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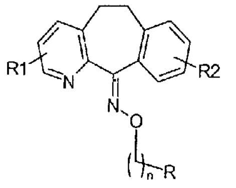
(54) Title: ANTIHISTAMINIC COMPOUNDS



(I)

(57) Abstract: (*E*)-oxime ether derivative of 5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one, compound of formula (I): wherein R in formula (I) is selected from formula (a, b, c, d, e, f, g, h, i) and their pharmaceutically acceptable salts useful as antihistaminic compounds.

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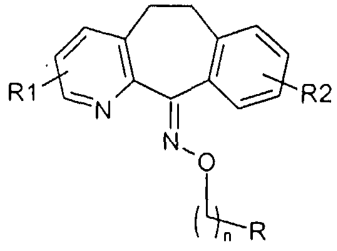
ANTIHISTAMINIC COMPOUNDS

The present invention relates to antihistaminic compounds which are *(E)*-oxime ether derivatives of 5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ones (earlier referred to as 4-aza-5-oxo-10,11-dihydro-dibenzo[a,d]cycloheptenes), compound of formula I,



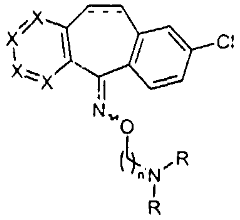
Formula I

wherein R, R_1 and R_2 are as defined in the later part of the text.

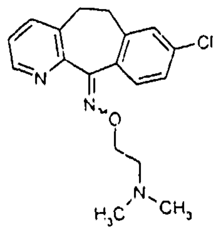
The compounds of the present invention are antihistaminic compounds useful in the treatment of histamine mediated disorders.

PRIOR ART

United States Patent No. 3,458,524 (referred to herein as **'524**, Indian reference not available) discloses oxime ethers of general formula II, their synthesis from aza-5-oxo-dibenzo[a,d]cycloheptenes or their 10,11-dihydro analogs, and their use as antihistaminic agents, wherein X is independently carbon or nitrogen and R is lower alkyl. Also, the patent exemplifies the synthesis of a compound of formula IA1 (X is N in position 1, n=2 and R is CH_3 in formula II) as per scheme 1.



Formula II



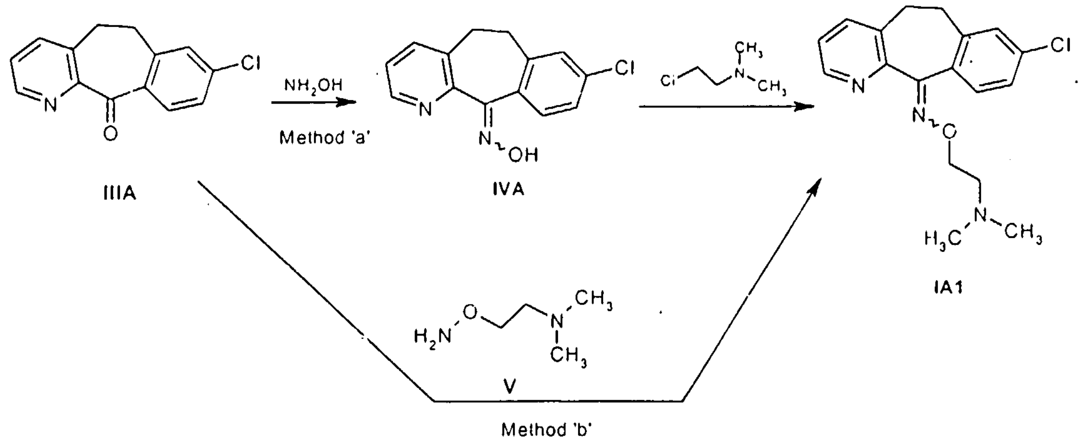
Formula IA1

Synthesis of compound of formula IA1 was achieved by the following two methods (scheme1):

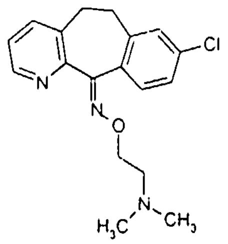
(a) Conversion of ketone of formula IIIA to an oxime of formula IVA, and its subsequent alkylation with 2-(dimethylamino)ethyl chloride, or

(b) by reaction of ketone of formula IIIA with 2-(dimethylamino)ethoxyamine of formula V.

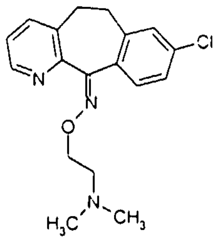
Scheme 1



The '524 does not disclose the geometry of compound of formula IA1, or for that matter the geometry of the compounds claimed of generic formula II. It is possible that by either of the methods (a & b, *vide supra*) described in the said patent, and exemplified for compound of formula IA1, there is the possibility of obtaining two geometric isomers of formulas Ia1 & Ia'1 which represent *(E)*-isomer & *(Z)*-isomer respectively of compound of formula IA1.



Formula Ia1

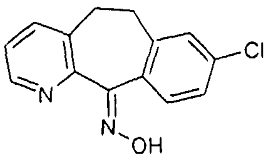


Formula Ia'1

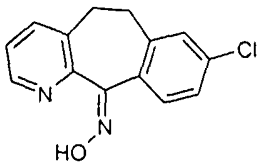
Both these isomers are expected to be co-produced by the methods (a & b) described.

The oxime IVA prepared (route a) is not purified as per the procedure described in the said patent, and would contain both *E* & *Z* oximes of formulas IVa & IVa' respectively. This was indeed found to be the case when we prepared in our laboratory the oxime as described in '524.

HPLC analysis of several batches of the oxime preparation as described in '524 revealed that it was a mixture of *E* & *Z* isomers of formulas IVa & IVa' in the ratio averaging about 58:42.



IVa



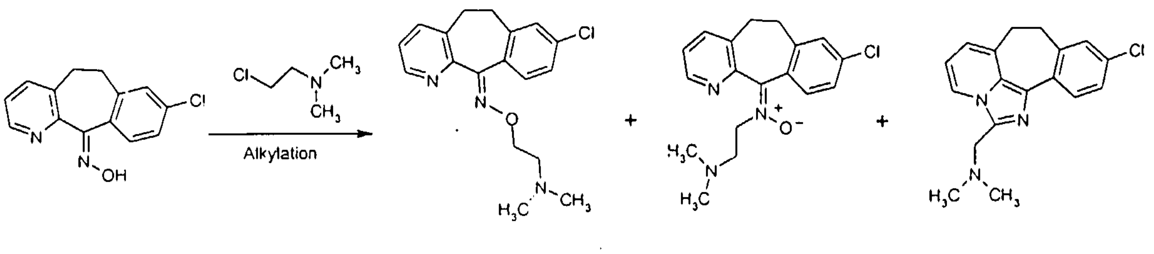
IVa'

The condensation of ketone of formula IIIA with 2-(dimethylamino)ethoxyamine of formula V (scheme1, method 'b') is also not expected to be specific although there could be some selectivity towards the formation of *E* isomer Ia1. This was in fact found to be the case when we prepared in our laboratory the oxime ether as described in '524 from ketone IIIA and 2-(dimethylamino)ethoxyamine (V). Analysis of the crude products by HPLC obtained from different batches by the method described in '524 revealed that they were indeed mixtures of *E* and *Z* isomers of formulas Ia1 and Ia'1 respectively in the ratio of about 64: 36.

BACKGROUND OF THE INVENTION:

It is very well known that the pharmacodynamic or pharmacokinetics profiles sometimes markedly differ for different geometric isomers of the same molecule. The antihistaminic activity of the individual geometric isomers viz. the *E* & *Z* isomers, of formulas Ia1 & Ia'1 respectively, is not reported hitherto in literature. We felt that it is important to understand the geometrical isomer that would predominantly contribute to the antihistaminic activity. Hence, the pure isomeric oximes of formulas IVa & IVa' were separated and individually alkylated so as to obtain pure *E* & *Z* compounds of formulas Ia1 and Ia'1, respectively. Incidentally it was found that alkylation of oxime of the pure *E* isomer of formula IVa led to the formation of two side products besides the expected alkylated product of formula Ia1. These two side products were separated by chromatography and characterized as nitrone of formula VI and a tetracyclic compound of formula VII, respectively (scheme 2).

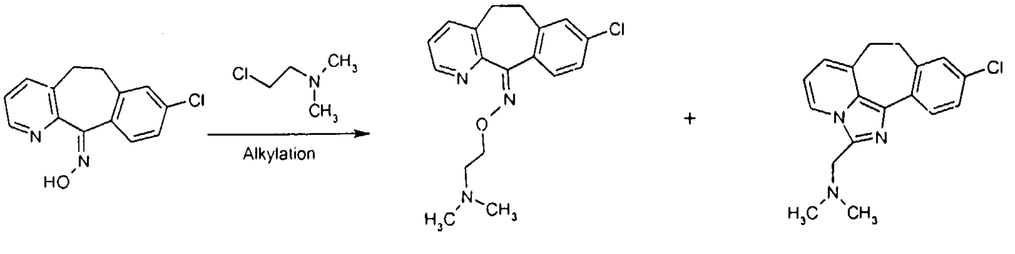
Scheme 2



IVa Ia1 VI VII

On the other hand alkylation on pure Z isomer of formula IVa' with 2-(dimethylamino)ethyl chloride under similar conditions produced the Z-alkylated product of fromula Ia'1 alongwith minor side product of formula VII, without appreciable formation of nitrone of formula VI. (Scheme 3)

Scheme 3



IVa' Ia'1 VII

We anticipated that the side products viz. nitrone of formula VI, and tetracyclic compound of formula VII could also be present to some extent alongwith the expected products of formula Ia1 & Ia'1 in the preparation of IA1 (by method 'a') as described in '**524** by conversion of ketone of formula IIIA to an oxime of formula IVA, and its subsequent alkylation with 2-(dimethylamino)ethyl chloride of formula V. Indeed when we carried out the oxime preparation and alkylated the resulting oxime of formula IVA with 2-(dimethylamino)ethyl chloride as per the process described '**524**, and when the resulting crude alkylated product was analyzed by

HPLC, three products were observed viz. the E & Z –alkylated products of formulas Ia1 and Ia'1 alongwith the nitrone of formula VI in the ratio of about 4.1: 1.0: 1.1, respectively.

The pure *E* & *Z* isomers of formulas Ia1 and Ia'1 were isolated and tested individually for antihistaminic activity in both in-vitro and in-vivo. Interestingly we discovered that the antihistaminic activity of the pure *E* isomer of formula Ia1, in both in-vitro and in-vivo was significantly higher than that of the corresponding *Z* isomer of formula Ia'1 (Table 1). We also isolated and tested the pure nitrone of formula VI and the tetracyclic compound of formula VII for their antihistaminic activity. Both these products were also found to possess antihistaminic activity, albeit much lower than that of the *(E)*-oxime ether of formula Ia1 (Table 1). From our observations, it is apparent that the biological activities described in **'524** for compounds of formula II are not for a pure single isomer but for mixtures of compounds, viz. the *E* & *Z* isomers, and the nitrone.

Table-1

Compound	**Mean IC_{50}, GP Ileum**	**Inhibitory dose in bronchospasm experiment, mg/kg**
Ia1	1.02×10^{-8}	0.005
Ia'1	7.37×10^{-7}	>4.0
VI	2.38×10^{-5}	0.5
VII	2.19×10^{-6}	>4.0

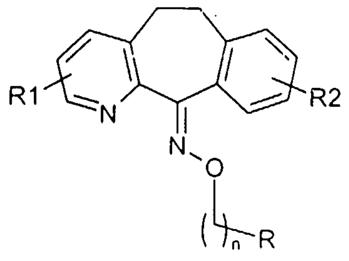
Encouraged by this interesting finding that the pure *E* isomer of formula Ia1 is markedly more potent in comparison to the corresponding *Z* isomer of formula Ia'1, we have synthesized a number of *(E)*-oxime ether derivatives of 5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ones, compounds of formula I. These compounds were found to have antihistaminic activity.

OBJECT OF THE INVENTION

The object of the present invention is to provide antihistaminic compounds of formula I and pharmaceutically acceptable salts thereof.

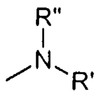
SUMMARY OF INVENTION

The present invention provides *(E)*-oxime ether derivative of 5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one, compound of formula I



formula I

wherein R in formula I is selected from



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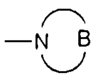

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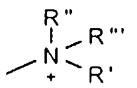

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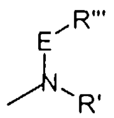

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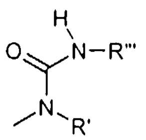

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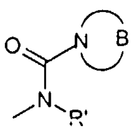

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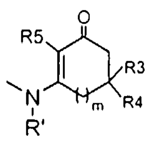

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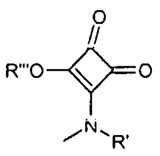

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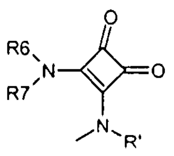

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wherein R', R", R'", R_3, R_4, R_5, R_6 & R_7 are selected from hydrogen, alkyl (C_1 to C_6 linear, branched or cyclo), tricylic fused ring such as adamantyl, unsaturated alkyl (C_1 to C_6 linear, branched or cyclo), heterocyclic (containing one or more of hetero atoms viz. N, S, O), aryl, heteroaryl (containing one or more of hetero atoms viz. N, S, O), alkylaryl, optionally further wherein any of R', R", R'", R_3, R_4, R_5, R_6 & R_7 groups above may be further substituted with one or more groups selected from saturated or unsaturated alkyl(C_1 to C_6 linear, branched or cyclo), alkoxy(C_1 to C_6 linear, branched or cyclo), halo, haloalkyl, haloalkoxy, alkylaryl, hydroxy, amino and its derivatives such as amide or carbamate;

carboxylic acids, C_1-C_6 alkylcarboxylic acids, acrylic acids, propargylic acids and their derivatives such as amides or substituted amides with alkyl (C_1–C_5) substitution or aryl substitution or cyclic amides (C_1 to C_7), esters (C_1 to C_5), N-hydroxyamides, or N-C_1 to C_5 alkoxyamides;

m is 0 to 2;

E is selected from O, S, NH, NR_8 wherein R_8 maybe C_1-C_6 linear, branched or cyclo alkyl group, C=O, CO_2, SO_2 and S=O; and

B is selected from -(CH2)$_p$- wherein p=2 to 7; and

$-CH(R_9)-(CH_2)_x-D-CH(R_{10})-(CH_2)_y-$ wherein D is O, NR_8, S or SO_2; x and y are independently 1 to 6; and R_8, R_9 & R_{10} are independently H, (C_1-C_6 linear, branched or cyclo) alkyl group;

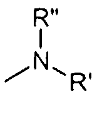
optionally B is part of arylheterocycles containing one or more of hetero atoms (viz., N, S, O);

R_1 and R_2 are selected from hydrogen, halogen, saturated or unsaturated C_1-C_6 linear, branched or cyclo alkyl group, haloalkyl, C_1-C_6 linear, branched or cyclo alkoxy or haloalkoxy, amino and its derivatives such as amide or carbamate; carboxylic acids, C_1-C_6 alkyl carboxylic acids, acrylic acids, propargylic acids and their derivatives as defined above;

and n is 2 to 6;

and pharmaceutically acceptable salts thereof.

More particularly the present invention provides *(E)*-oxime ether derivative of 5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one, compound of formula I wherein R in formula I is selected from



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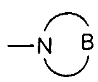

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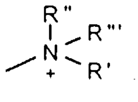

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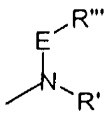

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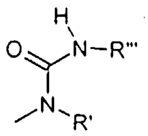

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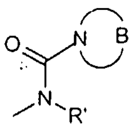

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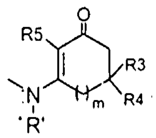

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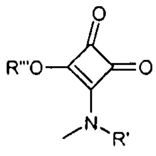

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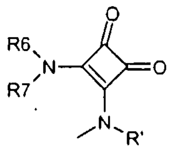

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R', R'', R''', R_3, R_4, R_5, R_6 & R_7 are selected from hydrogen, alkyl (C_1 to C_6 linear, branched or cyclo), tricylic fused ring such as adamantyl, unsaturated alkyl (C_1 to C_6 linear, branched or cyclo), aryl, alkylaryl, optionally further wherein any of R', R'', R''', R_3, R_4, R_5, R_6 & R_7 groups above may be further substituted with one or more groups selected from alkoxy, halo, haloalkyl, haloalkoxy, free carboxyl, hydroxy or amino groups;

m is 0 to 2;

E is selected from C=O, CO_2 and SO_2; and

B is selected from $-(CH2)_p-$ wherein p=2 to 7; and

$-CH(R_9)-(CH_2)_x-D-CH(R_{10})-(CH_2)_y-$ wherein D is O, NR_8, S or SO_2; x and y are independently 1 to 6; and R_8, R_9 & R_{10} are independently H, (C_1-C_6 linear, branched or cyclo) alkyl group;

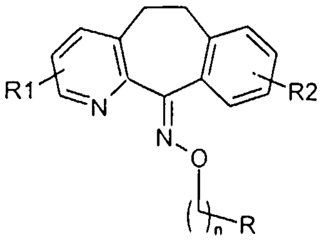
optionally B is part of arylheterocycles containing one or more of hetero atoms (viz., N, S, O);

R_1 and R_2 are selected from hydrogen, halogen, alkyl (C_1-C_6 linear, branched or cyclo), alkoxy (C_1-C_6 linear, branched or cyclo), haloalkoxy or haloalkyl; and

n is 2 to 6 and pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION:

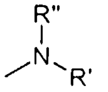
Accordingly, the present invention provides compound of formula I



Formula I

wherein R, R_1 and R_2 are as described above.

The compound of formula I , wherein R is



referred to herein as formula Ia.

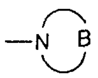
More particularly, the compounds of formula Ia are as given below in Table 2:

Table 2

Compd No.	R1	R2	R'	R"	n
Ia1	H	8-Cl	CH_3	CH_3	2
Ia2	H	8-Cl	CH_3	CH_3	3
Ia3	H	8-Cl	C_2H_5	C_2H_5	2
Ia4	H	8-Cl	n-C_3H_7	n-C_3H_7	2
Ia5	H	8-Cl	H	H	2
Ia6	H	8-Cl	CH_3	H	2
Ia7	H	8-Cl	H	CH_2CF_3	2
Ia8	H	8-Cl	H	$CH(CH_3)_2$	2
Ia9	H	8-Cl	H	Cyclopentyl	2
Ia10	H	8-Cl	CH_3	C_2H_5	2
Ia11	H	8-Cl	CH_3	CH_2CF_3	2
Ia12	H	8-Cl	CH_3	cyclopropylmethyl	2
Ia13	H	8-Cl	CH_3	$CH_2CH=CH_2$	2
Ia14	H	8-Cl	CH_3	propargyl	2
Ia15	H	8-Cl	CH_3	(3,4,5-trimethoxyphenyl)methyl	2
Ia16	H	8-Cl	CH_3	$CH_2COOC_2H_5$	2
Ia17	H	8-Cl	CH_3	CH_2COOH	2
Ia18	H	8-Cl	H	2-adamantyl	2

Ia19	H	8-Cl	H	(3,4,5-trimethoxyphenyl)methyl	2
Ia20	H	8-Cl	H	(2,4,6-trimethoxyphenyl)methyl	2
Ia21	H	8-Cl	H	(3,4-dimethoxyphenyl)methyl	2
Ia22	H	8-Cl	H	$CH_2CH=CHPh$ (E-configuration)	2
Ia23	H	8-Cl	H	(2,3,4-trimethoxyphenyl)methyl	2
Ia24	H	8-Cl	H	(2,6-dimethoxyphenyl)methyl	2
Ia25	H	8-Cl	H	(3-cyclopentyloxy-4-methoxyphenyl)methyl	2
Ia26	H	8-Cl	CH_3	(2,4,6-trimethoxyphenyl)methyl	2
Ia27	H	8-Cl	CH3	(3-cyclopentyloxy-4-methoxyphenyl)methyl	2
Ia28	H	8-Cl	CH_3	$CH_2CH=CHPh$ (E-configuration)	2
Ia29	H	8-Cl	CH_3	(2,3,4-trimethoxyphenyl)methyl	2
Ia30	H	8-Cl	CH_3	(3,4-dimethoxyphenyl)methyl	2
Ia31	H	8-Cl	CH3	2-admantyl	2
Ia32	H	8-Cl	CH3	(2,6-dimethoxyphenyl)methyl	2
Ia33	H	8-Cl	$CH_2CH=CHPh$ (E-configuration)	$CH_2CH=CHPh$ (E-configuration)	2
Ia34	H	8-Cl	$CH_2CH=CHPh$ (E-configuration)	(2,3,4-trimethoxyphenyl)methyl	2
Ia35	H	8-Cl	$CH_2CH=CHPh$ (E-configuration)	(3,4,5-trimethoxyphenyl)methyl	2
Ia36	H	8-Cl	CH_3	$-(CH_2)_2OH$	2
Ia37	H	8-Cl	CH_3	$CH_2C(OH)CH_3$	2
Ia38	H	8-Cl	CH_3	$CH_2CH(OH)CH_2OH$	2
Ia39	H	8-Cl	$CH(CH_3)_2$	$CH_2CH(OH)CH_2OH$	2
Ia40	H	8-Cl	$CH(CH_3)_2$	$CH_2CH(OH)CH_3$	2
Ia41	H	8-Cl	cyclopentyl	$CH_2CH(OH)CH_3$	2
Ia42	H	8-Cl	$CH_2C(OH)CH_3$	(3,4,5-trimethoxyphenyl)methyl	2
Ia43	H	8-Cl	CH_2CH_2OH	(2,3,4-trimethoxyphenyl)methyl	2
Ia44	H	8-Cl	CH_2CH_2OH	(2,4,6-trimethoxyphenyl)methyl	2

The compound of formula I wherein R is



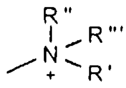
referred to herein as formula Ib.

More particularly, the compounds of formula Ib are as given below in Table 3:

Table 3

Compd No.	**R1**	**R2**	**B**	**n**
Ib1	H	8-Cl	$-CH_2-(CH_2)_2-CH_2-$	2
Ib2	H	8-Cl	$-CH_2-(CH_2)_3-CH_2-$	2
Ib3	H	8-Cl	$-CH_2-(CH_2)_4-CH_2-$	2

The compound of formula I wherein R is



referred to herein as formula Ic.

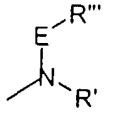
More particularly, the compounds of formula Ic are as given below in Table 4:

Table 4

Compd No. *	R1	R2	R'	R"	R'''	n
Ic1	H	8-Cl	CH_3	CH_3	CH_3	2
Ic2	H	8-Cl	C_2H_5	$CH_2CH=CH_2$	CH_3	2
Ic3	H	8-Cl	CH_3	(2,4,6-trimethoxyphenyl)methyl	CH_3	2
Ic4	H	8-Cl	CH_3	(3,4-dimethoxyphenyl)methyl	CH3	2
Ic5	H	8-Cl	CH_3	(2,3,4-trimethoxyphenyl)methyl	CH_3	2
Ic6	H	8-Cl	CH_3	(2,6-dimethoxypheny)methyl	CH_3	2
Ic7	H	8-Cl	$C_6H_5CH=CH_2$ (E-configuration)	$C_6H_5CH=CH_2$ (E-configuration)	CH_3	2

* *All compounds are as iodide salts*

The compound of formula I wherein R is



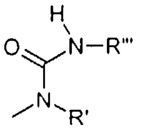
referred to herein as formula Id.

More particularly, the compounds of formula Id are as given below in Table 5:

Table 5

Compd No.	R1	R2	R'	E	R'''	n
Id1	H	8-Cl	H	CO_2	CH_3	2
Id2	H	8-Cl	H	CO_2	C_2H_5	2
Id3	H	8-Cl	H	CO	CH_3	2
Id4	H	8-Cl	CH_3	CO	$CH_2(2\text{-}Cl\text{-}C_6H_4)$	2
Id5	H	8-Cl	H	CO	$CH_2(2\text{-}Cl\text{-}C_6H_4)$	2
Id6	H	8-Cl	H	CO	$CH_2(3\text{-}OEt\text{-}4\text{-}COOH\text{-}C_6H_3)$	2
Id7	H	8-Cl	CH_3	CO	$CH_2(3\text{-}OEt\text{-}4\text{-}COOH\text{-}C_6H_3)$	2
Id8	H	8-Cl	H	SO_2	CH_3	2
Id9	H	8-Cl	CH_3	SO_2	CH_3	2
Id10	H	8-Cl	(2,3,4-trimethoxyphenyl) methyl	SO_2	CH_3	2
Id11	H	8-Cl	H	SO_2	$4\text{-}CH_3\text{-}C_6H_4$	2

The compound of formula I wherein R is



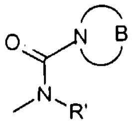
referred to herein as formula Ie.

More particularly, the compounds of formula Ie are as given below in Table 6:

Table 6

Compd. No.	R1	R2	R'	R'''	n
Ie1	H	8-Cl	H	cyclohexyl	2
Ie2	H	8-Cl	H	2-(trifluoromethyl)phenyl	2
Ie3	H	8-Cl	H	2,6-dichlorophenyl	2
Ie4	H	8-Cl	H	cyclopropyl	2
Ie5	H	8-Cl	H	$CH_2.CH=CH_2$	2
Ie6	H	8-Cl	H	2,3-dimethylphenyl	2
Ie7	H	8-Cl	H	2,3-dichlorophenyl	2
Ie8	H	8-Cl	H	4-(trifluoromethoxy)phenyl	2
Ie9	H	8-Cl	H	2-methylphenyl	2
Ie10	H	8-Cl	H	2,4-dichlorophenyl	2
Ie11	H	8-Cl	H	2-chlorophenyl	2
Ie12	H	8-Cl	H	3,5-bis(trifluoromethyl)phenyl	2
Ie13	H	8-Cl	H	cyclopropylmethyl	2
Ie14	H	8-Cl	H	$CH(CH_3)_2$	2
Ie15	H	8-Cl	H	cyclopentyl	2
Ie16	H	8-Cl	H	$CH(CH_3)_2$	2
Ie18	H	8-Cl	H	4-(trifluoromethyl)phenyl	2
Ie19	H	8-Cl	H	$C(CH_3)_3$	2
Ie20	H	8-Cl	H	CH_2CH_2Ph	2
Ie21	H	8-Cl	H	2,6-difluorophenyl	2
Ie22	H	8-Cl	H	*trans*-4-methyl-cyclohexyl	2
Ie23	H	8-Cl	H	4-chloro-2-(trifluoromethyl)phenyl	2
Ie24	H	8-Cl	CH_3	$CH_2.CH=CH_2$	2
Ie25	H	8-Cl	CH_3	cyclopropyl	2
Ie26	H	8-Cl	CH_3	*trans*-4-methyl-cyclohexyl	2
Ie27	H	8-Cl	CH_3	2-methylphenyl	2
Ie28	H	8-Cl	CH_3	2,3-dichlorophenyl	2
Ie29	H	8-Cl	CH3	cyclohexyl	2
Ie30	H	8-Cl	CH3	2-(trifluoromethyl)phenyl	2
Ie31	H	8-Cl	CH_3	2,6-dichlorophenyl	2
Ie32	H	8-Cl	CH3	Phenyl	2
Ie33	H	8-Cl	CH3	2,3-dimethylphenyl	2
Ie34	H	8-Cl	CH3	4-(trifluoromethyl)phenyl	2
Ie35	H	8-Cl	$CH(CH_3)_2$	cyclohexyl	2
Ie36	H	8-Cl	$CH(CH_3)_2$	2-(trifluoromethyl)phenyl	2
Ie37	H	8-Cl	$CH(CH_3)_2$	2,6-dichlorophenyl	2

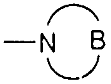
The compound of formula I wherein R is



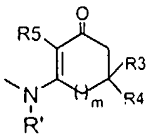
referred to herein as formula If.

More particularly, the compounds of formula If are as given below in Table 7:

Table 7

Compd. No.	R1	R2	R'		n
If1	H	8-Cl	H	*cis*-2,6dimethylpiperazin-1-yl	2
If2	H	8-Cl	CH3	*cis*-2,6dimethylpiperazin-1-yl	2

The compound of formula 1 wherein R is



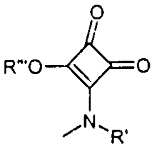
referred to herein as formula Ig.

More particularly, the compounds of formula Ig are as given below in Table 8:

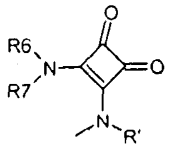
Table 8

Compd. No.	R1	R2	R3	R4	R5	R'	m	n
Ig1	H	8-Cl	H	H	H	H	0	2
Ig2	H	8-Cl	H	H	H	H	1	2
Ig3	H	8-Cl	H	H	CH_3	H	0	2
Ig4	H	8-Cl	H	H	CH_3	H	1	2
Ig5	H	8-Cl	CH_3	CH_3	H	H	1	2
Ig6	H	8-Cl	H	H	H	CH_3	0	2
Ig7	H	8-Cl	H	H	H	CH_3	1	2
Ig8	H	8-Cl	H	H	CH_3	CH_3	0	2
Ig9	H	8-Cl	H	H	CH_3	CH_3	1	2
Ig10	H	8-Cl	CH_3	CH_3	H	CH_3	1	2
Ig11	H	8-Cl	H	H	H	H	2	2

The compound of formula I wherein R is



referred to herein as formula Ih; and wherein



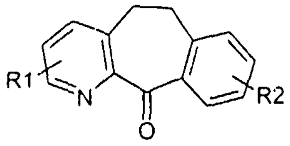
R is referred to herein as formula Ii.

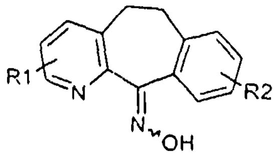
More particularly, the compounds of formula Ih and Ii are as given below in Table 9:

Table 9

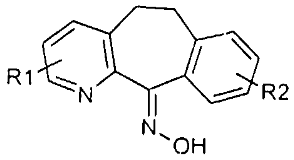
Compd. No.	R1	R2	R'	R'''	R6	R7	n
Ih1	H	8-Cl	H	CH_3			2
Ih2	H	8-Cl	H	C_2H_5			2
Ih3	H	8-Cl	H	$CH(CH_3)_2$			2
Ih4	H	8-Cl	CH_3	CH_3			2
Ih5	H	8-Cl	CH_3	C_2H_5			2
Ih6	H	8-Cl	CH_3	$CH(CH_3)_2$			2
Series Ii							
Ii1	H	8-Cl	CH_3		H	CH_3	2
Ii2	H	8-Cl	CH_3		H	C_2H_5	2
Ii3	H	8-Cl	CH_3		H	CH_2CF_3	2
Ii4	H	8-Cl	CH_3		H	$CH(CH_3)_2$	2
Ii5	H	8-Cl	CH_3		CH_3	CH_3	2
Ii6	H	8-Cl	CH_3		H	cyclopropyl	2
Ii7	H	8-Cl	CH_3		H	cyclopentyl	2
Ii8	H	8-Cl	CH_3		H	H	2
Ii9	H	8-Cl	CH_3		H	2,6-dichlorophenyl	2

Compounds of the present invention may be prepared using different routes. For instance, by a process comprising (a) reacting ketone of formula III with hydroxylamine or salts of hydroxylamine to yield oxime of formula IV(E/Z); (b) purifying the oxime of formula IV(E/Z) with a suitable solvent to obtain pure *(E)*-oxime of formula IV; and (c) treating the pure *(E)*-oxime of formula IV with an alkylating agent, optionally further derivatizing the alkylated compound, to yield compound of formula I.

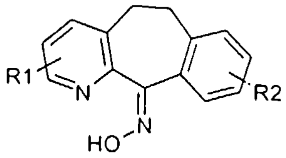




Formula III **Formula IV(E/Z)**



Formula IV



Formula IVZ

In one embodiment of the process of the present invention step (a) of the process comprises reaction of ketone of formula III with hydroxylamine or its acid addition salts in an alcoholic solvent such as ethanol or methanol, using an organic or an inorganic base, preferably an inorganic base such as alkali metal hydroxides or carbonates or acetates to yield oxime of formula IVE/Z.

In one embodiment of the process of the present invention step (b) comprises purifying the oxime of formula IVE/Z obtained in step (a) with a suitable solvent preferably an aprotic solvent, more preferably a ketonic solvent, to get pure *(E)*-oxime of formula IV.

In one embodiment of the process of the present invention step (c) the antihistaminic compounds of the general formula I are obtained by a simple and an efficient process comprising reaction of oxime of formula IV with a suitable alkylating agent. The alkylated compound could, if required, be further derivatized to compounds of the general formula I as described above.

Preferably the process of the present invention step (c) comprises reaction between the oxime of formula IV with an alkylating agent in the presence of a base and a facilitator, in an inert aprotic solvent, at desired temperature for requisite time. The resulting crude *(E)*-oxime ether is purified by standard methods.

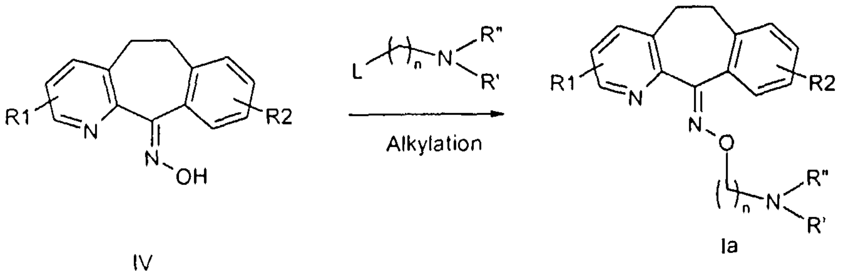
The base used in the process of the present invention step (c) may be an organic base or an inorganic base, preferably an inorganic base selected from alkali metal hydroxides, such as potassium hydroxide.

The inert aprotic solvent used in the process of the present invention step (c) may be an hydrocarbon solvent, preferably an aromatic hydrocarbon solvent such as toluene.

The facilitator used in the process of the present invention step (c) may be a quaternary ammonium salt or a cyclic or acyclic polyethers, preferably an acyclic polyether such as poly(ethylene glycol)-400 (PEG-400).

Series of compounds may be prepared by routes as illustrated below:

Series Ia

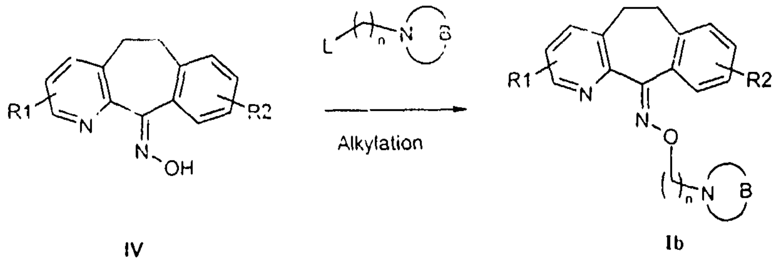


IV Ia

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.

The starting material for the preparation of IV may be prepared as in Belgian patent Number 647,043

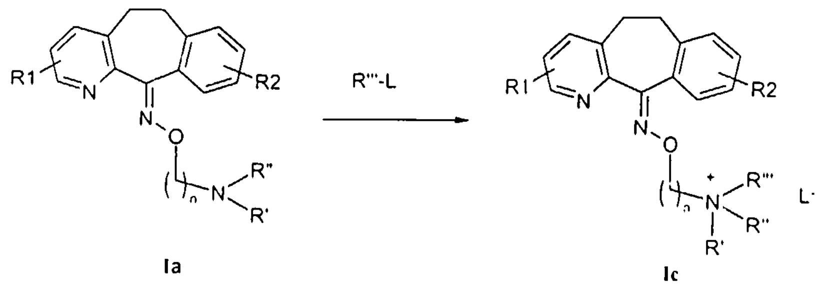
Series "Ib"



IV Ib

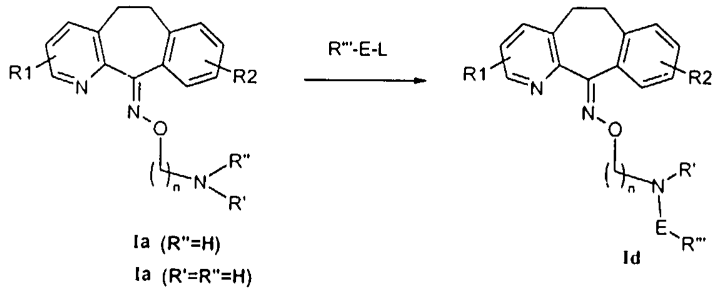
wherein L is a leaving group selected from halide, or an alkyl/arylsulfonate group for e.g. methanesulfonate or p-toluenesulfonate and the like.

Series "Ic"



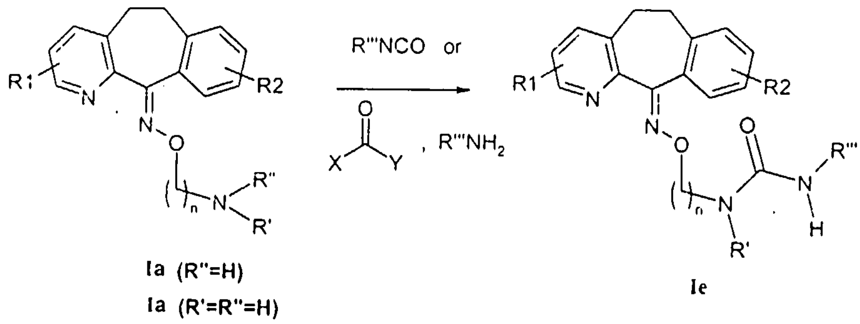
wherein L is a leaving group selected from halide, or an alkyl/arylsulfonate group for e.g. methanesulfonate or p-toluenesulfonate and the like.

Series "Id"



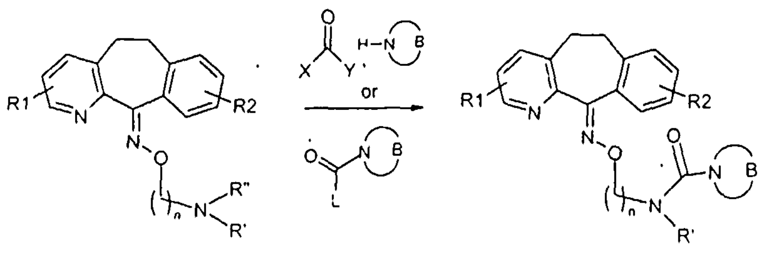
wherein L is a leaving group selected from a halide, aryloxy such as 4-nitrophenoxy and the like.

Series "Ie"



wherein X is a halide, and Y is a group displaceable by amine such as imidazolyl, aryloxy such as 4-nitrophenoxy, and the like.

Series "If"

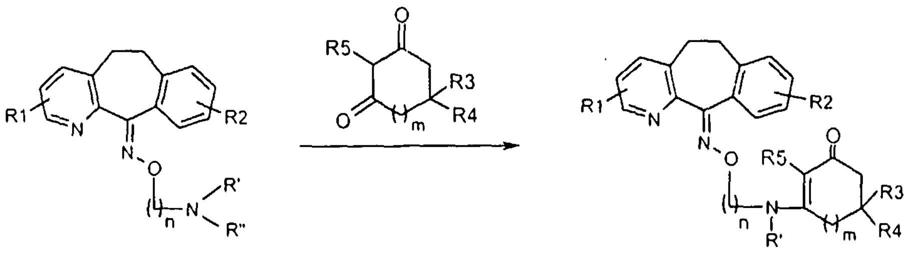


Ia (R''=H)
Ia (R'=R''=H)

If

wherein L is a leaving group selected from halide, X is halide or aryloxy such as 4-nitrophenoxy and the like and X and Y are as defined above

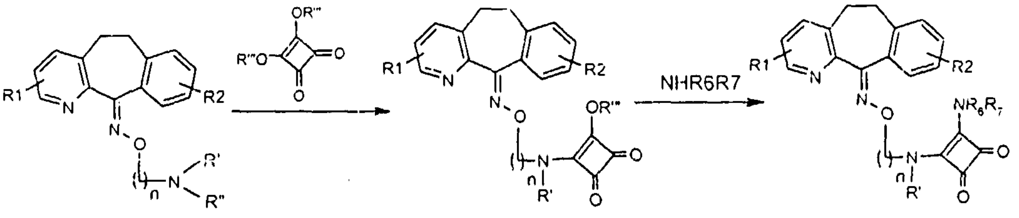
Series "Ig"



Ia (R''=H)
Ia (R'=R''=H)

Ig

Series "Ih" & Series "Ii"



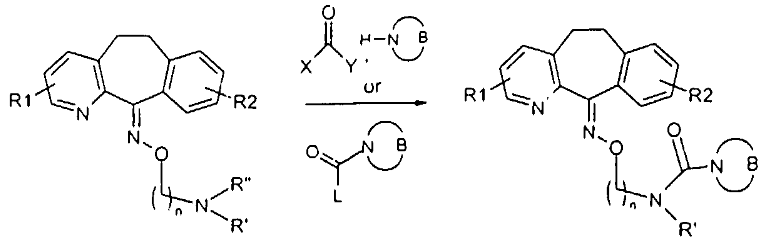
Ia (R''=H)
Ia (R'=R''=H)

Ih

Ii

Another aspect of the present invention relates to formulation of compound of formula I in suitable form, which can be administered to the patient.

Series "If"

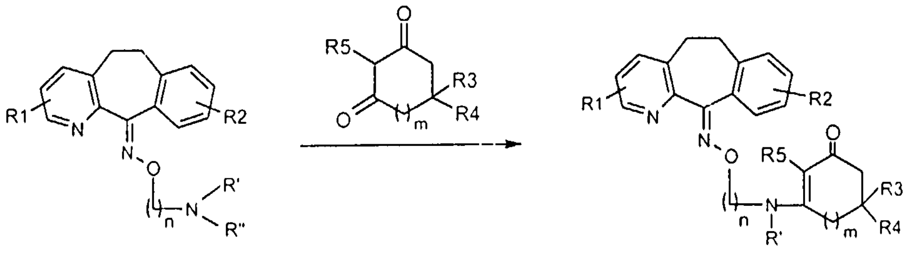


Ia (R"=H)
Ia (R'=R"=H)

If

wherein L is a leaving group selected from halide, X is halide or aryloxy such as 4-nitrophenoxy and the like and X and Y are as defined above

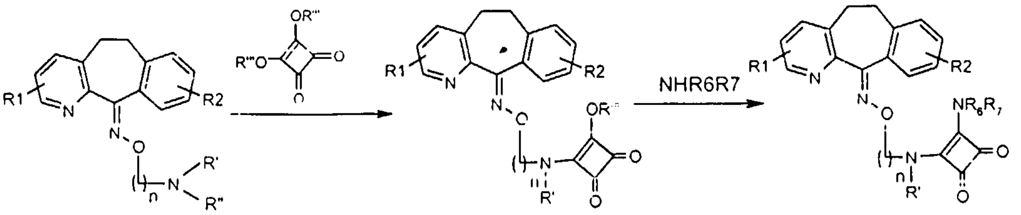
Series "Ig"



Ia (R"=H)
Ia (R'=R"=H)

Ig

Series "Ih" & Series "Ii"



Ia (R"=H)
Ia (R'=R"=H)

Ih

Ii

Another aspect of the present invention relates to formulation of compound of formula I in suitable form, which can be administered to the patient.

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.

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 opthalmic administration.

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.

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

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; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

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

The solid oral compositions may be prepared by conventional methods of blending, filling or tabletting 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.

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.

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.

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, anti-oxidant 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.

Compositions may contain from 0.01 % to 99.0% by weight of the active material, depending upon the method of administration.

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

The compound of formula I on being formulated is useful for various histamine mediated diseases. IC_{50}' s were determined for the compounds prepared by the present invention (using Guinea pig ileum functional assay method) for the estimation of antihistaminic potency (Table 10).

The invention is further illustrated but not restricted by the description in the following examples.

Examples

Example 1

Preparation of oxime of formula IVa:

To a suspension of 8-chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b] pyridin -11-one (formula **IIIA**) (100g, 0.410 mol) in ethanol (3500ml), hydroxylamine hydrochloride (171.25g, 2.46 mol) is added over a period of 20 minutes at ambient temperature and stirred for further 10 minutes. A solution of sodium hydroxide (103.49g, 2.587 mol) in water is then added and the mixture heated under reflux for 18.5 hrs. Cooled to 10-15° C and quenched with water (6000ml). The precipitated solid is filtered and dried to get the crude oxime containing mixture of *(E)* and *(Z)*-oximes.

The crude oxime mixture (100g) is suspended in acetone (3500ml) and stirred for 2 hrs at ambient temperature. The solid is filtered and dried to get pure *(E)*-isomer of 8-chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one oxime (formula **IVa**) (HPLC purity >97.0%). The mother liquor is concentrated and the residue is purified by flash chromatography to get the pure *(Z)*-isomer of 8-chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b] pyridin-11-one oxime of formula **IVa'**.

Example 2

a) Preparation of (*E*)-oxime ether of **Ia1**.

To a suspension of (*E*)- 8-chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one oxime (formula **IVa**) (5g, 0.019mol) in a mixture of toluene (60ml)- PEG-400 (20ml), is introduced at ambient temperature powdered potassium hydroxide (7.59gms, 0.135mol) and stirred for 10 minutes. 2-(Dimethylamino)ethyl chloride (11g, 0.095mol) is then added and stirred at ambient temperature for 24 hrs. Water is added, organic layer separated and the aqueous layer re-extracted with toluene (3x30ml). Combined organic layer is washed successively with water and brine, and degassed under reduced pressure to a get dark brown viscous liquid (6.15g). The crude material is purified by flash column chromatography to get pure compound of formula **Ia1** as the major component and pure tetracyclic compound of formula **VII** in minor quantity.

M.P. of **Ia1**: 78-80° C

^{1}H-NMR of **Ia1** ($CDCl_3$, δppm): 8.55(dd, J_1=4.64, J_2=1.55Hz, 1H), 7.47(dd, J_1=7.73m, J_2=1.46Hz,1H), 7.45(d, J=8.09Hz, 1H), 7.17-7.26, (m,3H), 4.41(t, 6.10Hz,2H), 3.16-3.05(m, 4H), 2.64(t, J=6.08Hz, 2H), 2.22(s, 6H)

^{13}C-NMR of **Ia1** ($CDCl_3$, δppm): 156.37(s), 151.87(s), 148.39(d), 140.09(s), 139.08(d), 135.37(s), 134.98(s), 132.28(s), 131.39(d), 128.90(d), 126.65(d), 124.45(d), 74.04(t), 58.54(t), 46.53(2q), 32.84(t), 32.12(t)

^{1}H-NMR of **VII** ($CDCl_3$, δppm): 8.16(d, J=8.40Hz,1H), 8.07(dd, J_1=5.35, J_2=2.7Hz,1H), 7.27(dd, J_1=8.42, J_2=2.23Hz,1H), 7.17(d, J=2.18Hz,1H), 6.53-6.49(m,2H), 3.91(s,2H), 3.02-3.09 (brm, 4H), 2.29(s, 6H)

^{13}C-NMR of **VII** ($CDCl_3$, δppm): 139.97(s), 137.06(s), 134.33(2s), 133.41(s), 131.32(s), 130.20(d), 129.43(s), 128.27(d), 127.33(d), 121.29(d), 116.96(d), 112.95(d), 57.08(t), 45.94(2q), 35.67(t), 33.50(t)

Compounds **Ia2 to Ia6** are prepared in the same manner as for **Ia1**, using the corresponding 2-chloroethylamine or its derivatives.

b) Preparation of *(Z)*-oxime ether of **Ia'1**: The *(Z)*-oxime ether of the formula **Ia'1** is prepared by following the procedure described above for **Ia1**, using the *(Z)*-oxime of formula **IVa'** in place of the *(E)*-oxime **IVa**.

^{1}H-NMR of **Ia'1** ($CDCl_3$, δppm): 8.51(dd, J_1=4.85; J_2=1.52Hz, 1H), 7.60(d, J=8.31Hz, 1H), 7.58(dd, J_1=7.65, J_2=1.46Hz,1H), 7.24-7.09(m, 3H),4.35(t, J=5.96Hz, 2H), 3.18-3.00(m, 4H), 2.68(t, J=5.90Hz, 2H), 2.24(s, 6H).

^{13}C-NMR of **Ia'1** ($CDCl_3$, δppm): 156.19(s), 153.86(s), 147.77(d), 140.18(s), 136.32(d), 135.66(s), 134.26(s), 131.83(s), 131.32(d), 130.76(d), 127.18(d), 124.43(d), 71.15(t), 58.19(t), 46.13(2q), 33.62(t), 30.31(t).

c) Preparation of nitrone of formula VI: To a stirred mixture of oxime of formula **IVa** (0.0193mol) and anhydrous potassium carbonate (0.116mol) in acetone (60ml), is added 2-(dimethylamino)ethyl chloride (0.079mol) and the mixture refluxed for 8 hours. The solids were filtered and the filtrate is concentrated. The residue is taken up in ehtyl acetate, washed with water, concentrated and degassed. The syrupy residue is purified by column chromatography to get pure nitrone **VI**.

^{1}H-NMR of **VI** ($CDCl_3$, δppm): 8.50(dd, J_1=4.73, J_2=1.54Hz, 1H), 7.91(d, J=8.42Hz, 1H), 7.58(dd, J=7.74,1.48Hz, 1H), 7.30-7.14(m,3H), 4.48-2.25(br, 8H),1.99(s, 6H).

^{13}C-NMR of **VI** ($CDCl_3$, δppm): 153.08(s), 147.83(d), 143.77(s), 139.87(s), 137.72(d), 136.25(s), 135.20(s), 131.60(d), 130.71(s), 130.16(d), 126.56(d), 124.87(d), 59.84(t), 57.47(t), 45.80(2q), 32.27(t), 30.71(t)

Example 3

Preparation of Ia7 to Ia9

These compounds are prepared by alkylation of **Ia5** with the corresponding alkyl halide in acetone using anhydrous potassium carbonate as a base.

Preparation of Ia10 to Ia16

Compounds **Ia10** to **Ia16** are prepared by alkylation of **Ia6** with the corresponding alkyl halide or haloalklyester in acetone using anhydrous potassium carbonate as a base.

Example 4

Preparation of Ia17

This compound is prepared by hydrolysis of **Ia16** with potassium hydroxide in ethanol.

Example 5

Preparation of Ia19

A mixture of 3,4,5-trimethoxybenzaldehyde (0.0033 mol) and **Ia5** (0.0033 mol) in toluene (20ml) is refluxed azeotropically for 21 hours with a catalytic amount of p-toluenesulfonic acid. Cooled to ambient temperature and water is added. The organic layer is separated and the aqueous layer is extracted with toluene (2x15ml). Combined organic layer is washed successively with water and brine, and degassed under reduced pressure to obtain the crude imine. Sodium borohydride (0.046mol) is added portionwise to the solution of the crude imine in methanol (10ml) at 10-15^{0}C. After stirring for 30 minutes the reaction mixture is concentrated under reduced pressure. The residue is quenched with water and extracted with ethyl acetate (3x15ml). Combined extract is washed successively with water and brine and degassed under reduced pressure. The residue is purified by flash column chromatography on silica gel to get the pure product of formula **Ia19**

Similarly are prepared compounds of formulas **Ia18** & **Ia20** to **Ia25** using the corresponding oxo compounds.

Example 6

Preparation of Ia26

Methyl iodide (0.001mol) is added into the stirred mixture of potassium carbonate (0.0015mol) and **Ia19** (0.001mol) in acetone (20ml) at 10-15°C over a period of 5 minutes. After stirring at 15° C for 30 minutes the mixture is concentrated under reduced pressure, water is added and extracted in methylene chloride (3x10 ml). The organic extract is washed with water and degassed under reduced pressure. The residue is purified by flash column chromatography on silica gel to get compound of formula **Ia26**.

Similarly are prepared compounds of formulas **Ia27** to **Ia32** using the corresponding oxime ethers and methyl iodide.

Compounds **Ia33** to **Ia35** are prepared using the corresponding oxime ethers and cinnamyl chloride.

Compound **Ia36**, **Ia43** & **Ia44** are prepared by similar alkylation of **Ia6**, **Ia23** & **Ia20** respectively, with 2-chloroethanol

Compounds **Ia38** & **Ia39** are prepared by similar alkylation of **Ia6** & **Ia8** respectively, with 3-chloro-1,2-propanediol.

Example 7

Preparation of Ia37

To a solution of **Ia6** (0.002mol) in 2-propanol (15ml) is added propylene oxide (0.01mol) at 0-5° C. The mixture is stirred for 12 hours and concentrated under reduced pressure. The crude product obtained is purified by flash chromatography to obtain pure compound of formula **Ia37**.

Similarly are prepared compounds of formulas **Ia40**, **Ia41** & **Ia42** from **Ia8**, **Ia9** & **Ia19** respectively using propylene oxide.

Example 8

Preparation of Ib1 to Ib3

These compounds are prepared in a similar manner as for **Ia1** using the corresponding (2-chloroethyl) cyclic amines.

Example 9

Preparation Ic1 to Ic6

These compounds are prepared in the same manner as **Ia26**, from the corresponding (dialkyamino)ethyl oxime ethers using molar excess of the corresponding alkyl halide to obtain the corresponding quatemary salts **Ic1** to **Ic6**.

Example 10

Preparation of Id1

Methyl chloroformate (0.00248mol) is added to a stirred mixture of compound of formula **Ia5** (0.001mol) and anhydrous potassium carbonate (0.004mol) in tetrahydrofuran (10ml) at ambient temperature and stirred for 2 hours. The mixture is concentrated under reduced pressure, quenched with water and extracted with methylene chloride. The extract is washed with brine and degassed under reduced pressure. The residue is purified by flash column chromatography on silica gel to get pure **Id1**.

Similarly compound of formula **Id2** is prepared using ethyl chloroformate in the place of methyl chloroformate.

Similarly compound of formula **Id3** is prepared using acetic anhydride in the place of methyl chloroformate and pyridine as base.

Similarly are prepared compounds of formulas **Id8, Id9** & **Id10** using methanesulfonyl chloride in the place of methyl chloroformate and using pyridine as base from **Ia5, Ia6** & **Ia23**, respectively.

Compound **Id11** is prepared similarly as above from **Ia5** and 4-toluenesulfonyl chloride in place of methanesulfonyl chloride

Example 11

Preparation of Id4

To a stirred solution of N-methylmorpholine (0.00165mol) and (2-chlorophenyl)acetic acid (0.00124mol) in methylene chloride (15ml), is added 2,2-dimethylpropionyl chloride (0.001030mol) at 0-5° C and stirred for 30mins. The mixture is then brought to ambient temperature, stirred for further 30mins, and again cooled to 0-5° C. A solution of compound of formula **Ia6** (0.00083mol) in methylene chloride is introduced into the reaction mixture at 0-5° C and then slowly brought to ambient temperature. It is quenched with water and is extracted with methylene chloride (3x15ml). Combined organic layer is washed with brine and degassed under reduced pressure. The residue is purified by flash column chromatography on silica gel to get the compound of formula **Id4**.

Similarly is prepared compound **Id5** using **Ia5** as starting material.

Compound **Id6** & **Id7** are prepared from **Ia5** & **Ia6** respectively, using (4-carbethoxy-3-ethoxyphenyl)acetic acid in the place of (2-chlorophenyl)acetic acid followed by hydrolysis of the ester.

Example 12

Preparation of Ie1

Cyclohexyl isocyanate (0.00132mol) is added to a solution of **Ia5** (0.00132mol) in tetrahydrofuran (10ml) at ambient temperature. After stirring for 2 hrs, the reaction mixture is concentrated under reduced pressure and the residue is purified by flash column chromatography on silica gel to get pure **Ie1**.

Similarly are prepared compounds of formulas **Ie2**. to **Ie23** by reacting **Ia5** with the corresponding isocyanates.

Similarly are prepared compounds of formulas **Ie24** to **Ie34** by reacting **Ia6** with the corresponding isocyanates.

Similarly are prepared compounds of formulas **Ie35** to **Ie37** by reacting **Ia8** with the corresponding isocyanates.

Example 13

Preparation of If1

To a solution of formula **Ia5** (0.002mol) in methylene chloride (15ml) and diisopropylethylamine (0.003) is added portionwise 4-nitrophenyl chloroformate (0.002mol) at ambient temperature. The mixture is stirred for 4 hours. The mixture is washed with water and concnetrated and degassed to obtain the 4-nitrophenyl carbamate derivative of **Ia5** as a yellow solid.

To a stirred solution of the above carbamate derivative in methylene chloride (10ml) at ambient temperature is added a solution of *cis*-2,6-dimethylpiperazine (0.00227mol) in methylene chloride (5ml), and stirred for 8 hours. Reaction mixture is quenched with water and extracted with methylene chloride. The organic extract is washed successively with 5% aqueous sodium hydroxide, water and brine and then degassed under reduced pressure. The residue is purified by flash column chromatography on silica gel to get the compound of formula **If1**.

Similarly compound of formula **If2** is prepared starting from compound **Ia6**.

Example 14

Preparation of Ig1

A mixture of cyclopentane-1,3-dione (0.00142mol) and **Ia5** (0.00095mol) in toluene (15ml) is heated under reflux for 6 hours. Cooled mixture to ambient temperature, water is added and the organic layer is separated. The aqueous layer is extracted with ethyl acetate (2x15ml). Combined organic extract is washed successively with aqueous sodium hydroxide solution

(0.5N; 1x15ml), water, and brine, and then degassed under pressure. The residue is purified by flash column chromatography to get the pure **Ig1**.

Similarly are prepared compounds **Ig2** to **Ig5** & **Ig11** from **Ia5** using the corresponding cyclic 1,3-diones.

Similarly are prepared compounds **Ig6** to **Ig10** from **Ia6** using the corresponding cyclic 1,3-diones.

Example 15

Preparation of Ih1

A mixture of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.0063mol) and **Ia5** (0.0063mol) in methanol (10ml) is stirred for 8 hrs at ambient temperature and then concentrated and degassed under reduced pressure. The residue is purified by flash column chromatography on silica gel to get pure **Ih1**.

Similarly are prepared compounds **Ih2** & **Ih3** from **Ia5** using the corresponding squarate ester.

Similarly are prepared compounds **Ih4** to **Ih6** from **Ia6** using the corresponding squarate ester.

Compound **Ii9** is prepared in a similar manner using **Ia6** and 3-methoxy-4-(2,6-dichlorophenyl)amino-cyclobut-3-en-1,2-dione at reflux condition.

Example 16

Preparation of Ii1

Triethylamine (0.023mol) and 30% aqueous methylamine solution (0.0167mol) are added sequentially to a solution **Ih1** (0.00068mol) in methanol (15ml) at 0-5° C. The mixture is gradually brought to ambient temperature and then concentrated under reduced pressure. The residue is quenched with water and is extracted into methylene chloride (2x15 ml). Combined extract is washed with brine and degassed under reduced pressure. The residue is purified by flash column chromatography on silica gel to get the pure **Ii1**.

Similarly are prepared compounds **Ii2 to Ii8** from **Ih1** using the corresponding amino compound.

Example 17

IC_{50} determination using isolated guinea pig ileum functional assay

Terminal segment of ileum of junction of Dunken 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, $CaCl_2$ 1.8 mM, $MgCl_2$ 1.05 mM, $NaHCO_3$ 11.9 mM, NaH_2PO_4 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 % O_2 and 5% CO_2 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^{-7}M) 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 IC_{50}.

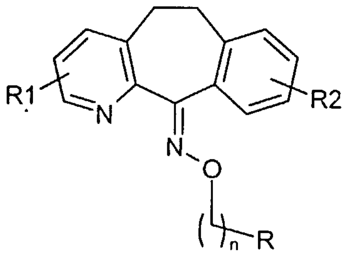
Table 10 : IC_{50} values for selected compounds

Compound No.	Mean IC_{50} (Molar concn.)
Ia1	1.02×10^{-8}
Ia2	3.5×10^{-8}
Ia3	2.88×10^{-9}
Ia5	7.63×10^{-6}
Ia6	8.7×10^{-9}
Ia10	6.6×10^{-8}
Ia11	5.12×10^{-6}
Ia15	1.2×10^{-7}
Ia16	6.2×10^{-6}

Ia17	$1.7\text{x}10^{-5}$
Ia18	$4.3\text{x}10^{-6}$
Ia19	$9.8\text{x}10^{-8}$
Ia22	$4.5\text{x}10^{-7}$
Ia23	$1.1\text{x}10^{-6}$
Ia24	$1.8\text{x}10^{-6}$
Ia25	$6.4\text{x}10^{-7}$
Ia27	$2.2\text{x}10^{-7}$
Ia28	$1.2\text{x}10^{-7}$
Ia29	$2.6\text{x}10^{-7}$
Ia30	$6.9\text{x}10^{-8}$
Ia31	$1.3\text{x}10^{-6}$
Ia33	$5.8\text{x}10^{-6}$
Ia34	$2.4\text{x}10^{-7}$
Ia35	$4.6\text{x}10^{-6}$
Ia36	$9.8\text{x}10^{-8}$
Ia37	$2.97\text{x}10^{-8}$
Ia42	$7.2\text{x}10^{-7}$
Ia44	$2.3\text{x}10^{-6}$
Ib1	$1.54\text{x}10^{-8}$
Ib2	$2.24\text{x}10^{-8}$
Ib3	$1.3\text{x}10^{-7}$
Ic3	$1.5\text{x}10^{-7}$
Ic4	$1.8\text{x}10^{-6}$
Ic6	$2\text{x}10^{-6}$
Ic7	$1.9\text{x}10^{-8}$
Id4	$3.2\text{x}10^{-6}$
Id9	$4.6\text{x}10^{-7}$
Id10	$6.8\text{x}10^{-7}$
Ie1	$>10^{-6}$
Ie29	$3.2\text{x}10^{-6}$
Ig1	$1.03\text{x}10^{-5}$
Ig2	$8.23\text{x}10^{-7}$
Ig6	$9.21\text{x}10^{-5}$
Ig7	$1.76\text{x}10^{-5}$
Ig10	1.32x10-5
Ih4	$>10^{-4}$
Ii1	$>10^{-4}$

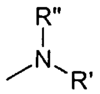
We claim:

1. (*E*)-oxime ether derivative of 5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one, compound of formula I



formula I

wherein R in formula I is selected from



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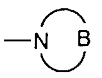

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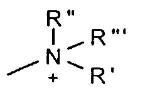

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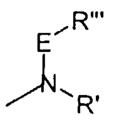

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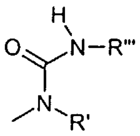

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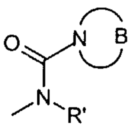

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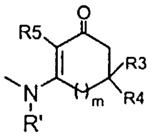

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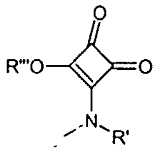

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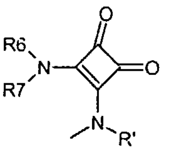


i

wherein R', R", R"', R_3, R_4, R_5, R_6 & R_7 are selected from hydrogen, alkyl (C_1 to C_6 linear, branched or cyclo), tricylic fused ring such as adamantyl, unsaturated alkyl (C_1 to C_6 linear, branched or cyclo), heterocyclic (containing one or more of hetero atoms viz. N, S, O), aryl, heteroaryl (containing one or more of hetero atoms viz. N, S, O), alkylaryl, optionally further wherein any of R', R", R"', R_3, R_4, R_5, R_6 & R_7 groups above may be further substituted with one or more groups selected from saturated or unsaturated alkyl(C_1 to C_6 linear, branched or cyclo), alkoxy(C_1 to C_6 linear, branched or cyclo), halo, haloalkyl, haloalkoxy, alkylaryl, hydroxy, amino and its derivatives such as amide or carbamate;

or wherein R', R", R"', R_3, R_4, R_5, R_6 & R_7 may be selected from the groups consisting of

carboxylic acids, C_1-C_6 alkylcarboxylic acids, acrylic acids, propargylic acids and their derivatives such as amides or substituted amides with alkyl (C_1–C_5) substitution or aryl substitution or cyclic amides (C_1 to C_7), esters (C_1 to C_5), N-hydroxyamides, or N-C_1 to C_5 alkoxyamides;

m is 0 to 2;

E is selected from O, S, NH, NR_8 wherein R_8 maybe C_1-C_6 linear, branched or cyclo alkyl group, C=O, CO_2, SO_2 and S=O; and

B is selected from -$(CH2)_p$- wherein p=2 to 7; and

–$CH(R_9)$-$(CH_2)_x$-D- $CH(R_{10})$- $(CH_2)_y$- wherein D is O, NR_8, S or SO_2; x and y are independently 1 to 6; and R_8, R_9 & R_{10} are independently H, (C_1-C_6 linear, branched or cyclo) alkyl oup;

optionally B is part of arylheterocycles containing one or more of hetero atoms (viz., N, S, O);

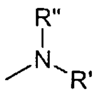
R_1 and R_2 are selected from hydrogen, halogen, saturated or unsaturated C_1-C_6 linear, branched or cyclo alkyl group, haloalkyl, C_1-C_6 linear, branched or cyclo alkoxy or haloalkoxy, amino and its derivatives such as amide or carbamate; carboxylic acids, C_1-C_6 alkyl carboxylic acids, acrylic acids, propargylic acids and their derivatives as defined above;

and n is 2 to 6;

and pharmaceutically acceptable salts thereof.

2. (*E*)-oxime ether derivative of 5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one, compound of formula I as claimed in claim 1

wherein R in formula I is selected from



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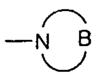

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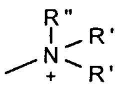

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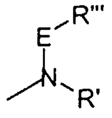

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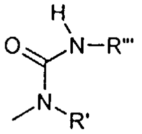

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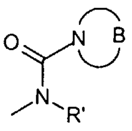

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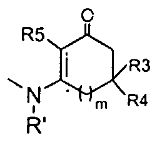

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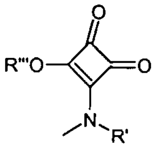

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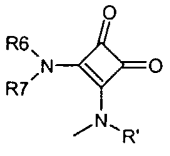


i

R', R'', R''', R_3, R_4, R_5, R_6 & R_7 are selected from hydrogen, alkyl (C_1 to C_6 linear, branched or cyclo), tricylic fused ring such as adamantyl, unsaturated alkyl (C_1 to C_6 linear, branched or cyclo), aryl, alkylaryl, optionally further wherein any of R', R'', R''', R_3, R_4, R_5, R_6 & R_7 groups above may be further substituted with one or more groups selected from alkoxy, halo, haloalkyl, haloalkoxy, free carboxyl, hydroxy or amino groups;

m is 0 to 2;

E is selected from C=O, CO_2 and SO_2; and

B is selected from $-(CH2)_p-$ wherein p=2 to 7; and

$-CH(R_9)-(CH_2)_x-D-CH(R_{10})-(CH_2)_y-$ wherein D is O, NR_8, S or SO_2; x and y are independently 1 to 6; and R_8, R_9 & R_{10} are independently H, (C_1-C_6 linear, branched or cyclo) alkyl group;

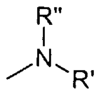
optionally B is part of arylheterocycles containing one or more of hetero atoms (viz., N, S, O);

R_1 and R_2 are selected from hydrogen, halogen, alkyl (C_1-C_6 linear, branched or cyclo), alkoxy (C_1-C_6 linear, branched or cyclo), haloalkoxy or haloalkyl; and

n is 2 to 6 and pharmaceutically acceptable salts thereof.

3. (*E*)-oxime ether derivative of 5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one, compound of formula I as claimed in claim 1 wherein

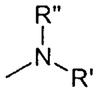
R is



R_1 is hydrogen; R_2 is 8-chloro; R' and R" are methyl; and n is 2;
and pharmaceutically acceptable salts thereof.

4. (*E*)-oxime ether derivative of 5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one, compound of formula I as claimed in claim 1 wherein

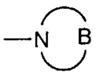
R is



R_1 is hydrogen; R_2 is 8-chloro; R' and R" are ethyl; and n is 2;
and pharmaceutically acceptable salts thereof.

5. (*E*)-oxime ether derivative of 5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one, compound of formula I as claimed in claim 1 wherein

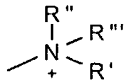
R is



R_1 is hydrogen; R_2 is 8-chloro; B is $-(CH_2)_p-$ wherein p is 4; and n is 2;
and pharmaceutically acceptable salts thereof.

6. (*E*)-oxime ether derivative of 5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one, compound of formula I as claimed in claim 1 wherein

R is

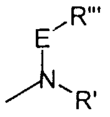


R_1 is hydrogen; R_2 is 8-chloro; R' and R" are $C_6H_5CH{=}CH_2$; R"' is methyl; L is I; and n is 2;

and pharmaceutically acceptable salts thereof.

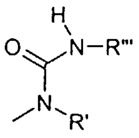
7. (*E*)-oxime ether derivative of 5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one, compound of formula I as claimed in claim 1 wherein

R is



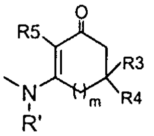
R_1 is hydrogen; R_2 is 8-chloro; R' and R''' are methyl; E is SO_2; and n is ;
and pharmaceutically acceptable salts thereof.

8. (*E*)-oxime ether derivative of 5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one, compound of formula I as claimed in claim 1 wherein
R is



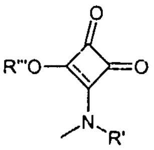
R_1 is hydrogen; R_2 is 8-chloro; R' is hydrogen; R''' is cyclohexyl; and n is 2;
and pharmaceutically acceptable salts thereof.

9. (*E*)-oxime ether derivative of 5,6-dihydro-benzo[5,6]cyclonepta[1,2-b]pyridin-11-one, compound of formula I as claimed in claim 1 wherein
R is



R_1 is hydrogen; R_2 is 8-chloro; R_3, R_4 and R_5 are hydrogen; R' is hydrogen; m is 1 and n is 2;
and pharmaceutically acceptable salts thereof.

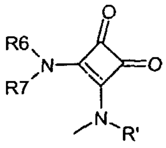
10. (*E*)-oxime ether derivative of 5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one, compound of formula I as claimed in claim 1 wherein
R is



R_1 is hydrogen; R_2 is 8-chloro; R' and R''' are methyl; and n is 2;
and pharmaceutically acceptable salts thereof.

11. (*E*)-oxime ether derivative of 5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one, compound of formula I as claimed in claim 1 wherein

R is



;

R_1 is hydrogen; R_2 is 8-chloro; R' is methyl; R_6 is hydrogen; R_7 is methyl; and n is 2; and pharmaceutically acceptable salts thereof.