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(54) **4-(DIARYLMETHYL)-1-PIPERAZINYL DERIVATIVES**

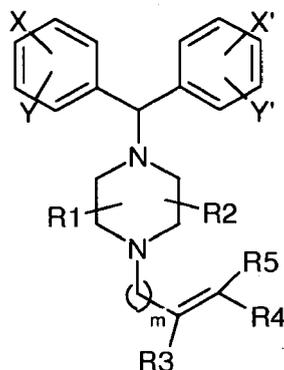
4-(DIARYLMETHYL)-1-PIPERAZINYL-DERIVATE
DERIVES DE 4-(DIARYLMETHYLE)-1-PIPERAZINYLE

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Description

[0001] The present invention relates to compound of formula I, 4-(diarylmethyl)-1-piperaziny derivatives with alkenyl moiety substituted at the 1-position of the piperazine unit.



Formula I

wherein X, Y, X' & Y' are selected from hydrogen, halogen, linear, branched or cyclo alkyl, alkyloxy and haloalkyl group; R₁ and R₂, are both hydrogen, R₃ and R₄ are selected from hydrogen linear, branched or cyclo alkyl groups and aryl, and optionally R₃ and R₄ together with the carbons to which they are attached form an aryl ring with a proviso that when R₃ & R₄ together do not form part of said aryl ring they may exist in either E or Z configuration;

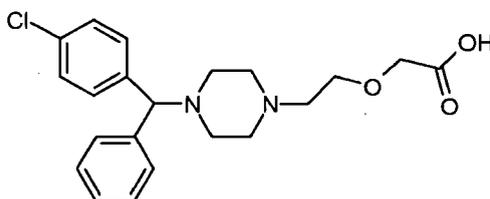
R₅ is (CH₂)_n-O-CH₂-CO-Z wherein n is 1 to 6; Z is selected from OH, OR, NRR', N(OR)R', wherein R & R' are selected from hydrogen, linear, branched or cyclo alkyl groups or C2 to C6 alkenyl or alkynyl groups; and m is selected from 1 to 6; and pharmaceutically acceptable salts thereof.

[0002] The R₅ group in formula I represents an alkyloxy acetic acid and its derivatives, such as an ester, an amide, a hydroxamic acid or a hydrazide. These compounds include their non-toxic pharmaceutically acceptable acid addition salts and those derived from alkali metals, alkaline earth metals or amines including hydroxyalkyl and polyhydroxy-alkylamines.

[0003] The compound of the present invention is an antihistaminic compound useful in the treatment of histamine mediated diseases.

PRIOR ART

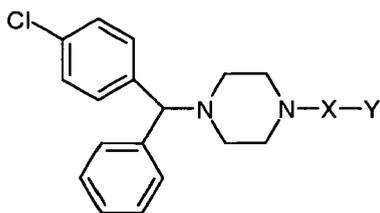
[0004] United States patent number 4525358 (Indian reference not available) discloses an antihistaminic compound cetirizine



which is used as an antiallergic, antihistaminic, bronchodilator or antispasmodic agent. It is useful in patients suffering from indications requiring the above mentioned effects. However, it is devoid of an olefinic side chain on the piperazine ring.

[0005] PCT publication WO 01/79188 discloses novel compounds of formula

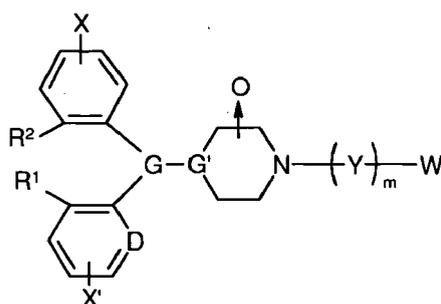
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10 which are more hydrophobic in nature than cetirizine as Y is substituted or unsubstituted carbocyclic, a heterocyclic, a polycyclic hydrocarbonyl, a heteropolycyclic, a carbocyclic arenyl, a heteropolycyclic arenyl or theophylline group.
[0006] PCT publication WO 00/58295 discloses new compounds of formula

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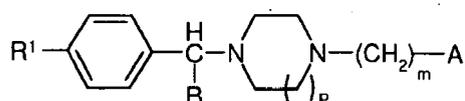
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for treating asthma, allergy and inflammatory disorders, wherein W or a substituent on the phenyl ring is a hydroxylamine.
[0007] European patent number 598123 discloses piperazine derivatives of formula

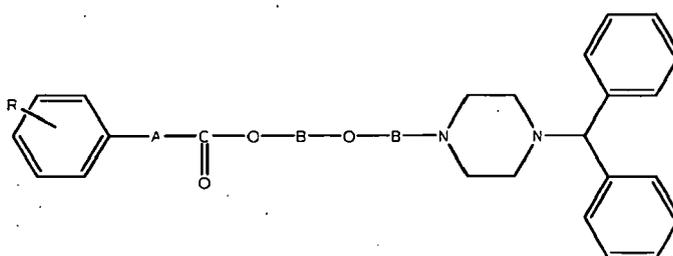
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which are different from compound of formula I as they do not contain an olefinic side chain on the piperazine ring.
[0008] FR 2 082 168 discloses compounds of the formula

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Where A is a bond or a saturated or unsaturated divalent C1-C6 hydrocarbon, B is a divalent C1 to C5 saturated hydrocarbon group and R represents any of a broad range of substituents of the aryl ring.

[0009] We have now found novel antihistaminic compounds.

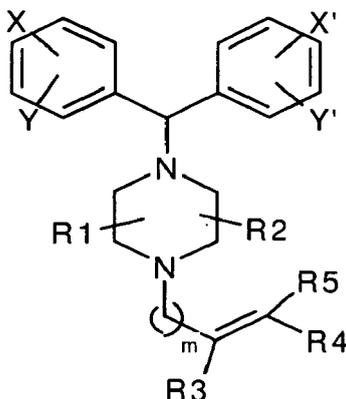
OBJECTS OF THE INVENTION:

[0010] The object of the present invention is to provide antihistaminic compound of formula I and pharmaceutically acceptable salts thereof.

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SUMMARY OF INVENTION:

[0011] A compound of formula I

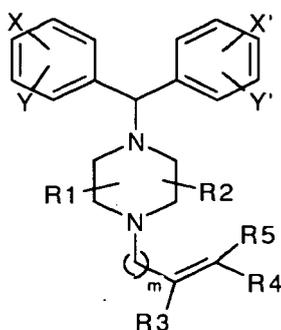


Formula I

wherein X, Y, X' & Y' are selected from hydrogen, halogen, linear, branched or cyclo alkyl, alkyloxy and haloalkyl group; R₁ and R₂, are both hydrogen, R₃ and R₄ are selected from hydrogen linear, branched or cyclo alkyl groups and aryl, and optionally R₃ and R₄ together with the carbons to which they are attached form an aryl ring with a proviso that when R₃ & R₄ together do not form part of said aryl ring they may exist in either E or Z configuration; R₅ is (CH₂)_n-O-CH₂-CO-Z wherein n is 1 to 6; Z is selected from OH, OR, NRR', N(OR)R', wherein R & R' are selected from hydrogen, linear, branched or cyclo alkyl groups or C2 to C6 alkenyl or alkynyl groups; and m is selected from 1 to 6; and pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION:

[0012] Accordingly, the present invention provides compound of formula I



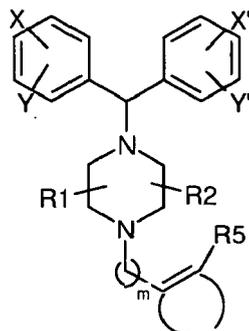
Formula I

wherein X, Y, X' & Y' are selected from hydrogen, halogen, linear, branched or cyclo alkyl, alkyloxy and haloalkyl group; R₁ and R₂, are both hydrogen, R₃ and R₄ are selected from hydrogen linear, branched or cyclo alkyl groups and aryl, and optionally R₃ and R₄ together with the carbons to which they are attached form an aryl ring with a proviso that when R₃ & R₄ together do not form part of said aryl ring they may exist in either E or Z configuration; R₅ is (CH₂)_n-O-CH₂-CO-Z wherein n is 1 to 6; Z is selected from OH, OR, NRR', N(OR)R', wherein R & R' are selected from hydrogen, linear, branched or cyclo alkyl groups or C2 to C6, alkenyl or alkynyl groups; and m is selected from 1 to 6; and pharmaceutically acceptable salts thereof.

[0013] The compound of the present invention wherein R₃ and R₄ together with the carbons to which they are attached form a monocyclic saturated or aryl or substituted aryl or heteroaryl or substituted heteroaryl ring containing one or more hetero atoms selected from N, S and O with a ring size ranging from 3 to 6 is referred to herein as compound of formula II

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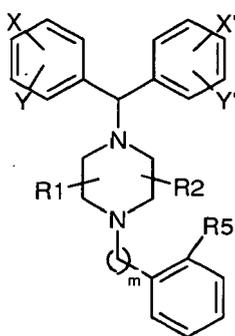
formula II

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[0014] The preferred compound of formula II is wherein the ring is a benzene ring

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formula II

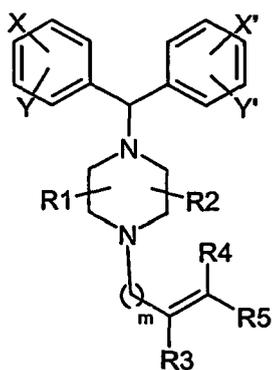
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[0015] The compound of the present invention wherein R_3 and R_4 are in *E* configuration, is referred to herein as compound of formula III,

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formula III

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[0016] Preferably, compound of formula I wherein

X , Y , X' & Y' are selected from hydrogen, chloro and fluoro;

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R_1 and R_2 , are hydrogen;

R_3 and R_4 are hydrogen existing in the *E* or *Z* configuration or optionally R_3 and R_4 together with the carbons to which they are attached form a benzene ring; and

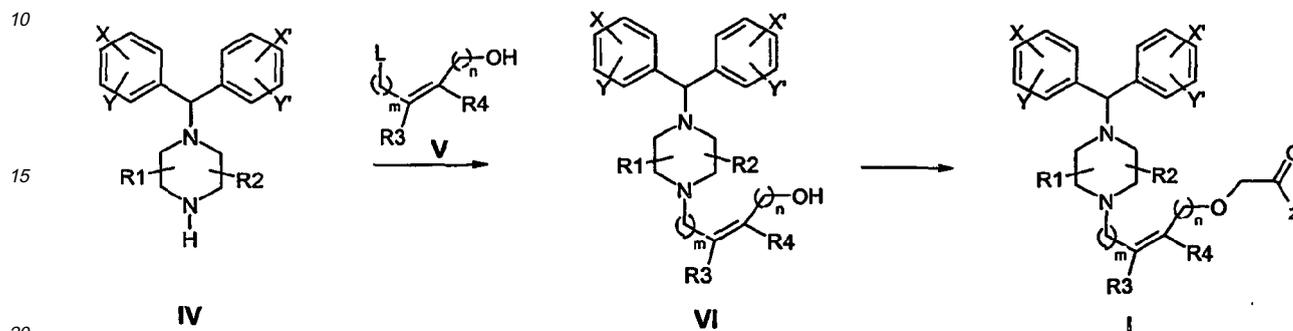
R_5 is CH_2-O-CH_2-CO-Z wherein Z is selected from OH and OR wherein R may be selected from methyl, ethyl and

isopropyl;
;and m is 1.

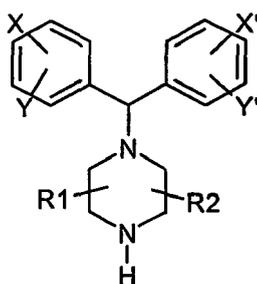
[0017] Compounds of the present invention may be prepared using different routes. For instance, as illustrated in Schemes 1 to 4.

5 [0018] In process as illustrated in Scheme 1

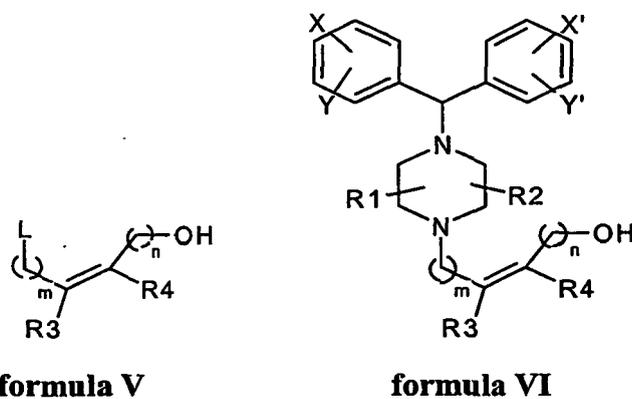
10 **Scheme 1**



25 compound of formula IV,



40 wherein X, Y, X', Y', R₁ and R₂ are as described above, is N-alkylated with compound of formula V wherein L is a leaving group selected from halo, or an alkyl or arylsulfonate group for e.g. methanesulfonate or p-toluenesulfonate and the like, to give compound of formula VI,

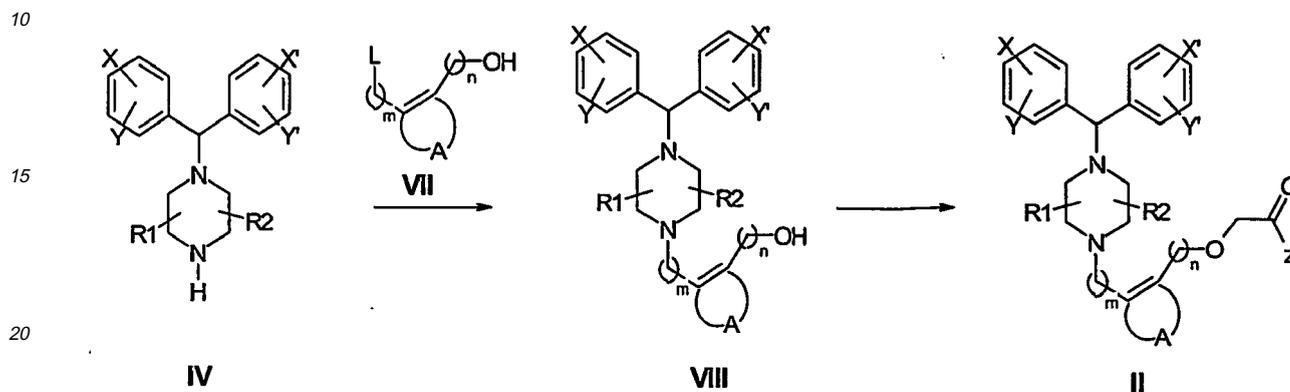


which is then reacted with X_1CH_2COZ wherein X_1 is halo group such as chloro to yield compound of formula I.

[0019] The starting material, compound of formula IV, may be prepared by known prior art such as Baltzly, R. et al, J. Org. Chem., 14, 775, 1949; Yung, D.K et al J. Pharm. Sci., 67(7), 1978.

[0020] In process as illustrated in Scheme 2,

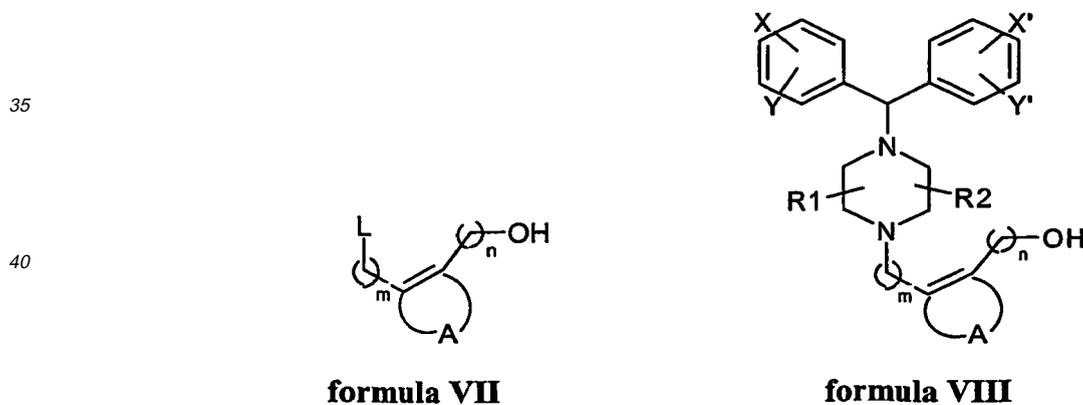
Scheme 2



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compound of formula I wherein R_3 and R_4 together form ring selected from cyclic, aryl or substituted aryl, heterocyclic aryl groups or substituted heterocyclic aryl groups containing one or more hetero atoms (viz., N, S, O) with a ring size ranging from 3 to 6, referred to herein as compound of formula II may be prepared by a process similar to that described above wherein compound of formula IV is N-alkylated with compound of formula VII wherein L is a leaving group selected from halo, or an alkyl or arylsulfonate group for e.g. methanesulfonate or p-toluenesulfonate and the like, to give compound of formula VIII,



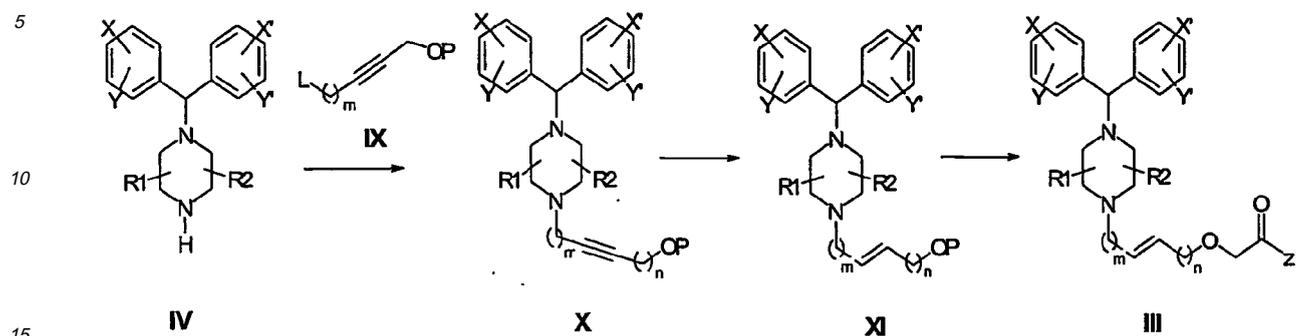
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which is then reacted with X_1CH_2COZ wherein X_1 is halo group such as chloro to yield compound of formula I.

[0021] In process as illustrated in Scheme 3,

Scheme 3

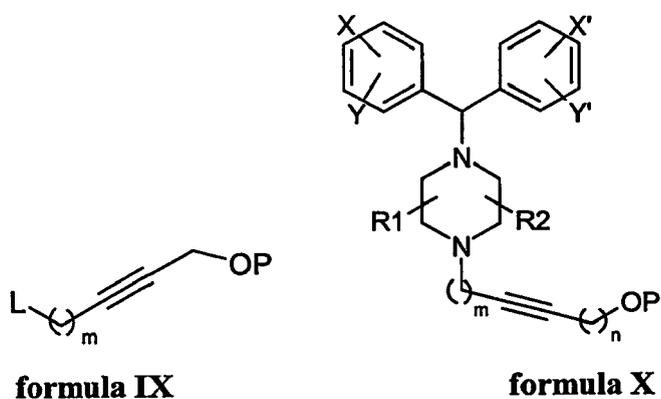


compound of formula I wherein R_3 and R_4 are hydrogen and in E or Z configuration, may be prepared by N-alkylating compound of formula IV with compound of formula IX,

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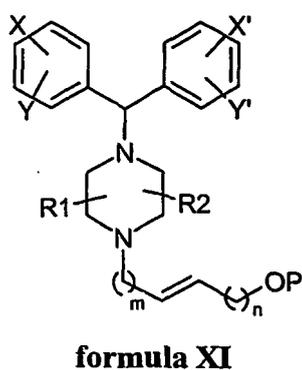
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wherein P maybe H or any protecting group such as acetate to give compound of formula X, which is reduced to give compound of formula XI. Compound of formula XI is then reacted, after removing the protecting group wherever required, with X_1CH_2COZ wherein X_1 is halo group such as chloro to yield compound of formula I.

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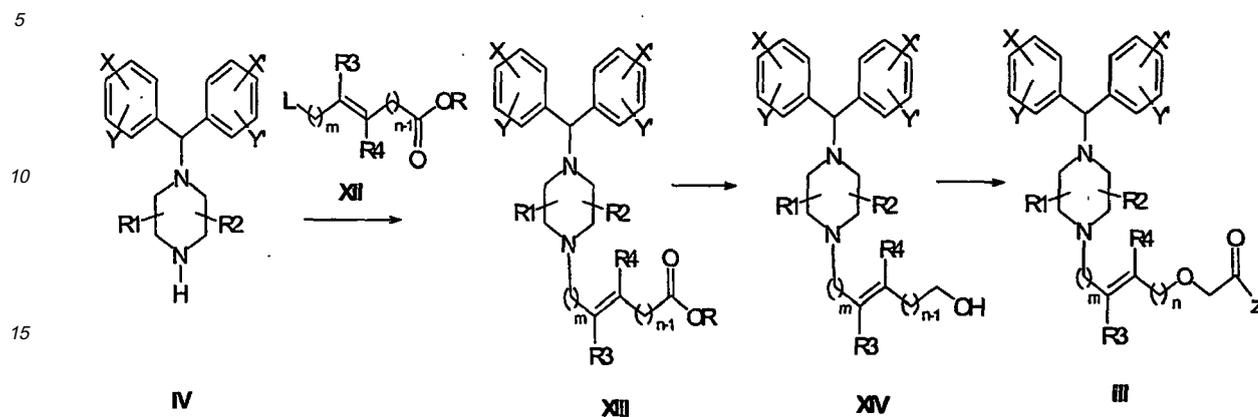
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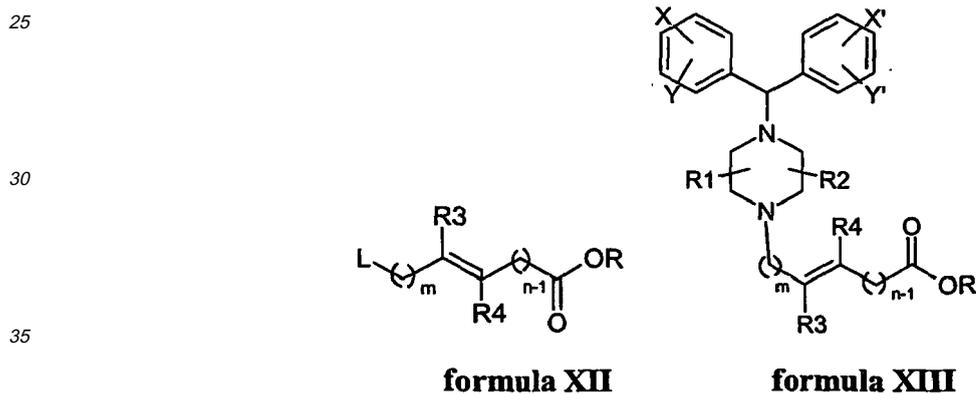
[0022] In process as illustrated in Scheme 4,

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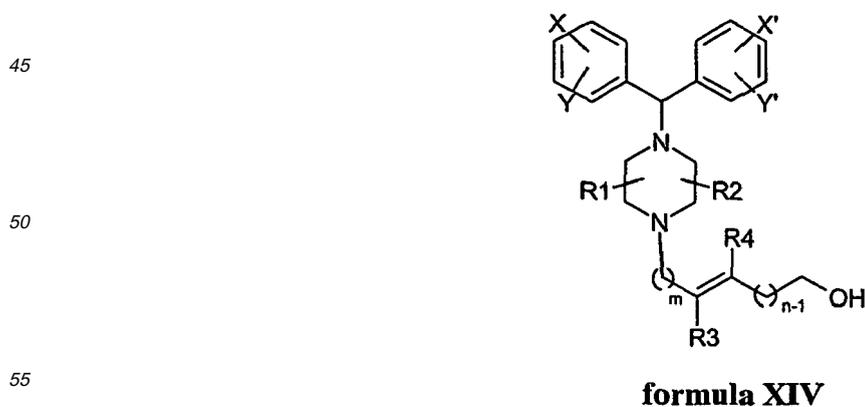
Scheme 4



20 compound of formula I wherein R_3 and R_4 are in E configuration may be prepared by N-alkylating compound of formula IV with compound of formula XII to give compound of formula XIII which is then reduced to yield compound of formula XIV.



40 [0023] Compound of formula XIV is treated with X_1CH_2COZ wherein X_1 is halo group such as chloro to yield compound of formula I.



[0024] Another aspect of the present invention relates to formulation of compound of formula I in suitable form, which

can be administered to the patient.

[0025] Compounds of the present invention can be provided as a pharmaceutical composition for use in the treatment of histamine mediated diseases. The composition comprises compound of formula I and pharmaceutically acceptable ingredients.

[0026] Such compositions may be prepared by admixing compound of formula I and pharmaceutically acceptable ingredients. Usually the compositions are adapted for oral administration. However, they may be adapted for other modes of administration, for example parenteral administration, sublingual, transdermal or ophthalmic administration.

[0027] The compositions may be in the form of tablets, capsules, powders, granules, nasal spray, aerosols, lozenges, ointments, creams, transdermal patches, reconstitutable powders, or liquid preparations, such as oral or sterile solutions or suspensions.

[0028] In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

[0029] Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycolate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

[0030] The compositions are preferably in a unit dosage form in an amount appropriate for the relevant daily dosage.

[0031] The solid oral compositions may be prepared by conventional methods of blending, filling or tableting known to those skilled in this art. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice.

[0032] Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavoring or coloring agents.

[0033] For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agent can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

[0034] For ophthalmic administration, sterile solution or suspension can be prepared. Ophthalmic solution can be prepared by dissolving the compound in water for injection along with suitable preservative, chelating agent, osmogen, viscosity enhancing agent, antioxidant and buffering agent. Solution is aseptically filtered and filled into suitable vials or bottles of suitable material. Similarly suspension can be prepared by aseptically dispersing the sterile compound in a sterile aqueous vehicle containing suitable preservative, chelating agent, osmogen, suspending agent, antioxidant and buffering agent. Preservative-free unit doses can also be prepared in similar way for solution as well as suspension and aseptically filled into unit dose containers.

[0035] Compositions may contain from 0.1 % to 99.0% by weight, preferably from 10-60% by weight, of the active material, depending upon the method of administration.

[0036] Composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

[0037] The compound of formula I on being formulated is useful for various histamine mediated diseases. IC₅₀ was determined for the compounds prepared by the present invention.

EXAMPLES

Example 1

4-{4-[Bis-(4-fluorophenyl)methyl]piperazin-1-yl}-(Z)-but-2-en-1-ol, (VIa, X=X'=4-F; Y=Y'=R1=R2=R3=R4=H; m=n=1):

[0038] A solution containing 1-[bis-(4-fluorophenyl)methyl]piperazine (140g, 0.485mol), toluene (700ml), 4-chloro-2-butene-1-ol (67.25g, 0.631mol), and diisopropylethylamine (125.8g, 0.971mol) is stirred at 47-49° C for 5hrs. Water (350ml) is added to the reaction mixture, the organic layer separated and the aqueous layer extracted with dichlorometh-

ane (2x200ml). The combined organic layer is washed with water (200ml), and concentrated to obtain crude product which is purified by flash column chromatography on silica gel using dichloromethane-methanol (9.6:0.4) as mobile phase to obtain pure product.

[0039] ¹H-NMR (CDCl₃, δppm): 2.15-2.80 (m, 8H), 3.01 (d, J=4.90Hz, 2H), 4.13 (d, J=3.96Hz, 2H), 4.20 (s, 1H), 5.55-5.75 (m, 1H), 5.75-6.00 (m, 1H), 6.96 (t, J=8.14Hz, 4H), 7.20-7.40 (m, 4H).

Example 2

(R,S)-4-{4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl}-(Z)-but-2-en-1-ol, [VIb(R,S), X=Cl; X'=Y=Y'=R1=R2=R3=R4=H; m=n=1]:

[0040] (R,S)-1-[(4-chlorophenyl)phenylmethyl]piperazine 8.0g is converted to (R,S)-4-{4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl}-(Z)-but-2-en-1-ol in a manner similar to example 1. Crude product is obtained as a syrupy mass, which is purified by flash column chromatography on silica gel using toluene-methanol (9:1) as mobile phase to obtain pure product.

[0041] ¹H-NMR (CDCl₃, δppm): 2.10-2.90 (m, 8H), 3.01 (d, J=5.75Hz, 2H), 4.13 (d, J=-5.25Hz, 2H), 4.19 (s, 1H), 5.50-5.75 (m, 1H), 5.75-6.00 (m, 1H), 7.00-7.40 (m, 9H).

Example 3

4-{4-Benzhydrylpiperazin-1-yl}-(Z)but-2-en-1-ol, (VIc, X=X'=Y=Y'=H; R1=R2=R3=R4=H; m=n=1):

[0042] A solution containing 1-benzhydrylpiperazine (3g, 0.0119mol), toluene (20ml), 4-chloro-2-butene-1-ol (1.65g, 0.0155mol), diisopropylethylamine (3.81g, 0.0295mol), and DMF (3ml) is stirred at 55-60° C for 5hrs. The reaction mass is quenched with water (20ml), organic layer separated and the aqueous layer extracted with dichloromethane (2x20ml). The organic extract is washed with water (10ml), and concentrated to obtain crude product, which is purified by flash column chromatography on silica gel using dichloromethane-methanol (9.3:0.7) as mobile phase to obtain pure product.

[0043] ¹H-NMR (CDCl₃, δppm): 2.10-2.80 (m, 8H), 3.01 (d, J=5.52Hz, 2H), 4.13 (dd, J₁=5.19Hz, J₂=0.68Hz, 2H), 4.21 (s, 1H), 5.50-5.75 (m, 1H), 5.75-6.00 (m, 1H), 7.00-7.50 (m, 10H).

Example 4

4-{4-[Bis-(2,4-difluorophenyl)methyl]piperazin-1-yl}-(Z)-but-2-en-1-ol, (VIId, X=X'=Y=Y'=F; R1=R2=R3=R4=H; m=n=1):

[0044] 1-[Bis-(2,4-difluorophenyl)methyl]piperazine (20.0g, 0.0617mol) is converted to 4-{4-[bis-(2,4-difluorophenyl)methyl]piperazin-1-yl}-(Z)-but-2-en-1-ol in a manner similar to example 1. Crude product is obtained as a syrupy mass, which is purified by flash column chromatography on silica gel using toluene-methanol (9:1) as mobile phase to obtain pure product.

[0045] ¹H-NMR (CDCl₃, δppm): 2.20-2.85 (m, 8H), 3.02 (dd, J₁=6.00Hz, J₂=0.74Hz, 2H), 4.14 (dd, J₁=5.31Hz, J₂=0.98Hz, 2H), 4.94 (s, 1H), 5.50-5.75 (m, 1H), 5.75-6.00 (m, 1H), 6.55-7.00 (m, 4H), 7.30-7.60 (m, 2H).

Example 5

4-{4-[Bis-(4-chlorophenyl)methyl]piperazin-1-yl}-(Z)-but-2-en-1-ol, (VIe, X=X'=Cl; Y=Y'=R1=R2=R3=R4=H; m=n=1):

[0046] 1-[Bis-(4-chlorophenyl)methyl] piperazine (5.044g) is converted to 4-{4-[bis-(4-chlorophenyl)methyl]piperazin-1-yl}-(Z)-but-2-en-1-ol in a manner similar to example 1. The crude product obtained is purified by flash column chromatography on silica gel using toluene-methanol (9:1) as mobile phase to obtain pure product.

[0047] ¹H-NMR (CDCl₃, δppm): 2.10-2.80 (m, 8H), 3.01 (d, J=5.87Hz, 2H), 4.13 (dd, J₁=5.26Hz, J₂=0.88, 2H), 4.18 (s, 1H), 5.50-5.75 (m, 1H), 5.75-6.00 (m, 1H), 7.00-7.40 (m, 8H).

Example 6

{2-{4-[Bis-(4-fluorophenyl)methyl]piperazin-1-yl-methyl}phenyl}methanol (VIIIa, X=X'=F; Y=Y'=R1=R2=H; m=n=1, A=benzene ring):

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[0048] 1-[Bis-(4-chlorophenyl)methyl] piperazine (5.0g, 0.0173mol) is converted to {2-{4-[bis-(4-fluorophenyl)methyl] piperazin-1-ylmethyl}phenyl}methanol using 2-(chloromethyl)benzyl alcohol, in a manner similar to example 1. The crude product obtained as brownish yellow syrup is purified by flash column chromatography on silica gel using toluene-methanol (9.2:0.8) as mobile phase to obtain pure product.

[0049] ¹H-NMR (CDCl₃, δppm): 2.00-2.80 (m, 8H), 3.6 (s, 2H), 4.18 (s, 1H), 4.57 (s, 2H), 6.70-7.03 (m, 4H), 7.05-7.40 (m, 8H).

Example 7

{2-{4-[(4-chlorophenyl)phenylmethyl]piperazin-1-ylmethyl}phenyl}methanol, (VIIIb, X=Cl; X'=Y=Y'=R1=R2=H; m=n=1, A=benzene ring):

[0050] 1-[Bis-(4-chlorophenyl)methyl] piperazine (4.0g, 0.0140mol) is converted to {2-{4-[(4-chlorophenyl)phenylmethyl]piperazin-1-ylmethyl}phenyl}methanol in a manner similar to example 1. The crude product obtained is purified by flash column chromatography on silica gel using toluene-methanol (9.2:0.8) as mobile phase to obtain pure product as a white foamy solid.

[0051] ¹H-NMR (CDCl₃, δppm): 2.00-2.80 (m, 8H), 3.60 (s, 2H), 4.16 (s, 1H), 4.56 (s, 2H), 6.86 (br, exchangeable by D₂O), 6.95-7.40 (m, 13H).

Example 8

4-{4-[Bis-(4-fluorophenyl)methyl]piperazin-1-yl}but-2-yn-1-ol (Xa, X=X'=4-F; Y=Y'-R1=R2=H; m=1):

Method A: Using 4-chloro-2-butyne-1-ol

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[0052] To a solution containing 1-[bis-(4-fluorophenyl)methyl]piperazine (300g, 1.040mol), tetrahydrofuran (1800ml) and diisopropylethylamine (242.1g, 1.873mol) is added dropwise 4-chloro-2-butyne-1-ol (130.5g, 1.248mol) during 1hr at 10-15° C. After stirring at 10-15° C for 1.5hr the temperature is gradually raised to 25-30° C and stirred for further 7hr. Thereafter, a solution of citric acid (437.3g, 2.08mol) in water (500ml) is added and the mixture is concentrated under reduced pressure at below 60° C to remove most of the solvent. The resulting aqueous mass is washed with toluene (2x400ml), basified to pH=9-10 and the product extracted into dichloromethane (2x400ml). The dichloromethane layer is washed with water (300ml) and degassed to obtain crude product, which is purified by flash column chromatography on silica gel using toluene-methanol (9:1) as mobile phase.,

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[0053] ¹H-NMR (CDCl₃, δppm): 1.84 (br, 1H, D₂O exchangeable), 2.20-2.80 (m, 8H), 3.31 (t, J=1.84Hz, 2H), 4.21 (s, 1H), 4.29 (t, J=1.80Hz, 2H), 6.80-7.05 (m, 4H), 7.10-7.50 (m, 4H).

40

Method B: Using 2-butyne-1,4-diol

[0054] A solution of methanesulfonyl chloride (48.69g, 0.425mol) and tetrahydrofuran (100ml) is added dropwise to a stirred solution of 2-butyne-1,4-diol (100g, 1.162mol) and diisopropylethylamine (62.45g, 0.483mol) in tetrahydrofuran (400ml) during 2hr at 0-5°C. After 1hr stirring at 0-5°C for 1hr the temperature is raised to 25-30°C and stirred for further 1hr. The reaction mixture is then cooled to 10-15°C, and to it is added diisopropylethylamine (99.34g, 0.769mol), followed by 1-[bis-(4-fluorophenyl)methyl]piperazine (110.81g, 0.384mol) in portions during 30min. The reaction mass is stirred at 10-15° C for 1hr and then at 25-30° C for further 8hrs. Toluene (500ml) is added to it and the contents washed with water (2x400ml). Thereafter, a solution of citric acid (161.52g, 0.769mol) in water (500ml) is added and the mixture is concentrated under reduced pressure at below 60° C to remove most of the solvent. The resulting aqueous mass is washed with hexane (2x250ml), basified to pH=9-10 and the product extracted into ethyl acetate (2x300ml). The ethyl acetate layer is washed with water (200ml) and degassed to obtain crude product which is purified by flash column chromatography on silica gel using toluene-methanol (9.3:0.7) as mobile phase to obtain pure product.

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Example 9

(R,S)-4-{4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}but-2-yn-1-ol (by method A in Example 8), (Xb, X=Cl; X'=Y=Y'=R1=R2=H; m=1):

[0055] A solution containing (R,S)-1-[(4-chlorophenyl)phenylmethyl]piperazine (10g, 0.0349mol), toluene (50ml), 4-chloro-2-butyne-1-ol (4.74g, 0.0453mol), and diisopropylethylamine (9.02g, 0.0698mol) is stirred at 45-50° C for 6hrs. The reaction mixture is quenched with water (20ml). The organic layer is separated and the aqueous layer extracted with dichloromethane (2x30ml). The organic layers is washed with water (20ml) and concentrated to obtain crude product as a syrupy mass, which is purified by flash column chromatography on silica gel using dichloromethane-methanol (9.6:0.4) as mobile phase to obtain pure product.

[0056] ¹H-NMR (CDCl₃, δppm): 1.88 (br, 1H), 2.20-2.75 (m, 8H), 3.31 (t, J=1.72Hz, 2H), 4.20 (s, 1H), 4.29 (t, J=1.63Hz, 2H), 7.05-7.50 (m, 9H).

Example 10

(R,S)-4-{4-[(4-fluorophenyl)phenylmethyl]piperazin-1-yl}but-2-yn-1-ol (by method B in Example 8), (Xc, X=F; X'=Y=Y'=R1=R2=H; m=1):

[0057] A solution of methanesulfonyl chloride (1.86g, 16.27mmol) and tetrahydrofuran (5ml) is added dropwise to a stirred solution of 2-butyne-1,4-diol (3.82g, 44.3mmol) and diisopropylethylamine (6.30g, 48.8mmol) in tetrahydrofuran (20ml) during 30min at 0-5°C. After 1hr stirring the temperature is raised to 25-30°C and stirred for further 1hr. The resulting mixture containing mesylate of 2-butyne-1,4-diol is added dropwise to a stirred solution of (R,S)-1-[(4-fluorophenyl)phenylmethyl]piperazine (4.0g, 14.79mmol) in tetrahydrofuran (25ml) during 1hr at 5-10°C. The reaction mass is stirred at 5-10°C for 1hr and then at 25-30° C for further 5hrs. Thereafter, citric acid (3.2g, 0.01523mol) is added and the mixture is concentrated under reduced pressure at below 60° C to remove most of the solvent. Water (50ml) is charged to the residual mass and the resulting aqueous layer washed with hexane (2x30ml), basified to pH=9-10 and the product extracted into dichloromethane (3x30ml). The dichloromethane layer is washed with water (25ml) and degassed to obtain crude product as a sticky solid, which is purified by flash column chromatography on silica gel using dichloromethane-methanol (9.2:0.8) as mobile phase to obtain pure product as a thick syrupy mass.

[0058] ¹H-NMR (CDCl₃, δppm): 1.87 (b), 2.25-2.70 (m, 8H), 3.30 (t, J=1.83Hz, 2H), 4.21 (s, 1H), 4.29 (t, J=1.78Hz, 2H), 6.85-7.02 (m, 2H), 7.13-7.42 (m, 7H).

Example 11

4-{4-[Bis-(4-fluorophenyl)methyl]piperazin-1-yl}-(E)-but-2-en-1-ol, (XIVa, X=X'=4-F; Y=Y'=R1=R2=R3=R4=H; m=n=1):

[0059] To a stirred solution of methyl 4-{4-[bis-(4-fluorophenyl)methyl]piperazin-1-yl}-(E)-but-2-enoate (380 g, 0.984mol) in tetrahydrofuran (1900ml) at -10 to 0° C is added dropwise DIBALH (560 g, 3.938mol, as 20% solution in toluene) during about 2-3 hrs. After completion of addition, the reaction mass is stirred for further 1.0 hrs at 0 to 10° C and then quenched by sequential addition of ethyl acetate (400ml) and water (800ml). After vigorous stirring for 2 hrs the mass is filtered. The organic layer is separated from the filtrate, washed with water (1500ml) and concentrated to get crude product.

The crude product is taken in toluene (2000ml), extracted into 10% acetic acid (2000ml), the aqueous extract basified to pH 9 -10 with 20% aqueous sodium hydroxide and the product extracted into dichloromethane (3x1500ml). The dichloromethane layer is washed with water (800ml), and concentrated to get a syrupy mass which is purified by flash column chromatography on silica gel using toluene-methanol (9:1) as mobile phase.

[0060] ¹H-NMR (CDCl₃, δppm): 1.70 (br, D₂O exchangeable), 2.20-2.70 (m, 8H), 3.00 (d, J=5.38Hz, 2H), 4.12 (d, J=4.40Hz, 2H), 4.21 (s, 1H), 5.65-5.90 (m, 2H), 6.85-7.05 (m, 4H), 7.28-7.40 (m, 4H).

Example 12

4-{4-[Bis-(4-fluorophenyl)methyl]piperazin-1-yl}-(E)-but-2-en-1-ol (XIa, X=X'=4-F; Y=Y'=R1=R2=H; m=1):

[0061] To a stirred solution of 4-{4-[bis-(4-fluorophenyl)methyl]piperazin-1-yl}but-2-yn-1-ol (135g, 0.379mol) in tetrahydrofuran (4300ml) at 5-10° C is added lithium aluminum hydride (43.1 g, 1.136mol) in portions during 3-4 hrs. The reaction mixture is stirred for further 5-6 hrs. and then quenched by addition of ethyl acetate (135ml), followed by water

(100 ml) at 5-10° C. The resulting mixture is filtered, the organic layer separated from the filtrate, and concentrated to get crude product, which is purified by flash column chromatography on silica gel using toluene-methanol (9:1) as mobile phase to obtain pure product.

[0062] ¹H-NMR (CDCl₃, δppm): 1.77 (br, D₂O exchangeable), 2.20-2.70 (m, 8H), 3.00 (d, J=4.91Hz, 2H), 4.11 (d, J=3.71Hz, 2H), 4.21 (s, 1H), 5.55-5.90 (m, 2H), 6.80-7.05 (m, 4H), 7.10-7.50 (m, 4H).

Example 13

(R,S)-4-{4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl}-(E)-but-2-en-1-ol, (XIb, X=Cl; X'=Y=Y'=R1=R2=H; m=1):

[0063] (R,S)-4-{4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl}but-2-yn-1-ol (3.5g) is converted to (R,S)-4-{4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl}-(E)-but-2-en-1-ol in a manner similar to example 12. Crude product is obtained as a syrupy mass, which is purified by flash column chromatography on silica gel using toluene-methanol (9:1) as mobile phase to obtain pure product.

[0064] ¹H-NMR (CDCl₃, δppm): 2.20-2.65 (m, 8H), 3.00 (d, J=4.83Hz, 2H), 4.11 (d, J=3.52Hz, 2H), 4.20 (s, 1H), 5.60-5.90 (m, 2H), 7.00-7.50 (m, 9H).

Example 12

(R,S)-4-{4-[(4-fluorophenyl)phenylmethyl]piperazin-1-yl}-(E)-but-2-en-1-ol (XIc, X=F; X'=Y=Y'=R1=R2=H; m=1):

[0065] (R,S)-4-{4-[(4-fluorophenyl)phenylmethyl]piperazin-1-yl}but-2-yn-1-ol (2.13g, 0.0063mol) is converted to (R,S)-4-{4-[(4-fluorophenyl)phenylmethyl]piperazin-1-yl}-(E)-but-2-en-1-ol in a manner similar to example 14. Crude product is obtained as a syrupy mass which is purified by flash column chromatography on silica gel using dichloromethane-methanol (9.3:0.7) as mobile phase to obtain pure product.

[0066] ¹H-NMR (CDCl₃, δppm): 1.71 (br, exchangeable by D₂O), 2.10-2.70 (m, 8H), 3.00 (d, J=5.23Hz, 2H), 4.11 (d, J=4.20Hz, 2H), 4.22 (s, 2H), 5.65-5.90 (m, 2H), 6.85-7.02 (m, 2H), 7.10-7.45 (m, 7H).

Example 15

Methyl 4-{4-[Bis-(4-fluorophenyl)methyl]piperazin-1-yl}-(E)-but-2-enoate, (XIIIa, X=X'=4-F; R=CH₃; Y=Y'=R1=R2=R3=R4=H; m=n=1):

[0067] A solution of methyl-4-bromocrotonate (46.56g, 0.260mol) in toluene (50ml) is added dropwise to a mixture containing 1-[bis-(4-fluorophenyl)methyl]piperazine (50g, 0.173mol), diisopropylethylamine (49.30g, 0.381mol) in toluene (250ml) at 25-30° C during 30 minutes. After stirring for 8hrs, the reaction mass is washed successively with water (2x150ml), 0.2N hydrochloric acid (3x 150ml), and water (150ml). To the organic layer at 5-10° C is added 3N hydrochloric acid (200ml), stirred and the aqueous layer containing product is separated. It is then washed with toluene (200ml), basified to pH = 9-10 with 20% sodium hydroxide solution and the product extracted into ethyl acetate (2x150ml). The organic layer is washed once with water (100ml), concentrated and degassed. The residue is triturated with hexane (150ml) and the solid filtered. The product is further purified by recrystallization from cyclohexane.

[0068] ¹H-NMR (CDCl₃, δppm): 1.63 (br, 1H, D₂O exchangeable), 2.20-2.65 (m, 8H), 3.13 (d, J=5.00Hz, 2H), 3.72 (s, 3H), 4.22 (s, 1H), 5.88-6.03 (m, 1H), 6.80-7.05 (m, 5H), 7.20-7.40 (m, 4H).

Example 16

Methyl 4-{4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl}-(E)-but-2-enoate, (XIIIb, X=Cl; X'=Y=Y'=R1=R2=R3=R4=H; m=n=1):

[0069] A solution containing (R,S)-1-[(4-chlorophenyl)phenylmethyl]piperazine (5g, 0.0174mol), DMF (30ml), methyl-4-bromocrotonate (4.7g, 0.0263mol), and diisopropylethylamine (6.75g, 0.0522mol) is stirred at 27-30° C for 6hrs. The reaction is quenched with water (40ml) and the product extracted into dichloromethane (3x30ml). The organic layer is washed with water (2x30ml) and concentrated to obtain crude product which is purified by flash column chromatography on silica gel using ethyl acetate-hexane (6.5:3.5) as mobile phase to obtain pure product.

[0070] ¹H-NMR (CDCl₃, δppm): 2.20-2.65 (m, 8H), 3.14 (dd, J₁=6.20Hz, J₂=1.39Hz, 2H), 3.72 (s, 3H), 4.20 (s, 1H), 5.85-6.05 (m, 1H), 6.8-7.05 (m, 1H), 7.05-7.50 (m, 9H).

Example 17**{4-[4-[Bis-(4-fluorophenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid dihydrochloride, (Ia):**

5 **[0071]** To a stirred solution of 4-[4-[bis-(4-fluorophenyl)methyl]piperazin-1-yl]-(Z)-but-2-en-1-ol (97.0g, 0.271mol) and potassium tert-butoxide (54.7g, 0.487mol) in anhydrous tert-butanol (776ml), preheated at 60-65° C for 1 hr., under nitrogen atmosphere, is added dry sodium chloroacetate (63g, 0.541mol). The reaction mass is then refluxed for further 5hrs. The mixture is then concentrated under reduced pressure at below 60° C until tert-butanol is completely removed. The residue is taken up in water (800ml) and washed with ethyl acetate (2x500ml). The aqueous solution is then acidified to pH 5-6, extracted into dichloromethane (3x500ml), washed dichloromethane layer with water (300ml), and concentrated to get crude product, which is purified by flash column chromatography on silica gel using toluene-methanol (4:1) as mobile phase to obtain pure product.

[0072] ¹H-NMR (CDCl₃, δppm): 2.40-2.80 (m, 4H), 2.80-3.20 (m, 4H), 3.65 (d, J=7.51Hz, 2H), 3.96 (s, 2H), 4.19 (d, J=4.51Hz, 2H), 4.32 (s, 1H), 5.00-5.30 (m, 1H), 5.30-6.10 (m, 1H), 6.80-7.05 (m, 4H), 7.00-7.50 (m, 4H)

15 **[0073]** A suspension of {4-[4-[bis-(4-fluorophenyl)methyl]piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid (83.8g, 0.201mol) and water (335ml) is acidified under stirring to pH 1-2 with 6N hydrochloric acid at 25-30°C. The solution is filtered, concentrated under reduced pressure at below 50° C (until volume of solution is around 170ml), and lyophilized to obtain the dihydrochloride salt.

20 **Example 18****(R,S)-{4-[4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid dihydrochloride, [Ib (R,S)]:**

25 **[0074]** (R,S)-4-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(Z)-but-2-en-1-ol (100.0g, 0.28mol) is converted to (R,S)-{4-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid in a manner similar to example 19. Crude product is obtained as a foamy solid which is purified by flash column chromatography on silica gel using toluene-methanol (4:1) as mobile phase to obtain pure product.

30 **[0075]** ¹H-NMR (CDCl₃, δppm): 2.40-2.75 (m, 4H), 2.75-3.20 (m, 4H), 3.62 (d, J=7.43Hz, 2H), 3.95 (s, 2H), 4.17 (d, J= 4.9Hz, 2H), 4.28 (s, 1H), 5.50-5.80 (m, 1H), 5.80-6.1 (m, 1H), 6.95-7.40 (m, 9H), 8.98 (br, exchangeable with D₂O)

[0076] It was converted to dihydrochloride salt as per example 17.

Example 1935 **[4-(4-Benzhydrylpiperazin-1-yl)-(Z)-but-2-enyloxy]acetic acid dihydrochloride, (Ic):**

[0077] 4-(4-Benzhydrylpiperazin-1-yl)-(Z)-but-2-en-1-ol (2.1g, 0.0065mol) is converted to [4-(4-benzhydrylpiperazin-1-yl)-(Z)-but-2-enyloxy]acetic acid in a manner similar to example 17. The crude product obtained as a foamy solid is purified by flash column chromatography on silica gel using toluene-methanol (8.5:1.5) as mobile phase to obtain pure product.

40 **[0078]** ¹H-NMR (CDCl₃, δppm): 2.40-2.85 (m, 4H), 2.85-3.20 (m, 4H), 3.68 (d, J=7.53Hz, 2H), 3.96 (s, 2H), 4.18 (d, J= 4.60Hz, 2H), 4.33 (s, 1H), 5.50-5.80 (m, 1H), 5.90-6.10 (m, 1H), 7.00-7.50 (m, 10H)

[0079] It is converted to dihydrochloride salt as per example 19.

45 **Example 20****{4-[4-[Bis-(2,4-difluorophenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid dihydrochloride, (Id):**

50 **[0080]** 4-[4-[Bis-(2,4-difluorophenyl)methyl]piperazin-1-yl]-(Z)-but-2-en-1-ol (6.2g, 0.0157mol) is converted {4-[4-[bis-(2,4-difluorophenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid in a manner similar to example 17. Crude product is obtained as a foamy solid which is purified by flash column chromatography on silica gel using toluene-methanol (4:1) as mobile phase to obtain pure product.

[0081] ¹H-NMR (CDCl₃, δppm): 2.20-2.75 (m, 4H), 2.75-3.20 (m, 4H), 3.57 (d, J=6.07Hz, 2H), 3.96 (s, 2H), 4.17 (d, J=3.90Hz, 2H), 4.99 (s, 1H), 5.50-6.10 (m, 2H), 6.45-7.0 (m, 4H), 7.20-7.65 (m, 2H), 9.87 (br)

55 **[0082]** The product is taken up in ethyl acetate (12ml), acidified with a solution of anhydrous HCl in ethyl acetate to pH 1.0 to 2.0, concentrated and degassed to get the dihydrochloride salt.

Example 21**{4-[4-[Bis-(4-chlorophenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid dihydrochloride, (Ie):**

5 **[0083]** 4-{4-[Bis-(4-chlorophenyl)methyl]piperazin-1-yl}-(Z)-but-2-en-1-ol (2.26g, mol) is converted to {4-[4-[bis-(4-chlorophenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid in a manner similar to example 17. Crude product obtained is purified by flash column chromatography on silica gel using toluene-methanol (4:1) as mobile phase to obtain pure product.

10 **[0084]** ¹H-NMR (CDCl₃, δppm): 2.50-2.80 (m, 4H), 2.80-3.20 (m, 4H), 3.60 (d, J=7.38Hz, 2H), 3.94 (s, 2H), 4.20 (d, J=4.08Hz, 2H), 4.31 (s, 1H), 5.23 (br, exchangeable with D₂O), 5.50-5.80 (m, 1H), 5.80-6.10 (m, 1H), 7.10-7.40 (m, 8H). The product was converted to dihydrochloride salt as in example 17.

Example 22

15 **{4-[4-[Bis-(4-fluorophenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid methyl ester dihydrochloride, (If):**

[0085] To a stirred solution of {4-[4-[bis-(4-fluorophenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid (35g, 0.084mol) in methanol (560ml), is added a solution of anhydrous HCl in ethyl acetate till pH is 1-2. The solution is refluxed for 2hrs, cooled to 25-30° C and stirred for 4hrs. The crystallized solid is filtered, washed with ethyl acetate (2x5ml), and dried in oven at 60-65° C to get the product.

20 **[0086]** ¹H-NMR (D₂O, δppm): 3.20-3.60 (m, 8H), 3.64 (s, 3H), 3.94 (d, J=7.66Hz, 2H), 4.00-4.20 (m, 4H), 5.31 (s, 1H), 5.50-5.78 (m, 1H), 5.90-6.20 (m, 1H), 6.85-7.15 (m, 4H), 7.30-7.60 (m, 4H).

25 **Example 23**

{4-[4-[Bis-(4-fluorophenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid ethyl ester dihydrochloride, (Ig):

30 **[0087]** To a stirred solution of {4-[4-[bis-(4-fluorophenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid (1.0g, 0.0024mol) in ethanol (20ml), is added a solution of anhydrous ethanolic HCl till pH is 1-2. The solution is refluxed for around 2hrs, cooled to 25-30°C and stirred for 4hrs. The crystallized solid is filtered, washed with ethanol (2x5ml), and dried in oven at 60-65° C to get the product.

35 **[0088]** ¹H-NMR (CDCl₃+DMSO-d₆, δppm): 1.28 (t, J=7.10Hz, 3H), 2.70-4.30 (m, 17H), 5.70-6.20 (m, 2H), 7.10 (t, J=8.62Hz, 4H), 7.40-7.80 (m, 4H).

Example 24

40 **{4-[4-[Bis-(4-fluorophenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid isopropyl ester dihydrochloride, (Ih):**

[0089] To a stirred solution of {4-[4-[bis-(4-fluorophenyl)methyl]piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid (1.0g, 0.0024mol) in isopropyl alcohol (20ml), is added a solution of anhydrous HCl in isopropyl alcohol till pH of solution is 1-2. The solution is refluxed for around 2hrs, cooled to 25-30°C and stirred for 4hrs. The crystallized solid is filtered, washed with isopropyl alcohol (2x5ml), and dried in oven at 60-65°C to get product 0.968g (75.85% yield).

45 **[0090]** ¹H-NMR (CDCl₃+DMSO-d₆, δppm): 1.23 (d, J=6.25Hz, 6H), 2.60-3.70 (m, 8H), 3.70-4.40 (m, 7H), 4.80-5.20 (m, 1H), 5.60-5.90 (m, 1H), 5.90-6.10 (m, 1H), 7.16 (t, J=8.56Hz, 4H), 7.40-7.90 (m, 4H).

Example 25

50 **(R,S)-{4-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid isopropyl ester dihydrochloride, (Ii):**

[0091] The preparation was carried out using (R,S)-{4-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid in a manner similar to example 24.

55 **[0092]** ¹H-NMR (CDCl₃+DMSO-d₆, δppm): 1.26 (d, J=6.26Hz, 6H), 2.80-3.70 (m, 8H), 3.80-4.15 (m, 3H), 4.21 (d, J=5.57Hz, 4H), 4.90-5.15 (m, 1H), 5.70-5.95 (m, 1H), 5.95-6.15 (m, 1H), 7.10-7.90 (m, 9H).

Example 26

(R,S)-{4-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid methyl ester dihydrochloride, (Ij):

[0093] To a stirred solution of (R,S)-{4-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid (1g, 0.0024mol) in methanol (20ml), is added a solution of anhydrous HCl in ethyl acetate till pH of the solution is 1-2. The solution is refluxed for 2hrs, cooled to 25-30°C, added anhydrous diethyl ether till slight haziness and stirred for 4hrs. The crystallized solid is filtered, washed with diethyl ether (2x5ml), and dried in oven at 60-65°C to get product.

[0094] ¹H-NMR (CDCl₃+DMSO-d₆, δppm): 3.10-3.90 (m, 8H), 3.73 (s, 3H), 3.90-4.30 (m, 7H), 5.70-6.00 (m, 1H), 6.00-6.20 (m, 1H), 7.10-7.50 (m, 5H), 7.50-8.00 (m, 4H).

Example 27

(R,S)-{4-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid ethyl ester dihydrochloride, (Ik):

[0095] The preparation was carried out using (R,S)-{4-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(Z)-but-2-enyloxy}acetic acid in a manner similar to example 25, to obtain the product.

[0096] ¹H-NMR (CDCl₃+DMSO-d₆, δppm): 1.27 (t, J=7.12Hz, 3H), 3.10-3.90 (m, 8H), 3.90-4.30 (m, 9H), 5.75-5.95 (m, 1H), 5.95-6.15 (m, 1H), 7.10-7.50 (m, 5H), 7.50-8.00 (m, 4H).

Example 28

{2-[4-[bis-(4-fluorophenyl)methyl]piperazin-1-ylmethyl]benzyloxy}acetic acid dihydrochloride, (IIa):

[0097] {2-[4-[Bis-(4-fluorophenyl)methyl]piperazin-1-ylmethyl]phenyl}methanol (5.0g, 0.0122mol) is converted to {2-[4-[Bis-(4-fluorophenyl)methyl]piperazin-1-ylmethyl]benzyloxy}acetic acid in a manner similar to example 17. Crude product obtained is purified by flash column chromatography on silica gel using toluene-methanol (8.5:1.5) as mobile phase to obtain pure product as a white foamy solid.

[0098] ¹H-NMR (CDCl₃, δppm): 2.40-2.75 (m, 4H), 2.75-3.20 (m, 4H), 4.06 (s, 2H), 4.10 (s, 2H), 4.28 (s, 1H), 4.58 (s, 2H), 6.70-7.10 (m, 4H), 7.10-7.50 (m, 8H).

[0099] The product is taken up in ethyl acetate (12ml), acidified with a solution of anhydrous HCl in ethyl acetate to pH 1.0 to 2.0, concentrated and degassed to get dihydrochloride salt as a white solid.

Example 29

(R,S) {2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-ylmethyl]benzyloxy}acetic acid dihydrochloride, (IIb):

[0100] {2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-ylmethyl]phenyl}methanol (4.0g, 9.83mmol) is converted to {2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-ylmethyl]benzyloxy}acetic acid in a manner similar to example 17. Crude product obtained as an off-white foamy solid is purified by flash column chromatography on silica gel using toluene-methanol (8.5:1.5) as mobile phase to obtain pure product as a white foamy solid.

[0101] ¹H-NMR (CDCl₃, δppm): 2.40-2.80 (m, 4H), 2.80-3.20 (m, 4H), 4.06 (s, 2H), 4.14 (s, 2H), 4.28 (s, 1H), 4.58 (s, 2H), 7.00-7.50 (m, 13H).

[0102] The product is converted to dihydrochloride salt using a solution of anhydrous HCl in ethyl acetate as in example 28.

Example 30

{4-[4-[Bis-(4-fluorophenyl)methyl]piperazin-1-yl]-(E)-but-2-enyloxy}acetic acid dihydrochloride, (IIIa):

[0103] To a stirred solution of 4-[4-[bis-(4-fluorophenyl)methyl]piperazin-1-yl]-(E)-but-2-en-1-ol (247.0g, 0.689mol) and potassium tert-butoxide (139.2g, 1.240mol) in anhydrous tert-butanol (2000ml), preheated at 60-65°C for 1 hr. under nitrogen atmosphere, is added dry sodium chloroacetate (160.5g, 1.378mol). The reaction mass is then refluxed for further 5hrs. The mixture is then concentrated under reduced pressure at below 60°C until tert-butanol is completely removed. The residue is taken up in water (1500ml) and washed with ethyl acetate (2 x 1500ml). The aqueous solution is then acidified to pH 5-6, extracted into dichloromethane (2 x 750ml), washed dichloromethane layer with water (300ml),

and concentrated to get crude product as a foamy solid. The crude product is purified by flash column chromatography on silica gel using toluene-methanol (4:1) as mobile phase. The product was converted to its dihydrochloride salt as in example 17.

[0104] ¹H-NMR (D₂O, δppm): 3.20-3.70 (m, 8H), 3.82 (d, J=6.79Hz, 2H), 3.93-4.05 (m, 4H), 5.35 (s, 1H), 5.65-5.80 (m, 1H), 5.97-6.12 (m, 1H), 6.80-7.00 (m, 4H), 7.36-7.50 (m, 4H).

Example 31

(R,S)-{4-[4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl]-(E)-but-2-enyloxy}acetic acid dihydrochloride, (IIIb):

[0105] (R,S)-4-{4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}-(E)-but-2-en-1-ol (1.9g, 0.0053mol) is converted to (R,S)-{4-[4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl]-(E)-but-2-enyloxy}acetic acid as in example 30. Crude product is obtained as a foamy solid which is purified by flash column chromatography on silica gel using toluene-methanol (8:2) as mobile phase to obtain pure product.

[0106] ¹H-NMR (CDCl₃, δppm): 2.40-2.75 (m, 4H), 2.75-3.20 (m, 4H), 3.30-3.50 (m, 2H), 3.93 (s, 2H), 4.00-4.15 (m, 2H), 4.26 (s, 1H), 5.70-6.00 (m, 2H), 6.82 (br), 7.00-7.50 (m, 9H)

[0107] It was converted to dihydrochloride salt as per example 17.

Example 32

(R,S)-{4-[4-[(4-fluorophenyl)phenylmethyl]piperazin-1-yl]-(E)-but-2-enyloxy}acetic acid dihydrochloride, (IIIc):

[0108] (R,S)-4-{4-[(4-Fluorophenyl)phenylmethyl]piperazin-1-yl}-(E)-but-2-en-1-ol (0.7g, 2.06mmol) is converted to (R,S)-{4-[4-[(4-fluorophenyl)phenylmethyl]piperazin-1-yl]-(E)-but-2-enyloxy}acetic acid as per example 30. The crude product obtained (0.77g) is purified by flash column chromatography on silica gel using toluene-methanol (3:2) as mobile phase to obtain pure product.

[0109] ¹H-NMR (CDCl₃, δppm): 2.40-3.20 (m, 8H), 3.20-3.50 (m, 2H), 3.92 (s, 2H), 4.00-4.15 (m, 2H), 4.26 (s, 1H), 5.65-5.95 (m, 2H), 6.80-7.03 (m, 2H), 7.07-7.50 (m, 7H), 10.70 (br, exchangeable).

[0110] It is converted to its dihydrochloride salt as in example 17.

IC₅₀ determination using isolated guinea pig ileum functional assay

[0111] Terminal segment of ileum of junction of Dunkin Hartley guinea pig, of about 10 cm from the ileo-caecal, separated from mesenteric attachments was immediately removed and placed in Tyrode solution of composition, NaCl 137.0mM, KCl 2.7 mM, CaCl₂ 1.8 mM, MgCl₂ 1.05 mM, NaHCO₃ 11.9 mM, NaH₂PO₄ 0.42 mM and glucose 5.6 mM, maintained at 35° C.

The lumen of the ileum was gently cleaned with Tyrode so as to remove any particle without affecting the mucosal layer of the tissue. Pieces of 1.5-2.0 cm length were cut and placed in the organ bath of 20ml capacity, attaching one end to the tissue holder and other to the transducer by a fine cotton thread. The system was previously calibrated before start of each experiment. Tissue was kept under a resting tension of 0.5-0.75g. The bath solution was continuously bubbled with 95 % O₂ and 5% CO₂ and maintained at 35° C temperature. After an initial 30 min of equilibration time the baseline was recorded and non-cumulative responses with sub maximal dose of histamine (7.2 X 10⁻⁷M) were initially recorded until the responses were reproducible. The contractions to this typical dose of histamine in absence (only vehicle) and presence of at least 3 different concentrations of the test compounds were recorded after 15min constant incubation time. The percentage inhibitions caused by different concentrations of test compounds were plotted against the log of molar concentrations of the test compounds for the determination of IC₅₀.

TABLE-1

The compound of formula I is tested for its activity in its hydrochloride salt form												
Comp d.	X	Y	X'	Y'	R ₁	R ₂	R ₃	R ₄	m	n	Z	IC ₅₀ (mean) ± SEM (moles)
5 10	la	4-F	H	4-F	H	H	H	H	1	1	OH	2.17 x 10 ⁻⁶ ± 4.23 x 10 ⁻⁷
15	lb	4-Cl	H	H	H	H	H	H	1	1	OH	2.13 X 10 ⁻⁷ ± 5.37 X 10 ⁻⁸
20	lc	H	H	H	H	H	H	H	1	1	OH	1.30 x 10 ⁻⁶ ± 4.17 x 10 ⁻⁷
25	ld	2-F	4-F	2-F	4-F	H	H	H	1	1	OH	2.26 x 10 ⁻⁶ ± 5.37 x 10 ⁻⁷
30	le	4-Cl	H	4-Cl	H	H	H	H	1	1	OH	3.27 X 10 ⁻⁷ ± 3.59 X 10 ⁻⁷
35	lf	4-F	H	4-F	H	H	H	H	1	1	OCH ₃	4.00 x 10 ⁻⁷ ± 2.91 x 10 ⁻⁷
40	lg	4-F	H	4-F	H	H	H	H	1	1	OC ₂ H ₅	4.09 x 10 ⁻⁷ ± 3.39 x 10 ⁻⁸
45	lh	4-F	H	4-F	H	H	H	H	1	1	O ^{iso} Pr	4.66 x 10 ⁻⁷ ± 1.20 x 10 ⁻⁸
50	li	4-Cl	H	H	H	H	H	H	1	1	O ^{iso} Pr	2.37 x 10 ⁻⁷ ± 3.54 x 10 ⁻⁹
55	lj	4-Cl	H	H	H	H	H	H	1	1	OCH ₃	4.66 x 10 ⁻⁷ ± 3.54 x 10 ⁻⁸
	lk	4-Cl	H	H	H	H	H	H	1	1	OC ₂ H ₅	7.35 x 10 ⁻⁷ ± 1.85 x 10 ⁻⁷

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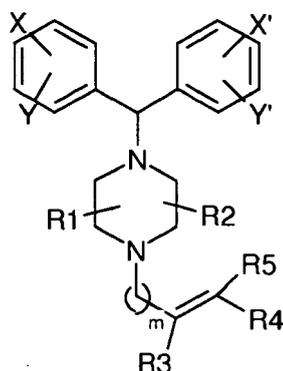
(continued)

The compound of formula I is tested for its activity in its hydrochloride salt form

Comp d.	X	Y	X'	Y'	R ₁	R ₂	R ₃	R ₄	m	n	Z	IC ₅₀ (mean) ± SEM (moles)
IIa	4-F	H	4-F	H	H	H	Part of benzene ring		1	1	OH	1.19 X 10 ⁻⁶ ± 7.01 X 10 ⁻⁷
IIb	4-Cl	H	H	H	H	H	Part of benzene ring		1	1	OH	5.64 X 10 ⁻⁷ ± 1.91 X 10 ⁻⁸
IIIa	4-F	H	4-F	H	H	H	H	H	1	1	OH	4.72 x 10 ⁻⁶ ± 5.90 x 10 ⁻⁶
IIIb	4-Cl	H	H	H	H	H	H	H	1	1	OH	3.93 x 10 ⁻⁷ ± 1.84 x 10 ⁻⁷
IIIc	4-F	H	H	H	H	H	H	H	1	1	OH	8.77 x 10 ⁻⁷ + 5.13 x 10 ⁻⁷
Cetirizine												3.16 x 10 ⁻⁶ ± 4.09 x 10 ⁻⁶

Claims

1. A compound of formula I



Formula I

wherein X, Y, X' & Y' are selected from hydrogen, halogen, linear, branched or cyclo alkyl, alkyloxy and haloalkyl

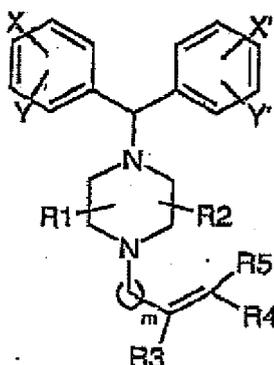
group; R₁ and R₂, are both hydrogen, R₃ and R₄ are selected from hydrogen, linear, branched or cyclo alkyl groups and aryl, and optionally R₃ and R₄ together with the carbons to which they are attached form an aryl ring with a proviso that when R₃ & R₄ together do not form part of said aryl ring they may exist in either *E* or *Z* configuration; R₅ is (CH₂)_n-O-CH₂-CO-Z wherein n is 1 to 6; Z is selected from OH, OR, NRR', N(OR)R', wherein R & R' are selected from hydrogen, linear, branched or cyclo alkyl groups or C2 to C6 alkenyl or alkynyl groups; and m is selected from 1 to 6; an pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1 wherein X, Y, X' & Y' are selected from hydrogen, chloro and fluoro; R₁ and R₂, are hydrogen; R₃ and R₄ are hydrogen existing in the *E* or *Z* configuration or optionally when they are in *Z*-configuration R₃ and R₄ together with the carbons to which they are attached form a benzene ring; and R₅ is CH₂-O-CH₂-CO-Z wherein Z is selected from OH and OR wherein R may be selected from methyl, ethyl and isopropyl; and m is 1.
3. A compound of claim 1, which is {4-[4-[Bis-(4-fluorophenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enoxy}acetic acid or its pharmaceutically acceptable salt.
4. A compound of claim 1, which is {4-[4-[(4-Chlorophenyl)phenylmethyl] piperazin-1-yl]-(Z)-but-2-enoxy}acetic acid or its pharmaceutically acceptable salt.
5. A compound of claim 1, which is [4-(4-Benzhydrylpiperazin-1-yl)-(Z)-but-2-enoxy]acetic acid or its pharmaceutically acceptable salt.
6. A compound of claim 1, which is {4-[4-[Bis-(2,4-difluorophenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enoxy}acetic acid or its pharmaceutically acceptable salt.
7. A compound of claim 1, which is {4-[4-[Bis-(4-chlorophenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enoxy}acetic acid or its pharmaceutically acceptable salt.
8. A compound of claim 1, which is {4-[4-[Bis-(4-fluorophenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enoxy}acetic acid methyl ester or its pharmaceutically acceptable salt.
9. A compound of claim 1, which is {4-[4-[Bis-(4-fluorophenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enoxy}acetic acid ethyl ester or its pharmaceutically acceptable salt.
10. A compound of claim 1, which is {4-[4-[Bis-(4-fluorophenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enoxy}acetic acid isopropyl ester or its pharmaceutically acceptable salt.
11. A compound of claim 1, which is {4-[4-[(4-chlorophenyl)phenylmethyl] piperazin-1-yl]-(Z)-but-2-enoxy}acetic acid isopropyl ester or its pharmaceutically acceptable salt.
12. A compound of claim 1, which is {4-[4-[(4-chlorophenyl)phenylmethyl] piperazin-1-yl]-(Z)-but-2-enoxy}acetic acid methyl ester or its pharmaceutically acceptable salt.
13. A compound of claim 1, which is {4-[4-[(4-chlorophenyl)phenylmethyl] piperazin-1-yl]-(Z)-but-2-enoxy}acetic acid ethyl ester or its pharmaceutically acceptable salt.
14. A compound of claim 1, which is {2-[4-[Bis-(4-fluorophenyl)methyl]piperazin-1-ylmethyl]benzyloxy}acetic acid or its pharmaceutically acceptable salt.
15. A compound of claim 1, which is {2-[4-[(4-Chlorophenyl)phenylmethyl] piperazin-1-ylmethyl]benzyl-oxy}acetic acid or its pharmaceutically acceptable salt.
16. A compound of claim 1, which is {4-[4-[Bis-(4-fluorophenyl)methyl]piperazin-1-yl]-(E)-but-2-enoxy}acetic acid or its pharmaceutically acceptable salt.

17. A compound of claim 1, which is {4-[4-[(4-Chlorophenyl)phenylmethyl] piperazin-1-yl]-(E)-but-2-enoxy}acetic acid or its pharmaceutically acceptable salt.
18. A compound of claim 1, which is {4-[4-[(4-Fluorophenyl)phenylmethyl] piperazin-1-yl]-(E)-but-2-enoxy}acetic acid or its pharmaceutically acceptable salt.
19. A pharmaceutical composition comprising compound of formula I as claimed in any of claims 1 to 18 and a pharmaceutically acceptable carrier.

Patentansprüche

1. Eine Verbindung gemäß Formel I,



Formel I

wobei X, Y, X' und Y' ausgewählt sind aus Wasserstoff, Halogen, linearer, verzweigter oder cyclo Alkyl-, Alkyloxy- und Haloalkylgruppe; R₁ und R₂ beide Wasserstoff sind, R₃ und R₄ ausgewählt sind aus Wasserstoff, linearen, verzweigten oder cyclo Alkylgruppen und Aryl, und wobei optional R₃ und R₄ zusammen mit den Kohlenstoffatomen, an die sie angelagert sind, einen Arylring bilden, mit der Maßgabe, dass R₃ und R₄ entweder in E oder Z Konfiguration vorliegen können, wenn sie zusammen nicht Teil des Arylrings sind;

wobei R₅ (CH₂)_n-O-CH₂-CO-Z ist, wobei n 1 bis 6 ist; wobei Z ausgewählt ist aus OH, OR, NRR', N(OR)R', wobei R und R' ausgewählt sind aus Wasserstoff, linearen, verzweigten oder cyclo Alkylgruppen oder C₂ bis C₆ Alkenyl- oder Alkynylgruppen; und wobei m ausgewählt ist aus 1 bis 6;

und pharmazeutisch verträgliche Salze davon.

2. Eine Verbindung gemäß Anspruch 1, wobei X, Y, X' und Y' ausgewählt sind aus Wasserstoff, Chlor und Fluor; R₁ und R₂ Wasserstoff sind; R₃ und R₄ Wasserstoff sind, der in der E oder Z Konfiguration vorliegt, oder wobei optional R₃ und R₄, wenn sie in Z Konfiguration vorliegen, zusammen mit den Kohlenstoffatomen, an die sie angelagert sind, einen Benzolring bilden; und wobei R₅ CH₂-O-CH₂-CO-Z ist, wobei Z ausgewählt ist aus OH und OR, wobei R ausgewählt werden kann aus Methyl, Ethyl und Isopropyl; und wobei m 1 ist.
3. Eine Verbindung gemäß Anspruch 1, wobei die Verbindung {4-[4-[Bis-(4-fluorophenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enoxy}essigsäure oder das pharmazeutisch verträgliche Salz davon ist.
4. Eine Verbindung gemäß Anspruch 1, wobei die Verbindung {4-[4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl]-(Z)-but-2-enoxy}essigsäure oder das pharmazeutisch verträgliche Salz davon ist.

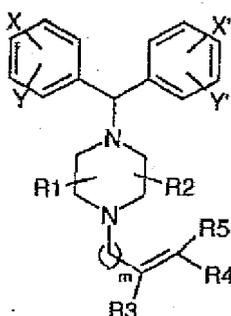
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5. Eine Verbindung gemäß Anspruch 1, wobei die Verbindung [4-(4-Benzhydrylpiperazin-1-yl)-(Z)-but-2-enyloxy]essigsäure oder das pharmazeutisch verträgliche Salz davon ist.
- 5 6. Eine Verbindung gemäß Anspruch 1, wobei die Verbindung {4-[4-[Bis-(2,4-difluorphenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enyloxy}essigsäure oder das pharmazeutisch verträgliche Salz davon ist.
7. Eine Verbindung gemäß Anspruch 1, wobei die Verbindung {4-[4-[Bis-(4-chlorphenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enyloxy}essigsäure oder das pharmazeutisch verträgliche Salz davon ist.
- 10 8. Eine Verbindung gemäß Anspruch 1, wobei die Verbindung {4-[4-[Bis-(4-fluorphenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enyloxy}essigsäuremethylester oder das pharmazeutisch verträgliche Salz davon ist.
9. Eine Verbindung gemäß Anspruch 1, wobei die Verbindung {4-[4-[Bis-(4-fluorphenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enyloxy}essigsäureethylester oder das pharmazeutisch verträgliche Salz davon ist.
- 15 10. Eine Verbindung gemäß Anspruch 1, wobei die Verbindung {4-[4-[Bis-(4-fluorphenyl)methyl]-piperazin-1-yl]-(Z)-but-2-enyloxy}essigsäureisopropylester oder das pharmazeutisch verträgliche Salz davon ist.
- 20 11. Eine Verbindung gemäß Anspruch 1, wobei die Verbindung {4-[4-[(4-Chlorphenyl)phenylmethyl]piperazin-1-yl]-(Z)-but-2-enyloxy}essigsäureisopropylester oder das pharmazeutisch verträgliche Salz davon ist.
12. Eine Verbindung gemäß Anspruch 1, wobei die Verbindung {4-[4-[(4-Chlorphenyl)phenylmethyl]piperazin-1-yl]-(Z)-but-2-enyloxy}essigsäuremethylester oder das pharmazeutisch verträgliche Salz davon ist.
- 25 13. Eine Verbindung gemäß Anspruch 1, wobei die Verbindung {4-[4-[(4-Chlorphenyl)phenylmethyl]piperazin-1-yl]-(Z)-but-2-enyloxy}essigsäureethylester oder das pharmazeutisch verträgliche Salz davon ist.
14. Eine Verbindung gemäß Anspruch 1, wobei die Verbindung {2-[4-[Bis-(4-fluorphenyl)methyl]piperazin-1-ylmethyl]benzyloxy}essigsäure oder das pharmazeutisch verträgliche Salz davon ist.
- 30 15. Eine Verbindung gemäß Anspruch 1, wobei die Verbindung {2-[4-[(4-Chlorphenyl)phenylmethyl]piperazin-1-ylmethyl]benzyl-oxy}essigsäure oder das pharmazeutisch verträgliche Salz davon ist.
- 35 16. Eine Verbindung gemäß Anspruch 1, wobei die Verbindung {4-[4-[Bis-(4-fluorphenyl)methyl]piperazin-1-yl]-(E)-but-2-enyloxy}essigsäure oder das pharmazeutisch verträgliche Salz davon ist.
17. Eine Verbindung gemäß Anspruch 1, wobei die Verbindung {4-[4-[(4-Chlorphenyl)phenylmethyl]piperazin-1-yl]-(E)-but-2-enyloxy}essigsäure oder das pharmazeutisch verträgliche Salz davon ist.
- 40 18. Eine Verbindung gemäß Anspruch 1, wobei die Verbindung {4-[4-[(4-Fluorphenyl)phenylmethyl]piperazin-1-yl]-(E)-but-2-enyloxy}essigsäure oder das pharmazeutisch verträgliche Salz davon ist.
19. Eine pharmazeutische Zusammensetzung, umfassend eine Verbindung gemäß Formel I wie in einem der Ansprüche 1 bis 18 beansprucht und einen pharmazeutisch verträglichen Träger.
- 45

Revendications

- 50 1. Composé de formule I :

55



Formule I

dans lequel X, Y, X' et Y' sont choisis parmi hydrogène, halogène, et les groupes alkyle linéaires, ramifiés ou cycliques, alkyloxy et haloalkyle ; R₁ et R₂ représentent tous deux hydrogène ; R₃ et R₄ sont choisis parmi hydrogène, les groupes alkyle linéaires, ramifiés ou cycliques, et aryle, et facultativement R₃ et R₄ forment un noyau aryle conjointement avec les carbones auxquels ils sont attachés à la condition que, lorsque R₃ et R₄ ne font pas partie ensemble dudit noyau aryle, ils peuvent exister dans la configuration soit E soit Z ; R₅ représente (CH₂)_n-O-CH₂-CO-Z où n est de 1 à 6 ; Z est choisi parmi OH, OR, NRR', N(OR) R', R et R' étant choisis parmi hydrogène, les groupes alkyle linéaires, ramifiés ou cycliques ou les groupes alcényle ou alcynyle de C2 à C6 ; et m est choisi parmi 1 à 6 ; et les sels pharmaceutiquement acceptable de ce composé.

2. Composé selon la revendication 1, dans lequel X, Y, X' et Y' sont choisis parmi hydrogène, chloro et fluoro ; R₁ et R₂ représentent hydrogène ; R₃ et R₄ représentent hydrogène existant dans la configuration E ou Z ou facultativement quand ils sont dans la configuration Z R₃ et R₄ forment un noyau benzène conjointement avec les carbones auxquels ils sont attachés ; et R₅ représente CH₂-O-CH₂-CO-Z, Z étant choisi parmi OH et OR, R pouvant être choisi parmi méthyle, éthyle et isopropyle ; et m est 1.
3. Composé selon la revendication 1, qui est l'acide {4-[4-[bis-(4-fluorophényl)méthyl]-pipérazin-1-yl]-(Z)-but-2-ényloxy}acétique ou son sel pharmaceutiquement acceptable.
4. Composé selon la revendication 1, qui est l'acide {4-[4-[(4-chlorophényl)phénylméthyl]pipérazin-1-yl]-(Z)-but-2-ényloxy}acétique ou son sel pharmaceutiquement acceptable.
5. Composé selon la revendication 1, qui est l'acide [4-(4-benzhydrylpipérazin-1-yl)-(Z)-but-2-ényloxy]acétique ou son sel pharmaceutiquement acceptable.
6. Composé selon la revendication 1, qui est l'acide {4-[4-[bis-(2,4-difluorophényl)méthyl]-pipérazin-1-yl]-(Z)-but-2-ényloxy}acétique ou son sel pharmaceutiquement acceptable.
7. Composé selon la revendication 1, qui est l'acide {4-[4-[bis-(4-chlorophényl)méthyl]-pipérazin-1-yl]-(Z)-but-2-ényloxy}acétique ou son sel pharmaceutiquement acceptable.
8. Composé selon la revendication 1, qui est l'ester méthylique de l'acide {4-[4-[bis-(4-fluorophényl)méthyl]-pipérazin-1-yl]-(Z)-but-2-ényloxy}acétique ou son sel pharmaceutiquement acceptable.
9. Composé selon la revendication 1, qui est l'ester éthylique de l'acide {4-[4-[bis-(4-fluorophényl)méthyl]-pipérazin-1-yl]-(Z)-but-2-ényloxy}acétique ou son sel pharmaceutiquement acceptable.
10. Composé selon la revendication 1, qui est l'ester isopropylique de l'acide {4-[4-[bis-(4-fluorophényl)méthyl]-pipérazin-1-yl]-(Z)-but-2-ényloxy}acétique ou son sel pharmaceutiquement acceptable.

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11. Composé selon la revendication 1, qui est l'ester isopropylique de l'acide {4-[4-[(4-chlorophényl)phénylméthyl]pipérazin-1-yl]-(Z)-but-2-ényloxy}acétique ou son sel pharmaceutiquement acceptable.
- 5 12. Composé selon la revendication 1, qui est l'ester méthylique de l'acide {4-[4-[(4-chlorophényl)phénylméthyl]pipérazin-1-yl]-(Z)-but-2-ényloxy}acétique ou son sel pharmaceutiquement acceptable.
13. Composé selon la revendication 1, qui est l'ester éthylique de l'acide {4-[4-[(4-chlorophényl)phénylméthyl]pipérazin-1-yl]-(Z)-but-2-ényloxy}acétique ou son sel pharmaceutiquement acceptable.
- 10 14. Composé selon la revendication 1, qui est l'acide {2-[4-[bis-(4-fluorophényl)méthyl]pipérazin-1-ylméthyl]benzyloxy}acétique ou son sel pharmaceutiquement acceptable.
- 15 15. Composé selon la revendication 1, qui est l'acide {2-[4-[(4-chlorophényl)phénylméthyl]pipérazin-1-ylméthyl]benzyloxy}acétique ou son sel pharmaceutiquement acceptable.
16. Composé selon la revendication 1, qui est l'acide {4-[4-[bis-(4-fluorophényl)méthyl]pipérazin-1-yl]-(E)-but-2-ényloxy}acétique ou son sel pharmaceutiquement acceptable.
- 20 17. Composé selon la revendication 1, qui est l'acide {4-[4-[(4-chlorophényl)phénylméthyl]pipérazin-1-yl]-(E)-but-2-ényloxy}acétique ou son sel pharmaceutiquement acceptable.
18. Composé selon la revendication 1, qui est l'acide {4-[4-[(4-fluorophényl)phénylméthyl]pipérazin-1-yl]-(E)-but-2-ényloxy}acétique ou son sel pharmaceutiquement acceptable.
- 25 19. Composition pharmaceutique comprenant un composé de formule I selon l'une quelconque des revendications 1 à 18 et un support pharmaceutiquement acceptable.

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REFERENCES CITED IN THE DESCRIPTION

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