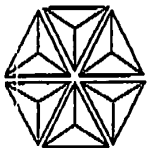


Bristol-Myers Squibb Company
Patent Department

FACSIMILE TRANSMITTAL SHEET

TO:	**Mary Till**
COMPANY:	**USPTO**
FAX NO.:	**571-273-7755**
FROM:	**Mary VanAtten**
TELEPHONE NO.:	**609-252-4379**
FACSIMILE NO.:	**(609) 252-4526**
DATE:	**August 28, 2006**
RE:	**Customer Number Changes**
Number of Pages:	17(including cover sheet)

COMMENTS:

Per our telephone conversation enclosed is a copy of our Request for Term Extension filed on August 15th via Express Mail.

Certificate under 37 CFR 1.10

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as Express Mail No. EV304414876US in an envelope addressed to:

Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

on August 15, 2006 .
Date

Mary VanAtte
Signature

Mary K. VanAtten
Type or printed name of person signing Certificate

Note: Each paper must have its own certificate of mailing, or this certificate must identify each submitted paper.

QA204 NP (U.S. Serial No. 09/548,929; U.S. Patent No. 6,596,746)

Request for Term Extension (15 pages)
U.S. Patent No. 6,596,746
Return Receipt Postcard

CASE :QA204 NP

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EV304414876US — Express Mail Label Number

August 15, 2006 — Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
JAGABANDHU DAS, ET AL
APPLICATION NO: **09/548929**
PATENT NO. **6,596,746**
FILED: **04/13/2000**
FOR: **CYCLIC PROTEIN TYROSINE KINASE INHIBITORS**

ART UNIT:
EXAMINER:

Commissioner for Patents
Mail Stop Patent Extension
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR TERM EXTENSION

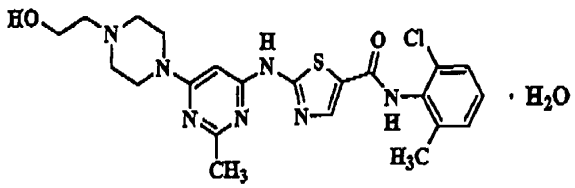
Sir:

The following request for an extension of the patent term is made under 35 U.S.C. §156. In accordance with this statute and 37 C.F.R. §1.740 the following information is provided following the recital of 37 C.F.R. § 1.740 (1)-(15).

(1) The approved product is SPRYCEL® (dasatinib) Tablets (20, 50 and 70 mg) for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib and for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy. The chemical name for dasatinib is N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate. The molecular formula is $C_{22}H_{26}ClN_7O_2S \cdot H_2O$ which corresponds to a formula weight of 506.02 (monohydrate)

Dasatinib has the following structural formula:

08/33/2006 CKHLOK 00000001 193880 6596746
01 FC:8457 1120.00 DA



(2) Regulatory review occurred under the Federal Food, Drug, and Cosmetic Act, Section 505 (Title 21 of the Code of Federal Regulations).

(3) Approval to market was received on June 28, 2006.

(4) The only active ingredient in SPRYCEL® Tablets is dasatinib. Dasatinib has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) This application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. §1.720(f) and the last day on which the application could be submitted is August 28, 2005.

(6) Extension is requested of U.S. Patent 6,596,746 which issued on July 22, 2003 to Bristol-Myers Squibb Company, by virtue of an assignment recorded on April 13, 2000, Reel/Frame 010749/0189. The inventors of the patent are Jagabandhu Das, Ramesh Padmanabha, Ping Chen, Derek J. Norris, Arthur M. P. Doweyko, Joel C. Barrish, and John Wityak. The expiration date of U.S. Patent 6,596,746 is April 13, 2020.

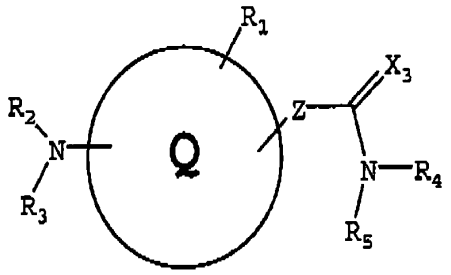
(7) A copy of U.S. Patent 6,596,746 is attached.

(8) This section is not applicable.

(9) U.S. Patent 6,596,746 claims dasatinib which is the active ingredient in the approved SPRYCEL® Tablets.

(a) Dasatinb is covered by independent claim 6 of U.S. Patent 6,596,746 because it claims the same compound N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide or salt thereof.

(b) Dasatinb is covered by independent claim 7 of U.S. Patent 6,596,746 which claims a method for the treatment of a protein tyrosine kinase-associated disorder, comprising the step of administering to a subject in need thereof an amount effective therefore of at least one compound of formula III or a salt thereof,



III

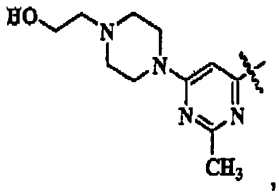
where

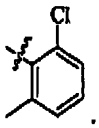
Q is thiazole;

Z is a single bond;

X_3 is O;

R_1 can be hydrogen, R_2 can be hydrogen and R_4 can be hydrogen,

R_3 can be  , and

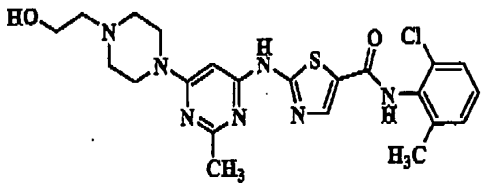
R_5 can be  .

(c) Dasatinib is covered by dependent claim 18 (depends from claim 7) of U.S. Patent 6,596,746, wherein the protein tyrosine kinase-associated disorder is a cancer.

(d) Dasatinib is covered by dependent claim 29 (depends from claim 7) of U.S. Patent 6,596,746, wherein the protein tyrosine kinase is Lyn.

(e) Dasatinib is covered by dependent claim 30 (depends from claim 7) of U.S. Patent 6,596,746, wherein the protein tyrosine kinase is Hck.

(f) Dasatinib is covered by dependent claim 42 (depends from claim 6) of U.S. Patent 6,596,746, which claims a pharmaceutical composition.

(g) Dasatinib is covered by independent claim 43 of U.S. Patent 6,596,746 which claims the same compound,  including salts thereof.

(h) Dasatinib is covered by dependent claim 44 (depends from claim 43) of U.S. Patent 6,596,746 directed to a method for the treatment of cancer.

(i) Dasatinib is covered by dependent claim 46 (depends from claim 43) of U.S. Patent 6,596,746, which claims a pharmaceutical composition.

(j) Dasatinib is covered by dependent claim 47 (depends from claim 43) of U.S. Patent 6,596,746, which claims a method for the treatment of a protein tyrosine kinase-associated disorder.

(10)(i)(A) The effective date of the investigational new drug (IND) application for dasatinib was April 3, 2003, 30 days after submission of the IND on March 4, 2003. The IND was assigned the number 66,971.

(B) The new drug application for dasatinib was submitted on December 28, 2005. The NDA for SPRYCEL® (dasatinib) Tablets for the treatment of chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib was assigned NDA 21-986 and for the treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy was assigned NDA 22-072.

(C) NDA 21-986 and NDA 22-072 were both approved on June 28, 2006.

(11) The following activities were undertaken by Bristol-Myers Squibb Company during the regulatory review period:

Date	Brief description of the activity
March 4, 2003	Submission of initial IND application
April 3, 2003	Deficiencies and Comments on IND
May 8, 2003	Submission of CA 180-002 change in protocol
May 13,2003	Comments from Biopharm Reviewer regarding IND
June 4, 2003	Submission of one Pharm/ Tox Report performed to evaluate the effects of BMS-354825 on platelet function
August 26, 2003	Submission of 4 Pharm/ Tox Reports - Study DS02138: Single-Dose Oral Toxicity in Rats - Study DS02147: Single-Dose Oral Toxicity in Monkeys - Study DS02158: One-Month Intermittent Dose Oral Toxicity Study in Rats - Study DS02159: One-Month Intermittent Dose Oral Toxicity Study in Monkeys
September 10, 2003	Submission of the Addendum to the Toxicology Integrated Summary Filed March 4, 2003
October 24, 2003	Email stating a permission to initiate study (Safe to proceed)
January 20, 2004	Submission of 2 Pharm/ Tox reports: - Study DS03025: Cytogenetics Study in Chinese Hamster Ovary Cells (930004234) - Study 03098: Single Dose Oral Administration Cadiovascular Safety Pharmacology Study in Monkeys (930005453)
February 9, 2004	Submission of CA 180-002 Amendment No. 2, Revised protocol No. 2
May 12, 2004	Submission of CA 180-002 Amendment No. 3, Revised protocol No. 3 and Administrative Letter
June 14, 2004	Submission of the Annual Report (March 5,2003 – April 3, 2004)
July 1, 2004	Submission of CA 180-003 Revised Protocol No. 1
July 12, 2004	Submission of CA 180-003 Amendment No. 2, and Revised Protocol No. 2
August 13, 2004	Submission of CA 180-002 Amendment No. 4, and Revised Protocol No. 4
September 2, 2004	Submission of 2 Pharm/ Tox Reports - Two-Weeks Oral Investigative Toxicity Study in Monkeys - Preclinical evaluation of the Pharmacokinetics and Metabolism of BMS-354825
September 20, 2004	Submission of CA 180-002 Amendment No. 5, and Revised Protocol No. 5

November 8, 2004	Submission of general Addendum 01 to Investigator Brochure Version No. 2
November 16, 2004	Submission CA 180-016 New Protocol
November 22, 2004	Submission of Background Document for End-Of -Phase 1 Meeting
November 23, 2004	Submission of CMC Amendment to support P2 studies (Triple Copies of Sub. 042 containing updating CMC information relating to the drug substance and drug product)
	Submission of CA 180-005, CA 180-006, CA 180-013, CA 180-015 and CA 180-017 New Protocols
November 29, 2004	Submission of a Request for Fast Track Designation
December 9, 2004	Submission of I Pharm/Tox Report Study MBA00038: Tissue Distribution of Radioactivity in Male-Long-Evans Rats following Oral administration of [^{14}C]BMS-354825 (930008720)
December 13, 2004	End of Phase 1 Meeting
December 22, 2004	Submission of a Request for Special Protocol Amendment (CMC)
January 10, 2005	Receipt Letter from CMC SN048 (12/23/04) for special stability Protocol Assessment of long term stability studies and analytical method for dissolution testing
	Special Stability Protocol assessment acknowledgement letter regarding SN048
January 25, 2005	Fast Track Designation
January 28, 2005	Submission of CA 180-002 Administrative letter and Revised Protocol 06
January 31, 2005	Submission of 1 Pharm/Tox Report Study DN04062: Thirteen-Day Oral Range- Finding Study in Pregnant Rabbits (930009355), dated 11-Jan-2005
February 16, 2005	Submission of Investigator Brochure Version No. 3
February 25, 2005	Submission of CA 180-019 New Protocol
February 28, 2005	Submission of IND Amendment (071) containing CMC information on the radiolabeled BMS-354825-03 drug substance, BMS-354825-08, and the corresponding drug product formulation ([14C] BMS-354825-08 for Oral Solution, 110 mg/Vial, Product Identification Number (PIN) 354825-H110-801)
March 2, 2005	Submission of CA 180-009 New Protocol
	Submission of CA 180-021 New Protocol
	Submission of CA 180-032 New Protocol
March 16, 2005	Submission of New Protocol CA 180-020
March 22, 2005	Submission of New Protocol CA 180-022

	Submission of an administrative letter sor CA 180-005, -006, -013, -015, -017, -019, and -032.
March 23, 2005	Submission of CA 180-003 Amendment No. 3 and Revised Protocol No. 3
April 8, 2005	Submission of CA 180-002 Amendment No. 6, and Revised Protocol No. 7; CA 180-020 Amendment No. 1
April 22, 2005	Submission of CA 180-009 Amendment No. 1 and revised Protocol No. 1 and CA 180-021 Administrative Letter
April 29, 2005	Submission of CA 180-035 New protocol
May 2, 2005	Submission of Background Document for 6/15/05 CMC EOP2 meeting
May 31, 2005	Submission of CA 180-003 Administrative Letter and Revised Protocol No. 4
June 2, 2005	Petition requesting immediate amendment of inclusion criteria of Phase 2 CML program
June 3, 2005	Submission of CA 180-034 New protocol; CA 180-034 Administrative Letter and Revised Protocol No. 1
June 6, 2005	BMS-354825 Trials Petition
June 8, 2005	Submission of CA 180-020 Revised Protocol No. 1, CA 180-022 Revised Protocol No. 1, Administrative letter; CA 180-035 Revised Protocol No. 1, Administrative Letter
	Submission of 4 Pharm/ Tox Reports - Study NAPR2675: Biotransformation of [^{14}C]BMS-354825 after Intravenous and Oral Administration to Bile Duct cannulated Rats (930010531 v1.0) - Study MBA00096: Mass Balance of Radioactivity after Oral Administration of [^{14}C]BMS-354825 to Male Rats (9300010421 v2.0) - Study MBA00097: Pharmacokinetics of Radiolabeled BMS-354825 and Excretion of radioactivity after Oral Administration of [^{14}C]BMS-354825 to Male Cynomologus Monkeys (930010419v1.0) - Study 930008306: Effects of BMS-354825 on bleeding Time and ex vivo Platelet function (130008306v.1.0)
June 14, 2005	CMC end of Phase 2 Meeting
June 16, 2005	Submission of Background Document for Pre-NDA Meeting
June 22, 2005	Submission of 2 Pharm/ Tox Reports - Study DN04080: Oral study of Embryo-Fetal Development in Rabbits (930010604v1.0) - Study MBA00127- Biliary Excretion of Radioactivity After Intravenous Administration of [^{14}C]BMS-354825 to Male Cynomologus Monkeys (930010809v1.0)
July 13, 2005	Submission of IND Amendment (180) to support BMS-354825-03 Film-coated Tablets, 70 mg to be used in BE study [CA 180037]

August 3, 2005	Submission of Investigator Brochure 04
August 15, 2005	Submission from BMS to request a Pre-NDA meeting
August 18, 2005	Submission of CA 180-002 Amendment 07 and Revised Protocol 08; CA 180-021 Amendment 01 and Revised Protocol 01
August 30, 2005	Pre-NDA Meeting Confirmation
August 31, 2005	Submission of Request for Orphan Drug Designation and Investigator Brochure Version 4.
September 6, 20005	Submission of CA 180-039 New Protocol; CA 180-009 Administrative Letter, CA 180-013 Amendment No. 2, Revised Protocol No. 1, CA 180-019, -020, -021, -022, -032 and -037 Administrative Letter
September 16, 2005	Submission of CA 180-005 Amendment No. 3 and Revised protocol No.1, CA 180-006 Amendment No. 3, and Revised Protocol No. 1
October 10, 2005	Submission of Request for Orphan Drug Designation
	Submission of CA 180-015 Amendment No. 3 and Revised Protocol No. 1
October 14, 2005	Submission of Background Document for Pre-NDA Meeting
	Submission of Request for Review of Proposed Trade Name for Dasatinib
October 17, 2005	Submission of Revised Core Statistical Analysis Plan for Dasatinib trials
November 7, 2005	Submission of Protocol Amendment No. 2 and Revised Protocol No. 1 for CA 180-017
November 14, 2005	FDA teleconference
November 18, 2005	Orphan Drug request #05-2146
November 28, 2005	Orphan Drug granted for treatment of chronic myelogenous leukemia request # 05-2124
December 2, 2005	Submission of CA 180-021 Administrative Letter, CA 180-035 Amendment No. 1 and Revised Protocol No. 2
December 6, 2005	User Fee Form Exclusion- received Orphan Drug Designation for this application
December 9, 2005	Rolling NDA Pre-Submission of Non-Clinical and Clinical Pharmacology sections of NDA
December 14, 2005	Draft of treatment IND Protocol
December 28, 2005	NDA Official Submission – request for accelerated approval and priority review
January 5, 2006	Treatment Protocol submission CA 180-033
January 5, 2006	Notification of New Drug Application Submission for (21-986) Dasatinib
	Submission of CA 180-017 Administrative Letter

	Submission of CA 180-033 Treatment Protocol for Dasatinib
January 10, 2006	Submission of Treatment Protocol Draft Informed Consent for CA 180-033
January 12, 2006	Request from FDA to confirm drug substance and drug product manufacturing, testing, packaging, and labeling sites for treatment protocol under review
January 24, 2006	Submission of CA 180-003 Amendment No. 4 and Revised Protocol No. 5
January 25, 2006	CMC request on treatment protocol
	Requested date for NDA presentation meeting at FDA
January 30, 2006	Request for most recent Investigator Brochure
January 31, 2006	Treatment Protocol CA 180-033 – Response to Questions
February 01, 2006	Investigator Brochure Version No. 5
February 3, 2006	FDA Notification that ECG's are ready for review
February 06, 2006	Permission granted to initiate treatment protocol CA 180-033
February 11, 2006	Request for list of investigators and information about background package for advisory committee meeting
February 13, 2006	FDA Fax: request for PK Information
February 14, 2006	Treatment IND protocol is in approvable status as result of 2/8/06 inspection
February 16, 2006	Submission of CA 180-033 Revised Protocol No. 1, included Final Informed Consent; Transfer of obligation for Protocol CA 180-033 to ICON Clinical Research, LP (CRO)
February 22, 2006	Submission of CA 180-011 New Protocol, CA 180-021 Amendment No. 2, Revised Protocol No. 2, CA 180-034 Administrative Letter, CA 180-035 Amendment No. 2 Revised Protocol No. 3, Investigator Brochure version No. 5
February 23, 2006	Submission of response to FDA fax dated 2/13/06
	NDA review meeting
	NDA Priority Review
March 2, 2006	FDA Fax: Request for information regarding hematologic data
March 6, 2006	FDA Fax: NDA Priority Review Status granted
March 7, 2006	Submission of response to FDA Fax dated March 2, 2006
March 9, 2006	FDA Fax: Request for information re dose relationship
March 10, 2006	NDA Filing letter
March 14, 2006	Submission of CA 180-035 Administrative Letter No. 2
March 21, 2006	Response to FDA Fax of March 9, 2006
March 22, 2006	Submission of revised carton and label
	FDA Fax: Clinical Request
March 23, 2006	FDA Fax: AESAE Request
March 30, 2006	FDA Fax: Request regarding study CA 180-003
	FDA Fax: Request for CMC information

April 4, 2006	Response to FDA Fax of 3/22/06 which will officially be submitted on 4/5/06
	Response to FDA Fax dated March 22, 2006 requesting additional information on study CA 180-015
April 7, 2006	FDA Fax: Request for clarification of how various drug substances differ from each other (BMS354825-02, BMS354825-03, BMS354825)
	Responses to FDA Fax dated March 23, 2006 regarding Integrated Analysis report dated 12/12/05Questions 1, 5 and 6
April 12, 2006	Request from FDA Protocol CA 180-002
April 13, 2006	Submission of CA 180-011 Administrative Letter 02 and 1 Pharm/Tox Report: - Study 930014293: Lacteal Excretion and Fetal Tissue Distribution of Radioactivity in Pregnant Female Spague Dawley Rats and Tissue Distribution of Radioactivity in Male and Non-Pregnant Female Spague Dawley Rats following Oral Administration of [^{14}C]BMS-354825-08
April 17, 2006	Response to FDA Fax dated April 7, 2006
April 18, 2006	Response to FDA Fax dated 30-Mar-06 Faxed related to drug substance section of NDA CMC section
	FDA Inspection Notification
April 19, 2006	Submission to solicit FDA review of 2 Pediatric Protocol (ca180-038 and CA 180-018) for dasatinib and two request input for the obtention of Pediatric Written Request for Chronic Myelogenous Leukemia (CML)
April 21, 2006	FDA Fax: CMC comment on long-term stability data
	FDA Fax: Request for PK Information
April 25, 2006	Submission of 12-month data from primary LTSS conducted on drug substance and commercial drug product
April 26, 2006	Response to FDA Fax dated April 21, 2006 requesting additional information on the datasets for dasatinib PK studies
April 27, 2006	Special exception requested for CA 180-033 Treatment Protocol
	FDA Fax: Special exception granted and it is acceptable to treat patients under Treatment Protocol CA 180-033
April 27, 2006	Submission of 120- Day Safety Update and Updated Draft Labeling
	Response to FDA Fax dated March 23, 2006 regarding SAS and data analysis, Questions 2 and 3
May 1, 2006	Submission of Background Document for advisory committee meeting sent on 5/1/06
May 2, 2006	Response to CMC Information Request Letter dated 30Mar06 regarding the NDA Drug Substance section
	Submission of Dasatinib ODAC briefing document

May 5, 2006	FDA agreed to BMS proposal not to conduct formal reproductive toxicity studies to support approval of 2nd line melanoma
May 8, 2006	Submission of CA 180-034 Amendment No. 1 and Revised Protocol No. 2; 4 Bioanalytical Reports for CA 180-021, CA 180-022 and CA 180-032
May 10, 2006	Transfer of Obligations to contract research organizations: ICON and Data Prep
May 17, 2006	Submission of Request of Proposed Trade Name
May 23, 2006	Dasatinib treatment protocol question
May 25, 2006	Submission of CA 180-051 draft protocol for FDA review and comments
	Request for FDA guidance on proposal to use observation or placebo as control in Phase 3 trial
May 31, 2006	Submission of Annual Report: interval covering April 4, 2005- April 3, 2006
June 1, 2006	Submission of CA 180-037 Final Clinical Study Report
	Request status of tradename Sprycel
June 8, 2006	Submission of CA 180-003 Administrative letter, CA 180-005 Administrative letter, CA 180-006 Administrative letter, CA 180-015 Administrative letter
June 9, 2006	Submission of Draft Population Pharmacokinetic Report
June 9, 2006	BMS email: tradename review status
June 13, 2006	FDA Request for provision of links or source materials for claims made in MOA section of label
June 16, 2006	Labeling comments from FDA
June 19, 2006	BMS will include an additional sentence in mechanism of action
	Revised label will be sent on 6/20/2006
June 20, 2006	New labeling guidance
	Revised labeling will not be submitted until 6/22/2006. Question re new labeling guidance
June 22, 2006	FDA proposed labeling
	List of proposed Phase IV commitments
June 23, 2006	Ketoconazole interaction study completed but report hasn't been submitted
	Revised labeling
June 26, 2006	BMS Comments and edits re FDA announcement of Approval
	BMS responses to Phase IV commitments
	FDA proposed labeling
June 27, 2006	FDA email: Agreements to Phase IV commitments
	Final revised labeling sent to FDA
	Final Phase IV Commitments sent to FDA
June 28, 2006	FDA request for change to carton and vial label
	FDA email: hepatic impairment and Phase IV commitment

	FDA request for bottle label and carton change
	Approval letter: we received from the FDA 2 NDA APPROVALS: - NDA 21,986 for CML indication - NDA 22,072 for Ph+ ALL indication

(12) In the opinion of applicant U.S. Patent 6,596,746 is eligible for the extension under 35 U.S.C. §156. Applicant believes that the extension should be for 76 days so that the expiration date for U.S. Patent 6,596,746 will be June 28, 2020. The term of the extension was calculated as follows:

IND effective from April 3, 2003 with the patent granted on July 22, 2003, until the NDA was filed on December 28, 2005, for a total of 890 days as calculated below:

July 22 - December 31, 2003	163 days
January 1 - December 31, 2004	366 days
January 1 - December 27, 2005	361 days
	890 days

NDA effective from December 28, 2005 until approval on June 28, 2005 for a total of 183 days.

1/2 IND + NDA = term of extension

445 + 183 = 628 days

As the 14 year effective patent term cap of 35 U.S.C. § 156(c)(3) applies in this situation, the patent should be extended until 14 years from June 28, 2006, or until June 28, 2020, or 76 days of patent term extension.

(13) Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extent sought in accordance with 37 C.F.R. §1.765.

(14) Authorization is given to charge the fee of $1,120.00 for receiving and acting upon the application for extension to the Deposit Account No. 19-3880 of the undersigned. Additionally, the Commissioner is authorized to charge any additional fee that may be required to the aforementioned Deposit Account.

(15) Please direct any inquiries and correspondence relating to the application for patent term extension to:

Mary VanAtten
Patent Department
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000
609-252-4338

Respectfully submitted,

Mary VanAtten

Mary K. VanAtten
Attorney for Applicant
Reg. No. 39,408
Phone: 609-252-4379

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000

Date: 8/15/06

US006596746B1

(12) **United States Patent**
Das et al.

(10) **Patent No.: US 6,596,746 B1**
(45) **Date of Patent: Jul. 22, 2003**

(54) **CYCLIC PROTEIN TYROSINE KINASE INHIBITORS**

(75) Inventors: **Jagabandhu Das**, Mercerville, NJ (US); **Ramesh Padmanabha**, Hamden, CT (US); **Ping Chen**, Belle Mead, NJ (US); **Derek J. Norris**, Trenton, NJ (US); **Arthur M. P. Doweyko**, Long Valley, NJ (US); **Joel C. Barrish**, Holland, PA (US); **John Wityak**, Robbinsville, NJ (US)

(73) Assignee: **Bristol-Myers Squibb Company**, Princeton, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/548,929**

(22) Filed: **Apr. 13, 2000**

Related U.S. Application Data

(60) Provisional application No. 60/129,510, filed on Apr. 15, 1999.

(51) **Int. Cl.**[7] **C07D 277/42**; A61K 31/426

(52) **U.S. Cl.** **514/370**; 548/194

(58) **Field of Search** 548/194; 514/370

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,505,055	A		4/1970	von Schmeling et al.
3,547,917	A	*	12/1970	Kulka 548/190
3,709,992	A		1/1973	von Schmeling et al.
3,725,427	A		4/1973	Harrison et al.
3,796,800	A		3/1974	Ariyan et al.
3,879,531	A		4/1975	Ariyan et al.
3,896,223	A		7/1975	Ariyan et al.
3,932,633	A		1/1976	O'Brien et al.
4,942,143	A		7/1990	Ohsaki et al.
4,980,346	A		12/1990	Balogh et al.
5,057,142	A		10/1991	Baasner et al.
5,064,825	A		11/1991	Chakravarty et al.
5,399,674	A		3/1995	Dannheim et al.
5,438,070	A		8/1995	Eicken et al.
5,498,630	A		3/1996	Phillion et al.
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(57) **ABSTRACT**

Novel cyclic compounds and salts thereof, pharmaceutical compositions containing such compounds, and methods of using such compounds in the treatment of protein tyrosine kinase-associated disorders such as immunologic and oncologic disorders.

49 Claims, No Drawings

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CYCLIC PROTEIN TYROSINE KINASE INHIBITORS

This application claims priority from provisional U.S. application Ser. No. 60/129,510, filed Apr. 15, 1999, the entirety of which is 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 conduction 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)).

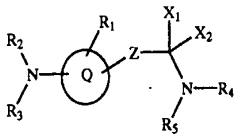
Enhanced activity of PTKs has been implicated in a variety of malignant and nonmalignant proliferative diseases. In addition, PTKs play a central role in the regulation of cells of the immune system. PTK inhibitors can thus impact a wide variety of oncologic and immunologic disorders. Such disorders 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}—;

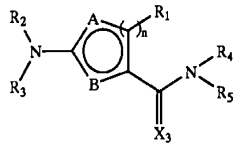
Z_7, Z_8, Z_9 and Z_{10}:
(1) are each independently hydrogen or Z_6;
(2) Z_7 and Z_8, or $Z_6$and Z_{10}, may together be alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted 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 $-C\equiv C-$, $-CH_2-C\equiv C-$, $-CH(CH_3)-C\equiv C-$ and $-C\equiv C-CH(C_2H_5)CH_2-$.

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 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 $—Z_{13}—NR_7R_8$ 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

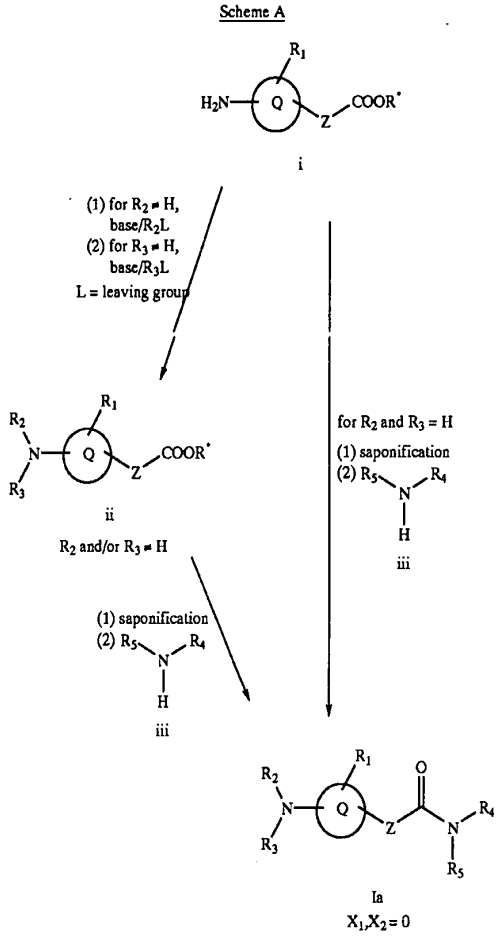
R_5 is selected from aryl groups or heteroaryl groups which are substituted with Z_1, Z_2 and one or more (such as one or two) groups Z_3.

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)).

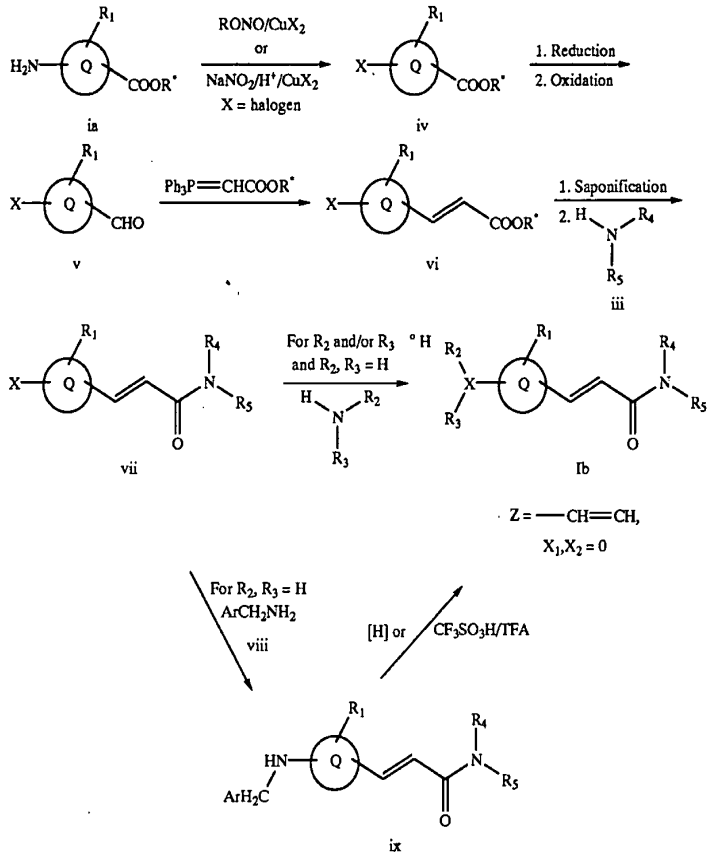
Scheme A



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.

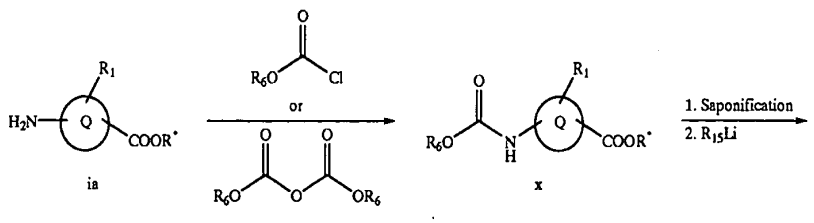
Scheme B



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



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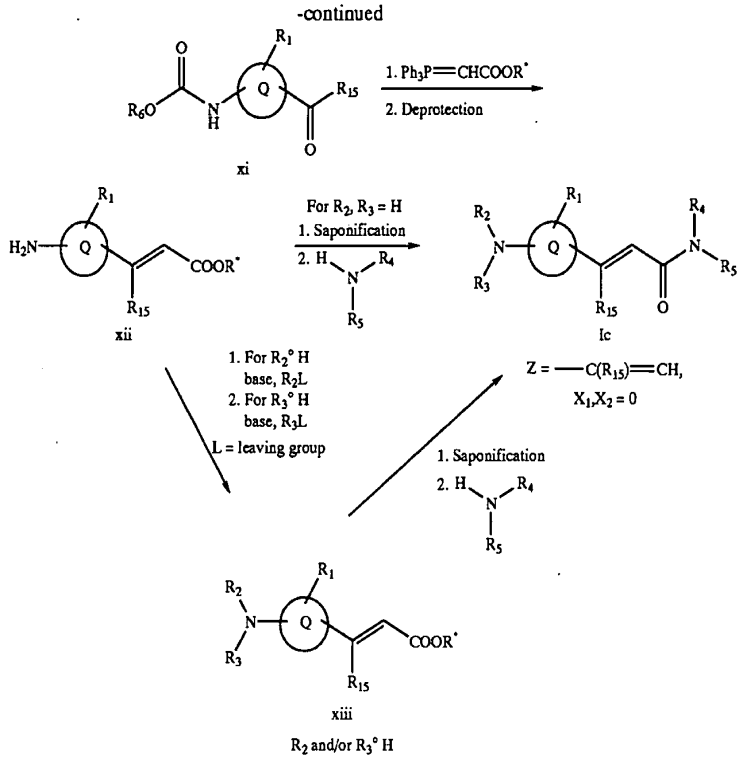

Scheme C illustrates a general method for forming compound Ic, which is a compound of formula I where Z is —R_{15}C=CH— and X_1 and X_2 together form =O. As shown in Scheme C, a 2-amino-compound ia can be reacted with a chloroformate or dicarbonate to form x, which can be saponified and treated with 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.

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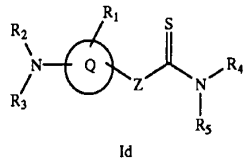
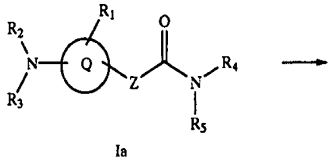


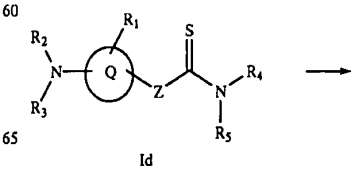
Scheme D illustrates a general method for forming compound Id, which is a compound of the formula I where X_1 and X_2 together form =S. The compounds of the formula Ia obtained in Scheme A may be converted into the corresponding thioamide Id using a reagent such as Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide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



Scheme E



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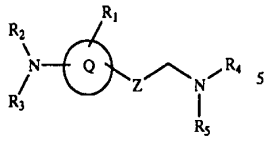

Ie

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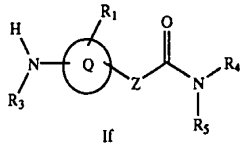


If

R_3=$COOR_6$

$X_1, X_2 = 0$

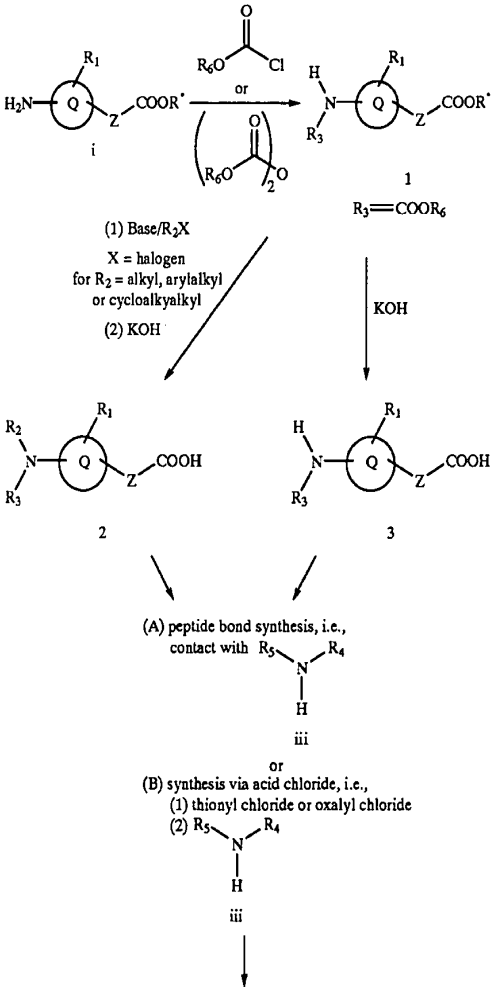
starting from 2: R_2 = alkyl, arylalkyl or cycloalkylalky

starting from 3: R_2 = H

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

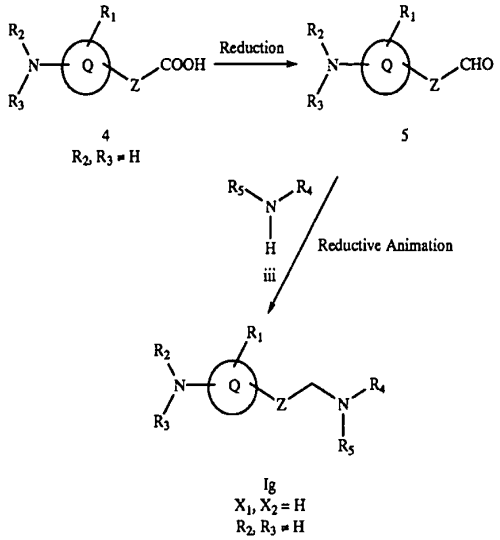


As shown in Scheme I, carboxylate i can be reacted with a chloroformate or dicarbonate to form 1. Compound 1 can be treated with a base such as sodium hydride, sodium/potassium hexamethyldisilazide, or lithium diisopropylamide (LDA), and an alkylating agent R_2X where X is halogen and R_2 is preferably 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.

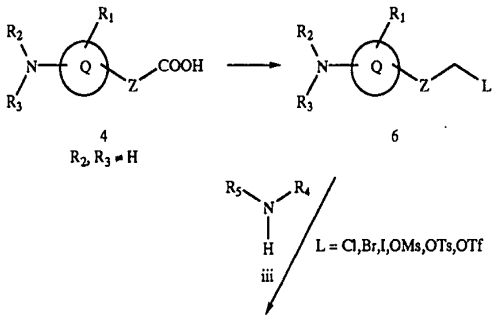
Scheme II



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



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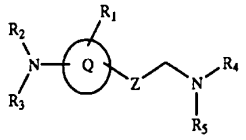
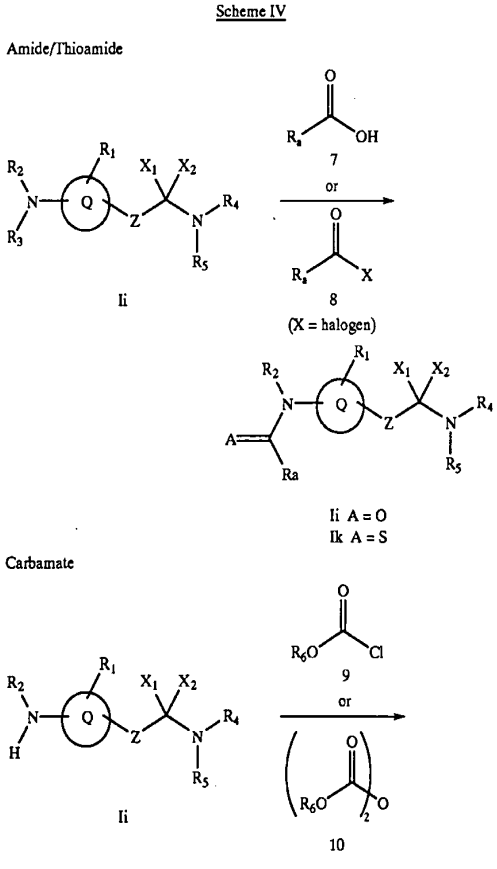


As shown in Scheme III, reduction of the acid 4 to a primary alcohol (for example, by treatment with borane/tetrahydrofuran, $LiAlH_4$, or via reduction of a mixed anhydride), followed by conversion by methods well known in the art (see March, Advanced Organic Chemistry, Wiley, 1985), provides 6 which 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



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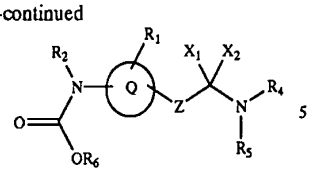
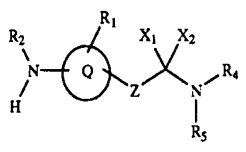
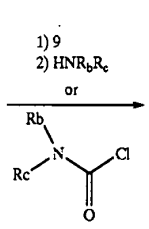


II

Urea/Thiourea



Ii

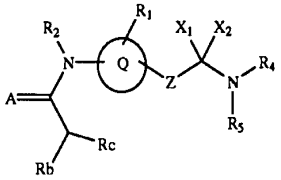


or

R_bNCO 13a

R_bNCS 13b

$[X_1,X_2 \neq H]$



Im A = O

In A = S

R_2 = any group as defined

R_3 = acyl or thioacyl

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.

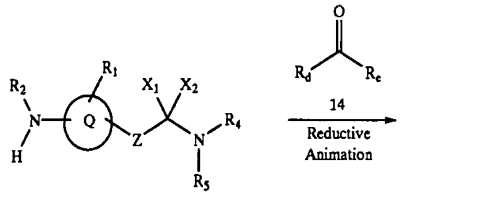
Amide Ij can be prepared by treatment of amine compound Ii with a carboxylic acid 7 in the presence of reagents which activate the carboxyl group for reaction as described above, for example BOP reagent, HATU, and carbodiimides such as DCC or EDCI either alone or in combination with a hydroxybenztriazole. 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.

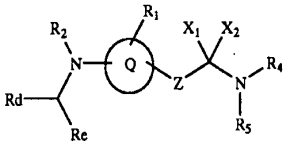
The urea Im may be prepared by treatment of amine compound Ii with either: 1) a chloroformate 9, such as phenylchloroformate, followed by reaction with an amine 11; 2) a carbamoyl chloride 12 in the presence of an acid scavenger such as diisopropylethylamine; or 3) reaction with an isocyanate 13a (where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

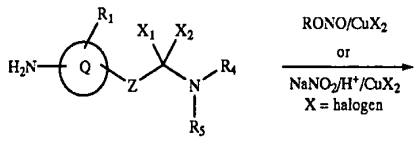
Scheme V



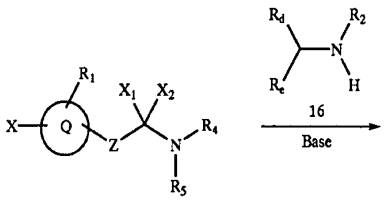
Io



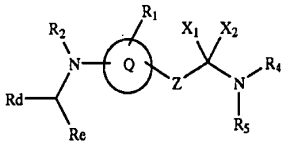
Ip



Iq



15



Ip

$[X_1,X_2 \neq H]$

R_2 = any group as defined other than acyl

R_3 = alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl or saturated heterocycle

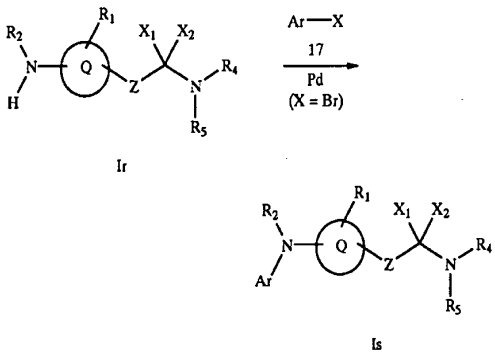
Scheme V illustrates a method which can be used for the preparation of Ip, which is a compound of the formula I where R_2 is any group as defined other than acyl, and which is selected such that the nitrogen to which it is attached is basic, R_3 is alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, 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



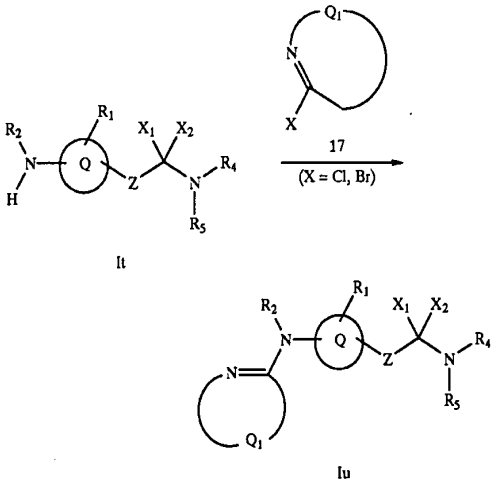
Ir

Is

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



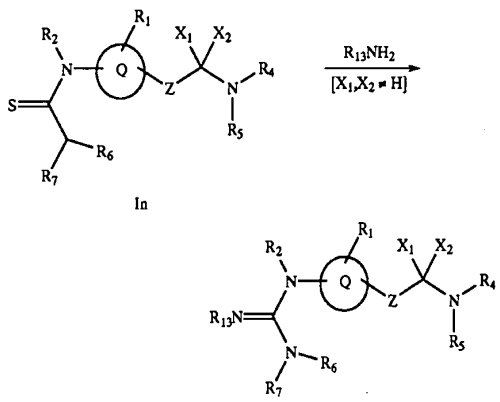
It

Iu

R_2 = any group as defined
R_3 = heteroaryl

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



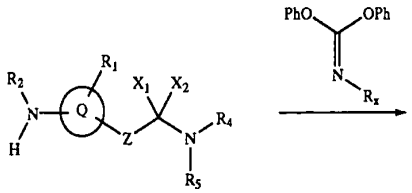
In

Iv

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.

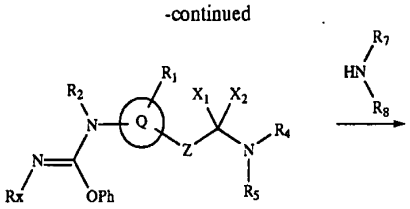
Alternatively, Compound In can be reacted with the appropriate amine in the presence of a mercury (II) salt such as mercuric chloride, or by other methods known in the literature, to form Iv.

Scheme IX

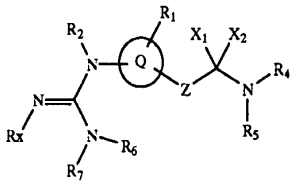


Ir

-continued



Iw [R_x—CO_2alkyl, CN, CO_2aryl]

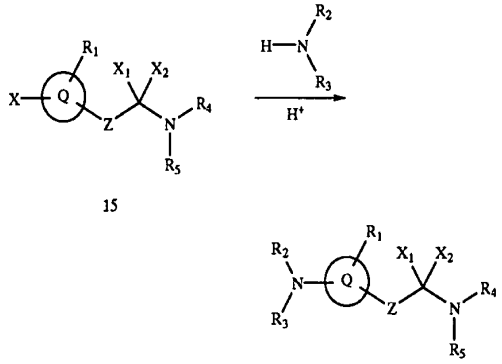


Iv
[X_1,X_2 = H]

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.

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

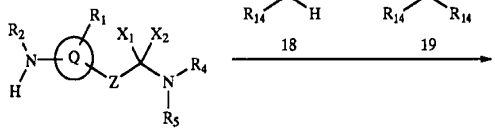


15

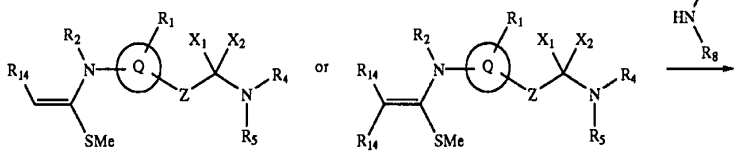
R_2 = aryl, heteroaryl, bicyclic-heteroaryl
R_3 = H, alkyl, aryl, heteroaryl, bicyclic-heteroaryl

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)).

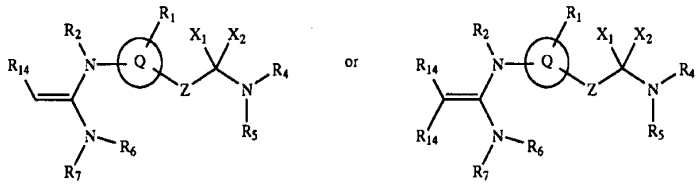
Scheme X



Ir



Ix Iv



Iz
[X_1,X_2 = H]

Iz*

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

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 dowaregulate 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 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.

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: Ser. No. 60/056,770, filed Aug. 25, 1997, Ser. No. 60/069,159, filed Dec. 9, 1997, Ser. No. 09/097,338, filed Jun. 15, 1998, Ser. No. 60/056,797, filed Aug. 25, 1997, Ser. No. 09/094,797, filed Jun. 15, 1998, Ser. No. 60/065,042, filed Nov. 10, 1997, Ser. No. 09/173,413, filed Oct. 15, 1998, Ser. No. 60,076,789, filed Mar. 4, 1998, and Ser. No. 09,262,525, filed Mar. 4, 1999. See the following documents and references cited therein: Hollenbaugh, D., Douthwright, J., McDonald, V., and Aruffo, A., "Cleavable CD40lg 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 (December 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. Ser. No. 09/506,481 filed Feb. 17, 2000; 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, 1 μM 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

(1) 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).

(2) 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 methylenel-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

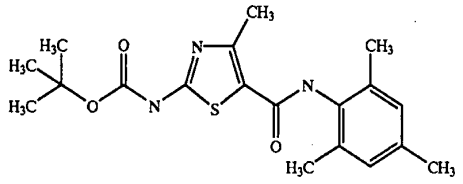
TFA=trifluoroacetic acid

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



A. 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

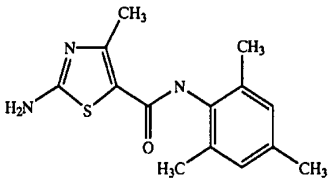
A 2 M solution of oxalyl chloride in dichloromethane (22.5 mL, 45 mmol) was added dropwise to a stirred suspension of 2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid (10 g, 38.72 mmol) in dichloromethane (150 mL) and N,N-dimethyl formamide (150 μL) at 0° C. The suspension gradually 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

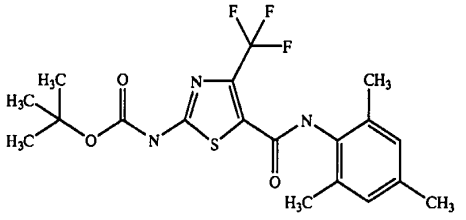
Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-methyl-5-thiazolecarboxamide



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



A. 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

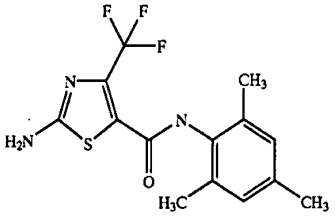
A stirred solution of ethyl-2-tert-butoxycarbonyloxyamino-4-trifluoromethyl-thiazole-5-carboxylate (6.5 g, 19.1 mmol) in methanol (100 mL) was treated with a 1N aq. NaOH solution (573 mL). The mixture was stirred at rt overnight. The solution was cooled to 0° C. and acidified with a 6 M aq. HCl solution to pH 1 and extracted with chloroform (150 mL, 6×). 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

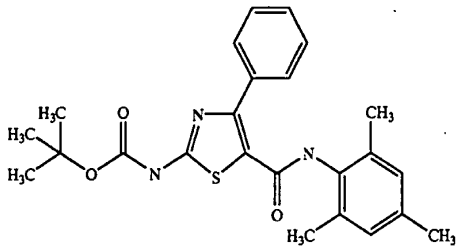
Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-trifluoromethyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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



A. 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

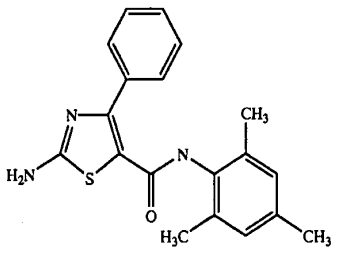
Compound 5C was prepared by an analogous method as that of 1C, except using 5B to give the title compound 5C as a white solid (90%).

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

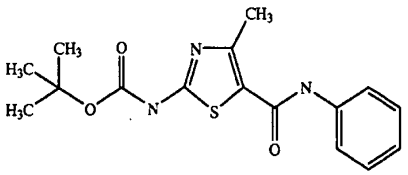
Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-phenyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

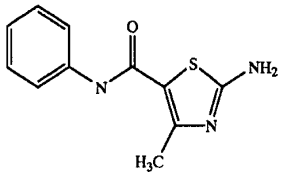
Preparation of [5-[[Phenylamino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



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

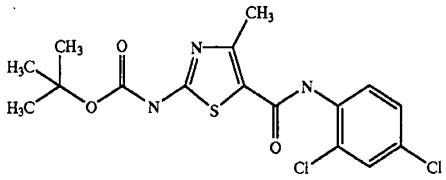
Preparation of 2-Amino-N-(phenyl)-4-methyl-5-thiazolecarboxamide, trifluoracetate



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

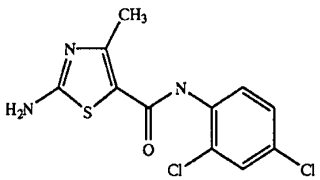
Preparation of [5-[[(2,4-Dichlorophenyl)amno]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



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

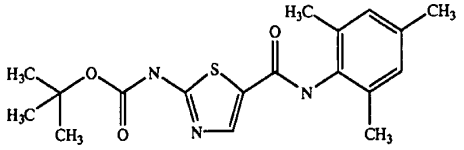
Preparation of 2-Amino-N-(2,4-dichlorophenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



A. 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

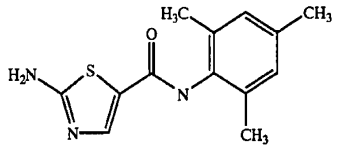
Compound 11C was prepared by an analogous method as that of 1C, except using 11B to give the title compound 11C.

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)



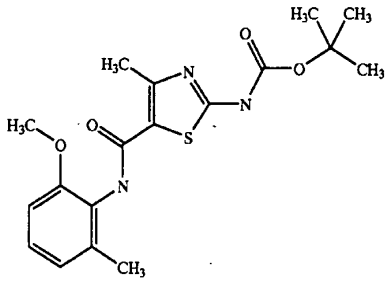
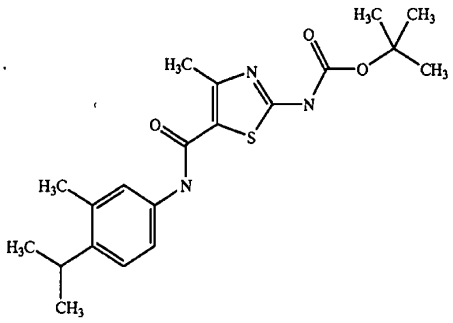
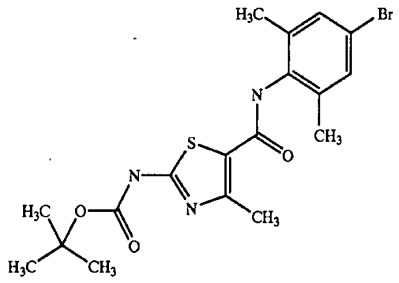
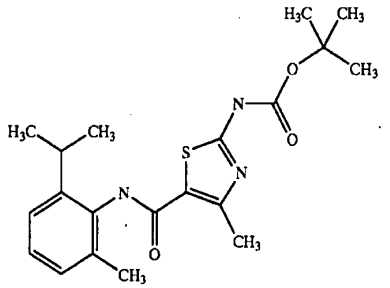
Compound 12 was prepared by an analogous method as that of 4, except using 11D to give the title compound 12 as a light yellow solid (88%).

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 4.6x50 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

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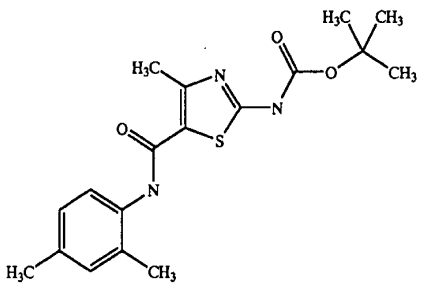
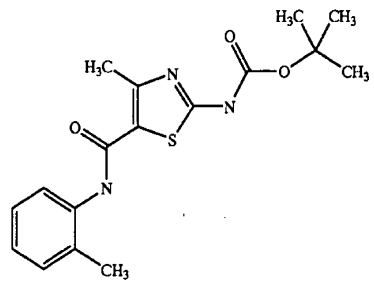
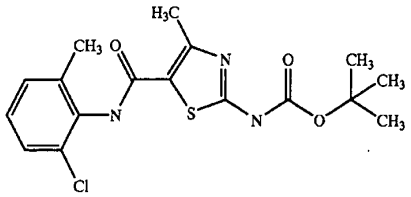
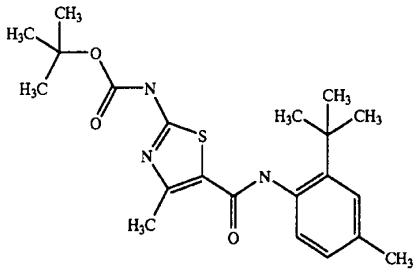
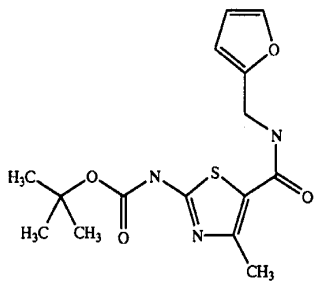
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
17		[5-[[(2,4-Dimethylphenyl)amino] carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.05
18		[4-Methyl-5-[[(2-methylphenyl)amino] carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.87
19		[5-[[(2-Chloro-6-methylphenyl)amino] 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

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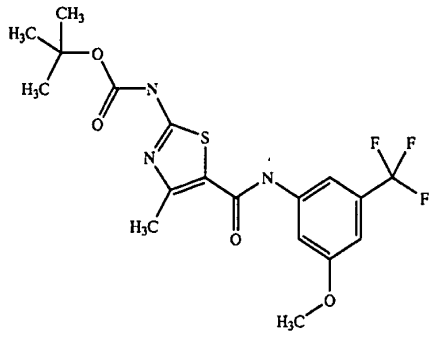
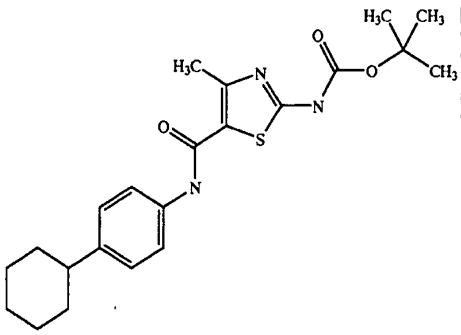
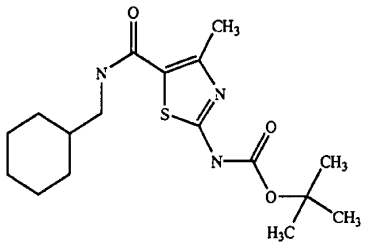
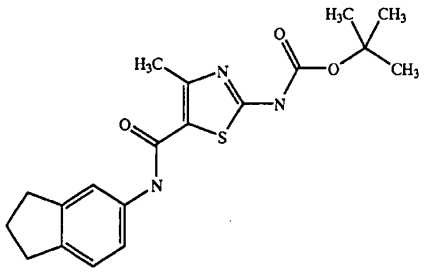
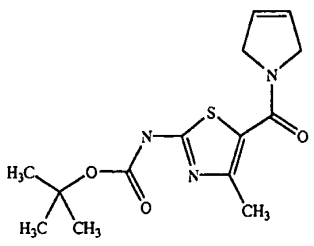
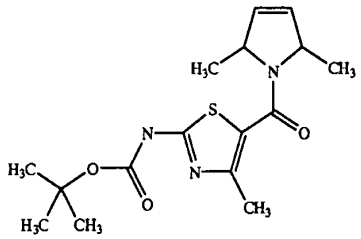
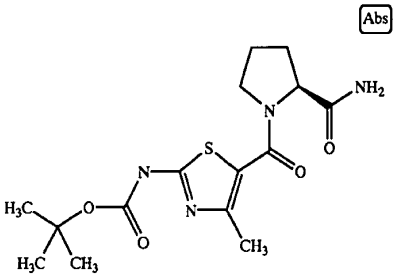
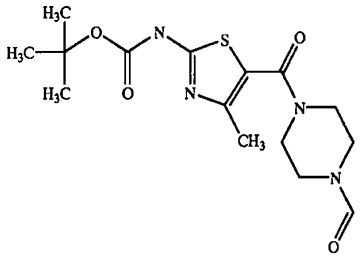
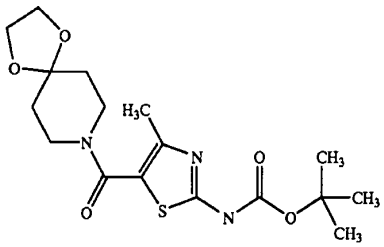
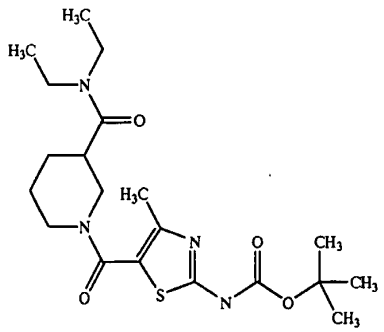
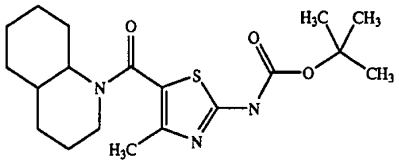
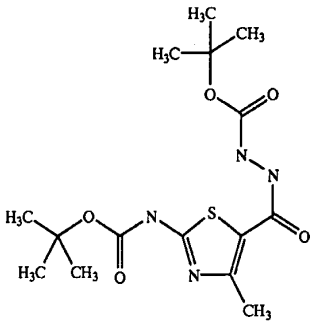
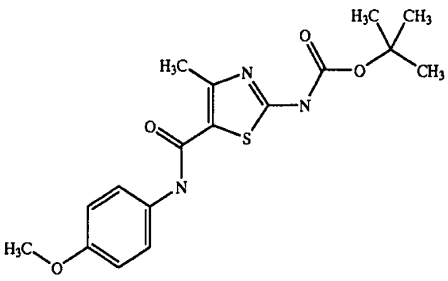
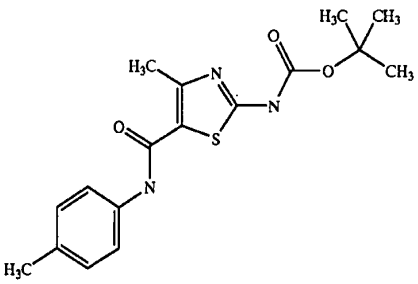
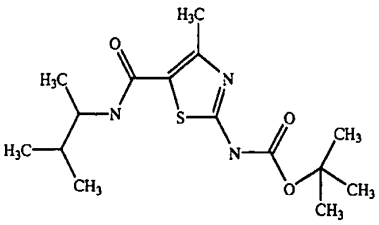
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
22		[5-[[[3-Methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.43
23		[5-[[(4-Cyclohexylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.78
24		[5-[[(Cyclohexyl methyl)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

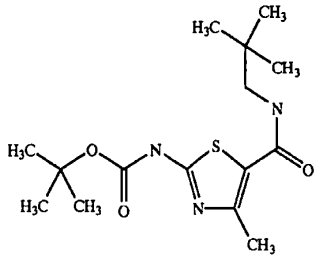
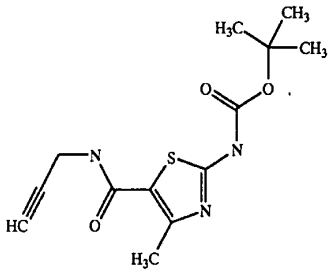
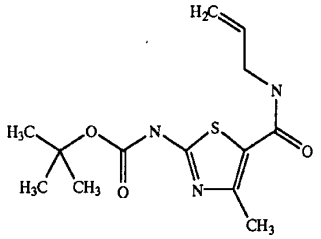
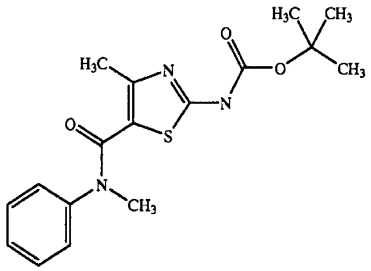
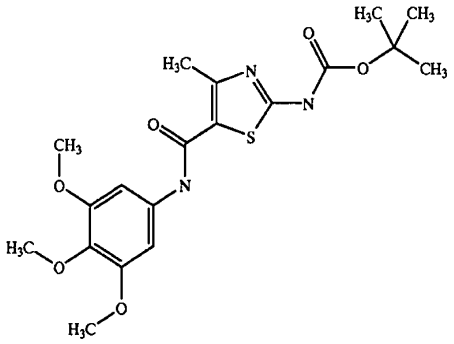
-continued

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

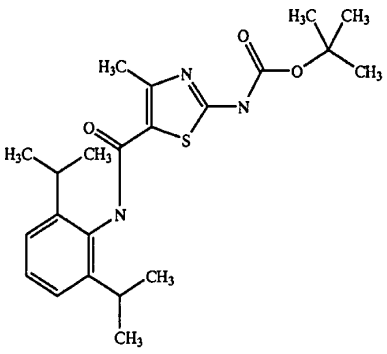
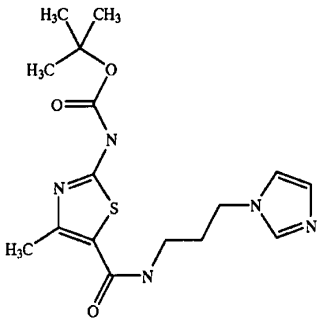
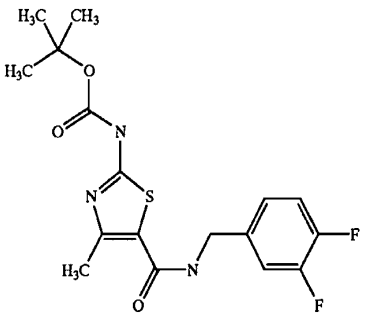
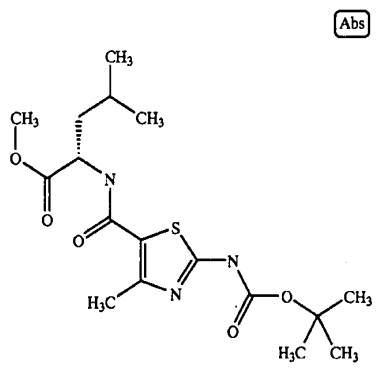
-continued

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

-continued

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

-continued

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

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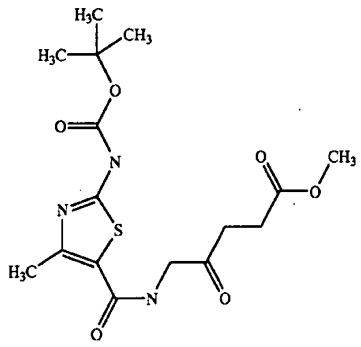
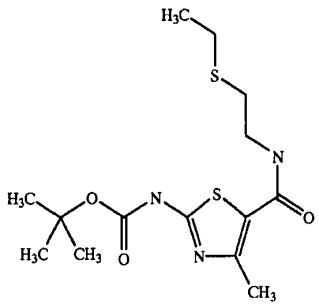
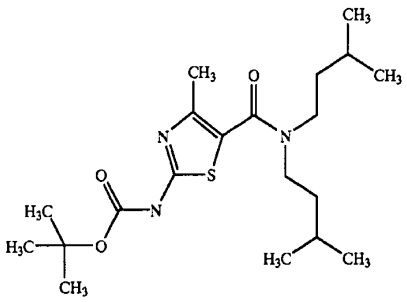
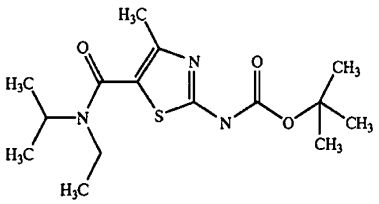
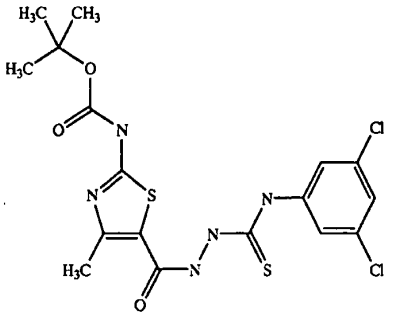
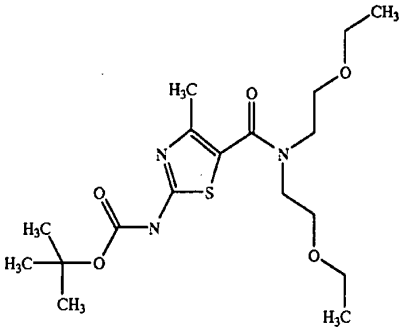
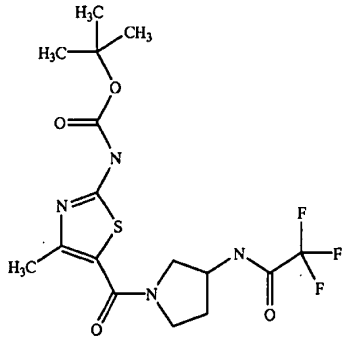
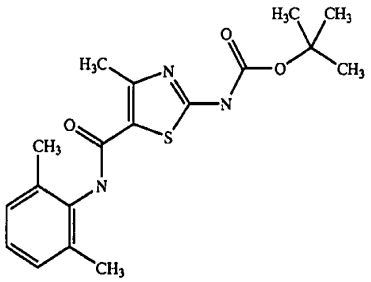
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
46		5-[[[2-[[(1,1-Dimethylethoxy)carbonyl] amino]-4-methyl-5-thiazolyl]carbonyl] amino]-4-oxopentanoic acid methyl ester	3.27
47		[5-[[[2-(Ethylthio) ethyl]amino]carbonyl]-4-methyl-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester	3.75
48		[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

-continued

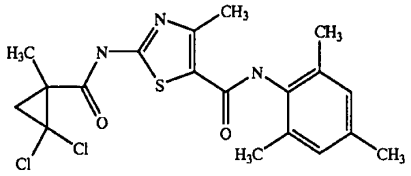
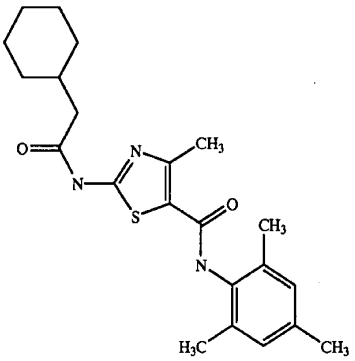
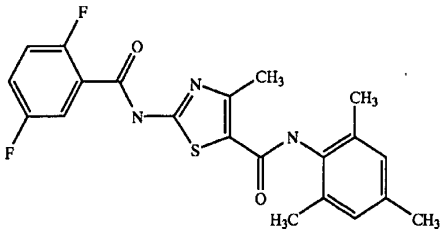
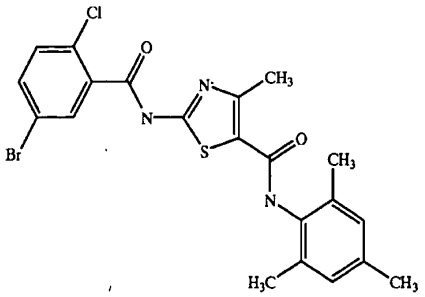
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
50		2-[[(1,1-Dimethylethoxy)carbonyl] amino]-4-methyl-5-thiazolecarboxylic acid 2-[[(3,5-dichlorophenyl)amino] thioxomethyl]hydrazide	4.66
51		[5-[[Bis(2-ethoxyethyl)amino] carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	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

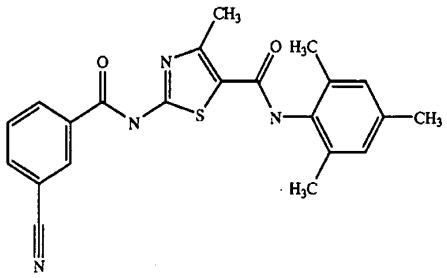
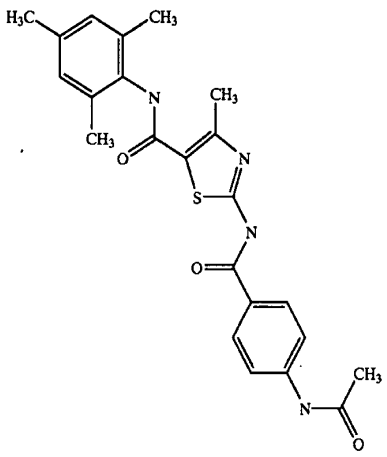
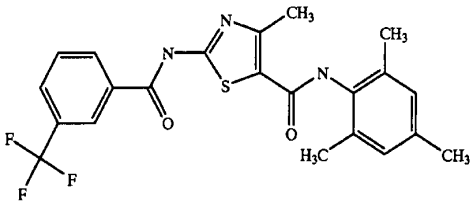
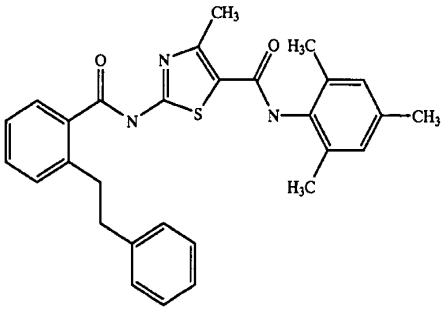
General Procedure

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

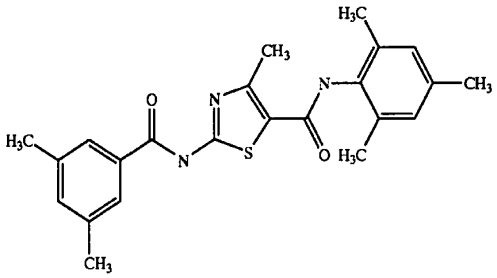
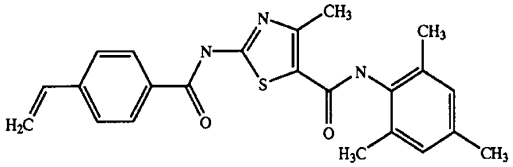
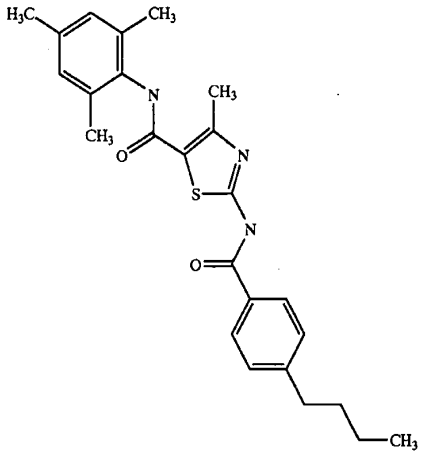
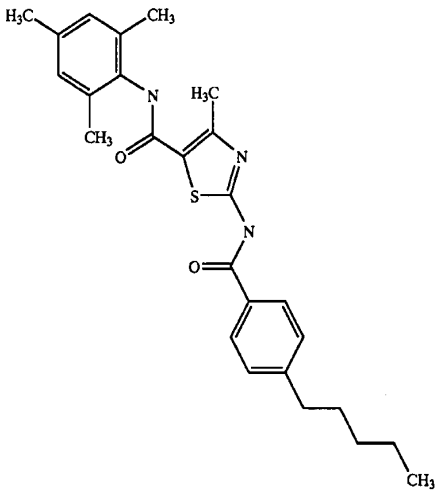
dichloromethane solution was passed through a Varian SCX cation exchange column (2 g, 6 cc) on a Gilson robot. The column was eluted sequentially with acetonitrile-methanol (10 mL, 4:1), methanol-2M methanolic ammonia (3 mL, 4:1), and 2 M methanolic ammonia solution (3 mL, 4×). The fractions were collected 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 4.6×50 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×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-[(Cyclohexyl acetyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.47
56		2-[(2,5-Difluoro-benzoyl)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

-continued

EX. No.	Compound Structure	Compound Name	HPLC Ret Time (min)
58		2-[(3-Cyano-benzoyl)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

-continued

EX. No.	Compound Structure	Compound Name	HPLC Ret Time (min)
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-trimethyl-phenyl)-5-thiazole-carboxamide	4.76

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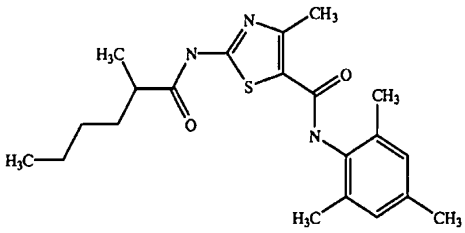
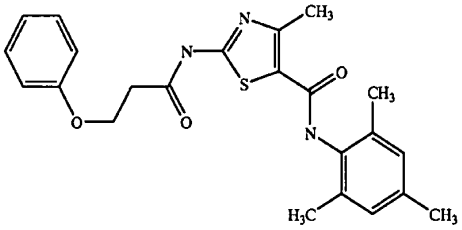
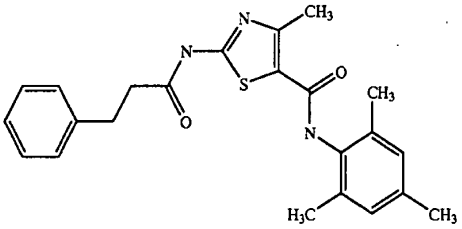
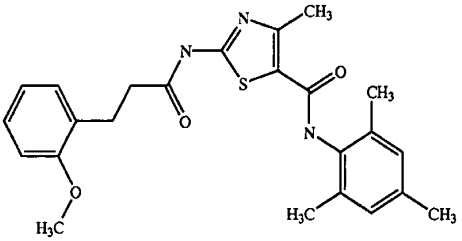
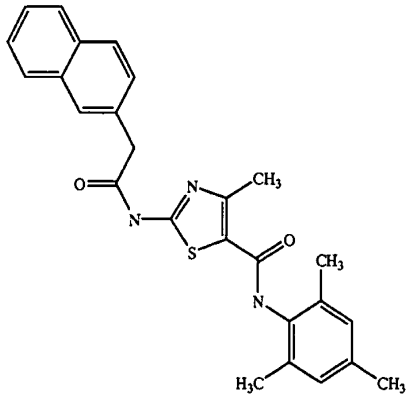
EX. No.	Compound Structure	Compound Name	HPLC Ret Time (min)
66		4-Methyl-2-[(2-methyl-1-oxohexyl)amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.41
67		4-Methyl-2-[(1-oxo-3-phenoxypropyl)amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.21
68		4-Methyl-2-[(1-oxo-3-phenylpropyl)amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.26
69		2-[[3-(2-Methoxy-phenyl)-1-oxopropyl]-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.31
70		4-Methyl-2-[(2-naphthalenylacetyl)-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.43

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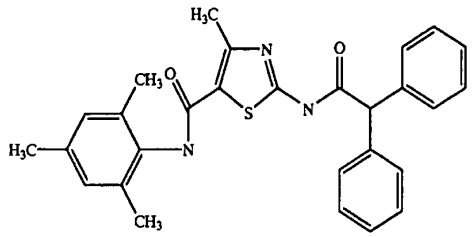
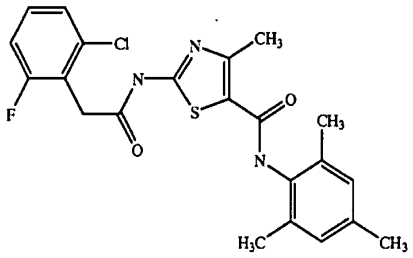
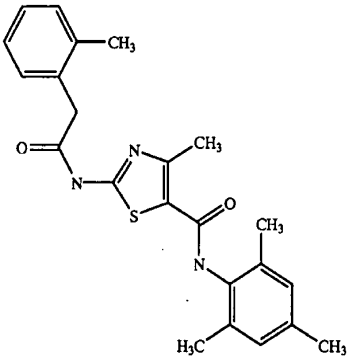
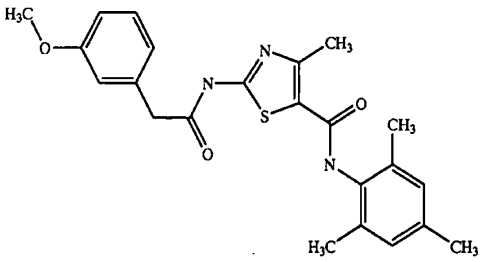
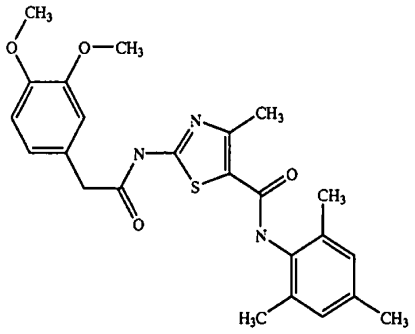
EX. No.	Compound Structure	Compound Name	HPLC Ret Time (min)
71		2-[(Diphenyl-acetyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.13
72		2-[[(2-Chloro-6-fluorophenyl)acetyl]-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.17
73		4-Methyl-2-[[(2-methylphenyl)-acetyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazolecarboxamide	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

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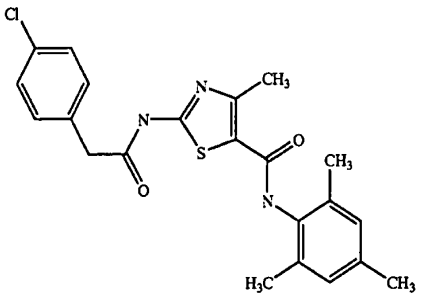
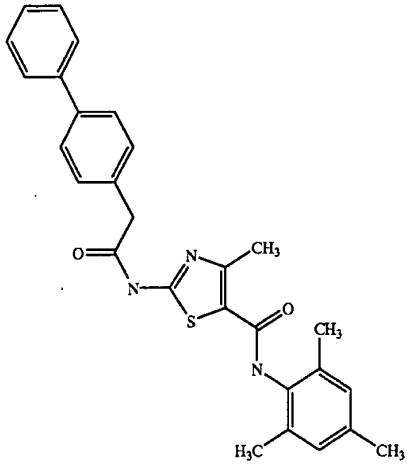
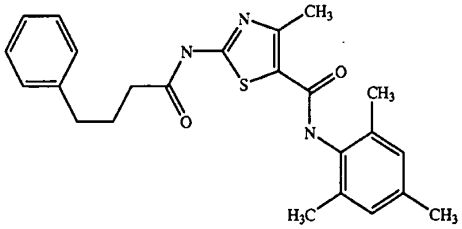
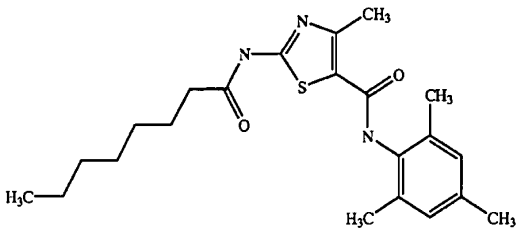
EX. No.	Compound Structure	Compound Name	HPLC Ret Time (min)
76		2-[[(4-Chloro-phenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.34
77		2-([1,1'-Biphenyl]-4-ylacetyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.60
78		4-Methyl-2-[(1-oxo-4-phenylbutyl)amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.40
79		4-Methyl-2-[(1-oxooctyl)amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.65

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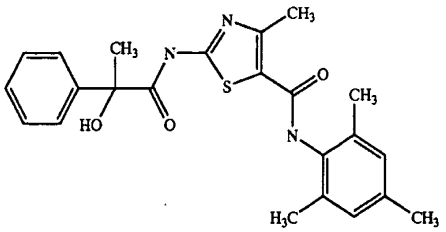
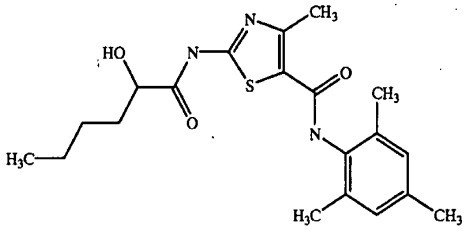
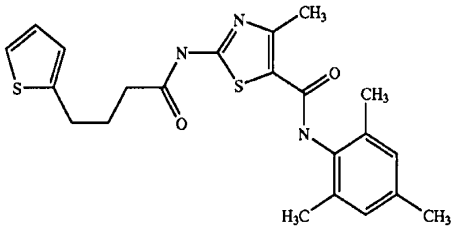
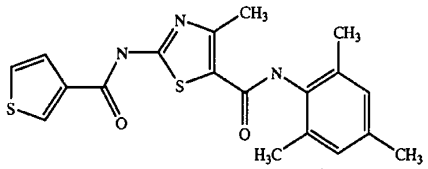
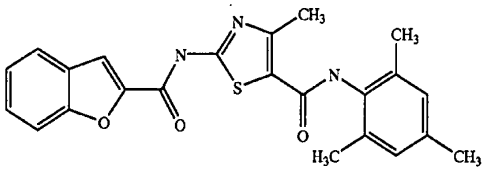
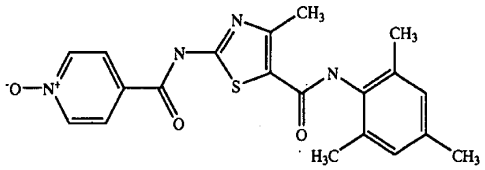
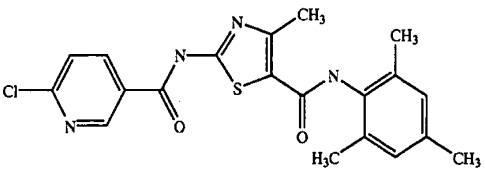
EX. No.	Compound Structure	Compound Name	HPLC Ret Time (min)
80		2-[(2-Hydroxy-2-phenyl-1-oxopropyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.13
81		2-[(2-Hydroxy-1-oxohexyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.14
82		4-Methyl-2-[[1-oxo-4-(2-thienyl)-butyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	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

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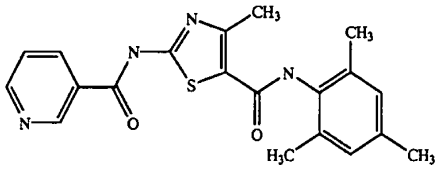
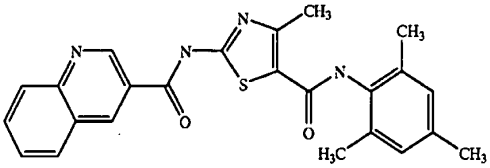
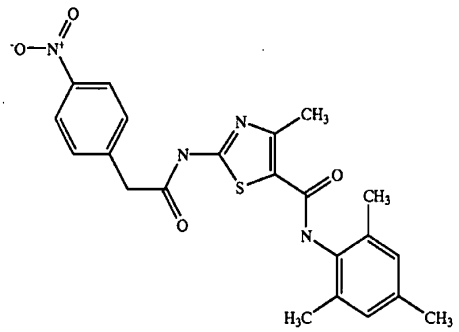
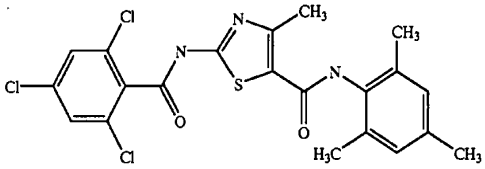
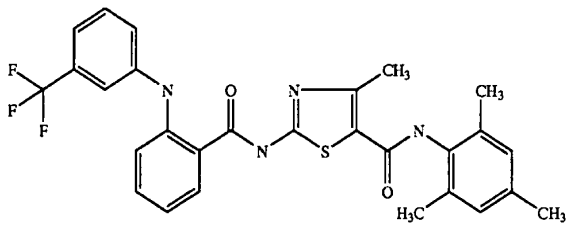
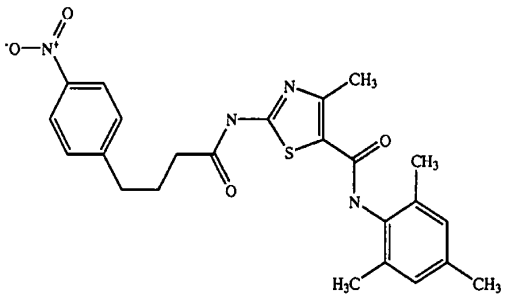
EX. No.	Compound Structure	Compound Name	HPLC Ret Time (min)
87		N-[4-Methyl-5-[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-3-pyridinecarboxamide	3.56
88		N-[4-Methyl-5-[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-3-quinolinecarboxamide	4.11
89		4-Methyl-2-[[(4-nitrophenyl)acetyl]-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	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

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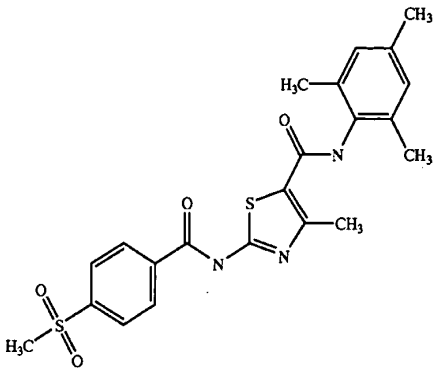
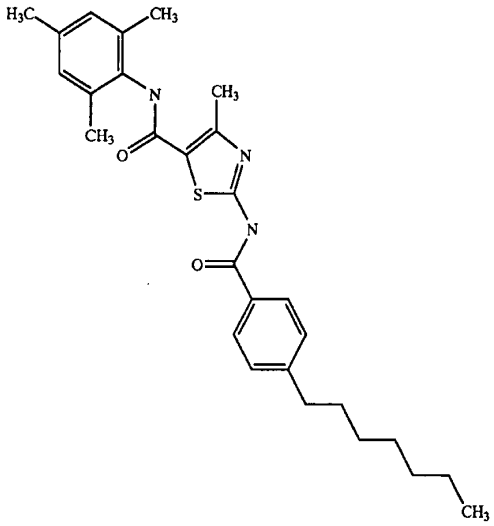
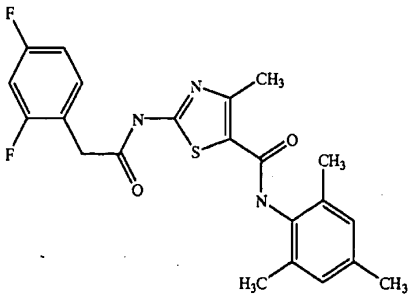
EX. No.	Compound Structure	Compound Name	HPLC Ret Time (min)
93		4-Methyl-2-[[4-(methyl-sulfonyl)-benzoyl]-amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	3.79
94		2-[(4-Heptylbenzoyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	
95		2-[[(2,4-Difluoro-phenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.15

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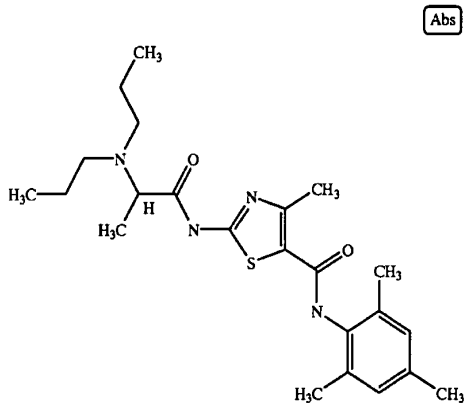
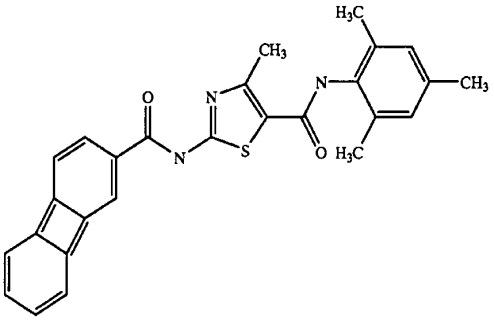
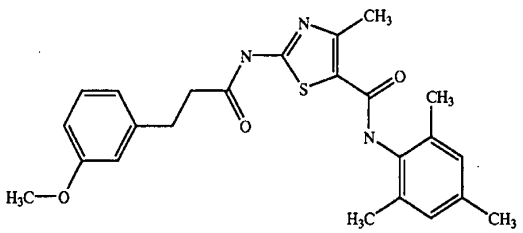
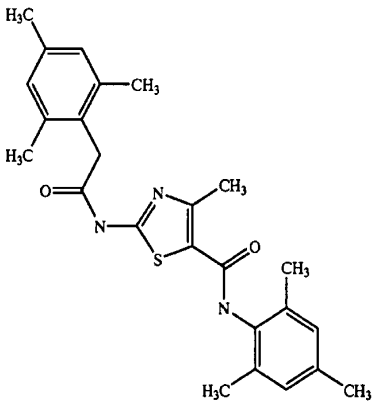
EX. No.	Compound Structure	Compound Name	HPLC Ret Time (min)
96		(S)-2-[[2-(Dipropylamino)-1-oxopropyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.20
97		2-[(2-Biphenyl-enecarbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.64
98		2-[[3-(3-Methoxyphenyl)-1-oxopropyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.26
99		4-Methyl-N-(2,4,6-trimethylphenyl)-2-[[(2,4,6-trimethyl-phenyl)acetyl]amino]-5-thiazolecarboxamide	4.52

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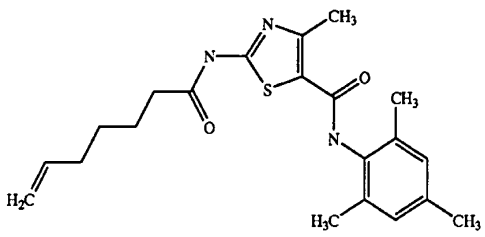
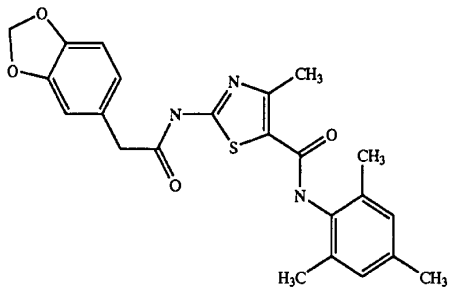
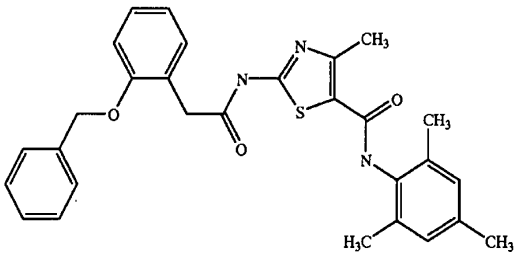
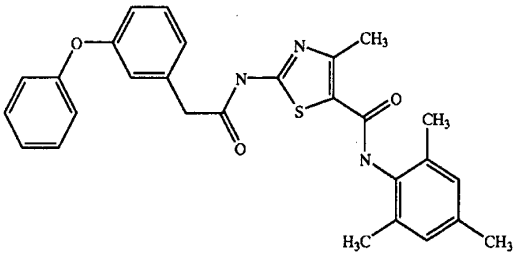
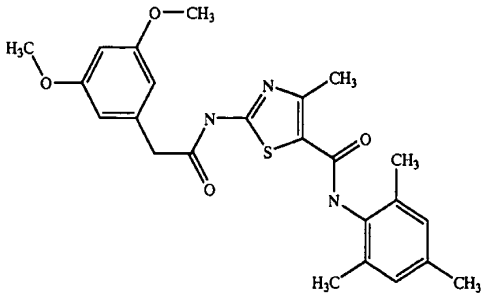
EX. No.	Compound Structure	Compound Name	HPLC Ret Time (min)
100		4-Methyl-2-[(1-oxo-6-heptenyl)amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.47
101		2-[[(1,3-Benzodioxol-5-yl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.07
102		4-Methyl-2-[[[2-(phenylmethoxy)phenyl] 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

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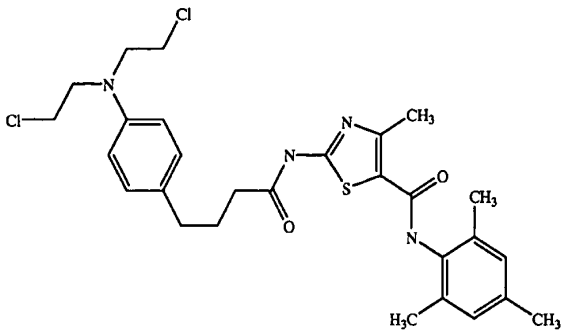
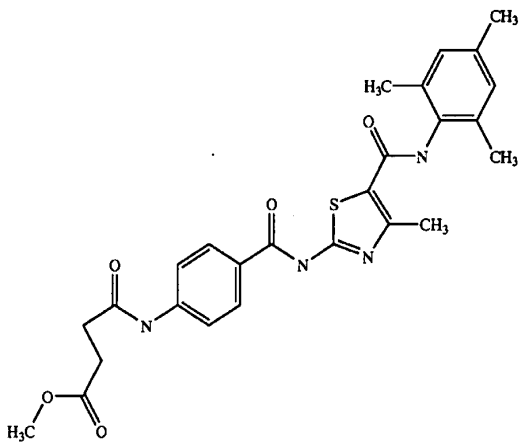
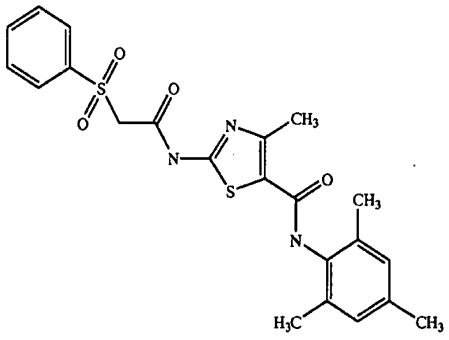
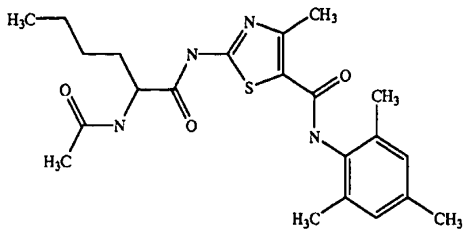
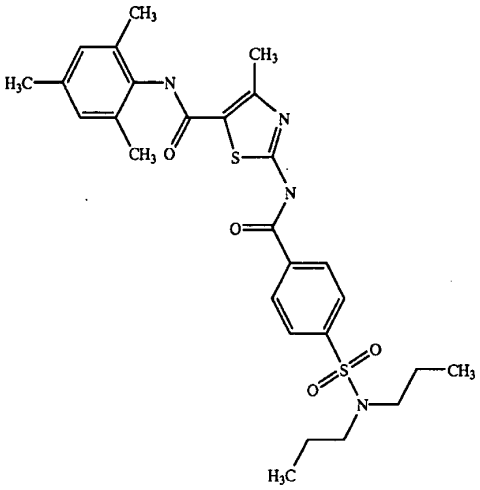
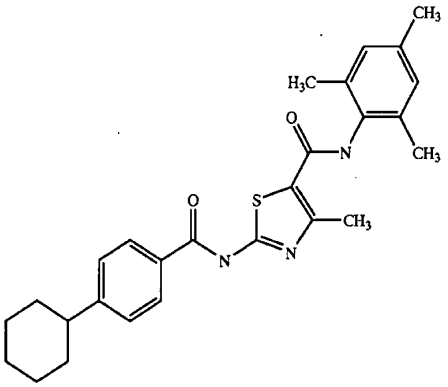
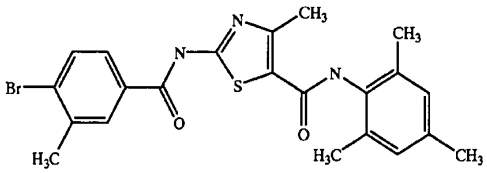
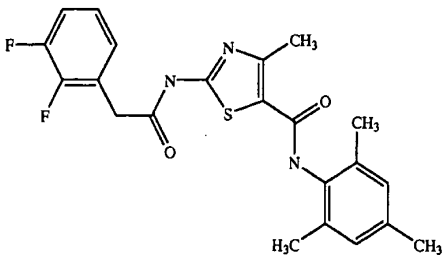
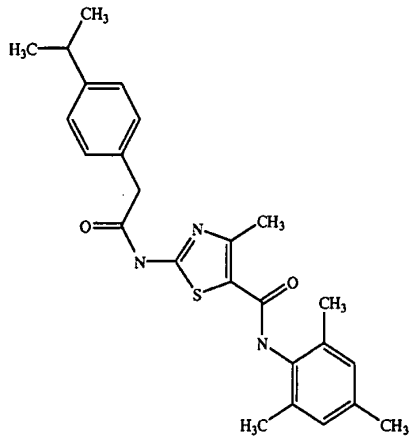
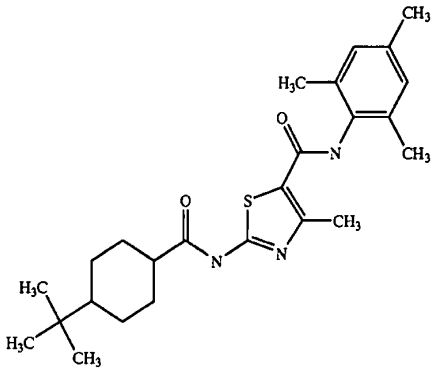
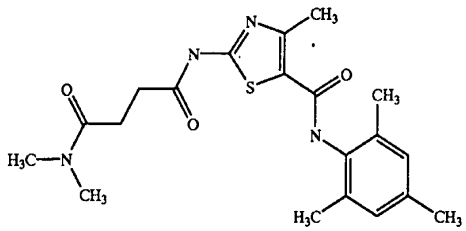
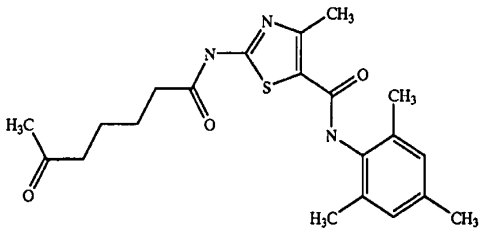
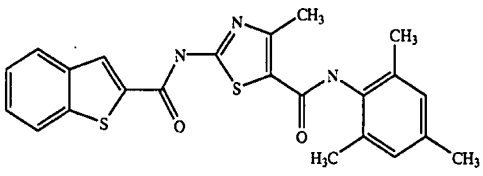
EX. No.	Compound Structure	Compound Name	HPLC Ret Time (min)
105		2-[[4-[4-[Bis(2-chloroethyl)amino]phenyl]-1-oxobutyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.75
106		4-[[4-[[[4-methyl-5-[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-amino]-carbonyl]phenyl]-amino]-4-oxobutanoic 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

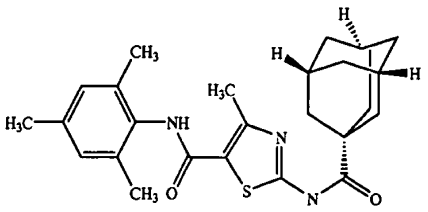
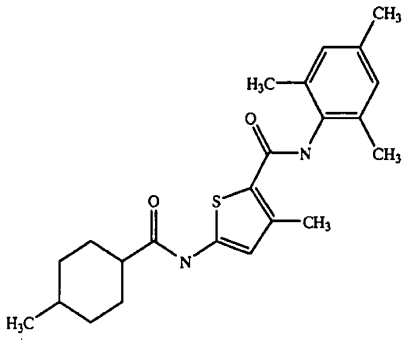
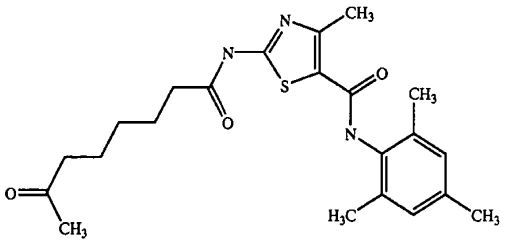
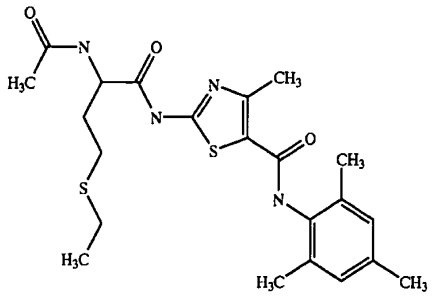
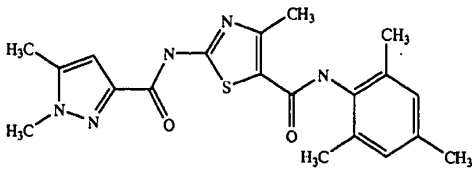
-continued

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

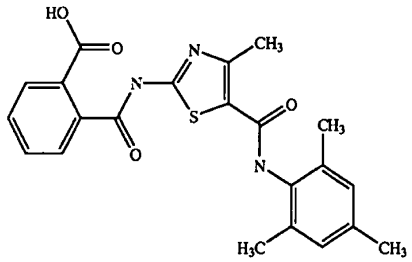
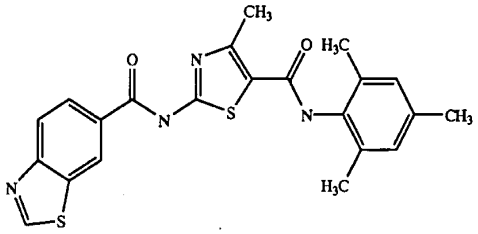
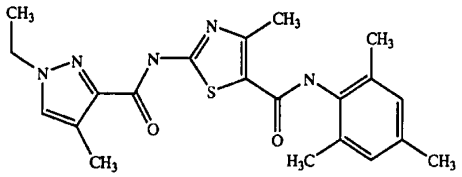
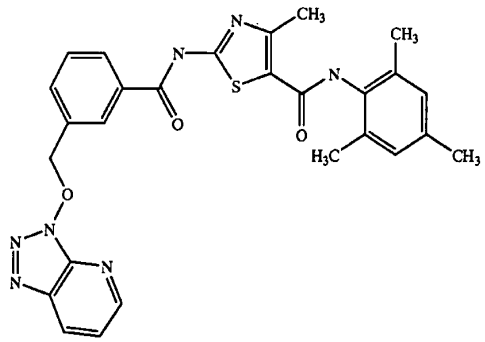
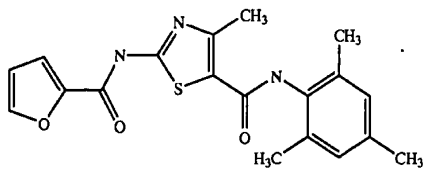
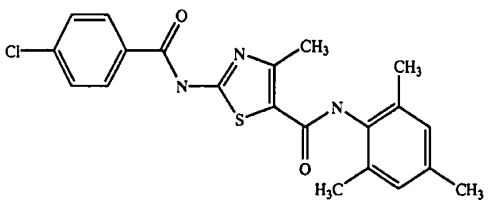
-continued

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

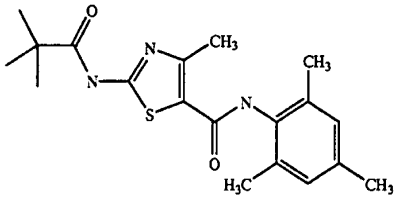
-continued

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

-continued

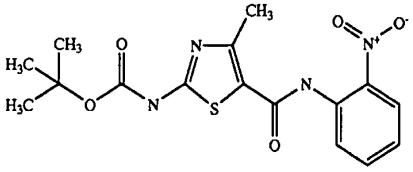
EX. No.	Compound Structure	Compound Name	HPLC Ret Time (min)
123		2-[[[4-methyl-5-(2,4,6-trimethylphenyl)amino] carbonyl]-2-thiazolyl]amino]carbonyl] benzoic acid	3.70
124		N-[4-Methyl-5-[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-6-benzo-thiazolecarboxamide	4.18
125		1-Ethyl-4-methyl-N-[4-methyl-5-[[(2,4,6-trimethylphenyl)-amino]carbonyl]-2-thiazolyl]-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

-continued

EX. No.	Compound Structure	Compound Name	HPLC Ret Time (min)
129		2-[(2,2-Dimethyl-1-oxopropyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.30

EXAMPLE 130

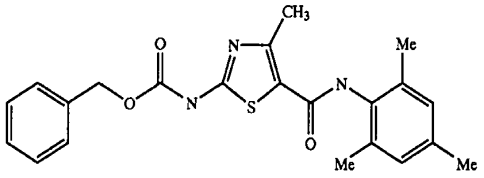
Preparation of [4-Methyl-5[[(2-nitrophenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



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



A. 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

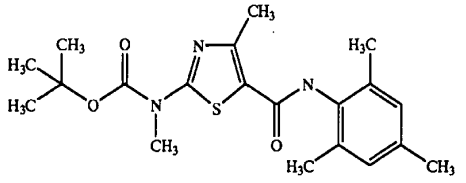
Compound 131B was prepared by an analogous method as that of 3B, except using 131A to give the title compound 131B as a white powder (77%).

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 (3×), 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

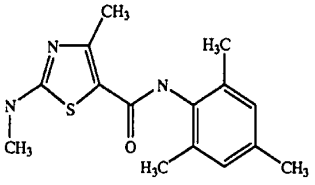
Preparation of Methyl[4-methyl-5-[[2,4,6-trimethylphenyl)amino] carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



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

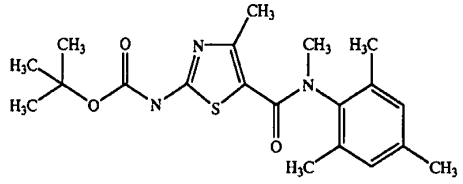
Preparation of 4-Methyl-2-(methylamino)-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

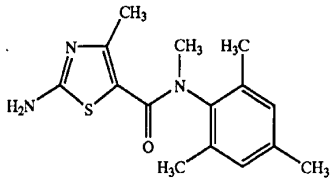
Preparation of [4-Methyl-5-[[methyl(2,4,6-trimethylphenyl)amino] carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



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

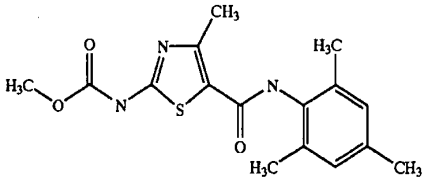
Preparation of 2-Amino-N,4-dimethyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

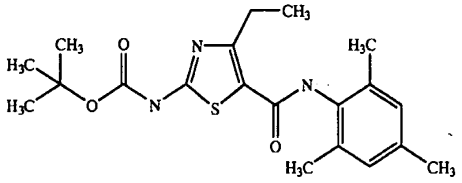
Preparation of [4-Methyl-5[[2,4,6-trimethylphenyl)amino] carbonyl]-2-thiazolyl]carbamic acid, methyl ester



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, 2×), 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

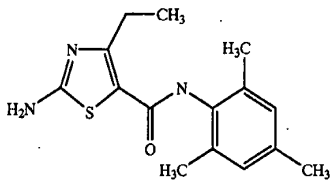
Preparation of [4-Ethyl-5[[2,4,6-trimethylphenyl)amino] carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



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

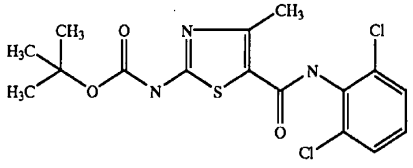
Preparation of 2-Amino-4-ethyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide, trifluoroacetate



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

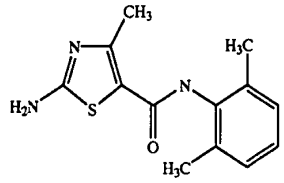
Preparation of [5-[[2,6-Dichlorophenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester



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, 3×), 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

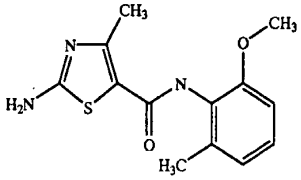
Preparation of 2-Amino-N-(2,6-dimethylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

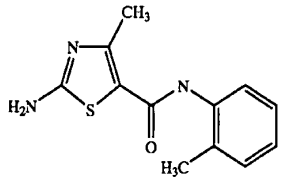
Preparation of 2-Amino-N-(2-methoxy-6-methylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

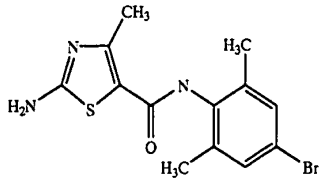
Preparation of 2-Amino-N-(2-methylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

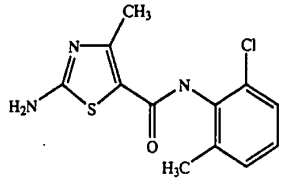
Preparation of 2-Amino-N-(2,6-dimethyl-4-bromophenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

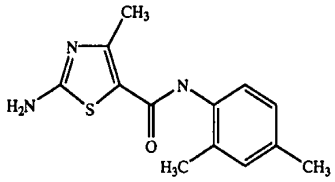
Preparation of 2-Amino-N-(2-chloro-6-methylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

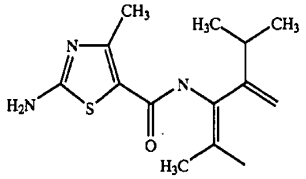
Preparation of 2-Amino-N-(2,4-dimethylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

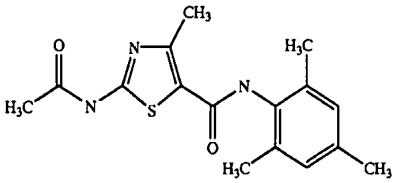
Preparation of 2-Amino-N-(2-methyl-6-isopropylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)



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

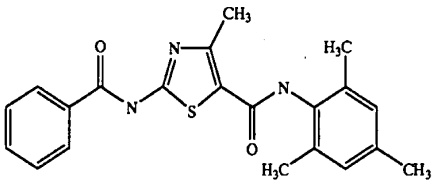


A mixture of 2 (54 mg, 0.2 mmol), acetic anhydride (22 μL, 0.23 mmol), dimethylaminopyridine (3 mg) in dichloromethane (4.5 mL) was stirred at rt for 4.5 h. The mixture was diluted with dichloromethane (65 mL) and washed with

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

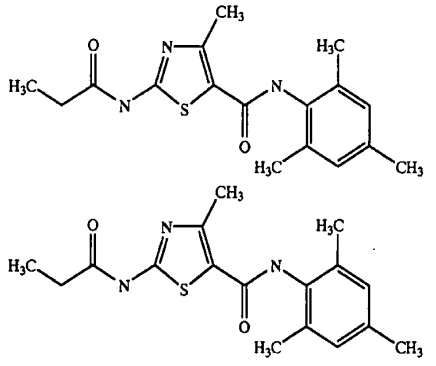
Preparation of 2-(Benzoylamino)-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



A solution of 2 (100 mg, 0.36 mmol) and benzoic anhydride (226 mg, 1 mmol) in dichioromethane (10 mL) and pyridine (2 mL) was stirred at rt overnight. The mixture was diluted with dichioromethane (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% Et()Ac in hexanes followed by 50%o 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

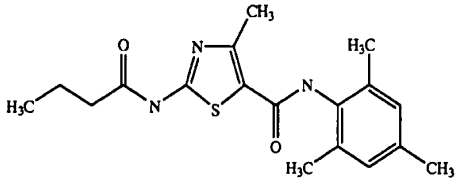
Preparation of 4-methyl-2-[(1-oxopropyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



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

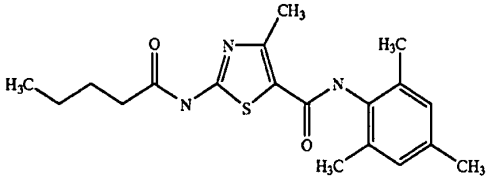
Preparation of 4-methyl-2-[(1-oxobutyll)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



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

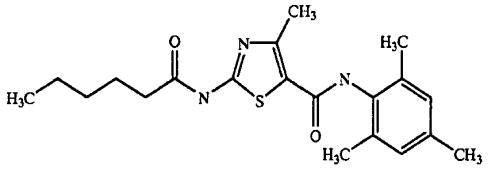
Preparation of 4-methyl-2-[(1-oxopentyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



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

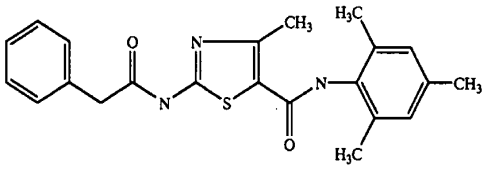
Preparation of 4-methyl-2-[(1-oxohexyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide



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

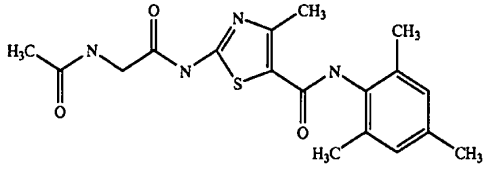


A solution of amine 2 (50 mg, 0.18 mmol), diisopropylethylamine (101 μL, 0.58 mmol), phenylacetic acid (27.2 mg, 0.20 mmol), 1-hydroxy-7-azabenzotriazole (29.4 mg, 0.22 mmol), and ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (42.2 mg, 0.22 mmol) in dichlo-

romethane (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

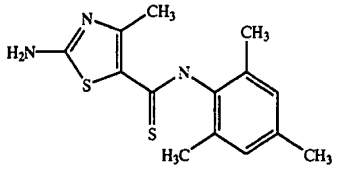
Preparation of 2-[[(Acetylamino)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-6-thiazolecarboxamide



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

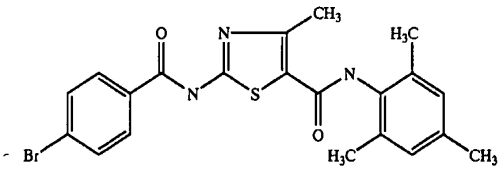
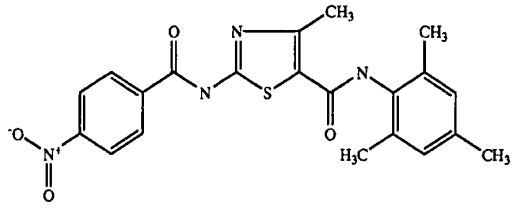


A suspension of 2 (50 mg, 0.18 mmol) and Lawesson reagent (44 mg, 0.11 mmol) in toluene (0.23 mL) was heated to 100° C. for 4h. Additional Lawesson reagent (44 mg, 0.11 mmol) was added and the mixture was heated for additional 3.5 h. The crude mixture was chromatographed on a silica gel column and eluted 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.

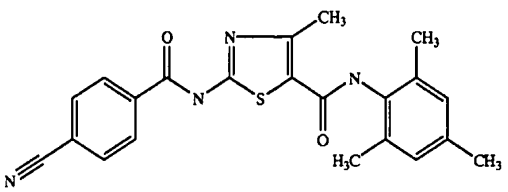
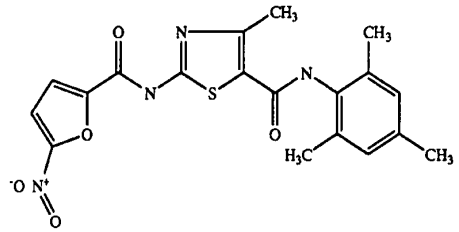
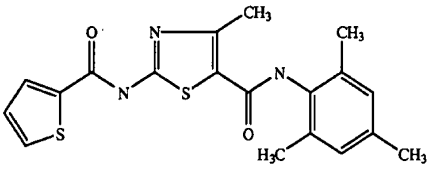
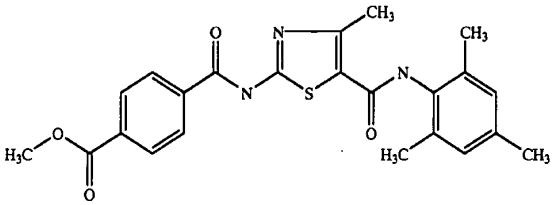
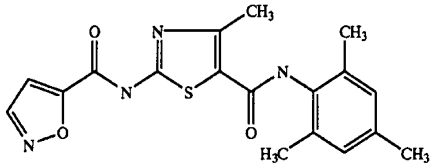
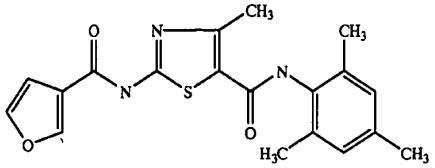
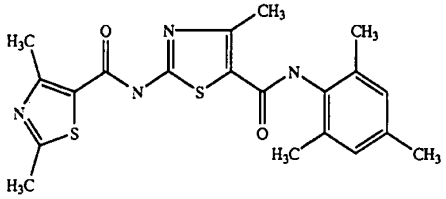
EXAMPLES 156 to 170

General Procedure

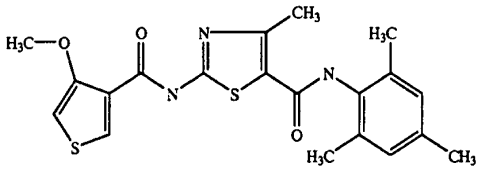
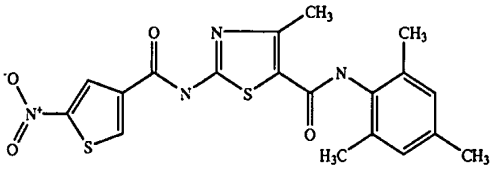
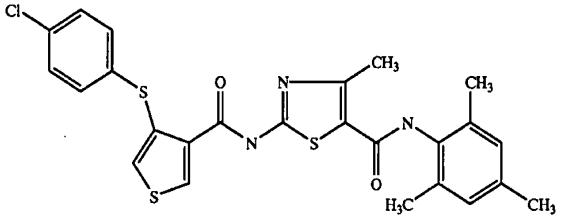
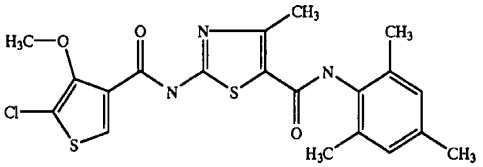
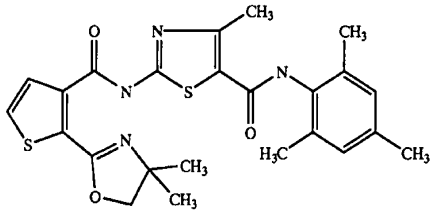
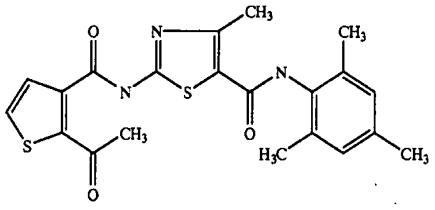
Compounds 156 to 170 were prepared following the procedure described below. Diisopropylethyl amine (60 μL, 0.34 mmol) was added to a mixture of amine 2 (30 mg, 0.11 mmol), appropriate carboxylic acid (0.13 mmol), 1-hydroxy-7-azabenzotriazole (19.5 mg, 0.14 mmol), and ethyl-3-(3-dimethylamino)-propyl 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 4.6x50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H_2O, 0.2% $H3PO_4$) 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

-continued

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

-continued

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

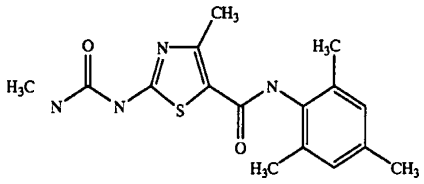
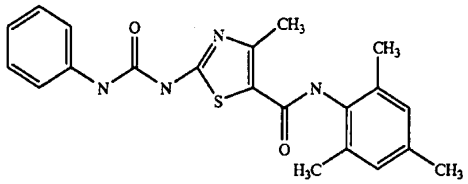
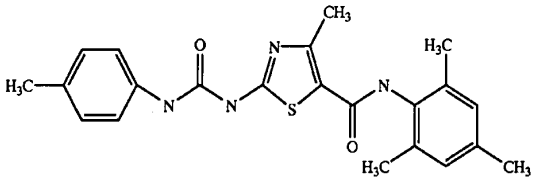
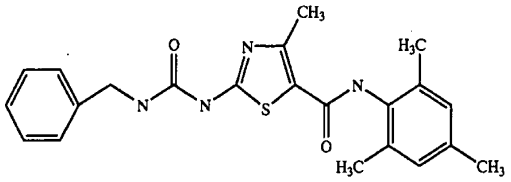
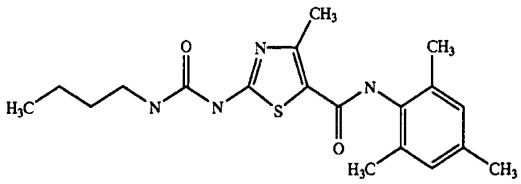
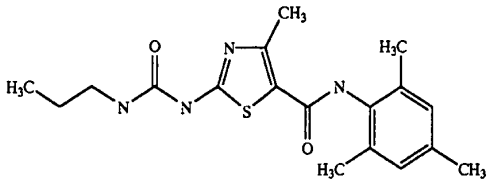
EXAMPLES 171 to 180

General Procedure

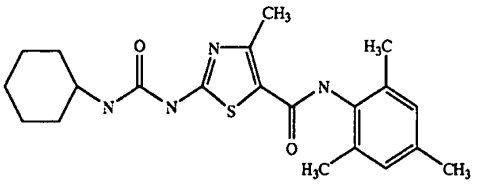
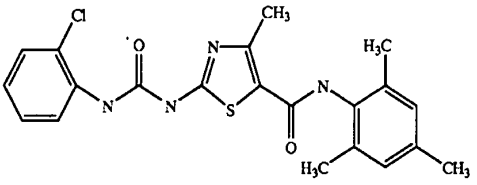
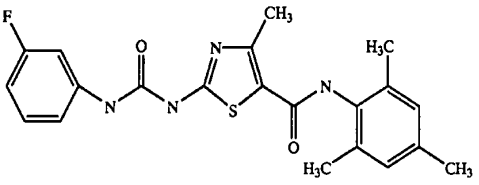
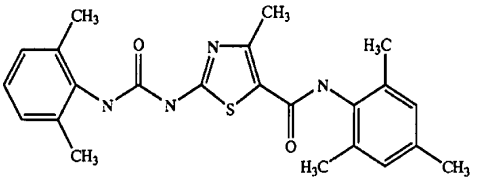
Compounds 171 to 180 were prepared following the procedure described below.

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 mmx7.5 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 mmx7.5 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.

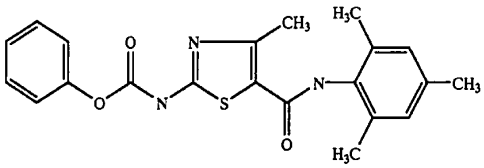
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
171		4-Methyl-2-[[(methylamino)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	24.48
172		4-Methyl-2-[[(phenylamino)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	30.45
173		4-Methyl-2-[[[(4-methylphenyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.81
174		4-Methyl-2-[[[(phenylmethyl)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

-continued

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



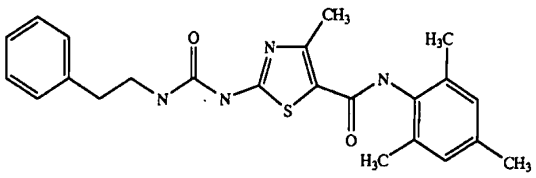
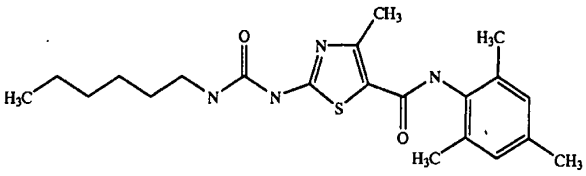
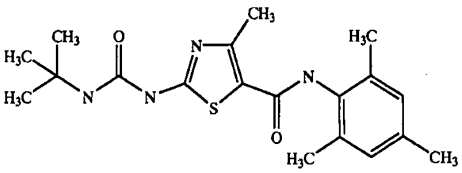
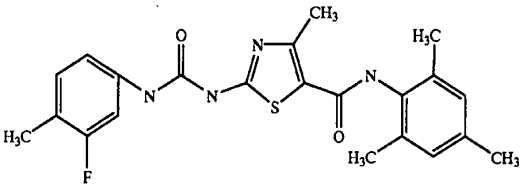
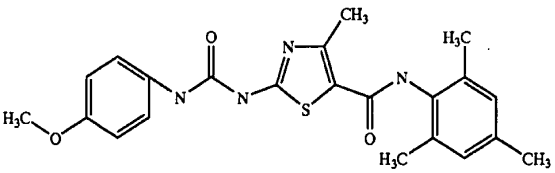
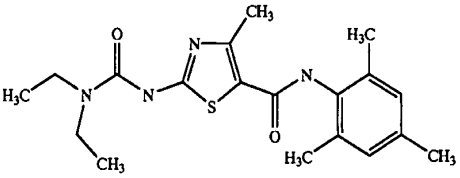
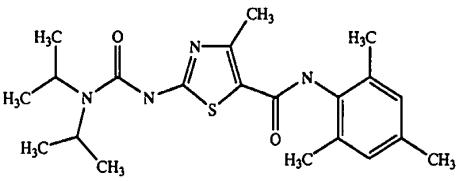
A 10% aq. $KHCO_3$ solution (170 mL) was added to a stirred solution of 2 (1.02 g, 3.7 mmol) in THF (130 mL). Phenylchloroformate (1.39 mL, 11.1 mmol) was added dropwise. The biphasic mixture was stirred at rt overnight, diluted with dichloromethane (200 mL) and washed with water (50 mL, 2×) and brine. 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.

EXAMPLE 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, 2×), 1 N aq. NaOH solution (1.5 mL, 2×). 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×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 4.6×50 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)
182		4-Methyl-2-[[[(2-phenylethyl)amino]-carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.83
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
185		2-[[[(3-Fluoro-4-methylphenyl) amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.92
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

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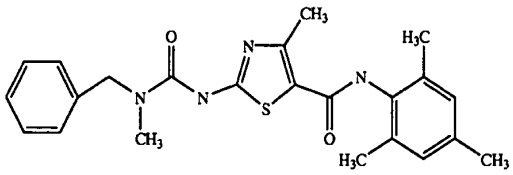
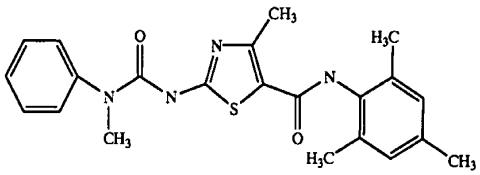
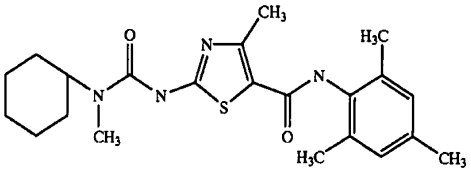
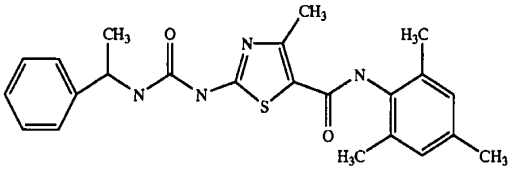
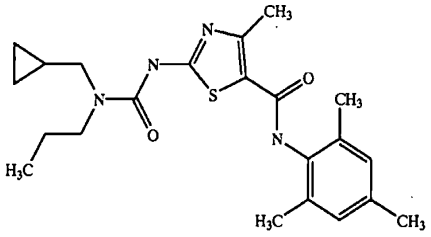
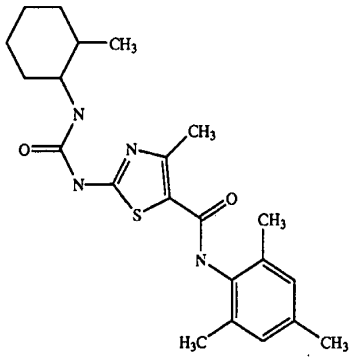
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
189		4-Methyl-2-[[[methyl-(phenylmethyl) amino]-carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.56
190		4-Methyl-2-[[(methyl-phenylamino)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.39
191		2-[[(Cyclohexylmethyl 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

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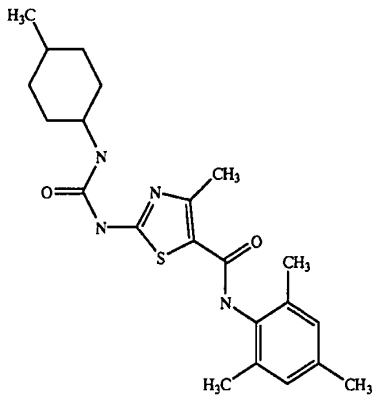
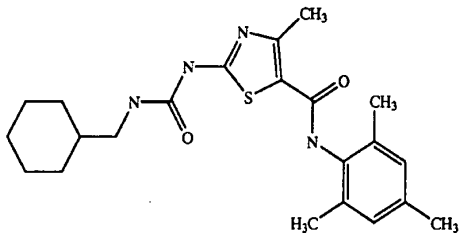
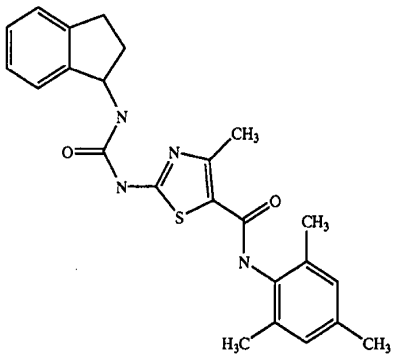
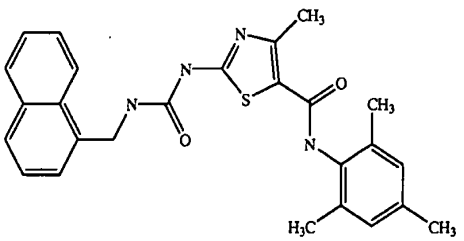
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
195		4-Methyl-2-[[[(4-methylcyclohexyl)-amino]carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.49
196		2-[[(Cyclohexyl-methyl)amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.49
197		2-[[[(2,3-Dihydro-1H-inden-1-yl)amino] 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

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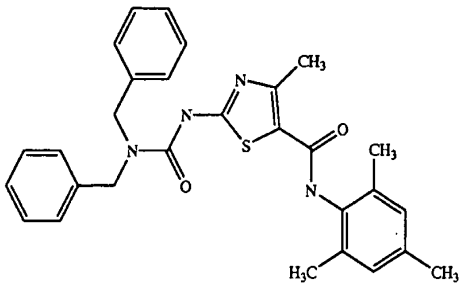
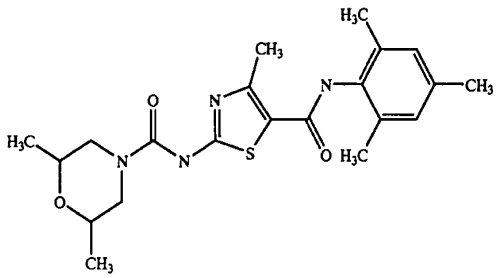
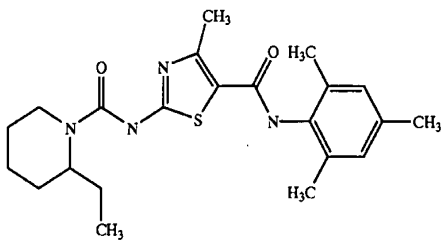
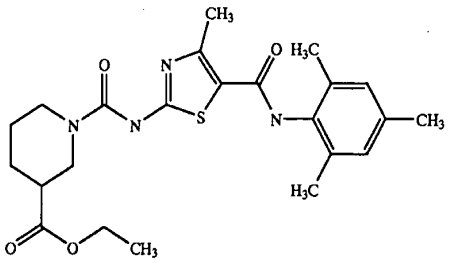
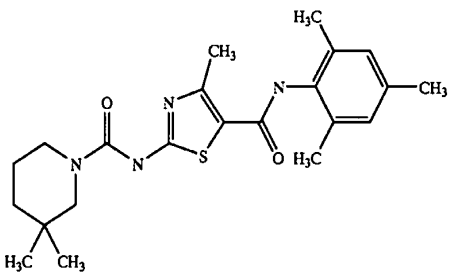
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
199		2-[[[Bis(phenylmethyl)amino]carbonyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.66
200		2,6-Dimethyl-N-[4-methyl-5-[[(2,4,6-trimethylphenyl)-amino]carbonyl]-2-thiazolyl]-4-morpholinecarboxamide	3.97
201		2-Ethyl-N-[4-methyl-5-[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-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

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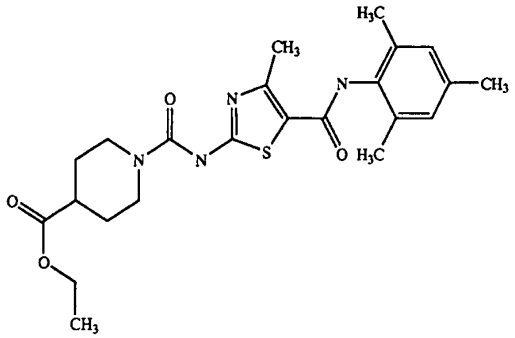
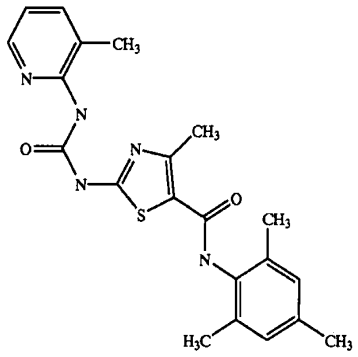
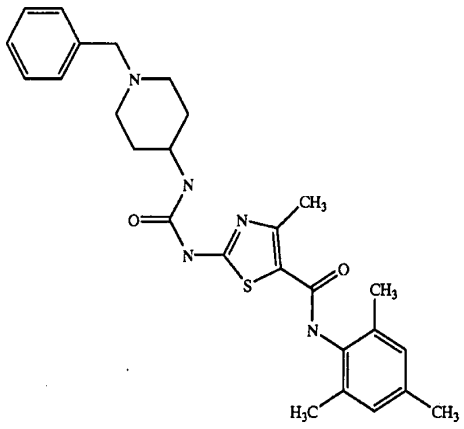
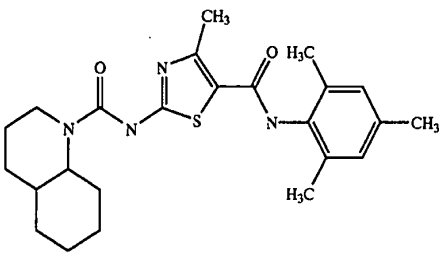
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
204		1-[[[4-Methyl-5-[[(2,4,6-trimethyl-phenyl)amino]carbonyl]-2-thiazolyl]-amino]carbonyl]-4-piperidinecarboxylic acid ethyl ester	4.06
205		4-Methyl-2-[[[(3-methyl-2-pyridinyl)-amino]carbonyl]-amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazolecarboxamide	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)-quinolinecar-boxamide	4.55

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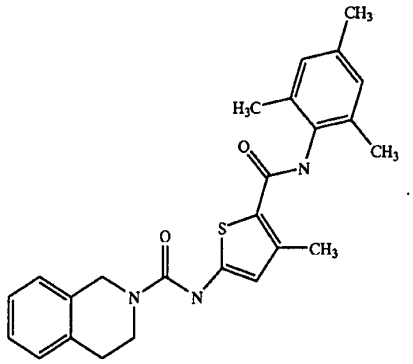
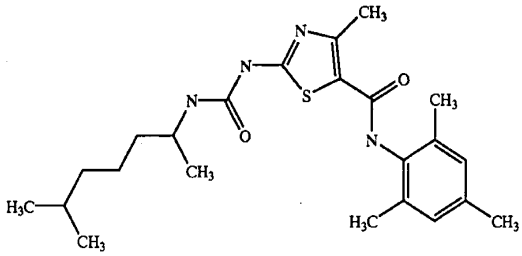
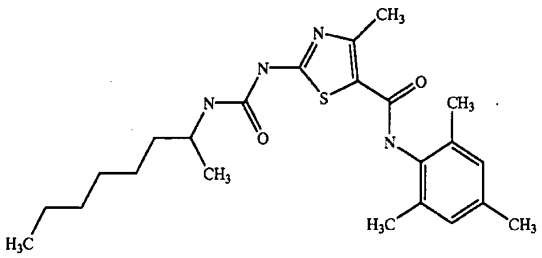
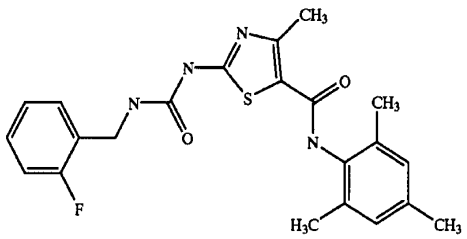
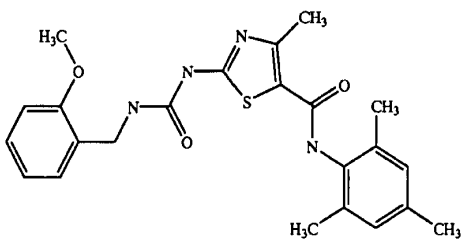
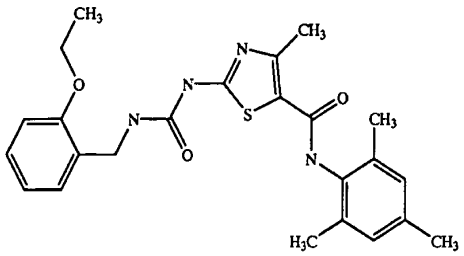
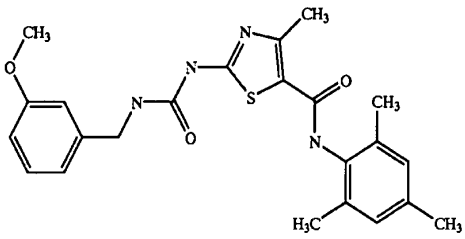
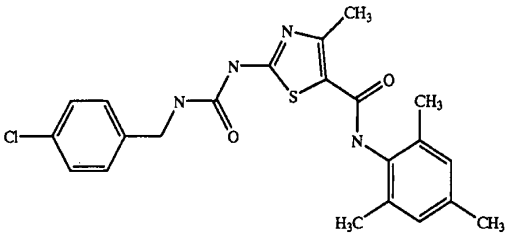
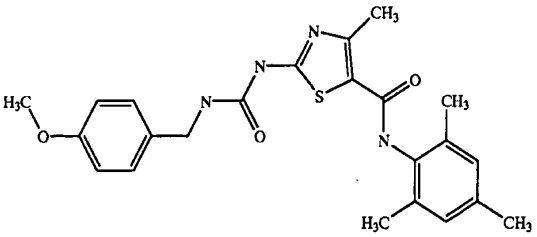
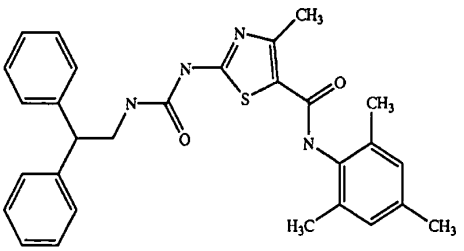
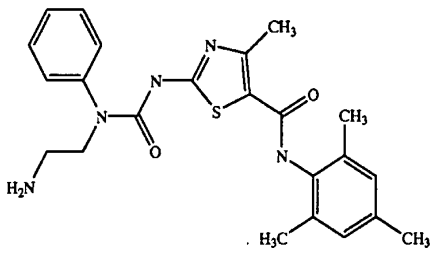
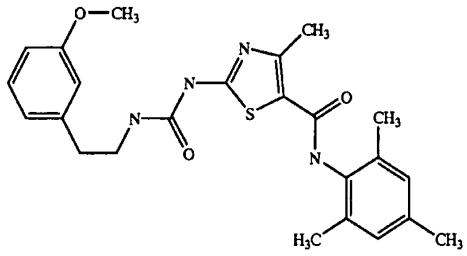
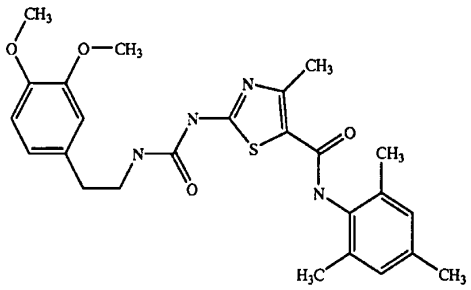
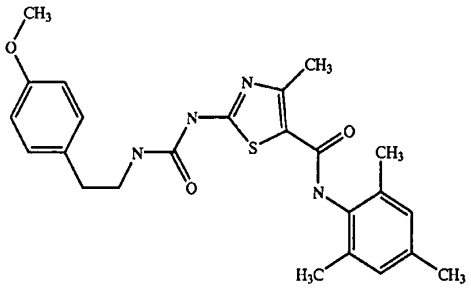
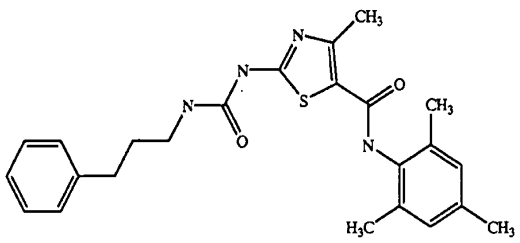
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
208		3,4-Dihydro-N-[4-methyl-5-[[(2,4,6-trimethylphenyl)-amino]carbonyl]-2-thiazolyl]-2(1H)-isoquinoline carboxamide	4.35
209		2-[[[(1,5-Dimethyl-hexyl)amino] carbonyl]-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.72
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

-continued

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

-continued

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
218		2-[[[(2-Aminoethyl)phenylamino] carbonyl]-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	3.70
219		2-[[[[2-(3-Methoxy-phenyl)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-Methoxy-phenyl)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-trimethyl-phenyl)-5-thiazole-carboxamide	4.40

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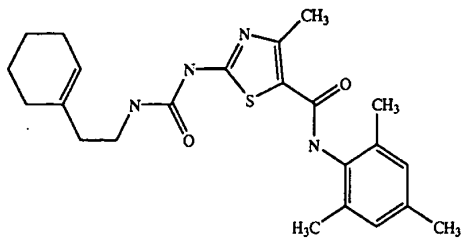
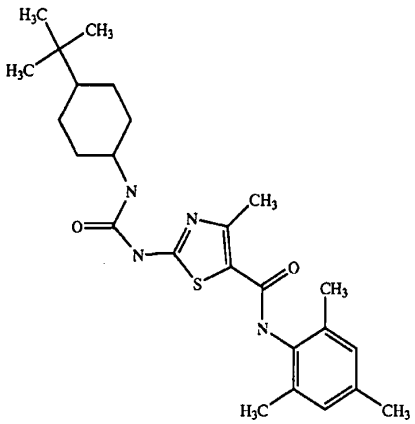
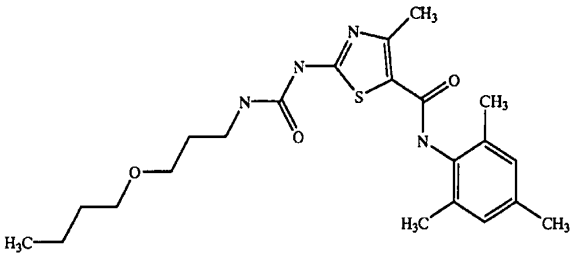
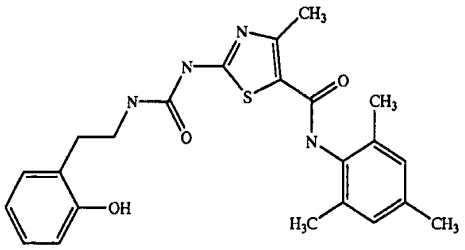
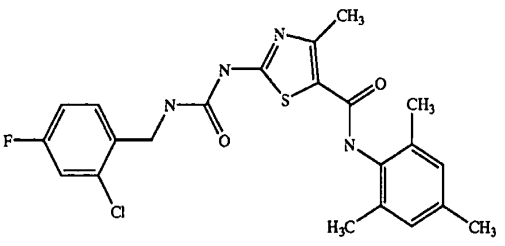
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
223		2-[[[[2-(Cyclohex-1-en-1-yl)ethyl]-amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.11
224		2-[[[[4-(1,1-Dimethylethyl)cyclo-hexyl]amino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	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

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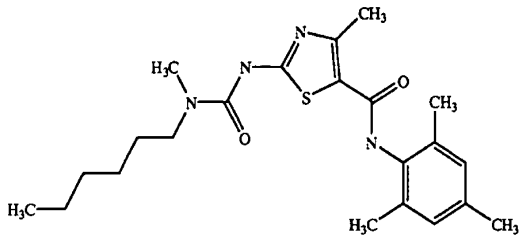
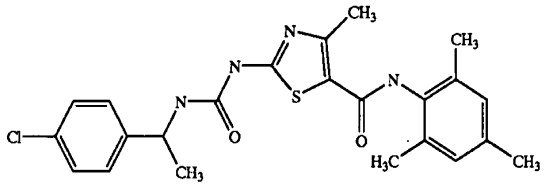
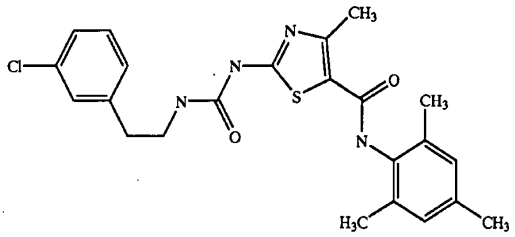
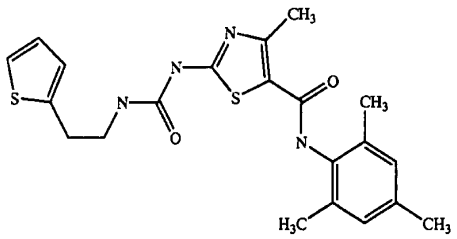
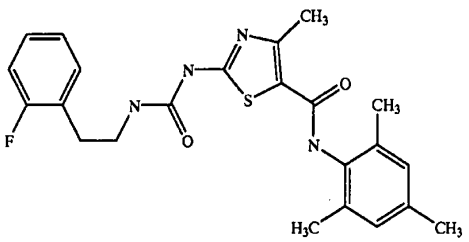
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
228		2-[[(Hexylmethylamino)carbonyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.65
229		2-[[[[1-(4-Chloro-phenyl)ethyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.42
230		2-[[[[2-(3-Chloro-phenyl)ethyl]amino] 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

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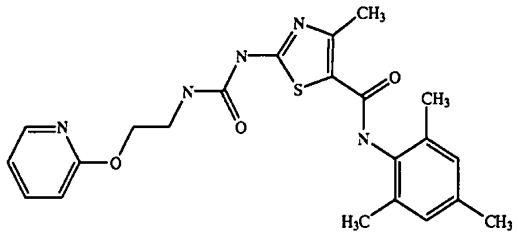
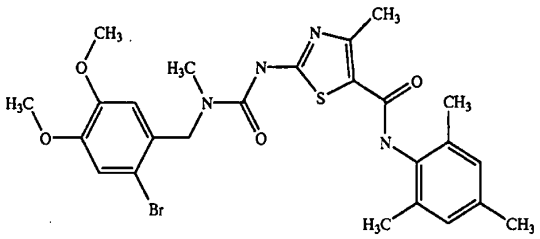
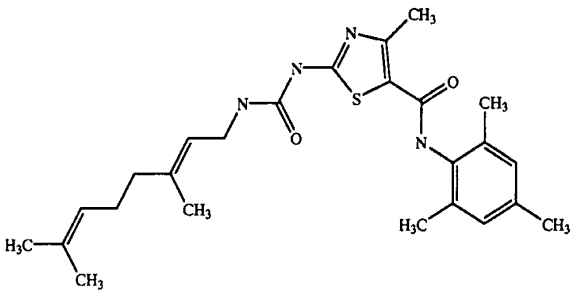
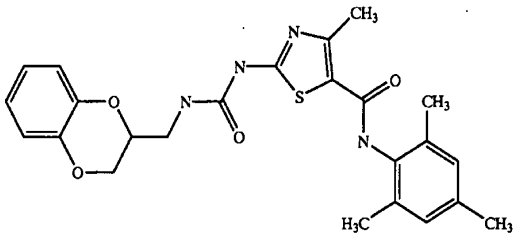
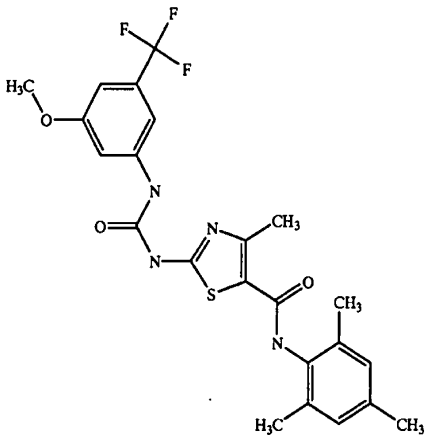
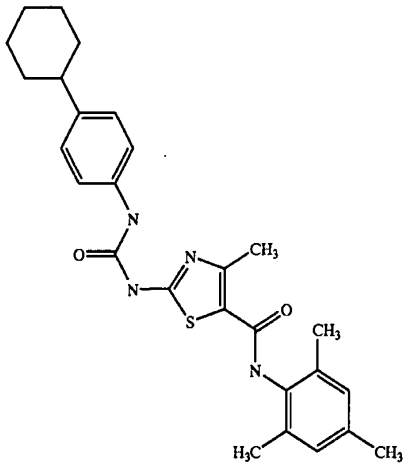
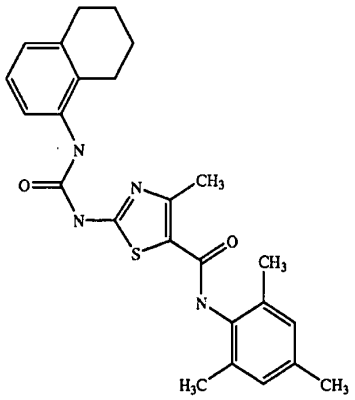
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
233		4-Methyl-2-[[[[2-(2-pyridinyloxy)ethyl]-amino]carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.28
234		2-[[[[(2-Bromo-4,5-dimethoxyphenyl) methyl]methylamino]carbonyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.87
235		(E)-2-[[[(3,7-Dimethyl-2,6-octa-dienyl)amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.34
236		2-[[[[(2,3-Dihydro-1,4-benzodioxin-2-yl)methyl]amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.27

EXAMPLES 237 to 285

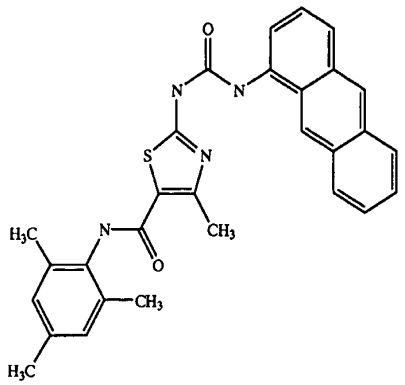
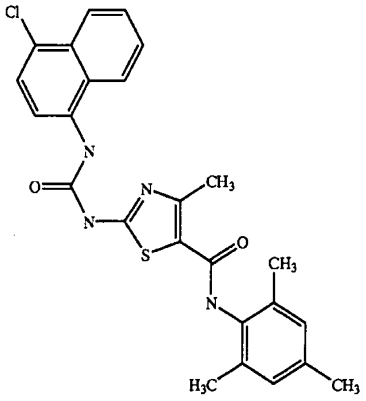
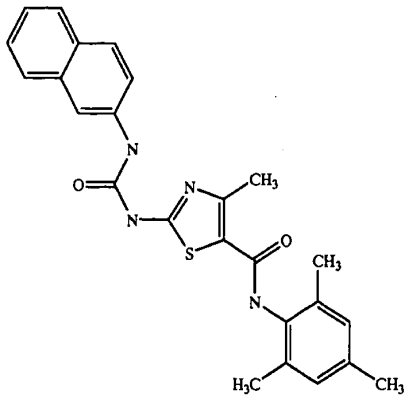
General Procedure

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

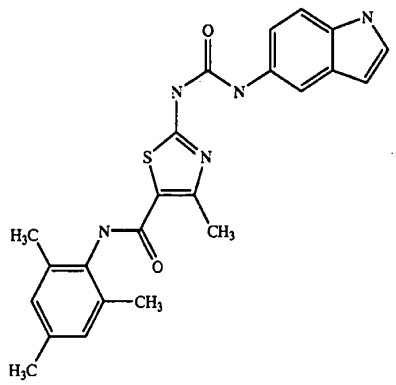
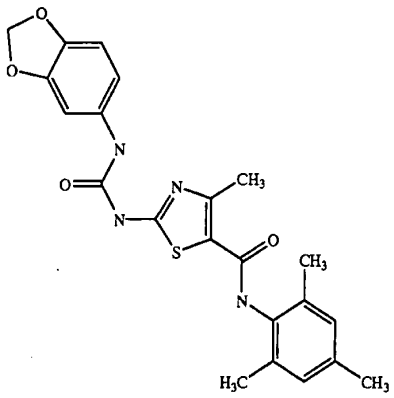
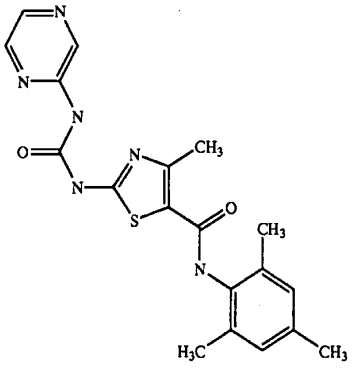
A solution of phenylcarbamate 181 (20 mg, 0.054 mmol) and the appropriate amine (0.08 mmol) in THF-acetonitrile (3 mL, 1:1) was stirred at rt overnight. The mixture was diluted with dichloromethane (4 mL) and washed with 1 N aq. HCl solution (1.5 mL, 2x), 1 N aq. NaOH solution (1.5 mL, 2x). The dichloromethane 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 4.6x50 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 mmx7.5 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

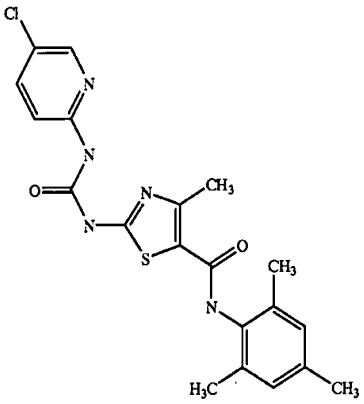
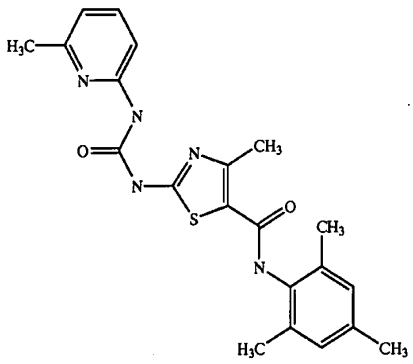
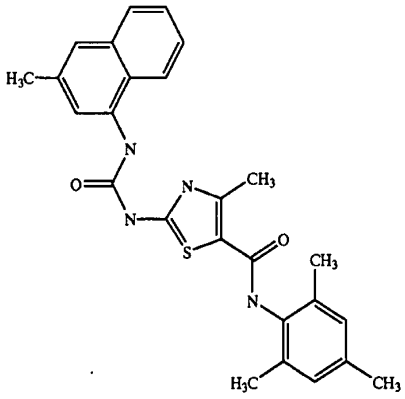
-continued

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

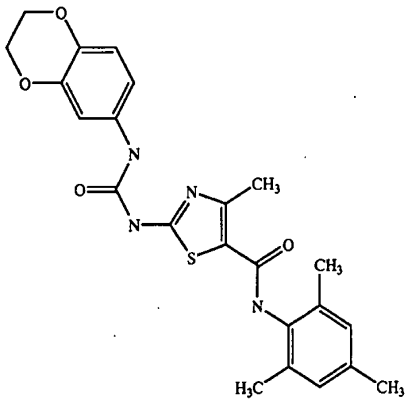
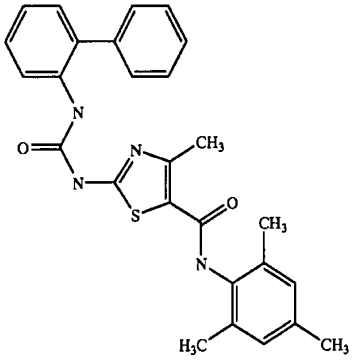
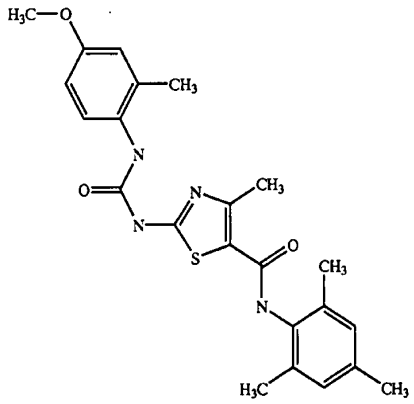
-continued

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

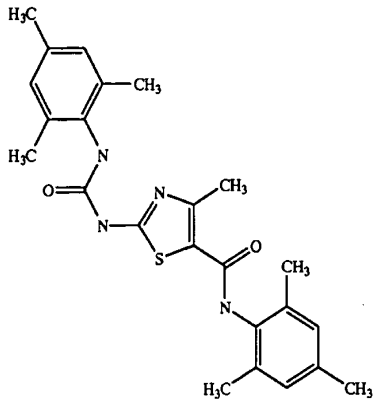
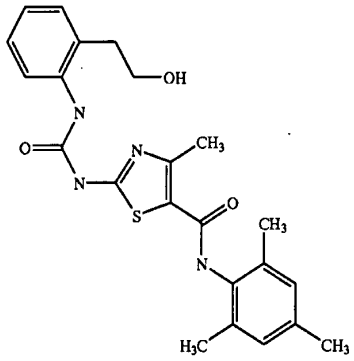
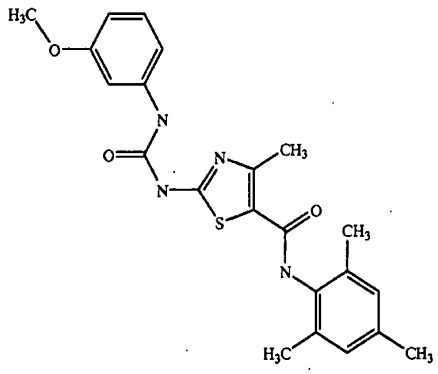
-continued

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

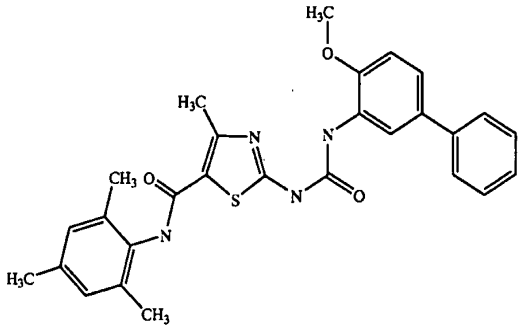
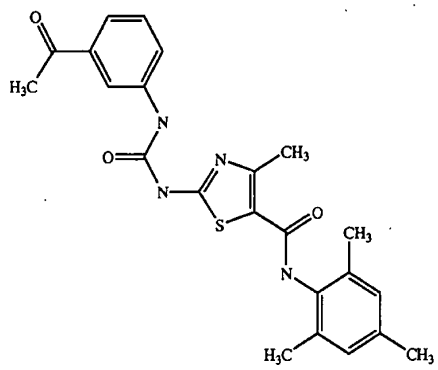
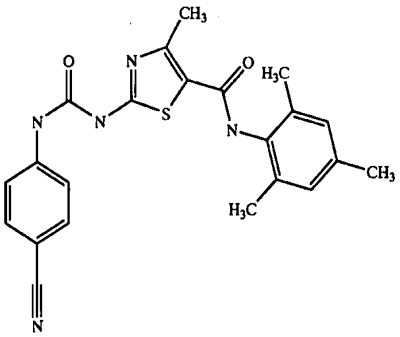
-continued

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

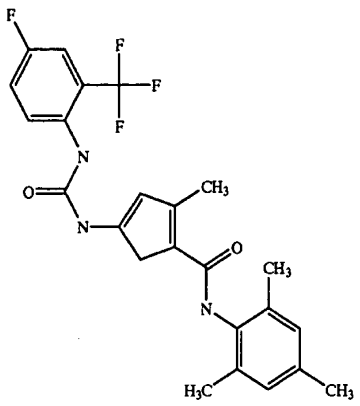
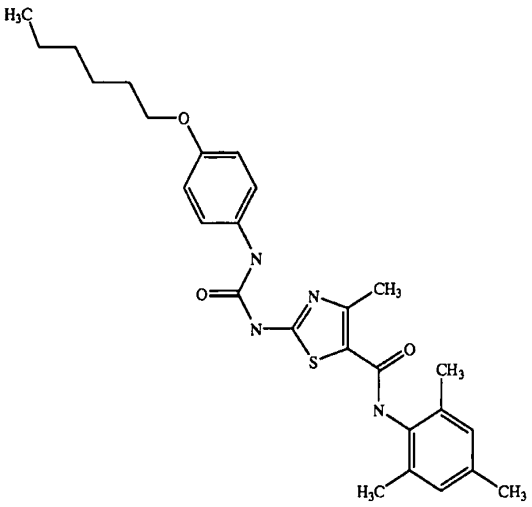
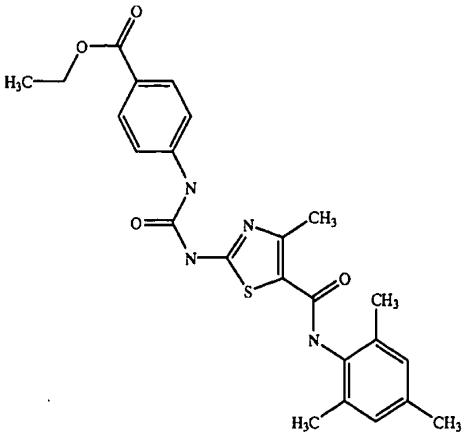
-continued

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
252		4-Methyl-N-(2,4,6-trimethylphenyl)-2-[[[(2,4,6-trimethylphenyl)amino]-carbonyl]amino]-5-thiazolecarboxamide	5.06
253		2-[[[[2-(2-Hydroxy-ethyl)phenyl]amino]car-bonyl]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

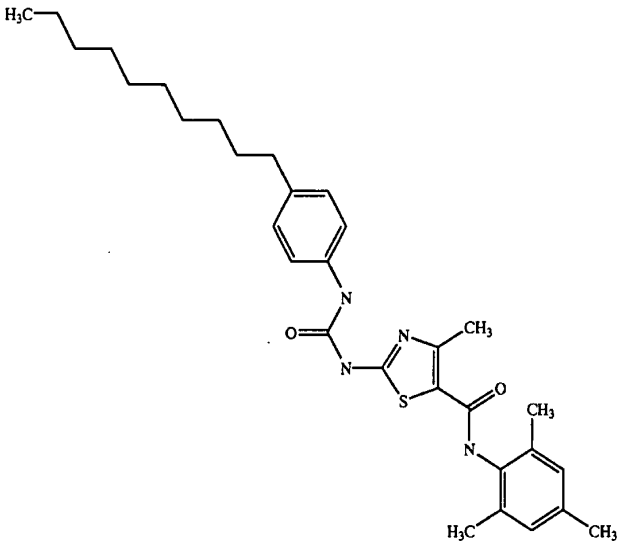
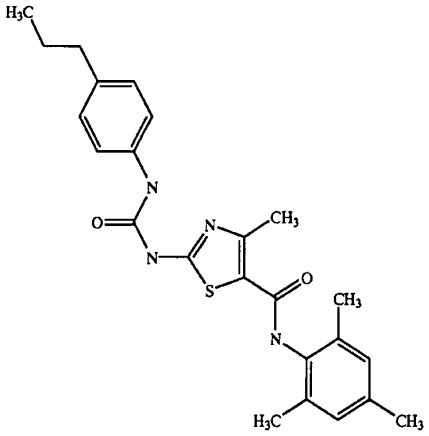
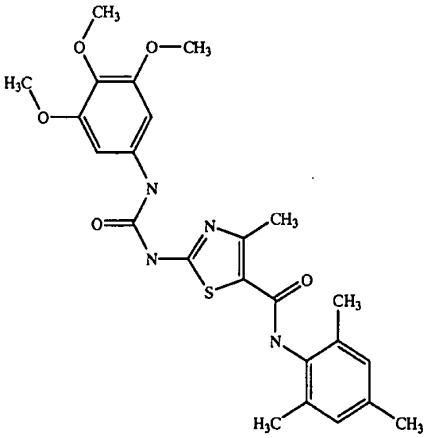
-continued

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

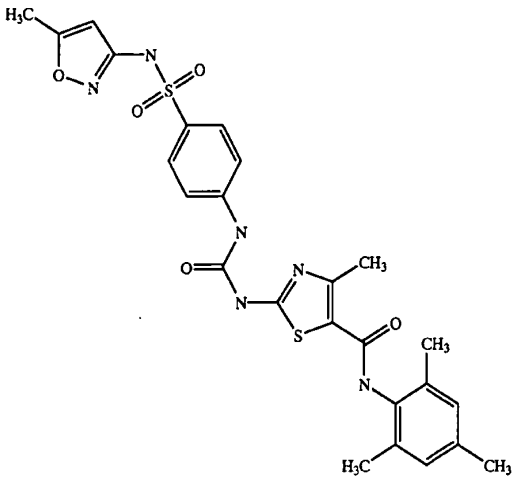
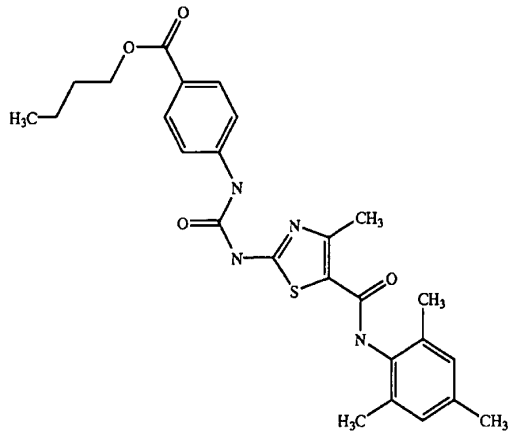
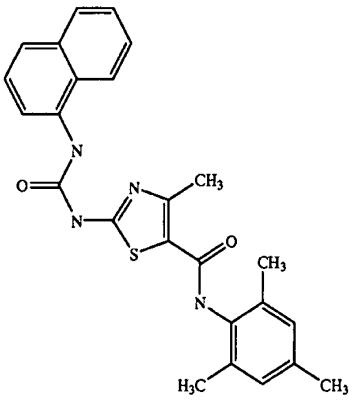
-continued

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

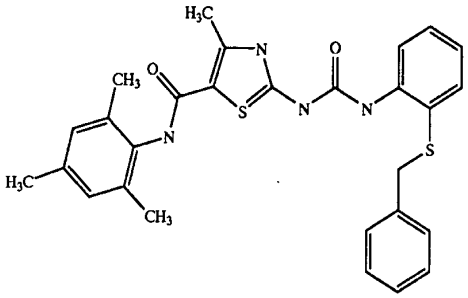
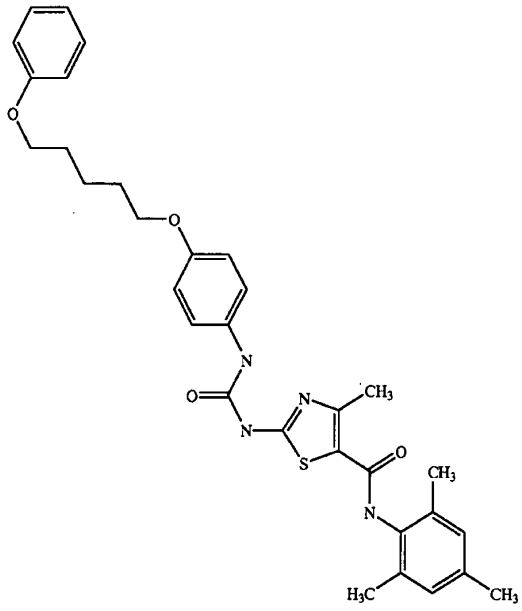
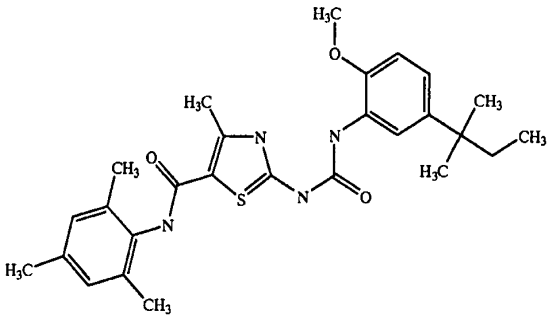
-continued

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

-continued

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

-continued

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

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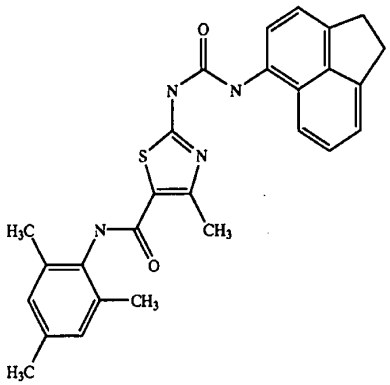
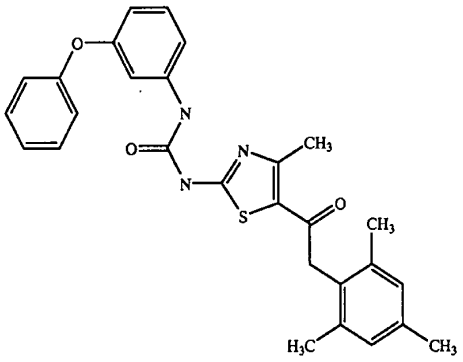
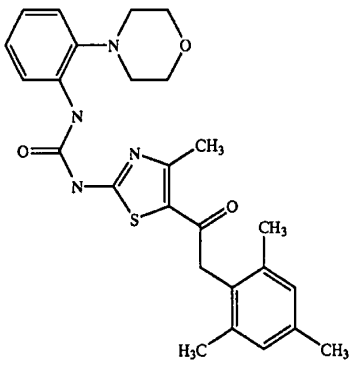
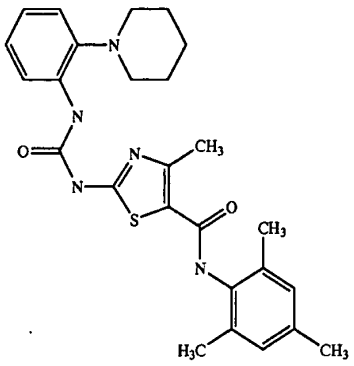
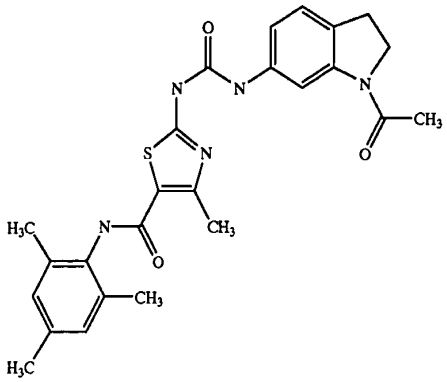
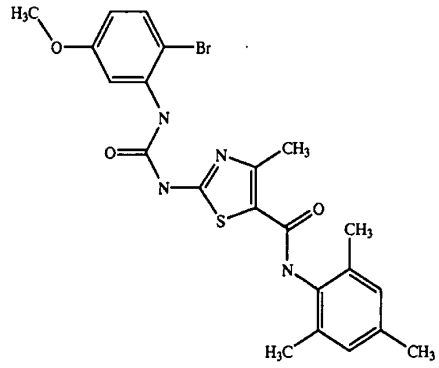
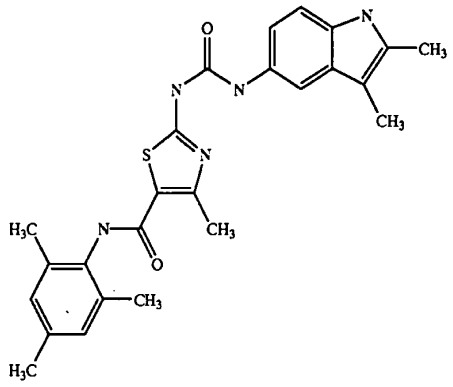
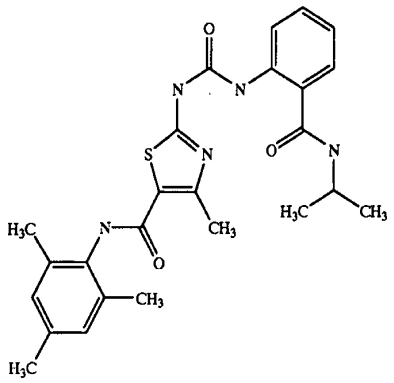
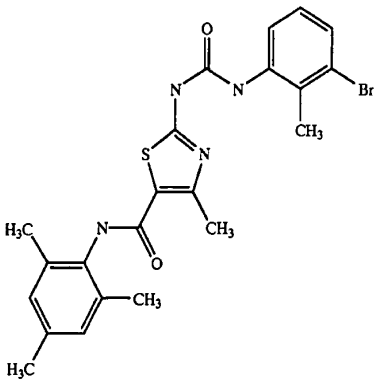
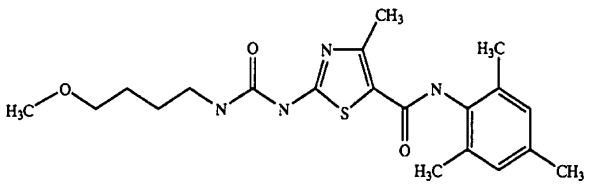
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
270		2-[[[(1,2-Dihydro-5-acenaphthylenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.70
271		4-Methyl-2-[[[(3-phenoxyphenyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.70
272		4-Methyl-2-[[[[2-(4-morpholinyl)phenyl]amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.01

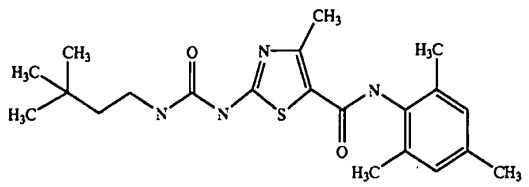
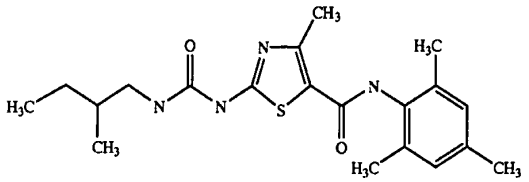
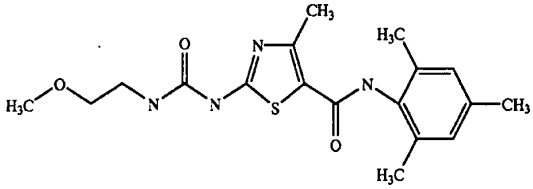
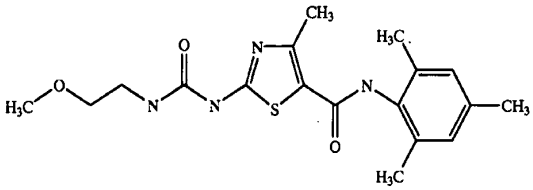
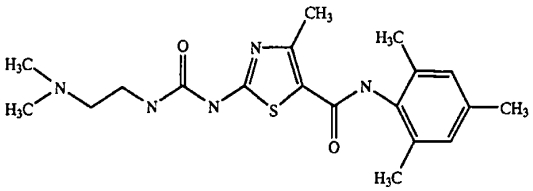
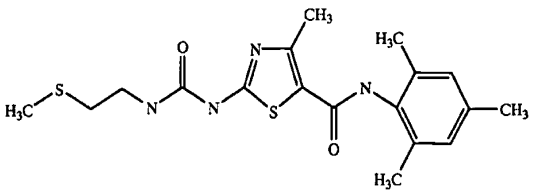
-continued

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

-continued

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

-continued

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
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]carbonyl]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-(Dimethylamino)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

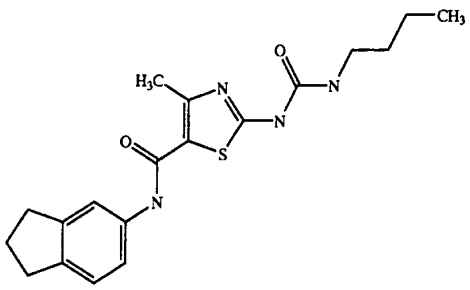
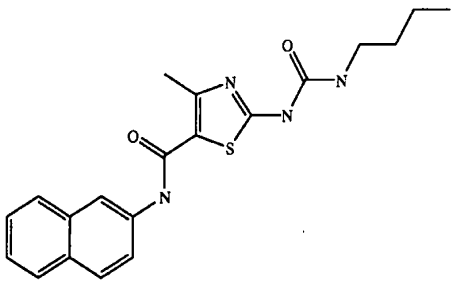
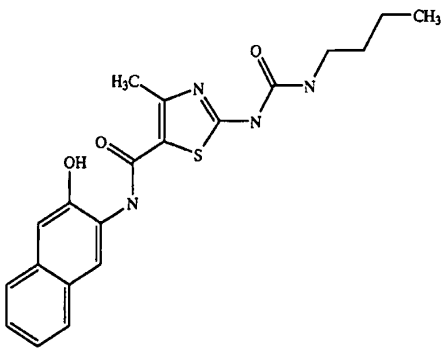
EXAMPLES 286 to 311

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 (3×). 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 20×100 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, 3×), 5% aq. $KHCO_3$ solution (6 mL, 3×), 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, 3×), satd. aq. $KHCO_3$ solution (3×), dried (Na_2SO_4), filtered and concentrated. The solid was washed with hexanes (2×) 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 4.6×50 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-naphthalenyl)-4-methyl-5-thiazolecarboxamide	4.24

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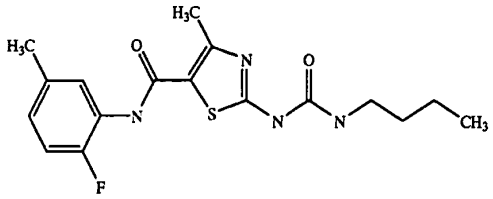
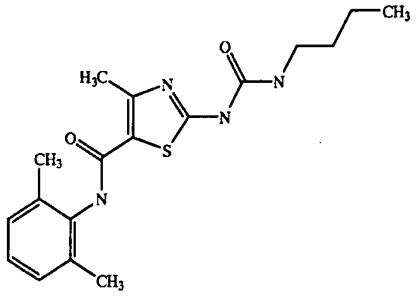
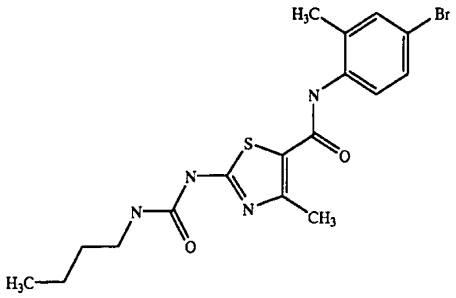
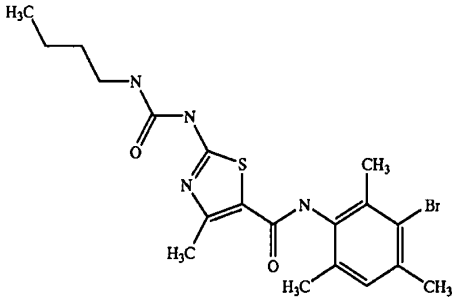
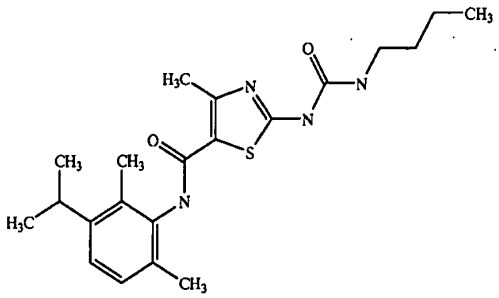
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
289		2-[[(Butylamino) carbonyl]amino]-N-(2-fluoro-5-methylphenyl)-4-methyl-5-thiazolecarboxamide	3.95
290		2-[[(Butylamino) carbonyl]amino]-N-(2,6-dimethylphenyl)-4-methyl-5-thiazole-carboxamide	3.78
291		N-(4-Bromo-2-methylphenyl)-2-[[(butylamino)carbonyl] 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

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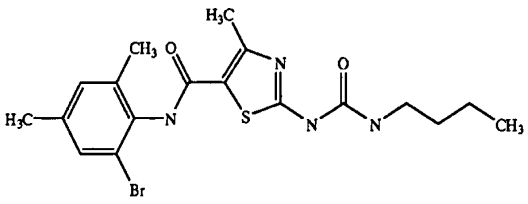
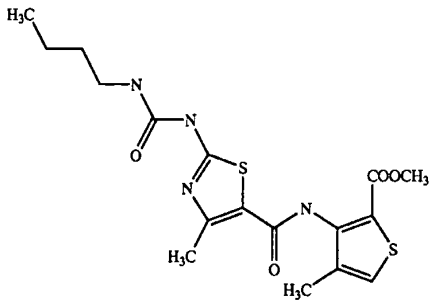
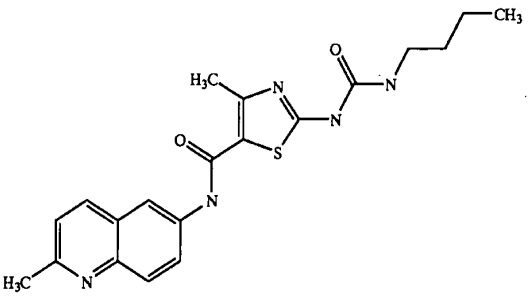
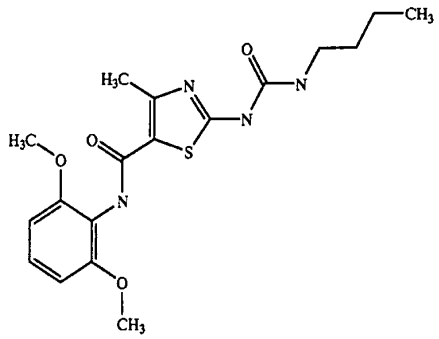
EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
294		N-(2-Bromo-4,6-dimethylphenyl)-2-[[(butylamino)carbonyl]amino]-4-methyl-5-thiazolecarboxamide	4.00
295		3-[[[2-[[(Butylamino)carbonyl]amino]-4-methyl-5-thiazolyl]-carbonyl]amino]-4-methyl-2-thiophene-carboxylic acid methyl ester	3.83
296		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