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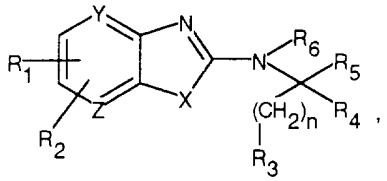
(54) Virsraksts: **Slāpekli saturoši heterocikliski savienojumi racēmiskā formā vai to individuālo enantiomēru formā**

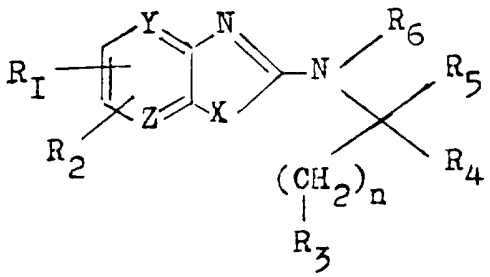
(57) Kopsavilkums: Jauni slāpekli saturoši heterocikliskie savienojumi ar formulu



kur:
X skābeklis vai sērs,
Y ogleklis vai slēpeklis,
Z ogleklis vai slāpeklis,
brīvā veidā vai to sāļu veidā var tikt lietoti kā cilvēka un siltasiņu dzīvnieku leikotriēnu biosintēzes inhibitori.

Izgudrojuma formula

1. Slāpekli saturoši heterocikliski savienojumi ar formulu (I)



kurā:

X ir O vai S;

Y ir C vai N;

Z ir C vai N,

ar noteikumu, ka Y un Z abi nav N;

R_1 un R_2, neatkarīgi viens no otra, ir ūdeņraža atoms, C_{1-6}alkilgrupa, halogēna atoms, trifluormetilgrupa, ciāngrupa, C_{1-6}alkoksigrupa; $-COOR_7$, kur R_7 ir ūdeņraža atoms vai C_{1-6}alkilgrupa; $-C(O)NR_8R_9$, kur R_8 un R_9, neatkarīgi viens no otra, ir ūdeņraža atoms, C_{1-3}alkilgrupa, metoksigrupa vai abi kopā veido piperidīna gredzenu; nitrogrupa; $-NR_{10}R_{11}$, kur R_{10} un R_{11} ir ūdeņraža atoms vai C_{1-6}alkilgrupa; $-C(O)R_{12}$, kur R_{12} ir C_{1-6}alkilgrupa; $-SO_2R_{12}$; $-NHC(O)R_{12}$; $-NHSO_2R_{12}$ vai $-SO_2NR_{13}R_{14}$, kur R_{13} un R_{14}, neatkarīgi viens no otra, ir ūdeņraža atoms vai C_{1-6}alkilgrupa;

R_3 ir metilgrupa, cikloheksilgrupa, fenilgrupa, kas neobligāti aizvietota ar halogēna atomu, trifluormetilgrupu, C_{1-4}alkilgrupu, C_{1-4}alkoksigrupu, $-SO_2R_{12}$, $-NHC(O)R_{12}$, $-NHSO_2R_{12}$, $-SO_2NR_{13}R_{14}$, kur R_{12}, R_{13} un R_{14} ir ar jau minētām nozīmēm vai arī nitrogrupa, vai arī R_3 ir 1-piperidinilgrupa, 2-, 3- vai 4-piridinilgrupa, morfolinilgrupa, tiomorfolinilgrupa, pirolidinilgrupa; imidazolilgrupa, kas neobligāti aizvietota ar C_{1-4}alkilgrupu pie slāpekļa atoma; 2-tiazolilgrupa, 2-metil-4-tiazolilgrupa; vai arī

R_3 ir di(C_{1-4}alkil)aminogrupa vai C_{1-4}alkoksigrupa;

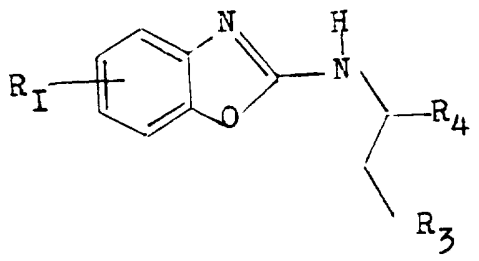
R_4 ir $-C(=O)OR_{16}$, kur R_{16} ir C_{1-4}alkilgrupa; $-C(O)NR_{17}R_{18}$, kur R_{17} un R_{18}, neatkarīgi viens no otra, ir ūdeņraža atoms, C_{1-3}alkilgrupa, metoksigrupa; vai abi kopā ar slāpekļa atomu veido morfolinilgrupu, piperidinilgrupu vai pirolidinilgrupu; fenilgrupa, neobligāti aizvietota ar halogēna atomu, C_{1-4}alkilgrupu, C_{1-4}alkoksigrupu; 3-metil-1,2,4-oksadiazol-5-ilgrupa; 2- vai 3-tienilgrupa; 2-, 3- vai 4- piridinilgrupa; 4-pirazolilgrupa; 2-imidazolilgrupa, neobligāti aizvietota pie slāpekļa atoma ar metilgrupu; 2-tiazolilgrupa, neobligāti aizvietota stāvoklī 4 ar metilgrupu; --C(=O)-R_{19}, kur R_{19} ir C_{1-3}alkilgrupa, fenilgrupa, 1-metilimidazol-2-ilgrupa; $-CH_2OR_{20}$, kur R_{20} ir C_{1-3}alkilgrupa; $-CH_2SR_{20}$; $-CH_2SO_2CH_3$; $-CH_2N(R_{20})_2$; $-CH_2HNC(=O)R_{21}$, kur R_{21} ir metilgrupa, aminogrupa , metilaminogrupa vai $-CH_2NHSO_2CH_3$; $-CH_2OC(=O)NHCH_3$;

R_5 un R_6 , neatkarīgi viens no otra, ir ūdeņraža atoms vai metilgrupa;
n ir 0, 1 vai 2,
pie nosacījuma, ka vienlaikus nav iespējamas šādas aizvietotāju kombinācijas:
(I) Y un Z abi ir C; R_1 un R_2 ir ūdeņraža atoms, halogēna atoms, C_{1-4}alkilgrupa, C_{1-4}alkoksigrupa, ciāngrupa, nitrogrupa vai trifluormetilgrupa; R_3 ir neaizvietota fenilgrupa; R_4 ir $-C(=O)OR_{16'}$, kur $R_{16'}$ ir ūdeņraža atoms, alkilgrupa, alkenilgrupa vai alkinilgrupa, $-C(=O)N(R_{18'})(R_{19'})$, kur $R_{18'}$ un $R_{19'}$ ir ūdeņraža atoms, C_{1-6}alkil-grupa, fenilgrupa vai alkoksigrupa, vai arī abas kopā ar slāpekļa atomu veido pirolidinilgrupu, piperidinilgrupu vai morfolinilgrupu, ciāngrupa vai $-C(=S)NH_2$;
(II) Y un Z ir C; R_4 ir $-C(=O)OCH_3$, R_1 un R_2 abi ir ūdeņraža atoms, R_3 ir 4-hidroksifenilgrupa, neaizvietota fenilgrupa vai 4-imidazolilgrupa,

pie tam minētie savienojumi var būt racēmiskā formā, individuālu enantiomēru formā, vai visu iepriekšminēto savienojumu sāļu veidā.

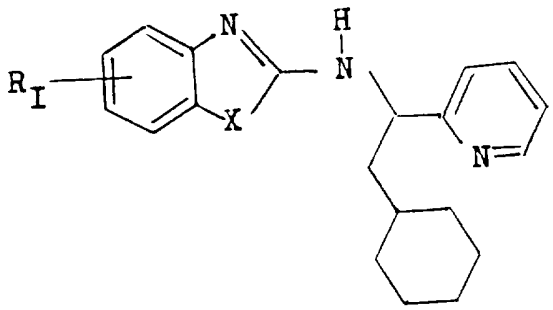
2. Savienojums pēc 1. punkta, kurā R_1 atrodas stāvoklī 5 un ir C_{1-3}alkilgrupa vai halogēna atoms, R_2 ir ūdeņraža atoms, R_3 ir cikloheksilgrupa, R_4 ir 2- vai 3-piridinilgrupa, R_5 ir ūdeņraža atoms, R_6 ir ūdeņraža atoms, X ir O vai S un n ir 1.

3. Savienojums pēc 1. punkta ar formulu



kurā R_1 ir ūdeņraža atoms, R_3 ir cikloheksilgrupa un R_4 ir fenilgrupa.

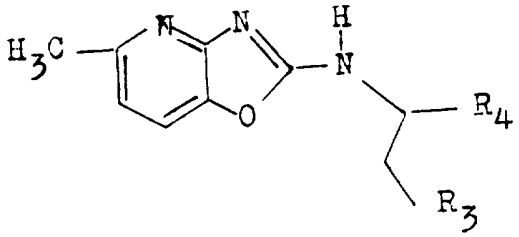
4. Savienojums pēc 1. punkta ar formulu



kurā X ir skābekļa atoms un R_1 ir 5-metilgrupa.

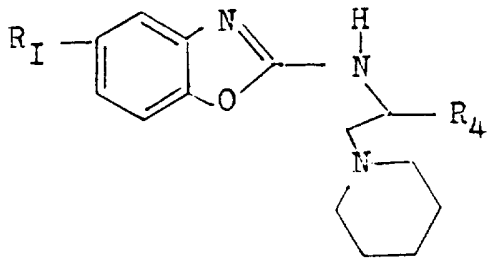
5. Savienojuma pēc 4. punkta enantiomērs.

6. Savienojums pēc 1. punkta ar formulu



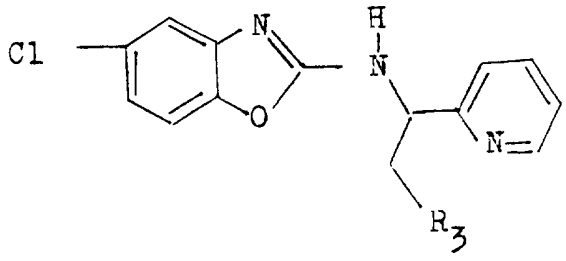
kurā R_4 ir cikloheksilgrupa un R_3 ir 2-piridinilgrupa.

7. Savienojuma pēc 1. punkta ar formulu



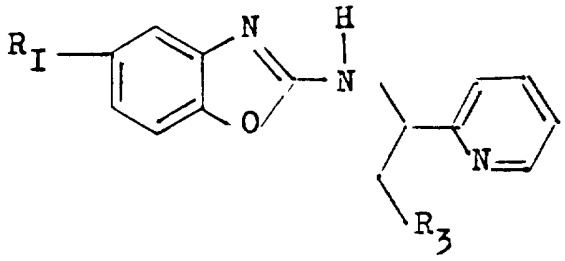
kurā R_1 ir izopropilgrupa, R_4 ir fenilgrupa, L-enantiomērs.

8. Savienojums pēc 1. punkta ar formulu



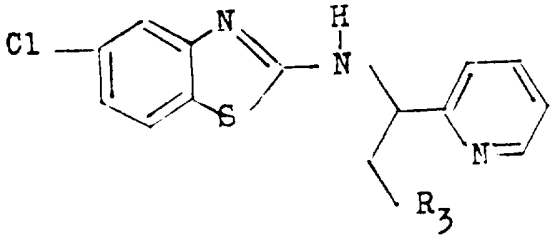
kurā R_3 ir cikloheksilgrupa.

9. Savienojums pēc 1. punkta ar formulu



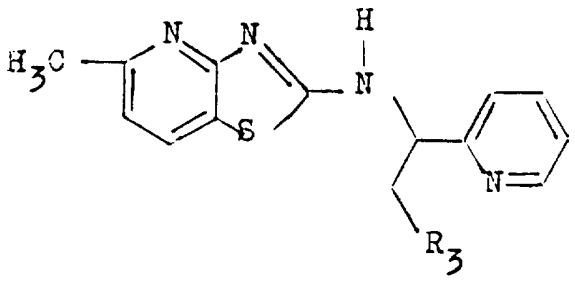
kurā R_1 ir izopropilgrupa, metilgrupa, hlora atoms vai metoksigrupa, R_3 ir 4-fluorfenilgrupa.

10. Savienojums pēc 1. punkta ar formulu



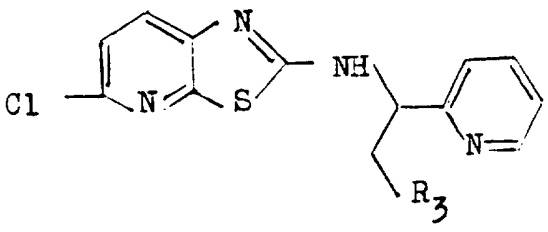
kurā R_3 ir 4-fluorfenilgrupa vai cikloheksilgrupa.

11. Savienojums pēc 1. punkta ar formulu



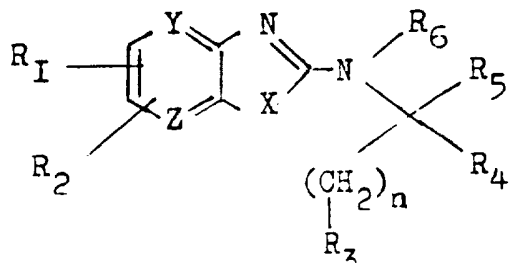
kurā R_3 ir cikloheksilgrupa.

12. Savienojums pēc 1. punkta ar formulu



kurā R_3 ir cikloheksilgrupa.

13. Zāļu līdzeklis, kas satur savienojumu ar formulu (I)



Formula I

kurā:

X ir O vai S;

Y ir C vai N;

Z ir C vai N,

ar noteikumu, ka Y un Z abi nav N;

R_1 un R_2, neatkarīgi viens no otra, ir ūdeņraža atoms, C_{1-6}alkilgrupa, halogēna atoms, trifluormetilgrupa, ciāngrupa, C_{1-6}alkoksigrupa; $-COOR_7$, kur R_7 ir ūdeņraža atoms vai C_{1-6}alkilgrupa; $-C(O)NR_8R_9$, kur R_8 un R_9, neatkarīgi viens no otra, ir ūdeņraža atoms, C_{1-3}alkilgrupa, metoksigrupa vai abi kopā veido piperidīna gredzenu; nitrogrupa; $-NR_{10}R_{11}$, kur R_{10} un R_{11} ir ūdeņraža atoms vai C_{1-6}alkilgrupa; $-C(O)R_{12}$, kur R_{12} ir C_{1-6}alkilgrupa; $-SO_2R_{12}$; $-NHC(O)R_{12}$; $-NHSO_2R_{12}$ vai $-SO_2NR_{13}R_{14}$, kur R_{13} un R_{14}, neatkarīgi viens no otra, ir ūdeņraža atoms vai C_{1-6}alkilgrupa;

R_3 ir metilgrupa, cikloheksilgrupa, fenilgrupa, kas neobligāti aizvietota ar halogēna atomu, trifluormetilgrupu, C_{1-4}alkilgrupu, C_{1-4}alkoksigrupu, $-SO_2R_{12}$, $-NHC(O)R_{12}$, $-NHSO_2R_{12}$, $-SO_2NR_{13}R_{14}$, kur R_{12}, R_{13} un R_{14} ir ar

jau minētām nozīmēm vai arī nitrogrupa, vai arī R_3 ir 1-piperidinilgrupa, 2-, 3- vai 4-piridinilgrupa, morfolinilgrupa, tiomorfolinilgrupa, pirolidinilgrupa; imidazolilgrupa, kas neobligāti aizvietota ar C_{1-4}alkilgrupu pie slāpekļa atoma; 2-tiazolilgrupa, 2-metil-4-tiazolilgrupa; vai arī

R_3 ir di(C_{1-4}alkil)aminogrupa vai C_{1-4}alkoksigrupa;

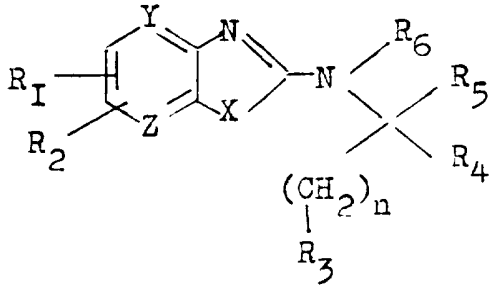
R_4 ir -C(=O)OR_{16}, kur R_{16} ir C_{1-4}alkilgrupa; -C(O)$NR_{17}R_{18}$, kur R_{17} un R_{18}, neatkarīgi viens no otra, ir ūdeņraža atoms, C_{1-3}alkilgrupa, metoksigrupa; vai abi kopā ar slāpekļa atomu veido morfolinilgrupu, piperidinilgrupu vai pirolidinilgrupu; fenilgrupa, neobligāti aizvietota ar halogēna atomu, C_{1-4}alkilgrupu, C_{1-4}alkoksigrupu; 3-metil-1,2,4-oksadiazol-5-ilgrupa; 2- vai 3-tienilgrupa; 2-, 3- vai 4-piridinilgrupa; 4-pirazolilgrupa; 2-tiazolilgrupa, neobligāti aizvietota stāvoklī 4 ar metilgrupu; --C(=O)-R_{19}, kur R_{19} ir C_{1-3}alkilgrupa, fenilgrupa, 1-metilimidazol-2-ilgrupa; -CH_2OR_{20}, kur R_{20} ir C_{1-3}alkilgrupa; -CH_2SR_{20}; -$CH_2SO_2CH_3$; -$CH_2N(R_{20})_2$; -$CH_2HNC(=O)R_{21}$, kur R_{21} ir metilgrupa, aminogrupa , metilaminogrupa vai -$CH_2NHSO_2CH_3$; -$CH_2OC(=O)NHCH_3$;

R_5 un R_6 , neatkarīgi viens no otra, ir ūdeņraža atoms vai metilgrupa;

n ir 0, 1 vai 2,

pie tam minētie savienojumi var būt racēmiskā formā, individuālu enantiomēru formā, vai visu iepriekšminēto savienojumu sāļu veidā.

14. Savienojuma ar formulu (I) ***pielietojums*** tāda zāļu līdzekļa ražošanai, kas paredzēts siltasiņu dzīvnieku ārstēšanai, inhibējot leikotriēnu biosintēzi, pie tam formulā (I)



X ir O vai S;

Y ir C vai N;

Z ir C vai N,

ar noteikumu, ka Y un Z abi nav N;

R_1 un R_2, neatkarīgi viens no otra, ir ūdeņraža atoms, C_{1-6}alkilgrupa, halogēna atoms, trifluormetilgrupa, ciāngrupa, C_{1-6}alkoksigrupa; $-COOR_7$, kur R_7 ir ūdeņraža atoms vai C_{1-6}alkilgrupa; $-C(O)NR_8R_9$, kur R_8 un R_9, neatkarīgi viens no otra, ir ūdeņraža atoms, C_{1-3}alkilgrupa, metoksigrupa vai abi kopā ar slāpekļa atomu veido piperidīna gredzenu; nitrogrupa; $-NR_{10}R_{11}$, kur R_{10} un R_{11} ir ūdeņraža atoms vai C_{1-6}alkilgrupa; $-C(O)R_{12}$, kur R_{12} ir C_{1-6}alkilgrupa; $-SO_2R_{12}$; $-NHC(O)R_{12}$; $-NHSO_2R_{12}$ vai $-SO_2NR_{13}R_{14}$, kur R_{13} un R_{14}, neatkarīgi viens no otra, ir ūdeņraža atoms vai C_{1-6}alkilgrupa;

R_3 ir metilgrupa, cikloheksilgrupa, fenilgrupa, kas neobligāti aizvietota ar halogēna atomu, trifluormetilgrupu, C_{1-4}alkilgrupu, C_{1-4}alkoksigrupu, $-SO_2R_{12}$, $-NHC(O)R_{12}$, $-NHSO_2R_{12}$, $-SO_2NR_{13}R_{14}$, kur R_{12}, R_{13} un R_{14} ir ar jau minētām nozīmēm vai arī nitrogrupa, vai arī R_3 ir 1-piperidinilgrupa, 2-, 3- vai 4-piridinilgrupa, morfolinilgrupa, tiomorfolinilgrupa, pirolidinilgrupa; imidazolilgrupa, kas neobligāti aizvietota ar C_{1-4}alkilgrupu pie slāpekļa atoma; 2-tiazolilgrupa, 2-metil-4-tiazolilgrupa; vai arī

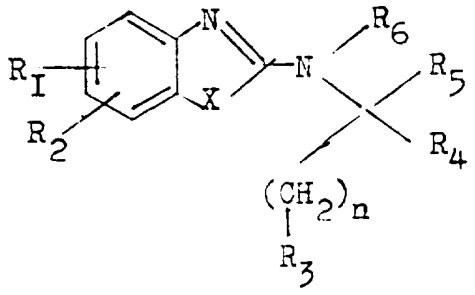
R_3 ir di(C_{1-4}alkil)aminogrupa vai C_{1-4}alkoksigrupa;

R_4 ir $-C(=O)OR_{16}$, kur R_{16} ir C_{1-4}alkilgrupa; $-C(O)NR_{17}R_{18}$, kur R_{17} un R_{18}, neatkarīgi viens no otra, ir ūdeņraža atoms, C_{1-3}alkilgrupa, metoksigrupa; vai abi kopā ar slāpekļa atomu veido morfolinilgrupu, piperidinilgrupu vai pirolidinilgrupu; fenilgrupa, neobligāti aizvietota ar halogēna atomu, C_{1-4}alkilgrupu, C_{1-4}alkoksigrupu; 3-metil-1,2,4-oksadiazol-5-ilgrupa; 2- vai 3-tienilgrupa; 2-, 3- vai 4-piridinilgrupa; 4-pirazolilgrupa; 2-imidazolilgrupa, neobligāti aizvietota pie slāpekļa atoma ar metilgrupu; 2-tiazolilgrupa, neobligāti aizvietota stāvoklī 4 ar metilgrupu; $-C(=O)-R_{19}$, kur R_{19} ir C_{1-3}alkilgrupa, fenilgrupa, 1-metilimidazol-2-ilgrupa; $-CH_2OR_{20}$, kur R_{20} ir C_{1-3}alkilgrupa; $-CH_2SR_{20}$; $-CH_2SO_2CH_3$; $-CH_2N(R_{20})_2$; $-CH_2HNC(=O)R_{21}$, kur R_{21} ir metilgrupa, aminogrupa, metilaminogrupa vai $-CH_2NHSO_2CH_3$;

n ir 0, 1 vai 2,

pie tam minētais savienojums var būt racēmiskā formā, individuāla enantiomēra formā, vai jebkura iepriekšminētā savienojuma sāls veidā.

15. Savienojums ar formulu



kurā:

X ir O;

R_1 un R_2, neatkarīgi viens no otra, ir ūdeņraža atoms, C_{1-6}alkilgrupa, halogēna atoms, trifluormetilgrupa, ciāngrupa, C_{1-6}alkoksigrupa; $-COOR_7$, kur R_7 ir ūdeņraža atoms vai C_{1-6}alkilgrupa; $-C(O)NR_8R_9$, kur R_8 un R_9, neatkarīgi viens no otra, ir ūdeņraža atoms, C_{1-3}alkilgrupa, metoksigrupa vai abi kopā veido piperidīna gredzenu; nitrogrupa; $-NR_{10}R_{11}$, kur R_{10} un R_{11} ir ūdeņraža atoms vai C_{1-6}alkilgrupa; $-C(O)R_{12}$, kur R_{12} ir C_{1-6}alkilgrupa; $-SO_2R_{12}$; $-NHC(O)R_{12}$; $-NHSO_2R_{12}$ vai $-SO_2NR_{13}R_{14}$, kur R_{13} un R_{14}, neatkarīgi viens no otra, ir ūdeņraža atoms vai C_{1-6}alkilgrupa;

R_3 ir metilgrupa, cikloheksilgrupa, fenilgrupa, kas neobligāti aizvietota ar halogēna atomu, trifluormetilgrupu, C_{1-4}alkilgrupu, C_{1-4}alkoksigrupu, $-SO_2R_{12}$, $-NHC(O)R_{12}$, $-NHSO_2R_{12}$, $-SO_2NR_{13}R_{14}$, kur R_{12}, R_{13} un R_{14} ir ar jau minētām nozīmēm vai arī nitrogrupa, vai arī R_3 ir 1-piperidinilgrupa, piridinilgrupa, morfolinilgrupa, pirolidinilgrupa; imidazolilgrupa, kas neobligāti aizvietota ar C_{1-4}alkilgrupu pie slāpekļa atoma;

R_4 ir $-C(=O)OR_{16}$, kur R_{16} ir C_{1-4}alkilgrupa; $-C(O)NR_{17}R_{18}$, kur R_{17} un R_{18}, neatkarīgi viens no otra, ir ūdeņraža atoms, C_{1-3}alkilgrupa, metoksigrupa; vai abi kopā ar slāpekļa atomu veido morfolinilgrupu, piperidinilgrupu vai pirolidinilgrupu; fenilgrupa, neobligāti aizvietota ar halogēna atomu,

C_{1-4}alkilgrupu, C_{1-4}alkoksigrupu; 3-metil-1,2,4-oksadiazol-5-ilgrupa; 2- vai 3-tienilgrupa; 2-, 3- vai 4-piridinilgrupa; 4-pirazolilgrupa; 2-imidazolilgrupa, neobligāti aizvietota pie slāpekļa atoma ar metilgrupu; 2-tiazolilgrupa, neobligāti aizvietota stāvoklī 4 ar metilgrupu; $-CH_2OR_{20}$, kur R_{20} ir C_{1-3}alkilgrupa; $-CH_2SR_{20}$; $-CH_2SO_2CH_3$; $-CH_2N(R_{20})_2$; $-CH_2HNC(=O)R_{21}$, kur R_{21} ir metilgrupa, aminogrupa, metilaminogrupa vai $-CH_2NHSO_2CH_3$; $-CH_2OC(=O)-NHCH_3$; $-C(=O)-R_{19}$, kur R_{19} ir C_{1-3}alkilgrupa, fenilgrupa, 1-metilimidazol-2-ilgrupa;

R_5 un R_6, neatkarīgi viens no otra, ir ūdeņraža atoms vai metilgrupa;

n ir 0, 1 vai 2,

pie nosacījuma, ka vienlaikus nav iespējamas šādas aizvietotāju kombinācijas:

(I) R_1 un R_2 ir ūdeņraža atoms, halogēna atoms, C_{1-4}alkilgrupa, C_{1-4}alkoksigrupa, ciāngrupa, nitrogrupa vai trifluormetilgrupa; R_3 ir neaizvietota fenilgrupa; R_4 ir $-C(=O)OR_{16'}$, kur $R_{16'}$ ir ūdeņraža atoms, alkilgrupa, alkenilgrupa vai alkinilgrupa, $-C(=O)N(R_{18'})(R_{19'})$, kur $R_{18'}$ un $R_{19'}$ ir ūdeņraža atoms, C_{1-6}alkilgrupa, fenilgrupa vai alkoksigrupa, vai arī abas kopā ar slāpekļa atomu veido pirolidinilgrupu, piperidinilgrupu vai morfolinilgrupu, ciāngrupa vai $-C(=S)NH_2$;

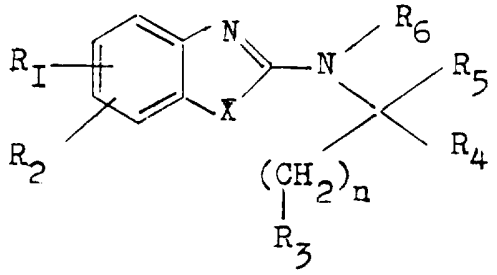
(II) R_4 ir $-C(=O)OCH_3$, R_1 un R_2 abi ir ūdeņraža atoms, R_3 ir 4-hidroksifenilgrupa, neaizvietota fenilgrupa vai 4-imidazolilgrupa,

pie tam minētie savienojumi var būt racēmiskā formā, individuālu vai pamatā tīru enantiomēru formā, vai visu iepriekšminēto savienojumu sāļu veidā.

16. Savienojums pēc 15. punkta, kurā R_1 un R_2 ir C_{1-6}alkilgrupa, halogēna atoms, trifluormetilgrupa, C_{1-6}alkoksigrupa vai $-SO_2NR_{13}R_{14}$, kur R_{13} un R_{14} ir ūdeņraža atoms vai C_{1-6}alkilgrupa; R_3 ir metilgrupa, cikloheksilgrupa, fenilgrupa, kas neobligāti aizvietota ar halogēna atomu, trifluormetilgrupu, C_{1-4}alkilgrupu vai C_{1-4}alkoksigrupu; 1-piperidinilgrupa vai piridinilgrupa; R_4 ir fenilgrupa, neobligāti aizvietota ar halogēna atomu,

C_{1-4}alkilgrupu vai C_{1-4}alkoksigrupu; 3-metil-1,2,4-oksadiazol-5-ilgrupa; 2-tienilgrupa; 2-, 3- vai 4-piridinilgrupa vai 1-metilimidazol-2-ilgrupa; n ir 1 vai 2.

17. Ārstnieciskais sastāvs, kas satur savienojumu ar formulu



kurā:

X ir O;

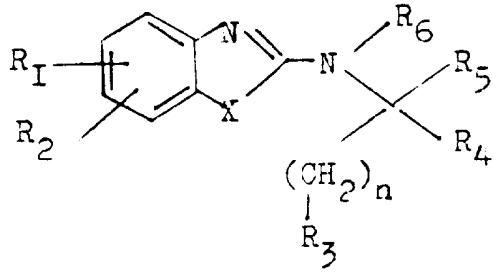
R_1 un R_2, neatkarīgi viens no otra, ir ūdeņraža atoms, C_{1-6}alkilgrupa, halogēna atoms, trifluormetilgrupa, ciāngrupa, C_{1-6}alkoksigrupa; $-COOR_7$, kur R_7 ir ūdeņraža atoms vai C_{1-6}alkilgrupa; $-C(O)NR_8R_9$, kur R_8 un R_9, neatkarīgi viens no otra, ir ūdeņraža atoms, C_{1-3}alkilgrupa, metoksigrupa vai abi kopā ar slāpekļa atomu veido piperidīna gredzenu; nitrogrupa; $-NR_{10}R_{11}$, kur R_{10} un R_{11} ir ūdeņraža atoms vai C_{1-6}alkilgrupa; $-C(O)R_{12}$, kur R_{12} ir C_{1-6}alkilgrupa; $-SO_2R_{12}$; $-NHC(O)R_{12}$; $-NHSO_2R_{12}$ vai $-SO_2NR_{13}R_{14}$, kur R_{13} un R_{14}, neatkarīgi viens no otra, ir ūdeņraža atoms vai C_{1-6}alkilgrupa;

R_3 ir metilgrupa, cikloheksilgrupa, fenilgrupa, kas neobligāti aizvietota ar halogēna atomu, trifluormetilgrupu, C_{1-4}alkilgrupu, C_{1-4}alkoksigrupu; $-SO_2R_{12}$, $-NHC(O)R_{12}$, $-NHSO_2R_{12}$, $-SO_2NR_{13}R_{14}$, kur R_{12}, R_{13} un R_{14} ir ar jau minētām nozīmēm vai arī nitrogrupa, vai arī R_3 ir 1-piperidinilgrupa,

piridinilgrupa, morfolinilgrupa, pirolidinilgrupa vai arī imidazolilgrupa, kas neobligāti aizvietota ar C_{1-4}alkilgrupu pie slāpekļa atoma;
R_4 ir $-CO_2R_{16}$, kur R_{16} ir C_{1-4}alkilgrupa; $-C(O)NR_{17}R_{18}$, kur R_{17} un R_{18}, neatkarīgi viens no otra, ir ūdeņraža atoms, C_{1-3}alkilgrupa, metoksigrupa; vai abi kopā ar slāpekļa atomu veido morfolinilgrupu, piperidinilgrupu vai pirolidinilgrupu; fenilgrupa, neobligāti aizvietota ar halogēna atomu, C_{1-4}alkilgrupu, C_{1-4}alkoksigrupu; 3-metil-1,2,4-oksadiazol-5-ilgrupa; 2- vai 3-tienilgrupa; 2-, 3- vai 4-piridinilgrupa; 4-pirazolilgrupa; 1-metil-2-imidazolilgrupa;
$-C(=O)-R_{19}$, kur R_{19} ir C_{1-3}alkil-grupa, fenilgrupa, 1-metilimidazol-2-ilgrupa;
R_5 un R_6 , neatkarīgi viens no otra, ir ūdeņraža atoms vai metilgrupa;
n ir 0, 1 vai 2,

pie tam minētais savienojums var būt racēmiskā formā, individuāla vai pamatā tīra enantiomēra formā, vai jebkura iepriekšminētā savienojuma sāls veidā.

18. Savienojuma ar ***pielietojums*** tāda zāļu līdzekļa ražošanai, kas paredzēts siltasiņu dzīvnieku ārstēšanai, inhibējot leikotriēnu biosintēzi, pie tam šī savienojuma formulā



X ir O;
R_1 un R_2, neatkarīgi viens no otra, ir ūdeņraža atoms, C_{1-6}alkilgrupa, halogēna atoms, trifluormetilgrupa, ciāngrupa, C_{1-6}alkoksigrupa; $-COOR_7$, kur R_7 ir ūdeņraža atoms vai C_{1-6}alkilgrupa; $-C(O)NR_8R_9$, kur R_8 un R_9, neatkarīgi viens no otra, ir ūdeņraža atoms, C_{1-3}alkilgrupa, metoksigrupa vai

abi kopā veido piperidīna gredzenu; nitrogrupa; $-NR_{10}R_{11}$, kur R_{10} un R_{11} ir ūdeņraža atoms vai C_{1-6}alkilgrupa; $-C(O)R_{12}$, kur R_{12} ir C_{1-6}alkilgrupa; $-SO_2R_{12}$; $-NHC(O)R_{12}$; $-NHSO_2R_{12}$ vai $-SO_2NR_{13}R_{14}$, kur R_{13} un R_{14}, neatkarīgi viens no otra, ir ūdeņraža atoms vai C_{1-6}alkilgrupa;

R_3 ir metilgrupa, cikloheksilgrupa, fenilgrupa, kas neobligāti aizvietota ar halogēna atomu, trifluormetilgrupu, C_{1-4}alkilgrupu, C_{1-4}alkoksigrupu, $-SO_2R_{12}$, $-NHC(O)R_{12}$, $-NHSO_2R_{12}$, $-SO_2NR_{13}R_{14}$, kur R_{12}, R_{13} un R_{14} ir ar jau minētām nozīmēm vai arī nitrogrupa, vai arī R_3 ir 1-piperidinilgrupa, piridinilgrupa, morfolinilgrupa, pirolidinilgrupa; imidazolilgrupa, kas neobligāti aizvietota ar C_{1-4}alkilgrupu pie slāpekļa atoma;

R_4 ir $-C(=O)OR_{16}$, kur R_{16} ir C_{1-4}alkilgrupa; $-C(O)NR_{17}R_{18}$, kur R_{17} un R_{18}, neatkarīgi viens no otra, ir ūdeņraža atoms, C_{1-3}alkilgrupa, metoksigrupa; vai abi kopā ar slāpekļa atomu veido morfolinilgrupu, piperidinilgrupu vai pirolidinilgrupu; fenilgrupa, neobligāti aizvietota ar halogēna atomu, C_{1-4}alkilgrupu, C_{1-4}alkoksigrupu; 3-metil-1,2,4-oksadiazol-5-ilgrupa; 2- vai 3-tienilgrupa; 2-, 3- vai 4-piridinilgrupa; 4-pirazolilgrupa;

1-metil-2-imidazolilgrupa;

$-C(=O)-R_{19}$, kur R_{19} ir C_{1-3}alkilgrupa, fenilgrupa, 1-metilimidazol-2-ilgrupa;

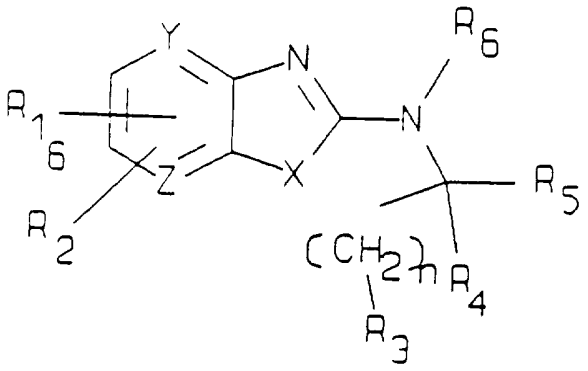
R_5 un R_6 , neatkarīgi viens no otra, ir ūdeņraža atoms vai metilgrupa;

n ir 0, 1 vai 2,

pie tam minētais savienojums var būt racēmiskā formā, individuāla vai pamatā tīra enantiomēra formā, vai jebkura iepriekšminētā savienojuma sāls veidā.

Nitrogen containing heterocyclic compounds in racemic form or in the form of individual enantiomers thereof

The invention relates to new chemicals substances having valuable pharmacological properties, especially to nitrogen containing heterocyclic compounds of the general formula (I)



wherein

X is O or S;

Y is C or N;

Z is C or N;

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

R_1 and R_2 are each, independent 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 hydrogen, C_1-C_3 alkyl, methoxy or together with N form a morpholine, pyrrolidine or piperidine ring; $-NO_2$; $-NR_{10}R_{11}$ wherein R_{10} and R_{11} are 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 hydrogen or C_1-C_6 alkyl,

R_3 is 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; SO_2R_{12}; $-NHC(O)R_{12}$, $-NHSO_2R_{12}$; $-SO_2NR_{13}R_{14}$ or NO_2; or R_3 may be 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 on nitrogen with C_1-C_4 alkyl, or a 2-thiazole ring or a 2-methyl-4-thiazole ring; R_3 may also be 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; or an amide of structure $-C(O)NR_{17}R_{18}$ wherein R_{17} and R_{18} are hydrogen, C_1-C_3 alkyl, methoxy or together with N form a morpholine ring, or together with N form a 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; or a 2-, 3-, or 4-pyridyl 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 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} = 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,

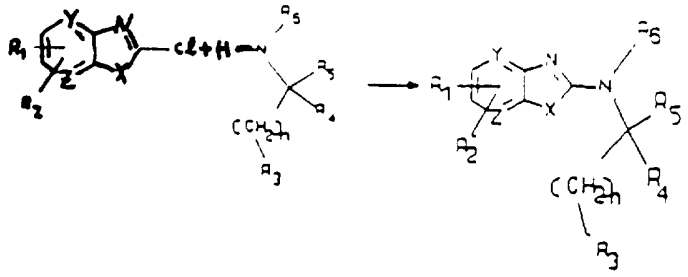
with the provisos that the following combination of substituents do not occur simultaneously: (i) Y and Z are both carbon; R_1 or R_2 are hydrogen, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, -CN, - NO_2 or $-CF_3$; R_3 is an unsubstituted phenyl; and R_4 is $-C(O)OR_{16'}$ wherein $R_{16'}$ is hydrogen, alkyl, alkenyl or alkynyl, $-C(O)N(R_{18'})(R_{19'})$ 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, -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,

in racemic form or in the form of individual enantiomers thereof which compounds are leukotriene biosynthesis inhibitors.

The novel compounds may be prepared by methods and processes 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.

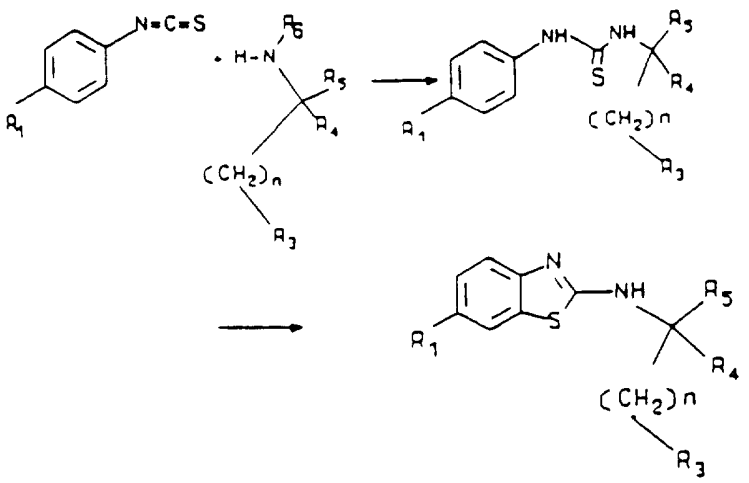
Scheme A



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.

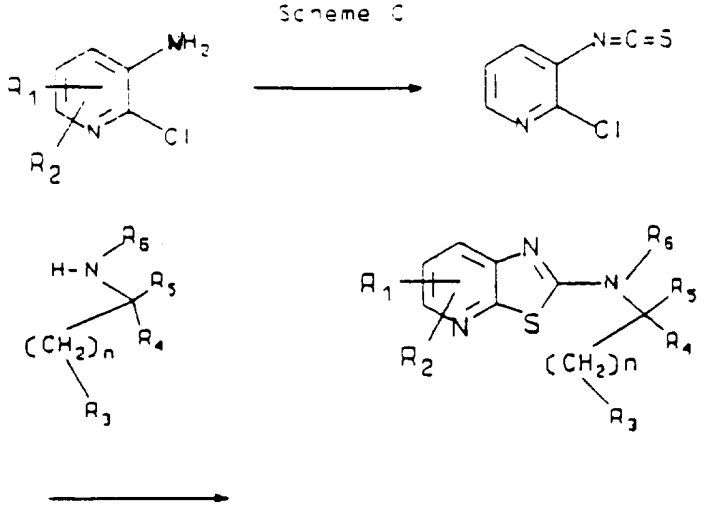
Alternatively, modification of a procedure known in the literature for preparation of 2-aminobenzothiazoles may be successfully employed for synthesis of compounds of general formula I. Such synthesis scheme is outlined hereinbelow as Scheme B.

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 with sulfuryl chloride or bromine in another inert solvent, again such as ether or perhaps chlorobenzene.

Scheme C

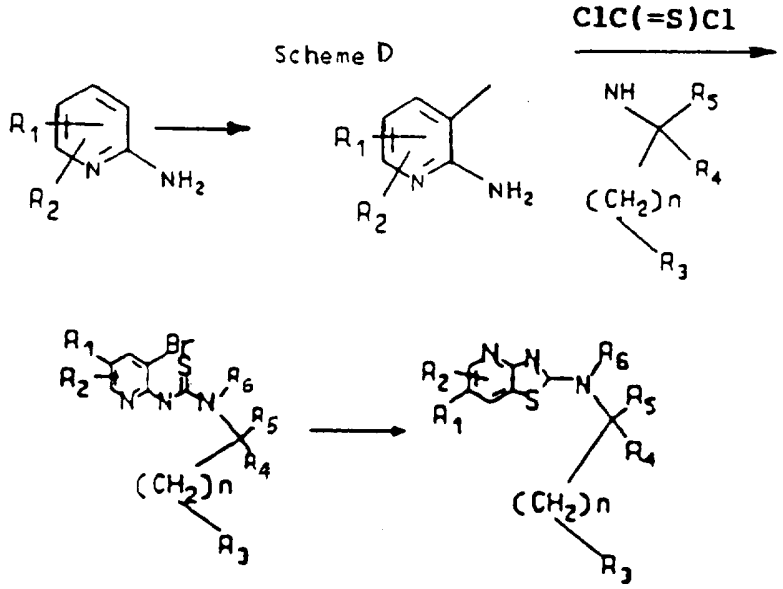


The synthesis of Scheme C can be employed for those compounds of general formula I wherein X is S and Z is N. A haloaminopyridine is converted to an isothiocyanate, for example by reaction with thiophosgene, in the presence of a base, such as sodium carbonate,

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

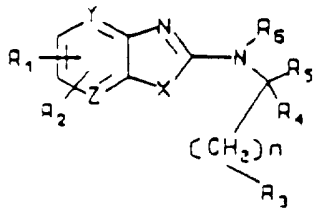
Scheme D

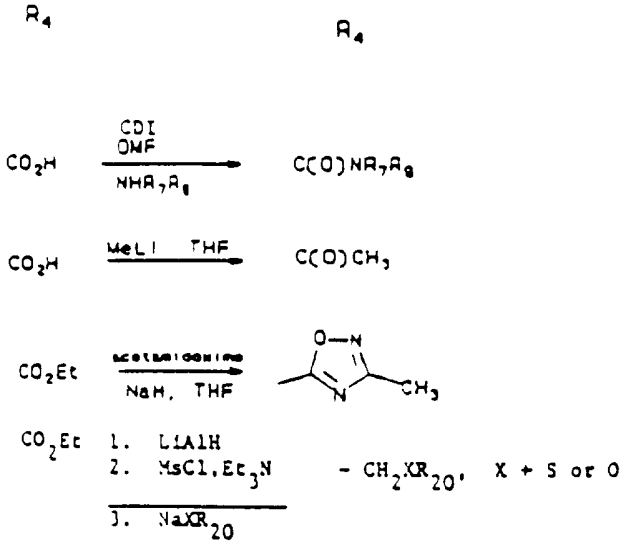


In Scheme D., the 3-halo-2-thiourea pyridine is heated in an inert solvent with base catalysis, for example K_2CO_3 in DMF. The intermediate 2-amino-3-halopyridine may be prepared, for example, by bromination of an optionally substituted 2-aminopyridine. The isothiocyanate may be prepared as described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

Scheme E





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 methods and schemes outlined hereinabove, if the starting amines used in Schemes I and II 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 follwoing examples show the preparation of novel compounds of general formula (I).

Example 1

Thionyl chloride (3.82 g, 32.1 mmol) was added dropwise to DL-N-(Benzothiazol-2-yl)phenylalanine hydrochloride (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 giving 2.25 g (6.9 mmol, 64%) mp 137-139°C.

Example 2

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

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, 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.

In analogous way the compounds of Tables 1 - 5 are prepared.

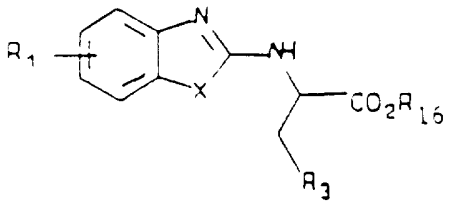


Table 1:

Comp No.	D/L[a]	R_1	R_3[b]	R_{16}	X	mp °C
1	DL	H	Ph4Cl	Et	S	Oil
2	DL	H	Ph4F	Et	S	129-131
3	DL	H	Ph4Br	Et	S	104-106
4	L	H	Ph4OBZ	Et	S	Oil
5	L	6-iPr	Ph	Et	S	Oil
6	L	6-iPr	Ph	Me	S	114-115
7	DL	6-OMe	Ph4Cl	Et	S	129-131
8	D	6-iPr	Ph	Me	S	115-116
9	DL	6-nBu	Ph4Cl	Et	S	113-114
10	L	6-Et	Ph	Et	S	102-104
11	L	H	Ph	t-Bu	S	50-52
12	L	5-Et	Ph	Et	S	Oil
13	L	5-Et	Cyh	Et	S	Oil
14	L	H	Cyh	Et	S	resin
15	L	H	Ph	Et	O	Oil
16	D	H	Ph	Et	O	Oil
17	L	5-iPr	Ph	Et	O	Oil
18	L	6-iPr	Ph	Et	O	Oil
19	L	H	Cyh	Me	O	Oil
20	D	H	Cyh	Me	O	Oil
21	L	5-iPr	Cyh	Me	O	Oil
22	L	5-Me	Cyh	Me	O	Oil
23	L	5-Me	Cyh	t-Bu	O	Oil
24	D	5-Me	Cyh	Me	O	Oil
25	DL	5-OMe	2Me4Thz	Et	O	Oil
26	DL	5-Cl	2-Thz	Et	O	Oil
27	DL	5-Cl	2Me4Thz	Et	O	Oil
28	DL	5-iPr	3-Py	Et	O	Oil
29	DL	5-iPr	4-Py	Et	O	Oil
30	DL	5-OMe	3-Py	Et	O	Oil
31	DL	5-iPr	2Me4Thz	Et	O	Oil

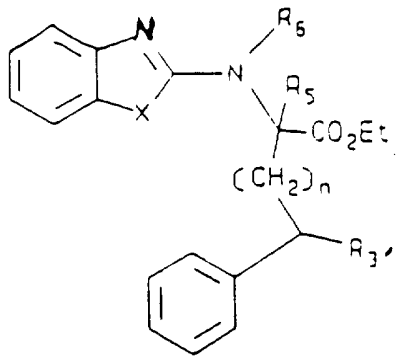
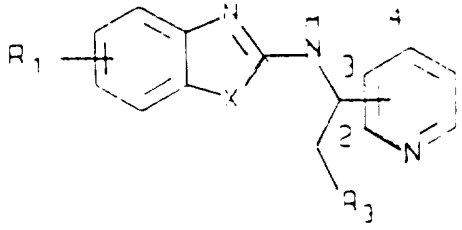


Table 1 (Continued)

Comp No.	D/L	R_6	R_5	$R_{3'}$	n	x	mp
32	DL	H	H	CH_3	0	S	Oil
33	DL	H	H	CH_3	0	S	Oil
34	DL	CH_3	H	H	0	S	Oil
35	DL	H	H	H	1	S	69.5-72
36	DL	H	CH_3	H	0	S	97-98
37	DL	H	CH_3	H	0	O	89-91.5

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

Table 2:



Comp. No.	D/L	X	R_1	R_3[a]	Pyridyl Isomer	mp°C
38	DL	O	H	Cyh	3	Resin
39	DL	O	5-Me	Cyh	2	104-105
40	DL	O	5-Me	Cyh	3	150-151
41	DL	O	5-Me	Cyh	4	188-189
42	DL	O	6-NO_2	Cyh	3	186-187.5
43	DL	O	5-NO_2	Cyh	3	189-190
44	DL	O	5-Cl	Cyh	3	186-187
45	(-)*	O	5-Me	Cyh	2	Oil
46	(+)*	O	5-Me	Cyh	2	Oil
47	(-)*	O	5-Me	Cyh	3	150-151
48	(+)*	O	5-Me	Cyh	3	150-151
49	DL	O	5-Cl	Cyh	2	132-134
50	DL	O	5-CO_2Me	Cyh	2	129-131
51	DL	O	5-Cl	Ph4F	2	112-114
52	DL	O	5-iPr	Ph4F	2	56-58
53	DL	O	5-CF_3	Cyh	2	91-93
54	DL	S	5-Cl	Ph4F	2	133-135
55	DL	S	5-Cl	Cyh	2	129-132
56	DL	O	5-iPr	Ph4Cl	2	65-67
57	DL	O	5-Cl	Ph4Cl	2	132-134
58	DL	O	5-iPr	Ph3Cl	2	51-52
59	DL	O	5-CO_2Me	Ph4F	2	151-152
60	DL	S	5-Cl	Cyh	2	129-132

* (-) and (+) refer to the levorotatory 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.

Table 2 con't:

Comp. No.	D/L	X	R_1	R_3[a]	Pyridyl Isomer	mp°C
61	DL	O	5-SO_2NMe_2	Ph4F	2	178-179
62	DL	O	5-Cl	Ph4NO_2	2	72-74
63	DL	O	5-F	Ph3Cl	2	131-133
64	DL	S	6-CF_3	Ph4F	2	149-150
65	DL	O	5-CF_3	Ph4F	2	105-107
66	DL	O	5-CF_3	Cyh	2	91-93
67	DL	O	5-F	Cyh	2	142-143.5
68	DL	O	5-F	Ph4F	2	117-119.5
69	DL	O	4,5-diF	Cyh	2	133-134
70	DL	O	5,6-diF	Cyh	2	131-133
71	DL	O	5,6-diF	Ph4F	2	143-144.5
72	DL	O	5-OMe	Ph4F	2	111-113
73	DL	O	5-NO_2	Ph4F	2	174-175
74	DL	O	5-iPr	2Me4Thz	2	116-117
75	DL	O	5-Cl	2Me4Thz	2	142-143
76	(-)*	O	5-Cl	Ph4F	2	Oil
77	(+)*	O	5-Cl	Ph4F	2	Oil

a. See footnote b, Table 1.

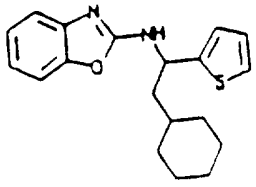


Table 3:

Comp. No.	D/L	mp°C
78	DL	108-110

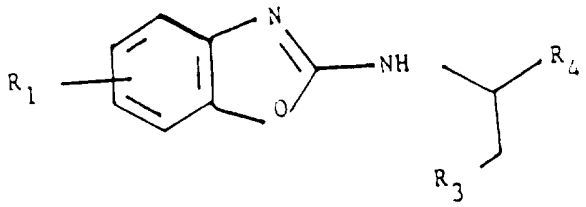
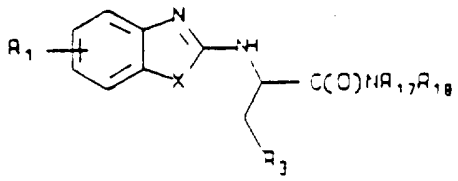


Table 4:

Comp. No.	D/L	R_1	R_3[a]	R_4	mp°C
79	L	5-iPr	Ph	CH_2OEt	Oil
80	L	5-iPr	Ph	CH_2OPr	Oil
81	L	5-Cl	Ph	CH_2OEt	Oil
82	DL	5-iPr	Ph4F	CH_2OMe	Oil
83	DL	5-iPr	Ph4F	CH_2OEt	Oil
84	DL	5-iPr	Ph4F	CH_2OnPr	Oil
85	DL	5-iPr	Ph4OMe	CH_2OMe	Oil
86	DL	5-iPr	3-Py	CH_2OMe	Oil
87	DL	5-iPr	2Me4Thz	Ch_2OMe	Oil
88	L	5-iPr	Ph3Cl	CH_2SMe	Oil
89	DL	5-iPr	3-Py	CH_2SMe	Oil
90	DL	5-iPr	4-Py	CH_2SMe	Oil
91	DL	5-iPr	2Me4Thz	CH_2SMe	Oil
92	DL	5-iPr	Ph	CH_2SO_2Me	resin
93	DL	5-iPr	3-Py	CH_2SO_2Me	88-92
94	DL	5-iPr	4-Py	CH_2SO_2Me	78-81
95	DL	5,6-diF	Ph4F	CH_2SO_2Me	179-181
96	L	5-iPr	Ph	CH_2NMe_2	Oil
97	L	5-iPr	Ph	$CH_2NHC(O)Me$	resin
98	L	5-iPr	Ph	$CH_2NHSO_2NMe_2$	resin
99	L	5-iPr	Ph	$CH_2NHC(O)NH_2$	resin
100	L	5-iPr	Ph	$CH_2OC(O)NHMe$	125-126

a. See footnote b, Table 1

Table 5



Comp No.	D/L	R_1	R_3[a]	R_{17}	R_{18}	X	m.p.°C
101	L	H	Ph	H	H	S	94-96
102	DL	H	Ph	Me	Me	S	Oil
103	DL	6-iPr	Ph	Et	H	S	161-163
104	L	H	Ph	Me	OMe	O	Resin
105	L	5-Me	Cyh	Me	OMe	O	Resin
106	L	5-Me	Cyh	b	b	O	Resin

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

Example 3

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

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.

In analogous way the compounds of Table 6 are prepared.

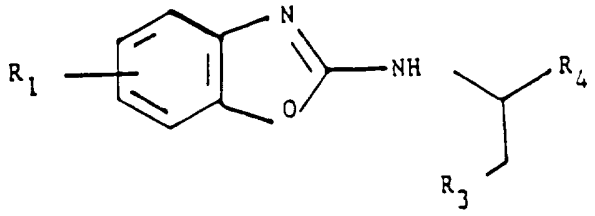


Table 6:

Comp. No.	D/L	R_1	R_3[a]	R_4[b]	mp°C
107	DL	5-Cl	Ph4F	2-Imid	248-250
108	DL	5-iPr	Ph4F	2-Imid	213-219
109	DL	5-iPr	2-Me4Thz	2-Imid	153-155
110	DL	5-iPr	Ph3Cl	2-Imid	210-213
111	DL	5-iPr	Ph3Cl	2-Thz	resin
112	DL	5-iPr	Ph3Cl	4Me2Thz	resin
113	DL	5-iPr	Ph	4-Pyraz	206-210

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

Example 4

2-(2-Cyclohexyl-1-phenylethylaminobenzoxazole

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.

In analogous way the compounds of Table 7 are prepared.

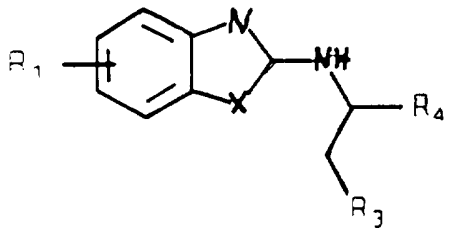


Table 7:

Table 3

Comp. No.	D/L[a]	R_1	R_3[b]	R_4[b]	X	m.p. °C
114	DL	H	Ph	Ph	S	54-56
115	'L'	H	Ph	Ph	S	Oil
116	'D'	H	Ph	Ph	S	Oil
117	DL	H	Ph	Ph	O	154-156
118	'D'	H	Cyh	Ph	O	141-143
119	'L'	H	Cyh	Ph	O	135.5-137
120	DL	5-iPr	Cyh	Ph	O	119-122
121	DL	H	Cyh	Ph4Cl	O	142-144
122	DL	H	Cyh	Ph4OMe	O	63-67
123	DL	H	Cyh	Ph3Me	O	136-138
124	DL	H	Cyh	Ph2Cl	O	146-148
125	DL	5-I	Cyh	Ph	O	186-187
126	DL	5-$NHSO_2CH_3$	Cyh	Ph	O	188-190

Table 7

Comp. No.	D/L[a]	R_1	R_3[b]	R_4[b]	X	m.p.' C
127	DL	5-$NHC(O)CH_3$	Cyh	Ph	O	145-147
128	DL	5-$NHC(O)NHCH_3$	Cyh	Ph	O	211-212
129	DL	5-CO_2H	Cyh	Ph	O	232-234
130	DL	5-$C(O)NH_2$	Cyh	Ph	O	181-183
131	DL	5-$C(O)NMe_2$	Cyh	Ph	O	194-196
132	DL	6-CO_2H	Cyh	Ph	S	271-272
133	DL	5-CN	Cyh	Ph	O	166-168
134	DL	C	Cyh	Ph	O	154-156
135	DL	CH_2OH	Cyh	Ph	O	187-189
136	DL	5-tetrazolyl	Cyh	Ph	O	188-191
137	DL	H	Cyh	Ph4F	O	144-145
138	L	5-Cl	NEt_2	Ph	O	242-244
139	L	5-iPr	$NnPr_2$	Ph	O	Oil
140	L	5-iPr	OEt	Ph	O	Oil
141	L	5-iPr	OnBu	Ph	O	Oil
142	L	5-tBu	morph	Ph	O	197-199
143	L	5-iPr	NEt_2	Ph	O	Oil
144	L	5-Cl	thiomorph	Ph	O	69-71

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

Example 5

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

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 silca 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 6

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

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 thru silica gel, eluting with CH_2Cl_2. Recrystallization from EtOH gave 0.75g product (2.2 mmol, 38%), mp 107-110°C.

In analogous way the compounds of Tables 8 - 13 are prepared.

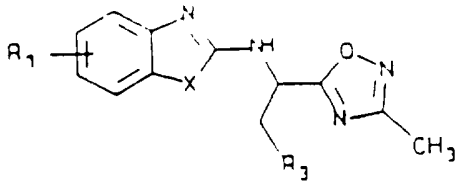


Table 8:

Comp. No.	D/L	R_1	R_3[a]	X	mp°C
145	DL	H	Ph	S	122-124
146	L	H	Ph	S	117-119
147	L	5-Et	Ph	S	134-136
148	L	H	Cyh	S	147-149
149	DL	5-iPr	Ph4F	O	86
150	DL	5-iPr	2Me4Thz	O	45-48

a. See footnote b, Table 1.

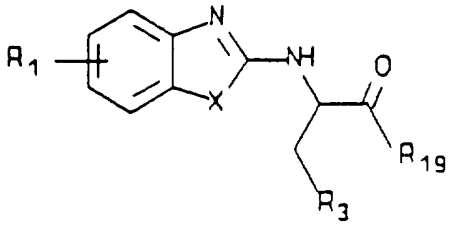


Table 9:

Comp. No.	D/L	R_1	R_3[a]	R_{19}	X	mp°C
151	L	H	Ph	CH_3	O	Oil
152	L	H	Ph	Ph	O	Resin
153	L	5-Me	Cyh	Ph	O	Resin
154	L	5-Me	Cyh	b	O	Resin

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

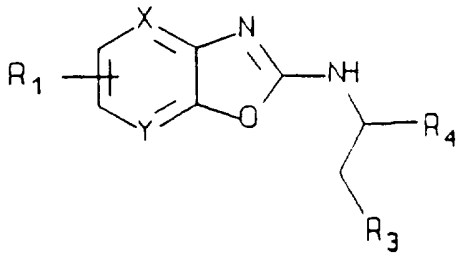


Table 10:

Comp. No.	D/L	X	Y	R_1	R_3[a]	R_4[a]	mp°C
155	L	N	C	H	Cyh	CO_2Me	147-149
156	DL	N	C	H	Cyh	Ph	189-190.5
157	DL	N	C	5-Me	Cyh	Ph	199-200
158	DL	N	C	5-Me	Cyh	2-Py	134-136
159	(-)*	N	C	5-Me	Cyh	2-Py	68-75
160	(+)*	N	C	5-Me	Cyh	2-Py	68-75
161	DL	N	C	5-Me	Cyh	3-Py	207-208
162	DL	N	C	S-Me	Ph4F	2-Py	66-69
163	DL	C	N	H	Cyh	Ph	133-134
164	DL	C	N	5-Me	Cyh	Ph	188-191

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

* See * Table 2.

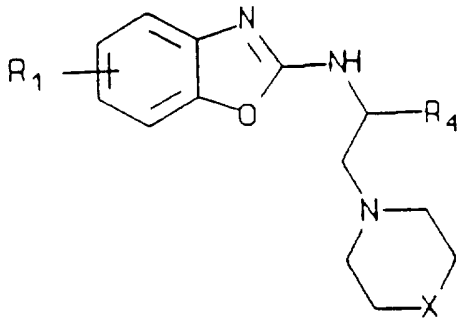


Table 11:

Comp. No.	DL	R_1	R_4	X	mp°C
165	L	5-iPr	Ph[b]	C	165[a]
166	L	5-Me	Ph	C	>150[a]
167	L	5-iPr	2-Py	C	128
168	L	5-iPr	2-Py	O	135-137.5

a. Dihydrochloride salt, broad melting range. (No. 143)
b. See footnote b, Table 1.

c. 2-Py = 2-pyridyl

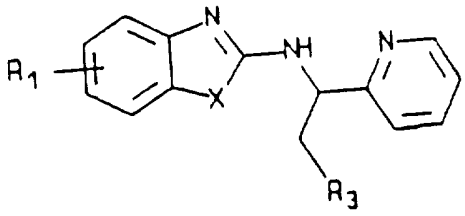


Table 12:

Comp. No.	DL	R_1	R_3[a]	mp°C
169	DL	5-Cl	2-Py	180-183
170	DL	5-iPr	2-Py	150-151[b]
171	DL	5-iPr	4-Py	145[b]
172	DL	5-iPr	3-Py	resin

a. 2-Py - 2-pyridyl, 4-Py = 4-Pyridyl, 3-Py = 3-Pyridyl
b. Tosylate salt

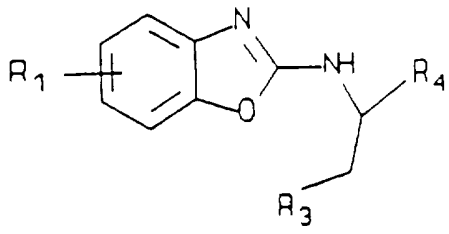


Table 13:

Comp. No.	DL	R_1	R_2	R_3	mp
173	L	5-iPr	$-CO_2Me$	C	143-146[a]
174	DL	5-iPr	d	Ph3Cl	168.5-170

a. Hydrochloride Salt
b. 1-methyl-imidazol-4-yl
c. 1-methyl-imidazol-2yl

Example 7

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

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.

Example 8

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

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.

In analogous way the compounds of Table 14 are prepared.

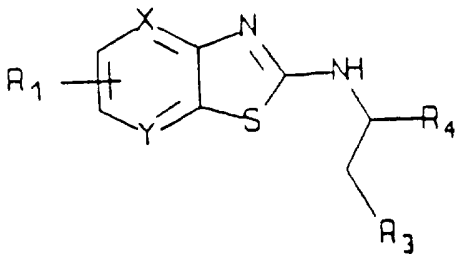


Table 14:

Comp. No.	DL	X	Y	R_1	R_4[b]	R_3[b]	mp°C
175	DL	C	N	H	3-Py	Cyh	222-224[a]
176	DL	C	N	H	2-Py	Cyh	176-178[a]
177	DL	C	N	5-Me-6-Br	2-Py	Cyh	215-217
178	DL	C	N	5-Me	2-Py	Cyh	109-113
179	DL	C	N	5-Me	3-Py	Cyh	174-175.5
180	DL	C	N	6-Cl	3-Py	Cyh	207-209
181	DL	C	N	6-Cl	2-Py	Cyh	180-182
182	DL	C	N	4-Me	2-Py	Cyh	144-146
183	DL	C	N	6-Cl	3-Py	Cyh	207-209
184	DL	C	N	6-Cl	2-Py	Ph4F	151-153
185	DL	C	N	5-Cl	2-Py	Ph4F	146-149
186	DL	N	C	6-Me	2-Py	Cyh	214-216
187	DL	N	C	5-Me-6-Br	2-Py	Cyh	209-210
188	DL	N	C	5-Me-6-Br	3-Py	Cyh	241-243.5
189	DL	N	C	5-Me	2-Py	Cyh	167-171
190	DL	N	C	6-Cl	2-Py	Cyh	198.5-200.5
191	DL	N	C	6-Cl	2-Py	Ph4F	204-205
192	DL	C	N	5-Me-6-Br	3-Py	Cyh	211-212
193	DL	N	C	6-Me	2-Py	Ph4F	184-185

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

Pharmacology

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 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 Tables 15 and 16 show % inhibition of LTB_4 biosynthesis by compounds of the invention at test concentrations indicated, with the determined IC_{50} shown in μM.

Table 15

Compound of example No.	IC_{50} (μM)
1	0.4
2	0.33
3	0.072
4	0.0069
5	0.028
6	0.35
7	0.027
8	< 1.0[a]

[a] greater than 50 % at this concentration

Table 16

Compound of example No.	IC_{50} (µM)
1	0.2
2	0.33
3	0.15
4	0.53
5	0.25
6	0.14
7	0.23
8	0.65
9	0.17
10	0.24
11	0.73
12	0.009
13	0.027
14	0.006
15	0.15
16	1.5
17	0.00052
18	0.22
19	0.0064
20	0.10
21	0.001
22	0.0017
23	< 0.3[a]
24	0.016
25	< 0.3[a]
26	< 0.3[a]
27	0.081
28	0.19
29	< 0.1[a]
31	< 0.03[a]
32	1.4
33	0.68
34	1.0
35	0.52
36	0.20
37	0.076
38	0.055
39	0.0031
40	0.024
41	0.19
42	0.035

[a] greater than 50 % at this concentration

Table 16 (continued)

Compound of example No.	IC_{50} (μM)
43	0.024
44	0.023
45	0.0013
46	0.045
47	0.016
48	< 1.0
49	0.002
50	0.012
51	0.019
52	0.012
53	0.0012
54	0.027
55	0.004
56	0.029
57	0.014
58	0.005
59	0.027
60	0.004
61	0.050
62	< 0.03[a]
63	< 0.03[a]
64	< 1.0[a]
65	0.008
66	0.001
67	0.002
68	0.021
69	0.004
70	0.001
71	0.024
72	0.011
73	< 0.03[a]
74	< 0.1[a]
75	< 0.1[a]
76	0.01
77	0.32
78	0.0062
79	0.016
80	0.22
81	0.029
82	< 0.03[a]
83	< 0.03[a]
84	< 0.3[a]

[a] greater than 50 % at this concentration

Table 16 (continued)

Compound of example No.	IC_{50} (µM)
85	< 0.03[a]
86	< 1.0[a]
87	< 0.3[a]
88	< 0.03[a]
89	< 1.0[a]
91	< 0.1[a]
92	< 0.03[a]
93	< 1.0[a]
96	< 0.3[a]
97	< 0.1[a]
98	< 0.1[a]
99	< 0.3[a]
100	0.063
101	3
102	3
103	3
104	< 1[a]
105	0.03
106	0.19
107	0.29
108	0.29
109	< 1.0[a]
110	< 0.03[a]
111	< 0.1[a]
112	< 0.03[a]
113	< 0.01[a]
114	0.16
115	0.082
116	0.28
117	< 1.0[a]
118	0.26
119	0.0036
120	0.0063
121	0.3
122	0.55
123	0.30
124	0.08
125	0.013
126	0.16
127	0.076
128	< 1.0[a]

[a] greater than 50 % at this concentration

Table 16 (continued)

Compound of example No.	IC_{50} (μM)
129	0.19
130	< 1.0[a]
131	0.17
132	0.22
133	0.15
134	< 1.0[a]
135	< 1.0[a]
136	0.16
137	0.17
138	0.35
139	< 300[a]
140	0.11
141	0.055
142	< 0.03[a]
143	< 0.3[a]
144	0.048
145	1.3
146	1.8
147	< 1.0[a]
148	0.12
149	< 0.3[a]
150	< 1.0[a]
151	< 1.0
152	< 0.3
153	< 1.0
154	0.023
155	0.21
156	0.078
157	0.028
158	0.026
159	0.015
160	0.17
161	0.3
162	< 0.3[a]
163	0.021
164	0.044
165	0.1
166	0.23
167	0.19
168	< 0.1[a]

[a] greater than 50 % at this concentration

Table 16 (continued)

Compound of example No.	IC_{50} (μM)
169	0.22
170	0.12
171	< 0.3[a]
172	< 0.3[a]
173	< 1[a]
174	< 0.1[a]
175	0.17
176	0.027
177	0.009
178	0.01
179	0.11
180	0.044
181	0.006
182	< 1.0[a]
183	0.044
184	0.110
185	0.280
186	0.031
187	0.0065
188	0.021
189	0.013
190	0.0039
191	0.028
192	< 1.0[a]
193	< 0.3[a]

[a] greater than 50 % at this concentration

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.

Table 16

Compound No.	Dose (Micrograms)*	N	% Inhibition
example 4	274	6	86
123	95	6	43
40	308	6	64
	28	4	64
	2.8	10	61
159	274	7	84
	28	6	64
	5.6	4	0

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

Antigen-induced mediator release in primates.

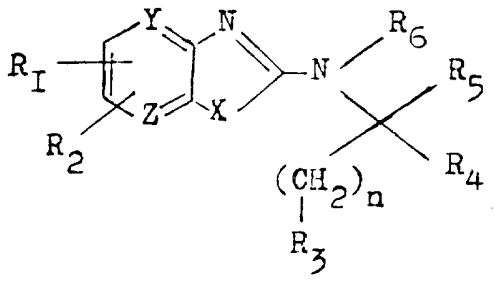
This model measures the ability of a compound to inhibit the formation of leukotriene C_4 (LTC_4) in the lungs of allergic cynomolgus monkeys following antigen challenge. Animals are anesthetized, intubated, and challenged with an Ascaris suum extract, given by aerosol. A bronchoalveolar lavage is performed 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.

Table 17

Compound No.	Dose(mg/mL)	N	% Inhibition
example 4	0.3	5	40
	1.0	5	60
	3.0	5	68
46	0.01	5	8
	0.03	4	63
	0.10	5	61
	0.30	4	82
	1.0	6	89
	10.0	4	96
77	0.01	5	8
	0.03	4	32
	1.0	6	76

WHAT IS CLAMED IS:

1.Nitrogen containing heterocyclic compounds having the folowing formula:



FORMULA 1

wherein

X is O or S;

Y is C or N;

Z is C or N;

with the proviso that Y and Z are not both N; R_1 and R_2 are each, independent of one another, hydrogen; C_1-C_6alkyl; halo; CF_3; nitrile; C_1-C_6alkoxy; $-CO_2R_7$ wherein R_7 is hydrogen or C_1-C_6alkyl; $-C(O)NR_8R_9$ wherein R_8 and R_9 are independently hydrogen, C_1-C_3alkyl, methoxy or together with N form a

piperidine ring, $-NO_2$; $-NR_{10}R_{11}$, wherein R_{10} and R_{11} are hydrogen or C_1-C_6alkyl; $-C(O)R_{12}$ wherein R_{12} is C_1-C_6alkyl; $-SO_2R_{12}$; $-NHC(O)R_{12}$; $-NHSO_2R_{12}$; or $-SO_2NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently hydrogen or C_1-C_6alkyl;

R_3 is methyl, cyclohexyl or an optionally substituted phenyl ring wherein the substituents are selected from halo, CF_3, C_1-C_4alkyl and C_1-C_4alkoxy; $-SO_2R_{12}$; $-NHC(O)R_{12}$;$-NHSO_2R_{12}$; $-SO_2NR_{13}R_{14}$, wherein R_{12}, R_{13} and R_{14} are as defined above, or NO_2; or R_3 may be 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 on nitrogen with C_{1-4}alkyl, a 2-thiazole ring or a 2-methyl-4-thiazole ring; R_3 may also be a dialkylamine (C_1-C_4) or an alkyl ether (C_1-C_4);

R_4 is an ester $-CO_2R_6$ wherein R_6 is C_1-C_4alkyl; or an amide of structure $-C(O)NR_{17}R_{18}$ wherein R_{17} and R_{18} are independently hydrogen, C_1-C_3alkyl, methoxy or together with N form a morpholine ring, or together with N form a piperidine or pyrrolidine ring; an optionally substituted phenyl ring wherein the substituents are selected from halo, C_1-C_4alkyl and C_1-C_4alkoxy; a 3-methyl-1,2,4-oxadiazol-5-yl group; a 2- or 3-thienyl group; or a 2-, 3-, or 4-pyridyl group; a 4-pyrazolyl group, 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_3alkyl, phenyl or 1-methylimidazol-2-yl; an ether $-CH_2OR_{20}$ where R_{20} is C_1-C_3alkyl, 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 $NHCH_3$, $-CH_2NHSO_2Me$; or a carbamate, $-CH_2OC(O)NHMe$;

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

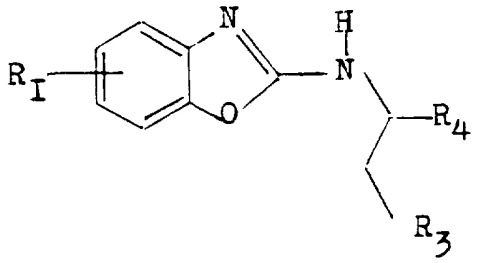
n is a integer 0, 1 or 2,

with the provisos that the following combination of substituents do not occur simultaneously; (1) Y and Z are both carbon; R_1 or R_2 are hydrogen, halo, C_1-C_4akoxy, -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, $-C(O)N(R_{18})(R_{19})$ wherein R_{18} and R_{19} are hydrogen, C_1-C_6alkyl, phenyl or alkoxy or together with N form a pyrrolidine, piperidine or morpholine ring, -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, in racemic form or in the form of individual enantiomers thereof and salts thereof.

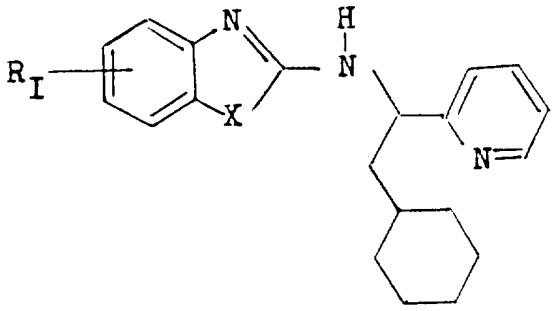
2. The compound as recited in claim 1 wherein R_1 is in the 5-position and is C_1-C_3alkyl or halo,
R_2 is hydrogen,
R_3 is cyclohexyl,
R_4 is 2-pyridyl or 3-pyridyl,
R_5 is hydrogen,
R_6 is hydrogen,
X is O or S,
and N is 1.

3. The compound as recited in claim 1



wherein
R_1 is hydrogen,
R_3 is cyclohexyl and
R_4 is phenyl.

4. The compound as recited in claim 1



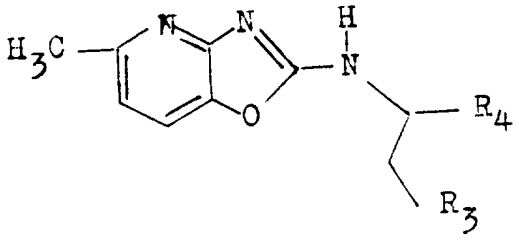
wherein

X is oxygen

and R_1 is 5-methyl.

5. The compound as recited in claim 4,the L-enantiomer thereof.

6. The compound as recited in claim 1

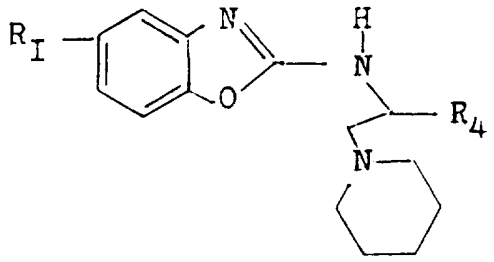


wherein

R_4 is cyclohexyl and

R_3 is 2-pyridine.

7. The compound as recited in claim 1



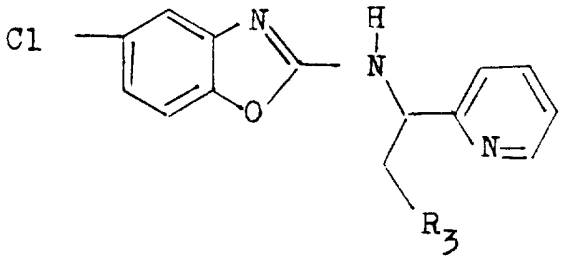
wherein

R_1 is isopropyl and

R_4 is phenyl,

the L-enantiomer.

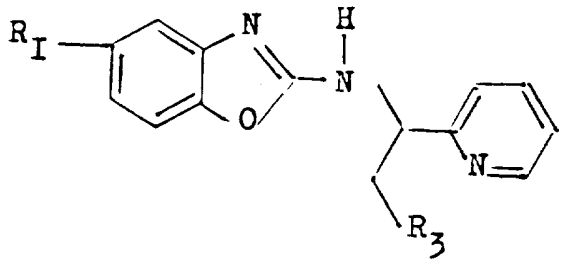
8. The compound as recited in Claim 1



wherein

R_3 is cyclohexyl.

9. The compound as recited in Claim 1



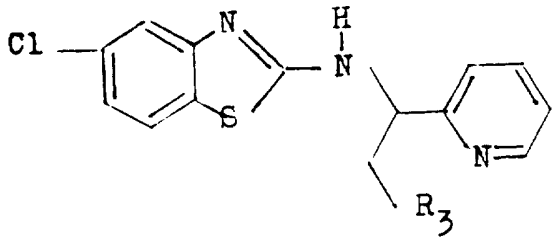
wherein

R_1 is isopropyl, methyl, chloro or methoxy

and

R_3 is 4-fluorophenyl.

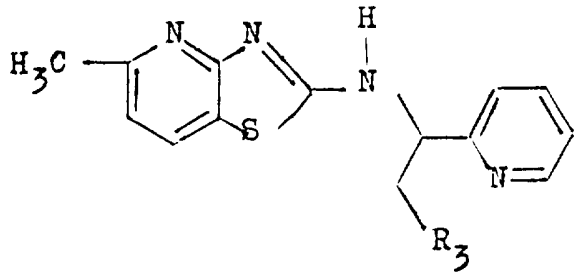
10. The compound as recited in claim 1



wherein

R_3 is 4-fluorophenyl or cyclohexyl.

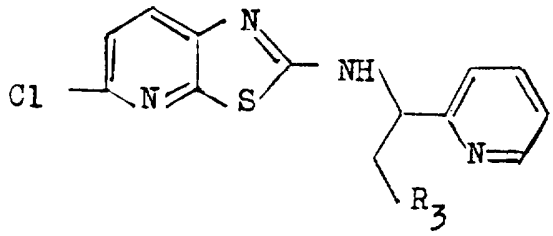
11. The compound as recited in Claim 1



wherein

R_3 is cyclohexyl.

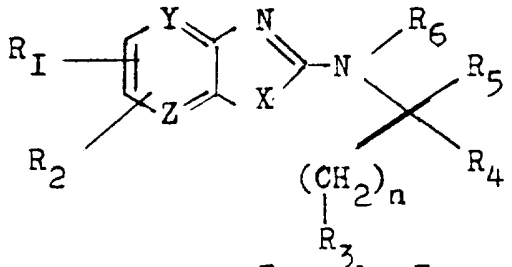
12. The compound as recited in claim 1



wherein

R_3 is cyclohexyl.

13. A pharmaceutical composition of matter comprising a compound having the following formula



Formula I

wherein

X is O or S;

Y is C or N;

Z is C or N;

with the proviso that Y and Z are not both N; R_1 and R_2 are each, independent of one another, hydrogen; C_1-C_6alkyl; halo; CF_3; nitrile; C_1-C_6alkoxy; $-CO_2R_7$ wherein R_7 is hydrogen or C_1-C_6alkyl; $-C(O)NR_8R_9$ wherein R_8 and R_9 are independently hydrogen, C_1-C_3alkyl, methoxy or together with N form a piperidine ring, $-NO_2$; $-NR_{10}R_{11}$, wherein R_{10} and R_{11} are hydrogen or C_1-C_6alkyl; $-C(O)R_{12}$ wherein R_{12} is C_1-C_6alkyl; $-SO_2R_{12}$; $-NHC(O)R_{12}$;$-NHSO_2R_{12}$; or $-SO_2NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently hydrogen or C_1-C_6alkyl;

R_3 is methyl, cyclohexyl or an optionally substituted phenyl ring wherein the substituents are selected from halo, CF_3, C_1-C_4alkyl and C_1-C_4alkoxy; $-SO_2R_{12}$; $-NHC(O)R_{12}$;$-NHSO_2R_{12}$; $-SO_2NR_{13}R_{14}$, wherein R_{12}, R_{13} and R_{14} are as defined above, or NO_2; or R_3 may be 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 on nitrogen with C_{1-4}alkyl, a 2-thiazole ring or a 2-methyl-4-thiazole ring; R_3 may also be a dialkylamine (C_1-C_4) or an alkyl ether (C_1-C_4); R_4 is an ester $-CO_2R_6$ wherein R_6 is C_1-C_4alkyl; or an amide of structure $-C(O)NR_{17}R_{18}$ wherein R_{17} and R_{18} are independently hydrogen, C_1-C_3alkyl, methoxy or together with N form a morpholine ring, or together with N form a piperidine or pyrrolidine ring; an optionally substituted phenyl ring wherein the substituents are selected from halo, C_1-C_4alkyl and C_1-C_4alkoxy; a 3-methyl-1,2,4-oxadiazol-5-yl group; a 2- or 3-thienyl group; or a 2-, 3-, or 4-pyridyl group; a 4-pyrazolyl group, 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_3alkyl, phenyl or 1-methylimidazol-2-yl; an ether $-CH_2OR_{20}$ where R_{20} is C_1-C_3alkyl, a thioether, $-CH_2SR_{20}$; a sulfone,

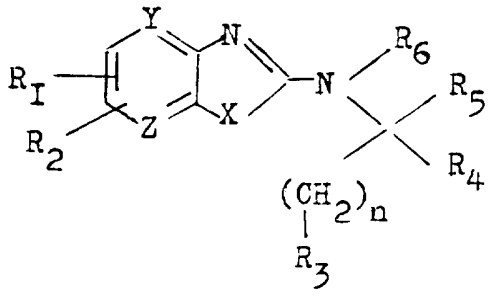
$-CH_2SO_2CH_3$; an amine, $-CH_2N(R_{20})_2$; an amine derivative, $-CH_2NHC(O)R_{21}$, where R_{21} is CH_3, NH_2, or $NHCH_3$, $-CH_2NHSO_2Me$; or a carbamate, $-CH_2OC(O)NHMe$;

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

n is a integer 0, 1 or 2,

in racemic form or in the form of individual enantiomers thereof and salts thereof.

14. Use of a compound for manufacturing a medicament for treating a disease in a warm-blooded animal through inhibition of leukotriene biosynthesis, the compound having the following formula (1)



Formula 1

wherein

X is O or S;

Y is C or N;

Z is C or N;

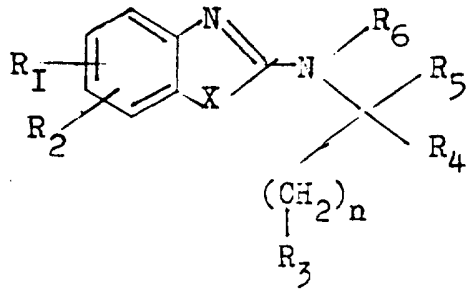
with the proviso that Y and Z are not both N; R_1 and R_2 are each, independent of one another, hydrogen; C_1-C_6alkyl; halo; CF_3; nitrile; C_1-C_6alkoxy; $-CO_2R_7$ wherein R_7 is hydrogen or C_1-C_6alkyl; $-C(O)NR_8R_9$ wherein R_8 and R_9 are independently hydrogen, C_1-C_3alkyl, methoxy or together with N form a piperidine ring, $-NO_2$; $-NR_{10}R_{11}$, wherein R_{10} and R_{11} are hydrogen or C_1-C_6alkyl; $-C(O)R_{12}$ wherein R_{12} is C_1-C_6alkyl; $-SO_2R_{12}$; $-NHC(O)R_{12}$; $-NHSO_2R_{12}$; or $-SO_2NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently hydrogen or C_1-C_6alkyl; R_3 is methyl, cyclohexyl or an optionally substituted phenyl ring wherein the substituents are selected from halo, CF_3, C_1-C_4alkyl and C_1-C_4alkoxy; $-SO_2R_{12}$; $-NHC(O)R_{12}$;$-NHSO_2R_{12}$; $-SO_2NR_{13}R_{14}$, wherein R_{12}, R_{13} and R_{14} are as defined above, or NO_2; or R_3 may be 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 on nitrogen with C_{1-4}alkyl, a 2-thiazole ring or a 2-methyl-4-thiazole ring; R_3 may also be a dialkylamine (C_1-C_4) or an alkyl ether (C_1-C_4); R_4 is an ester $-CO_2R_6$ wherein R_6 is C_1-C_4alkyl; or an amide of structure $-C(O)NR_{17}R_{18}$ wherein R_{17} and R_{18} are independently hydrogen, C_1-C_3alkyl, methoxy or together with N form a morpholine ring, or together with N form a piperidine or pyrrolidine ring; an optionally substituted phenyl ring wherein the substituents are selected from halo, C_1-C_4alkyl and C_1-C_4alkoxy; a 3-methyl-1,2,4-oxadiazol-5-yl group; a 2- or 3-thienyl group; or a 2-, 3-, or 4-pyridyl group; a 4-pyrazolyl group, 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_3alkyl, phenyl or 1-methylimidazol-2-yl; an ether $-CH_2OR_{20}$ where R_{20} is C_1-C_3alkyl, 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 $NHCH_3$, $-CH_2NHSO_2Me$; or a carbamate, $-CH_2OC(O)NHMe$;

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

n is a integer 0, 1 or 2,

in racemic form or in the form of individual enantiomers thereof and salts thereof.

15. A compound having the following formula:



wherein

X is O;

R_1 and R_2 are each, independent of one another, hydrogen; C_1-C_6alkyl; halo; CF_3; nitrile; C_1-C_6alkoxy; $-CO_2R_7$, wherein R_7 is hydrogen or C_1-C_6alkyl; $-C(O)NR_8R_9$ wherein R_8 and R_9 are independently hydrogen, C_1-C_3alkyl, methoxy or together with N form a piperidine ring; $-NO_2$; $-NR_{10}R_{11}$ wherein R_{10} and R_{11} are hydrogen or C_1-C_6alkyl; $-C(O)R_{12}$, wherein R_{12} is C_1-C_6alkyl; $-SO_2R_{12}$; $-NHC(O)R_{12}$; $-NHSO_2R_{12}$; or $-SO_2NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently hydrogen or C_1-C_6alkyl;

R_3 is methyl,cyclohexyl or an optionally substituted phenyl ring wherein the substituents are selected from halo, CF_3, C_1-C_4alkyl, C_1-C_4alkoxy, $-C(O)R_{12}$, wherein R_{12} is C_1-C_6alkyl; $-SO_2R_{12}$; $-NHC(O)R_{12}$; $-NHSO_2R_{12}$; or $-SO_2NR_{13}R_{14}$, wherein R_{12}, R_{13} and R_{14} are as defined above, or NO_2; or R_3 may be a 1-piperidinyl ring, a pyridine ring, a morpholine ring, a pyrrolidine ring, a

piperidino or an imidazole ring optionally substituted on nitrogen with C_1-C_4alkyl;

R_4 is an ester -CO_2R_{16} wherein R_{16} is C_1-C_4alkyl; or an amide of structure -$C(O)NR_{17}R_{18}$ wherein R_{17} and R_{18} are independently hydrogen, C_1-C_3alkyl, methoxy or together with N form a morpholine ring, or together with N form a piperidine or pyrrolidine ring; an optionally substituted phenyl ring wherein the substituents are selected from halo, C_1-C_4alkyl and C_1-C_4alkoxy; a 3-methyl-1,2,4-oxadiazol-5-yl group; a 2- or 3-thienyl group; or a 2-, 3-, or 4-pyridyl group; a 4-pyrazolyl group, a 2-imidazole group optionally substituted on the 4-position with a methyl; an ether -CH_2OR_{20} where R_{20} is C_1-C_3alkyl, a thiother, -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_2Me or a carbamate -OC(O)NHMe; a ketone $C(O)R_{19}$ wherein R_{19} is C_1-C_3alkyl, phenyl or 1-methylimidazol-2-yl;

R_5 and R_6 are independently or each other hydrogen or methyl; and n is an integer 0, 1 or 2,

with the provisos that the following combination of substituents do not occur simultaneously:

(i) R_1 or R_2 are hydrogen, halo, C_1-C_4alkyl, C_1-C_4alkoxy, -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 alkenyl, -$C(O)N(R_{18})(R_{19})$ wherein R_{18} and R_{19} are hydrogen, C_1-C_6alkyl, phenyl or alkoxy or together with N form a pyrrolidine, piperidine or morpholine ring, -CN or -$C(S)NH_2$; or

(ii) 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, in racemic form, or the pure or substantially pure enantiomer or a salt thereof.

16. The compound as recited in claim 15 wherein

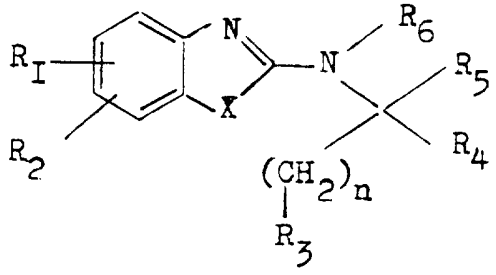
R_1 and R_2 are C_1-C_6alkyl, halo, CF_3, C_1-C_6alkoxy or -$SO_2NR_{13}R_{14}$ wherein R_{13} and R_{14} are hydrogen or C_1-C_6alkyl;

R_3 is methyl, cyclohexyl, an optionally substituted phenyl ring wherein the substituents are selected from halo, CF_3, C_1-C_4alkyl and C_1-C_4alkoxy, 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_4alkyl and C_1-C_4alkoxy, a 3-methyl-1,2,4-oxadiaxol-5-yl group; a 2-thienyl group; a 2-, 3-, or 4-pyridyl group; or a 1-methylimidazol-2-yl group,

n is 1 or 2.

17. A pharmaceutical composition of matter comprising a compound having the following formula



wherein

X is O,

R_1 and R_2 are each, independent of one another, hydrogen; C_1-C_6alkyl; halo; CF_3; nitrile; C_1-C_6alkoxy; $-CO_2R_7$, wherein R_7 is hydrogen or C_1-C_6alkyl; $-C(O)NR_8R_9$ wherein R_8 and R_9 are independently hydrogen, C_1-C_3alkyl, methoxy or together with N form a piperidine ring; $-NO_2$; $-NR_{10}R_{11}$ wherein R_{10} and R_{11} are hydrogen or C_1-C_6alkyl; $-C(O)R_{12}$, wherein R_{12} is C_1-C_6alkyl; $-SO_2R_{12}$; $-NHC(O)R_{12}$; $-NHSO_2R_{12}$; or $-SO_2NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently hydrogen or C_1-C_6alkyl;

R_3 is methyl, cyclohexyl or an optionally substituted phenyl ring wherein the substituents are selected from halo, CF_3, C_1-C_4alkyl, C_1-C_4alkoxy; $-SO_2R_{12}$; $-NHC(O)R_{12}$; $-NHSO_2R_{12}$; $-SO_2NR_{13}R_{14}$, wherein R_{12}, R_{13} and R_{14} are as defined above, or NO_2; or R_3 may be a 1-piperidinyl ring, a pyridine ring, a morpholine ring, a pyrrolidine ring, a piperidino or an imidazole ring optionally substituted on nitrogen with C_1-C_4alkyl;

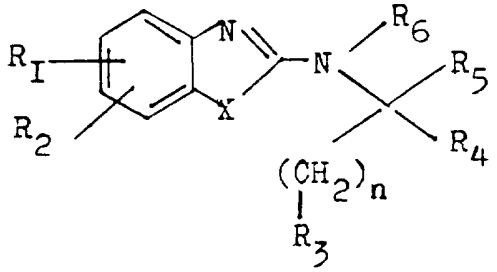
R_4 is an ester $-CO_2R_{16}$ wherein R_{16} is C_1-C_4alkyl; or an amide of structure $-C(O)NR_{17}R_{18}$ wherein R_{17} and R_{18} are independently hydrogen, C_1-C_3alkyl, methoxy or together with N form a morpholine ring, or together with N form a piperidine or pyrrolidine ring; an optionally substituted phenyl ring wherein the substituents are selected from halo, C_1-C_4alkyl and C_1-C_4alkoxy; a 3-methyl-1,2,4-oxadiazol-5-yl group; a 2- or 3-thienyl group; or a 2-, 3-, or 4-pyridyl group; a 4-pyrazolyl group, a 1-methylimidazol-2-yl group; a ketone $C(O)R_{19}$ wherein R_{19} is C_1-C_3alkyl, phenyl or 1-methylimidazol-2-yl;

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

n is an integer 0, 1 or 2,

in racemic form, or the pure or substantially pure enantiomer or a salt thereof.

18. Use of a compound for manufacturing a medicament for treating a disease in a warm-blooded animal through inhibition of leukotriene biosynthesis, the compound having the following formula:



wherein

X is O;

R_1 and R_2 are each, independent of one another, hydrogen; C_1-C_6alkyl; halo; CF_3; nitrile; C_1-C_6alkoxy; $-CO_2R_7$, wherein R_7 is hydrogen or C_1-C_6alkyl; $-C(O)NR_8R_9$ wherein R_8 and R_9 are independently hydrogen, C_1-C_3alkyl, methoxy or together with N form a piperidine ring; $-NO_2$; $-NR_{10}R_{11}$ wherein R_{10} and R_{11} are hydrogen or C_1-C_6alkyl; $-C(O)R_{12}$, wherein R_{12} is C_1-C_6alkyl; $-SO_2R_{12}$; $-NHC(O)R_{12}$; $-NHSO_2R_{12}$; or $-SO_2NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently hydrogen or C_1-C_6alkyl;

R_3 is methyl, cyclohexyl or an optionally substituted phenyl ring wherein the substituents are selected from halo, CF_3, C_1-C_4alkyl, C_1-C_4alkoxy; $-SO_2R_{12}$; $-NHC(O)R_{12}$; $-NHSO_2R_{12}$; $-SO_2NR_{13}R_{14}$, wherein R_{12}, R_{13} and R_{14} are as defined above, or NO_2; or R_3 may be a 1-piperidinyl ring, a pyridine ring, a morpholine ring, a pyrrolidine ring, a piperidino or an imidazole ring optionally substituted on nitrogen with C_1-C_4alkyl;

R_4 is an ester $-CO_2R_{16}$ wherein R_{16} is C_1-C_4alkyl; or an amide of structure $-C(O)NR_{17}R_{18}$ wherein R_{17} and R_{18} are independently hydrogen, C_1-C_3alkyl, methoxy or together with N form a morpholine ring, or together with N form a piperidine or pyrrolidine ring; an optionally substituted phenyl ring wherein the substituents are selected from halo, C_1-C_4alkyl and C_1-C_4alkoxy; a 3-methyl-1,2,4-oxadiazol-5-yl group; a 2- or 3-thienyl group; or a 2-, 3-, or 4-pyridyl group; a 4-pyrazolyl group, a 1-methylimidazol-2-yl group; a ketone $C(O)R_{19}$ wherein R_{19} is C_1-C_3alkyl, phenyl or 1-methylimidazol-2-yl;

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

n is an integer 0, 1 or 2,

in racemic form, or the pure or substantially pure enantiomer or a salt thereof.