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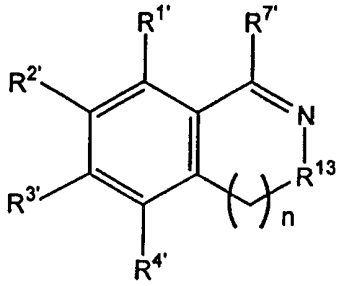
(54) Title: ARYLOXIME LINKERS IN THE SOLID-PHASE SYNTHESIS OF 3-AMINOBENZISOXAZOLES

(57) Abstract

In its first aspect, the invention is directed to a solid support mediated method for the synthesis of diverse polycyclic heterocycles according to general formula (V). A second aspect of the invention is directed to a solid support bound intermediate compound that optionally can be derivatized before a cyclization and displacement procedure provides a product. The intermediate is preferably stable to a wide range of chemical conditions thus allowing, if desired, for the chemical derivatization of the intermediate. A third aspect of the invention is directed to a library of polycyclic heterocycle compounds where said library contains a plurality of diverse library compounds of general formula (V). A fourth aspect of the invention is directed to a method for the synthesis of a library of diverse polycyclic heterocycles by the general method described. A fifth aspect of the invention is directed to an assay kit for the identification of lead compounds of the library described therein.



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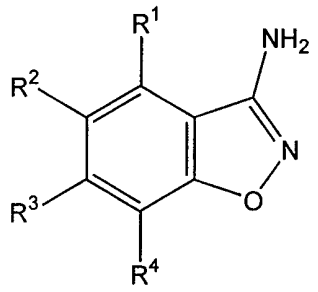
ARYLOXIME LINKERS IN THE SOLID-PHASE SYNTHESIS OF 3-AMINOBENZISOXAZOLES

BACKGROUND OF THE INVENTION

The present invention relates to a solid support mediated method for the synthesis of polycyclic heterocycle compounds, as well as intermediate compounds, a library of polycyclic heterocycle compounds, a method for the synthesis of a library of diverse polycyclic heterocycles and an assay kit for the identification of compounds having biological or other activity.

Compounds having the benzisoxazole scaffold (VIII) have been shown to have biological activity.



VIII

For example, Suh et al. teach compounds having the benzisoxazole scaffold that are potent LTB_4 receptor antagonists. (Suh, H.; Jeong, S.;Han, Y.N.; Lee, H.; Ryu, J. *Bioorg. Med. Chem. Lett.*, **1997**, 7, 389). Thus, since the potential for using polycyclic heterocycles as therapeutic drugs is known, an efficient preparation that facilitates the synthesis of single polycyclic heterocycle compounds and the generation of a diverse library of polycyclic heterocycle compounds would be useful. Polycyclic heterocycles have been synthesized according to chemistry known in the art by several groups. Much of the synthesis has relied on conventional "solvent" based chemistry. Solvent defined chemistry relies on the collision of discrete reactants within a solvent cage. The movement of reactants is controlled by kinetic and thermodynamic molecular fluid energetics. For example, Shutske et al. generated benzisoxazoles according to Scheme A, through the solvent defined

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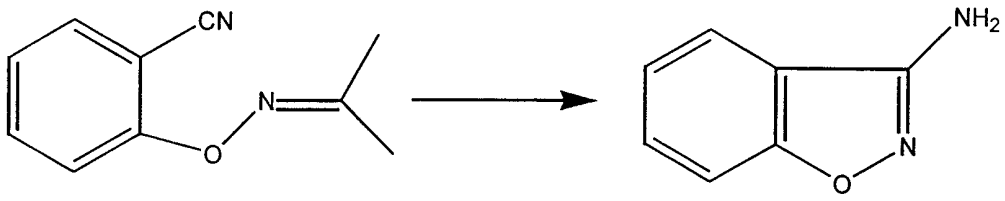
cyclization of cyano arylacetone oxime (Shutske, G.M.; Kapples, K.J.;*J. Hetrocyclic Chem,***1989**, 26, 1293).



Scheme A

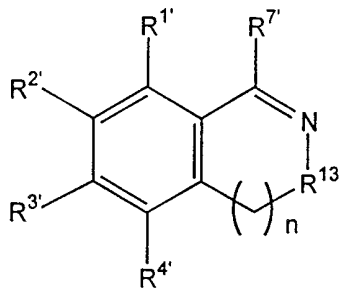
The desired product is isolated from a refluxing 1:1 ethanol:5% HCl solution of the corresponding aryl oxime.

An alternative method for the generation of the benzisoxazole ring system involves a cyclorelease reaction. Cyclorelease or cyclization and release are terms applied to a reaction that forms a cyclized system with simultaneous release of product from a solid support. Alternatively, the phrase, cyclization and displacement of product from a solid support, is used to mean the same reaction.

Combinatorial chemistry allows researchers to make collections, or libraries, of compounds by parallel synthesis of large numbers of derivatives of selected classes of organic compounds that can be screened for biological and other activities. By screening these compounds against key receptors or enzymes, useful structure-function data can be obtained, speeding the search for new therapeutic agents. A solid support mediated method for the synthesis of polycyclic heterocycle compounds and the use of this solid support mediated method for the synthesis of a library of diverse polycyclic heterocycles is desirable.

SUMMARY OF THE INVENTION

One aspect of this invention relates to a solid support mediated method for the synthesis of polycyclic heterocycle compounds (V):

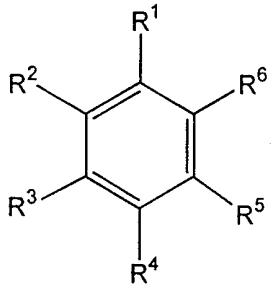


V

where n is an integer ≥ 0, preferably 0, 1, 2, or 3 and most preferably 0 or 1.

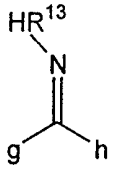
In the first aspect of the invention, polycyclic heterocycles of the general Formula (V) are synthesized according to a procedure comprising the steps of:

(a) reacting a compound (I):



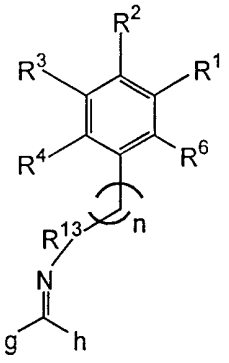
I

with a solid support bound member (III):



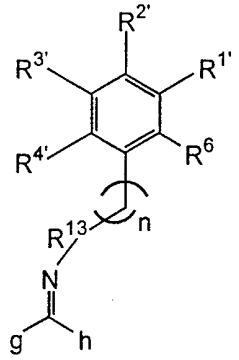
III

thereby yielding an intermediate (IV):



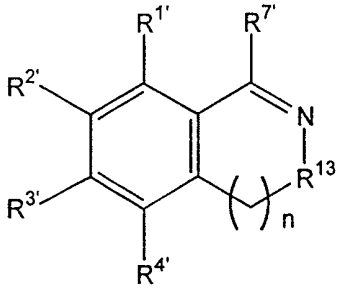
IV

(b) intermediate (IV) is optionally chemically derivatized where at least one of R^1, R^2, R^3 or R^4 is chemically altered to form a corresponding intermediate (IV'):



IV'

(c) causing a cyclization reaction whereby a compound (V) is displaced from the solid support.

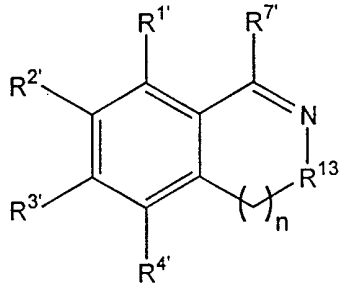


V

A second aspect of the invention is an intermediate compound of formula IV or IV' above. Because this intermediate may be chemically derivatized before

cyclization and displacement to thereby provide further options for the groups R^1, R^2, R^3 and R^4; the intermediate is preferably stable to a wide range of chemical conditions.

A third aspect of the invention is directed to a library of polycyclic heterocycle compounds where this library contains a plurality of diverse compounds (V):



V

A fourth aspect of the invention is directed to a method for the synthesis of a library of diverse polycyclic heterocycles by the general method described above.

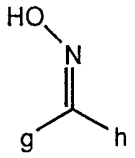
A fifth aspect of the invention is directed to an assay kit for the identification of compounds having biological or other activity, this kit comprising assay materials and well plate apparatus where each well in this apparatus contains a compound of the library described above.

DETAILED DESCRIPTION

Definition of terms

As used herein and in the appended claims the term "solid support" is intended to have a relatively broad meaning including, but not limited to, a resin, a polymer, a gel, glass beads, silica gel, a ceramic solid support or other solid composition.

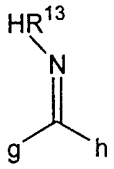
As used herein and in the appended claims the term "solid support bound oxime" means a solid support that at least has one oxime moiety chemically attached thereto. For example, one embodiment of this compound may be represented by the formula (IX):



IX

In formula (IX), g represents a solid support, such as defined above.

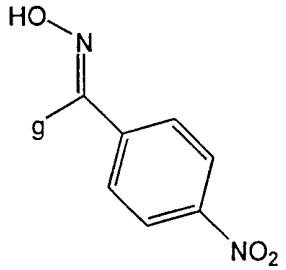
As used herein and in the appended claims the term "solid support bound member" means a solid support that has at least one functional moiety chemically attached thereto. For example, this may be represented by the formula (III):



III

As used herein and in the appended claims the term "oxime resin" means a solid support where the functional moiety is an oxime, and the solid support is a resin.

As used herein and in the appended claims the term "Kaiser resin" means an oxime functionalized polystyrene resin, an example of that is defined by E.T.Kaiser in a 1980 publication (Degrado, W.F.;Kaiser. E.T.; *J.Org. Chem.*,**1980**, 45, 1295). A preferred resin is an oxime functionalized polystyrene, such as an oxime-polystyrene resin derived from p-nitrobenzophenone polystyrene resin according to the following formula.



As used herein and in the appended claims, "halo" means a member selected from the group consisting of fluoro, chloro, bromo and iodo.

"Alkyl" is the radical of saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl group, and that groups may include one or more double or triple bonds. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone, and more preferably 20 or fewer and most preferred 10 or fewer. Likewise, preferred cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably have 3-6 carbons in the ring structure. Particularly preferred alkyl substituents include methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, iso-butyl, tert-butyl, sec-butyl, cyclobutyl, pentyl, hexyl, cyclohexyl, etc. Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to ten carbons, more preferably from one to six carbon atoms in its backbone structure. The aliphatic cyclic groups can be single or polycyclic containing between about 3 to 12 carbons per ring, but preferably between 3 and 9 carbons per ring.

"Haloalkyl" and "alkylhalo" both refer to mono- or poly- halogen radical substituted alkyl radicals, with the alkyl radicals having the analogous length and possible substitution as described above. Typically, these terms refer to groups of the formula X_n-(CX'X")$_m$-, where n and m are each independently an integer $\geq$ 1, and X, X' and X" are each independently hydrogen or halogen (so long as at least one of X, X' and X" are halogen).

"Hydroxyalkyl" and "alkylhydroxide" and "alkyl alcohol" all refer to a mono or poly hydroxide radical substituted alkyl radical, with the alkyl radicals having the analogous length and possible substitution as described above.

"Alkyloxyalkyl ether" and "alkyloxyaryl ether" both refer to ether functional radicals of either the dialkyl radical or the alkyl, aryl radical configuration, with the alkyl radicals and the aryl radicals having the analogous length and possible substitution to the alkyl and aryl radicals defined herein.

"Alkenyl" and "alkynyl" refer to unsaturated aliphatic substituents analogous in length and possible substitution to the alkyl radicals described above, but that contain at least one double or triple bond, respectively.

"Amino" means an amino radical substituted with up to 2 alkyl radicals as defined above or with 1 alkyl radical and a hydrogen radical, or with two or more hydrogen radicals or with the substitution required to complete the nitrogen's valence requirements.

"Aryl" as used herein includes 5-10 membered aromatic monocyclic or fused polycyclic moieties that may include from zero to four heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, naphthyline, benzathiazoline, benzothiapene, benzofurans, indole, quinoline, etc. The aryl group can be substituted at one or more positions with halo, alkyl, alkoxy, alkoxy carbonyl, haloalkyl, cyano, amino sulfonyl, aryl, sulfonyl, aminocarbonyl, carboxy, acylamino, alkyl sulfonyl, amino and substituted or unsubstituted substituents.

As used herein and in the appended claims, "heteroaryl" is a mono-, bi- or tricyclic, -N-, -O- or -S- heteroaryl substituent, such as benzofuran, benzothiophene, furan, imidazole, indole, isothiazole, oxazole, piperazine, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinoline, thiazole and thiophene.

As used herein and in the appended claims a "library" means a large number of chemical derivatives used in screening for biological activity or other activity. In general a library will have greater than 20 members, preferably the library will have at least 50 members, more preferably the library will have at least 96 members and most preferably the library will have at least 1000 members.

As used herein and in the appended claims "chemically derivatized" means the chemical manipulation such as addition to, oxidation of, substitution for, reduction of, or cyclization of the selected R group or R groups of the intermediate. Chemical derivatization also means the manipulation of two or more groups of the intermediate such that additional aryl or alkyl rings are formed and that rings may be

fused or unfused to the intermediate ring, and that new ring may be substituted with further chemically derivatizable substituents.

As used herein and in the appended claims "pharmaceutically acceptable salt" and "salts thereof" means organic or inorganic salts of the pharmaceutically important molecule. A pharmaceutically acceptable salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion or other counterion. The counterion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically important organic molecule may have more than one charged atom in its structure. Situations where multiple charged atoms are part of the molecule may have multiple counterions. Hence, the molecule of a pharmaceutically acceptable salt may contain one or more than one charged atoms and may also contain, one or more than one counterion. The desired charge distribution is determined according to methods of drug administration. Examples of pharmaceutically acceptable salts are well known in the art but, without limiting the scope of the present invention, exemplary presentations can be found in the *Physician's Desk Reference*, *The Merck Index*, *The Pharmacopoeia* and Goodman & Gilman's *The Pharmacological Basis of Therapeutics*.

As used herein and in the appended claims, "TFA" means trifluoro acetic acid, "HCl" means hydrochloric acid, "THF" means tetrahydrofuran, "DMF" means dimethylformamide, "DIPEA" means diisopropylethyl amine, "TMS" means a trimethyl silyl radical and "TBS" means a *t*-butyldimethyl silyl radical.

As used herein and in the appended claims "leaving group" means halo, oxo, thioxo radicals and activated alcohols such as a p-toluene sulfonyl activated alcohols and other groups that are susceptible to displacement and replacement by a nucleophile under selected conditions of temperature, solvent and time.

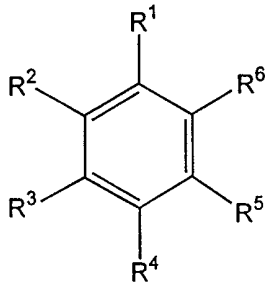
As used herein and in the appended claims "scaffold" means a common chemical structure found within a library of organic compounds. Similarly, within a combinatorial chemical library the scaffold forms the basis for a diverse series of chemical derivatization, additions and subtractions. Importantly, regardless of the

extent of the chemical derivatization performed on the scaffold, the product is within the scope of the combinatorial library.

All other acronyms and abbreviations have the corresponding meaning as published in journals relative to the art of organic chemistry.

A general method for making polycyclic heterocyles according to the first aspect of the invention involves the following method.

(a) reacting a compound of the formula (I):



I

where each of R^1, R^2, R^3 and R^4 is a stable moiety independently selected from the group consisting of halo, haloalkyl, cyano, nitro, R^a-Q-, R^a-Q-alkyl, R^a-Q-alkenyl, R^a-Q-alkynyl, R^a-Q-arylalkyl and R^a-Q-aryl;

R^a is hydrogen, alkyl, aryl or arylalkyl;

Q is a single bond, -O-, -NR^b-, -CO-, -NR^b-CO-, -CO-NR^b-, -CO-O-, -O-CO-, $S(O)_i$, -$S(O)_j$-NR^b-, -NR^b-$S(O)_j$;

i = 0, 1 or 2;

j = 1 or 2;

R^b is hydrogen, alkyl, aryl or arylalkyl, where R^a and R^b may together with the nitrogen to that they are attached form a ring, R^5 is selected from the group consisting of halo, nitro, and haloalkyl.

It is understood that each of R^1, R^2, R^3 and R^4 may be substituted one to three times with a substituent selected from the group consisting of alkyl, alkenyl, alkynyl, halo, hydroxy, alkoxy, alkylthio, sulfonyl, aryl, heteroaryl and where the substituents of the moieties substituted can themselves be substituted with one to three further substituents, if desired.

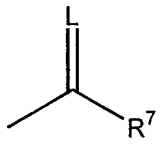
Particularly one of R^1, R^2, R^3 or R^4 is an haloalkyl, more particularly either R^1, R^3 or R^4 is a CF_3 radical and most particularly R^3 is a CF_3 radical. Particularly one of R^1, R^2, R^3 or R^4 is an hydroxyalkyl, more particularly one of R^1, R^2, R^3 or R^4 is methoxy and most particularly R^3 is a methoxy radical.

Particularly one of R^1, R^2, R^3 or R^4 is halo, cyano or nitro. When halo, one of R^1, R^2, R^3 or R^4 is bromo, and most particularly R^3 is bromo. When one of R^1, R^2, R^3 or R^4 is a cyano radical, R^3 is most particularly a cyano radical. When one of R^1, R^2, R^3 or R^4 is a nitro radical, R^3 is most particularly a nitro radical.

Particularly, R^5 is selected from fluoro, chloro or nitro.

If a 5,6 polycycle is desired, then R^5 is a halo. Also, R^5 is between C_1 to C_{12} haloalkyl, particularly R^5 is between C_1 to C_6 haloalkyl and more particularly R^5 is a halomethyl and most particularly R^5 is bromomethyl.

R^6 of formula (I) is selected from the group consisting of cyano and a radical of formula (II) where L is selected from the group consisting of -O-, -S- and -NH-.



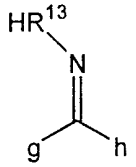
II

When R^6 is the radical of formula (II), L is preferably -O- or -S- and most preferably -O-.

R^7 of formula (II) is selected from the group consisting of alkyl, aryl, arylalkyl, alkyloxyalkyl, aryloxyalkyl, alkylamino, dialkylamino, arylamino, alkoxy carbonyl, amino, alkoxy, hydroxy and heteroaryl. Where R^6 is a radical of formula (II), then R^7 is preferably aryl and most preferably R^7 is phenyl.

In one embodiment R^5 is halomethyl and R^6 is cyano. In another embodiment, R^5 is halo, R^6 is formula (II), L is oxygen and R^7 is a phenyl radical. In another embodiment R^5 is halo and R^6 is cyano.

The compound (I) is reacted with the solid support bound member (III) under suitable conditions for a desired period of time and at a desired temperature such that the compound (I) is reacted with the compound (III).



III

Preferably in compound (III), g is a solid support selected from the group consisting of a resin, a polymer, a gel, glass beads, silica gel, a ceramic solid support or other solid composition. More preferably the solid support is a resin and most preferably the solid support is a polystyrene resin.

Likewise in compound (III), h is selected from the group consisting of alkyl and aryl. Preferably h is aryl, more preferably h is a substituted aryl and most preferably h is p-nitrophenyl.

Also in compound (III) above, R^{13} is selected from the group consisting of -NH-, -O- and -S-, most preferably R^{13} is -O-.

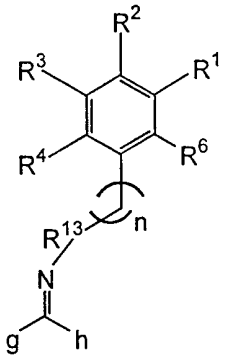
Suitable conditions for this reaction include having a suitable solvent mixture, a suitable temperature and reacting for a suitable period of time.

A suitable solvent mixture is preferably of basic pH. Preferably the base is an alkoxide, more preferably the base is an alkoxide of fewer than 5 carbons and most preferably the base is $K^{+-}OBu^{t}$. A suitable solvent is either protic or aprotic, preferably the solvent is aprotic and even more preferably the solvent is aprotic and anhydrous and most preferably the solvent is THF.

The reaction temperature is preferably between about 0° C and 85° C but more preferably between about 30° C and about 70° C and most preferably at about 55° C.

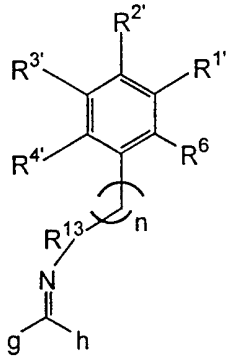
The reaction time is preferably between about 1 minute and 2 days, more preferably between about 1 hour and 1 day and most preferably between about 8 hours and 14 hours.

Under the above discussed preferred conditions the compounds (I) and (III) react forming an intermediate (IV) where $n \geq 0$, and g, h, R^1, R^2, R^3, R^4, R^6 and R^{13} are as defined above.



IV

This intermediate (IV) is optionally chemically derivatized prior to the cyclization and displacement procedure.to form a corresponding intermediate (IV'):



IV'

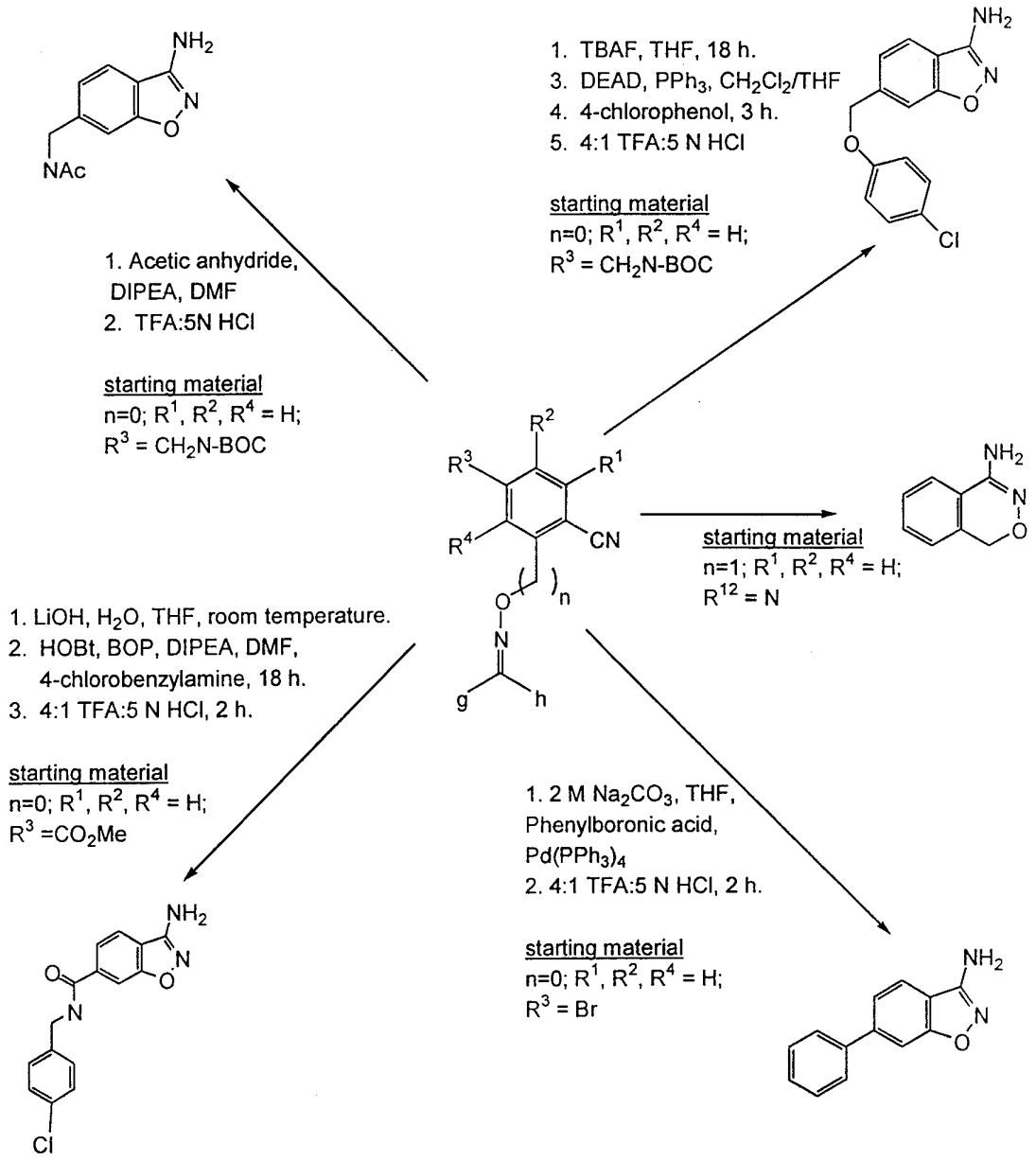
where the $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ substituents are each independently the same as substituents R^1, R^2, R^3 and R^4 respectively if not derivatized or are each independently the chemically derivatized substituents respectively.

Examples of chemical derivatization reactions include, but are not limited to, the following general derivatizations procedures.

Chemical reaction conditions suitable for BOC (t-butyloxycarbonyl) removal/acylation, TMS (trimethylsilyl) or other silicon based alcohol-protecting group removal (F^-/aqueous acid), Mitsunobu reaction (O. Mitsunobu, *Synthesis* **1981,** 1-28), Suzuki coupling (N. Miyaura, A. Suzuki, *Chem. Commun.* **1979,** 866), Horner-Emmons type olefinations (W.S. Wadsworth, Jr., W.D. Emmons, *J. Chem. Soc.* **83,** 1733 (1961)), reductive aminations (Klyeuv and Khidekel, *Russ. Chem. Rev.* **49,** 14-27 (1980)), Sonogashira coupling (S.I. Kahn, M.W. Grinstaff,

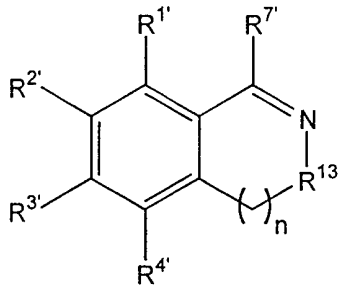
Tetrahedron Lett. **39**, 8031 (1998)), and ester hydrolysis/amidation reaction conditions. Specific examples of the above described chemical derivatization of the intermediate are in the included examples. The BOC protected nitrogen of the intermediate compound of Example **ix** is deprotected and reacted with acetic anhydride. The TBS (*t*-butyldimethyl silyl) protected alcohol of the intermediate compound of Example **x** is deprotected with tetrabutylamonium fluoride and reacted with a chlorophenol under Mitsunobu conditions to give the p-chlorophenyl ether derivatized intermediate. The methylene ester radical at R^3 of the intermediate of Example **xv** is subjected to ester hydrolysis/amidation providing the p-chlorophenyl methylaminocarbonyl methylenamide substituent.

Although optional, examples of preferred derivatizations are as discussed above, and as described in Scheme B.



Scheme B

After the optional derivatization of the intermediate, the cyclization and displacement reaction whereby the product (V) is formed.



V

In product (V), the $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ substituents are each independently the same as substituents R^1, R^2, R^3 and R^4 respectively if not derivatized or are each independently the chemically derivatized substituents respectively. Hence, each of $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ may be correspondingly the same as R^1, R^2, R^3 and R^4 or may represent the result of the optional chemical derivatization of the corresponding substituent, prior to cyclization and displacement. Also, chemical derivatization includes other ring formation or ring closure reactions such as where any two of $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ together form an aryl or an alkyl ring of between about 5 and 14 atoms.

$R^{7'}$ is amino, hydroxy or the same as R^7 above.

CONDITIONS SUITABLE FOR THE CYCLIZATION AND DISPLACEMENT PROCEDURE

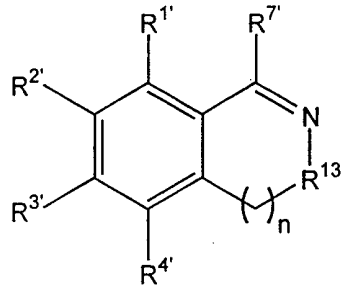
The temperature for the cyclization and displacement procedure may be between about 0° and 85° C but is preferably between about 30° and 70° and is most preferably at about 55° C.

The solvents suitable for the cyclization and displacement procedure include protic and aprotic solvent mixtures, aqueous and anhydrous solvent mixtures. A preferred solvent is TFA, a more preferred solvent mixture is TFA:H_2O a most preferred solvent mixture is TFA:5 N HCl/H_2O. Although a solvent mixture of TFA:5 N HCl/H_2O is most preferred, the ratio of this TFA:5 N HCl/H_2O mixture may vary between about 1:1 to about 99:1 TFA:5 N HCl/H_2O, but preferably is between about 80:1 to 1:1 TFA:5 N HCl/H_2O, and is most preferably at about 4:1 TFA:5 N HCl/H_2O.

The time for the cyclization and displacement reaction may vary, but generally is between about 1 minute and 4 days but preferably between about 1 hour and 20 hours.

A second aspect of the invention is directed to a solid support bound intermediate (IV) above. Optionally, the intermediate (IV) can be derivatized before the cyclization and displacement procedure to thereby provide further options for the groups R^1, R^2, R^3 and R^4 in the final product. The preferred, yet optional, derivatizations of the intermediate compound (IV), and preferred conditions whereby optional derivatizations occur are as described above.

A third aspect of the invention is directed to a library of polycyclic heterocycle compounds where the library contains a plurality of diverse compounds (V):



V

In compound (V),

where each of R^1, R^2, R^3 and R^4 is a stable moiety independently selected from the group consisting of halo, haloalkyl, cyano, nitro, R^a-Q-, R^a-Q-alkyl, R^a-Q-alkenyl, R^a-Q-alkynyl, R^a-Q-arylalkyl and R^a-Q-aryl;

R^a is hydrogen, alkyl, aryl or arylalkyl;

Q is a single bond, -O-, -NR^b-, -CO-, -NR^b-CO-, -CO-NR^b-, -CO-O-, -O-CO-, $S(O)_i$, -$S(O)_j$-NR^b-, -NR^b-$S(O)_j$;

i = 0, 1 or 2;

j = 1 or 2;

R^b is hydrogen, alkyl, aryl or arylalkyl, where R^a and R^b may together with the nitrogen to that they are attached form a ring, and $n \geq 0$; and

$R^{7'}$ is selected from the group consisting of alkyl, aryl, arylalkyl, alkyloxyalkyl, aryloxyalkyl, alkylamino, dialkylamino, arylamino, alkoxy carbonyl, amino, alkoxy, hydroxy and heteroaryl; and

R^{13} is selected from the group consisting of -NH-, -O- and -S-.

Preferred substituents for $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{7'}$, and values for n are as described above, in the included examples and the appended claims.

A fourth aspect according to the present invention preferably produces a library of compounds where the compounds comprise a diverse chemical library according to the general methods discussed above. All of the compounds in such a library have a common scaffold, e.g., compound (V).

When preparing a combinatorial library according to the present invention, diversity is introduced via the $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{7'}$, and R^{13} substituents as discussed more fully above. These substituents are selected to allow the creation of a chemically diverse library that, as one goal, maximizes the exploration of molecular spatial properties. Such maximization increases the likelihood of creating compounds that will be biologically active against selected targets.

A fifth aspect of the invention is directed to an assay kit for the identification of biologically active compounds, the kit comprising assay materials and a well plate apparatus where each well in the apparatus contains a compound of the library described above.

PARALLEL SYNTHESIS

The fourth and fifth aspects of the solid support mediated method of the invention may be carried out by way of parallel synthesis in any reaction vessel capable of holding the liquid reaction medium and having, preferably, inlet and outlet means.

For small-scale synthesis of multiple products, the solid support mediated method of the invention is preferably carried out in containers adaptable to parallel array syntheses. With parallel array synthesis, individual reaction products are prepared in each of multiple reaction zones. The reaction zones are physically

separated from one another in a reaction vessel. Compounds can be added to the reaction vessel by multiple delivery apparatus, automated or robotic apparatus, any of that may be either manually or computer controlled.

A preferred parallel synthesis embodiment of the present invention is a diverse polycyclic heterocycle compound library in the form of a plurality of wellplates, each wellplate having wells containing a separate reaction product (library compound). In such cases, their wellplate number and "x" column and "y" wellplate row coordinates conveniently identify the library compounds. The process of making the library of polycyclic heterocycle compounds may be conveniently carried out in a conventional wellplate apparatus. It is particularly advantageous to carry out the method of the invention in a standard wellplate apparatus such as a plastic 96 well microtiter plate.

Typically, the wellplate apparatus is in the form of a rigid or semi-rigid plate, the plate having a common surface containing openings of a plurality of reservoirs arranged in rows and columns. A standard form of wellplate apparatus is a rectangular plastic plate having 8 rows and 12 columns (total 96) of liquid retaining depressions, or reservoirs, on its surface. A wellplate apparatus may optionally have other elements of structure such as a top or cover (e.g., plastic or foil), a bottom in a form such as a plate or reservoir, clamping means to secure the wellplate and prevent loss of its contained compounds.

The polycyclic heterocycle library of compounds formed using the solid support mediated method aspects of the invention can be used to screen compounds for biological or other activity. Myriad biological assays are known in the art and can be used to screen the polycyclic heterocycle library of compounds.

SCREENING OF POLYCYCLIC HETEROCYCLE DERIVATIVE LIBRARIES

The libraries of diverse polycyclic heterocycle according to the solid support mediated method of the present invention (e.g., compounds (II)) may be screened for biological activity. Generally the library to be screened is exposed to a biological substance, usually a protein such as a receptor, enzyme, membrane binding protein

or antibody, and the presence or absence of an interaction between the heterocycle derivative and the biological substance is determined. Typically this will comprise determining whether the biological substance is bound to one or more of the members of the library. Such binding may be determined by attaching a label to the biological substance. Commonly used labels include fluorescent labels. Other methods of labeling may be used, such as radioactive labels. The degree of binding affinity may be determined by quantitating the amount or intensity of the bound label. Thus, various biologically active compounds may be selected by identifying that compounds bind the particular biological substance most effectively.

Illustrative additional assays include but are not limited to *in vitro* assays such as enzymatic inhibition, receptor - ligand binding, protein - protein interaction, andprotein - DNA interaction; cell based, functional assays such as transcriptional regulation, signal transduction / second messenger, and viral infectivity; add, incubate & read assays such as scintillation proximity assays (SPA), fluorescence polarization assay, fluorescence correlation spectroscopy, colorimetric biosensors, cellular reporter assays using reporter genes such as luciferase, green fluorescent protein, β-lactamase, and the like; and electrical cell impedance sensor assays.

All of the above assays are known in the art to be predictive of success for an associated disease state.

EXAMPLES

The following examples are provided as illustration only, and are not intended to limit this invention in any way.

General. Reagents obtained from commercial sources were used without further purification. Kaiser oxime resin **1** was purchased from Novabiochem with a loading capacity of 1.07 mmol/g. All NMR spectra (400 MHz) were recorded on a Varian Gemini-400 spectrometer. Mass spectra were obtained with either ESI or FAB as the ionization method. All purifications were carried out by radial chromatography (Chromatotron® model 8924, Harrison Research) using 1 mm silica gel plates (Analtech). Crude purities were estimated from integrated peak areas of

HPLC chromatographs with the UV detector monitoring at λ = 215 nm. Analytical HPLC setup: C_{18} Vydac® column with solvent gradient A = acetonitrile (0.1% TFA) and B = water (0.1% TFA) at 1 ml/min flow-rate. Unless otherwise noted, all HPLC retention times are given for an eluent gradient of 10% A to 60% A over 40 min.

The nomenclature of 3-aminobenzisoxazole compounds is based on the heterocycle numbering system (Shutske, G.M.; Kapples, K.J. *J. Heterocyclic Chem.* **1989**, *26*, 1293. For other examples of solution phase intramolecular nucleophilic additions to nitrile by nitrogen see: Kwok, R.; Pranc, P. *J. Org. Chem.* **1967**, *32*, 738. Blicke, F.F.; Zambito, A.J.; Stenseth, R.E.; *J. Org. Chem.* **1961**, *26*, 1826.) shown below:

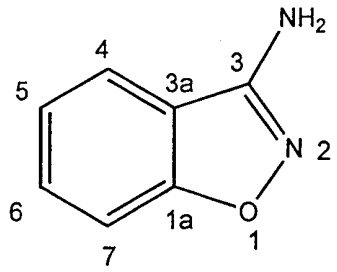
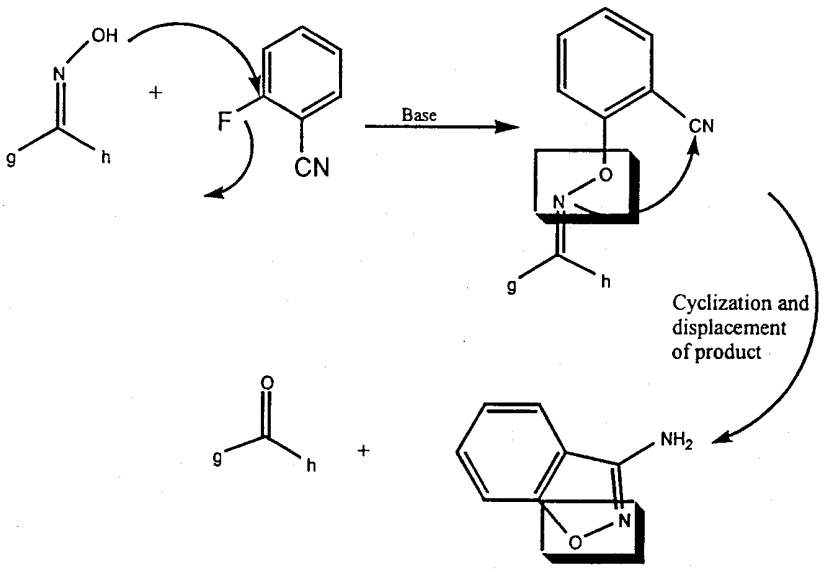


Table A lists representative moieties that are substituted for R on the designated position of the starting compound. Because the moieties are representative of a general class of organic substituents, it is meant that other organic substituents are chemically equivalent to those given in Table A and are within the scope of the invention and appended claims. For example, where the CF_3 radical replaces R^3, the placement of the same group in position 4, 5 or 6 is an equivalent analogue. Hence, the CF_3 placed at each of positions 3, 4, 5, 6 or any combination thereof is within the scope of this invention and appended claims. Furthermore the CF_3 group is, optionally, meant to represent an electron withdrawing group and can therefor be replaced by other electron withdrawing groups such as polyhalo-alkyl and be within the scope of this invention.

Although not wanting to be bound by a theoretical explanation of chemical mechanistic analysis, the following proposed mechanism is useful for explaining an embodiment of the invention.



In the proposed mechanism, the solid support bound oxime is reacted with the fluorobenzonitrile of Example 1 under suitable conditions to form the solid support bound intermediate. The solid support bound intermediate is optionally isolated and finally subjected to the cyclization and displacement procedure. As illustrated in Scheme III, the nitrogen and oxygen of the solid support bound oxime are involved in the cyclization and displacement reaction and become part of the polycyclic heterocycle.

Table A

Example Number	R	% yield of the resin bound intermediate	% isolated yield of the corresponding R substituted benzisoxazoles
i	H	64	76
ii	R^4=CF_3	83	62
iii	R^3=MeO	80	85
iv	R^3=CF_3	90	86
v	R^3=Br	90	78
vi	R^3=CN	69	68
vii	R^1=CF_3	69	75

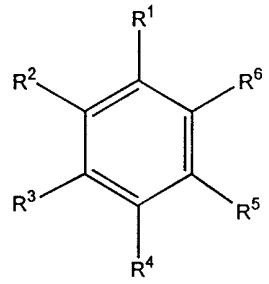
Example Number	R	% yield of the resin bound intermediate	% isolated yield of the corresponding R substituted benzisoxazoles
viii	R^2=NO_2	95	70

Although not limited to these exemplary reactions, it will become apparent to one of skill in the art through these examples and appended claims the broad range of chemical derivations and transformations that can, optionally, be performed on the solid support bound intermediate. The optional chemical derivatization of the solid support bound intermediate according to a broad range of chemistry with neither destruction of the solid support nor diminishment of the derivatized polycyclic heterocycle yield is a surprising result. Indeed, it is within the scope of this invention to allow the optional chemical derivatization of the solid support bound intermediate according to methods known in the art.

Although Table A demonstrates some examples, it is to be understood that the solid support mediated method according to one aspect of this invention includes analogues involving substituents at each available position of the aromatic scaffold, such as a tri or tetra substituted phenyl. Moreover, where R is methoxy, then a C_1 to C_{12} alkoxy is considered an equivalent analogue. And where the substituent group is Br, then another halo substituent such as -F or -Cl is an equivalent analogue.

The solid support mediated method according to the present invention further allows for the optional chemical derivatization of none, any, or all of R^1, R^2, R^3, R^4 substituents of the solid support bound intermediate as provided above. Indeed the solid support bound intermediate is preferably stable to a broad range of reaction conditions.

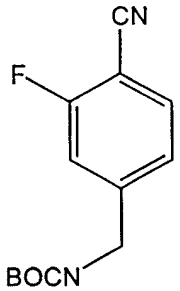
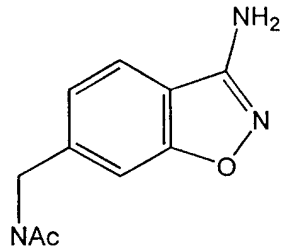
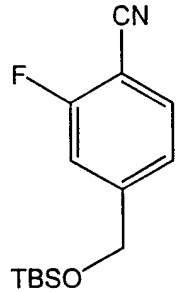
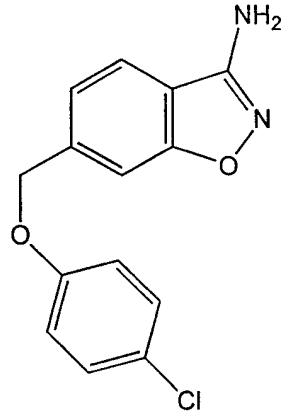
Table B lists substituted aromatic compounds (I), which are reacted with the solid support bound member, thereby forming the solid support bound intermediate (IV), are chemically derivatized with final cyclization and displacement of the corresponding polycyclic heterocycle.

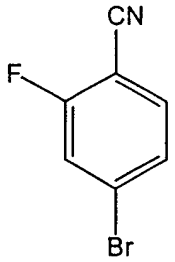
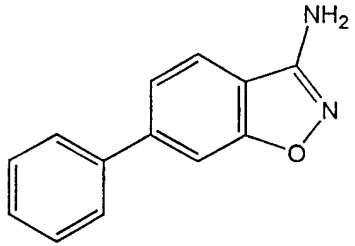
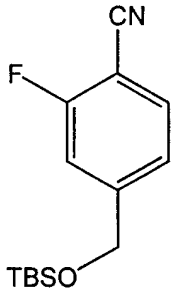
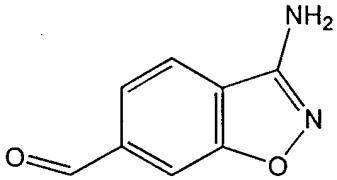
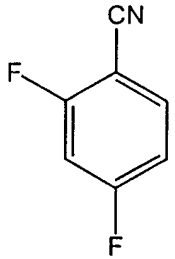
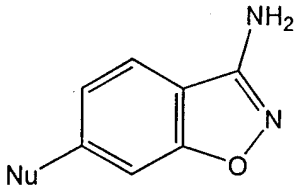


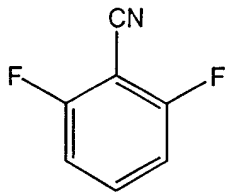
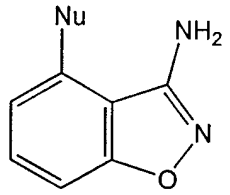
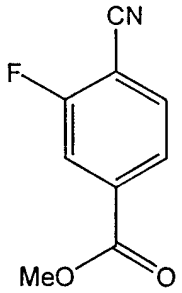
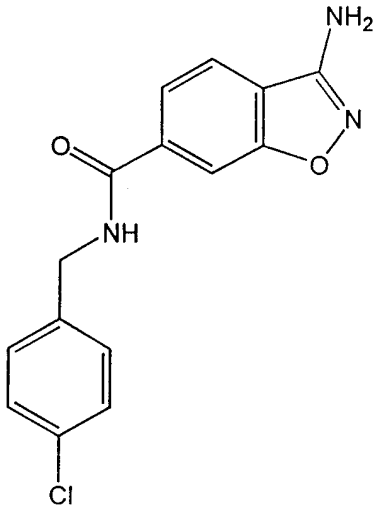
I

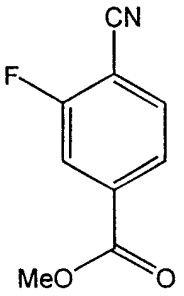
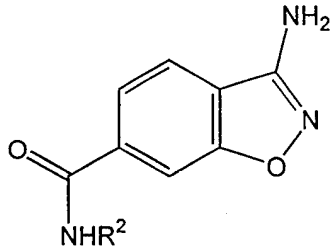
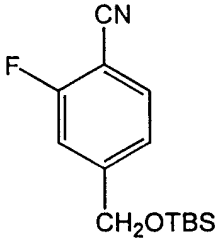
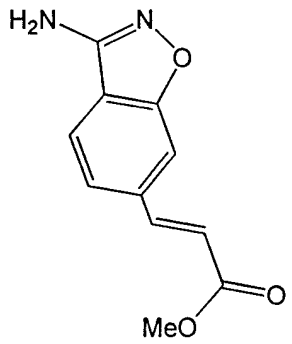
The compounds of Table B are synthesized according to the solid support mediated method of the present invention. This list is intended to demonstrate the diversity of compounds that are synthesized according to this invention and is not intended to limit the scope in any way.

Table B

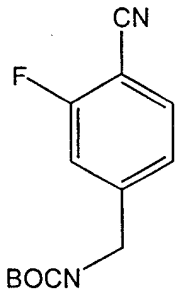
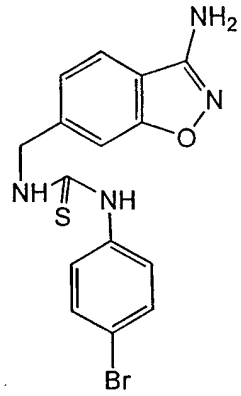
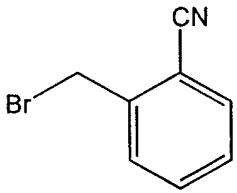
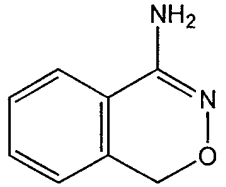
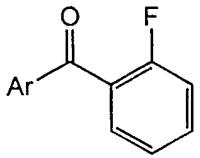
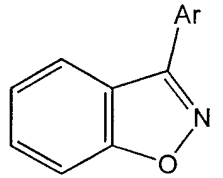
Example Number	Compound (I)	Reaction conditions	Product (V)
ix		1. Load onto resin 2. acetic anhydride, DIPEA, DMF 3. TFA:5N HCl	
x		1. Load onto resin 2. TBAF, THF, 18 h. 3. DEAD, PPh_3, CH_2Cl_2/THF 4-chlorophenol, 3 h. 4. 4:1 TFA:5 N HCl	

Example Number	Compound (I)	Reaction conditions	Product (V)
xi		1. Load onto resin 2. 2 M Na_2CO_3, THF, Phenylboronic acid, $Pd(PPh_3)_4$ 3. 4:1 TFA:5 N HCl, 2 h.	
xii		1. Load onto resin 2. TBAF 3. Oxidize 4. 4:1 TFA:5 N HCl, ~2 h.	
xiii		1. Load onto resin 2. Arylfluoride substitution (Nu:) 3. 4:1 TFA:5 N HCl, ~2 h.	

Example Number	Compound (I)	Reaction conditions	Product (V)
xiv		1. Load on resin 2. Arylfluoride substitution (Nu:) 3. 4:1 TFA:5 N HCl, ~2 h.	
xv		1. Load on resin 2. LiOH, H_2O, THF, room temperature. 3. HOBt, BOP, DIPEA, DMF, 4-chlorobenzylamine, 18 h. 4. 4:1 TFA:5 N HCl, 2 h.	

Example Number	Compound (I)	Reaction conditions	Product (V)
xvi		1. Load on resin 2. LiOH, H_2O, THF, room temperature. 3. HOBt, BOP, DIPEA, DMF, R^2-NH_2, 18 h. 4. 4:1 TFA:5 N HCl, 2 h.	
xvii		1. Load onto resin 2. TBAF 3. Oxidize 4. Horner-Emmons type olefination with $(EtO)_2POCH_2CO_2$-Me 5. 4:1 TFA:5 N HCl, 2 h.	

Example Number	Compound (I)	Reaction conditions	Product (V)
xviii		1. Load onto resin 2. TFA 3. 4-bromobenzoyl chloride 4. TFA:5N HCl	
xix		1. Load onto resin 2. TFA 3. 4-bromophenylisocyanate 4. TFA:5N HCl	

Example Number	Compound (I)	Reaction conditions	Product (V)
xx		1. Load onto resin 2. TFA 3. 4-bromophenyl-isothiocyanate 4. TFA:5N HCl	
xxi		1. Load onto resin 2. 4:1 TFA:5 N HCl, 8 h.	
xxii		1. Load onto resin 2. 4:1 TFA:5 N HCl, 8 h.	

Example Number	Compound (I)	Reaction conditions	Product (V)
xxiii		1. Load onto resin 2. Reductive amination, $NH(R^3)_2$ 5. 4:1 TFA:5 N HCl, 2 h.	

The resin bound intermediates of the present invention were surprisingly stable to conditions suitable for optional derivatizations such as, BOC removal/acylation, TBS removal and Mitsunobu coupling, Suzuki coupling, Sonogashira coupling, Hoerner-Emmons olefination, and ester hydrolysis/amidation reaction conditions. These and other reactions discussed were performed according to the following detailed chemical procedure.

General Synthetic Procedures

The following general synthetic procedures where used to synthesize the above mentioned products. Although the following procedures are specific to the formation of an intermediate and product with a designated "R" group, the desired intermediate and product can be obtained through replacement of the desired "R" group for the one designated in the procedure.

General Example 1

Formation of 3-aminobenzisoxazole : to 500 mg of high loading (1.07 mmol/g, 0.54 mmol) *p*-nitrobenzophenone oxime polystyrene resin (obtained from Novabiochem) in a 25 mL capacity Kontes Microfilter Funnel is added 7 mL of THF and 640 μL of potassium *t*-butoxide (1 M in THF, 0.642 mmol). This was shaken by hand for several minutes whereupon the resin turned a purple color. To this was added 2-fluorobenzonitrile (1.07 mmol, 214 mg) neat. The reaction vessel is placed in an oven fitted with a rotating device for 12 h. The oven was at the most preferred temperature of 55° C. The loaded resin was removed from the oven and allowed to cool for 1 h and rinsed with 2 x 5 mL of CH_2Cl_2, 2 x 5 mL of 5% TFA/CH_2Cl_2, 2 x 5 mL of isopropanol and 4 x 5 mL of MeOH. This was dried in a 35° C vacuum oven for 12 h. Next, 4 mL of TFA and 1mL of aqueous 5 N HCl were then added to the resin followed by turning for 2 h in a 55° C oven. The TFA/H_2O was collected and the resin was rinsed with 2 x 5 mL of CH_2Cl_2. These were combined and concentrated *in vacuo* to give the crude product (>98% purity by reverse phase HPLC) that was radial chromatographed on a 2 mm plate using 25%

EtOAc/Hexanes. Concentration of the product containing fractions gave pure (35 mg, 2 step yield = 49%, 74% yield based on loading).

General Example 2

Formation of 4-amino-1 H-2,3-benzoxazine : to 500 mg of high loading (1.07 mmol/g, 0.54 mmol) *p*-nitrobenzophenone oxime polystyrene resin (obtained from Novabiochem) in a 25 mL capacity Kontes Microfilter Funnel was added 7 mL of THF and 640 μL of potassium *t*-butoxide (1 M in THF, 0.642 mmol). This was shaken by hand for several minutes whereupon the resin turned a purple color. To this was added 2-(1-bromomethyl)benzonitrile (1.07 mmol) neat. The reaction vessel was placed in an oven fitted with a rotating device for 12 h. The oven was at the most preferred temperature of 55° C. The loaded resin was removed from the oven and allowed to cool for 1 h and rinsed with 2 x 5 mL of CH_2Cl_2, 2 x 5 mL of 5% TFA/CH_2Cl_2, 2 x 5 mL of isopropanol 4 x 5 mL of MeOH. This was dried in a 35° C vacuum oven for 12 h. Next, 4 mL of TFA and 1mL of aqueous 5 N HCl were then added to the resin followed by turning for 8 h in a 55° C oven. The TFA/H_2O was collected and the resin was rinsed with 2 x 5 mL of CH_2Cl_2. These were combined and concentrated *in vacuo* to give the crude product (>98% purity by reverse phase HPLC) that was radial chromatographed on a 2 mm plate using 25% EtOAc/Hexanes. Concentration of the product containing fractions gave pure product.

General Example 3

Formation of 3-amino-6- (N-acetylaminomethyl) benzisoxazole: to 500mg of high loading (1.07 mmol/g, 0.54 mmol) *p*-nitrobenzophenone oxime polystyrene resin (obtained from Novabiochem) in a 25 mL capacity Kontes Microfilter Funnel was added 7 mL of THF and 640 μL of potassium *t*-butoxide (1 M in THF, 0.642 mmol). This was shaken by hand for several minutes whereupon the resin turned a purple color. To this was added 4-(N-BOC-aminomethyl)-2-fluorobenzonitrile (1.07 mmol, 214 mg) neat. This reaction vessel was placed in a

55 °C oven fitted with a rotating device for 12 h. This was removed from the oven and allowed to cool for 1 h and rinsed with 2 x 5 mL of CH_2Cl_2, 2 x 5 mL of isopropanol, and 4 x 5 mL of isopropanol, and 4 x 5 mL of MeOH. This was dried in a 35 °C vacuum oven for 12 h. BOC-deprotection was achieved using 25% TFA/CH_2Cl_2 (7 mL) followed by shaking for 2 h. Resin was again rinsed with 2 x 5 mL of CH_2Cl_2, 2 x 5 mL of isopropanol, and 4 x 5 mL of MeOH. The resin was suspended in DMF followed by addition of acetic anhydride and diisopropylethylamine. This was allowed to shake for 3h and was rinsed with 2 x 5 mL of CH_2Cl_2, 2 x 5 mL of isopropanol, and 4 x 5 mL of MeOH. 4 mL of TFA and 1 mL of aqueous 5 N HCl were then added to the resin followed by turning for 2 h in a 55° C oven. The TFA/H_2O was collected and the resin was rinsed with 2 x 5 mL of CH_2Cl_2. These were combined and concentrated *in vacuo* to give the crude benziosoxazole product (98% purity by reverse phase HPLC) that was radial chromatographed on a 2 mm plate using 25% EtOAc/Hexanes. Concentration of the product containing fractions gave pure benzisoxazole product (35 mg, 4 step yield = 49%).

General Example 4

Formation of 3-amino-6- (*p*-chlorophenoxymethyl) benzisoxazole: to 500mg of high loading (1.07 mmol/g, 0.54 mmol) *p*-nitrobenzophenone oxime polystyrene resin (obtained from Novabiochem) in a 25 mL capacity Kontes Microfilter Funnel was added 7 mL of THF and 640 μL of potassium *t*-butoxide (1 M in THF, 0.642 mmol). This was shaken by hand for several minutes whereupon the resin turned a purple color. To this was added 4-(*tert*-butyldimethylsilyloxymethyl)-2-fluorobenzonitrile (1.07 mmol, 214 mg) neat. This reaction vessel was placed in a 55 °C oven fitted with a rotating device for 12 h. This was removed from the oven and allowed to cool for 1 h and rinsed with 2 x 5 mL of CH_2Cl_2, 2 x 5 mL of isopropanol, and 4 x 5 mL of MeOH. This was dried in a 35 °C vacuum oven for 12 h to give a Δwt = 82 mg (63% loading yield).TBS-deprotection was achieved using 1 M TBAF in THF (1.07 mL, 2 equiv.) followed by shaking for 18 h. The resin was

rinsed with 2 x 5 mL of CH_2Cl_2, 2 x 5 mL H_2O, 4 x 5 mL of MeOH. This was dried in a 35° C vacuum oven for 12 h. The resin was suspended in 8 mL of 1:1 THF/CH_2Cl_2 followed by addition of triphenylphosphine (700mg, 5 equiv.) and 4-chlorophenol (690 mg, 10 equiv.). This was shaken by hand followed by the slow addition of diisopropyl azodicarboxylate (0.53mL 5 equiv). This was allowed to shake for 3h and was rinsed with 2 x 5 mL of MeOH, 2 x 5 mL H_2O, and 4 x 5 mL of MeOH. 4 mL of TFA and 1 mL of aqueous 5 N HCl were then added to the resin followed by turning for 2 h in a 55 °C oven. The TFA/H_2O was collected and the resin was rinsed with 2 x 5 mL of CH_2Cl_2. These were combined and concentrated *in vacuo* (68% purity by reverse phase HPLC) that was radial chromatographed on a 2 mm plate using 25% EtOAc/Hexanes. Concentration of the product containing fractions gave pure benzisoxazole (49 mg, 4 step yield = 33%).

General Example 5

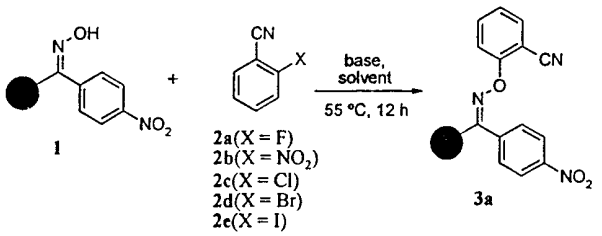
Loading Reaction. Nucleophilic aromatic substitution reactions have been extensively studied in solution. (Nudelman, N; Mancini, P.M.E.; Martinez, R.D.; Vottero, L.R. *J. Chem. Soc. Perkin Trans. 2* **1987**, 951. Miller, J. "Aromatic Nucleophilic Substitution"; Elsevier: Amsterdam, 1968. Bernasconi, C.F. *Acc. Chem. Res.* **1978**, *11*, 147) However, the extent to that this precedent could be applied to predict the outcome of these heterogenous reactions was not clear given the importance of resin swelling properties, site accessibility, etc. (Yan, B; Fell J. B.; Gnanasambandam, K. J. Org. Chem. 1996, 61, 7467.) Therefore, we studied the effect of the solvent, leaving group, and counterion on the solid phase loading reaction (Table 1). In comparing THF, MeCN, DMF, and DMSO, THF gave the best results, providing a 68% loading yield with 2-fluorobenzonitrile (**2a**) and 72% with 2-nitrobenzonitrile (**2b**). (Palermo, M.G. *Tetrahedron Lett.* **1996**, *37*, 2885.) A 20 to 30% decrease in the loading yield was observed for both **2a** and **2b** when DMF or DMSO was used as the solvent. Loading yields also decreased dramatically with the use of chloro- (**2c**), bromo- (**2d**), and iodo- (**2e**) benzonitriles.

The effect of the counterion on the loading reaction was evaluated with 2-

fluorobenzonitrile as the substrate in THF (Table 1, entry 1). The potassium salt of resin **1** gave the highest loading yields with potassium *tert*-butoxide ($KOBu^t$) giving slightly better results than potassium hexamethyldisilazide (KHMDS). Treatment of **1** with sodium hexamethyldisilazide (NaHMDS), gave a loading yield of 42% and, interestingly, no loading was observed with lithium hexamethyldisilazide (LiHMDS).

As described above, a variety of 2-fluorobenzonitriles can be loaded on the Kaiser resin (Lepore, S.D.; Wiley, M.R. *J. Org. Chem.* **1999**, *64*, 4547.). Although the presence of an electron withdrawing group facilitates loading at room temperature, substrates bearing either electron withdrawing groups or electron donating groups can be loaded in high yield in about 2 h at 55 °C. We also found that the loading reaction of 2-fluorobenzonitriles is not particularly sensitive to steric hindrance around the site of nucleophilic substitution.

Table 1. Effect of leaving group, solvent, and counterion on loading reactions.



			% loading yield of 3[a]			
entry	X	base	THF	MeCN	DMF	DMSO
1	F	$KOBu^t$	68	13	41	47
		KHMDS	55	-	-	-
		NaHMDS	42	-	-	-
		LiHMDS	<5	-	-	-
2	NO_2	$KOBu^t$	72	28	41	54
3	Cl	$KOBu^t$	<5	<5	<5	15
4	Br	$KOBu^t$	<5	-	-	-
5	I	$KOBu^t$	<5	-	-	-

[a]Determined by resin weight difference (average of 3 experiments)

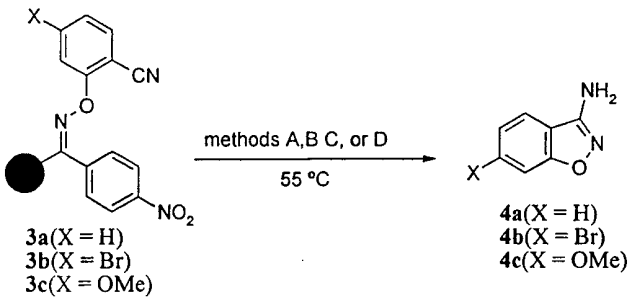
General Example 6

Studies on the acid stability of the aryl oxime linker. As previously reported, the use of 4:1 TFA/aqueous 5 N HCl at 55 °C for 2 h (Table 2, Method A) led to an efficient cyclorelease of a variety of substituted aminobenzisoxazoles. By contrast, we saw that the use of 99:1 TFA/H_2O at 55 °C (Table 2, Method B) with

intermediates bearing either inductively neutral or electron withdrawing substituents required significantly longer reaction times to reach completion. For example, hydrolysis of the resin bearing a bromo substituent *para* to the nitrile (Table 2, entry 2) using Method B required 4 days to give the corresponding aminobenzisoxazole **4b** in 65% yield. On the other hand, treatment of the *para*-methoxybenzonitrile derivative **3c** (Table 2, entry 3), under the same conditions, gave the methoxy-substituted product **4c** in 87 % isolated yield after only 2 h.

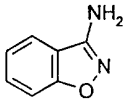
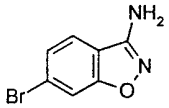
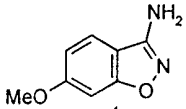
While the studies summarized above were important for identifying useful cyclorelease conditions, further experiments were performed in order to determine the acid stability profile of the linker under a variety of conditions commonly used for the removal of acid-sensitive protecting groups. The methoxy-substituted resin **3c** was selected for this study, since it is the most acid labile and therefore represents the worst case scenario. Upon treatment of the methoxy-substituted resin **3c** with 25% anhydrous TFA/CH_2Cl_2 at room temp for 2 h (Table 2, entry 3, Method C), conditions precedented for on-resin Boc removal, <5% of the cyclization product **4c** was removed from the resin. Even under more forcing conditions, with 100 % anydrous TFA at 55 °C (Table 2, entry 3, Method D) only 9% of the 3-aminobenzisoxazole product (>96% purity) was removed from the resin after 2 h. The aryl oxime linker was also stable to a number of milder aqueous acidic conditions that have been used for the removal of THP, silyl, and acetal protecting groups in solution. Thus, treatment of the resin **3c** with AcOH/THF/H_2O (3/1/1) at 55 °C for 12h (Corey, E.J.; Venkateswarlu, A. *J. Am. Chem. Soc.*, **1972**, *94*, 6190.) (Table 2, entry 3, Method E), or with TsOH/THF/H_2O at 55 °C for 12h (Thomas, E.J.; Williams, A.C. *J. Chem. Soc. Chem. Comm.*, **1987**, 992.) (Table 2, entry 3, Method F) gave no detectable release of material from the resin.

Table 2. Acid stability profile of the aryl oxime linker.



3a(X = H)
3b(X = Br)
3c(X = OMe)

4a(X = H)
4b(X = Br)
4c(X = OMe)

entry	X	product	method[a] (time)	yield[b] (% purity)
1	H	 **4a**	A (2 h) B (4 d)	78 (>96) 70 (65)
2	Br	 **4b**	A (2 h) B (4 d)	76 (>96) 53 (93)
3	MeO	 **4c**	A (2 h) B (2 h) C (2 h) D (2 h) E (12 h) F (12 h)	87 (>96) 85 (>96) <5 9 <5 <5

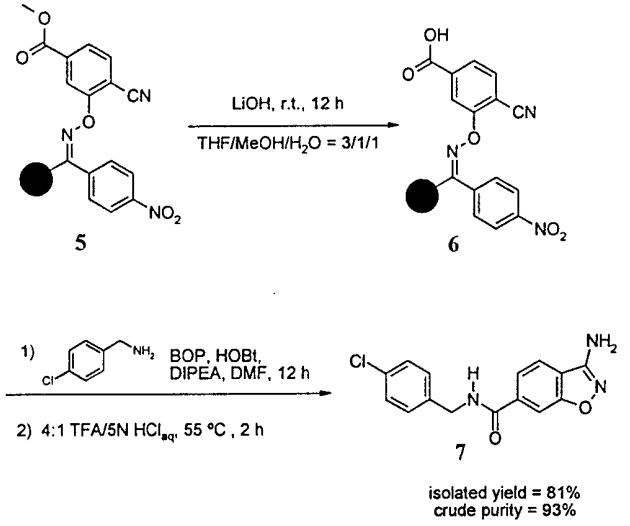
[a]Method A = 4:1 TFA/5N HCl, 55 °C. Method B = 99:1 TFA/H_2O, 55 °C. Method C = 25% THF/CH_2Cl_2, room temp. Method D = TFA, 55 °C. Method E = AcOH/THF/H_2O, 55 °C. Method F = TsOH/THF/H_2O, 55 °C.
[b]Isolated yield after chromatography and based on loading. Crude purity based on HPLC analysis.

General Example 7

Amide bond formation. Due to the importance of solid phase peptide synthesis, amide bond forming reactions have been the most widely performed and most highly developed solid phase reactions. (Kaldor, S.W.; Siegel, M.G. *Comb. Chem. Mol. Diversity Drug Discovery* **1998**, 307-335. Editors: Gordon, Eric M.; Kerwin, James F., Jr. Publisher: Wiley-Liss, New York, N. Y.) We have previously shown above that amides can be formed in the presence of an aryl oxime linker by

the reaction of an acid chloride or an acid anhydride with an aryl oxime-linked benzylamine. In the present study, we set out to demonstrate that an aryl oxime-linked acid could be coupled to an amine under standard peptide coupling conditions. By proceeding through the intermediacy of methyl ester **5**, we also sought to demonstrate the compatibility of the aryl oxime linker with the aqueous basic conditions required for saponification (Scheme 2). Thus, the potassium anion of the Kaiser resin **1** as coupled with methyl 3-fluoro-4-cyanobenzoate to give resin **5** in a 69% loading yield. Treatment of resin **5** with LiOH, in THF/MeOH/H_2O (3/1/1) at room temperature gave the corresponding acid (**6**) and no removal of the substrate from the resin was observed, demonstrating the stability of the aryl oxime linker under these conditions. Acid **6** was then coupled to 4-chlorobenzylamine to give the on-resin amide. Both the resin weight increase and chlorine analysis of the intermediate suggested that the coupling reaction went essentially to completion within 12 h. The resin was then treated with the standard cyclorelease conditions to give the desired amide **7** in a 3 step yield of 81% (93% crude purity).

Scheme 2. On-resin hydrolysis and amide bond formation.



Synthesis of 6-[(*p*-chlorophenyl)methylaminocarbonyl]-3-amino-1,2-benzisoxazole (7): to *p*-nitrobenzophenone oxime polystyrene (Kaiser) resin (500 mg, 1.07 mmol/g, 0.54 mmol) in a tared 25 mL Kontes Microfilter Funnel was added THF (7 mL) and potassium *t*-butoxide (640 μL, 1 M in THF, 0.642 mmol). After shaking by hand for several minutes, the resin turned a deep purple color. To this suspension was added 2-fluoro-4-(methoxycarbonyl)benzonitrile (1.07 mmol, 192 mg). The reaction vessel was rotated at 55 °C in a Robbins oven for 12 h to give resin **5** followed by cooling for 1 h. The resin was then rinsed with 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of MeOH, 2 × 5 mL of H_2O, and 4 × 5 mL of MeOH. The resin was dried in a 35 °C vacuum oven for 12 h to give a Δwt = 50.0 mg (58% loading yield). To effect ester hydrolysis, the resin was then suspended in THF (7 mL) followed by the addition of LiOH (39 mg, 1.61 mmol) dissolved in MeOH/H_2O (1:1, 2 mL) and rotated at room temp. for 12 h. The resin was then rinsed with 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of MeOH, 2 × 5 mL of H_2O, 2 × 5 mL of MeOH, and 2 × 5 mL of DMF. The resin was then suspended in DMF (7 mL) and to this was added *p*-chlorobenzylamine (261 μL, 2.14 mmol), 1-hydroxybenzotriazole hydrate (HOBt) (289 mg, 2.14 mmol), benzotriazole-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) (947 mg, 2.14 mmol), and diisopropylethylamine

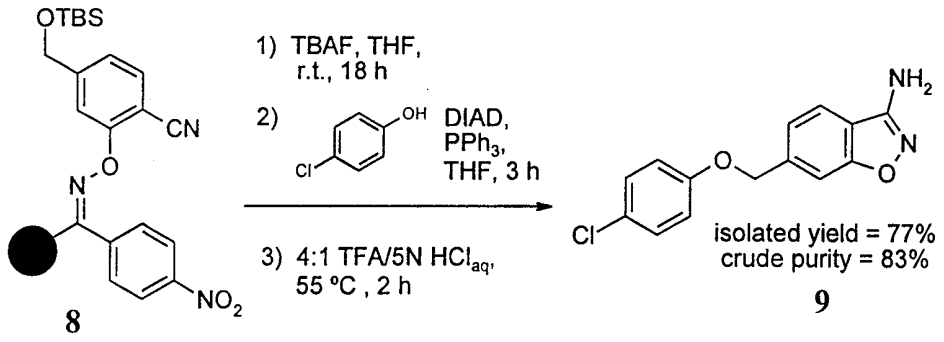
(DIPEA) (467 μL, 2.68 mmol). The reaction was allowed to proceed for 12 h at room temp. The resin was then rinsed 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of MeOH, 2 × 5 mL of H_2O, and 4 × 5 mL of MeOH. The resin was dried in a 35 °C vacuum oven for 12 h to give a Δwt = 84 mg. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin and the vessel was rotated for 2 h in a 55 °C oven. The TFA/HCl_{aq} was collected and the resin was rinsed with 2 × 5 mL of CH_2Cl_2. These washings were combined and concentrated *in vacuo* to give the crude product **7** (93% purity by reverse phase HPLC) that was purified by radial chromatography on a 2 mm plate eluting with 50% EtOAc/Hexanes. Concentration of the product containing fractions gave pure 6-[(*p*-chlorophenyl)-methylaminocarbonyl]-3-amino-1,2-benzisoxazole (**7**) (76 mg, 3 step yield = 81% based on the ester loading yield): HPLC retention time (eluent gradient 10%A to 60%A over 45 min) = 24.9 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (t, *J* = 5.6 Hz, 1H), 7.84 - 7.91 (m, 2H), 7.72 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.37 - 7.31 (m, 4H), 6.50 (bs, 2H), 4.45 (d, *J* = 6.0 Hz, 2H). MS (ESI) *m/z* 300 [^{35}Cl, $(M+H)^+$], 302 [^{37}Cl, $(M+H)^+$]. HRMS Calcd for $C_{17}H_{15}N_2O_3$ 295.1083, found 295.1079.

General Example 8

Phenolic Mitsunobu reaction. On-resin carbon-oxygen bond formation *via* the Mitsunobu reaction has been identified as an important tool in combinatorial chemistry (Kaldor, S.W.; Siegel, M.G. *Comb. Chem. Mol. Diversity Drug Discovery* **1998**, 307-335. Editors: Gordon, Eric M.; Kerwin, James F., Jr. Publisher: Wiley-Liss, New York, N. Y). Application of this reaction to an aryl oxime-linked substrate is shown in Scheme 3. Resin **8** was prepared by reacting the potassium anion of the Kaiser resin **1** with 2-fluoro-4-(*t*-butyl-dimethylsilyloxymethyl)-benzonitrile. The TBS-protecting group was removed using TBAF in THF. The on-resin alcohol was then treated with p-chlorophenol, triphenylphosphine and diisopropylazodicarboxylate (DIAD) in THF. (Krchnák, V.; Flegelová, Z.; Weichsel, A.S.; Lebl, M. *Tetrahedron Lett.* **1995**, *38*, 3345.) The best results were observed for reactions times of 3 h. Longer reaction times generally led to decreased purity in the crude cyclization

product. Cyclitive removal using the standard conditions then gave aryl ether **9** in a 77% yield (3 steps) and 83% crude purity.

Scheme 3. On-resin Mitsunobu reaction.



Synthesis of 6-[(*p*-chlorophenyl)oxymethyl]-3-amino-1,2-benzisoxazole (9): to *p*-nitrobenzophenone oxime polystyrene (Kaiser) resin (500 mg, 1.07 mmol/g, 0.54 mmol) in a tared 25 mL Kontes Microfilter Funnel was added THF (7 mL) and potassium *t*-butoxide (640 μL, 1 M in THF, 0.642 mmol). After shaking by hand for several minutes, the resin turned a deep purple color. To this suspension was added 2-fluoro-4-(*tert*-butyldimethylsilyloxymethly)-benzonitrile (1.07 mmol, 285 mg). The reaction vessel was rotated at 55 °C in a Robbins oven for 12 h to give resin **8** followed by cooling for 1 h. The resin was then rinsed with 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of MeOH, 2 × 5 mL of H_2O, and 4 × 5 mL of MeOH. The resin was dried in a 35 °C vacuum oven for 12 h to give a Δwt = 71.1 mg (54% loading yield). To effect TBS removal, the resin was then suspended in THF (6 mL) followed by the addition of TBAF (562 μL, 1 M in THF, 0.562 mmol) and rotated at room temperature for 12 h. The resin was then rinsed with 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of MeOH, 2 × 5 mL of H_2O, 2 × 5 mL of MeOH, and 2 × 5 mL of CH_2Cl_2. The resin was then suspended in CH_2Cl_2 (7 mL) and to this was added *p*-chlorophenol (690 mg, 5.35 mmol), triphenylphosphine (700 mg, 2.68 mmol), and diisopropyl-azodicarboxylate (DIAD) (530 μL, 2.68 mmol). The reaction was allowed to proceed for 1 h at room temp.

The resin was then rinsed 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of MeOH, 2 × 5 mL of H_2O, and 4 × 5 mL of MeOH. The resin was dried in a 35 °C vacuum oven for 12 h. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin and the vessel was rotated for 2 h in a 55 °C oven. The TFA/HCl_{aq} was collected and the resin was rinsed with 2 × 5 mL of CH_2Cl_2. These washings were combined and concentrated *in vacuo* to give the crude product **7** (83% purity by reverse phase HPLC) that was purified by radial chromatography on a 2 mm plate eluting with 50% EtOAc/Hexanes. Concentration of the product containing fractions gave pure 6-[(*p*-chlorophenyl)oxymethyl]-3-amino-1,2-benzisoxazole (**9**) (61 mg, 3 step yield = 77% based on loading yield): HPLC retention time (eluent gradient 10%A to 60%A over 45 min) = 37.5 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.84 - 7.91 (m, 2H), 7.72 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.44 (s, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.25 - 7.21 (m, 2H), 6.99 - 6.95 (m, 2H), 5.17 (bs, 2H), 1.22 (d, *J* = 6.4 Hz, 2H). MS (ESI) *m/z* 274 [^{35}Cl, $(M+H)^+$], 276 [^{37}Cl, $(M+H)^+$]. Anal Calc'd for $C_{14}H_{11}ClN_2O_2$: C, 61.21; H, 4.04; N, 10.2; Cl, 12.91. Found: C, 61.08; H, 4.32; N, 10.19; Cl, 12.47.

General Example 9

On-resin nucleophilic aromatic substitution. Recently, examples of on-resin nucleophilic aromatic displacement reactions have appeared in the literature. (Wijkmans, J.C.H.M.; Culshaw, A.J.; Baxter, A.D. *Mol. Diversity* **1998**, *3*, 117.) In order to evaluate the compatability of the aryl oxime linker with this reaction, a resin-attached fluorobenzonitrile (**10**) was prepared (Scheme 4). In order to avoid any regioselectivity issues in the loading reaction, the symmetrical 2,6-difluorobenzonitrile was chosen for this initial investigation. Resin **10** was then reacted with a variety of nucleophiles including an alkoxide (Plenkiewicz, H.; Dmowski, W. *J. Fluorine Chem.* **1998**, *89*, 213.), amine (Morales, G.A.; Corbett, J.W.; DeGrado, W.F. *J. Org. Chem.* **1998**, *63*, 1172. Vojkovsky, T.; Weichsel, A.; Patek, M. *J. Org. Chem.* **1998**, *63*, 3162. Dankwardt, S.M.; Newman, S.R.; Krstenanski, J.L. *Tetrahedron Lett.* **1995**, *36*, 4923.), and phenol (Kiselyov, A.S.; Eisenberg, S.; Luo, Y *Tetrahedron Lett.* **1999**, *40*, 2465.. Burgess, K.; Lim, D.;

Bois-Choussy, M.; Zhu, J. *Tetrahedron Lett.* **1997**, *38*, 3345.)) (Table 3). The potassium alkoxide of 4-chlorophenethanol (Table 3, entry 1) was prepared by treatment with 2 equivalents potassium *t*-butoxide. This salt was then added to a THF suspension of resin **10** to give the corresponding product **11a** after cyclorelease in a two step yield of 50%.

Scheme 4. Regioselective synthesis of 6-fluoro-3-aminobenzisoxazole.

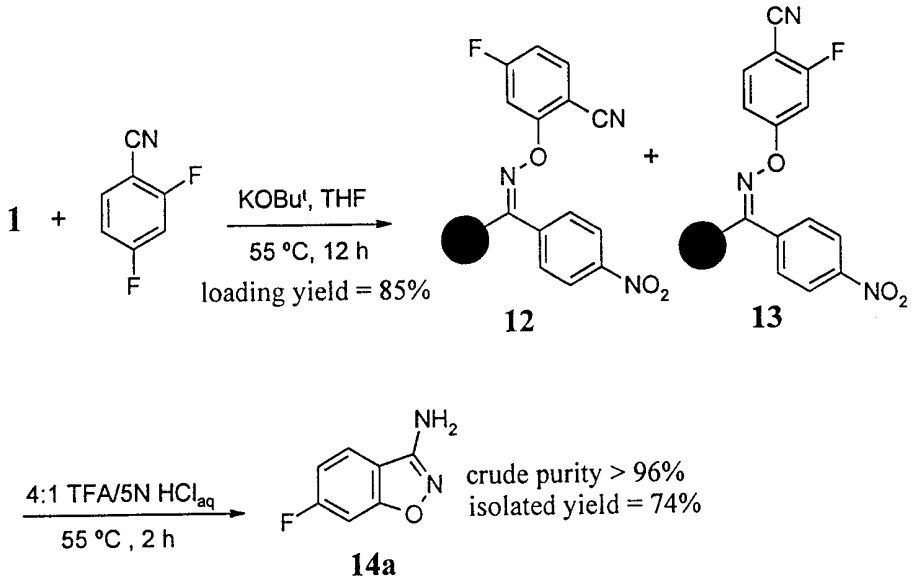
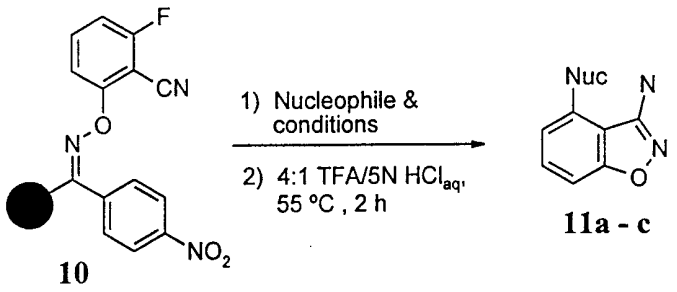
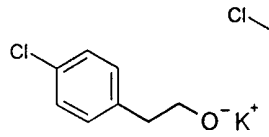
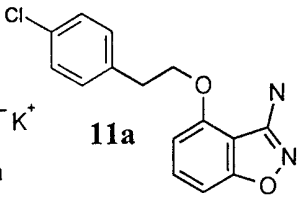
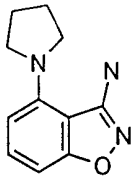
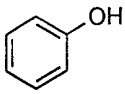
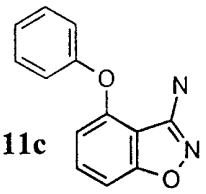


Table 3. On-resin nucleophilic aromatic substitution.



10 **11a - c**

entry	nucleophile & conditions	product	yield[a] (% purity)
1	 THF, 55 °C, 12 h	 **11a**	50 (95)
2	 55 °C, 8 h	THF CH_3CN DMF DMSO	 **11b**	18 32 58 (69)[b] 80 (94)[b]
3	 DMF, 55 °C, 36 h, K_2CO_3	 **11c**	48 (93)[b]

[a]Isolated yield after chromatography and based on loading. Crude purity based on HPLC analysis.
[b]Major impurity was the unreacted fluorine product (4-fluoro-3-aminobenzisoxazole)

Addition of pyrrolidine to **10** proved more challenging (Table 3, entry 2). In our initial attempt (THF, 6 h, 55 °C) the desired product **11b** was produced in low isolated yield as a result of incomplete displacement. The major impurity in this reaction was 4-fluoro-3-aminobenzisoxazole, the cyclization product of the unreacted starting material (**10**). In an attempt to increase the rate of the S_NAr reaction in THF,

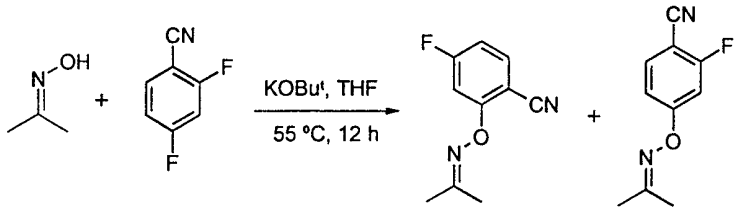
variations in the reaction time, number of equivalents of nucleophile, and the temperature were evaluated. Significant improvements were obtained with the use of alternate solvents. Although only a slight improvement was observed with acetonitrile (studies on the fluorine kinetic isotope effect in S_NAr reactions with aryl fluorides have shown that the use of acetonitrile as the reaction solvent leads to a different rate limiting step in the overall mechanism when compared with THF. Persson, J.; Axelsson, S.; Matsson, O. *J. Am. Chem. Soc.* **1996**, *118*, 20.), both DMF and DMSO produced a significant increase in the reaction rate. After 6 h at 55 °C in DMSO, followed by the cyclorelease reaction, compound **11b** was obtained in 94 % crude purity and subsequently isolated in 80 % yield.

Similar to the pyrrolidine S_NAr reaction discussed above, the nucleophilic addition of phenol to resin **10** (Table 3, entry 3) proceeded at a faster rate in DMSO and DMF compared with THF. However, even in these solvents, the addition reaction required 36 h to bring about high conversion of the phenol adduct. Aryl ether **11c** was then obtained in 48% yield (2 steps) and 93% crude purity after cyclitive removal.

In order to explore the question of regioselectivity, the loading reaction was next attempted with 2,4-difluorobenzonitrile. As illustrated in Scheme 4, this reaction could lead either to the desired aryloxime intermediate **12** through displacement of the 2-fluoro group, or to an undesired isomer **13** through displacement of the 4-fluoro group. Treatment of the unsymmetrical nitrile with the potassium salt of resin 1 gave a 85% loading yield based on weight. Although the ratio of **12** to **13** was not determined, the presumed mixture was then hydrolyzed under the standard cyclization conditions to yield a *single* product **14a** (as determined by HPLC and NMR) in 74% isolated yield. The high selectivity observed for the formation of the desired product could arise from either of two pathways. On one hand, the resin loading reaction may be quite selective for the 2-position, giving primarily **12**, and then subsequently **14a** upon cyclorelease. Alternatively, mixtures of the two isomeric aryloxime adducts could be formed with the hydrolysis of intermediate **12** occurring much more rapidly than **13**. In order gain insight into the relative

contributions of these two pathways, several experiments were performed. Scheme 5 depicts a solution phase model study for the loading reaction of 2,4-difluorobenzonitrile. In this experiment, the potassium salt of acetone oxime was treated with 2,4-difluorobenzonitrile and showed only a slight preference for the addition to the 2-position (1.4:1). (For related regioselectivity studies on solution phase S_NAr reactions, see (a) Wells, K.M.; Shi, Y.J.; Lynch, J.E.; Humphrey, G.R.; Volante, R.P.; Reider, P.J.; *Tetrahedron Lett.*, **1996**, *37*, 6439. (b) Sasajima, K.; Ona, K.; Katsube, J. ; Yamamoto, H.; *Chem. Pharm. Bull.*, **1978**, *26*, 2502.) Obviously such poor selectivity, if produced in the solid phase loading reaction, could not account for the >96% purity of cyclorelease product **14a**.

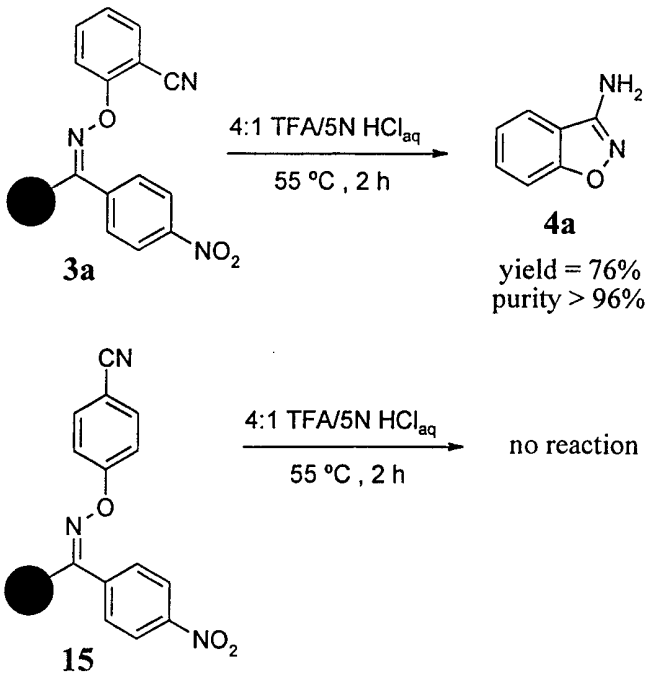
Scheme 5. Solution phase model of the loading reaction of 2,4-difluorobenzonitrile.



1.4 : 1

Scheme 6 illustrates a comparison of the relative rates of hydrolysis for analogous 2- *vs* 4-substituted aryloximes. Since the isolation of pure **12** and pure **13** was not practical, model resins **3a** and **15** were prepared from 2-fluorobenzonitrile and 4-fluorobenzonitrile respectively. As described previously, when resin **3a** was treated with the standard cyclitive removal conditions, complete conversion to 3-aminobenzisoxazole was observed after 2h.

Scheme 6. Comparison of the relative rates of oxime hydrolysis for 2- *versus* 4-substituted aryl oximes.



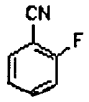
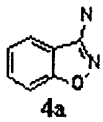
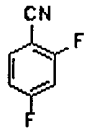
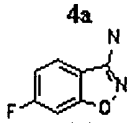
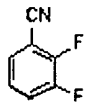
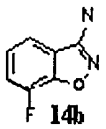
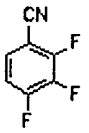
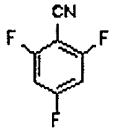
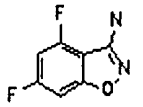
IR analysis of the recovered resin after hydrolysis showed complete disappearance of the nitrile peak, which had clearly been present in the starting material. Alternatively, upon exposure of the isomeric resin **15** to the same hydrolysis conditions, no organic material was released from the solid-phase. In this experiment, IR analysis of the recovered resin confirmed that the nitrile remained intact, apparently unaffected by exposure to the aqueous acid.

These observations led us to reexamine the reaction shown in Scheme 4. This time, resin **12** and **13** were recovered after the cyclorelease reaction was complete, and characterized by IR spectroscopy. The analysis revealed that a nitrile peak was still present on the resin, although the intensity of the nitrile was diminished relative to that observed prior to hydrolysis. These data support the hypothesis that the difference in the hydrolysis rates of intermediate **12** vs **13** serves as the primary source of selectivity in this reaction.

Having successfully achieved the selective functionalization of 2,4-difluorobenzonitrile a variety of additional unsymmetrical polyfluorobenzonitriles were carried through the same sequence. The results are presented in Table 4. In

all cases tested, HPLC analyses of the crude reaction mixtures confirmed that the desired product is selectively released from the solid phase.

Table 4. Regioselective synthesis of fluoro-3 -amino-benzisoxazoles.

entry	electrophile	loading (%)	product	yield[a] (% purity)
1		64	 **4a**	76 (>96)
2		85	 **14a**	74 (>96)
3		66	 **14b**	56 (>96)
5		66	 **14e**	27 (78)
7		79	 **14f**	31 (>96)

[a]Isolated yield after chromatography and based on loading. Crude purity based on HPLC analysis

5

Synthesis of resin 10: to *p*-nitrobenzophenone oxime polystyrene (Kaiser) resin (500 mg, 1.07 mmol/g, 0.54 mmol) in a tared 25 mL Kontes Microfilter Funnel was added THF (7 mL) and potassium *t*-butoxide (640 μL, 1 M in THF, 0.642 mmol). After shaking by hand for several minutes, the resin turned a deep purple color. To this suspension was added 2,6-difluorobenzonitrile (150 mg, 1.07 mmol). The reaction vessel was rotated at 55 °C in a Robbins oven for 8 h to give resin **10** followed by cooling for 1 h. The resin was then rinsed with 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of MeOH, 2 × 5 mL of H_2O, and 4 × 5 mL of MeOH. The resin was dried in a 35 °C vacuum oven for 12 h to give a Δwt = 40.1 mg (63% loading yield).

Synthesis of 4-[2-(*p*-chlorophenyl)ethoxy]-3-amino-1,2-benzisoxazole (11a): In a separate vial, 2-(*p*-chlorophenyl)ethanol (128 μL, 1.07 mmol) was dissolved in 1 mL of THF followed by the addition of potassium *t*-butoxide (1.07 mL, 1 M in THF, 1.07 mmol). This alkoxide solution was then added to a THF suspension (6 mL) of resin **10** (540.1 mg, assume 0.535 mmol). The reaction vessel was rotated for 12 h in a 55 °C oven. The resin was then rinsed 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of MeOH, 2 × 5 mL of H_2O, and 4 × 5 mL of MeOH. The resin was dried in a 35 °C vacuum oven for 3 h. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin and the vessel was rotated for 2 h in a 55 °C oven. The TFA/HCl_{aq} was collected and the resin was rinsed with 2 × 5 mL of

CH_2Cl_2. These washings were combined and concentrated *in vacuo* to give the crude product **11a** (>96% purity by reverse phase HPLC) which was purified by radial chromatography on a 2 mm plate eluting with 50% EtOAc/Hexanes. Concentration of the product containing fractions gave pure 6-[(*p*-chlorophenyl)oxymethyl]-3-amino-1,2-benzisoxazole (**11a**) (66 mg, 2 step yield = 68% based on loading yield): HPLC retention time (eluent gradient 10%A to 80%A over 45 min) = 31.8 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39 - 7.31 (m, 5H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 8.4, 1H), 5.72 (bs, 2H), 4.30 (t, *J* = 6.4 Hz, 2H), 3.12 (t, *J* = 6.4 Hz, 2H). MS (ESI) *m/z* 289 [^{35}Cl, $(M+H)^+$], 291 [^{37}Cl, $(M+H)^+$]. Anal Calc'd for $C_{15}H_{13}ClN_2O_2$: C, 62.41; H, 4.54; N, 9.70; Cl, 12.28. Found: C, 62.08; H, 4.61; N, 9.53; Cl, 12.41.

Synthesis of 4-pyrrolidino-3-amino-1,2-benzisoxazole (11b): to a DMSO suspension (7 mL) of resin **10** (540.1 mg, assume 0.535 mmol) was added pyrrolidine (134 μL, 1.61 mmol). The reaction vessel was rotated for 8 h in a 55 °C oven. The resin was then rinsed 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of MeOH, 2 × 5 mL of H_2O, and 4 × 5 mL of MeOH. The resin was dried in a 35 °C vacuum oven for 3 h. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin and the vessel was rotated for 2 h in a 55 °C oven. The TFA/HCl_{aq} was collected and the resin was rinsed with 2 × 5 mL of CH_2Cl_2. These washings were combined and concentrated *in vacuo* to give the crude product **11b** (94%

purity by reverse phase HPLC) which was purified by radial chromatography on a 2 mm plate eluting with 50% EtOAc/Hexanes. Concentration of the product containing fractions gave pure 4-pyrrolidino-3-amino-1,2-benzisoxazole (**11b**) (54 mg, 2 step yield = 80% based on loading yield): HPLC retention time (eluent gradient 5%A to 40%A over 45 min) = 27.9 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27 (t, J = 8.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.55 (d, J = 7.6, 1H), 5.62 (bs, 2H), 3.27- 3.20 (m, 4H), 1.92 - 1.83 (m, 4H). MS (ESI) *m/z* 204 $(M+H)^+$. Anal Calc'd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 64.46 H, 6.22; N, 20.11.

Synthesis of 4-phenoxy-3-amino-1,2-benzisoxazole (11c): to a DMF suspension (7 mL) of resin **10** (540.1 mg, assume 0.535 mmol) was added phenol (503 mg, 5.35 mmol) and K_2CO_3 (738 mg, 5.35 mmol). The reaction vessel was rotated for 36 h in a 55 °C oven. The resin was then rinsed 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of MeOH, 2 × 5 mL of H_2O, and 4 × 5 mL of MeOH. The resin was dried in a 35 °C vacuum oven for 3 h. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin and the vessel was rotated for 2 h in a 55 °C oven. The TFA/HCl_{aq} was collected and the resin was rinsed with 2 × 5 mL of CH_2Cl_2. These washings were combined and concentrated *in vacuo* to give the crude product **11c** (93% purity by reverse phase HPLC) which was purified by radial chromatography on a 2 mm plate eluting with 50% EtOAc/Hexanes.

Concentration of the product containing fractions gave pure 4-phenoxy-3-amino-1,2-benzisoxazole (**11c**) (38 mg, 2 step yield = 48% based on loading yield): HPLC retention time (eluent gradient 10%A to 90%A over 45 min) = 23.7 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 9.6 Hz, 1H), 7.26 - 7.15 (m, 3H), 7.10 (d, J = 8.4 Hz, 1H), 6.36 (d, J = 7.6 Hz, 1H), 6.02 (bs, 2H). MS (ESI) *m/z* 227 $(M+H)^+$. Anal Calc'd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.21 H, 4.06; N, 12.75.

General procedure for the synthesis of fluoro-3-amino-1,2-benzisoxazoles 14a - f: to *p*-nitrobenzophenone oxime polystyrene (Kaiser) resin (500 mg, 1.07 mmol/g, 0.54 mmol) in a tared 25 mL Kontes Microfilter Funnel was added THF (7 mL) and potassium *t*-butoxide (640 μL, 1 M in THF, 0.642 mmol). After shaking by hand for several minutes, the resin turned a deep purple color. To this suspension was added 2,4-difluorobenzonitrile (150 mg, 1.07 mmol). The reaction vessel was rotated at 55 °C in a Robbins oven for 12 h followed by cooling for 1 h. The resin was then rinsed with 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of MeOH, 2 × 5 mL of H_2O, and 4 × 5 mL of MeOH. The resin was dried in a 35 °C vacuum oven for 12 h to give a Δwt = 52.4 mg (90% loading yield). An IR analysis of the resin shows a nitrile stretching peak at 2230.3 cm^{-1}. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin and the vessel was rotated for 2 h in a 55 °C oven. The TFA/HCl_{aq} was collected and the resin was

rinsed with 2 × 5 mL of CH_2Cl_2. An IR analysis of the resin after the cyclorelease reaction shows a diminished nitrile stretching peak. The CH_2Cl_2 washings were combined and concentrated *in vacuo* to give the crude product **14a** (>96% purity by reverse phase HPLC) that was purified by radial chromatography on a 2 mm plate eluting with 50% EtOAc/Hexanes. Concentration of the product containing fractions gave pure **6-fluoro-3-aminobenzisoxazole (14a)**: (40mg, 2 step yield = 74% based on loading yield): HPLC retention time (eluent gradient 10%A to 60%A over 45 min) = 13.3 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.36 (dd, *J* = 9.6, 2.0 Hz, 1H), 7.11 (ddd, *J* = 11.2, 8.8, 2.4 1H), 6.44 (bs, 2H). MS (FD) *m/z* 152 M^+. Anal Calc'd for $C_7H_5FN_2O$: C, 55.27; H, 3.31; N, 18.41. Found: C, 55.21 H, 3.27; N, 18.20.

7-fluoro-3-aminobenzisoxazole (14b): (30mg, 2 step yield = 56% based on loading yield): >96% crude purity. HPLC retention time (eluent gradient 5%A to 40%A over 45 min) = 20.1 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.40 (ddd, *J* = 11.6, 8.4, 0.8 Hz, 1H), 7.21 (td, *J* = 8.0, 4.4 1H), 6.58 (bs, 2H). MS (FD) *m/z* 152 M^+. Anal Calc'd for $C_7H_5FN_2O$: C, 55.27; H, 3.31; N, 18.41. Found: C, 55.19 H, 3.45; N, 18.36.

6,7-difluoro-3-aminobenzisoxazole (14e): (23mg, 2 step yield = 27% based on loading yield): 78% crude purity. HPLC retention time (eluent gradient

5%A to 40%A over 45 min) = 27.6 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 - 7.61 (m, 1H), 7.36 - 7.30 (m, 1H), 6.62 (bs, 2H). MS (FD) *m/z* 171 M^+. HRMS Calcd for $C_7H_4F_2N_2O$ 171.0370, found 171.0368.

4,6-difluoro-3-aminobenzisoxazole (14f): (22mg, 2 step yield = 31% based on loading yield): >96% crude purity. HPLC retention time (eluent gradient 5%A to 40%A over 45 min) = 21.1 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.10 (td, *J* = 10.0, 2.0 Hz, 1H), 6.34 (bs, 2H). MS (FD) *m/z* 171 M^+. Anal Calc'd for $C_7H_4F_2N_2O$: C, 49.42; H, 2.37; N, 16.47. Found: C, 49.36 H, 2.38; N, 16.39.

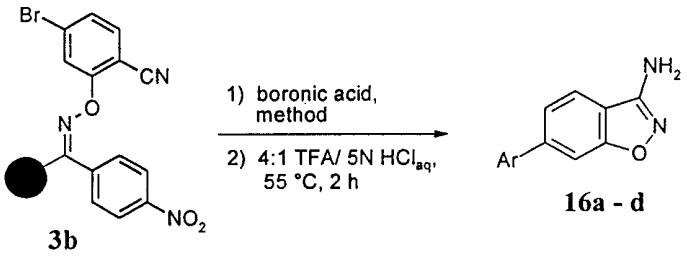
General Example 10

Carbon-carbon bond forming reactions. Compatibility with versatile methods for forming carbon-carbon bonds on-resin is an important measure of the suitability of any new linker. (Hanessian, S.; Xie, F.; *Tetrahedron Lett.*, **1998**, *39*, 737.) Our initial efforts focused on the application of catalytic palladium coupling chemistry such as the Suzuki and Sonogashira reactions. Thus, the arylbromide resin **3b** was prepared (Lepore, S.D.; Wiley, M.R. *J. Org. Chem.* **1999**, *64*, 4547.) and reacted with phenylboronic acid under a variety of palladium catalyzed coupling conditions, then hydrolyzed to give the biaryl product **16a** (Table 5). Initially, two sets of conditions that have previously been

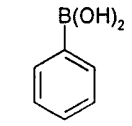
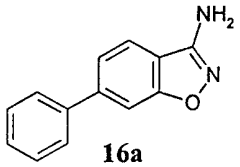
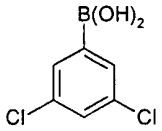
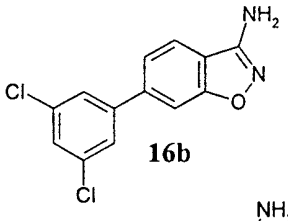
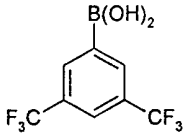
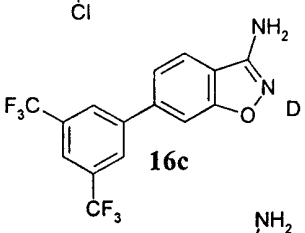
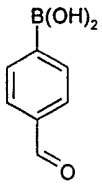
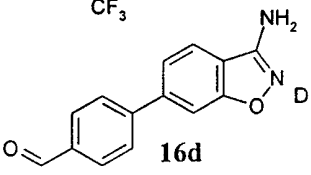
reported for on-resin Suzuki reactions were evaluated. Use of $Pd(PPh_3)_4$ with triethylamine/DMF for 12 h (Han, Y.; Walker S.D.; Young, R.N.; *Tetrahedron Lett.*, **1996**, *37*, 2703. Ruhland, B.; Bombrun, A.; Gallop, M.A.; *J. Org. Chem.*, **1997**, *62*, 7820.) produced **16a**, but led to the formation of numerous biproducts. Alternatively, the use of $Pd(PPh_3)_4$, with Na_2CO_3 in 1:1 DME/H_2O at reflux for 12 h (Frenette, R.; Friesen, R.W.; *Tetrahedron Lett.*, **1994**, *35*, 9177.), produced **16a** in 25 % isolated yield, contaminated only by the cyclization product of the unreacted arylbromide. Due to the superior purity observed with aqueous carbonate, optimization efforts focused on these conditions. Numerous reaction parameters were carefully varied including cosolvent (DMF, DMSO, and THF) and the stoichiometry of the catalyst, boronic acid and sodium carbonate. Although the crude purities were similar for the various solvents which were evaluated, in general THF (Backes, B.J.; Ellman, J.A.; *J. Am. Chem. Soc.*, **1994**, *116*, 11171) was found to give the highest rate of product formation, and therefore the highest isolated yields. Optimal results were obtained with 1.3 equivalents of 2N Na_2CO_3, at 55 °C, over 36h. The reaction was rather sensitive to deviation from these conditions, particularly with respect to the amount of added 2N Na_2CO_3. In control experiments, resin **3b** was treated with varying amounts of 2N Na_2CO_3 in THF at 55 °C over 36h, and no removal of organic material from the resin was observed. As Table 5 shows, the application of the optimized Suzuki conditions to several other substrates (Table 5, entries 2 - 4)

provided similar yields and purities.

Table 5. On-resin Suzuki reaction.



3b 16a - d

entry	boronic acid	product	method[a]	yield[b] (% purity)
1		 16a	A B C D	25 (50) 67 (60) 58 (91) 41 (>96)
2		 16b	D	54 (95)
3		 16c	D	46 (81)
4		 16d	D	43 (92)

[a]Conditions A - D all use 4.0 eq of boronic acid and 5% $Pd(PPh_3)_4$, and 36 h. A = 2.5 eq 2 M Na_2CO_3, DME, reflux; B = 1.0 eq 2 M Na_2CO_3, THF, 55 °C; C = 1.3 eq 2 M Na_2CO_3, THF, 55 °C; D = 1.5 eq 2 M Na_2CO_3, THF, 55 °C.

[b]Isolated yield after chromatography and based on loading. Crude purity based on HPLC analysis. Major impurity in all cases is 6-bromo-3-aminobenzisoxazole.

General procedure for the Suzuki coupling reactions with resin 3b: to *p*-nitrobenzophenone oxime polystyrene (Kaiser) resin (500 mg, 1.07 mmol/g, 0.54 mmol) in a tared 25 mL Kontes Microfilter Funnel was added THF (7 mL) and potassium *t*-butoxide (640 μL, 1 M in THF, 0.642 mmol). After shaking by hand for several minutes, the resin turned a deep purple color. To this suspension was added 4-bromo-2-fluorobenzonitrile (214 mg, 1.07 mmol). The reaction vessel was rotated at 55 °C in a Robbins oven for 12 h to give resin **3b** followed by cooling for 1 h. The resin was then rinsed with 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of MeOH, 2 × 5 mL of H_2O, and 4 × 5 mL of MeOH. The resin was dried in a 35 °C vacuum oven for 12 h to give a Δwt = 64 mg (66% loading yield). The resin was then suspended in THF and to this was added phenylboronic acid (261 mg, 2.14 mmol), Na_2CO_3 (348 μL, 2 M in H_2O, 2.14 mmol), and $Pd(PPh_3)_4$. The vessel was then rotated for 36 h in a 55 °C oven followed by rinsing with 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of MeOH, 2 × 5 mL of H_2O, and 4 × 5 mL of MeOH. The resin was dried in a 35 °C vacuum oven for 3 h. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin and the vessel was rotated for 2 h in a 55 °C oven. The TFA/HCl_{aq} was collected and the resin was rinsed with 2 × 5 mL of CH_2Cl_2. These washings were combined and concentrated *in vacuo* to give the crude product **16a** (91% purity by reverse phase HPLC) which was purified by radial chromatography on a 2 mm plate eluting with 50% EtOAc/Hexanes. Concentration of the product containing fractions gave pure **6-phenyl-3-amino-**

1,2-benzisoxazole (16a): (46 mg, 2 step yield = 58% based on loading yield): HPLC retention time (eluent gradient 10%A to 60%A over 45 min) = 13.3 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, *J* = 8.4 Hz, 1H), 7.74 - 7.70 (m, 2H), 7.68 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.48 - 7.43 (m, 2H), 7.40 - 7.35 (m, 1H), 6.42 (bs, 2H). MS (ESI) *m/z* 211 $(M+H)^+$. Anal Calc'd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.32. Found: C, 72.59 H, 4.86; N, 13.36.

6-(3,5-dichlorophenyl)-3-amino-1,2-benzisoxazole (16b): 2 step yield = 51% (based on loading yield). 95% crude purity. HPLC retention time (eluent gradient 20%A to 80%A over 45 min) = 30.4 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, *J* = 8.8 Hz, 1H), 7.82 (s, 1H), 7.81 (d, *J* = 1.6 Hz, 2H), 7.62 - 7.58 (m, 2H), 6.46 (bs, 2H). MS (FD) *m/z* 278 [^{35}Cl+^{35}Cl, M^+], 280 [^{35}Cl+^{37}Cl, $(M+H)^+$]. Anal Calc'd for $C_{13}H_8Cl_2N_2O$: C, 55.94; H, 2.89; N, 10.04. Found: C, 55.93 H, 2.60; N, 9.85.

6-(3,5-ditrifluoromethylphenyl)-3-amino-1,2-benzisoxazole (16c): 2 step yield = 45% (based on loading yield). 81% crude purity. HPLC retention time (eluent gradient 20%A to 80%A over 45 min) = 31.0 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (s, 2H), 8.11 (s, 1H), 7.98 (s, 2H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.76 - 7.71 (m, 2H), 6.49 (bs, 2H). MS (ESI) *m/z* 347 $(M+H)^+$. Anal Calc'd for $C_{15}H_8F_6N_2O$: C, 52.04; H, 2.33; N, 8.09. Found: C, 52.00 H, 2.06; N, 7.99.

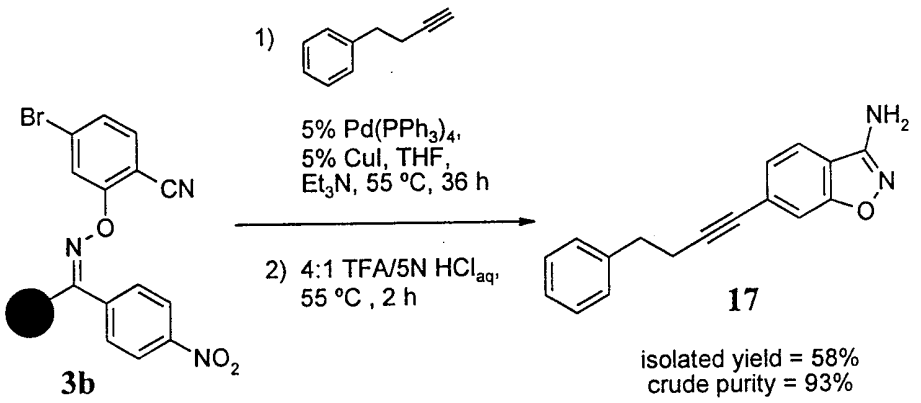
6-(4-formylphenyl)-3-amino-1,2-benzisoxazole (16d): 2 step yield = 43% (based on loading yield). 92% crude purity. HPLC retention time (eluent gradient 5%A to 40%A over 45 min) = 37.6 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 7.98 (s, 4H), 7.90 (d, J = 8.4 Hz, 1H), 7.82 (s, 1H), 7.63 (dd, J = 8.4, 1.6 Hz, 1H), 6.46 (bs, 2H). MS (ESI) *m/z* 239 $(M+H)^+$. HRMS Calcd for $C_{14}H_{10}N_2O_2$ $(M+H)^+$ 239.0821, found 239.1816.

General Example 11

Application of the Sonogashira reaction to resin **3b** proved less difficult than the Suzuki coupling. We were able to couple phenethylacetylene to **3b** to give alkyne **17** in a

58% 2-step yield using $Pd(PPh_3)_4$/CuI in THF (Scheme 8) (Kahn, S.I.; Grinstaff, M.W.; *Tetrahedron lett.*; **1998**, *39*, 8031.) Again, as in the Suzuki chemistry, significantly better results were obtained with THF as the reaction solvent. The $Pd_2(dba)_3$/CuI/Et_3N conditions described by Moore (Nelson, J.C.; Young, J.K.; Moore, J.S.; *J. Org. Chem.*, **1996**, *61*, 8160.) failed to give reasonable yields and purities.

Scheme 8. On-resin Sonogashira coupling.



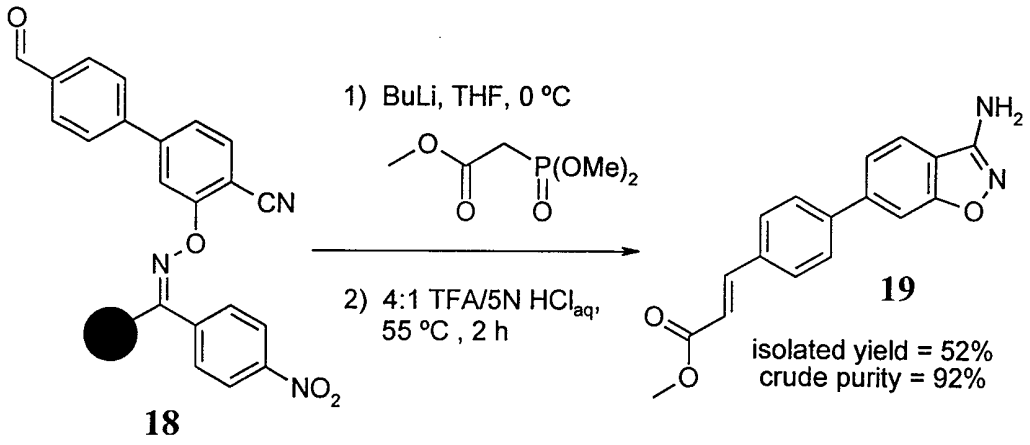
Sonogashira coupling with resin 3b: resin **3b** was prepared in 66% loading yield from 0.535 mmol of Kaiser oxime **1** as detailed above. The resin was then suspended in THF and to this was added 4-phenylbutyne (280 mg, 2.14 mmol), Et_3N (500 μL), CuI (5.1 mg, 0.027 mmol), and $Pd(PPh_3)_4$ (31 mg, 0.027 mmol). The vessel was then rotated for 36 h in a 55 °C oven followed by rinsing with 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of MeOH, 2 × 5 mL of H_2O, and 4 × 5 mL of MeOH. The resin was dried in a 35 °C vacuum oven for 3 h. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin and the vessel was rotated for 2 h in a 55 °C oven. The TFA/HCl_{aq} was collected and the resin was rinsed with 2 × 5 mL of CH_2Cl_2. These washings were combined and concentrated *in vacuo* to give the crude product **17** (93% purity by reverse phase HPLC) which was purified by radial chromatography on a 2 mm plate eluting with 50% EtOAc/Hexanes. Concentration of the product containing fractions gave pure **6-(4-phenylbutynyl)-3-amino-1,2-benzisoxazole (17):** (58 mg, 2 step yield =

58% based on loading yield): HPLC retention time (eluent gradient 20%A to 85%A over 45 min) = 26.2 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 8.0 Hz, 1H), 7.38 (s, 1H), 7.29 - 7.27 (m, 4H), 7.21 - 7.15 (m, 2H), 6.43 (bs, 2H), 2.84 (t, J = 7.6 Hz, 2H), 2.70 (t, J = 7.2 Hz, 2H). MS (ESI) *m/z* 263 $(M+H)^+$. HRMS Calcd for $C_{13}H_{10}N_2O$ 263.1184, found 263.1172.

General Example 12

The acquisition of aldehyde resin **18** (Scheme 9) from the Suzuki reaction with **3b** (Table 5, entry 4) provided an opportunity to evaluate the compatibility of the aryloxime linker with the Horner-Emmons olefination. Thus, treatment of **18** with the anion of trimethylphosphonoacetate in THF (preformed with n-BuLi at 0 °C) gave olefin **19** in 52% isolated yield (3-steps, based on loading of resin **1**) and 92% purity. (Chin, J.; Fell, B.; Shapiro, M.J.; Tomesch, J.; Wareing, J.R.; Bray, A.M.; *J. Org. Chem.*, **1997**, *62*, 538. Rotella, D.P.; *J. Am. Chem. Soc.*, **1996**, *118*, 12246.) The major impurity in this reaction is the cinnamic acid derivative which likely results from competing ester hydrolysis in the cyclitive removal step.

Scheme 9. On-resin Horner-Emmons olefination



Horner-Emmons olefination to give 19: to *p*-nitrobenzophenone oxime polystyrene (Kaiser) resin (500 mg, 1.07 mmol/g, 0.54 mmol) in a tared 25 mL Kontes Microfilter Funnel was added THF (7 mL) and potassium *t*-butoxide (640 μL, 1 M in THF, 0.642 mmol). After shaking by hand for several minutes, the resin turned a deep purple color. To this suspension was added 4-bromo-2-fluorobenzonitrile (214 mg, 1.07 mmol). The reaction vessel was rotated at 55 °C in a Robbins oven for 12 h to give resin **3b** followed by cooling for 1 h. The resin was then rinsed with 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of MeOH, 2 × 5 mL of H_2O, and 4 × 5 mL of MeOH. The resin was dried in a 35 °C vacuum oven for 12 h to give a Δwt = 64 mg (66% loading yield). The resin was then suspended in THF and to this was added 4-formylphenylboronic acid (482 mg, 3.21 mmol), Na_2CO_3 (348 μL, 2 M in H_2O, 0.696 mmol), and $Pd(PPh_3)_4$ (31 mg, 0.027 mmol). The

vessel was then rotated for 36 h in a 55 °C oven followed by rinsing with 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of MeCN, 2 × 5 mL of H_2O, and 4 × 5 mL of MeCN (care was taken to not rinse the resin with methanol in order to avoid methyl acetal formation). The resin was dried in a 35 °C vacuum oven for 3 h to give aldehyde resin **18**. In a separate vial, trimethylphosponoacetate (172 μL, 1.07 mmol) was dissolved in THF (4 mL) and cooled to 0 °C. To this vial was added BuLi (602 μL, 0.96 mmol, 1.6 M in hexanes) dropwise. This THF solution was then added dropwise by syringe to a suspension of resin **18** in THF (4 mL) and the vessel was rotated for 6 h at room temp. This was followed by rinsing with 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of MeOH, 2 × 5 mL of H_2O, and 4 × 5 mL of MeOH. The resin was then dried in a 35 °C vacuum oven for 3 h. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin and the vessel was rotated for 2 h in a 55 °C oven. The TFA/HCl_{aq} was collected and the resin was rinsed with 2 × 5 mL of CH_2Cl_2. These washings were combined and concentrated *in vacuo* to give the crude product **19** (92% purity by reverse phase HPLC) which was purified by radial chromatography on a 2 mm plate eluting with 50% EtOAc/Hexanes. Concentration of the product containing fractions gave pure **6-[4-(methoxycarbonylethylenyl)phenyl]-3-amino-1,2-benzisoxazole (19):** (47 mg, 3 step yield = 52% based on loading yield of resin **1**): HPLC retention time (eluent gradient 20%A to 85%A over 45 min) = 24.3 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.80 (s, 4H), 7.76 (s, 1H), 7.69 (d, *J* = 16.4

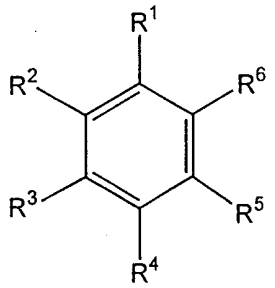
Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 16.4 Hz, 1H), 6.43 (bs, 2H), 3.71 (s, 3H). HRMS Calcd for $C_{17}H_{15}N_2O_3$ 295.1082, found 295.1088.

It should be understood that a wide range of changes and modifications can be made to the embodiments described above. It is therefore intended that the foregoing description illustrates rather than limits this invention, and that it is the appended claims, including all equivalents, which define this invention.

What is claimed is:

1. A method of synthesizing a polycyclic heterocycle comprising:

(a) reacting a compound of the formula (I):



I

where each of R^1, R^2, R^3 and R^4 is a stable moiety independently selected from the group consisting of halo, haloalkyl, cyano, nitro, R^a-Q-, R^a-Q-alkyl, R^a-Q-alkenyl, R^a-Q-alkynyl, R^a-Q-arylalkyl and R^a-Q-aryl;

R^a is hydrogen, alkyl, aryl or arylalkyl;

Q is a single bond, -O-, -NR^b-, -CO-, -NR^b-CO-, -CO-NR^b-, -CO-O-, -O-CO-, $S(O)_i$, -$S(O)_j$-NR^b-, -NR^b-$S(O)_j$;

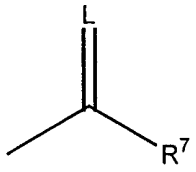
i is 0, 1 or 2;

j is 1 or 2;

R^b is hydrogen, alkyl, aryl or arylalkyl, where R^a and R^b may together with the nitrogen to which they are attached form a ring;

R^5 is halo, nitro, or haloalkyl;

R^6 is cyano or a group of the formula (II):

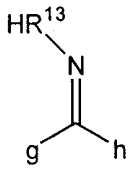


II

L is O, S or NH; and

R^7 is alkyl, aryl, arylalkyl, alkyloxyalkyl, aryloxyalkyl, alkylamino, dialkylamino, arylamino, alkoxycarbonyl, amino, alkoxy, hydroxy or heteroaryl;

with a compound of the formula (III):



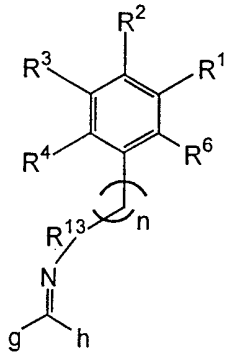
III

where g is a solid support;

h is alkyl, arylalkyl or aryl; and

R^{13} is -NH-, -O- or -S-;

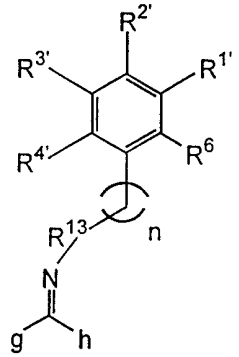
to form a corresponding intermediate of the formula (IV):



IV

where n is an integer ≥ 0, and g and h are as defined above;

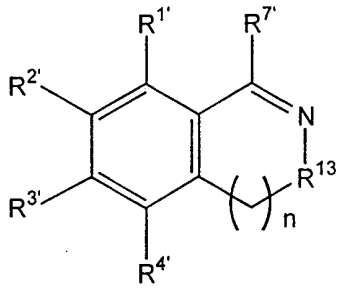
(b) optionally derivatizing one or more of R^1, R^2, R^3 and R^4 to form a corresponding intermediate of the formula (IV'); and



IV'

where the $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ substituents are each independently the same as substituents R^1, R^2, R^3 and R^4 respectively if not derivatized or are each independently the chemically derivatized substituents respectively; and

(c) cyclizing compound IV' to form a compound (V), which is displaced from the solid support;



V

where $R^{7'}$ is amino, hydroxy or the same as R^7.

2. The method of claim 1, wherein R^1, R^2, R^3 and R^4 are hydrogen, g is a polystyrene resin and h is p-nitrophenyl.

3. The method of claim 1, wherein at least one of R^1, R^2, R^3 and R^4 is chemically derivatized.

4. The method of claim 1, wherein R^1 is CF_3.

5. The method of claim 1, wherein R^3 is CF_3.

6. The method of claim 1, wherein R^4 is CF_3.

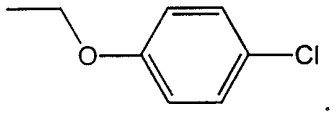
7. The method of claim 1, wherein R^3 is selected from the group consisting of hydroxy, hydroxyalkyl and alkoxy.

8. The method of claim 1, wherein R^3 is halo.

9. The method of claim 1, wherein R^2 is cyano.

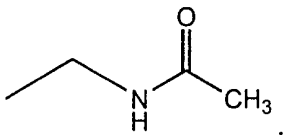
10. The method of claim 1, wherein R^3 is nitro.

11. The method of claim 1, wherein R^3 is $-CH_2$-O-TBS and $R^{3'}$ is a group of the formula (VI):



VI

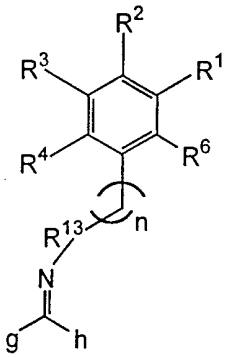
12. The method of claim 1, wherein R^3 is -CH_2-N-BOC and $R^{3'}$ is a group of the formula (VII):



VII

13. The method of claim 1, wherein R^5 is fluoro, chloro or nitro.

14. A compound of the formula (IV):



IV

where g is a solid support,

n is an integer ≥ 0,

h is alkyl, arylalkyl or aryl;

R^{13} is -NH-, -O- or -S-;

where each of R^1, R^2, R^3 and R^4 is a stable moiety independently selected from the group consisting of halo, haloalkyl, cyano, nitro, R^a-Q-, R^a-Q-alkyl, R^a-Q-alkenyl, R^a-Q-alkynyl, R^a-Q-arylalkyl and R^a-Q-aryl;

R^a is hydrogen, alkyl, aryl or arylalkyl;

Q is a single bond, -O-, -NR^b-, -CO-, -NR^b-CO-, -CO-NR^b-, -CO-O-, -O-CO-, $S(O)_i$, -$S(O)_j$-NR^b-, -NR^b-$S(O)_j$;

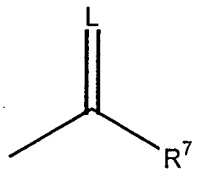
i is 0, 1 or 2;

j is 1 or 2;

R^b is hydrogen, alkyl, aryl or arylalkyl, where R^a and R^b may together with the nitrogen to which they are attached form a ring;

R^5 is halo, nitro, or haloalkyl, and

R^6 is cyano or a group of the formula (II):



(II)

L is -O-, -S- or -NH-; and

R^7 is alkyl, aryl, arylalkyl, alkyloxyalkyl, aryloxyalkyl, alkylamino, dialkylamino, arylamino, alkoxycarbonyl, amino, alkoxy, hydroxy or heteroaryl.

15. The compound of claim 14, wherein g is a polystyrene resin and h is a p-nitrophenyl and all, or any one of R^1, R^2, R^3 and R^4 is chemically derivatizable.

16. The compound of claim 14, wherein R^1, R^2, R^3 and R^4 are hydrogen.

17. The compound of claim 14, wherein R^1 is CF_3.

18. The compound of claim 14, wherein R^3 is CF_3.

19. The compound of claim 14, wherein R^4 is CF_3.

20. The compound of claim 14, wherein R^3 is methoxy.

21. The compound of claim 14, wherein R^3 is alkyl, dialkylamino, arylalkyl-amino, methylcarbonylalkyl, amino-CO-alkyl or heteroaryl.

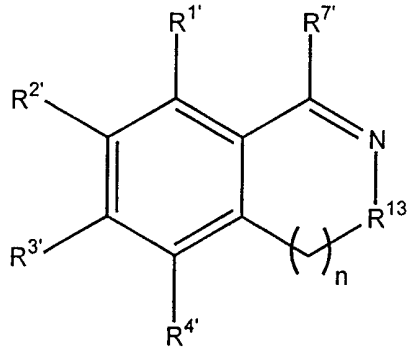
22. The compound of claim 14, wherein R^3 is halo.

23. The compound of claim 14, wherein R^2 is cyano.

24. The compound of claim 14, wherein R^2 is nitro.

25. The compound of claim 14, wherein R^5 is fluoro, chloro or nitro.

26. A library of polycyclic heterocycle compounds where said library contains a plurality of diverse compounds (V):



V

having diversity in at least one of the substituent groups $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{7'}$ and R^{13};

where each of R^1, R^2, R^3 and R^4 is a stable moiety independently selected from the group consisting of halo, haloalkyl, cyano, nitro, R^a-Q-, R^a-Q-alkyl, R^a-Q-alkenyl, R^a-Q-alkynyl, R^a-Q-arylalkyl and R^a-Q-aryl;

R^a is hydrogen, alkyl, aryl or arylalkyl;

Q is a single bond, -O-, -NR^b-, -CO-, -NR^b-CO-, -CO-NR^b-, -CO-O-, -O-CO-, $S(O)_i$, -$S(O)_j$-NR^b-, -NR^b-$S(O)_j$;

i = 0, 1 or 2;

j is 1, 2;

R^b is hydrogen, alkyl, aryl or arylalkyl, where R^a and R^b may together with the nitrogen to which they are attached form a ring;

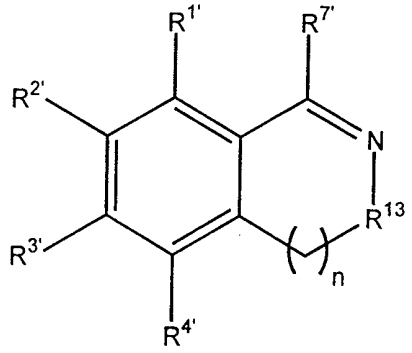
R^5 is halo, nitro, or haloalkyl, and

n is an integer ≥ 0;

$R^{7'}$ is alkyl, aryl, arylalkyl, alkyloxyalkyl, aryloxyalkyl, alkylamino, dialkylaminoarylamino, alkoxycarbonyl, amino, alkoxy, hydroxy or heteroaryl; and

R^{13} is -NH-, -O- or -S-.

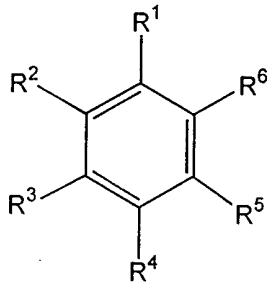
27. A process for preparing a combinatorial library of polycyclic heterocycle compounds of the formula (V):



V

having diversity in at least one of the substituent groups $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{7'}$ and R^{13} and where each library compound is made in a reaction zone, said process comprising:

(a) reacting a compound of the formula (I):



I

where each of R^1, R^2, R^3 and R^4 is a stable moiety independently selected from the group consisting of halo, haloalkyl, cyano, nitro, R^a-Q-, R^a-Q-alkyl, R^a-Q-alkenyl, R^a-Q-alkynyl, R^a-Q-arylalkyl and R^a-Q-aryl;

R^a is hydrogen, alkyl, aryl or arylalkyl;

Q is a single bond, -O-, -NR^b-, -CO-, -NR^b-CO-, -CO-NR^b-, -CO-O-, -O-CO-, $S(O)_i$, -$S(O)_j$-NR^b-, -NR^b-$S(O)_j$;

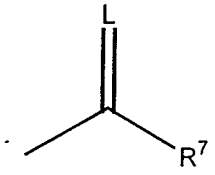
i is 0, 1 or 2;

j is 1 or 2;

R^b is hydrogen, alkyl, aryl or arylalkyl, where R^a and R^b may together with the nitrogen to which they are attached form a ring;

R^5 is halo, nitro, or haloalkyl, and

R^6 is cyano or a group of the formula (II):

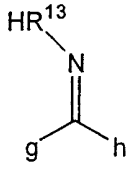


II

L is -O-, -S- or -NH-;

R^7 is alkyl, aryl, arylalkyl, alkyloxyalkyl, aryloxyalkyl, alkylamino, dialkylamino arylamino, alkoxycarbonyl, amino, alkoxy, hydroxy or heteroaryl;

with a compound of the formula (III):



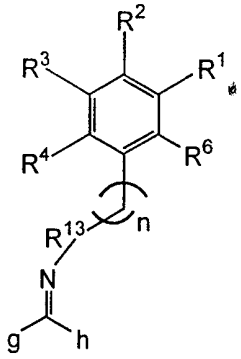
(III)

where g is a solid support;

h is alkyl, arylalkyl or aryl; and

R^{13} is -NH-, -O- or -S-;

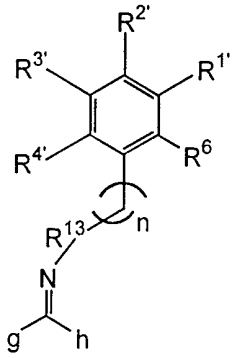
to form a corresponding intermediate of the formula (IV):



IV

where n is an integer ≥ 0, and g and h are as defined above;

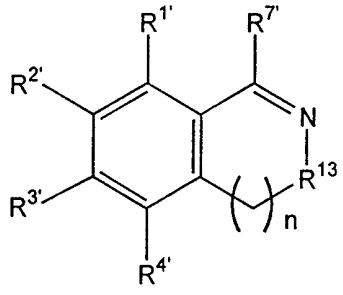
(b) optionally derivatizing one or more of R^1, R^2, R^3 and R^4 to form a corresponding intermediate of the formula (IV');



IV'

where the $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ substituents are each independently the same as substituents R^1, R^2, R^3 and R^4 respectively if not derivatized or are each independently the chemically derivatized substituents respectively; and

(c) cyclizing compound (IV') to form a compound of the formula (V), which is displaced from the solid support;

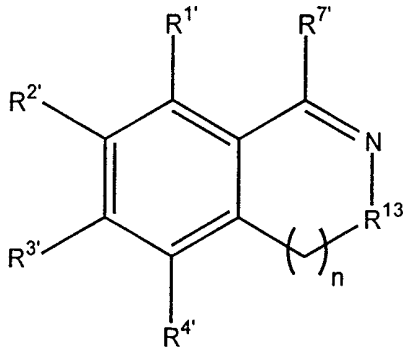


V

where $R^{7'}$ is amino, hydroxy or the same as R^7.

28. An assay kit for the identification of lead compounds, said kit comprising assay materials and well plate apparatus where each well in said apparatus contains a compound of the library of claim 26.

29. 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 compound of said library, where said structurally related compounds are of the formula (V):



V

having diversity in at least one of the substituent groups $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{7'}$ and R^{13};

where each of R^1, R^2, R^3 and R^4 is a stable moiety independently selected from the group consisting of halo, haloalkyl, cyano, nitro, R^a-Q-, R^a-Q-alkyl, R^a-Q-alkenyl, R^a-Q-alkynyl, R^a-Q-arylalkyl and R^a-Q-aryl;

R^a is hydrogen, alkyl, aryl or arylalkyl;

Q is a single bond, -O-, -NR^b-, -CO-, -NR^b-CO-, -CO-NR^b-, -CO-O-, -O-CO-, $S(O)_i$, -$S(O)_j$-NR^b-, -NR^b-$S(O)_j$;

i is 0, 1 or 2;

j is 1 or 2;

R^b is hydrogen, alkyl, aryl or arylalkyl, where R^a and R^b may together with the nitrogen to which they are attached form a ring; and

n is an integer ≥ 0;

$R^{7'}$ is alkyl, aryl, arylalkyl, alkyloxyalkyl, aryloxyalkyl, alkylamino, dialkylamino, arylamino, alkoxycarbonyl, amino, alkoxy, hydroxy or heteroaryl; and

R^{13} is -NH-, -O- or -S-.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/26803

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, data bases included: REGISTRY, CAPLUS, CAOLD, USPATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHUTSKE et al., A Novel Synthesis of 3-Amino-1,2-Benzisoxazoles - An Entry Into the Isoxazole [3,4,5-*ef*][1,4]Benzoxaepine Ring System. J. Heterocyclic Chem. September-October 1989, Vol. 26, pages 1293-1298, see entire document.	1-29
Y	US 5,510,240 A (LAM et al.) 23 April 1996 (23.04.1996), see columns 17-27.	28-29
X	EP 0 754 672 A1 (SHIONOGI & CO., LTD.) 22 January 1997 (22.01.97), see entire document, especially page 2, lines 26-53 and page 3, lines 19-46.	14-25

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 10 FEBRUARY 2000	Date of mailing of the international search report 23 FEB 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer GRACE HSU, PH.D. Telephone No. (703) 308-0196

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/26803

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	RIVERO et al. Equipment for the High-Throughput Organic Synthesis of Chemical Libraries. In: A Practical Guide to Combinatorial Chemistry. American Chemical Society: Washington, D.C. 1997, Edited by CZARNIK et al., pages 281-307, especially pages 284 and 286-287.	28-29
X	SUH et al. 3-Amino-1,2-Benxisoxazoles: A New Family of Potent Inhibitors of LTB_4 Binding to Human Neutrophils. Bioorganic & Medicinal Chemistry Letters. 1997, Vol. 7, No. 4, pages 389-392, see entire document.	26-29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/26803

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

B32B 27/04, 27/12, 5/02; C07D 223/04, 223/14, 231/00, 239/00, 241/00, 245/00, 249/00, 261/02, 275/02, 313/00, 403/00, 413/00; G01N 21/00, 33/543

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

422/61+, 63+; 436/518; 540/471+, 576+, 611+; 544/143+, 253+, 373+; 548/206+, 240+, 356.1+; 564/102+, 251+, 253+

B. FIELDS SEARCHED
US CL :

422/61+, 63+; 436/518; 540/471+, 576+, 611+; 544/143+, 253+, 373+; 548/206+, 240+, 356.1+; 564/102+, 251+, 253+