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(71) Applicant (for all designated States except US):
SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **VENKATRAMAN, Srikanth** [IN/US]; 29 Jamaica Street, Edison, NJ 08820 (US). **ANILKUMAR, Gopinadhan, N.** [IN/US]; 560 Darwin Boulevard, Edison, NJ 08820 (US). **CHEN, Kevin, X.** [US/US]; 9 Gloria Avenue, Edison, NJ 08820 (US). **VELAZQUEZ, Francisco** [MX/US]; 4 Alexandra Way, Clinton, NJ 08809 (US). **ZENG, Qingbei** [CN/US]; 509 Cinder Road, Edison, NJ 08820 (US). **LIU, Duan**

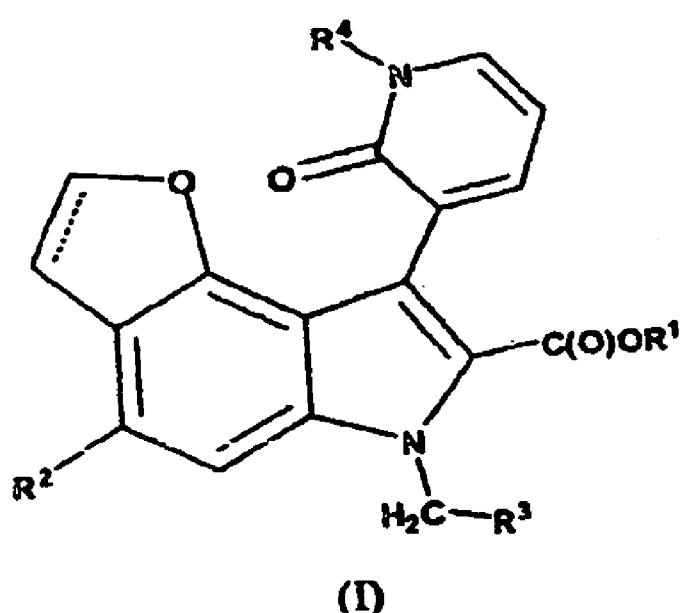
[CN/US]; 333 Washington Street, Arlington, MA 02474 (US). **JIANG, Yueheng** [US/US]; 5 Millstone Lane, Whitehouse Station, NJ 08889 (US). **KOZLOWSKI, Joseph, A.** [US/US]; 1066 Stuart Road, Princeton, NJ 08540 (US). **NJOROGE, F., George** [US/US]; 11 Softwood Way, Warren, NJ 07059 (US). **ROSENBLUM, Stuart, B.** [US/US]; 16 Steven Terrace, West Orange, NJ 07052 (US). **GAVALAS, Stephen, J.** [US/US]; 240 Stonytown Road, Manhasset, NY 11030 (US). **PINTO, Patrick, A.** [US/US]; 34 Battle Ridge Road, Morris Plains, NJ 07950 (US). **SELYUTIN, Oleg, B.** [US/US]; 14133 Marie Court, West Windsor, NJ 08550 (US). **VIBULBHAN, Bancha** [US/US]; 201 North 24th Street, Kenilworth, NJ 07033 (US).

(74) Agent: **BERGMAN, Jeffrey, P.**; Schering-plough Corporation, Patent Department, K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

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(54) Title: TRICYCLIC INDOLE DERIVATIVES AND METHODS OF USE THEREOF



(57) Abstract: The present invention relates to Tricyclic Indole Derivatives, compositions comprising at least one Tricyclic Indole Derivatives, and methods of using the Tricyclic Indole Derivatives for treating or preventing a viral infection or a virus-related disorder in a patient



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TRICYCLIC INDOLE DERIVATIVES AND METHODS OF USE THEREOF**FIELD OF THE INVENTION**

5 The present invention relates to Tricyclic Indole Derivatives, compositions comprising at least one Tricyclic Indole Derivatives, and methods of using the Tricyclic Indole Derivatives for treating or preventing a viral infection or a virus-related disorder in a patient.

BACKGROUND OF THE INVENTION

10 HCV is a (+)-sense single-stranded RNA virus that has been implicated as the major causative agent in non-A, non-B hepatitis (NANBH). NANBH is distinguished from other types of viral-induced liver disease, such as hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis delta virus (HDV), as well as from other forms of liver disease such as alcoholism and primary biliary cirrhosis.

15 Hepatitis C virus is a member of the hepacivirus genus in the family Flaviviridae. It is the major causative agent of non-A, non-B viral hepatitis and is the major cause of transfusion-associated hepatitis and accounts for a significant proportion of hepatitis cases worldwide. Although acute HCV infection is often asymptomatic, nearly 80% of cases resolve to chronic hepatitis. About 60% of patients develop liver disease with various clinical outcomes ranging 20 from an asymptomatic carrier state to chronic active hepatitis and liver cirrhosis (occurring in about 20% of patients), which is strongly associated with the development of hepatocellular carcinoma (occurring in about 1-5% of patients). The World Health Organization estimates that 170 million people are chronically infected with HCV, with an estimated 4 million living in the United States.

25 HCV has been implicated in cirrhosis of the liver and in induction of hepatocellular carcinoma. The prognosis for patients suffering from HCV infection remains poor as HCV infection is more difficult to treat than other forms of hepatitis. Current data indicates a four-year survival rate of below 50% for patients suffering from cirrhosis and a five-year survival rate of below 30% for patients diagnosed with localized resectable hepatocellular carcinoma.

30 Patients diagnosed with localized unresectable hepatocellular carcinoma fare even worse, having a five-year survival rate of less than 1%.

HCV is an enveloped RNA virus containing a single-stranded positive-sense RNA genome approximately 9.5 kb in length. The RNA genome contains a 5'-nontranslated region

(5' NTR) of 341 nucleotides, a large open reading frame (ORF) encoding a single polypeptide of 3,010 to 3,040 amino acids, and a 3'-nontranslated region (3'-NTR) of variable length of about 230 nucleotides. HCV is similar in amino acid sequence and genome organization to flaviviruses and pestiviruses, and therefore HCV has been classified as a third genus of the 5 family Flaviviridae.

The 5' NTR, one of the most conserved regions of the viral genome, contains an internal ribosome entry site (IRES) which plays a pivotal role in the initiation of translation of the viral polyprotein. A single long open reading frame encodes a polyprotein, which is co- or post-translationally processed into structural (core, E1, E2 and p7) and nonstructural (NS2, 10 NS3, NS4A, NS4B, NS5A, and NS5B) viral proteins by either cellular or viral proteinases. The 3' NTR consists of three distinct regions: a variable region of about 38 nucleotides following the stop codon of the polyprotein, a polyuridine tract of variable length with interspersed substitutions of cytidines, and 98 nucleotides (nt) at the very 3' end which are highly conserved among various HCV isolates. By analogy to other plus-strand RNA viruses, 15 the 3'-NTR is thought to play an important role in viral RNA synthesis. The order of the genes within the genome is: NH₂-C-E1-E2-p7-NS2-NS3-NS4A-NS4B-NS5A-NS5B-COOH.

Processing of the structural proteins core (C), envelope protein 1 and (E1, E2), and the p7 region is mediated by host signal peptidases. In contrast, maturation of the nonstructural (NS) region is accomplished by two viral enzymes. The HCV polyprotein is first cleaved by a 20 host signal peptidase generating the structural proteins C/E1, E1/E2, E2/p7, and p7/NS2. The NS2-3 proteinase, which is a metalloprotease, then cleaves at the NS2/NS3 junction. The NS3/4A proteinase complex (NS3 being a serine protease and NS4A acting as a cofactor of the NS3 protease), is then responsible for processing all the remaining cleavage junctions. RNA helicase and NTPase activities have also been identified in the NS3 protein. One-third of the 25 NS3 protein functions as a protease, and the remaining two-thirds of the molecule acts as the helicase/ATPase that is thought to be involved in HCV replication. NS5A may be phosphorylated and acts as a putative cofactor of NS5B. The fourth viral enzyme, NS5B, is a membrane-associated RNA-dependent RNA polymerase (RdRp) and a key component responsible for replication of the viral RNA genome. NS5B contains the "GDD" sequence 30 motif, which is highly conserved among all RdRps characterized to date.

Replication of HCV is thought to occur in membrane-associated replication complexes. Within these, the genomic plus-strand RNA is transcribed into minus-strand RNA, which in

turn can be used as a template for synthesis of progeny genomic plus-strands. At least two viral enzymes appear to be involved in this reaction: the NS3 helicase/NTPase, and the NS5B RNA-dependent RNA polymerase. While the role of NS3 in RNA replication is less clear, NS5B is the key enzyme responsible for synthesis of progeny RNA strands. Using

5 recombinant baculoviruses to express NS5B in insect cells and a synthetic nonviral RNA as a substrate, two enzymatic activities have been identified as being associated with it: a primer-dependent RdRp and a terminal transferase (TNTase) activity. It was subsequently confirmed and further characterized through the use of the HCV RNA genome as a substrate. Other studies have shown that NS5B with a C-terminal 21 amino-acid truncation expressed in
10 *Escherichia coli* is also active for *in vitro* RNA synthesis. On certain RNA templates, NS5B has been shown to catalyze RNA synthesis via a *de novo* initiation mechanism, which has been postulated to be the mode of viral replication *in vivo*. Templates with single-stranded 3' termini, especially those containing a 3'-terminal cytidylate moiety, have been found to direct
15 *de novo* synthesis efficiently. There has also been evidence for NS5B to utilize di- or tri-nucleotides as short primers to initiate replication.

It is well-established that persistent infection of HCV is related to chronic hepatitis, and as such, inhibition of HCV replication is a viable strategy for the prevention of hepatocellular carcinoma. Present treatment approaches for HCV infection suffer from poor efficacy and unfavorable side-effects and there is currently a strong effort directed to the discovery of HCV
20 replication inhibitors that are useful for the treatment and prevention of HCV related disorders. New approaches currently under investigation include the development of prophylactic and therapeutic vaccines, the identification of interferons with improved pharmacokinetic characteristics, and the discovery of agents designed to inhibit the function of three major viral proteins: protease, helicase and polymerase. In addition, the HCV RNA genome itself,
25 particularly the IRES element, is being actively exploited as an antiviral target using antisense molecules and catalytic ribozymes.

Particular therapies for HCV infection include α -interferon monotherapy and combination therapy comprising α -interferon and ribavirin. These therapies have been shown to be effective in some patients with chronic HCV infection. The use of antisense
30 oligonucleotides for treatment of HCV infection has also been proposed as has the use of free bile acids, such as ursodeoxycholic acid and chenodeoxycholic acid, and conjugated bile acids, such as taurooursodeoxycholic acid. Phosphonoformic acid esters have also been proposed as

potentially for the treatment of various viral infections including HCV. Vaccine development, however, has been hampered by the high degree of viral strain heterogeneity and immune evasion and the lack of protection against reinfection, even with the same inoculum.

5 The development of small-molecule inhibitors directed against specific viral targets has become a major focus of anti-HCV research. The determination of crystal structures for NS3 protease, NS3 RNA helicase, and NS5B polymerase, with and without bound ligands, has provided important structural insights useful for the rational design of specific inhibitors.

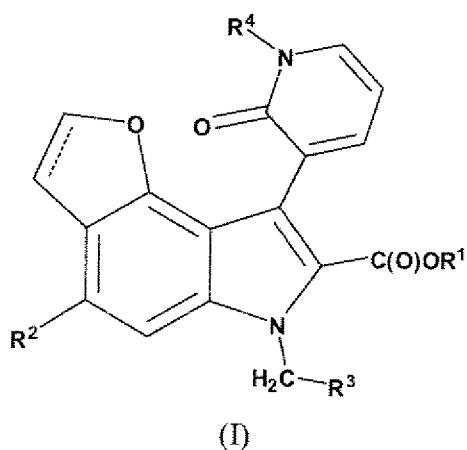
10 NS5B, the RNA-dependent RNA polymerase, is an important and attractive target for small-molecule inhibitors. Studies with pestiviruses have shown that the small molecule compound VP32947 (3-[((2-dipropylamino)ethyl)thio]-5H-1,2,4-triazino[5,6-b]indole) is a potent inhibitor of pestivirus replication and most likely inhibits the NS5B enzyme since resistant strains are mutated in this gene. Inhibition of RdRp activity by (-)β-L-2',3'-dideoxy-3'-thiacytidine 5'-triphosphate (3TC; lamivudine triphosphate) and phosphonoacetic acid also has been observed.

15 Despite the intensive effort directed at the treatment and prevention of HCV and related viral infections, there exists a need in the art for non-peptide, small-molecule compounds having desirable or improved physicochemical properties that are useful for inhibiting viruses and treating viral infections and virus-related disorders.

20

SUMMARY OF THE INVENTION

In one aspect, the present invention provides compounds having the formula:



25 and pharmaceutically acceptable salts, solvates, esters and prodrugs thereof, wherein the dotted line represents an optional and additional bond, and wherein:

R^1 is H, alkyl, alkenyl, -alkylene-OC(O)-alkyl, -alkylene-aryl, aminoalkyl or -alkylene-heterocycloalkyl;

R^2 is H, F, Cl or -CH₃;

R^3 is phenyl, naphthyl, nitrogen-containing heterocycloalkyl, nitrogen-containing

5 heterocycloalkenyl or nitrogen-containing heteroaryl, any of which can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from methyl, t-butyl, allyl, F, Cl, Br, -CN, -O-CH₂CH₃, -S(O)CH₃, -S(O)₂CH₃, -NH₂, -OH, -CH₂NH₂, -C(O)NH₂, -C(O)NHCH₃, -C(O)NH-cyclopropyl, hydroxyalkyl, -C(O)H, -C(O)CH₃, -C(O)O-isopropyl, -C(O)O-t-butyl, -CH₂C(O)-t-butyl, -OCH₃, -NHCH₃, -SCH₃, -C(O)NHCH₃,

10 -NHC(O)OCH₃, -NHC(O)O-isopropyl, -CH₂N(CH₃)₂, -OC(O)CH(CH₃)NHC(O)O-t-butyl, -OC(O)CH(CH₃)NH₂, -C(O)O-t-butyl, -CH₂C(O)O-t-butyl, -OCH₂CH₂N(CH₃)₂, morpholinyl, -CH₂OC(O)-t-butyl, -CH(=NOH), -CH(=NOCH₃), -NHC(O)CH₂N(CH₃)₂ and -NHC(O)O-t-butyl; and

R^4 is H or -C(O)O-alkyl.

15

The Compounds of Formula (I) (also referred to herein as the "Tricyclic Indole Derivatives") and pharmaceutically acceptable salts, solvates, esters and prodrugs thereof can be useful for treating or preventing a viral infection in a patient.

20 The Tricyclic Indole Derivatives or pharmaceutically acceptable salts, solvates, prodrugs or esters thereof can also be useful for treating or preventing a virus-related disorder in a patient.

Also provided by the invention are methods for treating or preventing a viral infection or a virus-related disorder in a patient, comprising administering to the patient an effective amount of at least one Tricyclic Indole Derivative.

25 The present invention further provides pharmaceutical compositions comprising an effective amount of at least one Tricyclic Indole Derivative or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and a pharmaceutically acceptable carrier. The compositions can be useful for treating or preventing a viral infection or a virus-related disorder in a patient.

30 The details of the invention are set forth in the accompanying detailed description below.

Although any methods and materials similar to those described herein can be used in the practice or testing of the present invention, illustrative methods and materials are now described. Other features, objects, and advantages of the invention will be apparent from the description and the claims. All patents and publications cited in this specification are 5 incorporated herein by reference.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides Tricyclic Indole Derivatives, pharmaceutical compositions comprising at least one Tricyclic Indole Derivative, and methods of using the 10 Tricyclic Indole Derivatives for treating or preventing a viral infection or a virus-related disorder in a patient.

Definitions and Abbreviations

The terms used herein have their ordinary meaning and the meaning of such terms is 15 independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. If a chemical compound is referred to using both a chemical structure and a chemical name and an ambiguity exists between the structure and the name, the structure 20 predominates. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "aminoalkyl," "haloalkyl," "alkoxy," etc...

As used herein, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

25 A "patient" is a human or non-human mammal. In one embodiment, a patient is a human. In another embodiment, a patient is a non-human mammal, including, but not limited to, a monkey, dog, baboon, rhesus, mouse, rat, horse, cat or rabbit. In another embodiment, a patient is a companion animal, including but not limited to a dog, cat, rabbit, horse or ferret. In one embodiment, a patient is a dog. In another embodiment, a patient is a cat.

30 The term "alkyl" as used herein, refers to an aliphatic hydrocarbon group, wherein one of the aliphatic hydrocarbon group's hydrogen atoms is replaced with a single bond. An alkyl group can be straight or branched and can contain from about 1 to about 20 carbon atoms. In

one embodiment, an alkyl group contains from about 1 to about 12 carbon atoms. In another embodiment, an alkyl group contains from about 1 to about 6 carbon atoms. Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, isopentyl, n-hexyl, isohexyl and neohexyl. An alkyl group 5 may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkenyl, alkynyl, -O-aryl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, cyano, -OH, -O-alkyl, -O-haloalkyl, -alkylene-O-alkyl, alkylthio, -NH₂, -NH(alkyl), -N(alkyl)₂, -NH-aryl, -NH-heteroaryl, -NHC(O)-alkyl, -NHC(O)NH-alkyl, -NHSO₂-alkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NH(cycloalkyl), -OC(O)-alkyl, -OC(O)-aryl, -OC(O)-cycloalkyl, -C(O)alkyl, -C(O)NH₂, -C(O)NH-alkyl, -C(O)OH and -C(O)O-alkyl. In one embodiment, an alkyl group is unsubstituted. In another embodiment, an alkyl group is a straight chain alkyl group. In another embodiment, an alkyl group is a branched alkyl group.

The term "aminoalkyl" as used herein, refers to an alkyl group, as defined above, 15 wherein at least one of the alkyl group's hydrogen atoms is replaced with a group having the formula -N(R')₂, wherein each occurrence of R' is independently selected from H and alkyl. In one embodiment, an aminoalkyl group's alkyl moiety is linear. In another embodiment, an aminoalkyl group's alkyl moiety is branched. Illustrative examples of aminoalkyl groups include, but are not limited to, -CH₂CH₂NH₂, -CH₂CH(NH₂)CH₃, -CH₂CH₂CH₂NH₂, -CH₂CH₂NHCH₃, -CH₂CH₂N(CH₃)₂, -CH₂CH(N(CH₃)₂)CH₃ and -CH₂CH₂CH₂N(CH₃)₂.

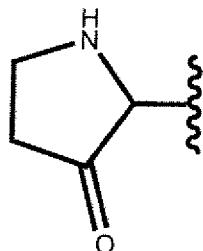
The term "alkylene" as used herein, refers to an alkyl group, as defined above, wherein 20 one of the alkyl group's hydrogen atoms is replaced with a bond. Illustrative examples of alkylene include, but are not limited to, -CH₂- , -CH₂CH₂- , -CH₂CH₂CH₂- , -CH₂CH₂CH₂CH₂- , -CH(CH₃)CH₂CH₂- , -CH₂CH(CH₃)CH₂- and -CH₂CH₂CH(CH₃)-. In one embodiment, an alkylene group is a straight chain alkylene group. In another embodiment, an alkylene group is a branched alkylene group.

The term "nitrogen-containing heteroaryl" as used herein, refers to an aromatic 30 monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, wherein one of the ring atoms is nitrogen, up to 3 remaining ring atoms can independently be O, N or S, and the remaining ring atoms are carbon atoms. In one embodiment, a nitrogen-containing heteroaryl group has 5 to 10 ring atoms. In another embodiment, a nitrogen-containing heteroaryl group is monocyclic and has 5 or 6 ring atoms. In another embodiment, a nitrogen-

containing heteroaryl group is bicyclic and has 9 or 10 ring atoms. A nitrogen-containing heteroaryl group can be joined via a ring carbon or ring nitrogen atom. A nitrogen or sulfur atom of a nitrogen-containing heteroaryl group can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. The term "nitrogen-containing heteroaryl" also encompasses 5 a nitrogen-containing heteroaryl group, as defined above, which has been fused to a benzene ring. Non-limiting examples of illustrative nitrogen-containing heteroaryls include pyridyl, pyrazinyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, indazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, 10 indolyl, azaindolyl, benzimidazolyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "nitrogen-containing heteroaryl" also refers to partially saturated nitrogen-containing multicyclic heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like. In one embodiment, a nitrogen- 15 containing heteroaryl group is a 6-membered monocyclic nitrogen-containing heteroaryl group. In another embodiment, a nitrogen-containing heteroaryl group is a 5-membered monocyclic nitrogen-containing heteroaryl group. In another embodiment, a nitrogen-containing heteroaryl group is a 9-membered bicyclic nitrogen-containing heteroaryl group. In another embodiment, a nitrogen-containing heteroaryl group is a 10-membered bicyclic nitrogen- 20 containing heteroaryl group.

The term "nitrogen-containing heterocycloalkyl" as used herein, refers to a non-aromatic saturated monocyclic or multicyclic ring system comprising 3 to about 10 ring atoms, wherein one of the ring atoms is nitrogen, up to 3 remaining ring atoms can independently O, N or S, and the remaining ring atoms are carbon atoms. In one embodiment, a nitrogen-containing heterocycloalkyl group has from about 5 to about 10 ring atoms. In another embodiment, a nitrogen-containing heterocycloalkyl group has 5 or 6 ring atoms. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Any --NH group in a nitrogen-containing heterocycloalkyl ring may exist protected such as, for example, as an -N(Boc), - 25 N(CBz), -N(Tos) group and the like; such protected nitrogen-containing heterocycloalkyl groups are considered part of this invention. The nitrogen or sulfur atom of a nitrogen-containing heterocycloalkyl group can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of illustrative monocyclic nitrogen-containing 30

heterocycloalkyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, lactam, and the like. A ring carbon atom of a nitrogen-containing heterocycloalkyl group may be functionalized as a carbonyl group. An illustrative example of such a nitrogen-containing heterocycloalkyl group is is pyrrolidonyl:



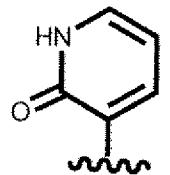
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In one embodiment, a nitrogen-containing heterocycloalkyl group is a monocyclic 6-membered nitrogen-containing monocyclic nitrogen-containing heterocycloalkyl group. In another embodiment, a nitrogen-containing heterocycloalkyl group is a 5-membered monocyclic nitrogen-containing heterocycloalkyl group. In another embodiment, a nitrogen-containing heterocycloalkyl group is a 9-membered bicyclic nitrogen-containing heterocycloalkyl group. In another embodiment, a nitrogen-containing heterocycloalkyl group is a 10-membered bicyclic nitrogen-containing heterocycloalkyl group.

10 In one embodiment, a nitrogen-containing heterocycloalkenyl group is used herein, refers to a nitrogen-containing heterocycloalkyl group, as defined above, wherein the nitrogen-containing heterocycloalkyl group contains from 3 to 10 ring atoms, and at least one endocyclic carbon-carbon or carbon-nitrogen double bond. In one embodiment, a nitrogen-containing heterocycloalkenyl group is bicyclic and has from 5 to 10 ring atoms. In another embodiment, a nitrogen-containing heterocycloalkenyl group is monocyclic and has 5 or 6 ring atoms. A nitrogen or sulfur atom of the nitrogen-containing heterocycloalkenyl can be optionally

15 oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of illustrative nitrogen-containing heterocycloalkenyl groups include 1,2,3,4-tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyran, pyridone, 2-pyridone, dihydrothiopyran, and the like. A ring carbon atom of a nitrogen-containing heterocycloalkenyl group may be functionalized as a carbonyl group. An illustrative example of such a nitrogen-containing heterocycloalkenyl group is:

10



In one embodiment, a nitrogen-containing heterocycloalkenyl group is a 6-membered nitrogen-containing monocyclic heterocycloalkenyl group. In another embodiment, a nitrogen-containing heterocycloalkenyl group is a 5-membered nitrogen-containing monocyclic

5 heterocycloalkenyl group. In another embodiment, a nitrogen-containing heterocycloalkenyl group is a 9-membered bicyclic nitrogen-containing heterocycloalkenyl group. In another embodiment, a nitrogen-containing heterocycloalkenyl group is a 10-membered nitrogen-containing bicyclic heterocycloalkenyl group.

The term "substituted," as used herein, means that one or more hydrogens on the 10 designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a 15 useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" as used herein, means optional substitution with the specified groups, radicals or moieties.

The terms "purified", "in purified form" or "in isolated and purified form" as used 20 herein, for a compound refers to the physical state of said compound after being isolated from a synthetic process (e.g. from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography, 25 recrystallization and the like), in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example,

5 T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term "prodrug" as used herein, refers to a compound (e.g., a drug precursor) that is transformed *in vivo* to provide a Tricyclic Indole Derivative or a pharmaceutically acceptable salt, hydrate or solvate thereof. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a Tricyclic Indole Derivative or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can 20 comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C₁–C₈)alkyl, (C₂–C₁₂)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxy carbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁–C₂)aminoalkyl(C₂–C₃)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C₁–C₂)alkyl, N,N-di(C₁–C₂)alkylcarbamoyl-(C₁–C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂–C₃)alkyl, 30 and the like.

Similarly, if a Tricyclic Indole Derivative contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a

group such as, for example, (C₁-C₆)alkanoyloxymethyl, 1-((C₁-C₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁-C₆)alkanoyloxy)ethyl, (C₁-C₆)alkoxycarbonyloxymethyl, N-(C₁-C₆)alkoxycarbonylaminomethyl, succinoyl, (C₁-C₆)alkanoyl, α -amino(C₁-C₄)alkanyl, arylacyl and α -aminoacyl, or α -aminoacyl- α -aminoacyl, where each α -aminoacyl group is

5 independently selected from the naturally occurring L-amino acids, P(O)(OH)₂, -P(O)(O(C₁-C₆)alkyl)₂ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a Tricyclic Indole Derivative incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for 10 example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C₁-C₁₀)alkyl, (C₃-C₇) cycloalkyl, benzyl, or R-carbonyl is a natural α -aminoacyl or natural α -aminoacyl, —C(OH)C(O)OY¹ wherein Y¹ is H, (C₁-C₆)alkyl or benzyl, —C(OY²)Y³ wherein Y² is (C₁-C₄) alkyl and Y³ is (C₁-C₆)alkyl, carboxy (C₁-C₆)alkyl, amino(C₁-C₄)alkyl or mono-15 N—or di-N,N-(C₁-C₆)aminoalkylalkyl, —C(Y⁴)Y⁵ wherein Y⁴ is H or methyl and Y⁵ is mono-N—or di-N,N-(C₁-C₆)aminoalkyl morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This 20 physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of illustrative solvates include ethanolates, methanolates, and the like. "Hydrate" is a 25 solvate wherein the solvent molecule is H₂O.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, 30 hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired

amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

5 The term "effective amount" as used herein, refers to an amount of Tricyclic Indole Derivative and/or an additional therapeutic agent, or a composition thereof that is effective in producing the desired therapeutic, ameliorative, inhibitory or preventative effect when administered to a patient suffering from a viral infection or virus-related disorder. In the combination therapies of the present invention, an effective amount can refer to each individual 10 agent or to the combination as a whole, wherein the amounts of all agents administered are together effective, but wherein the component agent of the combination may not be present individually in an effective amount.

Metabolic conjugates, such as glucuronides and sulfates which can undergo reversible conversion to the Tricyclic Indole Derivatives are contemplated in the present invention.

15 The Tricyclic Indole Derivatives may form salts, and all such salts are contemplated within the scope of this invention. Reference to a Tricyclic Indole Derivative herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a Tricyclic Indole 20 Derivative contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula I may be formed, for example, by 25 reacting a Tricyclic Indole Derivative with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, 30 fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as

tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use*. (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamine, t-butyl amine, choline, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g., methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g., decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g., benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds which can be metabolically converted to the compounds to the present invention include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl-, aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxyethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C₁₋₄alkyl, or C₁₋₄alkoxy or amino); (2) carboxylic acid esters obtained by esterification of a indole 2-carboxylic with a hydroxyl group of an alcohol, in which the alcohol is selected from straight or branched chain alkylalcohols (for example, ethanol, n-propanol, t-butanol, or n-butanol), alkoxyalkanols (for example, methoxyethanol-), aminoalkanols (for example, aminoethanol, methylaminoethanol, dimethylaminoethanol, dimethylaminopropanol), aralkanols (for example, benzyl alcohol), aryloxyalkanols (for example, phenoxyethanol), aryl alcohols

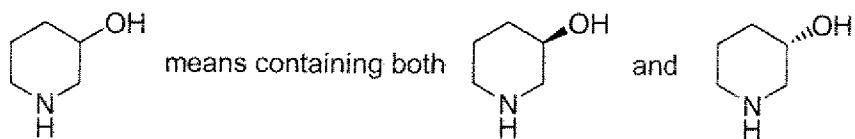
(for example, phenol optionally substituted with, for example, halogen, C₁₋₄alkyl, or C₁₋₄alkoxy or amino); (3) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (4) amino acid esters (for example, L-valyl or L-isoleucyl); (5) phosphonate esters and (6) mono-, di- or triphosphate esters. The phosphate esters may be further esterified 5 by, for example, a C₁₋₂₀ alcohol or reactive derivative thereof, or by a 2,3-di (C₆₋₂₄)acyl glycerol.

The Tricyclic Indole Derivatives may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the Tricyclic Indole Derivatives as well as mixtures thereof, including racemic mixtures, form 10 part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a Tricyclic Indole Derivative incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the 15 basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the 20 individual diastereomers to the corresponding pure enantiomers. Also, some of the Tricyclic Indole Derivatives may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

The straight line ——— as a bond generally indicates a mixture of, or either of, the possible isomers, non-limiting example(s) include, containing (R)- and (S)- stereochemistry.

25 For example,



A dashed line (----) represents an optional and additional bond.

As well known in the art, a bond drawn from a particular atom wherein no moiety is depicted at the terminal end of the bond indicates a methyl group bound through that bond to 30 the atom, unless stated otherwise. For example:



All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, hydrates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may

5 exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). For example, if a Tricyclic Indole Derivative incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as

10 mixtures, are embraced within the scope of the invention.

Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, positional isomers, racemates or prodrugs of the inventive compounds.

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are 20 replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Such compounds are useful as therapeutic, diagnostic or research reagents. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively.

25 Certain isotopically-labelled Tricyclic Indole Derivatives (e.g., those labeled with ^3H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^3H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some

circumstances. In one embodiment, one or more hydrogen atoms of a Compound of Formula (I) is replaced with a deuterium atom. Isotopically labelled Tricyclic Indole Derivatives can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent.

5 Polymorphic forms of the Tricyclic Indole Derivatives, and of the salts, solvates, hydrates, esters and prodrugs of the Tricyclic Indole Derivatives, are intended to be included in the present invention.

The following abbreviations are used below and have the following meanings:

10 BINAP is racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; CSA is camphorsulfonic acid; DBPD is 2-(Di-t-butylphosphino)biphenyl, DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene, DBN is 1,5-diazabicyclo[4.3.0]non-5-ene; DCC is dicyclohexylcarbodiimide; DCM is dichloromethane; Dibal-H is diisobutylaluminum hydride; DMF is dimethylformamide; EDCI is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide; HATU is N-(diethylamino)-

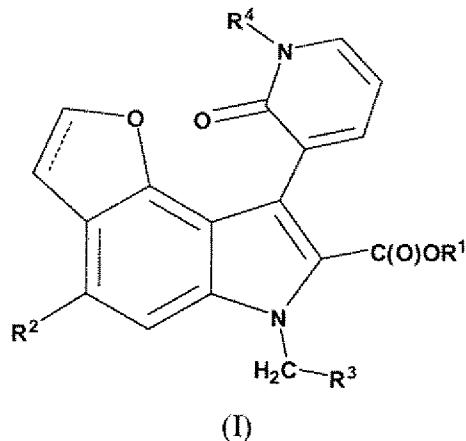
15 1H-1,2,3-triazolo[4,5-b]pyridine-1-ylmethylene]-N-methylmethanaminium Hexafluorophosphate N-oxide; HOBT is 1-hydroxybenzotriazole; LAH is lithium aluminum hydride; LDA is lithium diisopropylamide; m-CPBA is m-chloroperbenzoic acid; NaBH(OAc)₃ is sodium triacetoxyborohydride; NaBH₄ is sodium borohydride; NaBH₃CN is sodium cyanoborohydride; NaHMDS is sodium hexamethyl disilylazide; p-TsOH is

20 p-toluenesulfonic acid; p-TsCl is p-toluenesulfonyl chloride; PPTS is pyridinium p-toluenesulfonate; TMAD is N,N,N',N'-tetramethylazodicarboxamide; HRMS is high resolution mass spectrometry; HPLC is high performance liquid chromatography; LRMS is low resolution mass spectrometry; Tr is triphenylmethyl; Tris is tris (hydroxymethyl)aminomethane; THF is tetrahydrofuran; TFA is trifluoroacetic acid; Ci/mmol is Curie/mmol (a measure of specific activity); and Ki represents the dissociation constant for a

25 substrate/receptor complex.

The Tricyclic Indole Derivatives of Formula (I)

The present invention provides Tricyclic Indole Derivatives of Formula (I):



and pharmaceutically acceptable salts, solvates, esters and prodrugs thereof, wherein the dotted line represents an optional and additional bond and R¹, R², R³ and R⁴ are defined above.

5 In one embodiment, the optional and additional bond is present.
 In another embodiment, the optional and additional bond is absent.
 In one embodiment, R¹ is H or aminoalkyl.
 In another embodiment, R¹ is H.
 In another embodiment, R¹ is aminoalkyl.

10 In another embodiment, R¹ is alkylene-heterocycloalkyl.
 In still another embodiment, R¹ is alkyl.
 In one embodiment, R¹ is H, methyl, ethyl, n-propyl, -CH₂CH₂NH₂, -CH₂CH(NH₂)CH₃, -CH₂CH₂CH₂NH₂, -CH₂CH₂NHCH₃, -CH₂CH₂N(CH₃)₂, -CH₂CH(N(CH₃)₂)CH₃ or -CH₂CH₂CH₂N(CH₃)₂.

15 In another embodiment, R¹ is methyl, ethyl, n-propyl, -CH₂CH₂NH₂, -CH₂CH(NH₂)CH₃, -CH₂CH₂CH₂NH₂, -CH₂CH₂NHCH₃, -CH₂CH₂N(CH₃)₂, -CH₂CH(N(CH₃)₂)CH₃ or -CH₂CH₂CH₂N(CH₃)₂.
 In another embodiment, R¹ is -CH₂CH₂NH₂, -CH₂CH(NH₂)CH₃, -CH₂CH₂CH₂NH₂, -CH₂CH₂NHCH₃, -CH₂CH₂N(CH₃)₂, -CH₂CH(N(CH₃)₂)CH₃ or -CH₂CH₂CH₂N(CH₃)₂.

20 In still another embodiment, R¹ is -CH₂CH₂N(CH₃)₂.
 In another embodiment, R¹ is other than H.
 In another embodiment, R² is H or F.
 In another embodiment, R² is F.
 In still another embodiment, R² is H.

25 In one embodiment, R³ is phenyl.
 In another embodiment, R³ is naphthyl.

In another embodiment, R³ is nitrogen-containing heteroaryl or nitrogen-containing heterocycloalkenyl.

In yet another embodiment, R³ is nitrogen-containing heteroaryl.

In another embodiment, R³ is nitrogen-containing heterocycloalkyl.

5 In another embodiment, R³ is nitrogen-containing heterocycloalkenyl.

In one embodiment, R³ is phenyl.

In another embodiment, R³ is quinoline.

In another embodiment, R³ is isoquinoline.

In still another embodiment, R³ is 1,8-naphthyridine.

10 In another embodiment, R³ is quinazoline.

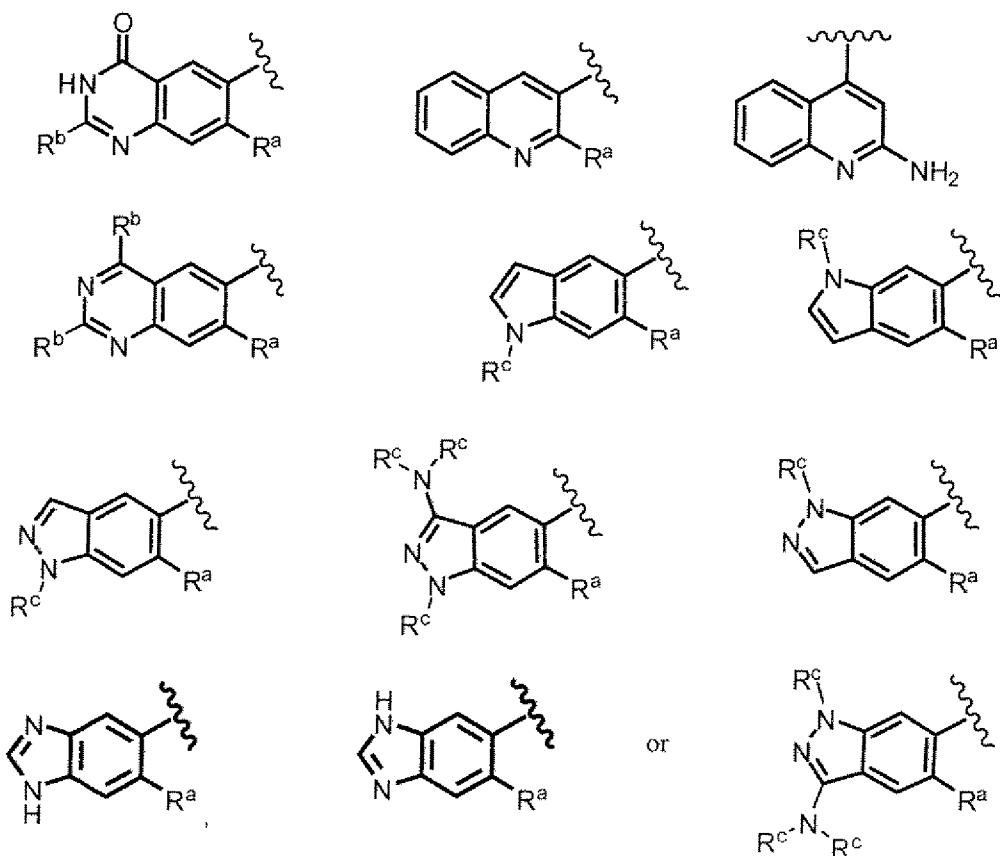
In yet another embodiment, R³ is benzimidazole.

In another embodiment, R³ is indazole.

In a further embodiment, R³ is quinolin-2-one.

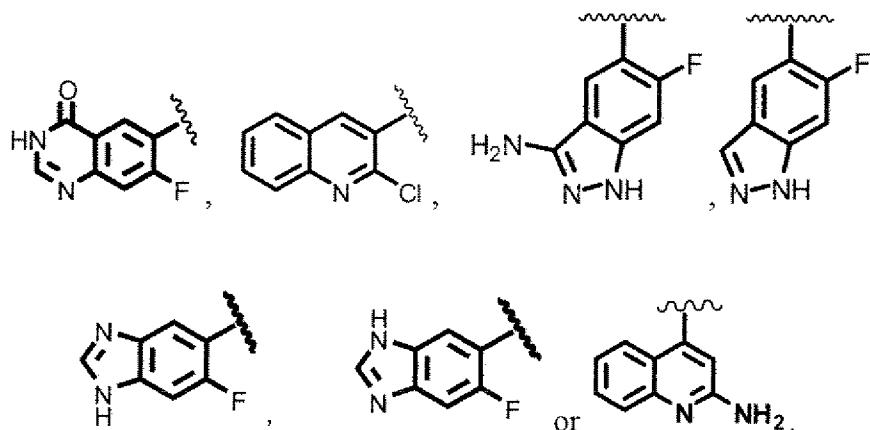
In one embodiment, R³ is:

15



wherein R^a is F, Cl or methyl; R^b is H, -OH, -NH₂ or methyl; and R^c is H or methyl.

In another embodiment, R³ is:



5

In one embodiment, R⁴ is H.

In another embodiment, R⁴ is -C(O)O-alkyl.

10 In another embodiment, R⁴ is -C(O)OCH₃.

In still another embodiment, R⁴ is -C(O)O-t-butyl.

In one embodiment, R¹ is H or aminoalkyl and R² is H or F.

In another embodiment, R¹ is H or aminoalkyl and R² is F.

In another embodiment, R¹ is H or aminoalkyl and R² is H.

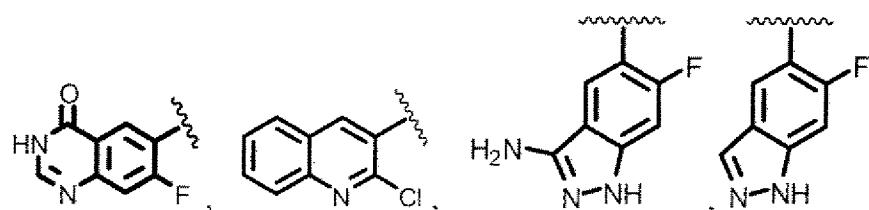
15 In one embodiment, R¹ is H or aminoalkyl; R² is H or F; and the optional and additional bond is present.

In one embodiment, R¹ is H or aminoalkyl; R² is H or F; and the optional and additional bond is absent.

20 In one embodiment, R¹ is H or aminoalkyl; R² is H or F; and R³ is nitrogen-containing heteroaryl or nitrogen-containing heterocycloalkenyl.

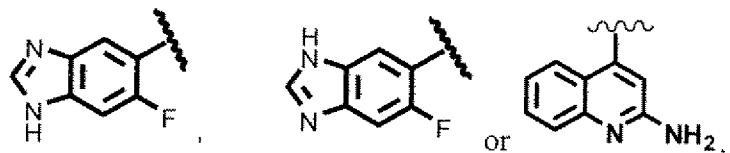
In another embodiment, R¹ is H or aminoalkyl; R² is H or F; and R³ is nitrogen-containing heteroaryl.

In another embodiment, R¹ is H or aminoalkyl; R² is H or F; and R³ is:



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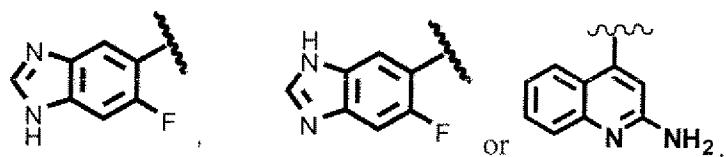
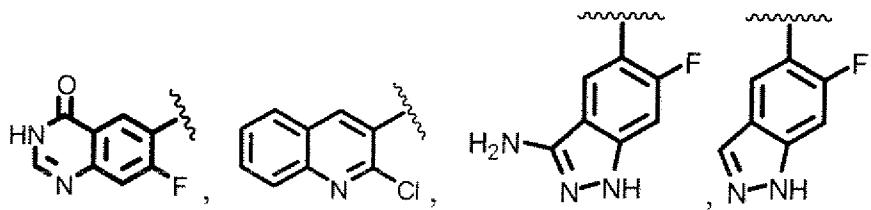
In another embodiment, R¹ is H or aminoalkyl; R² is H or F; R³ is nitrogen-containing heteroaryl or nitrogen-containing heterocycloalkenyl; and the optional and additional bond is present.

In another embodiment, R¹ is H or aminoalkyl; R² is H or F; R³ is nitrogen-containing heteroaryl or nitrogen-containing heterocycloalkenyl; and the optional and additional bond is absent.

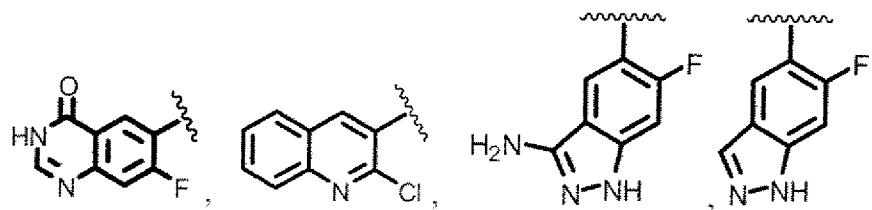
In another embodiment, R¹ is H or aminoalkyl; R² is H or F; R³ is nitrogen-containing heteroaryl; and the optional and additional bond is present.

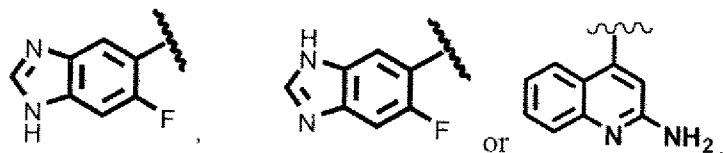
In another embodiment, R¹ is H or aminoalkyl; R² is H or F; R³ is nitrogen-containing heteroaryl; and the optional and additional bond is absent.

In another embodiment R¹ is H or aminoalkyl; R² is H or F; the optional and additional bond is present; and R³ is:



In another embodiment, R¹ is H or aminoalkyl; R² is H or F; the optional and additional bond is absent; and R³ is:





In one embodiment, R¹ is aminoalkyl and R² is H or F.

In another embodiment, R¹ is aminoalkyl and R² is F.

5 In another embodiment, R¹ is aminoalkyl and R² is H.

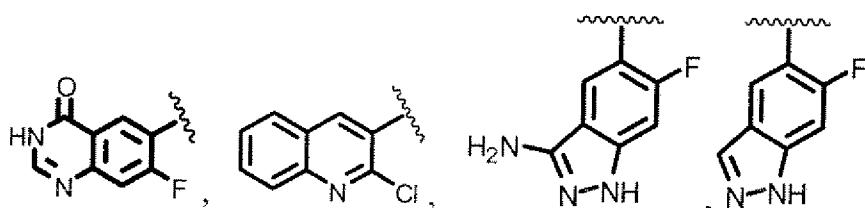
In one embodiment, R¹ is aminoalkyl; R² is H or F; and the optional and additional bond is present.

In one embodiment, R¹ is aminoalkyl; R² is H or F; and the optional and additional bond is absent.

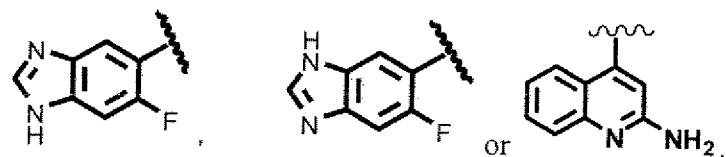
10 In one embodiment, R¹ is aminoalkyl; R² is H or F; and R³ is nitrogen-containing heteroaryl or nitrogen-containing heterocycloalkenyl.

In another embodiment, R¹ is aminoalkyl; R² is H or F; and R³ is nitrogen-containing heteroaryl.

In another embodiment, R¹ is aminoalkyl; R² is H or F; and R³ is:



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20 In another embodiment, R¹ is aminoalkyl; R² is H or F; R³ is nitrogen-containing heteroaryl or nitrogen-containing heterocycloalkenyl; and the optional and additional bond is present.

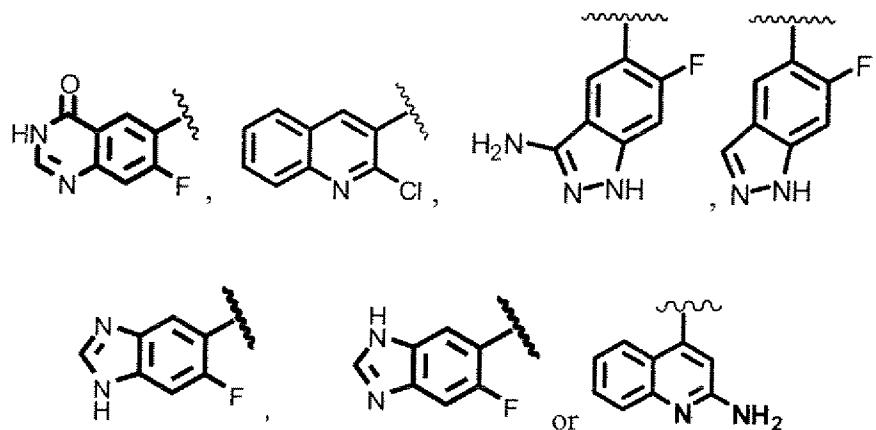
In another embodiment, R¹ is aminoalkyl; R² is H or F; R³ is nitrogen-containing heteroaryl or nitrogen-containing heterocycloalkenyl; and the optional and additional bond is absent.

25 In another embodiment, R¹ is aminoalkyl; R² is H or F; R³ is nitrogen-containing heteroaryl; and the optional and additional bond is present.

In another embodiment, R¹ is aminoalkyl; R² is H or F; R³ is nitrogen-containing heteroaryl; and the optional and additional bond is absent.

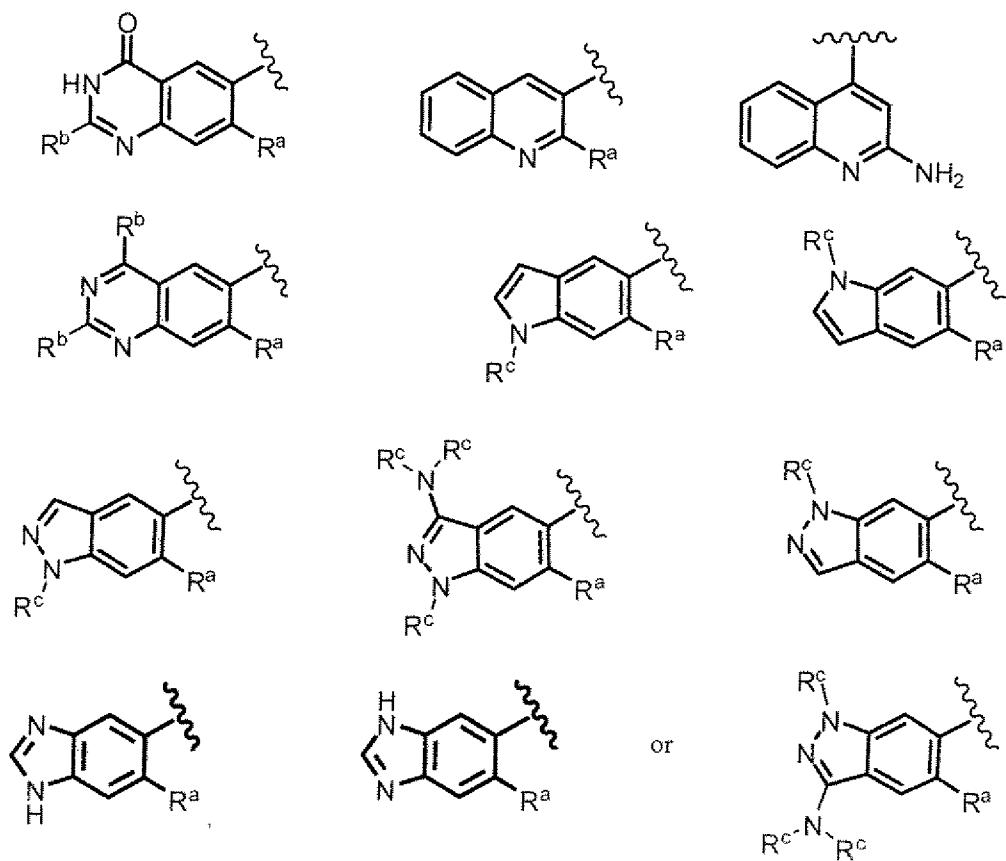
In another embodiment R¹ is aminoalkyl; R² is H or F; the optional and additional bond is present; and R³ is:

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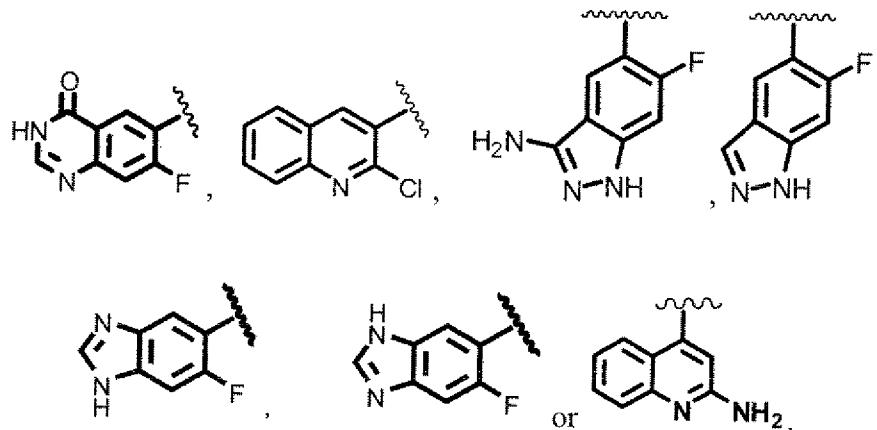
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In another embodiment, R¹ is aminoalkyl; R² is H or F; the optional and additional bond is absent; and R³ is:



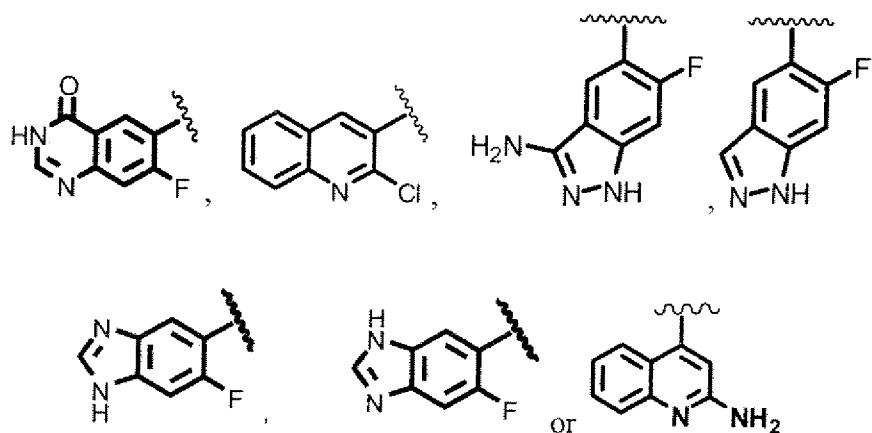
wherein R^a is F, Cl or methyl; R^b is H, -OH, -NH₂ or methyl; and R^c is H or methyl.

In another embodiment, R¹ is aminoalkyl; R² is H or F; the optional and additional bond is absent; and R³ is:



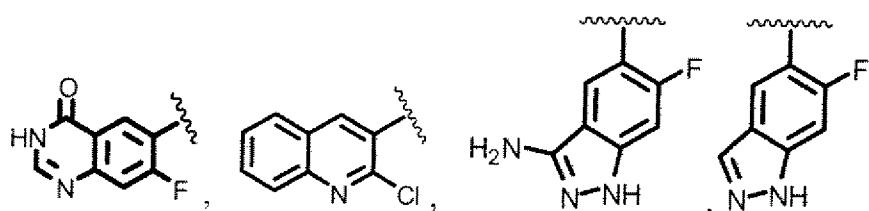
In one embodiment, R¹ is -CH₂CH₂N(CH₃)₂ and R² is F.

10 In another embodiment, R¹ is -CH₂CH₂N(CH₃)₂, R² is F, and R³ is:



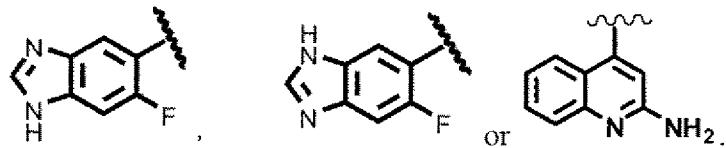
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In another embodiment, R¹ is -CH₂CH₂N(CH₃)₂; R² is H; the optional and additional bond is absent; and R³ is:



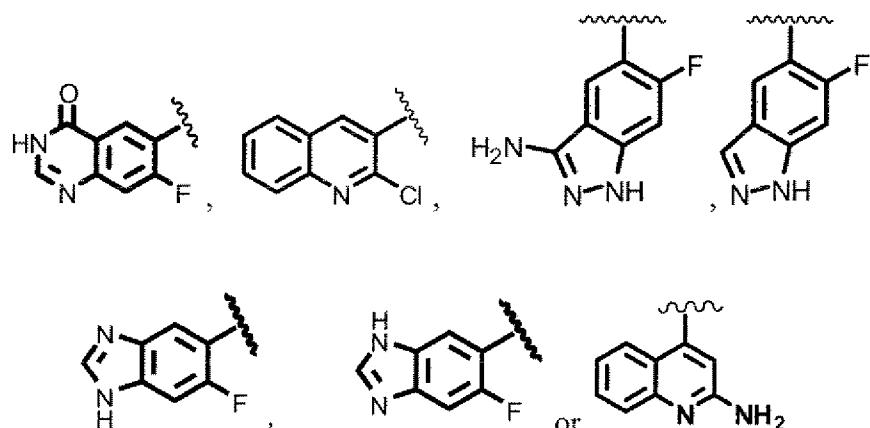
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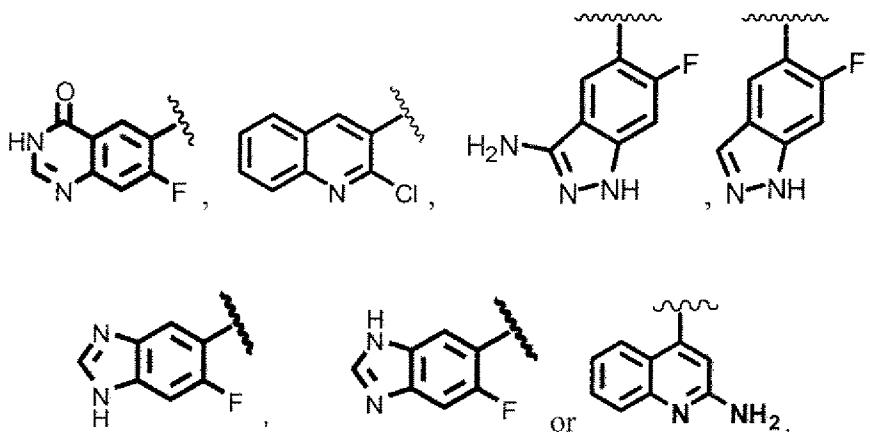
In still another embodiment, R^1 is $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$; R^2 is F; the optional and additional bond is absent; and R^3 is:

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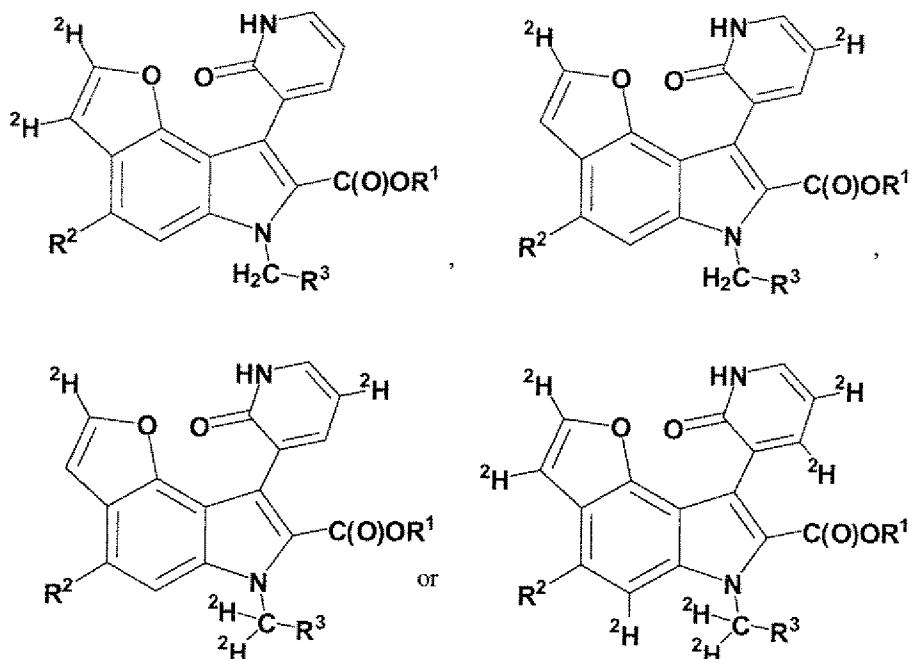
10 In another embodiment, R^1 is $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$; R^2 is F; the optional and additional bond is present; and R^3 is:

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In one embodiment, the Compounds of Formula (I) have the formula:

20



In one embodiment, one or more hydrogen atoms of a Compound of Formula (I) is replaced with a deuterium atom.

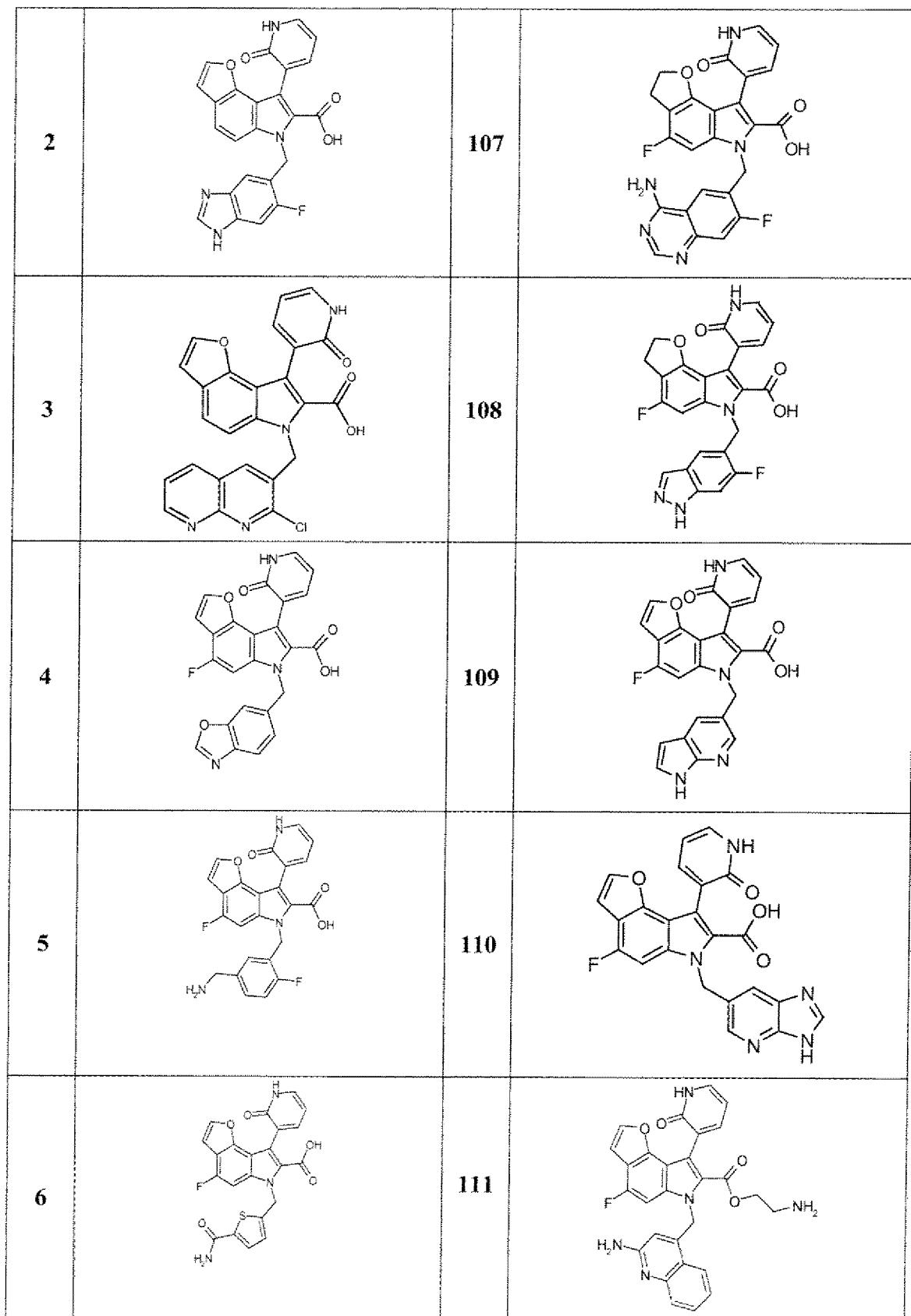
5 In another embodiment, for the Compounds of Formula (I), variables R¹, R² and R³ are selected independently from each other.

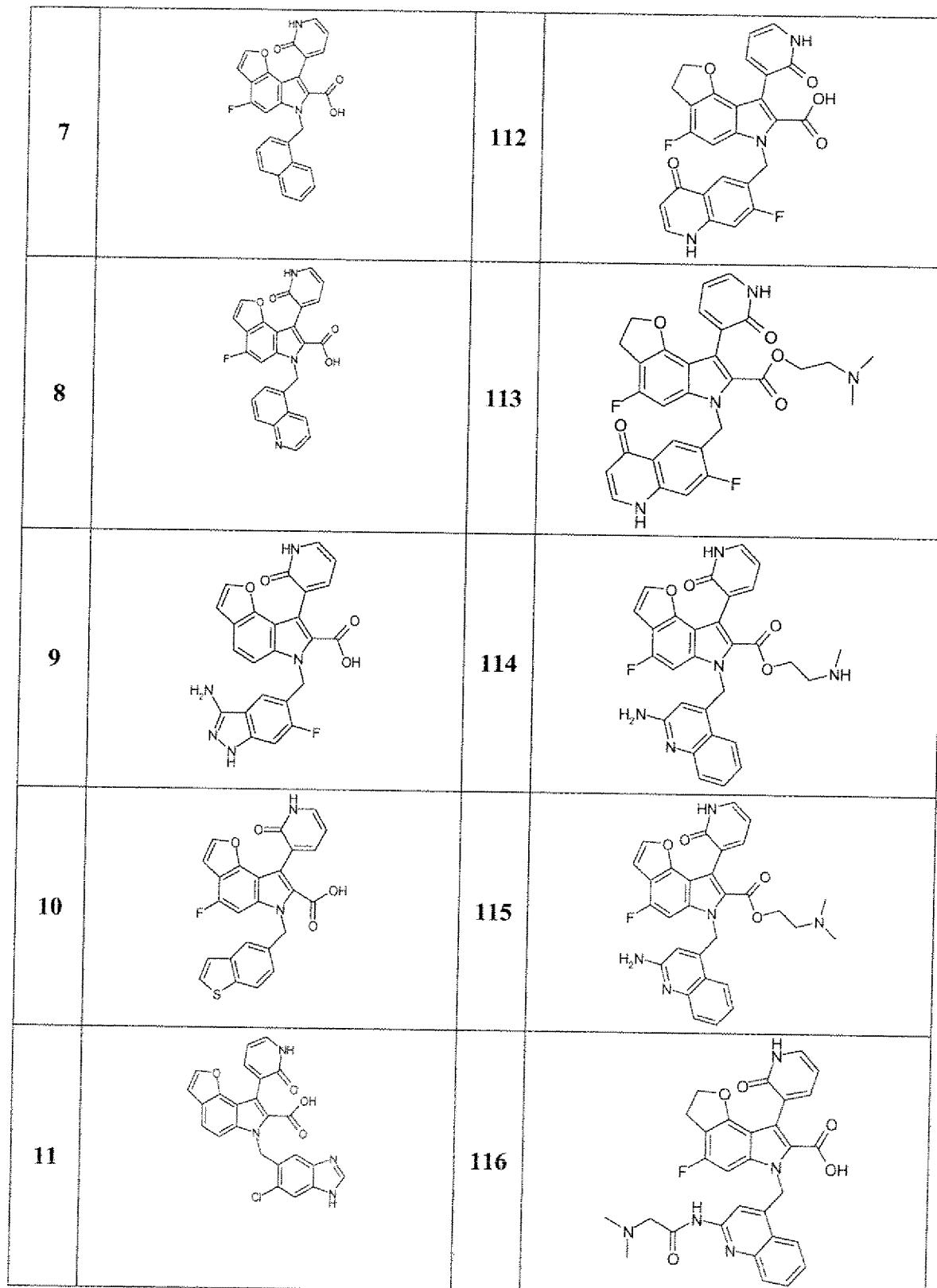
In another embodiment, a Compound of Formula (I) is in purified form.

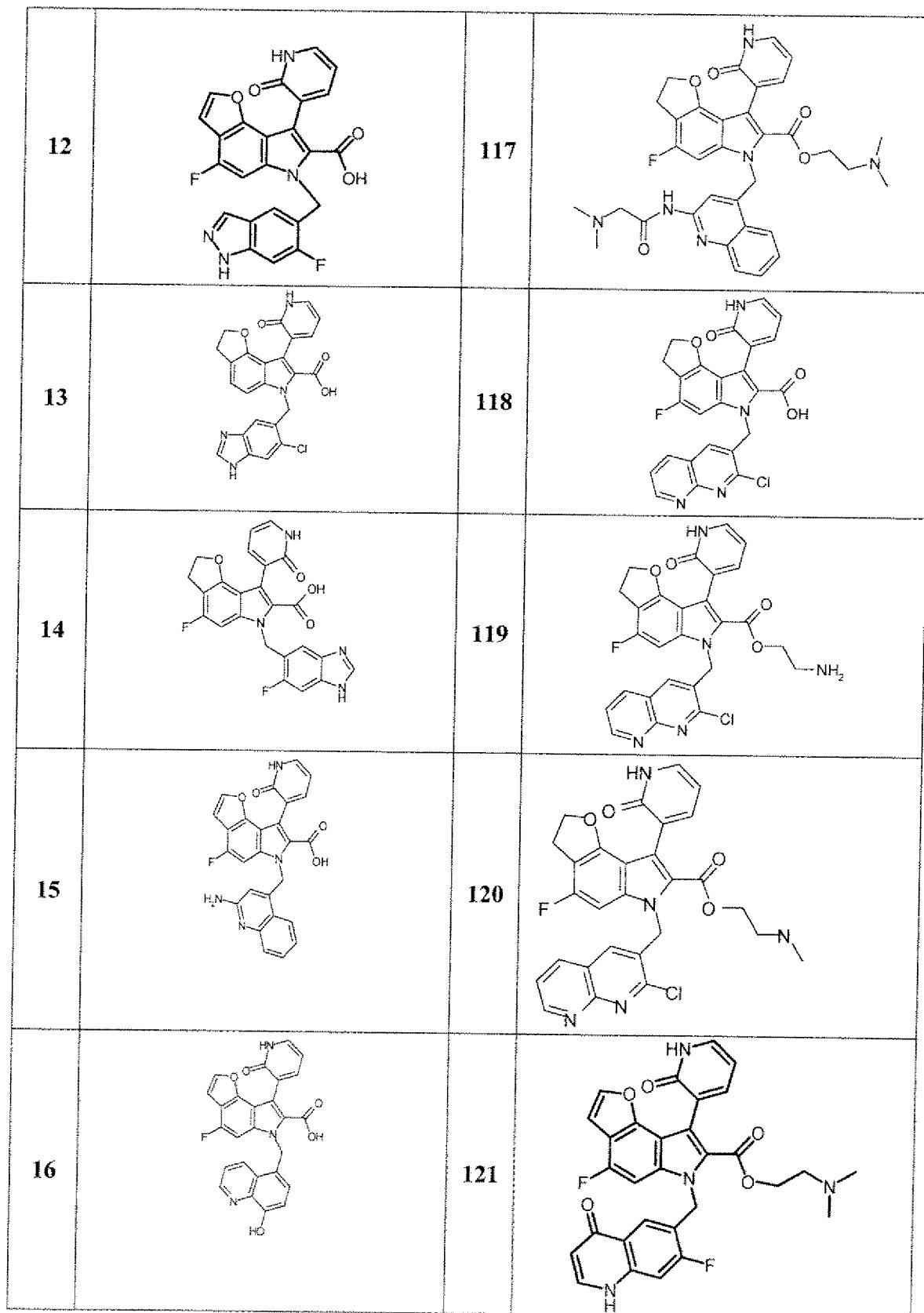
Non-limiting examples of the Compounds of Formula (I) include compounds 1-209 as set forth in the following table:

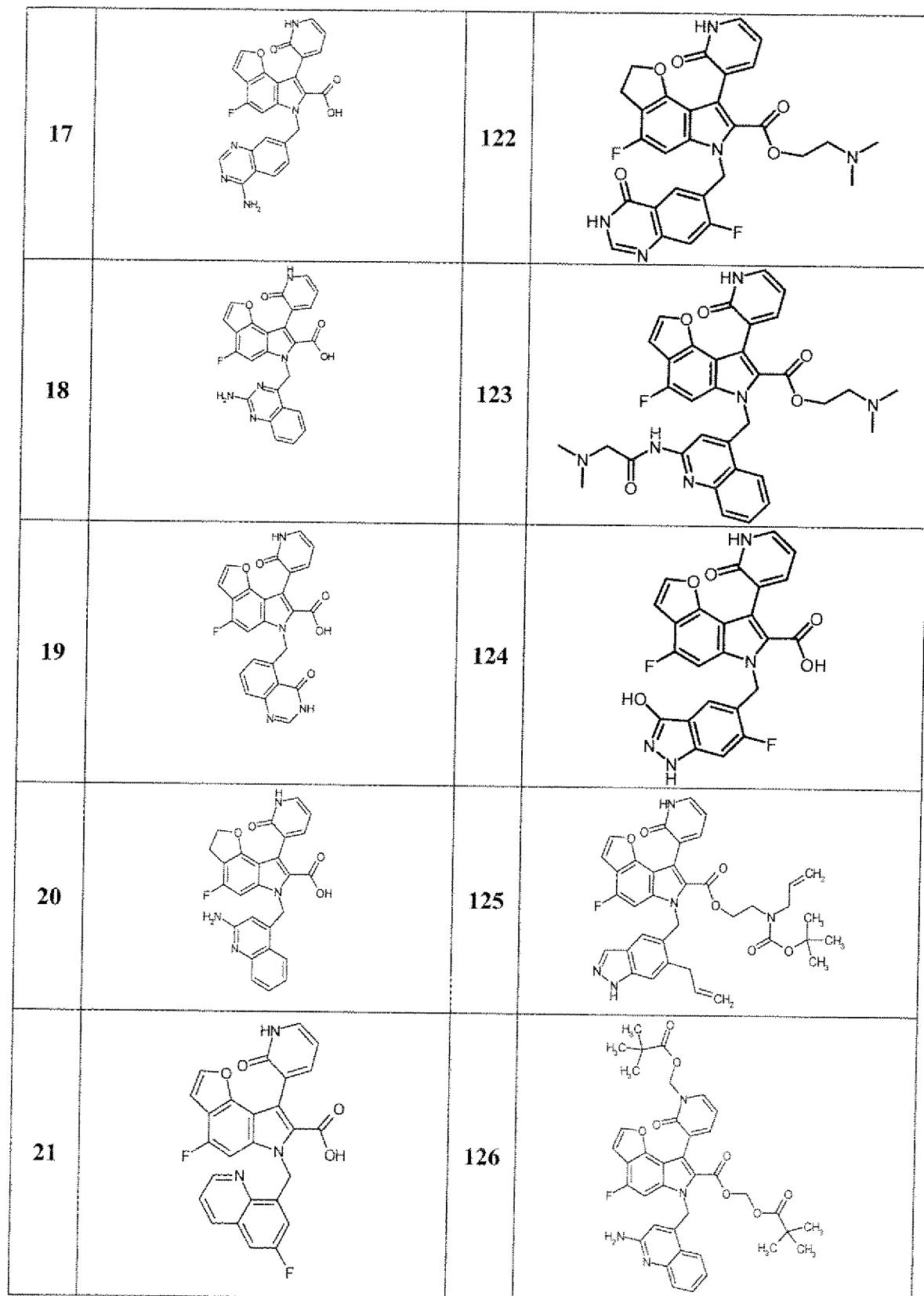
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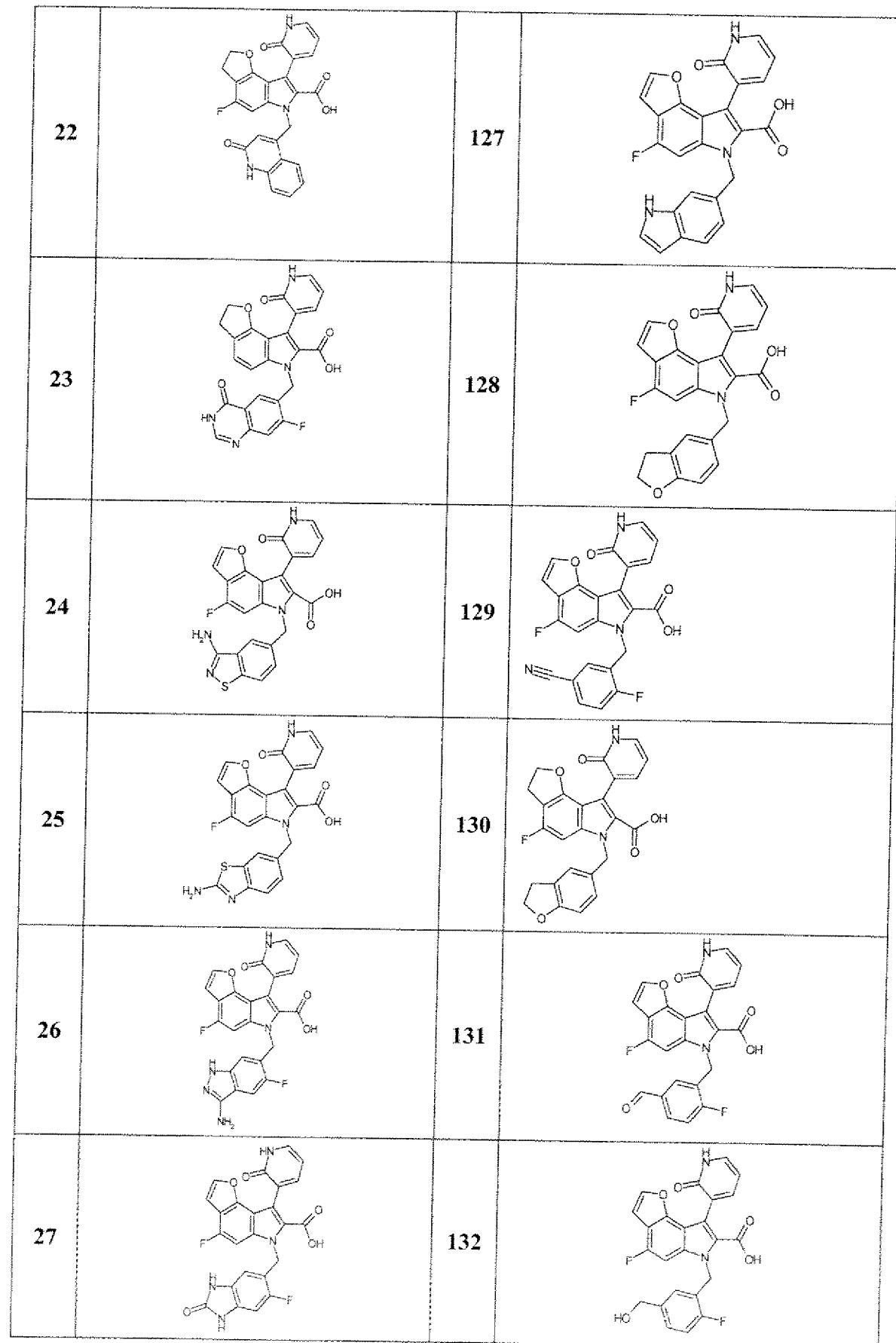
Cpd No.	Structure	Cpd No.	Structure
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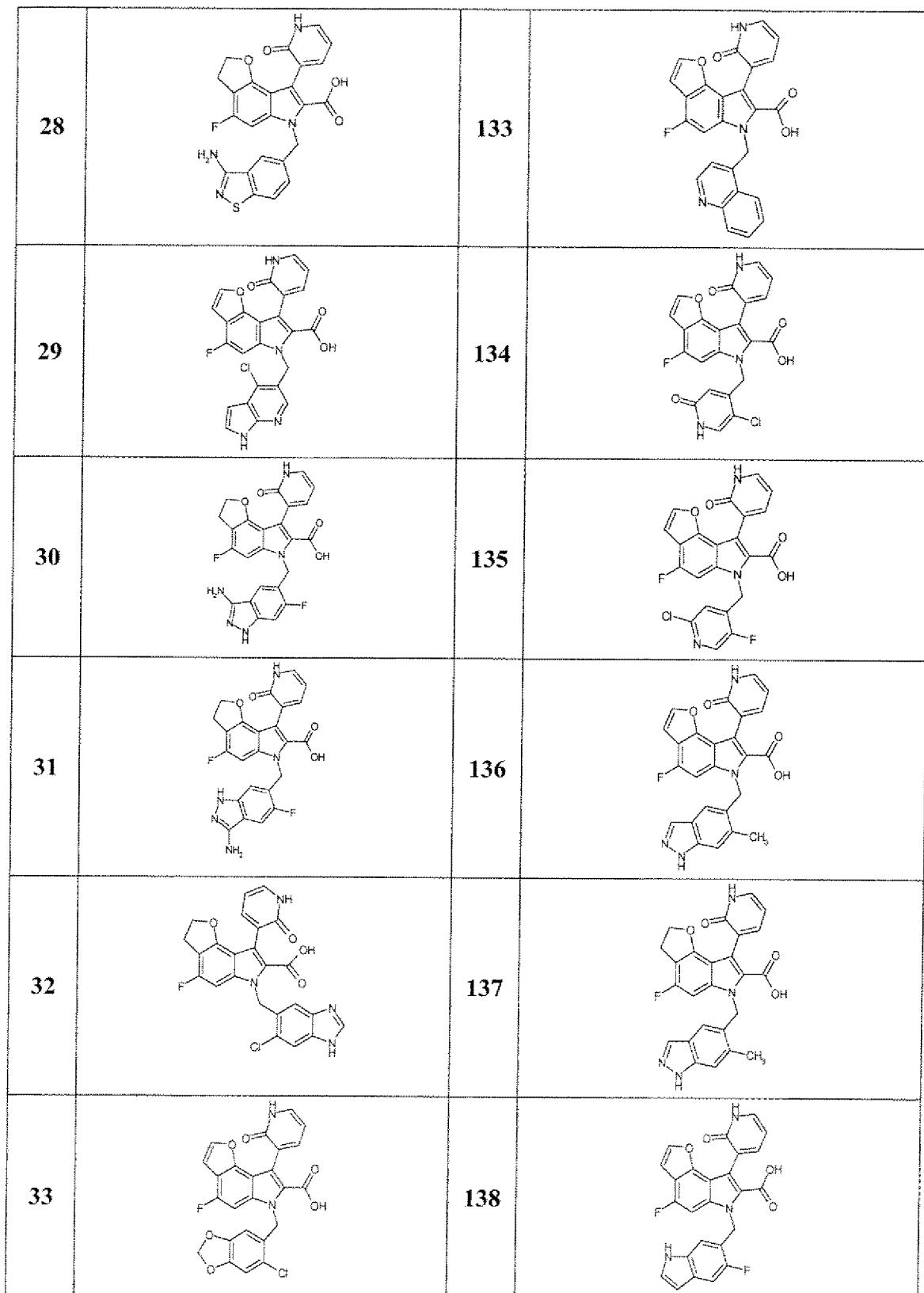


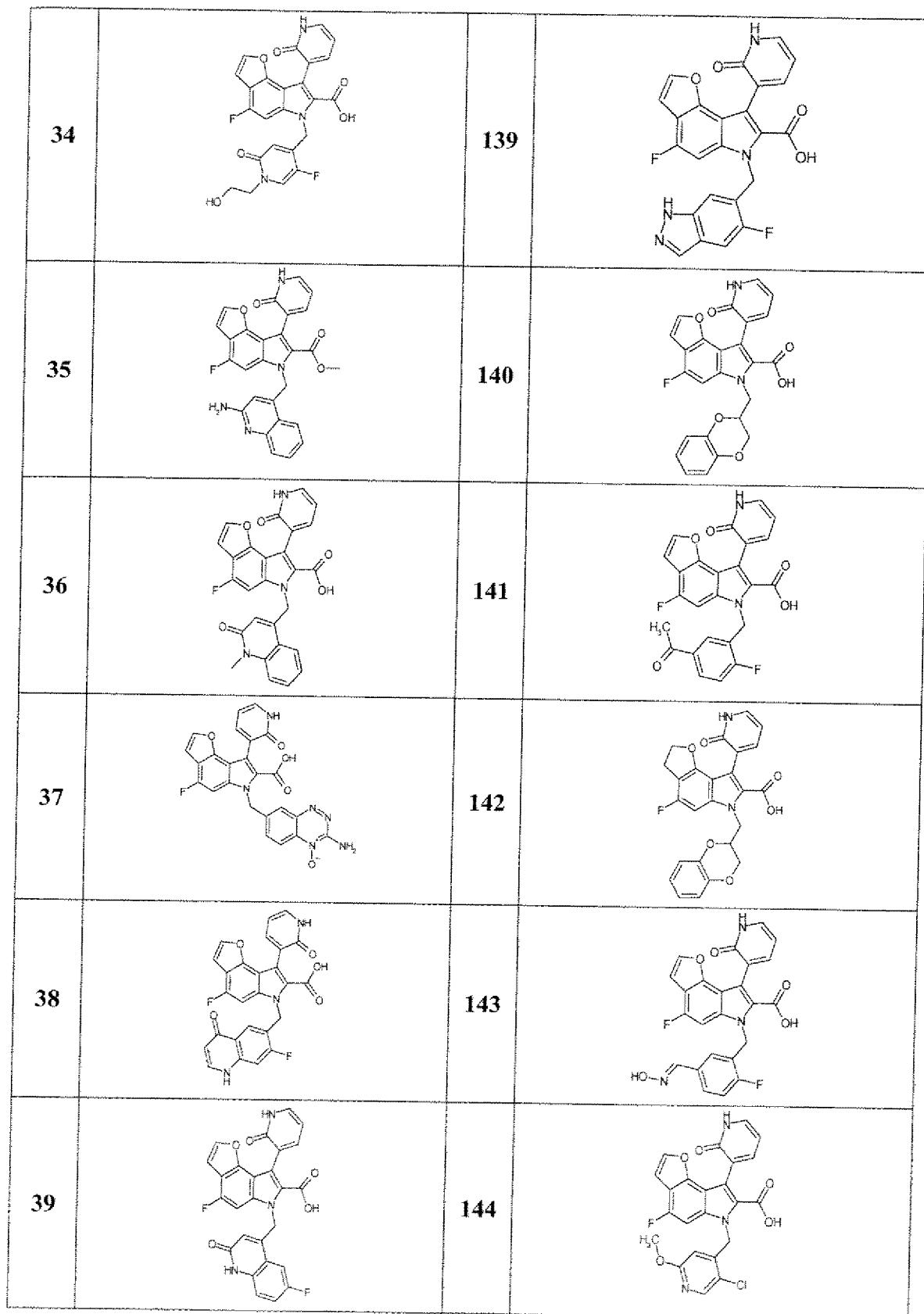


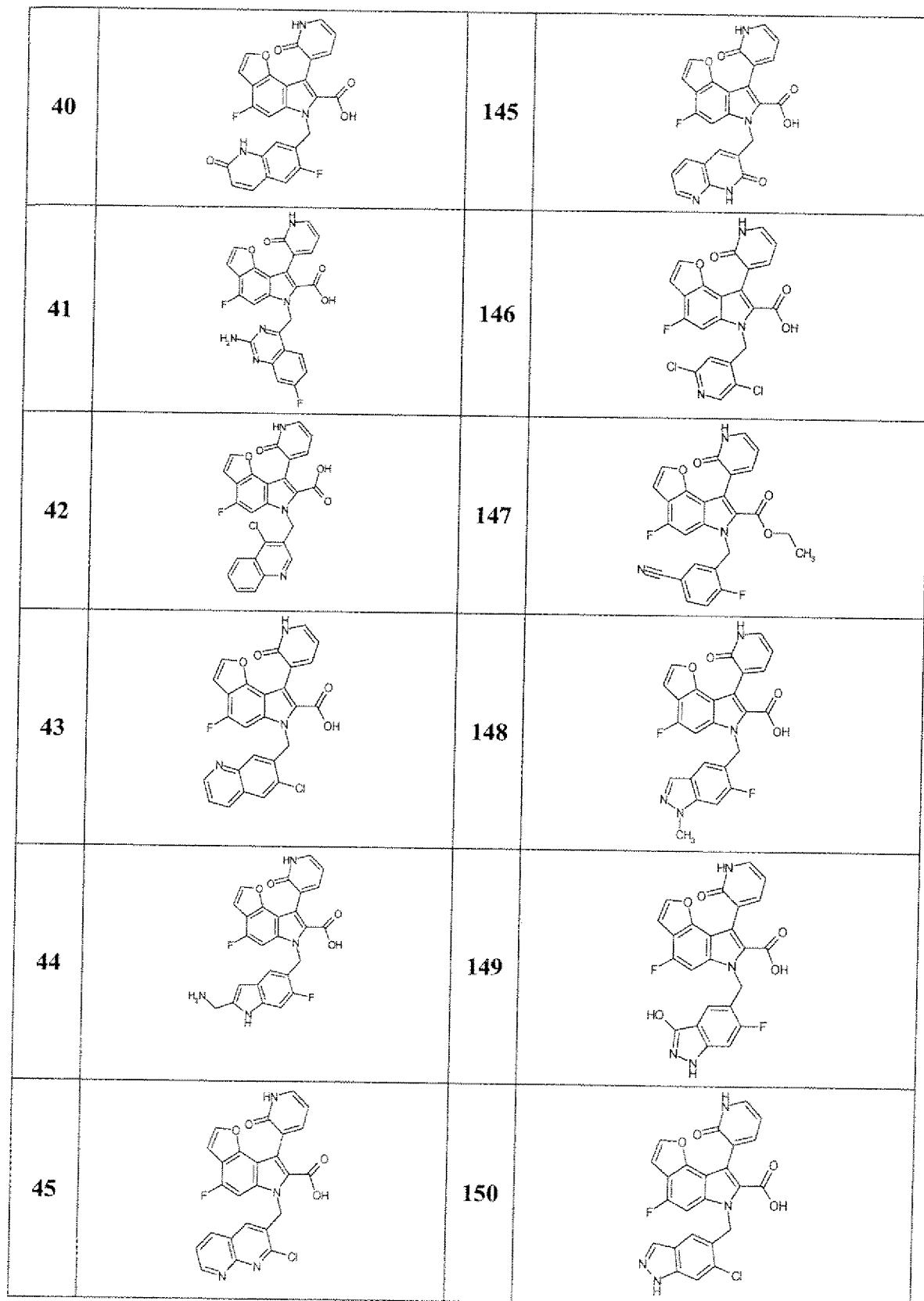


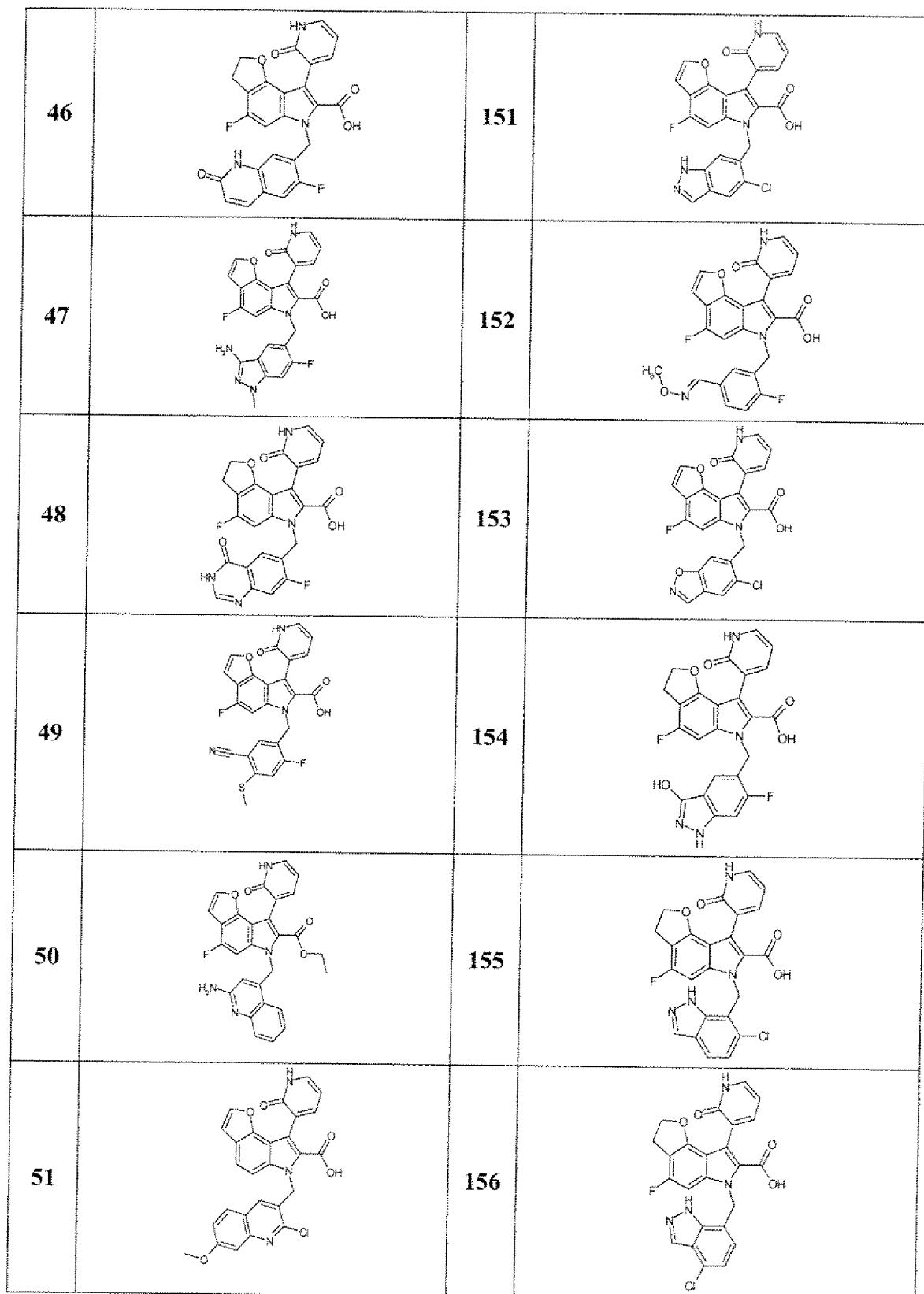


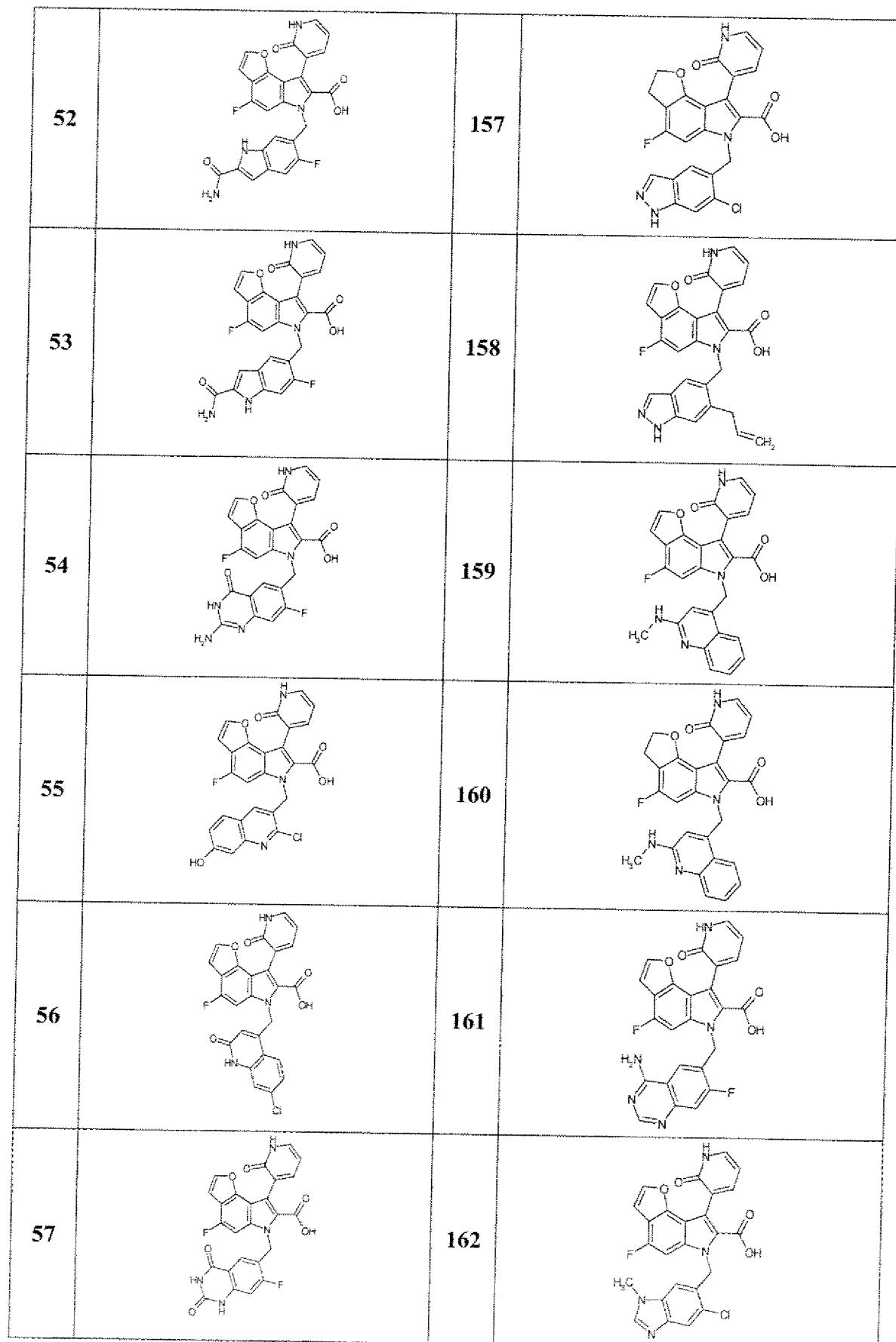




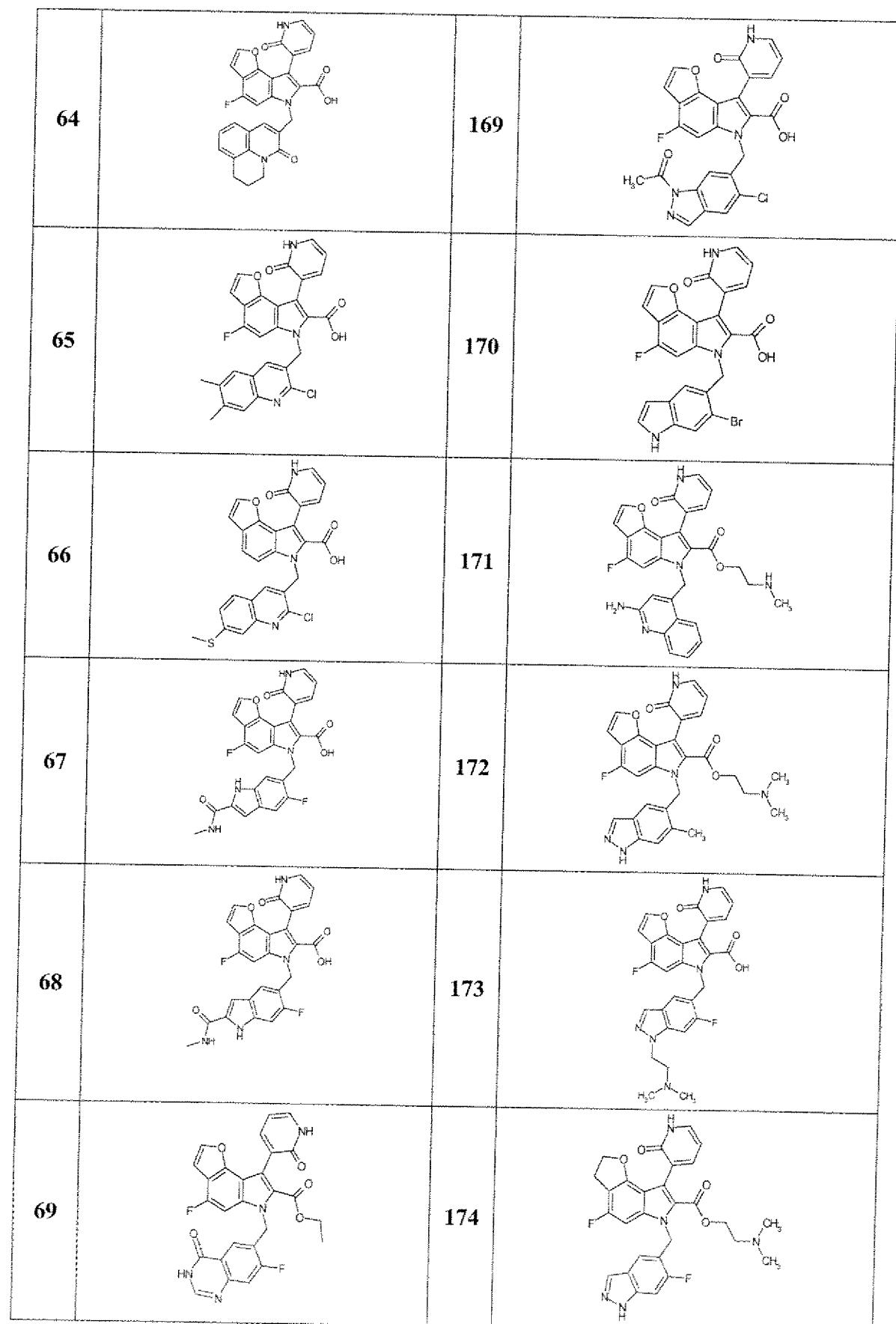


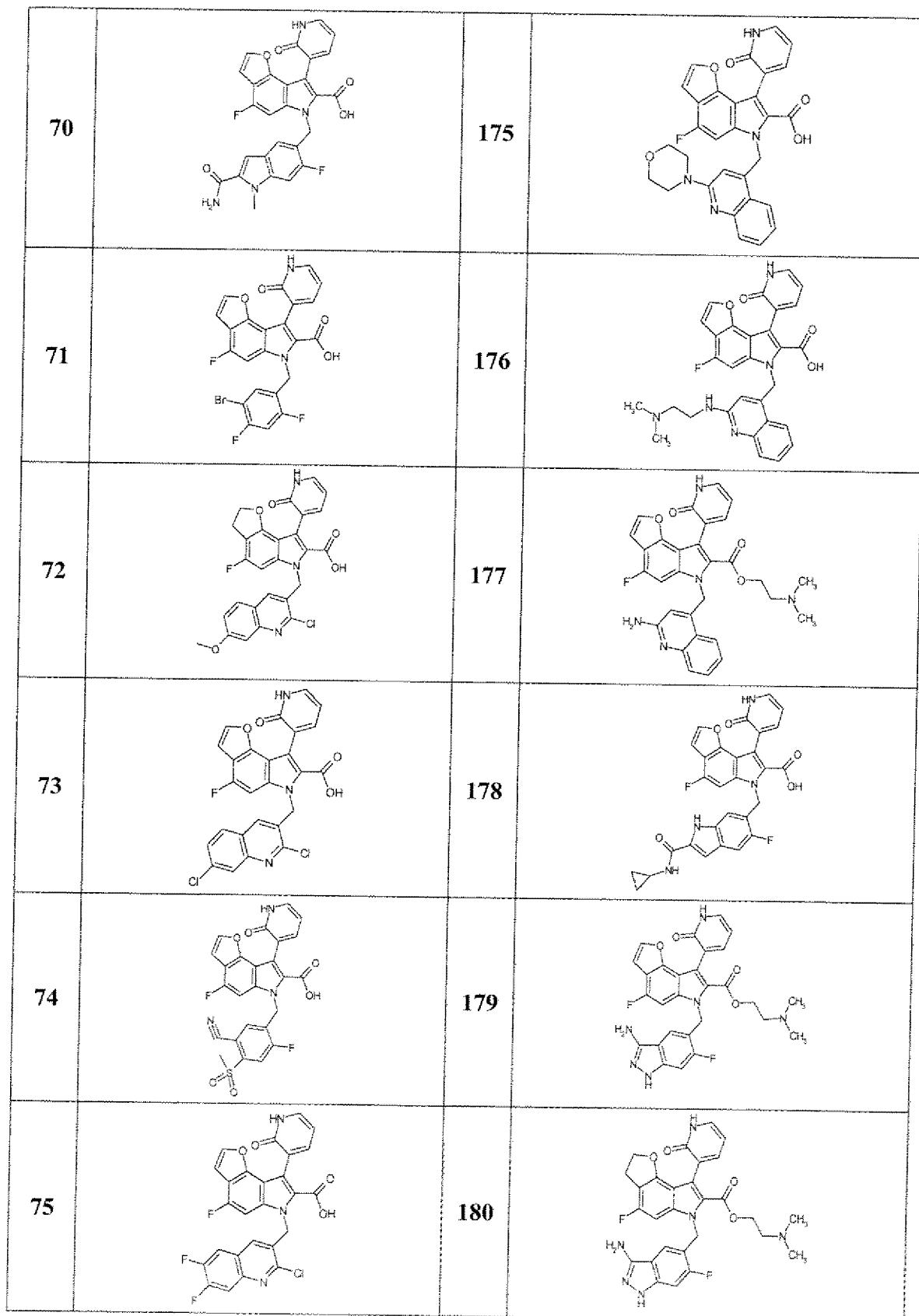


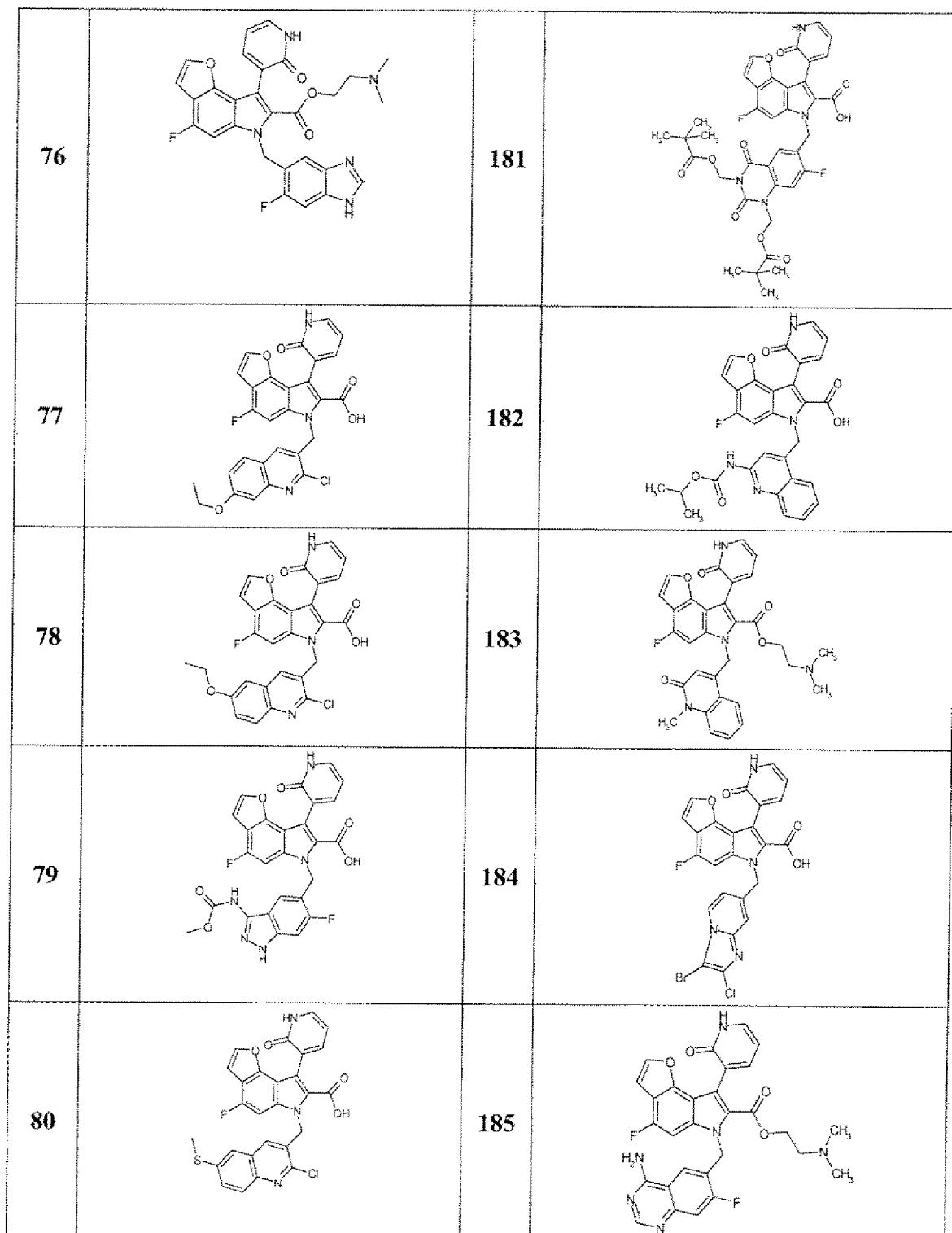




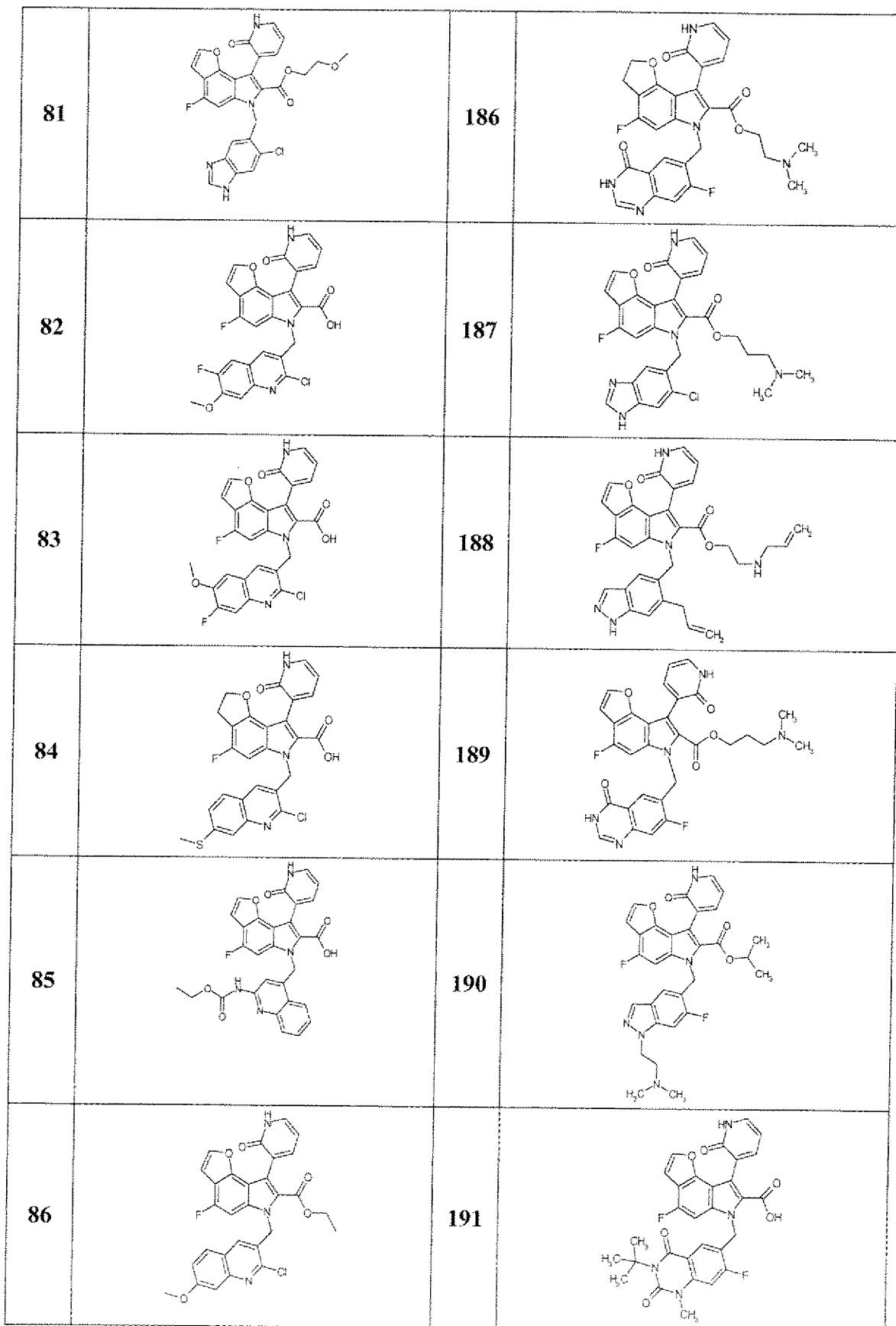
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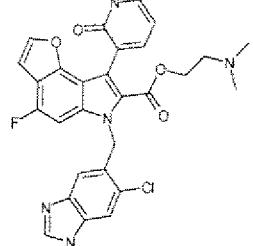
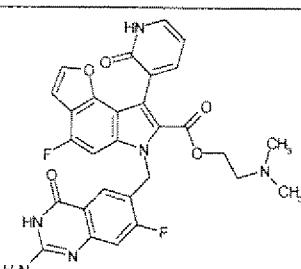
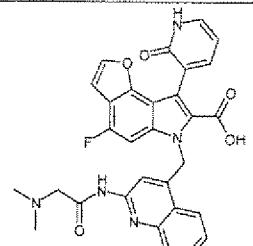
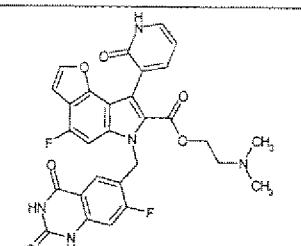
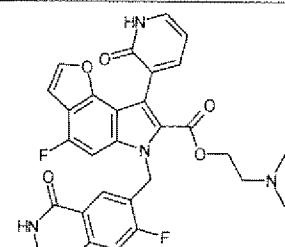
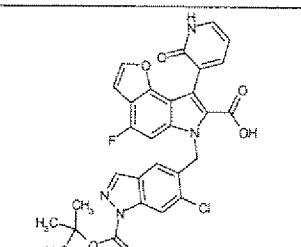
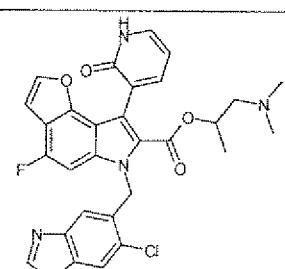
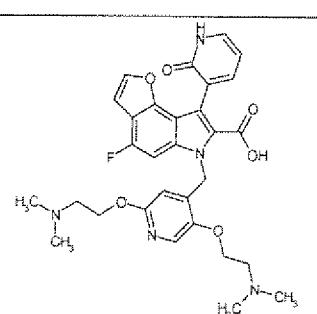
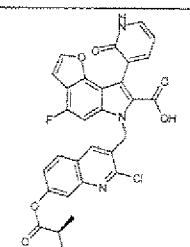
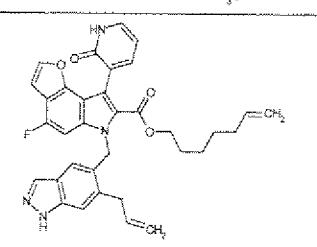
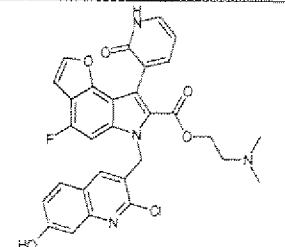
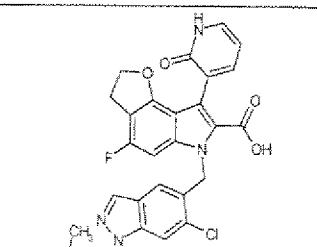




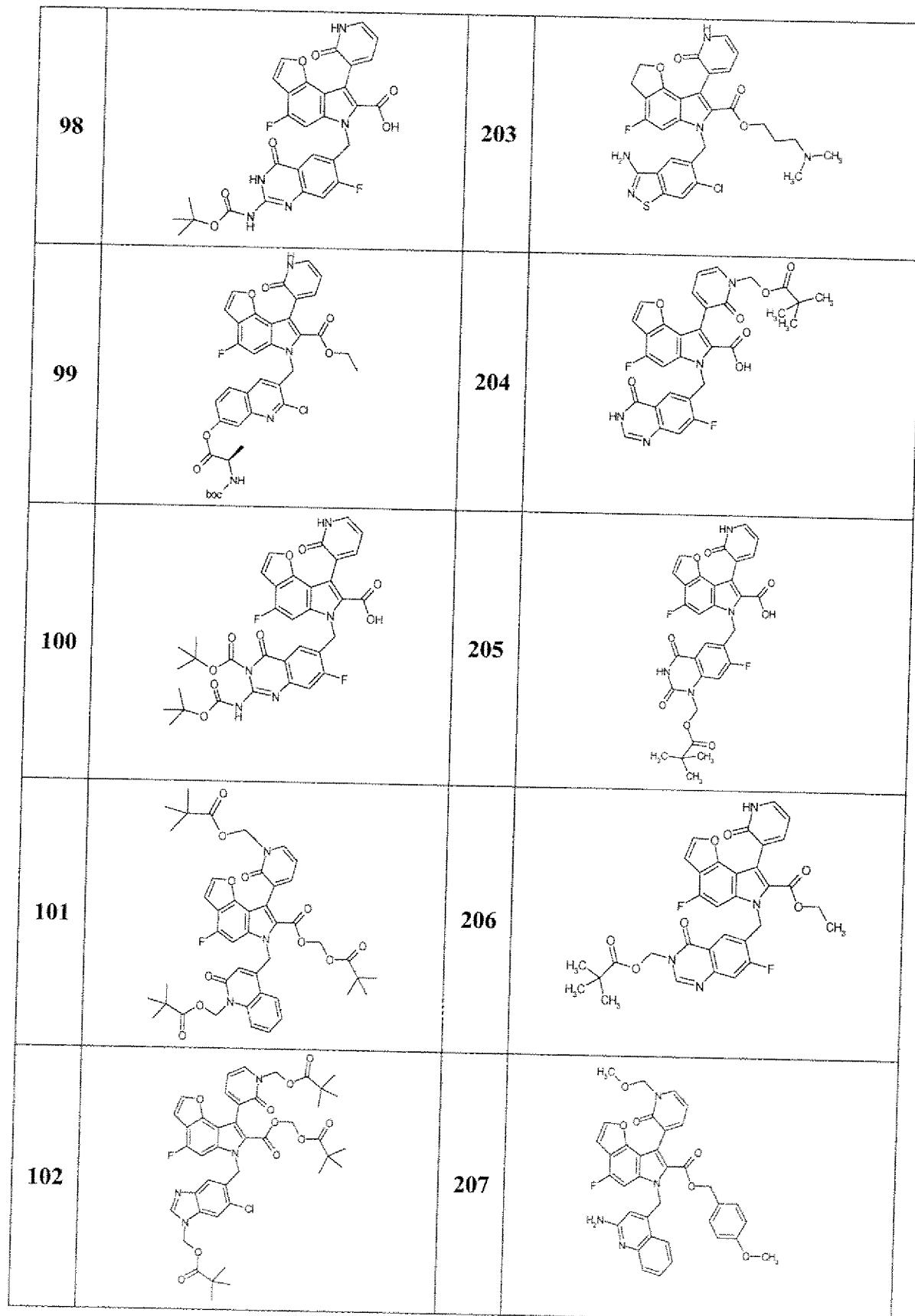


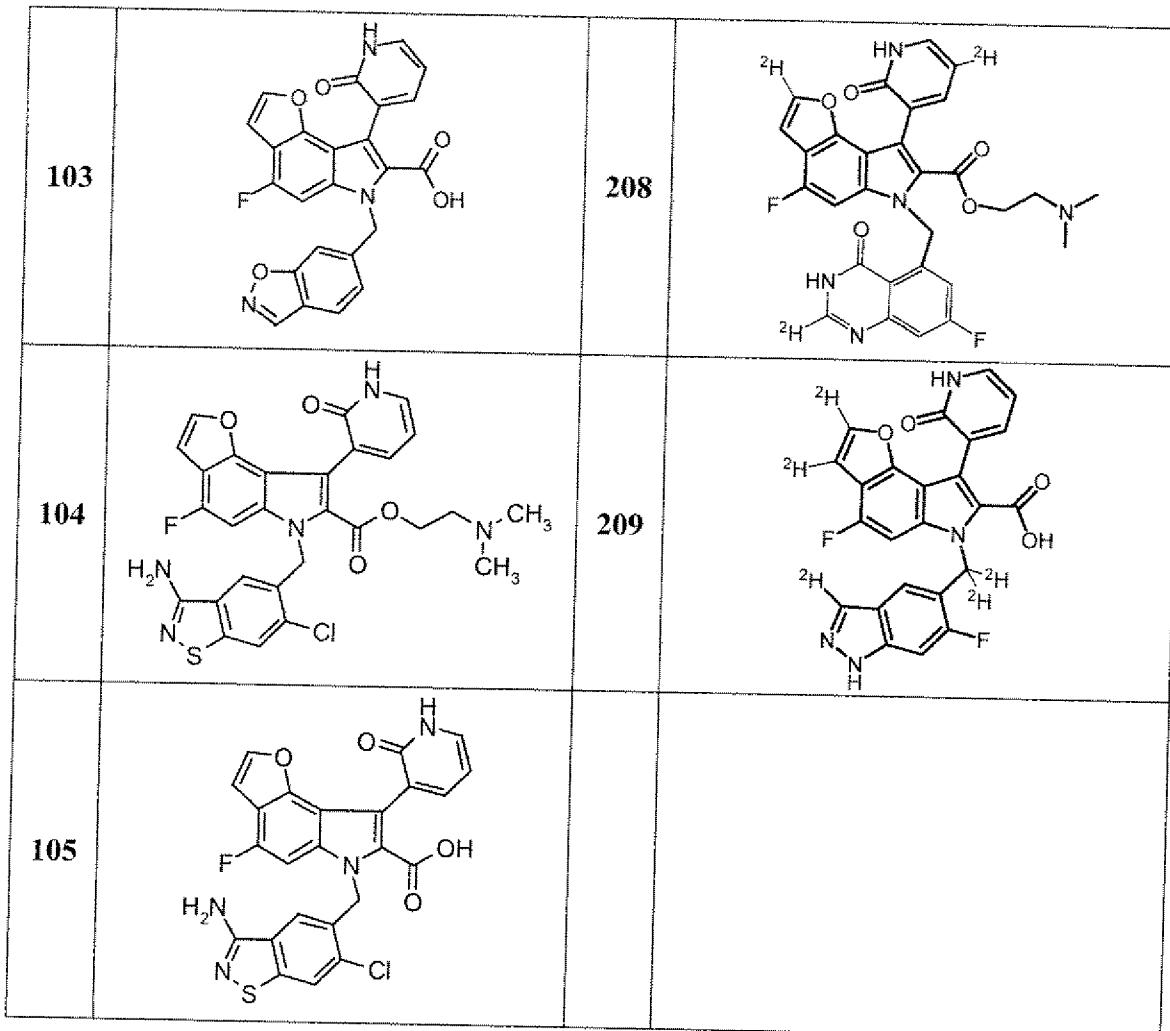
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and pharmaceutically acceptable salts, solvates, esters and prodrugs thereof.

5

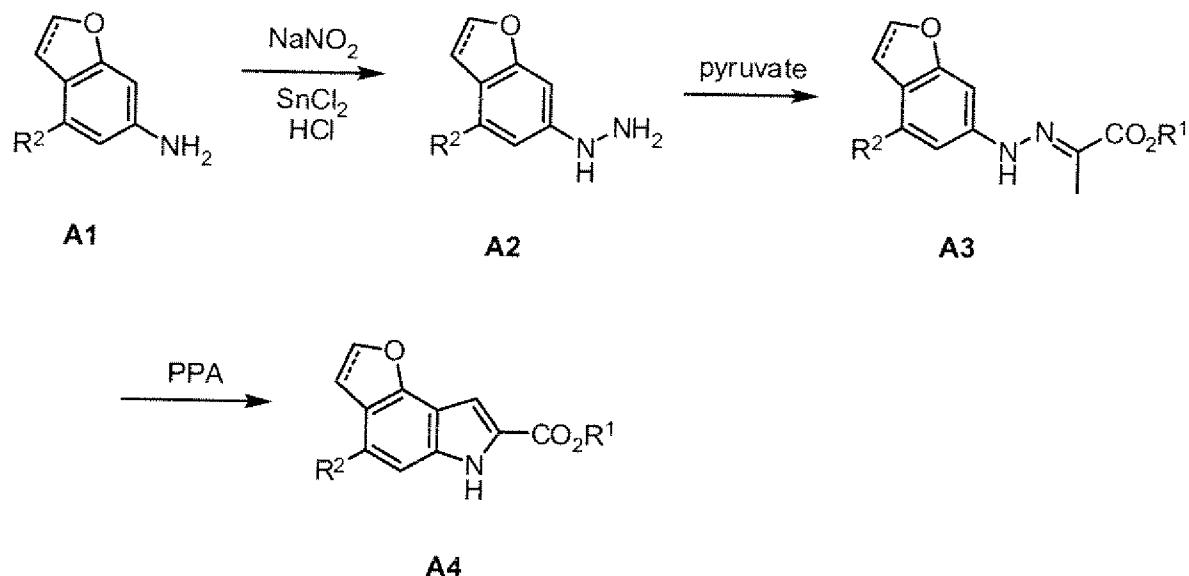
Methods For Making the Compounds of Formula (I)

The Compounds of Formula (I) may be prepared from known or readily prepared starting materials, following methods known to one skilled in the art of organic synthesis. Methods useful for making the Compounds of Formula (I) are set forth in the Examples below and generalized in Schemes 1-4. Alternative synthetic pathways and analogous structures will be apparent to those skilled in the art of organic synthesis. All stereoisomers and tautomeric forms of the compounds are contemplated.

Scheme 1 shows one method for preparing compounds of formula A4, which are useful intermediates for making of the Compounds of Formula (I).

10
15

Scheme 1



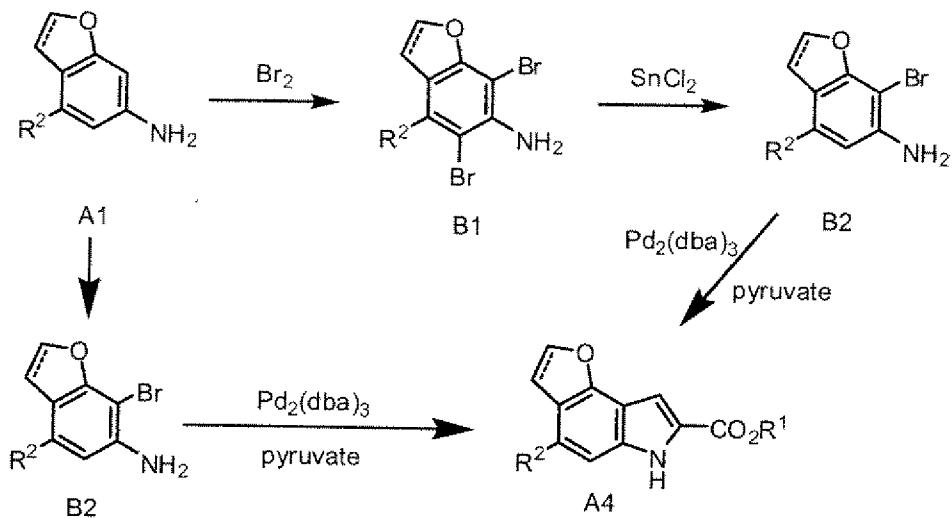
wherein R^1 and R^2 are defined above for the Compounds of Formula (I).

5 A 3,4-ring fused aniline compound of formula **A1** can be converted to an indole compound of formula **A4** using various indole syntheses that are well-known to those skilled in the art of organic synthesis, including but not limited to, a Fischer indole synthesis through intermediates of type **A2** and **A3**, using the method set forth in Nazare *et al.*, *Angew. Chem.*, 116:4626-4629 (2004).

10 Scheme 2 shows alternative methods useful for making the compounds of formula **A4**, which are useful intermediates for making the Compounds of Formula (I).

Scheme 2

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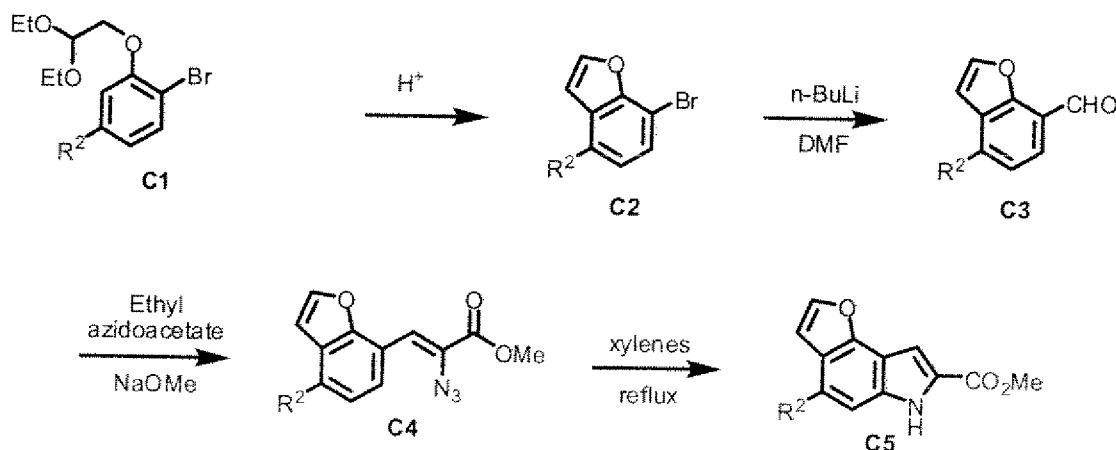
wherein R^1 and R^2 are defined above for the Compounds of Formula (I).

A 3,4-ring fused aniline compound of formula **A1** can be di-brominated to provide a compound of formula **B1**. Selective de-bromination of **B1** using $SnCl_2$ provides the corresponding monobromo compounds of formula **B2**, which under palladium catalyzed cyclization conditions in the presence of an appropriately substituted pyruvate derivative, can provide the compounds of formula **A4**. Alternatively, a compound of formula **A1** can be monobrominated to directly provide a compound of formula **B2**, which can then undergo a similar cyclization to provide a compound of formula **A4**.

Scheme 3 shows a method for making compounds of formula **C5**, which are useful intermediates for making of the Compounds of Formula (I), wherein the optional and additional bond is present and R^1 is methyl.

Scheme 3

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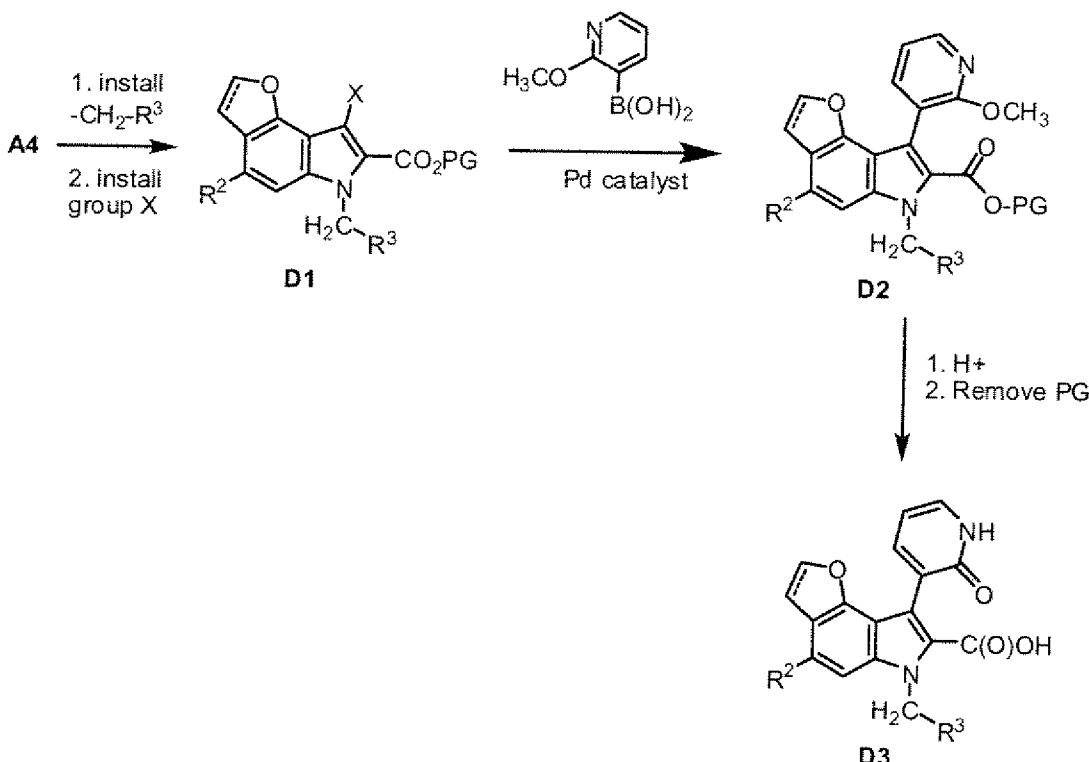


wherein R¹ and R² are defined above for the Compounds of Formula (I).

An ethoxy ether compound of formula **C1**, can be ring closed under acidic conditions (e.g., polyphosphoric acid or Amberlyst-15) to provide the bicyclic compounds of formula **C2**. A compound of formula **C2** can in turn be converted to an aromatic aldehyde of formula **C3** using n-butyllithium in DMF. A compound of formula **C3** can then undergo a condensation reaction in the presence of an alkyl azidoacetate, such as ethylazidoacetate, to provide the azido compounds of formula **C4** which can be subsequently cyclized under thermal conditions to provide the tricyclic indoles of formula **C5**.

Scheme 4 shows a method useful for making compounds of formula **D3**, which are useful intermediates for making of the Compounds of Formula (I).

Scheme 4



wherein X is Br, I, $-\text{OTf}$, $-\text{B}(\text{OH})_2$, $-\text{Sn}(\text{alkyl})_3$, $-\text{MgBr}$, $-\text{MgCl}$, $-\text{ZnBr}$, $-\text{ZnCl}$, or any metal which can participate in an organometallic cross-coupling reaction PG is a carboxy protecting group; and R^2 and R^3 are defined above for the Compounds of Formula (I).

An intermediate compound of formula **A4** can be converted to a 3-substituted indole of formula **D1** using methods well-known to one skilled in the art of organic synthesis. A compound of formula **D1**, wherein X is Br, I or $-\text{OTf}$, can then be coupled with 2-methoxypyridine-3-boronic acid using a Suzuki coupling or a similar organometallic cross-coupling reaction. Alternatively, a compound of formula **D1**, wherein X is $-\text{B}(\text{OH})_2$, $-\text{Sn}(\text{alkyl})_3$, $-\text{MgBr}$, $-\text{MgCl}$, $-\text{ZnBr}$, $-\text{ZnCl}$, or any metal which can participate in an organometallic cross-coupling reaction with 3-halo-2-methoxypyridine or 3-triflyl-2-methoxypyridine using well known organometallic cross-coupling method. Suitable cross-coupling methods include, but not limited to, a Stille coupling (see Choshi *et al.*, *J. Org. Chem.*, 62:2535-2543 (1997), and Scott *et al.*, *J. Am. Chem. Soc.*, 106:4630 (1984)), a Suzuki coupling (see Miyaura *et al.*, *Chem. Rev.*, 95:2457 (1995)), a Negishi coupling (see Zhou *et al.*, *J. Am. Chem. Soc.*, 127:12537-12530 (2003)), and a Kumada coupling (see Kumada, *Pure Appl. Chem.*, 52:669 (1980) and Fu *et al.*, *Angew. Chem.*, 114:4363 (2002)) to provide a compound of formula **D2**. The methoxypyridyl group of E2 can be converted to the

corresponding pyridine by treatment with acid, followed by removal of the protecting group of E2 to provide the compounds of formula **D3**, which correspond to the Compounds of Formula (I), wherein R¹ is H. The -C(O)OH group can be further derivatized to provide Compounds of Formula (I) wherein R² is other than H.

5 The starting material and reagents depicted above are either available from commercial suppliers such as Sigma-Aldrich (St. Louis, MO) and Acros Organics Co. (Fair Lawn, NJ), or can be prepared using methods well-known to those of skill in the art of organic synthesis.

10 One skilled in the art of organic synthesis will recognize that the synthesis of the core of the Compounds of Formula (I) may require the need for the protection of certain functional groups (*i.e.*, derivatization for the purpose of chemical compatibility with a particular reaction condition). Suitable protecting groups for the various functional groups of these compounds and methods for their installation and removal can be found in Greene *et al.*, *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, (1999).

15 One skilled in the art of organic synthesis will also recognize that one route for the synthesis of the core of the Compounds of Formula (I) may be more desirable than others, depending on the choice of appendage substituents. Additionally, one skilled in the art will recognize that in some cases the order of reactions may differ from that presented herein to avoid functional group incompatibilities and amend the synthetic route accordingly.

20 One skilled in the art of organic synthesis will recognize that the synthesis of certain cores of the Compounds of Formula (I) require the construction of an amide bond. Methods useful for making such amide bonds, include but are not limited to, the use of a reactive carboxy derivative (*e.g.*, acid halide, or ester at elevated temperatures) or the use of an acid with a coupling reagent (*e.g.*, EDCI, DCC, HATU, PyBrop) with an amine.

25 The preparation of ring systems contemplated in this invention have been described in the literature and in compendia such as "Comprehensive Heterocyclic Chemistry" editions I, II and III, published by Elsevier and edited by A.R. Katritzky & R JK Taylor. Manipulations of the required substitution patterns have also been described in the available chemical literature as summarized in compendia such as, for example, "Comprehensive Organic Chemistry" published by Elsevier and edited by DH R. Barton and W. D. Ollis; "Comprehensive Organic 30 Functional Group Transformations" edited by edited by A.R. Katritzky & R JK Taylor; and "Comprehensive Organic Transformation" published by Wiley-CVH and edited by R. C. Larock.

The starting materials used and the intermediates prepared using the methods set forth in schemes 1-4 above may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and alike. Such materials can be characterized using conventional means, including physical constants 5 and spectral data.

EXAMPLES

General Methods

Solvents, reagents, and intermediates that are commercially available were used as 10 received. Reagents and intermediates that are not commercially available were prepared in the manner as described below. ^1H NMR spectra were obtained on a Bruker Avance 500 (500 MHz) and are reported as ppm down field from Me₄Si with number of protons, multiplicities, and coupling constants in Hertz indicated parenthetically. Where LC/MS data are presented, analyses was performed using an Applied Biosystems API-100 mass spectrometer and 15 Shimadzu SCL-10A LC column: Altech platinum C18, 3 micron, 33 mm x 7mm ID; gradient flow: 0 minutes – 10% CH₃CN, 5 minutes – 95% CH₃CN, 5-7 minutes – 95% CH₃CN, 7 minutes – stop. The retention time and observed parent ion are given. Flash column chromatography was performed using pre-packed normal phase silica from Biotage, Inc. or 20 bulk silica from Fisher Scientific. Unless otherwise indicated, column chromatography was performed using a gradient elution of hexanes/ethyl acetate, from 100% hexanes to 100% ethyl acetate.

Example 1

Preparation of Intermediate Compound 1E

25

Step A – Synthesis of Compound 1A



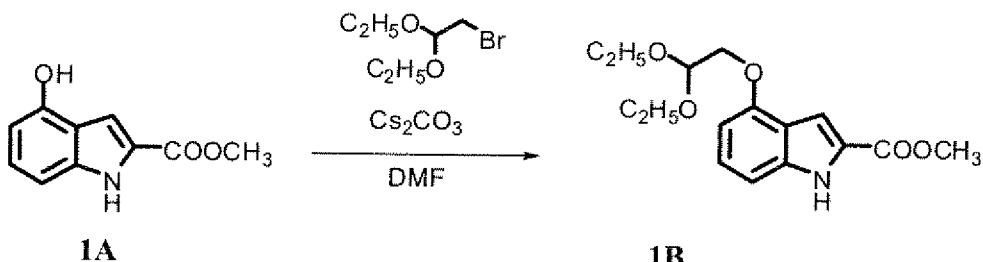
1A

A solution of 4-methoxy-1*H*-indole-2-carboxylic acid methyl ester (410 mg, 2.00 30 mmol) in CH₂Cl₂ (5 mL) was cooled to -78 °C and BBr₃ (6mL solution, 1M) was added. The

resulting reaction was then allowed to stir at 0 °C for 3 hours. The reaction mixture was then quenched using water and the resulting solution was extracted with EtOAc (200 mL). The combined organic layers were dried (MgSO_4), filtered, concentrated *in vacuo* and purified using flash column chromatography to provide compound **1A**.

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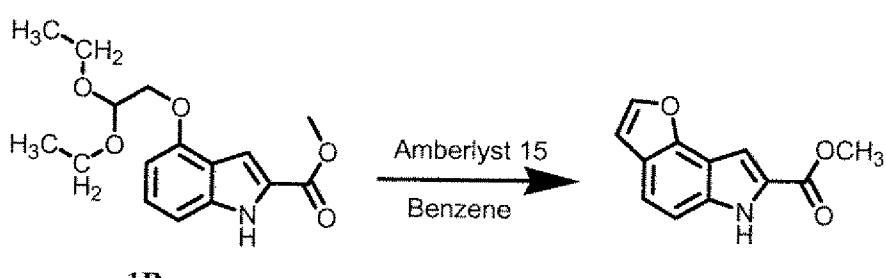
Step B – Synthesis of Compound 1B



To a solution of compound **1A** (2.5 g, 13.10 mmol) in DMF (50 mL) was added

10 Cs_2CO_3 (5.12 g, 15.72 mmol), then bromoacetaldehyde-diethylacetal (12.90 g, 65.6 mmol), and the resulting reaction was allowed to stir at reflux for 2 hours. The reaction mixture was cooled to room temperature, treated with aqueous NaOH (1M, 50 mL) and extracted into EtOAc (250 mL). The organic layers were combined, dried (MgSO_4), filtered, and concentrated *in vacuo* to provide a crude residue which was purified using flash column chromatography (Hexanes/EtOAc 0 to 100%) to provide compound **1B** as a colorless solid.

Step C – Synthesis of Compound 1C



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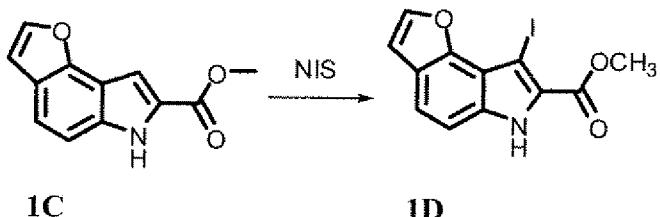
20 1B 10

To a solution of compound **1B** in benzene (60 mL) was added Amberlyst-15 strongly acidic resin (4.5 g) and the resulting reaction was heated to 70 °C and allowed to stir at this temperature for 4 hours. The reaction mixture was then cooled to room temperature, diluted with EtOAc (300 mL) and washed with aqueous NaHCO₃. The combined organic layers were dried (MgSO₄), filtered, concentrated *in vacuo* and purified using flash column

chromatography on silica gel (EtOAc/Hexanes, 0-30% EtOAc) to provide compound **1C** (1.2 g).

Step D – Synthesis of Compound 1D

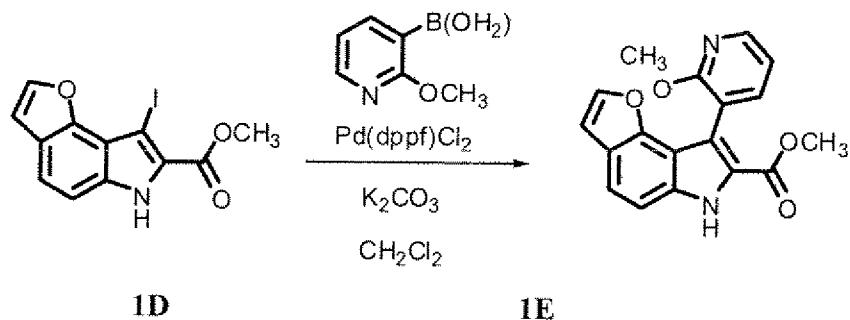
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To a solution of compound **1C** (2.00 g, 9.3 mmol) in DMF (20 mL) was added N-iodosuccinimide (2.29 g, 10.2 mmol) and the resulting reaction was allowed to stir at room temperature for 12 hours. The reaction mixture was then concentrated *in vacuo*, diluted with water and extracted into EtOAc (300 mL). The combined organic layers were dried (MgSO_4), filtered, and concentrated *in vacuo*. The resulting brown residue was diluted with a minimum amount of CH_2Cl_2 and triturated using hexanes. Compound **1D** separated out as a brown solid, which was filtered, then dried *in vacuo*. (Yield 2.6 g, 84%).

15

Step E – Synthesis of Compound 1E



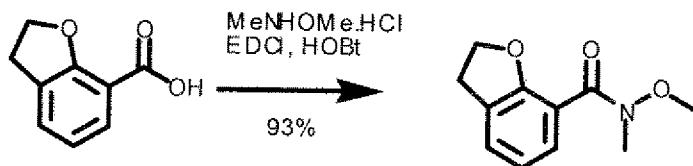
20 To a solution of compound **1D** (2.6 g, 7.6 mmol) in DME (40 mL) under nitrogen atmosphere was added with 2-methoxy-3-pyridyl boronic acid (3.5 g, 22.8 mmol) and Pd (dppf)₂Cl₂ (616 mg) and the resulting reaction was allowed to stir at room temperature under nitrogen for 0.5 hours. The reaction mixture was then treated with a solution of potassium carbonate (6.3 g, 45.6 mmol) in water (40 mL) and the resulting solution was heated to 90 °C
 25 and allowed to stir at this temperature for 1 hour. The reaction mixture was then diluted with EtOAc (300 mL) and the resulting solution was concentrated *in vacuo* to provide a crude

residue which was purified using flash column chromatography (EtOAc/Hexanes, 0 to 50% EtOAc) to provide compound **1E** as a solid (2.0 g).

Example 2

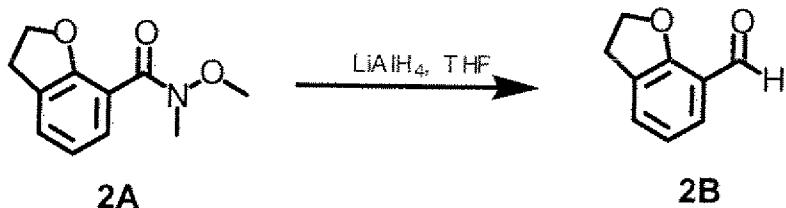
Preparation of Intermediate Compound 2F

Step A – Synthesis of Compound 2A



A suspension of 2,3-dihydro-benzofuran-7-carboxylic acid, (TCI, 20.0 g, 121.8 mmol) in 600 mL of dry acetonitrile was cooled to 0 °C and treated with N,O-dimethylhydroxylamine hydrochloride (14.25 g, 146.1 mmol). The reaction was allowed to stir for 10 minutes and EDCI (24.6 g, 158.3 mmol) was added, followed by HOBT (3.2 g, 24.2 mmol) and the resulting mixture was allowed to stir for 5 minutes. Triethylamine (365.4 mmol) was then added and the reaction mixture was allowed to stir for 18 hours at room temperature, then diluted with aqueous 1N HCl (250 mL) and extracted with ethyl acetate (1.0 L). The organic layer was sequentially washed with aqueous 10% potassium carbonate (200 mL), aqueous 1N HCl (200 mL), and brine (200 mL). The organic layer was then dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide compound **2A** (23.37 g, 93 %) as a colorless oil. M.S. found for $C_{11}H_{13}NO_3$; 230.11 ($M+Na$)⁺.

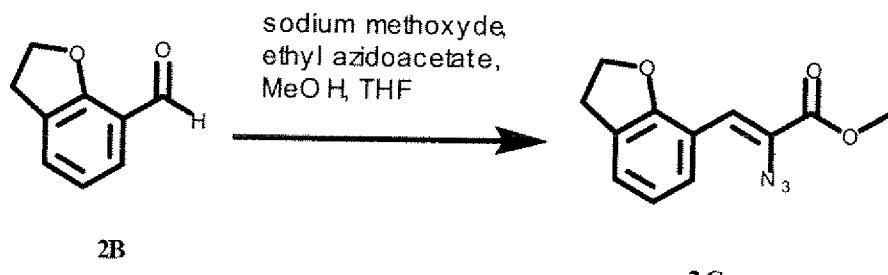
Step B – Synthesis of Compound 2B



25 A suspension of lithium aluminum hydride (pellets, 5.56 g, 146.5 mmol) in 500 mL of dry THF was allowed to stir at 55 °C for 18 hours under anhydrous atmosphere, then cooled to 0 °C, and a solution of compound **2A** (23.37 g, 112.7 mmol) in 500 mL of dry THF was added

over 45 minutes. The reaction mixture was allowed to stir at 0 °C for 30 minutes, then quenched by careful addition of aqueous 20% sodium hydrogen sulfate until gas evolution stopped. Additional aqueous 20% sodium hydrogen sulfate (approx. 5 mL) was added, and the resulting solution was vigorously allowed to stir for 15 minutes. The reaction mixture was 5 diluted with ether (500 mL) and hexanes (500 mL) and filtered through a short path of celite. The filtrate was concentrated *in vacuo* to provide a crude residue which was purified using medium pressure liquid chromatography (Biotage 75-M silica gel column, gradient: 0 to 30 % ethyl acetate in hexanes) to provide compound **2B** (9.00 g, 54 %) as a white solid. ¹H NMR (400 MHz, d₆-DMSO): δ 10.10 (s, 1H), 7.51 (q, J = 7.32 Hz & 5.13 Hz, 2H), 6.95 (t, J = 7.69 Hz, 1H), 4.69 (t, J = 8.79 Hz, 2H), 3.22 (t, J = 8.42 Hz, 2H).

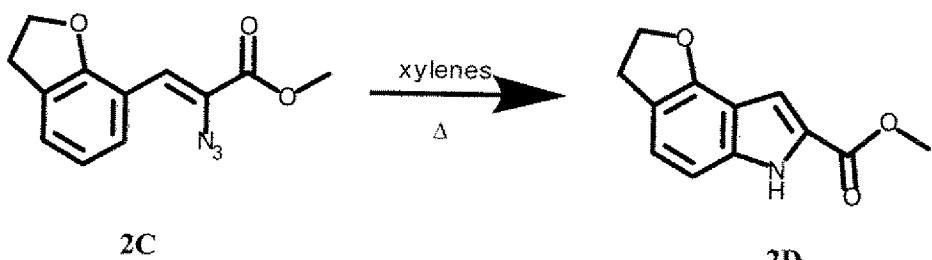
Step C – Synthesis of Compound 2C



15 A solution of freshly prepared sodium methoxide in methanol (2.5 eq, prepared by dissolving 1.94 g of sodium in 80 mL of methanol) was added dropwise (over 20 minutes) to a cooled (-20 °C, internal temperature) solution of compound **2B** (5.0 g, 33.74 mmol) and ethyl azidoacetate (10.9 g, 84.36 mmol) in 20 mL of dry methanol and 20 mL of dry THF. The 20 addition was carried such that the internal reaction temperature was not permitted to rise above -10 °C. The reaction was then allowed to stir at -10 °C for 1 hour, then allowed to warm to room temperature over 1 hour. The reaction mixture was then allowed to stir at room temperature for 1 hour (a white precipitate formed), and was then quenched with aqueous saturated ammonium chloride solution (10 mL). The resulting solution mixture was partitioned 25 between ethyl acetate (500 mL) and water (100 mL). The organic layer was washed with brine (80 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified using column chromatography on silica gel (Biotage 75-M column; gradient: 0 to 25% ethyl acetate in hexanes) to provide compound **2C** (4.20 g, 52 %) as a slightly yellow solid. ¹H NMR (400 MHz, d₆-DMSO): δ 7.96 (d, J = 8.06 Hz, 1H), 7.24 (d, J =

6.59 Hz, 1H), 7.01 (s, 1H), 6.88 (t, J = 7.69 Hz, 1H), 4.58 (t, J = 8.79 Hz, 2H), 3.84 (s, 3H), 3.21 (t, J = 8.79 Hz, 2H).

Step D – Synthesis of Compound 2D



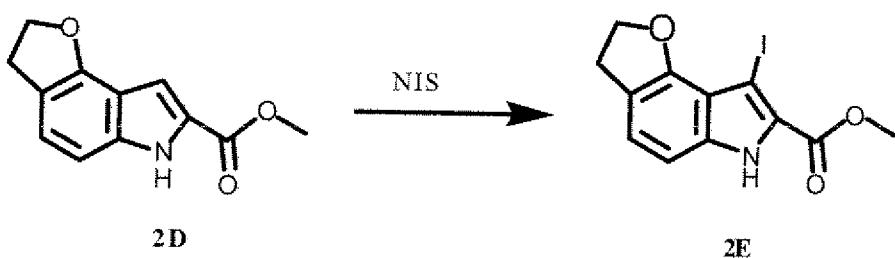
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A solution of compound **2C** (4.0 g, 16.31 mmol) in 60 mL of xylenes was heated to 150 °C and allowed to stir at this temperature for 10 minutes, then was cooled to room temperature, during which time a white solid formed. The suspension was stored as -20 °C in freezer for 1 hour, then filtered to provide compound **2D** as a white solid (1.0 g). The filtrate was concentrated *in vacuo*, and the resulting residue was purified using column chromatography on silica gel (Biotage 40-S column; gradient: 0 to 35% ethyl acetate in hexanes) to provide an additional amount of compound **2D** (290 mg). (Total yield = 1.29 g, 37%). ¹H NMR (400 MHz, d₆-DMSO): δ 11.91 (s, 1H), 7.12 (d, J= 8.06 Hz, 1H), 6.96 (s, 1H), 6.95 (d, J= 8.06 Hz, 1H), 4.65 (t, J= 8.79 Hz, 2H), 3.85 (s, 3H), 3.22 (t, J= 8.79 Hz, 2H).

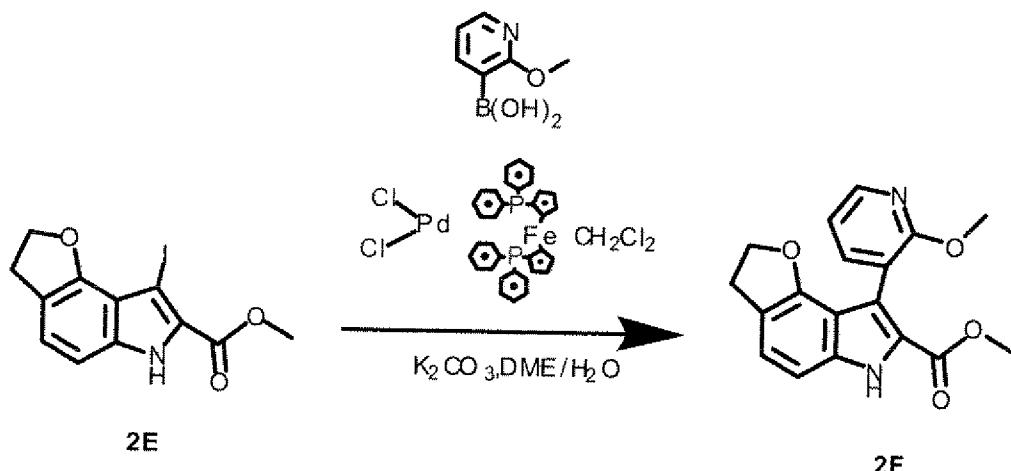
Step E—Synthesis of Compound 2E



To a solution of compound **59D** (1.45 g, 6.67 mmol) in 50 mL of chloroform and 20 mL of THF at 0 °C was added N-iodosuccinimide (1.65 g, 7.34 mmol). The resulting reaction was allowed to stir at 0 °C for 30 minutes, then warmed to room temperature and allowed to stir at this temperature for 30 minutes. The reaction mixture was then diluted with ethyl acetate (100 mL), and the resulting solution was sequentially washed with aqueous saturated sodium thiosulfate (20 mL), aqueous saturated sodium bicarbonate (20 mL) and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The

crude product was purified using column chromatography on silica gel (Biotage 40-S column; gradient: 0 to 40 % ethyl acetate in hexanes) to provide compound **59E** (190 mg, 10 %) as a white solid. M.S. found for $C_{12}H_{10}INO_3$: 343.87 ($M+H$)⁺.

5 *Step F – Synthesis of Compound 2F*

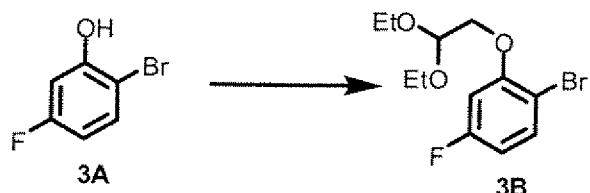


To a solution of compound **2E** (180 mg, 0.524 mmol) in 10 mL of 1,2-dimethoxyethane was added 2-methoxy-3-pyridine boronic acid (240 mg, 1.573 mmol) and the resulting mixture was de-gassed (vacuum/argon flush), and $\text{PdCl}_2(\text{dppf})_2$ (10 mol%, 42 mg) was added. The resulting mixture was allowed to stir for 15 minutes at room temperature and a solution of potassium carbonate (434 mg, 3.144 mmol) was added. The resulting brown reaction was heated to 90 °C and allowed to stir at this temperature for 45 minutes. The reaction mixture was then cooled to room temperature, and diluted with ethyl acetate (80 mL). The organic layer was washed sequentially with aqueous saturated sodium bicarbonate (10 mL) and brine (10 mL), then dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified using column chromatography on silica gel (Biotage 25-S column; gradient: 10 to 50 % ethyl acetate in hexanes) to provide compound **2F** (140 mg, 83 %) as a white solid. M.S. found for $C_{18}H_{16}N_2O_4$: 325.07 ($M+H$)⁺.

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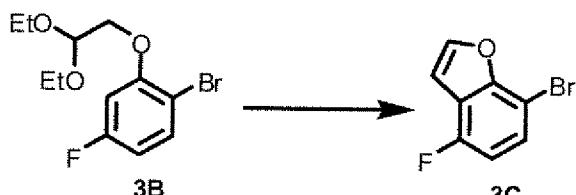
Example 3
 Preparation of Intermediate Compound **3L**

Step A – Synthesis of Compound 3B



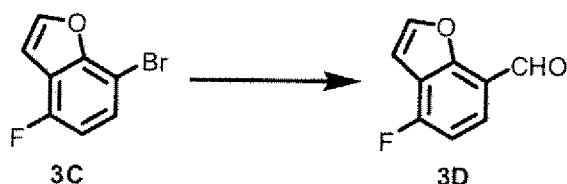
A solution of compound **3A**, (228.00 g, 1.19 mmol), Potassium carbonate (247.47 g, 1.79 mol) in DMF (3.00 L) was treated with 2-Bromo-1,1-diethoxyethane (197.54 mL, 1.31 mol) and heated at 135 °C for 7 hours. The reaction mixture was concentrated *in vacuo* and extracted with EtOAc (3x 2L). The combined organic layers were washed with aqueous NaOH (2M, 4 L). The organic layer was dried (MgSO_4), filtered, concentrated *in vacuo* to provide compound **3B** (362.00 g, 98%) which was used without further purification.

Step B – Synthesis of Compound 3C



A solution of compound **3B** (352.00 g, 1.15 mol) in toluene (2500 mL, 2.3 mol) was treated with polyphosphoric acid (370.00 g, 3.4 mol) and heated at reflux for 5 hours. The reaction mixture was concentrated *in vacuo*, diluted with water (3L) and then extracted with EtOAc (4 L). The organic layer was washed with aqueous NaOH (2L), filtered, concentrated *in vacuo* and purified using distillation at reduced pressure to provide compound **3C** (125.00 g, 50.8%). Bp. 80 °C (1mm/Hg) as a colorless liquid which solidified at room temperature. ¹H NMR (400 MHz, CDCl₃) δ 7.67 (d, 1 H, J = 2.2 Hz), 7.39 (dd, 1 H J = 5.1 & 3.7 Hz), 6.94 (d, 1 H, J = 2.2 Hz), 6.86 (t, 1 H, J = 8.8 Hz).

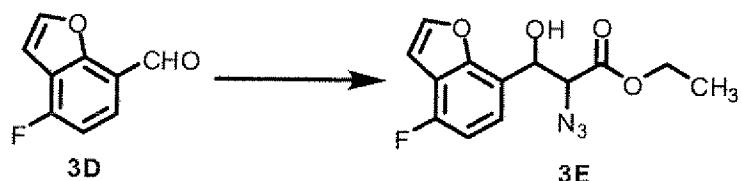
20 Step C – Synthesis of Compound 3D



A solution of compound **3C** (124.12 g, 577.25 mmol) in ether (2.0 L) was cooled to -78 °C and treated dropwise with a solution of 2.5 M of n-butyllithium in hexane (235.5 mL) and allowed to stir at -78 °C for 15 minutes. To this reaction mixture was added DMF (89.393

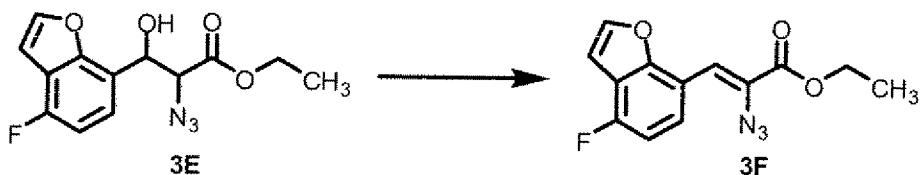
mL, 1.15 mol) and allowed to stir at -78 °C for 30 minutes. The reaction mixture was quenched with methanol (23.383 mL, 577.25 mmol) and warmed to room temperature. The reaction mixture was diluted with ether (300 mL) and the organic layer was washed with water (300 mL). The separated organic layer was dried (MgSO_4) filtered, concentrated *in vacuo* to provide 5 compound **3D** (89.00 g, 93.9%).

Step D – Synthesis of Compound 3E



A solution of compound **3D** (12.71 g, 77.45 mmol), lithium chloride (6.567 g, 154.9 mmol) and ethyl azidoacetate (20.00 g, 154.9 mmol; added as a 30% solution in CH_2Cl_2), diazabicyclo[5.4.0]undec-7-ene (23.16 mL, 154.9 mmol) and stirred for 2 hours. The completion of the reaction was followed by TLC ($\text{EtOAc}/\text{Hexanes}$ 1:4). Upon completion, the reaction mixture was diluted with ethyl acetate (1L) and washed with water and aqueous HCl (400 mL). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo* and the residue obtained was purified using flash column chromatography SiO_2 ($\text{EtOAc}/\text{Hexanes}$) to provide compound **3E** (18.3 g, 80.6%) as a colorless oil.

Step E – Synthesis of Compound 3F

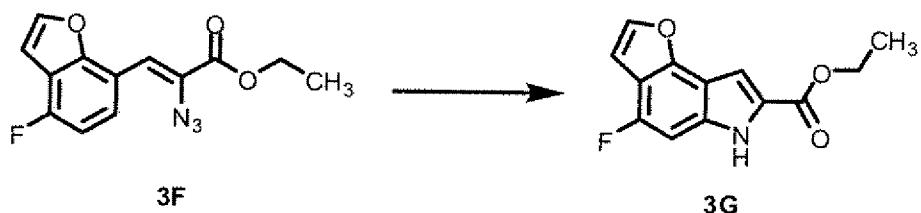


A solution of compound **3E** (15.7 g, 53.5 mmol) and methanesulfonyl chloride (8.29 mL, 107 mmol) in methylene chloride (87.7 mL, 1.37 mmol) at -30 °C was treated dropwise with a solution of triethylamine (52.2 mL, 375.0 mmol) in methylene chloride (100 mL). The reaction mixture was allowed to stir at -30 °C for 3 hours, diluted with aqueous saturated 20 sodium bicarbonate and methylene chloride (400 mL). The organic layer was separated and washed with water, aqueous HCl and brine. The organic layer was dried (MgSO_4), filtered, concentrated *in vacuo*, and purified using flash column chromatography (SiO_2 , 10% EtOAc in 25 $\text{EtOAc}/\text{Hexanes}$) to provide compound **3F** (11.5 g, 70.0%) as a colorless oil.

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(1:1) Hexanes/CH₂Cl₂) to provide compound **3F** (12.6 g, 85.5%).

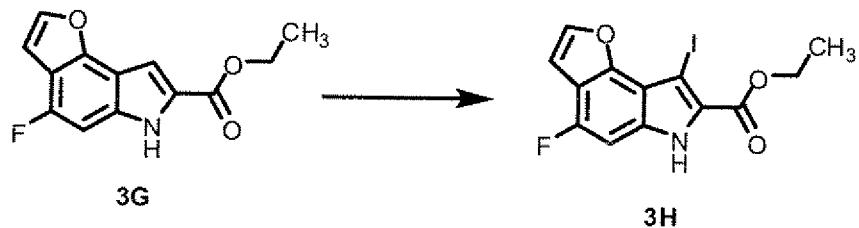
Step F – Synthesis of Compound 3G



5

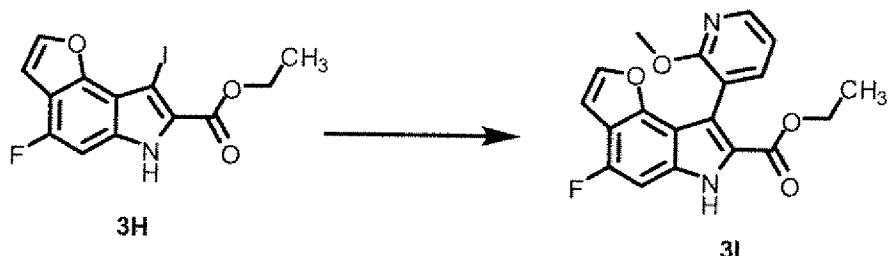
150 mL of xylenes was heated at 165 °C. To this boiling solution was added dropwise a solution of compound **3F** (11.2 g, 40.7 mmol) in Xylenes (70 mL, 189.4 mmol). The reaction mixture was stirred for additional 20.0 minutes and allowed to cool to room temperature to provide compound **3G** as a precipitate (7.00 g, 69.6%), which was filtered, washed with hexanes and dried *in vacuo*.

Step G – Synthesis of Compound 3H



15 To a solution of compound **3G** (15.88 g, 64.23 mmol) in DMF (100 mL) was added N-iodosuccinimide (15.90 g, 70.66 mmol) and allowed to stir at room temperature. for 2 hours. The reaction mixture was diluted with water (1000 mL) and extracted in EtOAc (1000 mL). The organic layer was washed with water (1000 mL), aqueous sodium thiosulfate (5% aqueous soln. 1L) and dried (MgSO_4). The organic layer was dried (MgSO_4), filtered, concentrated *in vacuo* to provide compound **3H** (22.30 g, 93.04%) as a solid.

Step H – Synthesis of Compound 3I

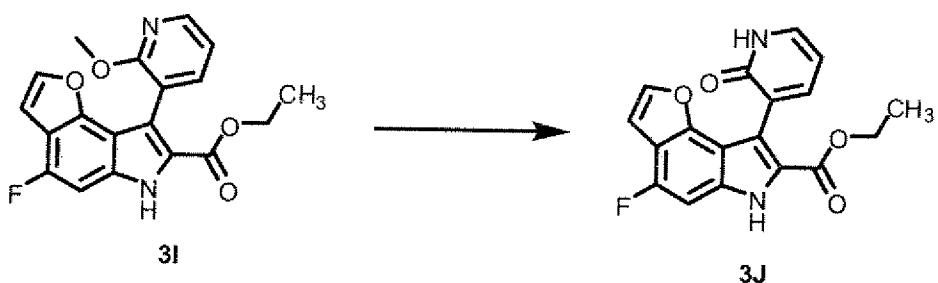


A solution of compound **3H** (22.000 g, 58.962 mmol), 2-methoxypyridin-3-ylboronic acid (13.527 g, 88.444 mmol), $(PPh_3)_2PdCl_2$ (4.13 g, 5.88 mmol) in 1,2-dimethoxyethane (250.0 mL) was degassed for 2 min and allowed to stir at room temperature for 15 minutes.

5 The orange reaction mixture was treated with a solution of potassium carbonate (30.53 g, 220.9 mmol) in water (250.0 mL) and allowed to stir at 90 °C for 3 hours. The yellow reaction turned orange dark with the disappearance of starting material (TLC). The reaction mixture was diluted with EtOAc (1000 mL) and washed with aqueous NaOH (500 mL, 1M), dried ($MgSO_4$), filtered, concentrated *in vacuo*, and purified using flash column chromatography

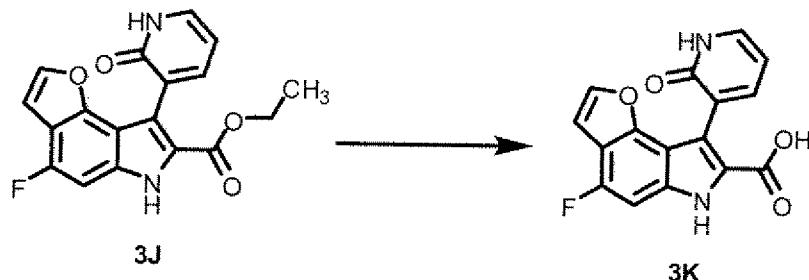
10 SiO_2 (THF/Hexanes 0--> 60%) to provide compound **3I** (16.65 g, 79.7%) as pale brown solid.

Step I – Synthesis of Compound 3J



15 A solution of compound **3I** (4.50 g, 12.7 mmol) in methanol (10 mL, 246.9 mmol) was treated with a solution of 4 M HCl in dioxane (100 mL) and heated at 90 °C for 3 hours in a pressure tube. The reaction mixture was concentrated *in vacuo* and the residue obtained was purified using flash column chromatography (SiO_2 , THF/Hexanes 0--> 100%) to provide compound **3J** as a colorless solid.

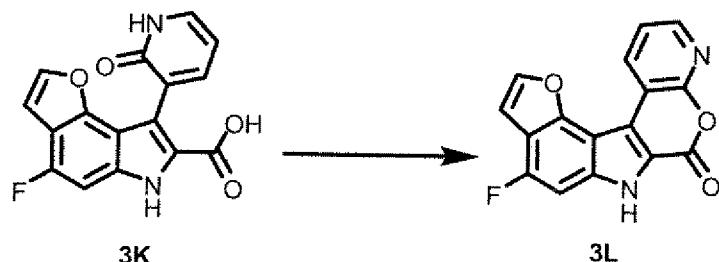
Step J – Synthesis of Compound 3K



A solution of compound **3J** (810.00 mg, 2.38 mmol) in water (25mL), THF (25mL) and methanol (25mL, 780.2 mmol) was treated with lithium hydroxide monohydrate (499.41 mg, 11.901 mmol) and heated at 80 °C for 1 hour. The reaction mixture was then acidified using

5 1N HCl, filtered and dried *in vacuo* to provide compound **3K** (627.00 mg, 84.4%) as colorless solid.

Step K – Synthesis of Compound 3L

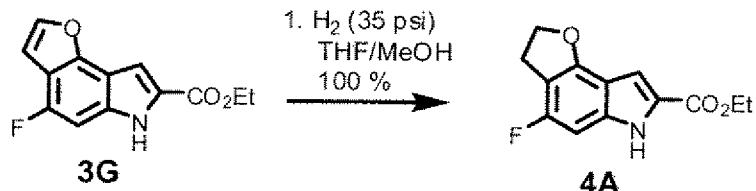


10 To a suspension of compound **3K** (8.00 g, 25.6 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (9.82 g, 51.2 mmol) in DMF (153.85 mL) was added triethylamine (35.71 mL, 256.2 mmol) and the reaction was stirred overnight at room temperature. The reaction mixture was concentrated *in vacuo* and the resulting residue was diluted with methanol (100 mL). The resulting precipitate was filtered

15 and dried to provide compound **3L** (5.90 g, 78.3%)

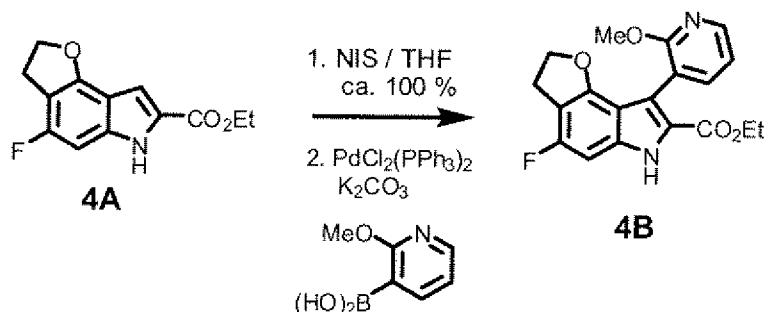
Example 4
Preparation of Intermediate Compound **4D**

20 *Step A – Synthesis of Compound 4A*



A solution of **3G** (5.0 g; 20.22 mmol) in 220 mL of a 2:1 MeOH/THF mixture was treated with a catalytic amount of 10 % palladium on carbon (5 mol%, 1.07 g). The mixture was hydrogenated at 35 psi for 18 hours. NMR of an aliquot showed complete conversion into product. The mixture was diluted with dichloromethane (300 mL) and the solids were removed by filtration through a short path of celite. The filtrate was concentrated *in vacuo* to provide the product **4A** (5.03 g; 99 %) as a white solid.

Step B – Synthesis of Compound 4B

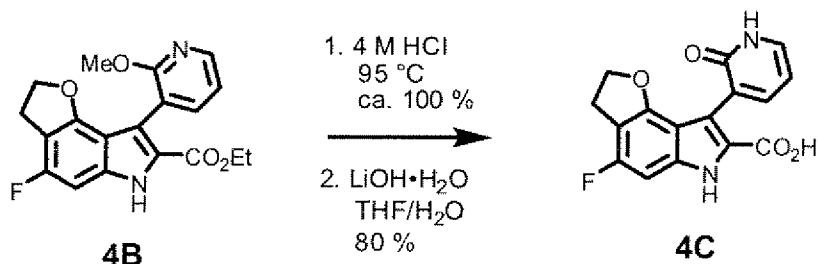


A solution of **4A** (7.81 g; 31.34 mmol) in 300 mL of THF was cooled to -78 °C and treated with a solution of N-iodosuccinimide (1.1 eq, 7.75 g in 100 mL of THF). The mixture was stirred for 20 min and TLC (25 % THF in hexanes) showed complete consumption of starting material. The reaction was quenched by addition of aqueous saturated sodium bicarbonate soln (100 mL). The mixture was allowed to reach room temperature and the product was dissolved in ethyl acetate (800 mL). The organic layer was washed with aqueous saturated sodium bicarbonate (100 mL) and brine (80 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product (ca. 100 %, 11.75 g) was used directly in the next reaction.

20 The product above (11.75 g; 40.44 mmol) was dissolved in 400 mL of 1,2-dimethoxyethane was treated with 2-methoxypyridine-3-boronic acid (2.0 eq, 12.3 g) and bis(triphenylphosphine)palladium(II) chloride (0.1 eq, 2.8 g). The mixture was stirred for 10 min followed by addition of aqueous potassium carbonate (4.0 eq, 80.8 mL of 2 M soln). The mixture was stirred at 90 °C and the progress of the reaction was followed by TLC (25 % THF

in hexanes). The reaction was completed after ~ 2 hours, then the mixture was diluted with ethyl acetate (600 mL) and washed with aqueous saturated sodium bicarbonate (2 x 200 mL) and brine (200 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude product as a brown solid. The crude product was 5 treated with acetonitrile (200 mL) and stirred in an oil bath at 90 °C. Acetonitrile was added in portions (50 mL) until the mixture became a homogeneous dark solution (approx. 300 mL). The heating bath was removed and the mixture was allowed to reach room temp. The mixture was then placed in a freezer (-20 °C) overnight. The mother liquor was removed (decantation) and the solids were washed with ether (50 mL). The crystallized product **4B** was dried under 10 high vacuum (11.66 g, 82 %) to provide a slightly yellow powder.

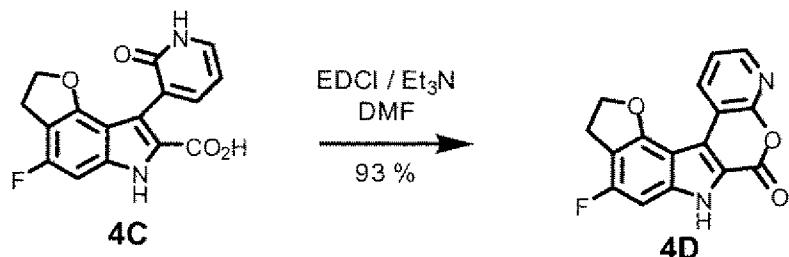
Step C – Synthesis of Compound 4C



15 Compound **4B** was divided into two batches and treated separately. Each batch was dissolved in 4 M HCl solution in dioxane (100 mL) and methanol (25 mL). The homogeneous solution was heated in a sealed tube (95 °C) until all starting material had been consumed. After 3 hour, the mixture was concentrated to dryness *in vacuo* to provide the crude product (ca 100 %, 7.97 g) as a slightly yellow solid which was used without further purification.

20 An aliquot of the product above (780 mg, 2.278 mmol) was dissolved in 40 mL of 1:1 THF/MeOH and water was added (10 mL). The resulting solution was treated with lithium hydroxide monohydrate (5.0 eq, 478 mg) and heated to 50 °C for 3 hours. TLC (50 % THF in dichloromethane) showed complete disappearance of the starting material. The mixture was treated with 15 mL of aqueous 1 M HCl and the volatiles were removed *in vacuo*. The crude 25 product was diluted with aqueous 1 M HCl (20 mL) and the solids recovered by filtration (whatman #1) and washed with ether (30 mL) to provide the product **4C** (560 mg, 78 %) as a slightly yellow solid.

Step D – Synthesis of Compound 4D

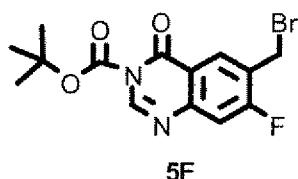


Compound **4C** (4.75 g, 15.11 mmol) was suspended in 150 mL of dry DMF and treated with EDCI (2.0 eq, 5.79 g) and triethylamine (10 eq, 21.2 mL, d 0.720). The mixture was stirred overnight at room temp. All the volatiles were removed *in vacuo* (high vacuum pump) and the residue was treated with methanol (30 mL). The product precipitated as a slightly yellow solid which was recovered by filtration. The product was washed with methanol (10 mL) and hexanes (20 mL) and concentrated *in vacuo* to provide **4D** (4.2 g; 93 %) as a slightly yellow solid.

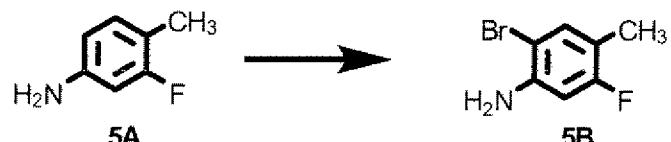
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Example 5

Preparation of Intermediate Compound 5G

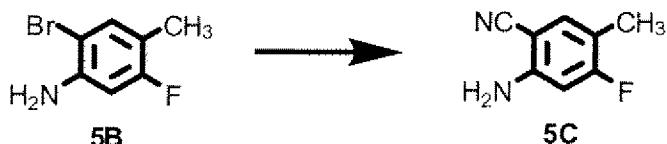


Step A – Synthesis of Compound 5B



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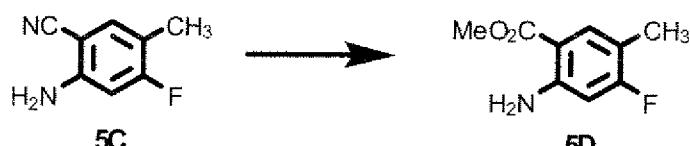
A mixture of compound **5A** (6.00 g, 47.9 mmol) and anhydrous potassium carbonate (6.70 g, 48.5 mmol) in anhydrous dichloromethane (130 mL) was cooled to -15 °C in a salt-ice bath and then added dropwise to a solution of bromine (7.70 g, 48.2 mmol) in anhydrous dichloromethane (80 mL). After addition was complete, the reaction was allowed to stir at -15 °C for 1 hour. Ice water (100 mL) was added to the reaction mixture and the aqueous layer was extracted with dichloromethane (2 x 100 mL). The combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to provide compound **5B** (11.0 g, quant.), which was used without further purification.

Step B – Synthesis of Compound 5C

Compound **5B** was dissolved in DMF (150 mL) and to this solution was added copper

5 (I) cyanide (11.0 g, 123 mmol). The mixture was heated to 160 °C and allowed to stir at this temperature for 20 hours. After being cooled to room temperature, with water (200 mL), iron (III) chloride (42.0 g, 155 mmol) and concentrated hydrochloric acid (20 mL) were added to the reaction mixture and the resulting reaction was stirred for 45 minutes. The reaction mixture was then basified to pH > 10 using commercial ammonium hydroxide solution. The 10 basic solution was then extracted with ethyl acetate (4 x 400 mL). The combined organic extracts were washed with water, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue obtained was purified using flash chromatography to provide compound **5C** (5.82 g, 81 %). ¹H NMR (400 MHz, d₆-DMSO): δ 7.34 (d, *J* = 8.4 Hz, 1H), 6.52 (d, *J* = 12.4 Hz, 1H), 6.10 (s, 2 H), 2.08 (s, 3 H).

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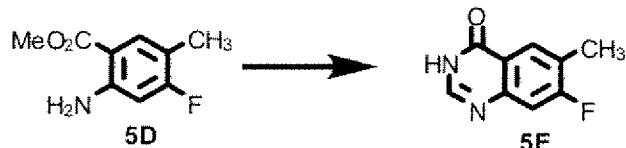
Step C – Synthesis of Compound 5D

To the solution of **5C** (2.0 g, 13.3 mmol) in anhydrous methanol (15 mL) at room

temperature was added concentrated sulfuric acid (4.0 mL). The reaction mixture was heated to

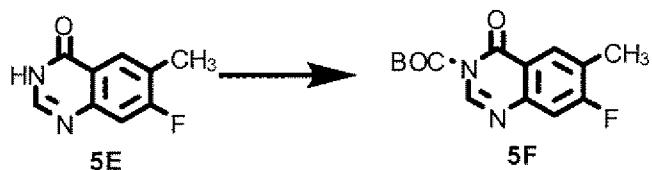
20 70 °C and stirred for four days. After cooled to room temperature, it was poured into with ice water. The mixture was then diluted with ethyl acetate (200 mL) and was made basic (pH > 10) with commercial ammonium hydroxide solution. The layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic solution was dried over MgSO₄ and concentrated *in vacuo* to provide the crude product which, was purified using flash 25 chromatography to provide compound **5D** (1.0 g, 41 %) and some recovered **5C**. ¹H NMR (400 MHz, d₆-DMSO): δ 7.61 (d, *J* = 8.8 Hz, 1H), 6.69 (s, 2 H), 6.51 (d, *J* = 12.0 Hz, 1 H), 3.77 (s, 3 H), 2.06 (s, 3 H).

Step D – Synthesis of Compound 5E



The solution of compound **5D** (500 mg, 2.73 mmol) in formamide (6.0 mL) was heated to 150 °C in an oil bath and stirred for 18 hours. After cooled to room temperature, ethyl acetate (100 mL) and water (100 mL) were added and the layers were separated. The organic solution was washed with water (2 x 60 mL), dried over MgSO₄ and concentrated *in vacuo* to provide the crude product **5E** (0.50 g, quant.) which, was used without further purification. MS found for C₉H₇FN₂O: 179.0 (M+H)⁺.

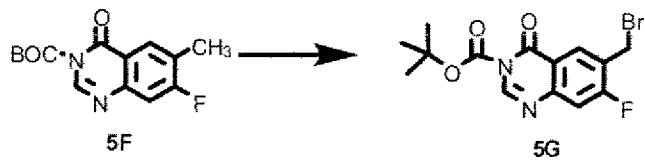
10 Step E – Synthesis of Compound 5F



To the solution of **5E** (from Step 4) in anhydrous THF (20 mL) at room temperature was added di-*tert*-butyl dicarbonate (1.84 g, 8.43 mmol), 4-dimethylaminopyridine (350 mg, 2.86 mmol) and triethyl amine (0.40 mL, 2.87 mmol). The reaction mixture was stirred for 18 hours. Ethyl acetate (100 mL) and water (100 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic solution was dried over MgSO₄ and concentrated *in vacuo* to provide the crude product which, was purified using flash chromatography to provide compound **5F** (285 mg, 36 %). MS found for C₁₄H₁₅FN₂O₃: 179.0 (M+H-100)⁺.

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Step F – Synthesis of Compound 5G



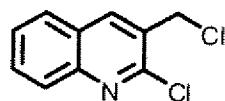
The mixture of **5F** (282 mg, 1.01 mmol), NBS (253 mg, 1.42 mmol) and AIBN (58 mg, 0.353 mmol) in anhydrous carbon tetrachloride (60 mL) was heated to 90 °C in an oil bath and stirred for 4 hours. After cooled to room temperature and concentrated *in vacuo*, the residue

was dissolved in ethyl acetate (100 mL) and water (100 mL). The layers were separated. The organic solution was washed with water (100 mL), dried over MgSO_4 and concentrated *in vacuo* to provide the crude product **5G** (453 mg, quant.) which, was used without further purification.

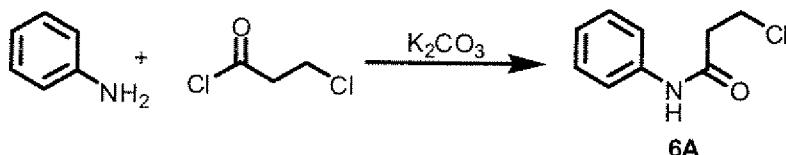
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Example 6

Preparation of Intermediate Compound **6B**

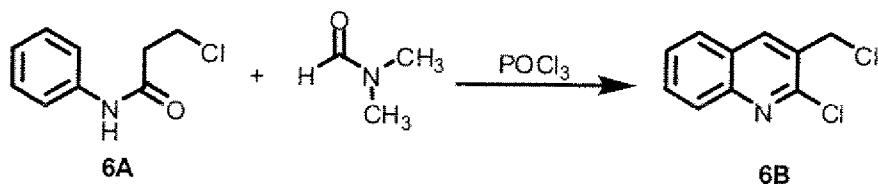
**6B**

Step A – Synthesis of Compound 6A



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A mixture of aniline (65.04 mL, 713.8 mmol), potassium carbonate (54.4 g, 394 mmol) and water (300 mL) were added to a 2000 mL flask. The resulting reaction was kept at room temperature using a room temperature water bath and stirred with a mechanic stirrer. 3-Chloropropionyl chloride (75.18 mL, 787.6 mmol) was added dropwise via additional funnel and the resulting suspension was allowed to stir at room temperature for 3 hours. The reaction mixture was filtered and the collected solid was washed sequentially with water (300 mL), aq. HCl (1M, 2 x 300 mL), and water (300 mL), then dried to provide compound **6A**, which was used without purification (114.5 g, 87%).

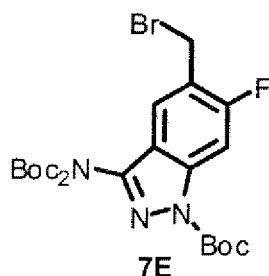
15
20 *Step B – Synthesis of Compound 6B*

N,N-Dimethylformamide (53.7 mL, 694 mmol) was charged into a three necked flask and cooled to 0 °C and treated with phosphoryl chloride (177.7 mL, 1906 mmol) dropwise. The reaction was stirred at that temperature for 10 min and treated with 3-Chloro-N-phenylpropanamide **6A** (50.00 g, 272.3 mmol) and stirred at room temperature. for 30 minutes.

The reaction mixture was heated at 80 °C for 3 h and slowly poured into ice. The solid separating out was filtered and washed extensively with water (2x1000 mL), aq. saturated sodium bicarbonate (500 mL), and taken in EtOAc (1L). The solution was dried (MgSO_4) filtered concentrated *in vacuo* and the residue obtained was recrystallized from boiling hexanes to provide compound **6B** (20 g).

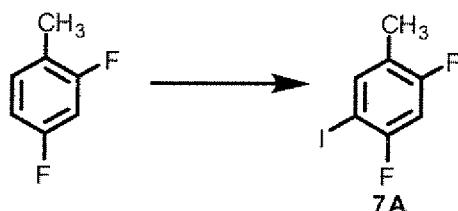
Example 7

Preparation of Intermediate Compound **7E**



10

*Step A – Synthesis of Compound **7A***

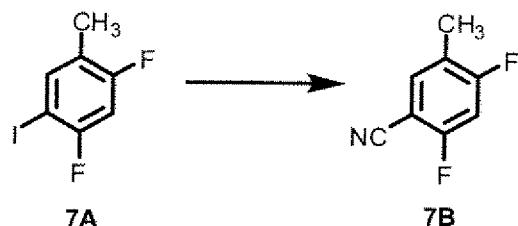


A solution of 2,4-difluorotoluene (4.72 g, 36.8 mmol) in trifluoroacetic acid (12.29 mL, 159.5 mmol) was cooled to 0 °C, then N-Iodosuccinimide (9.59 g, 42.6 mmol) was added and 15 the resulting reaction was allowed to stir at room temperature for about 15 hours. The reaction mixture was then concentrated *in vacuo* and the residue obtained was dissolved in hexanes (100 mL), washed with aqueous sodium thiosulfate (100 mL), brine (100 mL), then dried (MgSO_4), filtered and concentrated *in vacuo*. The resulting residue was purified using bulb-to-bulb distillation to provide compound **7A** (7.2 g, 77%) as a colorless oil.

20

*Step B – Synthesis of Compound **7B***

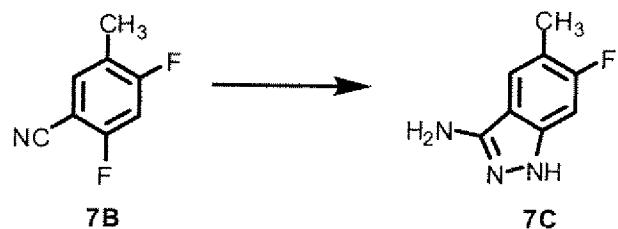
70



A solution of compound **7A** (7.11 g, 28.0 mmol), zinc cyanide (1.97 g, 16.8 mmol) and tetrakis(triphenylphosphine)palladium(0) (3.23 g, 2.80 mmol) in DMF (30 mL) was heated to 90 °C and allowed to stir at this temperature for 1.5 hours. The reaction mixture was

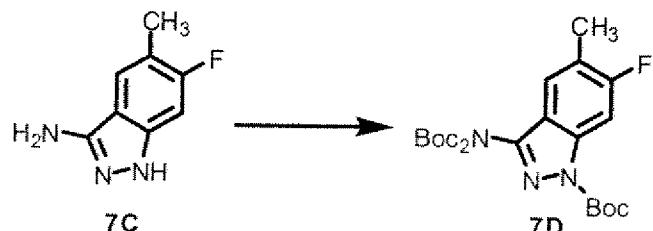
5 concentrated *in vacuo* and the residue obtained was taken up in water (400 mL) and extracted with ether (400 mL). The organic extract was washed with aqueous ammonium hydroxide solution (1N). The organic layer was dried (MgSO_4) filtered, concentrated *in vacuo* to provide a residue that was purified using flash column chromatography (SiO_2 , $\text{EtOAc}/\text{Hexanes}$) to provide a mixture that contained product and triphenylphosphine. This mixture was further 10 purified using sublimation at 1 mm/Hg at 45 °C to provide compound **7B** (1.8 g; Yield = 42%).

Step C – Synthesis of Compound 7C



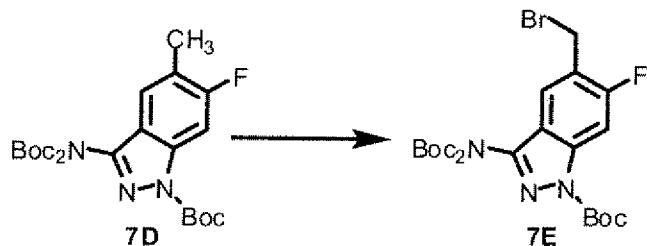
A solution of compound **7B** (1.400 g, 9.154 mmol) and hydrazine (0.700 mL, 22.3 mmol) in isopropyl alcohol (50 mL, 653.1 mmol), was heated to reflux and allowed to stir at 15 this temperature for 24 hours. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue obtained was purified using flash column chromatography (SiO_2 , Acetone/Hexanes 0 → 50%) to provide compound **7C** (330 mg, 22%).

20 *Step D – Synthesis of Compound 7D*



A solution of compound **7C** (330.00 mg, 1.998 mmol), di-tert-butyldicarbonate (2.6163 g, 11.98 mmol) and 4-dimethylaminopyridine (48.817 mg, 0.39959 mmol) in acetonitrile (15mL, 287.2 mmol) was heated to reflux and allowed to stir at this temperature for 2 hours. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, and the resulting residue was purified using flash column chromatography (SiO₂, EtOAc/Hexanes 0- 20 %) to provide compound **7D** (640.00 mg, 68%) as a colorless oil.

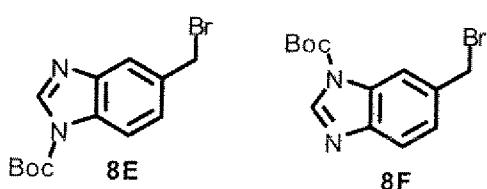
Step E - Synthesis of Compound 7E



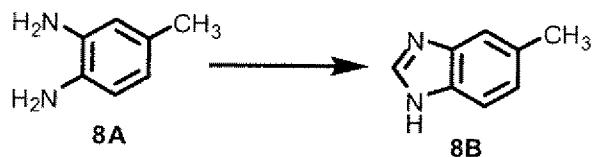
10 A solution of compound **7D** (630.00 mg, 1.3533 mmol), N-bromosuccinimide (337.22 mg, 1.8947 mmol) and benzoyl peroxide (65.563 mg, 0.27067 mmol) in carbon tetrachloride (20 mL) was heated to reflux and allowed to stir at this temperature for 3 hours. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue obtained was dissolved in EtOAc (300 mL). The resulting solution was washed with aqueous sodium 15 thiosulfate (100 mL), brine (100 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. The residue obtained was purified using flash column chromatography (SiO₂, EtOAc/Hexanes) to provide compound **7E** as a colorless oil.

Example 8

20 Preparation of Intermediate Compounds **8E** and **8F**

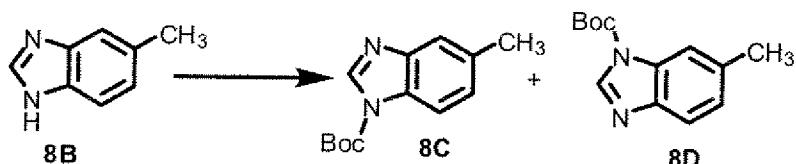


Step A – Synthesis of Compound 8B



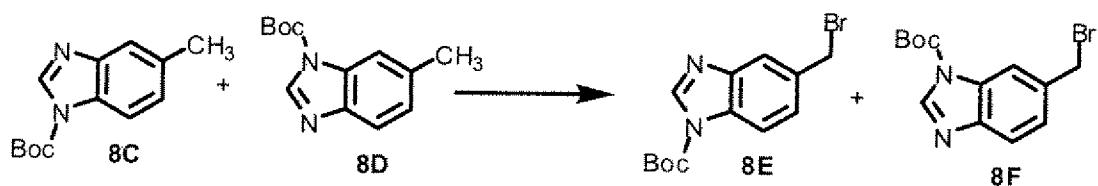
A solution of compound **8A** (3 g, 24.5 mmol) in trimethyl orthoformate (15 mL) was treated with 2 drops conc. HCl and heated to 80 °C for 2 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo* to provide compound **8B** (3.65 g), 5 which was used without further purification. M.S. found for C₈H₈N₂: 133.2 (M+H)⁺.

Step B – Synthesis of Compounds 8C and 8D



To a solution of compound **8B** (24.5 mmol) in CH₃CN (65 mL) was added di-tertbutyl 10 dicarbonate (5.89 g, 27.0 mmol), triethylamine (3.76 mL, 27.0 mmol) and 4-dimethylamino pyridine (300 mg, 2.45 mmol) and the resulting reaction was heated to 80 °C and allowed to stir at this temperature for 1.5 hours. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, and the residue obtained was purified using flash column chromatography (silica gel, EtOAc/Hexanes 5-20%) to provide a mixture of isomeric 15 compounds **8C** and **8D** (5.38 g, 94.3% yield over steps A and B).

Step C – Synthesis of Compounds 8E and 8F



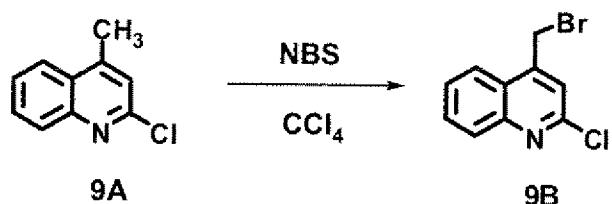
To a solution of compounds **8C** and **8D** (2 g, 8.61 mmol) in carbon tetrachloride (40 mL) was added N-bromosuccinimide (1.6 g, 9.04 mmol) and dibenzoyl peroxide (41.7 mg, 0.1722 mmol) and the resulting reaction was heated to 90 °C and allowed to stir at this temperature for 12 hours. The reaction was cooled to room temperature, solids were filtered off and the filtrate was washed with water, dried over sodium sulfate and concentrated *in vacuo*.

to provide compounds **8E** and **8F** (2.58 g) which was used without further purification. M.S. found for $C_{13}H_{15}BrN_2O_2$: 334.7 ($M+Na^+$).

Example 9

5

Preparation of Intermediate Compound **9B**



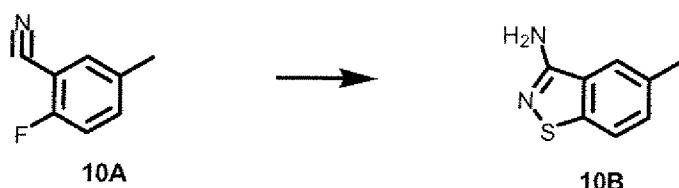
A mixture of compound **9A** (1.5 g, 8.44 mmol), NBS (1.8 g, 10.11 mmol) in carbon tetrachloride (50 mL) was heated to reflux, then benzoyl peroxide (0.21 g, 0.866 mmol) was added. The resulting suspension was allowed to stir at reflux for 19 hours, then cooled to room temperature and filtered. The filtrate was washed with saturated sodium carbonate, dried over sodium sulfate and concentrated *in vacuo* to provide a mixture (1.7 g) which contains about 50% of compound **9B**, and was used without further purification.

Example 10

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Preparation of Intermediate Compound 10D

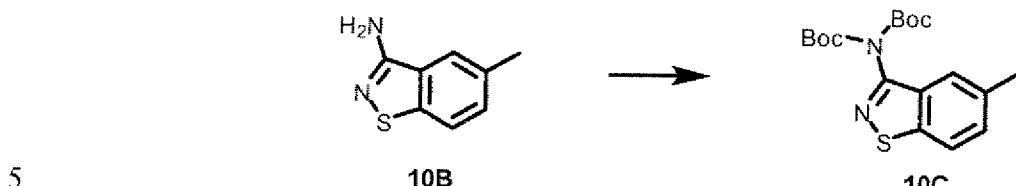
Step A – Synthesis of Compound 10B



A mixture of 2-fluoro-5-methylbenzonitrile (**10A**, 2.0 g; 14.799 mmol) and sodium sulfide (1.0 eq, 1.15 g) was dissolved in 150 mL of DMSO and heated at 70 °C overnight. The mixture was placed in an ice-water bath and treated with concentrated aqueous ammonium hydroxide (20 mL) and aqueous sodium hypochlorite (20 mL). The reaction mixture was allowed to warm to room temperature and stirred for 5 hours. The mixture was diluted with ethyl acetate (300 mL) and washed with water (2 x 60 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was adsorbed on silica gel and purified on a Biotage 40-M silica gel column (gradient: 0 to 30 % acetone in hexanes) to provide the product **10B** (860 mg; 36 %) as a white solid. ¹H-NMR

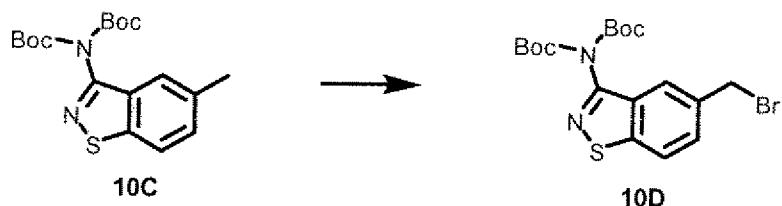
(CDCl₃; 400 MHz): δ 7.68 (1H, d, J = 8.54 Hz), 7.48 (1H, s), 7.33 (1H, d, J = 8.54 Hz), 4.89 (2H, broad s), 2.50 (3H, s).

Step B – Synthesis of Compound 10C



A solution of 5-methylbenzo[d]isothiazol-3-ylamine, (**10B**, 850 mg; 5.176 mmol) in dry acetonitrile (50 mL) was treated with Boc-anhydride (2.1 eq, 2.37 g) and heated to 50 °C. All starting material had been consumed after 2 h and the mixture was concentrated *in vacuo* to one third of its volume. The residue was dissolved in ethyl acetate (100 mL) and washed with 10 aqueous sodium hydrogen sulfate (20 mL), and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was adsorbed on silica gel and purified on a Biotage 40-M silica gel column (gradient: 0 to 10 % ethyl acetate in hexanes) to provide the product **10C** (1.7 g; 91 %) as a white powder. ¹H-NMR (CDCl₃; 400 MHz): δ 7.77 (1H, d, J = 8.54 Hz), 7.55 (1H, s), 7.38 (1H, dd, J = 1.83, 8.54 Hz), 2.51 (3H, s), 15 1.36 (18H, s). LR-MS (ESI): calcd for C₁₈H₂₅N₂O₄S [M+H]⁺ 365.15; found 365.23.

Step C – Synthesis of Compound 10D



A solution of N,N-bis-Boc-5-methylbenzo[d]isothiazol-3-ylamine (**10C**, 500 mg; 20 1.371 mmol) in 15 mL of carbon tetrachloride was treated N-bromosuccinimide (1.05 eq, 256 mg) and benzoyl peroxide (10 mol%; 33 mg). The solution was degassed (vacuum/argon flush) and then heated to 75 °C for 5 hours. The reaction mixture was concentrated to one third of its volume *in vacuo* and the residue was dissolved in ethyl acetate (50 mL). The solution was washed with aqueous saturated sodium bicarbonate soln (2 x 10 mL) and brine (10 mL). The 25 organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was adsorbed on silica gel and purified on a Biotage 40-S silica gel column (gradient:

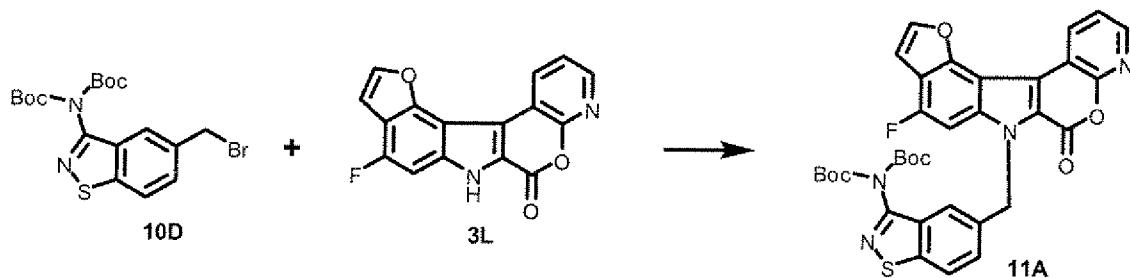
hexanes then 0 to 10 % ethyl acetate in hexanes) to provide the product **10D** (396 mg; 69 %) as a white solid. ¹H-NMR (CDCl₃; 400 MHz): δ 7.87 (1H, d, *J* = 8.54 Hz), 7.78 (1H, s), 7.58 (1H, dd, *J* = 1.83, 8.54 Hz), 4.63 (2H, s), 1.37 (18H, s). LR-MS (ESI): calcd for C₁₈H₂₄BrN₂O₄S [M+H]⁺ 445.06; found 445.24.

5

Example 11

Preparation of Compound **24**

*Step A – Synthesis of Compound **11A***



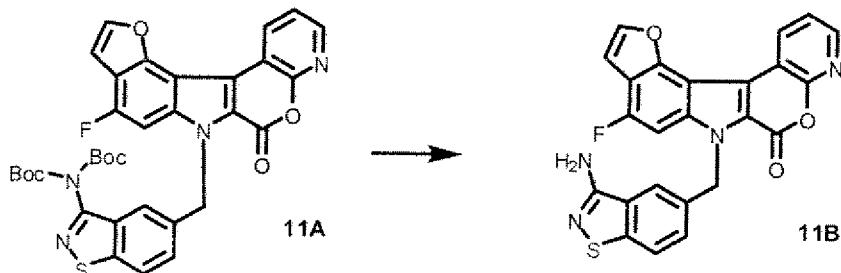
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A mixture of lactone **3L** (215 mg; 0.733 mmol) and N,N-bis-Boc-5-bromomethylbenzo[d]isothiazol-3-ylamine **10D** (1.2 eq, 390 mg) was suspended in dry DMF (7 mL) and treated with cesium carbonate (2.0 eq, 477 mg). The slurry was stirred overnight. The mixture was treated with water (10 mL) and the product was recovered by filtration (whatman #1). The solids were washed with water (2 x 5 mL) to provide the product **11A** (480 mg; 99 %) as a white solid which did not require further purification. ¹H-NMR (dmso-d₆; 400 MHz): δ 9.28 (1H, dd, *J* = 1.83, 7.93 Hz), 8.50 (1H, dd, *J* = 1.22, 4.88 Hz), 8.28 (1H, d, *J* = 2.44 Hz), 8.20 (1H, d, *J* = 8.54 Hz), 7.75 (1H, d, *J* = 10.37 Hz), 7.66 (2H, m), 7.36 (1H, s), 7.28 (1H, d, *J* = 1.83 Hz), 6.25 (2H, s), 1.12 (18H, s).

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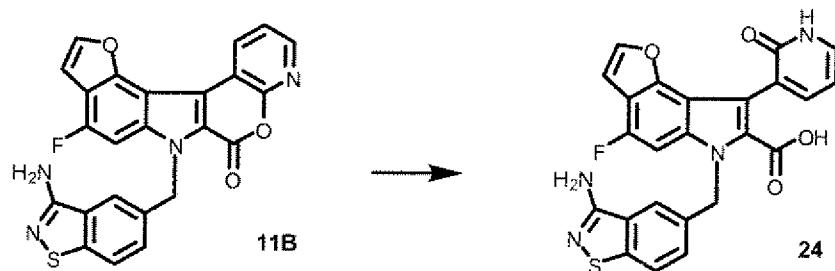
*Step B – Synthesis of Compound **11B***



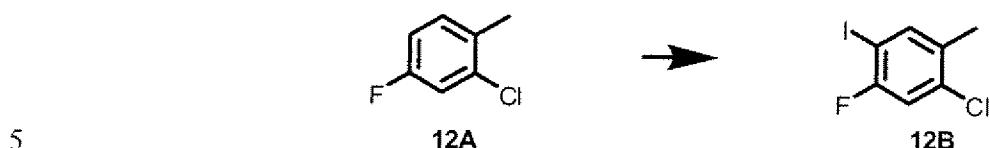
The N,N-bis-Boc protected aminoisothiazole **11A** (480 mg; 0.730 mmol) was treated with 4 M HCl in dioxane (15 mL). The resulting slurry was stirred for 3 h at which point no more starting material remained according to TLC (50 % ethyl acetate in hexanes). The mixture was concentrated *in vacuo* to provide the crude product **11B** (ca 99 %; 333 mg) as a 5 slightly yellow solid which was used without further purification. ¹H-NMR (dmso-d₆; 400 MHz): δ 9.28 (1H, dd, *J* = 1.83, 7.93 Hz), 8.50 (1H, dd, *J* = 1.83, 4.88 Hz), 8.28 (1H, d, *J* = 2.44 Hz), 7.95 (1H, d, *J* = 8.54 Hz), 7.77 (1H, s), 7.70 (2H, broad s), 7.65 (1H, dd, *J* = 4.88, 7.93 Hz), 7.61 (1H, d, *J* = 10.37 Hz), 7.58 (1H, dd, *J* = 1.83, 8.54 Hz), 7.28 (1H, d, *J* = 1.83 Hz), 6.14 (2H, s).

10

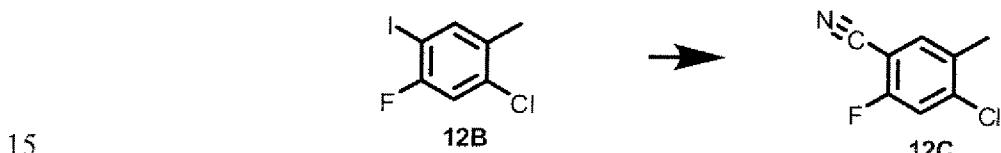
Step C – Synthesis of Compound 24



The lactone **11B** (100 mg; 0.219 mmol) was suspended in 3 mL of THF and 1 mL of 15 water followed by addition of lithium hydroxide monohydrate (5.0 eq, 46 mg). The reaction mixture was stirred for 2 h and TLC (50 % acetone in dichloromethane showed no more starting material left. Aqueous 1 M HCl was added (0.5 mL) and the THF was removed *in vacuo*. The residue was dissolved in DMF (8 mL) and injected into a semi-prep HPLC system using the following conditions: Delta Pak Column, C18, 5 micrometer, 300A; 300 x 30 mm 20 I.D.; Flow rate: 25 mL/min; Gradient: 5 % THF in water (0.01% TFA) for 5 min then increase to 90 % over 45 minutes. The fractions containing the product (37 - 39 min) according to MS were combined and concentrated *in vacuo* to provide the title compound **24** (48 mg; 48 %) as a white solid. ¹H-NMR (dmso-d₆; 400 MHz): δ 12.90 (1H, broad s), 11.75 (1H, broad s), 7.91 (1H, d, *J* = 2.44 Hz), 7.89 (1H, s), 7.80 (1H, d, *J* = 8.54 Hz), 7.66 (1H, dd, *J* = 2.44, 6.71 Hz), 7.46 (1H, d, *J* = 10.98 Hz), 7.40 (1H, dd, *J* = 1.83, 6.71 Hz), 7.10 (1H, d, *J* = 8.54 Hz), 7.06 (1H, d, *J* = 2.44 Hz), 6.73 (2H, broad s), 6.32 (1H, t, *J* = 6.71 Hz), 5.96 (2H, s). LR-MS (ESI): calcd for C₂₄H₁₆FN₄O₄S [M+H]⁺ 475.09; found 475.27.

Example 12Preparation of Intermediate Compound **12F***Step A – Synthesis of Compound 12B*

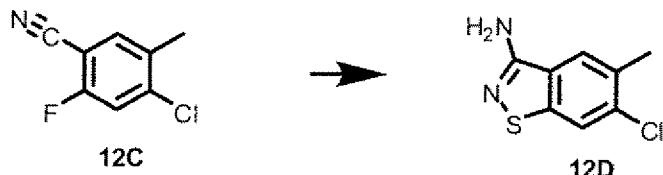
N-iodosuccinimide (1.1 eq; 17.1 g) was added to a solution of 2,4-difluoro toluene (12A, 10.0 g; 69.17 mmol; Alfa Aesar) in trifluoroacetic acid (46 mL). The reaction was set to stir for 12 hours. The volatiles were removed under reduced pressure; the remaining slurry was diluted with ether (400 mL) and washed with 5% aq sodium thiosulfate (5x40 mL), water (2x30 mL), and brine (40 mL). The organic layer was collected, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The reaction was purified via bulb to bulb distillation to provide product 12B as a colorless liquid (17 g; 91%)

Step B – Synthesis of Compound 12C

A solution of intermediate 12B (13.0 g; 48.06 mmol) and zinc cyanide (1 eq; 5.644 g) in N,N-dimethylformamide (50 mL) was treated with tetrakis (triphenylphosphine) palladium(0) (0.1 eq; 5.55 g) and heated at 90 °C for 12 hours. The reaction mixture was diluted with ether (600 mL) and ammonium hydroxide (1:1 concentrated ammonium hydroxide: water 200 mL). The organic layer was separated and washed with water (100 mL) and brine (100 mL), dried over magnesium sulfate, filtered, concentrated under reduced pressure, and purified over silica gel first eluting with hexanes, then with 20% ethyl acetate/hexanes. Product 12C (4.48 g; 33%) was afforded as a clear oil.

25 *Step C – Synthesis of Compound 12D*

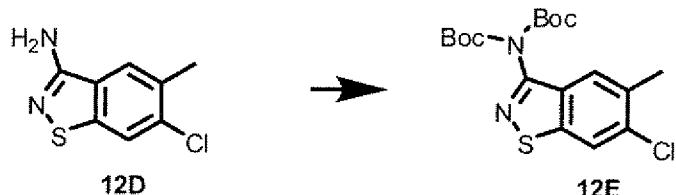
78



A solution of **12C** (2.25 g; 13.27 mmol) and sodium sulfide (1 eq; 1.035 g) was prepared in DMSO (130 mL) and heated at 70 °C overnight. The mixture was placed in an ice water bath and treated with concentrated aqueous ammonium hydroxide (30 mL) and aqueous sodium hypochlorite (30 mL). The reaction mixture was stirred for 5 h (temp from 0 to 25 °C). The mixture was diluted with ethyl acetate (400 mL) and washed with water (2x40 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was adsorbed on silica gel and purified on an ISCO 330G column (gradient: 0-30% acetone in hexanes), affording product **12D** (800 mg; 30.3%) as a white solid.

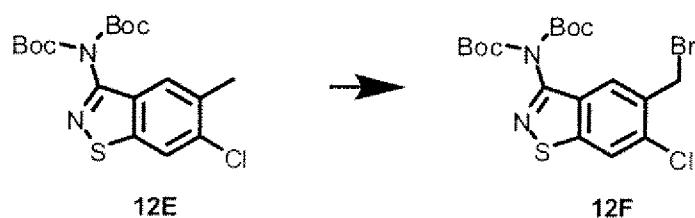
10

Step D – Synthesis of Compound 12E



A solution of intermediate **12D** (780 mg; 3.93 mmol) in dry acetonitrile (39 mL) was treated with Boc-anhydride (2.2 eq; 1.885 g) and heated to 50 °C. All starting material had 15 been consumed after 2 h and the mixture was concentrated *in vacuo* to one third of its volume. The residue was dissolved in ethyl acetate (100 mL) and washed with aqueous sodium hydrogen sulfate (20 mL) and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was adsorbed on silica gel and purified on a ISCO 80 gram column (gradient: 0 to 10% ethyl acetate in hexanes) to provide the 20 product **12E** (1.03 g; 66% yield) as a white solid.

Step E – Synthesis of Compound 12F



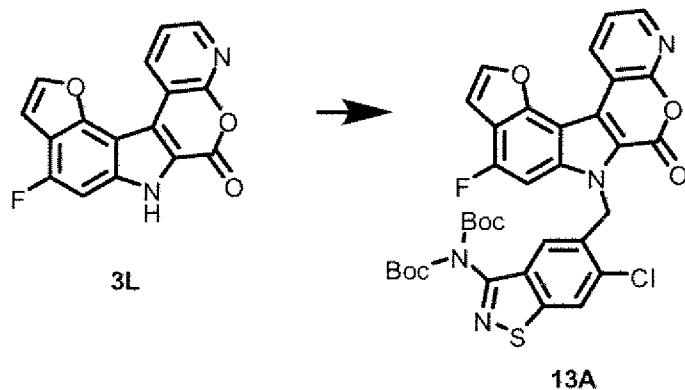
A solution of intermediate **12E** (400 mg; 1.003 mmol), N-Bromosuccinimide (1.05 eq; 187.4 mg), and benzoyl peroxide (0.1 eq; 24.3 mg) in dry carbon tetrachloride (10 mL) was prepared and heated at reflux for 12 hours. TLC (30% ethyl acetate in hexanes) revealed the reaction had partially progressed. The reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate (100 mL), washed with saturated aqueous sodium bicarbonate (25 mL) and brine (25 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then diluted with dichloromethane, adsorbed onto silica gel, and purified on ISCO (25-M Column; 0-40% ethyl acetate in hexanes). The fractions containing product were concentrated under reduced pressure affording intermediate **12F** (278 mg; 58%) as a clear yellow oil.

Example 13

Preparation of Compound **10S**

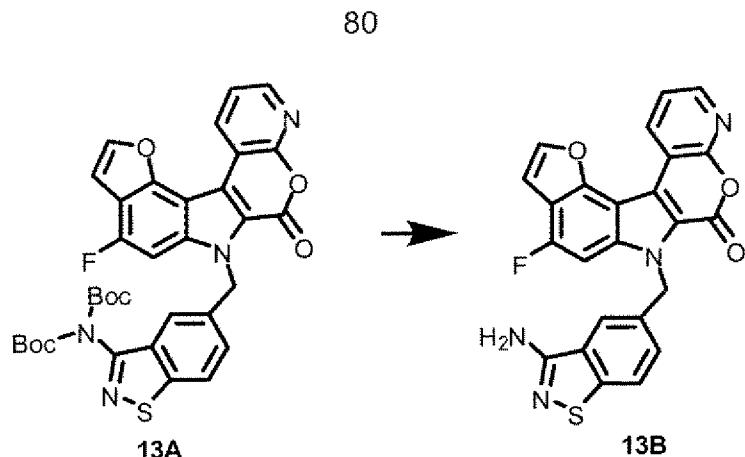
*Step A – Synthesis of Compound **13A***

15



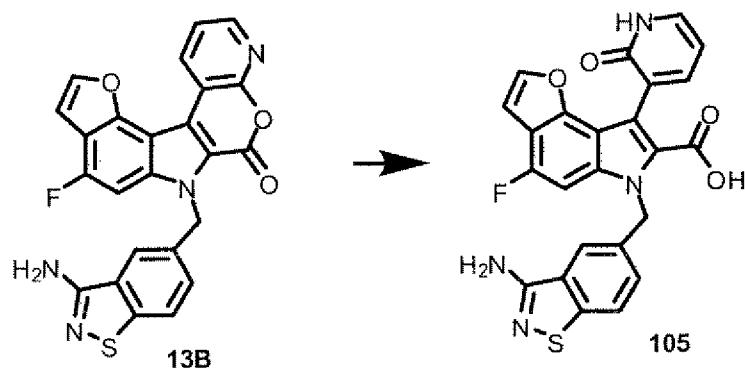
A mixture of lactone **3L** (163.05 mg, 0.554 mmol) in 10 mL of dry DMF was prepared and treated with N,N-bis-Boc-5-bromomethyl-6-chloro-benzo[d]isothiazol-3-ylamine **12F** (1.05 eq; 278 mg) and cesium carbonate (3.0 eq, 541.5 mg). The slurry was set to stir overnight. The mixture was treated with water (10 mL) and the product was recovered by filtration (watmann #1). The solid was washed with 1:1 hexanes: diethyl ether (15 mL) and dried under reduced pressure. The product **13A** was afforded as an off white solid (344.6 mg; 90%).

25 *Step B – Synthesis of Compound **13B***



Compound **13A** (330 mg; 0.477 mmol) was treated with a 1:1 solution of trifluoroacetic acid : dichloromethane (8 mL). The resulting solution was set to stir for 30 minutes. TLC (60% ethyl acetate in hexanes) revealed that the reaction was complete. The volatiles were removed under reduced pressure to provide crude product **13 B** (241 mg; 103%) as a slightly yellow solid which was used without further purification.

Step C – Synthesis of Compound 105

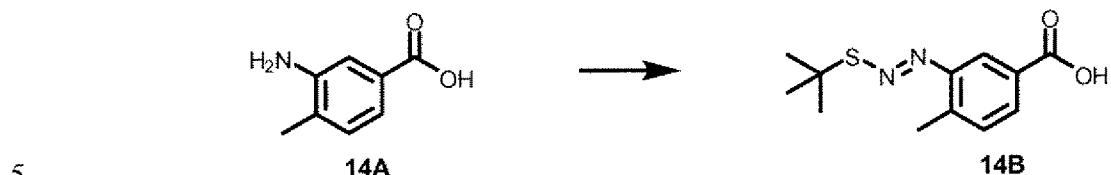


10 Lithium hydroxide monohydrate (4 eq; 51.3 mg) was added to a slurry of lactone **13B** (150 mg; 0.306 mmol) in 4:1 THF:H₂O (5 mL). The mixture was stirred for 2 hours. The reaction became a homogeneous solution and was quenched with 5 drops aqueous HCl (1N). The solution was concentrated to near dryness and diluted with 8 mL DMF. The compound was quickly taken into syringe, filtered, and injected into HPLC under the following
15 conditions; Column: Delta Pak, C18, 5 micrometer, 300 A; 300 x 30 mm I.D.; Flow rate: 30 mL/min; gradient: 10% THF in water (0.01% TFA) for 10 min isocratic, increase to 95% THF in water from 10 min to 60 minutes. Isocratic from min 60 to min 65 at 95% THF in water. The fractions containing product **105** (80 mg; 51.4%) were collected and concentrated under reduced pressure to provide a white solid. MS (M+H) = 475.5

Example 14

Preparation of Intermediate Compound 14G

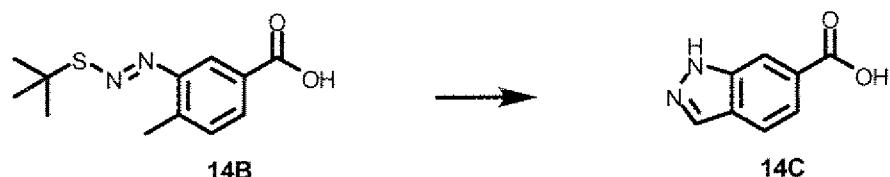
Step A – Synthesis of Compound 14B



To a stirred solution of aqueous HCl (15 mL of conc HCl in 50 mL of water) was added 3-amino-4-methyl benzoic acid (**14 A**, 5.0 g; 33.0 mmol). The mixture was cooled in an ice-water bath followed by slow addition of a solution of sodium nitrite (1.1 eq, 2.50 g) in water (12 mL). The mixture was stirred for 30 min at which point the mixture was a homogeneous 10 dark solution. A saturated aqueous solution of sodium acetate was added until pH 6 was attained. Sodium t-butylthiolate (0.5 eq, 1.85 g) was added in one portion. The reaction was stirred for 2 h and the resulting precipitate was collected by filtration (whatman #1), washed with water (20 mL) and concentrated *in vacuo* to provide the product **14B** (2.7 g; 64 %) as a tan solid.

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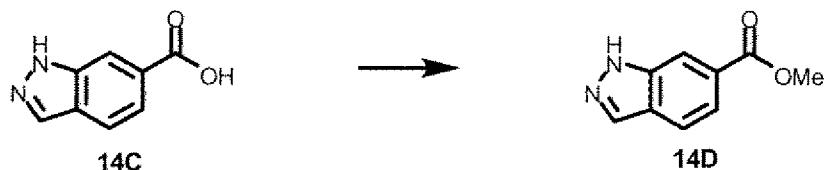
Step B – Synthesis of Compound 14C



To a stirred solution of potassium tert-butoxide (10.0 eq, 12.0 g) in DMSO (50 mL) was added a solution of t-butylidazaenyl benzoic acid **14B** (2.7 g; 10.70 mmol) in DMSO (30 mL). The mixture was stirred for 6 h and then diluted with ice and acidified with aqueous 1 M HCl until pH 5-6 was attained. The mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were washed with water (20 mL) and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in rotavap to provide the crude product **14C** as a slightly yellow solid which was used without further purification.

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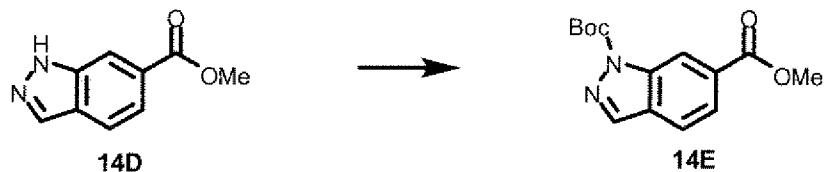
Step C – Synthesis of Compound 14D



A solution of 1H-indazole-6-carboxylic acid **14C** (1.73 g; 10.70 mmol) in toluene (80 mL) and methanol (30 mL) was treated with a solution of TMS-diazomethane (2 M soln in ether) until evolution of gas stopped. The reaction mixture was concentrated *in vacuo* and the residue was adsorbed on silica gel. The product was purified on a Biotage 40-M silica gel column (gradient: 0 to 20 % acetone in hexanes) to provide the product **14D** (950 mg; 50 % for two steps) as a slightly yellow solid. ¹H-NMR (CDCl₃; 400 MHz): δ 8.28 (1H, s), 8.16 (1H, s), 7.86 (1H, d, J = 8.54 Hz), 7.81 (1H, d, J = 8.54 Hz), 3.98 (3H, s). LR-MS (ESI): calcd for C₉H₉N₂O₂ [M+H]⁺ 177.07; found 177.20.

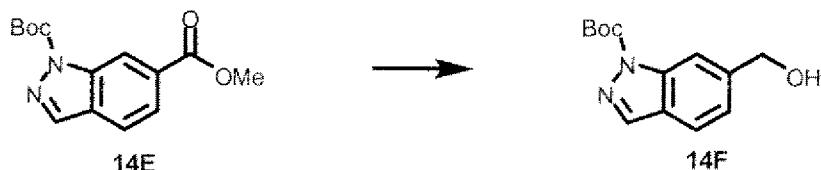
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Step D – Synthesis of Compound 14E



A solution of 1H-indazole-6-carboxylic acid methyl ester **14D** (840 mg; 4.76 mmol) in 25 mL of acetonitrile was treated with Boc-anhydride (1.05 eq, 1.09 g) and a catalytic amount of DMAP (tip of spatula). The mixture was stirred at 60 °C for 3 hours. The mixture was concentrated to half its volume in rotavap and then diluted with ethyl acetate (100 mL) and washed with aqueous saturated sodium bicarbonate (20 mL) and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was purified on a Biotage 40-M silica gel column (gradient: 0 to 20 % ethyl acetate in hexanes) to provide the product **14E** (1.2 g; 93 %) as a colorless oil. ¹H-NMR (CDCl₃; 400 MHz): δ 8.91 (1H, s), 8.22 (1H, s), 7.99 (1H, dd, J = 1.22, 8.54 Hz), 7.78 (1H, d, J = 8.54 Hz), 3.97 (3H, s), 1.74 (9H, s).

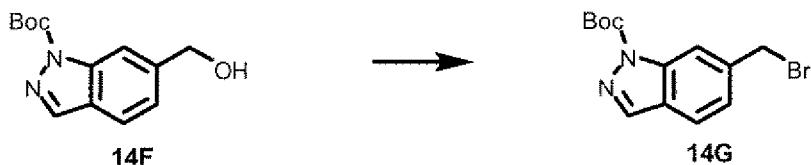
Step E – Synthesis of Compound 14F



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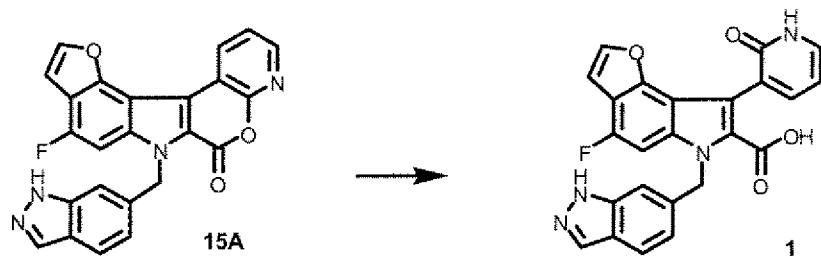
A solution of indazole **14E** (460 mg; 1.66 mmol) in 16 mL of dry THF was cooled to -78 °C and treated with lithium triethylborohydride (2.5 eq, 4.15 mL of a 1 M soln in THF). The reaction mixture was stirred at -78 °C and followed by TLC (25 % ethyl acetate in hexanes). The reaction was completed in about 1 h and quenched by addition of aqueous 5 saturated sodium hydrogen sulfate (3 mL). The mixture was extracted with ethyl acetate (100 mL) and washed with water (20 mL) and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in rotavap to provide the crude product as a colorless oil. The residue was chromatographed on a Biotage 40-S silica gel column (0 to 40 % 10 ethyl acetate in hexanes) to provide the following: des-Boc starting material (70 mg); alcohol product **14F** (160 mg; 40 %). ¹H-NMR (CDCl₃; 400 MHz): δ 8.19 (1H, s), 8.13 (1H, s), 7.67 (1H, d, J = 7.93 Hz), 7.30 (1H, d, J = 7.93 Hz), 5.13 (2H, s), 1.71 (9H, s).

Step F – Synthesis of Compound 14G



15 A solution of alcohol **14F** (160 mg; 0.644 mmol) in dry chloroform (12 mL) was placed in an ice-water bath and treated with pyridine (4.0 eq, 0.208 mL, d 0.978) and a solution of thionyl bromide (1.2 eq, 0.060 mL, d 2.683) in 1 mL of chloroform. The ice-water bath was removed and the reaction mixture was stirred at room temp for 30 minutes. TLC (30 % ethyl acetate in hexanes) showed about 40 % conversion and more thionyl bromide was added (0.2 eq). The mixture was heated to 70 °C for 10 minutes. Upon cooling the mixture was diluted with ethyl acetate (30 mL) and washed with aqueous saturated sodium bicarbonate (5 mL), aqueous sodium hydrogen sulfate (5 mL) and brine (5 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was purified on a Biotage 25-S silica gel column (gradient: 0 to 40 % ethyl acetate in hexanes) to provide the product 20 **14G** (76 mg; 38 %) as a colorless oil along with unreacted starting material (25 mg; 24 %). ¹H-NMR (CDCl₃; 400 MHz): δ 8.23 (1H, s), 8.14 (1H, s), 7.72 (1H, d, J = 8.54 Hz), 7.32 (1H, dd, J = 1.22, 8.54 Hz), 5.21 (1H, d, J = 12.20 Hz), 5.09 (1H, d, J = 12.20 Hz), 1.71 (9H, s).

Example 15

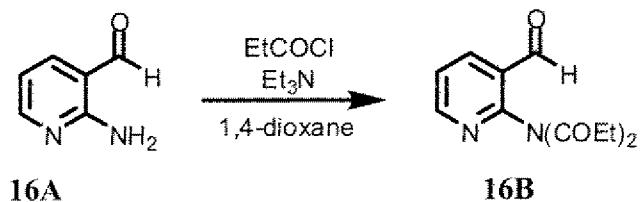


The lactone **15A** (0.213 mmol) was dissolved in 3 mL of THF and 1 mL of water 5 followed by addition of lithium hydroxide monohydrate (4.0 eq, 36 mg). The reaction mixture was stirred for 3 hours. Aqueous 1 M HCl was added (0.5 mL) and the THF was removed in rotavap. The residue was dissolved in DMF (15 mL) and injected into a semi-prep HPLC system using the following conditions: Delta Pak Column, C18, 5 micrometer, 300A; 300 x 30 mm I.D.; Flow rate: 25 mL/min; Gradient: 5 % THF in water (0.01% TFA) for 5 min then 10 increase to 90 % over 45 minutes. The fractions containing the product (31 & 32 min) according to MS were combined and concentrated in rotavap to provide the product **1** (16 mg; 17 %) as a white solid. ¹H-NMR (dmso-d₆; 400 MHz): δ 12.90 (2H, broad s), 11.74 (1H, broad s), 7.98 (1H, s), 7.91 (1H, d, J = 2.44 Hz), 7.67 (1H, d, J = 8.54 Hz), 7.65 (1H, dd, J = 1.83, 6.71 Hz), 7.47 (1H, d, J = 10.98 Hz), 7.40 (1H, dd, J = 1.83, 6.71 Hz), 7.10 (1H, s), 7.05 (1H, d, J = 2.44 Hz), 6.95 (1H, dd, J = 1.22, 8.54 Hz), 6.32 (1H, dd, J = 6.10, 6.71 Hz), 6.00 (2H, s). 15 LR-MS (ESI): calcd for C₂₄H₁₆FN₄O₄ [M+H]⁺ 443.12; found 443.28.

Example 16

Preparation of Intermediate Compound **16E**

20 *Step A – Synthesis of Compound 16B*

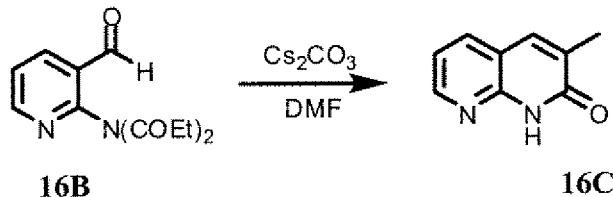


25 To a solution of **16A** (7.2 g, 58.8 mmol) in 1,4-dioxane (39 mL) at 0°C was added propionyl chloride (15.8 mL, 176.5 mmol) and Et₃N (24.6 mL, 176.5 mmol) with stirring. The

reaction mixture was stirred at room temperature for overnight. The solvent was removed under reduced pressure, and the resulting residue was taken up in EtOAc. The organic phase was washed with water, dried over MgSO₄, filtered, and concentrated *in vacuo* to provide a crude residue of **16B**.

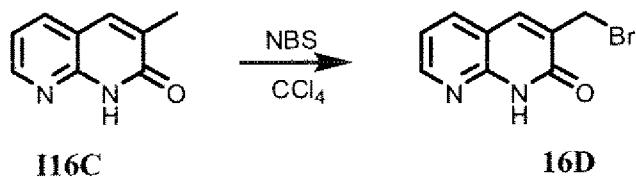
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Step B – Synthesis of Compound 16C



To a suspension of **16B** (crude residue from above) in DMF (60 mL) was added cesium carbonate (38 g, 117.6 mmol), and the resulting mixture was heated at 65°C for overnight. Reaction was cooled to room temperature, and the bulk of DMF was removed under reduced pressure. Water was then added to the crude residue and the mixture was filtered. The filter-cake was washed with water and EtOAc. 5.2 g of **16C** was collected as a pale yellow solid.

15 *Step C – Synthesis of Compound 16D*

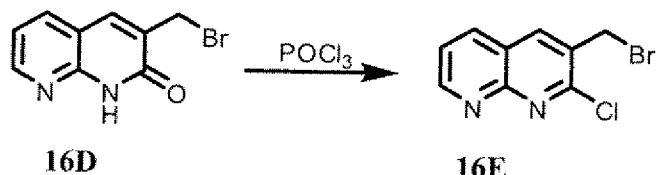


20 To a suspension of **16C** (0.8 g, 5 mmol) in CCl₄ (25 mL) was added NBS (38 g, 117.6 mmol), and benzoyl peroxide (61 mg, 0.25 mmol), and the resulting mixture was then heated at 90°C for 4 hours. Cooled the reaction to room temperature, and 300 mL of CH₂Cl₂ was added. The mixture was filtered, and filtrate was dried over MgSO₄, filtered, and concentrated *in vacuo* to provide 2 g of crude residue of **16D**.

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Step D – Synthesis of Compound 16E

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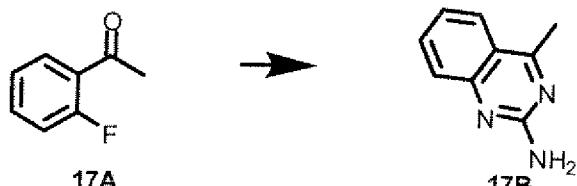
POCl₃ was added to a 100 mL round bottom flask containing crude **16D**. The resulting suspension was then heated at 88°C for 4 hours. Cooled the reaction to room temperature, and then poured into a 1 liter beaker containing ice. The resulting solution was neutralized to pH 8 using 6 N NaOH solution. Solid that precipitated from the solution was collected to provide 0.82 g of crude residue which was purified using column chromatography on silica gel (ISCO Combi-Flash Rf; gradient: 5 to 50 % ethyl acetate in hexanes) to provide 330 mg of compound **16E**.

Example 17

Preparation of Intermediate Compound **17D**

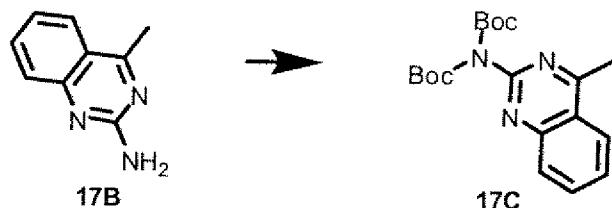
*Step A – Synthesis of Compound **17B***

15



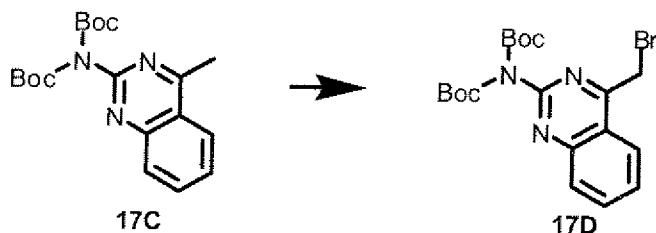
A mixture of ortho-fluoroacetophenone (**17A**, 3.45 g; 25 mmol) and guanidine carbonate (2 eq; 9.0 g) was prepared in 250 mL of N,N-dimethyl acetamide, set to stir, and heated at 135 °C under nitrogen purge overnight. The solvent was removed under reduced pressure and diluted with ethyl acetate (600 mL). The solution was washed with water (2x100 mL) and brine (40 mL). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The solid was dissolved in methylene dichloride, loaded on silica gel and dried under reduced pressure. The material was purified on ISCO (80 g column; 0-70% THF in Hexanes). Fractions containing product were collected and concentrated under reduced pressure to provide product **17B** as a crème colored solid (880 mg; 22%)

*Step B – Synthesis of Compound **17C***



A solution of 4-Methyl-quinazolin-2-ylamine **17B** (640 mg; 4.02 mmol) in 10 mL of dry acetonitrile was treated with a solution of Boc-anhydride (2.5 eq; 2.19 g) in 10.0 mL of dry acetonitrile. The resulting solution was treated with DMAP (0.2 eq; 98.2 mg). The mixture was set to stir overnight. TLC (50% THF in hexanes) showed a complete reaction. The mixture was diluted with ethyl acetate (500 mL) and washed with water (3x30 mL), and Brine (40 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was adsorbed on silica gel and purified on an ISCO column (120 g) (0% to 60% THF in hexanes). The fractions with product were collected and concentrated under reduced pressure to provide product **17C** as a light yellow-white solid (1.3 g, 90%).

Step C – Synthesis of Compound 17D

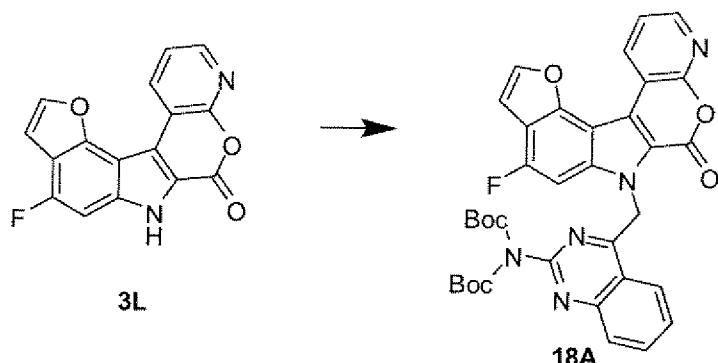


Intermediate **17C** (1.11 g; 3.09 mmol), N-Bromosuccinimide (1.05 eq; 577 mg), and benzoyl peroxide (0.1 eq; 75 mg) were combined in round bottom and diluted with dry carbon tetrachloride (31 mL). The reaction was stirred at room temperature for 10 minutes and then heated at reflux overnight. TLC (30% ethyl acetate in hexanes) revealed the reaction has partially progressed. The reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate (300 mL), and washed with sat. aqueous sodium bicarbonate (40 mL) and brine (40 mL), dried over magnesium sulfate, filtered, concentrated under reduced pressure, diluted with methylene dichloride, adsorbed onto silica gel, and purified on ISCO (25-M Column; 0-40% ethyl acetate in hexanes). The fractions containing product were concentrated under reduced pressure and afforded product as a clear oil in a 2:1 mixture of pure product **17D** and starting material (Total : 440 mg; 33%).

Example 18

Preparation of Compound 18

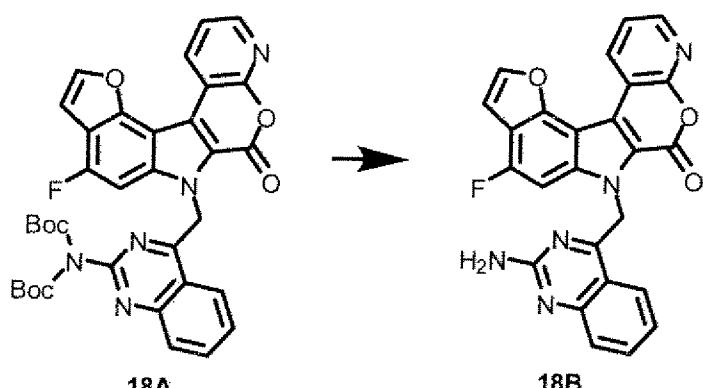
Step A – Synthesis of Compound 18A



5 A solution of lactone **3L** (244.1 mg, 0.83 mmol) in 10 mL of dry DMF was treated with N,N-bis-Boc-4-bromomethyl-quinazolin-2-ylamine 086951-092-36 (1.1 eq; 400 mg) and cesium carbonate (3.0 eq, 811 mg). The slurry was set to stir overnight. The reaction was quenched with water (5 mL), stirred for 10 minutes and dried under reduced pressure and heat. The residual paste was diluted with ethyl acetate (400 mL) and washed with water (2x30 mL) and brine (2x30 mL). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Product **18A** was afforded as a crude yellow gum and was not purified further (300 mg; 55%).

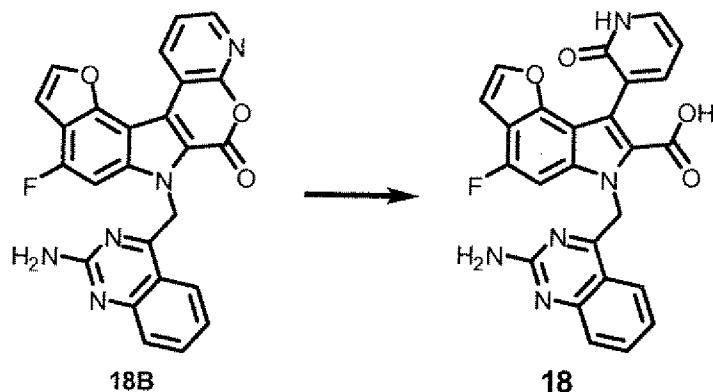
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Step B – Synthesis of Compound 18B



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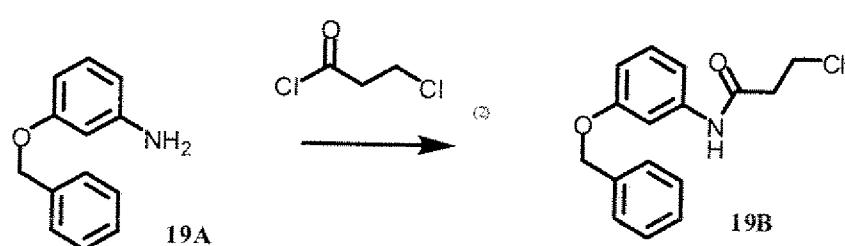
Lactone **18A** (380 mg; 0.631 mmol) was diluted with 5 mL methylene dichloride to which 5 mL difluoro acetic acid was added. The reaction was stirred for 3 hours. The reaction mixture was dried under reduced pressure and set to dry further under vacuum for 48 hours. Intermediate **18B** was used as is in the next reaction.

Step C – Synthesis of Compound 18

Lactone **18B** (150 mg; 0.332 mmol) was diluted with 5 mL THF: water.

Lithium Hydroxide monohydrate (2 eq, 27.9 mg) was added and the mixture was allowed to stir for 2

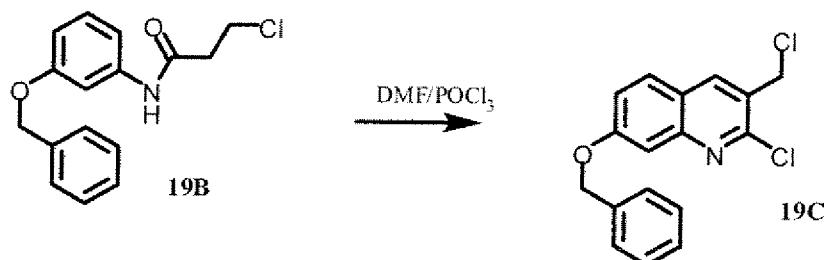
5 hrs. The reaction was quenched with 5 drops of HCl (1N). The solution was concentrated to near dryness and diluted with 8 mL DMF. The solution was quickly taken into syringe and injected into HPLC under the following conditions; Column: Delta Pak, C18, 5 micrometer, 300 A; 300 x 30 mm I.D.; Flow rate: 30 mL/min; gradient: 10% THF in water (0.01% TFA) for 10 min isocratic, increase to 95% THF in water from 10 min to 60 minutes. Isocratic from 10 min 60 to min 65 at 95% THF in water. The fractions containing product were collected and concentrated under reduced pressure to provide the title compound **18** as an off-white solid (30 mg; 20%).

Example 1915 Preparation of Intermediate Compound **19C***Step A – Synthesis of Compound 19B*

Compound **19A** (commercially available) (10.0 g, 50.25 mmol) was dissolved in water

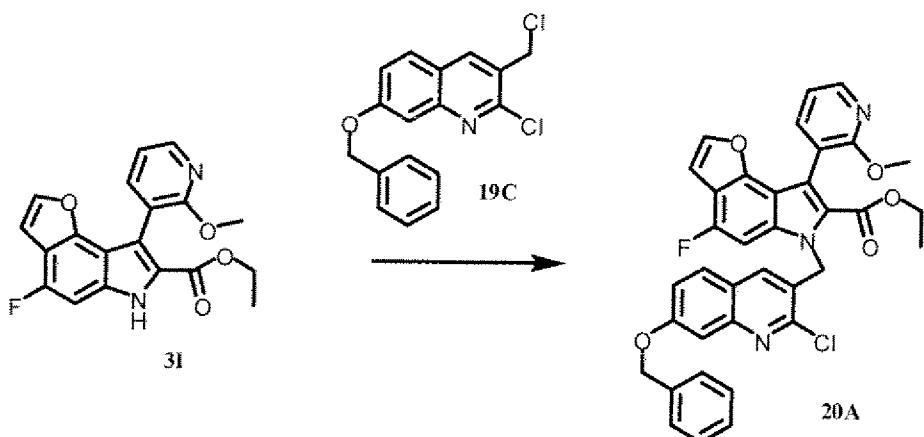
at room temperature and to resulting suspension K_2CO_3 (3.8 g, 27.64 mmol) was added. 3-

20 Chloro propionylchloride (7.0 g, 55.28 mmol) was added dropwise for 30 minutes and stirred for 2 hours at room temperature. The precipitate was filtered and washed with water, 1 N HCl, dried at 50 °C under vacuum overnight to provide 7.2 g of the product **19B**.

Step B – Synthesis of Compound 19C

To N,N-Dimethylformamide (3.6 g, 49.66 mmol) at 0 °C was added drop wise POCl₃

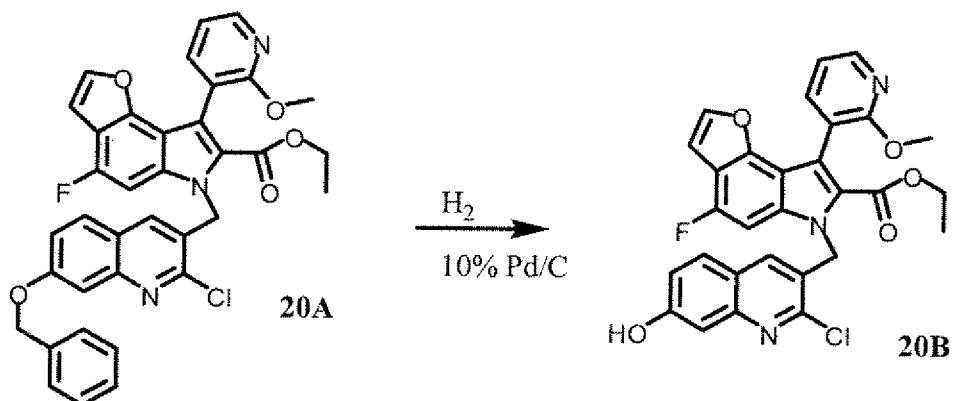
5 (26.6 g, 173.8 mmol) and stirred for 60 minutes, white precipitate was formed. The 7.2 g of the compound 19B was added by portion in reaction mixture and stirred for 24 hours at room temperature. Reaction mixture was diluted with ethyl acetate and slowly added to a beaker with ice, after ice was melted, organic layer was separated and washed with 0.5 N NaOH and water, brine, dried over sodium sulfate, and concentrated in vacuum, purified using flash chromatography, to provide compound 19C (5.5 g , 34 % after two steps). M.S. found: 318.04 (M+H)⁺.

Example 20**Preparation of Compound 55***15 Step A – Synthesis of Compound 20A*

To a solution of compound 3I (0.30 g, 0.85 mmol) in DMF (5 mL) was added cesium carbonate (0.28 g, 0.85 mmol) and chloride 19C (0.27 g, 0.85 mmol) and the resulting reaction 20 was allowed to stir at room temperature for 24 hours. The reaction mixture was diluted with EtOAc and washed with water, brine. The combined organic layers were dried (Na₂SO₄),

filtered, and concentrated *in vacuo*, and purified using flash chromatography, to provide compound **20A** (0.42 g, 77 %).

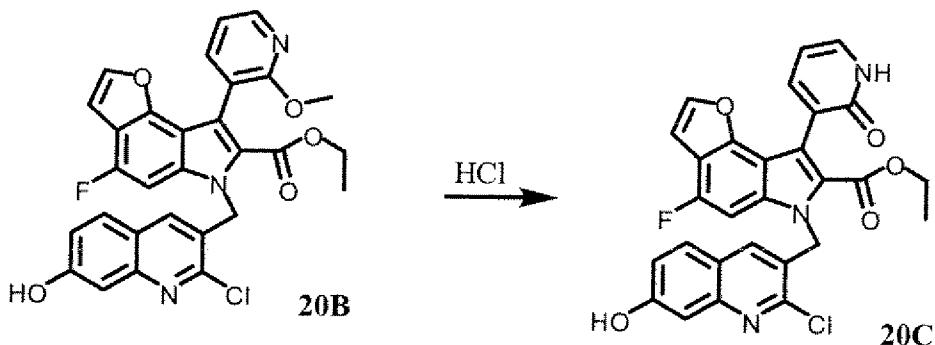
Step B – Synthesis of Compound 20B



To solution of the compound **20A** (0.42 g, 0.66 mM) in THF was added 10% Pd/C and treated with hydrogen in balloon for 24 hours. Reaction mixture was diluted with ethyl acetate and filtered through celite, concentrated *in vacuo*, purified using flash chromatography, to provide compound **20B** (0.2 g, 55 %).

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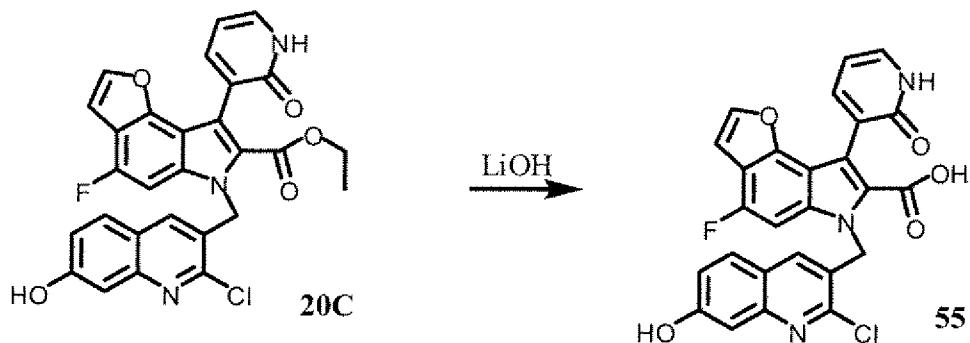
Step C – Synthesis of Compound 20C



Compound **20B** (200 mg, 0.37 mmol) was dissolved in 3 mL dioxane and 3 mL 4N HCl and the resulting reaction mixture was heated to 90 °C and allowed to remain at this 15 temperature for 5 hours. The reaction mixture was cooled to room temperature, and then concentrated *in vacuo* to provide a crude product which was purified using flash chromatography, to provide compound **20C** (150 mg, 77 %).

Step D – Synthesis of Compound 55

92



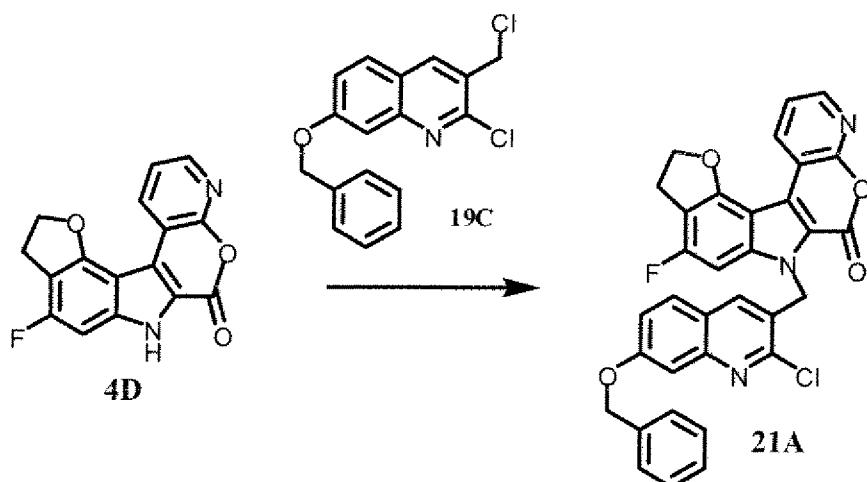
To a solution of compound **20C** (150 mg, 0.28 mmol) in water (5 mL)/THF (10 mL) was added lithium hydroxide (68 mg, 10 mmol) and the resulting reaction was allowed to stir at 65 °C for 5 hours. The reaction mixture was diluted with aqueous HCl and extracted into ethyl acetate. The combined organic layers were dried with Na₂SO₄, filtered, and concentrated *in vacuo* to provide 50 mg of the product **55**. M.S. found: 504.3 (M+H)⁺; ¹H NMR (500 MHz, DMSO): δ 10.41 (s, 1H), 7.97 (m, 1H), 7.74 (m, 1H), 7.62 (d, J = 9.1 Hz, 1H), 7.52 (d, J = 11.0 Hz, 1H), 7.44 (s, 1H), 7.16 (m, 1H), 7.11 (m, 1H), 7.08 (m, 1H), 7.05 (s, 1H), 6.36 (t, J = 6.9 Hz, 1H), 5.97 (s, 2H).

Example 21

Preparation of Compound **60**

Step A – Synthesis of Compound 21A

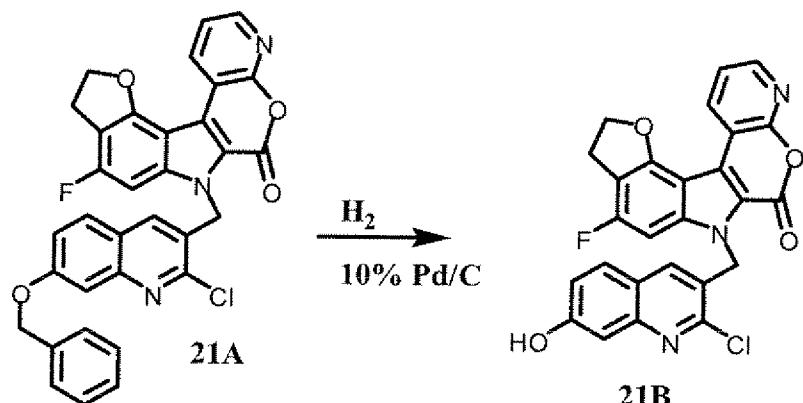
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To a solution of compound **4D** (0.65 g, 2.2 mmol) in DMF (10 mL) was added cesium carbonate (0.72 g, 2.2 mmol) and compound **19C** (0.71 g, 2.2 mmol) and the resulting reaction was allowed to stir at room temperature for 24 hours. The reaction mixture was diluted with EtOAc and washed with water, brine. The combined organic layers were dried (Na_2SO_4),

filtered, and concentrated *in vacuo*, and purified using flash chromatography, to provide compound **21A** (0.8 g, 68 %).

Step B – Synthesis of Compound 2IB

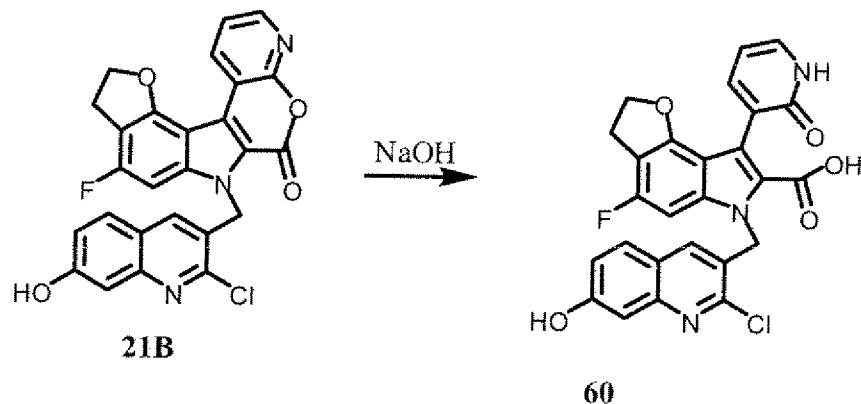


5

To solution of the compound **21A** (0.2 g, 0.35 mmol) in THF was added 10 % Pd/C and treated with hydrogen in balloon for 24 hours. Reaction mixture was diluted with Ethyl Acetate and filtered through celite, concentrated *in vacuo*, purified using flash chromatography, to provide compound **21B** (0.12 g, 71 %).

10

Step C – Synthesis of Compound 60

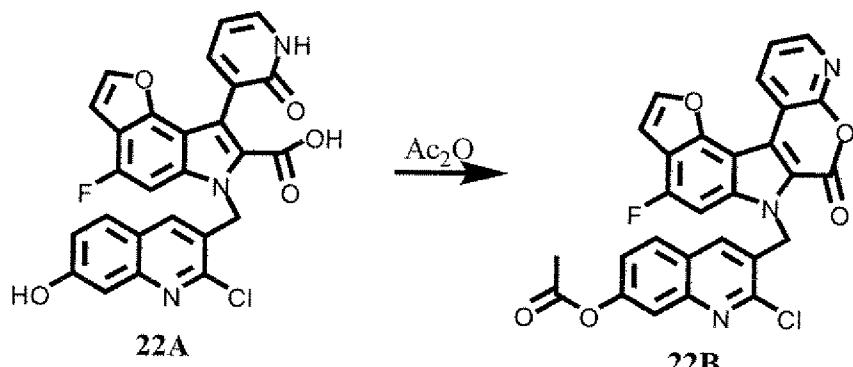


Compound **21B** (120 mg, 0.25 mmol) was dissolved in 5 mL THF and 2 mL 0.5N NaOH and stirred at room temperature. The reaction mixture was diluted with EtOAc and washed with water, brine. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*, product was washed with methanol, concentrated *in vacuo* to provide compound **60** (5 mg, 4%). M.S. found: 506.3 ($\text{M}+\text{H}$)⁺; ¹H NMR (500 MHz, DMSO): δ 10.39 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.54 (m, 1H), 7.36 (m, 1H), 7.16 (s, 1H), 7.10 (m, 1H), 7.06 (s, 1H), 6.97 (m, 1H), 5.83 (s, 2H), 4.67 (t, J = 8.5 Hz, 2H), 3.23 (t, J = 8.5 Hz, 2H).

Example 22

Preparation of Compound 92

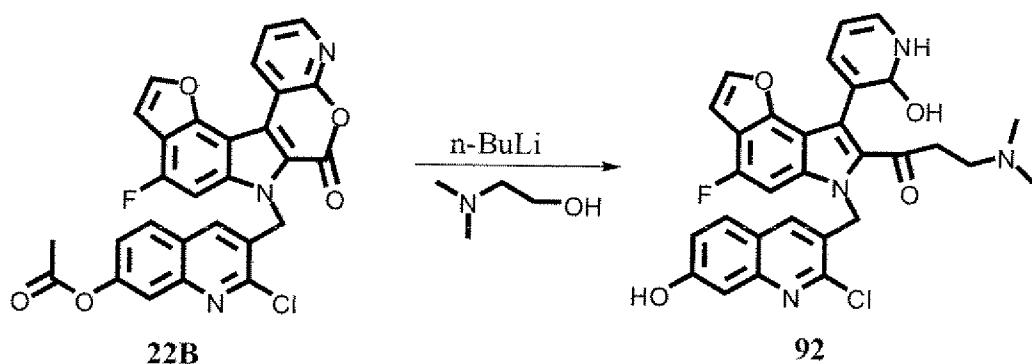
Step A – Synthesis of Compound 22B



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Compound **22A** (200 mg 0.4 mmol) was dissolved in 5 mL DMF at room temperature and 1 mL acetic anhydride. 1 mL triethyl amine was added and stirred for 1 hour at 60 °C. The reaction mixture was diluted with ethyl acetate and washed with water, brine. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*, product was washed with methanol, dried in vacuum for 24 hours to provide compound **22B** (77 mg, 37 %).

Step B – Synthesis of Compound 92



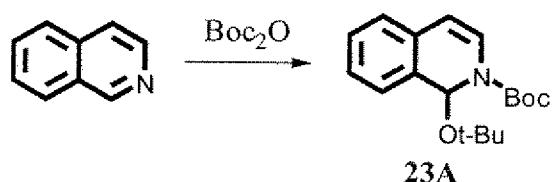
To solution of **22B** (77 mg, 0.15 mM) in 4 mL THF was added dropwise 1.6M n-BuLi (0.5 mL, 0.75 mmol) at -70°C and stirred for 10 minutes, reaction mixture was cooled to 0°C and solution of the N,N-dimethylethanol (80 mg, 0.90 mmol) in 4 mL THF was added and stirred for 1 hour. Solvent was evaporated, reaction mixture was separated on preparative HPLC to produce product **92** (14 mg, 17 %). M.S. found: 576 (M+H)⁺; ¹H NMR (500 MHz, CD₃OD): δ 8.13 (dd, J = 1.9 Hz, J = 6.9 Hz, 1H), 7.76 (d, J = 2.2 Hz, 1H), 7.68 (dd, J = 1.9 Hz, J = 6.9 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.29 (s, 1H), 7.22 (m, 2H), 7.10 (dd, J = 2.5 Hz, J = 8.8 Hz,

1H), 7.04 (d, J = 2.2 Hz, 1H), 6.77 (t, J = 6.6 Hz, 1H), 6.03 (s, 2H), 4.55 (t, J = 5.0 Hz, 2H), 3.36 (t, J = 5.0 Hz, 2H), 2.88 (s, 6H).

Example 23

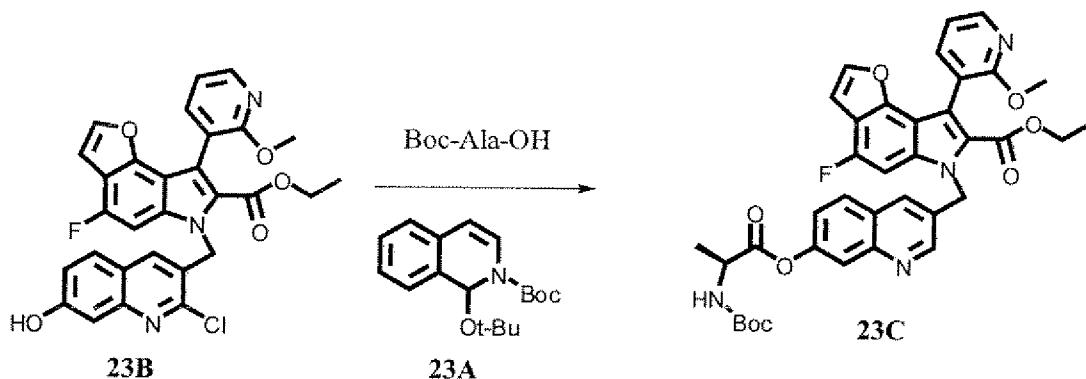
5 Synthesis of Compound 99

Step A – Synthesis of Compound 23A



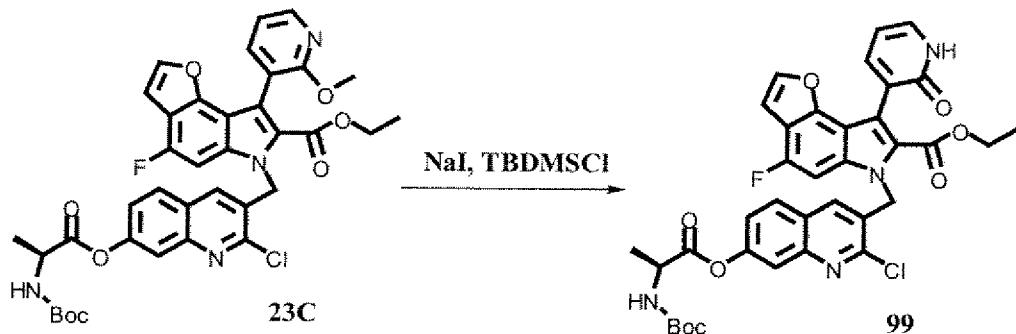
As per Ref: Tetrahedron, 2006, 62, 11599-11607, isoquinoline (3.8 g, 29.5 mmol) and di-*tert*-butyl dicarbonate (7.7 g, 35.4 mmol) were mixed in hexane and stirred at room temperature for 15 hours. Formed precipitate was filtered and concentrated *in vacuo* to produce product **23A** (BBDI) (2.5 g). This was used as the coupling reagent in the next step.

Step B – Synthesis of Compound 23C

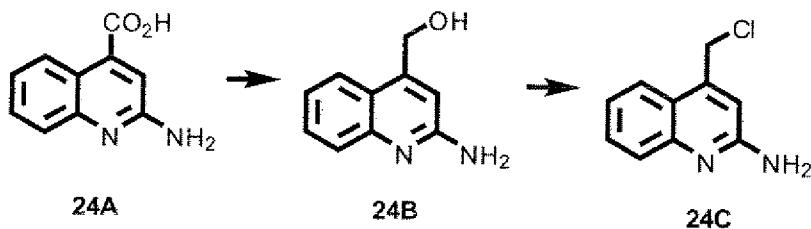


Compound **23B** (200 mg 0.36 mmol) was dissolved in 5 ml dioxane at room temperature and compound **23A** (327 mg 1.08 mM) was added and stirred for 30 minutes. Boc-Ala-OH (204 mg, 1.08 mmol) was added and stirred for 10 hours at room temperature. The reaction mixture was diluted with ethyl acetate and washed with 1N HCl, water, brine. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*, product was purified on flash chromatography, dried in vacuum for 24 hours to provide compound **23C** (160 mg, 61 %).

Step C – Synthesis of Compound 99



To solution of the **23C** (160 mg, 0.22 mmol) in 5 mL acetonitrile at 0 °C were added sodium iodide (1.5 eqv.) and tert-butyldimethylsilyl chloride (2 eqv.) and stirred at room temperature for 24 hours. Solvent was evaporated, reaction mixture was separated on flash LC to produce product **99** (70 mg, 45 %). M.S. found: 703.4 (M+H)⁺; ¹H NMR (500 MHz, CD₃OD): δ 7.9 (dd, J = 1.9 Hz, J = 6.9 Hz, 1H), 7.8 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 2.2 Hz, 1H), 7.72 (m, 1H), 7.57 (dd, J = 2.2 Hz, J = 6.3 Hz, 1H), 7.51 (s, 1H), 7.33 (m, 1H), 7.19 (d, J = 10.4 Hz, 1H), 7.00 (d, J = 2.2 Hz, 1H), 6.62 (t, J = 6.6 Hz, 1H), 6.08 (s, 2H), 4.41 (m, 1H), 4.11 (q, J = 7.3 Hz, 3H), 1.55 (d, J = 7.3 Hz, 3H), 1.48 (s, 9H), 1.04 (t, J = 7.3 Hz, 3H).

Example 24Preparation of Intermediate Compound **24C**

15 The starting materials **24A** (2.0 g, 10.6 mmol), lithium aluminum hydride (2.0 g, 52.7 mmol), and THF (100 ml) were added to a 250 ml round-bottomed flask. The resulting suspension was stirred at room temperature for 18 hours. The reaction was quenched with 10 ml of saturated ammonium chloride solution followed by 200 ml of ethyl acetate. After filtration, the organic layer was washed with brine (2x100 ml), dried over sodium sulfate, and concentrated under vacuum to provide **24B** as a yellowish solid (1.05 g, 59%).

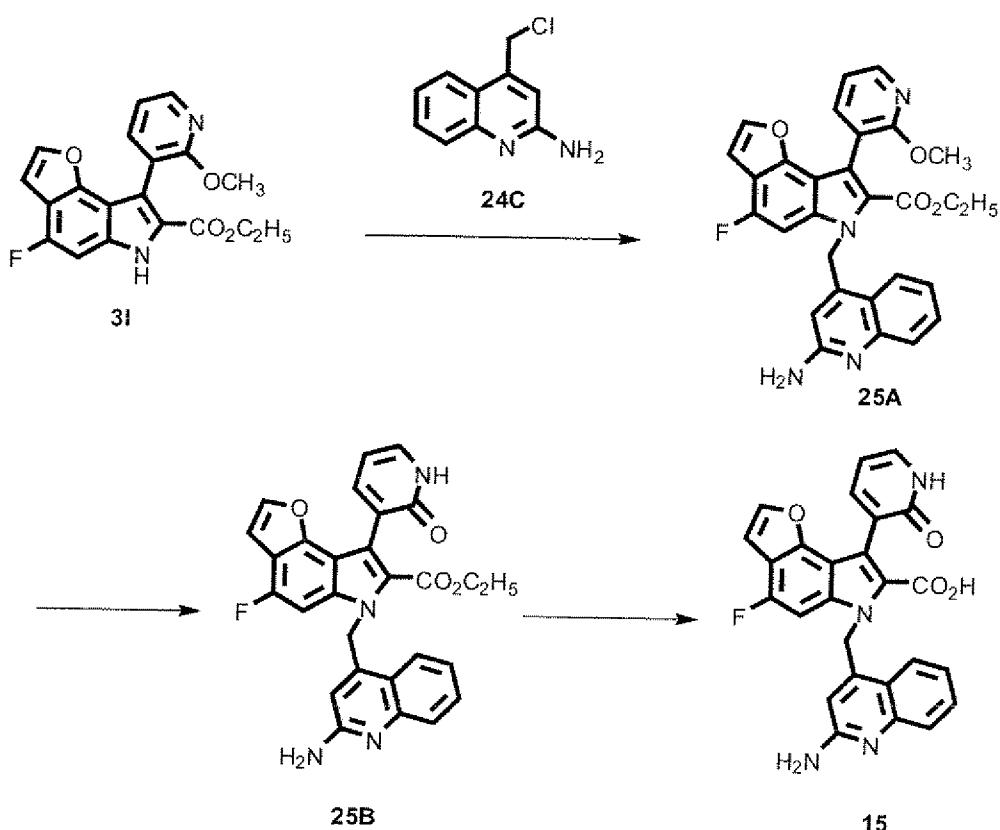
20 A 250 ml round-bottomed flask was charged with **24B** (1.05 g, 6.03 mmol) and thionyl chloride (10 ml). The resulting mixture was stirred at 60 °C for 4 hours before cooled to room temperature. After removal of excess of thionyl chloride, the residue was concentrated *in*

vacuo to provide **24C** as an orange solid (1.45 g). This crude material was used without further purification.

Example 25

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Preparation of Compound **15**



The suspension of **3I** (1.0 g, 2.8 mmol), crude **24C** (0.5 g, ~2.6 mmol), cesium carbonate (2.0 g, 6.16 mmol) and DMF (10 ml) was stirred at room temperature for 16 hours, 10 diluted with ethyl acetate (100 ml), and washed with brine (3X40 ml). The organic solution was dried over sodium sulfate and concentrated. The residue was purified using flash chromatography on silica gel using 0-5% methanol in dichloromethane as eluent to provide **15A** as an orange solid (0.88g, 62%). MS found 511.3 for $C_{29}H_{23}FN_4O_4 + H^+$.

Compound **25A** (0.88 g, 1.72 mmol) was dissolved in a 4.0 M solution of HCl in 1,4-dioxane (30.0 ml, 120 mmol) in a 75 ml pressure vessel. The resulting solution was stirred at 90 °C for 18 hours before cooled to room temperature. The mixture was transferred to a 250 ml round-bottomed flask and concentrated *in vacuo*. The residue was washed with methanol

(2x5 ml) and dried on house vacuum to provide **25B** as a white solid (0.62 g, 73%). MS found 497.3 for $C_{28}H_{21}FN_4O_4 + H^+$.

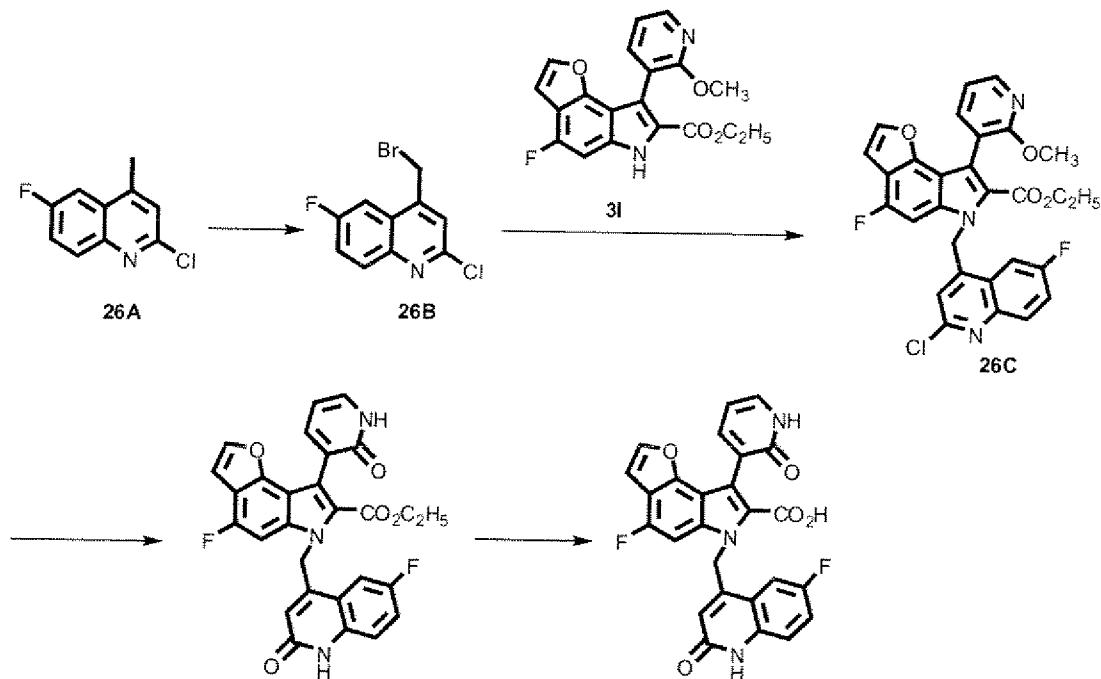
To the stirring mixture of **25B** (0.62 g, 1.25 mmol) in THF (12 ml) in a 100 ml round-bottomed flask was added with a solution of lithium hydroxide (5.0 ml of 1 M, 5.0 mmol). The 5 resulting solution was maintained refluxing for 1 day before cooled to room temperature.

After concentration *in vacuo*, the residue was dissolved in methanol (20 ml), neutralized with 1.0 M HCl aqueous solution (5 ml, 5.0 mmol) and then concentrated again. The residue was washed with water (2x50 ml) and dried on house vacuum to provide title compound **15** as a pale solid (0.55 g, 94%). MS found 469.3 for $C_{26}H_{17}FN_4O_4 + H^+$. 1H NMR (DMSO-d6) δ 8.20

10 (d, 1H, J = 9.5 Hz), 8.01 (d, 1H, J = 2.2 Hz), 7.80-7.76 (m, 1H), 7.71-7.67 (m, 2H), 7.57-7.40 (m, 3H), 7.13 (d, 1H, J = 2.2 Hz), 6.40 (t, 1H, J = 6.3 Hz), 6.31 (s, 2H), 5.84 (s, 1H).

Example 26

Preparation of Compound **39**



15

26D

39

Compound **26A** (3.0 g, 15.34 mmol), NBS (3.3 g, 18.54 mmol), and benzoyl peroxide (0.34 g, 1.4 mmol) were diluted with carbon tetrachloride (100 ml). The resulting mixture was refluxed for 15 hours before cooled to room temperature. After filtration, the filtrate was 20 washed with saturated sodium carbonate solution, dried over sodium sulfate, and concentrated

to deliver **26B** as a gel (4.1 g). This material was used for the next step without further purification.

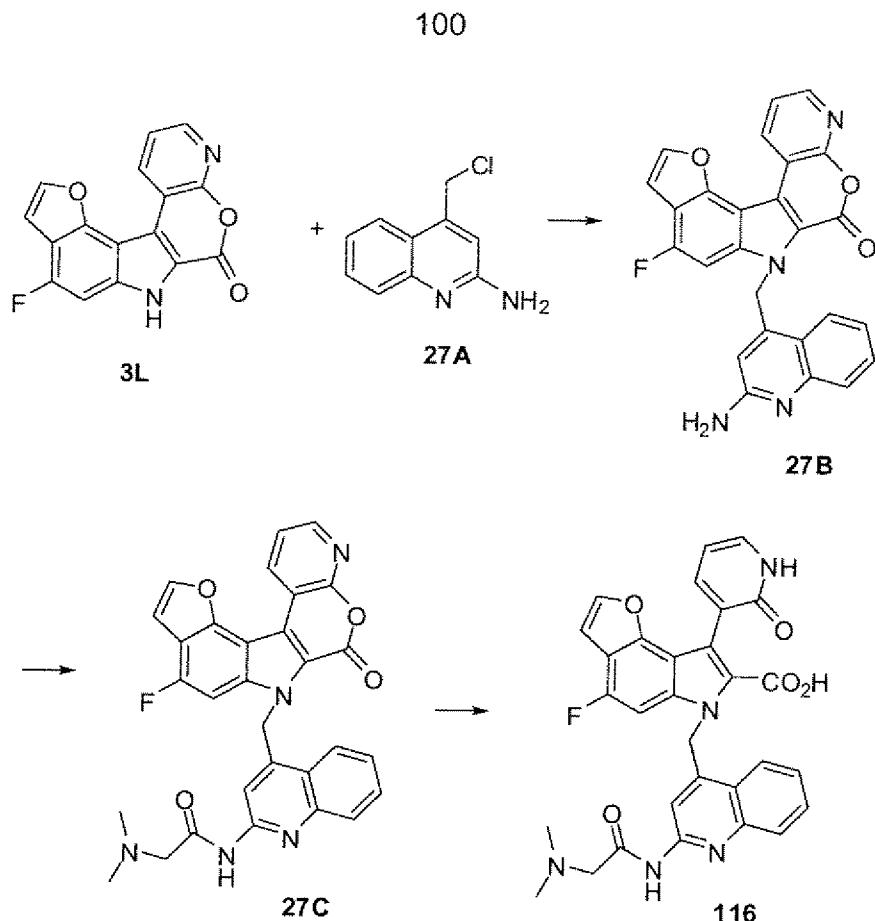
The suspension of **3I** (270 mg, 0.76 mmol), crude **26B** (1 g, ~2.5 mmol), cesium carbonate (0.5 g, 1.54 mmol) and DMF (3 ml) was stirred at room temperature for 16 hours, 5 diluted with ethyl acetate (100 ml), and washed with brine (3X40 ml). The organic solution was dried over sodium sulfate and concentrated. The residue was purified using flash chromatography on silica gel using 0-20% ethyl acetate in hexanes as eluent to deliver **26C** as solid (130 mg, 31%). MS found 548.3 for $C_{29}H_{20}ClF_2N_3O_4 + H^+$.

The starting material **26C** (130 mg, 0.237 mmol) was dissolved in a 4.0 M solution of 10 HCl in 1,4-dioxane (10.0 ml, 40 mmol) in a 75 ml pressure vessel. The resulting solution was stirred at 90 °C for 17 hours before cooled to room temperature. The mixture was transferred to a 250 ml round-bottomed flask and concentrated *in vacuo*. The residue was washed with methanol (2x5 ml) and dried on house vacuum to provide **26D** as a white solid (120 mg, 98%). MS found 516.3 for $C_{28}H_{19}F_2N_3O_5 + H^+$.

15 To the stirring mixture of **26D** (120 mg, 0.232 mmol) in THF (10 ml) in a 100 ml round-bottomed flask was added with a solution of lithium hydroxide (3.0 ml of 1 M, 3.0 mmol). The resulting solution was maintained refluxing for 19 hours before cooled to room temperature. After neutralization with 1.0 M HCl aqueous solution (3 ml, 3.0 mmol), the solution was concentrated *in vacuo*, washed with water (3x10 ml), and dried on house vacuum 20 to provide **39** as a white solid (103 mg, 91%). MS found 488.3 for $C_{26}H_{15}F_2N_3O_5 + H^+$. 1H NMR (CD₃OD) δ 10.18-10.12 (m, 2H), 9.97 (d, 1H, J = 2.2 Hz), 9.80-9.71 (m, 3H), 9.32 (d, 1H, J = 10.4 Hz), 9.24 (d, 1H, J = 2.2 Hz), 8.84 (t, 1H, J = 6.6 Hz), 8.62 (s, 2H), 8.02 (s, 1H).

Example 27

25 Preparation of Compound **116**



The suspension of **3L** (305 mg, 1.04 mmol), **27A** (300 mg, 1.57 mmol), cesium carbonate (1.97 g, 6.04 mmol) and DMF (5 ml) was stirred at room temperature for 20 hours. 5 Water (10mL) was added to the reaction mixture before filtration. The cake was washed with MeOH (2x1 ml), dried by air and then on house vacuum to provide **27B** as a light yellow powder (280 mg, 60%). This crude product is pure enough for the next reaction without further purification.

A solution of **27B** (40 mg, 0.089 mmol), dimethylaminoacetyl chloride hydrochloride 10 (147 mg, 0.93 mmol) and triethylamine (0.26 ml, 1.87 mmol) in THF (5 ml) in a 25 ml round-bottomed flask was stirred at room temperature for 72 hours. After evaporating off the solvents, water (3 mL) was added to the flask before filtration. The cake was washed with MeOH (2x 1mL), dried by air and then on house vacuum to provide **27C** as a yellow solid (36 mg, 75%). This crude product is pure enough for the next reaction without further purification.

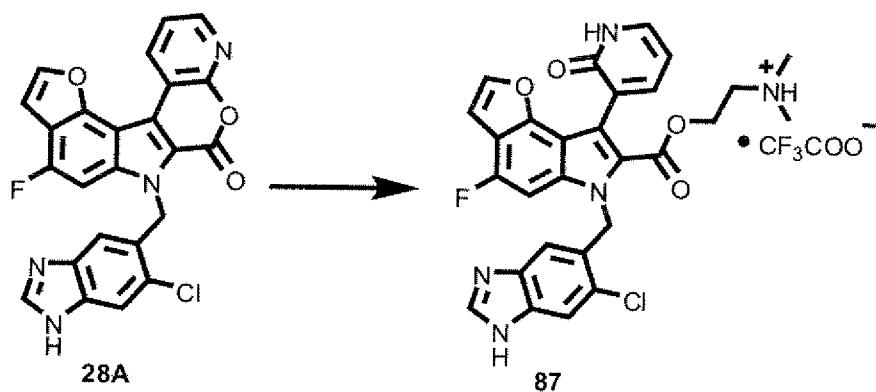
15 To the stirring mixture of **27C** (36 mg, 0.067 mmol) in THF (5 ml) in a 25 ml round-bottomed flask was added with a solution of lithium hydroxide (0.34 ml of 1 M, 0.34 mmol). The resulting solution was stirred at room temperature for 2 hours. Before concentration under

vacuum, the reaction mixture was neutralized with 1.0 M HCl aqueous solution (0.34 ml, 0.34 mmol). Water (3 ml) was added to the flask before filtration. The cake was washed with MeOH (2x 1mL), dried by air and then on house vacuum to provide title compound **116** as a yellow solid (34 mg, 92%). MS found 554.3 for $C_{30}H_{24}FN_5O_5 + H^+$.

5

Example 28

Preparation of Compound 87

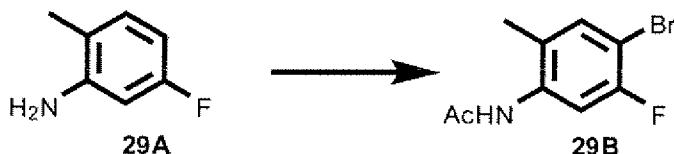


10

A solution of N,N-dimethylaminoethanol (0.134 g, 1.50 mmol) in anhydrous tetrahydrofuran (10.00 mL, 49.3 mmol) was cooled to -20 °C and treated dropwise with n-butyl lithium in hexane (2.5 M solution, 0.500 mL) and stirred for 10 minutes. To this mixture was added a solution of 6-((5-chloro-1H-benzo[d]imidazol-6-yl)methyl)-4-fluorofuro[2,3-e]pyrido[3',2':5,6]pyrano[3,4-b]indol-7(6H)-one (**28A**, 0.115 g, 0.250 mmol) in THF (4.00 mL, 49.3 mmol) and stirred at room temperature for 1h. The reaction mixture was quenched with trifluoroacetic acid (200 uL), concentrated in *vacuo* and the residue taken in DMF and purified using HPLC (C18-reverse phase) using following conditions: THF and water with 0.01% TFA to obtained 2-(dimethylamino)ethyl 6-((5-chloro-1H-benzo[d]imidazol-6-yl)methyl)-4-fluoro-8-(2-oxo-1,2-dihydropyridin-3-yl)-6H-furo[2,3-e]indole-7-carboxylate (Title compound **87**) (52.00 mg; Yield = 38.0%) as colorless solid. ¹H NMR (500 MHz, d₆-DMSO), δ, 12.09 (s, 1 H), 9.59 (s, 1 H), 8.64 (s, 1 H), 8.02 (d, 1 H, J = 2.0 Hz), 7.59 (dd, 1 H, J = 5.0 & 7.0 Hz), 7.91 (s, 2 H), 7.58 (dd, 1 H, J = 2.0 & 6.0 Hz), 7.48 (d, 1 H, J = 11.0 Hz), 7.15 (d, 1 H, J = 2.0 Hz), 6.55 (s, 1 H), 6.51 (t, 1H, J = 7.0 Hz), 6.00 (s, 2 H), 4.42-4.40 (m, 2 H), 3.29-3.27 (m, 2 H), 2.74 (s, 6 H).

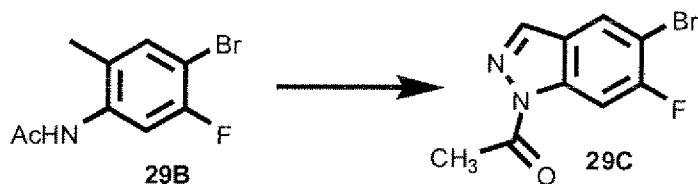
Example 29Preparation of Intermediate Compound **29G***Step A – Synthesis of Compound **29B***

5

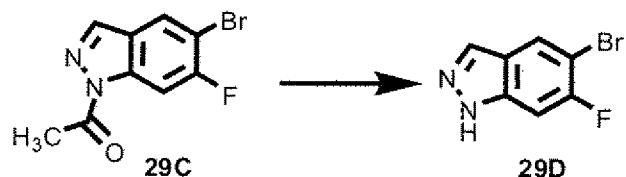


A solution of 5-fluoro-2-methylaniline (**29A**, 25 g, 200 mmol) in toluene (250 mL) was treated with acetic anhydride (25 mL, 226 mmol) heated at reflux for 1 hour. The reaction mixture was cooled when a colorless solid precipitated out which was filtered and washed with a mixture of ether and hexanes. The colorless solid was taken in acetic acid (150 mL) and treated dropwise with a solution of bromine (9.6 mL, 186 mmol) in acetic acid (20 mL) and stirred at room temperature for 12 hours. The solution was diluted with water and the solid separating out was filtered and washed to yield N-(4-bromo-5-fluoro-2-methylphenyl)acetamide (**29B**, 40 g) as a colorless solid.

15

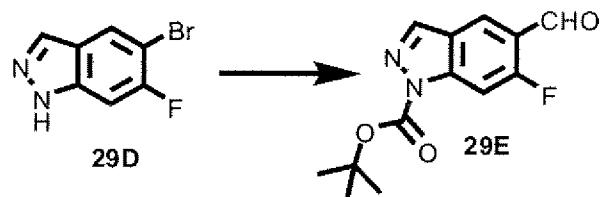
*Step B – Synthesis of Compound **29C***

A solution of N-(4-bromo-5-fluoro-2-methylphenyl)acetamide (**29B**, 10.00 g, 40.64 mmol) in chloroform (100 mL) was treated with acetic anhydride (11.5 mL, 122.0 mmol), potassium acetate (8.00 g, 81.5 mmol), and 18-Crown-6 (540.00 mg, 2.0430 mmol) and then with isoamyl nitrite (12.3 mL, 871 mmol) and heated at 65 °C for 12 hours. The reaction mixture was cooled to room temperature and treated with EtOAc (500 mL), washed with water, dried (MgSO_4), filtered, and then concentrated *in vacuo*. A pale yellow solid of 1-(5-bromo-6-fluoro-1H-indazol-1-yl)ethanone (**29C**) precipitated out. The initial filtrate was concentrated and the residue was purified using chromatography (SiO_2 , EtOAc/Hexanes) to yield more of product **29C**.

Step C – Synthesis of Compound 29D

5 A solution of 1-(5-bromo-6-fluoro-1H-indazol-1-yl)ethanone (**29C**, 5.0 g, 19.5 mmol) was treated with aq HCl (3M soln., 100 mL) and methanol (20 mL) and heated at 90 °C for 3h, when the reaction turns homogenous. The reaction mixture was cooled to room temperature and basified with aq. NaOH. A colorless solid precipitated out which was filtered and dried to yield 5-bromo-6-fluoro-1H-indazole (**29D**)

10

Step D – Synthesis of Compound 29E

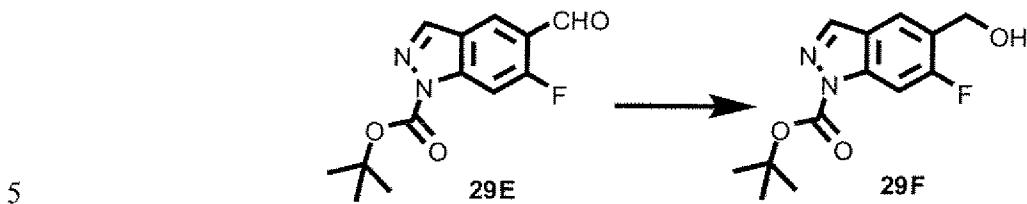
15 A solution of 5-bromo-6-fluoro-1H-indazole (**29D**, 3.50 g, 16.28 mmol) in tetrahydrofuran (200.00 mL) was treated with sodium hydride (60% in mineral oil, 1.172 g) at 0 °C and stirred at room temperature for 20 minutes. The reaction mixture was cooled to -78 °C (dry ice and acetone) and treated with 2.5 M of n-butyl lithium in hexane (8.2 mL, 20.3 mmol) dropwise. The reaction mixture was stirred at that temperature for 20 minutes and treated with DMF (5.06 mL, 65.11 mmol). The reaction mixture was slowly warmed to room temperature when the viscous solution turned fluidic and stirring was efficient. Analysis of TLC (40% EtOAc/Hexanes) indicated complete conversion of starting material to product. The reaction mixture was acidified with aq. HCl taken up in EtOAc (500 mL) washed with aq. HCl (100 mL), brine (100 mL), dried (MgSO_4), filtered, concentrated *in vacuo* and used as it is in next step. A solution of product 6-fluoro-1H-indazole-5-carbaldehyde (2.3 g) in THF (100 mL)

20 was treated with di-*tert*-butyldicarbonate (3.56 g, 16.28 mmol) and DMAP (300 mg) and stirred at room temperature for 3 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified using chromatography (SiO_2 , EtOAc/Hexanes gradient 0-40%) to

25

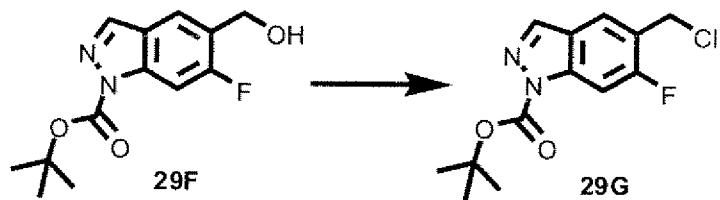
yield [2e] *tert*-butyl 6-fluoro-5-formyl-1*H*-indazole-1-carboxylate (**29E**, 3.5 g; Yield = 81%) as a colorless solid.

Step E – Synthesis of Compound **29F**



A solution of *tert*-butyl 6-fluoro-5-formyl-1*H*-indazole-1-carboxylate (**29E**, 3.55 g, 13.4 mmol) in methanol (50.00 mL) was treated with NaBH₄ (1.02 g, 26.9 mmol) at 0 °C and stirred for 1h. The reaction mixture was diluted with water and EtOAc (500 mL). The organic layer was separated and washed with aq. HCl (1M, 200 mL), aq. NaOH (1M, 200 mL) brine (200 mL) dried (MgSO₄), filtered, concentrated *in vacuo* and residue was purified using chromatography (SiO₂, EtOAc/hexanes) to yield *tert*-butyl 5-(hydroxymethyl)-6-fluoro-1*H*-indazole-1-carboxylate (**29F**, 3.00 g; Yield = 83.9%) as a colorless solid.

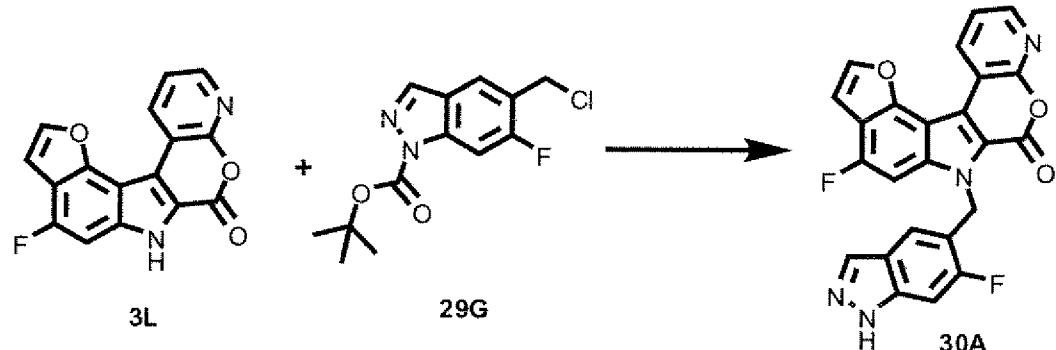
15 Step F – Synthesis of Compound **29G**



A solution of *tert*-butyl 5-(hydroxymethyl)-6-fluoro-1*H*-indazole-1-carboxylate (**29F**, 3.0g, 11.27 mmol) in methylene chloride (50.00 mL, 780.0 mmol) at room temperature was treated with pyridine (4.56 mL, 56.33 mmol) and methanesulfonyl chloride (1.31 mL) and stirred at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc (300 mL) washed with aq HCl (100 mL), brine (100 mL), dried (MgSO₄), filtered, concentrated *in vacuo*, and purified using chromatography (SiO₂, EtOAc/Hexanes) to yield *tert*-butyl 5-(chloromethyl)-6-fluoro-1*H*-indazole-1-carboxylate (**29G**, 1.9 g; Yield = 59%)

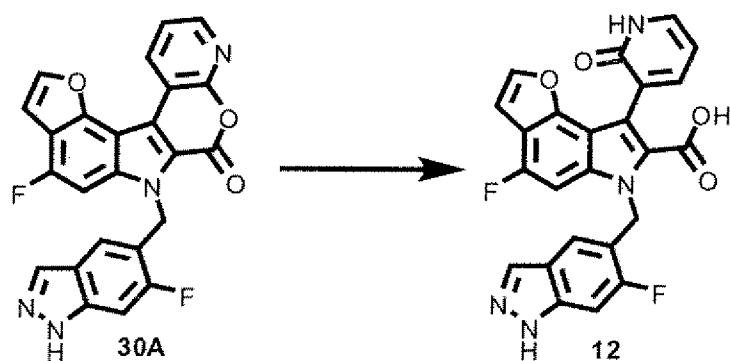
Example 30

Preparation of Compound 12

Step A – Synthesis of Compound 30A

A solution of **3L** (900 mg, 3.06 mmol) in DMF (40.00 mL, 516.6 mmol) was treated with **29G** (1.09 g, 3.84 mmol) and cesium carbonate (1.50 g, 4.59 mmol) and stirred at room temperature overnight. The reaction mixture was concentrated, diluted with CH_2Cl_2 (600 mL), washed with water, dried (MgSO_4), filtered, concentrated *in vacuo* and purified using chromatography (THF/Hexanes) to yield alkylated product (1.6 g; Yield = 96%; The purified solid was dissolved in CH_2Cl_2 (40 mL) and TFA (40 mL) and stirred at room temperature for 1 hour. The reaction mixture was concentrated and treated with ether and the resulting solid **30A** was filtered and dried.

10

15 *Step B – Synthesis of Compound 12*

A suspension of **30A** (900 mg, 2.04 mmol) in THF (40 mL, 493 mmol) and water (40 mL,) was treated with lithium hydroxide monohydrate (427 mg, 10.2 mmol) and stirred at room temperature for 3.5 h when the reaction mixture turns clear. The reaction mixture was

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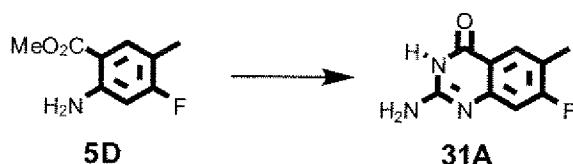
acidified with aq HCl and concentrated *in vacuo*. The solid separating out was filtered and purified using HPLC (reverse phase, C₁₈ column, Water/THF) to yield title compound **12**.

¹H NMR (500 MHz, D₆-dmso), δ , 13.11 (s, 1 H), 12.96 (s, 1 H), 11.77 (s, 1 H), 7.96 (s, 1 H), 7.94 (d, 1 H, J = 2.0 Hz), 7.69 (dd, 1 H, J = 1.6 & 7.0 Hz), 7.50 (d, 1 H, J = 11.0 Hz), 7.43 (d, 1 H, J = 6.5 Hz), 7.39 (d, 1H, J = 11.0 Hz), 7.09 (d, 1H, J = 2.0 Hz), 7.04 (d, 1 H, J = 7.5 Hz), 6.35 (t, 1 H, J = 7.0 Hz), 6.00 (s, 2 H).

Example 31

Preparation of Intermediate Compound **31C**

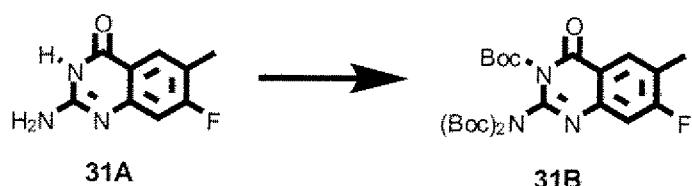
10 *Step A – Synthesis of Compound 31A*



A solid mixture of **5D** (2.66 g, 14.5 mmol), chloroformamidinium hydrochloride (2.6 g, 22.6 mmol) and methyl sulfone (8.5 g, 90.3 mmol) was heated to 150-160 °C in an oil bath with vigorous stirring. It became a clear solution after about 10 minutes. Heating was continued for a total of 2 hours. When cooled to room temperature, it became a solid. The material was taken up with water (200 mL), basified with commercial ammonium hydroxide. After stirred for 1 hour, the solid was collected through filtration. It was washed with water (20 mL) and concentrated *in vacuo* to provide crude product **31A** (2.93 g, quant.). MS found for C₉H₈FN₃O: 194.2 (M+H)⁺.

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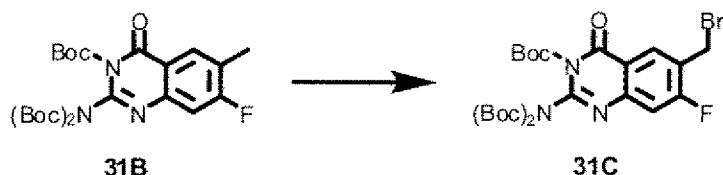
Step B – Synthesis of Compound 31B



Compound **31B** was prepared from **31A** according the procedures described above for the preparation of compound **5F**, and using 4 equivalents of (Boc)₂O. MS found for C₂₄H₃₂FN₃O₇: 394.3 (M+H-100)⁺.

Step C – Synthesis of Compound 31C

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A solution of compound **31B** (4.83 g, 9.8 mmol), N-bromosuccinimide (2.70 g, 15.2 mmol) and benzoyl peroxide (600 mg, 2.48 mmol) in carbon tetrachloride (300 mL) was heated to reflux and allowed to stir at this temperature for 18 hours. The reaction mixture was 5 cooled to room temperature, concentrated *in vacuo* and the residue obtained was dissolved in EtOAc (300 mL). The resulting solution was washed with aqueous sodium thiosulfate (100 mL), brine (100 mL), dried (MgSO_4), filtered, and concentrated *in vacuo* to provide intermediate compound **31C**, which was used without further purification. MS found for $\text{C}_{24}\text{H}_{31}\text{BrFN}_3\text{O}_7$: 472.3 ($\text{M}+\text{H}-100$)⁺.

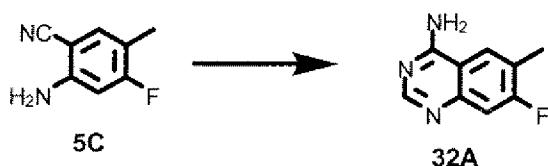
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Example 32

Preparation of Intermediate Compound **32C**

Step A – Synthesis of Compound 32A

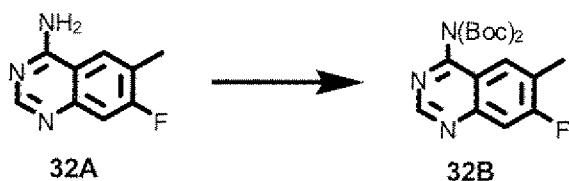
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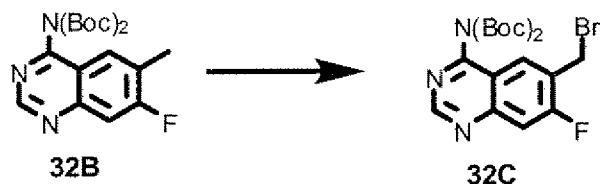
A solution of **5C** (0.20 g, 1.33 mmol) in formamide (15 mL) was heated to 150 °C and stirred for 18 hours. After cooled to room temperature, ethyl acetate (60 mL) and water (30 mL) were added and the layers were separated. The organic solution was washed with water (3x20 mL), dried (MgSO_4), filtered, and concentrated *in vacuo* to provide the crude product **32A** (0.22 g, 93 %). MS found for $\text{C}_9\text{H}_8\text{FN}_3$: 178.2 ($\text{M}+\text{H}$)⁺.

Step B – Synthesis of Compound 32B



Compound **32B** was prepared from **32A** according the procedures described above for the preparation of compound **5F**, except that 3.0 equivalent of (Boc)₂O was used in this reaction. MS found for C₁₉H₂₄FN₃O₄: 378.4 (M+H)⁺.

5 *Step C – Synthesis of Compound 32C*

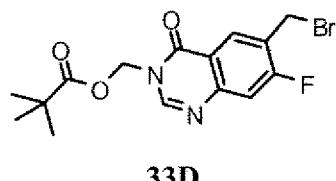


Compound **32C** was prepared from **32B** according the procedures described above for the preparation of compound **5G**. MS found for C₁₉H₂₃BrFN₃O₄: 458.3 (M+H)⁺.

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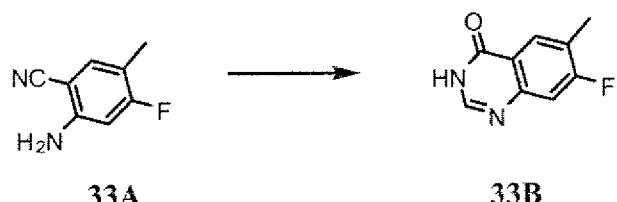
Example 33

Preparation of Intermediate Compound **33D**



Step A – Synthesis of Compound 33B

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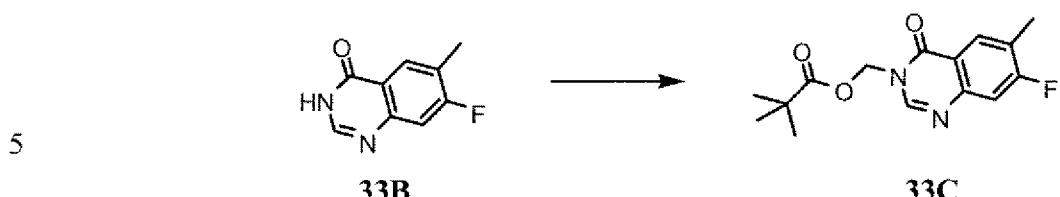


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To a suspension of compound **33A** (3.4 g, 22.7 mmol) in 98% formic acid (60 mL) was slowly added fuming sulfuric acid slowly (1 mL) and the resulting mixture was heated to reflux and allowed to stir at this temperature for 5 hours. The reaction mixture was cooled to room temperature then concentrated *in vacuo* and the residue obtained was diluted with EtOAc (300 mL) and water (300 mL). The layers were separated, and the aqueous solution was basified to pH 10 using aqueous ammonium hydroxide solution. The basic solution was extracted with ethyl acetate (2 x 200 mL) and the combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (2 x 400 mL), dried over magnesium sulfate,

filtered and concentrated *in vacuo* to provide the compound **33B** (3.17 g, 78%), which was used without further purification.

Step B – Synthesis of Compound 33C



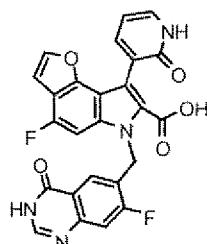
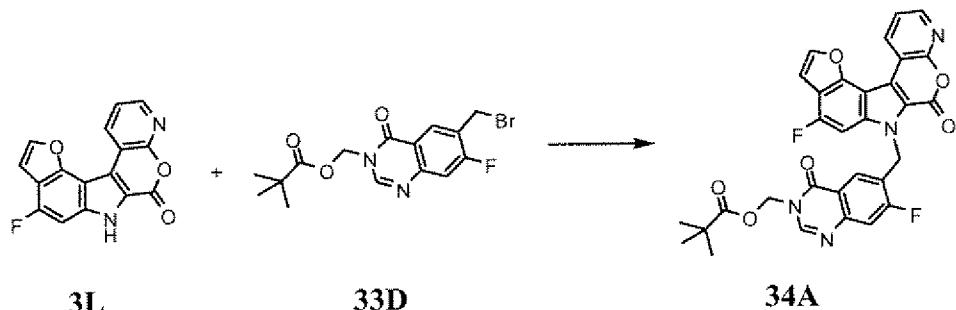
A suspension of compound **33B** (1.34 g, 7.52 mmol), chloromethyl pivalate (1.65 mL, 11.4 mmol) and anhydrous cesium carbonate (4.8 g, 14.8 mmol) in anhydrous DMF (60 mL) was allowed to stir at room temperature for 18 hours. The reaction mixture was then diluted 10 with EtOAc and water (150 mL each) and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 100 mL) and the combined organic extracts were washed with water (2 x 300 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide a crude residue which was purified using flash column chromatography on silica gel (0-60% ethyl acetate/hexanes) to provide compound **33C** (1.67 g, 76%).

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Step C – Synthesis of Compound 33D



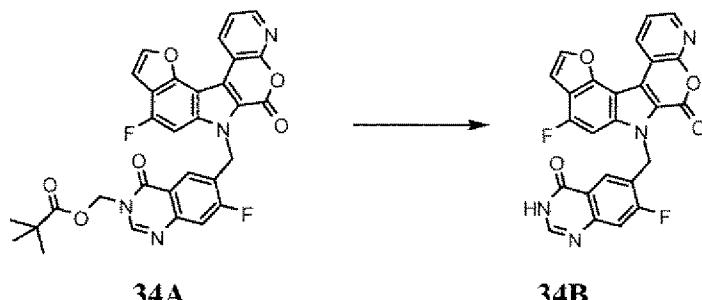
A solution of compound **33C** (1.65 g, 5.64 mmol), N-bromosuccinimide (1.41 g, 7.92 mmol) and benzoyl peroxide (410 mg, 1.69 mmol) in anhydrous carbon tetrachloride (150 mL) 20 was heated to 85 °C and allowed to stir at this temperature for 8 hours. The reaction mixture was allowed to cool to room temperature and was concentrated *in vacuo* to provide a crude residue which was dissolved in ethyl acetate (200 mL). To the resulting solution was added water (200 mL) and the mixture was transferred to a separatory funnel. The organic phase was 25 collected and washed with water (2 x 150 mL), dried over MgSO₄ and concentrated *in vacuo*. The residue obtained was purified using flash chromatography (0-60% ethyl acetate/hexanes) to provide compound **33D** (1.77 g, 85%).

Example 34Preparation of Intermediate Compound **89****89**5 *Step A – Synthesis of Compound 34A*

To a solution of compound **3L** (6.0 g, 20.4 mmol) and compound **33D** (7.95 g, 21.1 mmol) in DMF (500 mL) was added cesium carbonate (14.0 g, 43.0 mmol). The resulting reaction was allowed to stir at room temperature for 19 hours, then was diluted with ethyl acetate (200 mL) and water (200 mL). A precipitate formed and the mixture was filtered through a fritted funnel and the reaction flask was rinsed with additional EtOAc and water (1:1, total 600 mL), which was then also filtered. The filter cake was washed with EtOAc (200 mL) and water (150 mL) and dried under vacuum to provide a tan solid. The collected filtrate was separated and the aqueous layer was extracted with EtOAc (2 x 500 mL). The combined organic extracts were washed with water (3 x 1.0 L), dried (MgSO_4), filtered and concentrated *in vacuo* to provide a yellow solid residue. The yellow residue and the tan solid filter cake were combined to provide compound **34A** (12.1 g, quantitative), which was used in the next step without further purification. MS found for $\text{C}_{29}\text{H}_{23}\text{F}_2\text{N}_5\text{O}_5$: 585.5 ($\text{M}+\text{H}^+$).

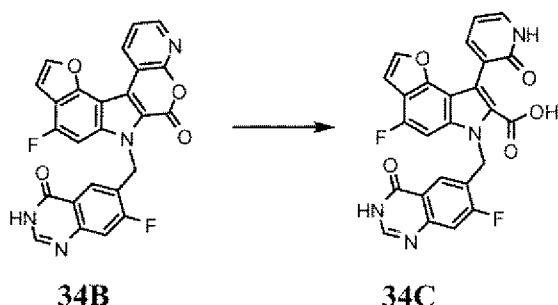
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Step B – Synthesis of Compound 34B



A solution of compound **34A** (11.6 g, 19.8 mmol) in a mixture of 4 M HCl in 1,4-dioxane and water (600 mL, 3:1 ratio, pre-mixed and cooled) was heated to 85°C and allowed to stir at this temperature for 3 hours. During the progress of the reaction, the reaction mixture turned from a suspension to a clear solution in about 5 minutes, then over the 3 hour reaction period, a large amount of white solid precipitate formed. The reaction mixture was cooled to room temperature and the resulting suspension was filtered through filter paper. The collected solid was washed with EtOAc, then water, and dried *in vacuo* to provide compound **34B** (8.99 g, 97%), which was used without further purification.

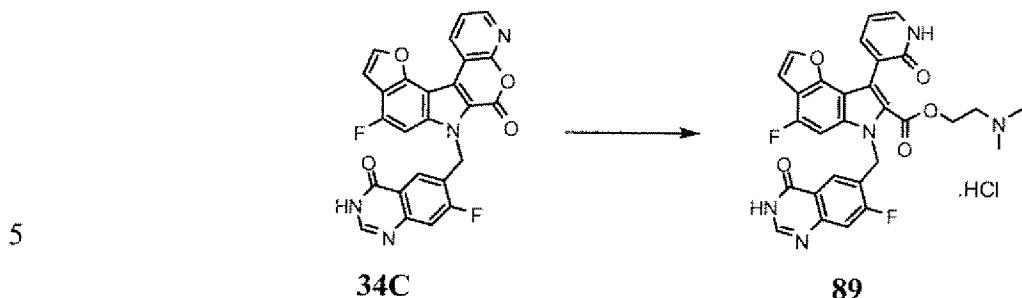
Step C – Synthesis of Compound 34C



To a solution compound **34B** (3.50 g, 7.44 mmol) in THF (100 mL) and water (100 mL) was added aqueous LiOH solution (22.0 mL, 1.0 M, 22.0 mmol). The resulting reaction was allowed to stir at room temperature for 3 hours, then was acidified to pH 5-6 using 1 N aqueous HCl solution (25 mL). The acidic solution was extracted with ethyl acetate (3 x 150 mL) and the combined organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide a crude residue which was purified using reverse-phase HPLC (10-100% acetonitrile/water (with 0.1% trifluoroacetic acid)) to provide compound **34C** (3.60 g, 99%). ¹H NMR (500 MHz, d₆-DMSO): δ 13.0 (bs, 1 H), 12.3 (bs, 1 H), 11.8 (bs, 1 H), 8.08 (s, 1 H), 7.96 (s, 1 H), 7.68-7.66 (m, 1 H), 7.53 (dd, *J* = 4.0, 11.0 Hz, 2 H), 7.42-7.41 (m,

2 H), 7.10 (s, 1 H), 6.34 (t, $J = 6.8$ Hz, 1 H), 6.01 (s, 2 H). MS found for $C_{25}H_{14}F_2N_4O_5$: 489.0 ($M + H$)⁺.

Step D – Synthesis of Compound 89



A solution of *N,N*-dimethylethanolamine (5.80 mL, 57.7 mmol) in 300 mL THF in a flame-dried flask was cooled to at -30°C and n-BuLi (1.6 M, 31.0 mL, 49.6 mmol) was added. The resulting reaction was allowed to stir for 10 minutes, then compound **34C** (4.50 g, 9.57 mmol) was added as a solid powder to the cold reaction mixture in one portion. The resulting suspension was allowed to stir at -30°C for 20 minutes, then the cooling bath was removed and the reaction mixture was allowed to warm to room temperature on its own and stir at this temperature for an additional 1 hour. The reaction mixture was then cooled to 0°C and HCl (4 M solution in dioxane, 30 mL) was added in one portion and a precipitate formed. The resulting solution was allowed to rest until the solid material settled at the bottom of the flask and the upper, clear solution was removed via pipette. The remaining solid material was triturated with water at a ratio of 4 mL/g to provide a white suspension, which was filtered through filter paper. The collected white solid material (3.5 g, 65 %) was then purified via one of two separate methods. The first method uses reverse-phase HPLC (C-18 column, 10-100 % acetonitrile/water/0.1% trifluoroacetic acid) wherein two molar equivalents of 1 N aqueous HCl solution were added to the combined HPLC fractions containing compound **89** prior to concentration to provide compound **89** as its hydrochloride salt. In the second purification method, the product is recrystallized from acetone/water (1:1, containing 2 molar equivalent of aqueous 1N HCl) to provide compound **89** as its hydrochloride salt. Compound **89** must be prepared as its HCl salt to prevent conversion back to compound **34C**.

Example 35

Spectroscopic Data For Illustrative Tricyclic Indole Derivatives

Mass spectrometry and ¹H NMR data was obtained for illustrative compounds of the present invention, using the instrumentation described above in the General Methods section. Data is presented in the tables below. Compound numbering refers to the compound numbering indicated in the above specification

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No.	LR-MS (M+H)	¹ H NMR
1	443.28	1H-NMR (dmso-d6; 400 MHz): δ 12.90 (2H, broad s), 11.74 (1H, broad s), 7.98 (1H, s), 7.91 (1H, d, J = 2.44 Hz), 7.67 (1H, d, J = 8.54 Hz), 7.65 (1H, dd, J = 1.83, 6.71 Hz), 7.47 (1H, d, J = 10.98 Hz), 7.40 (1H, dd, J = 1.83, 6.71 Hz), 7.10 (1H, s), 7.05 (1H, d, J = 2.44 Hz), 6.95 (1H, dd, J = 1.22, 8.54 Hz), 6.32 (1H, dd, J = 6.10, 6.71 Hz), 6.00 (2H, s). LR-MS (ESI): calcd for C24H16FN4O4 [M+H] ⁺ 443.12; found 443.28
2	443.41	1H NMR (500 MHz, D6-dmso), δ 12.98 (s, 1 H), 11.78 (s, 1 H), 11.72 (s, 1 H), 8.04 (d, 1 H, J = 8.0 Hz), 7.89 (d, 1 H, J = 2.5 Hz), 7.75 (dd, 1 H, J = 2.0 & 6.5 Hz), 7.61 (bt, 1 H, J = 7.0 Hz), 7.58 (d, 1 H, J = 9.0 Hz), 7.46-7.43 (m, 2 H), 7.39 (d, 1 H, J = 8.5 Hz), 7.33 (t, 1 H, J = 8.0 Hz), 7.01 (d, 1 H, J = 2.0 Hz), 6.38 (t, 1 H, J = 6.5 Hz), 6.20 (s, 2 H), 5.14 (s, 1 H)
3	444.39	NA
4	444.39	NA
5	450.42	1H NMR (400 MHz, D6-dmso, HCl salt), δ 11.77 (s, 1 H), 8.22 (s, 3 H), 7.92 (d, 1 H, J = 2.4 Hz), 7.65 (dd, 1 H, J = 1.6 & 6.4 Hz), 7.45-7.39 (m, 3 H), 7.30 (t, 1 H, J = 8.8 Hz), 7.07 (dd, 1 H, J = 0.4 & 2.4 Hz), 6.80 (dd, 1 H, J = 2.0 & 7.2 Hz), 6.33 (t, 1 H, J = 6.8 Hz), 5.92 (s, 2 H), 3.82 (q, 2 H, J = 5.6 Hz)
6	452.35	1H-NMR (400 MHz, in dmso-d6): δ 11.72 (1H, broad s), 7.90 (1H, d, J = 2.20 Hz), 7.86 (1H, s), 7.64 (1H, d, J = 10.98 Hz), 7.60 (1H, dd, J = 2.20, 7.32 Hz), 7.52 (1H, d, J = 3.66 Hz), 7.39 (1H, d, J = 4.39 Hz), 7.29 (1H, s), 7.08 (1H, d, J = 3.66 Hz), 7.06 (1H, d, J = 2.20 Hz), 6.30 (1H, t = 6.59 Hz), 6.02 (2H, s); LR-MS (ESI): calcd. for C22H15FN3O5S [M+H] ⁺ 452.07, found 452.35
7	453.45	NA
8	454.43	NA
9	458.42	1H NMR (400 MHz, D6-dmso), δ 12.84 (s, 1 H), 11.75 (s, 1 H), 11.44 (s, 1 H), 7.82 (d, 1 H, J = 2.4 Hz), 7.69 (dd, 1 H, J = 2.0 & 6.4 Hz), 7.52 & 7.45 (AB, 2 H, J = 8.8 Hz), 7.40 (dd, 1 H, J = 1.6 & 6.4 Hz), 7.14 (d, 1 H, J = 7.2 Hz), 7.00 (d, 1 H, J = 11.2 Hz), 6.95 (d, 1 H, J = 2.4 Hz), 6.34 (t, 1 H, J = 6.8 Hz), 5.92 (s, 2 H), 5.32 (bs, 2 H).
10	459.25	1H-NMR (dmso-d6; 400 MHz): δ 12.96 (2H, broad s), 11.75 (1H, broad s), 7.93 (2H, m), 7.74 (1H, d, J = 5.49 Hz), 7.67 (1H, dd, J = 1.83, 6.71 Hz), 7.59 (1H, s), 7.50 (1H, d, J = 10.98 Hz), 7.42 (1H, dd, J = 1.83, 6.71 Hz), 7.38 (1H, d, J = 5.49 Hz), 7.15 (1H, d, J = 8.54 Hz), 7.07 (1H, d, J = 2.44 Hz), 6.34 (1H, dd, J = 6.10, 6.71 Hz), 6.00 (2H, s). LR-MS (ESI): calcd for C25H16FN2O4S [M+H] ⁺ 459.08; found 459.25
11	459.86	NA
12	461.40	1H NMR (500 MHz, D6-dmso), δ 13.11 (s, 1 H), 12.96 (s, 1 H), 11.77 (s, 1 H), 7.96 (s, 1 H), 7.94 (d, 1 H, J = 2.0 Hz), 7.69 (dd, 1 H, J = 1.6 & 7.0 Hz), 7.50 (d, 1 H, J = 11.0 Hz), 7.43 (d, 1 H, J = 6.5 Hz), 7.39 (d, 1 H, J = 11.0 Hz), 7.09 (d, 1 H, J = 2.0 Hz), 7.04 (d, 1 H, J = 7.5 Hz), 6.35 (t, 1 H, J = 7.0 Hz), 6.00 (s, 2 H).
13	461.30	1H-NMR (400 MHz, in dmso-d6): δ 11.66 (1H, Broad s), 8.80 (1H, s), 7.91 (1H, s), 7.52 (1H, dd, J = 1.95, 6.84 Hz), 7.35 (1H, dd, J = 1.95, 6.35 Hz), 7.13 (1H, d, J = 8.3 Hz), 6.85 (1H, d, J = 8.79 Hz), 6.51 (1H, s), 6.29

		(1H, dd, J = 6.35, 6.84 Hz), 5.90 (2H, s), 4.56 (2H, t, J = 8.79 Hz), 3.16 (2H, t, J = 8.79 Hz); LR-MS (ESI): calcd. for C ₂₄ H ₁₈ CIN ₄ O ₄ [M+H] ⁺ 461.10, found 461.30
14	463.42	NA
15	469.3	¹ H NMR (DMSO-d6) δ 8.20 (d, 1H, J = 9.5 Hz), 8.01 (d, 1H, J = 2.2 Hz), 7.80-7.76 (m, 1H), 7.71-7.67 (m, 2H), 7.57-7.40 (m, 3H), 7.13 (d, 1H, J = 2.2 Hz), 6.40 (t, 1H, J = 6.3 Hz), 6.31 (s, 2H), 5.84 (s, 1H).
16	470.43	NA
17	470.44	NA
18	470.36	¹ H-NMR (400 MHz, in dmso-d6): δ 12.76 (1H, broad s), 11.76 (1H, broad s), 8.37 (1H, d, J = 8.30 Hz), 7.92 (1H, d, J = 2.44 Hz), 7.92 (1H, m), 7.65 (1H, dd, J = 2.44, 6.84 Hz), 7.61 (1H, d, J = 8.30 Hz), 7.52 (1H, d, J = 11.23 Hz), 7.52 (1H, m), 7.42 (1H, dd, J = 1.47, 6.35 Hz), 7.07 (1H, d, J = 2.44 Hz), 6.45 (2H, s), 6.34 (1H, dd, J = 6.35, 6.84 Hz); LR-MS (ESI): calcd. for C ₂₅ H ₁₇ FN ₅ O ₄ [M+H] ⁺ 470.13, found 470.36
19	471.42	NA
20	471.46	NA
21	472.42	NA
22	472.95	¹ H-NMR (dmso-d6; 400 MHz): δ 12.84 (1H, broad s), 11.69 (2H, broad s), 7.95 (1H, d, J = 7.93 Hz), 7.58 (1H, dd, J = 7.32, 7.93 Hz), 7.52 (1H, dd, J = 1.83, 6.71 Hz), 7.36 (2H, m), 7.29 (1H, dd, J = 7.32, 7.93 Hz), 6.94 (1H, d, J = 9.76 Hz), 6.28 (1H, t, J = 6.71 Hz), 6.03 (2H, s), 5.10 (1H, s), 4.66 (2H, dd, J = 8.54, 9.15 Hz), 3.22 (2H, dd, J = 8.54, 9.15 Hz). LR-MS (ESI): calcd for C ₂₆ H ₁₉ FN ₃ O ₅ [M+H] ⁺ 472.13; found 471.95
23	473.44	¹ H-NMR (dmso-d6; 400 MHz): δ 12.95 (1H, broad s), 12.31 (1H, d, J = 3.05 Hz), 11.67 (1H, broad s), 8.08 (1H, d, J = 3.66 Hz), 7.51 (1H, d, J = 11.59 Hz), 7.49 (1H, dd, J = 2.44, 7.32 Hz), 7.41 (1H, d, J = 7.93 Hz), 7.35 (1H, d, J = 6.10 Hz), 7.18 (1H, d, J = 8.54 Hz), 7.02 (1H, d, J = 8.54 Hz), 6.28 (1H, t, J = 6.71 Hz), 5.89 (2H, s), 4.56 (2H, t, J = 8.54 Hz), 3.18 (2H, t, J = 8.54 Hz)
24	475.27	¹ H-NMR (dmso-d6; 400 MHz): δ 12.90 (1H, broad s), 11.75 (1H, broad s), 7.91 (1H, d, J = 2.44 Hz), 7.89 (1H, s), 7.80 (1H, d, J = 8.54 Hz), 7.66 (1H, dd, J = 2.44, 6.71 Hz), 7.46 (1H, d, J = 10.98 Hz), 7.40 (1H, dd, J = 1.83, 6.71 Hz), 7.10 (1H, d, J = 8.54 Hz), 7.06 (1H, d, J = 2.44 Hz), 6.73 (2H, broad s), 6.32 (1H, t, J = 6.71 Hz), 5.96 (2H, s). LR-MS (ESI): calcd for C ₂₄ H ₁₆ FN ₄ O ₄ S [M+H] ⁺ 475.09; found 475.27
25	475.47	NA
26	476.42	¹ H NMR (500 MHz, D ₆ -dmso), δ 13.01 (s, 1H), 11.79 (s, 1H), 11.24 (s, 1H), 7.94 (d, 1H, J = 2.0 Hz), 7.67 (dd, 1H, J = 2 & 7.0 Hz), 7.50 (d, 1H, J = 11.0 Hz), 7.45 (d, 1H, J = 10.5 Hz), 7.44-7.42 (m, 1H), 7.08 (d, 1H, J = 2.0 Hz), 6.34 (dd, 2H, J = 6.5 & 10.5 Hz), 5.98 (s, 2H), 5.39 (b, 2H).
27	477.40	NA
28	477.34	¹ H-NMR (400 MHz, in dmso-d6): δ 12.84 (1H, Broad s), 11.64 (1H, Broad s), 7.89 (1H, s), 7.79 (1H, d, J = 8.3 Hz), 7.46 (1H, dd, J = 1.95, 6.84 Hz), 7.33 (1H, dd, J = 1.95, 6.35 Hz), 7.06 (1H, dd, J = 0.98, 8.3 Hz), 6.94 (1H, d, J = 10.25 Hz), 6.74 (2H, broad s), 6.25 (1H, dd, J = 6.84, 6.84 Hz), 5.81 (2H, s), 4.61 (2H, t, J = 8.79 Hz), 3.18, (2H, t, J = 8.79 Hz); LR-MS (ESI): calcd. for C ₂₄ H ₁₈ FN ₄ O ₄ S [M+H] ⁺ 477.10, found 477.34
29	477.85	NA
30	478.43	¹ H NMR (500 MHz, D ₆ -dmso), δ, 12.86 (s, 1H), 11.70 (s, 1H), 7.50 (dd, 1H, J = 2.0 & 6.5 Hz), 7.35 (dd, 1H, J = 2.0 & 6.5 Hz), 7.15 (d, 1H, J = 7.5 Hz), 7.03 (d, 1H, J = 11.0 Hz), 6.90 (d, 1H, J = 10.0 Hz), 6.27 (t, 1H, J = 6.5 Hz), 5.77 (s, 2H), 4.62 (t, 2H, J = 9.0 Hz), 3.20 (t, 2H, J =

		9.0 Hz); ¹³ C NMR (125 MHz, D6-dmso), d, 162.5, 161.5, 160.7, 158.8, 158.4, 156.5, 155.0, 154.9, 148.4, 140.6, 140.6, 140.5, 139.3, 139.2, 133.7, 127.2, 127.2, 125.7, 119.6, 119.6, 116.4, 116.3, 115.7, 110.4, 109.0, 105.0, 104.8, 104.8, 95.1, 94.8, 88.9, 88.7, 72.7, 42.8, 42.8, 25.8.
31	478.43	¹ H NMR (400 MHz, D6-dmso), d, 13.06 (s, 1 H), 11.67 (s, 1 H), 11.29 (s, 1 H), 7.49-7.45 (m, 2 H), 7.33 (dd, 1 H, J = 2.0 & 6.8 Hz), 6.90 (d, 1 H, J = 10.0 Hz), 6.31 (d, 1 H, J = 6.0 Hz), 6.26 (t, 1 H, J = 6.4 Hz), 5.82 (s, 2 H), 4.63 (t, 2 H), 3.19 (t, 2 H).
32	479.87	NA
33	481.84	NA
34	482.42	NA
35	483.48	NA
36	484.46	NA
37	487.42	NA
38	488.42	NA
39	488.3	¹ H NMR (CD3OD) δ 10.18-10.12 (m, 2H), 9.97 (d, 1H, J = 2.2 Hz), 9.80-9.71 (m, 3H), 9.32 (d, 1H, J = 10.4 Hz), 9.24 (d, 1H, J = 2.2 Hz), 8.84 (t, 1H, J = 6.6 Hz), 8.62 (s, 2H), 8.02 (s, 1H).
40	488.42	NA
41	488.42	¹ H-NMR (400 MHz, in dmso-d6): δ 11.74 (1H, broad s), 8.44 (1H, dd, J = 5.86, 8.79 Hz), 7.92 (1H, d, J = 1.95 Hz), 7.78 (2H, broad s), 7.65 (1H, dd, J = 1.95, 6.84 Hz), 7.51 (1H, d, J = 11.23 Hz), 7.42 (1H, dd, J = 1.95, 6.35 Hz), 7.37 (1H, ddd, J = 1.95, 8.79, 9.28 Hz), 7.30 (1H, dd, J = 2.44, 10.25 Hz), 7.07 (1H, d, J = 1.95 Hz), 6.41 (2H, s), 6.33 (1H, dd, J = 6.84, 6.35 Hz); LR-MS (ESI): calcd. for C ₂₅ H ₁₆ F ₂ N ₅ O ₄ [M+H] ⁺ 488.12, found 488.42
42	488.88	NA
43	488.88	NA
44	489.45	NA
45	489.87	¹ H NMR (500 MHz, d ₆ -DMSO) δ 12.9 (s, 1H), 11.80 (s, 1H), 9.06 (m, 1H), 8.36 (d, J = 8.2 Hz, 1H), 7.99 (s, 1H), 7.73 (d, J = 6.6 Hz, 1H), 7.61 (s, 1H), 7.58 (s, 1H), 7.45 (d, J = 6.0 Hz, 1H), 7.33 (s, 1H), 7.12 (s, 1H), 6.37 (t, J = 6.6 Hz, 1H), 6.06 (s, 2H).
46	490.44	NA
47	490.44	¹ H NMR (400 MHz, D6-dmso), δ 12.87 (s, 1 H), 11.76 (d, 1 H, J = 2.4 Hz), 7.92 (d, 1 H, J = 2.4 Hz), 7.67 (dd, 1 H, J = 2.0 & 6.8 Hz), 7.43 (d, 1 H, J = 10.8 Hz), 7.43-7.42 (m, 1 H), 7.23 (d, 1 H, J = 11.6 Hz), 7.10 (d, 1 H, J = 7.2 Hz), 7.07 (d, 1 H, J = 2.0 Hz), 6.35 (t, 1 H, J = 6.4 Hz), 5.91 (s, 2 H), 5.57 (bs, 2 H), 3.65 (s, 3H).
48	491.43	¹ H NMR (400 MHz, d ₆ -DMSO): δ 12.3 (bs, 1 H), 11.7 (bs, 1 H), 8.09 (s, 1 H), 7.51 (d, J = 11.2 Hz, 1H), 7.47 (d, J = 5.6 Hz, 1 H), 7.35 (d, J = 5.2 Hz, 1 H), 7.00 (d, J = 10.0 Hz, 1 H), 6.27 (t, J = 6.6 Hz, 1 H), 5.87 (s, 2 H), 4.65 (t, J = 8.6 Hz, 2 H), 3.22 (t, J = 8.6 Hz, 2 H). MS found for C ₂₅ H ₁₆ F ₂ N ₄ O ₅ : 491.0 (M+H) ⁺ .
49	492.48	NA
50	497.50	NA
51	500.91	NA
52	503.44	NA
53	503.44	NA
54	504.43	NA
55	504.88	¹ H NMR (500 MHz, DMSO): δ 10.41 (s, 1H), 7.97 (m, 1H), 7.74 (m, 1H), 7.62 (d, J = 9.1 Hz, 1H), 7.52 (d, J = 11.0 Hz, 1H), 7.44 (s, 1H), 7.16 (m, 1H), 7.11 (m, 1H), 7.08 (m, 1H), 7.05 (s, 1H), 6.36 (t, J = 6.9

56	504.88	Hz, 1H), 5.97 (s, 2H). NA
57	505.41	¹ H NMR (500 MHz, d ₆ -DMSO): δ 13.0 (bs, 1 H), 11.8 (bs, 1 H), 11.3 (bs, 1 H), 11.2 (bs, 1 H), 7.94 (d, J = 2.5 Hz, 1H), 7.64 (dd, J = 6.8, 1.8 Hz, 1 H), 7.49 (d, J = 11.0 Hz, 1 H), 7.42 (d, J = 5.0 Hz, 1 H), 7.33 (d, J = 8.0 Hz, 1 H), 7.09 (d, J = 2.5 Hz, 1 H), 6.94 (d, J = 10.5 Hz, 1 H), 6.33 (t, J = 6.5 Hz, 1 H), 5.90 (s, 2 H).
58	506.3	¹ H NMR (500 MHz, DMSO): δ 12.94 (s, 1H), 11.79 (s, 1H), 8.05 (dd, 1H, J = 5.67 Hz, 5.04 Hz), 7.98 (t, J = 1.57 Hz, 1.89 Hz, 1H), 7.72 (m, 3H), 7.57 (d, 1H, J = 10.7 Hz), 7.45 (d, 1H, J = 6 Hz), 7.21 (s, 1H), 7.12 (t, 1H, J = 1.57 Hz, 1.89 Hz), 6.36 (t, 1H, J = 6.6, 6.9 Hz), 6.03 (bs, 2H), M.S. found: 506.3 (M+H) ⁺ .
59	506.87	¹ H NMR (500 MHz, CD ₃ OD): δ 7.88 – 7.80 (m, 2H), 7.65 (d, J = 2.2 Hz, 1H), 7.58 (dd, J = 2.5 Hz, J = 9.8 Hz, 1H), 7.52 (s, 1H), 7.45 (dd, J = 1.9 Hz, J = 6.6 Hz, 1H), 7.33 (m, 1H), 6.98 (d, J = 10.4 Hz, 1H), 6.91 (d, J = 2.2 Hz, 1H), 6.51 (t, J = 6.6 Hz, 1H), 6.14 (s, 2H).
60	506.89	¹ H NMR (500 MHz, DMSO): δ 10.39 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.54 (m, 1H), 7.36 (m, 1H), 7.16 (s, 1H), 7.10 (m, 1H), 7.06 (s, 1H), 6.97 (m, 1H), 5.83 (s, 2H), 4.67 (t, J = 8.5 Hz, 2H), 3.23 (t, J = 8.5 Hz, 2H).

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#	LR-MS (M+H)	¹ H NMR DATA
61	508.48	
62	508.88	¹ H NMR (500 MHz, DMSO): δ 7.92–7.86 (m, 1H), 7.77 (d, J = 10.1 Hz, 1H), 7.54–7.40 (m, 3H), 7.25 (s, 1H), 6.72 (m, 1H), 6.30 (m, 1H), 5.96 (s, 2H), 4.57 (t, J = 8.5 Hz, 2H), 3.17 (t, J = 8.5 Hz, 2H).
63	510.49	NA
64	510.50	NA
65	516.93	NA
66	516.98	NA
67	517.47	NA
68	517.47	NA
69	517.47	NA
70	517.47	NA
71	518.26	¹ H-NMR (400 MHz, in dmso-d6): δ 13.00 (1H, broad s), 11.76 (1H, broad s), 7.92 (1H, d, J = 2.44 Hz), 7.65 (1H, dd, J = 1.95, 6.84 Hz), 7.54 (1H, m), 7.50 (1H, d, J = 10.74 Hz), 7.41 (1H, dd, J = 1.95, 6.84 Hz), 7.08 (1H, d, J = 2.44 Hz), 7.04 (1H, d, J = 7.81 Hz), 6.31 (1H, dd, J = 6.35, 6.84 Hz), 5.86 (2H, s); LR-MS (ESI): calcd. for C ₂₃ H ₁₃ BrF ₃ N ₂ O ₄ [M+H] ⁺ 517.00, found 517.20
72	520.92	NA
73	523.32	NA
74	524.48	NA
75	524.3	¹ H NMR (500 MHz, DMSO): δ 12.94 (s, 1H), 11.79 (s, 1H), 8.05 (m, 2H), 7.98 (t, J = 1.89 Hz, 1H), 7.73 (d, 1H, J = 6.62 Hz), 7.57 (d, J = 11 Hz, 1H), 7.45 (d, 1H, J = 5.67 Hz), 7.25 (s, 1H), 7.12 (t, J = 1.89 Hz, 1H), 6.36 (t, 1H, J = 6.2 Hz), 6.02 (bs, 2H). M.S. found: 524.3 (M+H) ⁺ .

76	532.52	NA
77	532.93	NA
78	532.93	NA
79	534.45	¹ H NMR (400 MHz, D6-dmso), δ 12.93 (s, 1 H), 12.62 (s, 1 H), 11.74 (s, 1 H), 9.70 (s, 1 H), 7.90 (d, 1 H, J = 2.4 Hz), 7.64 (dd, 1 H, J = 2.0 & 6.8 Hz), 7.47 (d, 1 H, J = 10.8 Hz), 7.40 (dd, 1 H, J = 2.0 & 6.4 Hz), 7.24 (d, 1 H, J = 10.8 Hz), 7.17 (bd, 1 H, J = 5.6 Hz), 7.05 (d, 1 H, J = 2.4 Hz), 6.32 (t, 1 H, J = 6.8 Hz), 5.96 (s, 2 H), 3.48 (S, 3 H).
80	534.97	NA
81	535.94	NA
82	536.90	¹ H NMR (500 MHz, CD ₃ OD): δ 7.84 (dd, J = 1.9 Hz, J = 6.9 Hz, 1H), 7.65 (d, J = 2.5 Hz, 1H), 7.50-7.38 (m, 4H), 6.95 (d, J = 10.4 Hz, 1H), 6.91 (d, J = 2.2 Hz, 1H), 6.51 (t, J = 6.6 Hz, 1H), 6.12 (s, 2H), 4.02 (s, 3H).
83	536.90	NA
84	536.99	NA
85	541.51	NA
86	546.96	NA
87	548.98	¹ H NMR (500 MHz, d6-DMSO, TFA salt), δ 12.09 (s, 1 H), 9.59 (s, 1 H), 8.64 (s, 1 H), 8.02 (d, 1 H, J = 2.0 Hz), 7.59 (dd, 1 H, J = 5.0 & 7.0 Hz), 7.91 (s, 2 H), 7.58 (dd, 1 H, J = 2.0 & 6.0 Hz), 7.48 (d, 1 H, J = 11.0 Hz), 7.15 (d, 1 H, J = 2.0 Hz), 6.55 (s, 1 H), 6.51 (t, 1H, J = 7.0 Hz), 6.00 (s, 2 H), 4.42-4.40 (m, 2 H), 3.29-3.27 (m, 2 H), 2.74 (s, 6 H).
88	554.55	NA
89	560.53	¹ H NMR (400 MHz, d ₆ -DMSO): δ 12.2 (bs, 1 H), 10.4 (bs, 1 H), 8.20 (s, 1 H), 8.04 (d, J = 2.0 Hz, 1H), 7.90 (dd, J = 7.4, 2.2 Hz, 1 H), 7.62 (d, J = 11.2 Hz, 1 H), 7.57 (d, J = 10.8 Hz, 1 H), 7.90 (dd, J = 6.6, 2.2 Hz, 1 H), 7.49 (d, J = 8.8 Hz, 1 H), 7.14 (d, J = 2.0 Hz, 1 H), 6.47 (t, J = 7.0 Hz, 1 H), 5.98 (s, 2 H), 4.46 (m, 2 H), 3.27 (m, 2 H), 2.71 (s, 3 H), 2.70 (s, 3 H).
90	563.01	¹ H NMR (400 MHz, D6-dmso), δ , 12.10 (s, 1 H), 9.38 (s, 1 H), 8.43 (s, 1 H), 8.00 (d, 1 H, J = 3.2 Hz), 7.95 (dd, 1 H, J = 4.8 & 6.8 Hz), 7.85 (s, 1 H), 7.57 (d, 1 H, J = 6.4 Hz), 7.47 (d, 1 H, J = 10.8 Hz), 7.13 (d, 1 H, J = 2.4 Hz), 6.51 (t, 1 H, J = 6.4 Hz), 6.46 (s, 1 H), 5.95 (d, 2 H, J = 3.2 Hz), 5.37-5.30 (m, 1 H), 3.27-3.21 (m, 1 H), 3.10-3.04 (m, 1 H), 2.76 (s, 6 H), 1.02 (d, 3 H, J = 6.4 Hz).
91	575.96	¹ H NMR (500 MHz, CD ₃ OD): δ 7.90 – 7.85 (m, 2H), 7.80 (d, J = 2.5 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.59-7.55 (m, 2H), 7.39 (dd, J = 2.2 Hz, J = 8.8 Hz, 1H), 7.15 (d, J = 10.4 Hz, 1H), 6.98 (d, J = 2.2 Hz, 1H), 6.62 (t, J = 6.6 Hz, 1H), 6.09 (s, 2H), 4.49 (q, J = 7.3 Hz, 1H), 1.77 (d, J = 7.3 Hz, 3H).
92	576.00	¹ H NMR (500 MHz, CD ₃ OD): δ 8.13 (dd, J = 1.9 Hz, J = 6.9 Hz, 1H), 7.76 (d, J = 2.2 Hz, 1H), 7.68 (dd, J = 1.9 Hz, J = 6.9 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.29 (s, 1H), 7.22 (m, 2H), 7.10 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 7.04 (d, J = 2.2 Hz, 1H), 6.77 (t, J = 6.6 Hz, 1H), 6.03 (s, 2H), 4.55 (t, J = 5.0 Hz, 2H), 3.36 (t, J = 5.0 Hz, 2H), 2.88 (s, 6H).
93	589.3	¹ H NMR (500 MHz, CD ₃ OD): δ 8.13 (dd, J = 1.89 Hz, 1.89 Hz, 1H), 7.76 (d, J = 2.2 Hz, 1H), 7.68 (dd, J = 1.89 Hz, 1.89 Hz, 1H), 7.60 (d, J = 9.14 Hz, 1H), 7.33 (m, 2H), 7.24 (d, J = 10 Hz, 1H), 7.17 (dd, J = 2.52 Hz, 2.52 Hz, 1H), 7.03 (d, J = 2.2 Hz, 1H), 6.76 (t, J = 6.62 Hz, 6.93 Hz, 1H), 6.04 (bs, 2H), 4.55 (m, 2H), 3.95 (s, 3H), 3.37 (m, 2H), 2.88 (s, 6H). M.S. found: 589.3 (M+H) ⁺ .
94	591.02	NA
95	591.55	NA
96	603.56	¹ H NMR (500 MHz, d ₆ -DMSO): δ 11.8 (bs, 1 H), 8.46 (s, 1 H), 7.96

		(d, $J = 2.4$ Hz, 1H), 7.67-7.65 (m, 1H), 7.59 (d, $J = 11.2$ Hz, 1H), 7.55 (d, $J = 10.0$ Hz, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.43 (d, $J = 7.2$ Hz, 1H), 7.10 (d, $J = 2.4$ Hz, 1H), 6.34 (t, $J = 7.0$ Hz, 1H), 6.03 (s, 2H), 5.80 (s, 2H), 1.07 (s, 9H). MS found for $C_{31}H_{24}F_2N_4O_7$: 603.7 ($M+H$) ⁺ .
97	604.01	NA
98	604.54	NA
99	704.13	¹ H NMR (500 MHz, CD ₃ OD): δ 7.9 (dd, $J = 1.9$ Hz, $J = 6.9$ Hz, 1H), 7.8 (d, $J = 8.8$ Hz, 1H), 7.73 (d, $J = 2.2$ Hz, 1H), 7.72 (m, 1H), 7.57 (dd, $J = 2.2$ Hz, $J = 6.3$ Hz, 1H), 7.51 (s, 1H), 7.33 (m, 1H), 7.19 (d, $J = 10.4$ Hz, 1H), 7.00 (d, $J = 2.2$ Hz, 1H), 6.62 (t, $J = 6.6$ Hz, 1H), 6.08 (s, 2H), 4.41 (m, 1H), 4.11 (q, $J = 7.3$ Hz, 3H), 1.55 (d, $J = 7.3$ Hz, 3H), 1.48 (s, 9H), 1.04 (t, $J = 7.3$ Hz, 3H).
100	704.66	NA
101	812.87	NA
102	820.29	NA
106	532.5	¹ HNMR (500 MHz, D ₆ -dmso), d 12.09 (s, 1H), 9.52 (s, 1H), 7.99 (d, 1H, $J = 2.0$ Hz), 7.99 (s, 1H), 7.94 (dd, 1H, $J = 2.0$ & 6.5 Hz) 7.61 (d, 1H, $J = 10.5$ Hz), 7.56 (dd, 1H, $J = 2.0$ & 6.5 Hz), 7.40 (d, 1H, $J = 11.0$ Hz), 7.16 (d, 1H, $J = 7.0$ Hz), 7.13 (d, 1H, $J = 2.0$ Hz), 6.51 (t, 1H, $J = 6.5$ Hz), 5.95 (s, 2H), 4.47 (bt, 2H, $J = 5.0$ Hz), 3.36-3.31 (m, 2H), 2.77 (s, 3H), 2.76 (s, 3H).

wherein NA = not available

No.	LR-MS (M+H)						
125	666.7	149	477.4	173	532.5	197	580.0
126	697.7	150	477.9	174	534.5	198	582.6
127	442.4	151	477.9	175	539.5	199	583.6
128	445.4	152	478.4	176	540.6	200	588.6
129	446.4	153	478.8	177	540.6	201	589.6
130	447.4	154	479.4	178	543.5	202	594.0
131	449.4	155	479.9	179	547.5	203	597.1
132	451.4	156	479.9	180	549.6	204	603.6
133	454.4	157	479.9	181	733.7	205	619.6
134	454.8	158	483.5	182	555.5	206	631.6
135	456.8	159	483.5	183	555.6	207	633.7
136	457.4	160	485.5	184	556.8		
137	459.5	161	488.4	185	559.5		
138	460.4	162	491.9	186	562.5		
139	461.4	163	491.9	187	563.0		
140	461.4	164	505.9	188	566.6		
141	463.4	165	507.4	189	574.6		
142	463.4	166	509.5	190	574.6		
143	464.4	167	511.9	191	575.5		
144	468.8	168	519.4	192	575.5		
145	471.4	169	519.9	193	576.5		

146	473.3	170	521.3	194	578.0		
147	474.4	171	526.5	195	578.6		
148	475.4	172	528.6	196	579.6		

Example 36

HCV NS5B Polymerase Inhibition Assay

An *in vitro* transcribed heteropolymeric RNA known as D-RNA or DCoH has been shown to be an efficient template for HCV NS5B polymerase (S.-E. Behrens *et al.*, EMBO J. 15: 12-22 (1996); WO 96/37619). A chemically synthesized 75-mer version, designated DCoH75, whose sequence matches the 3'-end of D-RNA, and DCoH75ddC, where the 3'-terminal cytidine of DCoH75 is replaced by dideoxycytidine, were used for assaying the NS5B enzyme activity as described in Ferrari *et al.*, *12th International Symposium on HCV and Related Viruses*, P-306 (2005). The sequence of the template RNA was: 5'-UGU GCC GGU CUU UCU GAA CGG GAU AUA AAC CUG GCC AGC UUC AUC GAA CAA GUU GCC GUG UCU AUG ACA UAG AUC-3'. A soluble C-terminal 21-amino acid truncated NS5B enzyme form (NS5BΔCT21, from HCV-Con 1 isolate, genotype 1b, Genbank accession number AJ238799) was produced and purified from Escherichia coli as C-terminal polyhistidine-tagged fusion protein as described in Ferrari *et al.*, *J. Virol.* 73:1649-1654 (1999). A typical assay contained 20 mM Hepes pH 7.3, 10 mM MgCl₂, 60 mM NaCl, 100 µg/ml BSA, 20 units/ml RNasin, 7.5 mM DTT, 0.1 µM ATP/GTP/UTP, 0.026 µM CTP, 0.25 mM GAU, 0.03 µM RNA template, 20 µCi/ml [³³P]-CTP, 2% DMSO, and 30 or 150 nM NS5B enzyme. Reactions were incubated at 22 °C for 2 hours, then stopped by adding 150 mM EDTA, washed in DE81 filter plate in 0.5M di-basic sodium phosphate buffer, pH 7.0, and counted using Packard TopCount after the addition of scintillation cocktail. Polynucleotide synthesis was monitored by the incorporation of radiolabeled CTP. The effect of the Compounds of Formula (I) on the polymerase activity was evaluated by adding various concentrations of a Compound of Formula (I), typically in 10 serial 2-fold dilutions, to the assay mixture. The starting concentrations ranged from 200 µM to 1 µM. An IC₅₀ value for the inhibitor, defined as the compound concentration that provides 50% inhibition of polymerase activity, was determined by fitting the cpm data to the Hill equation Y=100/(1+10^{((LogIC50-X)*HillSlope)}), where X is the logarithm of compound concentration, and Y is the % inhibition. Ferrari *et al.*, *12th International Symposium on HCV and Related Viruses*, P-306 (2005) described in detail this assay procedure. It should be noted

that such an assay as described is exemplary and not intended to limit the scope of the invention. The skilled practitioner can appreciate that modifications including but not limited to RNA template, primer, nucleotides, NS5B polymerase form, buffer composition, can be made to develop similar assays that yield the same result for the efficacy of the compounds and 5 compositions described in the invention.

NS5B polymerase inhibition data was calculated for selected compounds of the present invention using this method. All compounds tested demonstrated IC₅₀ values of between 1 nM and 1 mM.

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Example 37

Cell-Based HCV Replicon Assay

To measure cell-based anti-HCV activity of the a Compound of Formula (I), replicon cells were seeded at 5000 cells/well in 96-well collagen I-coated Nunc plates in the presence of the Compound of Formula (I). Various concentrations of a Compound of Formula (I), 15 typically in 10 serial 2-fold dilutions, were added to the assay mixture, with the starting concentration ranging from 250 μ M to 1 μ M. The final concentration of DMSO was 0.5%, fetal bovine serum was 5%, in the assay media. Cells were harvested on day 3 by the addition of 1x cell lysis buffer (Ambion cat #8721). The replicon RNA level was measured using real time PCR (Taqman assay). The amplicon was located in 5B. The PCR primers were: 5B.2F, 20 ATGGACAGGCGCCCTGA; 5B.2R, TTGATGGGCAGCTTGGTTTC; the probe sequence was FAM-labeled CACGCCATGCGCTGCGG. GAPDH RNA was used as endogenous control and was amplified in the same reaction as NS5B (multiplex PCR) using primers and VIC-labeled probe recommended by the manufacturer (PE Applied Biosystem). The real-time RT-PCR reactions were run on ABI PRISM 7900HT Sequence Detection System using the 25 following program: 48°C for 30 minutes, 95°C for 10 minutes, 40 cycles of 95°C for 15 sec, 60°C for 1 minute. The Δ CT values (CT_{5B}-CT_{GAPDH}) were plotted against the concentration of test compound and fitted to the sigmoid dose-response model using XLfit4 (MDL). EC₅₀ was defined as the concentration of inhibitor necessary to achieve Δ CT=1 over the projected baseline; EC₉₀ the concentration necessary to achieve Δ CT=3.2 over the baseline. 30 Alternatively, to quantitate the absolute amount of replicon RNA, a standard curve was established by including serially diluted T7 transcripts of replicon RNA in the Taqman assay. All Taqman reagents were from PE Applied Biosystems. Such an assay procedure was

described in detail in e.g. Malcolm *et al.*, *Antimicrobial Agents and Chemotherapy* 50: 1013-1020 (2006).

HCV replicon assay data was calculated for selected compounds of the present invention using this method. Numerous compounds of the present invention were tested and 5 all demonstrated EC₅₀ values less than 0.5 micromolar (μM). Compounds **89, 129, 131, 136, 150, 157, 161, 162, 164, 165, 170, 172, 174, 177, 185, 188** and **189** each demonstrated EC90 values less than 0.1 μM in this assay.

10

Uses of the Tricyclic Indole Derivatives

The Tricyclic Indole Derivatives are useful in human and veterinary medicine for treating or preventing a viral infection or a virus-related disorder in a patient. In accordance 15 with the invention, the Tricyclic Indole Derivatives can be administered to a patient in need of treatment or prevention of a viral infection or a virus-related disorder.

Accordingly, in one embodiment, the invention provides methods for treating a viral infection in a patient comprising administering to the patient an effective amount of at least one Tricyclic Indole Derivative or a pharmaceutically acceptable salt, solvate, ester or prodrug 20 thereof. In another embodiment, the invention provides methods for treating a virus-related disorder in a patient comprising administering to the patient an effective amount of at least one Tricyclic Indole Derivative or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

25

Treatment or Prevention of a Viral Infection

The Tricyclic Indole Derivatives can be used to treat or prevent a viral infection. In one embodiment, the Tricyclic Indole Derivatives can be inhibitors of viral replication. In a specific embodiment, the Tricyclic Indole Derivatives can be inhibitors of HCV replication. 30 Accordingly, the Tricyclic Indole Derivatives are useful for treating viral diseases and disorders related to the activity of a virus, such as HCV polymerase.

Examples of viral infections that can be treated or prevented using the present methods, include but are not limited to, hepatitis A infection, hepatitis B infection and hepatitis C infection.

35

In one embodiment, the viral infection is hepatitis C infection.

In one embodiment, the hepatitis C infection is acute hepatitis C. In another embodiment, the hepatitis C infection is chronic hepatitis C.

The compositions and combinations of the present invention can be useful for treating a patient suffering from infection related to any HCV genotype. HCV types and subtypes may 5 differ in their antigenicity, level of viremia, severity of disease produced, and response to interferon therapy as described in Holland *et al.*, *Pathology*, 30(2):192-195 (1998). The nomenclature set forth in Simmonds *et al.*, *J Gen Virol*, 74(Pt11):2391-2399 (1993) is widely used and classifies isolates into six major genotypes, 1 through 6, with two or more related 10 subtypes, e.g., 1a, 1b. Additional genotypes 7-10 and 11 have been proposed, however the phylogenetic basis on which this classification is based has been questioned, and thus types 7, 8, 9 and 11 isolates have been reassigned as type 6, and type 10 isolates as type 3 (see 15 Lamballerie *et al.*, *J Gen Virol*, 78(Pt1):45-51 (1997)). The major genotypes have been defined as having sequence similarities of between 55 and 72% (mean 64.5%), and subtypes within types as having 75%-86% similarity (mean 80%) when sequenced in the NS-5 region (see Simmonds *et al.*, *J Gen Virol*, 75(Pt 5):1053-1061 (1994)).

Treatment or Prevention of a Virus-Related Disorder

The Tricyclic Indole Derivatives can be used to treat or prevent a virus-related disorder. Accordingly, the Tricyclic Indole Derivatives are useful for treating disorders related to the 20 activity of a virus, such as liver inflammation or cirrhosis. Virus-related disorders include, but are not limited to, RNA-dependent polymerase-related disorders and disorders related to HCV infection.

Treatment or Prevention of a RNA-Dependent Polymerase-Related Disorder

25 The Tricyclic Indole Derivatives are useful for treating or preventing a RNA dependent polymerase (RdRp) related disorder in a patient. Such disorders include viral infections wherein the infective virus contains a RdRp enzyme.

Accordingly, in one embodiment, the present invention provides a method for treating a RNA dependent polymerase-related disorder in a patient, comprising administering to the 30 patient an effective amount of at least one Tricyclic Indole Derivative or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

Treatment or Prevention of a Disorder Related to HCV Infection

The Tricyclic Indole Derivatives can also be useful for treating or preventing a disorder related to an HCV infection. Examples of such disorders include, but are not limited to, cirrhosis, portal hypertension, ascites, bone pain, varices, jaundice, hepatic encephalopathy, 5 thyroiditis, porphyria cutanea tarda, cryoglobulinemia, glomerulonephritis, sicca syndrome, thrombocytopenia, lichen planus and diabetes mellitus.

Accordingly, in one embodiment, the invention provides methods for treating an HCV-related disorder in a patient, wherein the method comprises administering to the patient a therapeutically effective amount of at least one Tricyclic Indole Derivative, or a 10 pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

Combination Therapy

In another embodiment, the present methods for treating or preventing a viral infection or a virus-related disorder can further comprise the administration of one or more additional 15 therapeutic agents which are not Tricyclic Indole Derivatives.

In one embodiment, the additional therapeutic agent is an antiviral agent.

In another embodiment, the additional therapeutic agent is an immunomodulatory agent, such as an immunosuppressive agent.

Accordingly, in one embodiment, the present invention provides methods for treating a 20 viral infection in a patient, the method comprising administering to the patient: (i) at least one Tricyclic Indole Derivative, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and (ii) at least one additional therapeutic agent that is other than a Tricyclic Indole Derivative, wherein the amounts administered are together effective to treat or prevent a viral infection.

When administering a combination therapy of the invention to a patient, therapeutic 25 agents in the combination, or a pharmaceutical composition or compositions comprising therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. The amounts of the various actives in such combination therapy may be different amounts (different dosage amounts) or same amounts 30 (same dosage amounts). Thus, for non-limiting illustration purposes, a Tricyclic Indole Derivative and an additional therapeutic agent may be present in fixed amounts (dosage amounts) in a single dosage unit (e.g., a capsule, a tablet and the like). A commercial example

of such single dosage unit containing fixed amounts of two different active compounds is VYTORIN® (available from Merck Schering-Plough Pharmaceuticals, Kenilworth, New Jersey).

5 In one embodiment, the at least one Tricyclic Indole Derivative is administered during a time when the additional therapeutic agent(s) exert their prophylactic or therapeutic effect, or *vice versa*.

In another embodiment, the at least one Tricyclic Indole Derivative and the additional therapeutic agent(s) are administered in doses commonly employed when such agents are used as monotherapy for treating a viral infection.

10 In another embodiment, the at least one Tricyclic Indole Derivative and the additional therapeutic agent(s) are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a viral infection.

15 In still another embodiment, the at least one Tricyclic Indole Derivative and the additional therapeutic agent(s) act synergistically and are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a viral infection.

20 In one embodiment, the at least one Tricyclic Indole Derivative and the additional therapeutic agent(s) are present in the same composition. In one embodiment, this composition is suitable for oral administration. In another embodiment, this composition is suitable for intravenous administration. In another embodiment, this composition is suitable for subcutaneous administration. In still another embodiment, this composition is suitable for parenteral administration.

25 Viral infections and virus-related disorders that can be treated or prevented using the combination therapy methods of the present invention include, but are not limited to, those listed above.

In one embodiment, the viral infection is HCV infection.

30 The at least one Tricyclic Indole Derivative and the additional therapeutic agent(s) can act additively or synergistically. A synergistic combination may allow the use of lower dosages of one or more agents and/or less frequent administration of one or more agents of a combination therapy. A lower dosage or less frequent administration of one or more agents may lower toxicity of therapy without reducing the efficacy of therapy.

In one embodiment, the administration of at least one Tricyclic Indole Derivative and the additional therapeutic agent(s) may inhibit the resistance of a viral infection to these agents.

Non-limiting examples of additional therapeutic agents useful in the present compositions and methods include an interferon, an immunomodulator, a viral replication inhibitor, an antisense agent, a therapeutic vaccine, a viral polymerase inhibitor, a nucleoside inhibitor, a viral protease inhibitor, a viral helicase inhibitor, a virion production inhibitor, a viral entry inhibitor, a viral assembly inhibitor, an antibody therapy (monoclonal or polyclonal), and any agent useful for treating an RNA-dependent polymerase-related disorder.

In one embodiment, the additional therapeutic agent is a viral protease inhibitor.

10 In another embodiment, the additional therapeutic agent is a viral replication inhibitor.

In another embodiment, the additional therapeutic agent is an HCV NS3 protease inhibitor.

In another embodiment, the additional therapeutic agent is an HCV NS5B polymerase inhibitor.

15 In another embodiment, the additional therapeutic agent is a nucleoside inhibitor.

In another embodiment, the additional therapeutic agent is an interferon.

In one embodiment, the additional therapeutic agent is an HCV replicase inhibitor.

In another embodiment, the additional therapeutic agent is an antisense agent.

In another embodiment, the additional therapeutic agent is a therapeutic vaccine.

20 In a further embodiment, the additional therapeutic agent is a virion production inhibitor.

In another embodiment, the additional therapeutic agent is an antibody therapy.

In another embodiment, the additional therapeutic agent is an HCV NS2 inhibitor.

In another embodiment, the additional therapeutic agent is an HCV NS4A inhibitor.

25 In another embodiment, the additional therapeutic agent is an HCV NS4B inhibitor.

In another embodiment, the additional therapeutic agent is an HCV NS5A inhibitor.

In another embodiment, the additional therapeutic agent is an HCV NS3 helicase inhibitor.

In another embodiment, the additional therapeutic agent is an HCV IRES inhibitor.

30 In another embodiment, the additional therapeutic agent is an HCV p7 inhibitor.

In another embodiment, the additional therapeutic agent is an HCV entry inhibitor.

In another embodiment, the additional therapeutic agent is an HCV assembly inhibitor.

In one embodiment, the additional therapeutic agents comprise a protease inhibitor and a polymerase inhibitor.

In still another embodiment, the additional therapeutic agents comprise a protease inhibitor and an immunomodulatory agent.

5 In yet another embodiment, the additional therapeutic agents comprise a polymerase inhibitor and an immunomodulatory agent.

In another embodiment, the additional therapeutic agents comprise a protease inhibitor and a nucleoside.

10 In another embodiment, the additional therapeutic agents comprise an immunomodulatory agent and a nucleoside.

In one embodiment, the additional therapeutic agents comprise a protease inhibitor and a NS5A inhibitor.

In another embodiment, the additional therapeutic agents comprise a nucleoside and a NS5A inhibitor.

15 In another embodiment, the additional therapeutic agents comprise a protease inhibitor, an immunomodulatory agent and a nucleoside.

In still another embodiment, the additional therapeutic agents comprise a protease inhibitor, a nucleoside and a NS5A inhibitor.

20 In a further embodiment, the additional therapeutic agents comprise a protease inhibitor, a polymerase inhibitor and an immunomodulatory agent.

In another embodiment, the additional therapeutic agent is ribavirin.

HCV polymerase inhibitors useful in the present compositions and methods include, but are not limited to, VP-19744 (Wyeth/ViroPharma), PSI-7851 (Pharmasset), R7128 (Roche/Pharmasset), PF-868554/filibuvir (Pfizer), VCH-759 (ViroChem Pharma), HCV-796 (Wyeth/ViroPharma), IDX-184 (Idenix), IDX-375 (Idenix), NM-283 (Idenix/Novartis), R-1626 (Roche), MK-0608 (Isis/Merck), INX-8014 (Inhibitex), INX-8018 (Inhibitex), INX-189 (Inhibitex), GS 9190 (Gilead), A-848837 (Abbott), ABT-333 (Abbott), ABT-072 (Abbott), A-837093 (Abbott), BI-207127 (Boehringer-Ingelheim), BILB-1941 (Boehringer-Ingelheim), MK-3281 (Merck), VCH222 (ViroChem), VCH916 (ViroChem), VCH716(ViroChem), GSK-71185 (Glaxo SmithKline), ANA598 (Anadys), GSK-625433 (Glaxo SmithKline), XTL-2125 (XTL Biopharmaceuticals), and those disclosed in Ni *et al.*, *Current Opinion in Drug*

Discovery and Development, 7(4):446 (2004); Tan *et al.*, *Nature Reviews*, 1:867 (2002); and Beaulieu *et al.*, *Current Opinion in Investigational Drugs*, 5:838 (2004).

Other HCV polymerase inhibitors useful in the present compositions and methods include, but are not limited to, those disclosed in International Publication Nos. WO 5 08/082484, WO 08/082488, WO 08/083351, WO 08/136815, WO 09/032116, WO 09/032123, WO 09/032124 and WO 09/032125.

Interferons useful in the present compositions and methods include, but are not limited to, interferon alfa-2a, interferon alfa-2b, interferon alfacon-1 and PEG-interferon alpha conjugates. "PEG-interferon alpha conjugates" are interferon alpha molecules covalently attached to a PEG molecule. Illustrative PEG-interferon alpha conjugates include interferon alpha-2a (RoferonTM, Hoffman La-Roche, Nutley, New Jersey) in the form of pegylated interferon alpha-2a (e.g., as sold under the trade name PegasysTM), interferon alpha-2b (IntronTM, from Schering-Plough Corporation) in the form of pegylated interferon alpha-2b (e.g., as sold under the trade name PEG-IntronTM from Schering-Plough Corporation), 10 interferon alpha-2b-XL (e.g., as sold under the trade name PEG-IntronTM), interferon alpha-2c (Berofor AlphaTM, Boehringer Ingelheim, Ingelheim, Germany), PEG-interferon lambda (Bristol-Myers Squibb and ZymoGenetics), interferon alfa-2b alpha fusion polypeptides, interferon fused with the human blood protein albumin (AlbuferonTM, Human Genome Sciences), Omega Interferon (Intarcia), Locteron controlled release interferon 15 (Biolex/OctoPlus), Biomed-510 (omega interferon), Peg-IL-29 (ZymoGenetics), Locteron CR (Octoplus), IFN- α -2b-XL (Flamel Technologies), and consensus interferon as defined by determination of a consensus sequence of naturally occurring interferon alphas (InfergenTM, Amgen, Thousand Oaks, California).

Antibody therapy agents useful in the present compositions and methods include, but 25 are not limited to, antibodies specific to IL-10 (such as those disclosed in US Patent Publication No. US2005/0101770, humanized 12G8, a humanized monoclonal antibody against human IL-10, plasmids containing the nucleic acids encoding the humanized 12G8 light and heavy chains were deposited with the American Type Culture Collection (ATCC) as deposit numbers PTA-5923 and PTA-5922, respectively), and the like).

30 Examples of viral protease inhibitors useful in the present compositions and methods include, but are not limited to, a HCV protease inhibitor.

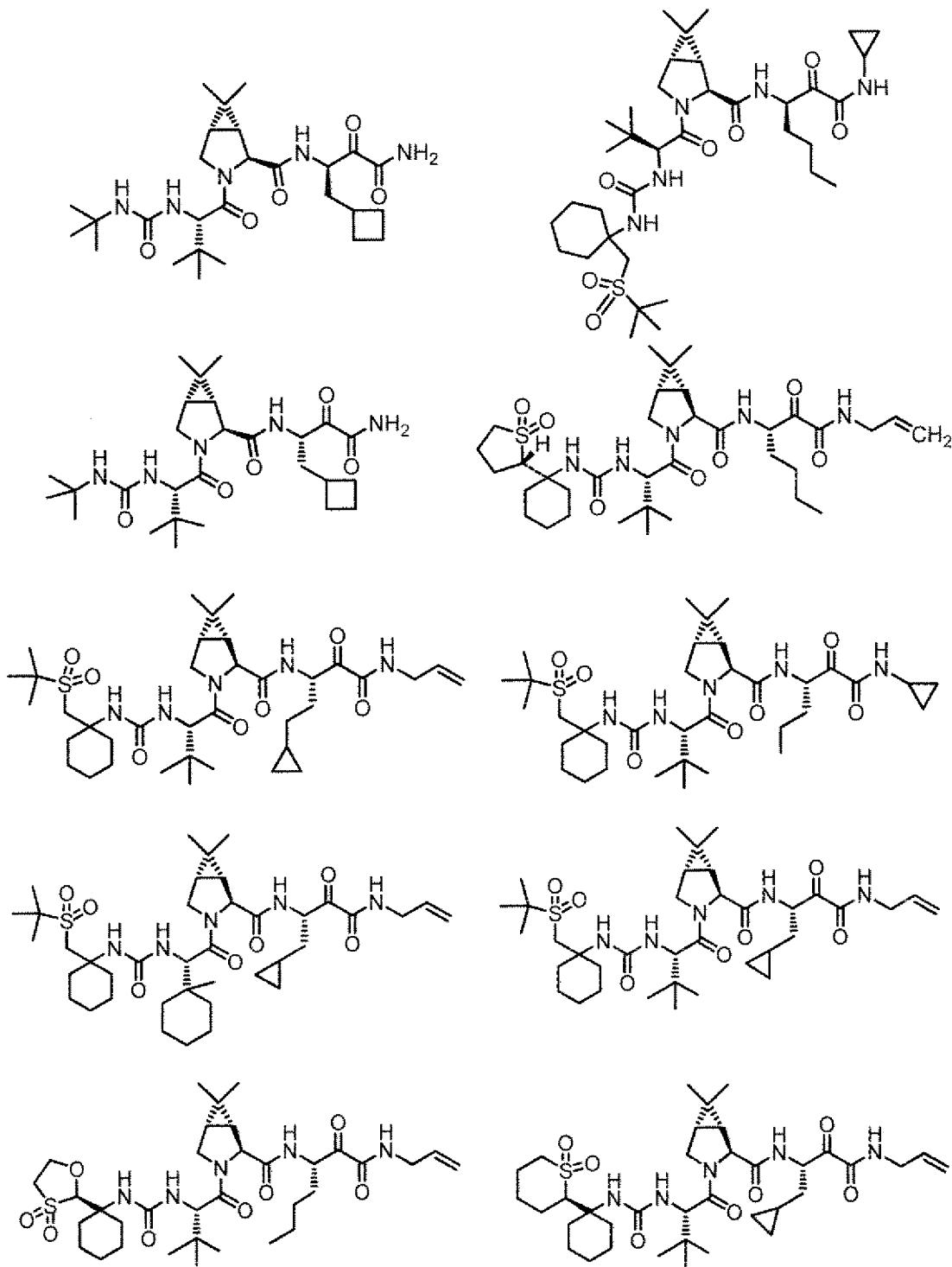
HCV protease inhibitors useful in the present compositions and methods include, but are not limited to, those disclosed in U.S. Patent Nos. 7,494,988, 7,485,625, 7,449,447, 7,442,695, 7,425,576, 7,342,041, 7,253,160, 7,244,721, 7,205,330, 7,192,957, 7,186,747, 7,173,057, 7,169,760, 7,012,066, 6,914,122, 6,911,428, 6,894,072, 6,846,802, 6,838,475, 5 6,800,434, 6,767,991, 5,017,380, 4,933,443, 4,812,561 and 4,634,697; U.S. Patent Publication Nos. US20020068702, US20020160962, US20050119168, US20050176648, US20050209164, US20050249702 and US20070042968; and International Publication Nos. WO 03/006490, WO 03/087092, WO 04/092161 and WO 08/124148.

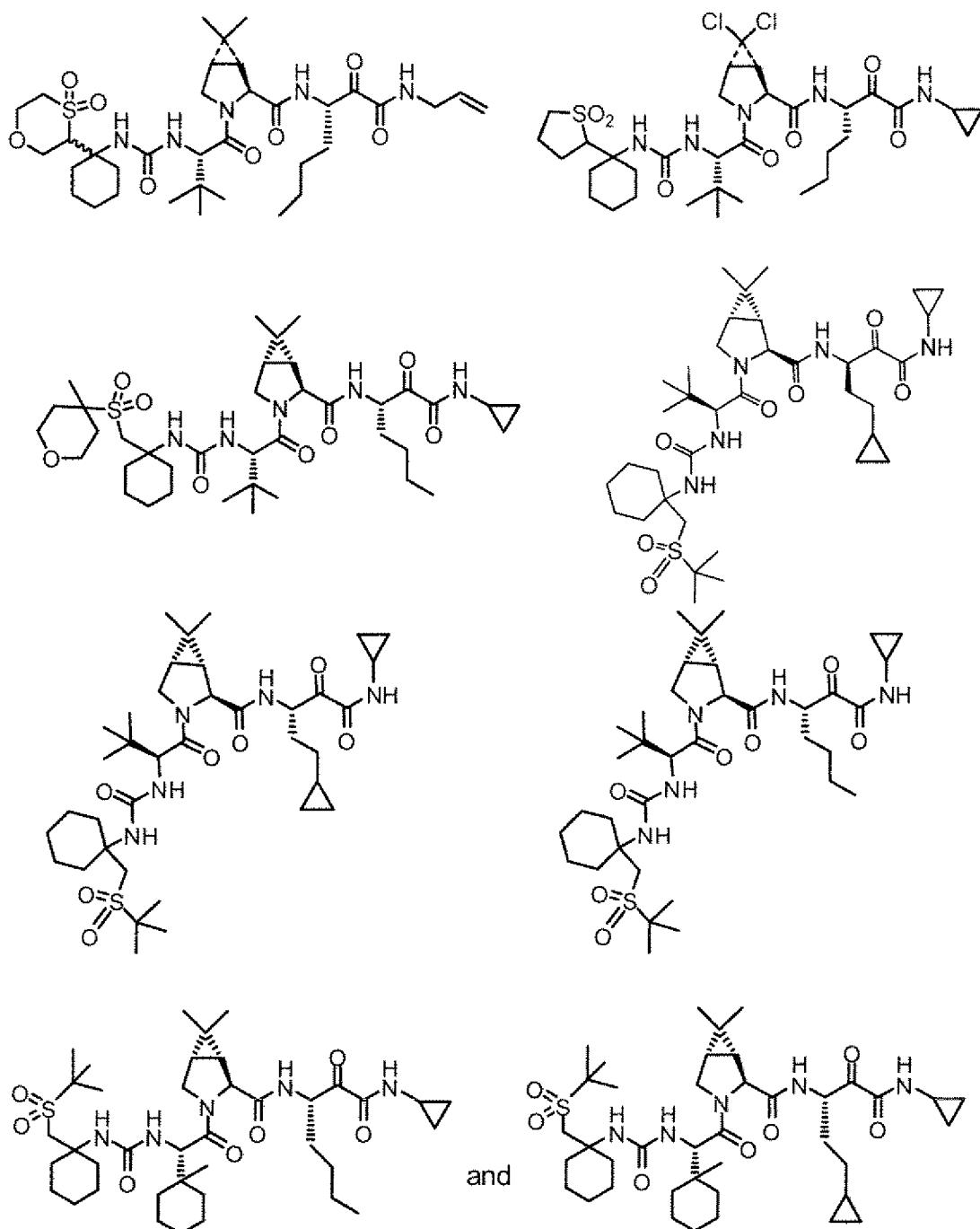
Additional HCV protease inhibitors useful in the present compositions and methods include, but are not limited to, SCH503034 (Boceprevir, Schering-Plough), SCH900518 (Schering-Plough), VX-950 (Telaprevir, Vertex), VX-500 (Vertex), VX-813 (Vertex), VBY-376 (Virobay), BI-201335 (Boehringer Ingelheim), TMC-435 (Medivir/Tibotec), ABT-450 (Abbott), MK-7009 (Merck), TMC-435350 (Medivir), ITMN-191/R7227 (InterMune/Roche), EA-058 (Abbott/Enanta), EA-063 (Abbott/Enanta), GS-9132 (Gilead/Achillion), ACH-1095 (Gilead/Achillion), IDX-136 (Idenix), IDX-316 (Idenix), ITMN-8356 (InterMune), ITMN-8347 (InterMune), ITMN-8096 (InterMune), ITMN-7587 (InterMune), PHX1766 (Phenomix), amprenavir, atazanavir, fosemprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, Kaletra (a combination of ritonavir and lopinavir) and TMC114.

Additional examples of HCV protease inhibitors useful in the present compositions and methods include, but are not limited to, those disclosed in Landro *et al.*, *Biochemistry*, 36(31):9340-9348 (1997); Ingallinella *et al.*, *Biochemistry*, 37(25):8906-8914 (1998); Llinàs-Brunet *et al.*, *Bioorg Med Chem Lett*, 8(13):1713-1718 (1998); Martin *et al.*, *Biochemistry*, 37(33):11459-11468 (1998); Dimasi *et al.*, *J Virol*, 71(10):7461-7469 (1997); Martin *et al.*, *Protein Eng*, 10(5):607-614 (1997); Elzouki *et al.*, *J Hepat*, 27(1):42-48 (1997); *BioWorld Today*, 9(217):4 (November 10, 1998); U.S. Patent Publication Nos. US2005/0249702 and US 2007/0274951; and International Publication Nos. WO 98/14181, WO 98/17679, WO 98/17679, WO 98/22496 and WO 99/07734 and WO 05/087731.

Further examples of HCV protease inhibitors useful in the present compositions and methods include, but are not limited to, the following compounds:

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Viral replication inhibitors useful in the present compositions and methods include, but
 5 are not limited to, HCV replicase inhibitors, IRES inhibitors, NS4A inhibitors, NS3 helicase
 inhibitors, NS5A inhibitors, ribavirin, AZD-2836 (Astra Zeneca), BMS-790052 (Bristol-Myers
 Squibb), viramidine, A-831 (Arrow Therapeutics); an antisense agent or a therapeutic vaccine.

In one embodiment, viral replication inhibitors useful in the present compositions and methods include, but are not limited to, HCV replicase inhibitors, IRES inhibitors, NS4A inhibitors, NS3 helicase inhibitors and NS5A inhibitors.

HCV NS4A inhibitors useful in the useful in the present compositions and methods 5 include, but are not limited to, those disclosed in U.S. Patent Nos. 7,476,686 and 7,273,885; U.S. Patent Publication No. US20090022688; and International Publication Nos. WO 2006/019831 and WO 2006/019832. Additional HCV NS4A inhibitors useful in the useful in the present compositions and methods include, but are not limited to, AZD2836 (Astra Zeneca) and ACH-806 (Achillion Pharmaceuticals, New Haven, CT).

10 HCV replicase inhibitors useful in the useful in the present compositions and methods include, but are not limited to, those disclosed in U.S. Patent Publication No. US20090081636.

Therapeutic vaccines useful in the present compositions and methods include, but are not limited to, IC41 (Intercell Novartis), CSL123 (Chiron/CSL), GI 5005 (Globeimmune), TG-4040 (Transgene), GNI-103 (GENimmune), Hepavaxx C (ViRex Medical), ChronVac-C 15 (Inovio/Tripep), PeviPROTM (Pevion Biotect), HCV/MF59 (Chiron/Novartis) and Civaair (NABI).

Examples of further additional therapeutic agents useful in the present compositions and methods include, but are not limited to, TT033 (Benitec/Tacere Bio/Pfizer), Sirna-034 (Sirna Therapeutics), GNI-104 (GENimmune), GI-5005 (GlobeImmune), IDX-102 (Idenix), 20 LevovirinTM (ICN Pharmaceuticals, Costa Mesa, California); Humax (Genmab), ITX-2155 (Ithrex/Novartis), PRO 206 (Progenics), HepaCide-I (NanoVirocides), MX3235 (Migenix), SCY-635 (Scynexis); KPE02003002 (Kemin Pharma), Lenoxta (VioQuest Pharmaceuticals), IET – Interferon Enhancing Therapy (Transition Therapeutics), Zadaxin (SciClone Pharma), VP 50406TM (Viropharma, Incorporated, Exton, Pennsylvania); Taribavirin (Valeant Pharmaceuticals); Nitazoxanide (Romark); Debio 025 (Debiopharm); GS-9450 (Gilead); PF-4878691 (Pfizer); ANA773 (Anadys); SCV-07 (SciClone Pharmaceuticals); NIM-881 (Novartis); ISIS 14803TM (ISIS Pharmaceuticals, Carlsbad, California); HeptazymeTM (Ribozyme Pharmaceuticals, Boulder, Colorado); ThymosinTM (SciClone Pharmaceuticals, San Mateo, California); MaxamineTM (Maxim Pharmaceuticals, San Diego, California); NKB-122 25 (JenKen Bioscience Inc., North Carolina); Alinia (Romark Laboratories), INFORM-1 (a combination of R7128 and ITMN-191); and mycophenolate mofetil (Hoffman-LaRoche, Nutley, New Jersey).

The doses and dosage regimen of the other agents used in the combination therapies of the present invention for the treatment or prevention of a viral infection or virus-related disorder can be determined by the attending clinician, taking into consideration the approved doses and dosage regimen in the package insert; the age, sex and general health of the patient; 5 and the type and severity of the viral infection or related disease or disorder. When administered in combination, the Tricyclic Indole Derivative(s) and the other agent(s) can be administered simultaneously (*i.e.*, in the same composition or in separate compositions one right after the other) or sequentially. This is particularly useful when the components of the combination are given on different dosing schedules, *e.g.*, one component is administered once 10 daily and another every six hours, or when the preferred pharmaceutical compositions are different, *e.g.*, one is a tablet and one is a capsule. A kit comprising the separate dosage forms is therefore advantageous.

Generally, a total daily dosage of the at least one Tricyclic Indole Derivative(s) alone, or when administered as combination therapy, can range from about 1 to about 2500 mg per 15 day, although variations will necessarily occur depending on the target of therapy, the patient and the route of administration. In one embodiment, the dosage is from about 10 to about 1000 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 1 to about 500 mg/day, administered in a single dose or in 2-4 divided doses. In still another embodiment, the dosage is from about 1 to about 100 mg/day, 20 administered in a single dose or in 2-4 divided doses. In yet another embodiment, the dosage is from about 1 to about 50 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 500 to about 1500 mg/day, administered in a single dose or in 2-4 divided doses. In still another embodiment, the dosage is from about 500 to about 1000 mg/day, administered in a single dose or in 2-4 divided doses. In yet another 25 embodiment, the dosage is from about 100 to about 500 mg/day, administered in a single dose or in 2-4 divided doses.

In one embodiment, when the additional therapeutic agent is INTRON-A interferon alpha 2b (commercially available from Schering-Plough Corp.), this agent is administered by subcutaneous injection at 3MIU(12 mcg)/0.5mL/TIW for 24 weeks or 48 weeks for first time 30 treatment.

In another embodiment, when the additional therapeutic agent is PEG-INTRON interferon alpha 2b pegylated (commercially available from Schering-Plough Corp.), this agent

is administered by subcutaneous injection at 1.5 mcg/kg/week, within a range of 40 to 150 mcg/week, for at least 24 weeks.

In another embodiment, when the additional therapeutic agent is ROFERON A interferon alpha 2a (commercially available from Hoffmann-La Roche), this agent is administered by subcutaneous or intramuscular injection at 3MIU(11.1 mcg/mL)/TIW for at least 48 to 52 weeks, or alternatively 6MIU/TIW for 12 weeks followed by 3MIU/TIW for 36 weeks.

In still another embodiment, when the additional therapeutic agent is PEGASUS interferon alpha 2a pegylated (commercially available from Hoffmann-La Roche), this agent is administered by subcutaneous injection at 180 mcg/1mL or 180 mcg/0.5mL, once a week for at least 24 weeks.

In yet another embodiment, when the additional therapeutic agent is INFERGEN interferon alfacon-1 (commercially available from Amgen), this agent is administered by subcutaneous injection at 9 mcg/TIW is 24 weeks for first time treatment and up to 15 mcg/TIW for 24 weeks for non-responsive or relapse treatment.

In a further embodiment, when the additional therapeutic agent is Ribavirin (commercially available as REBETOL ribavirin from Schering-Plough or COPEGUS ribavirin from Hoffmann-La Roche), this agent is administered at a daily dosage of from about 600 to about 1400 mg/day for at least 24 weeks.

In one embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from a HCV protease inhibitor, a HCV replication inhibitor, a nucleoside, an interferon, a pegylated interferon and ribavirin. The combination therapies can include any combination of these additional therapeutic agents.

In another embodiment, one or more compounds of the present invention are administered with one additional therapeutic agent selected from a HCV protease inhibitor, a HCV replication inhibitor, a nucleoside, an interferon, a pegylated interferon and ribavirin.

In another embodiment, one or more compounds of the present invention are administered with two additional therapeutic agents selected from a HCV protease inhibitor, a HCV replication inhibitor, a nucleoside, an interferon, a pegylated interferon and ribavirin.

In a specific embodiment, one or more compounds of the present invention are administered with a HCV protease inhibitor and ribavirin. In another specific embodiment,

one or more compounds of the present invention are administered with a pegylated interferon and ribavirin.

In another embodiment, one or more compounds of the present invention are administered with three additional therapeutic agents selected from a HCV protease inhibitor, a HCV replication inhibitor, a nucleoside, an interferon, a pegylated interferon and ribavirin.

In one embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from a HCV polymerase inhibitor, a viral protease inhibitor, an interferon, and a viral replication inhibitor. In another embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from a HCV polymerase inhibitor, a viral protease inhibitor, an interferon, and a viral replication inhibitor. In another embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from a HCV polymerase inhibitor, a viral protease inhibitor, an interferon, and ribavirin.

In one embodiment, one or more compounds of the present invention are administered with one additional therapeutic agent selected from a HCV polymerase inhibitor, a viral protease inhibitor, an interferon, and a viral replication inhibitor. In another embodiment, one or more compounds of the present invention are administered with ribavirin.

In one embodiment, one or more compounds of the present invention are administered with two additional therapeutic agents selected from a HCV polymerase inhibitor, a viral protease inhibitor, an interferon, and a viral replication inhibitor.

In another embodiment, one or more compounds of the present invention are administered with ribavirin, interferon and another therapeutic agent.

In another embodiment, one or more compounds of the present invention are administered with ribavirin, interferon and another therapeutic agent, wherein the additional therapeutic agent is selected from a HCV polymerase inhibitor, a viral protease inhibitor, and a viral replication inhibitor.

In still another embodiment, one or more compounds of the present invention are administered with ribavirin, interferon and a viral protease inhibitor.

In another embodiment, one or more compounds of the present invention are administered with ribavirin, interferon and an HCV protease inhibitor.

In another embodiment, one or more compounds of the present invention are administered with ribavirin, interferon and boceprevir or telaprevir.

In a further embodiment, one or more compounds of the present invention are administered with ribavirin, interferon and an HCV polymerase inhibitor.

5

Compositions and Administration

Due to their activity, the Tricyclic Indole Derivatives are useful in veterinary and human medicine. As described above, the Tricyclic Indole Derivatives are useful for treating or preventing a viral infection or a virus-related disorder in a patient in need thereof.

When administered to a patient, the Tricyclic Indole Derivatives can be administered as a component of a composition that comprises a pharmaceutically acceptable carrier or vehicle. The present invention provides pharmaceutical compositions comprising an effective amount of at least one Tricyclic Indole Derivative and a pharmaceutically acceptable carrier. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, *i.e.*, oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories.

Powders and tablets may be comprised of from about 0.5 to about 95 percent inventive composition. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate,

sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum, and the like. Sweetening and flavoring agents and preservatives may also be included where appropriate.

5 Liquid form preparations include solutions, suspensions and emulsions and may include water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

10 Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

15 For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

20 The Tricyclic Indole Derivatives of the present invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

25 Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize therapeutic effects, *i.e.*, antiviral activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

In one embodiment, the one or more Tricyclic Indole Derivatives are administered orally.

30 In another embodiment, the one or more Tricyclic Indole Derivatives are administered intravenously.

In another embodiment, the one or more Tricyclic Indole Derivatives are administered topically.

In still another embodiment, the one or more Tricyclic Indole Derivatives are administered sublingually.

5 In one embodiment, a pharmaceutical preparation comprising at least one Tricyclic Indole Derivative is in unit dosage form. In such form, the preparation is subdivided into unit doses containing effective amounts of the active components.

10 Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present compositions can contain, in one embodiment, from about 0.1% to about 99% of the Tricyclic Indole Derivative(s) by weight or volume. In various 15 embodiments, the present compositions can contain, in one embodiment, from about 1% to about 70% or from about 5% to about 60% of the Tricyclic Indole Derivative(s) by weight or volume.

15 The quantity of Tricyclic Indole Derivative in a unit dose of preparation may be varied or adjusted from about 1 mg to about 2500 mg. In various embodiment, the quantity is from about 10 mg to about 1000 mg, 1 mg to about 500 mg, 1 mg to about 100 mg, and 1 mg to about 100 mg.

20 For convenience, the total daily dosage may be divided and administered in portions during the day if desired. In one embodiment, the daily dosage is administered in one portion. In another embodiment, the total daily dosage is administered in two divided doses over a 24 hour period. In another embodiment, the total daily dosage is administered in three divided doses over a 24 hour period. In still another embodiment, the total daily dosage is administered in four divided doses over a 24 hour period.

25 The amount and frequency of administration of the Tricyclic Indole Derivatives will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. Generally, a total daily dosage of the Tricyclic Indole Derivatives range from about 0.1 to about 2000 mg per day, although variations will necessarily occur depending on the target of therapy, the patient and the route of administration. In one embodiment, the dosage is from about 1 to about 200 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 10 to about 2000 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 100 to about 2000

mg/day, administered in a single dose or in 2-4 divided doses. In still another embodiment, the dosage is from about 500 to about 2000 mg/day, administered in a single dose or in 2-4 divided doses.

The compositions of the invention can further comprise one or more additional therapeutic agents, selected from those listed above herein. Accordingly, in one embodiment, the present invention provides compositions comprising: (i) at least one Tricyclic Indole Derivative or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof; (ii) one or more additional therapeutic agents that are not a Tricyclic Indole Derivative; and (iii) a pharmaceutically acceptable carrier, wherein the amounts in the composition are together effective to treat a viral infection or a virus-related disorder.

Kits

In one aspect, the present invention provides a kit comprising a therapeutically effective amount of at least one Tricyclic Indole Derivative, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

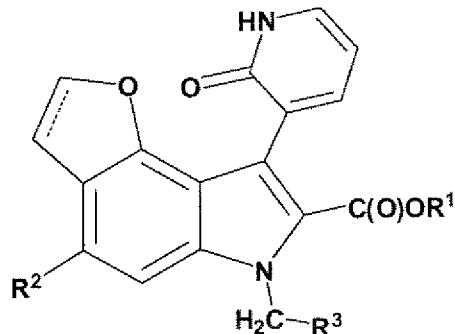
In another aspect the present invention provides a kit comprising an amount of at least one Tricyclic Indole Derivative, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and an amount of at least one additional therapeutic agent listed above, wherein the amounts of the two or more active ingredients result in a desired therapeutic effect. In one embodiment, the one or more Tricyclic Indole Derivatives and the one or more additional therapeutic agents are provided in the same container. In one embodiment, the one or more Tricyclic Indole Derivatives and the one or more additional therapeutic agents are provided in separate containers.

The present invention is not to be limited by the specific embodiments disclosed in the examples that are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

A number of references have been cited herein, the entire disclosures of which are incorporated herein by reference.

WHAT IS CLAIMED IS:

1. A compound having the formula:



(I)

and pharmaceutically acceptable salts, solvates, esters and prodrugs thereof,

wherein the dotted line represents an optional and additional bond, and wherein:

R^1 is H, alkyl, alkenyl, -alkylene-OC(O)-alkyl, -alkylene-aryl, aminoalkyl or -alkylene-heterocycloalkyl;

10 R^2 is H, F, Cl or -CH₃;

R^3 is phenyl, naphthyl, nitrogen-containing heterocycloalkyl, nitrogen-containing heterocycloalkenyl or nitrogen-containing heteroaryl, any of which can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from methyl, t-butyl, allyl, F, Cl, Br, -CN, -O-CH₂CH₃, -S(O)CH₃, -S(O)₂CH₃, -NH₂, -OH, -15 CH₂NH₂, -C(O)NH₂, -C(O)NHCH₃, -C(O)NH-cyclopropyl, hydroxyalkyl, -C(O)H, -C(O)CH₃, -C(O)O-isopropyl, -C(O)O-t-butyl, -CH₂C(O)-t-butyl, -OCH₃, -NHCH₃, -SCH₃, -C(O)NHCH₃, -NHC(O)OCH₃, -NHC(O)O-isopropyl, -CH₂N(CH₃)₂, -OC(O)CH(CH₃)NHC(O)O-t-butyl, -OC(O)CH(CH₃)NH₂, -C(O)O-t-butyl, -CH₂C(O)O-t-butyl, -OCH₂CH₂N(CH₃)₂, morpholinyl, -CH₂OC(O)-t-butyl, -CH(=NOH), -CH(=NOCH₃), -NHC(O)CH₂N(CH₃)₂ and -NHC(O)O-t-20 butyl; and

R^4 is H or -C(O)O-alkyl.

2. The compound of claim 1, wherein R^1 is H or aminoalkyl.

25 3. The compound of claim 2, wherein R^1 is -CH₂CH₂NH₂, -CH₂CH(NH₂)CH₃, -CH₂CH₂CH₂NH₂, -CH₂CH₂NHCH₃, -CH₂CH₂N(CH₃)₂, -CH₂CH(N(CH₃)₂)CH₃, or -CH₂CH₂CH₂N(CH₃)₂.

4. The compound of claim 3, wherein R¹ is -CH₂CH₂N(CH₃)₂.

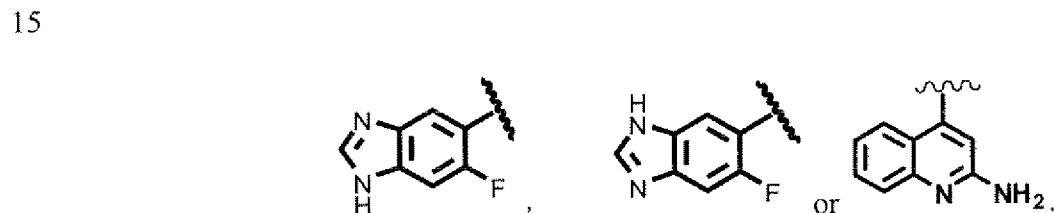
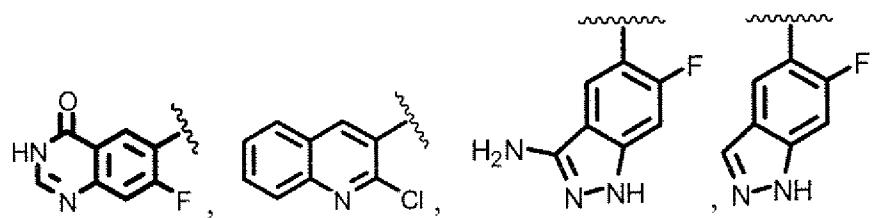
5. The compound of claim 1, wherein R² is H or F.

5
6. The compound of claim 2, wherein R² is H or F.

7. The compound of claim 1, wherein R³ is nitrogen-containing heteroaryl or nitrogen-containing heterocycloalkenyl.

10
8. The compound of claim 7, wherein R³ is nitrogen-containing heteroaryl.

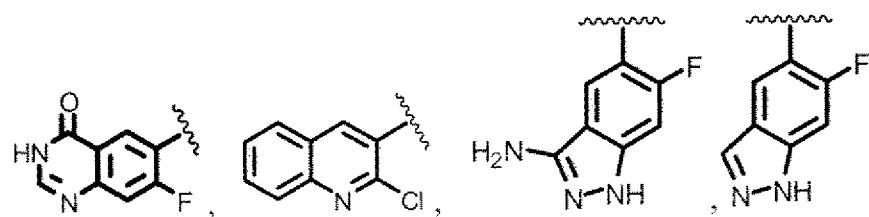
9. The compound of claim 8, wherein R³ is:

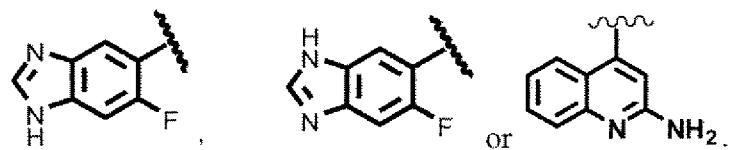


10. The compound of claim 6, wherein R³ is nitrogen-containing heteroaryl or nitrogen-
20 containing heterocycloalkenyl.

11. The compound of claim 10, wherein R³ is nitrogen-containing heteroaryl.

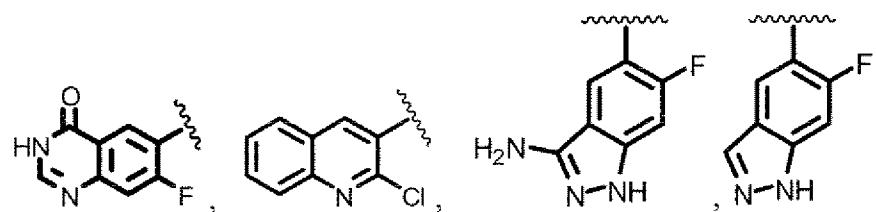
12. The compound of claim 11, wherein R³ is:



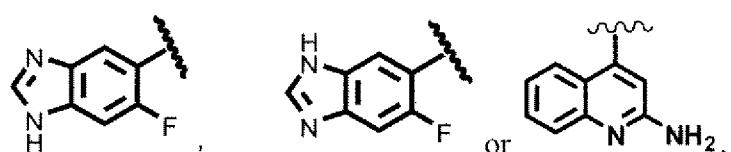


5 13. The compound of claim 4, wherein R² is F.

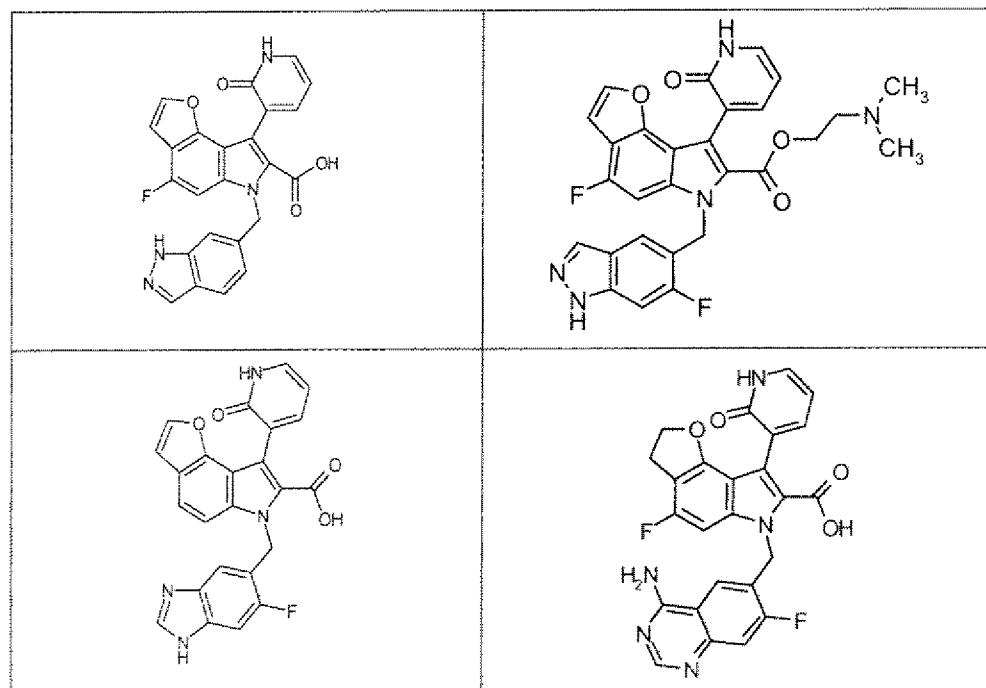
14. The compound of claim 13, wherein R³ is:

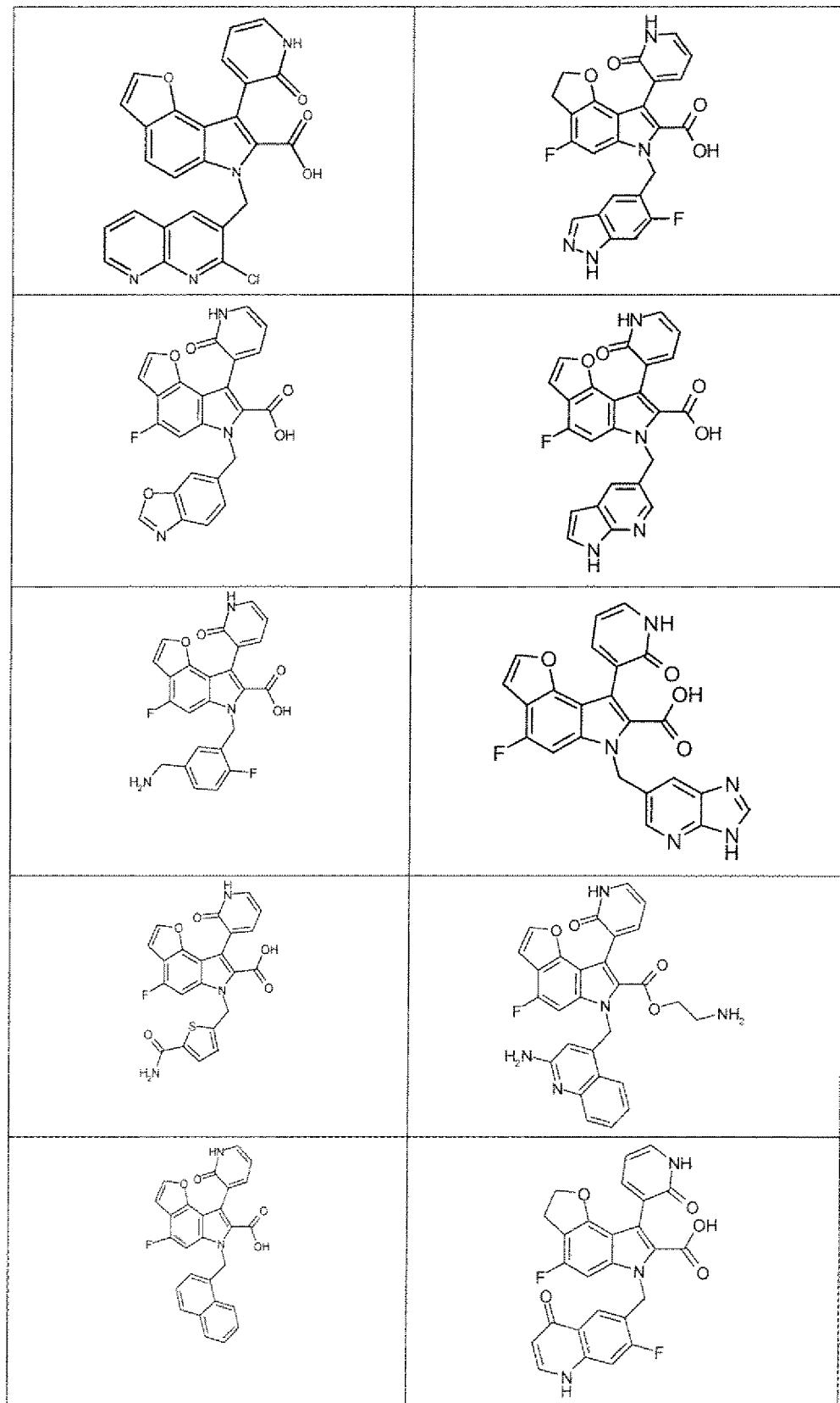


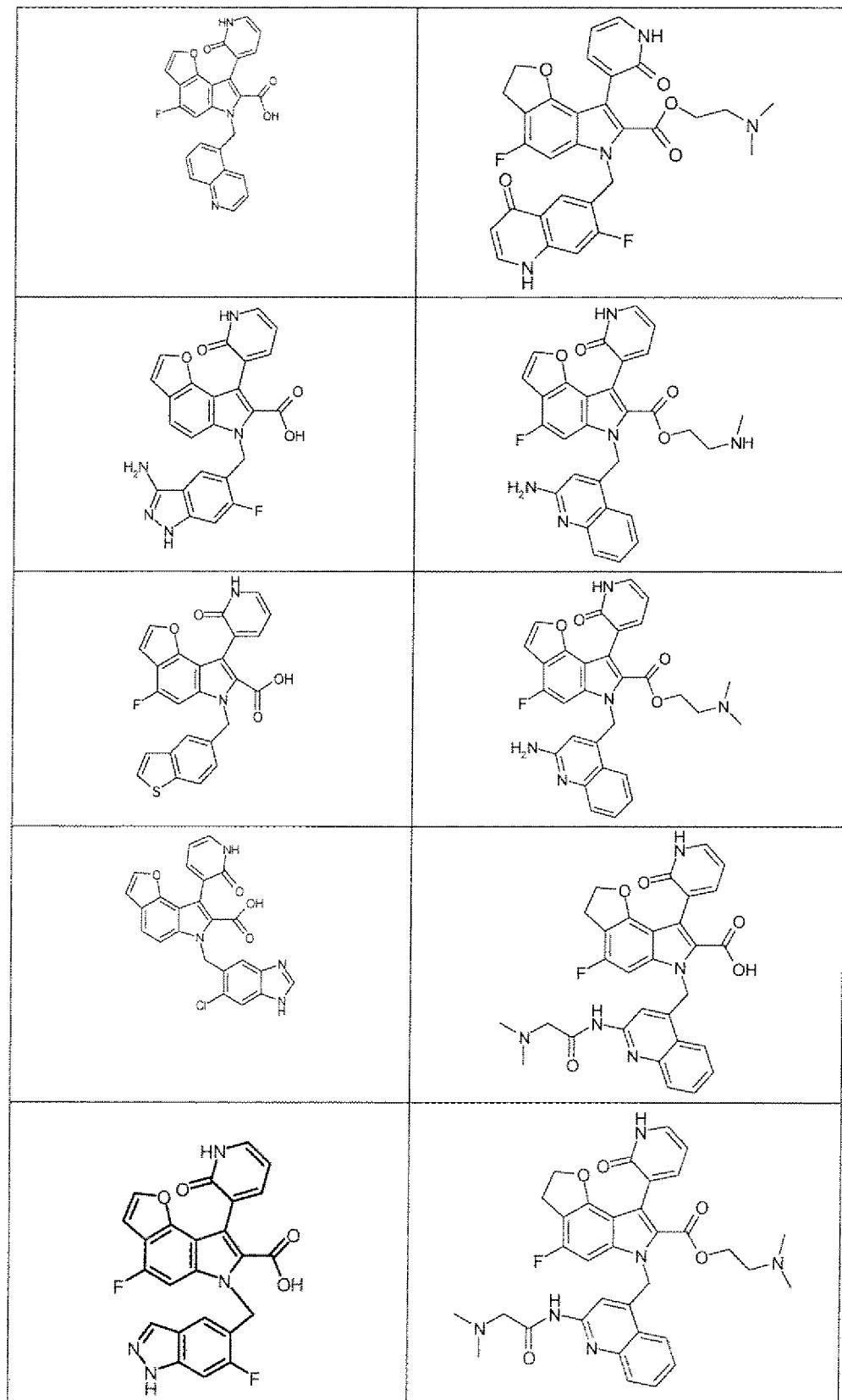
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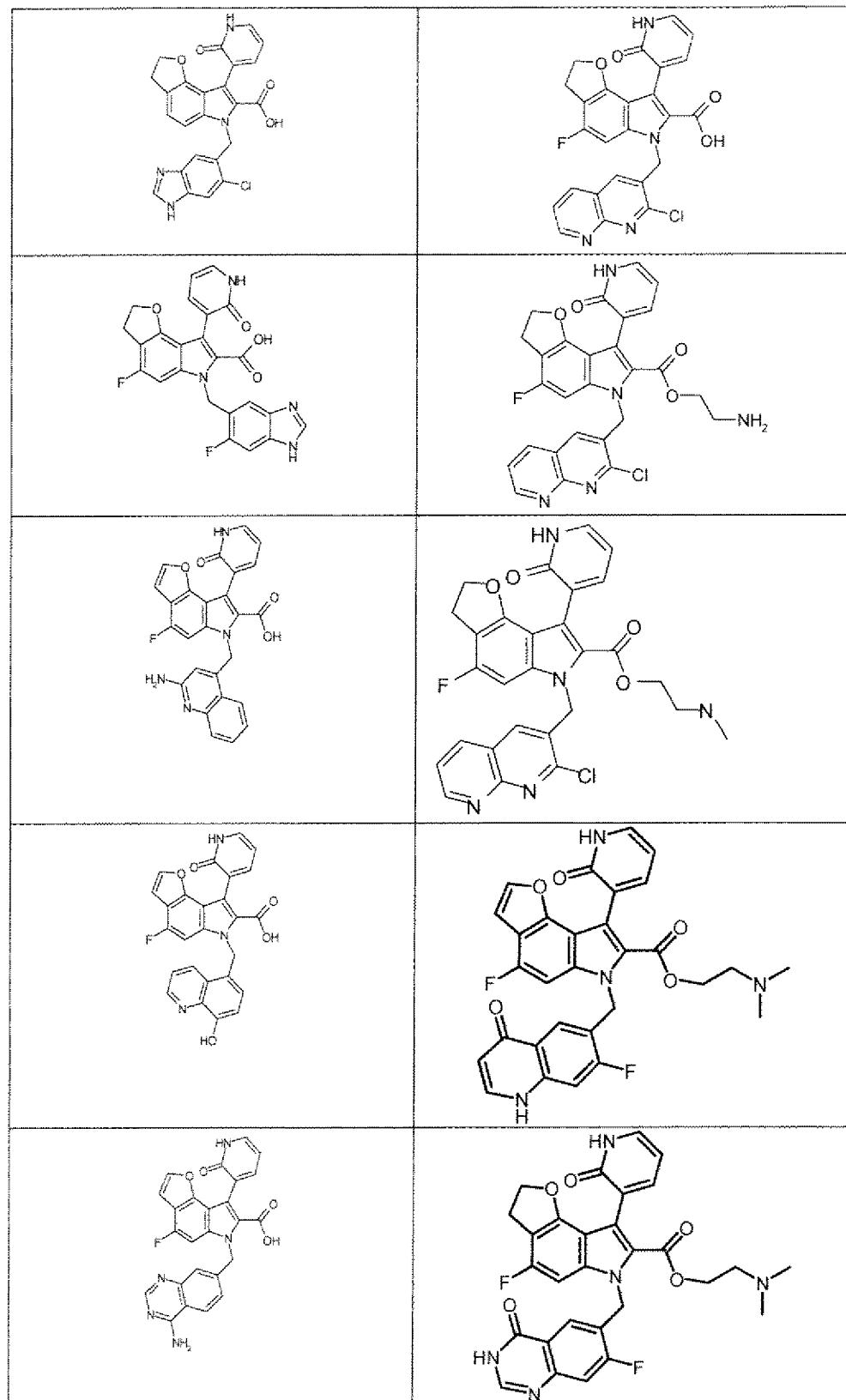


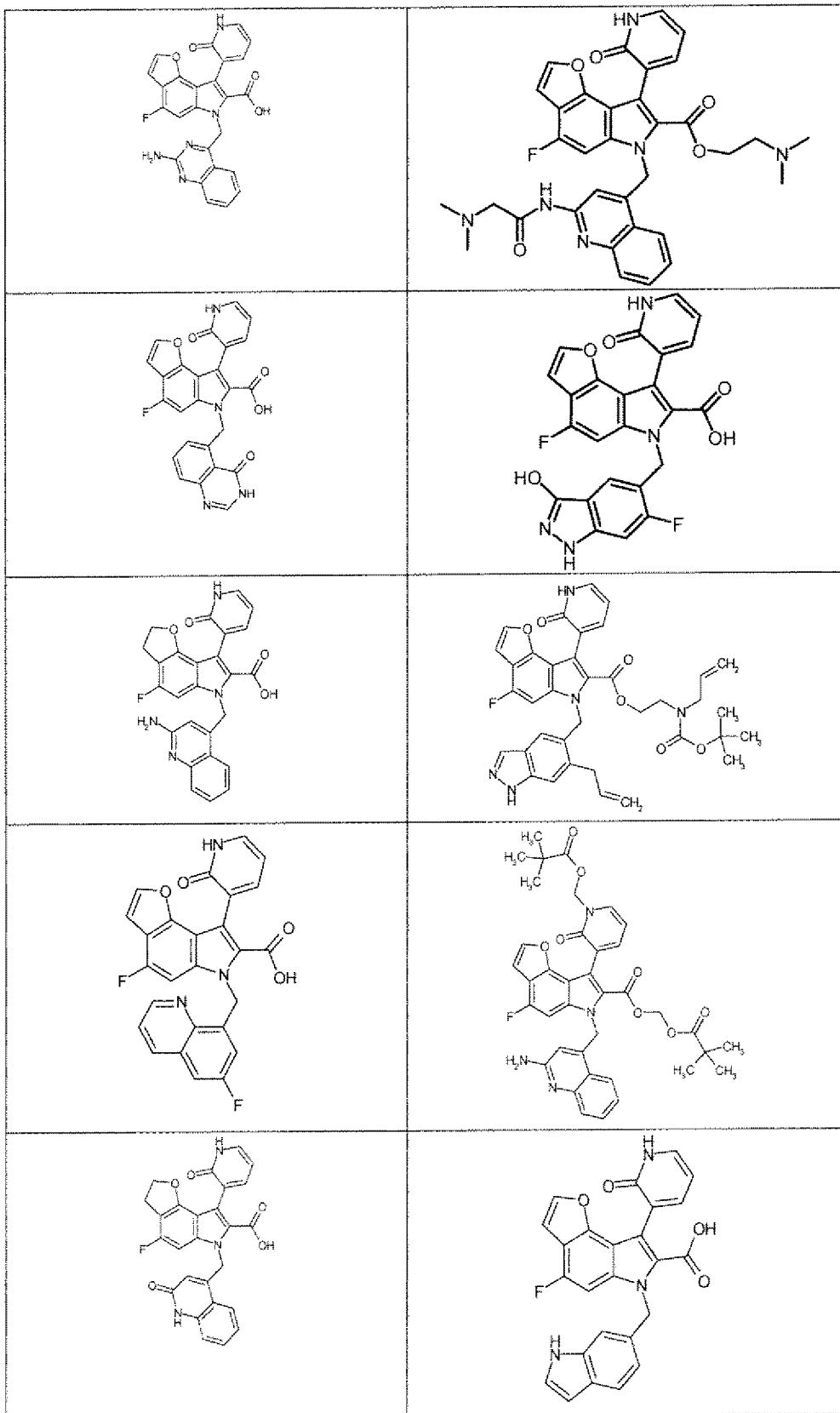
15. A compound having the structure:

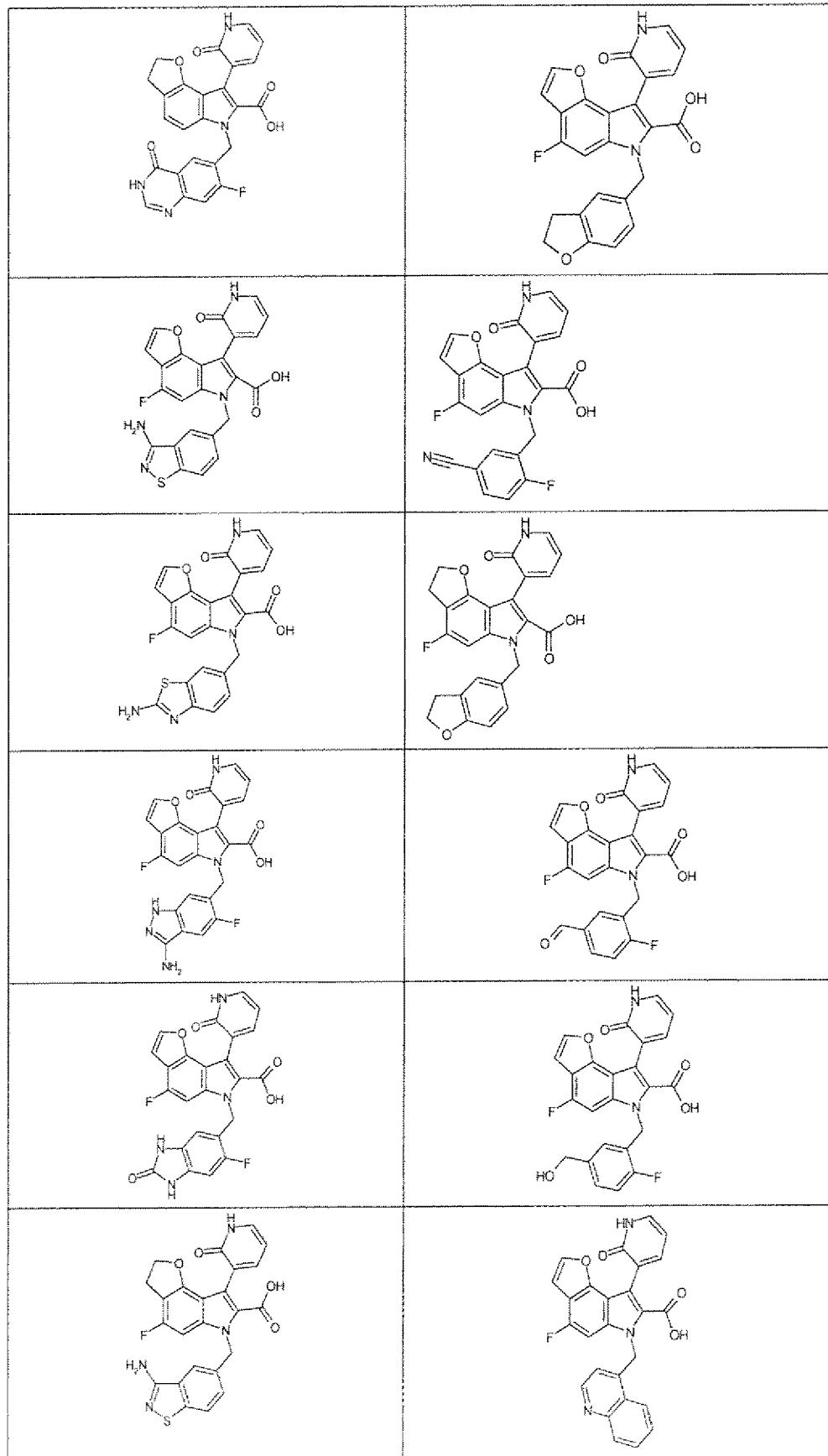


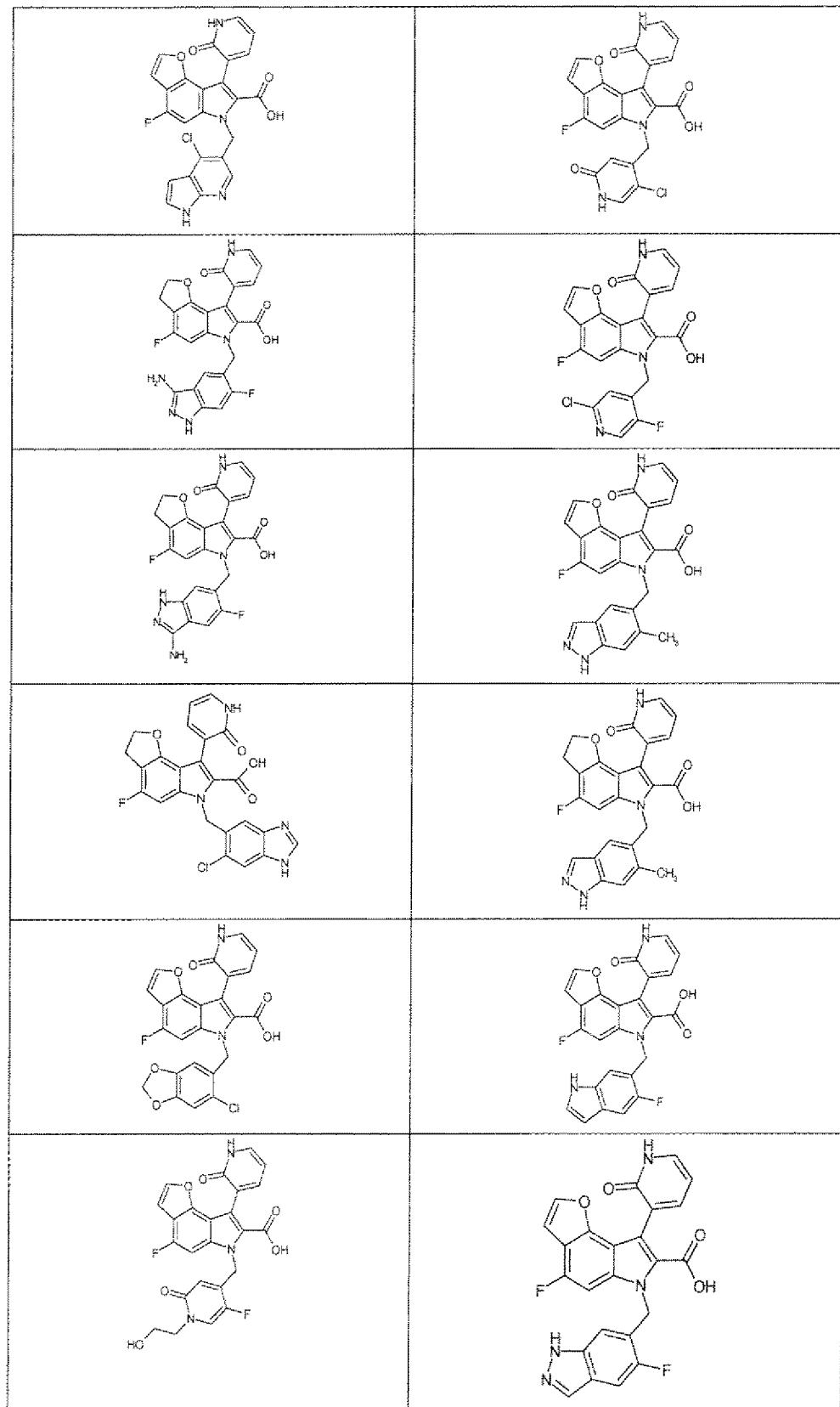


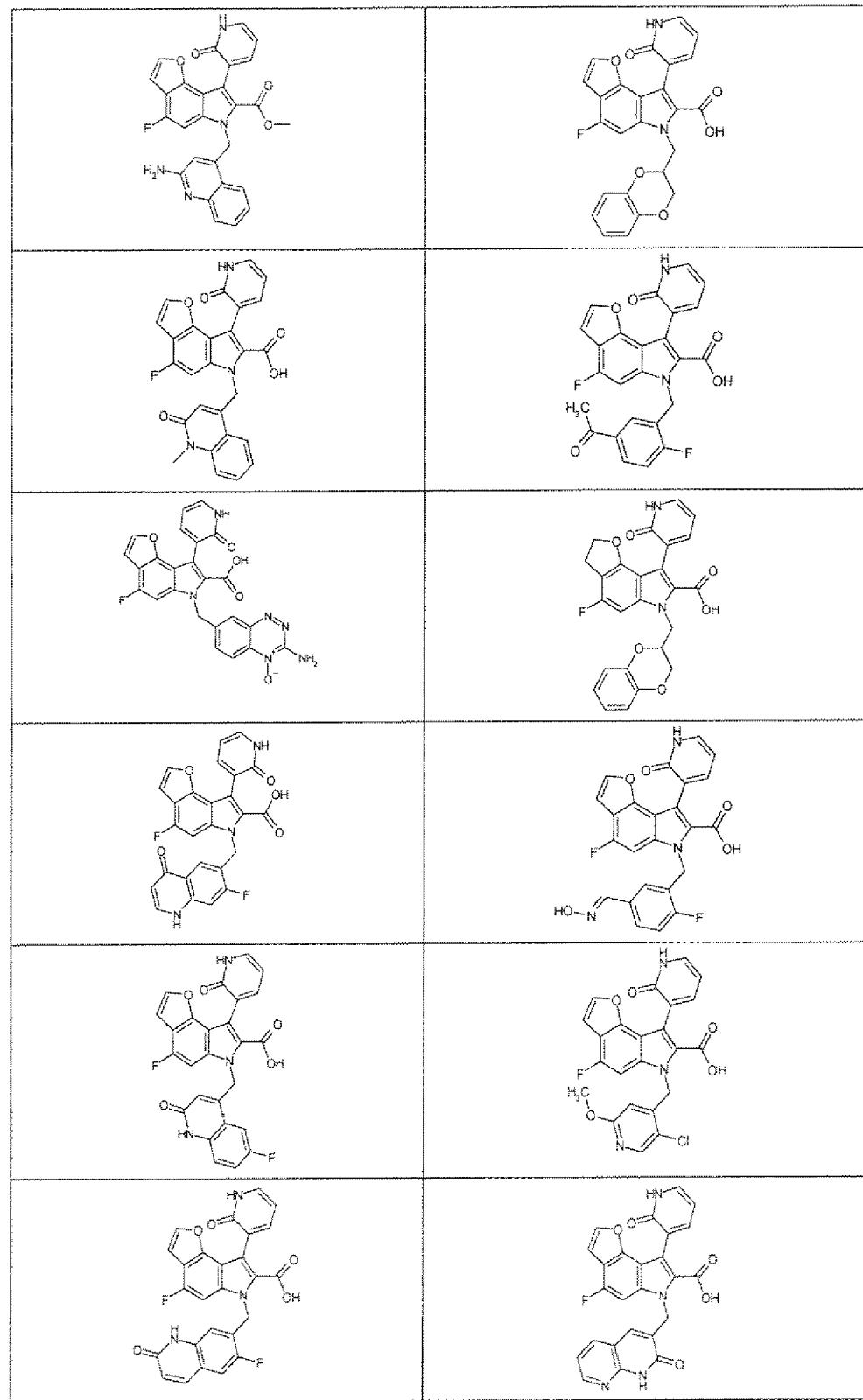




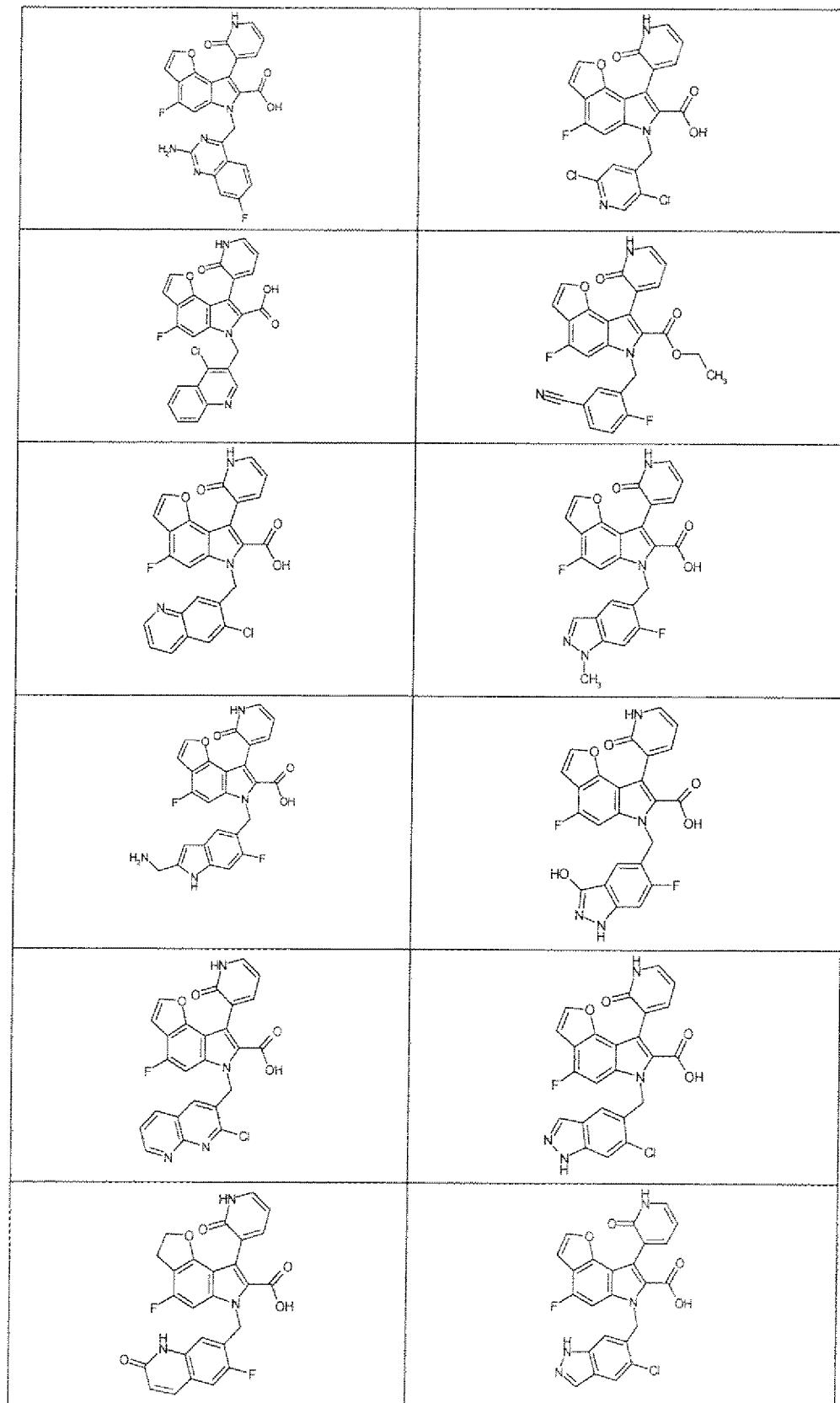


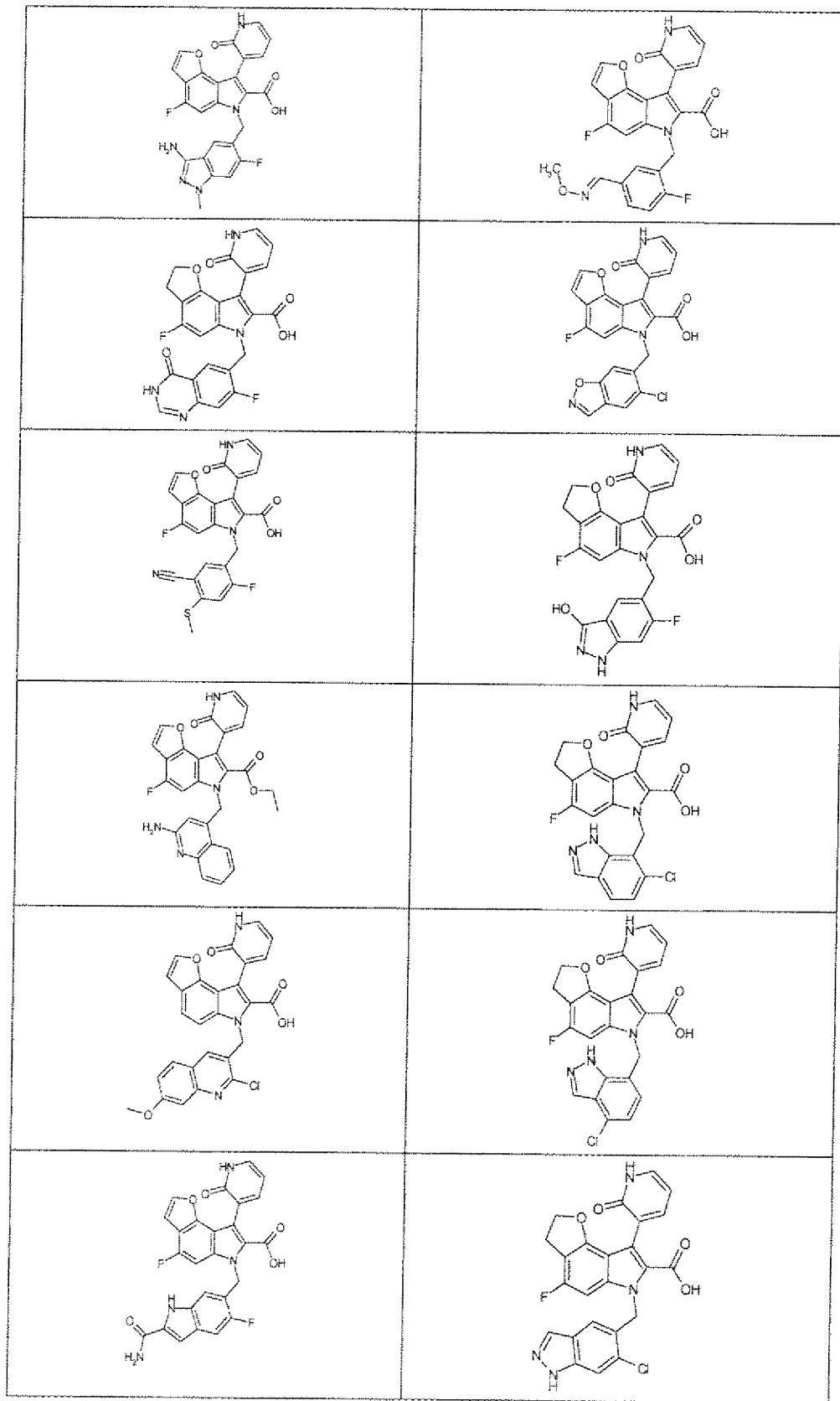


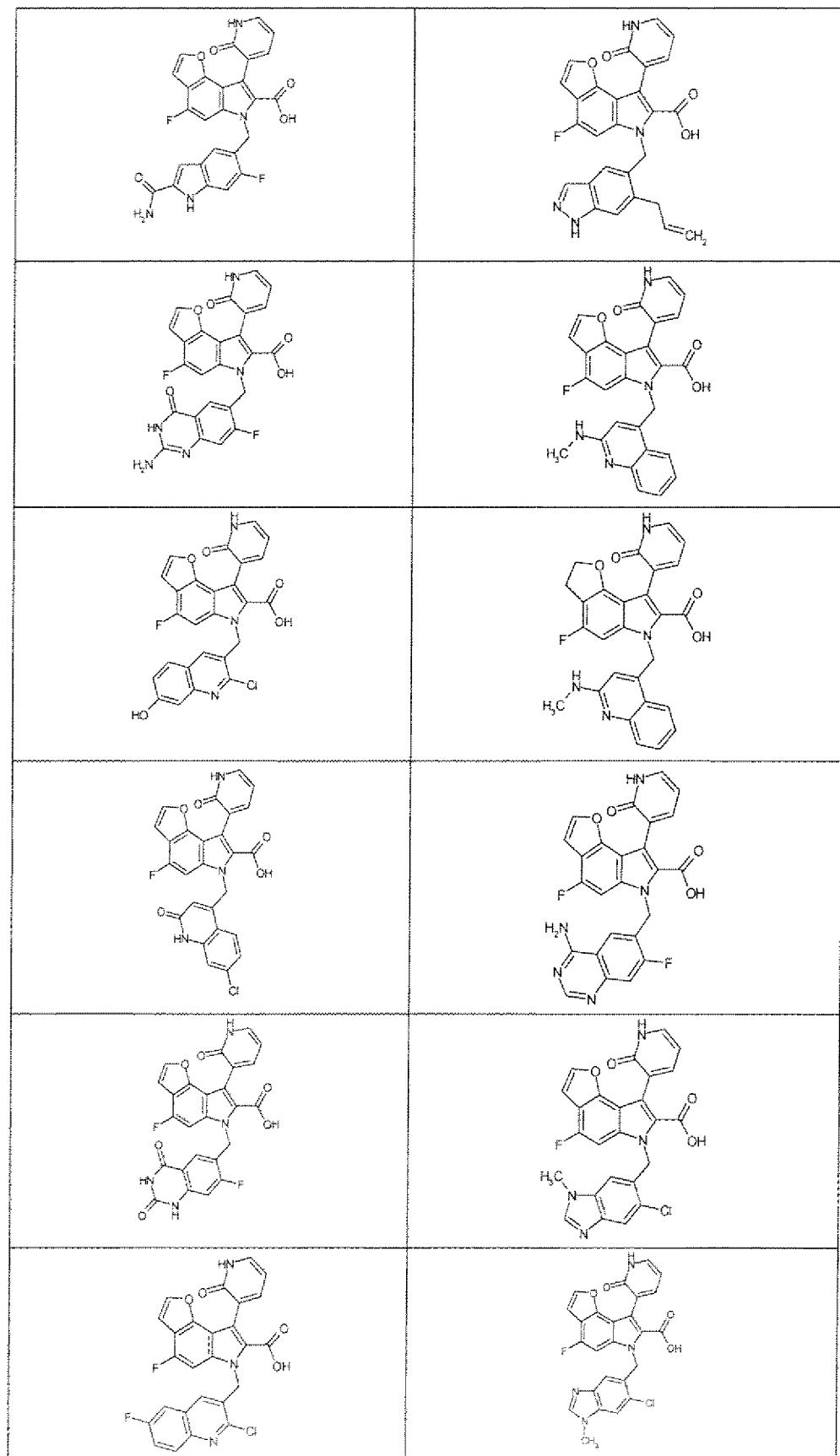


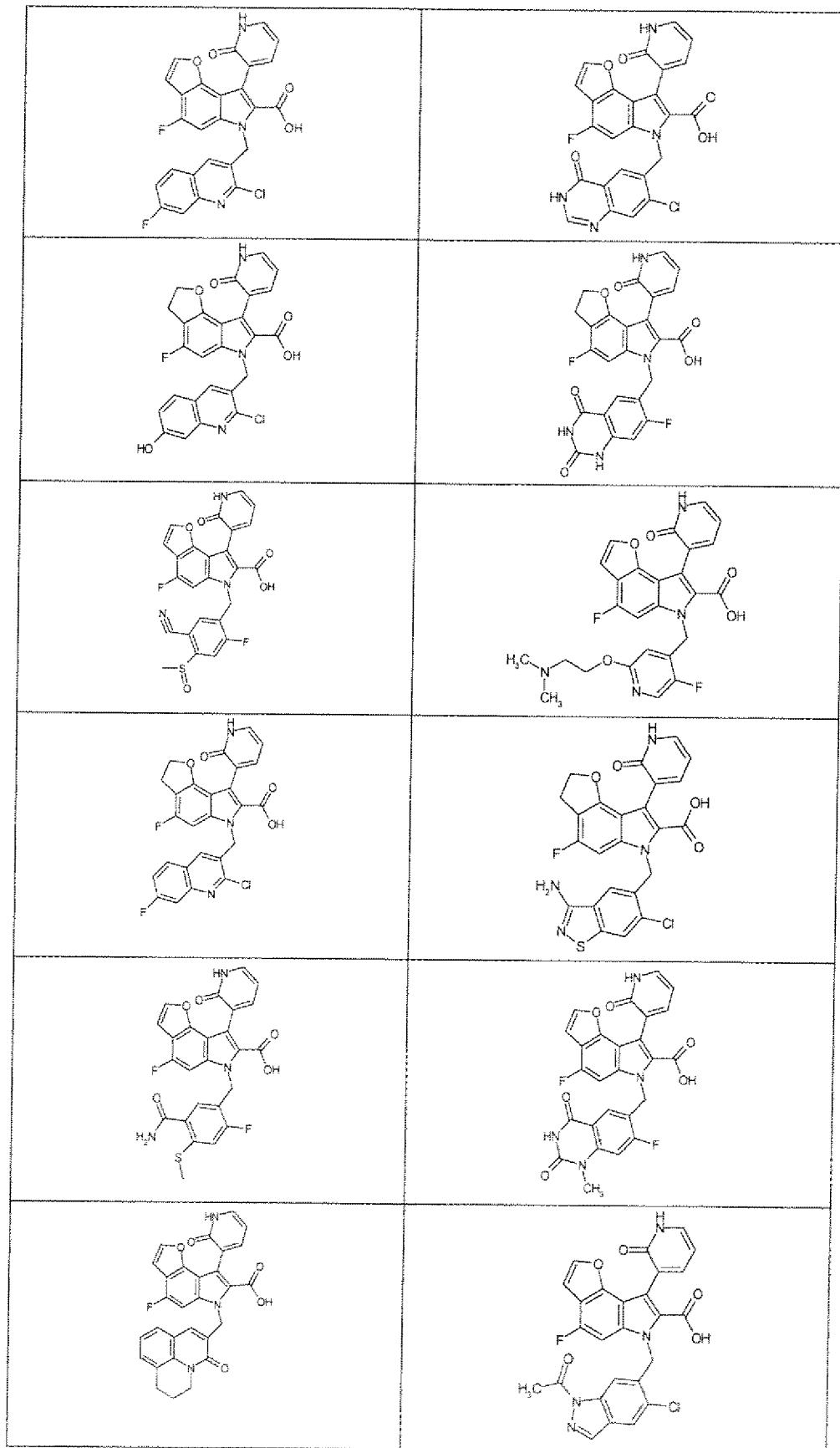


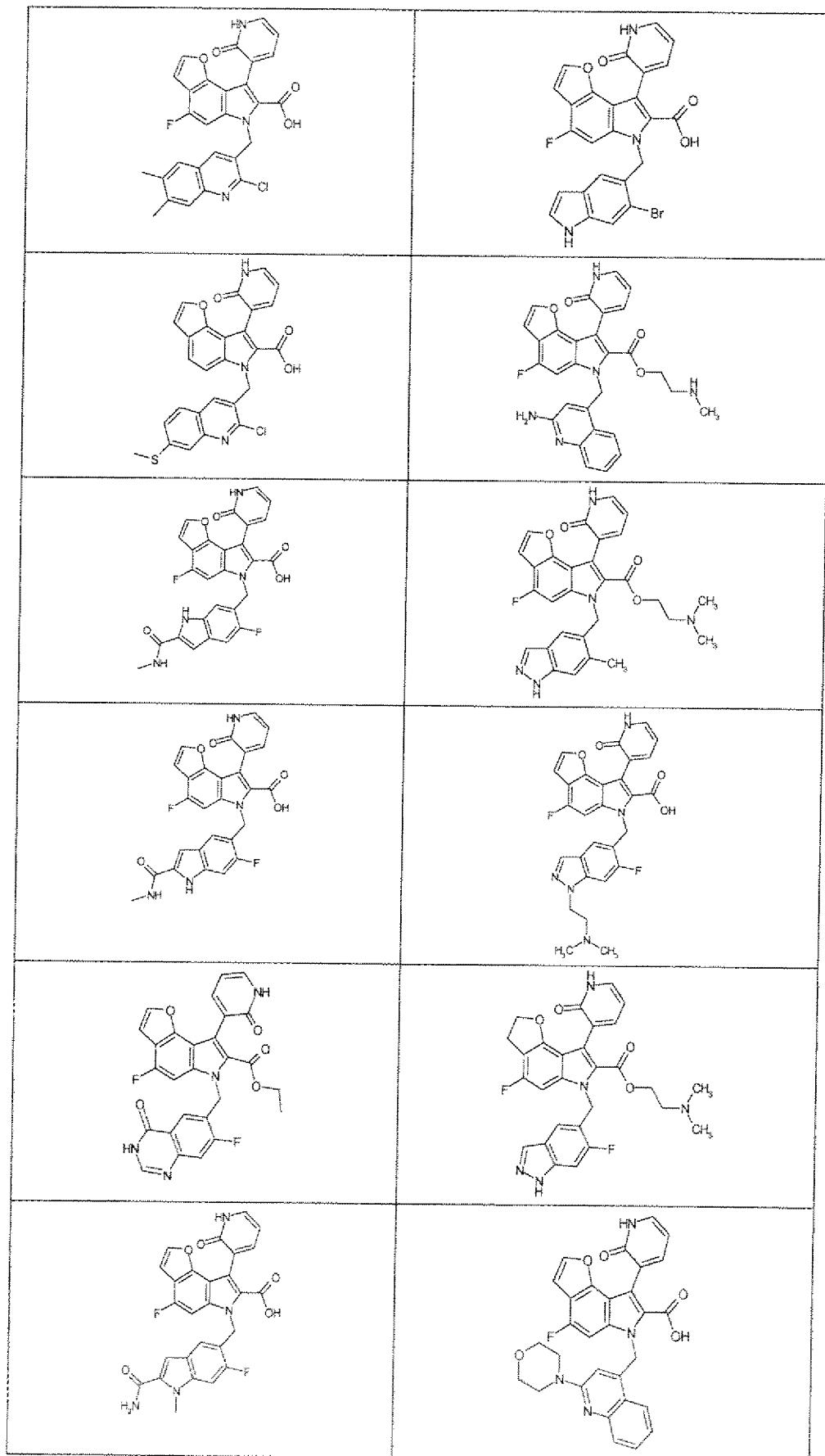
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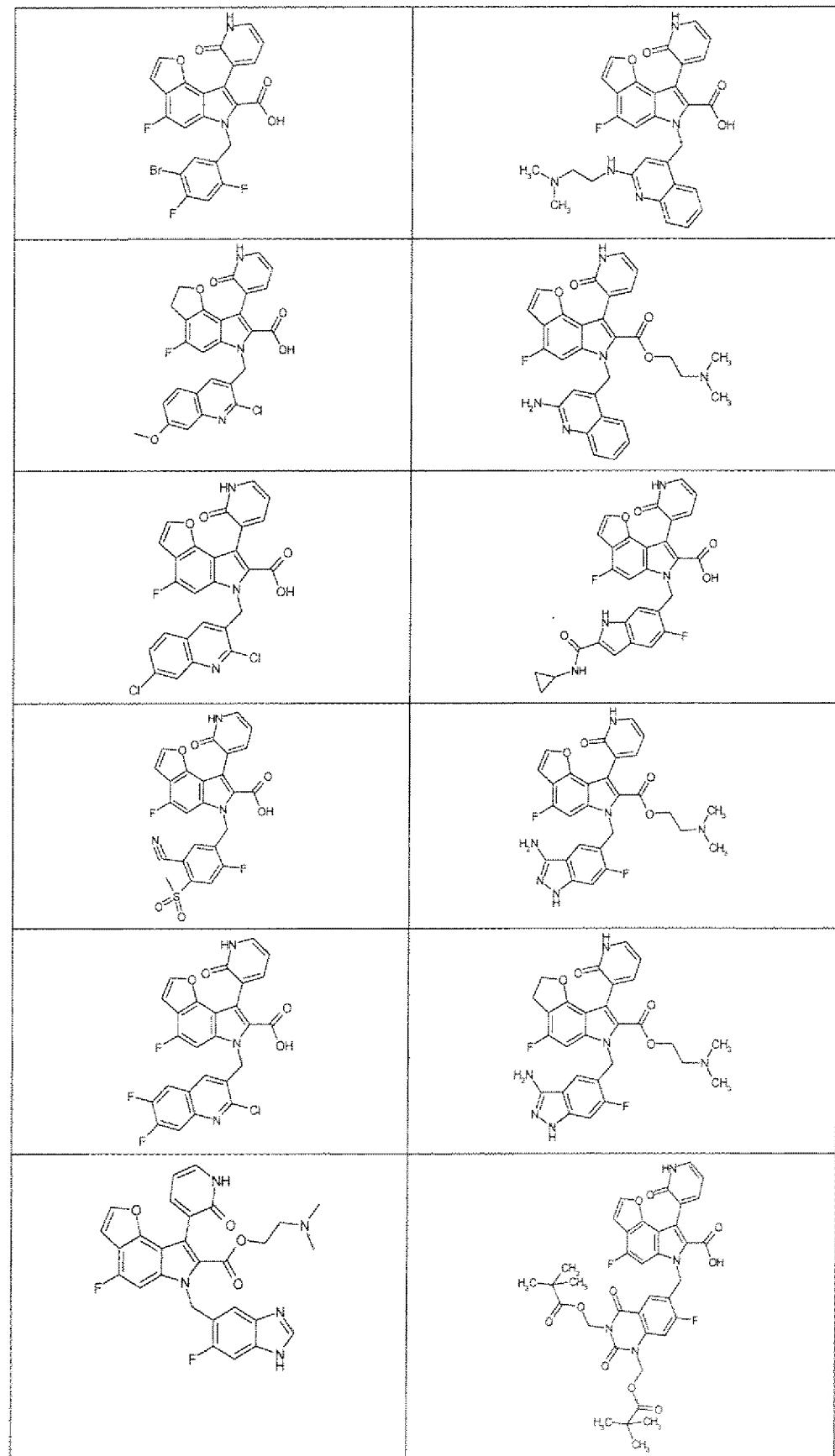


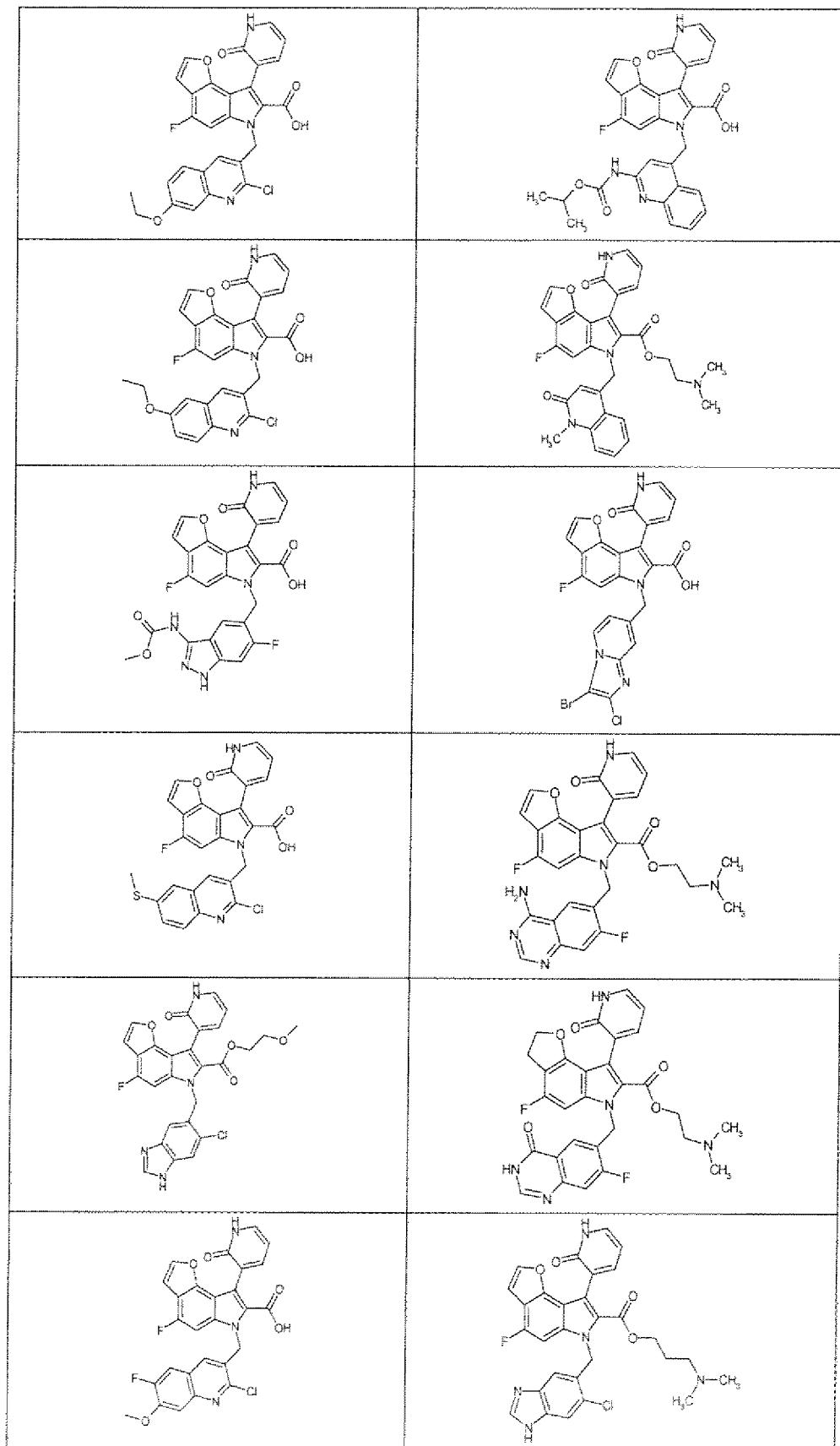


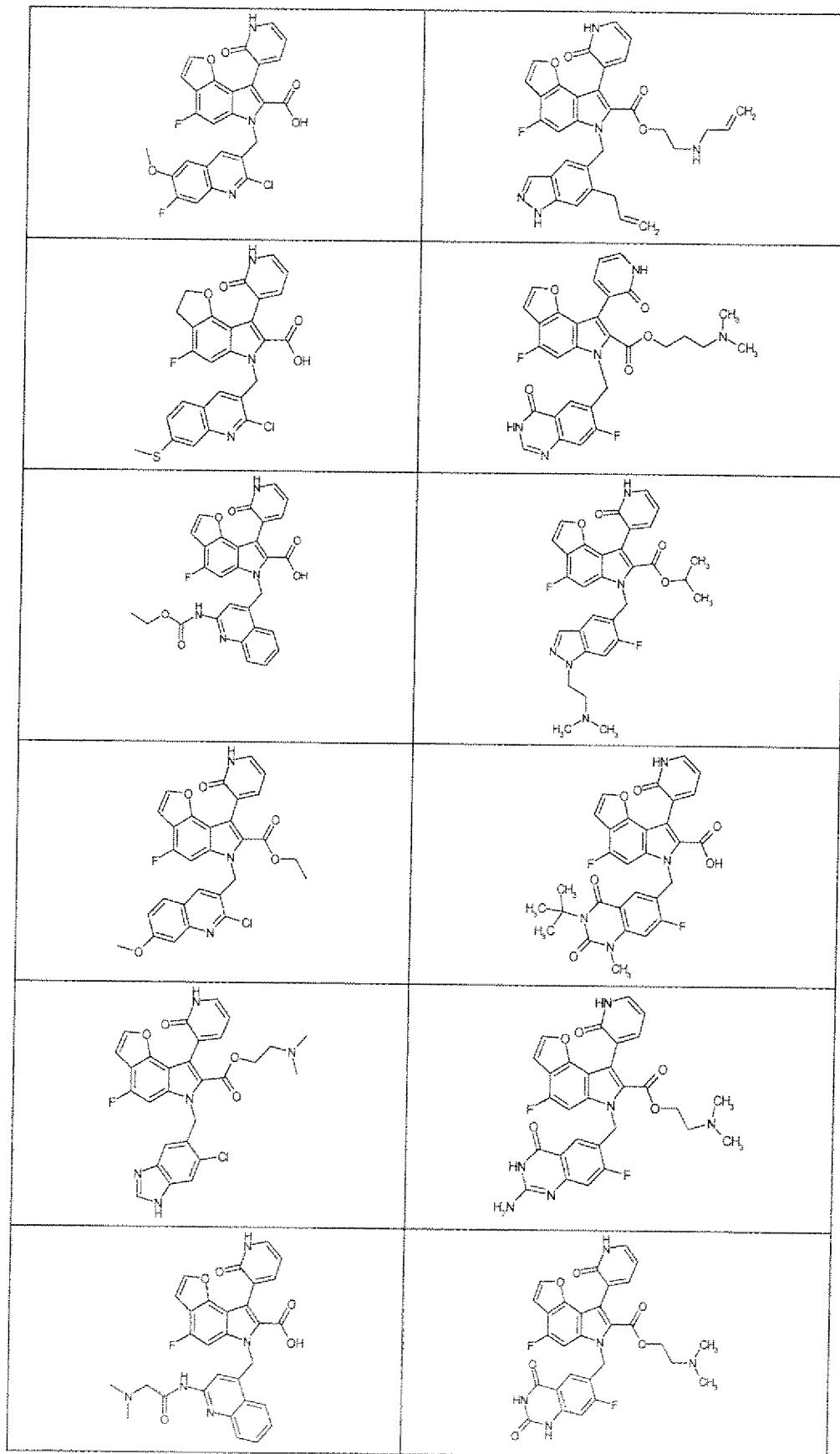


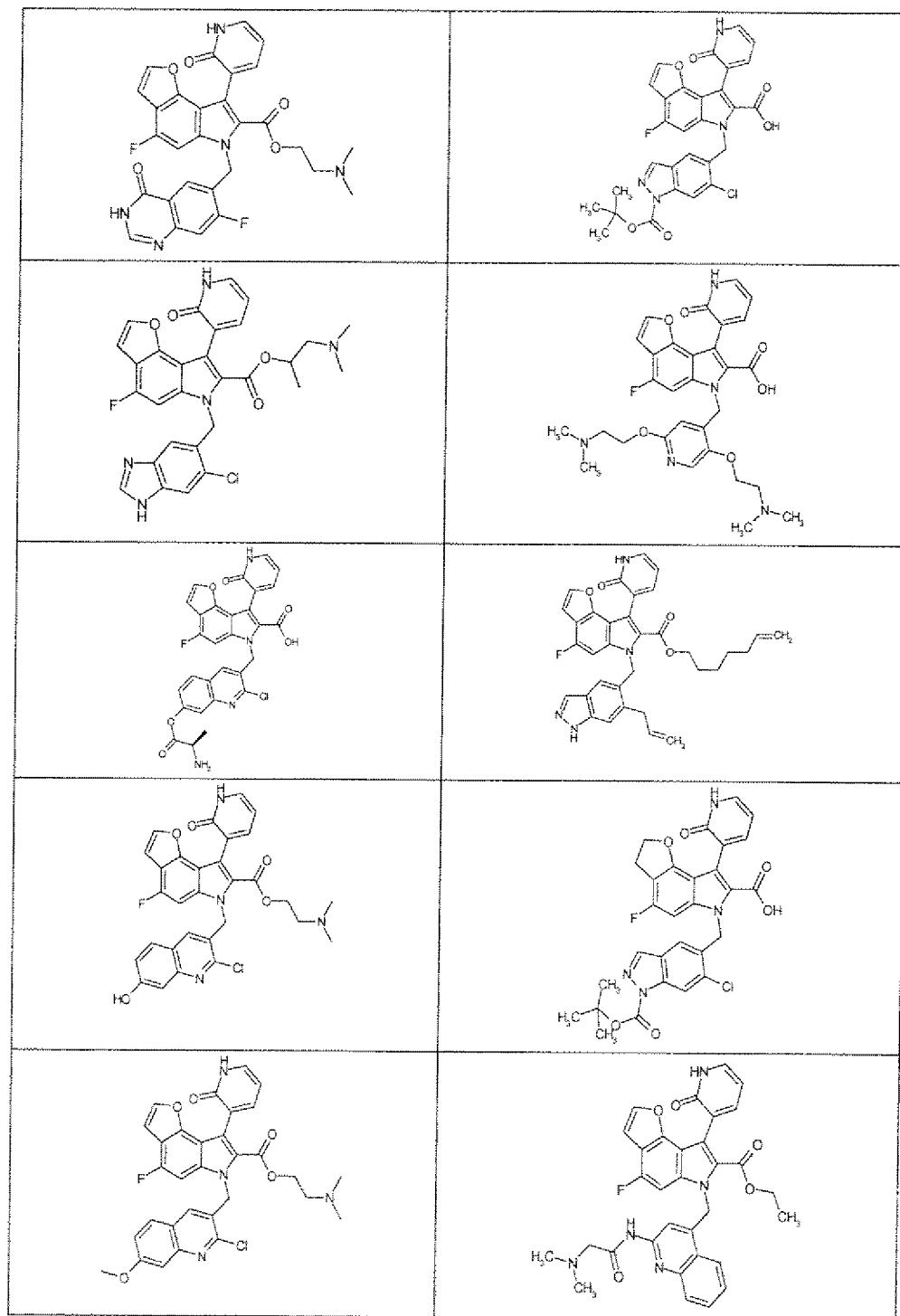


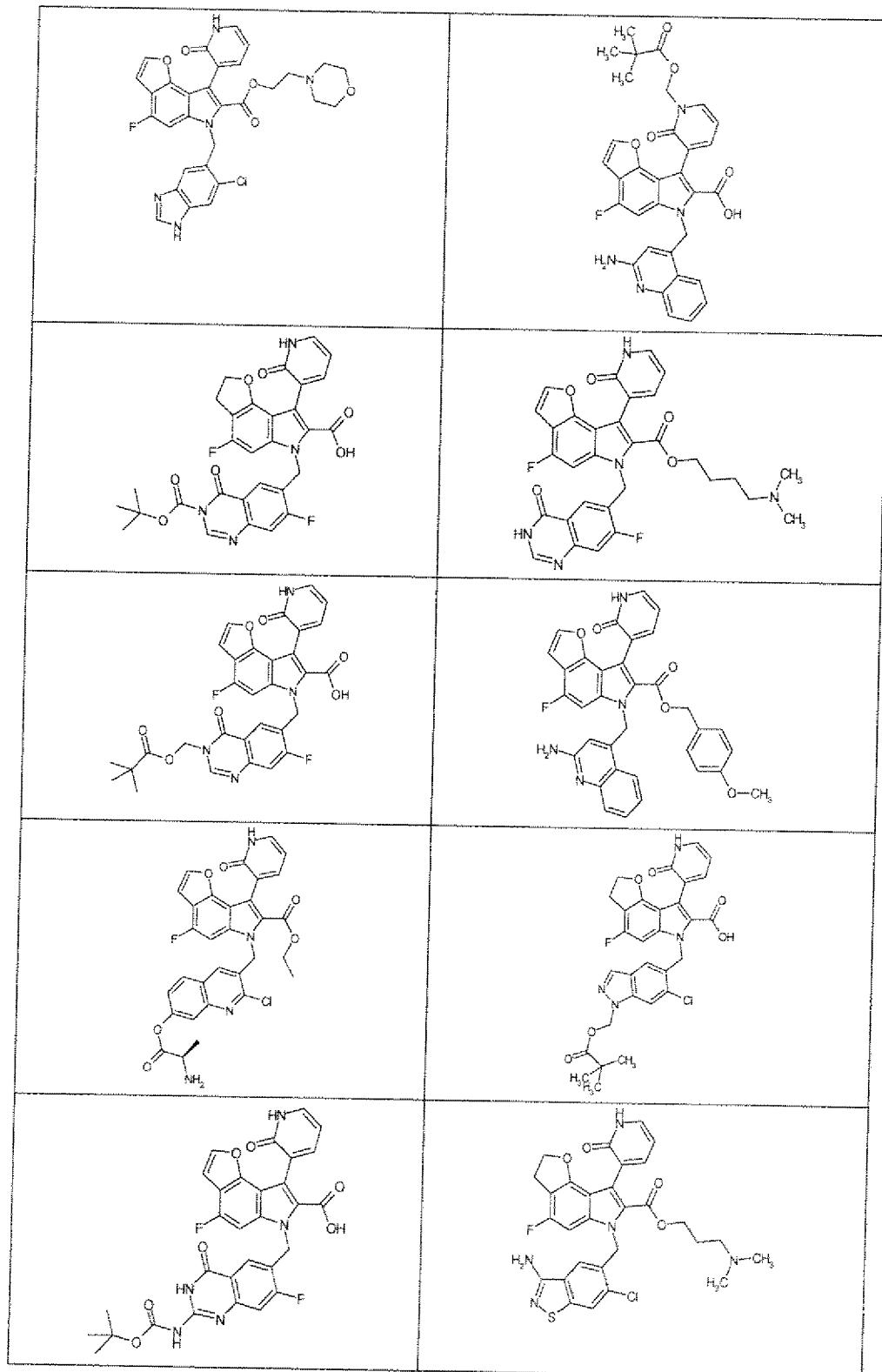


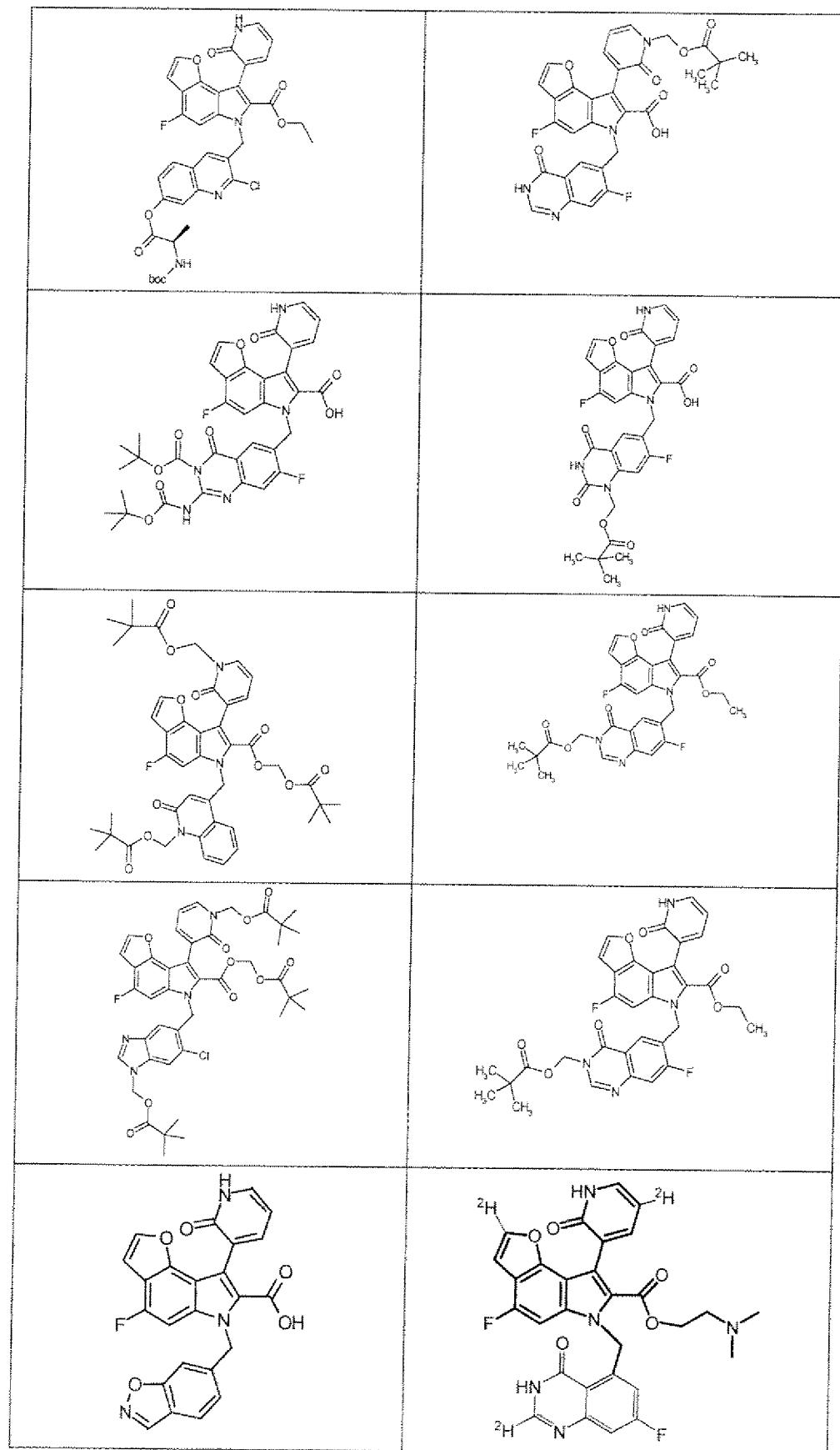


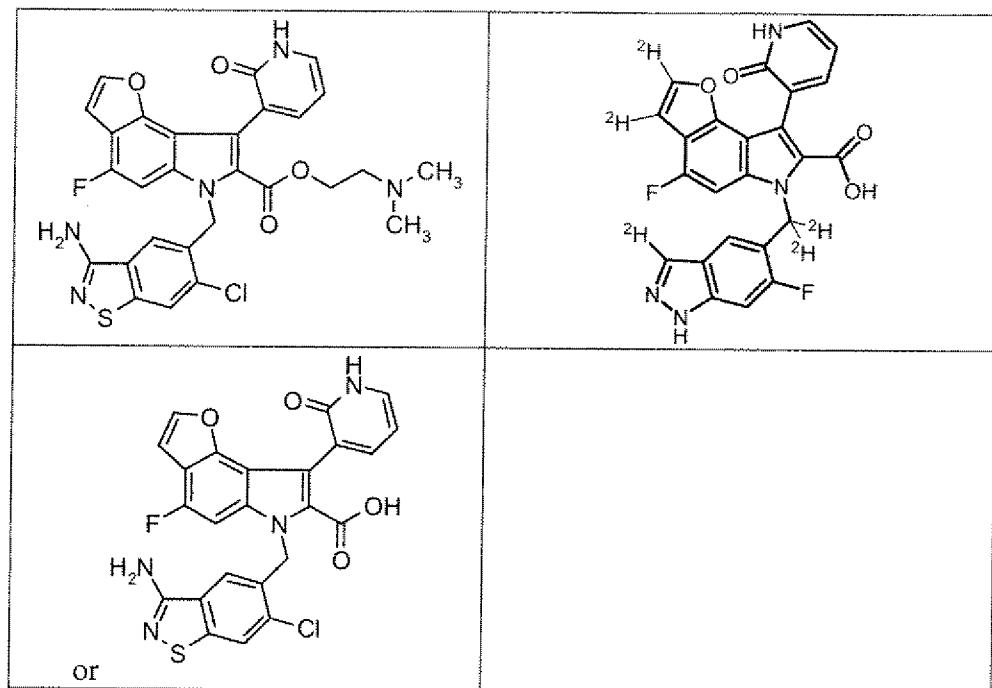






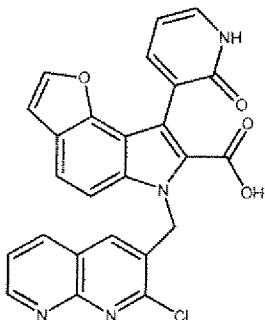






or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

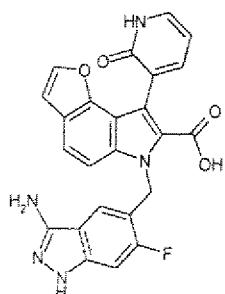
16. A compound having the structure:



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or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

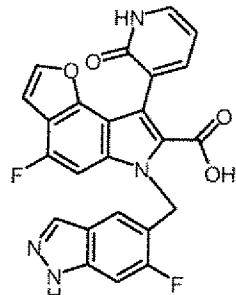
17. A compound having the structure:



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or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

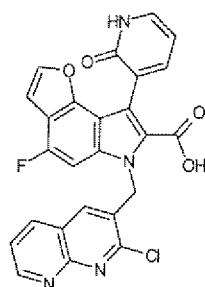
18. A compound having the structure:



or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

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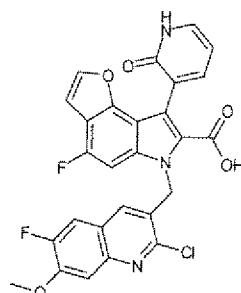
19. A compound having the structure:



or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

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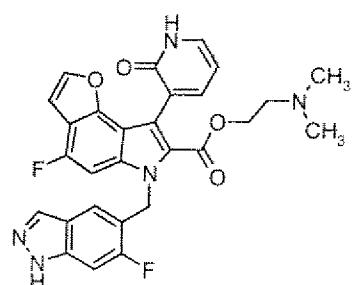
20. A compound having the structure:



or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

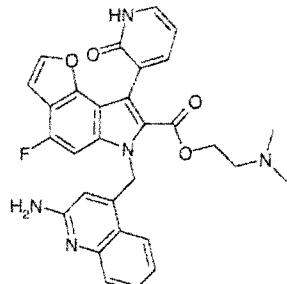
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21. A compound having the structure:



or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

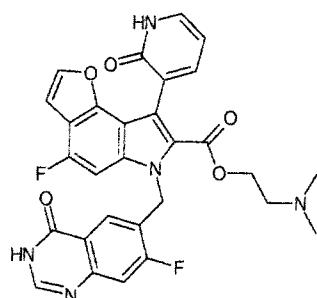
22. A compound having the structure:



or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

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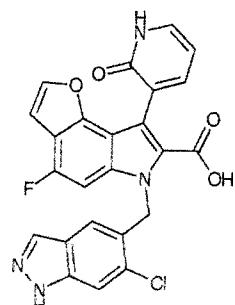
23. A compound having the structure:



or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

10

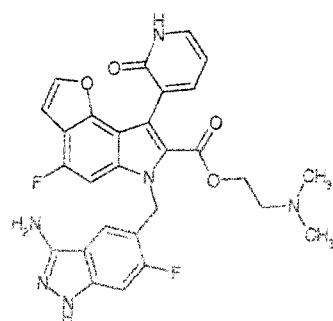
24. A compound having the structure:



or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

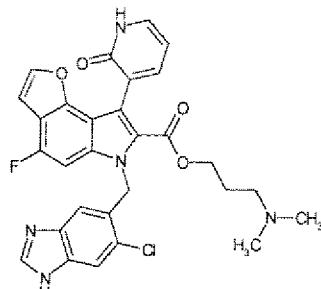
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25. A compound having the structure:



or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

26. A compound having the structure:



5 or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

27. A pharmaceutical composition comprising at least one compound of claim 1 or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable carrier.

28. The pharmaceutical composition of claim 27, further comprising at least one additional antiviral agent, wherein the additional agent is not a compound of claim 1

15 29. The pharmaceutical composition of claim 28, wherein the additional antiviral agent(s) are selected from: an HCV polymerase inhibitor; an interferon; a RNA replication inhibitor; an antisense agent; a therapeutic vaccine; a protease inhibitor; an antibody therapy (monoclonal or polyclonal); ribavirin; and any agent useful for treating an RNA-dependent polymerase-related disorder.

20

30. The pharmaceutical composition of claim 29, wherein the additional antiviral agent(s) comprise an agent useful for treating an RNA-dependent polymerase-related disorder

31. The pharmaceutical composition of claim 29, wherein the additional antiviral agent(s)
25 comprise an interferon.

32. The pharmaceutical composition of claim 31, wherein the interferon is interferon alfa-2a, interferon alfa-2b, interferon alfacon-1 or a pegylated interferon.

33. The pharmaceutical composition of claim 29, wherein the additional antiviral agent(s) comprise an HCV protease inhibitor.

5 34. The pharmaceutical composition of claim 33, wherein the HCV protease inhibitor is boceprevir or telaprevir.

35. The pharmaceutical composition of claim 29, wherein the additional antiviral agent(s) comprise an HCV polymerase inhibitor.

10 36. The pharmaceutical composition of claim 29, wherein the additional antiviral agent(s) comprise a viral replication inhibitor.

37. The pharmaceutical composition of claim 29, wherein the additional antiviral agent(s) comprise a viral entry inhibitor.

15 38. The pharmaceutical composition of claim 29, wherein the additional antiviral agent(s) comprise ribavirin.

20 39. The pharmaceutical composition of claim 38, wherein the additional antiviral agents further comprise an interferon.

40. The pharmaceutical composition of claim 39, wherein the additional antiviral agents further comprise an HCV protease inhibitor.

25 41. The pharmaceutical composition of claim 39, wherein the additional antiviral agents further comprise boceprevir or telaprevir.

42. A method for treating a viral infection in a patient, the method comprising administering to the patient an effective amount of at least one compound of claim 1 or a 30 pharmaceutically acceptable salt or solvate thereof.

43. The method of claim 42, further comprising administering to the patient at least one additional antiviral agent, wherein the additional agent is not a compound of claim 1, and wherein the amounts administered are together effective to treat a viral infection.

5 44. The method of claim 43, wherein the additional antiviral agent(s) is selected from: an interferon, an immunomodulator, a viral replication inhibitor, an antisense agent, a therapeutic vaccine, a viral polymerase inhibitor, a nucleoside inhibitor, a viral protease inhibitor, a viral helicase inhibitor, a virion production inhibitor, a viral entry inhibitor, a viral assembly inhibitor, an antibody therapy (monoclonal or polyclonal), and any agent useful for treating an
10 RNA-dependent polymerase-related disorder.

45. The method of claim 44, wherein the additional antiviral agent(s) comprise an agent useful for treating an RNA-dependent polymerase-related disorder.

15 46. The method of claim 44, wherein the additional antiviral agent(s) comprise an interferon.

47. The method of claim 46, wherein the interferon is interferon alfa-2a, interferon alfa-2b, inteferon alfacon-1 or a pegylated interferon.

20 48. The method of claim 44, wherein the additional antiviral agent(s) comprise an HCV protease inhibitor.

49. The method of claim 48, wherein the HCV protease inhibitor is boceprevir or
25 telaprevir.

50. The method of claim 44, wherein the additional antiviral agent(s) comprise an HCV polymerase inhibitor.

30 51. The method of claim 44, wherein the additional antiviral agent(s) comprise a viral replication inhibitor.

52. The method of claim 44, wherein the additional antiviral agent(s) comprise a viral entry inhibitor.

53. The method of claim 44, wherein the additional antiviral agent(s) comprise ribavirin.

54. The method of claim 53, wherein the additional antiviral agents further comprise an interferon.

55. The method of claim 54, wherein the additional antiviral agents further comprise an 10 HCV protease inhibitor.

56. The method of claim 54, wherein the additional antiviral agents further comprise boceprevir or telaprevir.

15 57. The method of claim 42, wherein the viral infection is HCV infection.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/046822

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D491/048 C07D519/00 A61P31/14 A61K31/4439 A61K31/444

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X, L	WO 2008/082484 A (SCHERING CORP [US]; CHEN KEVIN X [US]; VENKATRAMAN SRIKANTH [US]; NJOR) 10 July 2008 (2008-07-10) compounds 32, 41-42, 44, 75, 77-84, 86-87, 89, 91-103, 105 compounds 112-115, 121, 131, 141, 143, 153-154, 156-157, 160 compounds 166, 168, 187, 191, 220, 232-234, 236, 229-230 compounds 237, 239-265 earlier international application from the same applicant	1-57
A	WO 2005/034941 A (ANGELETTI P IST RICHERCHE BIO [IT]; AVOLIO SALVATORE [IT]; HARPER STEV) 21 April 2005 (2005-04-21) claims 1,15	1-57

Further documents are listed in the continuation of Box C.

See patent family annex.

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- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

22 September 2009

Date of mailing of the international search report

07/10/2009

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Miniejew, Catherine

INTERNATIONAL SEARCH REPORTInternational application No
PCT/US2009/046822**C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/084315 A (VIROPHARMA INC [US]; CONDON STEPHEN M [US]; JACKSON RANDY WILLIAM [US]) 15 September 2005 (2005-09-15) claim 7 -----	1-57

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No	
PCT/US2009/046822	

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 2008082484	A 10-07-2008	AR 064428	A1 01-04-2009	
		AU 2007339382	A1 10-07-2008	
		CL 36862007	A1 27-06-2008	
		EP 2064180	A1 03-06-2009	
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WO 2005034941	A 21-04-2005	AU 2004280120	A1 21-04-2005	
		CA 2541582	A1 21-04-2005	
		CN 1863528	A 15-11-2006	
		EP 1673081	A1 28-06-2006	
		JP 2007508286	T 05-04-2007	
		US 2007072911	A1 29-03-2007	
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WO 2005084315	A 15-09-2005	AU 2005218553	A1 15-09-2005	
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		CN 101098695	A 02-01-2008	
		EP 1765330	A2 28-03-2007	
		JP 2007526320	T 13-09-2007	
		US 2007219212	A1 20-09-2007	
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