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(54) Title: AMINO ACID INHIBITORS OF CYTOCHROME P450

(57) Abstract: Methods of inhibiting cytochrome P450 enzymes are provided that can be used for improving the treatment of dis-
eases by preventing degradation of drugs or other molecules by cytochrome P450. Pharmaceutical compositions are provided that
can act as boosters to improve the pharmacokinetics, enhance the bioavailability, and enhance the therapeutic effect of drugs that
undergo in vivo degradation by cytochrome P450 enzymes.



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Amino Acid Inhibitors of Cytochrome P450

This application claims the benefit of United States Provisional Application 61/030,524 filed February 21, 2008, which is incorporated by reference.

The technology described herein provides methods of inhibiting cytochrome P450 enzymes. The technology also provides methods of enhancing the therapeutic effect of drugs that are metabolized by cytochrome P450 enzymes, methods of decreasing the toxic effects of drugs that are metabolized to toxic by-products by cytochrome P450 enzymes, methods of increasing oral bioavailability of drugs that are metabolized by cytochrome p450 enzymes, and methods of curing diseases that are caused or exacerbated by the activity of cytochrome P450 enzymes.

Background

Cytochrome P450 proteins (CYP(s), or alternatively P450(s)) are a family of enzymes involved in the oxidative metabolism of both endogenous and exogenous compounds. P450 enzymes are widely distributed in the liver, intestines and other tissues (Krishna et al., *Clinical Pharmacokinetics*. 26:144-160, 1994). P450 enzymes catalyze the phase I reaction of drug metabolism, to generate metabolites for excretion. The classification of P450s is based on homology of the amino acid sequence (Slaughter et al *The Annals of Pharmacotherapy* 29:619-624, 1995). In mammals, there is over 55% homology of the amino acid sequence of CYP subfamilies. The differences in amino acid sequence constitute the basis for a classification of the superfamily of cytochrome P450 enzymes into families, subfamilies and isozymes.

When bound to carbon monoxide (CO), the CYP proteins display a maximum absorbance (peak) at 450 nm in the visible spectra, from which its name, cytochrome P450 is derived (Omura et al., J. Biol. Chem. **239**:2370, 1964). The proteins contain an iron cation and are membrane bound enzymes that can carry out electron transfer and energy transfer. Over 200 genes encoding cytochrome P450 proteins have been identified. Those genes have been divided among more than 30 gene families, which are organized into subfamilies that vary in regulation of gene expression and in amino acid sequence homology, substrate specificity, catalytic activity, and physiological role of the encoded enzymes.

Representative cytochrome P450 (CYP) genes and examples of the known substrates of CYP proteins encoded by those genes are discussed below. See also the

discussion in Klassen, ed., Casarett and Doull's Toxicology: The Basic Science of Poisons, McGraw-Hill, 1996, pp. 150 ff. Further information about cytochrome P450 substrates, can be found in Gonzales and other review articles cited above. Current information sources available via the Internet include the "Cytochrome P450 Homepage", maintained
 5 by David Nelson, the "Cytochrome P450 Database", provided by the Institute of Biomedical Chemistry & Center for Molecular Design, and the "Directory of P450-containing Systems", provided by Kirill N. Degtyarenko and Peter Fabian.

CYP1A1: diethylstilbestrol, 2- and 4-hydroxyestradiol

CYP1A2: acetaminophen, phenacetin, acetanilide (analgesics), caffeine, clozapine
 10 (sedative), cyclobenzaprine (muscle relaxant), estradiol, imipramine (antidepressant), mexillitene (antiarrhythmic), naproxen (analgesic), riluzole, tacrine, theophylline (cardiac stimulant, bronchodilator, smooth muscle relaxant), warfarin.

CYP2A6: coumarin, butadiene, nicotine

15 CYP2A13: nicotine

CYP2B1: phenobarbital, hexobarbital

CYP2C9: NSAIDs such as diclofenac, ibuprofen, and piroxicam; oral hypoglycemic agents such as tolbutamide and glipizide; angiotensin-2 blockers such as irbesartan, losartan, and valsartan; naproxen (analgesic); phenytoin (anticonvulsant,
 20 antiepileptic); sulfamethoxazole, tamoxifen (antineoplastic); torsemide; warfarin, flurbiprofen

CYP2C19: hexobarbital, mephobarbital, imipramine, clomipramine, citalopram, cycloguanil, the anti-epileptics phenytoin and diazepam, S-mephenytoin, diphenylhydantoin, lansoprazole, pantoprazole, omeprazole, pentamidine,
 25 propranolol, cyclophosphamide, progesterone

CYP2D6: antidepressants (imipramine, clomipramine, desimpramine), antipsychotics (haloperidol, perphenazine, risperidone, thioridazine), beta blockers (carvedilol, S-metoprolol, propafenone, timolol), amphetamine, codeine, dextromethorphan, fluoxetine, S-mexiletine, phenacetin, propranolol

30 CYP2E1: acetaminophen; chlorzoxazone (muscle relaxant), ethanol; caffeine, theophylline; dapsone, general anesthetics such as enflurane, halothane, and methoxyflurane; nitrosamines

CYP3A4: HIV Protease Inhibitors such as indinavir, ritonavir, lopinavir, amprenavir, tipranavir, darunavir, and saquinavir; HIV integrase inhibitors such as raltegravir,

Hepatitis C virus (HCV) protease inhibitors, benzodiazepines such as alprazolam, diazepam, midazolam, and triazolam; immune modulators such as cyclosporine; antihistamines such as astemizole and chlorpheniramine; HMG CoA Reductase inhibitors such as atorvastatin, cerivastatin, lovastatin, and simvastatin; channel blockers such as diltiazem, felodipine, nifedipine, nisoldipine, nitrendipine, and verapamil; antibiotics such as clarithromycin, erythromycin, and rapamycin; various steroids including cortisol, testosterone, progesterone, estradiol, ethinylestradiol, hydrocortisone, prednisone, and prednisolone; acetaminophen, aldrin, alfentanil, amiodarone, astemizole, benzphetamine, budesonide, carbamazepine, cyclophosphamide, ifosfamide, dapson, digitoxin, quinidine (anti-arrhythmic), etoposide, flutamide, imipramine, lansoprazole, lidocaine, losartan, omeprazole, retinoic acid, FK506 (tacrolimus), tamoxifen, taxol and taxol analogs such as taxotere, teniposide, terfenadine, buspirone, haloperidol (antipsychotic), methadone, sildenafil, trazodone, theophylline, toremifene, troleandomycin, warfarin, zatosetron, zonisamide.

CYP6A1: fatty acids

The efficacy of a drug can be dramatically affected by its metabolism in the body. In addition, the failure to maintain therapeutically effective amounts of a drug may also impact its long-term efficacy. This situation may arise particularly in treatment of infectious diseases, such as viral or bacterial infections, where the inability to maintain an effective therapeutic dose can lead to the infectious agent(s) becoming drug resistant. To avoid the consequences of metabolism and sustain a therapeutically effective amount of drugs that are rapidly metabolized in a subject, or a specific tissue of a subject, the drugs often must be administered in a sustained release formulation, given more frequently and/or administered in higher dose than more slowly metabolized drugs administered by the same routes.

A common pathway of metabolism for drugs containing lipophilic moieties is via oxidation by one or more CYP enzymes. The CYP enzyme pathway metabolizes many lipophilic drugs to more polar derivatives that are more readily excreted through the kidney or liver (renal or biliary routes). That pathway renders many compounds having strong biological efficacy that would otherwise be potentially powerful therapeutics essentially useless by virtue of their rapid metabolism, which results in short half-lives *in vivo*, particularly where drugs are administered by the oral route.

Poor bioavailability, particularly oral bioavailability, due to first pass CYP metabolism, which leads to elimination of drugs via the liver and/or intestinal routes, is a major reason for the failure of many drug candidates in clinical trials. Where extensive metabolism by intestinal CYP occurs, first pass metabolism can lead to poor drug
5 absorption from the GI tract. Similarly, extensive hepatic CYP metabolism can result in low circulating (plasma or blood) levels of a drug.

Alteration in drug metabolism by CYP proteins may have undesired or unexpected consequences. In some instances, metabolic by-products of CYP enzymes are highly toxic and can result in severe side effects, cancer, and even death. In other instances, alterations
10 in CYP metabolism due to the interaction of agents may produce undesirable results.

Some examples of drug metabolism by CYP proteins and the effects of other agents on the metabolites produced by CYP proteins include:

Acetaminophen: Ethanol up-regulates CYP2E1, which metabolizes acetaminophen to a reactive quinone. This reactive quinone intermediate, when produced in sufficient
15 amounts, causes liver damage and necrosis.

Sedatives: The sedative phenobarbital (PB) up-regulates several P450 genes, including those of the CYP2B and CYP3A subfamilies. Upregulation of these enzymes increases the metabolism and reduces the sedative effects of PB and the related sedative hexobarbital.

20 Antibiotics: The antibiotics rifampicin, rifampin, rifabutin, erythromycin, and related compounds are inducers of the CYP3A4 gene and are substrates of the enzyme product.

Anti-cancer agents: Taxol and taxotere are potent anti-cancer agents. Both drugs are extensively metabolized by CYP3A4 and have poor oral bioavailability. These drugs
25 are only efficacious in parenteral formulations, which, due to their poor solubility properties, are highly noxious to patients.

Nicotine: CYP2A6 and 2A13 convert nicotine, a non-toxic component of cigarette smoke, into NNK, a highly potent carcinogen that contributes to lung cancer from smoking.

30 Oral contraceptive/estrogen replacement therapy: Estrogens and estradiols are the active ingredients in oral contraceptives and in hormonal replacement therapies for post-menopausal women. Women who are also taking antibiotics such as rifampicin or erythromycin, or glucocorticoids such as dexamethasone, or who smoke, risk decreased

efficacy of the estrogen/estradiol treatments due to increased metabolism of these compounds by up-regulated CYP3A4 and/or CYP1A2 enzymes.

Dextromethorphan: CYP2D6 metabolizes dextromethorphan to dextrorphan. Individuals who express high levels of CYP2D6 (so-called rapid metabolizers) do not receive therapeutic benefits from dextromethorphan due to extensive first-pass metabolism and rapid systemic clearance.

Protease Inhibitors: Protease inhibitors and non-nucleoside reverse transcriptase inhibitors currently indicated for use in treatment of HIV or HCV are typically good substrates of cytochrome P450 enzymes; in particular, they are metabolized by CYP3A4 enzymes (*see e.g.*, Sahai, AIDS 10 Suppl 1:S21-5, 1996) with possible participation by CYP2D6 enzymes (Kumar et al., *J. Pharmacol. Exp. Ther.* 277(1):423-31, 1996). Although protease inhibitors are reported to be inhibitors of CYP3A4, some non-nucleoside reverse transcriptase inhibitors, such as nevirapine and efavirenz, are inducers of CYP3A4 (*see e.g.*, Murphy et al., *Expert Opin Invest Drugs* 5/9: 1183-99, 1996).

Human CYP isozymes are widely distributed among tissues and organs (Zhang et al., *Drug Metabolism and Disposition.* 27:804-809, 1999). With the exception of CYP1A1 and CYP2A13, most human CYP isozymes are located in the liver, but are expressed at different levels (Waziers J. *Pharmacol. Exp. Ther.* 253: 387, 1990). A solution to the problem of drug degradation and first-pass metabolism is to control the rate of drug metabolism. When the rates of drug absorption and metabolism reach a steady state, a maintenance dose can be delivered to achieve a desired drug concentration that is required for drug efficacy. Certain natural products have been shown to increase bioavailability of a drug. For example, the effect of grapefruit juice on drug pharmacokinetics is well known. See Edgar et al., *Eur. J. Clin. Pharmacol.* 42:313, (1992); Lee et al., *Clin. Pharmacol. Ther.* 59:62, (1996); Kane et al., *Mayo Clinic Proc.* 75:933, (2000). This effect of grapefruit juice is due to the presence of natural P450-inhibiting components. Other compounds also have been used for inhibition of P450. For example, the HIV-1 protease inhibitor Ritonavir® is now more commonly prescribed for use in combination with other, more effective HIV protease inhibitors because of its ability to “boost” those other compounds by inhibiting P450-mediated degradation.

Present methods of inhibiting cytochrome P450 enzymes are not wholly satisfactory because of toxicity issues, high cost, and other factors. For example, using ritonavir to inhibit cytochrome P450 is not desirable in disorders other than HIV infection. It is apparent, therefore, that new and improved methods of inhibiting cytochrome P450

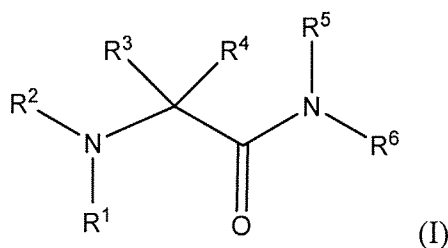
enzymes are greatly to be desired. In particular, methods where an inhibitor can be co-administered with another biologically active compound that is metabolized by cytochrome P450 enzymes are highly desirable.

Summary

5 The technology described herein provides, among other things, methods and compounds for inhibiting cytochrome P450 enzymes. The technology also provides methods of enhancing the therapeutic effect of drugs that are metabolized by cytochrome P450 enzymes, methods of decreasing the toxic effects of drugs that are metabolized to toxic by-products by cytochrome P450 enzymes, methods of increasing oral bioavailability
10 of drugs that are metabolized by cytochrome P450 enzymes, and methods of curing diseases that are caused or exacerbated by the activity of cytochrome P450 enzymes.

 An advantage of the technology described herein is that it provides improved inhibitors of cytochrome P450 enzymes. Another advantage is that it provides a method of controlling the pharmacokinetic properties of drugs. Another advantage is that it helps
15 control the rate of metabolism of drugs. Another advantage is that it controls the degradation of drugs. Another advantage is that it enhances the bioavailability of drugs. Another advantage is that it enhances the efficacy of drugs. Another advantage is that it boosts the efficacy of certain drugs so that the drugs can be administered at a lower concentration or dosage thereby reducing their toxicity. Another advantage is that these
20 properties can lower the overall cost associated with the treatment of disorders.

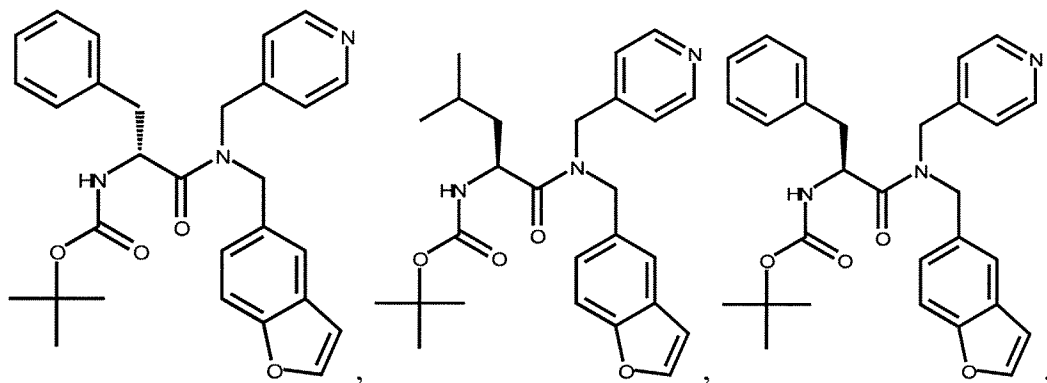
 In one aspect, the technology described herein provides both compounds of formula (I), and a method of inhibiting a cytochrome P450 monooxygenase enzyme by contacting it with a compound of formula (I) having the structure:

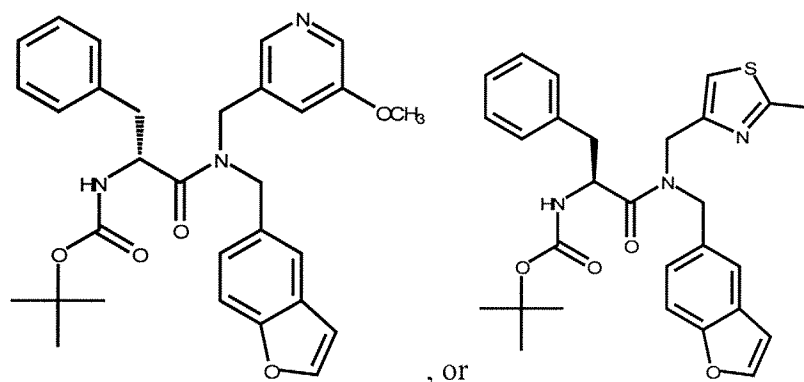


25 where:

each R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 independently is selected from the group consisting of H, optionally substituted C_1 - C_8 alkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted

heteroaralkyl, optionally substituted heterocyclo-, optionally substituted heterocycloalkylalkyl, $-\text{SO}_n(\text{R})$, and $-(\text{CH}_2)_{0-6}\text{CO}_n(\text{CH}_2)_{0-3}-\text{R}$;
 wherein at least one of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is $-\text{S}(\text{O})_n-(\text{CH}_2)_{0-3}-(\text{benzofuranyl})$,
 $-(\text{CH}_2)_{1-5}-\text{N}(\text{R})-(\text{SO}_2-\text{benzofuranyl})$, $-\text{C}(\text{O})_n-(\text{CH}_2)_{0-3}-(\text{benzofuranyl})$,
 5 $-(\text{CH}_2)_{1-5}-\text{N}(\text{R})(\text{C}(\text{O})-(\text{benzofuranyl}))$, or C_1-C_6 alkylene-(benzofuranyl), wherein
 said benzofuranyl substituent may be substituted with an optional substituent, and
 wherein the benzofuranyl group is not fused as part of a tricyclic system;
 each optional substituent is selected from the group consisting of halo, $-\text{CN}$, $-\text{NO}_2$,
 $-\text{CO}_n\text{R}$, $-\text{OC}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{C}(\text{S})\text{R}$, $-\text{C}(\text{S})\text{N}(\text{R})_2$, $-\text{SO}_n\text{N}(\text{R})_2$, $-\text{SR}$, $-\text{SO}_n\text{R}$,
 10 $-\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{CO}_n\text{R}$, $-\text{NRS}(\text{O})_n\text{R}$, $-\text{NRC}[\text{N}(\text{R})]\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{N}(\text{R})\text{CO}_n\text{R}$,
 $-\text{NRPO}_n\text{N}(\text{R})_2$, $-\text{NRPO}_n\text{OR}$, oxo, $=\text{N}-\text{OR}$, $=\text{N}-\text{N}(\text{R})_2$, $=\text{NR}$, $=\text{NNRC}(\text{O})\text{N}(\text{R})_2$,
 $=\text{NNRCO}_n\text{R}$, $=\text{NNRS}(\text{O})_n\text{N}(\text{R})_2$, $=\text{NNRS}(\text{O})_n(\text{R})\text{C}_1-\text{C}_8$ alkyl, $-\text{OR}$, C_1-C_8 alkyl, C_2-
 C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, heterocyclo, aryl,
 and heteroaryl;
 15 each R is independently selected from the group consisting of: H, C_1-C_8 alkyl, aryl,
 aralkyl, heteroaryl, and heteroaralkyl, and when R is directly bound to a nitrogen, R
 may additionally be selected from $-\text{C}(\text{O})_n\text{alkyl}$, $-\text{S}(\text{O})_n\text{alkyl}$, $\text{C}(\text{O})_n\text{-aryl}$,
 $-\text{S}(\text{O})_n\text{-aryl}$, or $-\text{S}(\text{O})_n\text{-heteroaryl}$, wherein when R is a group selected from aryl,
 aralkyl, heteroaryl, heteroaralkyl, $-\text{C}(\text{O})_n\text{-aryl}$, $-\text{S}(\text{O})_n\text{-aryl}$, or $-\text{S}(\text{O})_n\text{-heteroaryl}$,
 20 the group may substituted with one or more independently selected C_1-C_6 alkyls;
 each n is independently 1 or 2;
 provided that at least two of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are not H;
 provided that neither R^5 nor R^6 forms a ring with R^1 , R^2 , R^3 , or R^4 ; and
 provided that the compound is not





In another aspect, the technology provides a pharmaceutical composition comprising a pharmaceutically acceptable diluent, carrier, or excipient and a compound of formula (I), or any subgrouping thereof such as the compounds in Table I.

5 In yet another aspect, the technology provides a method of inhibiting cytochrome P450 monooxygenase in a subject, including administering to the subject an effective amount of a compound according to formula (I).

In still another aspect, the technology provides a method of reducing toxicity in a subject of a compound that is metabolized by cytochrome P450 monooxygenase to a toxic metabolite, the method including administering to the subject an effective amount of a
10 compound according to formula (I).

In some embodiments, where a compound of formula (I) is administered to a subject, the subject is a patient suffering from chronic pain, depression, epilepsy, psychosis, inflammation, cancer, cardiovascular disease, diabetes, neurodegenerative
15 disease such as Alzheimer's disease, and/or infection. In other embodiments, the patient is suffering from HCV or HIV infection.

In some embodiments, where a compound of formula (I) is administered with a drug whose efficacy is compromised due to degradation by cytochrome P450, the compound is administered prior to, and/or substantially contemporaneously with, the drug.
20 In other embodiments, the compound can be administered at least 30 minutes, at least 1 hour, at least 2 hours, or at least 12 hours prior to administration of the drug.

In some embodiments, the pharmaceutical composition comprises a compound of formula (I) and an effective amount of a drug whose efficacy is compromised due to degradation by cytochrome P450 monooxygenase. The drug can be, for example,
25 Cyclosporine, Tacrolimus (FK506), Sirolimus (rapamycin), Indinavir, Ritonavir, Saquinavir, Felodipine, Isradipine, Nicardipine, Nisoldipine, Nimodipine, Nitrendipine, Nifedipine, Verapamil, Etoposide, Tamoxifen, Vinblastine, Vincristine, Taxol,

Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin, Terfenadine, Loratadine, Astemizole, Alfentanil, Carbamazepine, Azithromycin, Clarithromycin, Erythromycin, Itraconazole, Rifabutin, Lidocaine, Cisapride, Sertraline, Pimozide, Triazolam, Anastrozole, Busulfan, Corticosteroids (dexamethasone, methylprednisone and prednisone), Cyclophosphamide, Cytarabine, Docetaxel, Doxorubicin, Erlotinib, Exemestane, Gefitinib, Idarubicin, Ifosfamide, Imatinib mesylate, Irinotecan, Ketoconazole, Letrozole, Paclitaxel, Teniposide, Tretinoin, Vinorelbine, quinidine, alprazolam, diazepam, midazolam, nelfinavir, chlorpheniramine, amlodipine, diltiazem, lercanidipine, cerivastatin, estradiol, hydrocortisone, progesterone, testosterone, alfentanil, aripiprazole, cafergot, caffeine, cilostazol, cocaine, codeine, dapsone, dextromethorphan, domperidone, eplerenone, fentanyl, finasteride, gleevec, haloperidol, irinotecan, Levo-Alpha Acetyl Methadol (LAAM), methadone, nateglinide, odansetron, propranolol, quinine, salmeterol, sildenafil, trazodone, vincristine, zaleplon, zolpidem., ixabepilone, Agenerase (APV), Aptivus (TPV), Crixivan (IDV), Invirase (SQV), Lexiva (FPV), Prezista (DRV), Reyataz (ATV) Viracept (NFV), Elvitegravir, Selzentry, Vicriviroc, Telaprevir, Telithromycin, tandospirone or buspirone.

Each of the aspects and embodiments of the technology discussed above can include one or more of the following embodiments of a compound of formula (I).

In some embodiments, R⁵ is an otherwise unsubstituted CH₂-4-benzofuranyl, CH₂-5-benzofuranyl, CH₂-6-benzofuranyl, or CH₂-7-benzofuranyl. R³ can be H and R⁴ can be selected from the group consisting of H, optionally substituted C₁-C₈ alkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted heterocyclo, and optionally substituted heterocycloalkylalkyl. R¹ can be optionally substituted C₁-C₈ alkyl. R² can be optionally substituted C₁-C₈ alkyl. R⁴ can be optionally substituted alkyl or optionally substituted heteroaralkyl. R⁶ can be H, optionally substituted C₁-C₈ alkyl, or optionally substituted heteroaralkyl. R¹ and R² can be optionally substituted C₁-C₈ alkyl. R³ can be H, R⁴ can be H, optionally substituted C₁-C₈ alkyl or optionally substituted heteroaralkyl, and R⁶ can be H, optionally substituted C₁-C₈ alkyl or optionally substituted heteroaralkyl.

In some embodiments, R³ is an otherwise unsubstituted CH₂-4-benzofuranyl, CH₂-5-benzofuranyl, CH₂-6-benzofuranyl, or CH₂-7-benzofuranyl.

In some embodiments, R⁴ can be H. In other embodiments, R⁴ can be H or C₁-C₈ alkyl. In still other embodiments, R⁴ can be H. R⁴ can be H and R⁵ can be H. R⁶ can be

selected from the group consisting of optionally substituted C₁-C₈ alkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted heterocyclo, and optionally substituted heterocycloalkylalkyl.

In some embodiments, R¹ can be an otherwise unsubstituted -CH₂-4-benzofuranyl, -CH₂-5-benzofuranyl, -CH₂-6-benzofuranyl, or -CH₂-7-benzofuranyl.

In some embodiments, a compound is selected from the compounds listed in Table 1.

In some embodiments, one or both of R³ and R⁴ is heteroarylalkyl.

In some embodiments, one or both of R³ and R⁴ is heteroarylmethyl.

In some embodiments, the cytochrome P450 monooxygenase is CYP3A4 or CYP3A5.

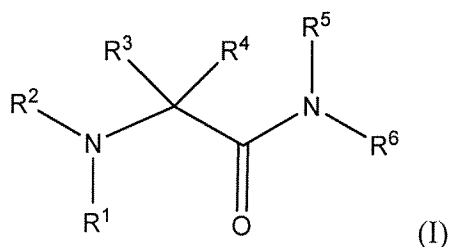
The details of one or more examples are set forth in the accompanying reaction schemes and description. Further features, aspects, and advantages of the technology will become apparent from the description, the schemes, and the claims.

Detailed Description

The technology described herein provides compounds and methods for inhibiting cytochrome P450 (CYP) enzymes. More particularly, the technology provides methods for enhancing the therapeutic effect of drugs in which the drug's efficacy is compromised due to degradation mediated by cytochrome P450. The methods include administering compounds or pharmaceutical compositions containing the compounds in any therapeutic regimen where one or more primary drugs is metabolized by a CYP. The compounds or pharmaceutical compositions can be administered when the primary drug either becomes inactive or is converted to a toxic metabolite due to metabolism by a CYP. The compounds or compositions can inhibit or reduce the rate of degradation of drugs that are effective against a variety of diseases and that are degraded by one or more cytochrome P450 enzymes. Upon co-administration, the compounds and compositions can, for example, maintain intracellular concentrations of the drugs at a therapeutic level for a sustained period of time. The methods are useful, for example, in treating a variety of disorders such as, cardiac arrhythmia, depression, psychosis, chronic pain, diabetes, neurodegenerative disease such as Alzheimer's disease, and infections such as HIV or HCV. The compounds or compositions can be administered either alone or in combination

with drugs such as analgesics, anti-depressants, anti-psychotics, antibiotics, anti-arrhythmics, steroids, anesthetics, muscle relaxants, cardiac stimulants, NSAIDs, anti-epileptics, or protease inhibitors, such as HIV or HCV protease inhibitors.

More particularly, in one aspect, the technology provides a compound, its
 5 stereoisomeric forms, and pharmacologically acceptable salts thereof, having the formula:



where:

each R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 independently is selected from the group consisting of
 H, optionally substituted C_1 - C_8 alkyl, optionally substituted C_3 - C_8 cycloalkyl,
 10 optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally
 substituted aralkyl, optionally substituted heteroaryl, optionally substituted
 heteroaralkyl, optionally substituted heterocyclo-, optionally substituted
 heterocycloalkylalkyl, $-SO_n(R)$, and $-(CH_2)_{0-6}CO_n(CH_2)_{0-3}-R$;

wherein at least one of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is $-S(O)_n-(CH_2)_{0-3}-(\text{benzofuranyl})$,
 15 $-(CH_2)_{1-5}-N(R)(-SO_2-\text{benzofuranyl})$, $-C(O)_n-(CH_2)_{0-3}-(\text{benzofuranyl})$,
 $-(CH_2)_{1-5}-N(R)(C(=O)-(\text{benzofuranyl}))$, or C_1 - C_6 alkylene- (benzofuranyl) , wherein
 said benzofuranyl substituent may be substituted with an optional substituent, and
 wherein the benzofuranyl group is not fused as part of a tricyclic system;

each optional substituent is selected from the group consisting of halo, $-CN$, $-NO_2$,
 20 $-CO_nR$, $-OC(=O)R$, $-C(=O)N(R)_2$, $-C(=S)R$, $-C(=S)N(R)_2$, $-SO_nN(R)_2$, $-SR$, $-SO_nR$,
 $-N(R)_2$, $-N(R)CO_nR$, $-NRS(=O)_nR$, $-NRC[=N(R)]N(R)_2$, $-N(R)N(R)CO_nR$,
 $-NRPO_nN(R)_2$, $-NRPO_nOR$, oxo, $=N-OR$, $=N-N(R)_2$, $=NR$, $=NNRC(O)N(R)_2$,
 $=NNRCO_nR$, $=NNRS(O)_nN(R)_2$, $=NNRS(O)_n(R)C_1-C_8$ alkyl, $-OR$, C_1-C_8 alkyl, C_2 -
 C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, heterocyclo, aryl,
 25 and heteroaryl;

each R is independently selected from the group consisting of: H , C_1-C_8 alkyl, aryl,
 aralkyl, heteroaryl, and heteroaralkyl, and when R is directly bound to a nitrogen, R
 may additionally be selected from $-C(O)_n\text{alkyl}$, $-S(O)_n\text{alkyl}$, $-C(O)_n\text{-aryl}$,
 $-S(=O)_n\text{-aryl}$, or $-S(=O)_n\text{-heteroaryl}$, wherein when R is a group selected from aryl,

aralkyl, heteroaryl, heteroaralkyl, $-C(O)_n\text{-aryl}$, $-S(=O)_n\text{-aryl}$, or $-S(=O)_n\text{-heteroaryl}$,

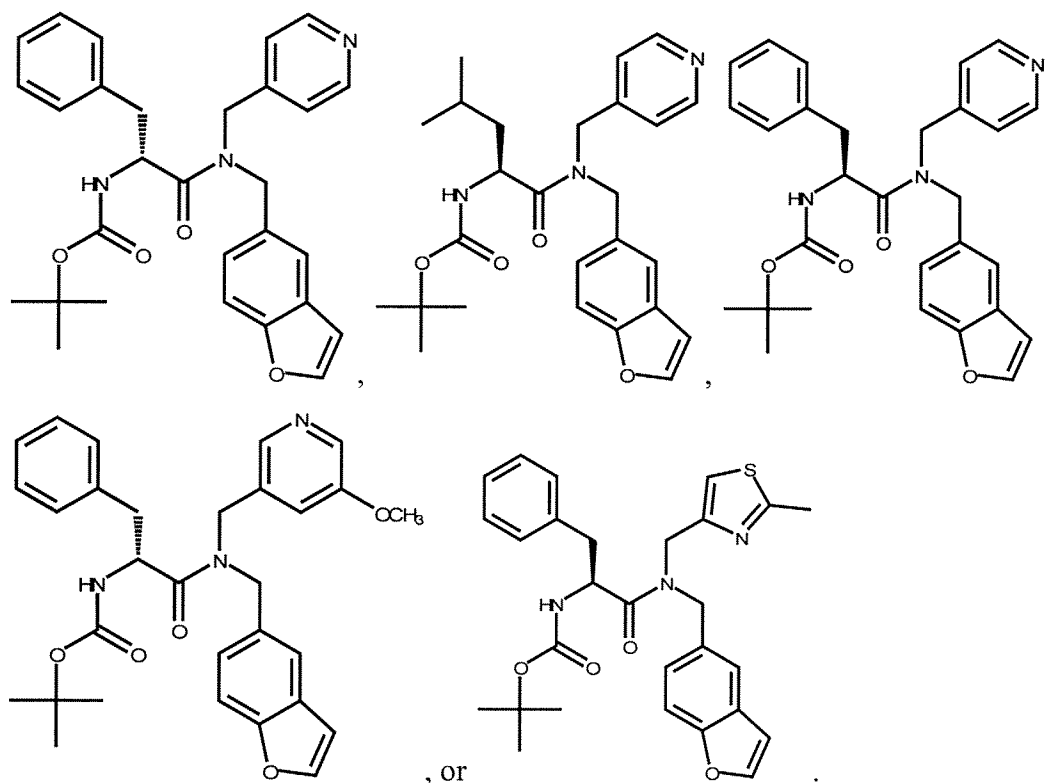
the group may substituted with one or more independently selected $C_1\text{-}C_6$ alkyls;

each n is independently 1 or 2;

provided that at least two of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are not H;

5 provided that neither R^5 nor R^6 forms a ring with R^1 , R^2 , R^3 , or R^4 ; and

provided that the compound is not



In one embodiment, subject to the same provisos recited above, the compound is a

10 compound where:

each R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 independently is selected from the group consisting of

H, optionally substituted $C_1\text{-}C_8$ alkyl, optionally substituted $C_3\text{-}C_8$ cycloalkyl,

optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally

substituted aralkyl, optionally substituted heteroaryl, optionally substituted

15 heteroaralkyl, optionally substituted heterocyclo, optionally substituted

heterocycloalkylalkyl, $-SO_n(R)$, and $-(CH_2)_{0-6}CO_n(CH_2)_{0-3}\text{-}R$;

wherein at least one of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is $-SO_n\text{-(benzofuranyl)}$,

$-C(=O)\text{-(benzofuranyl)}$, $-C(=O)O(CH_2)_{1-3}\text{-(benzofuranyl)}$, or $C_1\text{-}C_6$ alkylene-

(benzofuranyl), wherein said benzofuranyl substituent may be substituted with an

20 optional substituent and wherein the benzofuranyl group is not fused as part of a tricyclic system;

each optional substituent is selected from the group consisting of halo, -OC(=O)R, -C(=O)N(R)₂, -C(=S)R, -C(=S)N(R)₂, -SO_nN(R)₂, -SR, -SO_nR, -N(R)₂, -N(R)CO_nR, -NRS(=O)_nR, -NRC[=N(R)]N(R)₂, -N(R)N(R)CO_nR, -NRPO_nN(R)₂, -NRPO_nOR, oxo, -OR, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₈ cycloalkyl, C₅-C₈

5 cycloalkenyl, heterocyclo, aryl, and heteroaryl;

each R is independently selected from the group consisting of: H, C₁-C₈ alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, and when R is directly bound to a nitrogen, R may additionally be selected from -C(O)_nalkyl, -S(O)_nalkyl, -C(O)_n-aryl, -S(=O)_n-aryl, or -S(=O)_n-heteroaryl, wherein when R is a group selected from aryl, aralkyl, heteroaryl, heteroaralkyl, -C(O)_n-aryl, -S(=O)_n-aryl, or -S(=O)_n-heteroaryl, 10 the group may substituted with one or more independently selected C₁-C₆ alkyls; each n is independently 1 or 2.

In those embodiments where a benzofuranyl substituent group (radical) is recited, any benzofuranyl group may be present. Alternatively, where a benzofuranyl group is 15 recited the radical may be selected from any one or more of a 4-benzofuranyl, 5-benzofuranyl, 6-benzofuranyl, or a 7-benzofuranyl radical.

In another aspect, the technology provides a pharmaceutical composition. The pharmaceutical composition includes a compound according to the technology and a pharmaceutically acceptable diluent, carrier, or excipient.

20 In yet another aspect, the technology provides a method of inhibiting cytochrome P450 monooxygenase in a subject. The method includes administering to the subject an effective amount of a compound according to the technology.

In yet another aspect, the technology described herein provides a composition comprising a compound of formula (I) and an effective amount of a drug where the 25 efficacy of the drug is compromised due to degradation by cytochrome P450 monooxygenase. In some embodiments, the cytochrome P450 monooxygenase is CYP3A4 or CYP3A5.

In still another aspect, the technology provides a method of reducing toxicity in a subject of a compound that is metabolized by cytochrome P450 monooxygenase to a toxic 30 metabolite. The method includes administering to the subject an effective amount of a compound according to the technology.

Each of the aspects and embodiments of the technology discussed above can include one or more of the following embodiments, including the following embodiments of a compound of formula (I).

In some embodiments, R is independently selected from the group consisting of: H, C₁-C₈ alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, and when R is directly bound to a nitrogen, R may additionally be selected from -C(O)_nalkyl, -S(O)_nalkyl, -C(O)_n-aryl, -S(=O)_n-aryl, or -S(=O)_n-heteroaryl, wherein when R is a group selected from aryl, aralkyl, heteroaryl, heteroaralkyl, -C(O)_n-aryl, -S(=O)_n-aryl, or -S(=O)_n-heteroaryl, the group may substituted with one or more independently selected C₁-C₆ alkyls. In other embodiments, each R is independently selected from the group consisting of: H, C₁-C₈ alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, and when R is directly bound to a nitrogen, R may additionally be selected from -S(=O)_n-aryl, or -S(=O)_n-heteroaryl, wherein when R is a group selected from aryl, aralkyl, heteroaryl, heteroaralkyl, -S(=O)_n-aryl, or -S(=O)_n-heteroaryl, the group may substituted with one or more independently selected C₁-C₆ alkyls. In other embodiments, each R is independently selected from the group consisting of: H, C₁-C₈ alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, wherein when R is a group selected from aryl, aralkyl, heteroaryl, heteroaralkyl, the group may substituted with one or more independently selected C₁-C₆ alkyls. In another embodiment, R is selected from the group consisting of C₁-C₈ alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, each of which may be substituted with one or more independently selected C₁-C₆ alkyls.

In various embodiments, R⁵ is an otherwise unsubstituted CH₂-4-benzofuranyl, CH₂-5-benzofuranyl, CH₂-6-benzofuranyl, or CH₂-7-benzofuranyl. R³ can be H and R⁴ can be selected from the group consisting of H, optionally substituted C₁-C₈ alkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted heterocyclo, and optionally substituted heterocycloalkylalkyl. R¹ can be optionally substituted C₁-C₈ alkyl. R² can be optionally substituted C₁-C₈ alkyl. R⁴ can be optionally substituted alkyl or optionally substituted heteroaralkyl. R⁶ can be H, optionally substituted C₁-C₈ alkyl, or optionally substituted heteroaralkyl. R¹ and R² can be optionally substituted C₁-C₈ alkyl. R³ can be H, R⁴ can be H, optionally substituted C₁-C₈ alkyl or optionally substituted heteroaralkyl, and R⁶ can be H, optionally substituted C₁-C₈ alkyl or optionally substituted heteroaralkyl.

In some embodiments, R³ is an otherwise unsubstituted -CH₂-4-benzofuranyl, -CH₂-5-benzofuranyl, -CH₂-6-benzofuranyl, or -CH₂-7-benzofuranyl.

In some embodiments, R⁴ can be H or C₁-C₈ alkyl. In other embodiments, R⁴ can be H. In another embodiment, R⁴ can be H and R⁵ can be H.

In some embodiments, R⁶ can be selected from the group consisting of optionally substituted C₁-C₈ alkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted heterocyclo, and optionally substituted heterocycloalkylalkyl.

In some embodiments, R¹ can be an otherwise unsubstituted -CH₂-4-benzofuranyl, -CH₂-5-benzofuranyl, -CH₂-6-benzofuranyl, or -CH₂-7-benzofuranyl. In another embodiment, only one of R¹ and R³ is -CH₂-4-benzofuranyl, -CH₂-5-benzofuranyl, -CH₂-6-benzofuranyl, or -CH₂-7-benzofuranyl.

In certain embodiments, a compound is selected from the compounds listed in Table 1.

In various embodiments, one or both of R³ and R⁴ is heteroarylalkyl.

In some embodiments, one or both of R³ and R⁴ is heteroarylmethyl.

In certain embodiments, the cytochrome P450 monooxygenase is CYP3A4 or CYP3A5.

In various embodiments, the subject is a patient that is suffering from chronic pain, depression, epilepsy, psychosis, inflammation, cancer, cardiovascular disease, diabetes, and/or infection. The patient can be suffering from HCV or HIV infection.

In some embodiments, the compound is administered prior to, and/or substantially contemporaneously with, a drug wherein efficacy of said drug is compromised due to degradation by cytochrome P450 monooxygenase. The compound can be administered at least 30 minutes, at least 1 hour, at least 2 hours, or at least 12 hours prior to administration of the drug.

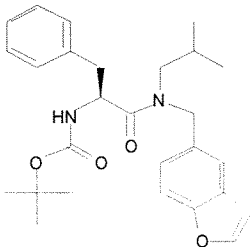
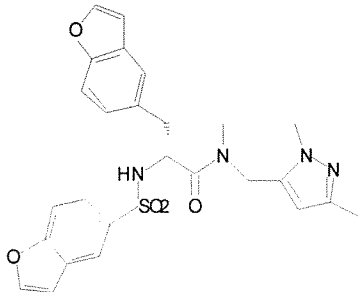
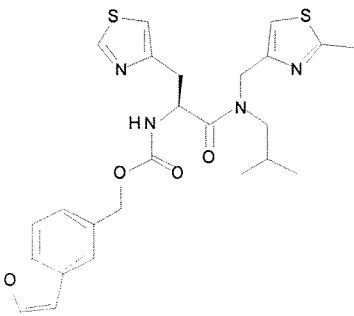
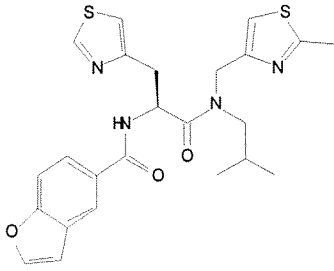
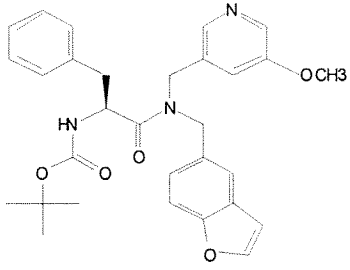
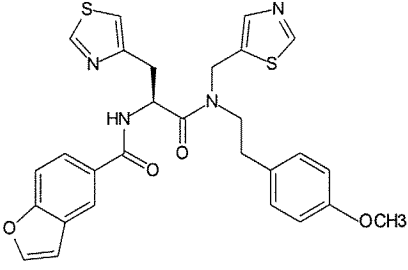
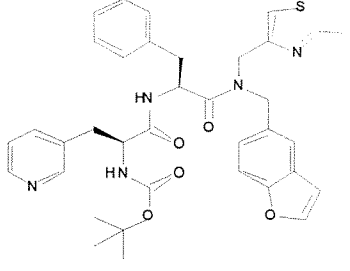
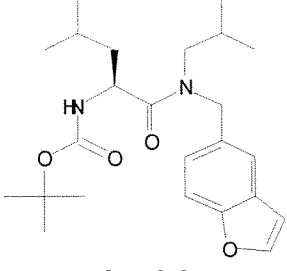
In certain embodiments, the composition includes an effective amount of a drug wherein efficacy of said drug is compromised due to degradation by cytochrome P450 monooxygenase.

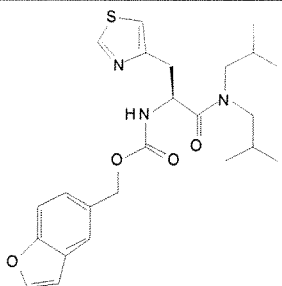
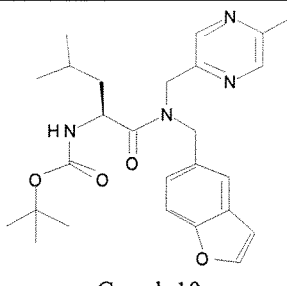
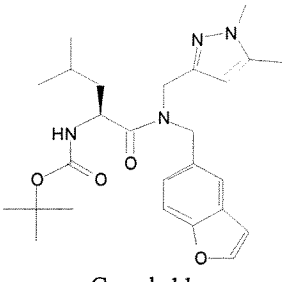
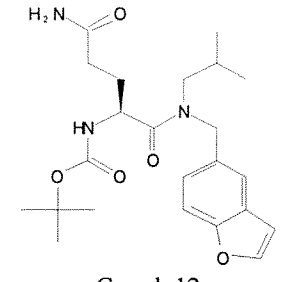
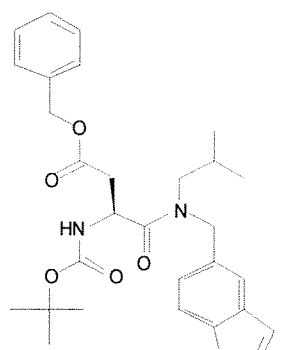
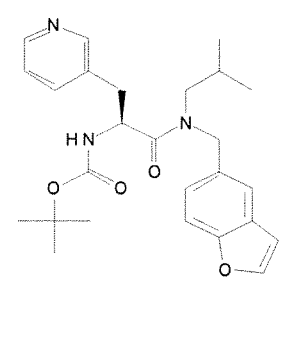
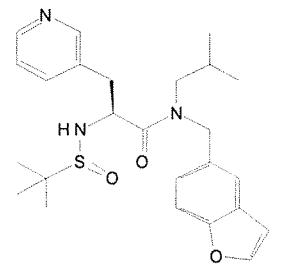
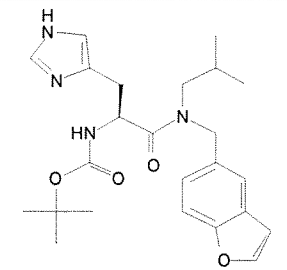
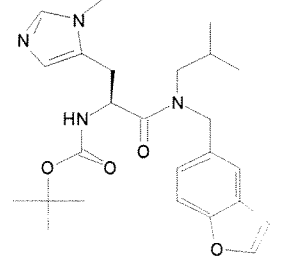
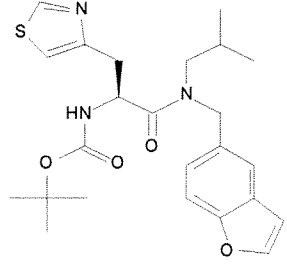
This technology described herein also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. The basic nitrogen can be quaternized with any agents known to those of ordinary skill in the art including, for example, lower alkyl halides, such as methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products can be obtained by such quaternization.

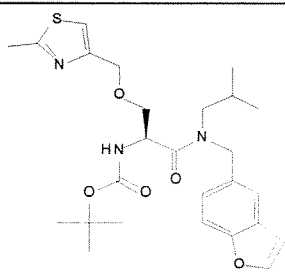
By way of illustration, exemplary compounds of formula (I) are shown in the Table 1 below, although it will be recognized that these examples are merely illustrative and not limiting. All shown compounds have an IC_{50} less than 100 nM for the metabolism of dibenzylfluorescein (DFB) by human liver microsomes (Xeno Tech, LLC, Lenexa, KS).

- 5 Where tested, the compound also have an IC_{50} less than 100 nM for the inhibition of DFB utilization by CYP 3A4.

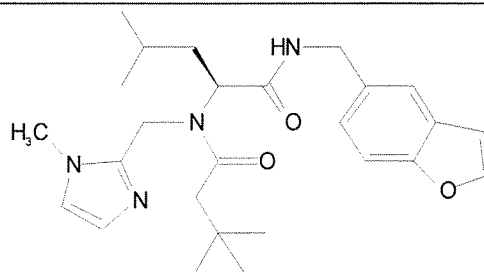
Table 1

 Cmpd. 1	 Cmpd. 2
 Compound 3	 Compound 4
 Compound 5	 Cmpd. 6
 Cmpd. 7	 Cmpd. 8

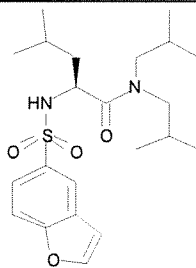
 Cmpd. 9	 Cmpd. 10
 Cmpd. 11	 Cmpd. 12
 Cmpd. 13	 Cmpd. 14
 Cmpd. 15	 Cmpd. 16
 Cmpd. 17	 Cmpd. 18



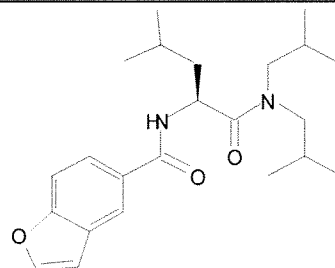
Cmpd. 19



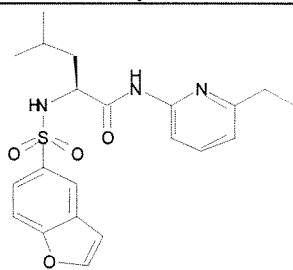
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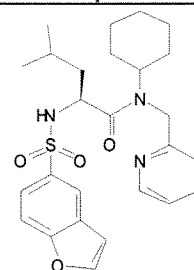
Cmpd. 21



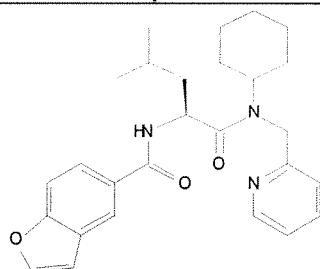
Cmpd. 22



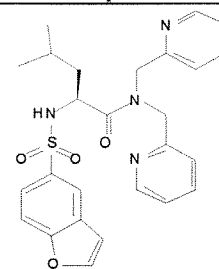
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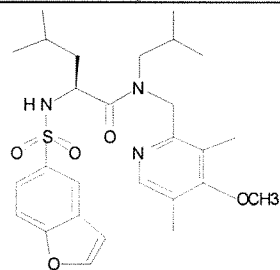
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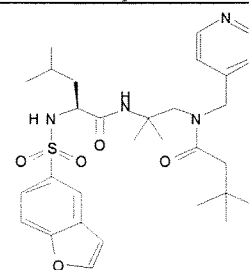
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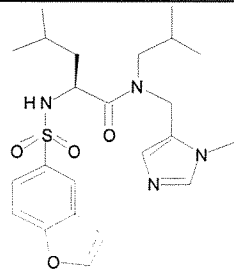
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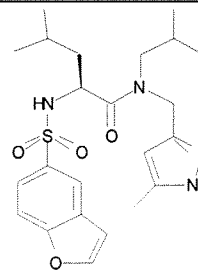
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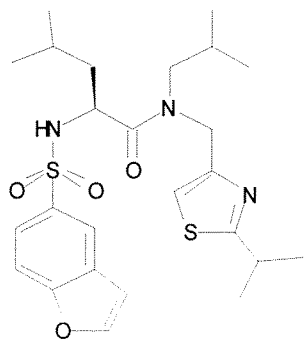
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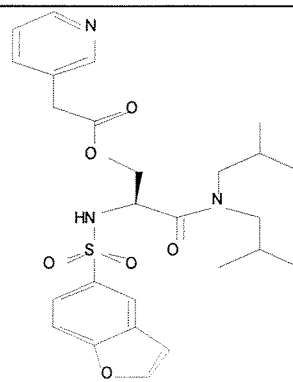
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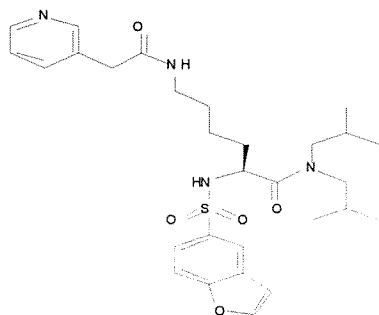
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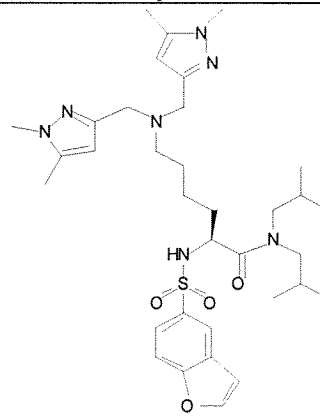
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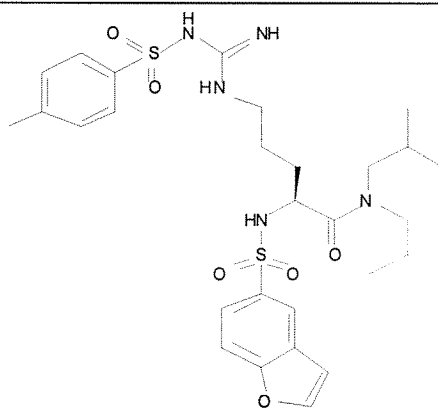
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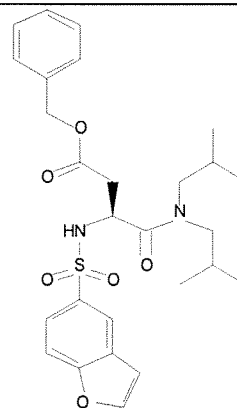
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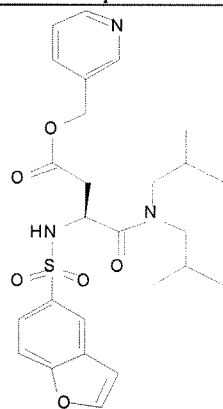
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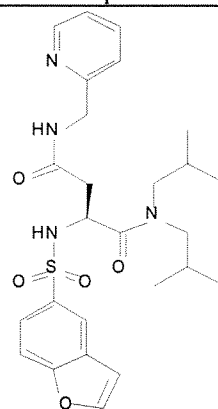
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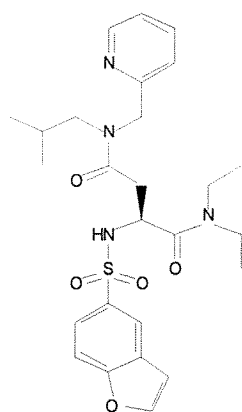
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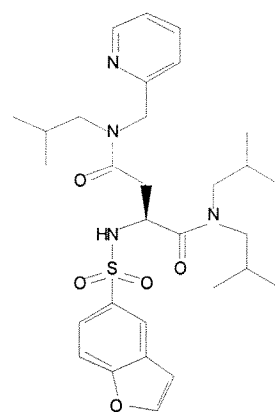
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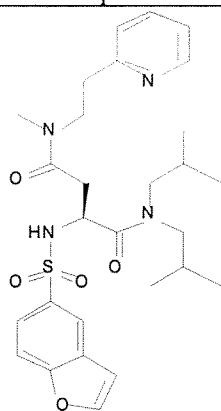
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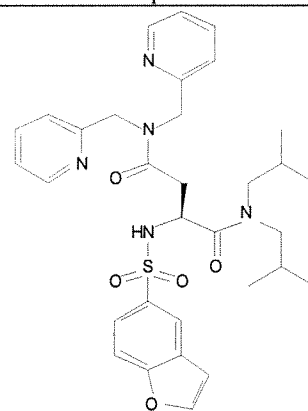
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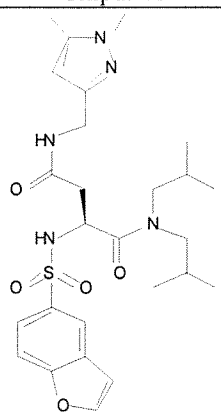
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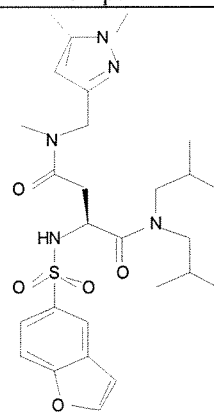
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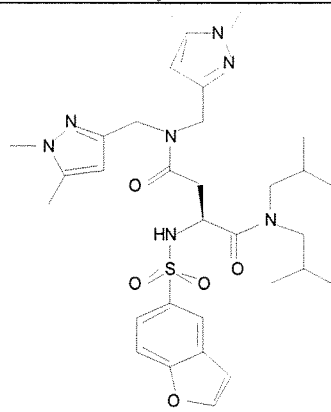
Cmpd. 42



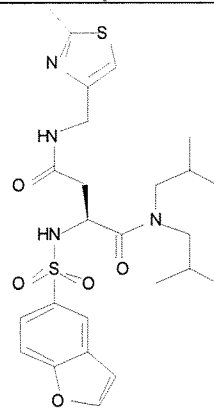
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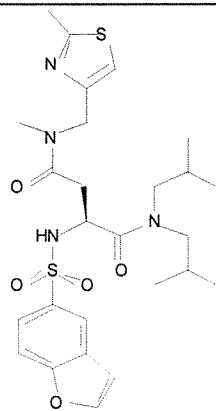
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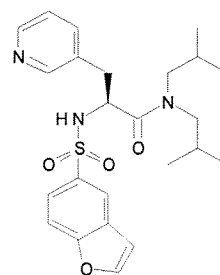
Cmpd. 45



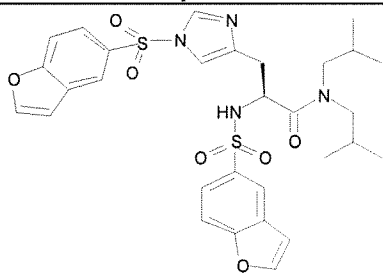
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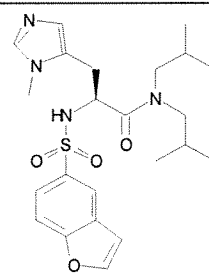
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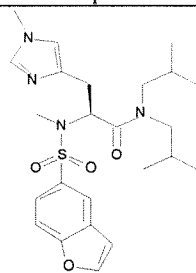
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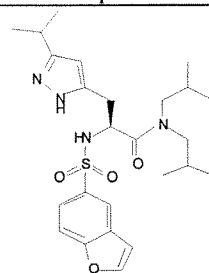
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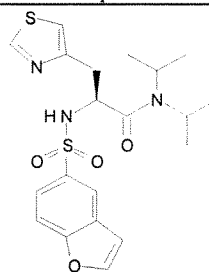
Cmpd. 50



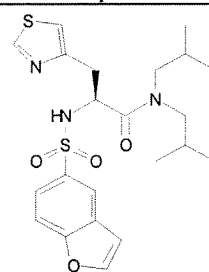
Cmpd. 51



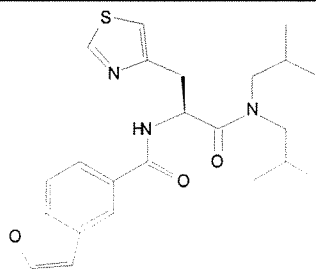
Cmpd. 52



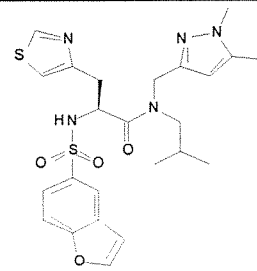
Cmpd. 53



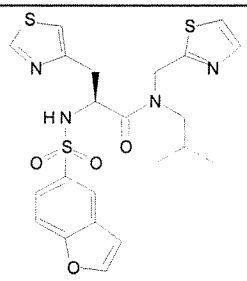
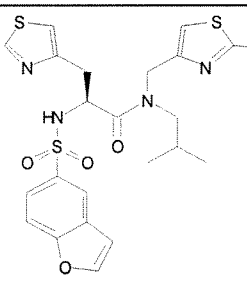
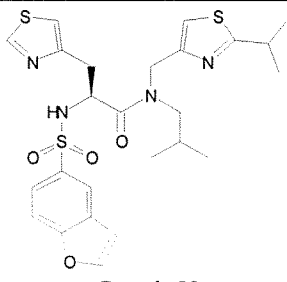
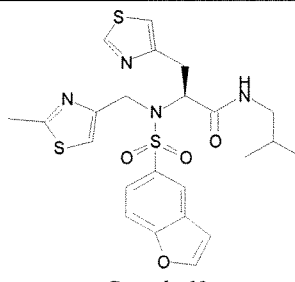
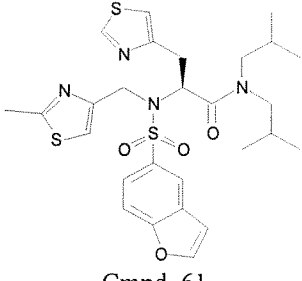
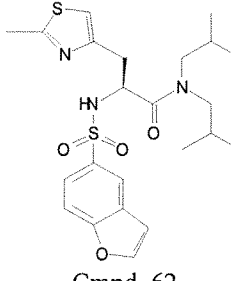
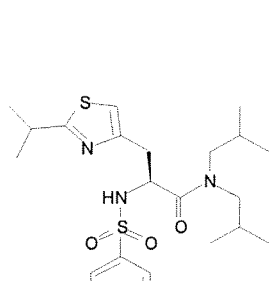
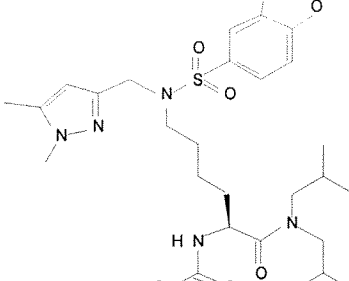
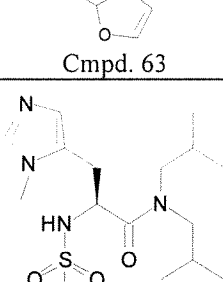
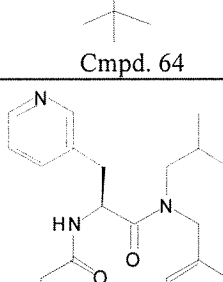
Cmpd. 54

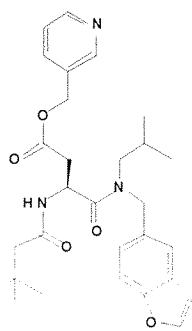


Cmpd. 55

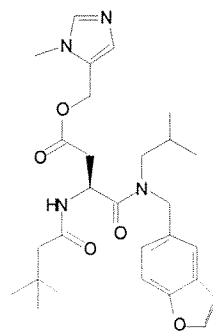


Cmpd. 56

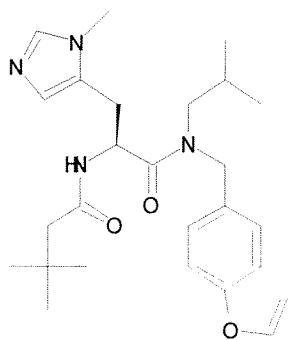
 Cmpd. 57	 Cmpd. 58
 Cmpd. 59	 Cmpd. 60
 Cmpd. 61	 Cmpd. 62
 Cmpd. 63	 Cmpd. 64
 Cmpd. 65	 Cmpd. 66



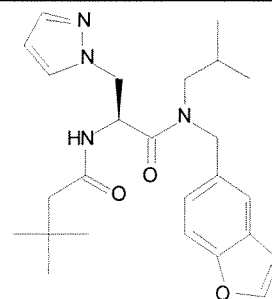
Cmpd. 67



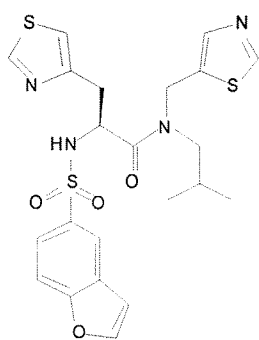
Cmpd. 68



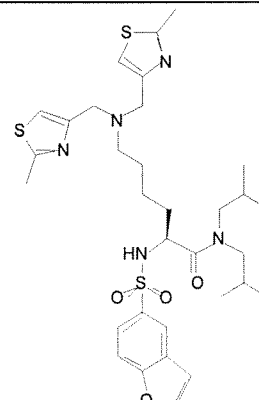
Cmpd. 69



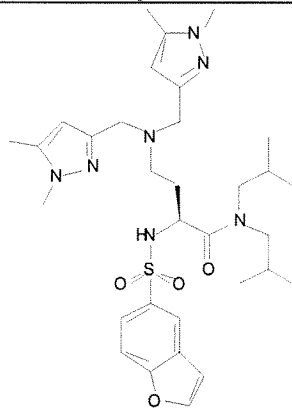
Cmpd. 70



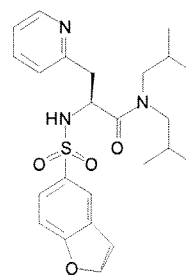
Cmpd. 71



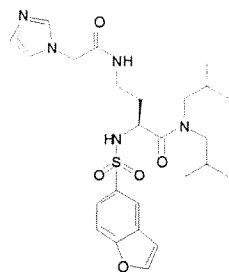
Cmpd. 72



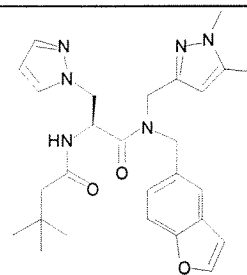
Cmpd. 73



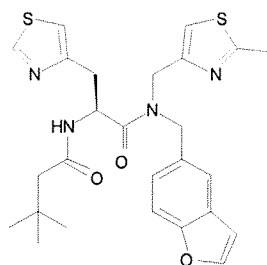
Cmpd. 74



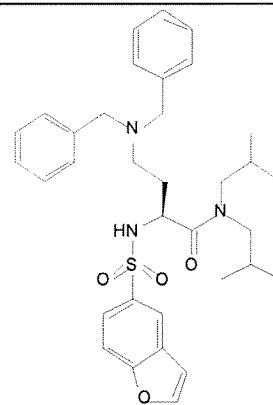
Cmpd. 75



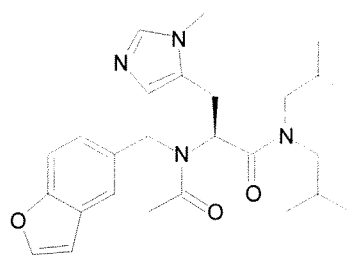
Cmpd. 76



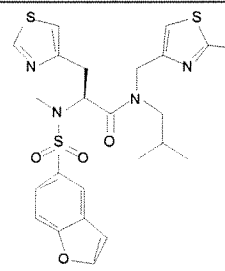
Cmpd. 77



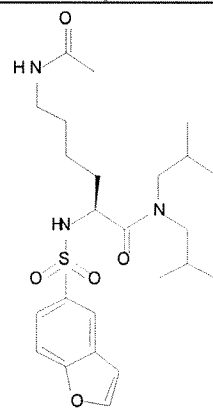
Cmpd. 78



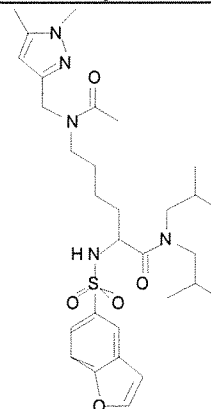
Cmpd. 79



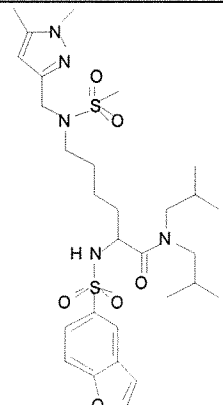
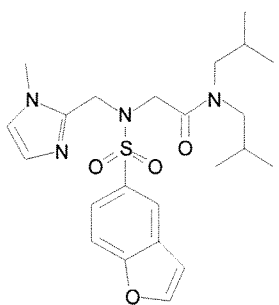
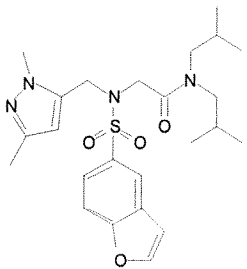
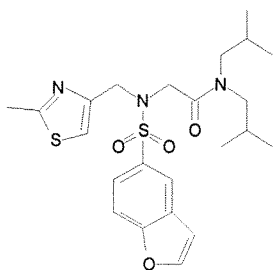
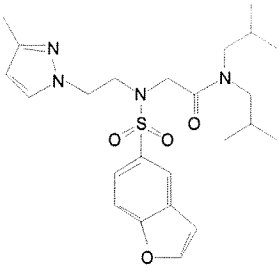
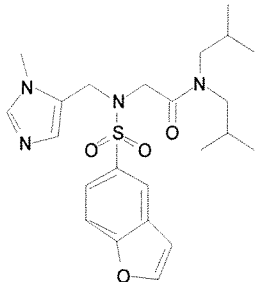
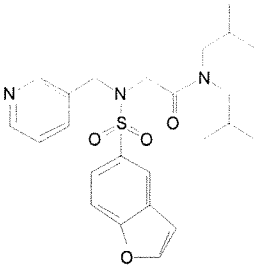
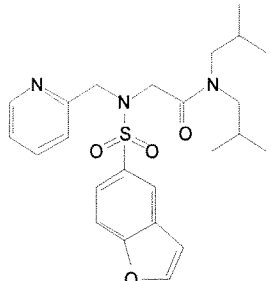
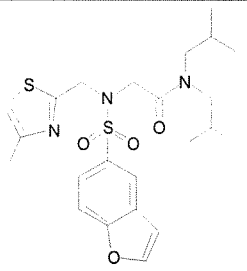
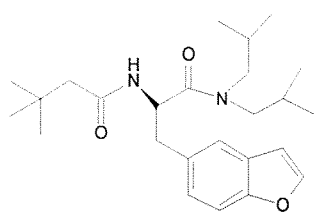
Cmpd. 80

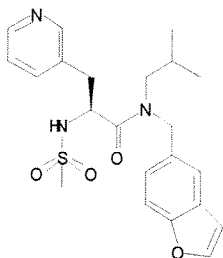
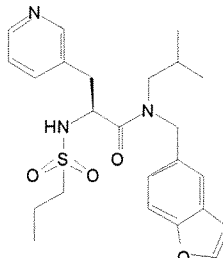
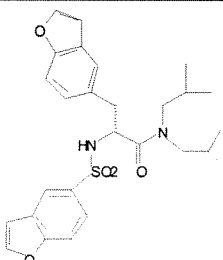
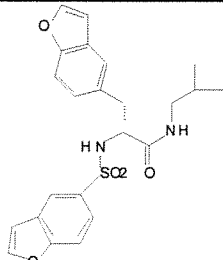
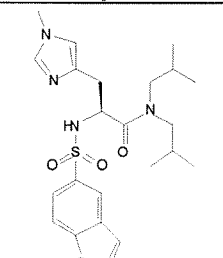
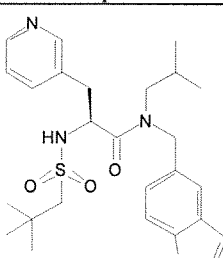
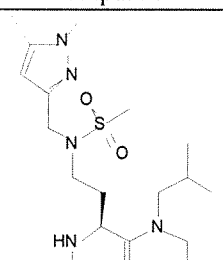
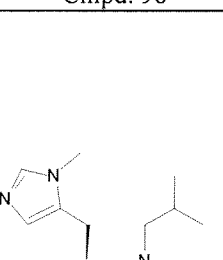
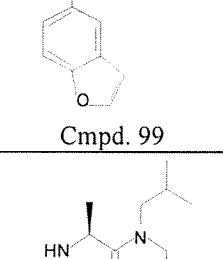
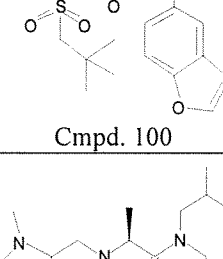


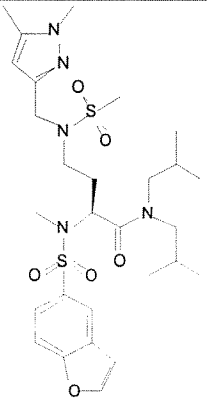
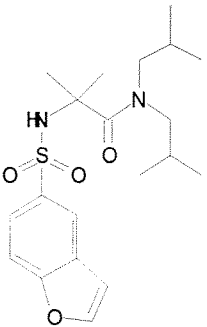
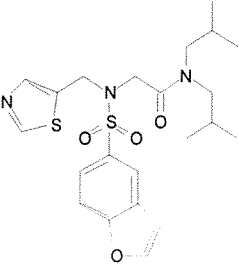
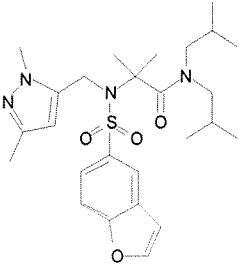
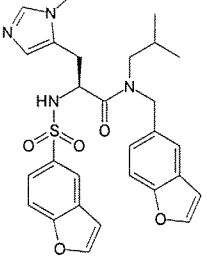
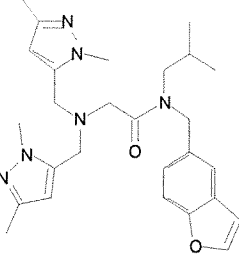
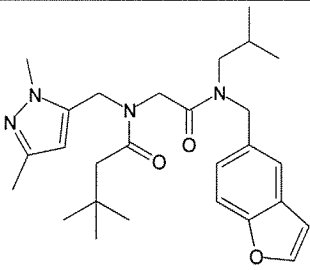
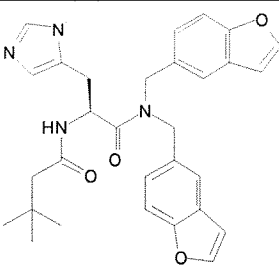
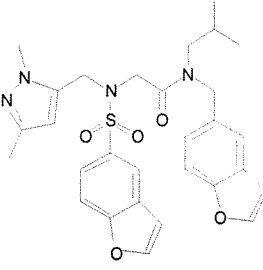
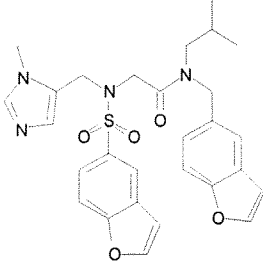
Cmpd. 81

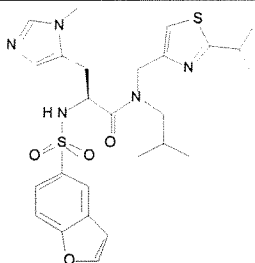
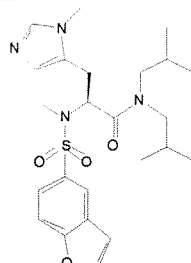
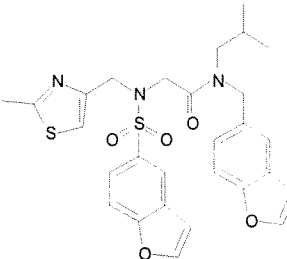
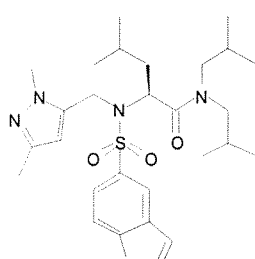
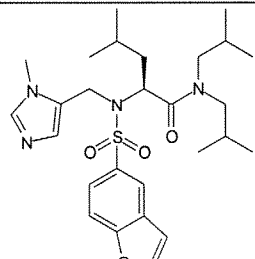
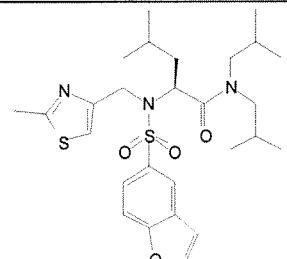
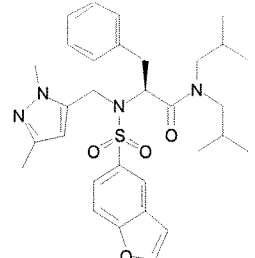
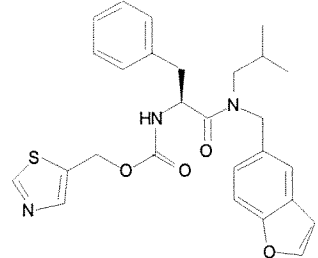
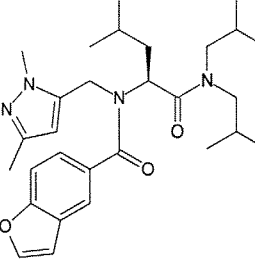
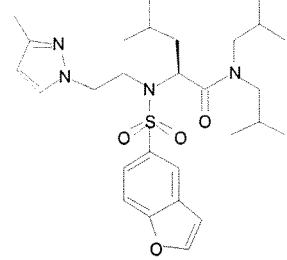


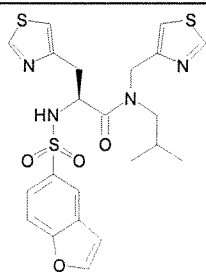
Cmpd. 82

 Cmpd. 83	 Cmpd. 84
 Cmpd. 85	 Cmpd. 86
 Cmpd. 87	 Cmpd. 88
 Cmpd. 89	 Cmpd. 90
 Cmpd. 91	 Cmpd. 92

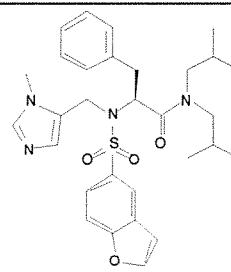
 Cmpd. 93	 Cmpd. 94
 Cmpd. 95	 Cmpd. 96
 Cmpd. 97	 Cmpd. 98
 Cmpd. 99	 Cmpd. 100
 Cmpd. 101	 Cmpd. 102

 Cmpd. 103	 Cmpd. 104
 Cmpd. 105	 Cmpd. 106
 Cmpd. 107	 Cmpd. 108
 Cmpd. 109	 Cmpd. 110
 Cmpd. 111	 Cmpd. 112

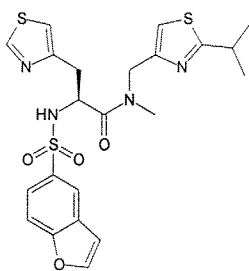
 Cmpd. 113	 Cmpd. 114
 Cmpd. 115	 Cmpd. 116
 Cmpd. 117	 Cmpd. 118
 Cmpd. 119	 Cmpd. 120
 Cmpd. 121	 Cmpd. 122



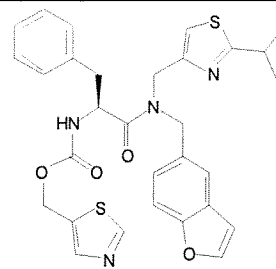
Cmpd. 123



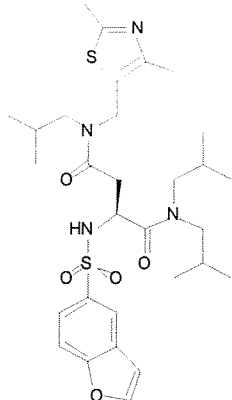
Cmpd. 124



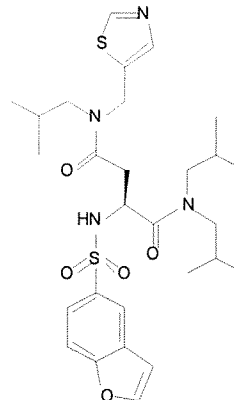
Cmpd. 125



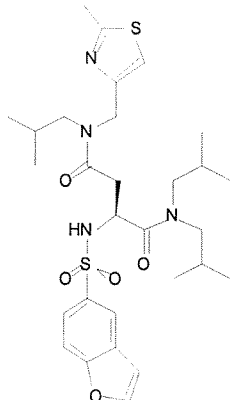
Cmpd. 126



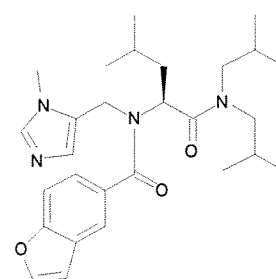
Cmpd. 127



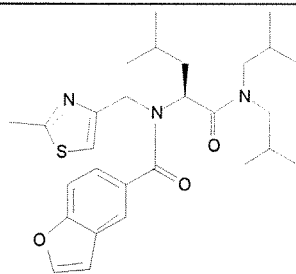
Cmpd. 128



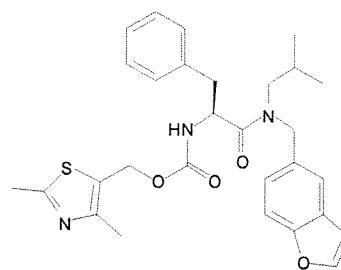
Cmpd. 129



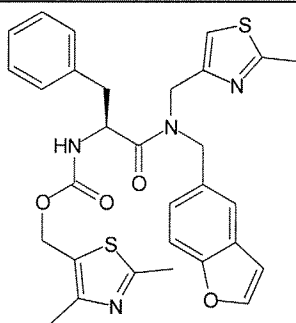
Cmpd. 130



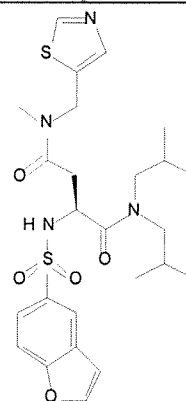
Cmpd. 131



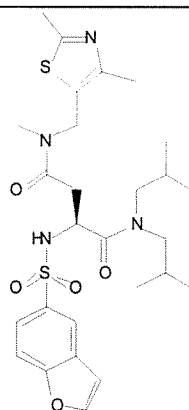
Cmpd. 132



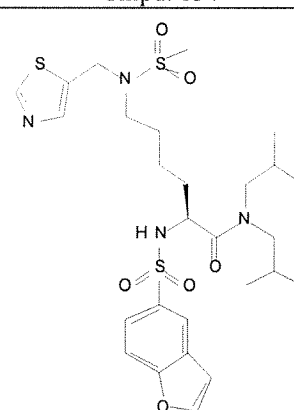
Cmpd. 133



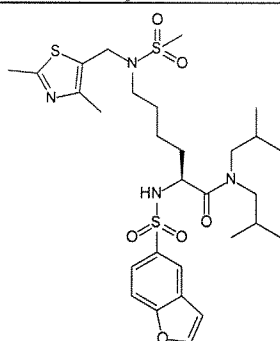
Cmpd. 134



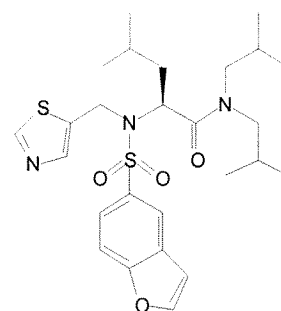
Cmpd. 135



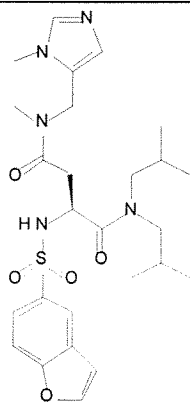
Cmpd. 136



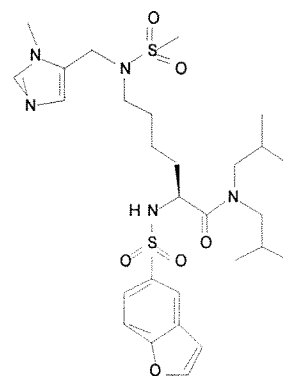
Cmpd. 137



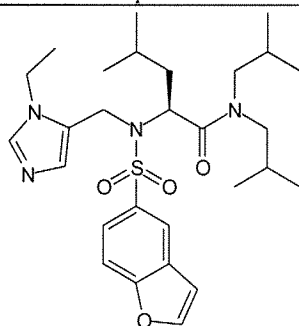
Cmpd. 138



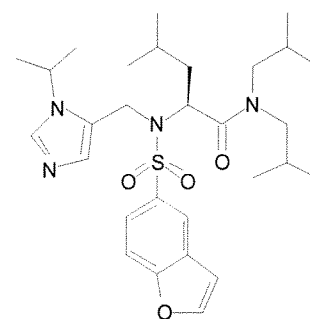
Cmpd. 139



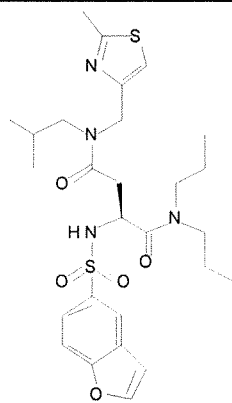
Cmpd. 140



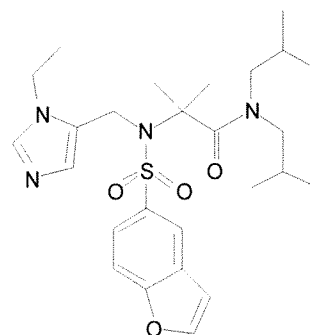
Cmpd. 141



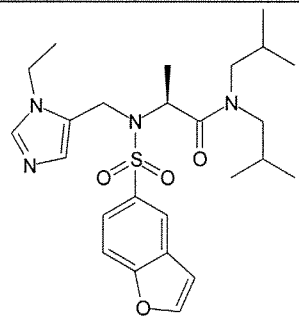
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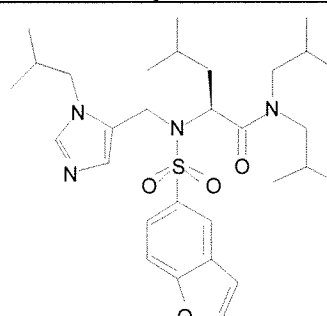
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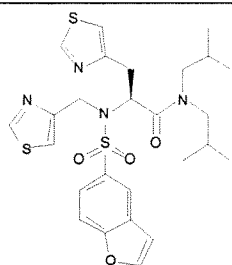
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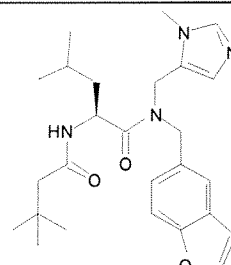
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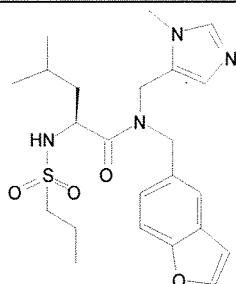
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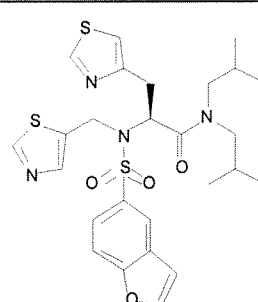
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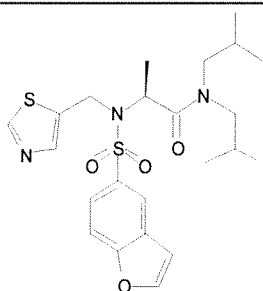
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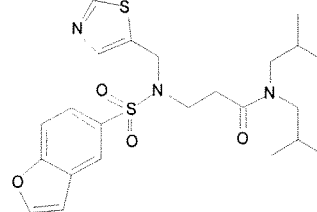
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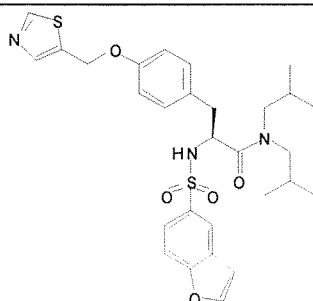
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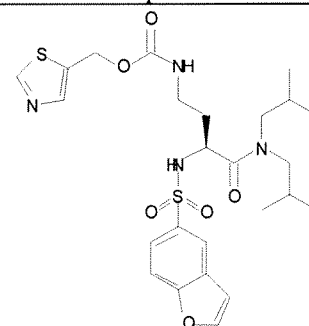
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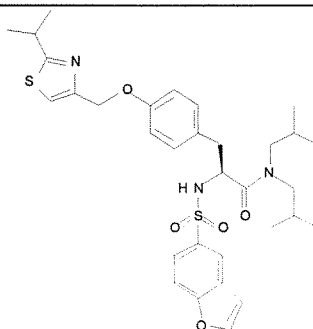
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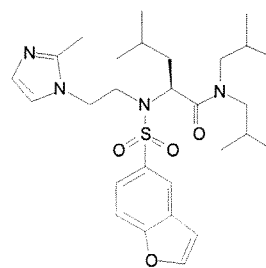
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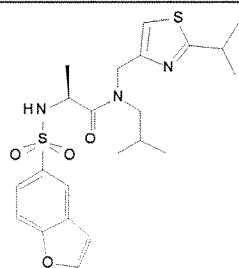
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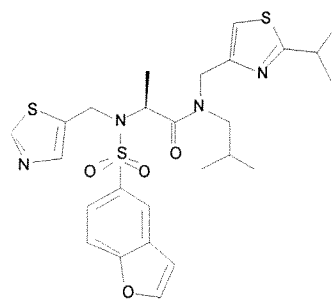
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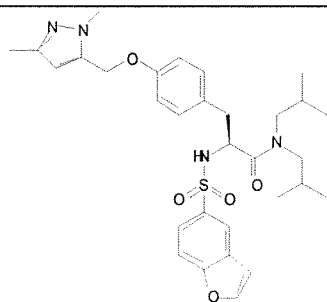
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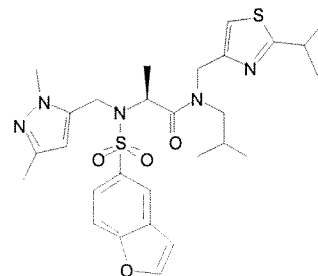
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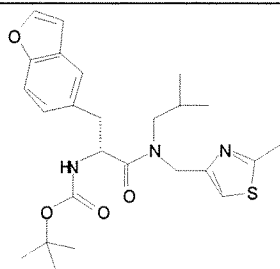
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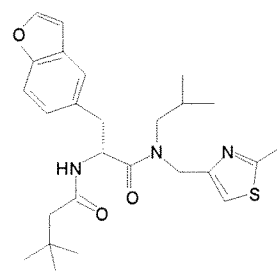
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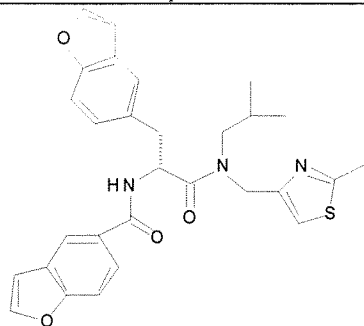
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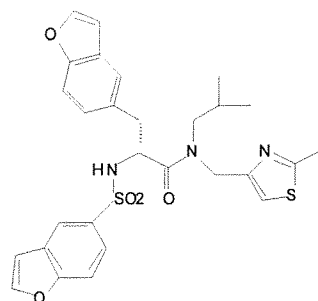
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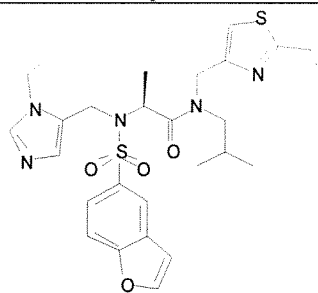
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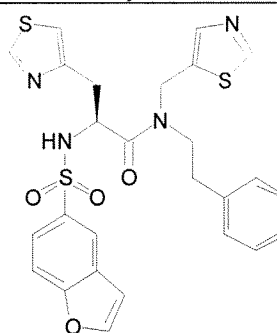
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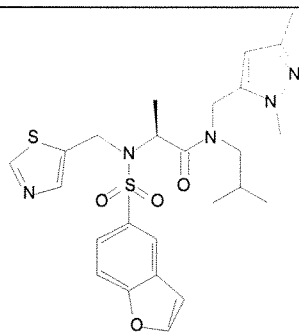
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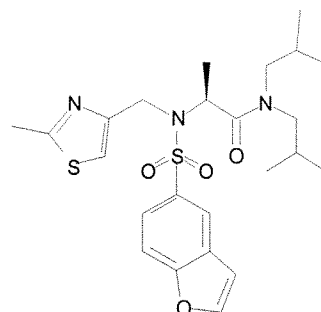
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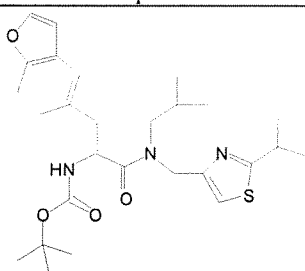
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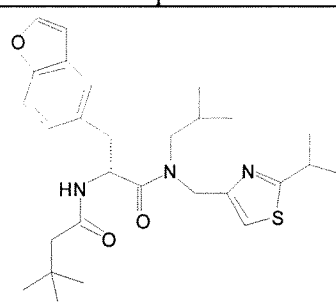
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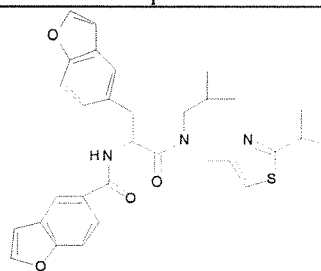
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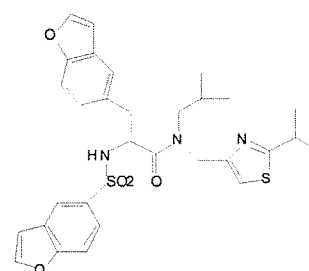
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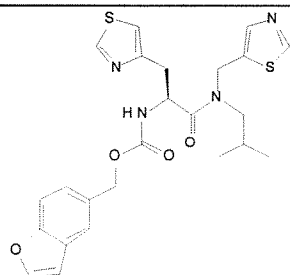
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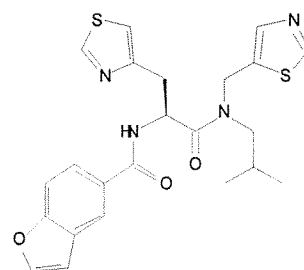
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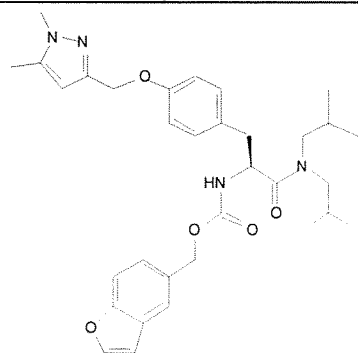
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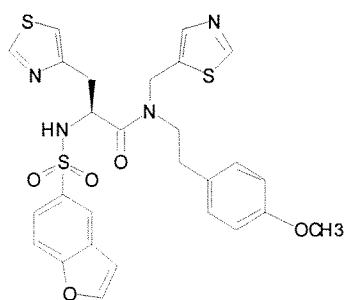
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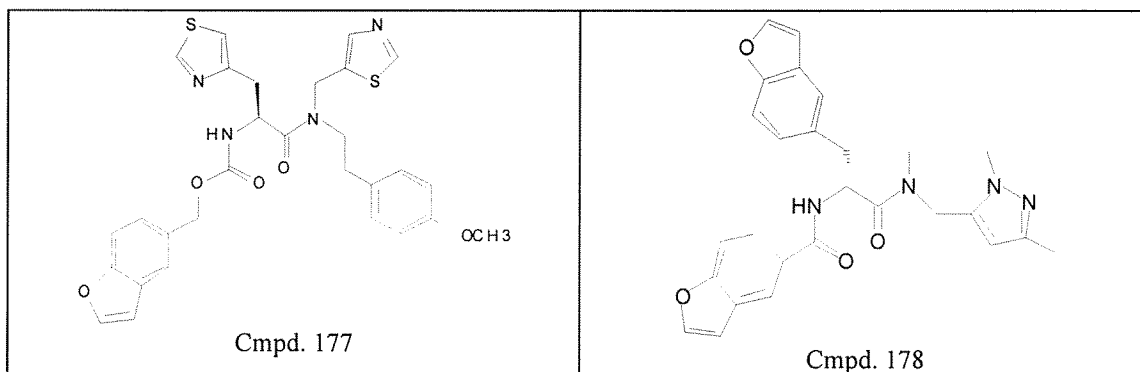
Cmpd. 174



Cmpd. 175



Cmpd. 176



The term “pharmaceutically effective amount” or “therapeutically effective amount” or “therapeutic dose” or “efficacious dose” refers to an amount that, when administered to a subject, is effective in inhibiting cytochrome P450 enough to reduce or prevent the *in vivo* degradation of a co-administered drug and thereby improve the pharmacokinetics of the drug and/or boost its efficacy. The term “treating” as used herein refers to the alleviation of symptoms of a particular disorder in a subject, such as a human patient, or the improvement of an ascertainable measurement associated with a particular disorder. The term “prophylactically effective amount” refers to an amount effective in preventing an infection, for example an HIV infection, in a subject, such as a human patient. As used herein, a “subject” refers to a mammal, including a human.

The term “co-administered drug” or “drug” refers to a compound given to a patient or subject, which may be a human, for prophylactic or therapeutic treatment. For example, a drug or a co-administered drug may be a compound or composition listed in the U.S. Pharmacopeia, or the Physician’s Desk Reference. In specific embodiments a drug or co-administered drug is selected from Cyclosporine, Tacrolimus (FK506), Sirolimus (rapamycin), Indinavir, Ritonavir, Saquinavir, Felodipine, Isradipine, Nicardipine, Nisoldipine, Nimodipine, Nitrendipine, Nifedipine, Verapamil, Etoposide, Tamoxifen, Vinblastine, Vincristine, Taxol, Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin, Terfenadine, Loratadine, Astemizole, Alfentanil, Carbamazepine, Azithromycin, Clarithromycin, Erythromycin, Itraconazole, Rifabutin, Lidocaine, Cisapride, Sertraline, Pimozide, Triazolam, Anastrozole, Busulfan, Corticosteroids (dexamethasone, methylprednisone and prednisone), Cyclophosphamide, Cytarabine, Docetaxel, Doxorubicin, Erlotinib, Exemestane, Gefitinib, Idarubicin, Ifosphamide, Imatinib mesylate, Irinotecan, Ketoconazole, Letrozole, Paclitaxel, Teniposide, Tretinoin, Vinorelbine, telithromycin, quinidine, alprazolam, diazepam, midazolam, nelfinavir, chlorpheniramine, amlodipine, diltiazem, lercanidipine, cerivastatin, estradiol,

hydrocortisone, progesterone, testosterone, alfentanil, aripiprazole, buspirone, cafergot, caffeine, cilostazol, cocaine, codeine, dapsone, dextromethorphan, docetaxel, domperidone, eplerenone, fentanyl, finasteride, gleevec, haloperidol, irinotecan, Levo-Alpha Acetyl Methadol (LAAM), methadone, nateglinide, odansetron, propranolol, 5 quinine, salmeterol, sildenafil, terfenadine, trazodone, vincristine, zaleplon, zolpidem., ixabepilone, Agenerase (APV), Aptivus (TPV), Crixivan (IDV), Invirase (SQV), Lexiva (FPV), Prezista (DRV), Reyataz (ATV) Viracept (NFV), Elvitegravir, Selzentry, Vicriviroc, Telaprevir, Telithromycin, tandospirone or buspirone. A drug may also be a compound that, because of its metabolism in a subject, may not otherwise be effective for 10 treating a condition in the subject unless administered with a compound that inhibits CYP activity.

The term “antiretroviral agent” as used herein refers to a compound that inhibits the ability of a retrovirus to effectively infect a host. Antiretroviral agents can inhibit a variety of process including the replication of viral genetic materials, or entry of retroviruses into 15 cells. In some embodiments, antiretroviral agents are selected from the group consisting of: protease inhibitor, a reverse transcriptase inhibitor, and a viral fusion inhibitor. In other embodiments the antiretroviral agents are selected from the group consisting of: abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zidovudine, elvucitabine, apricitabine, zalcitabine, delavirdine, efavirenz, nevirapine, rilpivirine, etravirine, 20 atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, Kaletra, nelfinavir, ritonavir, saquinavir, tipranavir, enfuvirtide, maraviroc, vicriviroc, raltegravir, elvitegravir, interferon, albuferon, telaprevir, boceprevir, and viramidine.

The term “lipophilic group” as used herein refers to a group that, when a part of a compound, increases the affinity or propensity of the compound to bind, attach or dissolve 25 in fat, lipid or oil rather than water. A measure of the lipophilicity or hydrophobicity of compounds of the technology can be calculated using the Hansch equation:

$$\text{Log } 1/C = kP$$

where C is the concentration of a compound in a given solvent and P is the hydrophobicity. Details of this method can be obtained from *J. Amer. Chem. Soc.*, 30 86:5175 (1964) and *Drug Design I*, edited by E. J. Ariens, Academic Press (1971), both of which are hereby incorporated by reference in their entirety.

Examples of a typical lipophilic group include, but are not limited to, alkyl groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, neopentyl, amyl, n-hexyl, n-heptyl, cyclohexyl, cycloheptyl, octyl, nonyl, decyl, undecyl,

and dodecyl, alkenes such as ethylene, propylene, butene, pentene, hexene, cyclohexene, heptene, cycloheptene, octene, cyclooctene, nonene, decene, undecene, dodecene, 1,3-butadiene, alkynes such as propyne and butyne, aryls such as phenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, aralkyls such as benzyl, heterocyclyls such as tetrahydrothiophene, dihydrobenzofuran, heteroaryls such as pyrrole, furan, thiophene, pyrazole, thiazole, indole, carbazole, benzofuran, benzothiophene, indazole, benzothiazole, purine, pyridine, pyridazine, pyrazine, triazine, quinoline, acridine, isoquinoline, and phenanthroline.

For small groups containing heteroatom substituents, such as small heterocycles with a high ratio of heteroatoms to carbon atoms, the introduction of substituents that reduce the heteroatom to carbon atom ratio renders the group lipophilic. For example, a triazole ring can be rendered more lipophilic by the introduction of alkyl substituents. Similarly, non-lipophilic substituents such as hydroxy or amido can be rendered lipophilic by introducing additional carbon atoms, for example by exchanging a hydroxymethyl group to a hydroxybenzyl group, or by exchanging a carboxamido group to a dialkyl carboxamido group.

The term “substituted”, whether preceded by the term “optionally” or not, and substitutions contained in formulas of this technology, include the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent. When more than one position in a given structure can be substituted with more than one substituent selected from a specified group, the substituents can be either the same or different at every position (for example, in the moiety $-N(R)_2$, the two R substituents can be the same or different). In those embodiments where a structure can be optionally substituted, any or all of the hydrogens present may be replaced by substituents. In some embodiments, 0-3 hydrogen atoms may be replaced. In other embodiments, 0 or 1 hydrogen atoms may be replaced. Substituents advantageously enhance cytochrome P450 inhibitory activity in permissive mammalian cells, or enhance deliverability by improving solubility characteristics or pharmacokinetic or pharmacodynamic profiles as compared to the unsubstituted compound. Enhancements to cytochrome P450 inhibitory activity, deliverability and pharmacokinetic parameters achieved by the addition of substituents may result in synergistic enhancement of a compound’s action and suitability for use in one or more applications.

Combinations of substituents and variables envisioned by this technology are limited to those that result in the formation of stable compounds. The term “stable”, as

used herein, refers to compounds that possess stability sufficient to allow manufacture, formulation, and administration to a mammal by methods known in the art. Typically, such compounds are stable at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week. In one embodiment, the
5 compounds have less than 5% degradation after storage in the dark at 40 °C or less, in the absence of moisture or other chemically reactive conditions. In another embodiment compounds have less than 10% degradation after storage in the dark at 40 °C or less, in the absence of moisture or other chemically reactive conditions.

The term “alkyl”, alone or in combination with any other term, refers to a straight-
10 chain or branched-chain saturated aliphatic hydrocarbon radical containing the specified number of carbon atoms, or where no number is specified, advantageously from 1 to about 12 or 1 to 15 carbon atoms. Examples of alkyl radicals include, but are not limited to: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, n-hexyl and the like.

15 The term “alkenyl”, alone or in combination with any other term, refers to a straight-chain or branched-chain mono- or poly-unsaturated aliphatic hydrocarbon radical containing the specified number of carbon atoms, or where no number is specified, advantageously from 2-6 or 2-10 carbon atoms. Alkenyl groups include all possible E and Z isomers unless specifically stated otherwise. Examples of alkenyl radicals include, but
20 are not limited to, ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, hexenyl, hexadienyl and the like.

The term “alkynyl,” alone or in combination with any other term, refers to a straight-chain or branched-chain hydrocarbon radical having one or more triple bonds containing the specified number of carbon atoms, or where no number is specified,
25 advantageously from 2 to about 10 carbon atoms. Examples of alkynyl radicals include, but are not limited to, ethynyl, propynyl, propargyl, butynyl, pentynyl and the like.

The term “alkoxy” refers to an alkyl ether radical, where the term “alkyl” is as defined above. Examples of suitable alkyl ether radicals include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and
30 the like.

The terms “alkylamino” or “dialkylamino” include amino radicals substituted by one or two alkyl groups, where the term “alkyl” is defined above, and the alkyl groups can be the same or different. Examples of suitable alkylamino and dialkylamino radicals

include, but are not limited to, methylamino, ethylamino, isopropylamino, dimethylamino, methylethylamino, ethylbutylamino and the like.

The term "halo" or "halogen" includes fluorine, chlorine, bromine or iodine. Halo may be limited to fluorine, chlorine, and bromine or fluorine and chlorine.

5 The term "haloalkyl" includes alkyl groups with one or more hydrogens replaced by halogens.

 The term "thioalkyl" includes alkyl radicals having at least one sulfur atom, where alkyl has the significance given above. An example of a thioalkyl is CH_3SCH_2- . The definition also encompasses the corresponding sulfoxide and sulfone of this thioalkyl,
10 $\text{CH}_3\text{S(O)CH}_2-$ and $\text{CH}_3\text{S(O)}_2\text{CH}_2-$ respectively. Unless expressly stated to the contrary, the terms "- SO_2- " and "- S(O)_2- " as used herein include sulfones or sulfone derivatives (*i.e.*, both appended groups linked to the S), and not a sulfinate ester.

 The terms "carboalkoxy" or "alkoxycarbonyl" include alkyl esters of a carboxylic acid. Examples of "carboalkoxy" or "alkoxycarbonyl" radicals include, but are not limited
15 to, ethoxycarbonyl (or carboethoxy), Boc (or t-butoxycarbonyl), Cbz (or benzyloxycarbonyl) and the like.

 The term "alkanoyl" includes acyl radicals derived from an alkanecarboxylic acid. Examples of alkanoyl radicals include, but are not limited to acetyl, propionyl, isobutyryl and the like.

20 The term "aryl," alone or in combination with any other term, refers to a carbocyclic aromatic radical (such as phenyl or naphthyl) containing a specified number of carbon atoms. In some embodiments, aryl radicals contain from 6-16 carbon atoms, and in other embodiments aryl radicals contain from 6 to 14 or 6-10 carbon atoms in their ring structures. Aryl radicals may be optionally substituted with one or more substituents
25 selected from alkyl, alkoxy, (for example methoxy), nitro, halo, amino, mono or dialkylamino, carboalkoxy, cyano, thioalkyl, alkanoyl, carboxylate, and hydroxy. Examples of aryl radicals include, but are not limited to phenyl, p-tolyl, 4-hydroxyphenyl, 1-naphthyl, 2-naphthyl, indenyl, indanyl, azulenyl, fluorenyl, anthracenyl and the like.

 The term "aralkyl", alone or in combination, includes alkyl radicals as defined
30 above in which one or more hydrogen atoms is replaced by an aryl radical as defined above. Examples of aralkyl radicals include, but are not limited to benzyl, 2-phenylethyl and the like. The alkyl radical of a aralkyl group may be an alkyl radical having 1 to 4, 1 to 6, 1 to 8, 2 to 4, 2 to 6 or 2 to 8 carbon atoms.

The term "carbocycle" refers to a non-aromatic, stable 3- to 8-membered carbon ring which can be saturated, mono-unsaturated or poly-unsaturated. The carbocycle can be attached at any endocyclic carbon atom which results in a stable structure. In some embodiments, carbocycles having 5-7 carbons may be employed, whereas in other
5 embodiments carbocycles having 5 or 6 carbon atoms may be employed.

The term "cycloalkyl", alone or in combination, includes alkyl radicals which contain from about 3 to about 8 carbon atoms and are cyclic. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "cycloalkenyl" alone or in combination includes alkenyl radicals as
10 defined above which contain about 3-8 carbon atoms and are cyclic.

In some embodiments of carbocycles, cycloalkyl or cycloalkenyl groups contain 3 or 4 carbon atoms in their ring structure. In other embodiments of carbocycles, cycloalkyl or cycloalkenyl groups contain 5 or 6 carbon atoms in their ring structure. In still other
15 embodiments of carbocycles, cycloalkyl or cycloalkenyl groups contain 7 or 8 carbon atoms in their ring structure.

The term "cycloalkylalkyl" includes alkyl radicals as defined above which are substituted by a cycloalkyl radical containing from about 3 to about 8 carbon atoms in some embodiments, or from about 3 to about 6 carbon atoms in other embodiments.

The term "heterocyclyl" or "heterocyclo" or "heterocycloalkyl" refers to a stable 3-
20 7 membered monocyclic heterocycle or 8-11 membered bicyclic heterocycle which is either saturated or partially unsaturated, and which can be optionally benzofused if monocyclic and which is optionally substituted on one or more carbon atoms by halogen, alkyl, alkoxy, oxo, and the like, and/or on a secondary nitrogen atom (*i.e.*, -NH-) by alkyl, aralkoxycarbonyl, alkanoyl, alkoxycarbonyl, arylsulfonyl, phenyl or phenylalkyl or on a
25 tertiary nitrogen atom (*i.e.*, +N-) by oxido and which is attached via a carbon atom. Each heterocycle consists of one or more carbon atoms and from one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. As used herein, the terms "nitrogen and sulfur heteroatoms" include oxidized forms of nitrogen and sulfur, and the quaternized form of any basic nitrogen. A heterocyclyl (heterocyclo or
30 heterocycloalkyl) radical can be attached at any endocyclic carbon or heteroatom which results in the creation of a stable structure. In some embodiments, the heterocycles are 5-7 membered monocyclic heterocycles, and 8-10 membered bicyclic heterocycles. Examples of such groups are imidazoliny, imidazolidiny, indazoliny, perhydropyridazyl, pyrroliny, pyrrolidiny, piperidiny, pyrazoliny, piperaziny, morpholiny,

thiamorpholinyl, thiazolidinyl, thiamorpholinyl sulfone, oxopiperidinyl, oxopyrrolidinyl, oxoazepinyl, tetrahydropyranyl, tetrahydrofuranyl, dioxolyl, dioxinyl, benzodioxolyl, dithiolyl, tetrahydrothienyl, sulfolanyl, dioxanyl, dioxolanyl, tetrahydrofurodihydrofuranyl, tetrahydropyranodihydrofuranyl, dihydropyranyl, tetrahydrofurofuranyl and
5 tetrahydropyranofuranyl.

The term "heteroaryl" refers to stable 5-6 membered monocyclic or 8-11 membered bicyclic or 13-16 membered tricyclic aromatic heterocycles where heterocycle is as defined above. In some embodiments, heteroatoms present in heteroaryl radicals are limited to one or more independently selected O, N or S atoms. Non-limiting examples of such groups
10 include imidazolyl, quinolyl, isoquinolyl, indolyl, indazolyl, pyridazyl, pyridyl, pyrrolyl, pyrazolyl, pyrazinyl, quinoxalyl, pyrimidinyl, furyl, thienyl, triazolyl, thiazolyl, carbolinyl, tetrazolyl, benzofuranyl, oxazolyl, benzoxazolyl, benzimidazolyl, benzthiazolyl, isoxazolyl, isothiazolyl, furazanyl, thiadiazyl, acridinyl, phenanthridinyl, and benzocinnolinyl.

15 The term "heterocycloalkylalkyl" refers to an alkyl radical as defined above which is substituted by a heterocycloalkyl radical as defined above. The alkyl radical of a heterocycloalkylalkyl group may be an alkyl radical having 1 to 4, 1 to 6, 1 to 8, 2 to 4, 2 to 6 or 2 to 8 carbon atoms.

The term "heteroaralkyl" alone or in combination, includes alkyl radicals as defined
20 above in which one or more hydrogen atom is replaced by a heteroaryl group as defined above. The alkyl radical of a heteroaralkyl group may be an alkyl radical having 1 to 4, 1 to 6, 1 to 8, 2 to 4, 2 to 6 or 2 to 8 carbon atoms.

As used herein, the compounds of this technology (*e.g.*, compounds of formula (I)) are defined to include pharmaceutically acceptable derivatives or prodrugs thereof. A
25 "pharmaceutically acceptable derivative or prodrug" includes a pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this technology which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this technology. In some embodiments it is desirable to employ derivatives and prodrugs that increase the bioavailability of the compounds of this technology when
30 such compounds are administered to a mammal (*e.g.*, by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (*e.g.*, the brain or lymphatic system) relative to the parent species. Examples of prodrugs of hydroxy containing compounds are amino acid esters or phosphonate or phosphate esters that can be cleaved *in vivo* hydrolytically or

enzymatically to provide the parent compound. These have the advantage of providing potentially improved solubility.

The compounds of this technology (*e.g.*, compounds of formula (I)) can contain one or more asymmetric carbon atoms and thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the technology described herein. Each stereogenic carbon can be of the R or S configuration. Although the specific compounds exemplified in this application can be depicted in a particular stereochemical configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned. Thus, the compounds provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures.

It is also to be understood that the compounds provided herein may have tautomeric forms. All such tautomeric forms are included within the scope of the instant disclosure. For example, a 3-enamino-2-oxindole where the amino group of the enamine has a hydrogen substituent has the tautomeric form of a 3-imino-2-hydroxyindole.

Also included in the present application are one or more of the various polymorphs of the compounds. A crystalline compound disclosed in the present application may have a single or may have multiple polymorphs, and these polymorphs are intended to be included as compounds of the present application. Also, where a single polymorph is noted, the polymorph may change or interconvert to one or more different polymorphs, and such polymorph or polymorph mixtures are included in the present application.

Preparation of Compounds

The compounds described herein can be prepared according to synthetic methods known in the art set forth, for example, in U.S. Patent No.: 6,319,946 to Hale *et al.*, W02008022345A2 (Eissenstat *et al.*) and in J.Med.Chem.36: 288-291 (1993), the disclosures of which are incorporated herein by reference in their entireties, together with procedures of the type described below. Reactions and processes for obtaining the compounds, particularly the formation of ester and amide linkages, may also be found in treatises and text, including, but not limited to, *Advanced Organic Synthesis*, 4th Edition, J. March, John Wiley & Sons, 1992 or *Protective Groups in Organic Synthesis* 3rd Edition, T. W. Green & P. G. M. Wuts, John Wiley & Sons, 1999, each of which is hereby incorporated by reference.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.),

Bachem (Torrance, Calif.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's *Reagents for Organic Syntheses*, Volumes 1-85 (John Wiley and Sons); Rodd's *Chemistry of Carbon Compounds*, Volumes 1-5 and Supplementals (Elsevier Science
5 Publishers, 1989); *Organic Reactions*, Volumes 1-71 (John Wiley and Sons), *Advanced Organic Synthesis*, 4th Edition, J. March, John Wiley & Sons, 1992, and Larock's *Comprehensive Organic Transformations* (VCH Publishers Inc., 1989).

Protective groups, such as those described in *Protective Groups in Organic Synthesis* 3rd Edition, T. W. Green & P. G. M. Wuts, John Wiley & Sons, 1999 may be
10 employed for a variety of purposes in the preparation of compounds encompassed by this disclosure. They may be employed to control the number or placement of substituents, or to protect functionalities that are otherwise unstable to reaction conditions employed for the introduction or modification of other substituents in a molecule. Where employed, such protective groups may be removed by suitable means. Alternatively, where the
15 protective group is desirable in the product they may be introduced and not removed.

While compounds encompassed by this disclosure may be prepared by a variety of methods known in the art, they may often be prepared from alpha-amino acids or the amide of an alpha-amino acid (alpha-amino acid amide). Whether starting with an alpha-amino acid or amide substituents present at R¹ and R² may be introduced by alkylating, acylating
20 or sulfonylating the amino nitrogen. Where an alpha-amino acid is employed as a starting material, reaction of the amino group may be accomplished prior to the introduction of the amide nitrogen with or without its pendant R⁵ and R⁶ functionalities. Alternatively, the amino group may be alkylated, acylated, or sulfonylated subsequent to the introduction of the amide nitrogen into the molecule.

25 Substituents may be introduced into the R³ and R⁴ positions of the molecule by a variety of means. In some embodiments, substituents at R³ and R⁴ may be present in starting amino acids or alpha-amino acid amides. For example, where it is desirable to prepare compounds having benzyl substituents at R³ or R⁴ phenylalaninamide (2-amino-3-phenylpropanamide) may be employed as a starting material. The desired products can be
30 produced by modification of the nitrogen atom present in the amine and/or amide of that compound. In addition, the stereochemistry the benzyl group (or other groups present in the starting amino acid) may be controlled by employing a chiral starting material such (2S)-2-amino-3-phenylpropanamide, which is available from Sigma-Aldrich.

Where it is necessary to protect amine functionalities in the synthetic process they may be unprotected by suitable reactions. For example, in the formation of compounds bearing R¹ and R² substituents where it is necessary to protect the amino group, Boc protective groups may be employed, Boc groups may be removed under acidic conditions, such as with trifluoroacetic acid, to provide amine functionalities that may be subject to a variety of reactions including, but not limited to, condensation with acid chlorides, anhydrides, sulfonyl chlorides, chloroformates, carbamoyl chloride, isocyanates and the like to provide the corresponding amide, sulfonamide, urethane, or urea.

Reductive amination of a primary amine by an aldehyde under acidic conditions, which provides a secondary amine, can also be employed to prepare substituted (*e.g.*, alkylated) amines. Once the secondary amine is formed it can also be subjected to condensation reactions to give the N-alkyl products (*e.g.*, N-alkyl amide). The substituted amines can be present at the alpha position of an amino acid or amino acid amide, in which case the substituents present on the amine will be the R¹ and R² groups or precursors thereof. Alternatively, the substituted amine may be reacted with the carboxyl group to form an amide functionality, in which case the substituents will be the R⁵ and R⁶ groups or precursors thereof. Where the carboxyl group is a substituent on an appropriately functionalized amino acid, condensation with the substituted amine can result in the direct production of compounds within the scope of this disclosure.

As with reductive amination, the reaction of epoxides with amines (*e.g.*, isobutylamine) can be employed to form substituted amines. Once formed, such substituted amines can be employed in the same fashion as the products of reductive amination.

By way of example, a benzofuran sulfonyl radical may be added by condensation of a benzofuransulfonyl chloride (*e.g.*, benzofuran-5-sulfonyl chloride) with an alpha-amino acid amide (*e.g.*, the amino nitrogen of NH₂-CH₂-C(=O)NH₂). Alkylation of the product can be accomplished using excess base and alkylating agent to produce compounds within the scope of this disclosure.

Assessment of Compounds

The potency of the compounds can be measured using assays, for example, an in vitro fluorometric assay. Typically, the ability of a test compound to inhibit P450 is assayed by determining the concentration of the test compound required to decrease the rate of metabolism of a CYP substrate (also referred to herein as reference compound) by half. The CYP substrate can be, for example, dibenzylfluorescein. The ability of a test

compound to inhibit the rate of metabolism of a reference compound by half is known as the IC₅₀ value. Human liver microsomes can be used for this purpose. Test compounds can be diluted with a suitable solvent, such as acetonitrile, in wells of a micro-titer plate. Known cytochrome P450 inhibitors such as ritonavir and ketoconazole can be used as
5 references. A suitable buffer solution and NADPH or an NADPH generating system such as, for example, G6P dehydrogenase can be used. After mixing the inhibitors with the buffer and NADPH system, the plates can be incubated for a suitable time at a suitable temperature. A solution containing human liver microsomes can be added. A buffer containing a fluorogenic substrate, such as dibenzylfluorescein (DBF), can be added and
10 the plates allowed to incubate for a suitable time at a suitable temperature. The IC₅₀ values for the test compounds can be measured by determining the amount of fluorescence in each well and analyzing the values using commercially available software programs such as, for example, Grafit® (Erithacus Software Ltd., Surrey, U.K.).

Increasing The Half-Life Of Therapeutics By Preventing Their Metabolism By 15 Cytochrome P450 Enzymes

CYP enzymes are responsible for the metabolic degradation of a variety of drug molecules (therapeutics). In many instances, those enzymes may largely determine the pharmacokinetics observed for drug molecules and control their bioavailability. Where CYP enzymes contribute to the metabolism of compounds, compositions that can inhibit
20 CYP enzymes can improve the pharmacokinetics and bioavailability of such drugs.

In certain embodiments, the technology provides methods for inhibiting cytochrome P450 monooxygenase by administering to a patient one or more compounds described herein. The compound can function as a potent cytochrome P450 inhibitor and can improve the pharmacokinetics of a drug (or a pharmaceutically acceptable salt thereof)
25 which is metabolized by cytochrome P450 monooxygenase. The compound or its pharmaceutically acceptable salt can be administered by itself or in combination with the another drug. When administered in combination, the two therapeutic agents (compound and drug) can be formulated as separate compositions which are administered at the same time or at different times, or the two therapeutic agents can be administered as a single
30 composition.

The compounds of the technology are effective for inhibiting a variety of CYP enzymes. In particular, many of the compounds are highly potent inhibitors of CYP3A4, which is responsible for degrading many pharmaceutically important drugs. Use of the compounds of the technology therefore permits reduced rates of drug degradation and

consequently extended durations of action *in vivo*. Consequently, these compounds are useful for “boosting” the activities of a variety of drugs, including, but not limited to, HIV protease inhibitors by inhibiting CYP3A4-mediated degradation of those inhibitors.

Drugs which are metabolized by cytochrome P450 monooxygenase and which benefit from coadministration with a compound of the technology include, but are not limited to, the immunosuppressants cyclosporine, FK-506 and rapamycin, the chemotherapeutic agents taxol and taxotere, the antibiotic clarithromycin and the HIV protease inhibitors A-77003, A-80987, indinavir, saquinavir, amprenavir, nelfinavir, fosamprenavir, lopinavir, atazanavir, darunavir, tipranavir, DMP-323, XM-450, BILA 2011 BS, BILA 1096 BS, BILA 2185 BS, BMS 186,318, LB71262, SC-52151, SC-629 (N,N-dimethylglycyl-N-(2-hydroxy-3-(((4-methoxyphenyl)sulphonyl)(2-methylpropyl)amino)-1-(phenylmethyl)propyl)-3-methyl-L-valinamide), PPL-100, SPI-256 and KNI-272.

In other examples, the drug may be a tyrosine kinase inhibitor, such as Gleevec (imatinib), Erlotinib, Sorafenib, Sunitinib, dasitinib, lapatinib, and the like. Other kinase inhibitors, such as serine/threonine kinase inhibitors, also may be “boosted.” Suitable kinase inhibitors for boosting also are described in Kéri et al.; “*Signal Transduction Therapy with Rationally Designed Kinase Inhibitors*,” Current Signal Transduction Therapy, 1, 67-95 67 (2006). The drug may also be an HSP90 inhibitor such as geldanamycin, herbimycin, and others, as described by Workman et al.: “*Drugging the cancer chaperone HSP90: Combinatorial therapeutic exploitation of oncogene addiction and tumor stress*” Workman, Ann N Y Acad Sci. 1113:202-216 (2007). In other examples, the drug may be an inhibitor of HCV NS3 protease, NS4a cofactor, NS4B, NS5a replicase or NS5B polymerase. Drugs for treating HIV include, in addition to HIV protease inhibitors, inhibitors of CD4-gp120 interaction, CCR5 and CXCR4 coreceptors, and inhibitors of the LEDGF-integrase interaction.

Protease inhibitors and non-nucleoside reverse transcriptase inhibitors currently indicated for use in treatment of HIV or HCV are typically good substrates of cytochrome p450 enzymes; in particular, they are metabolized by CYP3A4 enzymes (*see e.g.*, Sahai, AIDS 10 Suppl 1:S21-5, 1996) with possible participation by CYP2D6 enzymes (Kumar *et al.*, J. Pharmacol. Exp. Ther. 277(1):423-31, 1996). The compounds described herein can block the action and up-regulation of these enzymes, thus reducing the metabolism of the protease inhibitors, allowing for lower doses and reduction of sometimes serious side effects.

Some embodiments, described herein are directed to methods for improving the pharmacokinetics of an HIV protease inhibitor (or a pharmaceutically acceptable salt thereof), which is metabolized by cytochrome P450 monooxygenase. Those methods comprise co-administering to a subject or patient (*e.g.*, a human being) a compound of the technology or a pharmaceutically acceptable salt or co-crystal thereof and an HIV protease inhibitor. Such a combination of a compound of the technology (*e.g.*, a compound of formula (I)), or a pharmaceutically acceptable salt thereof, and an HIV protease inhibitor, or a pharmaceutically acceptable salt thereof, which is metabolized by cytochrome P450 monooxygenase is useful for inhibiting HIV protease in humans. The combination is also useful for the inhibition, treatment or prophylaxis of an HIV infection or AIDS (acquired immune deficiency syndrome) in humans. When administered in combination, the two therapeutic agents can be formulated as separate compositions which are administered at the same time or different times, or the two therapeutic agents can be administered as a single composition. In some embodiments the HIV protease inhibitors are selected from A-77003, A-80987, amprenavir atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, DMP-323, XM-450, BILA 2011 BS, BILA 1096 BS, BILA 2185 BS, BMS 186,318, LB71262, SC-52151, SC-629, (N,N-dimethylglycyl-N-(2-hydroxy-3-(((4-methoxyphenyl)sulphonyl)(2-methylpropyl)amino)-1-(phenylmethyl)propyl)-3-methyl-L-valinamide), PPL-100, SPI-256 or KNI-272.

Methods of Administration

The compounds of the technology can be administered in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. Included among such acid salts, for example, are the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate.

Other pharmaceutically acceptable salts include salts with an inorganic base, organic base, inorganic acid, organic acid, or basic or acidic amino acid. Inorganic bases which form pharmaceutically acceptable salts include alkali metals such as sodium or

potassium, alkali earth metals such as calcium and magnesium, aluminum, and ammonia. Organic bases which form pharmaceutically acceptable salts include trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine. Inorganic acids which form pharmaceutically acceptable salts include hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid. Organic acids appropriate to form salts include formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid. Basic amino acids used to form salts include arginine, lysine and ornithine. Acidic amino acids used to form salts include aspartic acid and glutamic acid.

The CYP inhibitory compounds described herein may be prepared and administered as a composition comprising a co-crystals with other compounds (co-crystal formers). "Co-crystal" as used herein means a crystalline material comprised of two or more unique solids at room temperature, each containing distinctive physical characteristics, such as structure, melting point and heats of fusion. Co-crystals are described, for example, in U.S. Pub. No.: 20070026078 A1, which is incorporated by reference in its entirety. They are also described in , N. A. Meanwell, Annual Reports in Medicinal Chemistry, Volume 43, 2008 and D. P. McNamara, Pharmaceutical Research, Vol. 23, No. 8, 2006., each of which is incorporated by reference in its entirety.

The technology also contemplates compositions which can be administered orally or non-orally in the form of, for example, granules, powders, tablets, capsules, syrup, suppositories, injections, emulsions, elixirs, suspensions or solutions, by mixing these effective components, individually or simultaneously, with pharmaceutically acceptable carriers, excipients, binders, diluents or the like.

As a solid formulation for oral administration, the composition can be in the form of powders, granules, tablets, pills and capsules. In these cases, the compounds can be mixed with at least one additive, for example, sucrose, lactose, cellulose sugar, mannitol, maltitol, dextran, starch, agar, alginates, chitins, chitosans, pectins, tragacanth gum, gum arabic, gelatins, collagens, casein, albumin, synthetic or semi-synthetic polymers or glycerides. These formulations can contain, as in conventional cases, further additives, for example, an inactive diluent, a lubricant such as magnesium stearate, a preservative such as paraben or sorbic acid, an anti-oxidant such as ascorbic acid, tocopherol or cysteine, a disintegrator, a binder, a thickening agent, a buffer, a sweetener, a flavoring agent and a perfuming agent. Tablets and pills can further be prepared with enteric coating.

Examples of liquid preparations for oral administration include pharmaceutically acceptable emulsions, syrups, elixirs, suspensions and solutions, which can contain an inactive diluent, for example, water.

As used herein, "non-orally" includes subcutaneous injection, intravenous
5 injection, intramuscular injection, intraperitoneal injection or instillation. Injectable preparations, for example sterile injectable aqueous suspensions or oil suspensions, can be prepared by known procedures in the fields concerned, using a suitable dispersant or wetting agent and suspending agent. The sterile injections can be, for example, a solution or a suspension, which is prepared with a non-toxic diluent administrable non-orally, such
10 as an aqueous solution, or with a solvent employable for sterile injection. Examples of usable vehicles or acceptable solvents include water, Ringer's solution and an isotonic aqueous saline solution. Further, a sterile non-volatile oil can usually be employed as solvent or suspending agent. A non-volatile oil and a fatty acid can be used for this purpose, including natural or synthetic or semi-synthetic fatty acid oil or fatty acid, and
15 natural or synthetic mono- or di- or tri-glycerides.

The pharmaceutical compositions can be formulated for nasal aerosol or inhalation and can be prepared as solutions in saline, and benzyl alcohol or other suitable preservatives, absorption promoters, fluorocarbons, or solubilizing or dispersing agents.

Rectal suppositories can be prepared by mixing the drug with a suitable vehicle, for
20 example, cocoa butter and polyethylene glycol, where the vehicle is in the solid state at ordinary temperatures and in the liquid state at body temperatures, where melting releases the drug.

The pharmaceutical composition can be easily formulated for topical administration with a suitable ointment containing one or more of the compounds suspended or dissolved
25 in a carrier, which include mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. In addition, topical formulations can be formulated with a lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetaryl alcohol, 2-octyldodecanol,
30 benzyl alcohol and water.

In some embodiments, the pharmaceutical compositions can include α -, β -, or γ -cyclodextrins or their derivatives. In certain embodiments, co-solvents such as alcohols can improve the solubility and/or the stability of the compounds in pharmaceutical

compositions. In the preparation of aqueous compositions, addition salts of the compounds can be suitable due to their increased water solubility.

Appropriate cyclodextrins are α -, β -, or γ -cyclodextrins (CDs) or ethers and mixed ethers thereof where one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C₁-C₆alkyl, such as methyl, ethyl or isopropyl, *e.g.*, randomly methylated β -CD; hydroxy C₁-C₆alkyl, particularly hydroxyethyl, hydroxypropyl or hydroxybutyl; carboxy C₁-C₆alkyl, particularly carboxymethyl or carboxyethyl; C₁-C₆alkyl-carbonyl, particularly acetyl; C₁-C₆alkyloxycarbonylC₁-C₆alkyl or carboxyC₁-C₆alkyloxyC₁-C₆alkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; C₁-C₆alkylcarbonyloxyC₁-C₆alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β -CD, randomly methylated β -CD, 2,6-dimethyl- β -CD, 2-hydroxyethyl- β -CD, 2-hydroxyethyl- γ -CD, hydroxypropyl- γ -CD and (2-carboxymethoxy)propyl- β -CD, and in particular 2-hydroxypropyl- β -CD (2-HP- β -CD).

The term "mixed ether" denotes cyclodextrin derivatives where at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl.

The compounds can be formulated in combination with a cyclodextrin or a derivative thereof as described in US Patent No. 5,707,975. Although the formulations described therein are with antifungal active ingredients, they are equally relevant for formulating compounds and compositions of the technology described herein (*e.g.*, compounds having the formula (I)). The formulations described therein are particularly suitable for oral administration and comprise an antifungal as active ingredient, a sufficient amount of a cyclodextrin or a derivative thereof as a solubilizer, an aqueous acidic medium as bulk liquid carrier and an alcoholic co-solvent that greatly simplifies the preparation of the composition. The formulations can also be rendered more palatable by adding pharmaceutically acceptable sweeteners and/or flavors.

Other convenient ways to enhance the solubility of the compounds of the technology in pharmaceutical compositions are described in WO 94/05263, WO 98/42318, EP-A-499,299 and WO 97/44014, all incorporated herein by reference.

In some embodiments, the compounds can be formulated in a pharmaceutical composition comprising a therapeutically effective amount of particles consisting of a solid dispersion comprising a compound of formula I, and one or more pharmaceutically acceptable water-soluble polymers.

The term "solid dispersion" defines a system in a solid state comprising at least two components, where one component is dispersed more or less evenly throughout the other component or components. When the dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase as defined in thermodynamics, such a solid dispersion is referred to as "a solid solution". Solid solutions are one suitable physical system because the components therein are usually readily bioavailable to the organisms to which they are administered.

The term "solid dispersion" also comprises dispersions which are less homogenous throughout than solid solutions. Such dispersions are not chemically and physically uniform throughout or comprise more than one phase.

The water-soluble polymer in the particles is conveniently a polymer that has an apparent viscosity of 1 to 100 mPa*s when dissolved in a 2 % aqueous solution at 20 °C.

Water-soluble polymers include hydroxypropyl methylcelluloses (HPMC). HPMC having a methoxy degree of substitution from about 0.8 to about 2.5 and a hydroxypropyl molar substitution from about 0.05 to about 3.0 are generally water soluble. Methoxy degree of substitution refers to the average number of methyl ether groups present per anhydroglucose unit of the cellulose molecule. Hydroxypropyl molar substitution refers to the average number of moles of propylene oxide which have reacted with each anhydroglucose unit of the cellulose molecule.

The particles as defined hereinabove can be prepared by first preparing a solid dispersion of the components, and then optionally grinding or milling that dispersion. Various techniques exist for preparing solid dispersions including melt-extrusion, spray-drying and solution-evaporation.

It can further be convenient to formulate the compounds in the form of nanoparticles which have a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than 1000 nm. Useful surface modifiers are believed to include those which physically adhere to the surface of the antiretroviral agent but do not chemically bond to the antiretroviral agent.

Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Surfactant surface modifiers include nonionic and anionic surfactants.

The compounds can also be incorporated in hydrophilic polymers and applied as a film over many small beads, thus yielding a composition with good bioavailability which

can conveniently be manufactured and which is suitable for preparing pharmaceutical dosage forms for oral administration. The beads comprise a central, rounded or spherical core, a coating film of a hydrophilic polymer and an antiretroviral agent and a seal-coating polymer layer. Materials suitable for use as cores are pharmaceutically acceptable and have appropriate dimensions and firmness. Examples of such materials are polymers, inorganic substances, organic substances, saccharides and derivatives thereof. The route of administration can depend on the condition of the subject, co-medication and the like.

Dosages of the compounds and compositions described herein are dependent on age, body weight, general health conditions, sex, diet, dose interval, administration routes, excretion rate, combinations of drugs and conditions of the diseases treated, while taking these and other necessary factors into consideration. Generally, dosage levels of between about 10 µg per day to about 5000 mg per day, preferably between about 25 mg per day to about 1000 mg per day of the compounds of the technology are useful for the inhibition of CYP enzymes. Typically, the pharmaceutical compositions of this technology will be administered from about 1 to about 3 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy.

The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). In some embodiments, such preparations contain from about 20% to about 80% active compound.

While these dosage ranges can be adjusted by a necessary unit base for dividing a daily dose, as described above, such doses are decided depending on the diseases to be treated, conditions of such diseases, the age, body weight, general health conditions, sex, diet of the patient then treated, dose intervals, administration routes, excretion rate, and combinations of drugs, while taking these and other necessary factors into consideration. For example, a typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 10% to about 80% active compound. The desired unit dose of the composition of this technology is administered once or multiple times daily.

In some embodiments, the technology contemplates compositions and formulations comprising one or more of the compounds in combination with one or more other drugs that can be metabolized or degraded by CYP.

The CYP inhibitors of this technology can be administered to a patient either as a single agent (for use with a separate dose of another drug) or in a combined dosage form with at least one other drug. Additional drugs also can be used to increase the therapeutic effect of these compounds.

5 The compounds of this technology can be administered to patients being treated with a drug that is metabolized by a CYP enzyme. Such drugs include, but are not limited to, anesthetics such as ropivacaine, enflurane, halothane, isoflurane, methoxyflurane, and sevoflurane; antiarrhythmics such as mexiletine; antidepressants such as amitriptyline, clomipramine, fluvoxamine, bupropion, and imipramine; anti-epileptics such as diazepam,
10 phenytoin, S-mephenytoin, and phenobarbitone; antihistamines such as astemizole, chlorpheniramine, and terfenadine; antipsychotics such as clozapine, olanzapine, and haloperidol; beta blockers such as carvedilol, S-metoprolol, propafenone, and timolol; calcium channel blockers such as amlodipine, diltiazem, felodipine, lercanidipine, nifedipine, nisoldipine, nitrendipine, and verapamil; hypoglycemic agents such as
15 tolbutamide and glipizide; immune modulators such as cyclosporine and tacrolimus; muscle relaxants such as cyclobenzaprine, tizanidine, and carisoprodol; steroids such as estradiol; antimigraine agents such as zolmitriptan; agents used to treat breathing ailments such as zileuton and theophylline; agents used to treat Alzheimer's disease such as tacrine; agents used to treat pain such as naproxen and acetaminophen; agents used to treat
20 amyotrophic lateral sclerosis such as riluzole; anti-nausea agents such as ondansetron; chemotherapeutics such as paclitaxel, ifosfamide, and cyclophosphamide; loop diuretics such as furosemide; antidiabetic agents such as repaglinide; statins such as cerivastatin; antimalarial agents such as amodiaquine; proton pump inhibitors such as lansoprazole, omeprazole, pantoprazole, and rabeprazole; and sulfonylureas such as glyburide,
25 glibenclamide, glipizide, glimepiride, and tolbutamide. Patients being treated with a protease inhibitor, a reverse transcriptase inhibitor, a viral fusion inhibitor, or an integrase inhibitor can also be treated with the compounds provided herein. The CYP inhibitors provided herein can be co-administered with the other drug(s). The compounds of the technology can also be administered in combination with other cytochrome P450 inhibitors
30 (*e.g.*, ritonavir), immunomodulators (*e.g.*, brosimone, anti-human alpha interferon antibody, IL-2, interferon alpha, and HE-2000), with antibiotics (*e.g.*, pentamidine isothionate) cytokines (*e.g.*, Th2), modulators of cytokines, chemokines or the receptors thereof (*e.g.*, CCR5) or hormones (*e.g.*, growth hormone) to ameliorate, combat, or eliminate infections as therapeutically appropriate.

CYP inhibitors can also be used as standalone therapeutics for CYP-mediated diseases, or as prophylactic agents for preventing the production of toxic metabolites. For example, an inhibitor of CYP2A6 or 2A13 can be used to ameliorate the carcinogenic effects of tobacco usage.

5 Such combination therapy in different formulations can be administered simultaneously, separately or sequentially. The CYP inhibitors can be administered prior to administration of the other drug to reduce CYP levels and minimize degradation of the drug. In specific embodiments, the CYP inhibitor is administered, 30 minutes, 1 hour, four hours, twelve hours or twenty four hours or more prior to initial administration of the other
10 drug. The CYP inhibitors tend to have a long half life *in vivo*, presumably as a result of inhibiting their own metabolism. This means that once treatment has begun, the CYP inhibitor may be administered less frequently than the drug, although the skilled artisan will recognize that different administration regimens may be needed in specific situations. In certain instances, the CYP inhibitor may be administered for a period of time sufficient
15 to reduce CYP levels in a subject sufficiently that a drug may be administered to the subject without additional dosing of the CYP inhibitor. Similarly, once CYP levels have been reduced, administration of the CYP inhibitor may not need to be carried out as frequently as administration of the drug. CYP inhibitors also can, in certain cases, induce expression of CYPs. The skilled artisan will appreciate that, in such cases, administration
20 of the CYP inhibitor may need to be more frequent. Alternatively, such combinations can be administered as a single formulation, whereby the active ingredients are released from the formulation simultaneously or separately.

The following examples illustrate further the technology but, of course, should not be construed in any way of limiting its scope.

25 **Examples**

Example 1: Assay of IC₅₀ for CYP inhibitors: Determinations using Dibenzylfluorescein Metabolism by Human Liver Microsomes

A microtiter plate based, fluorometric assay was used for the determination of the concentration of a test compound that will decrease by half the rate of metabolism by
30 human liver microsomes of dibenzylfluorescein, a CYP3A4 substrate,. The assay was run as described by Crespi *et al.* Anal. Biochem. 248:188-90 (1997).

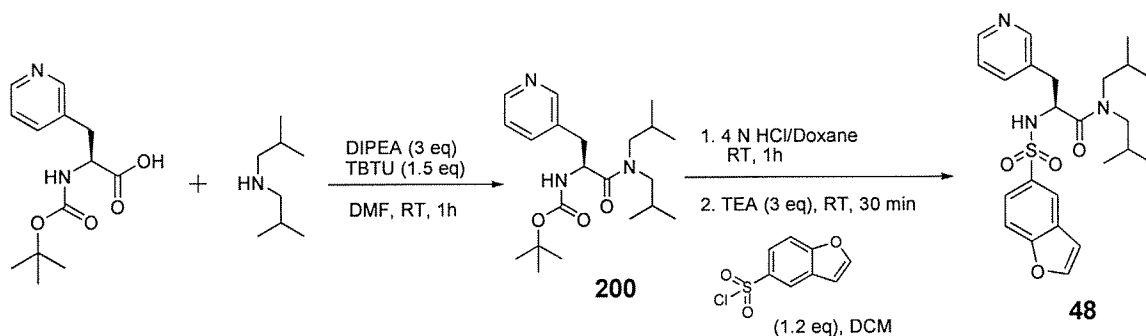
Test compounds were diluted in acetonitrile in wells of a polypropylene micro-titer plate (Denville Scientific, Inc. Metuchen, NJ). Three fold serial dilutions of the test article were made from the first well into the next seven wells of a row. Two wells of each row

were used for positive controls containing no test compound and two for negatives containing 500 μ M Ritonavir in acetonitrile. Test compounds in acetonitrile (0.004 mL) were added to wells of a micro-titer plate (Catalog No. 3598, Corning Costar, Cambridge, MA) containing a solution (0.096 mL) of 0.2 M KPO₄ Buffer (pH 7.4) and a NADPH generating system (2.6 mM NADP, 6.6 mM glucose-6-phosphate, 3.3 mM MgCl₂ and 0.8 Units/mL G6P dehydrogenase (BD/Gentest, Woburn, MA). The plates were incubated for 10 minutes at 37 °C. prior to addition of 0.1 mL of pre-warmed 0.1 mg/mL human liver microsomes (Xeno Tech, LLC, Lenexa, KS) in 0.2 M KPO₄ buffer containing 2 μ M dibenzylfluorescein (BD/Gentest, Woburn, MA). The plates were incubated for 10 minutes at 37 °C and the reaction are stopped by the addition of 0.075 mL of 2N NaOH. Plates were incubated at 37 °C for 1 hours prior to determining the amount of fluorescence in each well with a fluorescent plate reader (Spectra Max Gemini XS, Molecular Devices) at excitation/emission wavelengths of 485 and 538 nm (25 nm), respectively. Data were exported and analyzed using GraFit® (Erithacus Software Ltd., Surrey, U.K.). The background corrected data is fit to a 2-parameter equation for the determination of the IC₅₀.

Synthetic methods

The following experimental protocols are illustrative of the methods used to synthesize the compounds of the technology. Syntheses of the compounds below are exemplified, although the skilled artisan will recognize that these exemplary methods are of general applicability.

Example 2: (S)-2-(benzofuran-5-sulfonamido)-N,N-diisobutyl-3-(pyridin-3-yl)propanamide (48)



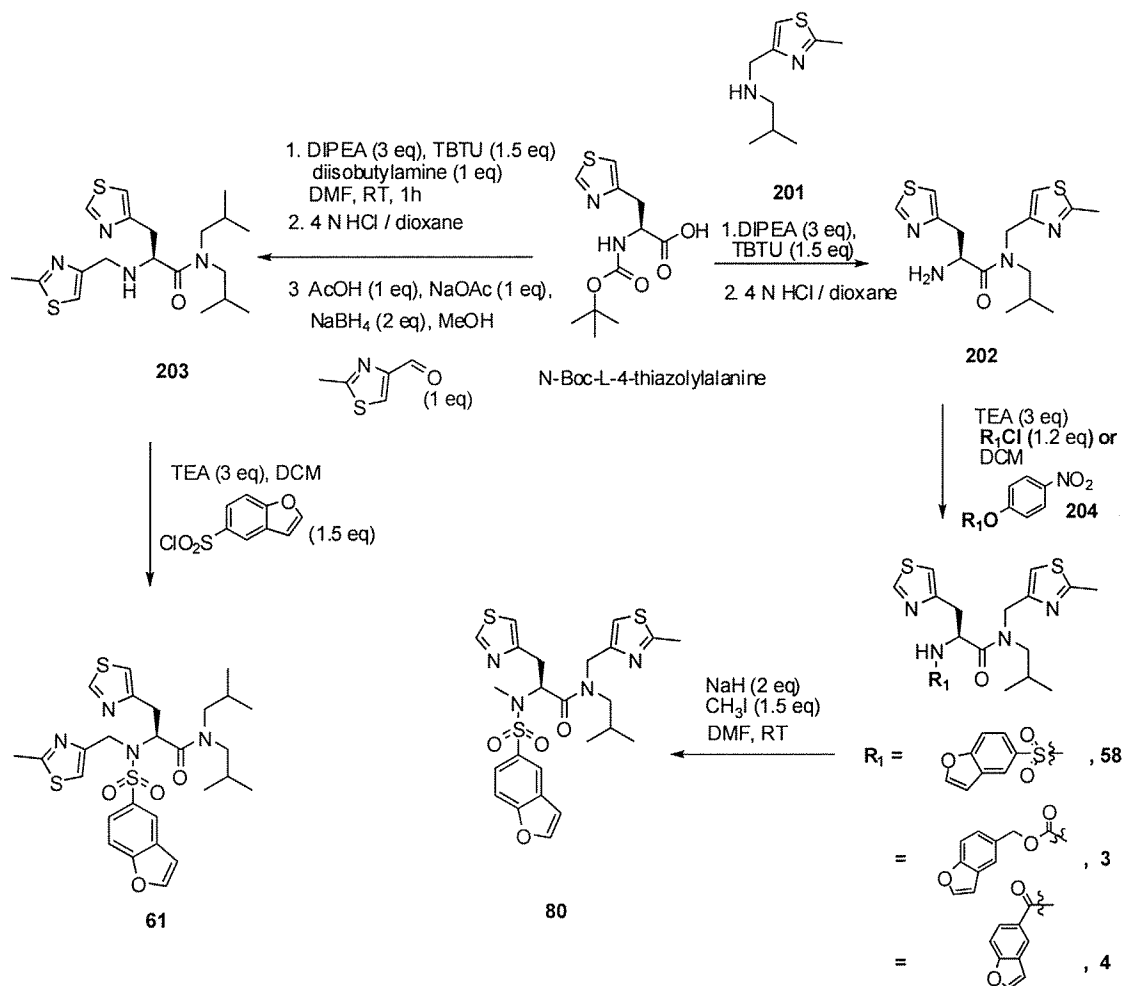
To a solution of Boc-L-3-(3-pyridyl)alanine (154 mg, 0.58 mmol) in DMF (2 ml) were added diisobutylamine (0.10 ml, 0.58 mmol), diisopropylethylamine (DIPEA) (0.30 ml, 1.74 mmol) and O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate

(TBTU) (330 mg, 0.87 mmol). The mixture was stirred for 1 hr at room temperature, quenched with saturated aqueous sodium bicarbonate (15 ml), and extracted with ethyl acetate (EtOAc) (20 ml). The organic phase was washed with brine (15 ml), dried over anhydrous MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (70% EtOAc in hexanes) to provide compound **200** (200 mg, 91%) as a white solid. $[\text{M}+\text{H}]^+$ 378.3, HPLC purity: >99%.

To a solution of compound **200** (200 mg, 0.53 mmol) in dichloromethane (5 ml) was added 4N HCl in dioxane (2 ml). The mixture was stirred for 1 hr at room temperature and concentrated *in vacuo*. To a solution of the resulting material in dichloromethane (5 ml) were added triethylamine (0.22 ml, 1.6 mmol) and benzofuran-5-sulfonyl chloride (138 mg, 0.64 mmol). After 30 min, water (10 ml) was added to quench the reaction. The aqueous phase was extracted with dichloromethane (5 ml) and the organic layer was washed with brine (10 ml), dried over magnesium sulfate and concentrated *in vacuo*. The crude material was purified by preparative TLC (EtOAc) to provide compound **48** (140 mg, 60%) as a white solid. $[\text{M}+\text{H}]^+$ 458.3, $[\text{2M}+\text{Na}]^+$ 937.2, HPLC purity: 97%.

Example 3: Synthesis of Compounds (3), (4), (61), (58), and (80)

The synthesis of compounds **3**, **4**, **61**, **58**, and **80** are outlined in the scheme below. The individual synthesis of those compounds are described in parts 3a to 3e of Example 3.



Example 3a: Preparation of (S)-N,N-diisobutyl-2-(N-((2-methylthiazol-4-yl)methyl)benzofuran-5-sulfonamido)-3-(thiazol-4-yl)propanamide (61)

To a solution of N-Boc-L-4-thiazolylalanine (100 mg, 0.37 mmol) in dimethylformamide (DMF) (2 ml) were added diisobutylamine (64 μ l, 0.37 mmol), DIPEA (0.19 ml, 1.10 mmol) and TBTU (180 mg, 0.56 mmol). The mixture was stirred for 1 hr at room temperature, quenched with saturated aqueous sodium bicarbonate (10 ml), and extracted with EtOAc (10 ml). The organic phase was washed with brine (15 ml), dried over anhydrous MgSO_4 and concentrated *in vacuo*. To a solution of the resulting material in dichloromethane (5 ml) was added 4N HCl in dioxane (2 ml). The mixture was stirred for 1 hr at room temperature and concentrated *in vacuo*. To a solution of the resulting compound (104 mg, 0.37 mmol) in methanol (4 ml) were added 2-methyl-1,3-thiazole-4-carboxaldehyde (47 mg, 0.37 mmol), acetic acid (21 μ l, 0.37 mmol) and sodium acetate (30 mg, 0.37 mmol). The mixture was stirred for 30 min at room temperature and then treated with sodium borohydride (28 mg, 0.74 mmol). After 1 hr, saturated aqueous sodium bicarbonate (5 ml) was added to quench the reaction. The aqueous phase was

extracted with EtOAc (15 ml) and the organic layer was washed with brine (10 ml), dried over anhydrous MgSO₄ and concentrated *in vacuo*. To a solution of compound **203** in dichloromethane (10 ml) were added triethylamine (150 μ l, 1.11 mmol) and benzofuran-5-sulfonyl chloride (120 mg, 0.56 mmol). After 30 min, water (10 ml) was added to quench the reaction. The aqueous phase was extracted with dichloromethane (5 ml) and the organic layer was washed with brine (10 ml), dried over anhydrous MgSO₄ and concentrated *in vacuo*. The crude material was purified by preparative TLC (10% MeOH in dichloromethane) to provide compound **61** (47 mg, 22%) as a colorless oil. $[M+H]^+$ 575.0, HPLC purity: >99%.

Example 3b: Preparation of (S)-2-(benzofuran-5-sulfonamido)-N-isobutyl-N-((2-methylthiazol-4-yl)methyl)-3-(thiazol-4-yl)propanamide (58)

To a solution of commercially available 2-methyl-1,3-thiazole-4-carboxaldehyde (102 mg, 0.80 mmol) in MeOH (4 ml) were added isobutylamine (0.16 ml, 1.6 mmol), acetic acid (50 μ l, 0.88 mmol) and sodium acetate (72 mg, 0.88 mmol). The mixture was stirred for 30 min at room temperature and treated with sodium borohydride (61 mg, 1.6 mmol). After 30 min, aqueous sodium bicarbonate (8 ml) was added to quench the reaction. The water phase was extracted with ethyl acetate (10 ml) and the organic layer was washed with brine (10 ml) and dried with magnesium sulfate and concentrated *in vacuo*. The crude material was purified by preparative TLC (10% MeOH in dichloromethane) to provide compound **201** (68 mg, 46%) as a colorless oil. $[M+H]^+$ 185.0, HPLC purity: >99%.

To a solution of N-Boc-L-4-thiazolylalanine (100 mg, 0.37 mmol) in DMF (2 ml) were added compound **201** (68 mg, 0.37 mmol), DIPEA (0.19 ml, 1.10 mmol) and TBTU (178 mg, 0.56 mmol). The mixture was stirred for 1 hr at room temperature, quenched with saturated aqueous sodium bicarbonate (10 ml), and extracted with EtOAc (10 ml). The organic phase was washed with brine (15 ml), dried over anhydrous MgSO₄ and concentrated *in vacuo*.

To a solution of the resulting material in dichloromethane (5 ml) was added 4N HCl in dioxane (2 ml). The mixture was stirred for 1 hr at room temperature and concentrated *in vacuo* to provide compound **202**. To a solution of compound **202** in dichloromethane (5 ml) were added triethylamine (0.15 ml, 1.1 mmol) and benzofuran-5-sulfonyl chloride (129 mg, 0.56 mmol). After 30 min, water (10 ml) was added to quench the reaction. The aqueous phase was extracted with dichloromethane (5 ml) and the

organic layer was washed with brine (10 ml), dried over magnesium sulfate and concentrated *in vacuo*. The crude material was purified by preparative TLC (EtOAc) to provide compound **58** (46 mg, 70%) as a white solid. $[M+H]^+$ 519.0, $[M+Na]^+$ 541.0, HPLC purity: 99%.

5 **Example 3c: Preparation of (S)-N-isobutyl-2-(N-methylbenzofuran-5-sulfonamido)-N-((2-methylthiazol-4-yl)methyl)-3-(thiazol-4-yl)propanamide (80)**

To a solution of compound **58** (76 mg, 0.15 mmol) in DMF (1 ml) were added sodium hydride (12 mg, 0.30 mmol) and iodomethane (14 μ l, 0.23 mmol). After 1 hr, 10 water (7 ml) was added to quench the reaction. The aqueous phase was extracted with EtOAc (10 ml) and the organic layer was washed with brine (5 ml), dried over anhydrous MgSO₄ and concentrated *in vacuo*. The crude material was purified by preparative TLC (EtOAc) to provide compound **80** (49 mg, 61%) as an oil. $[M+H]^+$ 533.0, HPLC purity: >99%.

15 **Example 3d: Preparation of (S)-benzofuran-5-ylmethyl 1-(isobutyl((2-methylthiazol-4-yl)methyl)amino)-1-oxo-3-(thiazol-4-yl)propan-2-ylcarbamate (3)**

To a solution of benzofuran-5-ylmethanol (503 mg, 3.40 mmol) in dichloromethane (8 ml) were added triethylamine (0.71 ml, 5.1 mmol) and bis(4-nitrophenyl)carbonate (1.0 20 g, 3.4 mmol). After 1 hr, water (10 ml) was added to quench the reaction. The aqueous phase was extracted with dichloromethane (5 ml) and the organic layer was washed with brine (10 ml), dried over magnesium sulfate and then concentrated *in vacuo*. The crude material was purified by flash column chromatography (70% EtOAc in hexanes) to provide compound **204** (920 mg, 86%) as a white solid. $[M+H]^+$ 314.0, HPLC purity: >99%.

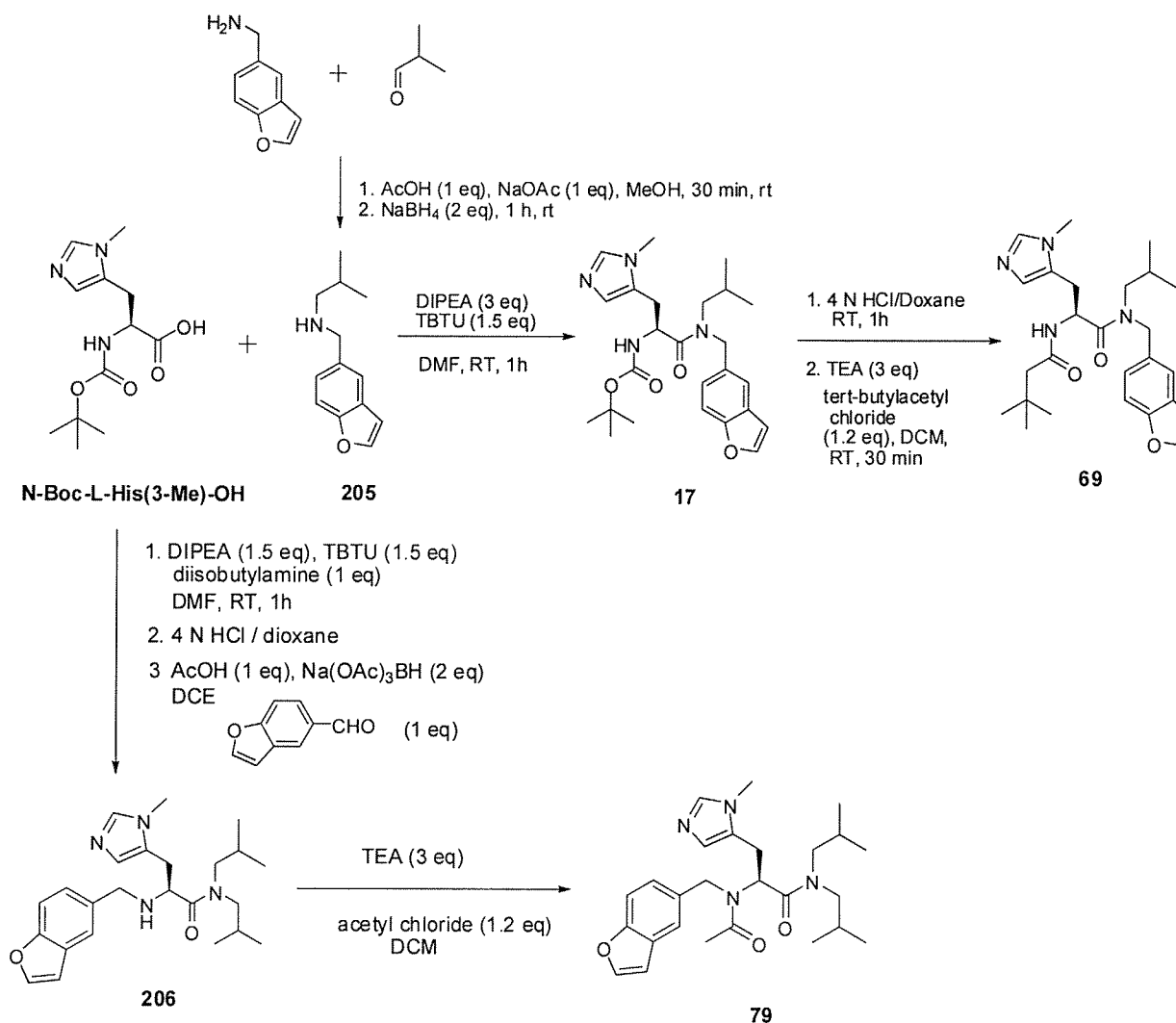
25 To a solution of compound **202** (45 mg, 0.13 mmol) in dichloromethane (5 ml) were added DIPEA (45 μ l, 0.26 mmol) and compound **204** (41 mg, 0.13 mmol). After 30 min, the mixture was concentrated *in vacuo*. The crude material was purified by preparative HPLC to provide compound **3** (33 mg, 50%) as a colorless oil. $[M+H]^+$ 513.0, HPLC purity: >99%.

30 **Example 3e: Preparation of (S)-N-(1-(isobutyl((2-methylthiazol-4-yl)methyl)amino)-1-oxo-3-(thiazol-4-yl)propan-2-yl)benzofuran-5-carboxamide (4)**

To a solution of compound **202** (33 mg, 0.097 mmol) in dichloromethane (4 ml) were added triethylamine (41 μ l, 0.29 mmol) and benzofuran-5-carbonyl chloride (21 mg, 0.12 mmol). After 30 min, the mixture was concentrated *in vacuo*. The crude material was purified by preparative TLC (EtOAc) to provide compound **4** (30 mg, 64%) as a colorless oil. $[M+H]^+$ 483.0, HPLC purity: >98%.

Example 4: Synthesis of Compounds (17), (69), and (79)

The synthesis of compounds **17**, **69**, and **79** are outlined in the scheme below. The individual synthesis of those compounds are described in parts 4a to 4c of Example 4.



Example 4a: Preparation of (S)-tert-butyl 1-((benzofuran-5-ylmethyl)(isobutyl)amino)-3-(1-methyl-1H-imidazol-5-yl)-1-oxopropan-2-ylcarbamate (**17**)

To a solution of benzofuran-5-yl-methylamine (212 mg, 1.44 mmol) in MeOH (8 ml) were added isobutyraldehyde (131 μ l, 1.44 mmol), acetic acid (82 μ l, 1.44 mmol) and

sodium acetate (118 mg, 1.44 mmol). The mixture was stirred for 30 min at room temperature and treated with sodium borohydride (109 mg, 2.88 mmol). After 1 hr, aqueous sodium bicarbonate (10 ml) was added to quench the reaction. The aqueous phase was extracted with EtOAc (15 ml) and the organic layer was washed with brine (10 ml),
5 dried over anhydrous MgSO_4 and concentrated *in vacuo*. The crude material was purified by preparative TLC (10% MeOH in dichloromethane) to provide compound **205** (260 mg, 89 %) as a white solid. $[\text{M}+\text{H}]^+$ **204.0**, HPLC purity: >99%.

To a solution of Boc-His(3-Me)-OH (200 mg, 0.74 mmol) in DMF (8 ml) were added compound **205** (150 mg, 0.74 mmol), DIPEA (387 μl , 2.20 mmol), and TBTU (356
10 mg, 1.11 mmol). The mixture was stirred for 1 hr at room temperature, quenched with saturated aqueous sodium bicarbonate (10 ml), and extracted with EtOAc (10 ml). The organic phase was washed with brine (10 ml), dried over anhydrous MgSO_4 and concentrated *in vacuo*. The crude material was purified by preparative TLC (10% MeOH in dichloromethane) to provide compound **17** (320 mg, 95 %) as a yellowish oil. $[\text{M}+\text{H}]^+$
15 **455.3**, purity: 97%.

Example 4b: Preparation of (S)-N-(1-((benzofuran-5-ylmethyl)(isobutyl)amino)-3-(1-methyl-1H-imidazol-5-yl)-1-oxopropan-2-yl)-3,3-dimethylbutanamide (69)

To a solution of compound **17** (320 mg, 0.70 mmol) in dichloromethane (4 ml) was added
20 4N HCl in dioxane (4 ml). The mixture was stirred for 1 hr at room temperature and concentrated *in vacuo*. To a solution of the resulting material were added triethylamine (293 μl , 0.49 mmol) and tert-butylacetyl chloride (117 μl , 0.84 mmol). After 30 min, water (10 ml) was added to quench the reaction. The aqueous phase was extracted with dichloromethane (5 ml) and the organic layer was washed with brine (10 ml), dried over
25 anhydrous MgSO_4 and concentrated *in vacuo*. The crude material was purified by preparative TLC (10% MeOH in dichloromethane) to provide compound **69** (220 mg, 70%) as a white solid. $[\text{M}+\text{H}]^+$ **453.3**, HPLC purity: 99%.

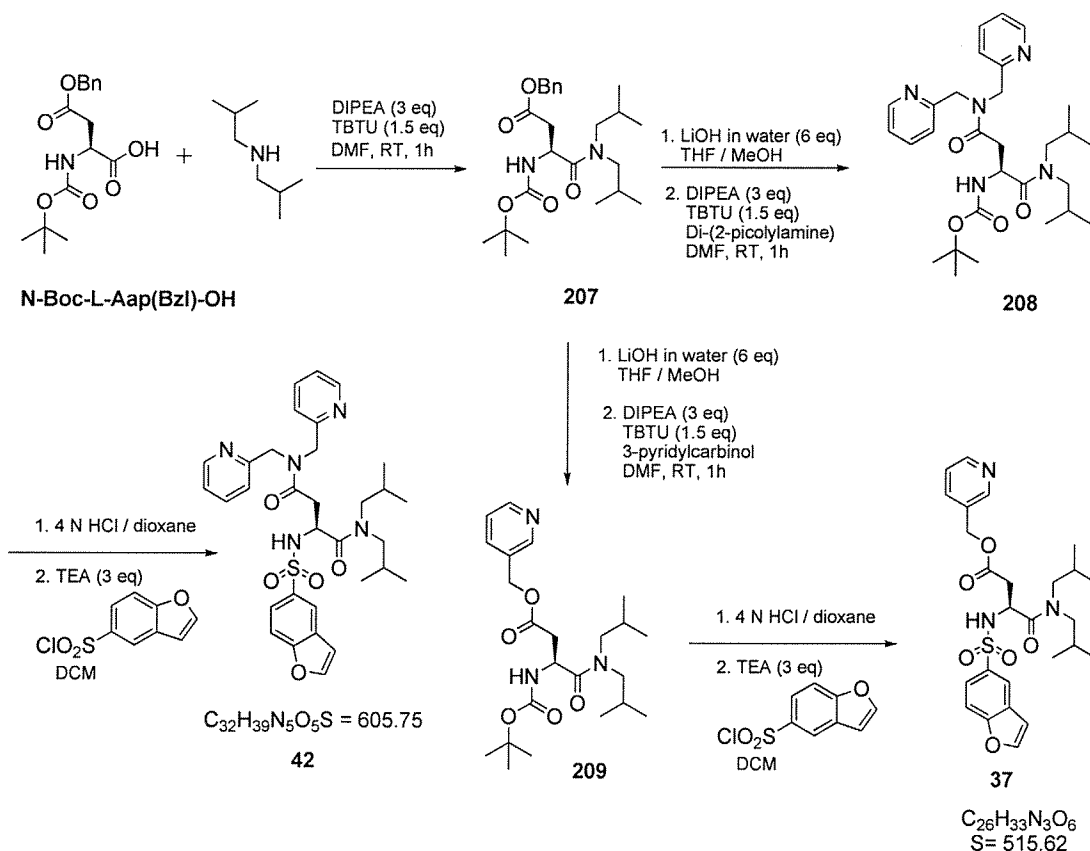
Example 4c: Preparation of (S)-2-(N-(benzofuran-5-ylmethyl)acetamido)-N,N-diisobutyl-3-(1-methyl-1H-imidazol-5-yl)propanamide (79)

To a solution of Boc-His(3-Me)-OH (543 mg, 1.86 mmol) in DMF (2 ml) were added diisobutylamine (320 μl , 1.86 mmol), DIPEA (430 μl , 2.79 mmol) and TBTU (900
30 mg, 2.79 mmol). The mixture was stirred for 1 hr at room temperature, quenched with saturated aqueous sodium bicarbonate (10 ml), and extracted with EtOAc (10 ml). The

organic phase was washed with brine (15 ml), dried over anhydrous MgSO_4 and concentrated *in vacuo*. To a solution of the resulting material in dichloromethane (5 ml) was added 4N HCl in dioxane (4 ml). The mixture was stirred for 1 hr at room temperature and concentrated *in vacuo*. To a solution of the resulting material (204 mg, 0.73 mmol) in 5 1,2-dichloroethane (10 ml) were added benzofuran-5-carbaldehyde (107 mg, 0.73 mmol) and acetic acid (42 μl , 0.73 mmol). The mixture was stirred for 30 min at room temperature and then treated with $\text{Na}(\text{OAc})_3\text{BH}$ (309 mg, 1.46 mmol). After 1 hr, saturated aqueous sodium bicarbonate (10 ml) was added to quench the reaction. The aqueous phase was extracted with EtOAc (15 ml) and the organic layer was washed with 10 brine (10 ml), dried over anhydrous MgSO_4 and concentrated *in vacuo*. To a solution of the resulting compound **206** (24 mg, 0.060 mmol) in dichloromethane (4 ml) were added triethylamine (24 μl , 0.17 mmol) and acetyl chloride (5 μl , 0.07 mmol). After 30 min, the mixture was concentrated *in vacuo*. The crude material was purified by preparative HPLC to provide compound **79** (8.0 mg, 28%) as a colorless oil. $[\text{M}+\text{H}]^+$ 453.3, HPLC purity: 15 >99%.

Example 5: Synthesis of Compounds (42) and (37)

The synthesis of compounds **42** and **37** are outlined in the scheme below. The individual synthesis of those compounds are described in parts 5a and 5b of Example 5.



Example 5a: Preparation of (S)-2-(benzofuran-5-sulfonamido)-N1,N1-diisobutyl-N4,N4-bis(pyridin-2-ylmethyl)succinamide (42)

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To a solution of Boc-L-Asp(Bzl)-OH (1.0 g, 3.1 mmol) in DMF (4 ml) were added the diisobutylamine (0.54 ml, 3.1 mmol), DIPEA (1.6 ml, 9.3 mmol) and TBTU (1.5 g, 4.7 mmol). The mixture was stirred for 1 hr at room temperature, quenched with saturated aqueous sodium bicarbonate (10 ml), and extracted with EtOAc (10 ml). The organic phase was washed with brine (10 ml), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (30% EtOAc in hexanes) to provide compound **207** (1.3 g, 100%) as a white solid. $[M+H]^+$ 435.2, $[M+Na]^+$ 457.2, $[2M+Na]^+$ 891.5, HPLC purity: 99%.

15

To a solution of compound **207** (490 mg, 1.10 mmol) in tetrahydrofuran/MeOH (3:1, 8 ml) was added lithium hydroxide in water (2.5M, 2.6 ml, 6.6 mmol). The mixture was stirred for 3 hrs at room temperature, quenched with aqueous 1N HCl (10 ml), and extracted with EtOAc (10 ml). The organic phase was washed with brine (10 ml), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography to provide (S)-3-(tert-butoxycarbonylamino)-4-

(diisobutylamino)-4-oxobutanoic acid (176 mg, 46%) as an oil. $[M+H]^+$ 345.2, HPLC purity: >99%.

To a solution of (S)-3-(tert-butoxycarbonylamino)-4-(diisobutylamino)-4-oxobutanoic acid (176 mg, 0.51 mmol) in DMF (1 ml) were added di-2-picolylamine (92 μ l, 0.51 mmol), DIPEA (0.27 ml, 1.5 mmol), and TBTU (290 mg, 0.77 mmol). The mixture was stirred for 1 hr at room temperature, quenched with saturated aqueous sodium bicarbonate (7 ml) and extracted with EtOAc (7 ml). The organic phase was washed with brine (10 ml), dried over anhydrous $MgSO_4$ and then concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc) to provide compound **208** (110 mg, 41%) as an oil. $[M+H]^+$ 526.2, $[M+Na]^+$ 548.3, HPLC purity: 99%.

To a solution of compound **208** (110 mg, 0.21 mmol) in dichloromethane (2 ml) was added 4N HCl in dioxane (1 ml). The mixture was stirred for 1 hr at room temperature and concentrated *in vacuo*. To a solution of the resulting material in dichloromethane (4 ml) were added triethylamine (88 μ l, 0.63 mmol) and benzofuran-5-sulfonyl chloride (68 mg, 0.32 mmol). After 30 min, water (5 ml) was added to quench the reaction. The aqueous phase was extracted with dichloromethane (5 ml) and the organic layer was washed with brine (5 ml), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by preparative TLC (10% dichloromethane in MeOH) to provide compound **42** (97 mg, 76%) as a colorless oil. $[M+H]^+$ 606.2, HPLC purity: 99%.

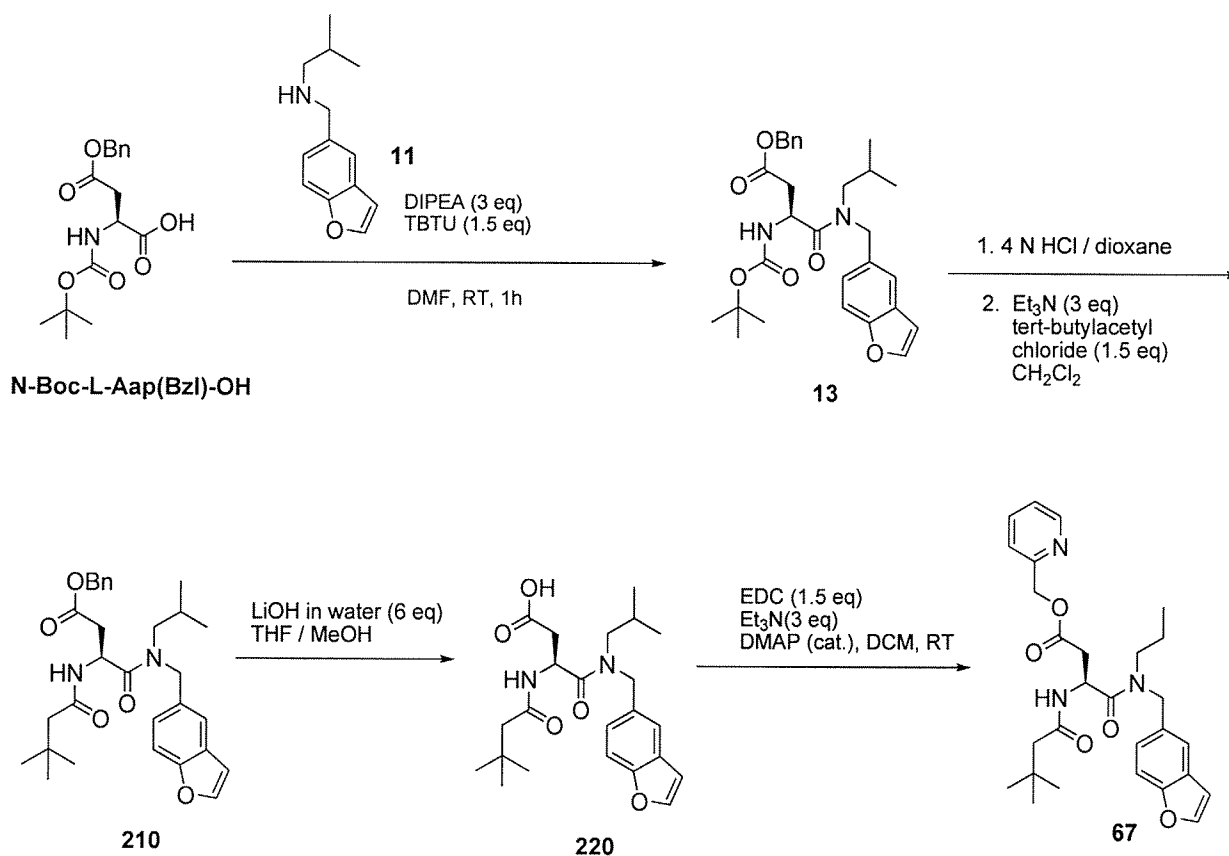
Example 5b: Preparation of (S)-pyridin-3-ylmethyl 3-(benzofuran-5-sulfonamido)-4-(diisobutylamino)-4-oxobutanoate (37)

To a solution of (S)-3-(tert-butoxycarbonylamino)-4-(diisobutylamino)-4-oxobutanoic acid (104 mg, 0.30 mmol) in dichloromethane (8 ml) were added 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (EDC) (58 mg, 0.30 mmol), triethylamine (42 μ l, 0.30 mmol), 3-pyridylcarbinol (34 μ l, 0.30 mmol) and a catalytic amount of 4-dimethylaminopyridine (DMAP) (10 mg). The mixture was stirred for 3 hrs at room temperature, quenched with water (10 ml), and extracted with dichloromethane (10 ml). The organic phase was washed with brine (10 ml), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by preparative TLC (50% EtOAc in hexanes) to provide compound **209** (80 mg, 60%) as a colorless oil. $[M+H]^+$ 436.2, $[M+Na]^+$ 458.3, $[2M+Na]^+$ 893.5, HPLC purity: 99%.

To a solution of compound **209** (80 mg, 0.18 mmol) in dichloromethane (2 ml) was added 4N HCl in dioxane (1 ml). The mixture was stirred for 1 hr at room temperature and concentrated *in vacuo*. To a solution of the resulting material in dichloromethane (4 ml) were added triethylamine (75 μ l, 0.54 mmol) and benzofuran-5-sulfonyl chloride (58 mg, 0.27 mmol). After 30 min, water (5 ml) was added to quench the reaction. The aqueous phase was extracted with dichloromethane (5 ml) and the organic layer was washed with brine (5 ml), dried over anhydrous MgSO_4 and then concentrated *in vacuo*. The crude material was purified by preparative HPLC to provide compound **37** (36 mg, 39%) as a colorless oil. $[\text{M}+\text{H}]^+$ 516.3, $[\text{2M}+\text{Na}]^+$ 1053.3, HPLC purity: >99%.

Example 6: Synthesis of Compounds (13) and (67)

The synthesis of compounds **13** and **67** are outlined in the scheme below. The individual synthesis of those compounds are described in parts 6a and 6b of Example 6.



Example 6a: Preparation of (S)-tert-butyl 1-((benzofuran-5-ylmethyl)(isobutyl)amino)-1,4-dioxo-5-phenylpentan-2-ylcarbamate (**13**)

To a solution of **N-Boc-L-Asp(Bzl)-OH** (576 mg, 1.78 mmol) in DMF (8 ml) were added compound **11** (160 mg, 0.79 mmol), DIPEA (744 μ l, 5.34 mmol), and TBTU (857 mg, 2.67 mmol). The mixture was stirred for 1 hr at room temperature, quenched with

saturated aqueous sodium bicarbonate (10 ml), and extracted with EtOAc (10 ml). The organic phase was washed with brine (10 ml), dried over anhydrous MgSO₄ and then concentrated *in vacuo*. The crude material was purified by flash column chromatography (50% EtOAc in hexanes) to provide compound **13** (395 mg, 97%) as a colorless oil.

5 **[M+H]⁺ 509.2, HPLC purity: >99%.**

**Example 6b: Preparation of Synthesis of (S)-pyridin-3-ylmethyl 4-
((benzofuran-5-ylmethyl)(isobutyl)amino)-3-(3,3-dimethylbutanamido)-4-
oxobutanoate (67)**

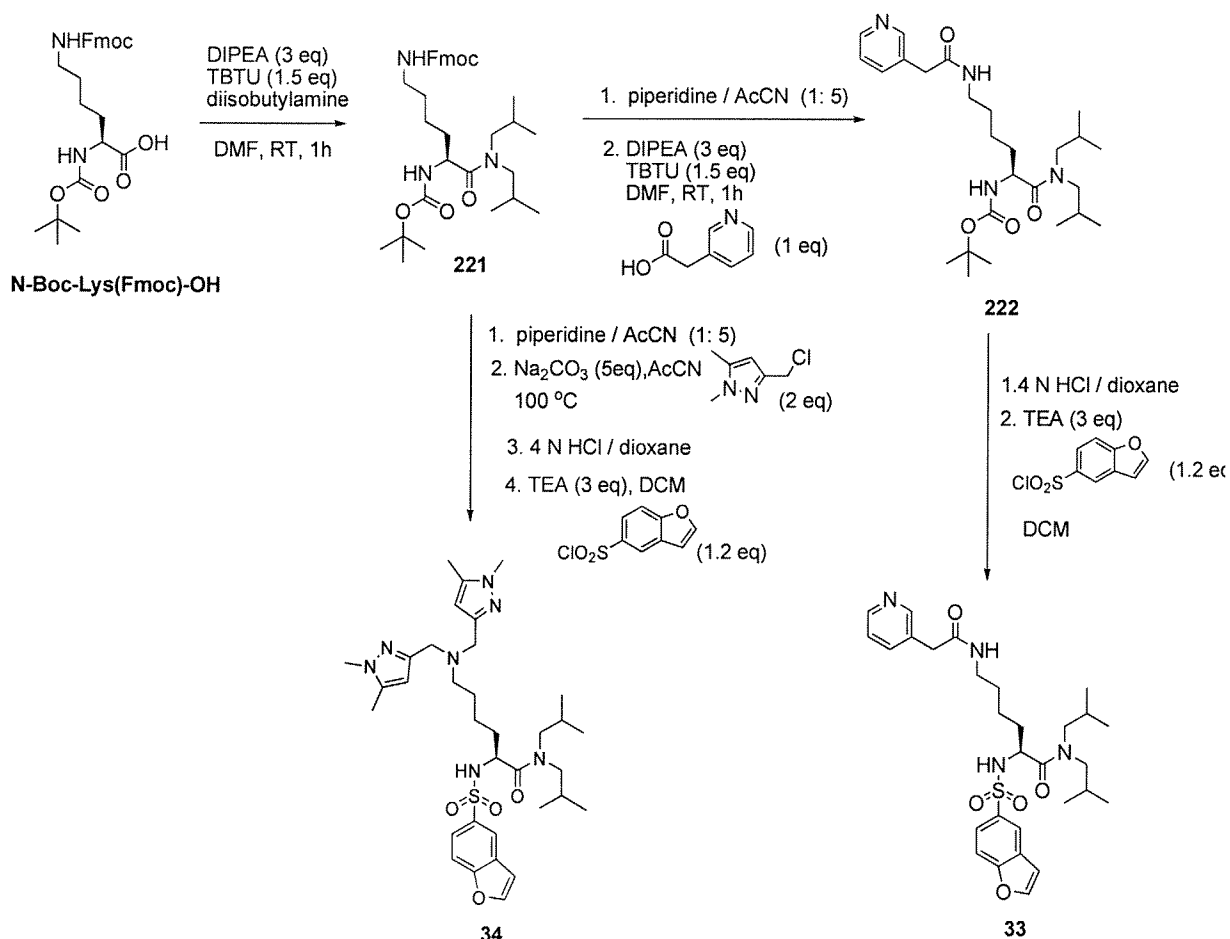
To a solution of compound **13** (395 mg, 0.77 mmol) in dichloromethane (4 ml) was
10 added 4N HCl in dioxane (4 ml). The mixture was stirred for 1 hr at room temperature and
concentrated *in vacuo*. To a solution of the resulting material in dichloromethane (8 ml)
were added triethylamine (321 μ l, 2.3 mmol) and tert-butylacetyl chloride (161 μ l, 1.16
mmol). After 30 min, water (5 ml) was added to quench the reaction. The aqueous phase
was extracted with dichloromethane (8 ml) and the organic layer was washed with brine (8
15 ml), dried over anhydrous MgSO₄ and then concentrated *in vacuo*. The residue was
purified by preparative TLC (30% EtOAc in hexanes) to provide compound **210** (273 mg,
70%) as a colorless oil. **[M+H]⁺ 507.2, HPLC purity: >99%.**

To a solution of compound **210** (273 mg, 70%) in tetrahydrofuran/MeOH (3:1, 16
ml) was added lithium hydroxide in water (2.5M, 1.3 ml, 3.2 mmol). The mixture was
20 stirred for 3 hrs at room temperature, quenched with 1N HCl (10 ml), and extracted with
EtOAc (10 ml). The organic phase was washed with brine (10 ml), dried over anhydrous
MgSO₄ and then concentrated *in vacuo*. The crude material was purified by preparative
TLC (20% dichloromethane in MeOH) to provide compound **220** (195 mg, 87%) as a
white solid. **[M+H]⁺ 417.3, HPLC purity: 99%.**

25 To a solution of compound **220** (95 mg, 0.22 mmol) in dichloromethane (8 ml)
were added EDC (63 mg, 0.33 mmol), triethylamine (92 μ l, 0.66 mmol), 3-pyridylcarbinol
(21 mg, 0.22 mmol) and a catalytic amount of DMAP (10 mg). The mixture was stirred
for 3 hrs at room temperature, quenched with water (10 ml), and extracted with
dichloromethane (10 ml). The organic phase was washed with brine (10 ml), dried over
30 anhydrous MgSO₄ and concentrated *in vacuo*. The crude material was purified by
preparative TLC (EtOAc) to provide compound **67** (30 mg, 27%) as a colorless oil.
[M+H]⁺ 508.3, HPLC purity: 99%.

Example 7: Synthesis of Compounds (33) and (34)

The synthesis of compounds **33** and **34** are outlined in the scheme below. The individual synthesis of those compounds are described in parts 7a and 7b of Example 7.



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Example 7a: Preparation of (S)-2-(benzofuran-5-sulfonamido)-N,N-diisobutyl-6-(2-(pyridin-3-yl)acetamido)hexanamide (33)

Compound **221** was prepared following the procedure for Scheme 1 except that instead of Boc-L-3-pyridylalanine Boc-L-Lys(Fmoc)-OH was used as the starting material.

10 Compound **221** (500 mg, 0.86 mmol) in 20% piperidine in acetonitrile (8 ml) was stirred for 1 hr at room temperature and concentrated *in vacuo*. To a solution of the resulting material in DMF (2 ml) were added the 3-pyridylacetic acid (49 mg, 0.28 mmol), DIPEA (0.15 ml, 0.84 mmol) and TBTU (135 mg, 0.42 mmol). The mixture was stirred for 1 hr at room temperature, quenched with saturated aqueous sodium bicarbonate (10 ml) and

15 extracted with EtOAc (10 ml). The organic phase was washed with brine (10 ml), dried over anhydrous MgSO_4 and concentrated *in vacuo*. The crude material was purified by

preparative TLC (10 % dichloromethane in MeOH) to provide compound **222** (80 mg, 81%) as a yellowish oil. $[M+H]^+$ 477.2, HPLC purity: 99%.

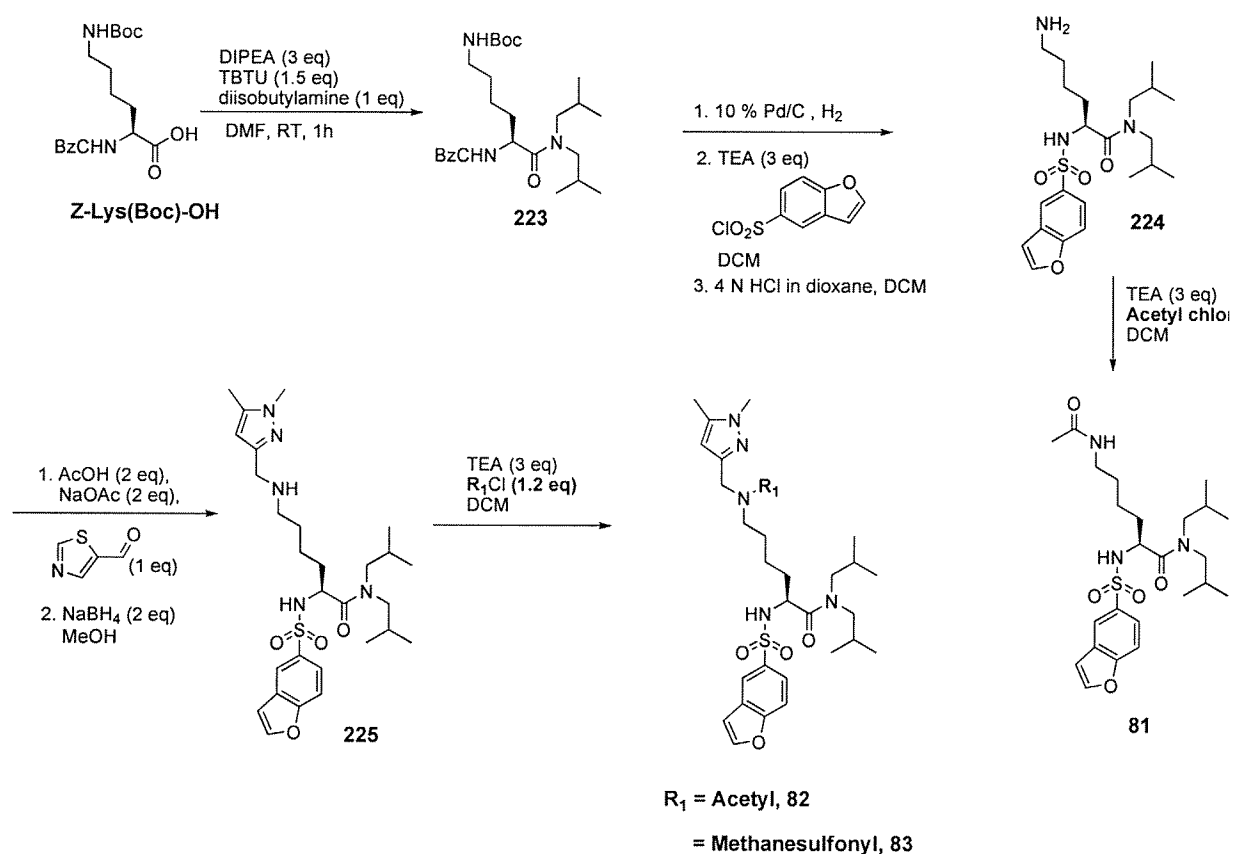
To a solution of compound **222** (80 mg, 0.17 mmol) in dichloromethane (4 ml) was added 4N HCl in dioxane (4 ml). The mixture was stirred for 1 hr at room temperature and concentrated *in vacuo*. To a solution of the resulting material in dichloromethane (10 ml) was added triethylamine (71 μ l, 0.51 mmol) and benzofuran-5-sulfonyl chloride (55 mg, 0.26 mmol). After 30 min, water (5 ml) was added to quench the reaction. The aqueous phase was extracted with dichloromethane (5 ml) and the organic layer was washed with brine (5 ml), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by preparative TLC (10% dichloromethane in MeOH) to provide compound **33** (65 mg, 67%) as a white solid. $[M+H]^+$ 557.3, HPLC purity: 99%.

Example 7b: Preparation of (S)-2-(benzofuran-5-sulfonamido)-6-(bis((1,5-dimethyl-1H-pyrazol-3-yl)methyl)amino)-N,N-diisobutylhexanamide (34)

A solution of compound **221** (30 mg, 0.083 mmol) in 20% piperidine in acetonitrile (2 ml) was stirred for 1 hr at room temperature and concentrated *in vacuo*. To a solution of the resulting material in acetonitrile (8 ml) were added sodium bicarbonate (16 mg, 0.19 mmol) and 3-(chloromethyl)-1,5-dimethyl-1H-pyrazole (24 mg, 0.17 mmol). The resulting mixture was stirred for 2 days at 100 °C. The mixture was quenched with water (5 ml), and extracted with EtOAc (8 ml). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. To a solution of the resulting material in dichloromethane (4 ml) was added 4N HCl in dioxane (4 ml). The mixture was stirred for 1 hr at room temperature and concentrated *in vacuo*. To a solution of the resulting material in dichloromethane (4 ml) was added triethylamine (35 μ l, 0.25 mmol) and benzofuran-5-sulfonyl chloride (27 mg, 0.12 mmol). After 30 min, water (5 ml) was added to quench the reaction. The aqueous phase was extracted with dichloromethane (5 ml) and the organic layer was washed with brine (5 ml), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by preparative TLC (10% dichloromethane in MeOH) to provide compound **34** (33 mg, 60%) as an oil. $[M+H]^+$ 654.3, HPLC purity: 99%.

Example 8: Synthesis of Compounds (81), (82) and (83)

The synthesis of compounds **81**, **82** and **83** are outlined in the scheme below. The individual synthesis of those compounds are described in parts 8a, 8b and 8c of Example 8.



5

Example 8a: Preparation of (S)-6-acetamido-2-(benzofuran-5-sulfonamido)-N,N-diisobutylhexanamide (81)

To a solution of Z-Lys(Boc)-OH (1.0 g, 2.6 mmol) in DMF (8 ml) were added diisobutylamine (0.46 ml, 2.6 mmol), DIPEA (1.4 ml, 7.8 mmol), and TBTU (1.2 g, 3.9 mmol). The mixture was stirred for 1 hr at room temperature, quenched with saturated aqueous sodium bicarbonate (20 ml), and extracted with EtOAc (20 ml). The organic phase was washed with brine (15 ml), dried over anhydrous MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (50% EtOAc in hexanes) to provide compound **223** (1.0 g, 80%) as an oil. [M+H]⁺ 492.3, HPLC purity: 99%.

To a solution of compound **223** (300 mg, 0.61 mmol) in 20% dichloromethane/MeOH (30 ml) was added 10% Pd/C (30 mg). The mixture was hydrogenated for 3 hrs at room temperature, filtered through Celite and concentrated *in vacuo*. To a solution of the resulting material in dichloromethane (8 ml) were added
5 triethylamine (0.25 ml, 1.83 mmol) and benzofuran-5-sulfonyl chloride (159 mg, 0.73 mmol). After 30 min, water (10 ml) was added to quench the reaction. The aqueous phase was extracted with dichloromethane (5 ml) and the organic layer was washed with brine (10 ml), dried over anhydrous MgSO₄ and concentrated *in vacuo*. To a solution of the
10 resulting material in dichloromethane (8 ml) was added 4N HCl in dioxane (4 ml). The mixture was stirred for 1 hr at room temperature and concentrated *in vacuo*. The crude material was purified by preparative TLC (10% dichloromethane in MeOH) to provide compound **224** (150 mg, 56%) as a white solid. **[M+H]⁺ 438.3, [2M+Na]⁺ 875.3, HPLC purity: 99%.**

To a solution of compound **224** (150 mg, 0.34 mmol) in dichloromethane (10 ml)
15 were added triethylamine (139 μ l, 1.00 mmol) and acetyl chloride (29 μ l, 0.41 mmol). After 10 min, the residue was concentrated *in vacuo* and purified by preparative HPLC to provide compound **81** (128 mg, 76%) as a white solid. **[M+H]⁺ 480.2, [2M+Na]⁺ 981.2, HPLC purity: 97%.**

**Example 8b: Preparation of (S)-2-(benzofuran-5-sulfonamido)-6-(N-((1,5-
20 dimethyl-1H-pyrazol-3-yl)methyl)acetamido)-N,N-diisobutylhexanamide (82)**

To a solution of compound **224** (150 mg, 0.34 mmol) in MeOH (4 ml) were added 1,5-dimethylpyrazole-3-carbaldehyde (42 mg, 0.34 mmol), acetic acid (39 μ l, 0.68 mmol) and sodium acetate (56 mg, 0.68 mmol). The mixture was stirred for 30 min at room temperature and then treated with sodium borohydride (26 mg, 0.68 mmol). After 1 hr,
25 saturated aqueous sodium bicarbonate (5 ml) was added to quench the reaction. The aqueous phase was extracted with EtOAc (15 ml) and the organic layer was washed with brine (10 ml), dried over anhydrous MgSO₄ and concentrated *in vacuo*. The residue was purified by preparative HPLC to provide compound **225** (185 mg, 100%) as a colorless oil. **[M+H]⁺ 546.3, HPLC purity: 99%.**

To a solution of compound **225** (100 mg, 0.18 mmol) in dichloromethane (10 ml)
30 were added triethylamine (54 μ l, 0.54 mmol) and acetyl chloride (15 μ l, 0.22 mmol). After 10 min, the solution was concentrated *in vacuo* and the residue was purified by preparative

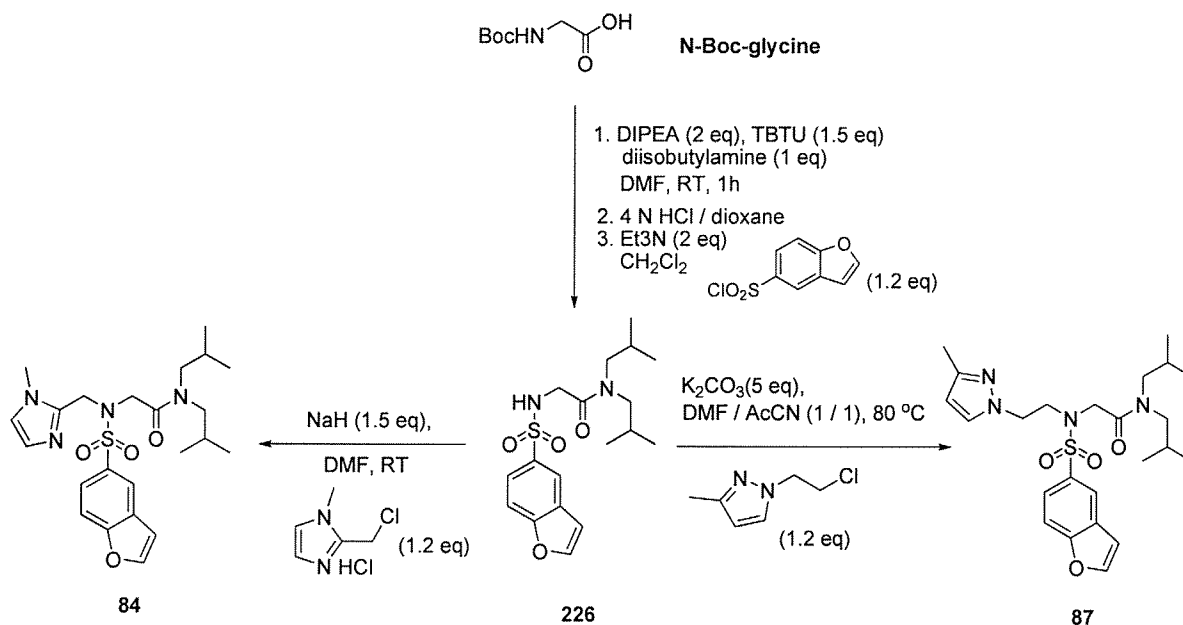
HPLC to provide compound **82** (45 mg, 43%) as a white solid. $[M+H]^+$ 588.3, HPLC purity: 99%.

Example 8c: Preparation of (S)-2-(benzofuran-5-sulfonamido)-6-(N-((1,5-dimethyl-1H-pyrazol-3-yl)methyl)methylsulfonamido)-N,N-diisobutylhexanamide (83)

To a solution of compound **225** (30 mg, 0.060 mmol) in dichloromethane (2 ml) were added triethylamine (23 μ l, 0.16 mmol) and methanesulfonyl chloride (5.0 μ l, 0.070 mmol). After 10 min, the mixture was concentrated *in vacuo* and the residue purified by preparative TLC to provide compound **83** (24 mg, 70%) as a colorless oil. $[M+H]^+$ 624.2, HPLC purity: 98%.

Example 9: Synthesis of Compounds (84) and (87)

The synthesis of compounds **84** and **87** are outlined in the scheme below. The individual synthesis of those compounds are described in parts 9a and 9b of Example 9.



Example 9a: Preparation of N,N-diisobutyl-2-(N-((1-methyl-1H-imidazol-2-yl)methyl)benzofuran-5-sulfonamido)acetamide (84)

To a solution of N-Boc-glycine (1.0 g, 5.7 mmol) in DMF (10 ml) were added diisobutylamine (0.10 ml, 11.4 mmol), DIPEA (1.9 ml, 11.4 mmol) and TBTU (2.7 g, 8.5 mmol). The mixture was stirred for 1 hr at room temperature, quenched with saturated aqueous sodium bicarbonate (15 ml), and extracted with EtOAc (20 ml). The organic

phase was washed with brine (15 ml), dried over anhydrous MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (30% EtOAc in hexanes) to provide tert-butyl 2-(diisobutylamino)-2-oxoethylcarbamate (1.6 g, 98%) as a colorless oil. $[\text{M}+\text{H}]^+$ 287.3, HPLC purity: 90%.

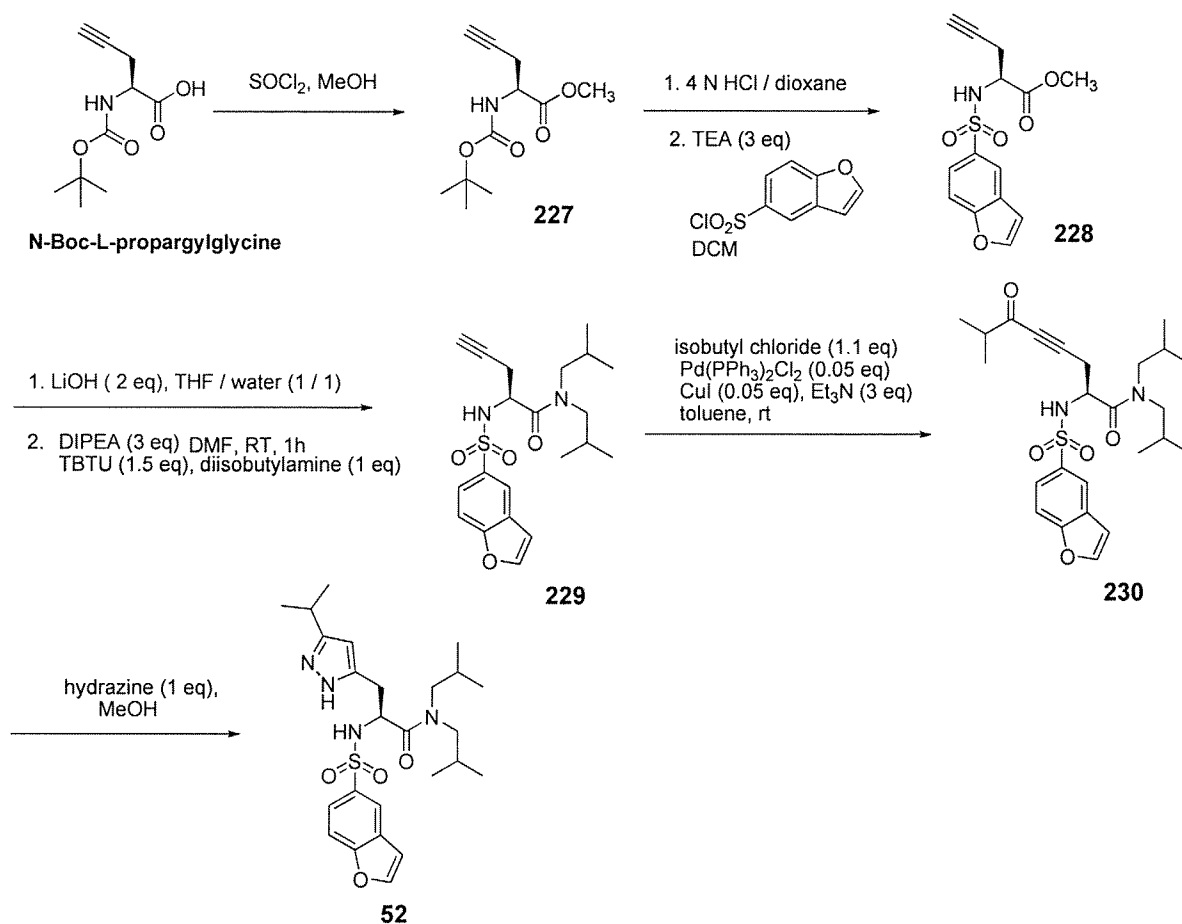
5 To a solution of tert-butyl 2-(diisobutylamino)-2-oxoethylcarbamate (1.6 g, 5.6 mmol) in dichloromethane (15 ml) was added 4N HCl in dioxane (8 ml). The mixture was stirred for 1 hr at room temperature and concentrated *in vacuo*. To a solution of the resulting material in dichloromethane (8 ml) were added triethylamine (1.6 ml, 11.2 mmol) and benzofuran-5-sulfonyl chloride (1.5 g, 6.7 mmol). After 30 min, water (15 ml) was
10 added to quench the reaction. The aqueous phase was extracted with dichloromethane (15 ml) and the organic layer was washed with brine (15 ml), dried over magnesium sulfate and concentrated *in vacuo*. The crude material was purified by flash column chromatography (40% EtOAc in hexanes) to provide compound **226** (1.6 g, 78%) as a white solid. $[\text{M}+\text{H}]^+$ 367.3, $[\text{2M}+\text{Na}]^+$ 755.0, HPLC purity: 99%.

15 To a solution of compound **226** (89 mg, 0.24 mmol) in DMF (2 ml) were added sodium hydride (14 mg, 0.36 mmol) and 2-(chloromethyl)-1-methyl-1H-imidazole HCl (48 mg, 0.29 mmol). After 1 hr, water (5 ml) was added to quench the reaction. The aqueous phase was extracted with EtOAc (5 ml) and the organic layer was washed with brine (5 ml), dried over anhydrous MgSO_4 and concentrated *in vacuo*. The residue was purified by
20 preparative TLC (10% dichloromethane in MeOH) to provide compound **84** (75 mg, 67%) as a white solid. $[\text{M}+\text{H}]^+$ 461.2, HPLC purity: >99%.

Example 9b: Preparation of N,N-diisobutyl-2-(N-(2-(3-methyl-1H-pyrazol-1-yl)ethyl)benzofuran-5-sulfonamido)acetamide (87)

To a solution of compound **226** (54 mg, 0.14 mmol) in DMF/acetonitrile (1:1, 4 ml)
25 were added potassium carbonate (97 mg, 0.70 mmol) and 1-(2-chloroethyl)-3-methyl-1H-pyrazole (22 mg, 0.15 mmol) and the resulting mixture stirred at 80 °C. After 3 hrs, water (7 ml) was added to quench the reaction. The aqueous phase was extracted with EtOAc (10 ml) and the organic layer was washed with brine (10 ml), dried over anhydrous MgSO_4 and concentrated *in vacuo*. The crude material was purified by preparative TLC (50% EtOAc
30 in hexanes) to provide compound **87** (35 mg, 53%) as a colorless oil. $[\text{M}+\text{H}]^+$ 475.2, HPLC purity: >99%.

Example 10: Preparation of (S)-2-(benzofuran-5-sulfonamido)-N,N-diisobutyl-3-(3-isopropyl-1H-pyrazol-5-yl)propanamide (52)



5 Compound **227** was prepared as described in *Organic Letters* 2000 Vol 2, No. 24, 3857-3860. To a solution of compound **227** (300 mg, 1.3 mmol) in dichloromethane (8 ml) was added 4N HCl in dioxane (1 ml). The mixture was stirred for 1 hr at room temperature and concentrated *in vacuo*. To a solution of the resulting material in dichloromethane (4 ml) were added triethylamine (558 μl , 4.0 mmol) and benzofuran-5-sulfonyl chloride (429 mg, 1.9 mmol). After 30 min, the mixture was concentrated *in vacuo*. The residue was purified by preparative TLC (50% EtOAc in hexanes) to provide
10 compound **228** (339 mg, 83%) as a colorless oil. $[\text{M}+\text{H}]^+$ 308.0, HPLC purity: >99%.

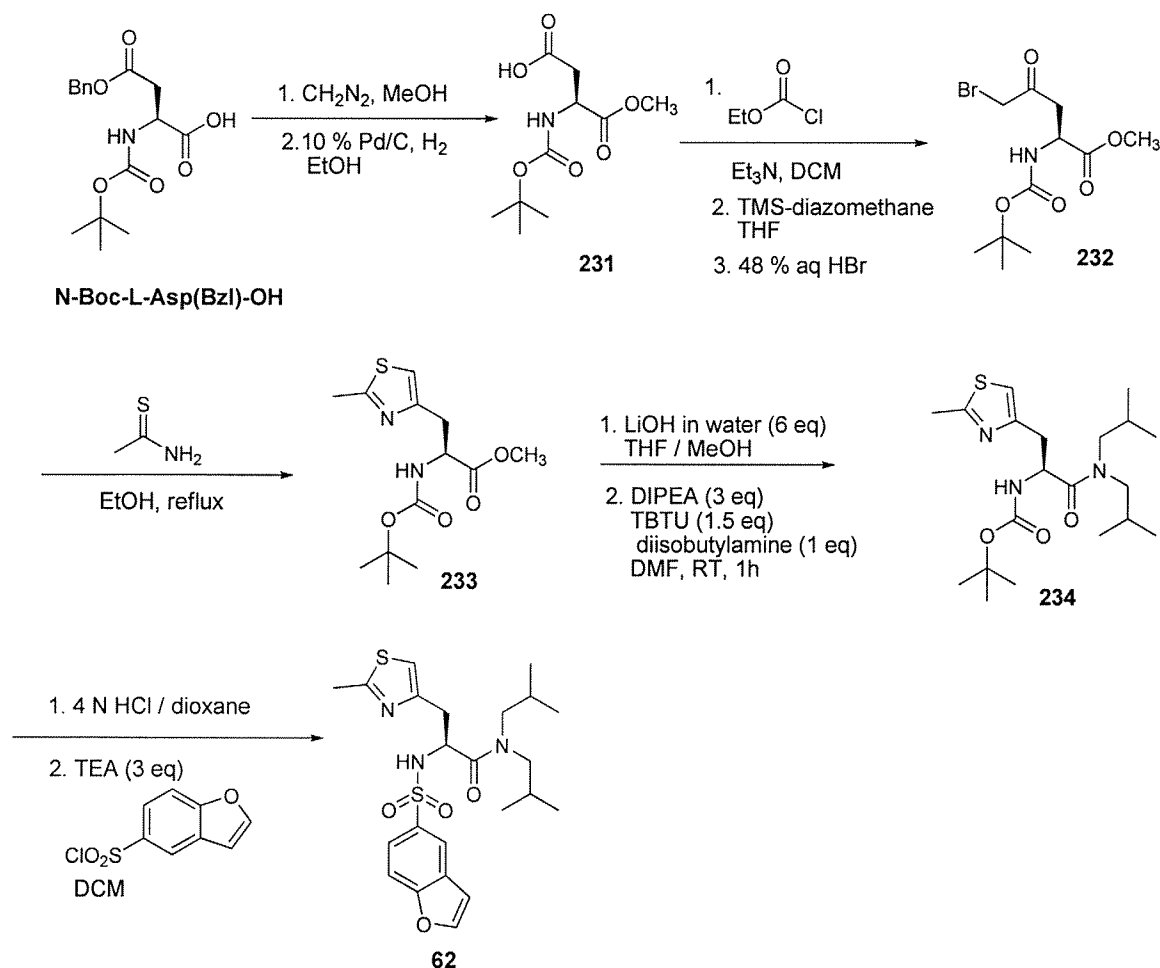
To a solution of compound **228** (339 mg, 1.1 mmol) in tetrahydrofuran/water (1:1, 8 ml) was added lithium hydroxide (53 mg, 2.2 mmol). The mixture was stirred for 3 hrs at
15 room temperature, quenched with aqueous 1N HCl (10 ml) and extracted with EtOAc (10

ml). The organic phase was washed with brine (10 ml), dried over anhydrous MgSO_4 and concentrated *in vacuo*. To a solution of the resulting compound in DMF (2 ml) were added diisobutylamine (0.20 ml, 1.1 mmol), DIPEA (0.60 ml, 3.3 mmol), and TBTU (620 mg, 1.7 mmol). The mixture was stirred for 1 hr at room temperature, quenched with saturated aqueous sodium bicarbonate (10 ml), and extracted with EtOAc (10 ml). The organic phase was washed with brine (10 ml), dried over anhydrous MgSO_4 and concentrated *in vacuo*. The crude material was purified by preparative TLC (50% EtOAc in hexanes) to provide compound **229** (102 mg, 23%) as a colorless oil. $[\text{M}+\text{H}]^+$ 405.0, HPLC purity: 99%.

Compound **52** was prepared using a procedure described in WO2005/044817. To a solution of compound **229** (102 mg, 0.25 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (9.0 mg, 0.013 mmol) and CuI (2.5 mg, 0.013 mmol) in triethylamine (104 μl , 0.75 mmol) and toluene (4 ml) was added isobutyryl chloride (29 μl , 0.28 mmol) at 0°C. The resulting mixture was stirred at room temperature overnight and treated with saturated aqueous sodium bicarbonate (5 ml). The organic phase was separated, dried over anhydrous MgSO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC (50% EtOAc in hexanes) to provide compound **230** (60 mg, 50%) as a yellowish oil. $[\text{M}+\text{H}]^+$ 475.2, $[\text{M}+\text{Na}]^+$ 497.2, HPLC purity: >99%.

To a solution of compound **230** (60 mg, 0.13 mmol) in MeOH (4 ml) was added hydrazine (5 μl , 0.15 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 30 min and then concentrated *in vacuo*. The residue was purified by preparative HPLC to provide compound **52** (30 mg, 41%) as a brownish oil. $[\text{M}+\text{H}]^+$ 489.2, HPLC purity: >99%.

Example 11: Preparation of (S)-2-(benzofuran-5-sulfonamido)-N,N-diisobutyl-3-(2-methylthiazol-4-yl)propanamide (62)



To a solution of Boc-L-Asp(Bzl)-OH (5.0 g, 15.5 mmol) in methanol (50 ml) was added diazomethane (7.8 ml, 15.5 mmol). The mixture was stirred for 1 hr at room temperature and concentrated *in vacuo*. To a solution of the resulting compound in ethanol (50 ml) was added 10% palladium on charcoal and the mixture hydrogenated for 3 hrs at room temperature, filtered through Celite and concentrated *in vacuo*. The crude material was purified by flash column chromatography (30% EtOAc in hexanes) to provide compound **231** (2.6 g, 69%) as a white solid. Compound **232** (2.0 g, 65%, colorless oil) was prepared as described in *Journal of Medicinal Chemistry*, 2007, Vol. 50, No. 8, 1850-1864.

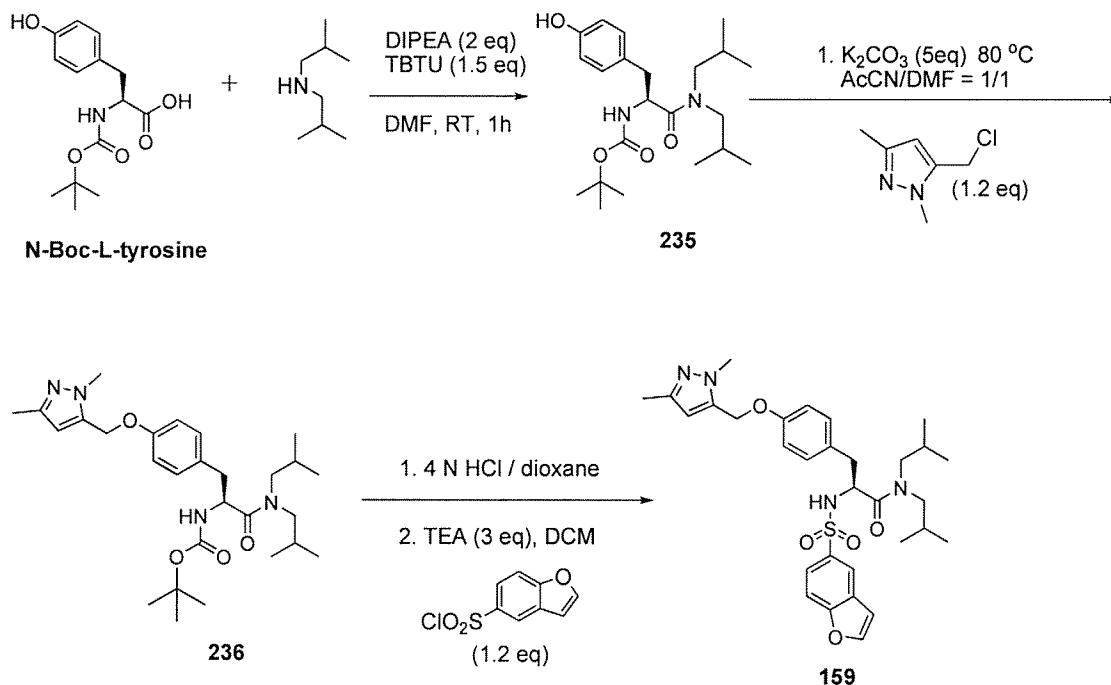
To a solution of compound **232** (200 mg, 0.62 mmol) in EtOH (4 ml) was added thioacetamide (40 μl , 0.68 mmol) and the resulting mixture refluxed at 90 °C. After 16 hrs, the mixture was concentrated *in vacuo*. The residue was purified by preparative TLC (50%

EtOAc in hexanes) to provide compound **233** (100 mg, 53%) as a yellowish oil. $[M+H]^+$ 301.0, HPLC purity: 90%.

To a solution of compound **233** (100 mg, 0.33 mmol) in tetrahydrofuran/MeOH (3:1, 5 ml) was added lithium hydroxide in water (2.5 M, 0.15 ml, 0.36 mmol). The mixture was stirred for 3 hrs at room temperature, quenched with aqueous 1N HCl (5 ml), and extracted with EtOAc (7 ml). The organic phase was washed with brine (5 ml), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. To a solution of the residue in DMF (2 ml) were added diisobutylamine (57 μ l, 0.33 mmol), DIPEA (0.17 ml, 0.99 mmol), and TBTU (159 mg, 0.49 mmol). The mixture was stirred for 1 hr at room temperature, quenched with saturated aqueous sodium bicarbonate (7 ml) and extracted with EtOAc (7 ml). The organic phase was washed with brine (10 ml), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by preparative TLC (50% EtOAc in hexanes) to provide compound **234** (83 mg, 64%) as a colorless oil. $[M+H]^+$ 398.3, HPLC purity: 99%.

To a solution of compound **234** (83 mg, 0.21 mmol) in dichloromethane (2 ml) was added 4N HCl in dioxane (2 ml). The mixture was stirred for 1 hr at room temperature and concentrated *in vacuo*. To a solution of the resulting material in dichloromethane (4 ml) were added triethylamine (88 μ l, 0.63 mmol) and benzofuran-5-sulfonyl chloride (68 mg, 0.32 mmol). After 30 min, water (4 ml) was added to quench the reaction. The aqueous phase was extracted with dichloromethane (5 ml) and the organic layer was washed with brine (4 ml), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by preparative TLC (50% EtOAc in hexanes) to provide compound **62** (45 mg, 45%) as a white solid. $[M+H]^+$ 478.0, $[2M+Na]^+$ 977.2, HPLC purity: 99%.

Example 11: Preparation of (S)-2-(benzofuran-5-sulfonamido)-3-(4-((1,3-dimethyl-1H-pyrazol-5-yl)methoxy)phenyl)-N,N-diisobutylpropanamide (159)



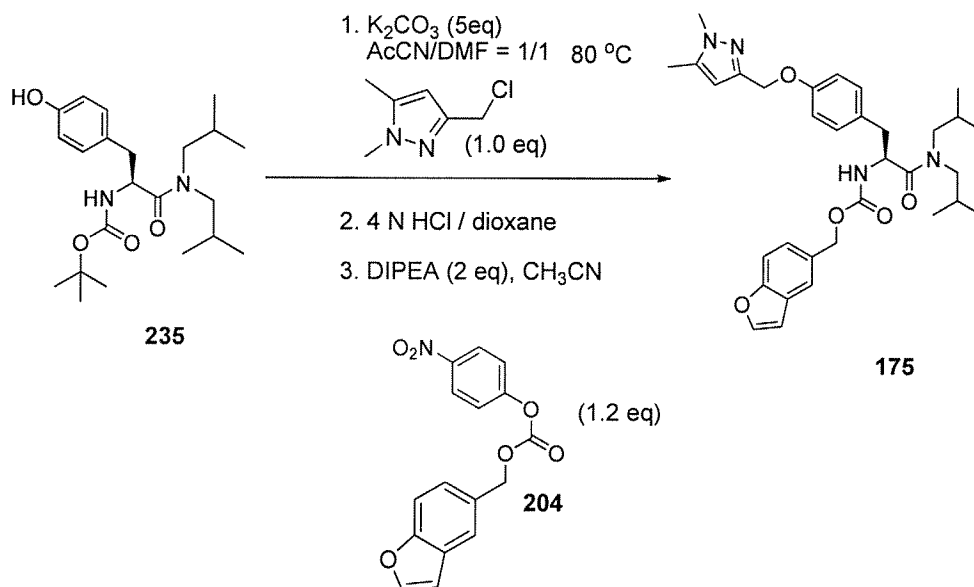
Compound **235** was prepared following the procedure for Scheme 1 except that instead of Boc-L-3-pyridylalanine N-Boc-L-tyrosine was used as the starting material. To a solution of compound **235** (205 mg, 0.52 mmol) in DMF/acetonitrile (1:1, 8 ml) were added potassium carbonate (359 mg, 2.6 mmol) and 5-chloromethyl-1,3-dimethylpyrazole (90 mg, 0.62 mmol). The mixture was stirred at 80 °C. After 3 hrs, water (7 ml) was added to quench the reaction. The aqueous phase was extracted with EtOAc (10 ml) and the organic layer was washed with brine (10 ml), dried over anhydrous $MgSO_4$ and then concentrated *in vacuo*. The crude material was purified by flash column chromatography (50% EtOAc in hexanes) to provide compound **236** (200 mg, 77%) as a colorless oil. **[M+H]⁺ 501.2, HPLC purity: >99%.**

To a solution of compound **236** (200 mg, 0.40 mmol) in dichloromethane (4 ml) was added 4N HCl in dioxane (4 ml). The mixture was stirred for 1 hr at room temperature and concentrated *in vacuo*. To a solution of the resulting material in dichloromethane (4 ml) was added triethylamine (63 μ l, 0.45 mmol) and benzofuran-5-sulfonyl chloride (39 mg, 0.18 mmol). After 30 min, water (5 ml) was added to quench the reaction. The aqueous phase was extracted with dichloromethane (5 ml) and the organic layer was washed with brine (5 ml), dried over anhydrous $MgSO_4$ and then concentrated *in*

vacuo. The crude material was purified by preparative TLC (EtOAc) to provide compound **159** (71 mg, 80%) as a white solid. $[M+H]^+$ 581.3, HPLC purity: >99%.

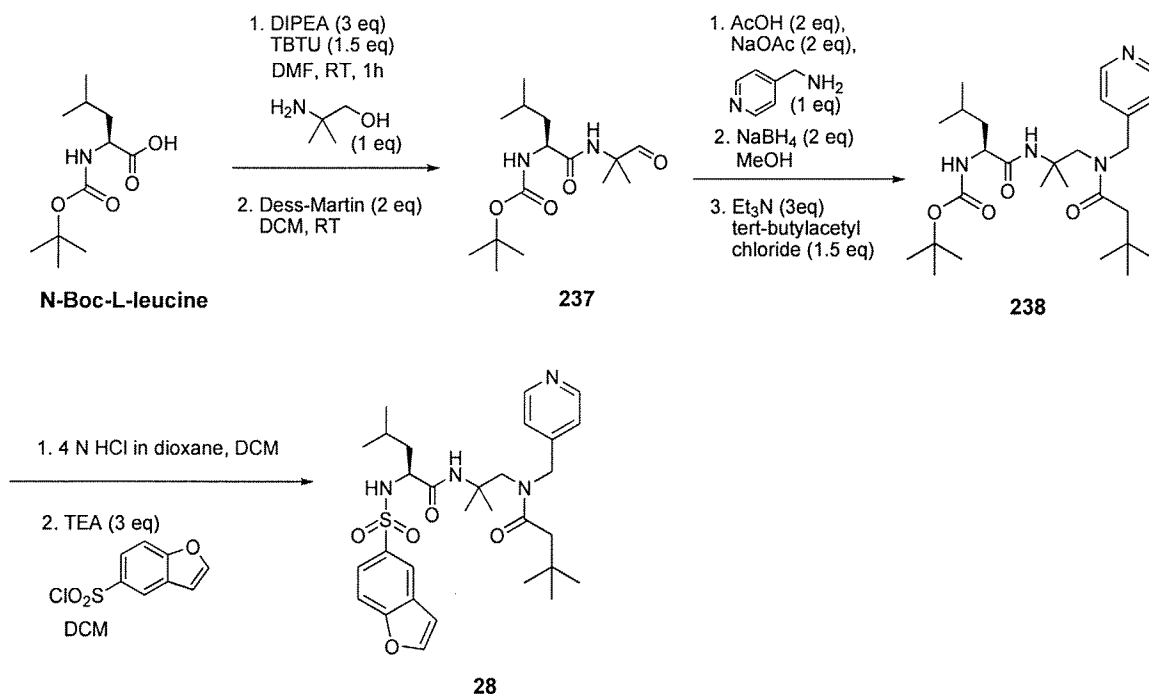
Example 12: Preparation of (S)-benzofuran-5-ylmethyl 1-(diisobutylamino)-3-(4-((1,5-dimethyl-1H-pyrazol-3-yl)methoxy)phenyl)-1-oxopropan-2-ylcarbamate (175)

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To a solution of compound **235** (197 mg, 0.50 mmol) in DMF/acetonitrile (1:1, 8 ml) were added potassium carbonate (346 mg, 2.50 mmol) and 3-chloromethyl-1,5-dimethylpyrazole (72 mg, 0.50 mmol). The mixture was stirred at 80 °C. After 3 hrs, water (7 ml) was added to quench the reaction. The aqueous phase was extracted with EtOAc (10 ml) and the organic layer was washed with brine (10 ml), dried over anhydrous MgSO₄ and then concentrated *in vacuo*. To a solution of the residue in dichloromethane (4 ml) was added 4N HCl in dioxane (4 ml). The mixture was stirred for 1 hr at room temperature and then concentrated *in vacuo*. To a solution of the residue in acetonitrile (4 ml) was added DIPEA (49 µl, 0.28 mmol) and compound **204** (53 mg, 0.17 mmol). After 30 min, water (10 ml) was added to quench the reaction. The aqueous phase was extracted with dichloromethane (10 ml) and the organic layer was washed with brine (5 ml), dried over anhydrous MgSO₄ and then concentrated *in vacuo*. The crude material was purified by preparative TLC (10% MeOH in dichloromethane) to provide compound **175** (24 mg, 30%) as a colorless oil. $[M+H]^+$ 575.0, HPLC purity: 98%.

Example 13: Preparation of (S)-2-(benzofuran-5-sulfonamido)-N-(1-(3,3-dimethyl-N-(pyridin-4-ylmethyl)butanamido)-2-methylpropan-2-yl)-4-methylpentanamide (28)



To a solution of Boc-L-leucine (1.0 g, 4.0 mmol) in DMF (4 ml) were added 2-amino-2-methyl-1-propanol (382 μ l, 4.0 mmol), DIPEA (2.1 ml, 12.0 mmol) and TBTU (1.9 g, 6.0 mmol). The mixture was stirred for 1 hr at room temperature, quenched with saturated aqueous sodium bicarbonate (15 ml), and extracted with EtOAc (20 ml). The organic phase was washed with brine (15 ml), dried over anhydrous MgSO₄ and concentrated *in vacuo*. To a solution of the residue in dichloromethane (12 ml) was added Dess-Martin periodinane (3.3 g, 8.0 mmol). The mixture was stirred for 2 hrs at room temperature. The mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (50% EtOAc in hexanes) to provide compound **237** (620 mg, 53%) as a white solid. **[M+H]⁺ 301.2, HPLC purity: 98%.**

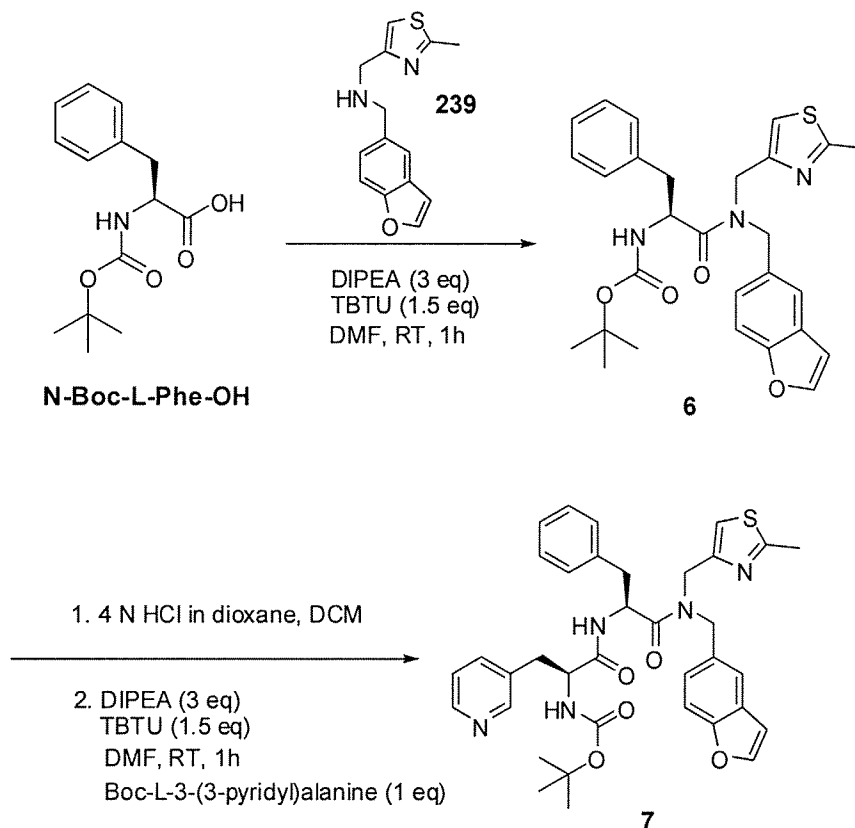
To a solution of compound **237** (123 mg, 0.41 mmol) in methanol (3 ml) were added 4-(aminomethyl)pyridine (41 μ l, 0.41 mmol), acetic acid (24 μ l, 0.41 mmol) and sodium acetate (34 mg, 0.41 mmol). The mixture was stirred for 30 min at room temperature and then treated with sodium borohydride (31 mg, 0.82 mmol). After 1 hr, saturated aqueous sodium bicarbonate (5 ml) was added to quench the reaction. The aqueous phase was extracted with EtOAc (8 ml) and the organic layer was washed with brine (5 ml), dried over anhydrous MgSO₄ and concentrated *in vacuo*. To a solution of the resulting material in dichloromethane (2 ml) were added triethylamine (71 μ l, 0.51 mmol) and tert-butylacetyl chloride (36 μ l, 0.26 mmol). The mixture was stirred for 1 hr at room temperature and concentrated *in vacuo*. The residue was purified by flash column

chromatography (50% EtOAc in hexanes) to provide compound **238** (49 mg, 59%) as a white solid. $[M+H]^+$ 491.2, $[M+Na]^+$ 513.3, HPLC purity: 98%.

To a solution of compound **238** (49 mg, 0.10 mmol) in dichloromethane (2 ml) was added 4N HCl in dioxane (2 ml). The mixture was stirred for 1 hr at room temperature and then concentrated *in vacuo*. To a solution of the resulting material in dichloromethane (4 ml) were added triethylamine (42 μ l, 0.32 mmol) and benzofuran-5-sulfonyl chloride (32 mg, 0.15 mmol). After 30 min, water (4 ml) was added to quench the reaction. The aqueous phase was extracted with dichloromethane (5 ml) and the organic layer was washed with brine (4 ml), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by preparative TLC (50% EtOAc in hexanes) to provide compound **28** (31 mg, 53%) as a white solid. $[M+H]^+$ 571.2, $[M+Na]^+$ 593.3, HPLC purity: 98%

Example 14: Synthesis of Compounds (6) and (7)

The synthesis of compounds **6** and **7** are outlined in the scheme below. The individual synthesis of those compounds are described in parts 14a, and 14b of Example 14.



Example 14a: Preparation of (S)-tert-butyl 1-((benzofuran-5-ylmethyl)((2-methylthiazol-4-yl)methyl)amino)-1-oxo-3-phenylpropan-2-ylcarbamate (6)

To a solution of benzofuran-5-yl-methylamine (65 mg, 0.44 mmol) in MeOH (4 ml) were added 2-methyl-1,3-thiazole-4-carbaldehyde (56 mg, 0.44 mmol), acetic acid (25 μ l, 0.44 mmol) and sodium acetate (36 mg, 0.44 mmol). The mixture was stirred for 30 min at room temperature and treated with sodium borohydride (33 mg, 0.88 mmol). After 1 hr, aqueous sodium bicarbonate (5 ml) was added to quench the reaction. The aqueous phase was extracted with EtOAc (7 ml) and the organic layer was washed with brine (5 ml), dried over anhydrous MgSO_4 and concentrated *in vacuo*. The crude material was purified by preparative TLC (10% MeOH in dichloromethane) to provide compound **239** (77mg, 68%) as a white solid. $[\text{M}+\text{H}]^+$ 259.0, HPLC purity: >99%.

To a solution of Boc-L-Phe-OH (41 mg, 0.15 mmol) in DMF (1 ml) were added compound **239** (40 mg, 0.15 mmol), DIPEA (79 μ l, 0.45 mmol), and TBTU (86 mg, 0.22 mmol). The mixture was stirred for 1 hr at room temperature, quenched with saturated aqueous sodium bicarbonate (7 ml), and extracted with EtOAc (4 ml). The organic phase was washed with brine (7 ml), dried over anhydrous MgSO_4 and concentrated *in vacuo*. The crude material was purified by preparative TLC (30% EtOAc in hexanes) to provide compound **6** (53 mg, 67%) as a white solid. $[\text{M}+\text{H}]^+$ 506.0, $[\text{M}+\text{Na}]^+$ 528.0, HPLC purity: >99%.

Example 14b: Preparation of tert-butyl (S)-1-((S)-1-((benzofuran-5-ylmethyl)((2-methylthiazol-4-yl)methyl)amino)-1-oxo-3-phenylpropan-2-ylamino)-1-oxo-3-(pyridin-3-yl)propan-2-ylcarbamate (7)

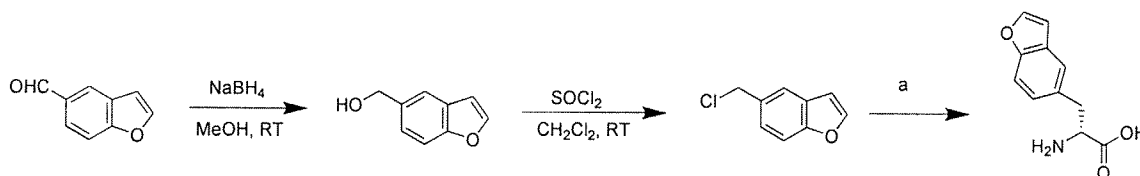
To a solution of compound **6** (30 mg, 0.06 mmol) in dichloromethane (2 ml) was added 4N HCl in dioxane (2 ml). The mixture was stirred for 1 hr at room temperature and then concentrated *in vacuo*. To a solution of residue in DMF (2 ml) were added N-Boc-L-3-(3-pyridyl)alanine (16 mg, 0.06 mmol), DIPEA (31 μ l, 0.18 mmol), and TBTU (34 mg, 0.090 mmol). The mixture was stirred for 1 hr at room temperature, quenched with saturated aqueous sodium bicarbonate (7 ml) and extracted with EtOAc (7 ml). The organic phase was washed with brine (10 ml), dried over anhydrous MgSO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc) to provide compound **7** (22 mg, 56%) as a white solid. $[\text{M}+\text{H}]^+$ 654.3, HPLC purity: 99%.

Example 15: A General procedure

Compounds of formula (I) bearing benzofuranyl groups at the alpha carbon may generally be prepared by the following procedure from benzofurylalanine, as follows.

D-Benzofurylalanine.HCl is dissolved in water and reacted with (Boc)₂O and 2 eq. 1N NaOH. After the completion of the reaction, solvent is removed *in vacuo* and the crude product purified to furnish the Boc derivative. This compound is reacted with a primary or a secondary amine (1 eq), TBTU (1.5 eq) and Et₃N (3 eq) in anhydrous DMF. After the completion of the reaction DMF is removed *in vacuo* and the crude material is purified to furnish the amide. The amide is reacted with 20% TFA/CH₂Cl₂ at room temperature. After the completion of the reaction, solvent is removed *in vacuo* and the residue is reacted with a carbonyl or sulfonyl chloride (1 eq), Et₃N (3 eq), and DMAP in CH₂Cl₂. After completion of the reaction solvent is removed and the crude product purified to furnish the target compound(s).

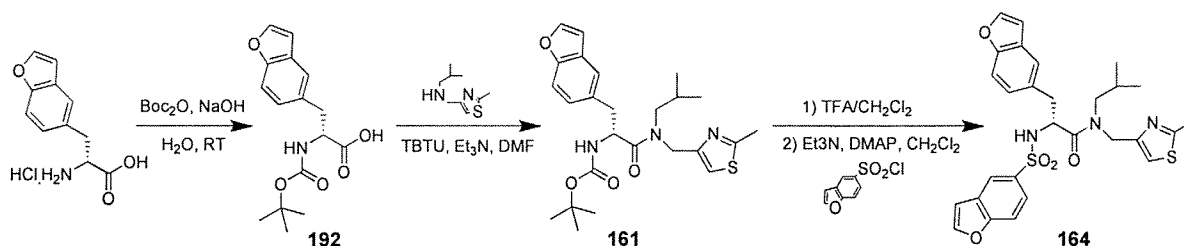
The preparation of D-benzofurylalanine for use in this general procedure may be conducted as described in the following example.

Example 16: Synthesis of D-benzofuryl alanine

A solution of 5-benzofurancarboxaldehyde (10 g, 68 mmol) in MeOH (40 mL) was cooled in an ice bath. NaBH₄ (3.84 g, 102 mmol) was added over a period of 2 hr and stirring continued for 20 min. Saturated NH₄Cl was added. The mixture was suspended in ethyl acetate (100 mL) and the solid was filtered off. The solution was concentrated, partitioned between ethyl acetate and brine, dried over anhydrous Na₂SO₄, concentrated and dried under high vacuum to furnish benzofuran-5-ylmethanol (10 g, 100%) as a solid, which was taken up in CH₂Cl₂ (60 mL) to which SOCl₂ (5.9 mL, 81 mmol) was added at room temperature. The reaction mixture was stirred for 3 hr. The reaction mixture was diluted with CH₂Cl₂, washed with a saturated solution of NaHCO₃, then brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo* to furnish 5-chloromethylbenzofuran (10 g, 90%) as an oil. This material was used without further purification to synthesize D-benzofurylalanine according to C. Behrens, *Tetrahedron* 56 (2000), 9443-9449.

Example 17: Synthesis of Compounds (161) and (164)

The synthesis of compounds **161** and **162** are outlined in the scheme below. The individual synthesis of those compounds are described in parts 17a and 17b of Example 17.



5

Example 17a: Preparation of (R)-tert-butyl 3-(benzofuran-5-yl)-1-(isobutyl((2-methylthiazol-4-yl)methyl)amino)-1-oxopropan-2-ylcarbamate

To a solution of D-benzofurylalanine.HCl (3.00 g, 12.4 mmol) in water (150 mL) was added 1N NaOH (25 mL) followed by di-tert-butyl dicarbonate (3.00 g, 13.7 mmol) and the mixture was stirred at RT for 20 hr. The pH was adjusted to 3 by the addition of 2 N HCl and the mixture then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and the solvent evaporated *in vacuo*. The crude material was purified by flash column chromatography using 10% MeOH in CH₂Cl₂ to furnish 2.2 g (58%) of compound **192** [M-H]⁻ 304.0, [M+H]⁺ - Boc 206.0.

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A solution of compound **192** (40 mg, 0.13 mmol), TBTU (63 mg, 195 mmol) and Et₃N in DMF (2 mL) was stirred at RT for 20 min and then added to a solution of 2-methyl-N-((2-methylthiazol-4-yl)methyl)methan-1-amine (24 mg, 0.13 mmol) in DMF (2 mL) and the resulting mixture stirred at RT for 3 hr. The DMF was removed *in vacuo* and the crude material was purified by Prep TLC using 4% MeOH in CH₂Cl₂ to furnish 45 mg (74%) of compound **161** as a white solid [M+H]⁺ 472.0, HPLC purity 95%.

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Example 17b: Preparation of (R)-2-(benzofuran-5-sulfonamido)-3-(benzofuran-5-yl)-N-isobutyl-N-((2-methylthiazol-4-yl)methyl)propanamide
164

Compound **161** (30 mg, 0.064 mmol) was stirred with 20% TFA/CH₂Cl₂ (5 mL) at RT for 20 min and then concentrated *in vacuo* to furnish the amine TFA salt. 10 mg (0.021 mmol) of this compound, Et₃N (9.0 μL, 0.063 mmol) and DMAP (1 mg, 0.008 mmol) in CH₂Cl₂ (1 mL) were added to a cold (ice bath) solution of 5-benzofuransulfonylchloride (5.4 mg, 0.025 mmol) in CH₂Cl₂ (1 mL). The reaction mixture was warmed to RT and stirred for 20 min. It was then concentrated *in vacuo* and the residue purified by Prep TLC

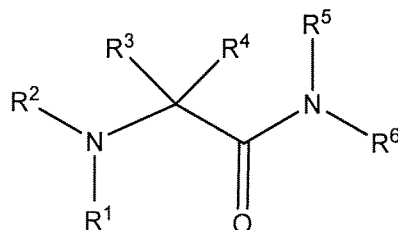
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using 4% MeOH in CH₂Cl₂ to furnish 9.0 mg (78%) compound **164** as a white solid
[M+H]⁺ 552.0, HPLC purity 95%.

Variations, modifications, and other implementations of what is described herein
will occur to those of ordinary skill in the art without departing from the spirit and the
5 scope of the technology. Accordingly, the technology is not to be limited only to the
preceding illustrative descriptions.

What is claimed is:

1. A compound, its stereoisomeric forms, and pharmacologically acceptable salts thereof, said compound having the formula:



where:

each R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 independently is selected from the group consisting of H, optionally substituted C_1 - C_8 alkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted heterocyclo-, optionally substituted heterocycloalkylalkyl, $-\text{SO}_n(\text{R})$, and $-(\text{CH}_2)_{0-6}\text{CO}_n(\text{CH}_2)_{0-3}-\text{R}$;

wherein at least one of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is $-\text{S}(\text{O})_n-(\text{CH}_2)_{0-3}-(\text{benzofuranyl})$, $-(\text{CH}_2)_{1-5}-\text{N}(\text{R})(-\text{SO}_2-\text{benzofuranyl})$, $-\text{C}(\text{O})_n-(\text{CH}_2)_{0-3}-(\text{benzofuranyl})$, $-(\text{CH}_2)_{1-5}-\text{N}(\text{R})(\text{C}(\text{O})-(\text{benzofuranyl}))$, or C_1 - C_6 alkylene-(benzofuranyl), wherein said benzofuranyl substituent may be substituted with an optional substituent, and wherein the benzofuranyl group is not fused as part of a tricyclic system;

each optional substituent is selected from the group consisting of halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_n\text{R}$, $-\text{OC}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{C}(\text{S})\text{R}$, $-\text{C}(\text{S})\text{N}(\text{R})_2$, $-\text{SO}_n\text{N}(\text{R})_2$, $-\text{SR}$, $-\text{SO}_n\text{R}$, $-\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{CO}_n\text{R}$, $-\text{NRS}(\text{O})_n\text{R}$, $-\text{NRC}[\text{N}(\text{R})]\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{N}(\text{R})\text{CO}_n\text{R}$, $-\text{NRPO}_n\text{N}(\text{R})_2$, $-\text{NRPO}_n\text{OR}$, oxo, $=\text{N}-\text{OR}$, $=\text{N}-\text{N}(\text{R})_2$, $=\text{NR}$, $=\text{NNRC}(\text{O})\text{N}(\text{R})_2$, $=\text{NNRCO}_n\text{R}$, $=\text{NNRS}(\text{O})_n\text{N}(\text{R})_2$, $=\text{NNRS}(\text{O})_n(\text{R})\text{C}_1$ - C_8 alkyl, $-\text{OR}$, C_1 - C_8 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, C_5 - C_8 cycloalkenyl, heterocyclo-, aryl, and heteroaryl;

each R is independently selected from the group consisting of: H, C_1 - C_8 alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, and when R is directly bound to a nitrogen, R may additionally be selected from $-\text{C}(\text{O})_n\text{alkyl}$, $-\text{S}(\text{O})_n\text{alkyl}$, $-\text{C}(\text{O})_n\text{-aryl}$, $-\text{S}(\text{O})_n\text{-aryl}$, or $-\text{S}(\text{O})_n\text{-heteroaryl}$, wherein when R is a group selected from aryl, aralkyl, heteroaryl, heteroaralkyl, $-\text{C}(\text{O})_n\text{-aryl}$, $-\text{S}(\text{O})_n\text{-aryl}$, or

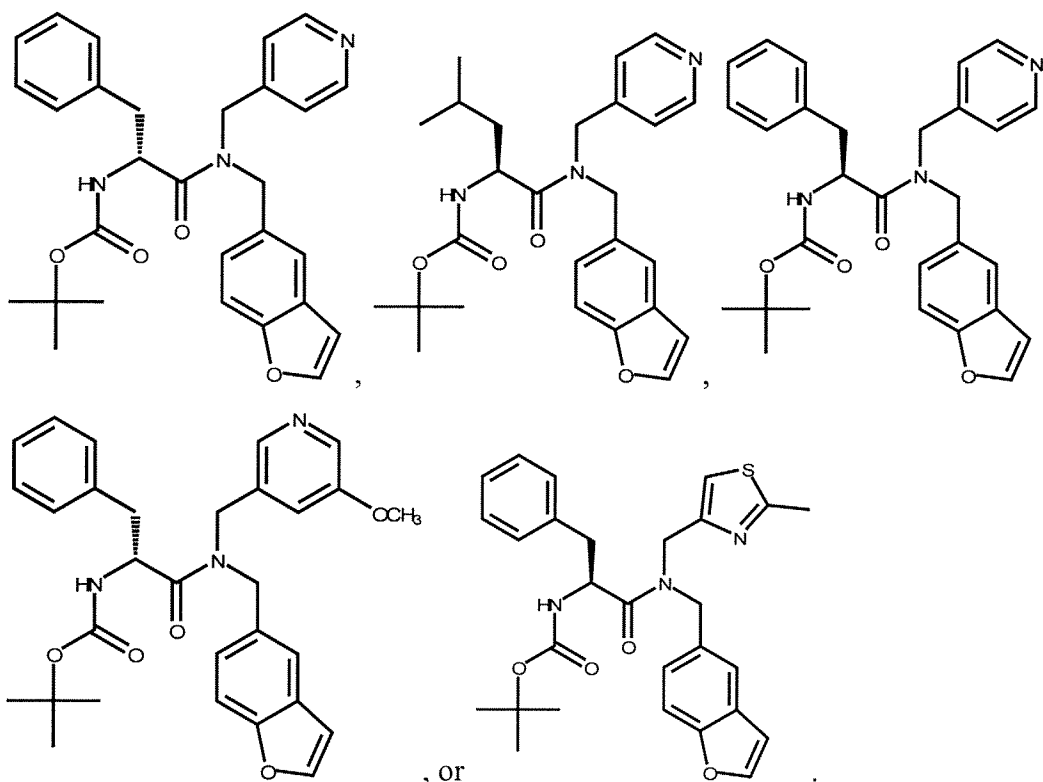
$-S(=O)_n$ -heteroaryl, the group may substituted with one or more independently selected C_1 - C_6 alkyls;

each n is independently 1 or 2;

provided that at least two of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are not H;

provided that neither R^5 nor R^6 forms a ring with R^1 , R^2 , R^3 , or R^4 ; and

provided that the compound is not



2. A compound, according to claim 1, wherein:

each R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 independently is selected from the group consisting of H, optionally substituted C_1 - C_8 alkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted heterocyclo, optionally substituted heterocycloalkylalkyl, $-SO_n(R)$, and $-(CH_2)_{0-6}CO_n(CH_2)_{0-3}-R$;

wherein at least one of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is $-S(O)_n$ -(benzofuranyl), $-C(O)_n$ -(benzofuranyl), $-C(=O)O(CH_2)_{1-3}$ -(benzofuranyl), or C_1 - C_6 alkylene-(benzofuranyl), wherein said benzofuranyl substituent may be substituted with an optional substituent and wherein the benzofuranyl group is not fused as part of a tricyclic system;

each optional substituent is selected from the group consisting of halo, $-\text{OC}(=\text{O})\text{R}$, $-\text{C}(=\text{O})\text{N}(\text{R})_2$, $-\text{C}(=\text{S})\text{R}$, $-\text{C}(=\text{S})\text{N}(\text{R})_2$, $-\text{SO}_n\text{N}(\text{R})_2$, $-\text{SR}$, $-\text{SO}_n\text{R}$, $-\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{CO}_n\text{R}$, $-\text{NRS}(=\text{O})_n\text{R}$, $-\text{NRC}[=\text{N}(\text{R})]\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{N}(\text{R})\text{CO}_n\text{R}$, $-\text{NRPO}_n\text{N}(\text{R})_2$, $-\text{NRPO}_n\text{OR}$, oxo, $-\text{OR}$, C_1 - C_8 alkyl, C_2 - C_6 alkenyl, C_3 - C_8 cycloalkyl, C_5 - C_8 cycloalkenyl, heterocyclo, aryl, and heteroaryl;

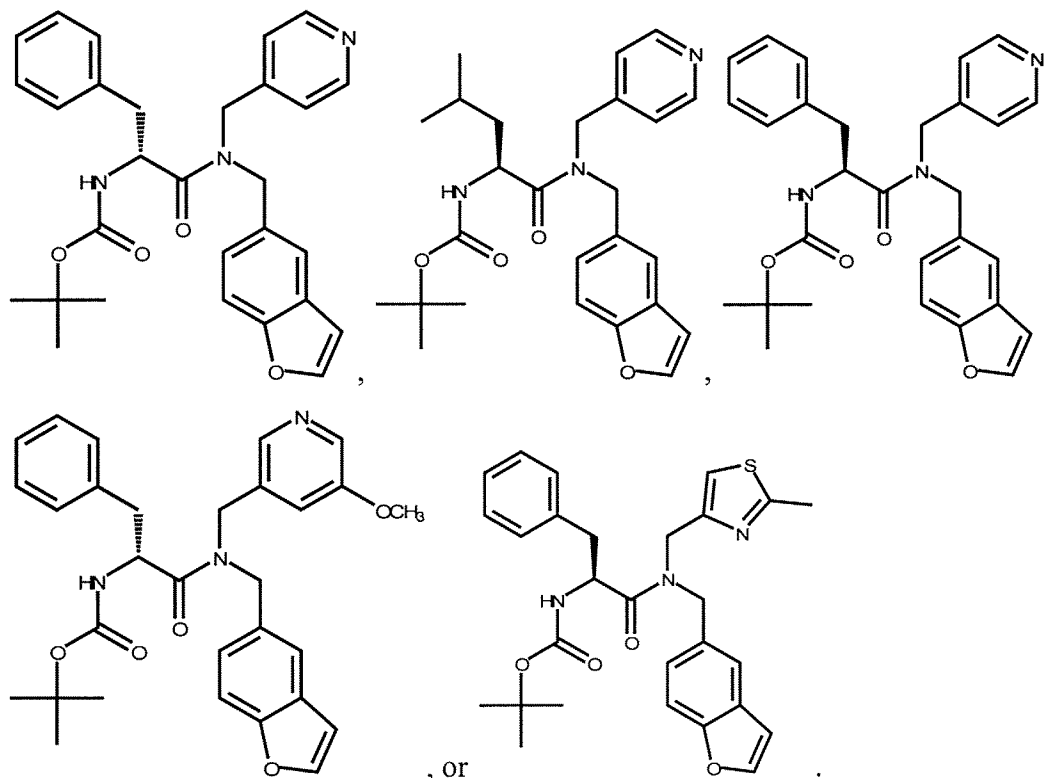
each R is independently selected from the group consisting of: H, C_1 - C_8 alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, and when R is directly bound to a nitrogen, R may additionally be selected from $-\text{C}(\text{O})_n\text{alkyl}$, $-\text{S}(\text{O})_n\text{alkyl}$, $-\text{C}(\text{O})_n\text{-aryl}$, $-\text{S}(=\text{O})_n\text{-aryl}$, or $-\text{S}(=\text{O})_n\text{-heteroaryl}$, wherein when R is a group selected from aryl, aralkyl, heteroaryl, heteroaralkyl, $-\text{C}(\text{O})_n\text{-aryl}$, $-\text{S}(=\text{O})_n\text{-aryl}$, or $-\text{S}(=\text{O})_n\text{-heteroaryl}$, the group may substituted with one or more independently selected C_1 - C_6 alkyls;

each n is independently 1 or 2;

provided that at least two of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are not H;

provided that neither R^5 nor R^6 forms a ring with R^1 , R^2 , R^3 , or R^4 ; and

provided that the compound is not



3. The compound according to claim 2, wherein:

each R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 independently is selected from the group consisting of H, optionally substituted C_1 - C_8 alkyl, optionally substituted C_3 - C_8 cycloalkyl,

optionally substituted cycloalkylalkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted heterocycloalkylalkyl, $-\text{SO}_n(\text{R})$, and $-(\text{CH}_2)_{0-6}\text{CO}_n(\text{CH}_2)_{0-3}-\text{R}$;

wherein at least one of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is $-\text{SO}_n(\text{benzofuranyl})$,

$-\text{C}(=\text{O})-(\text{benzofuranyl})$, or $\text{C}_1\text{-C}_3$ alkylene-(benzofuranyl), wherein said benzofuranyl substituent may be substituted with an optional substituent and wherein the benzofuranyl group is not fused as part of a tricyclic system;

each optional substituent is selected from the group consisting of halo, $-\text{OC}(=\text{O})\text{R}$, $-\text{C}(=\text{O})\text{N}(\text{R})_2$, $-\text{SO}_n\text{R}$, $-\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{CO}_n\text{R}$, $-\text{NRS}(=\text{O})_n\text{R}$, $-\text{NRC}[=\text{N}(\text{R})]\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{N}(\text{R})\text{CO}_n\text{R}$, $-\text{NRPO}_n\text{N}(\text{R})_2$, oxo, $-\text{OR}$, $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_5\text{-C}_8$ cycloalkenyl, heterocyclo, aryl, and heteroaryl;

each R is independently selected from the group consisting of: H, $\text{C}_1\text{-C}_8$ alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, and when R is directly bound to a nitrogen, R may additionally be selected from $-\text{C}(\text{O})_n\text{alkyl}$, $-\text{S}(\text{O})_n\text{alkyl}$, $-\text{C}(\text{O})_n\text{-aryl}$, $-\text{S}(=\text{O})_n\text{-aryl}$, or $-\text{S}(=\text{O})_n\text{-heteroaryl}$, wherein when R is a group selected from aryl, aralkyl, heteroaryl, heteroaralkyl, $-\text{C}(\text{O})_n\text{-aryl}$, $-\text{S}(=\text{O})_n\text{-aryl}$, or $-\text{S}(=\text{O})_n\text{-heteroaryl}$, the group may substituted with one or more independently selected $\text{C}_1\text{-C}_6$ alkyls.

4. The compound according to claim 3, wherein:

each R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 independently is selected from the group consisting of H, optionally substituted $\text{C}_1\text{-C}_8$ alkyl, optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, and $-(\text{CH}_2)_{0-6}\text{CO}_n(\text{CH}_2)_{0-3}-\text{R}$;

wherein at least one of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is $-\text{SO}_n(\text{benzofuranyl})$,

$-\text{C}(=\text{O})-(\text{benzofuranyl})$, or $\text{C}_1\text{-C}_3$ alkylene-(benzofuranyl), wherein said benzofuranyl is not otherwise substituted.

each optional substituent is selected from the group consisting of halo, $-\text{OC}(=\text{O})\text{R}$, $-\text{C}(=\text{O})\text{N}(\text{R})_2$, $-\text{SO}_n\text{R}$, $-\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{CO}_n\text{R}$, $-\text{NRS}(=\text{O})_n\text{R}$, $-\text{NRC}[=\text{N}(\text{R})]\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{N}(\text{R})\text{CO}_n\text{R}$, $-\text{NRPO}_n\text{N}(\text{R})_2$, oxo, $-\text{OR}$, $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_5\text{-C}_8$ cycloalkenyl, heterocyclo, aryl, and heteroaryl;

each R is independently selected from the group consisting of: H, $\text{C}_1\text{-C}_8$ alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, and when R is directly bound to a nitrogen, R may additionally be selected from $-\text{C}(\text{O})_n\text{alkyl}$, $-\text{S}(\text{O})_n\text{alkyl}$, $-\text{C}(\text{O})_n\text{-aryl}$,

-S(=O)_n-aryl, or -S(=O)_n-heteroaryl, wherein when R is a group selected from aryl, aralkyl, heteroaryl, heteroaralkyl, -C(O)_n-aryl, -S(=O)_n-aryl, or -S(=O)_n-heteroaryl, the group may substituted with one or more independently selected C₁-C₆ alkyls.

5. The compound according to one of claims 1-4, wherein at least one of R¹, R², R³, R⁴, R⁵, and R⁶ is -SO₂(benzofuranyl).

6. The compound according to one of claims 1-4, wherein at least one of R¹, R², R³, R⁴, R⁵, and R⁶ is -C(=O)-(benzofuranyl).

7. The compound according to one of claims 1-4, wherein at least one of R¹, R², R³, R⁴, R⁵, and R⁶ is -C(=O)O(CH₂)₁₋₃-(benzofuranyl).

8. The compound according to one of claims 1-4, wherein at least one of R¹, R², R³, R⁴, R⁵, and R⁶ is -CH₂-(benzofuranyl).

9. The compound according to one of claims 1-8, wherein at least three of R¹, R², R³, R⁴, R⁵, and R⁶ are not H.

10. The compound according to one of claims 1-8, wherein at least four of R¹, R², R³, R⁴, R⁵, and R⁶ are not H.

11. The compound according to one of claims 1-10 wherein one of R¹, R², R³, R⁴, R⁵, and R⁶ is -SO_n-(benzofuranyl), -C(=O)-(benzofuranyl), -C(=O)O(CH₂)₁₋₃-(benzofuranyl), or C₁-C₆ alkylene-(benzofuranyl), wherein said benzofuranyl present in said -SO_n-(benzofuranyl), -C(=O)-(benzofuranyl), -C(=O)O(CH₂)₁₋₃-(benzofuranyl) or C₁-C₆ alkylene-(benzofuranyl) may be substituted with an optional substituent and wherein the benzofuranyl group is not fused as part of a tricyclic system.

12. The compound according to one of claims 1-10 wherein two of R¹, R², R³, R⁴, R⁵, and R⁶ are independently selected from -SO_n-(benzofuranyl), -C(=O)-(benzofuranyl), -C(=O)O(CH₂)₁₋₃-(benzofuranyl), or C₁-C₆ alkylene-(benzofuranyl), wherein said benzofuranyl present in said -SO_n-(benzofuranyl), -C(=O)-(benzofuranyl), -C(=O)O(CH₂)₁₋₃-(benzofuranyl) or C₁-C₆ alkylene-(benzofuranyl) may be substituted with an optional substituent and wherein the benzofuranyl group is not fused as part of a tricyclic system.

13. The compound according to one of claims 1-10 wherein three or four of R¹, R², R³, R⁴, R⁵, and R⁶ are independently selected from -C₁-C₈ alkyl, -SO_n-(benzofuranyl), -C(=O)-(benzofuranyl), -C(=O)O(CH₂)₁₋₃-(benzofuranyl), or C₁-C₆ alkylene-

(benzofuranyl), wherein said benzofuranyl wherein said benzofuranyl present in said -SO_n-(benzofuranyl), -C(=O)-(benzofuranyl), -C(=O)O(CH₂)₁₋₃-(benzofuranyl) or C₁-C₆ alkylene-(benzofuranyl) may be substituted with an optional substituent and wherein the benzofuranyl group is not fused as part of a tricyclic system.

14. The compound according to one of claims 1-12 wherein at least one of R¹ or R² is not H.
15. The compound according to one of claims 1-12 wherein at least one of R³ or R⁴ is not H.
16. The compound according to one of claims 1-12 wherein at least one of R⁵ or R⁶ is not H.
17. The compound according to one of claims 1-12 wherein R¹ and R³ are not H.
18. The compound according to one of claims 1-12 wherein R¹ or R⁵ are not H.
19. The compound according to one of claims 1 or 2, wherein R⁵ is an otherwise unsubstituted -CH₂-4-benzofuranyl, -CH₂-5-benzofuranyl, -CH₂-6-benzofuranyl, or -CH₂-7-benzofuranyl.
20. The compound according to any one of claims 1, 2 or 19, wherein R³ is H and R⁴ is selected from the group consisting of H, optionally substituted C₁-C₈ alkyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted heterocyclo, and optionally substituted heterocycloalkylalkyl.
21. The compound according to any one of claims 1, 2, or 19-20 wherein R¹ or R² is optionally substituted C₁-C₈ alkyl.
22. The compound according to any one of claims 1, 2, or 19-21, wherein R² is -SO_n(R) or CO_n(CH₂)₀₋₃-R.
23. The compound according to any one of claims 1,2, or 19-22, wherein R⁴ is optionally substituted alkyl or optionally substituted heteroaralkyl.
24. The compound according to any one of claims 1,2, or 19-23, wherein R⁶ is H, optionally substituted C₁-C₈ alkyl, or optionally substituted heteroaralkyl.
25. The compound according to any one of claims 1-19, wherein R¹ or R² is -SO_n(R) or CO_n(CH₂)₀₋₃-R.

26. The compound according to claim 25, wherein R^3 is H, R^4 is H, optionally substituted C_1 - C_8 alkyl or optionally substituted heteroaralkyl, and R^6 is H, optionally substituted C_1 - C_8 alkyl or optionally substituted heteroaralkyl.

27. The compound according to claim 1 or claim 2, wherein R^3 is an otherwise unsubstituted $-CH_2$ -4-benzofuranyl, $-CH_2$ -5-benzofuranyl, $-CH_2$ -6-benzofuranyl, or $-CH_2$ -7-benzofuranyl.

28. The compound according to any one of claims 1, 2 or 27, wherein R^4 is H or C_1 - C_8 alkyl.

29. The compound according to any one of claims 1, 2, 27 or 28, wherein R^4 is H.

30. The compound according to any one of claims 1, 2, or 27-29, wherein R^4 is H and R^5 is H.

31. The compound according to any one of claims 1, 2, or 27-30, wherein R^6 is selected from the group consisting of optionally substituted C_1 - C_8 alkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted heterocyclo, and optionally substituted heterocycloalkylalkyl.

32. The compound according to any one of claims 1, 2, or 27-31, wherein R^6 is an otherwise unsubstituted $-CH_2$ -4-benzofuranyl, $-CH_2$ -5-benzofuranyl, $-CH_2$ -6-benzofuranyl, or $-CH_2$ -7-benzofuranyl.

33. The compound according to any one of claims 1-14, wherein at least one of R^3 and R^4 is heteroarylalkyl.

34. The compound according to claim to any one of claims 1-14, wherein at least one of R^3 and R^4 is heteroarylmethyl.

35. A compound according to any one of claims 1 to 34, selected from the compounds listed in Table 1.

36. A pharmaceutical composition comprising a compound according to any of claims 1-35 and a pharmaceutically acceptable diluent, carrier, or excipient.

37. The pharmaceutical composition according to claim 36, further comprising a drug that is not a compound of formula I, wherein efficacy of said drug is compromised due to degradation by cytochrome P450 monooxygenase.

38. The pharmaceutical composition according to claim 37, wherein said drug is selected from the group consisting: Cyclosporine, Tacrolimus (FK506), Sirolimus (rapamycin), Indinavir, Ritonavir, Saquinavir, Felodipine, Isradipine, Nicardipine, Nisoldipine, Nimodipine, Nitrendipine, Nifedipine, Verapamil, Etoposide, Tamoxifen, Vinblastine, Vincristine, Taxol, Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin, Terfenadine, Loratadine, Astemizole, Alfentanil, Carbamazepine, Azithromycin, Clarithromycin, Erythromycin, Itraconazole, Rifabutin, Lidocaine, Cisapride, Sertraline, Pimozide, Triazolam, Anastrozole, Busulfan, Corticosteroids (dexamethasone, methylprednisone and prednisone), Cyclophosphamide, Cytarabine, Docetaxel, Doxorubicin, Erlotinib, Exemestane, Gefitinib, Idarubicin, Ifosphamide, Imatinib mesylate, Irinotecan, Ketoconazole, Letrozole, Paclitaxel, Teniposide, Tretinoin, Vinorelbine, telithromycin, quinidine; alprazolam, diazepam, midazolam, nelfinavir, chlorpheniramine, amlodipine, diltiazem, lercanidipine, cerivastatin, estradiol, hydrocortisone, progesterone, testosterone, alfentanil, aripiprazole, buspirone, cafergot, caffeine, cilostazol, cocaine, codeine, dapsone, dextromethorphan, docetaxel, domperidone, eplerenone, fentanyl, finasteride, gleevec, haloperidol, irinotecan, Levo-Alpha Acetyl Methadol (LAAM), methadone, nateglinide, ondansetron, propranolol, quinine, salmeterol, sildenafil, terfenadine, trazodone, vincristine, zaleplon, zolpidem., ixabepilone, Agenerase (APV), Aptivus (TPV), Crixivan (IDV), Invirase (SQV), Lexiva (FPV), Prezista (DRV), Reyataz (ATV) Viracept (NFV), Elvitegravir, Selzentry, Vicriviroc, Telaprevir, Telithromycin, tandospirone and buspirone.

39. A method of inhibiting cytochrome P450 monooxygenase in a subject, comprising administering to said subject an effective amount of a compound according to any one of claims 1-35.

40. The method according to claim 39, wherein the cytochrome P450 monooxygenase is CYP3A4 or CYP3A5.

41. The method according to claim 39, wherein said subject is a patient suffering from chronic pain, depression, epilepsy, psychosis, inflammation, cancer, cardiovascular disease, diabetes, neurodegenerative disease, and/or infection.

42. The method according to claim 39, wherein the patient is suffering from HCV or HIV infection.

43. The method according to any one of claims 39 to 42, wherein the compound is administered prior to, and/or substantially contemporaneously with a drug,

wherein efficacy of said drug is compromised due to degradation by cytochrome P450 monooxygenase.

44. The method according to claim 43 wherein said drug is selected from the group consisting of Cyclosporine, Tacrolimus (FK506), Sirolimus (rapamycin), Indinavir, Ritonavir, Saquinavir, Felodipine, Isradipine, Nicardipine, Nisoldipine, Nimodipine, Nitrendipine, Nifedipine, Verapamil, Etoposide, Tamoxifen, Vinblastine, Vincristine, Taxol, Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin, Terfenadine, Loratadine, Astemizole, Alfentanil, Carbamazepine, Azithromycin, Clarithromycin, Erythromycin, Itraconazole, Rifabutin, Lidocaine, Cisapride, Sertraline, Pimozide, Triazolam, Anastrozole, Busulfan, Corticosteroids (dexamethasone, methylprednisone and prednisone), Cyclophosphamide, Cytarabine, Docetaxel, Doxorubicin, Erlotinib, Exemestane, Gefitinib, Idarubicin, Ifosfamide, Imatinib mesylate, Irinotecan, Ketoconazole, Letrozole, Paclitaxel, Teniposide, Tretinoin, Vinorelbine, telithromycin, quinidine, alprazolam, diazepam, midazolam, nelfinavir, chlorpheniramine, amlodipine, diltiazem, lercanidipine, cerivastatin, estradiol, hydrocortisone, progesterone, testosterone, alfentanil, aripiprazole, buspirone, cafergot, caffeine, cilostazol, cocaine, codeine, dapsone, dextromethorphan, docetaxel, domperidone, eplerenone, fentanyl, finasteride, gleevec, haloperidol, irinotecan, Levo-Alpha Acetyl Methadol (LAAM), methadone, nateglinide, odansetron, propranolol, quinine, salmeterol, sildenafil, terfenadine, trazodone, vincristine, zaleplon, zolpidem., ixabepilone, Agenerase (APV), Aptivus (TPV), Crixivan (IDV), Invirase (SQV), Lexiva (FPV), Prezista (DRV), Reyataz (ATV) Viracept (NFV), Elvitegravir, Selzentry, Vicriviroc, Telaprevir, Telithromycin, tandospirone and buspirone.

45. The method according to claim 43 or claim 44, wherein the compound is administered at least 30 minutes, at least 1 hour, at least 2 hours, or at least 12 hours prior to administration of said drug.

46. The method according to claim 43, wherein the compound is co-administered with a drug, wherein efficacy of said drug is compromised due to degradation by cytochrome P450 monooxygenase.

47. A method of reducing toxicity in a subject of a compound that is metabolized by cytochrome P450 monooxygenase to a toxic metabolite, comprising administering to said subject an effective amount of a compound according to any one of claims 1-32.

48. A method of treating a subject, wherein said subject is a patient that is suffering from a condition selected from the group consisting of chronic pain, depression, epilepsy, psychosis, neurodegenerative disease, inflammation, cancer, cardiovascular disease, diabetes, infection, HCV and HIV infection, comprising administering to said subject (a) an effective amount of a compound according to any one of claims 1-35 and a drug for treating said condition or (b) an effective amount of a composition according to claim 37 or 38.

49. The method according to claim 48, wherein said subject receives a drug selected from the group consisting of: Cyclosporine, Tacrolimus (FK506), Sirolimus (rapamycin), Indinavir, Ritonavir, Saquinavir, Felodipine, Isradipine, Nicardipine, Nisoldipine, Nimodipine, Nitrendipine, Nifedipine, Verapamil, Etoposide, Tamoxifen, Vinblastine, Vincristine, Taxol, Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin, Terfenadine, Loratadine, Astemizole, Alfentanil, Carbamazepine, Azithromycin, Clarithromycin, Erythromycin, Itraconazole, Rifabutin, Lidocaine, Cisapride, Sertraline, Pimozide, Triazolam, Anastrozole, Busulfan, Corticosteroids (dexamethasone, methylprednisone and prednisone), Cyclophosphamide, Cytarabine, Docetaxel, Doxorubicin, Erlotinib, Exemestane, Gefitinib, Idarubicin, Ifosfamide, Imatinib mesylate, Irinotecan, Ketoconazole, Letrozole, Paclitaxel, Teniposide, Tretinoin, Vinorelbine, telithromycin: quinidine; alprazolam, diazepam, midazolam, nelfinavir, chlorpheniramine, amlodipine, diltiazem, lercanidipine, cerivastatin, estradiol, hydrocortisone, progesterone, testosterone, alfentanil, aripiprazole, buspirone, cafergot, caffeine, cilostazol, cocaine, codeine, dapsone, dextromethorphan, docetaxel, domperidone, eplerenone, fentanyl, finasteride, gleevec, haloperidol, irinotecan, Levo-Alpha Acetyl Methadol (LAAM), methadone, nateglinide, odansetron, propranolol, quinine, salmeterol, sildenafil, terfenadine, trazodone, vincristine, zaleplon, zolpidem., ixabepilone, Agenerase (APV), Aptivus (TPV), Crixivan (IDV), Invirase (SQV), Lexiva (FPV), Prezista (DRV), Reyataz (ATV) Viracept (NFV), Elvitegravir, Selzentry, Vicriviroc, Telaprevir, Telithromycin, tandospirone and buspirone.

50. The method according to claim 48 or claim 49, wherein said subject is a human.

51. The use of a compound according to any one of claims 1-35 for the preparation of a pharmaceutical composition.

52. The use according to claim 51, wherein said pharmaceutical composition is a pharmaceutical composition for the treatment of chronic pain, depression, epilepsy, psychosis, inflammation, cancer, cardiovascular disease, neurodegenerative disease, diabetes, infection.

53. The use according to claim 52, where the composition is for treatment of an infection and the infection is an HCV or HIV infection.

54. The use according to claim 51 or 52, wherein the pharmaceutical composition further comprises a drug selected from the group consisting of: Cyclosporine, Tacrolimus (FK506), Sirolimus (rapamycin), Indinavir, Ritonavir, Saquinavir, Felodipine, Isradipine, Nicardipine, Nisoldipine, Nimodipine, Nitrendipine, Nifedipine, Verapamil, Etoposide, Tamoxifen, Vinblastine, Vincristine, Taxol, Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin, Terfenadine, Loratadine, Astemizole, Alfentanil, Carbamazepine, Azithromycin, Clarithromycin, Erythromycin, Itraconazole, Rifabutin, Lidocaine, Cisapride, Sertraline, Pimozide, Triazolam, Anastrozole, Busulfan, Corticosteroids (dexamethasone, methylprednisone and prednisone), Cyclophosphamide, Cytarabine, Docetaxel, Doxorubicin, Erlotinib, Exemestane, Gefitinib, Idarubicin, Ifosfamide, Imatinib mesylate, Irinotecan, Ketoconazole, Letrozole, Paclitaxel, Teniposide, Tretinoin, Vinorelbine, telithromycin, quinidine, alprazolam, diazepam, midazolam, nelfinavir, chlorpheniramine, amlodipine, diltiazem, lercanidipine, cerivastatin, estradiol, hydrocortisone, progesterone, testosterone, alfentanil, aripiprazole, buspirone, cafergot, caffeine, cilostazol, cocaine, codeine, dapsone, dextromethorphan, docetaxel, domperidone, eplerenone, fentanyl, finasteride, gleevec, haloperidol, irinotecan, Levo-Alpha Acetyl Methadol (LAAM), methadone, nateglinide, odansetron, propranolol, quinine, salmeterol, sildenafil, terfenadine, trazodone, vincristine, zaleplon, zolpidem., ixabepilone, Agenerase (APV), Aptivus (TPV), Crixivan (IDV), Invirase (SQV), Lexiva (FPV), Prezista (DRV), Reyataz (ATV) Viracept (NFV), Elvitegravir, Selzentry, Vicriviroc, Telaprevir, Telithromycin, tandospirone and buspirone.

55. The use according to one of claims 51 to 53, wherein the pharmaceutical composition further comprises an antiretroviral agent.