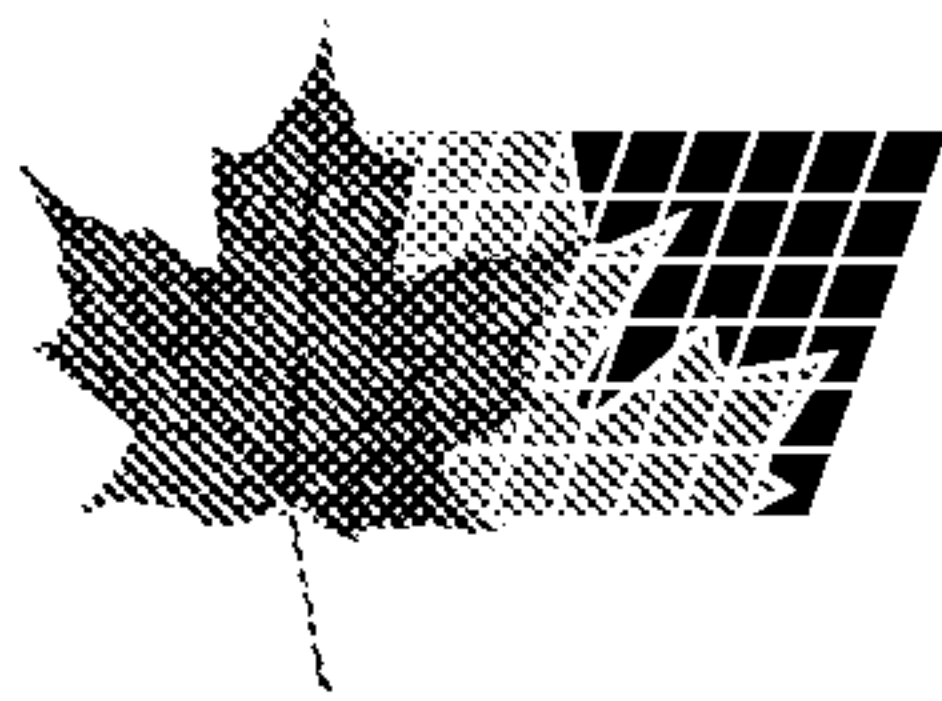




(72) MENDEL, DAVID, US

(71) ELI LILLY AND COMPANY, US

(51) Int.Cl.⁶ C07K 5/12, G01N 33/566, G01N 33/53, C07K 7/50, C12Q 1/00

(30) 1997/04/11 (60/043,532) US

(54) **ECHANTILLOTHEQUES COMBINATOIRES DE
MACROCYCLES PEPTIDOMIMETIQUES ET PROCEDES
CORRESPONDANTS**

(54) **COMBINATORIAL LIBRARIES OF PEPTIDOMIMETIC
MACROCYCLES AND PROCESSES THEREFOR**

(57) La présente invention concerne une échantillothèque diversifiée de composés macrocycliques peptidomimétiques, les procédés de préparation correspondants et un dispositif permettant de constituer une source facilement accessible de chacun des différents membres de l'échantillothèque. Ce dispositif convient à des nécessaires de dosage et comme élément remplaçable dans des machines à doser automatisées.

(57) The present invention relates to a novel diverse library of peptidomimetic macrocyclic compounds, processes for the preparation thereof, and to apparatus providing a readily accessible source of individual members of the library. The apparatus can be used in assay kits and as a replaceable element in automated assay machines.

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07K 5/12, 7/50, G01N 33/53, 33/566, C12Q 1/00	A1	(11) International Publication Number: WO 98/46631 (43) International Publication Date: 22 October 1998 (22.10.98)
(21) International Application Number: PCT/US98/07135 (22) International Filing Date: 8 April 1998 (08.04.98) (30) Priority Data: 60/043,532 11 April 1997 (11.04.97) US (71) Applicant (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indi- anapolis, IN 46285 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): MENDEL, David [US/US]; 11348 Woods Bay Lane, Indianapolis, IN 46236 (US). (74) Agents: COLLINS, Daniel, W. et al.; Eli Lilly and company, Lilly Corporate Center, Indianapolis, IN 46285 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: COMBINATORIAL LIBRARIES OF PEPTIDOMIMETIC MACROCYCLES AND PROCESSES THEREFOR (57) Abstract The present invention relates to a novel diverse library of peptidomimetic macrocyclic compounds, processes for the preparation thereof, and to apparatus providing a readily accessible source of individual members of the library. The apparatus can be used in assay kits and as a replaceable element in automated assay machines.		

-1-

COMBINATORIAL LIBRARIES OF PEPTIDOMIMETIC
MACROCYCLES AND PROCESSES THEREFOR

Field of the Invention

5

This Application claims the benefit of U.S. Provisional Application No. 60/043,532, filed April 11, 1997.

The present invention relates to diverse libraries of peptidomimetic organopeptide macrocyclic compounds,
10 combinatorial methods of making such libraries, and an apparatus for storing and providing a readily accessible source of such libraries. The apparatus harboring the present combinatorial libraries is a useful component of assay systems for identifying compounds for drug
15 development.

Background of the Invention

Research and development expenses account for a large
20 outlay of capital in the pharmaceutical industry. Synthesis of compounds is an expensive and time consuming phase of research and development. Historically, research chemists individually synthesized and analyzed high purity compounds for biological screening to develop
25 pharmaceutical leads. Although such methods were successful in bringing new drugs to the market, the limitations of individual synthesis and complete compound characterization considerably slowed the discovery of new pharmaceutically active compounds. The need for more
30 rapid and less expensive drug discovery methodology is increasingly important in today's competitive pharmaceutical industry.

-2-

Recently, modern drug discovery has utilized combinatorial chemistry to generate large numbers (10^2 - 10^6) of compounds generally referred to as "libraries".
5 An important objective of combinatorial chemistry is to generate a large number of novel compounds that can be screened to identify lead compounds for pharmaceutical research.

Theoretically, the total number of compounds which
10 may be produced for a given library is limited only by the number of reagents available to form substituents on the variable positions on the library's molecular scaffold. The combinatorial process lends itself to automation, both in the generation of compounds and in their biological
15 screening, thereby greatly enhancing the opportunity and efficiency of drug discovery.

Combinatorial chemistry may be performed in a manner where libraries of compounds are generated as mixtures with complete identification of the individual compounds
20 postponed until after positive screening results are obtained. However, a preferred form of combinatorial chemistry is "parallel array synthesis", where individual reaction products are simultaneously synthesized, but are retained in separate vessels. For example, the individual
25 library compounds can be prepared, stored, and assayed in separate wells of a microtiter plate, each well containing one member of the parallel array. The use of standardized microtiter plates or equivalent apparatus, is advantageous because such an apparatus is readily accessed by
30 programmed robotic machinery, both during library synthesis and during library sampling or assaying.

Combinatorial chemistry can be carried out in solution phase where both reactants are dissolved in
solution or in solid phase where one of the reactants is
35 covalently bound to a solid support. Typically, completion of the solution phase reactions in

-3-

combinatorial chemistry schemes are ensured by selecting high yielding chemical reactions and/or by using one reagent in considerable excess. When one reagent is used in excess, completion of the reaction produces a mixture
5 of a soluble product with at least one soluble unreacted reagent. Solid phase synthesis offers the advantage that the solid support-bound products are easily washed free of excess reagent. Solution phase synthesis typically requires use of one or more reaction mixture work-up
10 procedures to separate reaction product from unreacted excess reagent.

Combinatorial chemistry may be used at two distinct phases of drug development. In the discovery phase diverse libraries are created to find lead compounds. In
15 a second optimization phase, strong lead compounds are more narrowly modified to find optimal molecular configurations.

Small peptides as a class of compounds possess rich diversity and potent bioactivity and thus remain a vital
20 starting point for drug discovery. However, due to a litany of undesirable pharmacokinetic properties of peptides, peptidomimetics are frequently used to redeploy important peptide main chain and side chain pharmacophores onto less peptide-like scaffolds. Peptidomimetics vary
25 greatly in their resemblance to peptides. Success has been achieved with peptides containing hydrolytically stable amide surrogates, mixed organo-peptide frameworks, and with non-peptide scaffolds alike. Benzodiazepines, penicillins and cephalosporins are well-established
30 peptidomimetic drugs and it is easy to see that organo-peptide chimeras are essential to both rational design and combinatorial chemistry approaches to drug discovery.

Conformational restriction is important in drug pharmacology and efficacy because i) less flexible
35 molecules usually bind with much higher affinity to their targets because less energy is expended in freezing out

-4-

non-active conformations and ii) conformationally restricted peptides are usually less susceptible to digestion by proteases, hence are expected to be more active drugs. Thus, preparation of cyclic compounds has been an important drug discovery tactic to take advantage of those features. [See Hruby, Life Sciences, **31**, 189-199 (1982); Kates et al., Tet Lett **34**, in 1549-52 (1993); Kataoka et al., Biopolymers **32**, 1519-33 (1992); Szewczuk et al., Biochemistry **31**, 9132-40 (1992); Schiller et al., J. Med Chem., **34** 3125-32 (1991); Toniolo, Int. J. Pept. Prot. Res., **35**, 287-300 (1990); Veber et al., Nature, **280**, 512-4 (1979)]

Barker et al. [J. Med. Chem. **35**, 2040-8 (1992)] and McDowell and Gadek [JACS, **114**, 9245-9253, (1992)] have made constrained cyclic peptides having a single thioether bond (at the point of ring closure) and bearing the sequence Arginine-Glycine-Aspartic acid, a high affinity ligand for glycoprotein IIb-IIIa, an important receptor in the blood clotting cascade. Wen and Spatola have synthesized and characterized linear pseudopeptide libraries bearing 1 to 3 dialkylamino replacements "[Ψ CH₂NH]" for defined amide bonds [Abstract #60, Division of Medicinal Chemistry, American Chemical Society 207th National Meeting in San Diego, CA, March 13-17, 1994.] For other reports of linear and cyclic peptides bearing a single thioether replacement for an amide bond, see Paladino et al., Int. J. Pept. Prot. Res. **42**, 284-93 (1993); Anwer et al., Int. J. Pept. Prot. Res., **36**, 392-9 (1990); Spatola et al., Colloq. INSERM, **174**, 2nd Peptide Forum, 45-54 (1989); and Darlak et al., Pept. Proc. Eur. Pept. Symp. 20th, 634-6 (1989), June and Gayer, Eds.]

Summary of the Invention

The present invention is directed to the construction of a series of novel structurally related macrocyclic

-5-

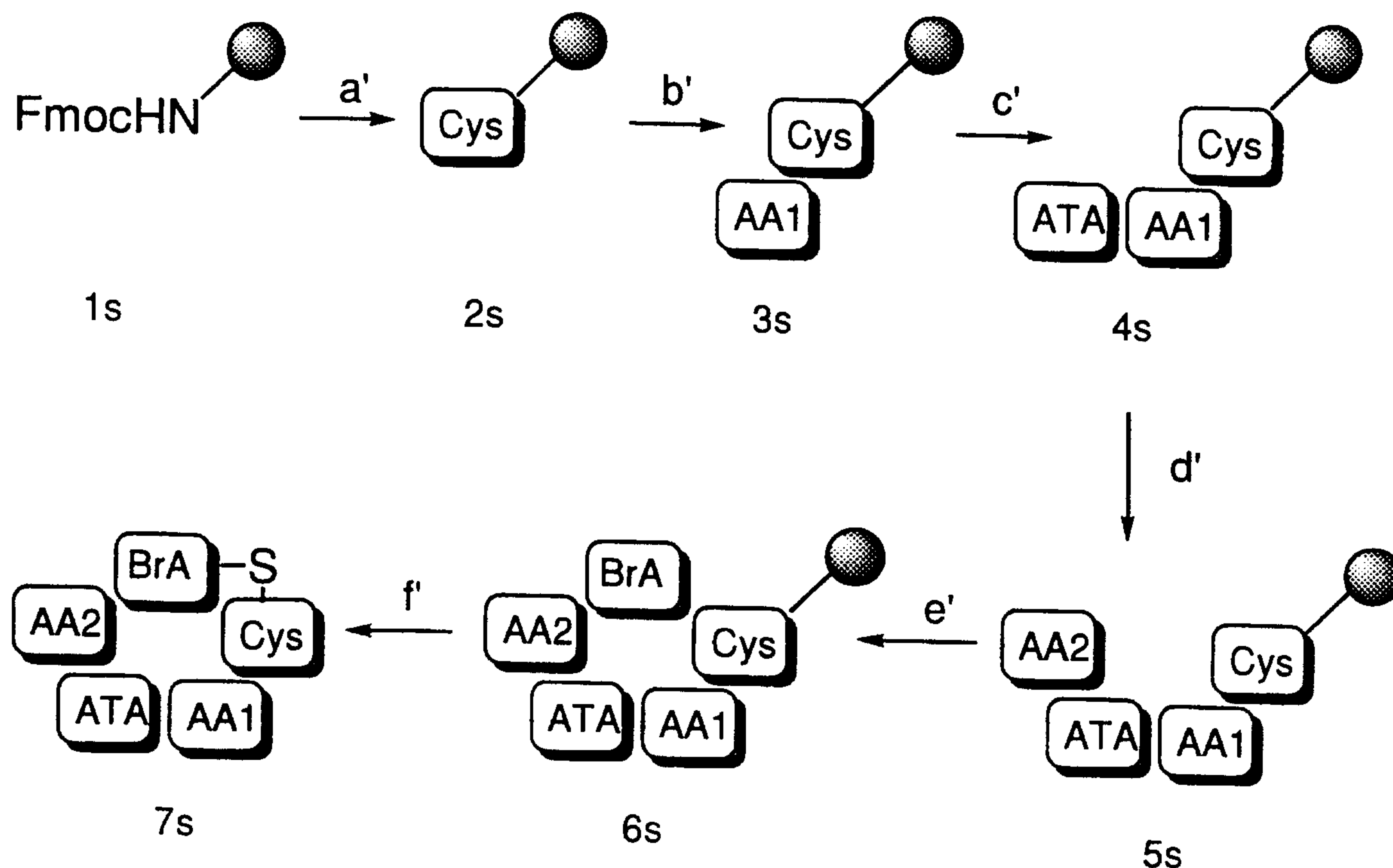
compounds from one or more aminothioether compounds or one or more of their corresponding sulfoxide or sulfone derivatives, collectively referred to herein as "ATAs". ATA compounds are used in combination with other ATAs and
5 other organic compounds that bear amine and acid functionality, to generate the present novel, diverse macrocyclic compounds having at least 2 sulfur linkages in the macrocycle ring structure, wherein the oxidation state of those linkages may vary. By linking ATAs together in
10 sequence, one may generate an oligomer with a backbone alternating between sulfur and amide linkages. Moreover, the flexibility of the present process for preparing the macrocyclic libraries enables construction of peptidomimetics that are not constrained to the normal
15 spacing or "register" found in normal peptides. The process also enables facile synthesis of macrocycle libraries having the same number or a different number of ring atoms of from about 12 to about 40 ring atoms. Libraries of these macrocyclic ATA compounds are screened
20 to identify lead compounds through their biological activity.

In their simplest form, ATAs are dipeptides where a thioether bridge replaces the central amide linkage, such as, for example, those described by Spatola, A.F., in
25 *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, B. Weinstein, Ed.; Marcel Dekker: New York, 1983; Vol. 7; pages 267-357. A facile synthesis of such compounds from commercially available amino acids or amino alcohols and mercapto acids provides a diverse array of
30 ATA compounds for use in preparation of novel macrocycle libraries described in the present invention. The diverse ATA compounds are used in combination with other organic compounds that bear amine and acid functionality, including both proteiogenic amino acids and non-
35 proteiogenic amino acids, to construct diverse libraries

-6-

of peptidomimetic macrocyclic compounds of the present invention.

The present invention is also directed to a simple and direct process for the production of diverse libraries of novel macrocyclic organo-peptide compounds useful in the identification of new pharmaceutical lead compounds. For example, as depicted in Scheme I below, the present library compounds may be easily prepared using solid phase synthesis techniques via carbodiimide-mediated coupling of one or more ATAs with proteiogenic and non-proteiogenic amino acids, followed by solid phase or solution phase cyclization by a thioetherforming intramolecular nucleophilic displacement reaction. The anchor residue and the terminal bromoacid, as well as the identity, number and coupling order of the intervening amino acid and ATA components all contribute to the unique structural identity of the macrocycle product.



Scheme I

20

Steps: a') N-Fmoc-rink amide MBHA resin, 30% piperidine in DMF, then 5 eq Fmoc-S-trityl-L-cysteine, diisopropyl carbodiimide/hydroxybenzotriazole (DIC/HOBT) in N-

-7-

methylypyrrolidinone (NMP); Steps b') through d') as for
Step a') but with the respective amino acid (AA) or ATA;
e') 30% piperidine in DMF, then 5eq bromoacetic
acid and DIC in NMP;
5 f') 38:1:1 trifluoroacetic acid (TFA):H₂O:Et₃SiH
for 2 hours, lyophilize, the 2 eq of diisopropylethylamine
in 1:1 CH₃CN:H₂O.

The library is created, stored, and used as an
apparatus comprising a two-dimensional array of
10 reservoirs, each reservoir containing a predetermined
library reaction product differing from those in adjacent
reservoirs.

Another embodiment of the present invention provides
an assay kit for the identification of pharmaceutical lead
15 compounds, said kit comprising assay materials and a well
plate apparatus or equivalent apparatus providing a two-
dimensional array of defined reservoirs. The well plate
apparatus provides a diverse combinatorial library,
wherein each well (reservoir) contains a unique macrocycle
20 compound, or stereoisomers and/or regioisomers thereof.
The well plate apparatus is used to provide multiple
reaction zones for making the library, to store the
library and to provide a readily accessible source of
library compounds.

25

Brief Description of the Drawings

Fig. 1 is a top view of a well plate in accordance
with this invention.

30 Fig. 2 is a side view of a well plate apparatus for
use in the process of this invention.

Detailed Description of the Invention

35 The term "assay kit" as used in accordance with the
present invention refers to an assemblage of two
cooperative elements, namely (1) a well plate apparatus
and (2) biological assay materials.

-8-

"Biological assay materials" are materials necessary to conduct a biological evaluation of the efficacy of any library compound in a screen relevant to a selected disease state.

5 A "library" is a collection of compounds created by a combinatorial chemical process, said compounds having a common scaffold with one or more variable substituents.

A "library compound" is an individual reaction product, a single compound or a mixture of isomers, in a
10 combinatorial library.

A "Lead compound" is a library compound in a selected combinatorial library for which the assay kit has revealed significant activity relevant to a selected disease state.

A "diverse library" means a library where the
15 substituents on the combinatorial library scaffold or core structure, are highly variable in constituent atoms, molecular weight, and structure, and the library, considered in its entirety, is not a collection of closely related homologues or analogues (compare to "directed
20 library").

A "directed library" is a collection of compounds created by a combinatorial chemical process, for the purpose of optimization of the activity of a lead compound, wherein each library compound has a common
25 scaffold, and the library, considered in its entirety, is a collection of closely related homologues or analogues to the lead compound (compare with "diverse library").

The term "scaffold" as used in accordance with the present invention comprises a peptidomimetic macrocycle
30 bearing at least two sulfur linking groups. The scaffold may be further derivatized using conventional combinatorial techniques.

"Substituents" are chemical radicals which are bonded to or incorporated onto the scaffold through the
35 combinatorial synthesis process. The different functional groups account for the diversity of the molecules

-9-

throughout the library and are selected to impart diversity of structure, function and biological activity to the scaffold in the case of diverse libraries, and optimization of a particular biological activity in the case of directed libraries.

"Reagent" means any chemical compound used in the combinatorial synthesis process to incorporate substituents on the scaffold of a library.

"Parallel array synthesis" refers to the method of conducting combinatorial chemical synthesis of libraries wherein the individual combinatorial library compounds are separately prepared and stored without prior and subsequent intentional mixing.

"Simultaneous synthesis" means making of library compounds within one production cycle of a combinatorial method (not making all library compounds at the same instant in time).

The "reaction zone" refers to the individual vessel location where the combinatorial chemical library compound preparation process of the invention is carried out and where the individual library compounds are synthesized. Suitable reaction zones include, but are not intended to be limited to the individual wells of a well plate apparatus.

"Well plate apparatus" refers to the structure capable of holding one or more library compounds in dimensionally fixed and defined positions.

"Non-interfering substituents" are those chemical radicals that do not significantly impede the process of the invention and yield stable aminothioether macrocyclic library compounds.

"Aryl" means one or more aromatic rings, each of 5 or 6 ring carbon atoms and includes substituted aryl having one or more non-interfering substituents. Multiple aryl rings may be fused, as in naphthyl, or unfused, as in biphenyl.

-10-

"Alkyl" means straight or branched chain or cyclic hydrocarbon having 1 to 20 carbon atoms.

"Substituted alkyl" is alkyl having one or more non-interfering substituents.

5 "Halo" means chloro, fluoro, iodo or bromo.

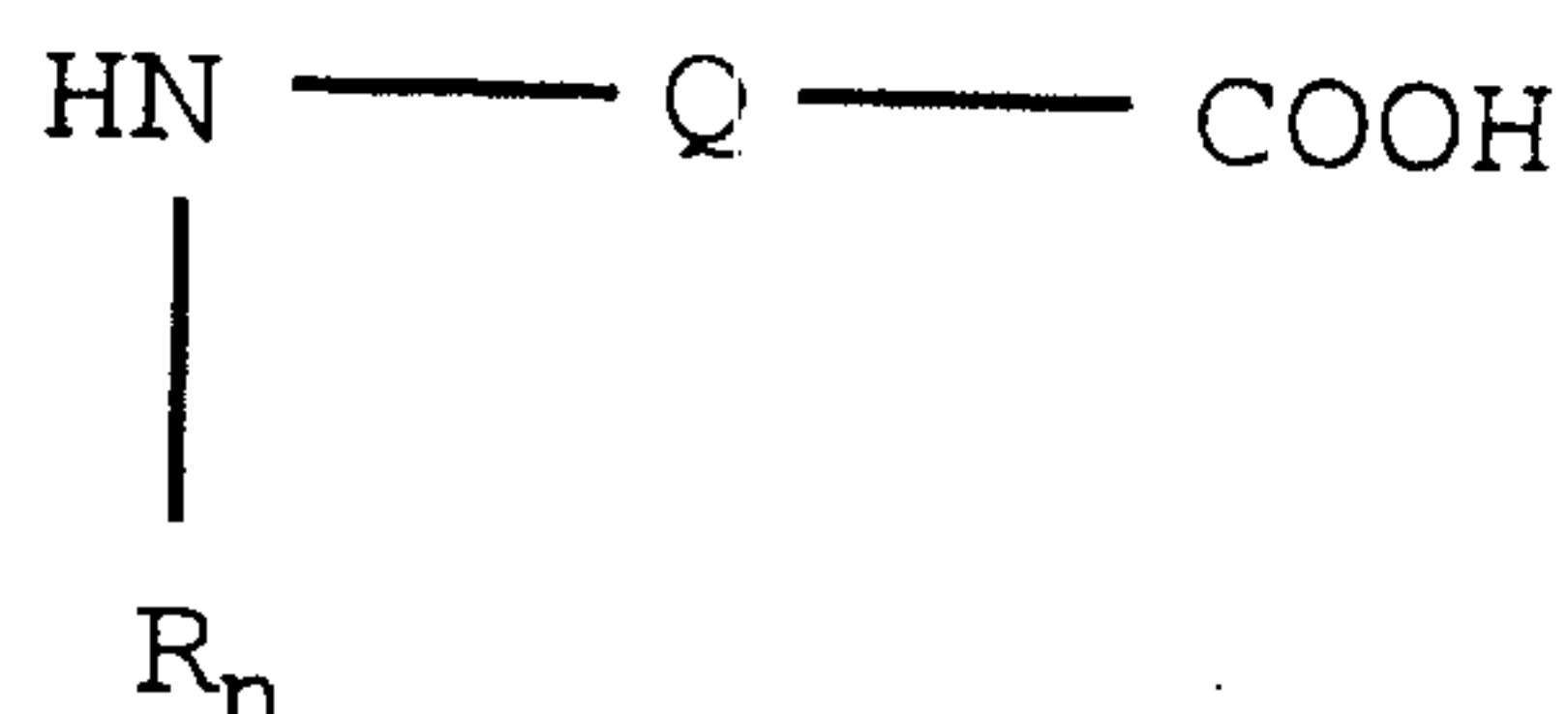
"Heterocycle" or "heterocyclic radical" means one or more rings of 5, 6 or 7 atoms with or without unsaturation or aromatic character, optionally substituted with one or more non-interfering substituents, and at least one ring atom which is not carbon. Preferred heteroatoms include sulfur, oxygen, and nitrogen. Multiple rings may be fused, as in quinoline or benzofuran, or unfused as in 4-phenylpyridine. Suitable substituents on the heterocyclic ring structure include, but are not limited to halo, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₁-C₁₀ alkylthio, arylthio, aryloxy, arylamino, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, di(C₁-C₁₀)-alkylamino, C₂-C₁₂ alkoxyalkyl, C₁-C₆ alkylsulfinyl, C₁-C₁₀ alkylsulfonyl, arylsulfonyl, 15 aryl, hydroxy, hydroxy(C₁-C₁₀)alkyl, aryloxy(C₁-C₁₀)alkyl, C₁-C₁₀ alkoxy carbonyl, aryloxy carbonyl, C₁-C₁₀ alkanoyloxy, aryloxyloxy, substituted alkoxy, fluoroalkyl, nitro, cyano, cyano(C₁-C₁₀)alkyl, C₁-C₁₀ alkanamido, aryloylamido, arylaminosulfonyl, sulfonamido, amidino, 25 carbamido, , carboxy, heterocyclic radical, nitroalkyl, and -(CH₂)_m-Z-(C₁-C₁₀ alkyl), where m is 1 to 8 and Z is oxygen or sulfur.

"Organic moiety" means a substituent comprising a non-interfering substituent covalently bonded through at least one carbon atom. Suitable substituents onto a 30 connecting carbon atom include, but are not limited to hydrogen, halo, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₁-C₁₀ alkylthio, arylthio, aryloxy, arylamino, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, di(C₁-C₁₀)-alkylamino, 35 C₂-C₁₂ alkoxyalkyl, C₁-C₆ alkylsulfinyl, C₁-C₁₀

-11-

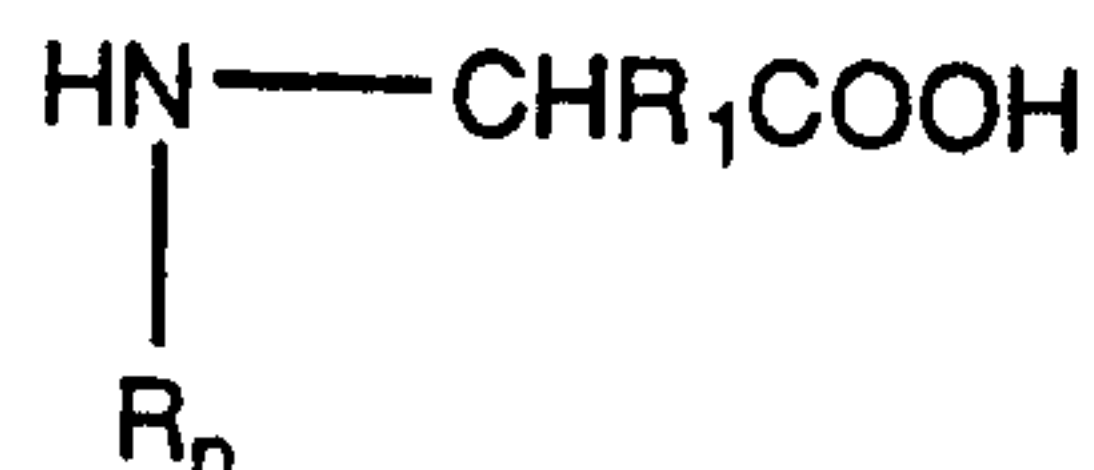
alkylsulfonyl, arylsulfonyl, aryl, hydroxy, hydroxy(C₁-C₁₀)alkyl, aryloxy(C₁-C₁₀)alkyl, C₁-C₁₀ alkoxy carbonyl, aryloxy carbonyl, C₁-C₁₀ alkanoyloxy, aryloyloxy, substituted (C₁-C₁₀) alkoxy, fluoroalkyl, nitro, cyano, cyano(C₁-C₁₀)alkyl, C₁-C₁₀ alkanamido, aryloylamido, arylaminosulfonyl, sulfonamido, amidino, carbamido, protected amino, protected carboxy, protected amino, carboxy, heterocyclic radical, nitroalkyl, and -(CH₂)_m-Z-(C₁-C₁₀ alkyl), where m is 1 to 8 and Z is oxygen or sulfur.

The term "amino acid" as used in accordance with the present invention includes the 20 proteiogenic amino acids encoded by the genetic code, as well as hydroxyproline, alpha-aminoisobutyric acid, sarcosine, citrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, beta-alanine, 4-aminobutyric acid and other compounds of the general formula:



wherein R_n is hydrogen or an organic moiety, and Q is an organic group comprising 1 to 12 carbon atoms and 0 to 4 heteroatoms selected from O, N and S; or R_n taken together with Q and the nitrogen atom to which they are bound form a 4 to 7-membered ring.

"Proteiogenic amino acids" are those amino acids of the formula



wherein R₁ is selected from the group consisting of hydrogen, methyl, isopropyl, isobutyl, sec-butyl, hydroxymethyl, 1-hydroxyethyl, sulfhydrylmethyl, 2(methylthio)ethyl, benzyl, 4-hydroxybenzyl,

-12-

3-indolylmethyl, carboxymethyl, 2-carboxyethyl,
carbamidomethyl, 2-carbamidoethyl, 4-aminobutyl,
3-guanadinypropyl and 4-imidazolylmethyl, and R_n is
hydrogen, or R_n and R_1 taken together with the common
5 bonded nitrogen atom form a pyrrolidine ring.

"Activated acid" or "activated acid group" refers to
a carboxylic acid that has been reacted to form a group -
C(O)X wherein X is a leaving group subject to nucleophilic
displacement by nucleophiles. Exemplary of the group X is
10 chloro (an acid chloride), -OC(O) R_x (an anhydride), or -
OR $_x$ (an active ester). Preparation of such activated acid
derivatives and their use in preparation of other acid
derivatives are well known in the art

"Acid reactive groups" refer to those nucleophilic
15 groups capable of reacting with activated acids to form a
covalent bond. Exemplary of acid reactive groups are -OH,
-SH or -NHR $_r$, where R_r is hydrogen or an organic moiety,
and stabilized carbon anions.

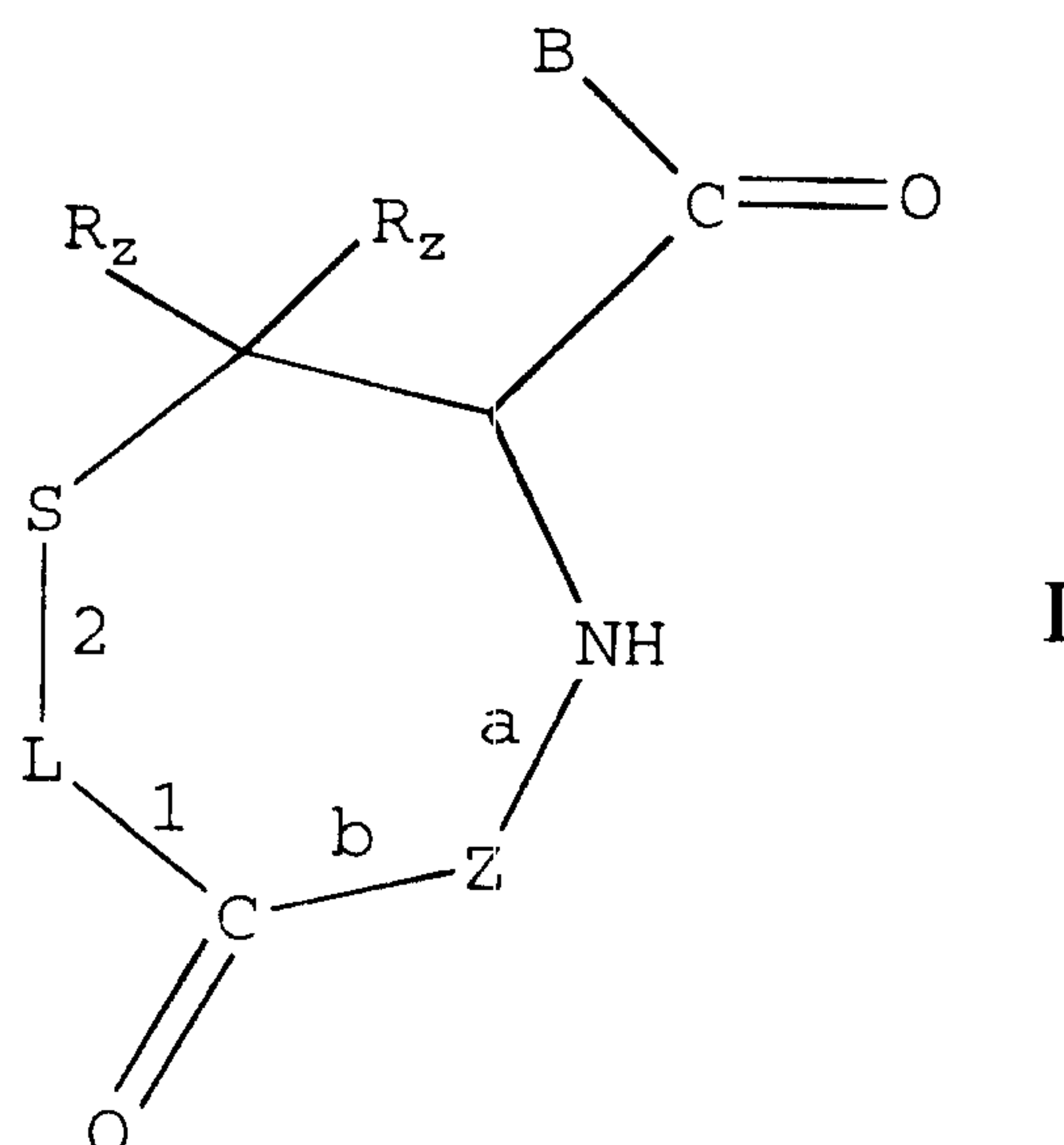
"Solid support" refers to a solvent insoluble
20 substrate having acid reactive groups for forming
cleavable covalent bonds with acid reagents, such as S-
protected amino-protected mercapto amino acids for use in
preparing the present library compounds.

The term "ring atoms" in defining this invention
25 refers to those atoms or "ring members" covalently bonded
serially, one to another, to form a ring structure.

A diverse library of macrocyclic compounds is
provided in accordance with the present invention. The
macrocycle library embodied as an apparatus of this
30 invention serves as a readily accessible source of diverse
macrocyclic compounds for use in identifying new
biologically active macrocyclic compounds through
pharmaceutical and agricultural candidate screening
assays, for use in studies defining structure/activity
35 relationships, and/or for use in clinical investigation.

-13-

According to the present invention, there is provided structurally related macrocyclic compounds of the formula

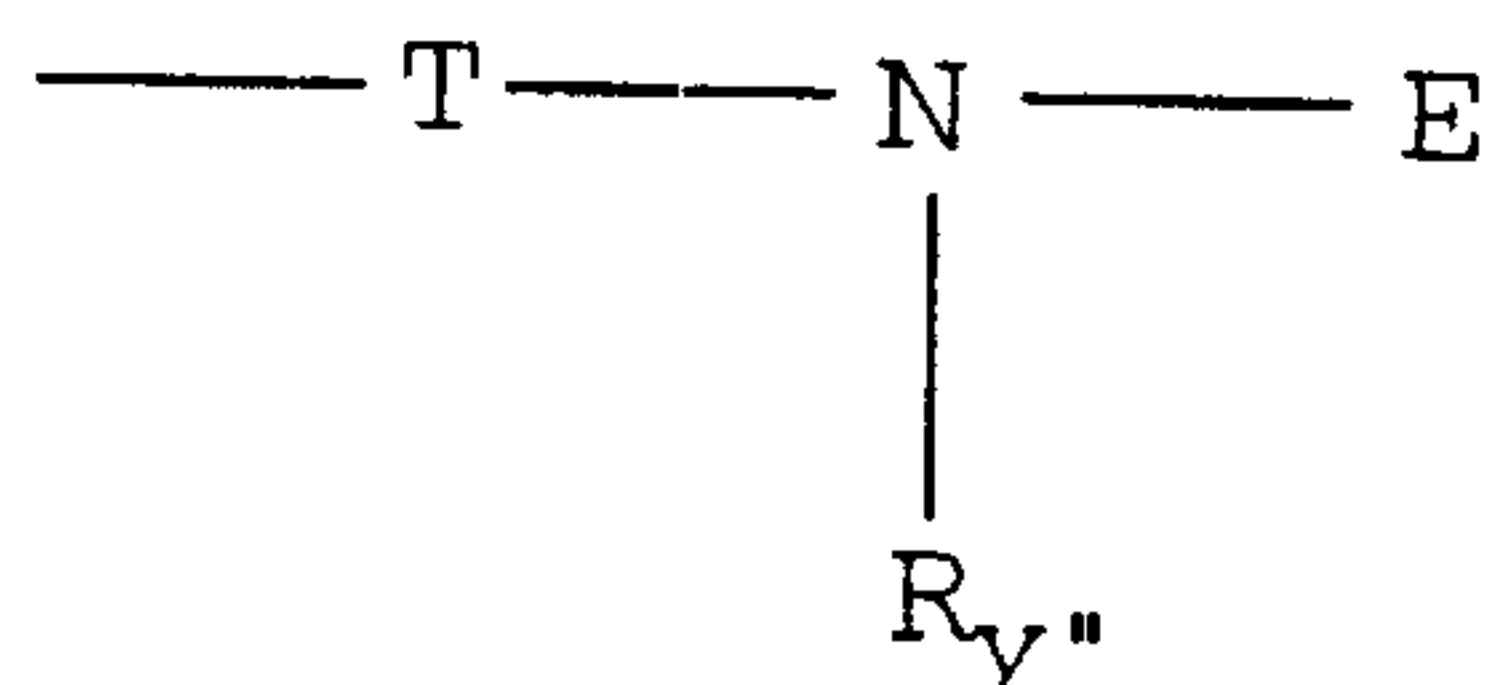


5 wherein

L is a divalent group of the formula ¹ (CH₂)₀₋₁-C₆H₄CH₂² or -CHR_a- wherein R_a is hydrogen or an organic moiety;

R_z is hydrogen or methyl;

10 B is hydroxy, or a group of the formula -NR_yR_t wherein R_y is hydrogen, alkyl, aryl or heterocycle, and R_t is hydrogen, a solid support, or R_t is a group of the formula



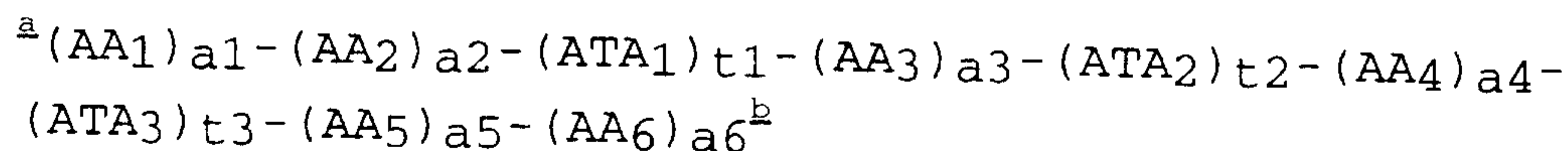
15 wherein E is hydrogen, a solid support or a substituent derived from an electrophilic reagent, T is a divalent linking group, and R_y'' is hydrogen or a substituent derived from an electrophilic reagent; or R_y and R_y'' taken together with the atoms to which they are bonded form a 6- to 7-membered ring or a bicyclic or
20 tricyclic ring comprising 6 to 12 carbon atoms; or R_y or R_y'' taken together with -T- and the atoms to which they are commonly bonded form a 4- to 7-membered ring; or R_y

-14-

and R_y" each taken together with T and the nitrogen atom to which they are respectively bonded form a 5- to 7-membered ring;

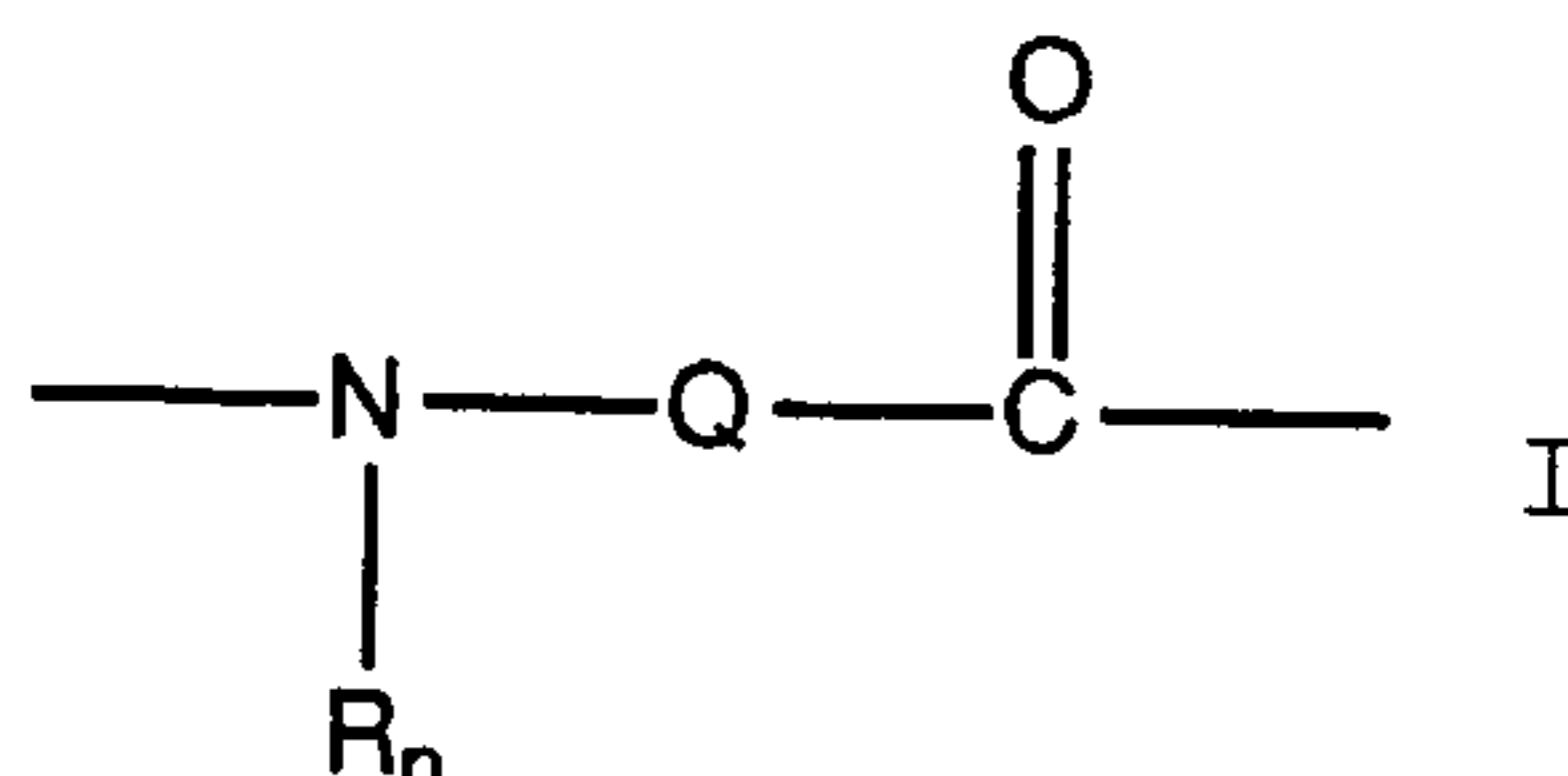
Z is a divalent group of the formula

5



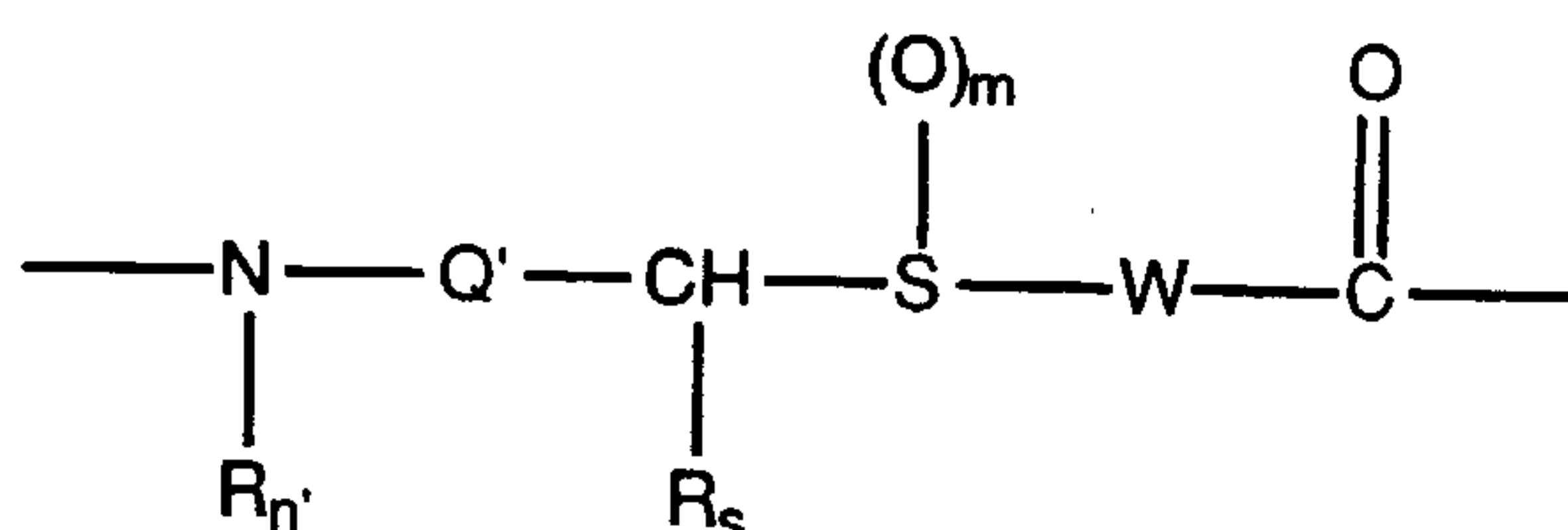
wherein each of AA₁-6 is independently a divalent group of the formula

10



and each of ATA₁-3 is independently a divalent sulfur-linked group of the formula

15



and wherein a₁, a₂, a₃, a₄, a₅, a₆, t₁, t₂, and t₃ are independently 0 or 1, provided that t₁ + t₂ + t₃ = 1, 2 or 3; and provided further that -Z- is selected to provide a 12- to 40-membered macrocycle ring of Formula I;

wherein in the above formulas for AA₁-6 and ATA₁-3, W is a divalent organic group comprising 1 to 12 carbon atoms and 0 to 4 heteroatoms selected from O, N and S;

25

Q and Q' are each independently an organic group comprising 1 to 12 carbon atoms and 0 to 4 heteroatoms selected from O, N and S;

30

-15-

m is 0, 1 or 2;

R_S is hydrogen or an organic moiety; and

R_n' is hydrogen, or an organic moiety, or R_n taken together with Q and the atoms to which they are bonded
5 form a 4- to 7-membered ring;

R_n' and R_S taken together with -Q'- and the atoms to which they are bonded form a 4- to 7-membered ring or a bicyclic or tricyclic ring comprising 6 to 12 carbon atoms; or

10 R_n' or R_S taken together with -Q'- and the atoms to which they are commonly bonded form a 4- to 7-membered ring.

The library compounds of this invention have a molecular weight of about 200 to about 1500, more
15 typically about 250 to about 1250. The present macrocycle library compounds as represented by Formula I include 12 to 40 ring atoms. In one embodiment the library compounds are constructed to have 12 to 24 ring atoms, at least two of which are sulfur. The ring atoms are derived from four
20 types of reactants during the solid phase synthesis: 1) a solid support-anchored orthogonally protected trifunctional (protected thiol, protected amino, carboxy) compound (viz. cysteine or penicillamine); 2) aminoacids, selected from proteiogenic amino acids and non-
25 proteiogenic amino acids; 3) ATAs (aminothioether acids and their corresponding sulfoxide and sulfone derivatives); and 4) alpha-halo acids, preferably alpha-bromo acids or carboxy- or carboxymethyl-substituted benzyl bromides. Generally, macrocycle synthesis is
30 initiated by deprotecting the support anchored amine functional group. The linear (or at least acyclic) macrocycle precursor is synthesized by serial peptide coupling of at least one ATA and zero, one or more amino acids. The resulting terminal amine functionality is
35 finally coupled, by peptide bond formation, to an alpha-halo acid or a carboxy/carboxymethyl substituted benzyl

-16-

bromide to provide an electrophilic (bromomethyl) terminus. Upon deprotection of the support-bound thiol and treatment with a non-nucleophilic base, the acyclic precursor undergoes intramolecular thioether-forming cyclization. Accordingly, the support bound orthogonally protected cysteine or penicillamine contributes 4 ring atoms to the macrocycle structure, use of an alpha-halo acid contributes two ring atoms, and use of a carboxy/carboxymethyl substituted benzyl bromide contributes 4 to 7 ring atoms to the macrocycle structure. The remaining ring members are determined by the nature, coupling order and number of the amino acids and ATAs coupled during synthesis of the acyclic support bound macrocycle precursor.

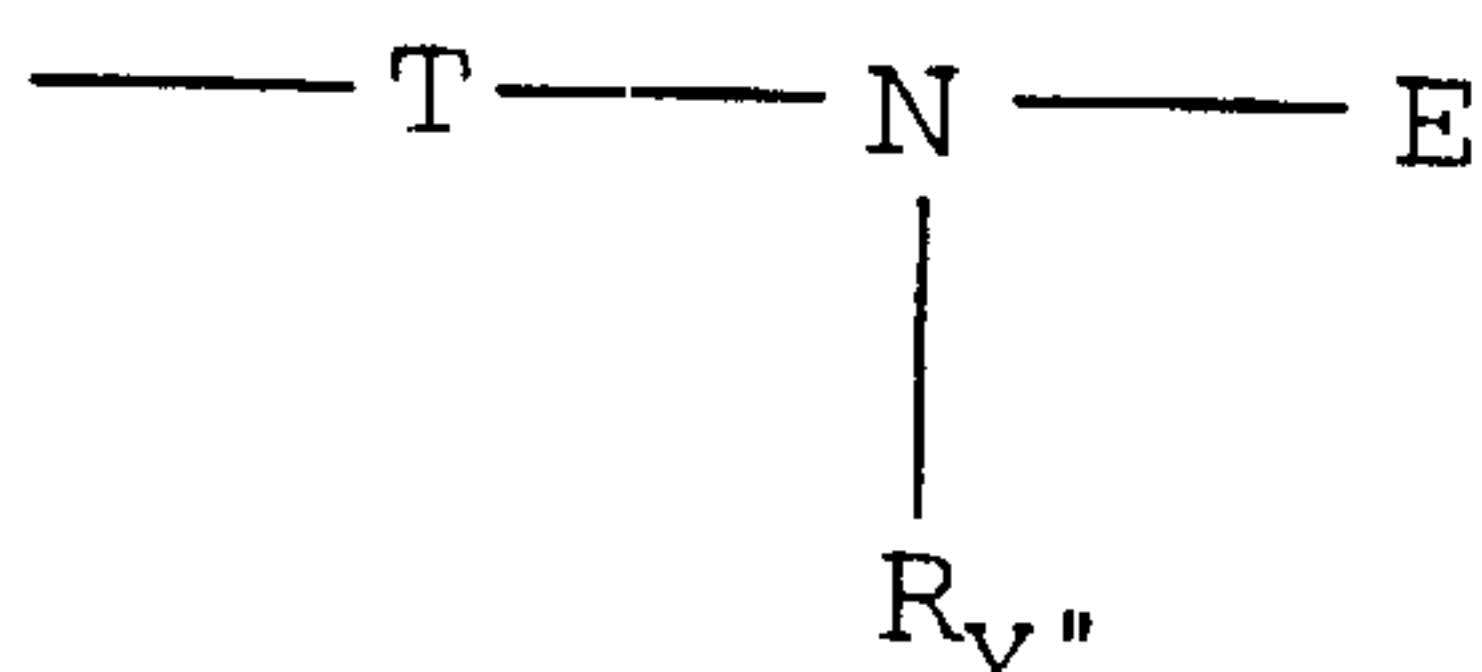
The libraries in accordance with this invention can be synthesized to have diversity in the number of ring atoms, or they can be prepared so that each member of the library has the same number of ring atoms with diversity in the library being introduced by the nature and coupling order of the component amino acids (AA₁₋₆) and ATAs. Additional elements of diversity can be introduced into the present macrocycle library by the preparation and use of solid supports having selected acid reactive groups such as, for example, those acid reactive groups derived from reaction of diamines with p-nitrophenylcarbonate Wang resin. Trifluoroacetic acid mediated cleavage of the synthesized macrocycles or acyclic macrocycle precursors from such diamine reacted resin provides a "side chain" having amine functionality that can be reacted with a wide variety of electrophilic reagents.

In one embodiment of the invention there is provided a diverse library of macrocycle compounds of Formula I wherein B is NH₂. Such library compounds are derived from the corresponding library compounds wherein B is a solid support, particularly a Rink-Amide AM resin or Rink-Amide MBHA resin by trifluoroacetic acid mediated cleavage of the

-17-

covalently bound library compound or its acyclic precursor from the solid support.

Another embodiment of the present invention provides macrocycle library compounds of Formula I wherein B is a group of the formula $-NR_YR_t$ wherein R_Y is hydrogen, alkyl, aryl or heterocycle and R_t is hydrogen, a solid support, or R_t is a group of the formula



wherein T, R_Y'' and E are as defined above. The compounds where E is hydrogen can be derived from corresponding library compounds wherein E is a solid support, particularly a Wang resin, by trifluoroacetic acid mediated cleavage, or they can be derived by cyclization of the corresponding acyclic polymers. The library compounds of Formula I wherein E is hydrogen are useful as core structures for the synthesis of directed macrocycle libraries having diversity in the group E through reactions with various electrophilic reagents to construct variable "side chain" functionality on the macrocycle library compounds.

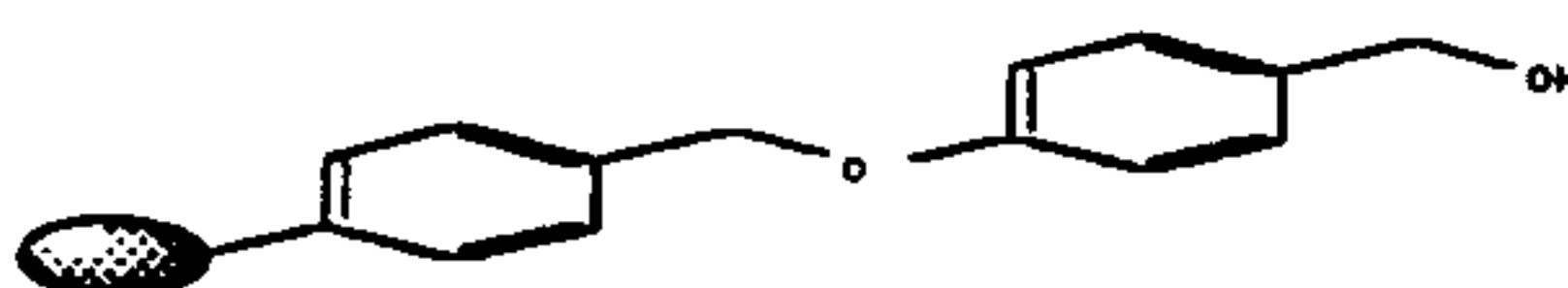
The library compounds of Formula I wherein the group B or E is a covalently bonded solid support (and the corresponding acyclic precursor compounds) also represent embodiments of the present invention. A general compilation of solid supports (resins) can be found in "Supports for Solid Phase Organic Synthesis," Martin Winter, pp 465-510, in Combinatorial Peptide and Non-peptide Libraries, edited by Günther Jung (1996), VCH Publishers (Weinheim, Germany). Many solid supports having acid reactive groups, such as hydroxy and primary or secondary amino groups (or precursors thereto) are commercially available. The acid reactive groups

-18-

covalently bound to solid supports are typically designed to have selectively cleavable covalent bonds linking it to the solid support. Illustrative of commercially available solid supports include, but are not intended to be limited to, the following resins:

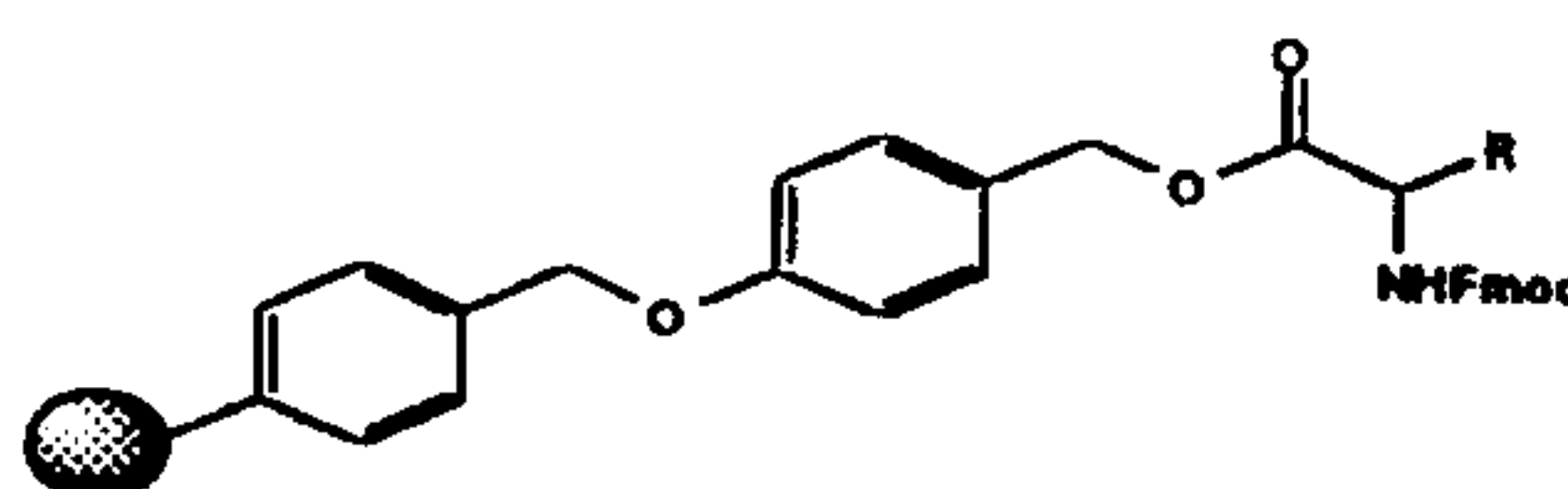
Wang resin (where the sphere represents commercial divinylbenzene-crosslinked polystyrene):

10

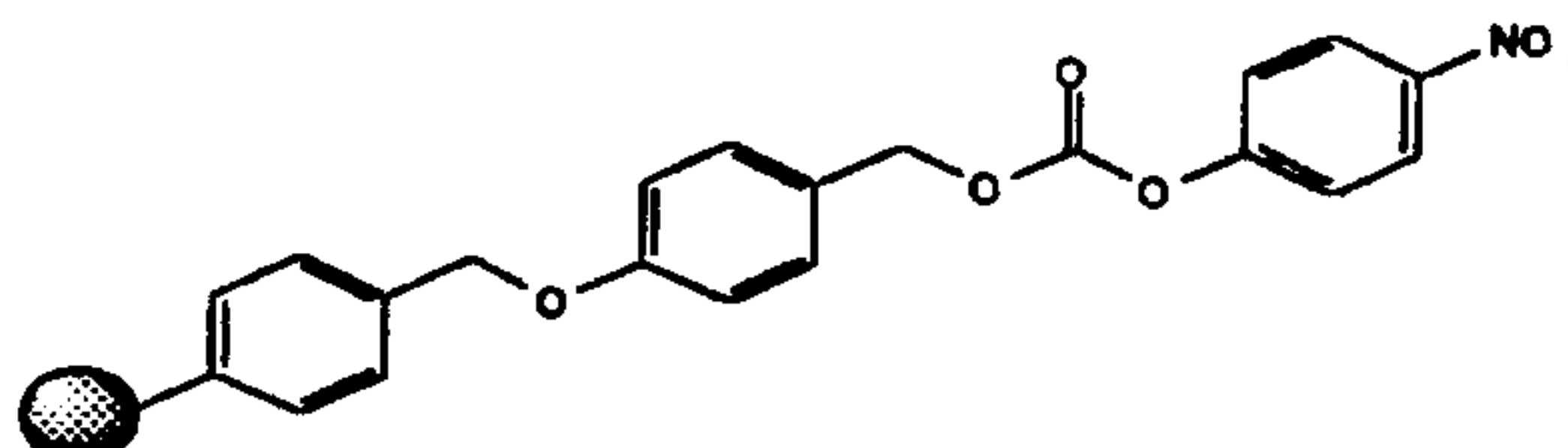


15

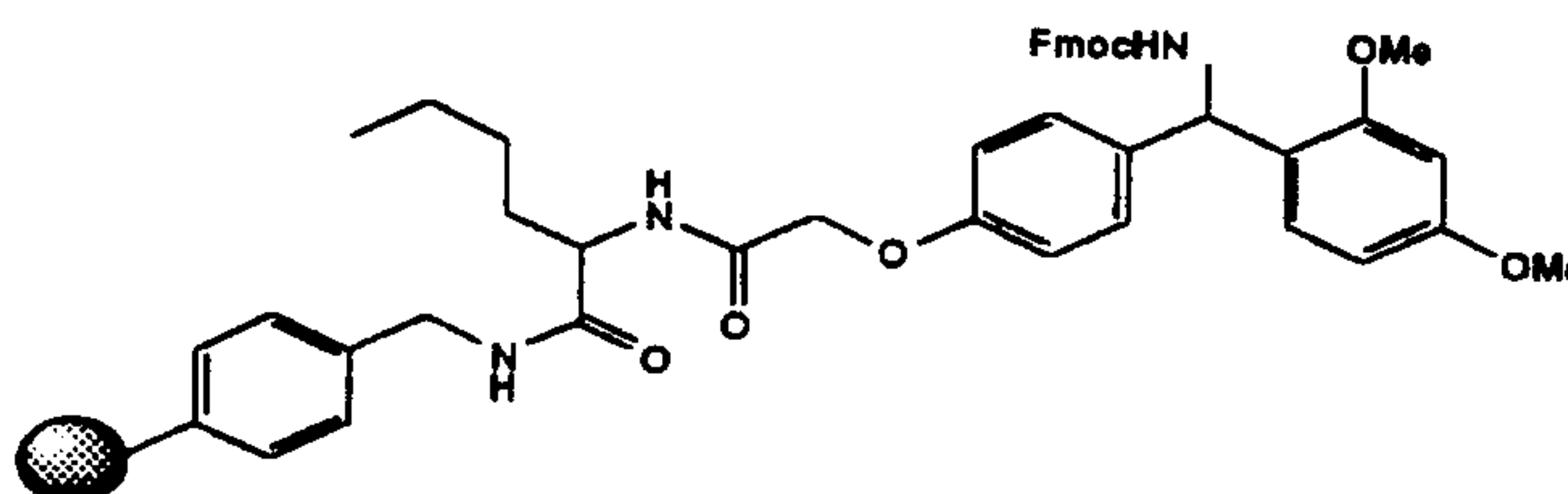
Wang resin functionalized with various amino acids (many varieties are commercially available):



20 Wang p-nitrophenylcarbonate resin:

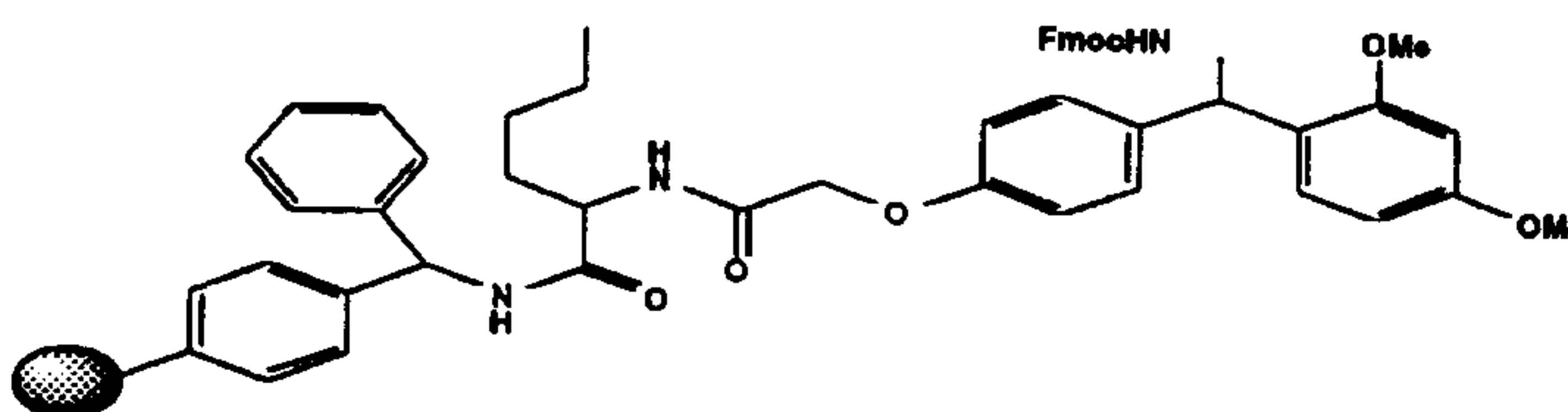


25 Rink Amide AM resin:



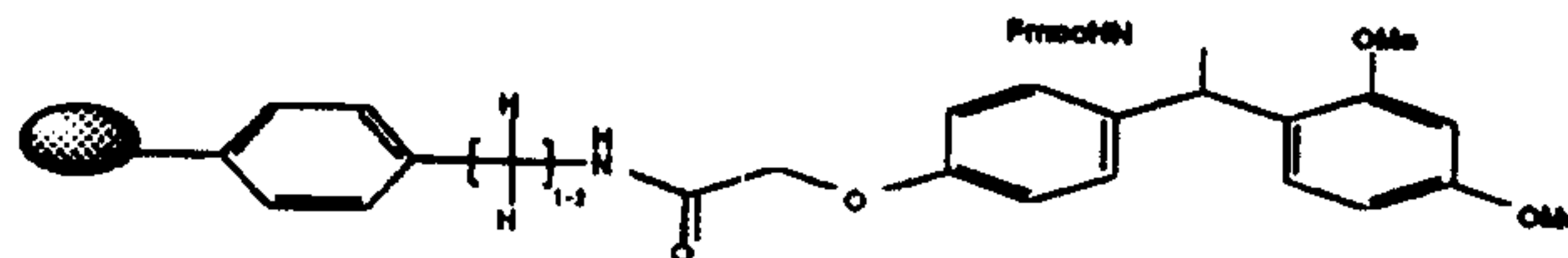
Rink Amide MBHA resin:

30

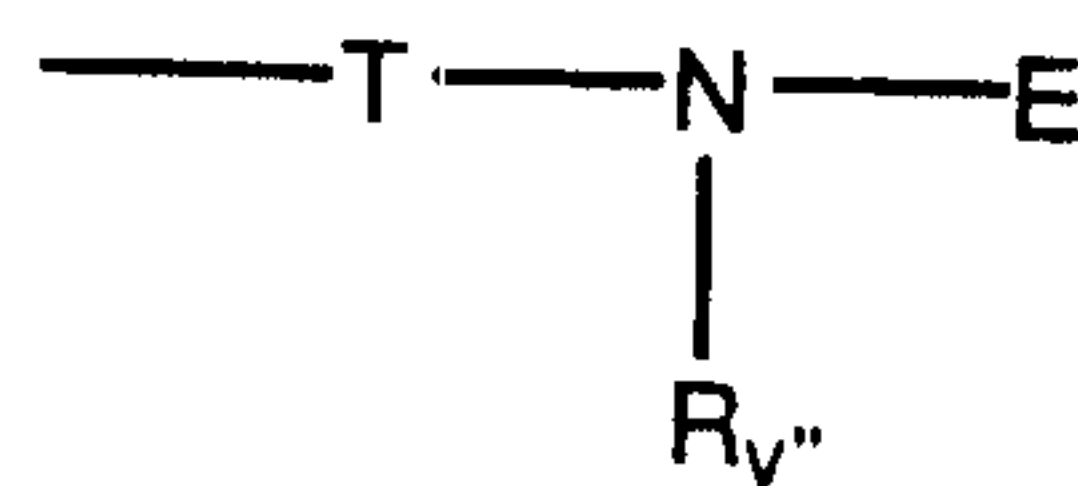


-19-

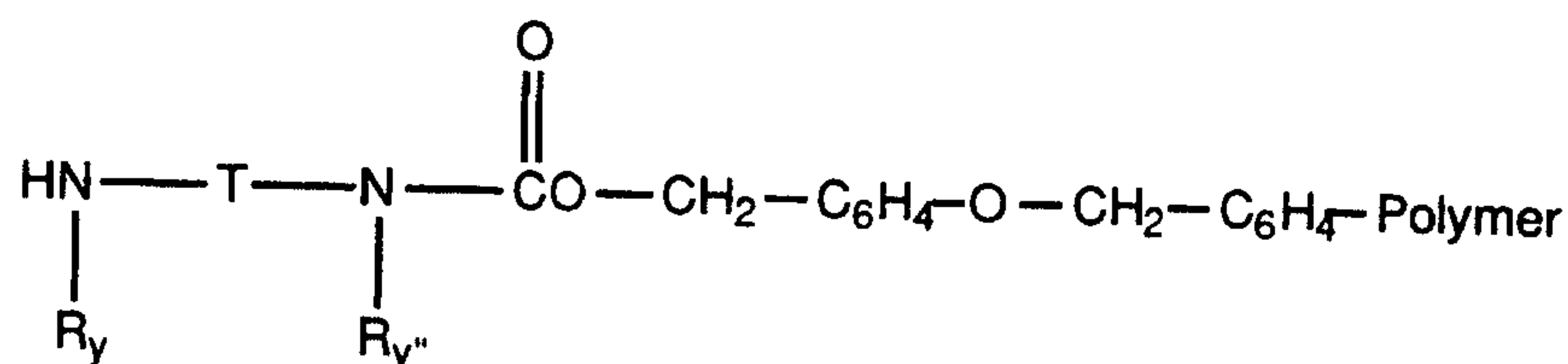
Knorr Resin:



The library compounds of Formula I of this invention
 5 wherein B is the group $-NR_YR_T$, R_T is a group of the
 formula



10 and wherein T and R_Y'' are as defined above and E is a
 solid support, are derived from the modified Wang resin
 bearing acid reactive groups of the formula



15 wherein R_Y , T, and R_Y'' are as defined above. The
 modified Wang resin is prepared by reacting Wang
 p-nitrophenylcarbonate resin with an excess of diamine of
 the formula



20 Exemplary of diamine compounds suitable for preparing
 modified Wang resins for use in preparing library
 compounds of this invention wherein E is a solid support
 or hydrogen (after cleavage) include, but are not intended
 to be limited to the following:

1,2-DIAMINOCYCLOHEXANE
 1,3-BIS(AMINOMETHYL)CYCLOHEXANE
 D-CYSTINE
 L-ARGININE
 2,6-DIAMINOPIMELIC ACID
 2,6-DIAMINOPIMELIC ACID

-20-

N-EPSILON-CBZ-L-LYSINE
N-EPSILON-ACETYL-L-LYSINE
N-(3-AMINOPROPYL)CYCLOHEXYLAMINE
ETHYLENEDIAMINE-N,N'-DIACETIC
ACID
N,N'-DIBENZYLETHYLENEDIAMINE
PIPERAZINE
2-METHYLPIPERAZINE
2,6-DIMETHYLPIPERAZINE
1-(2-AMINOETHYL)PIPERAZINE
4,4'-BIPIPERIDINE DIHYDROCHLORIDE
4-(AMINOMETHYL)PIPERIDINE
1,4-BIS(3-AMINOPROPYL)PIPERAZINE
HOMOPIPERAZINE
ACETALDEHYDE-AMMONIA TRIMER
ACETALDEHYDE-AMMONIA TRIMER
M-XYLYLENEDIAMINE
1,10-DIAMINODECANE
1,12-DIAMINODODECANE
N-ISOPROPYLETHYLENEDIAMINE
N-ETHYLETHYLENEDIAMINE
TETRAETHYLENEPENTAMINE
TRIETHYLENETETRAMINE
2-(2-AMINOETHYLAMINO)ETHANOL
DIETHYLENETRIAMINE
N-(N-PROPYL)ETHYLENEDIAMINE
N-(2-AMINOETHYL)-3-
AMINOPROPYLTRIMETHOXYLANE
TRIS(2-AMINOETHYL)AMINE
N-(2-AMINOETHYL)-1,3-
PROPANEDIAMINE
3,3'-IMINOBISSOPROPYLAMINE
1,4-DIAMINOBUTANE
1,5-DIAMINOPENTANE
1,6-HEXANEDIAMINE
1,7-DIAMINOHEPTANE
1,8-DIAMINOOCCTANE
1,9-DIAMINONONANE
N,N'-DIETHYL-2-BUTENE-1,4-DIAMINE
P-XYLYLENEDIAMINE
D-ARGININE MONOHYDROCHLORIDE
(+/-)-3-AMINOPIPERIDINE
DIHYDROCHLORIDE
2,2'-OXYBIS(ETHYLAMINE)
DIHYDROCHLORIDE
CYSTAMINE DIHYDROCHLORIDE
D-ORNITHINE HYDROCHLORIDE
D-LYSINE MONOHYDROCHLORIDE
AGMATINE SULFATE
2-METHYL-1,5-DIAMINOPENTANE
ISOPHORONEDIAMINE

-21-

2-N-BUTYLAMINOETHYLAMINE
1,4-DIAMINOCYCLOHEXANE
S-(2-AMINOETHYL)-L-CYSTEINE
HYDROCHLORIDE
N,N-DIETHYLDIETHYLENETRIAMINE
TERT-BUTYL N-(6-AMINOHEXYL) CARBAMATE
HYDROCHLORIDE
1,4-BIS(AMINOMETHYL) CYCLOHEXANE
1,8-DIAMINO-3,6-DIOXAOCANE
N-BENZYLETHYLENEDIAMINE
PIPERAZINE-2-CARBOXYLIC ACID
DIHYDROCHLORIDE
L-CYSTINE DIHYDROXAMATE
L-ARGININE HYDROXAMATE
HYDROCHLORIDE
DIAMINOBIOITIN
L-LYSINE HYDROXAMATE
HYDROCHLORIDE
L-LYSINAMIDE DIHYDROCHLORIDE
3-AMINOPYRROLIDINE
DIHYDROCHLORIDE
(1R,2R)-(-)-1,2-DIAMINOCYCLOHEXANE
(1S,2S)-(+)-1,2-DIAMINOCYCLOHEXANE
CIS-1,2-DIAMINOCYCLOHEXANE
TRANS-1,2-DIAMINOCYCLOHEXANE
L-CYSTINE
L-LYSINE
L(-)-ALPHA-AMINO-EPSILON-CAPROLACTAM
L-ARGININE MONOHYDROCHLORIDE
L-ARGININE MONOHYDROCHLORIDE
L-2,4-DIAMINOBUTYRIC ACID
DIHYDROCHLORIDE
L-ORNITHINE MONOHYDROCHLORIDE
L-ORNITHINE MONOHYDROCHLORIDE
DL-LYSINE MONOHYDROCHLORIDE
DL-LYSINE MONOHYDROCHLORIDE
L-LYSINE MONOHYDROCHLORIDE
DL-ORNITHINE MONOHYDROCHLORIDE
L-LYSINE DIHYDROCHLORIDE
DL-HOMOCYSTINE
TRANS-2,5-DIMETHYLPYPERAZINE
ETHAMBUTOL DIHYDROCHLORIDE
(1S,2S)-(-)-1,2-DIPHENYLETHYLENEDIAMINE
(1R,2R)-(+)-1,2-DIPHENYLETHYLENEDIAMINE
DL-CYSTINE

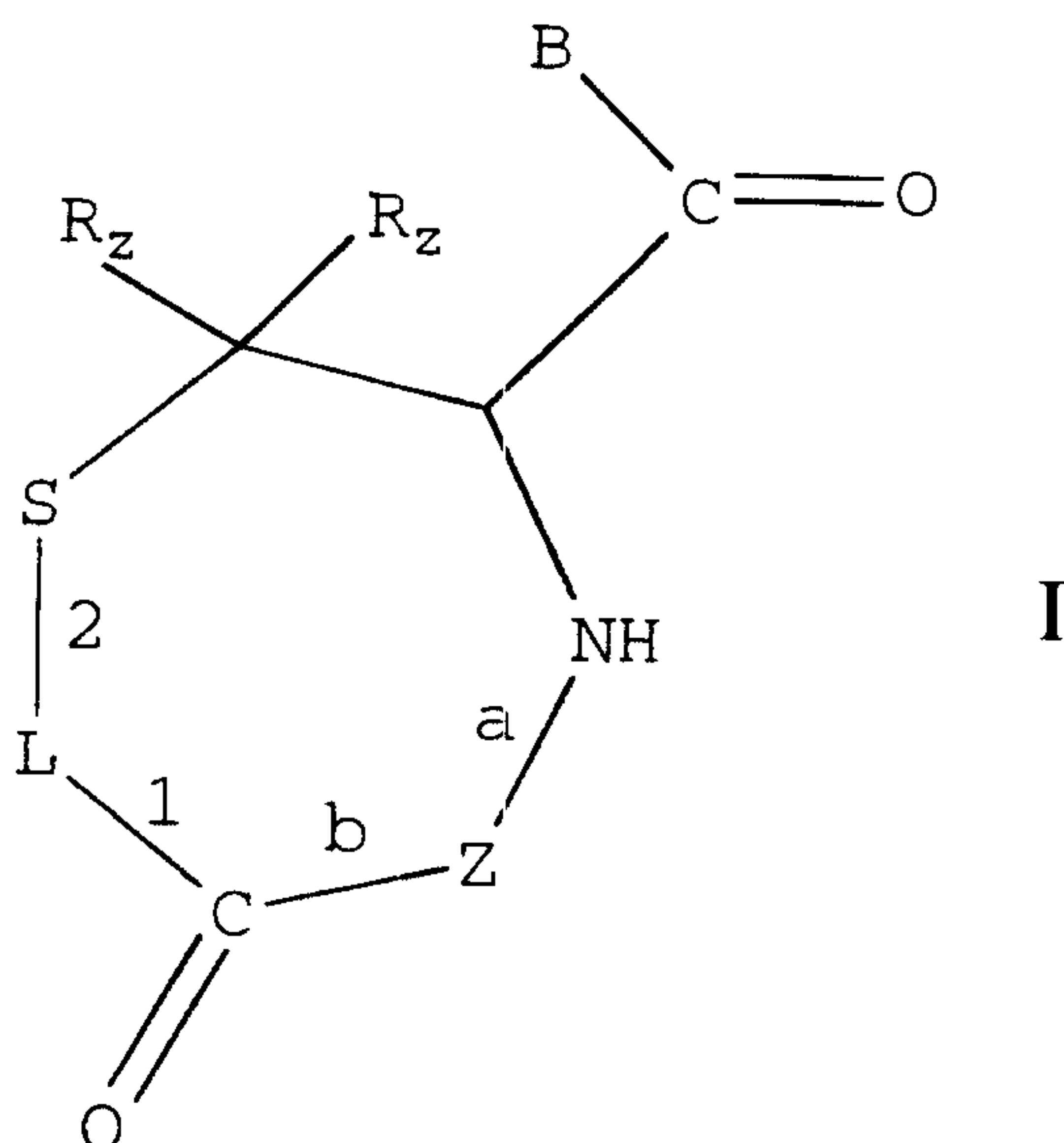
-22-

1,3-DIAMINOPENTANE
 (4S,5S)-4,5-DI(AMINOMETHYL)-2,2-DIMETHYLDIOXOLANE
 PIPERAZINE HEXAHYDRATE
 (S)-(+)-2-METHYLPIPERAZINE
 (S)-(+)-2-(AMINOMETHYL)PYRROLIDINE
 N1-ISOPROPYLDIETHYLENETRIAMINE
 (R)-(-)-2-METHYLPIPERAZINE
 N-PHENYL-4-PIPERIDINAMINE
 2-AMINO-6-FLUOROBENZYLAMINE
 2-AMINO BENZYLAMINE
 4-AMINO BENZYLAMINE,
 and the like.

In accordance with another embodiment of this invention there is provided a library of macrocycle compounds of Formula I wherein the divalent group Z is
 5 selected so that $a_1 + a_2 + a_3 + a_4 + a_5 + a_6 = 0$ to 6 in integral steps. In other words, one to six amino acids can be integrated into the macrocycle ring. In a related embodiment of the invention the library compounds are also defined so that $t_1 + t_2 + t_3 = 1, 2$ or 3. Illustrative of
 10 the divalent group Z in those embodiments include, but are not intended to be limited to:

a ATA₁ b ,
 a AA₁-ATA₁-ATA₂-AA₄ b ,
 15 a ATA₁-AA₃-ATA₂ b ,
 a AA₁-ATA₁-ATA₂-AA₄-AA₅ b ,
 a ATA₁-AA₃-AA₄-ATA₃ b ,
 a ATA₁-ATA₂-ATA₃-AA₅ b ,
 a AA₁-ATA₂-ATA₃-AA₅-AA₆ b ,
 20 a AA₃-ATA₂-AA₄ b ,
 a ATA₂-AA₄-ATA₃-AA₅ b ,
 a AA₁-ATA₁-ATA₂-ATA₃ b ,
 a AA₄-ATA₃-AA₅-AA₆ b ,
 a AA₁-ATA₁ b ,
 25 a ATA₁-AA₃ b , and
 a ATA₁-AA₃-ATA₂-ATA₃ b .

One preferred embodiment of the invention is a library of macrocyclic compounds of the formula

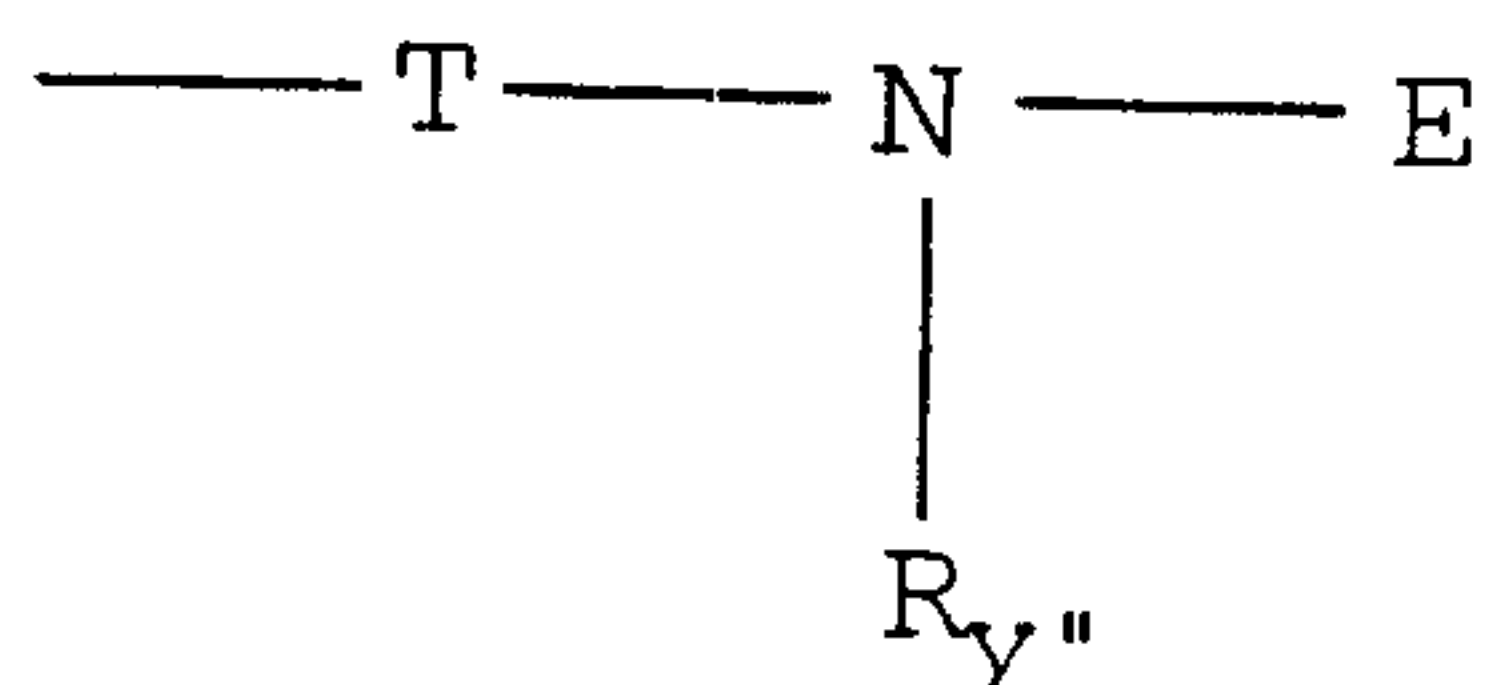


wherein

L is a divalent group of the formula $^1(\text{CH}_2)_{0-1}-\text{C}_6\text{H}_4\text{CH}_2^2$ or $-\text{CHR}_a-$ wherein R_a is hydrogen or an organic moiety;

R_Z is hydrogen or methyl;

10 B is hydroxy or a group of the formula $-NR_yR_t$ wherein R_y is hydrogen, alkyl, aryl or heterocycle, and R_t is hydrogen, a solid support, or R_t is a group of the formula



15 wherein E is hydrogen, a solid support or a
substituent derived from an electrophilic reagent, T is a
divalent linking group, and R_y" is hydrogen or a
substituent derived from an electrophilic reagent; or R_y
and R_y" taken together with the atoms to which they are
20 bonded form a 4- to 7-membered ring or a bicyclic or
tricyclic ring comprising 6 to 12 carbon atoms; or R_y or
R_y" taken together with -T- and the atoms to which they
are commonly bonded form a 6- to 7-membered ring or R_y and

-24-

R_y" each taken together with T and the nitrogen atom to which they are respectively bonded form a 5- to 7-membered ring;

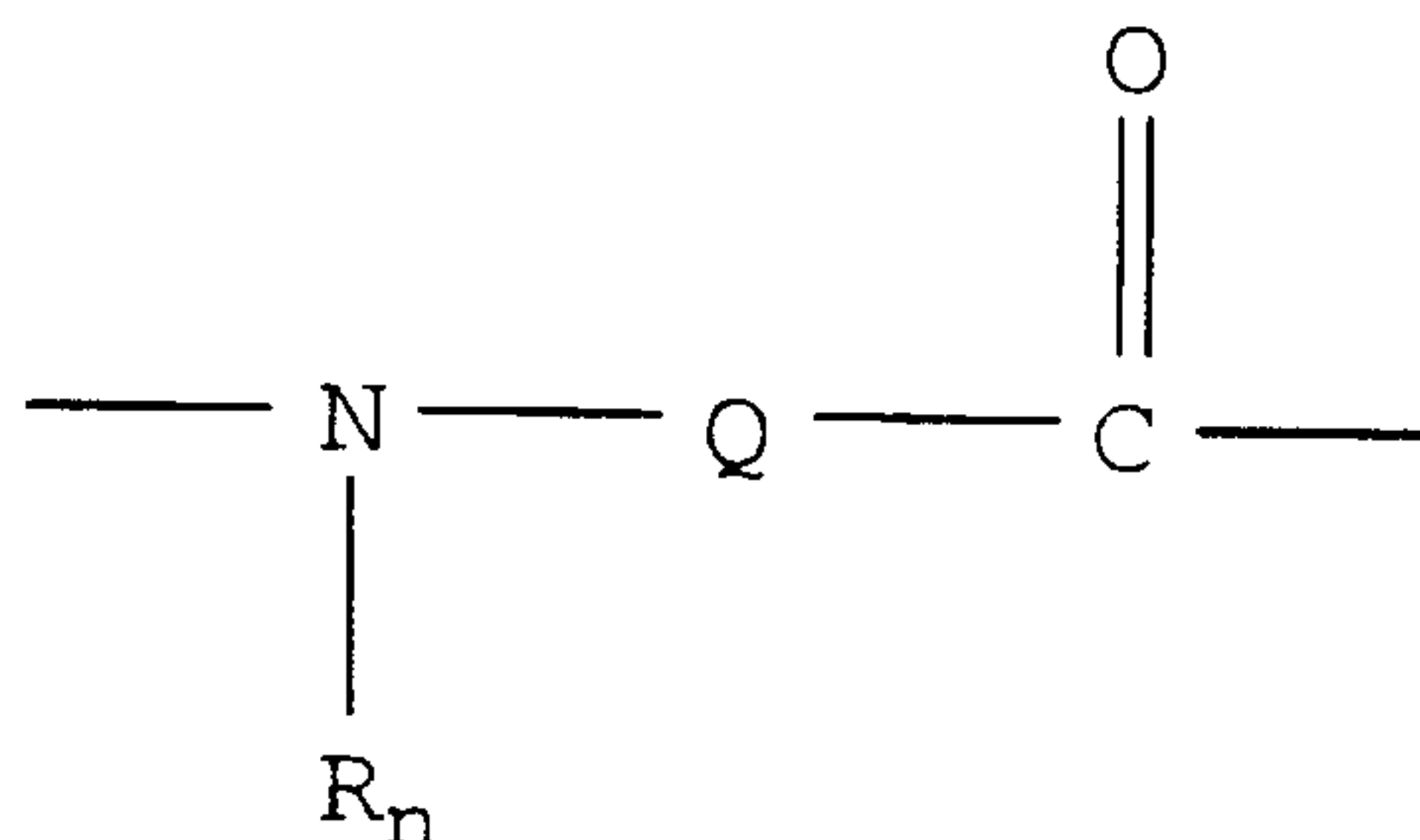
Z is a divalent group of the formula

5



wherein AA₁ and AA₃ are independently a divalent group of the formula

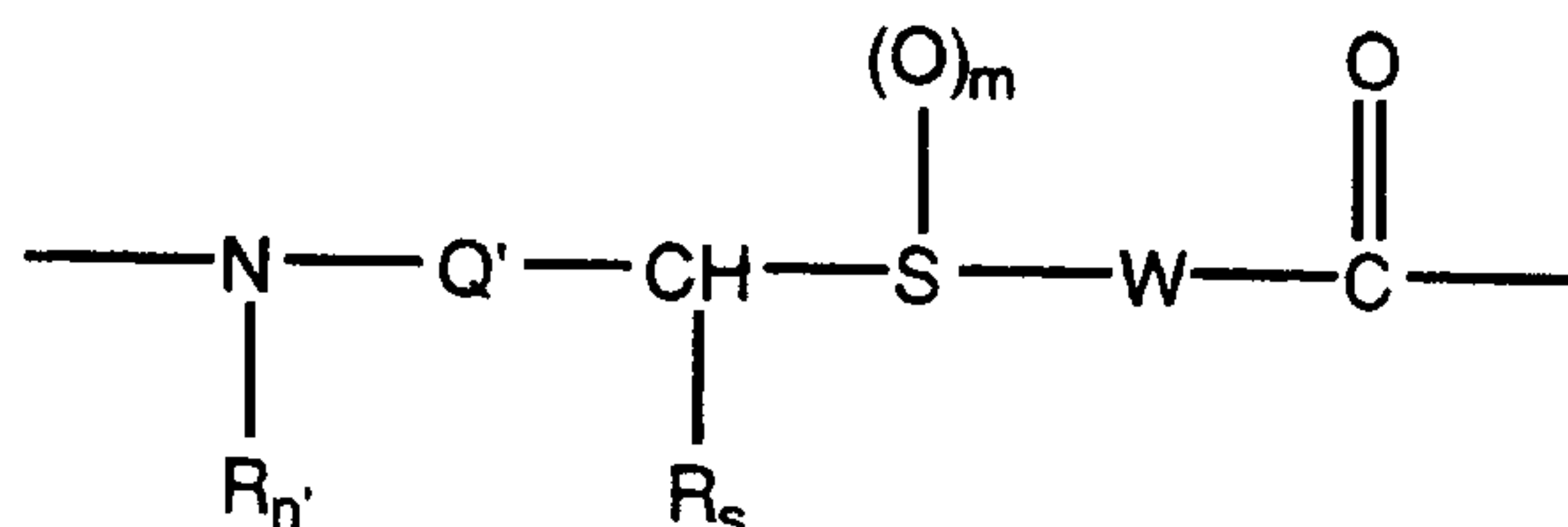
10



and

ATA is a divalent sulfur group of the formula

15



wherein W is a divalent organic group comprising 1 to 12 carbon atoms and 0 to 4 heteroatoms selected from the group consisting of O, N and S;

20

Q and Q' are each independently an organic group comprising 1 to 12 carbon atoms and 0 to 4 heteroatoms selected from O, N and S;

m is 0, 1 or 2;

R_s is hydrogen or an organic moiety; and

25

R_n' is hydrogen, or an organic moiety, or R_n taken together with Q and the atoms to which they are bonded form a 4- to 7-membered ring;

-25-

R_n' and R_s taken together with $-Q'$ - and the atoms to which they are bonded form a 4- to 7-membered ring or a bicyclic or tricyclic ring comprising 6 to 12 carbon atoms; or

5 R_n' or R_s taken together with $-Q'$ - and the atoms to which they are commonly bonded form a 4- to 7-membered ring.

Another embodiment of this invention provides a library of macrocycle compounds of Formula I wherein each
10 amino acid used to form the macrocycle is a proteiogenic amino acid.

Still another embodiment of this invention is directed to a library of macrocycle compounds of the Formula I above wherein Q and/or Q' is a group of the
15 formula



wherein R_1 is hydrogen, or a non-interfering
20 substituent; and

R_2 is hydrogen or an organic moiety; or

R_1 taken together with R_n forms a 4- to 7-membered ring, or R_1 taken together with R_s forms a 4- to 7-membered ring; or R_1 taken together with R_2 forms a 3- to
25 6-membered ring.

In still another embodiment there is provided a diverse library of macrocycle compounds of Formula I wherein W is a divalent organic group selected from the
30 group consisting of $-\text{CHR}_8-$, $-\text{CR}_4\text{R}_5\text{CR}_6\text{R}_7-$, and a 5- or 6-membered aromatic ring containing 0 to 4 heteroatoms selected from O, N and S;

-26-

wherein R₈ is hydrogen or an organic group;

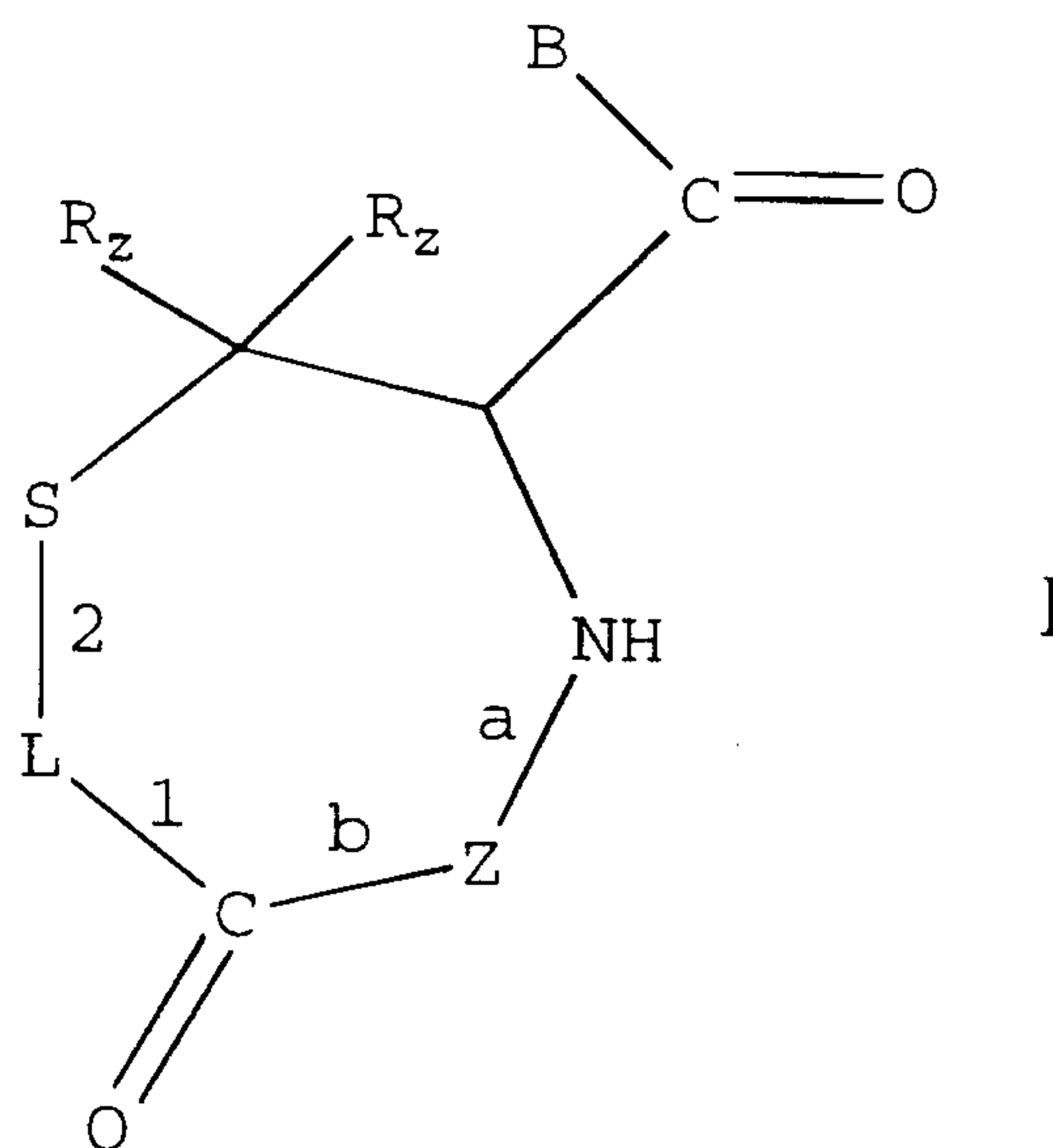
R₄, R₅, and R₆ are independently hydrogen or alkyl;

and

R₇ is hydrogen, hydroxy, protected hydroxy, amino or
 5 protected amino or substituted amino wherein the
 substituent is derived from an electrophilic group.

The present library compounds can be prepared using
 combinatorial synthesis protocols, or individual
 macrocycle library compounds can be prepared by standard
 10 chemical synthesis techniques and used as core structure
 for preparation of directed libraries.

Further in accordance with this invention there is
 provided a process for preparing a combinatorial library
 of compounds of the formula



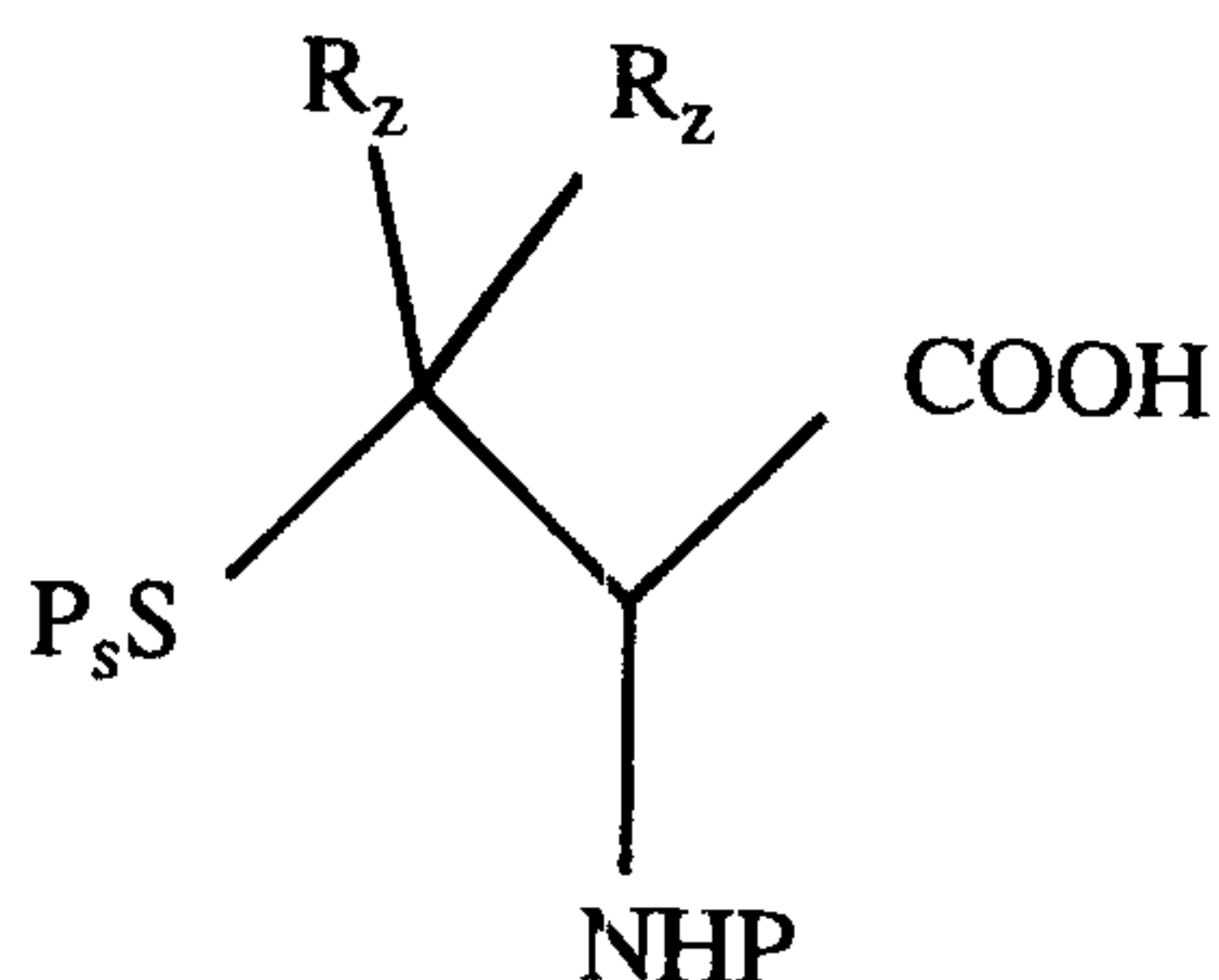
15

wherein L, Z, R_z and B are as defined above. The process
 comprises the steps of:

(a) covalently bonding an amino-protected, thiol-
 protected starting material of the formula

20

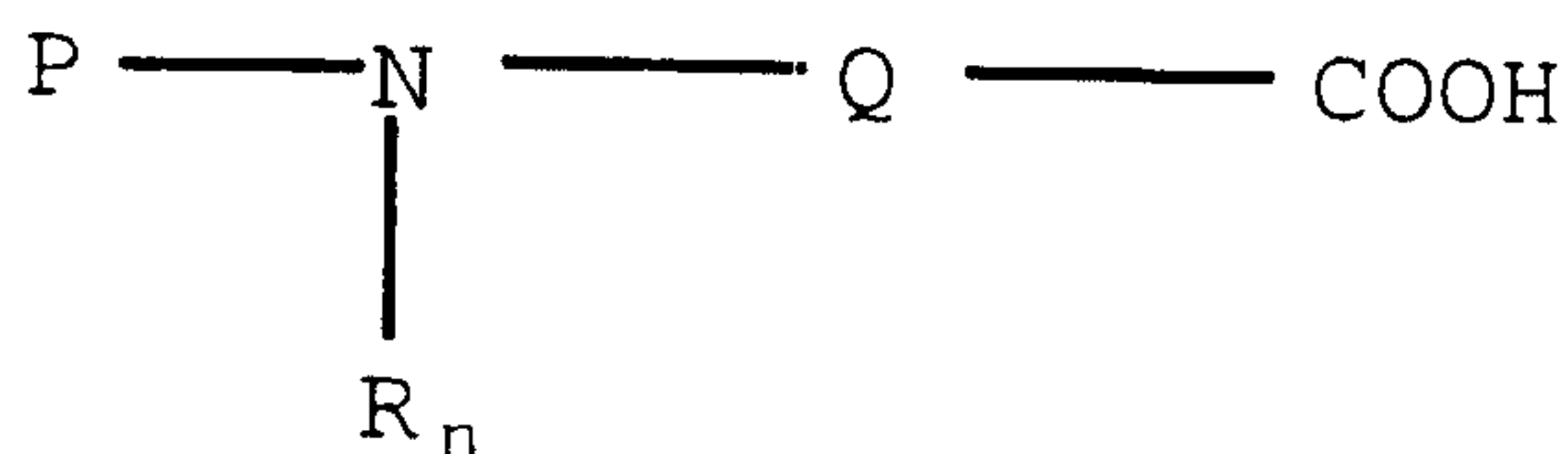
-27-



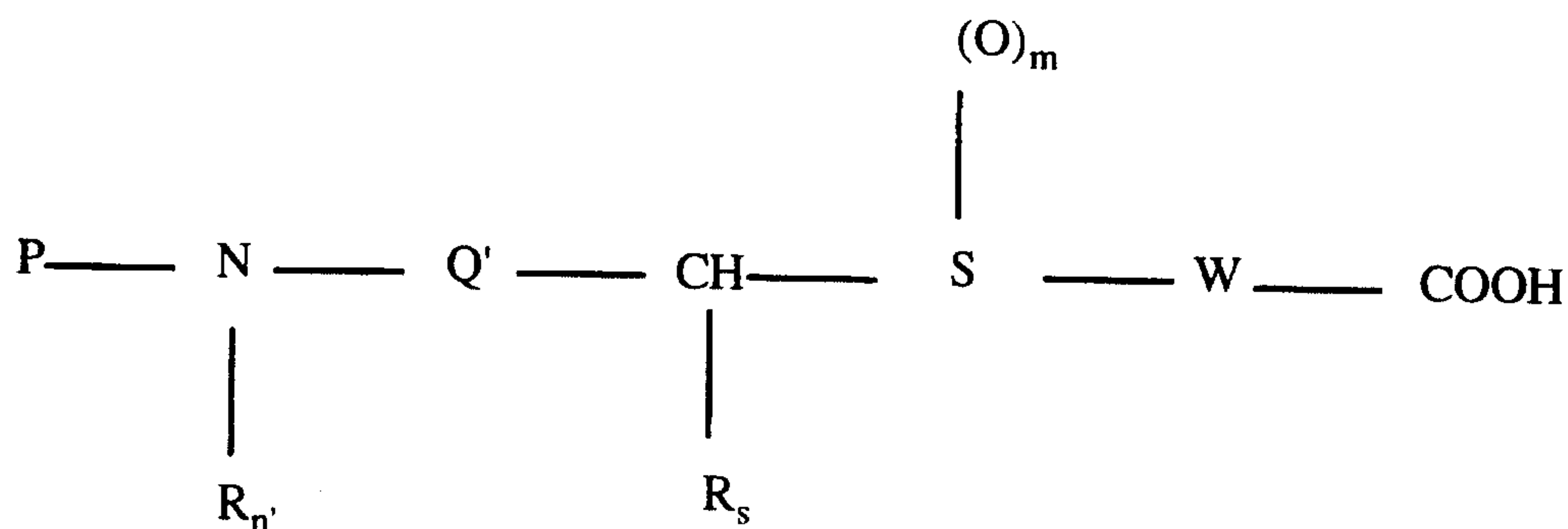
wherein R_z is defined as above, and P_s and P are thiol- and amino-protecting groups, respectively, to a solid support including acid reactive groups;

(b) removing the amino protecting group on the solid support bound starting material;

(c) coupling the resulting solid support bound thio-protected starting material with an amino-protected amino acid of the formula



or an amino-protected compound of the formula



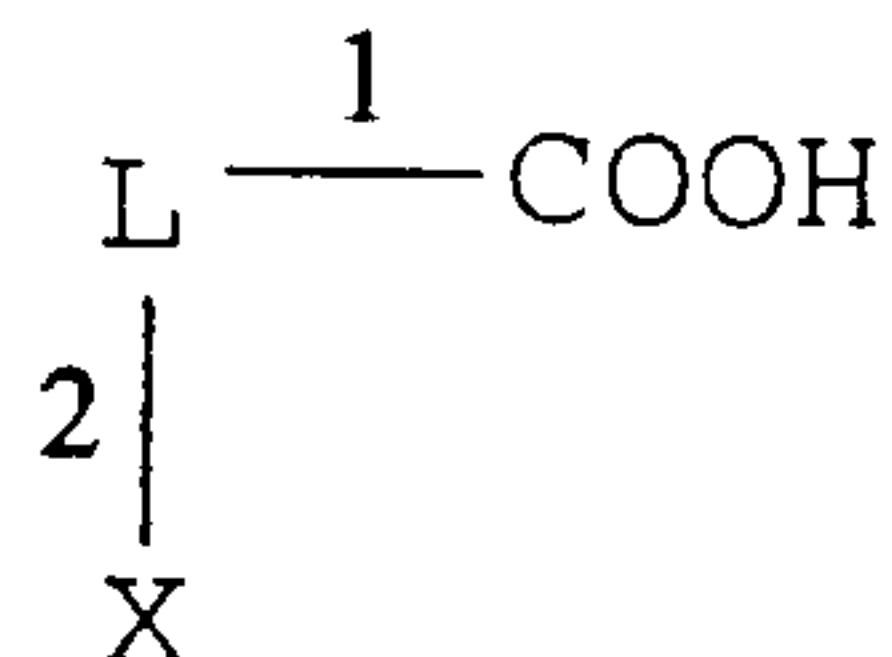
wherein in said formulas P is an amino-protecting group and, R_n , $R_{n'}$, Q , Q' , R_s , m and W are as defined above;

(d) removing the amino-protecting group from the coupled solid support bound product;

-28-

(e) optionally repeating step (c) and step (d) one or more times using the same or a different amino-protected amino acid or amino-protected thioether acid

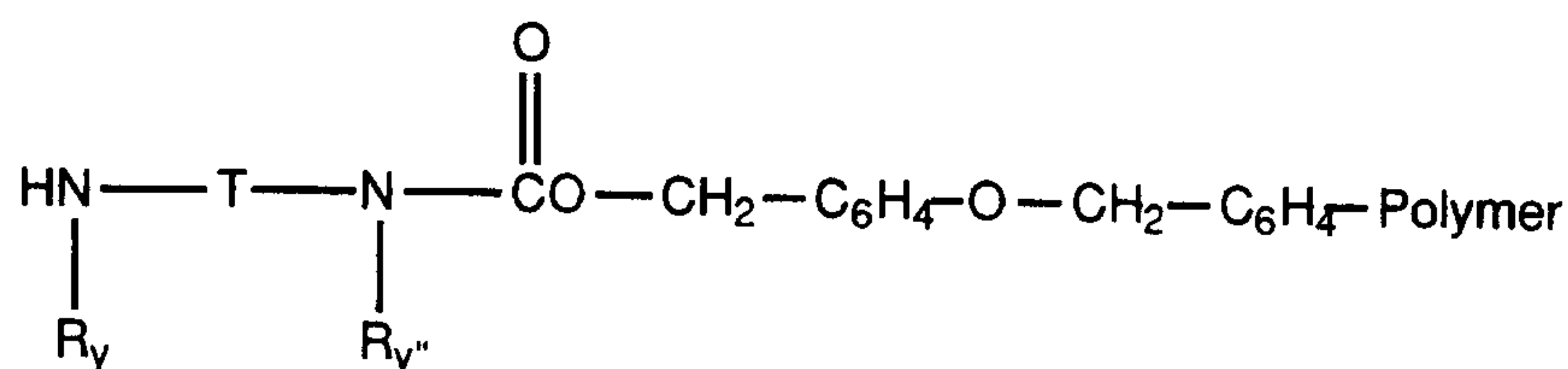
(f) coupling the solid support bound product with an
5 organic acid of the formula



wherein L is as defined above and X is a leaving group
10 subject to nucleophilic displacement;

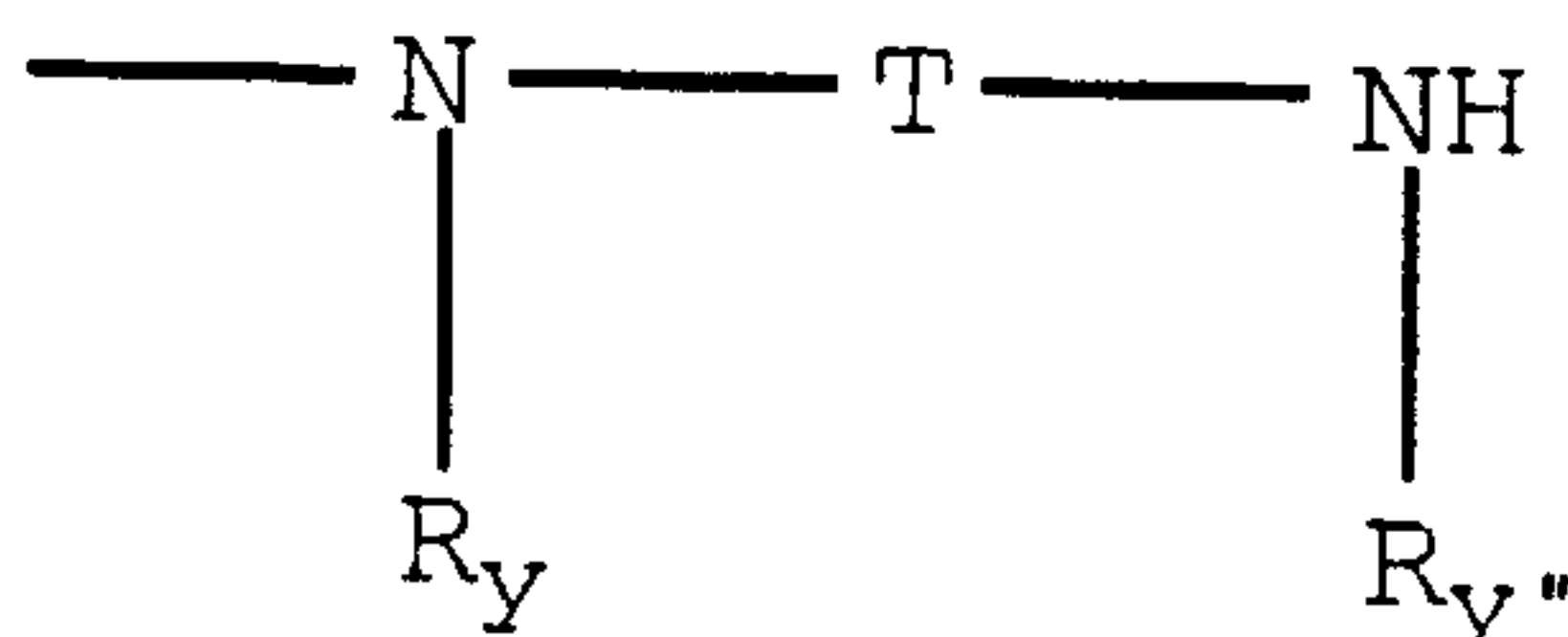
(g) removing the thiol-protecting group to enable macrocycle formation by nucleophilic displacement of the group X and cleaving the covalently bound product from the solid support; and

15 (h) when the acid reactive group on the solid support is a covalently bound group of the formula



20

optionally reacting the resulting product of Formula I wherein B is a group of the formula



25

with an amine reactive organic electrophilic agent;

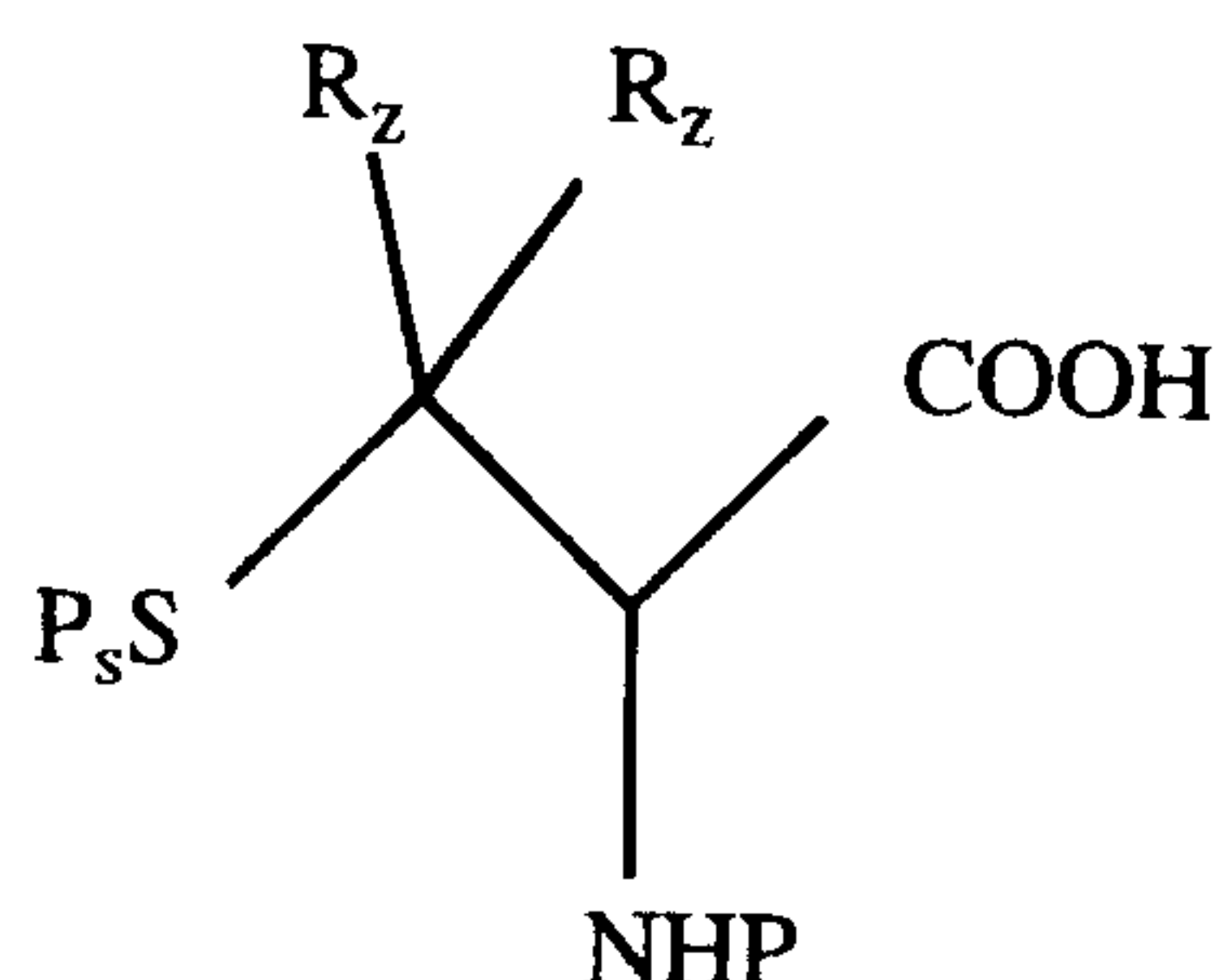
-29-

provided that at least one of the steps (c) and (e) is carried out using an amino-protected aminothioether acid.

Each of the reaction steps, whether conducted on solid phase or in solution phase, is carried out using a dry, inert, polar, aprotic solvent at a temperature of about 0° to about 30°C. In the case of solution phase reactions, stoichiometrically equivalent amounts or near stoichiometric amounts of reactants are typically employed. The use of solid phase synthesis for most of the process steps (the cyclization step can be conducted in solid phase or solution phase) allows the flexibility of using excess reagents to optimize yield without complicating product isolation. Using solid phase synthesis techniques, effective work-up to remove any excess reagents comprises washing the solid support bound product one or more times with reaction solvent. Suitable solvents for carrying out the process steps include dimethylformamide, dimethylsulfide, tetrahydrofuran, N-methylpyrrolidone, dioxane, ethyl acetate, diethyl ether and the like. The reaction steps can be carried out using standard combinatorial chemistry protocols to produce arrays of the present library compounds, or they can be carried out on larger scale using standard chemical synthesis, work-up, and product isolation and purification procedures.

The initial step in the process for preparation of the present library compounds of formula I comprises covalently bonding to a solid support an amino-protected, thiol-protected starting material of the formula

-30-



wherein R_z is defined as above, and P_s and P are thiol-protecting and amino-protecting groups, respectively, wherein the solid support includes covalently bound acid reactive groups (e.g. hydroxy or primary or secondary amino). Suitable thiol-protecting groups include, but are not intended to be limited to, trityl(triphenylmethyl), 4-methoxyphenyl-diphenylmethyl, di(4-methoxyphenyl)phenylmethyl, and the like. Exemplary of monovalent amino-protecting groups include, but are not intended to be limited to:

9-fluorenylmethyloxycarbonyl (Fmoc),
tert-butyloxycarbonyl (Boc),
 allyloxycarbonyl (Alloc),
 2-trimethylsilylethoxycarbonyl (Teoc),
 biphenylisopropylloxycarbonyl (Bpoc),
 nitroveratryloxycarbonyl (Nvoc),
 (4-methoxyphenyl)diphenylmethyl (MMTr),
 (4,4'-dimethoxyphenyl)phenylmethyl (DMT) and
 benzyloxycarbonyl (Cbz or Z),
 and the like.

Reaction conditions for the preparation of protected amines utilizing such protecting groups and conditions for the selective removal of such groups to provide the corresponding amines are well-known in the art. See for example, "Protective Groups in Organic Synthesis" 2nd ed., by Theodora W. Greene and Peter G.M. Wuts (1991), John Wiley and Sons (New York).

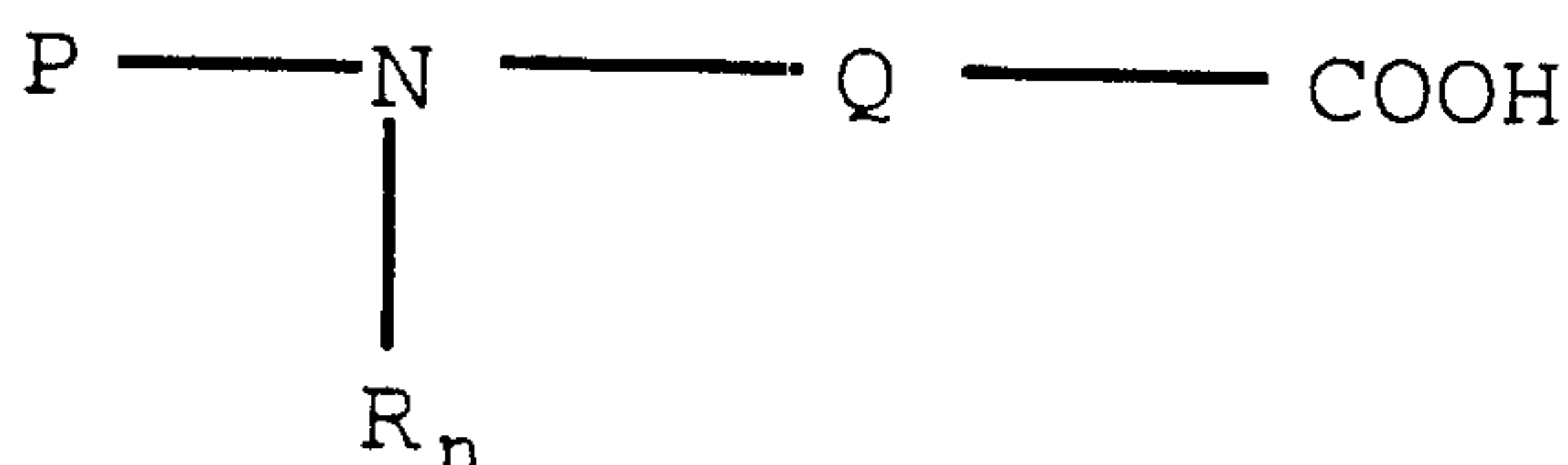
Covalent coupling of orthogonally protected cysteine or penicillamine to the solid support is carried out by forming an activated form of the acid, such as an active

-31-

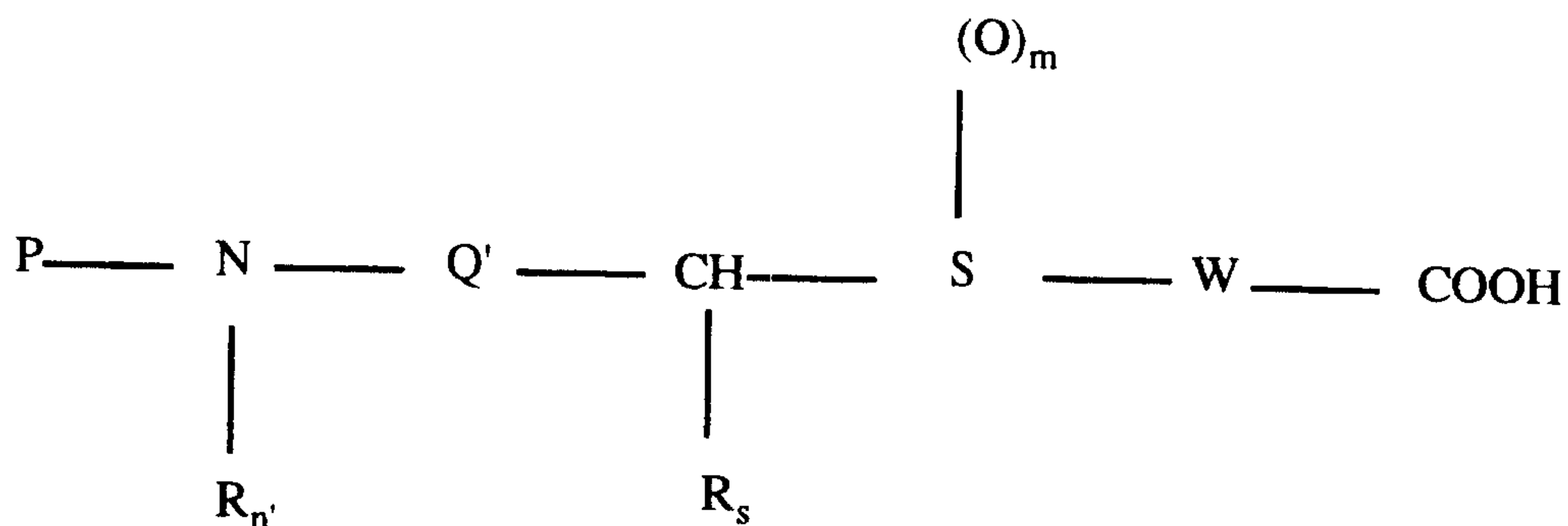
ester, and reacting the activated form with the solid support, typically using an excess (2-10 fold) of the activated form to optimize yield of the support-coupled product. Excess reagent is washed from the reacted solid support.

The support-coupled product is then reacted to remove amino-protecting groups using the protecting group dependent cleavage conditions. Thus, for example, the fluorenylmethyloxycarbonyl group, a preferred amino-protecting group for solid phase synthesis, is removed by treatment of the solid support bound product with from about 20% to about 30% piperidine in dimethylformamide.

The resulting solid support bound thio-protected starting material is then coupled with an amino-protected amino acid of the formula



or an amino-protected ATA of the formula



wherein P is an amino-protecting group and R_n , $\text{R}_{n'}$, Q, Q', R_s , m and W are as defined above. The coupling reaction is carried out under conditions paralleling those described above for coupling the orthogonally protected cysteine or penicillamine to the solid support using a 2-

-32-

10 fold excess of an activated form of the protected amino acid or ATA.

Any of a wide variety of commercially available or readily synthesized amino acids can be employed in this step. The protected amino acids typically have a molecular weight of about 75 to about 800. Exemplary of such amino acid reactants (and protected derivatives thereof) suitable for use in this process include, but are not intended to be limited to, the following:

10

1-AMINO-1-CYCLOPENTANECARBOXYLIC ACID
1-AMINO-1-CYCLOHEXANECARBOXYLIC ACID
N-ALPHA-CBZ-L-ARGININE
N-ALPHA-BENZOYL-L-ARGININE
CHLOROACETYL-L-TYROSINE
DL-M-TYROSINE
L-DOPA
4-BROMO-DL-PHENYLALANINE
DL-4-FLUOROPHENYLALANINE
DL-4-CHLOROPHENYLALANINE
O-METHYL-L-TYROSINE
O-BENZYL-L-TYROSINE
L-TYROSINE
3-iodo-L-TYROSINE
S-(TERT-BUTYLTHIO)-L-CYSTEINE HYDRATE
D-CYSTINE
S-TRITYL-L-CYSTEINE
S-METHYL-L-CYSTEINE
S-BENZYL-L-CYSTEINE
S-CARBOXYMETHYL-L-CYSTEINE
LANTHIONINE
L-ASPARTIC ACID
L-LEUCINE
DL-HOMOSERINE
L-HOMOPHENYLALANINE
DL-METHIONINE SULFOXIDE
L-METHIONINE SULFOXIMINE
D-METHIONINE
L-ETHIONINE
L-C-ALLYLGLYCINE
GAMMA-L-GLUTAMYL-L-GLUTAMIC ACID
L-GLUTAMIC ACID 5-METHYL ESTER
L-GLUTAMIC ACID GAMMA-BENZYL ESTER
L-GLUTAMIC ACID
L-ARGININE
L-ALPHA-AMINOADIPIC ACID
2,6-DIAMINOPIMELIC ACID

-33-

N-EPSILON-CBZ-L-LYSINE
N-EPSILON-ACETYL-L-LYSINE
N-CBZ-L-ALANINE
Z-L-SERINE
N-(TERT-BUTOXYCARBONYL)-L-PHENYLALANINE
5-BROMO-N-(CARBOXYMETHYL) ANTHRANILIC ACID
N-(4-HYDROXYPHENYL) GLYCINE
N-(TERT-BUTOXYCARBONYL) GLYCINE
N-CBZ-GLYCINE
HIPPURIC ACID
2-iodohippuric acid
2-HYDROXYHIPPURIC ACID
Z-L-ASPARTIC ACID
L-ASPARTYL-L-PHENYLALANINE METHYL ESTER
N-CBZ-L-GLUTAMIC ACID
N-ACETYL-L-GLUTAMIC ACID
DL-ALPHA-METHYLTYROSINE
N-CARBOBENZYLOXY-2-METHYLALANINE
2-(METHYLAMINO) ISOBUTYRIC ACID
ALPHA-HYDROXYHIPPURIC ACID
ETHYLENEDIAMINE-DI(O-HYDROXYPHENYLACETIC ACID)
D-(-)-P-HYDROXYPHENYLGLYCINE
D-PENICILLAMINE DISULFIDE
D-TERT-LEUCINE
DL-DOPS
DL-VALINE
DL-ISOLEUCINE
D-SERINE
D-PHENYLALANINE
DL-2-FLUOROPHENYLALANINE
6-HYDROXYDOPA
DL-3-FLUOROPHENYLALANINE
N-ACETYLGLYCINE
N-TRITYLGLYCINE
TRICINE
GUANIDOACETIC ACID
SARCOSINE
IMINODIACETIC ACID
ETHYLENEDIAMINE-N,N'-DIACETIC ACID
D-ALLO-THREONINE
N-CBZ-S-BENZYL-L-CYSTEINE
N-ACETYL-DL-PENICILLAMINE
DL-PENICILLAMINE
DL-CYSTEINE
DL-HOMOCYSTEINE
L-AZETIDINE-2-CARBOXYLIC ACID
L-CARNOSINE
DL-HISTIDINE
L-THIAZOLIDINE-4-CARBOXYLIC ACID
3,4-DEHYDRO-DL-PROLINE
3-AMINOPYRAZOLE-4-CARBOXYLIC ACID

-34-

DL-PROLINE
CIS-4-HYDROXY-D-PROLINE
DL-ALPHA-(2-THIENYL) GLYCINE
BETA-2-THIENYL-DL-ALANINE
L-ABRINE
D-TRYPTOPHAN
5-BROMO-DL-TRYPTOPHAN
5-FLUORO-DL-TRYPTOPHAN
DL-5-METHOXYTRYPTOPHAN
DL-5-HYDROXYTRYPTOPHAN
5-METHYL-DL-TRYPTOPHAN
6-FLUORO-DL-TRYPTOPHAN
1-METHYL-DL-TRYPTOPHAN
L-PIPECOLINIC ACID
NIPECOTIC ACID
ISONIPECOTIC ACID
NITRO-L-ARGININE
3-NITRO-L-TYROSINE
4-NITROHIPPURIC ACID
DL-HOMOCYSTEIC ACID
P-AMINOOXANILIC ACID
4-AMINOHIPPURIC ACID
ALBIZZIIN
DL-CITRULLINE
S-CARBAMYL-L-CYSTEINE
N-ALPHA-CBZ-L-ASPARAGINE
D-ASPARAGINE
N-CBZ-L-GLUTAMINE
L-GLUTAMINE
2,2-DIPHENYLGLYCINE
2-AMINOISOBUTYRIC ACID
D-(-)-ALPHA-PHENYLGLYCINE
DL-3-AMINO-3-PHENYLPROPIONIC ACID
D-ALANINE
DL-3-AMINO BUTYRIC ACID
DL-2-AMINO BUTYRIC ACID
D-NORVALINE
D-NORLEUCINE
DL-2-AMINO-N-CAPRYLIC ACID
DL-2-AMINO-N-CAPRYLIC ACID
GLYCINE
DL-ISOSERINE
DL-4-AMINO-3-HYDROXYBUTYRIC ACID
DL-3-AMINOISOBUTYRIC ACID
BETA-ALANINE
4-AMINO BUTYRIC ACID
5-AMINO VALERIC ACID
N-ALPHA-ACETYL-L-LYSINE
Z-L-VALINE
N-(4-NITROBENZOYL)-BETA-ALANINE
N-(4-AMINO BENZOYL)-BETA-ALANINE

-35-

1-AMINOCYCLOPROPANE-1-CARBOXYLIC ACID
(R)-(-)-N-(3,5-DINITROBENZOYL)-ALPHA-PHENYLGLYCINE
N-(3,5-DINITROBENZOYL)-DL-LEUCINE
(+/-)-3-AMINOADIPIC ACID
ALPHA-METHYL-DL-PHENYLALANINE
DL-2-AMINO-5-PHOSPHONOVALERIC ACID
DL-3-HYDROXYNORVALINE HYDRATE
(+/-)-INDOLINE-2-CARBOXYLIC ACID
BETA-(2-THIAZOLYL)-DL-ALANINE
L-GAMMA-CARBOXYGLUTAMIC ACID
L-2-(BENZYLOXYCARBONYLAMINO)-4-SULFAMOYLBUTYRIC ACID
L-2-AMINO-4-SULFAMOYLBUTYRIC ACID
1-AMINO-1-CYCLOPROPANECARBOXYLIC ACID HYDROCHLORIDE
SARCOSINE HYDROCHLORIDE
4-(METHYLAMINO)BUTYRIC ACID HYDROCHLORIDE
L-TYROSINE HYDROCHLORIDE
L-GLUTAMIC ACID HYDROCHLORIDE
D-ARGININE MONOHYDROCHLORIDE
N-EPSILON-METHYL-L-LYSINE HYDROCHLORIDE
L-HOMOARGININE HYDROCHLORIDE
2-AMINO-3-PHENYLBUTANOIC ACID HYDROCHLORIDE
(+/-)-1,2,3,4-TETRAHYDRO-3-ISOQUINOLINECARBOXYLIC
ACID HYDROCHLORIDE
DL-PIPECOLINIC ACID HYDROCHLORIDE
5-AMINOLEVULINIC ACID HYDROCHLORIDE
GLYCINE HYDROCHLORIDE
5-HYDROXY-DL-LYSINE HYDROCHLORIDE
DL-2,3-DIAMINOPROPIONIC ACID HYDROBROMIDE
DL-2,3-DIAMINOPROPIONIC ACID MONOHYDROCHLORIDE
DL-2,4-DIAMINOBUTYRIC ACID DIHYDROCHLORIDE
D-ORNITHINE HYDROCHLORIDE
D-ORNITHINE HYDROCHLORIDE
5-AMINOVALERIC ACID HYDROCHLORIDE
D-LYSINE MONOHYDROCHLORIDE
DL-2-AMINO-4-PHOSPHONO BUTYRIC ACID
DL-2-AMINO-4-PHOSPHONO BUTYRIC ACID
N-PHENYLGLYCINE
DL-2-AMINO-3-PHOSPHONOPROPIONIC ACID
N-CBZ-L-PHENYLALANINE
N-(CARBOXYMETHYL)ANTHRANILIC ACID
N-(P-TOLUOYL)-GLYCINE
L-ASPARTIC ACID MONOPOTASSIUM SALT
L-ASPARTIC ACID MONOPOTASSIUM SALT
N-CARBOBENZYLOXY-L-LEUCINE
N-CARBOBENZYLOXY-L-ISOLEUCINE
3-AMINO-2,3-DIHYDROBENZOIC ACID HYDROCHLORIDE
FMOC-L-VALINE
N-ALPHA-FMOC-L-ISOLEUCINE
FMOC-L-TRYPTOPHAN
N-ALPHA-FMOC-L-PHENYLALANINE
N-ALPHA-FMOC-L-ASPARAGINE

-36-

FMOC-L-LEUCINE
FMOC-L-METHIONINE
N-ALPHA-FMOC-L-GLUTAMINE
FMOC-GLYCINE
N-(TERT-BUTOXYCARBONYL)-L-TYROSINE
N-EPSILON-BOC-L-LYSINE
N-(TERT-BUTOXYCARBONYL)-L-ALANINE
N-(TERT-BUTOXYCARBONYL)-L-SERINE
N-(P-TOLUENESULFONYL)-L-PHENYLALANINE
STATINE
BOC-L-ASPARTIC ACID
N-ALPHA-BOC-L-ASPARAGINE
N-ALPHA-BOC-L-LYSINE
N-ALPHA-CBZ-L-LYSINE
N-(TERT-BUTOXYCARBONYL)-L-ISOLEUCINE
N-(TERT-BUTOXYCARBONYL)-D-METHIONINE,
DICYCLOHEXYLAMMONIUM SALT
BOC-L-ARGININE
DL-(2-FLUOROPHENYL)-GLYCINE
L-ALPHA-(2-AMINOETHOXYVINYL) GLYCINE HYDROCHLORIDE
N-P-TOSYLGLYCINE
BETA-GUANIDINOPROPIONIC ACID
N-(PHOSPHONOMETHYL)-GLYCINE
N-ALPHA-FMOC-D-TRYPTOPHAN
DL-3-(3,4-DIHYDROXYPHENYL) ALANINE
4-CHLORO-L-PHENYLALANINE
P-iodo-D-PHENYLALANINE
O-PHOSPHO-DL-TYROSINE
D-TYROSINE
DL-TYROSINE
3-FLUORO-DL-TYROSINE
D-ASPARTIC ACID
DL-ASPARTIC ACID
DL-LEUCINE
D-LEUCINE
L-HOMOSERINE
D-HOMOPHENYLALANINE
DL-HOMOPHENYLALANINE
DL-METHIONINE
L-METHIONINE
D-ETHIONINE
DL-ETHIONINE
DL-2-AMINO-4-PENTENOIC ACID
D-GLUTAMIC ACID
D-ARGININE
D-ALPHA-AMINOADIPIC ACID
DL-ALPHA-AMINOADIPIC ACID
N-CBZ-DL-ALANINE
N-CARBOBENZOXY-DL-SERINE
DL-THREONINE
L-ALPHA-METHYLTYROSINE

- 37 -

L-TERT-LEUCINE
D-VALINE
L-VALINE
D-ISOLEUCINE
L-ISOLEUCINE
DL-SERINE
L-SERINE
DL-PHENYLALANINE
L-PHENYLALANINE
L-CYSTINE
L-ALLO-THREONINE
D-THREONINE
L-THREONINE
D-PENICILLAMINE
L-PENICILLAMINE
L-CYSTEINE
L-HISTIDINE
D-PROLINE
L-PROLINE
CIS-4-HYDROXY-L-PROLINE
L-HYDROXYPROLINE
BETA-(2-THIENYL)-L-ALANINE
DL-TRYPTOPHAN
L-TRYPTOPHAN
L-5-HYDROXYTRYPTOPHAN
D-PIPECOLINIC ACID
DL-PIPECOLINIC ACID
L-CITRULLINE
L-ASPARAGINE
DL-ALPHA-PHENYLGLYCINE
L(+)-ALPHA-PHENYLGLYCINE
DL-ALANINE
L-ALANINE
(R)-(-)-2-AMINO BUTYRIC ACID
(S)-(+)-2-AMINO BUTYRIC ACID
DL-NORVALINE
L-NORVALINE
DL-NORLEUCINE
L-NORLEUCINE
DL-LYSINE
L-LYSINE
N-ACETYL-L-METHIONINE
N-(3,5-DINITROBENZOYL)-DL-ALPHA-PHENYLGLYCINE
(S)-(+)-N-(3,5-DINITROBENZOYL)-ALPHA-PHENYLGLYCINE
N-(3,5-DINITROBENZOYL)-L-LEUCINE
L-ARGININE MONOHYDROCHLORIDE
L-2,4-DIAMINO BUTYRIC ACID DIHYDROCHLORIDE
L-ORNITHINE MONOHYDROCHLORIDE
DL-LYSINE MONOHYDROCHLORIDE
L-LYSINE MONOHYDROCHLORIDE
N-(TERT-BUTOXYCARBONYL)-L-ASPARTIC ACID 4-BENZYL ESTER

-38-

N-ALPHA- (TERT-BUTOXYCARBONYL) -L-GLUTAMINE
N-ALPHA- (TERT-BUTOXYCARBONYL) -L-HISTIDINE
BOC-LEU H₂O
BOC-L-METHIONINE
N- (TERT-BUTOXYCARBONYL) -L-TRYPTOPHAN
N- (TERT-BUTOXYCARBONYL) -L-VALINE
L-CYSTEINE HYDROCHLORIDE MONOHYDRATE
Z-L-TRYPTOPHAN
DL-TERT-LEUCINE
BOC-L-THREONINE
N-CBZ-L-THREONINE
N-CBZ-L-HISTIDINE
3,4-DEHYDRO-L-PROLINE
NALPHA-ACETYL-L-ASPARAGINE
L-LYSINE DIHYDROCHLORIDE
L-BUTHIONINE- (S,R) -SULFOXIMINE
P-AMINO-D-PHENYLALANINE
DL-BUTHIONINE (S,R) -SULFOXIMINE
3-CHLORO-L-ALANINE HYDROCHLORIDE
(S) - (-) -INDOLINE-2-CARBOXYLIC ACID
N- (PHOSPHONOMETHYL) GLYCINE, MONOISOPROPYLAMINE SALT
MIMOSINE
D-HOMOSERINE
(+) -OCTOPINE
N-CARBOBENZYLOXY-L-GLUTAMIC ACID 1-METHYL ESTER
DL-CYSTINE
3- (CARBOXYMETHYLAMINOMETHYL) -4-HYDROXYBENZOIC ACID
CIS-3-HYDROXY-DL-PROLINE
(S) - (-) -1,2,3,4-TETRAHYDRO-3-ISOQUINOLINECARBOXYLIC
ACID
N- (GAMMA-L-GLUTAMYL) -1-NAPHTHYLAMIDE MONOHYDRATE
3- (3,4-DIHYDROXYPHENYL) -2-METHYL-L-ALANINE,
SESQUIHYDRATE
DL-2-METHYLGLUTAMIC ACID HEMIHYDRATE
N-METHYL-D-ASPARTIC ACID MONOHYDRATE
DL-3-PHENYLSERINE HYDRATE
3-METHYL-L-HISTIDINE HYDRATE
N- (4-NITROBENZOYL) -L-GLUTAMIC ACID HEMIHYDRATE
4-NITRO-DL-PHENYLALANINE HYDRATE
L-CYSTEIC ACID MONOHYDRATE
4-AMINO-DL-PHENYLALANINE HYDRATE
D-ASPARAGINE MONOHYDRATE
D-LYSINE HYDRATE
L- (+) -CANAVANINE SULFATE MONOHYDRATE
D-CYSTEINE HYDROCHLORIDE MONOHYDRATE
D-HISTIDINE MONOHYDROCHLORIDE MONOHYDRATE
DL-PENICILLAMINE ACETONE ADDUCT HYDROCHLORIDE
MONOHYDRATE
2-METHYLORNITHINE HYDROCHLORIDE MONOHYDRATE
3-AMINO-L-TYROSINE DIHYDROCHLORIDE MONOHYDRATE
4-AMINO-L-PHENYLALANINE HYDROCHLORIDE HEMIHYDRATE

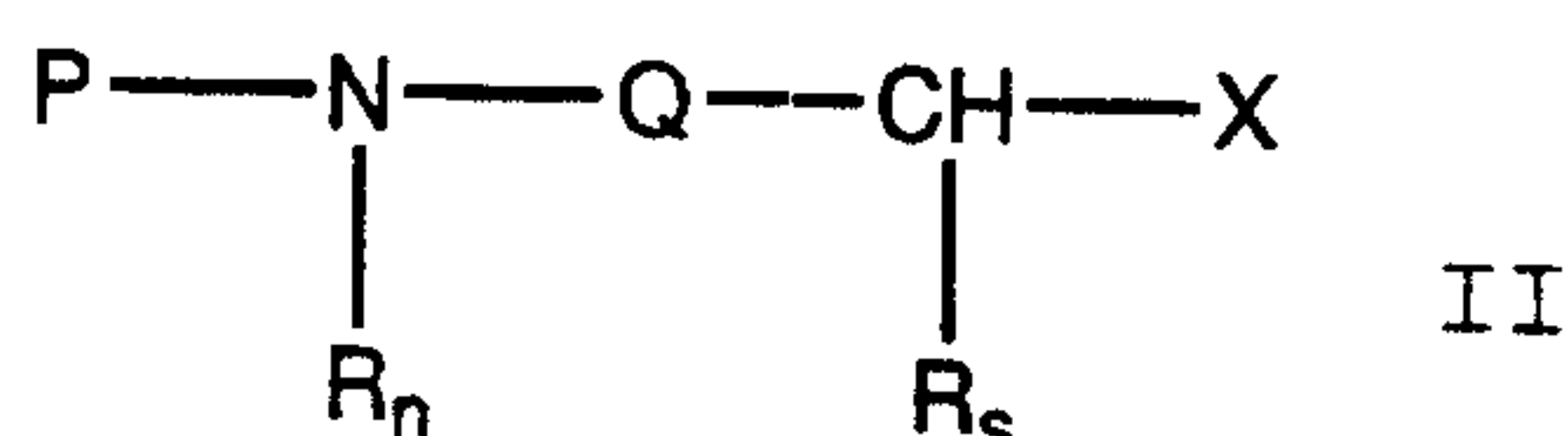
-39-

L-GLUTAMIC ACID, MONOSODIUM SALT, MONOHYDRATE
 3,5-DIIODO-L-TYROSINE DIHYDRATE
 N-(9-FLUORENYLMETHOXYCARBONYL)-L-ALANINE MONOHYDRATE
 3,5-DINITRO-L-TYROSINE MONOHYDRATE
 4-NITRO-L-PHENYLALANINE MONOHYDRATE
 DL-GLUTAMIC ACID MONOHYDRATE
 L-CYSTEINESULFINIC ACID MONOHYDRATE
 KAINIC ACID MONOHYDRATE
 4-AMINO-L-PHENYLALANINE HYDRATE
 IBOTENIC ACID MONOHYDRATE
 L-HISTIDINE MONOHYDROCHLORIDE MONOHYDRATE
 DL-HISTIDINE MONOHYDROCHLORIDE MONOHYDRATE
 DL-CYSTEINE HYDROCHLORIDE MONOHYDRATE
 DL-ARGININE HYDROCHLORIDE MONOHYDRATE
 L-LYSINE MONOHYDRATE
 L-ASPARAGINE MONOHYDRATE
 DL-ASPARAGINE MONOHYDRATE
 (S)-(-)-ALPHA-AMINOCYCLOHEXANECARBOXYLIC ACID HYDRATE
 N-BENZYLGLYCINE HYDROCHLORIDE
 2-AMINO-2-NORBORNANECARBOXYLIC ACID
 CIS-4-AMINO-1-CYCLOHEXANECARBOXYLIC ACID
 (+/-)-TRANS-3-AZABICYCLO(3.1.0)HEXANE-2-CARBOXYLIC ACID
 3-AZETIDINECARBOXYLIC ACID
 N-CARBOBENZYLOXY-L-TYROSINE HYDRATE
 4-HYDROXY-2,2,6,6-TETRAMETHYL-4-PIPERIDINECARBOXYLIC
 ACID,
 and the like.

It is to be understood that the amino acids utilized
 according to the present invention can also be selected
 from proteiogenic amino acids or optical isomers thereof.

5 ATAs for use in the process of this invention for
 preparation of macrocycle libraries are readily available
 by synthesis from available amino alcohols, more
 particularly protected-amino alcohol mesylates or
 tosylates, and mercapto acids.

10 In the first step in preparation of ATA compounds of
 the above formula wherein $m = 0$, an aminothioether acid, a
 compound of the formula



-40-

is reacted with about 1 to about 1.2 stoichiometric equivalents of a mercaptide salt of a mercapto compound of the formula



wherein in the above formulas P, R_n, R_s, X and W are defined above. The reaction is typically carried out in solution phase, and a solution of the compound of Formula II is added slowly to a solution of the mercaptide salt. The mercaptide salt is most typically generated by reacting the corresponding mercaptan in solution with about two stoichiometric equivalent amounts of an alkali metal alkoxide base, for example sodium methoxide. Other mercaptide forming bases can be used (e.g. alkali metal dimsyates or hydrides), but without advantage. Examples of suitable mercapto acids for use in preparing the library compounds of this invention include, but are not intended to be limited to, the following:

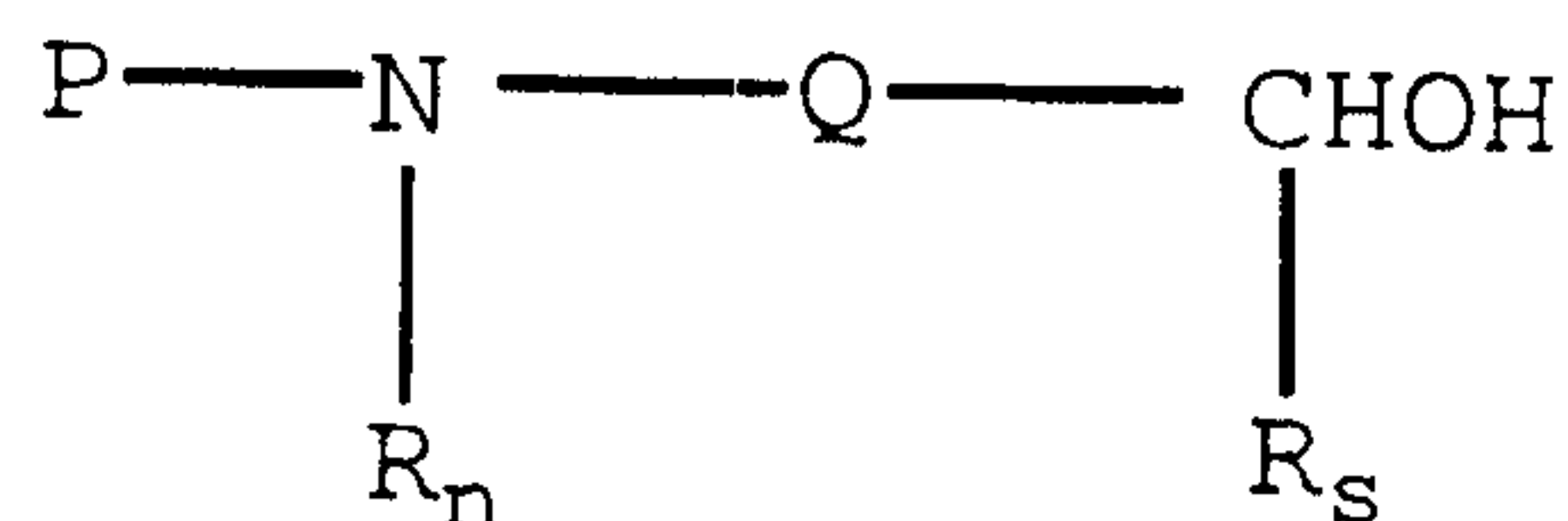
20

THIOSALICYLIC ACID
 N-ACETYL-DL-PENICILLAMINE
 DL-PENICILLAMINE
 2,3-DIMERCAPTOSUCCINIC ACID
 MERCAPTOSUCCINIC ACID
 N-(2-MERCAPTOPROPIONYL) GLYCINE
 N-ACETYL-L-CYSTEINE
 DL-CYSTEINE
 3-MERCAPTOPROPIONIC ACID
 DL-HOMOCYSTEINE
 2-MERCAPTONICOTINIC ACID
 D-CYSTEINE HYDROCHLORIDE
 3-MERCAPTOBENZOIC ACID
 4-MERCAPTOBENZOIC ACID
 DL-2-MERCAPTOMETHYL-3-GUANIDINOETHYLTHIOPROPANOIC ACID
 2-THIOURACIL-5-CARBOXYLIC ACID
 L-THIOHISTIDINE
 4-MERCAPTOBUTYRIC ACID
 CYS-GLY
 DL-THIORPHAN

-41-

4-MERCAPTOHYDROCINNAMIC ACID
 D-PENICILLAMINE
 L-PENICILLAMINE
 L-CYSTEINE
 DL-CYSTEINE HYDROCHLORIDE
 BOC-CYS-OH
 GLUTATHIONE
 D-CYSTEINE
 MESO-ALPHA, ALPHA'-DIMERCAPTOADIPIC ACID
 N-ACETYL-D-PENICILLAMINE
 MERCAPTOTETRAZOLYLACETIC ACID
 ALPHA-MERCAPTO-P-TOLUIC ACID
 6-AZA-2-THIOURACIL-5-CARBOXYLIC ACID
 2-THIOACETIC ACID-5-MERCAPTO-1,3,4-
 THIADIAZOLE
 N-ISOBUTYRYL-L-CYSTEINE
 N-ISOBUTYRYL-D-CYSTEINE
 CAPTOPRIL
 5-MERCAPTO-TETRAZOLE-1-PROPIONIC ACID
 SALOR S98,217-2
 2,6-CSBA (2-Cl-6-mercaptobenzoic acid)
 6-MERCAPTONICOTINIC ACID
 MAYBRIDGE RJC 01025,
 and the like.

In the preparation of aminothioether acid compounds
 the mercaptide salt is reacted with a compound of the
 Formula II. The substituent X is a good leaving group
 5 subject to nucleophilic displacement by the mercaptide
 salt. Exemplary of suitable X groups include, but are not
 intended to be limited to, mesylate, tosylate, halo, and
 the like. Compounds of Formula II are typically derived
 from an amino alcohol or protected-amino alcohol of the
 10 formula



wherein P, R_n, Q and R_s are as defined above. The amino
 alcohol is selected to have a molecular weight of about 60
 15 to about 450, most typically about 60 to about 300. In
 one preferred embodiment the amino alcohol starting

-42-

material is reacted with methane sulfonyl chloride to provide the corresponding mesylate in high yield using the mesylation protocol of Crossland and Servis [JOC **35**, 1952-6 (1970)]. Suitable amino alcohols for use in preparing
5 the present library compounds include, but are not intended to be limited to, the following:

TRANS-2-AMINOCYCLOHEXANOL HYDROCHLORIDE
3-AMINOMETHYL-3,5,5-TRIMETHYLCYCLOHEXANOL
(1R,2R)-(-)-PSEUDOEPHEDRINE
L-ADRENALINE
DL-HOMOSERINE
Z-L-SERINE
2-ANILINOETHANOL
N-ACETYLETHANOLAMINE
2-(METHYLAMINO) ETHANOL
N-BENZYLETHANOLAMINE
2-(ETHYLAMINO) ETHANOL
DIETHANOLAMINE
2-(PROPYLAMINO) ETHANOL
D-SERINE
(1S,2S)-(+)-2-AMINO-1-PHENYL-1,3-PROPANEDIOL
D-ALLO-THREONINE
DIISOPROPANOLAMINE
2-AMINO-2-METHYL-1,3-PROPANEDIOL
TRIS (HYDROXYMETHYL) AMINOMETHANE
N-METHYL-D-GLUCAMINE
DL-2-AMINO-3-METHYL-1-BUTANOL
L-ISOLEUCINOL
L-PHENYLALANINOL
DL-4-CHLOROPHENYLALANINOL
L-METHIONINOL
CIS-4-HYDROXY-D-PROLINE
L-PROLINOL
3-PYRROLIDINOL
3-PYRROLIDINOL
2-PIPERIDINEMETHANOL
2-PIPERIDINEETHANOL
3-PIPERIDINEMETHANOL
4-HYDROXYPIPERIDINE
2-AMINO-2-METHYL-1-PROPANOL
D-(-)-ALPHA-PHENYLGLYCINOL
(-)-NOREPHEDRINE
DL-2-AMINO-1-PROPANOL
(+/-)-2-AMINO-1-BUTANOL
2-AMINO-1-PHENYLETHANOL
DL-ISOSERINE
1-AMINO-2-PROPANOL

-43-

3-AMINO-1,2-PROPANEDIOL
DL-4-AMINO-3-HYDROXYBUTYRIC ACID
1,3-DIAMINO-2-PROPANOL
2-(2-AMINOETHYLAMINO) ETHANOL
ETHANOLAMINE
3-AMINO-1-PROPANOL
4-AMINO-1-BUTANOL
5-AMINO-1-PENTANOL
6-AMINO-1-HEXANOL
DL-2-AMINO-1-PENTANOL
DL-2-AMINO-1-HEXANOL
1-AMINO-1-CYCLOPENTANEMETHANOL
(1S,2S)-(+) -2-AMINO-3-METHOXY-1-PHENYL-1-PROPANOL
DL-PROPRANOLOL HYDROCHLORIDE
TRANS-4-AMINOCYCLOHEXANOL HYDROCHLORIDE
TRIS(HYDROXYMETHYL) AMINOMETHANE HYDROCHLORIDE
DL-SERINE METHYL ESTER HYDROCHLORIDE
L-SERINE ETHYL ESTER HYDROCHLORIDE
L-PHENYLEPHRINE HYDROCHLORIDE
3-HYDROXYPIPERIDINE HYDROCHLORIDE
DL-OCTOPAMINE HYDROCHLORIDE
DL-NORMETANEPHRINE HYDROCHLORIDE
ETHANOLAMINE HYDROCHLORIDE
3-HYDROXYPIPERIDINE
N-CYCLOHEXYLETHANOLAMINE
L-NORADRENALINE
L-ADRENALINE BITARTRATE
D-SPHINGOSINE
N-(TERT-BUTOXYCARBONYL) -L-SERINE
N-ACETYL-DL-SERINE
L-THREONINE METHYL ESTER HYDROCHLORIDE
L-ARGININIC ACID
D-GLUCOSAMINIC ACID
L-TYROSINOL HYDROCHLORIDE
L-SERINE BENZYL ESTER HYDROCHLORIDE
2-AMINO-2-METHYL-1-PROPANOL HYDROCHLORIDE
2-AMINO-1,3-PROPANEDIOL OXALATE
METHYL 3-AMINO-3-DEOXY-BETA-D-GLUCOPYRANOSIDE
2-AMINO-1,3-PROPANEDIOL
DL-SERINE HYDROXAMATE
L-SERINE BETA-NAPHTHYLAMIDE
N-CBZ-D-GLUCOSAMINE
N-(TERT-BUTOXYCARBONYL) ETHANOLAMINE
DL-THREONINE HYDROXAMATE
SER-BETA-ALA
N-T-BOC-L-HOMOSERINE
METHYL 3-AMINO-3-DEOXY-ALPHA-D-MANNOPYRANOSIDE
HYDROCHLORIDE
L-THREONINAMIDE HYDROCHLORIDE
3-AMINO-2,2-DIMETHYL-1-PROPANOL
L-HOMOSERINE

- 44 -

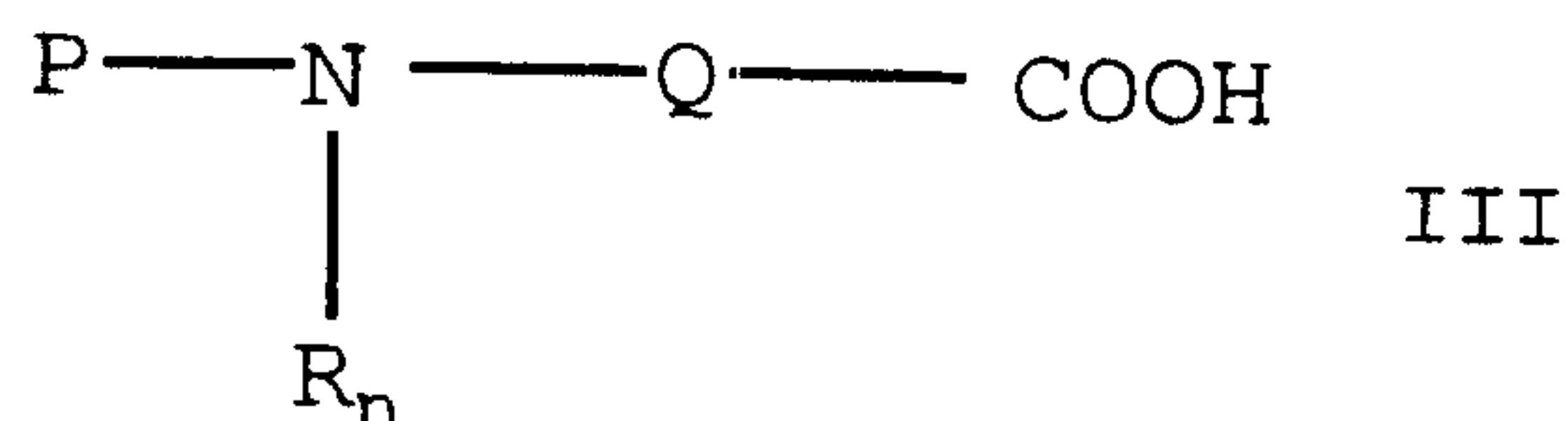
N-T-BOC-D-SERINE
N-CARBOBENZOXY-DL-SERINE
L-LEUCINOL
L-SERINE METHYL ESTER HYDROCHLORIDE
DL-THREONINE
DL-SERINE
L-SERINE
(+)-PSEUDOEPHEDRINE
(-)-EPHEDRINE
L-ALLO-THREONINE
D-THREONINE
L-THREONINE
L-VALINOL
D-VALINOL
D-PHENYLALANINOL
CIS-4-HYDROXY-L-PROLINE
L-HYDROXYPROLINE
D-PROLINOL
L-(+)-ALPHA-PHENYLGLYCINOL
(1S, 2R) - (+) - PHENYL-PROPANOLAMINE
(S) - (+) - 2-AMINO-1-PROPANOL
D-ALANINOL
(S) - (+) - 2-AMINO-1-BUTANOL
(R) - (-) - 2-AMINO-1-BUTANOL
(R) - (-) - 1-AMINO-2-PROPANOL
(S) - (+) - 1-AMINO-2-PROPANOL
(+)-EPHEDRINE HYDROCHLORIDE
D-MANNOSAMINE HYDROCHLORIDE
D(+)-NOREPHEDRINE HYDROCHLORIDE
NOREPHEDRINE HYDROCHLORIDE
BOC-L-THREONINE
N-CBZ-L-THREONINE
DL-ALLOTHREONINE
L-SERINAMIDE HYDROCHLORIDE
ALPHA-D-GLUCOSAMINE HYDROCHLORIDE
DL-METHIONINOL
(1S, 2R) - (+) - 2-AMINO-1, 2-DIPHENYLETHANOL
(1R, 2S) - (-) - 2-AMINO-1, 2-DIPHENYLETHANOL
S-BENZYL-L-CYSTEINOL
BOC-L-PHENYLALANINOL
L-HISTIDINOL DIHYDROCHLORIDE
D-(-)-THREO-2-AMINO-1-(4-NITROPHENYL)-1, 3-PROPANEDIOL
ETHAMBUTOL DIHYDROCHLORIDE
(+/-)-ARTERENOL BITARTRATE SALT
S-ALPHA-HYDROXYMETHYL TYROSINE
(1S, 2S) - (+) - THIOMICAMINE
CIS-2-AMINOMETHYL-1-CYCLOHEXANOL HYDROCHLORIDE
CIS-2-HYDROXYMETHYL-1-CYCLOHEXYLAMINE HYDROCHLORIDE
TRANS-2-AMINOMETHYL-1-CYCLOHEXANOL

-45-

TRANS-2-HYDROXYMETHYL-1-CYCLOHEXYLAMINE
 HYDROCHLORIDE
 DL-3-PHENYL SERINE HYDRATE
 N-(2-HYDROXYETHYL)CARBAMIC ACID BENZYL ESTER
 N-(TERT-BUTOXYCARBONYL)-L-SERINE METHYL ESTER
 (R)-(+)-3-HYDROXYPIPERIDINE HYDROCHLORIDE
 (S)-TERT-LEUCINOL
 N-TRITYL-L-SERINE METHYL ESTER
 3-PHENYL-DL-SERINE
 3-PHENYL-DL-SERINE
 (+/-)-NOREPINEPHRINE L-BITARTRATE HYDRATE
 (1S,2R)-(-)-CIS-1-AMINO-2-INDANOL
 4-AMINO-2-BUTANOL
 2-[2-(AMINOPHENYLTHIO)BENZYL ALCOHOL,
 and the like.

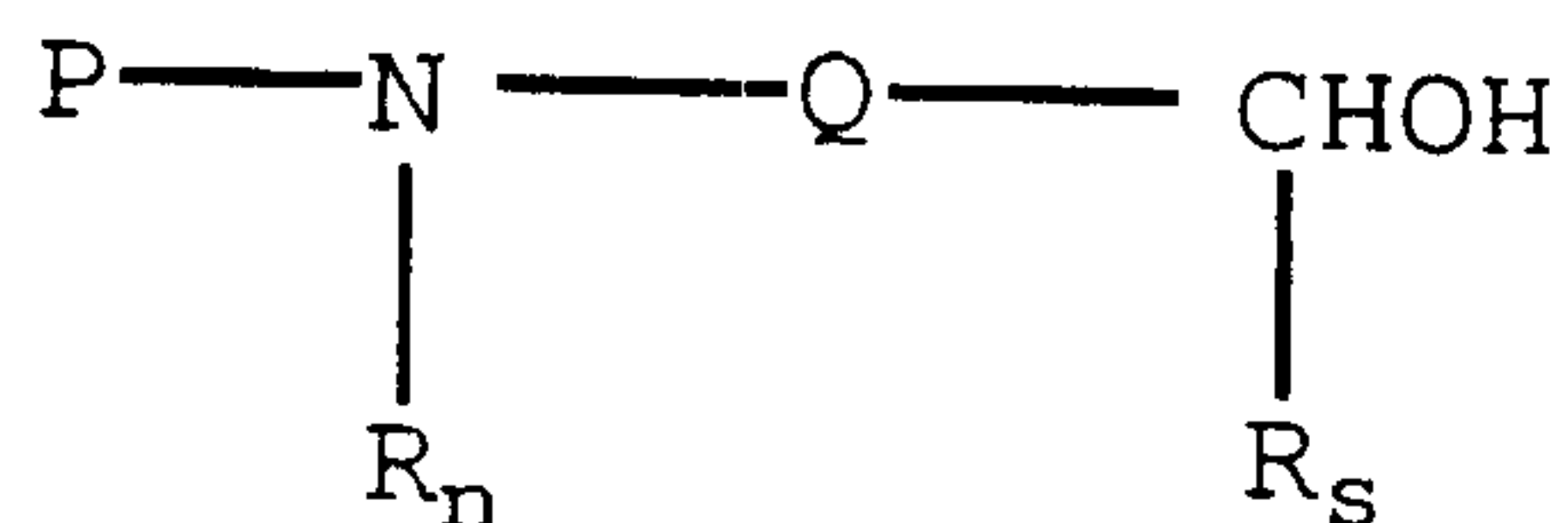
Amino alcohol starting materials can also be prepared
 in high yield from available amino acids and protected
 amino acids of the formula

5



wherein P, R_n and Q are as defined above. Available amino
 acid compounds can be protected with an amino-protecting
 group and converted in good yields to the corresponding
 protected-amino alcohols of the formula

10



15

For example, when R_s is hydrogen these compounds can be
 obtained from sodium borohydride reduction of the mixed
 carbonate formed, for example, between the starting acid
 and isobutyryl chloroformate. Any of the above
 exemplified amino acids are available for conversion to

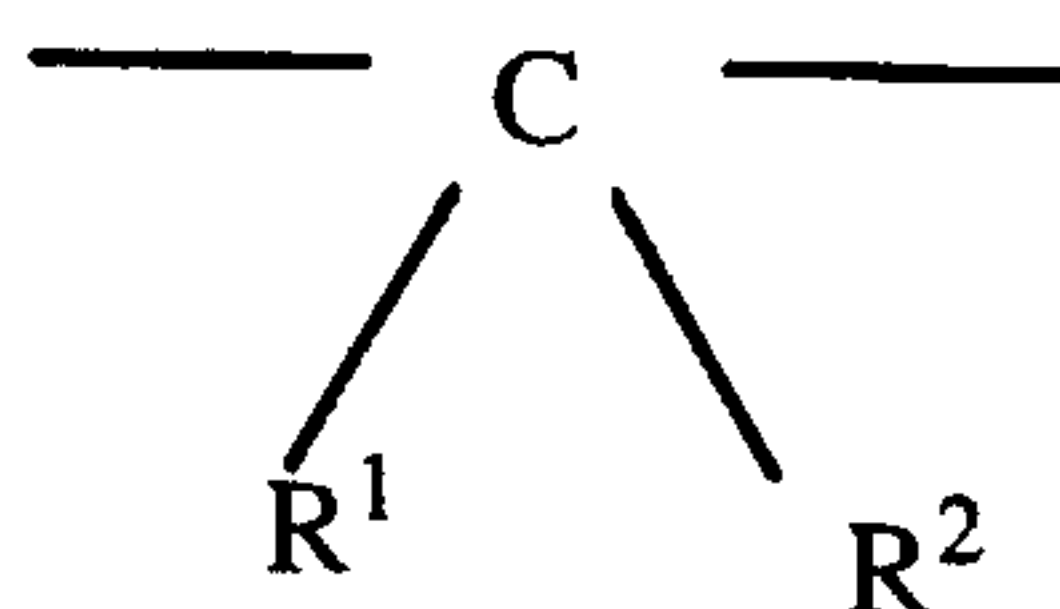
20

-46-

the corresponding amino alcohols for use in preparing amino thioether acids for use in this invention.

Where the thioether-forming reaction is carried out using a dialkali metal of a mercaptoacid in excess of a stoichiometric amount relative to the amino alcohol derived compound of Formula II above, the excess reagent frequently migrates with the thioether acid product on a flash silica column and cannot be removed by simple extraction. The excess acid can be separated from the product by dissolving the reaction mixture in ethyl acetate and adding a 2-fold molar excess of solid mercuric acetate to the solution. After 3-20 hours the resulting slurry is filtered through a celite pad, the filtrate containing the desired thioether product is subjected to flash chromatography on silica, and the chromatographed material is evaporated to provide the purified reaction product.

Reaction Scheme II below (bold-face numerals correspond to compound numerals in Scheme II) illustrates of the preparation of ATA compounds, for use in accordance with this invention using amino acid starting materials, such as, for example, amino acid **1** [Formula III, where P = R_n = hydrogen and Q =



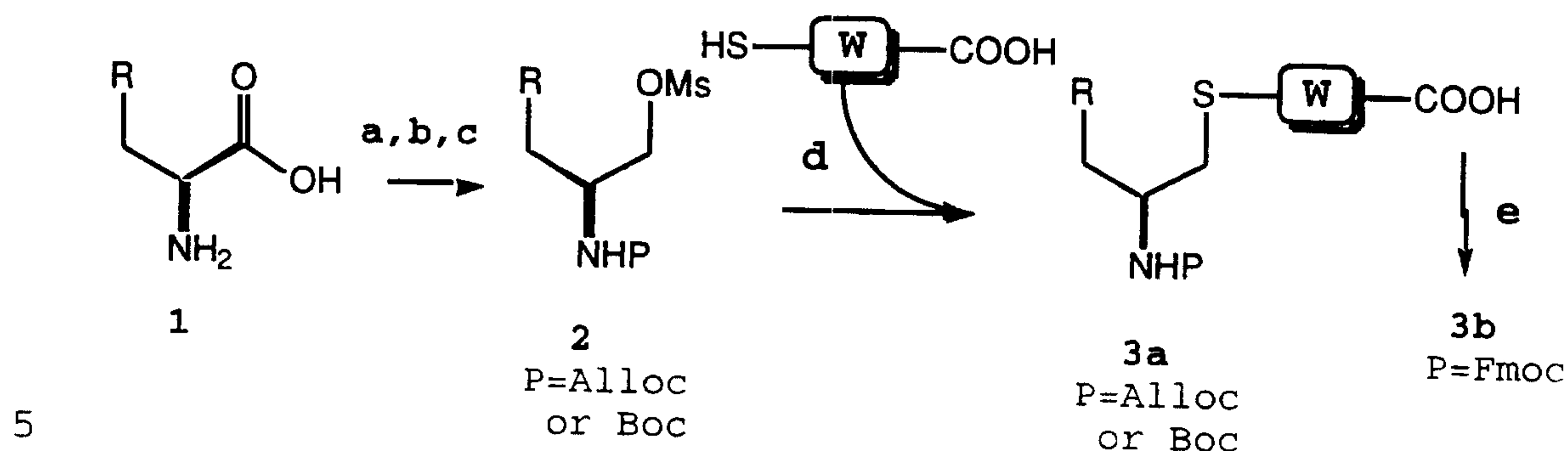
25

wherein R₁ is hydrogen and R₂ = CH₂R]. With reference to Scheme II below, amino acid **1** is protected, reduced to the corresponding alcohol, and then converted to mesylate **2**. The ATA is formed by condensing the disodium salt of a mercapto acid with mesylate **2** to form **3a**. The next step of the process involves exchanging protecting groups to yield a N-Fmoc-protected ATA **3b**. Each of the reaction

30

-47-

steps proceed smoothly and can be carried out on multigram scale.



Scheme II

- a) Allyl chloroformate or di-*t*-butyl dicarbonate, Na_2CO_3 , 1:1 H_2O :dioxane, 4°C , 90-95%, $\text{P}=\text{Alloc}$ or Boc , respectively;
- 10 b) isobutyryl chloroformate, *N*-methylmorpholine (NMM) in ethylene glycol dimethyl ether (DME), -15°C , then aq NaBH_4 , -15°C , 65-90%;
- c) $\text{CH}_3\text{SO}_2\text{Cl}$, TEA in THF, 4°C , 90-95%;
- d) mercapto acid (1eq), NaOMe (2eq) in DMF, r.t., 65-95%;
- 15 e) $\text{P}=\text{Alloc} \rightarrow \text{Fmoc}$, PPh_3 (0.25eq), $\text{Pd}(\text{PPh}_3)_4$ (0.03eq), HOAc (2eq) in THF, then Fmoc-*N*-hydroxysuccinimide ester, Na_2CO_3 in 1:1 H_2O :dioxane, 4°C to r.t., 50%; $\text{P}=\text{Boc} \rightarrow \text{Fmoc}$, 4N HCl in dioxane or EtOAc , 1.5h, then Na_2CO_3 and Fmoc-OSu in 1:1 H_2O :dioxane, 90-95%.

20 The aminothioether compounds can be converted to their corresponding sulfoxides ($m=1$) and sulfones ($m=2$) (included in the ATAs useful in accordance with this invention) by oxidation. The oxidation can be accomplished in high yields using stoichiometric amounts of any one of several oxidizing agents including *m*-chloroperbenzoic acid, periodate, and oxone (a mixture of potassium hydrogen persulfate, potassium bisulfate and potassium sulfate). The oxidation reaction is carried out in any one of a wide variety of solvents at a temperature of about -10°C to about 30°C . The preparation of sulfoxides and sulfones by oxidation of thioethers are well known in the art.

25

30

-48-

Oxidation of a sulfide to its corresponding sulfoxide:

- 1) . P. G. Hunt, J. I. Grayson, S. Warren and J. Durman J. Chem. Soc. Perkin Trans 1 (1986), p. 1939. [Uses m-CPBA (meta-chloro-peroxybenzoic acid) or sodium periodate to give desired products in 92-100% yield].
- 2) . D. M. Hedstrand, S. R. Byrn, A. T. McKenzie and P. L. Fuchs J. Org. Chem. **52** (1987), pp. 592-598.
- 3) . C. Jouen, M. C. Lasne and J. C. Pommelet Tet. Lett. **37** (1996), pp. 2413-2416.

Oxidation of a sulfide to its corresponding sulfone:

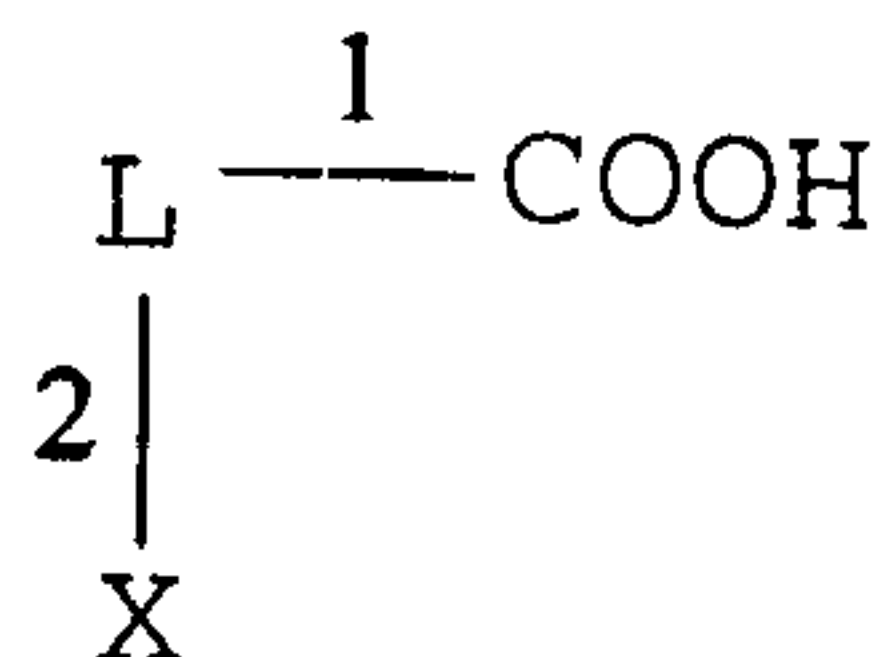
- 4) . B. M. Trost and R. Braslau J. Org. Chem. **53** (1988), pp. 532-537. [Uses Oxone from DuPont which is "...a mixture of potassium hydrogen persulfate, potassium bisulfate and potassium sulfate...."].

Amino-protected ATAs useful in the present process have a molecular weight of about 150 to about 800. A preferred amino-protecting group for the amino acids and ATAs used in this process is 9-fluorenyloxymethylcarbonyl.

According to the process of the present invention, following the first amino acid or ATA coupling reaction of process step (c) as described above, in process step (d) the amino-protecting group is removed from the solid support coupled product following the same procedures as described above for process step (b). Thereafter, process step (c) and process step (d) may be repeated one or more times using the same or a different amino-protected amino acid or amino-protected ATA. However, at least one of the process steps (c) and (e) is carried out using an amino-protected ATA.

In the next process step (f) for preparing the present library compounds, the support-bound product resulting from process step (d) (or process step (e), if optionally performed) is coupled with an organic acid of the formula

-49-



where L is as defined above and X is a leaving group subject to nucleophilic displacement. Exemplary of such acids include, but are not intended to be limited to:

- 5
bromoacetic acid
alpha-bromophenylacetic acid
alpha-bromopropionic acid
iodoacetic acid
10 chloroacetic acid
4-carboxybenzyl bromide
4-carboxymethylbenzyl bromide
3-carboxybenzyl bromide
2-carboxybenzyl bromide,
15 and the like.

The coupling of the organic acid with the terminal amino group on the solid support bound product is carried out under essentially the same reaction conditions and stoichiometry described above for the coupling of the
20 protected amino acids or the protected ATAs in steps (c) and (e) above except that the hydroxybenzotriazole (HOBT) reagent typically used with carbodiimides to form the intermediate "active" HOBT ester is not used in the coupling reaction mixture due to the fact that HOBT is
25 sufficiently nucleophilic that it reacts to displace the terminal leaving group. The coupling reaction proceeds without added HOBT via the active ester formed by the reaction of the organic acid and the carbodiimide reactant.

30 In the next step of the process for the preparation of the present macrocycle library compounds, the support-bound product from step (f) above is cyclized and cleaved from the solid support. While those two reactions can be

-50-

conducted in either order, i.e., cyclization before cleavage, or cleavage before cyclization, it is preferred that cyclization be conducted in solution phase after cleavage of the acyclic precursor from the solid support.

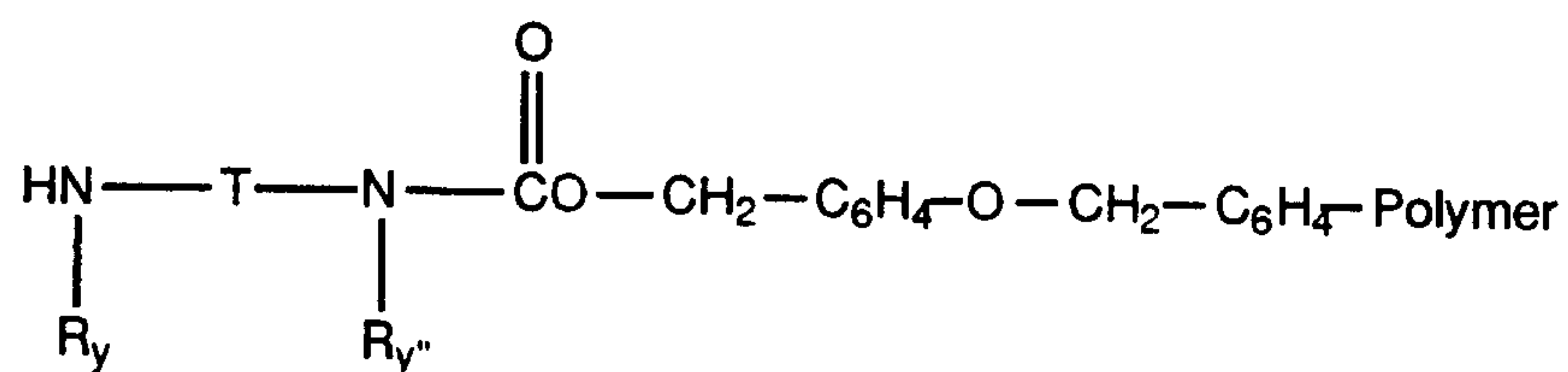
5 The optimum reaction conditions for cleavage of the product of step (f) or of the pre-cyclized product from the solid support are dependent on the nature of the acid reactive groups on the support. Typically such cleavage reactions are carried out by treating the solid support

10 with trifluoroacetic acid in the presence of water, optionally in the presence of triethylsilane, conditions which also effect removal of the thio-protecting group from the acyclic precursor product. The cleavage product is isolated by separation of the "cleavage cocktail"

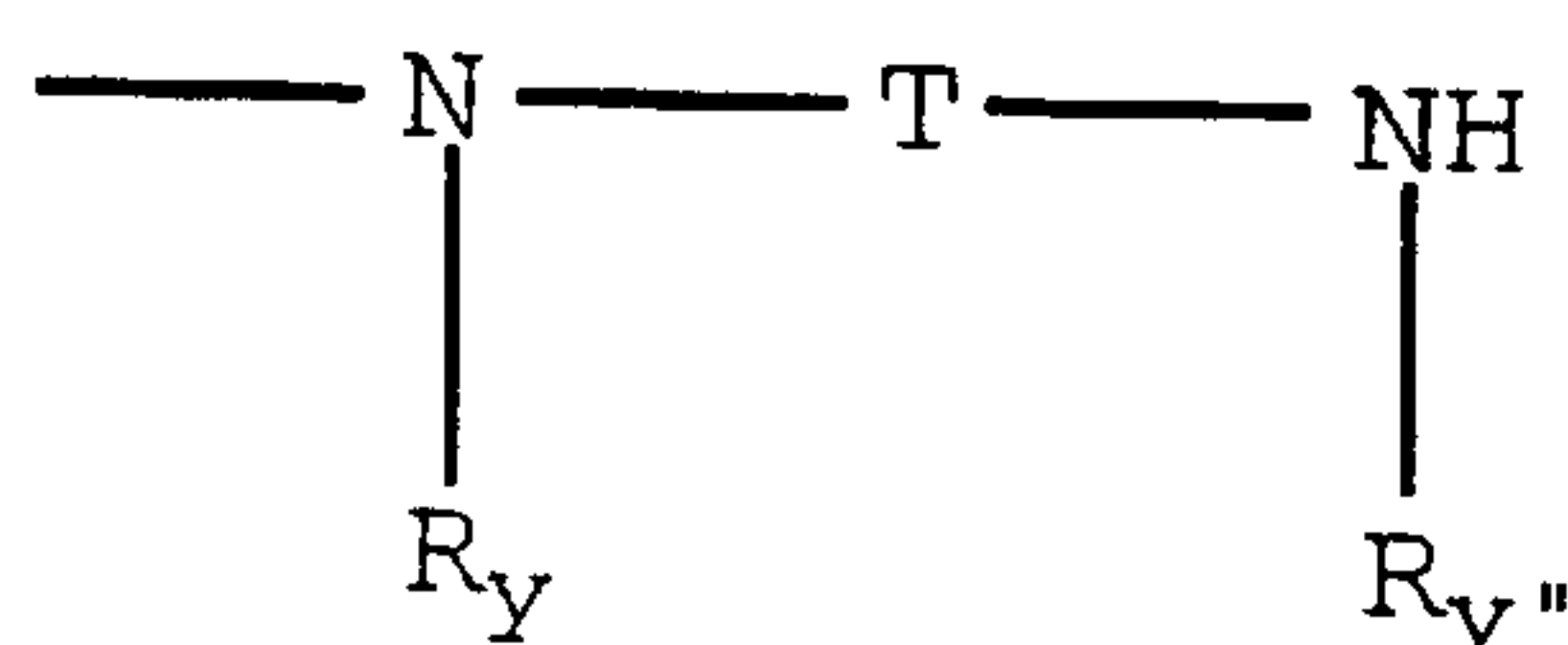
15 solution from the solid support and lyophilization of the "cleavage cocktail". Cyclization of the acyclic macrocycle precursor product can be efficiently carried out in solution in the presence of a non-nucleophilic base such as, for example, 2,6-lutidine, diisopropylethylamine

20 (DIPEA), and the like.

When the acid reactive group on the solid support comprises a covalently bound group of the formula



25 the product macrocycle library compounds of the invention are those of Formula I wherein B is a group of the formula



wherein R_y , T and $\text{R}_{y''}$ are as defined above. Such library

30 compounds are optionally reacted with an electrophilic agent having a molecular weight of about 30 to about 600

-51-

to provide library compounds of Formula I wherein E is a substituent derived from an electrophilic reagent. Suitable electrophilic agents include, but are not intended to be limited to, organic halides, acyl halides, sulfonic acid esters, organohaloformates, organosulfonyl halides, organic isocyanates, organic isothiocyanates, aldehydes, ketones, and the like. Examples of such electrophilic agents include, but are not intended to be limited to:

- 10 3,5-bis(trifluoromethyl)benzoyl chloride
- benzoyl chloride
- 2-bromobenzoyl chloride
- 2-fluorobenzoyl chloride
- 15 pentafluorobenzoyl chloride
- 2,4-difluorobenzoyl chloride
- 2,6-difluorobenzoyl chloride
- 2-chlorobenzoyl chloride
- 2,4-dichlorobenzoyl chloride
- 20 2,6-dichlorobenzoyl chloride
- o-acetylsalicyloyl chloride
- 2-methoxybenzoyl chloride
- 2,6-dimethoxybenzoyl chloride
- 2-(trifluoromethyl)benzoyl chloride
- 25 o-toluoyl chloride
- 3-bromobenzoyl chloride
- 3-fluorobenzoyl chloride
- 3-chlorobenzoyl chloride
- 3,4-dichlorobenzoyl chloride
- 30 m-anisoyl chloride
- 3,4-dimethoxybenzoyl chloride
- 3,4,5-trimethoxybenzoyl chloride
- 3,5-dimethoxybenzoyl chloride
- 3-ethoxybenzoyl chloride
- 35 isophthaloyl chloride
- trimesoyl chloride
- 3-(trifluoromethyl)benzoyl chloride
- m-toluoyl chloride
- 3-(chloromethyl) benzoyl chloride
- 40 4-bromobenzoyl chloride
- 4-fluorobenzoyl chloride
- 4-chlorobenzoyl chloride
- p-anisoyl-chloride
- 4-ethoxybenzoyl chloride
- 45 4-n-butoxybenzoyl chloride
- 4-n-hexyloxybenzoyl chloride
- 4-heptyloxybenzoyl chloride

-52-

	4-biphenylcarbonyl chloride
	terephthaloyl chloride
	4-(trifluoromethyl)benzoyl chloride
	4-tert-butylbenzoyl chloride
5	p-toluoyl chloride
	4-ethylbenzoyl chloride
	4-n-propylbenzoyl chloride
	4-butylbenzoyl chloride
	4-pentylbenzoyl chloride
10	4-hexylbenzoyl chloride
	4-n-heptylbenzoyl chloride
	methyl oxalyl chloride
	ethyl oxalyl chloride
	heptafluorobutyryl chloride
15	2-acetoxyisobutyryl chloride
	pivaloyl chloride
	3-chloropivaloyl chloride
	2-bromopropionyl chloride
	2,3-dibromopropionyl chloride
20	2,3-dichloropropionyl chloride
	o-acetylmandelic acid chloride
	itaconyl chloride
	methacryloyl chloride
	isobutyryl chloride
25	2-ethylhexanoyl chloride
	acetyl chloride
	bromoacetyl chloride
	chloroacetyl chloride
	phenoxyacetyl chloride
30	4-chlorophenoxyacetyl chloride
	methoxyacetyl chloride
	phenylacetyl chloride
	3,3-dimethylacryloyl chloride
	cinnamoyl chloride
35	fumaryl chloride
	ethyl malonyl chloride
	tert-butylacetyl chloride
	isovaleryl chloride
	undecanoyl chloride
40	lauroyl chloride
	myristoyl chloride
	palmitoyl chloride
	heptadecanoyl chloride
	stearoyl chloride
45	propionyl chloride
	3-bromopropionyl chloride
	3-chloropropionyl chloride
	hydrocinnamoyl chloride
	succinyl chloride
50	3-carbomethoxypropionyl chloride
	ethyl succinyl chloride

-53-

butyryl chloride
4-bromobutyryl chloride
4-chlorobutyryl chloride
valeryl chloride
5 5-chlorovaleryl chloride
adipoyl chloride
hexanoyl chloride
6-bromohexanoyl chloride
pimeloyl chloride
10 heptanoyl chloride
suberoyl chloride
octanoyl chloride
10-undecenoyl chloride
2-chloro-2,2-diphenylacetyl chloride
15 dichloroacetyl chloride
alpha-chlorophenylacetyl chloride
2-chloropropionyl chloride
2-iodobenzoyl chloride
4-iodobenzoyl chloride
20 cyclopropanecarbonyl chloride
trans-2-phenyl-1-cyclopropanecarbonyl chloride
cyclobutanecarbonyl chloride
cyclopentanecarbonyl chloride
3-cyclopentylpropionyl chloride
25 cyclohexanecarbonyl chloride
4-cyanobenzoyl chloride
2-furoyl chloride
1-naphthoyl chloride
2-naphthoyl chloride
30 thiophene-2-carbonyl chloride
2-thiopheneacetyl chloride
trimellitic anhydride chloride
2,6-pyridinedicarboxylic acid chloride
2-quinoxaloyl chloride
35 2-nitrobenzoyl chloride
3-nitrobenzoyl chloride
3,5-dinitrobenzoyl chloride
4-nitrobenzoyl chloride
3,4-dimethoxyphenylacetyl chloride
40 3-methyladipoyl chloride
3,5-dichlorobenzoyl chloride
2,5-difluorobenzoyl chloride
3,4-difluorobenzoyl chloride
9-fluorenone-4-carbonyl chloride
45 3,5-difluorobenzoyl chloride
(s)-(-)-n-(trifluoroacetyl)prolyl chloride
benzyloxyacetyl chloride
acetoxycetyl chloride
3-cyanobenzoyl chloride
50 2,5-dimethoxyphenylacetyl chloride
3-methoxyphenylacetyl chloride

-54-

	iminodibenzyl-5-carbonyl chloride
	2,4,6-trimethylbenzoyl chloride
	tetrafluorosuccinyl chloride
	perfluorooctanoyl chloride
5	diphenylacetyl chloride
	alpha-methyl valeroyl chloride
	methyl malonyl chloride
	ethyl glutaryl chloride
	5-bromovaleryl chloride
10	methyl adipyl chloride
	3-cyclohexenecarbonyl chloride
	3-isocyanato benzoyl chloride
	2,4,6-triisopropylbenzoyl chloride
	fluoroacetyl chloride
15	2-ethoxybenzoyl chloride
	piperonyloyl chloride
	2,4-dimethoxybenzoyl chloride
	2,3,5,6-tetrachloroterephthaloyl chloride
	5-(dimethylsulfamoyl)-2-methoxybenzoyl chloride
20	2-(4-chlorobenzoyl)benzoyl chloride
	2,2-bis(chloromethyl)propionyl chloride
	cinnamylidenemalonyl chloride
	2-phenoxypropionyl chloride
	2-phenylbutyryl chloride
25	2-ethylbutyryl chloride
	p-tolylacetyl chloride
	gamma-methylvaleroyl chloride
	3,3-dichloropivaloyl chloride
	1-methyl-1-cyclohexanecarboxylic acid chloride
30	2-(2,4,5-trichlorophenoxy)acetyl chloride
	4-chloro-3-nitrobenzoyl chloride
	4-methyl-3-nitrobenzoyl chloride
	2,3-dichlorobenzoyl chloride
	morpholine-4-carbonyl chloride
35	p-chlorophenylacetyl chloride
	bicyclo[2.2.1]heptane-2-carbonyl chloride
	d(-)-alpha-formyloxy-alpha-phenylacetyl chloride
	d(-)-alpha-phenylglycine chloride hydrochloride
	trifluoroacetyl chloride
40	pentafluoropropionyl chloride
	hexafluoroglutaryl chloride
	2-chlorocinnamoyl chloride
	o-methoxycinnamyl chloride
	5-nitro-2-furoyl chloride
45	2-chlorobutyryl chloride
	4-phenylazobenzoyl chloride
	4-n-amyloxybenzoyl chloride
	4-decylbenzoyl chloride
	4-octylbenzoyl chloride
50	dl-2-methylbutyryl chloride
	linolenoyl chloride

-55-

	linolelaidoyl chloride
	11h-eicosafluoroundecanoyl chloride
	9h-hexadecafluorononanoyl chloride
	2,3-difluorobenzoyl chloride
5	2-(benzoyloxymethyl)benzoyl chloride
	2,2-dimethylvaleroyl chloride
	3,5,5-trimethylhexanoyl chloride
	phenothiazine-10-carbonyl chloride
	3,4-dimethyl benzoyl chloride
10	(+)-p-(2-methylbutyl)benzoyl chloride
	2,4-dichlorophenoxyacetic chloride
	pentadecanoyl chloride
	nonadecanoyl chloride
	neoheptanoyl chloride
15	9-anthracenecarbonyl chloride
	2-ethoxy-1-naphthoyl chloride
	pyrrolidine carbonyl chloride
	m-(chlorosulfonyl)benzoyl chloride
	2-n-propyl-n-valeroyl chloride
20	2-chloro-4-nitrobenzoyl chloride
	2-phenoxybutyryl chloride
	2-chloronicotinyl chloride
	6-chloronicotinyl chloride
	4-(trifluoromethoxy)benzoyl chloride
25	2-(trifluoromethoxy)benzoyl chloride
	2,6-dichloropyridine-4-carbonyl chloride
	3-chlorobenzo[b]thiophene-2-carbonyl chloride
	4-chloromethylbenzoyl chloride
	neodecanoyl chloride
30	(phenylthio)acetyl chloride
	4-carbethoxyhexafluorobutyryl chloride
	octafluoroadipoyl chloride
	2-diazo-3,3,3-trifluoropropionylchloride
	2-bromobutyryl chloride
35	arachidoyl chloride
	cis-vaccenoyl chloride
	11-eicosenoyl chloride
	behenoyl chloride
	petroselinoyl chloride
40	palmitoleoyl chloride
	tridecanoyl chloride
	2-chloro-5-nitrobenzoyl chloride
	3-methylthiopropionyl chloride
	methyl 4-chlorocarbonylbenzoate
45	anthraquinone-2-carbonyl chloride
	carbazole-n-carbonyl chloride
	2-nitrophenoxyacetyl chloride
	2-bromo-2-methylpropionyl chloride
	2-fluoro-3-(trifluoromethyl)benzoyl chloride
50	2-fluoro-4-(trifluoromethyl)benzoyl chloride
	2-fluoro-5-(trifluoromethyl)benzoyl chloride

-56-

- 3-fluoro-5-(trifluoromethyl)benzoyl chloride
 4-fluoro-2-(trifluoromethyl)benzoyl chloride
 4-fluoro-3-(trifluoromethyl)benzoyl chloride
 2-fluoro-6-(trifluoromethyl)benzoyl chloride
 5 2,3,6-trifluorobenzoyl chloride
 2,4,5-trifluorobenzoyl chloride
 2,4-di(trifluoromethyl)benzoyl chloride
 2,6-di(trifluoromethyl)benzoyl chloride
 3-(trifluoromethoxy)benzoyl chloride
 10 m-(fluorosulfonyl)benzoyl chloride
 trans-1,2-cyclobutanedicarboxylic acid chloride
 3-cyclohexylpropionyl chloride
 4-ethyl-2,3-dioxo-1-piperazinecarbonylchloride
 isoxazole-5-carbonyl chloride
 15 bromodifluoroacetyl chloride
 erucoyl chloride
 2,4,6-trifluorobenzoyl chloride
 dichlorochrysanthemic acid chloride
 isononanoyl chloride
 20 1-adamantanecarbonyl chloride
 2,5-bis(trifluoromethyl)benzoyl chloride
 2,3,4-trifluorobenzoyl chloride
 2,3,4,5-tetrafluorobenzoyl chloride
 2,4,6-trichlorobenzoyl chloride
 25 2,4-dichloro-5-fluorobenzoyl chloride
 4-methoxyphenylacetyl chloride
 trans-3-(trifluoromethyl)cinnamoyl chloride
 3-(dichloromethyl) benzoyl chloride
 4-isocyanato benzoyl chloride
 30 heneicosanoyl chloride
 2-chloroisobutyryl chloride
 trans-4-nitrocinnamoyl chloride
 3,4,5-trifluorobenzoyl chloride
 5-fluoro-2-(trifluoromethyl)benzoyl chloride
 35 2,3,5-trifluorobenzoyl chloride
 2-chloro-4-fluorobenzoyl chloride
 (-)-alpha-chlorophenylacetyl chloride
 2-(para-tolylsulfonyl)acetyl chloride
 4-methyl-4-nitrohexanoyl chloride
 40 1-chloro-4-fluorosulfonyl-2-naphthoyl chloride
 2,3-dibromo-3-phenylpropionyl chloride
 2-menthoxyacetyl chloride
 2-phenyl-2-(phenylsulfonyl)acetyl chloride
 4,4,4-trifluorocrotonyl chloride
 45 4,4,4-trifluorobutyryl chloride
 3,4-dichloro-2,5-thiophenedicarbonyl chloride
 pentachlorobenzoyl chloride
 4,4,7,7-tetranitrosebacoyl chloride
 alpha,alpha-dimethylsuccinyl chloride
 50 alpha-bromoisovaleryl chloride
 benzoyl chloride

-57-

- oleoyl chloride
 methyl suberyl chloride
 gamma-linolenoyl chloride
 (-)-camphanic acid chloride
 5 4,4'-stilbenedicarbonyl chloride
 chlorinated benzoyl chloride
 (1r)-(+)-camphanic chloride
 2-(4-nitrophenoxy)tetradecanoyl chloride
 7-[(chlorocarbonyl)methoxy]-4-methylcoumarin
 10 n,n-bis(2-chloroethyl)carbamoyl chloride
 (s)-(-)-2-acetoxypropionyl chloride
 linoleoyl chloride
 3-chlorotetrafluoropropionyl chloride
 3,4-dichloropentafluorobutyryl chloride
 15 7h-dodecafluoroheptanoyl chloride
 5h-octafluoropentanoyl chloride
 perfluorononanoyl chloride
 3h-tetrafluoropropionyl chloride
 2-bromo-2,3,3,3-tetrafluoropropanoyl chloride
 20 arachidonoyl chloride
 pentachloropropionyl chloride
 4-decenoyl chloride
 tridecafluoroheptanoyl chloride
 undecafluorocyclohexanecarbonyl chloride
 25 4-n-nonylbenzoyl chloride
 3-(trichlorogermyl)propionylchloride
 3,4,5-triiodobenzoyl chloride
 2-(phenylthio)propionyl chloride
 2,2,2-triphenylacetyl chloride
 30 d(-)-alpha-azido-phenyl acetyl chloride
 4-azido-benzoyl chloride
 difluoroacetyl chloride
 5-chloropyrazine-2-carbonyl chloride
 n-(1-naphthalenesulfonyl)-l-phenylalanyl chloride
 35 n-(4-nitrophenylsulfonyl)-l-phenylalanyl chloride
 n-(p-toluenesulfonyl)-l-phenylalanyl chloride
 dimethylmalonyl chloride
 methyl sebacoyl chloride
 2,5-dichloropyridine-3-carbonyl chloride
 40 3-(2,5 xylyloxy) propionyl chloride,
 and the like.

Organic Halides:

- 45 benzyl bromide
 alpha-bromo-o-xylene
 alpha-bromo-m-xylene
 4-(tert-butyl)benzyl bromide
 alpha-bromo-p-xylene
 50 tert-butyl bromoacetate
 methyl bromoacetate

-58-

benzyl bromoacetate
ethyl bromoacetate
2-bromoacetophenone
2-bromo-2'-methoxyacetophenone
5 2-bromo-2',4'-dimethoxyacetophenone
2-bromo-2',5'-dimethoxyacetophenone
3-methoxyphenacyl bromide
2-bromo-4'-methoxyacetophenone
2-bromo-4'-phenylacetophenone
10 2-bromo-4'-methylacetophenone
ethyl bromopyruvate
1-bromopinacolone
1-bromo-2-butanone
1-bromo-2,2-dimethoxypropane
15 1-bromo-2,2-dimethylpropane
bromoacetaldehyde dimethyl acetal
bromoacetaldehyde diethyl acetal
1-bromo-2-methylpropane
1-bromo-2-ethylbutane
20 2-ethylhexyl bromide
1-bromodecane
1-bromoundecane
2-bromoacetamide
iodoacetamide
25 4-(bromomethyl)phenylacetic acid phenacyl ester
isopropyl bromoacetate
5-bromo-2-methyl-2-pentene
3,4-difluorobenzyl bromide
2,5-difluorobenzyl bromide
30 3,5-bis(trifluoromethyl)benzyl bromide
2-bromo-2'-nitroacetophenone
3,5-difluorobenzyl bromide
2,4-bis(trifluoromethyl)benzyl bromide
8-bromo-1-octanol
35 4-(bromomethyl)phenylacetic acid
methyl (r)-(+)-3-bromo-2-methylpropionate
4-iodobutyl acetate
7-acetoxy-4-bromomethylcoumarin
4-bromomethyl-6,7-dimethoxycoumarin
40 2,4-difluorobenzyl bromide
methyl 2-(bromomethyl)acrylate
3-bromopropionaldehyde dimethyl acetal.
(r)-(-)-3-bromo-2-methyl-1-propanol,
and the like.

45

Sulfonic Acid Esters:

ethyl trifluoromethanesulfonate
2,2,2-trifluoroethyl p-toluenesulfonate
50 2-chloroethyl-p-toluenesulfonate
1,3-propane sultone

-59-

5'-tosyladenosine
 1,4-butane sultone
 cyanomethyl benzenesulfonate
 hexadecyl methanesulfonate
 5 ethyl methanesulfonate
 2-chloroethyl methanesulfonate
 ethyl p-toluenesulfonate
 trans-2-hydroxycyclohexyl p-toluenesulfonate
 (2r)-(-)-glycidyl tosylate
 10 (s)-(+)-2-methylbutyl methanesulfonate
 (s)-(+)-2-methylbutyl p-toluenesulfonate
 (s)-(+)-1-phenyl-1,2-ethanediol 2-tosylate
 (2r)-(-)-glycidyl 3-nitrobenzenesulfonate
 propargyl benzenesulfonate
 15 2,2-dimethyl-1,3-dioxolan-4-ylmethyl p-
 toluenesulfonate
 (r)-(-)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl p-
 toluenesulfonate
 (s)-(+)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl p-
 20 toluenesulfonate
 1,2:5,6-di-o-isopropylidene-3-o-(methanesulfonyl)-
 alpha-
 d-glucofuranose
 ethyl 1-2-((methanesulfonyl)oxy)propionate
 25 (2s)-(+)-glycidyl tosylate
 (2s)-(+)-glycidyl 3-nitrobenzenesulfonate
 3-o-acetyl-6-o-benzoyl-5-o-(methanesulfonyl)-1,2-o-
 isopropylidene-alpha-d-glucofu
 (r)-(-)-1-benzyloxy-3-(p-tosyloxy)-2-propanol
 30 (s)-(+)-1-benzyloxy-3-(p-tosyloxy)-2-propanol
 ethyl 1-2-((trifluoromethanesulfonyl)oxy)propionate
 2-(2-chloroethoxy)ethyl methanesulfonate
 1-cyanoethyl p-toluenesulfonate,
 and the like.

35

Organohaloformates:

9-fluorenylmethyl chloroformate
 phenyl chloroformate
 40 4-chlorophenyl chloroformate
 methyl chloroformate
 benzyl chloroformate
 vinyl chloroformate
 isobutyl chloroformate
 45 2-ethylhexyl chloroformate
 ethyl chloroformate
 2-bromoethyl chloroformate
 2-chloroethyl chloroformate
 1-chloroethyl chloroformate
 50 allyl chloroformate
 n-propyl chloroformate

-60-

butyl chloroformate
 n-hexyl chloroformate
 octyl chloroformate
 2,2,2-trichloro-1,1-dimethylethyl chloroformate
 5 2,2,2-trichloroethyl chloroformate
 cholesteryl chloroformate
 4-nitrophenyl chloroformate
 4-nitrobenzyl chloroformate
 (-)-menthyl chloroformate
 10 4-t-butylcyclohexyl chloroformate
 cetyl chloroformate
 (+)-1-(9-fluorenyl)ethyl chloroformate
 isopropyl chloroformate
 3-chlorocyclohexyl chloroformate
 15 decyl chloroformate
 oleyl chloroformate
 octadecyl chloroformate
 butenediol bischloroformate
 2-chlorobenzyl chloroformate
 20 4-chlorobutyl chloroformate
 (+)-menthyl chloroformate
 4,5-dimethoxy-2-nitrobenzyl chloroformate
 cyclopentyl chloroformate
 t-butylcyclohexyl chloroformate
 25 menthylchloroformate
 p-tolyl chloroformate
 4-bromophenyl chloroformate
 4-fluorophenyl chloroformate
 4-methoxyphenyl chloroformate
 30 2-nitrophenyl chloroformate
 4-methoxycarbonylphenyl chloroformate
 1-chloro-2-methylpropyl chloroformate
 (+/-)-1,2,2,2-tetrachloroethyl chloroformate
 2,2-dichloroethyl chloroformate
 35 myristyl chloroformate
 cyclohexyl chloroformate
 chloromethyl chloroformate,
 and the like.

40 Organosulfonylhalides:

1-naphthalenesulfonyl chloride
 dansyl chloride
 2-naphthalenesulfonyl chloride
 45 2-acetamido-4-methyl-5-thiazolesulfonyl chloride
 2-thiophenesulfonyl chloride
 B-quinolinesulfonyl chloride
 benzenesulfonyl chloride
 pentafluorobenzenesulfonyl chloride
 50 2,5-dichlorobenzenesulfonyl chloride
 2-nitrobenzenesulfonyl chloride

-61-

- 2,4-dinitrobenzenesulfonyl chloride
 3,5-dichloro-2-hydroxybenzenesulfonyl chloride
 2,4,6-triisopropylbenzenesulfonyl chloride
 2-mesitylenesulfonyl chloride
 5 3-nitrobenzenesulfonyl chloride
 p-bromobenzenesulfonyl chloride
 4-fluorobenzenesulfonyl chloride
 4-chlorobenzenesulfonyl chloride
 4-chloro-3-nitrobenzenesulfonyl chloride
 10 pipsyl chloride
 4-nitrobenzenesulfonyl chloride
 4-methoxybenzenesulfonyl chloride
 4-tert-butylbenzenesulfonyl chloride
 p-toluenesulfonyl chloride
 15 trifluoromethanesulfonyl chloride
 trichloromethanesulfonyl chloride
 isopropylsulfonyl chloride
 methanesulfonyl chloride
 alpha-toluenesulfonyl chloride
 20 trans-beta-styrenesulfonyl chloride
 2,2,2-trifluoroethanesulfonyl chloride
 1-hexadecanesulfonyl chloride
 ethanesulfonyl chloride
 2-chloroethanesulfonyl chloride
 25 1-propanesulfonyl chloride
 3-chloropropanesulfonyl chloride
 1-butanessulfonyl chloride
 methyl 2-(chlorosulfonyl)benzoate
 2-nitro-4-(trifluoromethyl)benzenesulfonyl chloride
 30 3-(trifluoromethyl)benzenesulfonyl chloride
 1-octanesulfonyl chloride
 4-(trifluoromethoxy)benzenesulphonyl chloride
 (1r)-(-)-10-camphorsulfonyl chloride
 d-(+)-10-camphorsulfonyl chloride
 35 (+/-)-10-camphorsulfonyl chloride
 2-nitro-alpha-toluenesulfonyl chloride,
 and the like.
- Isocyanate Reagents:
- 40 trans-2-phenylcyclopropyl isocyanate
 phenyl isocyanate
 2-bromophenyl isocyanate
 2-fluorophenyl isocyanate
 45 2,4-difluorophenyl isocyanate
 2,6-difluorophenyl isocyanate
 2-chlorophenyl isocyanate
 2,3-dichlorophenyl isocyanate
 2,4-dichlorophenyl isocyanate
 50 2,5-dichlorophenyl isocyanate
 2,6-dichlorophenyl isocyanate

-62-

2-methoxyphenyl isocyanate
 2,4-dimethoxyphenyl isocyanate
 2,5-dimethoxyphenyl isocyanate
 2-ethoxyphenyl isocyanate
 5 2-(trifluoromethyl)phenyl isocyanate
 o-tolyl isocyanate
 2,6-dimethylphenyl isocyanate
 2-ethylphenyl isocyanate
 3-bromophenyl isocyanate
 10 3-fluorophenyl isocyanate
 3-chlorophenyl isocyanate
 3,4-dichlorophenyl isocyanate
 3-methoxyphenyl isocyanate
 3-(trifluoromethyl)phenyl isocyanate
 15 m-tolyl isocyanate
 4-bromophenyl isocyanate
 4-fluorophenyl isocyanate
 4-chlorophenyl isocyanate
 4-methoxyphenyl isocyanate
 20 ethyl 4-isocyanatobenzoate
 4-(trifluoromethyl)phenyl isocyanate
 p-tolyl isocyanate
 n-(chlorocarbonyl) isocyanate
 benzoyl isocyanate
 25 tert-butyl isocyanate
 (s)-(-)-alpha-methylbenzyl isocyanate
 isopropyl isocyanate
 methyl isocyanate
 ethyl isocyanatoacetate
 30 octadecyl isocyanate
 ethyl isocyanate
 2-chloroethyl isocyanate
 allyl isocyanate
 n-propyl isocyanate
 35 butyl isocyanate
 cyclohexyl isocyanate
 1-naphthyl isocyanate
 (r)-(-)-1-(1-naphthyl)ethyl isocyanate
 4-fluoro-3-nitrophenyl isocyanate
 40 2-nitrophenyl isocyanate
 3-nitrophenyl isocyanate
 4-nitrophenyl isocyanate
 2,6-diisopropylphenyl isocyanate
 benzyl isocyanate
 45 3-chloropropyl isocyanate
 ethoxycarbonyl isocyanate
 3,5-bis(trifluoromethyl)phenyl isocyanate
 2,4,6-tribromophenyl isocyanate
 2,5-difluorophenyl isocyanate
 50 2,4,5-trichlorophenyl isocyanate
 2,4,6-trichlorophenyl isocyanate

-63-

	2-methoxycarbonylphenyl isocyanate
	2-ethoxycarbonylphenyl isocyanate
	2-isopropylphenyl isocyanate
	2,3-dimethylphenyl isocyanate
5	4-methoxy-2-methylphenyl isocyanate
	2,4-dimethylphenyl isocyanate
	2,5-dimethylphenyl isocyanate
	2-ethyl-6-methylphenyl isocyanate
	3-cyanophenyl isocyanate
10	5-chloro-2,4-dimethoxyphenyl isocyanate
	3-chloro-4-methylphenyl isocyanate
	3,5-dichlorophenyl isocyanate
	5-chloro-2-methoxyphenyl isocyanate
	3,4,5-trimethoxyphenyl isocyanate
15	3,5-dimethoxyphenyl isocyanate
	3-(methylthio)phenyl isocyanate
	3-ethoxycarbonylphenyl isocyanate
	3-acetylphenyl isocyanate
	3,4-dimethylphenyl isocyanate
20	3,5-dimethylphenyl isocyanate
	2-methoxy-5-methylphenyl isocyanate
	3-ethylphenyl isocyanate
	4-chloro-2-methoxyphenyl isocyanate
	4-chloro-2-trifluoromethylphenyl isocyanate
25	4-chloro-3-trifluoromethylphenyl isocyanate
	4-iodophenyl isocyanate
	4-phenoxyphenyl isocyanate
	4-ethoxyphenyl isocyanate
	4-(methylthio)phenyl isocyanate
30	4-acetylphenyl isocyanate
	4-isopropylphenyl isocyanate
	4-ethylphenyl isocyanate
	4-n-butylphenyl isocyanate
	3-(dichloromethylsilyl)propyl isocyanate
35	octyl isocyanate
	4-methyl-3-nitrophenyl isocyanate
	4-chloro-2-nitrophenyl isocyanate
	2-methyl-4-nitrophenyl isocyanate
	4-methyl-2-nitrophenyl isocyanate
40	2-fluoro-5-nitrophenyl isocyanate
	2-methyl-5-nitrophenyl isocyanate
	3-bromopropyl isocyanate
	2,4,6-trimethylphenyl isocyanate
	2-isopropyl-6-methylphenyl isocyanate
45	2,6-diethylphenyl isocyanate
	5-chloro-2-methylphenyl isocyanate
	4-chloro-2-methylphenyl isocyanate
	4-(trifluoromethoxy)phenyl isocyanate
	4-trifluoromethylthiophenyl isocyanate
50	2,4-dibromophenyl isocyanate
	2,6-dibromo-4-ethylphenyl isocyanate

-64-

- 2,3,4,5-tetrachlorophenyl isocyanate
 2-chloro-5-trifluoromethylphenyl isocyanate
 2-chloro-6-methylphenyl isocyanate
 2-n-carbobutoxyphenyl isocyanate
 5 2,4,5-trimethylphenyl isocyanate
 2-methyl-6-(t-butyl)phenyl isocyanate
 2-ethyl-6-isopropylphenyl isocyanate
 3-chloro-2-methoxyphenyl isocyanate
 3-chloro-2-methylphenyl isocyanate
 10 3-chloro-4-fluorophenyl isocyanate
 4-cyanophenyl isocyanate
 4-bromo-2-methylphenyl isocyanate
 4-bromo-2,6-dimethylphenyl isocyanate
 2,6-dibromo-4-fluorophenyl isocyanate
 15 4-n-butoxyphenyl isocyanate
 4-butoxycarbonylphenyl isocyanate
 phenethyl isocyanate
 2-methyl-3-nitrophenyl isocyanate
 hexyl isocyanate
 20 hexadecyl isocyanate
 methylene bis(o-chlorophenyl isocyanate)
 4-chloro-3-nitrophenyl isocyanate
 2-chloro-4-nitrophenyl isocyanate
 4,5-dimethyl-2-nitrophenyl isocyanate
 25 2-chloro-5-nitrophenyl isocyanate
 2-methoxy-4-nitrophenyl isocyanate
 3-fluoro-4-methylphenyl isocyanate
 5-fluoro-2-methylphenyl isocyanate
 3,5-dicarbomethoxyphenyl isocyanate
 30 2,4-dichlorobenzyl isocyanate
 2-(methylthio)phenyl isocyanate
 n-(methoxycarbonyl)isocyanate
 n-(phenoxycarbonyl)isocyanate
 2-biphenyl isocyanate
 35 3-iodophenyl isocyanate
 4-phenylphenyl isocyanate
 tetrahydro-2-pyranyl isocyanate
 4-(tert-butyl)phenylisocyanate
 1-(4-bromophenyl)ethyl isocyanate
 40 isocyanatoacetic acid n-butyl ester
 dodecyl isocyanate
 6,7-methylenedioxy-4-isocyanate-methylcoumarin
 (r)-(+)-alpha-methylbenzyl isocyanate
 (+/-)-1-(1-naphthyl)ethyl isocyanate
 45 (s)-(+)-1-(1-naphthyl)ethyl isocyanate
 3,4-difluorophenyl isocyanate
 2-methoxy-5-nitrophenyl isocyanate
 undecyl isocyanate
 ethyl 2-isocyanato-4-methyl valerate
 50 ethyl 6-isocyanatohexanoate
 ethyl 2-isocyanato-4-methylthiobutyrate

-65-

ethyl 2-isocyanatopropionate
 ethyl 3-isocyanatopropionate
 ethyl 2-isocyanato-3-methylbutyrate
 tert-butyl 3-isothiocyantopropionate
 5 ethyl 2-isocyanato-3-phenylpropionate
 1,3-bis(isocyanatom ethyl)cyclohexane
 2-(trifluoromethoxy)phenyl isocyanate
 4-(chloromethyl) phenyl isocyanate
 1-adamantyl isocyanate
 10 1,3-bis(2-isocyanato-2-propyl)benzene
 n-amyl isocyanate
 n-heptyl isocyanate
 2-chloroethyl isocyanate, [ethyl-1,2-14c]
 1,1,3,3-tetramethylbutyl isocyanate
 15 3,5-dinitrophenyl isocyanate,
 and the like.

Aldehydes:

20 Ethyl 2-formyl-1-cyclopropanecarboxylate
 Cyclohexanecarboxaldehyde
 1,2,3,6-Tetrahydrobenzaldehyde
 Diphenylacetaldehyde
 2-Phenylpropionaldehyde
 25 2,3-Dimethylvaleraldehyde
 Isobutyraldehyde
 2,6-Dimethyl-5-hepten-1-al
 2-Methylbutyraldehyde
 2-Ethylbutyraldehyde
 30 2-Methylpentanal
 2-Ethylhexanal
 2-Methylundecanal
 Phenylacetaldehyde
 Isovaleraldehyde
 35 7-Methoxy-3,7-dimethyloctanal
 Undecanal
 Dodecanal
 Tridecanal
 Tetradecyl aldehyde
 40 Propionaldehyde
 3-Phenylpropionaldehyde
 3-(Methylthio)propionaldehyde
 Butyraldehyde
 Cis-4-decen-1-al
 45 N-valeraldehyde
 Hexanal
 Heptaldehyde
 Octanal
 Nonanal
 50 Decanal

-66-

	Undecylenic aldehyde
	Cis-11-hexadecenal
	Cis-13-octadecenal
	Cis-9-hexadecenal
5	2,5-Dimethoxy-3-tetrahydrofurancarboxaldehyde
	3,5,5-Trimethylhexanal
	Succinic semialdehyde
	(+/-)-3-Phenylbutyraldehyde
	2,6,6-Trimethyl-1-cyclohexene-1-acetaldehyde
10	Cyclopropanecarboxaldehyde
	3-Cyclohexylpropionaldehyde
	Hydroxycitronellal
	Cis-4-heptenal
	Cis-6-nonen-1-al
15	Tetrahydrocitrinal
	Cis-7-decen-1-al
	Cis-8-undecen-1-al
	3,5,6-Trimethyl-3-cyclohexene-1-carboxaldehyde
	Lyrar(r)
20	Bis(2-chlorophenyl)acetaldehyde
	2-Thioglyceraldehyde
	3-(4-Isopropylphenyl)isobutyraldehyde
	2-Ethyl-3-methylbutanal
	2-Ethylcaprylaldehyde
25	3-Methylvaleraldehyde
	3-Phenyl-3-(p-tosyl)propionaldehyde
	3-Hexenal
	3-(Methylthio)butanal
	Veltonal
30	Citronellal
	2-(Trifluoromethyl)propionaldehyde
	3,3-Dimethylbutyraldehyde
	Campholene aldehyde
	2-Formylpropionic acid methyl ester
35	5-Hydroxypentanal
	p-Methylphenylacetaldehyde
	Omega-ketoheptanoic acid
	4-Chlorophenylcyanoacetaldehyde
	Hexadecanal
40	Methyl 7-oxoheptanoate
	Diethyl formyl succinate
	4-Pregnene-20-beta-carboxaldehyde-3-one
	Cis-7-tetradecenal
	Cyclopentylmethanal
45	3,4-Dimethyl-3-cyclohexenylmethanal
	2,4,6-Trimethyl-3-cyclohexen-1-carboxaldehyde
	Adipic semialdehyde methyl ester
	Cis-14-methyl-8-hexadecenal
	Cis-3-hexen-1-al
50	Trans-4-decen-1-al
	2,2-Dichlorooctadecanal

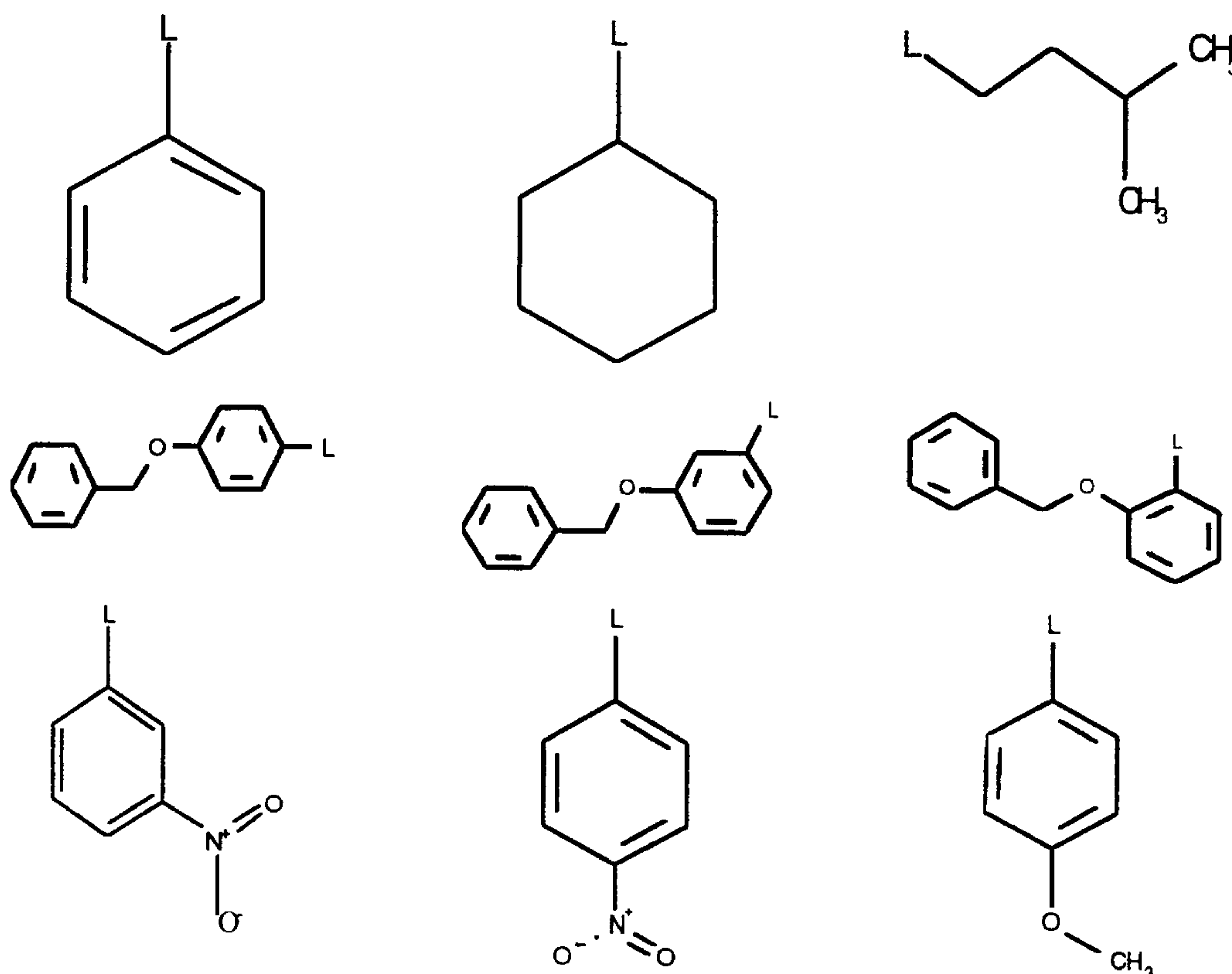
-67-

	2,2-Dichlorotetradecanal
	2,2-Dichlorooctanal
	2,2-Dichlorohexanal
	(r)-(+)-Citronellal
5	8-Methyl-7-nonenal
	2-(p-Tolyl)propionaldehyde
	Aldehyde C-11 MOA (2-methyldecanal)
	Alpha-methylhydrocinnamaldehyde
	(s)-(-)-Citronellal
10	4-Hydroxybutanal
	4-Oxobutyric acid methyl ester
	3,3,4,4,5,5,5-Heptafluoropentanal
	3-Methylbutanal-1-13c
	6-Methyl-3-cyclohexene-1-carboxaldehyde
15	4-(4-Methyl-2-pentenyl)-3-cyclohexene-1-carboxaldehyde
	3-Pentyn-1-al
	3-Pyridylacetaldehyde n-oxide
20	2,3-Dihydro-5-methoxy-3-phenyl-2-indolecarboxaldehyde
	2,4-Diphenyl-3-oxobutyraldehyde
	3,3,3-Triphenylpropionaldehyde
	2-Bromo-n-(3-formyl-1-methylpropyl)benzamide
	3-(Phenylthio)butyraldehyde
25	Diethyl 2-(diethoxymethyl)-3-formylsuccinate
	2-Chloro-3-(4-nitrophenyl)-propionaldehyde
	2-Acetoxypromionaldehyde
	2-Methyl-4-phenylpentanal
	(1r,2s,3r,4s)-(+)-2-Benzylloxy-3-formyl-oxybornane
30	5-(4'-Chlorophenoxy)-1-pentanal
	Boc-ala-CHO
	Boc-leu-CHO
	Boc-phe-CHO
	Boc-tyr(OBzl)-CHO
35	Boc-tyr(OMe)-CHO
	Boc-val-CHO
	4-Pentenal
	1-Formyl-6-(dimethylamino)fulvene
	1,4-Dioxaspiro(4.5)decane-7-acetaldehyde
40	Alpha-citronellal
	Diethyl 2-Acetamido-2-(2-formylethyl)malonate
	3,4,4,5,5,5-Hexafluoro-3-(trifluoromethyl)pentanal
	3,4,4,4-Tetrafluoro-3-(heptafluoropropoxy)butanal
	3,4,4,4-Tetrafluoro-3-(trifluoromethoxy)butanal
45	3,4,4,4-Tetrafluoro-3-(trifluoromethyl)butanal
	3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctanal
	3,3,3-Trifluoropropanal
	Beta,beta-dimethylhydrocinnamaldehyde
	5-Norbornene-2-carboxaldehyde
50	Chrysanthal
	9-Decenal

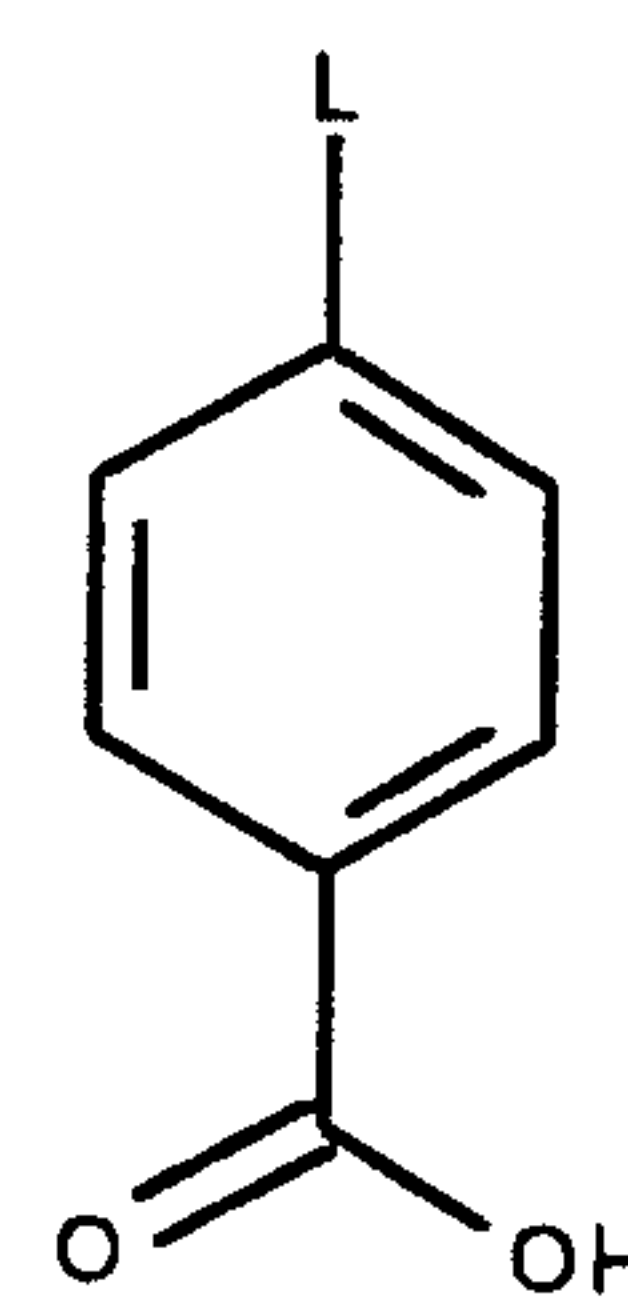
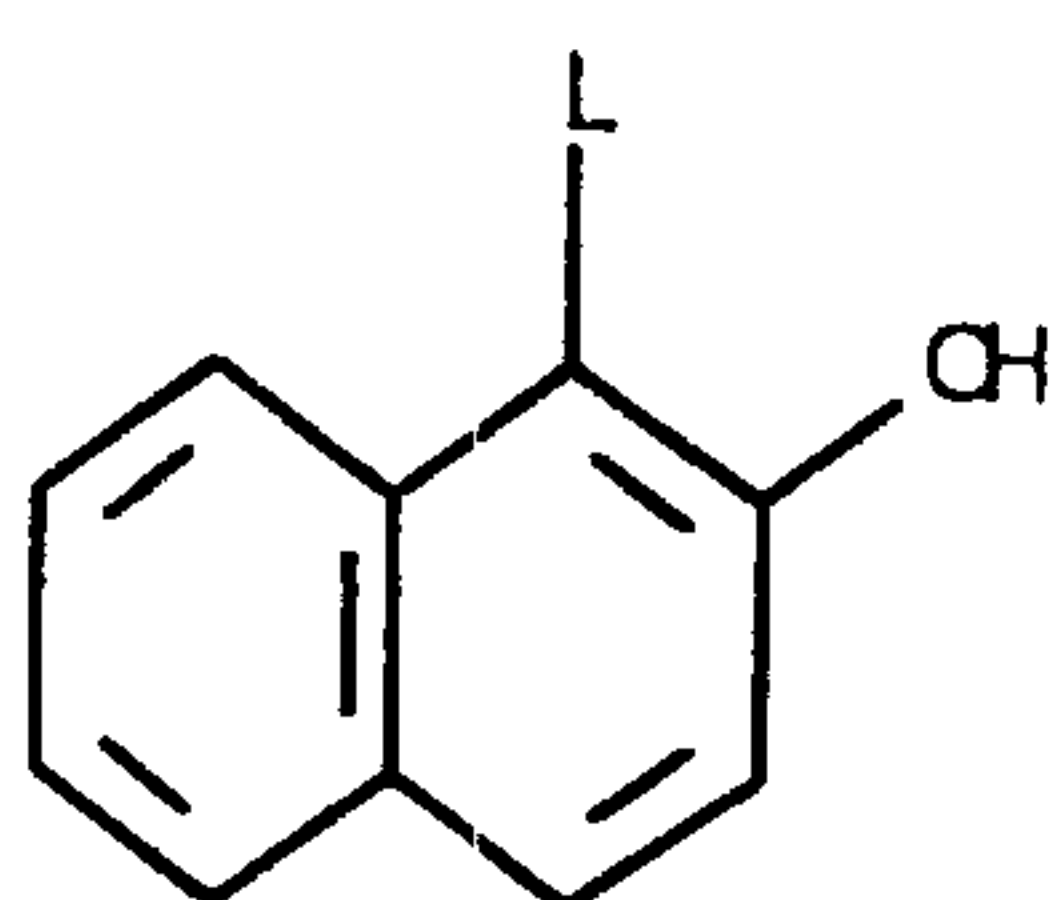
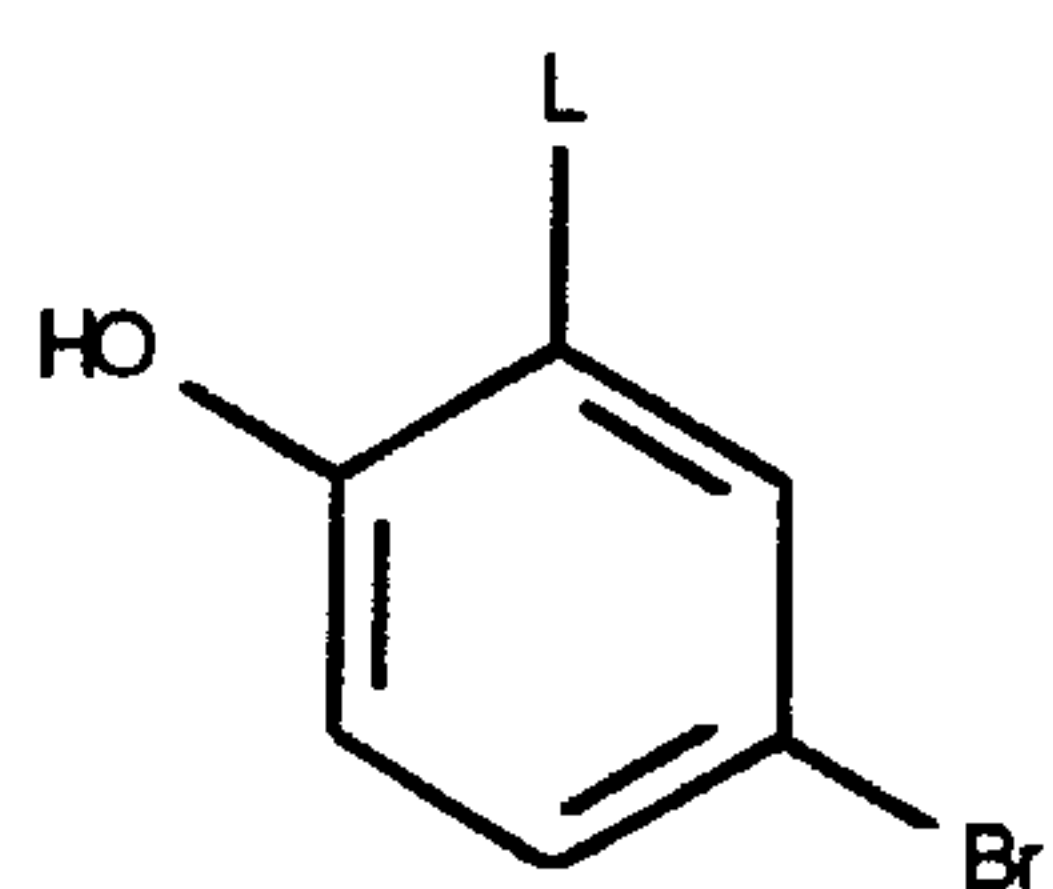
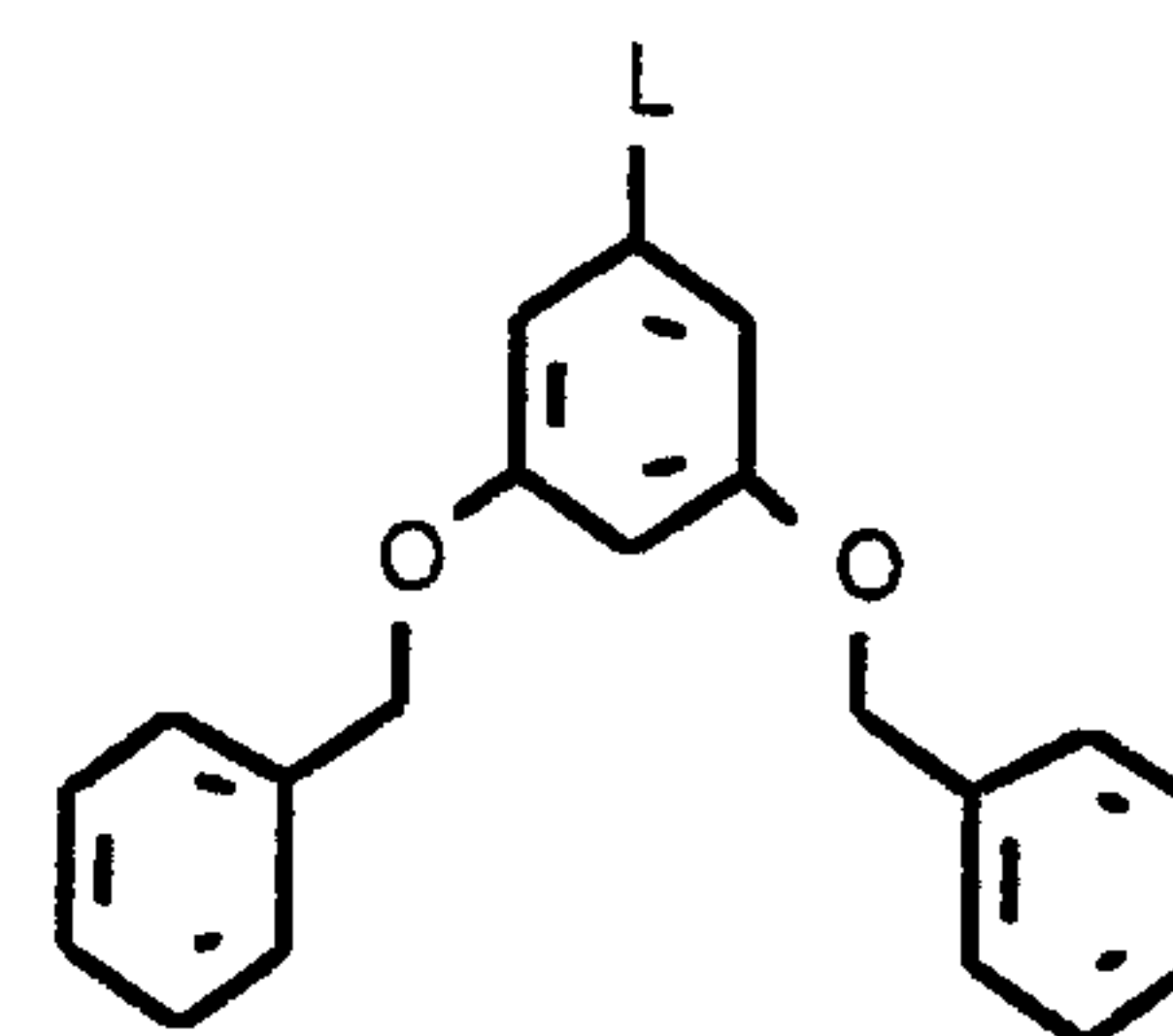
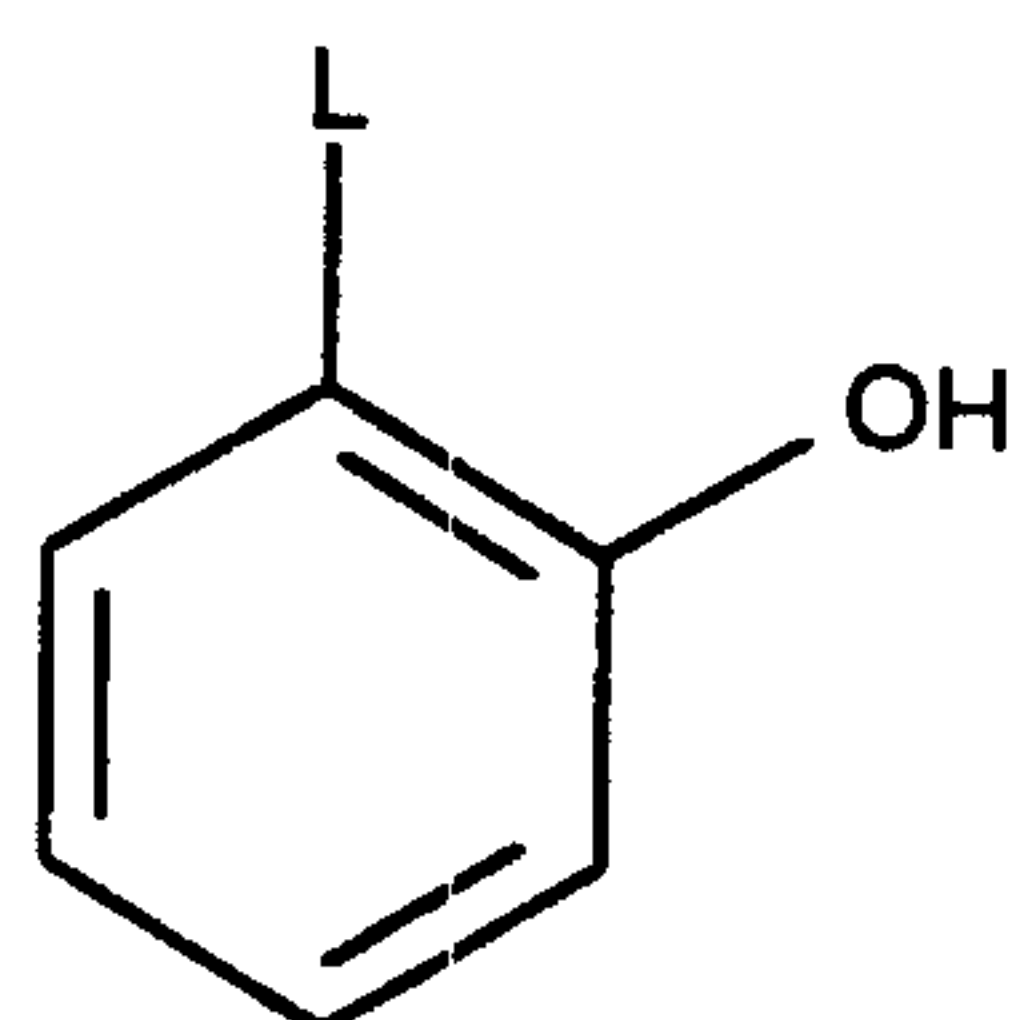
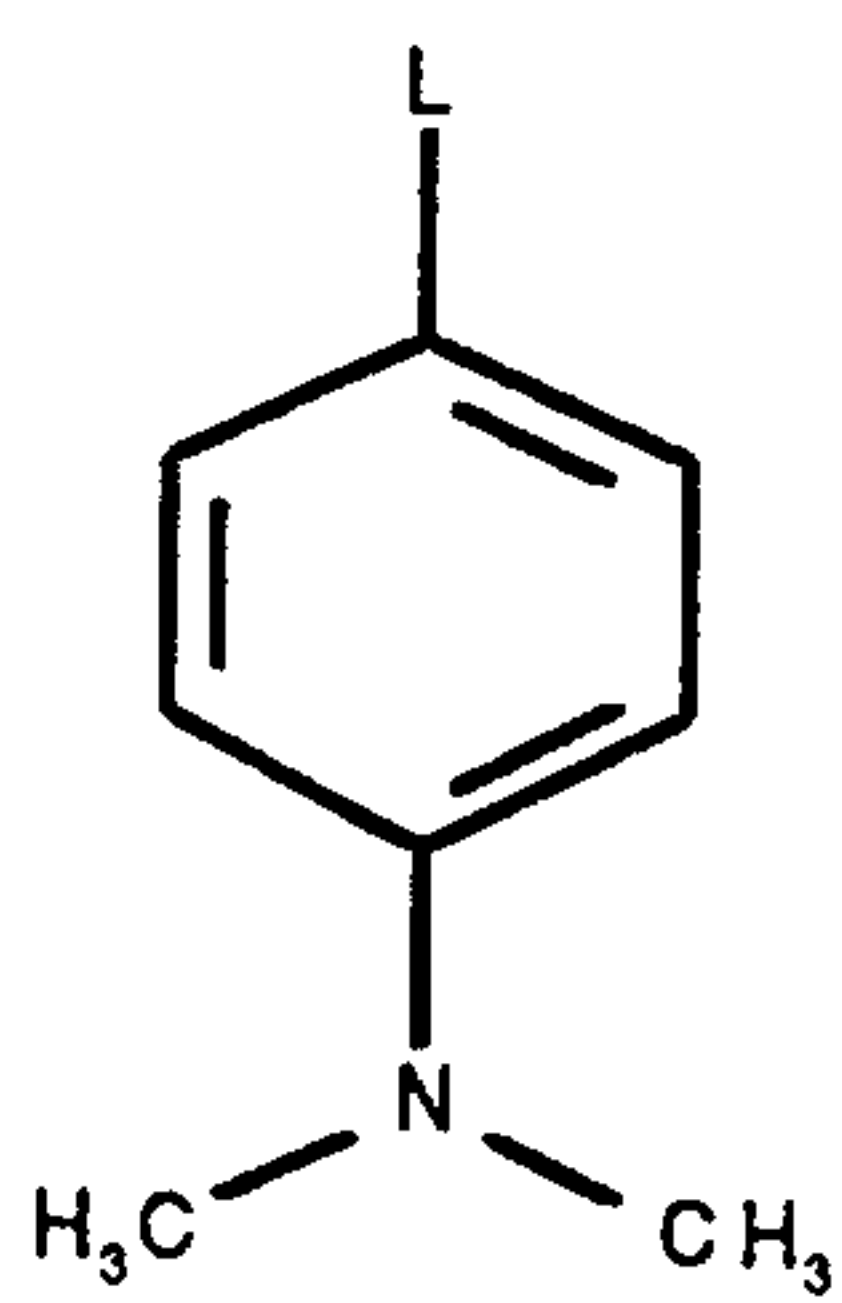
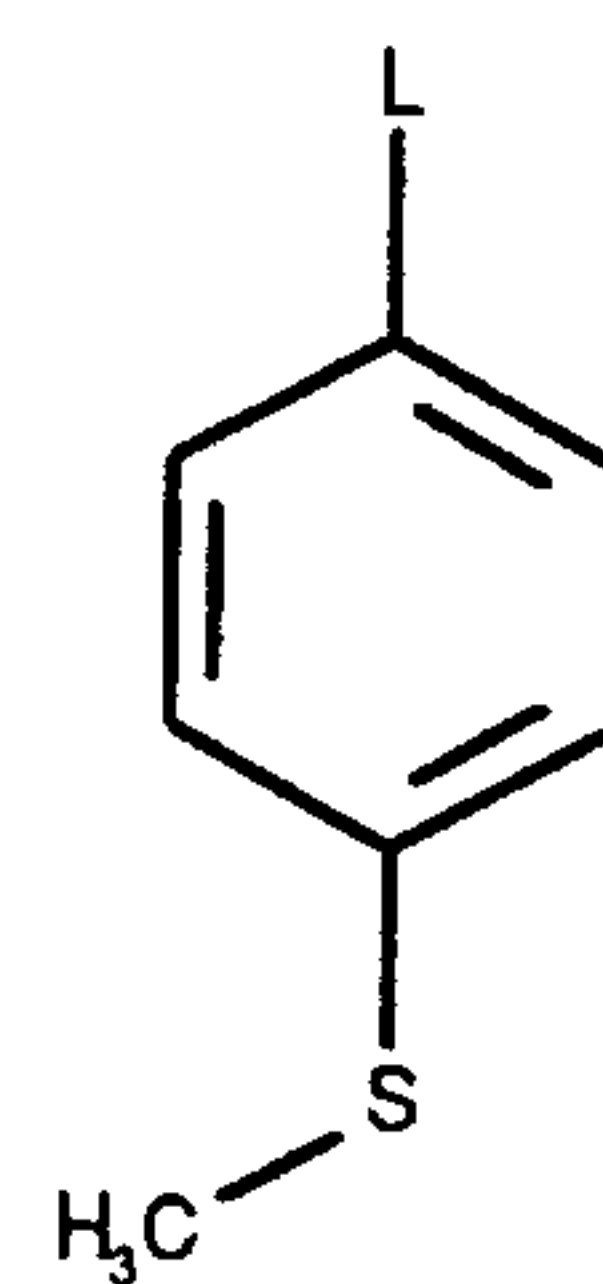
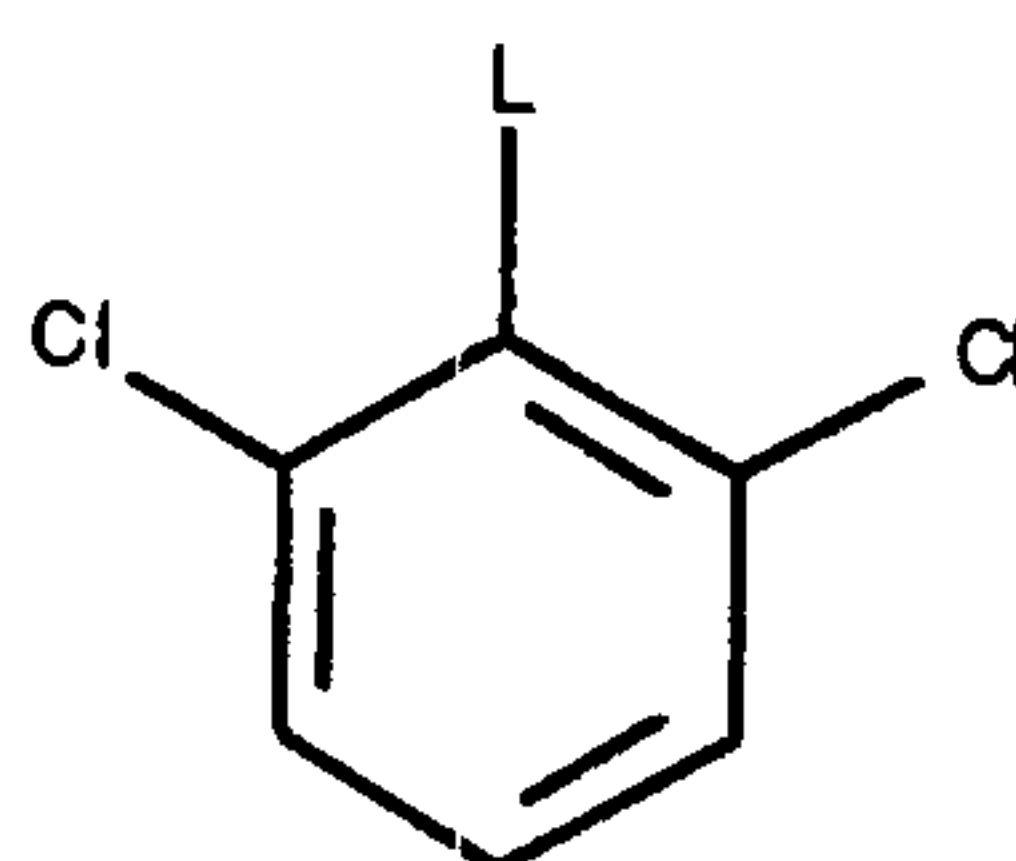
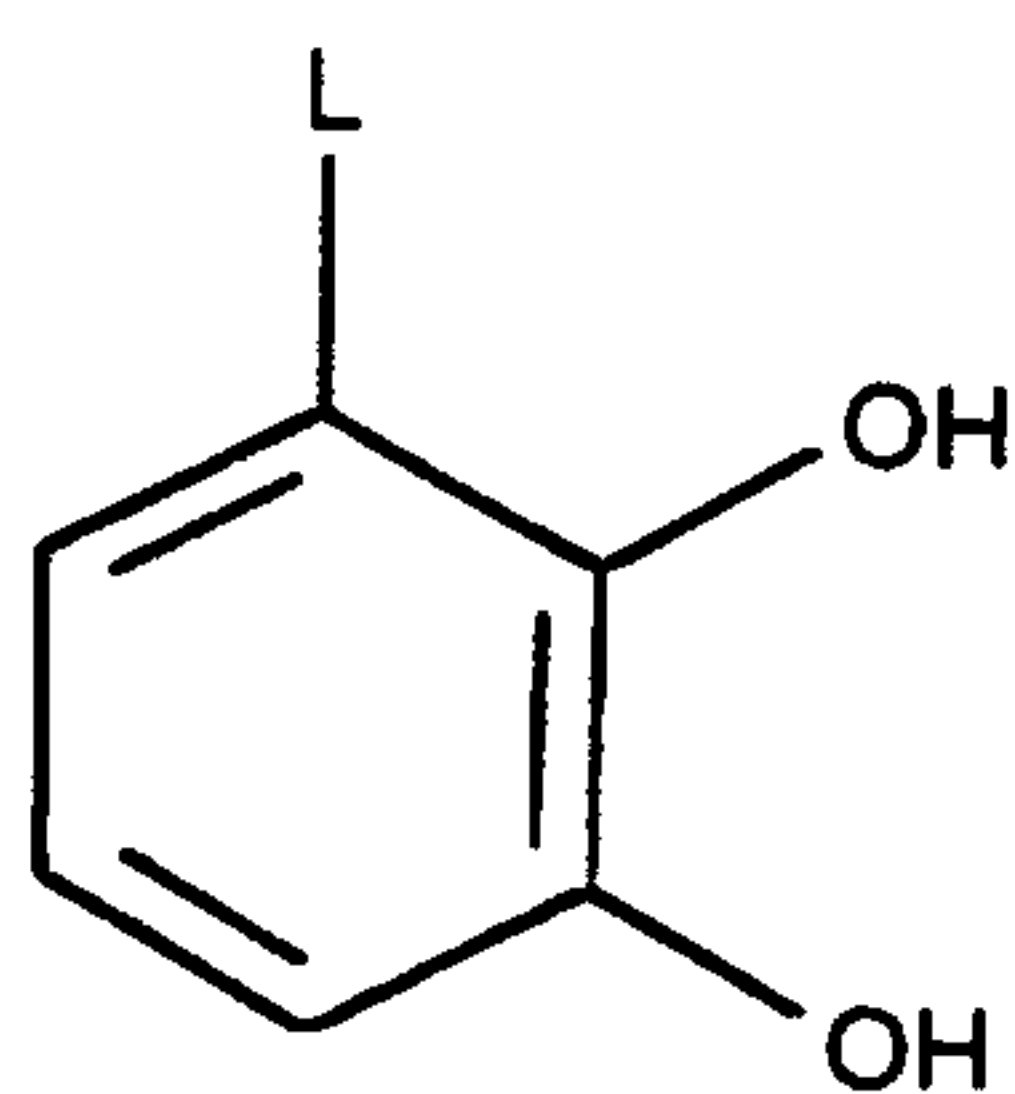
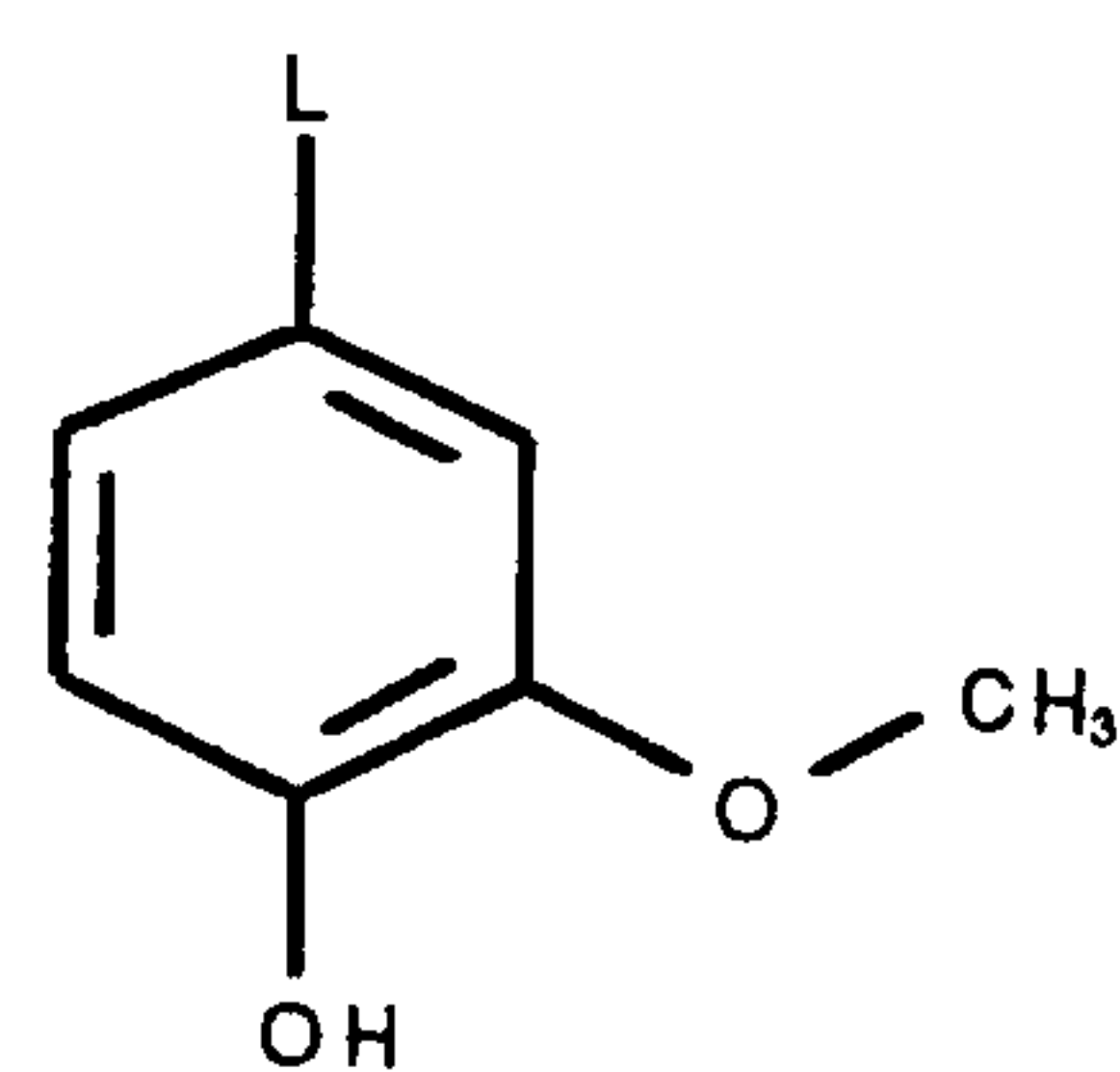
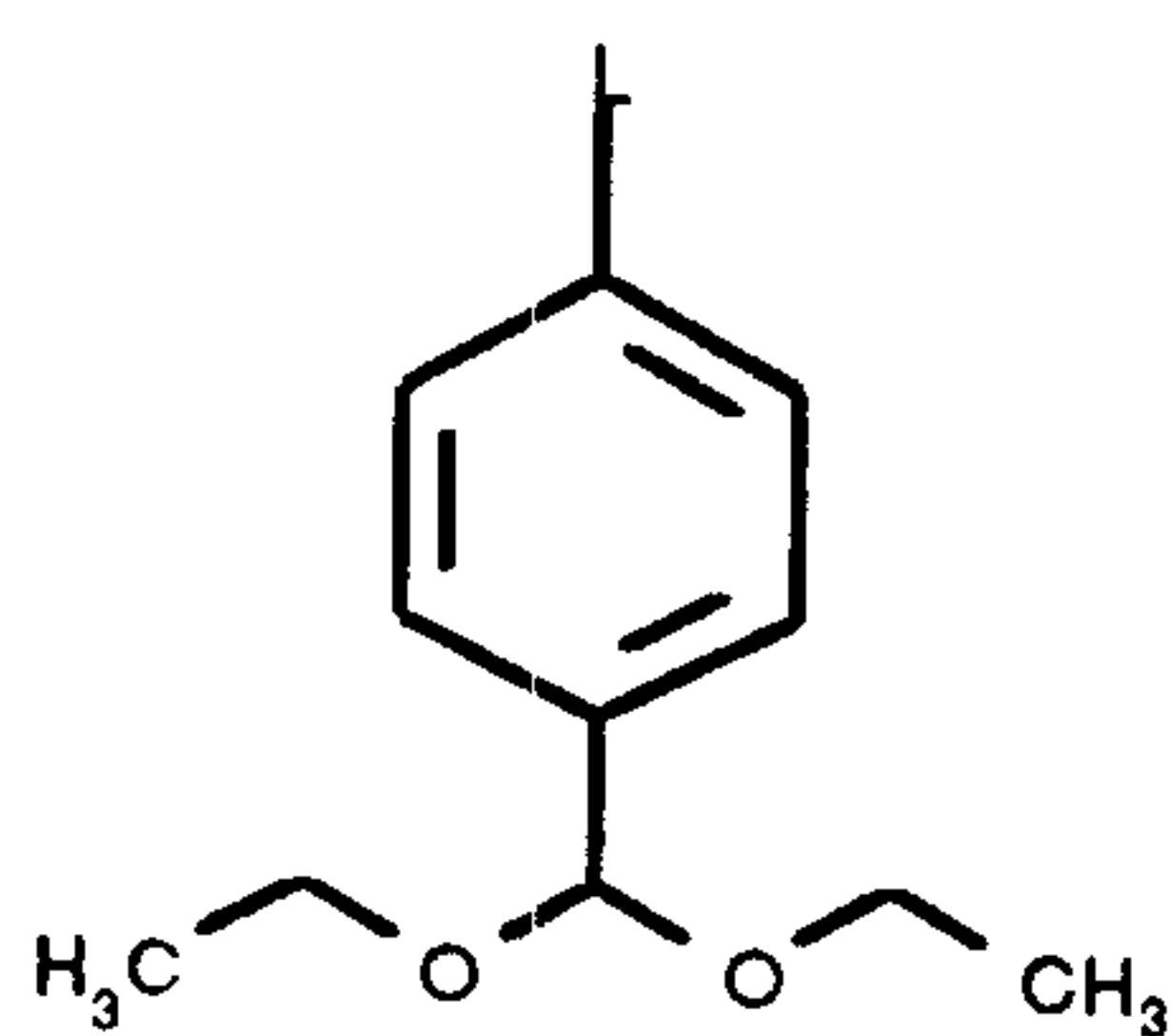
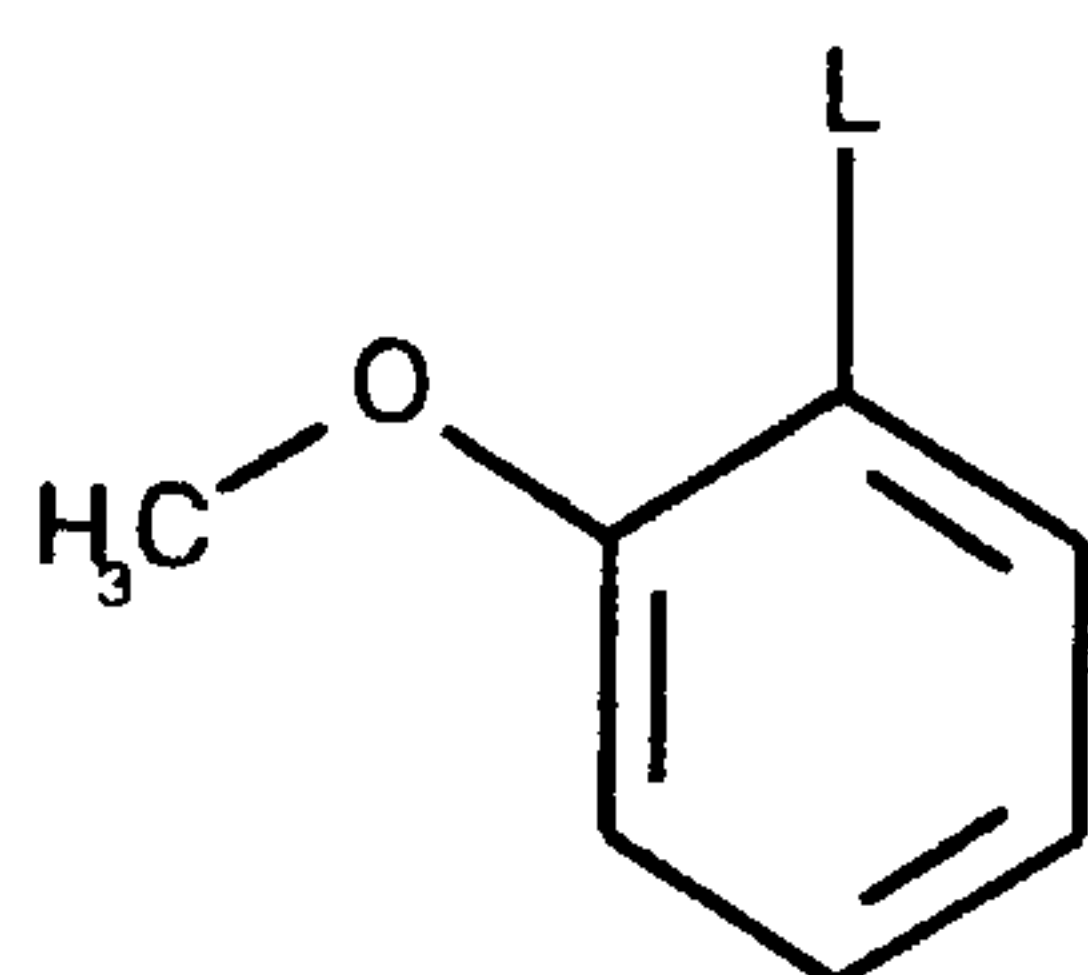
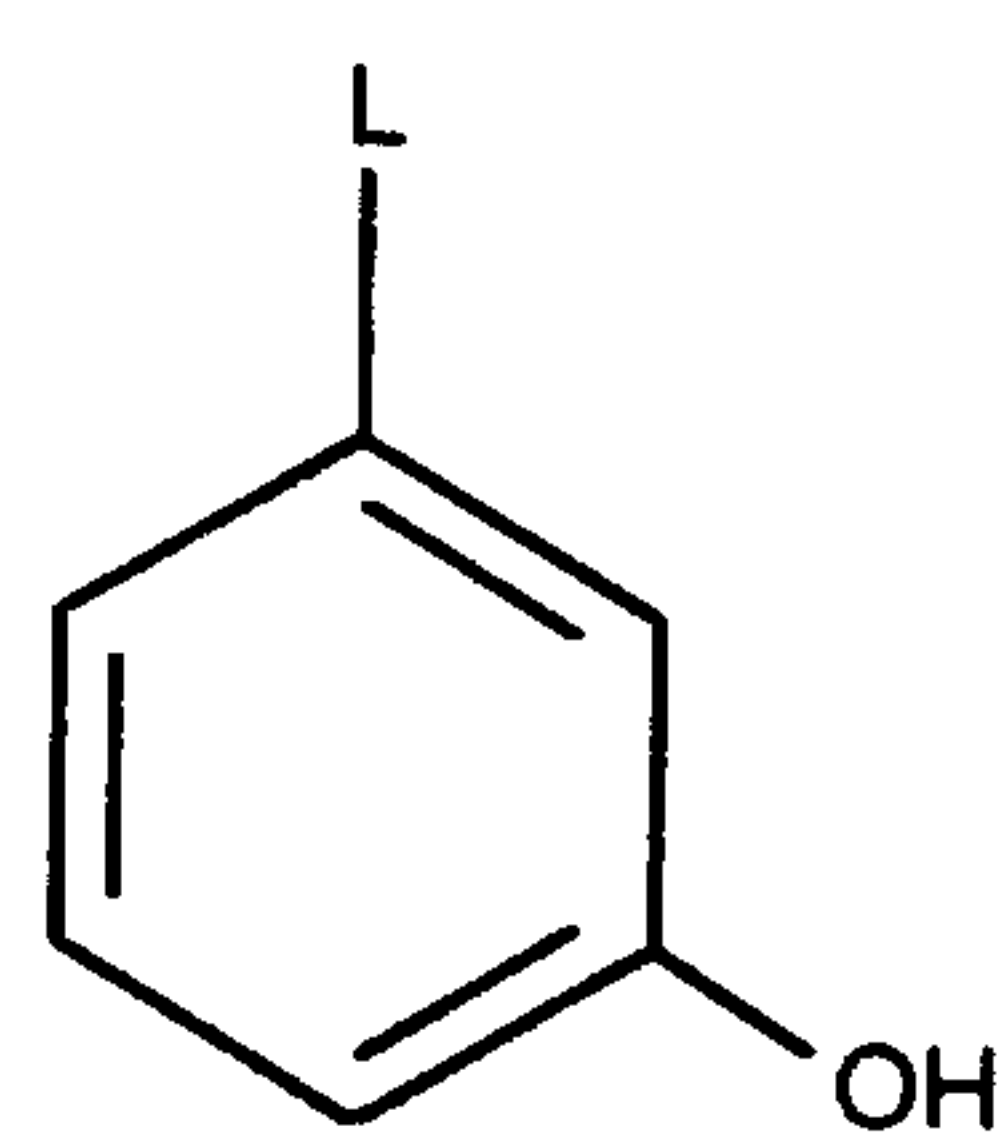
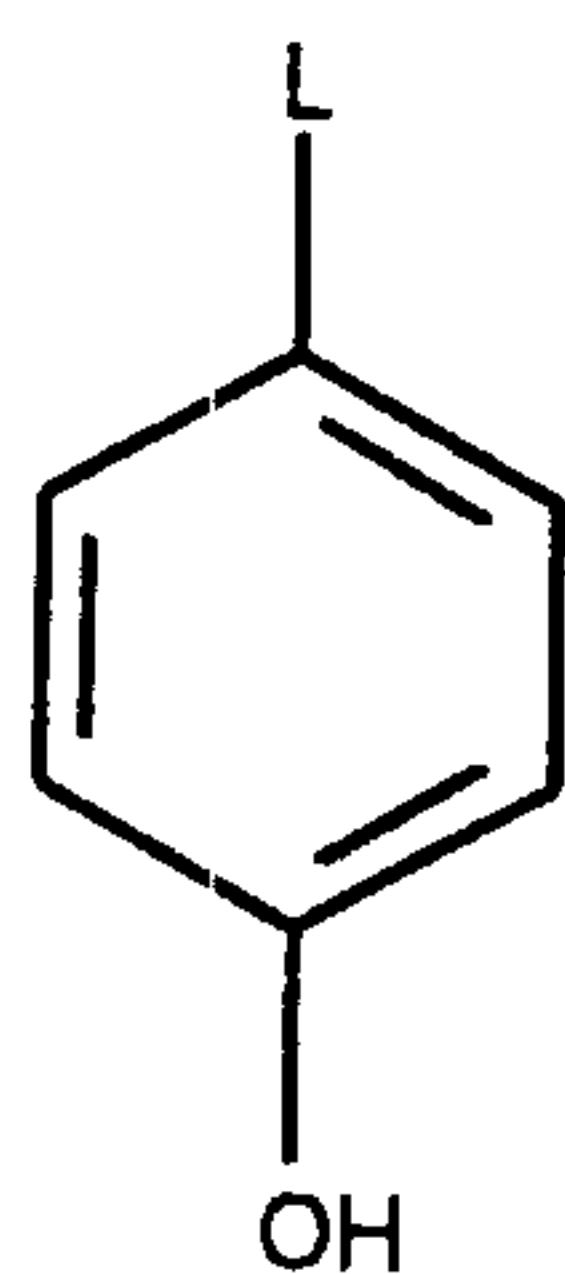
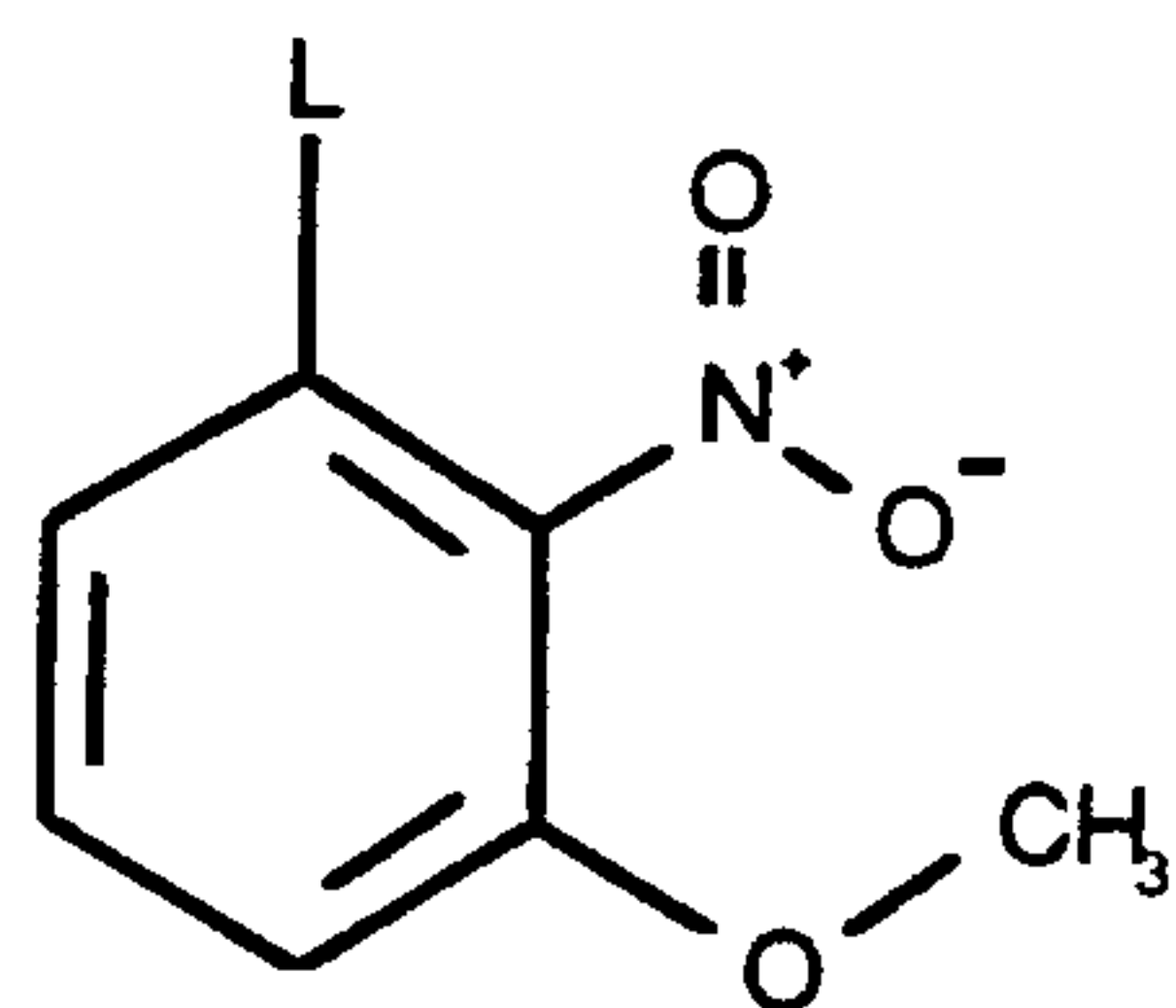
-68-

- Decyl aldehyde, [1-14c]
 4,4,4-Trifluorobutyraldehyde
 3-Methyl-3-butenal
 3-(5-Methyl-2-furyl)butanal
 5 3-Phenyl-4-pentenal
 Tert-butyl (s)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate
 Trans-2-dodecenal
 9,10-Dihydro-9,10-ethanoanthracene-11-carboxaldehyde
 10 Methyl hexyl acetaldehyde
 2,3-Dihydro-2-oxo-1H-imidazol-4-carboxaldehyde
 N-Acetylmuramic acid,
 and the like.

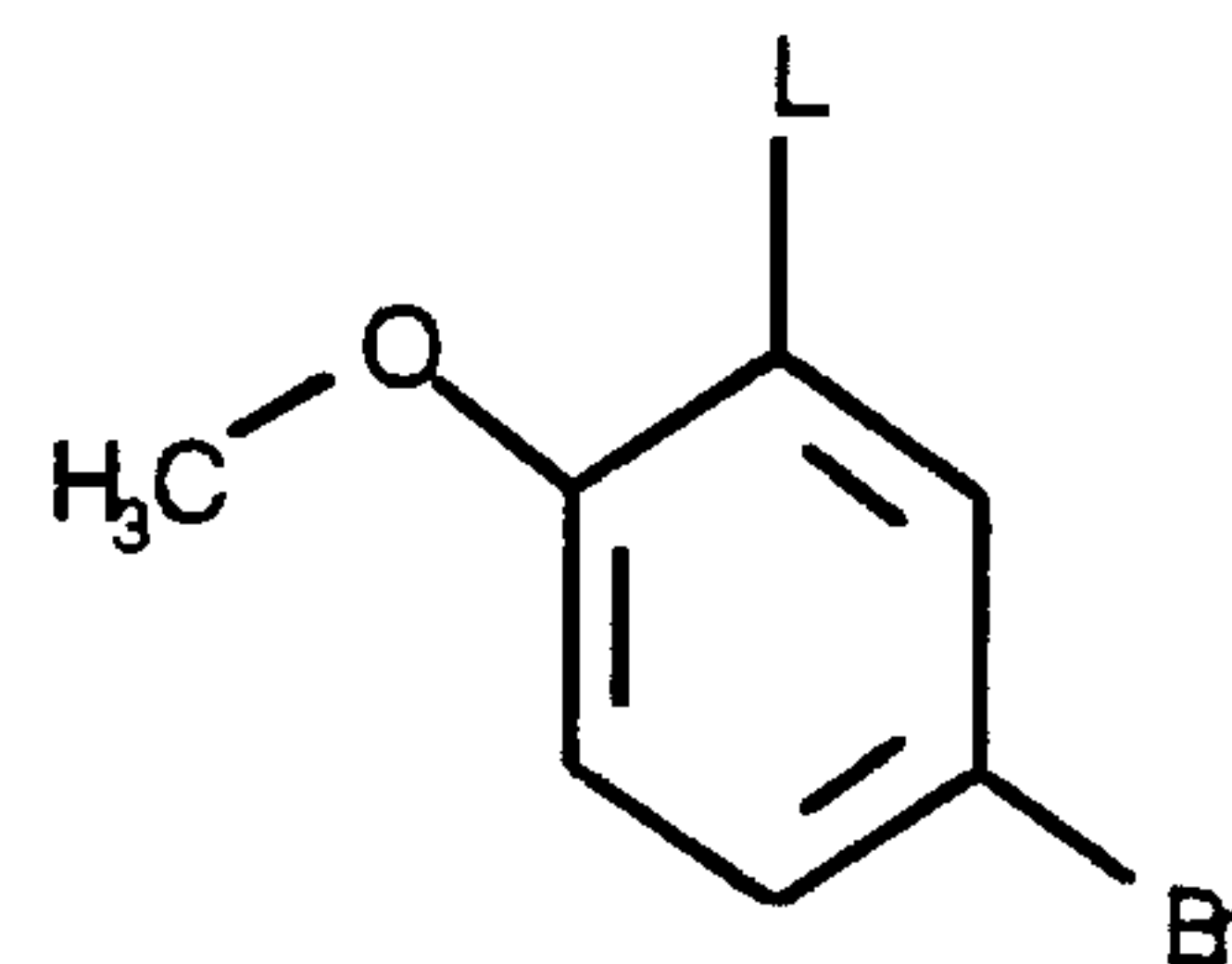
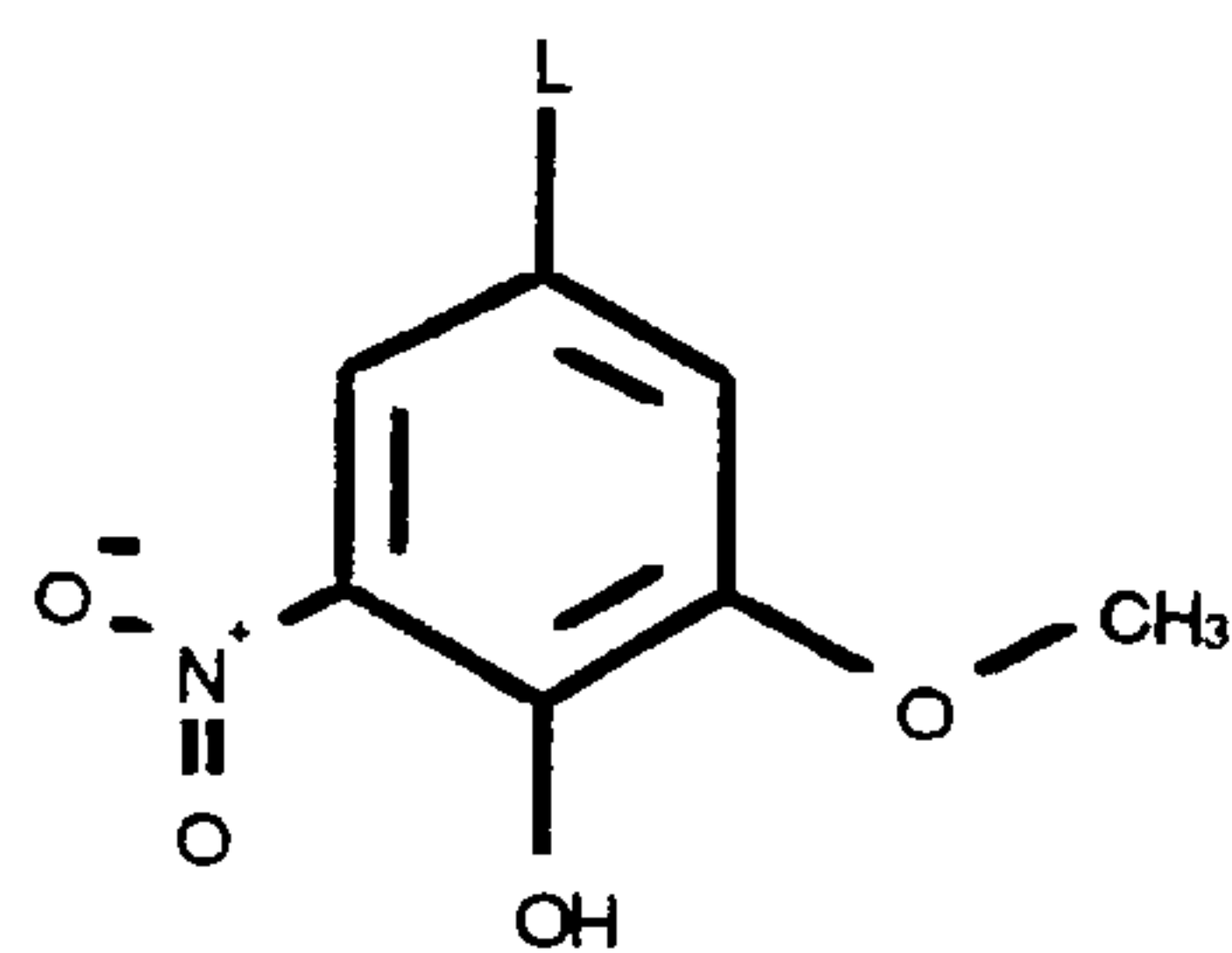
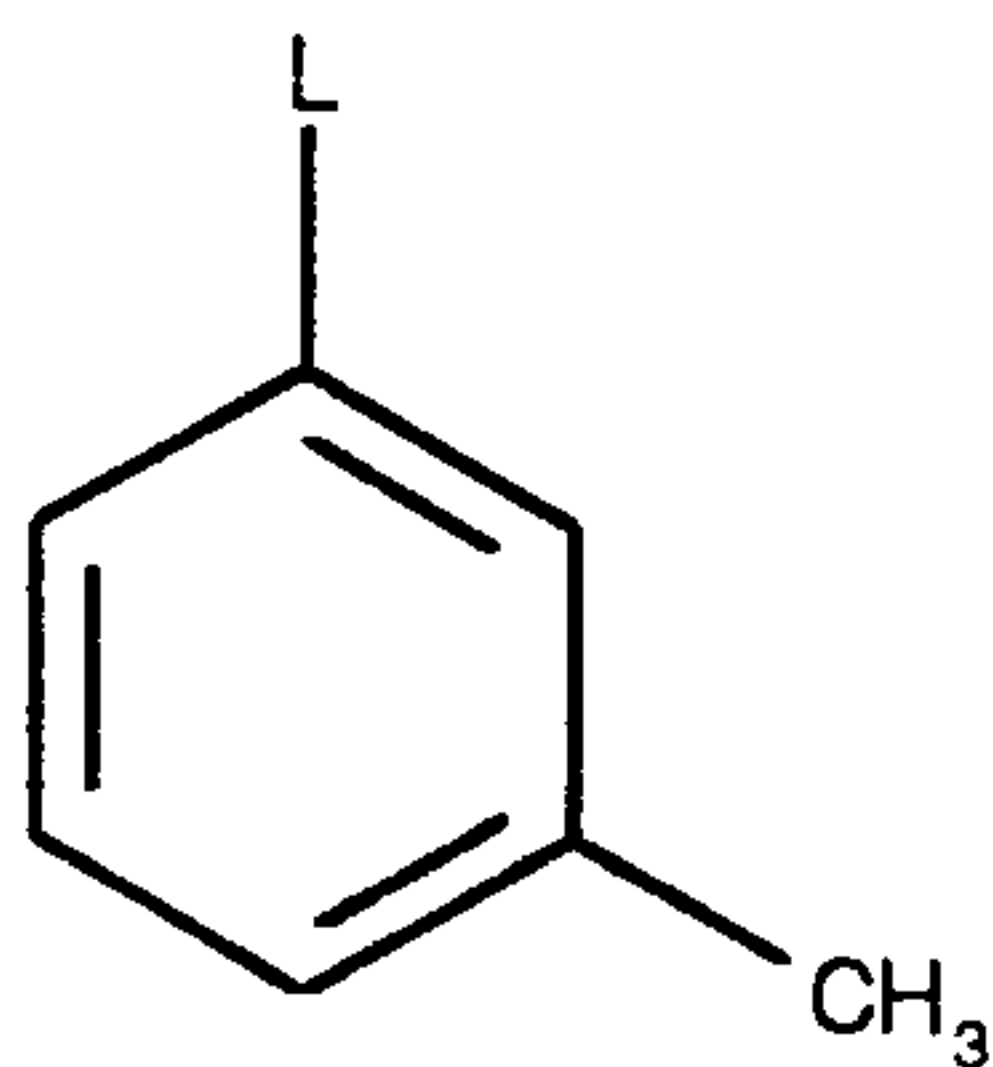
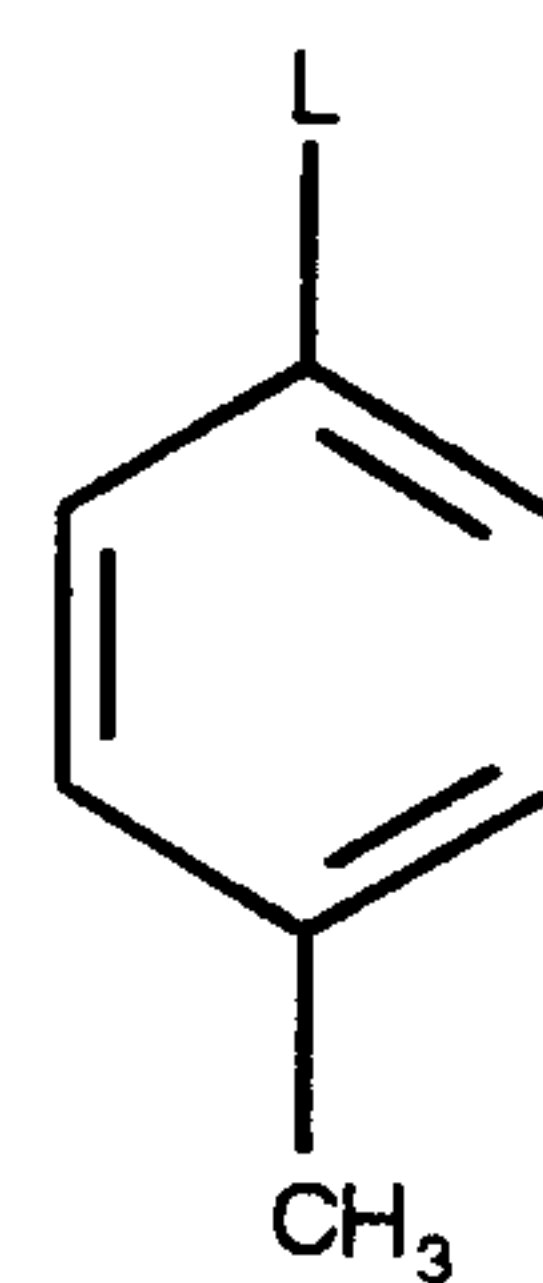
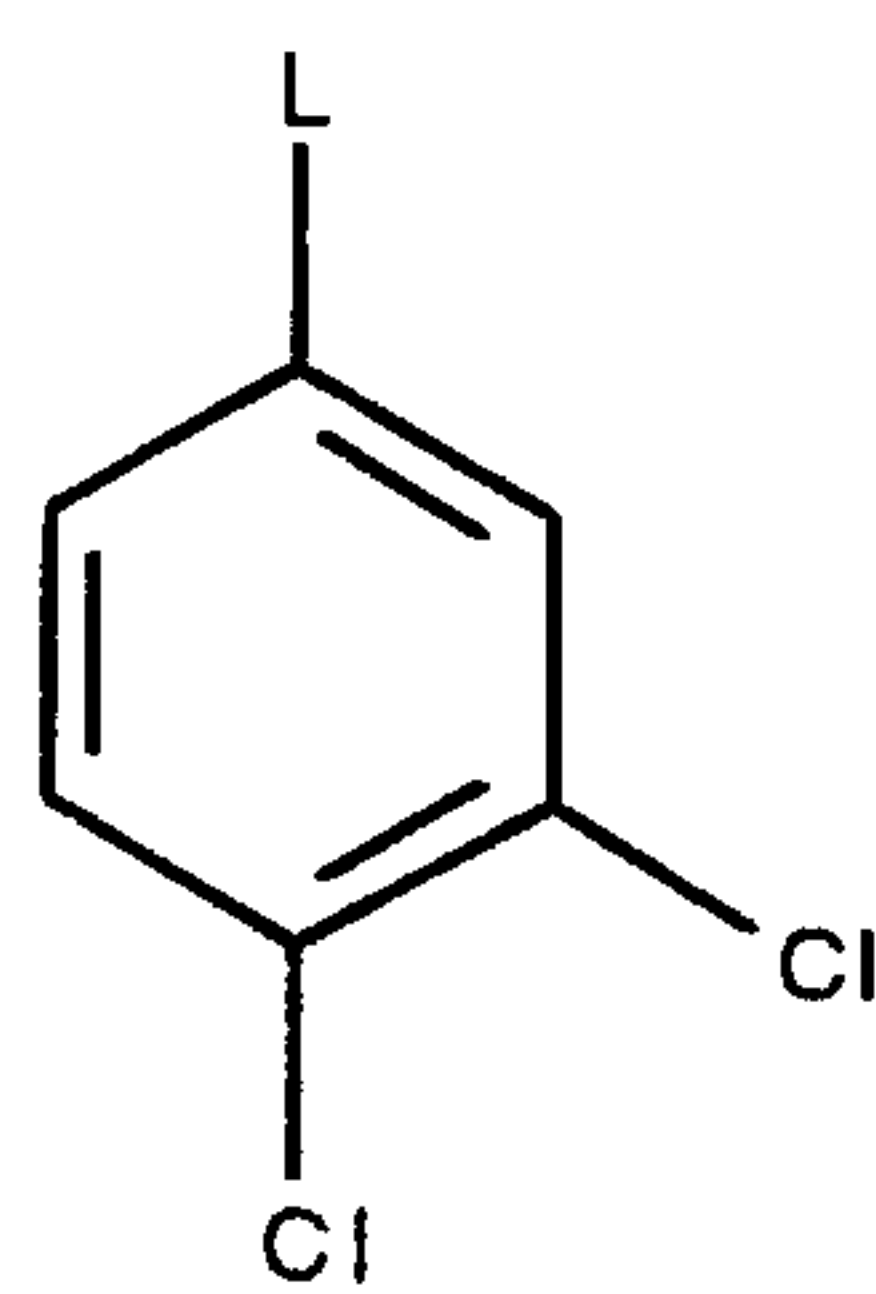
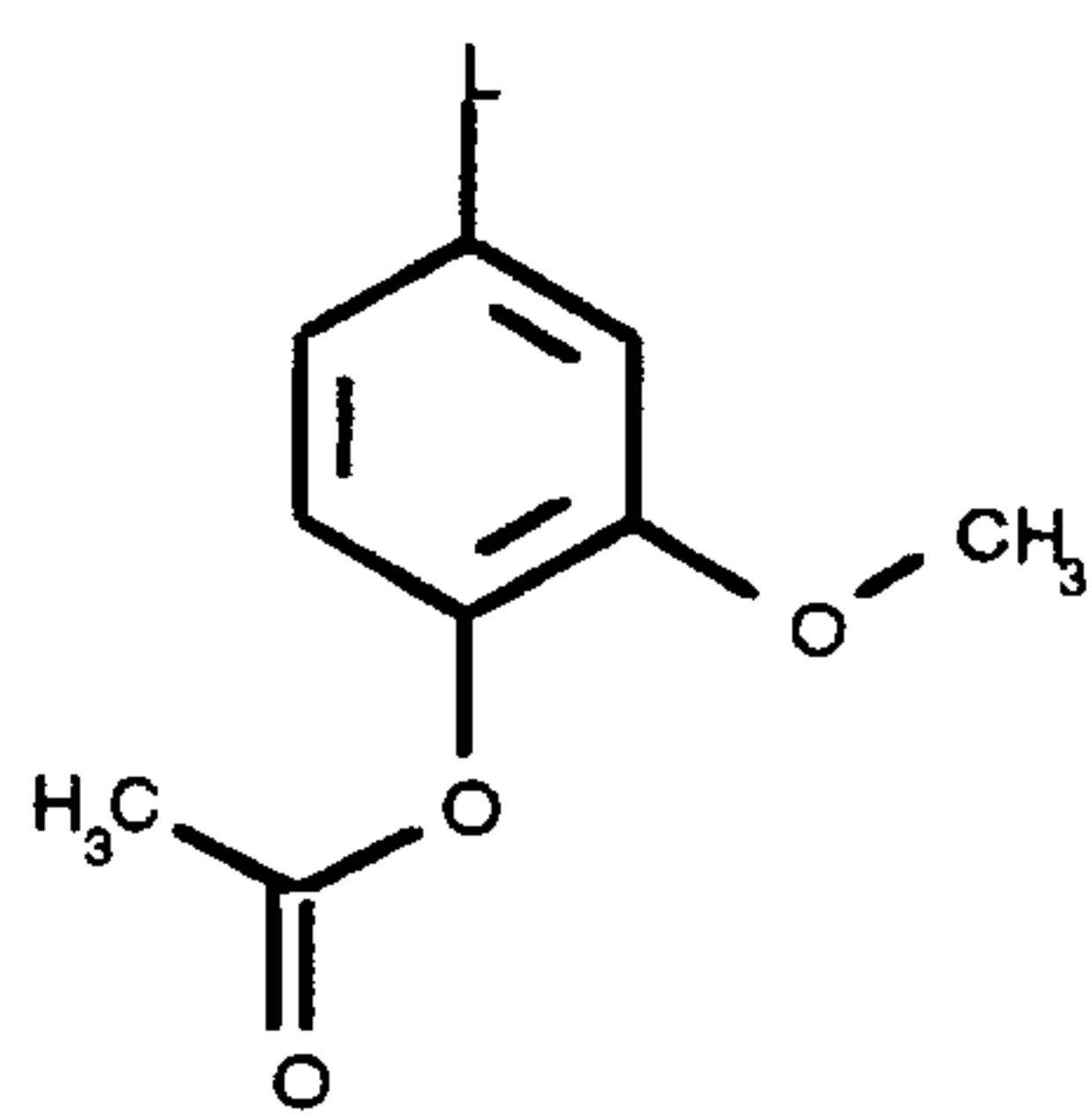
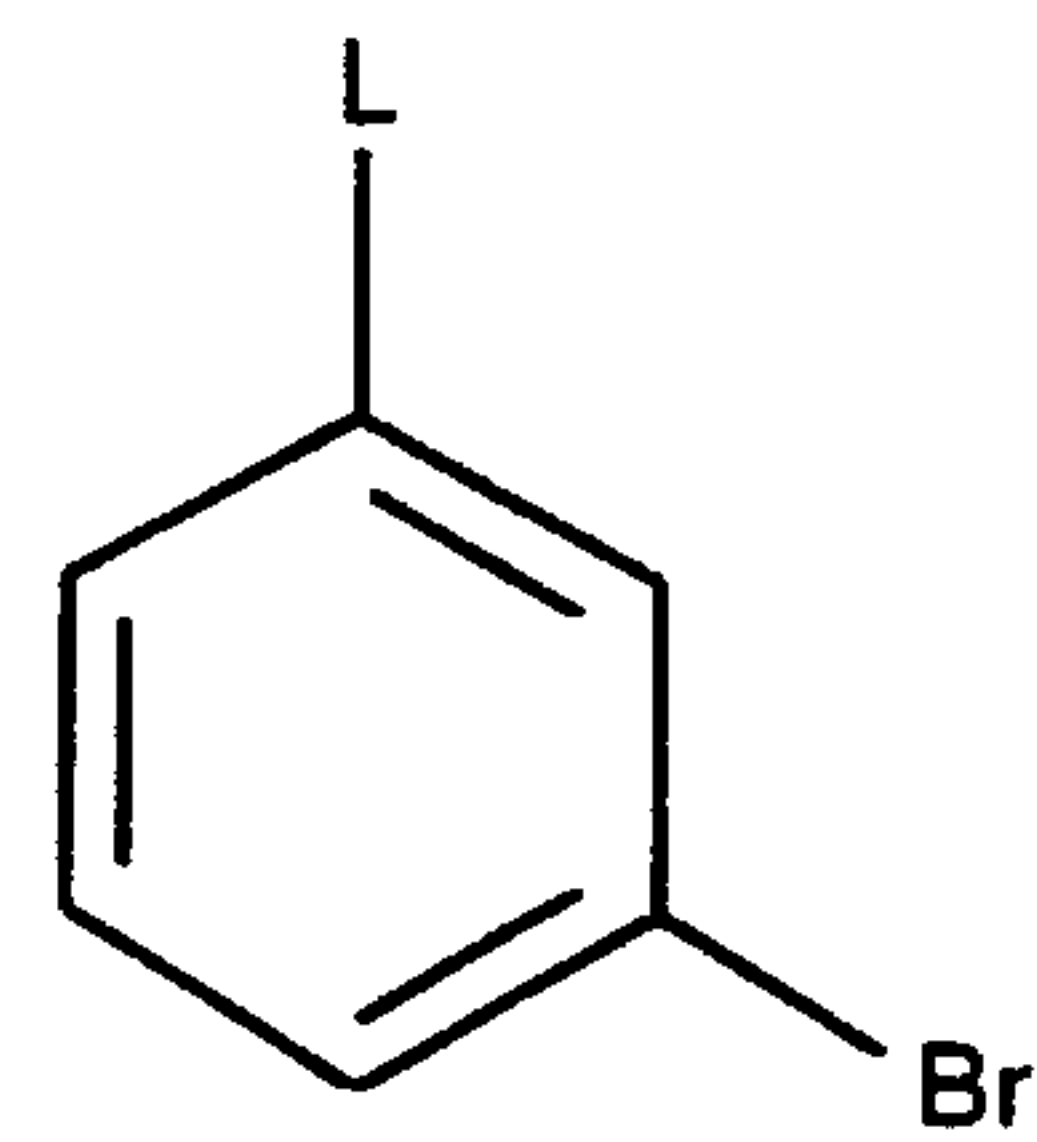
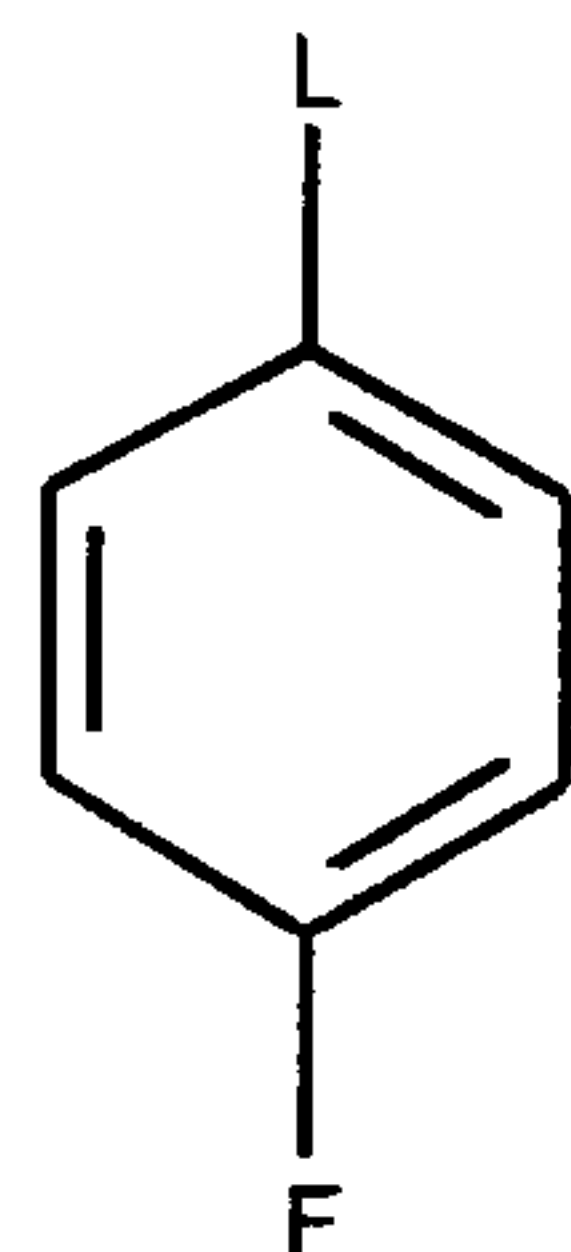
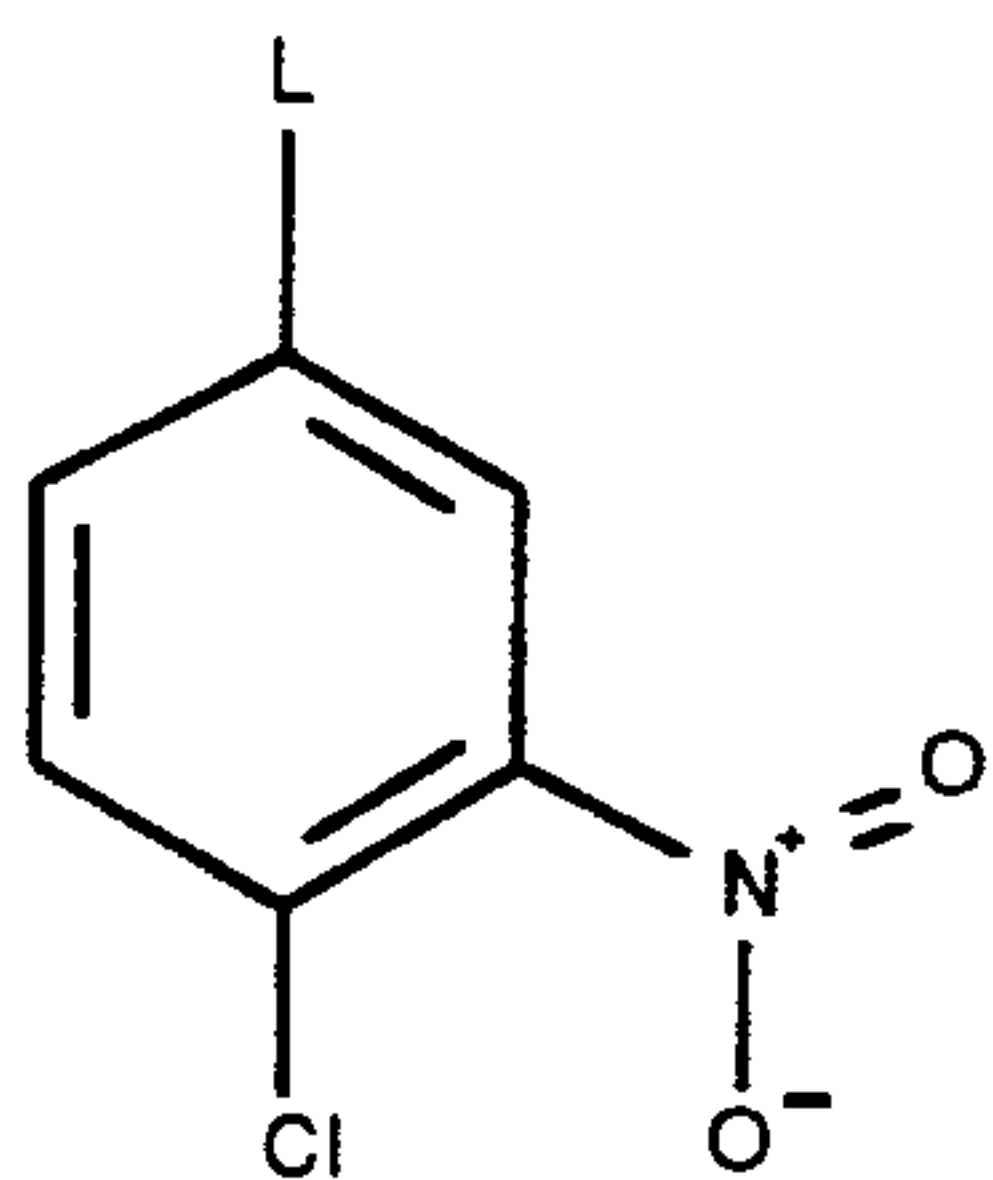
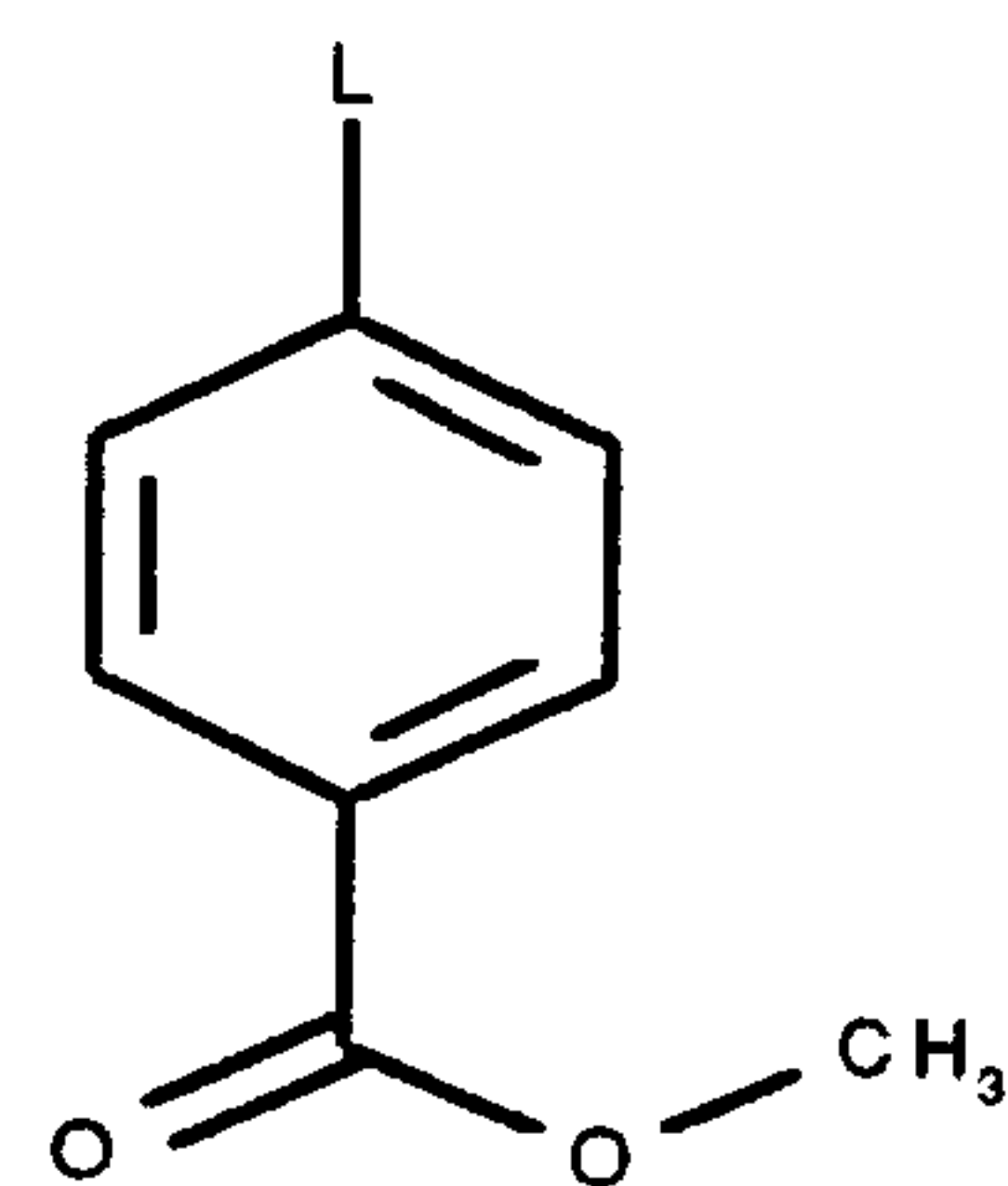
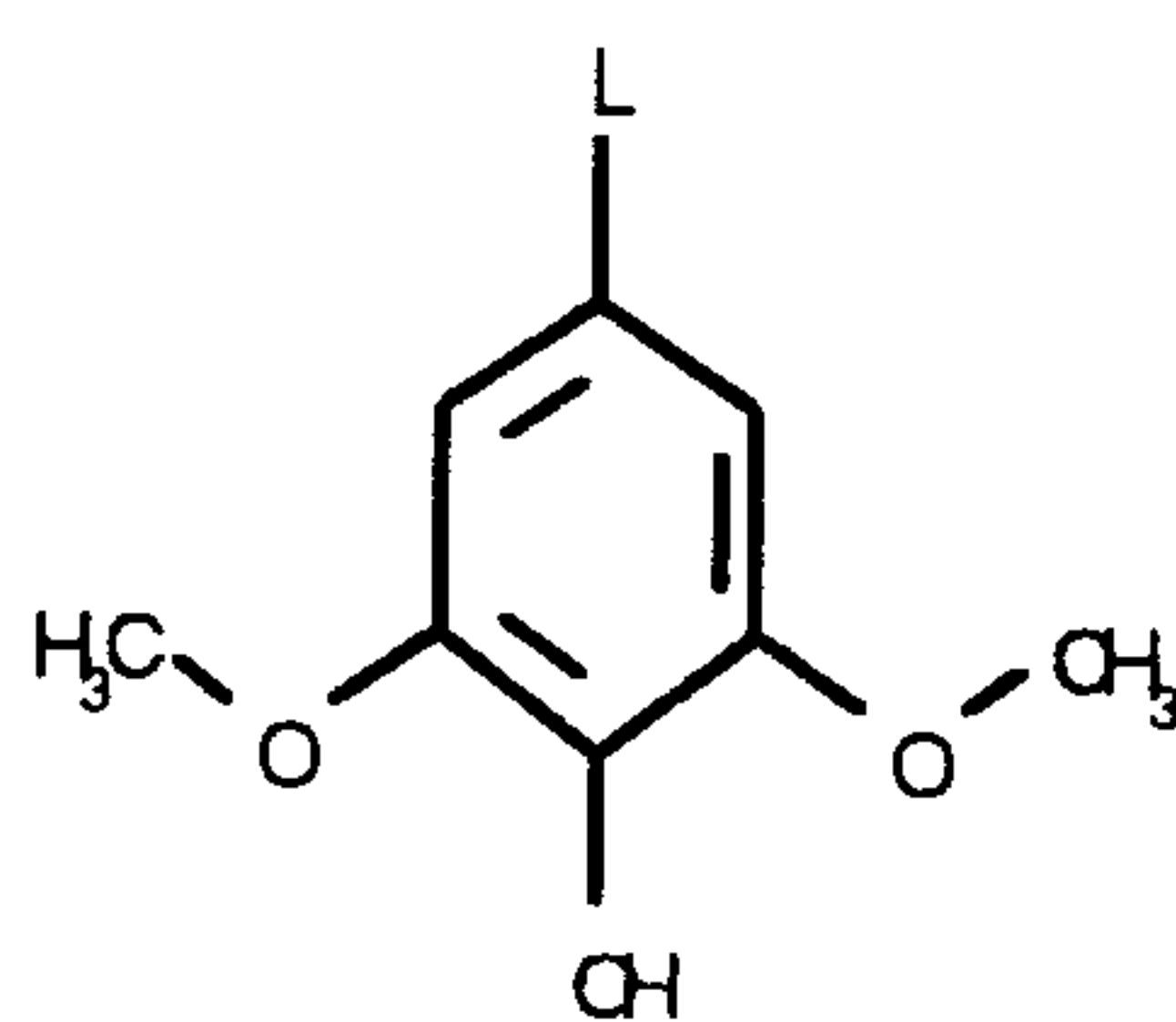
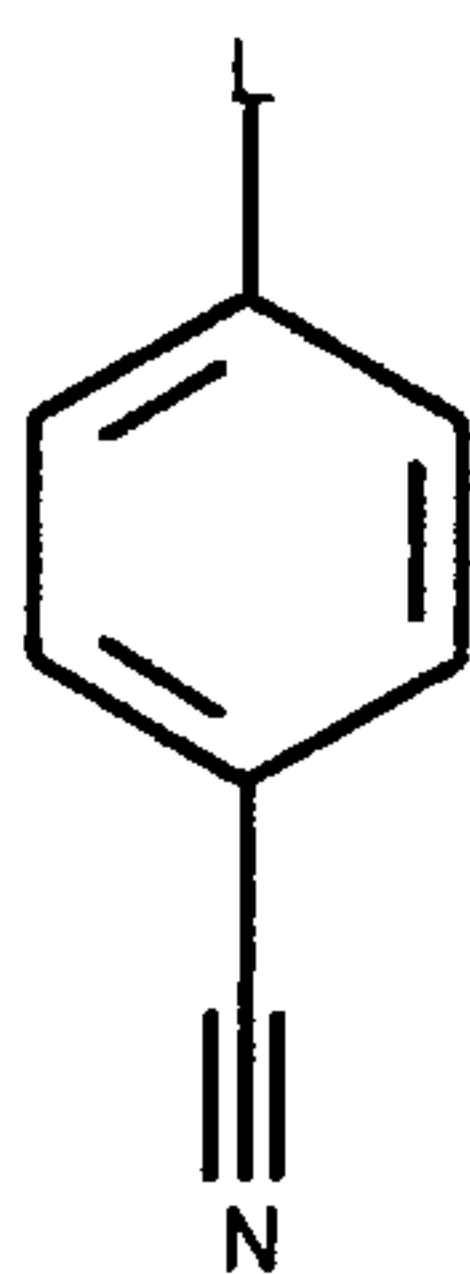
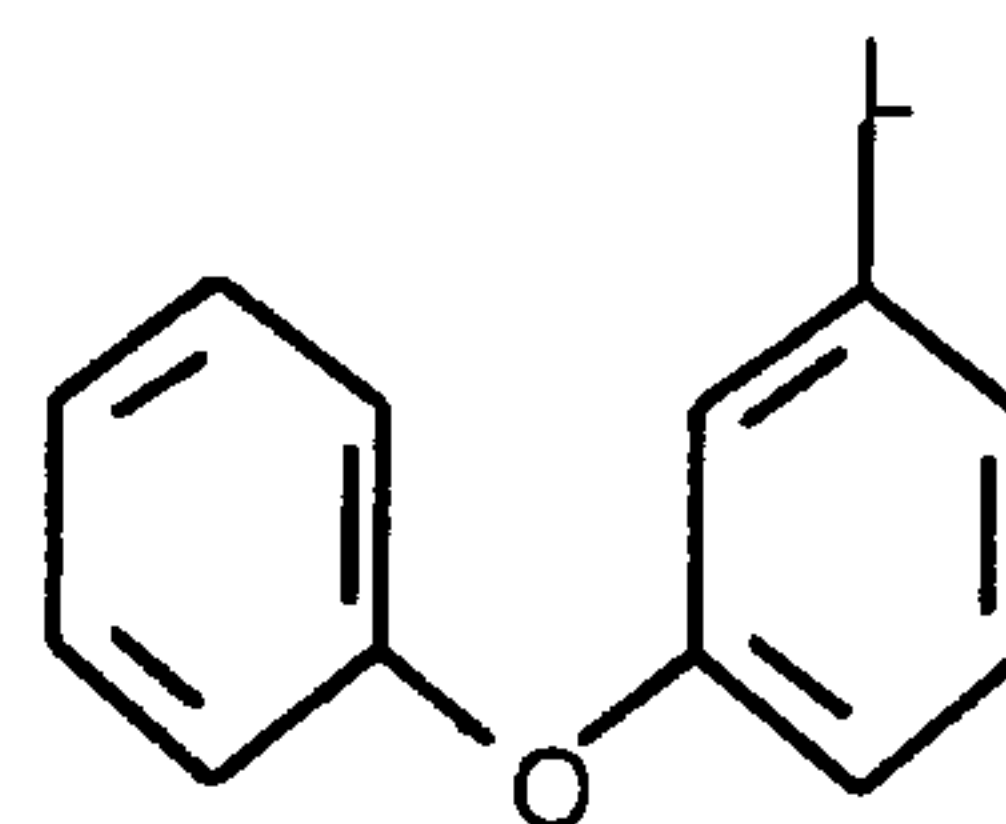
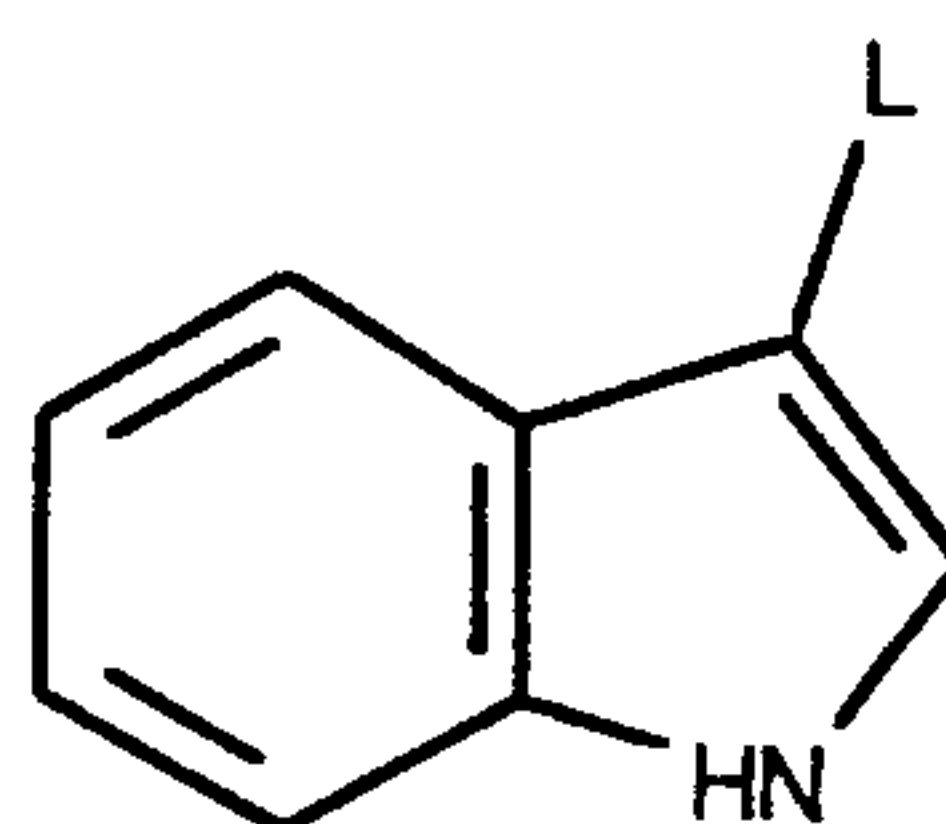
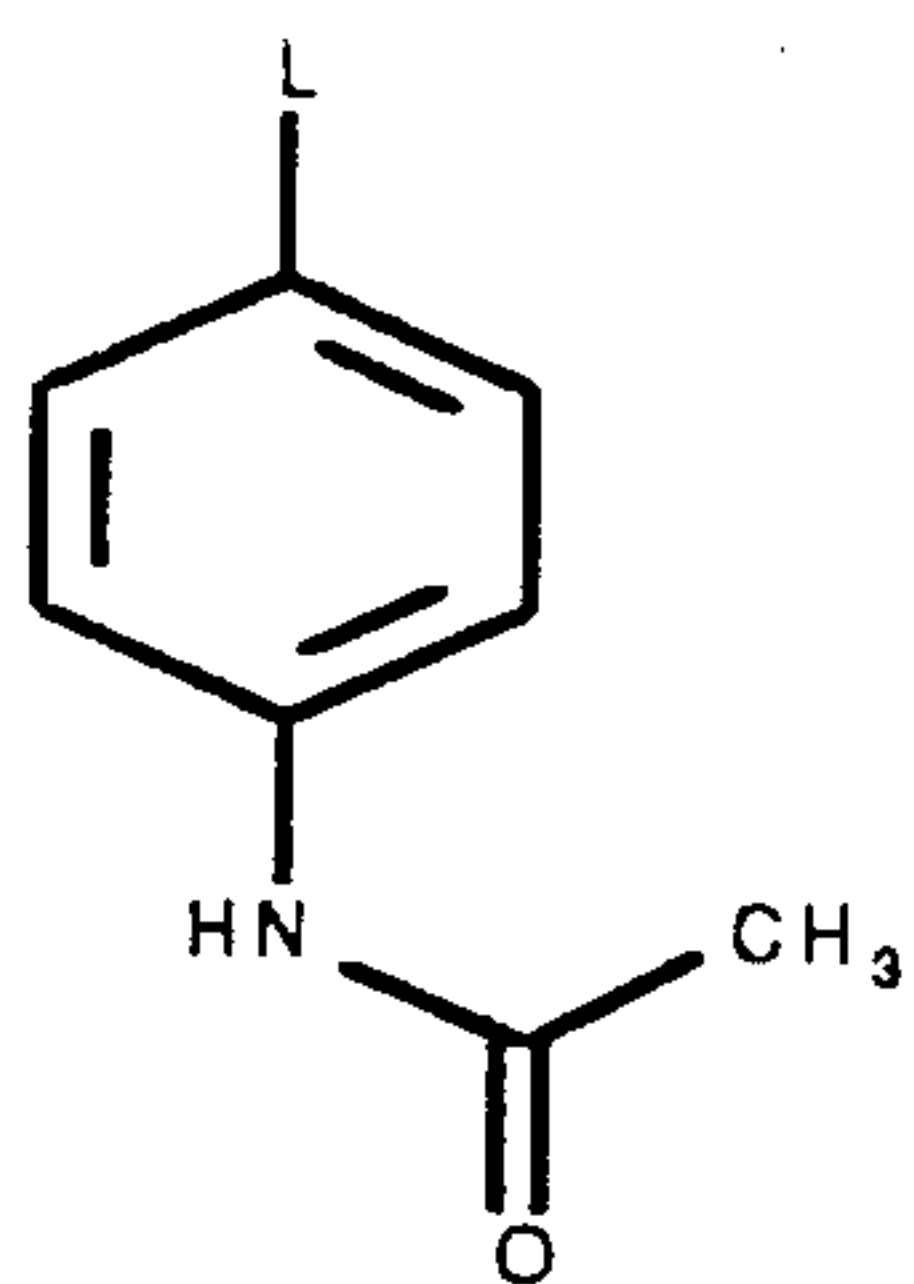
- 15 Other suitable aldehydes useful in preparation of the present libraries are further illustrated by the following formulas, wherein L is -CHO:



- 69 -



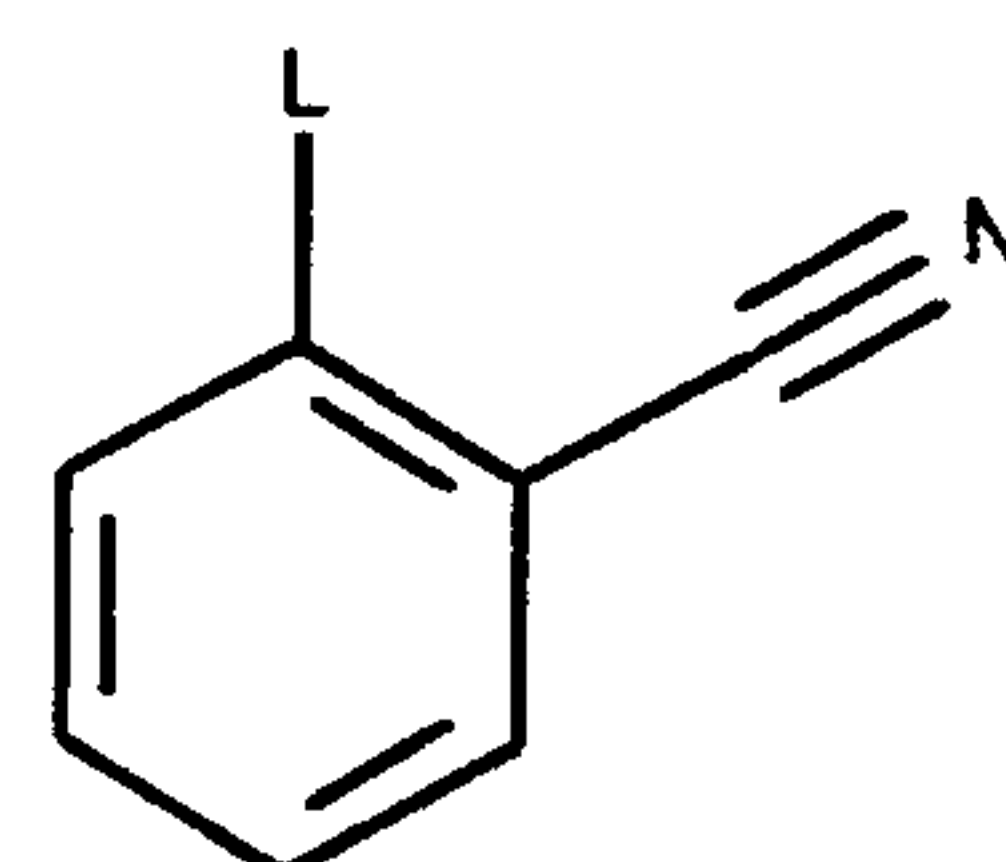
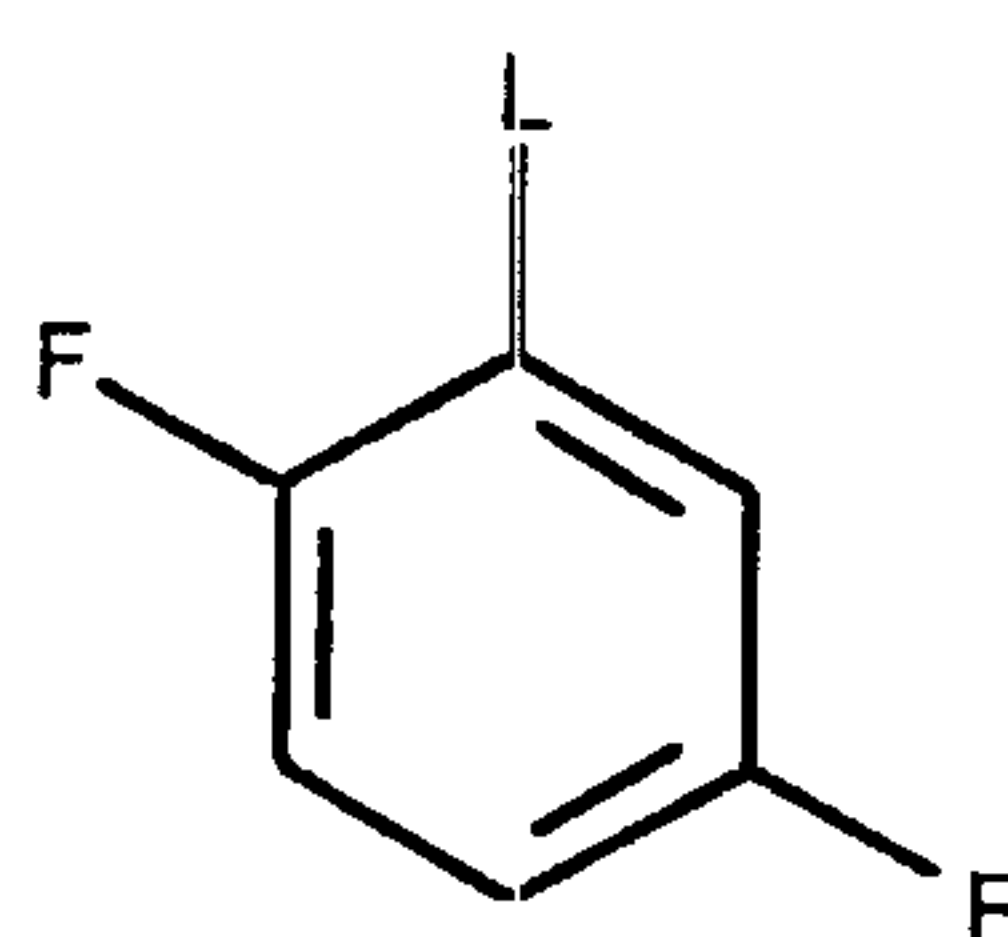
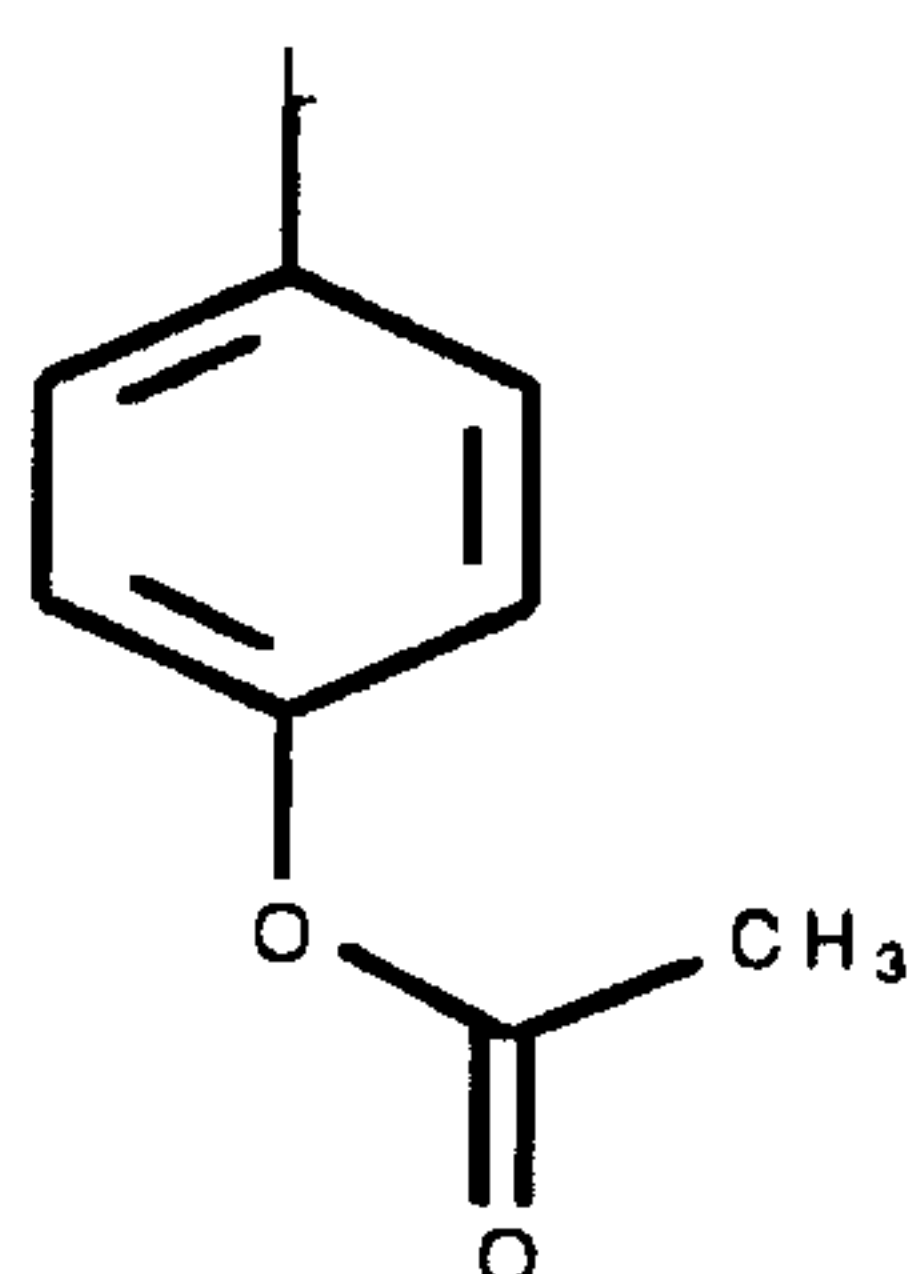
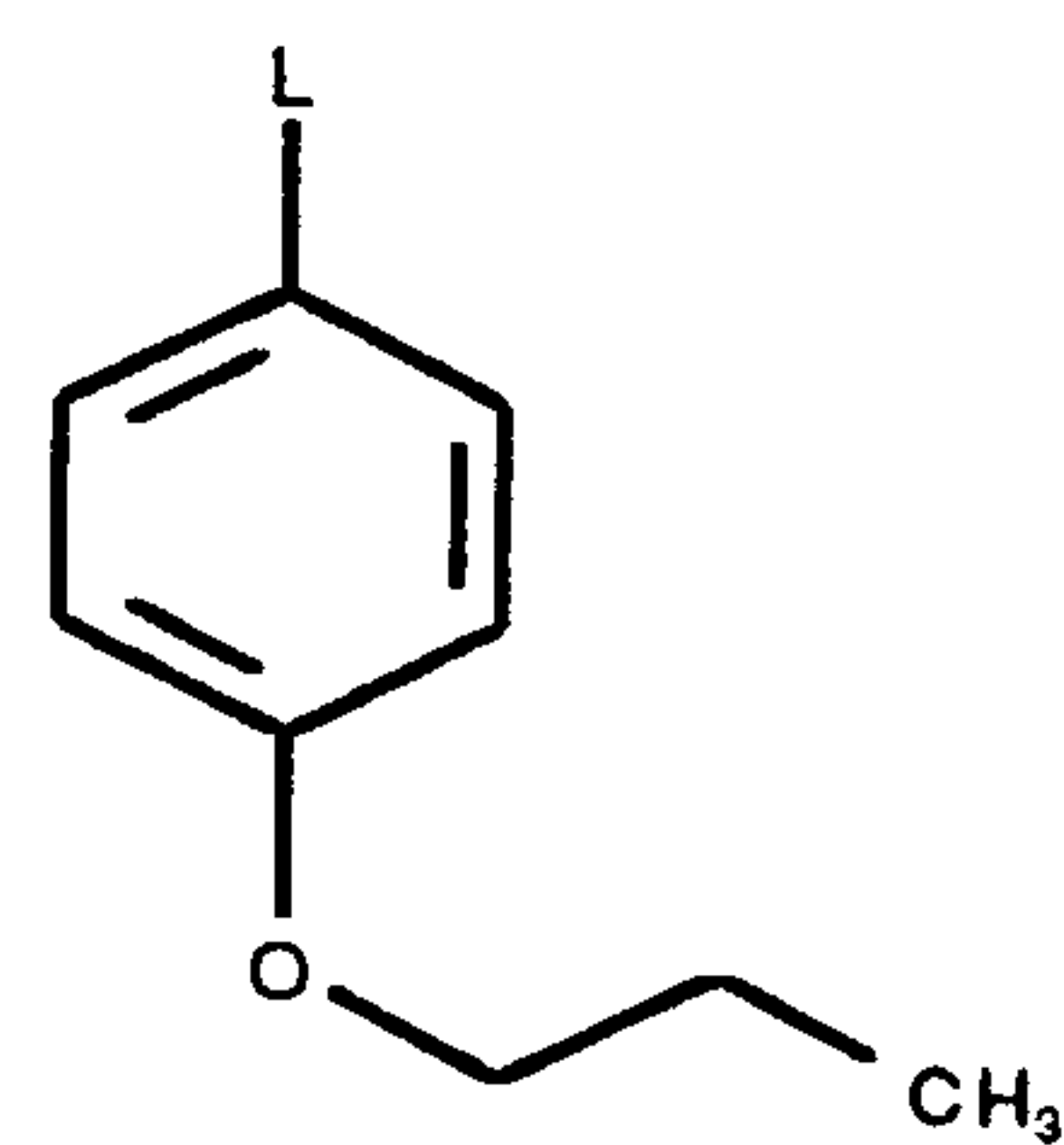
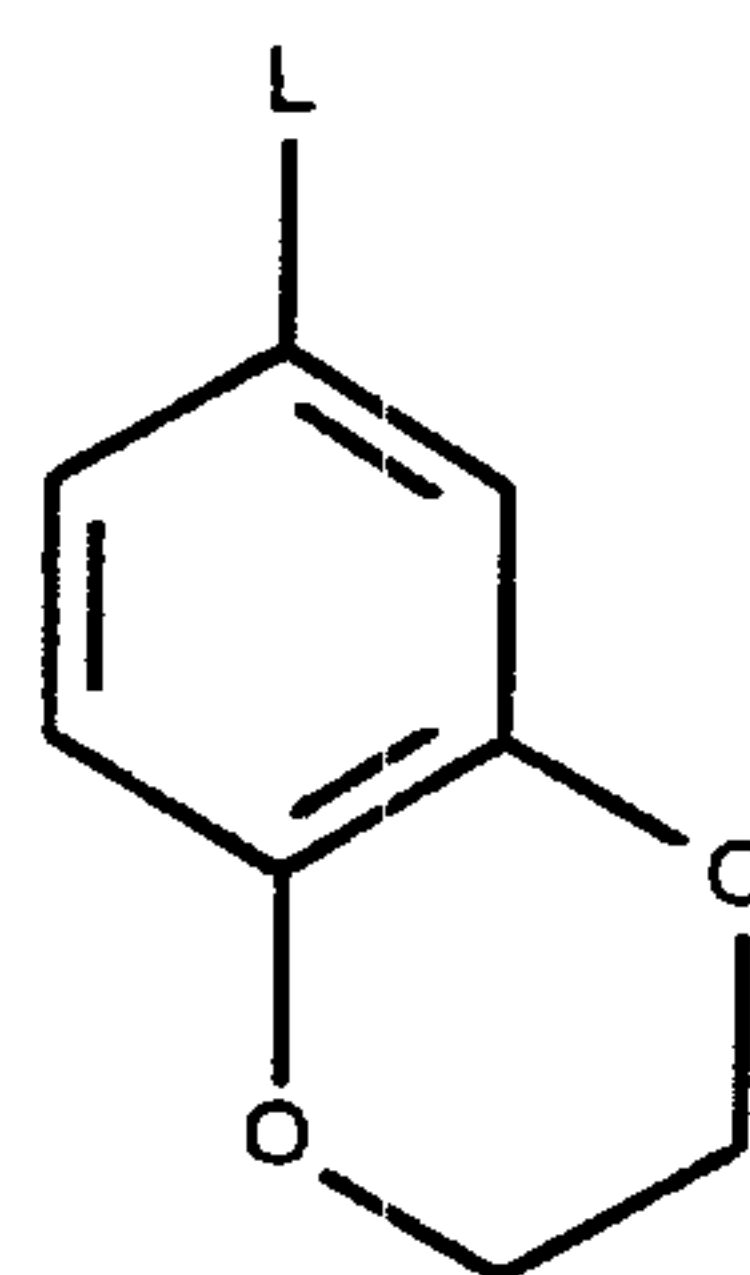
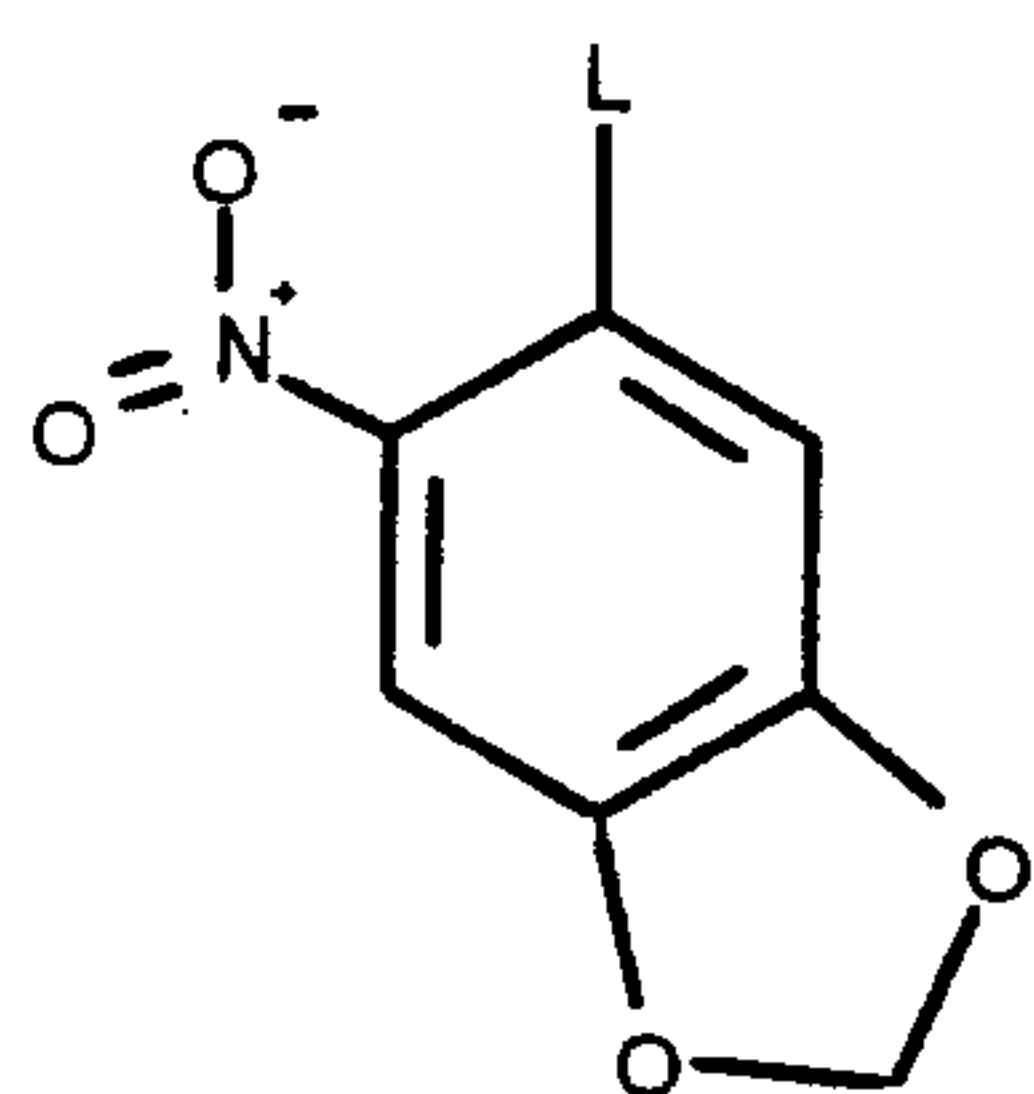
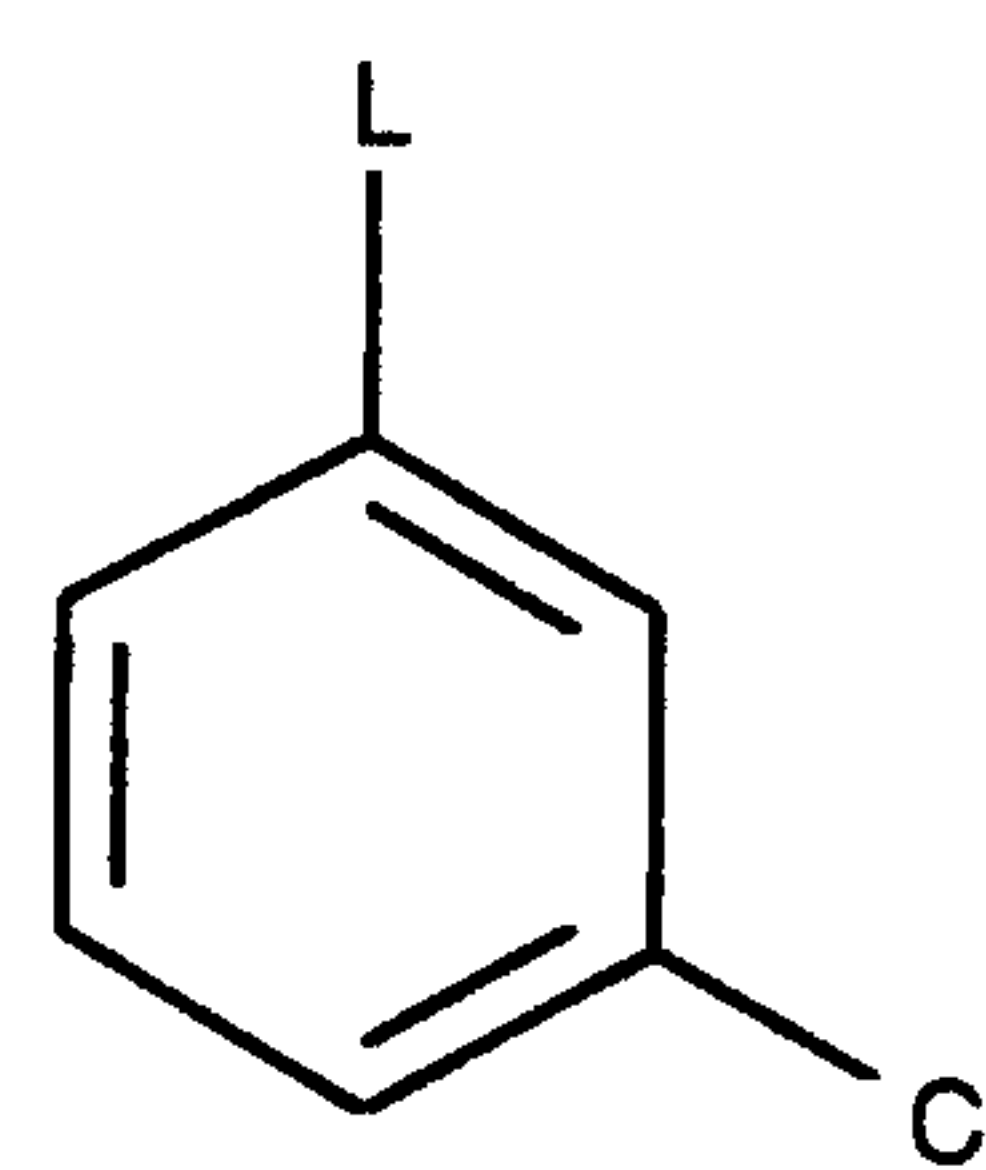
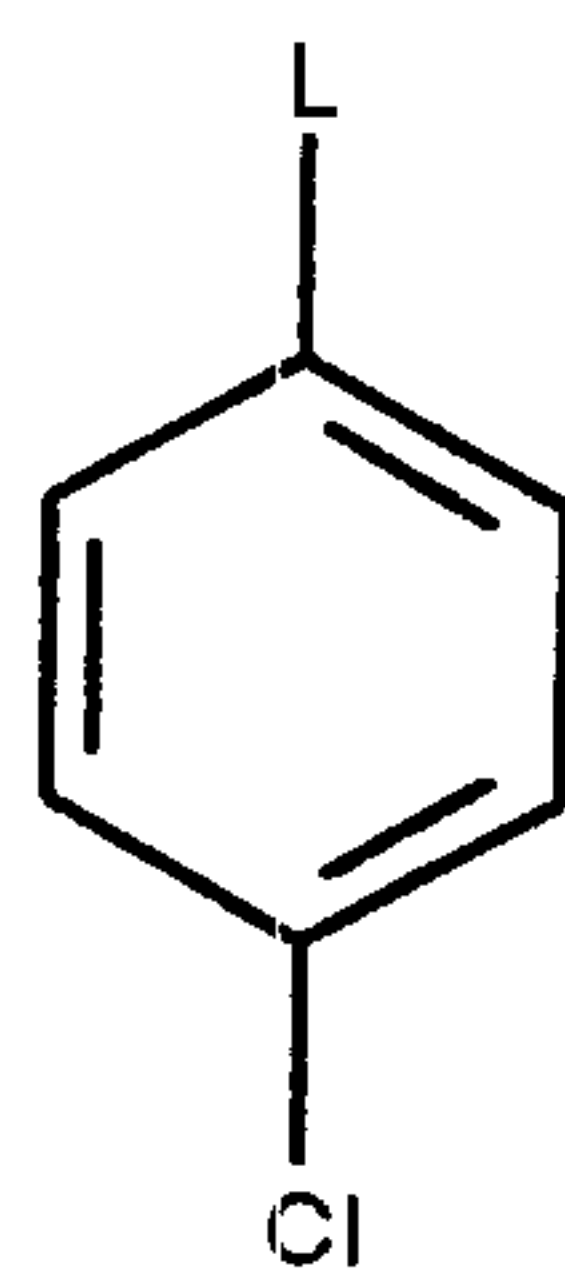
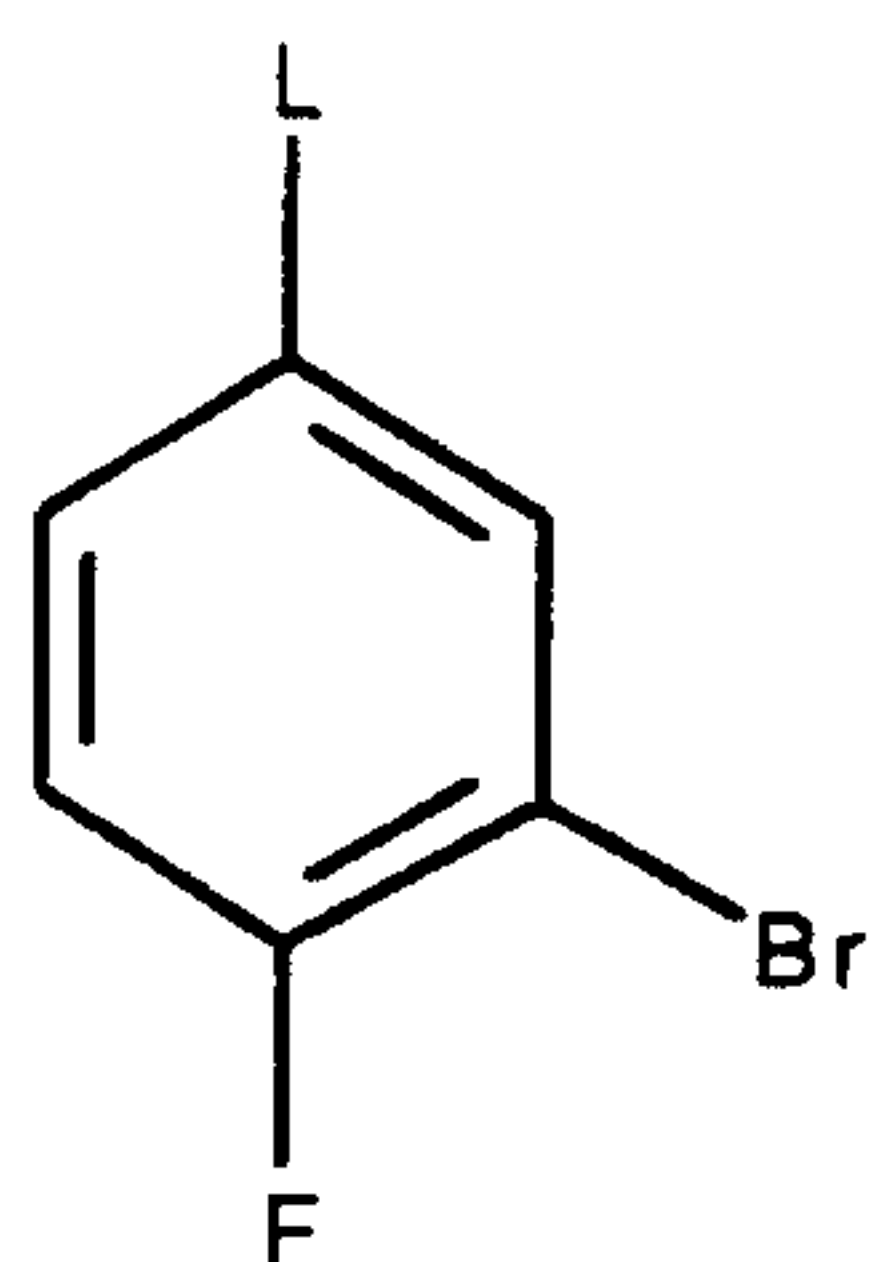
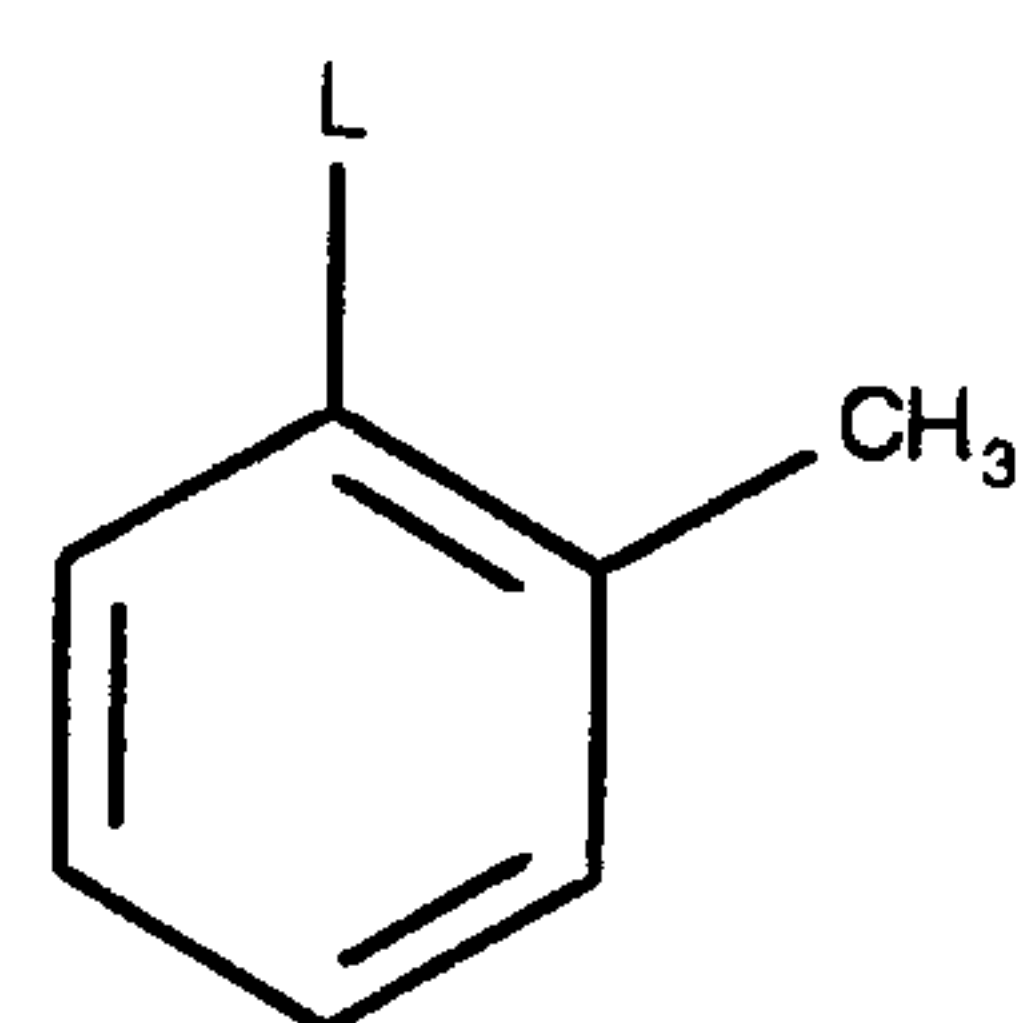
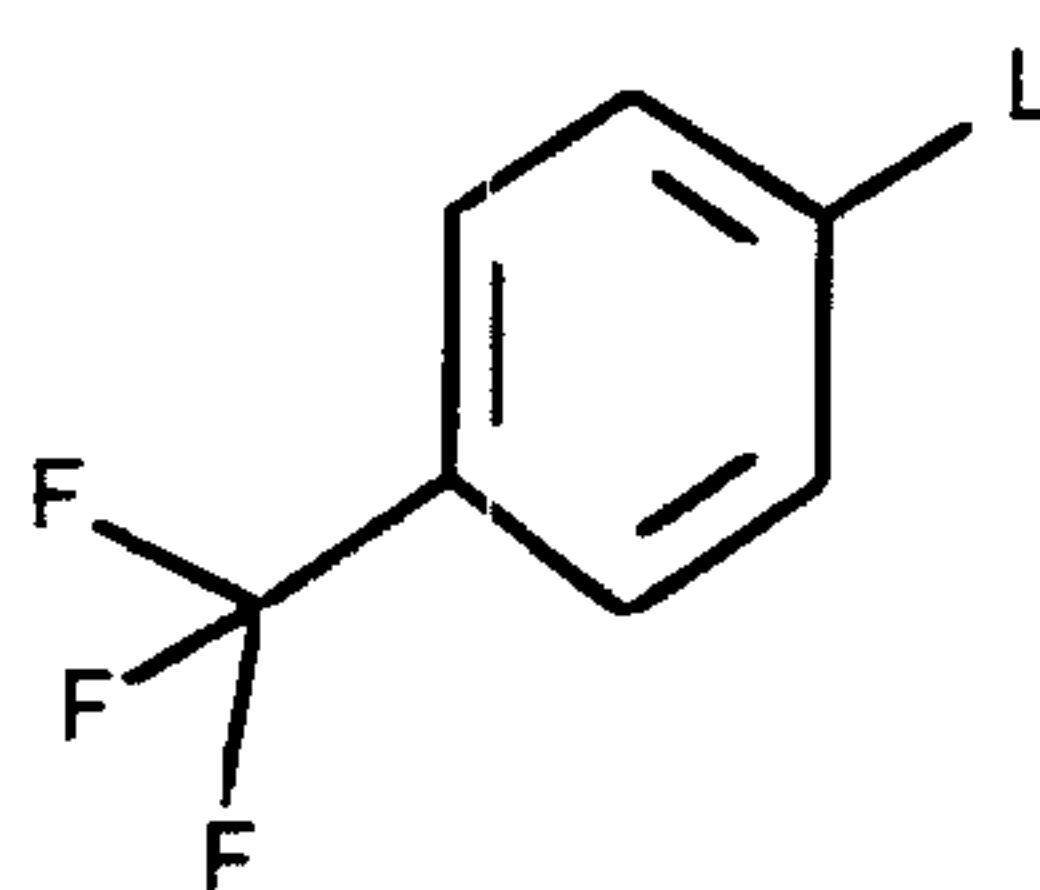
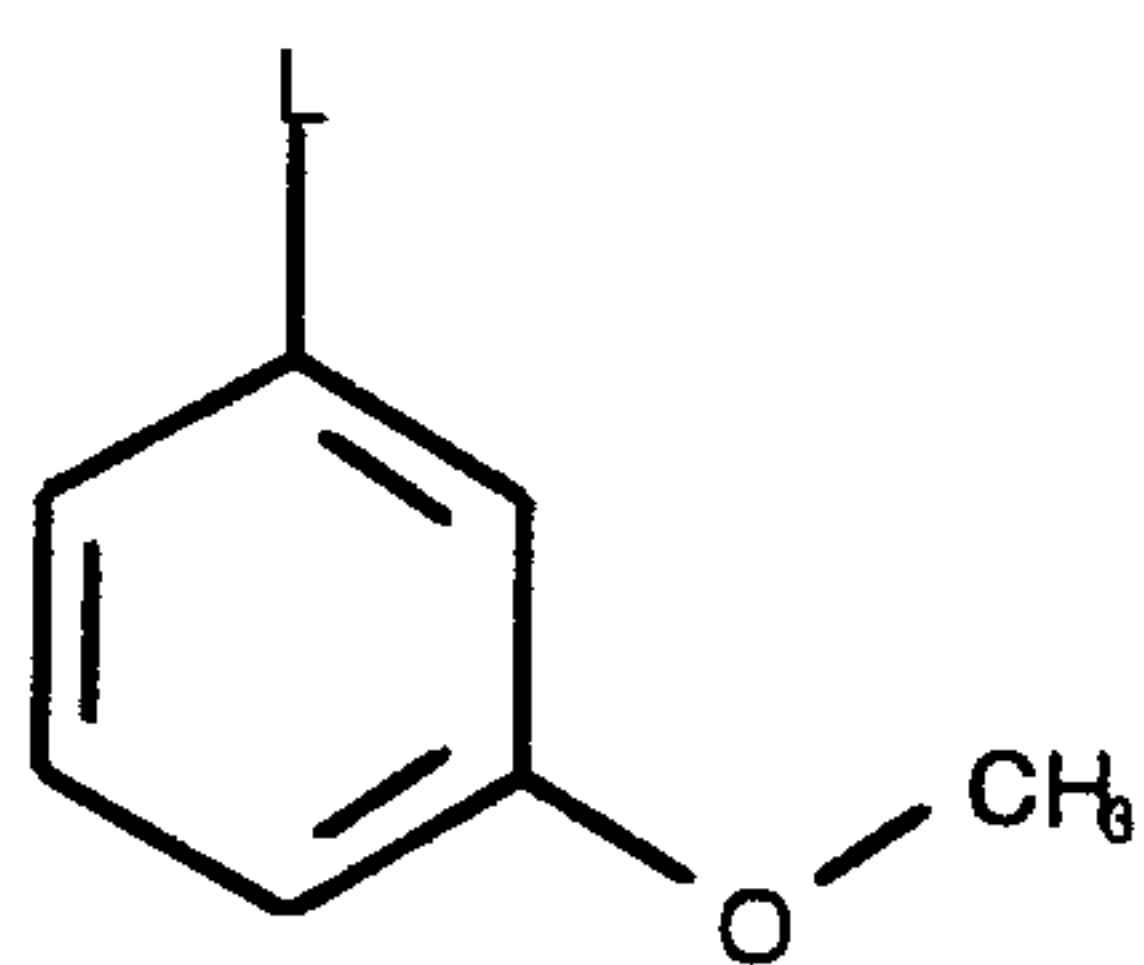
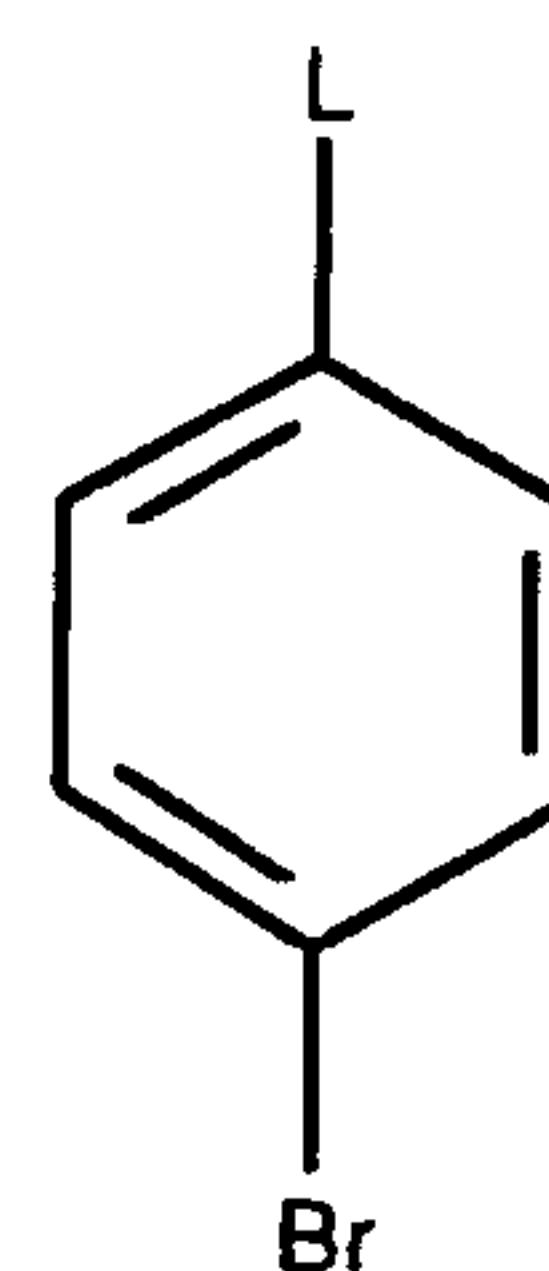
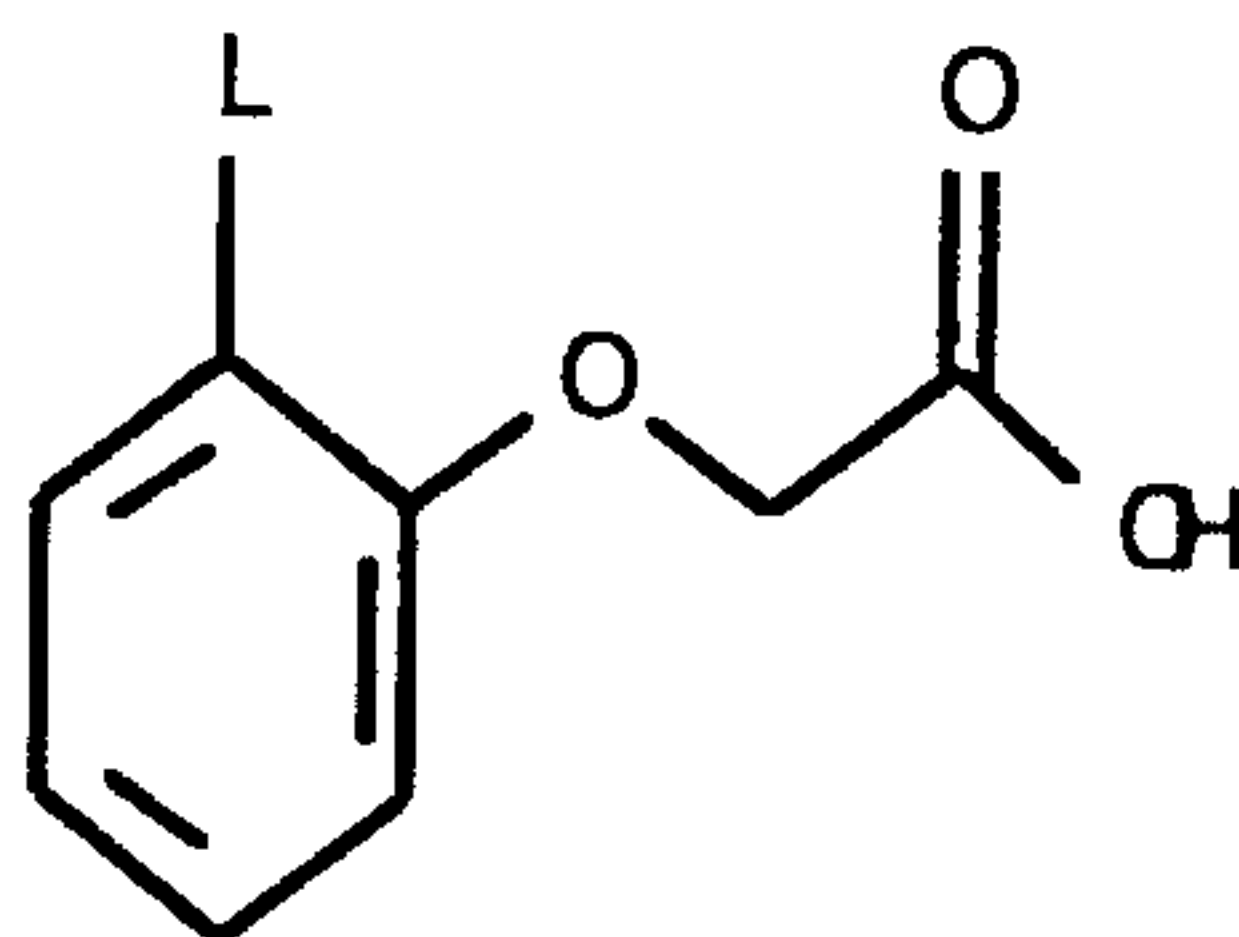
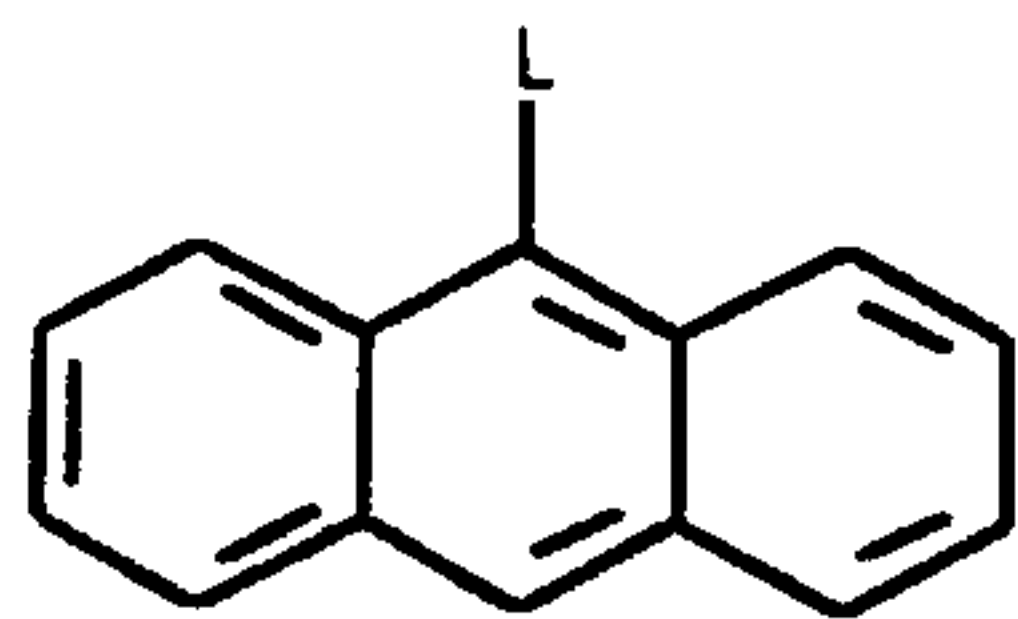
-70-



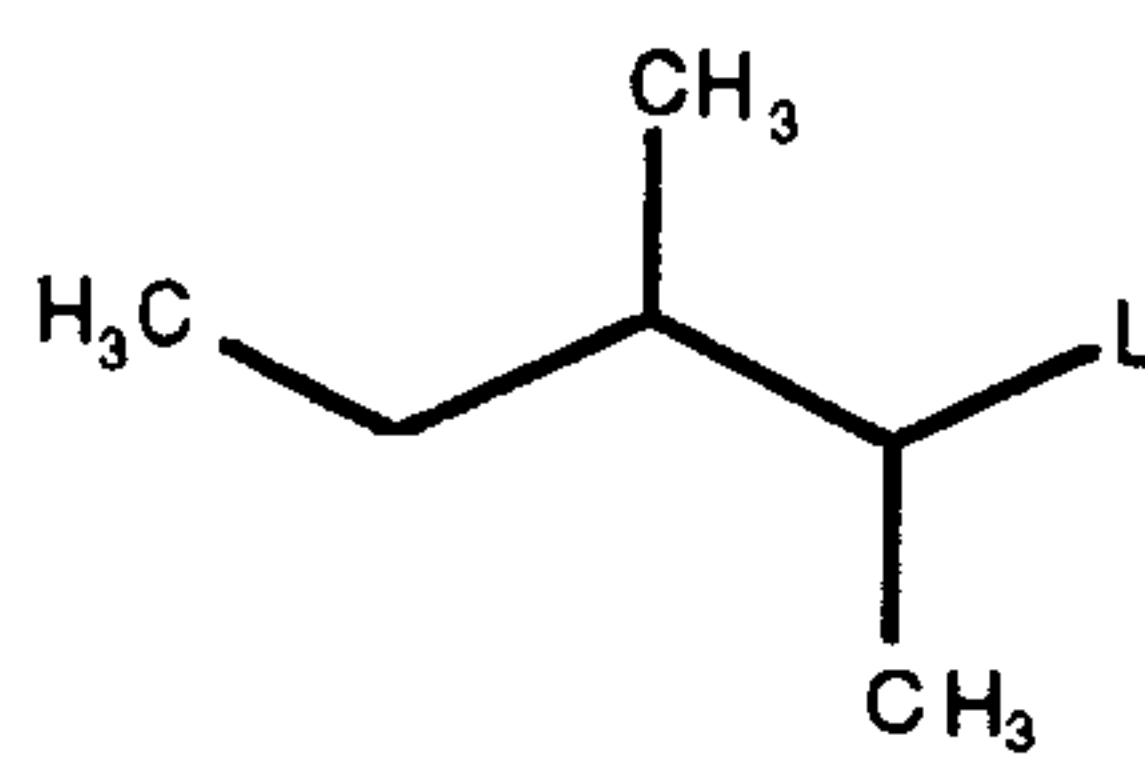
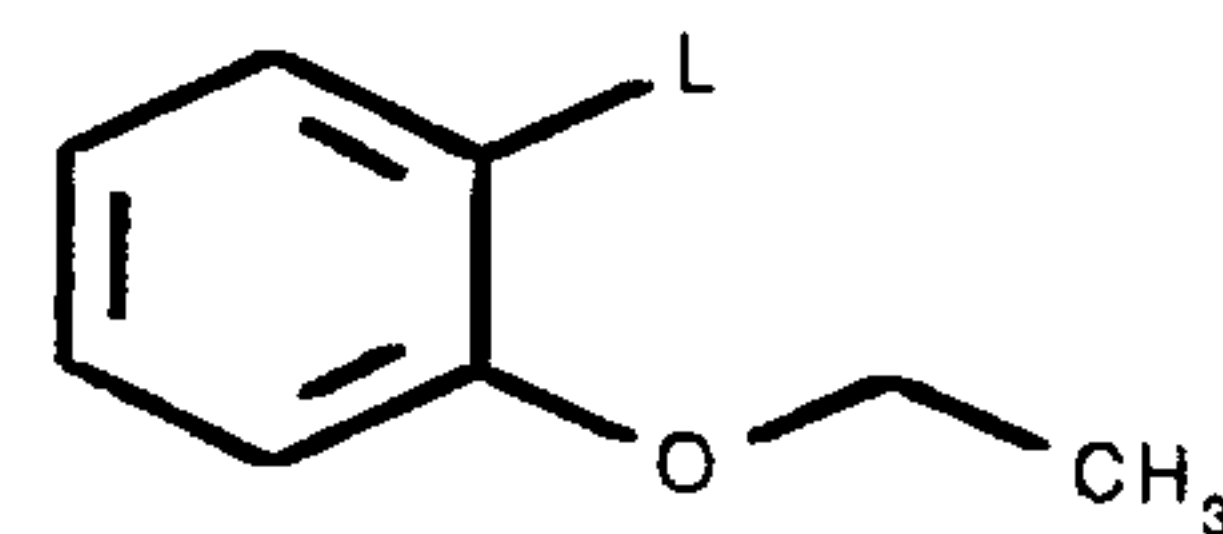
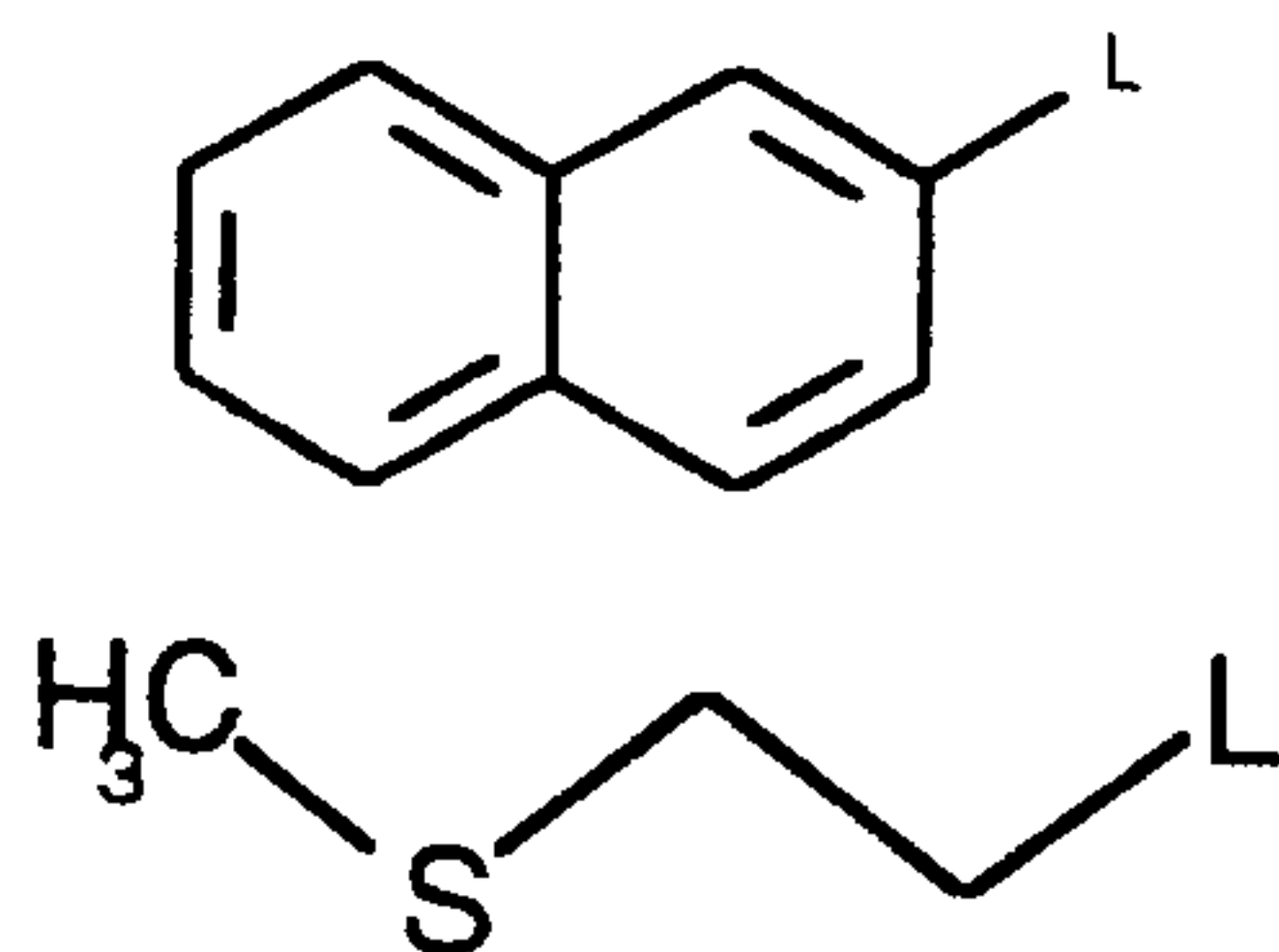
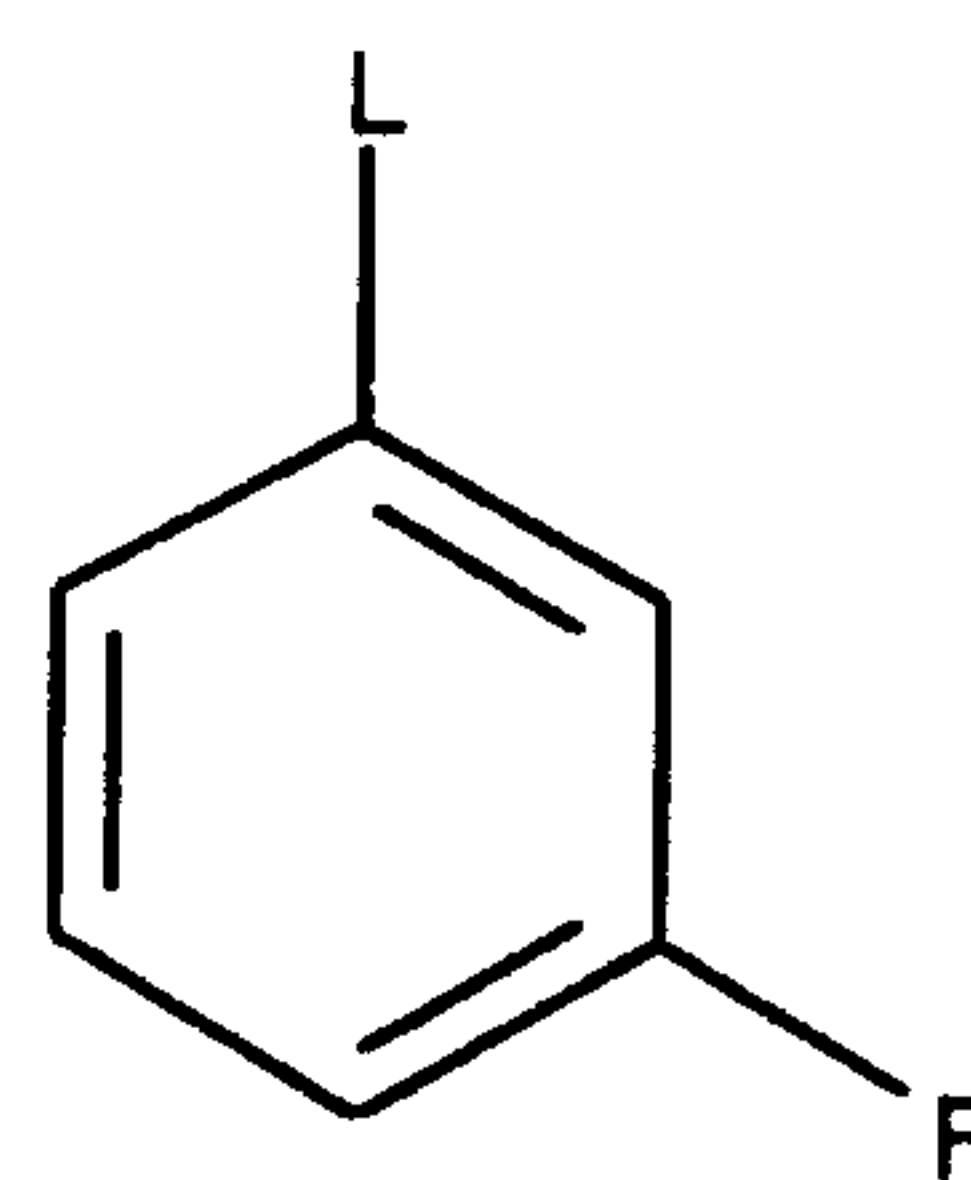
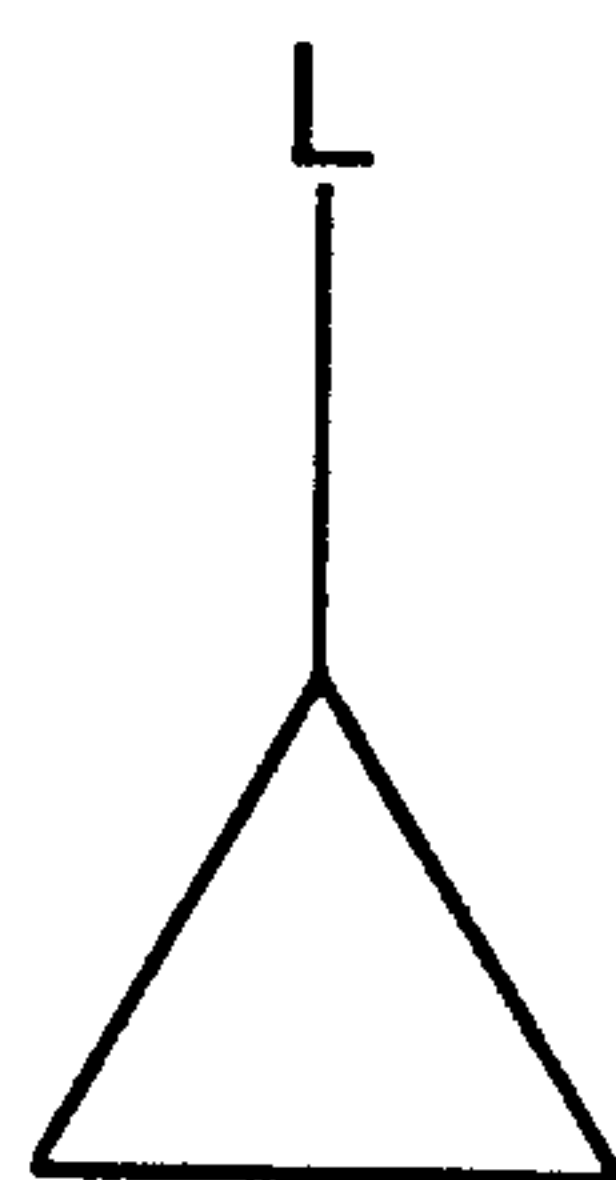
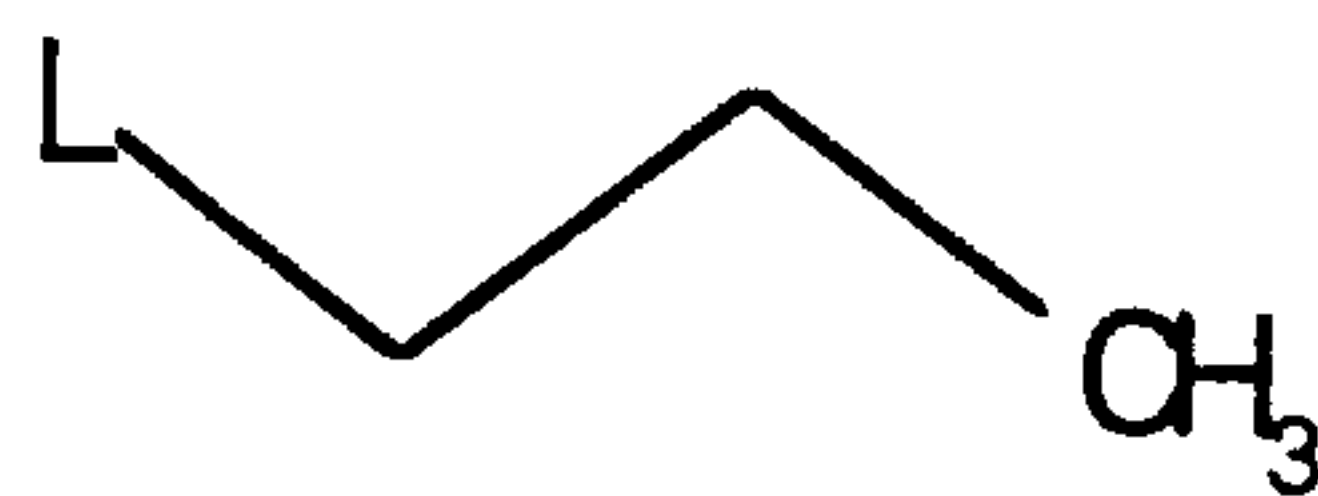
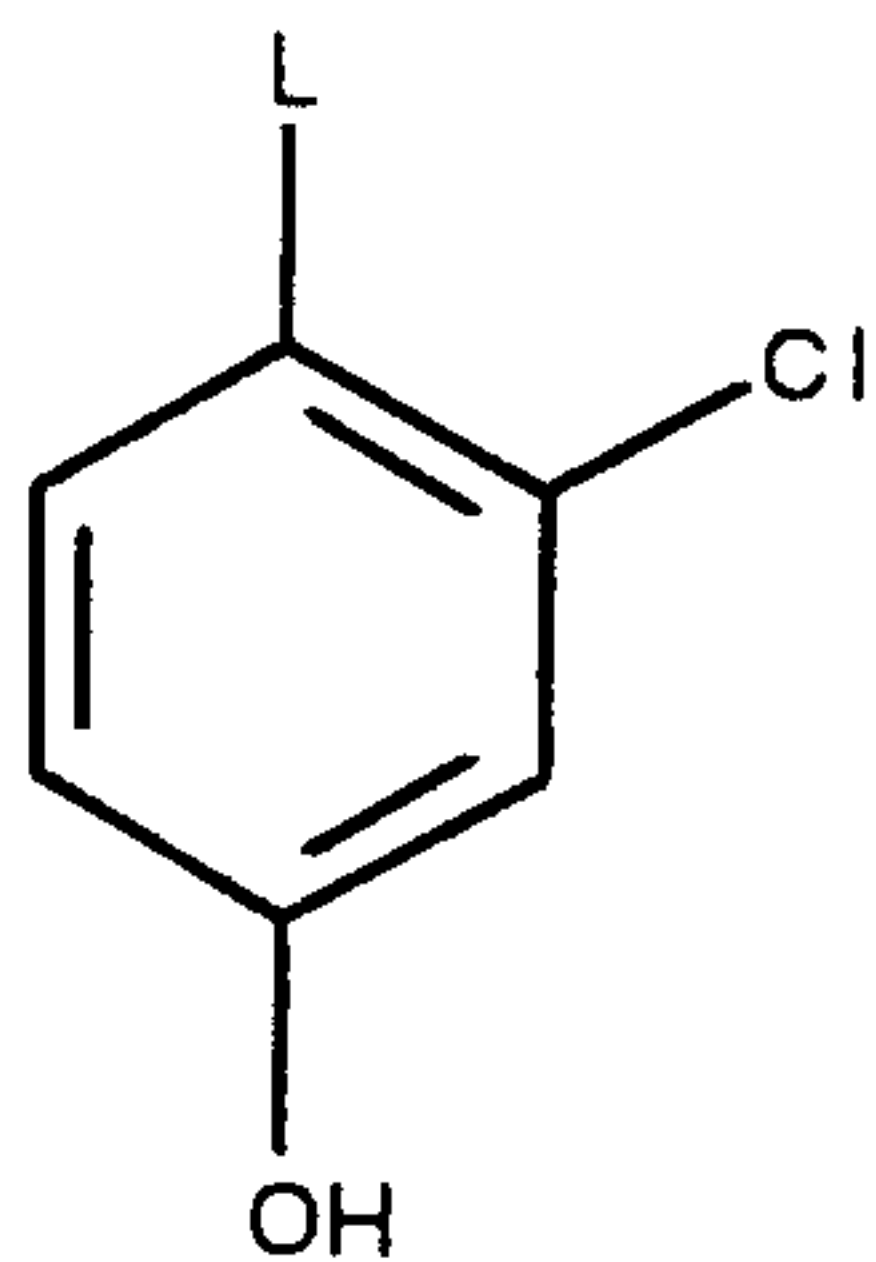
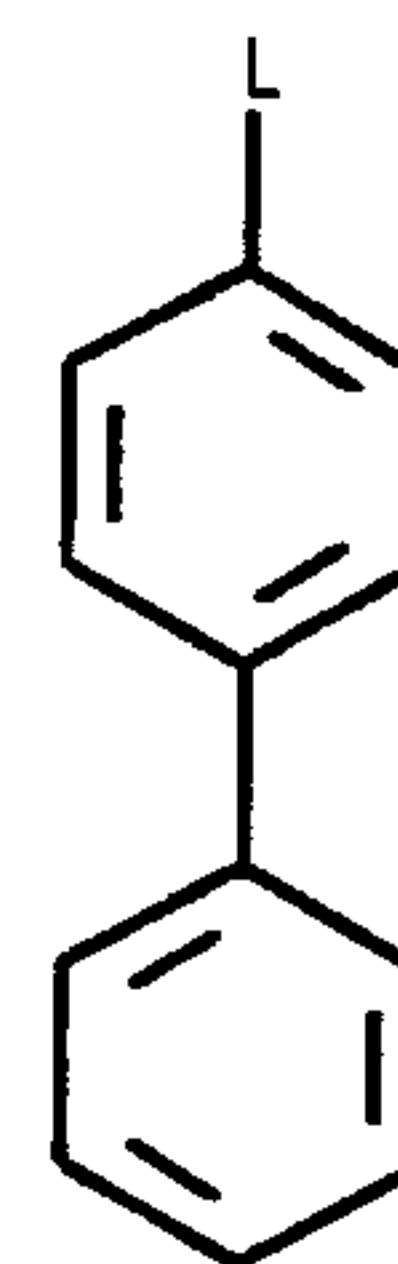
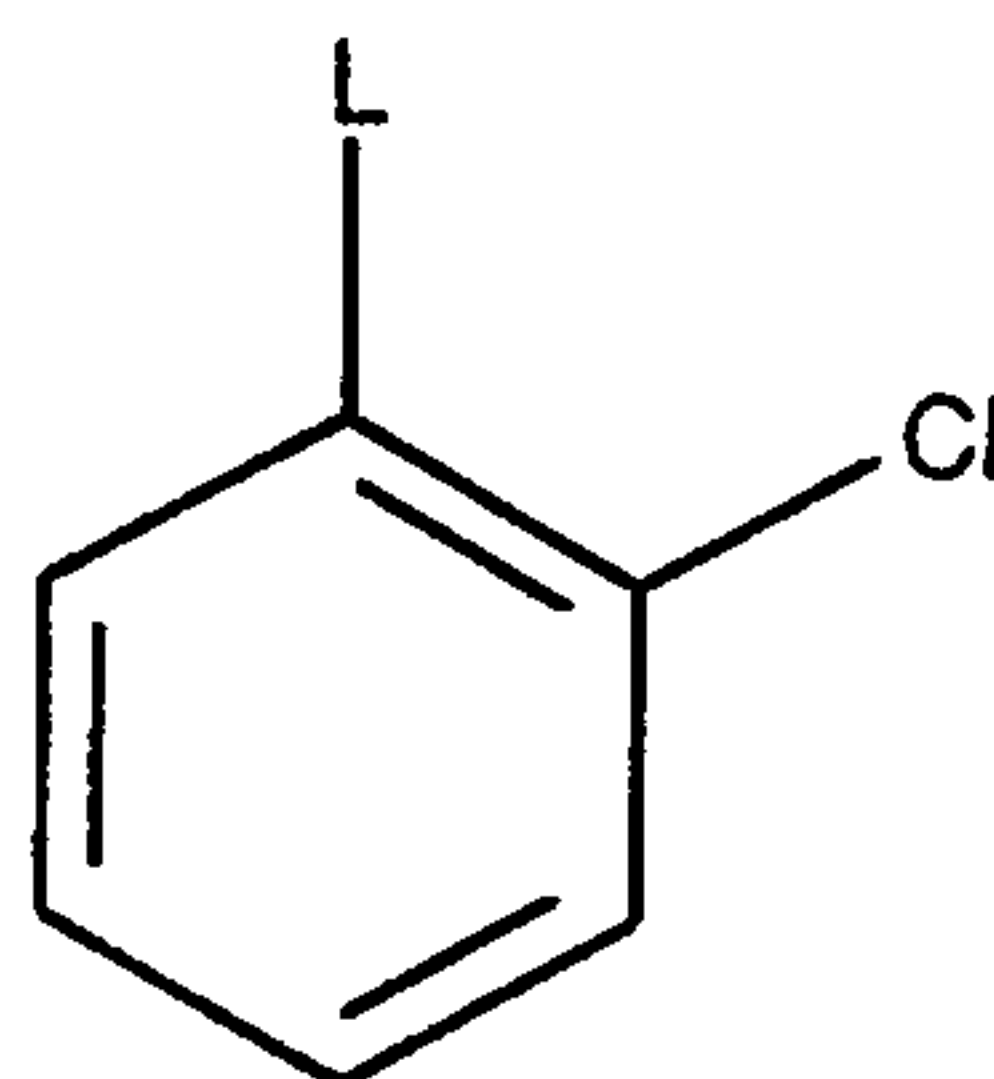
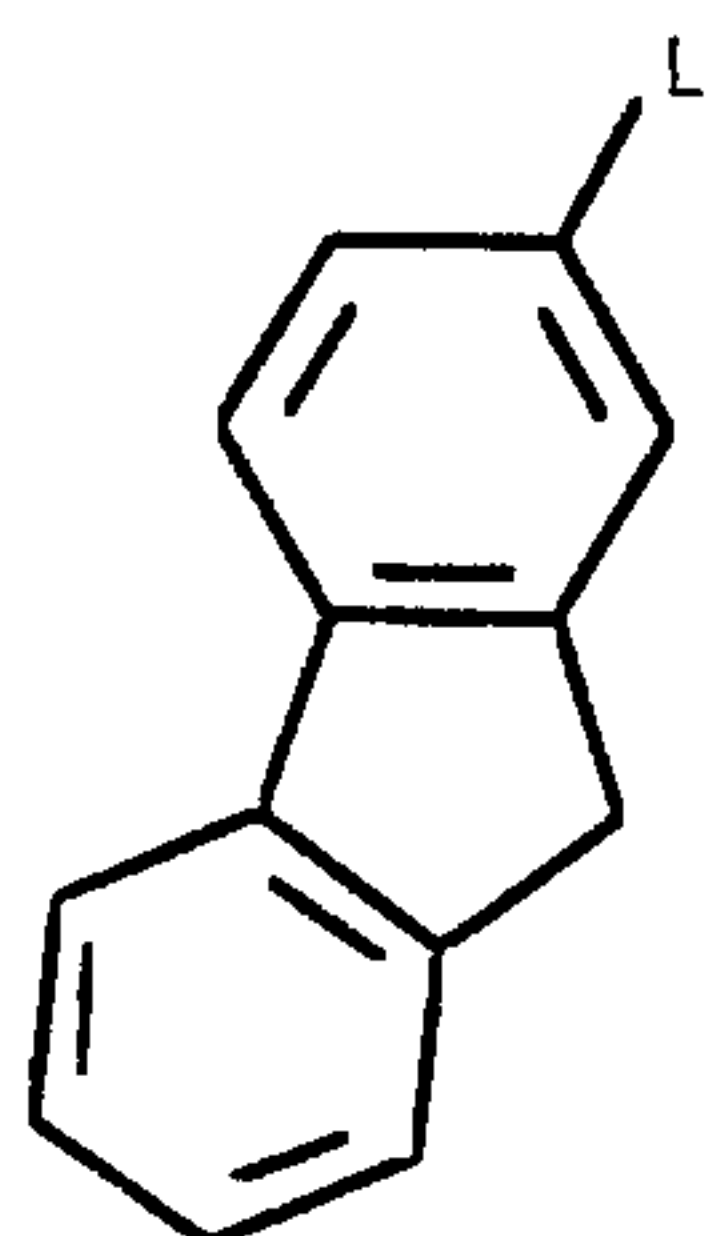
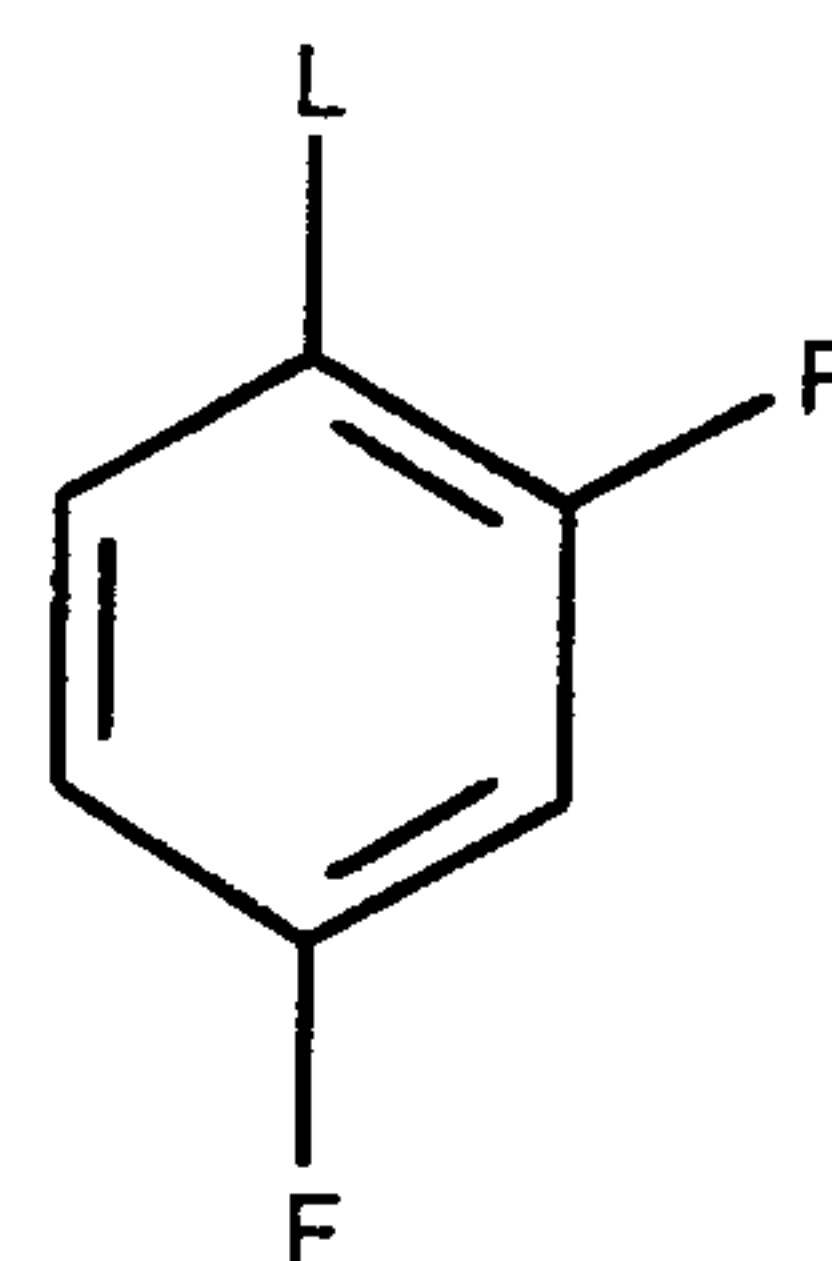
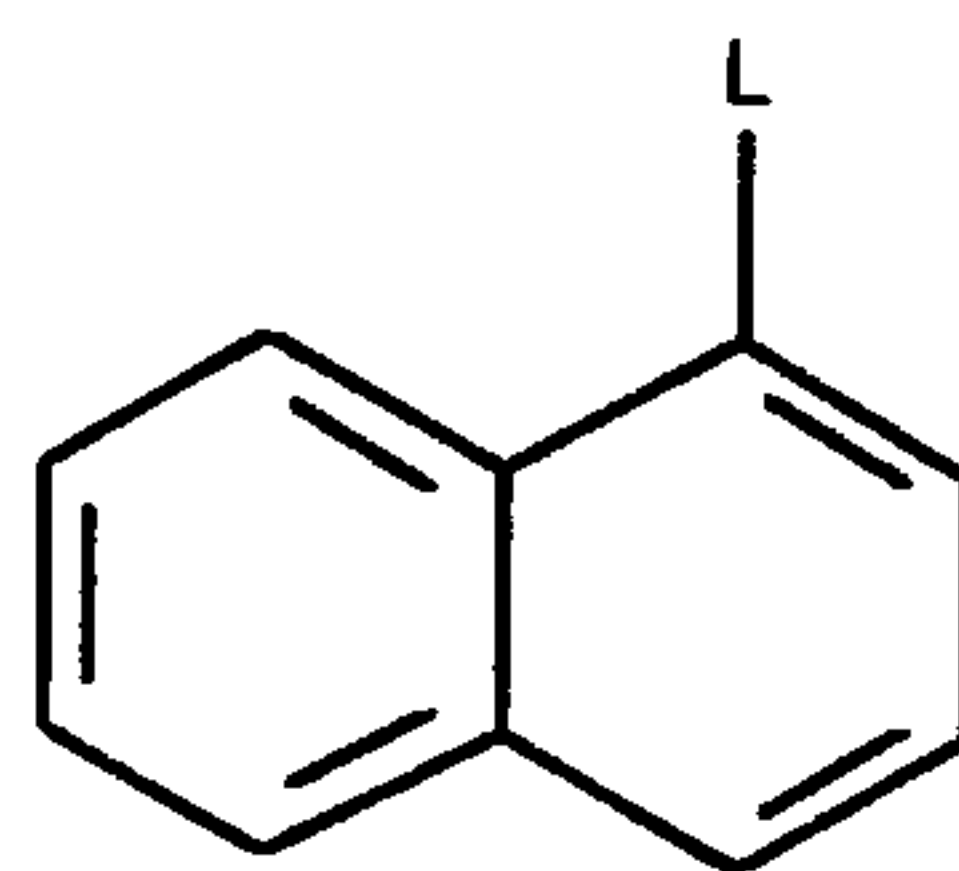
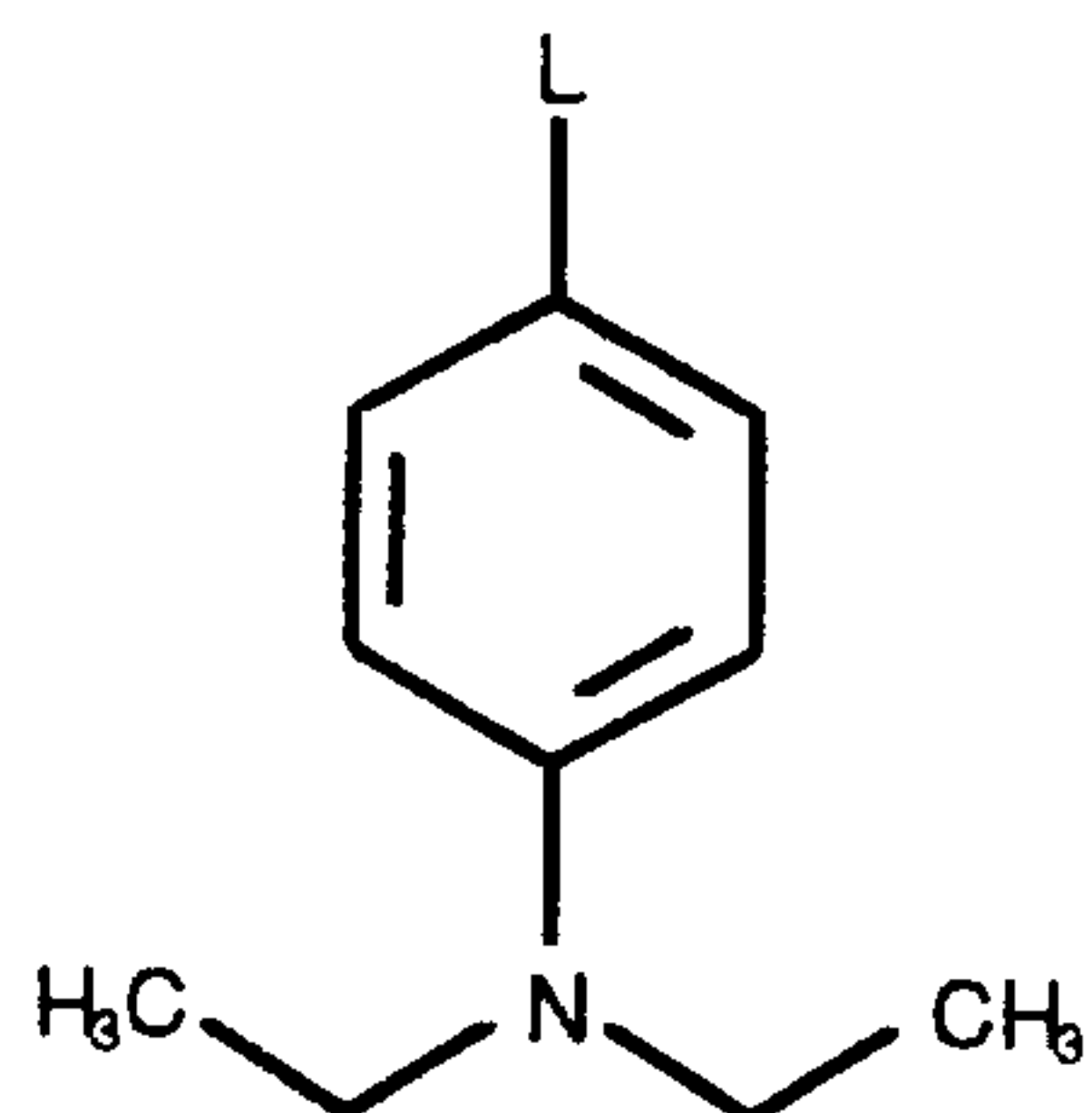
WO 98/46631

PCT/US98/07135

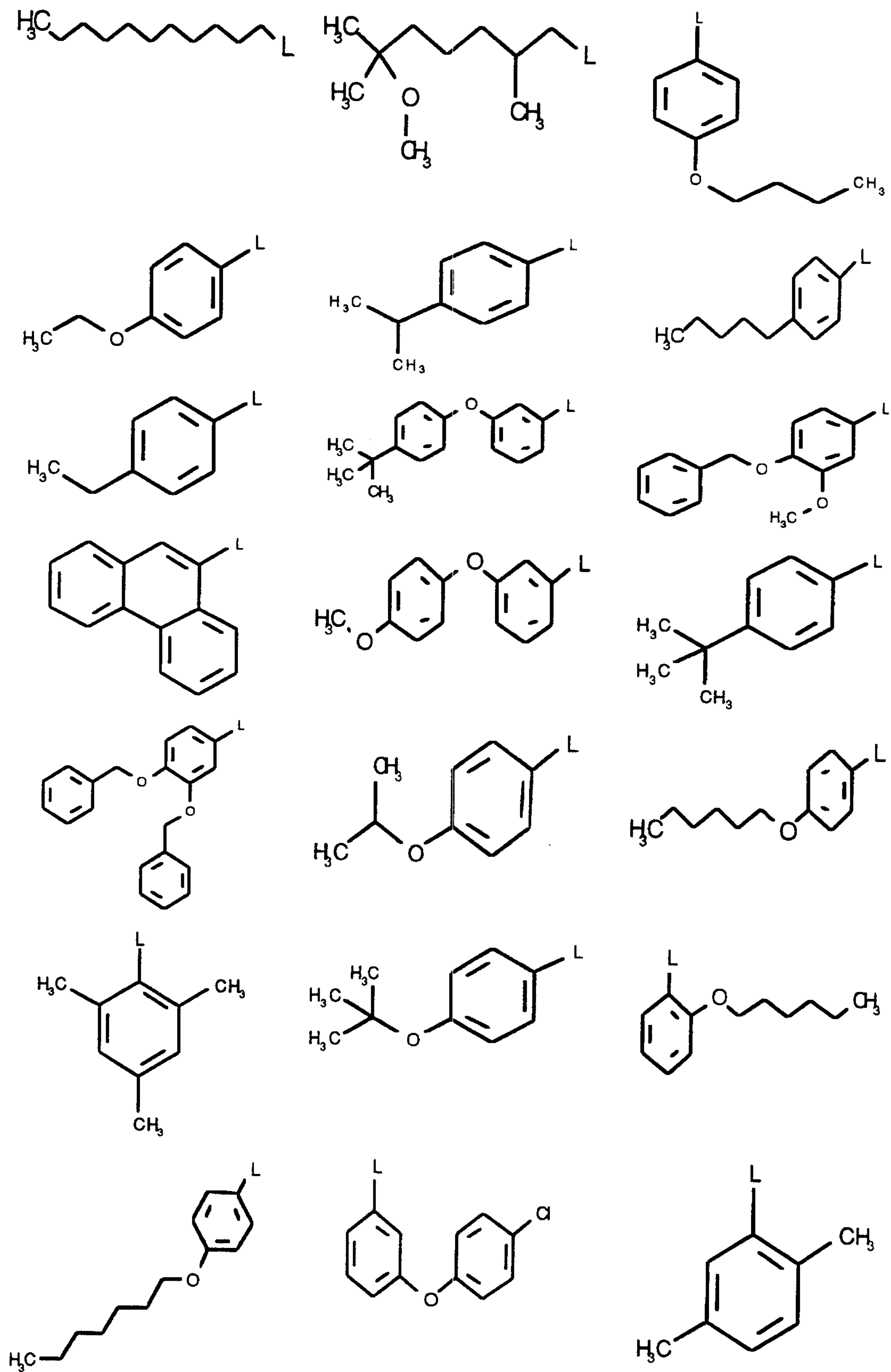
-71-



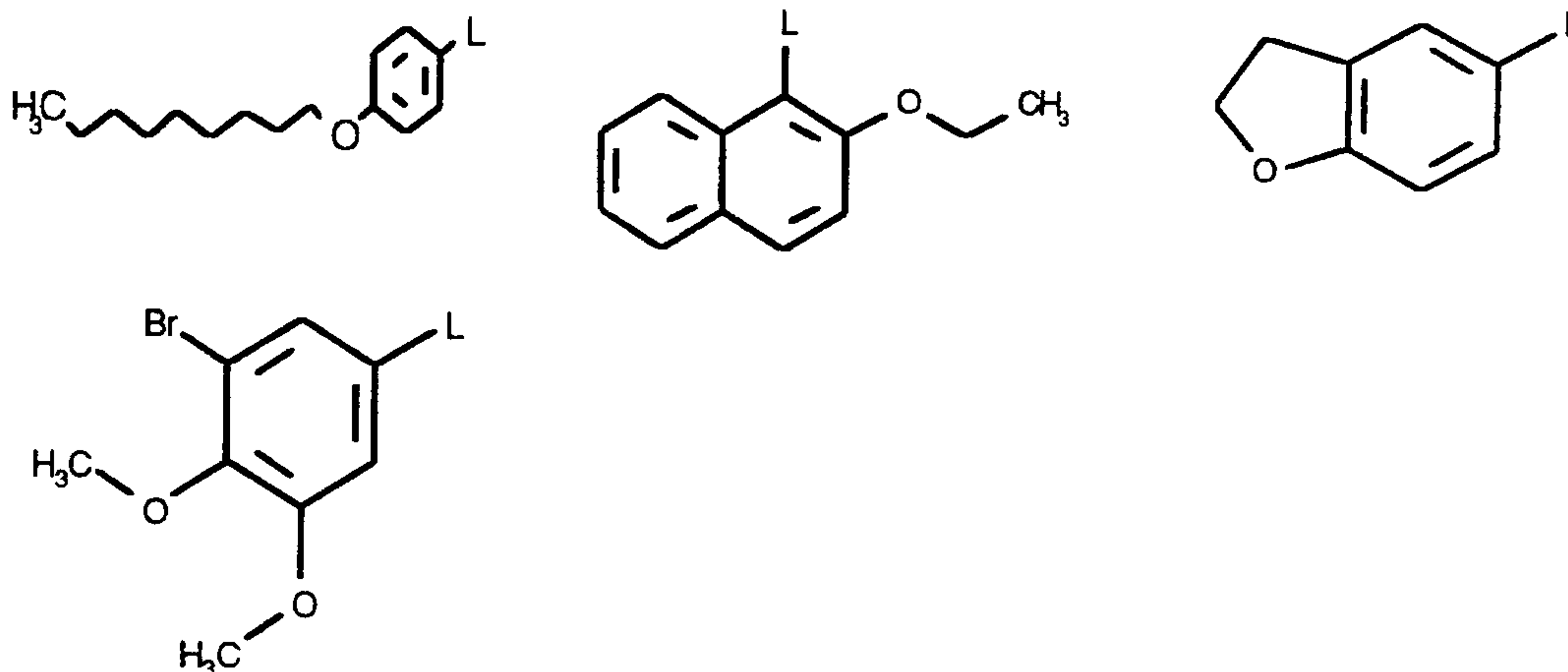
-72-



-73-



-74-



Ketones:

1-BROMO-2-BUTANONE
 2-FLUOROPHENYLACETONE
 4-FLUOROPHENYLACETONE
 3-TRIFLUOROMETHYLPHENYLACETONE
 1,1,1-TRIFLUORO-2,4-PENTANEDIONE
 FLUOROACETONE
 4'-CHLOROACETOACETANILIDE
 3-CHLORO-2-BUTANONE
 CHLOROACETONE
 1,3-DICHLOROACETONE
 METHYL 4-CHLOROACETOACETATE
 ETHYL 4-CHLOROACETOACETATE
 1-CHLORO-3-PENTANONE
 5-CHLORO-2-PENTANONE
 CYCLOTRIDECANONE
 CYCLOPENTADECANONE
 DICYCLOPROPYL KETONE
 CYCLOPROPYL METHYL KETONE
 (-)-THUJONE
 CYCLOBUTANONE
 2-CYCLOPENTEN-1-ONE
 3-METHYL-2-CYCLOPENTEN-1-ONE
 4-CYCLOPENTENE-1,3-DIONE
 1,3-CYCLOPENTANEDIONE
 2-METHYL-1,3-CYCLOPENTANEDIONE
 CYCLOPENTANONE
 2-CHLOROCYCLOPENTANONE
 CYCLOPENTANONE-2-CARBOXYLIC ACID METHYL ESTER
 ETHYL 2-OXOCYCLOPENTANECARBOXYLATE
 2-ACETYLCYCLOPENTANONE
 2-METHYLCYCLOPENTANONE
 2,4-DIMETHYLCYCLOPENTANONE
 3-METHYLCYCLOPENTANONE

-75-

BETA-IONONE
BETA-IONONE
ALPHA-IONONE
2-CYCLOHEXEN-1-ONE
3-ETHOXY-2-CYCLOHEXEN-1-ONE
3-METHYL-2-CYCLOHEXEN-1-ONE
4-CARBETHOXY-3-METHYL-2-CYCLOHEXEN-1-ONE
3,5-DIMETHYL-2-CYCLOHEXEN-1-ONE
ISOPHORONE
1,3-CYCLOHEXANEDIONE
2-ACETYL-1,3-CYCLOHEXANEDIONE
2-METHYL-1,3-CYCLOHEXANEDIONE
DIMEDONE
1,4-CYCLOHEXANEDIONE
DIMETHYL 1,4-CYCLOHEXANEDIONE-2,5-DICARBOXYLATE
DIETHYL 1,4-CYCLOHEXANEDIONE-2,5-DICARBOXYLATE
CYCLOHEXANONE
2-CHLOROCYCLOHEXANONE
2-NITROCYCLOHEXANONE
2-PHENYLCYCLOHEXANONE
2-(3-METHOXYPHENYL)CYCLOHEXANONE
ETHYL 2-CYCLOHEXANONECARBOXYLATE
ETHYL 4-METHYL-2-CYCLOHEXANONE-1-CARBOXYLATE
2-ACETYLCYCLOHEXANONE
L-MENTHONE
2-METHYLCYCLOHEXANONE
(+)-DIHYDROCARVONE
2,6-DIMETHYLCYCLOHEXANONE
ETHYL-2-CYCLOHEXANONE ACETATE
3-METHYLCYCLOHEXANONE
3,3,5,5-TETRAMETHYLCYCLOHEXANONE
4-PHENYLCYCLOHEXANONE
4-TERT-BUTYLCYCLOHEXANONE
4-METHYLCYCLOHEXANONE
4-ETHYLCYCLOHEXANONE
3,4,8,8A-TETRAHYDRO-8A-METHYL-1,6(2H,7H)-
NAPHTHALENEDIONE
2-ACETYL-1-TETRALONE
1-DECALONE
BETA-TETRALONE
1-METHYL-2-TETRALONE
6-METHOXY-2-TETRALONE
7-METHOXY-2-TETRALONE
2-DECALONE
CYCLOOCTANONE
CYCLONONANONE
ALPHA-ACETYL-PHENYLACETONITRILE
ANTI-PYRUVIC ALDEHYDE 1-OXIME
4-(4-HYDROXYPHENYL)-2-BUTANONE
1,3-ACETONEDICARBOXYLIC ACID

-76-

LEVULINIC ACID
4,6-DIOXOHEPTANOIC ACID
4-KETOPIMELIC ACID
3-ACETYL-1-PROPANOL
4-ANDROSTENE-3,17-DIONE
CYCLODECANONE
CYCLOUNDECANONE
CYCLODODECANONE
CIS-BICYCLO(3.3.0)OCTANE-3,7-DIONE
CIS-1,5-DIMETHYLBICYCLO(3.3.0)OCTANE-3,7-DIONE
2-INDANONE
2-CYCLOHEPTEN-1-ONE
CYCLOHEPTANONE
4-ACETYLBUTYRIC ACID
4-HYDROXY-4-METHYL-2-PENTANONE
3-HYDROXY-2-BUTANONE
HYDROXYACETONE
4-HYDROXY-3-METHYL-2-BUTANONE
1-BENZYL-3-PYRROLIDINONE
2-ACETYLBUTYROLACTONE
TETRAHYDROTHIOPHEN-3-ONE
TROPINONE
6-HYDROXYTROPINONE
4-OXO-TEMPO
N-CARBETHOXY-4-PIPERIDONE
N-BENZOYL-4-PIPERIDONE
1-ACETYL-4-PIPERIDONE
1-METHYL-4-PIPERIDONE
1-BENZYL-4-PIPERIDONE
1-(BETA-PHENYLETHYL)-4-PIPERIDONE
TETRAHYDRO-4H-PYRAN-4-ONE
1,4-CYCLOHEXANEDIONE MONO-2,2-DIMETHYLTRIMETHYLENE
KETAL
TETRAHYDROTHIOPYRAN-4-ONE
METHYLGLYOXAL
DIMETHYL ACETYLSUCCINATE
DIMETHYL 1,3-ACETONEDICARBOXYLATE
DIMETHYL 3-OXOADIPATE
4-(4-ACETOXYPHENYL)-2-BUTANONE
METHYL 2-CHLOROACETOACETATE
METHYLGLYOXAL DIMETHYL ACETAL
1,1-DIPHENYLACETONE
1,1-DIPHENYLACETONE
METHYL 4-ACETYL-5-OXOHEXANOATE
3-METHYLTHIO-2-BUTANONE
3-METHYLTHIO-2-BUTANONE
3-METHYL-2,4-PENTANEDIONE
3-ETHYL-2,4-PENTANEDIONE
ACETONE

-77-

(DIMETHYLAMINO) ACETONE
PHENOXYACETONE
METHOXYACETONE
DIMETHYL (2-OXOPROPYL) PHOSPHONATE
2-METHOXYPHENYLACETONE
3-METHOXYPHENYLACETONE
3,4-DIMETHOXYPHENYLACETONE
4-METHOXYPHENYLACETONE
4-METHOXYPHENYLACETONE
METHYL VINYL KETONE
4-METHOXY-3-BUTEN-2-ONE
4-METHOXY-3-BUTEN-2-ONE
BENZYLIDENEACETONE
BENZYLIDENEACETONE
ACETOACETANILIDE
O-ACETOACETANISIDIDE
O-ACETOACETOTOLUIDIDE
P-ACETOACETANISIDIDE
METHYL ACETOACETATE
BENZYL ACETOACETATE
BENZOYLACETONE
ACETYLACETONE
DIACETONE ACRYLAMIDE
ACETYLACETALDEHYDE DIMETHYL ACETAL
BENZYLACETONE
4-(4-METHOXYPHENYL)-2-BUTANONE
ACETONYLACETONE
5-HEXEN-2-ONE
N-TERT-BUTYLACETOACETAMIDE
TERT-BUTYL ACETOACETATE
4,4-DIMETHYL-2-PENTANONE
MESITYL OXIDE
PHORONE
6-METHYL-5-HEPTEN-2-ONE
GERANYLACETONE
GERANYLACETONE
DIISOPROPYL KETONE
3-METHYL-2-BUTANONE
METHYL ISOBUTYL KETONE
6-METHYL-2,4-HEPTANEDIONE
2,6-DIMETHYL-4-HEPTANONE
5-METHYL-2-HEXANONE
2-TRIDECANONE
DIETHYLAMINOACETONE
1-DIETHYLAMINO-3-BUTANONE
5-DIETHYLAMINO-2-PENTANONE
ETHYL 2,4-DIOXOVALERATE
ETHYL 2-CHLOROACETOACETATE
ETHYL 2-BENZYLACETOACETATE
DIETHYL ACETYLSUCCINATE

-78-

DIETHYL 2-ACETYLGLUTARATE
ETHYL 2-METHYLACETOACETATE
ETHYL ISOBUTYRYLACETATE
ETHYL ACETOACETATE
DIETHYL 1,3-ACETONEDICARBOXYLATE
ETHYL LEVULINATE
DIETHYL 4-OXOPIMELATE
ETHYL 4-ACETYL-5-OXOHEXANOATE
ETHYL 4-ACETYLBUTYRATE
DIETHYL 3-OXOPIMELATE
3-PENTEN-2-ONE
2-METHYL-3-PENTANONE
1-PHENYL-2-BUTANONE
ETHYL VINYL KETONE
ETHYL PROPIONYLACETATE
2,4-HEXANEDIONE
3-PENTANONE
3-METHYL-2-PENTANONE
5-METHYL-3-HEPTANONE
2-METHYL-3-HEXANONE
2-PENTANONE
ETHYL BUTYRYLACETATE
3-HEXANONE
3-HEXANONE
4-HEPTANONE
BUTYL LEVULINATE
2-METHYL-3-HEPTANONE
2-HEXANONE
3-HEPTANONE
5-NONANONE
2-HEPTANONE
DIMETHYL (2-OXOHEPTYL) PHOSPHONATE
3-OCTANONE
6-UNDECANONE
2-OCTANONE
3-NONANONE
4-DECANONE
7-TRIDECANONE
2-NONANONE
3-DECANONE
8-PENTADECANONE
2-DECANONE
3-UNDECANONE
9-HEPTADECANONE
2-UNDECANONE
10-NONADECANONE
2-METHOXYCYCLOHEXANONE
2-METHOXYETHYL ACETOACETATE
3-CHLOROACETYLACETONE
1,1-DICHLOROACETONE

6,7-DIMETHOXY-2-TETRALONE
4,4-DIMETHYL-2-CYCLOHEXEN-1-ONE
2-TERT-BUTYLCYCLOHEXANONE
N-(ACETOACETYL) GLYCINE
3,5-DIACETYLTETRAHYDROPYRAN-2,4,6-TRIONE
ALLYL ACETOACETATE
4-(TRIMETHYLSILYLOXY)-3-PENTEN-2-ONE
ETHYL DIACETOACETATE
(R)-(-)-4,4A,5,6,7,8-HEXAHYDRO-4A-METHYL-
2(3H)NAPHTHALENONE
4,4-DIMETHOXY-2,5-CYCLOHEXADIEN-1-ONE
3-OXOADIPIC ACID
TETRONIC ACID
METHYL 4-METHOXYACETOACETATE
DI-TERT-BUTYL 1,3-ACETONEDICARBOXYLATE
1,4-CYCLOHEXANEDIONE MONOETHYLENEKETAL
DIMETHYL (3-PHENOXYACETONYL) PHOSPHONATE
4-ACETOXY-2-BUTANONE
3-NONEN-2-ONE
1-HYDROXY-2-BUTANONE
5-METHYL-1,3-CYCLOHEXANEDIONE
2-METHYLTETRAHYDROFURAN-3-ONE
1-PROPYL-4-PIPERIDONE
5ALPHA-ANDROST-16-EN-3-ONE
2-CHLORO-5,5-DIMETHYL-1,3-CYCLOHEXANEDIONE
4-ACETYL-1-METHYL-1-CYCLOHEXENE
4-ACETYL-1-METHYL-1-CYCLOHEXENE
4-HEXEN-3-ONE
4-(TERT-BUTYLDIMETHYLSILYLOXY)-3-PENTEN-2-ONE
5-KETOHEXANENITRILE
ETHYL 2-(TRIMETHYLSILYLMETHYL) ACETOACETATE
ETHYL 4-HYDROXY-6-METHYL-2-OXO-3-CYCLOHEXENE-
1-CARBOXYLATE
METHYL 4-ALLYL-3,5-DIOXO-1-CYCLOHEXANECARBOXYLATE
METHYL 2-OXO-1-CYCLOHEPTANECARBOXYLATE
METHYL ETHYL KETONE
METHYL 3-OXOPENTANOATE
5-METHYL-3-HEXEN-2-ONE
4-(4-HYDROXY-3-METHOXYPHENYL)-3-BUTEN-2-ONE
(S)-(+)-2,3,7,7A-TETRAHYDRO-7A-METHYL-1H-INDENE-
1,5(6H)-DIONE
2-HYDROXYMETHYL-6-METHOXY-1,4-BENZOQUINONE
8-CYCLOHEXADECEN-1-ONE
8-MERCAPTOMENTHONE
2,2,6,6-TETRAMETHYL-4-PIPERIDONE HYDROCHLORIDE
METHYL 4-OXO-3-PIPERIDINECARBOXYLATE
HYDROCHLORIDE
ETHYL 1-BENZYL-3-OXOPIPERIDINE-4-CARBOXYLATE
HYDROCHLORIDE
1-ETHYL-3-PIPERIDONE HYDROCHLORIDE

-80-

METHYL 1-BENZYL-4-OXO-3-PIPERIDINE-CARBOXYLATE
HYDROCHLORIDE
1-BENZYL-3-CARBETHOXY-4-PIPERIDONE HYDROCHLORIDE
DELTA-AMINOLEVULINIC ACID, METHYL ESTER
HYDROCHLORIDE
5-AMINOLEVULINIC ACID HYDROCHLORIDE
1,4-DIAMINO-2-BUTANONE DIHYDROCHLORIDE
DIACETONAMINE HYDROGEN OXALATE
ACETOACETIC ACID LITHIUM SALT
S-TERT-BUTYL ACETOTHIOACETATE
ETHYL 4-OXOCYCLOHEXANECARBOXYLATE
1-ETHYL-4-PIPERIDONE
N-HYDROXYSUCCINIMIDYL ACETOACETATE
3-BROMO-2-BUTANONE
1,3-DIBROMOACETONE
(4-CHLOROPHENYLTHIO) PROPAN-2-ONE
3-AMINO-2-CYCLOHEXEN-1-ONE
2-(1-CYCLOHEXENYL) CYCLOHEXANONE
2-(BETA-CYANOETHYL) CYCLOHEXANONE
4-TERT-AMYLCYCLOHEXANONE
3-ACETYLACRYLIC ACID
TROPONE
METHYLSULFONYLACETONE
BIS(4-METHOXYBENZYLIDENE) ACETONE
BIS(4-METHOXYBENZYLIDENE) ACETONE
3,4-DIMETHOXYBENZYLIDENEACETONE
5-METHYL-5-HEXEN-2-ONE
2,6-DIMETHYL-3,5-HEPTANEDIONE
2-DODECANONE
3,5-HEPTANEDIONE
2,4-OCTANEDIONE
2,4-NONANEDIONE
5-DODECANONE
4-DODECANONE
3-DODECANONE
(METHYLTHIO) ACETONE
(+/-)-2-ETHOXYCYCLOHEXANONE
3-HEPTEN-2-ONE
3-OCTEN-2-ONE
2,6-DIMETHOXY-P-BENZOQUINONE
4-(P-HYDROXYPHENYL)-3-BUTEN-2-ONE
3,4-METHYLENEDIOXYBENZYLIDENE ACETONE
3,4-METHYLENEDIOXYBENZYLACETONE
PHENYLACETONE
2',5'-DICHOROACETOACETANILIDE
4-CHLOROPHENYLSULFONYLACETONE
4-CHLOROBENZYLIDENEACETONE
2,4,4-TRIMETHYLCYCLOPENTANONE
CYCLOHEXYLACETONE
3,3,5-TRIMETHYLCYCLOHEXANONE

-81-

4-PYRAZOLINO-2-BUTANONE
ACETOACETAMIDE
3-PHENYLAZOACETYLACETONE
3-N-BUTYL-2,4-PENTANEDIONE
3-ACETYLOCTANONE-2
SALOR S17,446-7
(BENZYLTHIO) ACETONE
6-PHENYLHEXA-3,5-DIEN-2-ONE
3-TRIDECANONE
5-PENTADECANONE
7-HEPTADECANONE
4-HEPTADECANONE
3-OCTADECANONE
N,N-DIETHYLACETOACETAMIDE
ETHYL 2-(PHENYLAZO) ACETOACETATE
DIETHYL ACETOMALONATE
ETHYL-2-N BUTYLACETOACETATE
(ETHYLTHIO) ACETONE
1-PHENYL-2-PENTANONE
1-PHENYL-2-HEXANONE
N-AMYL ISOPROPYL KETONE
7-PENTADECANONE
4-TRIDECANONE
5-TETRADECANONE
6-PENTADECANONE
7-HEXADECANONE
1-OCTEN-3-ONE
NOOTKATONE
CYCLOBUTYL METHYL KETONE
1-ISOPROPYL-4-PIPERIDONE
N,N-DIMETHYLACETOACETAMIDE
FURFURALACETONE
ACETOACET-M-XYLIDIDE
ETHYL 2-ETHYLACETOACETATE
DICYCLOHEXYL KETONE
CYCLOHEXYL METHYL KETONE
1,2:5,6-DI-O-ISOPROPYLIDENE-ALPHA-D-RIBO-3-
HEXOFURANOSULOSE
4-HYDROXYPYRIDINE
BENZYL ISOPROPYL KETONE
1,1,3-TRICHLOROACETONE
METHYL BUTYRYLACETATE
CHLORODIFLUOROACETYLACETONE
1-(2-FURYL)-1,3-BUTANEDIONE
4,6-NONANEDIONE
2-HEXADECANONE
N,N-DIMETHYL-2-CHLOROACETOACETAMIDE
3-ETHOXY-2-CYCLOPENTEN-1-ONE
2,6,6-TRIMETHYL-2-CYCLOHEXENE-1,4-DIONE
ETHYL 4-PIPERIDONE-3-CARBOXYLATE HYDROCHLORIDE

-82-

CYCLOPENTYLACETONE
4-ISOPROPYLCYCLOHEXANONE
(+/-)-2-ALLYLCYCLOHEXANONE
6-METHYL-3,5-HEPTADIEN-2-ONE
FLUORAL-P
FLUORAL-P
ISOPROPYL ACETOACETATE
N-METHYLACETOACETAMIDE
2-ETHYL-1,3-CYCLOPENTANEDIONE
3,5-DIMETHYL-4-HEPTANONE
EXO-2-CHLORO-5-OXO-BICYCLO[2.2.1]HEPTANE-SYN-
7-CARBOXYLIC ACID
ETHYL 2-OXO-CYCLOPENTYLACETATE
ETHYL-6-(2-OXOCYCLOPENTYL)-HEXANOATE
DIETHYL (2-OXOPROPYL) PHOSPHONATE
MAYBRIDGE BTBG 0108
4-ACETYLPYPERIDINE HYDROCHLORIDE
4-CYANO-4-PHENYLCYCLOHEXANONE
1,1,1-TRIFLUORO-5-METHYL-2,4-HEXANEDIONE
O-(CHLOROPHENYL) ACETONE
3-AMINO-5,5-DIMETHYL-2-CYCLOHEXEN-1-ONE
PHENYL SULFONYL ACETONE
1,3-DIPHENYL-2,4-PENTANEDIONE
3-ACETYLHEXANONE-2
1-PHENYL-2,4-PENTANEDIONE
3-HEXADECANONE
5-UNDECANONE
2-METHYL-3-DECANONE
4-UNDECANONE
6-TRIDECANONE
5-TRIDECANONE
1,1,1-TRIFLUORO-2,4-HEXANEDIONE
2-CYCLOPENTYLCYCLOPENTANONE
2-SEC-BUTYLCYCLOHEXANONE
2-BENZYLCYCLOHEXANONE
5-ACETYLVALERIC ACID
4-NITROPHENYL ACETONE
6-HEXADECANONE
5-HEXADECANONE
6-TETRADECANONE
1-HEXEN-3-ONE
2-CHLORO-6-FLUOROBENZYLIDENEACETONE
MAYBRIDGE CD 09843
3-CHLORO-5,5-DIMETHYL-2-CYCLOHEXEN-1-ONE
2-ACETOXY-3-BUTANONE
5-PHENYLCYCLOHEXANE-1,3-DIONE
TERT.-BUTYL-4-CHLOROACETOACETATE
ISOPROPYL 4-CHLOROACETOACETATE
3-METHYLENE-2,6-HEPTANEDIONE
(4-METHYLPHENYLTHIO) ACETONE

-83-

1-(THIEN-2-YL) BUT-1-EN-3-ONE
2-PENTADECANONE
ACETOACETOXYETHYL METHACRYLATE
4-PROPYLCYCLOHEXANONE
4-HYDROXY-2-BUTANONE
METHYL TRANS-4-OXO-2-PENTENOATE
METHYL TRANS-4-OXO-2-PENTENOATE
ISOBUTYL ACETOACETATE
2-N-HEXYLCYCLOPENTANONE
3-FLUOROPHENYLACETONE
BENZYL LEVULINATE
(R)-(+) -3-METHYLCYCLOHEXANONE
(R)-(+) -3-METHYLCYCLOPENTANONE
TRANS-1-DECALONE
(S)-(+) -10-METHYL-1(9) -OCTAL-2-ONE
(1S)-(-) -VERBENONE
DEHYDROACETIC ACID
PINONIC ACID
PINONIC ACID
1,3-DIAMINOACETONE DIHYDROCHLORIDE MONOHYDRATE
(5S)-5,6-ISOPROPYLIDENEDIOXY-6-METHYL-HEPTAN-2-ONE
N-OCTYL 4-CHLOROACETOACETATE
MAYBRIDGE KM 02248
BICYCLO[3.2.1]OCTAN-2-ONE
2-ADAMANTANONE
BICYCLO(3.3.1)NONAN-9-ONE
BICYCLO(3.3.1)NONANE-3,7-DIONE
(1R)-(+) -NOPINONE
NORCAMPHOR
NORCAMPHOR
NERYLACETONE
4,4-DIMETHYL-2-CYCLOPENTEN-1-ONE
4,4-DIPHENYL-2-CYCLOHEXEN-1-ONE
THIOTETRONIC ACID
4,4-DIMETHYL-1,3-CYCLOHEXANEDIONE
2-CHLORO-1,4-BENZOQUINONE
7-OXOOCTANOIC ACID
METHYL 3-OXO-6-OCTENOATE
5,5-DIMETHYL-2-PHENACYL-1,3-CYCLOHEXANEDIONE
5-OXOAZELAIC ACID
3-(2-HYDROXYETHYLAMINO) -5,5-DIMETHYL-2-CYCLOHEXEN-1-ONE
ABSCISIC ACID
ABSCISIC ACID
N-CARBETHOXY-4-TROPINONE
2-METHYLTETRAHYDROTHIOPHEN-3-ONE
CYCLOHEXIMIDE
PSEUDOPELLETIERINE HYDROCHLORIDE

-84-

DEHYDROCARNITINE HYDROCHLORIDE
 3-(PHENYLAMINO)-CYCLOHEX-2-ENE-1-ONE
 3-HEPTADECANONE
 EXO-2-BROMO-5-OXO-BICYCLO[2.2.1]HEPTANE-SYN-7-CARBOXYLIC ACID
 ANTI-3-OXOTRICYCLO(2.2.1.0²,6)HEPTANE-7-CARBOXYLIC ACID
 (+/-)-ISOPHORONE OXIDE
 PHTHALIMIDOACETONE
 1-PHENYL-1,4-PENTANEDIONE
 (+/-)-2-PHENYLCYCLOHEPTANONE
 ACETYLMALONONITRILE
 4-HYDROXY-3-METHOXYPHENYLACETONE
 5,7-DIMETHYL-3,5,9-DECATRIEN-2-ONE
 ETHYL 6-METHYL-2-OXO-3-CYCLOHEXENE-1-CARBOXYLATE
 3-CHLOROTETRONIC ACID
 2,4-DIHYDRO-5-METHYL-2-PHENYL-4-PROPIONYL-3H-PYRAZOL-3-ONE
 D-(-)-TAGATOSE
 3-(DIMETHYLAMINO)-5,5-DIMETHYL-2-CYCLOHEXEN-1-ONE
 (3AS,7AS)-(+)-HEXAHYDRO-3A-HYDROXY-7A-METHYL-1,5-INDANDIONE
 (+/-)-EXO-6-HYDROXYTROPINONE
 (1R-(1ALPHA,2BETA,3ALPHA))-(+)-3-METHYL-2-(NITROMETHYL)-5-OXOCYCLOPENTANEACETIC MENTHONE
 3-QUINUCLIDINONE HYDROCHLORIDE
 1,5-DIAMINO-3-OXAPENTANE
 1-DIMETHYLAMINO-BUT-1-EN-3-ONE
 (1R,3S)-2,2-DIMETHYL-3-(2-OXOPROPYL)-CYCLOPROPANEACETONITRILE
 (1S,3S)-3-ACETYL-2,2-DIMETHYLCYCLOBUTANE ACETONITRILE
 5,5-DIMETHYLHEXANE-2,4-DIONE
 3-ISOBUTOXY-2-CYCLOHEXEN-1-ONE
 3-METHYL-5-METHOXYCARBONYL-1-BENZYL-4-PIPERIDONE HYDROCHLORIDE
 3-METHYL-5-METHOXYCARBONYL-4-PIPERIDONE HYDROCHLORIDE
 DL-3-(1-ACETOXY-1-METHYLETHYL)-6-OXOHEPTANENITRILE
 DL-3-(1-METHYL-1-ETHENYL)-6-OXOHEPTANENITRILE
 ETHYL 2-OXO-1-CYCLOOCTANECARBOXYLATE
 METHYL (1R,3S)-2,2-DIMETHYL-3-(2-OXOPROPYL)-CYCLOPROPANEACETATE
 N-BENZYL PSEUDOPELLETIERINE
 D-(-)-FRUCTOSE
 (S)-(+)-ERYTHRULOSE HYDRATE
 2,2,6,6-TETRAMETHYL-4-PIPERIDONE MONOHYDRATE

-85-

1-BENZYL-3-PIPERIDONE HYDROCHLORIDE HYDRATE
 5-ISOPROPYL-1,3-CYCLOHEXANEDIONE HYDRATE
 D-(+)-SORBOSE
 L-(-)-SORBOSE
 METHYL JASMONATE
 N-BENZYL TROPINONE
 N-TERT-BUTOXYCARBONYL-4-PIPERIDONE
 (+/-)-BICYCLO(3.3.1)NONANE-2,6-DIONE
 ANTI-5-CARBOXYTRICYCLO[2.2.1.0(2,6)]HEPTAN-3-ONE
 EXO-2-CHLORO-SYN-7-HYDROXYMETHYL-5-EXO-BICYCLO[2.2.1]HEPTANE
 L-RIBULOSE HYDRATE
 4-ACETYL-2,4-DIHYDRO-5-METHYL-2-PHENYL-3H-PYRAZOL-3-ONE MONOHYDRATE
 2-ACETYL-5-NORBORNENE
 7-SYN-METHOXYMETHYL-5-NORBORNEN-2-ONE
 3-CHLORO-2-NORBORNANONE
 TRICYCLO[5.2.1.02,6]DECAN-8-ONE
 METHYL 4-METHOXY-2-EXO-3-CYCLOPENTENE-1-CARBOXYLATE
 5,5-DIMETHYL-3-(METHYLAMINO)-2-CYCLOHEXEN-1-ONE
 2-ACETYL-1,3-CYCLOPENTANEDIONE
 2,4-DIMETHOXYPHENYLACETONE
 2,6-DIPHENYLCYCLOHEXANONE
 5-HYDROXY-2-ADAMANTANONE
 3-METHOXY-2-CYCLOPENTEN-1-ONE
 2,2'-METHYLENEBIS(1,3-CYCLOHEXANEDIONE)
 (+/-)-7-OXABICYCLO(4.1.0)HEPTAN-2-ONE
 ETHYL 2-OXOCYCLOTRIDECANECARBOXYLATE
 2-(METHYLTHIO)CYCLOHEXANONE
 (S)-(+)-3,4,8,8A-TETRAHYDRO-8A-METHYL-1,6(2H,7H)-NAPHTHALENEDIONE,
 and the like.

Where aldehydes and ketones are utilized as the electrophilic reagent, the resulting imine compounds can be reduced using sodium borohydride or other borohydride reducing agents to provide the corresponding secondary amine (Formula I; $R_{y''}$ = hydrogen and E is a substituent derived from an electrophilic agent). Still further diversity can be introduced into the present library by reacting the secondary amine library compounds with an electrophilic reagent as described above to provide compounds of Formula I wherein $R_{y''}$ and E are each

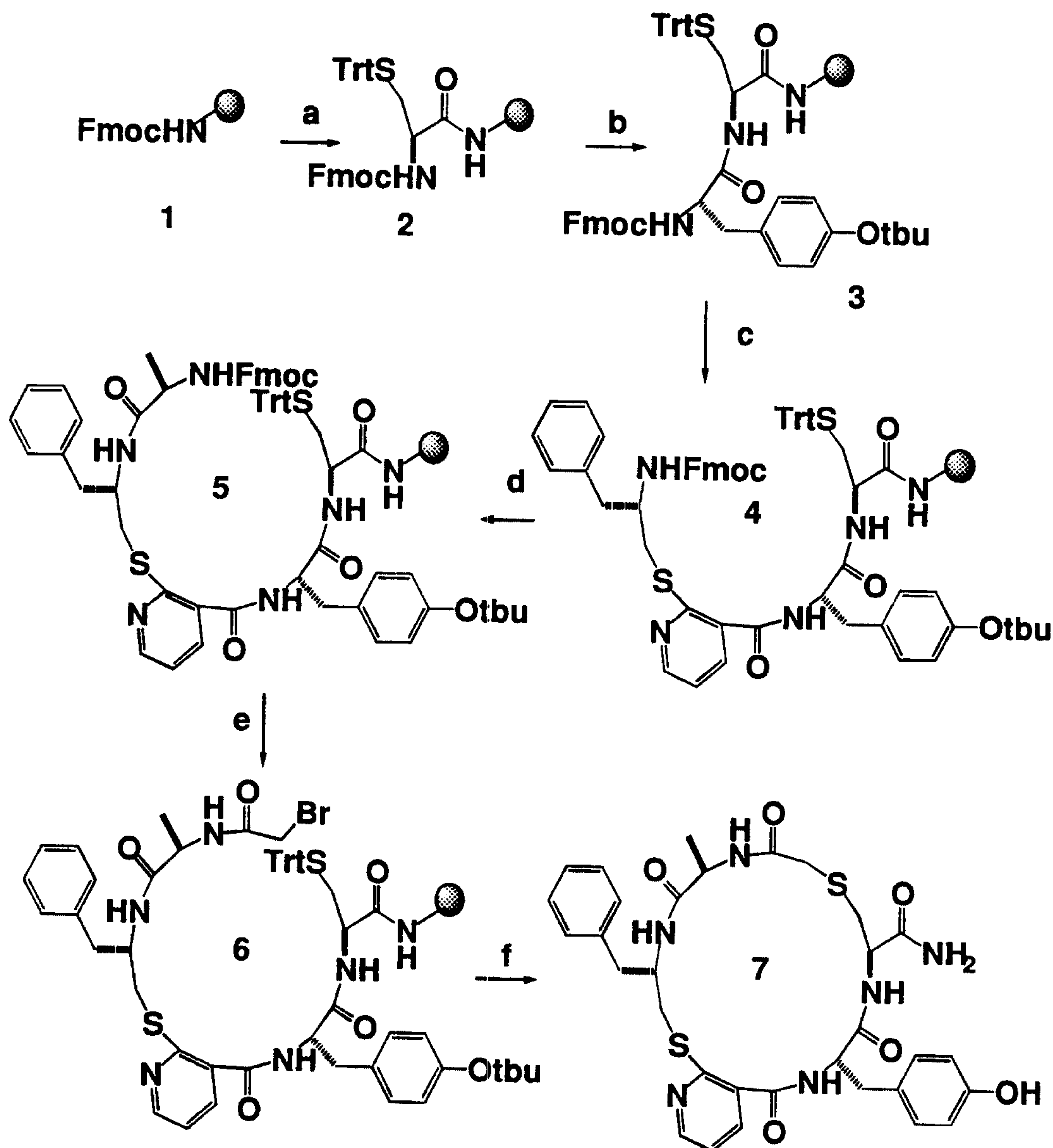
-86-

independently a substituent derived from an electrophilic reagent.

Solid phase synthesis methods have been modified in accordance with the present invention to provide a
5 general route to preparing the novel macrocycles of the present invention (See Scheme III). In one embodiment (bold-face numerals correspond to compound numerals in Scheme III), a foundation was laid by anchoring to solid support an orthogonally protected trifunctional compound
10 such as N-Fmoc-S-trityl-L-cysteine to give **2** (step a). The cycle was then built up (steps b,c,d) by coupling desired amino acid and ATA building blocks to provide intermediates such as **5**. To facilitate cyclization, a bromoacid was installed at the terminal position (step f)
15 to give intermediate **6**. Bromoamide **6** was then treated with trifluoroacetic acid (TFA) to liberate it from solid support and to unmask its side chain functional groups. Intramolecular attack of the revealed cysteine sulfhydryl function on the terminal alpha-bromoamide then formed
20 macrocycle **7**, a 19-membered bicycle that possesses a number of significant backbone modifications including two thioether linkages and the rigid 2-mercaptonicotinamide unit whose pyridine type nitrogen may accept hydrogen bonds.

25

- 87 -



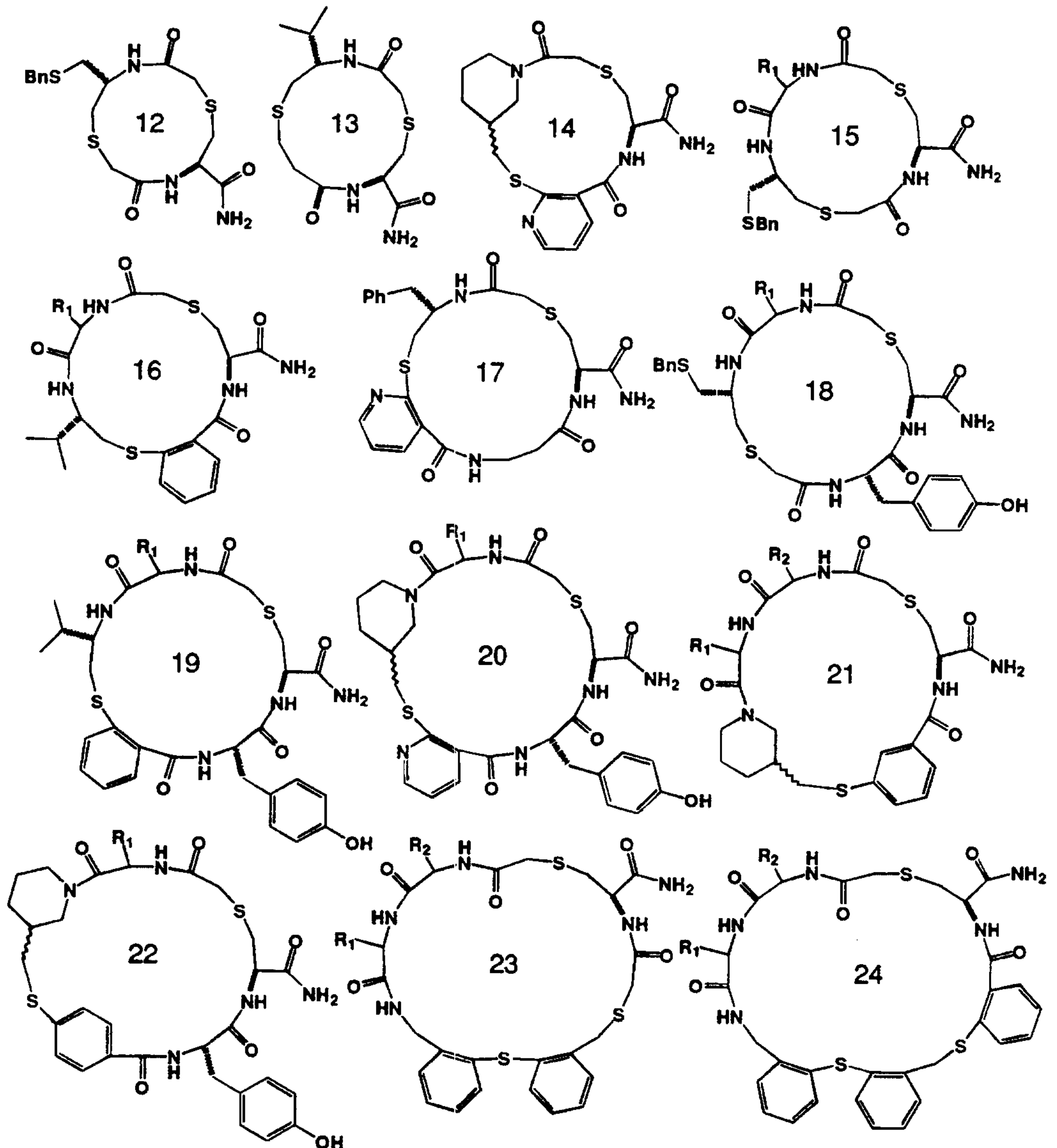
Scheme III

- 5 Method for assembling a specific pseudopeptide
 macrocycle (shaded spheres represent a solid support):
 a) Fmoc-Rink amide MBHA resin, 30% piperidine in DMF,
 then 5 eq Fmoc-S-trityl-L-cysteine, DIC/HOBT in NMP; b)
 as for a), but with 5 eq Fmoc-L-tyrosine-O-t-butyl
 ether; c) as for a), but with 5eq Fmoc-L-Phe[ψCH₂S]-2-
 10 mercaptonicotinate; d) as for a), but with 5eq Fmoc-D-
 alanine; e) 30% piperidine in DMF, then 5eq bromoacetic
 acid and DIC in NMP; f) 38:1:1 TFA:H₂O:Et₃SiH for 2h,
 lyophilize, wash (ether, 2x) then 2eq of
 15 diisopropylethylamine in 1:1 CH₃CN:H₂O, 24h.

-88-

Macrocyclization kinetics of **7** is accelerated by the addition of a base. LCMS is utilized for monitoring ring closure. The two major natural isotopes of bromine in linear material were plainly visible at 80 and 82 m.u. (mass units) over the calculated mass of the cycle. Ring closure was accompanied by a shift in HPLC retention time and a change in the mass spectrum to a non-doubled peak consistent with the mass calculated for cyclic product (for **7**, calculated MW=501.41, found MH⁺=502.2). Under the conditions described, LCMS revealed little or no dimer formation during closure of **7** or any of the other macrocycles made regardless of ring size or structural rigidity. HPLC traces of macrocycles bearing racemic ATAs, such as compound **32** as shown in Method B below, often displayed a pair of closely eluting peaks having similar abundance and identical mass spectra. Thus both ring diastereomers formed and were separable by HPLC.

By utilizing the large number of ATA building blocks and the large number of amino acids and amino/acid bearing compounds that are available commercially, large numbers of unique macrocyclic pseudopeptides can be synthesized. Approximately seven hundred macrocycles have been made using automated multiple parallel synthesis and representatives from this set are shown below (numerals shown within ring structures represent the number of macrocycle ring atoms and B_n is benzyl).



The synthesis method of the present invention allows the construction of a library of about 12- to about 24-
 5 membered macrocycles in integral steps. This capability is important for varying molecular size, volume and shape. Each library compound also contains at least two thioether linkages to enhance lipophilicity and protease resistance relative to simple cyclic peptides. The

-90-

position of one thioether is fixed at the cysteine or penicillamine used for ligation, but the other(s) can be installed at any internal site depending on the coupling order of the ATA and amino acid compounds. As judged by
5 LCMS, macrocyclization occurred readily with a variety of L- and D-amino acids without regard to sequence within the ring. Macrocycles containing single or multiple aryl backbone segments also formed readily, exemplified by compounds **14**, **16**, **17** and **19-24**. This is notable since aryl
10 backbones will impart structural rigidity to macrocycles. Even more important, ortho-(**20**), meta-(**21**) and para-substituted (**22**) aryl ring backbones all permitted efficient ring closure. Model building suggests that macrocycle conformational bias can be influenced by the
15 ortho- vs. meta- vs. para-substitution pattern of the ATAs used during construction. This is a highly desirable feature for *de novo* lead generation where the active shape(s) and conformation(s) are unknown.

The process of the present invention utilized in
20 preparation of a library of the macrocycle of Formula I above may be carried out in any vessel capable of holding the liquid reaction medium. In one embodiment, the process of the invention can be carried out in containers adaptable to parallel array synthesis. In particular,
25 the macrocycle library of this invention can be formed in a well plate apparatus 1 or 3 as illustrated in Figures 1 and 2, respectively, and as described in greater detail below. Such apparatus provide multiple reaction zones most typically in a two-dimensional array of defined
30 reservoirs, wherein one member of the macrocycle library of this invention is prepared in each reservoir. Thus the diverse macrocycle library of the present invention comprises a plurality of reservoir arrays (e.g. well plates), each reservoir or well containing a library
35 compound of the macrocycle library. Accordingly the library compounds are typically identified by reference

-91-

to their well plate number and their X column and Y row well plate coordinates.

Following simultaneous preparation of the library member compounds in the reservoir array, the compounds
5 can be transferred in whole or in part to other reservoir arrays (e.g. well plates), to prepare multiple copies of the library apparatus or to subject the library to additional reaction conditions. Copies of the library apparatus (daughter well plates, each comprising a 2-
10 dimensional array of defined reservoirs with each reservoir containing a predetermined member of the library) are useful as replaceable elements in automated assay machines. The apparatus of this invention allows convenient access to a wide variety of structurally
15 related macrocyclic compounds. One preferred reservoir array for use in making and using this invention is a multi-well titer plate, typically a 96-well microtiter plate.

Figure 1 illustrates the top surface of a well plate
20 apparatus (1) of the present invention. The well plate (1) is a plastic plate with 96-wells (depressions) capable of holding liquids for parallel array synthesis. Individual reaction products are prepared in each well and are labeled by the well plate coordinates. For
25 example, the library compound at location (2), is identified by the alpha numeric coordinate, "A6".

Figure 2 illustrates a side view of a modified well plate apparatus (2) for use in preparation of the library of the present invention. Well plate (3) contains wells
30 (4) with a filter (5), and a retaining frit (6), and a liquid reaction medium used in carrying out the process (7). The wells have an outlet at the bottom which is sealed by gasket (8) held in place by a top cover (9) and bottom cover (10) maintained in position by clamps (11).

35 Such well plates are typically prepared using conventional 96-well plates. A hole is drilled in the

-92-

bottom of each well in the plates and a porous frit is placed in the bottom of each well. The plate is then placed in the clamp assembly to seal the bottom of the wells.

5 Synthesis is initiated by adding reagents to their individual wells according to their assigned plate coordinates. The plate is then capped and tumbled to mix the reagents. Following completion of the reaction, the solvent and residual volatile reagents may be evaporated
10 with a Speed-vac. The residual products are redissolved in appropriate liquid solvent and the reaction products analyzed, for example, by thin layer chromatography, mass spectrometry and/or nuclear magnetic resonance spectrometry.

15 One embodiment of the present invention is an assay kit for the identification of pharmaceutical lead compounds. The assay kit comprises as essential parts, (1) a well plate apparatus (containing one of the tetrahydroquinoline compounds in each of its individual
20 wells), and (2) biological assay materials. The biological assay materials are generally known to be predictive of success for an associated disease state. Illustrative of biological assay materials useful in the kit of this invention include, but are not intended to be
25 limited to, those for conducting various assays such as:

In vitro assays:

Enzymatic inhibition,
Receptor-ligand binding,
30 Protein-Protein interaction,
Protein-DNA interaction,
and the like;
Cell based, functional assays:
Transcriptional regulation,
35 Signal transduction/Second messenger,
Viral Infectivity,

-93-

Bacteriocidal/Bacteriostatic,
Fungicidal/fungistatic,
and the like; and

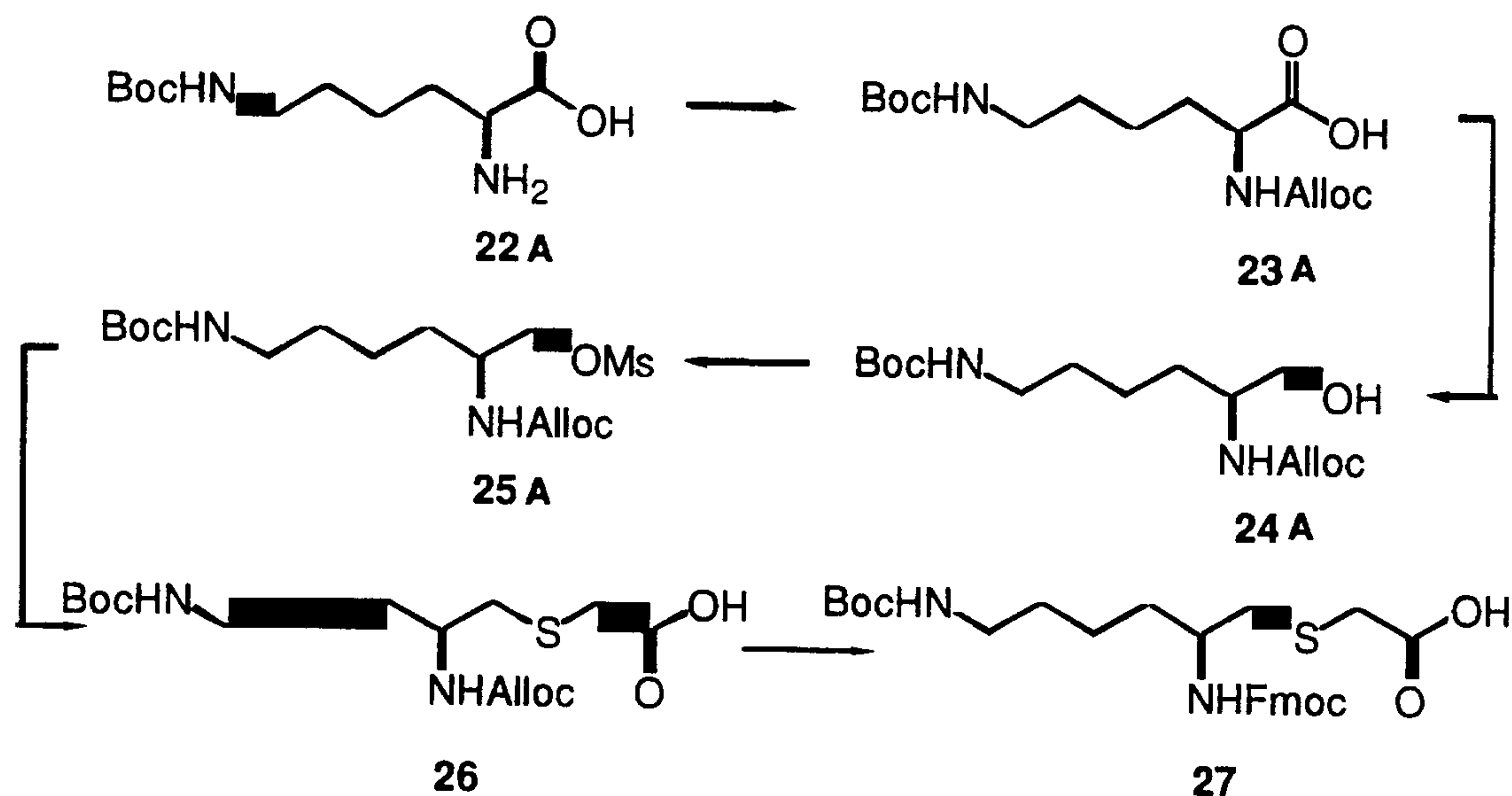
- 5 Add, Incubate, & Read assays:
 Scintillation Proximity Assays,
 Glucan Synthase (GS) inhibition assays,
 Angiotensin II IPA receptor binding assay,
 Endothelia converting enzyme [^{125}I] SPA assay,
10 HIV proteinase [^{125}I] SPA enzyme assay,
 Cholesteryl ester transfer (CETP) [^3H] SPA assay,
 Fluorescence Polarization Assays,
 Fluorescence Correlation Spectroscopy,
 Calorimetric biosensors,
15 Ca_2^+ -EGTA Dyes for Cell-based assays,
 Receptor Gene Constructs for cell based assays,
 Luciferase, green fluorescent protein, beta-
 lactamase,
 Electrical cell impedance sensor assays, and the
20 like,

and the like assays.

-94-

Preparation 1Methods for Constructing ATA compounds.

5

Method A

10

N-α-Fmoc-N-ε-Boc-L-Lys-[ψCH₂S]-Gly (27)

Referring to the Method A Scheme shown above (bold-face compound numerals correspond to bold-face compound numerals referred to below), in a one liter 3-necked flask fitted with a magnetic stir bar, 22.65 grams (92mmol) of commercially available N-ε-tert-butoxycarbonyl-L-lysine **22A** and 11.66 grams of sodium carbonate (110mmol) were added to 400ml of water and stirred to give a suspension. Addition of 400ml dioxane to the suspension produced a clear pale yellow solution on stirring. This solution was chilled on an ice-water bath with stirring, then 13.2 grams (11.72ml, 110mmol) of allyl chloroformate was added over several hours via a dropping funnel. Stirring was continued overnight without replenishing the ice bath to yield a light slurry.

The reaction mixture was basified with a few ml of 1N NaOH, then washed twice with 800ml portions of ethyl

-95-

acetate (EtOAc). The aqueous layer was acidified to pH ~3 with 1N sodium bisulfate (NaHSO₄) whereupon a heavy slurry formed. The slurry was extracted twice into 800ml portions of EtOAc, then the organic layers were combined, washed with saturated brine solution, dried over sodium sulfate (Na₂SO₄) and concentrated in vacuo to produce 35grams (>100%) of **23A**, a viscous pale yellow oil. TLC analysis (50:50:1 hexanes:EtOAc:Acetic acid) showed clean product and this was carried to the next step assuming quantitative yield. The crude mass of **23A** was dissolved in 150ml ethylene glycol dimethyl ether (DME), chilled to -15°C (ice/water/NaCl slurry) with stirring, then 9.3 grams (10.11ml) of N-methylmorpholine (NMM) was added and the solution re-chilled. Isobutyryl chloroformate (12.56 grams, 11.93ml) was then added in one portion to produce a heavy white precipitate and the resulting slurry was stirred vigorously for 10 minutes on the brine/ice bath. The slurry was filtered through a fritted funnel into a two liter erlenmeyer flask, retentate washed 5 times with 25ml portions of DME and the combined filtrate and rinses were re-chilled to -15°C prior to portion-wise addition of a solution 5.22 grams (138mmol, 1.5eq) sodium borohydride (NaBH₄) in 150ml water. Vigorous evolution of gas was observed after each portion of NaBH₄ was added and the mixture was stirred for an additional 10 minutes on the ice/brine bath to produce a colorless emulsion. TLC (3:1 CH₂Cl₂:EtOAc) revealed good conversion to the alcohol. The emulsion was made basic with a few ml 1N NaOH, then extracted three times with 600ml portions of EtOAc. The organic layers were combined, washed with saturated brine, then dried over Na₂SO₄ and concentrated in vacuo to yield 25 grams (86%) of crude product **24A** as a pale yellow oil.

The product was purified on a 500ml silica column packed and eluted with 7:3 CH₂Cl₂:EtOAc to afford 17.5 grams of a nearly colorless oil **24A**, 60% overall isolated

-96-

yield for alloc protection and acid reduction steps. In a 250ml roundbottom flask, a portion of pure **24A** (7.65 grams, 24mmol) was dissolved in 100ml dry THF under a nitrogen atmosphere, chilled on an ice bath then 5.06ml triethylamine (3.67 grams, 36mmol) was added via syringe. The solution was stirred for a few minutes on ice, then 2.06ml (3.05 grams, 26mmol) of methanesulfonyl chloride (MsCl) was added over a 10 minute period. The clear solution immediately turned cloudy on addition of the MsCl and became a heavy white suspension after all of the MsCl had been added. Stirring was continued for 10-15 minutes following MsCl addition when TLC (3:1 CH₂Cl₂:EtOAc) indicated complete consumption of starting alcohol. The slurry was filtered, retentate washed 3 times with 100ml portions of EtOAc, then the combined filtrate and washes were washed once with cold water, once with cold dilute hydrochloric acid, once with saturated sodium bicarbonate (NaHCO₃) and once with saturated brine before drying over Na₂SO₄ and concentration in vacuo. High vacuum drying of the residue produced 9.22 grams (96%) of **25A** as a colorless oil.

In a 250ml flame-dried flask fitted with a magnetic stir bar, 1.28 grams (0.97ml) of mercaptoacetic acid was dissolved in 30ml of dry dimethylformamide (DMF) under nitrogen atmosphere and to the mercapto acid was added via syringe 6.4ml (1.5 grams, 2eq) of a 25 weight percent solution of sodium methoxide in methanol (NaOMe/MeOH). The clear acid solution turned cloudy white during NaOMe/MeOH addition then returned to its clear and colorless appearance within 30 seconds after the addition was complete. 5 grams of mesylate **25A** dissolved in 15ml dry DMF was then added by pipette in one portion to the stirring dibasic acid and the resulting mixture stirred overnight at room temperature under a blanket of nitrogen. After ~15 hours of stirring, the mixture turned to a heavy slurry with a gray-pinkish color. TLC (50:50:1

-97-

hexanes:EtOAc:acetic acid) showed good conversion, so most DMF was removed with a rotovap at 45°C bath temperature to yield a grayish-white paste. The paste was dissolved in 200ml water with a few ml of 1N NaOH, and
5 the resulting turbid solution was washed 3 times with 150ml portions of ethyl ether. The partially clarified aqueous layer was then acidified to pH ~3 with NaHSO₄ to yield a heavy white slurry that was extracted 3 times with 200ml portions of EtOAc. The combined EtOAc extracts
10 were washed with saturated brine, dried over Na₂SO₄, then concentrated to afford 4.9 grams of **26** (98%) as an oil. The crude product looked relatively clean via TLC (50:50:1 hexanes:EtOAc:acetic acid) and was carried on without purification.

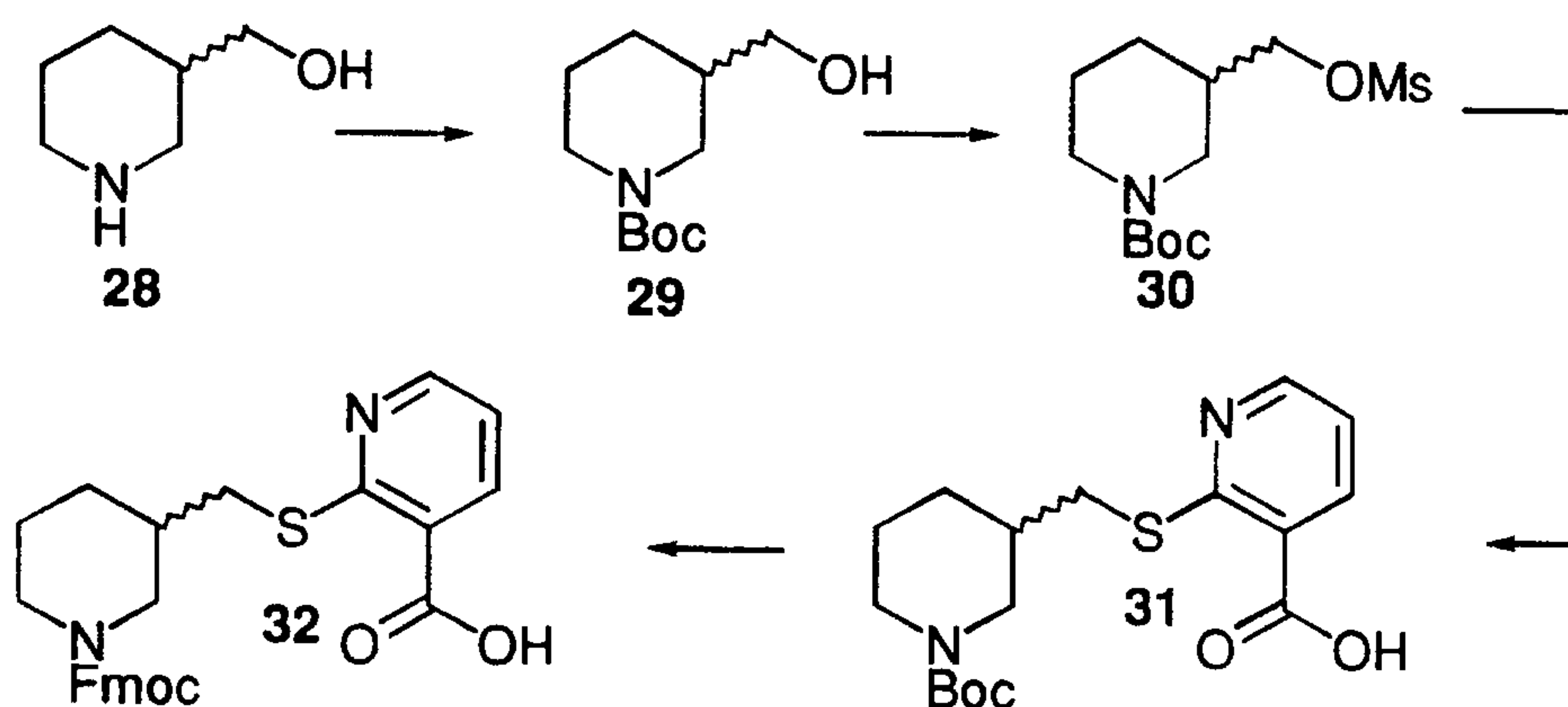
15 To 5.1 grams of **26** under nitrogen in a 250ml flame-dried flask fitted with stir bar was added 60ml dry THF via cannula and the mixture stirred to give a clear and colorless solution. The septum was then removed and in succession were added 3.36 grams solid 5,5-dimethyl-1,3-
20 cyclohexanedione (dimedone), 787 milligrams (0.25eq) of solid triphenylphosphine (PPh₃) and 693 milligrams (0.05eq) of solid tetrakis(triphenylphosphine)palladium(0) (Pd(PPh₃)₄) to produce a clear orange solution. The flask was recapped,
25 covered with aluminum foil and flushed with nitrogen while stirring at room temperature. TLC in 50:50:1 hexanes:EtOAc:acetic acid showed complete conversion of starting material to a baseline spot after about 1 hour of stirring. Solvent was removed with a rotovap to give
30 an orange oil that was then redissolved in 50ml EtOAc and extracted 4 times with 25ml portions of water. To the combined aqueous layers was then added 2 grams solid sodium carbonate and 100ml of dioxane.

The resulting light emulsion was chilled on an ice
35 bath and when the temperature of the solution was below 10°C, 4.46 grams of solid fluorenylmethyloxycarbonyl

-98-

chloride (Fmoc-Cl) was added portion-wise over a one hour period with stirring. The reaction mixture was then stirred overnight without replenishing the ice bath and TLC indicated good conversion of starting baseline material. Next added a few drops of 1N NaOH to the mixture and washed 3 times with 200ml portions of ethyl ether. The aqueous layer was then acidified to pH ~2 with 1N NaHSO₄ and the off-white slurry was extracted 3 times with 150ml portions of EtOAc. The EtOAc layers were combined, washed with saturated brine, dried over Na₂SO₄, then concentrated in vacuo to provide a yellow oil contaminated with dimedone. The oil was applied to a 500ml silica gel column packed with 50:50:1 hexanes:EtOAc:acetic acid and then eluted with the same solvent. Appropriate fractions were pooled, concentrated, then co-evaporated 3 times with toluene/EtOAc to azeotropically remove excess acetic acid. The resulting colorless oil was extensively dried under high vacuum to yield 2.2 grams (35%) of pure **27**.

20

Method B

Referring to the Method B Scheme shown above (bold-face compound numerals correspond to bold-face compound numerals referred to below), in a one liter 3-necked flask, 11.51 grams (100mmol) of **±3-piperidinemethanol (28)** and 10.6 grams (100mmol) sodium carbonate were

-99-

dissolved in 200ml of water, then 200ml of dioxane was added and the mixture stirred to produce a pale yellow light emulsion. To the stirring emulsion was next added 24 grams (110mmol) of di-tert-butyl-dicarbonate and stirring continued overnight. TLC (75:25 CH₂Cl₂:EtOAc) revealed complete conversion, so the light yellow slurry was stripped of dioxane, then extracted twice with 300ml portions of EtOAc. The organic layers were combined, washed with saturated brine, dried over Na₂SO₄, then concentrated in vacuo to yield 20.6 grams (95%) of clean **29** as an off-white solid.

To 20 grams (93mmol) of **29** under nitrogen in a flame-dried one liter flask equipped with a stir bar was added 400ml dry THF via cannula. The resulting pale yellow-tan solution was chilled on an ice-water bath, then 14.12 grams (19.44ml, 139mmol) of triethylamine was added by pipette and the solution stirred for a few minutes under nitrogen. Next, 11.72 grams (7.92ml, 102mmol) of methanesulfonyl chloride was added by syringe over a 10 minute period with vigorous stirring. The clear solution turned to a cloudy whitish-tan suspension immediately upon mesylate addition and became a heavy slurry within a few minutes after all methanesulfonyl chloride had been added. TLC (3:1 CH₂Cl₂:EtOAc) revealed complete conversion of the product within 10 minutes of final sulfonyl chloride addition. The slurry was filtered through a fritted funnel and the retentate rinsed 4 times with 100ml portions of EtOAc. The combined filtrate and rinses were then washed once each with cold water, cold dilute hydrochloric acid, saturated NaHCO₃, and saturated brine. The organic layer was dried over Na₂SO₄ and concentrated in vacuo to provide 26.94 grams (98%) of **30** as a pale yellow crystalline solid.

2-Mercaptonicotinic acid (11 grams, 71mmol) was dissolved under nitrogen in 400ml dry DMF under nitrogen in a one liter 3-necked flask fitted with a large egg-

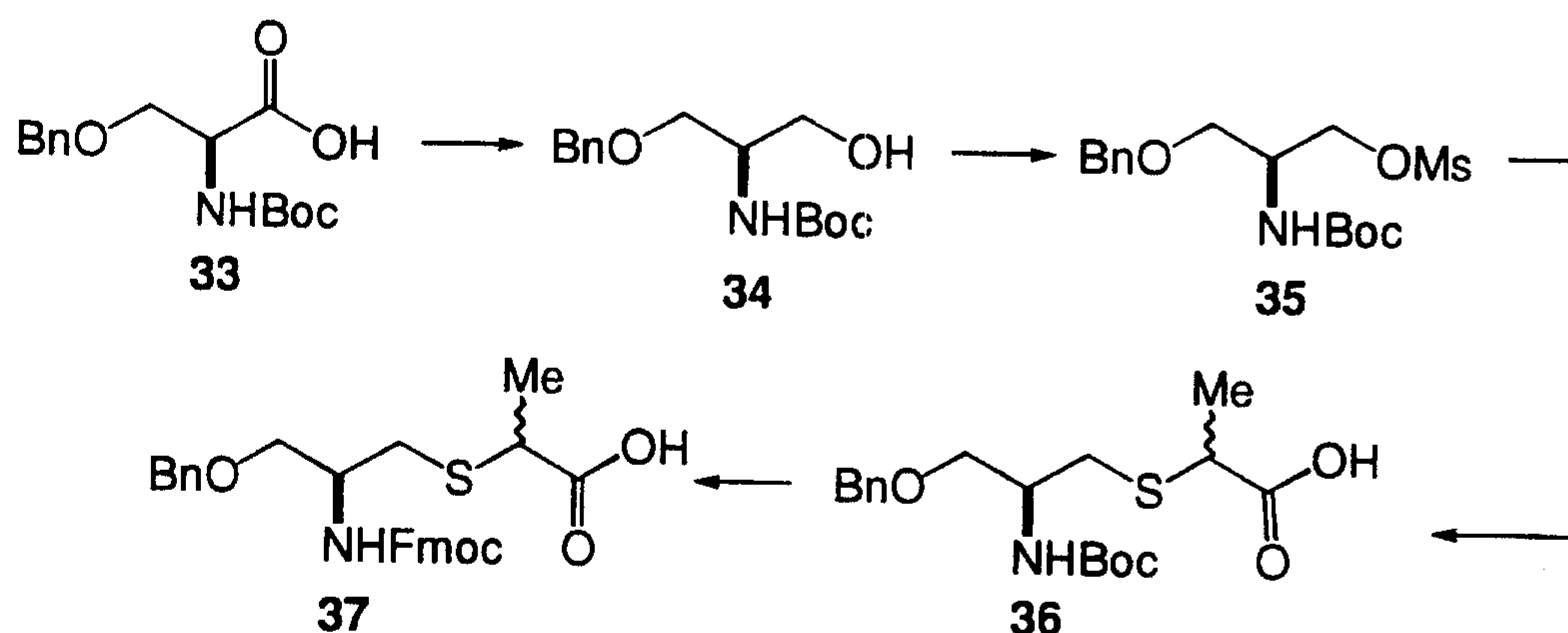
-100-

shaped stir bar to give a bright yellow solution. Next, 7.67 grams (32.5ml, 142mmol) of a 25 weight per cent solution of NaOMe in MeOH was added to the stirring mercaptonicotinic acid/DMF solution, then 20.8 grams (71mmol) of **30** dissolved in DMF (52ml final volume) was added by syringe pump over a two day period. The resulting deep yellow viscous slurry was stripped of DMF, then redissolved in 400ml of water. The turbid yellow aqueous solution was partially clarified by 3 washes with 300ml portions of ethyl ether. The partially clarified aqueous layer was acidified to pH ~2 with 1N NaHSO₄ to produce a heavy yellow slurry that was then extracted 3 times with 300ml portions of EtOAc. The organic layers were combined, washed with saturated brine, dried over Na₂SO₄, and concentrated in vacuo to provide 24.6 grams (98%) of crude **31** as a canary yellow solid.

The crude product was recrystallized from neat EtOAc to provide two crops of pale yellow crystals weighing 20.95 grams (83% isolated yield). Purified acid **31** (19 grams, 54mmol) was combined with 108ml of a 4N hydrochloric acid solution in dioxane and stirred in a one liter flask to produce a heavy white-caked precipitate. 100ml of dioxane was added to loosen the slurry and after one hour of stirring, TLC (50:50:1 hexanes:EtOAc:acetic acid) indicated complete conversion of starting material to a baseline product. A large part of the HCl was removed under light vacuum on a rotovap, then the remains were neutralized with 1N NaOH solution. To the neutralized solution was then added with stirring 250ml of water, 5.72 grams (54mmol) of solid sodium carbonate and another 100ml of dioxane. The resulting emulsion was chilled on an ice-water bath, then 19.12 grams (56.7mmol) of fluorenylmethyloxycarbonyl N-hydroxysuccinimide (Fmoc-OSu) was added portion-wise over a 10 minute period. Stirring was continued for 36 hours to produce an ivory slurry. Dioxane was removed in vacuo,

-101-

then the mixture was washed 3 times with 300ml portions of ethyl ether. The aqueous layer was then acidified to pH ~2 with 1N NaHSO₄ and the resulting heavy slurry extracted 3 times with 300ml portions of EtOAc. The combined EtOAc layers were washed with saturated brine, dried over Na₂SO₄, then concentrated and dried under high vacuum to yield 23.54 grams (92%) of **32** as pale yellow solid that was judged clean by TLC in 50:50:1 hexanes:EtOAc:acetic acid.

Method CN- α -Fmoc-O-benzyl-L-Ser-[ψ -CH₂S]-DL-Alanine (**37**)

Referring to the Method C Scheme shown above (bold-face compound numerals correspond to bold-face compound numerals referred to below), in a 500ml round-bottomed flask fitted with a magnetic stir bar, 25 grams (84.6 mmol) of N- α -Boc-O-benzyl-L-Serine (**33**) (Novabiochem, San Diego, CA, USA) was dissolved in 150 ml DME and chilled to -15°C with an ice/water/brine bath. 10.23 ml N-methylmorpholine (93 mmol, 1.1 eq) was added to the chilled solution, stirred a few minutes, then 12 ml of isobutyl chloroformate (93 mmol, 1.1 eq) was added in one portion at which time the solution quickly turned to a heavy white slurry. The slurry was stirred vigorously for 10 minutes on the brine/ice bath, then filtered

-102-

through a fritted funnel into a two liter erlenmeyer flask. The retentate was washed 5 times with 15 ml portions of DME and the combined filtrate and rinses were re-chilled to -15°C prior to portion-wise addition of a solution 5.3 grams (140mmol, 1.66eq) sodium borohydride (NaBH_4) in 100 ml water. Vigorous evolution of gas was observed after each portion of NaBH_4 was added. The mixture was stirred for an additional 10 minutes on the ice/brine bath to produce a colorless emulsion. TLC (3:1 CH_2Cl_2 :EtOAc) revealed good conversion to the alcohol. Reaction was quenched with 1000 ml of water and the resulting emulsion was made basic with a few ml 1N NaOH, then extracted three times with 300ml portions of EtOAc. The organic layers were combined, washed with saturated brine, then dried over Na_2SO_4 and concentrated in vacuo to yield a pale yellow oil. Product recrystallized from ~400 ml of 7:1 petroleum ether:diethyl ether to give 20.28 grams (85%) of alcohol **34** as white needles after washing with hexanes and drying under high vacuum.

In a 1000ml round-bottomed flask, a portion of pure **34** (9.0 grams, 32 mmol) was dissolved in 125 ml dry THF under a nitrogen atmosphere, chilled on an ice bath, then 6.69 ml triethylamine (4.86 grams, 48 mmol) was added via syringe. The solution was stirred for a few minutes on ice, then 2.73 ml (4.03 grams, 35.2 mmol) of methanesulfonyl chloride (MsCl) was added over a 10 minute period. The clear solution immediately turned cloudy on addition of the MsCl and became a heavy white suspension after all of the MsCl had been added. Stirring was continued for 10-15 minutes following MsCl addition when TLC (3:1 CH_2Cl_2 :EtOAc) indicated complete consumption of starting alcohol. The slurry was filtered, retentate washed 3 times with 100 ml portions of EtOAc, then the combined filtrate and washes were washed once with cold water, once with cold dilute hydrochloric acid, once with saturated sodium bicarbonate (NaHCO_3) and once with

-103-

saturated brine before drying over Na_2SO_4 and concentration in vacuo. High vacuum drying of the residue produced 12.7 grams (>100%) of **35** as a colorless oil.

In a 250ml flame-dried flask fitted with a magnetic stir bar, 1.91 grams (1.6 ml) of DL-thiolactic acid was dissolved in 40 ml of dry dimethylformamide (DMF) under nitrogen atmosphere and to the mercapto acid was added via syringe 8.24 ml (1.94 grams, 2eq) of a 25 weight percent solution of sodium methoxide in methanol (NaOMe/MeOH). About 5.4 grams of mesylate **35** (~15 mmol) dissolved in 35 ml dry DMF was then added by pipette in one portion to the stirring dibasic acid and the resulting mixture stirred overnight at room temperature under a blanket of nitrogen. After ~15 hours of stirring, the mixture turned to a heavy slurry with a grayish color. TLC (50:50:1 hexanes:EtOAc:acetic acid) showed good conversion, so most DMF was removed with a rotovap at 45°C bath temperature to yield a grayish-white paste. The paste was dissolved in 200ml water with a few ml of 1N NaOH, and the resulting turbid solution was washed 3 times with 150ml portions of ethyl ether. The partially clarified aqueous layer was then acidified to pH ~3 with NaHSO_4 to yield a heavy white slurry that was extracted 3 times with 200ml portions of EtOAc. The combined EtOAc extracts were washed with saturated brine, dried over Na_2SO_4 , then concentrated to afford 5.6 grams of **36** (101%) as an oil. The crude product looked relatively clean via TLC (50:50:1 hexanes:EtOAc:acetic acid) and was carried on without purification. 3.8 grams of **36** (10.4 mmol) in a 1000 ml round bottomed-flask was chilled on an ice-water bath and combined with 100 ml of a 4N hydrochloric acid solution in ethyl acetate. TLC (50:50:1 hexanes:EtOAc:acetic acid) indicated complete conversion of starting material to a baseline product within one hour of HCl addition. Most of the HCl was removed under vacuum on a rotovap, then the remains were dissolved in

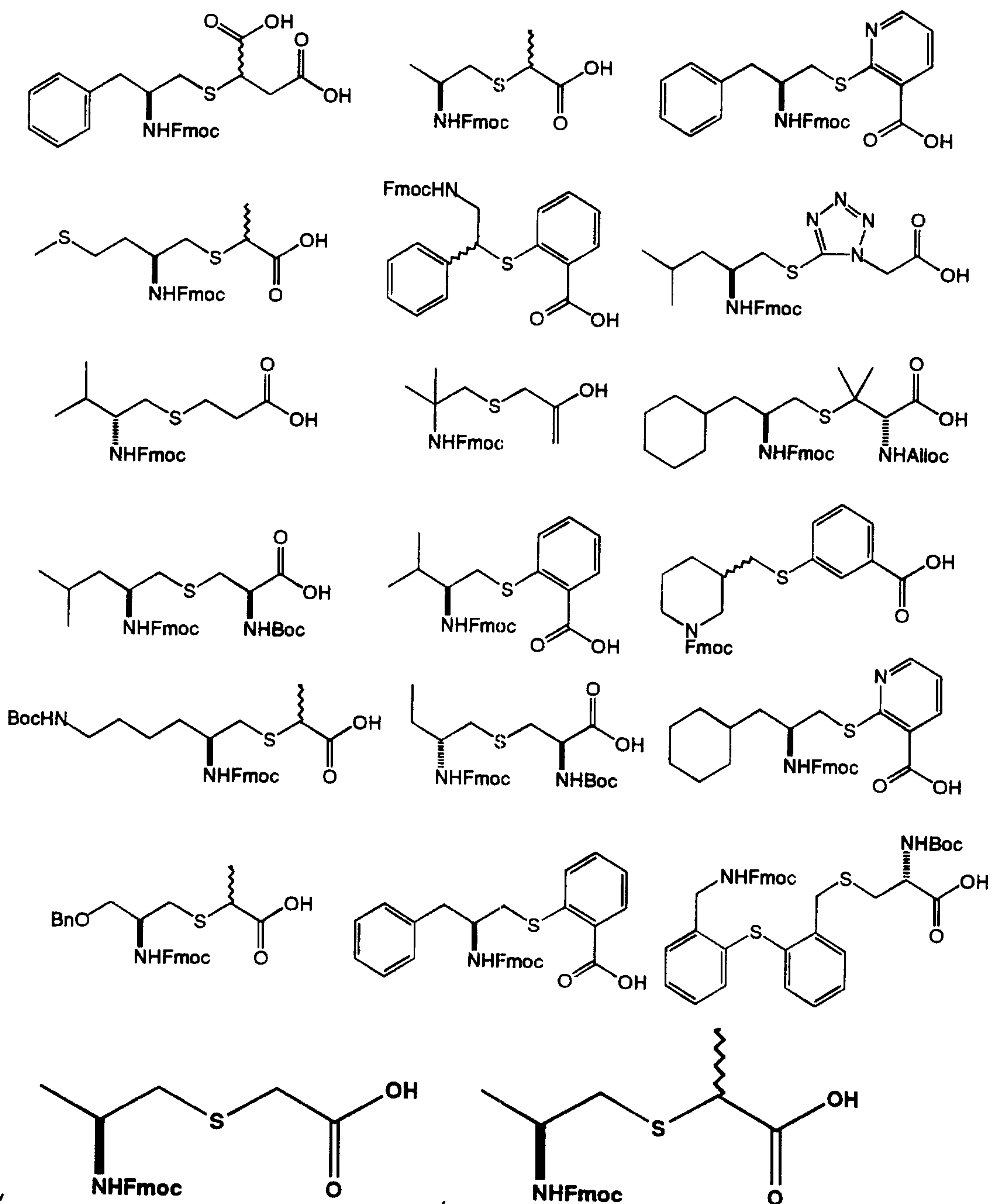
-104-

100 ml of water. To this solution was then added with stirring 4.4 grams (42 mmol, 4 eq) of solid sodium carbonate and then 75 ml of dioxane. The resulting emulsion was chilled on an ice-water bath, then 3.86 grams (11.4 mmol) of fluorenylmethyloxycarbonyl N-hydroxysuccinimide (Fmoc-OSu) was added portion-wise over a 10 minute period. Stirring was continued overnight and TLC (50:50:1 hexanes:EtOAc:acetic acid) of the resulting ivory slurry showed complete consumption of starting **36**. Dioxane was removed in vacuo, the mixture was diluted with 200 ml and then washed 3 times with 200ml portions of ethyl ether. The aqueous layer was then acidified to pH ~2 with 1N NaHSO₄ and the resulting slurry extracted 3 times with 100ml portions of EtOAc. The combined EtOAc layers were washed with saturated brine, dried over Na₂SO₄, then concentrated and dried under high vacuum to yield 5.6 grams (110%) of **37** as a colorless oil. Recrystallization from acetone-hexanes failed, but TLC (50:50:1 hexanes:EtOAc:acetic acid) indicated ~80% purity.

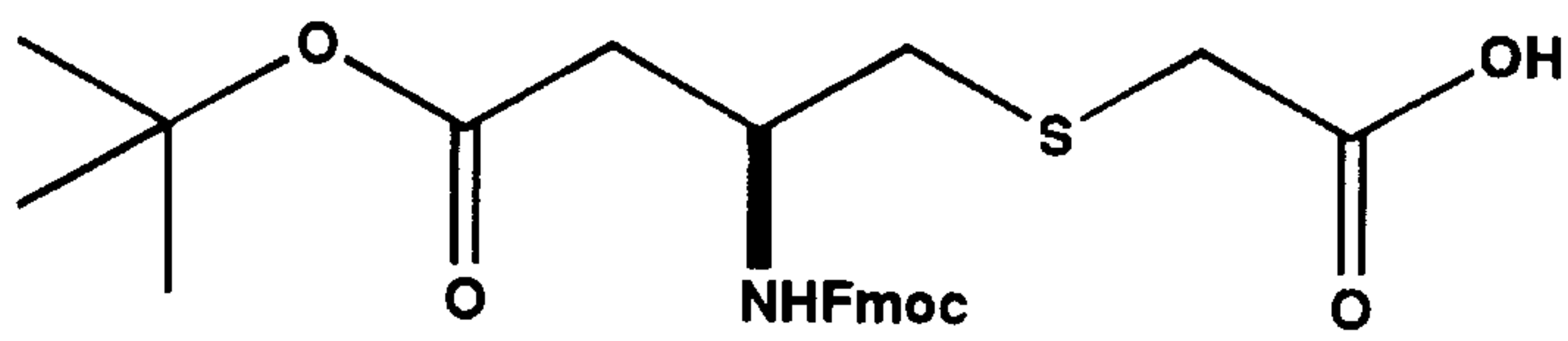
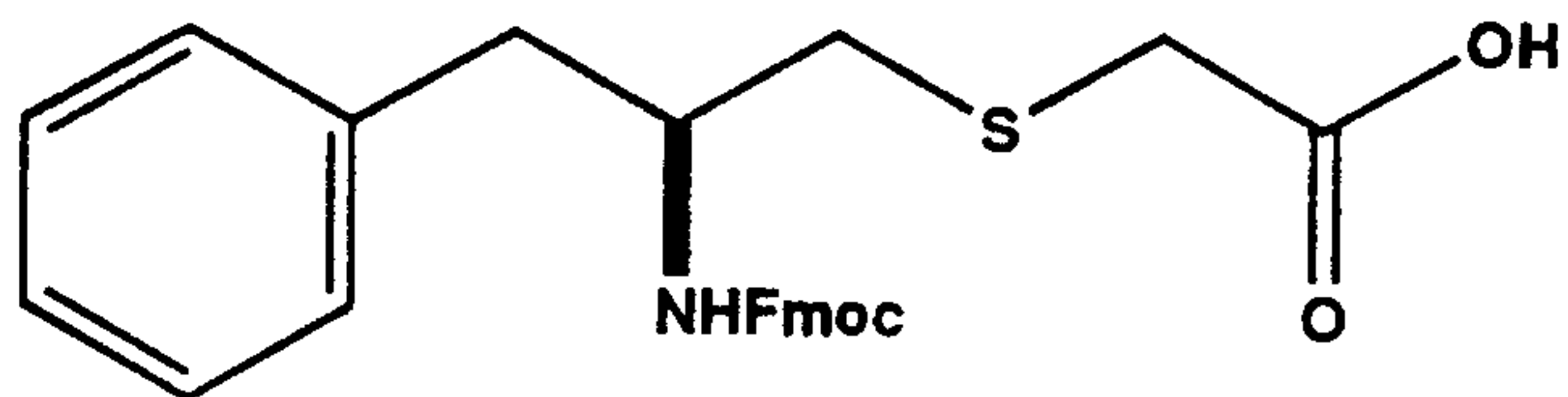
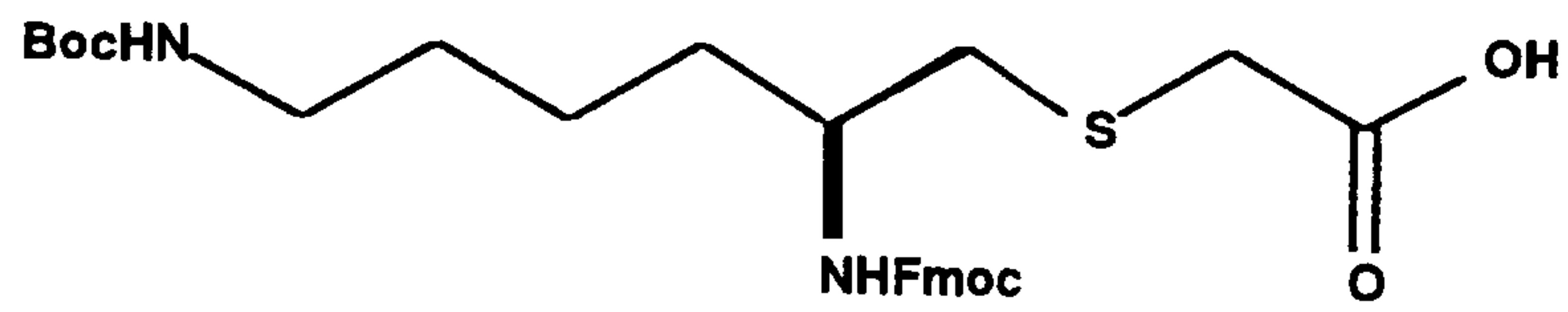
-105-

Preparation 2

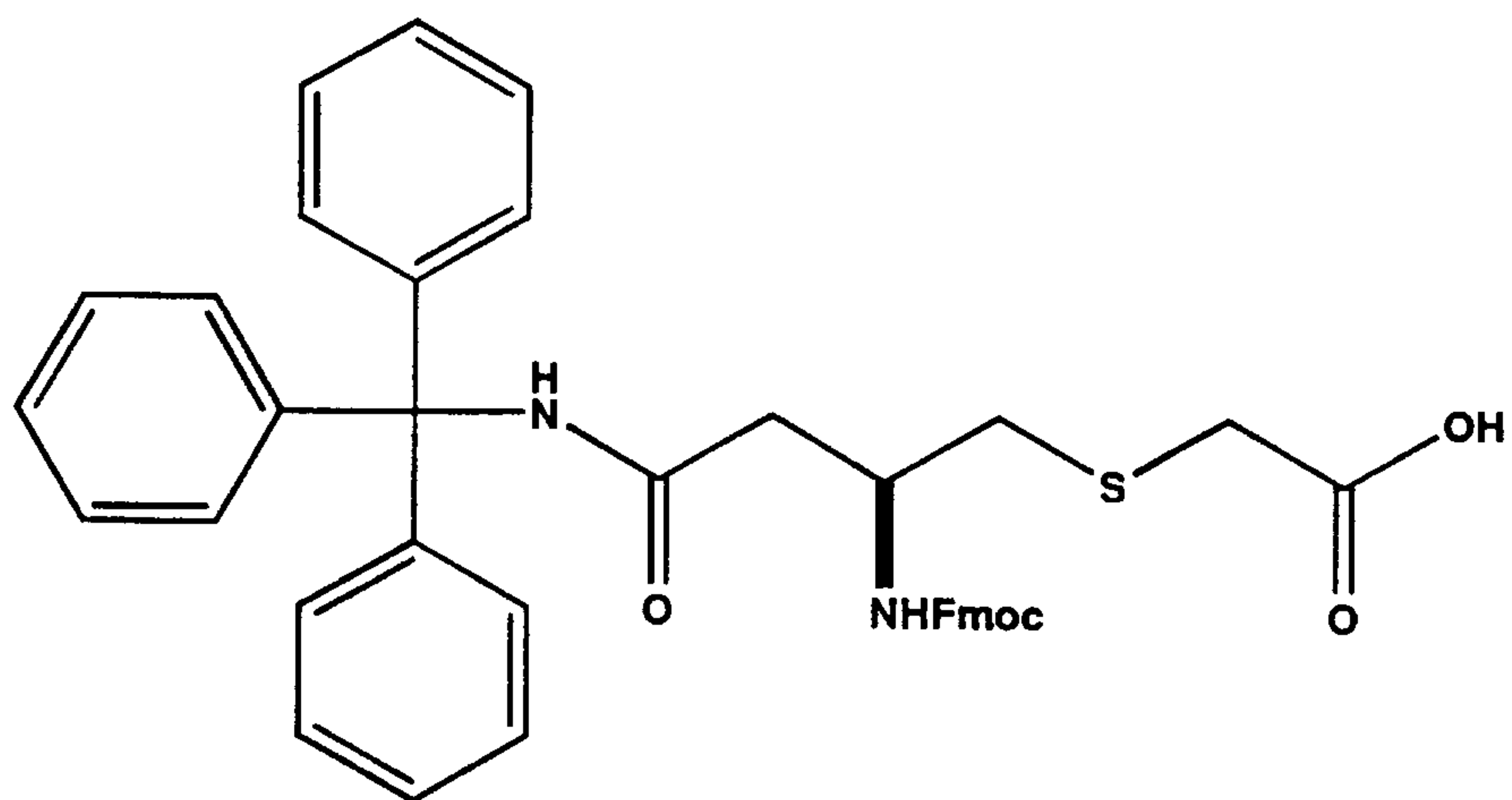
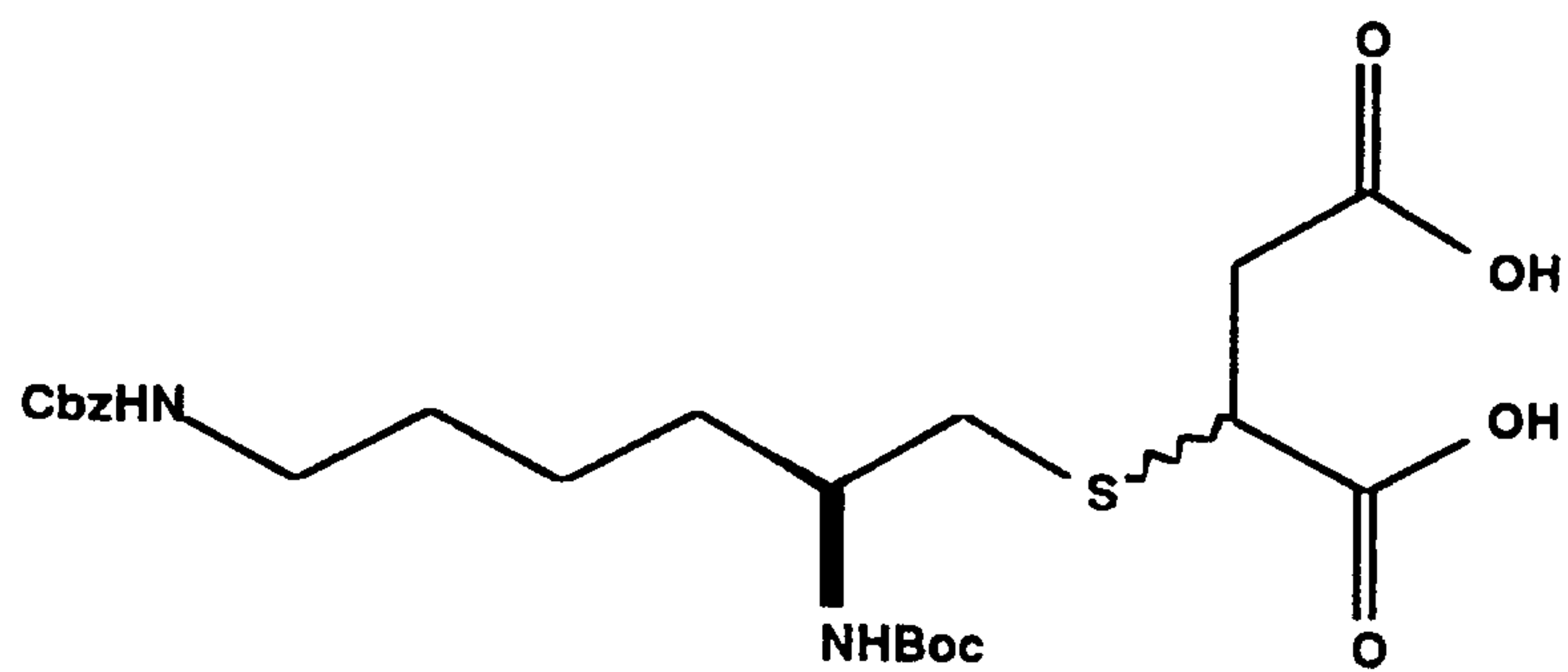
The following ATA compounds have been prepared in accordance with the general methods of Scheme II and can be utilized to form the macrocycle library of the present invention.



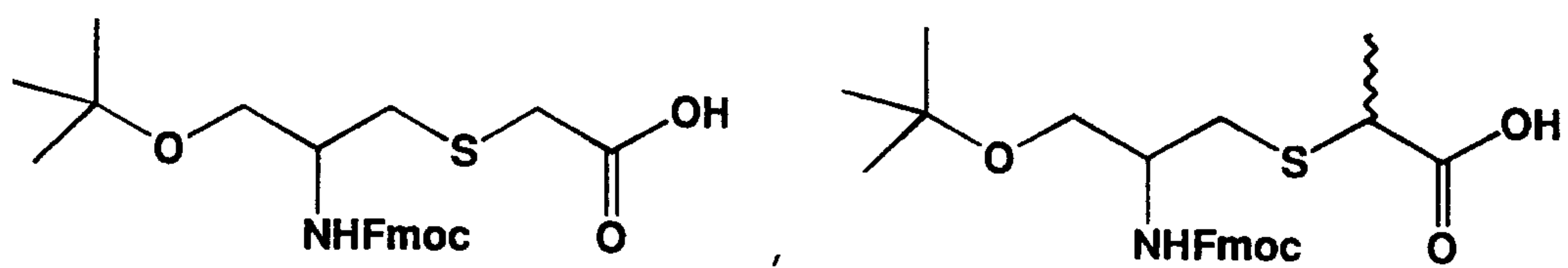
-106-



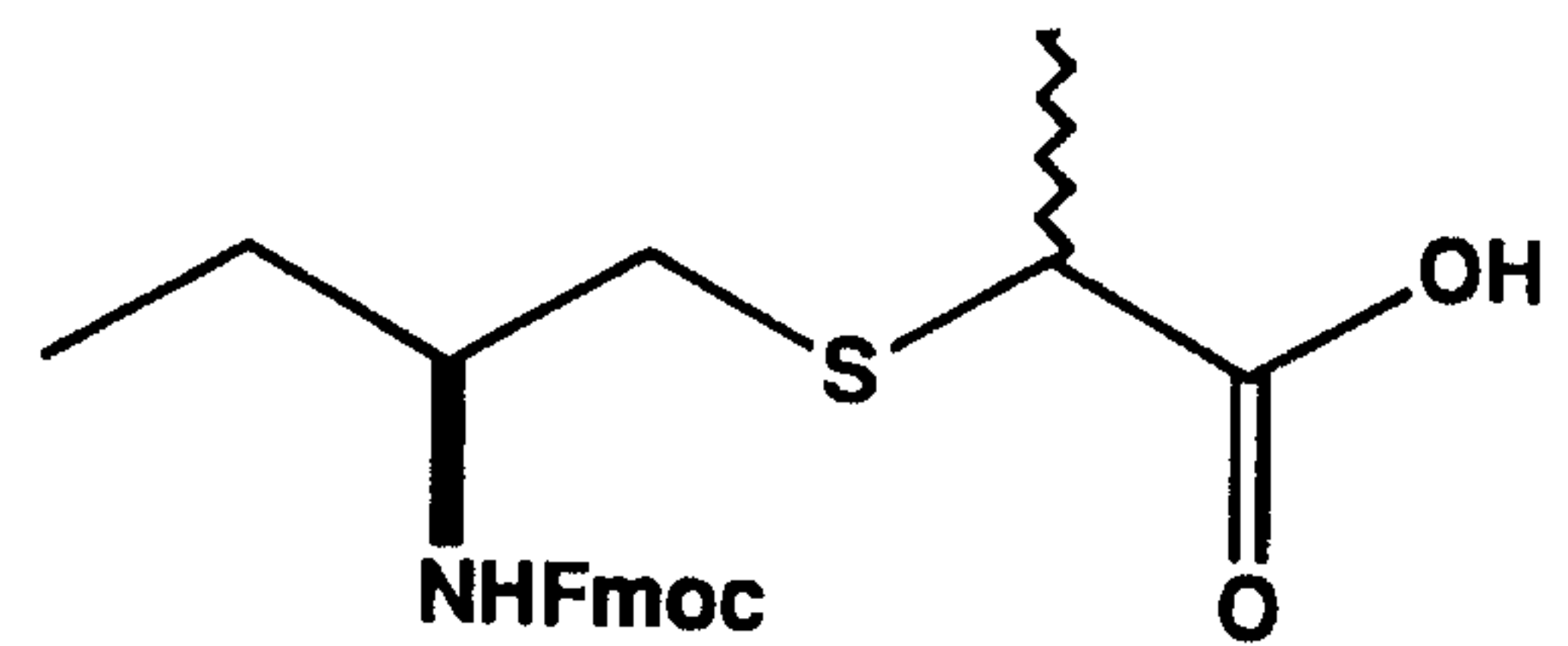
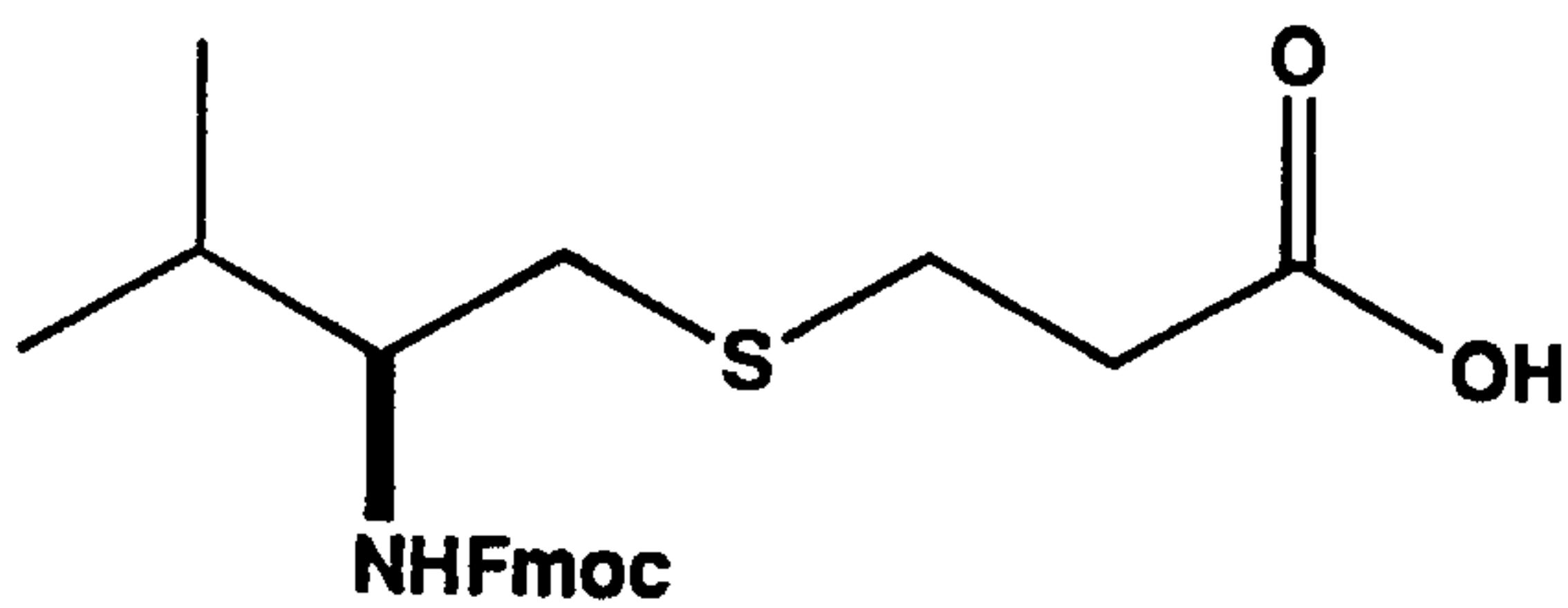
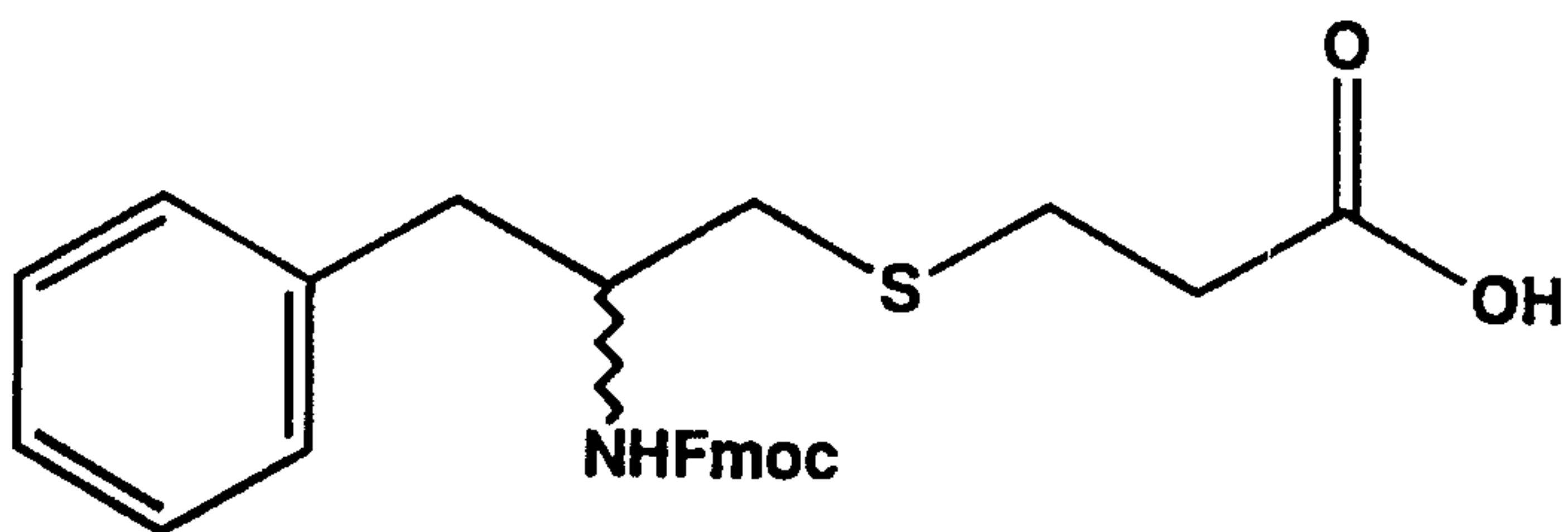
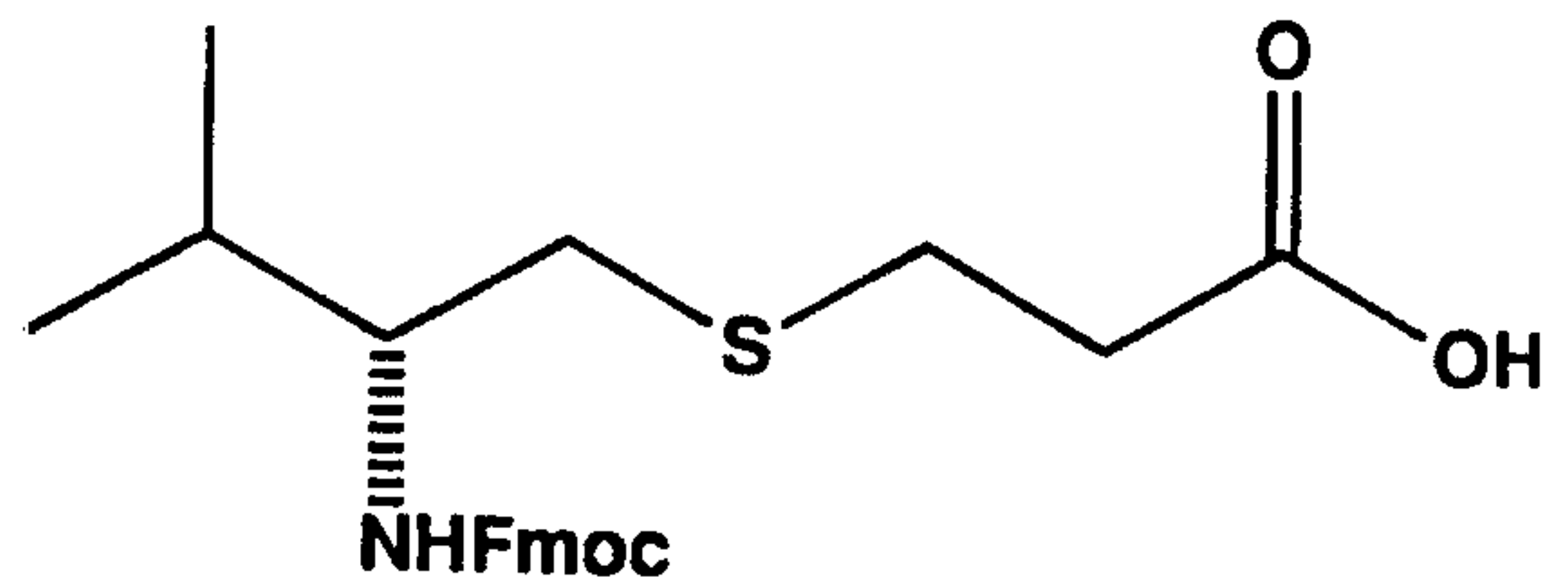
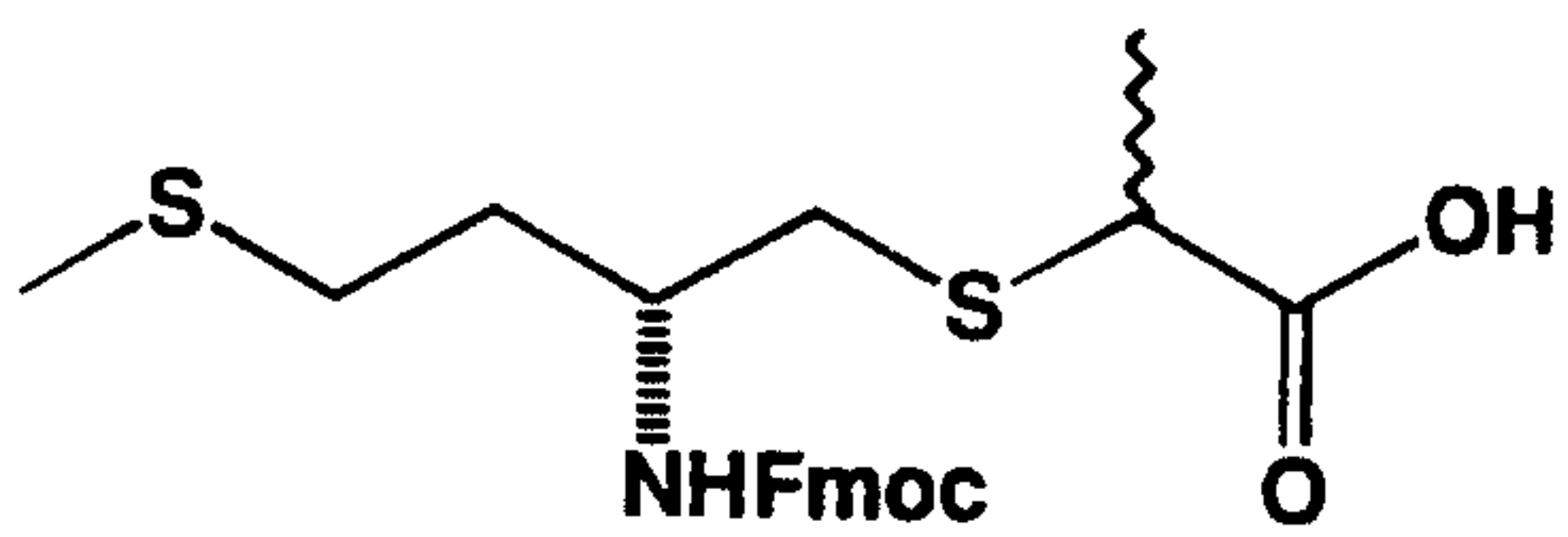
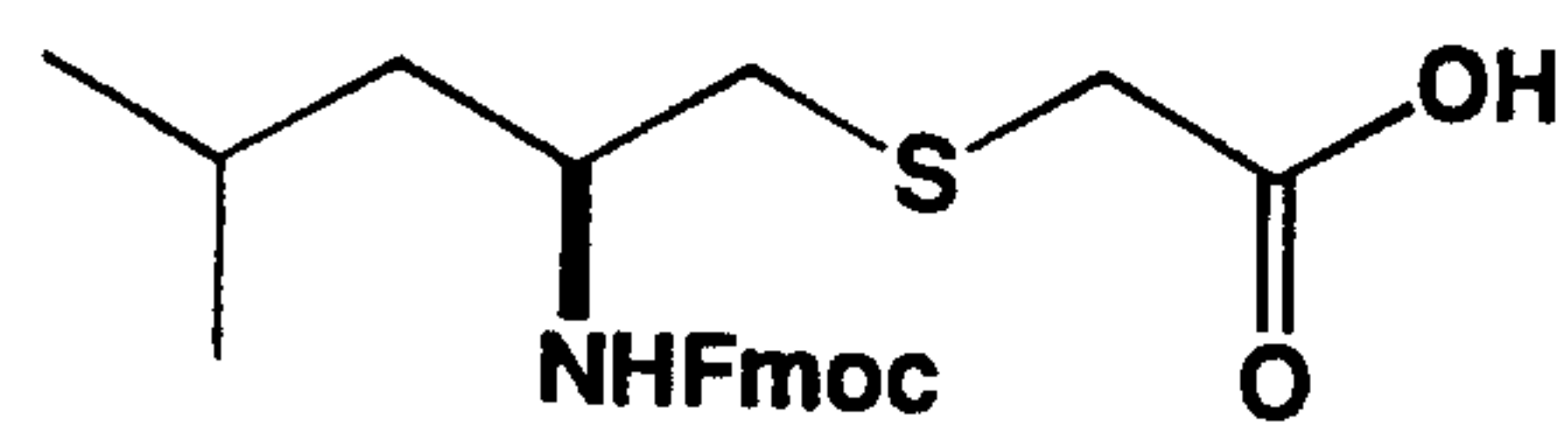
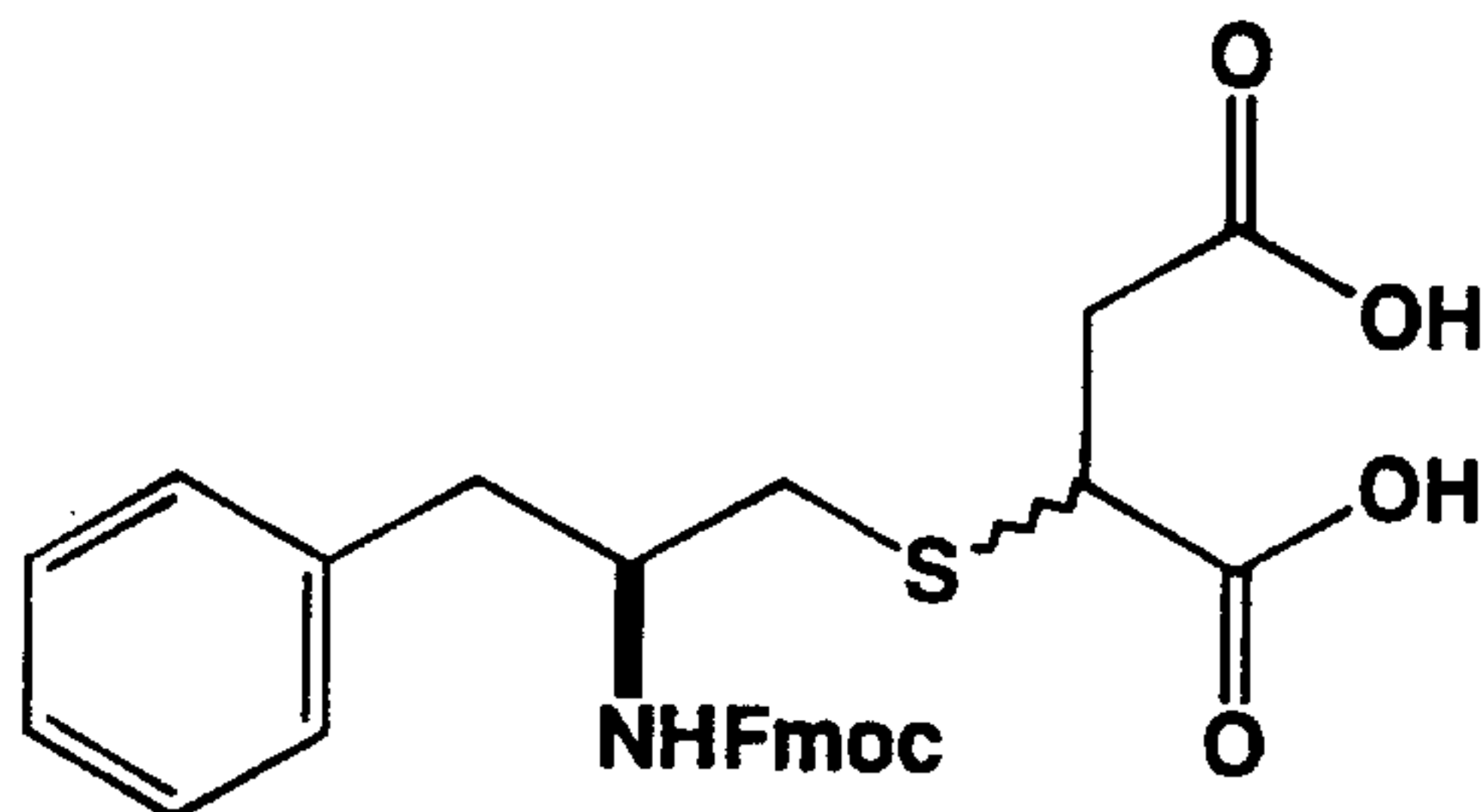
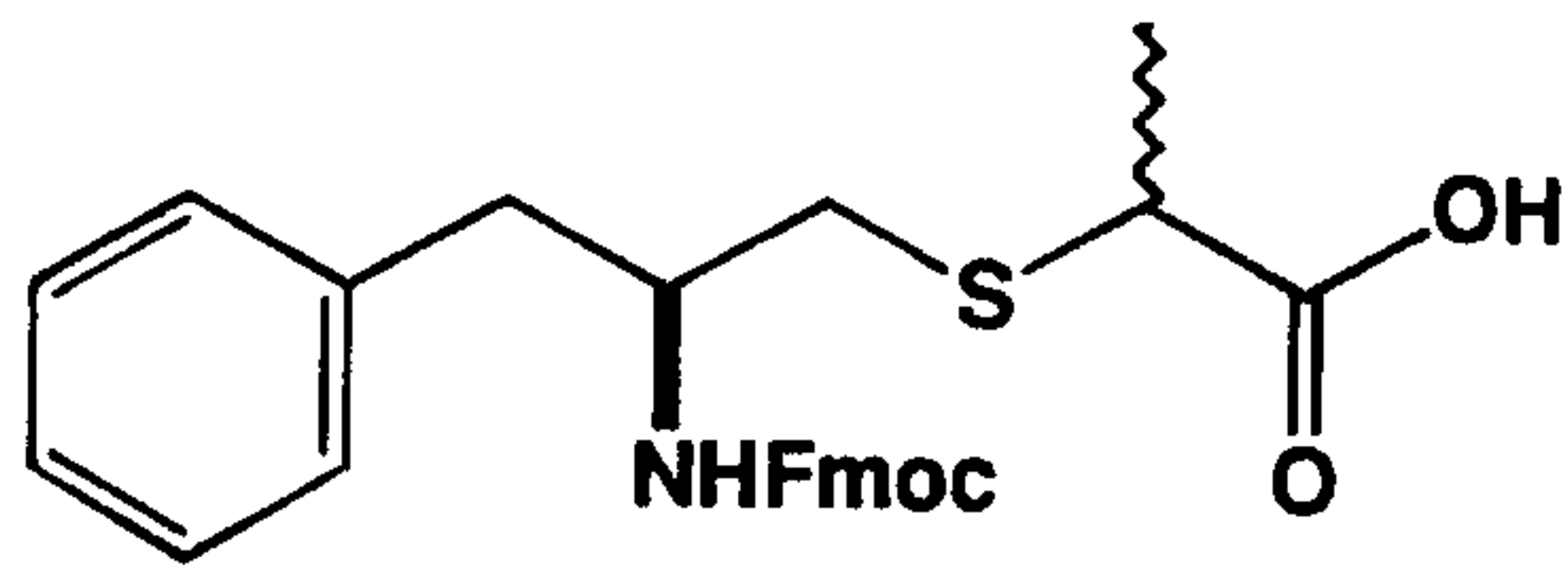
5



10



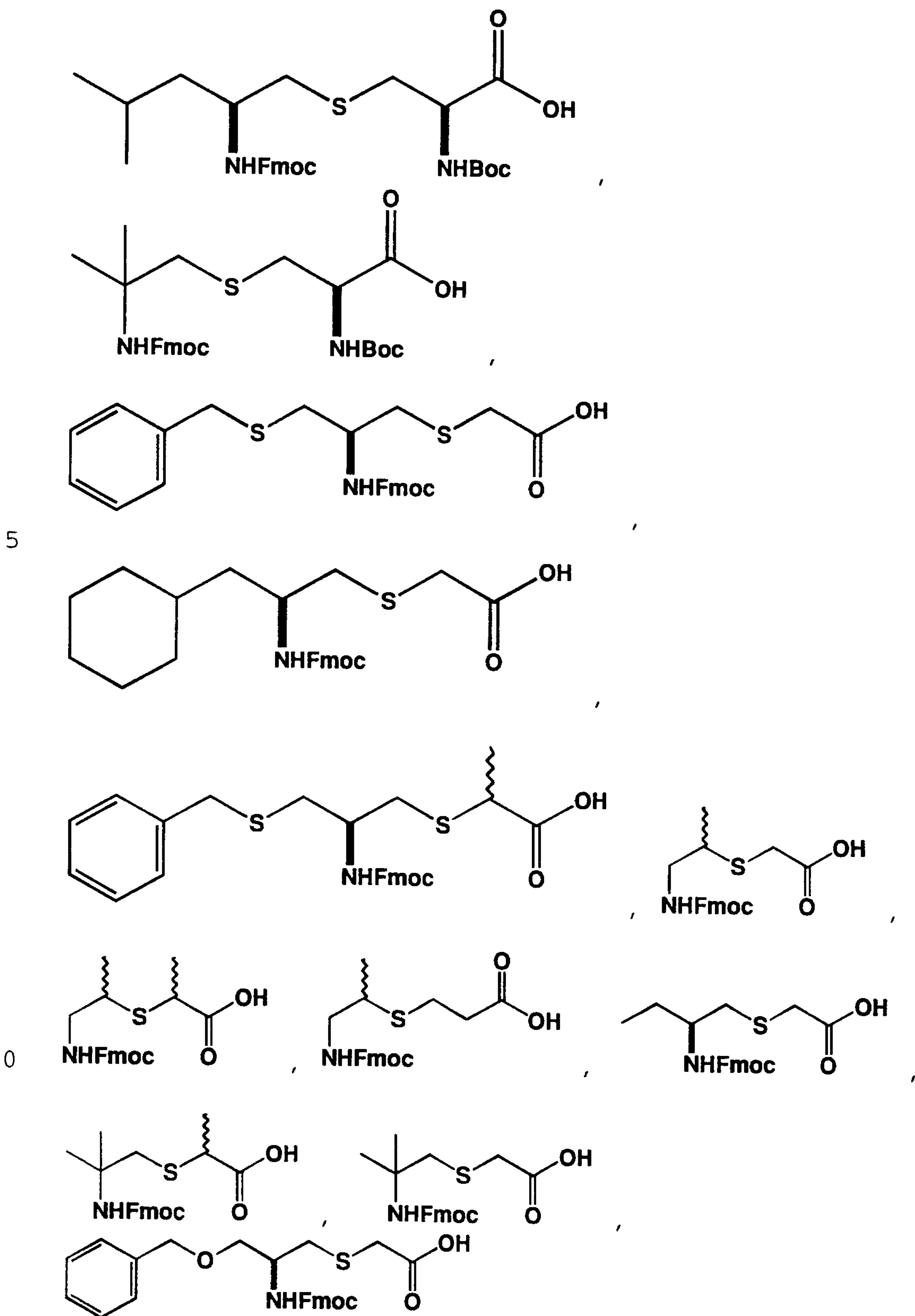
-107-



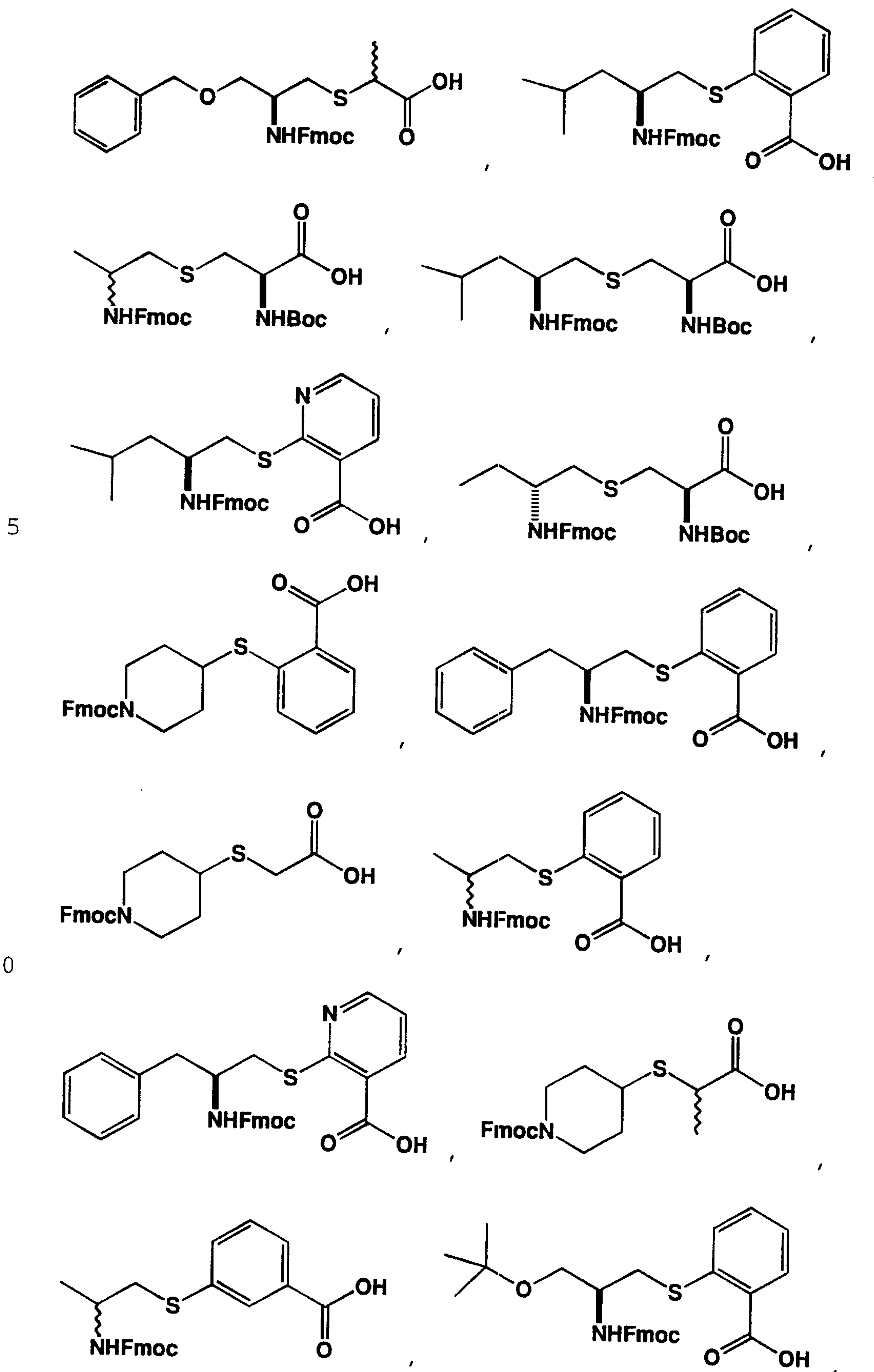
5

10

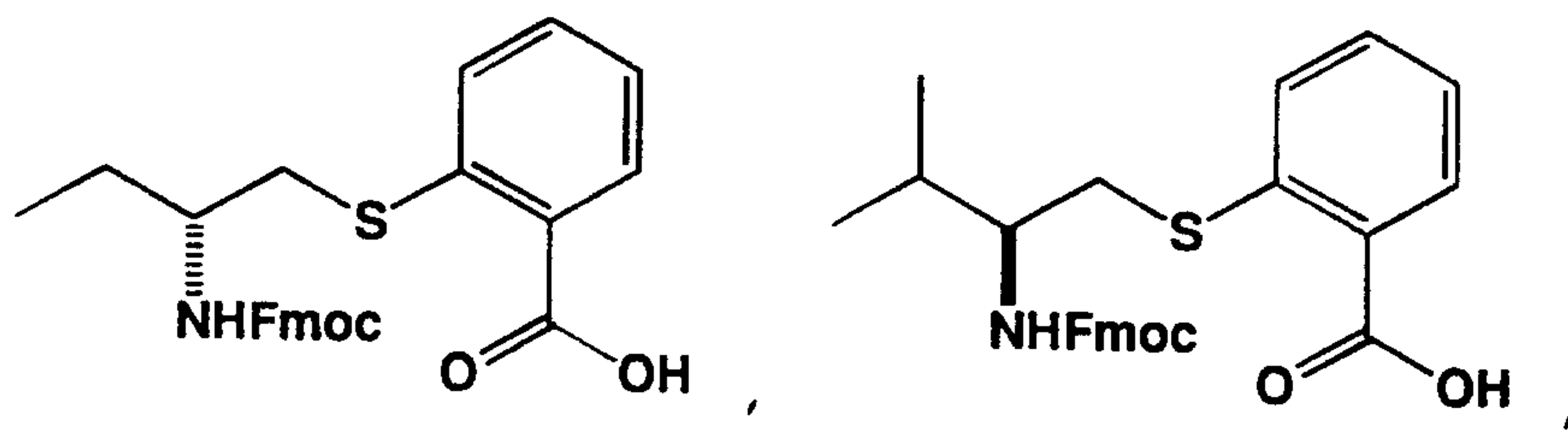
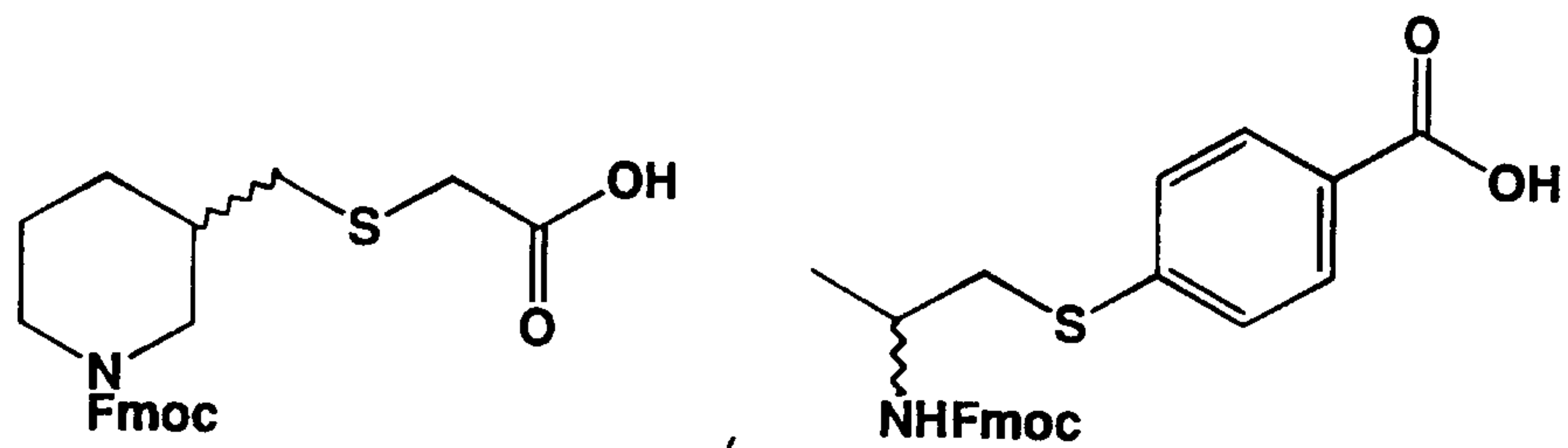
-108-



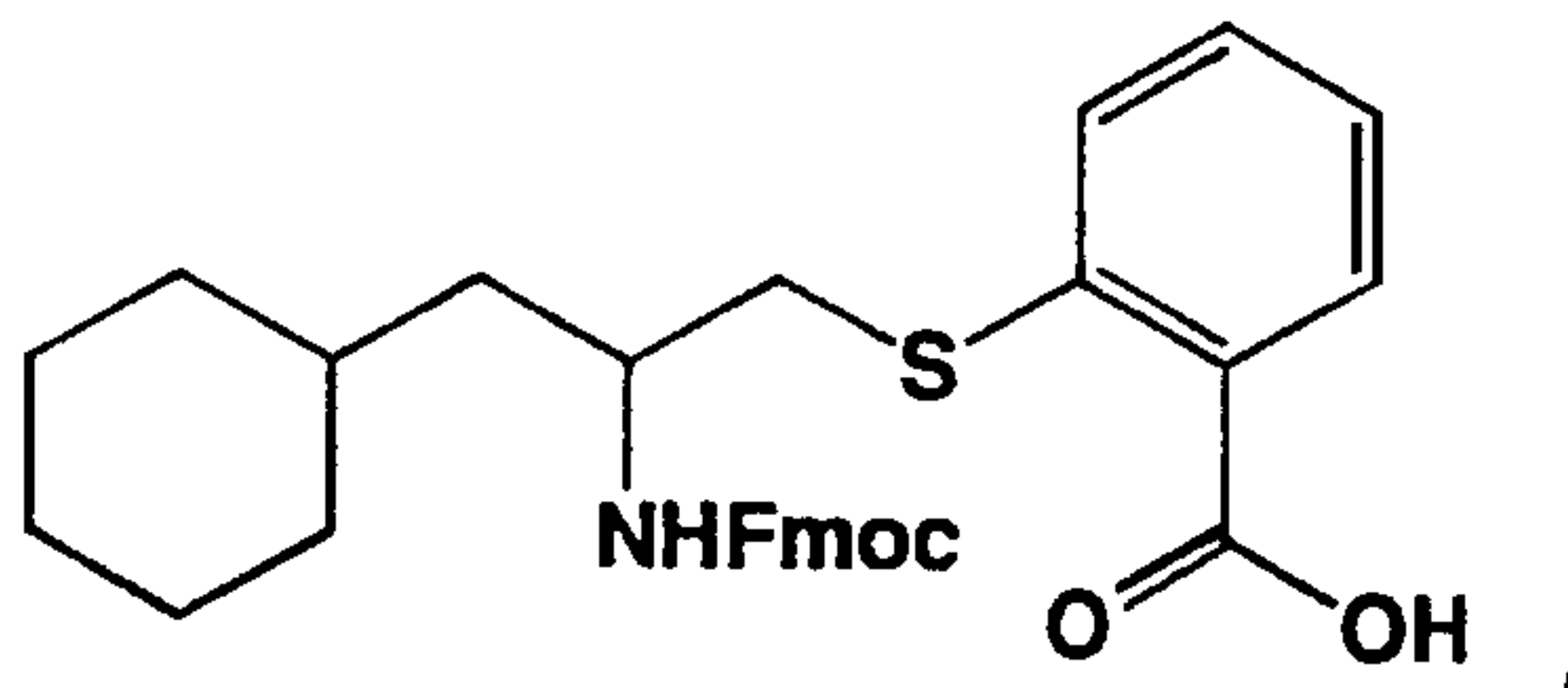
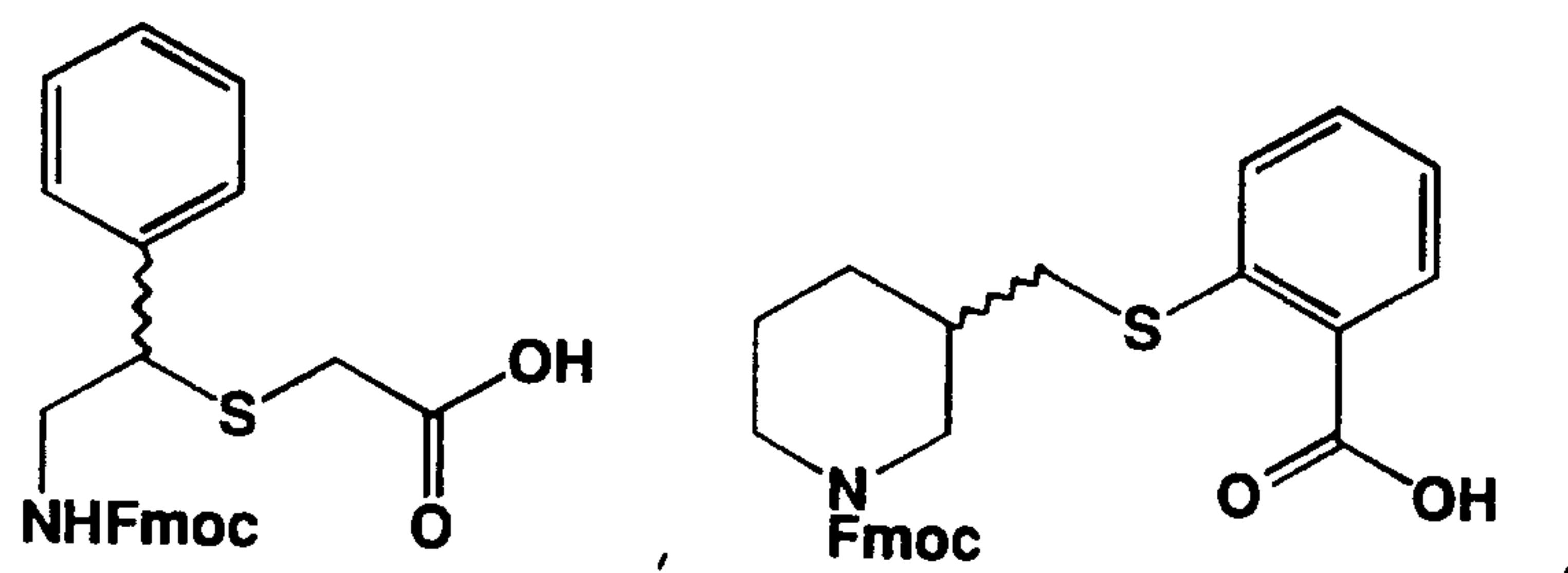
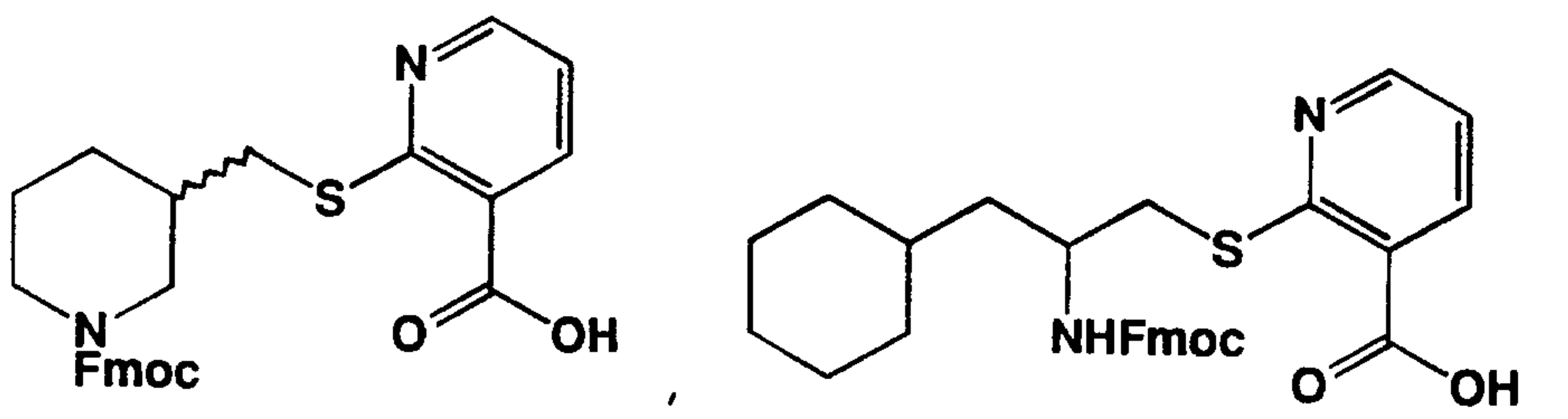
-109-



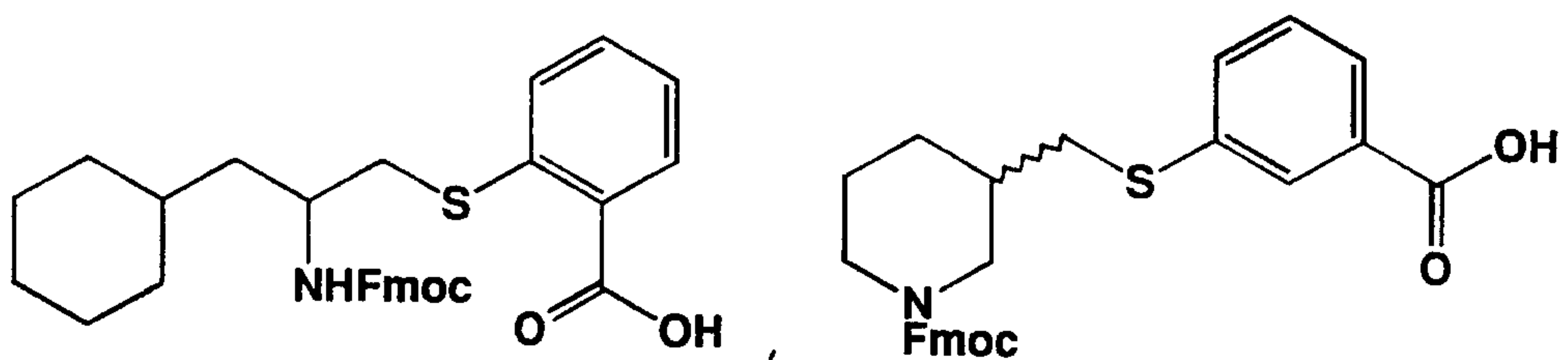
-110-



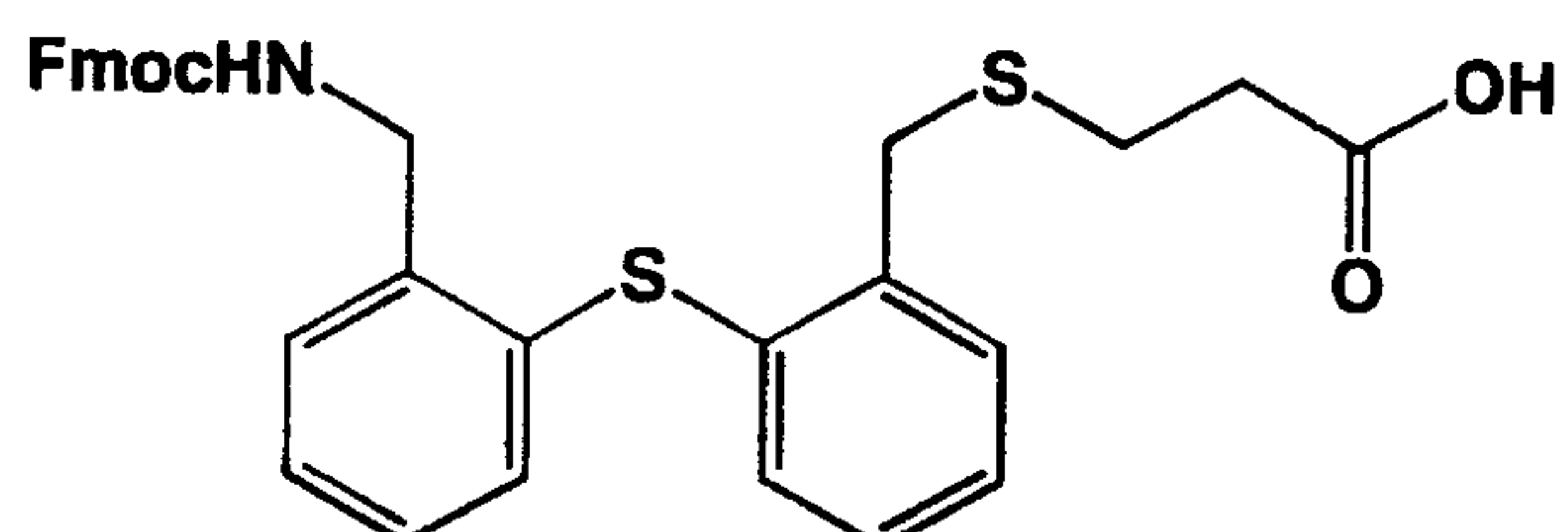
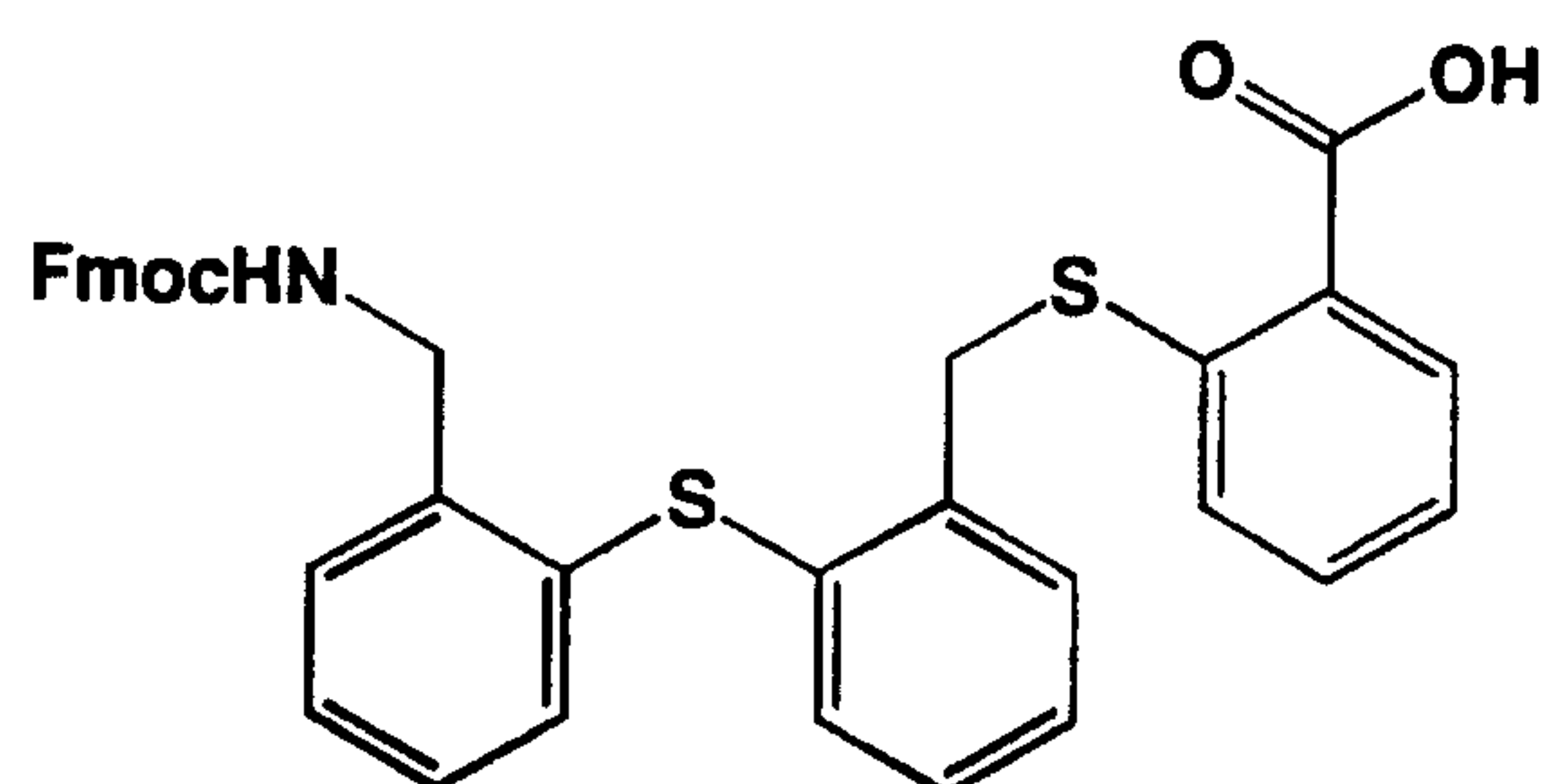
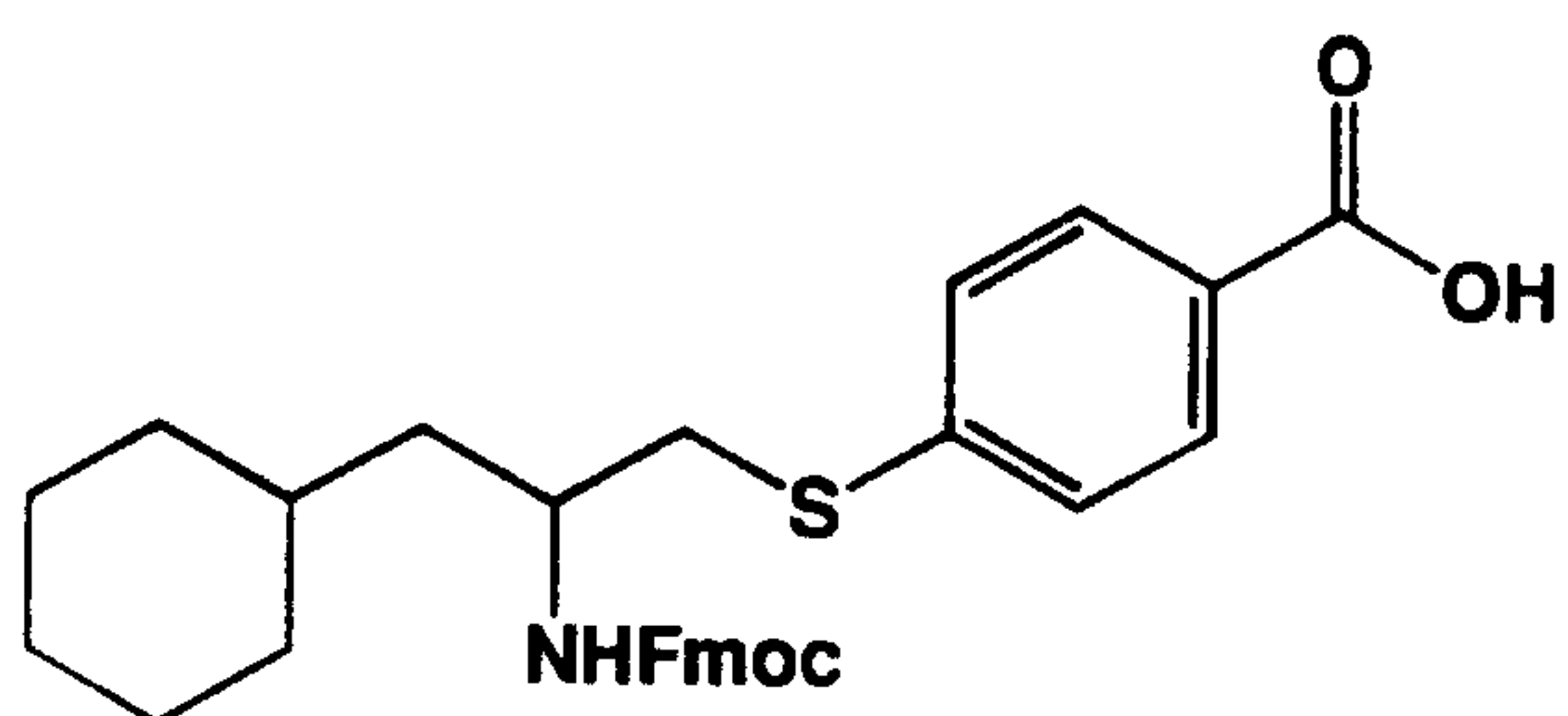
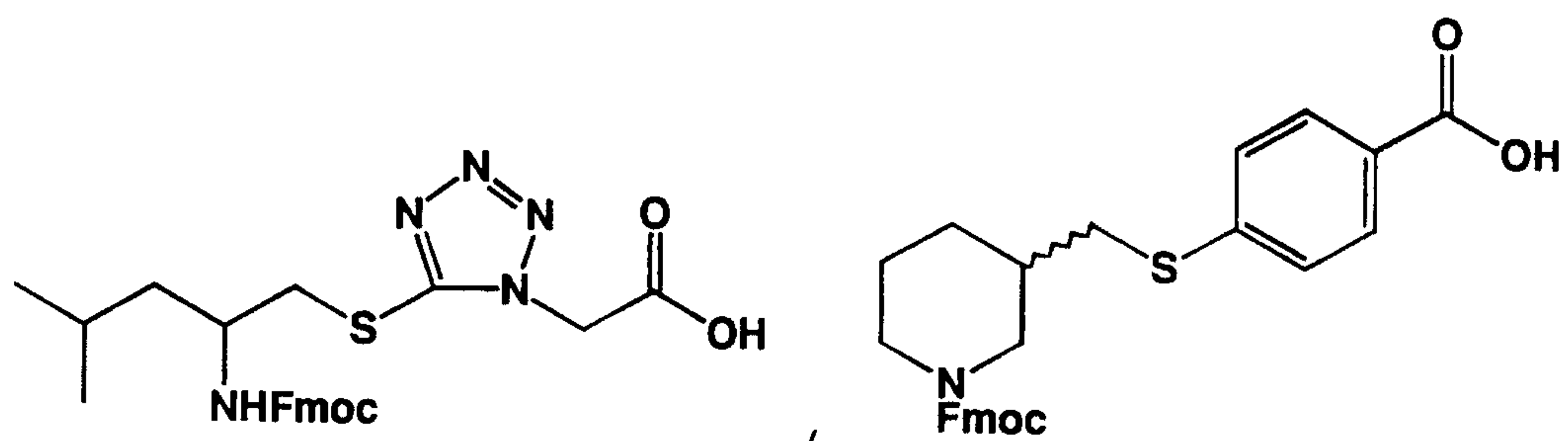
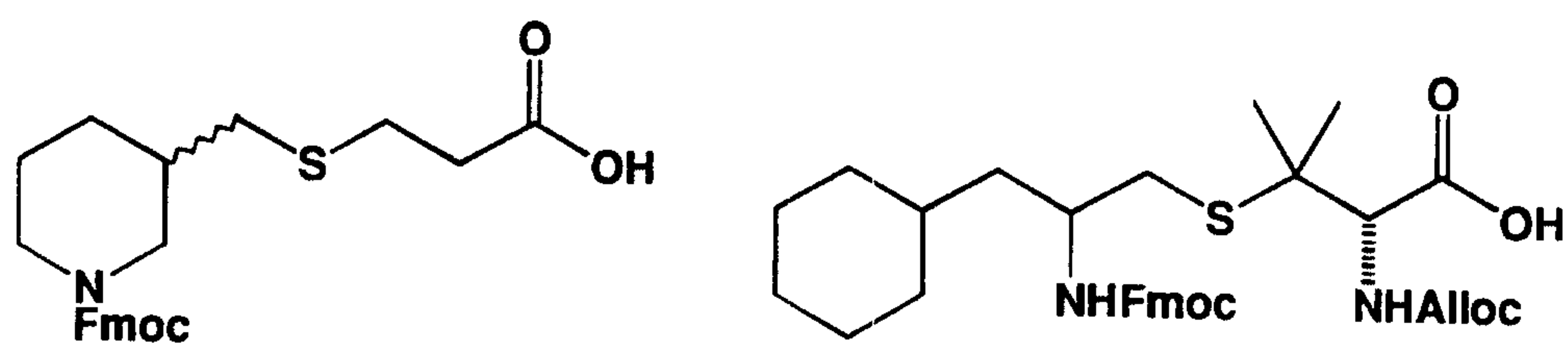
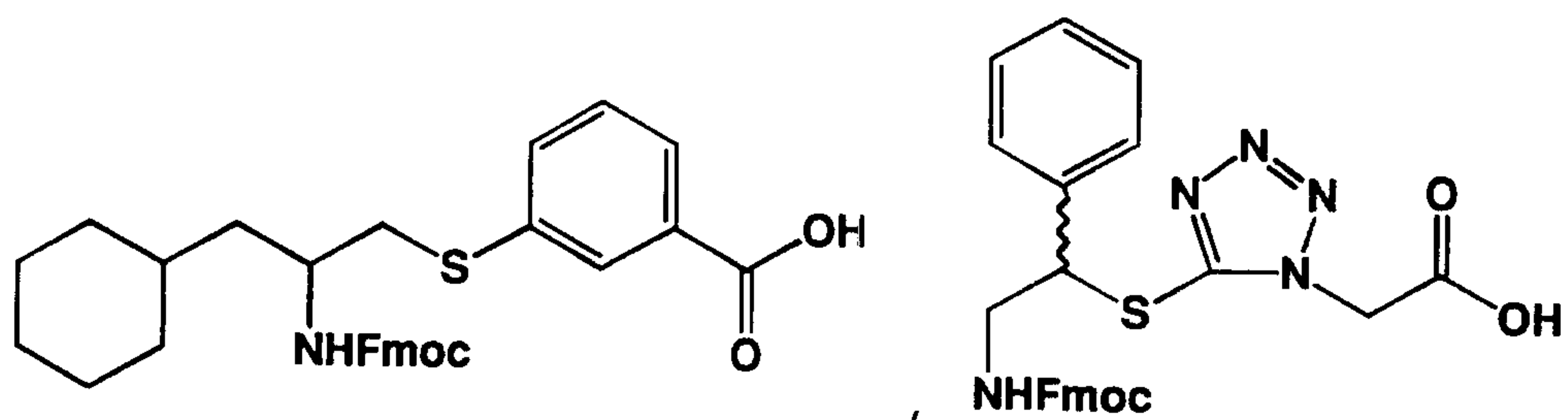
5



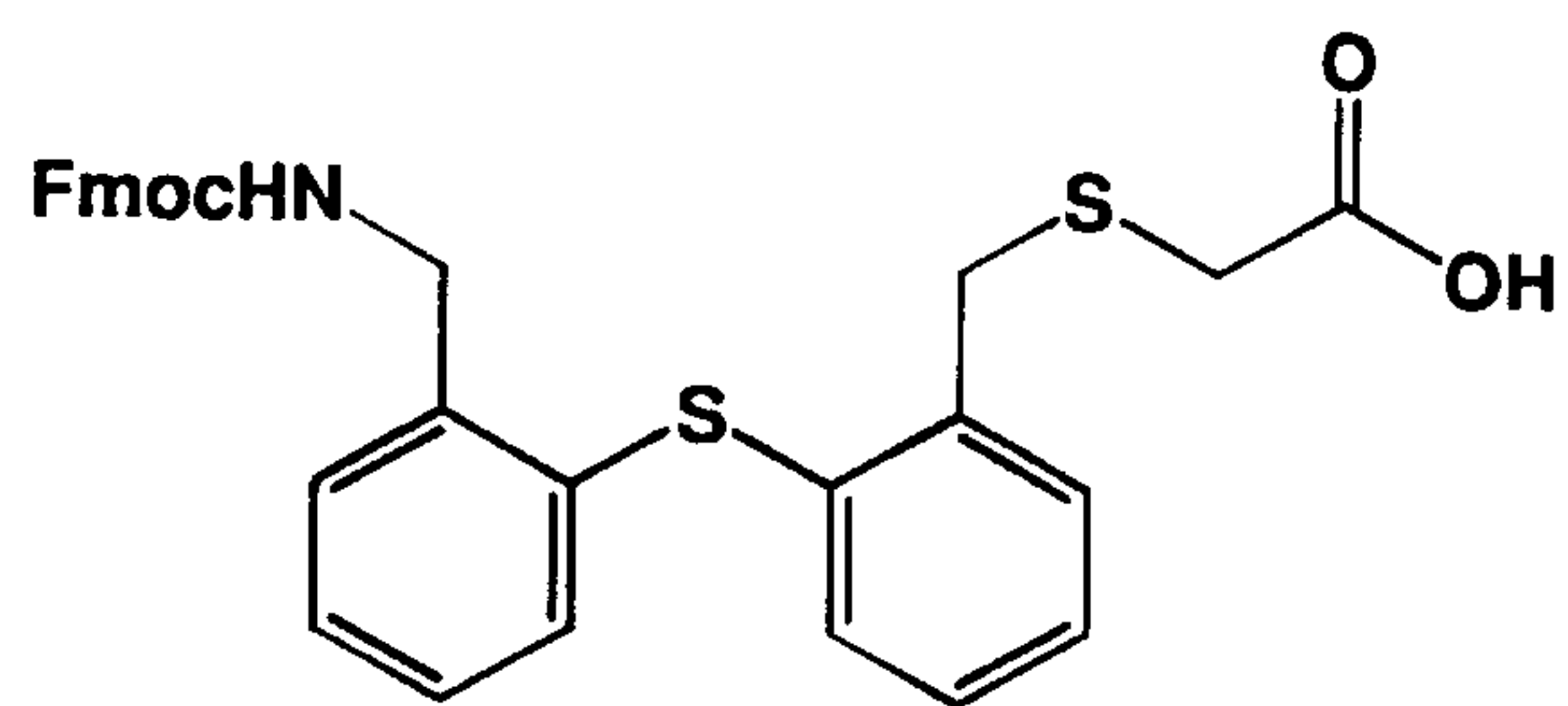
10



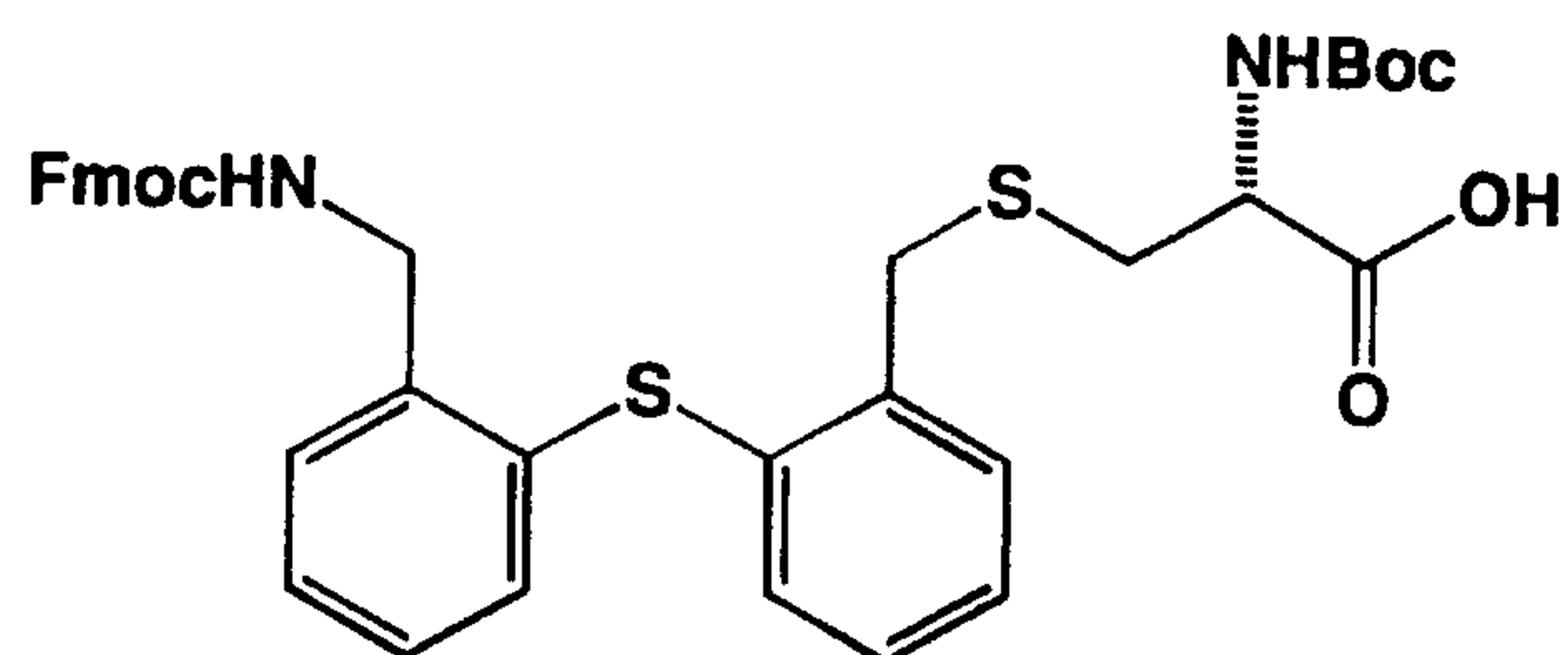
-111-



-112-

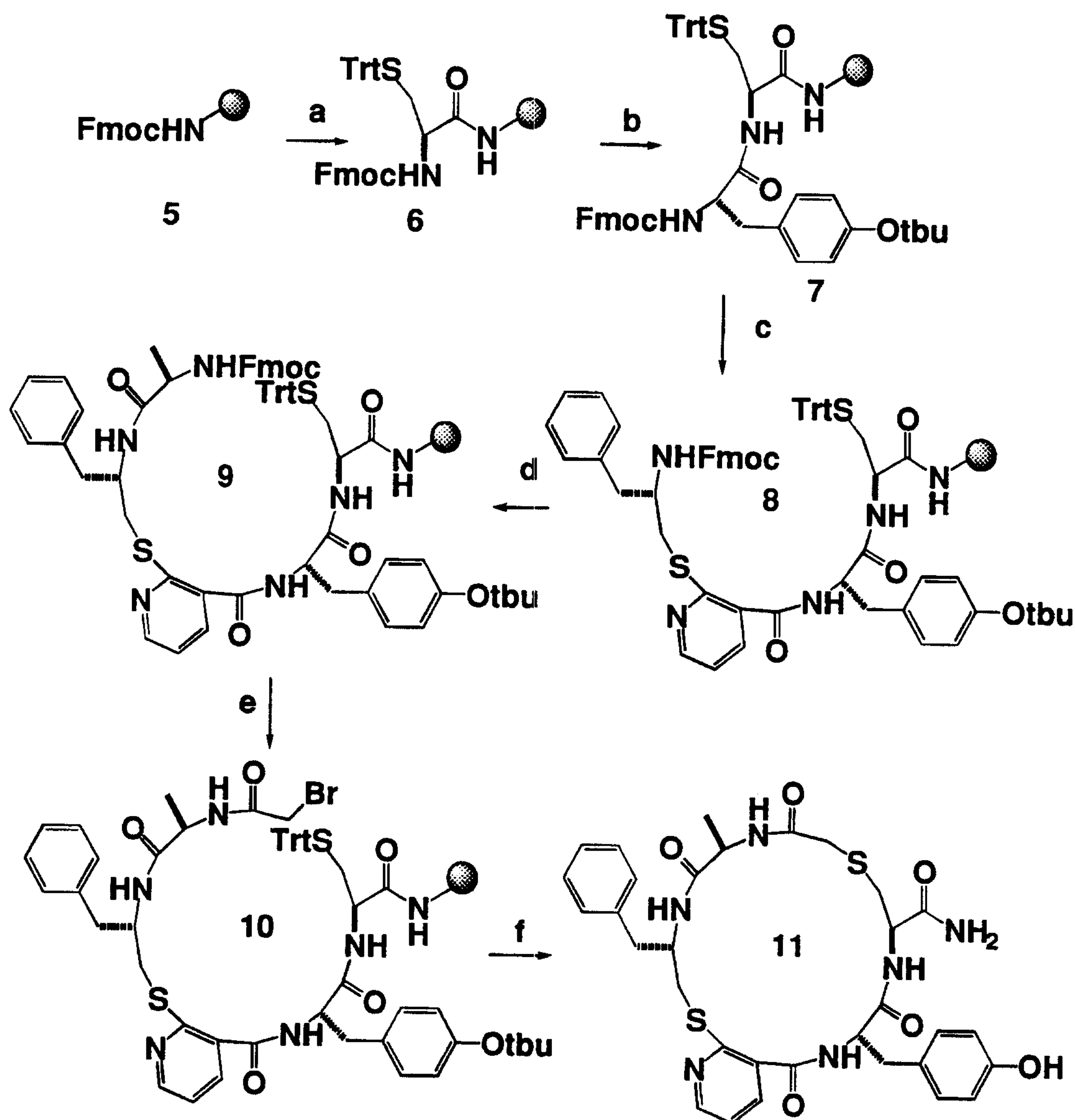


, and



Example 1

5

Method for Preparation of Libraries of Macrocyclic Pseudopeptides and Organopeptides

10

Cyclo -(Cys-Tyr-2-Nic[ψCH₂S]-Phe-D-Ala-α-acetate-
[ψCH₂S])-(11)

100mg (50micromoles) of Fmoc-Rink-Amide AM or Fmoc-Rink-Amide MBHA resin was placed in a polypropylene reaction vessel (one of 36 such vessels contained in the reaction block of an Advanced Chemtech Model 357 multiple

-114-

peptide synthesizer). Referring to Scheme III above (bold-face compound numerals and lettered steps correspond to bold-face numerals and lettered steps referred to below), steps **(a)** through **(e)** were performed robotically at room temperature according to a custom program. The resin was then washed twice with 1.5ml of N-methyl-pyrrolidinone (NMP). In Step **(a)**, the Fmoc protecting group was removed by agitating the resin with 1 ml of 30% piperidine in dimethylformamide (DMF) for 3 minutes. The resin was drained and a second 1ml portion of piperidine/DMF solution was added, agitated for 10 minutes, then drained. The resin was then washed and drained 5 to 6 times with 1.5ml portions of NMP. To the washed resin was then added 300uL of NMP followed by 1ml of a 0.5M solution of N-Fmoc-S-trityl-L-Cysteine (5 equivalents of protected amino acid to resin-bound amine) and 0.5M hydroxybenzotriazole (HOBT) in NMP and 250ul of a 1.0M solution of diisopropylcarbodiimide (DIC) in NMP. This mixture was then agitated for 45 min., drained and the resin rinsed 4 times with 1ml portions of NMP.

The coupling and rinse steps were repeated one time to yield resin-bound intermediate **6**. Single coupling was also acceptable in many cases. Intermediate **6** was then subjected piperidine, NMP washes and coupling as for step **(a)**, but with a 0.5M solution of N-Fmoc-L-Tyrosine-O-tert-butyl ether and 0.5M HOBT in NMP instead of the protected cysteine derivative to produce resin-bound intermediate **7**. In step **(c)**, **7** was subjected to the piperidine, washes and coupling regimen of steps **(a)** and **(b)**, but with a 0.5M solution of N-Fmoc-L-phenylalanyl-[Ψ CH₂S]-2-mercaptocotinate and 0.5M HOBT in NMP to give compound **8**.

Compound **9** was produced in step **(d)** by subjecting compound **8** to the piperidine wash and coupling conditions outlined in step **(a)** but with 0.5M N-Fmoc-D-Alanine and 0.5M HOBT in NMP. Terminal alpha-bromoamide **10** was made

-115-

in step (e) by treating compound 9 with piperidine/DMF, washing as in step (a), and coupling with a 0.5M solution of α -bromoacetic acid in NMP without added HOBT. HOBT is sufficiently nucleophilic to displace the bromine and should thus be omitted when coupling bromoacids.

After coupling of the terminal bromoacid, the resin was washed 4 times with 1.5ml portions of NMP, then 5 times with 1.5ml portions of methanol. After methanol washes were complete, resin containing attached compound 10 was dried at room temperature under high vacuum for at least 3 hours. The dried resin was transferred to a screw-capped vial and cleavage effected by agitating the resin with 2.5ml cleavage cocktail (38:1:1 trifluoroacetic acid(TFA):H₂O:triethylsilane (Et₃SiH) or 19:1 TFA:H₂O) for 1.5 hours at room temperature. Another 2 ml of cleavage cocktail was added and agitated for 1.5 hours, then the entire mixture was filtered through a porous plastic frit. The retentate was washed twice with 2.5 ml portions of water and the combined filtrate and washes were frozen and lyophilized to yield a yellow-orange amorphous solid. This solid was mixed vigorously with 20ml diethyl ether, chilled to -20°C and centrifuged at 15K rpm, 4°C for 10-15 minutes, then the ether was decanted. The remaining off-white pellet subjected to another ether wash and centrifugation run. Ether was decanted and the pellet allowed to air dry, at which time the white to off-white solid was dissolved in 10ml 1:1 CH₃CN:H₂O, filtered through a 0.45uM teflon filter disc, then lyophilized from a tared scintillation vial. The crude material was then cyclized by dissolution in 10ml 1:1 CH₃CN:H₂O plus 100uL of 1M DIPEA in CH₃CN.

Other bases that promoted efficient cyclization were 2,6-lutidine and proton sponge ([1,8-Bis(dimethylamino)naphthalene]). Triethylamine, pyridine and tetramethylguanidine were sufficiently nucleophilic to displace the bromine in preference to promoting

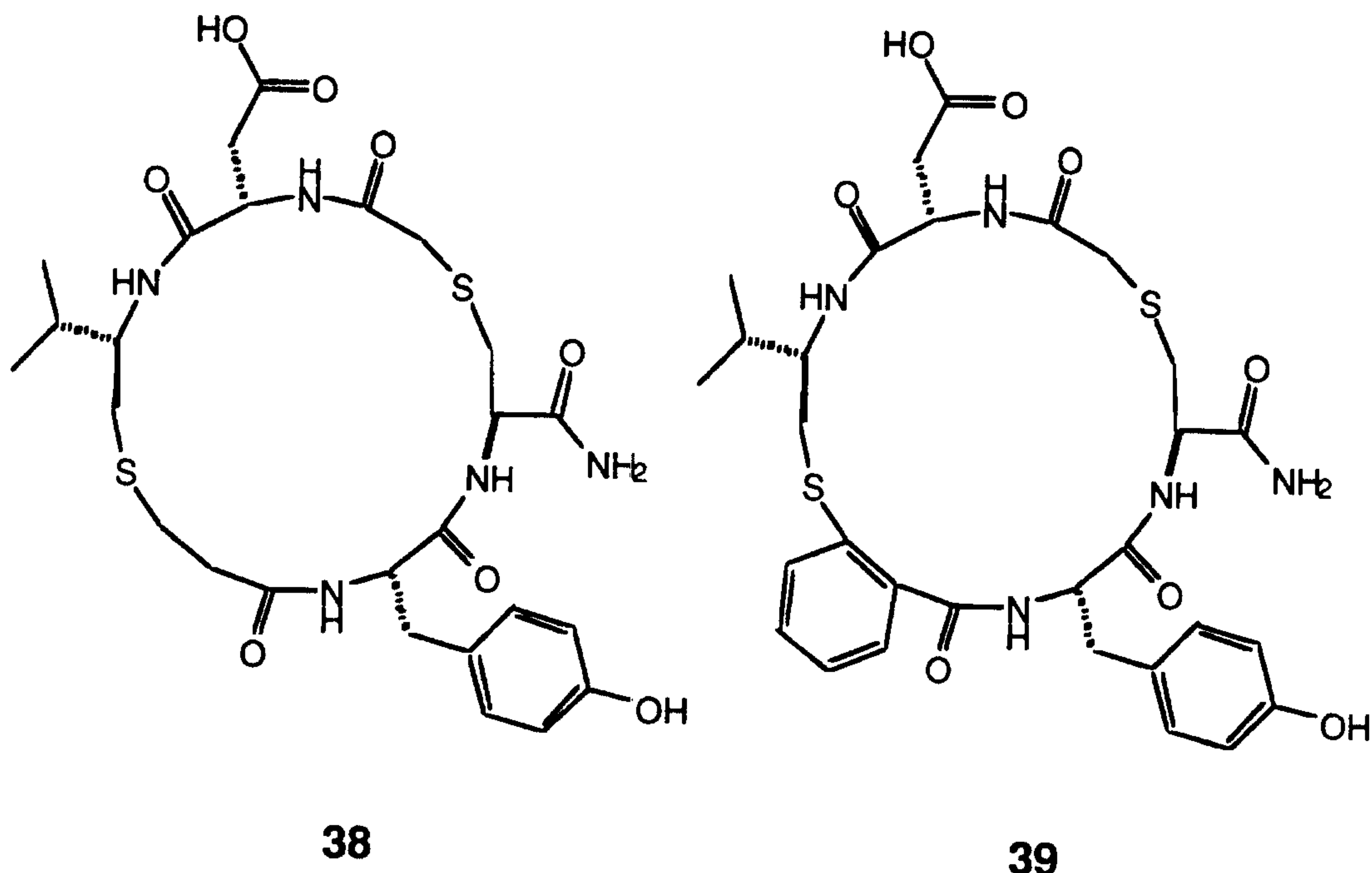
-116-

cyclization. Cyclization was allowed to proceed for 24 hours at room temperature. LCMS analysis showed a single major peak (purity~80%) having an MH⁺ of 502.2, consistent with the calculated mass for **11** of 501.4.

5 The abbreviations "Cys" and "BrA" represent cysteine and bromoacetic acid residues, respectively, and these two residues define the ligation point for ring closure. Although the majority of cycles synthesized to date use L-Cysteine for ring closure, a number of other cycles
10 have been successfully constructed with D-Cysteine. In addition, it is anticipated that other trifunctional compounds bearing an amine, an acid and a mercapto function (for example, penicillamine), are likely to function in the scheme as does the cysteine residue.
15 Also, other bromoacids will likely function in place of bromoacetic acid.

Macrocycles **38** and **39** below have been constructed and demonstrate ATA compatibility with commercially
20 available amino acids. Further, macrocycle **38** shows that ATAs provide easy access to novel macrocycles containing aryl backbone elements.

-117-

Example 2

5 Methods for Constructing Tailed Macrocyclic
 Pseudopeptides and Organopeptides.

10 According to a general method for constructing
 resins bearing both free amine group(s) and an acid
 labile carbamate linkage, described and shown below,
 11 grams (8.58 millimoles) of p-nitrophenyl carbonate
 Wang resin ("pNP-Wang" a commercially available
 material from Novabiochem, Catalog# 01-64-0123) was
 swollen with 75ml of 1:1 dichloromethane (DCM or
 15 CH₂Cl₂:N-methylpyrrolidinone (NMP), then combined with
 a 100ml solution containing 429mmols (5 equivalents) of
 the diamine of choice. The resulting bright yellow
 slurry is then agitated on a peptide shaker, rotor or
 other mixing device for 24-48 hours at room
 20 temperature. The slurry is next drained using a fritted
 funnel or peptide shaker flask, then washed with 200ml
 each of DCM, NMP and methanol. The wash cycle (DCM, NMP
 and methanol) is repeated twice more, then the resin is

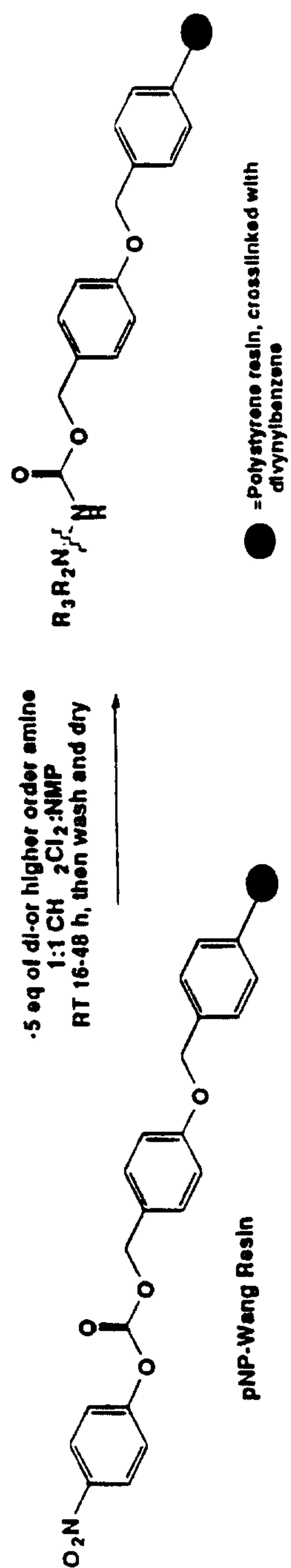
-118-

dried under high vacuum for several days to provide the desired product in quantitative yield based upon mass change.

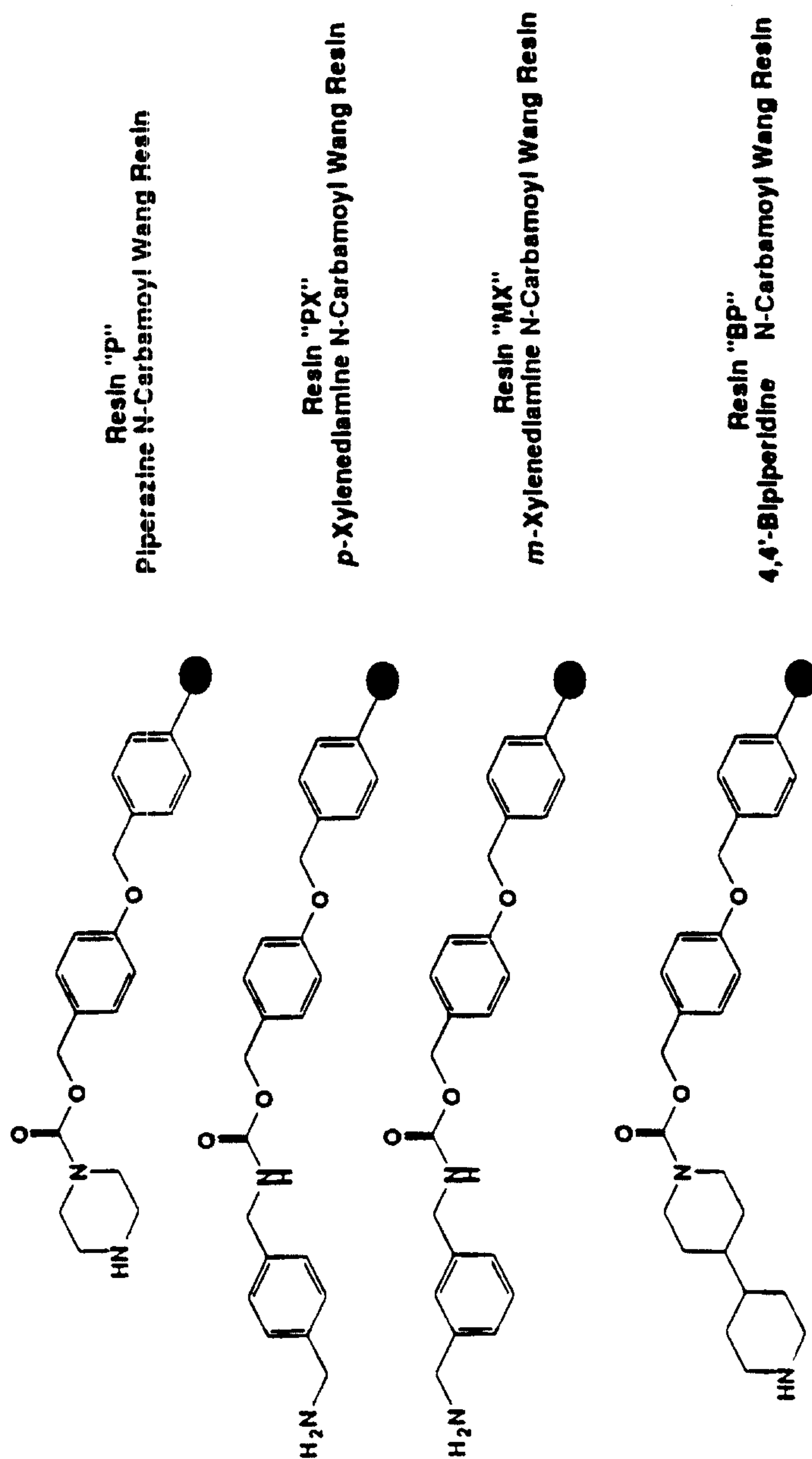
5 By this method was prepared piperazine-N-carbamoyl-Wang (resin P) (loading: 0.81mmol/gram of resin) as well as both *p*- and *m*-xylenediamine-N-carbamoyl-Wang resins (resins PX and MX, respectively at 0.78mmol/gram) in multigram quantities.

10 Alternatively, the desired diamine (or higher order amine) can be similarly attached to resin in situ by mixing at least a five-fold molar excess of di- or higher order amine with pNP-Wang resin in 1:1 DCM:NMP for 16-48 hours at room temperature. After washing as
15 above, the resin contains at least one free amino function ready for elaboration and at least one acid labile carbamoylated amine function as the link to resin.

General Scheme for Appending Diamines and Higher
Order Amines to pNP-Wang Resin

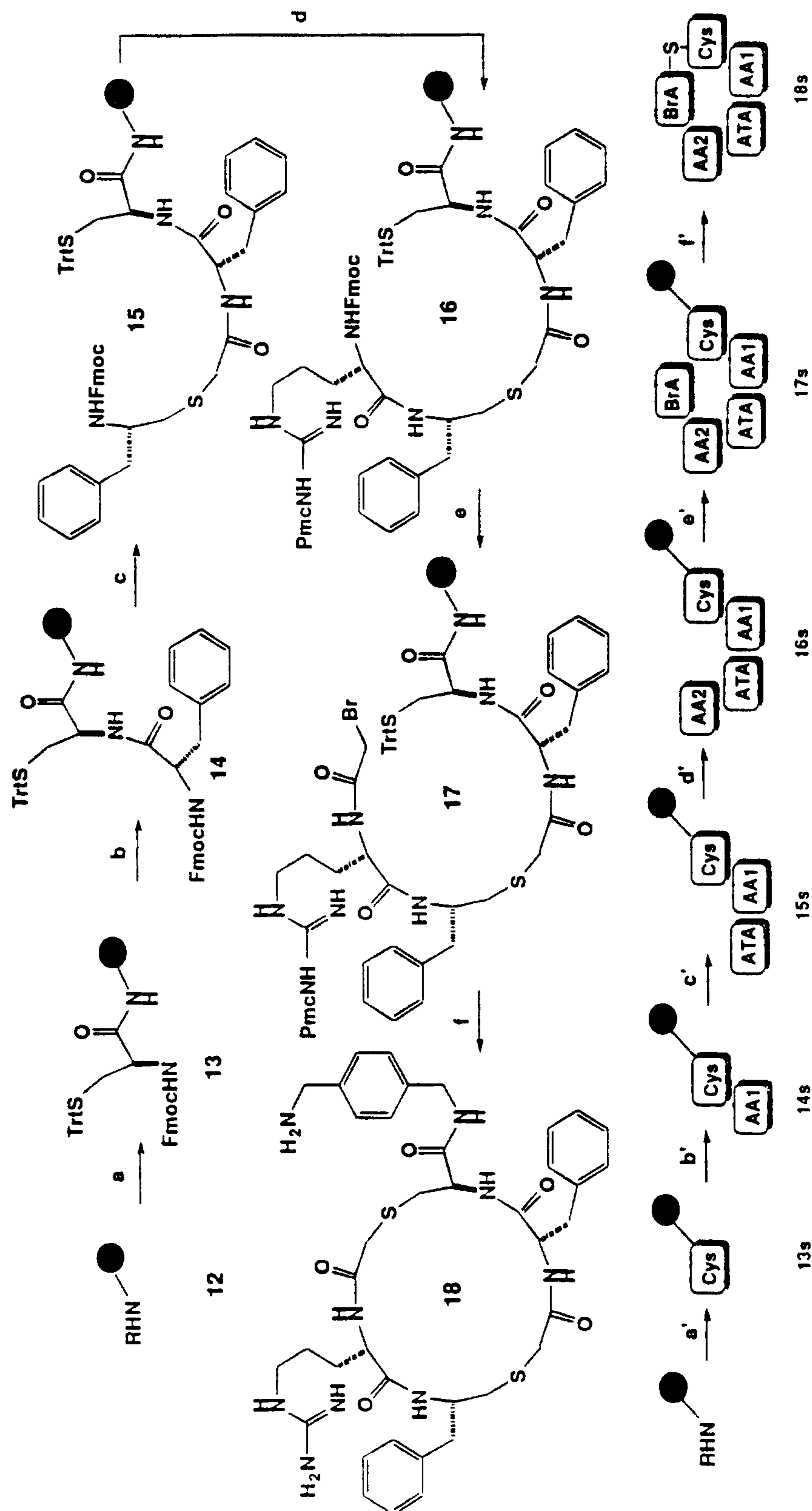


Some Specific Examples of Resin Generated as Described Above:



N-p-xylenediamino-Cyclo-(Cys-Phe-Gly[Ψ CH₂S]-Phe-Arg- α -acetate-[Ψ CH₂S]) (18, Scheme IV)

Scheme IV
 Scheme for Constructing Tailed Macrocycles
 Where 12=Resin Such as P, PX, MX, etc.



5 Steps: a) PX-Wang resin, then 5 eq Fmoc-S-trityl-L-cysteine, DIC/HOBT in NMP, wash; b) 30% piperidine in DMF, wash, then 5 eq Fmoc-L-phenylalanine; c) as for b), but with 5 eq of Fmoc-L-Phe[ψCH₂S]-Gly-OH; d) as for b), but with 5 eq of Fmoc-L-Arg(Pmc)-OH where Pmc is defined below; e) as for b), but with 5 eq bromoacetic acid and DIC in NMP without HOBT; f) 38:1:1 TFA:H₂O:Et₃SiH for 24 hr., lyophilize, then 2 eq of diisopropylethylamine in 1:1 CH₃CN:H₂O.

10 With respect to Scheme IV (bold-face compound numerals and lettered steps correspond to bold-face compound numerals and lettered steps referred to below), 65mg (50micromoles) of PX resin was placed in a polypropylene reaction vessel (one of 36 such vessels
15 contained in the reaction block of an Advanced Chemtech Model 357 multiple peptide synthesizer). Referring to Scheme IV, steps (**a**) through (**e**) were performed robotically at room temperature according to a cumtom program written by the bench chemist. The resin was
20

25

30

35

-121-

washed and drained twice with 1.5ml of N-methyl-pyrrolidinone (NMP). In Step (a), to washed resin was then added 300uL of NMP followed by 1ml of a 0.25M solution of N-Fmoc-S-trityl-L-Cysteine (5 equivalents of protected amino acid to resin-bound amine) and 0.25M hydroxybenzotriazole (HOBT) in NMP and 250ul of a 1.0M solution of diisopropylcarbodiimide (DIC) in NMP. This mixture was then agitated for 45 min., drained and the resin rinsed 4 times with 1ml portions of NMP. The coupling and rinse steps were repeated one time to yield resin-bound intermediate **13**. Single coupling was also acceptable in many cases. In Step (b), the Fmoc protecting group of **13** was removed by agitating resin with 1 ml of 30% piperidine in dimethylformamide (DMF) for 3 minutes. The resin was drained and a second 1ml portion of piperidine/DMF solution was added, agitated for 10 minutes, then drained. Resin was then washed and drained 5 to 6 times with 1.5ml portions of NMP. To washed resin was then added in succession 300uL of NMP, 1ml of a solution 0.25M each in N-Fmoc-L-Phenylalanine and HOBT and 250ul of a 1.0M solution of diisopropylcarbodiimide (DIC) in NMP. This mixture was then agitated for 45 min., drained and the resin rinsed 4 times with 1ml portions of NMP. The coupling and rinse steps were repeated one time to yield resin-bound intermediate **14**. In step (c), **14** was subjected to piperidine, washing and coupling regimen of step (b), but instead with N-Fmoc-L-phenylalanyl- $[\psi\text{CH}_2\text{S}]$ -glycine to give **15**. Compound **16** was produced in step d by subjecting **15** to the piperidine, wash and coupling conditions outlined in step (b) but with N-Fmoc-L-Arginine(Pmc) as the amino acid [where Pmc=2,2,5,7,8-Pentamethylchroman-6-sulfonyl, an acid labile arginine side chain protection function]. Terminal alpha-bromoamide **17** was made in step (e) by treating **16** with piperidine/DMF, washing as in step (b), and coupling

-122-

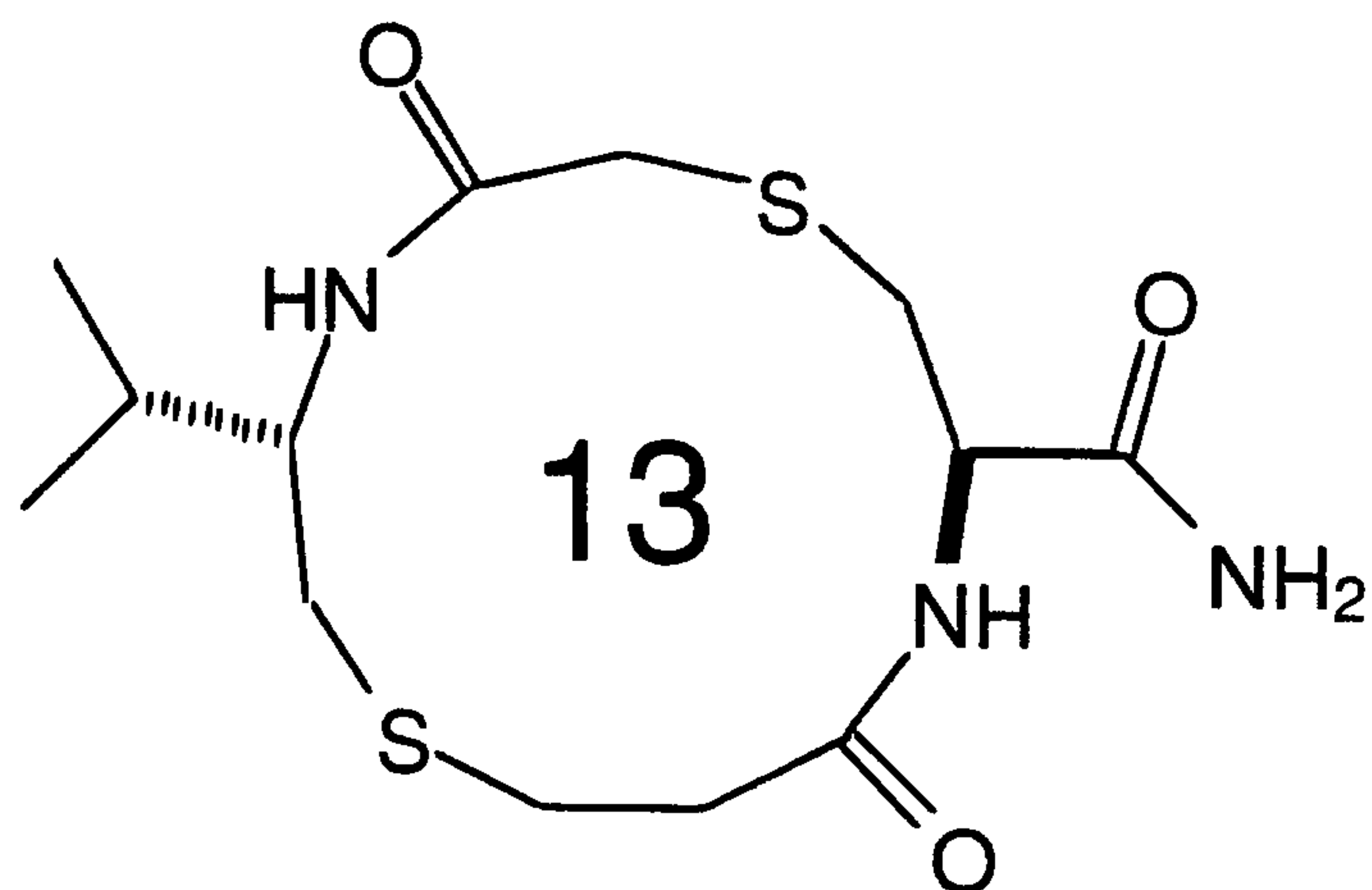
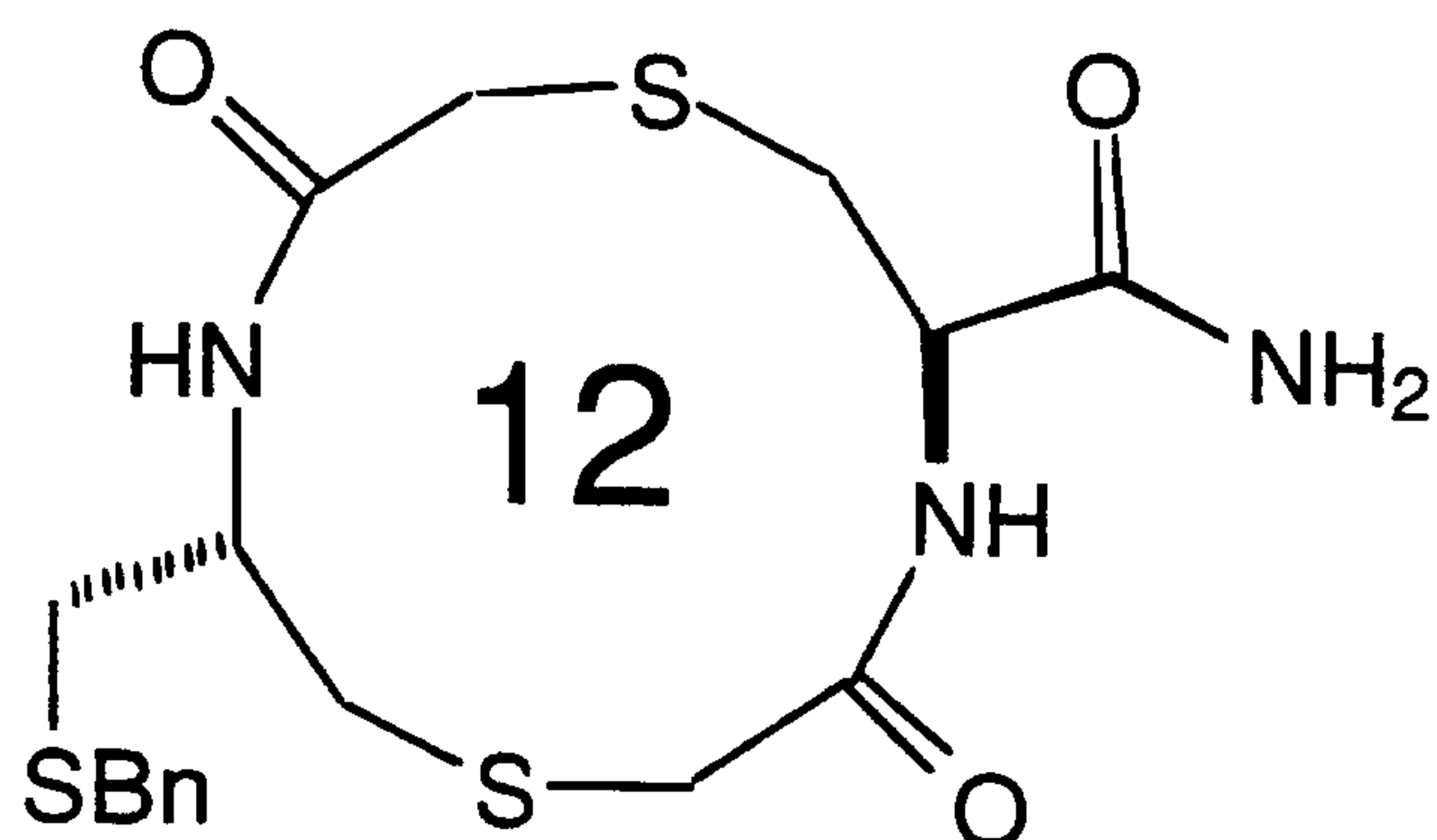
with a 0.25M solution of alpha-bromoacetic acid in NMP without added HOBT. HOBT is sufficiently nucleophilic to displace the bromine and should thus be omitted when coupling bromoacids in this step. After coupling of the terminal bromoacid, the resin was washed 4 times with 1.5ml portions of NMP, then 5 times with 1.5ml portions of methanol. After methanol washes were complete, resin containing attached **17** was dried at room temperature under high vacuum for at least 3 hours. The dried resin was transferred to a screw-capped vial and cleavage effected by agitating the resin with 2.5ml cleavage cocktail (38:1:1 trifluoroacetic acid(TFA):H₂O: triethylsilane (Et₃SiH) or 19:1 TFA:H₂O) for 1.5 hours at room temperature. Another 2 ml of cleavage cocktail was added and agitated for 1.5 hours, then the entire mixture was filtered through a porous plastic frit. The retentate was washed twice with 2.5 ml portions of water and the combined filtrate and washes were frozen and lyophilized to yield a yellow amorphous solid. Workup and cyclization were performed as in Example 1 above. Cyclization was allowed to proceed for 24 hours at room temperature. LCMS analysis showed a single major peak (purity~80%) having an MH⁺ of 790.4 and an [M+2H]²⁺ of 395.8, consistent with the calculated mass for **18** of 789.

The bottom part of the scheme depicts a generic form of the synthetic method used to construct macrocycles such as **18**. "Cys" and "BrA" represent the cysteine and bromoacetic acid residues, respectively and these two residues define the ligation point for ring closure. Though the majority of cycles synthesized used L-Cysteine for "Cys", a number of cycles were successfully constructed with D-Cysteine at the "Cys" position.

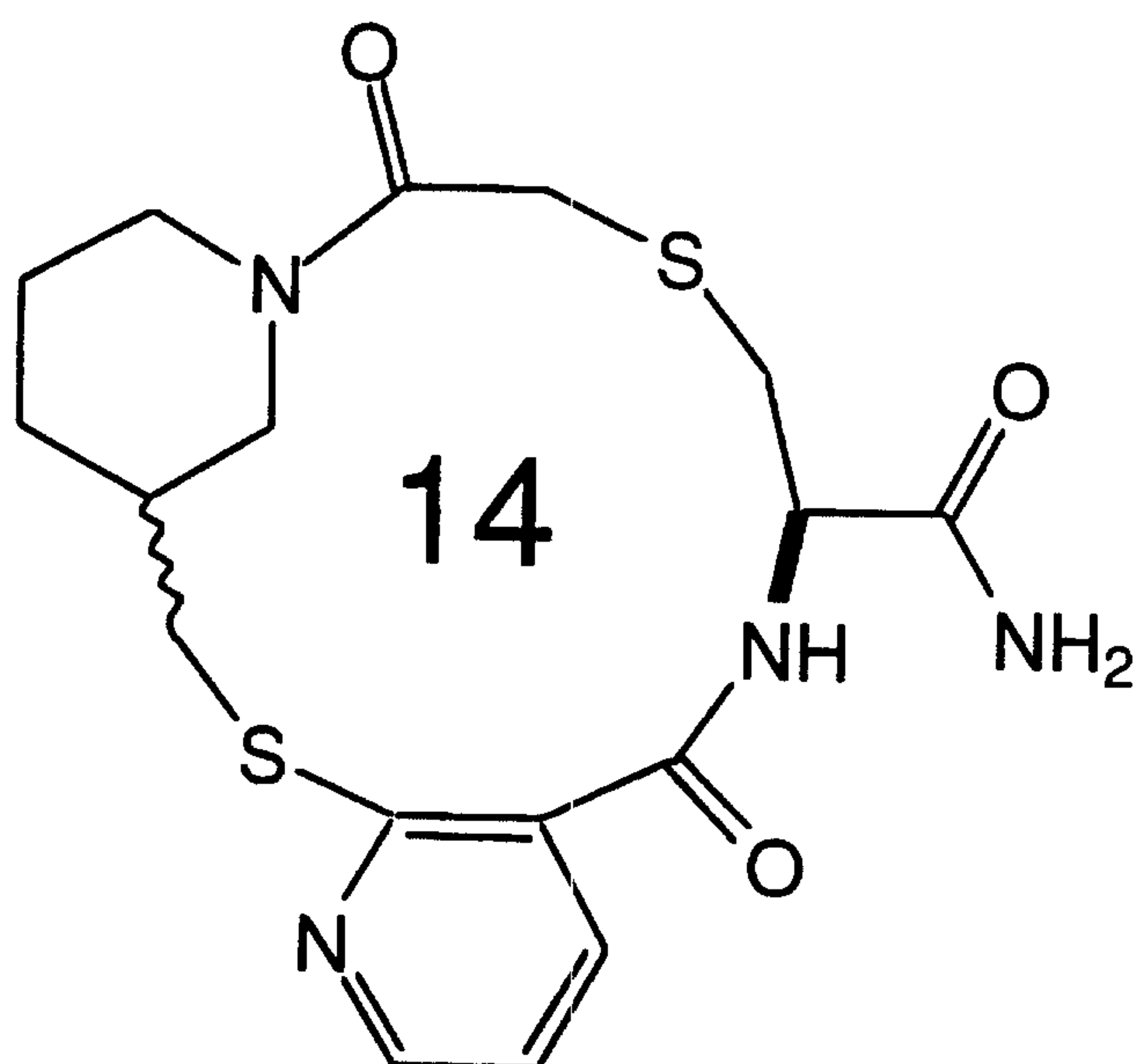
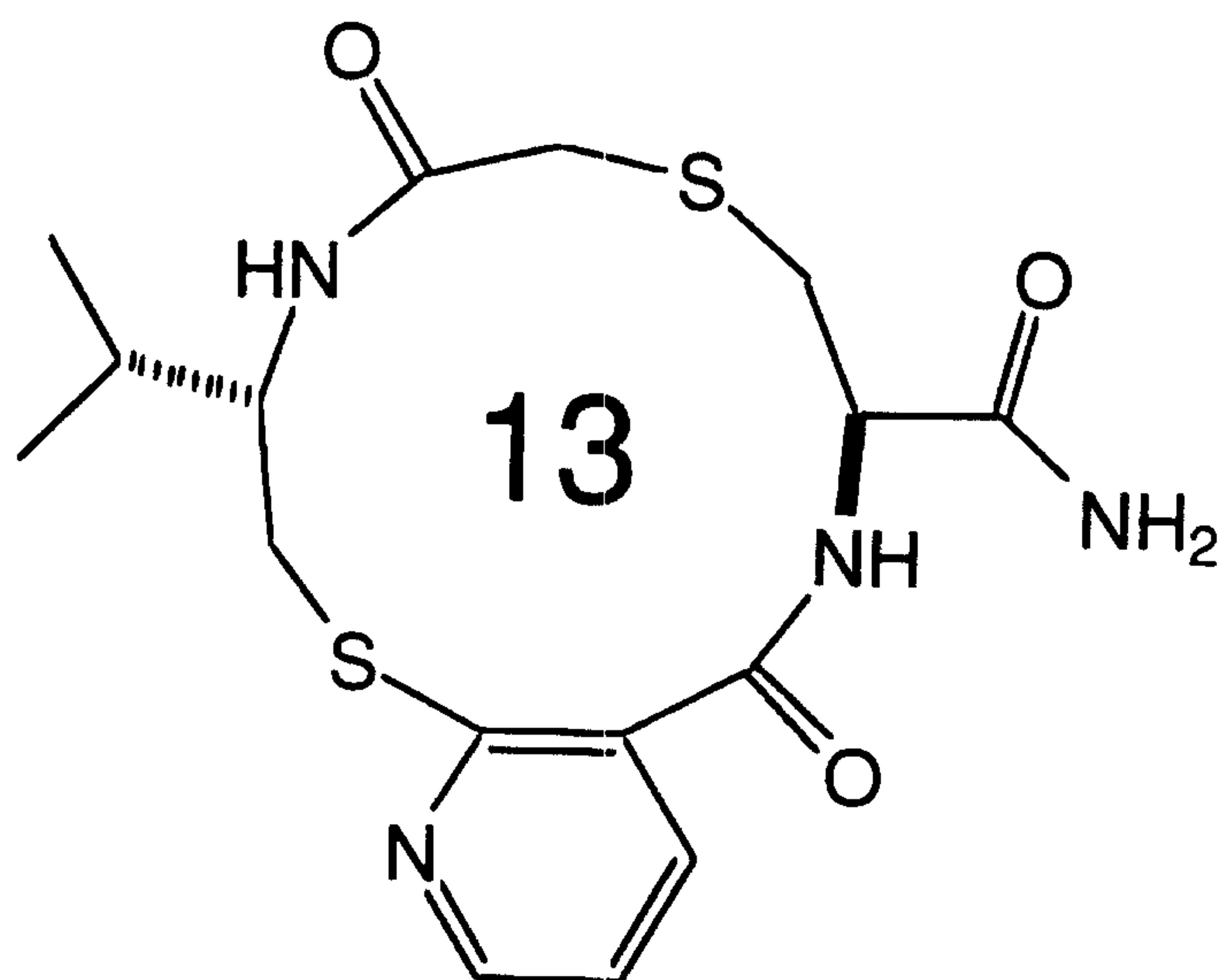
-123-

Example 3

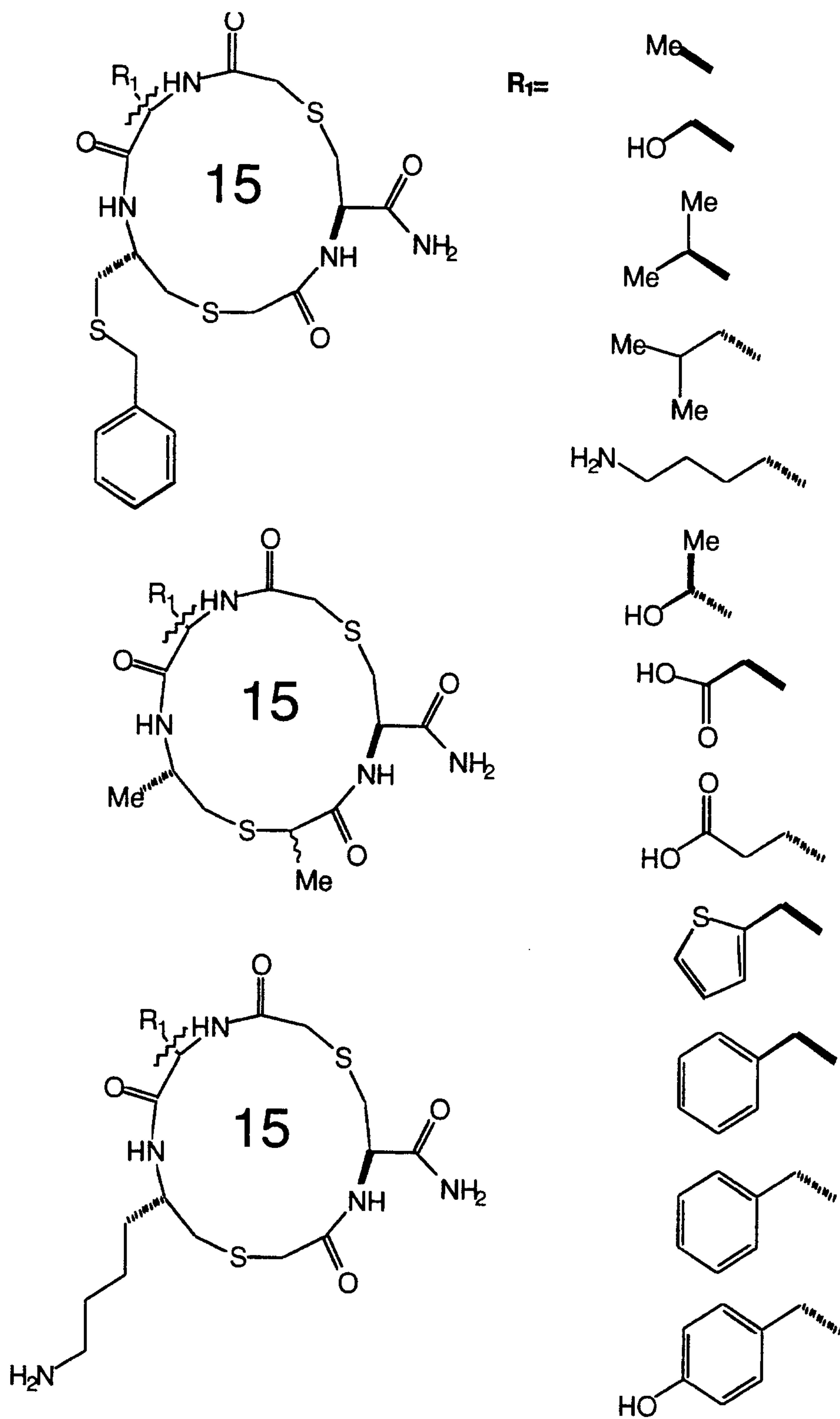
Following the procedures of Example 1 above, the following library compounds have been prepared. The number within the ring specifies the number of ring atoms.



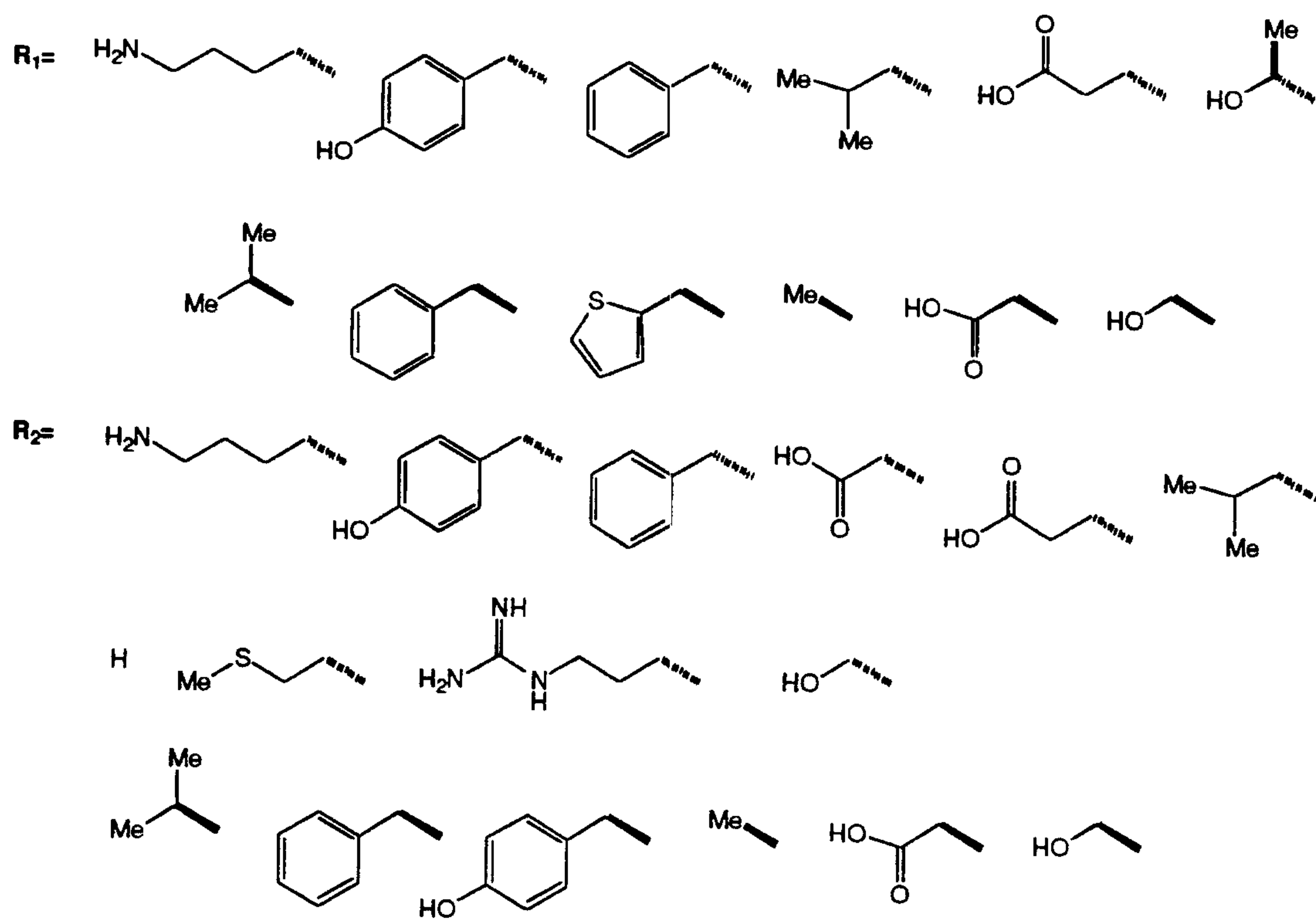
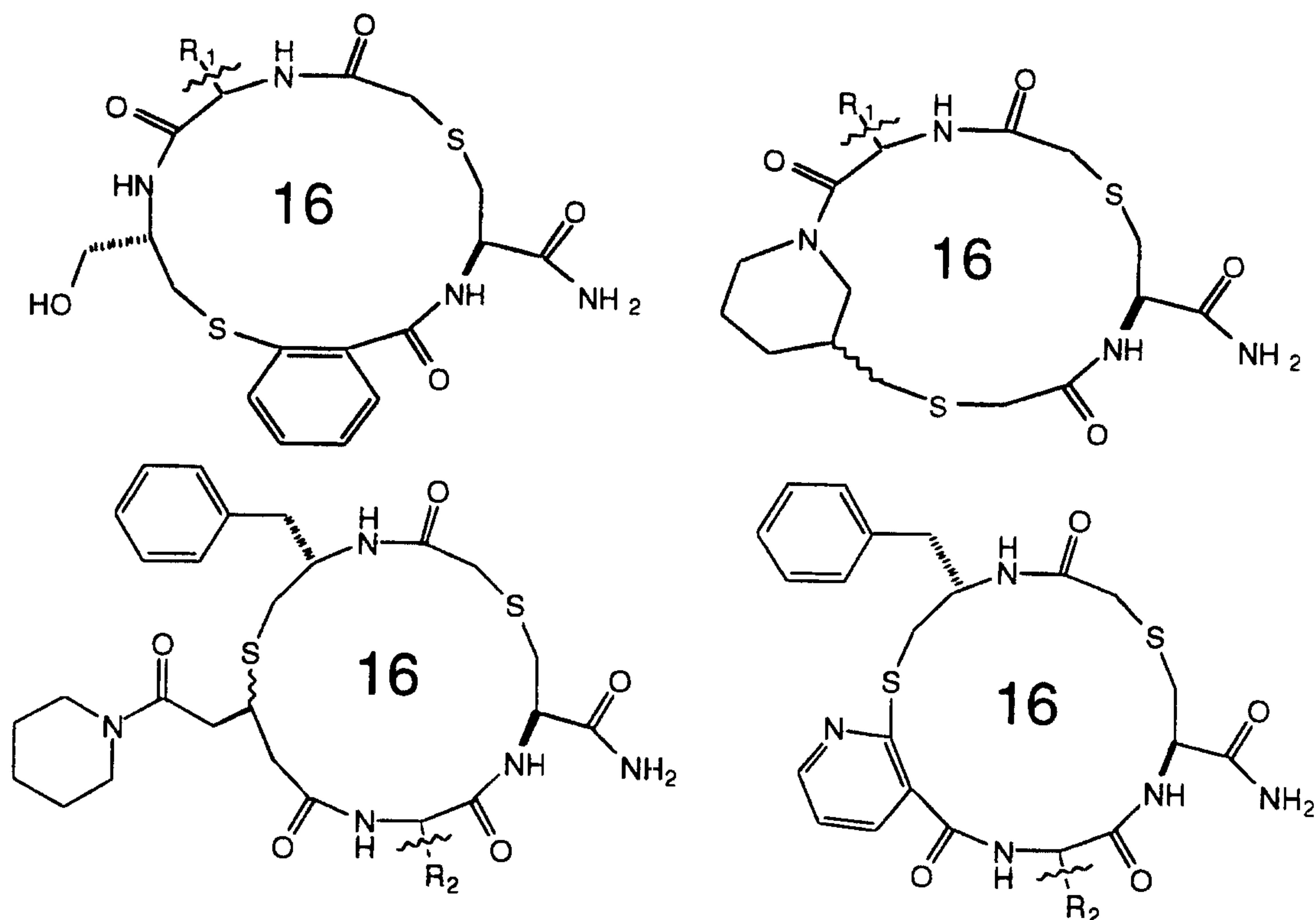
-124-



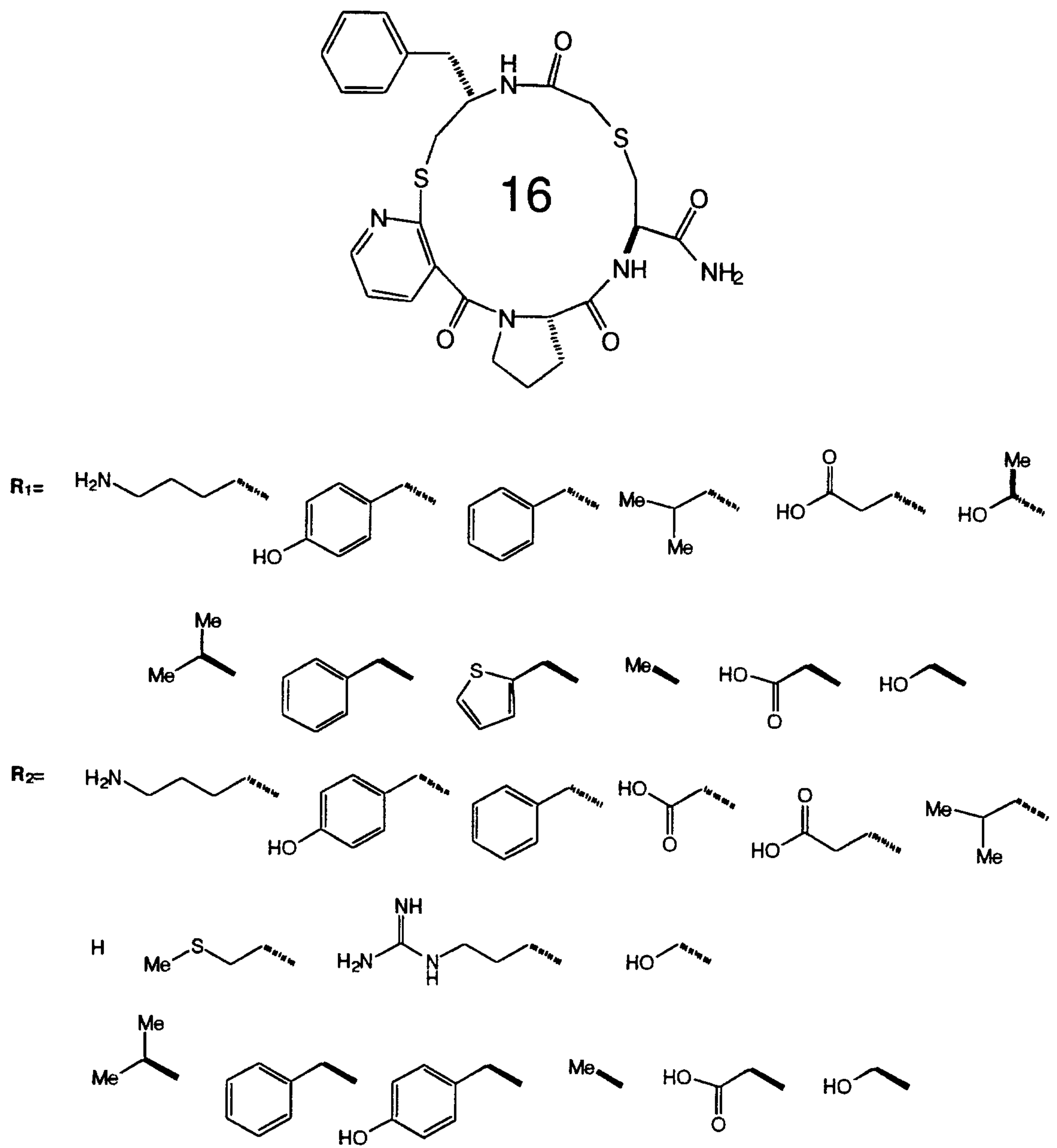
-125-



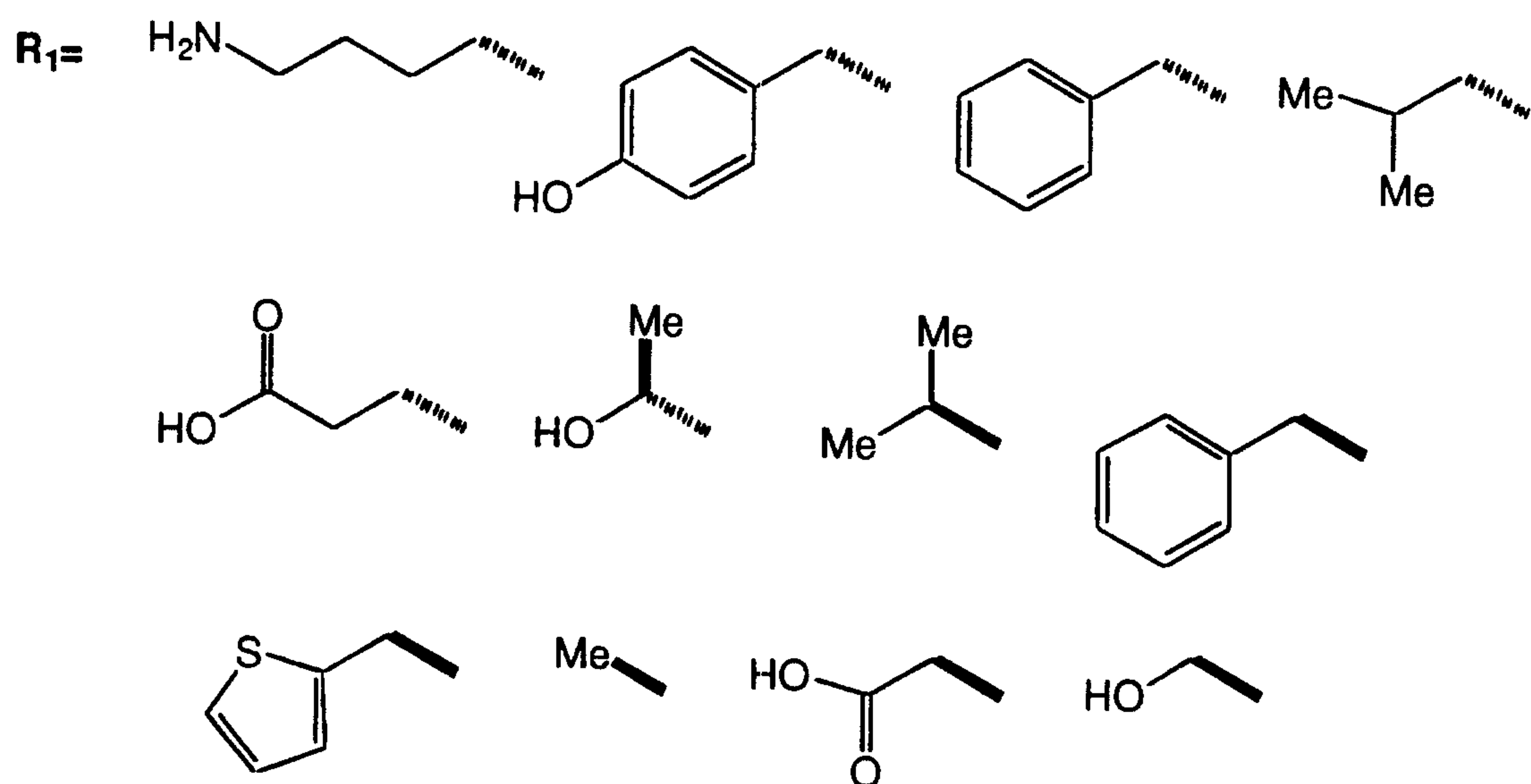
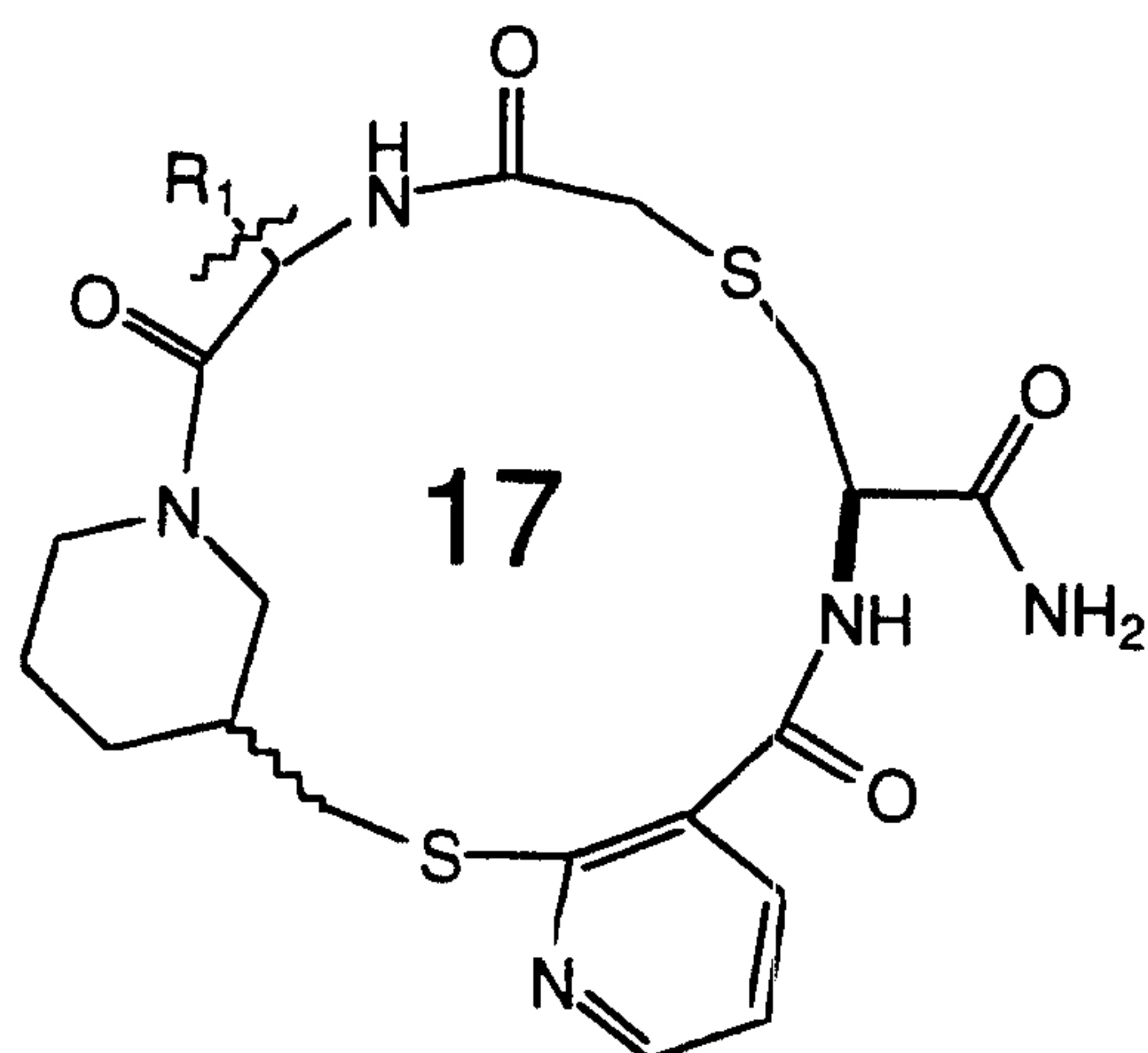
-126-



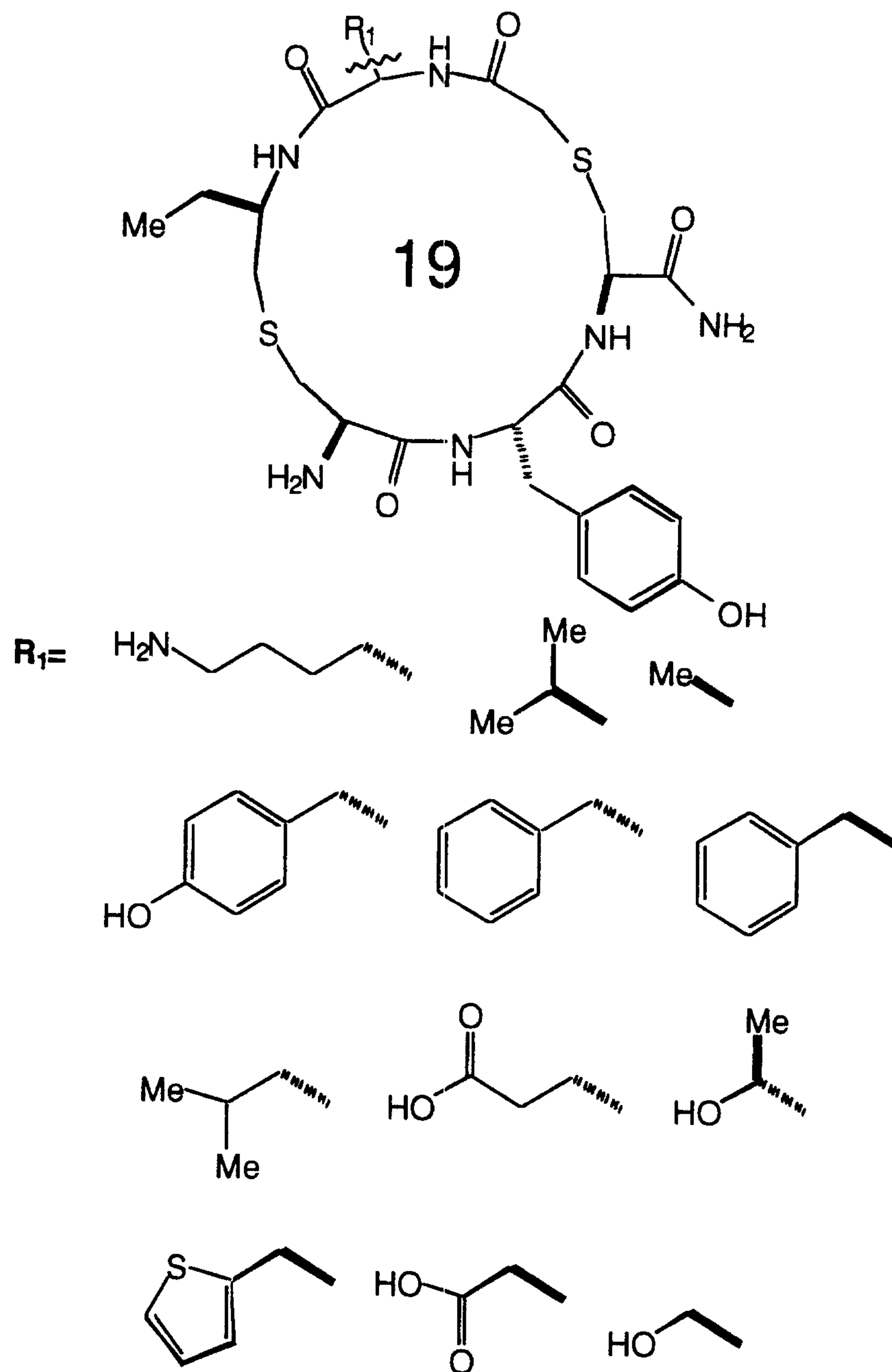
-127-



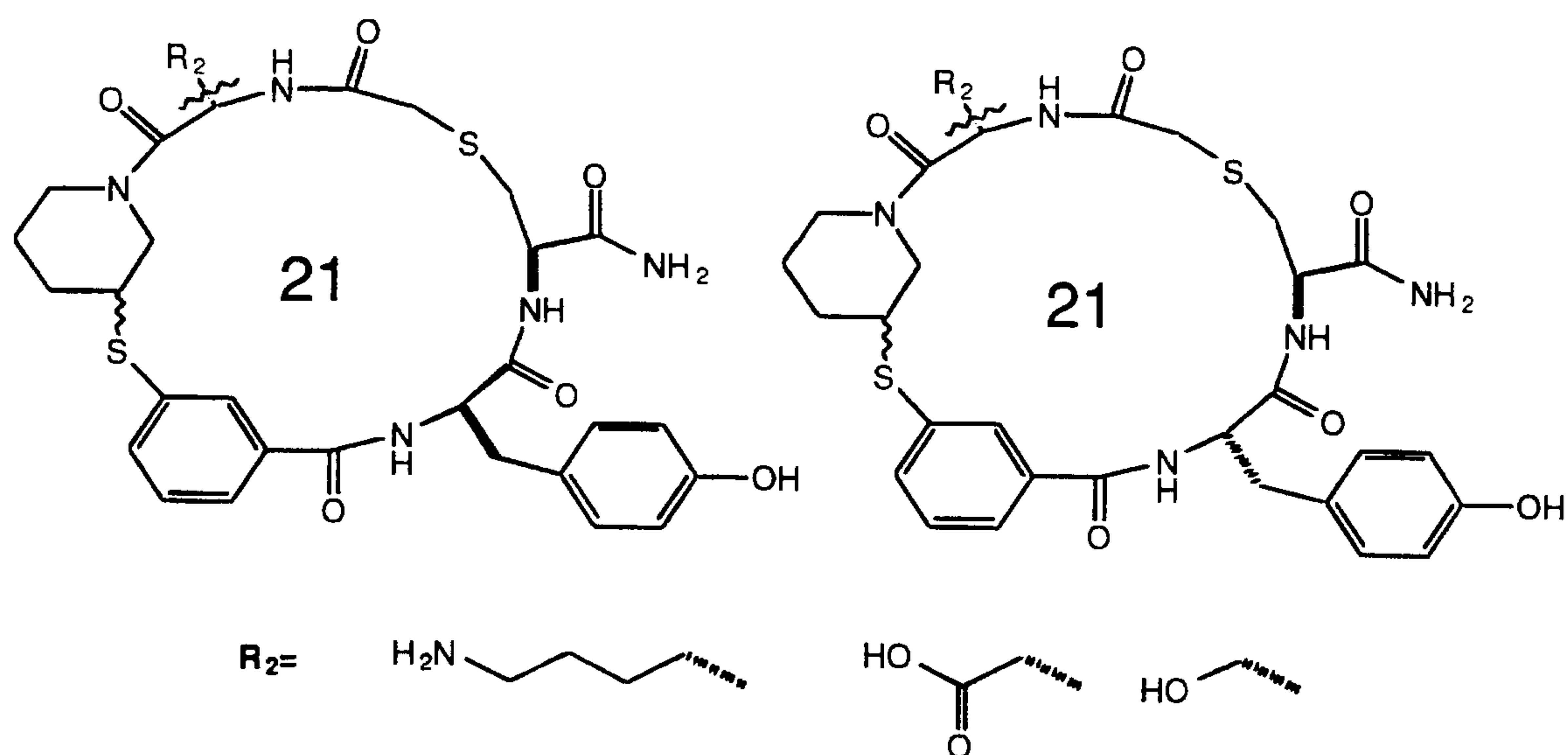
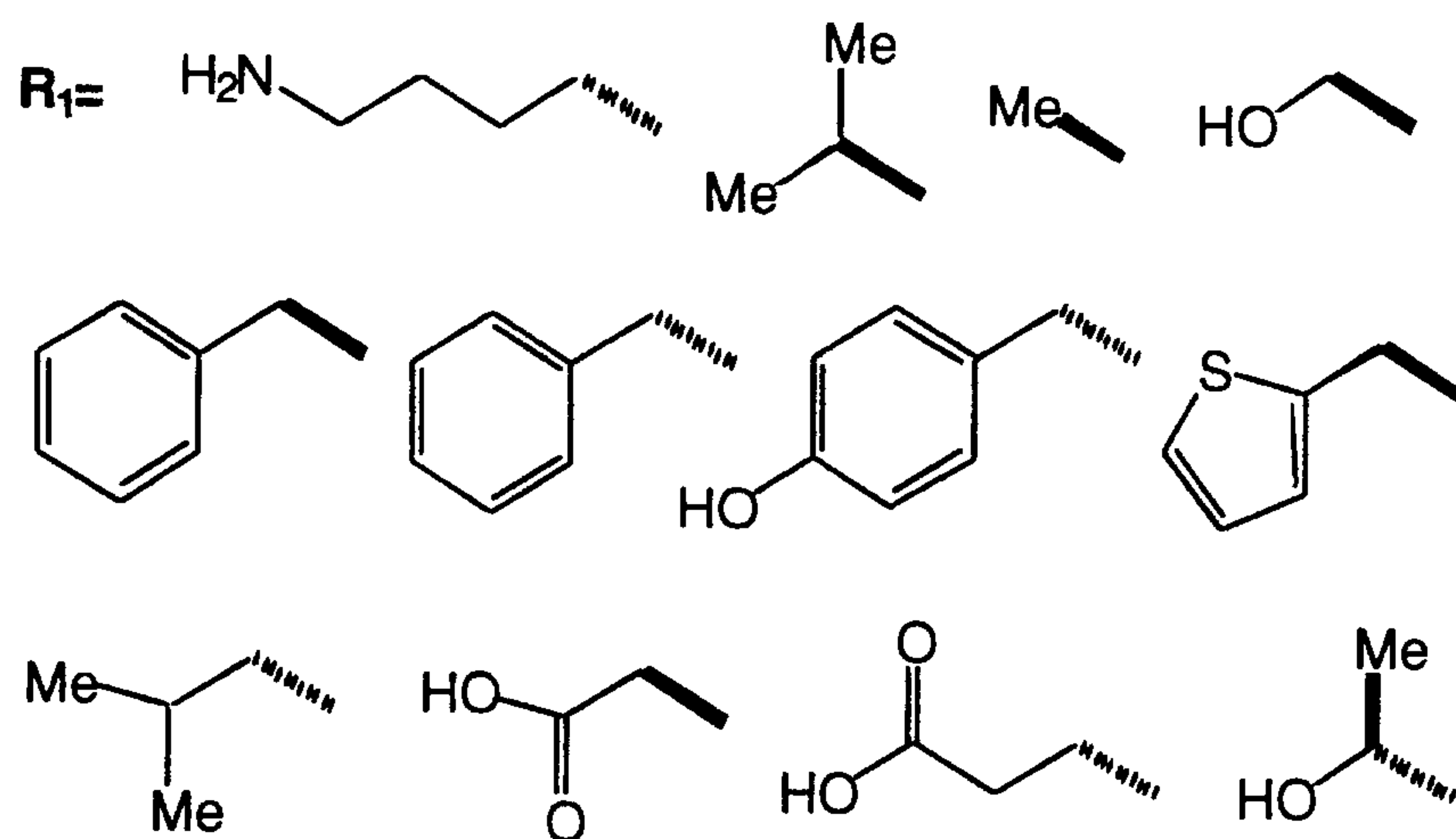
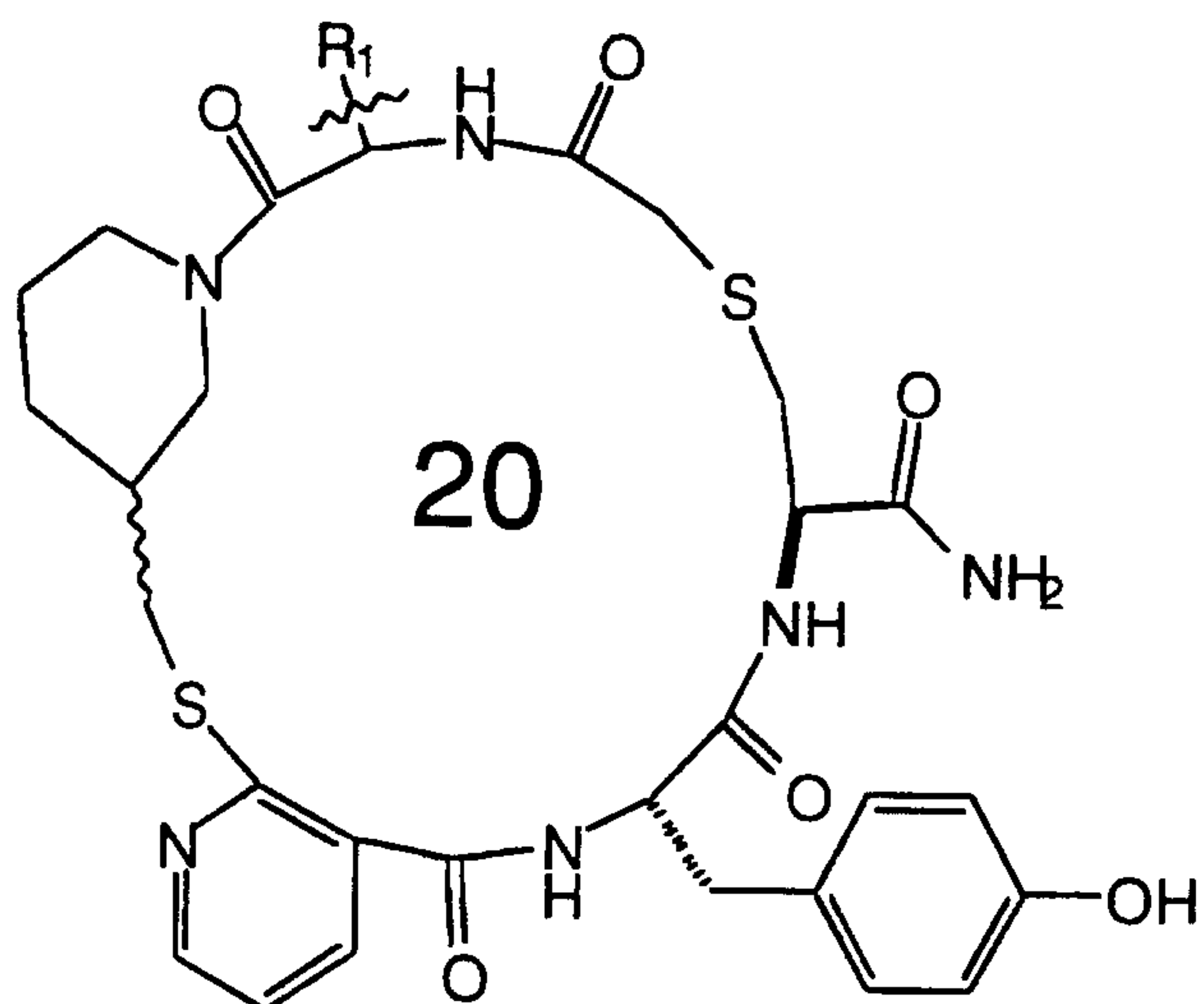
-128-



-130-



-131-



wherein E is hydrogen, a solid support or a substituent derived from an electrophilic reagent, T is a divalent linking group, and R_Y" is hydrogen or a substituent derived from an electrophilic reagent; or R_Y and R_Y" taken together with the atoms to which they are bonded form a 6- to 7-membered ring or a bicyclic or tricyclic ring comprising 6 to 12 carbon atoms; or R_Y or

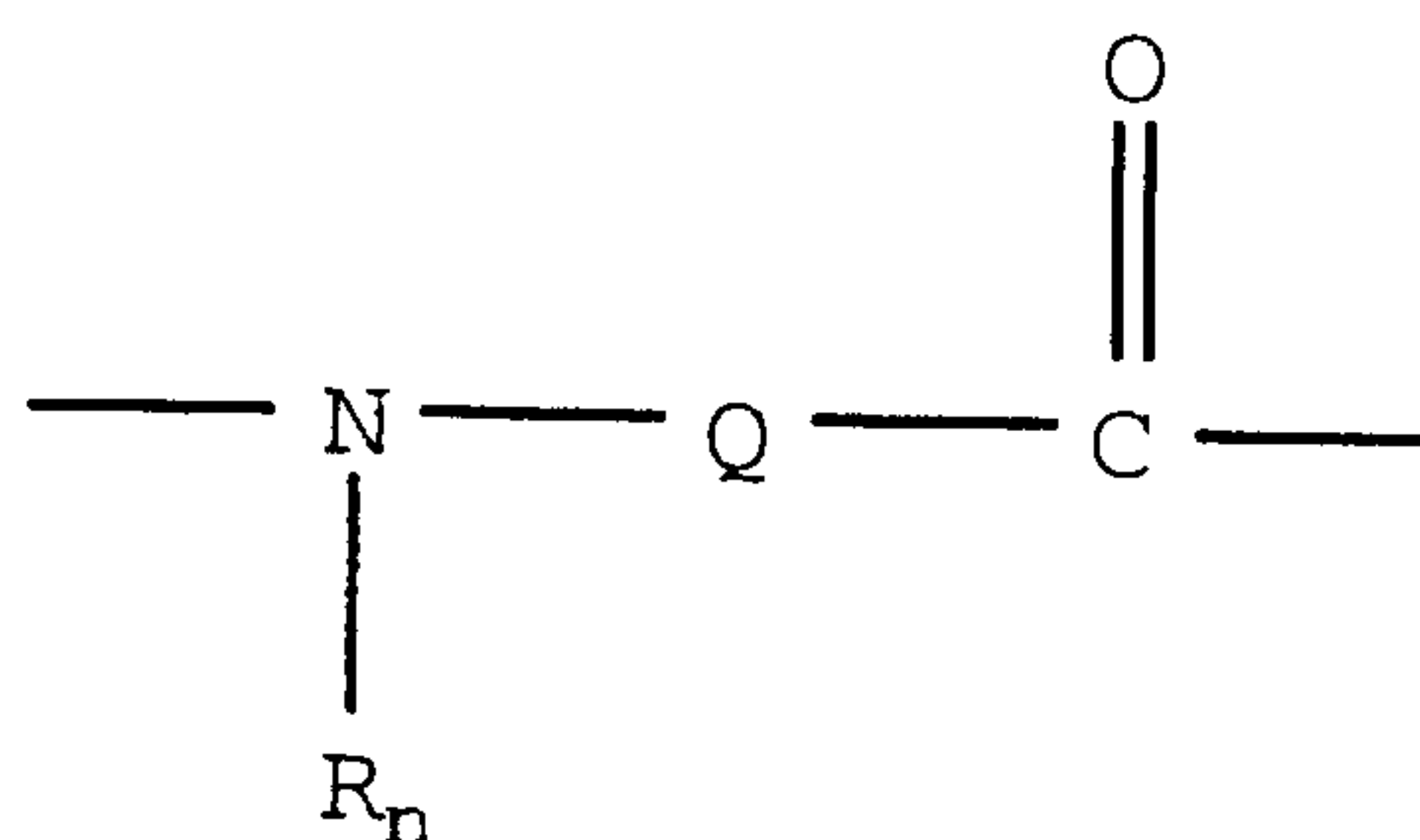
-133-

R_y" taken together with -T- and the atoms to which they are commonly bonded form a 4- to 7-membered ring or R_y and R_y" each taken together with T and the nitrogen atom to which they are respectively bonded form a 5- to 7-membered ring;

Z is a divalent group of the formula

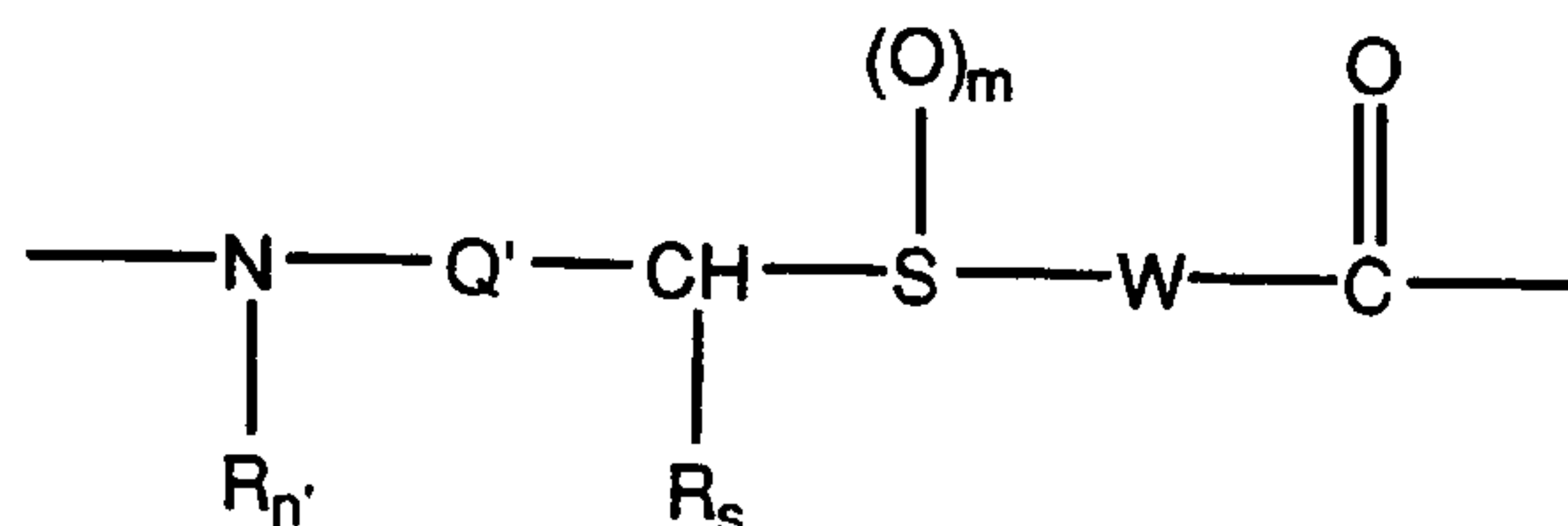
^a(AA₁)a₁-(AA₂)a₂-(ATA₁)t₁-(AA₃)a₃-(ATA₂)t₂-(AA₄)a₄-(ATA₃)t₃-(AA₅)a₅-(AA₆)a₆^b

wherein each of AA₁-6 is independently a divalent group of the formula



and

each of ATA₁-3 is independently a divalent sulfur group of the formula



and

wherein a₁, a₂, a₃, a₄, a₅, a₆, t₁, t₂, and t₃ are independently 0 or 1, provided that t₁ + t₂ + t₃ = 1, 2 or 3; and provided further that -Z- is selected to provide a 12- to 40-membered macrocycle ring of Formula I;

wherein in the above formulas for AA₁-6 and ATA₁-3,

-134-

W is a divalent organic group comprising 1 to 12 carbon atoms and 0 to 4 heteroatoms selected from O, N and S;

Q and Q' are each independently an organic group comprising 1 to 12 carbon atoms and 0 to 4 heteroatoms selected from O, N and S;

m is 0, 1 or 2;

R_S is hydrogen or an organic moiety; and

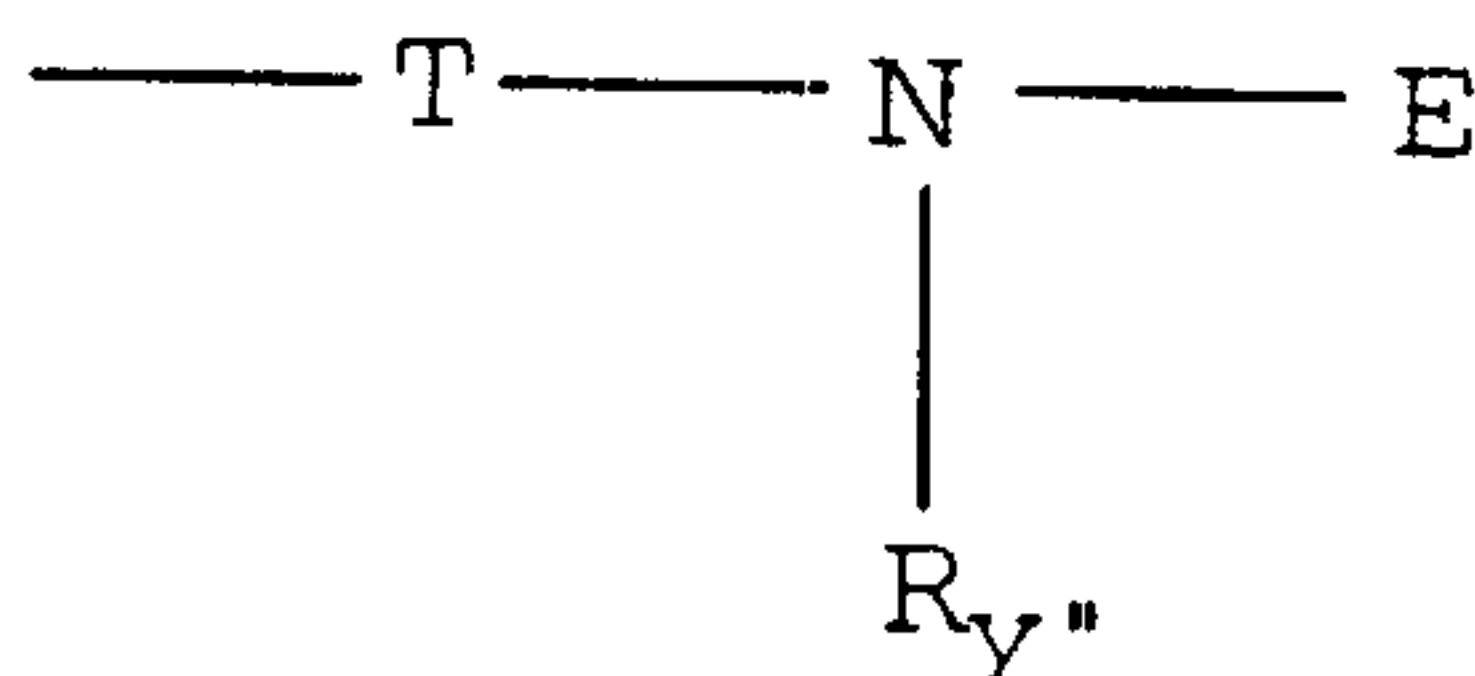
R_N' is hydrogen, or an organic moiety, or R_N taken together with Q and the atoms to which they are bonded form a 4- to 7-membered ring;

R_N' and R_S taken together with -Q'- and the atoms to which they are bonded form a 4- to 7-membered ring or a bicyclic or tricyclic ring comprising 6 to 12 carbon atoms; or

R_N' or R_S taken together with -Q'- and the atoms to which they are commonly bonded form a 4- to 7-membered ring.

2. The library of claim 1 wherein B is amino.

3. The library of claim 1 wherein B is a group of the formula -NR_YR_T wherein R_Y is hydrogen, alkyl, aryl or heterocycle and R_T is hydrogen, a solid support, or R_T is a group of the formula



4. The library of claim 3 wherein E is hydrogen.

5. The library of claim 3 wherein E is a substituent derived from an organic electrophilic agent.

-135-

6. The library of claim 1 wherein
 $a_1 + a_2 + a_3 + a_4 + a_5 + a_6 = 1, 2 \text{ or } 3.$

7. The library of claim 6 wherein
 $t_1 + t_2 + t_3 = 1 \text{ or } 2.$

8. The library of claim 1 wherein each -AA- is a
 divalent group derived from a proteiogenic amino acid and
 isomers thereof.

10

9. The library of claim 1 wherein W is a divalent
 organic group selected from the group consisting of
 -CHR₈-, -CR₄R₅CR₆R₇-, and a 5- or 6-membered aromatic
 ring containing 0 to 4 heteroatoms selected from O, N and
 15 S;

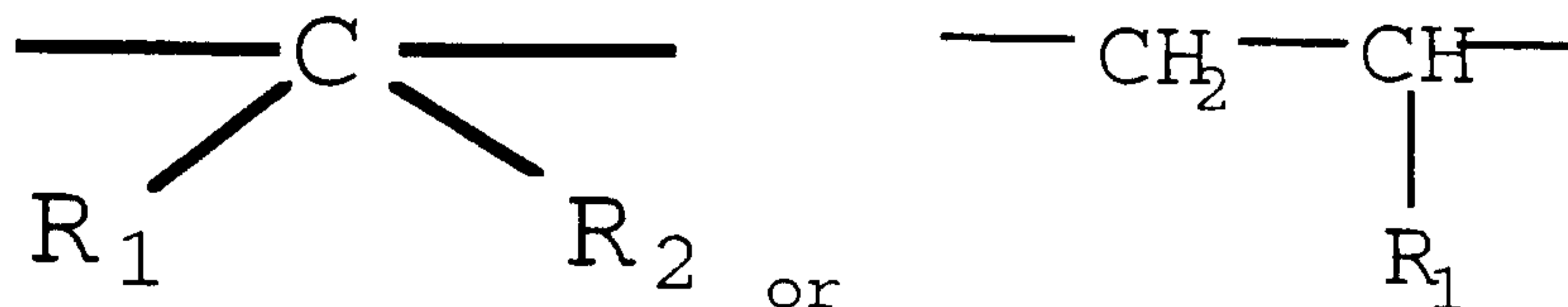
wherein R₈ is hydrogen or an organic group;

R₄, R₅, and R₆ are independently hydrogen or alkyl;
 and

R₇ is hydrogen, hydroxy, protected hydroxy, amino or
 20 protected amino or substituted amino wherein the
 substituent is derived from an electrophilic group.

10. The library of claim 1 wherein Q is a group of
 the formula

25



wherein R₁ is hydrogen, or a non-interfering
 substituent; and

30 R₂ is hydrogen or an organic moiety; or

R₁ taken together with R_n forms a 4- to 7-membered
 ring, or R₁ taken together with R_s forms a 4- to 7-
 membered ring; or R₁ taken together with R₂ forms a 3- to
 6-membered ring.

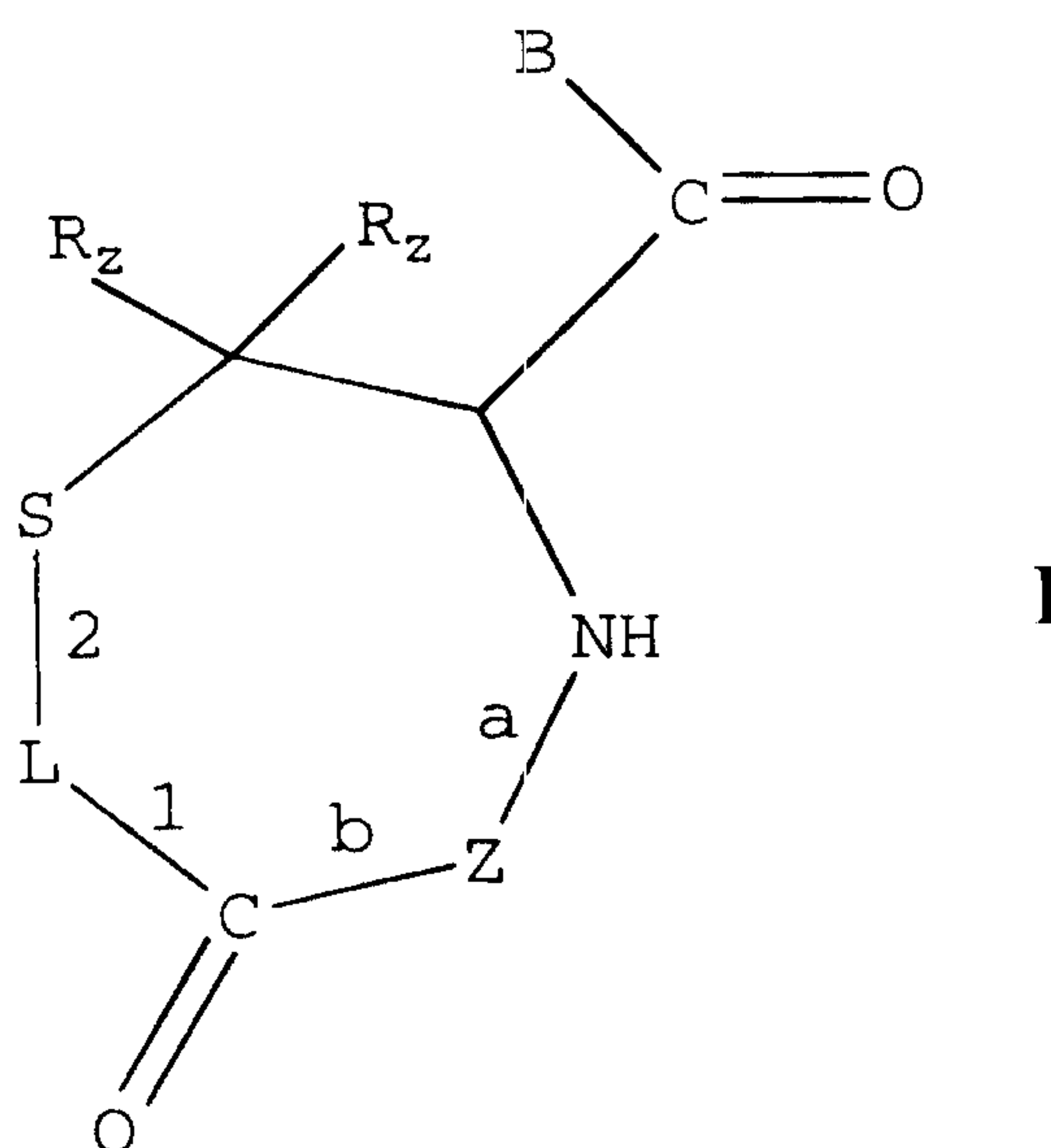
WO 98/46631

PCT/US98/07135

-136-

11. The library of claim 1 wherein -Z- is selected to provide a 12 to 24 membered macrocycle of Formula I.

5 12. A library of macrocyclic compounds of the formula



wherein

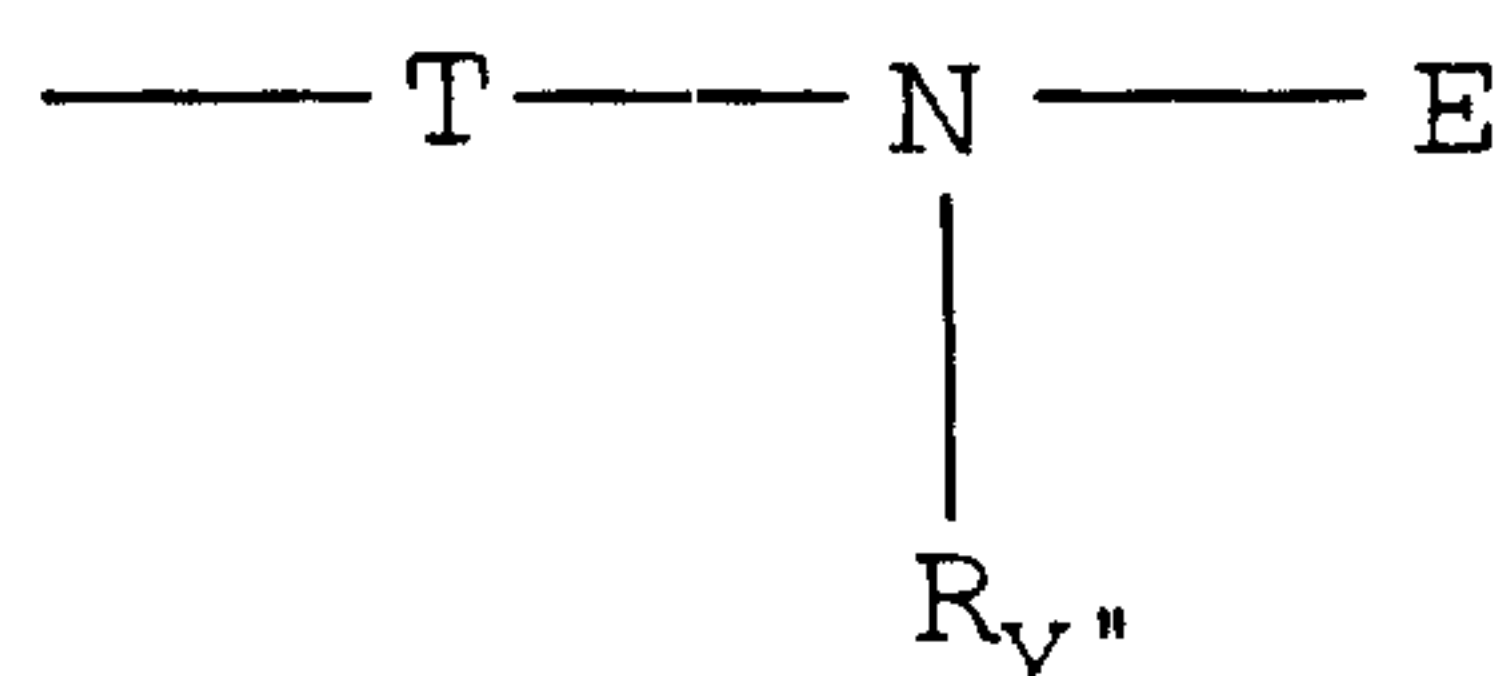
10 L is a divalent group of the formula ¹ (CH₂)₀₋₁-C₆H₄CH₂² or -CHR_a- wherein R_a is hydrogen or an organic moiety;

R_Z is hydrogen or methyl;

B is hydroxy or a group of the formula -NR_yR_t

wherein R_y is hydrogen, alkyl, aryl or heterocycle, and

15 R_t is hydrogen, a solid support, or R_t is a group of the formula



20 wherein E is hydrogen, a solid support or a substituent derived from an electrophilic reagent, T is a divalent linking group, and R_y'' is hydrogen or a substituent derived from an electrophilic reagent; or R_y and R_y'' taken together with the atoms to which they are

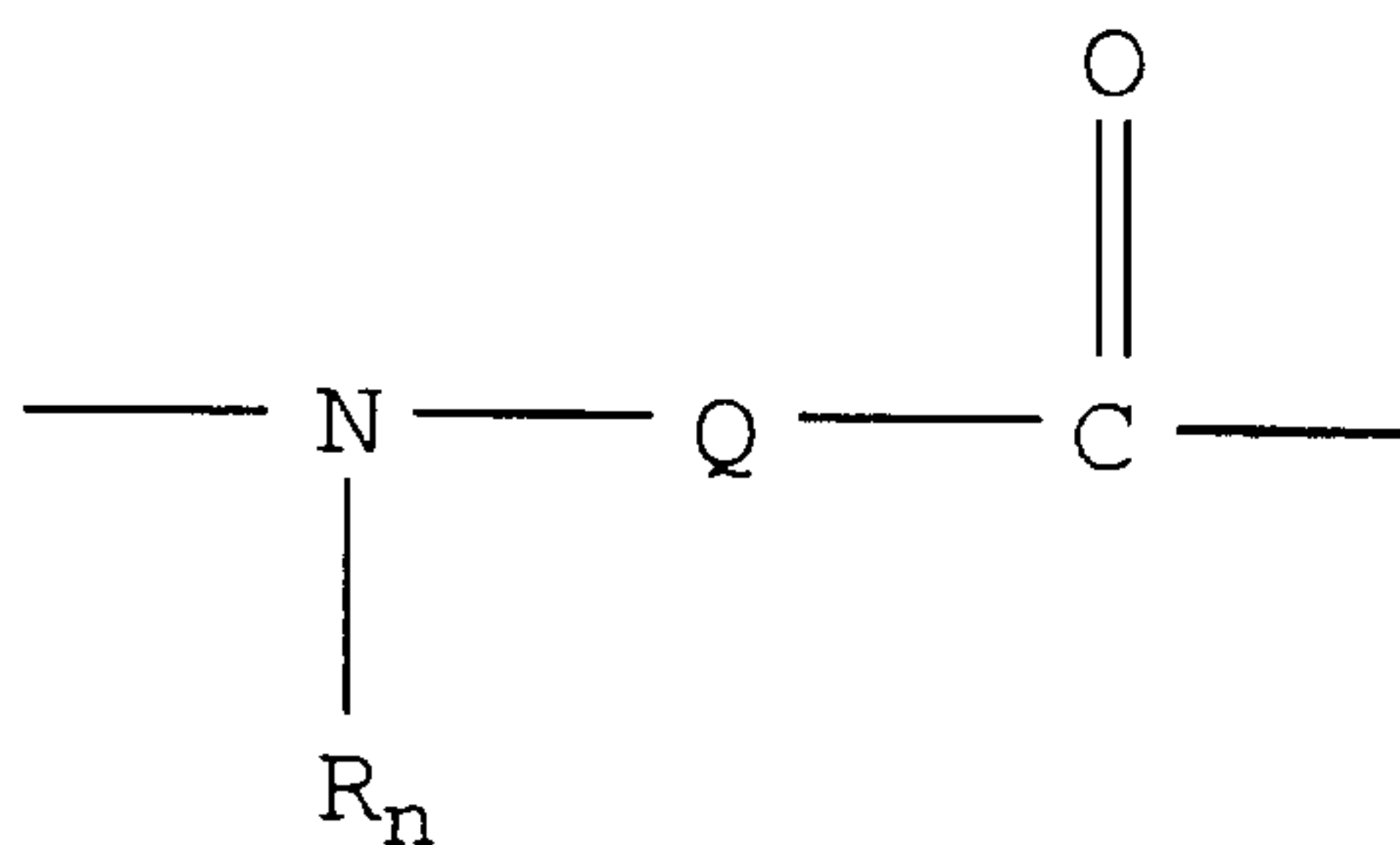
-137-

bonded form a 6- to 7-membered ring or a bicyclic or tricyclic ring comprising 6 to 12 carbon atoms; or R_Y or $R_{Y''}$ taken together with -T- and the atoms to which they are commonly bonded form a 4- to 7-membered ring or R_Y and $R_{Y''}$ each taken together with T and the nitrogen atom to which they are respectively bonded form a 5- to 7-membered ring;

Z is a divalent group of the formula

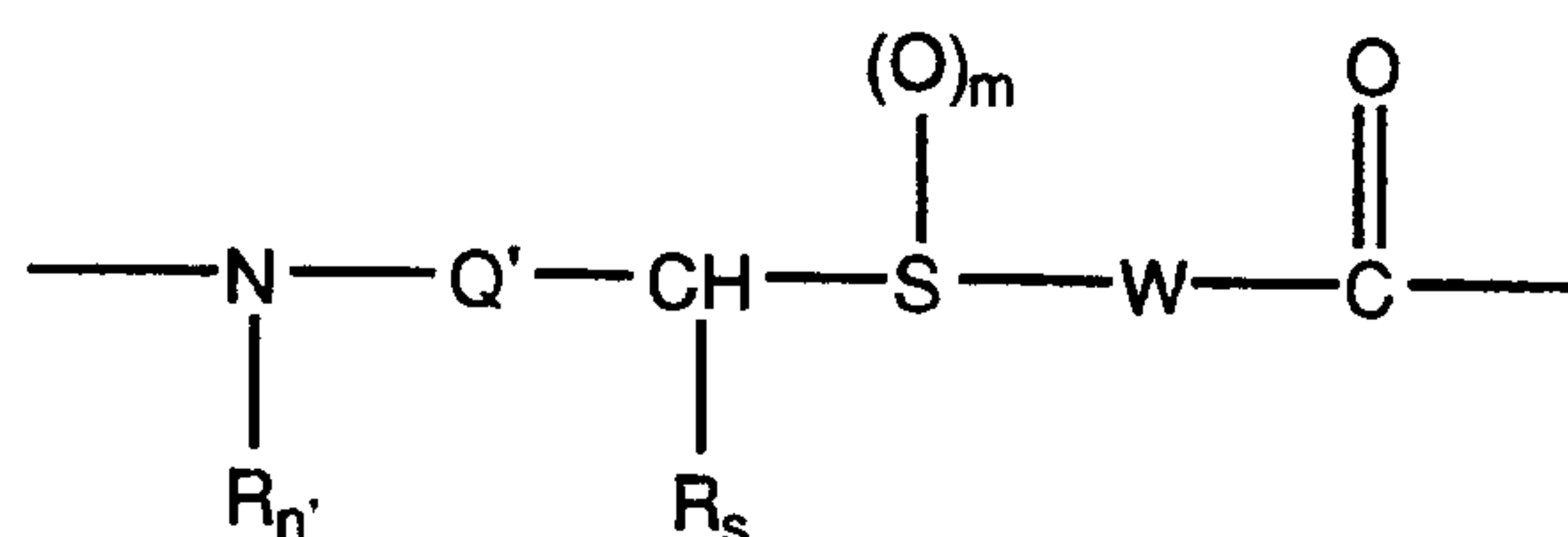


wherein AA_1 and AA_3 are independently a divalent group of the formula



and

ATA is a divalent sulfur group of the formula



wherein W is a divalent organic group comprising 1 to 12 carbon atoms and 0 to 4 heteroatoms selected from the group consisting of O, N and S;

Q and Q' are each independently an organic group comprising 1 to 12 carbon atoms and 0 to 4 heteroatoms selected from O, N and S;

m is 0, 1 or 2;

R_s is hydrogen or an organic moiety; and

-138-

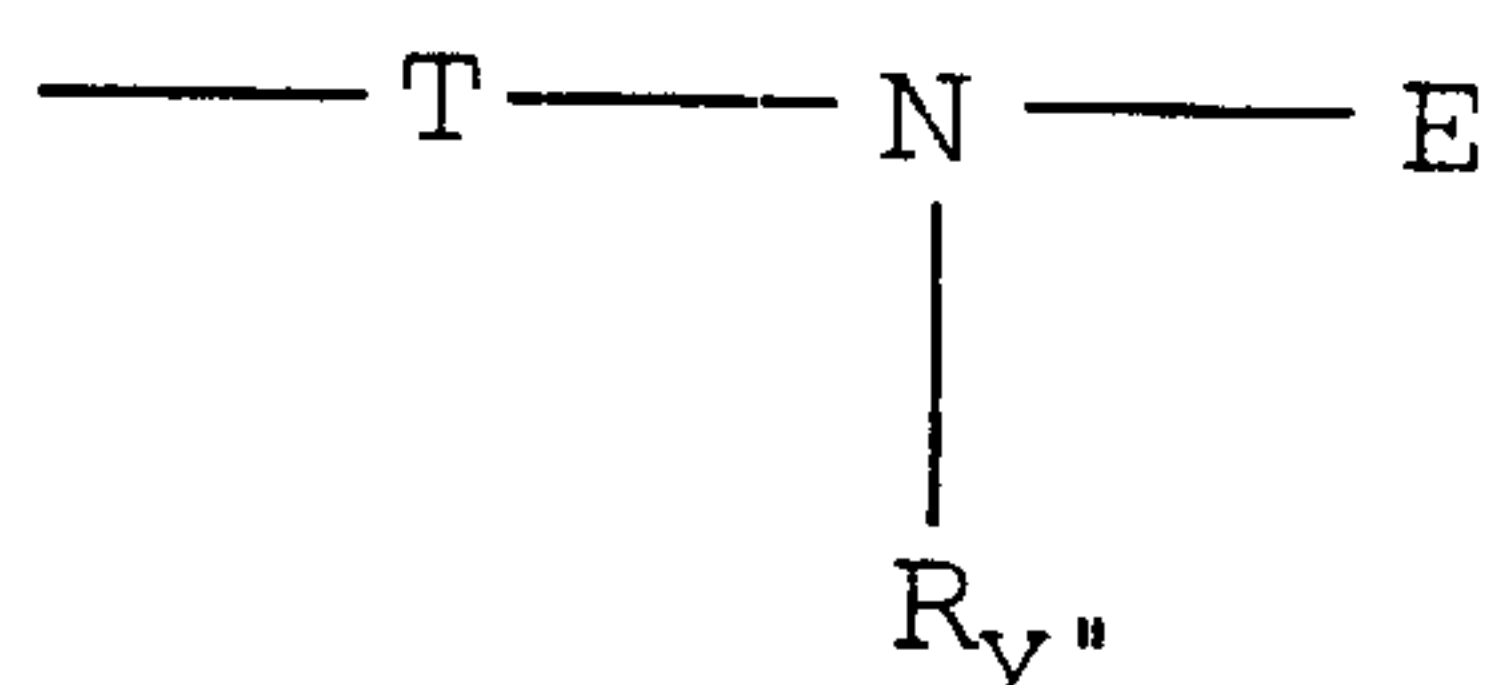
R_n' is hydrogen, or an organic moiety, or R_n taken together with Q and the atoms to which they are bonded form a 4- to 7-membered ring;

R_n' and R_s taken together with -Q'- and the atoms to which they are bonded form a 4- to 7-membered ring or a bicyclic or tricyclic ring comprising 6 to 12 carbon atoms; or

R_n' or R_s taken together with -Q'- and the atoms to which they are commonly bonded form a 4- to 7-membered ring.

13. The compound of claim 12 wherein B is amino.

14. The compound of claim 12 wherein B is a group of the formula $-NR_yR_t$ wherein R_y is hydrogen, alkyl, aryl or heterocycle, and R_t is hydrogen, a solid support, or R_t is a group of the formula



20

15. The compound of claim 14 wherein E is hydrogen.

16. The compound of claim 14 wherein E is an organic substituent derived from an electrophile.

25

17. The compound of claim 12 wherein W is a divalent organic group selected from the group consisting of $-CHR_8-$, $-CR_4R_5CR_6R_7-$, and a 5- or 6-membered aromatic ring containing 0 to 4 heteroatoms selected from O, N and S;

30

wherein R_8 is hydrogen or an organic group;

WO 98/46631

PCT/US98/07135

-139-

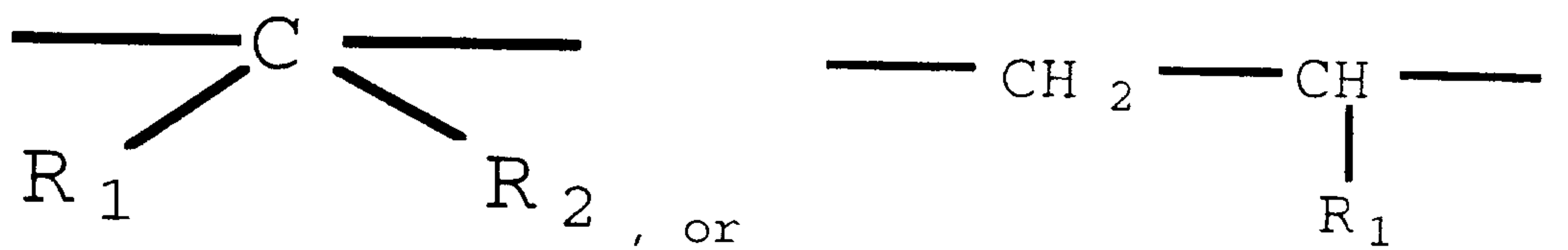
R4, R5, and R6 are independently hydrogen or alkyl;
and

R7 is hydrogen, hydroxy, protected hydroxy, amino or
protected amino or substituted amino wherein the
5 substituent is derived from an electrophilic group.

18. The compound of claim 12 wherein AA1 and AA3
are independently a divalent residue of a proteiogenic
amino acid or isomer thereof.

10

19. The compound of claim 12 wherein Q is a group
of the formula



15

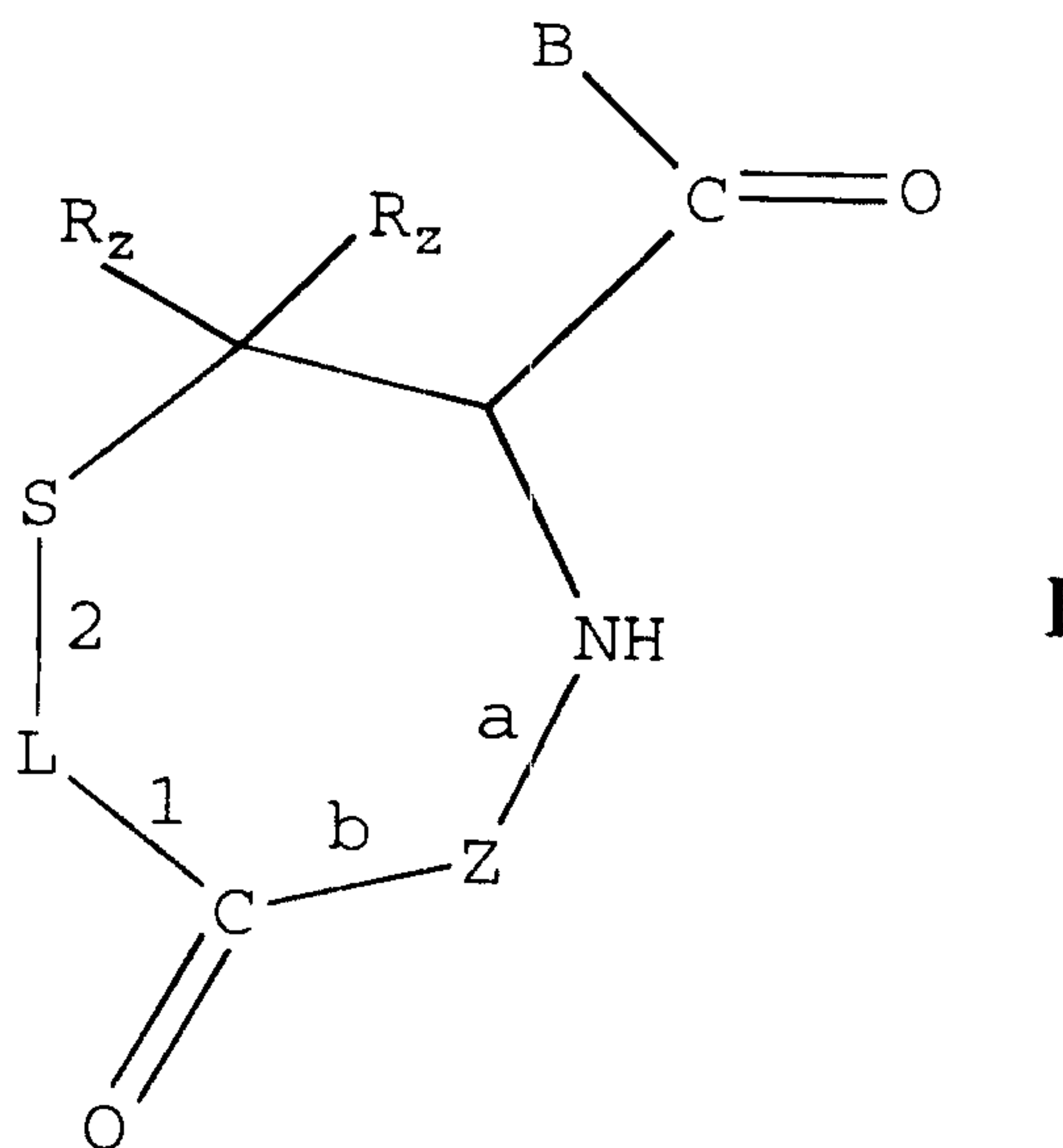
wherein R1 is hydrogen, an organic moiety or a non-
interfering substituent; and

R2 is hydrogen or an organic moiety; or

R1 taken together with R_n forms a 4- to 7-membered
20 ring, or R1 taken together with R_s forms a 4- to 7-
membered ring; or R1 taken together with R2 forms a 3- to
6-membered ring.

20. A process for preparing a diverse library of
25 structurally related macrocyclic compounds of the
formula

-140-



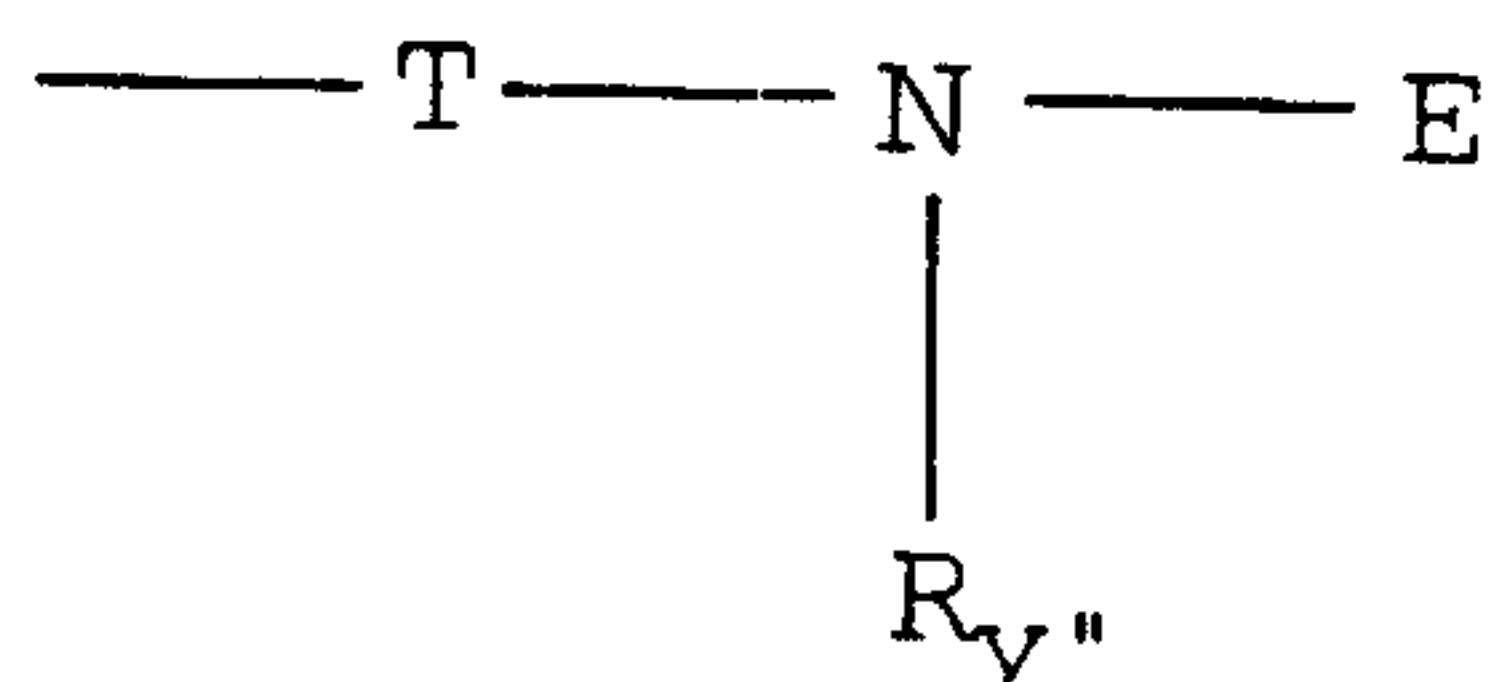
wherein

L is a divalent group of the formula ¹ (CH₂)₀₋₁-C₆H₄CH₂² or -CHR_a- wherein R_a is hydrogen or an organic moiety;

5 R_z is hydrogen or methyl;

B is hydroxy or a group of the formula -NR_yR_t wherein R_y is hydrogen, alkyl, aryl or heterocycle, and R_t is hydrogen, a solid support, or R_t is a group of the formula

10

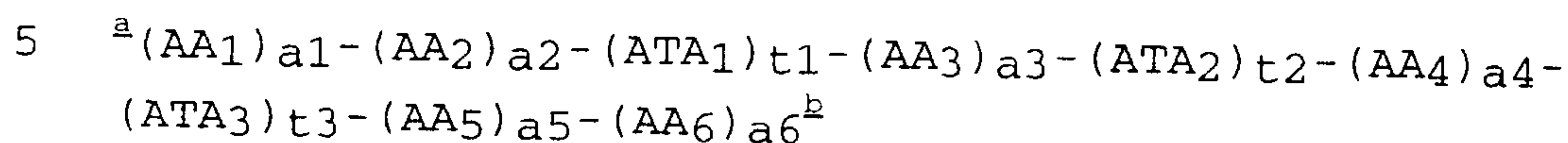


wherein E is hydrogen, a solid support or a substituent derived from an electrophilic reagent, T is a divalent linking group, and R_y'' is hydrogen or a substituent derived from an electrophilic reagent; or R_y and R_y'' taken together with the atoms to which they are bonded form a 4- to 7-membered ring or a bicyclic or tricyclic ring comprising 6 to 12 carbon atoms; or R_y or R_y'' taken together with -T- and the atoms to which they are commonly bonded form a 5- to 7-membered ring or R_y and R_y'' each taken together with T and the nitrogen atom

-141-

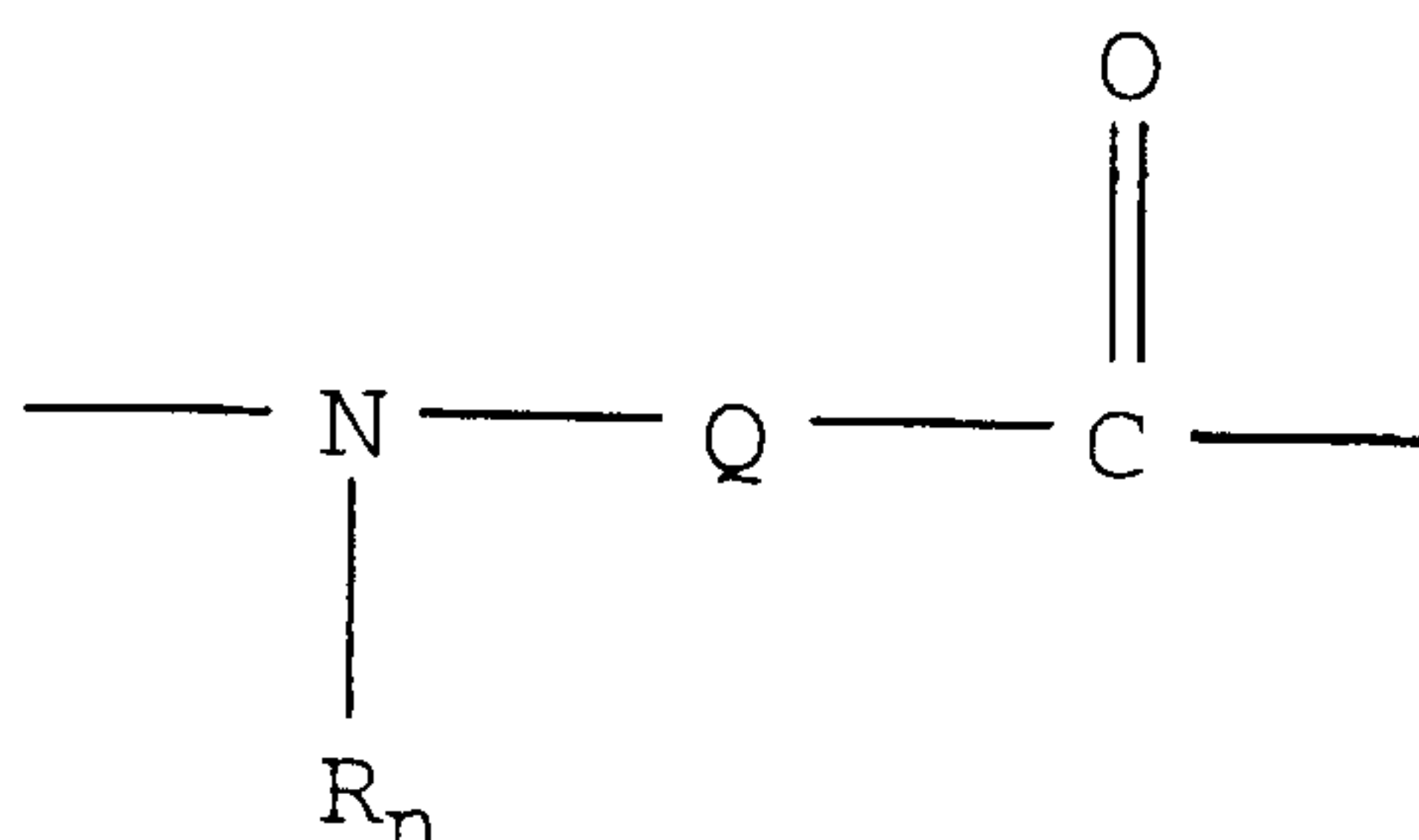
to which they are respectively bonded form a 5- to 6-membered ring;

Z is a divalent group of the formula



wherein each of AA₁-6 is independently a divalent group of the formula

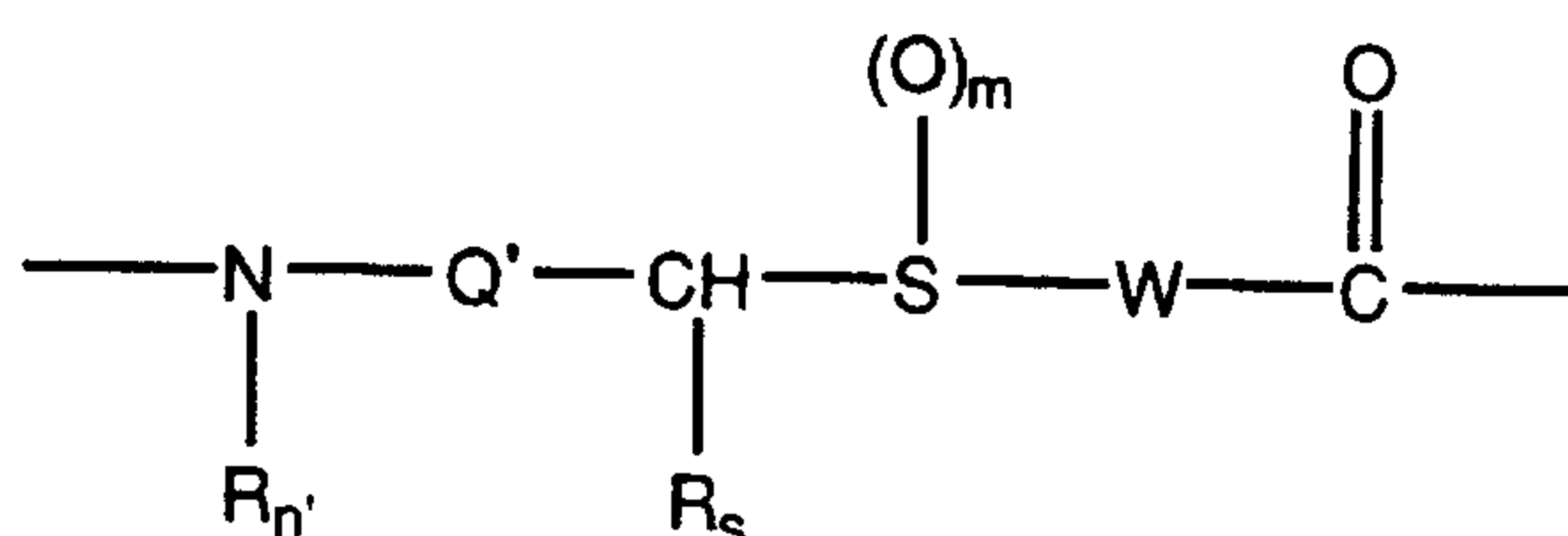
10



and

each of ATA₁-3 is independently a divalent sulfur group of the formula

15



and

wherein a₁, a₂, a₃, a₄, a₅, a₆, t₁, t₂, and t₃ are independently 0 or 1, provided that t₁ + t₂ + t₃ = 1, 2 or 3; and provided further that -Z- is selected to form a 12- to 40-membered macrocycle ring of Formula I;

wherein in the above formulas for AA₁-6 and ATA₁-3,

W is a divalent organic group comprising 1 to 12 carbon atoms and 0 to 4 heteroatoms selected from O, N and S;

25

Q and Q' are each independently an organic group comprising 1 to 12 carbon atoms and 0 to 4 heteroatoms selected from O, N and S;

WO 98/46631

PCT/US98/07135

-142-

m is 0, 1 or 2;

R_S is hydrogen or an organic moiety; and

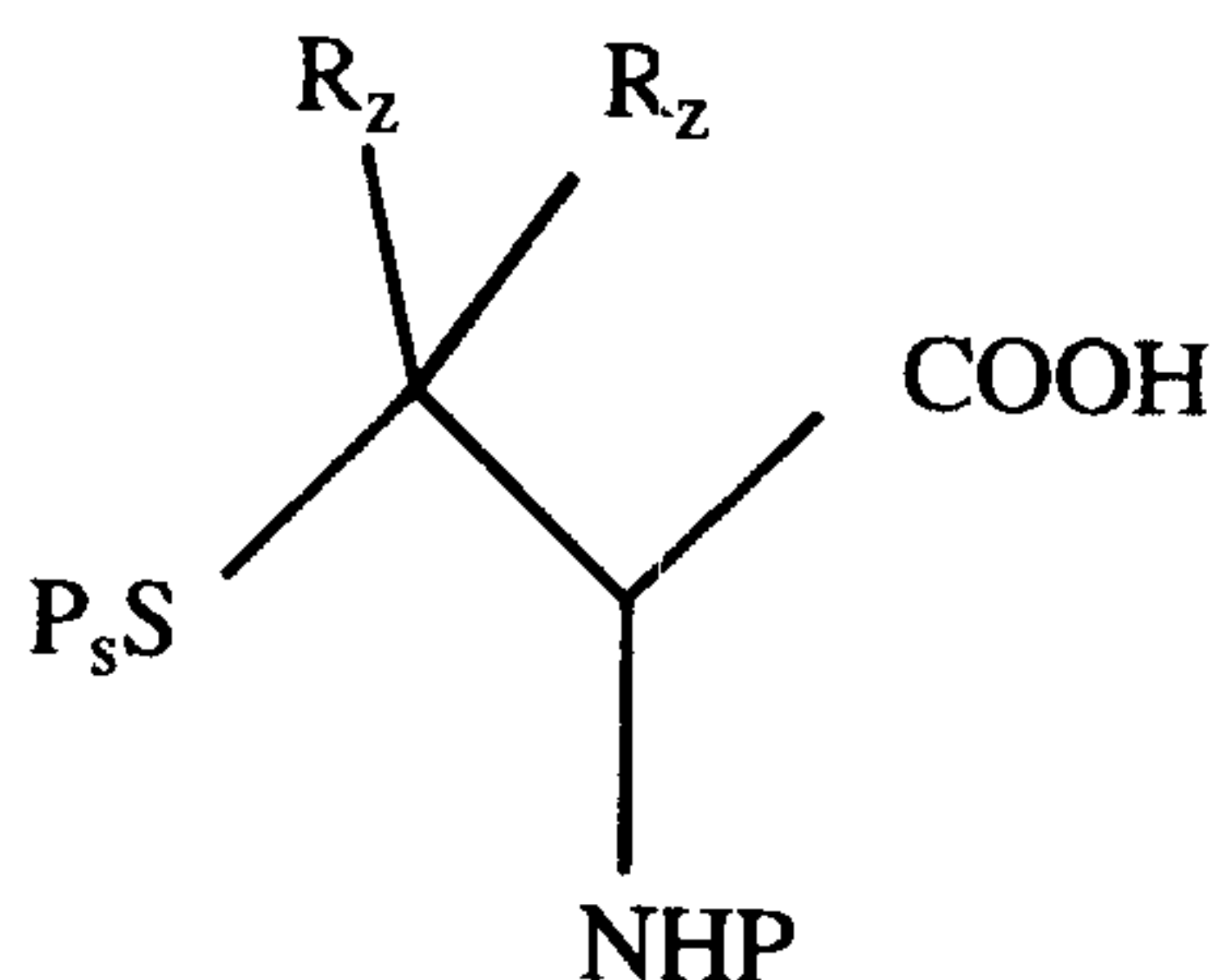
R_N' is hydrogen, or an organic moiety, or R_N taken together with Q and the atoms to which they are bonded form a 4- to 7-membered ring;

R_N' and R_S taken together with -Q'- and the atoms to which they are bonded form a 4- to 7-membered ring or a bicyclic or tricyclic ring comprising 6 to 12 carbon atoms; or

R_N' or R_S taken together with -Q'- and the atoms to which they are commonly bonded form a 4- to 7-membered ring;

wherein said process comprises the steps of

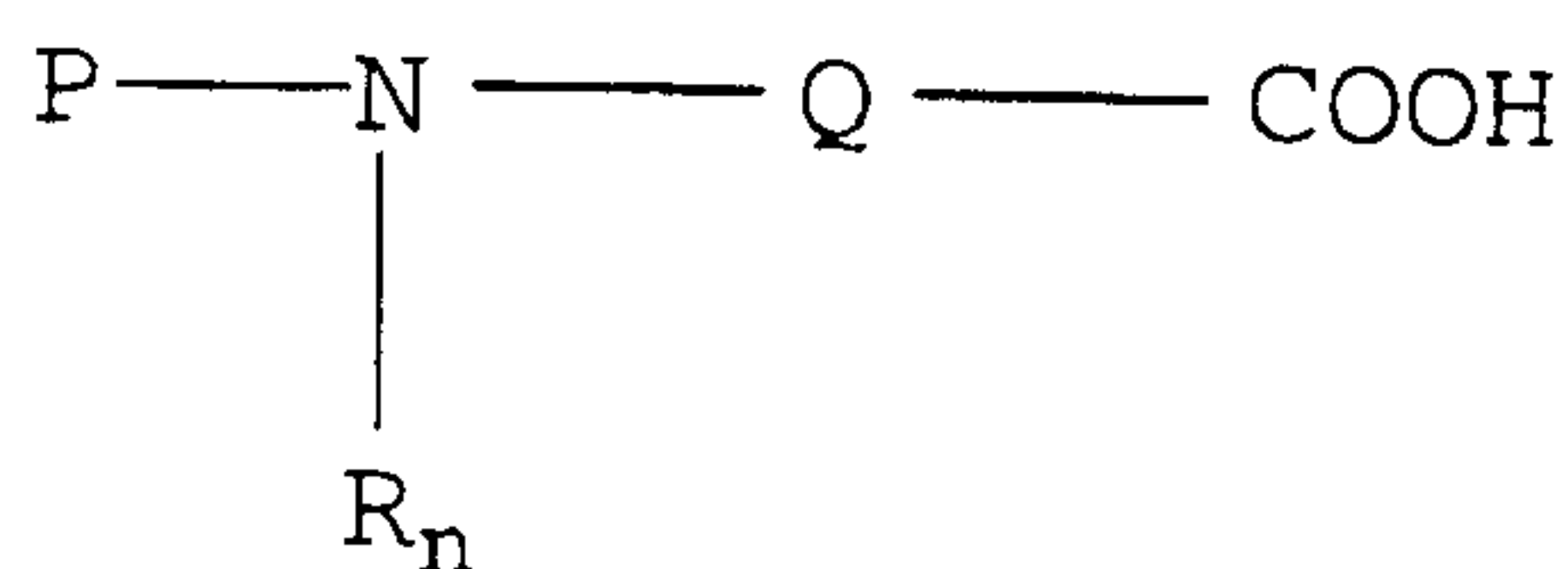
(a) covalently bonding an amino-protected, thiol-protected starting material of the formula



wherein R_Z is hydrogen or methyl, and P_s and P are thiol- and amino-protecting groups, respectively, to a solid support comprising acid reactive groups;

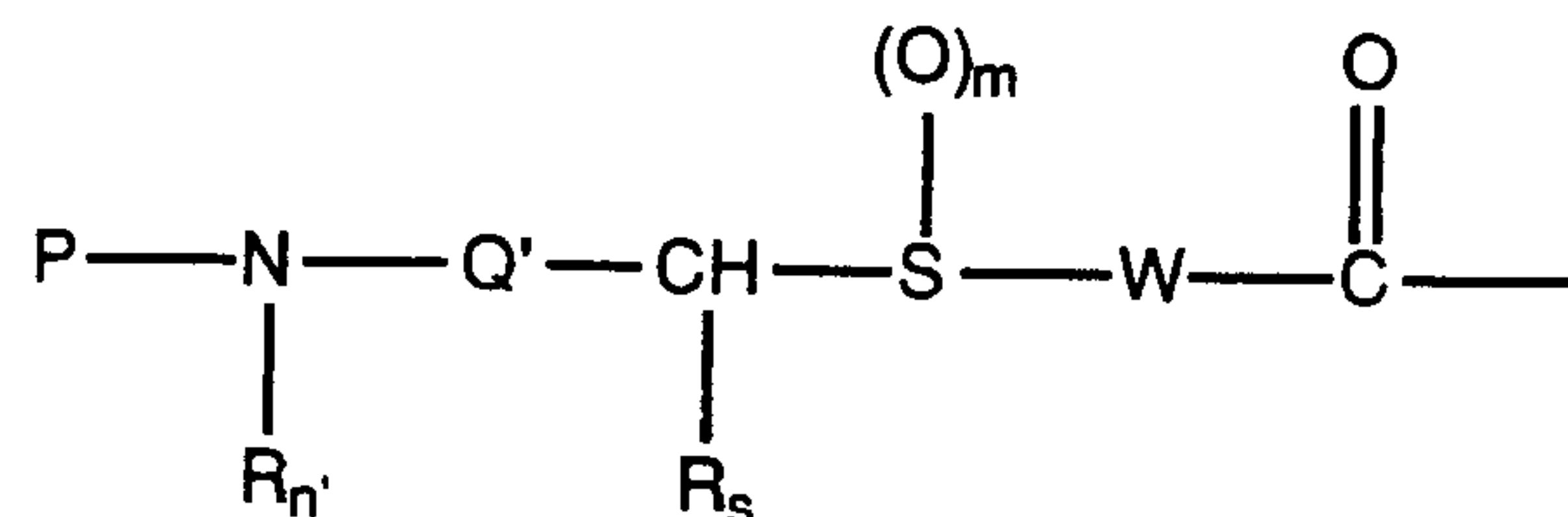
(b) removing the amino protecting group on the solid support-bound starting material;

(c) coupling the resulting solid support-bound thio-protected starting material with an amino-protected amino acid of the formula



-143-

or an amino-protected thioether acid of the formula

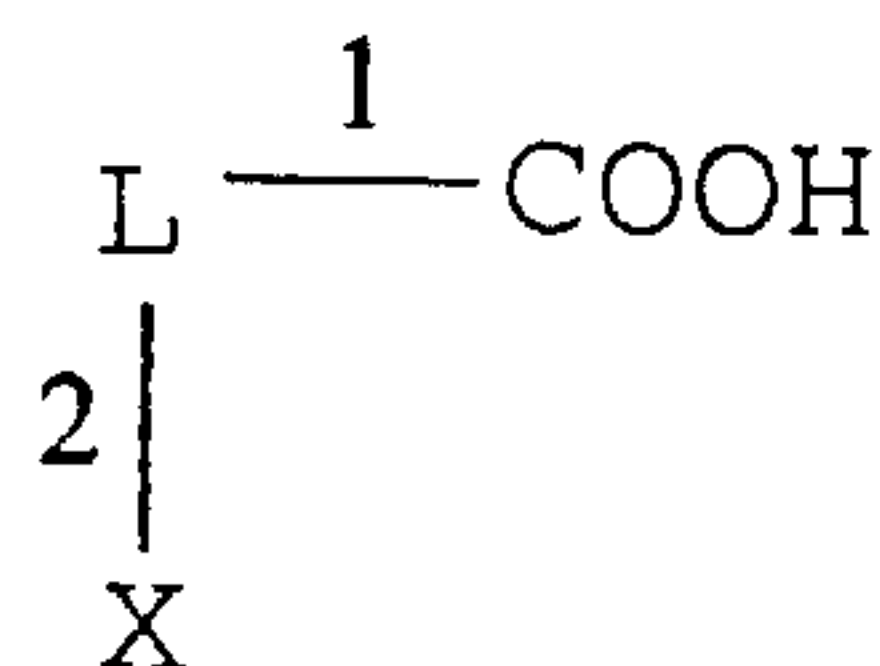


5 wherein in said formulas P is an amino-protecting group and, R_n , $\text{R}_{n'}$, Q, Q', R_s , m and W are as defined above;

(d) removing the amino-protecting group from the coupled solid support-bound product;

(e) optionally repeating step (c) and step (d) one
10 or more times using the same or a different amino-protected amino acid or amino-protected thioether acid

(f) coupling the solid support-bound product with an organic acid of the formula



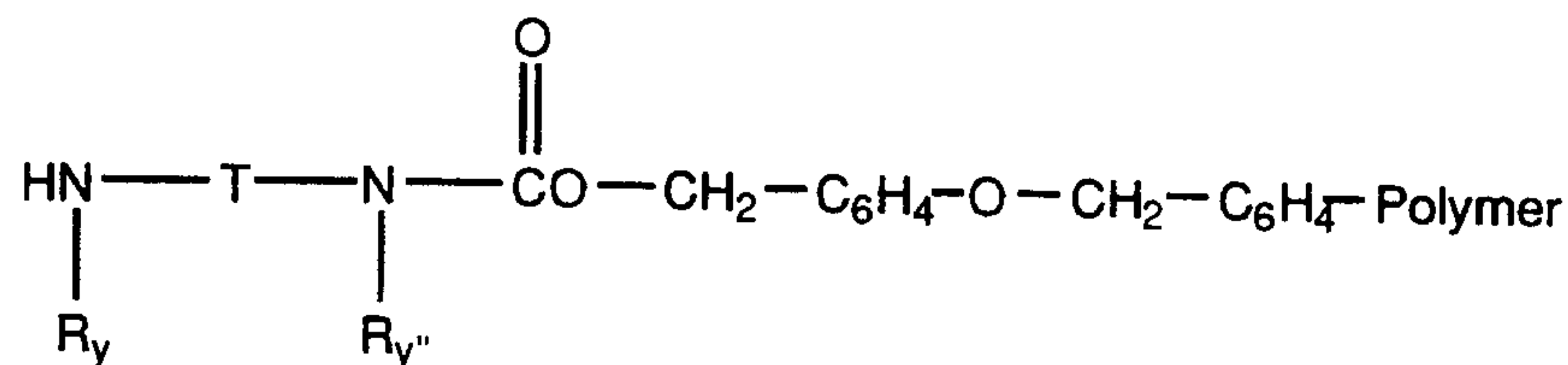
15

wherein L is as defined above and X is a leaving group subject to nucleophilic displacement;

(g) removing the thiol-protecting group to enable
20 macrocycle formation by nucleophilic displacement of the group X and cleaving the covalently bound product from the solid support; and

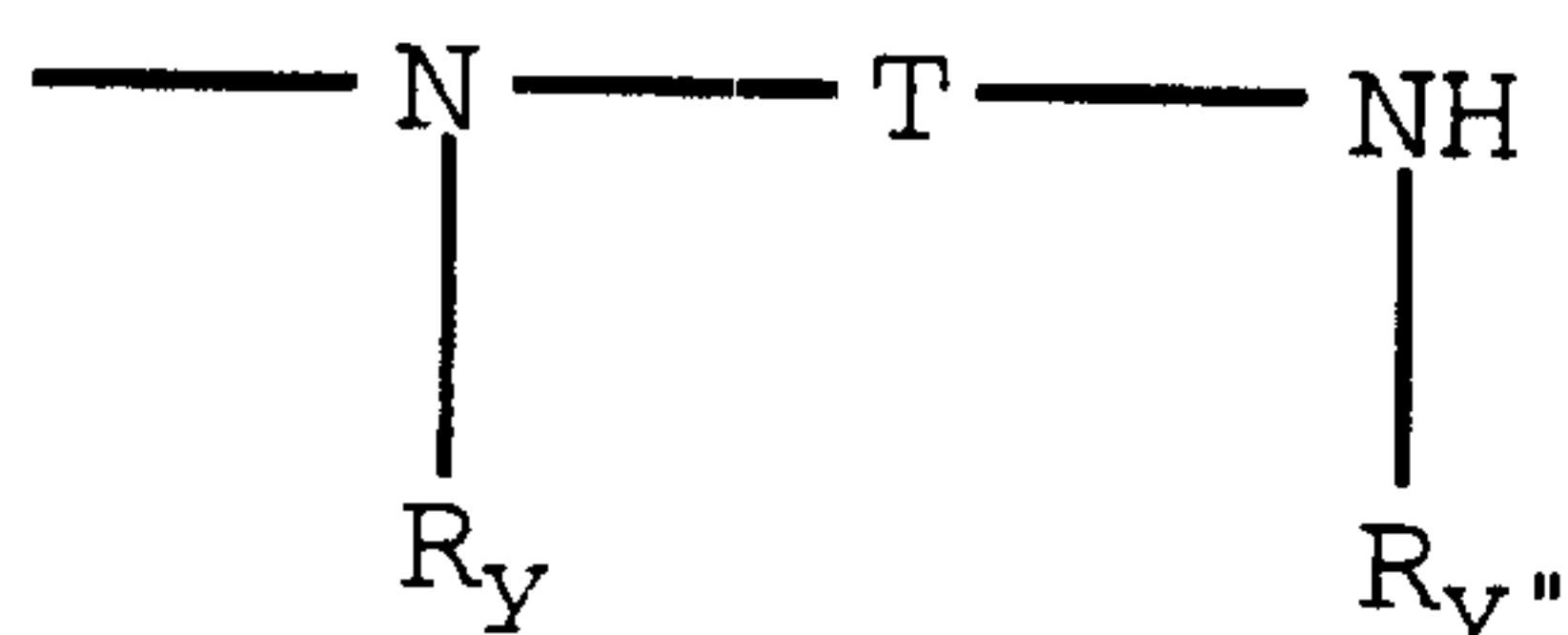
(h) when the acid reactive group on the solid
support is a covalently bound group of the formula

25



-144-

optionally reacting the resulting product of Formula I wherein B is a group of the formula



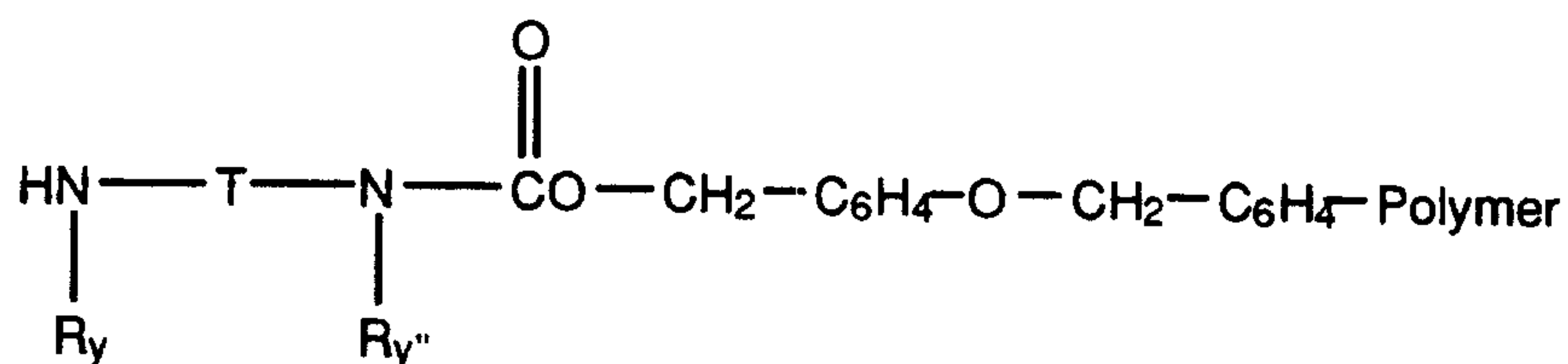
5

with an amine reactive organic electrophilic agent; provided that at least one of the steps (c) and (e) is carried out using an amino-protected aminothioether acid.

10

21. The process of claim 20 wherein the solid support is a Merrifield resin, Wang or Rink amide resin.

22. The process of claim 20 wherein the acid
15 reactive group on the solid support is a covalently bound group of the formula



20 23. The process of claim 22 wherein the product is reacted with an electrophilic agent having a molecular weight from about 30 to about 600 and selected from the group consisting of aldehydes, organic halides, acyl halides, sulfonic acid esters, organohaloformates,
25 organosulfonyl halides, organic isocyanates, organic isothiocyanates, aldehydes and ketones.

24. The process of claim 20 wherein the thiol-protecting group is removed to enable macrocycle
30 formation by nucleophilic displacement of the group X

-145-

before the covalently bound product is cleaved from the solid support.

25. The process of claim 20 wherein the thiol-
5 protecting group is removed to enable macrocycle formation by nucleophilic displacement of the group X after the covalently bound product is cleaved from the solid support.

10 26. The process of claim 20 wherein each amino-protected amino acid used in the process is a proteiogenic amino acid or isomer thereof.

15 27. The process of claim 26 wherein P is 9-fluorenylmethyloxy carbonyl.

20 28. The process of claim 10 wherein each protected amino acid used in the process has a molecular weight of about 75 to about 700.

29. The process of claim 20 wherein each aminothioether acid used in the process has a molecular weight of about 150 to about 800.

25 30. The process of claim 20 wherein steps (c) and (d) are repeated again using the same or a different amino-protected amino acid or thioether acid.

30 31. The process of claim 20 further comprising contacting the product of step (g) in solution with a non-nucleophilic base selected from 2,6-lutidine, diisopropylethylamine or proton sponge.

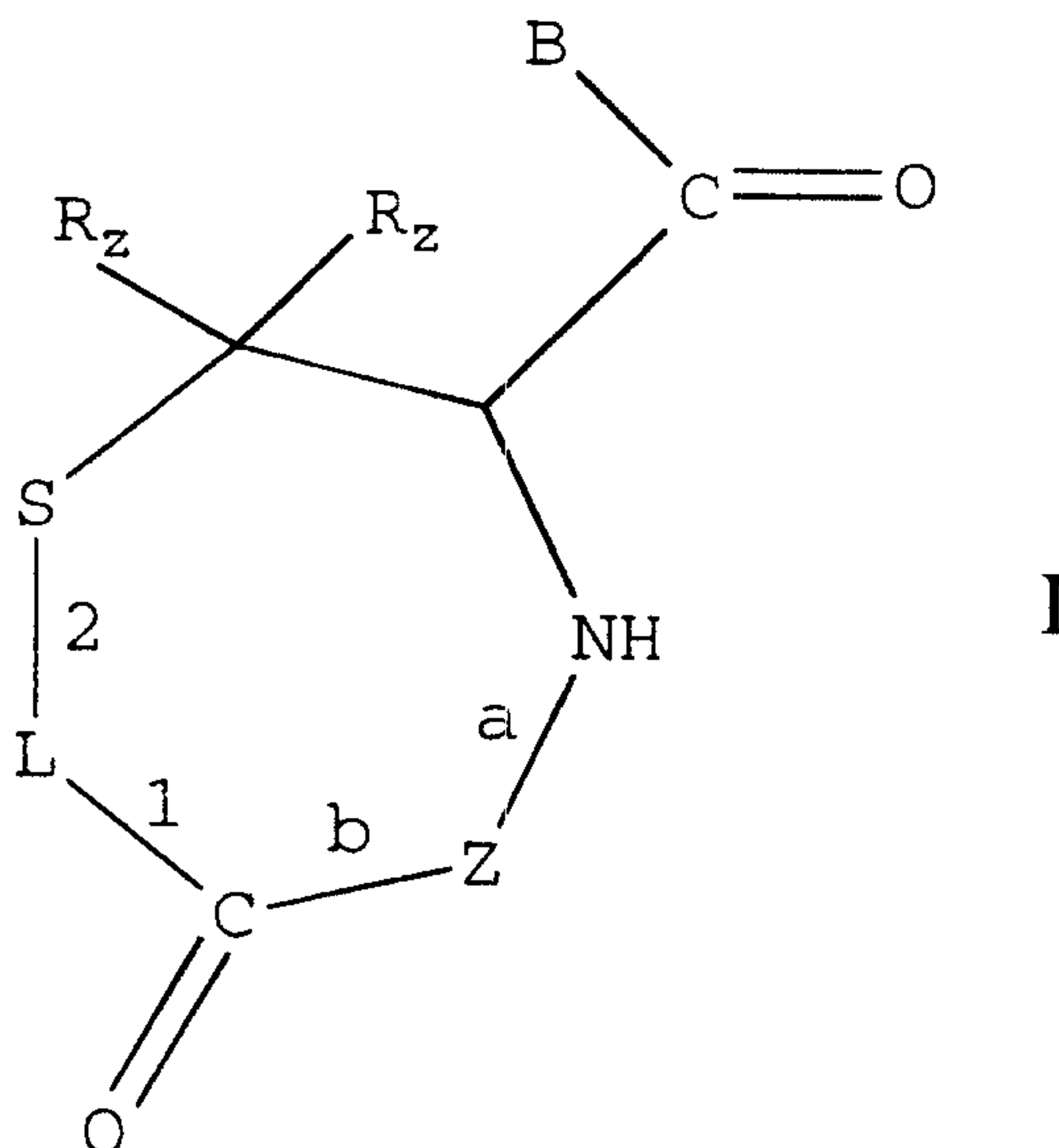
35 32. An assay kit for identification of pharmaceutical lead compounds, said kit comprising biological assay materials and a well plate apparatus

-146-

wherein each well in said apparatus contains a library compound of the library of claim 1.

33. The assay kit of claim 32 wherein the
5 biological materials are selected for performing at least
one assay test selected from the group consisting of *in*
vitro assays, cell based functional assays, and add,
incubate, and read assays.

10 34. An apparatus suitable as a replacement element
in an automated assay machine as a source of individual
members of a library of structurally related compounds,
said apparatus comprising a 2-dimensional array of
defined reservoirs, each reservoir containing a library
15 compound from said library, wherein said structurally
related compounds are of the formula



wherein

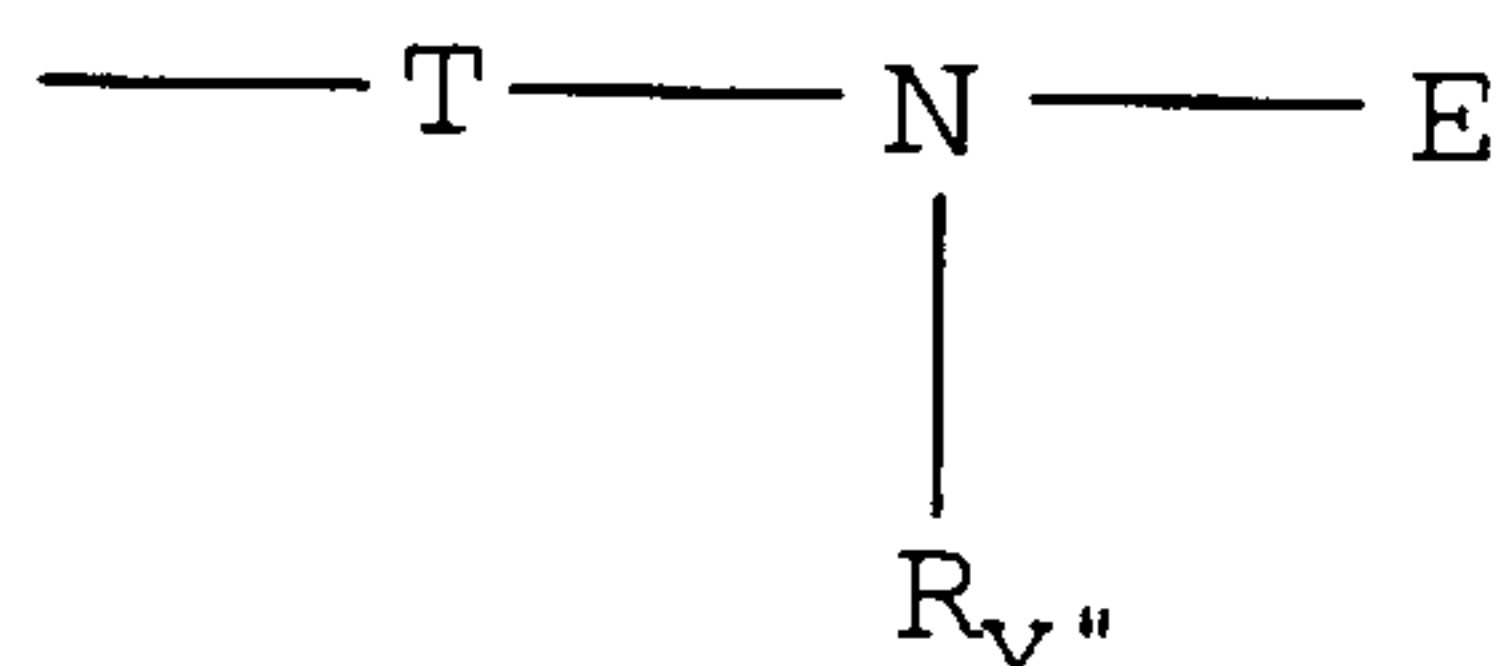
20 L is a divalent group of the formula $^1(\text{CH}_2)_{0-1}-\text{C}_6\text{H}_4\text{CH}_2^2$ or $-\text{CHR}_a-$ wherein R_a is hydrogen or an organic moiety;

R_z is hydrogen or methyl;

B is hydroxy or a group of the formula $-NR_yR_t$ wherein R_y is hydrogen, alkyl, aryl or heterocycle, and

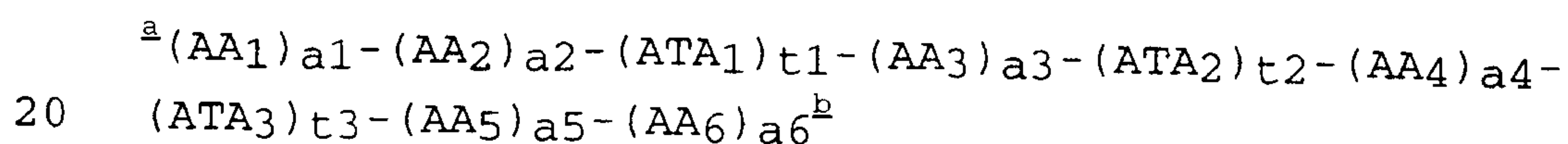
-147-

R_t is hydrogen, a solid support, or R_t is a group of the formula

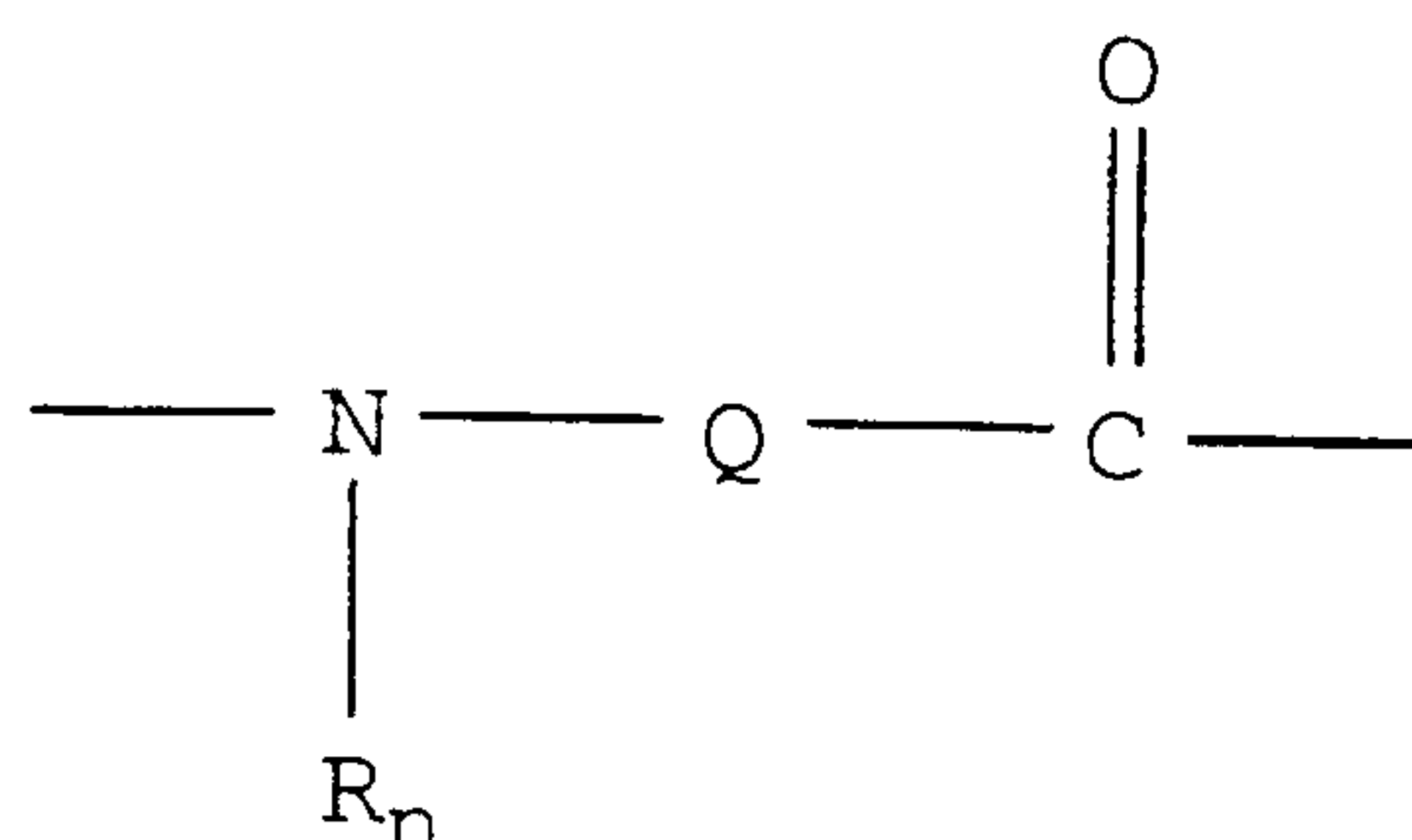


- 5 wherein E is hydrogen, a solid support or a substituent derived from an electrophilic reagent, T is a divalent linking group, and $R_{y''}$ is hydrogen or a substituent derived from an electrophilic reagent; or R_y and $R_{y''}$ taken together with the atoms to which they are
 10 bonded form a 6- to 7-membered ring or a bicyclic or tricyclic ring comprising 6 to 12 carbon atoms; or R_y or $R_{y''}$ taken together with -T- and the atoms to which they are commonly bonded form a 6- to 7-membered ring or R_y and $R_{y''}$ each taken together with T and the nitrogen atom
 15 to which they are respectively bonded form a 5- to 7-membered ring;

Z is a divalent group of the formula



wherein each of AA_1-6 is independently a divalent group of the formula

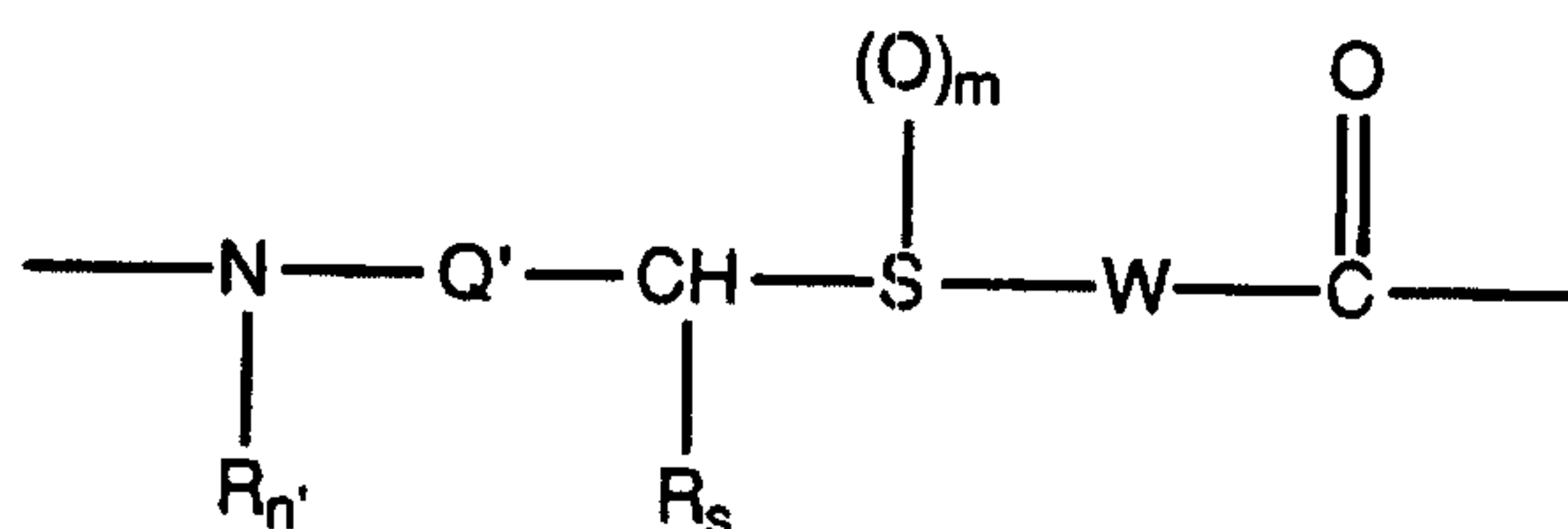


25

and

each of ATA_1-3 is independently a divalent sulfur group of the formula

-148-



and

wherein a1, a2, a3, a4, a5, a6, t1, t2, and t3 are
 5 independently 0 or 1, provided that $t1 + t2 + t3 = 1, 2$
 or 3; and provided further that -Z- is selected to form a
 12- to 40-membered macrocycle ring of Formula I;

wherein in the above formulas for AA₁₋₆ and ATA₁₋₃,

W is a divalent organic group comprising 1 to 12
 10 carbon atoms and 0 to 4 heteroatoms selected from O, N
 and S;

Q and Q' are each independently an organic group
 comprising 1 to 12 carbon atoms and 0 to 4 heteroatoms
 selected from O, N and S;

15 m is 0, 1 or 2;

R_s is hydrogen or an organic moiety; and

R_{n'} is hydrogen, or an organic moiety, or R_n taken
 together with Q and the atoms to which they are bonded
 form a 4- to 7-membered ring;

20 R_{n'} and R_s taken together with -Q'- and the atoms to
 which they are bonded form a 4- to 7-membered ring or a
 bicyclic or tricyclic ring comprising 6 to 12 carbon
 atoms; or

R_{n'} or R_s taken together with -Q'- and the atoms to
 25 which they are commonly bonded form a 4- to 7-membered
 ring.

35. The apparatus of claim 32 wherein the library
 compound in each reservoir is prepared in accordance with
 30 the process of claim 19 and wherein each reservoir
 provides one reaction zone.

WO 98/46631

PCT/US98/07135

-149-

36. The apparatus of claim 32 wherein the 2-dimensional array of defined reservoirs is a multi-well microtiter plate.

1/2

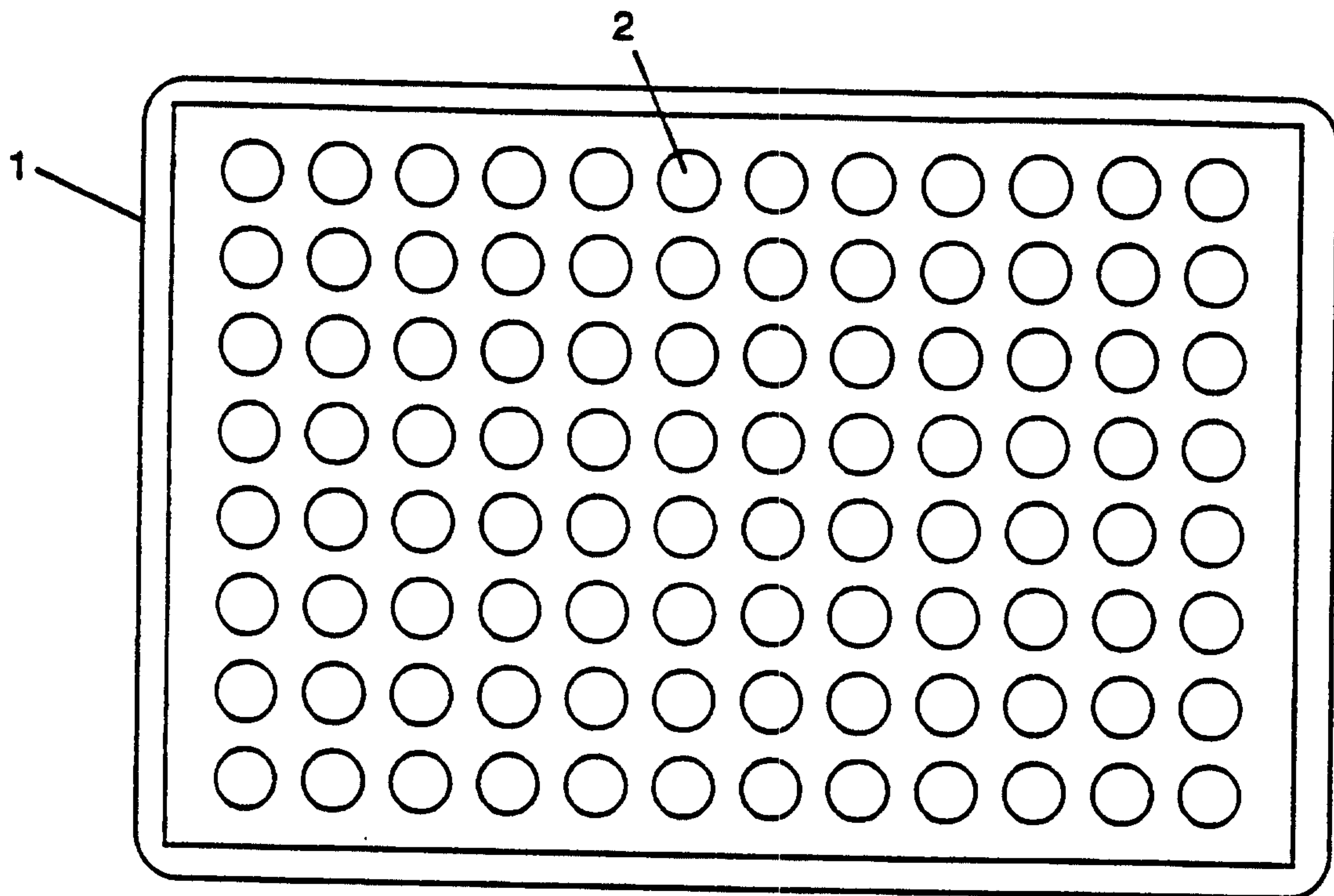


Figure 1

2/2

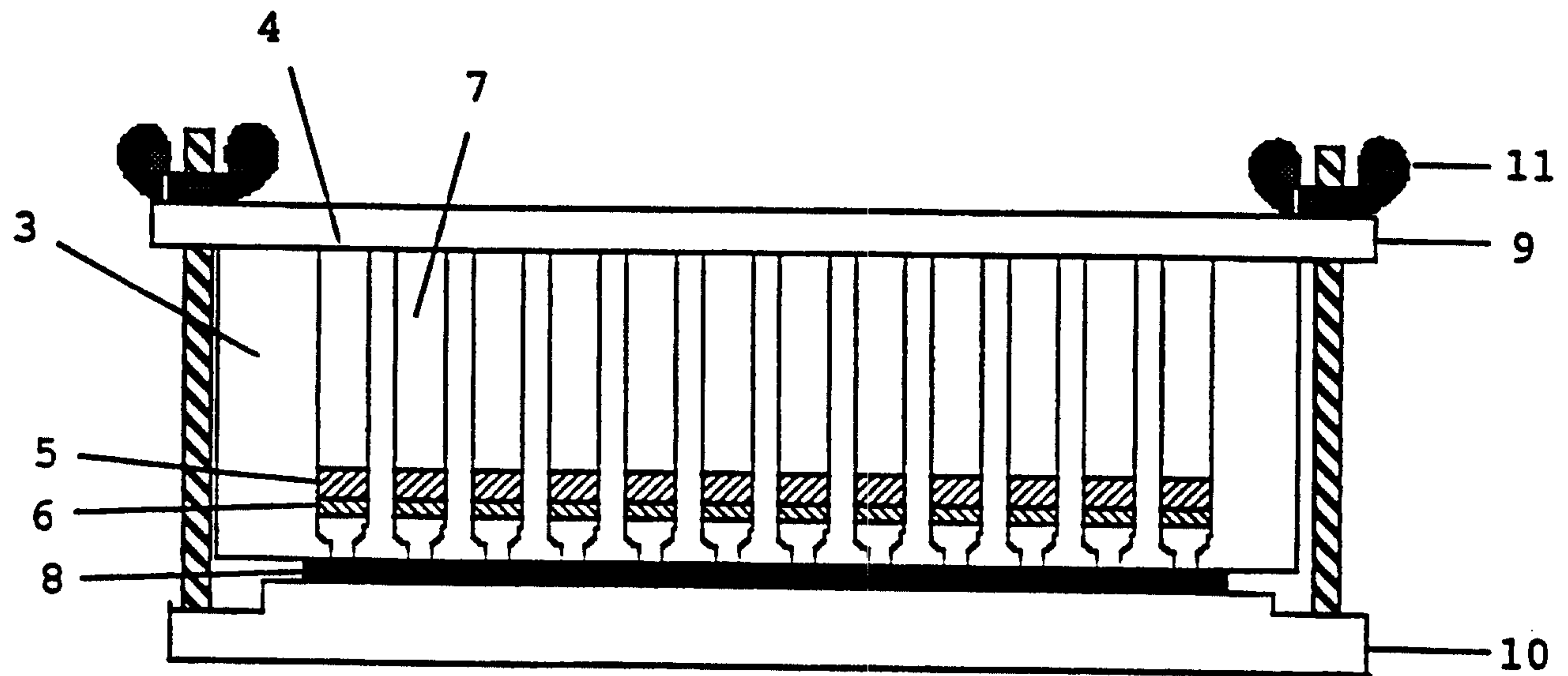


Figure 2