CYCLIC PROTEIN TYROSINE KINASE INHIBITORS

This application is a continuation-in-part application of U.S. Application Serial Number 09/548,929, filed on April 13, 2000, which claims priority from provisional U.S. Application Serial No. 60/129,510, filed on April 15, 1999, the entire contents of which are incorporated herein by reference.

Field of the Invention

The present invention relates to cyclic compounds and salts thereof, to methods of using such compounds in treating protein tyrosine kinase-associated disorders such as immunologic and oncologic disorders, and to pharmaceutical compositions containing such compounds.

Background of the Invention

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

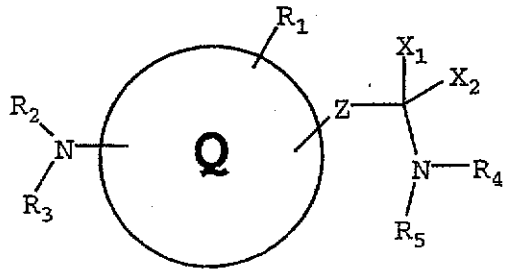
kinase activity", *Cell*, *61*, 203-212 (1990); and Ihle, J.N., "The Janus protein tyrosine kinases in hematopoetic cytokine signaling", *Sem. Immunol.*, *7*, 247-254 (1995)).

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

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

Summary of the Invention

The present invention provides cyclic compounds of the following formula I and salts thereof, for use as protein tyrosine kinase inhibitors:



I

where

Q is:

(1) a 5-membered heteroaryl ring;

(2) a 6-membered heteroaryl ring; or

(3) an aryl ring;

optionally substituted with one or more groups R_1;

Z is:

(1) a single bond;

(2) $-R_{15}C{=}CH-$; or

(3) $-(CH_2)_m-$, where m is 1 to 2;

X_1 and X_2 are each hydrogen, or together form =O or =S;

R_1 is:

(1) hydrogen or R_6,

where R_6 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, heterocyclo, or heterocycloalkyl, each of which

is unsubstituted or substituted with Z_1, Z_2 and one or more (preferably, one or two) groups Z_3;

(2) -OH or -OR_6;

(3) -SH or -SR_6;

(4) -$C(O)_2H$, -$C(O)_qR_6$, or -O-$C(O)_qR_6$, where q is 1 or 2;

(5) -SO_3H or -$S(O)_qR_6$;

(6) halo;

(7) cyano;

(8) nitro;

(9) -Z_4-NR_7R_8;

(10) -Z_4-$N(R_9)$-Z_5-$NR_{10}R_{11}$;

(11) -Z_4-$N(R_{12})$-Z_5-R_6;

(12) -$P(O)(OR_6)_2$;

R_2 and R_3 are each independently:

(1) hydrogen or R_6;

(2) -Z_4-R_6; or

(3) -Z_{13}-NR_7R_8;

R_4 and R_5:

(1) are each independently hydrogen or R_6;

(2) -Z_4-$N(R_9)$-Z_5-$NR_{10}R_{11}$;

(3) -$N(R_9)Z_4R_6$; or

(4) together with the nitrogen atom to which they are attached complete a 3- to 8-membered saturated or unsaturated heterocyclic ring which is unsubstituted or substituted with Z_1, Z_2 and Z_3, which heterocyclic ring may optionally have fused to it a benzene ring itself unsubstituted or substituted with Z_1, Z_2 and Z_3;

R_7, R_8, R_9, R_{10}, R_{11} and R_{12}:

(1) are each independently hydrogen or R_6;

(2) R_7 and R_8 may together be alkylene, alkenylene or heteroalkyl, completing a 3- to 8-membered saturated or unsaturated ring with the nitrogen atom to which they are attached, which ring is unsubstituted or substituted with Z_1, Z_2 and Z_3; or

(3) any two of R_9, R_{10} and R_{11} may together be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with Z_1, Z_2 and Z_3;

R_{13} is:

(1) cyano;

(2) nitro;

(3) $-NH_2$;

(4) -NHOalkyl;

(5) -OH;

(6) -NHOaryl;

(7) -NHCOOalkyl;

(8) -NHCOOaryl;

(9) $-NHSO_2$alkyl;

(10) $-NHSO_2$aryl;

(11) aryl;

(12) heteroaryl;

(13) -Oalkyl; or

(14) -Oaryl;

R_{14} is:

(1) $-NO_2$;

(2) -COOalkyl; or

(3) -COOaryl;

R_{15} is:

(1) hydrogen;

(2) alkyl;

(3) aryl;

(4) arylalkyl; or

(5) cycloalkyl;

Z_1, Z_2 and Z_3 are each independently:

(1) hydrogen or Z_6, where Z_6 is (i) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl; (ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or (iii) a group (i) or (ii) which is substituted by one or more of the following groups (2) to (16) of the definition of Z_1, Z_2 and Z_3;

(2) -OH or $-OZ_6$;

(3) -SH or $-SZ_6$;

(4) $-C(O)_qH$, $-C(O)_qZ_6$, or $-O-C(O)_qZ_6$;

(5) $-SO_3H$, $-S(O)_qZ_6$; or $S(O)_qN(Z_9)Z_6$;

(6) halo;

(7) cyano;

(8) nitro;

(9) $-Z_4-NZ_7Z_8$;

(10) $-Z_4-N(Z_9)-Z_5-NZ_7Z_8$;

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

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

(13) oxo;

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

(15) any two of Z_1, Z_2, and Z_3 may together be alkylene or alkenylene completing a 3- to 8-membered saturated

or unsaturated ring together with the atoms to which they are attached; or

(16) any two of Z_1, Z_2, and Z_3 may together be -O-$(CH_2)_r$-O- ,where r is 1 to 5, completing a 4- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached;

Z_4 and Z_5 are each independently:

(1) a single bond;

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

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

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

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

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

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

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

Z_7, Z_8, Z_9 and Z_{10}:

(1) are each independently hydrogen or Z_6;

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

(3) Z_7 or Z_8, together with Z_9, may be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with Z_1, Z_2 and Z_3;

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

(1) a single bond;

(2) alkylene;

(3) alkenylene; or

(4) alkynylene; and

Z_{13} is:

(1) a single bond;

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

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

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

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

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

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

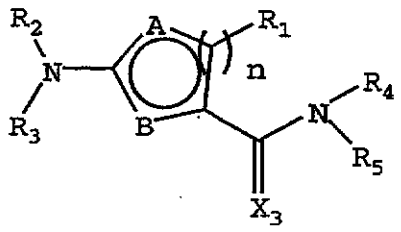
(8) $-Z_{11}-C(O)-O-Z_{12}-$;

(9) $-C(NR_{13})-$;

(10) $-C(CHR_{14})-$; or

(11) $-C(C(R_{14})_2)-$.

Compounds within formula I include compounds of the following formula II and salts thereof:



II

where

n is 1 or 2

A is selected from carbon and nitrogen;

B is selected from nitrogen, oxygen and sulfur;

X_3 is oxygen or sulfur; and

R_1, R_2, R_3, R_4 and R_5 are as described above.

Detailed Description of the Invention

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

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

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

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

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

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

The term "alkynylene" refers to a straight chain bridge of 2 to 5 carbon atoms that has a triple bond therein, is connected by single bonds, and may be substituted with 1 to 3 lower alkyl groups. Exemplary

alkynylene groups are -C≡C-, -CH_2-C≡C-, -$CH(CH_3)$-C≡C- and -C≡C-$CH(C_2H_5)CH_2$-.

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

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

The terms "halogen" and "halo" refer to fluorine, chlorine, bromine and iodine.

The term "unsaturated ring" includes partially unsaturated and aromatic rings.

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

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

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

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

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

The term "heteroaryl" refers to aromatic heterocyclic groups.

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

Where q is 1 or 2, "$-C(O)_qH$" denotes -C(O)-H or -C(O)-OH; "$-C(O)_qR_6$" or "$-C(O)_qZ_6$" denote, respectively, -C(O)-R_6 or -C(O)-OR_6, or -C(O)-Z_6 or -C(O)-OZ_6; "$-O-C(O)_qR_6$" or "$-O-C(O)_qZ_6$" denote, respectively, -O-C(O)-R_6 or -O-C(O)-OR_6, or -O-C(O)-Z_6 or -O-C(O)-OZ_6; and "$-S(O)_qR_6$" or "$-S(O)_qZ_6$" denote, respectively, -SO-R_6 or -SO_2-R_6, or -SO-Z_6 or -SO_2-Z_6.

Compounds of the formula I may in some cases form salts which are also within the scope of this invention. Reference to a compound of the formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. Zwitterions (internal or inner salts) are included within the term

"salt(s)" as used herein (and may be formed, for example, where the R substituents comprise an acid moiety such as a carboxyl group). Also included herein are quaternary ammonium salts such as alkylammonium salts. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are useful, for example, in isolation or purification steps which may be employed during preparation. Salts of the compounds of the formula I may be formed, for example, by reacting a compound I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

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

Exemplary basic salts (formed, for example, where the R substituents comprise an acidic moiety such as a carboxyl group) include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines,

N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. The basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula I, or a salt and/or solvate thereof. Solvates of the compounds of formula I are preferably hydrates.

All stereoisomers of the present compounds, such as those which may exist due to asymmetric carbons on the R substituents of the compound of the formula I, including enantiomeric and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations.

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

Preferred Compounds

Preferred compounds of the present invention are compounds of the formula I, and salts thereof, wherein Q is thiazole and wherein one or

more, and especially all, of Z, X_1, X_2 R_1, R_2, R_3, R_4, and R_5 are selected from the following definitions:

Z is a single bond;

R_1 is selected from hydrogen, halo, alkyl, aryl, alkoxy, alkoxycarbonyl, or aryloxycarbonyl and is more preferably hydrogen;

X_1 and X_2 together form =O or =S and more preferably form =O;

R_2 is hydrogen;

R_3 is selected from $-Z_4-R_6$ or $-Z_{18}-NR_7R_8$ and is more preferably $-Z_4-R_6$ wherein Z_4 is a single bond and R_6 is aryl or heteroaryl which is unsubstituted or substituted with Z_1, Z_2 and one or more (preferably, one or two) groups Z_3;

R_4 is hydrogen; and

R_5 is selected from aryl groups or heteroaryl groups which are substituted with Z_1, Z_2 and one or more (such as one or two) groups Z_3.

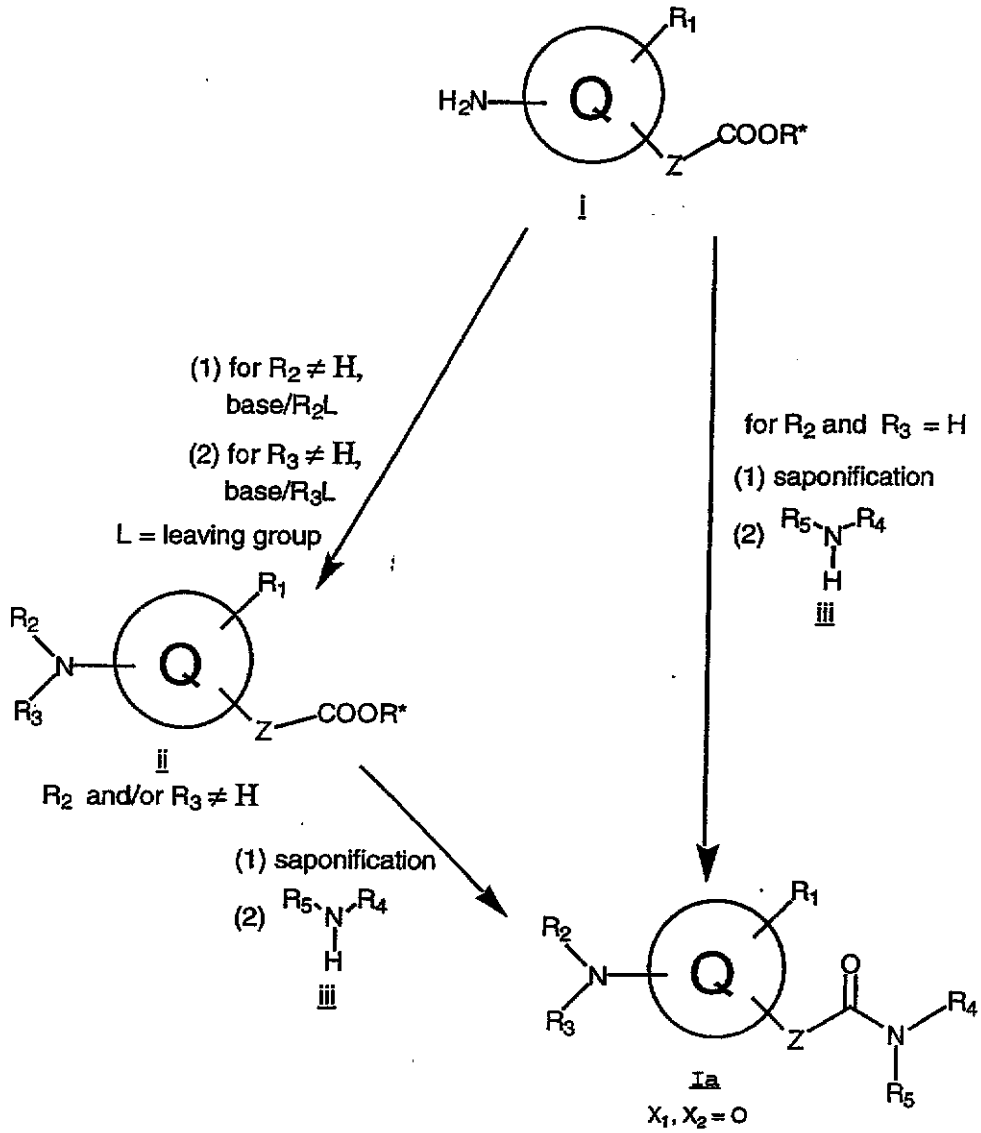
Methods of Preparation

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

The methods described herein may be carried out with starting materials and/or reagents in solution or alternatively, where appropriate, with one or more starting materials or reagents bound to a solid support (see (1) Thompson, L. A., Ellman, J. A., *Chemical Reviews*, *96*, 555-600 (1996); (2) Terrett, N. K., Gardner, M., Gordon, D. W., Kobylecki, R. J., Steele, J., *Tetrahedron*, *51*, 8135-8173 (1995); (3) Gallop, M. A., Barrett, R.

W., Dower, W. J., Fodor, S. P. A., Gordon, E. M., *Journal of Medicinal Chemistry*, *37*, 1233-1251 (1994); (4) Gordon, E. M., Barrett, R. W., Dower, W. J., Fodor, S. P. A., Gallop, M. A., *Journal of Medicinal Chemistry*, *37*, 1385-1401 (1994); (5) Balkenhohl, F., von dem Bussche-Hünnefeld, Lansky, A., Zechel, C., *Angewandte Chemie International Edition in English*, *35*, 2288-2337 (1996); (6) Balkenhohl, F., von dem Bussche-Hünnefeld, Lansky, A., Zechel, C., *Angewandte Chemie*, *108*, 2436-2487 (1996); and (7) Sofia, M. J., *Drugs Discovery Today*, *1*, 27-34 (1996)).

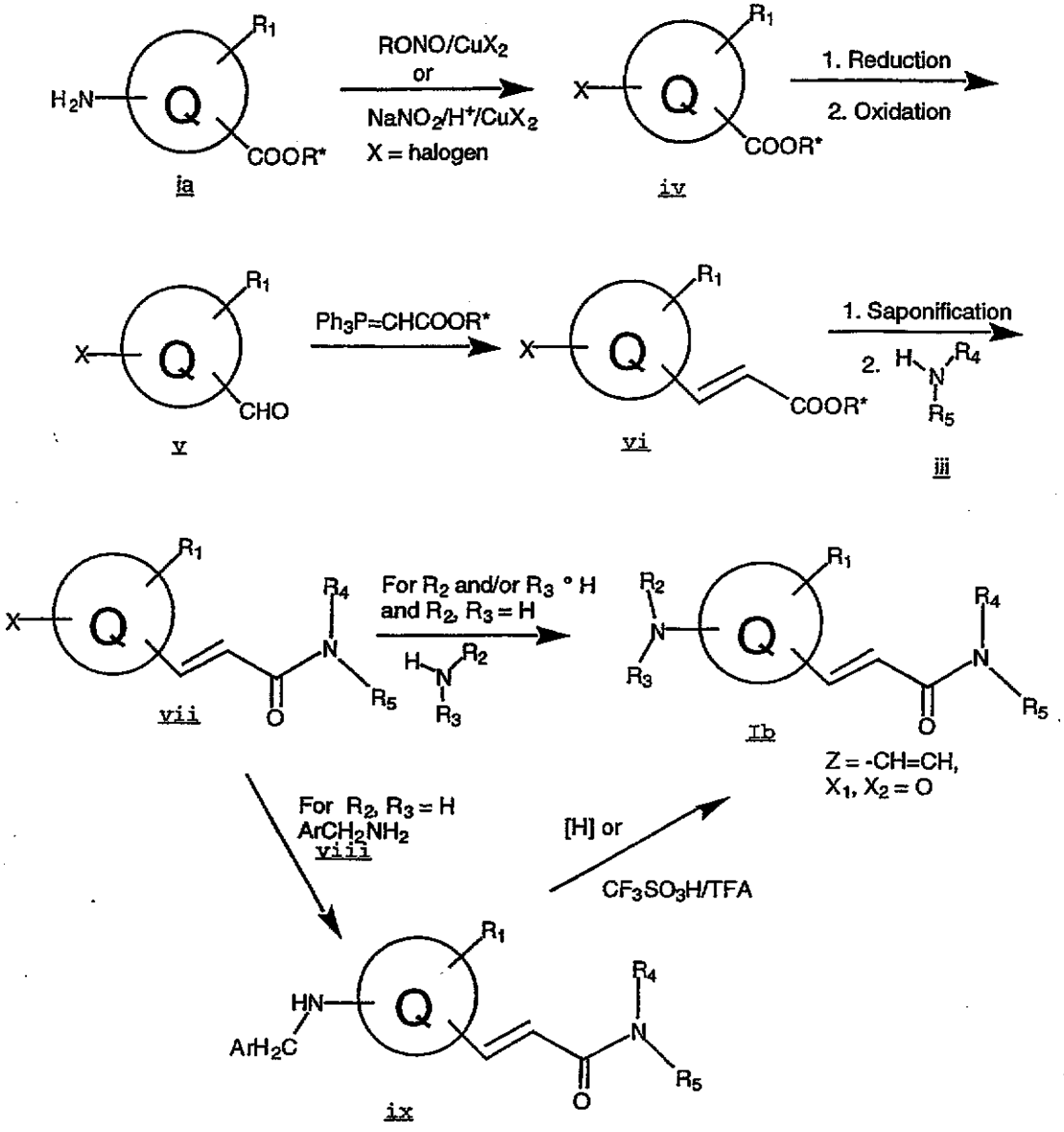
Scheme A


R1
H2N
Q
Z
COOR*
i
(1) for R2 ≠ H, base/R2L
(2) for R3 ≠ H, base/R3L
L = leaving group
for R2 and R3 = H
(1) saponification
(2) R5 N R4 H
iii
R2
N
R3
ii
R2 and/or R3 ≠ H
(1) saponification
(2) R5 N R4 H
iii
O
R4
R5
Ia
X1, X2 = O

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

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

Scheme B

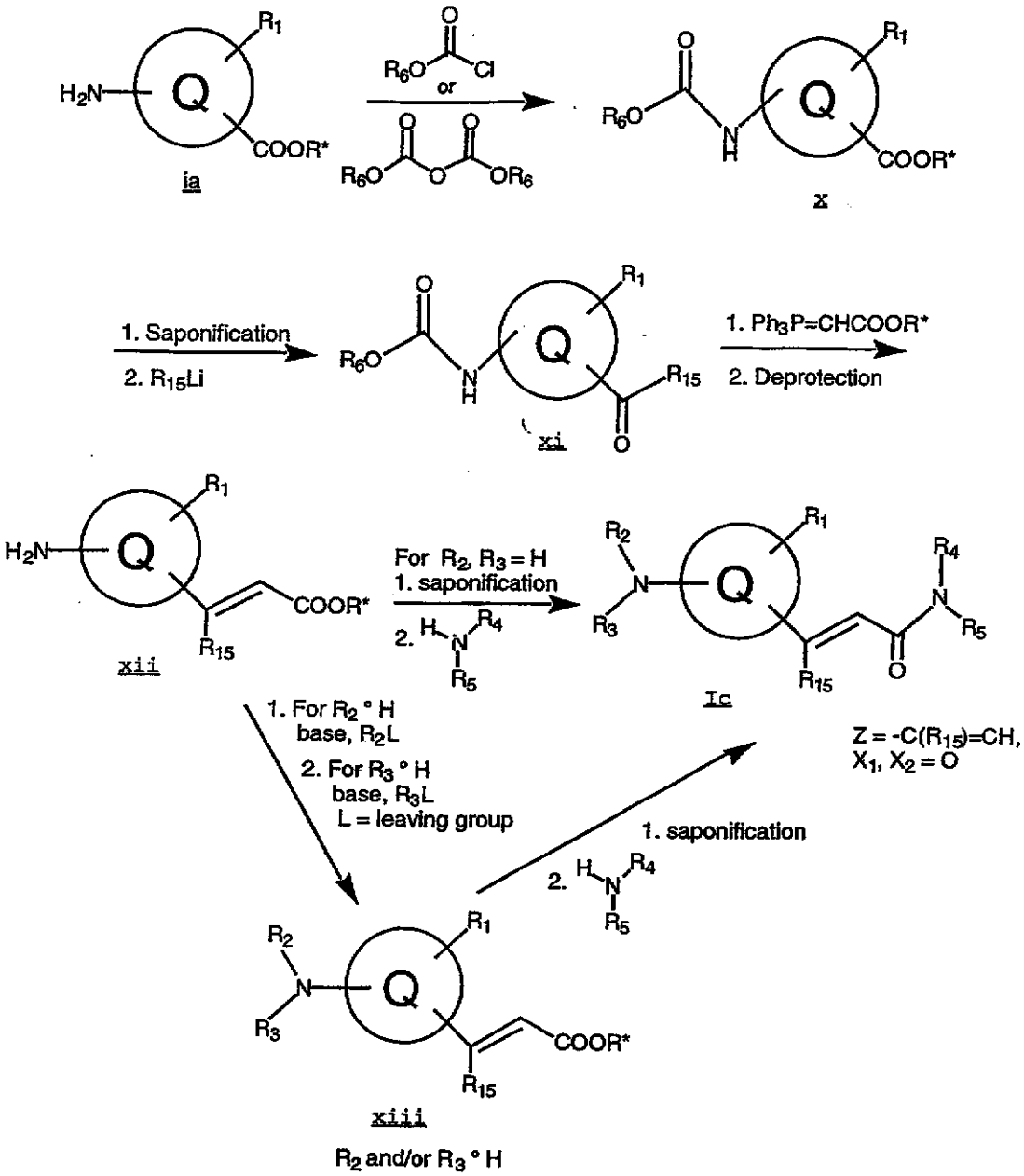

RONO/CuX2
or
NaNO2/H+/CuX2
X = halogen
1. Reduction
2. Oxidation
Ph3P=CHCOOR*
1. Saponification
2.
For R2 and/or R3 ° H
and R2, R3 = H
For R2, R3 = H
ArCH2NH2
viii
[H] or
CF3SO3H/TFA
Z = -CH=CH,
X1, X2 = O
ia
iv
v
vi
iii
vii
Ib
ix

5

Scheme B illustrates a general method for forming compound Ib, which is a compound of formula I where Z is -CH=CH- and X_1 and X_2 together form =O. As shown in Scheme B, a 2-halo-compound vi can be prepared by reacting an appropriately substituted 2-amino-compound ia with copper (ii) halide and an alkyl nitrite such as tert-butyl nitrite in an aprotic solvent such as acetonitrile to form 2-halo-compound iv (see *J. Het. Chem. 22*, 1621 (1985)). Compound iv can be reduced with a reducing agent such as sodium borohydride in ethanol or aqueous tetrahydrofuran to form an alcohol, which can be oxidized with an oxidizing agent such as pyridinium chlorochromate or pyridinium dichromate to form aldehyde v. Compound v can be reacted with an alkyl(triphenylphosphorylidene) acetate to form carboxylate vi. Compound vi can be saponified and then reacted with an amine iii by methods known to those skilled in the art to form vii. Compound vii can be reacted with an amine R_2R_3NH to form Ib where Z is -CH=CH- and X_1, X_2 together form =O. Alternatively, compounds of formula Ib where R_2 and R_3 are H, can be formed by reacting compound vii with an appropriately substituted benzyl amine such as 4-methoxybenzyl amine to form compound ix, which can be hydrogenolyzed or treated with an acid such as trifluoromethanesulfonic acid and trifluoroacetic acid in the presence of anisole to form Ib where R_2 and R_3 are hydrogen.

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

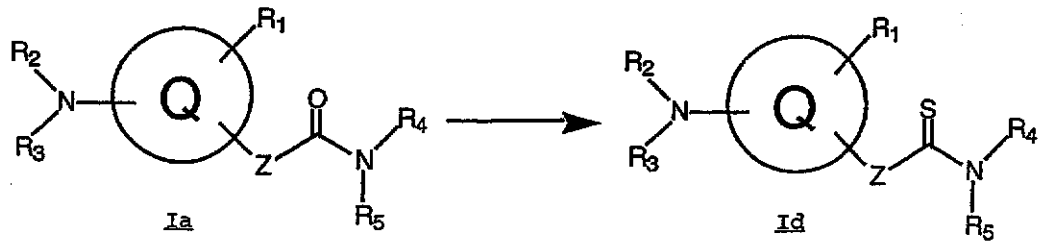
Scheme C


ia
x
1. Saponification
2. R15Li
xi
1. Ph3P=CHCOOR*
2. Deprotection
xii
For R2, R3 = H
1. saponification
2.
Ic
Z = -C(R15)=CH,
X1, X2 = O
1. For R2 ° H
base, R2L
2. For R3 ° H
base, R3L
L = leaving group
1. saponification
2.
xiii
R2 and/or R3 ° H

Scheme C illustrates a general method for forming compound Ic, which is a compound of formula I where Z is $-R_{15}C=CH-$ and X_1 and X_2 together form =O. As shown in Scheme C, a 2-amino-compound ia can be reacted with a chloroformate or dicarbonate to form x, which can be saponified and treated with an organolithium reagent to form compound xi. Compound xi may be reacted with an alkyl(triphenylphosphorylidene)acetate, followed by deprotection of the carbamate protecting group to form xii. Alternatively, compound Ic where R_2 and R_3 are hydrogen may be formed by saponification of xii followed by reaction with an amine R_4R_5NH by methods known to those skilled in the art. Alternatively, compound xii may be reacted with R_2L where L is a leaving group such as halogen (for example, in equimolar portions), optionally followed by reaction with R_3L (for example, in equimolar portions) to form xiii, which may be saponified and reacted with an amine R_4R_5NH by methods known to those skilled in the art to form Ia where R_2 and/or R_3 are other than hydrogen.

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

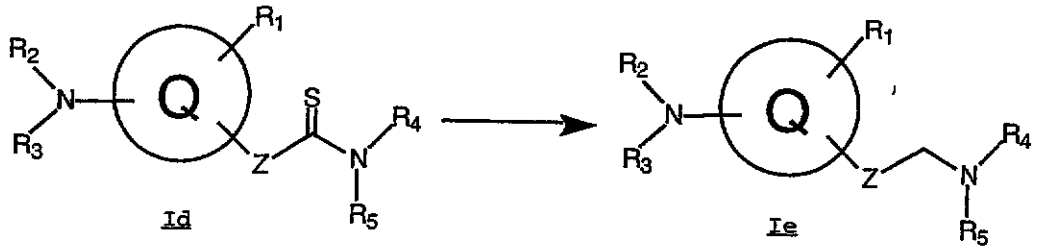
Scheme D



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

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

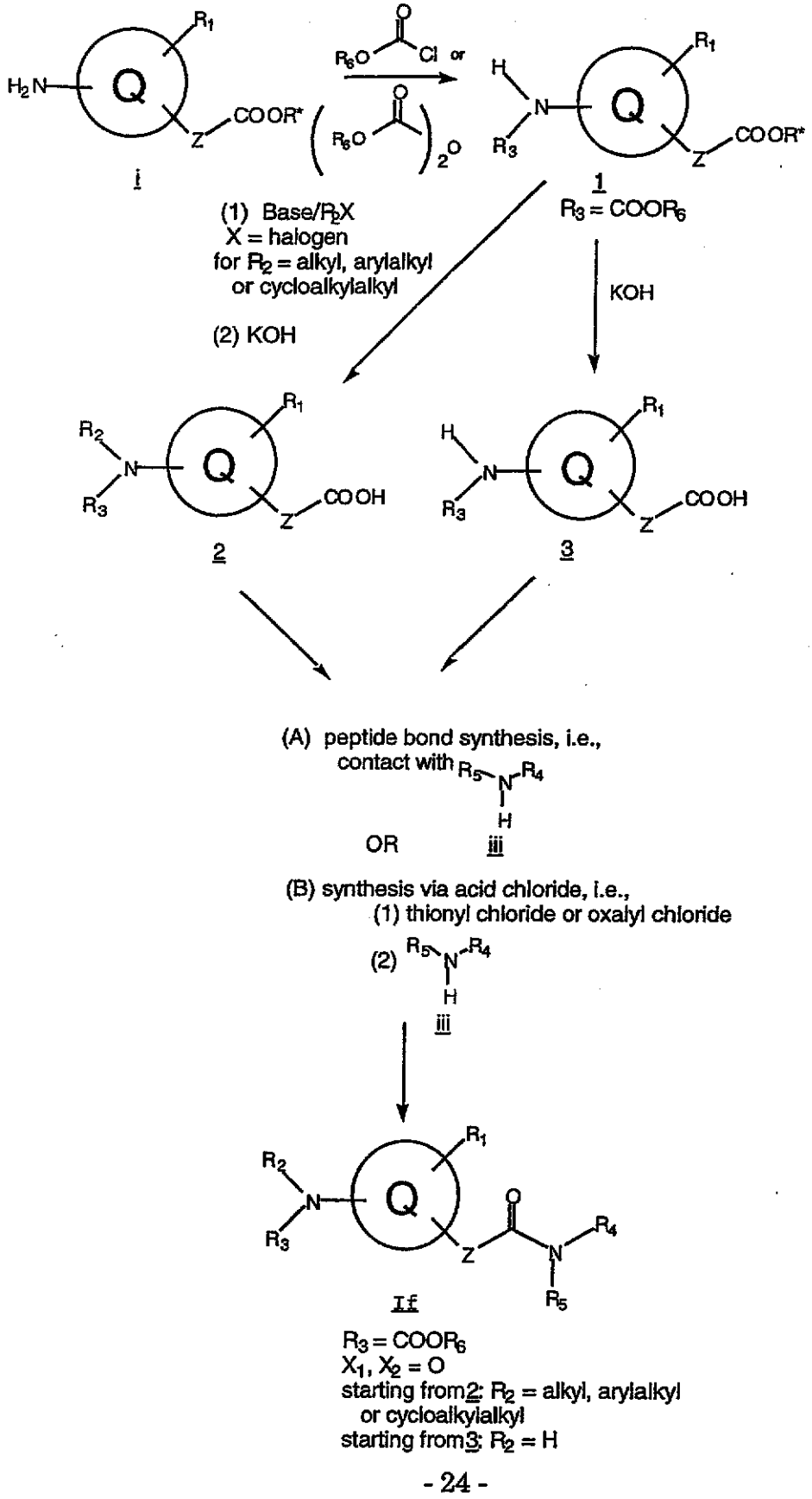
Scheme E



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

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

Scheme I



i

1

$R_3 = COOR_6$

2

3

If

$R_3 = COOR_6$

$X_1, X_2 = O$

starting from 2: R_2 = alkyl, arylalkyl or cycloalkylalkyl

starting from 3: $R_2 = H$

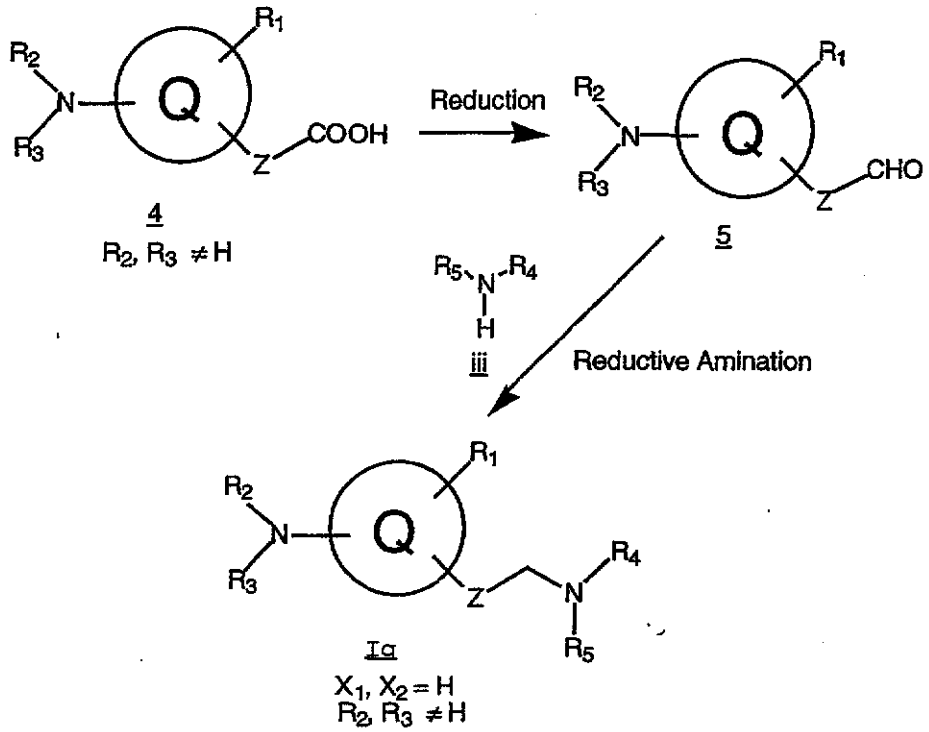
As shown in Scheme I, carboxylate i can be reacted with a chloroformate or dicarbonate to form 1. Compound 1 can be treated with a base such as sodium hydride, sodium/potassium hexamethyldisilazide, or lithium diisopropylamide (LDA), and an alkylating agent R_2X where X is halogen and R_2 is preferably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

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

triethylamine, diisopropylethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or an inorganic base such as sodium, potassium or cesium carbonate or sodium or potassium hydride. Alternatively, the acid halide of 2 may be prepared, for example, by reaction with thionyl chloride or oxalyl chloride, followed by subsequent reaction with amine iii to provide compound If, which is a compound of the formula I where R_3 is $COOR_6$, X_1 and X_2 together form =O, and R_2 is alkyl, arylalkyl or chycloalkylalkyl.

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

Scheme II

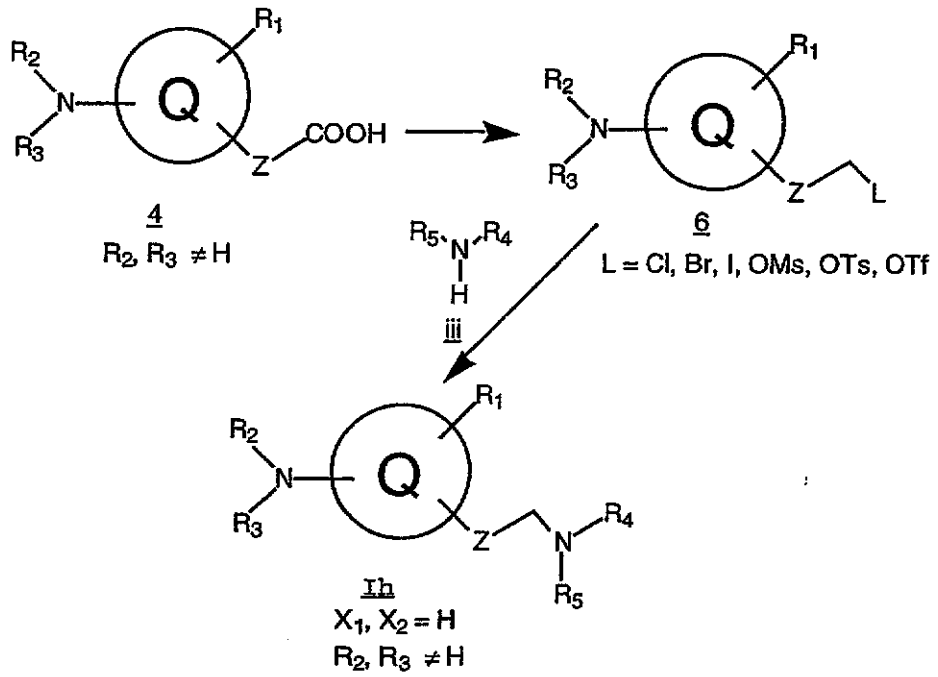

R1
R2
N
Q
R3
Z
COOH
4
R2, R3 ≠ H
Reduction
CHO
5
R5
N
R4
H
iii
Reductive Amination
Ia
X1, X2 = H
R2, R3 ≠ H

5

As shown in Scheme II, acid 4 where R_2 and R_3 are not hydrogen and are selected such that the nitrogen to which they are attached is non-basic, is reduced to the aldehyde 5 by methods well know in the art (see March, Advanced Organic Chemistry, Wiley, 1985). For example, the acid 4 may be converted to its corresponding ester followed by reduction with diisobutylaluminum hydride. Alternatively, the acid 4 may be reduced to the corresponding primary alcohol, for example, by treatment with borane/THF, $LiAlH_4$, or via reduction of a mixed anhydride, followed by subsequent oxidation to the aldehyde 5 using Cr(VI) (e.g., pyridinium chlorochromate, "PCC") or under Swern or Moffatt conditions (e.g., $(COCl)_2$/dimethylsulfoxide). The starting acid 4 may be obtained, for example, by saponification of ii.

Reductive amination (see Hudlicky, Reductions in Organic Chemistry, Wiley, 1984) of aldehyde 5 with amine iii in the presence of a reducing agent such as $NaBH_3CN$, $NaBH(OAc)_3$ (Ac = acetyl) or hydrogen and a palladium catalyst produces the amine compound Ig, which is a compound of the formula I where X_1 and X_2 are each hydrogen and R_2 and R_3 are each not hydrogen.

Scheme III

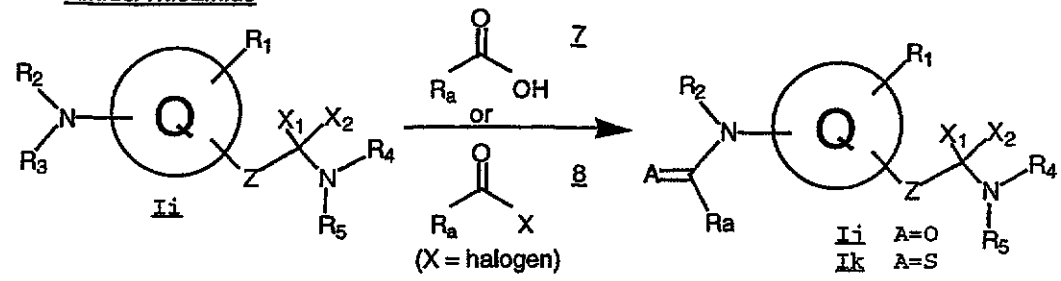


As shown in Scheme III, reduction of the acid **4** to a primary alcohol (for example, by treatment with borane/tetrahydrofuran, $LiAlH_4$, or via reduction of a mixed anhydride), followed by conversion by methods well known in the art (see March, Advanced Organic Chemistry, Wiley, 1985), provides **6** which contains a leaving group such as a halide, tosylate (OTs), mesylate (OMs) or triflate (OTf). The groups R_2 and R_3 are selected such that the resulting nitrogen to which they are attached is non-basic. Compound **6** can then be converted into compound Ih, which is a compound of the formula I where X_1 and X_2 are each hydrogen and R_2 and R_3 are each not hydrogen, by a displacement reaction with amine **iii**, preferably where amine **iii** is used in excess.

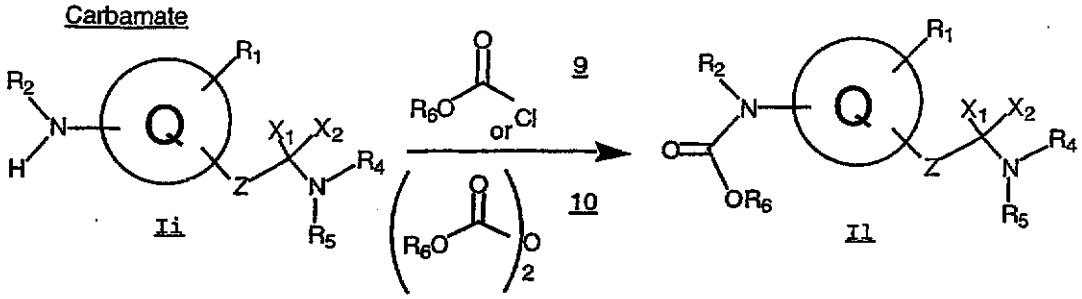
Scheme IV

R_2 = any group as defined
R_3 = acyl or thioacyl

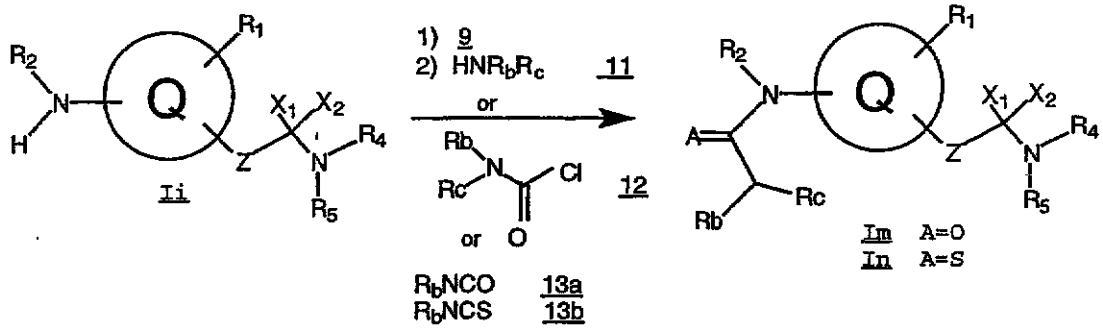
Amide/Thioamide



Carbamate



Urea/Thiourea



[$X_1, X_2 \neq H$]

Scheme IV illustrates methods which may be used for the preparation of compounds Ij, Ik, Il, Im and In. Ij, Ik, Il, Im and In are compounds of the formula I where R_2 is any group as defined, R_3 is an acyl or thioacyl group, X_1 and X_2 are not hydrogen, and R_1 is not a primary or secondary amine. Ij, Ik, Il, Im and In have other particular substituents which are specified in this Scheme and below. The starting compound Ii can be prepared by suitable methods described in Schemes A and D.

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

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

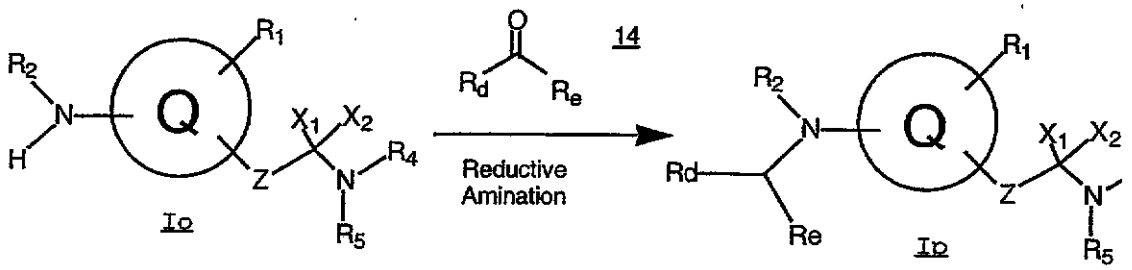
The urea Im may be prepared by treatment of amine compound Ii with either: 1) a chloroformate **9**, such as phenylchloroformate, followed by reaction with an amine **11**; 2) a carbamoyl chloride **12** in the presence of an acid scavenger such as diisopropylethylamine; or 3) reaction with an isocyanate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

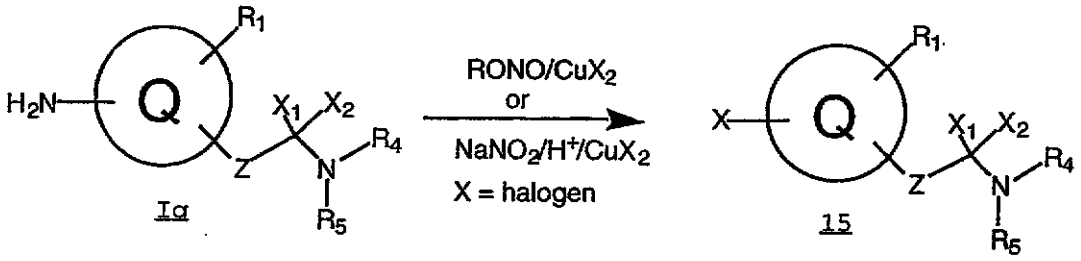
R_a is selected from those groups included in the definition of R_6 such that the group -C(=A)-R_a is an acyl or thioacyl group within the definition of R_3. R_b and R_c are selected from those groups included in the definitions

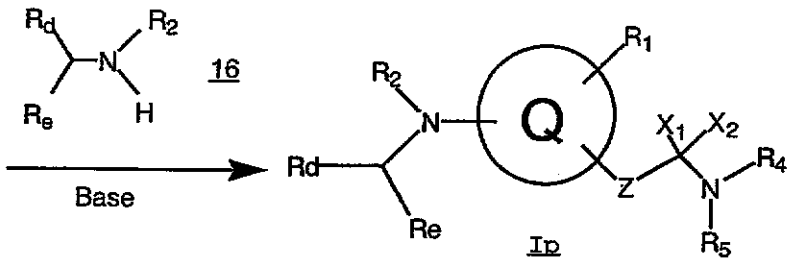
of R_7 and R_8, such that the group -C(=A)-N(R_b)(R_c) is an acyl or thioacyl group within the definition of R_3.

Scheme V

R_2 = any group as defined other than acyl
R_3 = alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl or saturated heterocycle







[X_1, X_2 ° H]

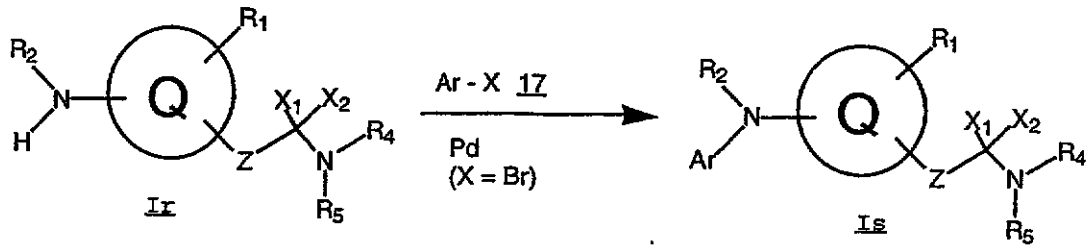
Scheme V illustrates a method which can be used for the preparation of Ip, which is a compound of the formula I where R_2 is any group as defined other than acyl, and which is selected such that the nitrogen to which it is attached is basic, R_3 is alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl,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

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

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

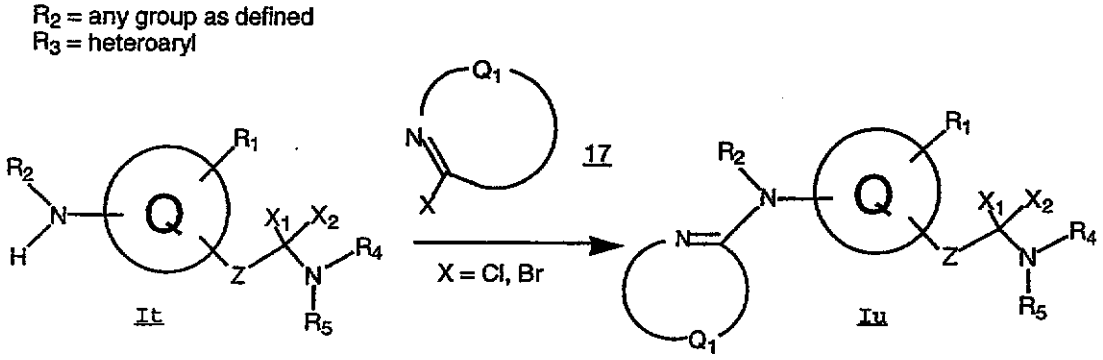
Scheme VI

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



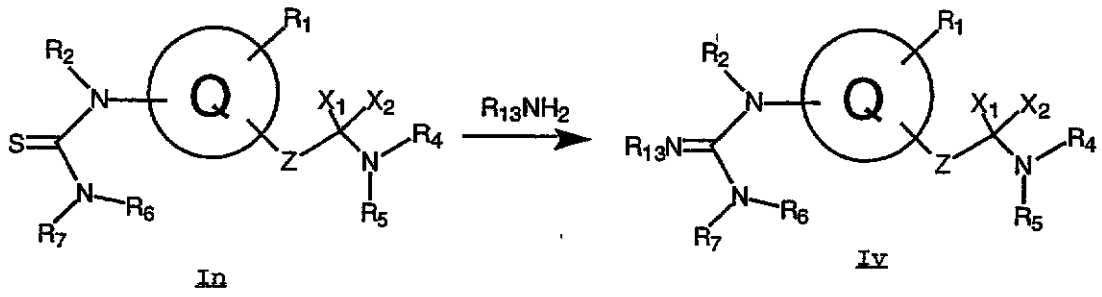
As shown in Scheme VI, when R_2 is any group as defined other than acyl, and is selected such that the nitrogen to which it is attached is basic, R_3 is aryl or heteroaryl, and X_1 and X_2 are not hydrogen, amine compound Ir may be reacted with a halophenyl or haloheteroaromatic group **17** in the presence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

Scheme VII



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

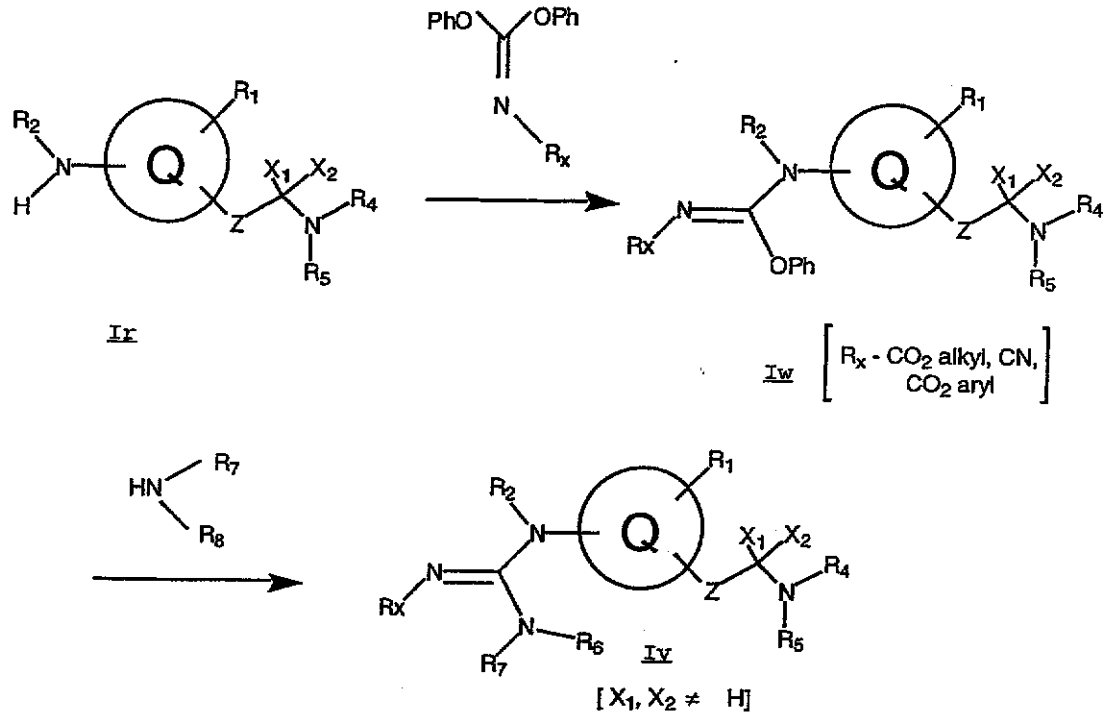
Scheme VIII



As shown in Scheme VIII, thiourea compound In (where X_1 and X_2 are not hydrogen) may be reacted with the appropriate amine in the presence of bis-(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP chloride) benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP-reagent), [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate (HATU) and carbodiimide, such as dicyclohexyl carbodiimide (DCC) or 3-ethyl-3'-(dimethylamino)propyl carbodiimide (EDCI) or diisopropyl carbodiimide (DIC) in the presence of an organic base such as triethylamine, diisopropylethylamine or dimethylaminopyridine in solvents such as dimethylformamide, dichloromethane or tetrahydrofuran to form compound Iv, which is a compound of the formula I having the particular substituents described in this Scheme.

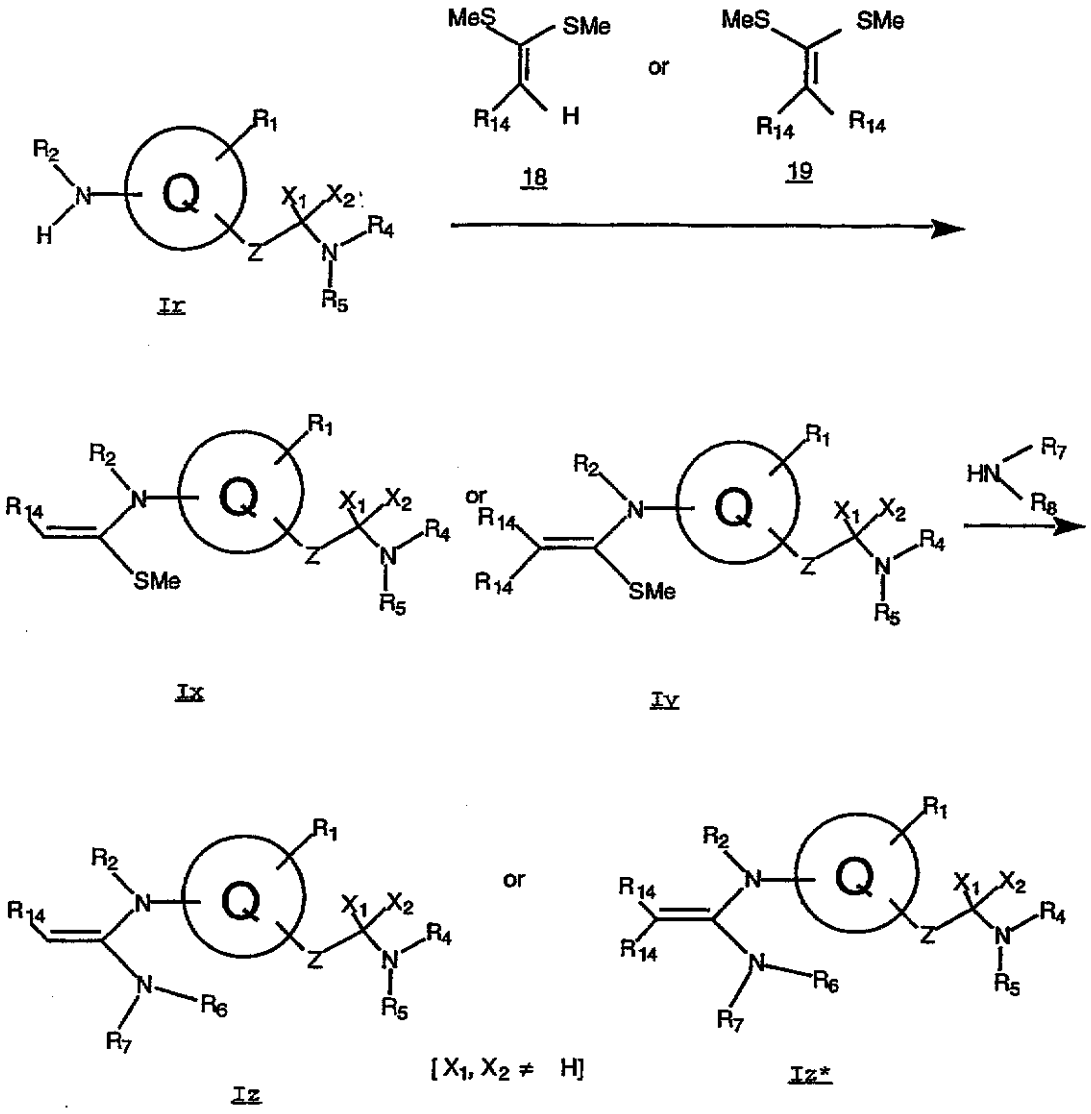
Alternatively, Compound In can be reacted with the appropriate amine in the presence of a mercury (II) salt such as mercuric chloride, or by other methods known in the literature, to form Iv.

Scheme IX



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

Scheme X

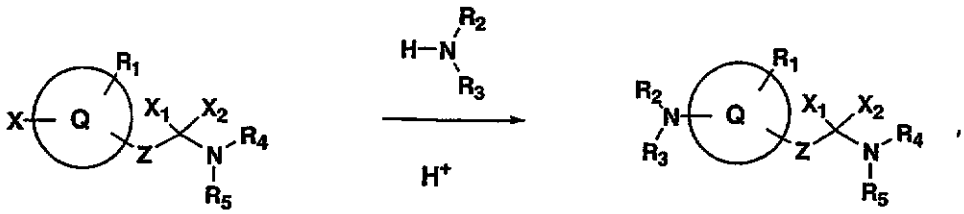


As shown in Scheme X, compound Ir (where X_1 and X_2 are not hydrogen) can be reacted with 18 or 19 either alone or in the presence of a base such as sodium hydride, sodium hexamethyl disilazide or dimethylaminopyridine in dimethyl formamide or tetrahydrofuran at room temperature or at higher temperature to form compounds Ix or Iy respectively, which can be reacted with an amine R_7R_8NH at room temperature or elevated temperature to form compounds Iz or Iz*

respectively. Compound Iz is a compound of the formula I having the particular substituents described in this Scheme. Compound Iz* is a compound of the formula I having the particular substituents described in this Scheme.

Scheme XI

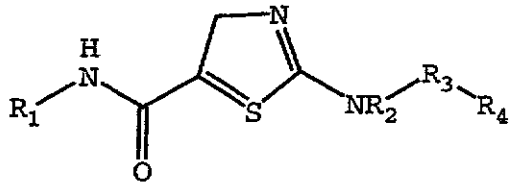
R_2 = aryl, heteroaryl, bicyclic-heteroaryl
R_3 = H, alkyl, aryl, heteroaryl, bicyclic-heteroaryl



15

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

The present invention further provides compounds of formula III:



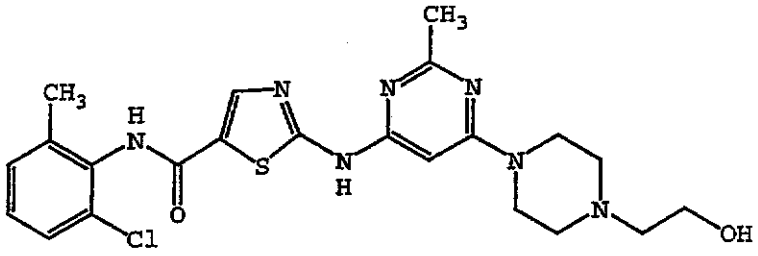
III

wherein:

each R_1, R_3 and R_4 is, independently, a heterocyclic group or an aryl group, optionally substituted with one or more substituents; and

R_2 is hydrogen or alkyl.

A preferred compound of the present invention is of formula IV:



IV

Utility

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

neutrophil activation are useful, for example, in the treatment of ischemia and reperfusion injury.

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

Use of the compounds of the present invention in treating protein tyrosine kinase-associated disorders is exemplified by, but is not limited to, treating a range of disorders such as: transplant (such as organ transplant, acute transplant or heterograft or homograft (such as is employed in burn treatment)) rejection; protection from ischemic or reperfusion injury such as ischemic or reperfusion injury incurred during organ transplantation, myocardial infarction, stroke or other causes; transplantation tolerance induction; arthritis (such as rheumatoid arthritis, psoriatic arthritis or osteoarthritis); multiple sclerosis; chronic obstructive pulmonary disease (COPD), such as emphysema; inflammatory bowel disease, including ulcerative colitis and Crohn's disease; lupus (systemic lupus erythematosis); graft vs. host disease; T-cell mediated hypersensitivity diseases, including contact hypersensitivity, delayed-type hypersensitivity, and gluten-sensitive enteropathy (Celiac disease); psoriasis; contact dermatitis (including that due to poison ivy); Hashimoto's thyroiditis; Sjogren's syndrome; Autoimmune Hyperthyroidism, such as Graves' Disease; Addison's disease (autoimmune disease of the adrenal glands); Autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome);

autoimmune alopecia; pernicious anemia; vitiligo; autoimmune hypopituatarism; Guillain-Barre syndrome; other autoimmune diseases; cancers, including cancers where Lck or other Src-family kinases such as Src are activated or overexpressed, such as colon carcinoma and thymoma, and cancers where Src-family kinase activity facilitates tumor growth or survival; glomerulonephritis; serum sickness; uticaria; allergic diseases such as respiratory allergies (asthma, hayfever, allergic rhinitis) or skin allergies; scleracierma; mycosis fungoides; acute inflammatory responses (such as acute respiratory distress syndrome and ishchemia/reperfusion injury); dermatomyositis; alopecia areata; chronic actinic dermatitis; eczema; Behcet's disease; Pustulosis palmoplanteris; Pyoderma gangrenum; Sezary's syndrome; atopic dermatitis; systemic schlerosis; and morphea. The present invention also provides a method for treating the aforementioned disorders such as atopic dermatitis by administration of any compound capable of inhibiting protein tyrosine kinase.

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

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

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

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

By virtue of their ability to inhibit HER1 and HER2 kinases, compounds of the present invention can also be used for the treatment of proliferative diseases, including psoriasis and cancer. The HER1 receptor kinase has been shown to be expressed and activated in many solid tumors including non-small cell lung, colorectal, and breast cancer.

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

The compounds of the present invention are useful for the treatment of cancers such as chronic myelogenous leukemia (CML), gastrointestinal stromal tumor (GIST), small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), ovarian cancer, melanoma, mastocytosis, germ cell tumors, acute myelogenous leukemia (AML), pediatric sarcomas, breast cancer, colorectal cancer, pancreatic cancer, prostate cancer and others known to be associated with protein tyrosine kinases such as, for example, SRC, BCR-ABL and c-KIT. The compounds

of the present invention are also useful in the treatment of cancers that are sensitive to and resistant to chemotherapeutic agents that target BCR-ABL and c-KIT, such as, for example, Gleevec® (STI-571).

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

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

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

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

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as

mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

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

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

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

When administered intravenously, the compounds of the present invention, including compounds of formula III and IV, are preferably administered using the formulations of the invention. Generally, the compounds of the present invention, including compounds of formula III and IV, are administered by IV infusion over a

period of from about 10 minutes to about 3 hours, preferably about 30 minutes to about 2 hours, more preferably about 45 minutes to 90 minutes, and most preferably about 1 hour. Typically, the compounds are administered intravenously in a dose of from about 0.5 mg/m^2 to 65 mg/m^2, preferably about 1 mg/m^2 to 50 mg/m^2, more preferably about 2.5 mg/m^2 to 30 mg/m^2, and most preferably about 25 mg/m^2. One of ordinary skill in the art would readily know how to convert doses from mg/kg to mg/m2 given either or both the height and or weight of the patient (See, e.g., http://www.fda.gov/cder/cancer/animalframe.htm).

As discussed above, compounds of the present invention, including compounds of formulae III and IV, can be administered orally, intravenously, or both. In particular, the methods of the invention encompass dosing protocols such as once a day for 2 to 10 days, preferably every 3 to 9 days, more preferably every 4 to 8 days and most preferably every 5 days. In one embodiment there is a period of 3 days to 5 weeks, preferably 4 days to 4 weeks, more preferably 5 days to 3 weeks, and most preferably 1 week to 2 weeks, in between cycles where there is no treatment. In another embodiment the compounds of the present invention, including compounds of formulae III or IV, can be administered orally, intravenously, or both, once a day for 3 days, with a period of preferably 1 week to 3 weeks in between cycles where there is no treatment. In yet another embodiment the compounds of the present invention, including compounds of formulae III or IV, can be administered orally, intravenously, or both, once a day for 5 days, with a period of preferably 1 week to 3 weeks in between cycles where there is no treatment.

In one preferred embodiment the treatment cycle for administration of the compounds of the present invention, including compounds of formulae III or IV, is once daily for 5 consecutive days and the period between treatment cycles is from 2 to 10 days, preferably one week. In one embodiment, a compound of the present invention, for example, a compound of formula III or formula IV, is administered once daily for 5 consecutive days, followed by 2 days when there is no treatment.

The compounds of the present invention, including compounds of formulae III or IV, can also be administered orally, intravenously, or both once every 1 to 10

weeks, preferably every 2 to 8 weeks, more preferably every 3 to 6 weeks, and even more preferably every 3 weeks.

In another method of the invention, the compounds of the present invention, including compounds of formulae III or IV, are administered in a 28 day cycle wherein the compounds are intravenously administered on days 1, 7, and 14 and orally administered on day 21. Alternatively, the compounds of the present invention, including compounds of formulae III or IV, are administered in a 28 day cycle wherein the compound of formulae I and II are orally administered on day 1 and intravenously administered on days 7, 14, and 28.

According to the methods of the invention, the compounds of the present invention, including compounds of formulae III or IV, are administered until the patient shows a response, for example, a reduction in tumor size, or until dose limiting toxicity is reached.

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

Exemplary such other therapeutic agents include the following: cyclosporins (e.g., cyclosporin A), CTLA4-Ig, antibodies such as anti-ICAM-3, anti-IL-2 receptor (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80, anti-CD86, monoclonal antibody OKT3, agents blocking the interaction between CD40 and gp39, such as antibodies specific for CD40 and/or gp39 (i.e., CD154), fusion proteins constructed from CD40 and gp39 (CD40Ig and CD8gp39), inhibitors, such as nuclear translocation inhibitors, of NF-kappa B function, such as deoxyspergualin (DSG), non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, steroids such as prednisone or dexamethasone, gold compounds, antiproliferative agents such as methotrexate, FK506 (tacrolimus, Prograf), mycophenolate mofetil, cytotoxic drugs such as

azathiprine and cyclophosphamide, TNF-α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor such as etanercept (Enbrel), rapamycin (sirolimus or Rapamune), leflunimide (Arava), and cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (Celebrex) and rofecoxib (Vioxx), or derivatives thereof, and the PTK inhibitors disclosed in the following U.S. Patent Applications, incorporated herein by reference in their entirety: Serial No. 60/056,770, filed 8/25/97 (Attorney Docket No. QA202*), Serial No. 60/069,159, filed 12/9/97 (Attorney Docket No. QA202a*), Serial No. 09/097,338, filed 6/15/98 (Attorney Docket No. QA202b), Serial No. 60/056,797, filed 8/25/97 (Attorney Docket No. QA205*), Serial No. 09/094,797, filed 6/15/98 (Attorney Docket No. QA205a), Serial No. 60/065,042, filed 11/10/97 (Attorney Docket No. QA207*), Serial No. 09/173,413, filed 10/15/98, (Attorney Docket No. QA207a), Serial No. 60,076,789, filed 3/4/98 (Attorney Docket No. QA208*), and Serial No. 09,262,525, filed 3/4/99 (Attorney Docket No. QA208a). See the following documents and references cited therein: Hollenbaugh, D., Douthwright, J., McDonald, V., and Aruffo, A., "Cleavable CD40Ig fusion proteins and the binding to sgp39", *J. Immunol. Methods* (Netherlands), *188(1)*, p. 1-7 (Dec 15 1995); Hollenbaugh, D., Grosmaire, L.S., Kullas, C.D., Chalupny, N.J., Braesch-Andersen, S., Noelle, R.J., Stamenkovic, I., Ledbetter, J.A., and Aruffo, A., "The human T cell antigen gp39, a member of the TNF gene family, is a ligand for the CD40 receptor: expression of a soluble form of gp39 with B cell co-stimulatory activity", *EMBO J* (England), *11(12)*, p 4313-4321 (Dec 1992); and Moreland, L.W. et al., "Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein, *New England J. of Medicine, 337(3)*, p. 141-147 (1997).

Exemplary classes of anti-cancer agents and cytotoxic agents include, but are not limited to: alkylating agents, such as nitrogen mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and

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

Representative examples of these classes of anti-cancer and cytotoxic agents include, but are not limited to, mechlorethamine hydrochlordie, cyclophosphamide, chlorambucil, melphalan, ifosfamide, busulfan, carmustin, lomustine, semustine, streptozocin, thiotepa, dacarbazine, methotrexate, thioguanine, mercaptopurine, fludarabine, pentastatin, cladribin, cytarabine, fluorouracil, doxorubicin hydrochloride, daunorubicin, idarubicin, bleomycin sulfate, mitomycin C, actinomycin D, safracins, saframycins, quinocarcins, discodermolides, vincristine, vinblastine, vinorelbine tartrate, etoposide, teniposide, paclitaxel, tamoxifen, estramustine, estramustine phosphate sodium, flutamide, buserelin, leuprolide,

pteridines, diyneses, levamisole, aflacon, interferon, interleukins, aldesleukin, filgrastim, sargramostim, rituximab, BCG, tretinoin, irinotecan hydrochloride, betamethosone, gemcitabine hydrochloride, altretamine, and topoteca and any analogs or derivatives thereof.

Preferred members of these classes include, but are not limited to paclitaxel, cisplatin, carboplatin, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, mitomycin C, ecteinascidin 743, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podophyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosidine, vindesine, and leurosine.

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

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

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

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

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

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

The protein tyrosine kinase of interest is incubated in kinase buffer (20 mM MOPS, pH7, 10 mM $MgCl_2$) in the presence of the test compound. The reaction is initiated by the addition of substrates to the final concentration of 1 μM ATP, 3.3 μCi/ml [33P] gamma-ATP, and 0.1 mg/ml acid denatured enolase (prepared as described in Cooper, J.A., Esch, F.S., Taylor, S.S., and Hunter, T., "Phosphorylation sites in enolase and lactate dehydrogenase utilized by tyrosine protein kinases in vivo and in vitro", *J. Biol. Chem., 259,* 7835-7841 (1984)). The reaction is stopped after 10 minutes by the addition of 10% trichloroacetic acid, 100 mM sodium pyrophosphate followed by 2 mg/ml bovine serum albumin. The labeled enolase protein substrate is precipitated at 4 degrees, harvested onto Packard Unifilter plates and counted in a Topcount scintillation counter to ascertain the protein tyrosine kinase inhibitory activity of the test compound (activity inversely proportional to the amount of labeled enolase protein obtained). The exact concentration of reagents and the amount of label can be varied as needed.

This assay is advantageous as it employs an exogenous substrate (enolase) for more accurate enzyme kinetics, and can be conducted in a 96-well format that is readily automated. In addition, His-tagged protein tyrosine kinases (described below) offer much higher production yields and purity relative to GST-protein tyrosine kinase fusion protein.

The protein tyrosine kinase may be obtained from commercial sources or by recombinant methods described herewith. For the preparation of recombinant Lck, human Lck was prepared as a His-tagged

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

Enzyme Assay Using HER1 or HER2

Compounds of interest were assayed in a kinase buffer that contained 20 mM Tris.HCl, pH 7.5, 10 mM $MnCl_2$, 0.5 mM dithiothreitol, bovine serum albumin at 0.1 mg/ml, poly(glu/tyr, 4:1) at 0.1 mg/ml, 1μM ATP, and 4 μCi/ml [gamma-^{33}P]ATP. Poly(glu/tyr, 4:1) is a synthetic polymer that serves as a phosphoryl acceptor and is purchased from Sigma Chemicals. The kinase reaction is initiated by the addition of enzyme and the reaction mixtures were incubated at 26°C for 1 h. The reaction is terminated by the addition of EDTA to 50 mM and proteins are precipitated by the addition of trichloroacetic acid to 5%. The precipitated proteins are recovered by filtration onto Packard Unifilter plates and the amount of radioactivity incorporated is measured in a Topcount scintillation counter.

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

as an untagged protein in insect cells. The recombinant protein was partially purified by ion-exchange chromatography.

Cell assays

3. Cellular tyrosine phosphorylation

Jurkat T cells are incubated with the test compound and then stimulated by the addition of antibody to CD3 (monoclonal antibody G19-4). Cells are lysed after 4 minutes or at another desired time by the addition of a lysis buffer containing NP-40 detergent. Phosphorylation of proteins is detected by anti-phosphotyrosine immunoblotting. Detection of phosphorylation of specific proteins of interest such as ZAP-70 is detected by immunoprecipitation with anti-ZAP-70 antibody followed by anti-phosphotyrosine immunoblotting. Such procedures are described in Schieven, G.L., Mittler, R.S., Nadler, S.G., Kirihara, J.M., Bolen, J.B., Kanner, S.B., and Ledbetter, J.A., "ZAP-70 tyrosine kinase, CD45 and T cell receptor involvement in UV and H_2O_2 induced T cell signal transduction", *J. Biol. Chem.*, *269*, 20718-20726 (1994), and the references incorporated therein. The Lck inhibitors inhibit the tyrosine phosphorylation of cellular proteins induced by anti-CD3 antibodies.

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

3. Calcium assay

Lck inhibitors block calcium mobilization in T cells stimulated with anti-CD3 antibodies. Cells are loaded with the calcium indicator dye indo-1, treated with anti-CD3 antibody such as the monoclonal antibody G19-4, and calcium mobilization is measured using flow cytometry by recording changes in the blue/violet indo-1 ratio as described in Schieven, G.L., Mittler, R.S., Nadler, S.G., Kirihara, J.M., Bolen, J.B., Kanner, S.B., and Ledbetter, J.A., "ZAP-70 tyrosine kinase, CD45 and T cell receptor involvement in UV and H_2O_2 induced T cell signal transduction", *J. Biol. Chem.*, *269*, 20718-20726 (1994), and the references incorporated therein.

3. Proliferation assays

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

The following Examples illustrate embodiments of the present invention, and are not intended to limit the scope of the claims. Abbreviations employed in the Examples are defined below. Compounds of the Examples are identified by the example and step in which they are prepared (for example, "1A" denotes the title compound of step A of Example 1), or by the example only where the compound is the title

compound of the example (for example, "2" denotes the title compound of Example 2).

Abbreviations

aq. = aqueous

conc. = concentrated

DMSO = dimethylsulfoxide

EtOAc = ethyl acetate

Et_2O = diethyl ether

h = hours

HATU = N-[dimethylamino-1H-1,2,3-triazolo-[4,5-b]pyridin-1-yl methylene]-N-methyl methanaminium hexafluorophosphate N-oxide

MeOH = methanol

MOPS = 4-morpholine-propanesulfonic acid

MS = mass spectrometry

Ret Time = retention time

RT = room temperature

satd. = saturated

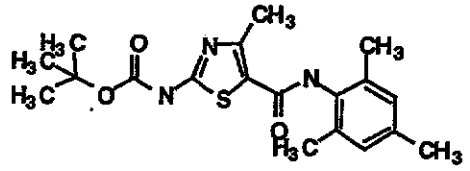
TFA = trifluoroacetic acid

THF = tetrahydrofuran

DMF= N,N-dimethylformamide

Example 1

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



3. Ethyl-2-*tert*-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylate

A suspension of ethyl-2-amino-4-methyl-thiazole-5-carboxylate (18.6 g, 100 mmol), di-t-butyldicarbonate (26.2 g, 120 mmol) and 4-dimethylaminopyridine (800 mg, 6.55 mmol) in dry tetrahydrofuran (300 mL) was stirred under nitrogen for 18 h. The solvent was evaporated *in vacuo*. The residue was suspended in dichloromethane (1 L) and filtered through a pad of celite. The filtrate was washed with 1 N aqueous HCl solution (300 mL, 2x), water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was triturated with hexanes. The solid was filtered and dried *in vacuo* to obtain the title compound (20 g, 72%) as a tan solid.

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

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

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

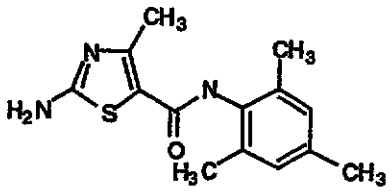
A 2 M solution of oxalyl chloride in dichloromethane (22.5 mL, 45 mmol) was added dropwise to a stirred suspension of 2-*tert*-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid (10 g, 38.72 mmol) in dichloromethane (150 mL) and N,N-dimethyl formamide (150 µL) at 0°C. The suspension gradually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

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

2,4,6-Trimethyl aniline (6.3 mL, 38.66 mmol) was added dropwise to a stirred solution of 2-*tert*-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid chloride (10.7 g, 38.66 mmol) in dichloromethane (150 mL) at 0°C. After 20 min, diisopropylethylamine (8.8 mL, 44.88 mmol) was added dropwise. The solution was allowed to warm to rt and stirred for an additional 2 h. The solvent was evaporated *in vacuo*. The residue was suspended in EtOAc (700 mL), washed with 1 N aq. HCl solution (300 mL, 2x), water, and brine; dried ($MgSO_4$), filtered and concentrated. The residue was triturated with ether to obtain the title compound (12.5 g, 86%) as a tan solid.

Example 2

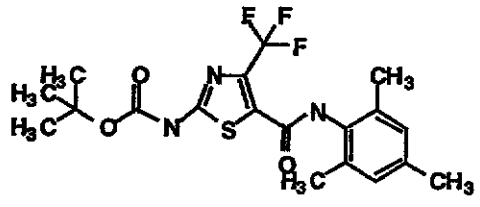
Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-methyl-5-thiazolecarboxamide



A solution of [5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester (10 g, 26.63 mmol) in trifluoroacetic acid (100 mL) was stirred at rt for 3 h. The solution was concentrated under reduced pressure and the residue was diluted with EtOAc (700 mL), washed with 5% aq. $KHCO_3$ solution (400 mL, 2x), water, and brine; dried ($MgSO_4$), filtered and concentrated. The residue was washed with ether (200 mL) and acetonitrile (100 mL) to obtain the title compound (6.7 g, 91%) as a white solid.

Example 3

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



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

A suspension of ethyl-2-amino-4-trifluoromethyl-thiazole-5-carboxylate (5.05 g, 21.02 mmol), di-t-butyldicarbonate (4.82 g, 22.07 mmol) and 4-dimethylaminopyridine (260 mg, 2.1 mmol) in dichloromethane (209 mL) was stirred under nitrogen for 1.5 h. The solvent was evaporated *in vacuo*. The residue was chromatographed on a silica gel column. Elution with 5%

EtOAc in hexanes, followed by 15% EtOAc in hexanes afforded the title compound (6.57 g, 92%) as a white solid.

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

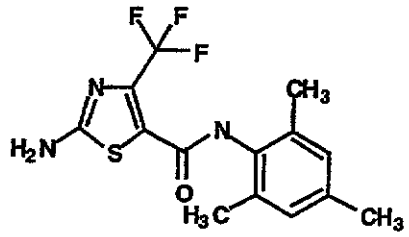
A stirred solution of ethyl-2-*tert*-butoxycarbonyloxyamino-4-trifluoromethyl-thiazole-5-carboxylate (6.5 g, 19.1 mmol) in methanol (100 mL) was treated with a 1N aq. NaOH solution (573 mL). The mixture was stirred at rt overnight. The solution was cooled to 0^0C and acidified with a 6 M aq. HCl solution to pH 1 and extracted with chloroform (150 mL, 6x). The chloroform extracts were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure and *in vacuo* to obtain the title acid (5.75 g, 96%) as a white solid.

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

4-Methylmorpholine (40 µL, 0.39 mmol) was added to a mixture of 2-*tert*-butoxycarbonyloxyamino-4-trifluoromethyl-thiazole-5-carboxylic acid (100 mg, 0.32 mmol), 2,4,6-trimethylaniline (45 µL, 0.32 mmol), and benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP reagent, 380 mg, 0.4 mmol) in DMF (2 mL). The solution was stirred at rt for 72 h, diluted with dichloromethane and washed with 0.25 M aq. $KHSO_4$ solution followed by satd. Aq. $KHCO_3$ solution. The dichloromethane extract was separated, dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 5% EtOAc in hexanes followed by 10% EtOAc in hexanes to obtain the title compound (90 mg, 65%) as a white solid.

Example 4

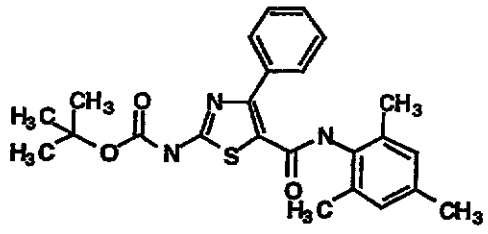
Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-trifluoromethyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

Example 5

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



3. Ethyl-2-*tert*-butoxycarbonyloxyamino-4-phenyl-thiazole-5-carboxylate

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

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

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

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

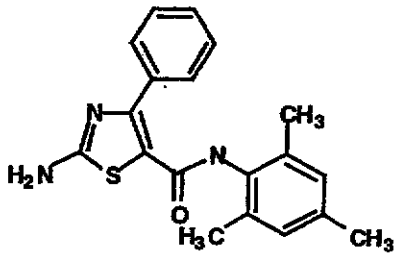
Compound **5C** was prepared by an analogous method as that of **1C**, except using **5B** to give the title compound **5C** as a white solid (90%).

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

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

Example 6

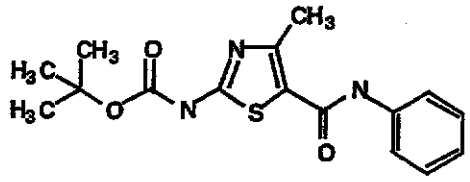
Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-phenyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

Example 7

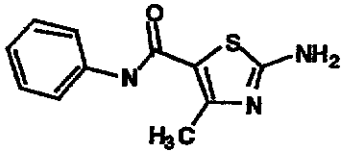
Preparation of [5-[[Phenylamino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



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

Example 8

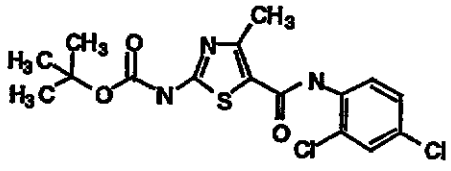
Preparation of 2-Amino-N-(phenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

Example 9

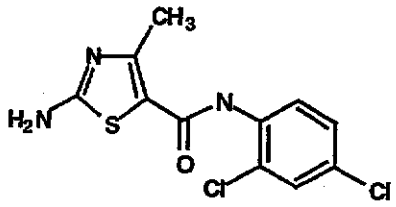
Preparation of [5-[[(2,4-Dichlorophenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



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

Example 10

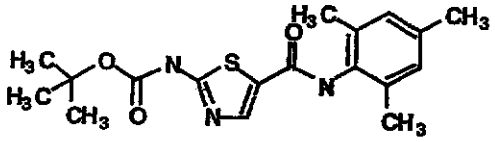
Preparation of 2-Amino-N-(2,4-dichlorophenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

Example 11

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



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

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

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

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

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

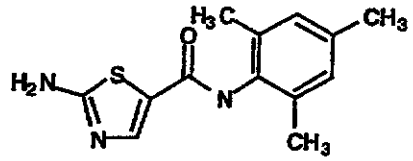
Compound **11C** was prepared by an analogous method as that of **1C**, except using **11B** to give the title compound **11C**.

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

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

Example 12

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



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

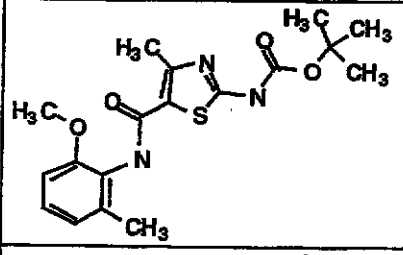
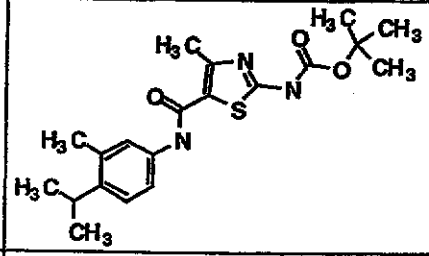
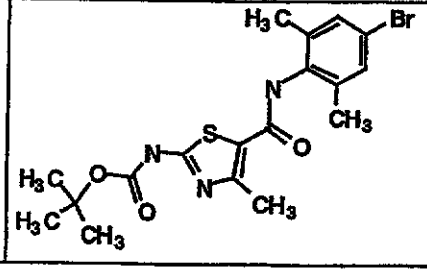
Examples 13 to 53

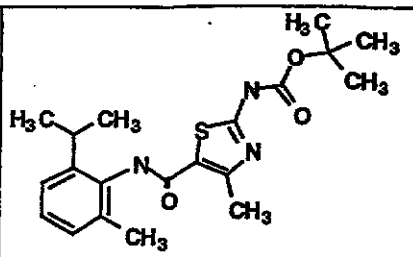
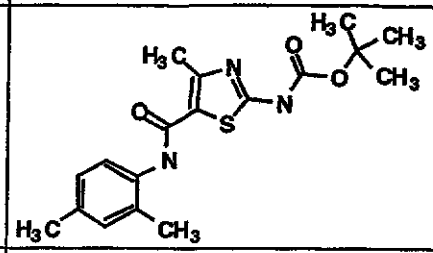
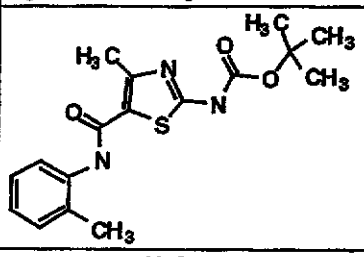
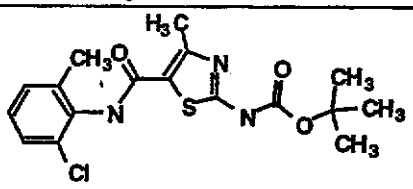
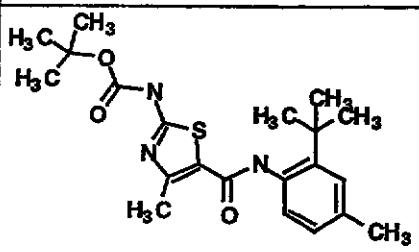
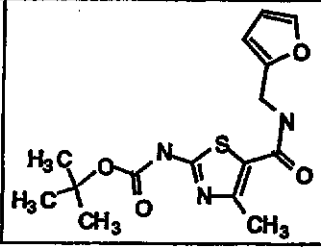
General Procedure

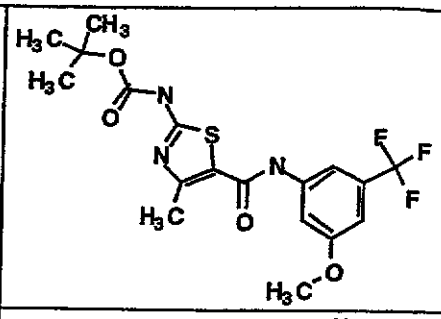
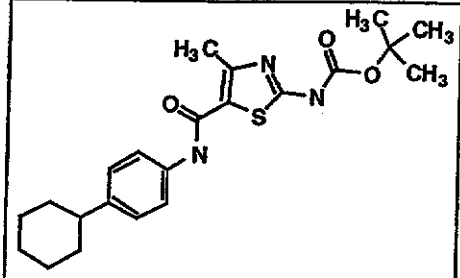
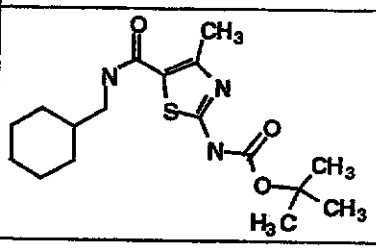
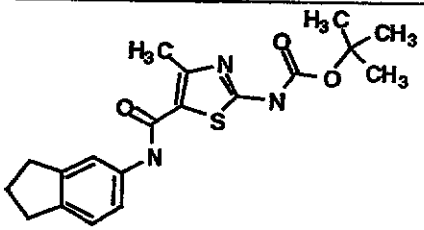
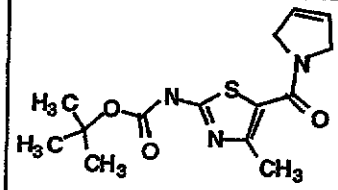
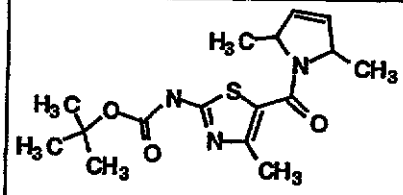
Compounds **13** to **53** were prepared following the procedure described below. Appropriate amines (0.40 mmol) and diisopropylethylamine (70 μL, 0.40 mmol) were added to a suspension of **1C** (100 mg, 0.36 mmol) in dichloromethane (3 mL). The solution was stirred mechanically in a sealed tube at rt for 16 h. The reaction mixtures were diluted with methanol (200 μL) and loaded in Varian SCX ion exchange columns (2 g/6 cc) pretreated with methanol-dichloromethane (8 mL, 1:1) followed by dichloromethane (8 mL). SCX Column filtration were performed using a Gilson robot unit. The column was washed sequentially with dichloromethane (9 mL),

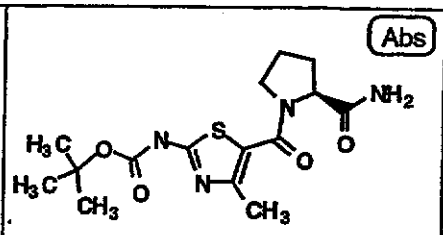
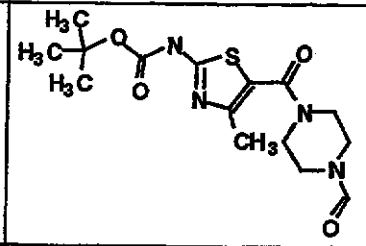
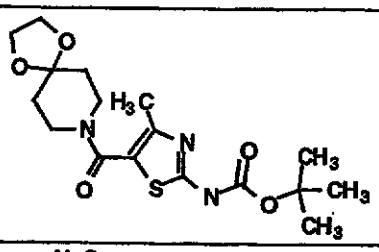
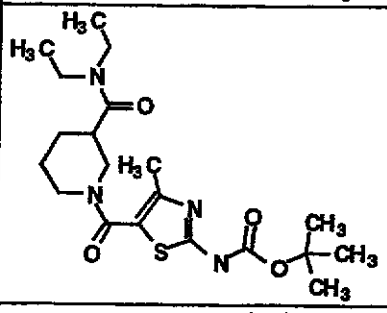
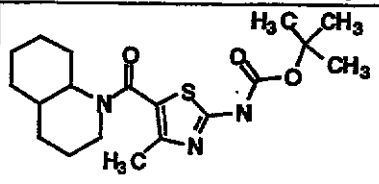
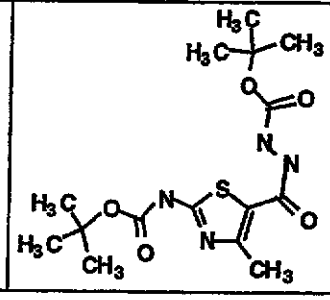
dichloromethane-methanol (9 mL, 4:1), dichloromethane-methanol (9 mL, 1:1), methanol (9 mL), 0.01 M ammonium hydroxide in methanol (9 mL) and 0.05 M ammonium hydroxide in methanol (9 mL). The elutes were collected separetely by the robot and then concentrated using a speed vac. Fractions containing the products were combined.

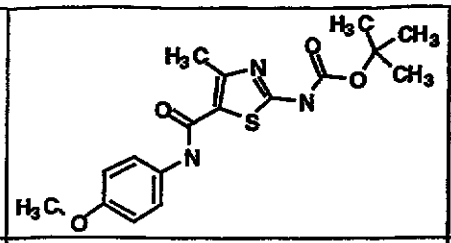
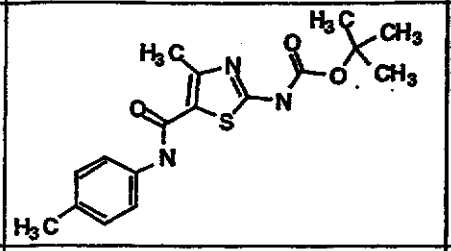
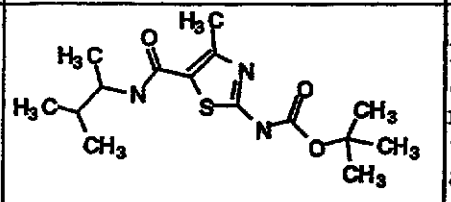
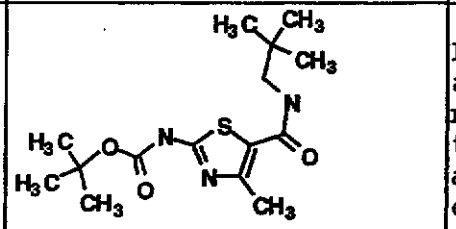
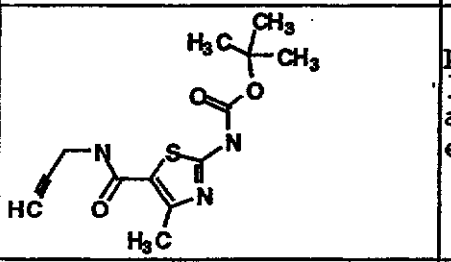
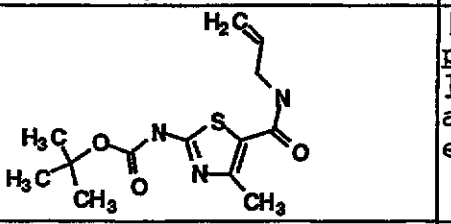
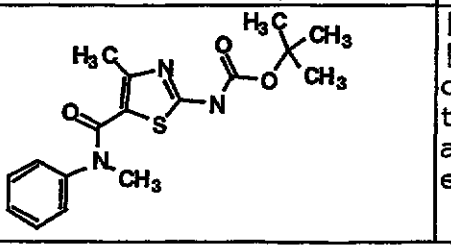
"HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H_2O, 0.2% H_3PO_4) to 100% solvent B (90% MeOH, 10% H_2O, 0.2% H_3PO_4), flow rate 4 mL/min, λ = 220 nM.

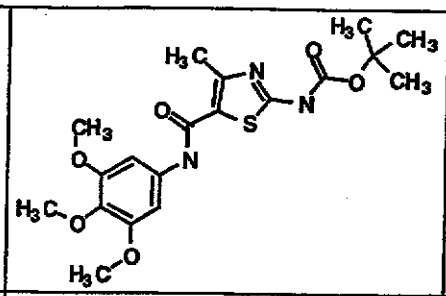
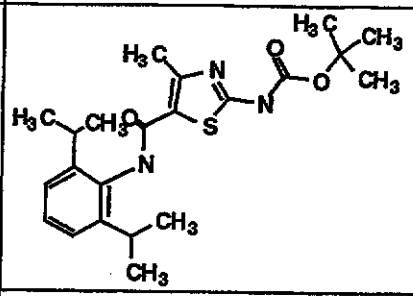
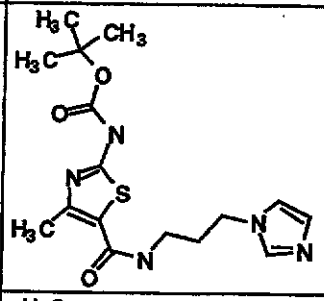
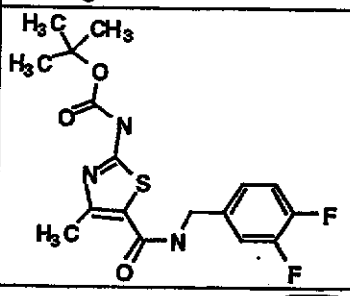
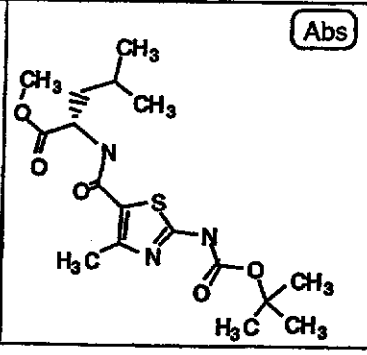
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
13		[5-[[(2-Methoxy-6-methylphenyl)amino]-carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.79
14		[4-Methyl-5-[[[3-methyl-4-(1-methyl-ethyl)phenyl] amino]-carbonyl]-2-thiazolyl]-carbamic acid 1,1-dimethylethyl ester	4.51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

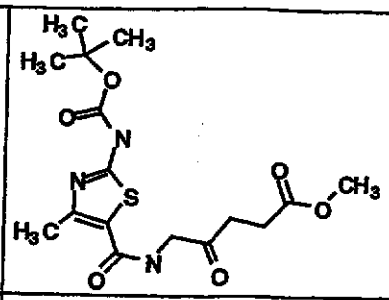
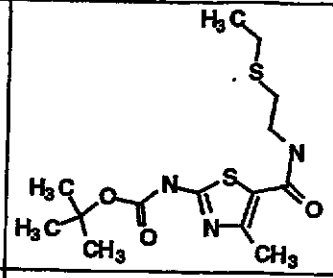
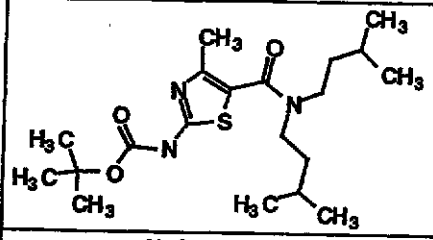
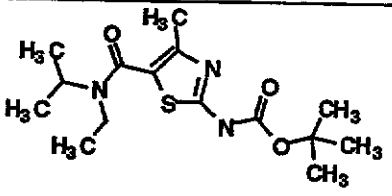
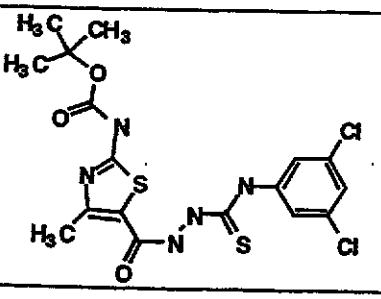
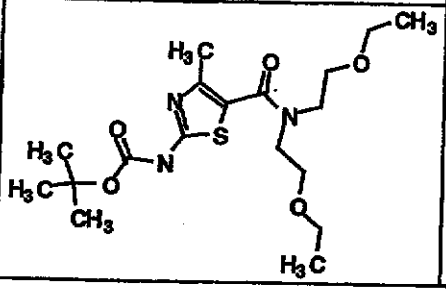
16		[4-Methyl-5-[[[2-methyl-6-(1-methylethyl)phenyl]-amino]carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.17
17		[5-[[(2,4-Dimethylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.05
18		[4-Methyl-5-[[(2-methylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.87
19		[5-[[(2-Chloro-6-methylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.86
20		[5-[[[2-(1,1-Dimethylethyl)-4-methylphenyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.30
21		[5-[[(2-Furanylmethyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.54

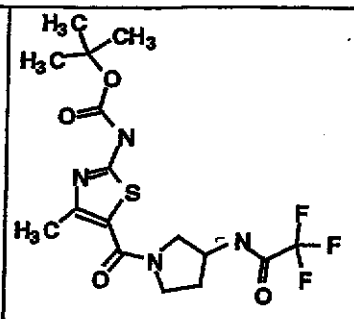
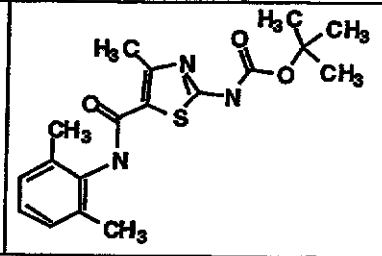
22		[5-[[[3-Methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.43
23		[5-[[(4-Cyclohexylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.78
24		[5-[[(Cyclohexylmethyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.21
25		[5-[[(2,3-Dihydro-1H-indenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.30
26		[5-[(2,5-Dihydro-1H-pyrrol-1-yl)carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.56
27		[5-[(2,5-Dihydro-2,5-dimethyl-1H-pyrrol-1-yl)carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.86

28		1-[[2-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-5-thiazolyl]carbonyl]-L-prolinamide	2.96
29		[5-[(4-Formyl-1-piperazinyl)carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	2.90
30		[5-(1,4-Dioxa-8-azaspiro[4.5]decan-8-ylcarbonyl)-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.54
31		[5-[[3-[(Diethylamino)carbonyl]-1-piperidinyl]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.66
32		[4-Methyl-5-[(octahydro-1-quinolinyl)carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.37
33		2-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-5-thiazolecarboxylic acid 2-[(1,1-dimethylethoxy)carbonyl]hydrazide	3.50

34		[5-[[(4-Methoxyphenyl) amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.83
35		[4-Methyl-5-[[(4-methylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.07
36		[5-[[(1,2-Dimethylpropyl) amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.87
37		[5-[[(2,2-Dimethylpropyl) amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.97
38		[4-Methyl-5-[(2-propynylamino)carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.22
39		[4-Methyl-5-[(2-propenylamino)carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.41
40		[4-Methyl-5-[(methylphenylamino) carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.75

41		[4-Methyl-5-[[(3,4,5-trimethoxyphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.84
42		[5-[[[2,6-Bis(1-methylethyl)phenyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.40
43		[5-[[[3-(1H-Imidazol-1-yl)propyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	2.45
44		[5-[[[(3,4-Difluorophenyl)methyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.97
45		N-[[2-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-5-thiazolyl]carbonyl]-L-leucine methyl ester	3.99

46		5-[[[2-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-5-thiazolyl]carbonyl]amino]-4-oxopentanoic acid methyl ester	3.27
47		[5-[[[2-(Ethylthio)ethyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.75
48		[5-[[Bis(3-methylbutyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.67
49		[5-[[Ethyl(1-methylethyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.84
50		2-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-5-thiazolecarboxylic acid 2-[[(3,5-dichlorophenyl)amino]thioxomethyl]hydrazide	4.66
51		[5-[[Bis(2-ethoxyethyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.83

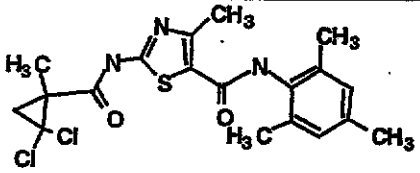
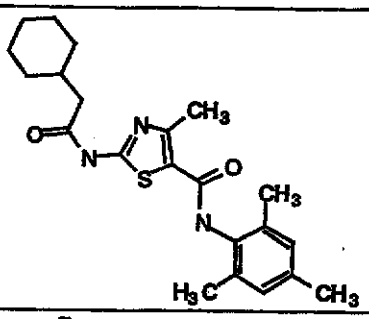
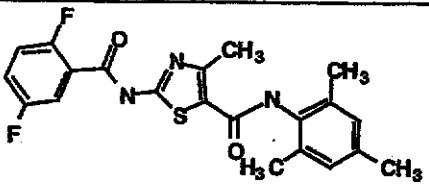
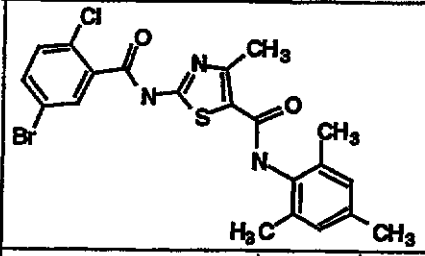
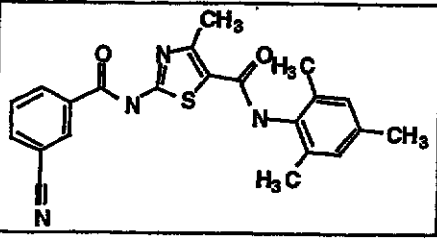
52		[4-Methyl-5-[[3-[(trifluoroacetyl)amino]-1-pyrrolidinyl]carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.47
53		[5-[[(2,6-Dimethylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.87

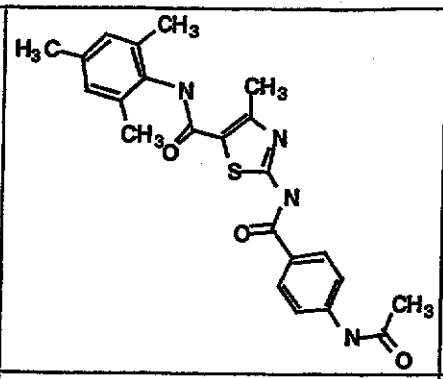
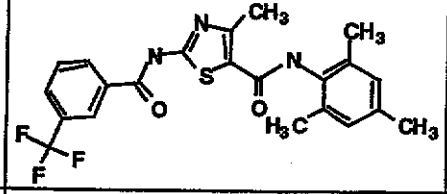
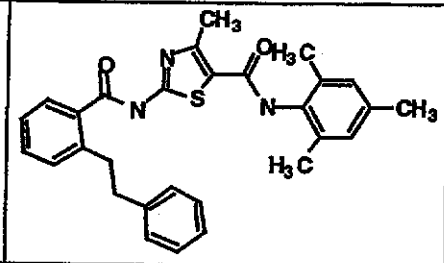
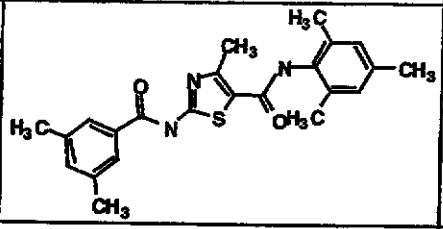
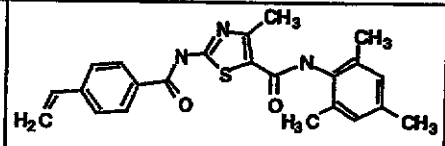
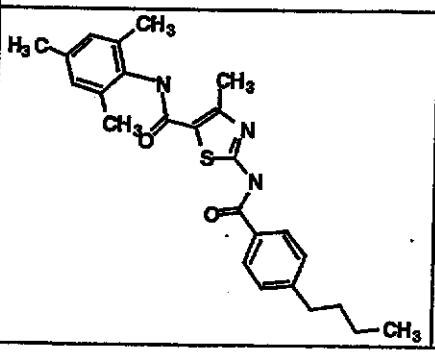
Examples 54 to 129

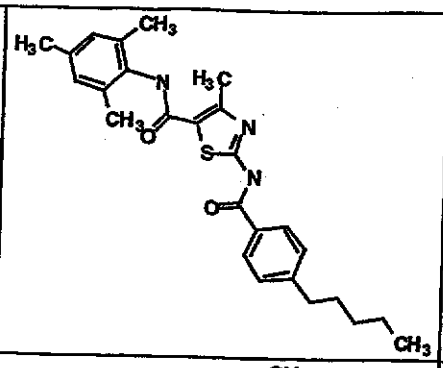
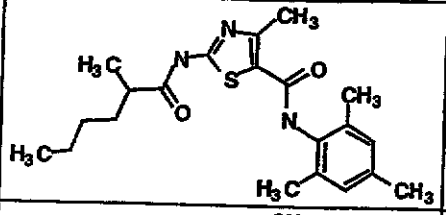
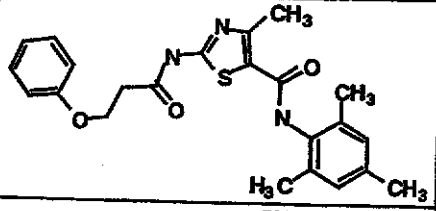
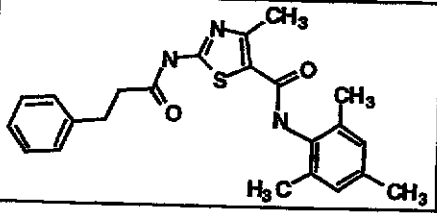
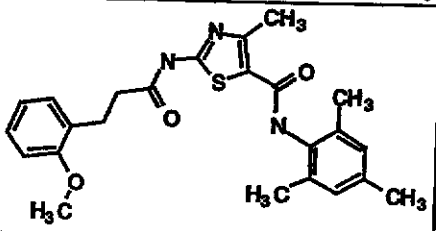
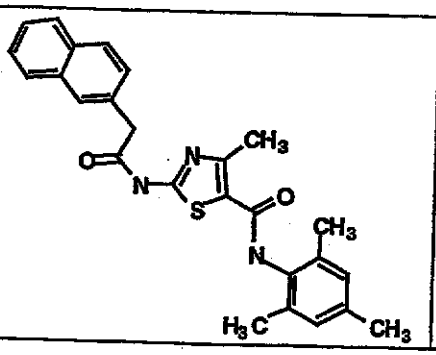
General Procedure

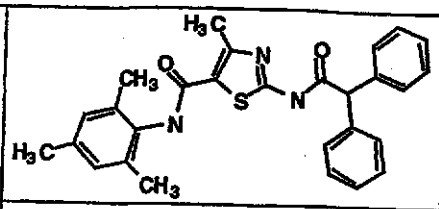
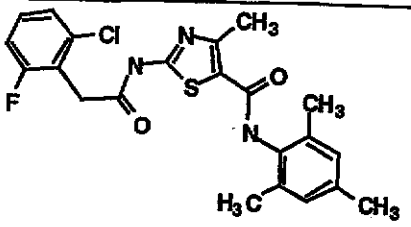
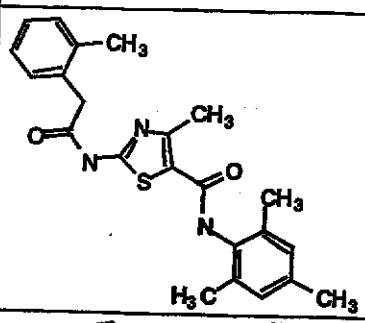
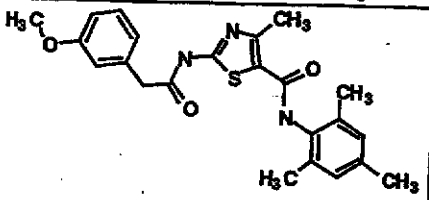
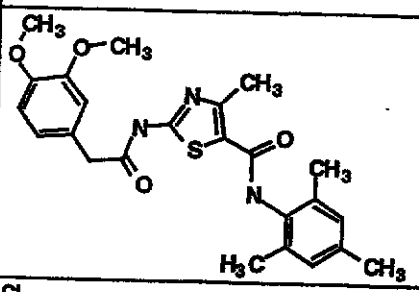
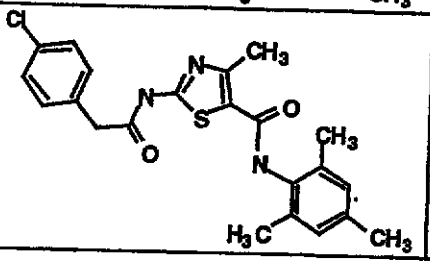
Compounds **54** to **129** were prepared following the procedure described below. Diisopropylethyl amine (60 µL, 0.34 mmol) was added to a mixture of amine **2** (30 mg, 0.11 mmol), appropriate carboxylic acid (0.13 mmol), 1-hydroxy-7-azabenzotriazole (19.5 mg, 0.14 mmol), and ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (26.8 mg, 0.14 mmol) in THF (0.4 mL). The mixture was heated in a sealed tube under argon at 45°C for 24 h. The reaction mixture was diluted with dichloromethane (4 mL) and washed with 2 N aq. HCl solution (2 mL, 3x). The dichloromethane solution was passed through a Varian SCX cation exchange column (2 g, 6 cc) on a Gilson robot. The column was eluted sequentially with acetonitrile-methanol (10 mL, 4:1), methanol-2M methanolic ammonia (3 mL, 4:1), and 2 M methanolic ammonia solution (3 mL, 4x). The fractions were collected separately using the Gilson robot. Fraction containing the product was concentrated and dried *in vacuo* . "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H_2O, 0.2% H_3PO_4) to 100%

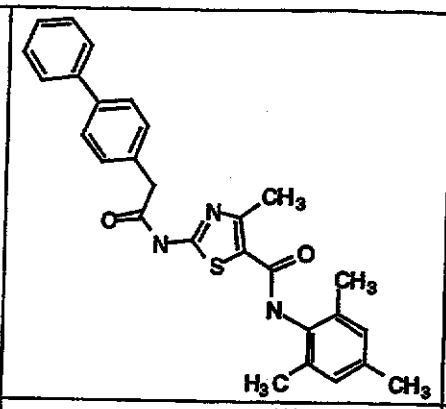
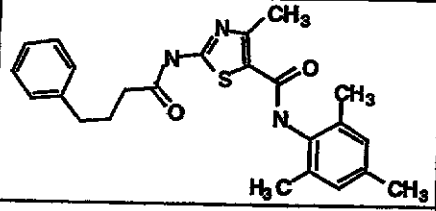
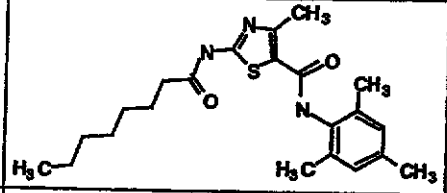
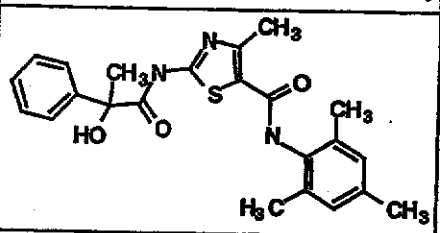
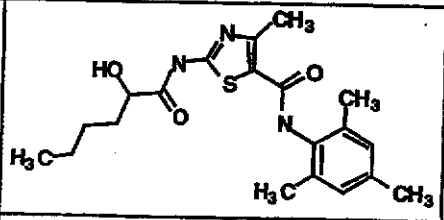
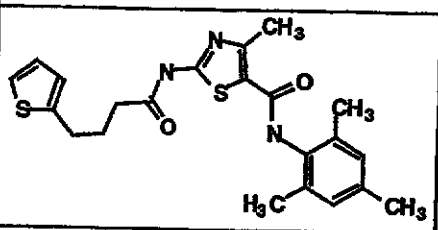
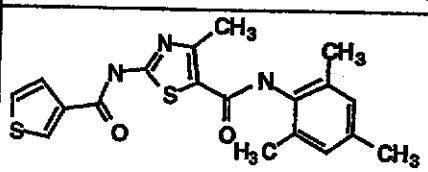
solvent B (90% MeOH, 10% H_2O, 0.2% H_3PO_4), flow rate 4 mL/min, λ = 220 nM for compounds **54 - 127**. For compounds **128 -129** HPLC conditions are: Zorbax S8-C18 4.5 mm x 7.5 cm short column, 8 min gradient starting from 100% solvent A (10% MeOH, 90% H_2O, 0.2% H_3PO_4) to 100% solvent B (90% MeOH, 10% H_2O, 0.2% H_3PO_4), flow rate 2.5 mL/min, λ = 217 nM.

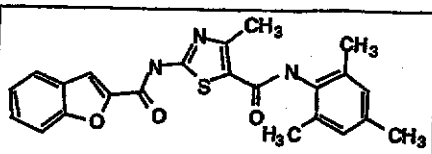
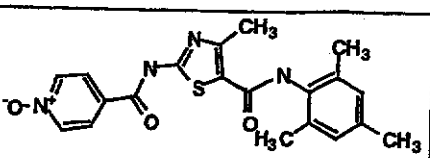
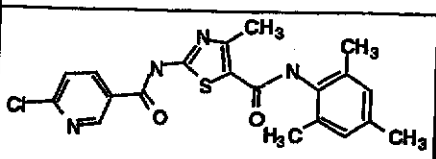
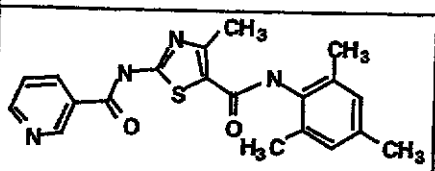
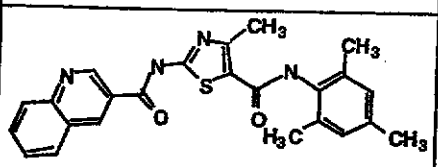
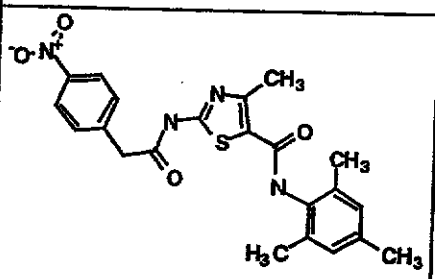
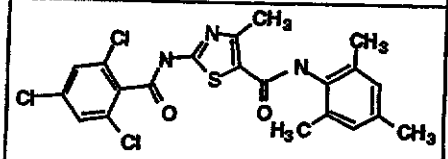
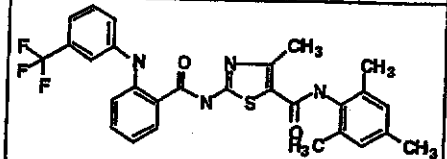
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
54		2-[[(2,2-Dichloro-1-methylcyclopropyl)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.22
55		2-[(Cyclohexylacetyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.47
56		2-[(2,5-Difluorobenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.15
57		2-[(5-Bromo-2-chlorobenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.37
58		2-[(3-Cyanobenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.06

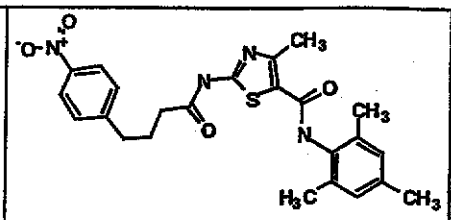
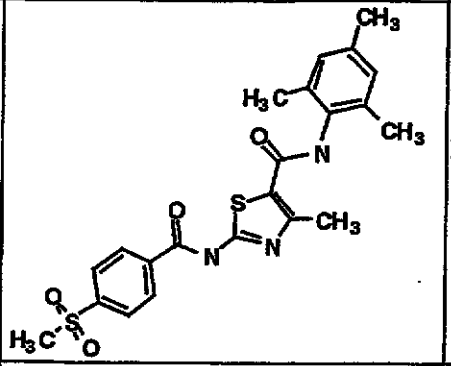
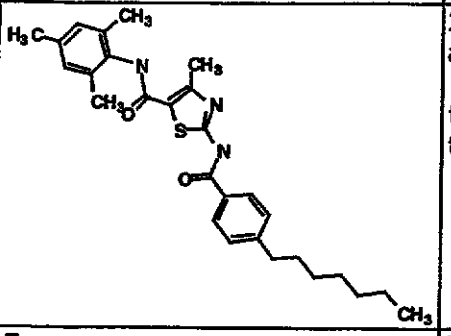
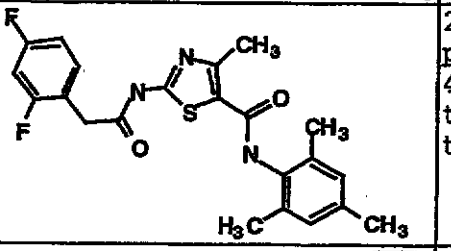
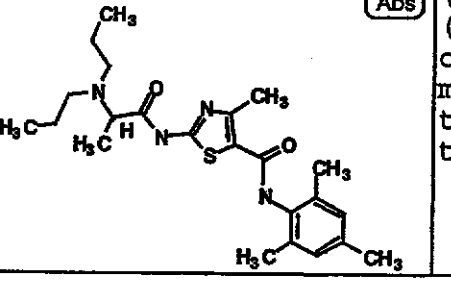
59		2-[[4-(Acetylamino)-benzoyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.60
60		4-Methyl-2-[[3-(trifluoromethyl)benzoyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.45
61		4-Methyl-2-[[2-(2-phenylethyl)benzoyl]-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.64
62		2-[(3,5-Dimethyl-benzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.49
63		2-[(4-Ethenyl-benzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	
64		2-[(4-Butyl-benzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.58

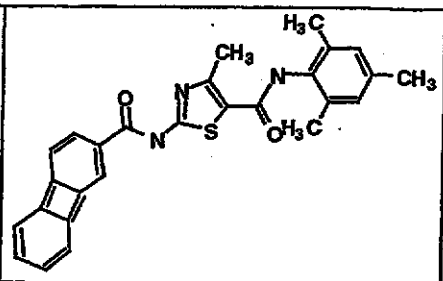
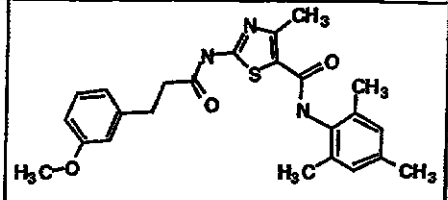
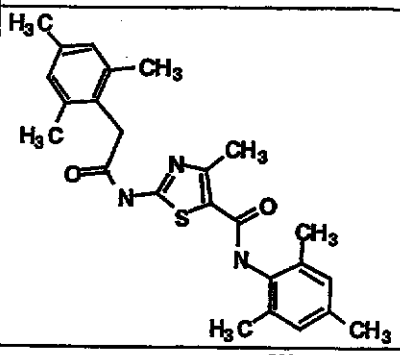
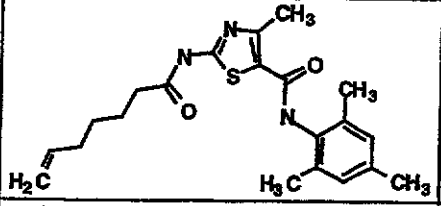
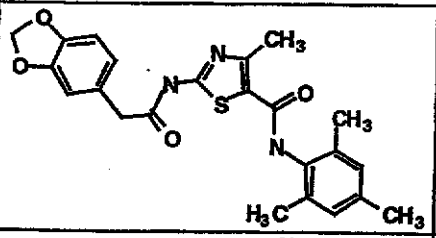
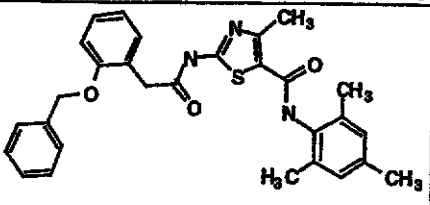
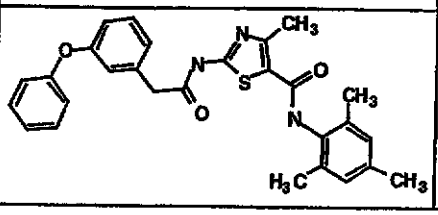
65		4-Methyl-2-[(4-pentylbenzoyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.76
66		4-Methyl-2-[(2-methyl-1-oxohexyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.41
67		4-Methyl-2-[(1-oxo-3-phenoxypropyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.21
68		4-Methyl-2-[(1-oxo-3-phenylpropyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.26
69		2-[[3-(2-Methoxyphenyl)-1-oxopropyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.31
70		4-Methyl-2-[(2-naphthalenylacetyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.43

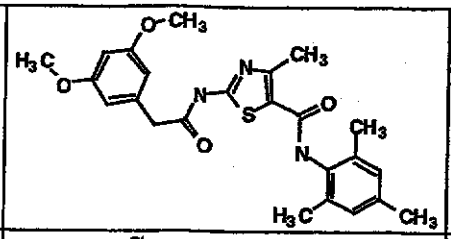
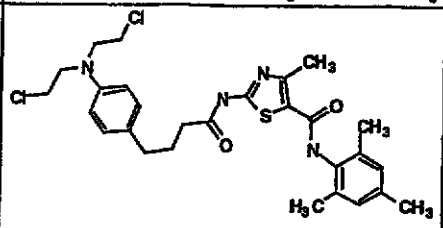
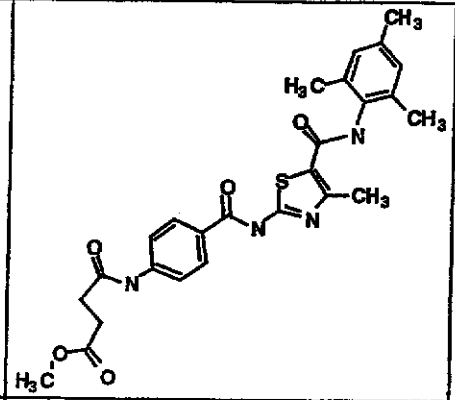
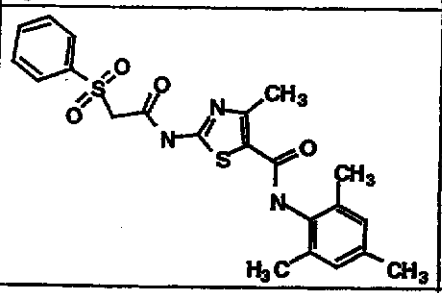
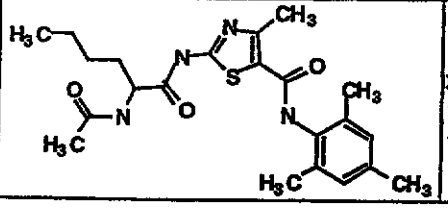
71		2-[(Diphenyl-acetyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.13
72		2-[[(2-Chloro-6-fluorophenyl)acetyl]-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.17
73		4-Methyl-2-[[(2-methylphenyl)-acetyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazolecarboxamide	3.95
74		2-[[(3-Methoxy-phenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.11
75		2-[[(3,4-Dimethoxy-phenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.90
76		2-[[(4-Chloro-phenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.34

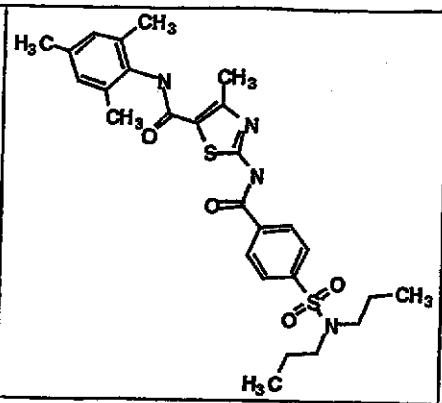
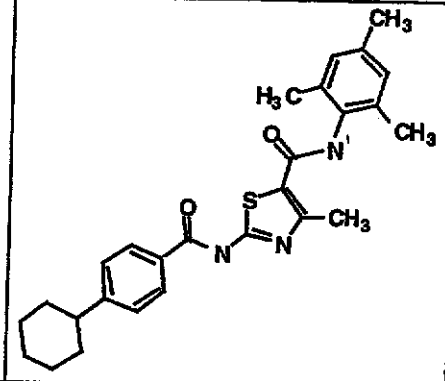
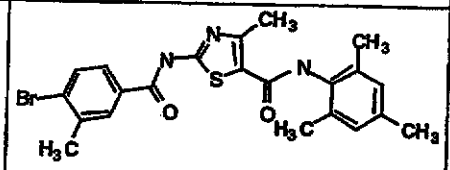
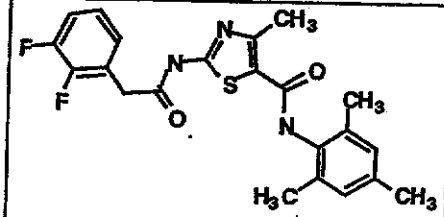
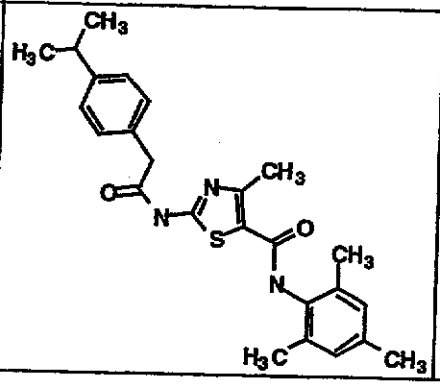
77		2-[([1,1'-Biphenyl]-4-ylacetyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.60
78		4-Methyl-2-[(1-oxo-4-phenylbutyl)amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.40
79		4-Methyl-2-[(1-oxooctyl)amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.65
80		2-[(2-Hydroxy-2-phenyl-1-oxopropyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.13
81		2-[(2-Hydroxy-1-oxohexyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.14
82		4-Methyl-2-[[1-oxo-4-(2-thienyl)-butyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.32
83		4-Methyl-2-[(3-thienylcarbonyl)amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.04

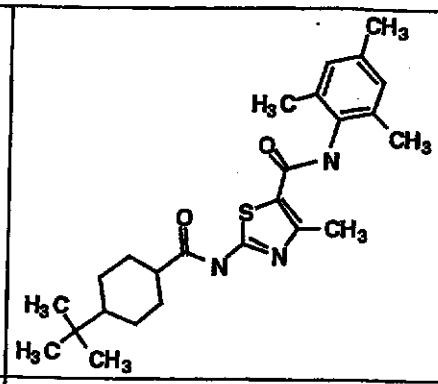
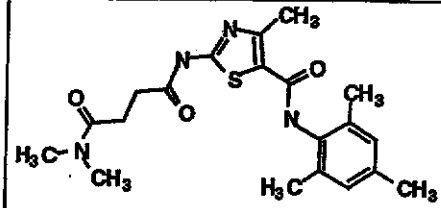
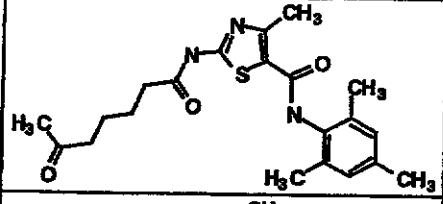
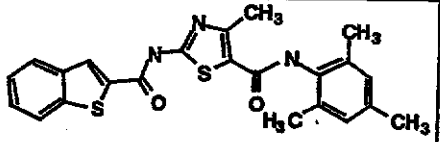
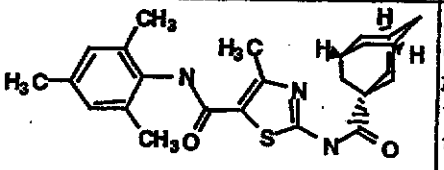
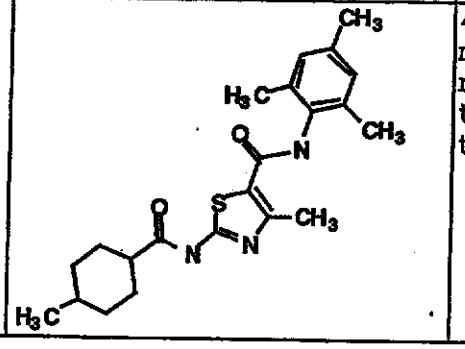
84		2-[(2-Benzofuranyl-carbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.37
85		N-[4-Methyl-5-[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-4-pyridinecarboxamide, N-oxide	3.50
86		6-Chloro-N-[4-methyl-5-[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-3-pyridinecarboxamide	4.08
87		N-[4-Methyl-5-[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-3-pyridinecarboxamide	3.56
88		N-[4-Methyl-5-[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-3-quinolinecarboxamide	4.11
89		4-Methyl-2-[[(4-nitrophenyl)acetyl]-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.08
90		4-Methyl-2-[(2,4,6-trichlorobenzoyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.45
91		4-Methyl-2-[[2-[[3-(trifluoromethyl)-phenyl]amino]benzoyl]-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.86

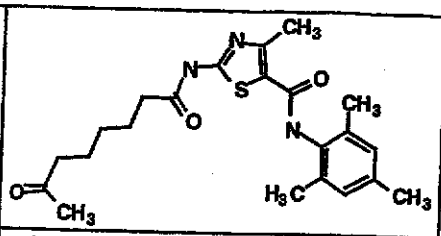
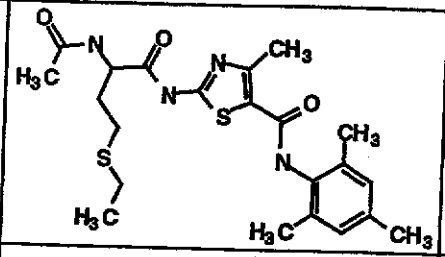
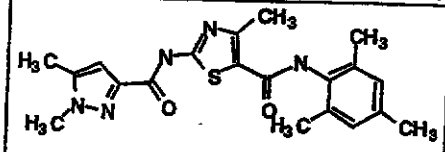
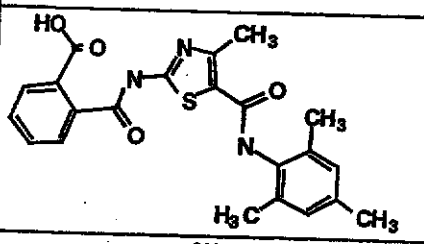
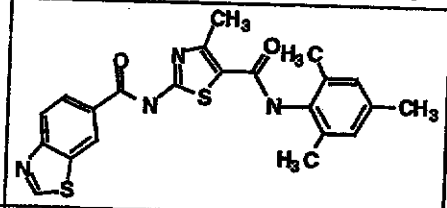
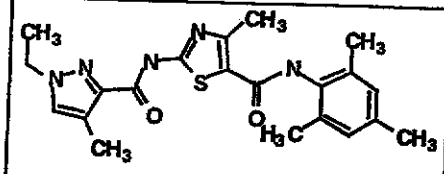
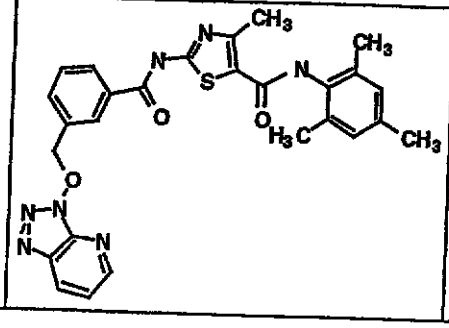
92		4-Methyl-2-[[4-(4-nitrophenyl)-1-oxobutyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.28
93		4-Methyl-2-[[4-(methyl-sulfonyl)-benzoyl]-amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	3.79
94		2-[(4-Heptylbenzoyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	
95		2-[[(2,4-Difluoro-phenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.15
96		(S)-2-[[2-(Dipropylamino)-1-oxopropyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.20

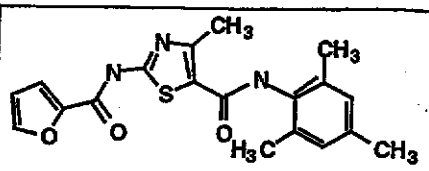
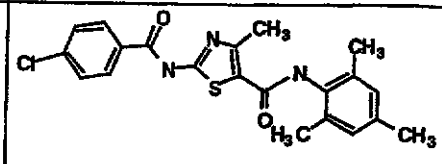
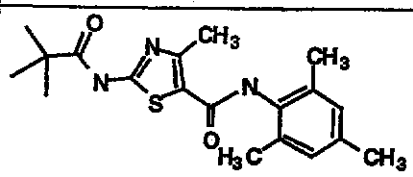
97		2-[(2-Biphenyl-enecarbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.64
98		2-[[3-(3-Methoxyphenyl)-1-oxopropyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.26
99		4-Methyl-N-(2,4,6-trimethylphenyl)-2-[[(2,4,6-trimethyl-phenyl)acetyl]amino]-5-thiazolecarboxamide	4.52
100		4-Methyl-2-[(1-oxo-6-heptenyl)amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.47
101		2-[[(1,3-Benzodioxol-5-yl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.07
102		4-Methyl-2-[[[2-(phenylmethoxy)phenyl]acetyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.46
103		4-Methyl-2-[[(3-phenoxyphenyl)acetyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.56

104		2-[(3,5-Dimethoxy-phenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.13
105		2-[[4-[4-[Bis(2-chloroethyl)amino]phenyl]-1-oxobutyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.75
106		4-[[4-[[[4-methyl-5-[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-amino]-carbonyl]phenyl]-amino]-4-oxobutanoic acid methyl ester	4.03
107		4-Methyl-2-[[(phenyl-sulfonyl)acetyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	3.77
108		2-[[2-(Acetylamino)-1-oxohexyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.99

109		2-[[4-[(Dipropyl-amino)sulfonyl]benzoyl]amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.51
110		2-[(4-Cyclohexyl-benzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.94
111		2-[(4-Bromo-3-methylbenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.80
112		2-[[(2,3-Difluorophenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.14
113		4-Methyl-2-[[[4-(1-methylethyl)phenyl]acetyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.56

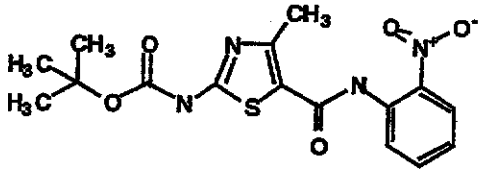
114		2-[[[4-(1,1-Dimethyl-ethyl)cyclohexyl]carbonyl]amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.85
115		N,N-Dimethyl-N'-[4-methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]butanediamide	3.50
116		2-[(1,6-Dioxohexyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.40
117		2-[(Benzo[b]thiophen-2-ylcarbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.53
118		2-[(1-Adamantyl-carbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.66
119		4-Methyl-2-[[(4-methylcyclohexyl)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.48

120		2-[(1,7-Dioxooctyl)-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	3.88
121		2-[[2-(Acetylamino)-4-(ethylthio)-1-oxobutyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.93
122		1,5-Dimethyl-N-[4-methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-1H-pyrazole-3-carboxamide	3.91
123		2-[[[4-methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]amino]carbonyl]benzoic acid	3.70
124		N-[4-Methyl-5-[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-6-benzo-thiazolecarboxamide	4.18
125		1-Ethyl-4-methyl-N-[4-methyl-5-[[(2,4,6-trimethylphenyl)-amino]carbonyl]-2-thiazolyl]-1H-pyrazole-3-carboxamide	4.09
126		4-Methyl-2-[[3-[(3H-1,2,3-triazolo[4,5-b]pyridin-3-yloxy)methyl]benzoyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.15

127		2-[(2-Furanyl-carbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.45
128		2-[(4-Chloro-benzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.85
129		2-[(2,2-Dimethyl-1-oxopropyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.30

Example 130

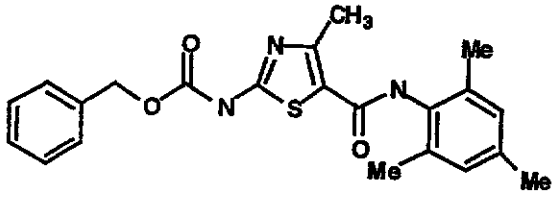
Preparation of [4-Methyl-5[[(2-nitrophenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



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

Example 131

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



3. Ethyl-2-benzyloxycarbonyloxyamino-4-methyl-thiazole-5-carboxylate

A 3 M aq. $NaHCO_3$ solution (10 mL, 30 mmol) was added to a stirred solution of ethyl-2-amino-4-methyl-thiazole-5-carboxylate (372 mg, 2 mmol) in THF (20 mL) at 0-5°C. Benzyl chloroformate (500 µL) was added. After 2 h, additional benzyl chloroformate (500 µL) and the biphasic solution was stirred for an additional 2 h at 0-5°C. The mixture was diluted with dichloromethane (50 mL) and water (30 mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on a silica gel column. Elution with 10% EtOAc in hexanes followed by 20% and 30% EtOAc in hexanes afforded the title compound (310 mg, 48%) as a white solid.

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

Compound **131B** was prepared by an analogous method as that of **3B**, except using **131A** to give the title compound **131B** as a white powder (77%).

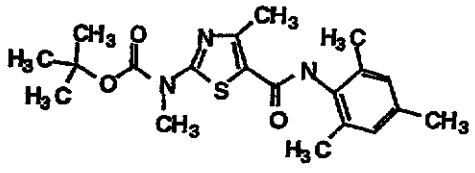
C. [4-Methyl-5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, phenylmethyl ester

Diisopropylethylamine (70 µL, 0.41 mmol) was added to a solution of **131B** (100 mg, 0.34 mmol), 2,4,6-trimethylaniline (60 µL, 0.41 mmol), and [O-(7-

azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate (HATU, 160 mg, 0.41 mmol). The mixture was stirred at rt for 24 h, diluted with EtOAc (20 mL) and washed with 2 N Aq. HCl solution (3x), brine, dried (Na_2SO_4), filtered and concentrated. The residue was triturated with ether (40 mL) to obtain the title compound (100 mg, 77%) as an off-white solid.

Example 132

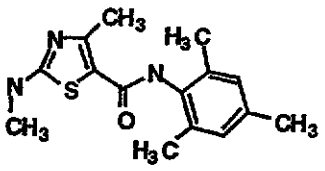
Preparation of Methyl[4-methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



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

Example 133

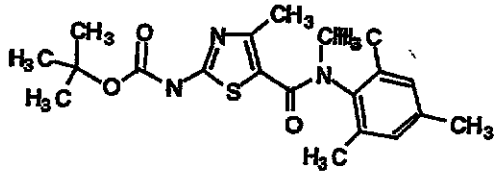
Preparation of 4-Methyl-2-(methylamino)-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

Example 134

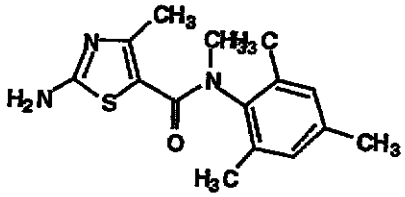
Preparation of [4-Methyl-5-[[methyl(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



Compound **134** was prepared by an analogous method as that of **1**, except using N-methyl-2,4,6-trimethylaniline to give the title compound **134** as a white solid (60%).

Example 135

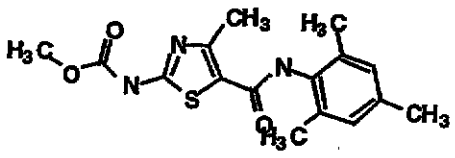
Preparation of 2-Amino-N,4-dimethyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

Example 136

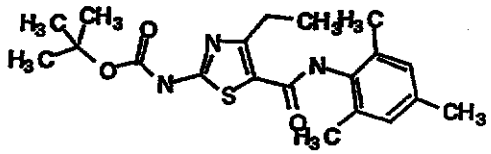
Preparation of [4-Methyl-5[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, methyl ester



A mixture of **2** (100 mg, 0.36 mmol), pyridine (87 µL, 1.08 mmol), methyl chloroformate (111 µL, 1.44 mmol) in dichloromethane (3 mL) was stirred at rt for 1.5 h. The solution was diluted with dichloromethane and washed with aq. $NaHCO_3$ solution (20 mL, 2x), brine; dried ($MgSO_4$), filtered and concentrated. The residue was triturated with ether to obtain the title compound (88 mg, 82%) as a white solid.

Example 137

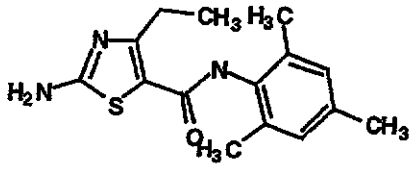
Preparation of [4-Ethyl-5[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



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

Example 138

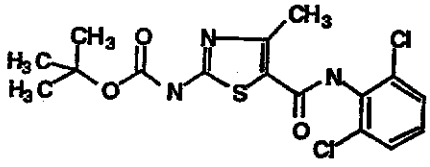
Preparation of 2-Amino-4-ethyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide, trifluoroacetate



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

Example 139

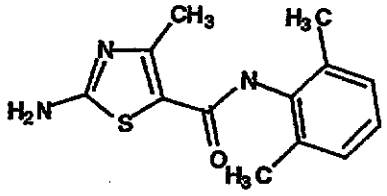
Preparation of [5-[[(2,6-Dichlorophenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



A 1 M solution of sodium bis-trimethylsilyl amide (290 μL, 0.29 mmol) was added to a stirred solution of 2,6-dichloroaniline (13.4 mg, 0.08 mmol) in THF (1 mL). After 30 min, the mixture was cooled to 0 °C and **1C** (30 mg, 0.11 mmol) was added in one portion. The mixture was allowed to warm to rt and stirred for 16 h. The solution was diluted with dichloromethane and washed with 2 N aq. HCl solution (2 mL, 3x), dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 30% EtOAc in hexanes to obtain the title compound (20 mg, 45%) as a light yellow solid.

Example 140

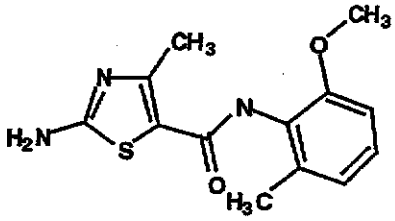
Preparation of 2-Amino-N-(2,6-dimethylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

Example 141

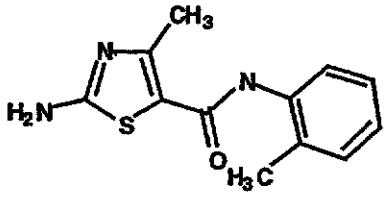
Preparation of 2-Amino-N-(2-methoxy-6-methylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

Example 142

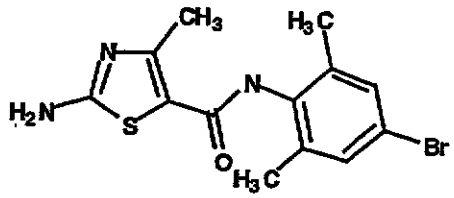
Preparation of 2-Amino-N-(2-methylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

Example 143

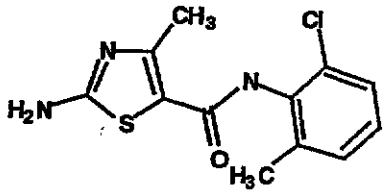
Preparation of 2-Amino-N-(2,6-dimethyl-4-bromophenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

Example 144

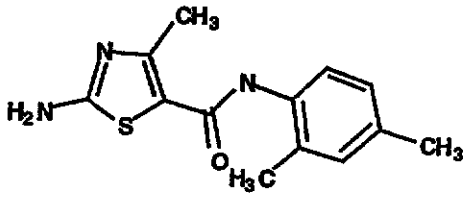
Preparation of 2-Amino-N-(2-chloro-6-methylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

Example 145

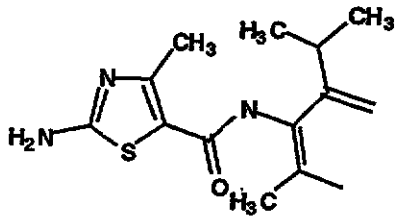
Preparation of 2-Amino-N-(2,4-dimethylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

Example 146

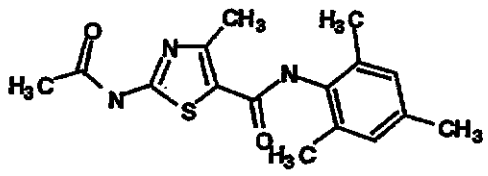
Preparation of 2-Amino-N-(2-methyl-6-isopropylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

Example 147

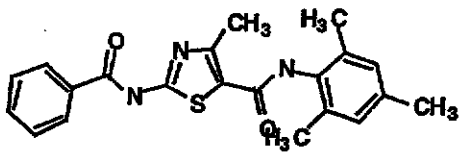
Preparation of 2-(Acetylamino)-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



A mixture of **2** (54 mg, 0.2 mmol), acetic anhydride (22 µL, 0.23 mmol), dimethylaminopyridine (3 mg) in dichloromethane (4.5 mL) was stirred at rt for 4.5 h. The mixture was diluted with dichloromethane (65 mL) and washed with 1 N aq. HCl solution (20 mL), water; dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 35% EtOAc in hexanes to obtain the title compound (43 mg, 69%) as a white solid.

Example 148

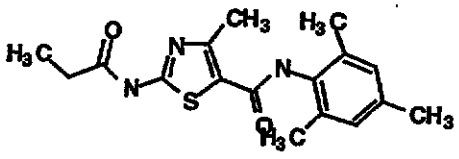
Preparation of 2-(Benzoylamino)-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



A solution of **2** (100 mg, 0.36 mmol) and benzoic anhydride (226 mg, 1 mmol) in dichloromethane (10 mL) and pyridine (2 mL) was stirred at rt overnight. The mixture was diluted with dichloromethane (50 mL) and washed with 2 N aq. HCl solution (15 mL, 2x), 10% aq. $NaHCO_3$ solution (20 mL, 2x); dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 30% EtOAc in hexanes followed by 50% EtOAc in hexanes to obtain the title compound contaminated with benzoic acid. The solid was dissolved in EtOAc (40 mL) and washed with satd. $KHCO_3$ solution (15 mL, 4x), dried ($MgSO_4$), filtered and concentrated to obtain the title compound (110 mg, 80%) as a white solid.

Example 149

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

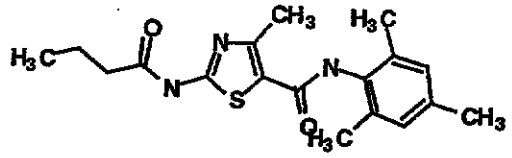


A mixture of **2** (100 mg, 0.36 mmol), propionic anhydride (332 µL, 2.58 mmol) in dichloromethane (10 mL) and pyridine (4 mL) was stirred at rt for 3 h. Dimethylaminopyridine (122 mg, 1 mmol) was added and the mixture was stirred for additional 1.5 h. The mixture was diluted with

dichloromethane and washed with 1 N aq. HCl solution (25 mL, 3x), aq. NaHCO3 solution (20 mL, 2x), water(20 mL), brine; dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 20% EtOAc in hexanes to obtain the title compound (81 mg, 68%) as a white solid.

Example 150

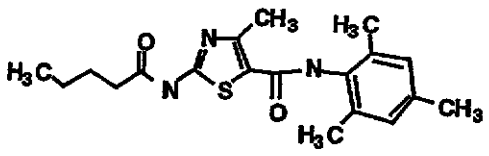
Preparation of 4-methyl-2-[(1-oxobutyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



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

Example 151

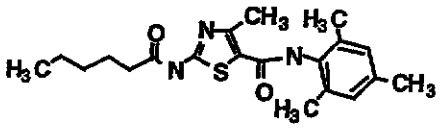
Preparation of 4-methyl-2-[(1-oxopentyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



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

Example 152

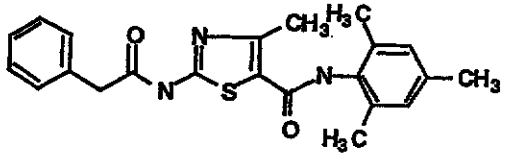
Preparation of 4-methyl-2-[(1-oxohexyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



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

Example 153

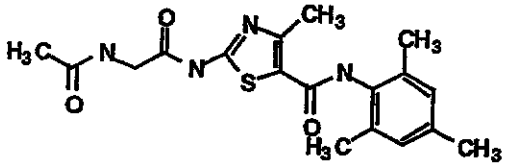
Preparation of 4-Methyl-2-[(phenylcetyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



A solution of amine **2** (50 mg, 0.18 mmol), diisopropylethylamine (101 μL, 0.58 mmol), phenylacetic acid (27.2 mg, 0.20 mmol), 1-hydroxy-7-azabenzotriazole (29.4 mg, 0.22 mmol), and ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (42.2 mg, 0.22 mmol) in dichloromethane (0.62 mL) was mechanically stirred in a sealed vial for 16 h. The reaction mixture was passed through a Varian SCX ion exchange column (2 g/6 cc) and eluted with acetonitrile-methanol (10 mL, 4:1) followed by 2 M methanolic ammonia solution (9 mL). Fractions containing the product were combined and then concentrated. The residue was dissolved in dichloromethane and washed with 2 N aq. HCl solution (3x), dried (Na_2SO_4), filtered and concentrated to obtain the title compound (39 mg, 55%) as a tan solid.

Example 154

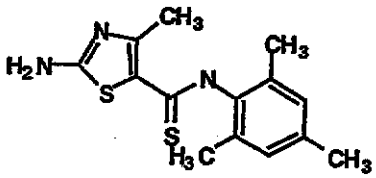
Preparation of 2-[[(Acetylamino)acetyl]aminol-4-methyl-N-(2,4,6-trimethylphenyl)-6-thiazolecarboxamide



A solution of amine **2** (50 mg, 0.18 mmol), diisopropylethylamine (400 μL, 2.3 mmol), N-acetylglycine (42 mg, 0.36 mmol), 1-hydroxy-7-azabenzotriazole (49 mg, 0.36 mmol), and ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (72 mg, 0.36 mmol) in THF (5 mL) was heated to 50°C overnight. The mixture was cooled, diluted with dichloromethane (60 mL) and washed with 2 N aq. HCl solution (20 mL), satd. Aq. $KHCO_3$ solution (20 mL), dried ($MgSO_4$), filtered and concentrated. The crude solid was triturated with ether (10 mL), filtered, and washed with ether (5 mL, 3x) to obtain the title compound (40 mg, 59%) as an off-white solid.

Example 155

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



A suspension of **2** (50 mg, 0.18 mmol) and Lawesson reagent (44 mg, 0.11 mmol) in toluene (0.23 mL) was heated to 100°C for 4h. Additional

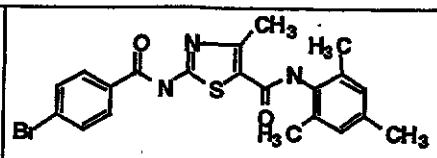
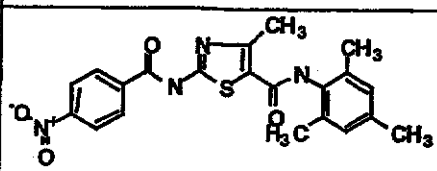
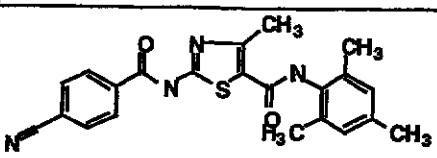
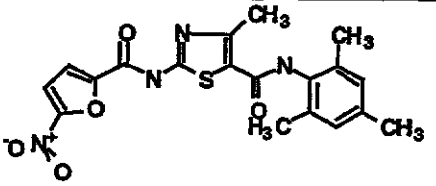
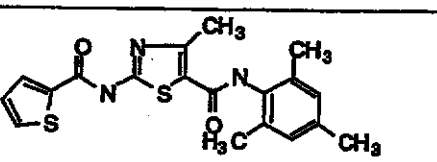
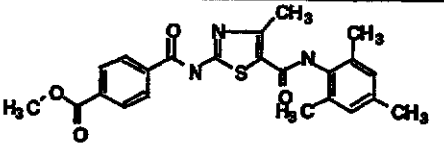
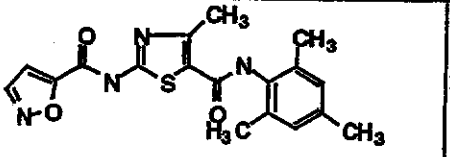
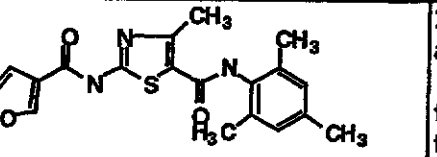
Lawesson reagent (44 mg, 0.11 mmol) was added and the mixture was heated for additional 3.5 h. The crude mixture was chromatographed on a silica gel column and eluted with 50% EtOAc in hexanes followed by 70% EtOAc in hexanes to obtain a a yellow solid which was triturated with hexanes (6 mL) to obtain the title compound (11 mg, 21%) as a yellow solid.

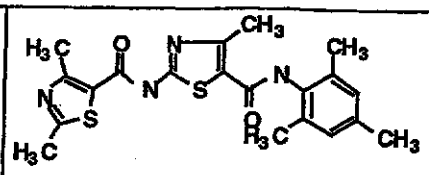
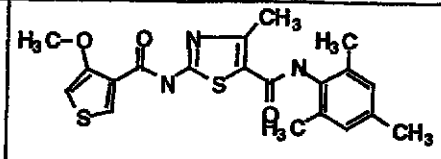
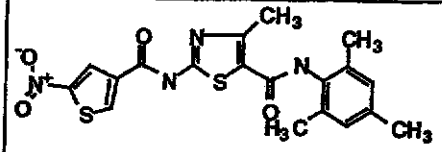
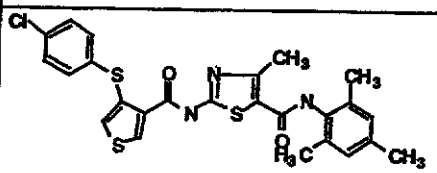
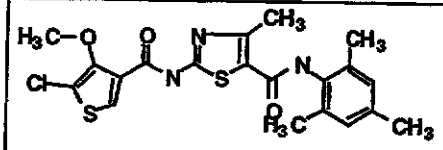
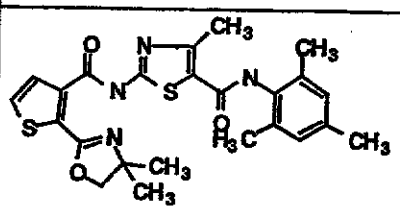
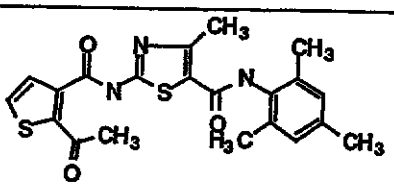
Examples 156 to 170

General Procedure

Compounds **156** to **170** were prepared following the procedure described below. Diisopropylethyl amine (60 μL, 0.34 mmol) was added to a mixture of amine **2** (30 mg, 0.11 mmol), appropriate carboxylic acid (0.13 mmol), 1-hydroxy-7-azabenzotriazole (19.5 mg, 0.14 mmol), and ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (26.8 mg, 0.14 mmol) in THF (1 mL). The mixture was heated in a sealed tube under argon at 45 °C for 24 h. The reaction mixture was diluted with dichloromethane (4 mL) and washed with 2 N aq. HCl solution (2 mL, 3x), dried (Na_2SO_4) and concentrated using a speedvac. The crude products were either triturated with dichloromethane-ether (5 mL, 1:1) or purified by silica gel chromatography (elution solvent: 50% EtOAC in hexanes and EtOAc). "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H_2O, 0.2% H_3PO_4) to 100% solvent B (90% MeOH, 10% H_2O, 0.2% H_3PO_4), flow rate 4 mL/min, λ = 220 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)

156		2-[(4-Bromobenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.03
157		4-Methyl-2-[(4-nitrobenzoyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.87
158		2-[(4-Cyanobenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.70
159		4-Methyl-2-[[(5-nitro-2-furanyl)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.63
160		4-Methyl-2-[(2-thienylcarbonyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.60
161		4-[[[4-Methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]amino]carbonyl]benzoic acid methyl ester	4.99
162		2-[(5-Isoxazolylcarbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.87
163		2-[(3-Furanylcarbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.54

164		2-[[(2,4-Dimethyl-5-thiazolyl)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.74
165		2-[[(4-Methoxy-3-thienyl)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.75
166		4-Methyl-2-[[(5-nitro-3-thienyl)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.78
167		2-[[[4-[(4-Chlorophenyl)thio]-3-thienyl]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.27
168		2-[[(5-Chloro-4-methoxy-3-thienyl)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.04
169		2-[[[2-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-3-thienyl]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.13
170		2-[[(2-Acetyl-3-thienyl)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.54

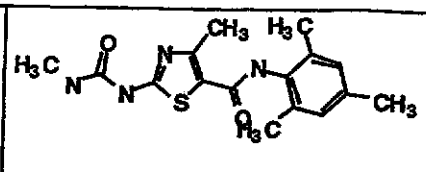
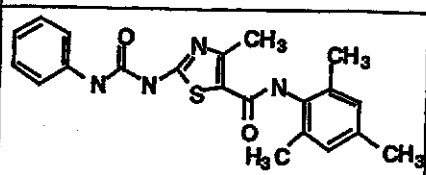
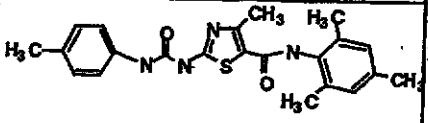
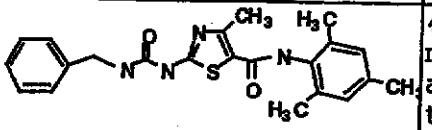
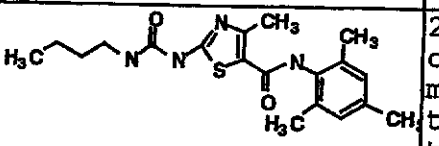
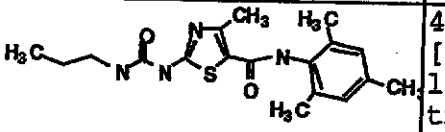
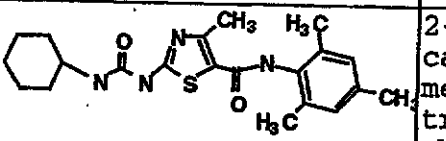
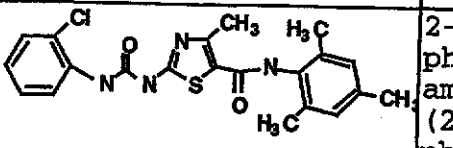
Examples 171 to 180

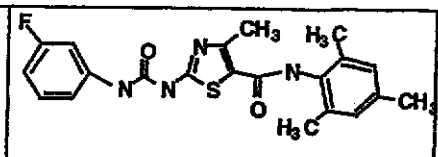
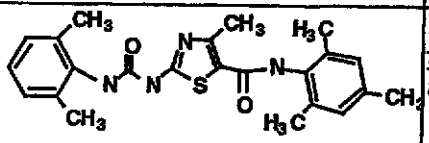
General Procedure

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

A mixture of **2** (80 mg, 0.29 mmol), appropriate isocyanate (0.87 mmol) and pyridine (2 mL) in THF (3.5 mL) was stirred at rt overnight. In some cases the reaction mixture was heated to 60-70°C for 5 h. Some of these reactions were carried out at rt overnight in the presence of catalytic N,N-dimethylaminopyridine. The reaction mixture was diluted with dichloromethane and washed with 1 N aq. HCl solution (3x), water, brine; dried ($MgSO_4$), filtered and concentrated. The crude product was purified either by trituration with ether or ether-hexanes mixture, or by chromatography on a silica gel column (elution solvent 20-40% EtOAc in hexanes) followed by trituration or by passing through Varian cation exchange SCX cartridge and sequentially eluted with methanol (5 mL), dichloromethane (5 mL), acetonitrile-methanol (10 mL, 4:1) and methanol-2 M methanolic ammonia (10 mL, 4:1) to obtain the title compound. "HPLC Ret Time" is the HPLC retention time under the following conditions: For compounds **171-172, 175,** and **177** HPLC conditions are: Zorbax S8-C18 4.5 mm x 7.5 cm short column, 30 min gradient starting from 100% solvent A (10% MeOH, 90% H_2O, 0.2% H_3PO_4) to 100% solvent B (90% MeOH, 10% H_2O, 0.2% H_3PO_4), flow rate 2.5 mL/min, λ = 217 nM. For the other compounds HPLC conditions are: Zorbax S8-C18 4.5 mm x 7.5 cm short column, 8 min gradient starting from 100% solvent A (10% MeOH, 90% H_2O, 0.2% H_3PO_4) to 100% solvent B (90% MeOH, 10% H_2O, 0.2% H_3PO_4), flow rate 2.5 mL/min, λ = 217 nM.

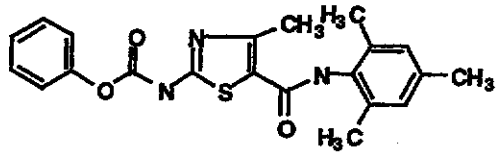
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)

171		4-Methyl-2-[[(methyl-amino)carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	24.48
172		4-Methyl-2-[[(phenyl-amino)carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	30.45
173		4-Methyl-2-[[[(4-methylphenyl)amino]-carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.81
174		4-Methyl-2-[[[(phenyl-methyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.52
175		2-[[(Butylamino) carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	30.49
176		4-Methyl-2-[[(propylamino)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	7.41
177		2-[[(Cyclohexylamino) carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	27.21
178		2-[[[(2-Chloro-phenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.99

179		2-[[[(3-Fluorophenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.87
180		2-[[[(2,6-Dimethyl-phenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.92

Example 181

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



A 10% aq. $KHCO_3$ solution (170 mL) was added to a stirred solution of 2 (1.02 g, 3.7 mmol) in THF (130 mL). Phenylchloroformate (1.39 mL, 11.1 mmol) was added dropwise. The biphasic mixture was stirred at rt overnight, diluted with dichloromethane (200 mL) and washed with water (50 mL, 2x) and brine. The organic extract was separated, dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 10% EtOAc in hexanes to obtain the title compound (980 mg, 69%) as a solid.

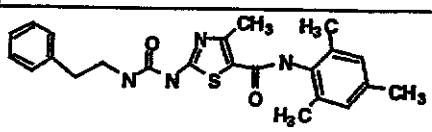
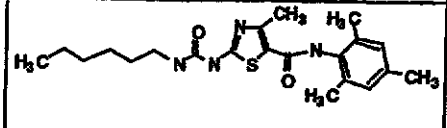
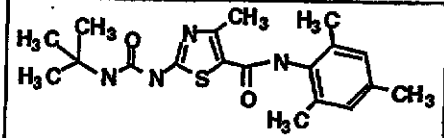
Examples 182 to 236

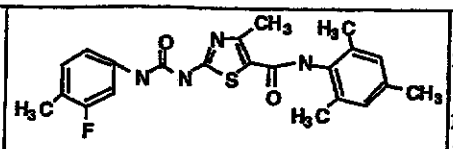
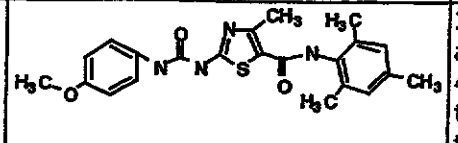
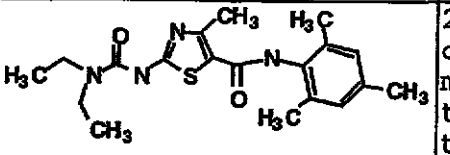
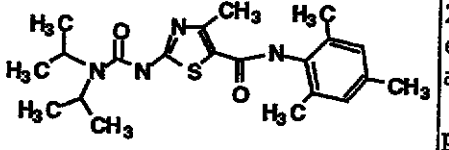
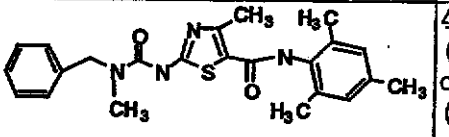
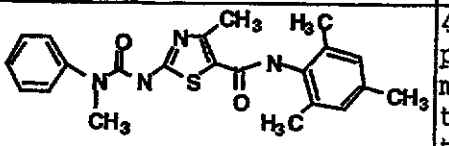
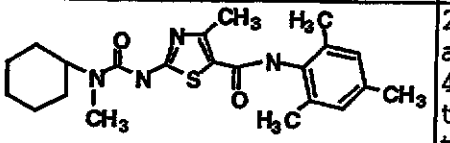
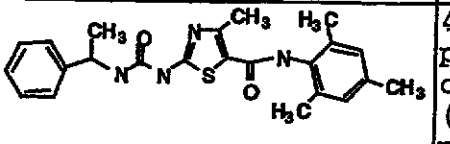
General Procedure

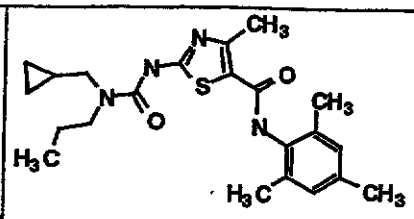
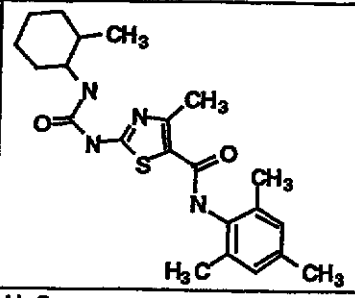
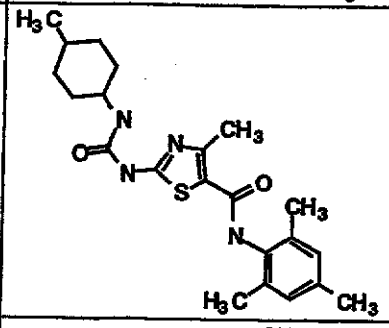
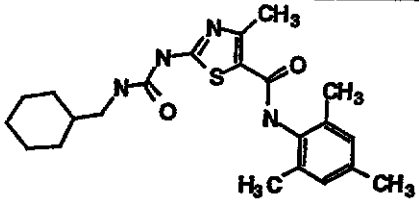
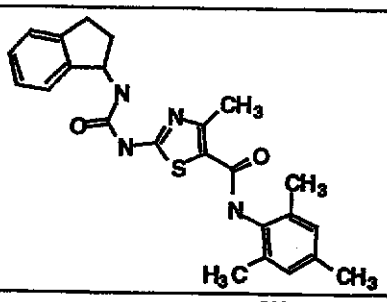
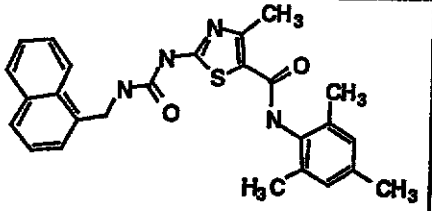
Compounds **182** to **236** were prepared following the procedure described below.

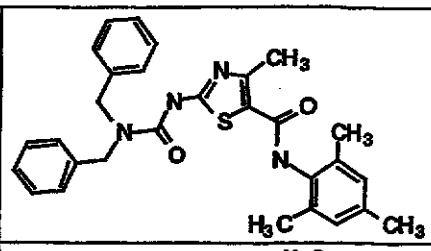
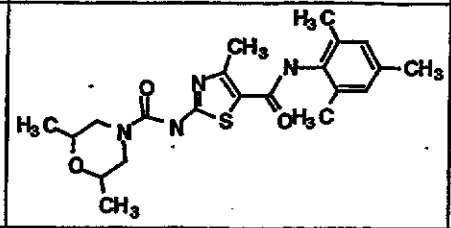
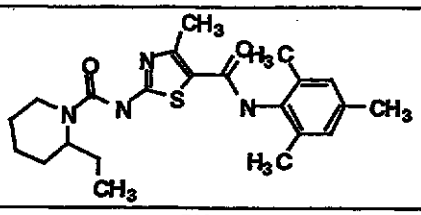
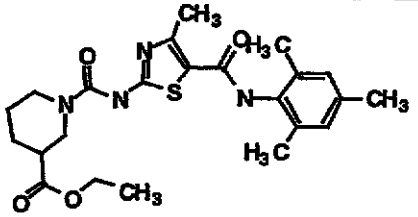
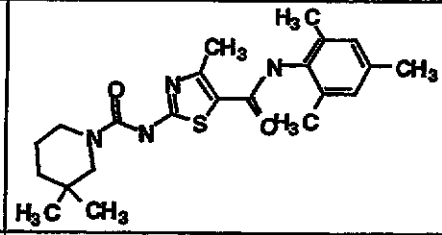
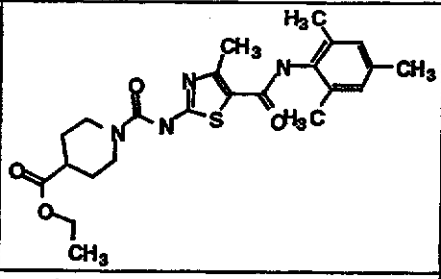
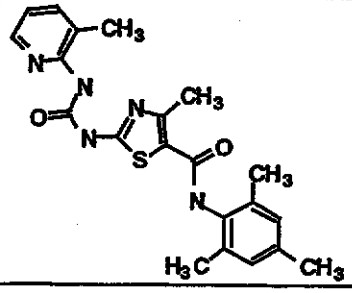
A solution of phenylcarbamate **181** (20 mg, 0.054 mmol) and the appropriate amine (0.08 mmol) in THF-acetonitrile (3 mL, 1:1) was stirred at rt overnight. Some of the reactions required heating to 60 °C for 4 h to overnight. The mixture was diluted with dichloromethane (4 mL) and washed with 1 N aq. HCl solution (1.5 mL, 2x), 1 N aq. NaOH solution (1.5 mL, 2x). The dichloromethane extract was separated, dried ($MgSO_4$), filtered and concentrated to obtain the title product.

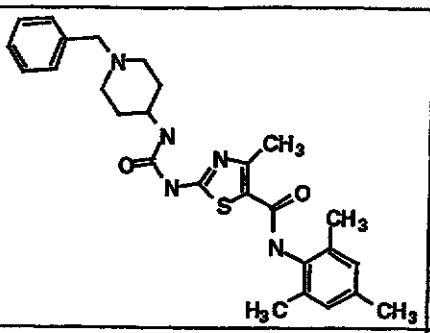
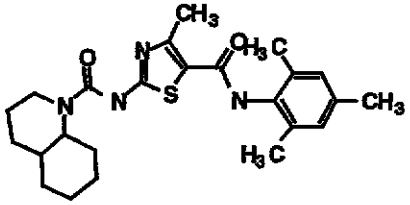
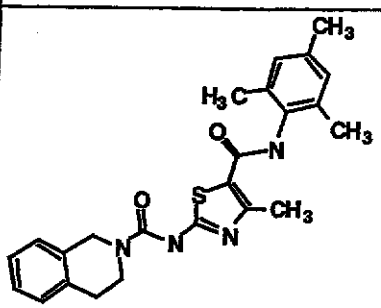
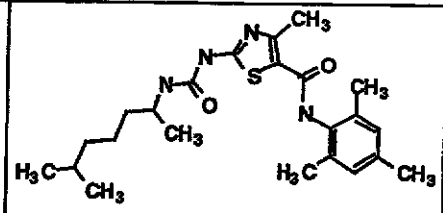
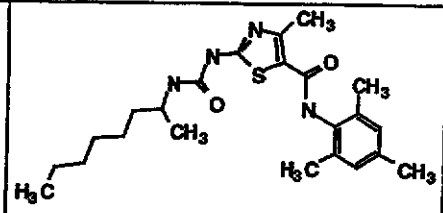
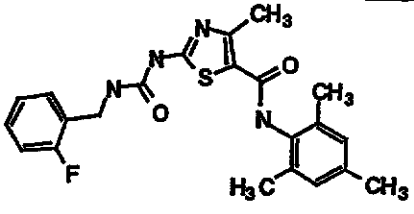
"HPLC Ret Time" is the HPLC retention time under the following conditions: For compounds **182-192** HPLC conditions are: Zorbax SB-C18 4.5 mm x 7.5 cm short column, 8 min gradient starting from 100% solvent A (10% MeOH, 90% H_2O, 0.2% H_3PO_4) to 100% solvent B (90% MeOH, 10% H_2O, 0.2% H_3PO_4), flow rate 2.5 mL/min, λ = 217 nM. For compounds **193-236** HPLC conditions are: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H_2O, 0.2% H_3PO_4) to 100% solvent B (90% MeOH, 10% H_2O, 0.2% H_3PO_4), flow rate 4 mL/min, λ = 220 nM.

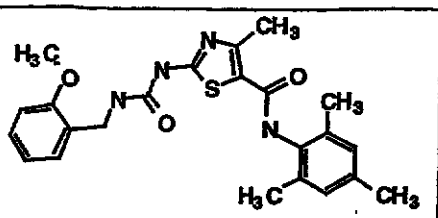
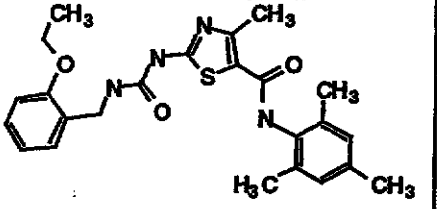
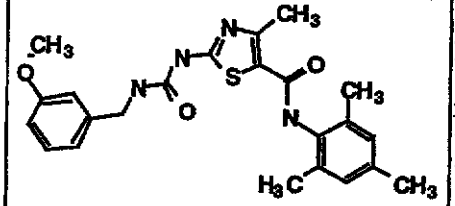
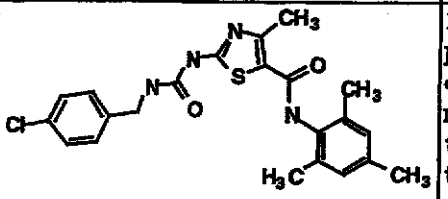
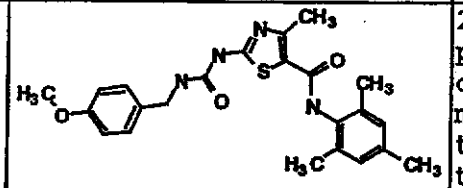
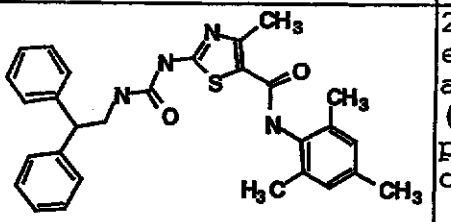
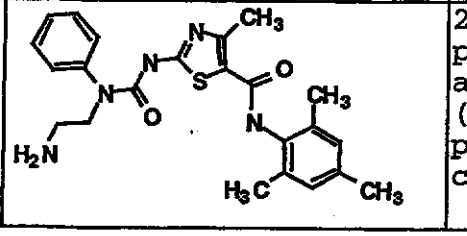
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
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183		2-[[(Hexylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	9.01
184		2-[[[(1,1-Dimethyl-ethyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.48

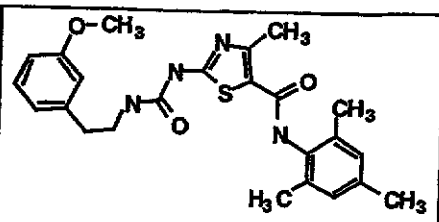
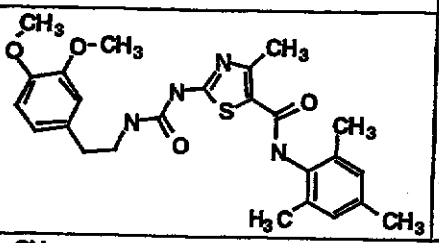
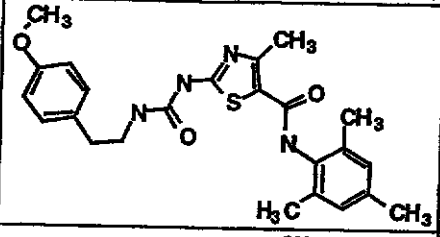
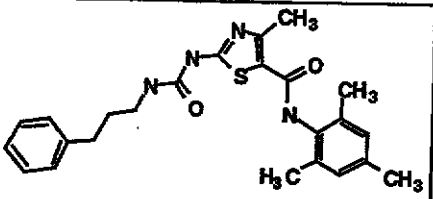
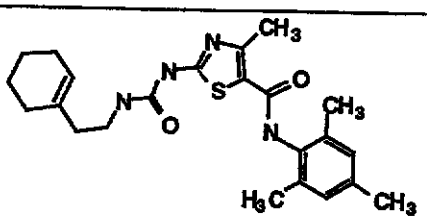
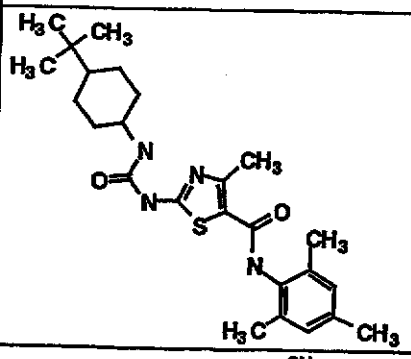
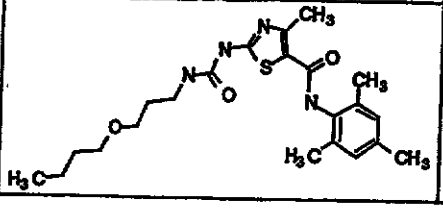
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186		2-[[[(4-Methoxyphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.57
187		2-[[(Diethylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.19
188		2-[[[Bis(1-methyl-ethyl)amino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.90
189		4-Methyl-2-[[[methyl-(phenylmethyl)amino]-carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.56
190		4-Methyl-2-[[(methyl-phenylamino)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.39
191		2-[[(Cyclohexylmethyl amino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.84
192		4-Methyl-2-[[[(1-phenylethyl)amino]-carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.47

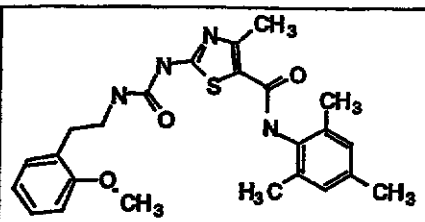
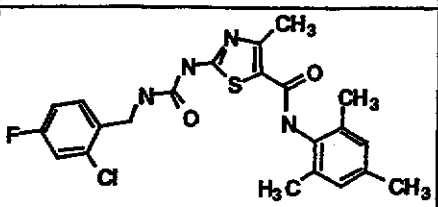
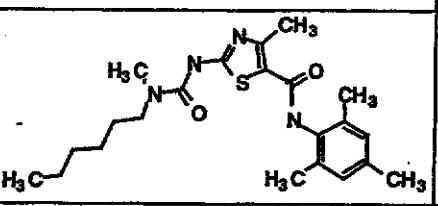
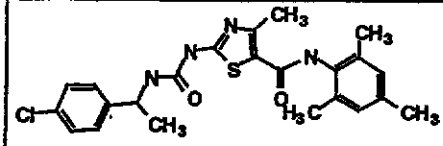
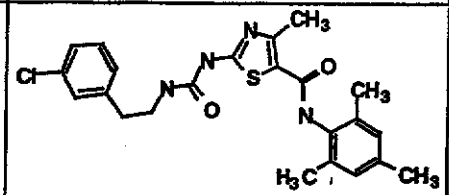
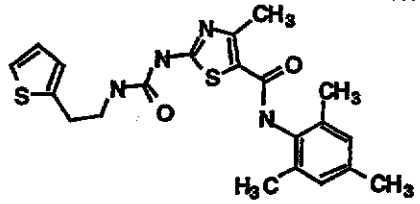
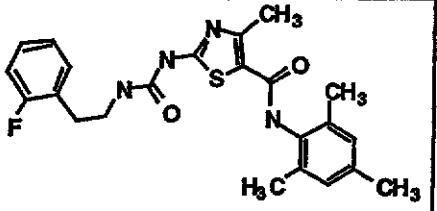
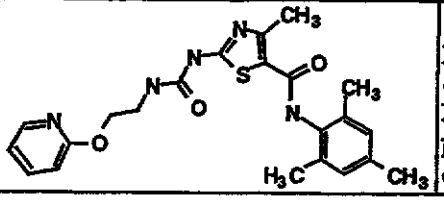
193		2-[[[(Cyclopropyl-methyl) propylamino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.36
194		4-Methyl-2-[[[(2-methylcyclohexyl)amino]carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.42
195		4-Methyl-2-[[[(4-methylcyclohexyl)-amino]carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.49
196		2-[[[(Cyclohexyl-methyl) amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.49
197		2-[[[(2,3-Dihydro-1H-inden-1-yl)amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.35
198		4-Methyl-2-[[[(1-naphthalenylmethyl)amino]carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.43

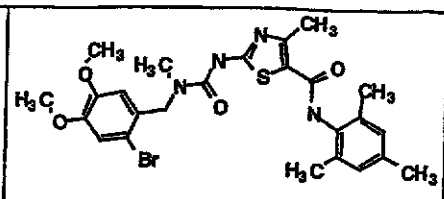
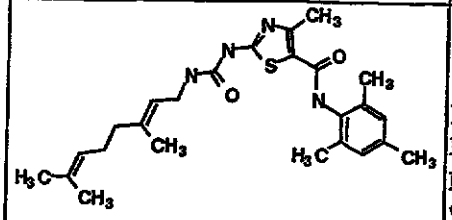
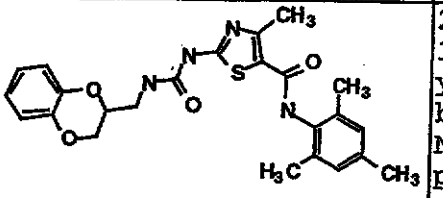
199		2-[[[Bis(phenylmethyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.66
200		2,6-Dimethyl-N-[4-methyl-5-[[(2,4,6-trimethylphenyl)-amino]carbonyl]-2-thiazolyl]-4-morpholinecarboxamide	3.97
201		2-Ethyl-N-[4-methyl-5-[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-1-piperidinecarboxamide	4.29
202		1-[[[4-Methyl-5-[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-amino]carbonyl]-3-piperidinecarboxylic acid ethyl ester	4.10
203		3,3-Dimethyl-N-[4-methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-1-piperidinecarboxamide	4.32
204		1-[[[4-Methyl-5-[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-amino]carbonyl]-4-piperidinecarboxylic acid ethyl ester	4.06
205		4-Methyl-2-[[[(3-methyl-2-pyridinyl)-amino] carbonyl]-amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazolecarboxamide	3.51

206		4-Methyl-2-[[[1-(phenylmethyl)-4-piperidinyl]amino]-carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	3.28
207		Octahydro-N-[4-methyl-5-[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-1(2H)-quinolinecarboxamide	4.55
208		3,4-Dihydro-N-[4-methyl-5-[[(2,4,6-trimethylphenyl)-amino] carbonyl]-2-thiazolyl]-2(1H)-isoquinoline carboxamide	4.35
209		2-[[[(1,5-Dimethyl-hexyl)amino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.72
210		4-Methyl-2-[[[(1-methylheptyl)amino]-carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.74
211		2-[[[[(2-Fluoro-phenyl)methyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.17

212		2-[[[[(2-Methoxy-phenyl)methyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.22
213		2-[[[[(2-Ethoxy-phenyl)methyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.36
214		2-[[[[(3-Methoxy-phenyl)methyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.13
215		2-[[[[(4-Chloro-phenyl)methyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.36
216		2-[[[[(4-Methoxy-phenyl)methyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.12
217		2-[[[(2,2-Diphenyl-ethyl)amino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.57
218		2-[[[(2-Aminoethyl) phenylamino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	3.70

219		2-[[[[2-(3-Methoxyphenyl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.26
220		2-[[[[2-(3,4-Dimethoxyphenyl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.05
221		2-[[[[2-(4-Methoxyphenyl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.25
222		4-Methyl-2-[[[(3-phenylpropyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.40
223		2-[[[[2-(Cyclohex-1-en-1-yl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.11
224		2-[[[[4-(1,1-Dimethylethyl)cyclohexyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.85
225		2-[[[(3-Butoxypropyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.33

226		2-[[[[2-(2-Methoxy-phenyl)ethyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.46
227		2-[[[[(2-Chloro-4-fluorophenyl)methyl]-amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.39
228		2-[[(Hexylmethylamino) carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.65
229		2-[[[[1-(4-Chloro-phenyl)ethyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.42
230		2-[[[[2-(3-Chloro-phenyl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.44
231		4-Methyl-2-[[[[2-(2-thienyl)ethyl]amino]-carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.18
232		2-[[[[2-(2-Fluoro-phenyl)ethyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.85
233		4-Methyl-2-[[[[2-(2-pyridinyloxy)ethyl]-amino]carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.28

234		2-[[[[(2-Bromo-4,5-dimethoxyphenyl)methyl]methylamino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.87
235		(E)-2-[[[(3,7-Dimethyl-2,6-octadienyl) amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.34
236		2-[[[[(2,3-Dihydro-1,4-benzodioxin-2-yl)methyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.27

Examples 237 to 285

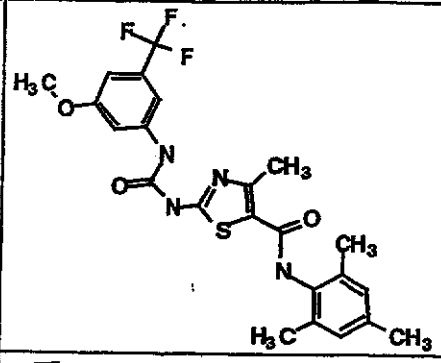
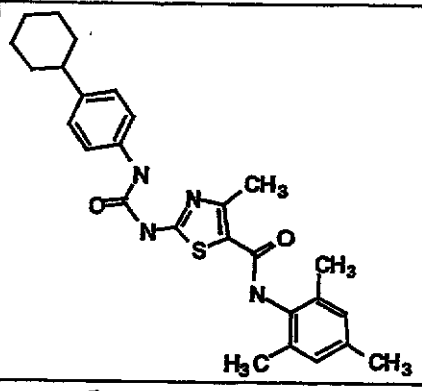
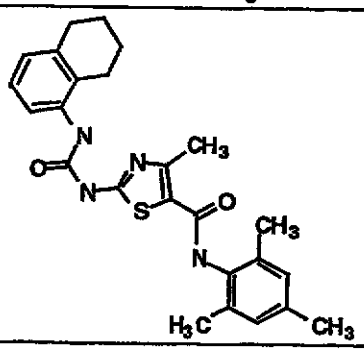
General Procedure

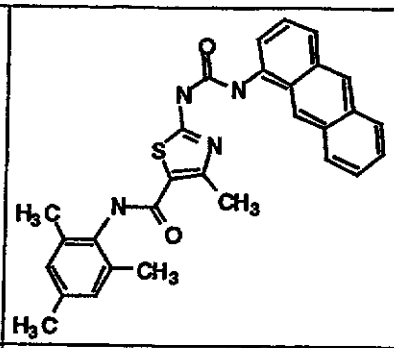
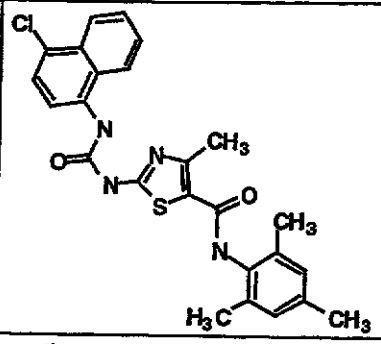
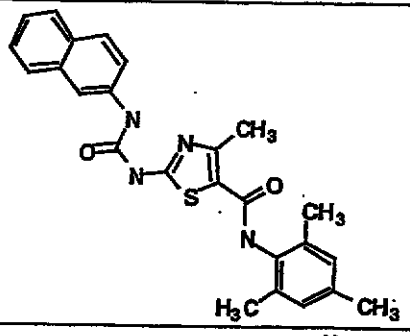
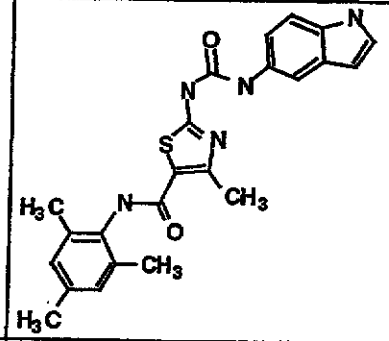
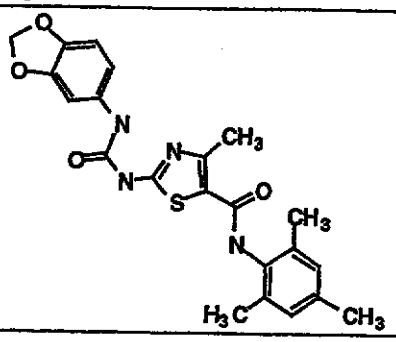
Compounds **237**to **285** were prepared following the procedure described below.

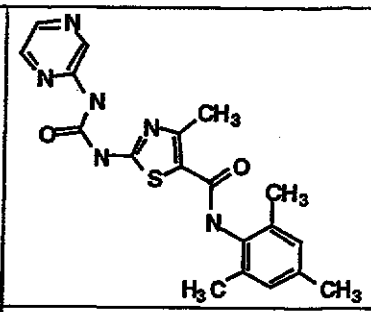
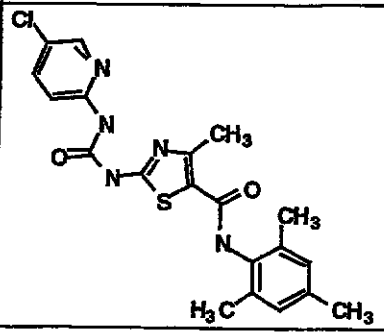
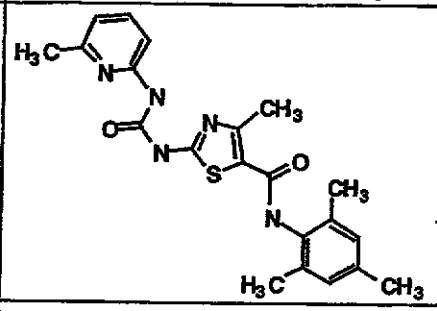
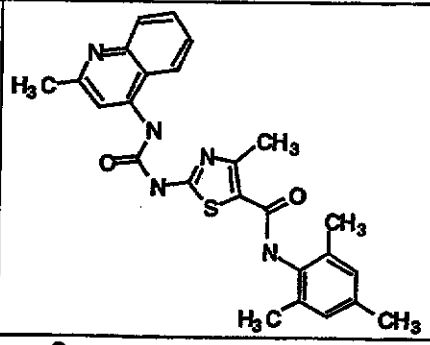
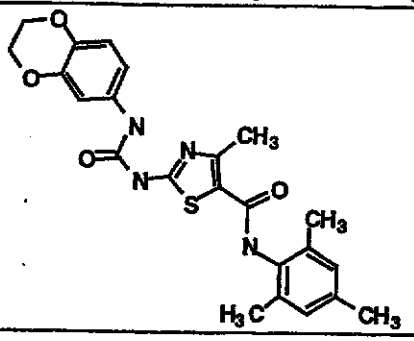
A solution of phenylcarbamate **181** (20 mg, 0.054 mmol) and the appropriate amine (0.08 mmol) in THF-acetonitrile (3 mL, 1:1) was stirred at rt overnight. The mixture was diluted with dichloromethane (4 mL) and washed with 1 N aq. HCl solution (1.5 mL, 2x), 1 N aq. NaOH solution (1.5 mL, 2x). The dichloromethane extract was separated, dried ($MgSO_4$), filtered and concentrated to obtain the title product.

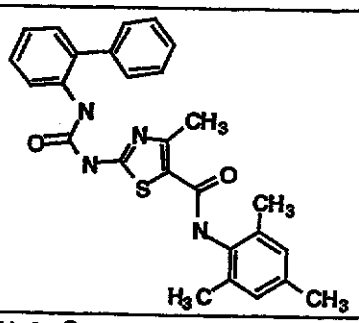
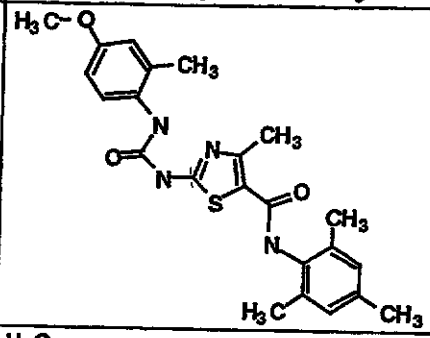
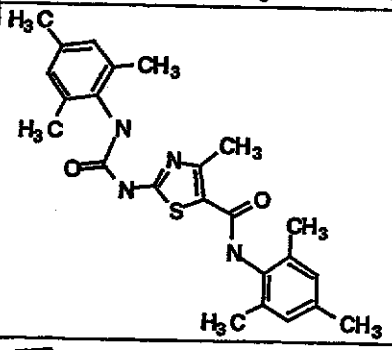
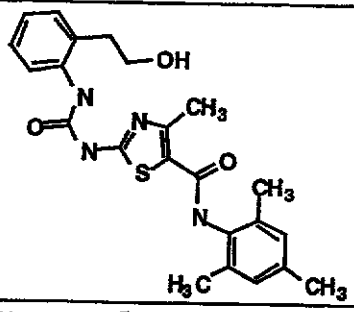
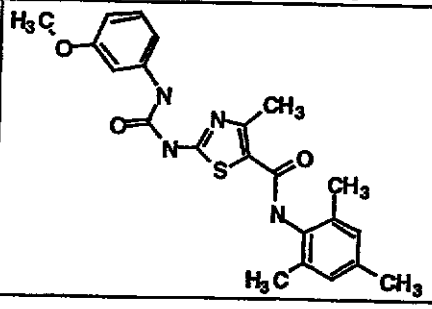
"HPLC Ret Time" is the HPLC retention time under the following conditions: For compounds **237-278** HPLC conditions are: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H_2O, 0.2% H_3PO_4) to 100% solvent B (90% MeOH, 10% H_2O, 0.2% H_3PO_4), flow rate 4 mL/min, λ = 220 nM. For compounds **279-285** HPLC conditions are: Zorbax S8-C18 4.5 mm x 7.5 cm short

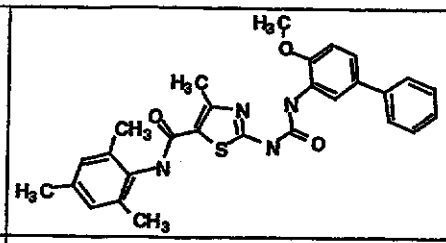
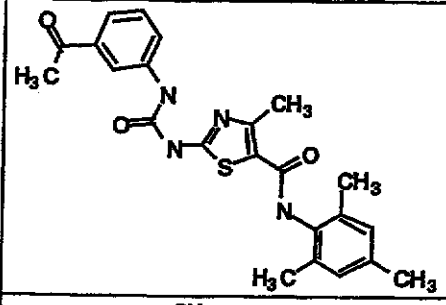
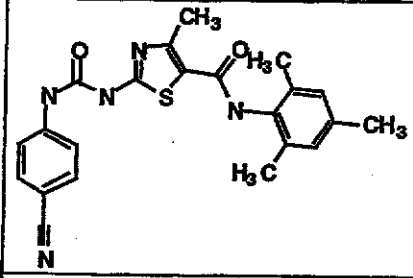
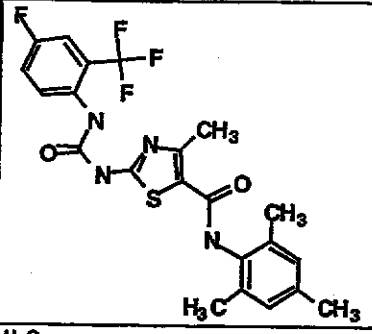
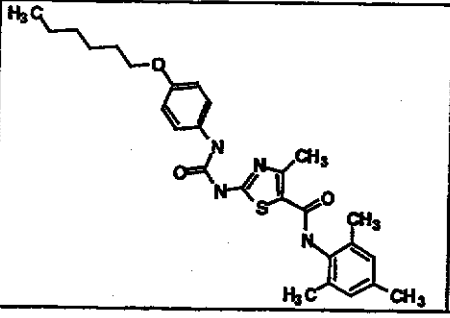
column, 8 min gradient starting from 100% solvent A (10% MeOH, 90% H_2O, 0.2% H_3PO_4) to 100% solvent B (90% MeOH, 10% H_2O, 0.2% H_3PO_4), flow rate 2.5 mL/min, λ = 217 nM.

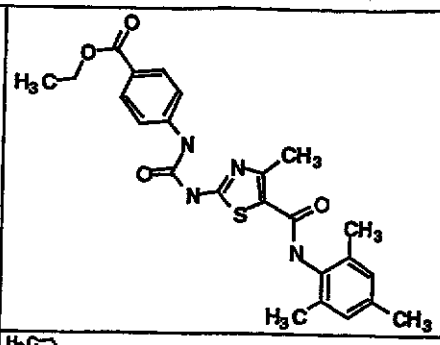
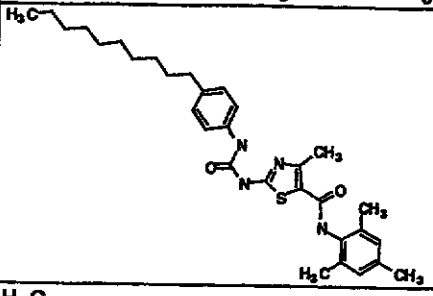
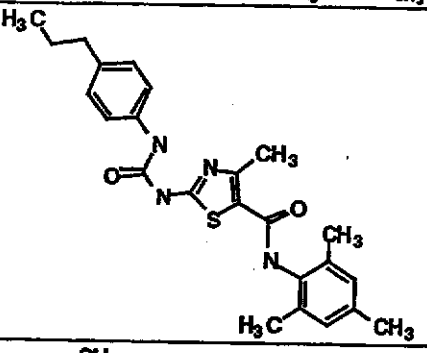
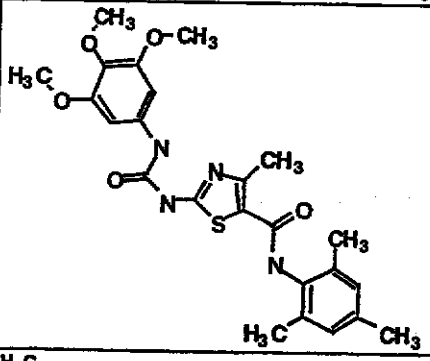
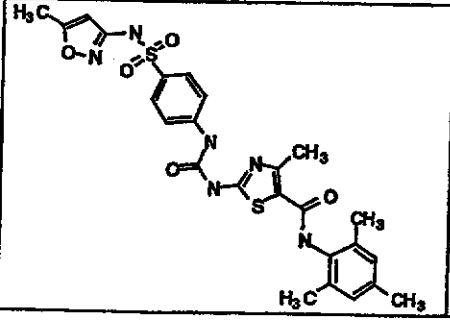
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
237		2-[[[[3-Methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.36
238		2-[[[(4-Cyclohexyl-phenyl) amino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide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

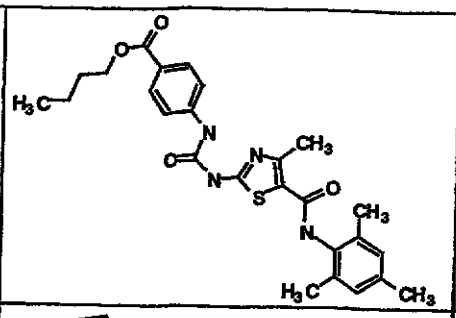
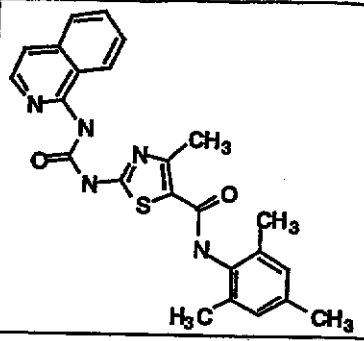
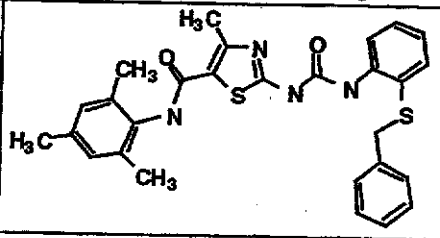
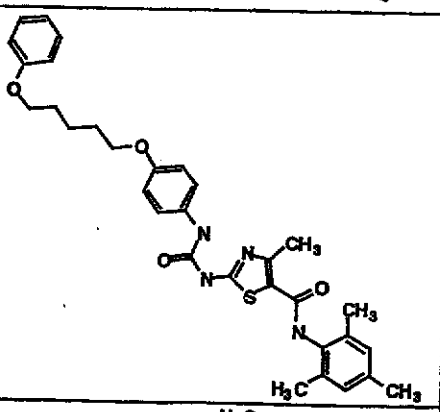
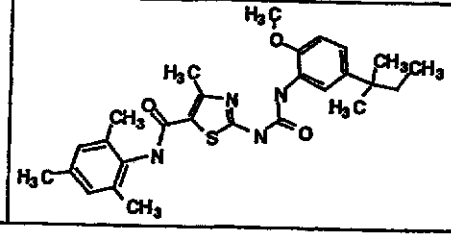
240		2-[[(1-Anthracenylamino) carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.82
241		2-[[[(4-Chloro-1-naphthalenyl)amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.76
242		4-Methyl-2-[[(2-naphthalenylamino)-carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.28
243		2-[[(1H-Indol-5-ylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.00
244		2-[[(1,3-Benzodioxol-5-ylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.76

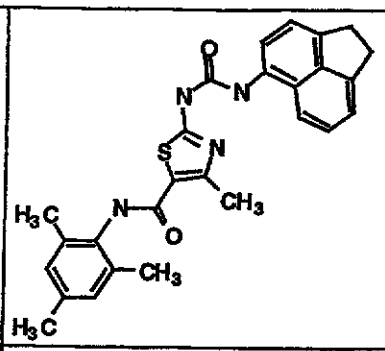
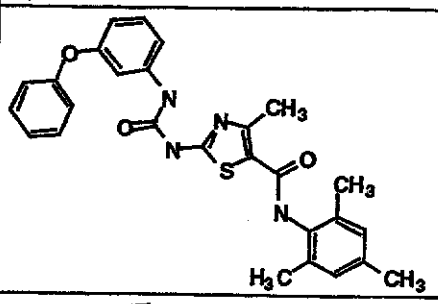
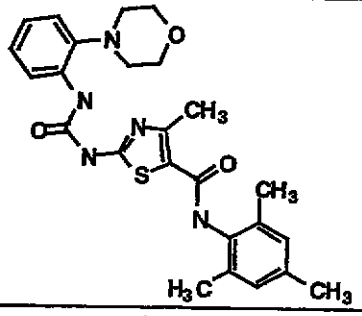
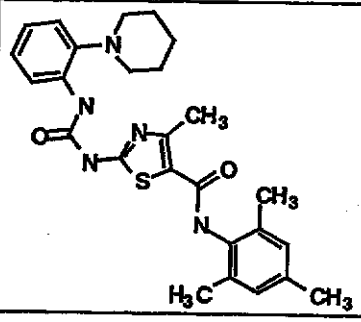
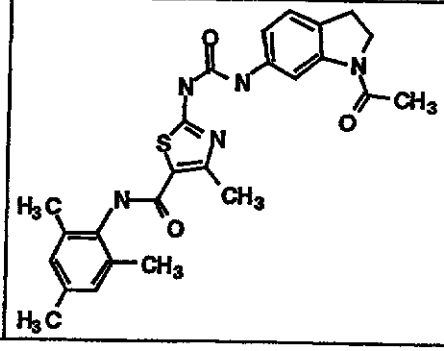
245		4-Methyl-2-[[(2-pyrazinylamino)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.84
246		2-[[[(5-Chloro-2-pyridinyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.38
247		4-Methyl-2-[[[(6-methyl-2-pyridinyl) amino]-carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.44
248		4-Methyl-2-[[[(2-methyl-4-quinolinyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.23
249		2-[[[(2,3-Dihydro-1,4-benzodioxin-6-yl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.72

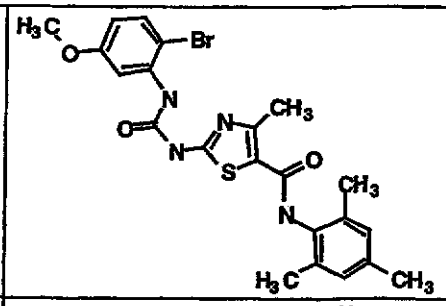
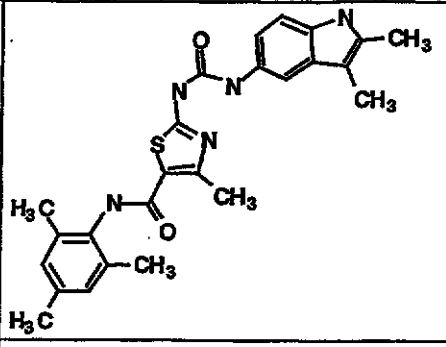
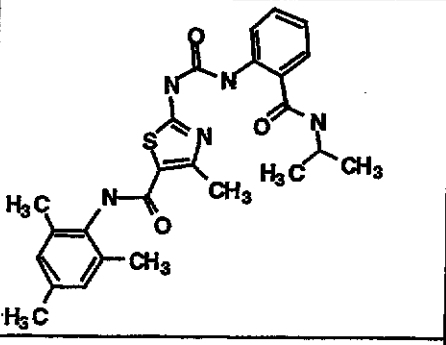
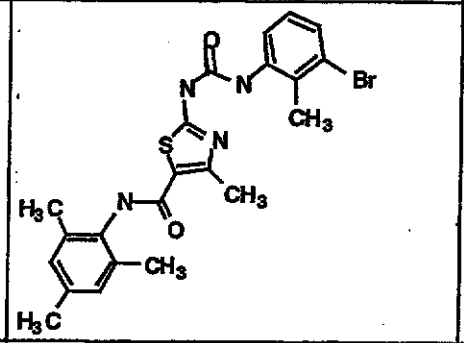
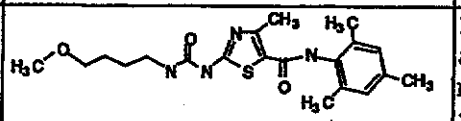
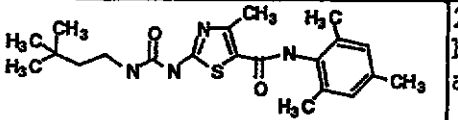
250		2-[[([1,1'-Biphenyl]-2-ylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.29
251		2-[[[(4-Methoxy-2-methylphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.80
252		4-Methyl-N-(2,4,6-trimethylphenyl)-2-[[[(2,4,6-trimethylphenyl)amino]-carbonyl]amino]-5-thiazolecarboxamide	5.06
253		2-[[[[2-(2-Hydroxyethyl)phenyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.02
254		2-[[[(3-Methoxyphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.86

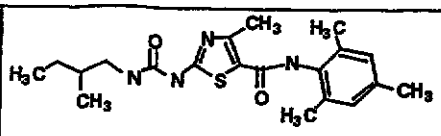
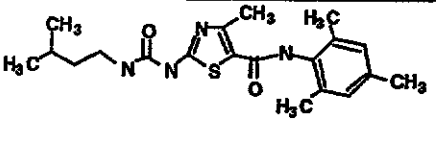
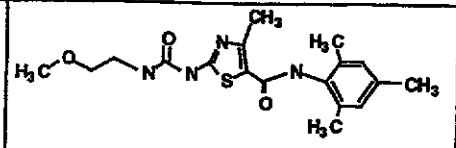
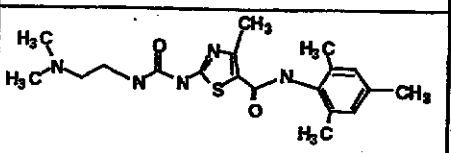
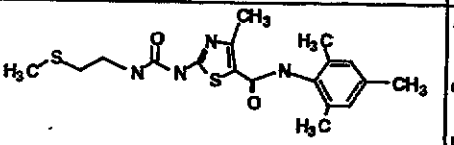
255		2-[[[(4-Methoxy[1,1'-biphenyl]-3-yl)amino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.81
256		2-[[[(3-Acetylphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.12
257		2-[[[(4-Cyanophenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.15
258		2-[[[[4-Fluoro-2-(trifluoromethyl)phenyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.99
259		2-[[[(4-Hexyloxyphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.42

260		4-[[[[4-Methyl-5-[[(2,4,6-trimethyl-phenyl) amino]carbonyl]-2-thiazolyl]-amino]-carbonyl]amino]benzoic acid ethyl ester	4.26
261		2-[[[(4-Decylphenyl)-amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	
262		4-Methyl-2-[[[(4-propylphenyl)amino]-carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.71
263		4-Methyl-2-[[[(3,4,5-trimethoxyphenyl)amino]-carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.67
264		4-Methyl-2-[[[[4-[[(5-methyl-3-isoxazolyl) amino]sulfonyl]phenyl]-amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.27

265		4-[[[[4-Methyl-5-[[(2,4,6-trimethyl phenyl)amino]carbonyl]-2-thiazolyl]-amino]carbonyl]-amino]-benzoic acid butyl ester	4.75
266		2-[[(1-Isoquinolinyl amino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.81
267		4-Methyl-2-[[[[2-[(phenyl-methyl)thio]-phenyl]amino]carbonyl]-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.42
268		4-Methyl-2-[[[[4-[(5-phenoxypentyl)oxy]phenyl]amino]carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.96
269		2-[[[[5-(1,1-Dimethyl-propyl)-2-methoxy-phenyl]amino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.76

270		2-[[[(1,2-Dihydro-5-acenaphthylenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.70
271		4-Methyl-2-[[[(3-phenoxyphenyl)amino]-carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.70
272		4-Methyl-2-[[[[2-(4-morpholinyl)phenyl]-amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.01
273		4-Methyl-2-[[[[2-(1-piperidinyl)phenyl]amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.55
274		2-[[[(1-Acetyl-2,3-dihydro-1H-indol-6-yl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.08

275		2-[[[(2-Bromo-5-methoxyphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.55
276		2-[[[(2,3-Dimethyl-1H-indol-5-yl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethyl phenyl)-5-thiazolecarboxamide	4.30
277		4-Methyl-2-[[[[2-[[(1-methylethyl)amino]carbonyl]phenyl]amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.82
278		2-[[[(3-Bromo-2-methylphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.60
279		2-[[[(4-Methoxybutyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	7.62
280		2-[[[(3,3-Dimethylbutyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	9.13

281		4-Methyl-2-[[[(2-methylbutyl)amino]-carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.90
282		4-Methyl-2-[[[(3-methylbutyl)amino]carbo-nyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.98
283		2-[[[(2-Methoxyethyl)-amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	7.30
284		2-[[[[2-(Dimethyl-amino)ethyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.73
285		4-Methyl-2-[[[[2-(methylthio)ethyl]amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.19

Examples 286 to 311

General Procedure

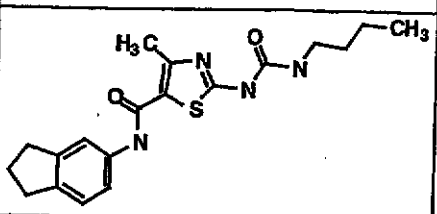
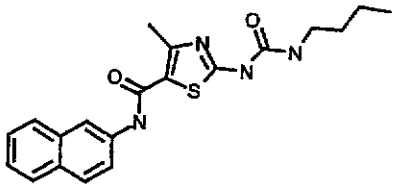
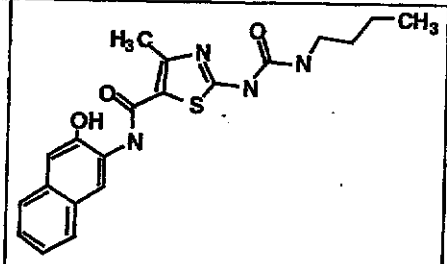
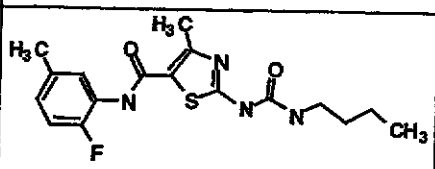
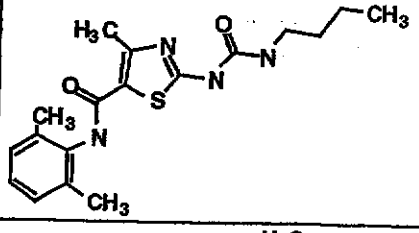
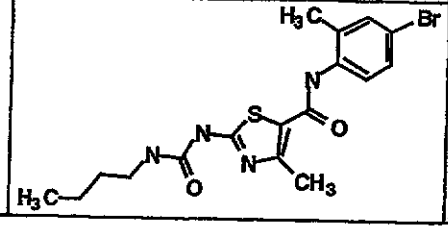
Compounds **286** to **311** with the exception of compound **307** were prepared following the procedure described below.

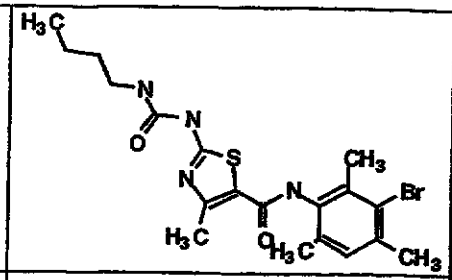
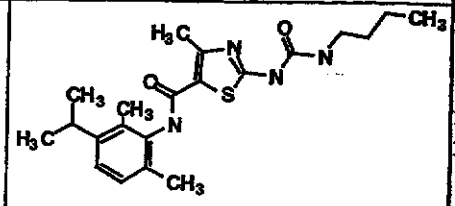
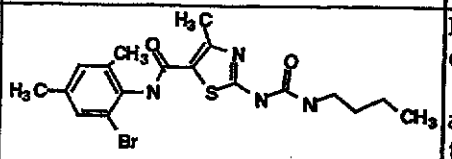
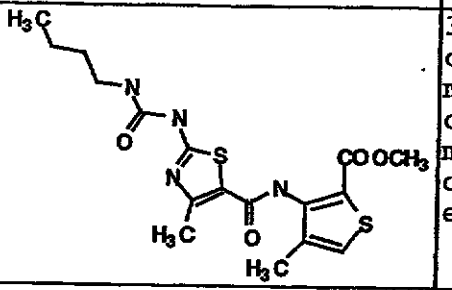
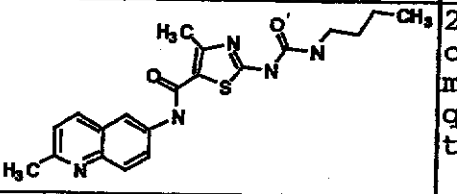
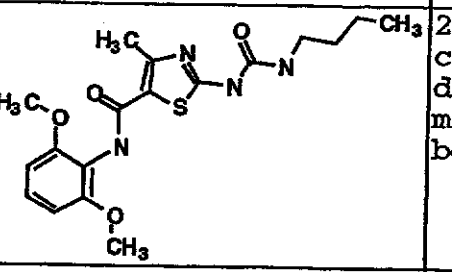
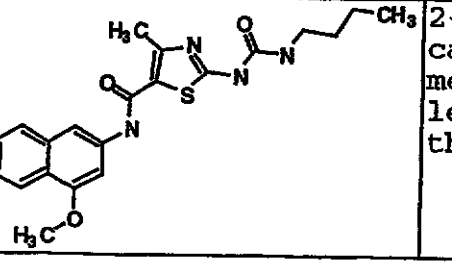
A solution of 2-[[(Butylamino)carbonyl]amino]-4-methyl-5-thiazole carboxylic acid chloride (30 mg, 0.11 mmol), appropriate amine (0.12 mmol) in THF (1 mL) was treated with diisopropylethyl amine (22.6 µL, 0.13 mmol). The mixture was purged with argon and stirred mechanically in a vial for 22 h, diluted with dichloromethane (4 mL) and washed with 2 N aq. HCl solution (3x). The organic extract was separated, dried (Na_2SO_4), filtered and concentrated. The crude products were purified either by truturation with dichloromethane-ether (1:1) or by silica gel

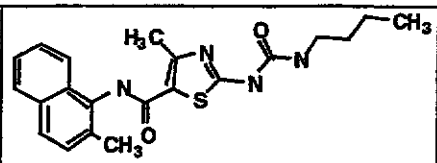
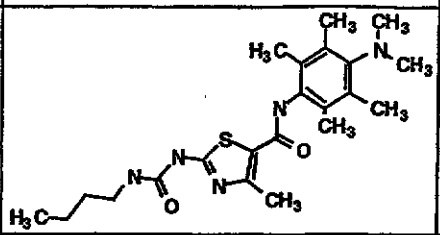
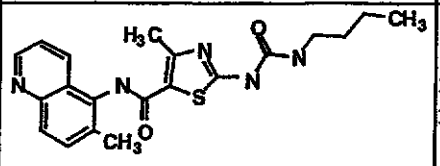
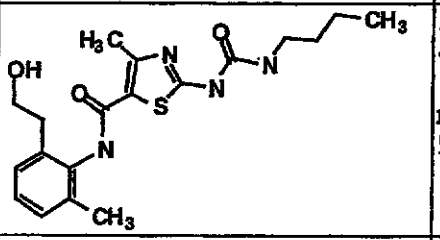
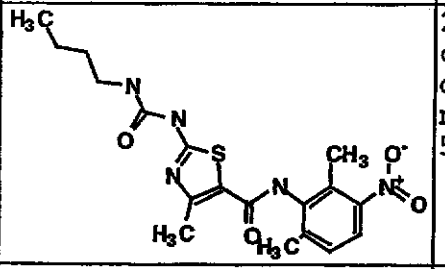
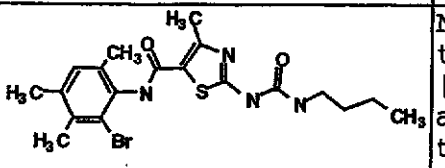
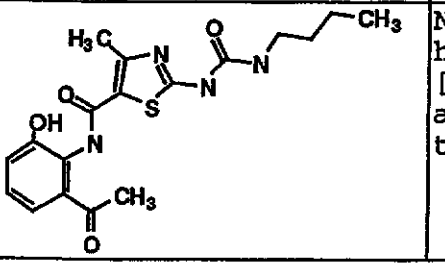
chromatography (elution solvent: 80% EtOAc in hexanes followed by EtOAc) or by automatic preparative HPLC (conditions: YMC S5 ODS A 20 x 100 mm Column, 10 min gradient starting from 30% solvent B (90% MeOH, 10% H_2O, 0.1% TFA) and 70% solvent A (10% MeOH, 90% H_2O, 0.1% TFA) to 100% solvent B, flow rate 20 mL/min, λ = 220 nM.

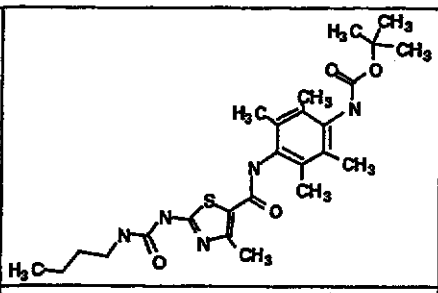
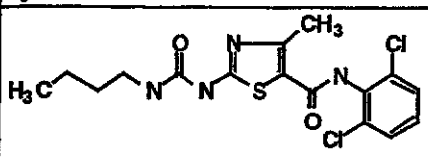
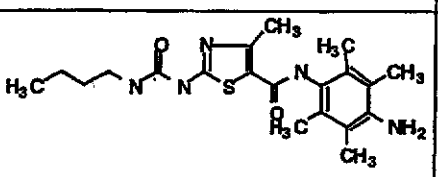
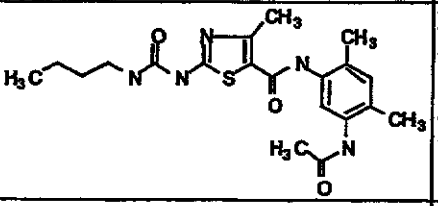
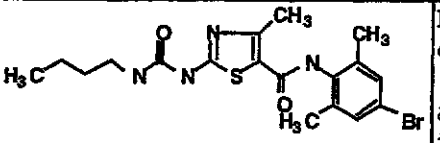
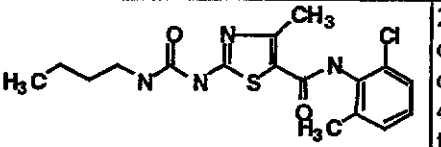
Compound **307** was prepared following the procedure described below. A suspension solution of 2-[[(Butylamino)carbonyl]amino]-4-methyl-5-thiazole carboxylic acid (100 mg, 0.36 mmol), and HATU (170 mg, 0.44 mmol) in DMF (3 mL) was treated with diisopropylethyl amine (62 mL, 0.44 mmol). The mixture was heated to 60°C for 2 h, cooled, diluted with dichloromethane (12 mL), washed with 8M aq. Urea solution in 2 N aq. HCl (6 mL, 3x), 5% aq. $KHCO_3$ solution (6 mL, 3x), dried (Na_2SO_4), filtered and concentrated. The residue was triturated with EtOAc-ether to obtain the mixed anhydride intermediate (102 mg, 74%) as a white solid. A 1 M solution of sodium bis(trimethylsilylamide) in THF (170 µL, 0.17 mmol) was added dropwise to a stirred solution of 2,6-dichloroaniline (19.4 mg, 0.12 mmol) in THF (1 mL). After 15 min, the mixed anhydride intermediate (41.3 mg, 0.11 mmol) was added in one portion. A few drops of DMF was added and the solution was stirred for 16 h. Additional 1 M solution of sodium bis(trimethylsilylamide) (110 µL) was added and the mixture was stirred for additional 2 h. The mixture was diluted with dichloromethane (4 mL) and washed with 2 N aq. HCl solution (2 mL, 3x), satd. Aq. $KHCO_3$ solution (3x), dried (Na_2SO_4), filtered and concentrated. The solid was washed with hexanes (2x) and the residue was chromatographed on a silica gel column. Elution with 80% EtOAc in hexanes followed by EtOAc afforded **307** (12 mg, 27%) as a light tan solid. "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H_2O, 0.2% H_3PO_4) to 100%

solvent B (90% MeOH, 10% H_2O, 0.2% H_3PO_4), flow rate 4 mL/min, λ = 220 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
286		2-[[(Butylamino) carbonyl]amino]-N-(2,3-dihydro-1H-inden-5-yl)-4-methyl-5-thiazole-carboxamide	4.20
287		2-[[(Butylamino) carbonyl]amino]-N-2-naphthalenyl-4-methyl-5-thiazolecarboxamide	4.20
288		2-[[(Butylamino) carbonyl]amino]-N-(3-hydroxy-2-naphtha-lenyl)-4-methyl-5-thiazolecarboxamide	4.24
289		2-[[(Butylamino) carbonyl]amino]-N-(2-fluoro-5-methylphenyl)-4-methyl-5-thiazolecarboxamide	3.95
290		2-[[(Butylamino) carbonyl]amino]-N-(2,6-dimethylphenyl)-4-methyl-5-thiazole-carboxamide	3.78
291		N-(4-Bromo-2-methylphenyl)-2-[[(butylamino)carbonyl] amino]-4-methyl-5-thiazolecarboxamide	4.12

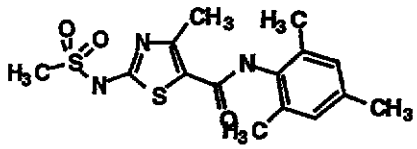
292		N-(3-Bromo-2,4,6-trimethylphenyl)-2-[[(butylamino)carbonyl]amino]-4-methyl-5-thiazolecarboxamide	4.28
293		2-[[(Butylamino)carbonyl]amino]-N-[2,6-dimethyl-3-(1-methylethyl)phenyl]-4-methyl-5-thiazolecarboxamide	4.28
294		N-(2-Bromo-4,6-dimethylphenyl)-2-[[(butylamino)carbonyl]amino]-4-methyl-5-thiazolecarboxamide	4.00
295		3-[[[2-[[(Butylamino)carbonyl]amino]-4-methyl-5-thiazolyl]-carbonyl] amino]-4-methyl-2-thiophene-carboxylic acid methyl ester	3.83
296		2-[[(Butylamino)carbonyl]amino]-4-methyl-N-(2-methyl-6-quinolinyl)-5-thiazolecarboxamide	2.98
297		2-[[(Butylamino)carbonyl]amino]-N-(2,6-dimethoxyphenyl)-4-methyl-5-thiazolecar-boxamide	3.39
298		2-[[(Butylamino)carbonyl]amino]-N-(4-methoxy-2-naphtha-lenyl)-4-methyl-5-thiazolecarboxamide	4.31

299		2-[[(Butylamino) carbonyl]amino]-N-(2-methyl-1-naphthalenyl)-4-methyl-5-thiazole-carboxamide	3.92
300		2-[[(Butylamino) carbonyl]amino]-N-[4-(dimethylamino)-2,3,5,6-tetramethyl-phenyl]-4-methyl-5-thiazolecarboxamide	3.14
301		2-[[(Butylamino) carbonyl]amino]-N-(6-methyl-5-quinolinyl)-4-methyl-5-thiazolecarboxamide	3.13
302		2-[[(Butylamino) carbonyl]amino]-N-[2-(2-hydroxyethyl)-6-methylphenyl]-4-methyl-5-thiazolecarboxamide	3.50
303		2-[[(Butylamino) carbonyl]amino]-N-(2,6-dimethyl-3-nitrophenyl)-4-methyl-5-thiazolecarboxamide	3.75
304		N-(2-Bromo-3,4,6-trimethylphenyl)-2-[[(butylamino)carbonyl]amino]-4-methyl-5-thiazolecarboxamide	4.12
305		N-(2-Acetyl-6-hydroxyphenyl)-2-[[(butylamino)carbonyl]amino]-4-methyl-5-thiazolecarboxamide	3.75

306		[4-[[[2-[[(Butylamino) carbonyl]amino]-4-methyl-5-thiazolyl]-carbonyl] amino]-2,3,5,6-tetramethyl-phenyl]carbamic acid 1,1-dimethylethyl ester	4.10
307		2-[[(Butylamino) carbonyl]amino]-N-(2,6-dichlorophenyl)-4-methyl-5-thiazolecarboxamide	4.42
308		N-(4-Amino-2,3,5,6-tetramethylphenyl)-2-[[(butylamino)carbonyl] amino]-4-methyl-5-thiazolecarboxamide	3.15
309		N-[5-(Acetylamino)-2,4-dimethylphenyl]-2-[[(butylamino)carbonyl] amino]-4-methyl-5-thiazolecarboxamide	3.52
310		N-(4-Bromo-2,6-dimethylphenyl)-2-[[(butylamino)carbonyl] amino]-4-methyl-5-thiazolecarboxamide	4.93
311		2-[[(Butylamino) carbonyl]amino]-N-(2-chloro-6-methylphenyl)-4-methyl-5-thiazolecarboxamide	4.51

Example 312

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



5

3. Ethyl-2-[(methylsulfonyl)amino]-4-methyl-thiazole-5-carboxylate

A stirred solution of ethyl-2-amino-4-methyl-thiazole-5-carboxylate (558 mg, 3 mmol) in dichloromethane (15 mL) and pyridine (5 mL) was treated with methanesulfonyl chloride (687 mg, 6 mmol) at rt overnight. The solution was diluted with dichloromethane (50 mL) and washed with 2N aq. HCl solution (15 mL, 3x), dried ($MgSO_4$), filtered and concentrated. The crude residue was diluted with ether (25 mL) and the solid was filtered, washed with 1:1 ether:hexane mixture (10 mL, 3x), and dried *in vacuo* to obtain the title compound (687 mg, 87%) as an off-white solid.

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

A stirred solution of Ethyl-2-[(methylsulfonyl)amino]-4-methyl-thiazole-5-carboxylate (300 mg, 1.14 mmol) in methanol (9 mL) was treated with a 1N NaOH solution (28.4 mL, 28.4 mmol). The mixture was stirred at rt overnight. The solution was cooled to 0 °C and acidified with 6N aq. HCl solution to pH 1. The solution was extracted with dichloromethane-chloroform mixture. The organic extract was dried (MgSO4), filtered and concentrated *in vacuo* to obtain the title acid (148 mg, 55%).

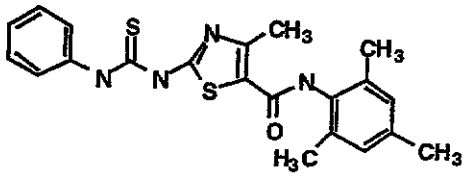
C.4-Methyl-2-[(methylsulfonyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide

Diisopropylethylamine (87 µL, 0.5 mmol) was added to a solution of **312 B** (99 mg, 0.42 mmol), 2,4,6-trimethylaniline (68 µL, 0.5 mmol), and [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate (HATU, 191 mg, 0.5 mmol) in DMF (3 mL). The mixture was stirred at rt overnight, diluted with EtOAc and washed with 0.5 N aq. HCl solution (15 mL), 10% aq. LiCl solution (25 mL, 3x), water (930 mL, 2x), brine, dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 50% EtOAc in hexanes, followed by

75% EtOAc in hexanes and 2% MeOH in EtOAc to obtain the title compound (19 mg, 13%) as a white solid.

Example 313

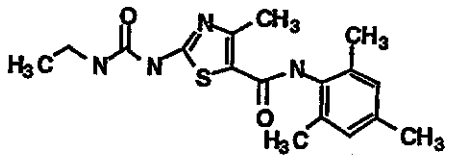
Preparation of 4-Methyl-2-[[(phenylamino)thiocarbonyl]amino)-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



A solution of 2 (45 mg, 0.16 mmol) and phenylisothiocyanate (43 mg, 0.32 mmol) in pyridine (2 mL) was heated to 80°C for 20 h. The mixture was cooled, diluted with dichloromethane-THF mixture (80 mL, 3:1) and washed with 2 N aq. HCl solution (15 mL, 2x). The organic extract was dried ($MgSO_4$), filtered and concentrated. The residue was diluted with EtOAc (20 mL) and the solid was filtered, washed with ether (10 mL, 3x), and dried *in vacuo* to obtain the title compound (35 mg, 52%) as an off-white solid.

Example 314

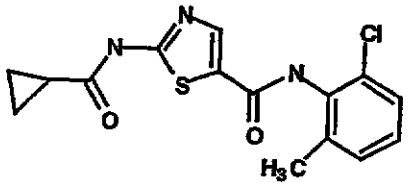
Preparation of 2-[[(Ethylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



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

Example 315

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



3. Ethyl-2-*tert*-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylate

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

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

A stirred solution of ethyl-2-*tert*-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylate (1.1 g, 4.2 mmol) in tetrahydrofuran-methanol (80 mL, 1:1) was treated with a 6N aq. NaOH solution (20 mL, 120 mmol). The mixture was stirred at rt for 24 h. Most of THF and methanol were removed by distillation under reduced pressure and the aq. Solution was acidified with 6 N aq. HCl solution (22 mL). The precipitated solid was

filtered, washed with water and ether, air dried followed by drying *in vacuo* to obtain the title acid (940 mg, 96%) as an off-white solid.

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

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

2-Chloro-6-methyl aniline (212 mg, 1.5 mmol) was added dropwise to a stirred solution of crude 2-*tert*-butoxycarbonyloxyamino-thiazole-5-carboxylic acid chloride (1 mmol) in dichloromethane (10 mL) at 0°C. Diisopropylethylamine (516 mg, 4 mmol) was added. The solution was allowed to warm to rt and stirred for 24 h, diluted with dichloromethane (60 mL) and washed with 2 N aq. HCl solution (15 mL). The organic extract was dried ($MgSO_4$), filtered and concentrated. The residue was diluted with EtOAc-ether (25 mL, 1:4) and the solid was filtered and washed with ether (5 mL, 4x), and dried *in vacuo* to obtain the title compound (175 mg, 48%) as a tan solid.

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

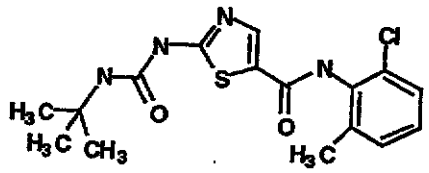
Compound **315D** was prepared by an analogous method as that of **2**, except using compound **315C** to give the title compound **315D** as a tan solid.

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

A solution of **315D** (50.6 mg, 0.19 mmol) and cyclopropanecarboxylic acid anhydride (302 mg, 1.96 mmol) in dioxane (2 mL) was heated to 93 °C overnight. The mixture was concentrated *in vacuo*, diluted with EtOAc and washed with satd. Aq. $KHCO_3$ solution (2x). The organic extract was dried (Na_2SO_4), filtered and concentrated. The residue was triturated with ether to obtain the title compound (11 mg, 17%) as a white solid.

Example 316

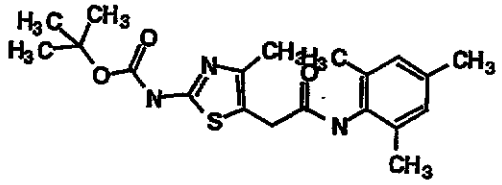
Preparation of 2-[[[(1,1-Dimethylethyl)aminolcarbonyllaminol-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide



Sodium hydride (19.2 mg, 0.8 mmol) was added to a solution of **315D** (48.3 mg, 0.18 mmol) and t-butylisocyanate (41 µL, 0.36 mmol) in THF (5 mL) at 0 °C. After 1 h, the mixture was diluted with EtOAc and washed with cold satd. Aq. Ammonium chloride solution. The aqueous layer was separated and extracted with EtOAc. The EtOAc extracts were combined, dried (Na_2SO_4), filtered and concentrated. The residue was purified by automatic preparative HPLC (conditions: YMC S5 ODS A 20 x 100 mm Column, 10 min gradient starting from 10% solvent B (90% MeOH, 10% H2O, 0.1% TFA) and 90% solvent A (10% MeOH, 90% H2O, 0.1% TFA) to 100% solvent B, flow rate 20 mL/min, λ = 220 nM to obtain the title compound (18 mg, 28%) as an off-white solid.

Example 317

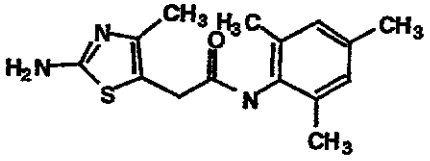
Preparation of 2-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazoleacetamide



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

Example 318

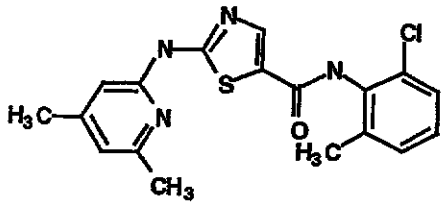
Preparation of 2-Amino-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazoleacetamide



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

Example 319

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



3. 2-Bromo-N-(2-chloro-6-methylphenyl)- 5-thiazolecarboxamide

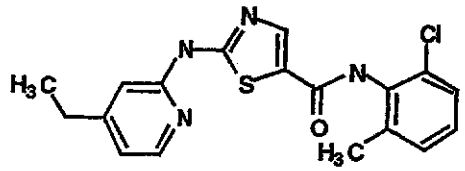
A solution of copper (II) bromide (2.68 g, 12 mmol) in acetonitrile (50 mL) was purged with nitrogen and cooled to 0 °C. t-Butyl nitrite (2 mL, 15 mmol) was added, followed by a solution of compound **315D** (2.68 g, 10 mmol) in acetonitrile (50 mL), The mixture was stirred at rt overnight and concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with satd. Aq. $NaHCO_3$ solution and the precipitate was removed by filtration. The organic extract was dried (Na_2SO_4), filtered and concentrated. The residue was crystallized from EtOAc/ether/hexanes mixture to obtain the title compound (1.68 g, 51%) as a yellow solid.

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

95% Sodium hydride (15 mg) was added to a mixture of **319A** (25 mg, 0.075 mmol) and 4,6-dimethyl-2-aminopyridine (37 mg, 0.302 mmol) in THF (1 mL). The mixture was heated to 60 °C overnight, cooled to rt and diluted with satd. Aq. Ammonium chloride solution. The mixture was extracted with EtOAc (2x). Organic extracts were combined, washed with water and dried (Na_2SO_4), filtered and concentrated. The residue was triturated with ether to obtain the title compound (17.5 mg, 63%) as a tan solid.

Example 320

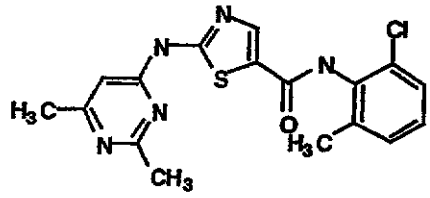
Preparation of N-(2-Chloro-6-methylphenyl)-2-[(4-ethyl-2-pyridinyl)amino]-5-thiazolecarboxamide



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

Example 321

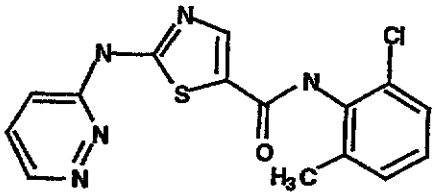
Preparation of N-(2-Chloro-6-methylphenyl)-2-[(2,6-dimethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide



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

Example 322

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



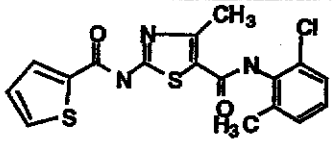
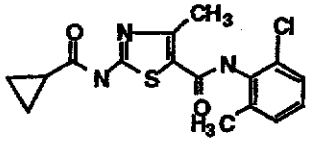
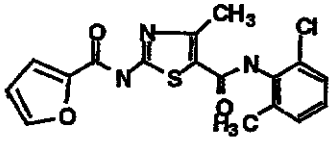
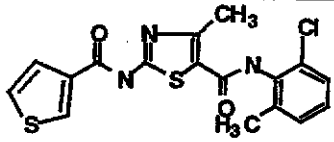
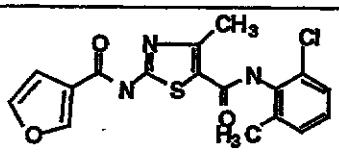
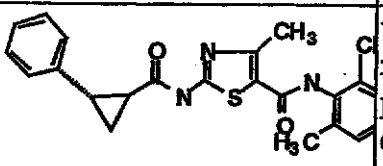
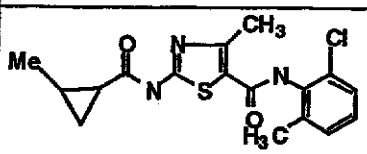
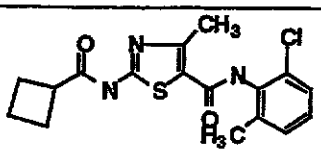
Compound **322** was prepared by an analogous method as that of **319B**, except using 3-aminopyridazine to give the title compound **322**.

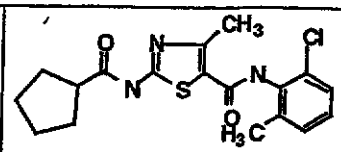
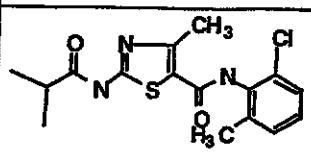
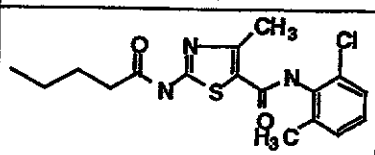
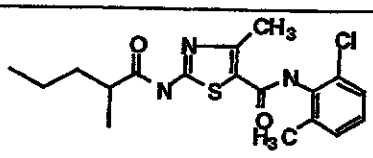
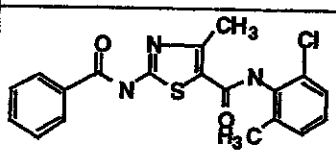
Examples 323 to 335

General Procedure

Compounds **323** to **335** were prepared following the procedure described below. Diisopropylethyl amine (60 μL, 0.34 mmol) was added to a mixture of amine **144** (31 mg, 0.11 mmol), appropriate carboxylic acid (0.13 mmol), 1-hydroxy-7-azabenzotriazole (19.5 mg, 0.14 mmol), and ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (26.8 mg, 0.14 mmol) in THF (0.4 mL). The mixture was heated in a sealed tube under argon at 50 °C for 24 h. The reaction mixture was diluted with dichloromethane (4 mL) and washed with 1 N aq. HCl solution. The dichloromethane solution was passed through a Varian Mega Bond Elut SCX cation exchange column (prewashed with methanol and equilibrated with acetonitrile-methanol (4:1). The column was eluted sequentially with acetonitrile-methanol (4:1), methanol-2M methanolic ammonia (4:1). Fractions containing the product were combined and concentrated in vacuo. "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H2O, 0.2% H3PO4) to

100% solvent B (90% MeOH, 10% H2O, 0.2% H3PO4), flow rate 4 mL/min, λ = 220 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
323		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2-thienyl-carbonyl)amino]-5-thiazolecarboxamide	3.70
324		N-(2-Chloro-6-methylphenyl)-2-[(cyclopropylcarbonyl)amino]-4-methyl-5-thiazolecarboxamide	3.41
325		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2-furanyl-carbonyl)amino]-5-thiazolecarboxamide	3.49
326		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(3-thienylcar-bonyl)amino]-5-thiazole-carboxamide	3.71
327		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(3-furanylcarbonyl)amino]-5-thiazolecarboxamide	3.57
328		trans-N-(2-Chloro-6-methylphenyl)-4-methyl-2-[[(2-phenylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide	4.09
329		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[[(2-methylcyclo-propyl)carbonyl]amino]-5-thiazolecarboxamide	3.65
330		N-(2-Chloro-6-methylphenyl)-2-[(cyclobutylcarbonyl)amino]-4-methyl-5-thiazolecarboxamide	3.63

331		N N-(2-Chloro-6-methylphenyl)-2-[(cyclopentylcarbonyl)amino]-4-methyl-5-thiazolecarboxamide	3.82
332		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2-methyl-1-oxopropyl)amino]-5-thiazolecarboxamide	3.50
333		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(1-oxopentyl)amino]-5-thiazolecarboxamide	3.79
334		N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2-methyl-1-oxopentyl)amino]-5-thiazolecarboxamide	3.90
335		2-(Benzoylamino)-N-(2-chloro-6-methylphenyl)-4-methyl-5-thiazolecarboxamide	3.79

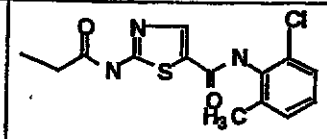
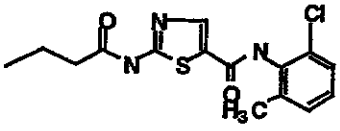
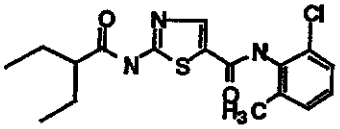
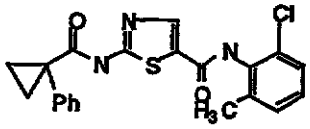
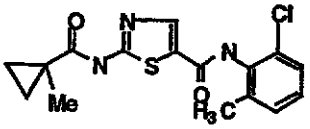
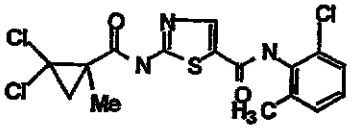
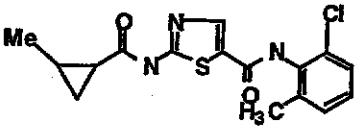
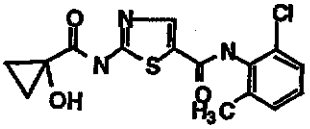
Examples 336 to 362

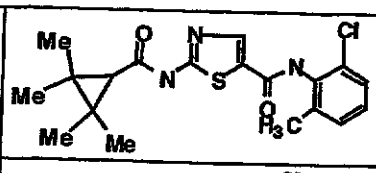
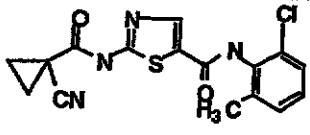
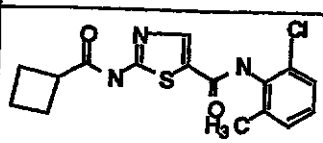
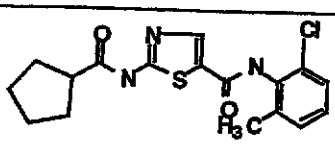
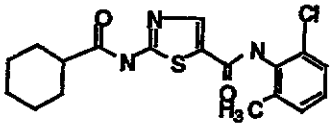
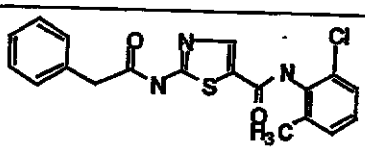
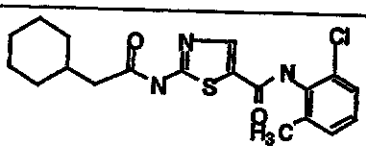
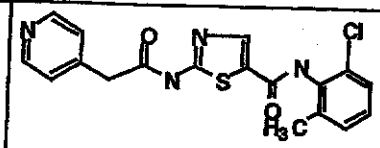
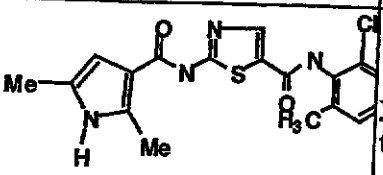
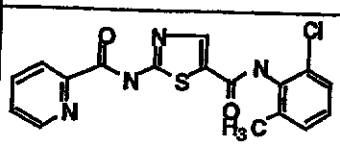
General Procedure

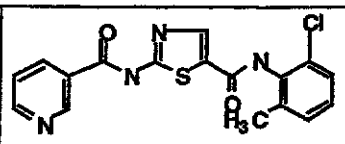
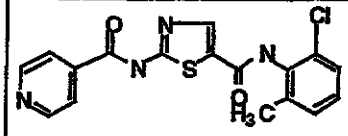
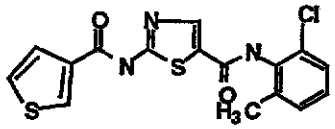
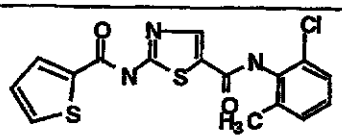
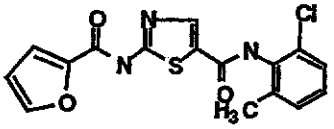
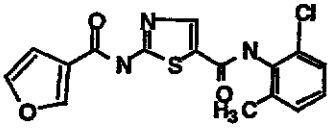
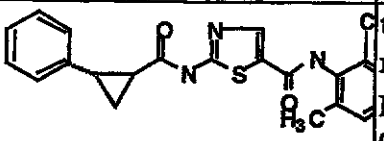
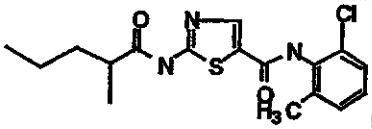
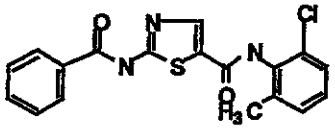
Compounds **336** to **362** were prepared by an analogous method as that of **323-335**, except using **315D** in place of **144**. The crude products were purified by automatic preparative HPLC (conditions: YMC S5 ODS A 20 x 100 mm Column, 10 min gradient starting from 10% solvent B (90% MeOH, 10% H2O, 0.1% TFA) and 90% solvent A (10% MeOH, 90% H2O, 0.1% TFA) to 100% solvent B, flow rate 20 mL/min, λ = 220 nM to obtain the title compounds **336-362.**

"HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H2O, 0.2% H3PO4) to

100% solvent B (90% MeOH, 10% H2O, 0.2% H3PO4), flow rate 4 mL/min, λ = 220 nM.

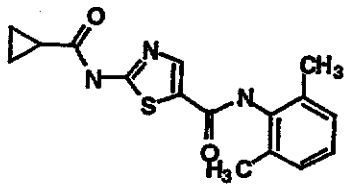
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
336		N-(2-Chloro-6-methylphenyl)-2-[(1-oxopropyl)amino]-5-thiazolecarboxamide	3.53
337		N-(2-Chloro-6-methylphenyl)-2-[(1-oxobutyl)amino]-5-thiazolecarboxamide	3.61
338		N-(2-Chloro-6-methylphenyl)-2-[(2-ethyl-1-oxobutyl)amino]-5-thiazolecarboxamide	3.54
339		N-(2-Chloro-6-methylphenyl)-2-[[(1-phenylcyclo-propyl)carbonyl]amino]-5-thiazolecarboxamide	3.86
340		N-(2-Chloro-6-methylphenyl)-2-[[(1-methylcyclo-propyl)carbonyl]amino]-5-thiazolecarboxamide	3.53
341		N-(2-Chloro-6-methylphenyl)-2-[[(2,2-dichloro-1-methylcyclo-propyl)carbonyl]amino]-5-thiazolecarboxamide	3.53
342		N-(2-Chloro-6-methylphenyl)-2-[[(2-methylcyclo-propyl)carbonyl]amino]-5-thiazolecarboxamide	3.53
343		N-(2-Chloro-6-methylphenyl)-2-[[(1-hydroxycyclopropyl)-carbonyl]amino]-5-thiazole-carboxamide	3.58

344		N-(2-Chloro-6-methylphenyl)-2-[[(2,2,3,3-tetramethylcyclo-propyl)carbonyl]amino]-5-thiazolecarboxamide	3.69
345		N-(2-Chloro-6-methylphenyl)-2-[[(1-cyanocyclopropyl)-carbonyl]amino]-5-thiazole-carboxamide	3.53
346		N-(2-Chloro-6-methylphenyl)-2-[(cyclobutylcarbonyl)amino]-5-thiazolecarboxamide	3.52
347		N-(2-Chloro-6-methylphenyl)-2-[(cyclopentylcarbonyl)amino]-5-thiazolecarboxamide	3.59
348		N-(2-Chloro-6-methylphenyl)-2-[(cyclohexylcarbonyl)amino]-5-thiazolecarboxamide	3.78
349		N-(2-Chloro-6-methylphenyl)-2-[(phenylacetyl)amino]-5-thiazolecarboxamide	3.62
350		N-(2-Chloro-6-methylphenyl)-2-[(cyclohexylacetyl)amino]-5-thiazolecarboxamide	4.07
351		N-(2-Chloro-6-methylphenyl)-2-[(4-pyridinylacetyl)amino]-5-thiazolecarboxamide	3.75
352		N-(2-Chloro-6-methylphenyl)-2-[[(2,5-dimethyl-1H-pyrrol-3-yl)carbonyl]amino]-5-thiazolecarboxamide	3.17
353		N-(2-Chloro-6-methylphenyl)-2-[(2-pyridinylcarbonyl)amino]-5-thiazolecarboxamide	3.07

354		N-(2-Chloro-6-methylphenyl)-2-[(3-pyridinylcarbonyl)amino]-5-thiazolecarboxamide	3.07
355		N-(2-Chloro-6-methylphenyl)-2-[(4-pyridinylcarbonyl)amino]-5-thiazolecarboxamide	3.61
356		N-(2-Chloro-6-methylphenyl)-2-[(3-thienylcarbonyl)amino]-5-thiazolecarboxamide	3.60
357		N-(2-Chloro-6-methylphenyl)-2-[(2-thienylcarbonyl)amino]-5-thiazolecarboxamide	3.61
358		N-(2-Chloro-6-methylphenyl)-2-[(2-furanylcarbonyl)amino]-5-thiazolecarboxamide	3.61
359		N-(2-Chloro-6-methylphenyl)-2-[(3-furanylcarbonyl)amino]-5-thiazolecarboxamide	3.69
360		trans-N-(2-Chloro-6-methylphenyl)-2-[[(2-phenylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide	3.98
361		N-(2-Chloro-6-methylphenyl)-2-[(2-methyl-1-oxopentyl)amino]-5-thiazolecarboxamide	3.90
362		2-(Benzoylamino)-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	3.61

Example 363

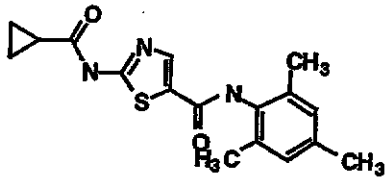
Preparation of 2-[(Cyclopropylcarbonyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide



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

Example 364

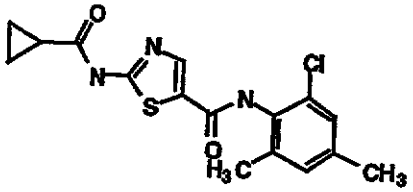
Preparation of 2-[(Cyclopropylcarbonyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



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

Example 365

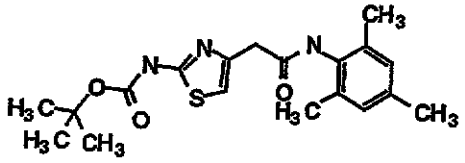
Preparation of N-(2-Chloro-4,6-dimethylphenyl)-2-[(cyclopropylcarbonyl)amino]-5-thiazolecarboxamide



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

Example 366

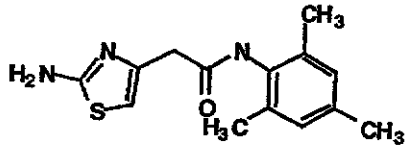
Preparation of [4-[2-Oxo-2-[(2,4,6-trimethylphenyl)amino]ethyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester



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

Example 367

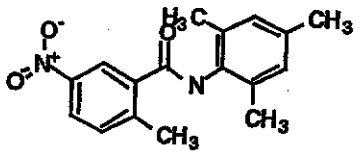
Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-thiazoleacetamide



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

Example 368

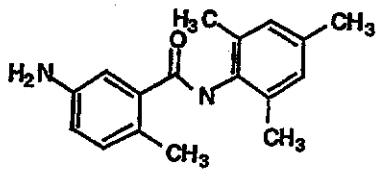
Preparation of 2-Methyl-5-nitro-N-(2,4,6-trimethylphenyl)benzamide



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

Example 369

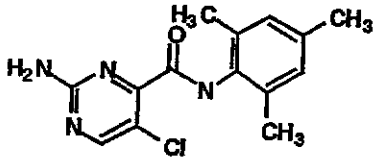
Preparation of 5-Amino-2-methyl-N-(2,4,6-trimethylphenyl)benzamide



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

Example 370

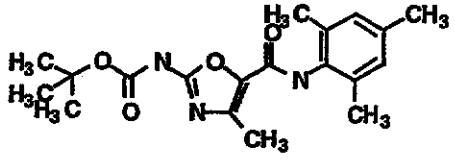
Preparation of 2-Amino-5-chloro-N-(2,4,6-trimethylphenyl)- 4-pyrimidinecarboxamide



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

Example 371

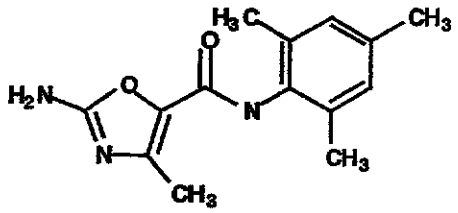
Preparation of [4-Methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]- 2-oxazolyl]carbamic acid 1,1-dimethylethyl ester



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

Example 372

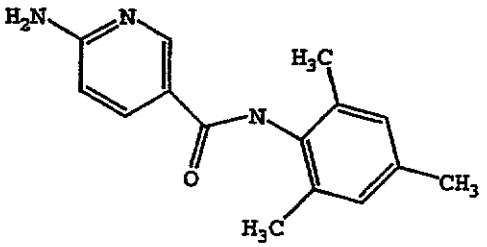
Preparation of 2-Amino-4-(methyl)-N-(2,4,6-trimethylphenyl)-5-oxazolecarboxamide, trifluoroacetate (1:1)



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

Example 373

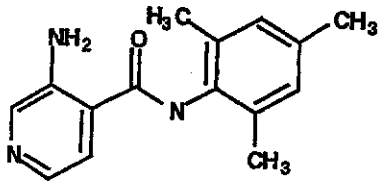
Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-5-pyridinecarboxamide



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

Example 374

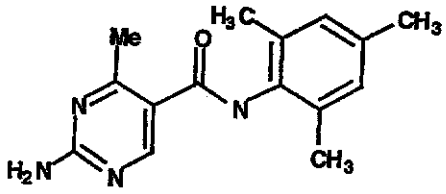
Preparation 3-Amino-N-(2,4,6-trimethylphenyl)-4-pyridinecarboxamide



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

Example 375

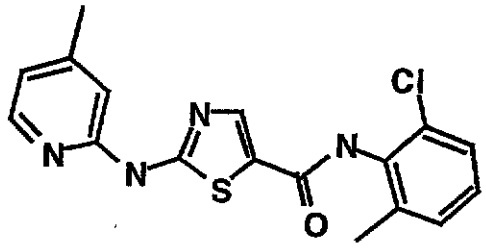
Preparation 2-Amino-4-methyl-N-(2,4,6-trimethylphenyl)-5-pyrimidinecarboxamide



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

Example 376

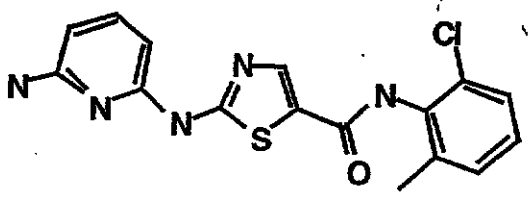
Preparation of N-(2-Chloro-6-methylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide



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

Example 377

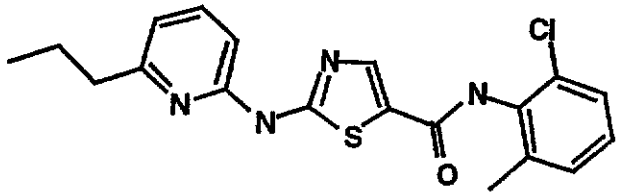
Preparation of 2-[(6-Amino-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide



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

Example 378

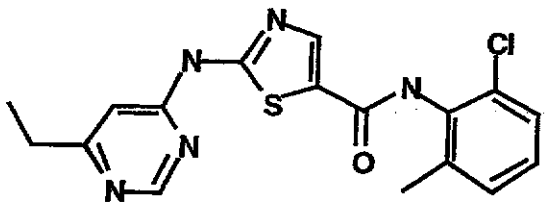
Preparation of N-(2-Chloro-6-methylphenyl)-2-[(6-propyl-2-pyridinyl)amino]-5-thiazolecarboxamide



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

Example 379

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

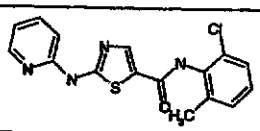
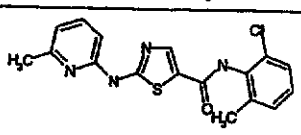
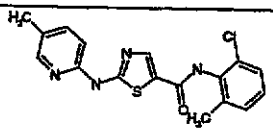
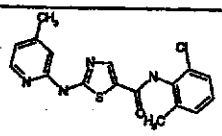
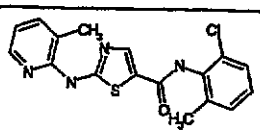


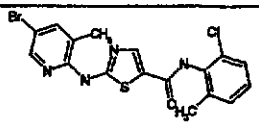
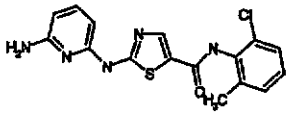
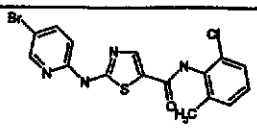
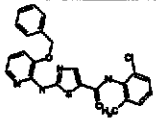
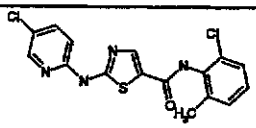
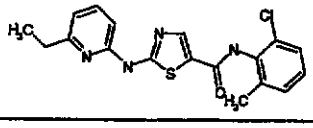
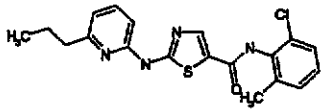
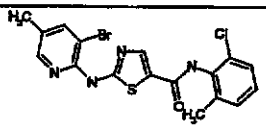
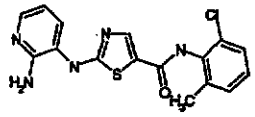
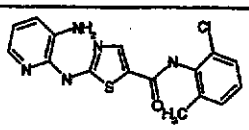
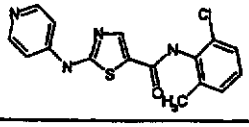
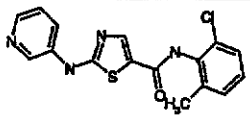
Compound **379** was prepared by an analogous method as that of **319B**, except using 4-amino-6-ethyl-pyrimidine to give the title compound **379** as a white solid.

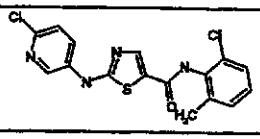
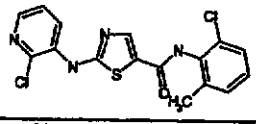
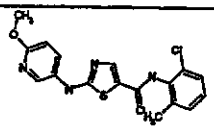
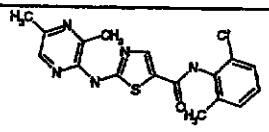
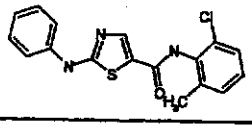
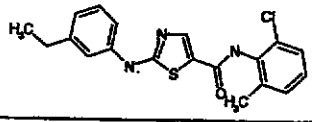
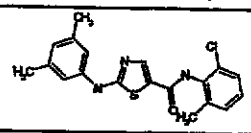
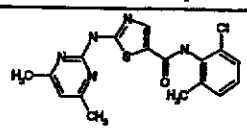
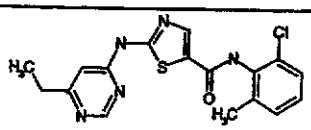
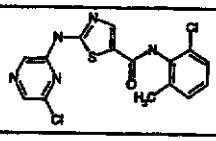
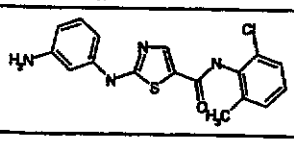
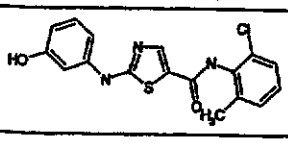
Examples 380 to 409

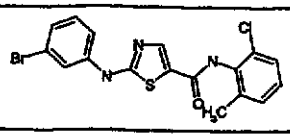
General Procedure

Compounds 380 to 409 were prepared by an analogous method as that of 319B. For the following examples 380 to 527 "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H_2O, 0.2% H_3PO_4) to 100% solvent B (90% MeOH, 10% H_2O, 0.2% H_3PO_4), flow rate 4 mL/min, λ = 220 nM. Where used, "HPLC Ret Time 'B'" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 33 mm Turbo Column, 2 min gradient starting from 100% solvent A (10% MeOH, 90% H_2O, 0.1% TFA) to 100% solvent B (90% MeOH, 10% H_2O, 0.1% TFA) with 1min at 100% solvent B, flow rate 4 mL/min, λ = 220 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
380		'N-(2-Chloro-6-methylphenyl)-2-(2-pyridinylamino)-5-thiazolecarboxamide	3.337
381		'N-(2-Chloro-6-methylphenyl)-2-[(6-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.61
382		'N-(2-Chloro-6-methylphenyl)-2-[(5-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.487
383		'N-(2-Chloro-6-methylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.293
384		'N-(2-Chloro-6-methylphenyl)-2-[(3-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.243

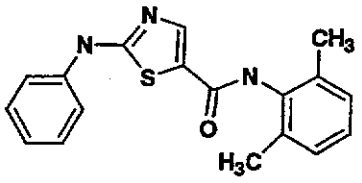
385		'2-[(5-Bromo-3-methyl-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	4.17
386		'2-[(6-Amino-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.817
387		'2-[(5-Bromo-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	4.023
388		'N-(2-Chloro-6-methylphenyl)-2-[[3-(phenylmethoxy)-2-pyridinyl]amino]-5-thiazolecarboxamide	4.143
389		'N-(2-Chloro-6-methylphenyl)-2-[(5-chloro-2-pyridinyl)amino]-5-thiazolecarboxamide	3.957
390		'N-(2-Chloro-6-methylphenyl)-2-[(6-ethyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.867
391		'N-(2-Chloro-6-methylphenyl)-2-[(6-propyl-2-pyridinyl)amino]-5-thiazolecarboxamide	4.083
392		'2-[(3-Bromo-5-methyl-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	4.077
393		'2-[(2-Amino-3-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.343
394		'2-[(3-Amino-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.777
395		'N-(2-Chloro-6-methylphenyl)-2-(4-pyridinylamino)-5-thiazolecarboxamide	2.493
396		'N-(2-Chloro-6-methylphenyl)-2-(3-pyridinylamino)-5-thiazolecarboxamide	2.47

397		'N-(2-Chloro-6-methylphenyl)-2-[(6-chloro-3-pyridinyl)amino]-5-thiazolecarboxamide	3.75
398		'N-(2-Chloro-6-methylphenyl)-2-[(2-chloro-3-pyridinyl)amino]-5-thiazolecarboxamide	3.443
399		'N-(2-Chloro-6-methylphenyl)-2-[(6-methoxy-3-pyridinyl)amino]-5-thiazolecarboxamide	3.517
400		'N-(2-Chloro-6-methylphenyl)-2-[(3,5-dimethyl-2-pyrazinyl)amino]-5-thiazolecarboxamide	3.583
401		'N-(2-Chloro-6-methylphenyl)-2-(phenylamino)-5-thiazolecarboxamide	3.697
402		'N-(2-Chloro-6-methylphenyl)-2-[(3-ethylphenyl)amino]-5-thiazolecarboxamide	4.107
403		'N-(2-Chloro-6-methylphenyl)-2-[(3,5-dimethylphenyl)amino]-5-thiazolecarboxamide	3.98
404		'N-(2-Chloro-6-methylphenyl)-2-[(4,6-dimethyl-2-pyrimidinyl)amino]-5-thiazolecarboxamide	3.51
405		'N-(2-Chloro-6-methylphenyl)-2-[(6-ethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide	2.943
406		'N-(2-Chloro-6-methylphenyl)-2-[(6-chloro-2-pyrazinyl)amino]-5-thiazolecarboxamide	3.763
407		'2-[(3-Aminophenyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.633
408		'N-(2-Chloro-6-methylphenyl)-2-[(3-hydroxyphenyl)amino]-5-thiazolecarboxamide	3.337

409		'2-[(3-Bromophenyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	4.12

Example 410

Preparation of N-(2,6-Dimethylphenyl)-2-(phenylamino)-5-thiazolecarboxamide



3. [5-[[(2,6-dimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

Compound **410A** was prepared by an analogous method as that of **315C**, except using 2,6-dimethylaniline.

B. 2-Amino-N-(2,6-dimethylphenyl)- 5-thiazolecarboxamide

Compound **410B** was prepared by an analogous method as that of **315D**, except using compound **410A**.

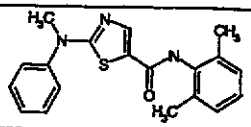
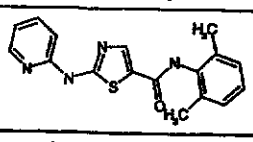
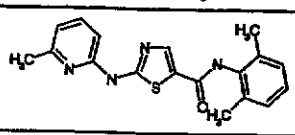
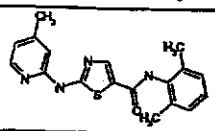
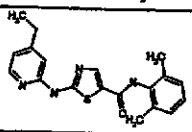
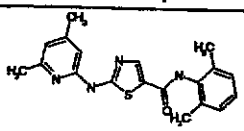
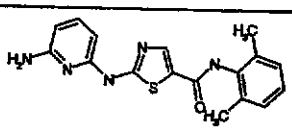
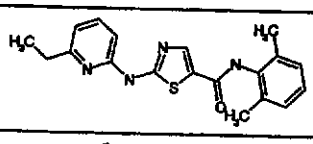
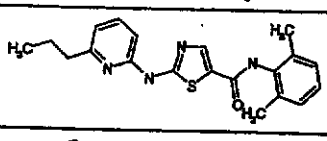
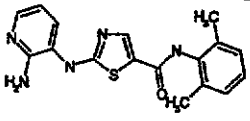
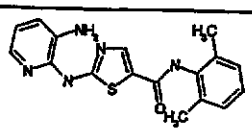
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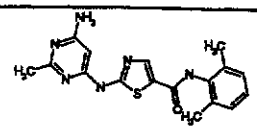
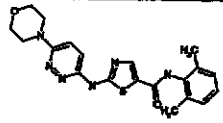
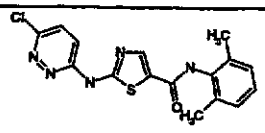
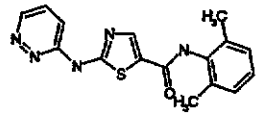
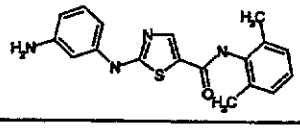
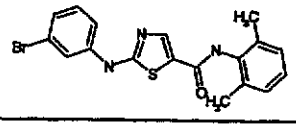
The title compound was prepared by an analogous method as that of **319B**, except using compound **410B** and aniline. HPLC Ret. Time 3.69min.

Examples 411 to 427

General Procedure

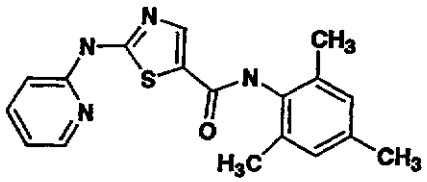
Compounds **411** to **427** were prepared by an analogous method as that of **319B**.

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

422		'2-[(6-Amino-2-methyl-4-pyrimidinyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide	2.71
423		'N-(2,6-Dimethylphenyl)-2-[[6-(4-morpholinyl)-3-pyridazinyl]amino]-5-thiazolecarboxamide	2.727
424		'2-[(6-Chloro-3-pyridazinyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide	3.46
425		'N-(2,6-Dimethylphenyl)-2-(3-pyridazinylamino)-5-thiazolecarboxamide	2.973
426		'2-[(3-Aminophenyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide	2.63
427		'2-[(3-Bromophenyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide	4.143

Example 428

Preparation of '2-(2-Pyridinylamino)-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



3. [5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

Compound **428A** was prepared by an analogous method as that of **315C**, except using 2,4,6-trimethylaniline.

B. 2-Amino-N-(2,6-dimethylphenyl)- 5-thiazolecarboxamide

Compound **428B** was prepared by an analogous method as that of **315D**, except using compound **428A**.

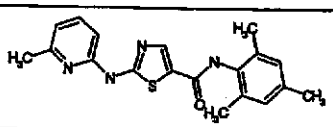
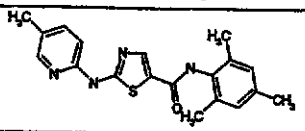
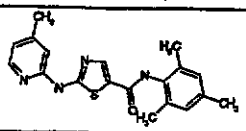
C. Title Compound

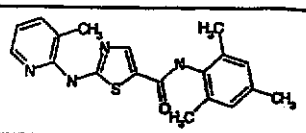
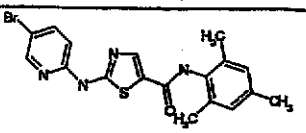
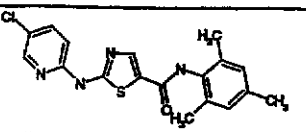
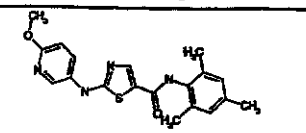
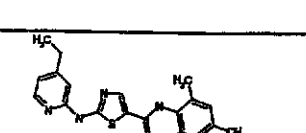
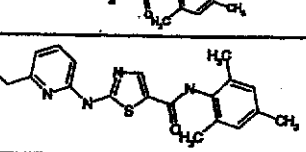
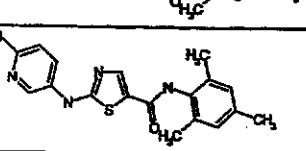
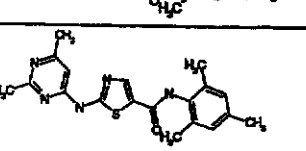
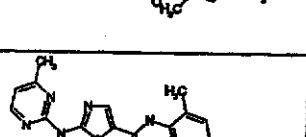
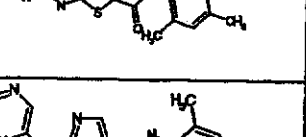
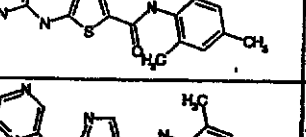
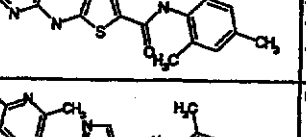
The title compound was prepared by an analogous method as that of **319B**, except using compound **428B** and 2-aminopyridine. HPLC Ret. Time 3.66min.

Examples 429 to 443

General Procedure

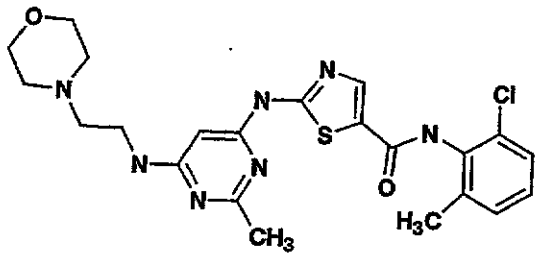
Compounds **429** to **443** were prepared by an analogous method as that of **319B**.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
429		'2-[(6-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.903
430		'2-[(5-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.8
431		'2-[(4-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.603

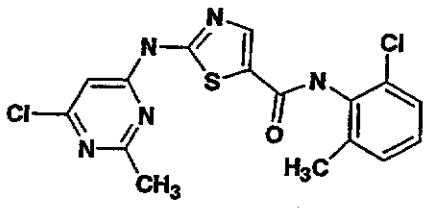
432		'2-[(3-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.56
433		'2-[(5-Bromo-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.263
434		'2-[(5-Chloro-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.203
435		'2-[(6-Methoxy-3-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.8
436		'2-[(4-Ethyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.86
437		'2-[(6-Ethyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.127
438		'2-[(6-Chloro-3-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.017
439		'2-[(2,6-Dimethyl-4-pyrimidinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	2.943
440		'2-[(4-Methyl-2-pyrimidinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.723
441		'2-(2-Pyrazinylamino)-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.65
442		'2-[(6-Chloro-2-pyrazinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.05
443		'2-[(3,5-Dimethyl-2-pyrazinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.877

Example 444

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



A



To a suspension of NaH (148mg, 6.17mmol) in THF (20mL) was added a solution of compound **315D** (551mg, 2.06mmol) in THF (10mL) and stirred at RT for 0.5h. A solution of 4,6-dichloro-2-methylpyrimidine (671.6mg, 4.12mmol) in THF (10mL) and stirred at RT overnight. The reaction was quenched with acetic acid and the solvent removed in vacuo. Water and saturated $NaHCO_3$ were added to the residue and extracted with CH_2Cl_2. The organic layer was removed in vacuo and the crude material purified by column chromatography to give **444A** (494mg).

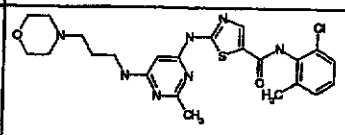
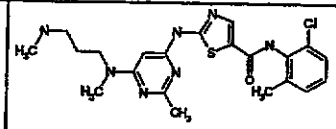
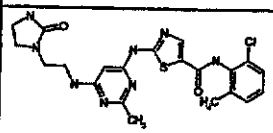
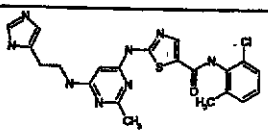
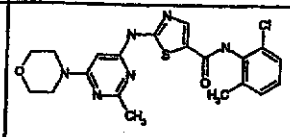
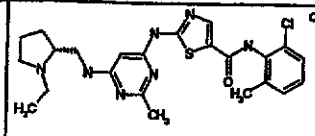
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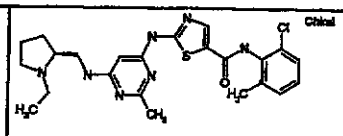
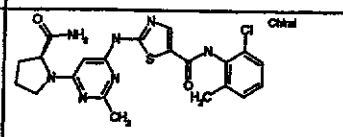
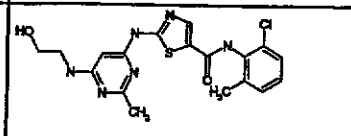
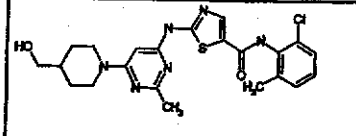
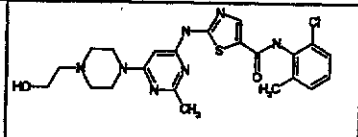
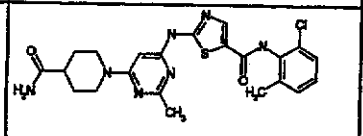
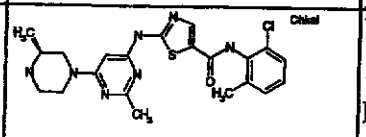
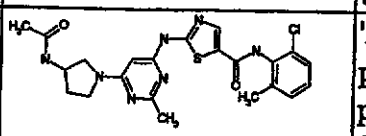
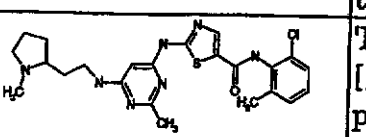
To compound **444A** (30mg) was added N-(2-aminoethyl)-morpholine (300µL) and the mixture was heated at 80°C for 2h. Water was added to the reaction and the product was collected by filtration. HPLC Ret. Time 2.357min.

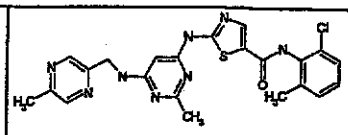
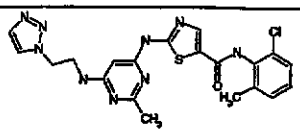
Examples 445 to 461

General Procedure

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

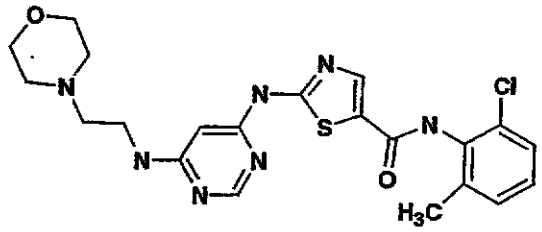
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
445		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[3-(4-morpholinyl)propyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.253
446		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[methyl[3-(methyl-amino)propyl]amino]-4-pyrimi-dinyl]amino]-5-thiazole-carboxamide	2.493
447		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[2-(tetrahydro-2-oxo-1H-imidazol-1-yl)ethyl]-amino]-4-pyri-midinyl]amino]-5-thiazole-carboxamide	2.71
448		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[(2-1H-imidazol-4-ylethyl)amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.303
449		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-(4-morpholinyl)-4-pyrimidinyl]amino]-5-thiazolecarboxamide	3.337
450		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[(2R)-1-ethyl-2-pyrrolidinyl]methyl]amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.703

451		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[(2S)-1-ethyl-2-pyrrolidinyl]methyl]amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.717
452		'2-[[6-[(2S)-2-(Aminocarbonyl)-1-pyrrolidinyl]-2-methyl-4-pyrimidinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.81
453		'N-(2-Chloro-6-methylphenyl)-2-[[6-[(2-hydroxyethyl)amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.677
454		'N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(hydroxymethyl)-1-piperidinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide	3.05
455		'N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.717
456		'1-[6-[[5-[[(2-Chloro-6-methylphenyl)amino]carbonyl]-2-thiazolyl]amino]-2-methyl-4-pyrimidinyl]-4-piperidinecarboxamide	2.863
457		'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[(3S)-3-methyl-1-piperazinyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.823
458		'2-[[6-[3-(Acetylamino)-1-pyrrolidinyl]-2-methyl-4-pyrimidinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	2.78
459		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(1-methyl-2-pyrrolidinyl)ethyl]amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.383

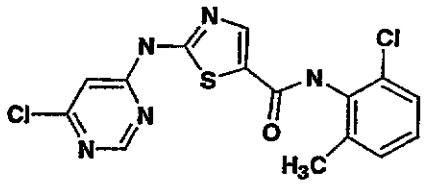
460		N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[(5-methyl-2-pyrazinyl)methyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	3.027
461		N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[2-(1H-1,2,3-triazol-1-yl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.78

Example 462

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



A



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

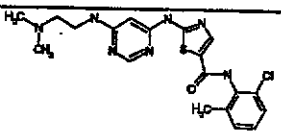
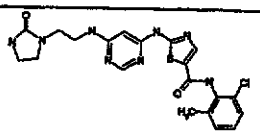
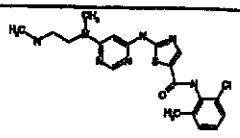
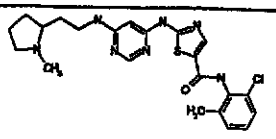
B. Title Compound

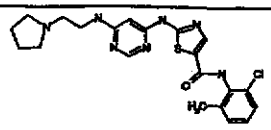
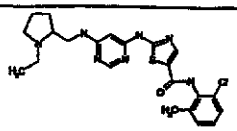
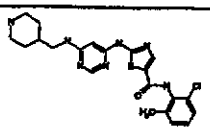
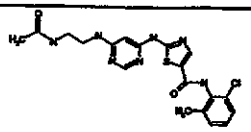
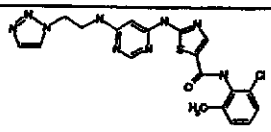
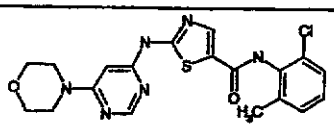
The title compound was prepared by an analogous method as that of **444B**, except using compound **462A** in place of compound **444A**. HPLC Ret. Time 2.553min.

Examples 463 to 472

General Procedure

Compounds **463** to **472** were prepared by an analogous method as that of **444B** by substituting the appropriate amine. "HPLC Ret Time 'B'" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 33 mm Turbo Column, 2 min gradient starting from 100% solvent A (10% MeOH, 90% H_2O, 0.1% TFA) to 100% solvent B (90% MeOH, 10% H_2O, 0.1% TFA) with 1min at 100% solvent B, flow rate 4 mL/min, λ = 220 nM.

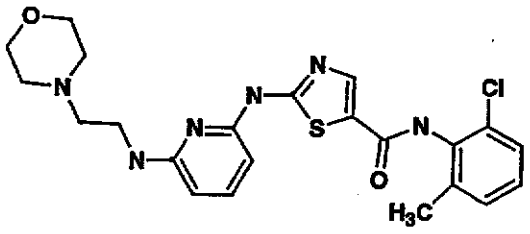
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
463		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(dimethyl-amino)-ethyl]amino]-4-pyrimidinyl]-amino]-5-thiazolecarboxamide	2.527
464		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(tetrahydro-2-oxo-1H-imidazol-1-yl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide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

467		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(1-pyrrolidinyl)-ethyl]amino]-4-pyrimidinyl]-amino]-5-thiazolecarboxamide	1.150 B
468		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[(1-ethyl-2-pyrrolidinyl-)methyl]amino]-4-pyrimi-dinyl]amino]-5-thiazole-carboxamide	1.237 B
469		'N-(2-Chloro-6-methylphenyl)-2-[[6-[(4-piperidinyl-methyl)amino]-4-pyrimi-dinyl]amino]-5-thiazole-carboxamide	1.160 B
470		'2-[[6-[[2-(Acetylamino)-ethyl]amino]-4-pyrimi-dinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazole-carboxamide	2.457 B
471		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(1H-1,2,3-triazol-1-yl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.897
472		'N-(2-Chloro-6-methylphenyl)-2-[[6-(4-morpholinyl)-4-pyrimidinyl]amino]-5-thiazolecarboxamide	3.437

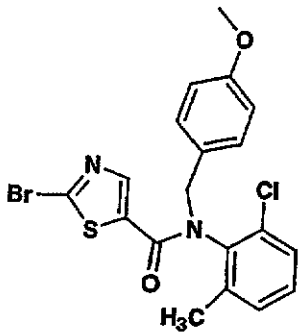
Example 473

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

5

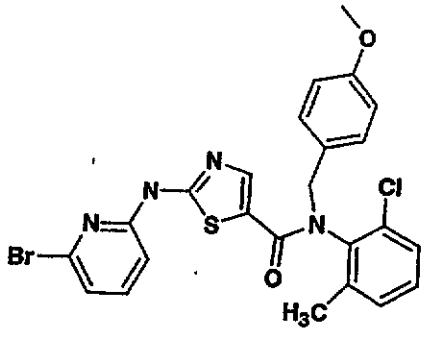


A.



To a suspension of NaH (2.83g,118mmol) in DMF (350mL) cooled to 0°C was added compound **319A** (31g, 93.5mmol). The mixture was stirred for 45min at 0°C then Bu_4NI (6.9g, 18.7mmol) was added followed by addition of 4-methoxy benzylchloride (18g, 115mmol). The reaction was allowed to warm to RT. After stirring overnight at RT the reaction was quenched slowly with acetic acid then the solvent removed in vacuo. To the residue was added water and neutralized with saturated aqueous $NaHCO_3$. The mixture was extracted 3 times with EtOAc and the combined organic layers washed with water then washed with saturated NaCl solution. The EtOAc layer was concentrated in vacuo and the residue purified by column chromatography to give **473A** (35g).

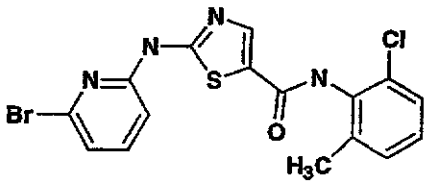
B



To compound **473A** (0.5g, 1.1mmol) dissolved in THF (50mL) was slowly added NaH (0.13g, 5.5mmol) followed by 2-bromo-6-aminopyridine (0.76g, 4.4mmol). The reaction was heated to reflux for 2h then cooled to RT and

quenched with acetic acid. The solvent was removed in vacuo then water and hexane was added and stirred at RT. The solid precipitate was collected by filtration and washed with water and Et_2O to give **473B** (0.48g)

C



To compound **473B** (0.48g) dissolved in TFA (5mL) was added anisole (2mL) followed by triflic acid (1mL). The reaction was stirred at RT for 3h then was slowly added to a rapidly stirred mixture of ice, saturated $NaHCO_3$, Et_2O and CH_2Cl_2. The mixture was stirred cold for 1h then the solid precipitate was collected by filtration and washed with water followed by Et_2O/CH_2Cl_2 mixture to give 473C (0.344g). HPLC Ret. Time 3.85min.

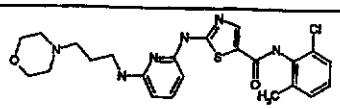
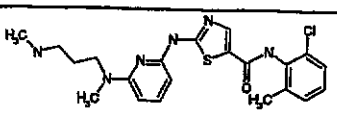
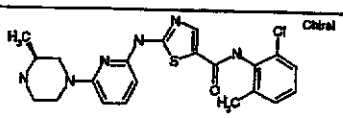
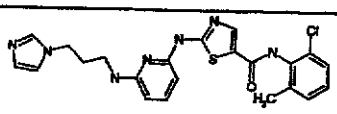
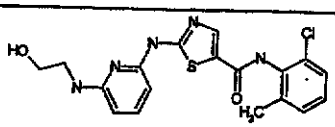
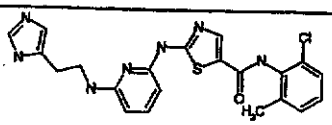
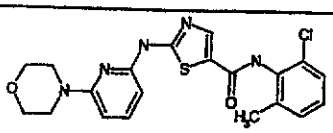
D. Title Compound

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

Examples 474 to 480

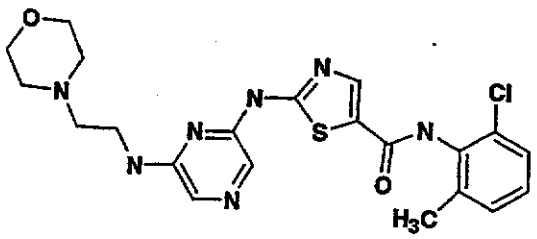
General Procedure

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

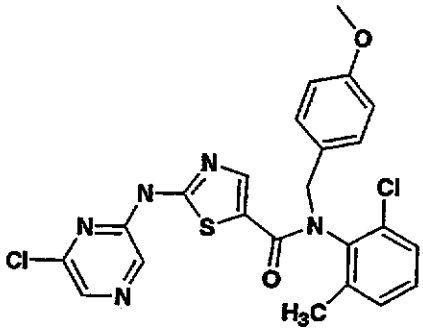
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
474		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[3-(4-morpholinyl)-propyl]amino]-2-pyridinyl]-amino]-5-thiazolecarboxamide	2.867
475		'N-(2-Chloro-6-methylphenyl)-2-[[6-[methyl[3-(methyl-amino)propyl]amino]-2-pyridinyl]amino]-5-thiazole-carboxamide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

Example 481

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

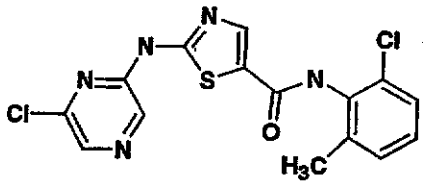


A.



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

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



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

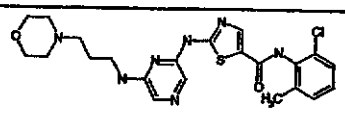
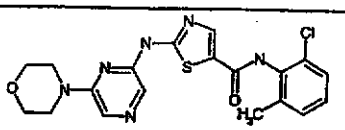
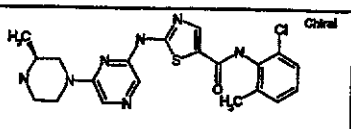
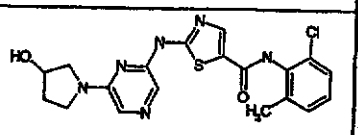
C. Title Compound

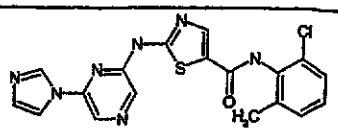
The title compound was prepared by an analogous method as that of **444B**, except using compound **406** in place of compound **444A**. HPLC Ret. Time 2.69min.

Examples 482 to 486

General Procedure

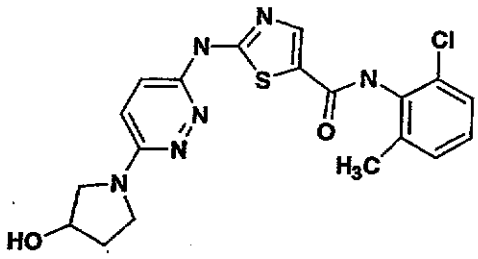
Compounds **482** to **486** were prepared by an analogous method as that of **481C** by substituting the appropriate amine.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
482		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[3-(4-morpholinyl)-propyl]amino]-2-pyrazinyl]-amino]-5-thiazolecarboxamide	2.783
483		'N-(2-Chloro-6-methylphenyl)-2-[[6-(4-morpholinyl)-2-pyrazinyl]amino]-5-thiazole-carboxamide	3.57
484		'N-(2-Chloro-6-methylphenyl)-2-[[6-[(3S)-3-methyl-1-piperazinyl]-2-pyrazinyl]-amino]-5-thiazolecarboxamide	2.743
485		'N-(2-Chloro-6-methylphenyl)-2-[[6-(3-hydroxy-1-pyrrolidinyl)-2-pyrazinyl]-amino]-5-thiazolecarboxamide	3.327

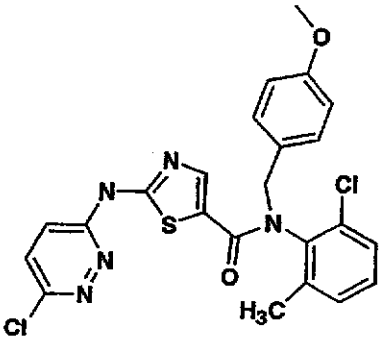
486		'N-(2-Chloro-6-methylphenyl)-2-[[6-(1H-imidazol-1-yl)-2-pyrazinyl]amino]-5-thiazolecarboxamide	2.68

Example 487

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

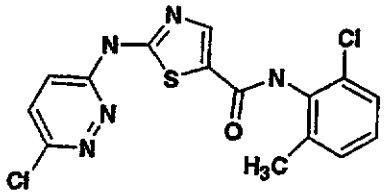


A.



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

B



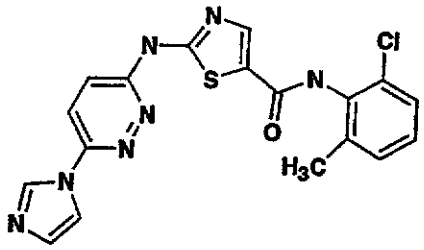
Compound **487B** was prepared by an analogous method as that of **473C**, except using compound **487A** in place of compound **473B**.

C. Title Compound

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

Example 488

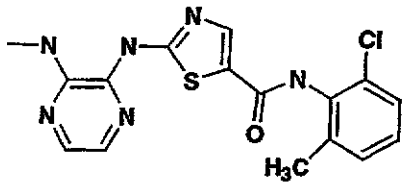
Preparation of N-(2-Chloro-6-methylphenyl)-2-[[6-(1H-imidazol-1-yl)-3-pyridazinyl]aminol-5-thiazolecarboxamide



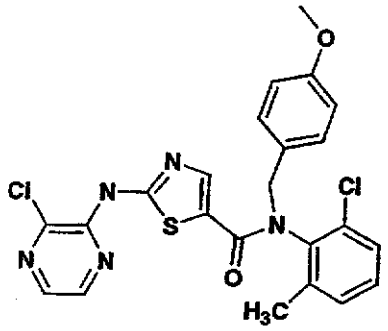
Compound **488** was prepared by an analogous method as that of **487C**, except using imidazole in place of 3-hydroxypyrrolidine. HPLC Ret. Time 2.61min.

Example 489

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

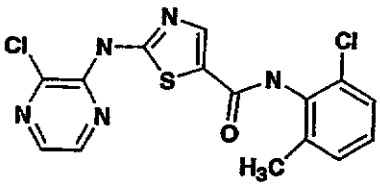


A.



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

B



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

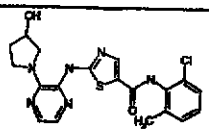
C. Title Compound

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

Examples 490 to 494

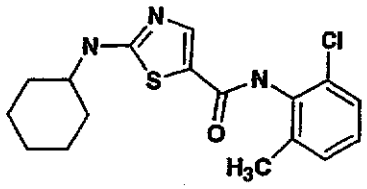
General Procedure

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

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
490		'N-(2-Chloro-6-methylphenyl)-2-[[3-(3-hydroxy-1-pyrrolidinyl)-2-pyrazinyl]amino]-5-thiazolecarboxamide	2.82

Example 495

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

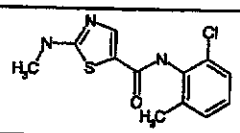


Compound **495** was prepared by an analogous method as that of **444B**, except using compound **319A** in place of compound **444A**, and using cyclohexylamine in place of N-(2-aminoethyl)-morpholine. HPLC Ret. Time 3.547min.

Examples 496 to 500

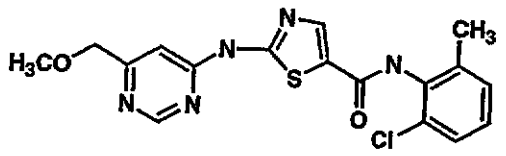
General Procedure

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

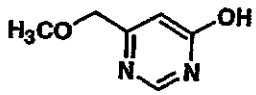
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
496		'N-(2-Chloro-6-methylphenyl)-2-(methylamino)-5-thiazolecarboxamide	2.357

Example 501

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

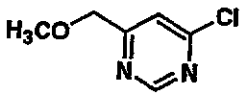


A



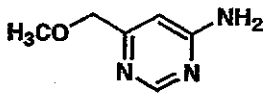
To the mixture of methyl 4-methoxyacetoacetate (14.6 g, 0.1 moL) and formami-dine hydrogen chloride salt (16.1 g, 0.2 moL) in 70 mL of dry MeOH was added a 25% solution of sodium methoxide (70 mL, 0.3 moL) in MeOH portionwise. A white precipitate was formed immediately. The reaction mixture was stirred at room temperature for 1.0 hr. Acetic acid (28.6 mL, 0.5 moL) was added and the reaction mixture was concentrated in vacuo. Water was added to the residue and the mixture was supersaturated with NaCl and extracted with EtOAc (x5). Combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give 8.13 g of compound **501A** as a yellow solid.

B



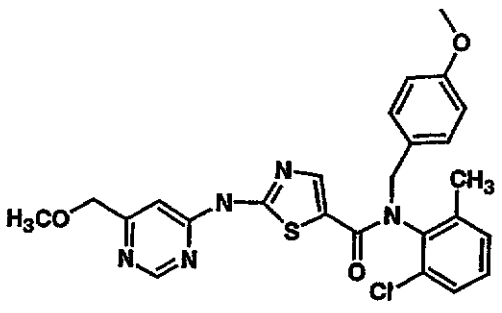
The mixture of compound **501A** (5.3 g, 37.8 mmoL) and $POCl_3$ (40 mL) was heated to reflux for 2.0 hrs. Concentration in vacuo and the residue was poured into a mixture of ice-CH_2Cl_2. The pH was adjusted to 6.5 to 7 using concentrated NH_4OH. The mixture was extracted with CH_2Cl_2 (x3) and combined extracts were dried over Na_2SO_4. Concentration in vacuo followed by flash chromatography (CH_2Cl_2-EtOAc: 9:1) on silica gel gave 5.33 g of compound **501B** as a pale yellow oil.

C



The mixture of compound **501B** (3.2 g, 20 mmoL) and NH_4OH (50 mL) was heated to 85.C in a pressure tube for 3.o hrs. After cooled to room temperature, the reaction mixture was concentrated in vacuo and the residue was triturated with ether to give 2.81 g of compound **501C** as a pale yellow solid.

D



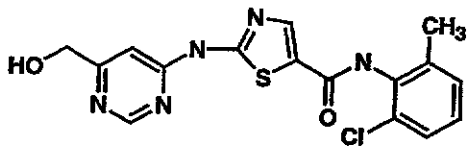
Compound **501D** was prepared from compound **501C** by a method analogous to that used for the preparation of compound **473B.**

E Title Compound

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

Example 502

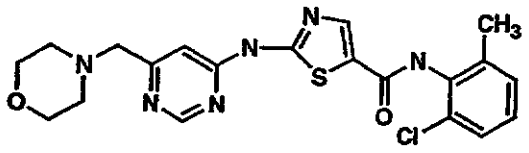
Preparation of N-(2-Chloro-6-methylphenyl)-2-[[6-(hydroxymethyl)-4-pyrimidinyl]amino]-5-thiazolecarboxamide



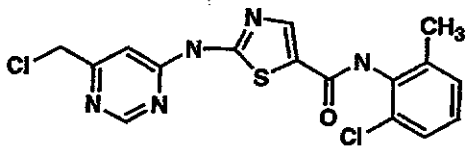
To a solution of compound **501** (56 mg, 0.144 mmoL) in dry CH_2Cl_2 (3.0 mL) cooled at 0.C was added neat BBr_3 (0.054 mL, 0.574 mmoL). The mixture was stirred for 1.0 hr at ambient temperature. MeOH was added slowly with care at 0.C and the resulting mixture was concentrated in vacuo. Water was added to the residue and pH was adjusted to 7 with Sat'd $NaHCO_3$. The white precipitate was collected by filtration, rinsed with water/ether and dried under high vacuum to give 52 mg of Compound **502** as an off-white solid. HPLC Retention time = 2.84 min.

Example 503

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



A



To a suspension of compound **502** (44.2 mg, 0.118 mmoL) in 0.5 mL of dry CH_2Cl_2 was added thionyl chloride (0.086 mL, 1.18 mmoL). The reaction mixture was stirred for 5.0 hrs. Concentration in vacuo and the residue was azeotropic evaporated with CH_2Cl_2 to give 56 mg of **503** as an yellow solid.

B Title Compound

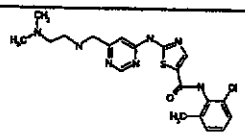
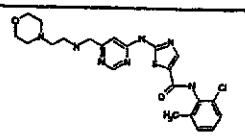
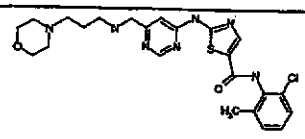
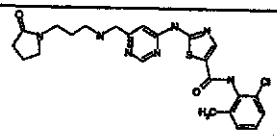
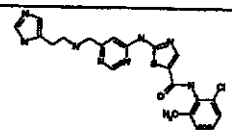
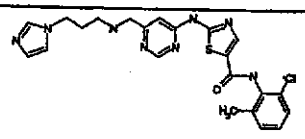
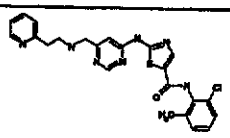
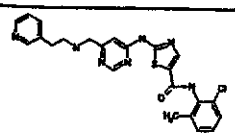
The mixture of compound **503A** (20 mg), morpholine (0.014 mL) and diisopropylethyl amine (0.09 mL) in 0.5 mL of dry dioxane was heated to 85.C for 4.0 hrs. Concentration in vacuo followed by flash chromatography (CH_2Cl_2-MeOH-NH_4OH: 95:5:0.5) on silica gel gave 15 mg of title compound as an off-white solid.

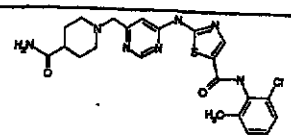
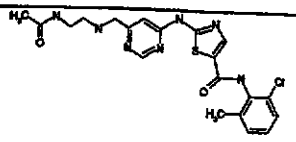
HPLC Retention time = 2.52 min.

Examples 504 to 513

General Procedure

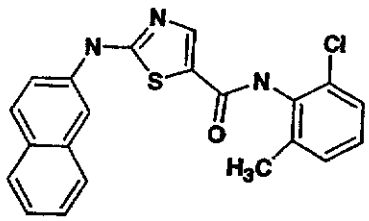
5 Compounds **504** to **513** were prepared from **503A** by a route analogous to that used for the preparation of **503**. The compounds of these examples have the structure:

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
504		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[2-(dimethylamino)ethyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.083
505		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[2-(4-morpholinyl)ethyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.593
506		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[3-(4-morpholinyl)propyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.163
507		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[3-(2-oxo-1-pyrrolidinyl)propyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.693
508		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[(2-1H-imidazol-4-ylethyl)amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	2.143
509		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[(3-1H-imidazol-1-ylpropyl)amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	1.103 B
510		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[2-(2-pyridinyl)ethyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide	1.113 B
511		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[2-(3-pyridinyl)ethyl]amino]methyl]-4-pyrimidinyl]amino]-5-	1.117 B

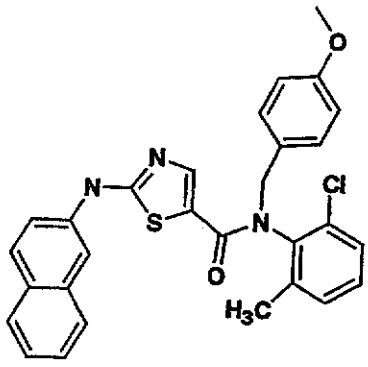
		thiazolecarboxamide	
512		'1-[[6-[[5-[[(2-Chloro-6-methylphenyl)amino]carbonyl]-2-thiazolyl]amino]-4-pyrimidinyl]methyl]-4-piperidinecarboxamide	1.207 B
513		'2-[[6-[[[2-(Acetylamino)ethyl]amino]methyl]-4-pyrimidinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	1.193 B

Example 514

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



A



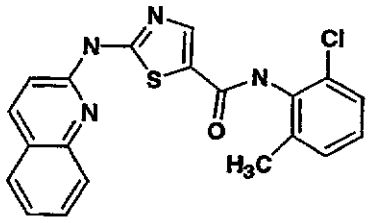
Compound **514A** was prepared from **473A** by an analogous method as that of **473B**, except using 2-aminonapthaline in place of 2-bromo-6-aminopyridine.

B. Title Compound

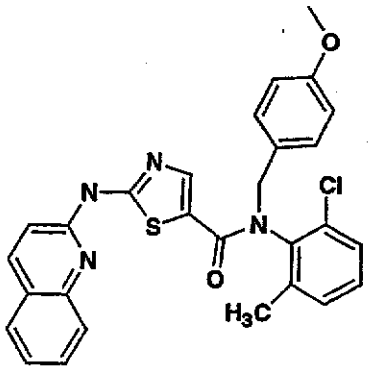
The title compound was prepared by an analogous method as that of **473C**, except using compound **514A** in place of compound **473B**. HPLC Ret. Time 4.11min.

Example 515

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



A



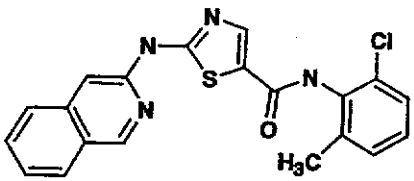
Compound **515A** was prepared from **473A** by an analogous method as that of **473B**, except using 2-aminoquinoline in place of 2-bromo-6-aminopyridine.

B. Title Compound

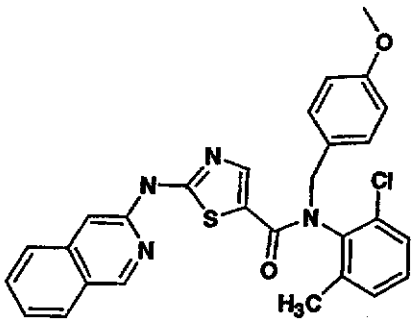
The title compound was prepared by an analogous method as that of **473C**, except using compound **515A** in place of compound **473B**. HPLC Ret. Time 3.94min.

Example 516

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



A



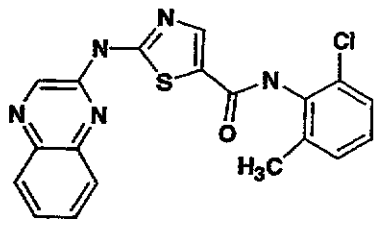
Compound **516A** was prepared from **473A** by an analogous method as that of **473B**, except using 3-aminoisoquinoline in place of 2-bromo-6-aminopyridine.

B. Title Compound

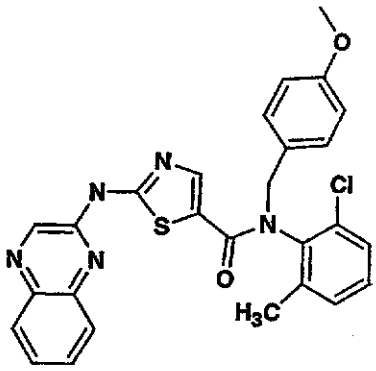
The title compound was prepared by an analogous method as that of **473C**, except using compound **516A** in place of compound **473B**. HPLC Ret. Time 3.94min.

Example 517

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



A



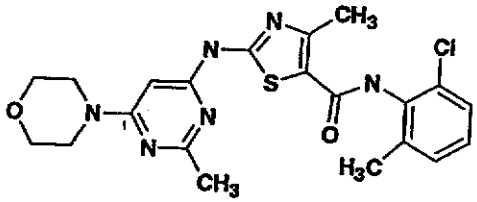
Compound **517A** was prepared from **473A** by an analogous method as that of **473B**, except using 2-aminoquinoxaline in place of 2-bromo-6-aminopyridine.

B. Title Compound

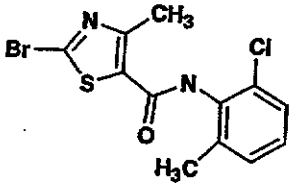
The title compound was prepared by an analogous method as that of **473C**, except using compound **517A** in place of compound **473B**. HPLC Ret. Time 3.927min.

Example 518

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

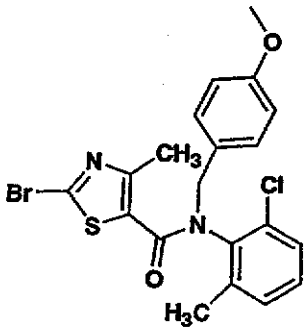


A



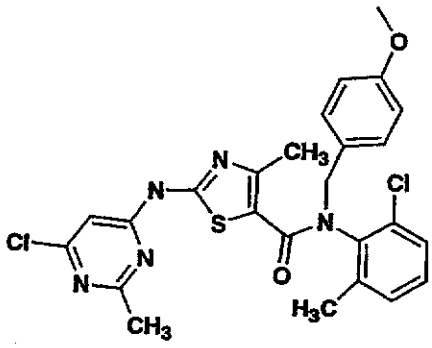
Compound **518A** was prepared from **144** by an analogous method as that of **319A**.

B



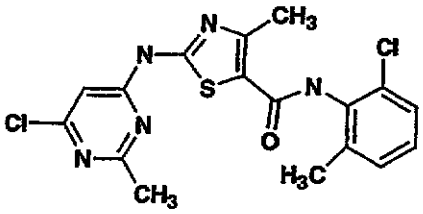
Compound **518B** was prepared by an analogous method as that of **473A**, except using **518A** in place of **319A**.

C



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

D



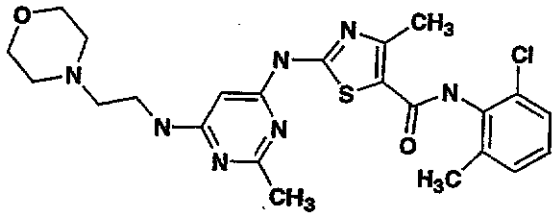
Compound **518D** was prepared by an analogous method as that of **473C**, except using **518C** in place of **473B**.

E. Title Compound

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

Example 519

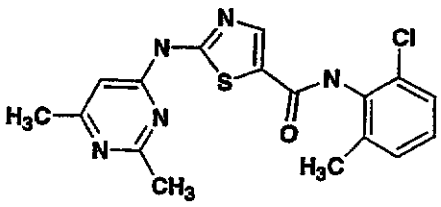
Preparation of N-(2-Chloro-6-methylphenyl)-4-methyl-2-[[2-methyl-6-[[2-(4-morpholinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide



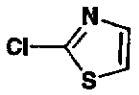
Compound **519** was prepared by an analogous method as that of **518E**, except using N-(2-aminoethyl)-morpholine in place of morpholine. HPLC Ret. Time 2.493min.

Example 520

Alternative preparation of compound **321**

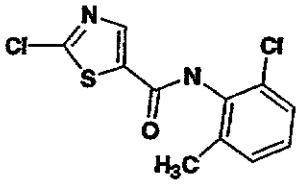


A



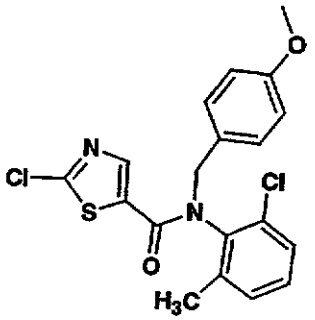
Compound **520A** was prepared from 2-aminothiazole according to the procedure described in UK Patent Application GB 2323595A.

B



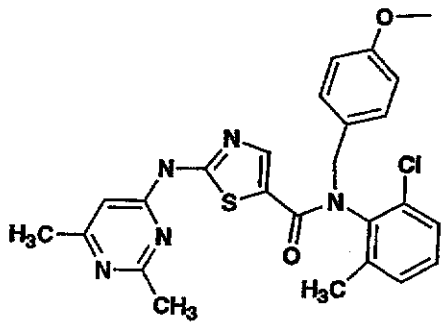
To a solution of compound **520A** (480 mg, 4.0 mmoL) in dry THF (10 mL) cooled at –78.C was added a 2.5M solution of n-BuLi (1.68 mL, 4.2 mmoL) in hexane dropwise via a syringe while kept the internal temperature below –75.C. Upon completion of addition, a beige suspension was obtained. The reaction mixture was stirred for 15 min at –78.C. A solution of 2-chloro-6-methyl phenyl isocyanate (0.6 mL, 4.4 mmoL) in 5 mL of dry THF was added and the reaction mixture was stirred for an additional 2.0 hrs at –78.C. Saturated aq. NH_4Cl solution (10 mL) was added, the mixture was partitioned between EtOAc-water and extracted with EtOAc (x2). The combined extracts were dried over Na_2SO_4 and concentration in vacuo to give, after recrystalization from EtOAc-hexane, 0.99 g of title compound as a pale yellow crystalline material.

C



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

D



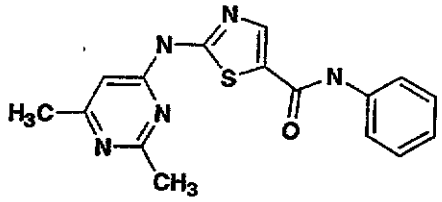
Compound **520D** was prepared from compound **520C** by a method analogous to that used for the preparation of compound **473B**.

3. Title Compound

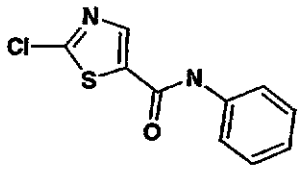
Compound **321** was prepared by a method analogous to that used for the preparation of compound **473C.**

Example 521

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

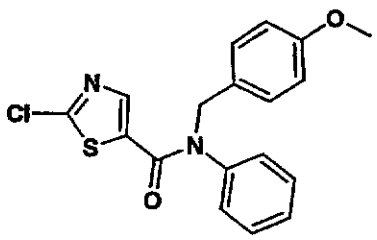


A



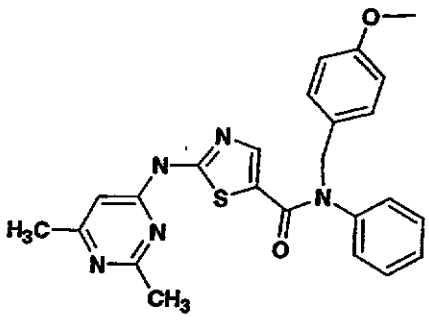
Compound **521A** was prepared by an analogous method as that of **520B**, except using phenylisocyanate in place of 2-chloro-6-methylphenylisocyanate.

B



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

C



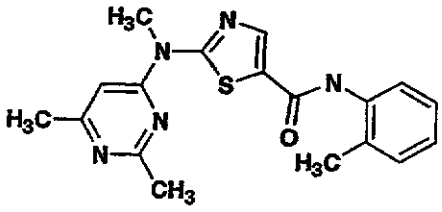
Compound **521C** was prepared from compound **521B** by a method analogous to that used for the preparation of compound **473B**.

D Title Compound

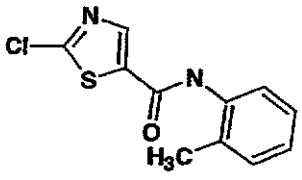
The title compound was prepared by a method analogous to that used for the preparation of compound **473C**. HPLC Ret. Time 1.3 min method B

Example 522

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

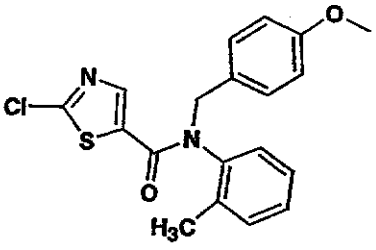


A



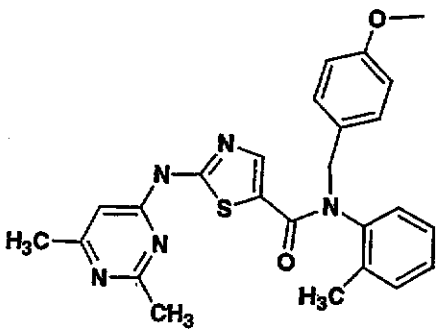
Compound **522A** was prepared by an analogous method as that of **520B**, except using 2-methylphenylisocyanate in place of 2-chloro-6-methylphenylisocyanate.

B



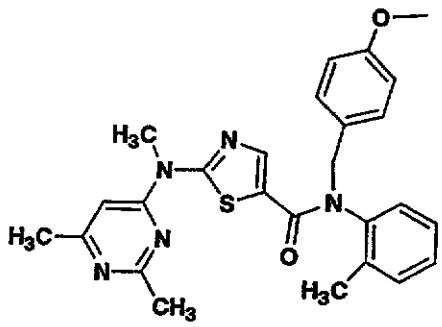
Compound **522B** was prepared by a method analogous to that used for the preparation of compound **473A**, using **522A** in place of **319A**.

C



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

D



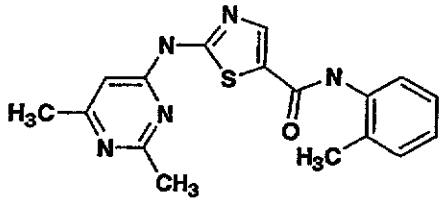
Sodium hydride (60% in oil; 40 mg; 1 mmol) was added to a solution of compound **522C** (280 mg; 0.61 mmol) in 2 ml of DMF at room temp. After stirring 30 minutes, iodomethane (0.2 ml; 3 mmol) was added and the reaction was stirred 4 hr. After the reaction mixture was partitioned between ethyl acetate (50 ml) and water (50 ml), the organic layer was washed with water (2 x 50 ml) and brine (50 ml). Drying ($MgSO_4$) and concentration afforded an oil that was chromatographed on a 2.5 x 15 cm silica gel column using 50-75% ethyl acetate/hexane. The pure fractions were concentrated and the residue was crystalized from ethyl acetate/hexane to afford 100 mg of **522D** as a light yellow solid.

E Title Compound

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

Example 523

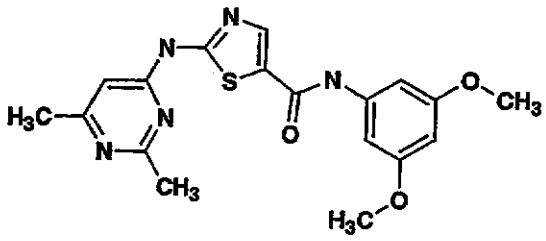
Preparation of '2-[(2,6-Dimethyl-4-pyrimidinyl)amino]-N-(2-methylphenyl)-5-thiazolecarboxamide



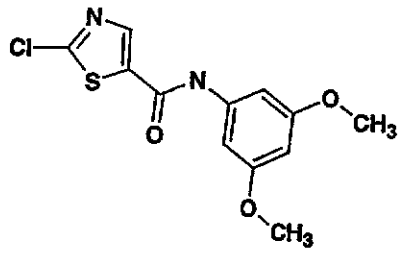
Compound **523** was prepared by a method analogous to that used for the preparation of compound **473C**, except using compound **522C** in place of **473B**. HPLC Ret. Time 1.24 min method B

Example 524

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

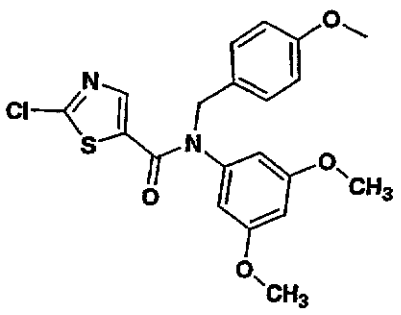


A



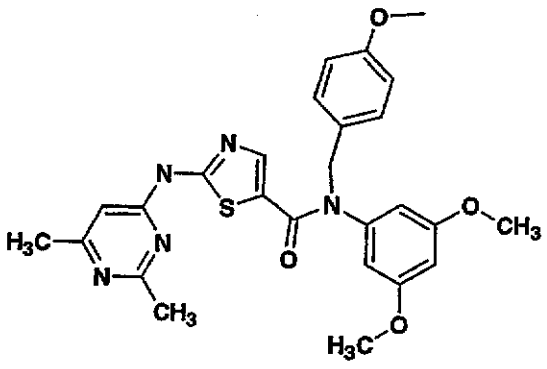
Compound **524A** was prepared by an analogous method as that of **520B**, except using 3,5-dimethoxyphenylisocyanate in place of 2-chloro-6-methylphenylisocyanate.

B



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

C



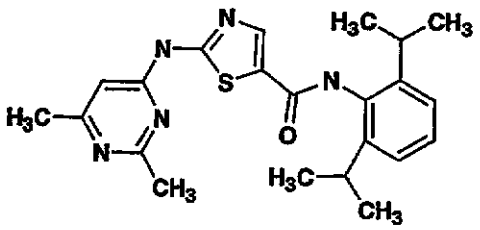
Compound **524C** was prepared from compound **524B** by a method analogous to that used for the preparation of compound **473B.**

D Title Compound

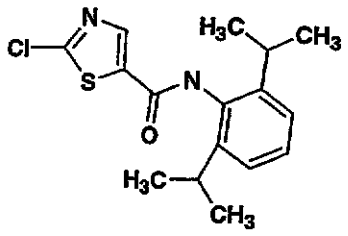
The title compound was prepared by a method analogous to that used for the preparation of compound **473C**, except using compound **524C** in place of compound **473B** HPLC Ret. Time 1.28 min method B

Example 525

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

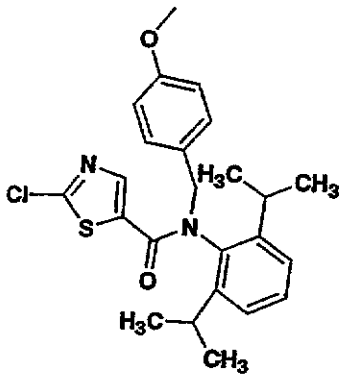


A



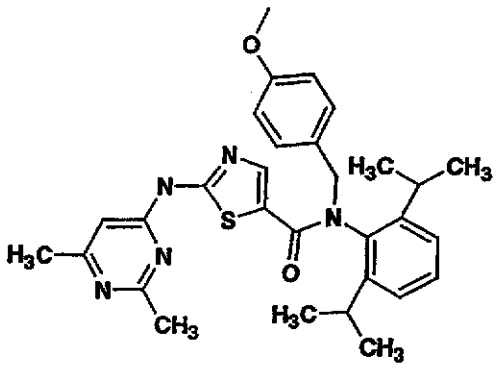
Compound **525A** was prepared by an analogous method as that of **520B**, except using 2,2-diisopropylphenylisocyanate in place of 2-chloro-6-methylphenylisocyanate.

B



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

C



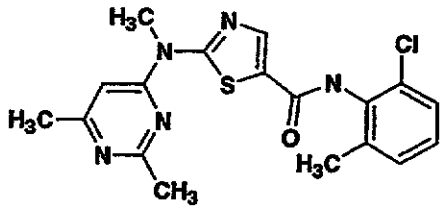
Compound **525C** was prepared from compound **525B** by a method analogous to that used for the preparation of compound **473B.**

D Title Compound

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

Example 526

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

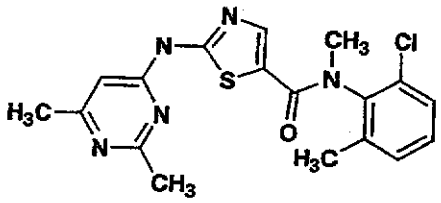


A mixture of compound **321** (110 mg; 0.29 mmol), potassium carbonate (138 mg; 1 mmol) and iodomethane (0.06 ml; 1 mmol) in DMF was stirred 2 hr at room temperature. After the reaction mixture was partitioned

between ethyl acetate (25 ml) and water (25 ml), the organic layer was washed with water (2 x 25 ml) and brine (25 ml). Drying ($MgSO_4$) and concentration afforded an oil that was chromatographed on a 2.5 x 15 cm silica gel column using 1-4% MeOH/CH_2Cl_2 and the fractions containing compound **526** were collected to give 20mg of product. HPLC Ret. Time 1.3min method B.

Example 527

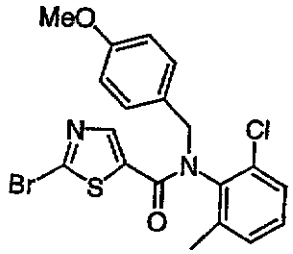
Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[(2,6-dimethyl-4-pyrimidinyl)amino]-N-methyl-5-thiazolecarboxamide



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

Example 528

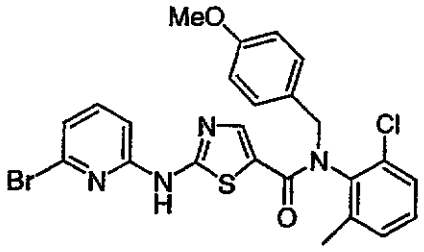
Preparation of 2-Bromo-N-, N-(2-chloro-6-methylphenyl)-(4-methoxybenzyl)-5-thiazolecarboxamide



To a cooled (0 °C) THF solution of 2-chloro-6-methyl aniline (2.86 mL, 23.3 mmol, 1.10 equiv) was added dropwise a 1.0 M solution of lithium bis(trimethylsilyl)amide (42.2 mL, 42.2 mmol, 2.00 equiv) via syringe. The homogeneous solution was allowed to stir for 5 minutes, and then a THF solution of ethyl 2-bromo-5-thiazolecarboxylate (5.00 g, 21.1 mmol, 1.00 equiv, prepared in a manner analogous to compound **319A**) was added via cannula. The solution was allowed to stir for 15 minutes until TLC analysis showed no remaining starting material. To the reaction was then added 4-methoxybenzyl chloride (7.15 mL, 52.7 mmol, 2.5 equiv), followed by a catalytic amount of tetrabutylammonium iodide (1.56 g, 4.22 mmol, 0.20 equiv). The homogeneous mixture was allowed to stir overnight at ambient temperature and then concentrated in vacuo. The residue was partitioned between ethyl acetate and water, and the organic extracts were washed with brine and dried over Na_2SO_4. After filtration and removal of solvent, the product was purified by flash chromatography (10-20% ethyl acetate in hexanes) to afford the title compound as a tan solid (47%).

Example 529

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

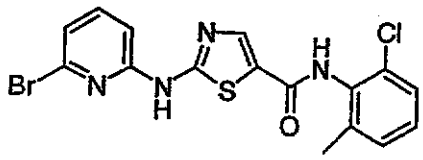


Compound **529** was prepared in an analogous manner to **319B**, except using **528** and 6-bromo-2-aminopyridine as the reactants.

Example 530

Preparation of N-(2-Chloro-6-methylphenyl)-2-[(6-bromo-

2-pyridinyl)amino]-5-thiazolecarboxamide

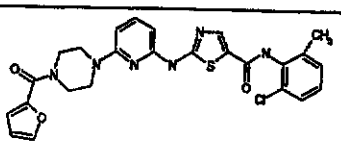


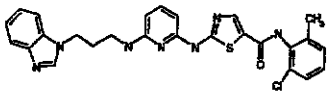
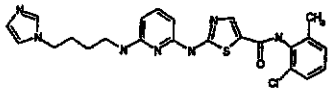
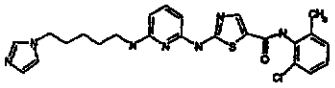
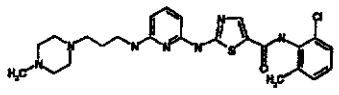
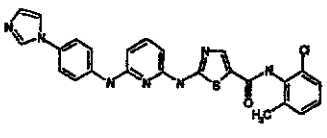
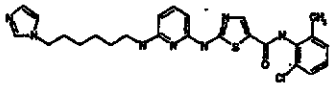
Compound **529** (0.500 g, 0.919 mmol, 1.00 equiv) was dissolved in 5 mL trifluoroacetic acid and charged at ambient temperature with 2 mL anisole followed by 1 mL trifluoromethanesulfonic acid. The dark red homogeneous solution was allowed to stir overnight, and then quenched by carefully pouring the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

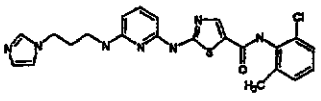
Examples 531-538

General Procedure

Compounds **531** to **538** were prepared to the general procedure described below. A 1-dram vial was charged with **530** and excess amine and heated to 90 °C overnight. The residue was then purified by reverse phase HPLC to afford the pure compound. For the following examples 531 to 555 "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC ODS-A C18 S7 3.0 x 50 mm, 2 min gradient starting from 100% solvent A (10% MeOH, 90% H_2O, 0.1% TFA) to 100% solvent B (90% MeOH, 10% H_2O, 0.1% TFA), flow rate 5 mL/min, λ = 220 nM.

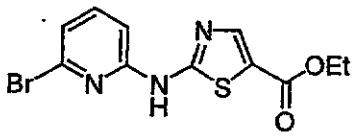
EX. NO.	Compound Structure	Compound Name	HPLC Ret time (min)
531		N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-furanylcarbonyl)-1-piperazinyl]-2-pyridinyl]amino]-5-	1.56

		thiazolecarboxamide	
532		'2-[[6-[[3-(1H-Benzimidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	1.41
533		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[4-(1H-imidazol-1-yl)butyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.24
534		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[5-(1H-imidazol-1-yl)pentyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.25
535		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[3-(4-methyl-1-piperazinyl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.14
536		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[4-(1H-imidazol-1-yl)phenyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.29
537		'N-(2-Chloro-6-methylphenyl)-2-[[6-[[6-(1H-imidazol-1-yl)hexyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.27

538		'N-(2-Chloro-6-methylphenyl)-2-[[6-[(3-1H-imidazol-1-ylpropyl)amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.24

Example 539

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

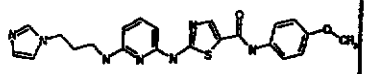
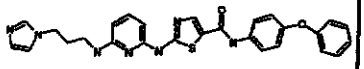
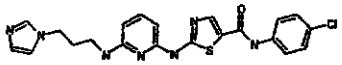
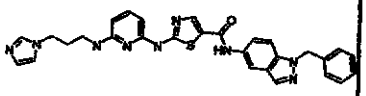
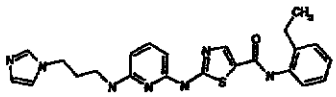
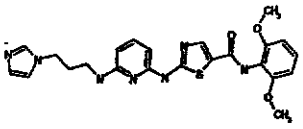
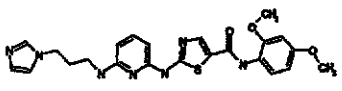


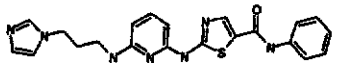
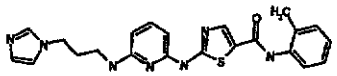
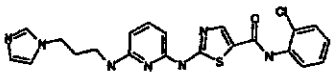
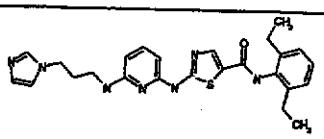
Compound **539** was prepared in an analogous manner to **319B**, except using ethyl 2-bromo-5-thiazolecarboxylate and 6-bromo-2-aminopyridine as the reactants.

Examples 540-550

General Procedure

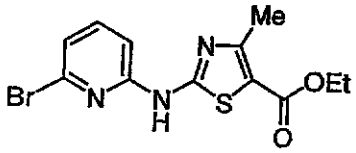
Compounds **540** to **550** were prepared according to the general procedure described below. Compound **539** was condensed with the appropriate aniline according to the procedure for example **528** to afford the afford the corresponding N-(4-methoxybenzyl)amide. The intermediate bromopyridine was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

EX. NO.	Compound Structure	Compound Name	HPLC Ret time (min)
540		'2-[[6-[[3-(1H-Imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-(4-methoxyphenyl)-5-thiazolecarboxamide	1.12
541		'2-[[6-[[3-(1H-Imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-(4-phenoxyphenyl)-5-thiazolecarboxamide	1.48
542		'N-(4-Chlorophenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.31
543		'2-[[6-[[3-(1H-Imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-[1-(phenylmethyl)-1H-indazol-5-yl]-5-thiazolecarboxamide	1.34
544		'N-(2-Ethylphenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.18
545		'N-(2,6-Dimethoxyphenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.11
546		'N-(2,4-Dimethoxyphenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.06

547		'2-[[6-[[3-(1H-Imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-phenyl-5-thiazolecarboxamide	1.06
548		'2-[[6-[[3-(1H-Imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-(2-methylphenyl)-5-thiazolecarboxamide	1.11
549		'N-(2-Chlorophenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.16
550		'N-(2,6-Diethylphenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide	1.29

Example 551

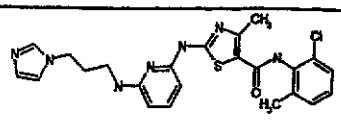
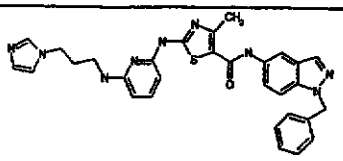
Preparation of Ethyl-2-[(6-bromo-2-pyridinyl)amino]-4-methyl-5-thiazolecarboxylate



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

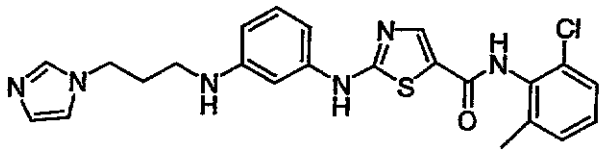
Examples 552 and 553

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

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

Example 554

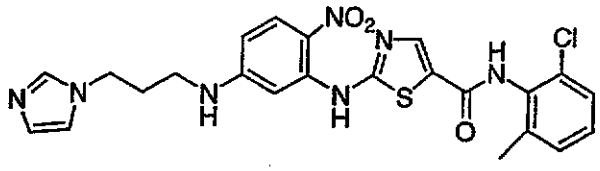
Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[3-[[3-(1H-imidazol-1-yl)propyl]amino]phenyl]amino]-5-thiazolecarboxamide



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

Example 555

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



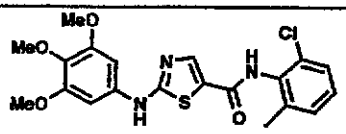
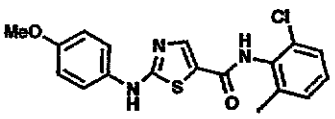
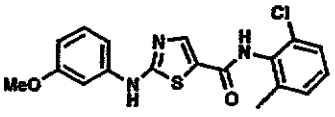
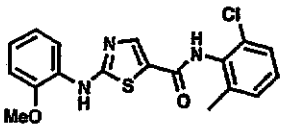
A solution of 2,4-difluoronitrobenzene (0.400 mL, 3.65 mmol, 1.00 equiv) in acetonitrile was charged with K_2CO_3 (0.605 g, 4.38 mmol, 1.20 equiv) followed by ethyl-2-amino-5-thiazolecarboxylate (0.628 g, 3.65 mmol, 1.00 equiv) as a solid. The heterogeneous mixture was sealed and heated to 120 °C overnight.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

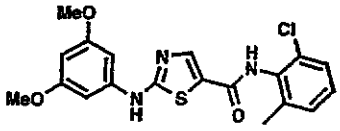
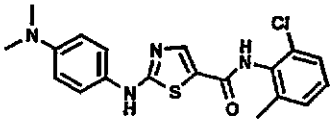
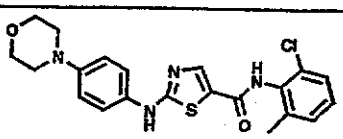
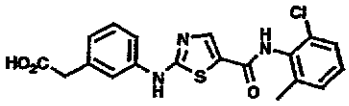
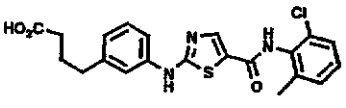
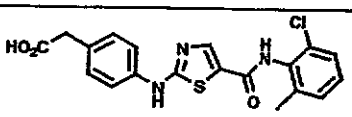
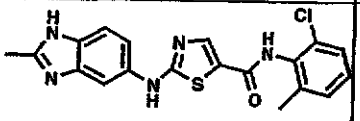
Examples 556-566

General Procedure:

Compounds **556** to **566** were prepared according to the general procedure described below. A mixture of 2-bromo-N-[2-chloro-6-methylphenyl]-5-thiazolecarboxamide **319A**, an aniline (1 eq), 1.0 N aqueous HCl (0.5 eq) in n-BuOH was heated overnight at 120°C in a sealed vial. This was diluted with methanol and the product was isolated by preparative HPLC (YMC S5 ODS 30 x 100 mm column eluted with a gradient comprised of

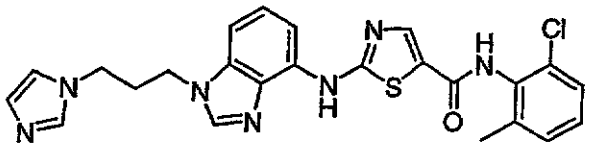
two solvent mixtures (mixture A: 10% MeOH, 90% water, and 0.1% TFA; mixture B: 90% MeOH, 10% water, and 0.1% TFA). For anilines substituted with a carboxylic acid group, the reaction mixture was treated with 1 N aqueous NaOH (5 eq) overnight before final purification of the product by HPLC. "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 OSD 4.6 x 30 mm (for **556** to **560**) or YMC S7 ODS 3 x 50 mm column (for **561** to **566**), 2 min gradient starting from 100% solvent A (10% MeOH, 90% H_2O, 0.1% TFA) to 100% solvent B (90% MeOH, 10% H_2O, 0.1% TFA), flow rate 5 mL/min, λ = 220 nM.

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

560		N-(2-Chloro-6-methyl-phenyl)-2-[(3,5-dimethoxyphenyl)-amino]-5-thiazolecarboxamide	1.55
561		N-(2-Chloro-6-methyl-phenyl)-2-[[4-(dimethylamino)-phenyl]amino]-5-thiazolecarboxamide	1.25
562		N-(2-Chloro-6-methylphenyl)-2-[[4-(4-morpholinyl)phenyl] amino]-5-thiazolecarboxamide	1.24
563		N-(2-Chloro-6-methylphenyl)-2-[[3-(carboxymethyl)-phenyl]amino]-5-thiazolecarboxamide	1.36
564		N-(2-Chloro-6-methylphenyl)-2-[[3-(3-carboxypropyl)-phenyl]amino]-5-thiazolecarboxamide	1.48
565		N-(2-Chloro-6-methylphenyl)-2-[[4-(carboxymethyl)phenyl]amino]-5-thiazolecarboxamide	1.35
566		N-(2-Chloro-6-methylphenyl)-2-[(2-methyl-1H-benzimidazol-5-yl)amino]-5-thiazolecarboxamide	1.27

Example 567

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

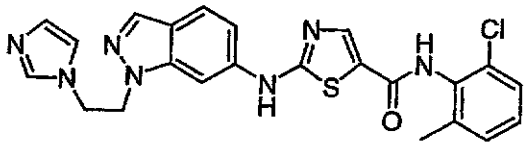


A mixture of 1-bromo-3-chloropropane (10 mL, 0.10 mmole), imidazole (6.81 gm, 0.10 mmole) in ethanolic NaOEt (41.3 mL, 21 wt%, 1.1 mmole) was heated at reflux for 1 hr. After cooling to RT, this was filtered and the filter cake was washed with EtOH. The solvent was removed from the filtrate to afford crude 3-chloro-1-(imidazo-1-yl)-propane as an oil. A portion of the crude chloride (1.07 gm, 7.40 mmole) was added to a mixture of 4-nitro-benzimidazole (1.09 gm, 6.66 mmole) and NaH (293 mg, 60% in oil, 8.14 mmole) in DMF (15 mL). After being heated at 60°C overnight and then 75°C for 3 hr, the solvent was removed. The residue was partitioned between water and a mixture of 10% MeOH in DCM. The organic phase was separated, dried (Na_2SO_4) and the solvents removed. Radial chromatography (4 mm silica gel plate that was eluted with a step gradient of DCM containing 2, 3, 4, ...10% MeOH) afforded the major product, 1-[3-imidazo-1-ylpropyl]-4-nitro-benzimidazole as a solid (513 mg, 28%). A mixture of this material (250 mg) and 10% palladium on charcoal (200 mg) in EtOH (10 mL) under a hydrogen atmosphere (balloon) was vigorously stirred for 1 hr. Removal of the catalyst by filtration and the solvent under reduced pressure left the crude 4-amino-1-[3-imidazo-1-ylpropyl]-benzimidazole as a solid. A portion of this material

(46 mg, 0.191 mmole) was added to a mixture of **319A** (63 mg, 1.0 eq), an aqueous solution of HCl (0.24 mL, 1.0 M, 1.25 eq) and n-BuOH (1 mL). This was heated in a sealed vial at 120°C for 44 hr. After cooling to RT, **567** (HPLC retention time (YMC ODS S5 4.6 x 30 mm): 1.20 min) was isolated by preparative HPLC.

Example 568

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

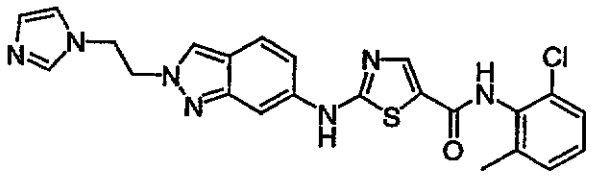


A mixture of 1-bromo-2-chloroethane (4.6 mL, 0.055 mole), imidazole (3.40 gm, 0.050 mole) in ethanolic NaOEt (19 mL, 21 wt%, 1 eq) was heated at reflux for 2 hr. After cooling to RT, the reaction was filtered and the filter cake was washed with EtOH. The solvent was removed from the filtrate to afford crude 2-chloro-1-(imidazo-1-yl)-ethane. A portion of the crude chloride (2.24 gm, 17.2 mmole) was added to a mixture of 6-nitro-indazole (1.63 gm, 10.0 mmole), K_2CO_3 (1.50 mg, 1.1 eq), and KI (1.70 gm, 1.1 eq) in DMF (15 mL). After being heated at 70°C overnight and then 90°C for 4 hr, the solvent was removed. The residue was partitioned between water and a mixture of 5% MeOH in DCM. The organic phase was separated, dried (Na_2SO_4) and the solvents removed. Radial chromatography (4mm

silica gel plate that was eluted with a step gradient of DCM containing 0, 1, 2% MeOH) afforded 659 mg of 1-[2-imidazo-1-ylethyl]-6-nitro-indazole and 450 mg of the isomeric 2-[2-imidazo-1-ylethyl]-6-nitro-indazole. A mixture of 1-[2-imidazo-1-ylethyl]-6-nitro-indazole (650 mg) and 10% palladium on charcoal (600 mg) in EtOH (10 mL) under a hydrogen atmosphere (balloon) was vigorously stirred overnight. Removal of the catalyst by filtration and the solvent under reduced pressure left the crude 6-amino-1-[2-imidazo-1-ylethyl]-indazole as a solid. A portion of this material (68.1 mg, 1.5 eq) was added to a mixture of **556** (99.3 mg, 0.300 mmole), an aqueous solution of HCl (0.45 mL, 1.0 M, 1.5 eq) and n-BuOH (1.5 mL). This was heated in a sealed vial at 120°C for 44 hr. After cooling to RT, **568** (HPLC retention time (YMC ODS S7 3 x 50 mm): 1.31 min) was isolated by preparative HPLC.

Example 569

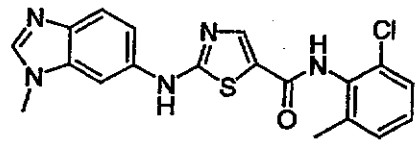
N-(2-Chloro-6-methylphenyl)-2-[[2-[2-(1H-imidazol-1-yl)ethyl]-2H-indazol-6-yl]amino]-5-thiazolecarboxamide



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

Example 570

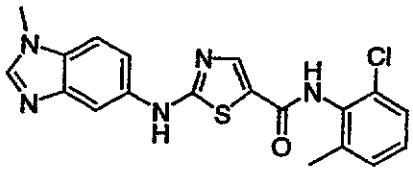
N-(2-Chloro-6-methylphenyl)-2-[(1-methyl-1H-benzimidazol-6-yl)aminol-5-thiazolecarboxamide



and

Example 571

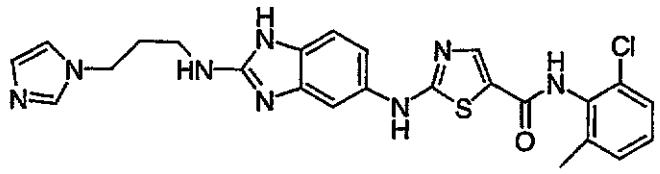
N-(2-Chloro-6-methylphenyl)-2-[(1-methyl-1H-benzimidazol-5-yl)aminol-5-thiazolecarboxamide



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

Example 572

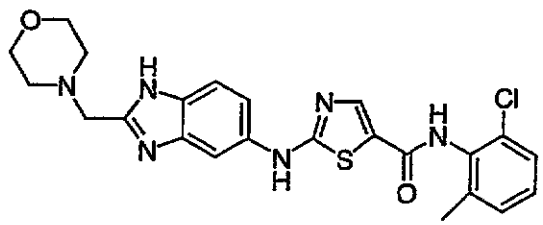
N-(2-Chloro-6-methylphenyl)-2-[[2-[3-(1H-imidazol-1-yl)propyl]amino]-1H-benzimidazol-5-yl]amino]-5-thiazolecarboxamide



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

Example 573

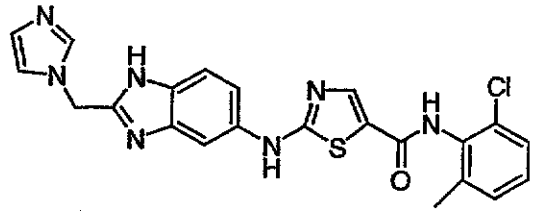
N-(2-Chloro-6-methylphenyl)-2-[[2-(4-morpholinylmethyl)-1H-benzimidazol-5-yl]amino]-5-thiazolecarboxamide



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

Example 574

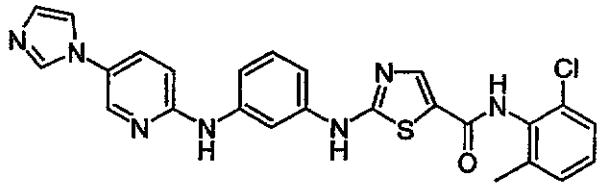
N-(2-Chloro-6-methylphenyl)-2-[[2-(1H-imidazol-1-ylmethyl)-1H-benzimidazol-5-yl]amino]-5-thiazolecarboxamide



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

Example 575

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

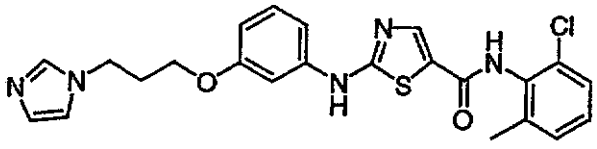


A mixture of 3-nitroaniline (2.91 gm, 21.1 mmole) and 2,5-dibromopyridine (5.0 gm, 1 eq) was heated at 185°C for 1 hr. After cooling to RT, the solid was broken up and treated with a mixture of saturated aq. $NaHCO_3$ and 10% MeOH in DCM. The suspended solid was collected by filtration and washed with a little 10% MeOH in DCM and then water to

leave, after drying, 3.72 gm of crude N-[5-bromo-pyridin-2-yl]-5-nitroaniline. A portion of this material (500 mg, 1.70 mmole) was combined with imidazole (116 mg, 1 eq), CuI (81 mg, 0.25 eq), and K_2CO_3 (235 mg, 1 eq) in DMF (2 mL) and the mixture was heated at 130°C for 2 days. After cooling to RT, the solvent was removed and the residue was partitioned between water and a mixture of 20% MeOH in DCM. The organic phase was removed, dried (Na_2SO_4), and the solvents removed to leave the crude N-[5-imidazo-1-yl]-pyridin-2-yl]-5-nitroaniline as a solid. This was taken and treated with 10% palladium on charcoal (650 mg) in EtOH under a hydrogen atmosphere for 1.5 hr. Removal of the catalyst and then the solvent left the crude N-[5-imidazo-1-yl]-pyridin-2-yl]-5-aminoaniline. It was purified by radial chromatography (4 mm silica gel plate that was eluted with a step gradient of DCM containing 1, 2, 3,...6% MeOH). The aniline was then coupled with **319A** as described for **570** to afford **575** (HPLC retention time (YMC ODS S5 4.6 x 30 mm): 1.42 min).

Example 576

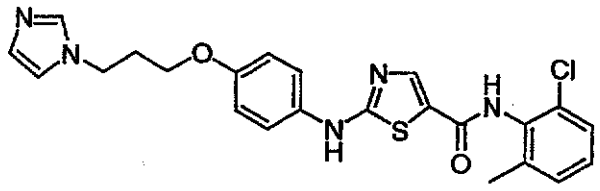
N-(2-Chloro-6-methylphenyl)-2-[[3-[3-(1H-imidazol-1-yl)propoxy]phenyl]amino]-5-thiazolecarboxamide



and

Example 577

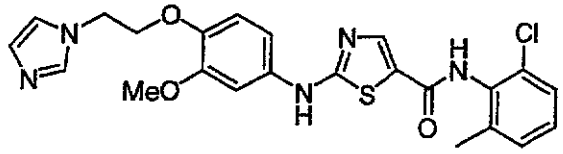
N-(2-Chloro-6-methylphenyl)-2-[[4-[3-(1H-imidazol-1-yl)propoxy]phenyl]amino]-5-thiazolecarboxamide



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

Example 578

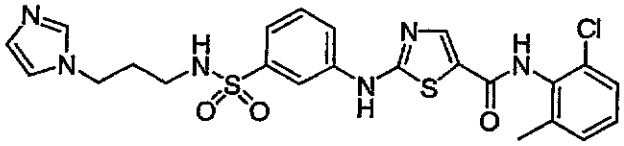
N-(2-Chloro-6-methylphenyl)-2-[[4-[2-(1H-imidazol-1-yl)ethoxy]-3-methoxyphenyl]amino]-5-thiazolecarboxamide



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

Example 579

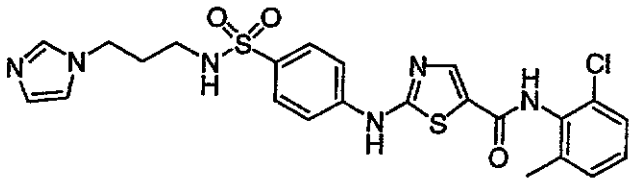
N-(2-Chloro-6-methylphenyl)-2-[[3-[[[3-(1H-imidazol-1-yl)propyl]amino]sulfonyl]phenyl]amino]-5-thiazolecarboxamide



and

Example 580

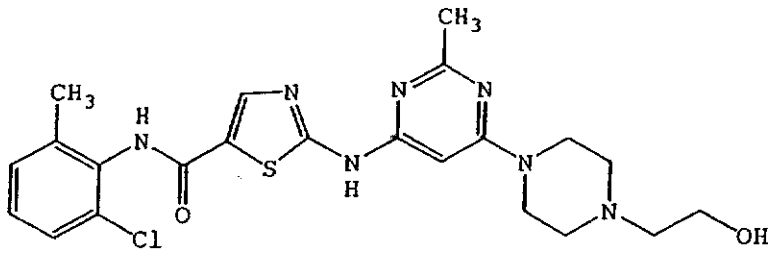
N-(2-Chloro-6-methylphenyl)-2-[[4-[[[3-(1H-imidazol-1-yl)propyl]amino]sulfonyl]phenyl]amino]-5-thiazolecarboxamide



3-Imidazo-1-yl-propylamine (2.04 mL, 2.5 eq) was added to a solution of 3-nitro-benzenesulfonyl chloride (1.5 gm, 6.77 mmole) in THF (20 mL) at

RT. After 1 hr, the solvent was removed and the residue was partitioned between water and a mixture of 10% MeOH in DCM. The organic phase was separated, washed with water and dried (Na2SO4). The crude N-[3-[imidazo-1-yl]-propyl]-3-nitro-benzenesulfonamide was treated with 10% palladium on charcoal (2 gm) in THF (60 mL) under a hydrogen atmosphere overnight. Removal of the catalyst and then the solvent left crude 3-amino-N-[3-[imidazo-1-yl]-propyl]-benzenesulfonamide which was then coupled with **319A** as described for **570** to afford **579** (HPLC retention time (YMC ODS S7 3 x 50 mm): 1.22 min). Beginning with 4-nitro-benzenesulfonyl chloride and 3-[imidazo-1-yl]-propylamine, **580** (HPLC retention time (YMC ODS S7 3 x 50 mm): 1.21 min) was prepared in a similar manner as **579**.

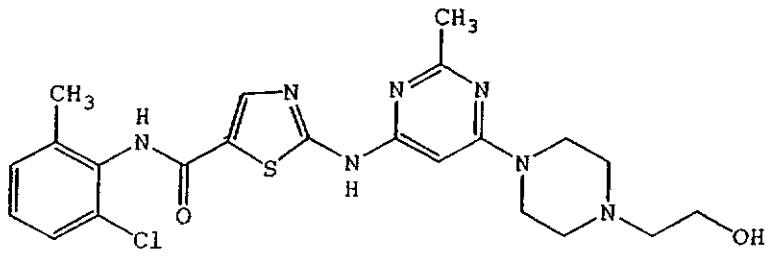
1. Use of a compound for the manufacture of a medicament for the oral treatment of cancer, said compound having a formula IV or a salt thereof:



IV

wherein the cancer is chronic myelogenous leukemia (CML).

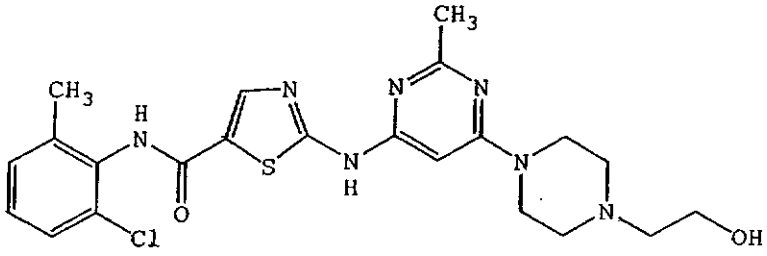
2. Use of a compound for the manufacture of a medicament for the oral treatment of cancer, said compound having a formula IV or a salt thereof:



IV

wherein the cancer is gastrointestinal stromal tumor (GIST).

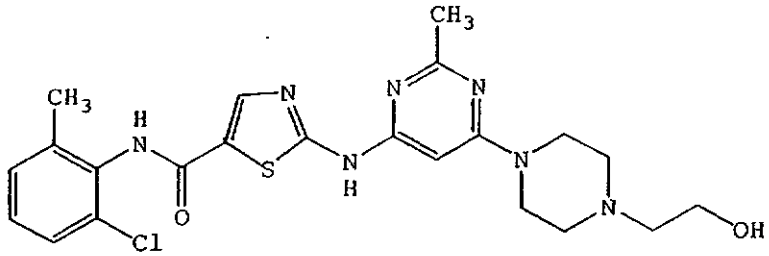
3. Use of a compound for the manufacture of a medicament for the oral treatment of cancer, said compound having a formula IV or a salt thereof:



IV

wherein the cancer is acute myelogenous leukemia (AML).

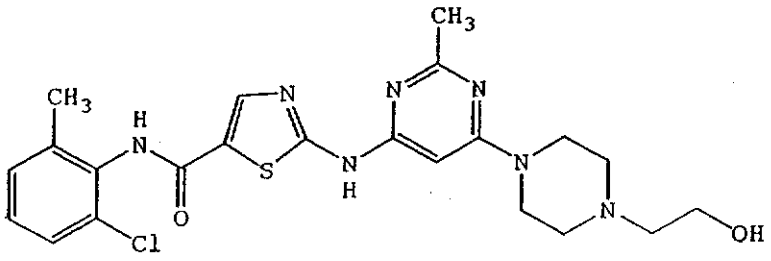
4. Use of a compound for the manufacture of a medicament for the oral treatment of cancer, said compound having a formula IV or a salt thereof:



IV

wherein the cancer is mastocytosis.

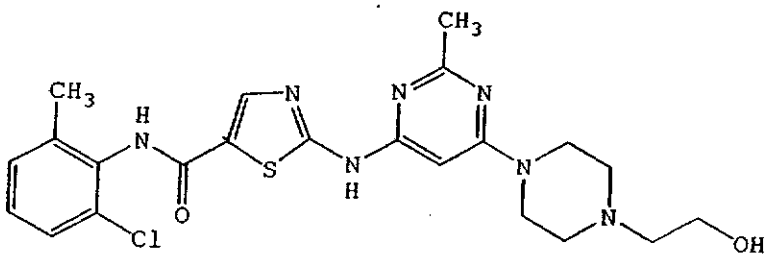
5. Use of a compound for the manufacture of a medicament for the oral treatment of cancer, said compound having a formula IV or a salt thereof:



IV

wherein the cancer is a germ cell tumor.

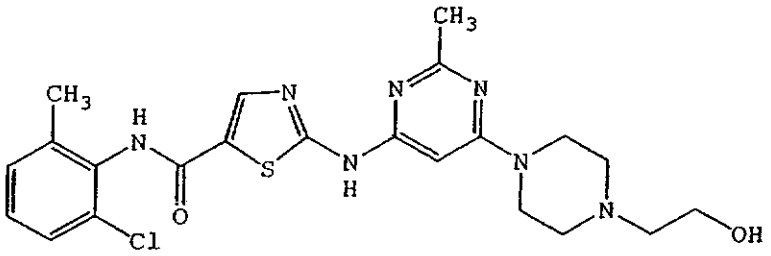
6. Use of a compound for the manufacture of a medicament for the oral treatment of cancer, said compound having a formula IV or a salt thereof:



IV

wherein the cancer is small cell lung cancer (SCLC).

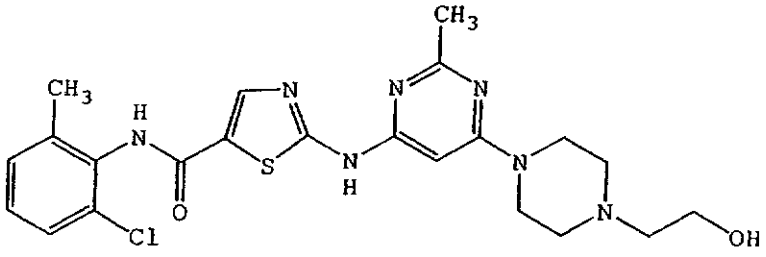
7. Use of a compound for the manufacture of a medicament for the oral treatment of cancer, said compound having a formula IV or a salt thereof:



IV

wherein the cancer is melanoma.

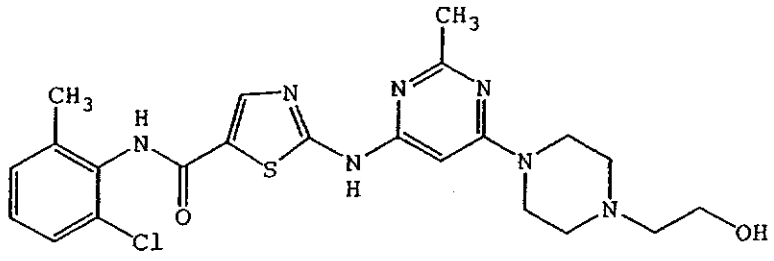
8. Use of a compound for the manufacture of a medicament for the oral treatment of cancer, said compound having a formula IV or a salt thereof:



IV

wherein the cancer is pancreatic cancer.

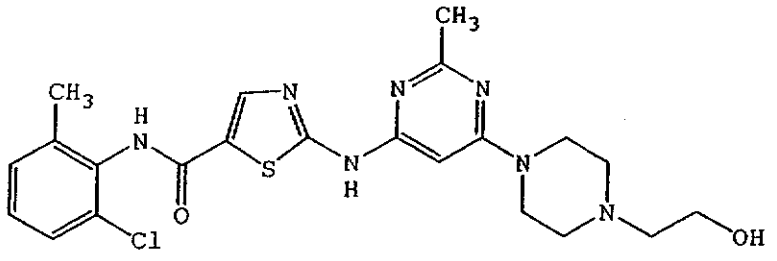
9. Use of a compound for the manufacture of a medicament for the oral treatment of cancer, said compound having a formula IV or a salt thereof:



IV

wherein the cancer is prostate cancer.

10. Use of a compound for the manufacture of a medicament for the oral treatment of cancer, said compound having a formula IV or a salt thereof:



IV

wherein the cancer is pediatric sarcoma.