LEUKOTRIENE BIOSYNTHESIS INHIBITORS

This invention relates to leukotriene biosythesis inhibiters, to processes for their preparation, to compositions containing them and to their use.

Leukotrienes (LTs) are potent, pro-inflammatory substances that are produced in the metabolism of arachidonic acid. Research results lead to the conclusion * in various inflammatory diseases, such as asthma, allergic rhinitis, rheumatoid arthritis, inflammatory bowel disease and psoriasis. Accordingly, inhibition of the biosynthesis of LTs has potential utility in the treatment of diseases in which inflammation and arachidonic acid metabolism have been implicated.

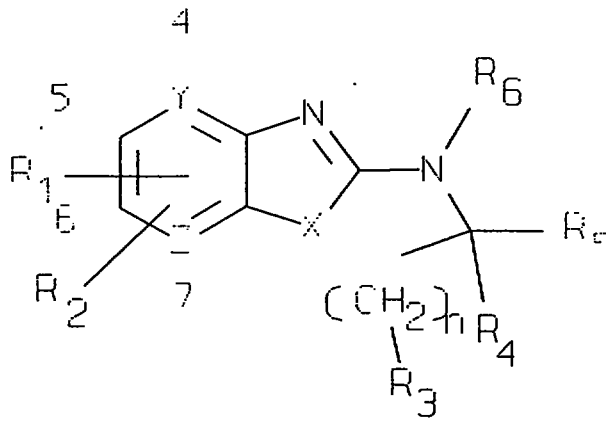
The biosynthesis of leukotrienes and their pathophysiology have been well documented. Many investigators have been seeking to block the pathophysiological effects of leukotrienes either by blocking their biosynthesis or by blocking their activity at the receptor level. Two recent reviews (J.H. Musser and A.F. Kreft, J. Med. Chem. 1992, 35,2501 and A. Shaw and R.D. Krell, J. Med. Chem. 1991, 34, 1235) describe the status of research in these areas, including results of clinical trials. Results of clinical trials such as those cited in these articles support the concept that agents that block the biosynthesis or activity of leukotrienes will be useful in asthma and other inflammatory diseases mentioned above.

According to one aspect of this invention, we provide various substituted benzoxazoles, benzothiazoles, oxazolopyridines and thiazolopyridines which have the ability to inhibit leukotriene biosynthesis. Such compounds have the general formula (I):

* that LTs play a role

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(I)

wherein

X is O or S;

Y is C or N;

Z is C or N;

R_1 and R_2 are each, independently of one another, hydrogen; C_1-C_6 alkyl; halo; CF_3; nitrile; C_1-C_6 alkoxy; -CO_2R_7 wherein R_7 is hydrogen or C_1-C_6 alkyl; -$C(O)NR_8R_9$ wherein R_8 and R_9 are independently hydrogen, C_1-C_3 alkyl, methoxy or together with the N atom form a morpholine, pyrrolidine or piperidine ring; -NO_2; -$NR_{10}R_{11}$ wherein R_{10} and R_{11} are independently hydrogen or C_1-C_6 alkyl;-$C(O)R_{12}$ wherein R_{12} is C_1-C_6 alkyl; -SO_2R_{12}; -$NHC(O)R_{12}$;-$NHSO_2R_{12}$; or -$SO_2NR_{13}R_{14}$ wherein R_{13} and R_{14} are independently hydrogen or C_1-C_6 alkyl;

R_3 is methyl, cyclohexyl or an unsubstituted or substituted phenyl ring wherein the substituents are selected from halo, CF_3, C_1-C_4 alkyl and C_1-C_4 alkoxy; NO_2; SO_2R_{12}, -$NHC(O)R_{12}$, -$NHSO_2R_{12}$ or -$SO_2NR_{13}R_{14}$ wherein R_{12}, R_{13} and R_{14} are as defined above; a 1-piperidinyl ring, a 2-, 3- or 4- pyridine ring, a morpholine ring, a thiomorpholine ring, a pyrrolidine ring, an imidazole

ring optionally substituted at the nitrogen with C_1-C_4 alkyl, or a 2-thiazole ring or a 2-methyl-4-thiazole ring; a dialkylamine (C_1-C_4) or an alkyl ether (C_1-C_4);

R_4 is an ester of structure $-CO_2R_{16}$ wherein R_{16} is C_1-C_4 alkyl; an amide of structure $-C(O)NR_{17}R_{18}$ wherein R_{17} and R_{18} are independently hydrogen, C_1-C_3 alkyl, methoxy or together with the N atom form a morpholine ring, piperidine or pyrrolidine ring; an unsubstituted or substituted phenyl ring wherein the substituents are selected from halo, C_1-C_4 alkyl or C_1-C_4 alkoxy; a 3-methyl-1,2,4-oxadiazol-5-yl group; a 2- or 3-thienyl group; a 2-, 3-, or 4-pyridyl group; a 4-pyrazolyl group; a 2-imidazole group optionally substituted at the N atom with a methyl group; a 2-thiazole group optionally substituted at the 4-position with a methyl; a ketone of structure $C(O)R_{19}$ wherein R_{19} is C_1-C_3 alkyl, phenyl or 1-methylimidazol-2-yl; an ether CH_2OR_{20} where R_{20} is C_1-C_3 alkyl; a thioether - CH_2SR_{20}; a sulfone - $CH_2SO_2CH_3$; an amine - $CH_2N(R_{20})_2$; an amine derivative - $CH_2NHC(O)R_{21}$, where R_{21} is CH_3 or $NHCH_3$; or $-CH_2NHSO_2Me_2$; or a carbamate - $CH_2OC(O)NHMe$;

R_5 and R_6 are independently of each other hydrogen or methyl; and

n is an integer 0, 1 or 2;

with the proviso that Y and Z are not both N; and with the further provisos that the following combination of substituents do not occur simultaneously:

(i) Y and Z are both carbon; R_1 or R_2 are hydrogen, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, CN, NO_2 or CF_3; R_3 is an unsubstituted phenyl; and R_4 is $-C(O)OR_{16'}$ wherein $R_{16'}$ is hydrogen, alkyl, alkenyl or alkynyl; or R_4 is $C(O)N(R_{18'})(R_{19'})$ wherein $R_{18'}$ and $R_{19'}$ are hydrogen, C_1-C_6

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alkyl, phenyl or alkoxy or together with the N atom form a pyrrolidine, piperidine or morpholine ring; or R_4 is -CN or $-C(S)NH_2$;

or (ii) Y and Z are both carbon; R_4 is $C(O)OCH_3$; R_1 and R_2 are both hydrogen, and R_3 is 4-hydroxyphenyl, unsubstituted phenyl or a 4-imidazole group.

Such compounds may be provided in racemic form, or the pure or substantially pure enantiomers may be isolated. The preferred compounds are those wherein the R_1 substituent is in the 5-position and is an C_1-C_3 alkyl group or halogen, the R_3 substituent is cyclohexyl, the R_6 substituent is hydrogen and n is 1.

In J. Pharm. Sci (57, p. 1695) by S. Advani and J. Sam (1968) four compounds are disclosed having a basic structure similar to that of Formula (I). The Advani publication, a publication on potential anti-neoplastic agents, discloses synthesis of these four compounds, but no biological activity is provided. In the Advani publication, Y and Z are both carbon, R_4 is $-CO_2C_2H_5$, R_1 and R_2 are both hydrogen and R_3 is $4-C_6H_4OH$, $-C_6H_5$, 4-imidazolyl or $-CH_2SCH_3$.

In DE 3419994 there are described compounds of general formula (I) wherein both Y and Z are C, X is O or S, R_1 and R_2 are hydrogen, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, CN, NO_2 or CF_3, and R_4 is $-C(O)OR_{16'}$ (wherein $R_{16'}$ is hydrogen, alkyl, alkenyl or alkynyl), or $-C(O)N(R_{18})(R_{19})$ (wherein R_{18} and R_{19} are hydrogen, C_1-C_6 alkyl, phenyl or alkoxy or together with N form a pyrrolidine, piperidine or morpholine ring), or -CN or $-C(S)NH_2$. The group referred to as "Y" in DE 3419994 consists of R_3 and the carbon chain, i.e. $(CH_2)_n$, shown in Formula (I) above. The groups at "Y" disclosed in the German publication are straight-chain or branched

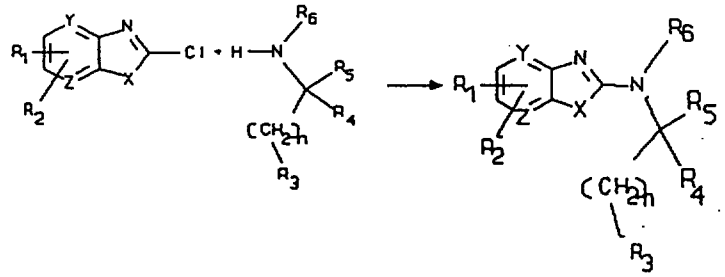
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alkyl (C_1-C_8), with one to three carbons between N and R_4, or the group designated "Z" is methylthioalkyl (one to three carbons in the alkyl) or phenylalkyl. Specifically not disclosed at R_3 is a cyclohexyl group or substituted phenyl. Also, not disclosed at R_4 are ketones or phenyl and heteroaromatic or heterocyclic rings. Finally, also not disclosed in the German publication is Y or Z being nitrogen. At R_6 the German publication discloses hydrogen and C_1-C_4 alkyl. Specifically not disclosed are the preferred compounds of the present invention. Compounds disclosed in the German publication are said to be useful for protecting crops against certain classes or types of herbicides.

The compounds of the present invention may be prepared by a variety of processes and such processes comprise further aspects of the invention. These are essentially similar to those known in the art and published in the literature. For example, compounds may be prepared by reaction of an appropriately substituted 2-chlorobenzoxazole, 2-chlorobenzothiazole, 2-chlorooxazolopyridine or 2-chlorothiazolopyridine with an amine, an amino acid or an amino acid ester. Such synthesis scheme is outlined herein below as Scheme A.

Scheme A

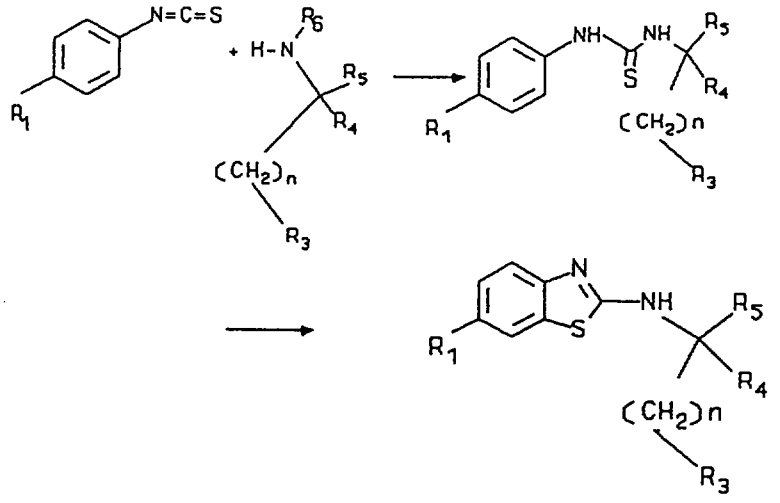


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The reaction of Scheme A may occur in an inert solvent, such as methylene chloride, toluene or DMSO, with a basic catalyst, such as triethylamine or NaOH. The optimum choice of both solvent and catalyst will depend on the nature of the reactants, as a person skilled in the art would recognize.

Alternatively, modification of a procedure known in the literature for preparation of 2-aminobenzothiazoles may be successfully employed for synthesis of compounds of general formula I. Such synthesis scheme is outlined hereinbelow as Scheme B.

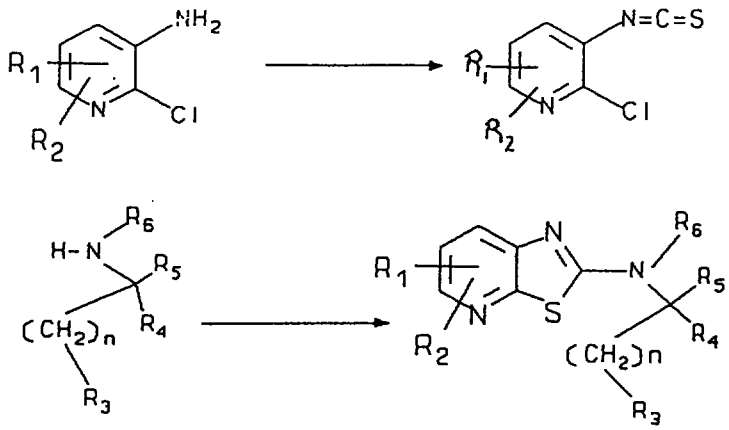
Scheme B



The procedure of Scheme B involves reaction of an appropriately substituted isothiocyanate with an amine or an amino acid ester in a suitable inert solvent, such as ether, followed by cyclization of the intermediate thiourea formed e.g. with sulfuryl chloride or bromine in another inert solvent, again such as ether or perhaps chlorobenzene.

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Scheme C

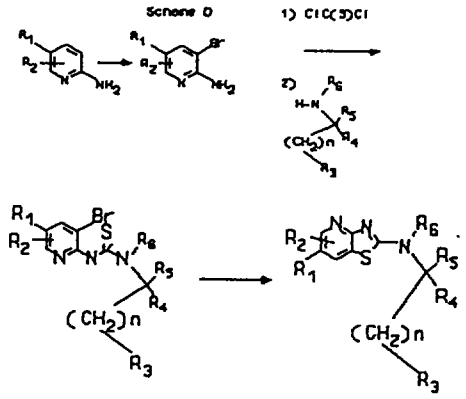


The synthesis of Scheme C can be employed for those compounds of general formula I wherein X is S and Z is N. A haloaminopyridine is converted to an isothiocyanate, for example by reaction with thiophosgene, in the presence of a base, such as sodium carbonate, in an inert solvent. Treatment of the isothiocyanate with an amine in an inert solvent yields a thiazolopyridine. With certain additional substituents on the 2-chloro-3-aminopyridine ring, an intermediate thiourea is isolated upon reaction with the isothiocyanate. In that case, cyclization to the thiazolopyridine product may be accomplished by heating in an inert solvent with either acid or base catalysis, for example in ethanolic HCl or DMF with K_2CO_3.

Isomeric thiazolopyridines may be prepared by

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cyclization of a 3-halo-2-thiourea substituted pyridine. Such a synthetic scheme is outlined hereinbelow as Scheme D.

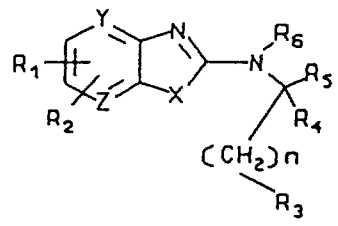


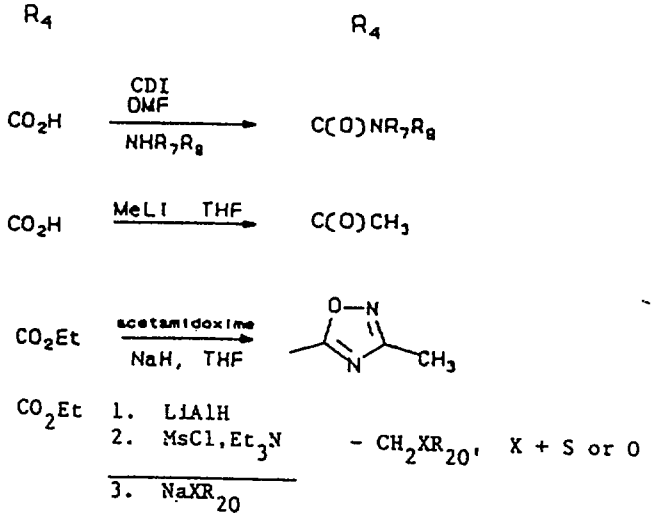
In Scheme D, the 3-halo-2-thiourea pyridine is heated in an inert solvent with base catalysis, for example K_2CO_3 in DMF. The intermediate 2-amino-3-halopyridine may be prepared, for example, by bromination of an optionally substituted 2-aminopyridine. The isothiocyanate may be prepared as described in Scheme C.

Compounds of general formula (I) wherein R_4 is an acid or an ester may be modified to yield compounds of general formula (I) wherein R_4 is an amide, a methyloxadiazole, a ketone, an ether, or thioether. One such scheme for modification is shown hereinbelow as Scheme E.

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All the general methods exemplified in Scheme E are well known to one skilled in the art, and are also published in the chemical literature.

Concerning the stereochemistry of compounds produced via the processes and schemes outlined hereinabove, if the starting amines used above are enantiomerically pure, then a single enantiomer of the end product, having either R or S configuration at the asymmetric carbon, will be recovered. By the same token, if the starting amine is racemic, that is, a mixture of R and S, then a racemic end product will be recovered. Racemic compounds may be separated into the individual enantiomers by methods known to one skilled in the art, for example, by resolution of a diastereomeric salt, chromatography on a chiral column, etc. In the text of this specification the designation for enantiomers of amino acids D and L, or racemic DL, will be used.

The following examples are illustrative of the present invention. As would be obvious to one skilled

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in the art, other compounds, such as where R_4 is pyrrolidine-amide, can be readily synthesized using the methods and procedures outline above.

Preparation

DL-N-(Benzothiazol-2-yl)phenylalanine hydrochloride

11.8 g phenylalanine (71.4 mmol) was added in portions to a suspension of 5.7 g powdered NaOH (143 mmol) in 50 ml DMSO, and stirred under nitrogen. 2-Chlorobenzothiazole (11 g, 65 mmol) was added over fifteen minutes at room temperature. The reaction was heated on an oil bath at about 95°C for 4 hours. The reaction mixture was then cooled, poured into 200 ml ice and water, and the pH of the resulting mixture was adjusted to about 1-2 by addition of 10N HCl.

More ice was added, and the mixture was then stirred and filtered. The white solid was dissolved in alkaline solution, stirred with celite, filtered, acidified with 2N HCl and filtered. The resulting solid was rinsed with water, then EtOH, and dried. The product (6.47 g, 19.3 mmol, 30%) melted at 250-251°C.

Example 1

DL-N-(Benzothiazol-2-yl)phenylalanine ethyl ester
Compound No. 4, Table 1

Thionyl chloride (3.82 g, 32.1 mmol) was added dropwise to the product from the above preparation (3.2 g, 10.7 mmol) suspended in 200 ml EtOH. The reaction was heated at reflux for four hours. The reaction mixture was then concentrated, the residue dissolved in EtOAc (75ml) and extracted with saturated Na_2CO_3 solution (2 X 50 ml), saturated NaCl solution (50 ml) dried (Na_2SO_4) and concentrated. The product was recrystallized from EtOH

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giving 2.25 g (6.9 mmol, 64%) mp 137-139°C.

Example 2

DL-N-(6-Isopropylbenzothiazol-2-yl)-4-chlorophenylalanine ethyl ester

Compound No. 7, Table 1

DL-4-Chlorophenylalanine ethyl ester hydrochloride(5g, 18.9 mmol) was converted to the free base using triethylamine. A solution of the free base in 75 ml ether was added to a solution of 4-isopropylphenylisothiocyanate in 150 ml ether, and cooled on an ice-salt bath. The temperature was maintained at about 0°C during addition. The reaction was stirred for four and one-half hours, at which time the reaction temperature was 12°C. The reaction mixture was filtered, the filtrate concentrated, and the resulting foamy residue triturated with petroleum ether while cooling on ice. This resulted in 6.1 g (15.1 mmol, 80%) N-(4-isopropylphenyl)-N'-[2-(4-chlorophenyl)-1-(ethoxycarbonyl)ethyl]thiourea, mp 73-75°C.

The intermediate product (6 g, 14.8 mmol) was dissolved in 25 ml chlorobenzene and cooled on an ice bath to 0°C. Sulfuryl chloride (2.76 g, 20.4 mmol) in 5 ml chlorobenzene was added dropwise. After five and one-half hours, the reaction mixture was concentrated, the residue dissolved in EtOAc (150 ml), washed with saturated Na_2CO_3 solution, then saturated NaCl solution, dried (Na_2SO_4) and concentrated. The product crystallized from EtOH, giving 4.07g(10.1 mmol, 68%), mp 105-107°C.

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Example 3

2-(2-Cyclohexyl-1-phenyl)ethylaminobenzoxazole

Compound No. 51, Table 3

A mixture of 1.12 g 2-chlorobenzoxazole (7.3 mmol), 1.48 g 2-cyclohexyl-1-phenylethylamine (7.3 mmol) and 0.88 g triethylamine (8.8 mmol) in 305 ml CH_2Cl_2, was refluxed for 31 hours. The reaction mixture was diluted with 50 ml CH_2Cl_2, extracted with water (1 X 50 ml), 1N HCl (1 X 50 ml), saturated NaCl (1 X 50 ml), dried (Na_2SO_4) and concentrated. The resulting solid was recrystallized from EtOH giving 1.4 g product (4.4 mmol, 60%) mp 129-131°C.

Example 4

L-2-[2-Cyclohexyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]amino-5-methylbenzoxazole

Compound No. 125, Table 6

0.47 g 60% NaH in mineral oil dispersion (0.28 g NaH, 11.8 mmol), 0.39 g acetamidoxime (5.3 mmol), 1.48 g N-(5-methylbenzoxazol-2-yl)cyclohexylalanine methyl ester (4.7 mmol), and several molecular sieves were combined in 20 ml THF and refluxed for two hours under nitrogen. The mixture was poured into water and extracted with EtOAc. The EtOAc was dried (Na_2SO_4) and concentrated. The product was purified by flash chromatography on silica gel (99 CH_2Cl_2 : 1 MeOH). After triturating with petroleum ether the product was obtained as a white solid, 70 mg, mp 118-119°C.

Example 5

L-N-(5-Methylbenzoxazol-2-yl)cyclohexylalanine-N'-methylamide

Compound No. 44, Table 2

A solution of 1.08 g L-N-(5-methylbenzoxazol-2-yl)-

cyclohexylalanine (3.6 mmol) in 15 ml CH_2Cl_2 was cooled on an ice bath. Carbonyldiimidazole (0.88g, 5.4 mmol) was added in portions. After one hour methylamine gas was bubbled into the reaction mixture for about forty-five minutes. The reaction was diluted with CH_2Cl_2, washed with water, saturated NaCl solution, dried (Na_2SO_4) and concentrated. The product was purified by flash chromatography on silica gel, eluting with 99 CH_2Cl_2:1 MeOH, followed by recrystallization from isopropanol giving 0.2 g product, m.p. 202-204°C.

Example 6

3-[(6-Isopropylbenzothiazol-2-yl)amino]-4-phenylbutan-2-one

Compound No. 128, Table 7

A solution of 2g N-(6-isopropylbenzothiazol-2-yl)phenylalanine (5.9 mmol) in 60 ml THF was cooled on an ice-salt bath to -5°C, under nitrogen. A solution of 1.4 N MeLi in ether (26 ml, 36.4 mmol) was added via syringe over about one minute. After two hours 10ml chlorotrimethylsilane (78 mmol) was added rapidly and the reaction warmed up to room temperature. The reaction was quenched with 1N HCl and the product extracted into ether, dried (Na_2SO_4) and concentrated. The product was purified by flash chromatography through silica gel, eluting with CH_2Cl_2. Recrystallization from EtOH gave 0.75g product (2.2 mmol, 38%), mp 107-110°C.

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Example 7

2-[(2-Cyclohexyl-1-phenylethyl)amino]thiazolo[5,4-b] pyridine

Compound No. 172, Table 11

A mixture of 1.28 g (10 mmol) 3-amino-2-chloropyridine, 2.1 g (20 mmol) sodium carbonate and 1.38 g (12 mmol) thiophosgene in 50 ml CH_2Cl_2 was stirred overnight at room temperature. The reaction mixture was poured into water, and extracted with CH_2Cl_2. The combined organic extracts were washed with saturated NaCl solution, dried (Na_2SO_4) and concentrated to give an oil. The product was purified by chromatography on silica gel, eluting with petroleum ether, giving 1.6 g thioisocyanate (9.4 mmol, 94%).

The thioisocyanate (0.516 g, 3.02 mmol) was added to a mixture of 0.66 g 2-cyclohexyl-1-phenylethylamine hydrochloride (2.75 mmol), and 0.278 g triethylamine (2.75 mmol) in 25 ml THF. The reaction was heated at reflux for two hours, poured into water, and extracted with ether. The organic extracts were washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated. Recrystallization of the residue from CH_2Cl_2 - petroleum ether gave 0.625 g product (1.84 mmol, 67%) mp 146-148°C.

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Example 8

2-{[2-Cyclohexyl-1-(2-pyridyl)ethyl]amino}-6-methylthiazolo-[4,5-b]pyridine

Compound No. 184, Table 11

Bromine (3.19 g) was added dropwise at 0°C to a solution of 2-amino-5-picoline in 75 ml CH_2Cl_2. After about two

hours at room temperature, the reaction was extracted with saturated sodium carbonate solution, then sodium thiosulfate solution. The combined aqueous extracts were washed with CH_2Cl_2, and the combined organic extracts washed with saturated NaCl, dried (Na_2SO_4) and concentrated giving 3.59 g crude material. The product was purified by flash chromatography on silica gel, eluting with petroleum ether with increasing amounts of CH_2Cl_2 (0-40%), giving 3.05 g 2-amino-3-bromo-5-picoline, m.p. 68-70°C.

To the above product (2.84 g, 15 mmol) in 50 ml CH_2Cl_2 with 3.18 g (30 mmol) sodium carbonate, was added 2.07 g (18 mmol) thiophosgene. After stirring overnight at room temperature, the reaction was extracted with water, the aqueous phase back extracted with CH_2Cl_2 and combined organic extracts washed with brine, dried ($MgSO_4$), and concentrated giving the isothiocyanate as an oily material that crystallized on standing (3.9 g) IR 2050 cm^{-1}.

To a solution of 1.0 g (4.3 mmol) of the isothiocyanate derivative and 1.04 g (4.3 mmol) of 2-cyclohexyl-1-phenylethylamine in 50 ml dry THF was added 438 mg (4.3 mmol) of Et_3N. The resulting mixture was refluxed for two hours. The triethylamine hydrochloride was filtered off and the filtrate concentrated to give the thiourea (1.6 g) which crystallized on standing.

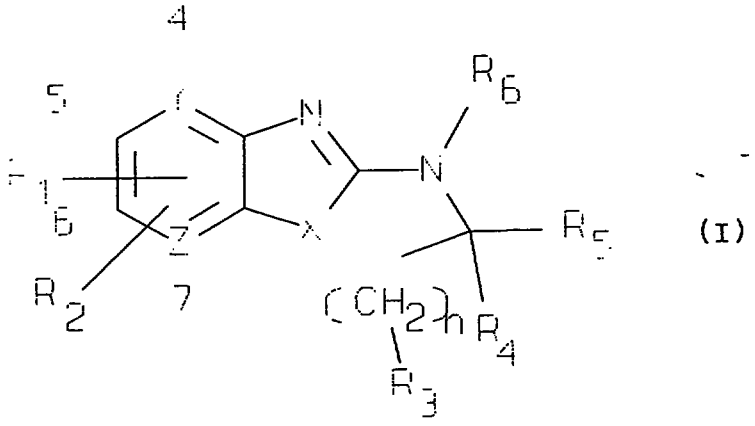
A mixture of 540 mg (1.15 mmol) of the thiourea and 317 mg (2.3 mmol) K_2CO_3 in 10 ml DMF was refluxed overnight. The reaction mixture was then poured into water and extracted with ether(3X) and CH_2Cl_2 (1X). The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated giving 450 mg product. Recrystallization from CH_2Cl_2/ether/petroleum ether gave 210 mg product, m.p. 213-214°C.

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According to a further aspect of the present invention, compounds of formula (I) as defined above appear useful in therapy.

According to another aspect of the present invention, we provide pharmaceutical compositions comprising as active ingredient at least one compound of formula (I)



wherein

X is O or S;

Y is C or N;

Z is C or N;

R_1 and R_2 are each, independently of one another, hydrogen; C_1-C_6 alkyl; halo; CF_3; nitrile; C_1-C_6 alkoxy; -CO_2R_7 wherein R_7 is hydrogen or C_1-C_6 alkyl; -$C(O)NR_8R_9$ wherein R_8 and R_9 are independently hydrogen, C_1-C_3 alkyl, methoxy or together with the N atom form a morpholine, pyrrolidine or piperidine ring; -NO_2; -$NR_{10}R_{11}$ wherein R_{10} and R_{11} are independently hydrogen or C_1-C_6 alkyl;-$C(O)R_{12}$ wherein R_{12} is C_1-C_6 alkyl; -SO_2R_{12}; -$NHC(O)R_{12}$;-$NHSO_2R_{12}$; or -$SO_2NR_{13}R_{14}$ wherein R_{13} and R_{14} are independently hydrogen or C_1-C_6 alkyl;

R_3 is methyl, cyclohexyl or an unsubstituted or substituted phenyl ring wherein the substituents are selected from halo, CF_3, C_1-C_4 alkyl and C_1-C_4 alkoxy; NO_2; SO_2R_{12}, -$NHC(O)R_{12}$, -$NHSO_2R_{12}$ or -$SO_2NR_{13}R_{14}$ wherein R_{12}, R_{13}

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and R_{14} are as defined above; a 1-piperidinyl ring, a 2-, 3- or 4- pyridine ring, a morpholine ring, a thiomorpholine ring, a pyrrolidine ring, an imidazole ring optionally substituted at the nitrogen with C_1-C_4 alkyl, or a 2-thiazole ring or a 2-methyl-4-thiazole ring; a dialkylamine (C_1-C_4) or an alkyl ether (C_1-C_4);

R_4 is an ester of structure $-CO_2R_{16}$ wherein R_{16} is C_1-C_4 alkyl; an amide of structure $-C(O)NR_{17}R_{18}$ wherein R_{17} and R_{18} are independently hydrogen, C_1-C_3 alkyl, methoxy or together with the N atom form a morpholine ring, piperidine or pyrrolidine ring; an unsubstituted or substituted phenyl ring wherein the substituents are selected from halo, C_1-C_4 alkyl or C_1-C_4 alkoxy; a 3-methyl-1,2,4-oxadiazol-5-yl group; a 2- or 3-thienyl group; a 2-, 3-, or 4-pyridyl group; a 4-pyrazolyl group; a 2-imidazole group optionally substituted at the N atom with a methyl group; a 2-thiazole group optionally substituted at the 4-position with a methyl; a ketone of structure $C(O)R_{19}$ wherein R_{19} is C_1-C_3 alkyl, phenyl or 1-methylimidazol-2-yl; an ether CH_2OR_{20} where R_{20} is C_1-C_3 alkyl; a thioether - CH_2SR_{20}; a sulfone - $CH_2SO_2CH_3$; an amine - $CH_2N(R_{20})_2$; an amine derivative - $CH_2NHC(O)R_{21}$, where R_{21} is CH_3 or $NHCH_3$; or $-CH_2NHSO_2Me_2$; or a carbamate - $CH_2OC(O)NHMe$;

R_5 and R_6 are independently of each other hydrogen or methyl; and

n is an integer 0, 1 or 2;

with the proviso that Y and Z are not both N;

in racemic form, or the pure or substantially pure enantiomer thereof, or a physiologically acceptable acid addition salt thereof in association with one or more pharmaceutically acceptable carriers, diluents or excipients.

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The compounds of this invention are potent inhibitors of leukotriene synthesis in warm-blooded animals.

The compounds according to the present invention may be administered to warm-blooded animals topically, perorally, parenterally, rectally or by the respiratory route as active ingredients in conventional pharmaceutical compositions, that is, comprising a pharmaceutical carrier or excipient and an effective amount of the active ingredient.

In another aspect, the present invention provides pharmaceutical compositions comprising a compound of formula I or a physiologically acceptable salt thereof, together with at least one pharmaceutical carrier or excipient.

Suitable vehicles or carriers for the above noted formulations are described in standard pharmaceutical texts, e.g. in "Remington's Pharmaceutical Sciences", 17th ed, Mack Publishing Company, Easton, Penn., 1985.

The dosage of the active compounds will vary with the form of administration and the particular active agent chosen. Furthermore, it will vary with the particular host under treatment. Generally, treatment is initiated with small increments until the optimum effect under the circumstances is reached.

With reference to systemic administration, the compound of formula I is administered at a dosage of 10 mcg to 1000 mcg per kilogram of body weight per day, although the aforementioned variations will occur. However, a dosage level that is in the range of from about 50 mcg to 500 mcg per kilogram of body weight per day is most desirably employed in order to achieve effective results.

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According to a yet further aspect of the present invention, we provide a method of preventing or treating inflammatory conditions or diseases or conditions in which arachidonic acid metabolism has been implicated in a warm blooded animal which comprises administering to the animal an effective amount of a compound of formula (I) as defined above in respect of compounds of formula (I) for use in the pharmaceutical compositions of this invention. Preferably, the method relates to the inhibition of the biosynthesis of leukotrienes.

According to another aspect of the present invention, we provide the use of compounds of formula (I) as defined above in respect of compounds of formula (I) for use in the pharmaceutical compositions of this invention, or physiologically acceptable salts thereof, for the preparation of medicaments for use in the prevention or treatment of inflammatory conditions and conditions or diseases in which arachadonic acid metabolism has been implicated. Such medicaments are also for use in the inhibition of the biosynthesis of leukotrienes.

Inhibition of LTB_4, biosynthesis in human polymorphonuclear leukocytes (PMNs)

The inhibition of leukotriene biosynthesis is measured by determining whether and to what extent test compounds can inhibit LTB_4 production from endogenous arachidonic acid in human peripheral blood leukocytes.

To 48-well tissue culture plates was added a solution of the test compound followed by addition of human polymorphonuclear leukocytes isolated from peripheral blood at a density of $1.5X10^6$ cells/well. Culture plates were preincubated for fifteen minutes with shaking at 28°C. Cells were stimulated with calcium ionophore

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A23187 at a final concentration of 2.5 μM for an additional ten minutes. The reaction was terminated by the addition of an EGTA solution (10 mM final concentration) followed by centrifugation at 1500 rpm at 10°C. Supernatants were stored at -70°C. LTB_4 levels were determined by RIA using a commercially available kit. Nonlinear regression analysis was used to calculate IC50 values.

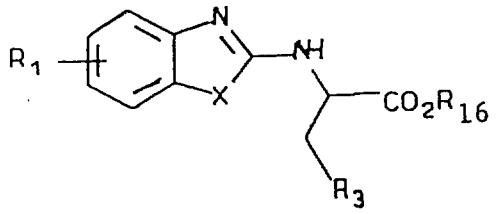
The following tables show % inhibition of LTB_4 biosynthesis by compounds of the invention at test concentrations indicated, with the determined IC_{50} shown in μM.

Also, in all the following Tables, R_2 is a hydrogen atom unless a double entry is entered for R_1 whereupon R_2 is the second entry.

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Table 1: Esters



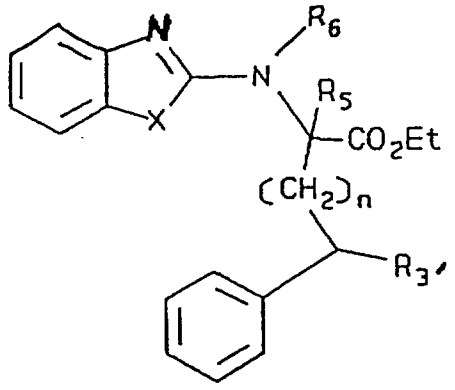
Comp No.	D/L[a]	R_1	R_3[b]	R_{16}	X	mp °C	IC_{50} (μM)
1	DL	H	Ph4Cl	Et	S	Oil	0.2
2	DL	H	Ph4F	Et	S	129-131	0.33
3	DL	H	Ph4Br	Et	S	104-106	0.15
4	DL	H	Ph	Et	S	137-139	0.4
5	L	H	Ph4OBZ	Et	S	Oil	0.53
6	L	6-iPr	Ph	Et	S	Oil	0.25
7	DL	6-iPr	Ph4Cl	Et	S	105-107	0.33
8	L	6-iPr	Ph	Me	S	114-115	0.14
9	DL	6-OMe	Ph4Cl	Et	S	129-131	0.23
10	D	6-iPr	Ph	Me	S	115-116	0.65
11	DL	6-nBu	Ph4Cl	Et	S	113-114	0.17
12	L	6-Et	Ph	Et	S	102-104	0.24
13	L	H	Ph	t-Bu	S	50-52	0.73
14	L	5-Et	Ph	Et	S	Oil	0.009
15	L	5-Et	Cyh	Et	S	Oil	0.027
16	L	H	Cyh	Et	S	resin	0.006
17	L	H	Ph	Et	O	Oil	0.15
18	D	H	Ph	Et	O	Oil	1.5
19	L	5-iPr	Ph	Et	O	Oil	0.00052
20	L	6-iPr	Ph	Et	O	Oil	0.22
21	L	H	Cyh	Me	O	Oil	0.0064
22	D	H	Cyh	Me	O	Oil	0.10
23	L	5-iPr	Cyh	Me	O	Oil	0.001
24	L	5-Me	Cyh	Me	O	Oil	0.0017
25	L	5-Me	Cyh	t-Bu	O	Oil	<0.3[d]
26	D	5-Me	Cyh	Me	O	Oil	0.016
27	DL	5-OMe	2Me4Thz	Et	O	Oil	<0.3[d]
28	DL	5-Cl	2-Thz	Et	O	Oil	<0.3[d]

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Comp No.	D/L[a]	R_1	R_3[b]	R_{16}	X	mp°C	IC_{50} (μM)
29	DL	5-Cl	2Me4Thz	Et	O	Oil	0.087
30	DL	5-iPr	3-Phy	Et	O	Oil	0.19
31	DL	5-iPr	4-Py	Et	O	Oil	<0.1[d]
32	DL	5-OMe	3-Py	Et	O	Oil	
33	DL	5-iPr	2Me4THz	Et	O	Oil	<0.03[d]

Table 1A: Esters (Continued)



Comp No.	D/L	R_6	R_5	R_3	n	X	mp°C	IC_{50} (μM)
34	DL	H	H	CH_3	O	S	Oil	1.4
35	DL	H	H	CH_3	O	S	Oil	0.68
36	DL	CH_3	H	H	O	S	Oil	1.0
37	DL	H	H	H	1	S	69.5-72	0.52
38	DL	H	CH_3	H	O	S	97-98	0.20
39	DL	H	CH_3	H	O	O	89-91.5	0.076

Footnotes (for TABLES 1 and 1A)

a. DL=racemic. L or D indicates one enantiomer with stereochemistry at chiral carbon analogous to the corresponding L or D amino acid.

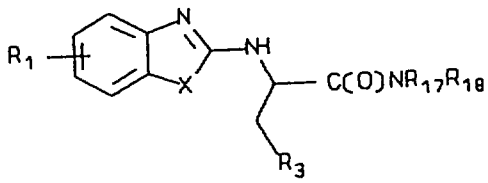
b. Ph= phenyl, PhX= substituted phenyl, Cyh= Cyclohexyl, 2-Thz = 2-Thiazolyl, 2Me4Thz = 2-methyl-4-thiazolyl, 3-Py = 3-pyridyl, 4-Py = 4-pyridyl

c. One of a pair of diastereomers

d. Greater than 50% inhibition at this concentration, IC_{50} not characterized further.

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Table 2: Ester Bioisosteres - Amides



Comp No.	D/L	R_1	R_3[a]	R_{17}	R_{18}	x	m.p.°C	IC_{50} (μM)
40	L	H	Ph	H	H	S	94-96	3
41	DL	H	Ph	Me	Me	S	Oil	3
42	DL	6-iPr	Ph	Et	H	S	161-163	3
43	L	H	Ph	Me	OMe	O	Resin	<1[c]
44	L	5-Me	Cyh	Me	H	O	202-204	0.072
45	L	5-Me	Cyh	Me	OMe	O	Resin	0.03
46	L	5-Me	Cyh	b	b	O	Resin	0.19

a. See footnote b, Table 1.
b. R_{17} and R_{18} with nitrogen make a piperidine ring.
c. See footnote d, Tables 1 and 1A.

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Table 3: Ester Bioisosteres - Phenyl

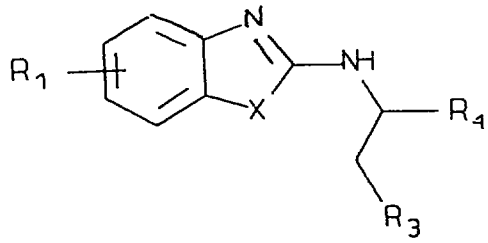


Table 3

Comp. No.	D/L[a]	R_1	R_3[b]	R_4[b]	X	m.p. °C	IC_{50} (μM)
47	DL	H	Ph	Ph	S	54-56	0.16
48	'L'	H	Ph	Ph	S	Oil	0.082
49	'D'	H	Ph	Ph	S	Oil	0.28
50	DL	H	Ph	Ph	O	154-156	<1.0[d]
51	DL	H	Cyh	Ph	O	129-131	0.0069
52	'D'	H	Cyh	Ph	O	141-143	0.26
53	'L'	H	Cyh	Ph	O	135.5-137	0.0036
54	DL	5-iPr	Cyh	Ph	O	119-122	0.0063
55	DL	H	Cyh	Ph4Cl	O	142-144	0.3
56	DL	H	Cyh	Ph4OMe	O	63-67	0.55
57	DL	H	Cyh	Ph3Me	O	136-138	0.30
58	DL	H	Cyh	Ph2Cl	O	146-148	0.08
59	DL	5-I	Cyh	Ph	O	186-187	0.013
60	DL	5-$NHSO_2CH_3$	Cyh	Ph	O	188-190	0.16
61	DL	5-$NHC(O)CH_3$	Cyh	Ph	O	145-147	0.076
62	DL	5-$NHC(O)NHCH_3$	Cyh	Ph	O	211-212	<1.0[d]
63	DL	5-CO_2H	Cyh	Ph	O	232-234	0.19
64	DL	5-$C(O)NH_2$	Cyh	Ph	O	181-183	<1.0[d]
65	DL	5-$C(O)NMe_2$	Cyh	Ph	O	194-196	0.17
66	DL	6-CO_2H	Cyh	Ph	S	271-272	0.22
67	DL	5-CN	Cyh	Ph	O	166-168	0.15
68	DL	C	Cyh	Ph	O	154-156	<1.0[d]
69	DL	CH_2OH	Cyh	Ph	O	187-189	<1.0[d]

Table 3

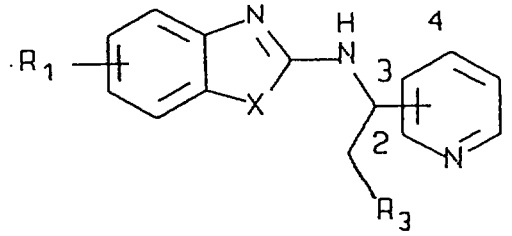
Comp. No.	D/L[a]	R_1	R_3[b]	R_4[b]	X	m.p. °C	IC_{50} (μM)
70	DL	5-tetrazolyl	Cyh	Ph	O	188-191	0.16
71	DL	H	Cyh	Ph4F	O	144-145	0.17
72	L	5-Cl	NEt_2	Ph	O	242-244	0.35
73	L	5-iPr	$NnPr_2$	Ph	O	Oil	<300[d]
74	L	5-iPr	OEt	Ph	O	Oil	0.11
75	L	5-iPr	OnBu	Ph	O	Oil	0.055
76	L	5-tBu	morph	Ph	O	197-199	<0.03[d]
77	L	5-iPr	NEt_2	Ph	O	Oil	<0.3[d]
78	L	5-Cl	thiomorph	Ph	O	69-71	0.048

a. DL = racemic. 'L' and 'D' = L=isomer designation based on potency being greater than 'D' isomer, and drawing analogy to esters where L and D are known.
b. See footnote b, Table 1, also morph = N-morpholinyl, thiomorph = N-thiomorpholinyl.
c. morpholinecarbonyl
d. See Footnote d, Table 1.

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Table 4: Ester Bioisosteres - Pyridyl



79	D/L	X	R_1	R_3[a]	Pyridyl Isomer	mp°C	IC_{50} (μM)
80	DL	O	H	Cyh	3	Resin	0.055
81	DL	O	5-Me	Cyh	2	104-105	0.0031
82	DL	O	5-Me	Cyh	3	150-151	0.024
83	DL	O	5-Me	Cyh	4	188-189	0.19
84	DL	O	6-NO_2	Cyh	3	186-187.5	0.035
85	DL	O	5-NO_2	Cyh	3	189-190	0.024
86	DL	O	5-Cl	Cyh	3	186-187	0.023
87	(-)*	O	5-Me	Cyh	2	Oil	0.0013
88	(+)*	O	5-Me	Cyh	2	Oil	0.045
89	(-)*	O	5-Me	Cyh	3	150-151	0.016
90	(+)*	O	5-Me	Cyh	3	150-151	<1.0
91	DL	O	5-Cl	Cyh	2	132-134	0.002
92	DL	O	5-CO_2Me	Cyh	2	129-131	0.012
93	DL	O	5-Cl	Ph4F	2	112-114	0.019
94	DL	O	5-iPr	Ph4F	2	56-58	0.012
95	DL	O	5-CF_3	Cyh	2	91-93	0.0012
96	DL	S	5-Cl	Ph4F	2	133-135	0.027
97	DL	S	5-Cl	Cyh	2	129-132	0.004
98	DL	O	5-iPr	Ph4Cl	2	65-67	0.029
99	DL	O	5-Cl	Ph4Cl	2	132-134	0.014
100	DL	O	5-iPr	Ph3Cl	2	51-52	0.005
101	DL	O	5-CO_2Me	Ph4F	2	151-152	0.027
102	DL	S	5-Cl	Cyh	2	129-132	0.004

* (-) and (+) refer to the laevorotatory and dextrorotatory enantiomer respectively. Enantiomers were separated by HPLC on a Chiralcel OD column eluting with hexane:i-PrOH:Et_2NH 950:50:1.

a. See footnote b, Table 1.

b. See footnote d, Table 1.

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Table 4 con't: Ester Bioisosteres - Pyridyl

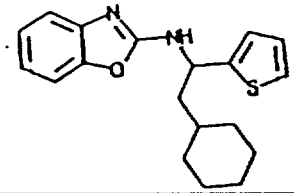
Comp. No.	D/L	X	R_1	R_3[a]	Pyridyl Isomer	mp°C	IC_{50} (μM)
103	DL	O	5-SO_2NMe_2	Ph4F	2	178-179	0.050
104	DL	O	5-Cl	Ph4NO_2	2	72-74	<0.03[b]
105	DL	O	5-F	Ph3Cl	2	131-133	<0.03[b]
106	DL	S	6-CF_3	Ph4F	2	149-150	<1.0[b]
107	DL	O	5-CF_3	Ph4F	2	105-107	0.008
108	DL	O	5-CF_3	Cyh	2	91-93	0.001
109	DL	O	5-F	Cyh	2	142-143.5	0.002
110	DL	O	5-F	Ph4F	2	117-119.5	0.021
111	DL	O	4,5-diF	Cyh	2	133-134	0.004
112	DL	O	5,6-diF	Cyh	2	131-133	0.001
113	DL	O	5,6-diF	Ph4F	2	143-144.5	0.024
114	DL	O	5-OMe	Ph4F	2	111-113	0.011
115	DL	O	5-NO_2	Ph4F	2	174-175	<0.03[b]
116	DL	O	5-iPr	2Me4Thz	2	116-117	<0.1[b]
117	DL	O	5-Cl	2Me4Thz	2	142-143	<0.1[b]
118	(-)*	O	5-Cl	Ph4F	2	Oil	0.01
119	(+)*	O	5-Cl	Ph4F	2	Oil	0.32

a. See footnote b, Table 1.
b. See footnote d, Table 1.

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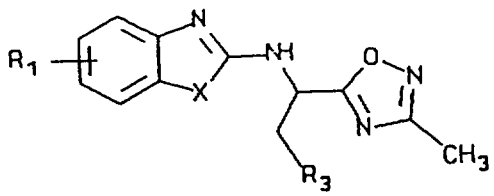


Table 5: Ester Bioisosteres - Thiophene



Comp. No.	D/L	mp°C	IC_{50} (μM)
120	DL	108-110	0.0062

Table 6: Ester Bioisosteres - Methyloxadiazole



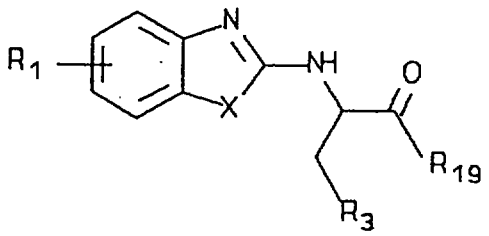
Comp. No.	D/L	R_1	R_3[a]	X	mp°C	IC_{50} (μM)
121	DL	H	Ph	S	122-124	1.3
122	L	H	Ph	S	117-119	1.8
123	L	5-Et	Ph	S	134-136	<1.0[b]
124	L	H	Cyh	S	147-149	0.12
125	L	5-Me	Cyh	O	118-119.5	0.028
126	DL	5-iPr	Ph4F	O	86	<0.3[b]
127	DL	5-iPr	2Me4Thz	O	45-48	<1.0[b]

a. See footnote b, Table 1.
b. See footnote d, Table 1.

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Table 7: Ester Bioisosteres - Ketones



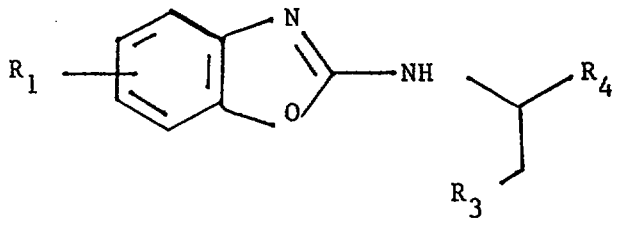
Comp. No.	D/L	R_1	R_3[a]	R_{19}	X	mp°C	IC_{50} (μM)
128	L	6-iPr	Ph	CH_3	S	107-110	0.35
129	L	H	Ph	CH_3	O	Oil	<1.0
130	L	H	Ph	Ph	O	Resin	<0.3
131	L	5-Me	Cyh	Ph	O	Resin	<1.0
132	L	5-Me	Cyh	b	O	Resin	0.023

a. See footnote b, Table 1.
b. 1-methyl-2-imidazolyl

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Table 8: Ester Bioisosteres - Miscellaneous Acyclic

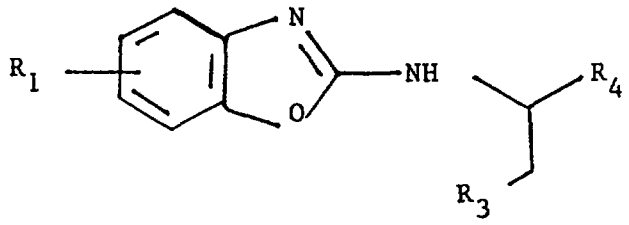


Comp. No.	D/L	R_1	R_3[a]	R_4	mp°C	IC_{50} - (μM)
133	L	5-iPr	Ph	CH_2OEt	Oil	0.016
134	L	5-iPr	Ph	CH_2OPr	Oil	0.22
135	L	5-Cl	Ph	CH_2OEt	Oil	0.029
136	DL	5-iPr	Ph4F	CH_2OMe	Oil	<0.03[b]
137	DL	5-iPr	Ph4F	CH_2OEt	Oil	<0.03[3]
138	DL	5-iPr	Ph4F	CH_2OnPr	Oil	<0.3[b]
139	DL	5-iPr	Ph4OMe	CH_2OMe	Oil	<0.03[b]
140	DL	5-iPr	3-Py	CH_2OMe	Oil	<1.0[b]
141	DL	5-iPr	2Me4Thz	Ch_2OMe	Oil	<0.3[b]
142	L	5-iPr	Ph3Cl	CH_2SMe	Oil	<0.03[b]
143	DL	5-iPr	3-Py	CH_2SMe	Oil	<1.0[b]
144	DL	5-iPr	4-Py	CH_2SMe	Oil	
145	DL	5-iPr	2Me4Thz	CH_2SMe	Oil	<0.1[b]
146	DL	5-iPr	Ph	CH_2SO_2Me	resin	<0.03[b]
147	DL	5-iPr	3-Py	CH_2SO_2Me	88-92	<1.0[b]
148	DL	5-iPr	4-Py	CH_2SO_2Me	78-81	
149	DL	5,6-diF	Ph4F	CH_2SO_2Me	179-181	
150	L	5-iPr	Ph	CH_2NMe_2	Oil	<0.3[b]
151	L	5-iPr	Ph	$CH_2NHC(O)Me$	resin	<0.1[b]
152	L	5-iPr	Ph	$CH_2NHSO_2NMe_2$	resin	<0.1[b]
153	L	5-iPr	Ph	$CH_2NHC(O)NH_2$	resin	<0.3[b]
154	L	5-iPr	Ph	$CH_2OC(O)NHMe$	125-126	0.063

a. See footnote b, Table 1
b. See footnote d, Table 1

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Table 9: Ester Bioisosteres: Miscellaneous Heterocycle



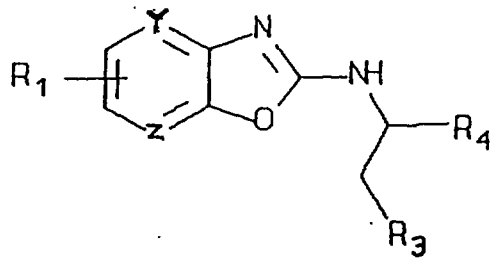
Comp. No.	D/L	R_1	R_3[a]	R_4[b]	mp°C	IC_{50} (μM)
155	DL	5-Cl	Ph4F	2-Imid	248-250	0.29
156	DL	5-iPr	Ph4F	2-Imid	213-219	0.09
157	DL	5-iPr	2-Me4Thz	2-Imid	153-155	<1.0[c]
158	DL	5-iPr	Ph3Cl	2-Imid	210-213	<0.03[c]
159	DL	5-iPr	Ph3Cl	2-Thz	resin	<0.1[c]
160	DL	5-iPr	Ph3Cl	4Me2Thz	resin	<0.03[c]
161	DL	5-iPr	Ph	4-Pyraz	206-210	<0.1[c]

a. See footnote b, Table 1.
b. 2-Imid = 2-imidazolyl, 2-Thz = 2-thiazolyl, 4Me2Thz = 4-methyl-2-thiazolyl, 4-Pyraz = 4-pyrazolyl
c. See footnote d, Table 1.

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Table 10: Oxazolopyridines

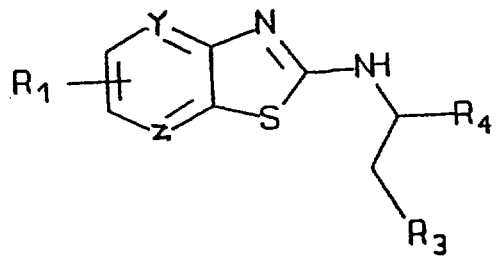


Comp. No.	D/L	Y	Z	R_1	R_3[a]	R_4[a]	mp°C	IC_{50} (μM)
162	L	N	C	H	Cyh	CO_2Me	147-149	0.21
163	DL	N	C	H	Cyh	Ph	189-190.5	0.078
164	DL	N	C	5-Me	Cyh	Ph	199-200	0.028
165	DL	N	C	5-Me	Cyh	2-Py	134-136	0.026
166	(-)*	N	C	5-Me	Cyh	2-Py	68-75	0.015
167	(+)*	N	C	5-Me	Cyh	2-Py	68-75	0.17
168	DL	N	C	5-Me	Cyh	3-Py	207-208	0.3
169	DL	N	C	5-Me	Ph4F	2-Py	66-69	<0.3[b]
170	DL	C	N	H	Cyh	Ph	133-134	0.021
171	DL	C	N	5-Me	Cyh	Ph	188-191	0.044

a. See footnote b Table 1. Also 2-Py = 2-pyridyl, 3-Py =3-pyridyl.
b. See footnote d, Table 1.
* See * Table 4.

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Table 11: Thiazolopyridines

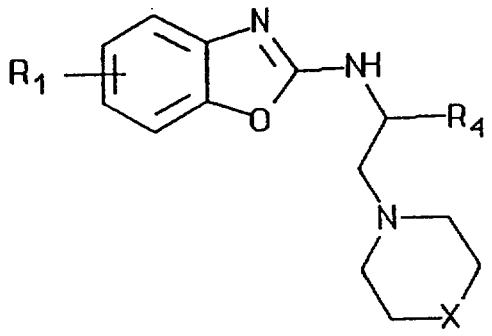


Comp. No.	DL	Y	Z	R_1	R_4[b]	R_3[b]	mp°C	IC_{50} (μM)
172	DL	C	N	H	Ph	Cyh	146-148	0.027
173	DL	C	N	H	3-Py	Cyh	222-224[a]	0.17
174	DL	C	N	H	2-Py	Cyh	176-178[a]	0.027
175	DL	C	N	5-Me-6-Br	2-Py	Cyh	215-217	0.009
176	DL	C	N	5-Me	2-Py	Cyh	109-113	0.01
177	DL	C	N	5-Me	3-Py	Cyh	174-175.5	0.11
178	DL	C	N	6-Cl	3-Py	Cyh	207-209	0.044
179	DL	C	N	6-Cl	2-Py	Cyh	180-182	0.006
180	DL	C	N	4-Me	2-Py	Cyh	144-146	<1.0[c]
181	DL	C	N	6-Cl	3-Py	Cyh	207-209	0.044
182	DL	C	N	6-Cl	2-Py	Ph4F	151-153	0.110
183	DL	C	N	5-Cl	2-Py	Ph4F	146-149	0.280
184	DL	N	C	6-Me	2-Py	Cyh	214-216	0.031
185	DL	N	C	5-Me-6-Br	2-Py	Cyh	209-210	0.0065
186	DL	N	C	5-Me-6-Br	3-Py	Cyh	241-243.5	0.021
187	DL	N	C	5-Me	2-Py	Cyh	167-171	0.013
188	DL	N	C	6-Cl	2-Py	Cyh	198.5-200.5	0.0039
189	DL	N	C	6-Cl	2-Py	Ph4F	204-205	0.028
190	DL	C	N	5-Me-6-Br	3-Py	Cyh	211-212	<1.0[c]
191	DL	N	C	6-Me	Ph	Cyh	213-214	<1.0[c]
192	DL	N	C	6-Me	2-Py	Ph4F	184-185	<0.3[c]

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a. Hydrochloride salt.
b. See footnote b Table 1. Also 2-Py = 2-pyridyl, 3-Py = 3-pyridyl.
c. See footnote d, Table 1.

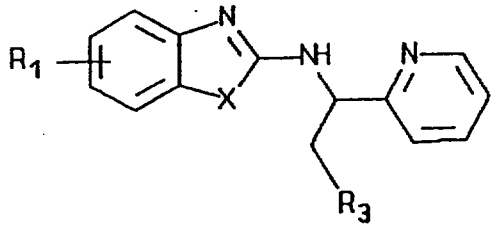
Table 12: Miscellaneous Compounds



Comp. No.	DL	R_1	R_4	X	mp°C	IC_{50} (μM)
193	L	5-iPr	Ph[b]	C	165[a]	0.1
194	L	5-Me	Ph	C	>150[a]	0.23
195	L	5-iPr	2-Py	C	128	0.19
196	L	5-iPr	2-Py	O	135-137.5	<0.1[c]

a. Dihydrochloride salt, broad melting range. (No.143)
b. See footnote b, Table 1.
c. See footnote d, Table 1.
d. 2-Py = 2-pyridyl

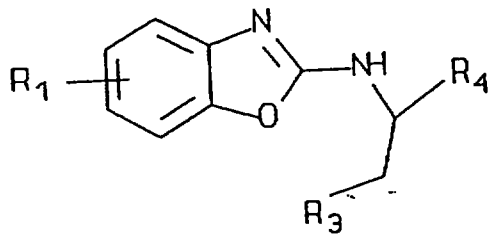
Table 13: Miscellaneous Compounds



Comp. No.	DL	R_1	R_3[a]	X	mp°C	IC_{50} (μM)
197	DL	5-Cl	2-Py	O	180-183	0.22
198	DL	5-iPr	2-Py	O	150-151[b]	0.12
199	DL	5-iPr	4-Py	O	145[b]	<0.3[c]
200	DL	5-iPr	3-Py	O	resin	<0.3[c]

a. 2-Py = 2-pyridyl, 4-Py = 4-Pyridyl, 3-Py = 3-Pyridyl
b. Tosylate salt
c. See footnote d, Table 1.

Table 14: Miscellaneous Compounds



Comp. No.	DL	R_1	R_4	R_3	mp	IC_{50} (μM)
201	L	5-iPr	$-CO_2Me$	C	143-146[a]	<1[b]
202	DL	5-iPr	d	Ph3Cl	168.5-170	<0.1[b]

a. Hydrochloride Salt
b. See footnote d, Table 1.
c. 1-methyl-imidazol-4-yl
d. 1-methyl-imidazol-2yl

Antigen-induced bronchoconstriction in guinea pigs.

This model measures the ability of a compound to block the leukotriene component of antigen-induced bronchoconstriction. Male Hartley guinea pigs are actively sensitized to ovalbumin, pretreated with mepyramine and indomethacin (to block the histamine and cyclooxygenase metabolite components respectively), and test compound (by aerosol administration). The guinea pigs are challenged with antigen (inhaled ovalbumin). Pulmonary function is measured by oscillatory mechanics as described by W.W. Wolyniec et al. (Agents and Actions 1991, 34, 1/2, 73). Results are expressed as percent inhibition of bronchoconstriction (resistance) in the test compound treated guinea pigs compared to placebo treated controls.

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Table 15

Compound No.	Dose (Micrograms)*	N	% Inhibition
51	274	6	86
56	95	6	43
81	308	6	64
	28	4	64
	2.8	10	61
165	274	7	84
	28	6	64
	5.6	4	0

*Refers to amount of test compound inhaled by guinea pig. Compounds administered by aerosolized freon/ethanol solution from metered dose inhaler.

Antigen-induced mediator release in primates.

This model measures the ability of a compound to inhibit the formation of leukotriene C_4 (LTC_4) in the lungs of allergic cynomolgus monkeys following antigen challenge. Animals are anesthetized, intubated, and challenged with an Ascaris suum extract, given by aerosol. A bronchoalveolar lavage is performed 20 minutes later and LTC_4 is quantitated by radioimmunoassay. Test compounds are adminstered by aerosol 10 minutes prior to antigen challenge and their effect is expressed as percent inhibition of LTC_4 production compared to untreated controls.

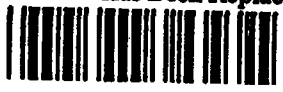
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Table 16

Compound No.	Dose(mg/ml)	N	% Inhibition
51	0.3	5	40
	1.0	5	60
	3.0	5	68
87	0.01	5	8
	0.03	4	63
	0.10	5	61
	0.30	4	82
	1.0	6	89
	10.0	4	96
118	0.01	5	8
	0.03	4	32
	1.0	6	76

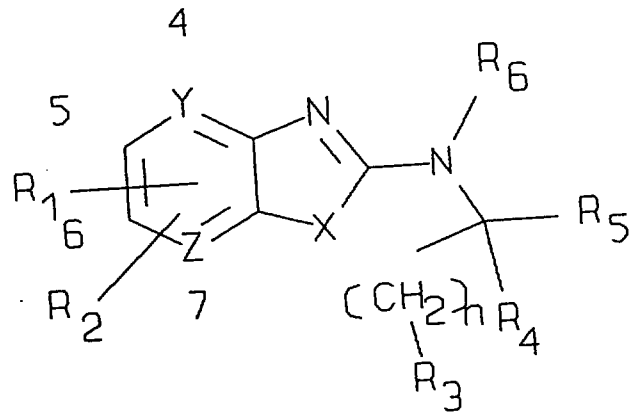
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CLAIMS

1. Compounds of formula (I)



(I)

wherein

X is O or S;

Y is C or N;

Z is C or N;

R_1 and R_2 are each, independently of one another, hydrogen; C_1-C_6 alkyl; halo; CF_3; nitrile; C_1-C_6 alkoxy; $-CO_2R_7$ wherein R_7 is hydrogen or C_1-C_6 alkyl; $-C(O)NR_8R_9$ wherein R_8 and R_9 are independently hydrogen, C_1-C_3 alkyl, methoxy or together with the N atom form a morpholine, pyrrolidine or piperidine ring; $-NO_2$; $-NR_{10}R_{11}$ wherein R_{10} and R_{11} are independently hydrogen or C_1-C_6 alkyl;$-C(O)R_{12}$ wherein R_{12} is C_1-C_6 alkyl; $-SO_2R_{12}$; $-NHC(O)R_{12}$;$-NHSO_2R_{12}$; or $-SO_2NR_{13}R_{14}$ wherein R_{13} and R_{14} are independently hydrogen or C_1-C_6 alkyl;

R_3 is methyl, cyclohexyl or an unsubstituted or substituted phenyl ring wherein the substituents are selected from halo,

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CF_3, C_1-C_4 alkyl and C_1-C_4 alkoxy; NO_2; SO_2R_{12}, $-NHC(O)R_{12}$, $-NHSO_2R_{12}$ or $-SO_2NR_{13}R_{14}$ wherein R_{12}, R_{13} and R_{14} are as defined above; a 1-piperidinyl ring, a 2-, 3- or 4- pyridine ring, a morpholine ring, a thiomorpholine ring, a pyrrolidine ring, an imidazole ring optionally substituted at the nitrogen with C_1-C_4 alkyl, or a 2-thiazole ring or a 2-methyl-4-thiazole ring; a dialkylamine (C_1-C_4) or an alkyl ether (C_1-C_4);

R_4 is an ester of structure $-CO_2R_{16}$ wherein R_{16} is C_1-C_4 alkyl; an amide of structure $-C(O)NR_{17}R_{18}$ wherein R_{17} and R_{18} are independently hydrogen, C_1-C_3 alkyl, methoxy or together with the N atom form a morpholine ring, piperidine or pyrrolidine ring; an unsubstituted or substituted phenyl ring wherein the substituents are selected from halo, C_1-C_4 alkyl or C_1-C_4 alkoxy; a 3-methyl-1,2,4-oxadiazol-5-yl group; a 2- or 3-thienyl group; a 2-, 3-, or 4-pyridyl group; a 4-pyrazolyl group; a 2-imidazole group optionally substituted at the N atom with a methyl group; a 2-thiazole group optionally substituted at the 4-position with a methyl; a ketone of structure $C(O)R_{19}$ wherein R_{19} is C_1-C_3 alkyl, phenyl or 1-methylimidazol-2-yl; an ether CH_2OR_{20} where R_{20} is C_1-C_3 alkyl; a thioether - CH_2SR_{20}; a sulfone - $CH_2SO_2CH_3$; an amine - $CH_2N(R_{20})_2$; an amine derivative $-CH_2NHC(O)R_{21}$, where R_{21} is CH_3, NH_2 or $NHCH_3$; $-CH_2NHSO_2NMe_2$; or a carbamate - $CH_2OC(O)NHMe$;

R_5 and R_6 are independently of each other hydrogen or methyl; and

n is an integer 0, 1 or 2;

and salts thereof;

in racemic form, or the pure or substantially pure enantiomer thereof;

with the proviso that Y and Z are not both N, and with the further provisos that the following combination of

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substituents do not occur simultaneously:

(i) Y and Z are both carbon; R_1 or R_2 are hydrogen, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, CN, NO_2 or CF_3; R_3 is an unsubstituted phenyl; and R_4 is $-C(O)OR_{16'}$ wherein $R_{16'}$ is hydrogen, alkyl, alkenyl or alkynyl; or R_4 is $-C(O)N(R_{18'})(R_{19'})$ wherein $R_{18'}$ and $R_{19'}$ are hydrogen, C_1-C_6 alkyl, phenyl or alkoxy or together with the N atom form a pyrrolidine, piperidine or morpholine ring; or R_4 is -CN or $-C(S)NH_2$;

or (ii) Y and Z are both carbon; R_4 is $C(O)OCH_3$; R_1 and R_2 are both hydrogen, and R_3 is 4-hydroxyphenyl, unsubstituted phenyl or a 4-imidazole group.

2. Compounds of formula (I) as claimed in claim 1 wherein X, Y, Z, R_1, R_2, R_4, R_5, R_6 and n are as defined in claim 1, and R_3 is cyclohexyl or an optionally substituted phenyl ring wherein the substituents are selected from halo, CF_3, C_1-C_4 alkyl, C_1-C_4 alkoxy; $-SO_2R_{12}$, $NHC(O)R_{12}$, $HNSO_2R_{12}$, $SO_2NR_{13}R_{14}$ in which R_{12}, R_{13} and R_{14} are as defined in claim 1; NO_2; or R_3 may be a pyridine ring, a morpholine ring, a pyrrolidine ring, a piperidino or an imidazole ring optionally substituted on nitrogen with C_1-C_4 alkyl, preferably compounds wherein X is O, and Y and Z are C.

3. Compounds of formula (I) as claimed in claim 2 wherein

R_1 and R_2 are independently C_1-C_6 alkyl, halo, CF_3, C_1-C_6 alkoxy or $-SO_2NR_{13}R_{14}$, wherein R_{13} and R_{14} are hydrogen or C_1-C_6 alkyl;

R_3 is cyclohexyl; an optionally substituted phenyl ring wherein the substituents are selected from halo, CF_3, C_1-C_4 alkyl and C_1-C_4 alkoxy; a 1-piperidinyl ring or pyridine ring;

R_4 is an optionally substituted phenyl ring wherein the substituents are selected from halo, C_1-C_4 alkyl and C_1-C_4 alkoxy; a 3-methyl-1,2,4-oxadiaxol-5-yl group; a 2-thienyl

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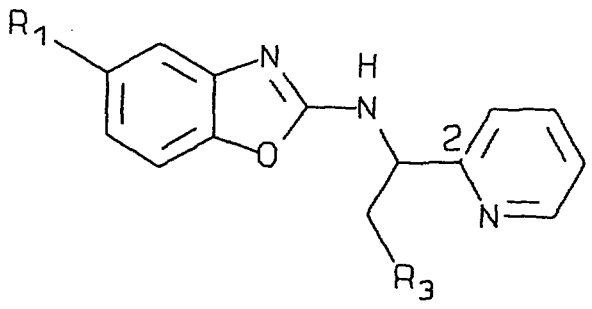
group; a 2-, 3-, or 4-pyridyl group; or a 1-methylimidazol-2-yl group;

and n is 1 or 2.

4. Compounds as claimed in Claim 2 wherein
R_1 is in the 5-position and is C_1-C_3 alkyl or halo,
R_2 is hydrogen,
R_3 is cyclohexyl,
R_4 is 2-pyridyl or 3-pyridyl,
R_5 is hydrogen,
R_6 is hydrogen,
X is O or S.
and n is 1.

5. A compound as claimed in claim 1 selected from
2-(2-Cyclohexyl-1-phenyl) ethylaminobenzoxazole;
2-{[2-(Cyclohexyl-1-(2-pyridyl)ethyl]amino}benzoxazole;
L-2-{[2-cyclohexyl-1-(2-pyridyl)ethyl]amino}benzoxazole;
2-{[2-Cyclohexyl-1-(2-pyridyl)ethyl]amino}-5-methyl-benzoxazole;
L-2-{(2-Cyclohexyl-1-phenyl)ethylamino}-5-isopropylbenzoxazole;
2-{[2-Cyclohexyl-1-(2-pyridyl)ethyl]amino}-5-chlorobenzoxazole; and salts thereof.

6. Compounds of formula (X)



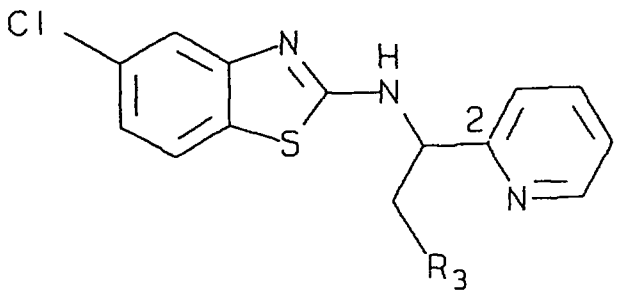
(X)

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wherein
R_1 is isopropyl, methyl, chloro or methoxy
and
R_3 is 4-fluorophenyl.

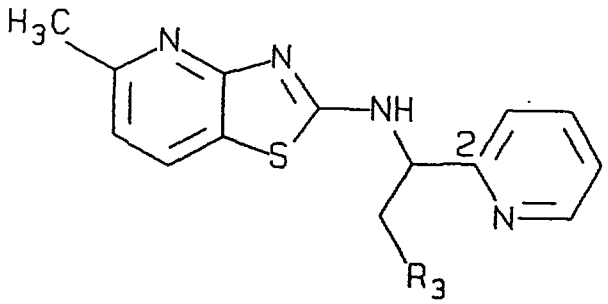
7. Compounds of formula (XI)



(XI)

wherein
R_3 is 4-fluorophenyl or cyclohexyl.

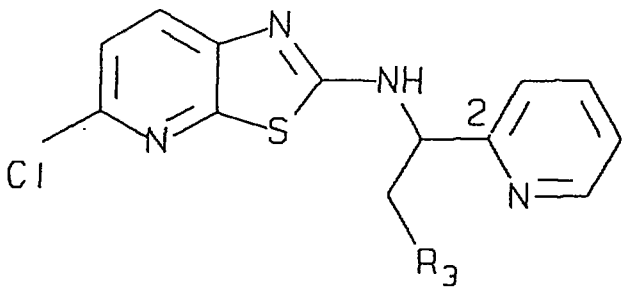
8. A compound of formula (XII)



(XII)

wherein
R_3 is cyclohexyl.

9. A compound of formula (XIII)



(XIII)

wherein

R_3 is cyclohexyl.

10. The compound as claimed in any one of claims 1 to 9, the L-enantiomer thereof.

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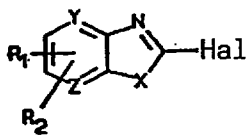




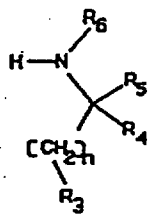
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11. Process for the preparation of a compound of general formula I as claimed in any one of claims 1 to 10, characterized in that

A) a compound



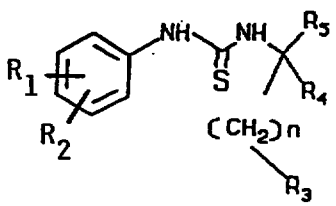
is reacted with an amine



or reactive derivative thereof (wherein X, Y, Z, R_1, R_2, R_3, R_4, R_5, R_6 and n are as defined in any one of claims 1 to 10, in an inert solvent in the presence of a basic catalyst;

B) for the preparation of a compound I where X is S, Y and Z are C and R^6 is H

a compound



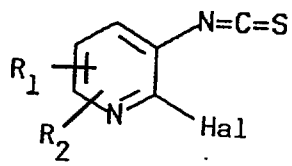
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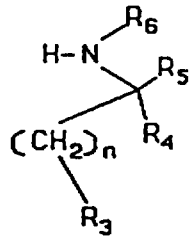
wherein R_1, R_2, R_3, R_4, R_5 and n are defined as in claim 1 is cyclized;

C) for the preparation of a compound I wherein X is S, Y is C and Z is N and R_1, R_2, R_3, R_4, R_5, R_6 and n are defined as in any one of claims 1 to 10,

a compound



is reacted with an amine



or reactive derivative thereof

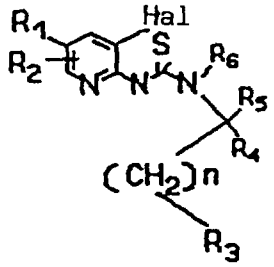
wherein R_1, R_2, R_3, R_4, R_5, R_6 and n are as defined above and Hal is halogen;

D) for the preparation of a compound I wherein X is S, Y is N and Z is C and R_1, R_2, R_3, R_4, R_5, R_6 and n are defined as in claim 1

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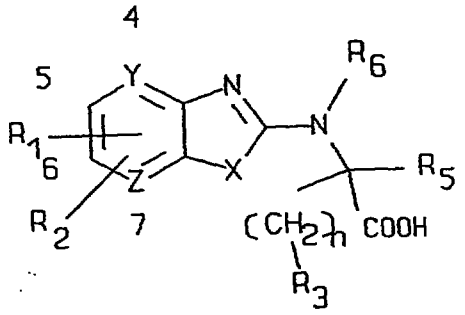
a compound



wherein R_1, R_2, R_3, R_4, R_5, R_6 and n are defined as above and Hal is halogen, is cyclized;

E) for the preparation of a compound I wherein R_4 is $-CO_2R_{16}$ and X, Y, Z, R_1, R_2, R_3, R_5, R_6, R_{16} and n are as defined in claim 1

reaction of an acid



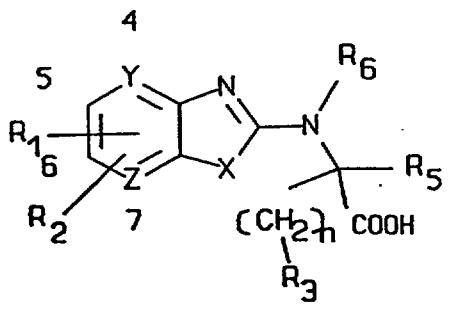
with an alcohol $R_{16}OH$ or a reactive derivative thereof,
wherein X, Y, Z, R_1, R_2, R_3, R_5, R_6, R_{16} and n are as defined above;

F) for the preparation of a compound I wherein R_4 is $-C(O)NR_{17}R_{18}$ and X, Y, Z, R_1, R_2, R_3, R_5, R_6, R_{17}, R_{18} and n are as defined in claim 1

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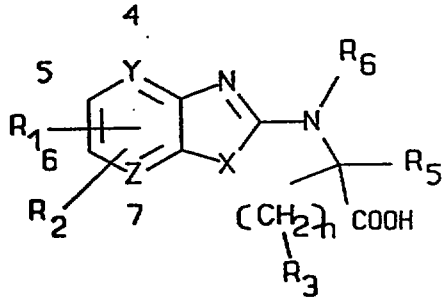
reaction of an acid



with an appropriately substituted amine $NHR_{17}R_{18}$, wherein R_{17} and R_{18} are defined as above;

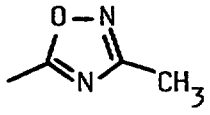
G) for the preparation of a compound I wherein R_4 is $-C(O)CH_3$ and X, Y, Z, R_1, R_2, R_3, R_5, R_6, R_{19} and n are defined as in claim 1 ,

reaction of a compound



with lithium methyl;

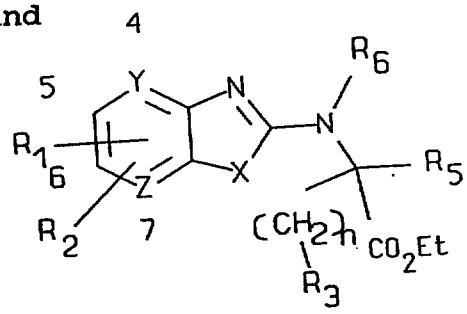
H) for the preparation of a compound I wherein R_4 is



and X, Y, Z, R_1, R_2, R_3, R_5, R_6 and n is as defined in claim 1

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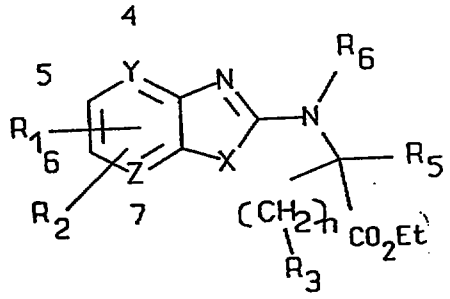
reaction of a compound



wherein X, Y, Z, R_1, R_2, R_3, R_5, R_6 and n are defined as above with acetamidoxime;

I) for the preparation of a compound I wherein R_4 is $-CH_2OR_{20}$ or $-CH_2SR_{20}$ and X, Y, Z, R_1, R_2, R_3, R_5, R_6, R_{20} and n are defined as in claim 1

reaction of a compound

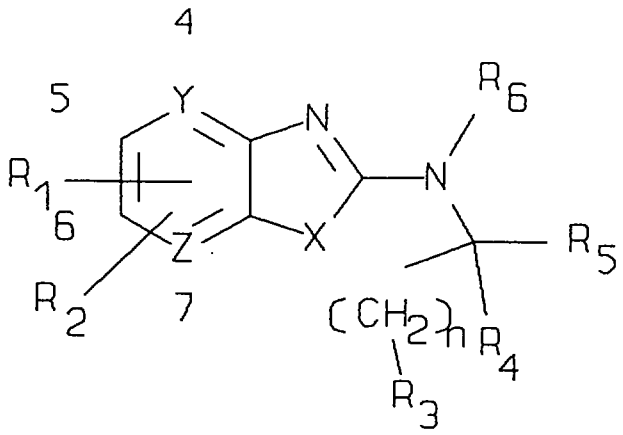


wherein X, Y, Z, R_1, R_2, R_3, R_5, R_6 and n are as defined above with $NaOR_{20}$ or $NaSR_{20}$, respectively;

followed by the isolation of the racemate and/or the individual enantiomer and/or by salt formation.

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12. Pharmaceutical compositions comprising as active ingredient at least one compound of formula (I)



(I)

wherein

X is O or S;

Y is C or N;

Z is C or N;

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with the proviso that Y and Z are not both N;
R_1 and R_2 are each, independently of one another, hydrogen; C_1-C_6 alkyl; halo; CF_3; nitrile; C_1-C_6 alkoxy; $-CO_2R_7$ wherein R_7 is hydrogen or C_1-C_6 alkyl; $-C(O)NR_8R_9$ wherein R_8 and R_9 are independently, hydrogen, C_1-C_3 alkyl, methoxy or together with the N atom form a morpholine, pyrrolidine or piperidine ring; $-NO_2$; $-NR_{10}R_{11}$ wherein R_{10} and R_{11} are independently hydrogen or C_1-C_6 alkyl; $-C(O)R_{12}$ wherein R_{12} is C_1-C_6 alkyl; $-SO_2R_{12}$; $-NHC(O)R_{12}$; $-NHSO_2R_{12}$; or $-SO_2NR_{13}R_{14}$ wherein R_{13} and R_{14} are independently hydrogen or C_1-C_6 alkyl;

R_3 is methyl, cyclohexyl or an optionally substituted phenyl ring wherein the substituents are selected from halo, CF_3, C_1-C_4 alkyl and C_1-C_4 alkoxy; $-SO_2R_{12}$, $NHC(O)R_{12}$, $-NHSO_2R_{12}$, or $-SO_2NR_{13}R_{14}$ in which R_{12}, R_{13} and R_{14} are as defined above; NO_2; a 1-piperidinyl ring, a 2-, 3- or 4- pyridine ring, a morpholine ring, a thiomorpholine ring, a pyrrolidine ring, or an imidazole ring optionally substituted at the nitrogen atom with C_1-C_4 alkyl, a 2-thiazole ring or a 2-methyl-4-thiazole ring; a dialkylamine (C_1-C_4) or an alkyl ether (C_1-C_4);

R_4 is an ester $-CO_2R_{16}$ wherein R_{16} is C_1-C_4 alkyl; or an amide of structure $-C(O)NR_{17}R_{18}$ wherein R_{17} and R_{18} are independently hydrogen, C_1-C_3 alkyl, methoxy or together with the N atom form a morpholine ring, or together with the N atom form a piperidine or pyrrolidine ring; an optionally substituted phenyl ring wherein the substituents are selected from halo, C_1-C_4 alkyl and C_1-C_4 alkoxy; a 3-methyl-1,2,4-oxadiazol-5-yl group; a 2- or 3-thienyl group; a 2-, 3-, or 4-pyridyl group; a 4-pyrazolyl group; a 2-imidazole group optionally substituted on N with a methyl group; a 2-thiazole group optionally substituted on the 4-position with a methyl; a ketone $C(O)R_{19}$ wherein R_{19} is C_1-C_3 alkyl, phenyl or 1-methylimidazol-2-yl; an ether $-CH_2OR_{20}$ where R_{20} is C_1-C_3 alkyl; a thioether, $-CH_2SR_{20}$; a sulfone, $-CH_2SO_2CH_3$; an amine, $-CH_2N(R_{20})_2$; an amine derivative, $-CH_2NHC(O)R_{21}$ where R_{21} is CH_3, NH_2 or $NHCH_3$; $-CH_2NHSO_2NMe_2$; or a carbamate, $-CH_2OC(O)NHMe$;

* C L H S *

R_5 and R_6 are independently of each other hydrogen or methyl; and
n is an integer 0, 1 or 2;
in racemic form, or the pure or substantially pure enantiomer thereof, or a physiologically acceptable acid addition salt thereof in association with one or more pharmaceutically acceptable carriers, diluents or excipients.

13. Pharmaceutical compositions as claimed in claim 12 wherein the compounds of formula (I) are as defined in any one of claims 1 to 10.

14. The use of a compound of formula (I) as defined in any one of claims 1 to 10, 12 or 13 or a physiologically acceptable salt thereof for the preparation of a medicament for use in the prevention or treatment of inflammatory conditions and conditions or diseases in which arachidonic acid metabolism has been implicated.

15. The use as claimed in claim 14 for the preparation of a medicament for the inhibition of the biosynthesis of leukotrienes.

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