

(19)



(11)

**EP 1 169 038 B9**

(12)

**CORRECTED EUROPEAN PATENT SPECIFICATION**

(15) Correction information:

**Corrected version no 1 (W1 B1)**

**Corrections, see**

**Claims EN 1-2**

(51) Int Cl.:

**A61K 31/426** <sup>(2006.01)</sup> **C07C 237/40** <sup>(2006.01)</sup>  
**C07D 213/81** <sup>(2006.01)</sup> **C07D 213/82** <sup>(2006.01)</sup>  
**C07D 231/38** <sup>(2006.01)</sup> **C07D 233/90** <sup>(2006.01)</sup>  
**C07D 239/42** <sup>(2006.01)</sup> **C07D 263/48** <sup>(2006.01)</sup>  
**C07D 277/56** <sup>(2006.01)</sup> **C07D 409/12** <sup>(2006.01)</sup>  
**C07D 417/12** <sup>(2006.01)</sup>

(48) Corrigendum issued on:

**10.07.2013 Bulletin 2013/28**

(86) International application number:

**PCT/US2000/009753**

(45) Date of publication and mention

of the grant of the patent:

**08.08.2012 Bulletin 2012/32**

(87) International publication number:

**WO 2000/062778 (26.10.2000 Gazette 2000/43)**

(21) Application number: **00922102.9**

(22) Date of filing: **12.04.2000**

(54) **CYCLIC PROTEIN TYROSINE KINASE INHIBITORS**

CYCLISCHE PROTEIN-TYROSINKINASEHEMMER

INHIBITEURS CYCLIQUES DE PROTEINE TYROSINE KINASE

(84) Designated Contracting States:

**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU  
MC NL PT SE**

• **WITYAK, John**

**Robbinsville, NJ 08691 (US)**

(30) Priority: **15.04.1999 US 129510 P**

(74) Representative: **Vossius & Partner**

**Siebertstrasse 4  
81675 München (DE)**

(43) Date of publication of application:

**09.01.2002 Bulletin 2002/02**

(56) References cited:

**EP-A- 0 275 312 EP-A- 0 276 177  
EP-A- 0 315 502 EP-A- 0 928 790  
WO-A-00/24724 WO-A-01/56567  
WO-A-98/57937 WO-A2-98/28282  
DE-A- 3 220 118 GB-A- 1 437 137  
US-A- 3 547 917**

(60) Divisional application:

**10013204.2 / 2 308 833**

(73) Proprietor: **Bristol-Myers Squibb Company**

**Princeton NJ 08543-4000 (US)**

(72) Inventors:

- **DAS, Jagabandhu**  
**Mercerville, NJ 08619 (US)**
- **PADMANABHA, Ramesh**  
**Hamden, CT 06518 (US)**
- **CHEN, Ping**  
**Belle Mead, NJ 08502 (US)**
- **NORRIS, Derek, J.**  
**Pennington, NJ 08534-5135 (US)**
- **DOWEYKO, Arthur, M., P.**  
**Long Valley, NJ 07853 (US)**
- **BARRISH, Joel, C.**  
**Richboro, PA 18954 (US)**

- **PATENT ABSTRACTS OF JAPAN vol. 0135, no. 17 (P-962), 20 November 1989 (1989-11-20) & JP 1210949 A (FUJIPHOTO FILM CO LTD), 24 August 1989 (1989-08-24)**
- **PATENT ABSTRACTS OF JAPAN vol. 0135, no. 01 (C-652), 10 November 1989 (1989-11-10) & JP 1 199955 A (FUJIPHOTO FILM CO LTD), 11 August 1989 (1989-08-11)**

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

**EP 1 169 038 B9**

- DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1998, KASSAB, RAFIKA RAMADAN: "Some reactions with 2-imino 4-thiazolidone" XP002292173 retrieved from STN Database accession no. 1998:726008 & AL-AZHAR BULLETIN OF SCIENCE , 8(1), 1-6 CODEN: ABSCE7; ISSN: 1110-2535, 1997,
- PHILLIPS W G ET AL: "THIAZOLE CARBOXANILIDE FUNGICIDES: A NEW STRUCTURE-ACTIVITY RELATIONSHIP FOR SUCCINATE DEHYDROGENASE INHIBITORS" PESTICIDE SCIENCE, ELSEVIER APPLIED SCIENCE PUBLISHER. BARKING, GB, vol. 38, no. 1, 1993, pages 1-7, XP000654631 ISSN: 0031-613X
- ODA, M. ET AL.: "Structure-activity relationships of N-(1,1,3-trimethylindan-4-yl)carboxamide fungicides" J. PESTICIDE SCI., vol. 18, no. 3, 1993, pages 245-251, XP009034823
- WOBIG, D.: "Darstellung von Thiazolo[4,5-d]-v-triazin-7(6H)-onen" LIEBIGS ANNALEN DER CHEMIE, vol. 12, 1984, pages 1994-1997, XP001183045
- ABDEL-LATEEF M F-A ET AL: "SYSTEMIC AND CHEMOTHERAPEUTIC FUNGICIDAL ACTIVITY-CHEMICAL STRUCTURE RELATIONSHIP OF SOME 4-METHYL-5-THIAZOLECARBOXYLIC ACID DERIVATIVES. - LABORATORY SCREENING TESTS" ACTA PHYTOPATHOLOGICA ACADEMIAE SCIENTIARUM HUNGARICAE, vol. 8, no. 3/4, 1973, pages 269-282, XP000614059
- ALDRICH CHEMICAL COMPANY, 1992 Catalog, page 51, entries 25,301-4 and 28,457-2, page 98 entry A8,980-4. XP002930612.
- CHUPP J.P.: 'A novel synthesis of 2,4-thiophenediamines and their behavior as stable reactive enamines' J. HETEROCYCLIC CHEM., vol. 7, no. 2, 1970, pages 285 - 289, XP002930613
- EREMEEV A.V. ET AL.: 'Addition of isocyanates and isothiocyanates to 2-amino-3-phenylcarbamoylazirine' KHIM. GETEROTSIKL. SOEDIN., no. 2, 1986, pages 277 - 278, XP002930614
- ALI M.I. ET AL.: 'Reactions with naphthoylacetanilides' EGYPT J. CHEM., vol. 22, no. 3, 1979, pages 179 - 188, XP002930615
- FRY D.W.: 'Recent advances in tyrosine kinase inhibitors' ANNUAL REPORTS IN MEDICINAL CHEMISTRY, vol. 31, 1996, pages 151 - 160, XP002930616

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

**Description****Field of the Invention**

**[0001]** The present invention relates to cyclic compounds and salts thereof, to such compounds for use in treating protein tyrosine kinase-associated disorders such as immunologic and oncologic disorders, and to pharmaceutical compositions containing such compounds.

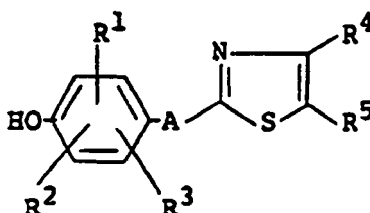
**Background of the Invention**

**[0002]** Protein tyrosine kinases (PTKs) are enzymes which, in conjunction with ATP as a substrate, phosphorylate tyrosine residues in peptides and proteins. These enzymes are key elements in the regulation of cell signaling including cell proliferation and cell differentiation. PTKs comprise, *inter alia*, receptor tyrosine kinases (RPTKs), including members of the epidermal growth factor kinase family (e.g., HER1 and HER2), platelet derived growth factor (PDGF), and kinases that play a role in angiogenesis (Tie-2 and KDR); and, in addition, non-receptor tyrosine kinases, including members of the Syk, JAK and Src (e.g. Src, Fyn, Lyn, Lck and Blk) families (see Bolen, J.B., Rowley, R.B., Spana, C., and Tsygankov, A.Y., "The src family of tyrosine protein kinases in hemopoietic signal transduction", FASEB J., 6, 3403-3409 (1992); Ullrich, A. and Schlessinger, J., "Signal transduction by receptors with tyrosine kinase activity", Cell, 61, 203-212 (1990); and Ihle, J.N., "The Janus protein tyrosine kinases in hematopoietic cytokine signaling", Sem. Immunol., 7, 247-254 (1995)).

**[0003]** Enhanced activity of PTKs has been implicated in a variety of malignant and nonmalignant proliferative diseases. In addition, PTKs play a central role in the regulation of cells of the immune system. PTK inhibitors can thus impact a wide variety of oncologic and immunologic disorders. Such disorders may be ameliorated by selective inhibition of a certain receptor or non-receptor PTK, such as Lck, or due to the homology among PTK classes, by inhibition of more than one PTK by an inhibitor.

**[0004]** A PTK of particular interest is Lck which is found in T cells where it is involved in phosphorylating key protein substrates. It is required for productive antigen receptor signaling and cell activation. In the absence of Lck activity, the T cell receptor (TCR) zeta chain is not phosphorylated, the kinase ZAP-70 is not activated, and  $\text{Ca}^{2+}$  mobilization essential for T cell activation does not occur (see Weiss, A. and Littman, D.R., "Signal transduction by lymphocyte antigen receptors", Cell, 76, 263-274 (1994); Iwashima, M., Irving, B.A., van Oers, N.S.C., Chan, A.C., and Weiss, A., "Sequential interactions of the TCR with two distinct cytoplasmic tyrosine kinases", Science, 263, 1136-1139 (1994); and Chan, A.C., Dalton, M., Johnson, R., Kong, G., Wang, T., Thoma, R., and Kurosaki, T., "Activation of ZAP-70 kinase activity by phosphorylation of tyrosine 493 is required for lymphocyte antigen receptor function", EMBO J., 14, 2499-2508 (1995)). Inhibitors of Lck are thus useful in the treatment of T-cell mediated disorders such as chronic diseases with an important T cell component, for example rheumatoid arthritis, multiple sclerosis and lupus, as well as acute diseases where T cells are known to play an essential role, for example acute transplant rejection and delayed-type hypersensitivity (DTH) reactions.

**[0005]** EP 0 275 312 (A1) describes a thiazole derivate of the general formula

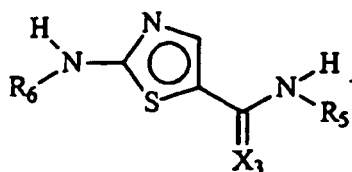


wherein  $\text{R}^1$  and  $\text{R}^2$  are the same or different and each is a  $\text{C}_1\text{-C}_6$  alkyl group,  $\text{R}^3$  is a hydrogen atom or a  $\text{C}_1\text{-C}_6$  alkyl group,  $\text{R}^2$  and  $\text{R}^3$  may combinedly form a  $-(\text{CH}_2)_4-$  group,  $\text{R}^4$  and  $\text{R}^5$  are the same or different and each is a hydrogen or halogen atom or a  $\text{C}_1\text{-C}_{20}$  alkyl, phenyl, phenylthio,  $\text{C}_1\text{-C}_6$  alkylthio or  $\text{C}_1\text{-C}_6$  alkylthio- $\text{C}_1\text{-C}_6$  alkyl, nitro,  $\text{C}_1\text{-C}_6$  alkoxy-carbonyl- $\text{C}_2\text{-C}_6$  alkenyl, carboxy- $\text{C}_2\text{-C}_6$  alkenyl, carbazoyl, carboxyl, carboxy- $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_1\text{-C}_6$  alkoxy-carbonyl- $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_1\text{-C}_6$  alkoxy-carbonyl, piperidinocarbonyl, N,N-di( $\text{C}_1\text{-C}_6$  alkyl)-aminocarbonyl, N-phenylaminocarbonyl or hydroxy- $\text{C}_1\text{-C}_6$  alkyl group, and A is an imino group, an oxygen or sulfur atom or a sulfinyl, sulfonyl or  $\text{C}_1\text{-C}_6$  alkylene group, to the exclusion of the cases where  $\text{R}^3$  is a hydrogen atom,  $\text{R}^4$  is a  $\text{C}_1\text{-C}_6$  alkyl or phenyl group,  $\text{R}^5$  is a hydrogen atom and A is an imino group; and salts thereof.

**Summary of the Invention**

**[0006]** The present invention relates to a thiazole compound of formula II or a salt thereof, to such a compound or salt thereof for use in the treatment of protein tyrosine kinase-associated disorder, and to a pharmaceutical composition comprising at least one such compound.

**[0007]** Compounds of formula II are defined as follows:

**II**

wherein

X<sub>3</sub> is oxygen or sulfur;

R<sub>5</sub> is an aryl group which is substituted with one or more groups selected from alkyl and halo;

R<sub>6</sub> is:

aryl or heteroaryl which is substituted with Z<sub>1</sub>, Z<sub>2</sub> and one or more groups Z<sub>3</sub>, wherein

a) said aryl is substituted with at least one group Z<sub>3</sub> where Z<sub>3</sub> is -Z<sub>4</sub>-NZ<sub>7</sub>Z<sub>8</sub> where Z<sub>4</sub> is a bond, Z<sub>7</sub> is hydrogen or alkyl, and Z<sub>8</sub> is heterocyclo-substituted alkyl; or

b) said heteroaryl is substituted with at least one group Z<sub>3</sub> where Z<sub>3</sub> is -Z<sub>4</sub>-NZ<sub>7</sub>Z<sub>8</sub> where Z<sub>4</sub> is a bond, Z<sub>7</sub> is hydrogen or alkyl, and Z<sub>8</sub> is heterocyclo-substituted alkyl; or

c) said heteroaryl is substituted with at least one group Z<sub>3</sub> where Z<sub>3</sub> is alkyl;

Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub> are each independently:

(1) hydrogen or Z<sub>6</sub>, where Z<sub>6</sub> is (i) alkyl, alkenyl, alkynyl, cycloalkyl, cyctoalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl; (ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or (iii) a group (i) or (ii) which is substituted by one or more of the following groups (2) to (16) of the definition of Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>;

(2) -OH or -OZ<sub>6</sub>;

(3) -SH or -SZ<sub>6</sub>;

(4) -C(O)<sub>q</sub>H, -O(O)<sub>q</sub>Z<sub>6</sub>, or -O-C(O)<sub>q</sub>Z<sub>6</sub>, where q is 1 or 2;

(5) -SO<sub>3</sub>H, -S(O)<sub>q</sub>Z<sub>6</sub>; or S(O)<sub>q</sub>N(Z<sub>9</sub>)Z<sub>6</sub>;

(6) halo;

(7) cyano;

(8) nitro;

(9) -Z<sub>4</sub>-NZ<sub>7</sub>Z<sub>8</sub>;

(10) -Z<sub>4</sub>-N(Z<sub>9</sub>-Z<sub>5</sub>-NZ<sub>7</sub>Z<sub>8</sub>);

(11) -Z<sub>4</sub>-N(Z<sub>10</sub>)Z<sub>5</sub>-Z<sub>6</sub>;

(12) -Z<sub>4</sub>-N(Z<sub>10</sub>)-Z<sub>5</sub>-H;

(13) oxo;

(14) -O-C(O)-Z<sub>6</sub>;

(15) any two of Z<sub>1</sub>, Z<sub>2</sub>, and Z<sub>3</sub> may together be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached; or

(16) any two of Z<sub>1</sub>, Z<sub>2</sub>, and Z<sub>3</sub> may together be -O-(CH<sub>2</sub>)<sub>r</sub>-O-, where r is 1 to 5, completing a 4- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached;

Z<sub>4</sub> and Z<sub>5</sub> are each independently:

(1) a single bond;

(2) -Z<sub>11</sub>-S(O)<sub>q</sub>-Z<sub>12</sub>-;

(3) -Z<sub>11</sub>-C(O)-Z<sub>12</sub>-;

- (4)  $-Z_{11}-C(S)-Z_{12}-$ ;  
 (5)  $-Z_{11}-O-Z_{12}-$ ;  
 (6)  $-Z_{11}-S-Z_{12}-$ ;  
 (7)  $-Z_{11}-O-C(O)-Z_{12}$ ; or  
 (8)  $-Z-C(O)-O-Z_{12}-$ ;

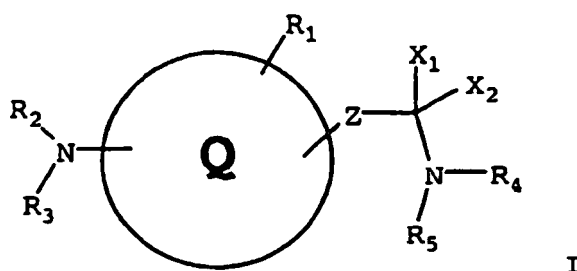
$Z_7, Z_8, Z_9$  and  $Z_{10}$ :

- (1) are each independently hydrogen or  $Z_6$ ;  
 (2)  $Z_7$  and  $Z_8$ , or  $Z_6$  and  $Z_{10}$ , may together be alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with  $Z_1, Z_2$  and  $Z_3$ ; or  
 (3)  $Z_7$  or  $Z_8$ , together with  $Z_9$ , may be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with  $Z_1, Z_2$  and  $Z_3$ ;

$Z_{11}$  and  $Z_{12}$  are each independently:

- (1) a single bond;  
 (2) alkylene;  
 (3) alkenylene; or  
 (4) alkynylene.

**[0008]** Herein described are also cyclic compounds of the following formula I and salts thereof, for use as protein tyrosine kinase inhibitors:



where  
 Q is:

- (1) a 5-membered heteroaryl ring;  
 (2) a 6-membered heteroaryl ring; or  
 (3) an aryl ring;  
 optionally substituted with one or more groups  $R_1$ ;

Z is:

- (1) a single bond;  
 (2)  $-R_{16}C=CH-$ ; or  
 (3)  $-(CH_2)_m-$ , where m is 1 to 2;

$X_1$  and  $X_2$  are each hydrogen, or together form  $=O$  or  $=S$ ;  
 $R_1$  is:

- (1) hydrogen or  $R_6$ ,  
 where  $R_6$  is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, heterocyclo, or heterocycloalkyl, each of which is unsubstituted or substituted with  $Z_1, Z_2$  and one or more (preferably, one or two) groups  $Z_3$ ;  
 (2)  $-OH$  or  $-OR_6$ ;

- (3) -SH or -SR<sub>6</sub>;  
 (4) -C(O)<sub>2</sub>H, -C(O)<sub>q</sub>R<sub>6</sub>, or -O-C(O)<sub>q</sub>R<sub>6</sub>, where q is 1 or 2;  
 (5) -SO<sub>3</sub>H or -S(O)<sub>q</sub>R<sub>6</sub>;  
 (6) halo;  
 (7) cyano;  
 (8) nitro;  
 (9) -Z<sub>4</sub>-NR<sub>7</sub>R<sub>8</sub>;  
 (10) -Z<sub>4</sub>-N(R<sub>9</sub>)-Z<sub>5</sub>-NR<sub>10</sub>R<sub>11</sub>;  
 (11) -Z<sub>4</sub>-N(R<sub>12</sub>)-Z<sub>5</sub>-R<sub>6</sub>;  
 (12) -P(O)(OR)<sub>2</sub>;

R<sub>2</sub> and R<sub>3</sub> are each independently:

- (1) hydrogen or R<sub>6</sub>;  
 (2) -Z<sub>4</sub>-R<sub>6</sub>; or  
 (3) -Z<sub>13</sub>-NR<sub>7</sub>R<sub>8</sub>;

R<sub>4</sub> and R<sub>5</sub>:

- (1) are each independently hydrogen or R<sub>6</sub>;  
 (2) -Z<sub>4</sub>-N(R<sub>9</sub>)-Z<sub>5</sub>-NR<sub>10</sub>R<sub>11</sub>;  
 (3) -N(R<sub>9</sub>)Z<sub>4</sub>R<sub>6</sub>; or  
 (4) together with the nitrogen atom to which they are attached complete a 3- to 8-membered saturated or unsaturated heterocyclic ring which is unsubstituted or substituted with Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>, which heterocyclic ring may optionally have fused to it a benzene ring itself unsubstituted or substituted with Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>;

R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub> and R<sub>12</sub>:

- (1) are each independently hydrogen or R<sub>6</sub>;  
 (2) R<sub>7</sub> and R<sub>8</sub> may together be alkylene, alkenylene or heteroalkyl, completing a 3- to 8-membered saturated or unsaturated ring with the nitrogen atom to which they are attached, which ring is unsubstituted or substituted with Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>; or  
 (3) any two of R<sub>9</sub>, R<sub>10</sub> and R<sub>11</sub> may together be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>;

R<sub>13</sub> is:

- (1) cyano;  
 (2) nitro;  
 (3) -NH<sub>2</sub>;  
 (4) -NHOalkyl;  
 (5) -OH;  
 (6) -NHOaryl;  
 (7) -NHCOOalkyl;  
 (8) -NHCOOaryl;  
 (9) -NHSO<sub>2</sub>alkyl;  
 (10) -NHSO<sub>2</sub>aryl;  
 (11) aryl;  
 (12) heteroaryl;  
 (13) -Oalkyl; or  
 (14) -Oaryl;

R<sub>14</sub> is:

- (1) -NO<sub>2</sub>;  
 (2) -COOalkyl; or  
 (3) -COOaryl;

R<sub>15</sub> is:

- (1) hydrogen;
- (2) alkyl;
- (3) aryl;
- (4) arylalkyl; or
- (5) cycloalkyl;

Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub> are each independently:

- (1) hydrogen or Z<sub>6</sub>, where Z<sub>6</sub> is (i) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl; (ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or (iii) a group (i) or (ii) which is substituted by one or more of the following groups (2) to (16) of the definition of Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>;
- (2) -OH or -OZ<sub>6</sub>;
- (3) -SH or -SZ<sub>6</sub>;
- (4) -C(O)<sub>q</sub>H, -C(O)<sub>q</sub>Z<sub>6</sub>, or -O-C(O)<sub>q</sub>Z<sub>6</sub>;
- (5) -SO<sub>3</sub>H, -S(O)<sub>q</sub>Z<sub>6</sub>; or S(O)<sub>q</sub>N(Z<sub>9</sub>)Z<sub>6</sub>;
- (6) halo;
- (7) cyano;
- (8) nitro;
- (9) -Z<sub>4</sub>-NZ<sub>7</sub>Z<sub>8</sub>;
- (10) -Z<sub>4</sub>-N(Z<sub>9</sub>)-Z<sub>5</sub>-NZ<sub>7</sub>Z<sub>8</sub>;
- (11) -Z<sub>4</sub>-N(Z<sub>10</sub>)-Z<sub>5</sub>-Z<sub>6</sub>;
- (12) -Z<sub>4</sub>-N(Z<sub>10</sub>)-Z<sub>5</sub>-H;
- (13) oxo;
- (14) -O-C(O)-Z<sub>6</sub>;
- (15) any two of Z<sub>1</sub>, Z<sub>2</sub>, and Z<sub>3</sub> may together be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached; or
- (16) any two of Z<sub>1</sub>, Z<sub>2</sub>, and Z<sub>3</sub> may together be -O-(CH<sub>2</sub>)<sub>r</sub>-O-, where r is 1 to 5, completing a 4- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached;

Z<sub>4</sub> and Z<sub>5</sub> are each independently:

- (1) a single bond;
- (2) -Z<sub>11</sub>-S(O)<sub>q</sub>-Z<sub>12</sub>;
- (3) -Z<sub>11</sub>-C(O)-Z<sub>12</sub>;
- (4) -Z<sub>11</sub>-C(S)-Z<sub>12</sub>;
- (5) -Z<sub>11</sub>-O-Z<sub>12</sub>;
- (6) -Z<sub>11</sub>-S-Z<sub>12</sub>;
- (7) -Z<sub>11</sub>-O-C(O)-Z<sub>12</sub>; or
- (8) -Z<sub>11</sub>-C(O)-O-Z<sub>12</sub>;

Z<sub>7</sub>, Z<sub>8</sub>, Z<sub>9</sub> and Z<sub>10</sub>:

- (1) are each independently hydrogen or Z<sub>6</sub>;
- (2) Z<sub>7</sub> and Z<sub>8</sub>, or Z<sub>6</sub> and Z<sub>10</sub>, may together be alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>; or
- (3) Z<sub>7</sub> or Z<sub>8</sub>, together with Z<sub>9</sub>, may be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>;

Z<sub>11</sub> and Z<sub>12</sub> are each independently:

- (1) a single bond;
- (2) alkylene;
- (3) alkenylene; or

(4) alkynylene; and

$Z_{13}$  is:

- (1) a single bond;
- (2)  $-Z_{11}-S(O)_q-Z_{12}-$ ;
- (3)  $-Z_{11}-C(O)-Z_{12}-$ ;
- (4)  $-Z_{11}-C(S)-Z_{12}-$ ;
- (5)  $-Z_{11}-O-Z_{12}-$ ;
- (6)  $-Z_{11}-S-Z_{12}-$ ;
- (7)  $-Z_{11}-O-C(O)-Z_{12}-$ ;
- (8)  $-Z_{11}-C(O)-O-Z_{12}-$ ;
- (9)  $-C(NR_{13})-$ ;
- (10)  $-C(CHR_{14})-$ ; or
- (11)  $-C(C(R_{14})_2)-$ .

**[0009]** Compounds within formula I include the inventive compounds of formula II and salts thereof; the compounds of formula I, except the inventive compounds of formula II and salts thereof, are described for illustrative purposes only (not according to the invention).

### Detailed Description of the Invention

**[0010]** The following are definitions of terms used in this specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification, individually or as part of another group, unless otherwise indicated.

**[0011]** The terms "alk" or "alkyl" refer to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms. The expression "lower alkyl" refers to alkyl groups of 1 to 4 carbon atoms.

**[0012]** The term "alkenyl" refers to straight or branched chain hydrocarbon groups of 2 to 10, preferably 2 to 4, carbon atoms having at least one double bond. Where an alkenyl group is bonded to a nitrogen atom, it is preferred that such group not be bonded directly through a carbon bearing a double bond.

**[0013]** The term "alkynyl" refers to straight or branched chain hydrocarbon groups of 2 to 10, preferably 2 to 4, carbon atoms having at least one triple bond. Where an alkynyl group is bonded to a nitrogen atom, it is preferred that such group not be bonded directly through a carbon bearing a triple bond.

**[0014]** The term "alkylene" refers to a straight chain bridge of 1 to 5 carbon atoms connected by single bonds (e.g.,  $-(CH_2)_x-$  wherein x is 1 to 5), which may be substituted with 1 to 3 lower alkyl groups.

**[0015]** The term "alkenylene" refers to a straight chain bridge of 2 to 5 carbon atoms having one or two double bonds that is connected by single bonds and may be substituted with 1 to 3 lower alkyl groups. Exemplary alkenylene groups are  $-CH=CH-CH=CH-$ ,  $-CH_2-CH=CH-$ ,  $-CH_2-CH=CH-CH_2-$ ,  $-C(CH_3)_2CH=CH-$  and  $-CH(C_2H_5)-CH=CH-$ .

**[0016]** The term "alkynylene" refers to a straight chain bridge of 2 to 5 carbon atoms that has a triple bond therein, is connected by single bonds, and may be substituted with 1 to 3 lower alkyl groups. Exemplary alkynylene groups are  $-C\equiv C-$ ,  $-CH_2-C\equiv C-$ ,  $-CH(CH_3)-C\equiv C-$  and  $-C\equiv C-CH(C_2H_5)CH_2-$ .

**[0017]** The terms "ar" or "aryl" refer to aromatic cyclic groups (for example 6 membered monocyclic, 10 membered bicyclic or 14 membered tricyclic ring systems) which contain 6 to 14 carbon atoms. Exemplary aryl groups include phenyl, naphthyl, biphenyl and anthracene.

**[0018]** The terms "cycloalkyl" and "cycloalkenyl" refer to cyclic hydrocarbon groups of 3 to 12 carbon atoms.

**[0019]** The terms "halogen" and "halo" refer to fluorine, chlorine, bromine and iodine.

**[0020]** The term "unsaturated ring" includes partially unsaturated and aromatic rings.

**[0021]** The terms "heterocycle", "heterocyclic" or "heterocyclo" refer to fully saturated or unsaturated, including aromatic (i.e. "heteroaryl") cyclic groups, for example, 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring systems, which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system.

**[0022]** Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydro-



pyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothieryl, triazolyl, triazinyl, and the like.

**[0023]** Exemplary bicyclic heterocyclic groups include indolyl, benzothiazolyl, benzoxazolyl, benzodioxolyl, benzothienyl, quinuclidinyl, quinolinyl, tetra-hydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl) or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), tetrahydroquinolinyl and the like.

**[0024]** Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

**[0025]** The term "heteroaryl" refers to aromatic heterocyclic groups.

**[0026]** Exemplary heteroaryl groups include pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furyl, thienyl, oxadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazolyl, triazinyl, and the like.

**[0027]** Where q is 1 or 2, "-C(O)<sub>q</sub>H" denotes -C(O)-H or -C(O)-OH; "-C(O)<sub>q</sub>R<sub>6</sub>" or "-C(O)<sub>q</sub>Z<sub>6</sub>" denote, respectively, -C(O)-R<sub>6</sub> or -C(O)-OR<sub>6</sub>, or -C(O)-Z<sub>6</sub> or -C(O)-OZ<sub>6</sub>; "-O-C(O)<sub>q</sub>R<sub>6</sub>" or "-O-C(O)<sub>q</sub>Z<sub>6</sub>" denote, respectively, -O-C(O)-R<sub>6</sub> or -O-C(O)-OR<sub>6</sub>, or -O-C(O)-Z<sub>6</sub> or -O-C(O)-OZ<sub>6</sub>; and "-S(O)<sub>q</sub>R<sub>6</sub>" or "-S(O)<sub>q</sub>Z<sub>6</sub>" denote, respectively, -SO-H<sub>6</sub> or -SO<sub>2</sub>-H<sub>6</sub>, or -SO-Z<sub>6</sub> or -SO<sub>2</sub>-Z<sub>6</sub>.

**[0028]** Compounds of the formula I may in some cases form salts. Reference to a compound of the formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. Zwitterions (internal or inner salts) are included within the term "salt(s)" as used herein (and may be formed, for example, where the R substituents comprise an acid moiety such as a carboxyl group). Also included herein are quaternary ammonium salts such as alkylammonium salts. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are useful, for example, in isolation or purification steps which may be employed during preparation. Salts of the compounds of the formula I may be formed, for example, by reacting a compound I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

**[0029]** Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates, 2-naphthalenesulfonates, nicotines, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates, undecanoates, and the like.

**[0030]** Exemplary basic salts (formed, for example, where the R substituents comprise an acidic moiety such as a carboxyl group) include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines, N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. The basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

**[0031]** All stereoisomers of the present compounds including enantiomeric and diastereomeric forms, are contemplated within the scope of this description. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations.

**[0032]** Throughout the specification, groups and substituents thereof are chosen to provide stable moieties and compounds.

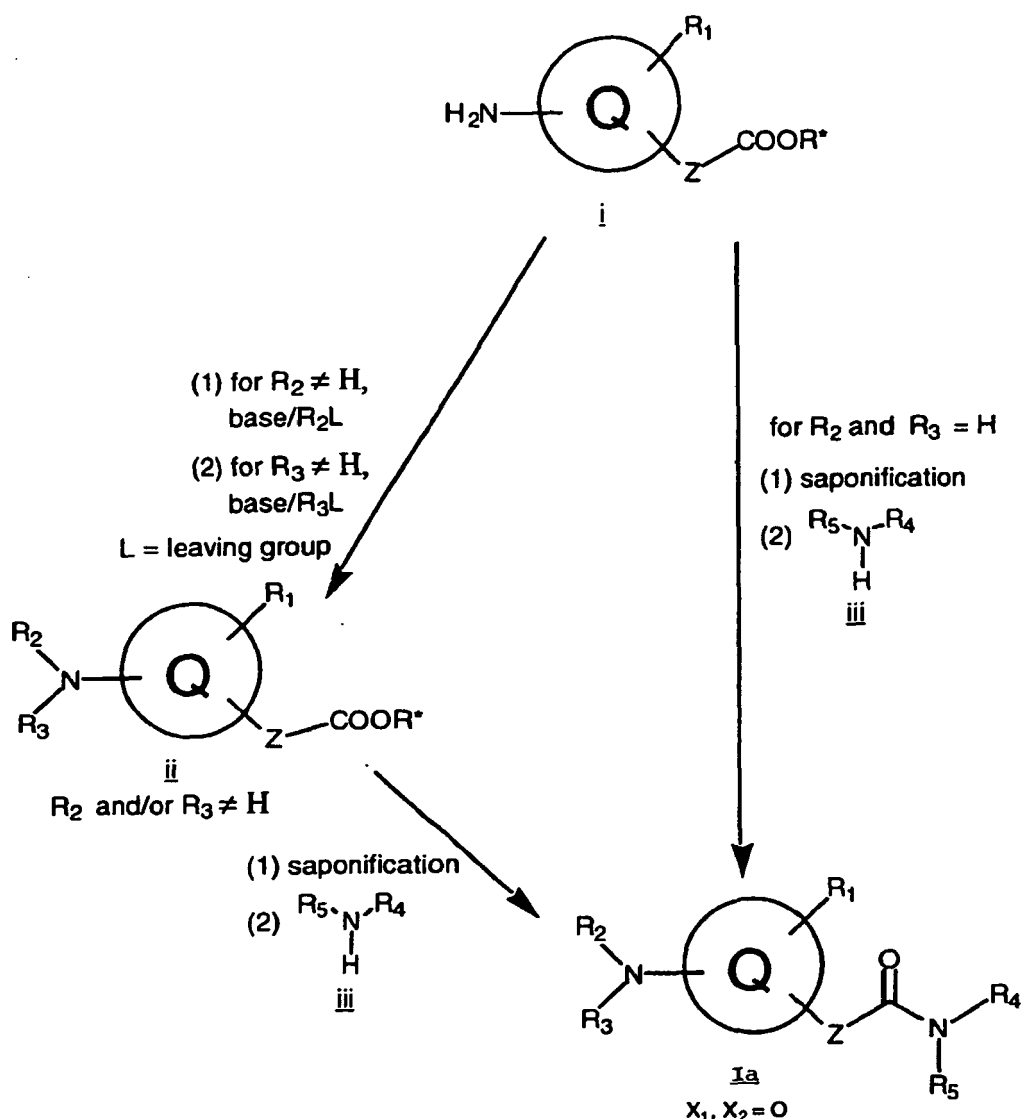
#### Methods of Preparation

**[0033]** The compounds of the formula I may be prepared by methods such as those illustrated in the following Schemes A through E and I through XI. Solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. Starting materials are commercially available or readily prepared by one of ordinary skill in the art. Constituents of compounds are as defined elsewhere in the specification or as specifically defined in a scheme.

**[0034]** The methods described herein may be carried out with starting materials and/or reagents in solution or alter-

natively, where appropriate, with one or more starting materials or reagents bound to a solid support (see (1) Thompson, L. A., Ellman, J. A., Chemical Reviews, 96, 555-600 (1996); (2) Terrett, N. K., Gardner, M., Gordon, D. W., Kobylecki, R. J., Steele, J., Tetrahedron, 51, 8135-8173 (1995); (3) Gallop, M. A., Barrett, R. W., Dower, W. J., Fodor, S. P. A., Gordon, E. M., Journal of Medicinal Chemistry, 37, 1233-1251 (1994); (4) Gordon, E. M., Barrett, R. W., Dower, W. J., Fodor, S. P. A., Gallop, M. A., Journal of Medicinal Chemistry, 37, 1385-1401 (1994); (5) Balkenhohl, F., von dem Bussche-Hünnefeld, Lansky, A., Zechel, C., Angewandte Chemie International Edition in English, 35, 2288-2337 (1996); (6) Balkenhohl, F., von dem Bussche-Hünnefeld, Lansky, A., Zechel, C., Angewandte Chemie, 108, 2436-2487 (1996); and (7) Sofia, M. J., Drugs Discovery Today, 1, 27-34 (1996)).

### Scheme A

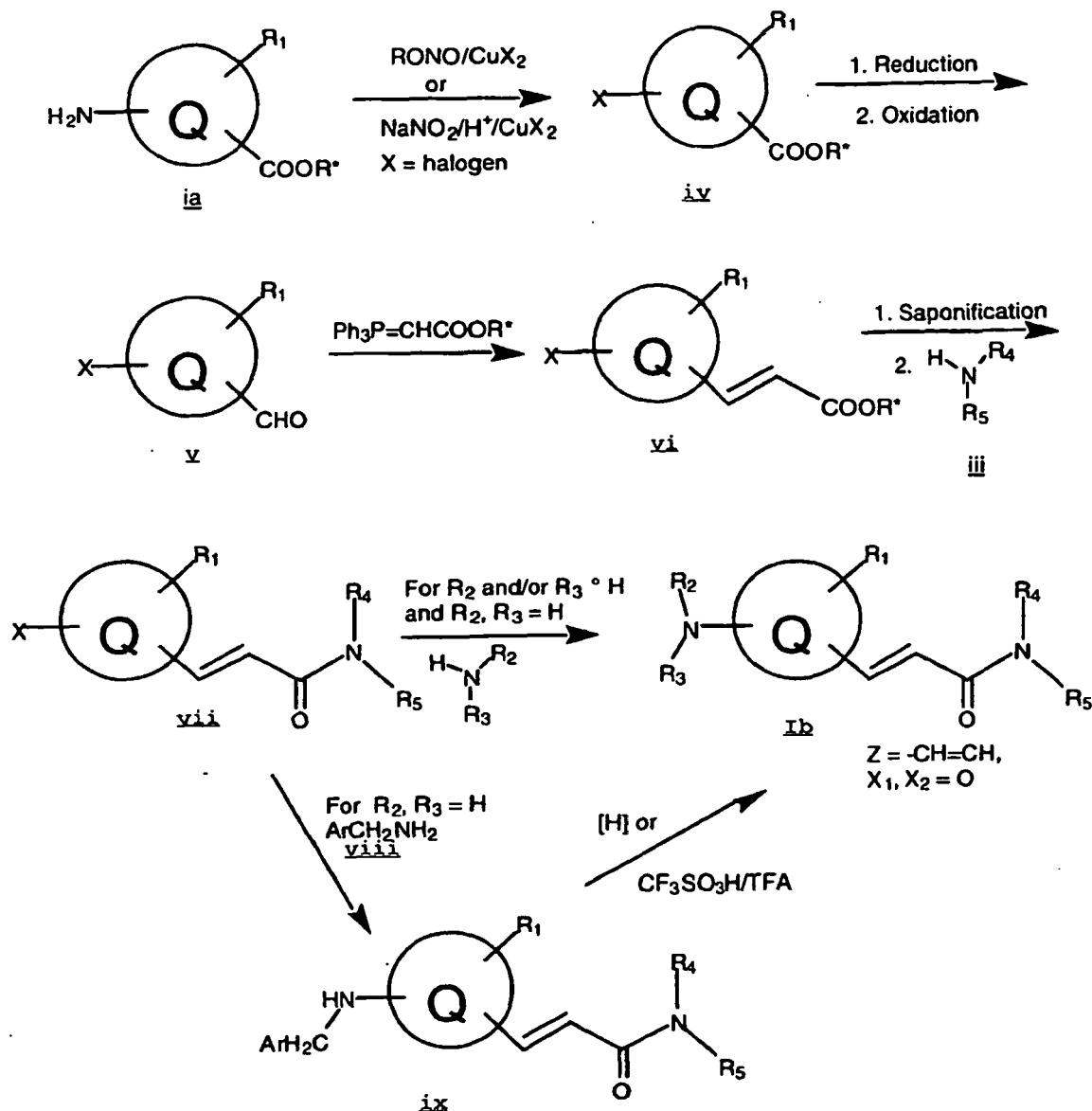


**[0035]** Scheme A illustrates a general method for forming compound Ia, which is a compound of the formula I where  $X_1$  and  $X_2$  together form  $=O$ . As shown in Scheme A, compound Ia where  $R_2$  and  $R_3$  are hydrogen may be formed by saponification of **i** ( $R^*$  is a carboxyl protecting group such as alkyl or arylalkyl) followed by reaction with amine **iii** by methods known in the art. Alternatively **i** may be reacted with  $R_2L$ , where L is a leaving group such as halogen (for example, in equimolar portions), optionally followed by reaction with  $R_3L$  (for example, in equimolar portions) to form **ii**. Also alternatively, **i** may be subjected to reductive amination using the appropriate aldehyde or ketone to form **ii**. The compound **ii** may then be saponified and reacted with amine **iii** under conditions known to those skilled in the art, to

form Ia where  $R_2$  and/or  $R_3$  are other than hydrogen.

[0036] Methods for preparing preferred substituents on the compounds I are illustrated in the following Schemes I to XI.

### Scheme B

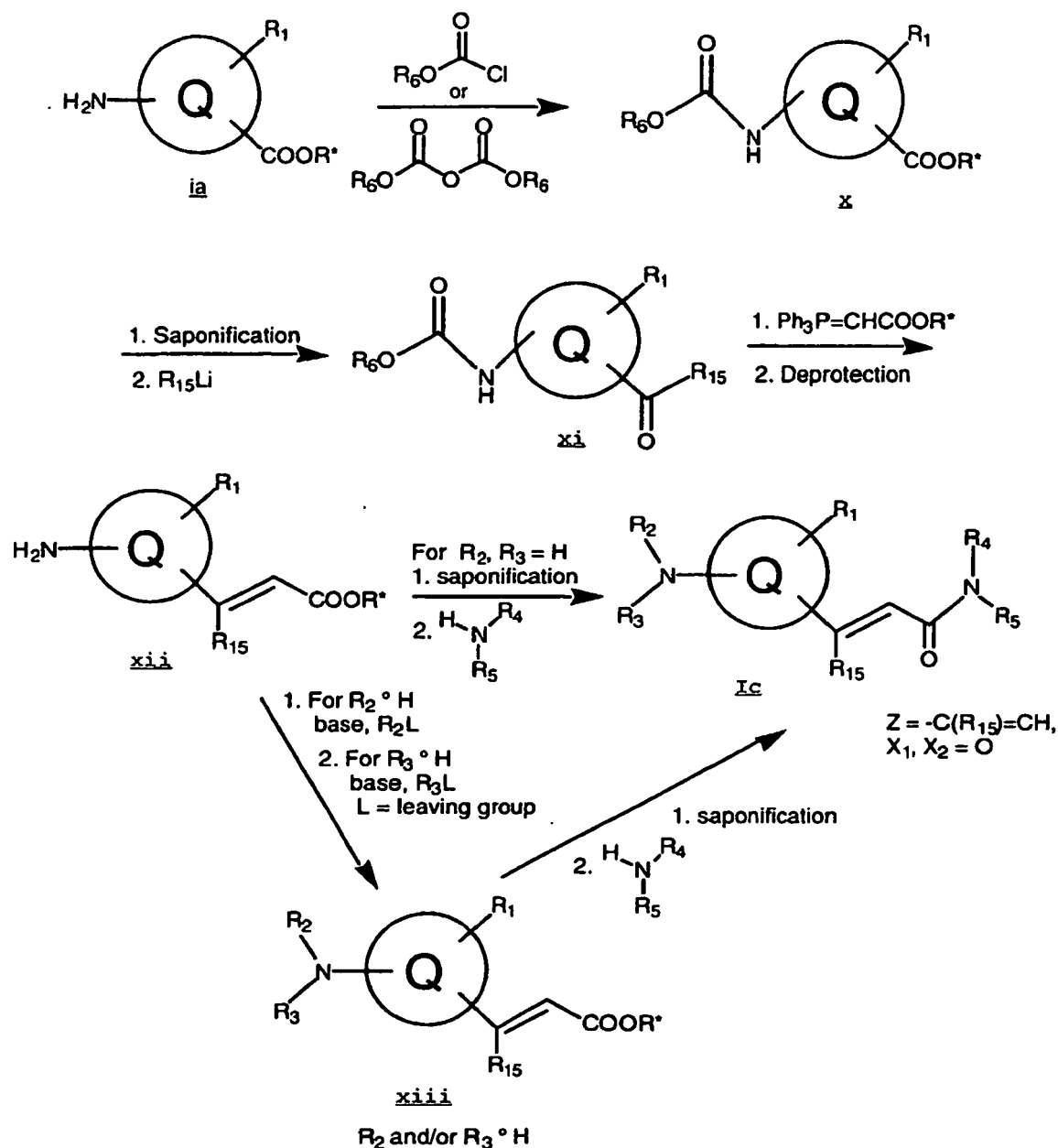


[0037] Scheme B illustrates a general method for forming compound Ib, which is a compound of formula I where Z is  $-\text{CH}=\text{CH}-$  and  $\text{X}_1$  and  $\text{X}_2$  together form  $=\text{O}$ . As shown in Scheme B, a 2-halo-compound vi can be prepared by reacting an appropriately substituted 2-amino-compound ia with copper (ii) halide and an alkyl nitrite such as tert-butyl nitrite in an aprotic solvent such as acetonitrile to form 2-halo-compound iv (see J. Het. Chem. 22, 1621 (1985)). Compound iv can be reduced with a reducing agent such as sodium borohydride in ethanol or aqueous tetrahydrofuran to form an alcohol, which can be oxidized with an oxidizing agent such as pyridinium chlorochromate or pyridinium dichromate to form aldehyde v. Compound v can be reacted with an alkyl(triphenylphosphorylidene) acetate to form carboxylate vi. Compound vi can be saponified and then reacted with an amine iii by methods known to those skilled in the art to form vii. Compound vii can be reacted with an amine  $\text{R}_2\text{R}_3\text{NH}$  to form Ib where Z is  $-\text{CH}=\text{CH}-$  and  $\text{X}_1, \text{X}_2$  together form  $=\text{O}$ . Alternatively, compounds of formula Ib where  $\text{R}_2$  and  $\text{R}_3$  are H, can be formed by reacting compound vii with an appropriately substituted benzyl amine such as 4-methoxybenzyl amine to form compound ix, which can be hydrogenolyzed or treated with an acid such as trifluoromethanesulfonic acid and trifluoroacetic acid in the presence of anisole to form

Ib where  $R_2$  and  $R_3$  are hydrogen.

[0038] Methods for preparing preferred substituents on the compounds I are illustrated in the following Schemes I to XI.

### Scheme C

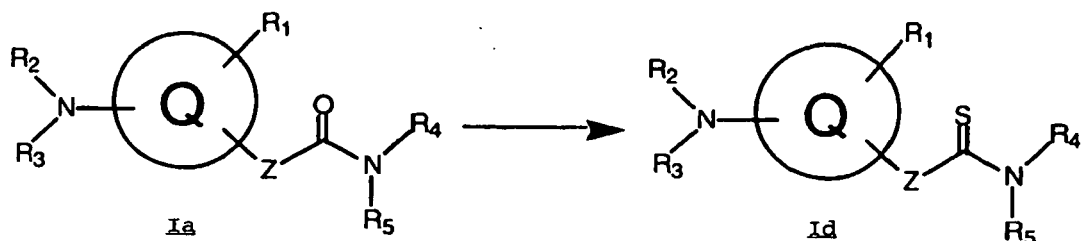


[0039] Scheme C illustrates a general method for forming compound Ic, which is a compound of formula I where Z is  $-\text{R}_{15}\text{C}=\text{CH}-$  and  $\text{X}_1$  and  $\text{X}_2$  together form  $=\text{O}$ . As shown in Scheme C, a 2-amino-compound Ia can be reacted with a chloroformate or dicarbonate to form x, which can be saponified and treated with an organolithium reagent to form compound xi. Compound xi may be reacted with an alkyl(triphenylphosphorylidene)acetate, followed by deprotection of the carbamate protecting group to form xii. Alternatively, compound Ic where  $\text{R}_2$  and  $\text{R}_3$  are hydrogen may be formed by saponification of xii followed by reaction with an amine  $\text{R}_4\text{R}_5\text{NH}$  by methods known to those skilled in the art. Alternatively, compound xii may be reacted with  $\text{R}_2\text{L}$  where L is a leaving group such as halogen (for example, in equimolar portions), optionally followed by reaction with  $\text{R}_3\text{L}$  (for example, in equimolar portions) to form xiii, which may be saponified

and reacted with an amine  $R_4R_5NH$  by methods known to those skilled in the art to form Ia where  $R_2$  and/or  $R_3$  are other than hydrogen.

**[0040]** Methods for preparing preferred substituents on the compounds I are illustrated in the following Schemes I to XI.

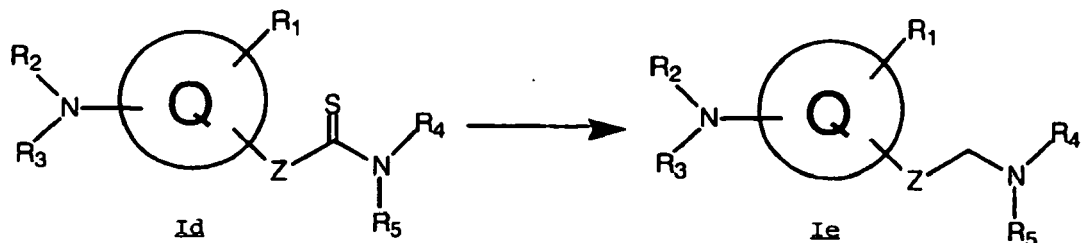
### Scheme D



**[0041]** Scheme D illustrates a general method for forming compound Id, which is a compound of the formula I where  $X_1$  and  $X_2$  together form  $=S$ . The compounds of the formula Ia obtained in Scheme A may be converted into the corresponding thioamide Id using a reagent such as Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (see Bull. Soc. Chim. Belg., 87, 223 (1978)).

**[0042]** Methods for preparing preferred substituents on the compounds I are illustrated in the following Schemes I to XI.

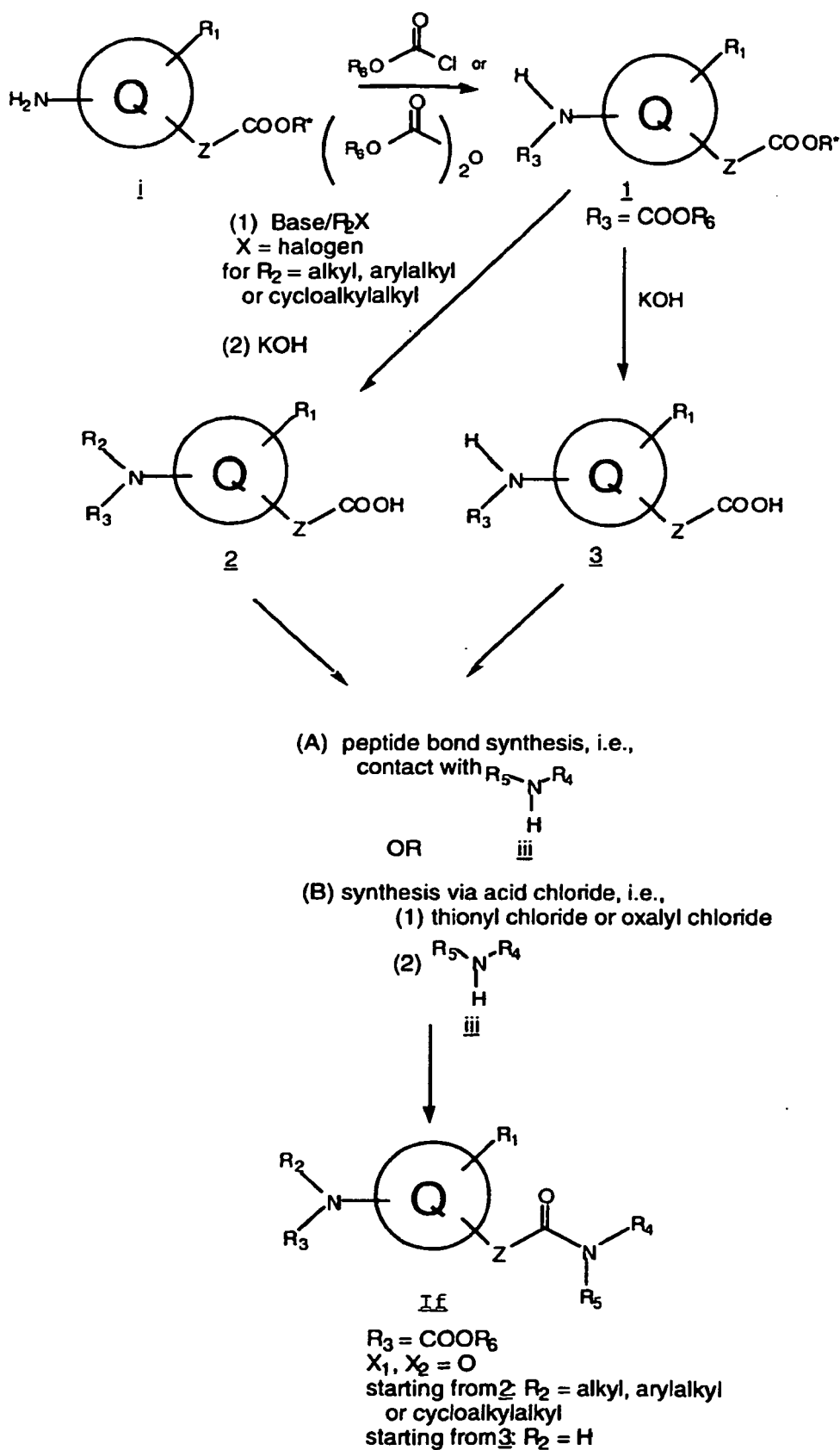
### Scheme E



**[0043]** Scheme E illustrates a general method for forming compound Ie, which is a compound of the formula I where  $X_1$  and  $X_2$  are each hydrogen. As shown in Scheme E, the compound of the formula Id obtained in Scheme D may be converted into the corresponding amine Ie by reduction, for example, by reaction with Raney nickel.

**[0044]** Methods for preparing preferred substituents on the compounds I are illustrated in the following Schemes I to XI.

## Scheme I



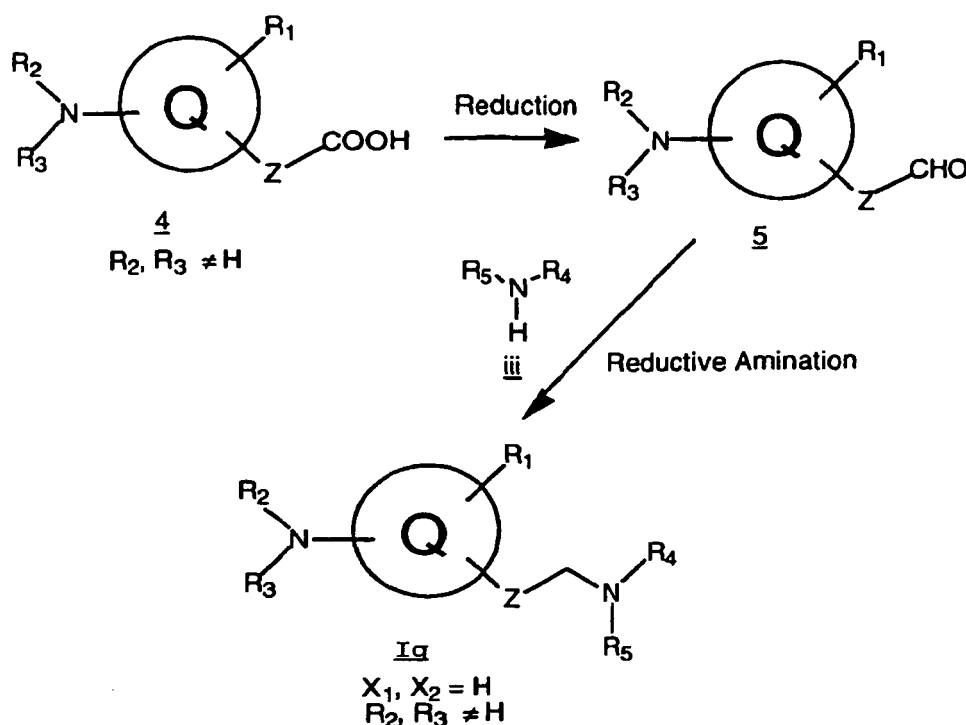
[0045] As shown in Scheme I, carboxylate i can be reacted with a chloroformate or dicarbonate to form 1. Compound

**1** can be treated with a base such as sodium hydride, sodium/potassium hexamethyldisilazide, or lithium diisopropylamide (LDA), and an alkylating agent  $R_2X$  where  $X$  is halogen and  $R_2$  is preferably alkyl, arylalkyl, or cycloalkylalkyl, and then saponified with an aqueous base such as potassium hydroxide to give **2**. Alternatively, **1** can be subjected to reductive amination using the appropriate aldehyde or ketone and saponified with an aqueous base such as potassium hydroxide to give **2**. Compound **1** may, alternatively, be simply saponified with an aqueous base such as potassium hydroxide to give **3** where  $R_2$  is hydrogen.

**[0046]** Acid **2** may be reacted with an amine **iii** using reaction conditions well known in the art for peptide bond synthesis (see, for example, Bodanszky and Bodanszky, *The Practice of Peptide Chemistry*, Springer-Verlag, 1984; Bodanszky, *Principles of Peptide Synthesis*, Springer-Verlag, 1984) to give the compound **Id** which is a compound of the formula I where  $X_1$  and  $X_2$  together form  $=O$ ,  $R_3$  is  $COOR_6$ , and, since **2** is the starting material,  $R_2$  is preferably alkyl, arylalkyl or cycloalkylalkyl. For example, reagents which activate the carboxyl group of **2** for reaction with the amine **iv** include bis-(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP chloride), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent), [O-(7-azabenzotriazol-1-yl)-1,3,3-tetramethyluronium] hexafluorophosphate (HATU), and carbodiimides such as dicyclohexylcarbodiimide (DCC) or 3-ethyl-3'-(dimethylamino)propylcarbodiimide (EDCI) either alone or in combination with a hydroxybenzotriazole. Alternatively, the activated ester intermediate can be isolated and then treated with the appropriate amine **iv** in a nonprotic solvent such as tetrahydrofuran (THF) or dimethylformamide (DMF) in the presence of a base, for example, an organic base such as sodium/potassium hexamethyldisilazide, triethylamine, diisopropylethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or an inorganic base such as sodium, potassium or cesium carbonate or sodium or potassium hydride. Alternatively, the acid halide of **2** may be prepared, for example, by reaction with thionyl chloride or oxalyl chloride, followed by subsequent reaction with amine **iii** to provide compound **If**, which is a compound of the formula I where  $R_3$  is  $COOR_6$ ,  $X_1$  and  $X_2$  together form  $=O$ , and  $R_2$  is alkyl, arylalkyl or cycloalkylalkyl.

**[0047]** Similar reactions as employed above for the conversion of **2** to **If** may be used to convert **3** to **If** where  $R_3$  is  $COOR_6$ ,  $X_1$  and  $X_2$  together form  $=O$ , and  $R_2$  is hydrogen.

## Scheme II

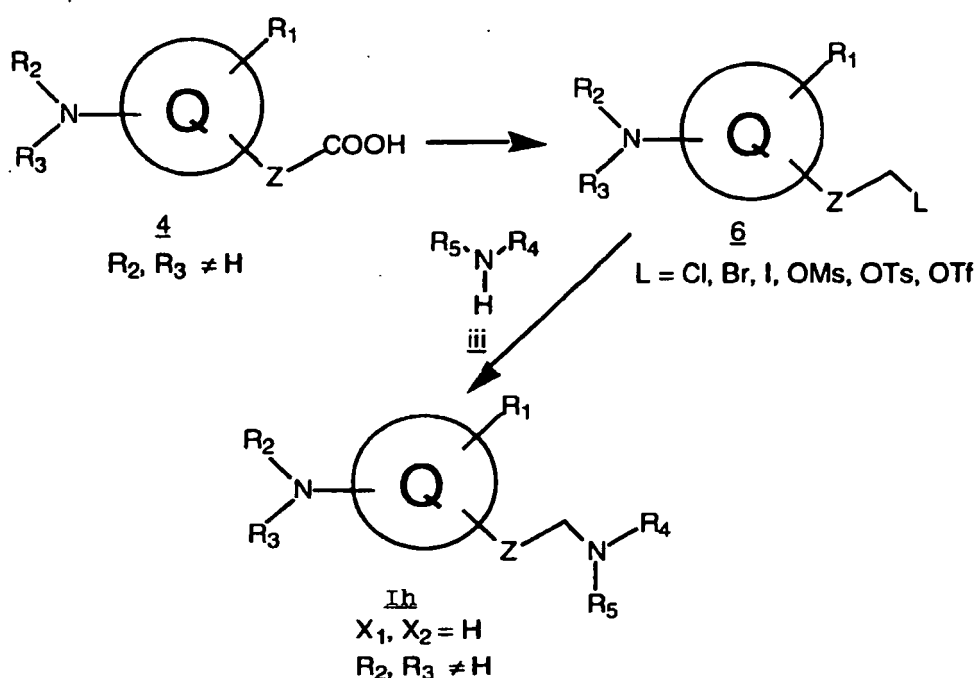


**[0048]** As shown in Scheme II, acid **4** where  $R_2$  and  $R_3$  are not hydrogen and are selected such that the nitrogen to

which they are attached is non-basic, is reduced to the aldehyde **5** by methods well known in the art (see March, Advanced Organic Chemistry, Wiley, 1985). For example, the acid **4** may be converted to its corresponding ester followed by reduction with diisobutylaluminum hydride. Alternatively, the acid **4** may be reduced to the corresponding primary alcohol, for example, by treatment with borane/THF,  $\text{LiAlH}_4$ , or via reduction of a mixed anhydride, followed by subsequent oxidation to the aldehyde **5** using  $\text{Cr(VI)}$  (e.g., pyridinium chlorochromate, "PCC") or under Swern or Moffatt conditions (e.g.,  $(\text{COCl})_2/\text{dimethylsulfoxide}$ ). The starting acid **4** may be obtained, for example, by saponification of **ii**.

**[0049]** Reductive amination (see Hudlicky, Reductions in Organic Chemistry, Wiley, 1984) of aldehyde **5** with amine **iii** in the presence of a reducing agent such as  $\text{NaBH}_3\text{CN}$ ,  $\text{NaBH}(\text{OAc})_3$  ( $\text{Ac} = \text{acetyl}$ ) or hydrogen and a palladium catalyst produces the amine compound **Ig**, which is a compound of the formula I where  $\text{X}_1$  and  $\text{X}_2$  are each hydrogen and  $\text{R}_2$  and  $\text{R}_3$  are each not hydrogen.

### Scheme III

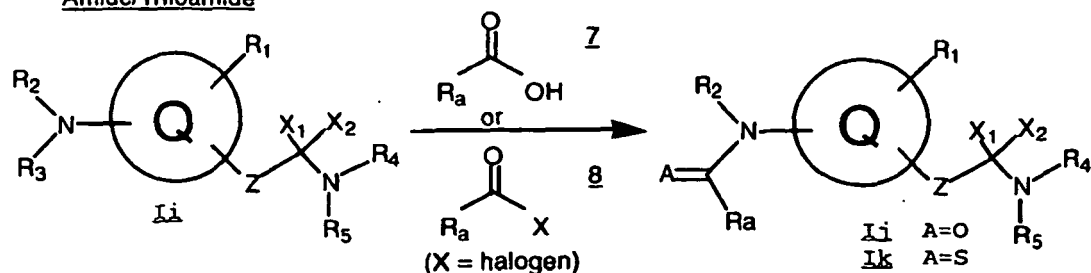
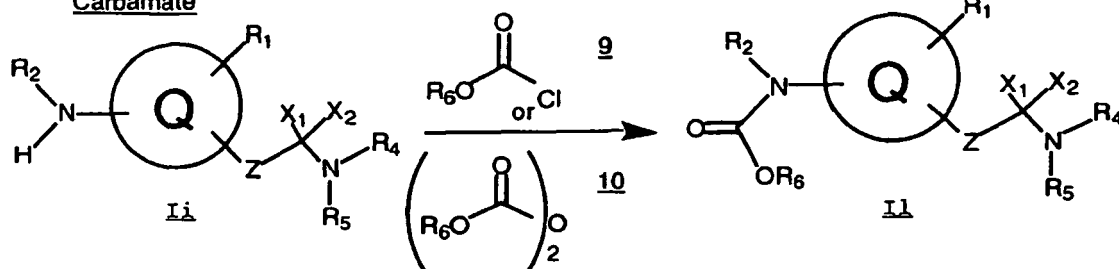
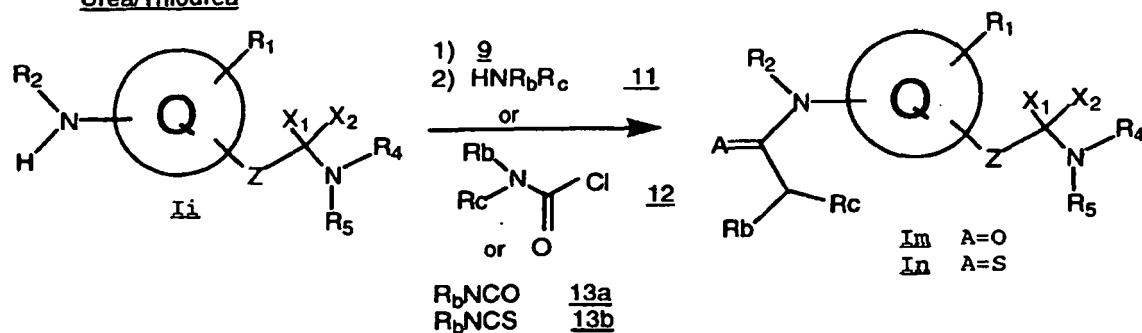


**[0050]** As shown in Scheme III, reduction of the acid **4** to a primary alcohol (for example, by treatment with borane/tetrahydrofuran,  $\text{LiAlH}_4$ , or via reduction of a mixed anhydride), followed by conversion by methods well known in the art (see March, Advanced Organic Chemistry, Wiley, 1985), provides **6** which contains a leaving group such as a halide, tosylate (OTs), mesylate (OMs) or triflate (OTf). The groups  $\text{R}_2$  and  $\text{R}_3$  are selected such that the resulting nitrogen to which they are attached is non-basic. Compound **6** can then be converted into compound **Ih**, which is a compound of the formula I where  $\text{X}_1$  and  $\text{X}_2$  are each hydrogen and  $\text{R}_2$  and  $\text{R}_3$  are each not hydrogen, by a displacement reaction with amine **iii**, preferably where amine **iii** is used in excess.



## Scheme IV

$R_2$  = any group as defined  
 $R_3$  = acyl or thioacyl

Amide/ThioamideCarbamateUrea/Thiourea

[ $X_1, X_2 \neq H$ ]

**[0051]** Scheme IV illustrates methods which may be used for the preparation of compounds Ij, Ik, II, Im and In. Ij, Ik, II, Im and In are compounds of the formula I where  $R_2$  is any group as defined,  $R_3$  is an acyl or thioacyl group,  $X_1$  and  $X_2$  are not hydrogen, and R is not a primary or secondary amine. Ij, Ik, II, Im and In have other particular substituents which are specified in this Scheme and below. The starting compound Ii can be prepared by suitable methods described in Schemes A and D.

**[0052]** Amide Ij can be prepared by treatment of amine compound Ii with a carboxylic acid 7 in the presence of reagents which activate the carboxyl group for reaction as described above, for example BOP reagent, HATU, and carbodiimides such as DCC or EDCI either alone or in combination with a hydroxybenztriazole. Alternatively, the acid halide 8 may be reacted with amine compound Ii in the presence of an acid scavenger such as diisopropylethylamine. The corresponding thioamide Ik can be prepared by the treatment of amide Ii (where  $X_1, X_2 \neq O$ ) with Lawesson's reagent as described above.

**[0053]** Carbamate II can be prepared by treatment of amine compound Ii with a chloroformate 9 or dicarbonate 10 in the presence of an acid scavenger such as diisopropylethylamine.

**[0054]** The urea Im may be prepared by treatment of amine compound Ii with either: 1) a chloroformate 9, such as phenylchloroformate, followed by reaction with an amine 11; 2) a carbamoyl chloride 12 in the presence of an acid scavenger such as diisopropylethylamine; or 3) reaction with an isocyanate 13a (where  $R_c$  in Im = H). The corresponding thiourea In may be prepared by treatment of amine compound Ii with a thioisocyanate 13b.

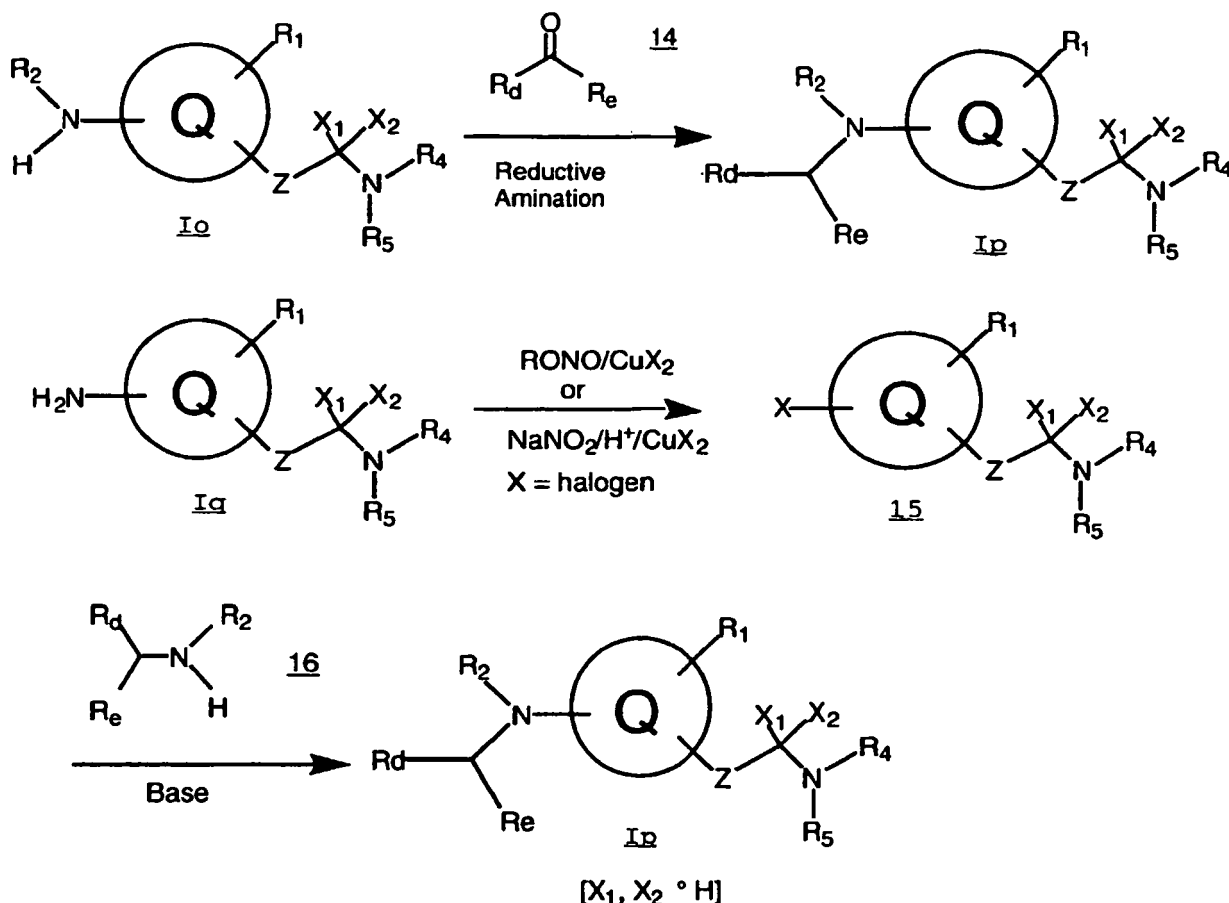
**[0055]**  $R_a$  is selected from those groups included in the definition of  $R_6$  such that the group  $-C(=A)-R_a$  is an acyl or

thioacyl group within the definition of  $R_3$ .  $R_b$  and  $R_c$  are selected from those groups included in the definitions of  $R_7$  and  $R_8$ , such that the group  $-C(=A)-N(R_b)(R_c)$  is an acyl or thioacyl group within the definition of  $R_3$ .

### Scheme V

$R_2$  = any group as defined other than acyl

$R_3$  = alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl or saturated heterocycle



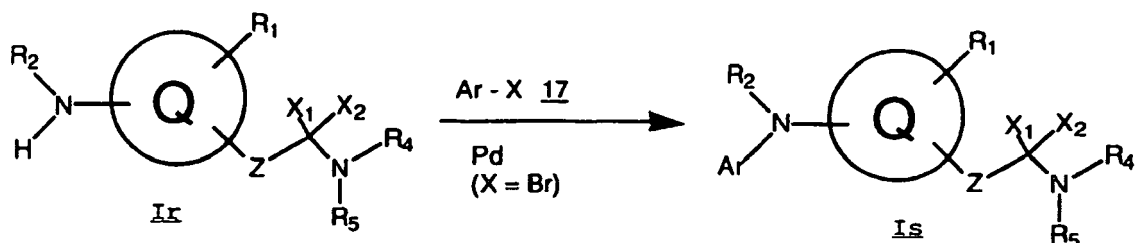
**[0056]** Scheme V illustrates a method which can be used for the preparation of Ip, which is a compound of the formula I where  $R_2$  is any group as defined other than acyl, and which is selected such that the nitrogen to which it is attached is basic,  $R_3$  is alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl, or saturated heterocycle, and  $X_1$  and  $X_2$  are not hydrogen. The starting compounds Io and Iq can be prepared by suitable methods described in Schemes A and D.

**[0057]** As shown in Scheme V, amine compound Io is reacted with an aldehyde or ketone **14** under reductive amination conditions described above to give the amine Ip. Compound Ip may also be prepared by treatment of an amine compound Iq, where  $R_2$  and  $R_3$  are hydrogen, with t-butyl nitrite or sodium nitrite in the presence of a copper (II) halide to give the halo-substituted compound **15**, followed by displacement with amine **16** in the presence of a base such as sodium or potassium hydride or the like (see Lee et al., J. Heterocyclic Chemistry, 22, 1621 (1985)).

**[0058]**  $R_d$  and  $R_e$  are independently selected from hydrogen, alkyl, aryl, cycloalkyl or cycloalkenyl, or together are alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring, such that the group  $-CH(R_d)(R_e)$  is a group within the definition of  $R_3$ .

Scheme VI

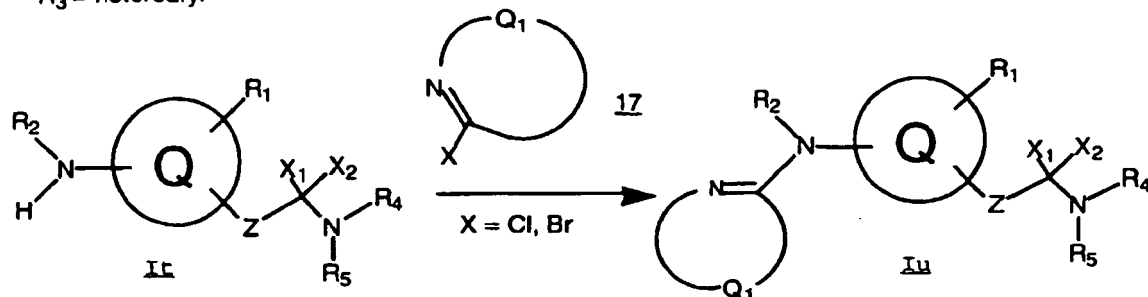
$R_2$  = any group as defined other than acyl  
 $R_3$  = aryl, heteroaryl



**[0059]** As shown in Scheme VI, when  $R_2$  is any group as defined other than acyl, and is selected such that the nitrogen to which it is attached is basic,  $R_3$  is aryl or heteroaryl, and  $X_1$  and  $X_2$  are not hydrogen, amine compound **Ir** may be reacted with a halophenyl or haloheteroaromatic group **17** in the presence of a palladium (0) catalyst (see J. Am. Chem. Soc., 118, 7215 (1996)) to give amine **Is**, which is a compound of the formula I having the particular substituents described in this Scheme. The starting compound **Ir** can be prepared by suitable methods described in Schemes A and D.

Scheme VII

$R_2$  = any group as defined  
 $R_3$  = heteroaryl



**[0060]** As shown in Scheme VII, when  $R_2$  is any group as defined and  $R_3$  is a heteroaromatic group, amine compound **Ir** may be reacted, in the presence of a base if needed, with a 2-halosubstituted heteroaromatic compound **17** where  $Q_1$ , together with atoms to which it is bonded, forms a 5- or 6-membered monocyclic or 10- to 12-membered bicyclic heteroaromatic group (such as forming 2-chloropyridine or 2-chloropyrimidine) to give the amine **Iu**, where **Iu** is a compound of the formula I having the particular substituents described in this Scheme. The starting compound **Ir** can be prepared by suitable methods described in Schemes A and D.

## 10



20

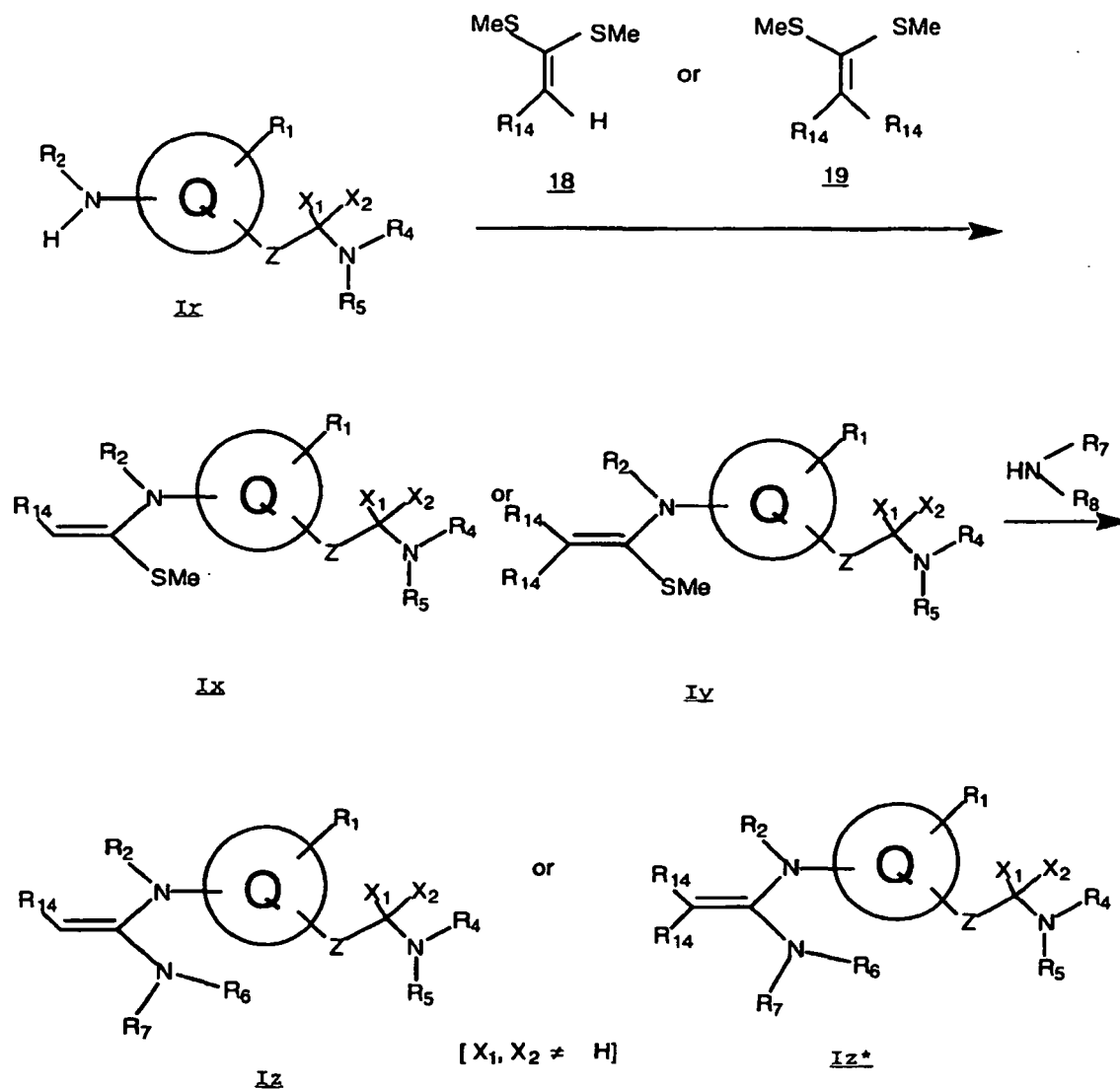
25

## 30



[0063] As shown in Scheme IX, amine Ir (where  $X_1$  and  $X_2$  are not hydrogen) can be reacted with diphenylcyanocarbo-  
 bonimide either alone or in the presence of a base such as sodium hydride, sodium hexamethyldisilazide or dimeth-  
 ylamino-pyridine in acetonitrile, tetrahydrofuran, or dimethylformamide at room temperature or elevated temperature to  
 form intermediate compound Iw. Compound Iw can be reacted with an amine  $R_7R_8NH$  to form compound Iv, which is a  
 compound of the formula I having the particular substituents described in this Scheme.

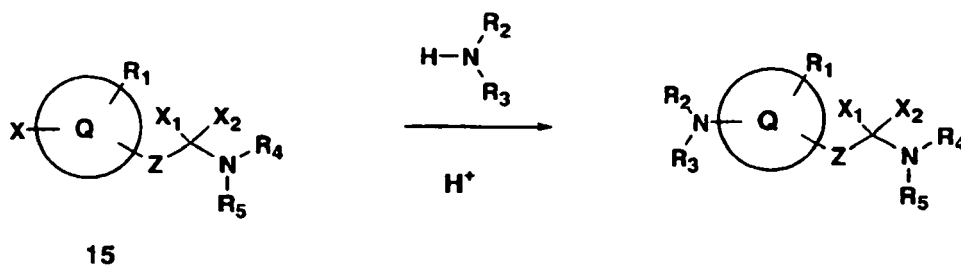
## Scheme X



[0064] As shown in Scheme X, compound Ir (where  $X_1$  and  $X_2$  are not hydrogen) can be reacted with 18 or 19 either  
 alone or in the presence of a base such as sodium hydride, sodium hexamethyl disilazide or dimethylamino-pyridine in  
 dimethyl formamide or tetrahydrofuran at room temperature or at higher temperature to form compounds Ix or Iv respec-  
 tively, which can be reacted with an amine  $R_7R_8NH$  at room temperature or elevated temperature to form compounds  
 Iz or Iz\* respectively. Compound Iz is a compound of the formula I having the particular substituents described in this  
 Scheme. Compound Iz\* is a compound of the formula I having the particular substituents described in this Scheme.

Scheme XI

**R<sub>2</sub> = aryl, heteroaryl, bicyclic-heteroaryl**  
**R<sub>3</sub> = H, alkyl, aryl, heteroaryl, bicyclic-heteroaryl**



**[0065]** As shown in Scheme XI, compounds of formula I can also be prepared from **15** by treatment with the defined amine in the presence of an acid catalyst (for example, see: Gunzenhauser et al., *Helv. Chim. Acta*, 71, 33 (1988)).

## Utility

**[0066]** The compounds of the present invention inhibit protein tyrosine kinases, especially Src-family kinases such as Lck, Fyn, Lyn, Src, Yes, Hck, Fgr and Blk, and are thus useful in the treatment, including prevention and therapy, of protein tyrosine kinase-associated disorders such as immunologic and oncologic disorders. The compounds inhibit also receptor tyrosine kinases including HER1 and HER2 and are therefore useful in the treatment of proliferative disorders such as psoriasis and cancer. The ability of these compounds to inhibit HER1 and other receptor kinases will also permit their use as anti-angiogenic agents to treat disorders such as cancer and diabetic retinopathy. "Protein tyrosine kinase-associated disorders" are those disorders which result from aberrant tyrosine kinase activity, and/or which are alleviated by the inhibition of one or more of these enzymes. For example, Lck inhibitors are of value in the treatment of a number of such disorders (for example, the treatment of autoimmune diseases), as Lck inhibition blocks T cell activation. The treatment of T cell mediated diseases, including inhibition of T cell activation and proliferation, is particularly preferred. Compounds which selectively block T cell activation and proliferation are preferred. Compounds of the present invention which block the activation of endothelial cell PTK by oxidative stress, thereby limiting surface expression of adhesion molecules that induce neutrophil binding, and which inhibit PTK necessary for neutrophil activation are useful, for example, in the treatment of ischemia and reperfusion injury.

**[0067]** The present invention thus provides compounds for use in the treatment of protein tyrosine kinase-associated disorders by administering to a subject in need thereof at least one compound of the formula I in an amount effective therefor. Other therapeutic agents such as those described below may be employed with the inventive compounds in the present methods. Such other therapeutic agent(s) may be administered prior to, simultaneously with or following the administration of the compound(s) of the present invention.

**[0068]** Use of the compounds of the present invention in treating protein tyrosine kinase-associated disorders is exemplified by treating a range of disorders such as: transplant (such as organ transplant, acute transplant or heterograft or homograft (such as is employed in burn treatment)) rejection; protection from ischemic or reperfusion injury such as ischemic or reperfusion injury incurred during organ transplantation, myocardial infarction, stroke or other causes; transplantation tolerance induction; arthritis (such as rheumatoid arthritis, psoriatic arthritis or osteoarthritis); multiple sclerosis; chronic obstructive pulmonary disease (COPD), such as emphysema; inflammatory bowel disease, including ulcerative colitis and Crohn's disease; lupus (systemic lupus erythematosus); graft vs. host disease; T-cell mediated hypersensitivity diseases, including contact hypersensitivity, delayed-type hypersensitivity, and gluten-sensitive enteropathy (Celiac disease); psoriasis; contact dermatitis (including that due to poison ivy); Hashimoto's thyroiditis; Sjogren's syndrome; Autoimmune Hyperthyroidism, such as Graves' Disease; Addison's disease (autoimmune disease of the adrenal glands); Autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome); autoimmune alopecia; pernicious anemia; vitiligo; autoimmune hypopituitarism; Guillain-Barre syndrome; other autoimmune diseases; cancers, including cancers where Lck or other Src-family kinases such as Src are activated or overexpressed, such as colon carcinoma and thymoma, and cancers where Src-family kinase activity facilitates tumor growth or survival; glomerulonephritis; serum sickness; urticaria; allergic diseases such as respiratory allergies (asthma, hayfever, allergic rhinitis) or skin allergies; scleroderma; mycosis fungoides; acute inflammatory responses (such as acute respiratory distress syn-

drome and ischemia/reperfusion injury); dermatomyositis; alopecia areata; chronic actinic dermatitis; eczema; Behcet's disease; Pustulosis palmoplantaris; Pyoderma gangrenosum; Sezary's syndrome; atopic dermatitis; systemic sclerosis; and morphea. The present invention also provides compounds for use in treating the aforementioned disorders such as atopic dermatitis by administration of any compound capable of inhibiting protein tyrosine kinase.

**[0069]** Src-family kinases other than Lck, such as Hck and Fgr, are important in the Fc gamma receptor responses of monocytes and macrophages. Compounds of the present invention inhibit the Fc gamma dependent production of TNF alpha in the monocyte cell line THP-1 that does not express Lck. The ability to inhibit Fc gamma receptor dependent monocyte and macrophage responses results in additional anti-inflammatory activity for the present compounds beyond their effects on T cells. This activity is especially of value, for example, in the treatment of inflammatory diseases such as arthritis or inflammatory bowel disease. In particular, the present compounds are of value for the treatment of autoimmune glomerulonephritis and other instances of glomerulonephritis induced by deposition of immune complexes in the kidney that trigger Fc gamma receptor responses leading to kidney damage.

**[0070]** In addition, Src family kinases other than Lck, such as Lyn and Src, are important in the Fc epsilon receptor induced degranulation of mast cells and basophils that plays an important role in asthma, allergic rhinitis, and other allergic disease. Fc epsilon receptors are stimulated by IgE-antigen complexes. Compounds of the present invention inhibit the Fc epsilon induced degranulation responses, including in the basophil cell line RBL that does not express Lck. The ability to inhibit Fc epsilon receptor dependent mast cell and basophil responses results in additional anti-inflammatory activity for the present compounds beyond their effect on T cells. In particular, the present compounds are of value for the treatment of asthma, allergic rhinitis, and other instances of allergic disease.

**[0071]** The combined activity of the present compounds towards monocytes, macrophages, T cells, etc. may be of value in the treatment of any of the aforementioned disorders.

**[0072]** In a particular embodiment, the compounds of the present invention are useful for the treatment of the aforementioned exemplary disorders irrespective of their etiology, for example, for the treatment of transplant rejection, rheumatoid arthritis, multiple sclerosis, chronic obstructive pulmonary disease, inflammatory bowel disease, lupus, graft v. host disease, T-cell mediated hypersensitivity disease, psoriasis, Hashimoto's thyroiditis, Guillain-Barre syndrome, cancer, contact dermatitis, allergic disease such as allergic rhinitis, asthma, ischemic or reperfusion injury, or atopic dermatitis whether or not associated with PTK.

**[0073]** By virtue of their ability to inhibit HER1 and HER2 kinases, compounds of the present invention can also be used for the treatment of proliferative diseases, including psoriasis and cancer. The HER1 receptor kinase has been shown to be expressed and activated in many solid tumors including non-small cell lung, colorectal, and breast cancer. Similarly, the HER2 receptor kinase has been shown to be overexpressed in breast, ovarian, lung and gastric cancer. Monoclonal antibodies that downregulate the abundance of the HER2 receptor or inhibit signaling by the HER1 receptor have shown anti-tumor efficacy in preclinical and clinical studies. It is therefore expected that inhibitors of the HER1 and HER2 kinases will have efficacy in the treatment of tumors that depend on signaling from either of the two receptors. These compounds are expected to have efficacy either as single agent or in combination with other chemotherapeutic agents such as paclitaxel (Taxol), doxorubicin hydrochloride (adriamycin), and cisplatin (Platinol). See the following documents and references cited therein: Cobleigh, M. A., Vogel, C. L., Tripathy, D., Robert, N. J., Scholl, S., Fehrenbacher, L., Wolter, J. M., Paton, V., Shak, S., Lieberman, G., and Slamon, D. J., "Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease", J. of Clin. Oncol. 17(9), p. 2639-2648 (1999); Baselga, J., Pfister, D., Cooper, M. R., Cohen, R., Burtneess, B., Bos, M., D'Andrea, G., Seidman, A., Norton, L., Gunnett, K., Falcey, J., Anderson, V., Waksal, H., and Mendelsohn, J., "Phase I studies of anti-epidermal growth factor receptor chimeric antibody C225 alone and in combination with cisplatin", J. Clin. Oncol. 18(4), p. 904-914 (2000).

**[0074]** The present invention also provides pharmaceutical compositions comprising at least one of the compounds of the formula II capable of treating a protein tyrosine kinase-associated disorder in an amount effective therefor, and a pharmaceutically acceptable vehicle or diluent. The compositions of the present invention may contain other therapeutic agents as described below, and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

**[0075]** The compounds of the formula II may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The present compounds may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices

such as subcutaneous implants or osmotic pumps. The present compounds may also be administered liposomally.

**[0076]** Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The present compounds may also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations may also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g., Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

**[0077]** Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

**[0078]** Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

**[0079]** Exemplary compositions for rectal administration include suppositories which may contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

**[0080]** Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

**[0081]** The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for an adult human of from about 0.1 to 100 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats and the like, subject to protein tyrosine kinase-associated disorders.

**[0082]** The compounds of the present invention may be employed alone or in combination with each other and/or other suitable therapeutic agents useful in the treatment of protein tyrosine kinase-associated disorders such as PTK inhibitors other than those of the present invention, antiinflammatories, antiproliferatives, chemotherapeutic agents, immunosuppressants, anticancer agents and cytotoxic agents.

**[0083]** Exemplary such other therapeutic agents include the following: cyclosporins (e.g., cyclosporin A), CTLA4-Ig, antibodies such as anti-ICAM-3, anti-IL-2 receptor (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80, anti-CD86, monoclonal antibody OKT3, agents blocking the interaction between CD40 and gp39, such as antibodies specific for CD40 and/or gp39 (i.e., CD154), fusion proteins constructed from CD40 and gp39 (CD40Ig and CD8gp39), inhibitors, such as nuclear translocation inhibitors, of NF-kappa B function, such as deoxyspergualin (DSG), non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, steroids such as prednisone or dexamethasone, gold compounds, antiproliferative agents such as methotrexate, FK506 (tacrolimus, Prograf), mycophenolate mofetil, cytotoxic drugs such as azathioprine and cyclophosphamide, TNF- $\alpha$  inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor such as etanercept (Enbrel), rapamycin (sirolimus or Rapamune), leflunimide (Arava), and cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (Celebrex) and rofecoxib (Vioxx), or derivatives thereof, and the PTK inhibitors disclosed in the following U.S. Patent Applications: Serial No. 60/056,770, filed 8/25/97 (Attorney Docket No. QA202\*), Serial No. 60/069,159, filed 12/9/97 (Attorney Docket No. QA202a\*), Serial No. 09/097,338, filed 6/15/98 (Attorney Docket No. QA202b), Serial No. 60/056,797, filed 8/25/97 (Attorney Docket No. QA205\*), Serial No. 09/094,797, filed 6/15/98 (Attorney Docket No. QA205a), Serial No. 60/065,042, filed 11/10/97 (Attorney Docket No. QA207\*), Serial No. 09/173,413, filed 10/15/98, (Attorney Docket No. QA207a), Serial No. 60,076,789, filed 3/4/98 (Attorney Docket No. QA208\*), and Serial No. 09,262,525, filed 3/4/99 (Attorney Docket No. QA208a). See the following documents and references cited therein: Hollenbaugh, D., Douthwright, J., McDonald, V., and Aruffo, A., "Cleavable CD40Ig fusion proteins and the binding to gp39", J. Immunol. Methods (Netherlands), 188(1), p. 1-7 (Dec 15 1995); Hollenbaugh, D., Grosmaire, L.S., Kullas, C.D., Chalupny, N.J., Braesch-Andersen, S., Noelle, R.J., Stamenkovic, I., Ledbetter, J.A., and



Aruffo, A., "The human T cell antigen gp39, a member of the TNF gene family, is a ligand for the CD40 receptor: expression of a soluble form of gp39 with B cell co-stimulatory activity", EMBO J (England), 11(12), p 4313-4321 (Dec 1992); and Moreland, L.W. et al., "Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein, New England J. of Medicine, 337(3), p. 141-147 (1997).

**[0084]** Exemplary classes of anti-cancer agents and cytotoxic agents include alkylating agents, such as nitrogen mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and triazenes; antimetabolites, such as folate antagonists, purine analogues, and pyrimidine analogues; antibiotics, such as anthracyclines, bleomycins, mitomycin, dactinomycin, and plicamycin; enzymes, such as L-asparaginase; farnesyl-protein transferase inhibitors; hormonal agents, such as glucocorticoids, estrogens/antiestrogens, androgens/antiandrogens, progestins, and luteinizing hormone-releasing hormone antagonists, octreotide acetate; microtubule-disruptor agents, such as ecteinascidins or their analogs and derivatives; microtubule-stabilizing agents such as paclitaxel (Taxol®), docetaxel (Taxotere®), and epothilones A-F or their analogs or derivatives; plant-derived products, such as vinca alkaloids, epipodophyllotoxins, taxanes; and topoisomerase inhibitors; prenyl-protein transferase inhibitors; and miscellaneous agents such as, hydroxyurea, procarbazine, mitotane, hexamethylmelamine, platinum coordination complexes such as cisplatin and carboplatin; and other agents used as anti-cancer and cytotoxic agents such as biological response modifiers, growth factors; immune modulators, and monoclonal antibodies. The compounds of the invention may also be used in conjunction with radiation therapy.

**[0085]** Representative examples of these classes of anti-cancer and cytotoxic agents include mechlorethamine hydrochloride, cyclophosphamide, chlorambucil, melphalan, ifosfamide, busulfan, carmustine, lomustine, semustine, streptozocin, thiopeta, dacarbazine, methotrexate, thioguanine, mercaptopurine, fludarabine, pentastatin, cladribin, cytarabine, fluorouracil, doxorubicin hydrochloride, daunorubicin, idarubicin, bleomycin sulfate, mitomycin C, actinomycin D, safracins, saframycins, quinocarcins, discodermolides, vincristine, vinblastine, vinorelbine tartrate, etoposide, teniposide, paclitaxel, tamoxifen, estramustine, estramustine phosphate sodium, flutamide, buserelin, leuprolide, pteridines, diynes, levamisole, aflacon, interferon, interleukins, aldesleukin, filgrastim, sargramostim, rituximab, BCG, tretinoin, irinotecan hydrochloride, betamethosone, gemcitabine hydrochloride, altretamine, and topotecan and any analogs or derivatives thereof.

**[0086]** Preferred members of these classes include paclitaxel, cisplatin, carboplatin, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, mitomycin C, ecteinascidin 743, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podophyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosine, vindesine, and leurosine.

**[0087]** Examples of anti-cancer and other cytotoxic agents include the following: epothilone derivatives as found in U.S. Serial No. 09/506,481 filed February 17, 2000 (Attorney Docket No. LD186); German Patent No. 4138042.8; WO 97/19086, WO 98/22461, WO 98/25929, WO 98/38192, WO 99/01124, WO 99/02224, WO 99/02514, WO 99/03848, WO 99/07692, WO 99/27890, WO 99/28324, WO 99/43653, WO 99/54330, WO 99/54318, WO 99/54319, WO 99/65913, WO 99/67252, WO 99/67253, and WO 00/00485; cyclin dependent kinase inhibitors as found in WO 99/24416; and prenyl-protein transferase inhibitors as found in WO 97/30992 and WO 98/54966.

**[0088]** The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

**[0089]** The following assays can be employed in ascertaining the degree of activity of a compound ("test compound") as a PTK inhibitor.

Compounds described in the following Examples have been tested in one or more of these assays, and have shown activity.

#### *Enzyme Assay Using Lck, Fyn, Lyn, Hck, Fgr, Src, Blk or Yes*

**[0090]** The following assay has been carried out using the protein tyrosine kinases *Lck*, *Fyn*, *Lyn*, *Hck*, *Fgr*, *Src*, *Blk* and *Yes*.

**[0091]** The protein tyrosine kinase of interest is incubated in kinase buffer (20 mM MOPS, pH7, 10 mM MgCl<sub>2</sub>) in the presence of the test compound. The reaction is initiated by the addition of substrates to the final concentration of 1 μM ATP, 3.3 μCi/ml [33P] gamma-ATP, and 0.1 mg/ml acid denatured enolase (prepared as described in Cooper, J.A., Esch, F.S., Taylor, S.S., and Hunter, T., "Phosphorylation sites in enolase and lactate dehydrogenase utilized by tyrosine protein kinases in vivo and in vitro", J. Biol. Chem., 259, 7835-7841 (1984)). The reaction is stopped after 10 minutes by the addition of 10% trichloroacetic acid, 100 mM sodium pyrophosphate followed by 2 mg/ml bovine serum albumin. The labeled enolase protein substrate is precipitated at 4 degrees, harvested onto Packard Unifilter plates and counted in a Topcount scintillation counter to ascertain the protein tyrosine kinase inhibitory activity of the test compound (activity inversely proportional to the amount of labeled enolase protein obtained). The exact concentration of reagents and the amount of label can be varied as needed.

**[0092]** This assay is advantageous as it employs an exogenous substrate (enolase) for more accurate enzyme kinetics,

and can be conducted in a 96-well format that is readily automated. In addition, His-tagged protein tyrosine kinases (described below) offer much higher production yields and purity relative to GST-protein tyrosine kinase fusion protein.

**[0093]** The protein tyrosine kinase may be obtained from commercial sources or by recombinant methods described herewith. For the preparation of recombinant Lck, human Lck was prepared as a His-tagged fusion protein using the Life Technologies (Gibco) baculovirus vector pFastBac Hta (commercially available) in insect cells. A cDNA encoding human Lck isolated by PCR (polymerase chain reaction) was inserted into the vector and the protein was expressed using the methods described by the manufacturer. The Lck was purified by affinity chromatography. For the production of Lck in insect cells using baculovirus, see Spana, C., O'Rourke, E.C., Bolen, J.B., and Fargnoli, J., "Analysis of the tyrosine kinase p56lck expressed as a glutathione S-transferase protein in *Spodoptera frugiperda* cells," Protein expression and purification, Vol. 4, p. 390-397 (1993). Similar methods may be used for the recombinant production of other Src-family kinases.

#### *Enzyme Assay Using HER1 or HER2*

**[0094]** Compounds of interest were assayed in a kinase buffer that contained 20 mM Tris.HCl, pH 7.5, 10 mM MnCl<sub>2</sub>, 0.5 mM dithiothreitol, bovine serum albumin at 0.1 mg/ml, poly(glu/tyr, 4:1) at 0.1 mg/ml, 1 μM ATP, and 4 μCi/ml [gamma-<sup>33</sup>P]ATP. Poly(glu/tyr, 4:1) is a synthetic polymer that serves as a phosphoryl acceptor and is purchased from Sigma Chemicals. The kinase reaction is initiated by the addition of enzyme and the reaction mixtures were incubated at 26°C for 1 h. The reaction is terminated by the addition of EDTA to 50 mM and proteins are precipitated by the addition of trichloroacetic acid to 5%. The precipitated proteins are recovered by filtration onto Packard Unifilter plates and the amount of radioactivity incorporated is measured in a Topcount scintillation counter.

**[0095]** For the preparation of recombinant HER1, the cytoplasmic sequence of the receptor were expressed in insect cells as a GST fusion protein, which was purified by affinity chromatography as described above for Lck. The cytoplasmic sequence of HER2 was subcloned into the baculovirus expression vector pBlueBac4 (Invitrogen) and was expressed as an untagged protein in insect cells. The recombinant protein was partially purified by ion-exchange chromatography.

#### *Cell assays*

##### (1) Cellular tyrosine phosphorylation

**[0096]** Jurkat T cells are incubated with the test compound and then stimulated by the addition of antibody to CD3 (monoclonal antibody G19-4). Cells are lysed after 4 minutes or at another desired time by the addition of a lysis buffer containing NP-40 detergent. Phosphorylation of proteins is detected by anti-phosphotyrosine immunoblotting. Detection of phosphorylation of specific proteins of interest such as ZAP-70 is detected by immunoprecipitation with anti-ZAP-70 antibody followed by anti-phosphotyrosine immunoblotting. Such procedures are described in Schieven, G.L., Mittler, R.S., Nadler, S.G., Kirihaara, J.M., Bolen, J.B., Kanner, S.B., and Ledbetter, J.A., "ZAP-70 tyrosine kinase, CD45 and T cell receptor involvement in UV and H<sub>2</sub>O<sub>2</sub> induced T cell signal transduction", J. Biol. Chem., 269, 20718-20726 (1994), and the references incorporated therein. The Lck inhibitors inhibit the tyrosine phosphorylation of cellular proteins induced by anti-CD3 antibodies.

**[0097]** For the preparation of G19-4, see Hansen, J.A., Martin, P.J., Beatty, P.G., Clark, E.A., and Ledbetter, J.A., "Human T lymphocyte cell surface molecules defined by the workshop monoclonal antibodies," in Leukocyte Typing I, A. Bernard, J. Boumsell, J. Dausett, C. Milstein, and S. Schlossman, eds. (New York: Springer Verlag), p. 195-212 (1984); and Ledbetter, J.A., June, C.H., Rabinovitch, P.S., Grossman, A., Tsu, T.T., and Imboden, J.B., "Signal transduction through CD4 receptors: stimulatory vs. inhibitory activity is regulated by CD4 proximity to the CD3/T cell receptor", Eur. J. Immunol., 18, 525 (1988).

##### (2) Calcium assay

**[0098]** Lck inhibitors block calcium mobilization in T cells stimulated with anti-CD3 antibodies. Cells are loaded with the calcium indicator dye indo-1, treated with anti-CD3 antibody such as the monoclonal antibody G19-4, and calcium mobilization is measured using flow cytometry by recording changes in the blue/violet indo-1 ratio as described in Schieven, G.L., Mittler, R.S., Nadler, S.G., Kirihaara, J.M., Bolen, J.B., Kanner, S.B., and Ledbetter, J.A., "ZAP-70 tyrosine kinase, CD45 and T cell receptor involvement in UV and H<sub>2</sub>O<sub>2</sub> induced T cell signal transduction", J. Biol. Chem., 269, 20718-20726 (1994), and the references incorporated therein.

##### (3) Proliferation assays

**[0099]** Lck inhibitors inhibit the proliferation of normal human peripheral blood T cells stimulated to grow with anti-CD3

plus anti-CD28 antibodies. A 96 well plate is coated with a monoclonal antibody to CD3 (such as G19-4), the antibody is allowed to bind, and then the plate is washed. The antibody bound to the plate serves to stimulate the cells. Normal human peripheral blood T cells are added to the wells along with test compound plus anti-CD28 antibody to provide co-stimulation. After a desired period of time (e.g., 3 days), the [3H]-thymidine is added to the cells, and after further incubation to allow incorporation of the label into newly synthesized DNA, the cells are harvested and counted in a scintillation counter to measure cell proliferation.

**[0100]** The following Examples 319 to 321, 376, 378, 379, 381 to 385, 390 to 392, 400, 404, 405, 413 to 416, 418, 419, 422, 429 to 432, 436, 437, 439, 440, 443 to 462, 464, 466 to 469, 471, 473, 474, 477, 479, 481, 482, 493, 503, 512, 520, 523, 525, 532 to 535, 537, 538, 542, 544, 548 to 550, 554, 555, and 566 to 574 illustrate embodiments of the present invention. All other examples are not according to the invention.

Abbreviations employed in the Examples are defined below. Compounds of the Examples are identified by the example and step in which they are prepared (for example, "1A" denotes the title compound of step A of Example 1), or by the example only where the compound is the title compound of the example (for example, "2" denotes the title compound of Example 2).

#### Abbreviations

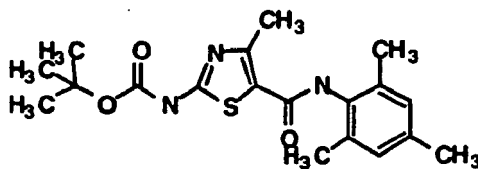
#### [0101]

aq. =	aqueous
conc. =	concentrated
DMSO =	dimethylsulfoxide
EtOAc =	ethyl acetate
Et <sub>2</sub> O =	diethyl ether
h =	hours
HATU =	N-[dimethylamino-1H-1,2,3-triazolo-[4,5-b]pyridin-1-yl methylene]-N-methyl methanaminium hexafluorophosphate N-oxide
MeOH =	methanol
MOPS =	4-morpholine-propanesulfonic acid
MS =	mass spectrometry
Ret Time =	retention time
RT =	room temperature
satd. =	saturated
TFA =	trifluoroacetic acid
THF =	tetrahydrofuran
DMF =	N,N-dimethylformamide

#### Example 1

Preparation of [5-[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-methyl-2-thiazoyl]carbamic acid, 1,1-dimethylethyl ester

#### [0102]



#### A. Ethyl-2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylate

**[0103]** A suspension of ethyl-2-amino-4-methyl-thiazole-5-carboxylate (18.6 g, 100 mmol), di-t-butyldicarbonate (26.2 g, 120 mmol) and 4-dimethylaminopyridine (800 mg, 6.55 mmol) in dry tetrahydrofuran (300 mL) was stirred under nitrogen for 18 h. The solvent was evaporated *in vacuo*. The residue was suspended in dichloromethane (1 L) and filtered through a pad of celite. The filtrate was washed with 1 N aqueous HCl solution (300 mL, 2x), water and brine, dried (MgSO<sub>4</sub>), and concentrated *in vacuo*. The residue was triturated with hexanes. The solid was filtered and dried *in vacuo* to obtain the title compound (20 g, 72%) as a tan solid.

B. 2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid

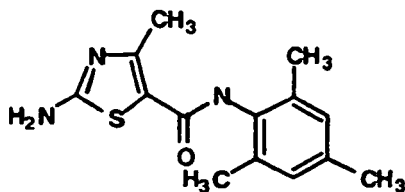
**[0104]** A stirred solution of ethyl-2-tert-butoxycarbonyloxyamino-4-methylthiazole-5-carboxylate (10 g, 34.95 mmol) in tetrahydrofuran-ethanol (250 mL, 2:3) was treated with a 6N KOH solution (250 mL). The mixture was heated to 55°C overnight. The solution was cooled to 0°C and acidified with concd. HCl to pH 1. The solvent was evaporated *in vacuo*. The residue was washed with water, diethyl ether, dried *in vacuo* over anhydrous phosphorous pentoxide to obtain the title acid (6 g, 89%) as a white solid.

C. 2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid chloride

**[0105]** A 2 M solution of oxalyl chloride in dichloromethane (22.5 mL, 45 mmol) was added dropwise to a stirred suspension of 2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid (10 g, 38.72 mmol) in dichloromethane (150 mL) and N,N-dimethyl formamide (150 µL) at 0°C. The suspension gradually became homogenous after addition was complete. The solution was allowed to warm to room temperature and stirred at rt for 1.5 h. The solvent was evaporated *in vacuo* and the residue was coevaporated with toluene (300 mL, 2x) and then dried *in vacuo* to obtain the title acid chloride (10.7 g, 99%) as a tan solid.

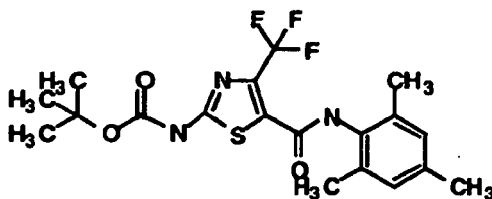
D. 15-[[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

**[0106]** 2,4,6-Trimethyl aniline (6.3 mL, 38.66 mmol) was added dropwise to a stirred solution of 2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid chloride (10.7 g, 38.66 mmol) in dichloromethane (150 mL) at 0°C. After 20 min, diisopropylethylamine (8.8 mL, 44.88 mmol) was added dropwise. The solution was allowed to warm to rt and stirred for an additional 2 h. The solvent was evaporated *in vacuo*. The residue was suspended in EtOAc (700 mL), washed with 1 N aq. HCl solution (300 mL, 2x), water, and brine; dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was triturated with ether to obtain the title compound (12.5 g, 86%) as a tan solid.

Example 2Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-methyl-5-thiazolecarboxamide**[0107]**

**[0108]** A solution of [5-[[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester (10 g, 26.63 mmol) in trifluoroacetic acid (100 mL) was stirred at rt for 3 h. The solution was concentrated under reduced pressure and the residue was diluted with EtOAc (700 mL), washed with 5% aq. KHCO<sub>3</sub> solution (400 mL, 2x), water, and brine; dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was washed with ether (200 mL) and acetonitrile (100 mL) to obtain the title compound (6.7 g, 91%) as a white solid.

Example 3Preparation of [5-[[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-trifluoromethyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester**[0109]**



#### A. Ethyl-2-*tert*-butoxycarbonyloxyamino-4-trifluoromethyl-thiazole-5-carboxylate

**[0110]** A suspension of ethyl-2-amino-4-trifluoromethyl-thiazole-5-carboxylate (5.05 g, 21.02 mmol), di-*t*-butyldicarbonate (4.82 g, 22.07 mmol) and 4-dimethylaminopyridine (260 mg, 2.1 mmol) in dichloromethane (209 mL) was stirred under nitrogen for 1.5 h. The solvent was evaporated *in vacuo*. The residue was chromatographed on a silica gel column. Elution with 5% EtOAc in hexanes, followed by 15% EtOAc in hexanes afforded the title compound (6.57 g, 92%) as a white solid.

#### B. 2-*Tert*-butoxycarbonyloxyamino-4-trifluoromethyl-thiazole-5-carboxylic acid

**[0111]** A stirred solution of ethyl-2-*tert*-butoxycarbonyloxyamino-4-trifluoromethyl-thiazole-5-carboxylate (6.5 g, 19.1 mmol) in methanol (100 mL) was treated with a 1N aq. NaOH solution (573 mL). The mixture was stirred at rt overnight. The solution was cooled to 0°C and acidified with a 6 M aq. HCl solution to pH 1 and extracted with chloroform (150 mL, 6x). The chloroform extracts were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure and *in vacuo* to obtain the title acid (5.75 g, 96%) as a white solid.

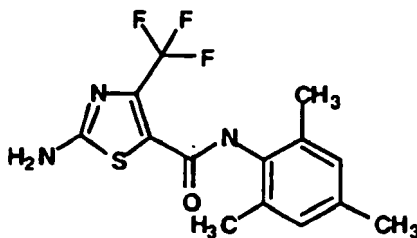
#### C. [5-[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-trifluoromethyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

**[0112]** 4-Methylmorpholine (40 µL, 0.39 mmol) was added to a mixture of 2-*tert*-butoxycarbonyloxyamino-4-trifluoromethyl-thiazole-5-carboxylic acid (100 mg, 0.32 mmol), 2,4,6-trimethylaniline (45 µL, 0.32 mmol), and benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP reagent, 380 mg, 0.4 mmol) in DMF (2 mL). The solution was stirred at rt for 72 h, diluted with dichloromethane and washed with 0.25 M aq. KHSO<sub>4</sub> solution followed by satd. aq. KHCO<sub>3</sub> solution. The dichloromethane extract was separated, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 5% EtOAc in hexanes followed by 10% EtOAc in hexanes to obtain the title compound (90 mg, 65%) as a white solid.

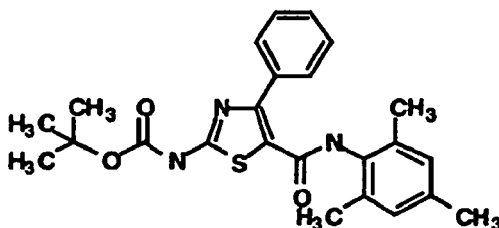
#### Example 4

##### Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-trifluoromethyl-5-thiazolecarboxamide, trifluoroacetate (1:1)

**[0113]**



**[0114]** A solution of [5-[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-trifluoromethyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester (120 mg, 0.28 mmol) in trifluoroacetic acid (5 mL) was stirred at 0°C for 1 h. The solution was concentrated under reduced pressure and the residue was coevaporated with ether to obtain a yellow solid which was triturated with hexanes to obtain the title compound (96 mg, 76%) as a light yellow solid.

Example 5Preparation of [5-[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-phenyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester**[0115]**A. Ethyl-2-tert-butoxycarbonyloxyamino-4-phenyl-thiazole-5-carboxylate

**[0116]** Compound **5A** was prepared by an analogous method as that of **3A**, except using ethyl-2-amino-4-phenyl-thiazole-5-carboxylate to give the title compound **5A** as a white solid (90.5%).

B. 2-Tert-butoxycarbonyloxyamino-4-phenyl-thiazole-5-carboxylic acid

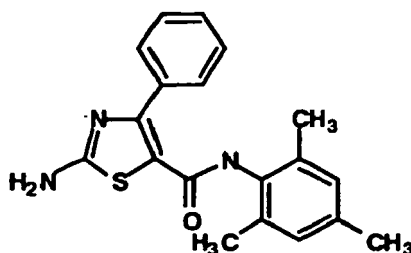
**[0117]** Compound **5B** was prepared by an analogous method as that of **3B**, except using **5A** to give the title compound **5B** as a white solid (99%).

C. 2-Tert-butoxycarbonyloxyamino-4-phenyl-thiazole-5-carboxylic acid chloride

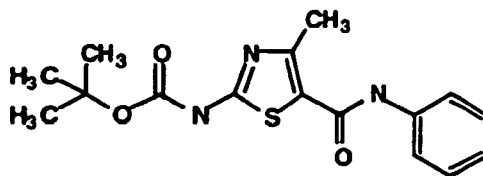
**[0118]** Compound **5C** was prepared by an analogous method as that of **1C**, except using **5B** to give the title compound **5C** as a white solid (90%).

D. [5-[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-phenyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

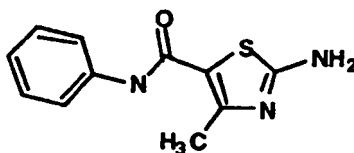
**[0119]** Compound **5D** was prepared by an analogous method as that of **1D**, except using **5C** to give the title compound **5D** as a light yellow solid (93%).

Example 6Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-phenyl-5-thiazolecarboxamide, trifluoroacetate (1:1)**[0120]**

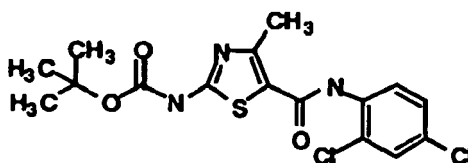
**[0121]** Compound **6** was prepared by an analogous method as that of **4**, except using **5D** to give the title compound **6** as a white solid (68%).

Example 7Preparation of [5-[Phenylaminolcarbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester**[0122]**

**[0123]** Compound was prepared by an analogous method as that of **1D**, except using aniline in place of 2,4,6-trimethylaniline and triethylamine in place of diisopropylethylamine to give the title compound **7** as an off-white solid (76%).

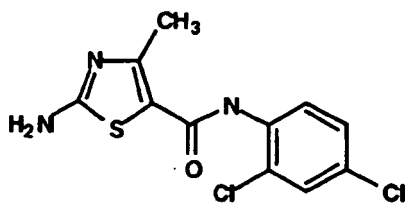
Example 8Preparation of 2-Amino-N-(phenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)**[0124]**

**[0125]** Compound **8** was prepared by an analogous method as that of **4**, except using **7** to give the title compound **8** as a white solid (68%).

Example 9Preparation of [5-[(2,4-Dichlorophenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester**[0126]**

**[0127]** Compound **9** was prepared by an analogous method as that of **1D**, except using 2,4-dichloroaniline to give the title compound **9** as a white solid (28%).

Example 10Preparation of 2-Amino-N-(2,4-dichlorophenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)**[0128]**

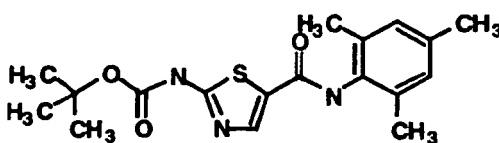


**[0129]** Compound **10** was prepared by an analogous method as that of **4**, except using **9** to give the title compound **8** as a white solid (100%).

#### Example 11

Preparation of 5-[(2,4,6-Trimethylphenyl)amino]carbonyl-2-thiazolyl carbamic acid, 1,1-dimethylethyl ester

**[0130]**



A. Ethyl-2-*tert*-butoxycarbonyloxyamino-thiazole-5-carboxylate

**[0131]** Compound **11A** was prepared by an analogous method as that of **3A**, except using ethyl-2-amino-thiazole-5-carboxylate to give the title compound **11A** as a white solid (79.5%).

B. 2-*Tert*-butoxycarbonyloxyamino -thiazole-5-carboxylic acid

**[0132]** Compound **11B** was prepared by an analogous method as that of **3B**, except using **11A** to give the title compound **11B** as a white solid (95.5%).

C. 2-*Tert*-butoxycarbonyloxyamino-thiazole-5-carboxylic acid chloride

**[0133]** Compound **11C** was prepared by an analogous method as that of **1C**, except using **11B** to give the title compound **11C**.

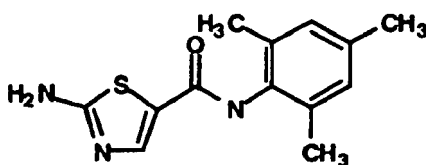
D. 5-[(2,4,6-Trimethylphenyl)amino]carbonyl-2-thiazolyl carbamic acid, 1,1-dimethylethyl ester

**[0134]** Compound **11D** was prepared by an analogous method as that of **1D**, except using **11C** to give the title compound **11D** as an off-white solid (70%).

#### Example 12

Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-phenyl-5-thiazolecarboxamide, trifluoroacetate (1:1)

**[0135]**



**[0136]** Compound **12** was prepared by an analogous method as that of **4**, except using **11D** to give the title compound **12** as a light yellow solid (88%).



## Examples 13 to 53

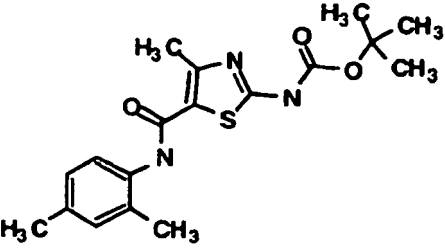
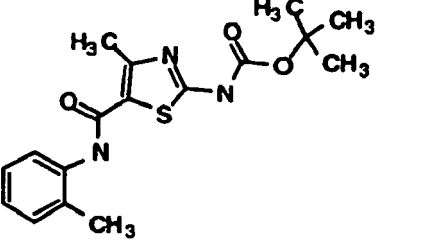
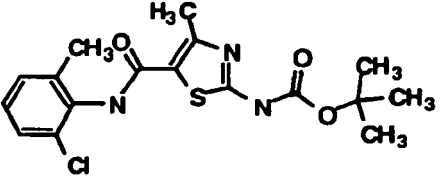
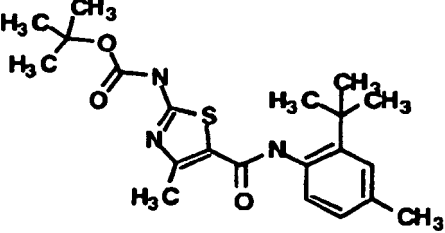
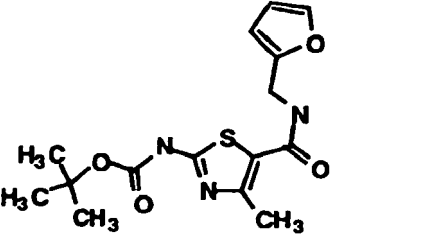
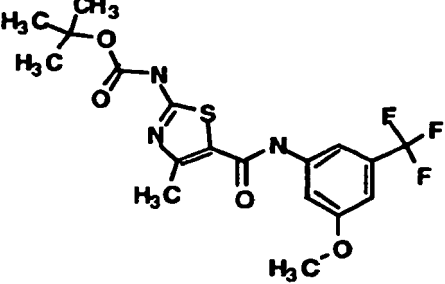
## General Procedure

**[0137]** Compounds **13** to **53** were prepared following the procedure described below. Appropriate amines (0.40 mmol) and diisopropylethylamine (70  $\mu$ L, 0.40 mmol) were added to a suspension of **1C** (100 mg, 0.36 mmol) in dichloromethane (3 mL). The solution was stirred mechanically in a sealed tube at rt for 16 h. The reaction mixtures were diluted with methanol (200  $\mu$ L) and loaded in Varian SCX ion exchange columns (2 g/6 cc) pretreated with methanol-dichloromethane (8 mL, 1:1) followed by dichloromethane (8 mL). SCX Column filtration were performed using a Gilson robot unit. The column was washed sequentially with dichloromethane (9 mL), dichloromethane-methanol (9 mL, 4:1), dichloromethane-methanol (9 mL, 1:1), methanol (9 mL), 0.01 M ammonium hydroxide in methanol (9 mL) and 0.05 M ammonium hydroxide in methanol (9 mL). The elutes were collected separately by the robot and then concentrated using a speed vac. Fractions containing the products were combined.

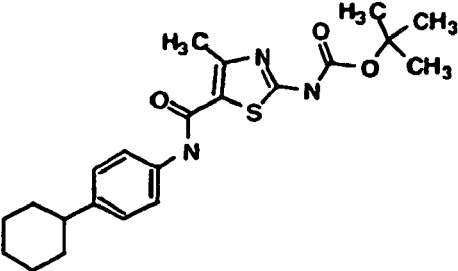
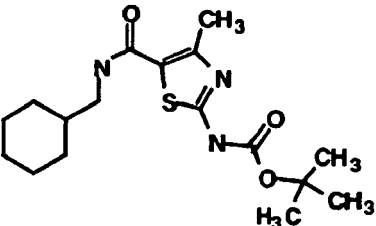
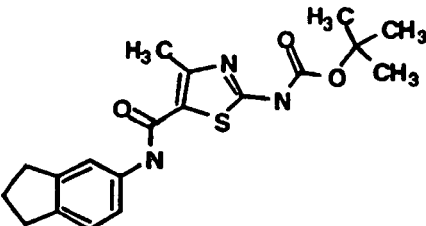
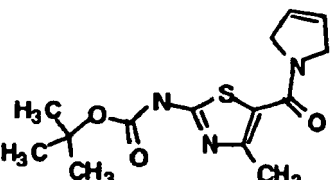
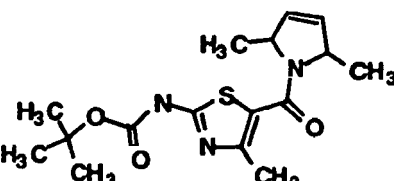
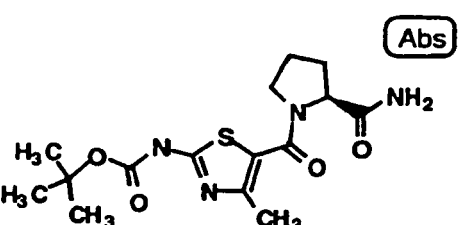
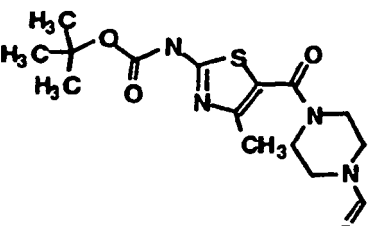
**[0138]** "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballistic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>), flow rate 4 mL/min,  $\lambda$  = 220 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
<b>13</b>		[5-[[[2-Methoxy-6-methylphenyl]amino]-carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.79
<b>14</b>		[4-Methyl-5-[[[3-methyl-4-(1-methyl-ethyl)phenyl]amino]-carbonyl]-2-thiazolyl]-carbamic acid 1,1-dimethylethyl ester	4.51
<b>15</b>		[5-[[[4-Bromo-2,6-dimethylphenyl]amino]-carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethyl-ethyl ester	4.24
<b>16</b>		[4-Methyl-5-[[[2-methyl-6-(1-methylethyl)phenyl]-amino]carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.17

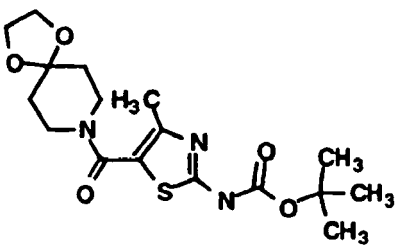
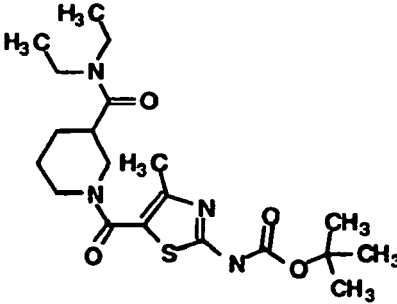
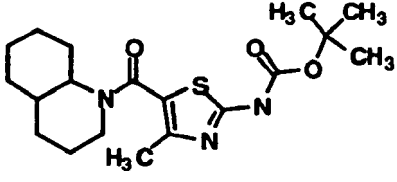
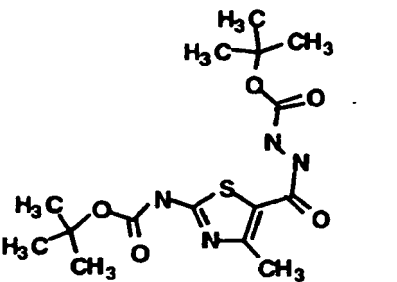
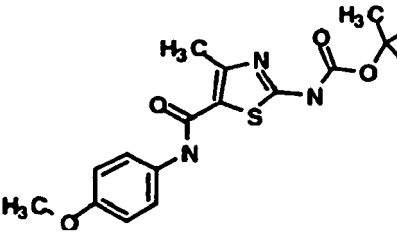
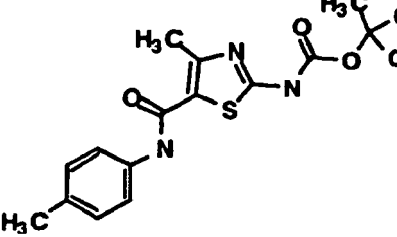
(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
17		[5-[[[2,4-Dimethylphenyl]amino]carbonyl]-4-methyl-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester	4.05
18		[4-Methyl-5-[[[2-methylphenyl]amino]carbonyl]-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester	3.87
19		[5-[[[2-Chloro-6-methylphenyl]amino]carbonyl]-4-methyl-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester	3.86
20		[5-[[[2-(1,1-Dimethylethyl)-4-methylphenyl]amino]carbonyl]-4-methyl-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester	4.30
21		[5-[[[2-Furanylmethyl]amino]carbonyl]-4-methyl-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester	3.54
22		[5-[[[3-Methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]-4-methyl-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester	4.43

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
23		[5-[[[4-(Cyclohexylphenyl) amino ]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.78
24		[5-[(Cyclohexyl methyl)amino] carbonyl] -4-methyl-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester	4.21
25		[5-[[[2,3-Dihydro-1H-indenyl) amino]carbonyl ]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.30
26		[5-[(2,5-Dihydro-1H-pyrrol-1-yl) carbonyl]-4-methyl-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester	3.56
27		[5-[(2,5-Dihydro-2,5-dimethyl-1H-pyrrol-1-yl)carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.86
28		1-[[2-[[[(1,1-Dimethylethoxy) carbonyl ]amino]-4-methyl-5-thiazolyl]carbonyl]-L-prolinamide	2.96
29		[5-[(4-Formyl-1-piperazinyl) carbonyl]-4-methyl-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester	2.90

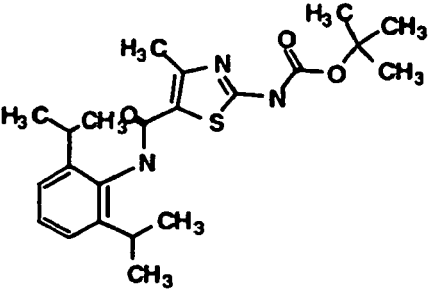
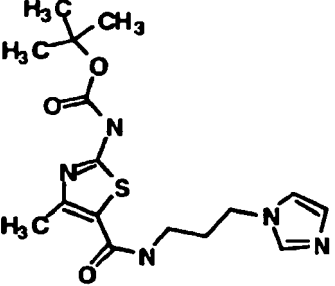
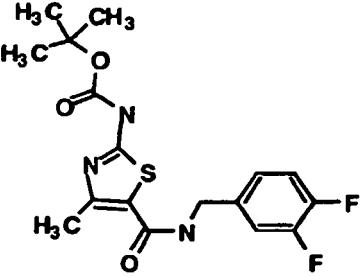
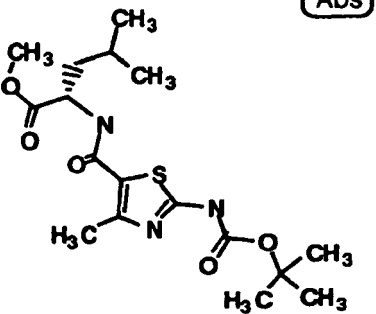
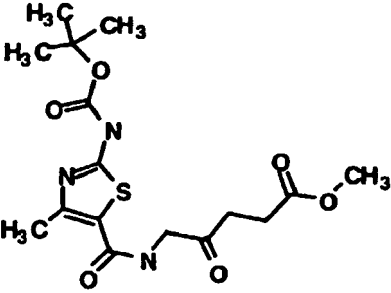
(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
30		[5-(1,4-Dioxo-8-azaspiro[4.5]decan-8-ylcarbonyl)-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.54
31		[5-[[3-[(Diethylamino) carbonyl]-1-piperidinyl] carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.66
32		[4-Methyl-5-[(octahydro-1-quinoliny)carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.37
33		2-[[[(1,1-Dimethylethoxy) carbonyl]amino]-4-methyl-5-thiazolecarboxylic acid 2-[[[(1,1-dimethylethoxy) carbonyl] hydrazide	3.50
34		[5-[[[4-Methoxyphenyl] amino] carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.83
35		[4-Methyl-5-[[[4-methylphenyl] amino] carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.07

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
36		[5-[[[(1,2-Dimethylpropyl) amino] carbonyl]-4-methyl-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester	3.87
37		[5-[[[(2,2-Dimethylpropyl) amino] carbonyl]-4-methyl-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester	3.97
38		[4-Methyl-5-[(2-propynylamino) carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.22
39		[4-Methyl-5-[(2-propenylamino) carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.41
40		[4-Methyl-5-[(methylphenylamino) carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.75
41		[4-Methyl-5-[[[(3,4,5-trimethoxyphenyl) amino] carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.84

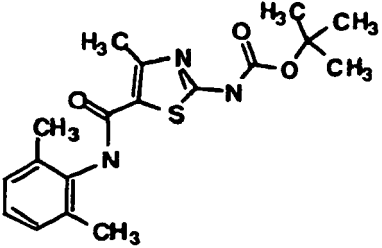
(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
42		[5-[[[2,6-Bis(1-methylethyl)phenyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.40
43		[5-[[[3-(1H-imidazol-1-yl)propyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	2.45
44		[5-[[[(3,4-Difluorophenyl)methyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.97
45		N-[2-[[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-5-thiazolyl]carbonyl]-L-leucine methyl ester	3.99
46		5-[[[2-[[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-5-thiazolyl]carbonyl]amino]-4-oxopentanoic acid methyl ester	3.27

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
47		[5-[[[2-(Ethylthio) ethyl]amino] carbonyl]-4-methyl-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester	3.75
48		[5-[[Bis(3-methylbutyl)amino] carbonyl]-4-methyl-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester	4.67
49		[5-[[Ethyl(1-methylethyl)amino] carbonyl]-4-methyl-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester	3.84
50		2-[[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-5-thiazolecarboxylic acid 2-[[[(3,5-dichlorophenyl)amino]thioxomethyl]hydrazide]	4.66
51		[5-[[Bis(2-ethoxyethyl)amino] carbonyl]-4-methyl-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester	3.83
52		[4-Methyl-5-[[3-[(trifluoroacetyl)amino]-1-pyrrolidinyl]carbonyl]-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester	3.47

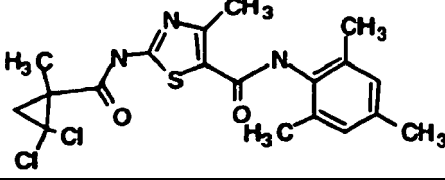
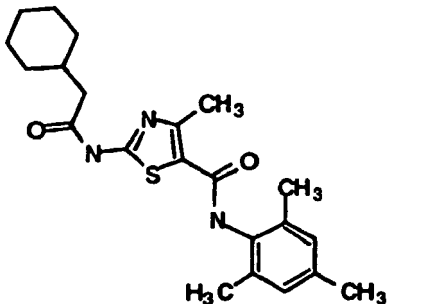
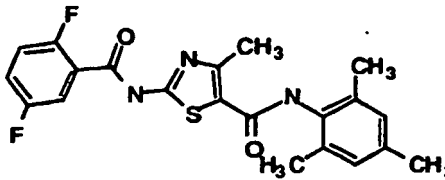
(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
53		[5-[[[(2,6-Dimethylphenyl)amino] carbonyl]-4-methyl-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester	3.87

## Examples 54 to 129

## General Procedure

**[0139]** Compounds **54** to **129** were prepared following the procedure described below. Diisopropylethyl amine (60  $\mu$ L, 0.34 mmol) was added to a mixture of amine **2** (30 mg, 0.11 mmol), appropriate carboxylic acid (0.13 mmol), 1-hydroxy-7-azabenzotriazole (19.5 mg, 0.14 mmol), and ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (26.8 mg, 0.14 mmol) in THF (0.4 mL). The mixture was heated in a sealed tube under argon at 45°C for 24 h. The reaction mixture was diluted with dichloromethane (4 mL) and washed with 2 N aq. HCl solution (2 mL, 3x). The dichloromethane solution was passed through a Varian SCX cation exchange column (2 g, 6 cc) on a Gilson robot. The column was eluted sequentially with acetonitrile-methanol (10 mL, 4:1), methanol-2M methanolic ammonia (3 mL, 4:1), and 2 M methanolic ammonia solution (3 mL, 4x). The fractions were collected separately using the Gilson robot. Fraction containing the product was concentrated and dried *in vacuo*. "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballistic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>), flow rate 4 mL/min,  $\lambda$  = 220 nM for compounds **54** - **127**. For compounds **128** - **129** HPLC conditions are: Zorbax S8-C18 4.5 mm x 7.5 cm short column, 8 min gradient starting from 100% solvent A (10% MeOH, 90% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>), flow rate 2.5 mL/min,  $\lambda$  = 217 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
54		2-[[[(2,2-Dichloro-1-methylcyclopropyl) carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.22
55		2-[(Cyclohexyl acetyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.47
56		2-[(2,5-Difluorobenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.15



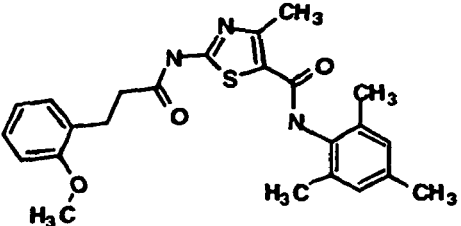
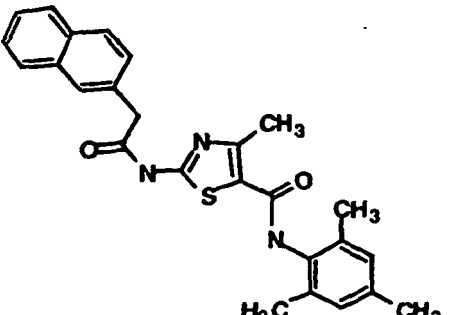
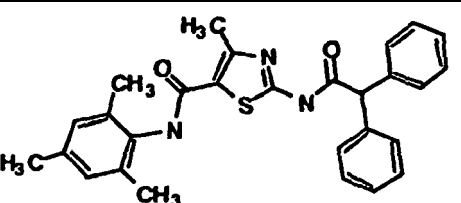
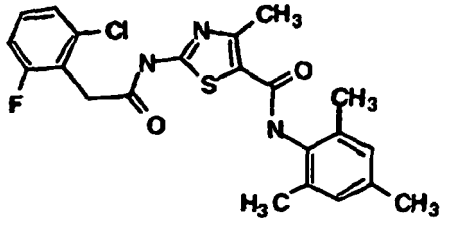
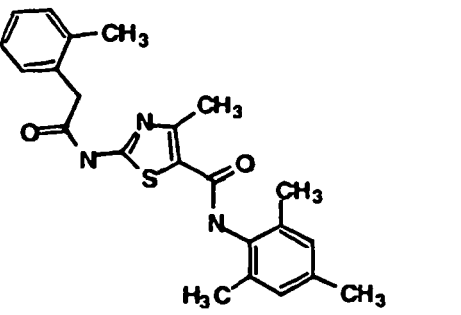
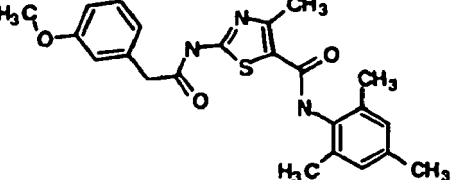
(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
57		2-[(5-Bromo-2-chlorobenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.37
58		2-[(3-Cyano-benzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.06
59		2-[[4-(Acetylamino)-benzoyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.60
60		4-Methyl-2-[[3-(trifluoromethyl)benzoyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.45
61		4-Methyl-2-[[2-(2-phenylethyl)benzoyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.64
62		2-[(3,5-Dimethyl-benzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.49

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
63		2-[(4-Ethenyl-benzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	
64		2-[(4-Butyl-benzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.58
65		4-Methyl-2-[(4-pentylbenzoyl)amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.76
66		4-Methyl-2-[(2-methyl-1-oxohexyl)amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.41
67		4-Methyl-2-[(1-oxo-3-phenoxypropyl)amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.21
68		4-Methyl-2-[(1-oxo-3-phenylpropyl)amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.26

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
69		2-[[3-(2-Methoxy-phenyl)-1-oxopropyl]-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.31
70		4-Methyl-2-[(2-naphthalenylacetyl)-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.43
71		2-[(Diphenyl-acetyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.13
72		2-[(2-Chloro-6-fluorophenyl)acetyl]-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.17
73		4-Methyl-2-[(2-methylphenyl)-acetyl] amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazolecarboxamide	3.95
74		2-[(3-methoxy-phenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.11

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
75		2-[[[(3,4-Dimethoxy-phenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.90
76		2-[[[(4-Chloro-phenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.34
77		2-[[[(1,1'-Biphenyl)-4-ylacetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.60
78		4-Methyl-2-[(1-oxo-4-phenylbutyl)amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.40
79		4-Methyl-2-[(1-oxooctyl)amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.65
80		2-[(2-Hydroxy-2-phenyl-1-oxopropyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.13

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
81		2-[(2-Hydroxy-1-oxohexyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.14
82		4-Methyl-2-[[1-oxo-4-(2-thienyl)-butyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.32
83		4-Methyl-2-[(3-thienylcarbonyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.04
84		2-[(2-Benzofuranyl-carbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.37
85		N-[4-Methyl-5-[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-4-pyridinecarboxamide, N-oxide	3.50
86		6-Chloro-N-[4-methyl-5-[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-3-pyridinecarboxamide	4.08
87		N-[4-Methyl-5-[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-3-pyridinecarboxamide	3.56
88		N-[4-Methyl-5-[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-3-quinolinecarboxamide	4.11

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
89		4-Methyl-2-[[[(4-nitrophenyl)acetyl]-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.08
90		4-Methyl-2-[(2,4,6-trichlorobenzoyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.45
91		4-Methyl-2-[[2-[[3-(trifluoromethyl)-phenyl]amino]benzoyl]-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.86
92		4-Methyl-2-[[4-(4-nitrophenyl)-1-oxobutyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.28
93		1-Methyl-2-[[4-(methylsulfonyl)-benzoyl]-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.79
94		2-[(4-Heptylbenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	

(continued)

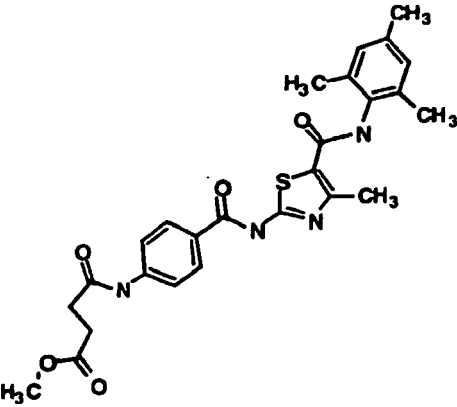
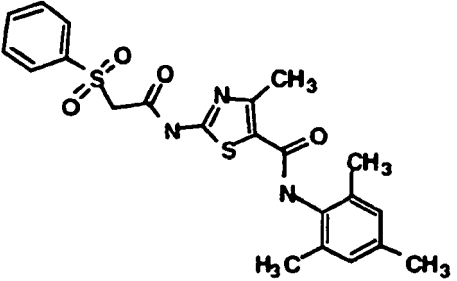
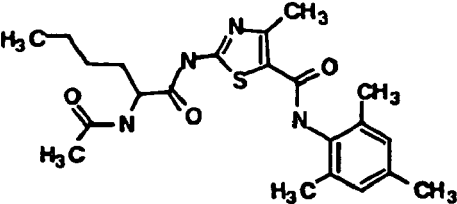
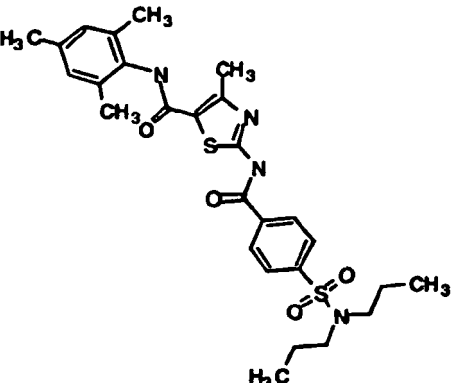
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
95		2-[(2,4-Difluoro-phenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.15
96		(S)-2-[[2-(Dipropylamino)-1-oxopropyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.20
97		2-[(2-Biphenyl-enecarbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.64
98		2-[[3-(3-Methoxyphenyl)-1-oxopropyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.26
99		4-Methyl-N-(2,4,6-trimethylphenyl)-2-[[[(2,4,6-trimethyl-phenyl)acetyl]amino]-5-thiazolecarboxamide	4.52

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
100		4-Methyl-2-[(1-oxo-6-heptenyl) amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.47
101		2-[[[(1,3-Benzodioxol-5-yl)acetyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.07
102		4-Methyl-2-[[[2-(phenylmethoxy) phenyl] acetyl] amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.46
103		4-Methyl-2-[[[3-phenoxyphenyl)acetyl]a mino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.56
104		2-[[[(3,5-Dimethoxy-phenyl)acetyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.13
105		2-[[4-[4-[Bis(2-chloroethyl)amino]phen yl]-1-oxobutyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.75



(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
106		4-[[[4-methyl-5-[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-amino]-carbonyl]phenyl]-amino]-4-oxobutanoic acid methyl ester	4.03
107		4-Methyl-2-[[[(phenyl-sulfonyl)acetyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	3.77
108		2-[[[2-(Acetylamino)-1-oxohexyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.99
109		2-[[[4-[(Dipropyl-amino)sulfonyl]benzoyl]amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.51

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
110		2-[(4-Cyclohexyl-benzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.94
111		2-[(4-Bromo-3-methylbenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.80
112		2-[(2,3-Difluorophenyl)acetyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.14
113		4-Methyl-2-[[[4-(1-methylethyl)phenyl]acetyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.56
114		2-[[[4-(1,1-Dimethyl-ethyl)cyclohexyl]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.85

(continued)

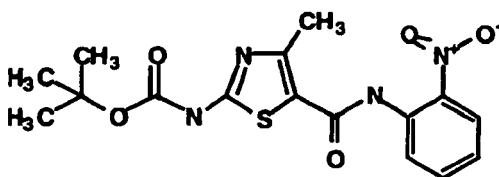
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
115		N,N-Dimethyl-N'-[4-methyl-5-[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]butanediamide	3.50
116		2-[(1,6-Dioxohexyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.40
117		2-[(Benzo[b]thiophen-2-ylcarbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.53
118		2-[(1-Adamantyl-carbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.66
119		4-Methyl-2-[[[(4-methylcyclohexyl)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.48
120		2-[(1,7-Dioxooctyl)-amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.88
121		2-[[2-(Acetylamino)-4-(ethylthio)-1-oxobutyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.93

(continued)

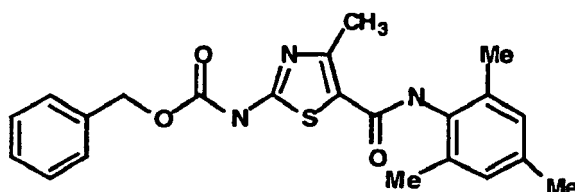
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
122		1,5-Dimethyl-N-[4-methyl-5-[[[(2,4,6-trimethylphenyl)amino] carbonyl]-2-thiazolyl]-1H-pyrazole-3-carboxamide	3.91
123		2-[[[4-methyl-5-[[[(2,4,6-trimethylphenyl)amino] carbonyl]-2-thiazolyl]amino] carbonyl]benzoic acid	3.70
124		N-[4-Methyl-5-[[[(2,4,6-trimethylphenyl)amino] carbonyl]-2-thiazolyl]-6-benzothiazolecarboxamide	4.18
125		1-Ethyl-4-methyl-N-[4-methyl-5-[[[(2,4,6-trimethylphenyl)amino] carbonyl]-2-thiazolyl]-1H-pyrazole-3-carboxamide	4.09
126		4-Methyl-2-[[[3-[(3H-1,2,3-triazolo[4,5-b]pyridin-3-yl)oxy)methyl]benzoyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.15
127		2-[(2-Furanyl-carbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.45
128		2-[(4-Chloro-benzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.85

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
129		2-[(2,2-Dimethyl-1-oxopropyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.30

Example 130Preparation of [4-Methyl-5-[(2-nitrophenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester**[0140]**

**[0141]** 2-Nitroaniline (55 mg, 0.4 mmol) and diisopropylethylamine (70  $\mu$ L, 0.4 mmol) were added dropwise to a stirred solution of 2-*tert*-butoxycarbonyloxylamino-4-methyl-thiazole-5-carboxylic acid chloride 1C (100 mg, 0.36 mmol) in dichloromethane (3 mL). After 16 h at rt, 4-N,N-dimethylaminopyridine (22 mg, 0.18 mmol) was added and the mixture was stirred for additional 3.5 h. The solvent was evaporated in vacuo. The residue was chromatographed on a silica gel column. Elution with 5% EtOAc in hexanes followed by 20% EtOAc in hexanes afforded the title compound (15 mg, 11%) as a yellow solid.

Example 131Preparation of [4-Methyl-5-[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, phenylmethyl ester**[0142]**A. Ethyl-2-benzyloxycarbonyloxylamino-4-methyl-thiazole-5-carboxylate

**[0143]** A 3 M aq.  $\text{NaHCO}_3$  solution (10 mL, 30 mmol) was added to a stirred solution of ethyl-2-amino-4-methyl-thiazole-5-carboxylate (372 mg, 2 mmol) in THF (20 mL) at 0-5°C. Benzyl chloroformate (500  $\mu$ L) was added. After 2 h, additional benzyl chloroformate (500  $\mu$ L) and the biphasic solution was stirred for an additional 2 h at 0-5°C. The mixture was diluted with dichloromethane (50 mL) and water (30 mL). The organic layer was separated, dried ( $\text{MgSO}_4$ ), filtered and concentrated. The residue was chromatographed on a silica gel column. Elution with 10% EtOAc in hexanes followed by 20% and 30% EtOAc in hexanes afforded the title compound (310 mg, 48%) as a white solid.

B. 2-Benzyloxycarbonyloxylamino-4-methyl-thiazole-5-carboxylic acid

**[0144]** Compound **131B** was prepared by an analogous method as that of **3B**, except using **131A** to give the title

compound **131B** as a white powder (77%).

C. [4-Methyl-5-[[[(2,4,6-Trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, phenylmethyl ester

**[0145]** Diisopropylethylamine (70  $\mu$ L, 0.41 mmol) was added to a solution of **131B** (100 mg, 0.34 mmol), 2,4,6-trimethylaniline (60  $\mu$ L, 0.41 mmol), and [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate (HATU, 160 mg, 0.41 mmol). The mixture was stirred at rt for 24 h, diluted with EtOAc (20 mL) and washed with 2 N Aq. HCl solution (3x), brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated. The residue was triturated with ether (40 mL) to obtain the title compound (100 mg, 77%) as an off-white solid.

Example 132

Preparation of Methyl[4-methyl-5-[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

**[0146]**

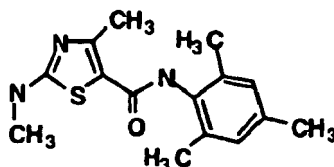


**[0147]** Compound **132** was prepared by an analogous method as that of **1**, except using ethyl-2-*tert*-butoxycarbonyloxyaminomethyl-4-methyl-thiazole-5-carboxylate to give the title compound **132** as a tan solid.

Example 133

Preparation of 4-Methyl-2-(methylamino)-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide, trifluoroacetate (1:1)

**[0148]**

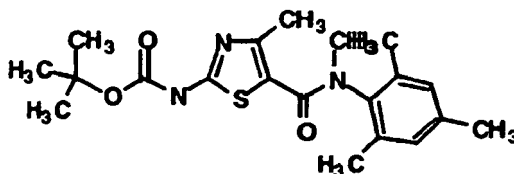


**[0149]** Compound **133** was prepared by an analogous method as that of **4**, except using **132** to give the title compound **133** as a white solid (91%).

Example 134

Preparation of [4-Methyl-5-[[[methyl(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

**[0150]**



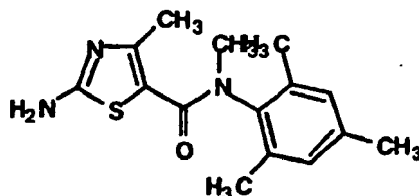
**[0151]** Compound **134** was prepared by an analogous method as that of **1**, except using N-methyl-2,4,6-trimethylaniline

to give the title compound **134** as a white solid (60%).

#### Example 135

Preparation of 2-Amino-N,4-dimethyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide, trifluoroacetate (1:1)

[0152]

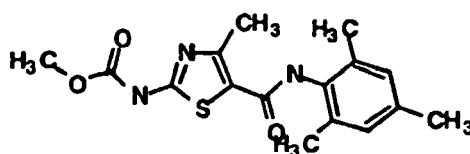


[0153] Compound **135** was prepared by an analogous method as that of **4**, except using **134** to give the title compound **135** as a white solid (97%).

#### Example 136

Preparation of [4-Methyl-5[[2,4,6-trimethylphenyl]amino]carbonyl]-2-thiazolyl]carbamic acid, methyl ester

[0154]

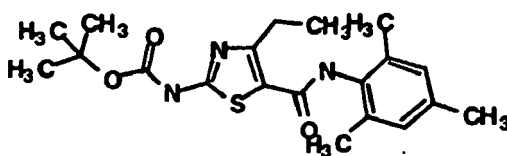


[0155] A mixture of **2** (100 mg, 0.36 mmol), pyridine (87  $\mu$ L, 1.08 mmol), methyl chloroformate (111  $\mu$ L, 1.44 mmol) in dichloromethane (3 mL) was stirred at rt for 1.5 h. The solution was diluted with dichloromethane and washed with aq.  $\text{NaHCO}_3$  solution (20 mL, 2x), brine; dried ( $\text{MgSO}_4$ ), filtered and concentrated. The residue was triturated with ether to obtain the title compound (88 mg, 82%) as a white solid.

#### Example 137

Preparation of [4-Ethyl-5[[2,4,6-trimethylphenyl]aminolcarbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

[0156]

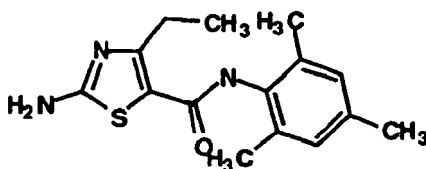


[0157] Compound **137** was prepared by an analogous method as that of **1**, except using methyl-2-amino-4-ethyl-thiazole-5-carboxylate to give the title compound **137** as a white solid (70%).

#### Example 138

Preparation of 2-Amino-4-ethyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide, trifluoroacetate

[0158]

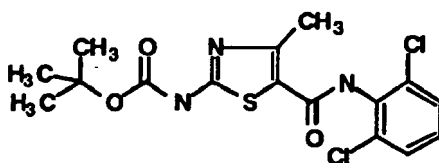


**[0159]** Compound **138** was prepared by an analogous method as that of **4**, except using **137** to give the title compound **138** as a white solid (89%).

#### Example 139

Preparation of [5-[(2,6-Dichlorophenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

**[0160]**

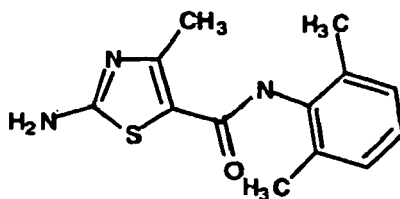


**[0161]** A 1M solution of sodium bis-trimethylsilyl amide (290  $\mu$ L, 0.29 mmol) was added to a stirred solution of 2,6-dichloroaniline (13.4 mg, 0.08 mmol) in THF (1 mL). After 30 min, the mixture was cooled to 0 °C and 1C (30 mg, 0.11 mmol) was added in one portion. The mixture was allowed to warm to rt and stirred for 16 h. The solution was diluted with dichloromethane and washed with 2 N aq. HCl solution (2 mL, 3x), dried ( $\text{MgSO}_4$ ), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 30% EtOAc in hexanes to obtain the title compound (20 mg, 45%) as a light yellow solid.

#### Example 140

Preparation of 2-Amino-N-(2,6-dimethylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)

**[0162]**



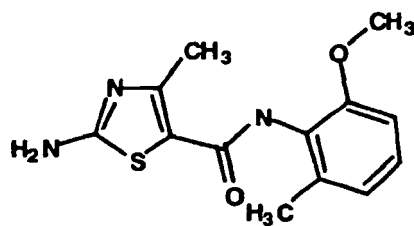
**[0163]** Compound **140** was prepared by an analogous method as that of **4**, except using 53 to give the title compound **140** as a light tan solid (100%).

#### Example 141

Preparation of 2-Amino-N-(2-methoxy-6-methylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)

**[0164]**



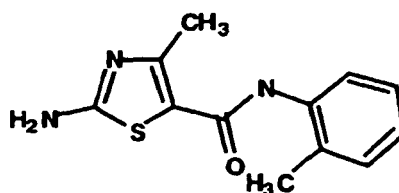


**[0165]** Compound **141** was prepared by an analogous method as that of **4**, except using **13** to give the title compound **141** as an off-white solid (100%).

#### Example 142

Preparation of 2-Amino-N-(2-methylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)

**[0166]**

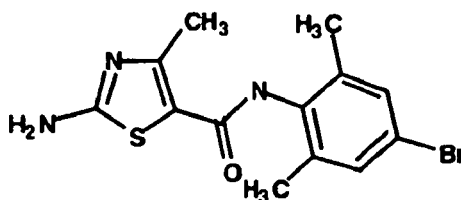


**[0167]** Compound **142** was prepared by an analogous method as that of **4**, except using **18** to give the title compound **142** as a light tan solid (90%).

#### Example 143

Preparation of 2-Amino-N-(2,6-dimethyl-4-bromophenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)

**[0168]**

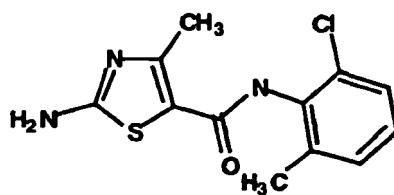


**[0169]** Compound **143** was prepared by an analogous method as that of **4**, except using **15** to give the title compound **143** as a light tan solid (70%).

#### Example 144

Preparation of 2-Amino-N-(2-chloro-6-methylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)

**[0170]**

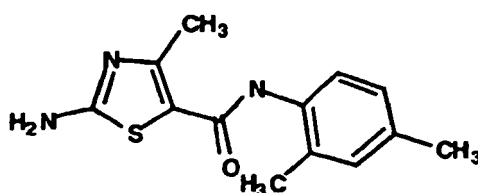


[0171] Compound **144** was prepared by an analogous method as that of **4**, except using **19** to give the title compound **144** as a light tan solid (81%).

#### Example 145

Preparation of 2-Amino-N-(2,4-dimethylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)

[0172]

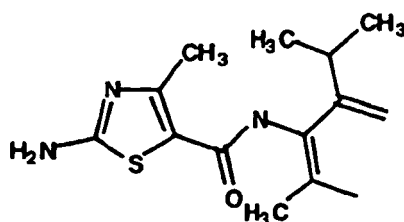


[0173] Compound **145** was prepared by an analogous method as that of **4**, except using **17** to give the title compound **145** as a light tan solid (68%).

#### Example 146

Preparation of 2-Amino-N-(2-methyl-6-isopropylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)

[0174]

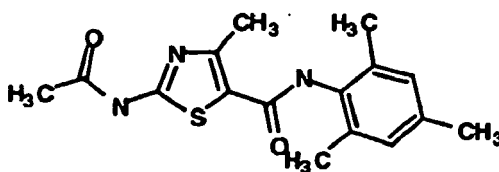


[0175] Compound **146** was prepared by an analogous method as that of **4**, except using **16** to give the title compound **146** as a light tan solid (100%).

#### Example 147

Preparation of 2-(Acetylamino)-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide

[0176]

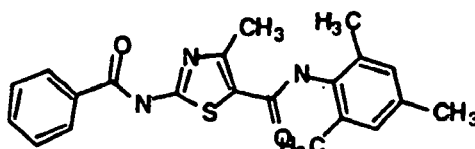


**[0177]** A mixture of **2** (54 mg, 0.2 mmol), acetic anhydride (22  $\mu$ L, 0.23 mmol), dimethylaminopyridine (3 mg) in dichloromethane (4.5 mL) was stirred at rt for 4.5 h. The mixture was diluted with dichloromethane (65 mL) and washed with 1 N aq. HCl solution (20 mL), water; dried ( $\text{MgSO}_4$ ), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 35% EtOAc in hexanes to obtain the title compound (43 mg, 69%) as a white solid.

#### Example 148

#### Preparation of 2-(Benzoylamino)-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide

**[0178]**

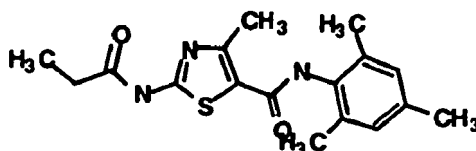


**[0179]** A solution of **2** (100 mg, 0.36 mmol) and benzoic anhydride (226 mg, 1 mmol) in dichloromethane (10 mL) and pyridine (2 mL) was stirred at rt overnight. The mixture was diluted with dichloromethane (50 mL) and washed with 2 N aq. HCl solution (15 mL, 2x), 10% aq.  $\text{NaHCO}_3$  solution (20 mL, 2x); dried ( $\text{MgSO}_4$ ), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 30% EtOAc in hexanes followed by 50% EtOAc in hexanes to obtain the title compound contaminated with benzoic acid. The solid was dissolved in EtOAc (40 mL) and washed with satd.  $\text{KHCO}_3$  solution (15 mL, 4x), dried ( $\text{MgSO}_4$ ), filtered and concentrated to obtain the title compound (110 mg, 80%) as a white solid.

#### Example 149

#### Preparation of 4-methyl-2-[(1-oxopropyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide

**[0180]**

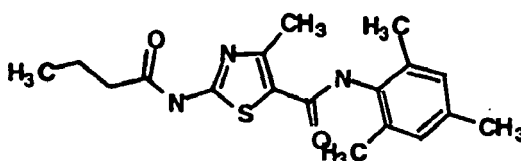


**[0181]** A mixture of **2** (100 mg, 0.36 mmol), propionic anhydride (332  $\mu$ L, 2.58 mmol) in dichloromethane (10 mL) and pyridine (4 mL) was stirred at rt for 3 h. Dimethylaminopyridine (122 mg, 1 mmol) was added and the mixture was stirred for additional 1.5 h. The mixture was diluted with dichloromethane and washed with 1 N aq. HCl solution (25 mL, 3x), aq.  $\text{NaHCO}_3$  solution (20 mL, 2x), water (20 mL), brine; dried ( $\text{MgSO}_4$ ), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 20% EtOAc in hexanes to obtain the title compound (81 mg, 68%) as a white solid.

#### Example 150

#### Preparation of 4-methyl-2-[(1-oxobutyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide

**[0182]**

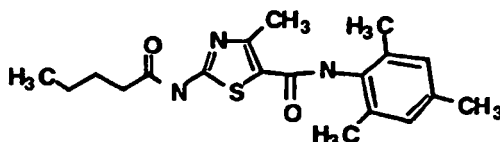


**[0183]** Compound 150 was prepared by an analogous method as that of 149, except using butyric anhydride to give the title compound 150 as a white solid (76%).

#### Example 151

Preparation of 4-methyl-2-[(1-oxopentyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide

**[0184]**

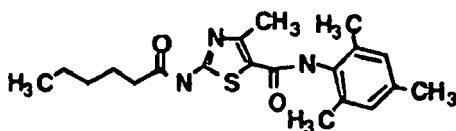


**[0185]** Compound 151 was prepared by an analogous method as that of 149, except using valeric anhydride to give the title compound 151 as a white solid (77%).

#### Example 152

Preparation of 4-methyl-2-[(1-oxohexyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide

**[0186]**

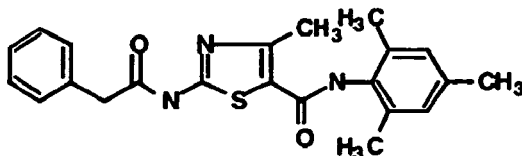


**[0187]** Compound 152 was prepared by an analogous method as that of 149, except using hexanoic anhydride to give the title compound 152 as a white solid (75%).

#### Example 153

Preparation of 4-Methyl-2-[(phenylcetyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide

**[0188]**

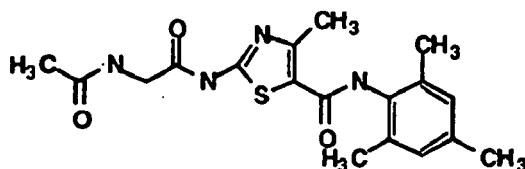


**[0189]** A solution of amine 2 (50 mg, 0.18 mmol), diisopropylethylamine (101  $\mu$ L, 0.58 mmol), phenylacetic acid (27.2 mg, 0.20 mmol), 1-hydroxy-7-azabenzotriazole (29.4 mg, 0.22 mmol), and ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (42.2 mg, 0.22 mmol) in dichloromethane (0.62 mL) was mechanically stirred in a sealed vial for 16 h. The reaction mixture was passed through a Varian SCX ion exchange column (2 g/6 cc) and eluted with acetonitrile-methanol (10 mL, 4:1) followed by 2 M methanolic ammonia solution (9 mL). Fractions containing the product were combined and then concentrated. The residue was dissolved in dichloromethane and washed with 2 N aq. HCl solution (3x), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated to obtain the title compound (39 mg, 55%) as a tan solid.

## Example 154

## Preparation of 2-[[[(Acetylamino)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-6-thiazolecarboxamide

[0190]

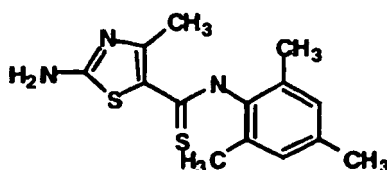


[0191] A solution of amine **2** (50 mg, 0.18 mmol), diisopropylethylamine (400  $\mu$ L, 2.3 mmol), N-acetylglycine (42 mg, 0.36 mmol), 1-hydroxy-7-azabenzotriazole (49 mg, 0.36 mmol), and ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (72 mg, 0.36 mmol) in THF (5 mL) was heated to 50°C overnight. The mixture was cooled, diluted with dichloromethane (60 mL) and washed with 2 N aq. HCl solution (20 mL), satd. aq.  $\text{KHCO}_3$  solution (20 mL), dried ( $\text{MgSO}_4$ ), filtered and concentrated. The crude solid was triturated with ether (10 mL), filtered, and washed with ether (5 mL, 3x) to obtain the title compound (40 mg, 59%) as an off-white solid.

## Example 155

## Preparation of 2-Amino-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarbothioamide

[0192]



[0193] A suspension of **2** (50 mg, 0.18 mmol) and Lawesson reagent (44 mg, 0.11 mmol) in toluene (0.23 mL) was heated to 100°C for 4h. Additional Lawesson reagent (44 mg, 0.11 mmol) was added and the mixture was heated for additional 3.5 h. The crude mixture was chromatographed on a silica gel column and eluted with 50% EtOAc in hexanes followed by 70% EtOAc in hexanes to obtain a yellow solid which was triturated with hexanes (6 mL) to obtain the title compound (11 mg, 21%) as a yellow solid.

## Examples 156 to 170

## General Procedure

[0194] Compounds **156** to **170** were prepared following the procedure described below. Diisopropylethyl amine (60  $\mu$ L, 0.34 mmol) was added to a mixture of amine **2** (30 mg, 0.11 mmol), appropriate carboxylic acid (0.13 mmol), 1-hydroxy-7-azabenzotriazole (19.5 mg, 0.14 mmol), and ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (26.8 mg, 0.14 mmol) in THF (1 mL). The mixture was heated in a sealed tube under argon at 45 °C for 24 h. The reaction mixture was diluted with dichloromethane (4 mL) and washed with 2 N aq. HCl solution (2 mL, 3x), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated using a speedvac. The crude products were either triturated with dichloromethane-ether (5 mL, 1:1) or purified by silica gel chromatography (elution solvent: 50% EtOAc in hexanes and EtOAc). "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballistic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90%  $\text{H}_2\text{O}$ , 0.2%  $\text{H}_3\text{PO}_4$ ) to 100% solvent B (90% MeOH, 10%  $\text{H}_2\text{O}$ , 0.2%  $\text{H}_3\text{PO}_4$ ), flow rate 4 mL/min,  $\lambda$  = 220 nm.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
156		2-[(4-Bromobenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.03
157		4-Methyl-2-[(4-nitrobenzoyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.87
158		2-[(4-Cyanobenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.70
159		4-Methyl-2-[[[(5-nitro-2-furanyl)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.63
160		4-Methyl-2-[(2-thienylcarbonyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.60
161		4-[[[4-Methyl-5-[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]amino]carbonyl]benzoic acid methyl ester	4.99
162		2-[(5-Isoxazolylcarbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.87
163		2-[(3-Furanylcarbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.54
164		2-[[[(2,4-Dimethyl-5-thiazolyl)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.74

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
165		2-[[[(4-Methoxy-3-thienyl) carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.75
166		4-Methyl-2-[[[(5-nitro-3-thienyl) carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.78
167		2-[[[4-[(4-Chlorophenyl)thio]-3-thienyl]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.27
168		2-[[[(5-Chloro-4-methoxy-3-thienyl) carbonyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.04
169		2-[[[2-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-3-thienyl]carbonyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.13
170		2-[[[(2-Acetyl-3-thienyl)carbonyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.54

## Examples 171 to 180

## General Procedure

**[0195]** Compounds **171** to **180** were prepared following the procedure described below.

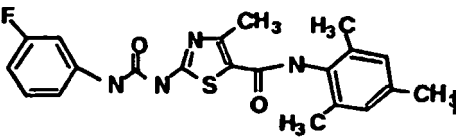
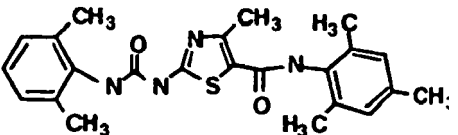
**[0196]** A mixture of **2** (80 mg, 0.29 mmol), appropriate isocyanate (0.87 mmol) and pyridine (2 mL) in THF (3.5 mL) was stirred at rt overnight. In some cases the reaction mixture was heated to 60-70°C for 5 h. Some of these reactions were carried out at rt overnight in the presence of catalytic N,N-dimethylaminopyridine. The reaction mixture was diluted with dichloromethane and washed with 1 N aq. HCl solution (3x), water, brine; dried (MgSO<sub>4</sub>), filtered and concentrated. The crude product was purified either by trituration with ether or ether-hexanes mixture, or by chromatography on a silica gel column (elution solvent 20-40% EtOAc in hexanes) followed by trituration or by passing through Varian cation exchange SCX cartridge and sequentially eluted with methanol (5 mL), dichloromethane (5 mL), acetonitrile-methanol (10 mL, 4:1) and methanol-2 M methanolic ammonia (10 mL, 4:1) to obtain the title compound. "HPLC Ret Time" is the HPLC retention time under the following conditions: For compounds **171-172**, **175**, and **177** HPLC conditions are: Zorbax S8-C18 4.5 mm x 7.5 cm short column, 30 min gradient starting from 100% solvent A (10% MeOH, 90% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>), flow rate 2.5 mL/min, λ = 217 nm. For the other compounds HPLC conditions are: Zorbax S8-C18 4.5 mm x 7.5 cm short column, 8 min gradient starting from 100% solvent A (10% MeOH, 90% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>), flow rate 2.5

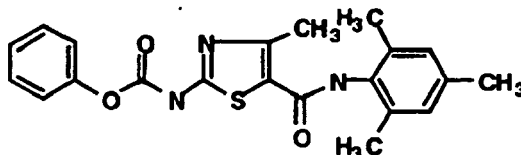
mL/min,  $\lambda$  = 217 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
171		4-Methyl-2-[[[(methyl-amino) carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	24.48
172		4-Methyl-2-[[[(phenyl-amino) carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	30.45
173		4-methyl-2-[[[(4-methylphenyl) amino]-carbonyl] amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.81
174		4-Methyl-2-[[[(phenyl-methyl) amino]carbonyl] amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.52
175		2-[[[(Butylamino) carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	30.49
176		4-Methyl-2-[[[(propylamino) carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	7.41
177		2-[[[(Cyclohexylamino) carbonyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	27.21
178		2-[[[(2-Chloro-phenyl)amino] carbonyl] amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.99



(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
179		2-[[[(3-Fluorophenyl) amino] carbonyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.87
180		2-[[[(2,6-Dimethyl-phenyl) amino] carbonyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazole-carboxamide	8.92

Example 181Preparation of [5-[[[(2,4,6-Trimethylphenyl) amino] carbonyl]-4-methyl-2-thiazolyl] carbamic acid, phenyl ester**[0197]**

**[0198]** A 10% aq.  $\text{KHCO}_3$  solution (170 mL) was added to a stirred solution of 2 (1.02 g, 3.7 mmol) in THF (130 mL). Phenylchloroformate (1.39 mL, 11.1 mmol) was added dropwise. The biphasic mixture was stirred at rt overnight, diluted with dichloromethane (200 mL) and washed with water (50 mL, 2x) and brine. The organic extract was separated, dried ( $\text{MgSO}_4$ ), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 10% EtOAc in hexanes to obtain the title compound (980 mg, 69%) as a solid.

Examples 182 to 236General Procedure

**[0199]** Compounds **182** to **236** were prepared following the procedure described below.

**[0200]** A solution of phenylcarbamate **181** (20 mg, 0.054 mmol) and the appropriate amine (0.08 mmol) in THF-acetonitrile (3 mL, 1:1) was stirred at rt overnight. Some of the reactions required heating to 60 °C for 4 h to overnight. The mixture was diluted with dichloromethane (4 mL) and washed with 1 N aq. HCl solution (1.5 mL, 2x), 1 N aq. NaOH solution (1.5 mL, 2x). The dichloromethane extract was separated, dried ( $\text{MgSO}_4$ ), filtered and concentrated to obtain the title product.

**[0201]** "HPLC Ret Time" is the HPLC retention time under the following conditions: For compounds 182-192 HPLC conditions are: Zorbax SB-C18 4.5 mm x 7.5 cm short column, 8 min gradient starting from 100% solvent A (10% MeOH, 90%  $\text{H}_2\text{O}$ , 0.2%  $\text{H}_3\text{PO}_4$ ) to 100% solvent B (90% MeOH, 10%  $\text{H}_2\text{O}$ , 0.2%  $\text{H}_3\text{PO}_4$ ), flow rate 2.5 mL/min,  $\lambda$  = 217 nM. For compounds 193-236 HPLC conditions are: YMC S5 ODS 4.6 x 50 mm Ballistic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90%  $\text{H}_2\text{O}$ , 0.2%  $\text{H}_3\text{PO}_4$ ) to 100% solvent B (90% MeOH, 10%  $\text{H}_2\text{O}$ , 0.2%  $\text{H}_3\text{PO}_4$ ), flow rate 4 mL/min,  $\lambda$  = 220 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
182		4-Methyl-2-[[[(2-phenylethyl)amino]-carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazole-carboxamide	8.83
183		2-[[[(Hexylamino) carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	9.01
184		2-[[[(1,1-Dimethyl-ethyl)amino] carbonyl]a mino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.48
185		2-[[[(3-Fluoro-4-methylphenyl) amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.92
186		2-[[[(4-Methoxyphenyl) amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.57
187		2-[[[(Diethylamino) carbonyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.19
188		2-[[[Bis(1-methyl-ethyl)amino] carbonyl]-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.90
189		4-Methyl-2-[[[methyl-(phenylmethyl) amino]-carbonyl] amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.56
190		4-Methyl-2-[[[(methyl-phenylamino)carbonyl]a nino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.39
191		2-[[[(Cyclohexylmethyl amino) carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.84

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
192		4-Methyl-2-[[[(1-phenylethyl) amino]-carbonyl] amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.47
193		2-[[[(Cyclopropyl-methyl) propylamino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.36
194		4-Methyl-2-[[[(2-methylcyclohexyl)amino ] carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.42
195		4-Methyl-2-[[[(4-methylcyclohexyl)-amino] carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.49
196		2-[[[(Cyclohexyl-methyl) amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.49
197		2-[[[(2,3-Dihydro-1H-inden-1-yl) amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.35

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
198		4-Methyl-2-[[[(1-naphthalenylmethyl)amino]carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.43
199		2-[[[Bis(phenylmethyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.66
200		2,6-Dimethyl-N-[4-methyl-5-[[[(2,4,6-trimethylphenyl)-amino]carbonyl]-2-thiazolyl]-4-morpholinecarboxamide	3.97
201		2-Ethyl-N-[4-methyl-5-[[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-1-piperidinecarboxamide	4.29
202		1-[[[4-Methyl-5-[[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-amino]carbonyl]-3-piperidinecarboxylic acid ethyl ester	4.10
203		3,3-Dimethyl-N-[4-methyl-5-[[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-1-piperidinecarboxamide	4.32

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
204		1-[[[4-Methyl-5-[[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-amino]carbonyl]-4-piperidinecarboxylic acid ethyl ester	4.06
205		4-Methyl-2-[[[(3-methyl-2-pyridinyl)-amino]carbonyl]-amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazolecarboxamide	3.51
206		4-Methyl-2-[[[1-(phenylmethyl)-4-piperidinyl]amino]-carbonyl]-amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	3.28
207		Octahydro-N-[4-methyl-5-[[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-1(2H)-quinolinecarboxamide	4.55
208		3,4-Dihydro-N-[4-methyl-5-[[[(2,4,6-trimethylphenyl)-amino]carbonyl]-2-thiazolyl]-2(1H)-isoquinoline carboxamide	4.35
209		2-[[[(1,5-Dimethyl-hexyl)amino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.72

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
210		4-Methyl-2-[[[(1-methylheptyl)amino]-carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazole-carboxamide	4.74
211		2-[[[(2-Fluoro-phenyl)methyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.17
212		2-[[[(2-Methoxy-phenyl)methyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.22
213		2-[[[(2-Ethoxy-phenyl)methyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.36
214		2-[[[(3-Methoxy-phenyl)methyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.13
215		2-[[[(4-Chloro-phenyl)methyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.36
216		2-[[[(4-Methoxy-phenyl)methyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.12

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
217		2-[[[(2,2-Diphenyl-ethyl)amino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.57
218		2-[[[(2-Aminoethyl)phenylamino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	3.70
219		2-[[[2-(3-Methoxy-phenyl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.26
220		2-[[[2-(3,4-Dimethoxyphenyl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.05
221		2-[[[2-(4-Methoxy-phenyl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.25
222		4-Methyl-2-[[[(3-phenylpropyl)amino]carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.40
223		2-[[[2-(Cyclohex-1-en-1-yl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.11

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
224		2-[[[4-(1,1-Dimethylethyl)cyclohexyl]amino]carbonyl]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazole-carboxamide	4.85
225		2-[[[(3-Butoxypropyl) amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.33
226		2-[[[2-(2-Methoxy-phenyl)ethyl] amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.46
227		2-[[[(2-Chloro-4-fluorophenyl) methyl]-amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.39
228		2-[[[(Hexylmethylamino) carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.65
229		2-[[[1-(4-Chloro-phenyl)ethyl] amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.42
230		2-[[[2-(3-Chloro-phenyl)ethyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazole-carboxamide	4.44



(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
231		4-Methyl-2-[[[2-(2-thienyl)ethyl]amino]-carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.18
232		2-[[[2-(2-Fluoro-phenyl)ethyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.85
233		4-Methyl-2-[[[2-(2-pyridinyloxy)ethyl]-amino]carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.28
234		2-[[[2-(2-Bromo-4,5-dimethoxyphenyl)methyl]methylamino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.87
235		(E)-2-[[[2-(3,7-Dimethyl-2,6-octadienyl)amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.34
236		2-[[[2-(2,3-Dihydro-1,4-benzodioxin-2-yl)methyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.27

Examples 237 to 285*General Procedure*

**[0202]** Compounds **237** to **285** were prepared following the procedure described below.

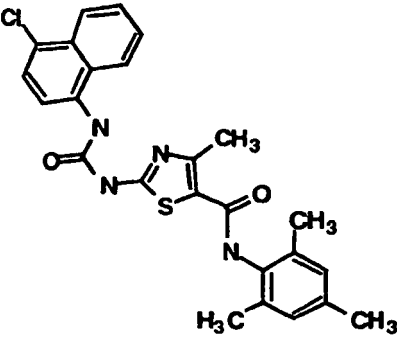
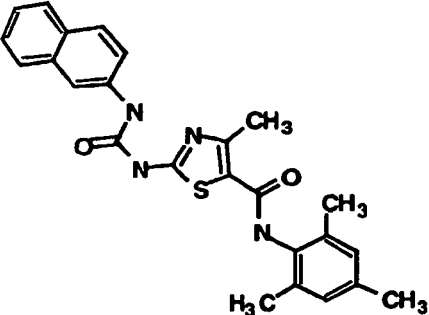
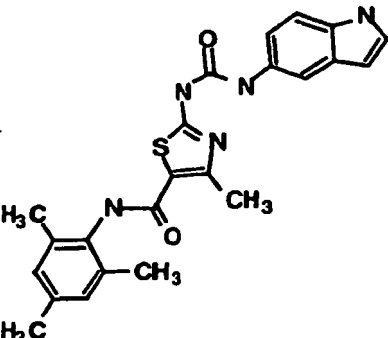
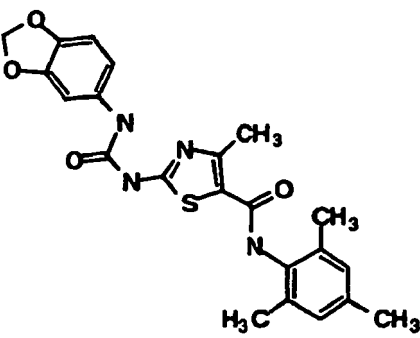
**[0203]** A solution of phenylcarbamate **181** (20 mg, 0.054 mmol) and the appropriate amine (0.08 mmol) in THF-acetonitrile (3 mL, 1:1) was stirred at rt overnight. The mixture was diluted with dichloromethane (4 mL) and washed with 1 N aq. HCl solution (1.5 mL, 2x), 1 N aq. NaOH solution (1.5 mL, 2x). The dichloromethane extract was separated, dried (MgSO<sub>4</sub>), filtered and concentrated to obtain the title product.

**[0204]** "HPLC Ret Time" is the HPLC retention time under the following conditions: For compounds 237-278 HPLC conditions are: YMC S5 ODS 4.6 x 50 mm Ballistic Column, 4 min gradient starting from 100% solvent A (10% MeOH,

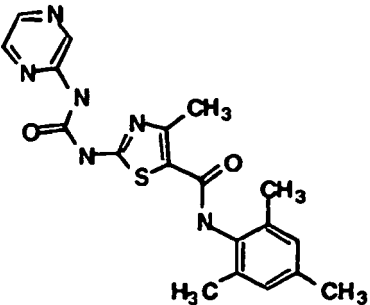
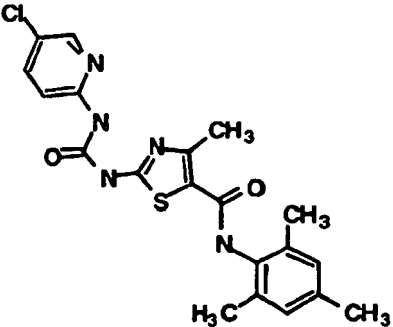
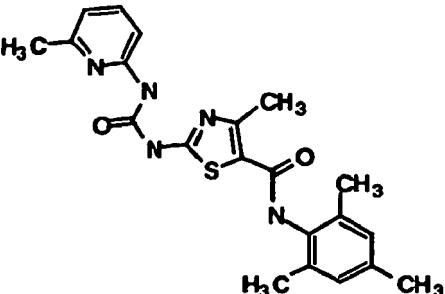
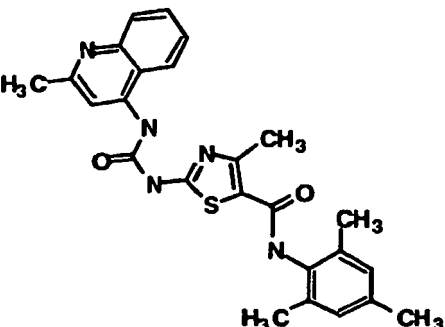
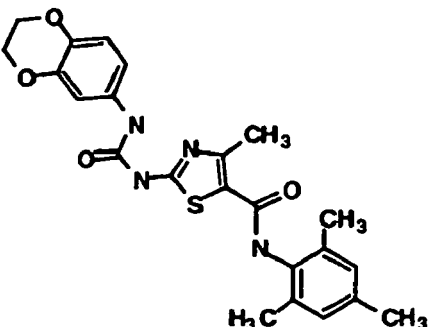
90% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>), flow rate 4 mL/min,  $\lambda$  = 220 nM. For compounds **279-285** HPLC conditions are: Zorbax S8-C18 4.5 mm x 7.5 cm short column, 8 min gradient starting from 100% solvent A (10% MeOH, 90% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>), flow rate 2.5 mL/min,  $\lambda$  = 217 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
237		2-[[[3-Methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.36
238		2-[[[4-Cyclohexyl-phenyl]amino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.73
239		4-Methyl-2-[[[(5,6,7,8-tetrahydro-1-naphthalenyl)amino]-carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.38
240		2-[[[(1-Anthracenylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.82

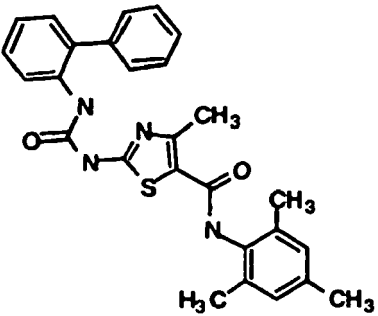
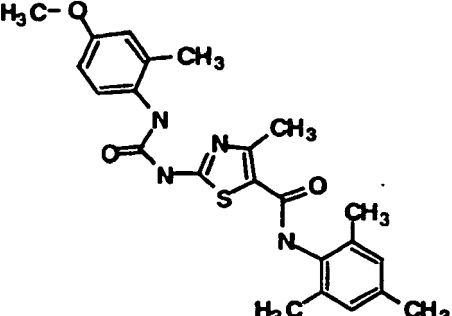
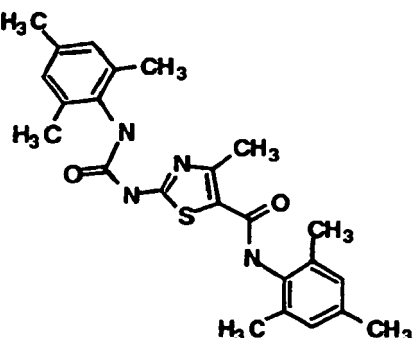
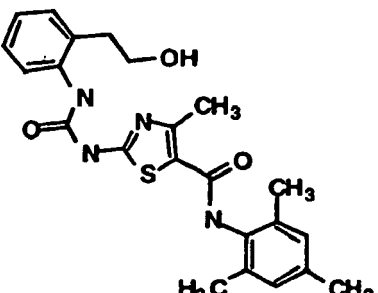
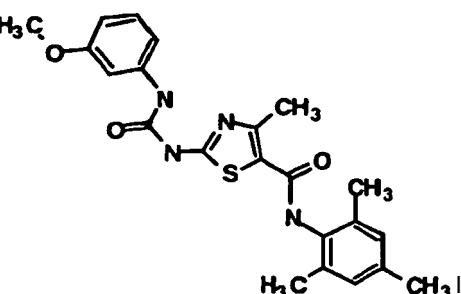
(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
241		2-[[[(4-Chloro-1-naphthalenyl)amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.76
242		4-Methyl-2-[[[(2-naphthalenylamino)-carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.28
243		2-[[[(1H-Indol-5-ylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.00
244		2-[[[(1,3-Benzodioxol-5-ylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.76

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
245		4-Methyl-2-[[[(2-pyrazinylamino) carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	3.84
246		2-[[[(5-Chloro-2-pyridinyl)amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.38
247		4-Methyl-2-[[[(6-methyl-2-pyridinyl) amino]-carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.44
248		4-Methyl-2-[[[(2-methyl-4-quinolinyl)amino] carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.23
249		2-[[[(2,3-Dihydro-1,4-benzodioxin-6-yl)amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.72

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
250		2-[[[1,1'-Biphenyl]-2-ylamino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.29
251		2-[[[4-Methoxy-2-methylphenyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.80
252		4-Methyl-N-(2,4,6-trimethylphenyl)-2-[[[(2,4,6-trimethylphenyl)amino]carbonyl]amino]-5-thiazolecarboxamide	5.06
253		2-[[[2-(2-Hydroxy-ethyl)phenyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.02
254		2-[[[3-Methoxyphenyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.86

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
255		2-[[[(4-Methoxy[1,1'-biphenyl]-3-yl)amino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.81
256		2-[[[(3-Acetylphenyl) amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.12
257		2-[[[(4-Cyanophenyl) amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.15
258		2-[[[(4-Fluoro-2-(trifluoromethyl) phenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.99
259		2-[[[(4-Hexyloxyphenyl) amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.42

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
260		4-[[[4-Methyl-5-[(2,4,6-trimethyl-phenyl) amino] carbonyl]-2-thiazolyl]-amino]-carbonyl]amino]benzoic acid ethyl ester	4.26
261		2-[[[4-(Decylphenyl)-amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	
262		4-Methyl-2-[[[4-(propylphenyl) amino]-carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.71
263		4-Methyl-2-[[[3,4,5-trimethoxyphenyl) amino]-carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.67

(continued)

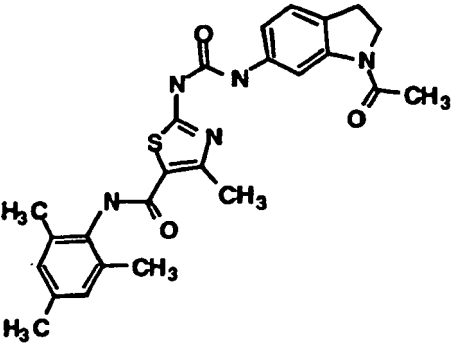
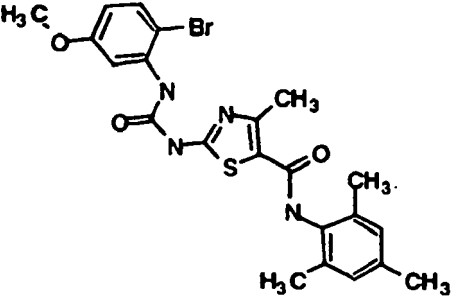
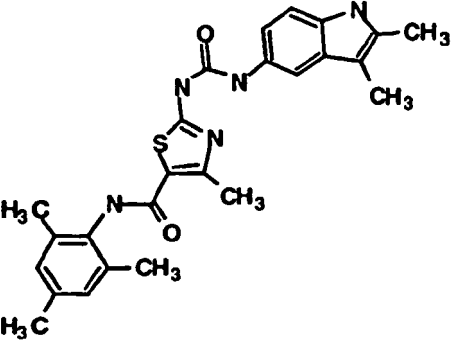
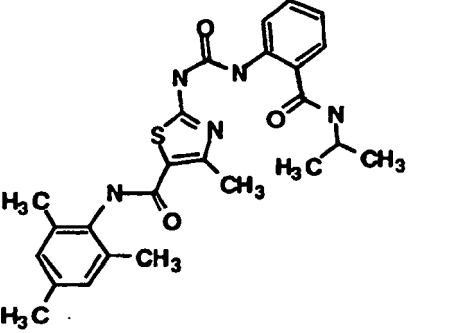
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
264		4-Methyl-2-[[[4-[[[(5-methyl-3-isoxazolyl) amino]sulfonyl] phenyl]-amino]carbonyl] amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.27
265		4-[[[4-Methyl-5-[[[(2,4,6-trimethyl phenyl)amino] carbonyl]-2-thiazolyl]-amino] carbonyl]-amino]-benzoic acid butyl ester	4.75
266		2-[[[(1-Isoquinolinyl amino) carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.81
267		4-Methyl-2-[[[2-[(phenyl-methyl) thio]-phenyl]amino] carbonyl]-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.42
268		4-Methyl-2-[[[4-[(5-phenoxypropyl)oxy]phenyl] amino]carbonyl] amino]-N-(2,4,6-trimethylphenyl)-5-thiazole-carboxamide	4.96



(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
269		2-[[[5-(1,1-Dimethyl-propyl)-2-methoxy-phenyl]amino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.76
270		2-[[[1,2-Dihydro-5-acenaphthylenyl]amino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazole-carboxamide	4.70
271		4-Methyl-2-[[[3-phenoxyphenyl]amino]carbonyl]-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.70
272		4-Methyl-2-[[[2-(4-morpholinyl)phenyl]amino]carbonyl]-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.01
273		4-Methyl-2-[[[2-(1-piperidinyl)phenyl]amino]carbonyl]-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.55

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
274		2-[[[(1-Acetyl-2,3-dihydro-1H-indol-6-yl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.08
275		2-[[[(2-Bromo-5-methoxyphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.55
276		2-[[[(2,3-Dimethyl-1H-indol-5-yl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.30
277		4-Methyl-2-[[[2-[[[(1-methylethyl)amino]carbonyl]phenyl]amino]carbonylamino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.82

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
278		2-[[[(3-Bromo-2-methyl-phenyl) amino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.60
279		2-[[[(4-Methoxybutyl) amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	7.62
280		2-[[[(3,3-Dimethyl-butyl)amino] carbonyl]-amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	9.13
281		4-Methyl-2-[[[(2-methylbutyl) amino]-carbonyl] amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.90
282		4-Methyl-2-[[[(3-methylbutyl) amino]carbo-nyl] amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.98
283		2-[[[(2-Methoxyethyl)-amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	7.30
284		2-[[[[2-(Dimethyl-amino)ethyl] amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.73
285		4-Methyl-2-[[[[2-(methylthio) ethyl]amino] carbonyl] amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.19

Examples 286 to 311

General Procedure

[0205] Compounds 286 to 311 with the exception of compound 307 were prepared following the procedure described

below.

**[0206]** A solution of 2-[[[(Butylamino)carbonyl]amino]-4-methyl-5-thiazole carboxylic acid chloride (30 mg, 0.11 mmol), appropriate amine (0.12 mmol) in THF (1 mL) was treated with diisopropylethyl amine (22.6  $\mu$ L, 0.13 mmol). The mixture was purged with argon and stirred mechanically in a vial for 22 h, diluted with dichloromethane (4 mL) and washed with 2 N aq. HCl solution (3x). The organic extract was separated, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated. The crude products were purified either by trituration with dichloromethane-ether (1:1) or by silica gel chromatography (elution solvent: 80% EtOAc in hexanes followed by EtOAc) or by automatic preparative HPLC (conditions: YMC S5 ODS A 20 x 100 mm Column, 10 min gradient starting from 30% solvent B (90% MeOH, 10%  $\text{H}_2\text{O}$ , 0.1% TFA) and 70% solvent A (10% MeOH, 90%  $\text{H}_2\text{O}$ , 0.1% TFA) to 100% solvent B, flow rate 20 mL/min,  $\lambda$  = 220 nM. Compound **307** was prepared following the procedure described below.

**[0207]** A suspension solution of 2-[[[(Butylamino)carbonyl]amino]-4-methyl-5-thiazole carboxylic acid (100 mg, 0.36 mmol), and HATU (170 mg, 0.44 mmol) in DMF (3 mL) was treated with diisopropylethyl amine (62 mL, 0.44 mmol). The mixture was heated to 60°C for 2 h, cooled, diluted with dichloromethane (12 mL), washed with 8M aq. Urea solution in 2 N aq. HCl (6 mL, 3x), 5% aq.  $\text{KHCO}_3$  solution (6 mL, 3x), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated. The residue was triturated with EtOAc-ether to obtain the mixed anhydride intermediate (102 mg, 74%) as a white solid. A 1M solution of sodium bis(trimethylsilylamide) in THF (170  $\mu$ L, 0.17 mmol) was added dropwise to a stirred solution of 2,6-dichloroaniline (19.4 mg, 0.12 mmol) in THF (1 mL). After 15 min, the mixed anhydride intermediate (41.3 mg, 0.11 mmol) was added in one portion. A few drops of DMF was added and the solution was stirred for 16 h. Additional 1 M solution of sodium bis(trimethylsilylamide) (110  $\mu$ L) was added and the mixture was stirred for additional 2 h. The mixture was diluted with dichloromethane (4 mL) and washed with 2 N aq. HCl solution (2 mL, 3x), satd. aq.  $\text{KHCO}_3$  solution (3x), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated. The solid was washed with hexanes (2x) and the residue was chromatographed on a silica gel column. Elution with 80% EtOAc in hexanes followed by EtOAc afforded **307** (12 mg, 27%) as a light tan solid. "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballistic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90%  $\text{H}_2\text{O}$ , 0.2%  $\text{H}_3\text{PO}_4$ ) to 100% solvent B (90% MeOH, 10%  $\text{H}_2\text{O}$ , 0.2%  $\text{H}_3\text{PO}_4$ ), flow rate 4 mL/min,  $\lambda$  = 220 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
286		2-[[[(Butylamino) carbonyl] amino]-N-(2,3-dihydro-1H-inden-5-yl)-4-methyl-5-thiazole-carboxamide	4.20
287		2-[[[(Butylamino) carbonyl] amino]-N-2-naphthalenyl-4-methyl-5-thiazolecarboxamide	4.20
288		2-[[[(Butylamino) carbonyl] amino]-N-(3-hydroxy-2-naphthalenyl)-4-methyl-5-thiazolecarboxamide	4.24
289		2-[[[(Butylamino) carbonyl] amino]-N-(2-fluoro-5-methylphenyl)-4-methyl-5-thiazolecarboxamide	3.95

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
290		2-[[[(Butylamino) carbonyl] amino]-N-(2,6-dimethylphenyl)-4-methyl-5-thiazole-carboxamide	3.78
291		N-(4-Bromo-2-methylphenyl)-2-[[[(butylamino)carbonyl] amino]-4-methyl-5-thiazolecarboxamide	4.12
292		N-(3-Bromo-2,4,6-trimethylphenyl)-2-[[[(butylamino)carbonyl] amino]-4-methyl-5-thiazolecarboxamide	4.28
293		2-[[[(Butylamino) carbonyl] amino]-N-[2,6-dimethyl-3-(1-methylethyl)phenyl]-4-methyl-5-thiazolecarboxamide	4.28
294		N-(2-Bromo-4,6-dimethylphenyl)-2-[[[(butylamino)carbonyl] amino]-4-methyl-5-thiazolecarboxamide	4.00
295		3-[[[2-[[[(Butylamino) carbonyl] amino]-4-methyl-5-thiazolyl]-carbonyl]amino]-4-methyl-2-thiophene-carboxylic acid methyl ester	3.83
296		2-[[[(Butylamino) carbonyl] amino]-4-nethyl-N-(2-methyl-6-quinoliny)-5-thiazolecarboxamide	2.98

(continued)

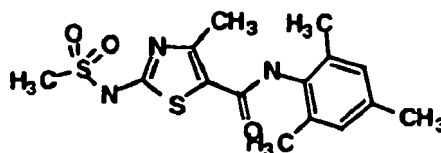
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
297		2-[[[(Butylamino) carbonyl] amino]-N-(2,6-dimethoxyphenyl)-4-methyl-5-thiazolecarboxamide	3.39
298		2-[[[(Butylamino) carbonyl] amino]-N-(4-methoxy-2-naphthalenyl)-4-methyl-5-thiazolecarboxamide	4.31
299		2-[[[(Butylamino) carbonyl] amino]-N-(2-methyl-1-naphthalenyl)-4-methyl-5-thiazolecarboxamide	3.92
300		2-[[[(Butylamino) carbonyl] amino]-N-[4-(dimethylamino)-2,3,5,6-tetramethyl-phenyl]-4-methyl-5-thiazolecarboxamide	3.14
301		2-[[[(Butylamino) carbonyl] amino]-N-(6-methyl-5-quinoliny)-4-methyl-5-thiazolecarboxamide	3.13
302		2-[[[(Butylamino) carbonyl] amino]-N-[2-(2-hydroxyethyl)-6-methylphenyl]-4-methyl-5-thiazolecarboxamide	3.50

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
303		2-[[[(Butylamino) carbonyl] amino]-N-(2,6-dimethyl-3-nitrophenyl)-4-methyl-5-thiazolecarboxamide	3.75
304		N-(2-Bromo-3,4,6-trimethylphenyl)-2-[[[(butylamino)carbonyl] amino]-4-methyl-5-thiazolecarboxamide	4.12
305		N-(2-Acetyl-6-hydroxyphenyl)-2-[[[(butylamino)carbonyl] amino]-4-methyl-5-thiazolecarboxamide	3.75
306		[4-[[[2-[[[(Butylamino) carbonyl] amino]-4-methyl-5-thiazolyl]-carbonyl] amino]-2,3,5,6-tetramethyl-phenyl] carbamic acid 1,1-dimethylethyl ester	4.10
307		2-[[[(Butylamino) carbonyl] amino]-N-(2,6-dichlorophenyl)-4-methyl-5-thiazolecarboxamide	4.42
308		N-(4-Amino-2,3,5,6-tetramethylphenyl)-2-[[[(butylamino)carbonyl] amino]-4-methyl-5-thiazolecarboxamide	3.15
309		N-[5-(Acetylamino)-2,4-dimethylphenyl]-2-[[[(butylamino)carbonyl] amino]-4-methyl-5-thiazolecarboxamide	3.52

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
310		N-(4-Bromo-2,6-dimethylphenyl)-2-[[[butylamino]carbonyl]amino]-4-methyl-5-thiazolecarboxamide	4.93
311		2-[[[Butylamino] carbonyl] amino]-N-(2-chloro-6-methylphenyl)-4-methyl-5-thiazolecarboxamide	4.51

Example 312Preparation of 4-Methyl-2-[(methylsulfonyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide**[0208]**A. Ethyl-2-[(methylsulfonyl)amino]-4-methyl-thiazole-5-carboxylate

**[0209]** A stirred solution of ethyl-2-amino-4-methyl-thiazole-5-carboxylate (558 mg, 3 mmol) in dichloromethane (15 mL) and pyridine (5 mL) was treated with methanesulfonyl chloride (687 mg, 6 mmol) at rt overnight. The solution was diluted with dichloromethane (50 mL) and washed with 2N aq. HCl solution (15 mL, 3x), dried (MgSO<sub>4</sub>), filtered and concentrated. The crude residue was diluted with ether (25 mL) and the solid was filtered, washed with 1:1 ether:hexane mixture (10 mL, 3x), and dried *in vacuo* to obtain the title compound (687 mg, 87%) as an off-white solid.

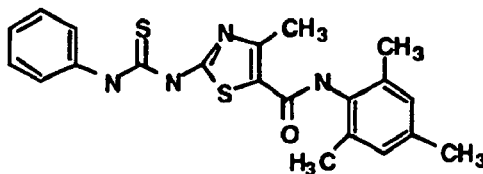
B. 2-[(Methylsulfonyl)amino]-4-methyl-thiazole-5-carboxylic acid

**[0210]** A stirred solution of Ethyl-2-[(methylsulfonyl)amino]-4-methyl-thiazole-5-carboxylate (300 mg, 1.14 mmol) in methanol (9 mL) was treated with a 1N NaOH solution (28.4 mL, 28.4 mmol). The mixture was stirred at rt overnight. The solution was cooled to 0 °C and acidified with 6N aq. HCl solution to pH 1. The solution was extracted with dichloromethane-chloroform mixture. The organic extract was dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to obtain the title acid (148 mg, 55%).

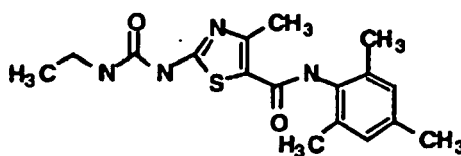
C. 4-Methyl-2-1(methylsulfonyl)aminol-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide

**[0211]** Diisopropylethylamine (87 μL, 0.5 mmol) was added to a solution of **312 B** (99 mg, 0.42 mmol), 2,4,6-trimethylaniline (68 μL, 0.5 mmol), and [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate (HATU, 191 mg, 0.5 mmol) in DMF (3 mL). The mixture was stirred at rt overnight, diluted with EtOAc and washed with 0.5 N aq. HCl solution (15 mL), 10% aq. LiCl solution (25 mL, 3x), water (930 mL, 2x), brine, dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 50% EtOAc in hexanes, followed by 75% EtOAc in hexanes and 2% MeOH in EtOAc to obtain the title compound (19 mg, 13%) as a white solid.

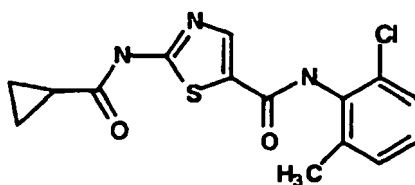


Example 313Preparation of 4-Methyl-2-[[[(phenylamino)thiocarbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide**[0212]**

**[0213]** A solution of **2** (45 mg, 0.16 mmol) and phenylisothiocyanate (43 mg, 0.32 mmol) in pyridine (2 mL) was heated to 80°C for 20 h. The mixture was cooled, diluted with dichloromethane-THF mixture (80 mL, 3:1) and washed with 2 N aq. HCl solution (15 mL, 2x). The organic extract was dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was diluted with EtOAc (20 mL) and the solid was filtered, washed with ether (10 mL, 3x), and dried *in vacuo* to obtain the title compound (35 mg, 52%) as an off-white solid.

Example 314Preparation of 2-[[[(Ethylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide**[0214]**

**[0215]** Compound **314** was prepared by an analogous method as that of compounds **171-180**, using ethylisocyanate to give the title compound **314** as a white solid (65%).

Example 315Preparation of N-(2-Chloro-6-methylphenyl)-2-[(cyclopropylcarbonyl)amino]-5-thiazolecarboxamide**[0216]**A. Ethyl-2-tert-butoxycarbonyloxylamino-4-methyl-thiazole-5-carboxylate

**[0217]** A suspension of ethyl-2-amino-thiazole-5-carboxylate (972 mg, 6 mmol, B. Plouvrier, C. Bailly, R. Houssin, j-P. Henlchart Heterocycles 32(4), 693-701, 1991 and H. J. Becker, J. de Jonge Rec. Trav. Chim, 61, 463, 1942 ), di-*t*-butyldicarbonate (1.94 g, 9 mmol) and 4-dimethylaminopyridine (73 mg, 0.6 mmol) in dry tetrahydrofuran (75 mL) was stirred under nitrogen for 24 h. The solvent was evaporated *in vacuo*. The residue was suspended in ether (50 mL). The solid was washed with ether (10 mL, 3x), and dried *in vacuo* to obtain the title compound (1.1 g, 70%).

B. 2-*tert*-butoxycarbonyloxyamino-thiazole-5-carboxylic acid

[0218] A stirred solution of ethyl-2-*tert*-butoxycarbonyloxyamino-4-methylthiazole-5-carboxylate (1.1 g, 4.2 mmol) in tetrahydrofuran-methanol (80 mL, 1:1) was treated with a 6N aq. NaOH solution (20 mL, 120 mmol). The mixture was stirred at rt for 24 h. Most of THF and methanol were removed by distillation under reduced pressure and the aq. Solution was acidified with 6 N aq. HCl solution (22 mL). The precipitated solid was filtered, washed with water and ether, air dried followed by drying *in vacuo* to obtain the title acid (940 mg, 96%) as an off-white solid.

C. 5-[[[(2-chloro-6-methylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

[0219] A 2 M solution of oxalyl chloride in dichloromethane (1 mL, 2 mmol) was added dropwise to a stirred solution of 2-*tert*-butoxycarbonyloxyamino-thiazole-5-carboxylic acid (234 mg, 1 mmol) in THF (10 mL) and N,N-dimethyl formamide (few drops). The solution was stirred at rt for 4 h. The solvent was evaporated under reduced pressure, and *in vacuo* to obtain the crude acid chloride.

[0220] 2-Chloro-6-methyl aniline (212 mg, 1.5 mmol) was added dropwise to a stirred solution of crude 2-*tert*-butoxycarbonyloxyamino-thiazole-5-carboxylic acid chloride (1 mmol) in dichloromethane (10 mL) at 0°C. Diisopropylethylamine (516 mg, 4 mmol) was added. The solution was allowed to warm to rt and stirred for 24 h, diluted with dichloromethane (60 mL) and washed with 2 N aq. HCl solution (15 mL). The organic extract was dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was diluted with EtOAc-ether (25 mL, 1:4) and the solid was filtered and washed with ether (5 mL, 4x), and dried *in vacuo* to obtain the title compound (175 mg, 48%) as a tan solid.

D. 2-Amino-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide

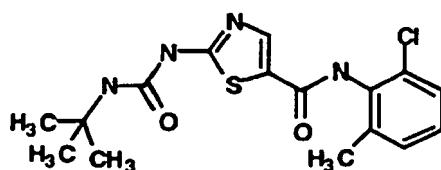
[0221] Compound **315D** was prepared by an analogous method as that of **2**, except using compound **315C** to give the title compound **315D** as a tan solid.

E. 2-[(Cyclopropylcarbonyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide

[0222] A solution of **315D** (50.6 mg, 0.19 mmol) and cyclopropanecarboxylic acid anhydride (302 mg, 1.96 mmol) in dioxane (2 mL) was heated to 93 °C overnight. The mixture was concentrated *in vacuo*, diluted with EtOAc and washed with satd. aq. KHCO<sub>3</sub> solution (2x). The organic extract was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was triturated with ether to obtain the title compound (11 mg, 17%) as a white solid.

Example 316Preparation of 2-[[[(1,1-Dimethylethyl)amino]carbonyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide

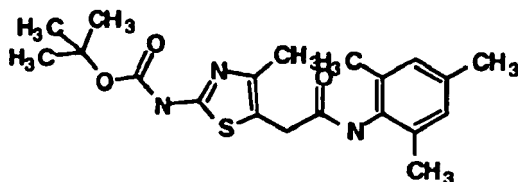
[0223]



[0224] Sodium hydride (19.2 mg, 0.8 mmol) was added to a solution of **315D** (48.3 mg, 0.18 mmol) and *t*-butylisocyanate (41 µL, 0.36 mmol) in THF (5 mL) at 0 °C. After 1 h, the mixture was diluted with EtOAc and washed with cold satd. aq. ammonium chloride solution. The aqueous layer was separated and extracted with EtOAc. The EtOAc extracts were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was purified by automatic preparative HPLC (conditions: YMC S5 ODS A 20 x 100 mm Column, 10 min gradient starting from 10% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.1% TFA) and 90% solvent A (10% MeOH, 90% H<sub>2</sub>O, 0.1% TFA) to 100% solvent B, flow rate 20 mL/min, λ = 220 nm) to obtain the title compound (18 mg, 28%) as an off-white solid.

Example 317Preparation of 2-[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazoleacetamide

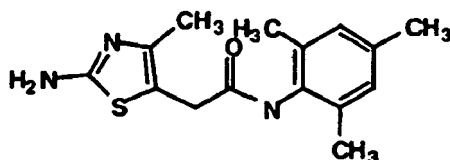
[0225]



Compound **317** was prepared by an analogous method as that of **1**, except using methyl-2-amino-4-methyl-thiazole-5-acetate to give the title compound **317** as an off-white solid.

Example 318Preparation of 2-Amino-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazoleacetamide

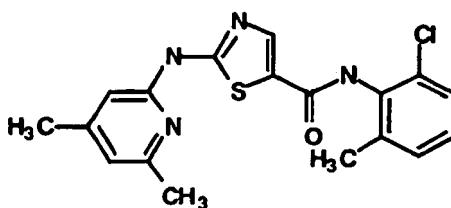
[0227]



Compound **318** was prepared by an analogous method as that of **2**, except using **317** to give the title compound **318** as a light brown solid.

Example 319Preparation of N-(2-Chloro-6-methylphenyl)-2-[(4,6-dimethyl-2-pyridinyl)amino]-5-thiazolecarboxamide

[0229]

A. 2-Bromo-N-(2-chloro-6-methylphenyl)- 5-thiazolecarboxamide

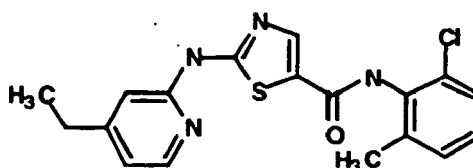
A solution of copper (II) bromide (2.68 g, 12 mmol) in acetonitrile (50 mL) was purged with nitrogen and cooled to 0 °C. t-Butyl nitrite (2 mL, 15 mmol) was added, followed by a solution of compound **315D** (2.68 g, 10 mmol) in acetonitrile (50 mL). The mixture was stirred at rt overnight and concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with satd. aq. NaHCO<sub>3</sub> solution and the precipitate was removed by filtration. The organic extract was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was crystallized from EtOAc/ether/hexanes mixture to obtain the title compound (1.68 g, 51%) as a yellow solid.

B. N-(2-Chloro-6-methylphenyl)-2-[(4,6-dimethyl-2-pyridinyl)amino]-5-thiazolecarboxamide

[0231] 95% Sodium hydride (15 mg) was added to a mixture of **319A** (25 mg, 0.075 mmol) and 4,6-dimethyl-2-aminopyridine (37 mg, 0.302 mmol) in THF (1 mL). The mixture was heated to 60 °C overnight, cooled to rt and diluted with satd. aq. ammonium chloride solution. The mixture was extracted with EtOAc (2x). Organic extracts were combined, washed with water and dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was triturated with ether to obtain the title compound (17.5 mg, 63%) as a tan solid.

Example 320Preparation of N-(2-Chloro-6-methylphenyl)-2-[(4-ethyl-2-pyridinyl)amino]-5-thiazolecarboxamide

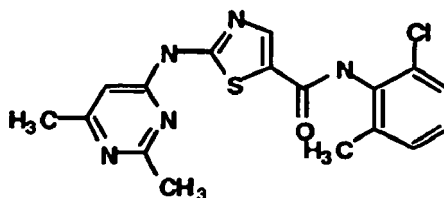
[0232]



[0233] Compound **320** was prepared by an analogous method as that of **319B**, except using 4-ethyl-2-aminopyridine to give the title compound **320**.

Example 321Preparation of N-(2-Chloro-6-methylphenyl)-2-[(2,6-dimethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide

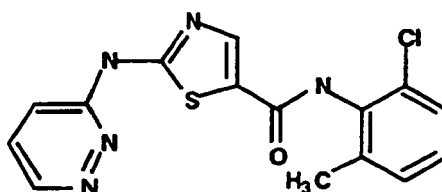
[0234]



[0235] Compound **321** was prepared by an analogous method as that of **319B**, except using 2,6-dimethyl-4-aminopyrimidine to give the title compound **321**.

Example 322Preparation of N-(2-Chloro-6-methylphenyl)-2-(3-pyridazinylamino)-5-thiazolecarboxamide

[0236]



[0237] Compound **322** was prepared by an analogous method as that of **319B**, except using 3-aminopyridazine to give the title compound **322**.

## Examples 323 to 335

## General Procedure

**[0238]** Compounds **323** to **335** were prepared following the procedure described below. Diisopropylethyl amine (60  $\mu$ L, 0.34 mmol) was added to a mixture of amine **144** (31 mg, 0.11 mmol), appropriate carboxylic acid (0.13 mmol), 1-hydroxy-7-azabenzotriazole (19.5 mg, 0.14 mmol), and ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (26.8 mg, 0.14 mmol) in THF (0.4 mL). The mixture was heated in a sealed tube under argon at 50 °C for 24 h. The reaction mixture was diluted with dichloromethane (4 mL) and washed with 1 N aq. HCl solution. The dichloromethane solution was passed through a Varian Mega Bond Elut SCX cation exchange column (prewashed with methanol and equilibrated with acetonitrile-methanol (4:1). The column was eluted sequentially with acetonitrile-methanol (4:1), methanol-2M methanolic ammonia (4:1). Fractions containing the product were combined and concentrated in vacuo. "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballistic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>), flow rate 4 mL/min,  $\lambda$  = 220 nm.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
<b>323</b>		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2-thienyl-carbonyl)amino]-5-thiazolecarboxamide	3.70
<b>324</b>		N-(2-Chloro-6-methylphenyl)-2-[(cyclopropylcarbonyl)amino]-4-methyl-5-thiazolecarboxamide	3.41
<b>325</b>		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2-furanyl-carbonyl)amino]-5-thiazolecarboxamide	3.49
<b>326</b>		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(3-thienylcarbonyl)amino]-5-thiazolecarboxamide	3.71
<b>327</b>		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(3-furanylcarbonyl)amino]-5-thiazolecarboxamide	3.57
<b>328</b>		trans-N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2-phenylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide	4.09
<b>329</b>		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2-methylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide	3.65

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
330		N-(2-Chloro-6-methylphenyl)-2-[(cyclobutylcarbonyl)amino]-4-methyl-5-thiazolecarboxamide	3.63
331		N N-(2-Chloro-6-methylphenyl)-2-[(cyclopentylcarbonyl)amino]-4-methyl-5-thiazolecarboxamide	3.82
332		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2-methyl-1-oxopropyl)amino]-5-thiazolecarboxamide	3.50
333		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(1-oxopentyl)amino]-5-thiazolecarboxamide	3.79
334		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2-methyl-1-oxopentyl)amino]-5-thiazolecarboxamide	3.90
335		2-(Benzoylamino)-N-(2-chloro-6-methylphenyl)-4-methyl-5-thiazolecarboxamide	3.79

Examples 336 to 362*General Procedure*

**[0239]** Compounds **336** to **362** were prepared by an analogous method as that of **323-335**, except using **315D** in place of **144**. The crude products were purified by automatic preparative HPLC (conditions: YMC S5 ODS A 20 x 100 mm Column, 10 min gradient starting from 10% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.1% TFA) and 90% solvent A (10% MeOH, 90% H<sub>2</sub>O, 0.1% TFA) to 100% solvent B, flow rate 20 mL/min,  $\lambda$  = 220 nM to obtain the title compounds **336-362**.

**[0240]** "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballistic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H<sub>2</sub>O 0.2% H<sub>3</sub>PO<sub>4</sub>) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>), flow rate 4 mL/min,  $\lambda$  = 220 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
336		N-(2-Chloro-6-methylphenyl)-2-[(1-oxopropyl)amino]-5-thiazolecarboxamide	3.53

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
337		N-(2-Chloro-6-methylphenyl)-2-[(1-oxobutyl)amino]-5-thiazolecarboxamide	3.61
338		N-(2-Chloro-6-methylphenyl)-2-[(2-ethyl-1-oxobutyl)amino]-5-thiazolecarboxamide	3.54
339		N-(2-Chloro-6-methylphenyl)-2-[[1-phenylcyclo-propyl)carbonyl]amino]-5-thiazolecarboxamide	3.86
340		N-(2-Chloro-6-methylphenyl)-2-[[1-methylcyclo-propyl)carbonyl]amino]-5-thiazolecarboxamide	3.53
341		N-(2-Chloro-6-methylphenyl)-2-[[2,2-dichloro-1-methylcyclo-propyl)carbonyl]amino]-5-thiazolecarboxamide	3.53
342		N-(2-Chloro-6-methylphenyl)-2-[[2-methylcyclo-propyl)carbonyl]amino]-5-thiazolecarboxamide	3.53
343		N-(2-Chloro-6-methylphenyl)-2-[[1-hydroxycyclopropyl)-carbonyl]amino]-5-thiazole-carboxamide	3.58
344		N-(2-Chloro-6-methylphenyl)-2-[[2,2,3,3-tetramethylcyclo-propyl)carbonyl]amino]-5-thiazolecarboxamide	3.69
345		N-(2-Chloro-6-methylphenyl)-2-[[1-cyanocyclopropyl)-carbonyl]amino]-5-thiazole-carboxamide	3.53
346		N-(2-Chloro-6-methylphenyl)-2-[(cyclobutylcarbonyl)amino]-5-thiazolecarboxamide	3.52
347		N-(2-Chloro-6-methylphenyl)-2-[(cyclopentylcarbonyl)amino]-5-thiazolecarboxamide	3.59

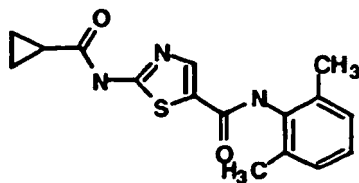
(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
348		N-(2-Chloro-6-methylphenyl)-2-[(cyclohexylcarbonyl)amino]-5-thiazolecarboxamide	3.78
349		N-(2-Chloro-6-methylphenyl)-2-[(phenylacetyl)amino]-5-thiazolecarboxamide	3.62
350		N-(2-Chloro-6-methylphenyl)-2-[(cyclohexylacetyl)amino]-5-thiazolecarboxamide	4.07
351		N-(2-Chloro-6-methylphenyl)-2-[(4-pyridinylacetyl)amino]-5-thiazolecarboxamide	3.75
352		N-(2-Chloro-6-methylphenyl)-2-[[2,5-dimethyl-1H-pyrrol-3-yl]carbonyl]amino]-5-thiazolecarboxamide	3.17
353		N-(2-Chloro-6-methylphenyl)-2-[(2-pyridinylcarbonyl)amino]-5-thiazolecarboxamide	3.07
354		N-(2-Chloro-6-methylphenyl)-2-[(3-pyridinylcarbonyl)amino]-5-thiazolecarboxamide	3.07
355		N-(2-Chloro-6-methylphenyl)-2-[(4-pyridinylcarbonyl)amino]-5-thiazolecarboxamide	3.61
356		N-(2-Chloro-6-methylphenyl)-2-[(3-thienylcarbonyl)amino]-5-thiazolecarboxamide	3.60
357		N-(2-Chloro-6-methylphenyl)-2-[(2-thienylcarbonyl)amino]-5-thiazolecarboxamide	3.61



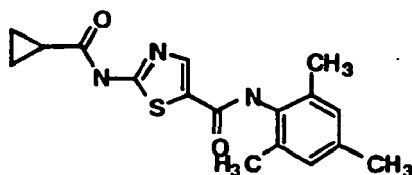
(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
358		N-(2-Chloro-6-methylphenyl)-2-[(2-furanylcarbonyl)amino]-5-thiazolecarboxamide	3.61
359		N-(2-Chloro-6-methylphenyl)-2-[(3-furanylcarbonyl)amino]-5-thiazolecarboxamide	3.69
360		trans-N-(2-Chloro-6-methylphenyl)-2-[[2-(2-phenylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide	3.98
361		N-(2-Chloro-6-methylphenyl)-2-[(2-methyl-1-oxopentyl)amino]-5-thiazolecarboxamide	3.90
362		2-(Benzoylamino)-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	3.61

Example 363Preparation of 2-[(Cyclopropylcarbonyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide**[0241]**

**[0242]** Compound **363** was prepared by an analogous method as that of 315, except using 2,6-dimethylaniline to give the title compound **363**.

Example 364Preparation of 2-[(Cyclopropylcarbonyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide**[0243]**

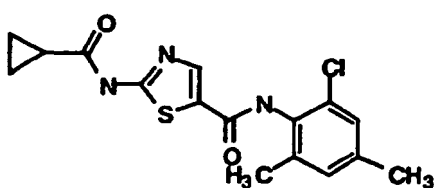


**[0244]** Compound **364** was prepared by an analogous method as that of **315**, except using 2,4, 6-trimethylaniline to give the title compound **364**.

#### Example 365

Preparation of N-(2-Chloro-4,6-dimethylphenyl)-2-[(cyclopropylcarbonyl)amino]-5-thiazolecarboxamide

**[0245]**

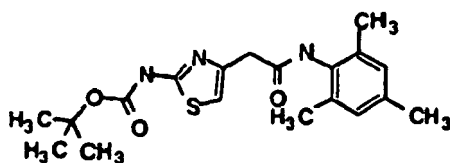


**[0246]** Compound **365** was prepared by an analogous method as that of **315**, except using 2-chloro-4,6-dimethylaniline to give the title compound **365**.

#### Example 366

Preparation of [4-[2-Oxo-2-[(2,4,6-trimethylphenyl)amino]ethyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester

**[0247]**

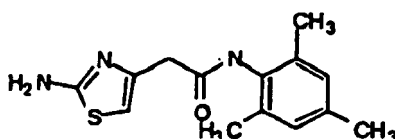


**[0248]** Compound **366** was prepared by an analogous method as that of 1 except, using 2-*tert*-butoxycarbonyloxyamino-thiazole-4-acetic acid to give the title compound **366** as a white solid.

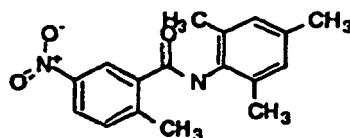
#### Example 367

Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-thiazoleacetamide

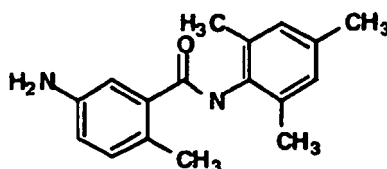
**[0249]**



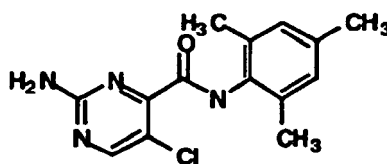
**[0250]** Compound **367** was prepared by an analogous method as that of 4, except using **365** to give the title compound **367** as a white solid.

Example 368Preparation of 2-Methyl-5-nitro-N-(2,4,6-trimethylphenyl)benzamide**[0251]**

**[0252]** Compound 368 is an intermediate and was prepared by an analogous method as that of 3, except using 2-methyl-5-nitrobenzoic acid to give the title compound **368** as a white solid.

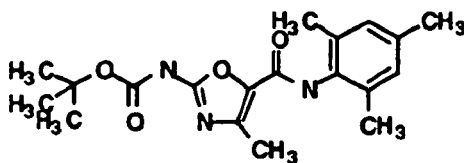
Example 369Preparation of 5-Amino-2-methyl-N-(2,4,6-trimethylphenyl)benzamide**[0253]**

**[0254]** 10% Palladium on charcoal (30 mg) was added to a stirred solution of 368 (149 mg, 0.5 mmol) in EtOAc (50 mL). The reaction flask was equipped with a hydrogen filled balloon via a three-way stopcock. Air inside the flask was evacuated under reduced pressure and the flask filled with hydrogen from the balloon. After 4 h, the catalyst was filtered, washed with EtOAc (5 mL, 5x). The filtrate was concentrated to obtain the title compound (133 mg, 99%) as a white solid.

Example 370Preparation of 2-Amino-5-chloro-N-(2,4,6-trimethylphenyl)-4-pyrimidinecarboxamide**[0255]**

**[0256]** Compound **370** was prepared by an analogous method as that of 3, except using 2-amino-5-chloro-pyrimidine-4-carboxylic acid to give the title compound **370** as a white solid.

Example 371Preparation of [4-Methyl-5-[(2,4,6-trimethylphenyl)amino]carbonyl]-2-oxazolyl]carbamic acid 1,1-dimethylethyl ester**[0257]**

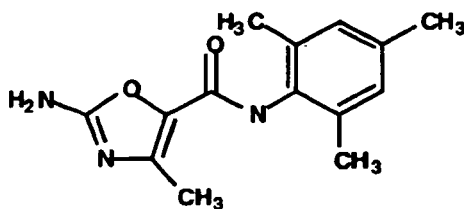


[0258] Compound **371** was prepared by an analogous method as that of **1**, except using 2-*tert*-butoxycarbonyloxyamino-4-methyl-5-oxazolecarboxylic acid to give the title compound **371** as a light yellow foam.

#### Example 372

Preparation of 2-Amino-4-(methyl)-N-(2,4,6-trimethylphenyl)-5-oxazolecarboxamide, trifluoroacetate (1:1)

[0259]

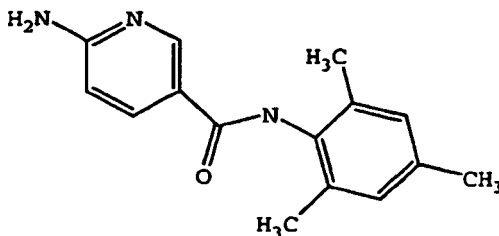


[0260] Compound **372** was prepared by an analogous method as that of **4**, except using **369** to give the title compound **372** as a white solid.

#### Example 373

Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-5-pyridinecarboxamide

[0261]

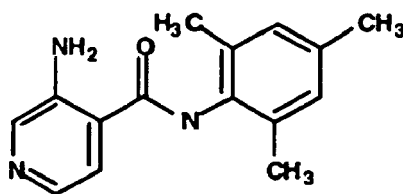


[0262] Compound **373** was prepared by an analogous method as that of **3**, except using 6-aminonicotinic acid to give the title compound **373** as a white solid.

#### Example 374

Preparation 3-Amino-N-(2,4,6-trimethylphenyl)-4-pyridinecarboxamide

[0263]

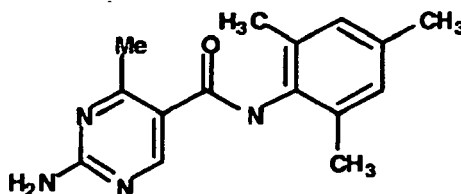


**[0264]** Compound **374** was prepared by an analogous method as that of **3**, except using 3-amino-4-pyridinecarboxylic acid to give the title compound **374** as a white solid.

#### Example 375

Preparation 2-Amino-4-methyl-N-(2,4,6-trimethylphenyl)-5-pyrimidinecarboxamide

**[0265]**

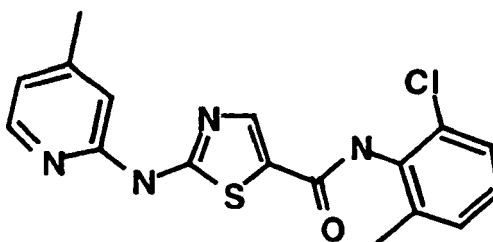


**[0266]** Compound **375** was prepared by an analogous method as that of **3**, except using 2-amino-4-methyl-5-pyrimidinecarboxylic acid to give the title compound **375** as a white solid.

#### Example 376

Preparation of N-(2-Chloro-6-methylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide

**[0267]**

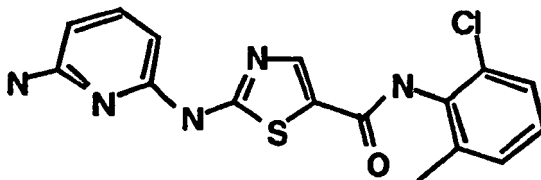


**[0268]** Compound **376** was prepared by an analogous method as that of **319B**, except using 2-amino-4-methyl-pyridine to give the title compound **376** as an off-white solid.

#### Example 377

Preparation of 2-[(6-Amino-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide

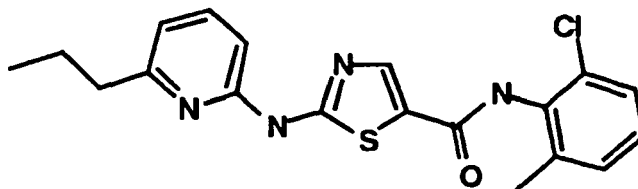
**[0269]**



**[0270]** Compound **377** was prepared by an analogous method as that of **319B**, except using 2,6-diaminopyridine to give the title compound **377** as a light brown solid solid.

Example 378Preparation of N-(2-chloro-6-methylphenyl)-2-[(6-propyl-2-pyridinyl)amino]-5-thiazolecarboxamide

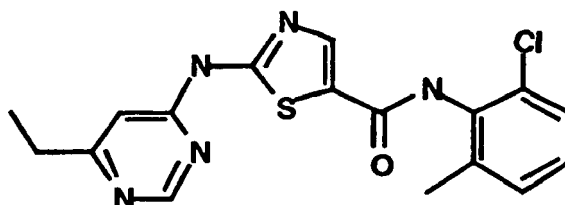
[0271]



Compound **378** was prepared by an analogous method as that of **319B**, except using 2-amino-6-propyl-pyridine to give the title compound **378** as an off-white solid.

Example 379Preparation of N-(2-Chloro-6-methylphenyl)-2-[(6-ethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide

[0273]



Compound **379** was prepared by an analogous method as that of **319B**, except using 4-amino-6-ethyl-pyrimidine to give the title compound **379** as a white solid.

Examples 380 to 409**General Procedure**

Compounds 380 to 409 were prepared by an analogous method as that of 319B. For the following examples 380 to 527 "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballistic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>), flow rate 4 mL/min,  $\lambda$  = 220 nM. Where used, "HPLC Ret Time 'B'" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 33 mm Turbo Column, 2 min gradient starting from 100% solvent A (10% MeOH, 90% H<sub>2</sub>O, 0.1% TFA) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.1% TFA) with 1min at 100% solvent B, flow rate 4 mL/min,  $\lambda$  = 220 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
<b>380</b>		'N-(2-Chloro-6-methylphenyl)-2-(2-pyridinylamino)-5-thiazolecarboxamide	3.337
<b>381</b>		'N-(2-Chloro-6-methylphenyl)-2-[(6-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.61

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
5 382		'N-(2-Chloro-6-methylphenyl)-2-[(5-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.487
10 383		'N-(2-Chloro-6-methylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.293
15 384		'N-(2-Chloro-6-methylphenyl)-2-[(3-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.243
20 385		'2-[(5-Bromo-3-methyl-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	4.17
25 386		'2-[(6-Amino-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.817
30 387		'2-[(5-Bromo-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	4.023
35 388		'N-(2-Chloro-6-methylphenyl)-2-[[3-(phenylmethoxy)-2-pyridinyl]amino]-5-thiazolecarboxamide	4.143
40 389		'N-(2-Chloro-6-methylphenyl)-2-[(5-chloro-2-pyridinyl)amino]-5-thiazolecarboxamide	3.957
45 390		'N-(2-Chloro-6-methylphenyl)-2-[(6-ethyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.867
50 391		'N-(2-Chloro-6-methylphenyl)-2-[(6-propyl-2-pyridinyl)amino]-5-thiazolecarboxamide	4.083
55 392		'2-[(3-Bromo-5-methyl-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	4.077
393		'2-[(2-Amino-3-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.343

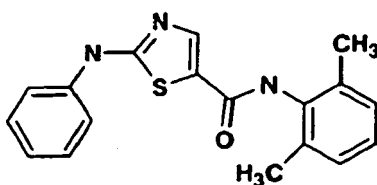
(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
394		'2-[(3-Amino-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.777
395		'N-(2-Chloro-6-methylphenyl)-2-(4-pyridinylamino)-5-thiazolecarboxamide	2.493
396		'N-(2-Chloro-6-methylphenyl)-2-(3-pyridinylamino)-5-thiazolecarboxamide	2.47
397		'N-(2-Chloro-6-methylphenyl)-2-[(6-chloro-3-pyridinyl)amino]-5-thiazolecarboxamide	3.75
398		'N-(2-Chloro-6-methylphenyl)-2-[(2-chloro-3-pyridinyl)amino]-5-thiazolecarboxamide	3.443
399		'N-(2-Chloro-6-methylphenyl)-2-[(6-methoxy-3-pyridinyl)amino]-5-thiazolecarboxamide	3.517
400		'N-(2-Chloro-6-methylphenyl)-2-[(3,5-dimethyl-2-pyrazinyl)amino]-5-thiazolecarboxamide	3.583
401		'N-(2-Chloro-6-methylphenyl)-2-(phenylamino)-5-thiazolecarboxamide	3.697
402		'N-(2-Chloro-6-methylphenyl)-2-[(3-ethylphenyl)amino]-5-thiazolecarboxamide	4.107
403		'N-(2-Chloro-6-methylphenyl)-2-[(3,5-dimethylphenyl)amino]-5-thiazolecarboxamide	3.98
404		'N-(2-Chloro-6-methylphenyl)-2-[(4,6-dimethyl-2-pyrimidinyl)amino]-5-thiazolecarboxamide	3.51
405		'N-(2-Chloro-6-methylphenyl)-2-[(6-ethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide	2.943



(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
406		'N-(2-Chloro-6-methylphenyl)-2-[(6-chloro-2-pyrazinyl)amino]-5-thiazolecarboxamide	3.763
407		'2-[(3-Aminophenyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.633
408		'N-(2-Chloro-6-methylphenyl)-2-[(3-hydroxyphenyl)amino]-5-thiazolecarboxamide	3.337
409		'2-[(3-Bromophenyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	4.12

Example 410Preparation of 'N-(2,6-Dimethylphenyl)-2-(phenylamino)-5-thiazolecarboxamide**[0276]**

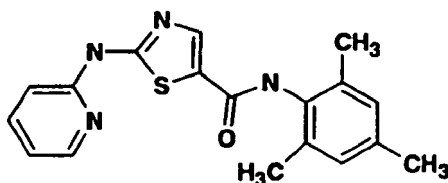
A. [5-[(2,6-dimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

**[0277]** Compound **410A** was prepared by an analogous method as that of **315C**, except using 2,6-dimethylaniline.B. 2-Amino-N-(2,6-dimethylphenyl)- 5-thiazolecarboxamide**[0278]** Compound **410B** was prepared by an analogous method as that of 315D, except using compound **410A**.C. Title Compound**[0279]** The title compound was prepared by an analogous method as that of **319B**, except using compound **410B** and aniline. HPLC Ret. Time 3.69min.Examples 411 to 427**General Procedure****[0280]** Compounds **411** to **427** were prepared by an analogous method as that of **319B**.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
411		'N-(2,6-Dimethylphenyl)-2-(methylphenylamino)-5-thiazolecarboxamide	3.667
412		'N-(2,6-Dimethylphenyl)-2-(2-pyridinylamino)-5-thiazolecarboxamide	3.297
413		'N-(2,6-Dimethylphenyl)-2-[(6-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.587
414		'N-(2,6-Dimethylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.222
415		'N-(2,6-Dimethylphenyl)-2-[(4-ethyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.54
416		'N-(2,6-Dimethylphenyl)-2-[(4,6-dimethyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.543
417		'2-[(6-Amino-2-pyridinyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide	2.807
418		'N-(2,6-Dimethylphenyl)-2-[(6-ethyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.847
419		'N-(2,6-Dimethylphenyl)-2-[(6-propyl-2-pyridinyl)amino]-5-thiazolecarboxamide	4.057
420		'2-1(2-amino-3-pyridinyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide	2.337
421		'2-[(3-Amino-2-pyridinyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide	2.737
422		'2-[(6-Amino-2-methyl-4-pyrimidinyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide	2.71

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
423		'N-(2,6-Dimethylphenyl)-2-[[6-(4-morpholinyl)-3-pyridazinyl]amino]-5-thiazolecarboxamide	2.727
424		'2-[(6-Chloro-3-pyridazinyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide	3.46
425		'N-(2,6-Dimethylphenyl)-2-(3-pyridazinylamino)-5-thiazolecarboxamide	2.973
426		'2-[(3-Aminophenyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide	2.63
427		'2-[(3-Bromophenyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide	4.143

Example 428Preparation of '2-(2-Pyridinylamino)-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide**[0281]**

A. [5-[[2,4,6-trimethylphenyl]amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

**[0282]** Compound **428A** was prepared by an analogous method as that of **315C**, except using 2,4,6-trimethylaniline.B. 2-Amino-N-(2,6-dimethylphenyl)- 5-thiazolecarboxamide**[0283]** Compound **428B** was prepared by an analogous method as that of **315D**, except using compound **428A**.C. Title Compound**[0284]** The title compound was prepared by an analogous method as that of **319B**, except using compound **428B** and 2-aminopyridine. HPLC Ret. Time 3.66min.

## Examples 429 to 443

## General Procedure

5 [0285] Compounds 429 to 443 were prepared by an analogous method as that of 319B.

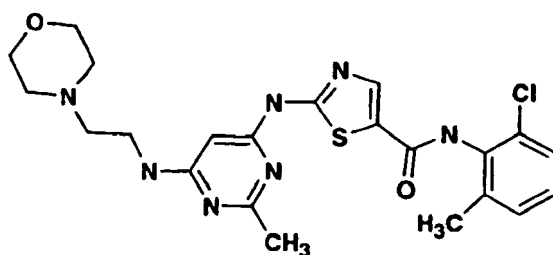
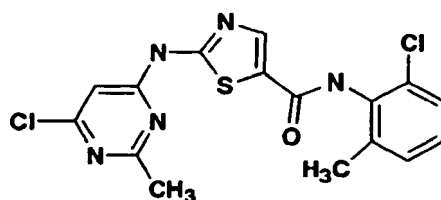
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
429		'2-[(6-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.903
430		'2-[(5-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.8
431		'2-[(4-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.603
432		'2-[(3-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.56
433		'2-[(5-Bromo-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.263
434		'2-[(5-Chloro-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.203
435		'2-[(6-Methoxy-3-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.8
436		'2-[(4-Ethyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.86
437		'2-[(6-Ethyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.127
438		'2-[(6-Chloro-3-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.017
439		'2-[(2,6-Dimethyl-4-pyrimidinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	2.943

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
440		'2-[(4-Methyl-2-pyrimidinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.723
441		'2-(2-Pyrazinylamino)-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.65
442		'2-[(6-Chloro-2-pyrazinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.05
443		'2-[(3,5-Dimethyl-2-pyrazinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.877

Example 444

Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[2-(4-morpholinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide

**[0286]**A**[0287]**

**[0288]** To a suspension of NaH (148mg, 6.17mmol) in THF (20mL) was added a solution of compound **315D** (551mg, 2.06mmol) in THF (10mL) and stirred at RT for 0.5h. A solution of 4,6-dichloro-2-methylpyrimidine (671.6mg, 4.12mmol) in THF (10mL) and stirred at RT overnight. The reaction was quenched with acetic acid and the solvent removed in vacuo. Water and saturated NaHCO<sub>3</sub> were added to the residue and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was removed in vacuo and the crude material purified by column chromatography to give **444A** (494mg).

## B. Title Compound

**[0289]** To compound **444A** (30mg) was added N-(2-aminoethyl)-morpholine (300 $\mu$ L) and the mixture was heated at 80°C for 2h. Water was added to the reaction and the product was collected by filtration. HPLC Ret. Time 2.357min.

## Examples 445 to 461

## General Procedure

**[0290]** Compounds **445** to **461** were prepared by an analogous method as that of **444B** by substituting the appropriate amine.

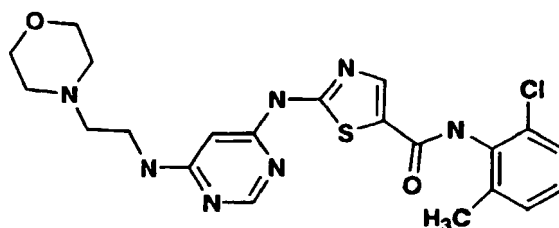
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
<b>445</b>		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[3-(4-morpholinyl)propyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.253
<b>446</b>		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[methyl[3-(methyl-amino)propyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.493
<b>447</b>		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[2-(tetrahydro-2-oxo-1H-imidazol-1-yl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.71
<b>448</b>		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[(2-1H-imidazol-4-ylethyl)amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.303
<b>449</b>		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-(4-morpholinyl)-4-pyrimidinyl]amino]-5-thiazolecarboxamide	3.337
<b>450</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[(2R)-1-ethyl-2-pyrrolidinyl]methyl]amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.703
<b>451</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[(2S)-1-ethyl-2-pyrrolidinyl]methyl]amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.717
<b>452</b>		'2-[[6-[(2S)-2-(Aminocarbonyl)-1-pyrrolidinyl]-2-methyl-4-pyrimidinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.81
<b>453</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-[(2-hydroxyethyl)amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.677

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
454		'N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(hydroxymethyl)-1-piperidyl]-2-methyl-4-pyrimidinyl] amino]-5-thiazolecarboxamide	3.05
455		'N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.717
456		'1-[6-[[5-[[2-(2-Chloro-6-methylphenyl)amino]carbonyl]-2-thiazolyl]amino]-2-methyl-4-pyrimidinyl]-4-piperidinecarboxamide	2.863
457		'N-(2-Chloro-6-methylphenyl)-2-[[6-[2-methyl-6-[(3S)-3-methyl-1-piperazinyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.823
458		'2-[[6-[3-(Acetylamino)-1-pyrrolidinyl]-2-methyl-4-pyrimidinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.78
459		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(1-methyl-2-pyrrolidinyl)ethyl]amino]-2-methyl-4-pyrimidinyl] amino]-5-thiazolecarboxamide	2.383
460		'N-(2-Chloro-6-methylphenyl)-2-[[6-[2-methyl-6-[(5-methyl-2-pyrazinyl)methyl] amino]-4-pyrimidinyl] amino]-5-thiazolecarboxamide	3.027
461		'N-(2-Chloro-6-methylphenyl)-2-[[6-[2-methyl-6-[[2-(1H-1,2,3-triazol-1-yl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.78

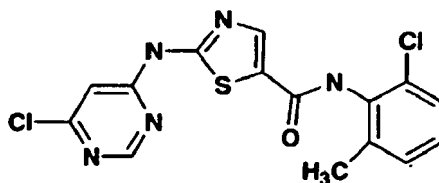
Example 462

Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(4-morpholinyl)ethyl]amino]-4pyrimidinyl]amino]-5-thiazolecarboxamide

**[0291]**

A

[0292]



[0293] Compound **462A** was prepared by an analogous method as that of **444A**, except using 4,6-dichloropyrimidine.

B. Title Compound

[0294] The title compound was prepared by an analogous method as that of **444B**, except using compound **462A** in place of compound **444A**. HPLC Ret. Time 2.553min.

Examples 463 to 472

### General Procedure

[0295] Compounds **463** to **472** were prepared by an analogous method as that of **444B** by substituting the appropriate amine. "HPLC Ret Time 'B'" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 33 mm Turbo Column, 2 min gradient starting from 100% solvent A (10% MeOH, 90% H<sub>2</sub>O, 0.1% TFA) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.1% TFA) with 1min at 100% solvent B, flow rate 4 mL/min,  $\lambda$  = 220 nm.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
<b>463</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(dimethyl-amino)-ethyl]amino]-4-pyrimidinyl]-amino]-5-thiazolecarboxamide	2.527
<b>464</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(tetrahydro-2-oxo-1H-imidazol-1-yl)ethyl]amino]-4-pyrimidinyl] amino]-5-thiazolecarboxamide	2.797
<b>465</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-[methyl [2-(methylamino)-ethyl] amino]-4-pyrimidinyl]-amino]-5-thiazolecarboxamide	1.137 B
<b>466</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(1-methyl-2-pyrrolidinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	1.113 B
<b>467</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(1-pyrrolidinyl)-ethyl] amino]-4-pyrimidinyl]-amino]-5-thiazolecarboxamide	1.150 B
<b>468</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[(1-ethyl-2-pyrrolidinyl)-methyl]amino]-4-pyrimidinyl] amino]-5-thiazolecarboxamide	1.237 B



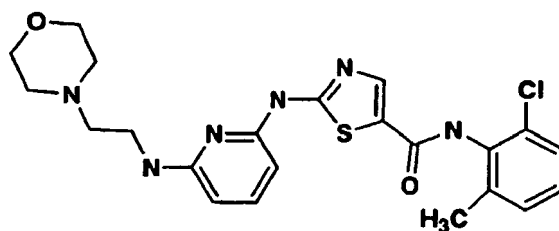
(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
469		'N-(2-Chloro-6-methylphenyl)-2-[[6-[(4-piperidinyl-methyl)amino]-4-pyrimidinyl]amino]-5-thiazole-carboxamide	1.160 B
470		'2-[[6-[[2-(Acetylamino)-ethyl]amino]-4-pyrimidinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazole-carboxamide	2.457 B
471		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(1H-1,2,3-triazol-1-yl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.897
472		'N-(2-Chloro-6-methylphenyl)-2-[[6-(4-morpholinyl)-4-pyrimidinyl]amino]-5-thiazolecarboxamide	3.437

## Example 473

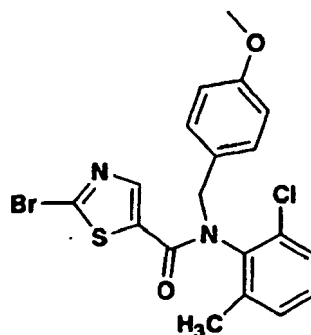
Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(4-morpholinyl)ethyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide

[0296]



A.

[0297]

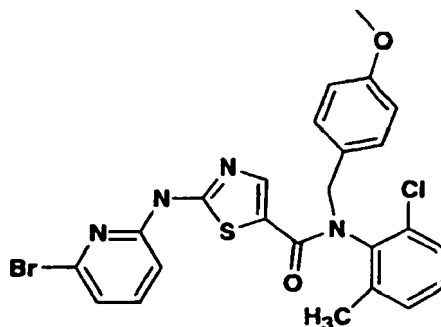


[0298] To a suspension of NaH (2.83g, 118mmol) in DMF (350mL) cooled to 0°C was added compound **319A** (31g, 93.5mmol). The mixture was stirred for 45min at 0°C then Bu<sub>4</sub>NI (6.9g, 18.7mmol) was added followed by addition of 4-methoxy benzylchloride (18g, 115mmol). The reaction was allowed to warm to RT. After stirring overnight at RT the

reaction was quenched slowly with acetic acid then the solvent removed in vacuo. To the residue was added water and neutralized with saturated aqueous  $\text{NaHCO}_3$ . The mixture was extracted 3 times with EtOAc and the combined organic layers washed with water then washed with saturated NaCl solution. The EtOAc layer was concentrated in vacuo and the residue purified by column chromatography to give **473A** (35g).

B

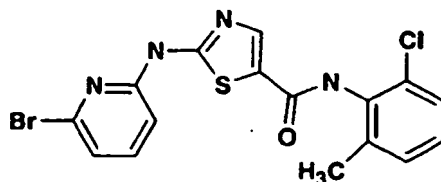
[0299]



[0300] To compound **473A** (0.5g, 1.1mmol) dissolved in THF (50mL) was slowly added NaH (0.13g, 5.5mmol) followed by 2-bromo-6-aminopyridine (0.76g, 4.4mmol). The reaction was heated to reflux for 2h then cooled to RT and quenched with acetic acid. The solvent was removed in vacuo then water and hexane was added and stirred at RT. The solid precipitate was collected by filtration and washed with water and  $\text{Et}_2\text{O}$  to give **473B** (0.48g)

C

[0301]



[0302] To compound **473B** (0.48g) dissolved in TFA (5mL) was added anisole (2mL) followed by triflic acid (1mL). The reaction was stirred at RT for 3h then was slowly added to a rapidly stirred mixture of ice, saturated  $\text{NaHCO}_3$ ,  $\text{Et}_2\text{O}$  and  $\text{CH}_2\text{Cl}_2$ . The mixture was stirred cold for 1h then the solid precipitate was collected by filtration and washed with water followed by  $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$  mixture to give **473C** (0.344g). HPLC Ret. Time 3.85min.

D. Title Compound

[0303] The title compound was prepared by an analogous method as that of **444B**, except using compound **473C** in place of compound **444A**. HPLC Ret. Time 2.80min.

Examples 474 to 480

#### General Procedure

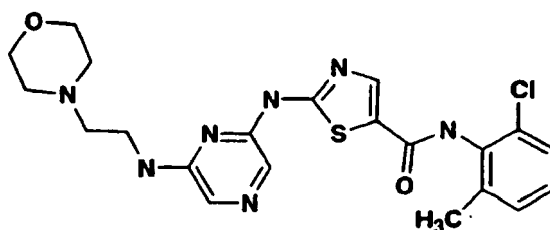
[0304] Compounds **474** to **480** were prepared by an analogous method as that of **473D** by substituting the appropriate amine.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
474		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[3-(4-morpholinyl)-propyl]amino]-2-pyridinyl]-amino]-5-thiazolecarboxamide	2.867
475		'N-(2-Chloro-6-methylphenyl)-2-[[6-[methyl[3-(methyl-amino)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	3.067
476		'N-(2-Chloro-6-methylphenyl)-2-[[6-[(3S)-3-methyl-1-piperazinyl]-2-pyridinyl]-amino]-5-thiazolecarboxamide	2.827
477		'N-(2-Chloro-6-methylphenyl)-2-[[6-[(3-1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]-amino]-5-thiazolecarboxamide	2.83
478		'N-(2-Chloro-6-methylphenyl)-2-[[6-[(2-hydroxyethyl)amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	3.077
479		'N-(2-Chloro-6-methylphenyl)-2-[[6-[(2-1H-imidazol-1-ylethyl)amino]-2-pyridinyl]-amino]-5-thiazolecarboxamide	2.903
480		'N-(2-Chloro-6-methylphenyl)-2-[[6-(4-morpholinyl)-2-pyridinyl] amino]-5-thiazolecarboxamide	3.727

#### Example 481

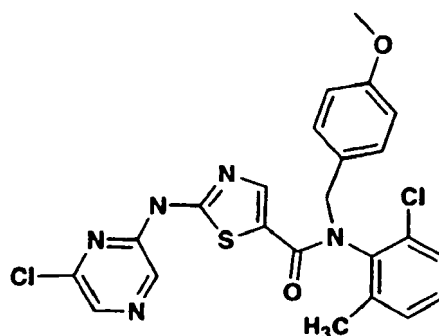
Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(4-morpholinyl)ethyl]amino]-2-pyrazinyl] amino]-5-thiazolecarboxamide

[0305]



A.

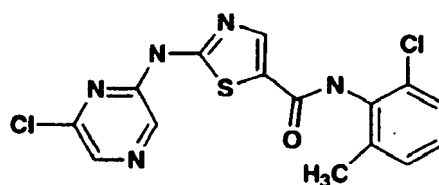
[0306]



**[0307]** Compound **481A** was prepared by an analogous method as that of **473B**, except using compound 2-chloro-6-aminopyrazine in place of compound 2-bromo-6-aminopyridine.

B. (alternate synthesis for compound **406**)

**[0308]**



**[0309]** Compound **406** was prepared by an analogous method as that of **473C**, except using compound **481A** in place of compound **473B**.

C. Title Compound

**[0310]** The title compound was prepared by an analogous method as that of **444B**, except using compound **406** in place of compound **444A**. HPLC Ret. Time 2.69min.

Examples 482 to 486

#### General Procedure

**[0311]** Compounds **482** to **486** were prepared by an analogous method as that of **481C** by substituting the appropriate amine.

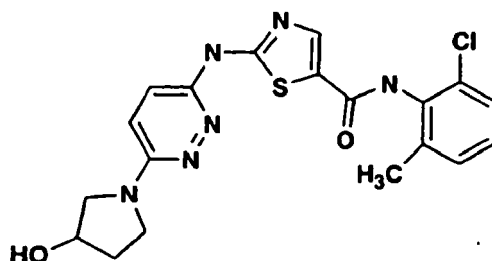
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
<b>482</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[3-(4-morpholinyl)-propyl] amino]-2-pyrazinyl]-amino]-5-thiazolecarboxamide	2.783
<b>483</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-(4-morpholinyl)-2-pyrazinyl] amino] -5-thiazole-carboxamide	3.57
<b>484</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-[(3S)-3-methyl-1-piperazinyl]-2-pyrazinyl]-amino] -5-thiazolecarboxamide	2.743

(continued)

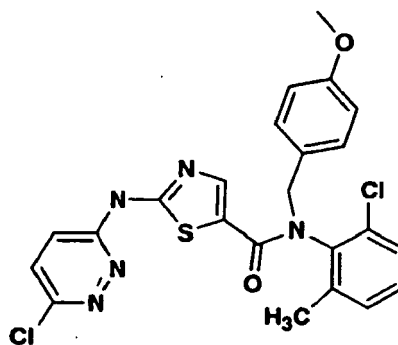
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
485		'N-(2-Chloro-6-methylphenyl)-2-[[6-(3-hydroxy-1-pyrrolidinyl)-2-pyrazinyl]-amino]-5-thiazolecarboxamide	3.327
486		'N-(2-Chloro-6-methylphenyl)-2-[[6-(1H-imidazol-1-yl)-2-pyrazinyl] amino] -5-thiazolecarboxamide	2.68

Example 487

Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-(3-hydroxy-1-pyrrolidinyl)-3-pyridazinyl]amino]-5-thiazolecarboxamide

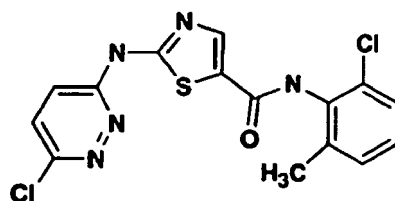
**[0312]**

A.

**[0313]**

**[0314]** Compound **487A** was prepared by an analogous method as that of **473B**, except using compound 3-chloro-5-aminopyridazine in place of compound 2-bromo-6-aminopyridine.

B**[0315]**



[0316] Compound **487B** was prepared by an analogous method as that of **473C**, except using compound **487A** in place of compound **473B**.

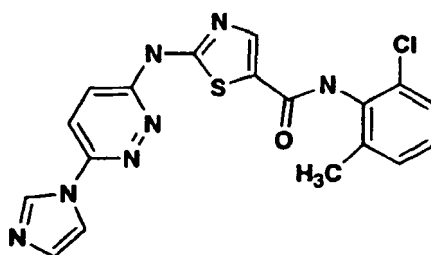
C. Title Compound

[0317] The title compound was prepared by an analogous method as that of **444B**, except using compound **487B** in place of compound **444A**, and 3-hydroxypyrrolidine in place of N-(2-aminoethyl)-morpholine. HPLC Ret. Time 2.493min.

#### Example 488

Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-(1H-imidazol-1-yl)-3-pyridazinyl] amino]-5-thiazolecarboxamide

[0318]

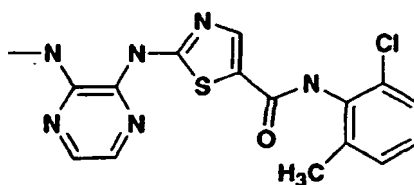


[0319] Compound **488** was prepared by an analogous method as that of **487C**, except using imidazole in place of 3-hydroxypyrrolidine. HPLC Ret. Time 2.61min.

#### Example 489

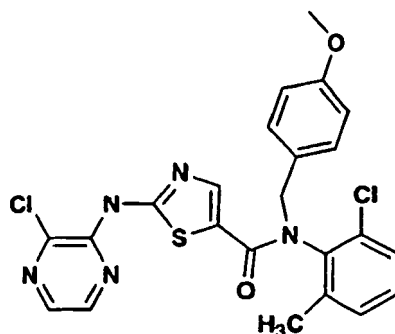
Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[3-(methylamino)-2-pyrazinyl] amino]-5-thiazolecarboxamide

[0320]



A.

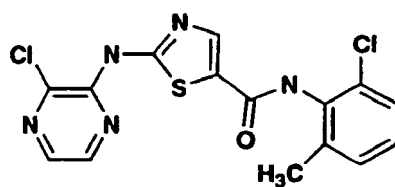
[0321]



[0322] Compound **489A** was prepared by an analogous method as that of **473B**, except using compound 2-chloro-3-aminopyrazine in place of compound 2-bromo-6-aminopyridine.

B

[0323]



[0324] Compound **489B** was prepared by an analogous method as that of **473C**, except using compound **489A** in place of compound **473B**.

C. Title Compound

[0325] The title compound was prepared by an analogous method as that of **444B**, except using compound **489B** in place of compound **444A**, and using methylamine in place of N-(2-aminoethyl)-morpholine. HPLC Ret. Time 2.81min.

Examples 490 to 494

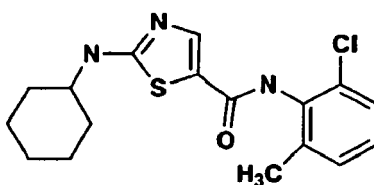
#### General Procedure

[0326] Compounds **490** to **494** were prepared by an analogous method as that of **489C** by substituting the appropriate amine.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
<b>490</b>		'N-(2-Chloro-6-methylphenyl)-2-[[3-(3-hydroxy-1-pyrrolidinyl)-2-pyrazinyl]amino]-5-thiazolecarboxamide	2.82
<b>491</b>		'N-(2-Chloro-6-methylphenyl)-2-[[3-(cyclopropylamino)-2-pyrazinyl]amino]-5-thiazolecarboxamide	2.94
<b>492</b>		'N-(2-Chloro-6-methylphenyl)-2-[[3-(4-morpholinyl)-2-pyrazinyl]amino]-5-thiazolecarboxamide	3.643

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
493		'N-(2-Chloro-6-methylphenyl)-2-[[[3-[[2-(4-morpholinyl)ethyl]amino]-2-pyrazinyl]amino]-5-thiazolecarboxamide	2.72
494		'2-[[[3-[[2-(Acetylamino)ethyl]amino]-2-pyrazinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.933

Example 495Preparation of 'N-(2-Chloro-6-methylphenyl)-2-(Cyclohexylamino)-5-thiazolecarboxamide**[0327]**

**[0328]** Compound **495** was prepared by an analogous method as that of **444B**, except using compound **319A** in place of compound **444A**, and using cyclohexylamine in place of N-(2-aminoethyl)-morpholine. HPLC Ret. Time 3.547 min.

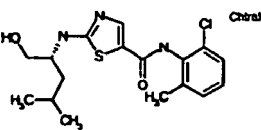
Examples 496 to 500**General Procedure**

**[0329]** Compounds **496** to **500** were prepared by an analogous method as that of **495** by substituting the appropriate amine.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
496		'N-(2-Chloro-6-methylphenyl)-2-(methylamino)-5-thiazolecarboxamide	2.357
497		'N-(2-Chloro-6-methylphenyl)-2-(cyclopropylamino)-5-thiazolecarboxamide	2.887
498		'N-(2-Chloro-6-methylphenyl)-2-[(phenylmethyl)amino]-5-thiazolecarboxamide	3.500
499		'2-[[[2-(Acetylamino)ethyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.483



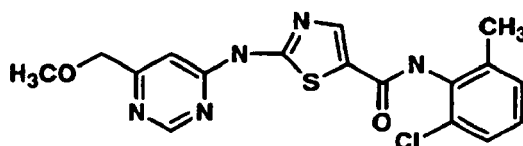
(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
500		'N-(2-Chloro-6-methylphenyl)-2-[[[(1R)-1-(hydroxymethyl)-3-methylbutyl]amino]-5-thiazolecarboxamide	3.407

## Example 501

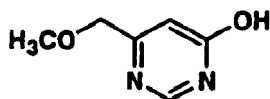
Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-(methoxymethyl)-4-pyrimidinyl]amino]-5-thiazolecarboxamide

## [0330]



A

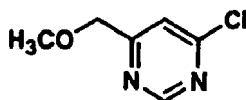
## [0331]



**[0332]** To the mixture of methyl 4-methoxyacetoacetate (14.6 g, 0.1 mol) and formamidine hydrogen chloride salt (16.1 g, 0.2 mol) in 70 mL of dry MeOH was added a 25% solution of sodium methoxide (70 mL, 0.3 mol) in MeOH portionwise. A white precipitate was formed immediately. The reaction mixture was stirred at room temperature for 1.0 hr. Acetic acid (28.6 mL, 0.5 mol) was added and the reaction mixture was concentrated in vacuo. Water was added to the residue and the mixture was supersaturated with NaCl and extracted with EtOAc (x5). Combined extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to give 8.13 g of compound **501A** as a yellow solid.

B

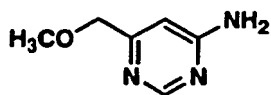
## [0333]



**[0334]** The mixture of compound **501A** (5.3 g, 37.8 mmol) and POCl<sub>3</sub> (40 mL) was heated to reflux for 2.0 hrs. Concentration in vacuo and the residue was poured into a mixture of ice-CH<sub>2</sub>Cl<sub>2</sub>. The pH was adjusted to 6.5 to 7 using concentrated NH<sub>4</sub>OH. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (x3) and combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration in vacuo followed by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub> EtOAc: 9:1) on silica gel gave 5.33 g of compound **501B** as a pale yellow oil.

C

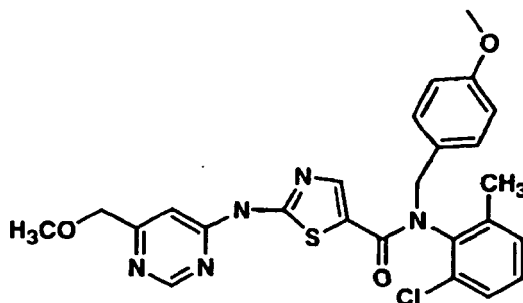
## [0335]



**[0336]** The mixture of compound **501B** (3.2 g, 20 mmol) and  $\text{NH}_4\text{OH}$  (50 mL) was heated to 85.C in a pressure tube for 3.0 hrs. After cooled to room temperature, the reaction mixture was concentrated in vacuo and the residue was triturated with ether to give 2.81 g of compound 501C as a pale yellow solid.

D

**[0337]**



**[0338]** Compound **501D** was prepared from compound 501C by a method analogous to that used for the preparation of compound **473B**.

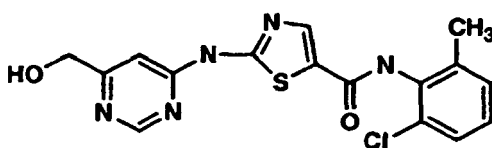
E Title Compound

**[0339]** The title compound was prepared from compound **501D** by a method analogous to that used for the preparation of compound **473C**. HPLC Retention time = 3.25 min.

#### Example 502

Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-((hydroxymethyl)amino)-4-pyrimidinyl]amino]-5-thiazolecarboxamide

**[0340]**

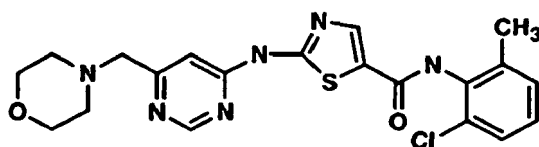


**[0341]** To a solution of compound **501** (56 mg, 0.144 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (3.0 mL) cooled at 0.C was added neat  $\text{BBr}_3$  (0.054 mL, 0.574 mmol). The mixture was stirred for 1.0 hr at ambient temperature. MeOH was added slowly with care at 0.C and the resulting mixture was concentrated in vacuo. Water was added to the residue and pH was adjusted to 7 with Sat'd  $\text{NaHCO}_3$ . The white precipitate was collected by filtration, rinsed with water/ether and dried under high vacuum to give 52 mg of Compound **502** as an off white solid. HPLC Retention time = 2.84 min.

#### Example 503

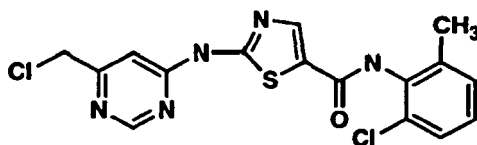
Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-(4-morpholinylmethyl)-4-pyrimidinyl]amino]-5-thiazolecarboxamide

**[0342]**



A

[0343]



[0344] To a suspension of compound **502** (44.2 mg, 0.118 mmol) in 0.5 mL of dry  $\text{CH}_2\text{Cl}_2$  was added thionyl chloride (0.086 mL, 1.18 mmol). The reaction mixture was stirred for 5.0 hrs. Concentration in vacuo and the residue was azeotropic evaporated with  $\text{CH}_2\text{Cl}_2$  to give 56 mg of **503** as an yellow solid.

B Title Compound

[0345] The mixture of compound **503A** (20 mg), morpholine (0.014 mL) and diisopropylethyl amine (0.09 mL) in 0.5 mL of dry dioxane was heated to 85.C for 4.0 hrs. Concentration in vacuo followed by flash chromatography ( $\text{CH}_2\text{Cl}_2$ -MeOH- $\text{NH}_4\text{OH}$ : 95:5:0.5) on silica gel gave 15 mg of title compound as an off-white solid. HPLC Retention time = 2.52 min.

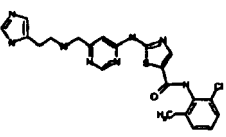
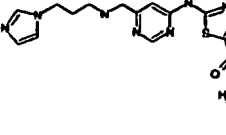
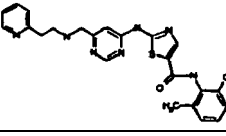
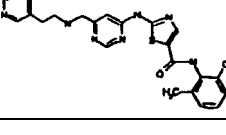
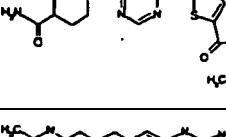
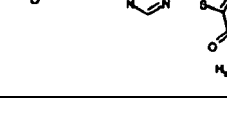
## Examples 504 to 513

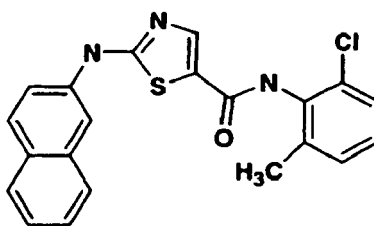
## General Procedure

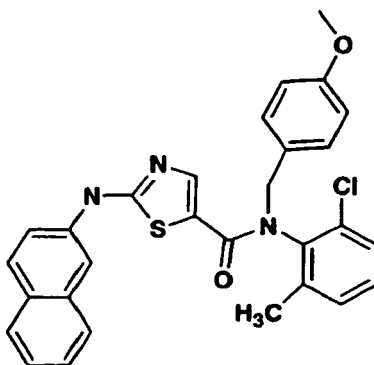
[0346] Compounds **504** to **513** were prepared from **503A** by a route analogous to that used for the preparation of **503**. The compounds of these examples have the structure:

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
<b>504</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[2-(dimethylamino)ethyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.083
<b>505</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[2-(4-morpholinyl)ethyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.593
<b>506</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[3-(4-morpholinyl)propyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.163
<b>507</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[3-(2-oxo-1-pyrrolidinyl)propyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.693

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
508		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[(2-1H-imidazol-4-ylethyl)amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.143
509		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[(3-1H-imidazol-1-ylpropyl)amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	1.103 B
510		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[(2-(2-pyridinyl)ethyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	1.113 B
511		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[(2-(3-pyridinyl)ethyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	1.117 B
512		'1-[[6-[[5-[[[(2-Chloro-6-methylphenyl)amino]carbonyl]-2-thiazolyl]amino]-4-pyrimidinyl]methyl]-4-piperidinecarboxamide	1.207 B
513		'2-[[6-[[[2-(Acetylamino)ethyl]amino]methyl]-4-pyrimidinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	1.193 B

Example 514Preparation of 'N-(2-Chloro-6-methylphenyl)-2-(2-naphthalenylamino)-5-thiazolecarboxamide**[0347]**A**[0348]**



[0349] Compound **514A** was prepared from **473A** by an analogous method as that of **473B**, except using 2-aminonaphthalene in place of 2-bromo-6-aminopyridine.

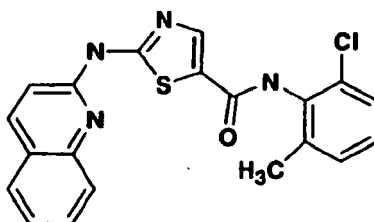
B. Title Compound

[0350] The title compound was prepared by an analogous method as that of **473C**, except using compound **514A** in place of compound **473B**. HPLC Ret. Time 4.11min.

#### Example 515

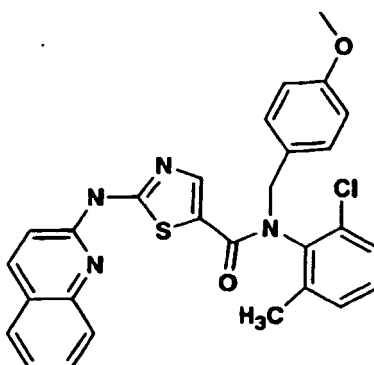
Preparation of 'N-(2-Chloro-6-methylphenyl)-2-(2-quinolinylamino)-5-thiazolecarboxamide

[0351]



A

[0352]



[0353] Compound **515A** was prepared from **473A** by an analogous method as that of **473B**, except using 2-aminoquinoline in place of 2-bromo-6-aminopyridine.

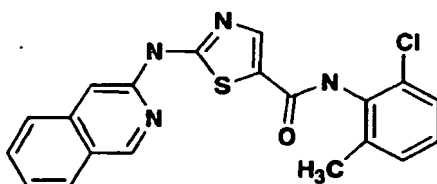
## B. Title Compound

**[0354]** The title compound was prepared by an analogous method as that of **473C**, except using compound **515A** in place of compound **473B**. HPLC Ret. Time 3.94min.

## Example 516

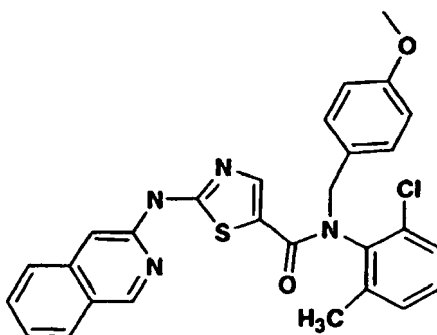
Preparation of 'N-(2-Chloro-6-methylphenyl)-2-(3-isoquinolinylamino)-5-thiazolecarboxamide

**[0355]**



A

**[0356]**



**[0357]** Compound **516A** was prepared from **473A** by an analogous method as that of **473B**, except using 3-aminoisoquinoline in place of 2-bromo-6-aminopyridine.

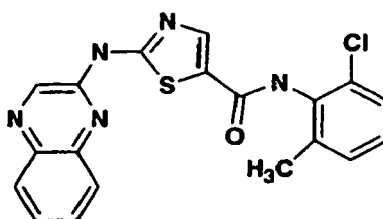
## B. Title Compound

**[0358]** The title compound was prepared by an analogous method as that of **473C**, except using compound **516A** in place of compound **473B**. HPLC Ret. Time 3.94min.

## Example 517

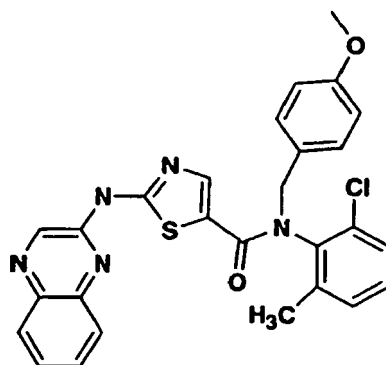
Preparation of 'N-(2-Chloro-6-methylphenyl)-2-(2-quinoxalinyloxy)-5-thiazolecarboxamide

**[0359]**



A

[0360]



[0361] Compound **517A** was prepared from **473A** by an analogous method as that of **473B**, except using 2-amino-quinoline in place of 2-bromo-6-aminopyridine.

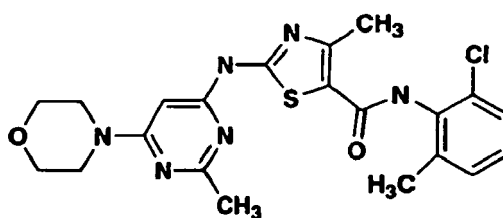
B. Title Compound

[0362] The title compound was prepared by an analogous method as that of **473C**, except using compound **517A** in place of compound **473B**. HPLC Ret. Time 3.927min.

Example 518

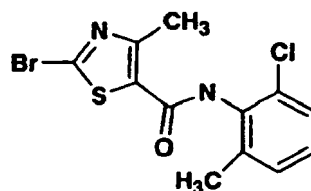
Preparation of 'N-(2-Chloro-6-methylphenyl)-4-methyl-2-[[2-methyl-6-(4-morpholinyl)-4-pyrimidinyl]amino]-5-thiazole-carboxamide

[0363]



A

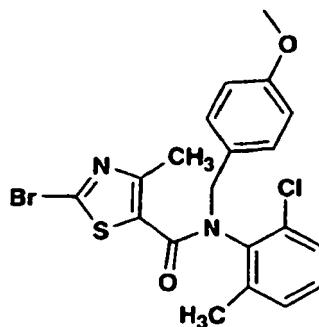
[0364]



[0365] Compound **518A** was prepared from **144** by an analogous method as that of **319A**.

B

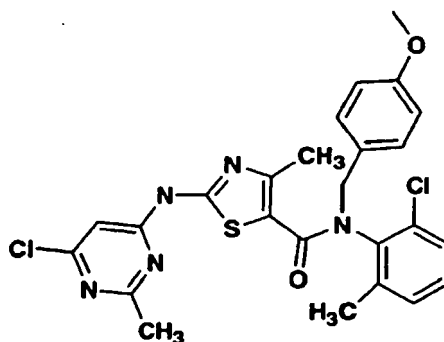
[0366]



[0367] Compound **518B** was prepared by an analogous method as that of **473A**, except using **518A** in place of **319A**.

C

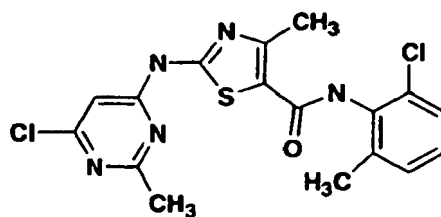
[0368]



[0369] Compound **518C** was prepared by an analogous method as that of **473B**, except using **518B** in place of **473A**, and 4-amino-6-chloro-2-methylpyrimidine in place of 2-amino-6-bromopyridine.

D

[0370]



[0371] Compound **518D** was prepared by an analogous method as that of **473C**, except using **518C** in place of **473B**.

E. Title Compound

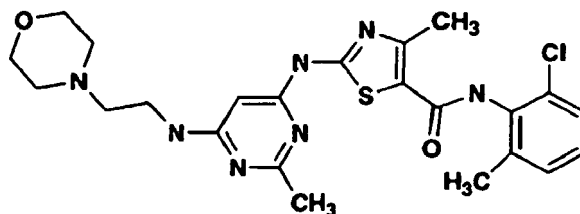
[0372] The title compound was prepared by an analogous method as that of **444B**, except using compound **518D** in place of compound **444A**, and morpholine in place of N-(2-aminoethyl)-morpholine. HPLC Ret. Time 3.397min.



## Example 519

Preparation of 'N-(2-Chloro-6-methylphenyl)-4-methyl-2-[[2-methyl-6-[[2-(4-morpholinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide

[0373]

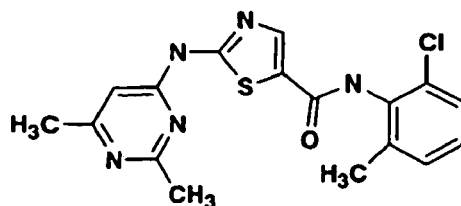


[0374] Compound **519** was prepared by an analogous method as that of **518E**, except using N-(2-aminoethyl)-morpholine in place of morpholine. HPLC Ret. Time 2.493min.

## Example 520

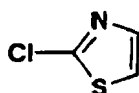
Alternative preparation of compound **321**

[0375]



A

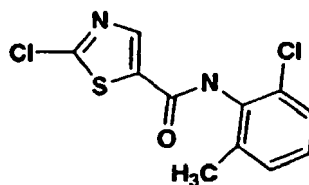
[0376]



[0377] Compound **520A** was prepared from 2-aminothiazole according to the procedure described in UK Patent Application GB 2323595A.

B

[0378]

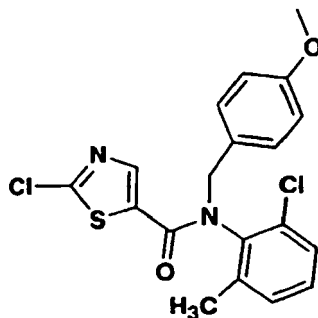


[0379] To a solution of compound **520A** (480 mg, 4.0 mmol) in dry THF (10 mL) cooled at -78.C was added a 2.5M

solution of n-BuLi (1.68 mL, 4.2 mmol) in hexane dropwise via a syringe while kept the internal temperature below -75.C. Upon completion of addition, a beige suspension was obtained. The reaction mixture was stirred for 15 min at -78.C. A solution of 2-chloro-6-methyl phenyl isocyanate (0.6 mL, 4.4 mmol) in 5 mL of dry THF was added and the reaction mixture was stirred for an additional 2.0 hrs at -78.C. Saturated aq. NH<sub>4</sub>Cl solution (10 mL) was added, the mixture was partitioned between EtOAc-water and extracted with EtOAc (x2). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentration in vacuo to give, after recrystallization from EtOAc-hexane, 0.99 g of title compound as a pale yellow crystalline material.

C

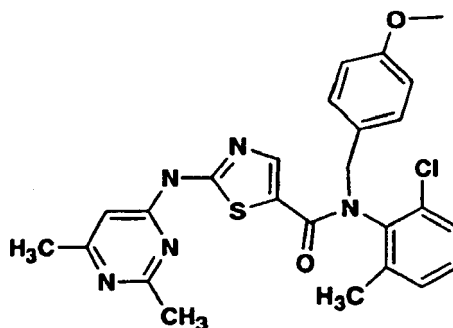
[0380]



Compound **520C** was prepared by a method analogous to that used for the preparation of compound **473A**, using **520B** in place of **319A**.

D

[0382]



Compound **520D** was prepared from compound **520C** by a method analogous to that used for the preparation of compound **473B**.

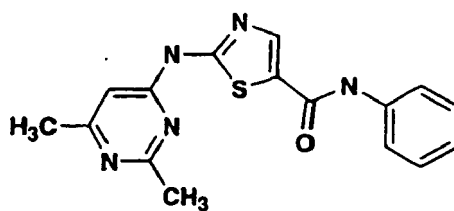
E. Title Compound

Compound **321** was prepared by a method analogous to that used for the preparation of compound **473C**.

#### Example 521

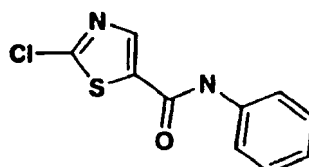
Preparation of '2-[(2,6-Dimethyl-4-pyrimidinyl)aminol-N-phenyl-5-thiazolecarboxamide

[0385]



A

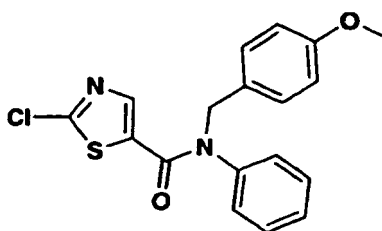
[0386]



[0387] Compound **521A** was prepared by an analogous method as that of **520B**, except using phenylisocyanate in place of 2-chloro-6-methylphenylisocyanate.

B

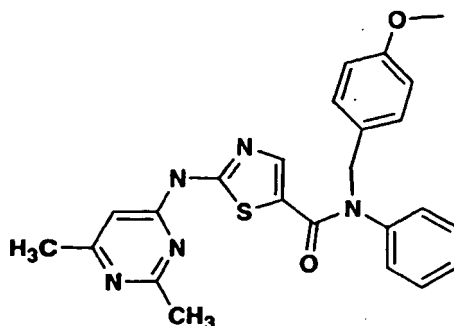
[0388]



[0389] Compound **521B** was prepared by a method analogous to that used for the preparation of compound **473A**, using **521A** in place of **319A**.

C

[0390]



[0391] Compound **521C** was prepared from compound **521B** by a method analogous to that used for the preparation of compound **473B**.

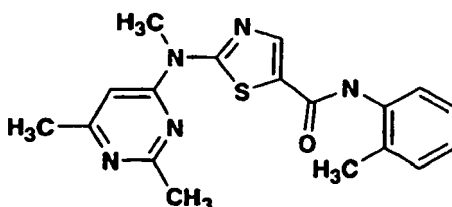
D Title Compound

**[0392]** The title compound was prepared by a method analogous to that used for the preparation of compound **473C**.  
HPLC Ret. Time 1.3 min method B

Example 522

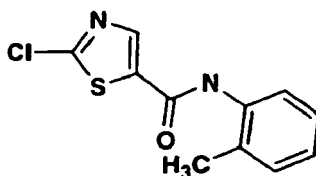
Preparation of '2-[(2,6-Dimethyl-4-pyrimidinyl)methylamino]-N-(2-methylphenyl)-5-thiazolecarboxamide

**[0393]**



A

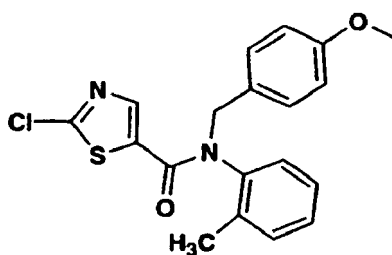
**[0394]**



**[0395]** Compound **522A** was prepared by an analogous method as that of **520B**, except using 2-methylphenylisocyanate in place of 2-chloro-6-methylphenylisocyanate.

B

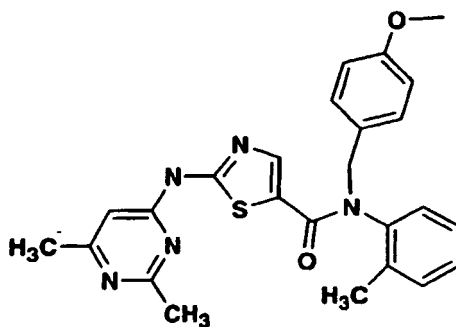
**[0396]**



**[0397]** Compound **522B** was prepared by a method analogous to that used for the preparation of compound **473A**, using **522A** in place of **319A**.

C

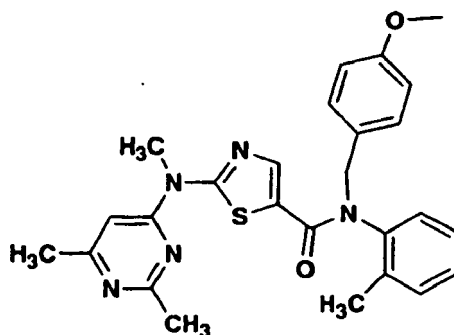
**[0398]**



[0399] Compound **522C** was prepared from compound **522B** by a method analogous to that used for the preparation of compound **473B**.

D

[0400]



[0401] Sodium hydride (60% in oil; 40 mg; 1 mmol) was added to a solution of compound **522C** (280 mg; 0.61 mmol) in 2 ml of DMF at room temp. After stirring 30 minutes, iodomethane (0.2 ml; 3 mmol) was added and the reaction was stirred 4 hr. After the reaction mixture was partitioned between ethyl acetate (50 ml) and water (50 ml), the organic layer was washed with water (2 x 50 ml) and brine (50 ml). Drying ( $\text{MgSO}_4$ ) and concentration afforded an oil that was chromatographed on a 2.5 x 15 cm silica gel column using 50-75% ethyl acetate/hexane. The pure fractions were concentrated and the residue was crystallized from ethyl acetate/hexane to afford 100 mg of **522D** as a light yellow solid.

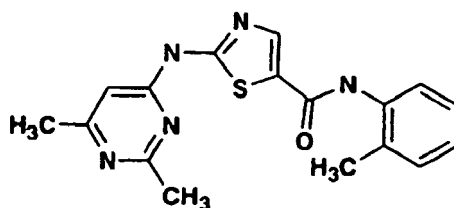
E Title Compound

[0402] The title compound was prepared by a method analogous to that used for the preparation of compound **473C**. HPLC Ret. Time 1.21 min method B

#### Example 523

Preparation of '2-[(2,6-Dimethyl-4-pyrimidinyl)amino]-N-(2-methylphenyl)-5-thiazolecarboxamide

[0403]



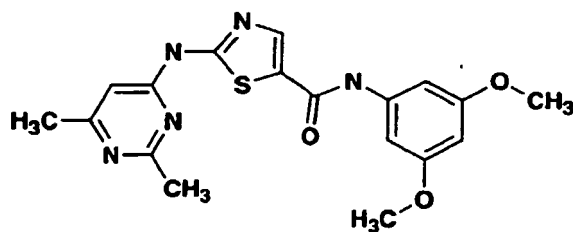
[0404] Compound **523** was prepared by a method analogous to that used for the preparation of compound **473C**,

except using compound **522C** in place of **473B**. HPLC Ret. Time 1.24 min method B

#### Example 524

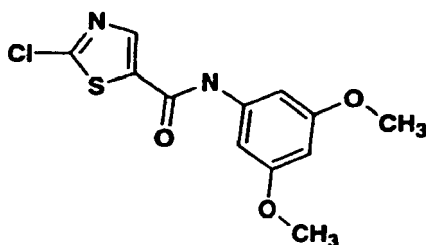
Preparation of 'N-(3,5-Dimethoxyphenyl)-2-[(2,6-dimethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide

[0405]



A

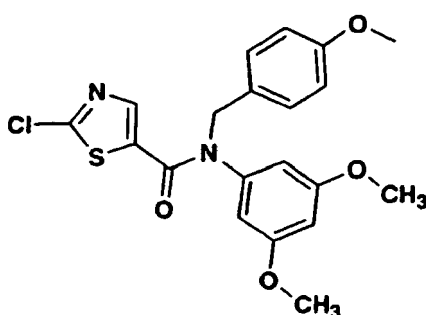
[0406]



[0407] Compound **524A** was prepared by an analogous method as that of **520B**, except using 3,5-dimethoxyphenyl-isocyanate in place of 2-chloro-6-methylphenylisocyanate.

B

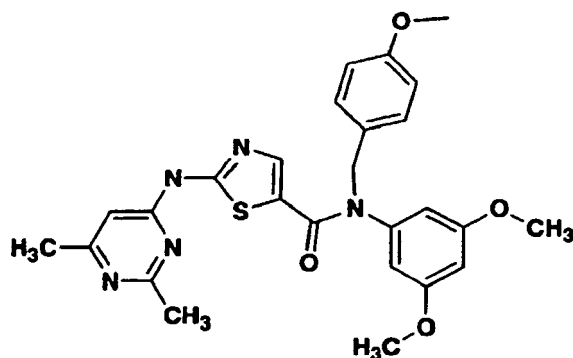
[0408]



[0409] Compound **524B** was prepared by a method analogous to that used for the preparation of compound **473A**, using **524A** in place of **319A**.

C

[0410]



[0411] Compound **524C** was prepared from compound **524B** by a method analogous to that used for the preparation of compound **473B**.

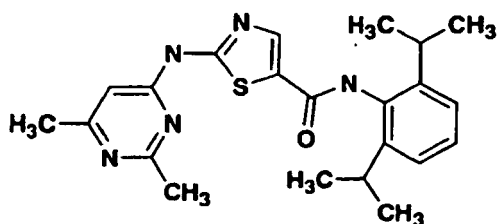
D Title Compound

[0412] The title compound was prepared by a method analogous to that used for the preparation of compound **473C**, except using compound **524C** in place of compound **473B** HPLC Ret. Time 1.28 min method B

#### Example 525

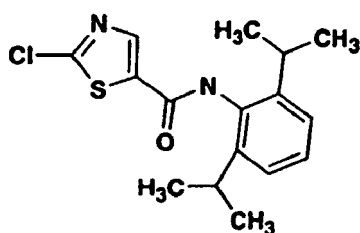
Preparation of N'-[2,6-Bis(1-methylethyl)phenyl]-2-[(2,6-dimethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide

[0413]



A

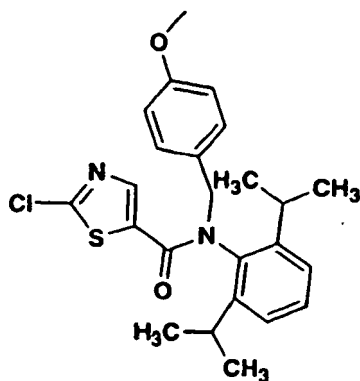
[0414]



[0415] Compound **525A** was prepared by an analogous method as that of **520B**, except using 2,2-diisopropylphenylisocyanate in place of 2-chloro-6-methylphenylisocyanate.

B

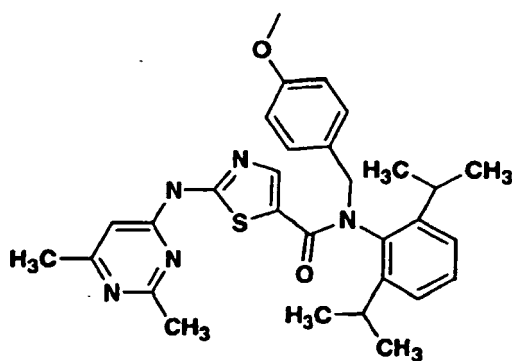
[0416]



[0417] Compound **525B** was prepared by a method analogous to that used for the preparation of compound **473A**, using **525A** in place of **319A**.

C

[0418]



[0419] Compound **525C** was prepared from compound **525B** by a method analogous to that used for the preparation of compound **473B**.

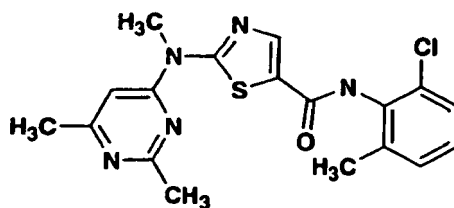
D Title Compound

[0420] The title compound was prepared by a method analogous to that used for the preparation of compound **473C**, except using compound **525C** in place of compound **473B**. HPLC Ret. Time 1.6 min method B

#### Example 526

Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[(2,6-dimethyl-4-pyrimidinyl)methylamino]5-thiazolecarboxamide

[0421]



[0422] A mixture of compound **321** (110 mg; 0.29 mmol), potassium carbonate (138 mg; 1 mmol) and iodomethane (0.06 ml; 1 mmol) in DMF was stirred 2 hr at room temperature. After the reaction mixture was partitioned between ethyl

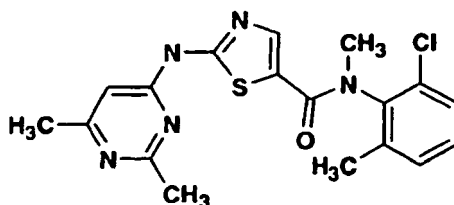


acetate (25 ml) and water (25 ml), the organic layer was washed with water (2 x 25 ml) and brine (25 ml). Drying (MgSO<sub>4</sub>) and concentration afforded an oil that was chromatographed on a 2.5 x 15 cm silica gel column using 1-4% MeOH/CH<sub>2</sub>Cl<sub>2</sub> and the fractions containing compound **526** were collected to give 20mg of product. HPLC Ret. Time 1.3min method B.

#### Example 527

Preparation of N-(2-Chloro-6-methylphenyl)-2-[(2,6-dimethyl-4-pyrimidinyl)amino]-N-methyl-5-thiazolecarboxamide

[0423]

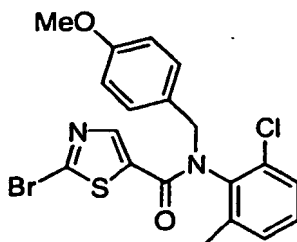


[0424] Compound **527** was prepared by a method analogous to that used for the preparation of compound **526**, except the fractions containing compound **527** were collected to give 60mg of product. HPLC Ret. Time 1.23 min method B

#### Example 528

Preparation of 2-Bromo-N,N-(2-chloro-6-methylphenyl)-(4-methoxybenzyl)-5-thiazolecarboxamide

[0425]

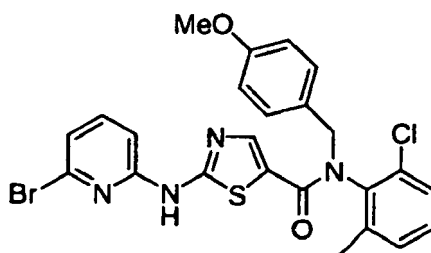


[0426] To a cooled (0 °C) THF solution of 2-chloro-6-methyl aniline (2.86 mL, 23.3 mmol, 1.10 equiv) was added dropwise a 1.0 M solution of lithium bis(trimethylsilyl)amide (42.2 mL, 42.2 mmol, 2.00 equiv) via syringe. The homogeneous solution was allowed to stir for 5 minutes, and then a THF solution of ethyl 2-bromo-5-thiazolecarboxylate (5.00 g, 21.1 mmol, 1.00 equiv, prepared in a manner analogous to compound **319A**) was added via cannula. The solution was allowed to stir for 15 minutes until TLC analysis showed no remaining starting material. To the reaction was then added 4-methoxybenzyl chloride (7.15 mL, 52.7 mmol, 2.5 equiv), followed by a catalytic amount of tetrabutylammonium iodide (1.56 g, 4.22 mmol, 0.20 equiv). The homogeneous mixture was allowed to stir overnight at ambient temperature and then concentrated in vacuo. The residue was partitioned between ethyl acetate and water, and the organic extracts were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and removal of solvent, the product was purified by flash chromatography (10-20% ethyl acetate in hexanes) to afford the title compound as a tan solid (47%).

#### Example 529

Preparation of N,N-(2-Chloro-6-methylphenyl)-(4-methoxybenzyl)-2-[(6-bromo-2-pyridinyl)amino]-5-thiazolecarboxamide

[0427]

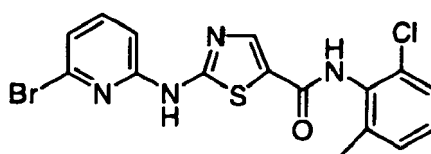


**[0428]** Compound **529** was prepared in an analogous manner to **319B**, except using **528** and 6-bromo-2-aminopyridine as the reactants.

#### Example 530

Preparation of N-(2-Chloro-6-methylphenyl)-2-[(6-bromo-2-pyridinyl)amino]-5-thiazolecarboxamide

**[0429]**



**[0430]** Compound **529** (0.500 g, 0.919 mmol, 1.00 equiv) was dissolved in 5 mL trifluoroacetic acid and charged at ambient temperature with 2 mL anisole followed by 1 mL trifluoromethanesulfonic acid. The dark red homogeneous solution was allowed to stir overnight, and then quenched by carefully pouring the solution into an ice/sodium bicarbonate mixture. A white solid was filtered off and washed sequentially with water, 1:1 hexane/ether, and ether to afford the title compound (41%).

#### Examples 531-538

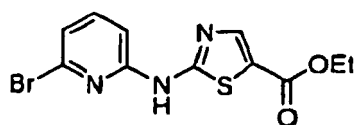
##### General Procedure

**[0431]** Compounds **531** to **538** were prepared to the general procedure described below. A 1-dram vial was charged with **530** and excess amine and heated to 90 °C overnight. The residue was then purified by reverse phase HPLC to afford the pure compound. For the following examples 531 to 555 "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC ODS-A C18 S7 3.0 x 50 mm, 2 min gradient starting from 100% solvent A (10% MeOH, 90% H<sub>2</sub>O, 0.1% TFA) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.1% TFA), flow rate 5 mL/min, λ = 220 nm.

EX. NO.	Compound Structure	Compound Name	HPLC Ret time (min)
<b>531</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-furanylcarbonyl)-1-piperazinyl]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.56
<b>532</b>		'2-[[6-[3-(1H-Benzimidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	1.41
<b>533</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(1H-imidazol-1-yl)butyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.24

(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret time (min)
534		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[5-(1H-imidazol-1-yl)pentyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.25
535		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[3-(4-methyl-1-piperazinyl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.14
536		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[4-(1H-imidazol-1-yl)phenyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.29
537		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[6-(1H-imidazol-1-yl)hexyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.27
538		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.24

Example 539Preparation of Ethyl-2-[(6-bromo-2-pyridinyl)amino]-5-thiazolecarboxylate**[0432]**

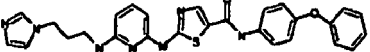
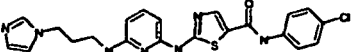
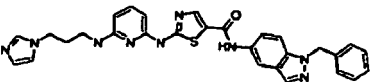
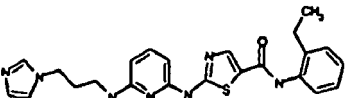
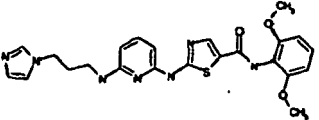
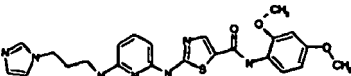
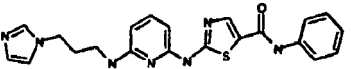
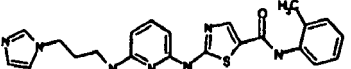
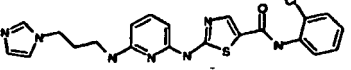
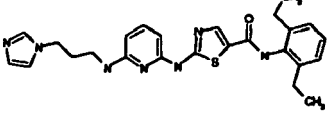
**[0433]** Compound 539 is an intermediate and was prepared in an analogous manner to **319B**, except using ethyl 2-bromo-5-thiazolecarboxylate and 6-bromo-2-aminopyridine as the reactants.

Examples 540-550General Procedure

**[0434]** Compounds **540** to **550** were prepared according to the general procedure described below. Compound **539** was condensed with the appropriate aniline according to the procedure for example **528** to afford the corresponding N-(4-methoxybenzyl)amide. The intermediate bromopyridine was then reacted with N-(3-aminopropyl)-imidazole according to the procedure for examples **531** to **538** to afford the corresponding diaminopyridine. Removal of the 4-methoxybenzyl group according to the procedure described for example **530** followed by purification by reverse phase preparative HPLC afforded compounds **540** to **550**.

EX. NO.	Compound Structure	Compound Name	HPLC Ret time (min)
540		'2-[[6-[[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-(4-methoxyphenyl)-5-thiazolecarboxamide	1.12

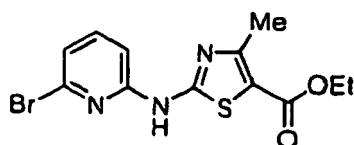
(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret time (min)
541		'2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl] amino]-N-(4-phenoxyphenyl)-5-thiazolecarboxamide	1.48
542		'N-(4-Chlorophenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl] amino]-2-pyridinyl] amino]-5-thiazolecarboxamide	1.31
543		'2-[[6-[[3-(1H-imidazol-1-yl)propyl] amino]-2-pyridinyl]amino]-N-[1-(phenylmethyl)-1H-indazol-5-yl]-5-thiazolecarboxamide	1.34
544		'N-(2-Ethylphenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl] amino]-5-thiazolecarboxamide	1.18
545		'N-(2,6-Dimethoxyphenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl] amino]-2-pyridinyl] amino]-5-thiazolecarboxamide	1.11
546		'N-(2,4-Dimethoxyphenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl] amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.06
547		'2-[[6-[[3-(1H-imidazol-1-yl)propyl] amino]-2-pyridinyl]amino]-N-phenyl-5-thiazolecarboxamide	1.06
548		'2-[[6-[[3-(1H-imidazol-1-yl)propyl] amino]-2-pyridinyl] amino]-N-(2-methylphenyl)-5-thiazolecarboxamide	1.11
549		'N-(2-Chlorophenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl] amino]-5-thiazolecarboxamide	1.16
550		'N-(2,6-Diethylphenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl] amino]-5-thiazolecarboxamide	1.29

Example 551

Preparation of Ethyl-2-[(6-bromo-2-pyridinyl)amino]-4-methyl-5-thiazolecarboxylate

**[0435]**



**[0436]** Compound 551 is an intermediate and was prepared in an analogous manner to **319B**, except using ethyl 2-bromo-4-methyl-5-thiazolecarboxylate and 6-bromo-2-aminopyridine as the reactants.

#### Examples 552 and 553

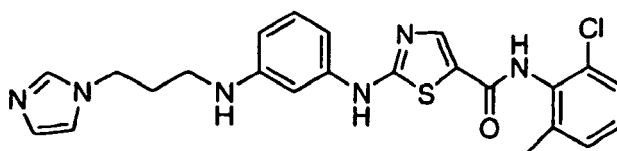
**[0437]** Compounds **552** and **553** were prepared using a similar procedure described for the preparation of compounds **540** to **550**, except using compound **551** as the starting material.

EX. NO.	Compound Structure	Compound Name	HPLC Ret time (min)
<b>552</b>		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-4-methyl-5-thiazolecarboxamide	1.19
<b>553</b>		'2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-4-methyl-N-[1-(phenylmethyl)-1H-indazol-5-yl]-5-thiazolecarboxamide	1.35

#### Example 554

Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[3-[[3-(1H-imidazol-1-yl)propyl]amino]phenyl]amino]-5-thiazolecarboxamide

#### **[0438]**

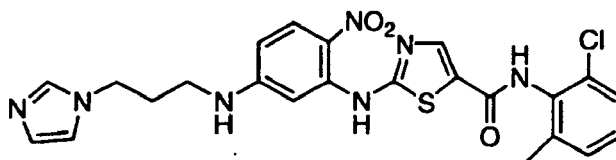


**[0439]** A solution of **528** (0.127 g, 0.281 mmol, 1.00 equiv) and 3-[N,N-(tert-butoxycarbonyl)-(3-aminopropyl)-imidazol-1-yl]-1,3-phenylenediamine (0.178 g, 0.563 mmol, 2.00 equiv) in 0.200 mL DMSO was heated at 120 °C in a sealed vial overnight. Purification by reverse phase preparative HPLC followed by deprotection according to the procedure for compound **530** afforded the title compound.

#### Example 555

Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[5-[[3-(1H-imidazol-1-yl)propyl]amino]-2-nitrophenyl]amino]-5-thiazolecarboxamide

#### **[0440]**



**[0441]** A solution of 2,4-difluoronitrobenzene (0.400 mL, 3.65 mmol, 1.00 equiv) in acetonitrile was charged with  $K_2CO_3$  (0.605 g, 4.38 mmol, 1.20 equiv) followed by ethyl-2-amino-5-thiazolecarboxylate (0.628 g, 3.65 mmol, 1.00 equiv) as a solid. The heterogeneous mixture was sealed and heated to 120°C overnight. The solution was filtered and then concentrated in vacuo. Purification by flash chromatography afforded ethyl-2-[(3-fluoro-6-nitro-1-phenyl)amino]-5-thiazolecarboxylate as a yellow solid (9%). This intermediate was coupled with 2-chloro-6-methyl aniline according to the procedure for compound 528 to afford N-(2-Chloro-6-methylphenyl)-2-[3-(fluoro-6-nitro-1-phenyl)amino]-5-thiazolecarboxamide (21%). The title compound was synthesized by reacting this intermediate with excess N-(3-aminopropyl)-imidazole at 80°C followed by purification by reverse phase preparative HPLC.

#### Examples 556-566

##### General Procedure:

**[0442]** Compounds **556** to **566** were prepared according to the general procedure described below. A mixture of 2-bromo-N-[2-chloro-6-methylphenyl]-5-thiazolecarboxamide **319A**, an aniline (1 eq), 1.0 N aqueous HCl (0.5 eq) in n-BuOH was heated overnight at 120°C in a sealed vial. This was diluted with methanol and the product was isolated by preparative HPLC (YMC S5 ODS 30 x 100 mm column eluted with a gradient comprised of two solvent mixtures (mixture A: 10% MeOH, 90% water, and 0.1% TFA); mixture B: 90% MeOH, 10% water, and 0.1% TFA). For anilines substituted with a carboxylic acid group, the reaction mixture was treated with 1 N aqueous NaOH (5 eq) overnight before final purification of the product by HPLC. "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 OSD 4.6 x 30 mm (for **556** to **560**) or YMC S7 ODS 3 x 50 mm column (for **561** to **566**), 2 min gradient starting from 100% solvent A (10% MeOH, 90%  $H_2O$ , 0.1% TFA) to 100% solvent B (90% MeOH, 10%  $H_2O$ , 0.1% TFA), flow rate 5 mL/min,  $\lambda = 220$  nm.

EX. NO.	Compound Structure	Compound Name	HPLC Ret time (min)
556		N-(2-Chloro-6-methylphenyl)-2-[(3,4,5-trimethoxy-phenyl)amino]-5-thiazolecarboxamide	1.63
557		N-(2-Chloro-6-methylphenyl)-2-[(4-methoxy-phenyl)amino]-5-thiazolecarboxamide	1.63
558		N-(2-Chloro-6-methylphenyl)-2-[(3-methoxy-phenyl)amino]-5-thiazolecarboxamide	1.70
559		N-(2-Chloro-6-methylphenyl)-2-[(2-methoxy-phenyl)amino]-5-thiazolecarboxamide	1.65
560		N-(2-Chloro-6-methylphenyl)-2-[(3,5-dimethoxyphenyl)-amino]-5-thiazolecarboxamide	1.55

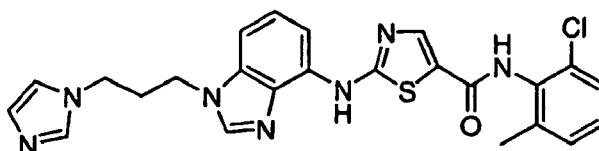
(continued)

EX. NO.	Compound Structure	Compound Name	HPLC Ret time (min)
561		N-(2-Chloro-6-methylphenyl)-2-[[4-(dimethylamino)-phenyl]amino]-5-thiazolecarboxamide	1.25
562		N-(2-Chloro-6-methylphenyl)-2-[[4-(4-morpholinyl)phenyl]amino]-5-thiazolecarboxamide	1.24
563		N-(2-Chloro-6-methylphenyl)-2-[[3-(carboxymethyl)-phenyl]amino]-5-thiazolecarboxamide	1.36
564		N-(2-Chloro-6-methylphenyl)-2-[[3-(3-carboxypropyl)-phenyl]amino]-5-thiazolecarboxamide	1.48
565		N-(2-Chloro-6-methylphenyl)-2-[[4-(carboxymethyl)phenyl]amino]-5-thiazolecarboxamide	1.35
556		N-(2-Chloro-6-methylphenyl)-2-[(2-methyl-1H-benzimidazol-5-yl)amino]-5-thiazolecarboxamide	1.27

## Example 567

N-(2-Chloro-6-methylphenyl)-2-[[1-[3-(1H-imidazol-1-yl)propyl]-1H-benzimidazol-4-yl]amino]-5-thiazolecarboxamide

## [0443]



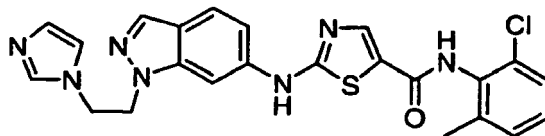
**[0444]** A mixture of 1-bromo-3-chloropropane (10 mL, 0.10 mmole), imidazole (6.81 gm, 0.10 mmole) in ethanolic NaOEt (41.3 mL, 21 wt%, 1.1 mmole) was heated at reflux for 1 hr. After cooling to RT, this was filtered and the filter cake was washed with EtOH. The solvent was removed from the filtrate to afford crude 3-chloro-1-(imidazo-1-yl)-propane as an oil. A portion of the crude chloride (1.07 gm, 7.40 mmole) was added to a mixture of 4-nitro-benzimidazole (1.09 gm, 6.66 mmole) and NaH (293 mg, 60% in oil, 8.14 mmole) in DMF (15 mL). After being heated at 60°C overnight and then 75°C for 3 hr, the solvent was removed. The residue was partitioned between water and a mixture of 10% MeOH in DCM. The organic phase was separated, dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvents removed. Radial chromatography (4 mm silica gel plate that was eluted with a step gradient of DCM containing 2, 3, 4, ...10% MeOH) afforded the major product, 1-[3-imidazo-1-ylpropyl]-4-nitro-benzimidazole as a solid (513 mg, 28%). A mixture of this material (250 mg) and 10% palladium on charcoal (200 mg) in EtOH (10 mL) under a hydrogen atmosphere (balloon) was vigorously stirred for 1 hr. Removal of the catalyst by filtration and the solvent under reduced pressure left the crude 4-amino-1-[3-imidazo-1-ylpropyl]-benzimidazole as a solid. A portion of this material (46 mg, 0.191 mmole) was added to a mixture of **319A** (63 mg, 1.0 eq), an aqueous solution of HCl (0.24 mL, 1.0 M, 1.25 eq) and n-BuOH (1 mL). This was heated in a sealed vial at 120°C for 44 hr. After cooling to RT, **567** (HPLC retention time (YMC ODS S5 4.6 x 30 mm): 1.20 min) was isolated

by preparative HPLC.

#### Example 568

N-(2-Chloro-6-methylphenyl)-2-[[1-[2-(1H-imidazol-1-yl)ethyl]-1H-indazol-6-yl]amino]-5-thiazolecarboxamide

[0445]

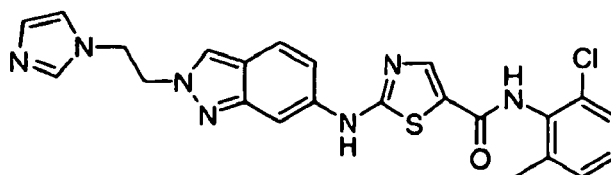


[0446] A mixture of 1-bromo-2-chloroethane (4.6 mL, 0.055 mole), imidazole (3.40 gm, 0.050 mole) in ethanolic NaOEt (19 mL, 21 wt%, 1 eq) was heated at reflux for 2 hr. After cooling to RT, the reaction was filtered and the filter cake was washed with EtOH. The solvent was removed from the filtrate to afford crude 2-chloro-1-(imidazo-1-yl)-ethane. A portion of the crude chloride (2.24 gm, 17.2 mmole) was added to a mixture of 6-nitro-indazole (1.63 gm, 10.0 mmole), K<sub>2</sub>CO<sub>3</sub> (1.50 mg, 1.1 eq), and KI (1.70 gm, 1.1 eq) in DMF (15 mL). After being heated at 70°C overnight and then 90°C for 4 hr, the solvent was removed. The residue was partitioned between water and a mixture of 5% MeOH in DCM. The organic phase was separated, dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvents removed. Radial chromatography (4mm silica gel plate that was eluted with a step gradient of DCM containing 0, 1, 2% MeOH) afforded 659 mg of 1-[2-imidazo-1-ylethyl]-6-nitro-indazole and 450 mg of the isomeric 2-[2-imidazo-1-ylethyl]-6-nitro-indazole. A mixture of 1-[2-imidazo-1-ylethyl]-6-nitro-indazole (650 mg) and 10% palladium on charcoal (600 mg) in EtOH (10 mL) under a hydrogen atmosphere (balloon) was vigorously stirred overnight. Removal of the catalyst by filtration and the solvent under reduced pressure left the crude 6-amino-1-[2-imidazo-1-ylethyl]-indazole as a solid. A portion of this material (68.1 mg, 1.5 eq) was added to a mixture of **556** (99.3 mg, 0.300 mmole), an aqueous solution of HCl (0.45 mL, 1.0 M, 1.5 eq) and n-BuOH (1.5 mL). This was heated in a sealed vial at 120°C for 44 hr. After cooling to RT, **568** (HPLC retention time (YMC ODS S7 3 x 50 mm): 1.31 min) was isolated by preparative HPLC.

#### Example 569

N-(2-Chloro-6-methylphenyl)-2-[[2-(2-(1H-imidazol-1-yl)ethyl)-2H-indazol-6-yl]amino]-5-thiazolecarboxamide

[0447]

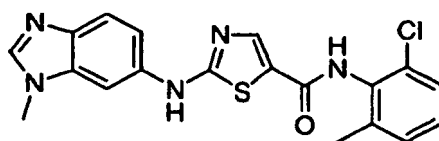


[0448] Beginning with the isomeric 2-[2-imidazo-1-ylethyl]-6-nitro-indazole, **569** (HPLC retention time (YMC ODS S7 3 x 50 mm): 1.28 min) was prepared in the same manner as **568**.

#### Example 570

N-(2-Chloro-6-methylphenyl)-2-[(1-methyl-1H-benzimidazol-6-yl)amino]-5-thiazolecarboxamide

[0449]



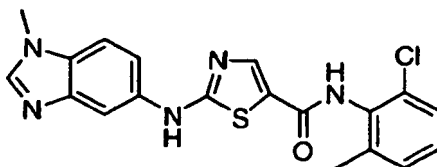


and

Example 571

N-(2-Chloro-6-methylphenyl)-2-[(1-methyl-1H-benzimidazol-5-yl)amino]-5-thiazolecarboxamide

[0450]

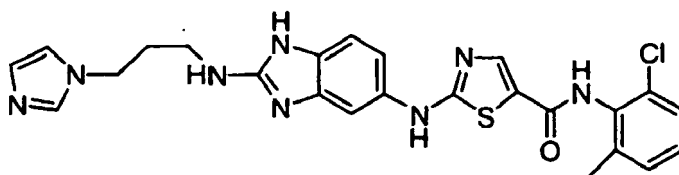


[0451] Beginning with 5-nitrobenzimidazole and methyl iodide, **570** (HPLC retention time (YMC ODS S7 3 x 50 mm): 1.23 min) and **571** (HPLC retention time (YMC ODS S7 3 x 50 mm): 1.23 min) were prepared in the same manner as compounds **557** and **558**.

Example 572

N-(2-Chloro-6-methylphenyl)-2-[[2-[3-(1H-imidazol-1-yl)propyl]amino]-1H-benzimidazol-5-yl]aminol-5-thiazolecarboxamide

[0452]

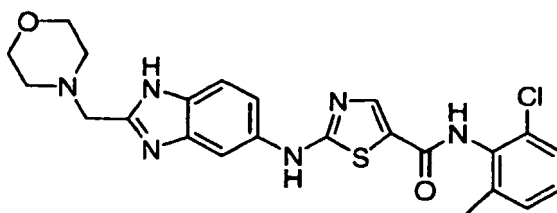


[0453] A mixture of 2-chloro-5-nitro-benzimidazole (985 mg, 5.0 mmole) and 1-(3-aminopropyl)-imidazole (1.8 mL, 3 eq) in toluene (15 mL) was heated at reflux for 5 hr. The reaction was partitioned between EtOAc and brine to give a precipitate that was collected by filtration. Flash chromatography of this material (silica gel; stepwise gradient elution with mixtures of DCM containing 1, 2, 3,...10% MeOH) afforded 2-[3-[imidazo-1-yl]-propylamino]-5-nitro-benzimidazole (550mg) as a solid. This material was combined with 10% Pd on charcoal (500 mg), suspended in EtOH, and stirred under a hydrogen atmosphere (balloon) overnight. Removal of the catalyst by filtration and the solvent under reduced pressure left the crude 5-amino-2-[3-imidazo-1-ylpropylamino]- benzimidazole as a solid. A portion of this material (77 mg, 0.30 mmole) was added to a mixture of **319A** (99 mg, 1.0 eq), an aqueous solution of HCl (0.60 mL, 1.0 M, 2 eq) and n-BuOH (1.5 mL). This was heated in a sealed vial at 120°C for 20 hr. After cooling to RT, **572** (HPLC retention time (YMC ODS S7 3 x 50 mm): 1.20 min) was isolated by preparative HPLC.

Example 573

N-(2-Chloro-6-methylphenyl)-2-[[2-(4-morpholinylmethyl)-1H-benzimidazol-5-yl]amino]-5-thiazolecarboxamide

[0454]

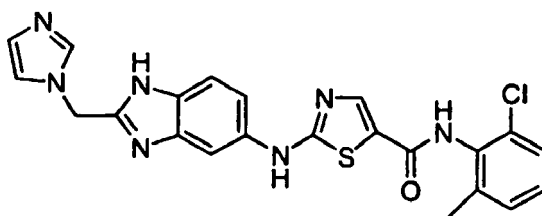


**[0455]** A mixture of 3,4-diamino-nitrobenzene (15.3 g, 0.10 mole) and chloroacetic acid (14.18 gm, 1.5 eq) in 5.0 N aqueous HCl (80 mL) was heated at reflux for 1 hr. After cooling to RT, the reaction was filtered through celite and the filtrate was stored at 0°C for 2 days. The crystals that formed, were collected and recrystallized from a mixture of EtOH and water to give 7.2 gm of the hydrogen chloride salt of 2-chloromethyl-5-nitro-benzimidazole. A portion of this salt (528 mg, 2.13 mmole) and morpholine (1.31 mL, 7 eq) in toluene (15 mL) were heated at reflux for 4 hr. After cooling to RT, the reaction was filtered and the filter cake was washed with toluene. The solvent was removed from the filtrate to leave the crude 2-[N-morpholinylmethyl]-5-nitro-benzimidazole as an oil. A portion of this material (657 mg) and 10% palladium on charcoal (650 mg) in EtOH (10 mL) was stirred overnight under a hydrogen atmosphere (balloon). Removal of the catalyst by filtration and the solvent left the crude 5-amino-2-[N-morpholinylmethyl]-benzimidazole as an oil. A portion of this material was coupled with **556** as described for **570** to afford **573** (HPLC retention time (YMC ODS S7 3 x 50 mm): 0.92 min).

#### Example 574

N-(2-Chloro-6-methylphenyl)-2-[[2-(1H-imidazol-1-ylmethyl)-1H-benzimidazol-5-yl]amino]-5-thiazolecarboxamide

#### [0456]

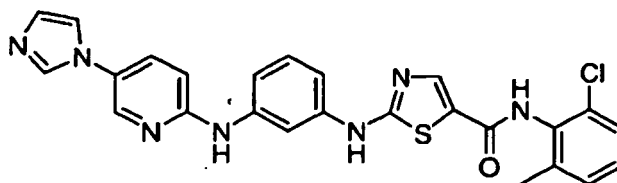


**[0457]** Beginning with imidazole and 2-chloromethyl-5-nitro-benzimidazole compound **574** (HPLC retention time (YMC ODS S7 3 x 50 mm): 1.17 min) was prepared in the same manner as compounds **570**.

#### Example 575

N-(2-Chloro-6-methylphenyl)-2-[[3-[[5-(1H-imidazol-1-yl)-2-pyridinyl]amino]phenyl]amino]-5-thiazolecarboxamide

#### [0458]

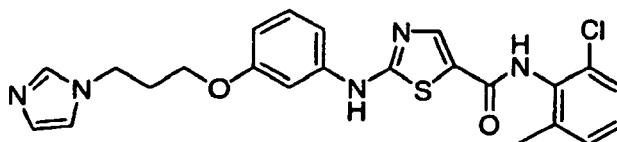


**[0459]** A mixture of 3-nitroaniline (2.91 gm, 21.1 mmole) and 2,5-dibromopyridine (5.0 gm, 1 eq) was heated at 185°C for 1 hr. After cooling to RT, the solid was broken up and treated with a mixture of saturated aq. NaHCO<sub>3</sub> and 10% MeOH in DCM. The suspended solid was collected by filtration and washed with a little 10% MeOH in DCM and then water to leave, after drying, 3.72 gm of crude N-[5-bromo-pyridin-2-yl]-5-nitroaniline. A portion of this material (500 mg, 1.70 mmole) was combined with imidazole (116 mg, 1 eq), CuI (81 mg, 0.25 eq), and K<sub>2</sub>CO<sub>3</sub> (235 mg, 1 eq) in DMF (2 mL) and the mixture was heated at 130°C for 2 days. After cooling to RT, the solvent was removed and the residue was partitioned between water and a mixture of 20% MeOH in DCM. The organic phase was removed, dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvents removed to leave the crude N-[5-imidazo-1-yl]-pyridin-2-yl]-5-nitroaniline as a solid. This was taken and treated with 10% palladium on charcoal (650 mg) in EtOH under a hydrogen atmosphere for 1.5 hr. Removal of the catalyst and then the solvent left the crude N-[5-imidazo-1-yl]-pyridin-2-yl]-5-aminoaniline. It was purified by radial chromatography (4 mm silica gel plate that was eluted with a step gradient of DCM containing 1, 2, 3,... 6% MeOH). The aniline was then coupled with **319A** as described for **570** to afford **575** (HPLC retention time (YMC ODS S5 4.6 x 30 mm): 1.42 min).

## Example 576

N-(2-Chloro-6-methylphenyl)-2-[[3-[3-(1H-imidazol-1-yl)propoxy]phenyl]amino]-5-thiazolecarboxamide

[0460]

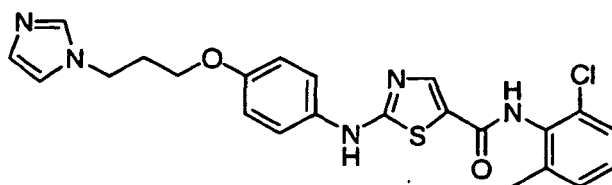


and

## Example 577

N-(2-Chloro-6-methylphenyl)-2-[[4-[3-(1H-imidazol-1-yl)propoxy]phenyl]amino]-5-thiazolecarboxamide

[0461]

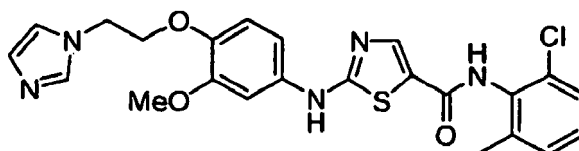


[0462] A suspension of 3-nitrophenol (837 mg, 6.02 mmole), 1-chloro-3-[imidazo-1-yl]-propane (871 mg, 1 eq),  $K_2CO_3$  (3.3 gm, 4 eq) and NaI (1.0 gm, 1.1 eq) in DMF was heated at 120°C for 6 hr. After cooling to RT, the reaction was filtered and the filter cake was washed with DMF. The solvent was removed from the filtrate and the residue was chromatographed (radial chromatography; 4 mm silica gel plate that was eluted with a step gradient of DCM containing 0, 1, 2.5, 5, 7.5% MeOH) to afford 400 mg of 3-[3-imidazo-1-ylpropyloxy]-nitrobenzene. This was treated with 10% palladium on charcoal (400 mg) in EtOH under a hydrogen atmosphere for 4 hr. Removal of the catalyst and the solvent left 3-[3-imidazo-1-ylpropyloxy]-aniline was then coupled with **319A** as described for **570** to afford **576** (HPLC retention time (YMC ODS S5 4.6 x 30 mm): 1.33 min). Beginning with 4-nitrophenol and 1-chloro-3-[imidazo-1-yl]-propane **577** (HPLC retention time (YMC ODS S5 4.6 x 30 mm): 1.42 min) was prepared in a similar manner as **576**.

## Example 578

N-(2-Chloro-6-methylphenyl)-2-[[4-(2-(1H-imidazol-1-yl)ethoxy)-3-methoxyphenyl]amino]-5-thiazolecarboxamide

[0463]

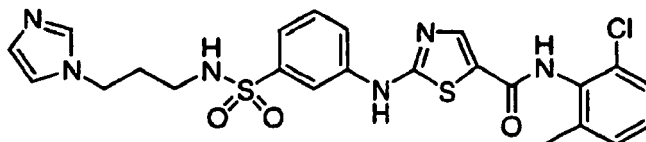


[0464] Beginning with 2-methoxy-4-nitrophenol and 1-chloro-3-[imidazo-1-yl]-ethane, **578** (HPLC retention time (YMC ODS S5 4.6 x 30 mm): 1.35 min) was prepared in a similar manner as **576**.

## Example 579

N-(2-Chloro-6-methylphenyl)-2-[[[3-[(1H-imidazol-1-yl)propyl]amino]sulfonyl]phenyl]amino]-5-thiazolecarboxamide

[0465]

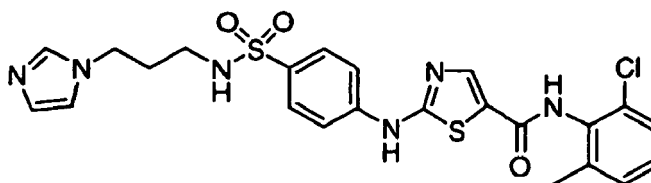


and

## Example 580

N-(2-Chloro-6-methylphenyl)-2-[[4-[[[3-(1H-imidazol-1-yl)propyl]amino]sulfonyl]phenyl]amino]-5-thiazolecarboxamide

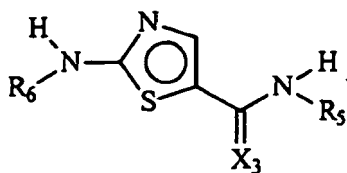
[0466]



[0467] 3-Imidazo-1-yl-propylamine (2.04 mL, 2.5 eq) was added to a solution of 3-nitro-benzenesulfonyl chloride (1.5 gm, 6.77 mmole) in THF (20 mL) at RT. After 1 hr, the solvent was removed and the residue was partitioned between water and a mixture of 10% MeOH in DCM. The organic phase was separated, washed with water and dried (Na<sub>2</sub>SO<sub>4</sub>). The crude N-[3-[imidazo-1-yl]-propyl]-3-nitro-benzenesulfonamide was treated with 10% palladium on charcoal (2 gm) in THF (60 mL) under a hydrogen atmosphere overnight. Removal of the catalyst and then the solvent left crude 3-amino-N-[3-[imidazo-1-yl]-propyl]-benzenesulfonamide which was then coupled with **319A** as described for **570** to afford **579** (HPLC retention time (YMC ODS S7 3 x 50 mm): 1.22 min). Beginning with 4-nitro-benzenesulfonyl chloride and 3-[imidazo-1-yl]-propylamine, **580** (HPLC retention time (YMC ODS S7 3 x 50 mm): 1.21 min) was prepared in a similar manner as **579**.

## Claims

1. A cyclic compound of the following formula II or a salt thereof:



II

wherein

X<sub>3</sub> is oxygen or sulfur;R<sub>5</sub> is an aryl group which is substituted with one or more groups selected from alkyl and halo;R<sub>6</sub> is:

aryl or heteroaryl which is substituted with Z<sub>1</sub>, Z<sub>2</sub> and one or more groups Z<sub>3</sub>, wherein

- a) said aryl is substituted with at least one group  $Z_3$  where  $Z_3$  is  $-Z_4-NZ_7Z_8$  where  $Z_4$  is a bond,  $Z_7$  is hydrogen or alkyl, and  $Z_8$  is heterocyclo-substituted alkyl; or
- b) said heteroaryl is substituted with at least one group  $Z_3$  where  $Z_3$  is  $-Z_4-NZ_7Z_8$  where  $Z_4$  is a bond,  $Z_7$  is hydrogen or alkyl, and  $Z_8$  is heterocyclo-substituted alkyl; or
- c) said heteroaryl is substituted with at least one group  $Z_3$  where  $Z_3$  is alkyl;

$Z_1$ ,  $Z_2$  and  $Z_3$  are each independently:

- (1) hydrogen or  $Z_6$ , where  $Z_6$  is (i) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl; (ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or (iii) a group (i) or (ii) which is substituted by one or more of the following groups (2) to (16) of the definition of  $Z_1$ ,  $Z_2$  and  $Z_3$ ;
- (2) -OH or -O $Z_6$ ;
- (3) -SH or -S $Z_6$ ;
- (4) -C(O) $_q$ H, -C(O) $_q$  $Z_6$ , or -O-C(O) $_q$  $Z_6$ , where  $q$  is 1 or 2;
- (5) -SO $_3$ H, -S(O) $_q$  $Z_6$ ; or S(O) $_q$ N( $Z_9$ ) $Z_6$ ;
- (6) halo;
- (7) cyano;
- (8) nitro;
- (9)  $-Z_4-NZ_7Z_8$ ;
- (10)  $-Z_4-N(Z_9)-Z_5-NZ_7Z_8$ ;
- (11)  $-Z_4-N(Z_{10})-Z_5-Z_6$ ;
- (12)  $-Z_4-N(Z_{10})-Z_5-H$ ;
- (13) oxo;
- (14) -O-C(O)- $Z_6$ ;
- (15) any two of  $Z_1$ ,  $Z_2$ , and  $Z_3$  may together be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached; or
- (16) any two of  $Z_1$ ,  $Z_2$ , and  $Z_3$  may together be -O-(CH $_2$ ) $_r$ -O-, where  $r$  is 1 to 5, completing a 4- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached;

$Z_4$  and  $Z_5$  are each independently:

- (1) a single bond;
- (2)  $-Z_{11}-S(O)_q-Z_{12}-$ ;
- (3)  $-Z_{11}-C(O)-Z_{12}-$ ;
- (4)  $-Z_{11}C(S)-Z_{12}-$ ;
- (5)  $-Z_{11}-O-Z_{12}-$ ;
- (6)  $-Z_{11}-S-Z_{12}-$ ;
- (7)  $-Z_{11}-O-C(O)-Z_{12}-$ ; or
- (8)  $-Z_{11}-C(O)-O-Z_{12}-$ ;

$Z_7$ ,  $Z_8$ ,  $Z_9$  and  $Z_{10}$ :

- (1) are each independently hydrogen or  $Z_6$ ;
- (2)  $Z_7$  and  $Z_8$ , or  $Z_6$  and  $Z_{10}$ , may together be alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and  $Z_3$ ; or
- (3)  $Z_7$  or  $Z_8$ , together with  $Z_9$ , may be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and  $Z_3$ ;

$Z_{11}$  and  $Z_{12}$  are each independently:

- (1) a single bond;
- (2) alkylene;
- (3) alkenylene; or
- (4) alkynylene.

2. The compound or salt thereof according to claim 1 selected from the group consisting of:

N-(2-Chloro-6-methylphenyl)-2-[(4,6-dimethyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 N-(2-Chloro-6-methylphenyl)-2-[(4-ethyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 N-(2-Chloro-6-methylphenyl)-2-[(2,6-dimethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide;  
 N-(2-Chloro-6-methylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 N-(2-Chloro-6-methylphenyl)-2-[(6-propyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 N-(2-Chloro-6-methylphenyl)-2-[(6-ethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[(6-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[(5-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[(3-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 '2-[(5-Bromo-3-methyl-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[(6-ethyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[(6-propyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 '2-[(3-Bromo-5-methyl-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[(3,5-dimethyl-2-pyrazinyl)amino]-5-thiazolecarboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[(4,6-dimethyl-2-pyrimidinyl)amino]-5-thiazolecarboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[(6-ethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide;  
 'N-(2,6-Dimethylphenyl)-2-[(6-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 'N-(2,6-Dimethylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 'N-(2,6-Dimethylphenyl)-2-[(4-ethyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 'N-(2,6-Dimethylphenyl)-2-[(4,6-dimethyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 'N-(2,6-Dimethylphenyl)-2-[(6-ethyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 'N-(2,6-Dimethylphenyl)-2-[(6-propyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 '2-[(6-Amino-2-methyl-4-pyrimidinyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide;  
 '2-[(6-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;  
 '2-[(5-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;  
 '2-[(4-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;  
 '2-[(3-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;  
 '2-[(4-Ethyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;  
 '2-[(6-Ethyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;  
 '2-[(2,6-Dimethyl-4-pyrimidinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;  
 '2-[(4-Methyl-2-pyrimidinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;  
 '2-[(3,5-Dimethyl-2-pyrazinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[2-(4-morpholinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazole-  
 carboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[3-(4-morpholinyl)propyl]amino]-4-pyrimidinyl]amino]-5-thiazole-  
 carboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[methyl-[3-(methylamino)propyl]-amino]-4-pyrimidinyl]amino]-5-  
 thiazolecarboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[2-(tetrahydro-2-oxo-1H-imidazol-1-yl)ethyl]amino]-4-pyrimidi-  
 nyl]amino]-5-thiazolecarboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[(2-1H-imidazol-4ylethyl)amino]-4-pyrimidinyl]amino]-5-thiazole-  
 carboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-(4-morpholinyl)-4-pyrimidinyl]-amino]-5-thiazolecarboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[(2R)-1-ethyl-2-pyrrolidinyl]methyl]amino]-2-methyl-4-pyrimidinyl]amino]-  
 5-thiazolecarboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[(2S)-1-ethyl-2-pyrrolidinyl]methyl]amino]-2-methyl-4-pyrimidinyl]amino]-  
 5-thiazolecarboxamide;  
 '2-[[6-[(2S)-2-(Aminocarbonyl)-1-pyrrolidinyl]-2-methyl-4-pyrimidinyl]amino]-N-(2-chloro-6-methylphenyl)-5-  
 thiazolecarboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[[6-[(2-hydroxyethyl)amino]-2-methyl-4-pyrimidinyl]-amino]-5-thiazolecarbox-  
 amide;  
 'N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(hydroxymethyl)-1-piperidinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazole-  
 carboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thia-  
 zolecarboxamide;

'1-[6-[[5-[(2-Chloro-6-methylphenyl)amino]carbonyl]-2-thiazolyl]amino]-2-methyl-4-pyrimidinyl]-4-piperidine-carboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[(3S)-3-methyl-1-piperazinyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

5 '2-[[6-[3-(Acetyl-amino)-1-pyrrolidinyl]-2-methyl-4-pyrimidinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(1-methyl-2-pyrrolidinyl)ethyl]amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

10 'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[5-methyl-2-pyrazinyl)methyl]-amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[2-(1H-1,2,3-triazol-1-yl)ethyl]-amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(4-morpholinyl)ethyl]amino]-4-pyrimidinyl]-amino]-5-thiazolecarboxamide;

15 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(tetrahydro-2-oxo-1H-imidazol-1-yl)ethyl]-amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(1-methyl-2-pyrrolidinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

20 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(1-pyrrolidinyl)ethyl]amino]-4-pyrimidinyl]-amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[1-ethyl-2-pyrrolidinyl)methyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[4-piperidinyl)methyl]amino]-4-pyrimidinyl]-amino]-5-thiazolecarboxamide;

25 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(1H-1,2,3-triazol-1-yl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(4-morpholinyl)ethyl]amino]-2-pyridinyl]-amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[3-(4-morpholinyl)propyl]amino]-2-pyridinyl]-amino]-5-thiazolecarboxamide;

30 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(1H-imidazol-1-ylethyl)amino]-2-pyridinyl]-amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(4-morpholinyl)ethyl]amino]-2-pyrazinyl]-amino]-5-thiazolecarboxamide;

35 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[3-(4-morpholinyl)propyl]amino]-2-pyrazinyl]-amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[3-[[2-(4-morpholinyl)ethyl]amino]-2-pyrazinyl]-amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-(4-morpholinyl)methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

40 '1-[[6-[[5-[(2-Chloro-6-methylphenyl)amino]carbonyl]-2-thiazolyl]amino]-4-pyrimidinyl)methyl]-4-piperidinecarboxamide;

'2-[(2,6-Dimethyl-4-pyrimidinyl)amino]-N-(2-methylphenyl)-5-thiazolecarboxamide;

'N-[2,6-Bis(1-methylethyl)phenyl]-2-[(2,6-dimethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide;

45 '2-[[6-[[3-(1H-Benzimidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[4-(1H-imidazol-1-yl)butyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[5-(1H-imidazol-1-yl)pentyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

50 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[3-(4-methyl-1-piperazinyl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[6-(1H-imidazol-1-yl)hexyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

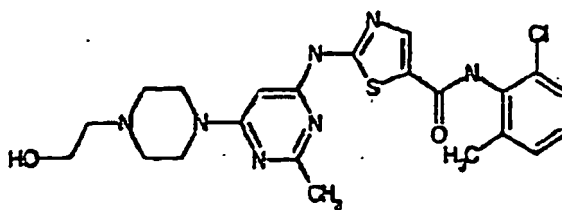
55 'N-(4-Chlorophenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

'N-(2-Ethylphenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

'2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-(2-methylphenyl)-5-thiazolecarboxamide;

'N-(2-Chlorophenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;  
 'N-(2,6-Diethylphenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[[3-[[3-(1H-imidazol-1-yl)propyl]amino]phenyl]amino]-5-thiazolecarboxamide;  
 'N-(2-Chloro-6-methylphenyl)-2-[[5-[[3-(1H-imidazol-1-yl)propyl]amino]-2-nitrophenyl]amino]-5-thiazolecarboxamide;  
 N-(2-Chloro-6-methylphenyl)-2-[(2-methyl-1H-benzimidazol-5-yl)amino]-5-thiazolecarboxamide;  
 N-(2-Chloro-6-methylphenyl)-2-[[1-[3-(1H-imidazol-1-yl)propyl]-1H-benzimidazol-4-yl]amino]-5-thiazolecarboxamide;  
 N-(2-Chloro-6-methylphenyl)-2-[[1-[2-(1H-imidazol-1-yl)ethyl]-1H-indazol-6-yl]amino]-5-thiazolecarboxamide;  
 N-(2-Chloro-6-methylphenyl)-2-[[2-[2-(1H-imidazol-1-yl)ethyl]-2H-indazol-6-yl]amino]-5-thiazolecarboxamide;  
 N-(2-Chloro-6-methylphenyl)-2-[(1-methyl-1H-benzimidazol-6-yl)amino]-5-thiazolecarboxamide;  
 N-(2-Chloro-6-methylphenyl)-2-[(1-methyl-1H-benzimidazol-5-yl)amino]-5-thiazolecarboxamide;  
 N-(2-Chloro-6-methylphenyl)-2-[[2-[3-(1H-imidazol-1-yl)propyl]amino]-1H-benzimidazol-5-yl]amino]-5-thiazolecarboxamide;  
 N-(2-Chloro-6-methylphenyl)-2-[[2-(4-morpholinylmethyl)-1H-benzimidazol-5-yl]amino]-5-thiazolecarboxamide;  
 N-(2-Chloro-6-methylphenyl)-2-[[2-(1H-imidazol-1-ylmethyl)-1H-benzimidazol-5-yl]amino]-5-thiazolecarboxamide;

3. The compound of claim 1, wherein the compound of formula II is the following compound



or a salt thereof.

4. A compound of any of claims 1 to 3 or a salt thereof for use in the treatment of protein tyrosine kinase-associated disorder, wherein said protein tyrosine kinase-associated disorder is transplant rejection, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, lupus, graft vs. host disease, T-cell mediated hypersensitivity disease, psoriasis, Hashimoto's thyroiditis, Guillain-Barre syndrome, cancer, contact dermatitis, allergic disease, asthma, ischemic or reperfusion injury, atopic dermatitis, allergic rhinitis, chronic obstructive pulmonary disease, or diabetic retinopathy.

5. The compound for use according to claim 4, wherein said protein tyrosine kinase is Lck, Fyn, Lyn, Hck, Fgr, Src, Yes, Blk, HER1, or HER2.

6. The compound for use according to claim 4, wherein said compound as defined in claims 1 to 3 or salt thereof is to be administered, simultaneously or sequentially, with an anti-inflammatory, antiproliferative, chemotherapeutic agent, immunosuppressant, anti-cancer, cytotoxic agent or PTK inhibitor other than a compound as defined in claims 1 to 3 or salt thereof.

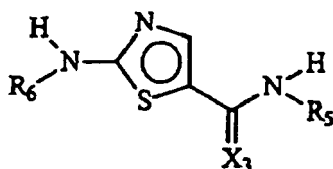
7. The compound for use according to claim 6, wherein said compound of the formula II or salt thereof is to be administered with one or more of: another PTK inhibitor; cyclosporin A; CTLA4-Ig; antibodies selected from anti-ICAM-3, anti-IL-2 receptor (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80, anti-CD86, and monoclonal antibody OKT3; agents blocking the interaction between CD40 and gp39; fusion proteins constructed from CD40 and gp39; inhibitors of NF-kappa B function; non-steroidal anti-inflammatory drugs (NSAIDs); steroids; gold compounds; antiproliferative agents; FK506 (tacrolimus, Prograf); mycophenolate mofetil; cytotoxic drugs; TNF- $\alpha$  inhibitors; anti-TNF antibodies or soluble TNF receptor; rapamycin (sirolimus or Rapamune); leflunimide; cyclooxygenase-2 inhibitors; paclitaxel, cisplatin, carboplatin, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, mitomycin C, ecteinascidin 743, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin, etoposide, etoposide phosphate, teniposide, melphalan, vinblastine, vincristine, leurosine, vindesine, and leurosine.



8. A pharmaceutical composition for the treatment of a protein tyrosine kinase-associated disorder, comprising a pharmaceutically acceptable vehicle or diluent and at least one compound of claim 1.
9. The pharmaceutical composition for the treatment of a protein tyrosine kinase-associated disorder according to claim 8, comprising a pharmaceutically acceptable vehicle or diluent and the compound of claim 3.

## Patentansprüche

1. Cyclische Verbindung mit der folgenden Formel II, oder ein Salz davon:



II

wobei:

X<sub>3</sub> Sauerstoff oder Schwefel ist;

R<sub>5</sub> eine Arylgruppe ist, die mit einer oder mehreren, aus Alkyl und Halogen ausgewählten Gruppen substituiert ist;

R<sub>6</sub> Aryl oder Heteroaryl ist, das mit Z<sub>1</sub>, Z<sub>2</sub> und einer oder mehreren Gruppen Z<sub>3</sub> substituiert ist, wobei

- a) das Aryl mit mindestens einer Gruppe Z<sub>3</sub> substituiert ist, wobei Z<sub>3</sub>-Z<sub>4</sub>-NZ<sub>7</sub>Z<sub>8</sub> ist, wobei Z<sub>4</sub> eine Bindung, Z<sub>7</sub> Wasserstoff oder Alkyl und Z<sub>8</sub> ein mit einem Heterocyclus substituiertes Alkyl ist; oder
- b) das Heteroaryl mit mindestens einer Gruppe Z<sub>3</sub> substituiert ist, wobei Z<sub>3</sub>-Z<sub>4</sub>-NZ<sub>7</sub>Z<sub>8</sub> ist, wobei Z<sub>4</sub> eine Bindung, Z<sub>7</sub> Wasserstoff oder Alkyl und Z<sub>8</sub> ein mit einem Heterocyclus substituiertes Alkyl ist; oder
- c) das Heteroaryl mit mindestens einer Gruppe Z<sub>3</sub> substituiert ist, wobei Z<sub>3</sub> ein Alkyl ist;

Z<sub>1</sub>, Z<sub>2</sub> und Z<sub>3</sub> jeweils unabhängig voneinander sind:

(1) Wasserstoff oder Z<sub>6</sub>, wobei Z<sub>6</sub> (i) Alkyl, Alkenyl, Alkynyl, Cycloalkyl, Cycloalkylalkyl, Cycloalkenyl, Cycloalkenylalkyl, Aryl, Aralkyl, Alkylaryl, Cycloalkylaryl, Heterocyclyl oder Heterocycloalkyl ist; (ii) eine Gruppe (i), die selbst mit einer oder mehreren gleichen oder unterschiedlichen Gruppen (i) substituiert ist; oder (iii) eine Gruppe (i) oder (ii), die mit einer oder mehreren der folgenden Gruppen (2) bis (16) gemäß der Definition von Z<sub>1</sub>, Z<sub>2</sub> und Z<sub>3</sub> substituiert ist;

(2) -OH oder -OZ<sub>6</sub>;

(3) -SH oder -SZ<sub>6</sub>;

(4) -C(O)qH, -C(O)<sub>q</sub>Z<sub>6</sub> oder -O-C(O)<sub>q</sub>Z<sub>6</sub>, wobei q gleich 1 oder 2 ist;

(5) -SO<sub>3</sub>H, -S(O)<sub>q</sub>Z<sub>6</sub> oder S(O)<sub>q</sub>N(Z<sub>9</sub>)Z<sub>6</sub>;

(6) Halogen;

(7) Cyano;

(8) Nitro;

(9) -Z<sub>4</sub>-NZ<sub>7</sub>Z<sub>8</sub>;

(10) -Z<sub>4</sub>-N(Z<sub>9</sub>)-Z<sub>5</sub>-NZ<sub>7</sub>Z<sub>8</sub>;

(11) -Z<sub>4</sub>-N(Z<sub>10</sub>)-Z<sub>5</sub>-Z<sub>6</sub>;

(12) -Z<sub>4</sub>-N(Z<sub>10</sub>)-Z<sub>5</sub>-H;

(13) Oxo

(14) -O-C(O)-Z<sub>6</sub>;

(15) je zwei von Z<sub>1</sub>, Z<sub>2</sub> und Z<sub>3</sub> können zusammen Alkylen oder Alkenylen sein und zusammen mit den Atomen, an die sie gebunden sind, einen 3- bis 8-gliedrigen gesättigten oder ungesättigten Ring vervollständigen; oder

(16) je zwei von Z<sub>1</sub>, Z<sub>2</sub> und Z<sub>3</sub> können zusammen -O-(CH<sub>2</sub>)<sub>r</sub>-O- sein, wobei r gleich 1 bis 5 ist, und zusammen mit den Atomen, an die sie gebunden sind, einen 4- bis 8-gliedrigen gesättigten oder ungesättigten Ring vervollständigen;

Z<sub>4</sub> und Z<sub>5</sub> jeweils unabhängig voneinander sind:

- (1) eine Einfachbindung;
- (2) -Z<sub>11</sub>S(O)-Z<sub>12</sub>-;
- (3) -Z<sub>11</sub>-C(O)-Z<sub>12</sub>-;
- (4) -Z<sub>11</sub>C(S)-Z<sub>12</sub>-;
- (5) -Z<sub>11</sub>-O-Z<sub>12</sub>-;
- (6) -Z<sub>11</sub>-S-Z<sub>12</sub>-;
- (7) -Z<sub>11</sub>-O-C(O)-Z<sub>12</sub>-; oder
- (8) -Z<sub>11</sub>-C(O)-O-Z<sub>12</sub>-;

Z<sub>7</sub>, Z<sub>8</sub>, Z<sub>9</sub> und Z<sub>10</sub>:

- (1) jeweils unabhängig voneinander Wasserstoff oder Z<sub>6</sub> sind;
- (2) Z<sub>7</sub> und Z<sub>8</sub> oder Z<sub>6</sub> und Z<sub>10</sub> zusammen Alkylen oder Alkenylen sein können und zusammen mit den Atomen, an die sie gebunden sind, einen 3- bis 8-gliedrigen gesättigten oder ungesättigten Ring vervollständigen; wobei der Ring nichtsubstituiert oder mit Z<sub>1</sub>, Z<sub>2</sub> und Z<sub>3</sub> substituiert ist; oder
- (3) Z<sub>7</sub> oder Z<sub>8</sub> zusammen mit Z<sub>9</sub> Alkylen oder Alkenylen sein können und zusammen mit den Stickstoffatomen, an die sie gebunden sind, einen 3- bis 8-gliedrigen gesättigten oder ungesättigten Ring vervollständigen; wobei der Ring nichtsubstituiert oder mit Z<sub>1</sub>, Z<sub>2</sub> und Z<sub>3</sub> substituiert ist;

Z<sub>11</sub> und Z<sub>12</sub> jeweils unabhängig voneinander sind:

- (1) eine Einfachbindung;
- (2) Alkylen;
- (3) Alkenylen; oder
- (4) Alkinylen.

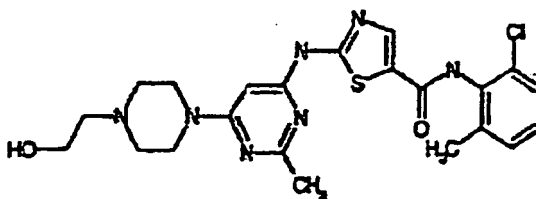
## 2. Verbindung oder ein Salz davon nach Anspruch 1, ausgewählt aus:

N-(2-Chlor-6-methylphenyl)-2-[(4,6-dimethyl-2-pyridinyl)amino]-5-thiazolcarboxamid;  
 N-(2-Chlor-6-methylphenyl)-2-[(4-ethyl-2-pyridinyl)amino]-5-thiazolcarboxamid;  
 N-(2-Chlor-6-methylphenyl)-2-[(2,6-dimethyl-4-pyrimidinyl)amino]-5-thiazolcarboxamid;  
 N-(2-Chlor-6-methylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-thiazolcarboxamid;  
 N-(2-Chlor-6-methylphenyl)-2-[(6-propyl-2-pyridinyl)amino]-5-thiazolcarboxamid;  
 N-(2-Chlor-6-methylphenyl)-2-[(6-ethyl-4-pyrimidinyl)amino]-5-thiazolcarboxamid;  
 N-(2-Chlor-6-methylphenyl)-2-[(6-methyl-2-pyridinyl)amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[(5-methyl-2-pyridinyl)amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[(3-methyl-2-pyridinyl)amino]-5-thiazolcarboxamid;  
 '2-[(5-Brom-3-methyl-2-pyridinyl)amino]-N-(2-chlor-6-methylphenyl)-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[(6-ethyl-2-pyridinyl)amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[(6-propyl-2-pyridinyl)amino]-5-thiazolcarboxamid;  
 '2-[(3-Brom-5-methyl-2-pyridinyl)amino]-N-(2-chlor-6-methylphenyl)-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[(3,5-dimethyl-2-pyrazinyl)amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[(4,6-dimethyl-2-pyrimidinyl)amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[(6-ethyl-4-pyrimidinyl)amino]-5-thiazolcarboxamid;  
 'N-(2,6-Dimethylphenyl)-2-[(6-methyl-2-pyridinyl)amino]-5-thiazolcarboxamid;  
 'N-(2,6-Dimethylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-thiazolcarboxamid;  
 'N-(2,6-Dimethylphenyl)-2-[(4-ethyl-2-pyridinyl)amino]-5-thiazolcarboxamid;  
 'N-(2,6-Dimethylphenyl)-2-[(4,6-dimethyl-2-pyridinyl)amino]-5-thiazolcarboxamid;  
 'N-(2,6-Dimethylphenyl)-2-[(6-ethyl-2-pyridinyl)amino]-5-thiazolcarboxamid;  
 'N-(2,6-Dimethylphenyl)-2-[(6-propyl-2-pyridinyl)amino]-5-thiazolcarboxamid;  
 '2-[(6-Amino-2-methyl-4-pyrimidinyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolcarboxamid;  
 '2-[(6-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolcarboxamid;  
 '2-[(5-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolcarboxamid;  
 '2-[(4-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolcarboxamid;  
 '2-[(3-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolcarboxamid;

'2-[(4-Ethyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolcarboxamid;  
 '2-[(6-Ethyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolcarboxamid;  
 '2-[(2,6-Dimethyl-4-pyrimidinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolcarboxamid;  
 '2-[(4-Methyl-2-pyrimidinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolcarboxamid;  
 5 '2-[(3,5-Dimethyl-4-pyrazinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[2-methyl-6-[[2-(4-morpholinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[2-methyl-6-[[3-(4-morpholinyl)propyl]amino]-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 10 'N-(2-Chlor-6-methylphenyl)-2-[[2-methyl-6-[methyl-[3-(methylamino)propyl]amino]-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[2-methyl-6-[[2-(tetrahydro-2-oxo-1H-imidazol-1-yl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[2-methyl-6-[[2-(1H-imidazol-4-ylethyl)amino]-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 15 'N-(2-Chlor-6-methylphenyl)-2-[[2-methyl-6-(4-morpholinyl)-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[[(2R)-1-ethyl-2-pyrrolidinyl]methyl]amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[[(2S)-1-ethyl-2-pyrrolidinyl]methyl]amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 20 '2-[[6-[(2S)-2-Aminocarbonyl]-1-pyrrolidinyl]-2-methyl-4-pyrimidinyl]amino]-N-(2-chlor-6-methylphenyl)-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[6-[(2-hydroxyethyl)amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[6-[4-(hydroxymethyl)-1-piperidinyl-2-methyl-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 25 'N-(2-Chlor-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl-2-methyl-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 '1-[6-[[5-[(2-Chlor-6-methylphenyl)amino]carbonyl]-2-thiazolyl]amino]-2-methyl-4-pyrimidinyl]-4-piperidincaboxamid;  
 30 'N-(2-Chlor-6-methylphenyl)-2-[[2-methyl-6-[(3S)-3-methyl-1-piperazinyl]-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 '2-[[6-[3-(Acetylamino)-1-pyrrolidinyl]-2-methyl-4-pyrimidinyl]amino]-N-(2-chlor-6-methylphenyl)-5-thiazolcarboxamid;  
 35 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[2-(1-methyl-2-pyrrolidinyl)ethyl]amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[2-methyl-6-[[5-methyl-2-pyrazinyl]methyl]amino]-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[2-methyl-6-[[2-(1H)-1,2,3-triazol-1-yl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 40 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[2-(4-morpholinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[2-tetrahydro-2-oxo-1H-imidazol-1-yl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[2-(1-methyl-2-pyrrolidinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 45 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[2-(1-pyrrolidinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[1-ethyl-2-pyrrolidinyl]methyl]amino]-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[4-piperidinylmethyl]amino]-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 50 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[2-(1H-1,2,3-triazolyl-1-yl)-ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[2-(4-morpholinyl)ethyl]amino]-2-pyridinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[3-(4-morpholinyl)propyl]amino]-2-pyridinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[3-1H-imidazol-1-ylpropyl]amino]-2-pyridinyl]amino]-5-thiazolcarboxamid;  
 55 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[2-1H-imidazol-1-ylethyl]amino]-2-pyridinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[2-(4-morpholinyl)ethyl]amino]-2-pyrazinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[3-(4-morpholinyl)propyl]amino]-2-pyrazinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[3-[[2-(4-morpholinyl)ethyl]amino]-2-pyrazinyl]amino]-5-thiazolcarboxamid;

'N-(2-Chlor-6-methylphenyl)-2-[[6-(4-morpholinylmethyl)-4-pyrimidinyl]amino]-5-thiazolcarboxamid;  
 '1-[[6-[[5-[(2-Chlor-6-methylphenyl)amino]carbonyl]-2-thiazolyl]amino]-4-pyrimidinyl]methyl]-4-piperidincarboxamid;  
 '2-[(2,6-Dimethyl-4-pyrimidinyl)amino]-N-(2-methylphenyl)-5-thiazolcarboxamid;  
 'N-(2,6-Bis(1-methylethyl)phenyl)-2-[(2,6-dimethyl-4-pyrimidinyl)amino]-5-thiazolcarboxamid;  
 '2-[[6-[[3-(1H-Benzimidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-(2-chlor-6-methylphenyl)-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[4-(1H-imidazol-1-yl)butyl]amino]-2-pyridinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[5-(1H-imidazol-1-yl)pentyl]amino]-2-pyridinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[3-(4-methyl-1-piperazinyl)propyl]amino]-2-pyridinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[6-(1H-imidazol-1-yl)hexyl]amino]-2-pyridinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolcarboxamid;  
 'N-(4-Chlorophenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Ethylphenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolcarboxamid;  
 '2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-(2-methylphenyl)-5-thiazolcarboxamid;  
 'N-(2-Chlorophenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolcarboxamid;  
 'N-(2,6-Diethylphenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[3-[[3-(1H-imidazol-1-yl)propyl]amino]phenyl]amino]-5-thiazolcarboxamid;  
 'N-(2-Chlor-6-methylphenyl)-2-[[5-[[3-(1H-imidazol-1-yl)propyl]amino]-2-nitrophenyl]amino]-5-thiazolcarboxamid;  
 N-(2-Chlor-6-methylphenyl)-2-[[2-(2-methyl-1H-benzimidazol-5-yl)amino]-5-thiazolcarboxamid;  
 N-(2-Chlor-6-methylphenyl)-2-[[1-[3-(1H-imidazol-1-yl)propyl]-1H-benzimidazol-4-yl]amino]-5-thiazolcarboxamid;  
 N-(2-Chlor-6-methylphenyl)-2-[[1-[2-(1H-imidazol-1-yl)ethyl]-1H-indazol-6-yl]amino]-5-thiazolcarboxamid;  
 N-(2-Chlor-6-methylphenyl)-2-[[2-[2-(1H-imidazol-1-yl)ethyl]-2H-indazol-6-yl]amino]-5-thiazolcarboxamid;  
 N-(2-Chlor-6-methylphenyl)-2-[(1-methyl-1H-benzimidazol-6-yl)amino]-5-thiazolcarboxamid;  
 N-(2-Chlor-6-methylphenyl)-2-[(1-methyl-1H-benzimidazol-5-yl)amino]-5-thiazolcarboxamid;  
 N-(2-Chlor-6-methylphenyl)-2-[[2-[3-(1H-imidazol-1-yl)propyl]amino]-1H-benzimidazol-5-yl]amino]-5-thiazolcarboxamid;  
 N-(2-Chlor-6-methylphenyl)-2-[[2-(4-morpholinylmethyl)-1H-benzimidazol-5-yl]amino]-5-thiazolcarboxamid;  
 N-(2-Chlor-6-methylphenyl)-2-[[2-(1H-imidazol-1-ylmethyl)-1H-benzimidazol-5-yl]amino]-5-thiazolcarboxamid.

3. Verbindung nach Anspruch 1, wobei die Verbindung gemäß Formel II die folgende Verbindung



oder ein Salz davon ist.

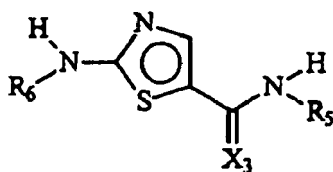
4. Verbindung nach einem der Ansprüche 1 bis 3 oder ein Salz davon zur Verwendung bei der Behandlung einer Protein-Tyrosin-Kinase-assoziierten Erkrankung, wobei die Protein-Tyrosin-Kinase-assoziierte Erkrankung eine Transplantatabstoßung, Rheumatoidarthritis, multiple Sklerose, entzündliche Darmerkrankung, Lupus, Transplantat-gegen-Empfänger-Reaktion, durch T-Zellen vermittelte Überempfindlichkeitsreaktion, Psoriasis, Hashimoto-Thyreoiditis, Guillain-Barré-Syndrom, Krebs, Kontaktdermatitis, Allergie, Asthma, ischämische oder Reperfusionsschädigung, atopische Dermatitis, allergische Rhinitis, chronisch-obstruktive Lungenerkrankung oder diabetische Retinopathie ist.
5. Verbindung zur Verwendung nach Anspruch 4, wobei die Protein-Tyrosin-Kinase Lck, Fyn, Lyn, Hck, Fgr, Src, Yes, Blk, HER1 oder HER2 ist.
6. Verbindung zur Verwendung nach Anspruch 4, wobei die in den Ansprüchen 1 bis 3 definierte Verbindung oder ein

Salz davon gleichzeitig oder nacheinander zusammen mit einem antiinflammatorischen oder antiproliferativen Mittel, Chemotherapeutikum, Immunsuppressivum, Antikrebsmittel, zytotoxischen Mittel oder einem anderen Protein-Tyrosin-Kinase-Hemmer (PTK-Hemmer) als einer in den Ansprüchen 1 bis 3 definierten Verbindung oder einem Salz davon zu verabreichen ist.

7. Verbindung zur Verwendung nach Anspruch 6, wobei die Verbindung gemäß Formel II oder ein Salz davon zusammen mit einer oder mehreren der folgenden Verbindungen zu verabreichen ist: einem anderen PTK-Hemmer; Cyclosporin A; CTLA4-Ig; Antikörpern, die unter Anti-ICAM-3, Anti-IL-2-Rezeptor (Anti-Tac), Anti-CD45RB, Anti-CD2, Anti-CD3 (OKT-3), Anti-CD4, Anti-CD80, Anti-CD86 und dem monoklonalen Antikörper OKT3 ausgewählt sind; Mitteln, welche die Interaktion zwischen CD40 und gp39 blockieren; Fusionsproteinen, die aus CD40 und gp39 konstruiert sind; Inhibitoren der NF-kappa B-Funktion; nichtsteroidalen Entzündungshemmern (NSAIDs), Steroiden; Goldverbindungen; antiproliferativen Mitteln; FK506 (Tacrolimus, Prograf); Mycophenolat-Mofetil; zytotoxischen Medikamenten; TNF- $\alpha$ -Hemmern, Anti-TNF-Antikörpern oder einem löslichen TNF-Rezeptor, Rapamycin (Sirolimus oder Rapamune); Leflunimid; Cyclooxygenase-2-Hemmer; Paclitaxel, Cisplatin, Carboplatin, Doxorubicin, Carminomycin, Daunorubicin, Aminopterin, Methotrexat, Methopterin, Mitomycin C, Ecteinascidin 743, Porfiromycin, 5-Fluoruracil, 6-Mercaptopurin, Gemcitabin, Cytosinarabinosid, Podophyllotoxin, Etoposid, Etoposidphosphat, Teniposid, Melphalan, Vinblastin, Vincristin, Leurosidin, Vindesin und Leurosine.
8. Pharmazeutische Zusammensetzung zur Behandlung einer Protein-Tyrosin-Kinase-assoziierten Erkrankung, wobei die Zusammensetzung ein pharmazeutisch akzeptierbares Vehikel oder Verdünnungsmittel und mindestens eine Verbindung von Anspruch 1 aufweist.
9. Pharmazeutische Zusammensetzung zur Behandlung einer Protein-Tyrosin-Kinase-assoziierten Erkrankung nach Anspruch 8, wobei die Zusammensetzung ein pharmazeutisch akzeptierbares Vehikel oder Verdünnungsmittel und die Verbindung von Anspruch 3 aufweist.

## Revendications

1. Composé cyclique de la formule II suivante ou un sel de celui-ci:



II

dans lequel:

$X_3$  est un oxygène ou un soufre;

$R_5$  est un groupe aryle qui est substitué avec un ou plusieurs groupes choisis parmi un alkyle et un halo;

$R_6$  est:

un aryle ou un hétéroaryle qui est substitué avec  $Z_1$ ,  $Z_2$  et un ou plusieurs groupes  $Z_3$ , dans lequel:

- a) ledit aryle est substitué avec au moins un groupe  $Z_3$  où  $Z_3$  est  $-Z_4-NZ_7Z_8$ , où  $Z_4$  est une liaison,  $Z_7$  est un hydrogène ou un alkyle et  $Z_8$  est un alkyle substitué par un hétérocycle; ou
- b) ledit hétéroaryle est substitué avec au moins un groupe  $Z_3$  où  $Z_3$  est  $-Z_4-NZ_7Z_8$ , où  $Z_4$  est une liaison,  $Z_7$  est un hydrogène ou un alkyle et  $Z_8$  est un alkyle substitué par un hétérocycle; ou
- c) ledit hétéroaryle est substitué avec au moins un groupe  $Z_3$  où  $Z_3$  est un alkyle;

$Z_1$ ,  $Z_2$  et  $Z_3$  sont chacun indépendamment:

- (1) un hydrogène ou  $Z_6$ , où  $Z_6$  est (i) un alkyle, un alcényle, un alcynyle, un cycloalkyle, un cycloalkylalkyle,

un cycloalcényle, un cycloalcénylalkyle, un aryle, un aralkyle, un alkylaryle, un cycloalkylaryle, un hétéro-cyclo ou un hétérocycloalkyle; (ii) un groupe (i) qui est lui-même substitué par un ou plusieurs des groupes (i) identiques ou différents; ou (iii) un groupe (i) ou (ii) qui est substitué par un ou plusieurs des groupes (2) à (16) suivants de la définition de  $Z_1$ ,  $Z_2$  et  $Z_3$ ;

(2) -OH ou -O $Z_6$ ;

(3) -SH ou -S $Z_6$ ;

(4) -C(O) $_q$ H, -C(O) $_q$  $Z_6$  ou -O-C(O) $_q$  $Z_6$ , où  $q$  est 1 ou 2;

(5) -SO $_3$ H, -S(O) $_q$  $Z_6$ ; ou S(O) $_q$ N( $Z_9$ ) $Z_6$ ;

(6) un halo;

(7) un cyano;

(8) un nitro;

(9) - $Z_4$ -N $Z_7$  $Z_8$ ;

(10) - $Z_4$ -N( $Z_9$ )- $Z_5$ -N $Z_7$  $Z_8$ ;

(11) - $Z_4$ -N( $Z_{10}$ )- $Z_5$ - $Z_6$ ;

(12) - $Z_4$ -N( $Z_{10}$ )- $Z_5$ -H;

(13) un oxo;

(14) -O-C(O)- $Z_6$ ;

(15) deux quelconques de  $Z_1$ ,  $Z_2$  et  $Z_3$  peuvent être ensemble un alkylène ou un alcénylène complétant un cycle de 3 à 8 membres saturé ou insaturé accompagnés des atomes auxquels ils sont attachés; ou

(16) deux quelconques de  $Z_1$ ,  $Z_2$  et  $Z_3$  peuvent être ensemble -O-(CH $_2$ ) $_r$ -O-, où  $r$  est de 1 à 5, complétant un cycle de 4 à 8 membres saturé ou insaturé accompagnés des atomes auxquels ils sont attachés;

$Z_4$  et  $Z_5$  sont chacun indépendamment:

(1) une liaison simple;

(2) - $Z_{11}$ -S(O) $_q$ - $Z_{12}$ ;

(3) - $Z_{11}$ -C(O)- $Z_{12}$ ;

(4) - $Z_{11}$ -C(S)- $Z_{12}$ ;

(5) - $Z_{11}$ -O- $Z_{12}$ ;

(6) - $Z_{11}$ -S- $Z_{12}$ ;

(7) - $Z_{11}$ -O-C(O)- $Z_{12}$ ; ou

(8) - $Z_{11}$ -C(O)-O- $Z_{12}$ ;

$Z_7$ ,  $Z_8$ ,  $Z_9$  et  $Z_{10}$ :

(1) sont chacun indépendamment un hydrogène ou  $Z_6$ ;

(2)  $Z_7$  et  $Z_8$ , ou  $Z_6$  et  $Z_{10}$ , peuvent être ensemble un alkylène ou un alcénylène, complétant un cycle de 3 à 8 membres saturé ou insaturé accompagnés des atomes auxquels ils sont attachés, lequel cycle est non substitué ou substitué avec  $Z_1$ ,  $Z_2$ , et  $Z_3$ ; ou

(3)  $Z_7$  ou  $Z_8$ , accompagné de  $Z_9$ , peuvent être un alkylène ou un alcénylène complétant un cycle de 3 à 8 membres saturé ou insaturé accompagnés des atomes d'azote auxquels ils sont attachés, lequel cycle est non substitué ou substitué avec  $Z_1$ ,  $Z_2$  et  $Z_3$ ;

$Z_{11}$  et  $Z_{12}$  sont chacun indépendamment:

(1) une liaison simple;

(2) un alkylène;

(3) un alcénylène; ou

(4) un alcynylène.

2. Composé ou un sel de celui-ci selon la revendication 1 choisi dans le groupe constitué de:

N-(2-chloro-6-méthylphényl)-2-[(4,6-diméthyl-2-pyridinyl)amino]-5-thiazolecarboxamide;

N-(2-chloro-6-méthylphényl)-2-[(4-éthyl-2-pyridinyl)amino]-5-thiazolecarboxamide;

N-(2-chloro-6-méthylphényl)-2-[(2,6-diméthyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide;

N-(2-chloro-6-méthylphényl)-2-[(4-méthyl-2-pyridinyl)amino]-5-thiazolecarboxamide;

N-(2-chloro-6-méthylphényl)-2-[(6-propyl-2-pyridinyl)amino]-5-thiazolecarboxamide;

N-(2-chloro-6-méthylphényl)-2-[(6-éthyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide;

'N-(2-chloro-6-méthylphényl)-2-[(6-méthyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 'N-(2-chloro-6-méthylphényl)-2-[(5-méthyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 'N-(2-chloro-6-méthylphényl)-2-[(4-méthyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 'N-(2-chloro-6-méthylphényl)-2-[(3-méthyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 5 '2-[(5-bromo-3-méthyl-2-pyridinyl)amino]-N-(2-chloro-6-méthylphényl)-5-thiazolecarboxamide;  
 'N-(2-chloro-6-méthylphényl)-2-[(6-éthyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 'N-(2-chloro-6-méthylphényl)-2-[(6-propyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 '2-[(3-bromo-5-méthyl-2-pyridinyl)amino]-N-(2-chloro-6-méthylphényl)-5-thiazolecarboxamide;  
 'N-(2-chloro-6-méthylphényl)-2-[(3,5-diméthyl-2-pyrazinyl)amino]-5-thiazolecarboxamide;  
 10 'N-(2-chloro-6-méthylphényl)-2-[(4,6-diméthyl-2-pyrimidinyl)amino]-5-thiazolecarboxamide;  
 'N-(2-chloro-6-méthylphényl)-2-[(6-éthyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide;  
 'N-(2,6-diméthylphényl)-2-[(6-méthyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 N-(2,6-diméthylphényl)-2-[(4-méthyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 'N-(2,6-diméthylphényl)-2-[(4-éthyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 15 'N-(2,6-diméthylphényl)-2-[(4,6-diméthyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 'N-(2,6-diméthylphényl)-2-[(6-éthyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 'N-(2,6-diméthylphényl)-2-[(6-propyl-2-pyridinyl)amino]-5-thiazolecarboxamide;  
 '2-[(6-amino-2-méthyl-4-pyrimidinyl)amino]-N-(2,6-diméthylphényl)-5-thiazolecarboxamide;  
 '2-[(6-méthyl-2-pyridinyl)amino]-N-(2,4,6-triméthylphényl)-5-thiazolecarboxamide;  
 20 '2-[(5-méthyl-2-pyridinyl)amino]-N-(2,4,6-triméthylphényl)-5-thiazolecarboxamide;  
 '2-[(4-méthyl-2-pyridinyl)amino]-N-(2,4,6-triméthylphényl)-5-thiazolecarboxamide;  
 '2-[(3-méthyl-2-pyridinyl)amino]-N-(2,4,6-triméthylphényl)-5-thiazolecarboxamide;  
 '2-[(4-éthyl-2-pyridinyl)amino]-N-(2,4,6-triméthylphényl)-5-thiazolecarboxamide;  
 '2-[(6-éthyl-2-pyridinyl)amino]-N-(2,4,6-triméthylphényl)-5-thiazolecarboxamide;  
 25 '2-[(2,6-diméthyl-4-pyrimidinyl)amino]-N-(2,4,6-triméthylphényl)-5-thiazolecarboxamide;  
 '2-[(4-méthyl-2-pyrimidinyl)amino]-N-(2,4,6-triméthylphényl)-5-thiazolecarboxamide;  
 '2-[(3,5-diméthyl-2-pyrazinyl)amino]-N-(2,4,6-triméthylphényl)-5-thiazolecarboxamide;  
 'N-(2-chloro-6-méthylphényl)-2-[[2-méthyl-6-[[2-(4-morpholinyl)éthyl]amino]-4-pyrimidinyl]-amino]-5-thiazole-  
 carboxamide;  
 30 N-(2-chloro-6-méthylphényl)-2-[[2-méthyl-6-[[3-(4-morpholinyl)propyl]amino]-4-pyrimidinyl]-amino]-5-thiazole-  
 carboxamide;  
 'N-(2-chloro-6-méthylphényl)-2-[[2-méthyl-6-[méthyl-[3-(méthylamino)propyl] amino]-4-pyrimidinyl] amino]-5-  
 thiazolecarboxamide;  
 'N-(2-chloro-6-méthylphényl)-2-[[2-méthyl-6-[[2-(tétrahydro-2-oxo-1H-imidazol-1-yl)-éthyl]-amino]-4-pyrimidi-  
 35 nyl]amino]-5-thiazolecarboxamide;  
 'N-(2-chloro-6-méthylphényl)-2-[[2-méthyl-6-[(2-1H-imidazol-4-yléthyl)amino]-4-pyrimidinyl]-amino]-5-thiazole-  
 carboxamide;  
 'N-(2-chloro-6-méthylphényl)-2-[[2-méthyl-6-(4-morpholinyl)-4-pyrimidinyl]amino]-5-thiazole-carboxamide;  
 'N-(2-chloro-6-méthylphényl)-2-[[6-[[[(2R)-1-éthyl-2-pyrrolidinyl]méthyl] amino]-2-méthyl-4-pyrimidinyl] amino]-  
 40 5-thiazolecarboxamide;  
 'N-(2-chloro-6-méthylphényl)-2-[[6-[[[(2S)-1-éthyl-2-pyrrolidinyl]méthyl]amino]-2-méthyl-4-pyrimidinyl]amino]-  
 5-thiazolecarboxamide;  
 '2-[[6-[(2S)-2-(aminocarbonyl)-1-pyrrolidinyl]-2-méthyl-4-pyrimidinyl]amino]-N-(2-chloro-6-méthylphényl)-5-  
 thiazolecarboxamide;  
 45 'N-(2-chloro-6-méthylphényl)-2-[[6-[(2-hydroxyéthyl)amino]-2-méthyl-4-pyrimidinyl]amino]-5-thiazolecarboxa-  
 mide;  
 'N-(2-chloro-6-méthylphényl)-2-[[6-[4-(hydroxyméthyl)-1-pipéridinyl]-2-méthyl-4-pyrimidinyl]-amino]-5-thiazo-  
 lecarboxamide;  
 'N-(2-chloro-6-méthylphényl)-2-[[6-[4-(2-hydroxyéthyl)-1-pipérazinyl]-2-méthyl-4-pyrimidinyl]-amino]-5-thiazo-  
 50 lecarboxamide;  
 '1-[6-[[5[[2-chloro-6-méthylphényl]amino]carbonyl]-2-thiazolyl]amino]-2-méthyl-4-pyrimidinyl]-4-pipéridinecar-  
 boxamide;  
 'N-(2-chloro-6-méthylphényl)-2-[[2-méthyl-6-[(3S)-3-méthyl-1-pipérazinyl]-4-pyrimidinyl]amino]-5-thiazolecar-  
 boxamide;  
 55 '2-[[6-[3-(acétylamino)-1-pyrrolidinyl]-2-méthyl-4-pyrimidinyl]amino]-N-(2-chloro-6-méthyl-phényl)-5-thiazole-  
 carboxamide;  
 'N-(2-chloro-6-méthylphényl)-2-[[6-[[2-(1-méthyl-2-pyrrolidinyl)éthyl]amino]-2-méthyl-4-pyrimidinyl]amino]-5-  
 thiazolecarboxamide;

'N-(2-chloro-6-méthylphényl)-2-[[2-méthyl-6-[[5-méthyl-2-pyrazinyl)méthyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'N-(2-chloro-6-méthylphényl)-2-[[2-méthyl-6-[[2-(1H-1,2,3-triazol-1-yl)éthyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

5 'N-(2-chloro-6-méthylphényl)-2-[[6-[[2-(4-morpholiny)éthyl] amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'N-(2-chloro-6-méthylphényl)-2-[[6-[[2-(tétrahydro-2-oxo-1H-imidazol-1-yl)éthyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

10 'N-(2-chloro-6-méthylphényl)-2-[[6-[[2-(1-méthyl-2-pyrrolidinyl)éthyl] amino]-4-pyrimidinyl]-amino]-5-thiazolecarboxamide;

'N-(2-chloro-6-méthylphényl)-2-[[6-[[2-(1-pyrrolidinyl)éthyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'N-(2-chloro-6-méthylphényl)-2-[[6-[[1-éthyl-2-pyrrolidinyl)méthyl]amino]-4-pyrimidinyl]-amino]-5-thiazolecarboxamide;

15 'N-(2-chloro-6-méthylphényl)-2-[[6-[[4-pipéridinyl)méthyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

N-(2-chloro-6-méthylphényl)-2-[[6-[[2-(1H-1,2,3-triazol-1-yl)éthyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'N-(2-chloro-6-méthylphényl)-2-[[6-[[2-(4-morpholiny)éthyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

20 'N-(2-chloro-6-méthylphényl)-2-[[6-[[3-(4-morpholiny)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

'N-(2-chloro-6-méthylphényl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

'N-(2-chloro-6-méthylphényl)-2-[[6-[[2-(1H-imidazol-1-yl)éthyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

25 'N-(2-chloro-6-méthylphényl)-2-[[6-[[2-(4-morpholiny)éthyl]amino]-2-pyrazinyl]amino]-5-thiazolecarboxamide;

'N-(2-chloro-6-méthylphényl)-2-[[6-[[3-(4-morpholiny)propyl]amino]-2-pyrazinyl]amino]-5-thiazolecarboxamide;

N-(2-chloro-6-méthylphényl)-2-[[3-[[2-(4-morpholiny)éthyl]amino]-2-pyrazinyl]amino]-5-thiazolecarboxamide;

30 'N-(2-chloro-6-méthylphényl)-2-[[6-[[4-morpholiny)méthyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'1-[[6-[[5-[[2-chloro-6-méthylphényl]amino]carbonyl]-2-thiazolyl]amino]-4-pyrimidinyl)méthyl]-4-pipéridinecarboxamide;

'2-[[2,6-diméthyl-4-pyrimidinyl]amino]-N-(2-méthylphényl)-5-thiazolecarboxamide;

'N-[2,6-bis(1-méthyléthyl)phényl]-2-[[2,6-diméthyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

35 '2-[[6-[[3-(1H-benzimidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-(2-chloro-6-méthylphényl)-5-thiazolecarboxamide;

'N-(2-chloro-6-méthylphényl)-2-[[6-[[4-(1H-imidazol-1-yl)butyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

'N-(2-chloro-6-méthylphényl)-2-[[6-[[5-(1H-imidazol-1-yl)pentyl] amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

40 'N-(2-chloro-6-méthylphényl)-2-[[6-[[3-(4-méthyl-1-pipérazinyl)propyl] amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

'N-(2-chloro-6-méthylphényl)-2-[[6-[[6-(1H-imidazol-1-yl)hexyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

45 'N-(2-chloro-6-méthylphényl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

'N-(4-chlorophényl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

'N-(2-éthylphényl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

'2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-(2-méthylphényl)-5-thiazolecarboxamide;

50 'N-(2-chlorophényl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

'N-(2,6-diéthylphényl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

'N-(2-chloro-6-méthylphényl)-2-[[3-[[3-(1H-imidazol-1-yl)propyl]amino]phényl]amino]-5-thiazolecarboxamide;

'N-(2-chloro-6-méthylphényl)-2-[[5-[[3-(1H-imidazol-1-yl)propyl]amino]-2-nitrophényl]amino]-5-thiazolecarboxamide;

55 N-(2-chloro-6-méthylphényl)-2-[[2-méthyl-1H-benzimidazol-5-yl]amino]-5-thiazolecarboxamide;

N-(2-chloro-6-méthylphényl)-2-[[1-[3-(1H-imidazol-1-yl)propyl]-1H-benzimidazol-4-yl]amino]-5-thiazolecarboxamide;

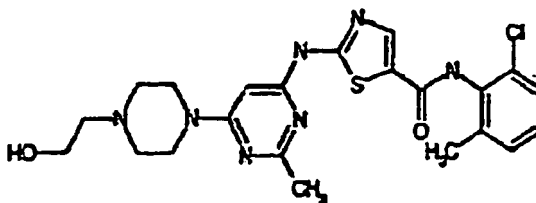
N-(2-chloro-6-méthylphényl)-2-[[1-[2-(1H-imidazol-1-yl)éthyl]-1H-indazol-6-yl]amino]-5-thiazolecarboxamide;

N-(2-chloro-6-méthylphényl)-2-[[2-[2-(1H-imidazol-1-yl)éthyl]-2H-indazol-6-yl]amino]-5-thiazolecarboxamide;



N-(2-chloro-6-méthylphényl)-2-[(1-méthyl-1H-benzimidazol-6-yl)amino]-5-thiazolecarboxamide;  
 N-(2-chloro-6-méthylphényl)-2-[(1-méthyl-1H-benzimidazol-5-yl)amino]-5-thiazolecarboxamide;  
 N-(2-chloro-6-méthylphényl)-2-[[2-[3-(1H-imidazol-1-yl)propyl] amino]-1H-benzimidazol-5-yl]amino]-5-thiazolecarboxamide;  
 N-(2-chloro-6-méthylphényl)-2-[[2-(4-morpholinylméthyl)-1H-benzimidazol-5-yl]amino]-5-thiazolecarboxamide;  
 N-(2-chloro-6-méthylphényl)-2-[[2-(1H-imidazol-1-ylméthyl)-1H-benzimidazol-5-yl]amino]-5-thiazolecarboxamide.

3. Composé selon la revendication 1, où le composé de la formule II est le composé suivant:



ou un sel de celui-ci.

4. Composé selon l'une quelconque des revendications 1 à 3 ou un sel de celui-ci pour une utilisation dans le traitement d'un trouble associé à une protéine tyrosine kinase, dans lequel ledit trouble associé à une protéine tyrosine kinase est un rejet de transplant, une polyarthrite rhumatoïde, une sclérose en plaques, une maladie intestinale inflammatoire, un lupus, une maladie de greffe contre hôte, une maladie d'hypersensibilité induite par les cellules T, un psoriasis, une thyroïdite de Hashimoto, un syndrome de Guillain-Barré, un cancer, une dermatite de contact, une maladie allergique, un asthme, une lésion ischémique ou consécutive à une perfusion, une dermatite atopique, une rhinite allergique, une maladie pulmonaire obstructive chronique ou une rétinopathie diabétique.
5. Composé pour une utilisation selon la revendication 4, dans lequel ladite protéine tyrosine kinase est Lck, Fyn, Lyn, Hck, Fgr, Src, Yes, Blk, HER1 ou HER2.
6. Composé pour une utilisation selon la revendication 4, où ledit composé tel que défini dans les revendications 1 à 3 ou un sel de celui-ci est à administrer, simultanément ou séquentiellement, avec un agent anti-inflammatoire, anti-prolifératif, chimiothérapeutique, un immunosuppresseur, un anti-cancer, un agent cytotoxique ou un inhibiteur de PTK autre qu'un composé tel que défini dans les revendications 1 à 3 ou un sel de celui-ci.
7. Composé pour une utilisation selon la revendication 6, où ledit composé de la formule II ou un sel de celui-ci est à administrer avec un ou plusieurs parmi: un autre inhibiteur de PTK; une cyclosporine A; CTLA4-Ig; des anticorps choisis parmi anti-ICAM-3, un récepteur d'anti-IL-2 (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80, anti-CD86 et un anticorps monoclonal OKT3; des agents bloquant l'interaction entre CD40 et gp39; des protéines de fusion construites à partir de CD40 et de gp39; des inhibiteurs de la fonction NF-kappa B; des médicaments anti-inflammatoires non stéroïdiens (NSAIDs); des stéroïdes; des composés d'or; des agents anti-prolifératifs; FK506 (tacrolimus, Prograf); le mycophénolate mofétil; des médicaments cytotoxiques; des inhibiteurs de TNF- $\alpha$ ; des anticorps anti-TNF ou un récepteur de TNF soluble; la rapamycine (sirolimus ou Rapamune); le léflunimide; des inhibiteurs de cyclooxygénase-2; le paclitaxel, le cisplatine, le carboplatine, la doxorubicine, la carminomycine, la daunorubicine, l'aminoptérine, le méthotrexate, la méthoptérine, la mitomycine C, l'ectéinascidine 743, la porfiromycine, le 5-fluorouracile, la 6-mercaptopurine, la gemcitabine, l'arabinoside de cytosine, la podophyllotoxine, l'étoposide, le phosphate d'étoposide, le téniposide, le melphalan, la vinblastine, la vincristine, la leurosine, la vindésine et la leurosine.
8. Composition pharmaceutique pour le traitement d'un trouble associé à une protéine tyrosine kinase, comprenant un véhicule ou un diluant pharmaceutiquement acceptable et au moins un composé de la revendication 1.
9. Composition pharmaceutique pour le traitement d'un trouble associé à une protéine tyrosine kinase selon la revendication 8, comprenant un véhicule ou un diluant pharmaceutiquement acceptable et le composé de la revendication 3.

## REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

## Patent documents cited in the description

- EP 0275312 A1 [0005]
- US 056770 P [0083]
- US 82597 P [0083]
- US 09097338 B [0083]
- US 60056797 B [0083]
- US 82597 A [0083]
- US 09094797 B [0083]
- US 60065042 B [0083]
- US 09173413 B [0083]
- US 60076789 B [0083]
- US 09262525 B [0083]
- US 09506481 B [0087]
- DE 4138042 [0087]
- WO 9719086 A [0087]
- WO 9822461 A [0087]
- WO 9825929 A [0087]
- WO 9838192 A [0087]
- WO 9901124 A [0087]
- WO 9902224 A [0087]
- WO 9902514 A [0087]
- WO 9903848 A [0087]
- WO 9907692 A [0087]
- WO 9927890 A [0087]
- WO 9928324 A [0087]
- WO 9943653 A [0087]
- WO 9954330 A [0087]
- WO 9954318 A [0087]
- WO 9954319 A [0087]
- WO 9965913 A [0087]
- WO 9967252 A [0087]
- WO 9967253 A [0087]
- WO 0000485 A [0087]
- WO 9924416 A [0087]
- WO 9730992 A [0087]
- WO 9854966 A [0087]
- GB 2323595 A [0377]

## Non-patent literature cited in the description

- **BOLEN, J.B. ; ROWLEY, R.B. ; SPANA, C. ; TSYG-ANKOV, A.Y.** The src family of tyrosine protein kinases in hemopoietic signal transduction. *FASEB J.*, 1992, vol. 6, 3403-3409 [0002]
- **ULLRICH, A. ; SCHLESSINGER, J.** Signal transduction by receptors with tyrosine kinase activity. *Cell*, 1990, vol. 61, 203-212 [0002]
- **IHLE, J.N.** The Janus protein tyrosine kinases in hematopoietic cytokine signaling. *Sem. Immunol.*, 1995, vol. 7, 247-254 [0002]
- **WEISS, A. ; LITTMAN, D.R.** Signal transduction by lymphocyte antigen receptors. *Cell*, 1994, vol. 76, 263-274 [0004]
- **IWASHIMA, M. ; IRVING, B.A. ; VAN OERS, N.S.C. ; CHAN, A.C. ; WEISS, A.** Sequential interactions of the TCR with two distinct cytoplasmic tyrosine kinases. *Science*, 1994, vol. 263, 1136-1139 [0004]
- **CHAN, A.C. ; DALTON, M. ; JOHNSON, R. ; KONG, G. ; WANG, T. ; THOMA, R. ; KUROSAKI, T.** Activation of ZAP-70 kinase activity by phosphorylation of tyrosine 493 is required for lymphocyte antigen receptor function. *EMBO J.*, 1995, vol. 14, 2499-2508 [0004]
- **THOMPSON, L. A. ; ELLMAN, J. A.** *Chemical Reviews*, 1996, vol. 96, 555-600 [0034]
- **TERRETT, N. K. ; GARDNER, M. ; GORDON, D. W. ; KOBYLECKI, R. J. ; STEELE, J.** *Tetrahedron*, 1995, vol. 51, 8135-8173 [0034]
- **GALLOP, M. A. ; BARRETT, R. W. ; DOWER, W. J. ; FODOR, S. P. A. ; GORDON, E. M.** *Journal of Medicinal Chemistry*, 1994, vol. 37, 1233-1251 [0034]
- **GORDON, E. M. ; BARRETT, R. W. ; DOWER, W. J. ; FODOR, S. P. A. ; GALLOP, M. A.** *Journal of Medicinal Chemistry*, 1994, vol. 37, 1385-1401 [0034]
- **BALKENHOHL, F. ; VON DEM BUSSCHE-HÜNNFELD ; LANSKY, A. ; ZECHEL, C.** *Angewandte Chemie International Edition in English*, 1996, vol. 35, 2288-2337 [0034]
- **BALKENHOHL, F. ; VON DEM BUSSCHE-HÜNNFELD ; LANSKY, A. ; ZECHEL, C.** *Angewandte Chemie*, 1996, vol. 108, 2436-2487 [0034]
- **SOFIA, M. J.** *Drugs Discovery Today*, 1996, vol. 1, 27-34 [0034]
- *J. Het. Chem.*, 1985, vol. 22, 1621 [0037]
- *Bull. Soc. Chim. Belg.*, 1978, vol. 87, 223 [0041]
- **BODANSZKY ; BODANSZKY.** *The Practice of Peptide Chemistry*. Springer-Verlag, 1984 [0046]
- **BODANSZKY.** *Principles of Peptide Synthesis*. Springer-Verlag, 1984 [0046]

- **MARCH.** Advanced Organic Chemistry. Wiley, 1985 [0048] [0050]
- **HUDLICKY.** Reductions in Organic Chemistry. Wiley, 1984 [0049]
- **LEE et al.** *J. Heterocyclic Chemistry*, 1985, vol. 22, 1621 [0057]
- *J. Am. Chem. Soc.*, 1996, vol. 118, 7215 [0059]
- **GUNZENHAUSER et al.** *Helv. Chim. Acta*, 1988, vol. 71, 33 [0065]
- **COBLEIGH, M. A. ; VOGEL, C. L. ; TRIPATHY, D. ; ROBERT, N. J. ; SCHOLL, S. ; FEHRENBACHER, L. ; WOLTER, J. M. ; PATON, V. ; SHAK, S. ; LIEBERMAN, G.** Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J. of Clin. Oncol.*, 1999, vol. 17 (9), 2639-2648 [0073]
- **BASELGA, J. ; PFISTER, D. ; COOPER, M. R. ; COHEN, R. ; BURTNES, B. ; BOS, M. ; D'ANDREA, G. ; SEIDMAN, A. ; NORTON, L. ; GUNNETT, K.** Phase I studies of anti-epidermal growth factor receptor chimeric antibody C225 alone and in combination with cisplatin. *J. Clin. Oncol.*, 2000, vol. 18 (4), 904-914 [0073]
- **HOLLENBAUGH, D. ; DOUTHWRIGHT, J. ; McDONALD, V. ; ARUFFO, A.** Cleavable CD40lg fusion proteins and the binding to sgp39. *J. Immunol. Methods*, 15 December 1995, vol. 188 (1), 1-7 [0083]
- **HOLLENBAUGH, D. ; GROSMIRE, L.S. ; KULLAS, C.D. ; CHALUPNY, N.J. ; BRAESCH-ANDERSEN, S. ; NOELLE, R.J. ; STAMENKOVIC, I. ; LEDBETTER, J.A. ; ARUFFO, A.** The human T cell antigen gp39, a member of the TNF gene family, is a ligand for the CD40 receptor: expression of a soluble form of gp39 with B cell co-stimulatory activity. *EMBO J*, December 1992, vol. 11 (12), 4313-4321 [0083]
- **MORELAND, L.W. et al.** Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *J. of Medicine*, 1997, vol. 337 (3), 141-147 [0083]
- **COOPER, J.A. ; ESCH, F.S. ; TAYLOR, S.S. ; HUNTER, T.** Phosphorylation sites in enolase and lactate dehydrogenase utilized by tyrosine protein kinases in vivo and in vitro. *J. Biol. Chem.*, 1984, vol. 259, 7835-7841 [0091]
- **SPANNA, C. ; O'ROURKE, E.C. ; BOLEN, J.B. ; FARGNOLI, J.** Analysis of the tyrosine kinase p56lck expressed as a glutathione S-transferase protein in *Spodoptera frugiperda* cells. *Protein expression and purification*, 1993, vol. 4, 390-397 [0093]
- **SCHIEVEN, G.L. ; MITTLER, R.S. ; NADLER, S.G. ; KIRIHARA, J.M. ; BOLEN, J.B. ; KANNER, S.B. ; LEDBETTER, J.A.** ZAP-70 tyrosine kinase, CD45 and T cell receptor involvement in UV and H<sub>2</sub>O<sub>2</sub> induced T cell signal transduction. *J. Biol. Chem.*, 1994, vol. 269, 20718-20726 [0096] [0098]
- **HANSEN, J.A. ; MARTIN, P.J. ; BEATTY, P.G. ; CLARK, E.A. ; LEDBETTER, J.A.** Human T lymphocyte cell surface molecules defined by the workshop monoclonal antibodies. Springer Verlag, 1984, 195-212 [0097]
- **LEDBETTER, J.A. ; JUNE, C.H. ; RABINOVITCH, P.S. ; GROSSMAN, A. ; TSU, T.T. ; IMBODEN, J.B.** Signal transduction through CD4 receptors: stimulatory vs. inhibitory activity is regulated by CD4 proximity to the CD3/T cell receptor. *Eur. J. Immunol.*, 1988, vol. 18, 525 [0097]
- **B. PLOUVLER ; C. BAILLY ; R. HOUSSIN ; J-P. HENLCHART.** *Heterocycles*, 1991, vol. 32 (4), 693-701 [0217]
- **H. J. BECKER ; J. DE JONGE.** *Rec. Trav. Chim.*, 1942, vol. 61, 463 [0217]