ANTIMICROBIAL COMPOUNDS AND METHODS OF MAKING AND USING THE SAME

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application No. 61/252,478 filed on October 16, 2009; U.S. Provisional Patent Application No. 61/314,287 filed on March 16, 2010; and U.S. Provisional Patent Application No. 61/358,201 filed on June 24, 2010. The contents of the aforementioned applications are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

The present invention relates generally to the field of antimicrobial compounds and to methods of making and using them. These compounds are useful for treating, preventing, and reducing the risk of microbial infections in humans and animals.

BACKGROUND

Since the discovery of penicillin in the 1920s and streptomycin in the 1940s, many new compounds have been discovered or specifically designed for use as antibiotic agents. It was once thought that infectious diseases could be completely controlled or eradicated with the use of such therapeutic agents. However, such views have been challenged because strains of cells or microorganisms resistant to currently effective therapeutic agents continue to evolve. Almost every antibiotic agent developed for clinical use has ultimately encountered problems with the emergence of resistant bacteria. For example, resistant strains of Gram–positive bacteria such as methicillin–resistant staphylococci, penicillin–resistant streptococci, and vancomycin–resistant enterococci have developed. Resistant bacteria can cause serious and even fatal results for infected patients. *See, e.g.*, Lowry, F.D. "Antimicrobial Resistance: The Example of *Staphylococcus aureus*," *J. Clin. Invest.*, vol. 111, no. 9, pp. 1265–1273 (2003); and Gold, H.S. and Moellering, R.C., Jr., "Antimicrobial–Drug Resistance," *N. Engl. J. Med.*, vol. 335, pp. 1445–53 (1996).

The discovery and development of new antibacterial agents have been for decades a major focus in many pharmaceutical companies. Nonetheless, in more recent years there has been an exodus of pharmaceutical companies from this area of research and drug development. As a consequence of this exodus, there have been very few new antibiotics entering the market. This lack of new antibiotics is particularly disturbing, especially at a

time when bacterial resistance to current therapies is increasing both in the hospital and community settings.

In the search for new antibiotic agents, researchers have tried combining or linking various portions of antibiotic molecules to create multifunctional or hybrid compounds Other researchers have tried making derivatives of known classes of antibiotics, e.g., telithromycin, which is sold under the trade name Ketek®, is a derivative of erythromycin. However, these approaches have met with limited success.

An approach to developing new antimicrobial compounds is to design modulators, for example, inhibitors, of bacterial ribosome function. By modulating or inhibiting bacterial ribosome function such antimicrobial compounds could interfere with essential processes such as RNA translation and protein synthesis, thereby providing an antimicrobial effect. In fact, some antibiotic compounds such as erythromycin, clindamycin, and linezolid are known to bind to the ribosome.

The present invention utilizes a structure based drug design approach for discovering and developing new antimicrobial agents. This approach starts with the high resolution X–ray crystal of the ribosome to design new classes of antimicrobial compounds having specific chemical structures, ribosome binding characteristics, and antimicrobial activity. This structure based drug discovery approach is described in the following publication: Franceschi, F. and Duffy, E.M., "Structure–based drug design meets the ribosome", *Biochemical Pharmacology*, vol. 71, pp. 1016–1025 (2006).

Based on this structure based drug design approach, the present invention describes new chemical classes of antimicrobial compounds useful for treating bacterial infections in humans and animals. Without being limited by theories, these compounds are believed to inhibit bacterial ribosome function by binding to the ribosome. By taking advantage of these ribosome binding sites, the antimicrobial compounds of the present invention can provide better activity, especially against resistant strains of bacteria, than current antibiotic compounds.

The present invention utilizes a structure based drug design approach for discovering and developing new antimicrobial agents. This approach starts with the high resolution X–ray crystal of the ribosome to design new classes of antimicrobial compounds having specific chemical structures, ribosome binding characteristics, and desired antimicrobial activity.

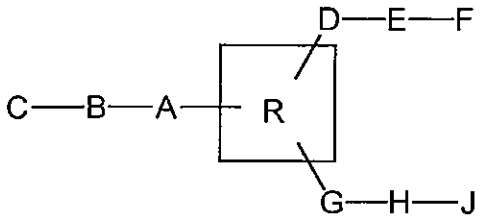
This structure based drug discovery approach is described in the following publication: Franceschi, F. and Duffy, E.M., "Structure–based drug design meets the ribosome", *Biochemical Pharmacology*, vol. 71, pp. 1016–1025 (2006).

The present invention therefore fills an important ongoing need for providing new antimicrobial agents, particularly for antimicrobial agents, having activity against resistant pathogenic bacterial organisms.

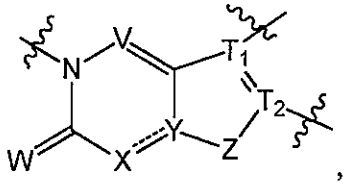
SUMMARY OF THE INVENTION

The present invention relates generally to the field of antimicrobial compounds and to methods of making and using them. These compounds are useful for treating, preventing, and reducing the risk of microbial infections in humans and animals. The present invention also provides pharmaceutically acceptable salts, esters, *N*–oxides, and prodrugs of these compounds.

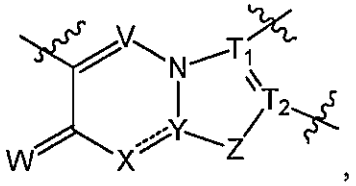
The present invention provides compounds having the structure:



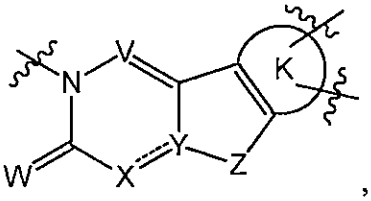
wherein R is a chemical moiety selected from:



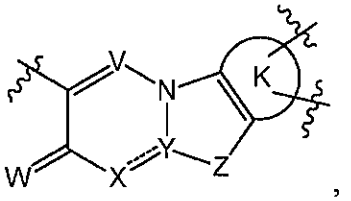
,



,



, or



,

wherein K represents a fused 5 to 7 member saturated, unsaturated, or aromatic carbocyclic or heterocyclic ring system,

wherein T^1 is a carbon atom or N, such that when T^1 is N, –D–E–F is absent,

wherein T^2 is a carbon atom or N, such that when T^2 is N, –G–H–J is absent,

wherein both T^1 and T^2 are not both simultaneously N,

wherein V is independently selected from $-CR^{4a}-$ or –N–,

W is O, NR^1, NOR^1, or S, alternatively W= is selected from the combination of HO– and H– both attached to the same carbon atom or the combination of (C_{1-8} alkyl)O– and H– both attached to the same carbon atom;

X---Y represents a single bond or a double bond such that when X---Y is a single bond, X is selected from O, NR^2, and $S(O)_n$ and Y is C–R^3, and when X---Y is a double bond, X is N and Y is a carbon atom,

Z is selected from the group consisting of O, NR^4, $S(O)_n$, or NH,

R^1 is selected from H and C_{1-8} alkyl,

R^2 is selected from H and C_{1-8} alkyl,

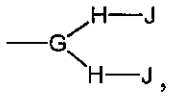
R^3 is selected from H and C_{1-8} alkyl,

R^4 is selected from H and C_{1-8} alkyl,

R^{4a} is selected from H and C_{1-8} alkyl,

n is 0, 1, or 2,

alternatively –G–H–J is selected from



wherein each H and J are independently selected,

C–B–A–, –D–E–F, and –G–H–J are chemical moieties, wherein

A, D and G are independently selected from the group consisting of:

(a) a single bond, (b) –(C_{1-8} alkyl)– , (c) –(C_{2-8} alkenyl)–, (d) –(C_{2-8} alkynyl)–, wherein

i) 0–4 carbon atoms in any of (b)–(d) immediately above optionally is replaced by a moiety selected from the group consisting of –O–, $-S(O)_p-$, $-NR^6-$, –(C=O)–, $-S(O)_pNR^6-$, $-NR^6S(O)_p-$, and $-NR^6S(O)_pNR^6-$,

ii) any of (b)–(d) immediately above optionally is substituted with one or more R^5 groups, and

iii) any of (b)–(d) immediately above optionally is substituted with –(C_{1-8} alkyl)–R^5 groups;

(e) –O–, (f) –NR^6–, (g) –$S(O)_p$–, (h) –C(O)–, (i) –C(O)O–, (j) –OC(O)–, k) –OC(O)O–, (l) –C(O)NR^6–, (m) –NR^6CO–, (n) –NR^6C(O)NR^6–, (o) –C(=NR^6)–, (p) –C(=NR^6)O–, (q) –OC(=NR^6)–, (r) –C(=NR^6)NR^6–, (s) –NR^6C(=NR^6)–, (t) –C(=S)–, (u) –C(=S)NR^6–, (v) –NR^6C(=S)–, (w) –C(O)S–, (x) –SC(O)–, (y) –OC(=S)–, (z) –C(=S)O–, (aa) –NR^6(CNR^6)NR^6–, (bb) –CR^6R^6C(O)–, (cc) –C(O)NR^6(CR^6R^6)$_t$–, (dd) a 3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (ee) a 3–14 member saturated, unsaturated, or aromatic carbocycle, and (ff) –(CR^6R^6)$_t$–,

wherein (dd) or (ee) is optionally substituted with one or more R^5 groups;

B, E, and H are independently selected from the group consisting of:

(a) a single bond,

(b) a 3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

(c) a 3–14 member saturated, unsaturated, or aromatic carbocycle,

wherein (b) or (c) is optionally substituted with one or more R^5 groups;

(d) –(C_{1-8} alkyl)–, (e) –(C_{2-8} alkenyl)–, (f) –(C_{2-8} alkynyl)–, wherein

i) 0–4 carbon atoms in any of (d)–(f) immediately above optionally is replaced by a moiety selected from the group consisting of –O–, –$S(O)_p$–, –NR^6–, –(C=O)–, –C(=NR^6)–, –$S(O)_pNR^6$–, –$NR^6S(O)_p$–, and –$NR^6S(O)_pNR^6$–,

ii) any of (d)–(f) immediately above optionally is substituted with one or more R^5 groups, and

iii) any of (d)–(f) immediately above optionally is substituted with –(C_{1-8} alkyl)–R^5 groups;

and (g) –(CR^6R^6)$_t$–,

C, F, and J are independently selected from the group consisting of:

(a) hydrogen, (c) F, (d) Cl, (e) Br, (f) I, (g) $-CF_3$, (h) –CN, (i) $-N_3$ (j) $-NO_2$, (k) – $NR^6(CR^6R^6)_tR^8$, (l) $-OR^8$, (m) $-S(O)_p(CR^6R^6)_tR^8$, (n) $-C(O)(CR^6R^6)_tR^8$, (o) – $OC(O)(CR^6R^6)_tR^8$, (p) $-SC(O)(CR^6R^6)_tR^8$, (q) $-C(O)O(CR^6R^6)_tR^8$, (r) – $NR^6C(O)(CR^6R^6)_tR^8$, (s) $-C(O)NR^6(CR^6R^6)_tR^8$, (t) $-C(=NR^6)(CR^6R^6)_tR^8$, (u) – $C(=NNR^6R^6)(CR^6R^6)_tR^8$, (v) $-C(=NNR^6C(O)R^6)(CR^6R^6)_tR^8$, (w) – $C(=NOR^8)(CR^6R^6)_tR^8$, (x) $-NR^6C(O)O(CR^6R^6)_tR^8$, (y) $-OC(O)NR^6(CR^6R^6)_tR^8$, (z) – $NR^6C(O)NR^6(CR^6R^6)_tR^8$, (aa) $-NR^6S(O)_p(CR^6R^6)_tR^8$, (bb) $-S(O)_pNR^6(CR^6R^6)_tR^8$, (cc) $-NR^6S(O)_pNR^6(CR^6R^6)_tR^8$, (dd) $-NR^6R^8$, (ee) $-NR^6(CR^6R^6)R^8$, (ff) –OH, (gg) – NR^8R^8, (hh) $-OCH_3$, (ii) $-S(O)_pR^8$, (jj) $-NC(O)R^8$, (kk) $-NR^6C(NR^6)NR^6R^8$, (ll) a C_{1-8} alkyl group, (mm) a C_{2-8} alkenyl group, (nn) a C_{2-8}alkynyl group, (oo) a 3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (pp) a 3–14 member saturated, unsaturated, or aromatic carbocycle, (qq) – $(CR^6R^6)_tNR^6(CR^6R^6)_tR^8$, (rr) $-N[(CR^6R^6)_tR^8][C=O(CR^6R^6)_tR^8]$, (ss) – $(CR^6R^6)_tN[(CR^6R^6)_tR^8][(CR^6R^6)_tR^8]$, (tt) $-(CR^6R^6)_tNR^6(C=O)(CR^6R^6)_tR^8$, (uu) – haloalkyl, (vv) $-C(O)(CR^6)[(CR^6R^6)_tR^8]R^8$, (ww) $-(CR^6R^6)_tC(O)NR^8R^8$, (xx) – $(CR^6R^6)_tC(O)O(CR^6R^6)_tR^8$, (yy) $-NR^6C(O)CR^8R^8R^8$, (zz) $-N[(CR^6R^6)_tR^8]C(O)R^8$, and (aaa) $-S(O)_pNR^8R^8$;

wherein (ll) through (pp) is optionally substituted with one or more R^7 groups;

R^5 is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) – NO_2, (j) $-NR^6R^6$, (k) $-OR^8$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C_{1-8}$ alkyl, (n) $-C_{1-8}$ alkenyl, (o) – C_{1-8} alkynyl, (p) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (q) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (r) –haloalkyl, (s) $-SR^6$, (t) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and (u) –3–14 member saturated, unsaturated, or aromatic carbocycle;

alternatively, two R^5 groups are taken together to form a carbocycle;

wherein (m) through (r) and (t) through (u) is optionally substituted with one or more R^8;

R^6 is selected from (a) hydrogen, (b) $-C_{1-8}$ alkyl or alternatively two R^6 groups are taken together to form a carbocycle, (c) –haloalkyl, (d) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and (e) –3–14 member saturated, unsaturated, or aromatic carbocycle;

wherein (b) through (e) is optionally substituted with one or more R^8;

R^7 is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) $-NO_2$, (j) $-NR^6R^6$, (k) $-OR^6$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C_{1-8}$ alkyl, (n) $-C_{1-8}$ alkenyl, (o) $-C_{1-8}$ alkynyl, (p) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (q) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (r) –haloalkyl, (s) $-NR^6R^8$, (t) $-OR^8$, (u) $-(CR^6R^6)_tNR^6R^8$, (v) $-CR^6R^8R^8$, (w) $-SR^6$, (x) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (y) –3–14 member saturated, unsaturated, or aromatic carbocycle, (z) $-(CR^6R^6)_tC(O)NR^8R^8$, (aa) $-S(O)_pR^8$, (bb) $-NR^6C(O)NR^6R^6$, (cc) $-NR^6C(O)R^6$, and (dd) $-C(=NR^6)NR^6R^6$;

wherein (m) through (q) and (x) through (y) are optionally substituted with one or more R^9;

R^8 is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) $-NO_2$, (j) $-NR^6R^9$, (k) $-OR^9$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C_{1-8}$ alkyl, (n) $-C_{1-8}$ alkenyl, (o) $-C_{1-8}$ alkynyl, (p) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (q) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (r) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (s) –3–14 member saturated, unsaturated, or aromatic carbocycle, (t) –haloalkyl, (u) $-C(O)(CR^6R^6)_tR^9$, (v) $-SR^6$, (w) $-OC(O)(CR^6R^6)_tR^9$, (x) $-NR^6C(O)NR^6R^9$, (y)–$NR^6C(O)R^9$, (z) $-NR^6(CNR^9)(NR^6R^6)$, (aa) $-ONR^6(CNR^6)NR^6R^6$, (bb) $-C(=NR^9)NR^6R^6$, (cc) $-S(O)_pR^9$, (dd) $-(CR^6R^6)_tC(O)NR^6R^9$, (ee) $-(CR^6R^6)_tOR^9$, and (ff) $-(CR^6R^6)_tNR^6R^9$;

wherein (m) through (s) is optionally substituted with one or more R^9;

R^9 is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) $-NO_2$, (j) $-NR^6R^{10}$, (k) $-OR^6$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C(O)(CR^6R^6)_tNR^6R^6$, (n) $-C_{1-8}$ alkyl, (o) $-C_{1-8}$ alkenyl, (p) $-C_{1-8}$ alkynyl, (q) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (r) –3–14 member saturated, unsaturated, or aromatic carbocycle, (s) –haloalkyl, (t) $-(CR^6R^6)_tOR^6$, (u) $-O(CR^6R^6)_tNR^6R^{10}$, (v) $-C(O)R^6$, (w) $-SR^6$, (x) $-C(O)OR^{10}$, (y) $-S(O)_pR^6$, (z) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (aa) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (bb) $-O(CR^6R^6)_tOR^6$, (cc) $-C(=NR^6)NR^6R^6$, (dd) $-ONR^6R^6$, (ee) $-NR^6C(O)NR^6R^6$, (ff) $-O(CR^6R^6)_tOR^6$, (gg) $-NR^6C(O)R^6$, and (hh) $-(CR^6R^6)_tNR^6R^{10}$;

wherein (n) through (r) and (z) through (aa) is optionally substituted with one or more R^{10};

R^{10} is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) $-NO_2$, (j) $-NR^6R^6$, (k) $-OR^6$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C(O)(CR^6R^6)_tNR^6R^6$, (n) $-C_{1-8}$ alkyl, (o) $-C_{1-8}$ alkenyl, (p) $-C_{1-8}$ alkynyl, (q) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (r) –3–14 member saturated, unsaturated, or aromatic carbocycle, (s) –haloalkyl, (t) $-(CR^6R^6)_tOR^6$, (u) $-O(CR^6R^6)_tNR^6R^6$, (v) $-C(O)R^6$, (w) $-SR^6$, (x) $-C(O)OR^6$, (y) $-S(O)_pR^6$, (z) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (aa) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (bb) $-O(CR^6R^6)_tOR^6$, (cc) $-C(=NR^6)NR^6R^6$, (dd) $-ONR^6R^6$, (ee) $-NR^6C(O)NR^6R^6$, (ff) $-O(CR^6R^6)_tOR^6$, (gg) $-NR^6C(O)R^6$, and (hh) $-(CR^6R^6)_tNR^6R^6$;

optionally, wherein either the group –D–E–F or the group –G–H–J is absent, but both –D–E–F and –G–H–J are not simultaneously absent;

p is 0, 1, or 2, and

t is 0, 1, 2, or 3,

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

In addition, the invention provides methods of synthesizing the foregoing compounds. Following synthesis, a therapeutically effective amount of one or more of the compounds can be formulated with a pharmaceutically acceptable carrier for administration to a human or animal for use as antimicrobial agents, particularly as antibacterial agents. In certain embodiments, the compounds of the present invention are useful for treating, preventing, or reducing the risk of microbial infections or for the manufacture of a medicament for treating, preventing, or reducing the risk of microbial infections. Accordingly, the compounds or the formulations can be administered, for example, via oral, parenteral, intravenous, otic, ophthalmic, nasal, or topical routes, to provide an effective amount of the compound to the human or animal.

The foregoing and other aspects and embodiments of the invention can be more fully understood by reference to the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a family of compounds that can be used as antimicrobial agents, more particularly as antibacterial agents.

The present invention includes pharmaceutically acceptable salts, esters, tautomers, N–oxides, and prodrugs thereof.

The compounds described herein can have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom can be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and can be isolated as a mixture of isomers or as separate isomeric forms. All chiral, diastereomeric, racemic, and geometric isomeric forms of a structure are intended, unless specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. All tautomers of shown or described

compounds are also considered to be part of the present invention. Furthermore, the invention also includes metabolites of the compounds described herein.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C–13 and C–14.

When any variable (*e.g.*, R^6) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with one or more R^6 moieties, then R^6 at each occurrence is selected independently from the definition of R^6. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds within a designated atom's normal valency.

A chemical structure showing a dotted line representation for a chemical bond indicates that the bond is optionally present. For example, a dotted line drawn next to a solid single bond indicates that the bond can be either a single bond or a double bond.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent can be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent can be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

In cases wherein there are nitrogen atoms in the compounds of the present invention, these, where appropriate, can be converted to *N*–oxides by treatment with an oxidizing agent (e.g., MCPBA and/or hydrogen peroxides). Thus, shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its *N*–oxide (N→O) derivative, as appropriate.

One approach to developing improved anti–proliferative and anti–infective agents is to provide modulators (for example, inhibitors) of ribosome function.

Ribosomes are ribonucleoproteins, which are present in both prokaryotes and eukaryotes. Ribosomes are the cellular organelles responsible for protein synthesis. During gene expression, ribosomes translate the genetic information encoded in a messenger RNA

into protein (Garrett *et al.* (2000) "*The Ribosome: Structure, Function, Antibiotics and Cellular Interactions,*" American Society for Microbiology, Washington, D.C.).

Ribosomes comprise two nonequivalent ribonucleoprotein subunits. The larger subunit (also known as the "large ribosomal subunit") is about twice the size of the smaller subunit (also known as the "small ribosomal subunit"). The small ribosomal subunit binds messenger RNA (mRNA) and mediates the interactions between mRNA and transfer RNA (tRNA) anticodons on which the fidelity of translation depends. The large ribosomal subunit catalyzes peptide bond formation, i.e. the peptidyl–transferase reaction of protein synthesis, and includes, at least, three different tRNA binding sites known as the aminoacyl, peptidyl, and exit sites. The aminoacyl site or A–site accommodates the incoming aminoacyl–tRNA that is to contribute its amino acid to the growing peptide chain. Also, the A space of the A–site is important. The peptidyl site or P–site accommodates the peptidyl–tRNA complex, i.e., the tRNA with its amino acid that is part of the growing peptide chain. The exit or E–site accommodates the deacylated tRNA after it has donated its amino acid to the growing polypeptide chain.

1. Definitions

"Isomerism" means compounds that have identical molecular formulae but that differ in the nature or the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereoisomers", and stereoisomers that are non-superimposable mirror images are termed "enantiomers", or sometimes optical isomers. A carbon atom bonded to four nonidentical substituents is termed a "chiral center".

"Chiral isomer" means a compound with at least one chiral center. It has two enantiomeric forms of opposite chirality and may exist either as an individual enantiomer or as a mixture of enantiomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has 2^{n-1}enantiomeric pairs, where n is the number of chiral centers. Compounds with more than one chiral center may exist as either an individual diastereomer or as a mixture of diastereomers, termed a "diastereomeric mixture". When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that

chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog. (Cahn et al, *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn et al., *Angew. Chem.* 1966, 78, 413; Cahn and Ingold, *J. Chem. Soc.* 1951 (London), 612; Cahn et al., *Experientia* 1956, 12, 81; Cahn, J., *Chem. Educ.* 1964, 41, 116).

"Geometric Isomers" means the diastereomers that owe their existence to hindered rotation about double bonds. These configurations are differentiated in their names by the prefixes cis and trans, or Z and E, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

Further, the structures and other compounds discussed in this application include all atropic isomers thereof. "Atropic isomers" are a type of stereoisomer in which the atoms of two isomers are arranged differently in space. Atropic isomers owe their existence to a restricted rotation caused by hindrance of rotation of large groups about a central bond. Such atropic isomers typically exist as a mixture, however as a result of recent advances in chromatography techniques, it has been possible to separate mixtures of two atropic isomers in select cases.

"Tautomers" refers to compounds whose structures differ markedly in arrangement of atoms, but which exist in easy and rapid equilibrium. It is to be understood that compounds of present invention may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be within the scope of the invention, and the naming of the compounds does not exclude any tautomer form.

Some compounds of the present invention can exist in a tautomeric form which are also intended to be encompassed within the scope of the present invention.

The compounds, salts and prodrugs of the present invention can exist in several tautomeric forms, including the enol and imine form, and the keto and enamine form and geometric isomers and mixtures thereof. All such tautomeric forms are included within the scope of the present invention. Tautomers exist as mixtures of a tautomeric set in solution. In solid form, usually one tautomer predominates. Even though one tautomer may be described, the present invention includes all tautomers of the present compounds

A tautomer is one of two or more structural isomers that exist in equilibrium and are readily converted from one isomeric form to another. This reaction results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers can be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. The concept of tautomers that are interconvertable by tautomerizations is called tautomerism.

Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism, is exhibited by glucose. It arises as a result of the aldehyde group (-CHO) in a sugar chain molecule reacting with one of the hydroxy groups (-OH) in the same molecule to give it a cyclic (ring-shaped) form.

Tautomerizations are catalyzed by: Base: 1. deprotonation; 2. formation of a delocalized anion (e.g. an enolate); 3. protonation at a different position of the anion; Acid: 1. protonation; 2. formation of a delocalized cation; 3. deprotonation at a different position adjacent to the cation.

Common tautomeric pairs are: ketone - enol, amide - nitrile, lactam - lactim, amide - imidic acid tautomerism in heterocyclic rings (e.g. in the nucleobases guanine, thymine, and cytosine), amine - enamine and enamine - enamine. An example below is included for illustrative purposes, and the present invention is not limited to this example:



The terms "crystal polymorphs" or "polymorphs" or "crystal forms" means crystal structures in which a compound (or salt or solvate thereof) can crystallize in different crystal packing arrangements, all of which have the same elemental composition. Different crystal forms usually have different X-ray diffraction patterns, infrared spectral, melting points, density hardness, crystal shape, optical and electrical properties, stability and solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate. Crystal polymorphs of the compounds can be prepared by crystallization under different conditions.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom, usually a carbon, oxygen, or nitrogen atom, is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (e.g., C=C, C=N, N=N, etc.).

As used herein, the term "anomeric carbon" means the acetal carbon of a glycoside.

As used herein, the term "glycoside" is a cyclic acetal.

As used herein, "alkyl" is intended to include both branched and straight–chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example C_{1-6} alkyl is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkyl groups. Some examples of alkyl include, but are not limited to, methyl, ethyl, n–propyl, i–propyl, n–butyl, s–butyl, t–butyl, n–pentyl, s–pentyl, n–hexyl, n–heptyl, and n–octyl.

As used herein, "alkenyl" is intended to include hydrocarbon chains of either straight or branched configuration and one or more unsaturated carbon–carbon bonds that can occur in any stable point along the chain, such as ethenyl and propenyl. For example C_{2-6} alkenyl is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups.

As used herein, "alkynyl" is intended to include hydrocarbon chains of either straight or branched configuration and one or more triple carbon–carbon bonds that can occur in any stable point along the chain, such as ethynyl and propynyl. For example, C_{2-6} alkynyl is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups.

Furthermore, "alkyl", "alkenyl", and "alkynyl" are intended to include moieties which are diradicals, i.e., having two points of attachment, an example of which in the present invention is when D is selected from these chemical groups. A nonlimiting example of such an alkyl moiety that is a diradical is $-CH_2CH_2-$, i.e., a C_2 alkyl group that is covalently bonded via each terminal carbon atom to the remainder of the molecule. The alkyl diradicals are also known as "alkylenyl" radicals. The alkenyl diradicals are also known as "alkenylenyl" radicals. The alkynyl diradicals are also known as "alkynylenyl" radicals..

As used herein, "cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. C_{3-8} cycloalkyl is intended to include C_3, C_4, C_5, C_6, C_7, and C_8 cycloalkyl groups.

As used herein "counterion" is used to mean a positively or negatively charged species present in conjunction with an ion of opposite charge. A nonlimiting example of a counterion is an ion or ions present to counterbalance the charge or charges on an organic compound. Nonlimiting examples of counterions include chloride, bromide, hydroxide, acetate, sulfate, and ammonium.

As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo, and iodo substituents.

As used herein, "haloalkyl" is intended to include both branched and straight–chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ wherein v = 1 to 3 and w = 1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl.

As used herein, "alkoxy" refers to an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. C_{1-6} alkoxy, is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. C_{1-6} alkoxy, is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, and C_8 alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n–propoxy, i–propoxy, n–butoxy, s–butoxy, t–butoxy, n–pentoxy, s–pentoxy, n–heptoxy, and n–octoxy.

As used herein, "alkylthio" refers to an alkyl group as defined above with the indicated number of carbon atoms attached through a sulfur bridge. C_{1-6} alkylthio, is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkylthio groups. C_{1-6} alkylthio, is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, and C_8 alkylthio groups.

As used herein, "carbocycle" or "carbocyclic ring" is intended to mean, unless otherwise specified, any stable 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12–membered monocyclic, bicyclic or tricyclic ring, any of which can be saturated, unsaturated (including partially and fully unsaturated), or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl,

cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl. As shown above, bridged rings are also included in the definition of carbocycle (e.g., [2.2.2]bicyclooctane). A bridged ring occurs when one or more carbon atoms link two non–adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring can also be present on the bridge. Fused (e.g., naphthyl and tetrahydronaphthyl) and spiro rings are also included.

As used herein, the term "heterocycle" means, unless otherwise stated, a stable 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12–membered monocyclic, bicyclic or tricyclic ring which is saturated, unsaturated (including partially and fully unsaturated), or aromatic, and consists of carbon atoms and one or more ring heteroatoms, e.g., 1 or 1–2 or 1–3 or 1–4 or 1–5 or 1–6 heteroatoms, independently selected from nitrogen, oxygen, and sulfur, and including any bicyclic or tricyclic group in which any of the above–defined heterocyclic rings is fused or attached to a second ring (e.g., a benzene ring). The nitrogen and sulfur heteroatoms can optionally be oxidized (i.e., N→O and $S(O)_p$, wherein p = 1 or 2). When a nitrogen atom is included in the ring it is either N or NH, depending on whether or not it is attached to a double bond in the ring (i.e., a hydrogen is present if needed to maintain the tri–valency of the nitrogen atom). The nitrogen atom can be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, as defined). The heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein can be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle can optionally be quaternized. Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more atoms (i.e., C, O, N, or S) link two non–adjacent carbon or nitrogen atoms. Preferred bridges include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon–nitrogen group. When a ring is bridged, the substituents recited for the ring can also be present on the bridge. Spiro and fused rings are also included.

As used herein, the term "aromatic heterocycle" or "heteroaryl" is intended to mean a stable 5, 6, 7, 8, 9, 10, 11, or 12–membered monocyclic or bicyclic aromatic ring which consists of carbon atoms and one or more heteroatoms, e.g., 1 or 1–2 or 1–3 or 1–4 or 1–5 or 1–6 heteroatoms, independently selected from nitrogen, oxygen, and sulfur. In the case of bicyclic heterocyclic aromatic rings, only one of the two rings needs to be aromatic (e.g., 2,3–dihydroindole), though both can be (e.g., quinoline). The second ring can also be fused or bridged as defined above for heterocycles. The nitrogen atom can be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, as defined). The nitrogen and sulfur heteroatoms can optionally be oxidized (i.e., N→O and $S(O)_p$, wherein p = 1 or 2). In certain compounds, the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azabicyclooctanonyl, azepanyl, azetidinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, benzodioxoly, benzooxadiazoly, carbazolyl, 4a*H*–carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, cycloheptyl, decahydroquinolinyl, dihydrobenzodioxinyl, 2*H*,6*H*–1,5,2–dithiazinyl, dihydrofuro[2,3–*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolidinylimine, imidazolinyl, imidazolyl, imidazolonyl, 1*H*–indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H–indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, methylbenztriazolyl, methylfuranyl, methylimidazolyl, methylthiazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3–oxadiazolyl, 1,2,4–oxadiazolyl, 1,2,5–oxadiazolyl, 1,3,4–oxadiazolyl, oxazolidinyl, oxazolidinonyl, oxazolyl, oxindolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperazinonyl, piperidinyl, piperidenyl, piperidonyl, 4–piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyridinonyl, pyridyl, pyrimidinyl, pyrroldionyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H–pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*–quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl,

tetrahydroquinolinyl, tetrazolyl, 6*H*–1,2,5–thiadiazinyl, 1,2,3–thiadiazolyl, 1,2,4–thiadiazolyl, 1,2,5–thiadiazolyl, 1,3,4–thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, thiomorpholinyldioxidyl, triazinyl, triazolopyrimidinyl, 1,2,3–triazolyl, 1,2,4–triazolyl, 1,2,5–triazolyl, 1,3,4–triazolyl, and xanthenyl.

As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non–toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non–toxic inorganic or organic acids. For example, such conventional non–toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2–acetoxybenzoic, 2–hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodide, hydroxymalcic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, and toluene sulfonic.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non–aqueous media like ether, ethyl

acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, USA, p. 1445 (1990).

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention can be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

As used herein, "stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

As used herein, the term "patient", as used herein, means the human or animal (in the case of an animal, more typically a mammal) subject that would be subjected to a surgical or invasive medical procedure. Such patient or subject could be considered to be in need of the methods of reducing the risk of or preventing the infection due to a surgical procedure or an invasive medical procedure. Such patient or subject can also be considered to be in need of peri–operative prophylaxis.

As used herein, the term "treating" means to provide a therapeutic intervention to cure or ameliorate an infection.

As used herein, the term "preventing", as used herein means, to completely or almost completely stop an infection from occurring, for example when the patient or subject is

predisposed to an infection or at risk of contracting an infection. Preventing can also include inhibiting, i.e. arresting the development, of an infection.

As used herein, the term "reducing the risk of", as used herein, means to lower the likelihood or probability of an infection occurring, for example when the patient or subject is predisposed to an infection or at risk of contracting an infection.

As used herein, "unsaturated" refers to compounds having at least one degree of unsaturation (*e.g.*, at least one multiple bond) and includes partially and fully unsaturated compounds.

As used herein, the term "effective amount" refers to an amount of a compound, or a combination of compounds, of the present invention effective when administered alone or in combination as an antimicrobial agent. For example, an effective amount refers to an amount of the compound present in a composition, a formulation or on a medical device given to a recipient patient or subject sufficient to elicit biological activity, for example, anti–infective activity, such as e.g., anti–microbial activity, anti–bacterial activity, anti–fungal activity, anti–viral activity, or anti–parasitic activity.

The term "prophylactically effective amount" means an effective amount of a compound or compounds, of the present invention that is administered to prevent or reduce the risk of an infection due to a surgical procedure or an invasive medical procedure.

It is to be further understood that the representations for "Hydrogen Bond Acceptor – Hydrogen Bond Acceptor – Hydrogen Bond Donor" and "Hydrogen Bond Acceptor – Hydrogen Bond Acceptor – Hydrogen Bond Acceptor" are meant to indicate the relative orientation of the hydrogen bond acceptors and donor and not meant to limit that such groups are directly connected together as it is contemplated that additional atoms or groups of atoms can be included between such groups.

In the specification, the singular forms also include the plural, unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In the case of conflict, the present specification will control. As used herein, "mammal" refers to human and non–human patients.

As used herein, the term "therapeutically effective amount" refers to a compound, or a combination of compounds, of the present invention present in or on a recipient in an amount

sufficient to elicit biological activity, for example, anti–microbial activity, anti–fungal activity, anti–viral activity, anti–parasitic activity, anti–diarrheal activity, and/or anti–proliferative activity. The combination of compounds is preferably a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme Regul.* vol. 22, pp. 27–55 (1984), occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub–optimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased anti–proliferative and/or anti–infective effect, or some other beneficial effect of the combination compared with the individual components.

As used herein, the term "RNA microhelix binding site" refers to the ribofunctional locus of the large ribosomal subunit occupied by the RNA microhelix of Formula III. The RNA microhelix binding site defines at least a portion of or overlaps with the E–site.

As used herein, the term "A–site" refers to the ribofunctional locus occupied by an aminoacyl–tRNA molecule immediately prior to its participation in the peptide–bond forming reaction.

As used herein, the term "E–site" refers to the ribofunctional locus occupied by a deacylated tRNA molecule following its participation in the peptide–bond forming reaction.

As used herein, the term "P–site" refers to the ribofunctional locus occupied by a peptidyl–tRNA at the time it participates in the peptide–bond forming reaction.

As used herein, the term "A–space" refers to the portion of the A–site within the peptidyl transferase center in which the amino acid portion of the aminoacylated t–RNA binds, or alternatively the portion of the A–site in which the oxazolidinone ring of linezolid binds.

As used herein and in reference to a ribosome or ribosomal subunit, the terms "a portion of" or "a portion of the three–dimensional structure of" are understood to mean a portion of the three–dimensional structure of a ribosome or ribosomal subunit, including charge distribution and hydrophilicity/hydrophobicity characteristics, formed by at least three, more preferably at least three to ten, and most preferably at least ten amino acid residues and/or nucleotide residues of the ribosome or ribosomal subunit. The residues forming such a portion can be, for example, (i) contiguous residues based upon, for example, a primary

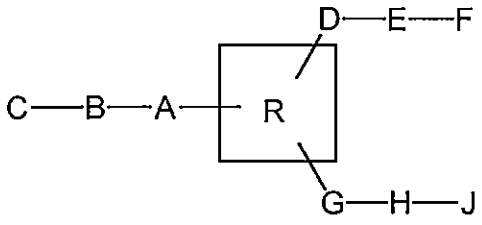
sequence of a ribosomal RNA or ribosomal protein, (ii) residues which form a contiguous portion of the three–dimensional structure of the ribosome or ribosomal subunit, or (c) a combination thereof. As used herein and in reference to the RNA microhelix, the terms "a portion of" or "a portion of the three–dimensional structure of" are understood to mean a portion of the three–dimensional structure of RNA microhelix, including charge distribution and hydrophilicity/hydrophobicity characteristics, formed by at least three, more preferably at least three to ten atoms of one or more core residues of Formula III. The atoms forming such a portion can be, for example, (i) solvent inaccessible atoms buried within the core of the RNA microhelix, (ii) solvent accessible atoms of the RNA microhelix, or (iii) a combination thereof.

All percentages and ratios used herein, unless otherwise indicated, are by weight.

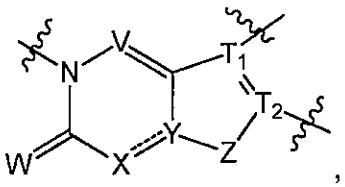
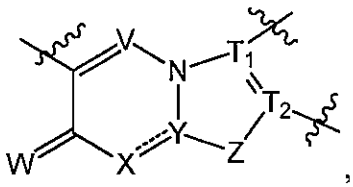
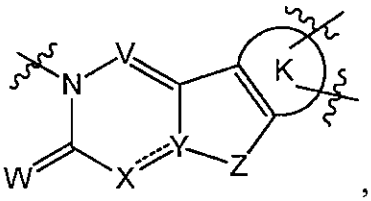
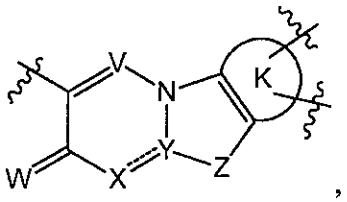
Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes are described as having, including, or comprising specific process steps, it is contemplated that compositions of the present invention also consist essentially of, or consist of, the recited components, and that the processes of the present invention also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions are immaterial so long as the invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

2. Compounds of the Invention

The present invention provides compounds having the structure:



wherein R is a chemical moiety selected from:


,

,

, or

,

wherein Ⓚ represents a fused 5 to 7 member saturated, unsaturated, or aromatic carbocyclic or heterocyclic ring system,

wherein T^1 is a carbon atom or N, such that when T^1 is N, –D–E–F is absent,

wherein T^2 is a carbon atom or N, such that when T^2 is N, –G–H–J is absent,

wherein both T^1 and T^2 are not both simultaneously N,

wherein V is independently selected from $-CR^{4a}-$ or –N–,

W is O, NR^1, NOR^1, or S, alternatively W= is selected from the combination of HO– and H– both attached to the same carbon atom or the combination of (C_{1-8} alkyl)O– and H– both attached to the same carbon atom;

X---Y represents a single bond or a double bond such that when X---Y is a single bond, X is selected from O, NR^2, and $S(O)_n$ and Y is C–R^3, and when X---Y is a double bond, X is N and Y is a carbon atom,

Z is selected from the group consisting of O, NR^4, $S(O)_n$, or NH,

R^1 is selected from H and C_{1-8} alkyl,

R^2 is selected from H and C_{1-8} alkyl,

R^3 is selected from H and C_{1-8} alkyl,

R^4 is selected from H and C_{1-8} alkyl,

R^{4a} is selected from H and C_{1-8} alkyl,

n is 0, 1, or 2,

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

In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein [R] further comprises a hydrogen bond donor moiety or an additional hydrogen bond acceptor moiety.

In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein [R] is a chemical moiety comprising at least two hydrogen bond acceptor moieties and at least one hydrogen bond donor moiety.

In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein the hydrogen bond acceptor moieties and hydrogen bond donor moieties are in the orientation of

Hydrogen Bond Acceptor – Hydrogen Bond Acceptor – Hydrogen Bond Donor.

As used above the term "in the orientation of" does not mean that the hydrogen bond donor or acceptor moieties are necessarily directly connected together as there can be other intervening atoms or groups of atoms in between the hydrogen bond donor or acceptor moieties.

In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein the hydrogen bond acceptor moieties are within 5 Å of each other and the hydrogen bond donor moiety is within 5 Å of a hydrogen bond acceptor moiety.

In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein the hydrogen bond acceptor moieties are within 3 Å of each other and the hydrogen bond donor moiety is within 3 Å of a hydrogen bond acceptor moiety.

In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein the hydrogen bond acceptor moieties are comprised within a ring structure, wherein said ring structure is a single ring structure or a fused multiple ring structure.

In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein [R] is a chemical moiety comprising at least three hydrogen bond acceptor moieties.

In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein the hydrogen bond acceptor moieties are in the orientation of

Hydrogen Bond Acceptor – Hydrogen Bond Acceptor – Hydrogen Bond Acceptor.

As used above the term "in the orientation of" does not mean that the hydrogen bond donor or acceptor moieties are necessarily directly connected together as there can be other intervening atoms or groups of atoms in between the hydrogen bond acceptor moieties.

In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein each hydrogen bond acceptor moiety is within about 5 Å of at least one other hydrogen bond acceptor moiety.

In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein each hydrogen bond acceptor moiety is within about 3 Å of at least one other hydrogen bond acceptor moiety.

In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein at least two of the hydrogen bond acceptor moieties are comprised within a ring structure, wherein said ring structure is a single ring structure or a fused multiple ring structure.

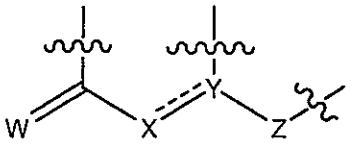
In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein said hydrogen bond acceptor moieties are independently selected from the group consisting of a carbonyl group, a thiocarbonyl group, an imine group, an alkyl substituted imine group, a sulfoxide group, a sulfone group, an oxime group, an alkyl substituted oxime group, a hydrazone group, a monoalkyl or dialkyl substituted hydrazone group, an oxygen ether (–O–) group, a sulfide, also known as a thioether group (–S–), a hydroxy group, an alkoxy group, an amino group, a monoalkyl or dialkyl substituted amino group, and a nitro group.

In some embodiments, the present invention relates to a compound of a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein said hydrogen bond donor moiety is selected from the group consisting of a hydroxy group, a thiol group, an amino group, and a monosubstituted amino group.

In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein



comprises the structural moiety



wherein W is O, NR^1, NOR^1, or S, alternatively W= is selected from the combination of HO– and H– both attached to the same carbon atom or the combination of (C_{1-8} alkyl)O– and H– both attached to the same carbon atom;

X---Y represents a single bond or a double bond such that when X---Y is a single bond, X is selected from O, NR^2, and $S(O)_n$ and Y is C–R^3, and when X---Y is a double bond, X is N and Y is a carbon atom,

Z is selected from the group consisting of O, NR^4, or $S(O)_n$,

R^1 is selected from H and C_{1-8} alkyl,

R^2 is selected from H and C_{1-8} alkyl,

R^3 is selected from H and C_{1-8} alkyl,

R^4 is selected from H and C_{1-8} alkyl,

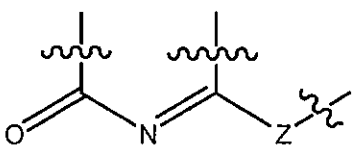
and n is 0, 1, or 2.

In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein W is O, NR^1, NOR^1, or S; wherein R^4 is selected from hydrogen and C_{1-6} alkyl.

In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein



comprises the structural moiety



wherein Z is selected from the group consisting of O, NR^4, or $S(O)_n$;

R^4 is selected from hydrogen and C_{1-6} alkyl,

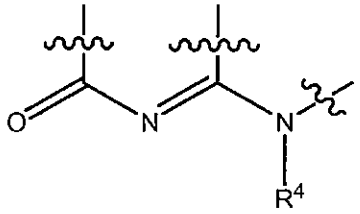
and

n is 0, 1, and 2.

In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein

R

comprises the structural moiety



wherein R^4 is selected from H and C_{1-6} alkyl.

In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein R^4 is hydrogen.

In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein

R

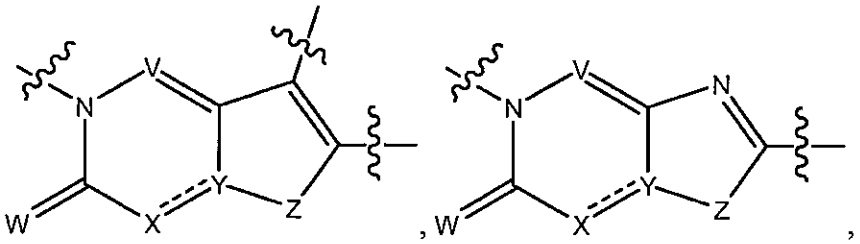
comprises a pyrrolocytosine moiety or a derivative thereof.

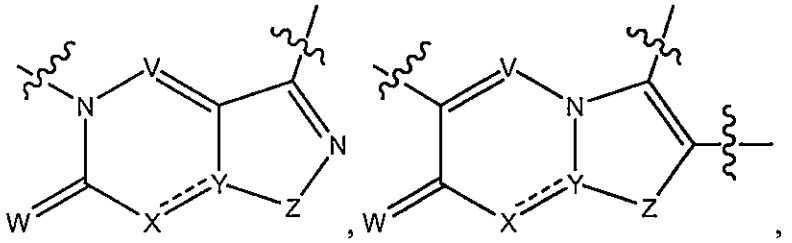
In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein R^4 is hydrogen.

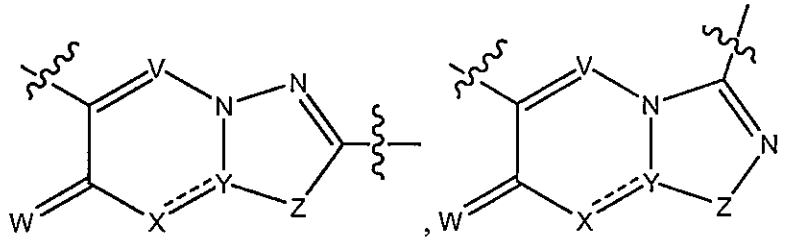
In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein

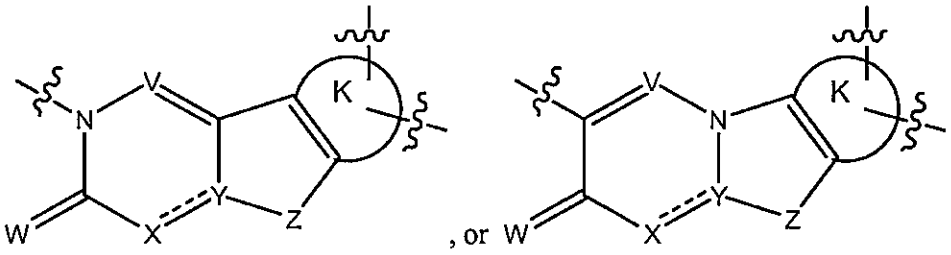
R

comprises the structural moiety









wherein Ⓚ represents a fused 5 to 7 member saturated, unsaturated, or aromatic carbocyclic or heterocyclic ring system,

wherein V is independently selected from $-CR^{4a}-$ or $-N-$,

W is O, NR^1, NOR^1, or S, alternatively W= is selected from the combination of HO– and H– both attached to the same carbon atom or the combination of (C_{1-8} alkyl)O– and H– both attached to the same carbon atom;

X---Y represents a single bond or a double bond such that when X---Y is a single bond, X is selected from O, NR^2, and $S(O)_n$ and Y is C–R^3, and when X---Y is a double bond, X is N and Y is a carbon atom,

Z is selected from the group consisting of O, NR^4, $S(O)_n$, or NH,

R^1 is selected from H and C_{1-8} alkyl,

R^2 is selected from H and C_{1-8} alkyl,

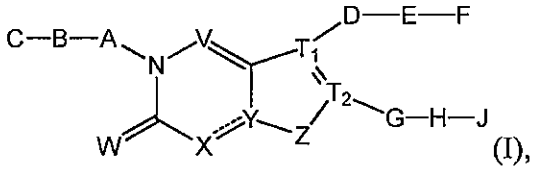
R^3 is selected from H and C_{1-8} alkyl,

R^4 is selected from H and C_{1-8} alkyl,

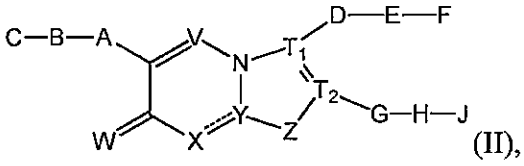
R^{4a} is selected from H and C_{1-8} alkyl,

n is 0, 1, or 2.

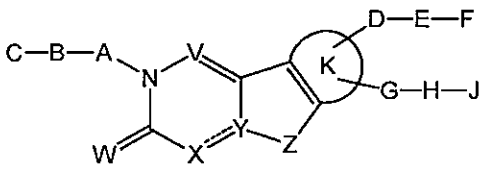
In some embodiments, the present invention relates to a compound having the formula:



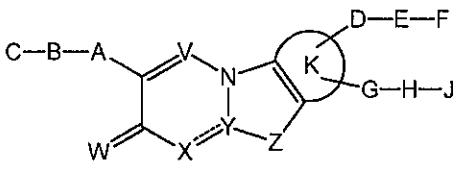
(I),



(II),



(III), or



(IV),

wherein Ⓚ represents a fused 5 to 7 member saturated, unsaturated, or aromatic carbocyclic or heterocyclic ring system,

wherein T^1 is a carbon atom or N, such that when T^1 is N, –D–E–F is absent,

wherein T^2 is a carbon atom or N, such that when T^2 is N, –G–H–J is absent,

wherein both T^1 and T^2 are not both simultaneously N,

wherein V is independently selected from $-CR^{4a}-$ or –N–,

W is O, NR^1, NOR^1, or S, alternatively W= is selected from the combination of HO– and H– both attached to the same carbon atom or the combination of (C_{1-8} alkyl)O– and H– both attached to the same carbon atom;

X---Y represents a single bond or a double bond such that when X---Y is a single bond, X is selected from O, NR^2, and $S(O)_n$ and Y is C–R^3, and when X---Y is a double bond, X is N and Y is a carbon atom,

Z is selected from the group consisting of O, NR^4, $S(O)_n$, or NH,

R^1 is selected from H and C_{1-8} alkyl,

R^2 is selected from H and C_{1-8} alkyl,

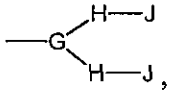
R^3 is selected from H and C_{1-8} alkyl,

R^4 is selected from H and C_{1-8} alkyl,

R^{4a} is selected from H and C_{1-8} alkyl,

n is 0, 1, or 2,

alternatively –G–H–J is selected from



wherein each H and J are independently selected,

C–B–A–, –D–E–F, and –G–H–J are chemical moieties, wherein

A, D and G are independently selected from the group consisting of:

(a) a single bond, (b) –(C_{1-8} alkyl)– , (c) –(C_{2-8} alkenyl)–, (d) –(C_{2-8} alkynyl)–, wherein

i) 0–4 carbon atoms in any of (b)–(d) immediately above optionally is replaced by a moiety selected from the group consisting of –O–, $S(O)_p$, $–NR^6–$, –(C=O)–, $–S(O)_pNR^6–$, $–NR^6S(O)_p–$, and $–NR^6S(O)_pNR^6–$,

ii) any of (b)–(d) immediately above optionally is substituted with one or more R^5 groups, and

iii) any of (b)–(d) immediately above optionally is substituted with –(C_{1-8} alkyl)–R^5 groups;

(e) –O–, (f) $–NR^6–$, (g) $–S(O)_p–$, (h) –C(O)–, (i) –C(O)O–, (j) –OC(O)–, k) –OC(O)O–, (l) $–C(O)NR^6–$, (m) $–NR^6CO–$, (n) $–NR^6C(O)NR^6–$, (o) $–C(=NR^6)–$, (p) $–C(=NR^6)O–$, (q) $–OC(=NR^6)–$, (r) $–C(=NR^6)NR^6–$, (s) $–NR^6C(=NR^6)–$, (t) –C(=S)–, (u) $–C(=S)NR^6–$, (v) $–NR^6C(=S)–$, (w) –C(O)S–, (x) –SC(O)–, (y) –OC(=S)–, (z) –C(=S)O–, (aa) $–NR^6(CNR^6)NR^6–$, (bb) $–CR^6R^6C(O)–$, (cc) $–C(O)NR^6(CR^6R^6)_t–$, (dd)

a 3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

(ee) a 3–14 member saturated, unsaturated, or aromatic carbocycle, and

(ff) $-(CR^6R^6)_t-$,

wherein (dd) or (ee) is optionally substituted with one or more R^5 groups;

B, E, and H are independently selected from the group consisting of:

(a) a single bond,

(b) a 3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

(c) a 3–14 member saturated, unsaturated, or aromatic carbocycle,

wherein (b) or (c) is optionally substituted with one or more R^5 groups;

(d) $-(C_{1-8}$ alkyl)–, (e) $-(C_{2-8}$ alkenyl)–, (f) $-(C_{2-8}$ alkynyl)–, wherein

i) 0–4 carbon atoms in any of (d)–(f) immediately above optionally is replaced by a moiety selected from the group consisting of –O–, $-S(O)_p-$, $-NR^6-$, $-(C=O)-$, $-C(=NR^6)-$, $-S(O)_pNR^6-$, $-NR^6S(O)_p-$, and $-NR^6S(O)_pNR^6-$,

ii) any of (d)–(f) immediately above optionally is substituted with one or more R^5 groups, and

iii) any of (d)–(f) immediately above optionally is substituted with $-(C_{1-8}$ alkyl)–R^5 groups;

and (g) $-(CR^6R^6)_t-$,

C, F, and J are independently selected from the group consisting of:

(a) hydrogen, (c) F, (d) Cl, (e) Br, (f) I, (g) $-CF_3$, (h) –CN, (i) $-N_3$ (j) $-NO_2$, (k) $-NR^6(CR^6R^6)_tR^8$, (l) $-OR^8$, (m) $-S(O)_p(CR^6R^6)_tR^8$, (n) $-C(O)(CR^6R^6)_tR^8$, (o) $-OC(O)(CR^6R^6)_tR^8$, (p) $-SC(O)(CR^6R^6)_tR^8$, (q) $-C(O)O(CR^6R^6)_tR^8$, (r) $-NR^6C(O)(CR^6R^6)_tR^8$, (s) $-C(O)NR^6(CR^6R^6)_tR^8$, (t) $-C(=NR^6)(CR^6R^6)_tR^8$, (u) $-C(=NNR^6R^6)(CR^6R^6)_tR^8$, (v) $-C(=NNR^6C(O)R^6)(CR^6R^6)_tR^8$, (w) $-C(=NOR^8)(CR^6R^6)_tR^8$, (x) $-NR^6C(O)O(CR^6R^6)_tR^8$, (y) $-OC(O)NR^6(CR^6R^6)_tR^8$, (z) $-NR^6C(O)NR^6(CR^6R^6)_tR^8$, (aa) $-NR^6S(O)_p(CR^6R^6)_tR^8$, (bb) $-S(O)_pNR^6(CR^6R^6)_tR^8$,

(cc) $-NR^6S(O)_pNR^6(CR^6R^6)_tR^8$, (dd) $-NR^6R^8$, (ee) $-NR^6(CR^6R^6)R^8$, (ff) –OH, (gg) – NR^8R^8, (hh) $-OCH_3$, (ii) $-S(O)_pR^8$, (jj) $-NC(O)R^8$, (kk) $-NR^6C(NR^6)NR^6R^8$, (ll) a C_{1-8} alkyl group, (mm) a C_{2-8} alkenyl group, (nn) a C_{2-8}alkynyl group, (oo) a 3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (pp) a 3–14 member saturated, unsaturated, or aromatic carbocycle, (qq) – $(CR^6R^6)_tNR^6(CR^6R^6)_tR^8$, (rr) $-N[(CR^6R^6)_tR^8][C=O(CR^6R^6)_tR^8]$, (ss) – $(CR^6R^6)_tN[(CR^6R^6)_tR^8][(CR^6R^6)_tR^8]$, (tt) $-(CR^6R^6)_tNR^6(C=O)(CR^6R^6)_tR^8$, (uu) – haloalkyl, (vv) $-C(O)(CR^6)[(CR^6R^6)_tR^8]R^8$, (ww) $-(CR^6R^6)_tC(O)NR^8R^8$, (xx) – $(CR^6R^6)_tC(O)O(CR^6R^6)_tR^8$, (yy) $-NR^6C(O)CR^8R^8R^8$, (zz) $-N[(CR^6R^6)_tR^8]C(O)R^8$, and (aaa) $-S(O)_pNR^8R^8$;

wherein (ll) through (pp) is optionally substituted with one or more R^7 groups;

R^5 is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) – NO_2, (j) $-NR^6R^6$, (k) $-OR^8$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C_{1-8}$ alkyl, (n) $-C_{1-8}$ alkenyl, (o) – C_{1-8} alkynyl, (p) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (q) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (r) –haloalkyl, (s) $-SR^6$, (t) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and (u) –3–14 member saturated, unsaturated, or aromatic carbocycle; alternatively, two R^5 groups are taken together to form a carbocycle

wherein (m) through (r) and (t) through (u) is optionally substituted with one or more R^8;

R^6 is selected from (a) hydrogen, (b) $-C_{1-8}$ alkyl or alternatively two R^6 groups are taken together to form a carbocycle, (c) –haloalkyl, (d) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and (e) –3–14 member saturated, unsaturated, or aromatic carbocycle;

wherein (b) through (c) is optionally substituted with one or more R^8;

R^7 is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) – NO_2, (j) $-NR^6R^6$, (k) $-OR^6$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C_{1-8}$ alkyl, (n) $-C_{1-8}$ alkenyl, (o) – C_{1-8} alkynyl, (p) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (q) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (r) –haloalkyl, (s) $-NR^6R^8$, (t) $-OR^8$, (u) $-(CR^6R^6)_tNR^6R^8$, (v) $-CR^6R^8R^8$, (w) $-SR^6$, (x) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (y) –3–14 member saturated, unsaturated, or aromatic carbocycle, (z) $-(CR^6R^6)_tC(O)NR^8R^8$, (aa) – $S(O)_pR^8$, (bb) $-NR^6C(O)NR^6R^6$, (cc) $-NR^6C(O)R^6$, and (dd) $-C(=NR^6)NR^6R^6$;

wherein (m) through (q) and (x) through (y) are optionally substituted with one or more R^9;

R^8 is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) – NO_2, (j) $-NR^6R^9$, (k) $-OR^9$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C_{1-8}$ alkyl, (n) $-C_{1-8}$ alkenyl, (o) – C_{1-8} alkynyl, (p) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (q) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (r) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (s) –3–14 member saturated, unsaturated, or aromatic carbocycle, (t) –haloalkyl, (u) $-C(O)(CR^6R^6)_tR^9$, (v) $-SR^6$, (w) $-OC(O)(CR^6R^6)_tR^9$, (x) $-NR^6C(O)NR^6R^9$, (y)–$NR^6C(O)R^9$, (z) – $NR^6(CNR^9)(NR^6R^6)$, (aa) $-ONR^6(CNR^6)NR^6R^6$, (bb) $-C(=NR^9)NR^6R^6$, (cc) $-S(O)_pR^9$, (dd) – $(CR^6R^6)_tC(O)NR^6R^9$, (ee) $-(CR^6R^6)_tOR^9$, and (ff) $-(CR^6R^6)_tNR^6R^9$;

wherein (m) through (s) is optionally substituted with one or more R^9;

R^9 is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) – NO_2, (j) $-NR^6R^{10}$, (k) $-OR^6$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C(O)(CR^6R^6)_tNR^6R^6$, (n) $-C_{1-8}$ alkyl, (o) $-C_{1-8}$ alkenyl, (p) $-C_{1-8}$ alkynyl, (q) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting

of nitrogen, oxygen, and sulfur, (r) –3–14 member saturated, unsaturated, or aromatic carbocycle, (s) –haloalkyl, (t) $-(CR^6R^6)_tOR^6$, (u) $-O(CR^6R^6)_tNR^6R^{10}$, (v) $-C(O)R^6$, (w) $-SR^6$, (x) $-C(O)OR^{10}$, (y) $-S(O)_pR^6$, (z) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (aa) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (bb) $-O(CR^6R^6)_tOR^6$, (cc) $-C(=NR^6)NR^6R^6$, (dd) $-ONR^6R^6$, (ee) $-NR^6C(O)NR^6R^6$, (ff) $-O(CR^6R^6)_tOR^6$, (gg) $-NR^6C(O)R^6$, and (hh) $-(CR^6R^6)_tNR^6R^{10}$;

wherein (n) through (r) and (z) through (aa) is optionally substituted with one or more R^{10};

R^{10} is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) $-NO_2$, (j) $-NR^6R^6$, (k) $-OR^6$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C(O)(CR^6R^6)_tNR^6R^6$, (n) $-C_{1-8}$ alkyl, (o) $-C_{1-8}$ alkenyl, (p) $-C_{1-8}$ alkynyl, (q) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (r) –3–14 member saturated, unsaturated, or aromatic carbocycle, (s) –haloalkyl, (t) $-(CR^6R^6)_tOR^6$, (u) $-O(CR^6R^6)_tNR^6R^6$, (v) $-C(O)R^6$, (w) $-SR^6$, (x) $-C(O)OR^6$, (y) $-S(O)_pR^6$, (z) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (aa) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (bb) $-O(CR^6R^6)_tOR^6$, (cc) $-C(=NR^6)NR^6R^6$, (dd) $-ONR^6R^6$, (ee) $-NR^6C(O)NR^6R^6$, (ff) $-O(CR^6R^6)_tOR^6$, (gg) $-NR^6C(O)R^6$, and (hh) $-(CR^6R^6)_tNR^6R^6$;

optionally, wherein either the group –D–E–F or the group –G–H–J is absent, but both –D–E–F and –G–H–J are not simultaneously absent;

p is 0, 1, or 2, and

t is 0, 1, 2, or 3,

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

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, where A is:

(a) a 3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

(b) a 3–14 member saturated, unsaturated, or aromatic carbocycle, or

(c) a single bond,

where (a) or (b) is optionally substituted with one or more R^5 groups.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, where B is (a) –(C_{1-8} alkyl)–, (b) –(C_{2-8} alkenyl)–, (c) –(C_{2-8} alkynyl)-, or (d) a single bond, where

i) 0–4 carbon atoms in any of (a)–(c) immediately above optionally is replaced by a moiety selected from the group consisting of –O–, –$S(O)_p$–, –NR^6–, –(C=O)–, –C(=NR^6)–, –$S(O)_pNR^6$–, and –$NR^6S(O)_pNR^6$–,

ii) any of (a)–(c) immediately above optionally is substituted with one or more R^5 groups, and/or

iii) any of (a)–(c) immediately above optionally is substituted with –(C_{1-8} alkyl)–R^5 groups.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, where C is (a) NH_2, (b) –NHC(=NH)NH_2 or (c) hydrogen.

The invention relates to a pharmaceutically acceptable salt, ester, tautomer, or prodrug of a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, wherein

A is

(a) a 4–7 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

(b) a 4–7 member saturated, unsaturated, or aromatic carbocycle, or

(c) a single bond,

wherein (a) or (b) is optionally substituted with one or more R^5 groups.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, wherein A is azepanyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,

phenyl, pyridyl, cyclohexenyl, cyclohexadienyl, dihydropyridyl, furanyl, tetrahydrofuranyl, tetrahydropyridyl, azetidinyl, pyrrolidinyl, piperidinyl, or piperidenyl;
wherein A optionally is substituted with one or more R^5 groups.

Alternatively, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, wherein A is a single bond.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, wherein B is $-(C_{1-8}$ alkyl$)-$, where

i) 0–4 carbon atoms optionally is replaced by a moiety selected from –O–, $-S(O)_p-$, $-NR^6-$, –(C=O)– , $-S(O)_pNR^6-$, or $-NR^6S(O)_pNR^6-$,

ii) (a)B optionally is substituted with one or more R^5 groups, and/or

iii) B optionally is substituted with $-(C_{1-8}$ alkyl$)-R^5$ groups.

Alternatively, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, wherein B is a single bond.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, wherein C is $-NHC(=NH)NH_2$.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, wherein the group D-E-F represents hydrogen.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, wherein G is

(a) a 3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

(b) a 3–14 member saturated, unsaturated, or aromatic carbocycle, or

(c) a single bond;

wherein (a) or (b) is optionally substituted with one or more R^5 groups.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, wherein G is s

(a) a 4–7 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

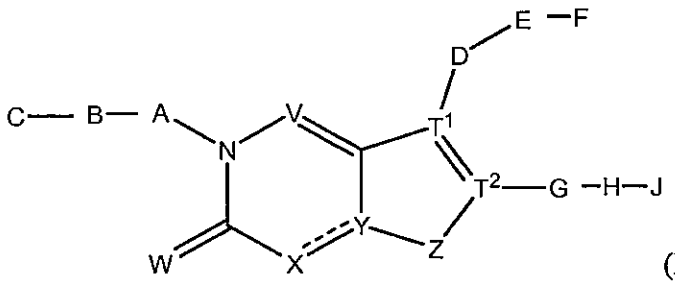
(b) a 4–7 member saturated, unsaturated, or aromatic carbocycle, or

(c) a single bond;

wherein (a) or (b) is optionally substituted with one or more R^5 groups.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, wherein G is azepanyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl, pyridyl, cyclohexenyl, cyclohexadienyl, dihydropyridyl, furanyl, tetrahydrofuranyl, tetrahydropyridyl, azetidinyl, pyrrolidinyl, piperidinyl, piperidenyl, or a single bond.

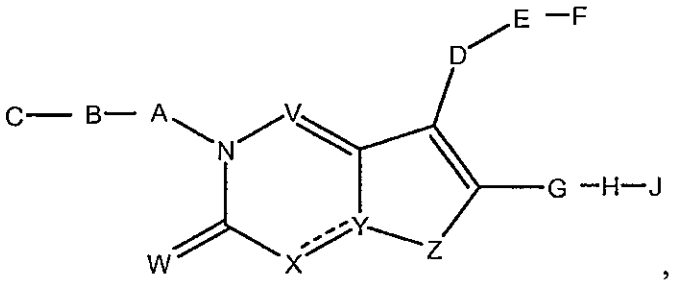
In some embodiments, the present invention relates to a compound having the formula :



(I)

wherein C–B–A–, –D–E–F, –G–H–J, W, X, Y, Z, V, T^1, and T^2 are defined above, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

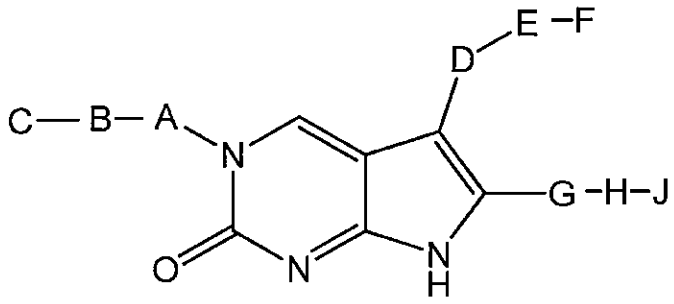
In some embodiments, the present invention relates to a compound having the formula:



,

wherein C–B–A–, –D–E–F, –G–H–J, W, X, Y, Z, and V are as defined above, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

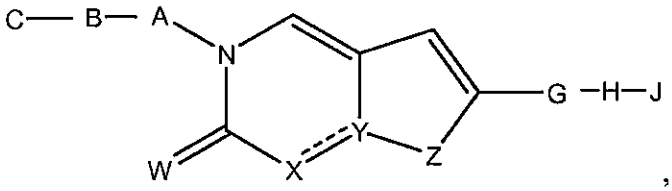
In some embodiments, the present invention relates to a compound having the formula:



(Ia),

wherein C–B–A–, –D–E–F, and –G–H–J are defined above, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

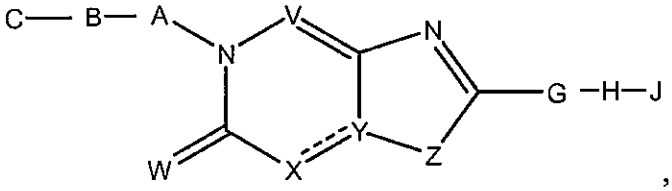
In some embodiments, the present invention relates to a compound having the formula:



,

wherein C–B–A–,–G–H–J, W, X, Y, and Z are as defined above, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

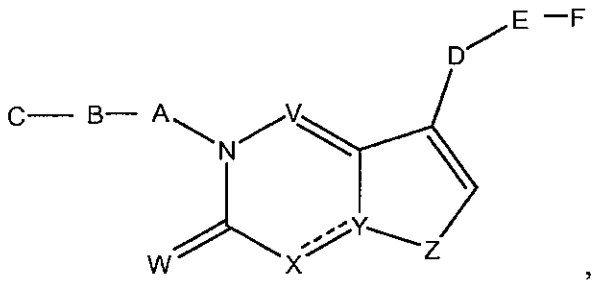
In some embodiments, the present invention relates to a compound having the formula:



,

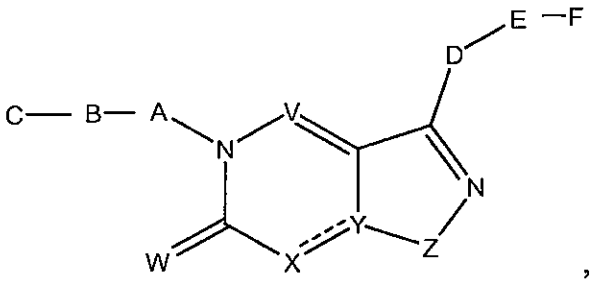
wherein C–B–A–,–G–H–J, W, X, Y, Z, and V are defined as in formula I, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

In some embodiments, the present invention relates to a compound having the formula:



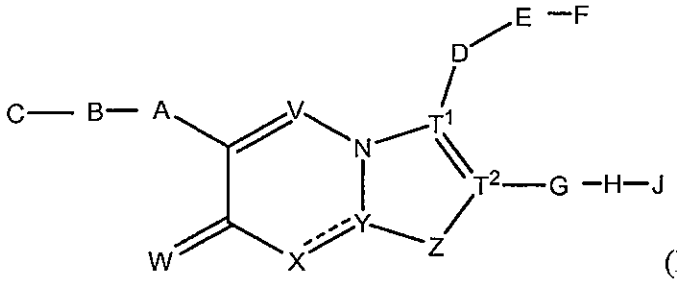
wherein C–B–A–, –D–E–F, W, X, Y, Z, and V are defined as in formula I, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

In some embodiments, the present invention relates to a compound having the formula:



wherein C–B–A–, –D–E–F, –G–H–J, W, X, Y, Z, and V are defined as in formula I, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

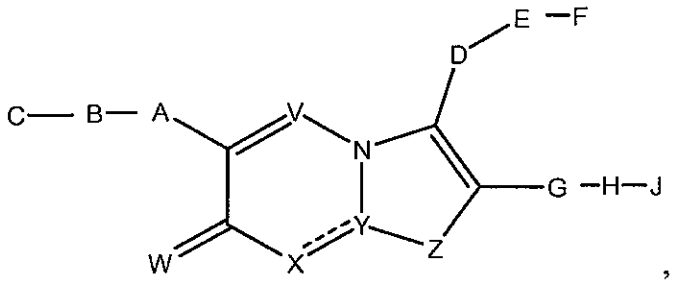
In some embodiments, the present invention relates to a compound having the formula:



(II),

wherein C–B–A–, –D–E–F, –G–H–J, W, X, Y, Z, V, T^1, and T^2 are defined as in formula II above, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

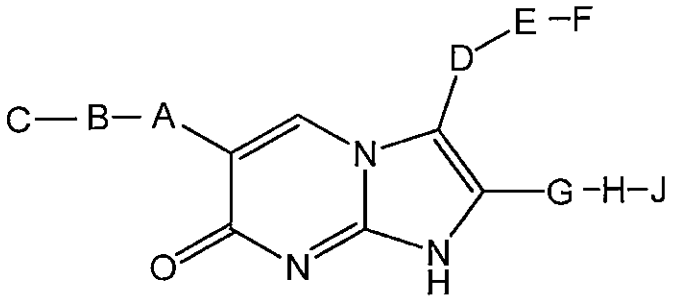
In some embodiments, the present invention relates to a compound having the formula:



,

wherein C–B–A–, –D–E–F, –G–H–J, W, X, Y, Z, and V are defined as in formula II, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

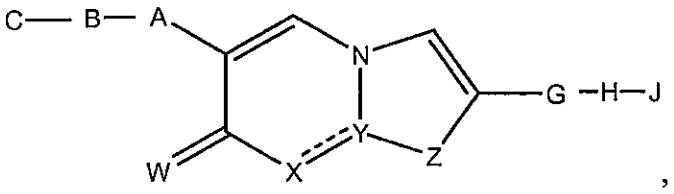
In some embodiments, the present invention relates to a compound having the formula:



(IIa)

wherein C–B–A–, –D–E–F, and –G–H–J are defined above, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

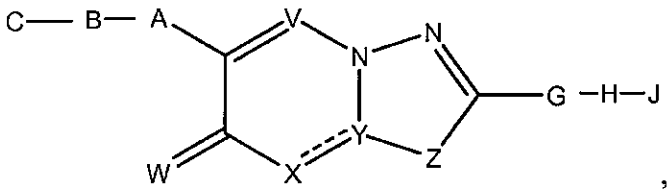
In some embodiments, the present invention relates to a compound having the formula:



,

wherein C–B–A–,–G–H–J, W, X, Y, and Z are defined as in formula II, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

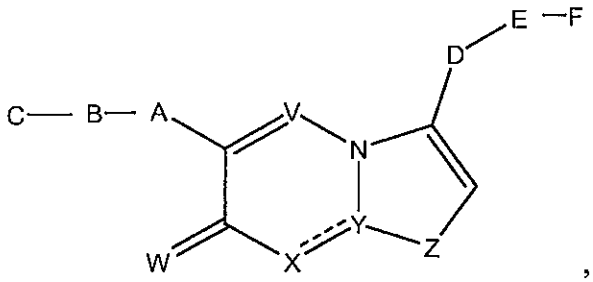
In some embodiments, the present invention relates to a compound having the formula:



,

wherein C–B–A–,–G–H–J, W, X, Y, Z, and V are defined as in formula II, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

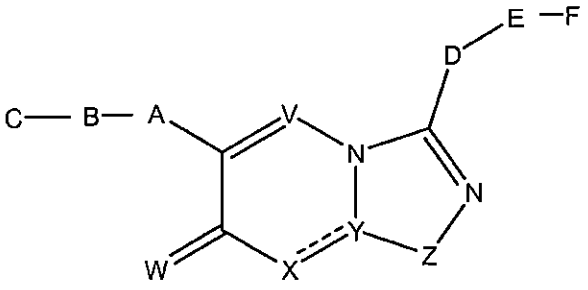
In some embodiments, the present invention relates to a compound having the formula:



,

wherein C–B–A–, –D–E–F, W, X, Y, Z, and V are defined as in formula II, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

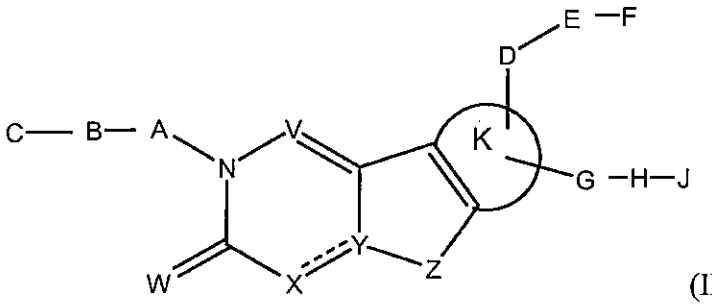
In some embodiments, the present invention relates to a compound having the formula:



,

wherein C–B–A–, –D–E–F, W, X, Y, Z, and V are defined as in formula II, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

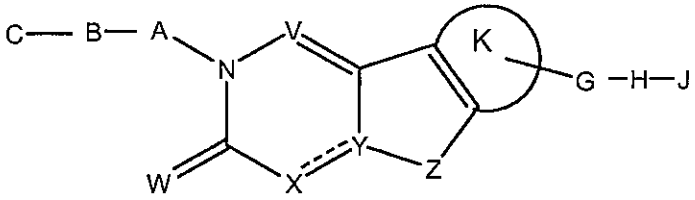
In some embodiments, the present invention relates to a compound having the formula:



(III),

wherein C–B–A–, –D–E–F, –G–H–J, W, X, Y, Z, V and K are defined as in formula III, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

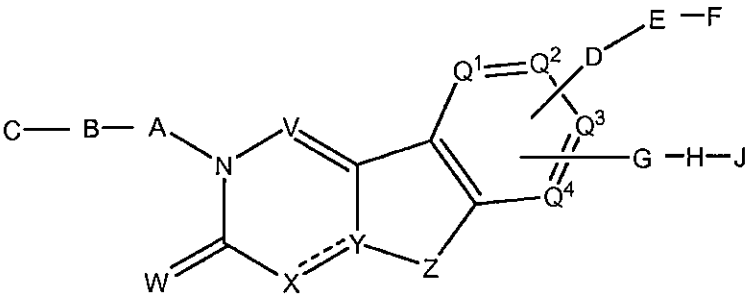
In some embodiments, the present invention relates to a compound having the formula:



wherein C–B–A–,–G–H–J, W, X, Y, Z, V and K are defined as in formula III, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

In some embodiments, the present invention relates to a compound or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein Ⓚ represents a fused six member saturated, unsaturated or aromatic carbocyclic or heterocyclic ring system.

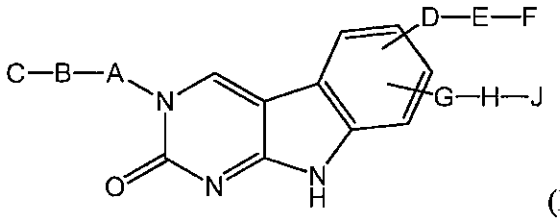
In some embodiments, the present invention relates to a compound having the formula:



wherein C–B–A–, D–E–F, –G–H–J , W, X, Y, Z, V and K are defined as in formula III; and Q^1, Q^2, Q^3, and Q^4 are independently selected from a nitrogen atom, a carbon atom, or CH, wherein –D–E–F, and –G–H–J when present, are each attached to a carbon atom;

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

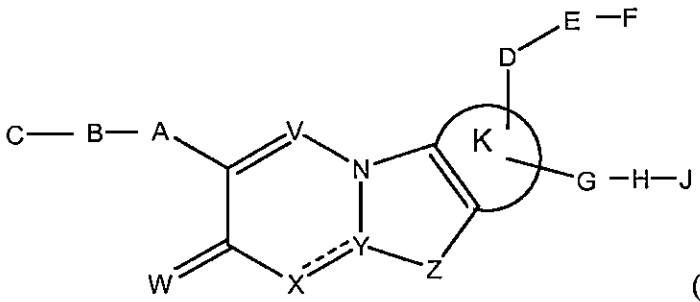
In some embodiments, the present invention relates to a compound having the formula:



(IIIa),

wherein C–B–A–, D–E–F, and –G–H–J are defined as in formula III; or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

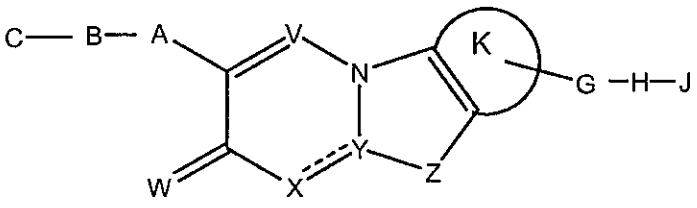
In some embodiments, the present invention relates to a compound having the formula:



(IV)

wherein C–B–A–,–D–E–F, –G–H–J, W, X, Y, Z, V and K are defined as in formula IV, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

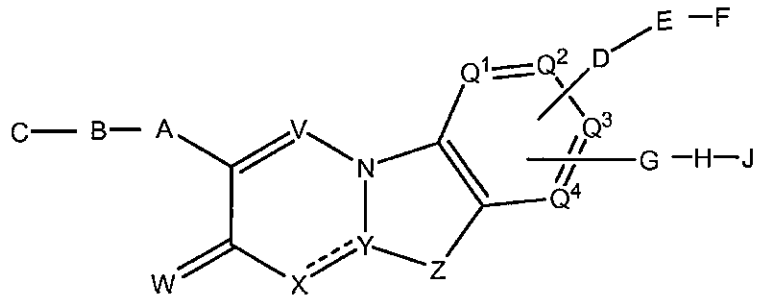
In some embodiments, the present invention relates to a compound having the formula:



wherein C–B–A–,–G–H–J, W, X, Y, Z, V and K are defined as in formula IV, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

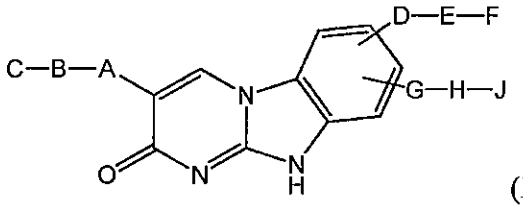
In some embodiments, the present invention relates to a compound according to formula IV, or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein Ⓚ represents a fused six member saturated, unsaturated or aromatic carbocyclic or heterocyclic ring system.

In some embodiments, the present invention relates to a compound having the formula:



wherein C–B–A–, –D–E–F, –G–H–J, W, X, Y, Z, V and K are defined as in formula IV; and Q^1, Q^2, Q^3, and Q^4 are independently selected from a nitrogen atom, a carbon atom, or CH, wherein –D–E–F, and –G–H–J when present, are each attached to a carbon atom; or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

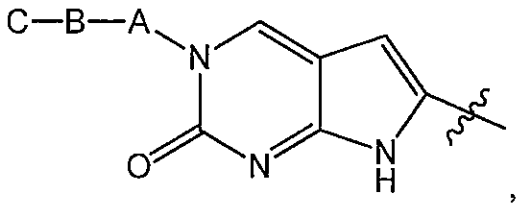
In some embodiments, the present invention relates to a compound having the formula:



(IVa)

wherein C–B–A–, D–E–F, and –G–H–J are defined as in formula IV; or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

In some embodiments, the present invention relates to a compound having the formula:



,

wherein A is

(a) a 3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

(b) a 3–14 member saturated, unsaturated, or aromatic carbocycle, or

(c) a single bond,

wherein (a) or (b) is optionally substituted with one or more R^5 groups;

B is (a) –(C_{1-8} alkyl)–, (b) –(C_{2-8} alkenyl)–, (c) –(C_{2-8} alkynyl)–, or (d) a single bond, wherein

i) 0–4 carbon atoms in any of (a)–(c) immediately above optionally is replaced by a moiety selected from the group consisting of –O–, –$S(O)_p$–, –NR^6–, –(C=O)–, –C(=NR^6)–, –$S(O)_pNR^6$–, and –$NR^6S(O)_pNR^6$–,

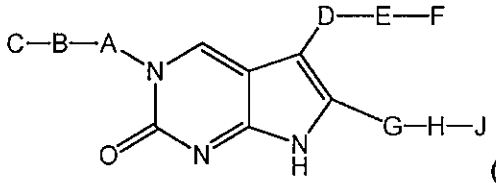
ii) any of (a)–(c) immediately above optionally is substituted with one or more R^5 groups, and/or

iii) any of (a)–(c) immediately above optionally is substituted with –(C_{1-8} alkyl)–R^5 groups, and

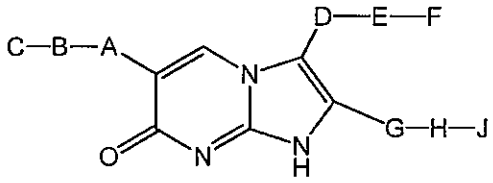
C is selected from (a) NH_2, (b) –NHC(=NH)NH_2 and (c) hydrogen,

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

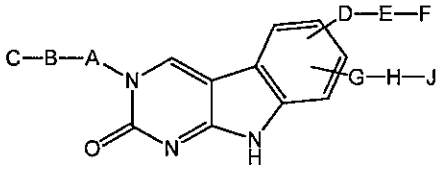
In some embodiments, the present invention relates to a compound having the formula:



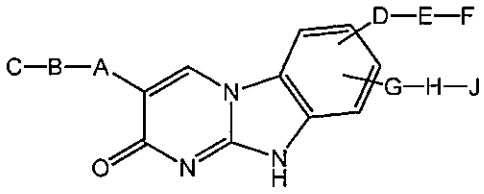
(Ia),



(IIa),



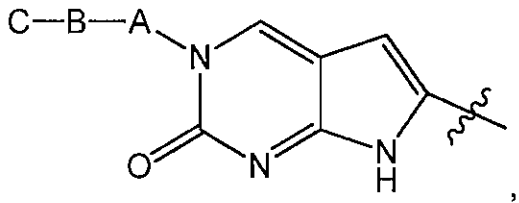
(IIIa), or



(IVa),

wherein C–B–A–, D–E–F, and –G–H–J are defined as in formula I, II, III, and IV; or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

In some embodiments, the present invention relates to a compound having the formula:



wherein A is azepanyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl, pyridyl, cyclohexenyl, cyclohexadienyl, dihydropyridyl, furanyl, tetrahydrofuranyl, tetrahydropyridyl, azetidinyl, pyrrolidinyl, piperidinyl, or piperidenyl, wherein A optionally is substituted with one or more R^5 groups;

or, A is a single bond;

B is (a) $-(C_{1-8}$ alkyl$)-$, wherein

i) 0–4 carbon atoms in (a) immediately above optionally is replaced by a moiety selected from the group consisting of $-O-$, $-S(O)_p-$, $-NR^6-$, $-(C=O)-$, $-S(O)_pNR^6-$, and $-NR^6S(O)_pNR^6-$,

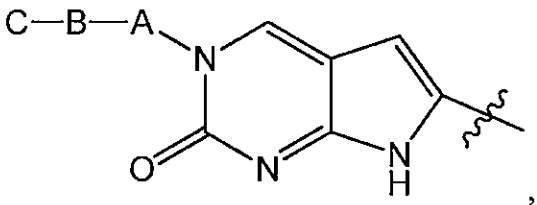
ii) (a) immediately above optionally is substituted with one or more R^5 groups, and/or

iii) (a) immediately above optionally is substituted with $-(C_{1-8}$ alkyl$)-R^5$ groups;

or, B is a single bond;

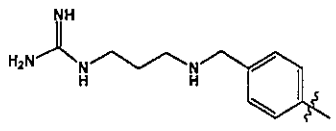
C is (a) NH_2, (b) $-NHC(=NH)NH_2$ or (c) hydrogen.

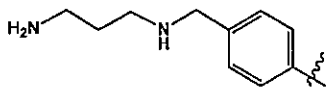
In some embodiments, the present invention relates to a compound having the formula:

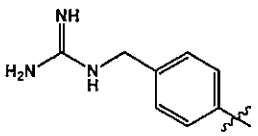


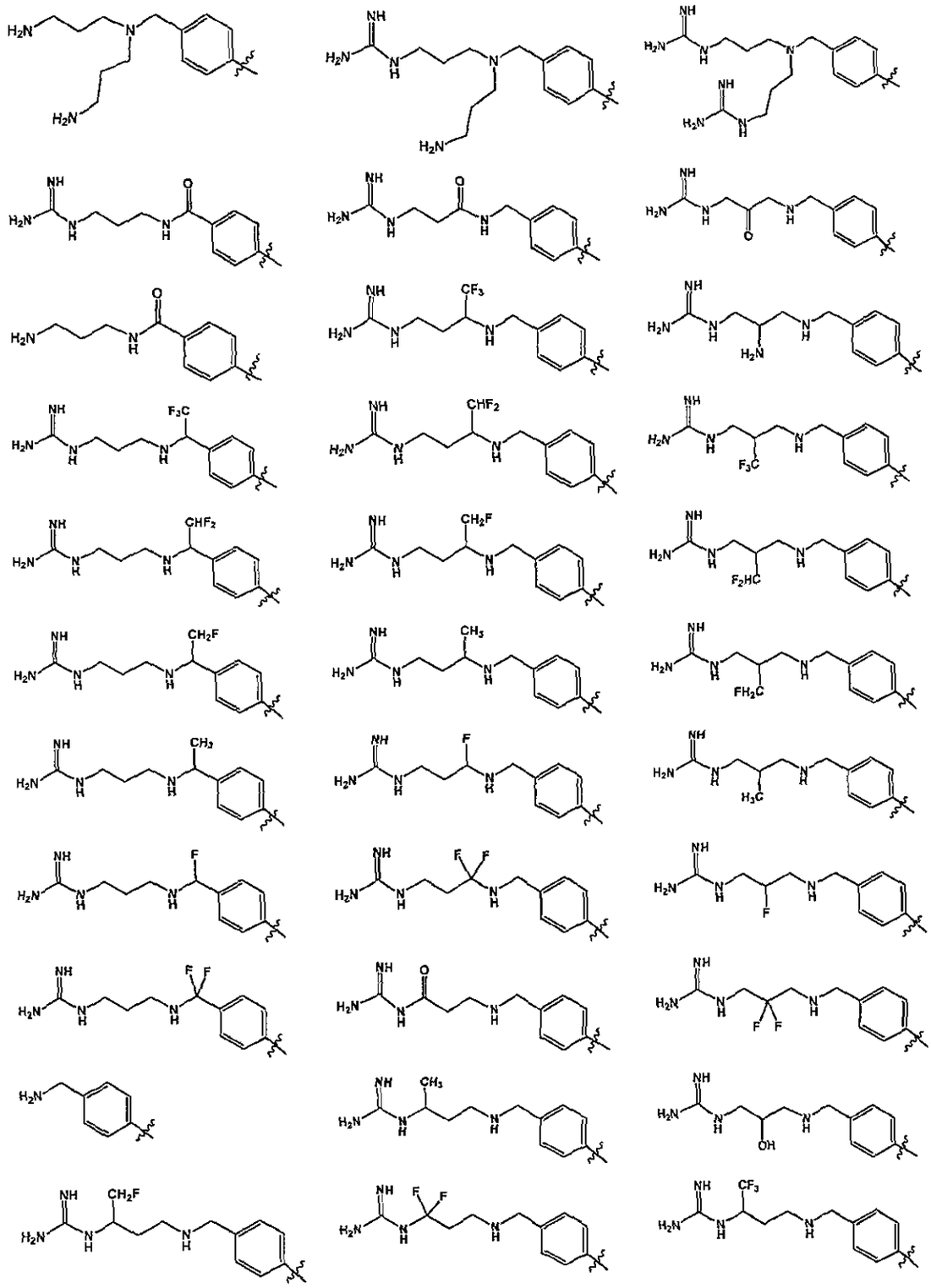
wherein C–B–A– is selected from:

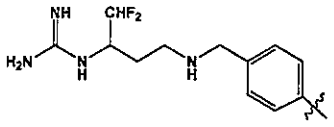
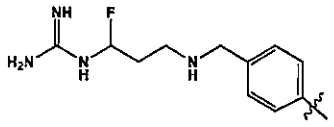
hydrogen,





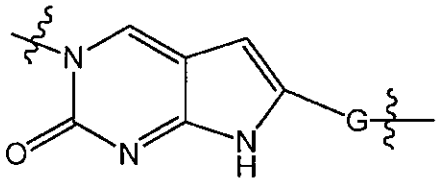




or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

In some embodiments, the present invention relates to a compound having the formula:



wherein G is s

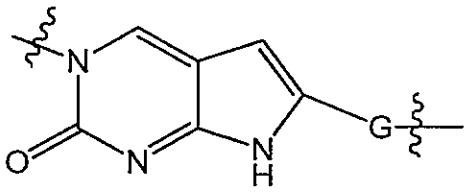
(a) a 3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

(b) a 3–14 member saturated, unsaturated, or aromatic carbocycle, or

(c) a single bond;

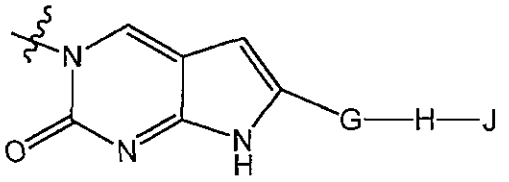
wherein (a) or (b) is optionally substituted with one or more R^5 groups, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

In some embodiments, the present invention relates to a compound having the formula:



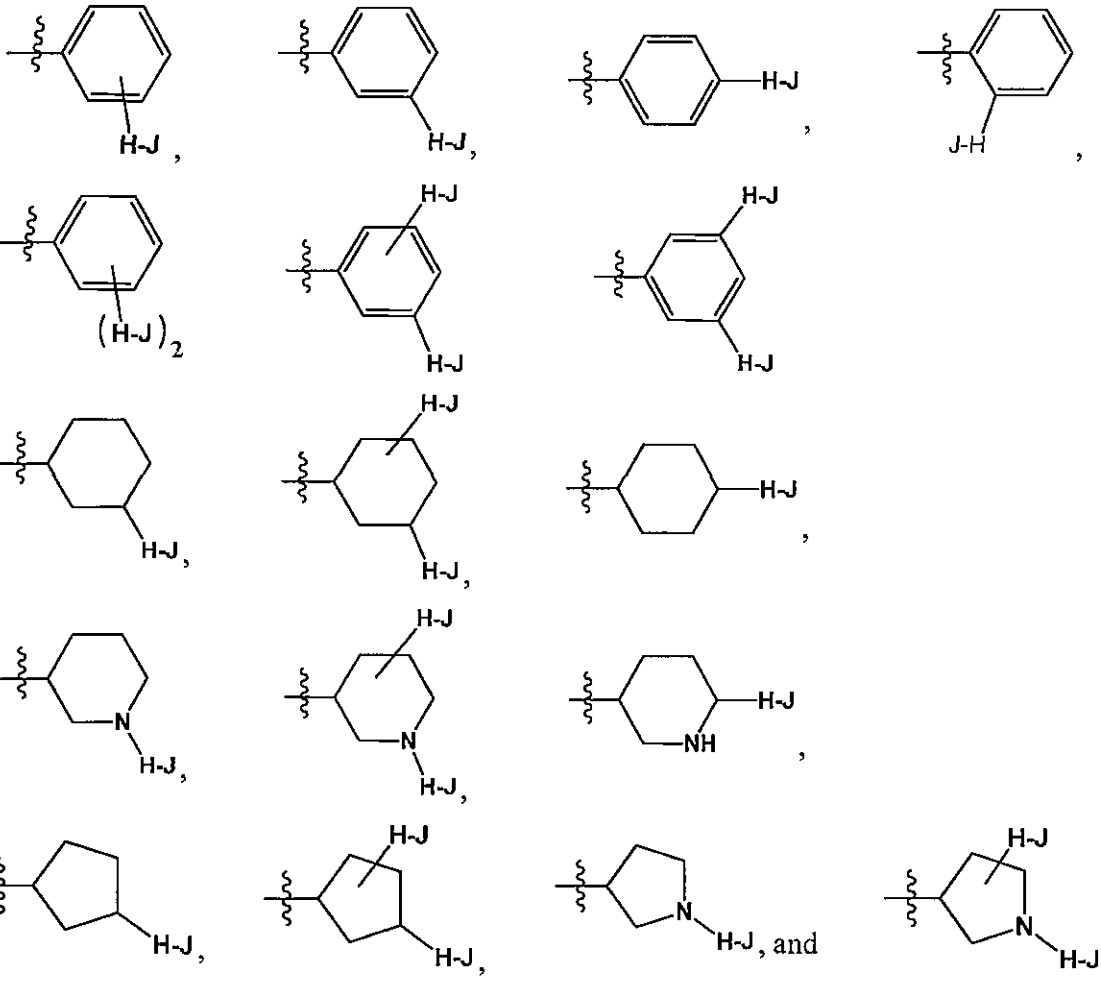
wherein G is azepanyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl, pyridyl, cyclohexenyl, cyclohexadienyl, dihydropyridyl, furanyl, tetrahydrofuranyl, tetrahydropyridyl, azetidinyl, pyrrolidinyl, piperidinyl, piperidenyl, or a single bond; or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

In some embodiments, the present invention relates to a compound having the formula:



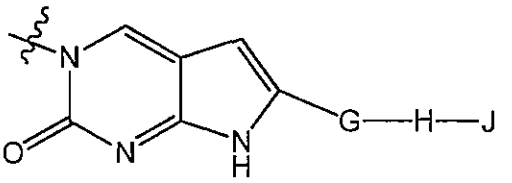
wherein –G–H–J is selected from:

hydrogen,

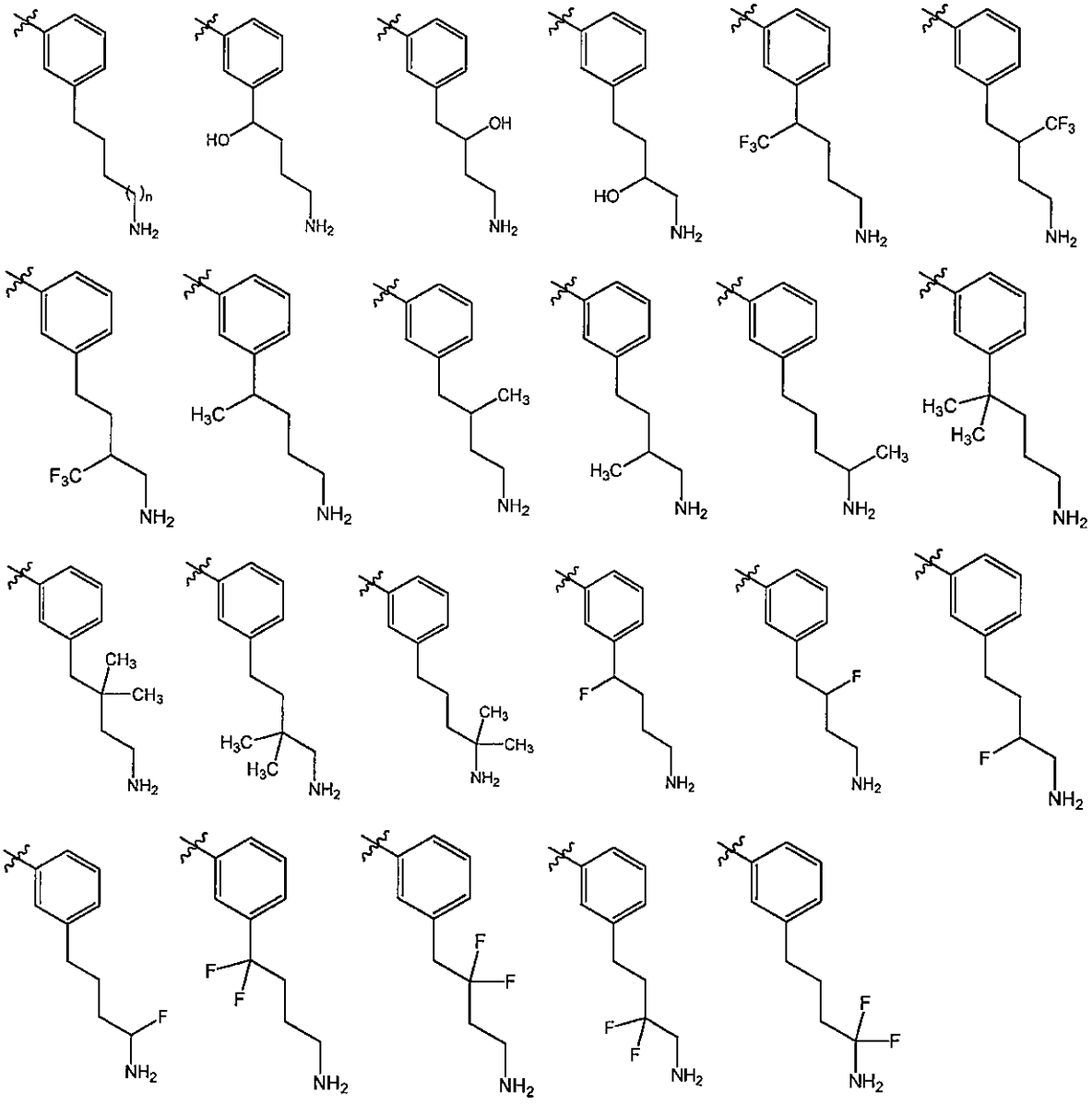


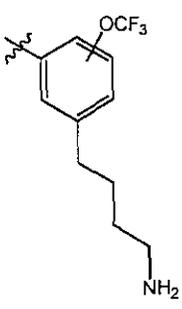
or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

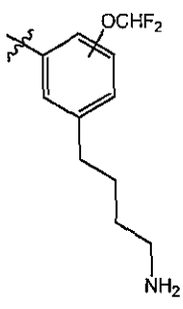
In some embodiments, the present invention relates to a compound having the formula:

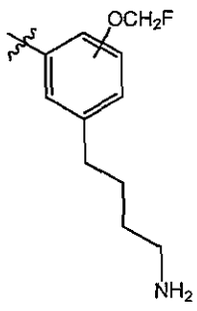


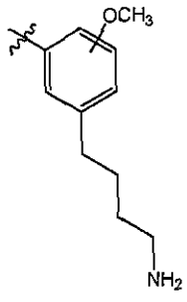
hydrogen,

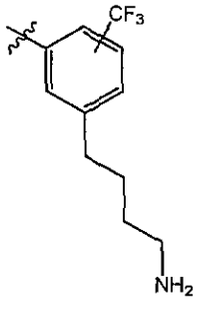


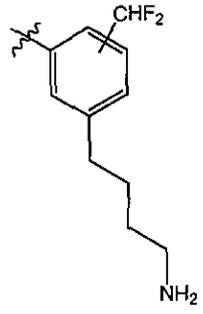

OCF3
NH2

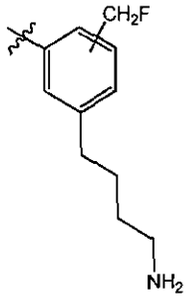

OCHF2
NH2

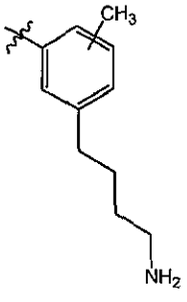

OCH2F
NH2

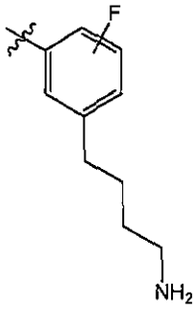

OCH3
NH2

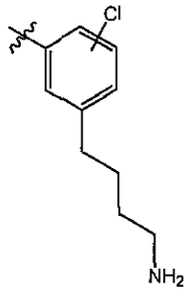

CF3
NH2

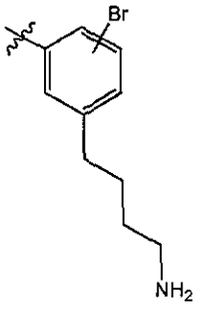

CHF2
NH2

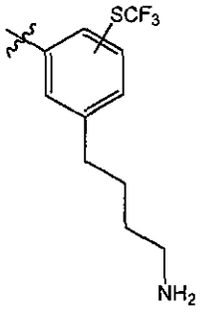

CH2F
NH2

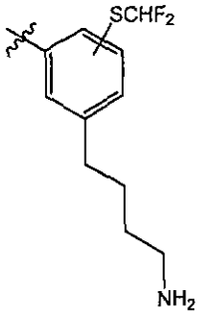

CH3
NH2

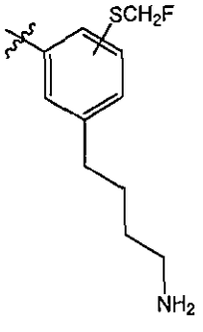

F
NH2

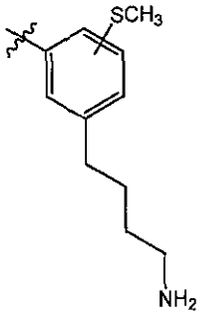

Cl
NH2

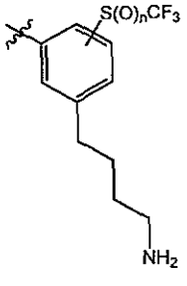

Br
NH2

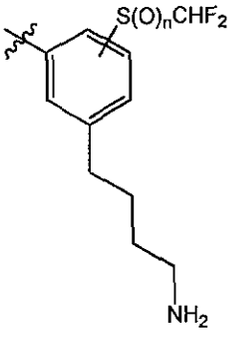

SCF3
NH2

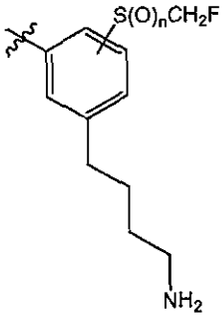

SCHF2
NH2

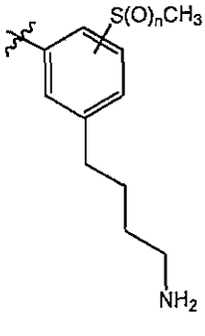

SCH2F
NH2

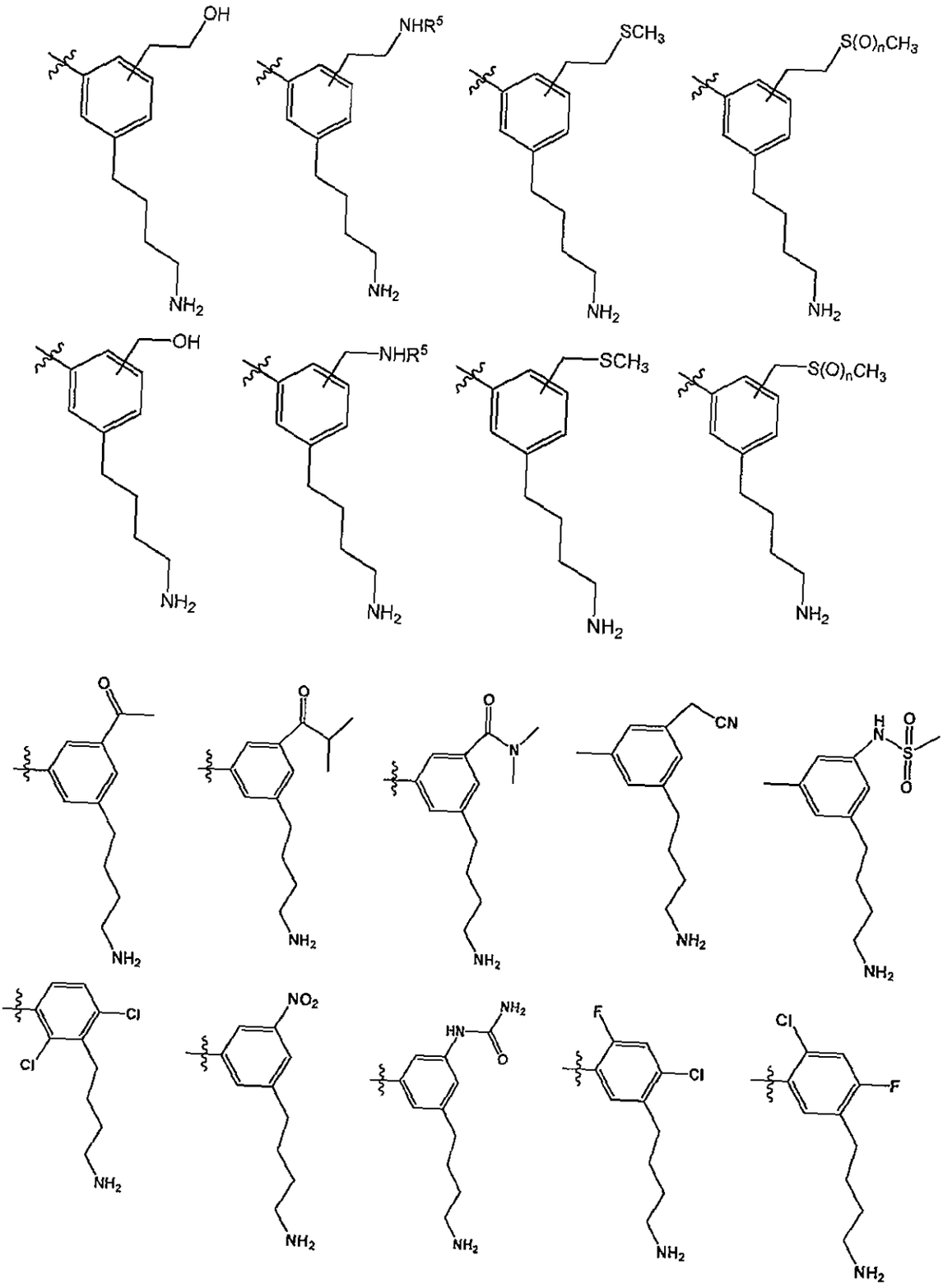

SCH3
NH2

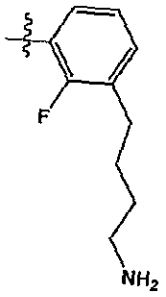
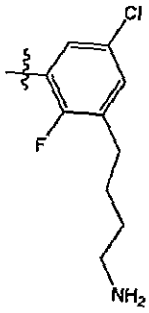
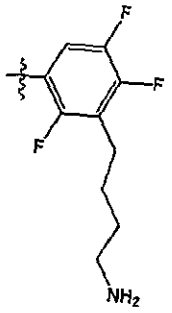
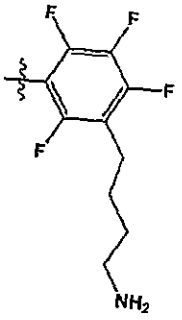
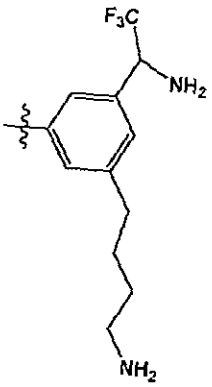
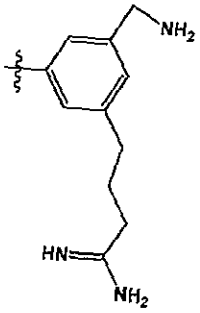
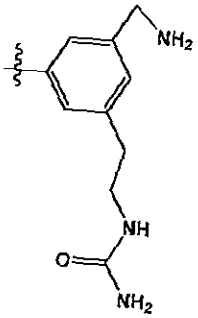
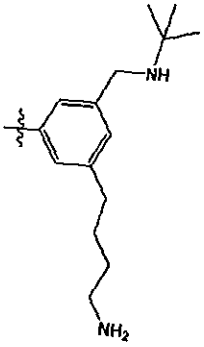
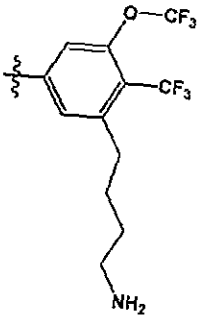
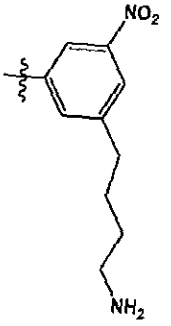
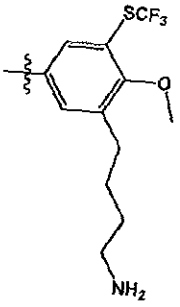
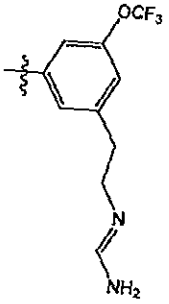
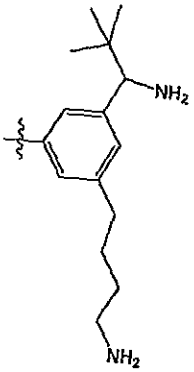
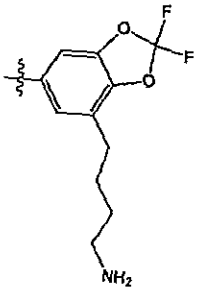
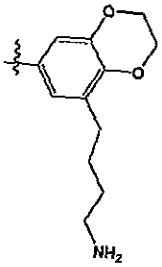
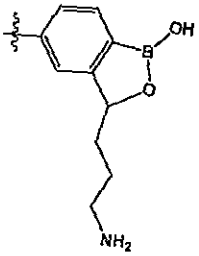
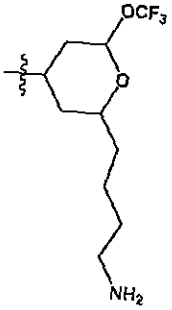
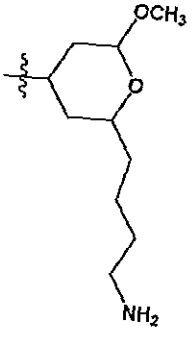
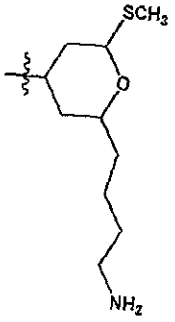

S(O)nCF3
NH2

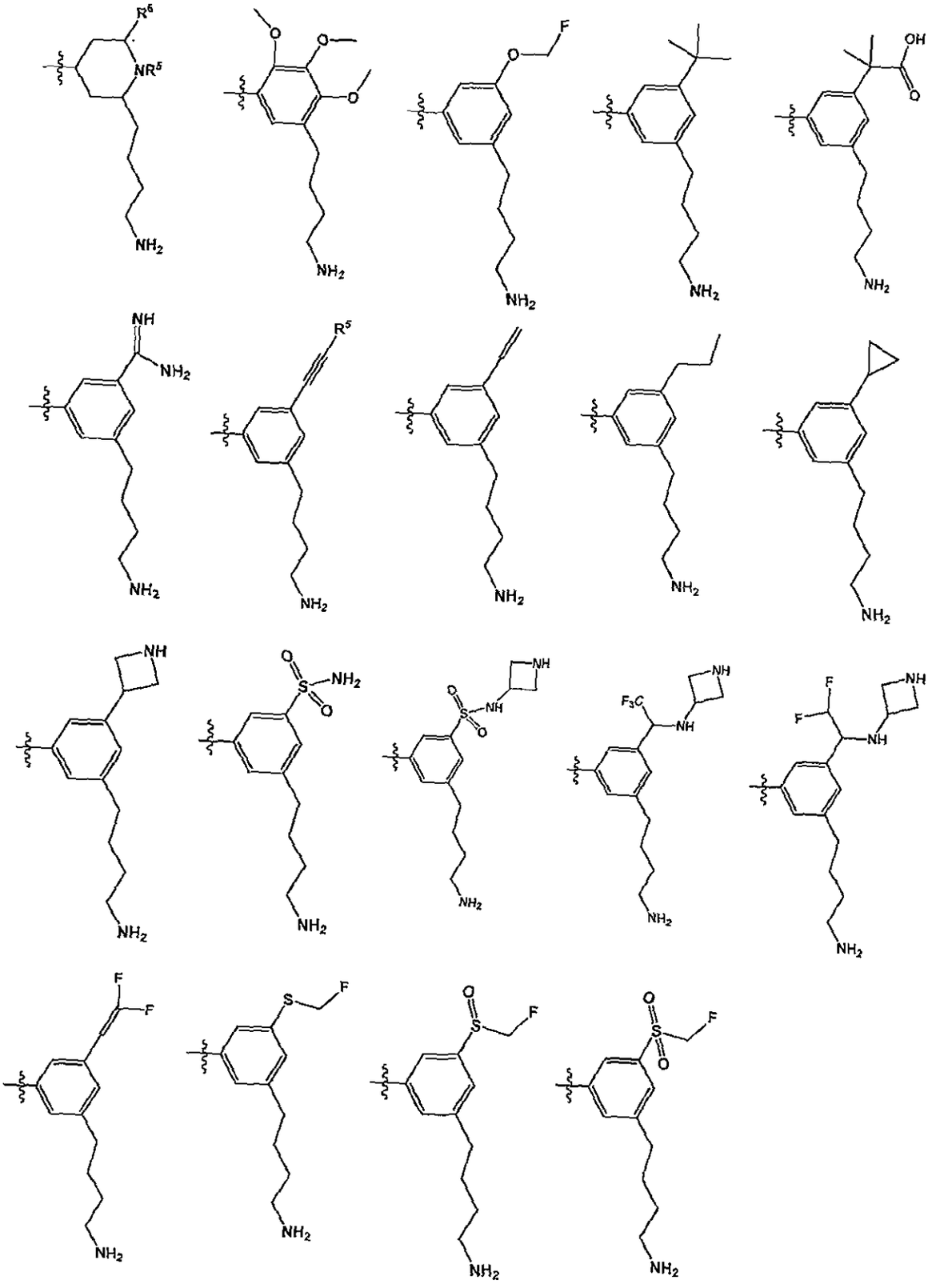

S(O)nCHF2
NH2

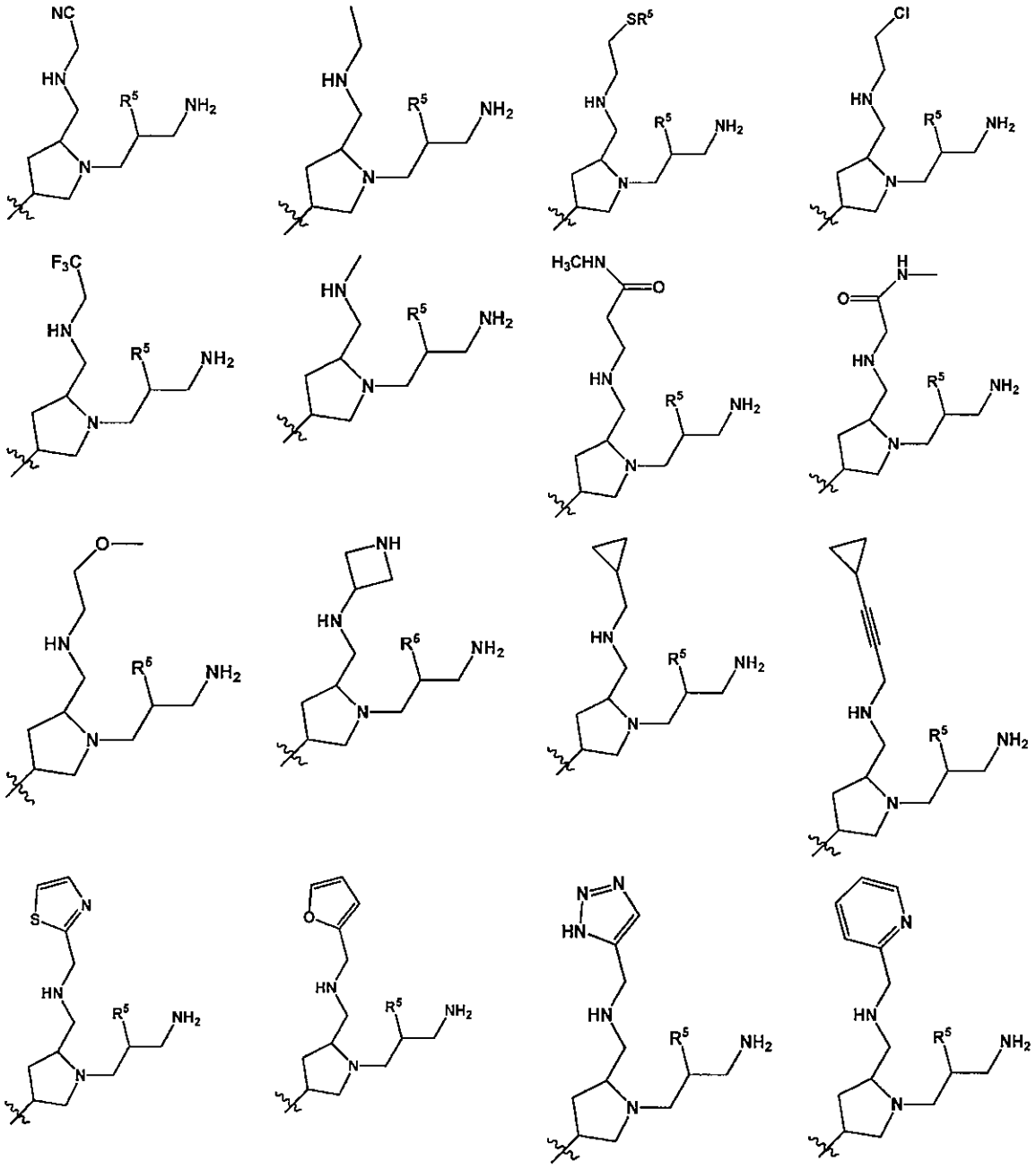

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NH2

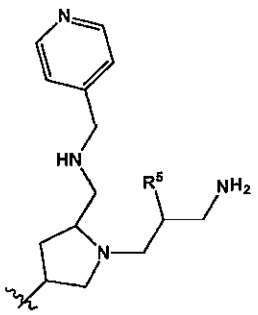
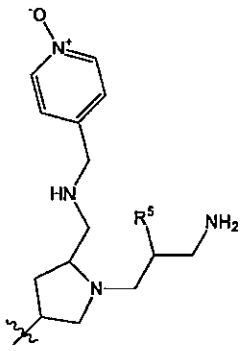
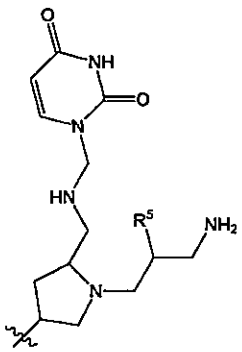
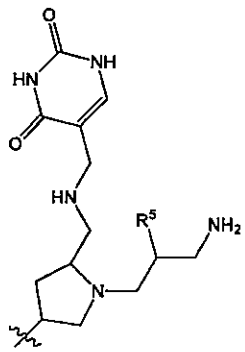

S(O)nCH3
NH2


OH
NHR5
SCH3
S(O)nCH3
NH2
O
CN
H
N
S
Cl
NO2
HN
F

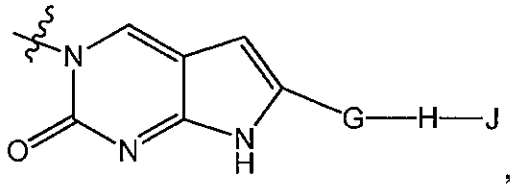




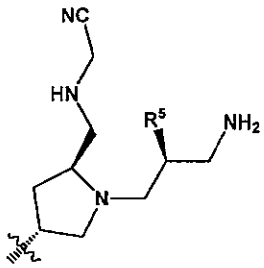
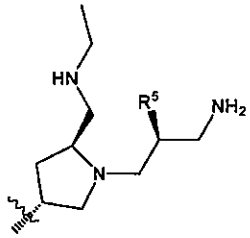
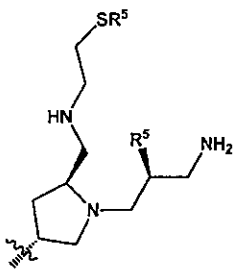
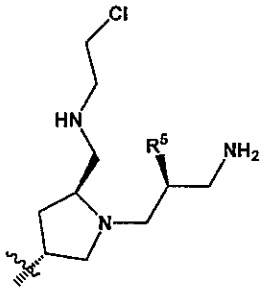
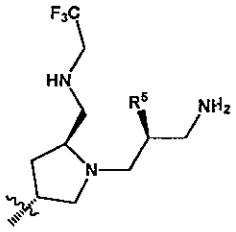
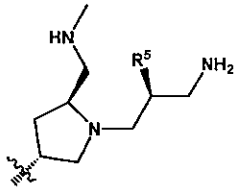
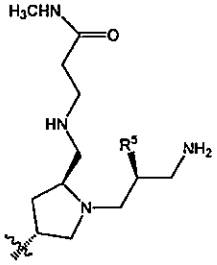
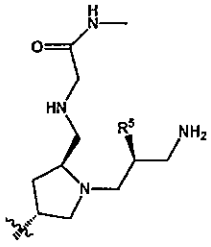
, wherein n is 0, 1, or 2, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

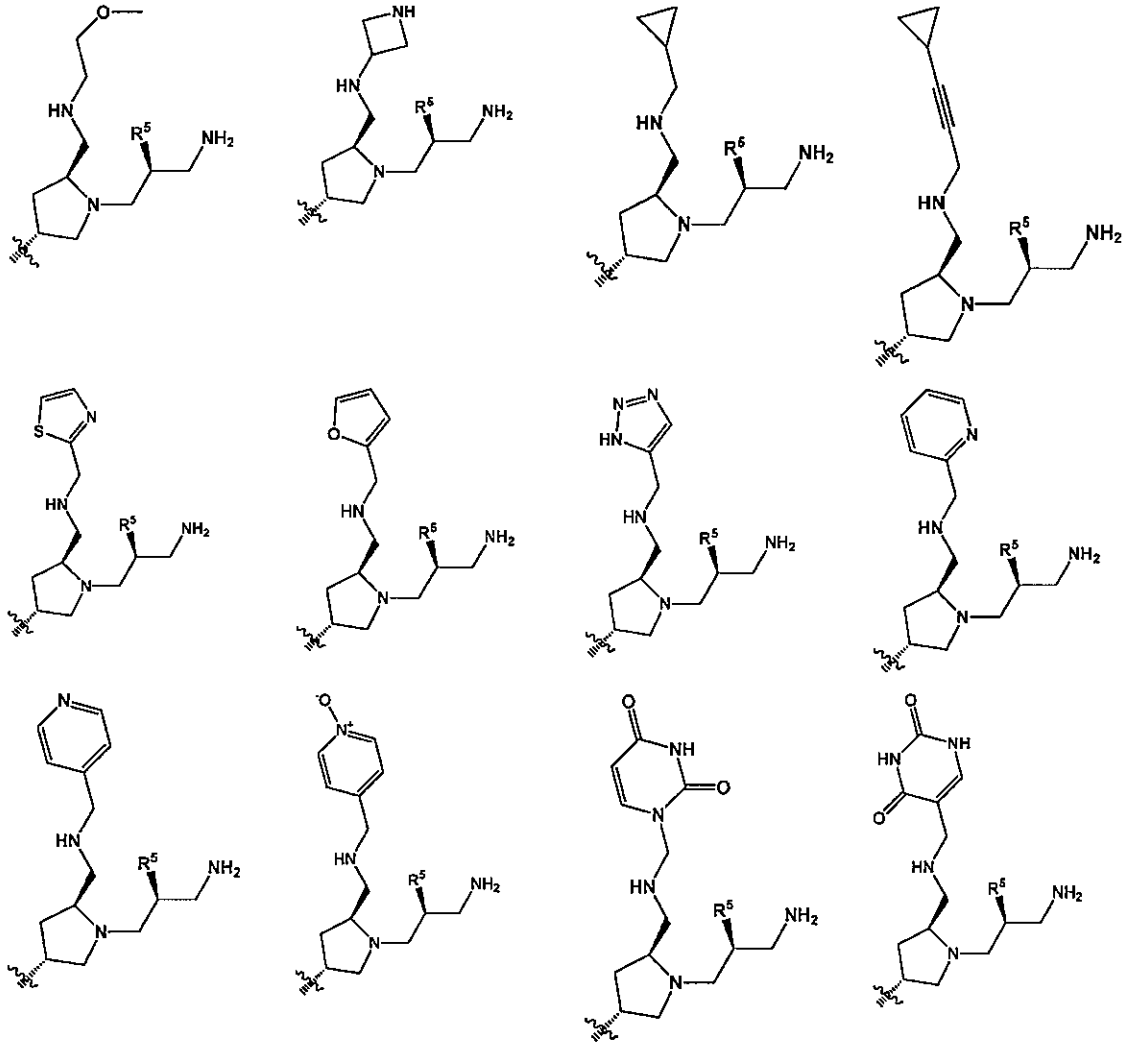
In some embodiments, the present invention relates to a compound having the formula:



,

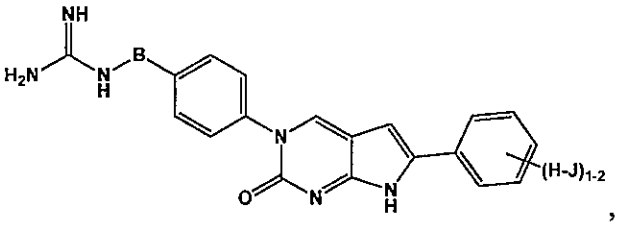
wherein –G–H–J is selected from:



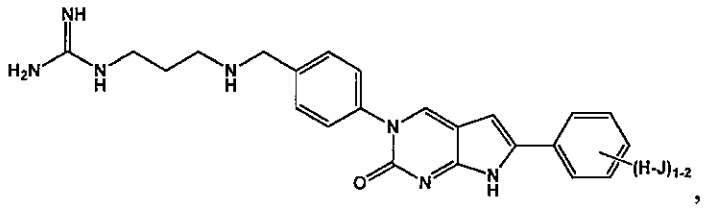
or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof.

In some embodiments, the present invention relates to a compound according to formula:



wherein B is C_{1-8} alkyl, where 0-4 carbon atom is optionally substituted with NH, wherein each –H–J is independently selected from CF_3, OCF_3, and $-(C_{1-8})$ alkyl-NH_2, or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof.

In some embodiments, the present invention relates to a compound according to formula:



wherein each –H–J is independently selected from CF_3, OCF_3, and $-(C_{1-8})$ alkyl-NH_2, or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof.

In some embodiments, the present invention relates to a compound containing R^5, wherein R^5 is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) $-NO_2$, (j) $-NH_2$, (k) $-OR^6$, (l) $-NHC(=NH)NH_2$, (m) $-C_{1-8}$ alkyl, (n) $-C_{1-8}$ alkenyl, (o) $-C_{1-8}$ alkynyl, (p) $-(C_{1-8}$ alkyl) –(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (q) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (r) –haloalkyl, (s) $-SR^6$, (t) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and (u) –3–14 member saturated, unsaturated, or aromatic carbocycle; alternatively, two R^5 groups are taken together to form a carbocycle; or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

In some embodiments, the present invention relates to a compound containing R^6 wherein R^6 is selected from (a) hydrogen, (b) $-C_{1-8}$ alkyl or alternatively two R^6 groups are taken together to form a carbocycle, (c) –haloalkyl, (d) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and (e) –3–14 member saturated, unsaturated, or aromatic carbocycle; or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

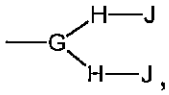
In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa, or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein W, when present, is O, NR^1, NOR^1, or S.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa, or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein X---Y, when present, is a double bond and X is N and Y is a carbon atom.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa, or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein R^5 is OR^6, and R^6 is CF_3.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa, or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein R^5 is CF_3.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa, or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein –G–H–J is selected from



wherein each –H–J is independently selected from $-O-CF_3$ and $-(C_{1-8}$ alkyl)-NH_2.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa, or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein R^{4a}, when present, is hydrogen.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa, or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein Z, when present, is NR^4.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, IVa, or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, wherein R^4 is hydrogen.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, or IVa, or a pharmaceutically acceptable salt, ester, tautomer, or pro-drug thereof, that binds to a ribosome.

In some embodiments, the present invention relates to a compound according to formula I, II, III, IV, Ia, IIa, IIIa, or IVa, or a pharmaceutically acceptable salt, ester,

tautomer, or pro-drug thereof, that binds to the ribosome wherein the ribosome is a bacterial ribosome.

In some embodiments, the present invention relates to a compound according to any of the compounds in Table 1 or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

In some embodiments, the present invention relates to a pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, and a pharmaceutically acceptable carrier.

In some embodiments, the present invention relates to a method for treating or reducing the risk of a disease state in a human or animal comprising administering to a human or animal in need thereof an effective amount of a compound of the invention or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

In some embodiments, the present invention relates to a method of treating a microbial infection in a human or animal comprising administering to the human or animal an effective amount of a compound of the invention, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

In some embodiments, the present invention relates to the use of a compound of the invention, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, in the manufacture of a medicament for treating a microbial infection in a human or animal.

In some embodiments, the present invention relates to a method of treating, preventing or reducing the risk of a microbial infection in a human or animal comprising administering to the human or animal an effective amount of a compound according to formula I, II, III, IV, Ia, IIa, IIIa, or IVa, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, or use of a compound of the invention, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, in the manufacture of a medicament for treating, preventing, or reducing the risk of a microbial infection in a human or animal,

wherein the microbial infection is selected from the group consisting of:

a skin infection, a Gram positive infection, a Gram negative infection, nosocomial pneumonia, community acquired pneumonia, post–viral pneumonia, hospital acquired pneumonia/ventilator associated pneumonia, a respiratory tract infection such as chronic respiratory tract infection (CRTI), acute pelvic infection, a complicated skin and skin

structure infection, a skin and soft tissue infection (SSTI) including uncomplicated skin and soft tissue infections (uSSTI)s and complicated skin and soft tissue infections, an abdominal infection, a complicated intra-abdominal infection, a urinary tract infection, bacteremia, septicemia, endocarditis, an atrio–ventricular shunt infection, a vascular access infection, meningitis, surgical prophylaxis, a peritoneal infection, a bone infection, a joint infection, a methicillin–resistant *Staphylococcus aureus* infection, a vancomycin–resistant *Enterococci* infection, a linezolid–resistant organism infection, a *Bacillus anthracis* infection, a *Francisella tularensis* infection, a *Yersinia pestis* infection, and tuberculosis.

In some embodiments, the present invention relates to a method of treating, preventing or reducing the risk of a complicated intra-abdominal infection in a human or animal comprising administering to the human or animal an effective amount of a compound according to formula I, II, III, IV, Ia, IIa, IIIa, or IVa, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, or to the use of a compound of the invention, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, in the manufacture of a medicament for treating, preventing or reducing the risk of a complicated intra-abdominal infection in a human or animal,

wherein the complicated intra-abdominal infection is selected from polymicrobial infections such as abscess due to *Escherichia coli*, *Clostridium clostridioforme*, *Eubacterium lentum*, *Peptostreptococcus spp.*, *Bacteroides fragilis*, *Bacteroides distasonis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Streptococcus anginosus*, *Streptococcus constellatus*, *Enterococcus faecalis*, *Proteus mirabilis*, or *Clostridium perfringens*.

In some embodiments, the present invention relates to a method of treating, preventing or reducing the risk of a complicated skin and skin structure infection in a human or animal comprising administering to the human or animal an effective amount of a compound according to formula I, II, III, IV, Ia, IIa, IIIa, or IVa, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, or to the use of a compound of the invention, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, in the manufacture of a medicament for treating, preventing or reducing the risk of a complicated skin and skin structure infection,

wherein the complicated skin and skin structure infection is selected from diabetic foot infections without osteomyelitis due to *Staphylococcus aureus* (methicillin susceptible and resistant isolates), *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Bacteroides fragilis*, *Peptostreptococcus species*, *Porphyromonas asaccharolytica*, or *Prevotella bivia*.

In some embodiments, the present invention relates to a method of treating, preventing, or reducing the risk of a community acquired pneumonia in a human or animal comprising administering to the human or animal an effective amount of a compound according to formula I, II, III, IV, Ia, IIa, IIIa, or IVa, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, or to the use of a compound of the invention, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, in the manufacture of a medicament for treating, preventing or reducing the risk of community acquired pneumonia,

wherein the community acquired pneumonia is due to *Streptococcus pneumoniae* (penicillin susceptible and resistant isolates) including cases with concurrent bacteremia, *Haemophilus influenzae* (including beta-lactamase positive isolates), *Moraxella catarrhalis*, or atypical bacteria like *Mycoplasma spp.*

In some embodiments, the present invention relates to a method of treating, preventing, or reducing the risk of a complicated urinary tract infection in a human or animal comprising administering to the human or animal an effective amount of a compound according to formula I, II, III, IV, Ia, IIa, IIIa, or IVa, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, or to the use of a compound of the invention, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, in the manufacture of a medicament for treating, preventing or reducing the risk of a complicated urinary tract infection,

wherein the complicated urinary tract infection is selected from pyelonephritis due to *Escherichia coli*, concurrent bacteremia, or *Klebsiella pneumoniae*.

In some embodiments, the present invention relates to a method of treating, preventing, or reducing the risk of an acute pelvic infection in a human or animal comprising administering to the human or animal an effective amount of a compound according to formula I, II, III, IV, Ia, IIa, IIIa, or IVa, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, or to the use of a compound of the invention, or a

pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, in the manufacture of a medicament for treating, preventing or reducing the risk of an cute pelvic infection,

wherein the acute pelvic infection (including, e.g., postpartum endomyometritis, septic abortion and post surgical gynecologic infections) is due to *Streptococcus agalactiae*, *Escherichia coli*, *Bacteroides fragilis*, *Porphyromonas asaccharolytica*, *Peptostreptococcus spp.*, or *Prevotella bivia*.

In some embodiments, the present invention relates to a method of treating, preventing, or reducing the risk of a hospital acquired pneumonia/ventilator associated pneumonia in a human or animal comprising administering to the human or animal an effective amount of a compound according to formula I, II, III, IV, Ia, IIa, IIIa, or IVa, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, or to the use of a compound of the invention, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, in the manufacture of a medicament for treating, preventing or reducing the risk of hospital acquired pneumonia/ventilator associated pneumonia,

wherein the hospital acquired pneumonia/ventilator associated pneumonia is due to *Streptococcus pneumoniae* (penicillin susceptible and resistant isolates), *Staphylococcus aureus* (methicillin susceptible and resistant isolates), *Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter spp., Stenotrophomonas maltophilia, Haemophilus influenzae* (including beta-lactamase positive isolates), or *Legionella pneumophilia*.

In some embodiments, the present invention relates to a method of treating, preventing, or reducing the risk of a microbial infection due to an aerobic or facultative gram-positive microorganism in a human or animal comprising administering to the human or animal an effective amount of a compound according to formula I, II, III, IV, Ia, IIa, IIIa, or IVa, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, or to the use of a compound of the invention, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, in the manufacture of a medicament for treating, preventing or reducing the risk of a microbial infection due to an aerobic or facultative gram-positive microorganism,

wherein the aerobic or facultative gram-positive microorganism is selected from: *Staphylococcus aureus* (methicillin susceptible and resistant isolates), *Streptococcus pneumoniae* (penicillin susceptible and resistant isolates), *Enterococcus spp.* (vancomycin

susceptible and resistant isolates), *Streptococcus agalactiae*, *Streptococcus pyogenes*, or *Staphylococcus epidermidis* (methicillin susceptible and resistant isolates).

In some embodiments, the present invention relates to a method of treating, preventing, or reducing the risk of a microbial infection due to an aerobic and facultative gram-negative microorganism in a human or animal comprising administering to the human or animal an effective amount of a compound according to formula I, II, III, IV, Ia, IIa, IIIa, or IVa, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, or to the use of a compound of the invention, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, in the manufacture of a medicament for treating, preventing or reducing the risk of a microbial infection due to an aerobic or facultative gram-positive microorganism,

wherein the aerobic and facultative gram-negative microorganism is selected from: *Escherichia coli* (including ESBL and KPC producing isolates), *Haemophilus influenzae* (including Beta-lactamase positive isolates), *Klebsiella pneumoniae* (including ESBL and KPC producing isolates), *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Morganella morganii*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Acinetobacter baumanni*, *Moraxella catarrhalis*, *Proteus mirabilis*, *Citrobacter koseri*, *Haemophilus parainfluenzae*, *Klebsiella oxytoca (including ESBL and KPC producing isolates)*, *Proteus vulgaris*, *Providencia rettgeri*, and *Providencia stuartii*.

In some embodiments, the present invention relates to a method of treating, preventing, or reducing the risk of a microbial infection due to an anaerobic microorganism in a human or animal comprising administering to the human or animal an effective amount of a compound according to formula I, II, III, IV, Ia, IIa, IIIa, or IVa, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, or to the use of a compound of the invention, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, in the manufacture of a medicament for treating, preventing or reducing the risk of a microbial infection due to an anaerobic microorganism

wherein the anaerobic microorganism is: *Bacteroides fragilis*, *Bacteroides distasonis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Clostridium clostridioforme*, *Eubacterium lentum*, *Peptostreptococcus species*, *Porphyromonas asaccharolytica*, *Prevotella bivia*, *Bacteroides vulgates*, *Clostridium perfringens*, or *Fusobacterium spp.*

In some embodiments, the present invention relates to a method of treating or reducing the risk of a microbial infection in a human or animal comprising administering to the human or animal an effective amount of a compound according to formula I, II, III, IV, Ia, IIa, IIIa, or IVa, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, or to the use of a compound of the invention, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, in the manufacture of a medicament for treating, preventing or reducing the risk of a microbial infection,

wherein the microorganism is *Legionella pneumophilia.*

In some embodiments, the present invention relates to a method or use wherein the compound of the invention, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, is administered otically, ophthalmically, nasally, orally, parentally, or topically.

In some embodiments, the present invention relates to a method of synthesizing a compound of the invention, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

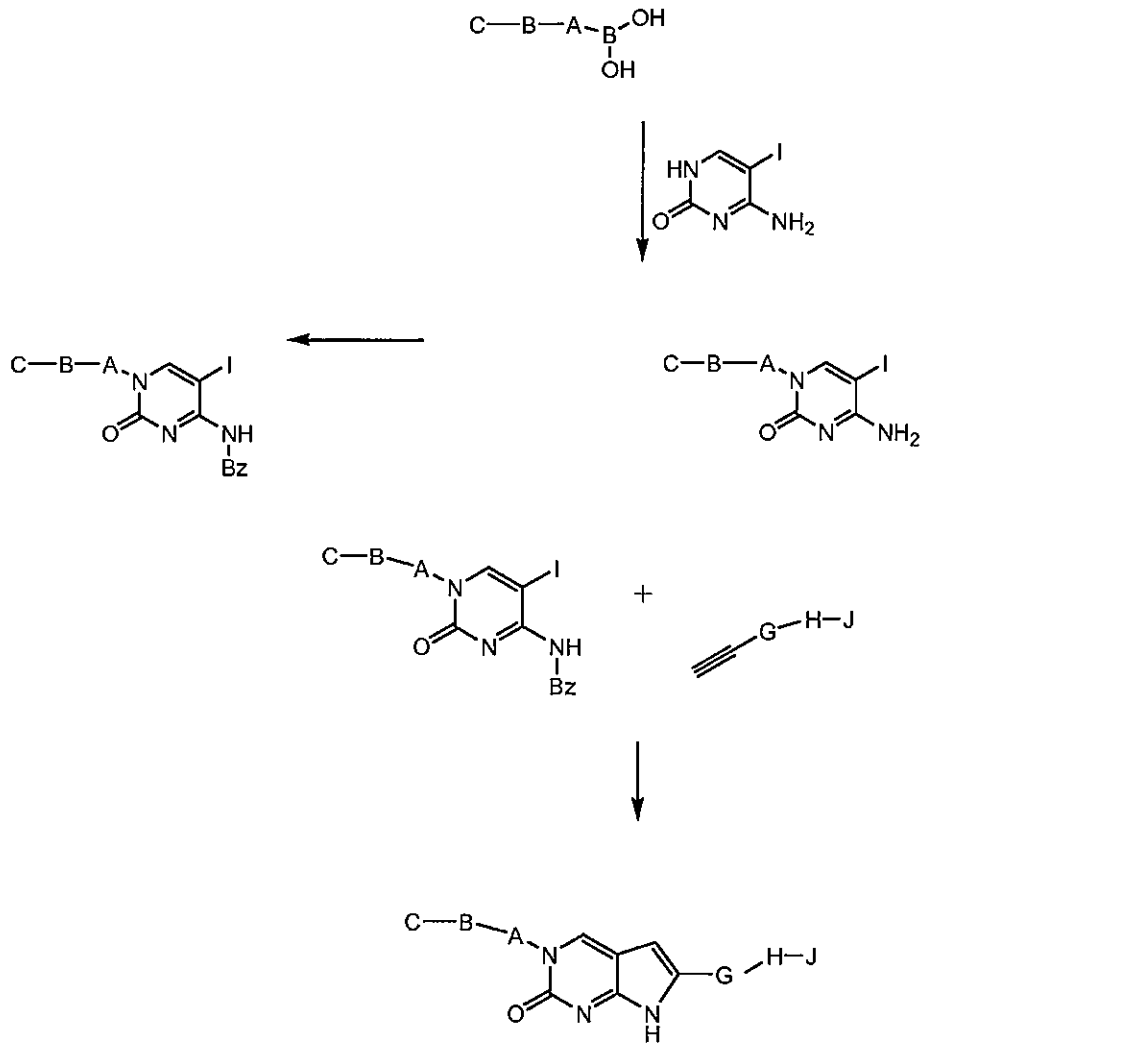
In some embodiments, the present invention relates to a medical device containing a compound of the invention, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

In some embodiments, the present invention relates to a medical device containing a compound of the invention, wherein the device is a stent.

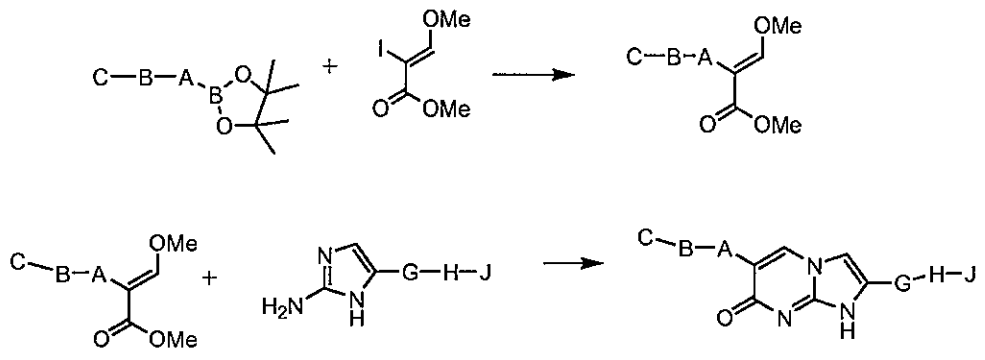
3. Synthesis of the Compounds of the Invention

The invention provides methods for making the compounds of the invention. The following **Schemes 1a–5a** depict exemplary routes in general terms for synthesizing the compounds of the present invention. More specific chemical details are provided in the Examples.

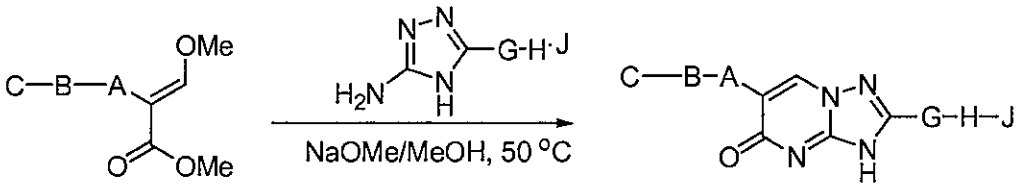
Scheme 1a – Pyrrolocytosines



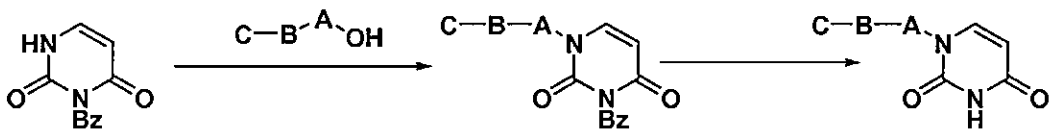
Scheme 2a – Pyrroloisocytosines

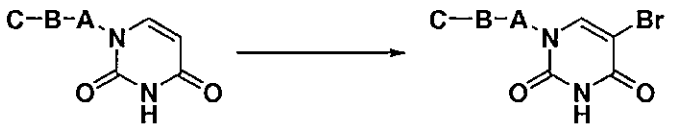


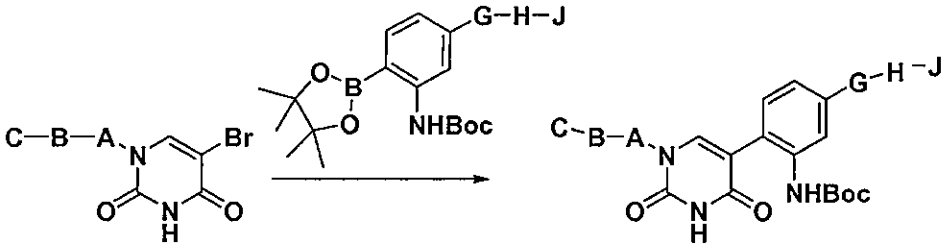
Scheme 3a– Triazolisocytosines

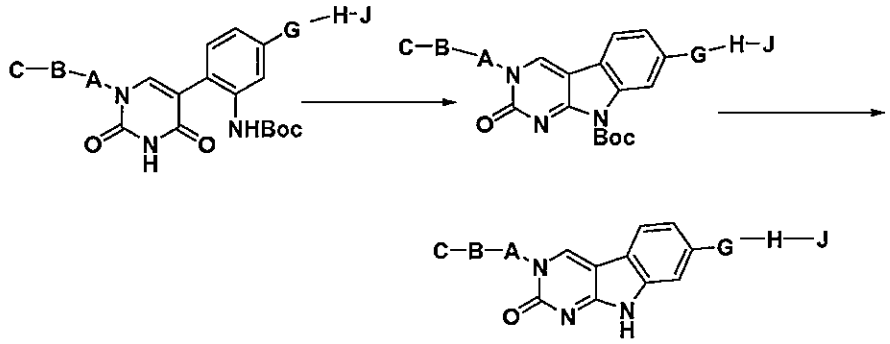


Scheme 4a – [6,5,6] –pyrrolocytosines

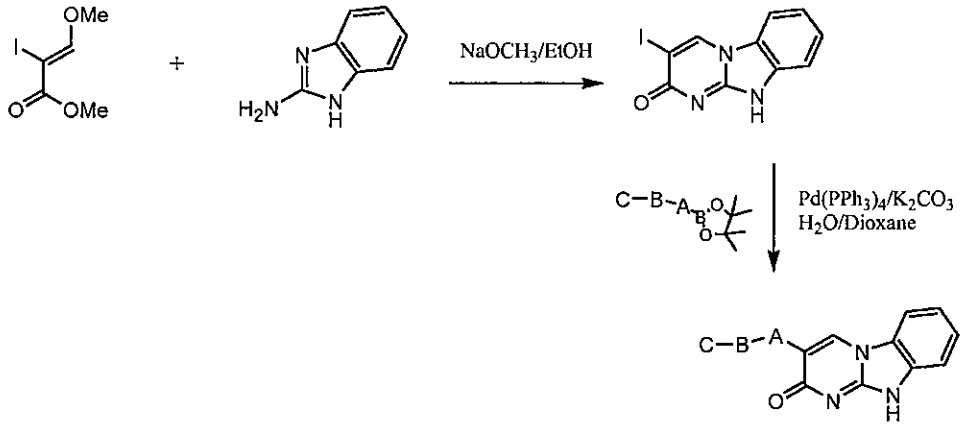








Scheme 5a – [6,5,6]–pyrroloisocytosines



4. Characterization of Compounds of the Invention

Compounds designed, selected and/or optimized by methods described above, once produced, can be characterized using a variety of assays known to those skilled in the art to determine whether the compounds have biological activity. For example, the molecules can be characterized by conventional assays, including but not limited to those assays described below, to determine whether they have a predicted activity, binding activity and/or binding specificity.

Furthermore, high–throughput screening can be used to speed up analysis using such assays. As a result, it can be possible to rapidly screen the molecules described herein for activity, for example, as anti–cancer, anti–bacterial, anti–fungal, anti–parasitic or anti–viral agents. Also, it can be possible to assay how the compounds interact with a ribosome or ribosomal subunit and/or are effective as modulators (for example, inhibitors) of protein

synthesis using techniques known in the art. General methodologies for performing high–throughput screening are described, for example, in Devlin (1998) High Throughput Screening, Marcel Dekker; and U.S. Patent No. 5,763,263. High–throughput assays can use one or more different assay techniques including, but not limited to, those described below.

(1) *Surface Binding Studies*. A variety of binding assays can be useful in screening new molecules for their binding activity. One approach includes surface plasmon resonance (SPR) that can be used to evaluate the binding properties of molecules of interest with respect to a ribosome, ribosomal subunit or a fragment thereof.

SPR methodologies measure the interaction between two or more macromolecules in real–time through the generation of a quantum–mechanical surface plasmon. One device, (BIAcore Biosensor RTM from Pharmacia Biosensor, Piscataway, N.J.) provides a focused beam of polychromatic light to the interface between a gold film (provided as a disposable biosensor "chip") and a buffer compartment that can be regulated by the user. A 100 nm thick "hydrogel" composed of carboxylated dextran that provides a matrix for the covalent immobilization of analytes of interest is attached to the gold film. When the focused light interacts with the free electron cloud of the gold film, plasmon resonance is enhanced. The resulting reflected light is spectrally depleted in wavelengths that optimally evolved the resonance. By separating the reflected polychromatic light into its component wavelengths (by means of a prism), and determining the frequencies that are depleted, the BIAcore establishes an optical interface which accurately reports the behavior of the generated surface plasmon resonance. When designed as above, the plasmon resonance (and thus the depletion spectrum) is sensitive to mass in the evanescent field (which corresponds roughly to the thickness of the hydrogel). If one component of an interacting pair is immobilized to the hydrogel, and the interacting partner is provided through the buffer compartment, the interaction between the two components can be measured in real time based on the accumulation of mass in the evanescent field and its corresponding effects of the plasmon resonance as measured by the depletion spectrum. This system permits rapid and sensitive real–time measurement of the molecular interactions without the need to label either component.

(2) *Fluorescence Polarization*. Fluorescence polarization (FP) is a measurement technique that can readily be applied to protein–protein, protein–ligand, or RNA–ligand

interactions in order to derive IC_{50}s and Kds of the association reaction between two molecules. In this technique one of the molecules of interest is conjugated with a fluorophore. This is generally the smaller molecule in the system (in this case, the compound of interest). The sample mixture, containing both the ligand–probe conjugate and the ribosome, ribosomal subunit or fragment thereof, is excited with vertically polarized light. Light is absorbed by the probe fluorophores, and re–emitted a short time later. The degree of polarization of the emitted light is measured. Polarization of the emitted light is dependent on several factors, but most importantly on viscosity of the solution and on the apparent molecular weight of the fluorophore. With proper controls, changes in the degree of polarization of the emitted light depends only on changes in the apparent molecular weight of the fluorophore, which in–turn depends on whether the probe–ligand conjugate is free in solution, or is bound to a receptor. Binding assays based on FP have a number of important advantages, including the measurement of IC_{50}s and Kds under true homogenous equilibrium conditions, speed of analysis and amenity to automation, and ability to screen in cloudy suspensions and colored solutions.

(3) *Protein Synthesis*. It is contemplated that, in addition to characterization by the foregoing biochemical assays, the compound of interest can also be characterized as a modulator (for example, an inhibitor of protein synthesis) of the functional activity of the ribosome or ribosomal subunit.

Furthermore, more specific protein synthesis inhibition assays can be performed by administering the compound to a whole organism, tissue, organ, organelle, cell, a cellular or subcellular extract, or a purified ribosome preparation and observing its pharmacological and inhibitory properties by determining, for example, its inhibition constant (IC_{50}) for inhibiting protein synthesis. Incorporation of ^{3}H leucine or ^{35}S methionine, or similar experiments can be performed to investigate protein synthesis activity. A change in the amount or the rate of protein synthesis in the cell in the presence of a molecule of interest indicates that the molecule is a modulator of protein synthesis. A decrease in the rate or the amount of protein synthesis indicates that the molecule is a inhibitor of protein synthesis.

(4) *Antimicrobial assays and other evaluation.* Furthermore, the compounds can be assayed for anti–proliferative or anti–infective properties on a cellular level. For example, where the target organism is a microorganism, the activity of compounds of interest can be

assayed by growing the microorganisms of interest in media either containing or lacking the compound. Growth inhibition can be indicative that the molecule can be acting as a protein synthesis inhibitor. More specifically, the activity of the compounds of interest against bacterial pathogens can be demonstrated by the ability of the compound to inhibit growth of defined strains of human pathogens. For this purpose, a panel of bacterial strains can be assembled to include a variety of target pathogenic species, some containing resistance mechanisms that have been characterized. Use of such a panel of organisms permits the determination of structure–activity relationships not only in regards to potency and spectrum, but also with a view to obviating resistance mechanisms.

Minimum inhibitory concentrations (MICs) are determined by the microdilution method, typically in a final volume of 100 microliters, according to protocols outlined by The Clinical and Laboratory Standards Institute [CLSI; formerly the National Committee for Clinical Laboratory Standards (NCCLS)]. See CLSI: Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard–fifth edition. Wayne, PA: NCCLS; 2000. The assays can be also be performed in microtiter trays according to conventional methodologies as published by the CLSI. See CLSI. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard–Seventh Edition. CLSI Document M7–A7 [ISBN 1–56238–587–9] CLSI, 940 West Valley Road, Suite 1400, Wayne Pennsylvania 19087–1898 USA, 2006).

The antimicrobial and other drug properties of the compounds can further be evaluated in various *in vivo* mammalian assays, such as a mouse or rat peritonitis infectious models, skin and soft tissue models (often referred to as the thigh model), or a mouse pneumonia model. There are septicemia or organ infection models known to those skilled in the art. These efficacy models can be used as part of the evaluation process and can be used as a guide of potential efficacy in humans. Endpoints can vary from reduction in bacterial burden to lethality. For the latter endpoint, results are often expressed as a PD_{50} value, or the dose of drug that protects 50% of the animals from mortality.

To further assess a compound's drug–like properties, measurements of inhibition of cytochrome P450 enzymes and phase II metabolizing enzyme activity can also be measured either using recombinant human enzyme systems or more complex systems like human liver microsomes. Further, compounds can be assessed as substrates of these metabolic enzyme

activities as well. These activities are useful in determining the potential of a compound to cause drug–drug interactions or generate metabolites that retain or have no useful antimicrobial activity.

To get an estimate of the potential of the compound to be orally bioavailable, one can also perform solubility and Caco–2 assays. The latter is a cell line from human epithelium that allows measurement of drug uptake and passage through a Caco–2 cell monolayer often growing within wells of a 24–well microtiter plate equipped with a 1 micron membrane. Free drug concentrations can be measured on the basolateral side of the monolayer, assessing the amount of drug that can pass through the intestinal monolayer. Appropriate controls to ensure monolayer integrity and tightness of gap junctions are needed. Using this same system one can get an estimate of P–glycoprotein mediated efflux. P–glycoprotein is a pump that localizes to the apical membrane of cells, forming polarized monolayers. This pump can abrogate the active or passive uptake across the Caco–2 cell membrane, resulting in less drug passing through the intestinal epithelial layer. These results are often done in conjunction with solubility measurements and both of these factors are known to contribute to oral bioavailability in mammals. Measurements of oral bioavailability in animals and ultimately in man using traditional pharmacokinetic experiments will determine the absolute oral bioavailability.

Experimental results can also be used to build models that help predict physical–chemical parameters that contribute to drug–like properties. When such a model is verified, experimental methodology can be reduced, with increased reliance on the model predictability.

5. Formulation and Administration

The compounds of the invention can be useful in the prevention or treatment of a variety of human or other animal, including mammalian and non mammalian, disorders, including for example, bacterial infection, fungal infections, viral infections, diarrhea, parasitic diseases, and cancer. It is contemplated that, once identified, the active molecules of the invention can be incorporated into any suitable carrier prior to use. The dose of active molecule, mode of administration and use of suitable carrier will depend upon the intended recipient and target organism. The formulations, both for veterinary and for human medical use, of compounds according to the present invention typically include such compounds in association with a pharmaceutically acceptable carrier.

The carrier(s) should be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient. Pharmaceutically acceptable carriers, in this regard, are intended to include any and all solvents, dispersion media, coatings, anti–bacterial and anti–fungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds (identified or designed according to the invention and/or known in the art) also can be incorporated into the compositions. The formulations can conveniently be presented in dosage unit form and can be prepared by any of the methods well known in the art of pharmacy/microbiology. In general, some formulations are prepared by bringing the compound into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

A pharmaceutical composition of the invention should be formulated to be compatible with its intended route of administration. Examples of routes of administration include oral, otic, ophthalmic, nasal, or parenteral, for example, intravenous, intradermal, inhalation, transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial

agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide.

Useful solutions for oral or parenteral administration can be prepared by any of the methods well known in the pharmaceutical art, described, for example, in Remington's Pharmaceutical Sciences, (Gennaro, A., ed.), Mack Pub., (1990). Formulations for parenteral administration can also include glycocholate for buccal administration, methoxysalicylate for rectal administration, or citric acid for vaginal administration. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Suppositories for rectal administration also can be prepared by mixing the drug with a non–irritating excipient such as cocoa butter, other glycerides, or other compositions which are solid at room temperature and liquid at body temperatures. Formulations also can include, for example, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, and hydrogenated naphthalenes. Formulations for direct administration can include glycerol and other compositions of high viscosity. Other potentially useful parenteral carriers for these drugs include ethylene–vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation administration can contain as excipients, for example, lactose, or can be aqueous solutions containing, for example, polyoxyethylene–9–lauryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Retention enemas also can be used for rectal delivery.

Formulations of the present invention suitable for oral administration can be in the form of: discrete units such as capsules, gelatin capsules, sachets, tablets, troches, or lozenges, each containing a predetermined amount of the drug; a powder or granular composition; a solution or a suspension in an aqueous liquid or non–aqueous liquid; or an oil–in–water emulsion or a water–in–oil emulsion. The drug can also be administered in the form of a bolus, electuary or paste. A tablet can be made by compressing or moulding the drug optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the drug in a free–flowing form such as a powder or

granules, optionally mixed by a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets can be made by moulding, in a suitable machine, a mixture of the powdered drug and suitable carrier moistened with an inert liquid diluent.

Oral compositions generally include an inert diluent or an edible carrier. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients. Oral compositions prepared using a fluid carrier for use as a mouthwash include the compound in the fluid carrier and are applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose; a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filter sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation include vacuum drying and freeze–drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile–filtered solution thereof.

Formulations suitable for intra–articular administration can be in the form of a sterile aqueous preparation of the drug that can be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems can also be used to present the drug for both intra–articular and ophthalmic administration.

Formulations suitable for topical administration, including eye treatment, include liquid or semi–liquid preparations such as liniments, lotions, gels, applicants, oil–in–water or water–in–oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops. Formulations for topical administration to the skin surface can be prepared by dispersing the drug with a dermatologically acceptable carrier such as a lotion, cream, ointment or soap. Particularly useful are carriers capable of forming a film or layer over the skin to localize application and inhibit removal. For topical administration to internal tissue surfaces, the agent can be dispersed in a liquid tissue adhesive or other substance known to enhance adsorption to a tissue surface. For example, hydroxypropylcellulose or fibrinogen/thrombin solutions can be used to advantage. Alternatively, tissue–coating solutions, such as pectin–containing formulations can be used.

For inhalation treatments, inhalation of powder (self–propelling or spray formulations) dispensed with a spray can, a nebulizer, or an atomizer can be used. Such formulations can be in the form of a fine powder for pulmonary administration from a powder inhalation device or self–propelling powder–dispensing formulations. In the case of self–propelling solution and spray formulations, the effect can be achieved either by choice of a valve having the desired spray characteristics (*i.e.,* being capable of producing a spray

having the desired particle size) or by incorporating the active ingredient as a suspended powder in controlled particle size. For administration by inhalation, the compounds also can be delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.,* a gas such as carbon dioxide, or a nebulizer.

Systemic administration also can be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants generally are known in the art, and include, for example, for transmucosal administration, detergents and bile salts. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds typically are formulated into ointments, salves, gels, or creams as generally known in the art.

The active compounds can be prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

Oral or parenteral compositions can be formulated in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals. Furthermore, administration can be by periodic injections of a bolus, or can be made more continuous by intravenous, intramuscular or intraperitoneal administration from an external reservoir (*e.g.,* an intravenous bag).

Where adhesion to a tissue surface is desired the composition can include the drug dispersed in a fibrinogen–thrombin composition or other bioadhesive. The compound then can be painted, sprayed or otherwise applied to the desired tissue surface. Alternatively, the drugs can be formulated for otic, ophthalmic, nasal, parenteral or oral administration to humans or other mammals, for example, in therapeutically effective amounts, *e.g.,* amounts that provide appropriate concentrations of the drug to target tissue for a time sufficient to induce the desired effect.

Where the active compound is to be used as part of a transplant procedure, it can be provided to the living tissue or organ to be transplanted prior to removal of tissue or organ from the donor. The compound can be provided to the donor host. Alternatively or, in addition, once removed from the donor, the organ or living tissue can be placed in a preservation solution containing the active compound. In all cases, the active compound can be administered directly to the desired tissue, as by injection to the tissue, or it can be provided systemically, e.g., by otic, ophthalmic, nasal, oral or parenteral administration, using any of the methods and formulations described herein and/or known in the art. Where the drug comprises part of a tissue or organ preservation solution, any commercially available preservation solution can be used to advantage. For example, useful solutions known in the art include Collins solution, Wisconsin solution, Belzer solution, Eurocollins solution and lactated Ringer's solution.

The compounds of the present invention can be administered directly to a tissue locus by applying the compound to a medical device that is placed in contact with the tissue. An example of a medical device is a stent, which contains or is coated with one or more of the compounds of the present invention.

For example, an active compound can be applied to a stent at the site of vascular injury. Stents can be prepared by any of the methods well known in the pharmaceutical art. See, e.g., Fattori, R. and Piva, T., "Drug Eluting Stents in Vascular Intervention," Lancet, 2003, 361, 247–249; Morice, M. C., "A New Era in the Treatment of Coronary Disease?" European Heart Journal, 2003, 24, 209–211; and Toutouzas, K. et al., "Sirolimus–Eluting Stents: A Review of Experimental and Clinical Findings," Z. Kardiol., 2002, 91(3), 49–57. The stent can be fabricated from stainless steel or another bio–compatible metal, or it can be made of a bio–compatible polymer. The active compound can be linked to the stent surface,

embedded and released from polymer materials coated on the stent, or surrounded by and released through a carrier which coats or spans the stent. The stent can be used to administer single or multiple active compounds to tissues adjacent to the stent.

Active compound as identified or designed by the methods described herein can be administered to individuals to treat disorders (prophylactically or therapeutically). In conjunction with such treatment, pharmacogenomics (*i.e.,* the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) can be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician can consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer a drug as well as tailoring the dosage and/or therapeutic regimen of treatment with the drug.

In therapeutic use for treating, or combating, bacterial infections in mammals, the compounds or pharmaceutical compositions thereof will be administered otically, ophthalmically, nasally, orally, parenterally and/or topically at a dosage to obtain and maintain a concentration, that is, an amount, or blood–level or tissue level of active component in the animal undergoing treatment which will be anti–microbially effective. Generally, an effective amount of dosage of active component will be in the range of from about 0.1 to about 100, more preferably from about 1.0 to about 50 mg/kg of body weight/day. The amount administered will also likely depend on such variables as the type and extent of disease or indication to be treated, the overall health status of the particular patient, the relative biological efficacy of the compound delivered, the formulation of the drug, the presence and types of excipients in the formulation, and the route of administration. Also, it is to be understood that the initial dosage administered can be increased beyond the above upper level in order to rapidly achieve the desired blood–level or tissue level, or the initial dosage can be smaller than the optimum and the daily dosage can be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose can also be divided into multiple doses for administration, for example, two to four times per day.

Various disease states or conditions in humans and other mammals are found to be caused by or mediated by nonsense or missense mutations. These mutations cause or mediate the disease state or condition by adversely affecting, for example, protein synthesis, folding, trafficking and/or function. Examples of disease states or conditions in which an appreciable percentage of the disease or condition is believed to result from nonsense or missense mutations include hemophilia (factor VIII gene), neurofibromatosis (NF1 and NF2 genes), retinitis pigmentosa (human USH2A gene), bullous skin diseases like Epidermolysis bullosa pruriginosa (COL7A1 gene), cystic fibrosis (cystic fibrosis transmembrane regulator gene), breast and ovarian cancer (BRCA1 and BRCA2 genes), Duchenne muscular dystrophy (dystrophin gene), colon cancer (mismatch repair genes, predominantly in MLH1 and MSH2), and lysosomal storage disorders such as Neimann–Pick disease (acid sphingomyelinase gene). See Sanders CR, Myers JK. Disease–related misassembly of membrane proteins. Annu Rev Biophys Biomol Struct. 2004;33:25–51; National Center for Biotechnology Information (U.S.) Genes and disease Bethesda, MD : NCBI, NLM ID: 101138560; and Raskó, István; Downes, C S Genes in medicine : molecular biology and human genetic disorders 1st ed. London ; New York : Chapman & Hall, 1995. NLM ID: 9502404. The compounds of the present invention can be used to treat or prevent a disease state in a mammal caused or mediated by such nonsense or missense mutations by administering to a mammal in need thereof an effective amount of the present invention to suppress the nonsense or missense mutation involved in the disease state.

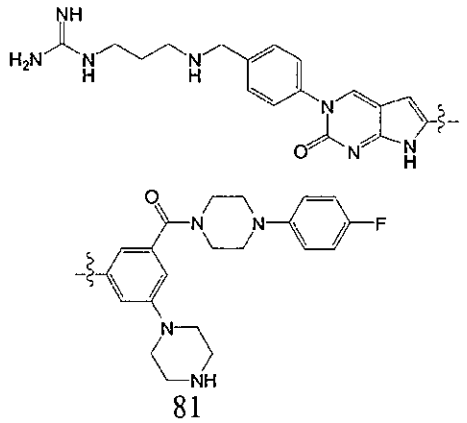
6. Examples

Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance 300 or Avance 500 spectrometer, or in some cases a GE–Nicolet 300 spectrometer. Common reaction solvents were either high performance liquid chromatography (HPLC) grade or American Chemical Society (ACS) grade, and anhydrous as obtained from the manufacturer unless otherwise noted. "Chromatography" or "purified by silica gel" refers to flash column chromatography using silica gel (EM Merck, Silica Gel 60, 230–400 mesh) unless otherwise noted.

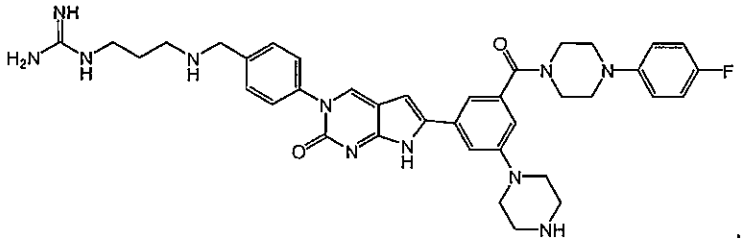
The compounds of the present invention can be prepared using known chemical transformations adapted to the particular situation at hand..

Some of the abbreviations used in the following experimental details of the synthesis of the examples are defined below: h or hr = hour(s); min = minute(s); mol = mole(s); mmol = millimole(s); M = molar; μM = micromolar; g = gram(s); μg = microgram(s); rt = room temperature; L = liter(s); mL = milliliter(s); Et_2O = diethyl ether; THF = tetrahydrofuran; DMSO = dimethyl sulfoxide; EtOAc = ethyl acetate; Et_3N = triethylamine; *i*–Pr_2NEt or DIPEA = diisopropylethylamine; CH_2Cl_2= methylene chloride; $CHCl_3$ = chloroform; $CDCl_3$ = deuterated chloroform; CCl_4 = carbon tetrachloride; MeOH = methanol; CD_3OD= deuterated methanol; EtOH = ethanol; DMF = dimethylformamide; BOC = *t*–butoxycarbonyl; CBZ = benzyloxycarbonyl; TBS = *t*–butyldimethylsilyl; TBSCl = *t*–butyldimethylsilyl chloride; TFA = trifluoroacetic acid; DBU = diazabicycloundecene; TBDPSCl = *t*–butyldiphenylchlorosilane; Hunig's Base = *N,N*–diisopropylethylamine; DMAP = 4–dimethylaminopyridine; CuI = copper (I) iodide; MsCl = methanesulfonyl chloride; NaN_3 = sodium azide; Na_2SO_4= sodium sulfate; $NaHCO_3$= sodium bicarbonate; NaOH = sodium hydroxide; $MgSO_4$= magnesium sulfate; K_2CO_3 = potassium carbonate; KOH = potassium hydroxide; NH_4OH = ammonium hydroxide; NH_4Cl = ammonium chloride; SiO_2 = silica; Pd–C = palladium on carbon; $Pd(dppf)Cl_2$ = dichloro[1,1'–bis(diphenylphosphino)ferrocene] palladium (II).

Exemplary compounds synthesized in accordance with the invention are listed in Table 1. A bolded or dashed bond is shown to indicate a particular stereochemistry at a chiral center, whereas a wavy bond indicates that the substituent can be in either orientation or that the compound is a mixture thereof. It should also be known that in the interest of conserving space, the chemical structures of some compounds have been split into two parts with the two points of connection each being indicated by a bond crossed by a wavy line. See, e.g. compound 755, which was drawn in two parts as:



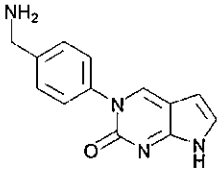
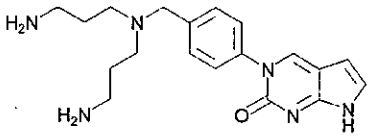
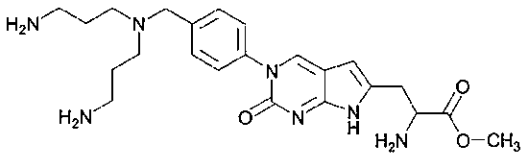
but corresponds to the complete chemical structure:

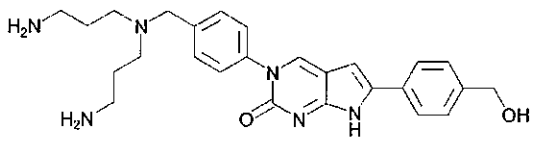
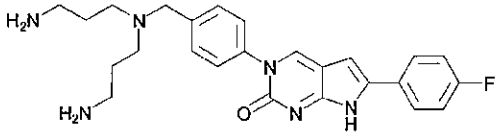
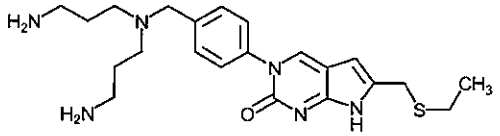
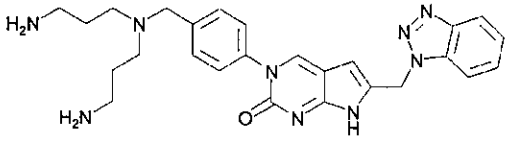
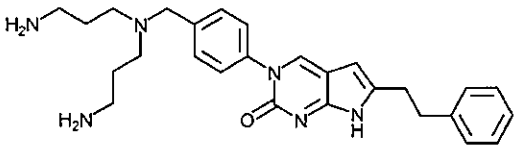
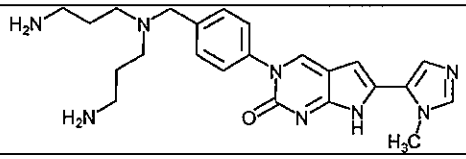
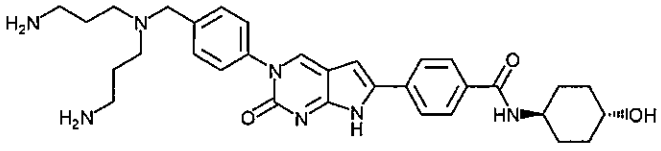
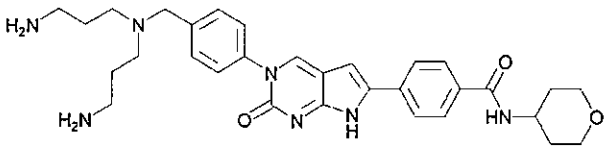


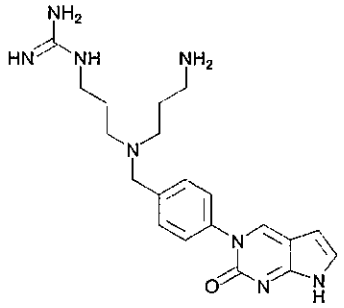
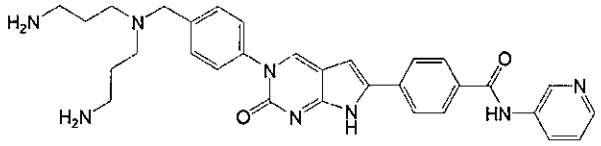
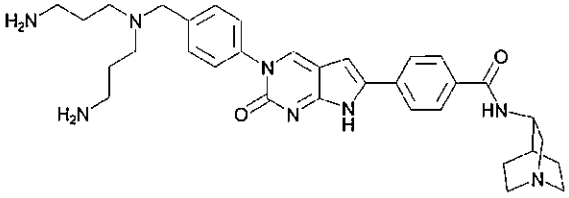
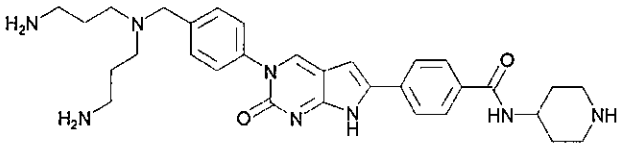
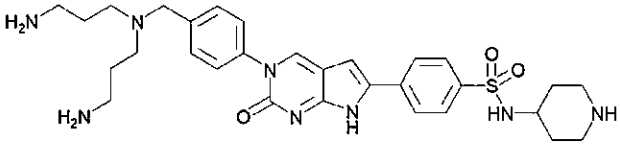
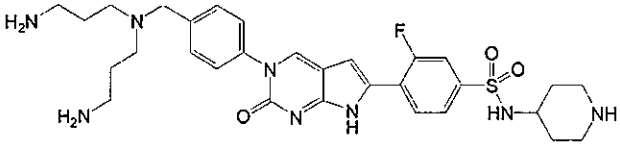
The compounds of the present invention can be prepared, formulated, and delivered as salts, esters, and prodrugs. For convenience, the compounds are generally shown without indicating a particular salt, ester, or prodrug form.

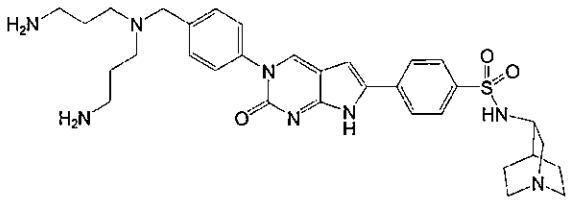
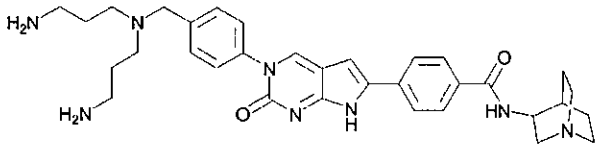
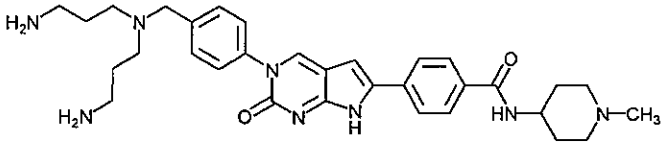
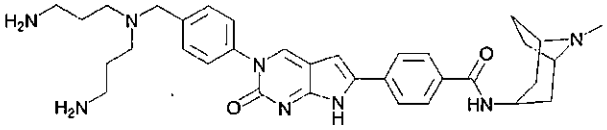
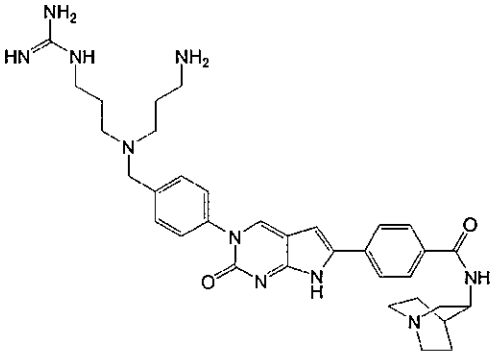
Compounds of the present invention are shown in Table 1. LCMS (liquid chromatography mass spectral) data are provided, where available. When data is not available this is indicated by "NA". The LCMS data are provided using the convention for *m/z* in the format, $[M + H]^+$, except where otherwise indicated.

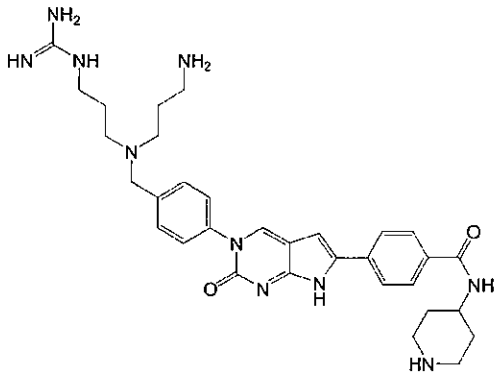
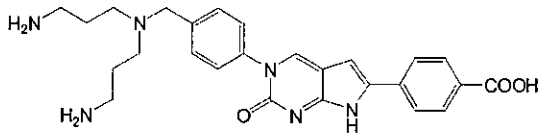
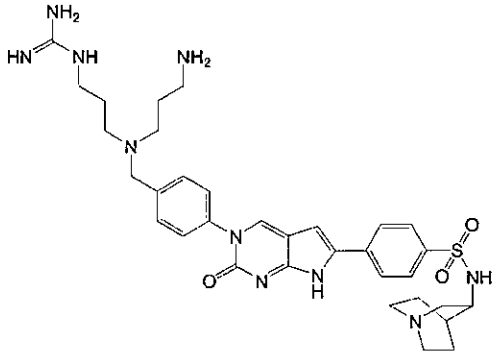
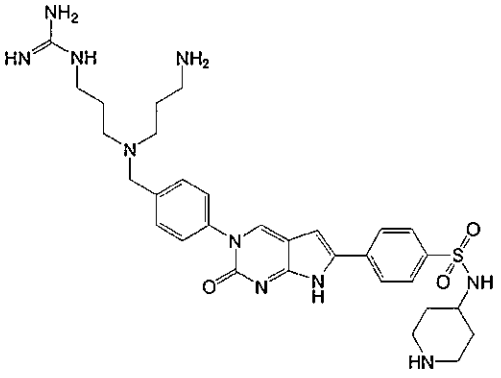
Table 1.

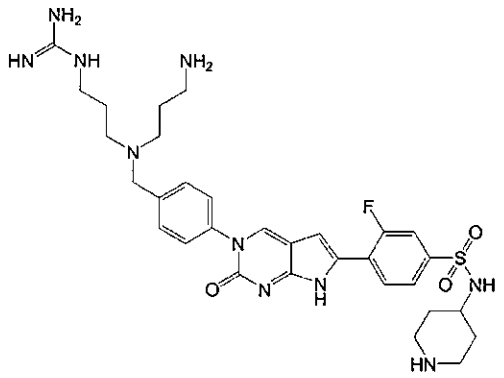
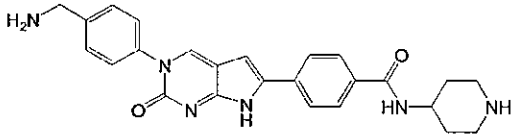
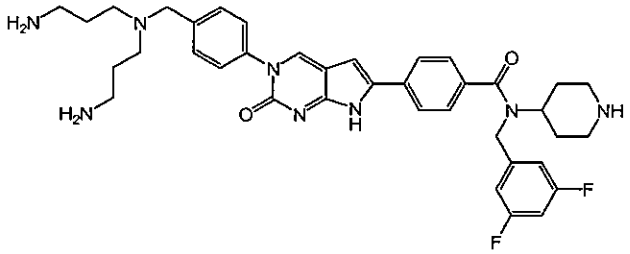
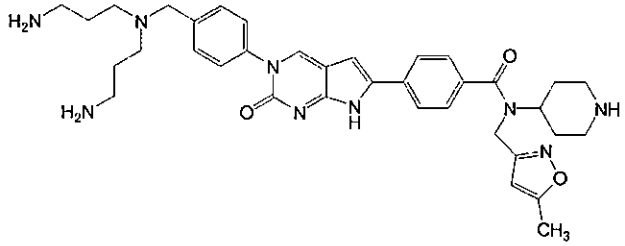
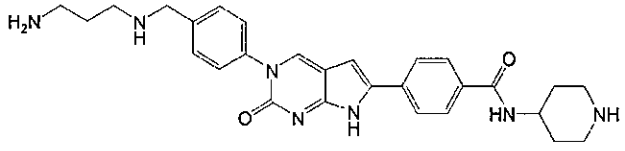
Comp. No.	Structure	LCMS
142		241.00
154		355.10
169		456.20

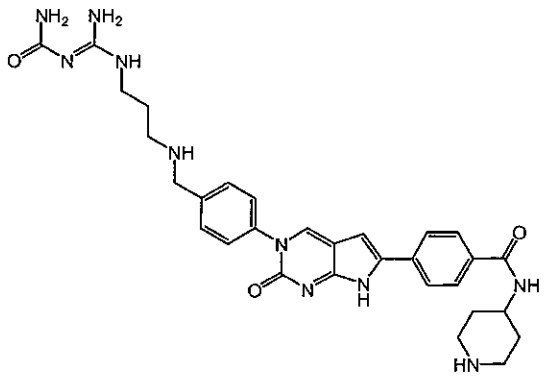
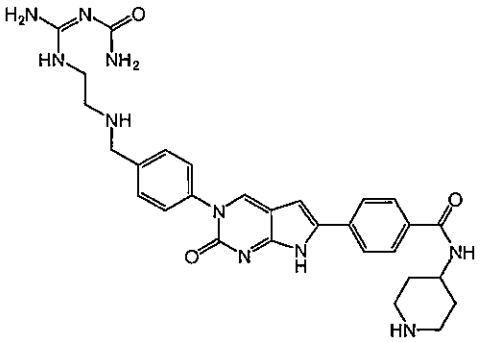
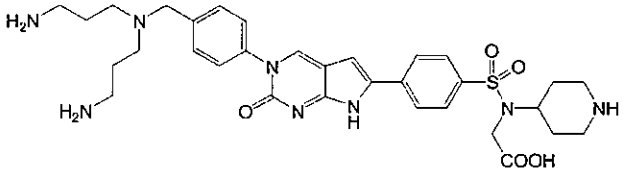
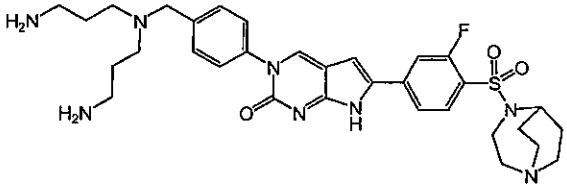
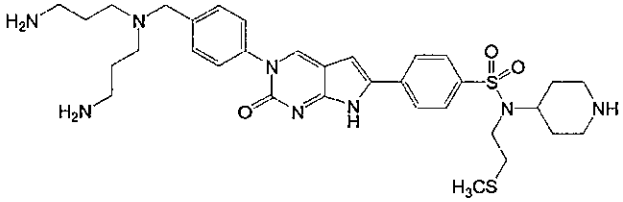
179		461.30
180		449.20
181		486.10
182		486.10
183		459.20
184		435.00
192		572.30
193		558.30

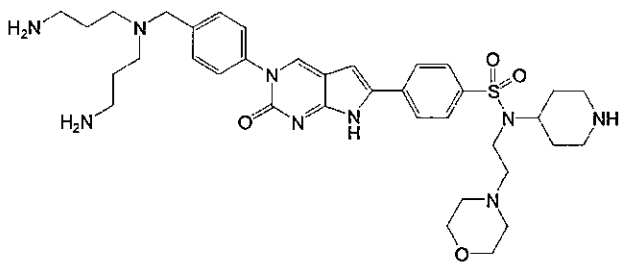
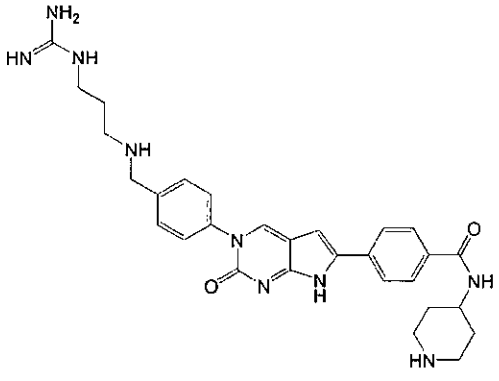
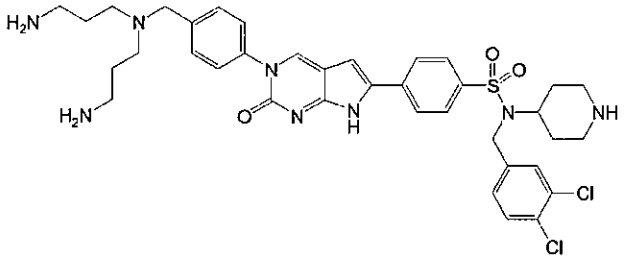
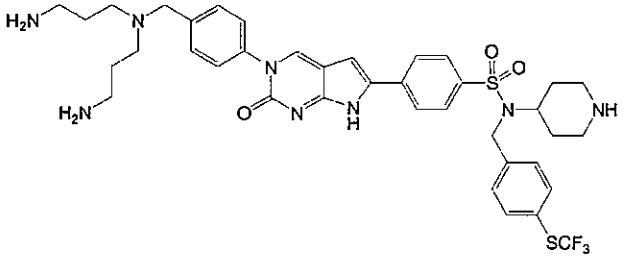
194		397.20
195		551.30
196		583.30
197		557.30
198		593.20
200		611.30

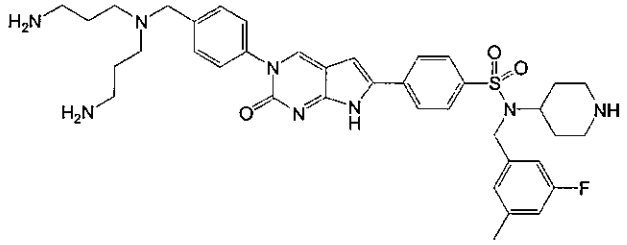
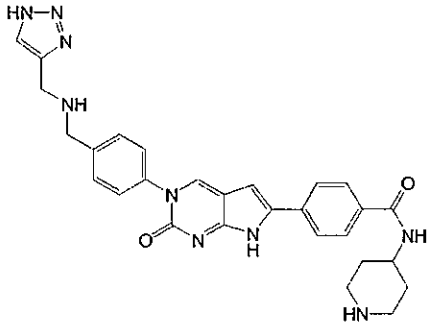
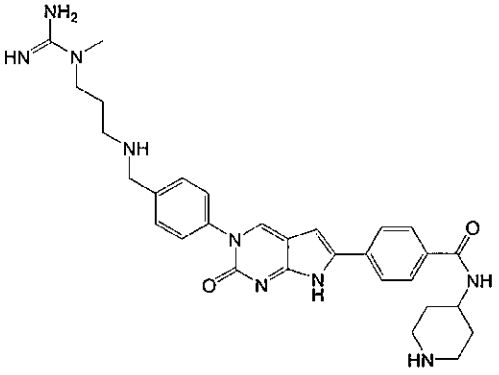
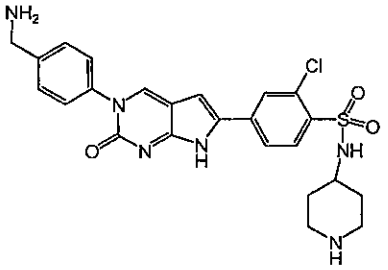
201		619.40
203		583.10
204		571.30
206		597.70
216		625.30

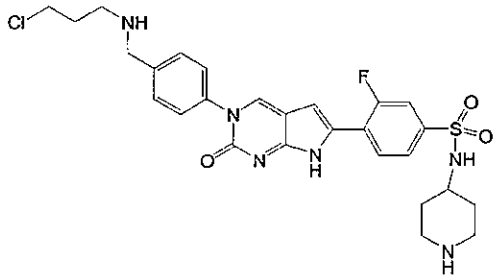
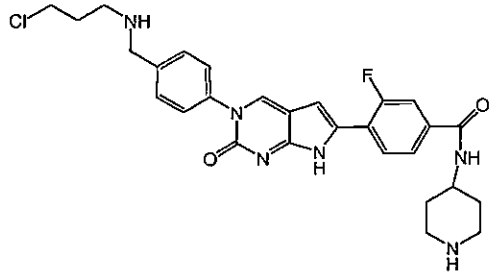
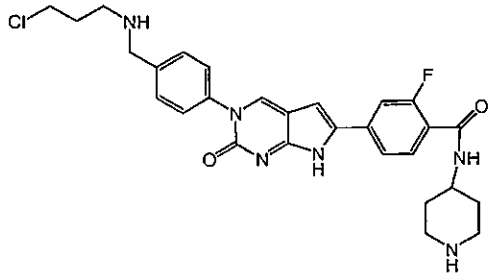
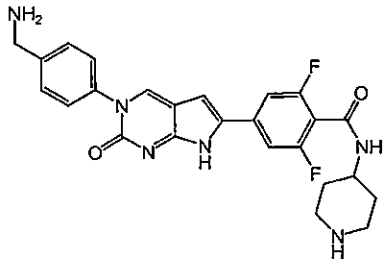
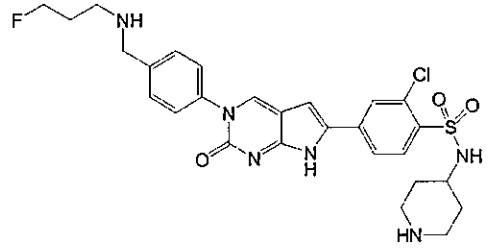
217		559.30
218		475.20
219		661.40
220		635.50

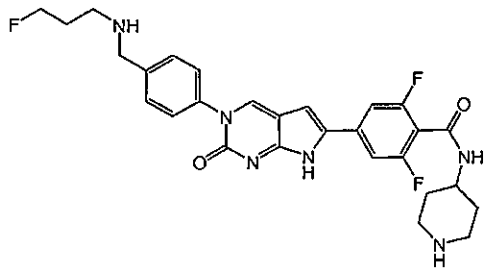
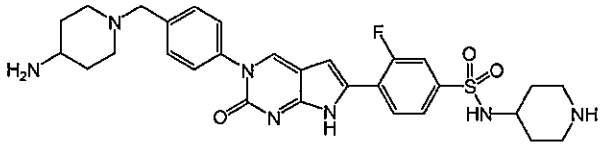
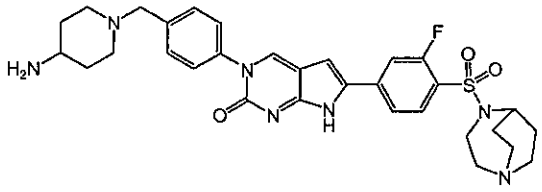
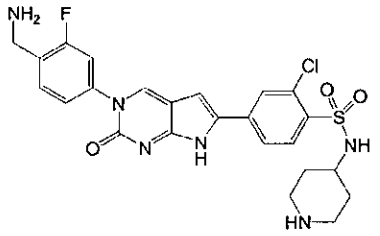
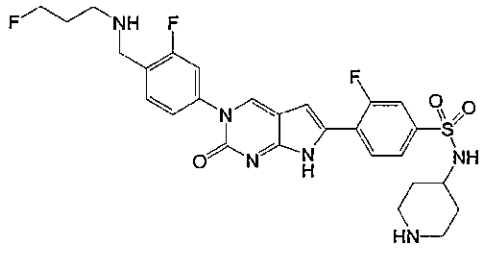
221		653.30
224		443.80
225		683.40
226		652.49
227		501.20

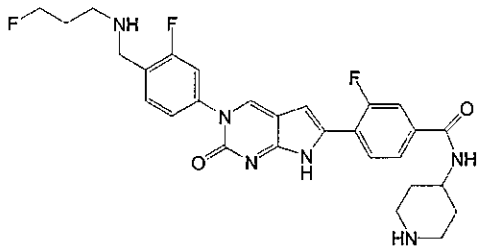
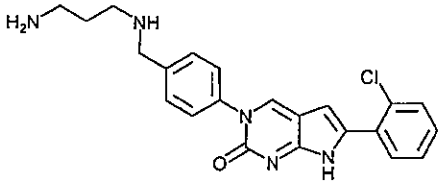
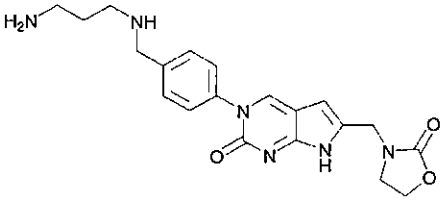
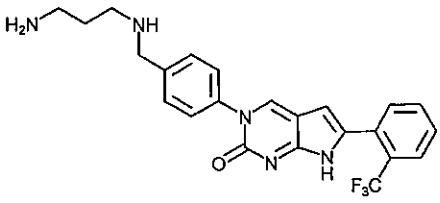
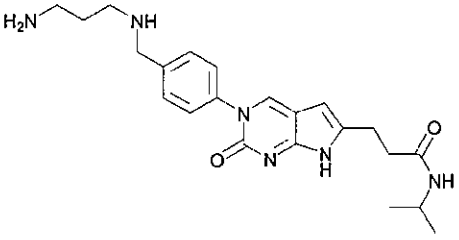
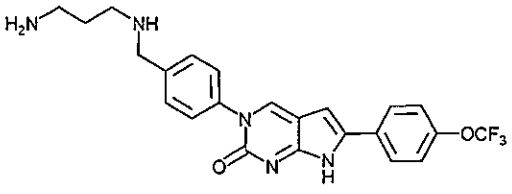
228		585.30
229		572.40
230		651.70
231		637.30
232		667.60

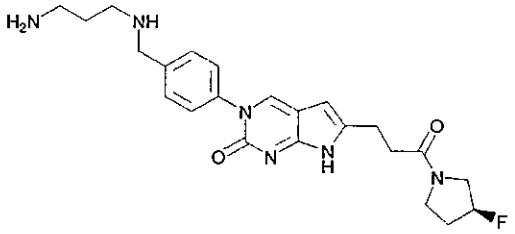
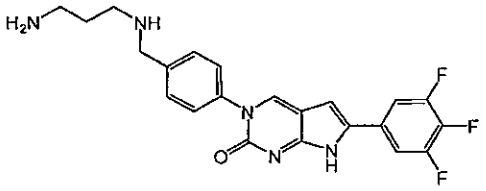
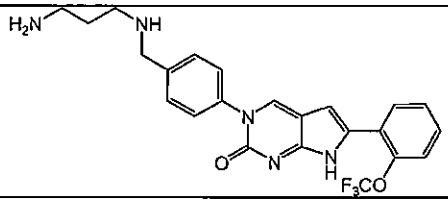
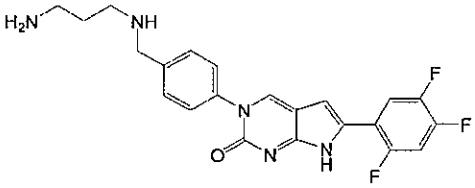
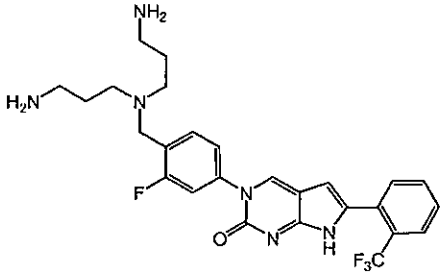
233		706.60
234		542.40
235		753.70
236		783.50

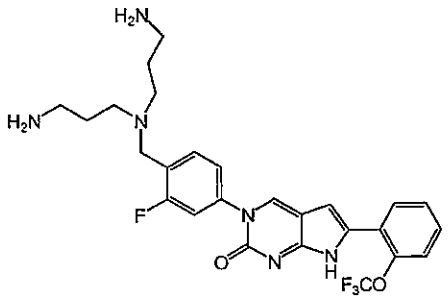
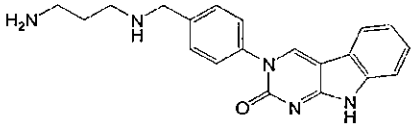
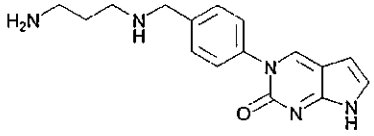
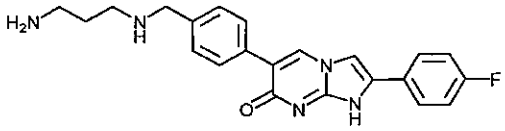
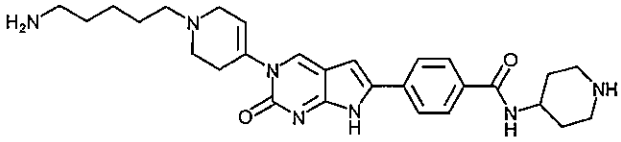
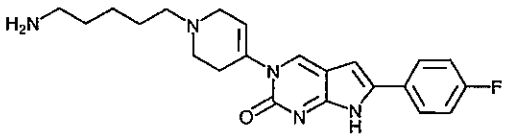
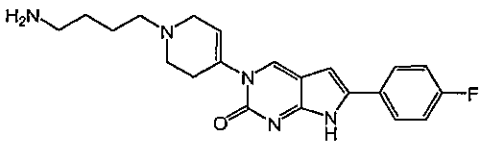
237		715.60
240		524.40
241		556.40
245		513.10

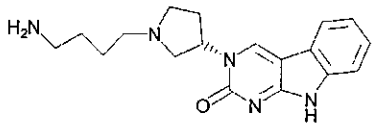
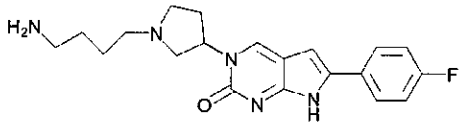
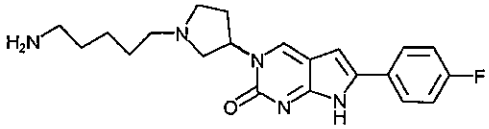
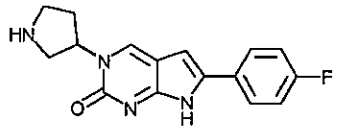
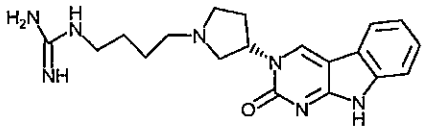
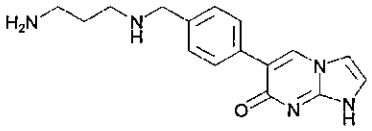
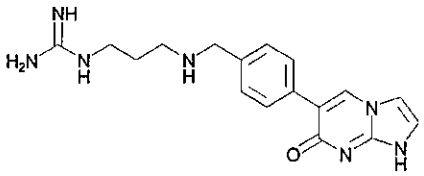
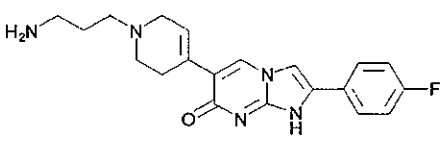
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253		537.60
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258		479.20
261		573.40

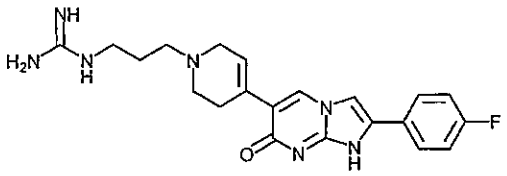
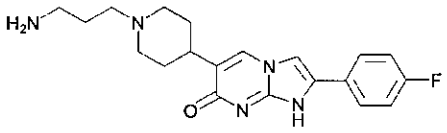
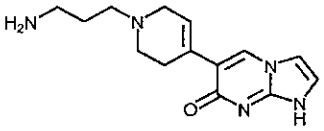
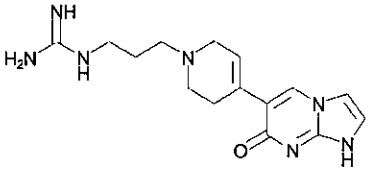
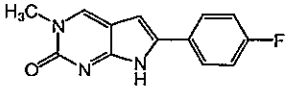
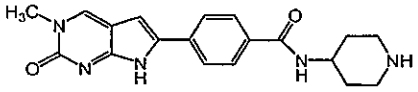
262		539.30
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279		575.30

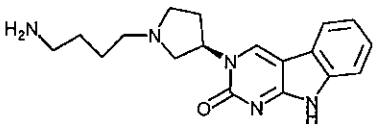
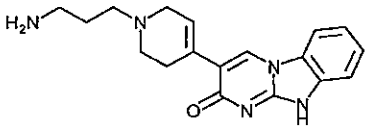
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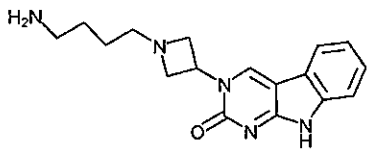
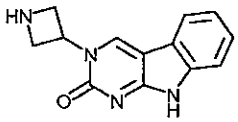
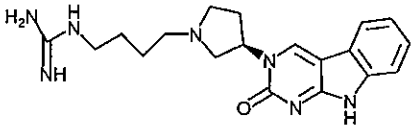
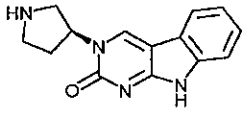
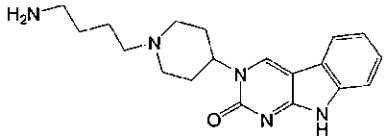
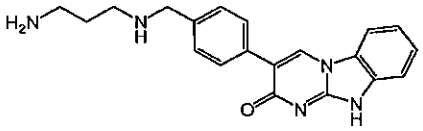
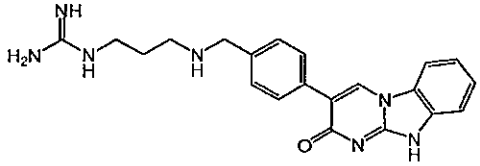
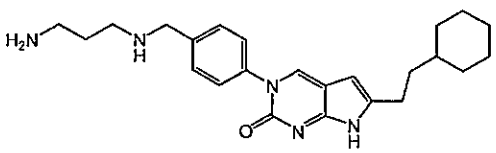
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318		517.30

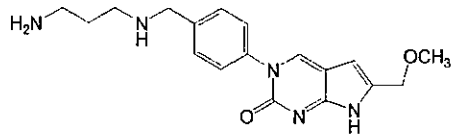
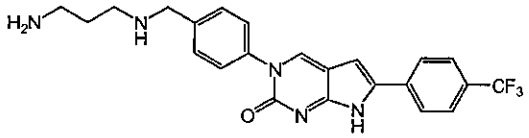
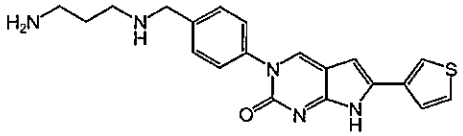
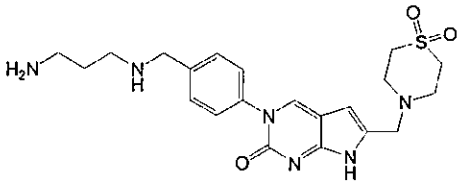
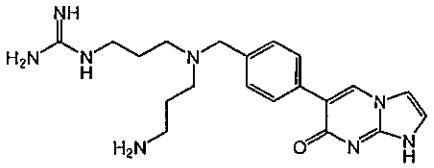
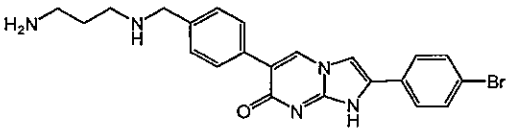
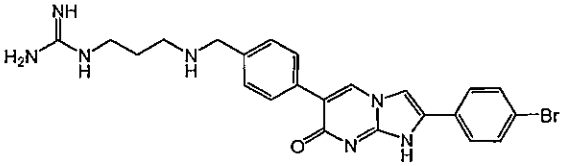
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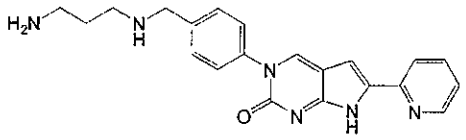
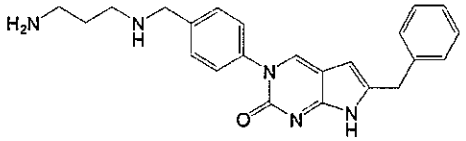
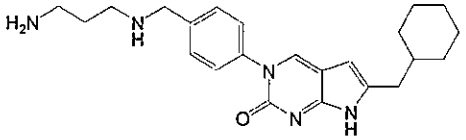
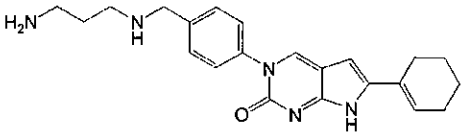
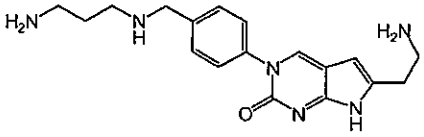
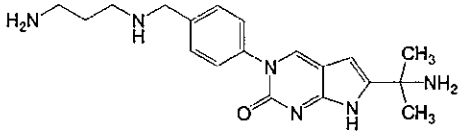
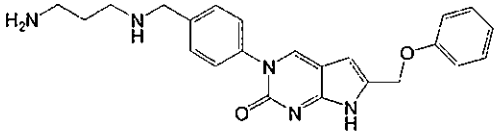
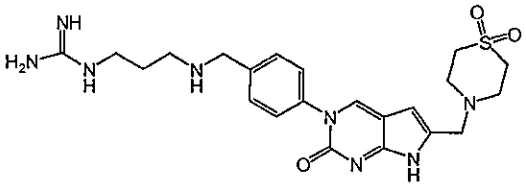
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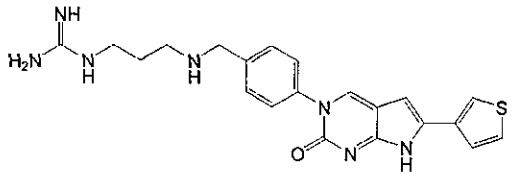
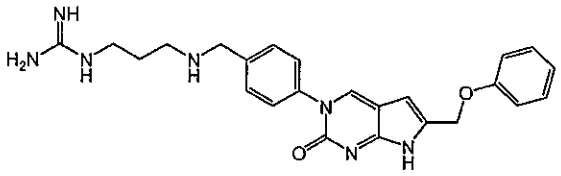
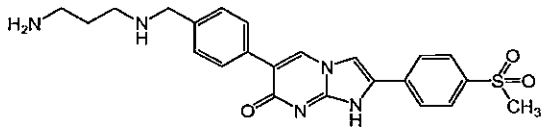
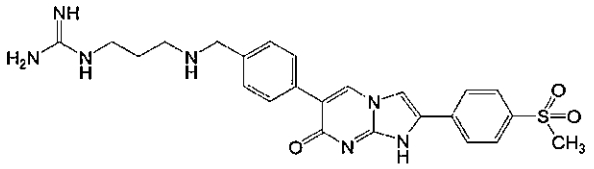
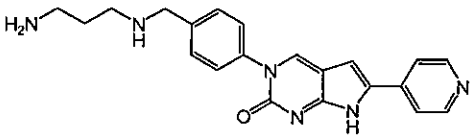
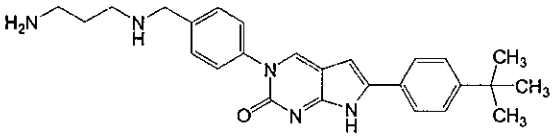
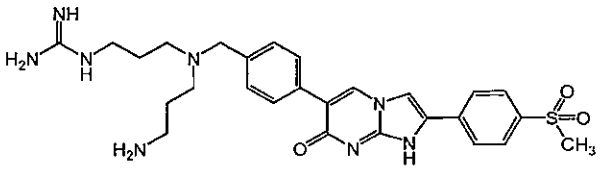
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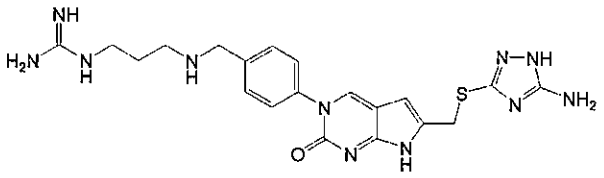
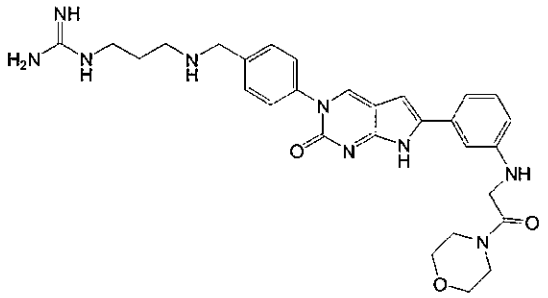
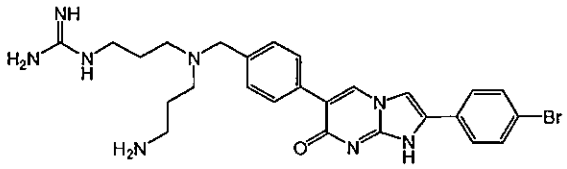
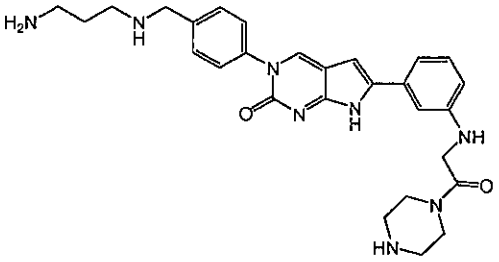
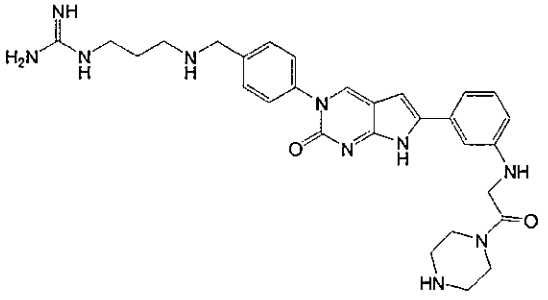
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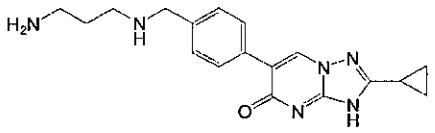
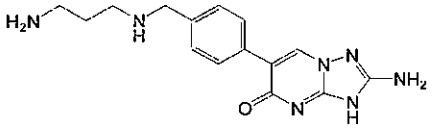
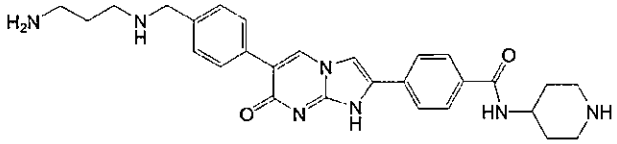
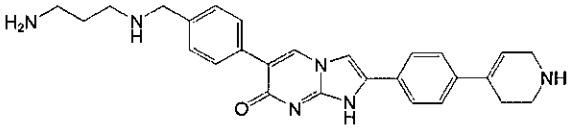
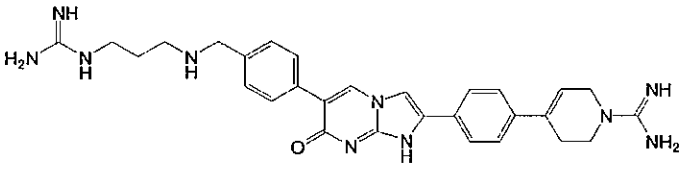
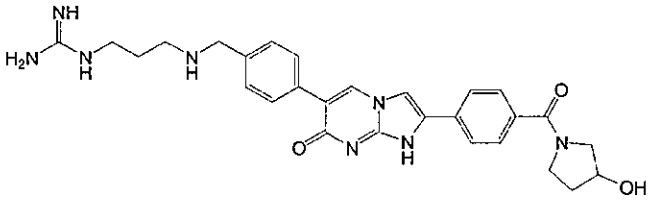
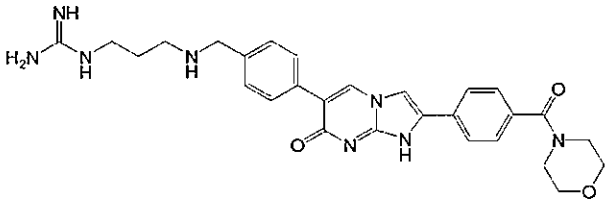
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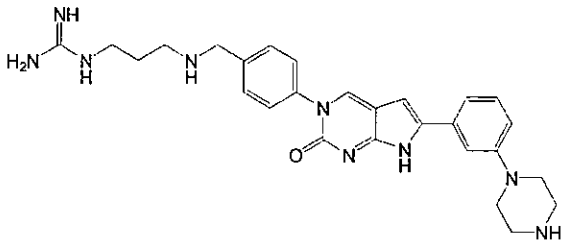
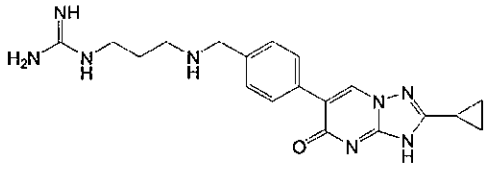
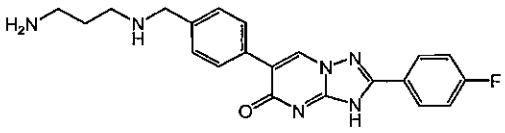
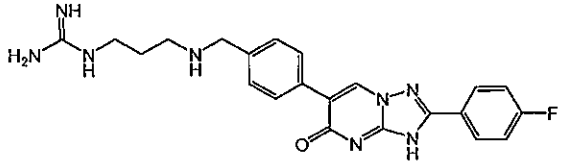
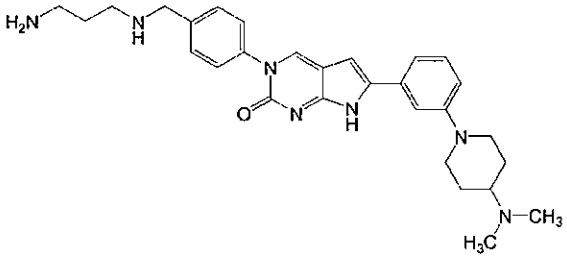
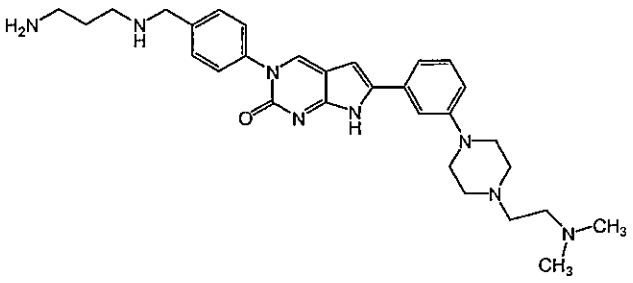
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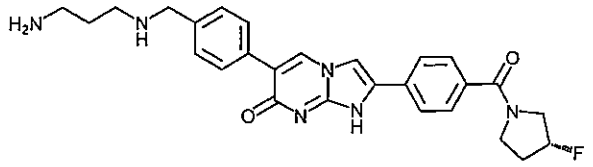
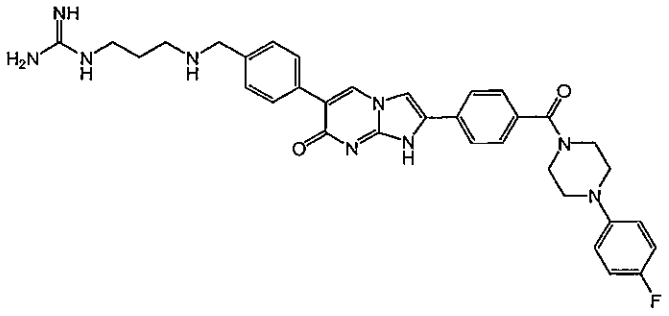
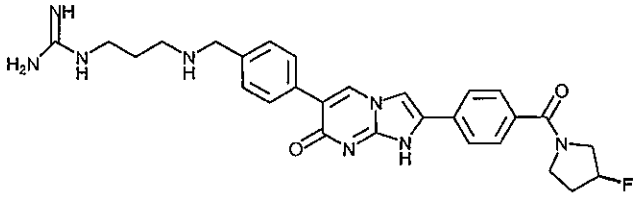
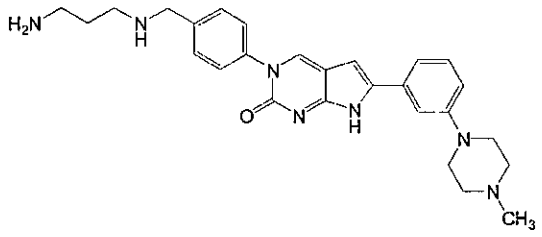
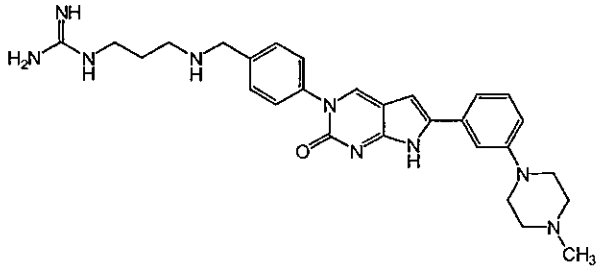
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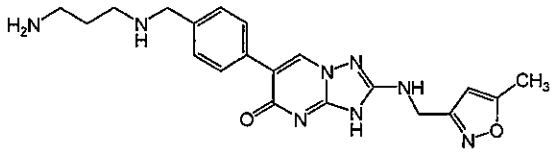
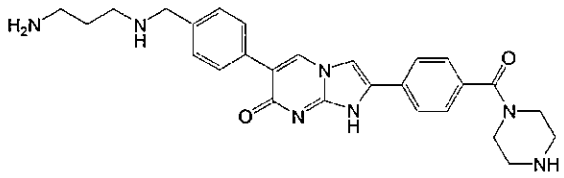
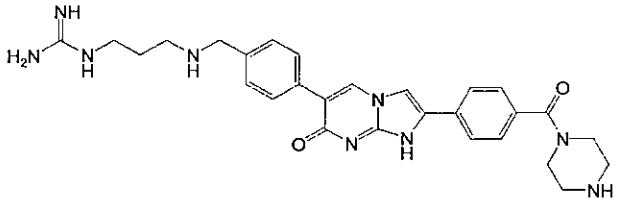
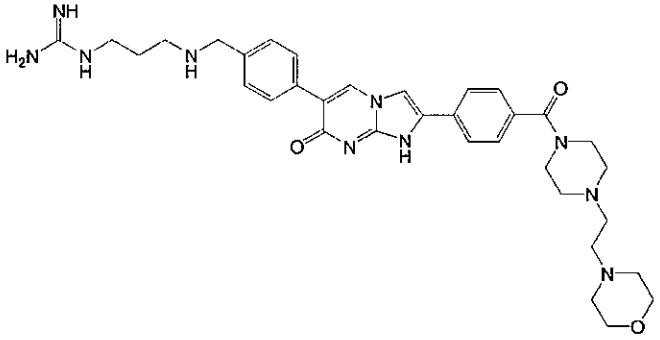
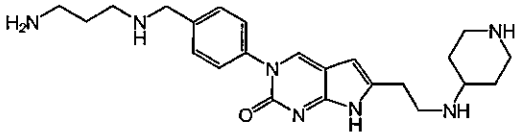
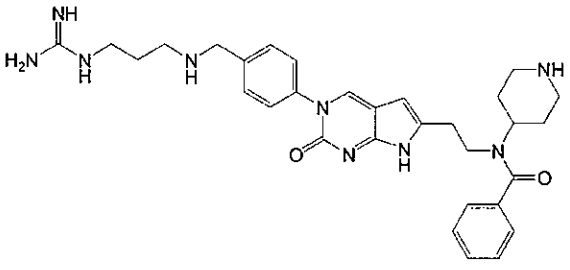
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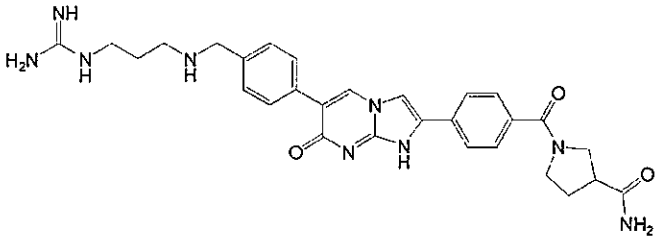
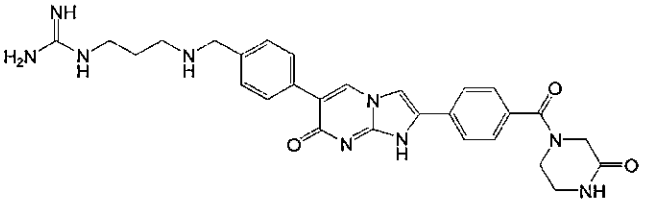
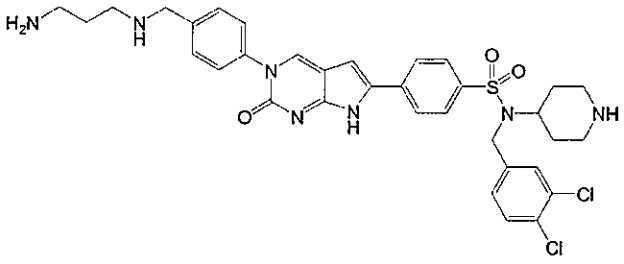
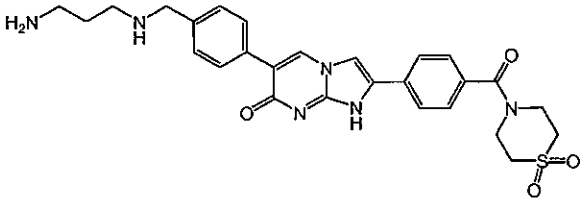
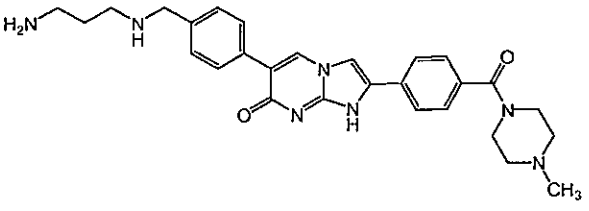
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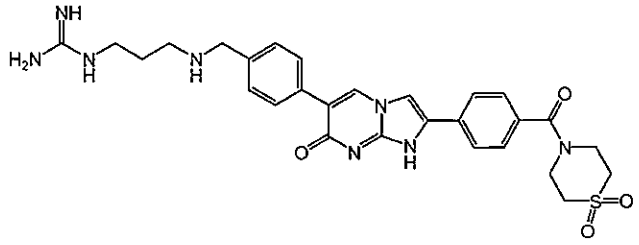
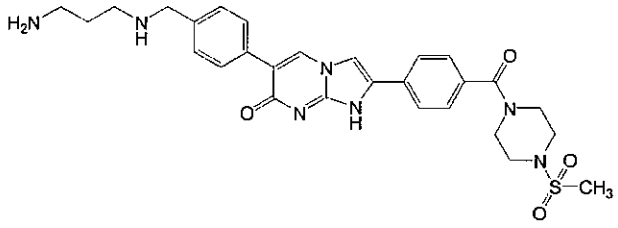
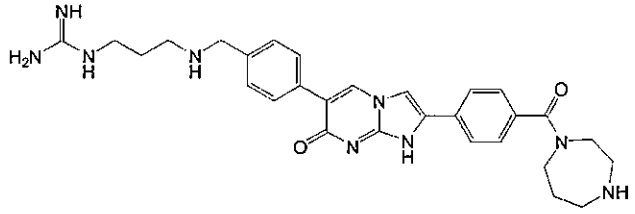
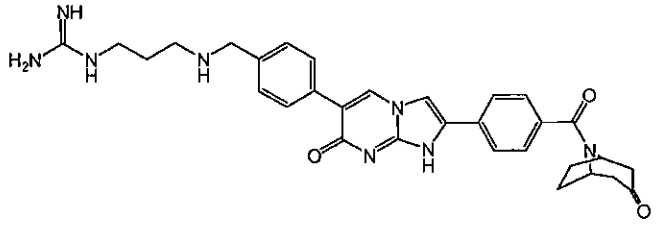
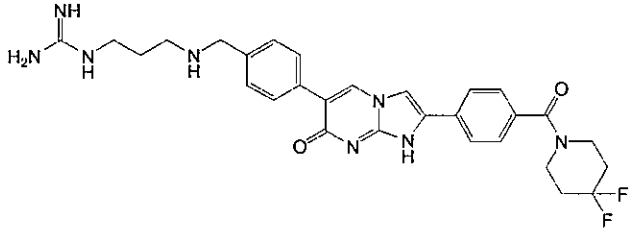
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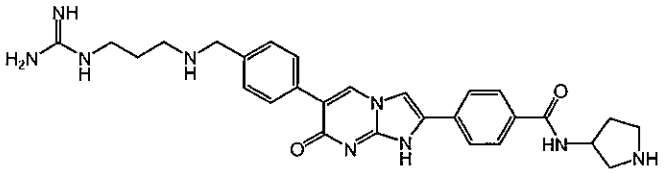
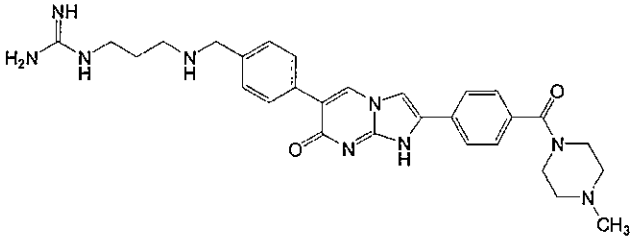
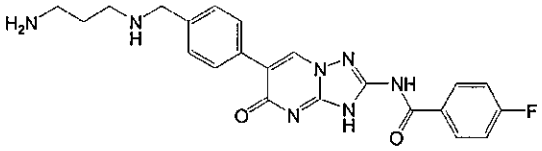
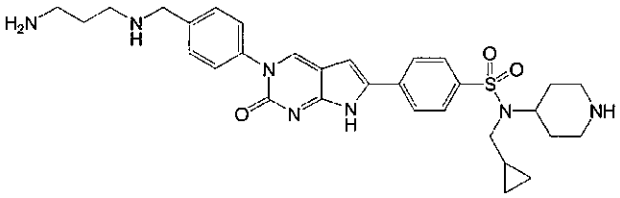
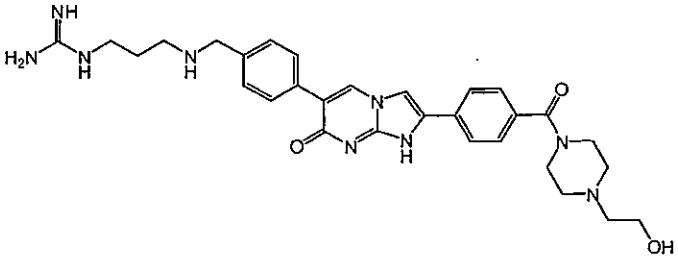
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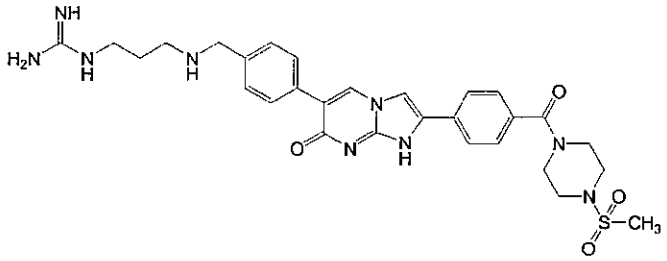
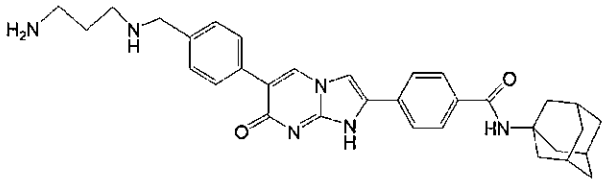
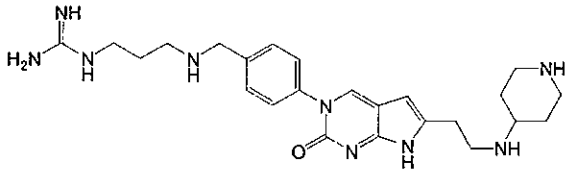
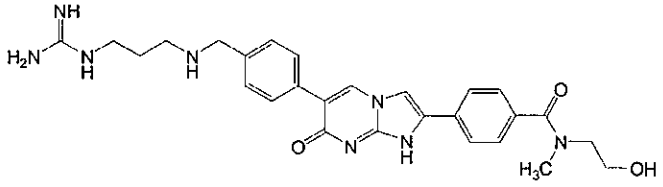
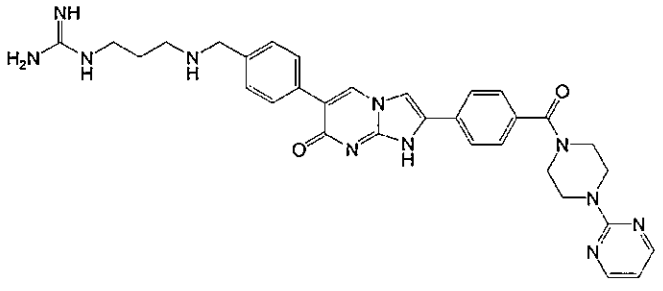
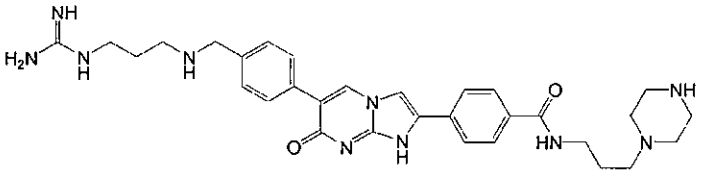
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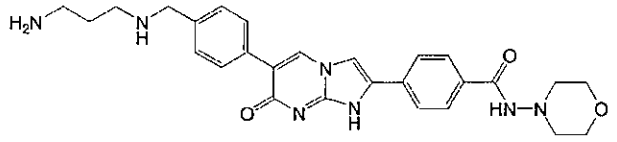
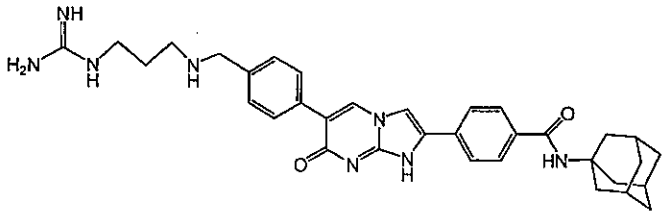
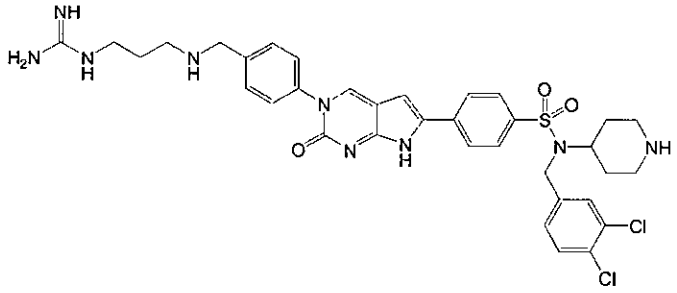
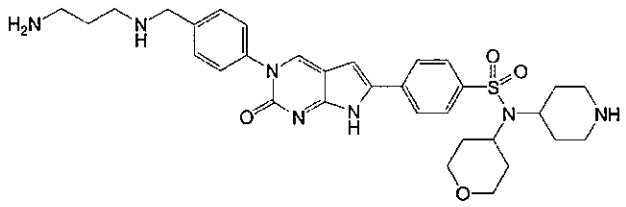
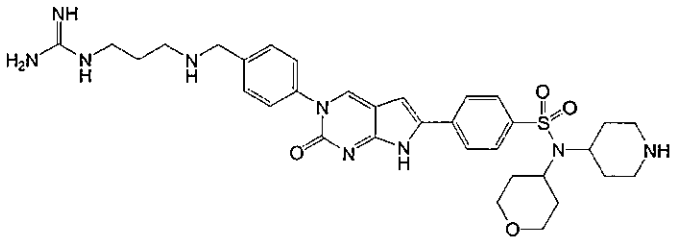
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684		641.30
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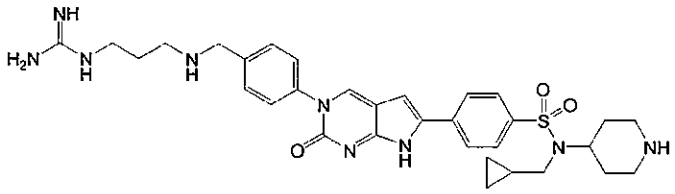
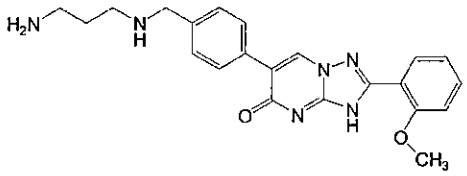
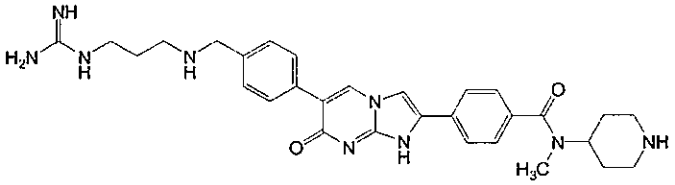
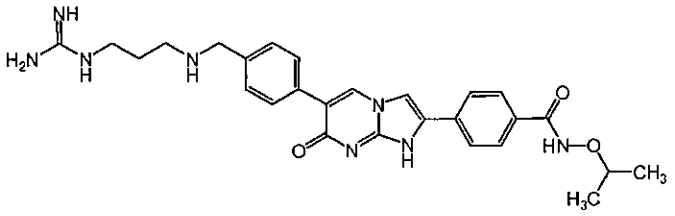
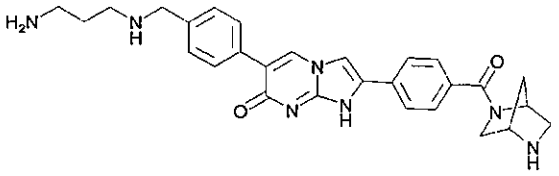
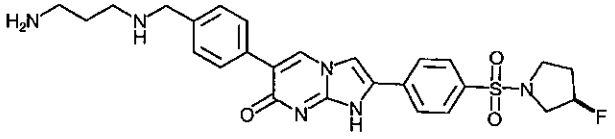
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693		542.10
697		694.10
698		N/A
699		N/A

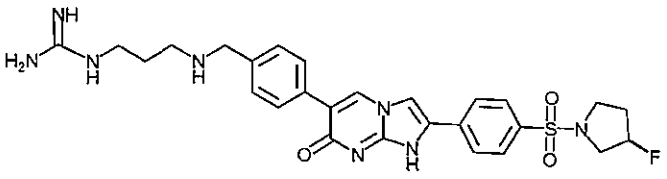
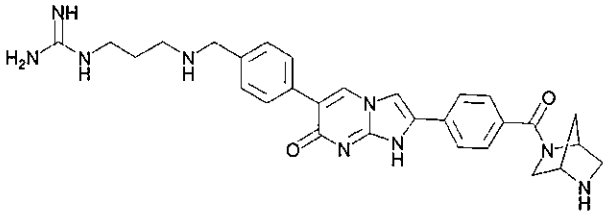
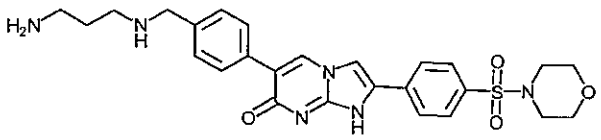
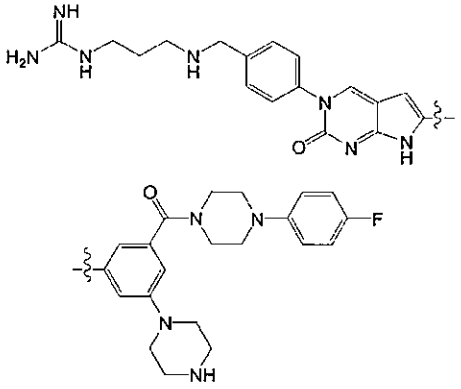
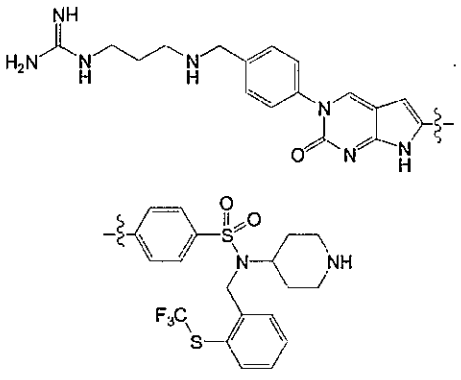
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701		564.10
702		543.10
703		567.20
704		563.20

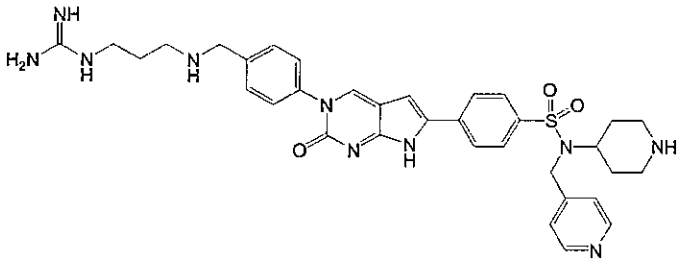
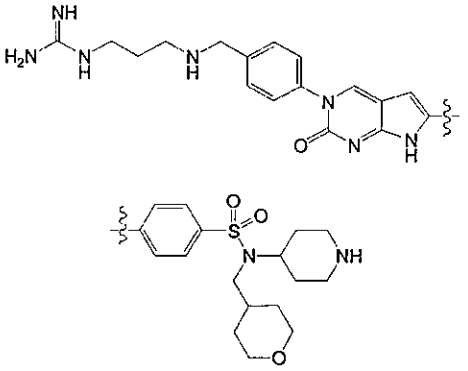
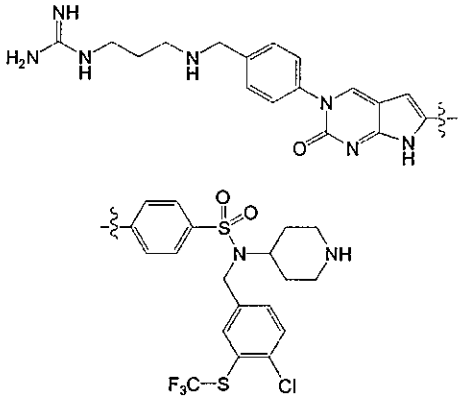
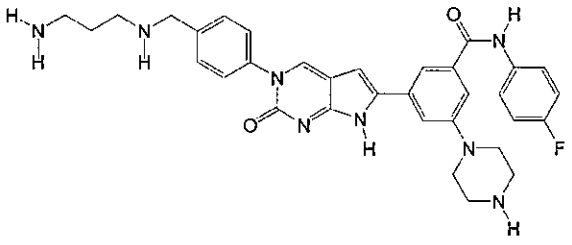
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706		542.30
709		436.00
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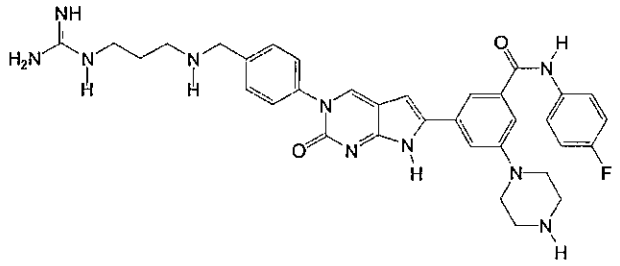
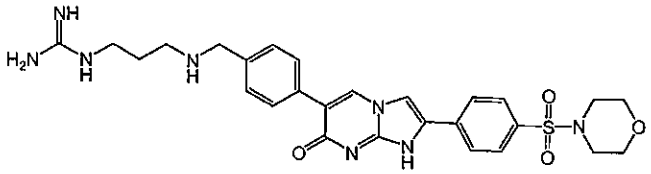
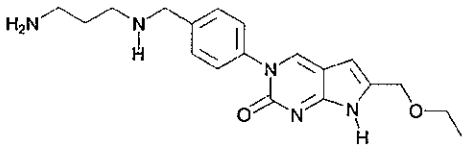
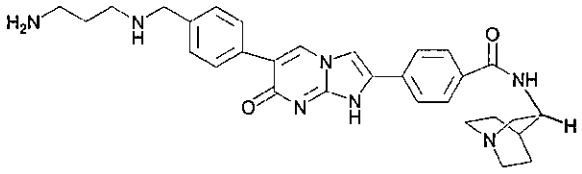
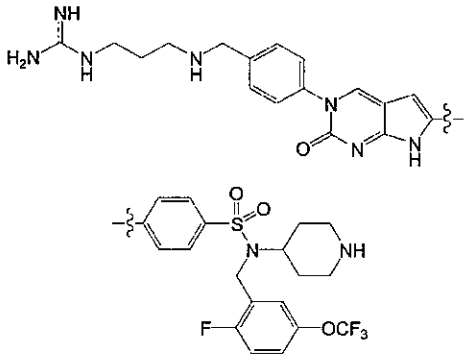
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719		466.00
720		517.10
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722		585.20

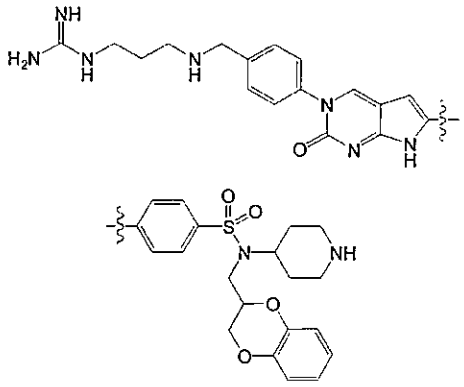
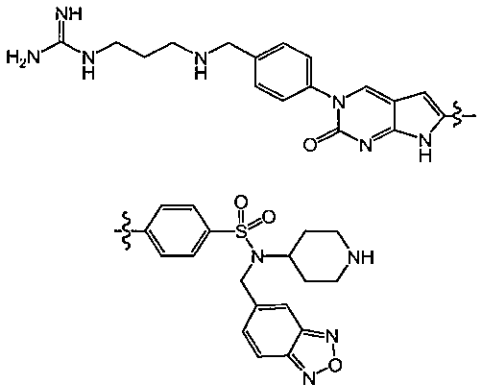
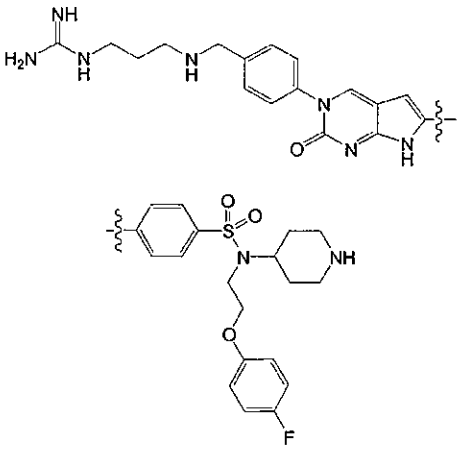
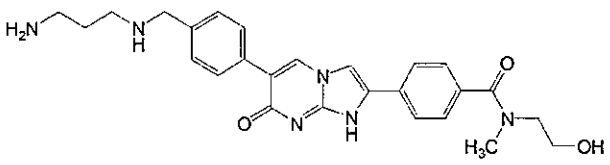
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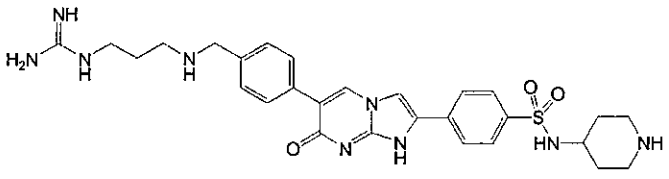
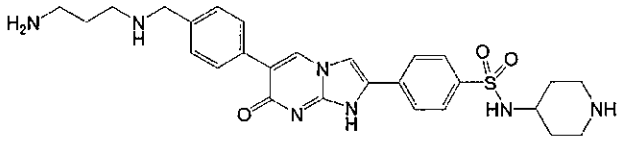
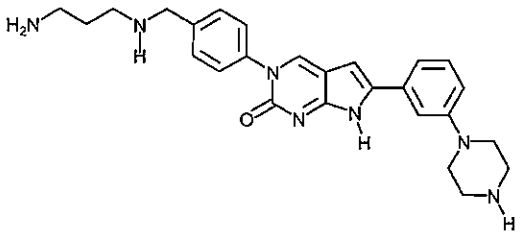
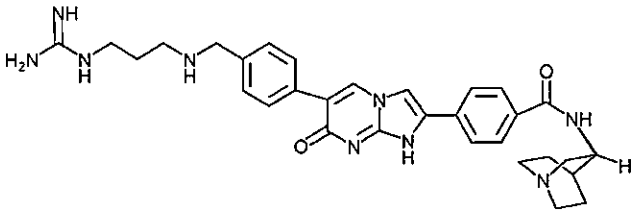
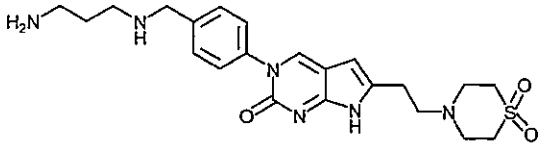
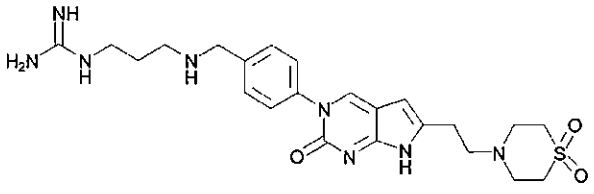
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736		556.10
737		517.20
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743		525.10

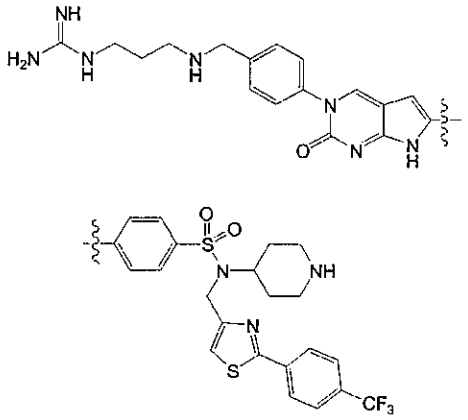
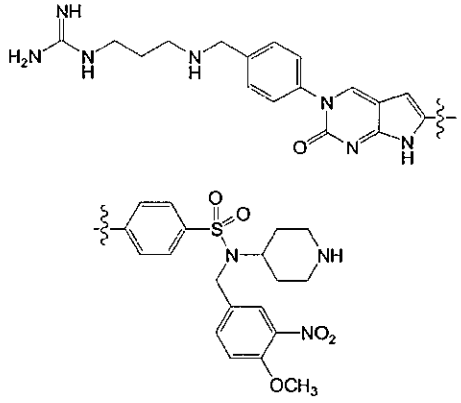
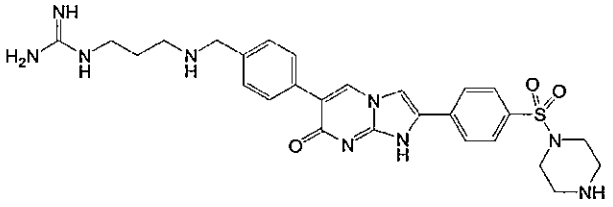
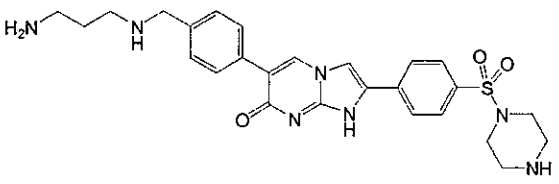
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756		768.00

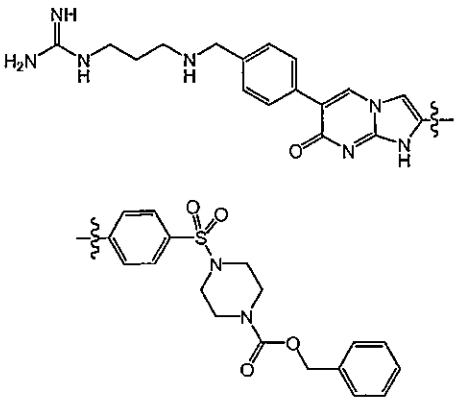
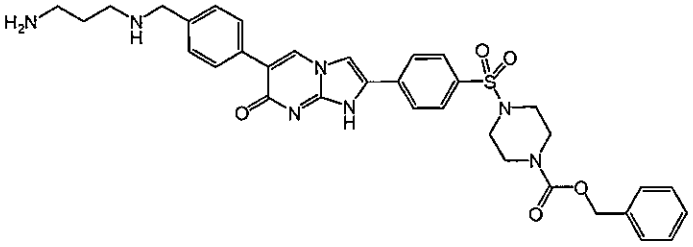
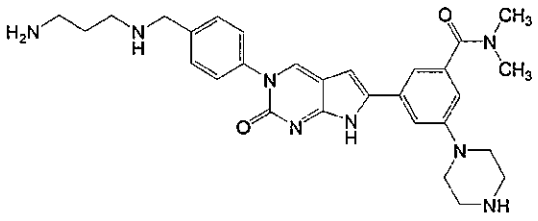
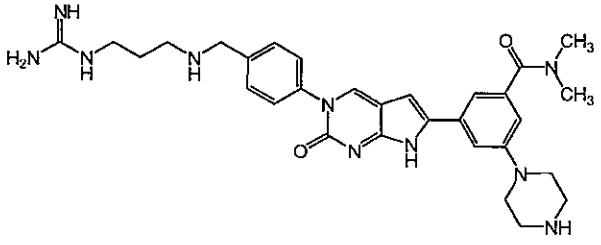
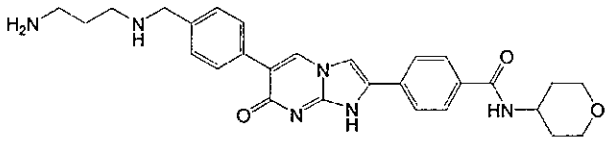
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759		802.00
760		595.30

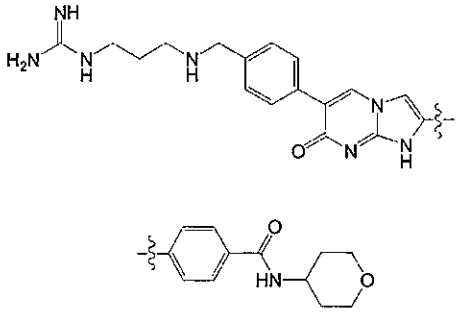
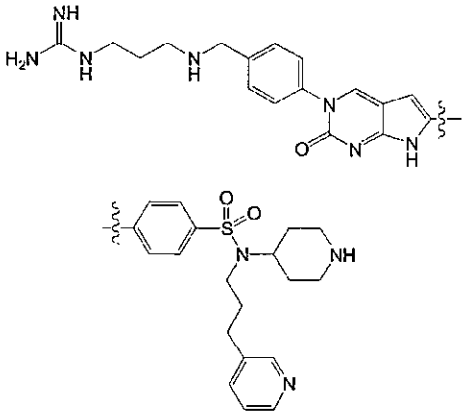
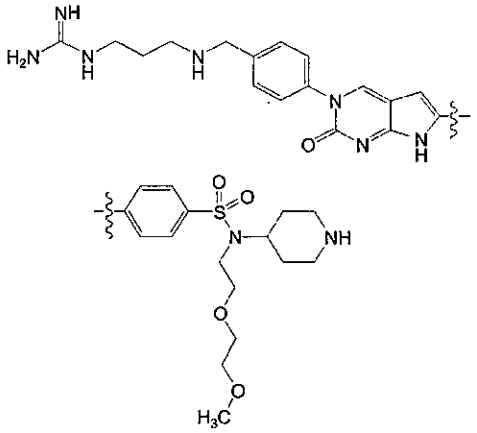
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762		565.20
764		356.00
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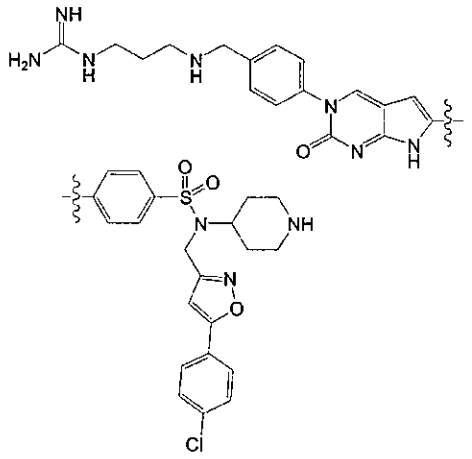
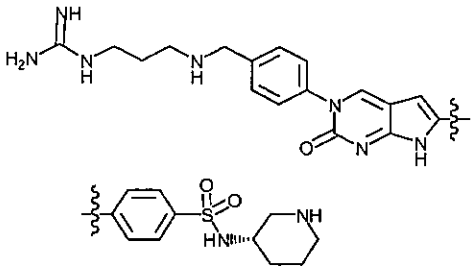
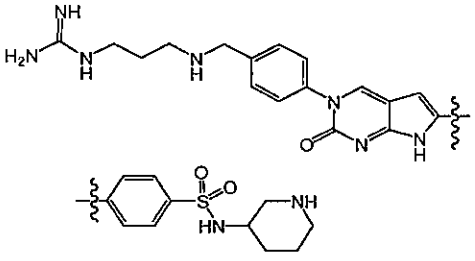
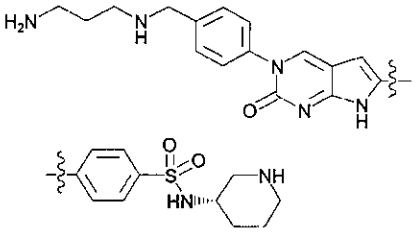
768		726.00
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771		475.20

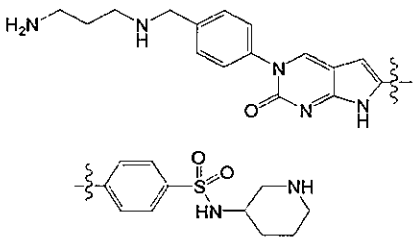
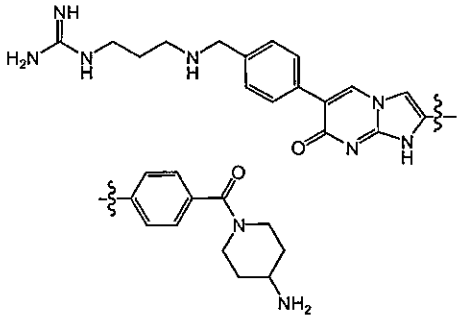
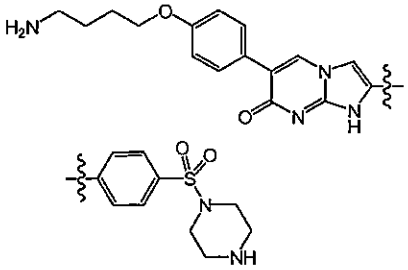
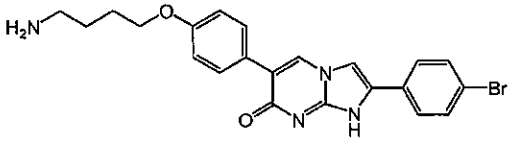
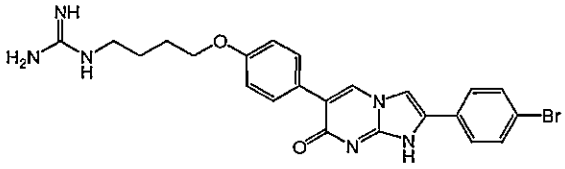
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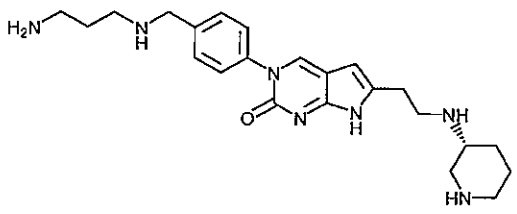
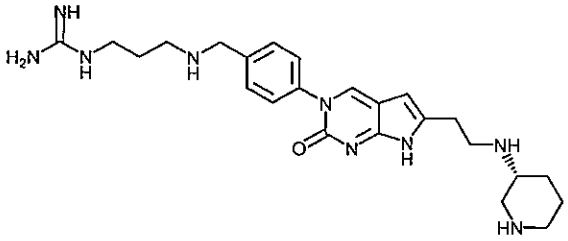
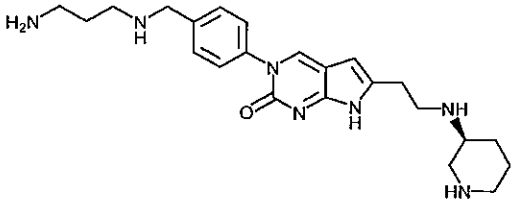
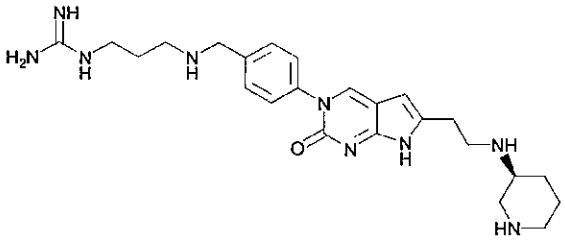
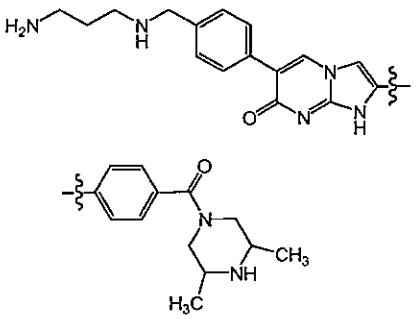
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787		743.00
788		564.20
789		522.00

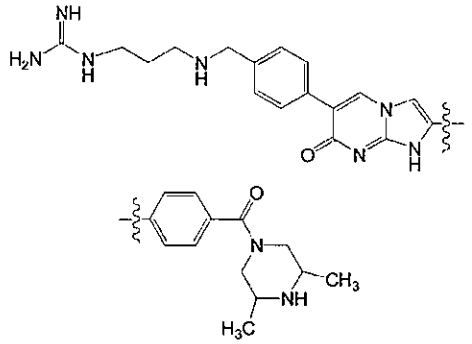
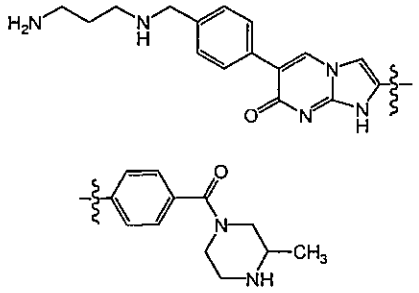
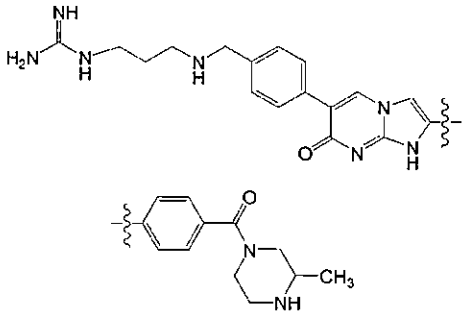
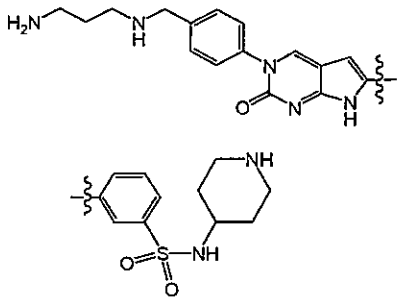
790		698.30
791		656.30
796		529.00
797		571.00
799		502.20

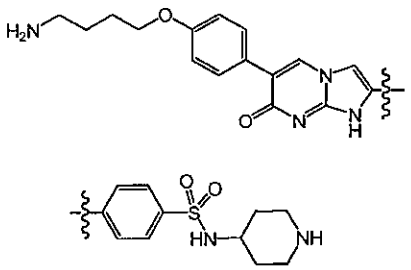
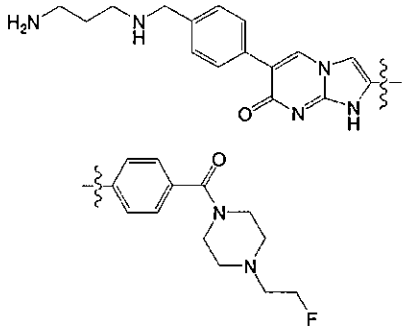
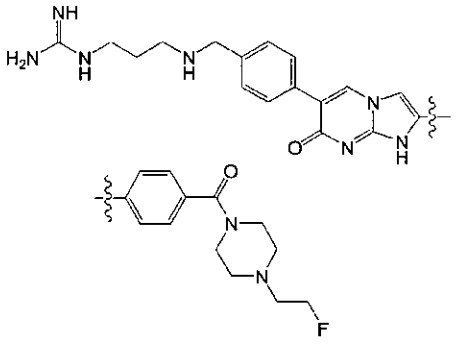
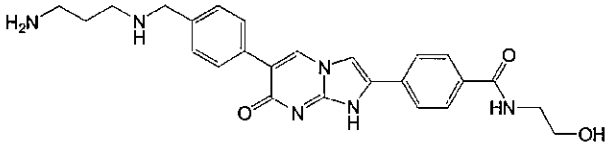
800		544.30
801		697.00
802		680.00

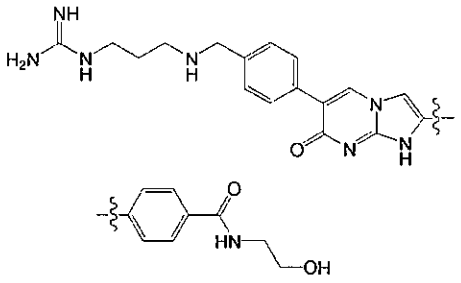
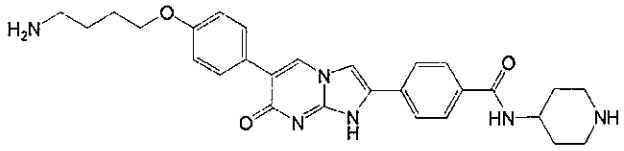
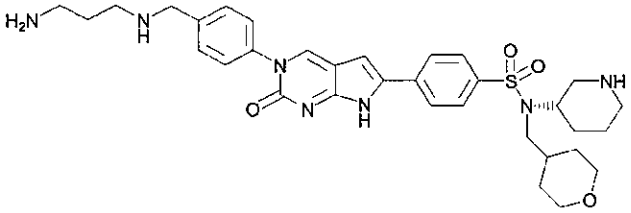
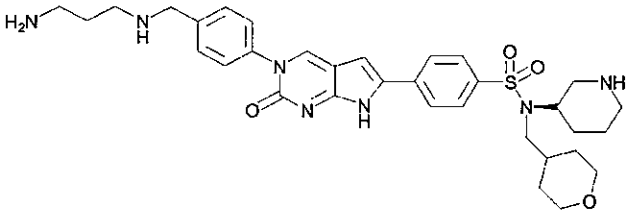
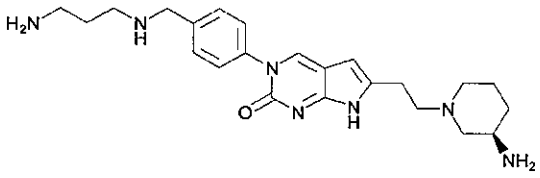
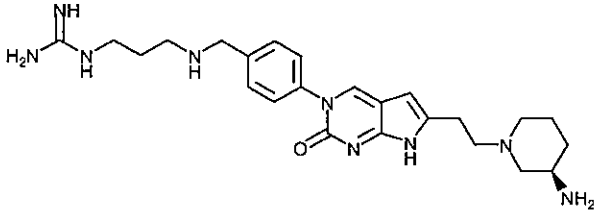
803		769.00
804		N/A
805		N/A
806		N/A

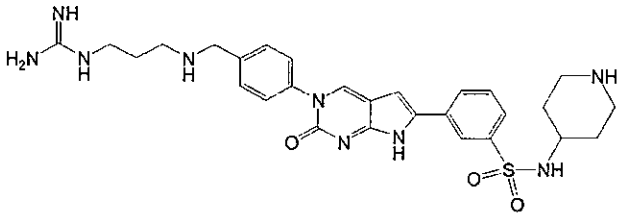
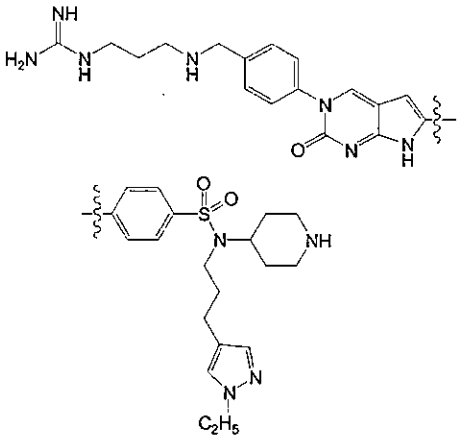
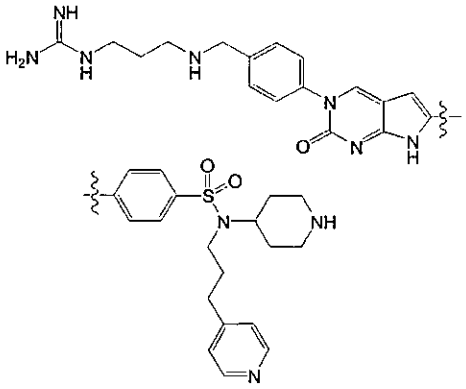
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808		542.30
809		523.20
810		453.00
813		497.10

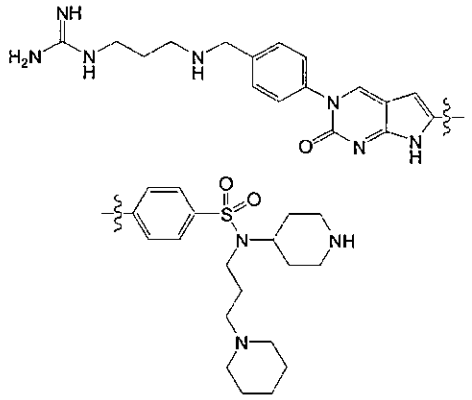
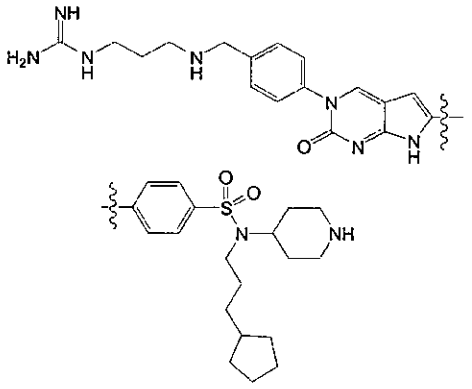
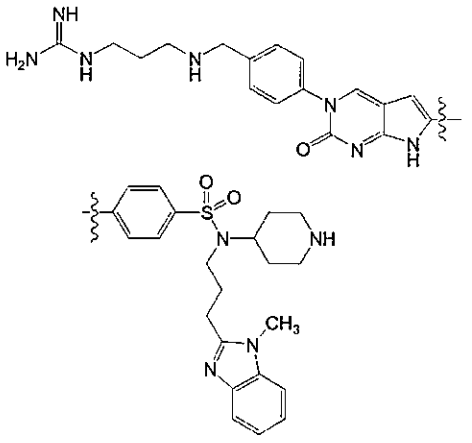
814		424.00
815		466.00
816		424.00
817		466.00
819		514.30

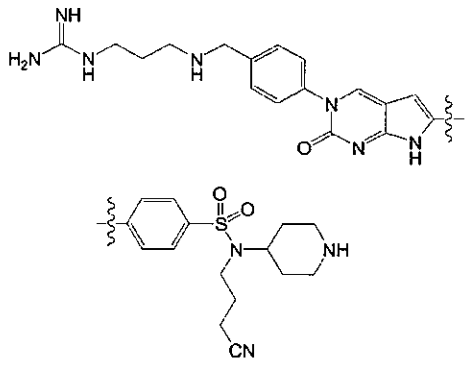
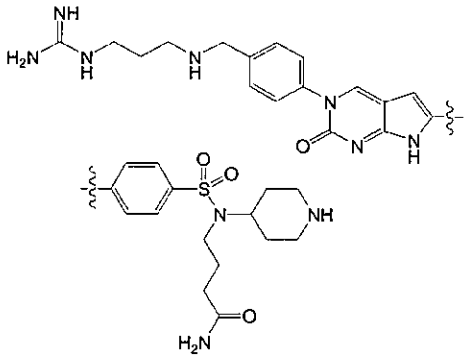
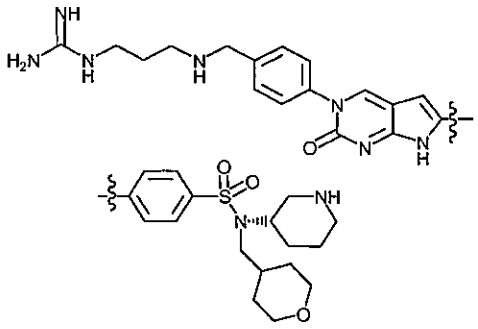
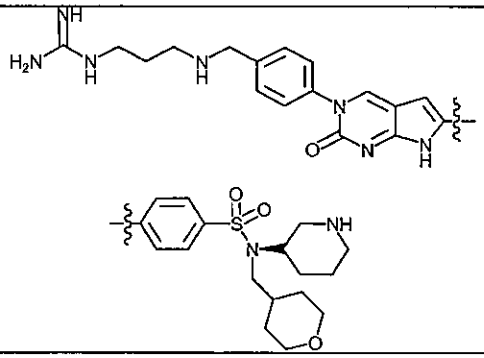
820		556.30
821		500.20
822		542.30
823		536.10

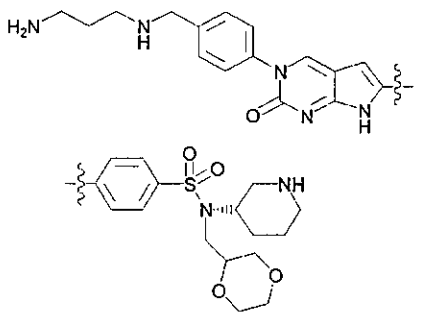
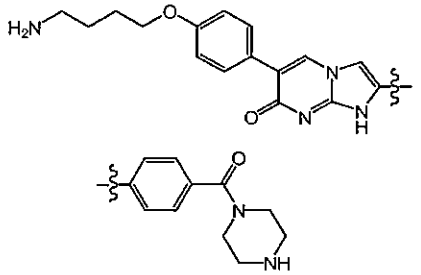
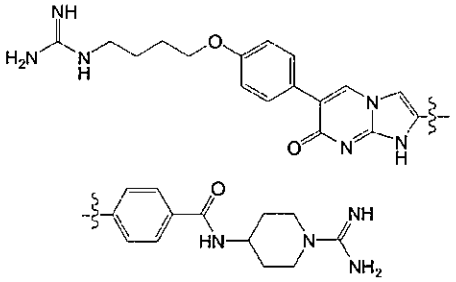
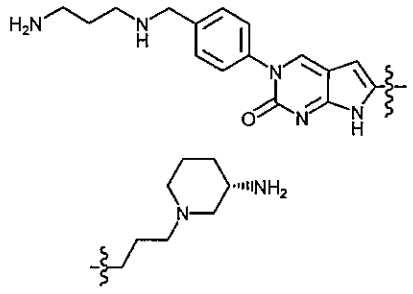
824		N/A
825		532.20
826		574.30
827		461.20

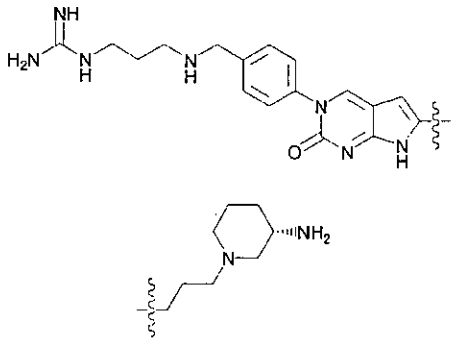
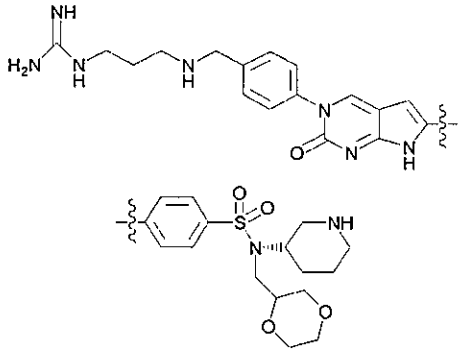
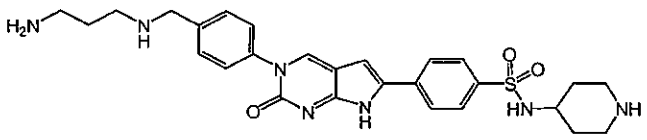
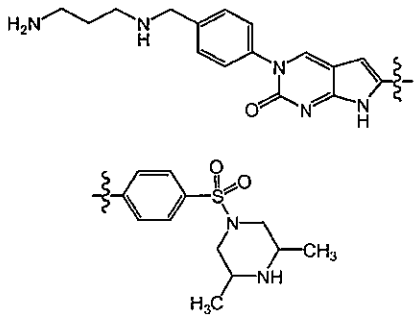
828		503.10
829		501.40
830		634.30
831		634.30
834		438.00
835		480.00

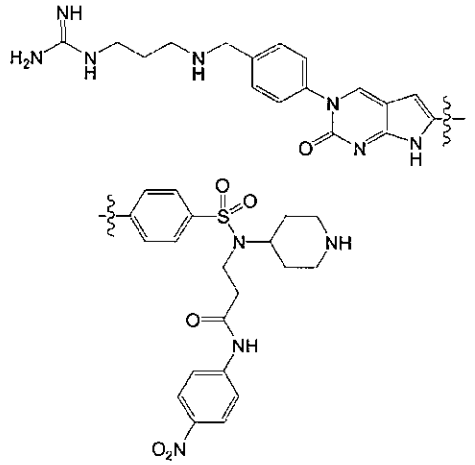
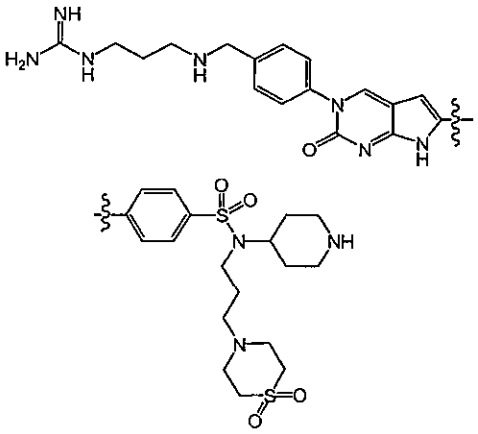
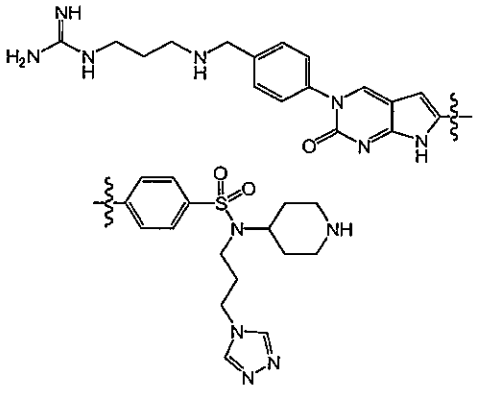
836		578.30
837		714.00
838		697.00

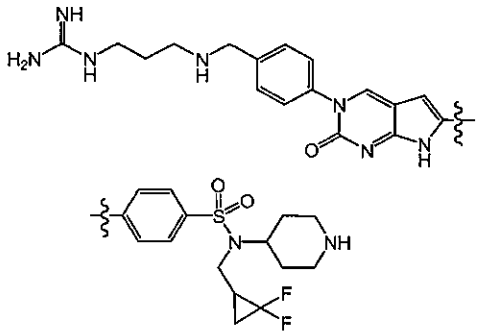
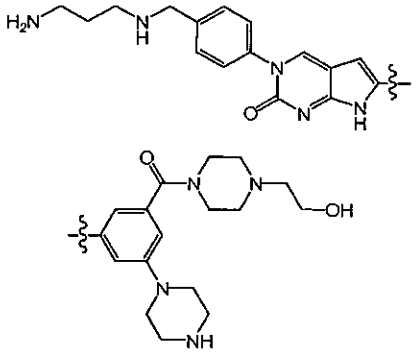
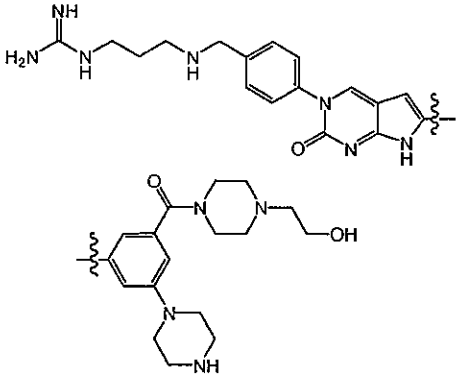
839		703.00
840		688.00
841		750.00

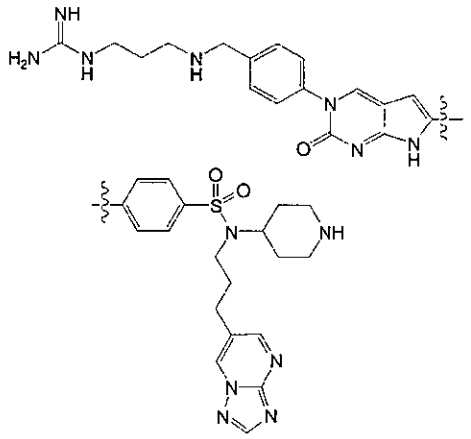
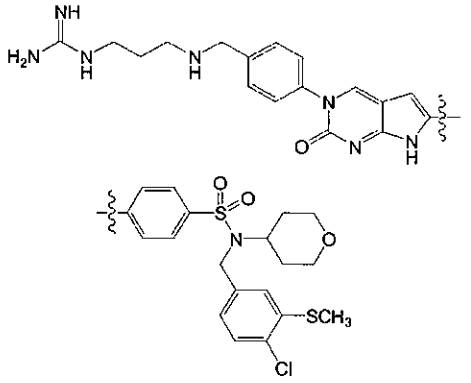
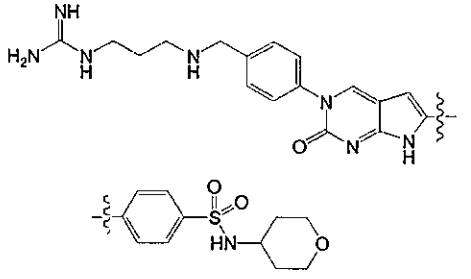
842		645.00
843		663.00
844		676.40
845		676.40

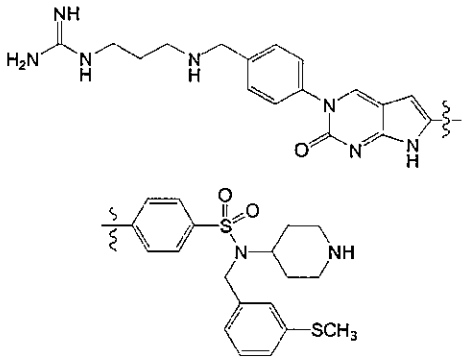
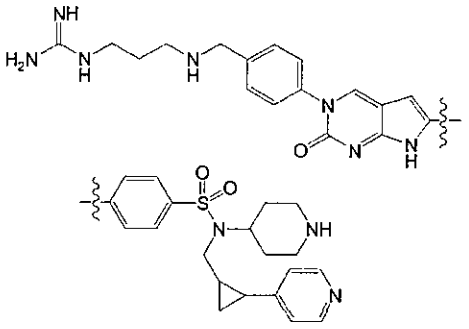
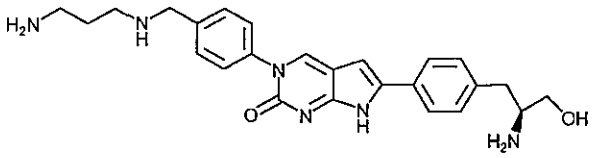
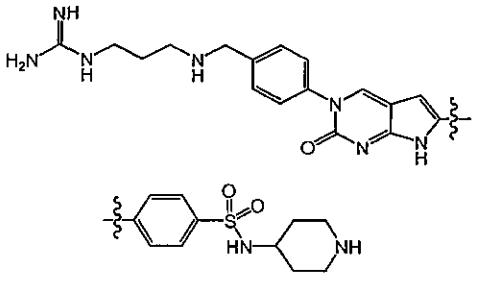
846		636.30
847		487.20
848		585.30
849		438.00

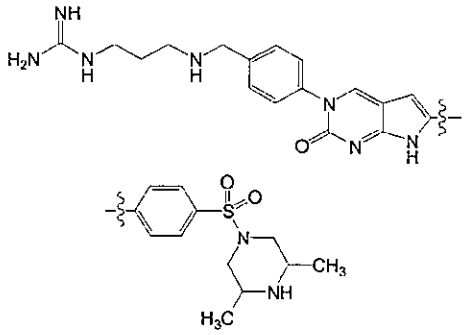
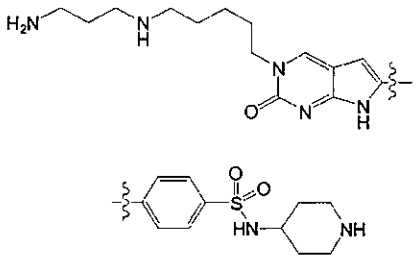
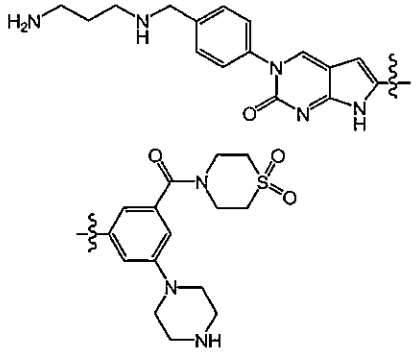
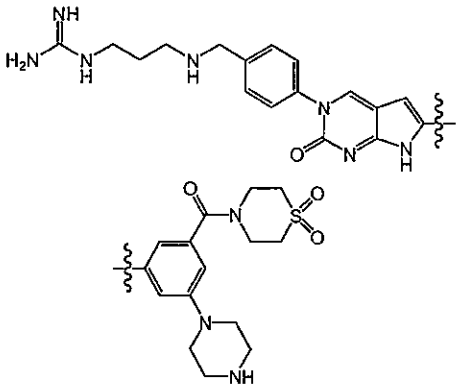
850		480.00
851		678.40
852		536.20
853		550.30

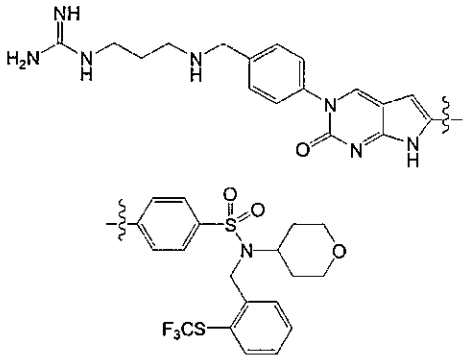
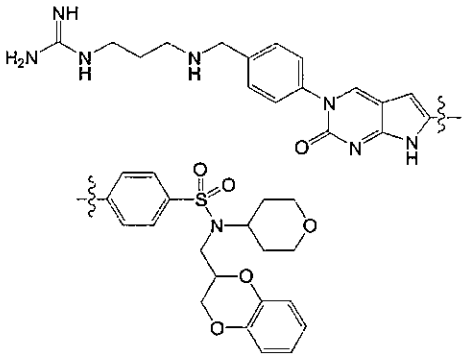
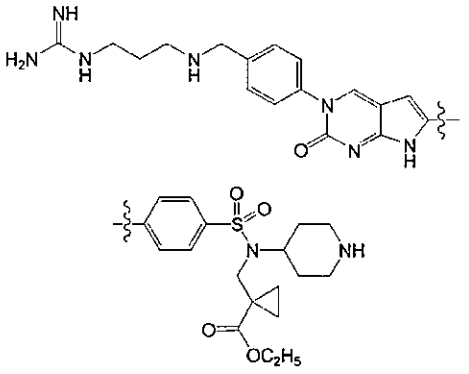
854		770.00
855		753.00
856		687.00

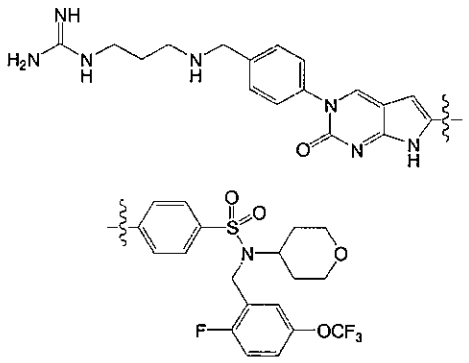
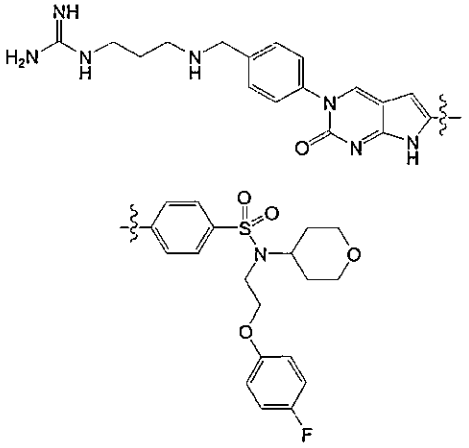
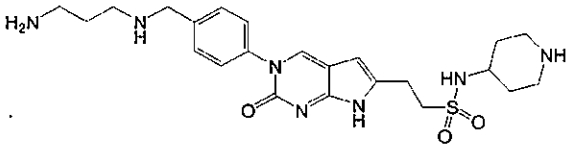
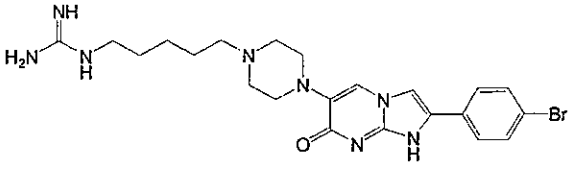
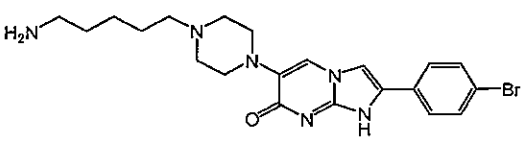
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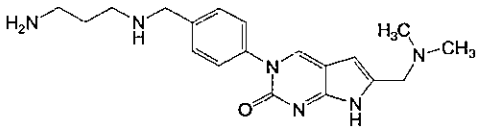
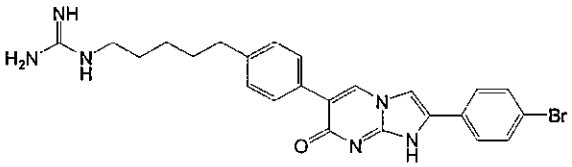
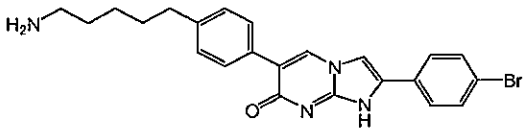
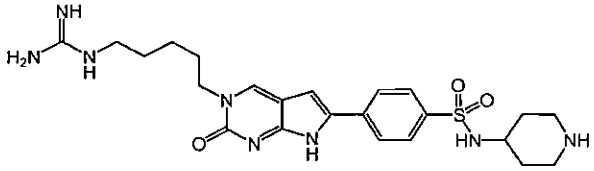
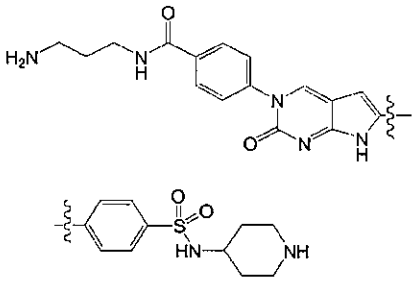
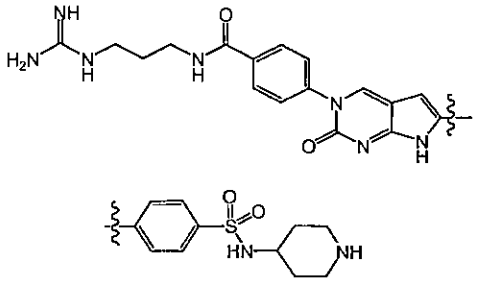
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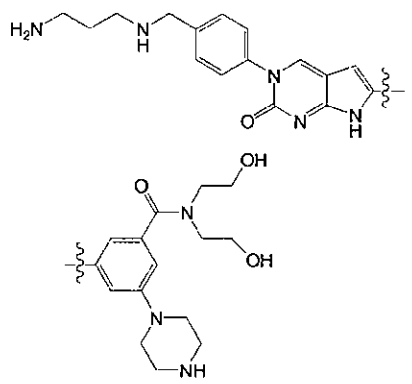
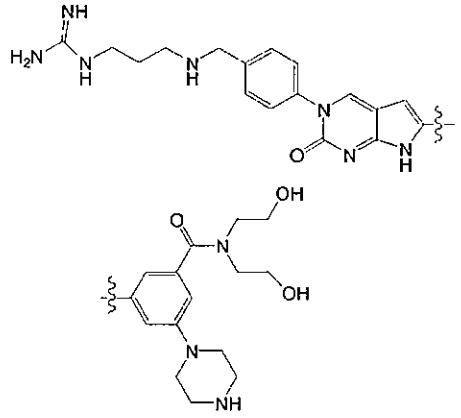
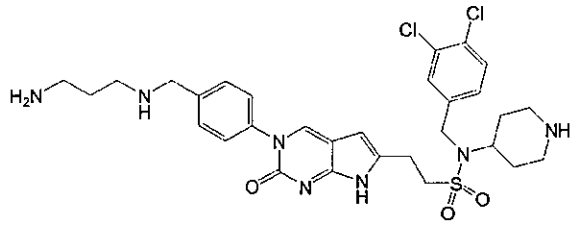
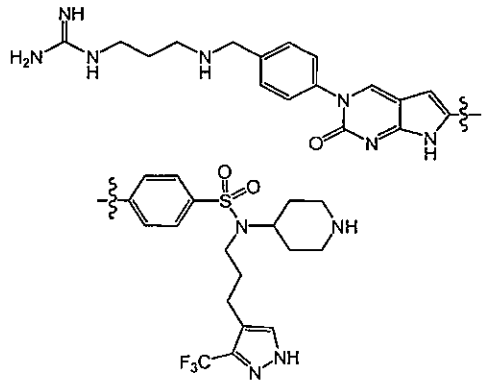
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866		709.00
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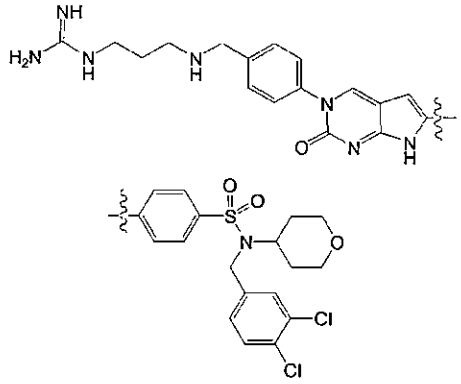
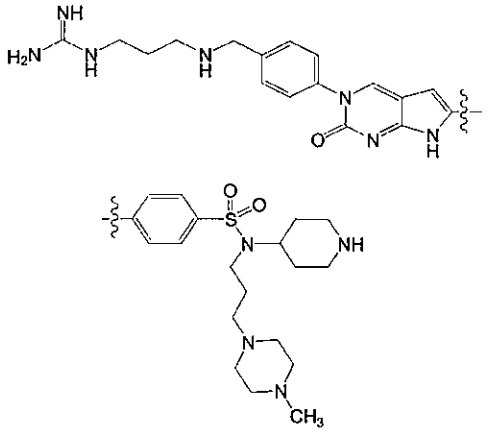
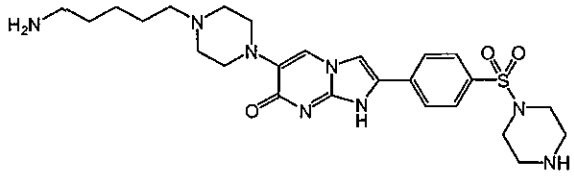
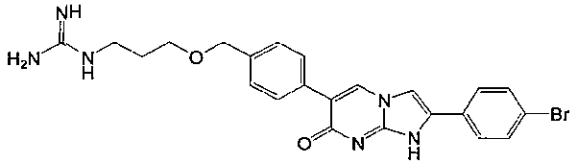
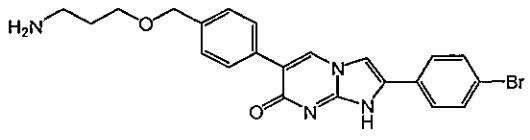
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874		619.00
875		661.00

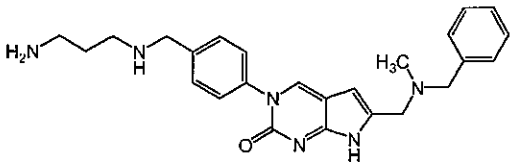
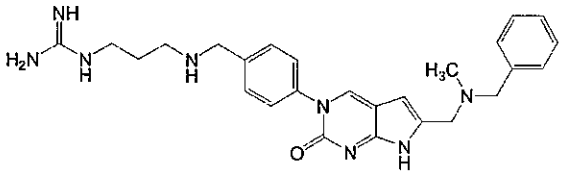
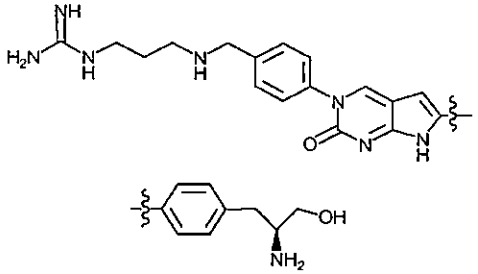
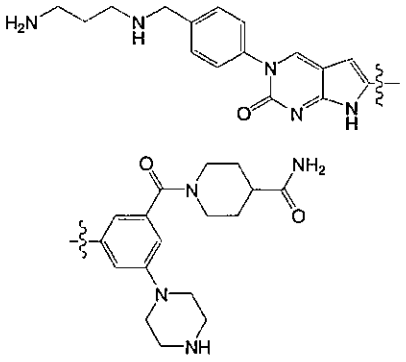
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878		704.00

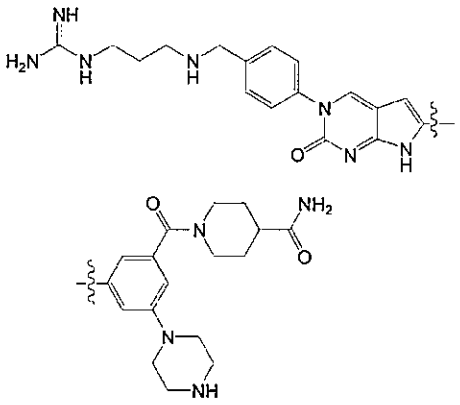
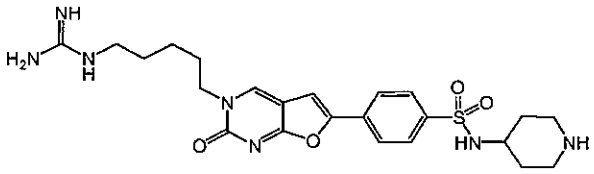
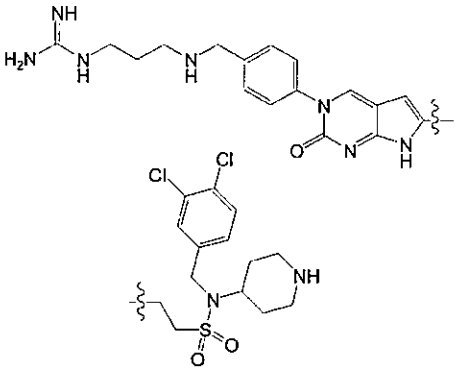
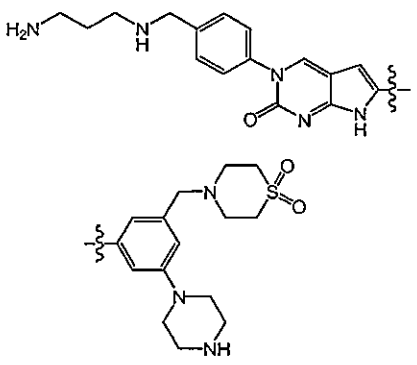
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883		461.10

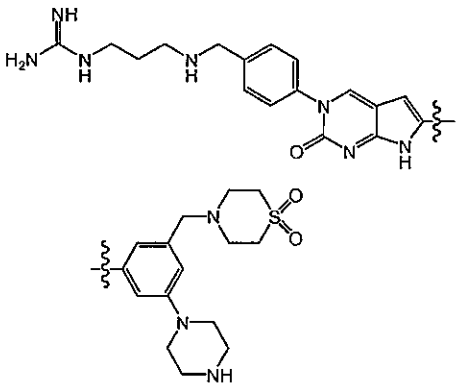
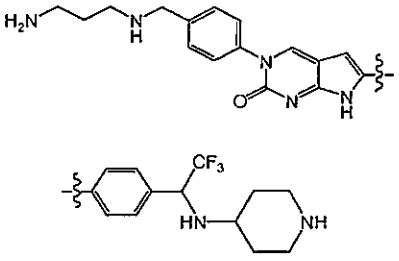
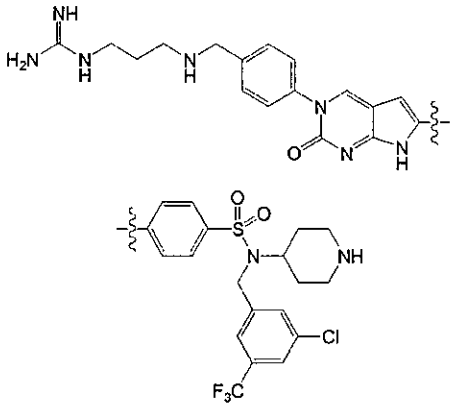
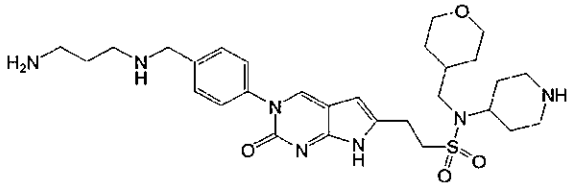
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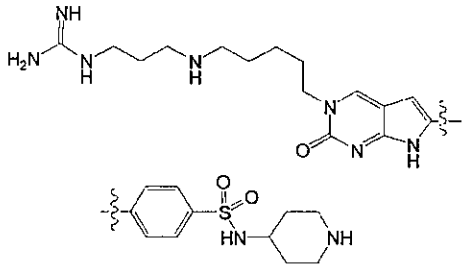
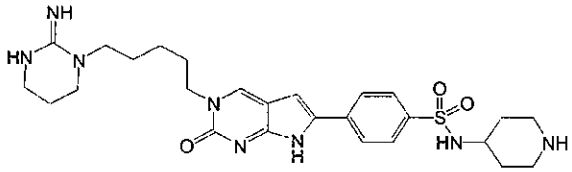
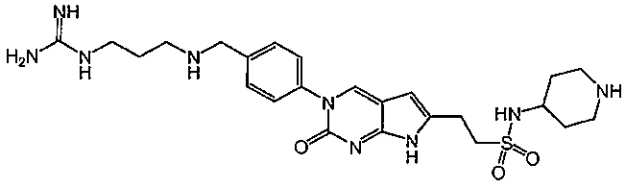
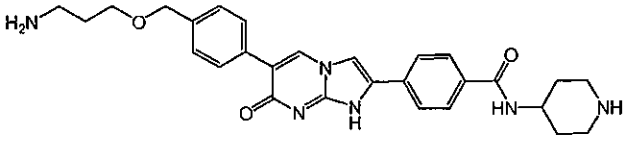
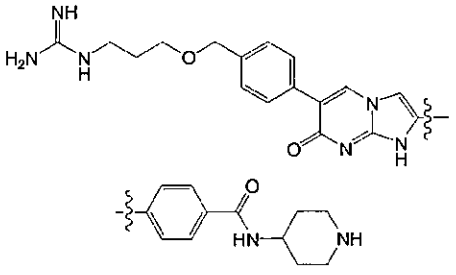
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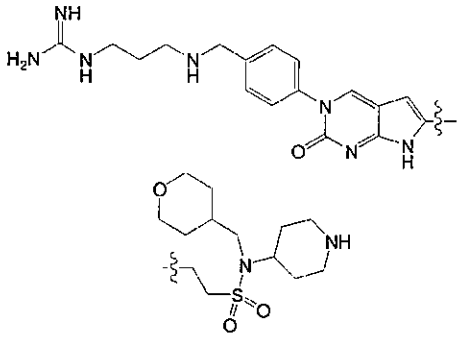
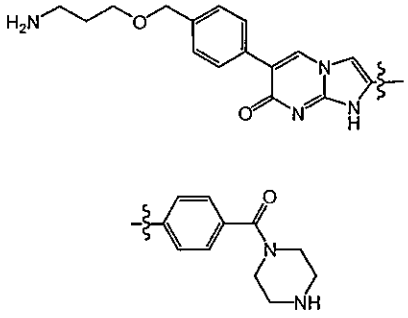
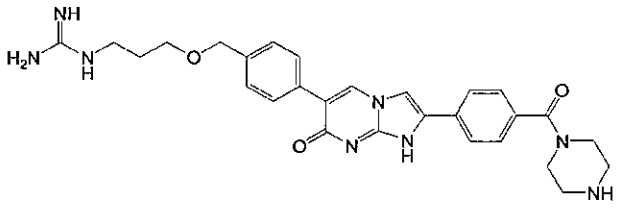
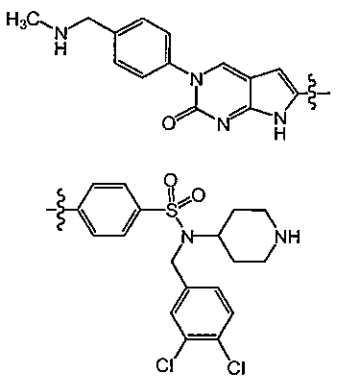
898		737.00
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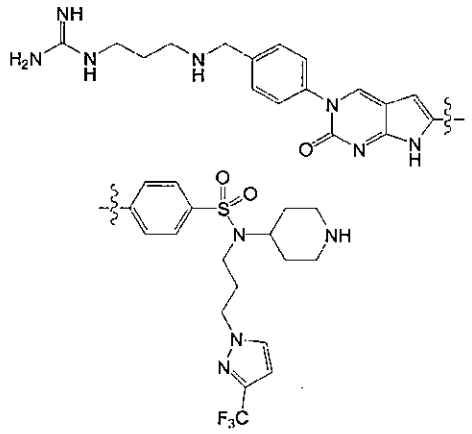
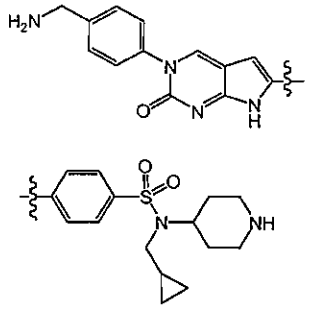
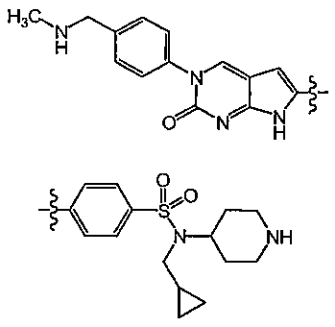
905		431.20
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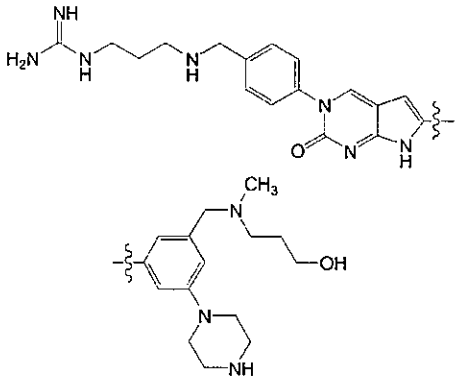
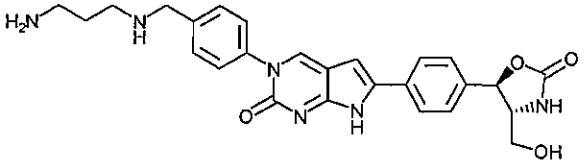
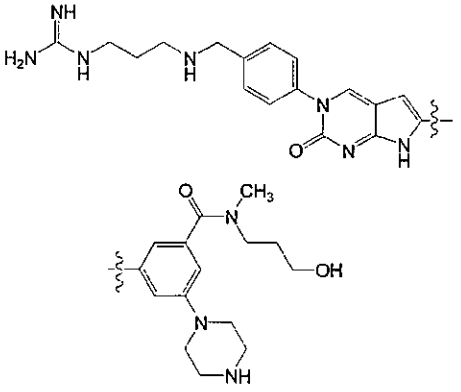
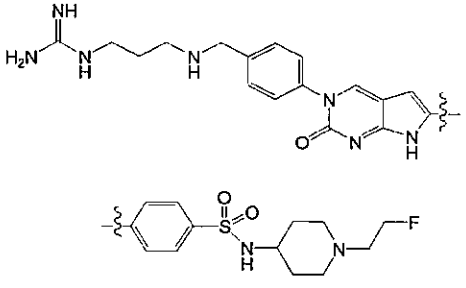
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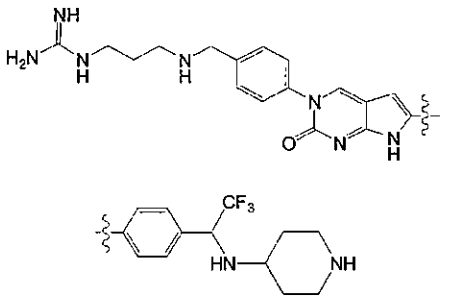
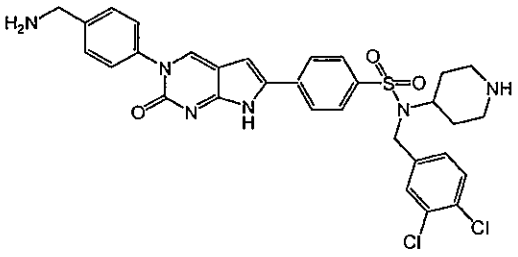
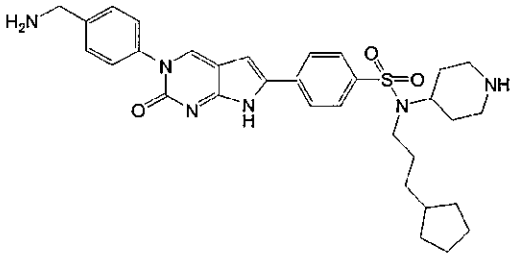
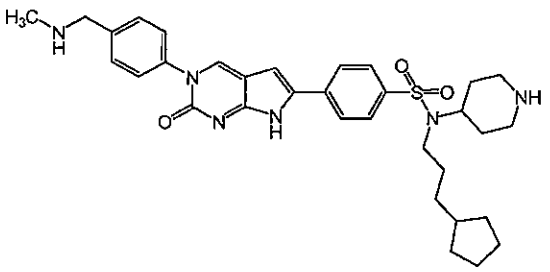
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922		770.00
923		586.30

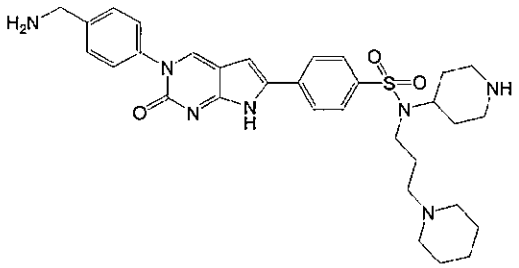
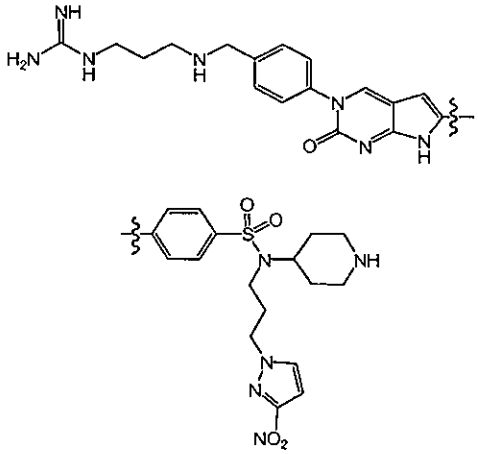
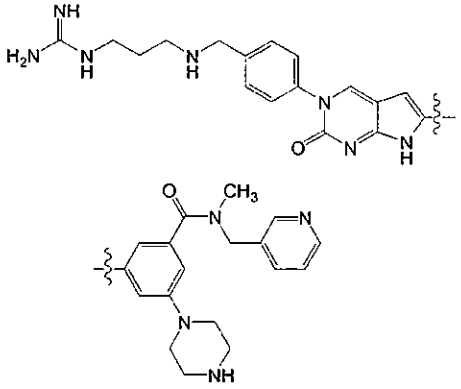
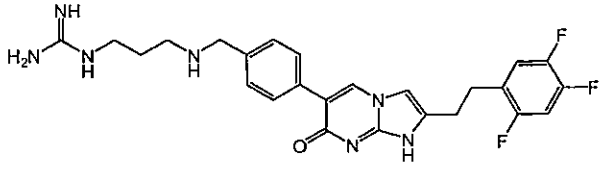
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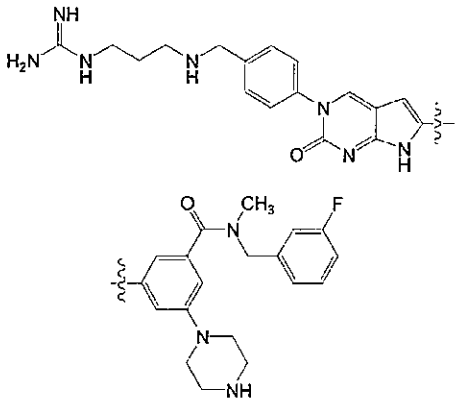
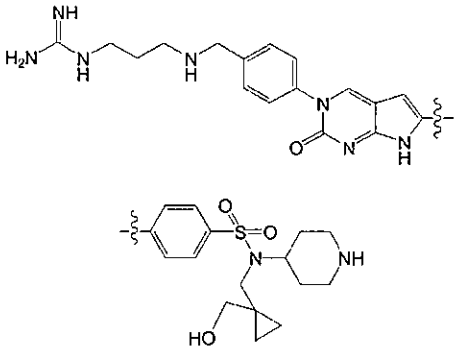
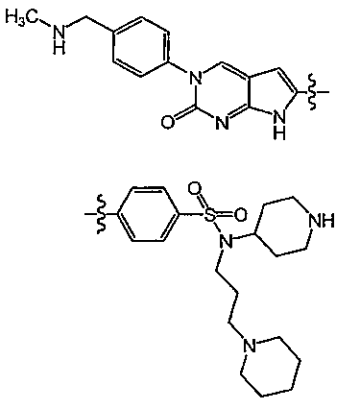
930		628.40
931		487.30
932		529.30
933		651.00

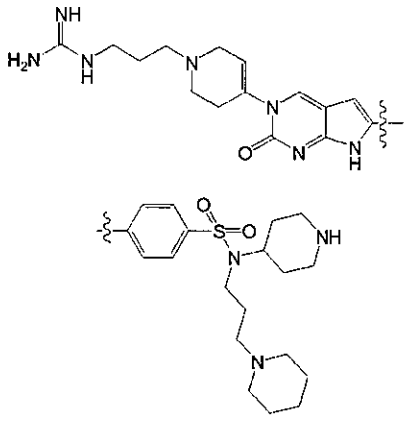
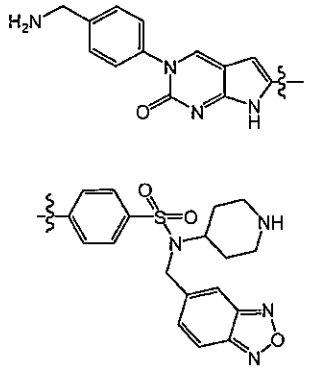
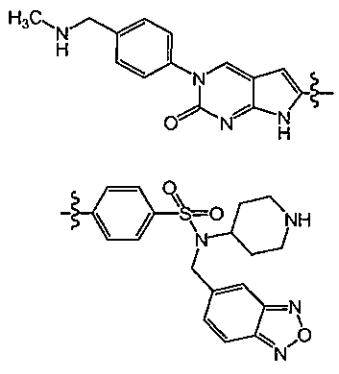
934		754.00
935		533.00
936		547.00

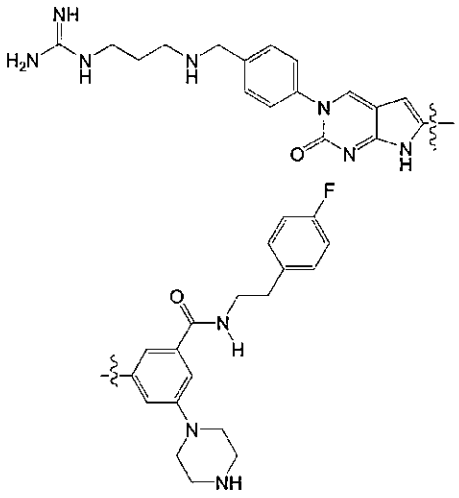
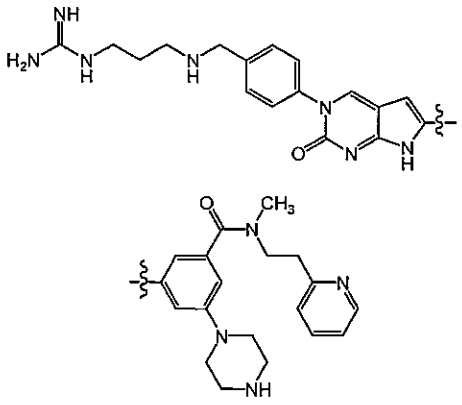
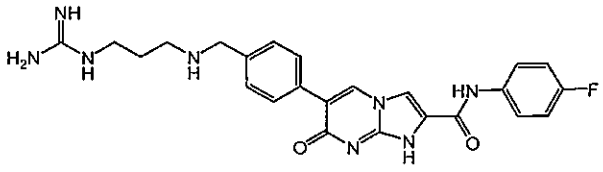
937		601.00
939		488.80
940		615.00
943		624.73

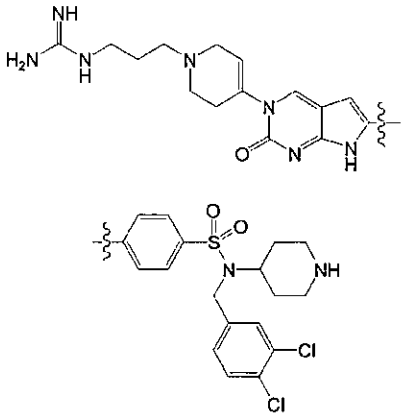
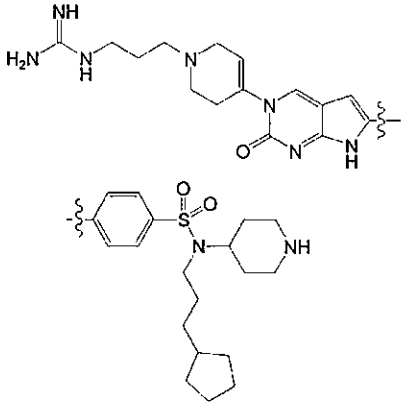
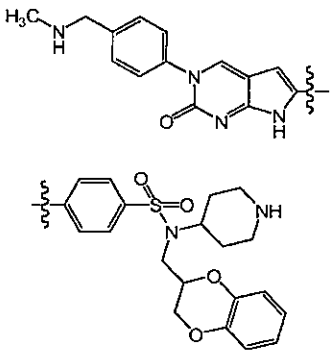
944		596.40
945		637.00
946		589.00
947		603.00

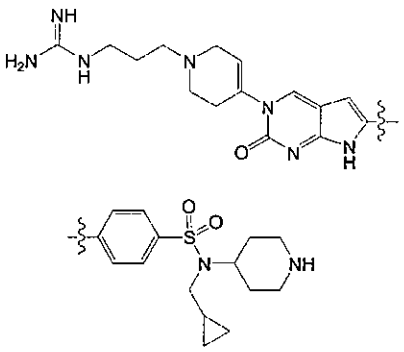
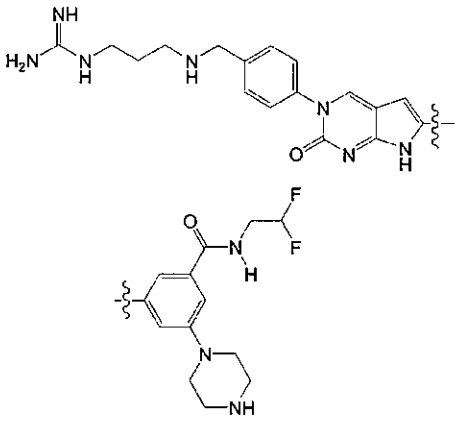
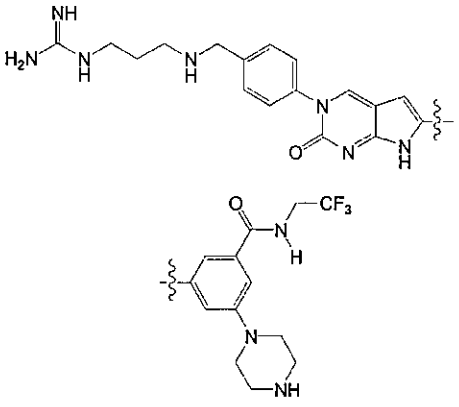
948		604.00
949		731.00
951		648.00
952		498.20

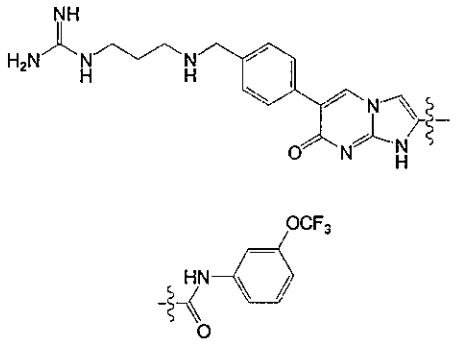
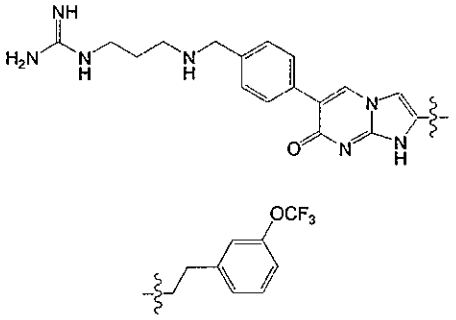
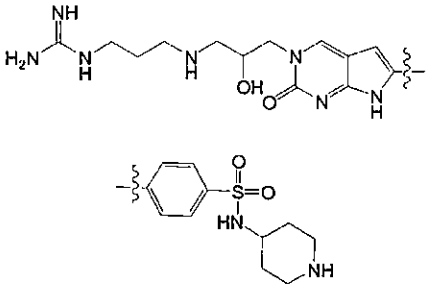
957		665.40
958		662.00
959		618.00

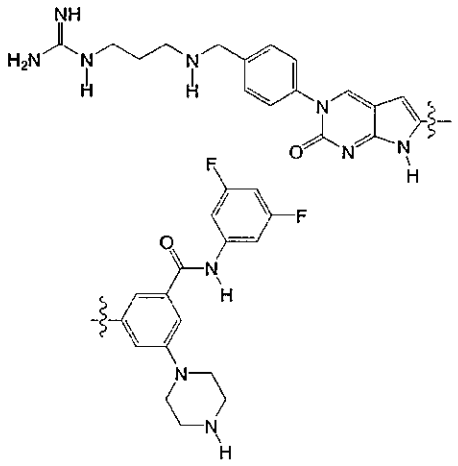
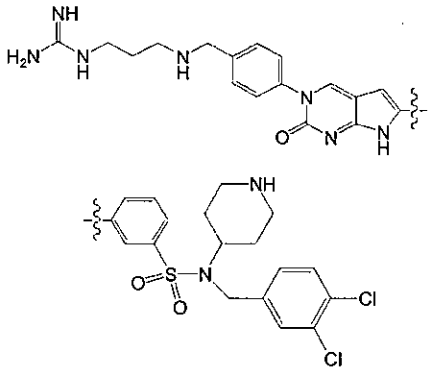
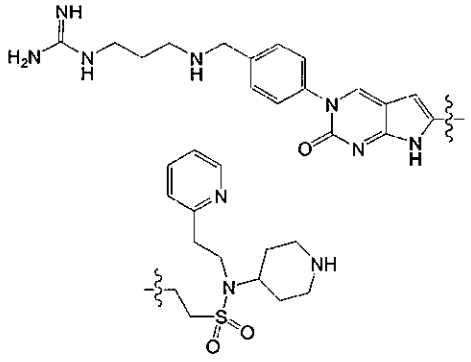
960		679.00
961		611.00
962		625.00

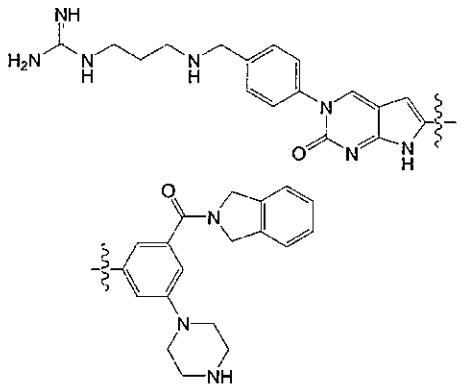
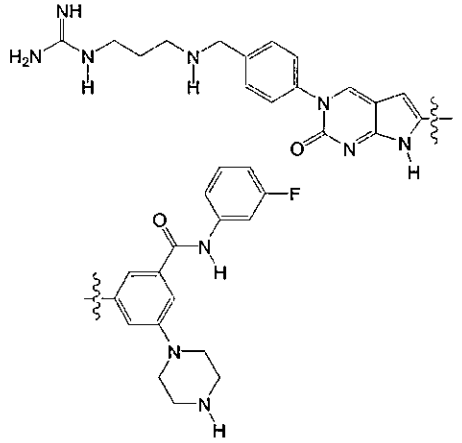
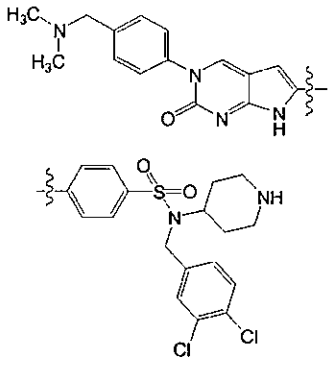
963		665.00
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965		477.20

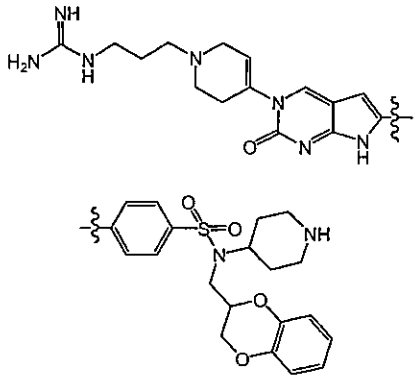
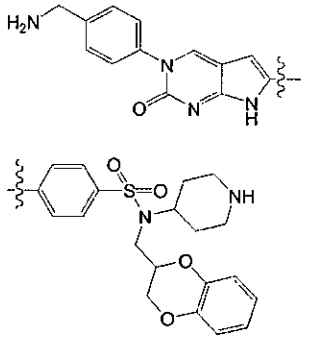
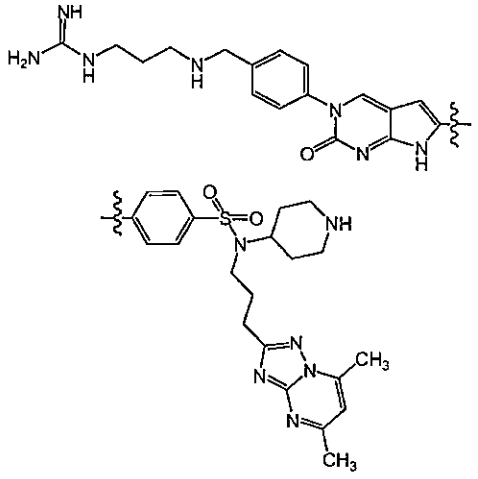
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967		664.00
968		641.00

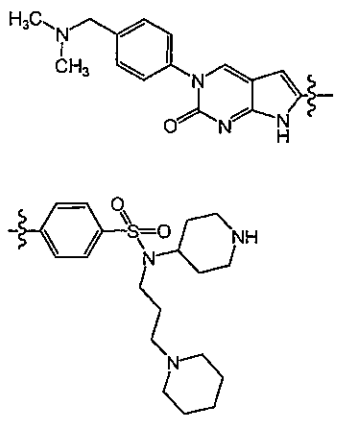
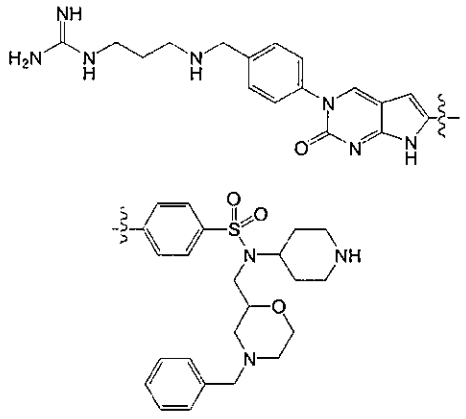
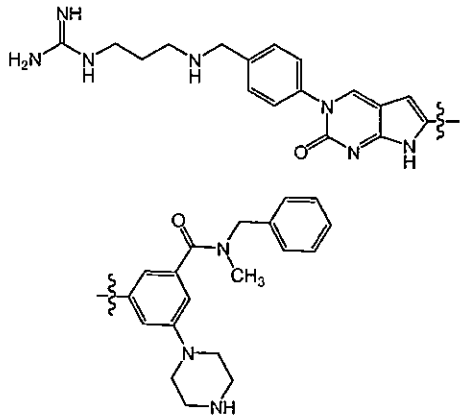
969		608.00
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971		625.00

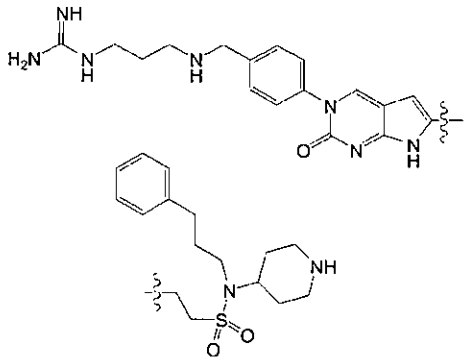
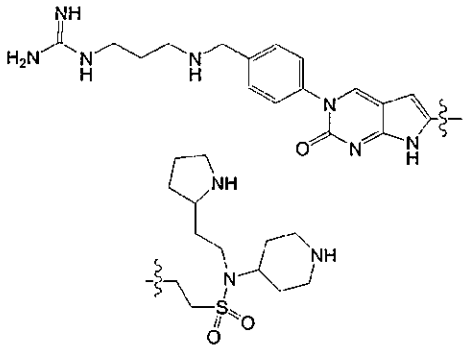
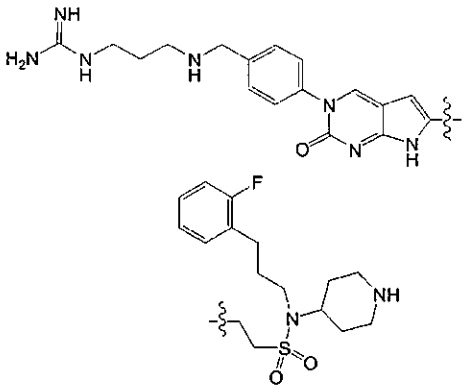
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977		546.70

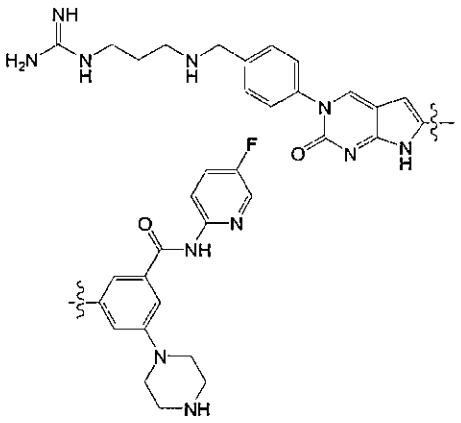
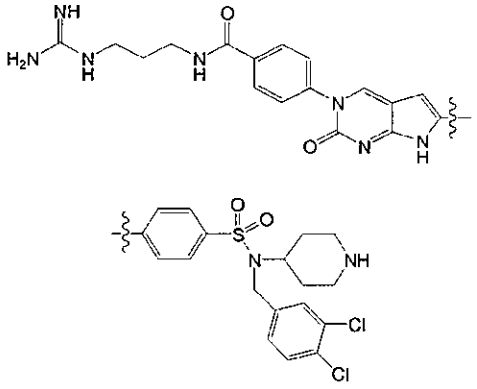
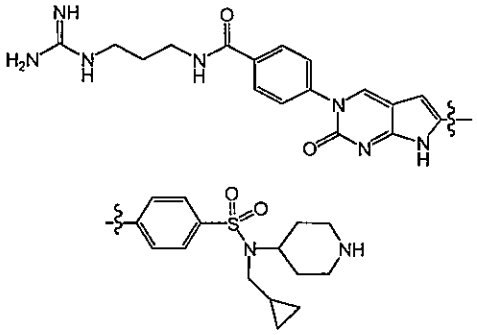
978		655.40
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980		636.60

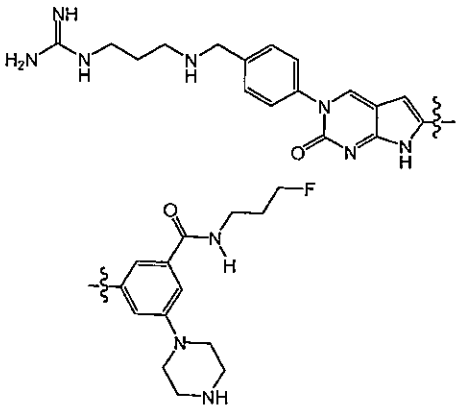
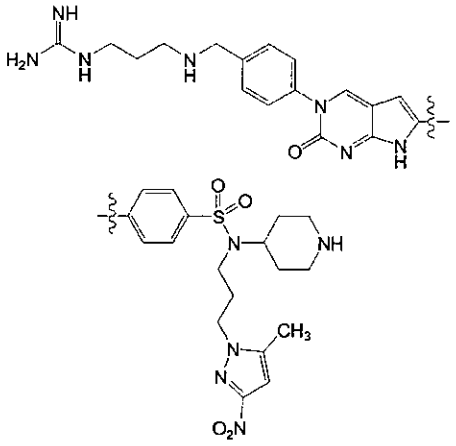
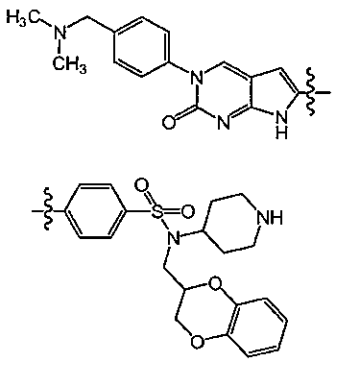
981		645.00
982		637.00
983		665.00

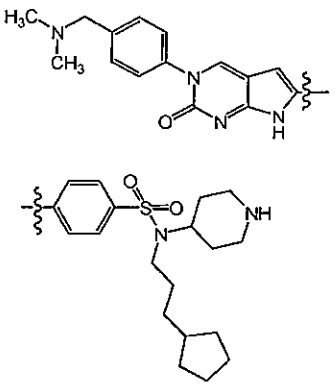
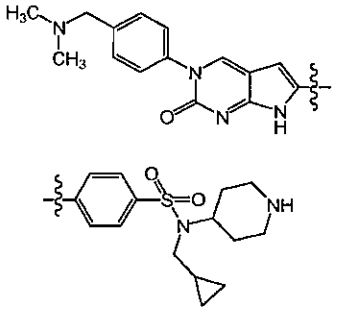
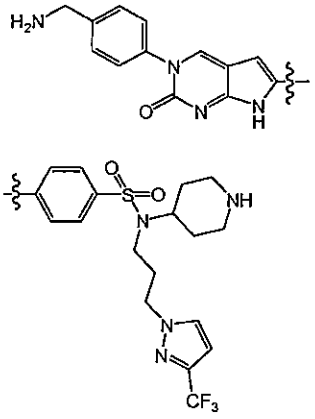
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985		627.00
986		766.00

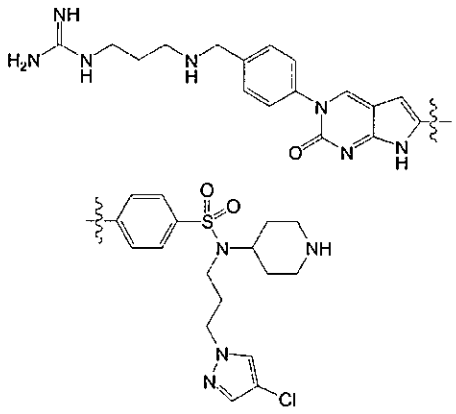
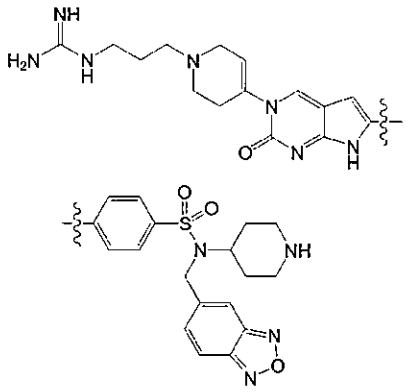
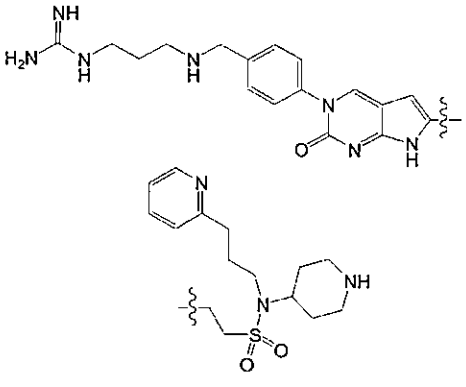
987		632.00
988		767.00
989		647.00

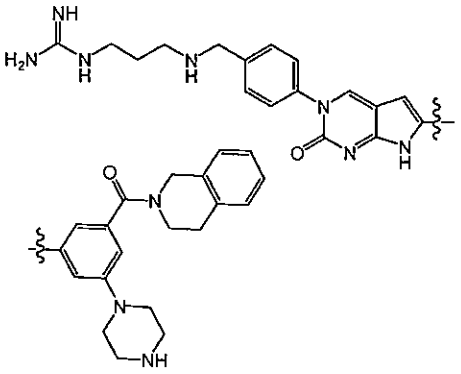
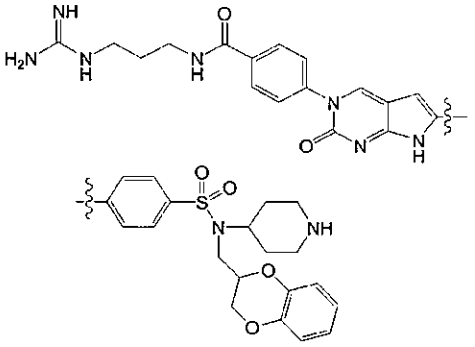
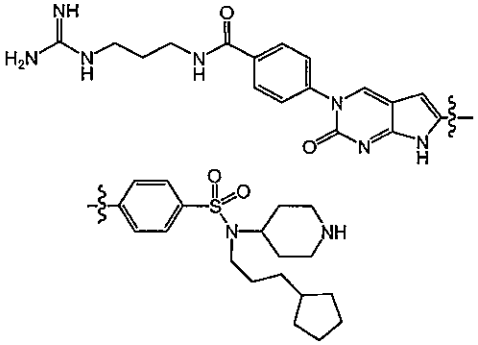
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991		627.40
992		666.50

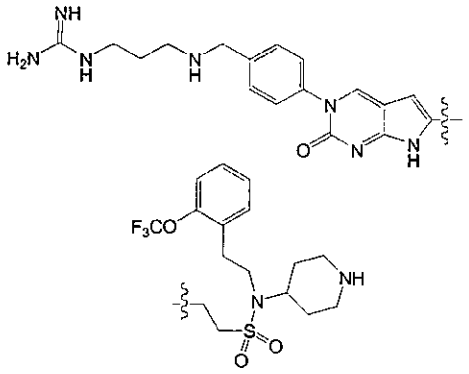
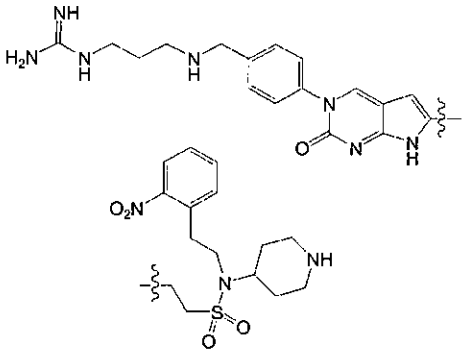
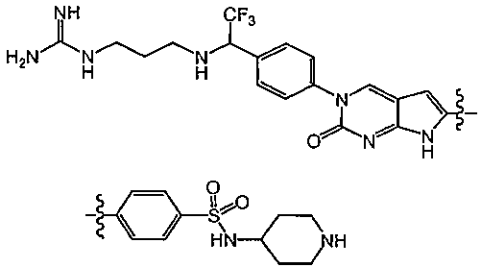
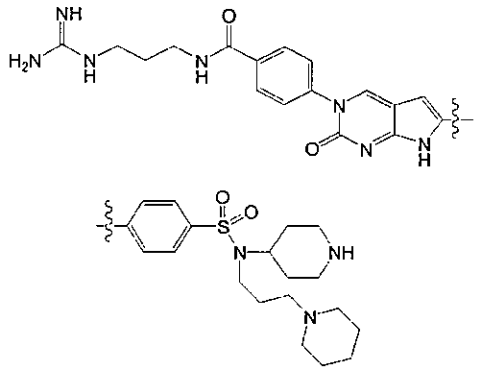
994		638.40
995		752.00
996		646.40

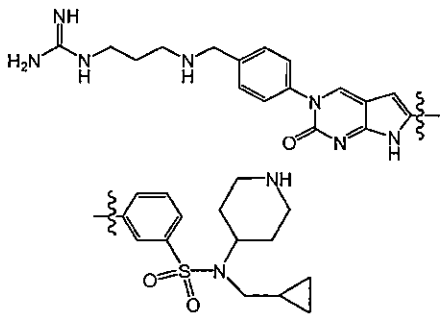
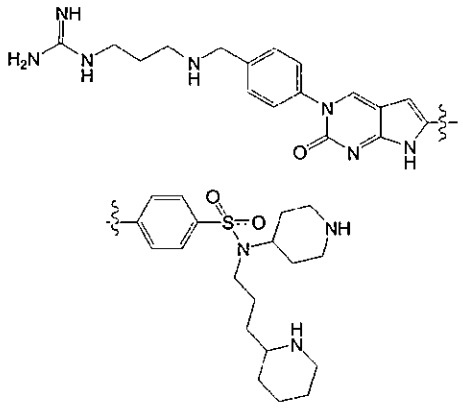
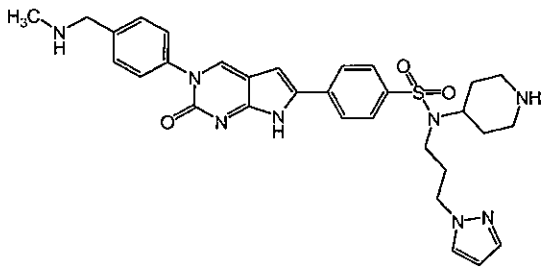
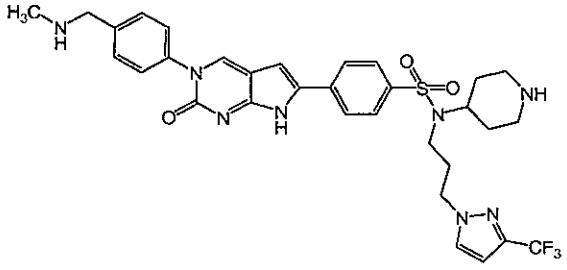
997		603.00
998		745.00
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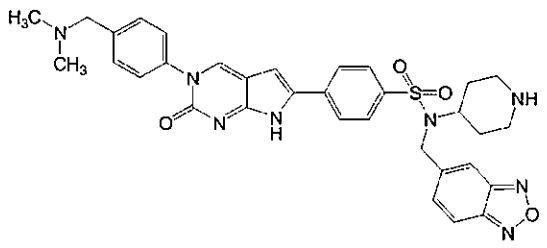
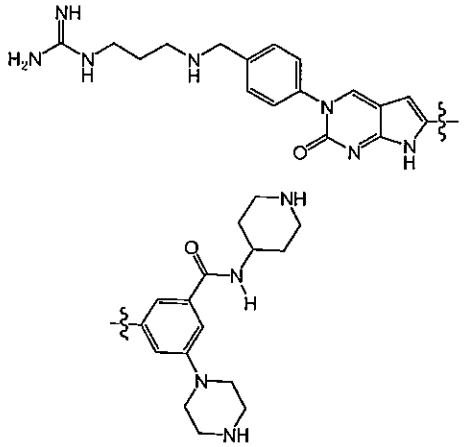
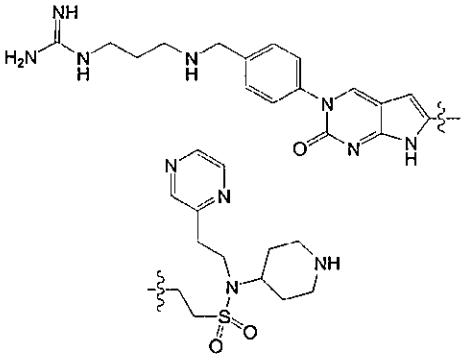
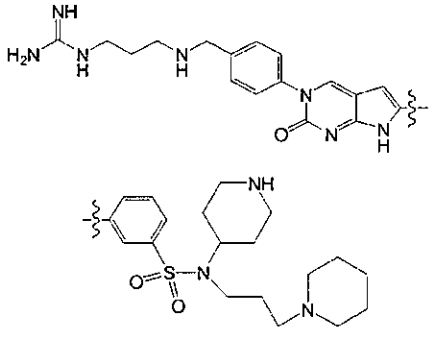
1000		617.00
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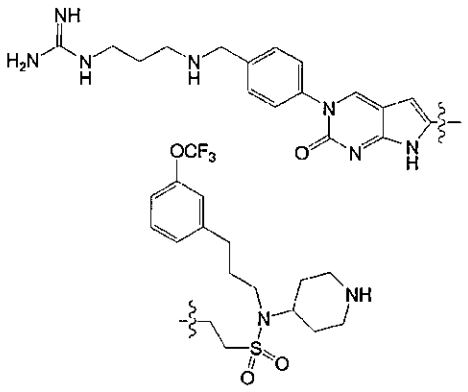
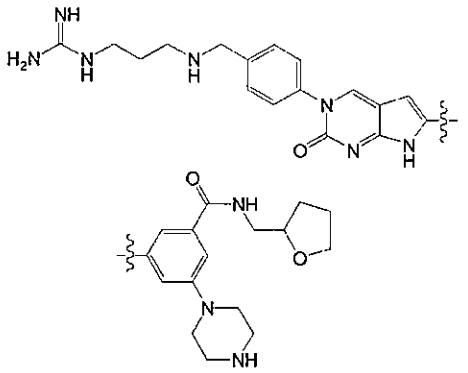
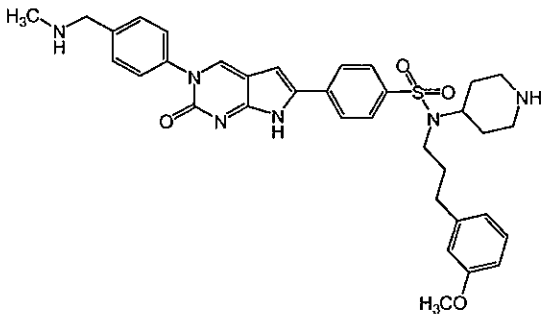
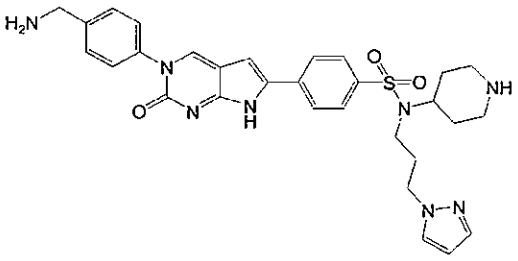
1003		720.00
1004		686.00
1005		649.60

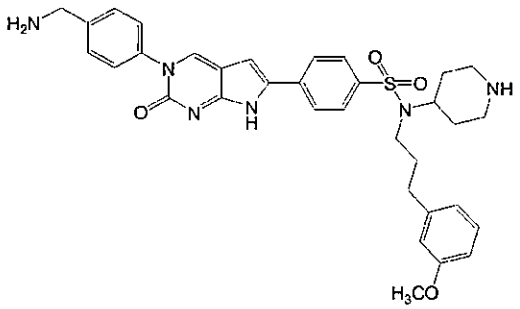
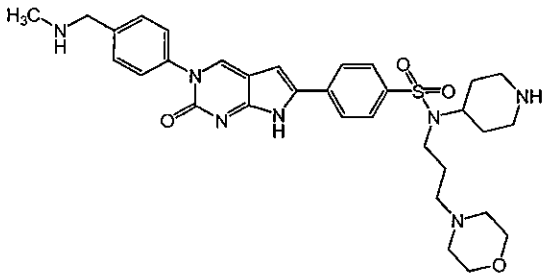
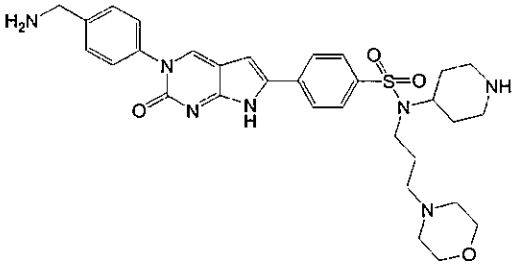
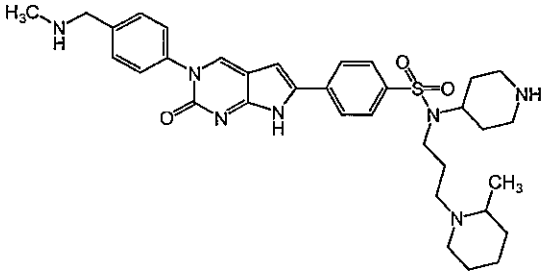
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1010		740.40
1011		702.00

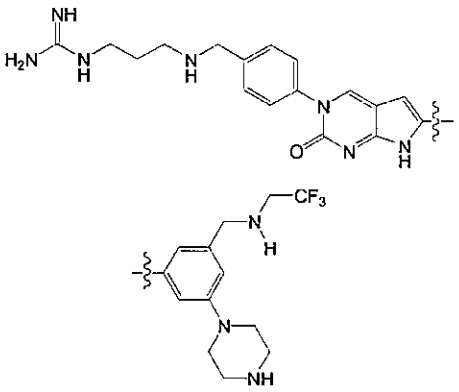
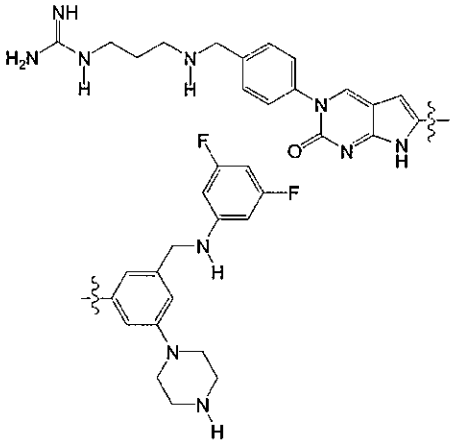
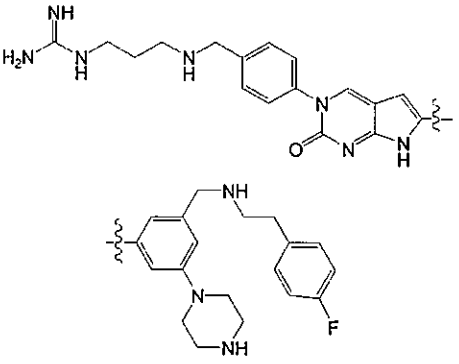
1012		718.50
1013		680.50
1015		646.30
1017		717.40

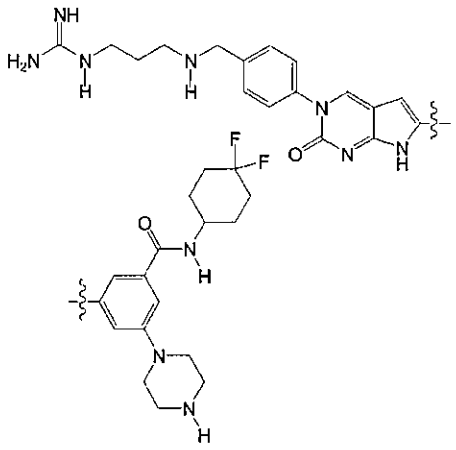
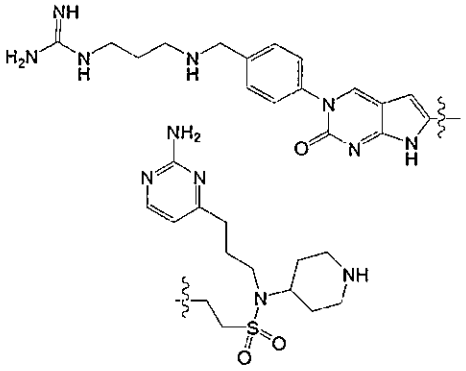
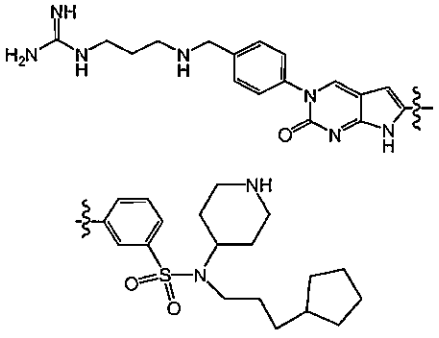
1018		632.40
1019		703.00
1020		601.00
1021		669.00

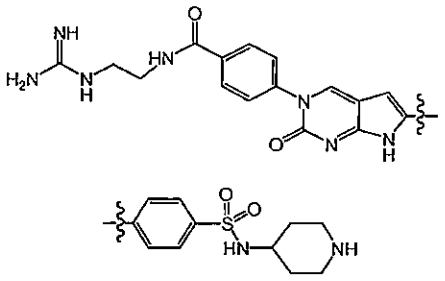
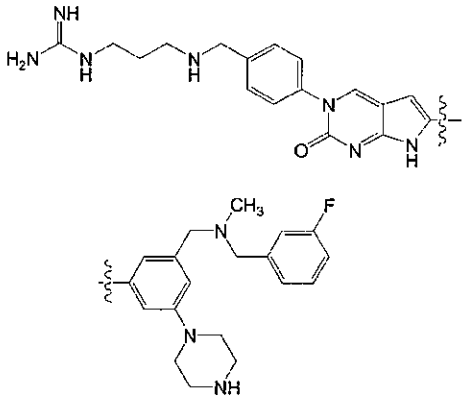
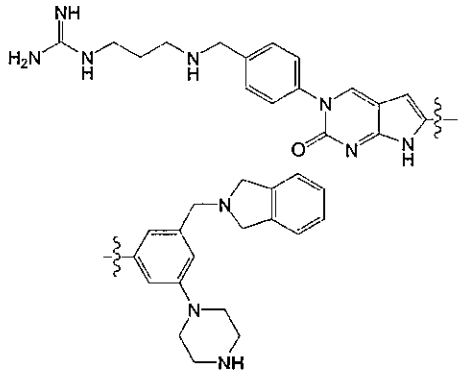
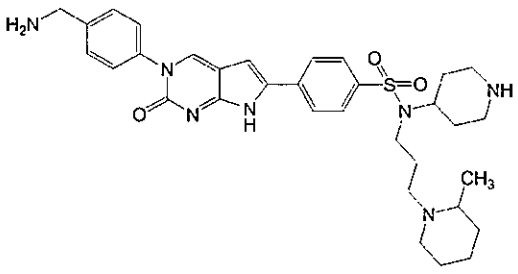
1022		639.00
1023		626.00
1024		636.40
1027		703.40

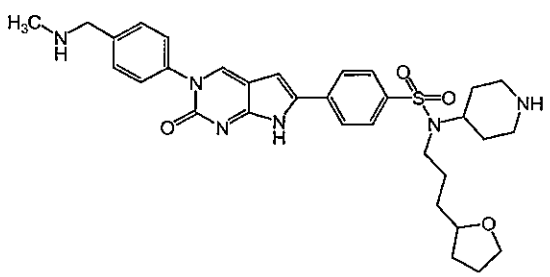
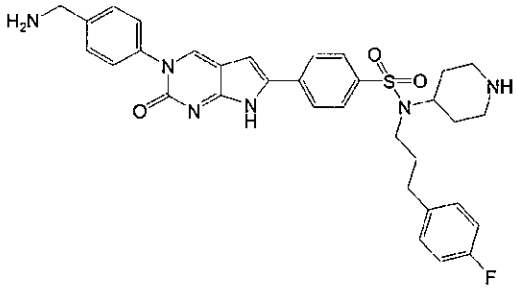
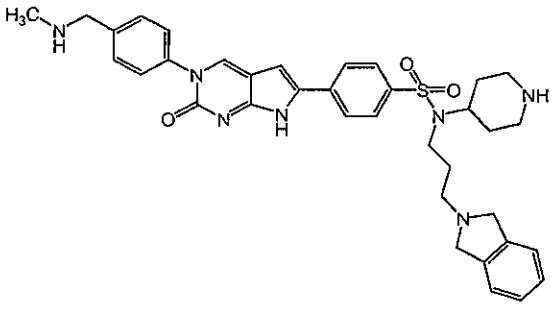
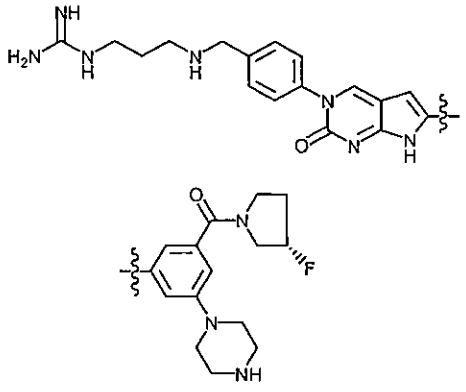
1028		732.30
1029		627.40
1034		641.00
1035		587.00

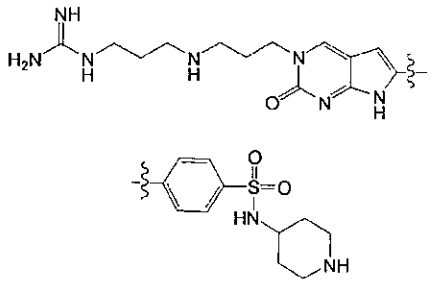
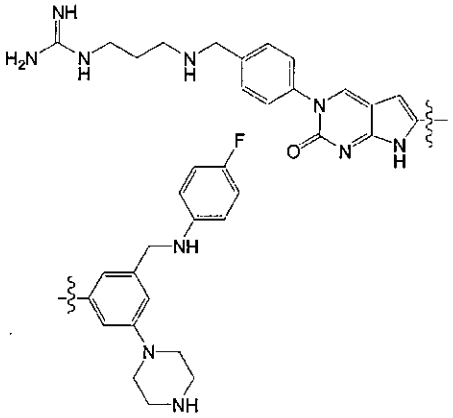
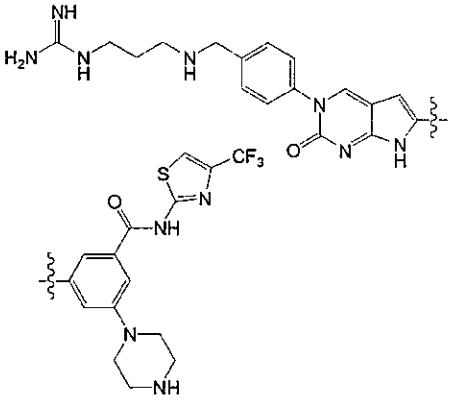
1036		627.00
1037		620.00
1038		606.00
1039		632.00

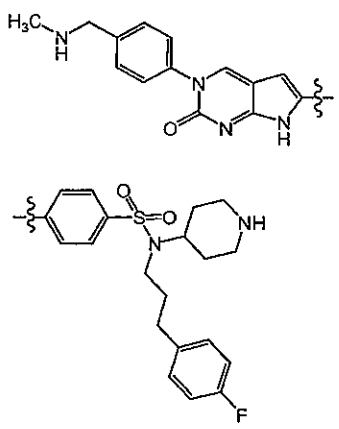
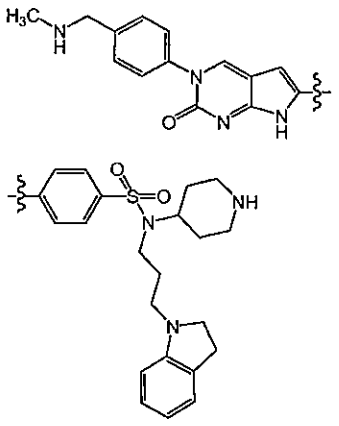
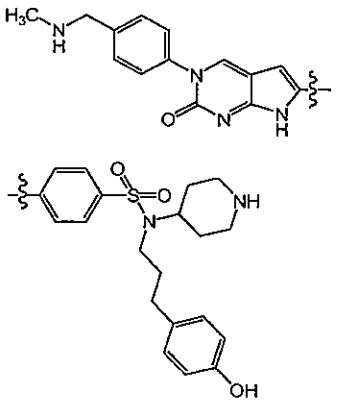
1040		611.00
1043		641.30
1044		651.40

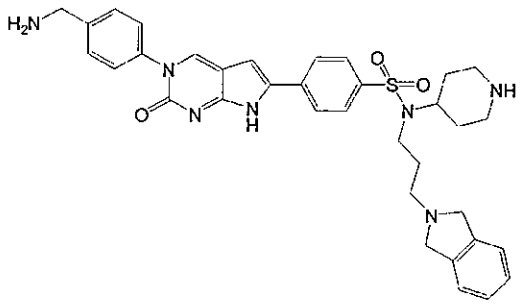
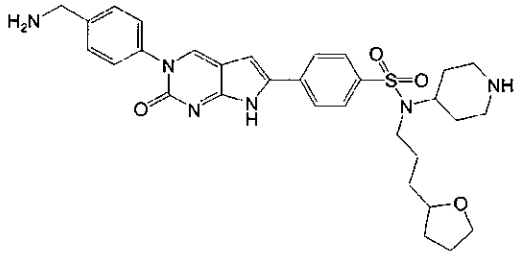
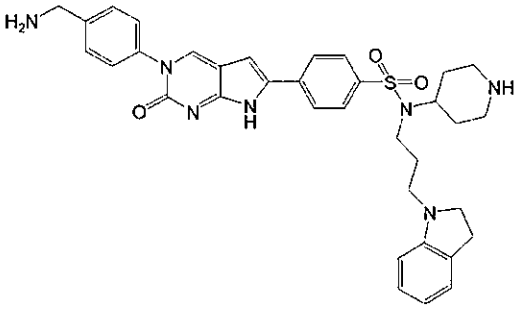
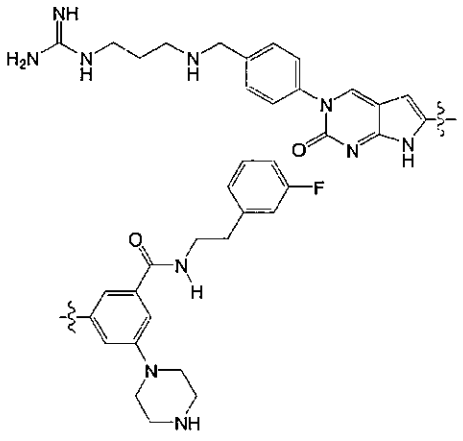
1045		661.30
1046		665.30
1047		688.40

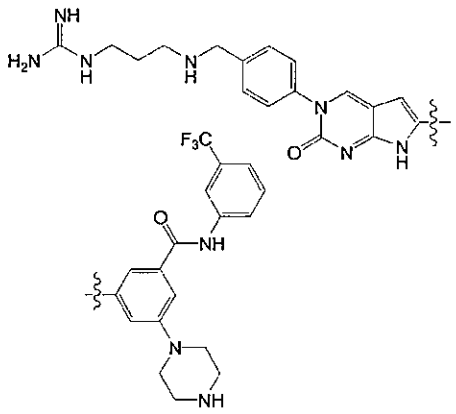
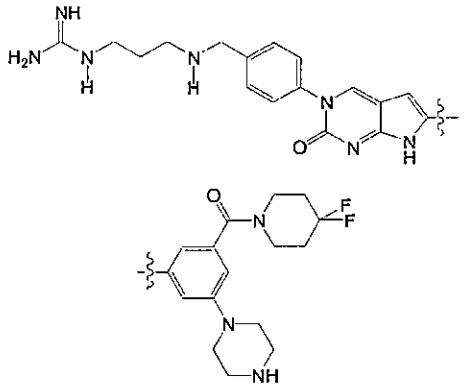
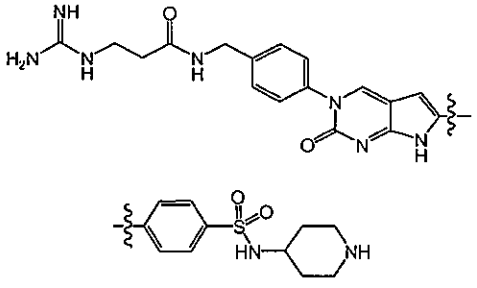
1048		578.30
1049		651.40
1050		631.00
1051		618.00

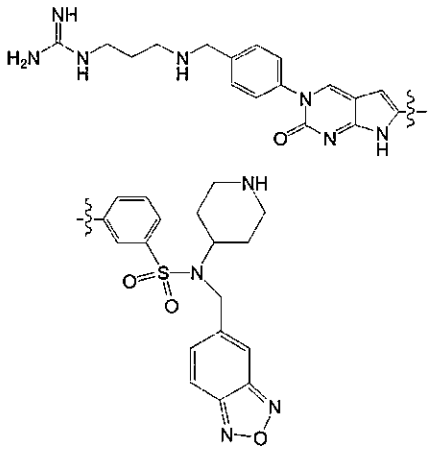
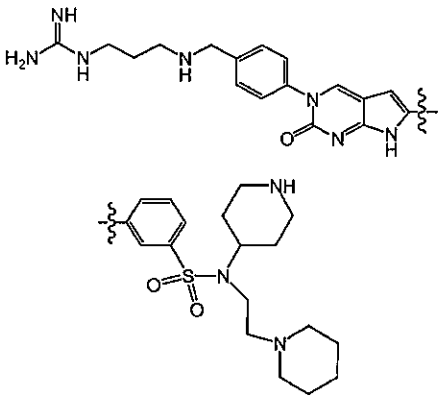
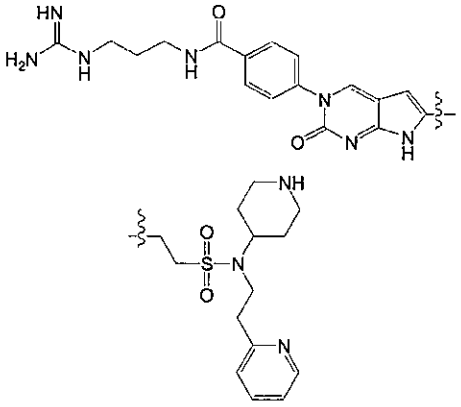
1052		605.00
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1057		615.30

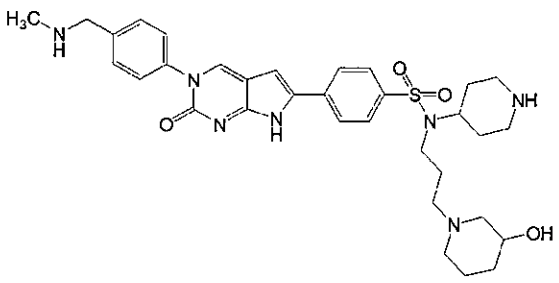
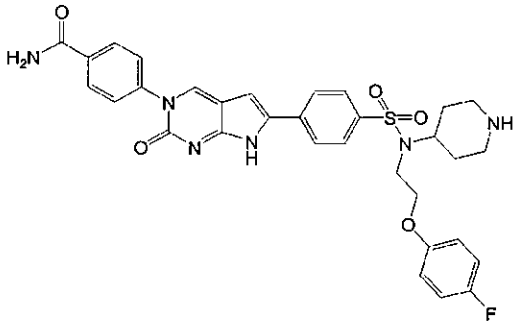
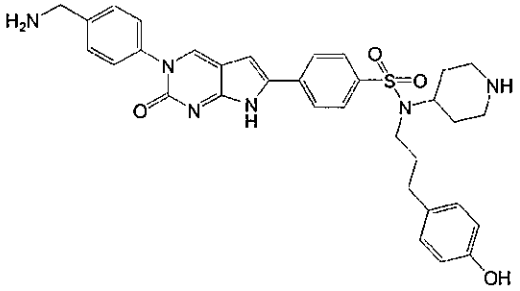
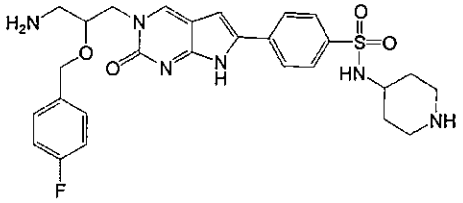
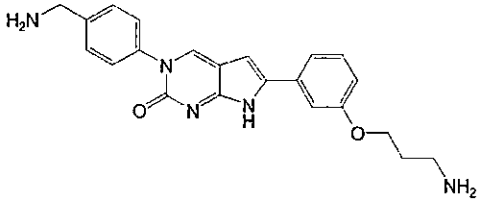
1059		530.30
1060		623.00
1061		694.30

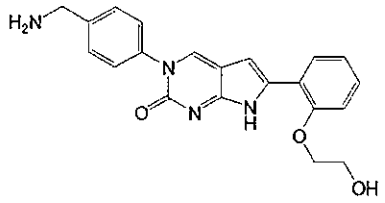
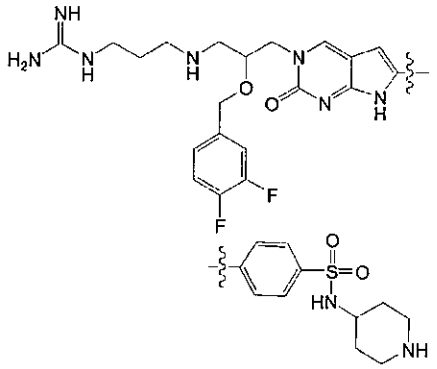
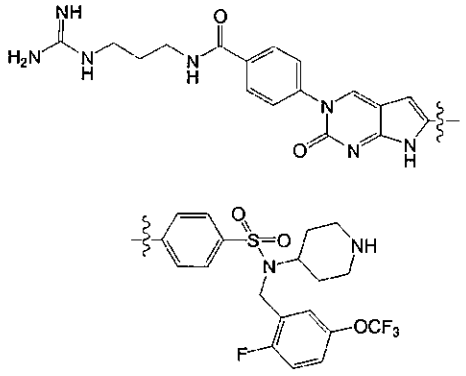
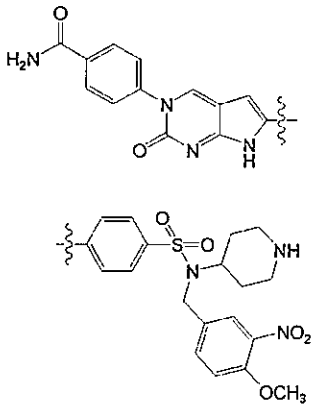
1062		629.00
1063		652.00
1064		627.00

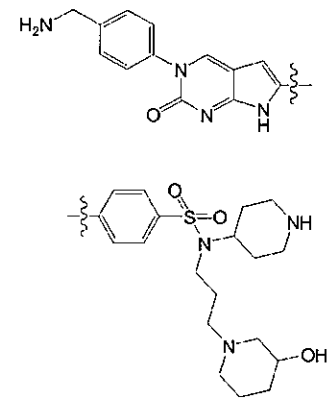
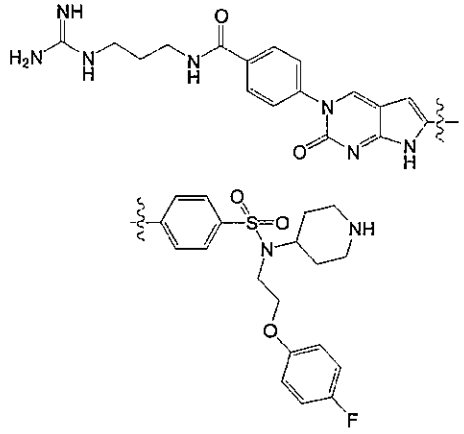
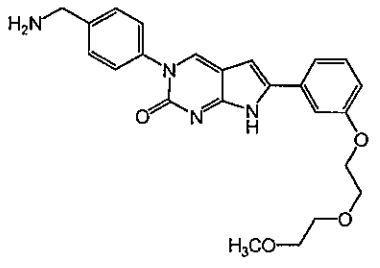
1065		638.00
1066		591.00
1067		638.00
1068		665.40

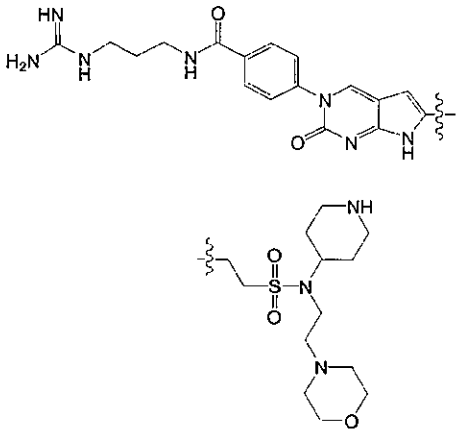
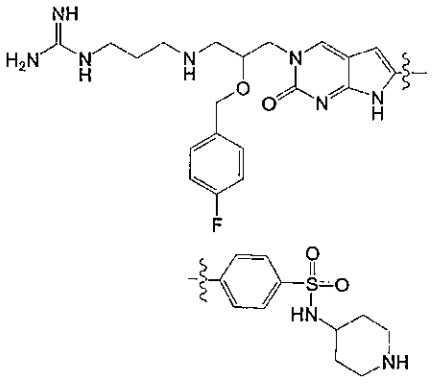
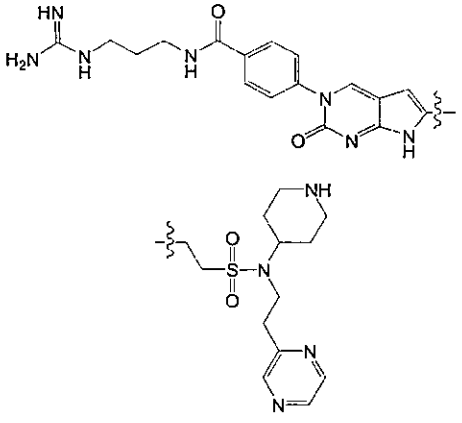
1069		687.00
1074		647.30
1075		592.20

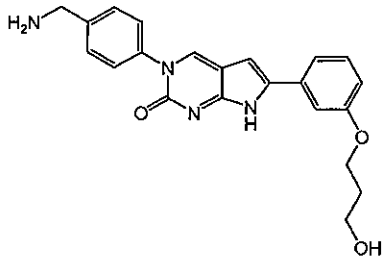
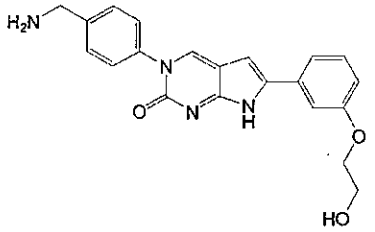
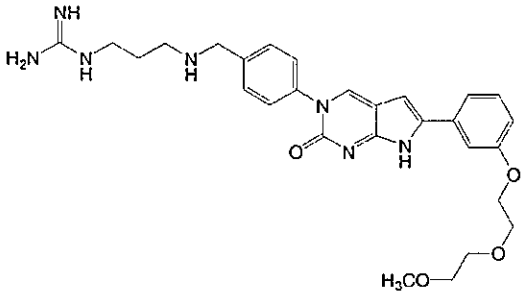
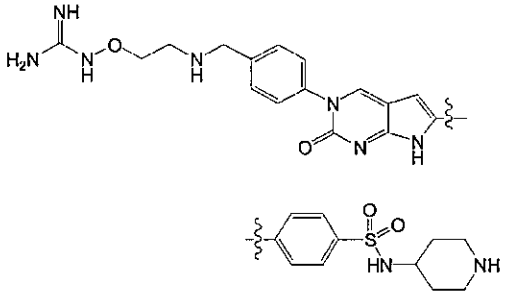
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1077		689.40
1078		649.40

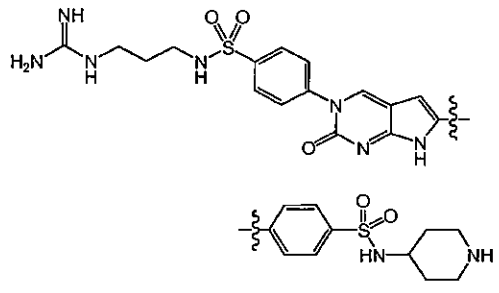
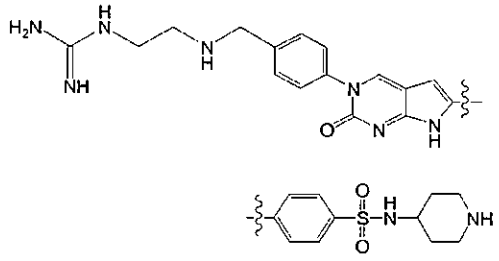
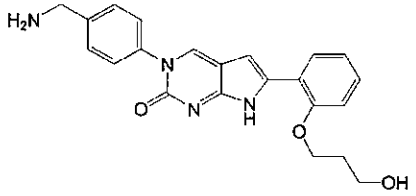
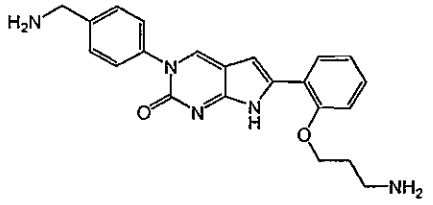
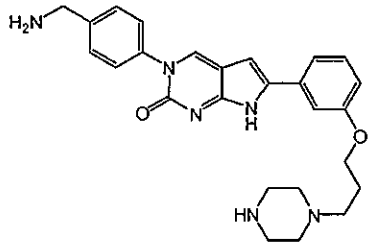
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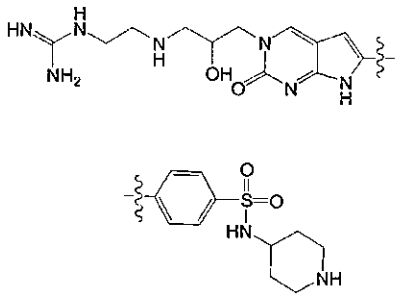
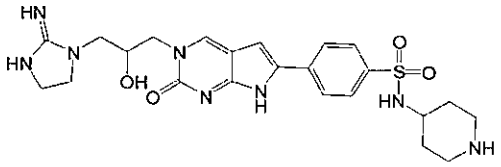
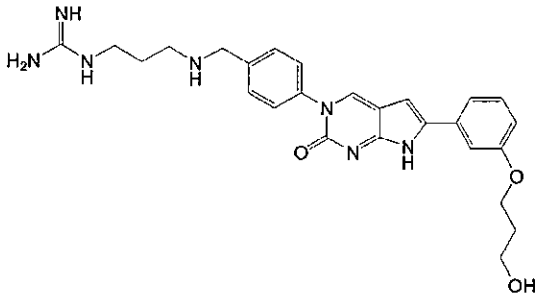
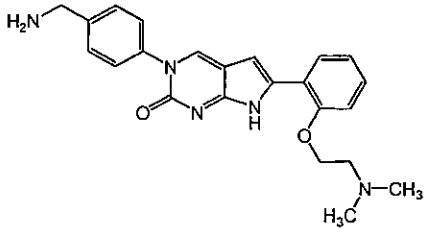
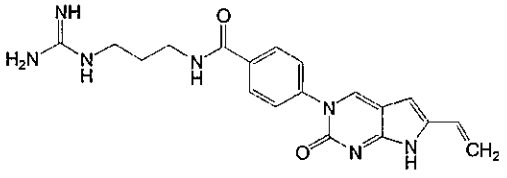
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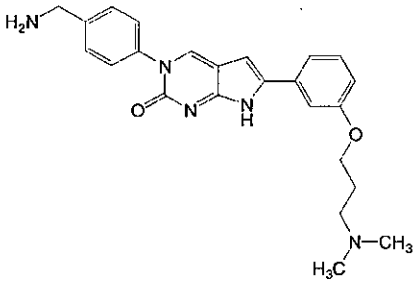
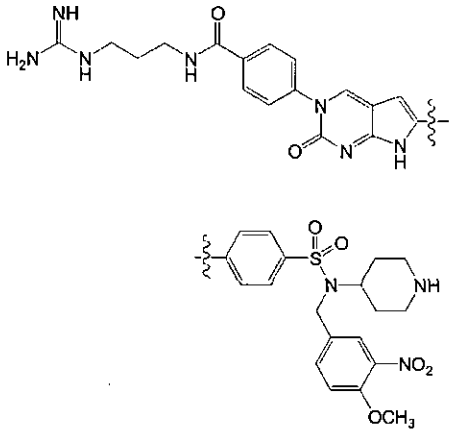
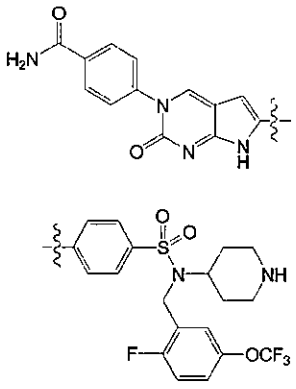
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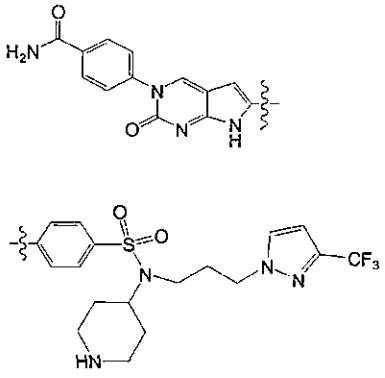
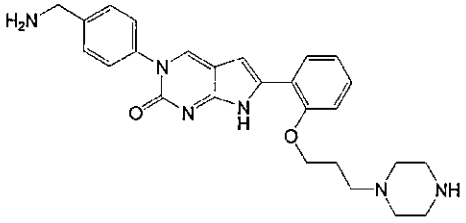
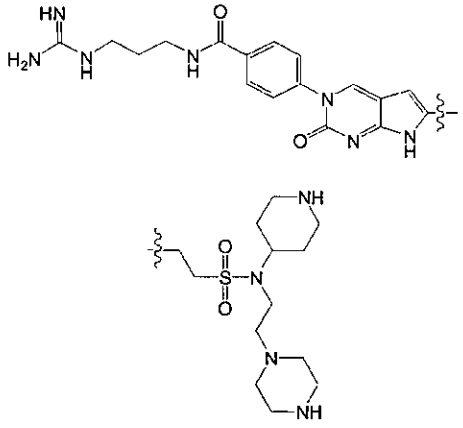
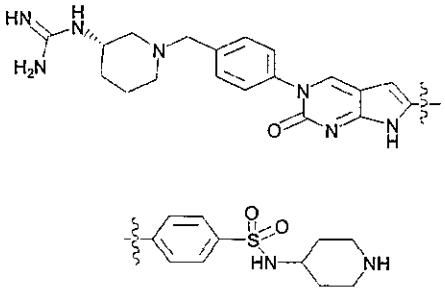
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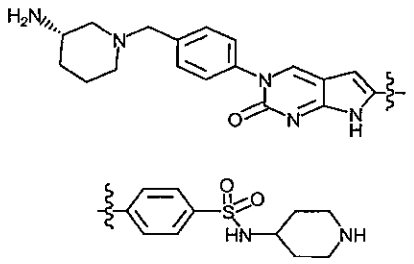
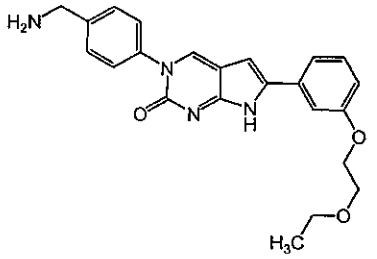
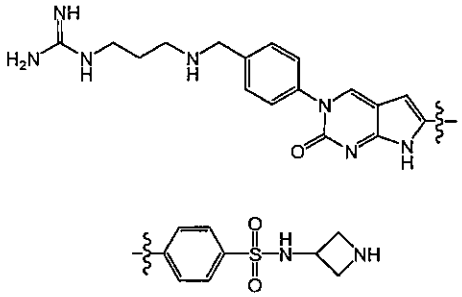
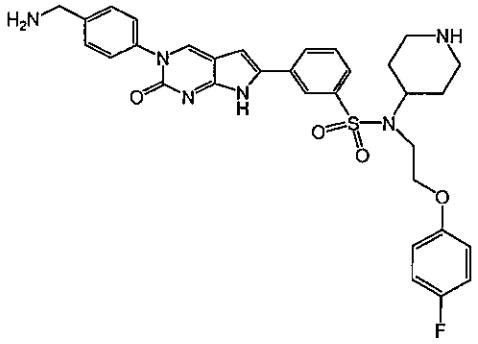
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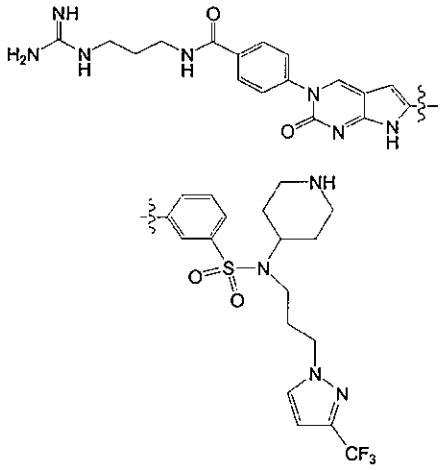
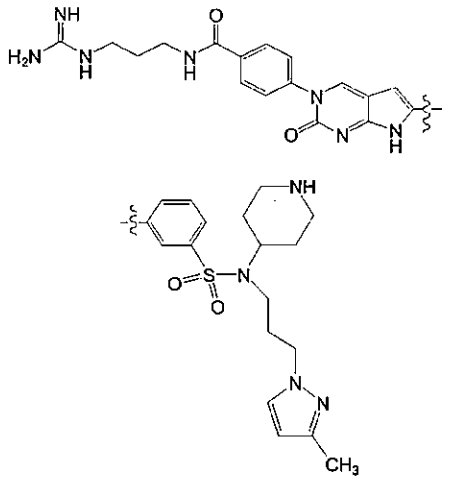
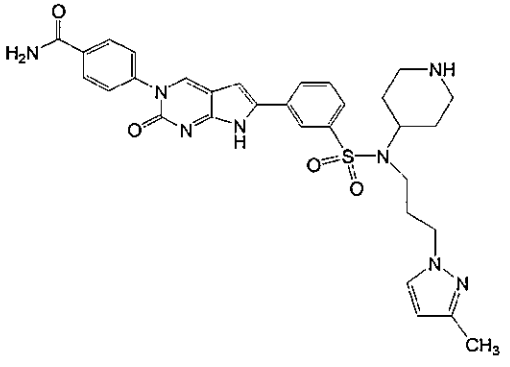
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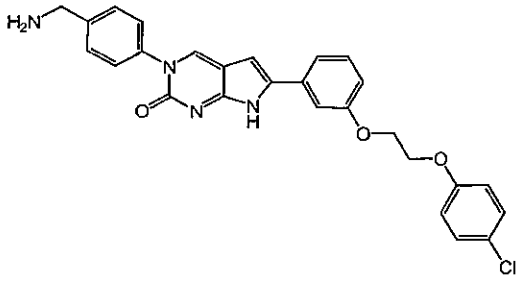
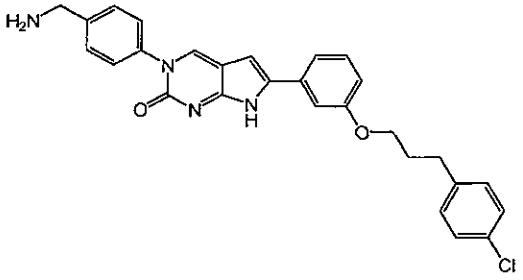
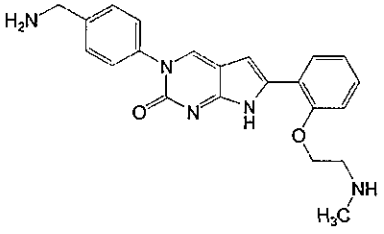
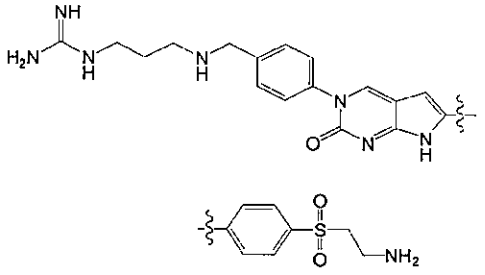
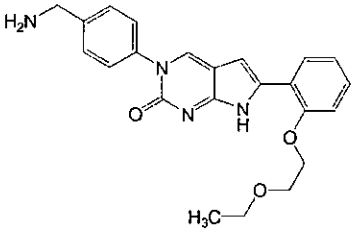
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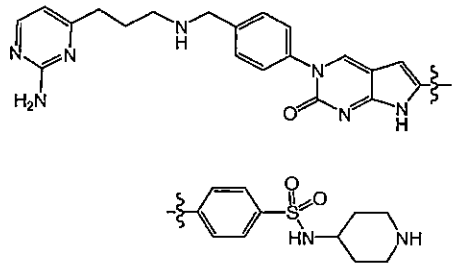
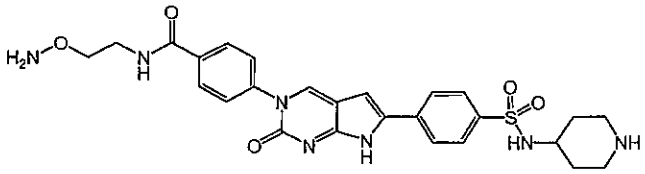
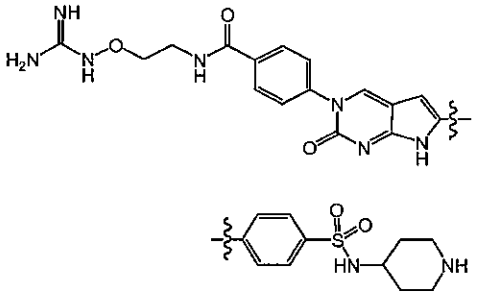
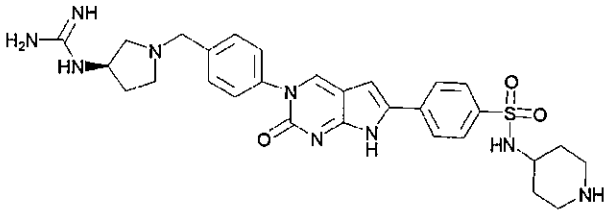
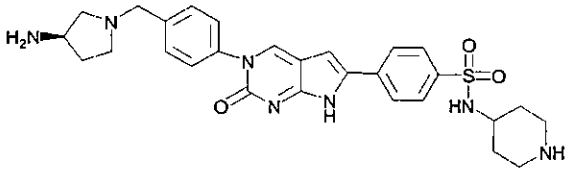
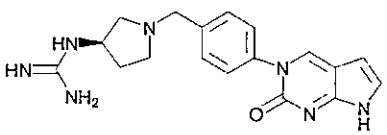
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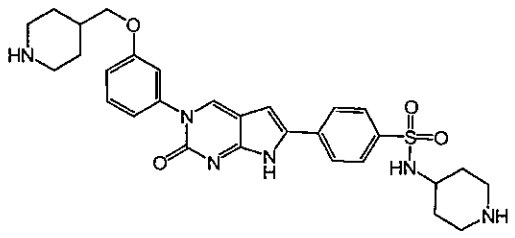
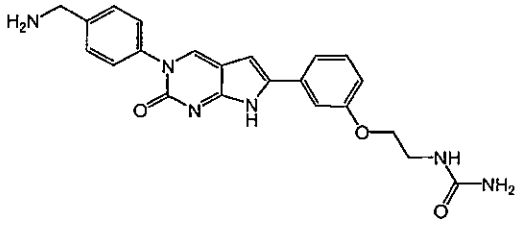
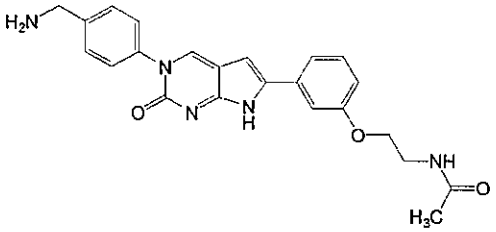
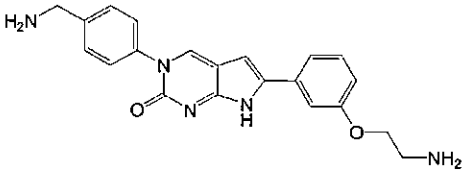
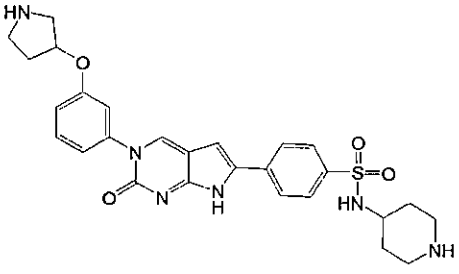
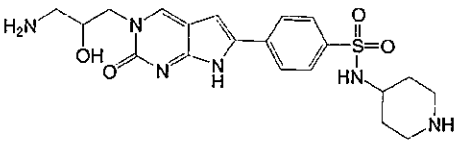
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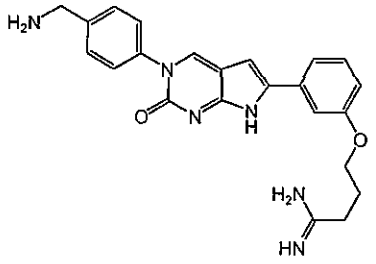
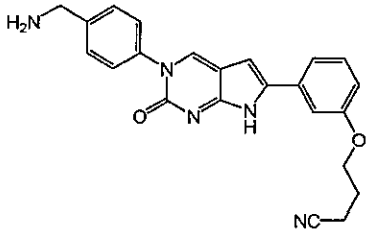
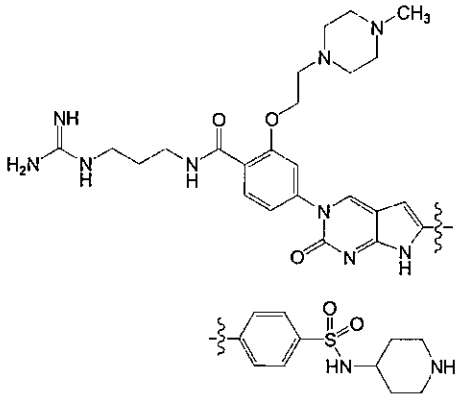
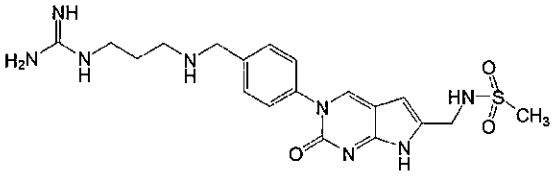
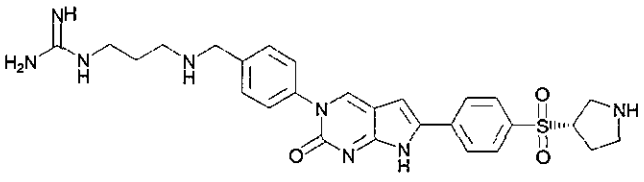
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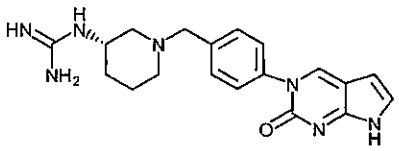
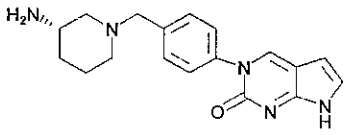
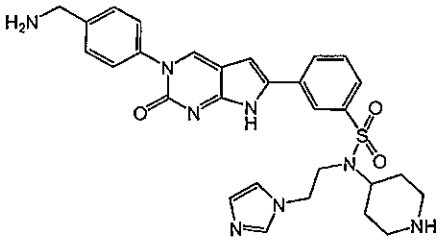
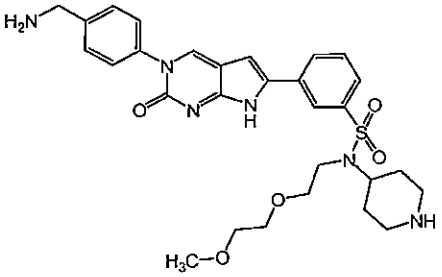
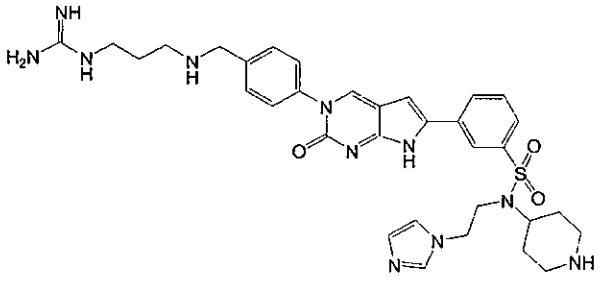
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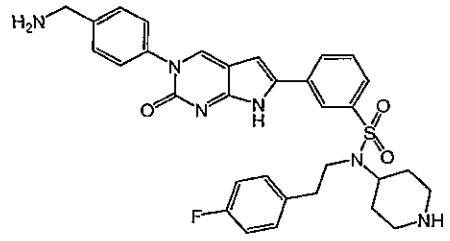
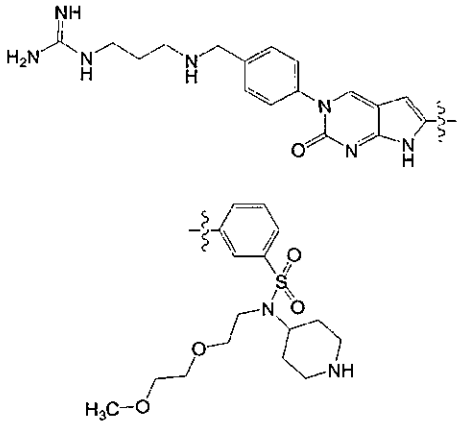
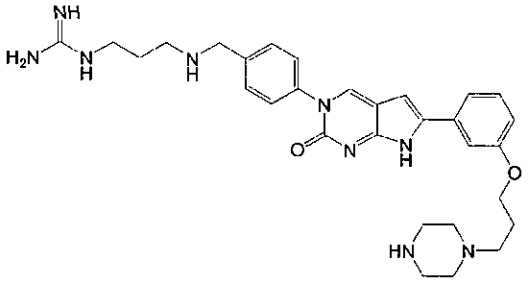
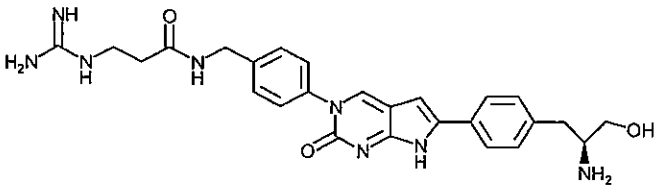
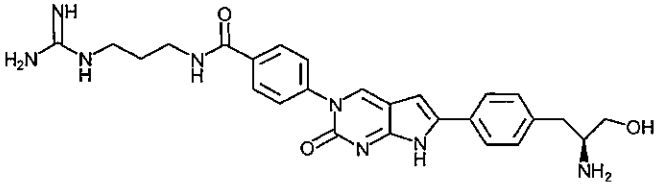
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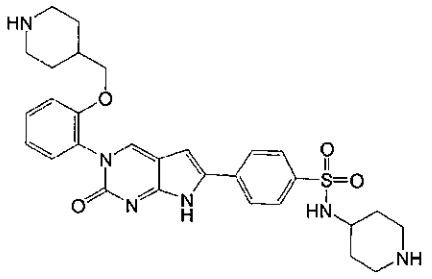
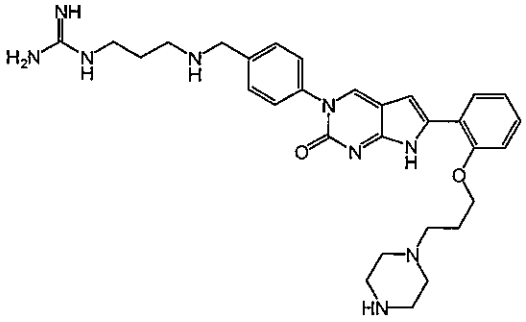
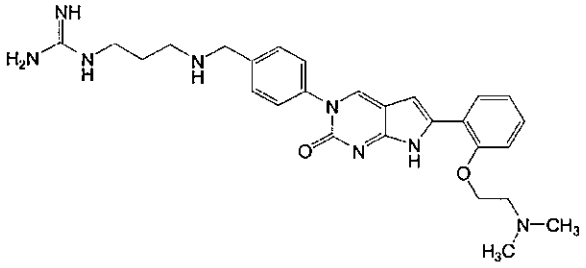
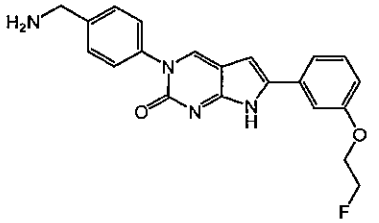
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1137		594.20
1138		590.20
1139		448.20
1140		352.00

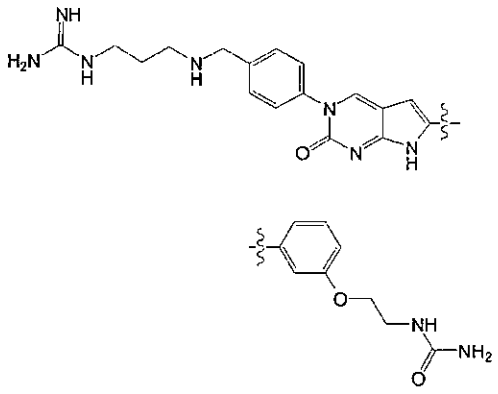
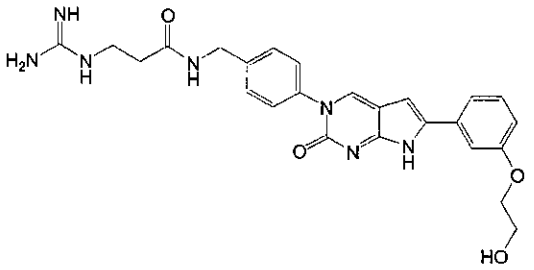
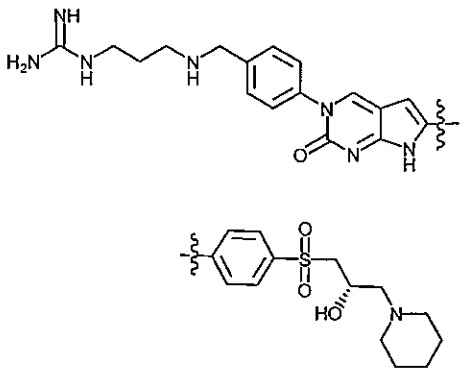
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1143		418.10
1144		376.20
1148		535.10
1149		447.00

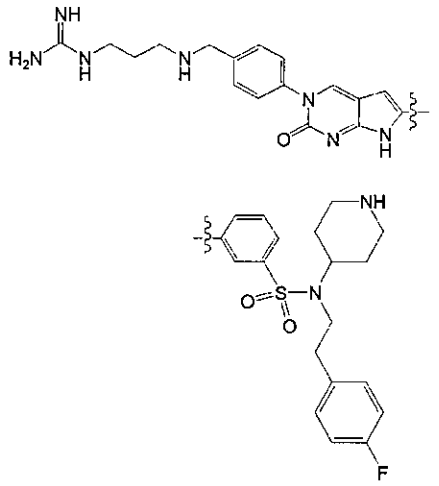
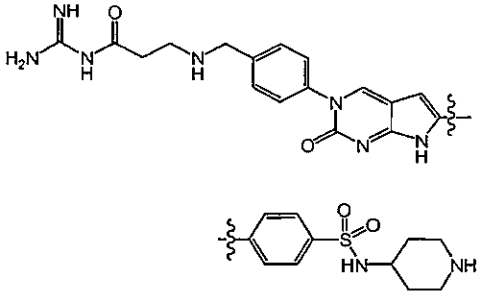
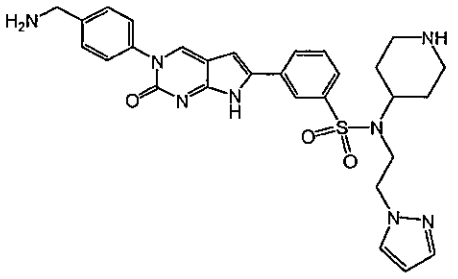
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1152		734.40
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1154		549.10

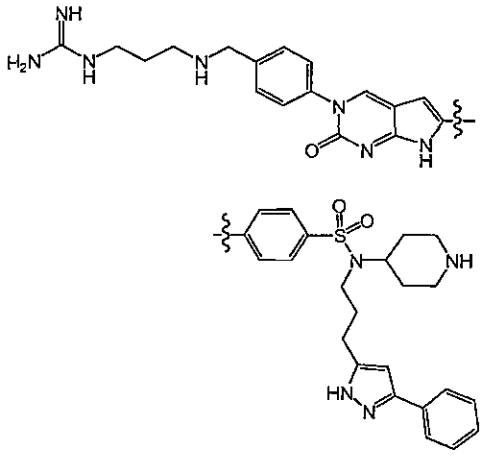
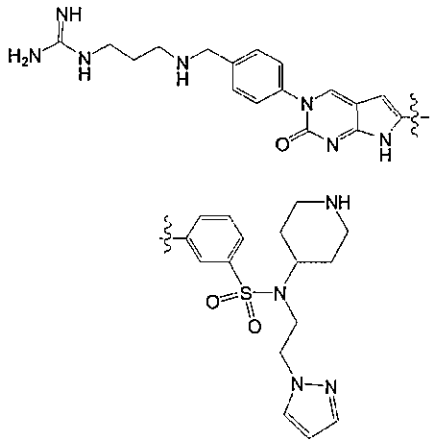
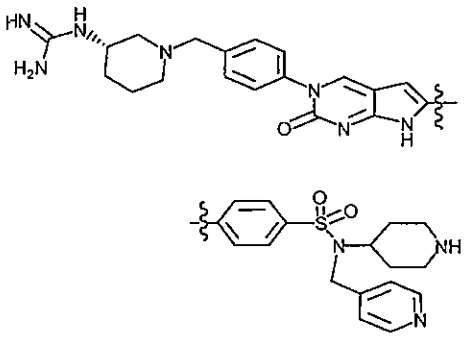
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1156		324.10
1157		573.00
1158		581.00
1159		NA

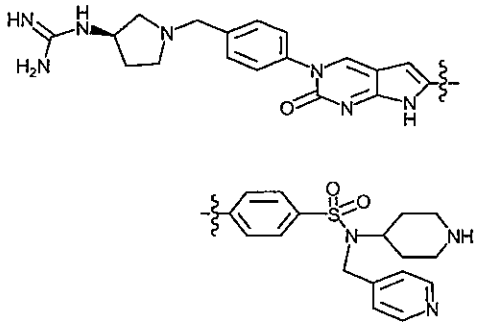
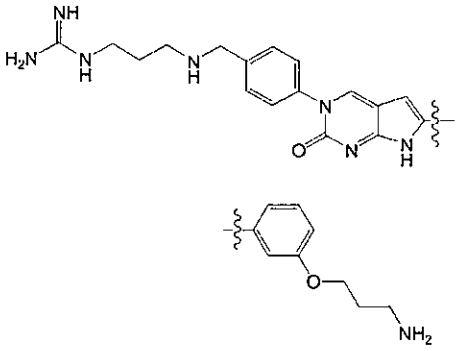
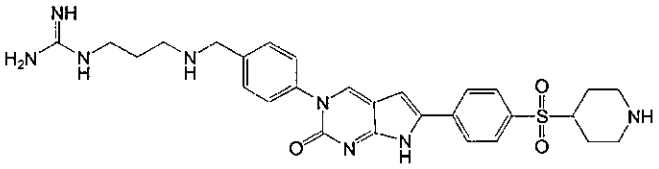
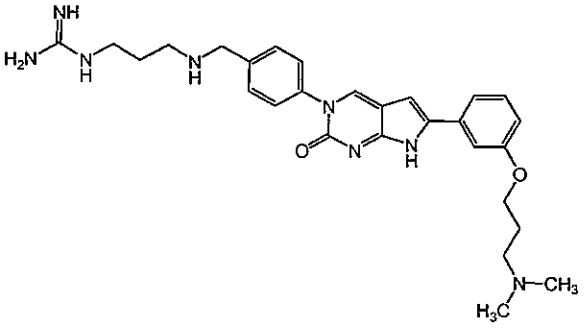
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1161		680.00
1162		558.00
1163		503.20
1164		503.20

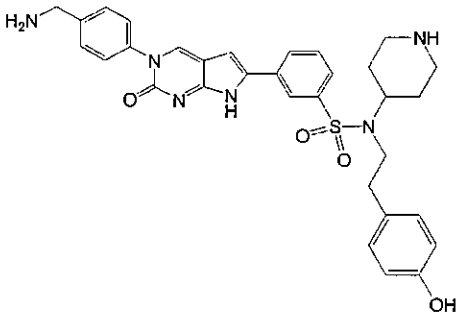
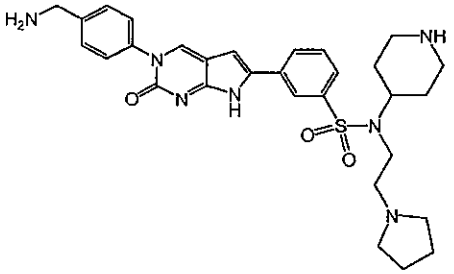
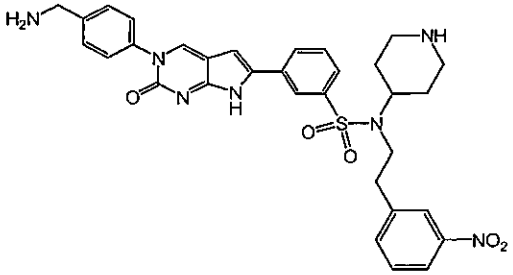
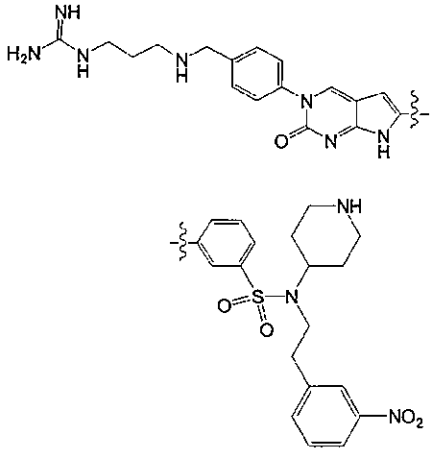
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1166		558.00
1167		503.20
1168		379.00

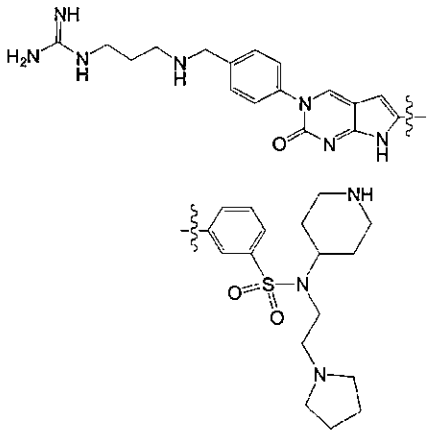
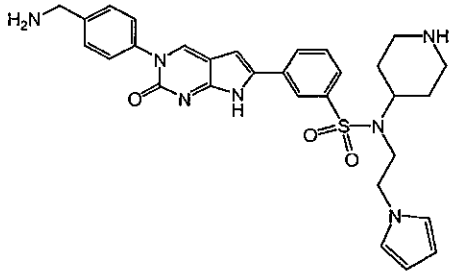
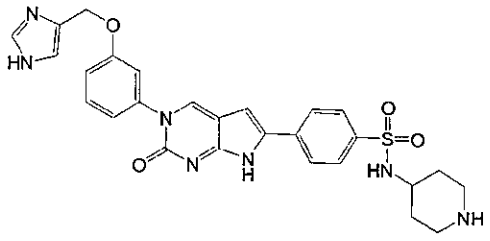
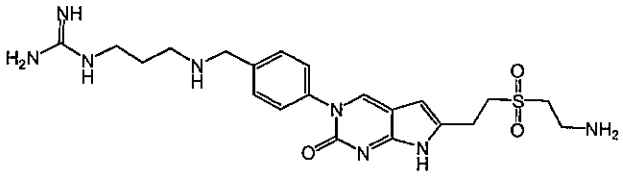
1169		512.20
1170		490.20
1171		621.30

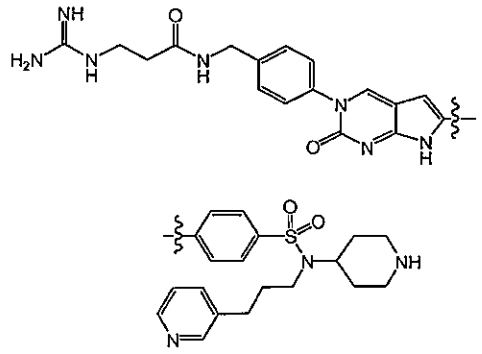
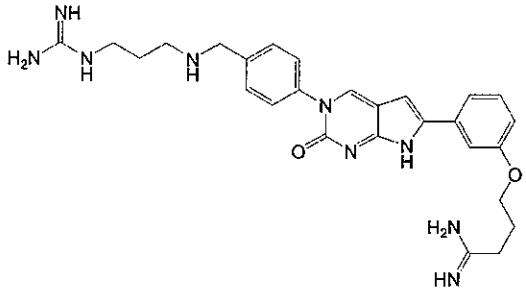
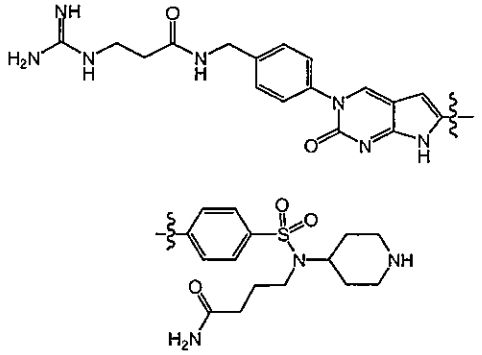
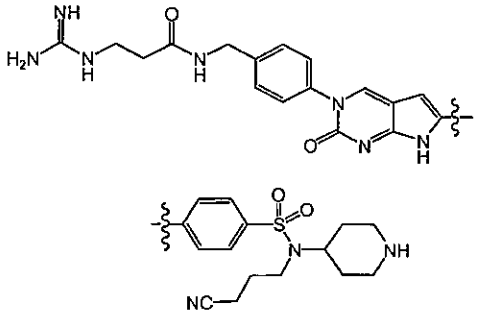
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1173		NA
1174		573.00

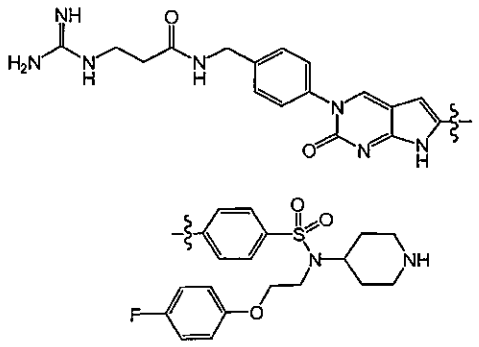
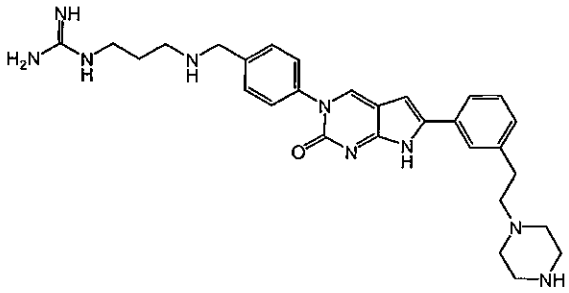
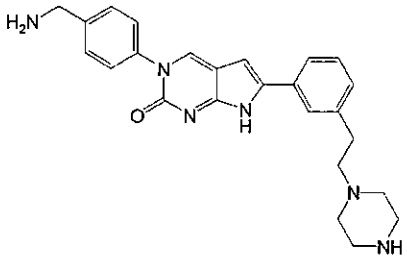
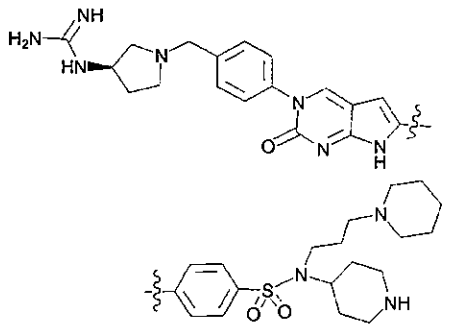
1175		762.00
1176		672.00
1177		695.10

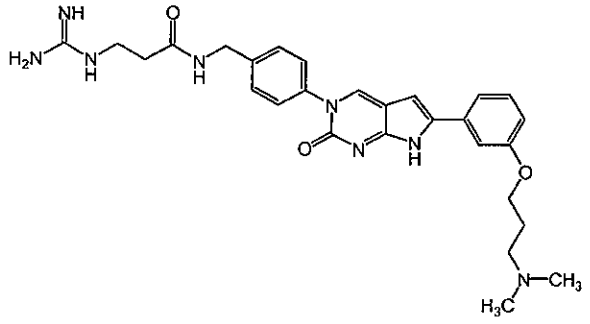
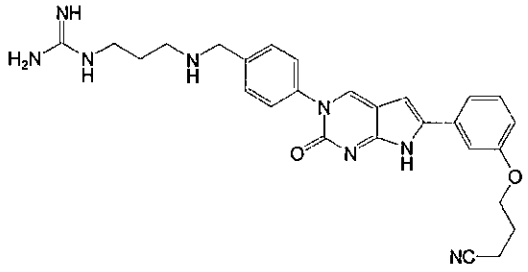
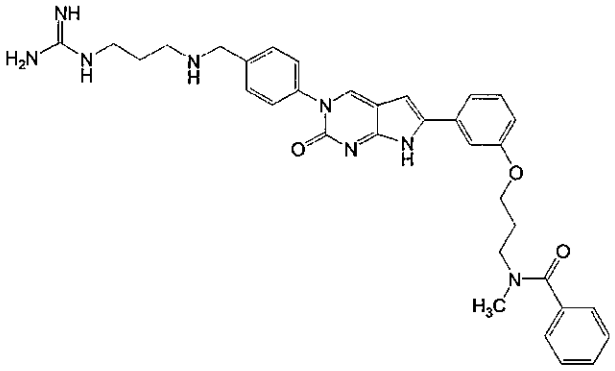
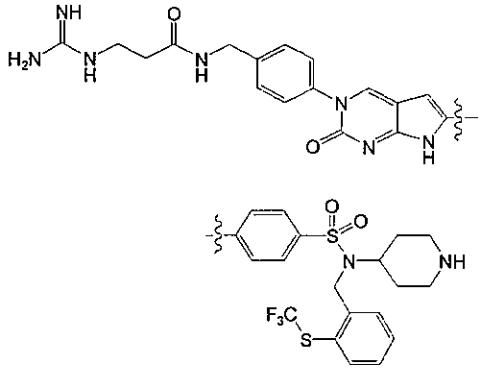
1178		681.20
1179		489.20
1180		563.10
1181		517.30

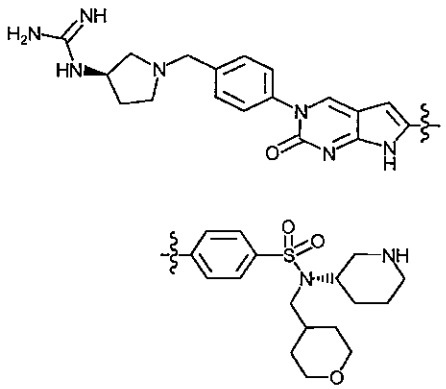
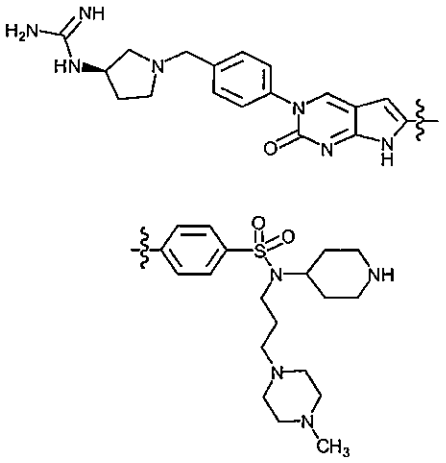
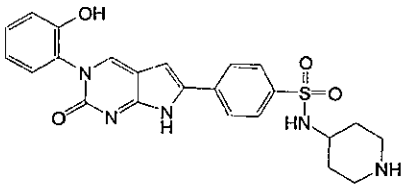
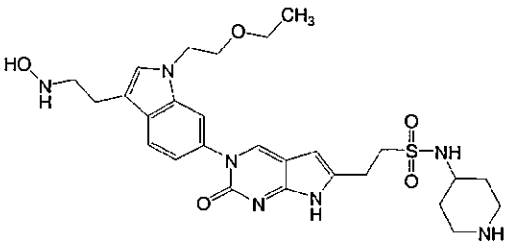
1182		599.00
1183		576.00
1184		628.00
1185		727.00

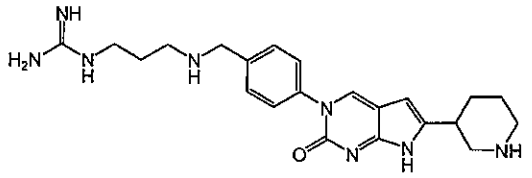
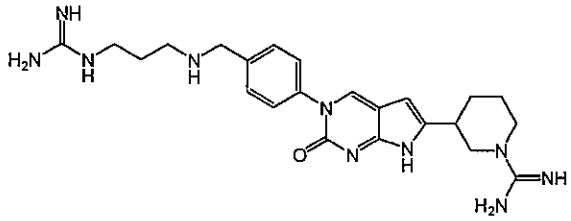
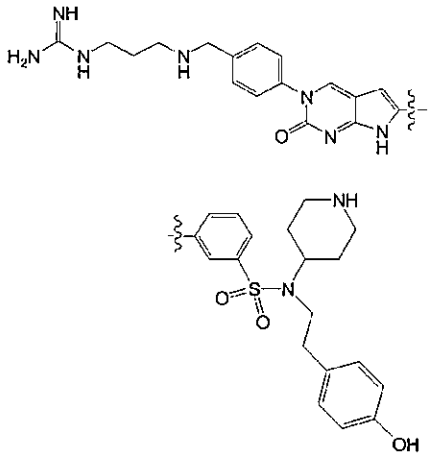
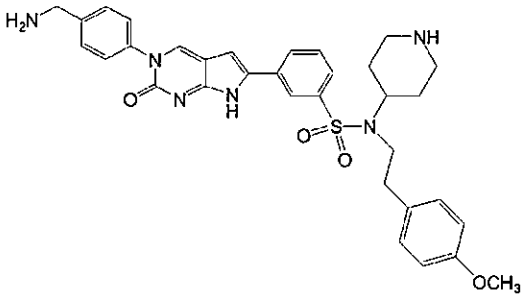
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1187		572.00
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1189		475.10

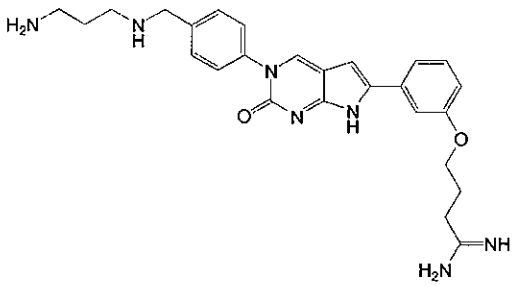
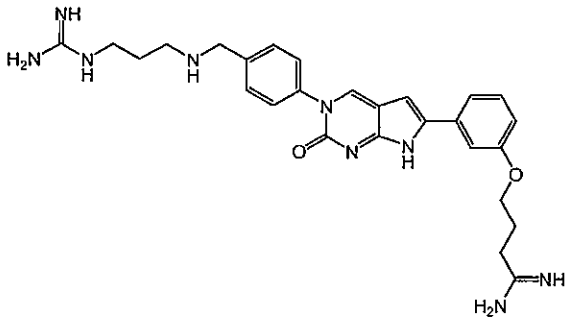
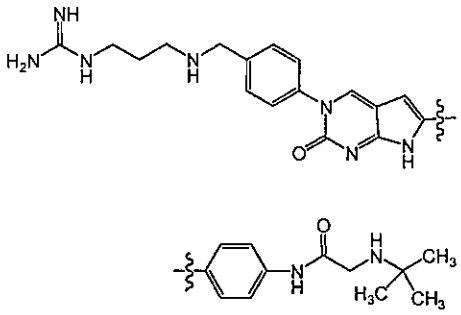
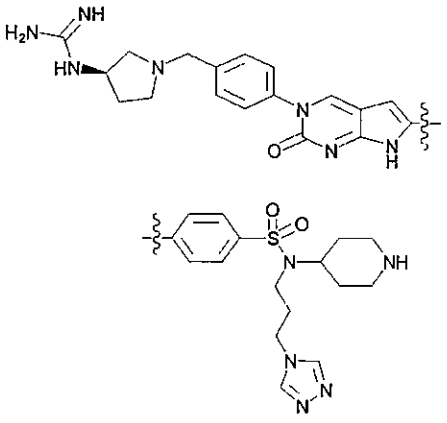
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1191		516.00
1194		677.20
1195		659.30

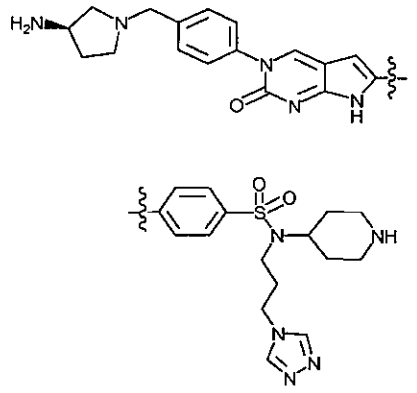
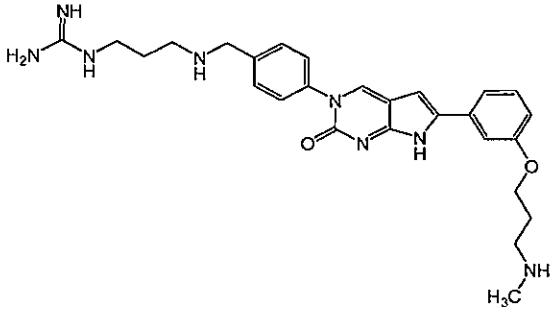
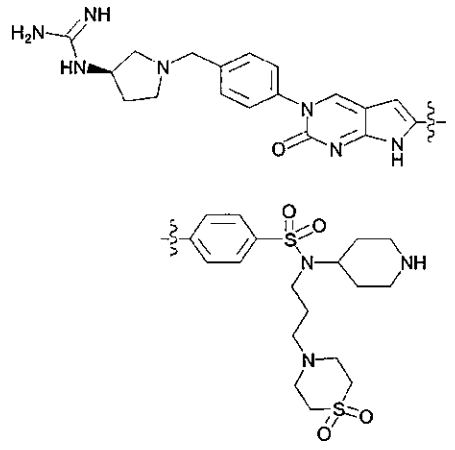
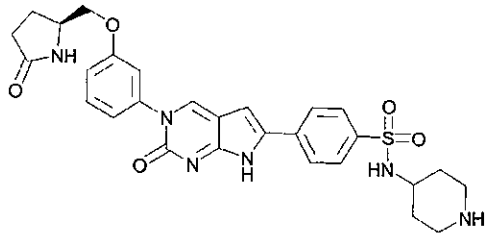
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1199		528.00
1200		429.00
1201		715.40

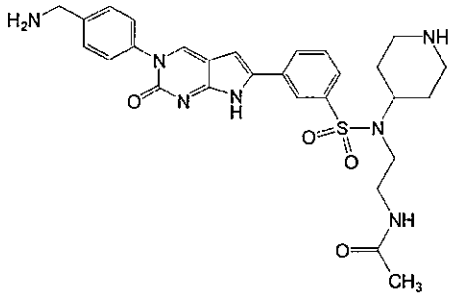
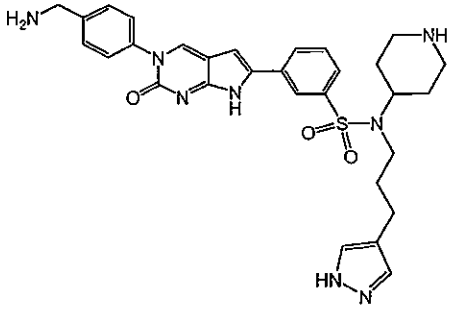
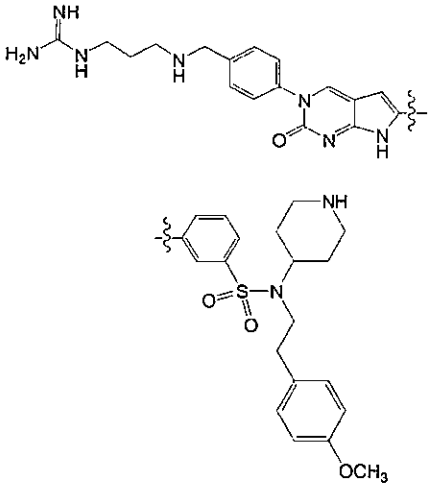
1202		531.40
1203		499.00
1204		607.30
1205		782.30

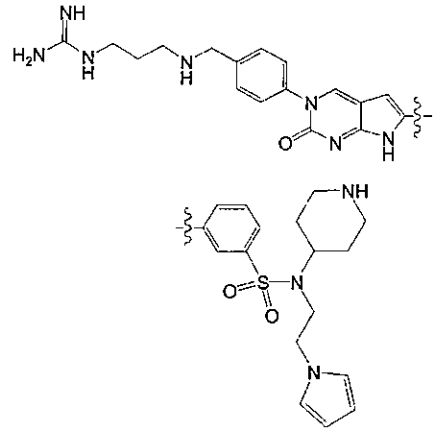
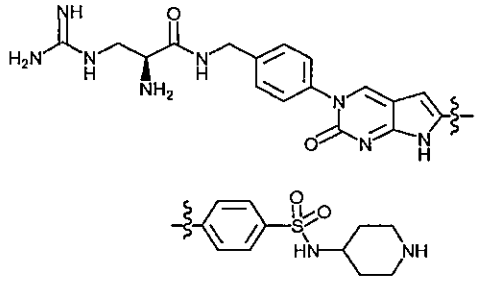
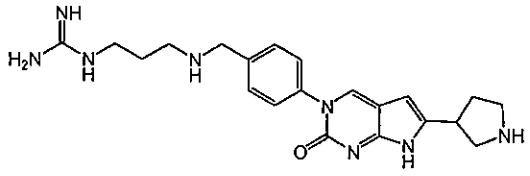
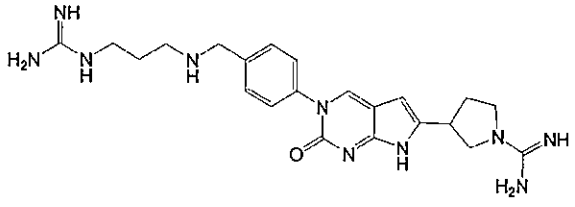
1206		688.40
1207		730.30
1208		466.00
1209		572.10

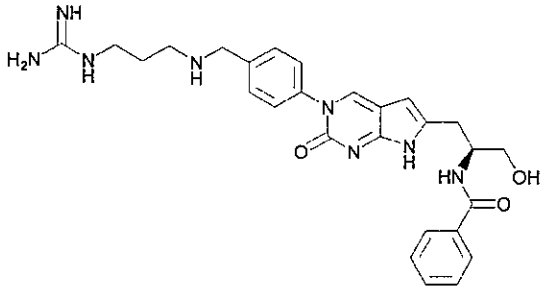
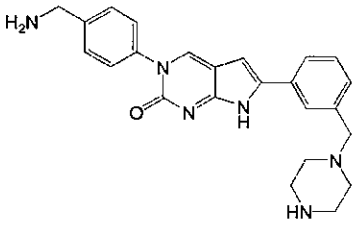
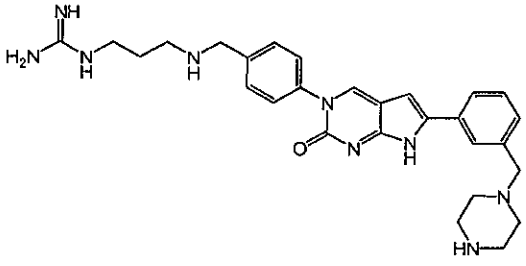
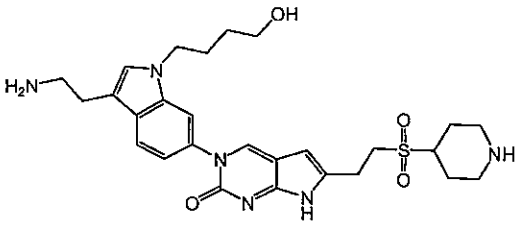
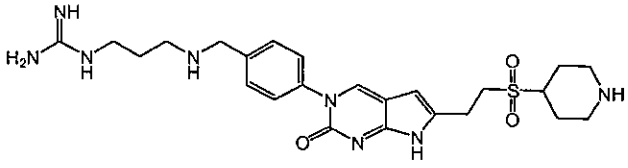
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1211		465.20
1214		698.00
1215		613.00

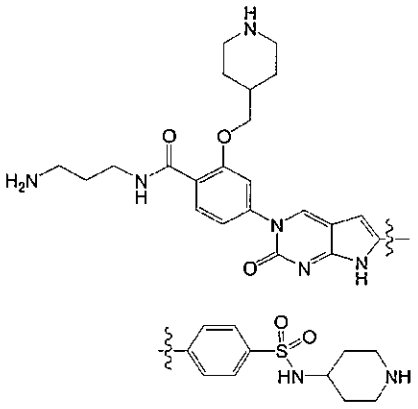
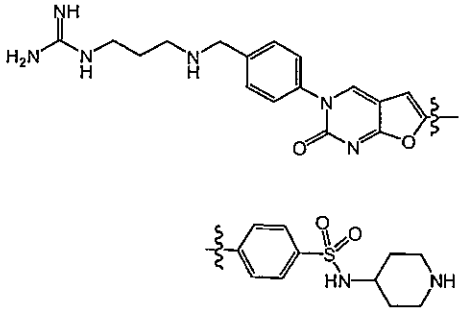
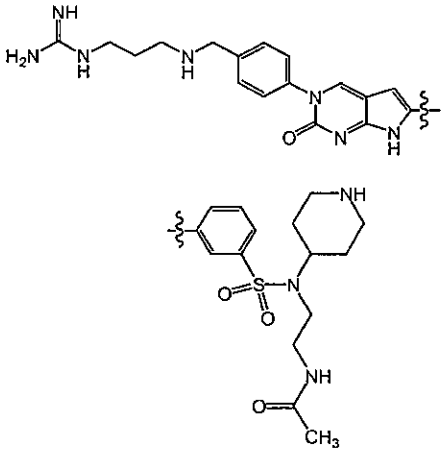
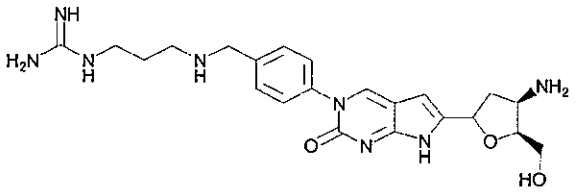
1216		474.00
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1218		544.10
1219		699.30

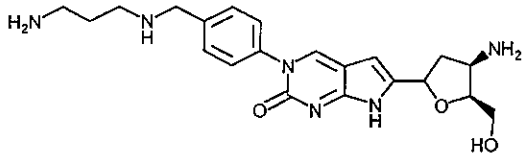
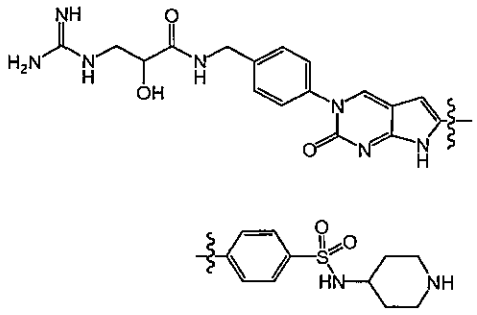
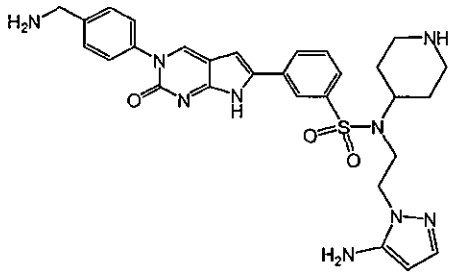
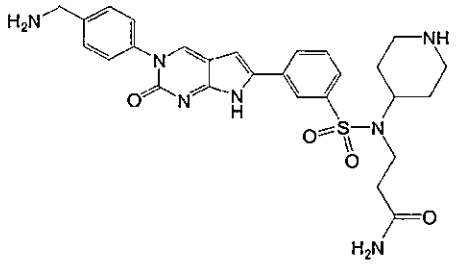
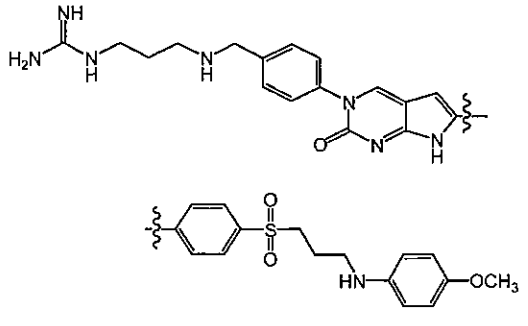
1220		657.30
1221		503.20
1222		765.30
1223		563.10

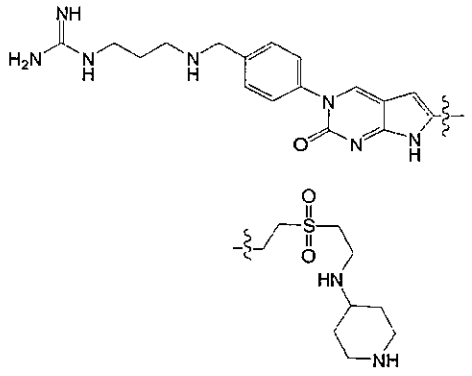
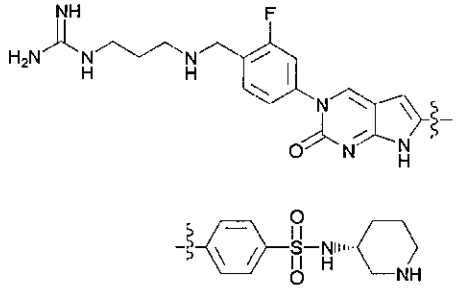
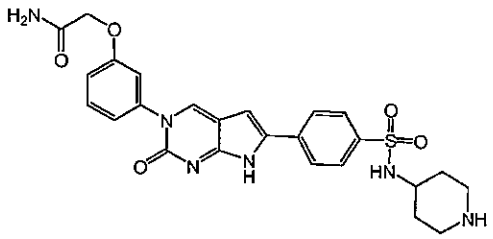
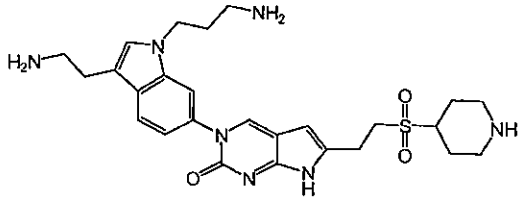
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1226		712.00

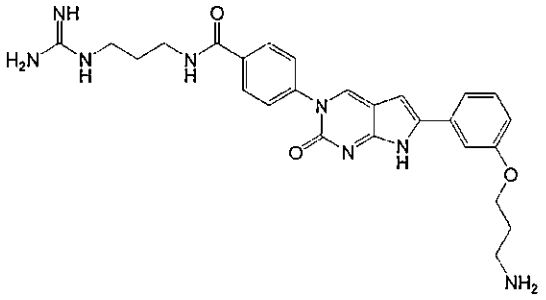
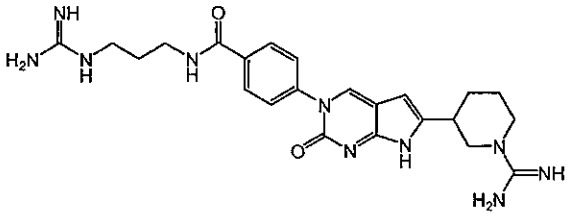
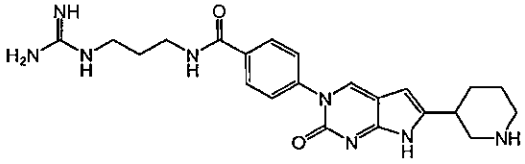
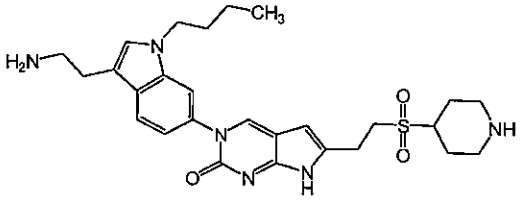
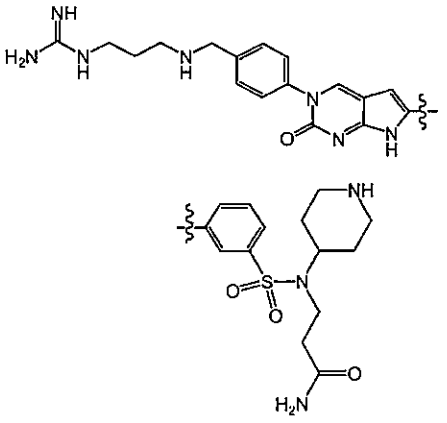
1227		671.00
1228		607.20
1229		409.10
1230		451.00

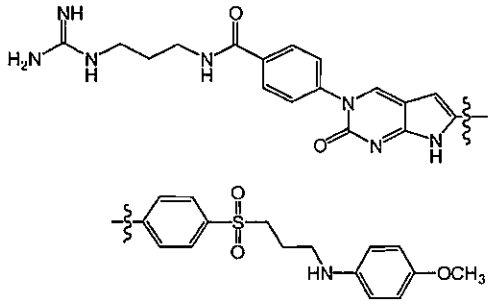
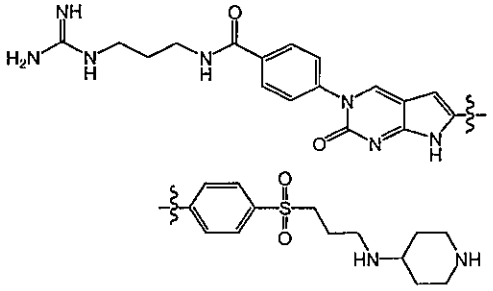
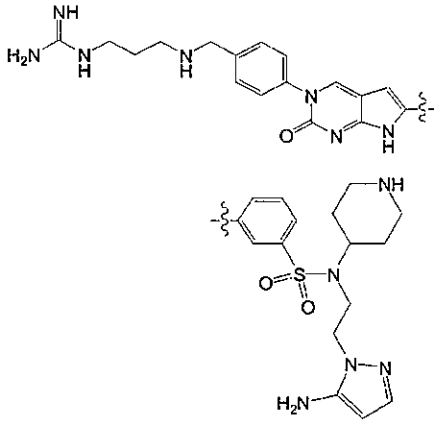
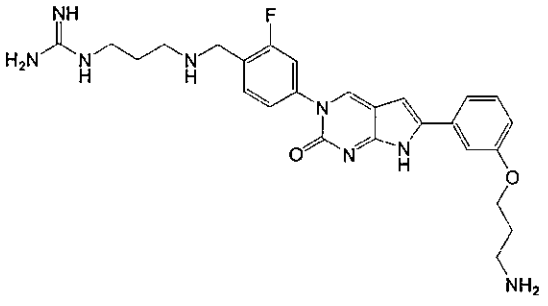
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1233		514.00
1239		541.10
1240		515.30

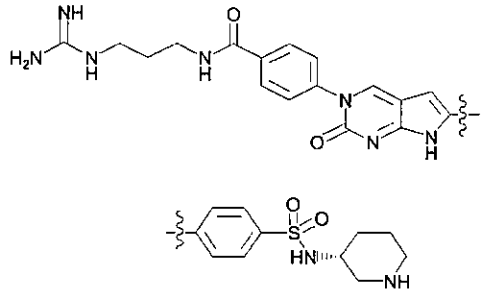
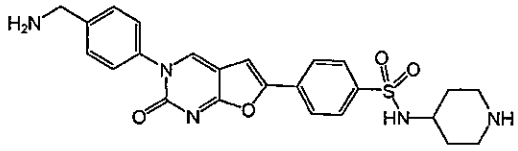
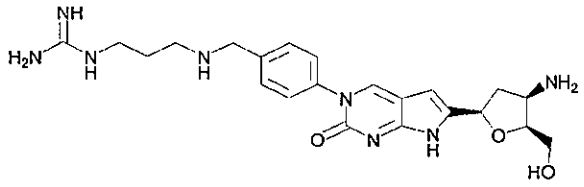
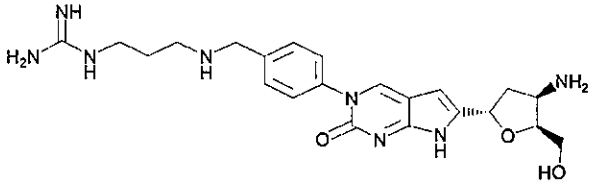
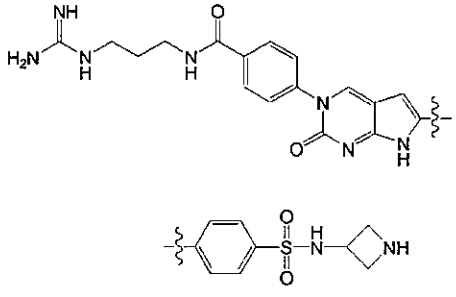
1241		663.10
1242		579.10
1243		663.00
1245		455.10

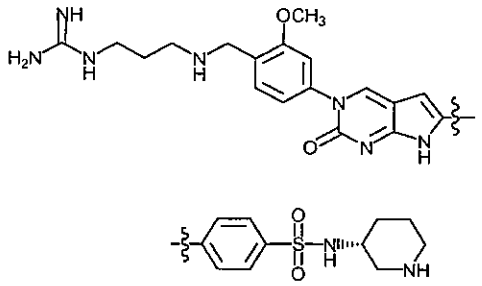
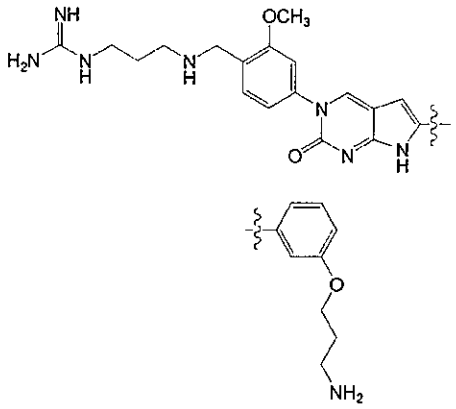
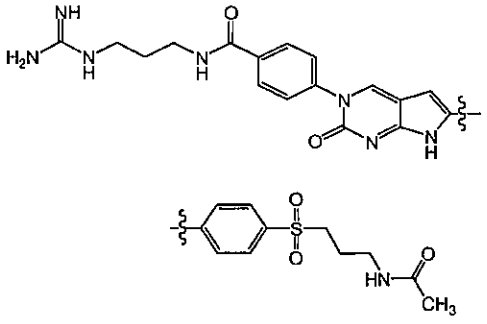
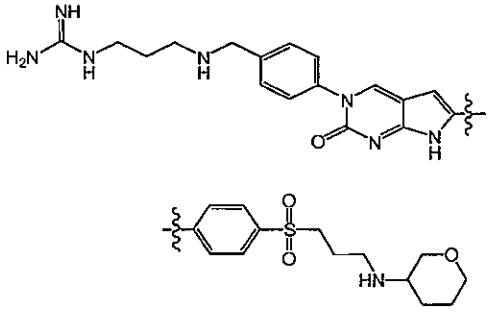
1246		413.20
1247		608.10
1248		588.00
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1250		643.00

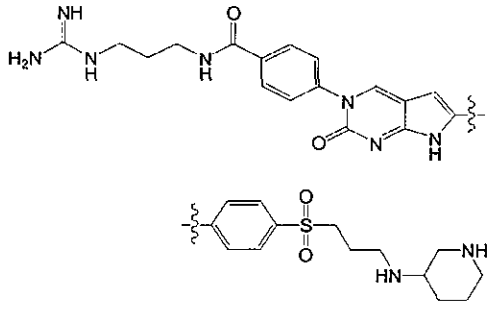
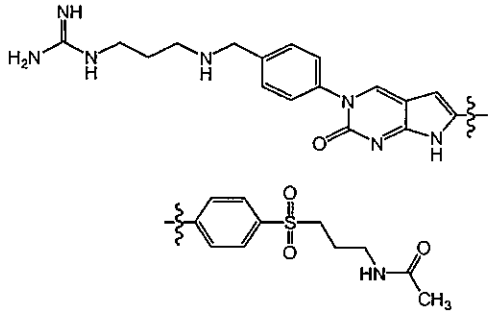
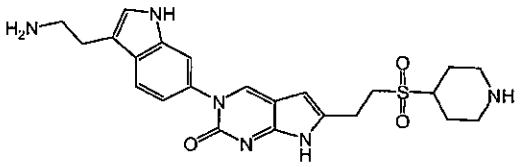
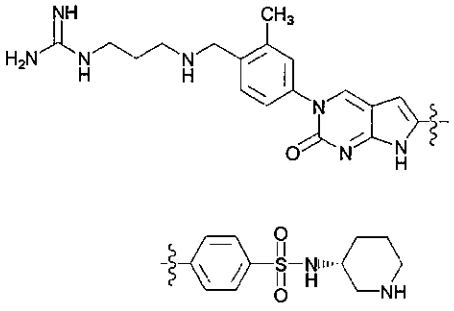
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1254		528.00

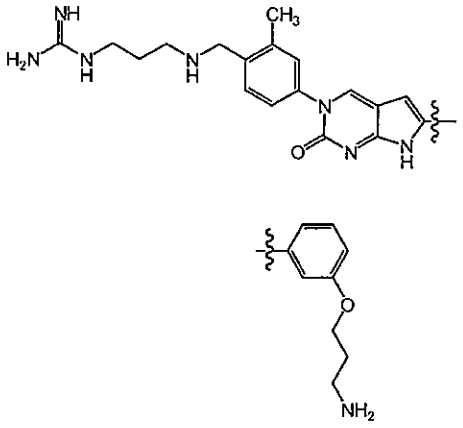
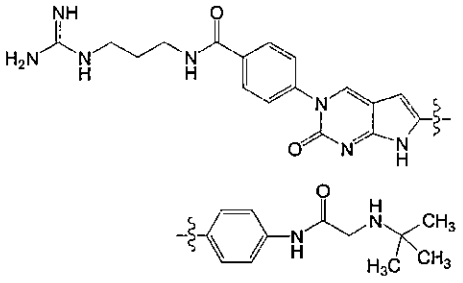
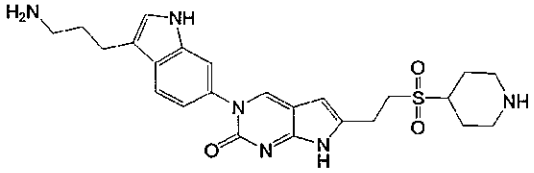
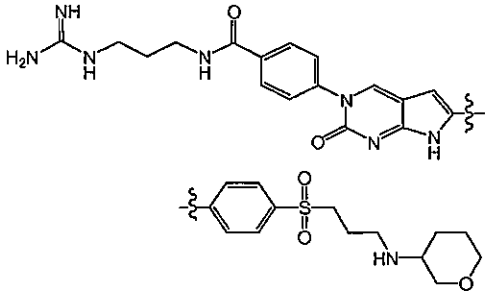
1255		503.10
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1257		437.10
1258		525.10
1259		649.00

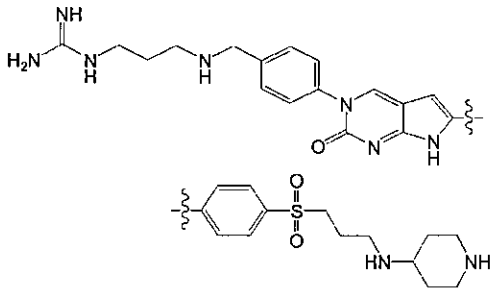
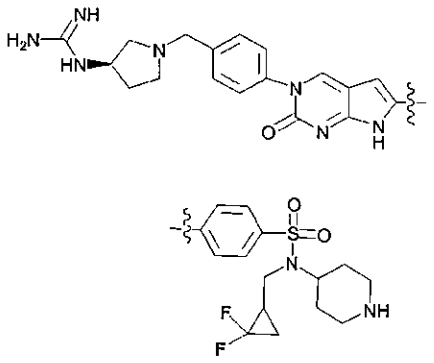
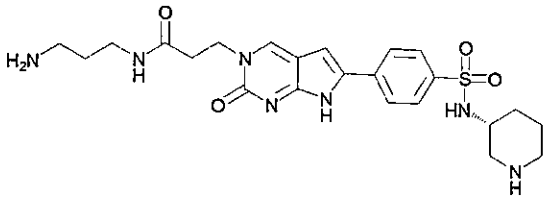
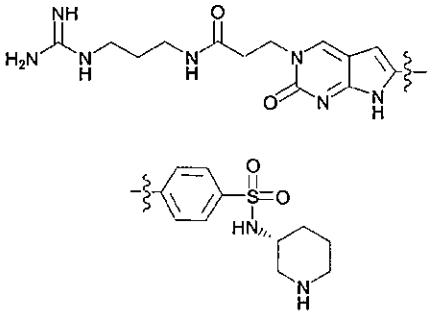
1260		657.00
1261		634.00
1262		687.00
1263		507.00

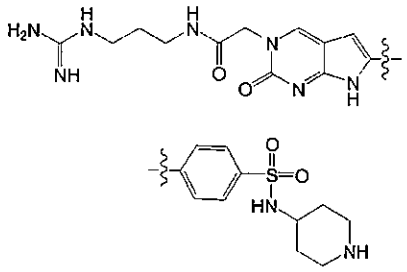
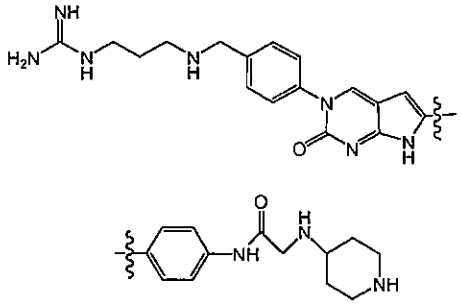
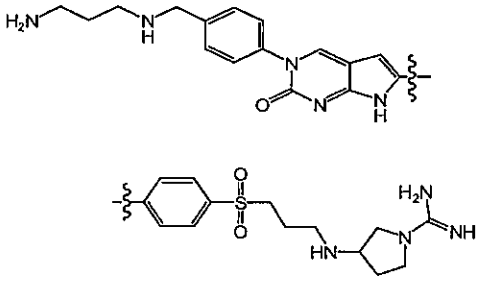
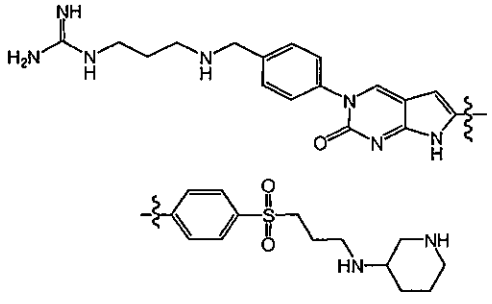
1264		592.50
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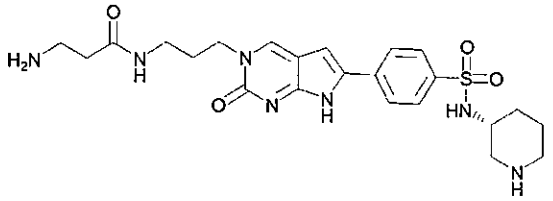
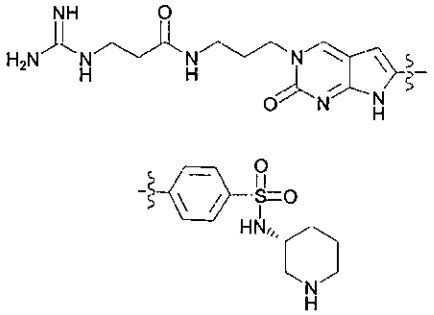
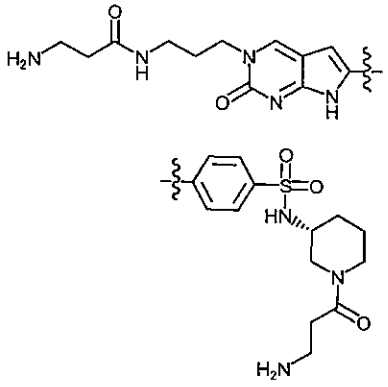
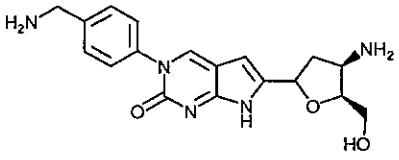
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1273		519.30
1274		593.00
1275		621.00

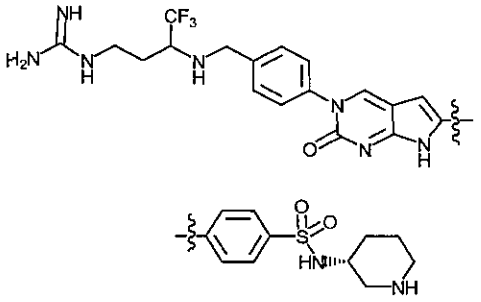
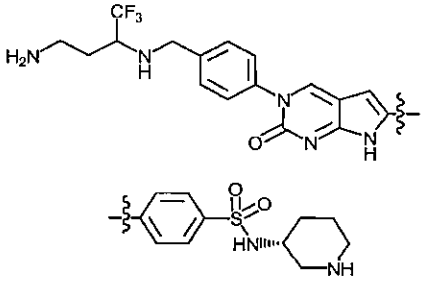
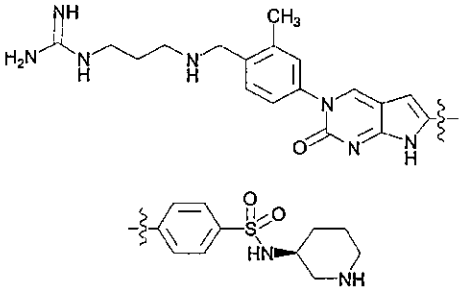
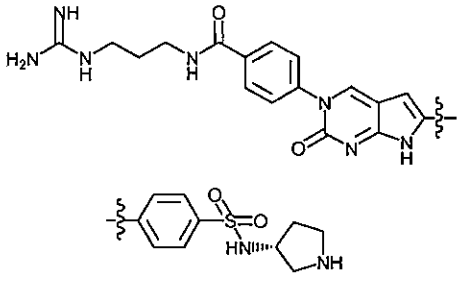
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1278		469.00
1279		592.00

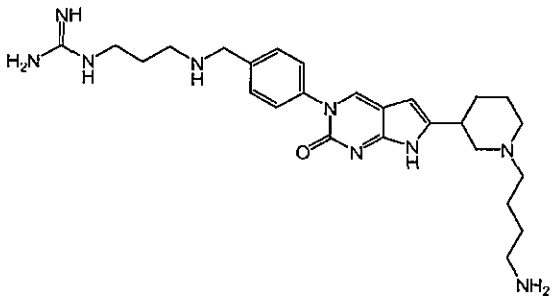
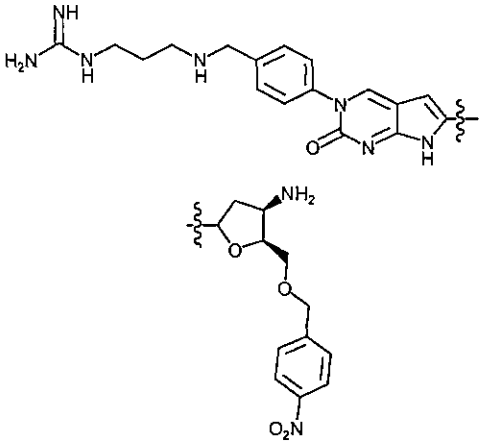
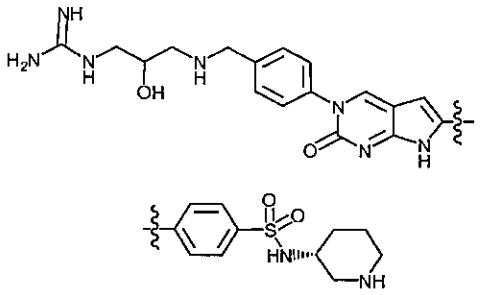
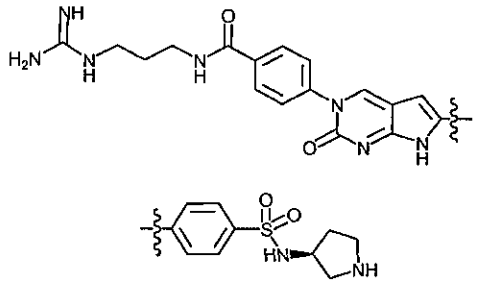
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1281		558.70
1282		482.80
1284		635.00

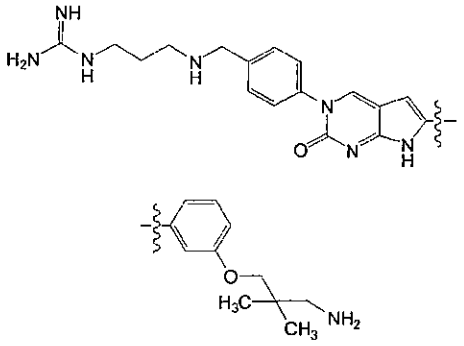
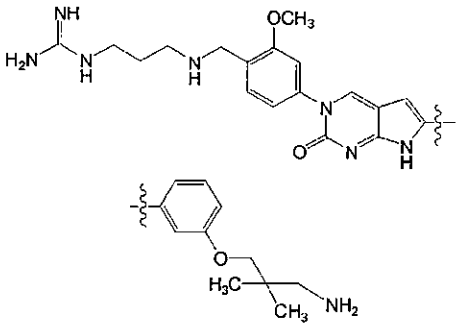
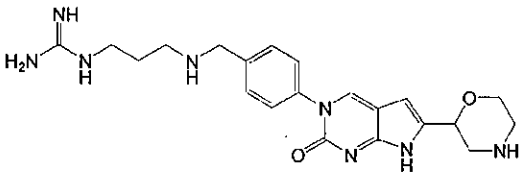
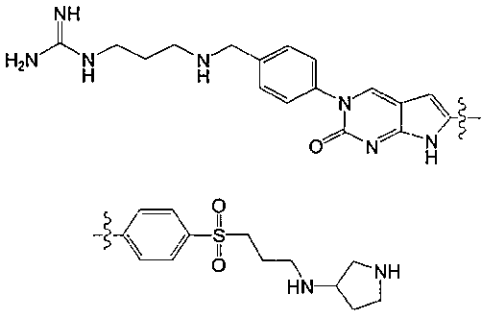
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1286		680.10
1287		501.90
1288		544.10

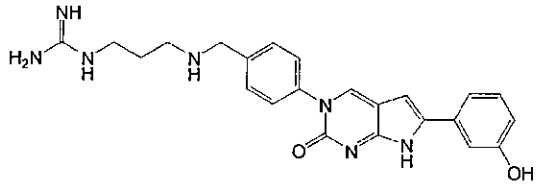
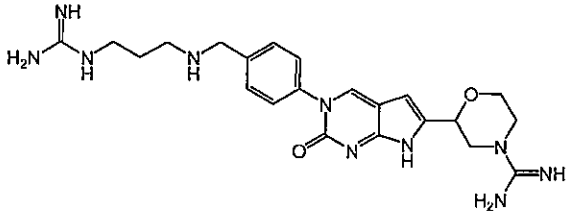
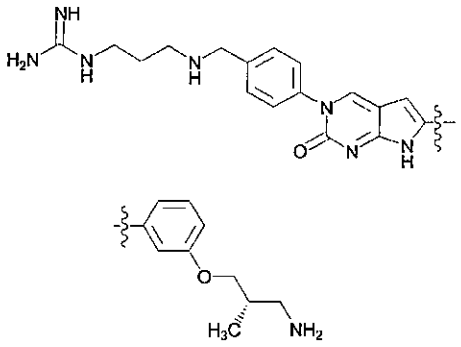
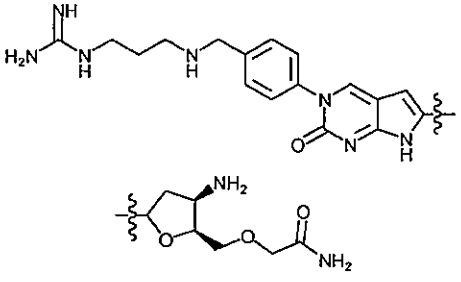
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1290		570.60
1292		606.00
1293		620.00

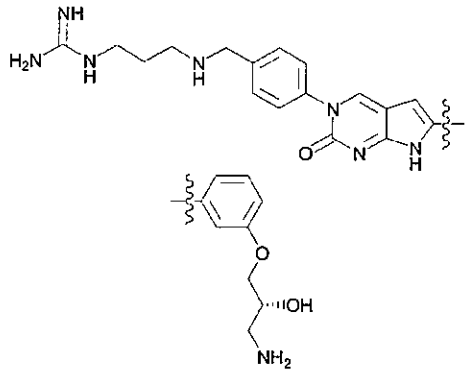
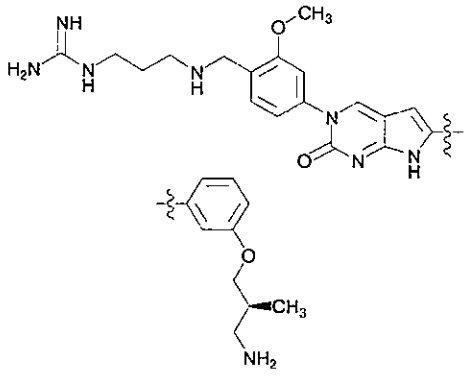
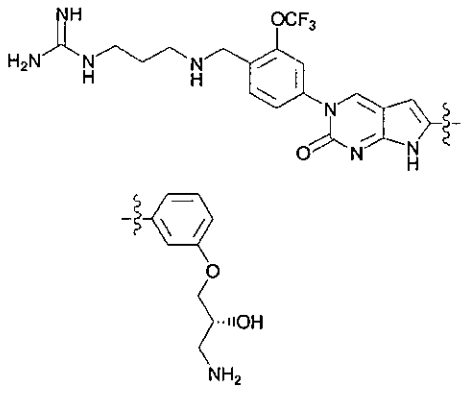
1298		502.30
1299		544.30
1300		573.00
1301		355.10

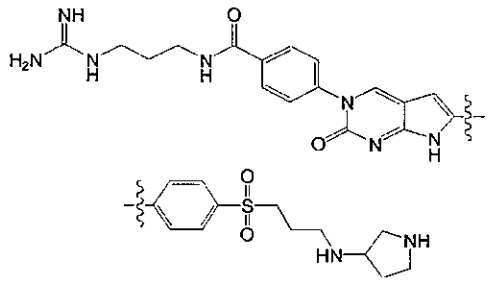
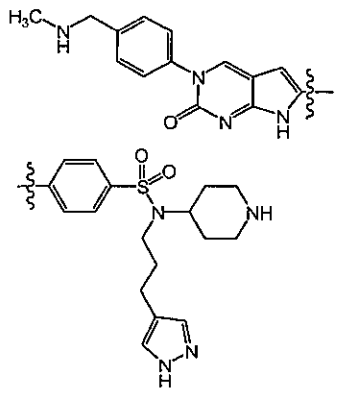
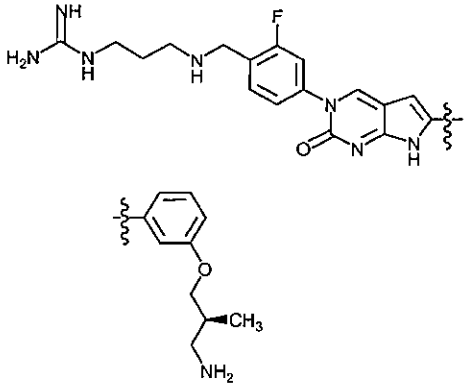
1306		646.37
1307		604.10
1309		592.00
1310		579.00

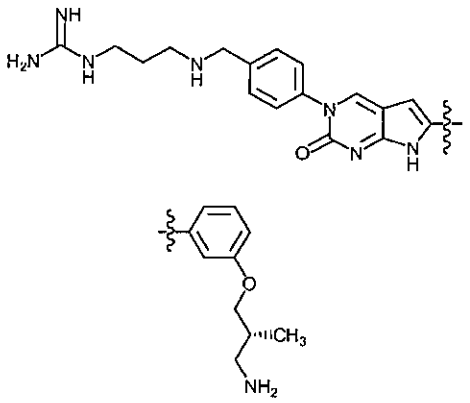
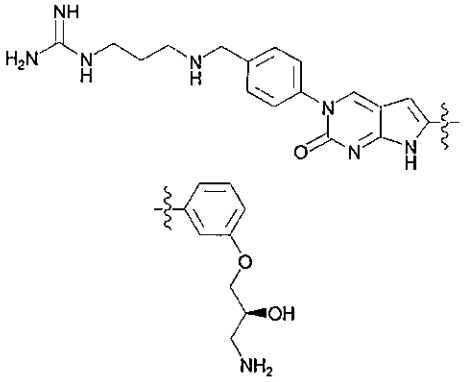
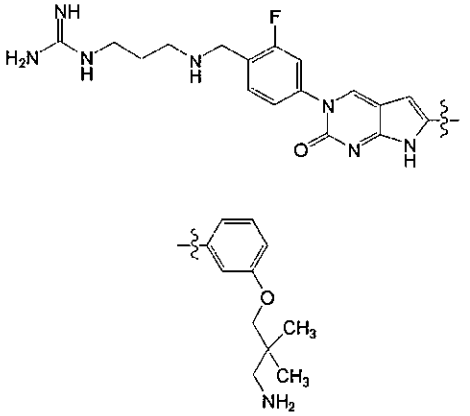
1316		491.1
1324		590.2
1325		594.3
1326		578.4

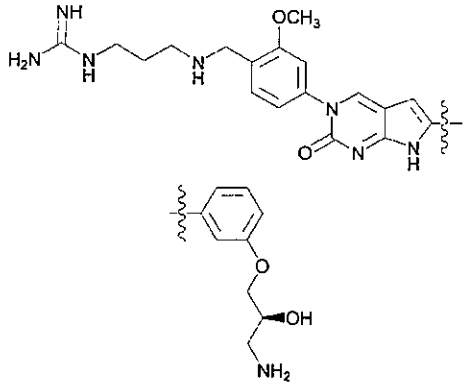
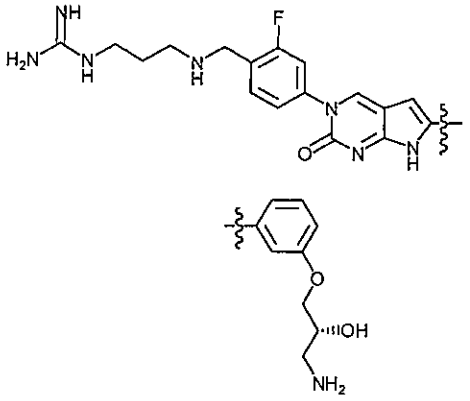
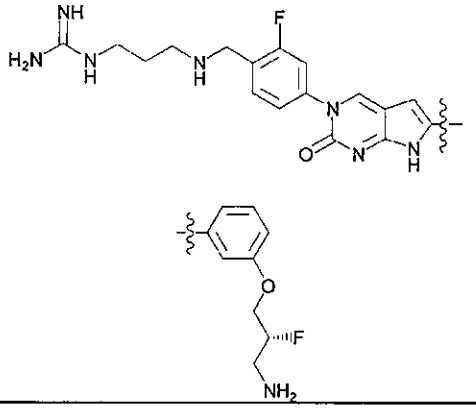
1327		517.2
1328		547.5
1329		425.8
1330		606

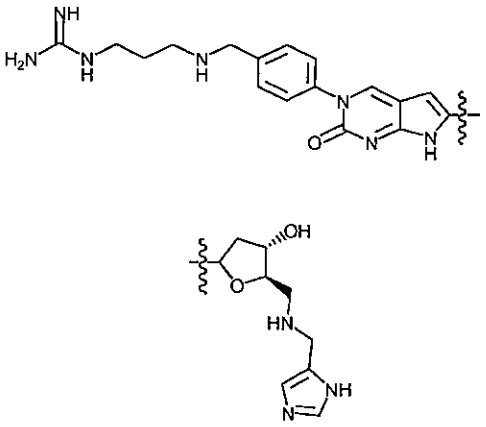
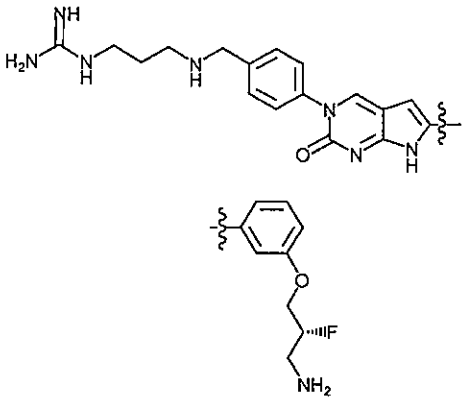
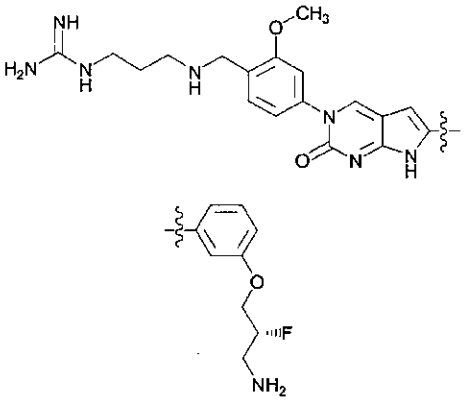
1334		432.1
1335		466.8
1336		503.0
1342		512.4

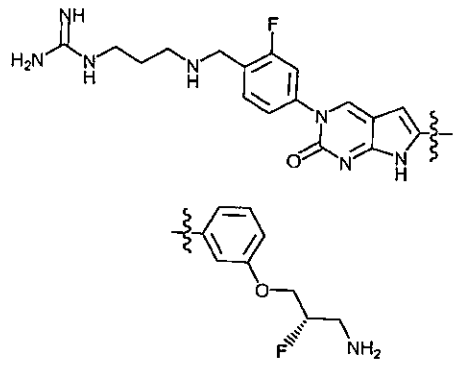
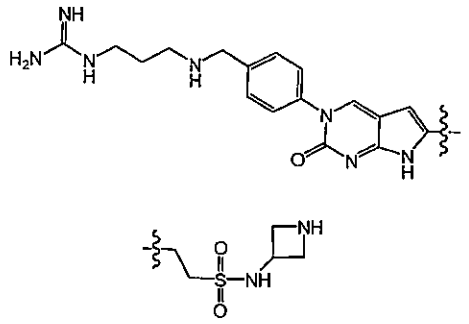
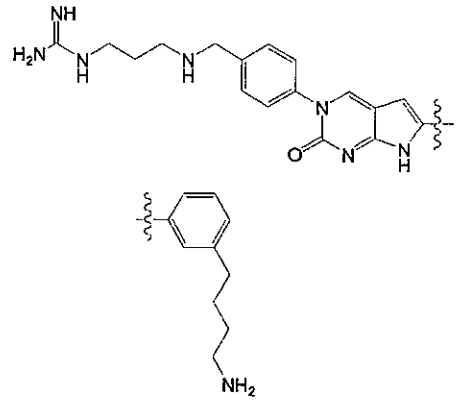
1343		505.8
1344		533.6
1349		535.3

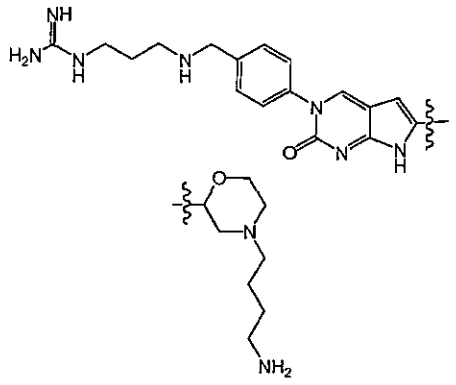
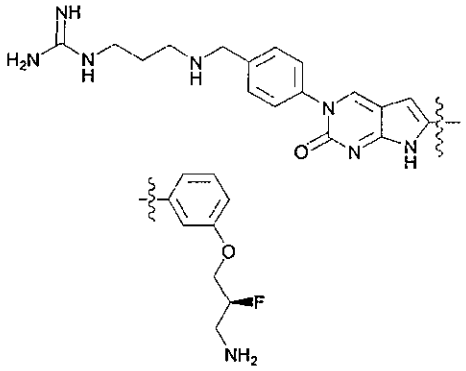
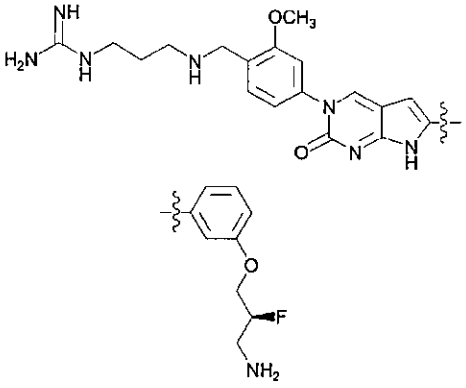
1350		620
1351		601
1352		521.00

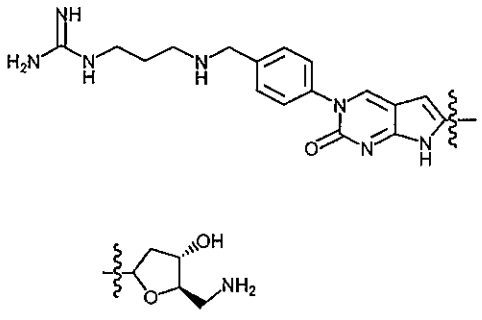
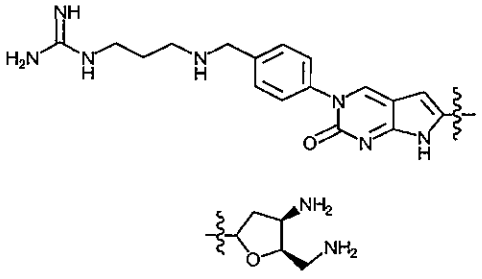
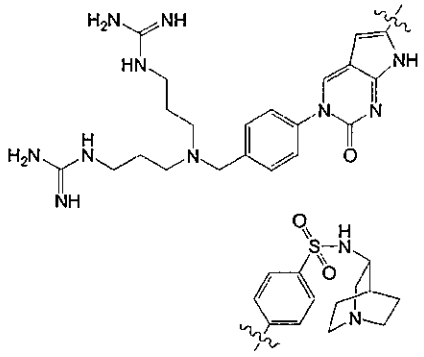
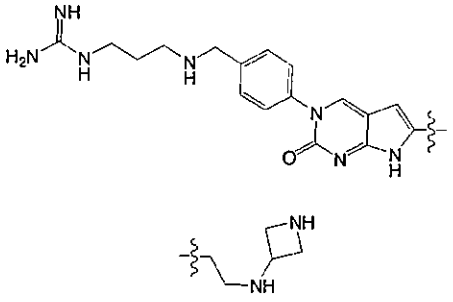
1359		502.8
1360		505.8
1361		535.4

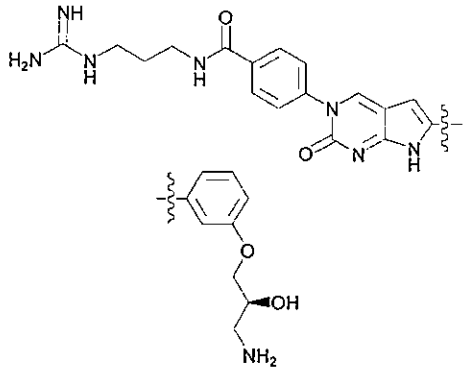
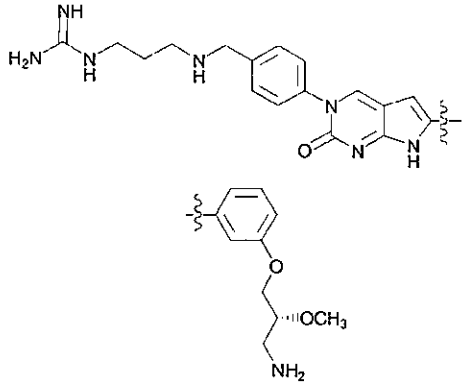
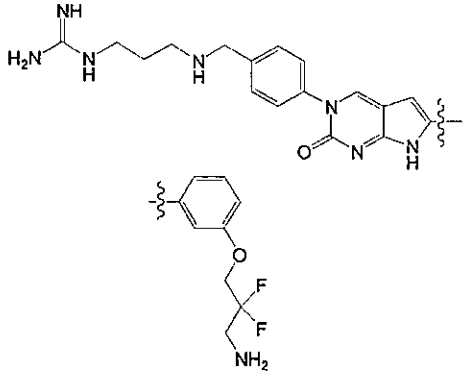
1365		535.1
1366		523.1
1367		525.00

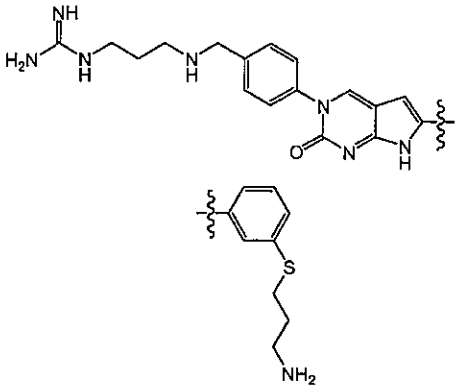
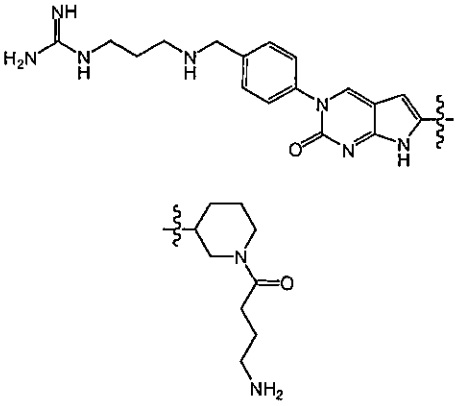
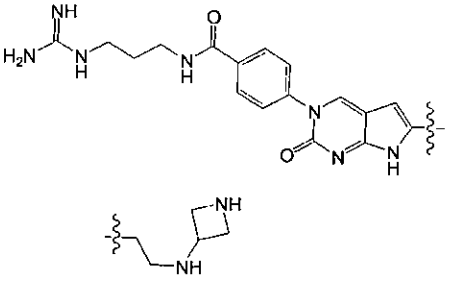
1371		535.4
1372		507.00
1373		536.9

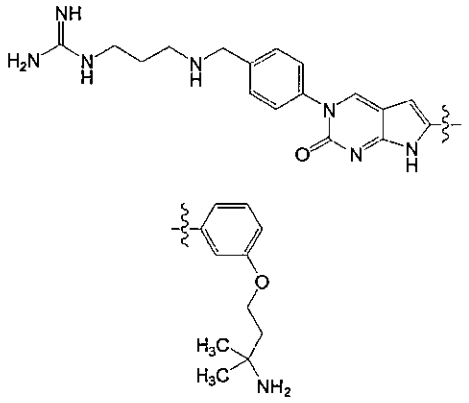
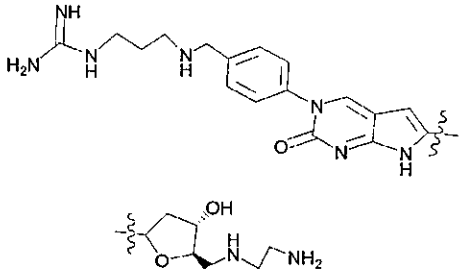
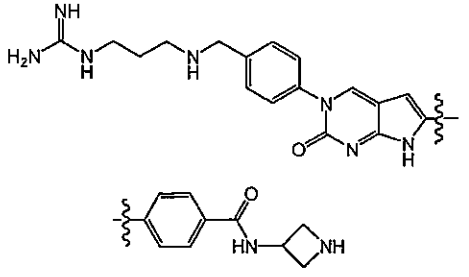
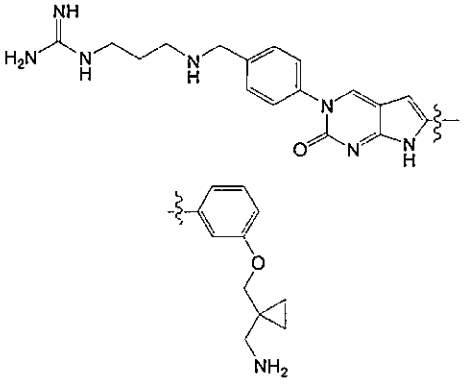
1374		525.00
1379		502.2
1380		487.6

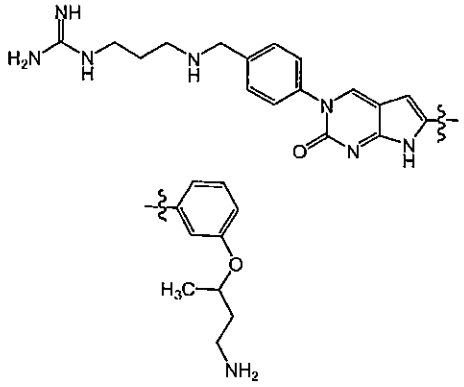
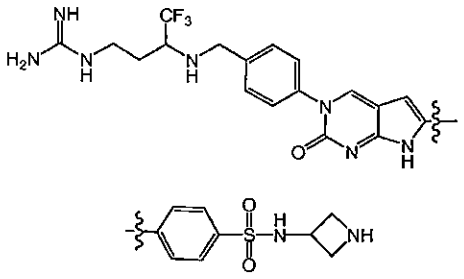
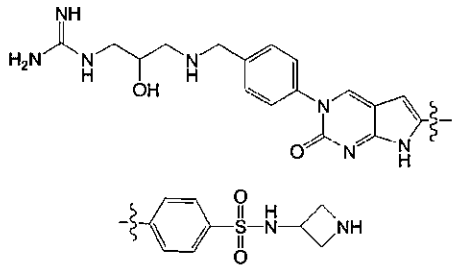
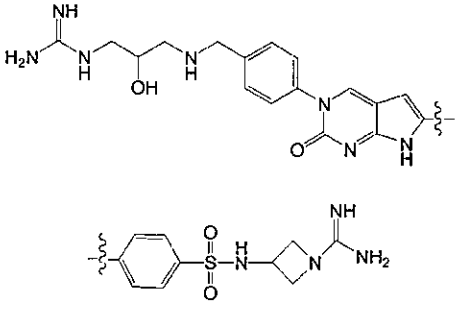
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1390		507.3
1391		N/A

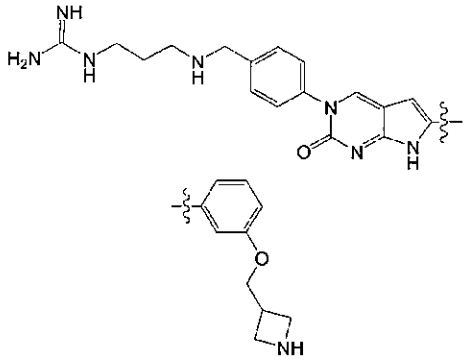
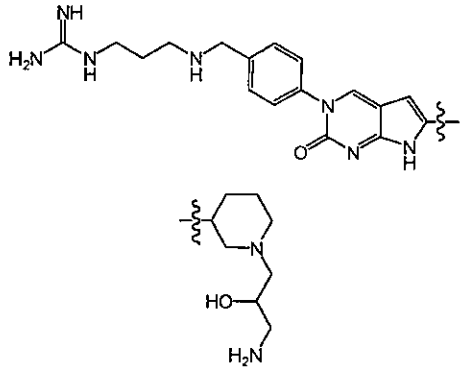
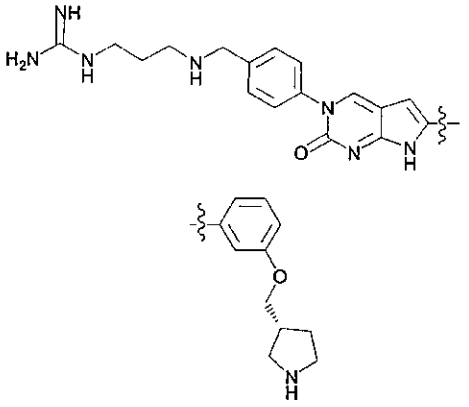
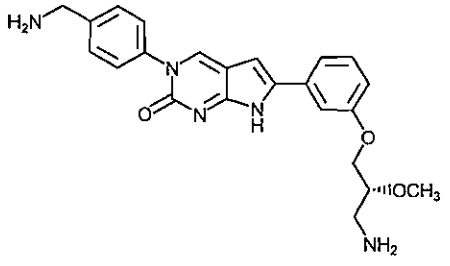
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1393		455.3
1397		704.2
1398		438.00

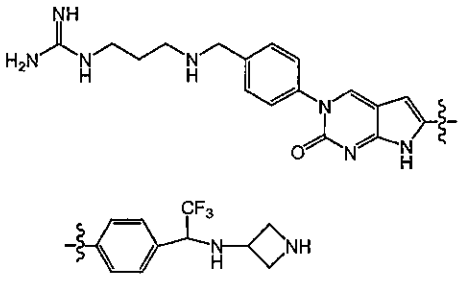
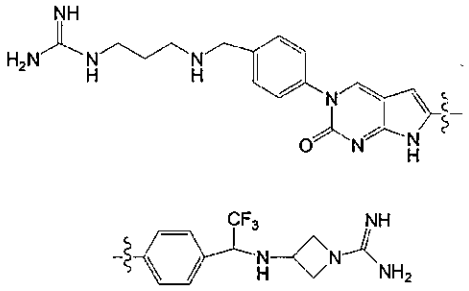
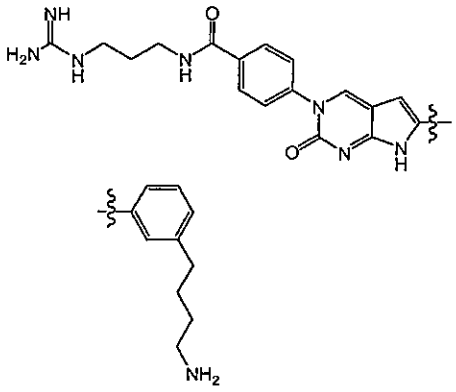
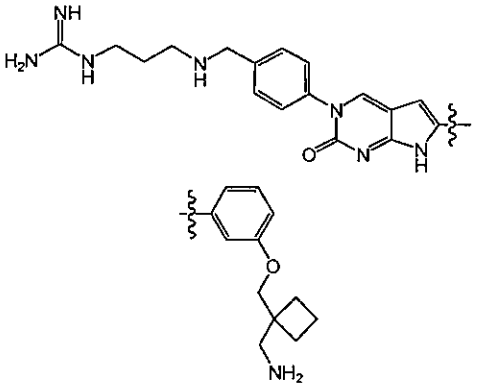
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1400		519.7
1404		525.00

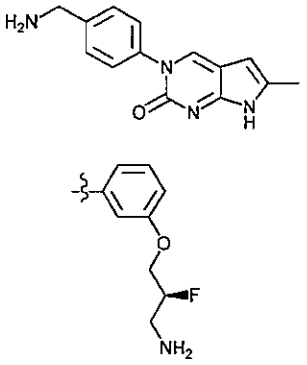
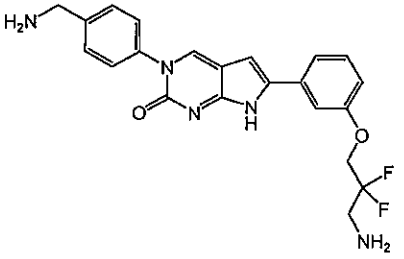
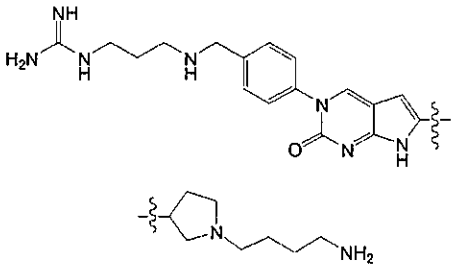
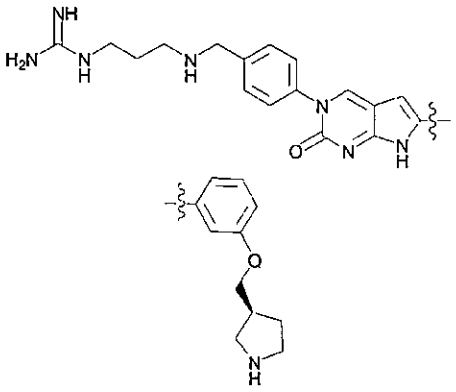
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1406		508.3
1408		452.00

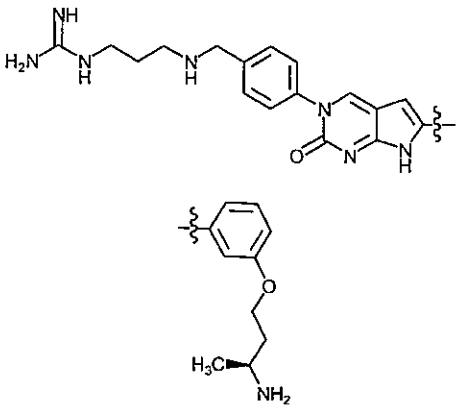
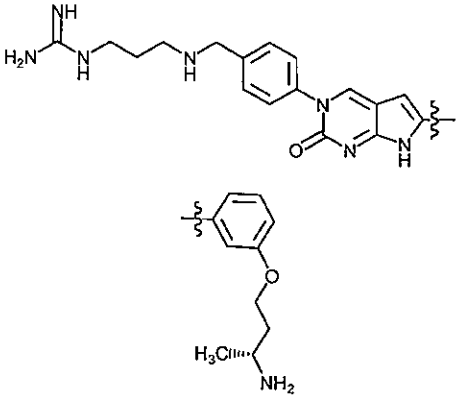
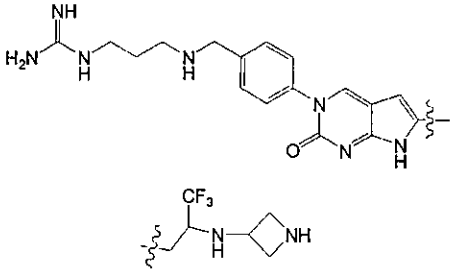
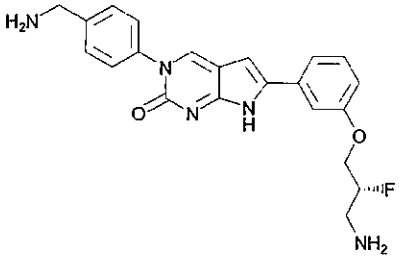
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1411		498.4
1412		514.8
1413		514.4

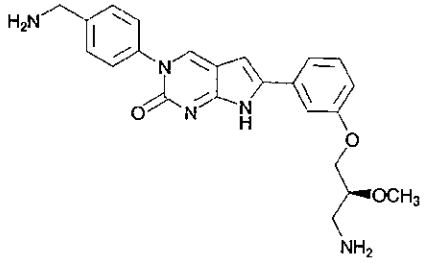
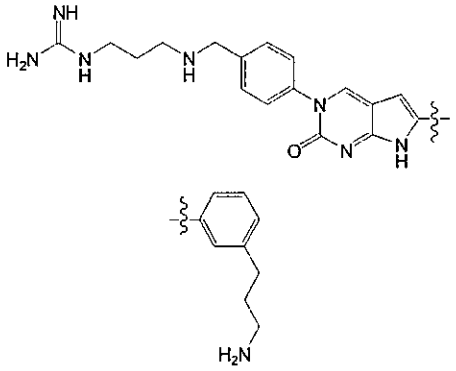
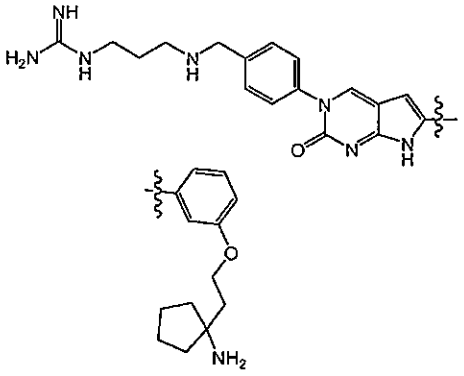
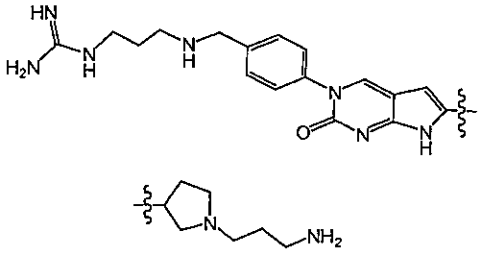
1414		503.2
1415		618.1
1416		566.3
1417		608.6

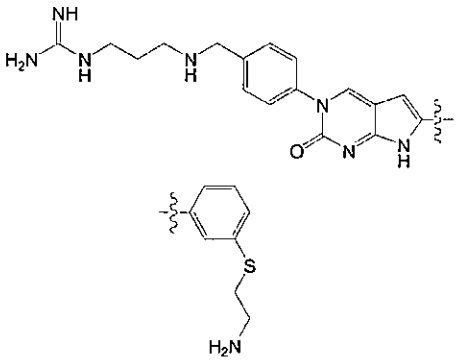
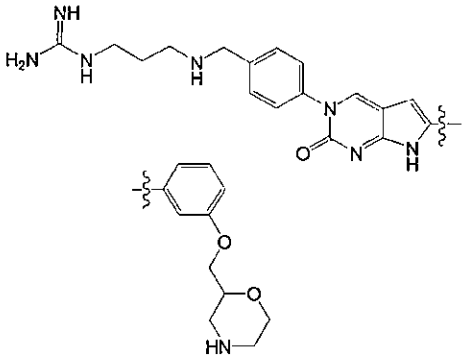
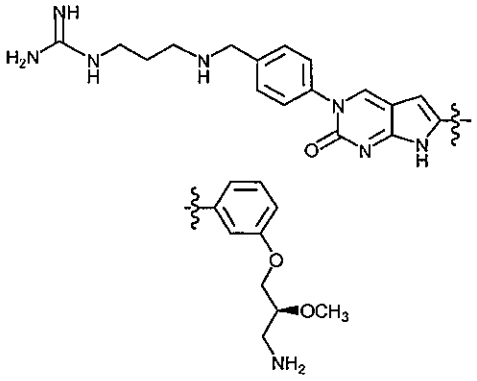
1418		501.00
1422		496.4
1423		515.00
1428		420.00

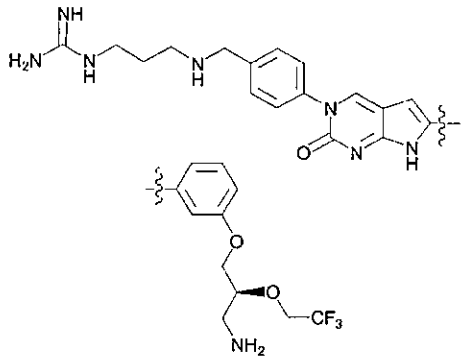
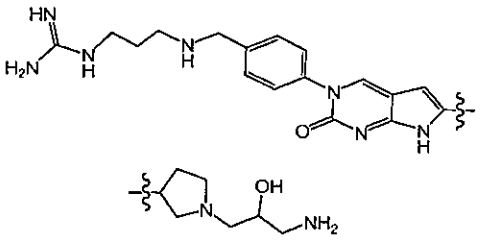
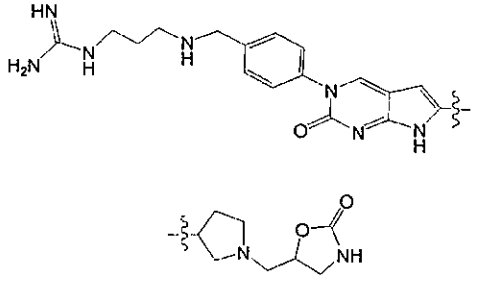
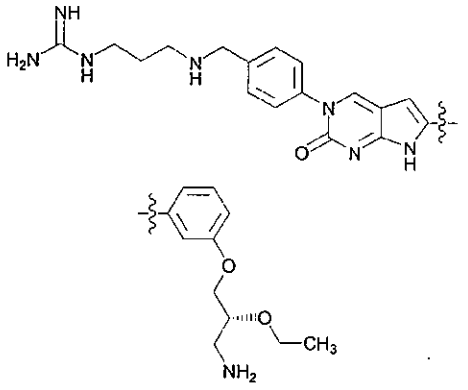
1431		568.2
1432		610.1
1433		501.1
1434		529.0

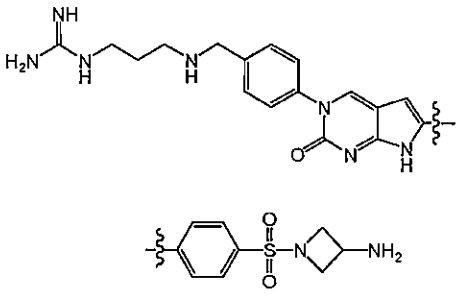
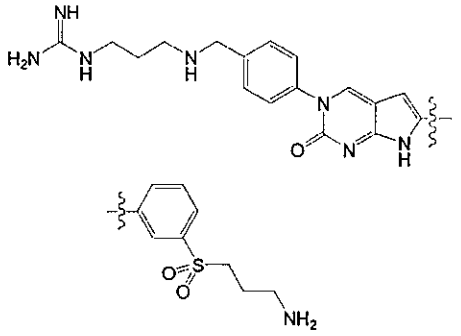
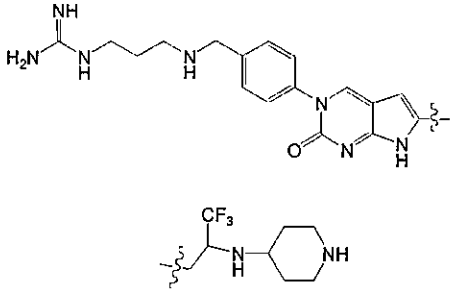
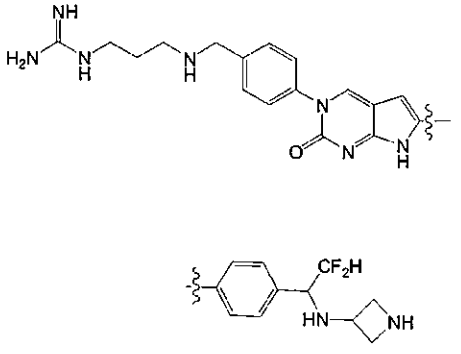
1435		408.00
1436		426.00
1437		480.3
1438		515.3

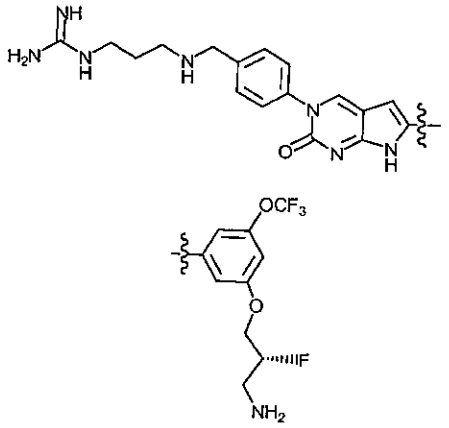
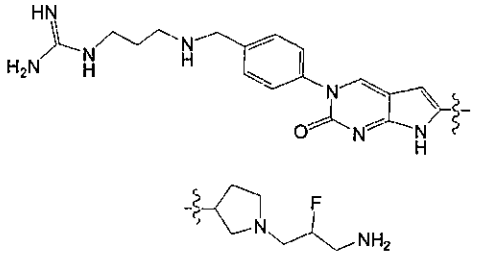
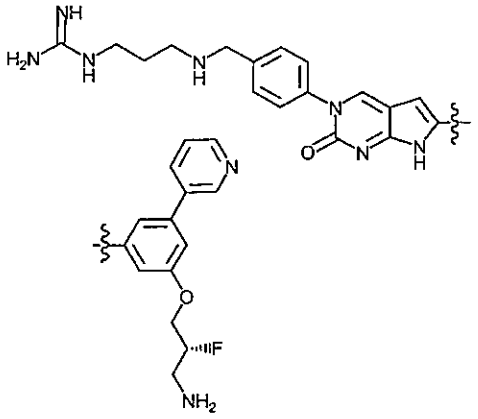
1439		503.2
1440		503.2
1442		505.8
1443		408.00

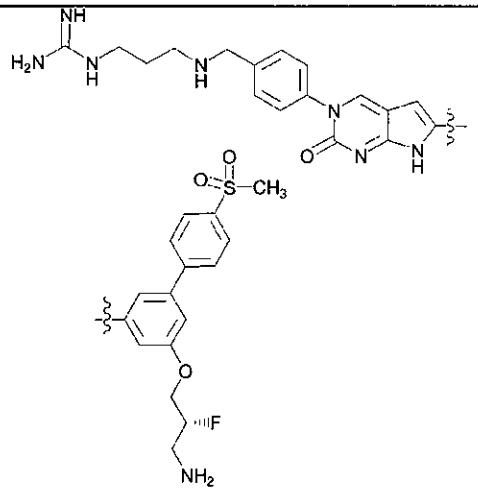
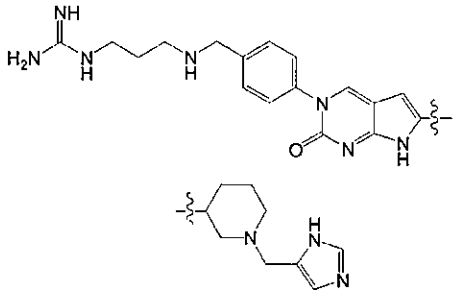
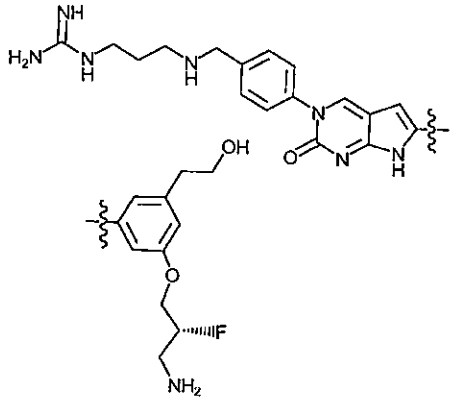
1444		419.5
1446		473.5
1447		543.6
1448		466.2

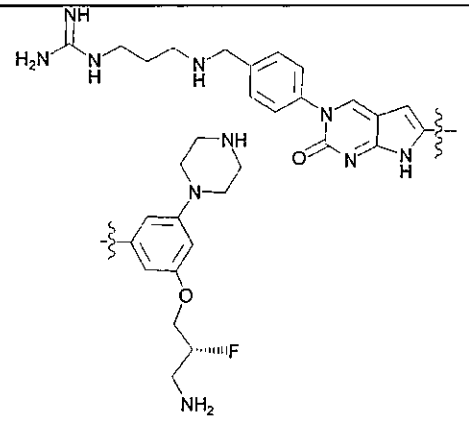
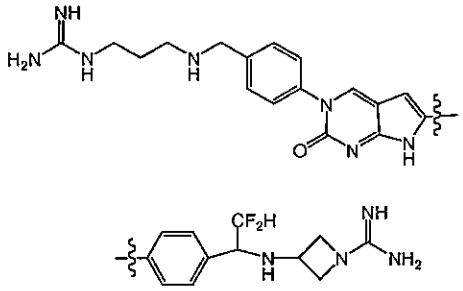
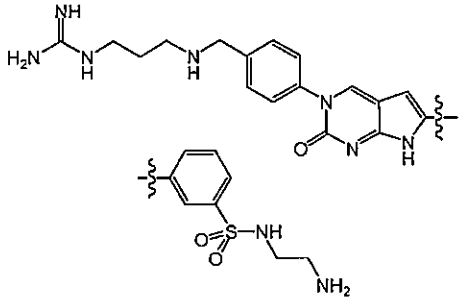
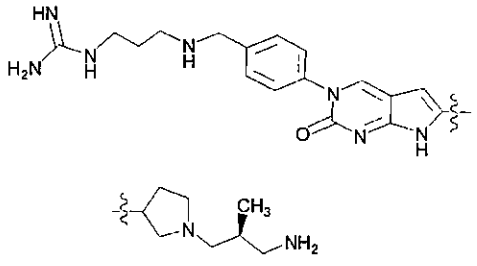
1451		491.5
1452		531.00
1453		518.7

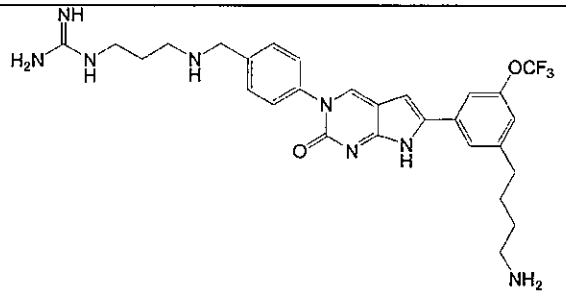
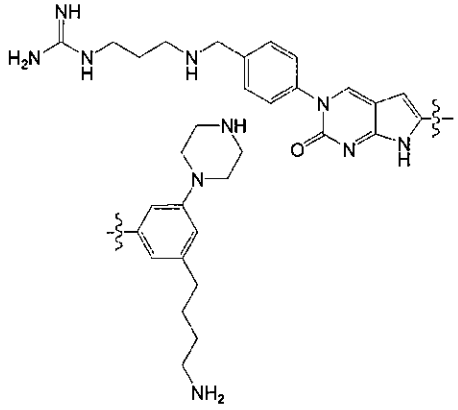
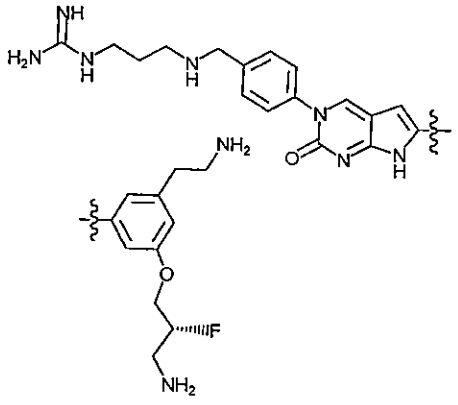
1455		587.00
1456		482.1
1457		508.2
1458		533.7

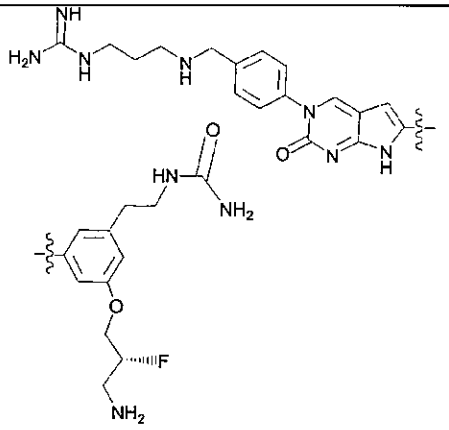
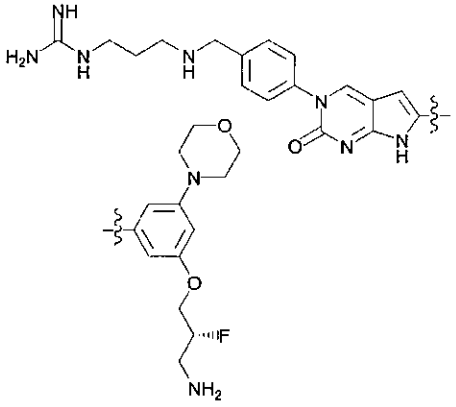
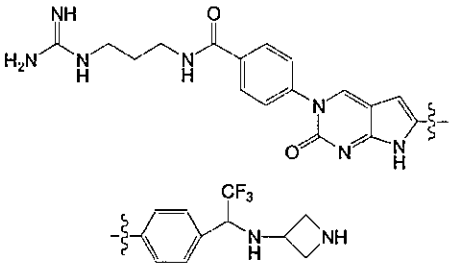
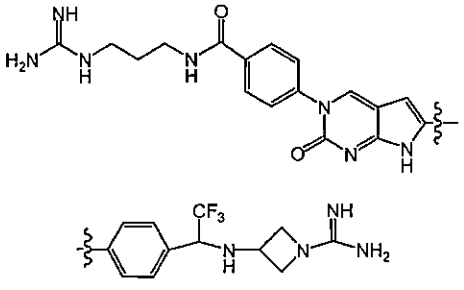
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1460		537.1
1461		534.7
1462		550.7

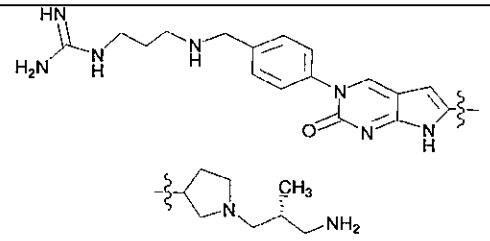
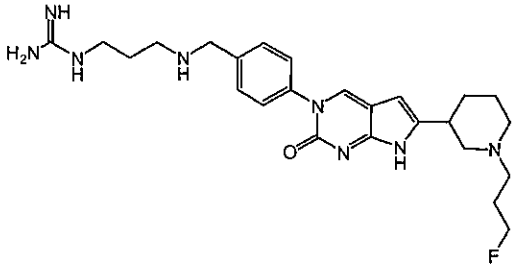
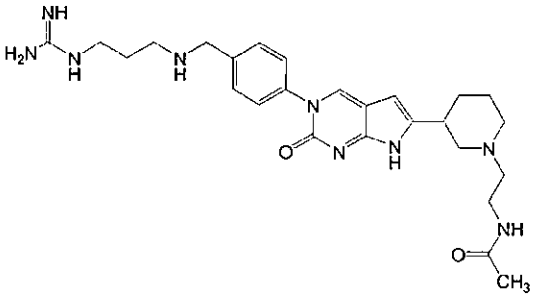
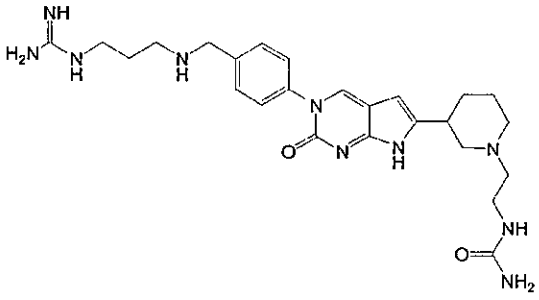
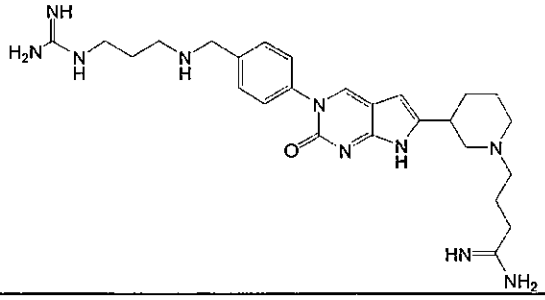
1463		591.00
2000a		485.10
2001a		584.40
2002a		661.30

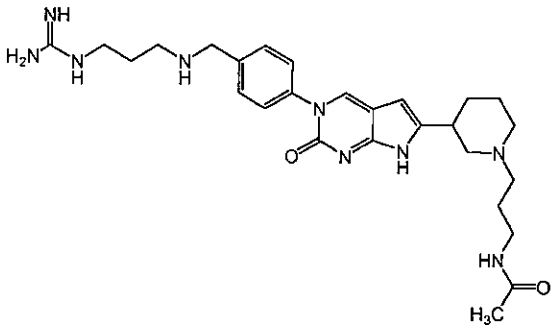
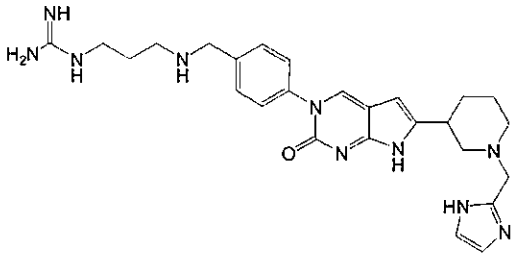
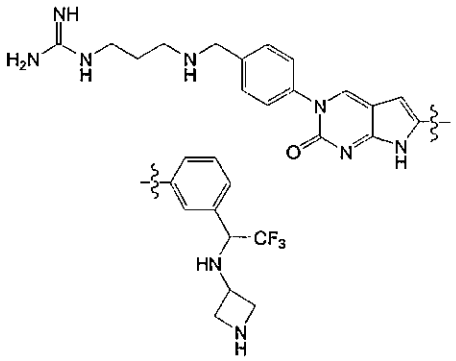
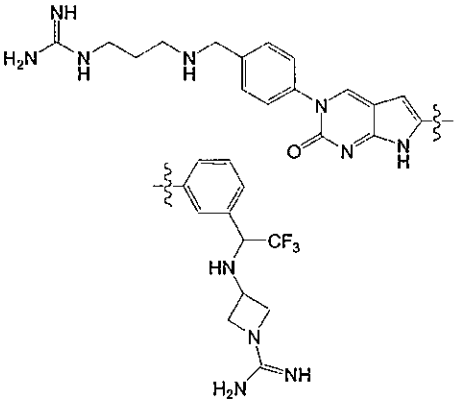
		
2003a		503.0
2004a		551.00
2005a		591.60

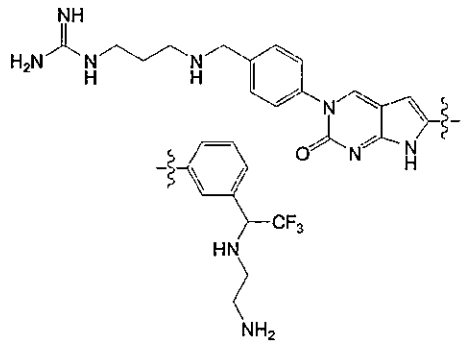
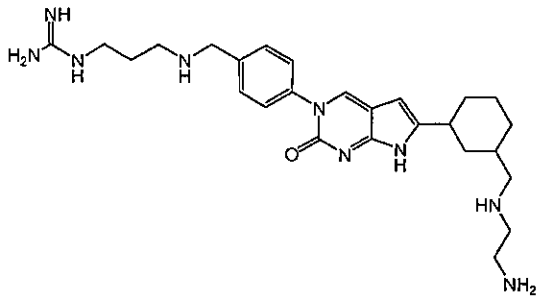
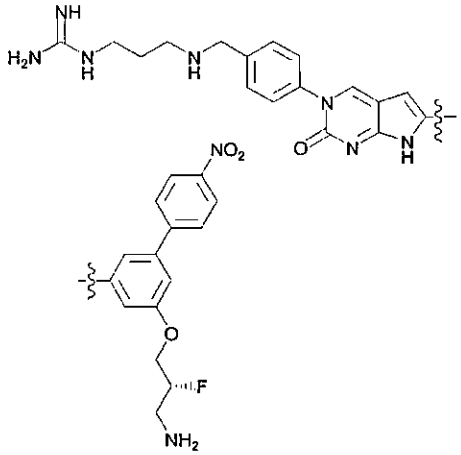
		
2006a		592.60
2007a		538.1
2008a		480.20
2009a		571.12

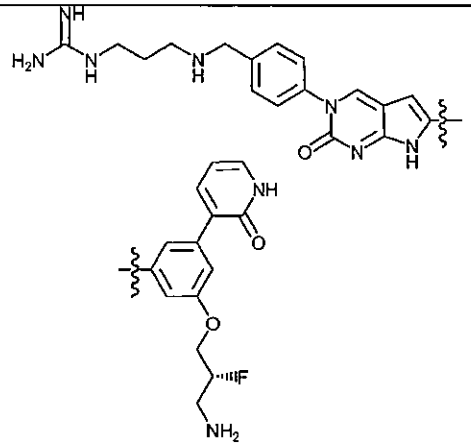
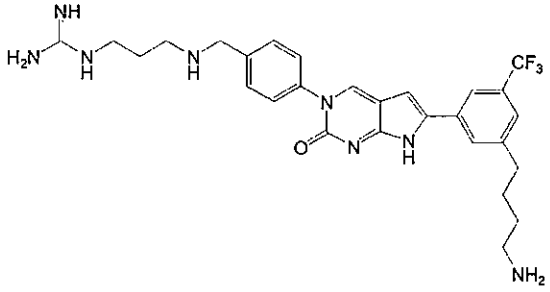
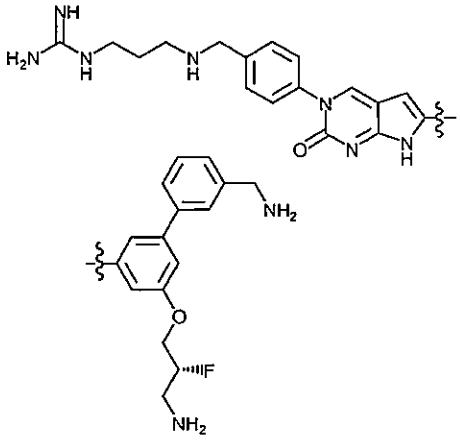
		
2010a		571.40
2011a		550.00
2012a		593.00

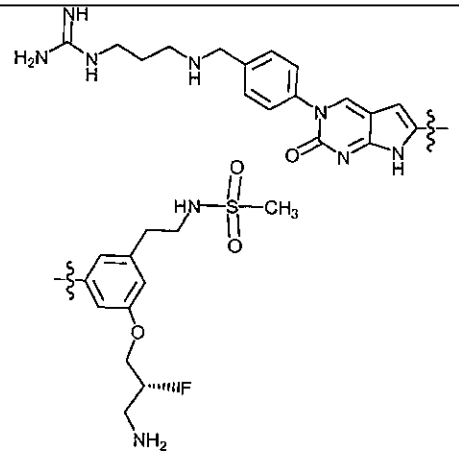
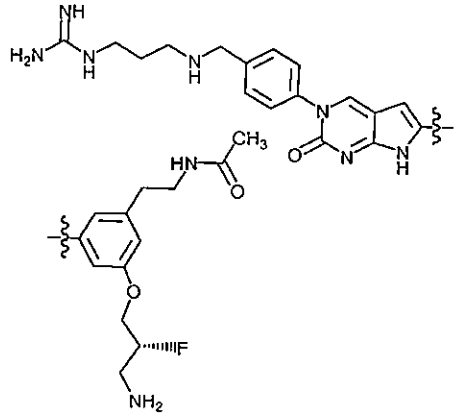
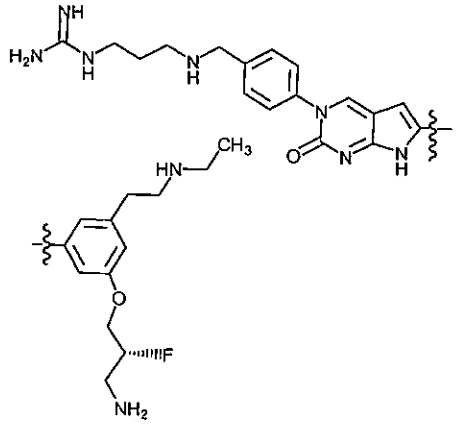
		
2013a		592.30
2014a		582.80
2015a		624.30
2016a		480.30

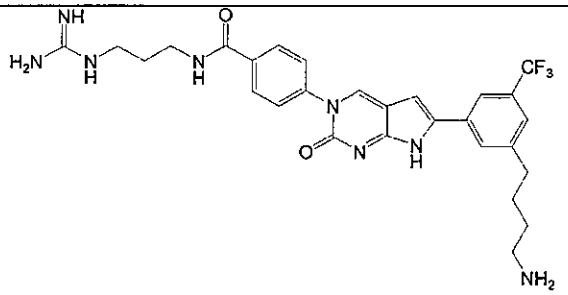
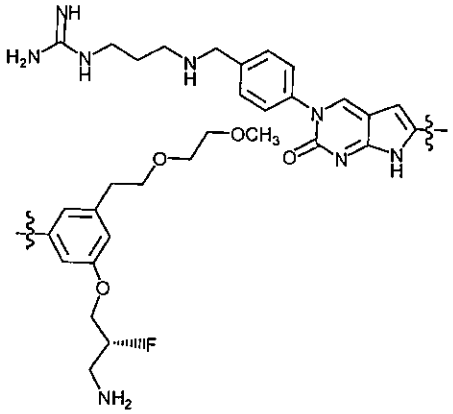
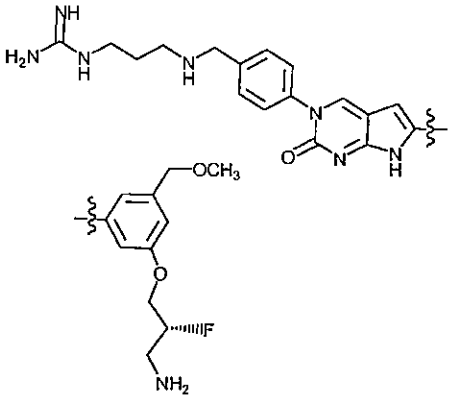
		
2017a		482.9
2018a		508.3
2019a		509.0
2020a		507.4

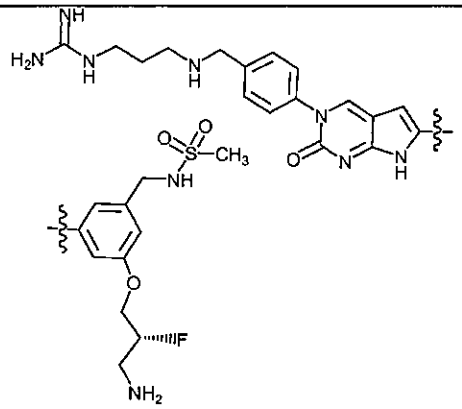
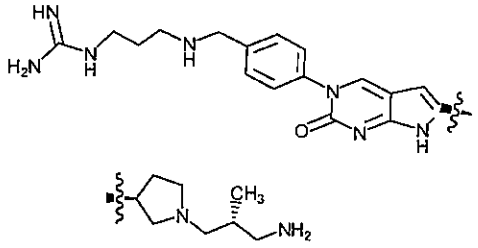
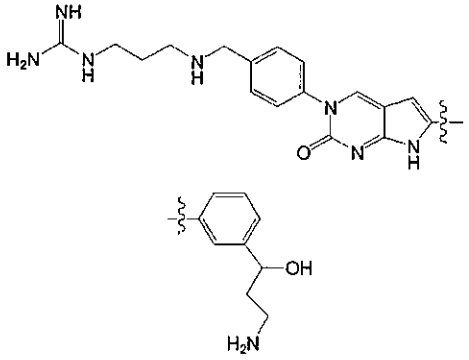
2021a		522.1
2022a		502.9
2023a		600.40 [M+ Na 23]
2024a		610.10

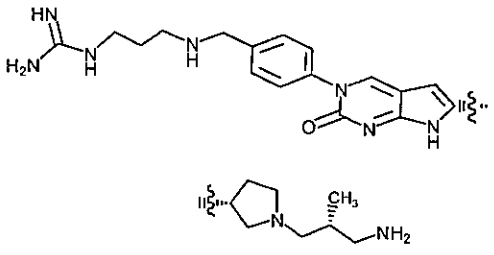
2025a		556.10
2026a		495.20
2027a		628.30
2028a		600.30

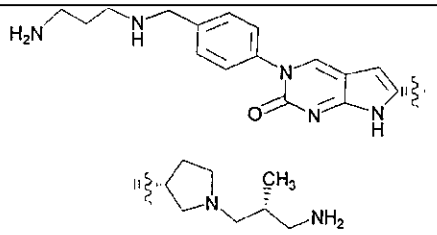
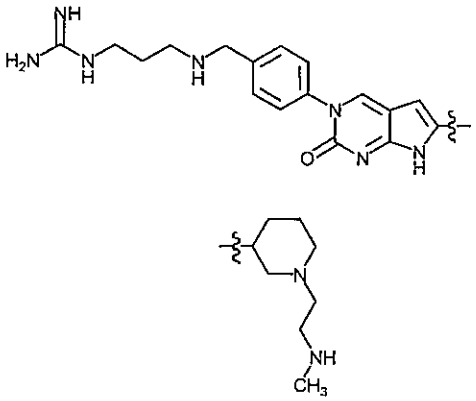
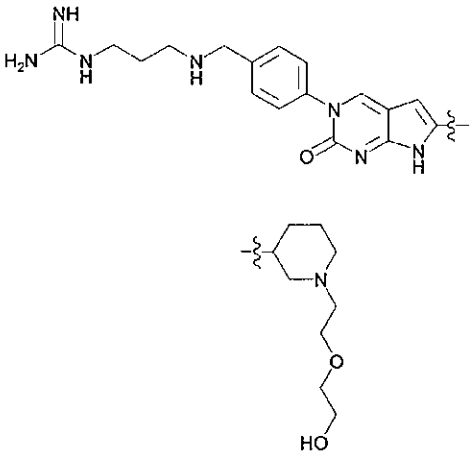
		
2029a		555.30
2030a		612.30
2031a		628.00

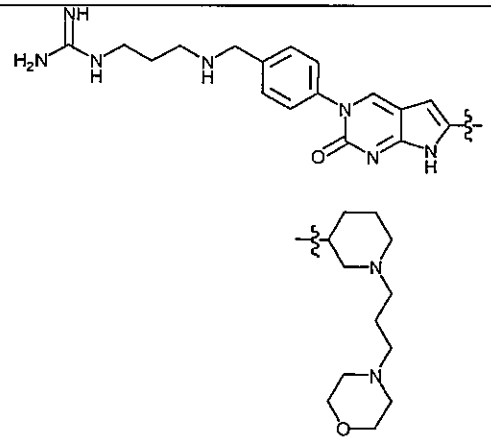
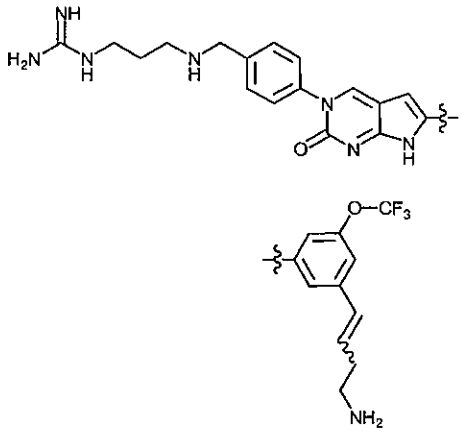
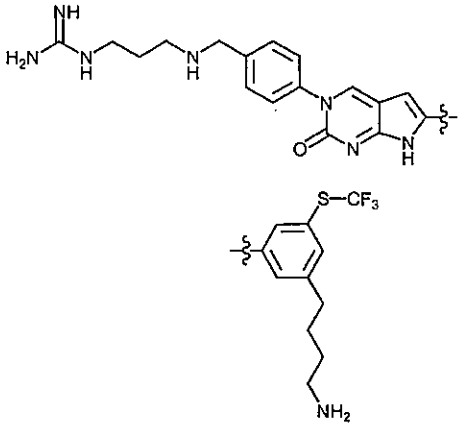
		
2032a		592.50
2033a		578.00
2034a		569.10

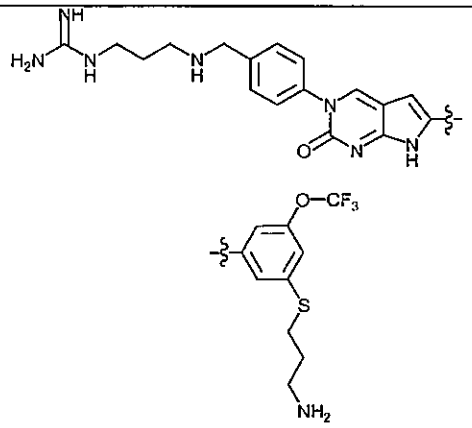
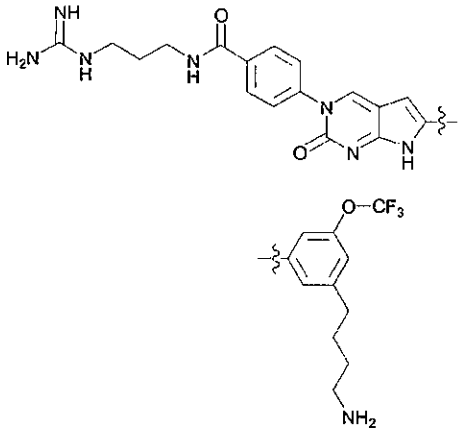
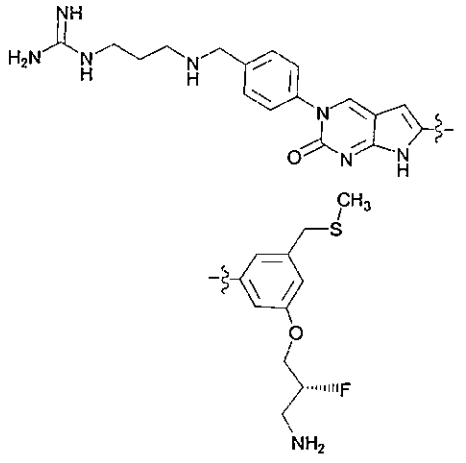
		
2035a		609.50
2036a		551.4
2037a		614.3

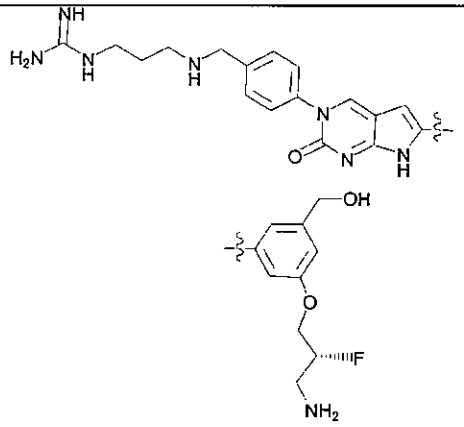
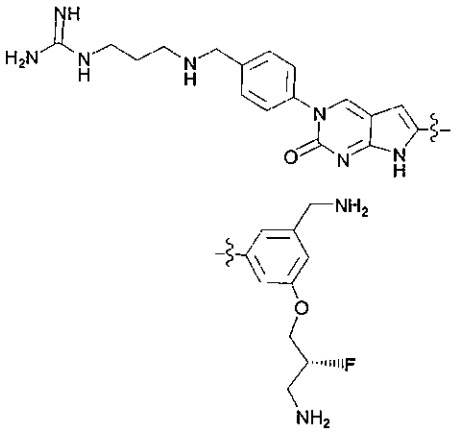
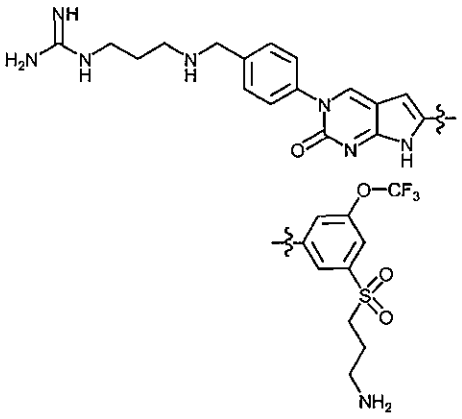
		
2038a		480.30
2039a		498.80

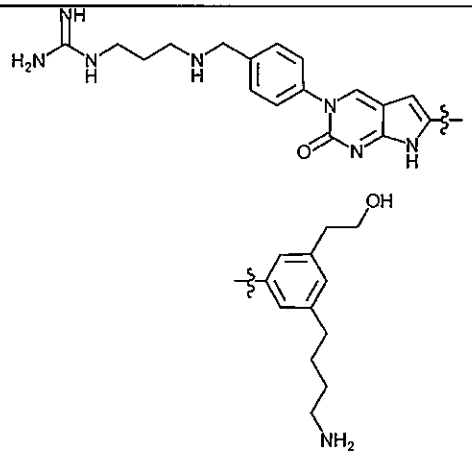
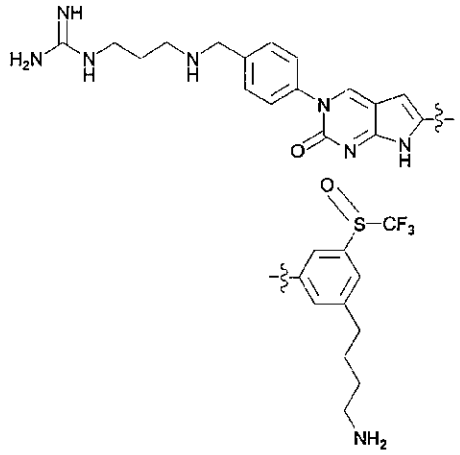
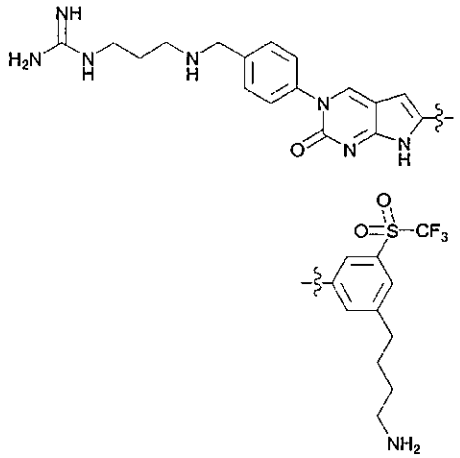
2040a		480.2
2041a		437.3

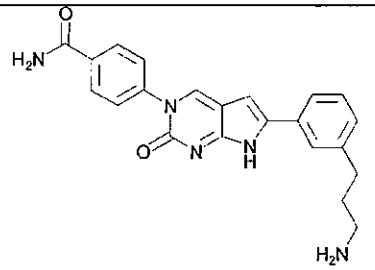
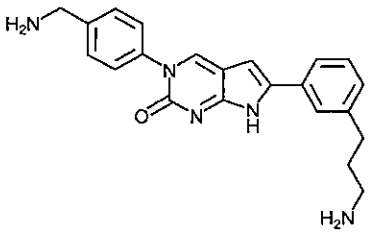
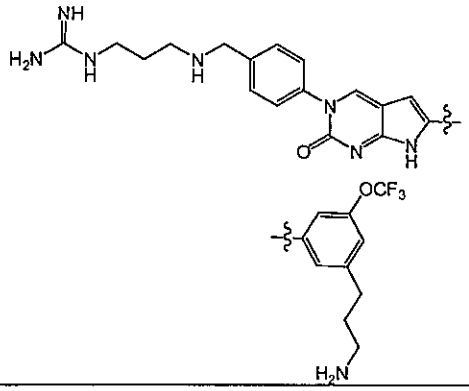
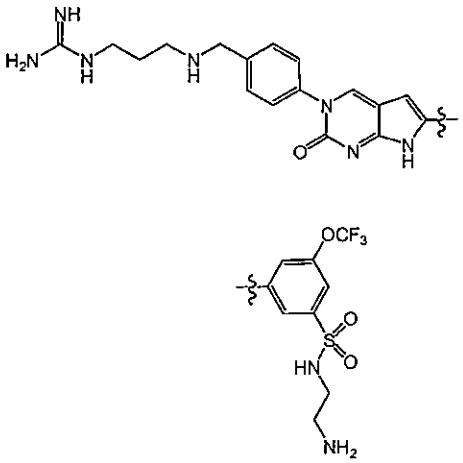
		
2042a		480.0
2043a		511.0
2044a		550.0

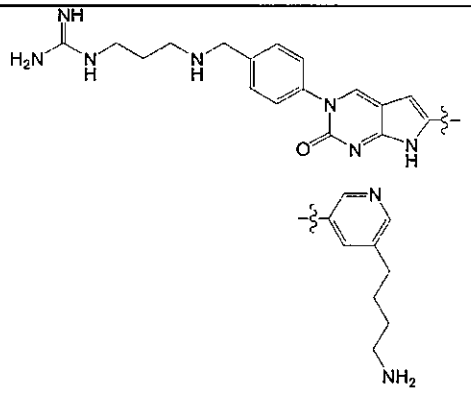
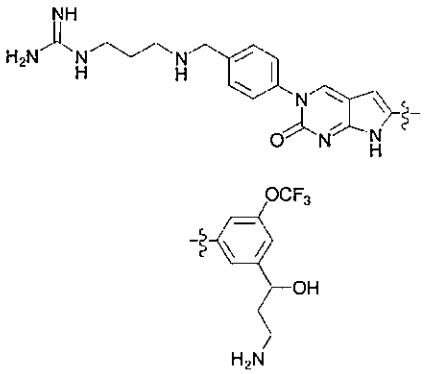
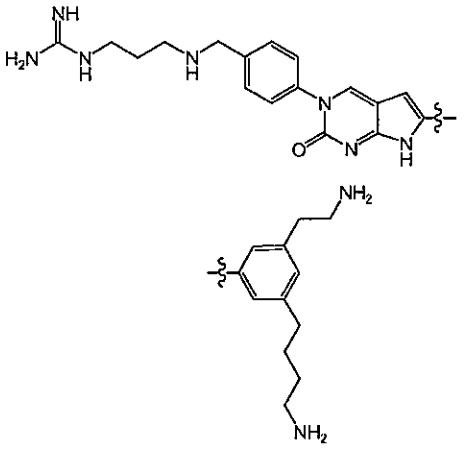
		
2045a		569.5
2046a		587.0
2047a		589.4

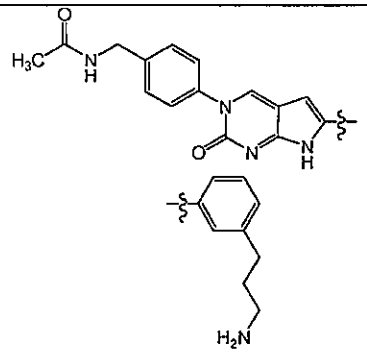
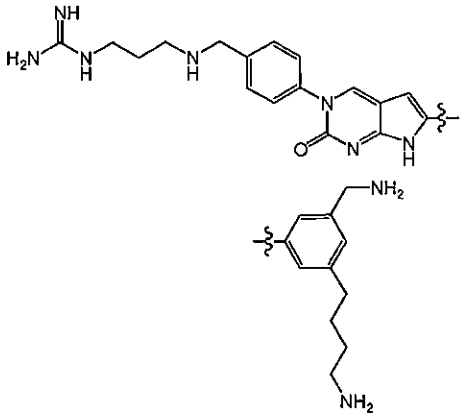
		
2048a		585.6
2049a		568.2
2050a		537.6

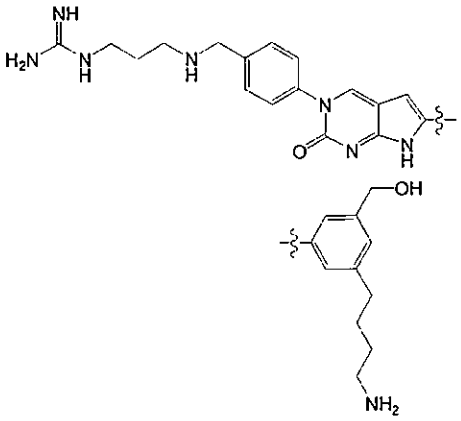
		
2051a		535.7
2052a		621.3
2053a		531.0

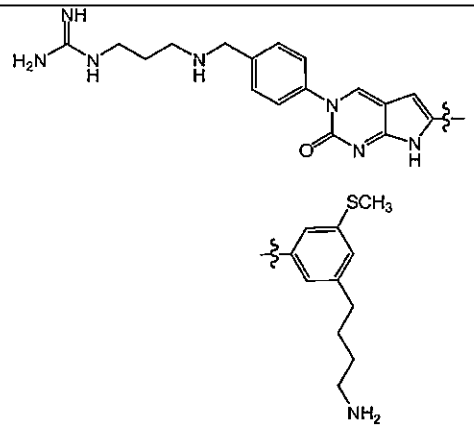
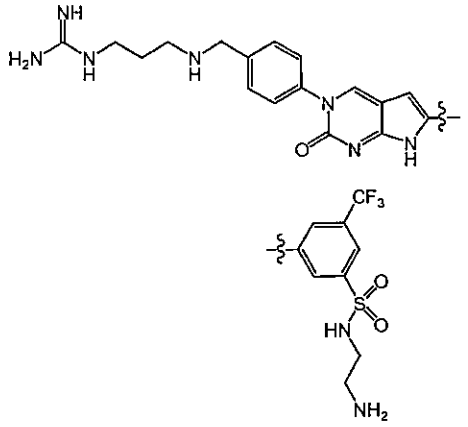
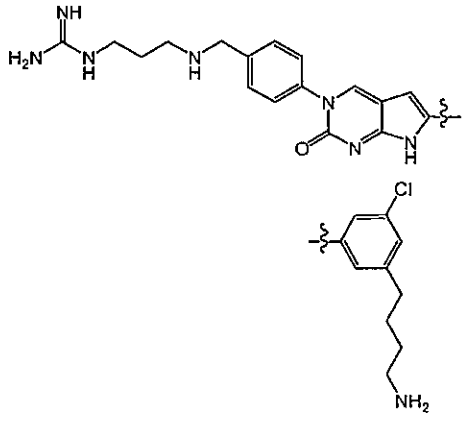
		
2054a		603.0
2055a		619.0
2056a		388.6

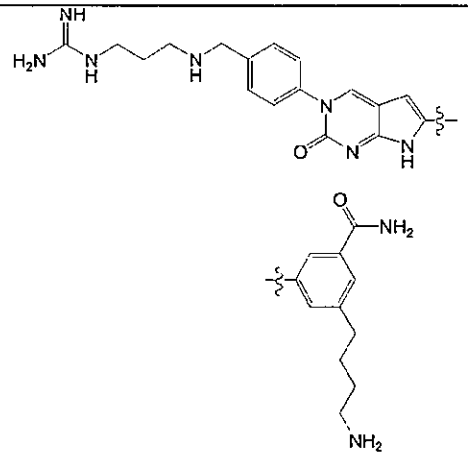
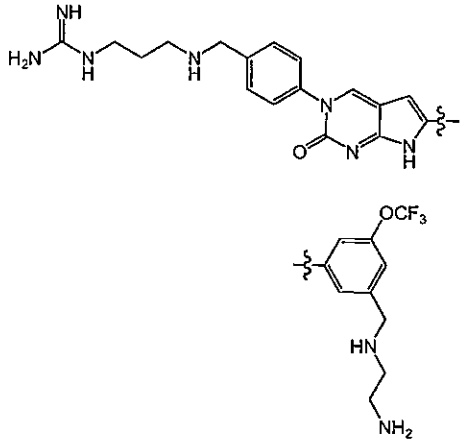
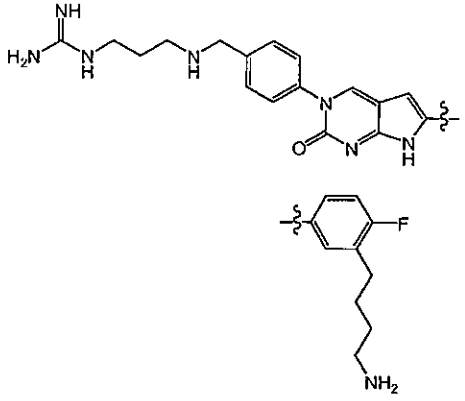
		
2057a		374.6
2058a		557.1
2059a		622.1
2060a		488.3

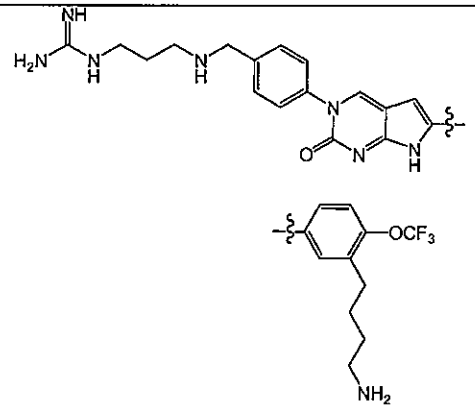
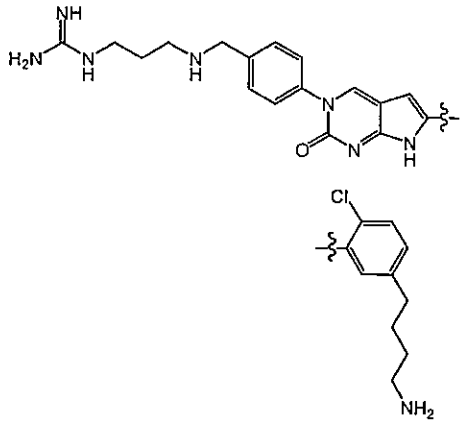
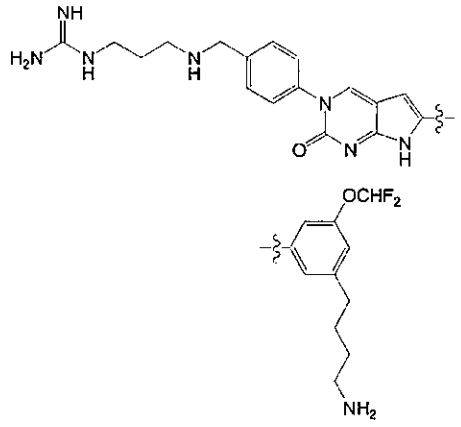
		
2061a		573.3
2062a		530.2
2063a		416.3

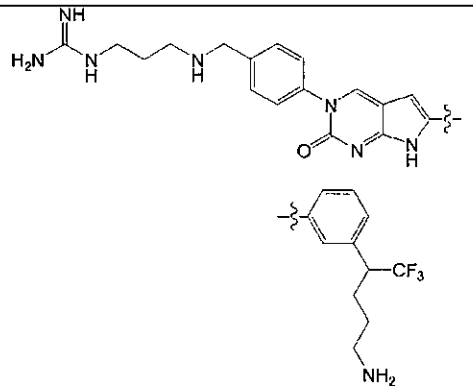
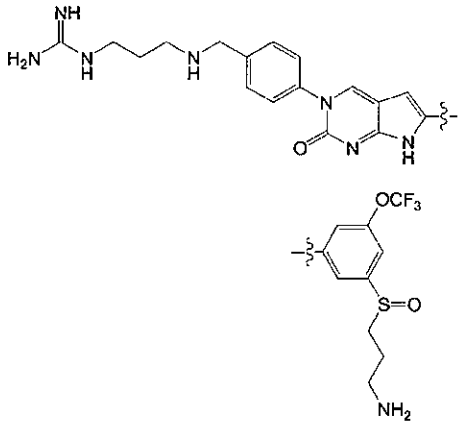
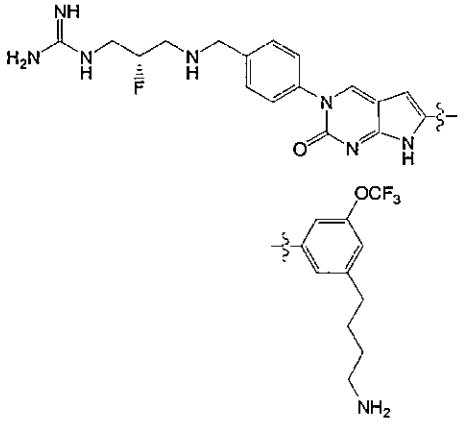
		
2064a		516.3

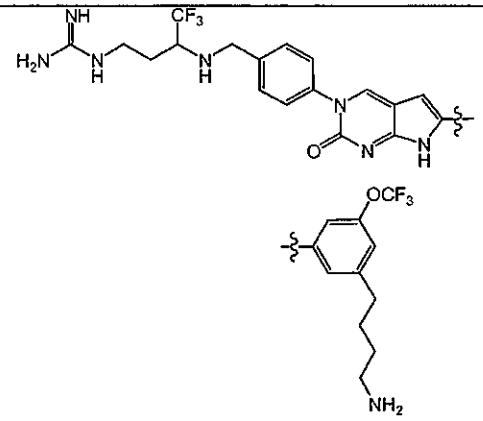
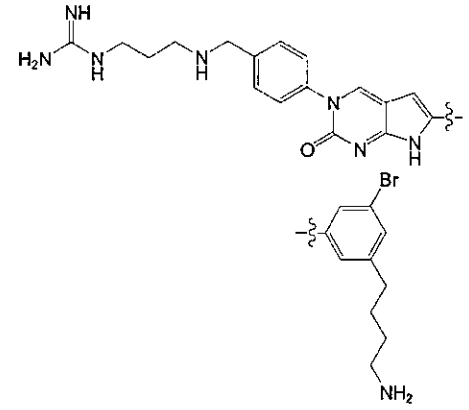
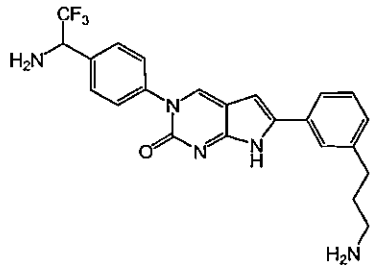
2065a		517.3
2066a		533.2

		
2067a		606.3
2068a		521.3
2069a		530.0

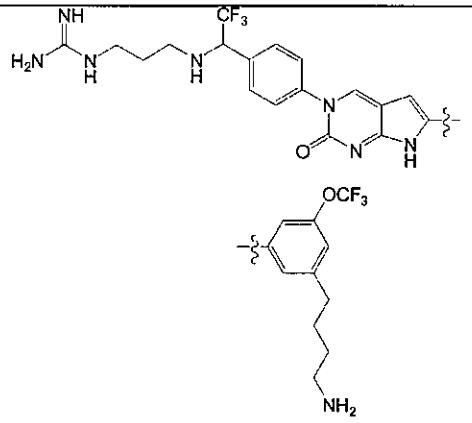
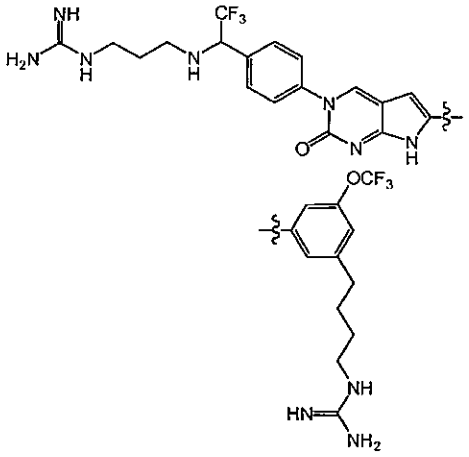
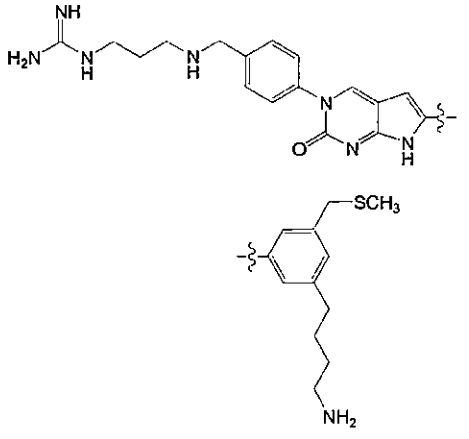
		
2070a		572.3
2071a		505.3
2072a		571.3

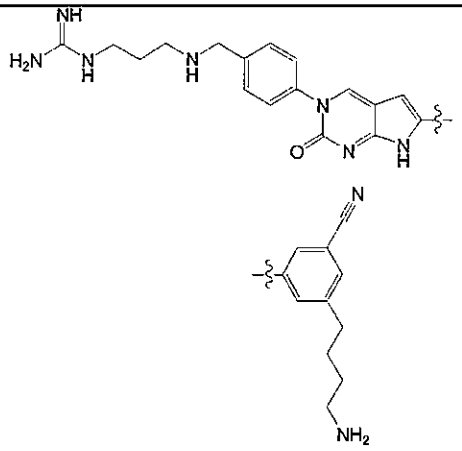
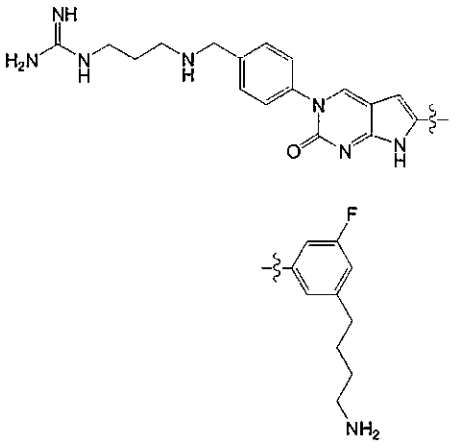
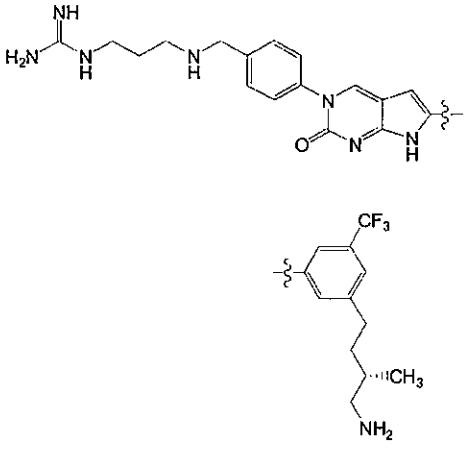
		
2073a		521.3
2074a		553.3
2075a		555.1

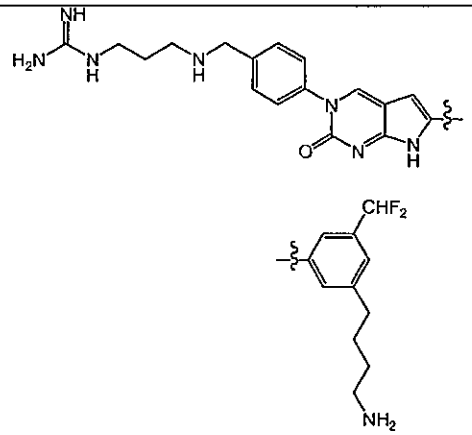
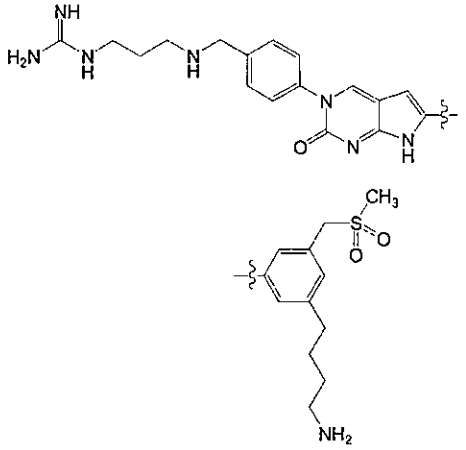
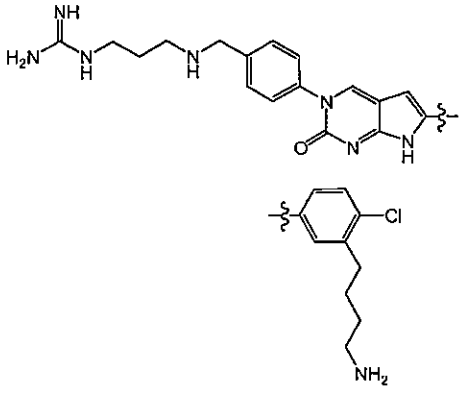
		
2076a		605.1
2077a		589.1
2078a		639.1

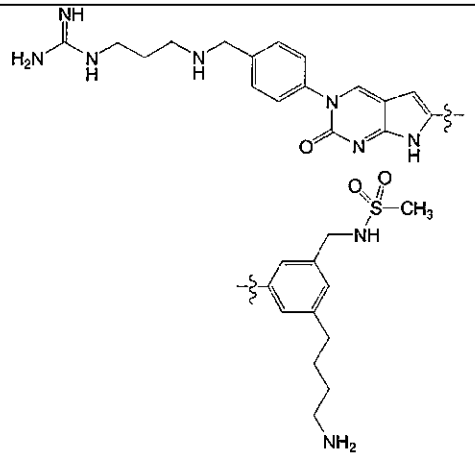
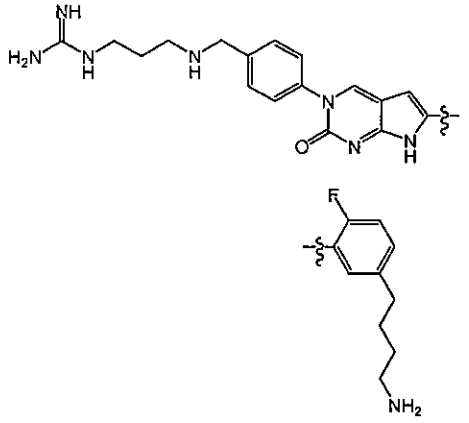
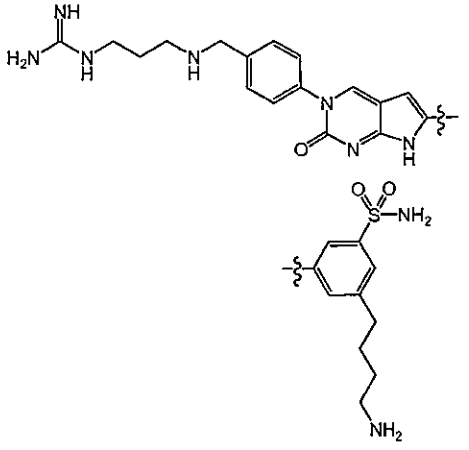
		
2079a		567.0
2080a		442.1

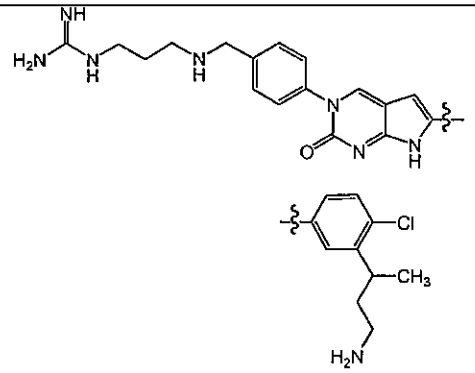
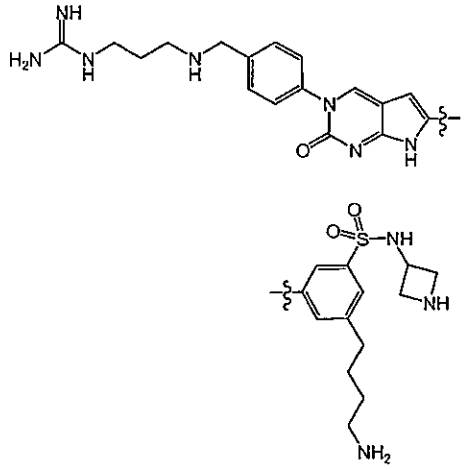
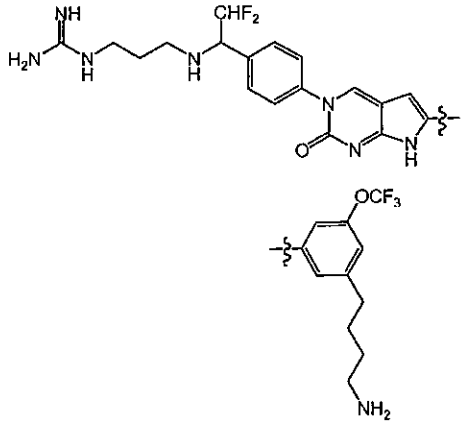
2081a		639.2

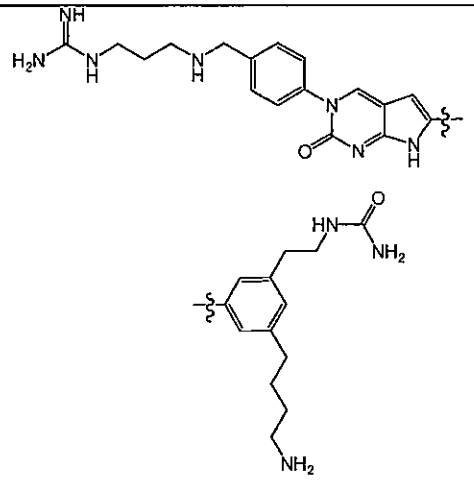
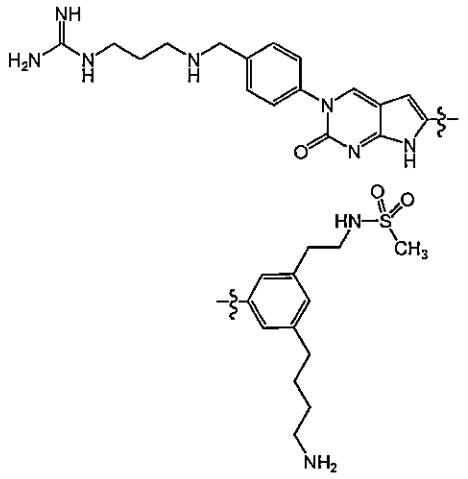
		
2082a		681.1
2083a		547.1
2084a		512.1

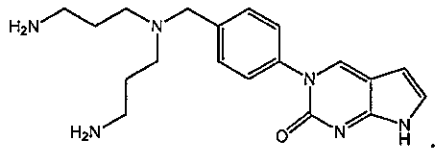
		
2085a		505.1
2086a		569.1
2087a		537.1

		
2088a		579.1
2089a		521.2
2090a		594.2

		
2091a		505.2
2092a		566.1
2093a		521.1

		
2094a		621.1
2095a		621.2
2096a		574.1

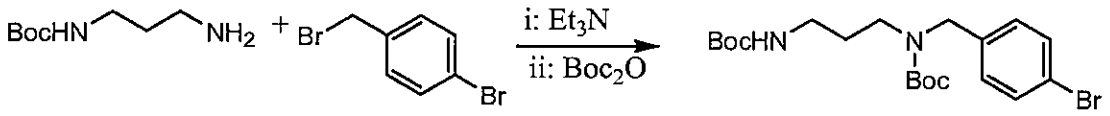
		
2097a		608.2

In further embodiments, the compounds of the present invention do not encompass a compound having the structure: .

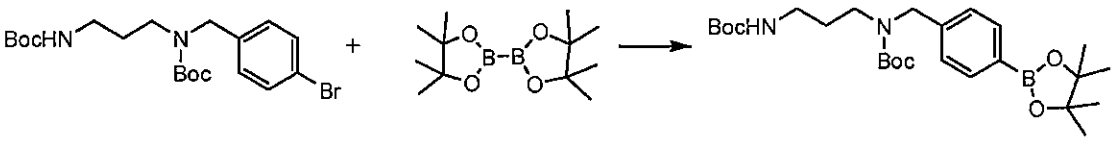
The compounds of the present invention can be made using synthetic chemical techniques well known to those of skill in the art.

EXAMPLES

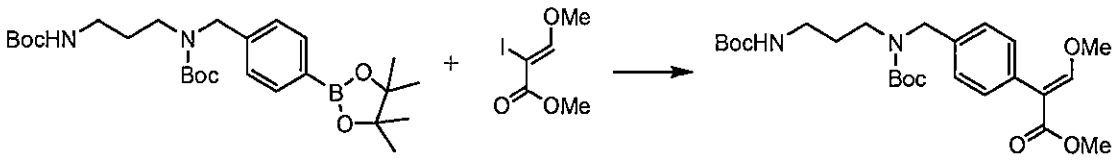
Example 1 – Synthesis of Compound 682



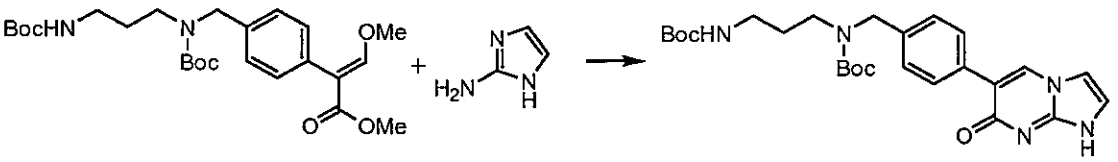
{3–[(4–Bromo–benzyl)–*tert*–butoxycarbonyl–amino]–propyl}–carbamic acid *tert*–butyl ester: A solution of 1–bromo–4–bromomethyl–benzene (17.79 g, 71.17 mmol) in toluene (50 mL) was dropwise added to a mixture of 3–Amino–propyl)–carbamic acid tert–butyl ester (16.1 g, 92.51 mmol), triethylamine (29.6 ml, 213.5 mmol) in toluene (200 mL) over 30 min. at 80 °C. The resulted mixture was heated at 80 °C for additional 2 h before cooled to 0 °C. Di–*tert*–butyl pyrocarbonate (23.5 g, 107.80 mmol) was added at 0 °C. After 2 h, the mixture was warmed to rt and stirred overnight, diluted with EtOAc (500 mL) and washed with water (300 mL), brine (300 mL). The organic solution was concentrated and purified by flash chromatography (10% – 25% EtOAc in heptane) to give desired product (16.15 g, 51%) as colorless oil. ^{1}NMR (300 MHz, $CDCl_3$): δ 7.44 (d, J = 8.4 Hz, 2H), 7.01 (br, 2H), 5.16 (br.s, 0.5H),4.62 (br.s, 0.5H), 4.34 (br, 2H), 3.40 (m, 2H), 3.10 (m, 2H), 1.65 (m, 2H), 1.43 (br.s, 18H).



(3–*tert*–Butoxycarbonylamino–propyl)–[4–(4,4,5,5–tetramethyl–[1,3,2]dioxaborolan–2–yl)–benzyl]–carbamic acid *tert*–butyl ester: A mixture of {3–[(4–Bromo–benzyl)–*tert*–butoxycarbonyl–amino]–propyl}–carbamic acid *tert*–butyl ester (16.15 g, 36.46 mmol), bispinacolate boronate (10.20, 40.11 mmol), KOAc (10.72 g, 109.38 mmol), $Pd(PPh_3)_4$ (0) (2.03 g, 1.82 mmol) and DMF (80 mL) was heated at 80 °C for 16 h under argon atmosphere. The reaction mixture was diluted with EtOAc (500 mL), washed with water (300 mL) and brine (300 mL). The organic solution was concentrated and purified by flash chromatography (10% – 30% EtOAc in heptane) to give desired product (14.15 g, 80%) as colorless oil. ^{1}NMR (300 MHz, $CDCl_3$): δ 7.76 (d, J = 8.1 Hz, 2H), 7.01 (br.s, 2H), 5.16 (br.s, 0.5H),4.62 (br.s, 0.5H), 4.40 (br, 2H), 3.28 (m, 2H), 3.08 (m, 2H), 1.50 (m, 2H), 1.43 (br.s, 18H), 1.34 (s, 12H).

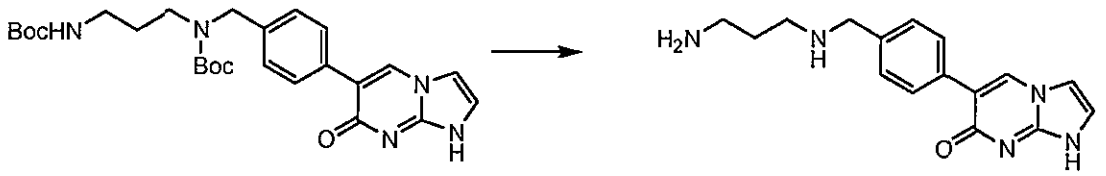


2–(4–{[*tert*–Butoxycarbonyl–(3–*tert*–butoxycarbonylamino–propyl)–amino]–methyl}–phenyl)–3–methoxy–acrylic acid methyl ester: A mixture of (3–*tert*–butoxycarbonylamino–propyl)–[4–(4,4,5,5–tetramethyl–[1,3,2]dioxaborolan–2–yl)–benzyl]–carbamic acid *tert*–butyl ester (6.00g, 12.25 mmol), 2–iodo–3–methoxy–acrylic acid methyl ester (4.45 g, 18.38 mmol), K_3PO_4 (7.79 g, 36.75 mmol), $Pd(PPh_3)_4$ (0) (0.68 g, 0.61 mmol), dioxane (60 mL) and water (12 mL) was degassed and heated at 80 °C for 20 h under argon atmosphere. The reaction mixture was diluted with EtOAc (500 mL), washed with water (300 mL) and brine (300 mL). The organic solution was concentrated and purified by flash chromatography (0% – 30% EtOAc in heptane) to give desired product (5.35 g, 91%) as brown oil. ^{1}NMR (300 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.20 (br.d, 2H), 5.20 (br.s, 0.5H), 4.62 (br.s, 0.5H), 4.39 (br, 2H), 3.86 (s, 3H), 3.74 (s, 3H), 3.27 (m, 2H), 3.08 (m, 2H), 1.62 (m, 2H), 1.50 (br.d, 9H), 1. 43 (s, 9H). LCMS (EI) m/z: 501 ($M+Na^+$).

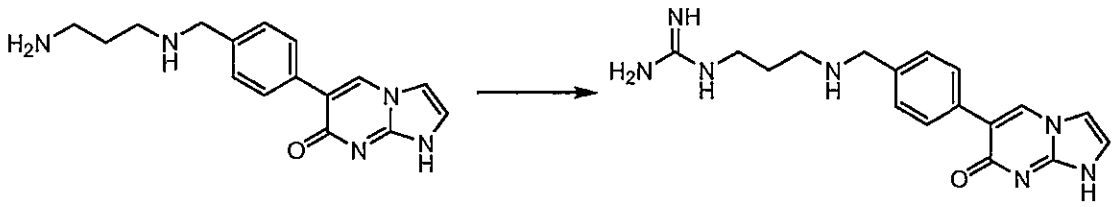


(3–{tert–Butoxycarbonyl–[4–(7–oxo–1,7–dihydro–imidazo[1,2–a]pyrimidin–6–yl)–benzyl]–amino}–propyl)–carbamic acid tert–butyl ester: To a mixture of 2–(4–{[tert–Butoxycarbonyl–(3–tert–butoxycarbonylamino–propyl)–amino]–methyl}–phenyl)–3–methoxy–acrylic acid methyl ester (97 mg, 0.2 mmol), 1*H*–imidazol–2–ylamine sulfate (29 mg, 0.223 mmol) and ethanol (10 mL) was added a solution of sodium methoxide (0.5 mL, 0.5 M in methanol, 0.25 mmol). The resulted mixture was refluxed for 18h, additional 0.5 mL of sodium methoxide (0.5 M in methanol, 0.5 mmol) was added and continued to reflex for 20h. The reaction was concentrated and diluted with EtOAc (30 mL) and washed with water (20 mL), brine (20 mL). The EtOAc solution was concentrated. The crude product was purified by flash chromatography (10% methanol in dichloromethane) to give desired

product (48 mg, 48%) as white solid. ^{1}NMR (300 MHz, CD_3OD): δ 8.40 (s, 1H), 7.59 (br.s, 2H), 7.29 (m, 4H), 4.46 (s, 2H), 3.23 (m, 2H), 3.02 (m, 2H), 1.68 (m, 2H), 1.52 (br.d, 9H), 1. 42 (s, 9H). LCMS (EI) m/z: 498.1 ($M+H^+$).

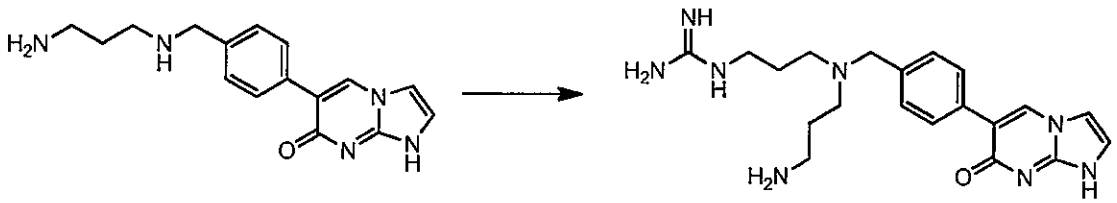


6–{4–[(3–Amino–propylamino)–methyl]–phenyl}–1H–imidazo[1,2–a]pyrimidin–7–one hydrochloride salt (hydrochloride salt of compound 563): {(3–{tert–Butoxycarbonyl–[4–(7–oxo–1,7–dihydro–imidazo[1,2–a]pyrimidin–6–yl)–benzyl]–amino}–propyl)–carbamic acid tert–butyl ester (48 mg, 0.097 mmol) was dissolved in CH_2Cl_2 (5 mL), TFA (1 mL) was added and stirred at room temperature for 2h. The reaction mixture was concentrated and 3 mL of 0.6 N HCl and 2 mL of acetonitrile were added and stirred for 0.5 h, concentrated to a *ca.* 3 mL and lyophilized to give the title compound (35 mg, 100%). . ^{1}NMR (300 MHz, CD_3OD): δ 8.90 (s, 1H), 7.79 (s, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.67 (s, 1H), 4.33 (s, 2H), 3.23 (t, J = 8.1 Hz, 2H), 3.06 (t, J = 7.5 Hz, 2H), 2.15 (m, 2H). LCMS (EI) m/z: 297.1 ($M+H^+$).



N–{3–[4–(7–Oxo–1,7–dihydro–imidazo[1,2–a]pyrimidin–6–yl)–benzylamino]–propyl}–guanidine hydrochloride salt (hydrochloride salt of compound 564): To a mixture of compound 563 (26 mg, 0.07 mmol), Hunig's base (90 mg, 0.70 mmol) and DMF (10 mL) was added *N,N*–bis–Boc–1–guanylpyrazole (22 mg, 0.07 mmol). The reaction mixture was stirred at room temperature overnight and diluted with water (30 mL), extracted with EtOAc (50 mL x 3). The organic solution was concentrated and purified by PTLC (2N NH_3 in methanol/ CH_2Cl_2, 1:4) to give the guandylated product as white solid (30 mg, 80%) which was dissolved in 3 mL of CH_2Cl_2 and 1 mL of TFA was added. The resulted mixture was stirred overnight and concentrated. 3 mL of 0.6 N HCl and 2 mL of acetonitrile were added

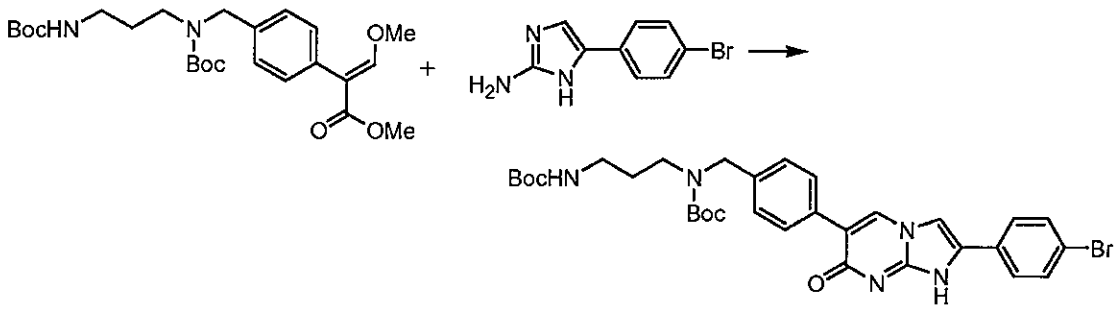
and stirred for 0.5 h, concentrated to a *ca.* 3 mL and lyophilized to give the title compound (20 mg, 100%) . ^{1}NMR (300 MHz, D_2O): δ 8.41 (s, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 2.1 Hz, 1H), 7.35 (d, J = 2.1 Hz, 1H), 4.27 (s, 2H), 3.25 (t, J = 6.9 Hz, 2H), 3.12 (m, 2H), 1.96 (m, 2H). LCMS (EI) m/z: 339.7 ($M+H^+$).



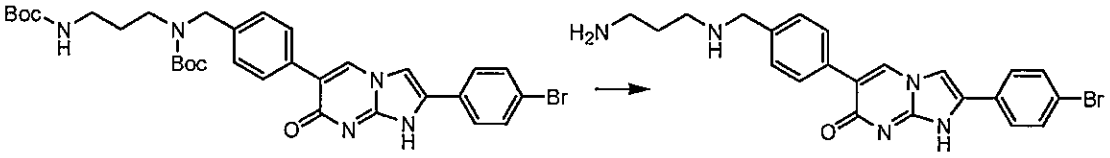
N–(3–{(4–Amino–butyl)–[4–(7–oxo–1,7–dihydro–imidazo[1,2–a]pyrimidin–6–yl)–benzyl]–amino}–propyl)–guanidine hydrochloride salt (hydrochloride salt of compound 616): To a mixture of compound 563 (26 mg, 0.07 mmol), Hunig's base (90 mg, 0.70 mmol) and DMF (10 mL) was added *N,N*–bis–Boc–1–guanylpyrazole (22 mg, 0.07 mmol). The reaction mixture was stirred at room temperature overnight and diluted with water (30 mL), extracted with EtOAc (50 mL x 3). The organic solution was concentrated and purified by PTLC (2N NH_3 in methanol/ CH_2Cl_2, 1:4) to give the guandylated product as white solid (30 mg, 80%).

A mixture of the guandylated compound (27 mg, 0.05 mmol), (3–Oxo–propyl)–carbamic acid tert–butyl ester (9 mg, 0.05 mmol), acetic acid (6 mg, 0.1 mmol) and CH_2Cl_2 (5 mL) was stirred for 30 min at room temperature before sodium cyanoborohydride (13 mg, 0.2 mmol) was added. The resulted mixture was stirred overnight, diluted with CH_2Cl_2 (15 mL), washed with saturated sodium bicarbonate solution. The CH_2Cl_2 solution was concentrated and purified by PTLC (2N NH_3 in methanol/ CH_2Cl_2, 1:9) to give the desired tertiary amine as white solid (13 mg, 37%).

The tertiary amine product (13 mg, 0.0187 mmol) was dissolved in 3 mL of CH_2Cl_2 and 1 mL of TFA was added. The resulted mixture was stirred overnight and concentrated. 3 mL of 0.6 N HCl and 2 mL of acetonitrile were added and stirred for 0.5 h, concentrated to a *ca.* 3 mL and lyophilized to give the title compound (9.4 mg, 100%) . ^{1}NMR (300 MHz, CD_3OD): δ 8.99 (s, 1H), 7.86 (d, J = 2.1 Hz, 1H), 7.81 (br.s, 4H), 7.74 (d, J = 2.1 Hz, 1H), 4.55 (s, 2H), 3.36(m, 6H), 3.05 (m, 2H), 2.22(m, 2H), 2.09 (m, 2H). LCMS (EI) m/z: 396.9 ($M+H^+$).

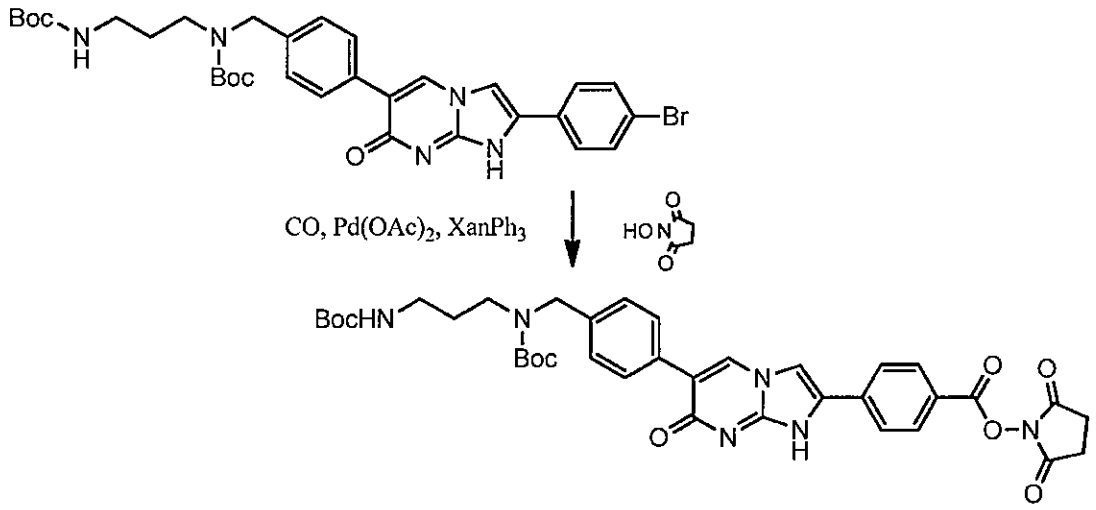


{4–[2–(4–Bromo–phenyl)–7–oxo–1,7–dihydro–imidazo[1,2–a]pyrimidin–6–yl]–benzyl}–(3–tert–butoxycarbonylamino–propyl)–carbamic acid tert–butyl ester: To a mixture of 2–(4–{[tert–Butoxycarbonyl–(3–tert–butoxycarbonylamino–propyl)–amino]–methyl}–phenyl)–3–methoxy–acrylic acid methyl ester (5.70 g, 11.92 mmol), 5–(4–bromo–phenyl)–1*H*–imidazol–2–ylamine (2.84g, 11.92 mmol) and ethanol (60 mL) was added a solution of sodium methoxide (12 mL, 0.5 M in methanol, 6 mmol). The resulted mixture was refluxed for 18h, additional 12 mL of sodium methoxide (0.5 M in methanol, 6 mmol) was added and continued to reflex for 20h. The reaction was concentrated and diluted with EtOAc (300 mL) and washed with water (200 mL), brine (200 mL). The EtOAc solution was concentrated. The crude product was purified by flash chromatography (0% – 8% Methanol in dichloromethane) to give desired product (4.05 g, 52%) as brown solid. ^{1}NMR (300 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.54 (m, 2H), 7.35(s, 1H), 7.27 (d, J = 8.1 Hz, 2H), 5.25 (br.s, 0.5H), 4.70 (br.s, 0.5H), 4.44 (s, 2H), 3.29 (m, 2H), 3.11 (m, 2H), 1.67 (m, 2H), 1.52 (br.d, 9H), 1. 44 (s, 9H). LCMS (EI) m/z: 654 ($M+H^+$).

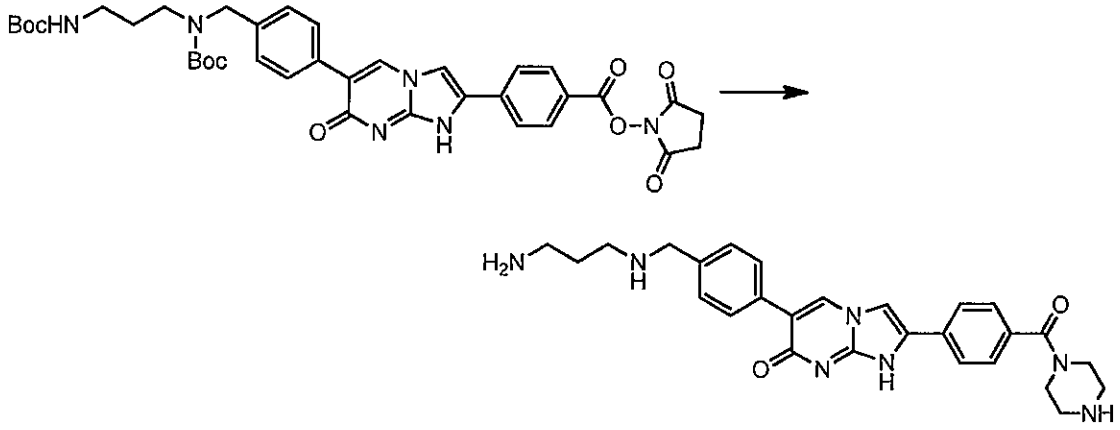


6–{4–[(3–Amino–propylamino)–methyl]–phenyl}–2–(4–bromo–phenyl)–1*H*–imidazo[1,2–a]pyrimidin–7–one hydrochloride salt (hydrochloride salt of compound 617): {4–[2–(4–Bromo–phenyl)–7–oxo–1,7–dihydro–imidazo[1,2–a]pyrimidin–6–yl]–benzyl}–(3–tert–butoxycarbonylamino–propyl)–carbamic acid tert–butyl ester (100 mg, 0.153 mmol) was dissolved in CH_2Cl_2 (5 mL), TFA (1 mL) was added and stirred at room temperature for 2h. The reaction mixture was concentrated and 3 mL of 0.6 N HCl and 2 mL of acetonitrile were added and stirred for 0.5 h, concentrated to a *ca.* 3 mL and lyophilized to

give the title compound (80 mg, 100%). . ^{1}NMR (300 MHz, CD_3OD): δ 8.99 (s, 1H), 8.24 (s, 1H), 7.75 (m, 8H), 4.30 (s, 2H), 3.32 (t, J = 8.1 Hz, 2H), 3.09 (t, J = 7.5 Hz, 2H), 2.17 (m, 2H). LCMS (EI) m/z: 454 ($M+H^+$).



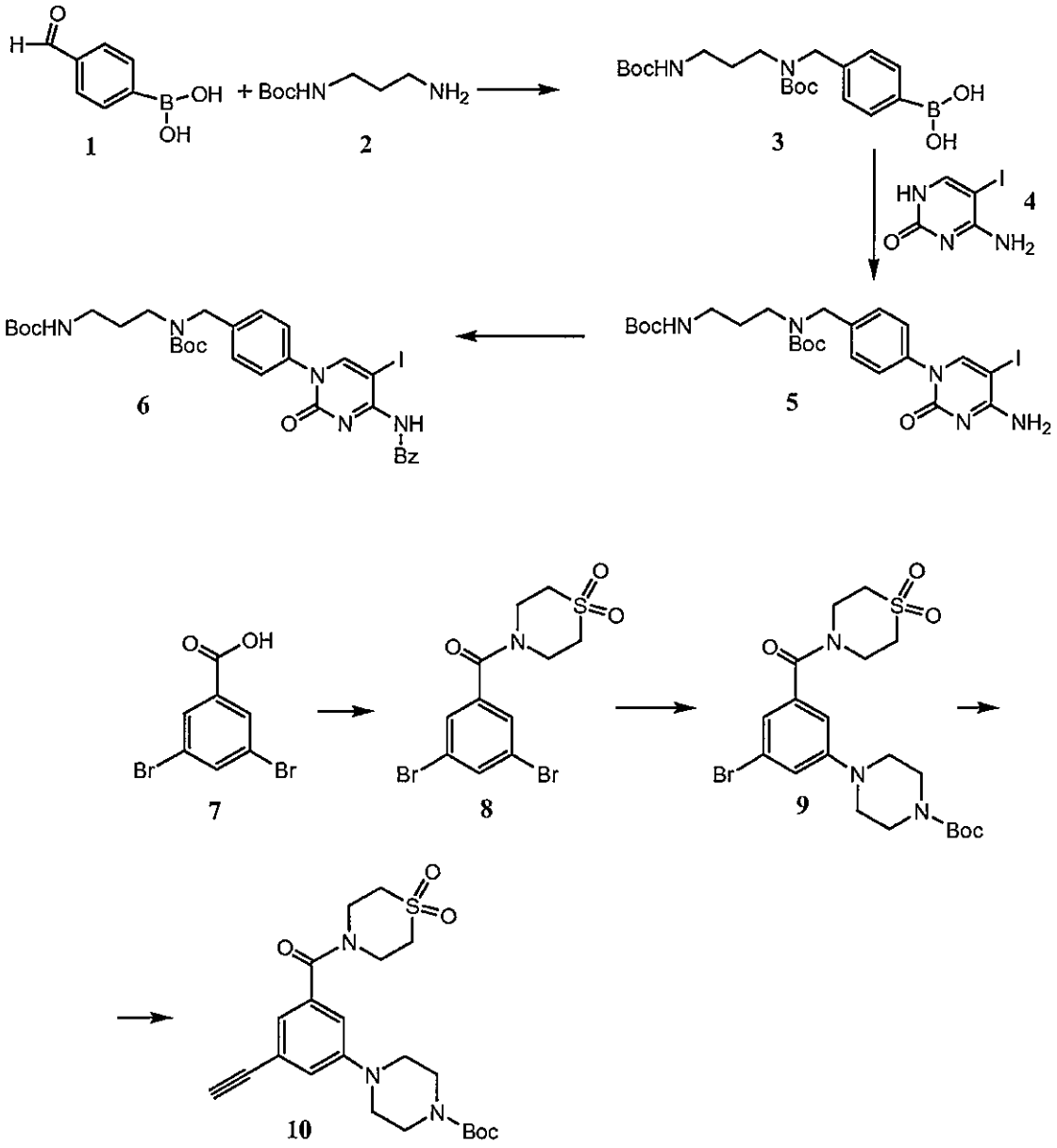
4–[6–(4–{[tert–Butoxycarbonyl–(3–tert–butoxycarbonylamino–propyl)–amino]–methyl}–phenyl)–7–oxo–1,7–dihydro–imidazo[1,2–a]pyrimidin–2–yl]–benzoic acid 2,5–dioxo–pyrrolidin–1–yl ester: A mixture of {4–[2–(4–bromo–phenyl)–7–oxo–1,7–dihydro–imidazo[1,2–a]pyrimidin–6–yl]–benzyl}–(3–*tert*–butoxycarbonylamino–propyl)–carbamic acid tert–butyl ester (1.50 g, 2.3 mmol), hydroxysuccilimide (0.40 g, 3.45 mmol), 9,9–dimethyl–4,5–bis(diphenylphosphino)xanthene (67 mg, 0.115 mmol), palladium acetate (26 mg, 0.115 mmol), triethylamine (700 mg, 6.9 mmol) and DMSO (3 mL) in a sealed tube was degassed and refilled with carbon monooxide (20 psi). The reaction mixture was heated at 80 °C for 16 h. After cooled to room temperature, the reaction mixture was diluted with water (30 mL), extracted with CH_2Cl_2 (50 mL x 3). The CH_2Cl_2 solution was concentrated and purified by flash chromatography (0–10% methanol in CH_2Cl_2) to afford activated ester as brown solid (1.0 g, 61%). ^{1}NMR (300 MHz, $CDCl_3$): δ 8.14 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.96 (s, 1H), 7.64 (d, J = 9.1 Hz, 2H), 5.59 (s, 1H), 7.45 (d, J = 9.1 Hz, 2H), 5.25 (br.s, 0.5H), 4.69 (br.s, 0.5H), 4.45 (s, 2H), 3.29 (m, 2H), 3.11 (m, 2H), 2.92 (s, 4H), 1.67 (m, 2H), 1.52 (br.d, 9H), 1. 44 (s, 9H). LCMS (EI) m/z: 715 ($M+H^+$).



6-{4-[(3-Amino-propylamino)-methyl]-phenyl}-2-[4-(piperazine-1-carbonyl)-phenyl]-1H-imidazo[1,2-a]pyrimidin-7-one hydrochloride salt (hydrochloride salt of 682): A mixture of 4-[6-(4-{[*tert*-butoxycarbonyl-(3-*tert*-butoxycarbonylamino-propyl)-amino]-methyl}-phenyl)-7-oxo-1,7-dihydro-imidazo[1,2-a]pyrimidin-2-yl]-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester, 1-boc-priperazine (229 mg, 1.23 mmol) and CH_2Cl_2 (5 mL) was stirred at room temperature overnight, concentrated and purified by flash chromatography (0-10% methanol in CH_2Cl_2) to afford desired amide as white solid (330 mg, 76%), ^{1}NMR (300 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.85 (d, *J* = 13.8 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.42 (s, 1H), 7.26 (d, *J* = 13.8 Hz, 2H), 5.35 (br.s, 0.5H), 4.95 (br.s, 0.5H), 4.44 (s, 2H), 3.70 (m, 2H), 3.44 (m, 6H), 3.20 (m, 2H), 3.10 (m, 2H), 1.67 (m, 2H), 1.52 (br.d, 9H), 1.48 (s, 9H)1. 44 (s, 9H). LCMS (EI) m/z: 786 ($M+H^+$).

The amide product (330 mg) was dissolved in CH_2Cl_2 (5 mL), TFA (1 mL) was added and stirred at room temperature for 2h. The reaction mixture was concentrated and 4 mL of 0.6 N HCl and 4 mL of acetonitrile were added and stirred for 0.5 h, concentrated to a *ca.* 5 mL and lyophilized to give the title compound (250 mg, 100%) . ^{1}NMR (300 MHz, CD_3OD): δ 9.02 (s, 1H), 8.34 (s, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H), 7.71 (d, J = 8.1 Hz, 2H), 4.35 (s, 2H), 3.90 (br.s, 4H), 3.34 (m, 2H), 3.25 (t, J = 7.5 Hz, 2H), 3.12 (t, J = 7.8 Hz, 2H), 2.17 (m, 2H). LCMS (EI) m/z: 486.1 ($M+H^+$).

Example 2 – Synthesis of Pyrrolocytosines



Synthesis of compound 3:

Compound **2** (65.0 g, 373 mmol) was dissolved in ethanol (150 mL). The flask was purged with argon. Compound **1** (55.93 g, 373 mmol) was then added and the mixture was stirred at room temperature for 2 h. The reaction solution was then added via addition funnel, over 20 minutes, to a suspension of $NaBH_4$ (14.18 g, 373 mmol) in toluene (150 mL), at 0°C. The ice bath was removed, and the resulting mixture was stirred at room temperature for 3h. 1N HCl

(750 mL) was added to the solution, and the mixture was stirred at room temperature for 30 min. K_2CO_3 (205.9 g, 1.49 mol), Boc_2O (81.41 g, 373 mmol), and THF (200 mL) were added to the solution, and stirred at room temperature for 23 h. Reaction solution was partitioned between EtOAc and 1:1 brine/H_2O. The aqueous layer was washed with EtOAc (2 x 300 mL). The combined organic layers were washed with brine (500 mL); dried over Na_2SO_4; filtered, and concentrated. The crude product was purified by Combi Flash chromatography, in 3 portions, affording the product as a white solid (119.43 g, 78 %); ^{1}H–NMR (300 MHz, $CDCl_3$) δ 1.43 (bs, 18H), 1.63 (m, 2H), 2.95–3.30 (m, 4H), 4.45 (m, 2H), 5.93 (bs, 1H), 7.22 (bs, 1H), 7.34 (bs, 1H), 7.78 (d: 8Hz, 1H), 8.19 (d: 8Hz, 1H).

Synthesis of compound 5:

To a mixture of compound **3** (42.28 g, 103.5 mmol) and compound **4** (24.54 g, 103.5 mmol) were added MeOH (3 L) and H_2O (750 mL). The mixture was stirred vigorously open to air, at room temperature, for 30 min. $Cu(OAc)_2 \cdot H_2O$ (20.67g, 103.5 mmol) was then added followed by TMEDA (18.63 mL, 124.3 mmol). The solution was stirred open to air, at room temperature, for 5 h. Once the reaction was complete, the solution was concentrated to 0.7 L, and then partitioned between CH_2Cl_2 (700 mL) and 20% NH_4OH/H_2O saturated with NH_4Cl (500 mL). The aqueous layer was washed with CH_2Cl_2 (500 mL, 200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by Combi Flash chromatography: A: CH_2Cl_2 B: 15:1 CH_2Cl_2/ 2N NH_3/MeOH, 0–100 % B over 85 min. (two 330g columns). This gave the product as a white solid (35.52 g, 58 %); LCMS (ESI): *m/e* 600 $(M+H)^+$.

Synthesis of compound 6:

Compound **5** (10.0 g, 16.68 mmol) was dissolved in THF (40 mL). The flask was purged with argon. Pyridine (40 mL) was then added followed by BzCl (3.10 mL, 26.69 mmol). The solution was stirred at room temperature under argon atmosphere for 3 h. MeOH (4 mL) was added, the mixture was stirred at room temperature for 10 min, and then it was partitioned between EtOAc (200 mL), heptane (100 mL), and 5% $KHCO_3/H_2O$ (200 mL). The aqueous layer was washed with EtOAc (100 mL, 50 mL). The combined organic layers were washed with 5% $KHCO_3/H_2O$ (300 mL); dried over Na_2SO_4; filtered, and concentrated.

The crude product was purified by Combi Flash chromatography: 0–100% EtOAc / heptane, over 55 min. (330 g column). The product was obtained as an off–white powder (9.81 g, 84%); LCMS (ESI): *m/e* 704 $(M+H)^+$.

Synthesis of compound 8:

3,5–Dibromobenzoic acid **7** (3.35 g, 11.97 mmol) was dissolved in DMF (30 mL). TBTU (5.38 g, 16.76 mmol) was added and the solution was stirred under argon, at 22 °C, for 5 min. Diisopropylethyl amine (4.95 mL, 29.92 mmol) was added, immediately followed by thiapiperazine S,S–dioxide (2.26 g, 16.76 mmol). The mixture was stirred at 22°C for 24 h, and then it was partitioned between EtOAc (200 mL) and 3% $KHCO_3/H_2O$ (300 mL). The organic phase was washed with H_2O (200 mL), and then with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (200 g) using 3% (2.5M NH_3/MeOH)/CH_2Cl_2. This gave compound **8** (1.72 g; 36%) as a solid; ^{1}H–NMR (300 MHz, DMSO–d6) δ 3.10–3.30 (m, 4H), 3.64 (m, 2H), 3.98 (m, 2H), 7.75 (d: 2.0 Hz, 2H), 7.97 (t: 2.0Hz, 1H).

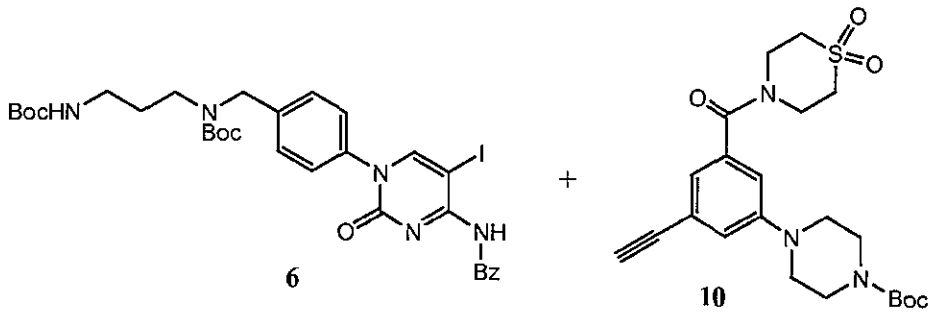
Synthesis of compound 9:

Compound **8** (1.72 g, 4.33 mmol), N–Boc–piperazine (931 mg, 5.0 mmol), K_2CO_3 (1.26 g, 9.1 mmol), CuI (83 mg, 0.43 mmol), and L–proline (100 mg, 0.87 mmol) were suspended in dimethyl sulfoxide (15 mL). The mixture was purged with argon, and then stirred under argon at 85 °C, for 20 h. After cooling to ambient temperature, the mixture was partitioned between water (150 mL) and EtOAc (200 mL), the organic phase was washed with water (100 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography on silica gel (200 g) using 2% (2.5M NH_3/MeOH)/CH_2Cl_2. This gave compound **9** (0.65 g; 30%) as a solid; ^{1}H–NMR (300 MHz, DMSO–d6) δ 1.42 (s, 9H), 3.12–3.28 (m, 8H), 3.44 (m, 4H), 3.64 (m, 2H), 4.00 (m, 2H), 7.02 (bs, 2H), 7.17 (bs, 1H).

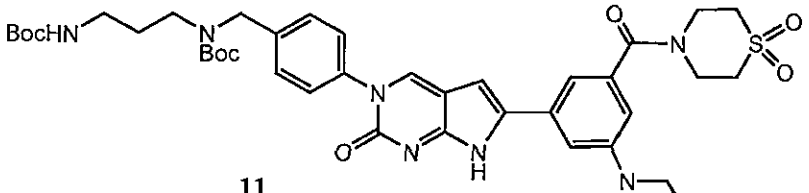
Synthesis of compound 10:

Compound **9** (0.63 g, 1.25 mmol) was dissolved in THF (10 mL). The solution was placed in a pressure vessel, purged with argon, and then CuI (60 mg, 0.313 mmol), $Pd(PPh_3)_4$ (145 mg, 0.125 mmol), Et_3N (1.40 mL, 10 mmol), and trimethylsilyl acetylene (0.353 mL, 2.5 mmol)

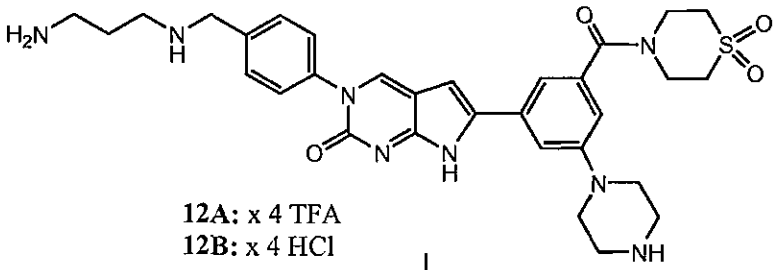
were added. The vessel was sealed, and the mixture was stirred at 45–50 °C. After 3 h, the mixture was diluted with EtOAc (30 mL), concentrated, and then purified by flash chromatography on silica gel (120 g) using 70% EtOAc – 30% heptane. This gave a semisolid (1.2 g) which was dissolved in MeOH (70 mL). The solution was purged with argon, K_2CO_3 (1.0 g) was added, and the mixture was stirred under argon, at 45 °C, for 30 min. The mixture was filtered, concentrated, and purified by flash chromatography on silica gel (120 g) using 75% EtOAc – 25% heptane. This gave compound **10** (0.425 g, 76%) as a white, solid foam; LCMS (ESI): *m/e* 448 $(M+H)^+$.



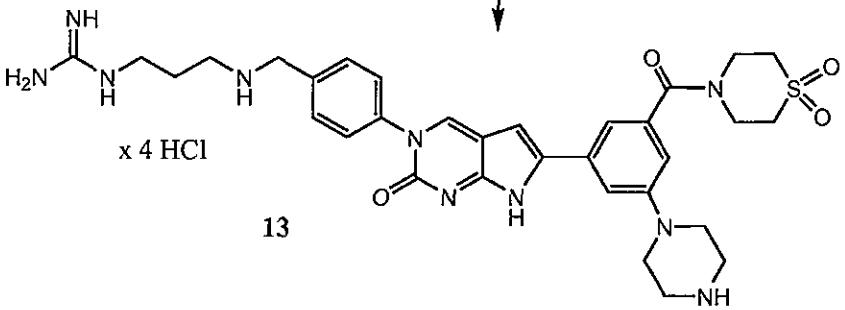
6 + 10



11



12A: x 4 TFA
12B: x 4 HCl



x 4 HCl

13

Synthesis of compound 11:

Compound **6** (669 mg, 0.95 mmol) and compound **10** (425 mg, 0.95 mmol) were placed in a pressure vessel, and anhydrous DMF (15 mL) was added. The solution was purged with argon, and then CuI (46 mg, 0.24 mmol), $Pd(PPh_3)_4$ (110 mg, 0.095 mmol), and Et_3N (1.06 mL, 7.6 mmol) were added, the vessel was sealed, and the mixture was stirred at 22 °C, for 15 min. Subsequently, the temperature was increased to 80–85 °C, and the mixture was stirred for 14 h. It was cooled to ambient temperature, MeOH (10 mL) was added, the vessel was sealed, and the mixture was stirred at 90 °C for 3 h. After cooling to ambient temperature, the mixture was partitioned between sat. KH_2PO_4/H_2O (250 mL) and EtOAc (200 mL), the organic phase was washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (150 g) using 5% (2.5M NH_3/MeOH)/CH_2Cl_2. This gave compound **11** (490 mg; 56%) as a yellow solid; LCMS (ESI): *m/e* 920 $(M+H)^+$.

Synthesis of compounds 12A and 12B:

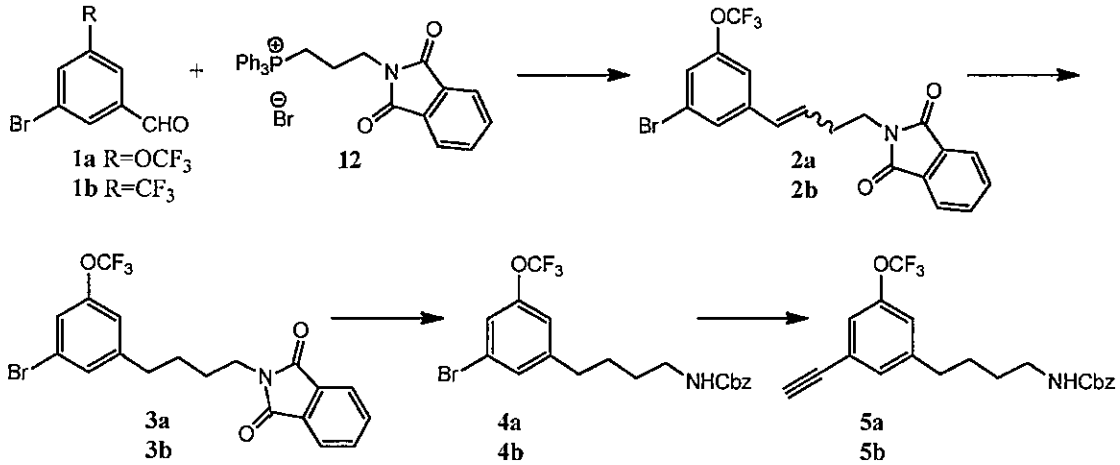
Compound **11** (490 mg, 0.533 mmol) was dissolved in CH_2Cl_2 (20 mL), trifluoroacetic acid (20 mL) was added, and the mixture was stirred at 22 °C for 40 min. CH_2Cl_2 (30 mL) was added, and the mixture was concentrated *in vacuo* to a viscous oil. Water (3 mL) and EtOH (70 mL) were added, the mixture was concentrated, affording crude compound **12A** as a solid residue. This residue was dissolved in [(10% MeOH–90% H_2O)+0.15%TFA] (40 mL). An aliquot (10 mL) was injected on a Dynamax 41.4 mm, C–18 prep HPLC Unit (guard +column), which was eluted with a gradient of solvents of 10% – 55% (MeOH/H_2O + 0.15% TFA), over 40 min. The pure fractions were combined and concentrated with EtOH, to dryness. This sample was treated with 1N HCl / H_2O (5 mL) and EtOH (70 mL), and concentrated. This operation was repeated; the solid thus obtained was lyophilized from H_2O–MeCN (4:1), affording compound **12B** (78 mg) as a yellow powder; LCMS (ESI): *m/e* 619 $(M+H)^+$.

Synthesis of compound 13:

A solution of compound **12A** in the mixture of solvents [(10% MeOH–90% H_2O)+0.15%TFA], described above, (30 mL, 0.40 mmol), was concentrated with EtOH, to a

viscous oil. This sample was dissolved in a mixture of DMF (10 mL) and diisopropylethyl amine (0.53 mL, 3.20 mmol). N,*N'*–Bis–Boc–1–guanylpyrazole (149 mg, 0.48 mmol) was added, and the mixture was stirred at 22 °C, for 15 h. EtOH (80 mL) was added, and the mixture was concentrated *in vacuo* (<1 mm Hg, 45 °C) to a viscous oil, which was dissolved in a mixture of CH_2Cl_2 (25 mL) and trifluoroacetic acid (30 mL). The mixture was stirred at 22 °C, for 2 h, and then CH_2Cl_2 (70 mL) was added, the solution was concentrated, the residue was dissolved in MeOH (30 mL) and treated with Amberslyst A26(OH) resin (10 g). The mixture was stirred for 1 h, filtered, and the filtrate was concentrated to a semisolid. This sample was purified by preparative HPLC: Dynamax 41.4 mm, C–18 prep HPLC Unit (guard +column), which was eluted with a gradient of solvents of 10% – 55% (MeOH/H_2O + 0.15% TFA), over 40 min. The pure fractions were combined and concentrated with EtOH, to dryness. This sample was treated with 1N HCl / H_2O (5 mL) and EtOH (70 mL), and concentrated. This operation was repeated; the solid thus obtained was lyophilized from H_2O–MeCN (4:1), affording compound **13** (122 mg) as a yellow powder; LCMS (ESI): *m/e* 661 $(M+H)^+$.

Example 3-Synthesis of Compounds 2009a ("a" series) and 2029a ("b" series)



Synthesis of 2a and 2b:

A mixture of phosphonium salt **12** (5.24 g, 9.88 mmol), **1a** (or **1b**) (2.65 g, 9.88 mmol), K_2CO_3 (1.36 g, 9.88 mmol), and 18-crown-6 (catalytic amount) in toluene (50 mL) was

heated at reflux under argon overnight. Upon completion, the mixture was cooled to rt and water was added. The aqueous layer was extracted with ethyl acetate (3 x 75 mL) and the combined organics were dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel chromatography (2:1 heptane/ethyl acetate). Compound **2a** was isolated cleanly as mixture of *E* and *Z* isomers (3.78 g, 87% yield).

Synthesis of 3a and 3b:

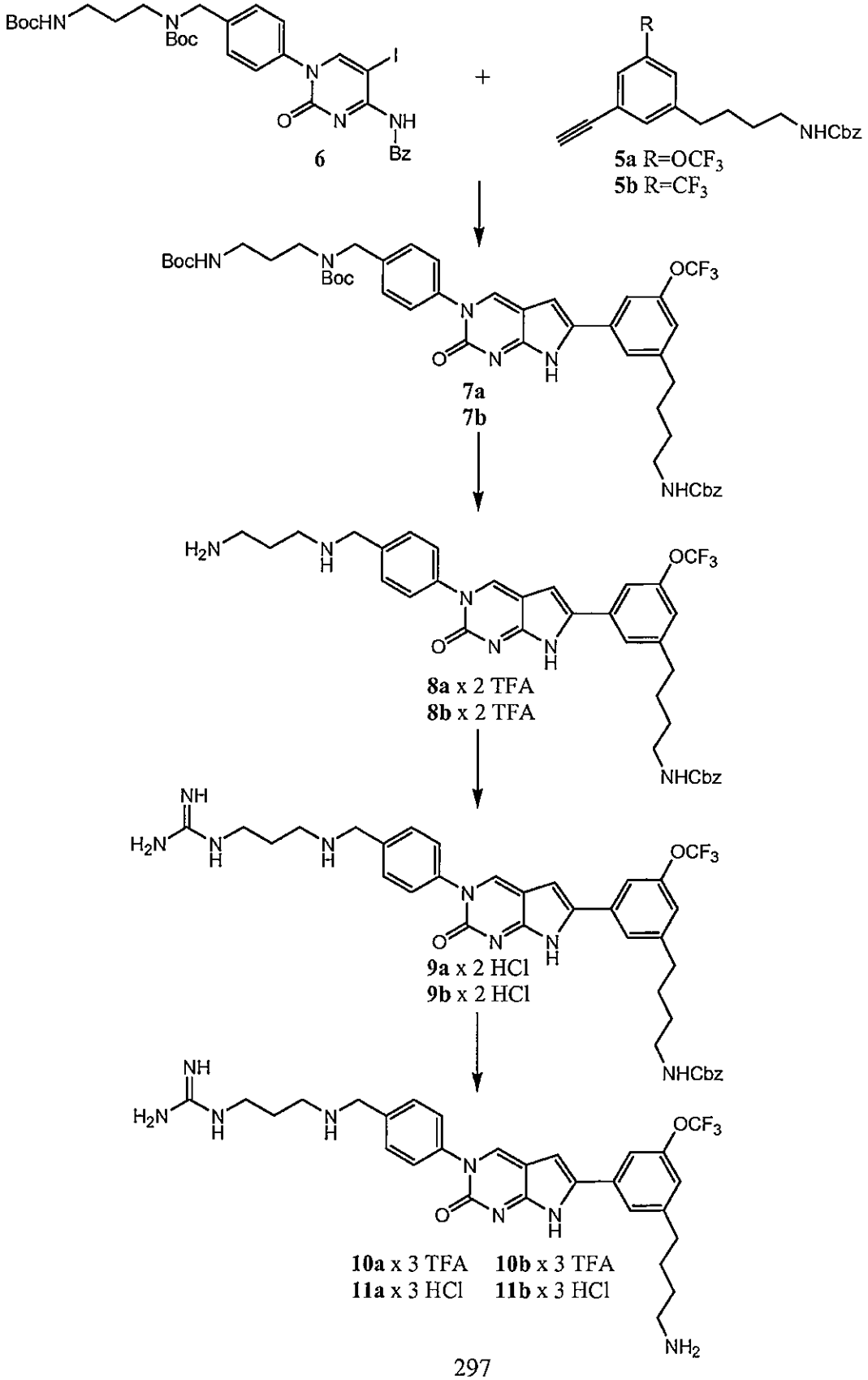
To a flask containing phthalimide **2a** (3.78 g, 8.58 mmol) (or **2b**) in ethyl acetate was added 10% Pd/C (0.76 g, 20% w/w). The flask was evacuated and filled with hydrogen via a balloon assembly. Stirring at rt was continued for 45 minutes at which time the contents were purged with argon. After filtering the mixture through celite, solvent was evaporated to provide the desired product **3a** in quantitative yield (3.77 g).

Synthesis of 4a and 4b:

In a screw-cap pressure tube, **3a** (3.70 g, 8.37 mmol) (or **3b**) was dissolved in anhydrous ethanol. Hydrazine monohydrate (1.62 mL, 33.5 mmol) was added to the solution and heat was applied at 65 °C for 8 h. After cooling to rt, the slurry was filtered to remove the white solid byproduct and the resulting solution was concentrated to dryness. Water was added and the aqueous layer was extracted three times with ethyl acetate. The combined organics were then washed with water and brine and dried over $NaSO_4$. Evaporation of solvent provided a clear, colorless oil (2.32 g, 89% yield) that was redissolved in dichloromethane (75 mL) and treated at 0 °C with benzyl chloroformate (1.27 mL, 8.94 mmol) and triethylamine (2.07 mL, 14.9 mmol). After 1 h of stirring, water was added and the organic layer was collected, dried with $NaSO_4$, and concentrated. Purification of the crude residue by silica gel chromatography (2:1 heptane/ethyl acetate) furnished **4a** as a viscous oil. (3.06 g, 92% yield)

Synthesis of 5a and 5b:

Compound **5a** (and **5b**) was prepared via the same two-step Sonogashira-deprotection sequence used for the synthesis of alkyne **10**. Starting from 1.5 g **4a**, the desire product was obtained in 53% yield (0.69 g).


BocHN
N
Boc
I
N
O
N
NH
Bz
6
+
R
NHCbz
5a R=OCF3
5b R=CF3
BocHN
N
Boc
OCF3
N
O
N
N
H
7a
7b
NHCbz
H2N
N
H
OCF3
N
O
N
N
H
8a x 2 TFA
8b x 2 TFA
NHCbz
NH
H2N
N
H
N
H
OCF3
N
O
N
N
H
9a x 2 HCl
9b x 2 HCl
NHCbz
NH
H2N
N
H
N
H
OCF3
N
O
N
N
H
10a x 3 TFA
10b x 3 TFA
11a x 3 HCl
11b x 3 HCl
NH2

Synthesis of 7a and 7b:

Pyrrolocytosine **7a** (and **7b**) was prepared from the coupling of common intermediate **6** and alkyne **5a** (and **5b**, respectively) according to the procedure described above for the synthesis of **11**. Starting from 690 mg of **5a**, 1.23 g of the desired compound was obtained as an orange-brown solid (81%); LCMS (ESI) m/e 863.4 $(M+1)^+$.

Synthesis of 8a and 8b:

Boc-deprotection of **7a** (0.60 g, 0.69 mmol) (and **7b**) was accomplished with trifluoroacetic acid as described for the preparation of **12A** (note to attorney: provisional patent app numbering). Alternatively, this transformation was carried out by treating the starting material with 8 mL of 6N HCl and anhydrous EtOH (30 mL) at 50 °C (2 h). Following solvent evaporation, the crude residue (from either approach) was taken to the next step without further purification. LCMS (ESI) m/e 663.3 $(M+1)^+$.

Synthesis of 9a and 9b:

Guanidine formation was carried out according to the protocol used to prepare compound **13** (note to attorney: provisional patent app numbering) except that starting material **8a** (~0.48 g, 0.65 mmol) (and **8b**) was used as a crude oil or semisolid rather than a MeOH-water solution. Removal of the Boc groups was facilitated by dissolving the protected guanidine intermediate in 35 mL of anhydrous ethanol, followed by the addition of 10 mL of 6N HCl. The solution was heated to 70 °C for 3 h. Upon cooling, the mixture was concentrated and dried further by azcotroping with additional anhydrous ethanol. The yellow-brown solid was used directly in the next step without further purification.

Synthesis of 11a and 11b:

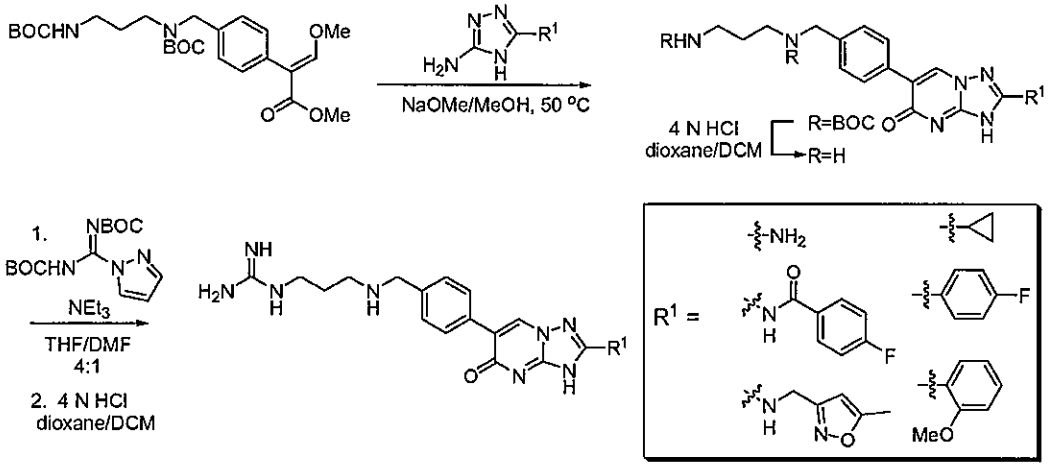
Under argon, guanidine **9a** (or **9b**) was dissolved in 30 mL of trifluoroacetic acid. Thioanisole (0.5 mL) was added dropwise and the solution was stirred at rt for 3-4 h. Upon completion, solvent was evaporated affording an oil or semisolid. Diethyl ether was added and the liquid layer containing most of the residual thioanisole was decanted. Crude **10a** was then dissolved in [(20% MeOH-90% H_2O)+0.15%TFA] (20 mL). An aliquot (10 mL) was injected on a Dynamax 41.4 mm, C-18 prep HPLC Unit (guard+column), which was eluted with

a gradient of solvents of 10% - 65% (MeOH/H_2O + 0.15% TFA), over 45 min. The pure fractions were combined and concentrated with EtOH to dryness. This sample was treated with 1N HCl/H_2O (5 mL) and EtOH (70 mL), and concentrated. This operation was repeated; the solid thus obtained was lyophilized from H_2O-MeCN (4:1), affording compound **11a** as a yellow powder (171 mg); LCMS (ESI) m/e 571.2 $(M+1)^+$; ^1H NMR (300 MHz, D_2O) δ 1.50-1.61 (m, 4H), 1.87-1.97 (m, 2H), 2.56 (bs, 2H), 2.87 (bs, 2H), 3.08 (t, J=6.9 Hz, 2H), 3.20 (t, J=6.9 Hz, 2H), 4.25 (s, 2H), 6.60 (s, 1H), 7.02 (s, 1H), 7.21 (s, 1H), 7.32 (s, 1H), 7.41 (d, J=8.7, 2H), 7.57 (d, J=8.7 Hz, 2H), 8.28 (s, 1H)

Data for **11b**: LCMS (ESI) m/e 555.3 $(M+1)^+$; ^1H NMR (300 MHz, D_2O) δ 1.33-1.46 (m, 4H), 1.72-1.80 (m, 2H), 2.44-2.47 (m, 2H), 2.70-2.75 (m, 2H), 2.84 (t, J=8.0 Hz, 2H), 3.03 (t, J=8.0 Hz, 2H), 4.09 (s, 2H), 6.51 (s, 1H), 7.25-7.27 (m, 3H), 7.40-7.44 (m, 3H), 7.51 (s, 1H), 8.13 (s, 1H).

Example 4 – Synthesis of Triazolopyrimidinones

Scheme 1. Synthetic route used for the preparation of [1,2,4]triazolo[1,5-*a*]pyrimidin-5-ones



Representative Example:

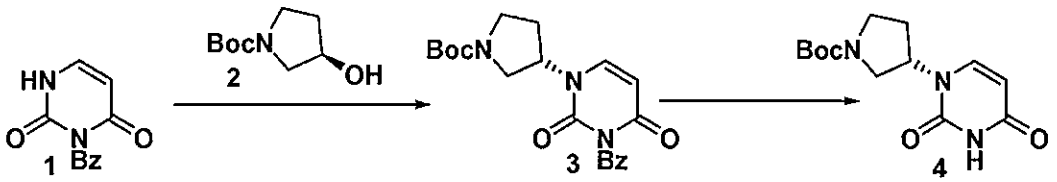
6–{4–[(3–Amino–propylamino)–methyl]–phenyl}–2–(4–fluoro–phenyl)–3H–[1,2,4]triazolo[1,5–a]pyrimidin–5–one. To 2–(4–{[tert–Butoxycarbonyl–(3–tert–butoxycarbonylamino–propyl)–amino]–methyl}–phenyl)–3–methoxy–acrylic acid methyl

ester (1.13 g, 2.16 mmol) in 10 mL of methanol was added 5–(4–fluorophenyl)–3–amino–1,2,4–triazole (0.50 g, 2.81 mmol). A 0.5 M solution of sodium methoxide in methanol (5.6 mL, 2.81 mmol) was added dropwise and the orange–colored mixture was gradually heated to 50 °C, where it was maintained overnight. Upon completion, methanol was removed in vacuo and the residue was partitioned between 100 mL of dichloromethane and 100 mL of water. The organic layer was collected, dried over Na_2SO_4 and concentrated to an orange–yellow precipitate. The crude material was loaded onto a silica gel column and eluted as follows: 5 minutes at 40 mL/min with 100:0 CH_2Cl_2/MeOH; 15 minutes at 40 mL/min with 95:5 CH_2Cl_2/MeOH; 15 at 40 mL/min minutes with 90:10 CH_2Cl_2/MeOH at which point the desired product was collected from the column. Evaporation of the solvent provided a slightly yellow precipitate that was triturated with ether to yield 560 mg of white powder (44% yield). Removal of the BOC–protecting groups was then accomplished by dissolving the solid in 10 mL of dichloromethane, followed by the addition of 3 mL of trifluoroacetic acid. After 1 h at room temperature, complete conversion was observed. After the addition of dichloroethane (10 mL), the volatiles were removed under reduced pressure. Formation of the HCl salt was promoted by the addition of approximately 3 mL of aq. 1 N HCl and subsequent evaporation of the water. Lyophilization (aq. 1 N HCl/acetonitrile) provided 396 mg (90% from BOC–protected compound) of the desired product as a white powder: ^{1}H NMR (300 MHz, DMSO) δ 1.99–2.09 (m, 2H, CH_2), δ 2.90–3.02 (m, 4H, NCH_2), δ 4.17 (bs, 2H, CH_2Ar), δ 7.38 (t, J = 8.9 Hz, 2H, Ar), δ 7.66 (d, J = 8.4 Hz, 2H, Ar), δ 7.76 (d, J = 8.4 Hz, 2H, Ar), δ 8.07–8.12 (m, 3H, Ar, NH), δ 8.99 (s, 1H, CH=C), δ 9.54 (bs, 2H, NH), δ 13.4 (bs, 1H, NH); LCMS (ES^+) *m/z* 393.0 (MH^+).

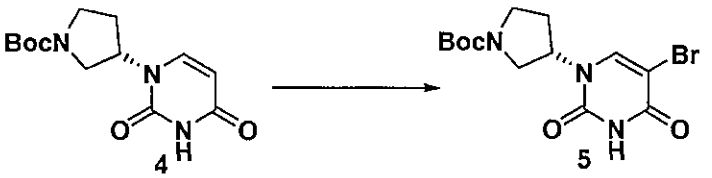
N–(3–{4–[2–(4–Fluoro–phenyl)–5–oxo–3,5–dihydro–[1,2,4]triazolo[1,5–a]pyrimidin–6–yl]–benzylamino}–propyl)–guanidine. To the HCl salt (250 mg, 0.54 mmol) suspended in DMF/THF (5:1, 5.4 mL), was added triethylamine (0.301 mL, 2.16 mmol). *N,N'*–Bis–BOC–1–guanylpyrazole (167 mg, 0.54 mmol) was then added to the solution and the progress of the reaction was monitored by LCMS. After 5 h, the solvents were evaporated by azeotroping with toluene/EtOH (a small amount of DMF remained). The crude material was partitioned between dichloromethane and water. The layers were separated and the aqueous phase was extracted two times with additional dichloromethane. The combined organics

were washed with brine, dried over Na_2SO_4, and concentrated to provide the oil as a crude mixture. Purification was accomplished via preparative TLC (2000 μm plate, 10% MeOH/ CH_2Cl_2) and after removal of solvent, a while solid was obtained. Deprotection of the diamine and formation of the HCl salt were performed as described above to provide 145 mg (53% yield) after lyophilization: ^{1}H NMR (300 MHz, DMSO) δ 1.86–1.93 (m, 2H, CH_2), δ 2.89–2.95 (m, 2H, NCH_2), δ 3.20–3.27 (m, 2H, NCH_2), δ 4.19 (bs, 2H, CH_2Ar), δ 7.35 (t, J = 9.0 Hz, 2H, Ar), δ 7.63 (d, J = 7.8 Hz, 2H, Ar), δ 7.68 (d, J = 7.8 Hz, 2H, Ar), δ 8.07–8.12 (m, 2H, Ar), δ 8.99 (s, 1H, CH=C), δ 9.35 (bs, 2H, NH), δ 13.4 (bs, 1H, NH); LCMS (ES^+) *m/z* 435.3 (MH^+).

Example 5 – Synthesis of Compound 562

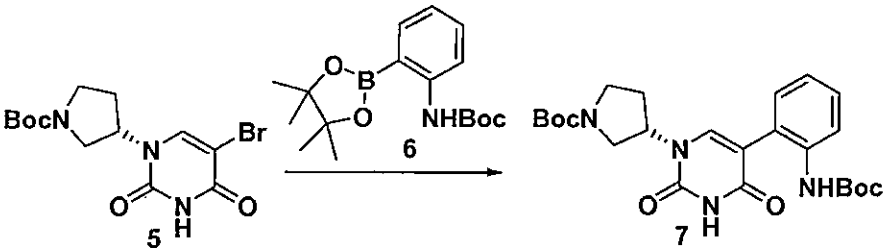


3–(2, 4–Dioxo–3,4–dihydro–2*H*–pyrimidine–1–yl)–pyrrolidine–1–carboxylic acid *tert*–butyl ester(4): To a suspension of **1** (1g, 5.3mmol) and **2** (1.26g, 5.87mmol) in tetrahydrofuran was added DIAD (1.16ml, 5.87mmol) drop wise and stirred overnight at ambient temperature. The clear solution was concentrated under reduced pressure to thick liquid. The crude mixture was purified by flash chromatography over silica gel (50–60% ethyl acetate–heptanes) to afford pure **3**. LCMS (EI) *m/z* 408.1 ($M+Na^+$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (2H, d), 7.67 (1H, t), 7.50 (2H, t), 7.27 (1H, d), 5.87 (1H, d), 5.14 (1H, m), 3.78 (1H, dd), 3.54 (3H. m), 2.34 (1H, m), 2.11 (1H, m), 1.49 (9H, s). A solution of **3** (2g) in 2N NH_3–MeOH (30mL) was stirred overnight at ambient temperature. The solution was evaporated under reduced pressure and the crude mixture thus obtained was purified by flash chromatography over silica gel (70–100% ethyl acetate–dichloromethane) to give pure **4** as a white solid. LCMS (EI) *m/z* 281.1 $(M+H)^+$ ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.41 (1H, bs), 7.18 (1H, d), 5.78 (1H, d), 5.17 (1H, m), 3.76 (1H, dd), 3.52 (3H. m), 2.33 (1H, m), 2.07 (1H, m), 1.48 (9H, s).

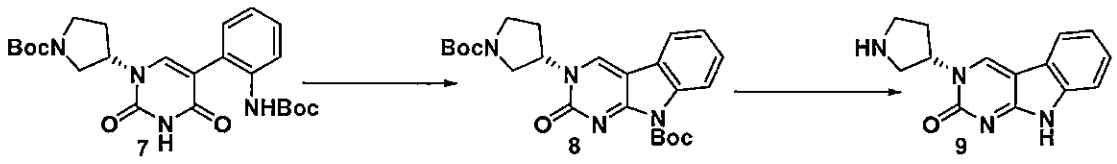


3-(5-Bromo-2, 4-Dioxo-3,4-dihydro-2*H*-pyrimidine-1-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester(5). To a mixture of **4** (0.6g, 2.13mmol) and *N*-bromosuccinimide (0.456g, 2.56mmol) was added DMF (15mL) and stirred at ambient temperature for 3-4h. The solution was partitioned between ethyl acetate (50mL) and 10% $Na_2S_2O_3$ (40mL). Organic layer was separated, washed with brine (3x50mL), dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. The crude material was purified by flash chromatography over silica gel (70% ethyl acetate-dichloromethane) to give pure **5**.

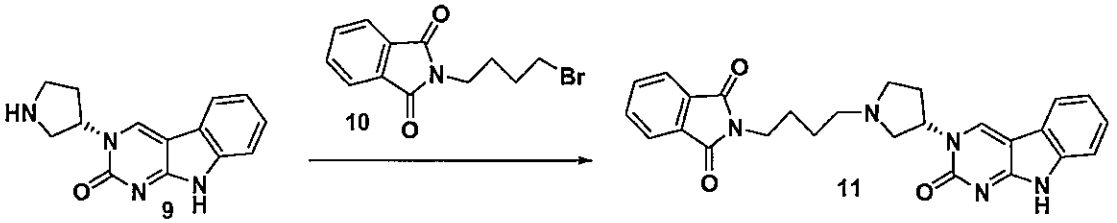
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.08 (1H, bs), 7.43 (1H, s), 5.14 (1H, m), 3.78 (1H, dd), 3.53 (3H. m), 2.35 (1H, m), 2.08 (1H, m), 1.49 (9H, s).



3-{5-(2-*tert*-Butoxycarbonylamine-phenyl)-2, 4-dioxo-3, 4-dihydro-2*H*-pyrimidine-1-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester(7). To a mixture of **5** (0.515g, 1.43mmol), **6** (0.547g, 1.72mmol), Pd $(PPh_3)_4$ (0.165g, 10mol %) and K_2CO_3 (0.592g, 4.29mmol) was added dioxane (8mL) and water (2mL). The suspension was purged with Argon under vacuum and heated at 90^{0}C in a sealed tube. After 15h the solution was concentrated and partitioned between ethyl acetate (50mL) and brine (30mL). Organic layer was separated, washed with brine (2x30mL), dried (anhydrous Na_2SO_4), evaporated and purified by flash chromatography over silica gel (50-70% ethyl acetate – dichloromethane) to give the title compound 7. LCMS (EI) *m/z* 495.1 $(M+Na)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.28 (1H, b), 7.75 (1H, d), 7.40 (1H, t), 7.28 (1H, s), 7.12 (1H, t), 7.05 (1H, d), 5.23 (1H, m), 5.11 (1H, dd), 3.45 (3H, m), 2.35 (1H, m), 2.11 (1H, m), 1.48 (9H, s), 1.45 (9H, s).

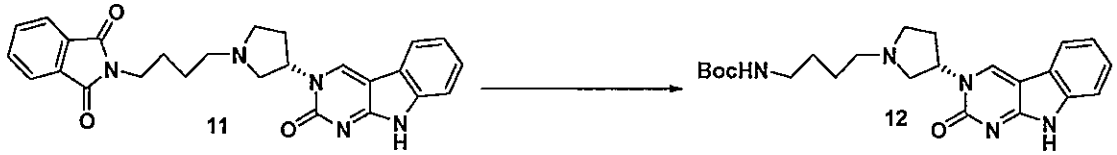


3–Pyrrolidin–3–yl–3,9–dihydro–1,3,9–triaza–fluoren–2–one (9). To a mixture of 7 (0.3g, 0.635mmol) and 2–Mesitylenesulfonyl chloride (0.278g, 1.27mmol) was added dichloromethane (5mL) followed by triethyl amine (0.176mL, 1.27mmol) and *N*, *N* dimethylamino pyridine (0.039g, 0.312mmol). This reaction solution was stirred under inert atmosphere for 3h after which DBU (0.191mL, 1.27mmol) was added and stirred overnight at ambient temperature. It was quenched with cold water and partitioned between ethyl acetate (50mL) and brine (30mL). Organic layer was separated, washed with brine (3x30mL), dried (anhydrous Na_2SO_4) and evaporated under reduced pressure. The crude material, thus obtained, was purified by flash chromatography over silica gel (70% ethyl acetate – dichloromethane) to give **8**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (1H, d), 8.09 (1H, s), 7.60 (1H, d), 7.42 (1H, t), 7.27 (1H, t), 5.44 (1H, m), 3.86 (1H, m), 3.60 (1H, m), 2.48 (1H, m), 2.25 (1H, m), 1.73 (9H, s), 1.51 (9H, m). A solution of **8** (0.2g) in dichloromethane (10mL) was treated with TFA (3mL) and stirred at ambient temperature for 2h. The solution was evaporated under reduce pressure and dried under vacuum to afford **9**. LCMS (EI) *m/z* 276.3 $(M+Na)^+$. This TFA salt of **9** was used for the next step without further purification.

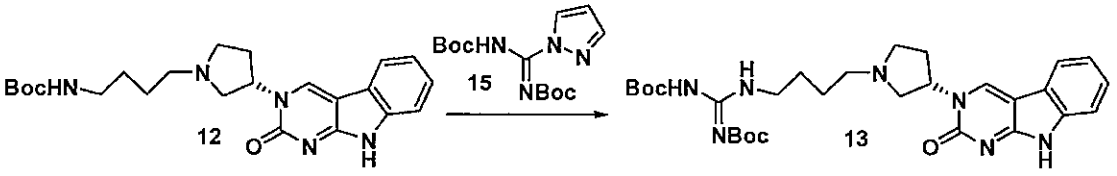


2–{4–[3–(2–Oxo–2,9–dihydro–1,3,9–triaza–fluoren–3–yl)–pyrrolidine–1–yl]}–isoindole–1,3–dione (11): The TFA salt of **9** was neutralized with tri–ethyl amine (0.245mL, 1.762mmol) in CH_3CN (10mL) and treated with bromide **10** (0.148g, 0.528mmol) and stirred at ambient temperature. After 3 days, the solution was concentrated and the crude material

was purified by flash chromatography over silica gel (10% methanol in dichloromethane).to give 11 (0.08g). LCMS (EI) *m/z* 456.1 $(M+H)^+$.

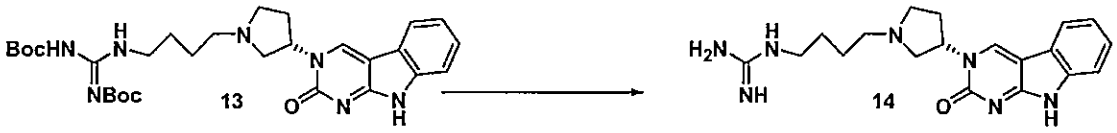


{4–[3–(2–Oxo–2,9–dihydro–1,3,9–triaza–fluoren–3–yl)–pyrrolidine–1–yl]}–carbamic acid *tert*–butyl ester (12): To a solution of 11 (0.08g, 0.176mmol) in ethanol (8mL) was added excess hydrazine (0.1mL) and stirred at ambient temperature for 3h, then heated to 50^0C for another 3h. The solution was concentrated and dissolved in tetrahydrofuran (3mL) and water (3mL). Then was added Boc_2O (0.384g, 1.76mmol) and K_2CO_3 (.1g, 0.7mmol) and stirred at ambient temperature overnight. The solution was concentrated under reduced pressure and partitioned between ethyl acetate (30mL) and brine (30mL). Organic layer was separated and aqueous layer was back extract with ethyl acetate (4x10mL). All organic layers were combined together, dried (anhydrous Na_2SO_4), filtered and concentrated. The crude material was purified by flash chromatography over silica gel (10% methanol in dichloromethane) to afford **12**. LCMS (EI) *m/z* 426 $(M+H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.93 (1H, s), 7.71 (2H, dd), 7.38 (1H, t), 7.20 (1H, t), 5.67 (1H, bt), 4.75 (1H, m), 3.29 (1H, t), 3.20 (2H, d), 3.10 (1H, d), 2.60 (4H, m), 2.23 (1H, q), 1.90 (1H, m), 1.62 (4H, bs), 1.43 (9H, s).



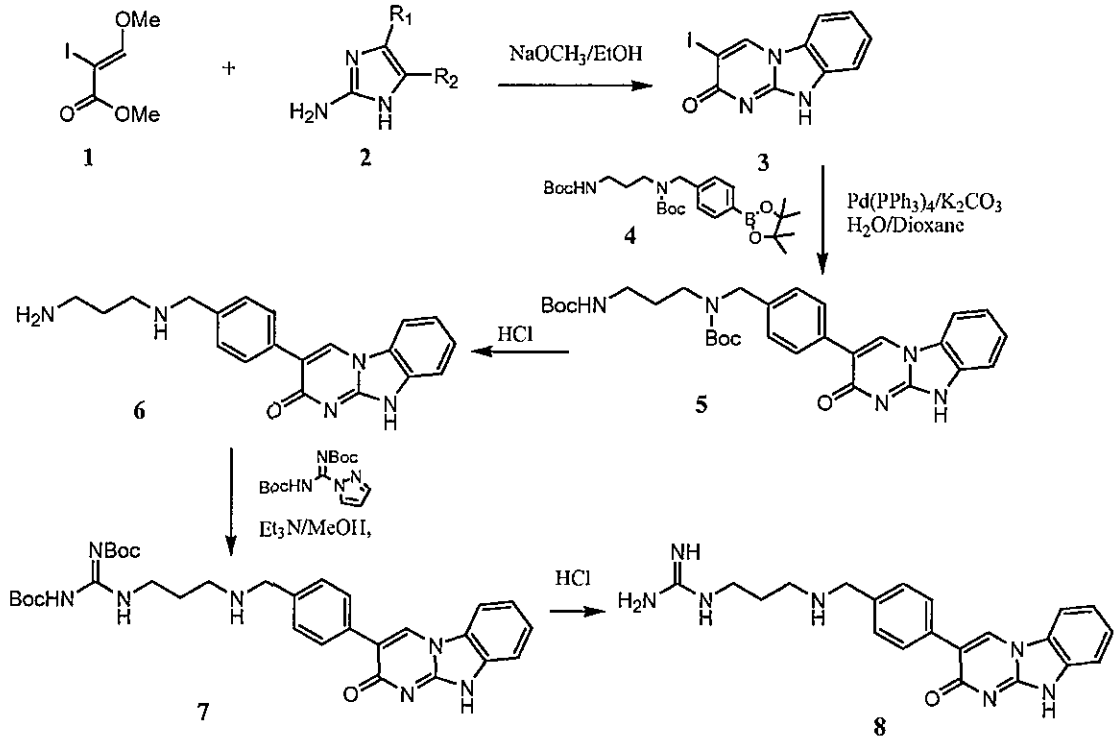
Guanidine intermediate 13: TFA (1mL) was added to a solution of **12** (40mg) in dichloromethane (4mL) and stirred at ambient temperature for 1h. The solution was evaporated under reduced pressure and co–evaporated with dichloromethane (3x3mL). This TFA salt was treated with 0.6N HCl (2mL). After 2h, this solution was lyophilized. LCMS (EI) *m/z* 325.8 $(M+H)^+$. ^{1}H NMR (300 MHz, D_2O): δ 8.65 (1H, s), 7.69 (1H, d), 7.37 (1H,

dd), 7.28 (1H, t), 7.22 (1H, t), 5.15 (1H, m), 4.05 (1H, d), 4.01 (1H, t), 3.60 (1H, t), 3.30 (3H, m), 3.00 (2H, t), 2.98 (1H, m), 2.54 (1H, m), 1.80 (2H, m), 1.72 (2H, m). To a mixture of this hydrochloride salt (0.03g, 0.0753mmol) was and (*tert*– Butoxycarbonylimino–pyrazol–1–yl–methyl)–carbamic acid *tert*–butyl ester, 15 (0.035g, 0.113mmol) was added DMF (2mL) followed by Hunig's base (0.131mL, 0.753mmol). The solution was stirred at ambient temperature for 2h and then diluted with ethyl acetate (30mL). The ethyl acetate layer was washed with brine (3x20mL), dried (anhydrous Na_2SO_4), filtered evaporated under reduced pressure. The crude material was purified by flash chromatography over silica gel (10% methanol in dichloromethane) to afford **13** (30mg) as white solid. LCMS (EI) *m/z* 568.2 $(M+H)^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.97 (1H, s), 8.41 (1H, bt), 7.67 (2H, dd), 7.36 (1H, t), 7.18 (1H, t), 5.67 (1H, m), 3.51 (2H, q), 3.32 (1H, q), 3.15 (1H, d), 2.63 (4H, m), 2.10 (1H, m), 1.99 (1H, m), 1.70 (4H, m), 1.48 (9H, s), 1.47 (9H, s).



***N*–{4–[3–(2–Oxo–2,9–dihydro–1,3,9–triaza–fluoren–3–yl)–pyrrolidine–1–yl]–butyl}–guanidine (14):** To a solution of compound **13** (0.028g) in dichloromethane (4mL) was added TFA (2mL) and stirred at ambient temperature for 3h. After that the solution was concentrated and co –evaporated with dichloromethane (3x4mL), dried under vacuum and dissolved in 0.6N HCl (2mL) and lyophilized to afford pure **14** as hydrochloride salt (0.028g). LCMS (EI) *m/z* 368.2 $(M+H)^+$. ^1H NMR (300 MHz, D_2O): δ 8.67 (1H, s), 7.68 (1H, d), 7.32 (1H, dd), 7.29 (1H, t), 7.20 (1H, t), 5.14 (1H, m), 4.14 (1H, d), 3.93 (1H, t), 3.50 (1H, t), 3.24 (2H, m), 3.16 (2H, t), 2.70 (1H, m), 2.67 (1H, m), 2.65 (1H, m), 1.70 (2H, m), 1.57 (2H, m).

Example 6 – Synthesis of Compound 602



(3–tert–Butoxycarbonylamino–propyl)–[4–(2–oxo–2,10–dihydro–benzo[4,5]imidazo[1,2–a]pyrimidin–3–yl)–benzyl]–carbamic acid tert–butyl ester (5). To a mixture of 2–iodo–3–methoxy–acrylic acid methyl ester (**1**,1.21 g, 5 mmol), 1*H*–benzoimidazol–2–ylamine (**2**, 0.67 g, 5 mmol) and ethanol (30 mL) was added a solution of sodium methoxide (10 mL, 0.5 M in methanol, 5 mmol). The resulted mixture was refluxed for 3h and concentrated to afford 3–iodo–10H–benzo[4,5]imidazo[1,2–a]pyrimidin–2–one (**3**). A mixture of (3–*tert*–butoxycarbonylamino–propyl)–[4–(4,4,5,5–tetramethyl–[1,3,2]dioxaborolan–2–yl)–benzyl]–carbamic acid *tert*–butyl ester (**4**, 490 mg, 1 mmol), **3** (311 mg, 1 mmol), K_2CO_2 (414 g, 3 mmol), $Pd(PPh_3)_4$ (0) (41 mg, 0.05 mmol), ethanol (6 mL), dioxane (2 mL) and water (2 mL) was degassed and heated at 80 °C for 20 h under argon atmosphere. The reaction mixture was diluted with EtOAc (500 mL), washed with water (300 mL) and brine (300 mL). The organic solution was concentrated and purified by flash chromatography (0% – 6% MeOH in methanechloride) to give desired product **5** (170 mg, 31%) as light yellow solid. LCMS (EI) m/z: 570 ($M+Na^+$).

3–{4–[(3–Amino–propylamino)–methyl]–phenyl}–10H–benzo[4,5]imidazo[1,2–a]pyrimidin–2–one hydrochloride salt (601): Compound **5** (170 mg, 0.31 mmol) was dissolved in CH_2Cl_2 (5 mL), TFA (1 mL) was added and stirred at room temperature for 2h. The reaction mixture was concentrated and 3 mL of 0.6 N HCl and 2 mL of acetonitrile were added and stirred for 0.5 h, concentrated to a *ca.* 3 mL and lyophilized to give the title compound (150 mg, 100%). ^{1}NMR (300 MHz, CD_3OD): δ 9.43 (s, 1H), 8.27 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 7.8 Hz, 2H), 7.75 (d, J = 7.8 Hz, 3H), 7.69 (t, J = 8.2 Hz, 1H), 7.62 (t, J = 8.2 Hz, 1H), 4.35 (s, 2H), 3.25 (t, J = 8.1 Hz, 2H), 3.10 (t, J = 7.5 Hz, 2H), 2.18 (m, 2H). LCMS (EI) m/z: 348.1 ($M+H^+$).

N–{3–[4–(2–Oxo–2,10–dihydro–benzo[4,5]imidazo[1,2–a]pyrimidin–3–yl)–benzylamino]–propyl}–guanidine hydrochloride salt (602): To a mixture of RX–6817 (110 mg, 0.16 mmol), Hunig's base (720 mg, 5.8 mmol) and acetonitrile (10 mL) was added *N,N*–bis–Boc–1–guanylpyrazole (50 mg, 0.16 mmol). The reaction mixture was stirred at room temperature overnight and diluted with water (30 mL), extracted with EtOAc (50 mL x 3). The organic solution was concentrated and purified by flash chromatography (2N NH_3 in methanol/ CH_2Cl_2, 0–10%) to give the guandylated product 7 as white solid (60 mg) which was dissolved in 3 mL of CH_2Cl_2 and 1 mL of TFA was added. The resulted mixture was stirred overnight and concentrated. 3 mL of 0.6 N HCl and 2 mL of acetonitrile were added and stirred for 0.5 h, concentrated to a *ca.* 3 mL and lyophilized to give the title compound (40 mg). ^{1}NMR (300 MHz, CD_3OD): δ 9.41 (s, 1H), 8.25 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 7.8 Hz, 2H), 7.74 (d, J = 7.8 Hz, 3H), 7.68 (t, J = 8.2 Hz, 1H), 7.60 (t, J = 8.2 Hz, 1H), 4.34 (s, 2H), 3.31 (m, 2H), 3.20 (t, J = 7.5 Hz, 2H), 2.07 (m, 2H). LCMS (EI) m/z: 390.1 ($M+H^+$).

Example 7 – Antimicrobial activity

The compounds of the present invention were tested for antimicrobial activity. These data are presented in Table 2. The compounds were run against *Eschericia coli* strain ATCC25922 using a standard microdilution assay to determine minimum inhibitory concentrations (MICs). The data is presented whereby a "+" indicates that the compound has an MIC value of 16 micrograms/ml or less and a "–" indicates that the compound has an MIC value greater than 16 micrograms/ml. A "N/A" means that data is unavailable. It will be

recognized by one skilled in the art that the compounds can be assessed against other bacterial organisms and that the presentation of data for activity against *Eschericia coli* is illustrative and in no way is intended to limit the scope of the present invention. The compounds of the present invention can be assayed against a range of other microorganisms depending upon the performance activity desired to be gathered. Furthermore, the "+", "–", and "N/A" representation and the selection of a cutoff value of 16 micrograms/ml is also illustrative and in no way is intended to limit the scope of the present invention. For example, a "–" is not meant to indicate that the compound necessarily lacks activity or utility, but rather that its MIC value against the indicated microorganism is greater than 16 micrograms/ml.

Table 2.

Compound Number	E. coli ATCC25922 MIC
142	–
152	–
154	–
169	–
179	–
180	–
181	–
182	–
183	–
184	+
192	–
193	–
194	+
195	–
196	+
197	+
198	+
200	+
201	+
203	+
204	+
206	+
216	+
217	+
218	–
219	+
220	+
221	+
224	+
225	+
226	–
227	+
228	+
229	+
230	–
231	+
232	+
233	+
234	+
235	+
236	+

Compound Number	E. coli ATCC25922 MIC
237	+
240	–
241	+
245	–
250	–
253	–
254	–
258	+
261	–
262	–
263	+
264	–
272	–
279	–
280	–
288	–
289	–
292	–
293	–
296	–
298	–
306	–
309	–
310	–
318	–
333	–
335	–
498	–
506	–
507	+
508	–
511	–
542	–
559	–
560	–
561	–
562	–
563	–
564	+
565	–
566	–
567	–
571	–

Compound Number	E. coli ATCC25922 MIC
572	–
580	–
581	–
586	–
587	–
590	–
591	–
596	–
597	–
600	–
601	–
602	+
609	–
610	–
611	–
612	–
613	–
616	+
617	–
618	–
620	–
621	–
622	–
623	–
624	+
625	–
626	–
628	–
629	+
630	–
631	–
632	–
633	–
634	+
635	+
636	–
637	–
640	+
644	+
645	+
646	–
647	–
648	+

Compound Number	E. coli ATCC25922 MIC
649	+
650	+
653	–
654	–
655	+
661	–
662	–
663	–
665	+
666	–
668	–
670	–
673	–
677	+
678	+
679	–
682	+
683	+
684	–
687	+
688	+
692	–
693	+
697	+
698	–
699	–
700	–
701	–
702	+
703	–
704	–
705	+
706	+
709	–
711	+
713	+
716	–
717	–
719	+
720	+
721	–
722	+
723	–

Compound Number	E. coli ATCC25922 MIC
724	+
725	+
726	+
727	+
728	+
734	–
736	+
737	–
742	+
743	–
744	–
745	+
746	–
755	+
756	+
757	+
758	+
759	+
760	+
761	+
762	–
764	–
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767	+
768	+
769	+
770	+
771	+
772	+
773	+
775	+
778	+
784	–
785	–
786	+
787	+
788	+
789	+
790	+
791	–
796	+
797	+
799	–

Compound Number	E. coli ATCC25922 MIC
800	–
801	+
802	+
803	+
804	+
805	+
806	+
807	+
808	+
809	–
810	–
813	–
814	+
815	+
816	+
817	+
819	+
820	+
821	+
822	+
823	+
824	–
825	–
826	–
827	–
828	+
829	–
830	–
831	+
834	+
835	+
836	+
837	+
838	+
839	+
840	+
841	+
842	+
843	+
844	+
845	+
846	+
847	–

Compound Number	E. coli ATCC25922 MIC
848	+
849	+
850	+
851	+
852	+
853	+
854	+
855	+
856	+
857	+
860	–
861	–
862	+
863	–
864	–
865	+
866	+
867	+
871	+
872	+
873	+
874	–
875	+
876	–
877	–
878	+
879	+
880	–
881	+
882	–
883	–
884	–
885	–
886	–
887	–
892	+
893	+
894	–
895	+
896	–
897	+
898	–
899	+

Compound Number	E. coli ATCC25922 MIC
900	–
901	–
902	–
905	–
906	–
907	+
910	–
911	–
912	–
913	+
914	–
915	+
918	+
922	+
923	+
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926	+
927	–
928	+
930	+
931	–
932	–
933	–
934	+
935	–
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937	+
939	–
940	+
943	+
944	+
945	–
946	–
947	–
948	–
949	+
951	–
952	–
957	+
958	+
959	–
960	+

Compound Number	E. coli ATCC25922 MIC
961	–
962	–
963	+
964	–
965	–
966	+
967	+
968	–
969	+
970	+
971	+
974	–
975	–
977	+
978	+
979	+
980	+
981	+
982	+
983	–
984	+
985	–
986	–
987	–
988	+
989	+
990	+
991	+
992	+
994	+
995	+
996	+
997	+
998	+
999	–
1000	–
1001	–
1002	–
1003	+
1004	+
1005	+
1009	+
1010	+

Compound Number	E. coli ATCC25922 MIC
1011	+
1012	+
1013	+
1015	+
1017	+
1018	+

1019	+
1020	–
1021	–
1022	–
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1027	+
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2027a	+
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INCORPORATION BY REFERENCE

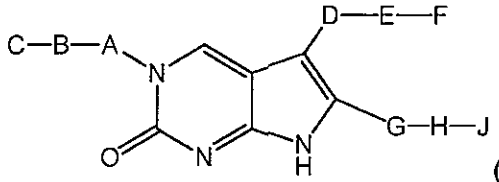
The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

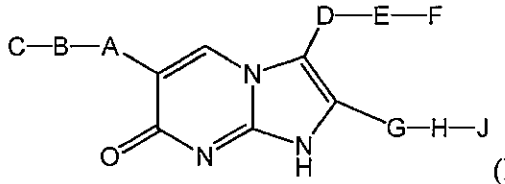
The invention can be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

What is claimed is:

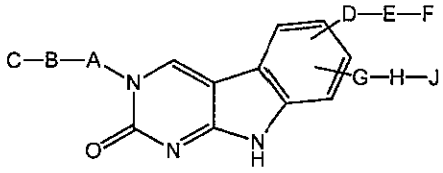
1. A compound having the formula:



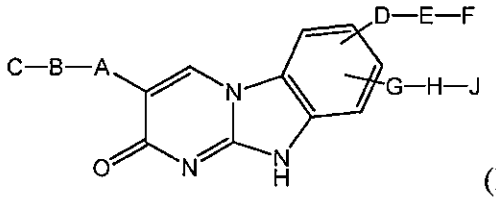
(Ia),



(IIa),

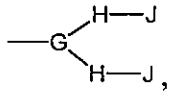


(IIIa), or



(IVa),

wherein –G–H–J alternatively is selected from



,

wherein each H and J are independently selected,

C–B–A–, –D–E–F, and –G–H–J are chemical moieties, wherein

A, D and G are independently selected from the group consisting of:

(a) a single bond, (b) –(C_{1-8} alkyl)– , (c) –(C_{2-8} alkenyl)–, (d) –(C_{2-8} alkynyl)–, wherein

i) 0–4 carbon atoms in any of (b)–(d) immediately above optionally is replaced by a moiety selected from the group consisting of –O–, $S(O)_p$, –NR^6–, –(C=O)–, –$S(O)_pNR^6$–, –$NR^6S(O)_p$–, and –$NR^6S(O)_pNR^6$–,

ii) any of (b)–(d) immediately above optionally is substituted with one or more R^5 groups, and

iii) any of (b)–(d) immediately above optionally is substituted with –(C_{1-8} alkyl)–R^5 groups;

(e) –O–, (f) –NR^6–, (g) –$S(O)_p$–, (h) –C(O)–, (i) –C(O)O–, (j) –OC(O)–, k) –OC(O)O–, (l) –C(O)NR^6–, (m) –NR^6CO–, (n) –NR^6C(O)NR^6–, (o) –C(=NR^6)–, (p) –C(=NR^6)O–, (q) –OC(=NR^6)–, (r) –C(=NR^6)NR^6–, (s) –NR^6C(=NR^6)–, (t) –C(=S)–,

(u) $-C(=S)NR^6-$, (v) $-NR^6C(=S)-$, (w) $-C(O)S-$, (x) $-SC(O)-$, (y) $-OC(=S)-$, (z) $-C(=S)O-$, (aa) $-NR^6(CNR^6)NR^6-$, (bb) $-CR^6R^6C(O)-$, (cc) $-C(O)NR^6(CR^6R^6)_t-$, (dd) a 3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (ee) a 3–14 member saturated, unsaturated, or aromatic carbocycle, and (ff) $-(CR^6R^6)_t-$,

wherein (dd) or (cc) is optionally substituted with one or more R^5 groups;

B, E, and H are independently selected from the group consisting of:

(a) a single bond,

(b) a 3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

(c) a 3–14 member saturated, unsaturated, or aromatic carbocycle,

wherein (b) or (c) is optionally substituted with one or more R^5 groups;

(d) $-(C_{1-8}$ alkyl$)-$, (e) $-(C_{2-8}$ alkenyl$)-$, (f) $-(C_{2-8}$ alkynyl$)-$, wherein

i) 0–4 carbon atoms in any of (d)–(f) immediately above optionally is replaced by a moiety selected from the group consisting of $-O-$, $-S(O)_p-$, $-NR^6-$, $-(C=O)-$, $-C(=NR^6)-$, $-S(O)_pNR^6-$, $-NR^6S(O)_p-$, and $-NR^6S(O)_pNR^6-$,

ii) any of (d)–(f) immediately above optionally is substituted with one or more R^5 groups, and

iii) any of (d)–(f) immediately above optionally is substituted with $-(C_{1-8}$ alkyl$)-R^5$ groups;

and (g) $-(CR^6R^6)_t-$,

C, F, and J are independently selected from the group consisting of:

(a) hydrogen, (c) F, (d) Cl, (e) Br, (f) I, (g) $-CF_3$, (h) $-CN$, (i) $-N_3$ (j) $-NO_2$, (k) $-NR^6(CR^6R^6)_tR^8$, (l) $-OR^8$, (m) $-S(O)_p(CR^6R^6)_tR^8$, (n) $-C(O)(CR^6R^6)_tR^8$, (o) $-OC(O)(CR^6R^6)_tR^8$, (p) $-SC(O)(CR^6R^6)_tR^8$, (q) $-C(O)O(CR^6R^6)_tR^8$, (r) $-NR^6C(O)(CR^6R^6)_tR^8$, (s) $-C(O)NR^6(CR^6R^6)_tR^8$, (t) $-C(=NR^6)(CR^6R^6)_tR^8$, (u) $-C(=NNR^6R^6)(CR^6R^6)_tR^8$, (v) $-C(=NNR^6C(O)R^6)(CR^6R^6)_tR^8$, (w) –

$C(=NOR^8)(CR^6R^6)_tR^8$, (x) $-NR^6C(O)O(CR^6R^6)_tR^8$, (y) $-OC(O)NR^6(CR^6R^6)_tR^8$, (z) $-NR^6C(O)NR^6(CR^6R^6)_tR^8$, (aa) $-NR^6S(O)_p(CR^6R^6)_tR^8$, (bb) $-S(O)_pNR^6(CR^6R^6)_tR^8$, (cc) $-NR^6S(O)_pNR^6(CR^6R^6)_tR^8$, (dd) $-NR^6R^8$, (ee) $-NR^6(CR^6R^6)R^8$, (ff) $-OH$, (gg) $-NR^8R^8$, (hh) $-OCH_3$, (ii) $-S(O)_pR^8$, (jj) $-NC(O)R^8$, (kk) $-NR^6C(NR^6)NR^6R^8$, (ll) a C_{1-8} alkyl group, (mm) a C_{2-8} alkenyl group, (nn) a C_{2-8}alkynyl group, (oo) a 3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (pp) a 3–14 member saturated, unsaturated, or aromatic carbocycle, (qq) $-(CR^6R^6)_tNR^6(CR^6R^6)_tR^8$, (rr) $-N[(CR^6R^6)_tR^8][C=O(CR^6R^6)_tR^8]$, (ss) $-(CR^6R^6)_tN[(CR^6R^6)_tR^8][(CR^6R^6)_tR^8]$, (tt) $-(CR^6R^6)_tNR^6(C=O)(CR^6R^6)_tR^8$, (uu) – haloalkyl, (vv) $-C(O)(CR^6)[(CR^6R^6)_tR^8]R^8$, (ww) $-(CR^6R^6)_tC(O)NR^8R^8$, (xx) $-(CR^6R^6)_tC(O)O(CR^6R^6)_tR^8$, (yy) $-NR^6C(O)CR^8R^8R^8$, (zz) $-N[(CR^6R^6)_tR^8]C(O)R^8$, and (aaa) $-S(O)_pNR^8R^8$;

wherein (ll) through (pp) is optionally substituted with one or more R^7 groups;

R^5 is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) $-CN$, (h) $-N_3$ (i) $-NO_2$, (j) $-NR^6R^6$, (k) $-OR^8$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C_{1-8}$ alkyl, (n) $-C_{1-8}$ alkenyl, (o) $-C_{1-8}$ alkynyl, (p) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (q) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (r) –haloalkyl, (s) $-SR^6$, (t) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and (u) –3–14 member saturated, unsaturated, or aromatic carbocycle; alternatively, two R^5 groups are taken together to form a carbocycle wherein (m) through (r) and (t) through (u) is optionally substituted with one or more R^8;

R^6 is selected from (a) hydrogen, (b) $-C_{1-8}$ alkyl or alternatively two R^6 groups are taken together to form a carbocycle, (c) –haloalkyl, (d) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting

of nitrogen, oxygen, and sulfur, and (e) –3–14 member saturated, unsaturated, or aromatic carbocycle;

wherein (b) through (e) is optionally substituted with one or more R^8;

R^7 is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) $-NO_2$, (j) $-NR^6R^6$, (k) $-OR^6$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C_{1-8}$ alkyl, (n) $-C_{1-8}$ alkenyl, (o) $-C_{1-8}$ alkynyl, (p) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (q) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (r) –haloalkyl, (s) $-NR^6R^8$, (t) $-OR^8$, (u) $-(CR^6R^6)_tNR^6R^8$, (v) $-CR^6R^8R^8$, (w) $-SR^6$, (x) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (y) –3–14 member saturated, unsaturated, or aromatic carbocycle, (z) $-(CR^6R^6)_tC(O)NR^8R^8$, (aa) $-S(O)_pR^8$, (bb) $-NR^6C(O)NR^6R^6$, (cc) $-NR^6C(O)R^6$, and (dd) $-C(=NR^6)NR^6R^6$;

wherein (m) through (q) and (x) through (y) are optionally substituted with one or more R^9;

R^8 is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) $-NO_2$, (j) $-NR^6R^9$, (k) $-OR^9$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C_{1-8}$ alkyl, (n) $-C_{1-8}$ alkenyl, (o) $-C_{1-8}$ alkynyl, (p) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (q) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (r) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (s) –3–14 member saturated, unsaturated, or aromatic carbocycle, (t) –haloalkyl, (u) $-C(O)(CR^6R^6)_tR^9$, (v) $-SR^6$, (w) $-OC(O)(CR^6R^6)_tR^9$, (x) $-NR^6C(O)NR^6R^9$, (y) $-NR^6C(O)R^9$, (z) $-NR^6(CNR^9)(NR^6R^6)$, (aa) $-ONR^6(CNR^6)NR^6R^6$, (bb) $-C(=NR^9)NR^6R^6$, (cc) $-S(O)_pR^9$, (dd) $-(CR^6R^6)_tC(O)NR^6R^9$, (cc) $-(CR^6R^6)_tOR^9$, and (ff) $-(CR^6R^6)_tNR^6R^9$;

wherein (m) through (s) is optionally substituted with one or more R^9;

R^9 is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) – NO_2, (j) $-NR^6R^{10}$, (k) $-OR^6$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C(O)(CR^6R^6)_tNR^6R^6$, (n) $-C_{1-8}$ alkyl, (o) $-C_{1-8}$ alkenyl, (p) $-C_{1-8}$ alkynyl, (q) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (r) –3–14 member saturated, unsaturated, or aromatic carbocycle, (s) –haloalkyl, (t) $-(CR^6R^6)_tOR^6$, (u) $-O(CR^6R^6)_tNR^6R^{10}$, (v) $-C(O)R^6$, (w) $-SR^6$, (x) $-C(O)OR^{10}$, (y) $-S(O)_pR^6$, (z) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (aa) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (bb) $-O(CR^6R^6)_tOR^6$, (cc) $-C(=NR^6)NR^6R^6$, (dd) $-ONR^6R^6$, (ee) – $NR^6C(O)NR^6R^6$, (ff) $-O(CR^6R^6)_tOR^6$, (gg) $-NR^6C(O)R^6$, and (hh) $-(CR^6R^6)_tNR^6R^{10}$;

wherein (n) through (r) and (z) through (aa) is optionally substituted with one or more R^{10};

R^{10} is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) – NO_2, (j) $-NR^6R^6$, (k) $-OR^6$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C(O)(CR^6R^6)_tNR^6R^6$, (n) $-C_{1-8}$ alkyl, (o) $-C_{1-8}$ alkenyl, (p) $-C_{1-8}$ alkynyl, (q) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (r) –3–14 member saturated, unsaturated, or aromatic carbocycle, (s) –haloalkyl, (t) $-(CR^6R^6)_tOR^6$, (u) $-O(CR^6R^6)_tNR^6R^6$, (v) $-C(O)R^6$, (w) $-SR^6$, (x) $-C(O)OR^6$, (y) $-S(O)_pR^6$, (z) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (aa) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (bb) $-O(CR^6R^6)_tOR^6$, (cc) $-C(=NR^6)NR^6R^6$, (dd) $-ONR^6R^6$, (ee) – $NR^6C(O)NR^6R^6$, (ff) $-O(CR^6R^6)_tOR^6$, (gg) $-NR^6C(O)R^6$, and (hh) $-(CR^6R^6)_tNR^6R^6$;

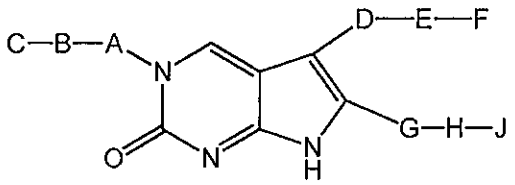
optionally, wherein either the group –D–E–F or the group –G–H–J is absent, but both –D–E–F and –G–H–J are not simultaneously absent;

p is 0, 1, or 2, and

t is 0, 1, 2, or 3,

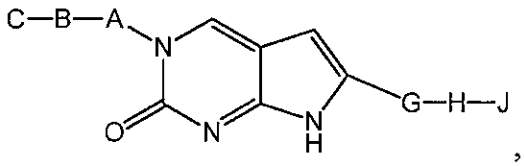
or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

2. The compound according to Claim 1 having the formula:



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

3. The compound according to Claim 2 having the formula:



,

wherein D and E are single bonds and F is hydrogen, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

4. The compound according to Claim 3, wherein

A is selected from

(a) a 3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

(b) a 3–14 member saturated, unsaturated, or aromatic carbocycle, and

(c) a single bond,

wherein (a) or (b) is optionally substituted with one or more R^5 groups;

B is selected from (a) $-(C_{1-8}$ alkyl)–, (b) $-(C_{2-8}$ alkenyl)–, (c) $-(C_{2-8}$ alkynyl)–, (d) a single bond, wherein

i) 0–4 carbon atoms in any of (a)–(c) immediately above optionally is replaced by a moiety selected from the group consisting of –O–, $-S(O)_p$–, $-NR^6$–, –(C=O)–, $-C(=NR^6)$–, $-S(O)_pNR^6$–, and $-NR^6S(O)_pNR^6$–,

ii) any of (a)–(c) immediately above optionally is substituted with one or more R^5 groups, and

iii) any of (a)–(c) immediately above optionally is substituted with $-(C_{1-8}$ alkyl)–R^5 groups, and

C is selected from (a) NH_2, (b) $-NHC(=NH)NH_2$ and (c) hydrogen,

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

5. The compound according to Claim 4, wherein

A is selected from azepanyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl, pyridyl, cyclohexenyl, cyclohexadienyl, dihydropyridyl, furanyl, tetrahydrofuranyl, tetrahydropyridyl, azetidinyl, pyrrolidinyl, piperidinyl, and piperidenyl,

wherein any of A immediately above optionally is substituted with one or more R^5 groups;

alternatively, A is a single bond;

B is selected from (a) $-(C_{1-8}$ alkyl$)-$, wherein

i) 0–4 carbon atoms in (a) immediately above optionally is replaced by a moiety selected from the group consisting of $-O-$, $-S(O)_p-$, $-NR^6-$, $-(C=O)-$, $-S(O)_pNR^6-$, and $-NR^6S(O)_pNR^6-$,

ii) (a) immediately above optionally is substituted with one or more R^5 groups, and

iii) (a) immediately above optionally is substituted with $-(C_{1-8}$ alkyl$)-R^5$ groups; and

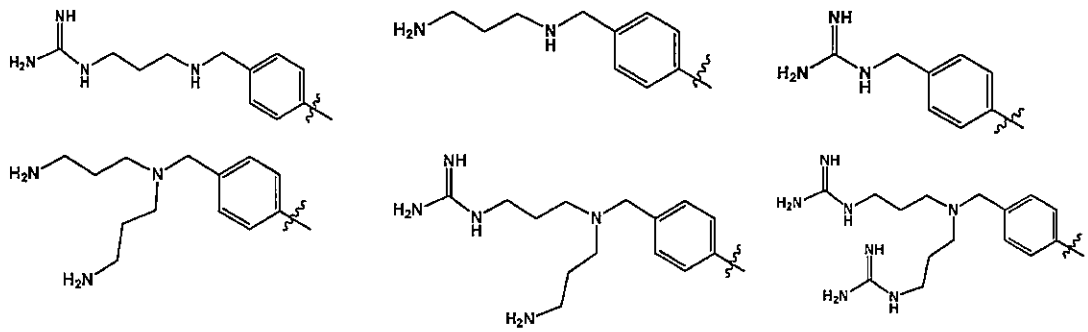
alternatively, B is a single bond;

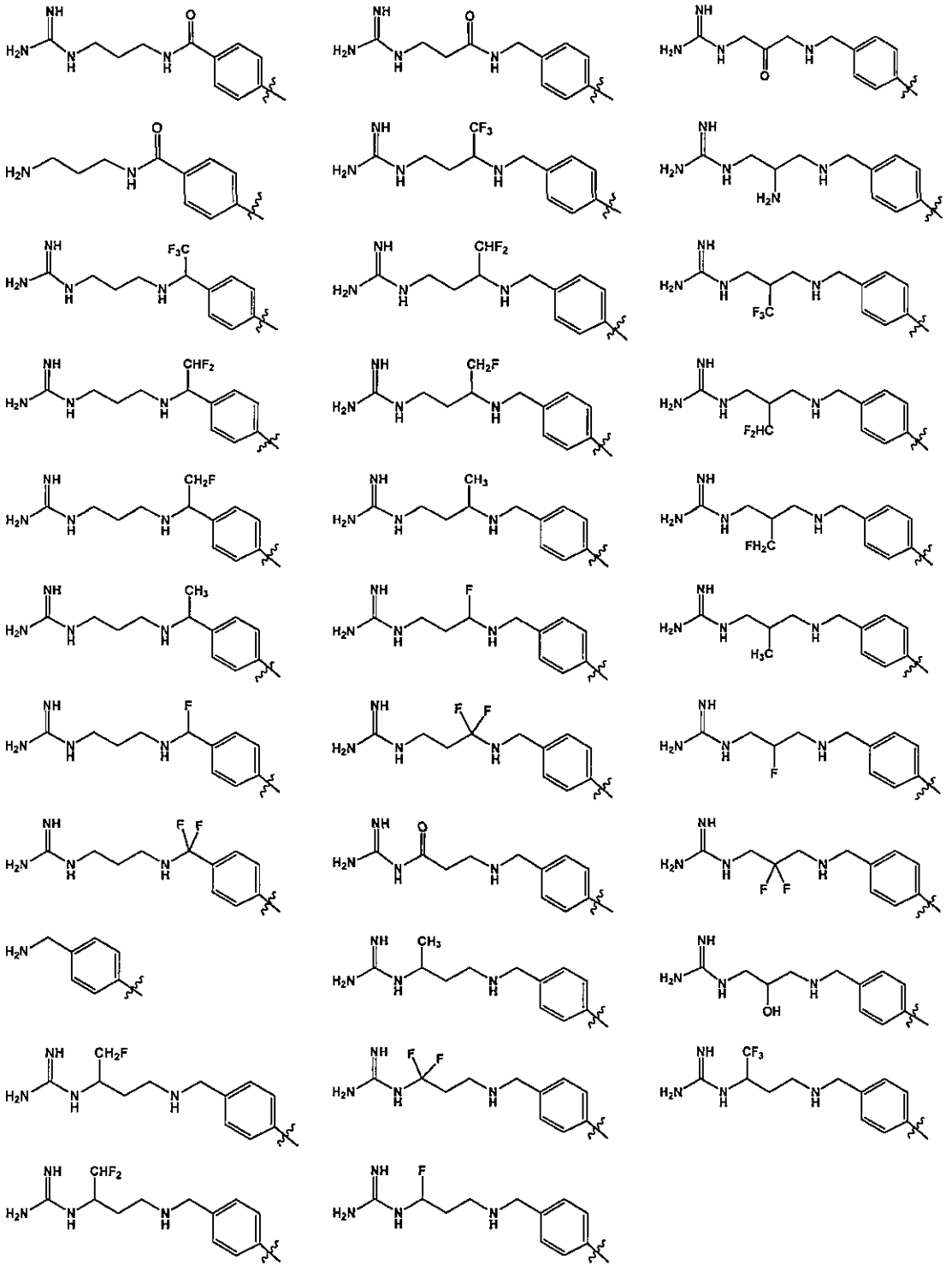
C is selected from (a) NH_2, (b) $-NHC(=NH)NH_2$ and (c) hydrogen;

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

6. The compound according to Claim 5, wherein C–B–A– is selected from the group consisting of:

hydrogen,





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

7. The compound according to Claim 3, wherein G is selected from

(a) a 3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and

(b) a 3–14 member saturated, unsaturated, or aromatic carbocycle,

(c) a single bond;

wherein (a) or (b) is optionally substituted with one or more R^5 groups, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

8. The compound according to Claim 4, wherein R^5 is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) $-NO_2$, (j) $-NH_2$, (k) $-OR^6$, (l) $-NHC(=NH)NH_2$, (m) $-C_{1-8}$ alkyl, (n) $-C_{1-8}$ alkenyl, (o) $-C_{1-8}$ alkynyl, (p) $-(C_{1-8}$ alkyl) –(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (q) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (r) –haloalkyl, (s) $-SR^6$, (t) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and (u) –3–14 member saturated, unsaturated, or aromatic carbocycle; alternatively, two R^5 groups are taken together to form a carbocycle; or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

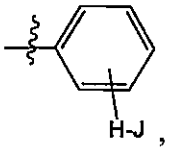
9. The compound according to Claim 4, wherein R^6 is selected from (a) hydrogen, (b) $-C_{1-8}$ alkyl or alternatively two R^6 groups are taken together to form a carbocycle, (c) –haloalkyl, (d) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and (e) –3–14 member saturated, unsaturated, or aromatic carbocycle; or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

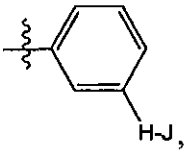
10. The compound according to Claim 7, wherein G is selected from azepanyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl, pyridyl, cyclohexenyl, cyclohexadienyl, dihydropyridyl, furanyl, tetrahydrofuranyl, tetrahydropyridyl, azetidinyl, pyrrolidinyl,

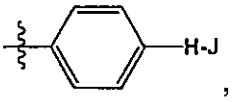
piperidinyl, piperidenyl, and a single bond; or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

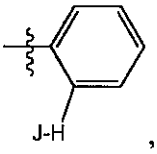
11. The compound according to Claim 10, wherein –G–H–J is selected from:

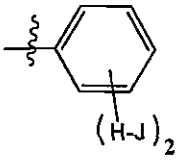
hydrogen,

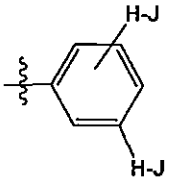


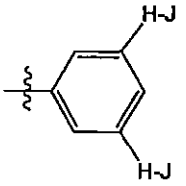
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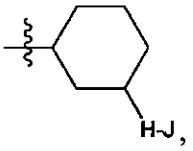
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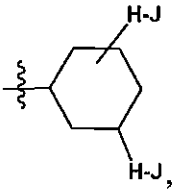
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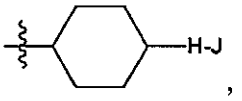
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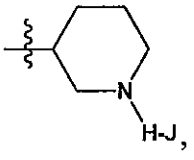


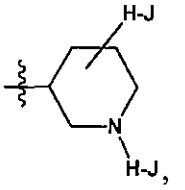


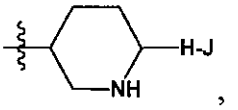


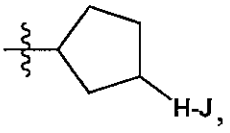
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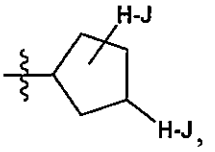
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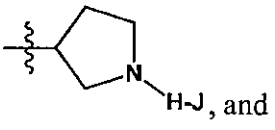
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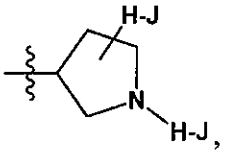
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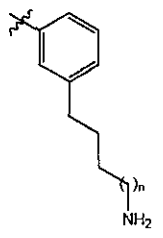
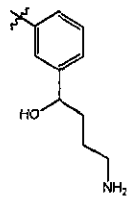
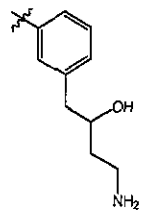
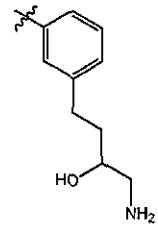
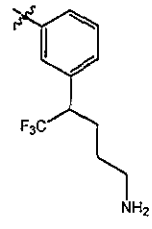
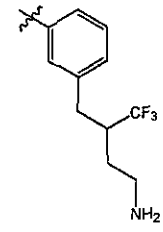
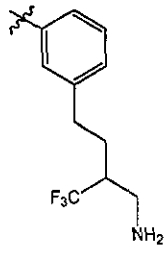
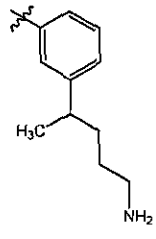
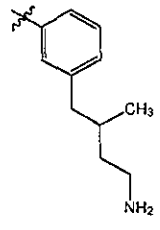
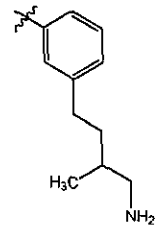
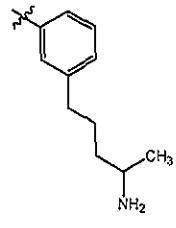
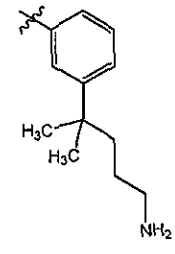
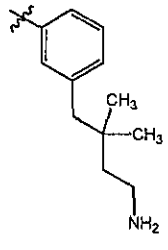
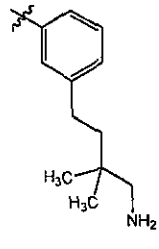
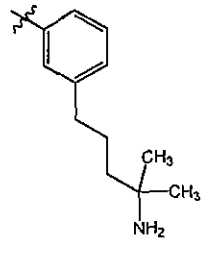
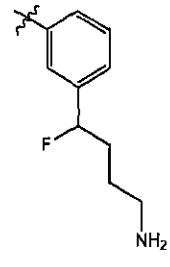
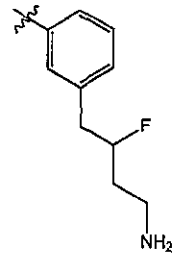
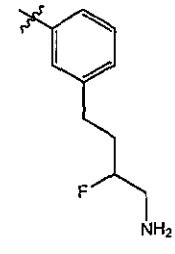
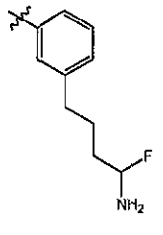
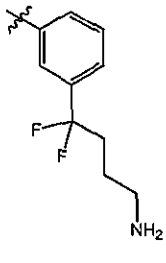
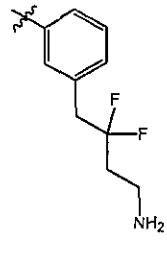
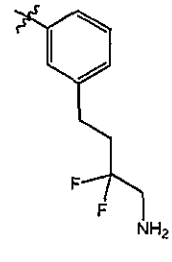
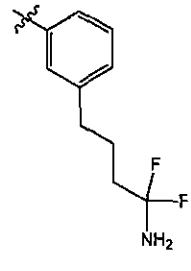
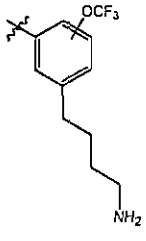
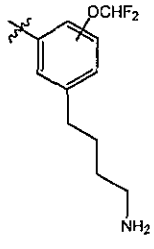
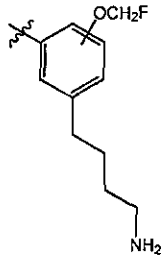
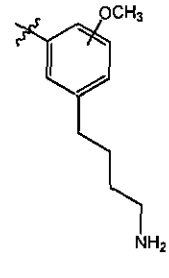
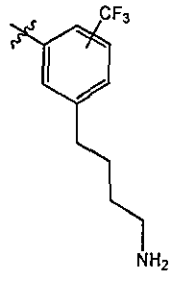
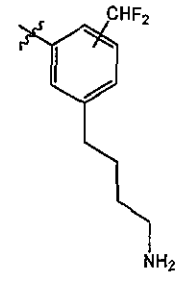
, and


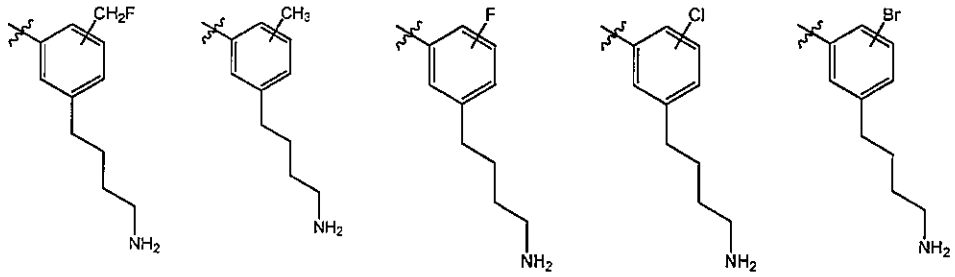
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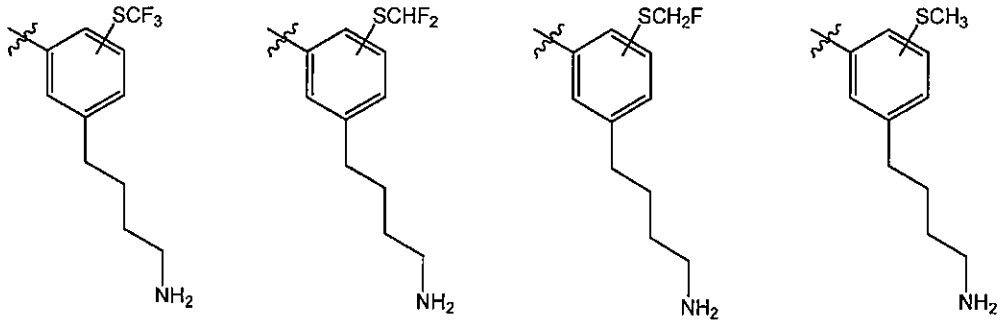
or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

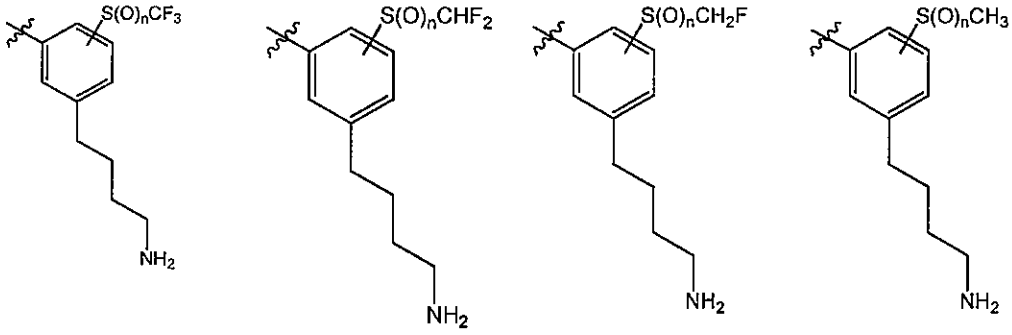
12. The compound according to Claim 11, wherein each –G–H–J is selected from:

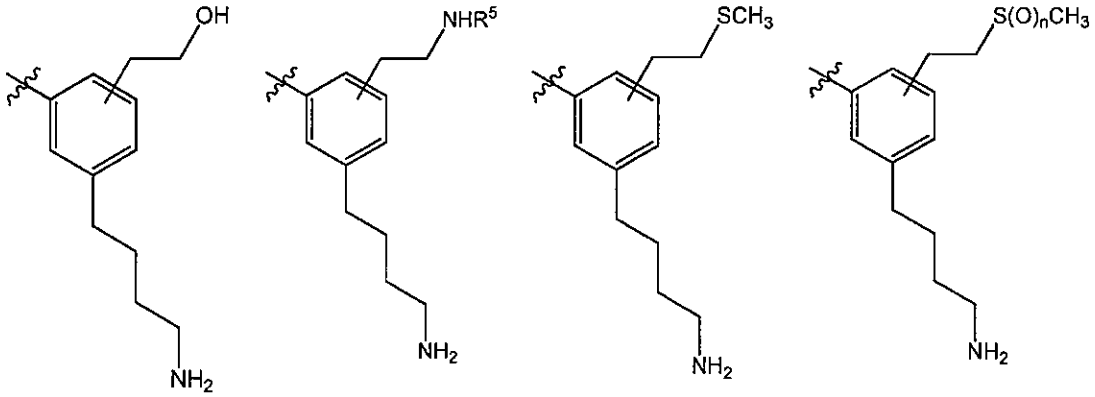
hydrogen,

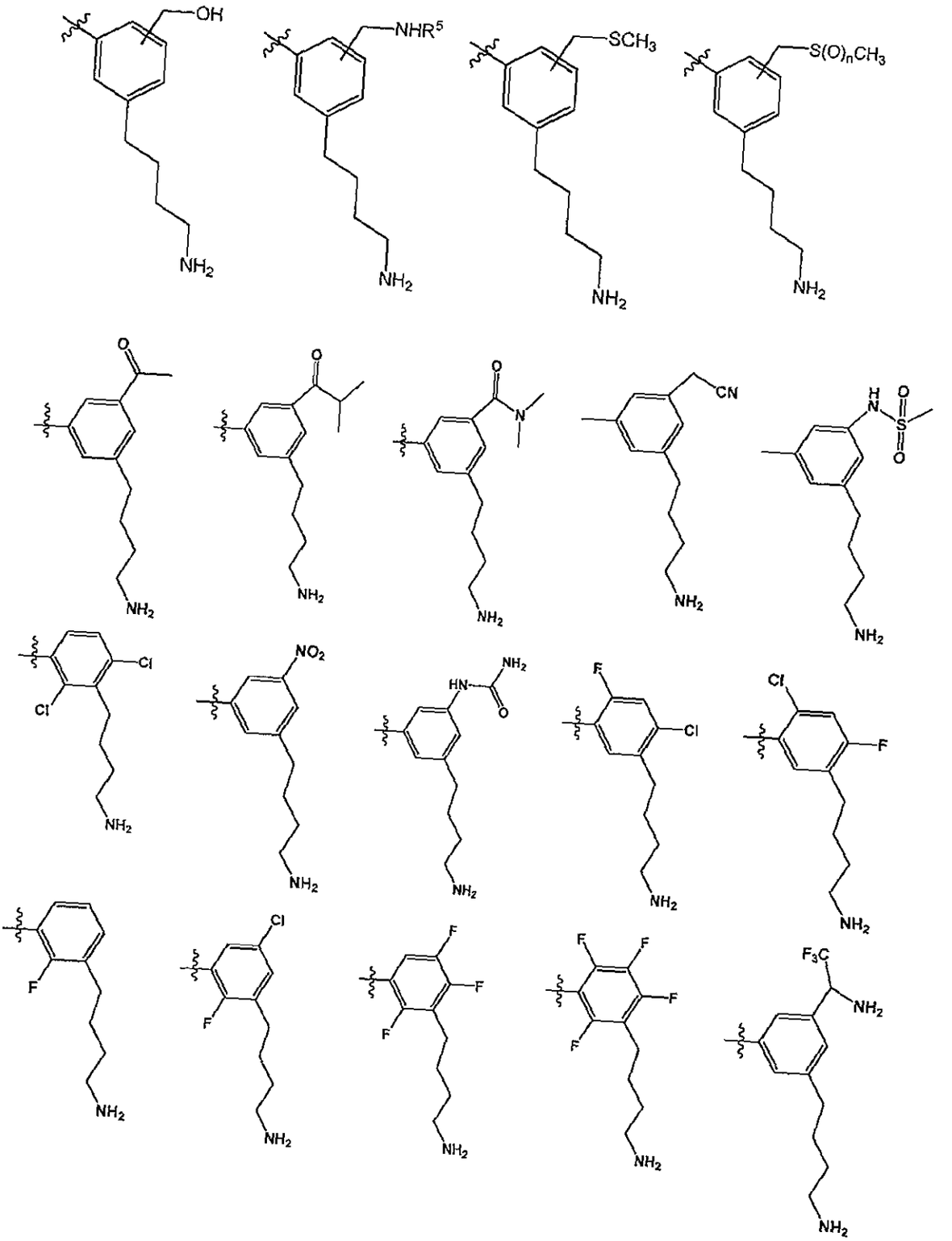






























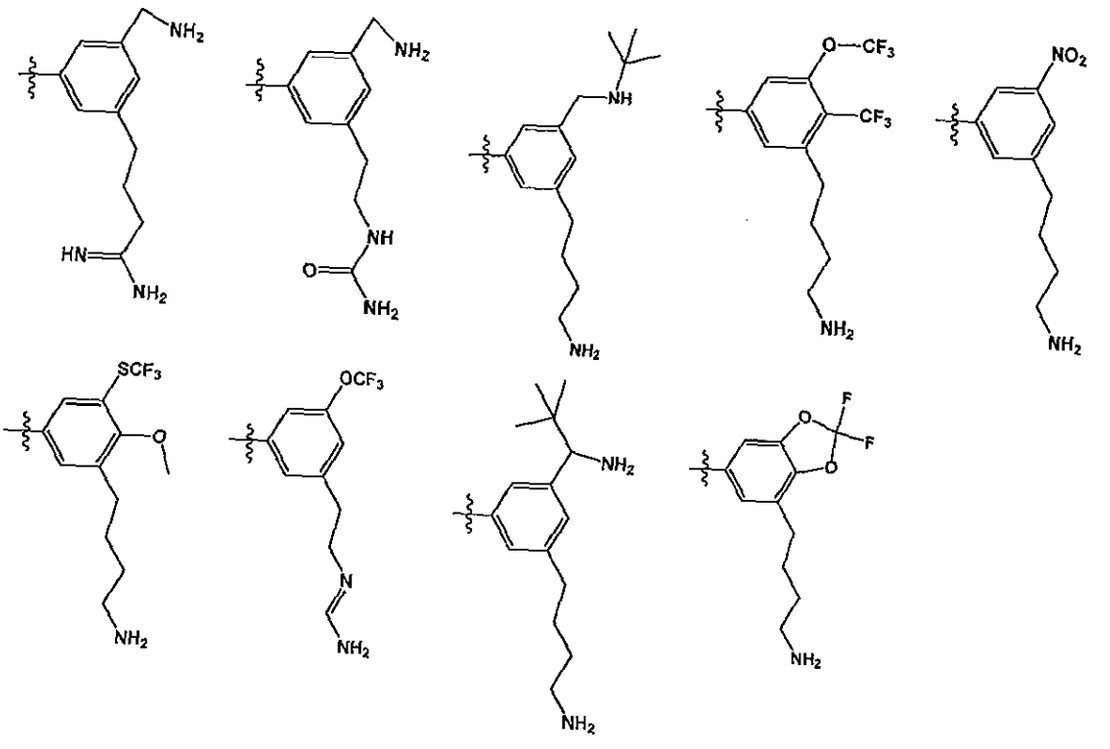

CH2F
NH2
CH3
NH2
F
NH2
Cl
NH2
Br
NH2

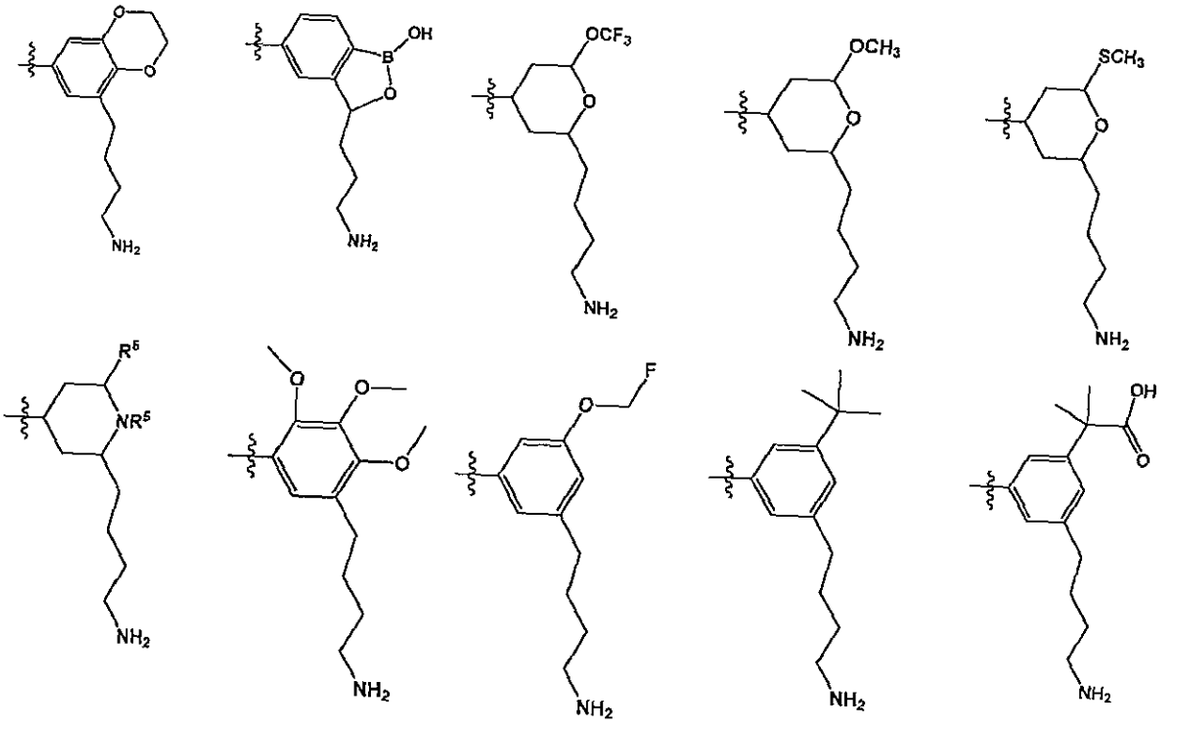

SCF3
NH2
SCHF2
NH2
SCH2F
NH2
SCH3
NH2

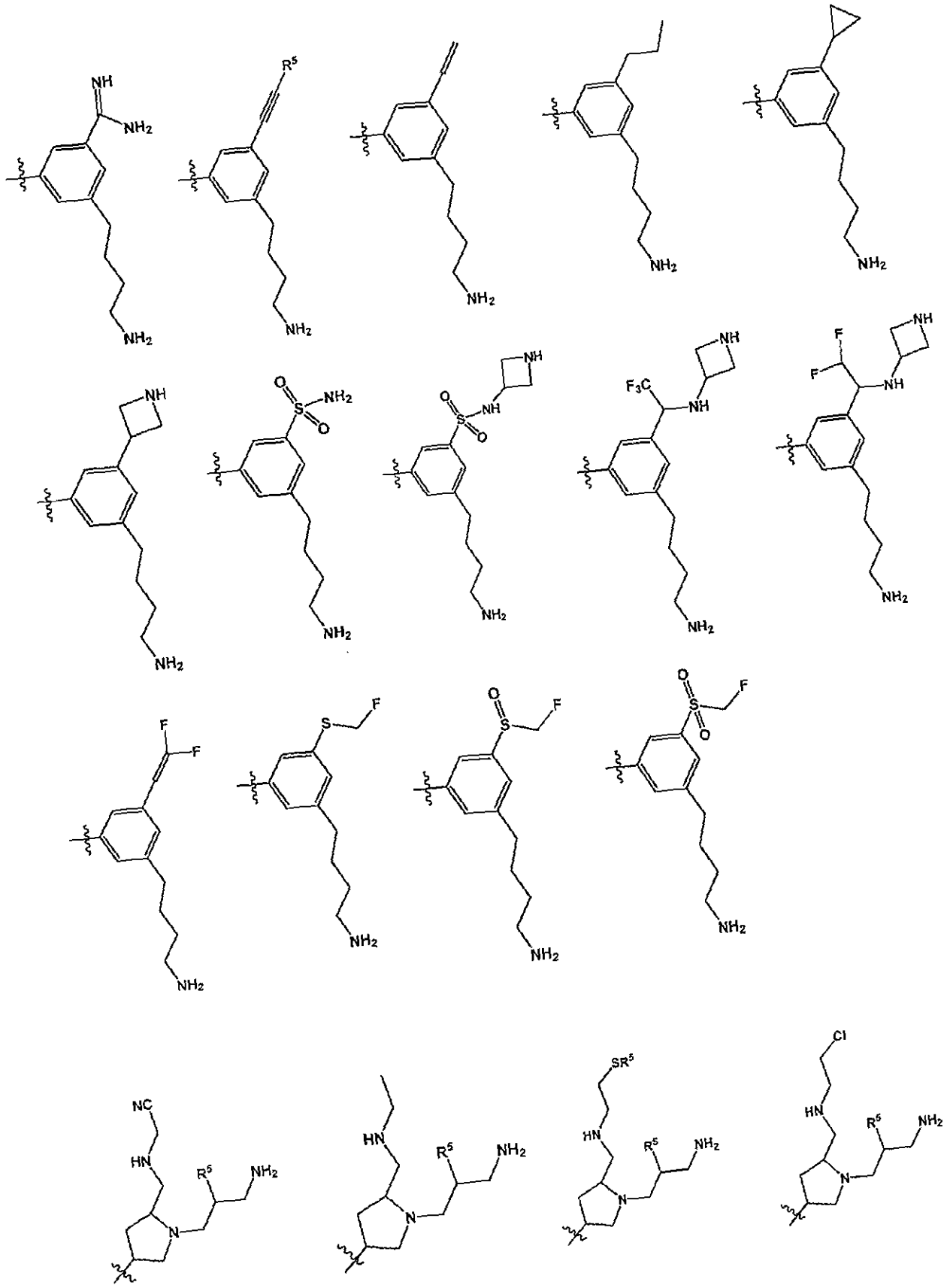

S(O)nCF3
NH2
S(O)nCHF2
NH2
S(O)nCH2F
NH2
S(O)nCH3
NH2

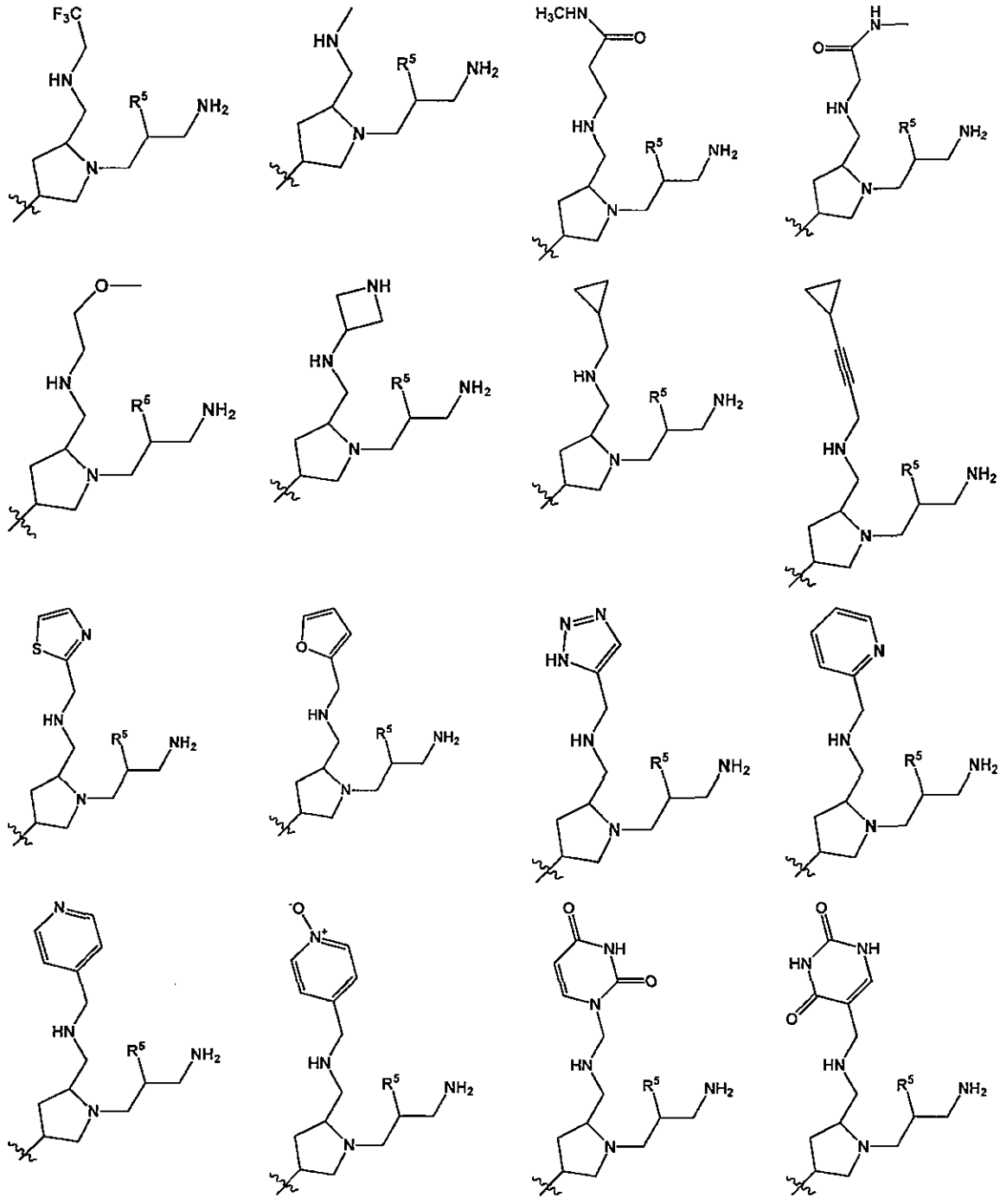

OH
NH2
NHR5
NH2
SCH3
NH2
S(O)nCH3
NH2


OH
NHR5
SCH3
S(O)nCH3
NH2
O
N
CN
H
S
Cl
NO2
HN
F
CF3









, wherein n is 0, 1, or 2,

further wherein R^5 is as defined in Claim 8,

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

13. The compound according to any of claims 1 to 12 that binds to a ribosome.

14. The compound according to claim 13, wherein the ribosome is a bacterial ribosome.

15. The compound according to any of the compounds in Table 1 or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

16. The pharmaceutical composition comprising a compound according to any one of claims 1–15, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, and a pharmaceutically acceptable carrier.

17. A method for treating, preventing, or reducing the risk of a disease state in a human or animal comprising administering to a human or animal in need thereof an effective amount of a compound according to any one of claims 1–15, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

18. A method of treating a microbial infection in a human or animal comprising administering to the human or animal an effective amount of a compound according to any one of claims 1–15, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

19. The use of a compound according to any one of claims 1–15, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, in the manufacture of a medicament for treating a microbial infection in a human or animal.

20. A method of treating, preventing, or reducing the risk of a microbial infection in a human or animal comprising administering to the human or animal an effective amount of a compound according to any one of claims 1–15, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, wherein the microbial infection is selected from the group consisting of:

a skin infection, a Gram positive infection, a Gram negative infection, nosocomial pneumonia, community acquired pneumonia, post–viral pneumonia, hospital acquired pneumonia/ventilator associated pneumonia, a respiratory tract infection such as

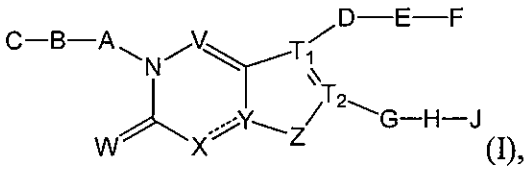
chronic respiratory tract infection (CRTI), acute pelvic infection, a complicated skin and skin structure infection, a skin and soft tissue infection (SSTI) including uncomplicated skin and soft tissue infections (uSSTI)s and complicated skin and soft tissue infections, an abdominal infection, a complicated intra-abdominal infection, a urinary tract infection, bacteremia, septicemia, endocarditis, an atrio–ventricular shunt infection, a vascular access infection, meningitis, surgical prophylaxis, a peritoneal infection, a bone infection, a joint infection, a methicillin–resistant *Staphylococcus aureus* infection, a vancomycin–resistant *Enterococci* infection, a linezolid–resistant organism infection, a Bacillus anthracis infection, a Francisella tularensis infection, a Yersinia pestis infection, and tuberculosis.

21. The method or use according to any one of claims 17–20 wherein the compound, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof, is administered otically, ophthalmically, nasally, orally, parenterally, topically, or intravenously.

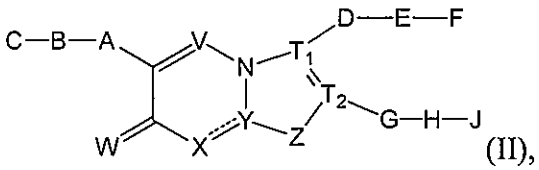
22. A method of synthesizing a compound according to any of claims 1–15, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

23. A stent containing a compound according to any one of claims 1-15, or a pharmaceutically acceptable salt, ester, tautomer, or prodrug thereof.

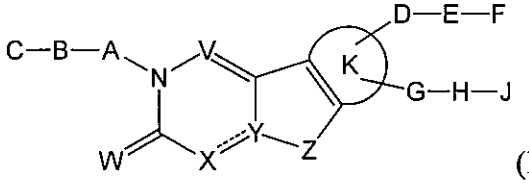
24. A compound having the formula:



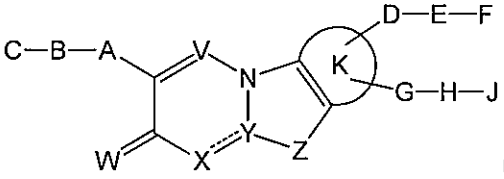
(I),



(II),



(III), or



(IV),

wherein Ⓚ represents a fused 5 to 7 member saturated, unsaturated, or aromatic carbocyclic or heterocyclic ring system,

wherein T^1 is a carbon atom or N, such that when T^1 is N, –D–E–F is absent,

wherein T^2 is a carbon atom or N, such that when T^2 is N, –G–H–J is absent,

wherein both T^1 and T^2 are not both simultaneously N,

wherein V is independently selected from $–CR^{4a}–$ or –N–,

W is O, NR^1, NOR^1, or S, alternatively W= is selected from the combination of HO– and H– both attached to the same carbon atom or the combination of (C_{1-8} alkyl)O– and H– both attached to the same carbon atom;

X– – –Y represents a single bond or a double bond such that when X– – –Y is a single bond, X is selected from O, NR^2, and $S(O)_n$ and Y is $C–R^3$, and when X– – –Y is a double bond, X is N and Y is a carbon atom,

Z is selected from the group consisting of O, NR^4, $S(O)_n$, or NH,

R^1 is selected from H and C_{1-8} alkyl,

R^2 is selected from H and C_{1-8} alkyl,

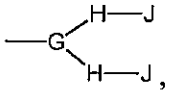
R^3 is selected from H and C_{1-8} alkyl,

R^4 is selected from H and C_{1-8} alkyl,

R^{4a} is selected from H and C_{1-8} alkyl,

n is 0, 1, or 2,

alternatively –G–H–J is selected from



wherein each H and J are independently selected,

C–B–A–, –D–E–F, and –G–H–J are chemical moieties, wherein

A, D and G are independently selected from the group consisting of:

(a) a single bond, (b) –(C_{1-8} alkyl)– , (c) –(C_{2-8} alkenyl)–, (d) –(C_{2-8} alkynyl)–, wherein

i) 0–4 carbon atoms in any of (b)–(d) immediately above optionally is replaced by a moiety selected from the group consisting of –O–, $–S(O)_p–$, $–NR^6–$, –(C=O)–, $–S(O)_pNR^6–$, $–NR^6S(O)_p–$, and $–NR^6S(O)_pNR^6–$,

ii) any of (b)–(d) immediately above optionally is substituted with one or more R^5 groups, and

iii) any of (b)–(d) immediately above optionally is substituted with –(C_{1-8} alkyl)–R^5 groups;

(e) –O–, (f) –NR^6–, (g) –$S(O)_p$–, (h) –C(O)–, (i) –C(O)O–, (j) –OC(O)–, k) –OC(O)O–, (l) –C(O)NR^6–, (m) –NR^6CO–, (n) –NR^6C(O)NR^6–, (o) –C(=NR^6)–, (p) –C(=NR^6)O–, (q) –OC(=NR^6)–, (r) –C(=NR^6)NR^6–, (s) –NR^6C(=NR^6)–, (t) –C(=S)–, (u) –C(=S)NR^6–, (v) –NR^6C(=S)–, (w) –C(O)S–, (x) –SC(O)–, (y) –OC(=S)–, (z) –C(=S)O–, (aa) –NR^6(CNR^6)NR^6–, (bb) –CR^6R^6C(O)–, (cc) –C(O)NR^6(CR^6R^6)$_t$–, (dd) a 3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (ee) a 3–14 member saturated, unsaturated, or aromatic carbocycle, and (ff) –(CR^6R^6)$_t$–,

wherein (dd) or (ee) is optionally substituted with one or more R^5 groups;

B, E, and H are independently selected from the group consisting of:

(a) a single bond,

(b) a 3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

(c) a 3–14 member saturated, unsaturated, or aromatic carbocycle,

wherein (b) or (c) is optionally substituted with one or more R^5 groups;

(d) –(C_{1-8} alkyl)–, (e) –(C_{2-8} alkenyl)–, (f) –(C_{2-8} alkynyl)–, wherein

i) 0–4 carbon atoms in any of (d)–(f) immediately above optionally is replaced by a moiety selected from the group consisting of –O–, –$S(O)_p$–, –NR^6–, –(C=O)–, –C(=NR^6)–, –$S(O)_p$$NR^6$–, –$NR^6$$S(O)_p$–, and –$NR^6$$S(O)_p$$NR^6$–,

ii) any of (d)–(f) immediately above optionally is substituted with one or more R^5 groups, and

iii) any of (d)–(f) immediately above optionally is substituted with –(C_{1-8} alkyl)–R^5 groups;

and (g) –(CR^6R^6)$_t$–,

C, F, and J are independently selected from the group consisting of:

(a) hydrogen, (c) F, (d) Cl, (e) Br, (f) I, (g) $-CF_3$, (h) –CN, (i) $-N_3$ (j) $-NO_2$, (k) – $NR^6(CR^6R^6)_tR^8$, (l) $-OR^8$, (m) $-S(O)_p(CR^6R^6)_tR^8$, (n) $-C(O)(CR^6R^6)_tR^8$, (o) – $OC(O)(CR^6R^6)_tR^8$, (p) $-SC(O)(CR^6R^6)_tR^8$, (q) $-C(O)O(CR^6R^6)_tR^8$, (r) – $NR^6C(O)(CR^6R^6)_tR^8$, (s) $-C(O)NR^6(CR^6R^6)_tR^8$, (t) $-C(=NR^6)(CR^6R^6)_tR^8$, (u) – $C(=NNR^6R^6)(CR^6R^6)_tR^8$, (v) $-C(=NNR^6C(O)R^6)(CR^6R^6)_tR^8$, (w) – $C(=NOR^8)(CR^6R^6)_tR^8$, (x) $-NR^6C(O)O(CR^6R^6)_tR^8$, (y) $-OC(O)NR^6(CR^6R^6)_tR^8$, (z) – $NR^6C(O)NR^6(CR^6R^6)_tR^8$, (aa) $-NR^6S(O)_p(CR^6R^6)_tR^8$, (bb) $-S(O)_pNR^6(CR^6R^6)_tR^8$, (cc) $-NR^6S(O)_pNR^6(CR^6R^6)_tR^8$, (dd) $-NR^6R^8$, (ee) $-NR^6(CR^6R^6)R^8$, (ff) –OH, (gg) – NR^8R^8, (hh) $-OCH_3$, (ii) $-S(O)_pR^8$, (jj) $-NC(O)R^8$, (kk) $-NR^6C(NR^6)NR^6R^8$, (ll) a C_{1-8} alkyl group, (mm) a C_{2-8} alkenyl group, (nn) a C_{2-8}alkynyl group, (oo) a 3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (pp) a 3–14 member saturated, unsaturated, or aromatic carbocycle, (qq) – $(CR^6R^6)_tNR^6(CR^6R^6)_tR^8$, (rr) $-N[(CR^6R^6)_tR^8][C=O(CR^6R^6)_tR^8]$, (ss) – $(CR^6R^6)_tN[(CR^6R^6)_tR^8][(CR^6R^6)_tR^8]$, (tt) $-(CR^6R^6)_tNR^6(C=O)(CR^6R^6)_tR^8$, (uu) – haloalkyl, (vv) $-C(O)(CR^6)[(CR^6R^6)_tR^8]R^8$, (ww) $-(CR^6R^6)_tC(O)NR^8R^8$, (xx) – $(CR^6R^6)_tC(O)O(CR^6R^6)_tR^8$, (yy) $-NR^6C(O)CR^8R^8R^8$, (zz) $-N[(CR^6R^6)_tR^8]C(O)R^8$, and (aaa) $-S(O)_pNR^8R^8$;

wherein (ll) through (pp) is optionally substituted with one or more R^7 groups;

R^5 is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) – NO_2, (j) $-NR^6R^6$, (k) $-OR^8$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C_{1-8}$ alkyl, (n) $-C_{1-8}$ alkenyl, (o) – C_{1-8} alkynyl, (p) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (q) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (r) –haloalkyl, (s) $-SR^6$, (t) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and (u) –3–14 member saturated, unsaturated, or aromatic carbocycle;

alternatively, two R^5 groups are taken together to form a carbocycle;

wherein (m) through (r) and (t) through (u) is optionally substituted with one or more R^8;

R^6 is selected from (a) hydrogen, (b) $-C_{1-8}$ alkyl or alternatively two R^6 groups are taken together to form a carbocycle, (c) –haloalkyl, (d) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and (e) –3–14 member saturated, unsaturated, or aromatic carbocycle;
wherein (b) through (e) is optionally substituted with one or more R^8;

R^7 is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) $-NO_2$, (j) $-NR^6R^6$, (k) $-OR^6$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C_{1-8}$ alkyl, (n) $-C_{1-8}$ alkenyl, (o) $-C_{1-8}$ alkynyl, (p) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (q) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (r) –haloalkyl, (s) $-NR^6R^8$, (t) $-OR^8$, (u) $-(CR^6R^6)_tNR^6R^8$, (v) $-CR^6R^8R^8$, (w) $-SR^6$, (x) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (y) –3–14 member saturated, unsaturated, or aromatic carbocycle, (z) $-(CR^6R^6)_tC(O)NR^8R^8$, (aa) $-S(O)_pR^8$, (bb) $-NR^6C(O)NR^6R^6$, (cc) $-NR^6C(O)R^6$, and (dd) $-C(=NR^6)NR^6R^6$;
wherein (m) through (q) and (x) through (y) are optionally substituted with one or more R^9;

R^8 is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) –CN, (h) $-N_3$ (i) $-NO_2$, (j) $-NR^6R^9$, (k) $-OR^9$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C_{1-8}$ alkyl, (n) $-C_{1-8}$ alkenyl, (o) $-C_{1-8}$ alkynyl, (p) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (q) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (r) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (s) –3–14 member saturated, unsaturated, or aromatic carbocycle, (t) –haloalkyl, (u) $-C(O)(CR^6R^6)_tR^9$, (v) $-SR^6$, (w) $-OC(O)(CR^6R^6)_tR^9$, (x) $-NR^6C(O)NR^6R^9$, (y)$-NR^6C(O)R^9$, (z) –

$NR^6(CNR^9)(NR^6R^6)$, (aa) $-ONR^6(CNR^6)NR^6R^6$, (bb) $-C(=NR^9)NR^6R^6$, (cc) $-S(O)_pR^9$, (dd) $-(CR^6R^6)_tC(O)NR^6R^9$, (ee) $-(CR^6R^6)_tOR^9$, and (ff) $-(CR^6R^6)_tNR^6R^9$;

wherein (m) through (s) is optionally substituted with one or more R^9;

R^9 is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) $-CN$, (h) $-N_3$ (i) $-NO_2$, (j) $-NR^6R^{10}$, (k) $-OR^6$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C(O)(CR^6R^6)_tNR^6R^6$, (n) $-C_{1-8}$ alkyl, (o) $-C_{1-8}$ alkenyl, (p) $-C_{1-8}$ alkynyl, (q) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (r) –3–14 member saturated, unsaturated, or aromatic carbocycle, (s) –haloalkyl, (t) $-(CR^6R^6)_tOR^6$, (u) $-O(CR^6R^6)_tNR^6R^{10}$, (v) $-C(O)R^6$, (w) $-SR^6$, (x) $-C(O)OR^{10}$, (y) $-S(O)_pR^6$, (z) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (aa) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (bb) $-O(CR^6R^6)_tOR^6$, (cc) $-C(=NR^6)NR^6R^6$, (dd) $-ONR^6R^6$, (ee) $-NR^6C(O)NR^6R^6$, (ff) $-O(CR^6R^6)_tOR^6$, (gg) $-NR^6C(O)R^6$, and (hh) $-(CR^6R^6)_tNR^6R^{10}$;

wherein (n) through (r) and (z) through (aa) is optionally substituted with one or more R^{10};

R^{10} is selected from (a) hydrogen, (b) F, (c) Cl, (d) Br, (e) I, (f) $-CF_3$, (g) $-CN$, (h) $-N_3$ (i) $-NO_2$, (j) $-NR^6R^6$, (k) $-OR^6$, (l) $-NR^6(CNR^6)NR^6R^6$, (m) $-C(O)(CR^6R^6)_tNR^6R^6$, (n) $-C_{1-8}$ alkyl, (o) $-C_{1-8}$ alkenyl, (p) $-C_{1-8}$ alkynyl, (q) –3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (r) –3–14 member saturated, unsaturated, or aromatic carbocycle, (s) –haloalkyl, (t) $-(CR^6R^6)_tOR^6$, (u) $-O(CR^6R^6)_tNR^6R^6$, (v) $-C(O)R^6$, (w) $-SR^6$, (x) $-C(O)OR^6$, (y) $-S(O)_pR^6$, (z) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), (aa) $-(C_{1-8}$ alkyl)–(3–14 member saturated, unsaturated, or aromatic carbocycle), (bb) $-O(CR^6R^6)_tOR^6$, (cc) $-C(=NR^6)NR^6R^6$, (dd) $-ONR^6R^6$, (cc) $-NR^6C(O)NR^6R^6$, (ff) $-O(CR^6R^6)_tOR^6$, (gg) $-NR^6C(O)R^6$, and (hh) $-(CR^6R^6)_tNR^6R^6$;

optionally, wherein either the group –D–E–F or the group –G–H–J is absent, but both –D–E–F and –G–H–J are not simultaneously absent;

p is 0, 1, or 2, and

t is 0, 1, 2, or 3,

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