

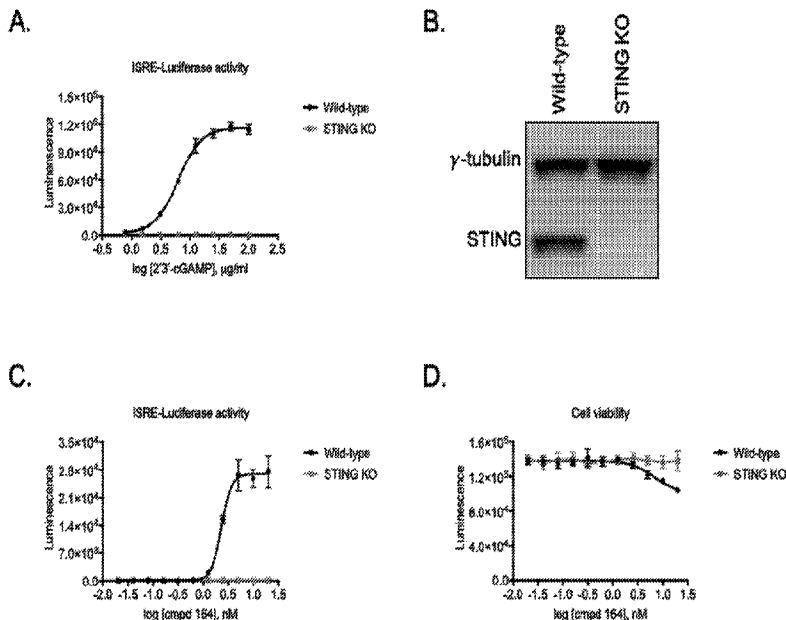


(86) Date de dépôt PCT/PCT Filing Date: 2019/02/21
(87) Date publication PCT/PCT Publication Date: 2019/08/29
(45) Date de délivrance/Issue Date: 2023/02/28
(85) Entrée phase nationale/National Entry: 2020/08/18
(86) N° demande PCT/PCT Application No.: US 2019/018899
(87) N° publication PCT/PCT Publication No.: 2019/165032
(30) Priorité/Priority: 2018/02/21 (US62/633,409)

(51) Cl.Int./Int.Cl. *C07D 403/04* (2006.01),
A61K 31/501 (2006.01), *A61K 31/506* (2006.01),
A61K 31/517 (2006.01), *A61K 31/536* (2006.01),
A61K 31/5365 (2006.01), *A61K 47/68* (2017.01),
A61K 9/127 (2006.01), *A61P 35/00* (2006.01),
C07D 401/14 (2006.01), *C07D 403/14* (2006.01),
C07D 405/14 (2006.01), ...

(72) Inventeurs/Inventors:
LAIRSON, LUKE L., US;
CHIN, EMILY N., US;
CHATTERJEE, ARNAB, US;
KUMAR, MANOJ, US;
...

(54) Titre : COMPOSES DE 6(1H-IMIDAZOLYL)PYRIDAZINE COMME AGONISTES DE GENES DE STIMULATION D'INTERFERON (STING)
(54) Title: 6(1H-IMIDAZOLYL)PYRIDAZINE COMPOUNDS AS AGONISTS OF STIMULATOR OF INTERFERON GENES STING



(57) Abrégé/Abstract:

The invention provides compounds having STimulator of Interferon Genes (STING) agonistic bioactivity that can be used in the treatment of tumors in patients afflicted therewith. The compounds are of formula (I): as defined herein. Compounds for practice of

(51) Cl.Int./Int.Cl. (suite/continued) *C07D 413/14* (2006.01), *C07D 471/04* (2006.01), *C07D 498/04* (2006.01)

(72) **Inventeurs(suite)/Inventors(continued)**: ALBERO, ANA MARIA GAMO, US; PETRASSI, MIKE, US; SCHULTZ, PETER, US; YU, CHENGUANG, US; TAMIYA, JUNKO, US; VERNIER, WILLIAM, US; GUPTA, ANIL, US; MODUKURI, RAMKUMAR, US

(73) **Propriétaires(suite)/Owners(continued)**: THE SCRIPPS RESEARCH INSTITUTE, US

(74) **Agent**: BERESKIN & PARR LLP/S.E.N.C.R.L., S.R.L.

(57) **Abrégé(suite)/Abstract(continued)**:

a method of the invention can be delivered via oral delivery for systemic exposure, as well as delivered intratumorally. Antitumor therapy using a compound of formula (I) can further comprise administration of an effective dose of an immune-checkpoint targeting drug.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

29 August 2019 (29.08.2019)



(10) International Publication Number

WO 2019/165032 A1

(51) International Patent Classification:

A61K 31/497 (2006.01) C07D 403/14 (2006.01)

C07D 403/04 (2006.01)

(21) International Application Number:

PCT/US2019/018899

(22) International Filing Date:

21 February 2019 (21.02.2019)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/633,409 21 February 2018 (21.02.2018) US

(71) Applicant: THE SCRIPPS RESEARCH INSTITUTE

[US/US]; 10550 North Torrey Pines Road, La Jolla, CA 92037 (US).

(72) Inventors: LAIRSON, Luke, L.;

2670 Curlew Street, San Diego, CA 92103 (US). CHIN, Emily, N.; 206 Park Blvd., Unit 504, San Diego, CA 92101 (US). CHATTERJEE, Arnab; 13268 Torrey Crest Court, San Diego, CA

92129 (US). KUMAR, Manoj; 4162 Camino Islay, San Diego, CA 92122 (US). ALBERO, Ana, Maria, Gamo; 10550 North Torrey Pines Road, La Jolla, CA 92037 (US). PETRASSI, Mike; 4695 Serenata Place, San Diego, CA 92130 (US). SCHULTZ, Peter; 1650 La Jolla Rancho Road, La Jolla, CA 92037 (US). YU, Chenguang; 9152 Regents Road, La Jolla, CA 92037 (US). TAMIYA, Junko; 934 Daisy Avenue, Carlsbad, California 92011 (US). VERNIER, William; 1080 Park Hill Place, Vista, California 92081 (US). GUPTA, Anil; 2038 Thomas Avenue, #6, San Diego, California 92109 (US). MODUKURI, Ramkumar; 7710 Main Street, #2013, Houston Texas 77030 (US).

(74) Agent: FITTING, Thomas et al.; The Scripps Research Institute, 10550 North Torrey Pines Road, Mail Drop TPC-8, La Jolla, CA 92037 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,

(54) Title: AGONISTS OF STIMULATOR OF INTERFERON GENES STING

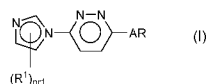
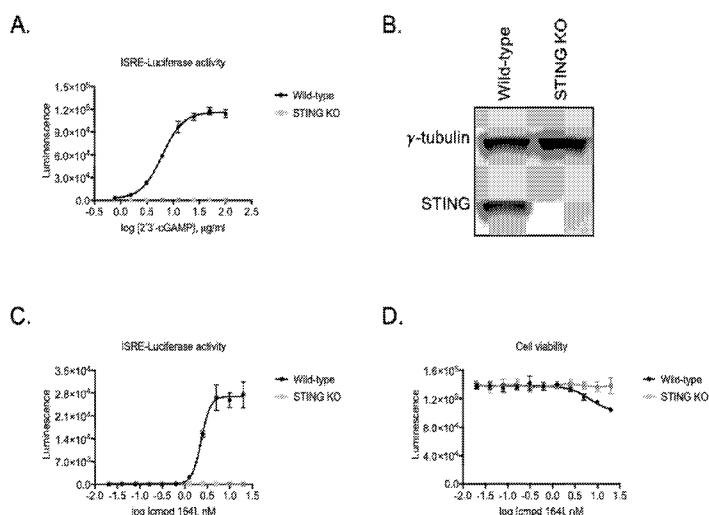


Fig. 1



(57) **Abstract:** The invention provides compounds having STimulator of Interferon Genes (STING) agonistic bioactivity that can be used in the treatment of tumors in patients afflicted therewith. The compounds are of formula (I): as defined herein. Compounds for practice of a method of the invention can be delivered via oral delivery for systemic exposure, as well as delivered intratumorally. Antitumor therapy using a compound of formula (I) can further comprise administration of an effective dose of an immune-checkpoint targeting drug.

[Continued on next page]

WO 2019/165032 A1

HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

6-(1H-IMIDAZOLYL)PYRIDAZINE COMPOUNDS AS AGONISTS OF STIMULATOR OF INTERFERON GENES STING

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the priority of U.S. provisional application Ser. No. 62/633,409, filed Feb. 21, 2018.

BACKGROUND

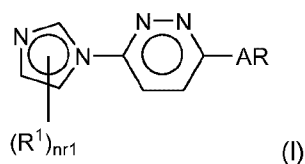
The cGAS-STING signaling pathway plays a critical role in the innate immune response that mammalian host cells mount to eliminate diverse DNA and RNA viruses. STING (Stimulator of Interferon Genes) is an endoplasmic reticulum (ER) resident signaling protein, partially localized to mitochondria-associated membranes, which is broadly expressed in both immune and non-immune cell types. In response to cyclic dinucleotides (CDNs), including 2'-3' cGAMP produced in response to cytosolic DNA by cyclic GMP-AMP synthase (cGAS), STING translocates to the perinuclear region where it rapidly induces type I interferon (IFN) and pro-inflammatory cytokine production in a TBK1-/IRF3-dependent fashion. STING has also been found to directly bind cytosolic DNA, although the physiological relevance of direct DNA sensing activity remains to be fully characterized.

Recent work has demonstrated that STING plays essential roles in immune responses to tumor cells. Efficient tumor-initiated T cell priming within the tumor microenvironment requires interferon-beta (IFN- β) production by resident dendritic cells and the expression of IFN- β has been demonstrated to be dependent upon activation of the STING pathway (1). Indeed, intratumoral delivery of nucleotide-based STING agonists have been demonstrated to induce the profound regression of established tumors in syngeneic mouse models (1). In addition, activation of the STING pathway has also been demonstrated to significantly contribute to the anti-tumor effect of radiation, via IFN- β mediated immune response within the irradiated tumor microenvironment.

SUMMARY

In various embodiments, the invention provides an agonist of the Stimulator of Interferon Genes (STING), which can be used in the treatment of tumors.

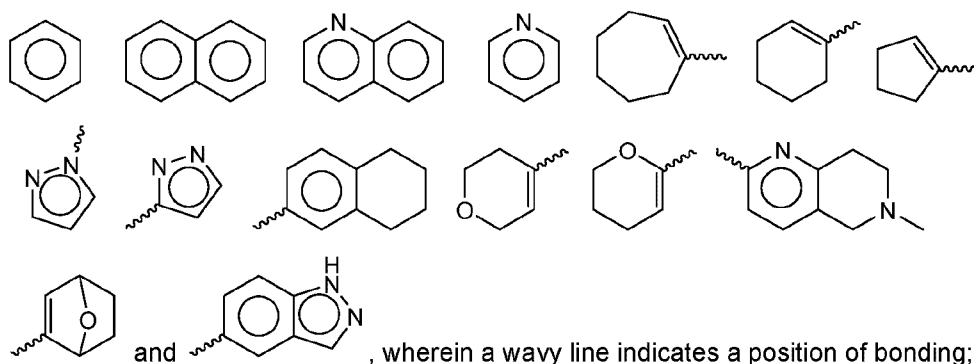
For instance, the invention can provide a method of stimulating expression of interferon genes, comprising administering to a patient an effective dose of an agonist of the Stimulator of Interferon Genes (STING), comprising a compound of formula (I) (below), and a method of treating a tumor in a patient, comprising administering to the patient an effective dose of an agonist of the Stimulator of Interferon Genes (STING), comprising a compound of formula (I)



wherein each R^1 is independently (C1-C4)alkyl, or CN, n_{r1} is 0, 1, 2, or 3, provided that each R^1 is bonded to a carbon atom; and,

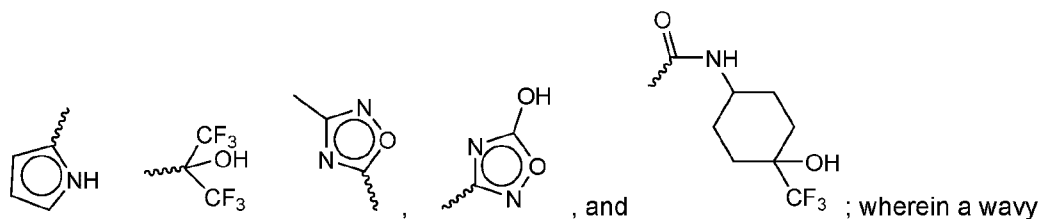
AR is a group of formula $-C(=O)N(R)Ar^1$;

wherein Ar^1 is chosen from the group consisting of:



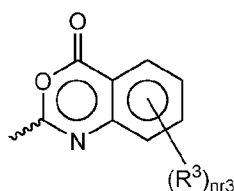
wherein any Ar^1 is substituted with n_{r2} independently selected R^2 groups chosen from the group consisting of :

-(C1-C4)-alkyl, -(C1-C4)-alkylo, -(C1-C4)-alkyloC(O), -CN, -halo, -(C3-C7)cycloalkyl, -(C1-C4)-alkoC(O), -COOH, (C3-C7)-cycloalkyloC(O), -CN, -F, -Cl, -SF₅, -methylenedioxy, -difluoromethylenedioxy, -ethylenedioxy, -CF₃, -OCF₃, -C(O)NH₂, -C(O)NH(CH₂)₂OH, -CH₂OH, -NR₂, -C(/)ONH-arginine, -C(O)O(CH₂)₂NR₂,



or,

AR is a group of formula



wherein R^3 is selected from the group consisting of

(C1-C4)-alkyl, (C1-C4)-alkylo, (C1-C4)-alkyloC(O), CN, halo, (C3-C7)cycloalkyl, (C1-C4)-alkOC(O), COOH, (C3-C7)-cycloalkyloC(O), CN, F, Cl, $-SF_5$, methylenedioxy, difluoromethylenedioxy, ethylenedioxy, CF_3 , $-OCF_3$, $CONH_2$, $CONH(CH_2)_2OH$, CH_2OH , NR_2 , $CONH$ -arginine, and $C(O)O(CH_2)_2NR_2$; and $nr3 = 0, 1, 2$, or 3 ;

or a pharmaceutically acceptable salt thereof.

More specifically, the method can be carried out using a compound of formula (I), wherein $n1$ is 0 ; or $n1$ is 1 or 2 and R^1 is methyl.

More specifically, the method can be carried out using a compound of formula (I), wherein X is a methyl, ethyl, or isopropyl carboxylic ester. Further, the method can be carried out using a compound of formula (I), wherein X is a 1,1,1,3,3,3-hexafluoropropan-2-ol-2-yl group. Further, the method can be carried out using a compound of formula (I), wherein Ar is phenyl. Further, the method can be carried out using a compound of formula (I), Further, the method can be carried out using a compound of formula (I), wherein R^2 is independently selected fluoro, chloro, (C1-C4)alkyl, trifluoromethyl, or cyano, and $n2$ is 1 or 2 ; or two R^2 together form a methylenedioxy group.

Additionally, a method of the invention can be carried out using an effective dose of any one of the specific compounds disclosed in the application; see, for example, Tables 1, 2, and 5.

In various embodiments, the method of treatment of a tumor can further comprise administering an effective dose of the compound of formula (I) or of any of the specific compounds disclosed herein via oral or intratumoral administration, or both.

In various embodiments, the method of treatment of a tumor can further comprise administering an effective dose of the compound of formula (I) or of any of the specific compounds disclosed herein, wherein administering comprises administering the compound to the patient as an antibody-drug conjugate, or in a liposomal formulation.

In various embodiments, the method of treatment of a tumor can further comprise administering an effective dose of the compound of formula (I) or of any of the specific compounds disclosed herein, further comprising administration of an effective dose of an immune-checkpoint targeting drug. For example, the immune-checkpoint targeting drug can be an anti-PD-L1 antibody, anti-PD-1 antibody, anti-CTLA-4 antibody, or an anti-4-1BB antibody.

In various embodiments, the method of treatment of a tumor can further comprise administering an effective dose of the compound of formula (I) or of any of the specific compounds disclosed herein, further comprising administration of ionizing radiation or anticancer drugs.

The invention also can include a novel compound of formula (I) as disclosed and claimed herein.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1:

Wild-type and STING KO THP-1 ISRE-Luciferase reporter cells were treated with increasing doses of 2'3'-cGAMP and reporter activity (luminescence) was assessed 48 h after treatment (A). Lack of STING protein expression was confirmed in STING KO THP-1 cells by western blot with gamma-tubulin used as a protein loading control (B). Wild-type and STING KO THP-1 reporter cells were treated with increasing doses of Compound 164 (Cmpd 164) and reporter activity and cell viability were assessed 24 h after treatment (C-D).

Figure 2:

Wild-type and STING KO THP-1 cells were stimulated with poly(dA:dT), a known activator of both RIG-I and cGAS-dependent signaling cascades, and downstream target gene expression was assessed 48 h later by qPCR (A). Wild-type and STING KO THP-1 cells were stimulated with 2'3'-cGAMP or Cmpd 164 at the indicated doses and activation of type I interferon signaling was assessed by gene expression analysis of *IFNB1* (B) and interferon stimulated genes, *IFIT3* (C) and *CXCL10* (D).

Figure 3:

The c-terminal domain of human STING protein (amino acids 138-379) was incubated with 2'3'-cGAMP [100 μ M] (A) or Cmpd 181 [100 μ M] (B) and 1X fluorescent dye followed by exposure to increasing temperature. The melting temperature (T_m) was calculated using the derivative method and the change in melting temperature (ΔT_m) induced by ligand binding was obtained by normalizing to the appropriate vehicle control (C).

DETAILED DESCRIPTION

There is significant interest in the development of STING pathway agonists for diverse immuno-oncology applications. Most notably, STING pathway agonists have significant potential application as part of combination therapies involving immune-checkpoint targeting drugs, in patients that fail to respond to checkpoint blockade alone.

We have established a robust platform for identifying non-nucleotide small molecule STING agonists. This has been established using a primary assay involving a human THP-1 cell line carrying an IRF-inducible reporter with 5 copies of the IFN signaling response

element. Counter screens, involving alternative reporter constructs, rodent cell-based assays, as well as cGAS and STING knock-out cell lines, are used to eliminate luciferase artifacts and ensure human-rodent cross species reactivity, as well as pathway selectivity. Biochemical assays, involving cGAS enzymatic activity and STING protein binding assays, are used to identify the specific target of identified hits. To date, from an initial screen of ~100,000 compounds we have identified at least one novel highly tractable bona fide STING agonist scaffold Compound 164, Table 1, $EC_{50} \sim 1 \mu M$, Table 1), which induces interferon-stimulated gene signature expression in relevant cell types and type I IFN protein expression in human PBMCs with efficacy that is comparable to that observed for 2'-3' cGAMP. The observed activity of Compound 164, Table 1, in wild-type and cGAS knockout cells, as well as the observed lack of activity in STING knockout cells, provides evidence that this compound series functions by directly acting as STING agonists. Further evidence is provided by STING protein thermal shift data. A preliminary medicinal chemistry effort, involving the design, synthesis, and testing of ~100 analogs within the series, has identified key features of the molecule that are required for activity and has led to the identification of derivatives with ~10-fold improvements in cell-based potency (by for example modulating the substitution pattern on the aniline ring) and ~50-fold improvement in plasma stability (by modulating the size of the substituent of the ester).

"Treating" or "treatment" within the meaning herein refers to an alleviation of symptoms associated with a disorder or disease, or inhibition of further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder, or curing the disease or disorder. Similarly, as used herein, an "effective amount" or a "therapeutically effective amount" of a compound of the invention refers to an amount of the compound that alleviates, in whole or in part, symptoms associated with the disorder or condition, or halts or slows further progression or worsening of those symptoms, or prevents, or provides prophylaxis for, the disorder or condition. In particular, a "therapeutically effective amount" refers to an amount that is effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount is also one in which any toxic or detrimental effects of compounds of the invention are outweighed by the therapeutically beneficial effects.

The expression "effective amount", when used to describe therapy to an individual suffering from a disorder, refers to the quantity or concentration of a compound of the invention that is effective to inhibit or otherwise act on STING in the individual's tissues wherein STING involved in the disorder, wherein such inhibition or other action occurs to an extent sufficient to produce a beneficial therapeutic effect.

The term "pharmaceutically acceptable salts" refers to nontoxic inorganic or organic acid and/or base addition salts.

Standard abbreviations for chemical groups such as are well known in the art are used; e.g., Me = methyl, Et = ethyl, i-Pr = isopropyl, Bu = butyl, t-Bu = tert-butyl, Ph = phenyl, Bn = benzyl, Ac = acetyl, Bz = benzoyl, and the like.

The terms "halo" or "halogen" or "halide" by themselves or as part of another substituent mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom, preferably, fluorine, chlorine, or bromine.

A "haloalkyl" group includes mono-halo alkyl groups, poly-halo alkyl groups wherein all halo atoms can be the same or different, and per-halo alkyl groups, wherein all hydrogen atoms are replaced by the same or differing halogen atoms, such as fluorine and/or chlorine atoms. Examples of haloalkyl include trifluoromethyl, 1,1-dichloroethyl, 1,2-dichloroethyl, 1,3-dibromo-3,3-difluoropropyl, perfluorobutyl, and the like.

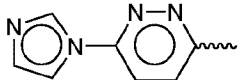
Aryl groups are cyclic aromatic hydrocarbons that do not contain heteroatoms in the ring. An aromatic compound, as is well-known in the art, is a multiply-unsaturated cyclic system that contains $4n+2$ π electrons where n is an integer. Thus aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, indacenyl, fluorenyl, phenanthrenyl, triphenylenyl, pyrenyl, naphthacenyl, chrysenyl, biphenylenyl, anthracenyl, and naphthyl groups. In some embodiments, aryl groups contain about 6 to about 14 carbons in the ring portions of the groups. Aryl groups can be unsubstituted or substituted, as defined above. Representative substituted aryl groups can be mono-substituted or substituted more than once, such as, but not limited to, 2-, 3-, 4-, 5-, or 6-substituted phenyl or 2-8 substituted naphthyl groups, which can be substituted with carbon or non-carbon groups such as those listed above.

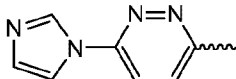
Heterocyclyl groups or the term "heterocyclyl" includes aromatic and non-aromatic ring compounds containing 3 or more ring members, of which one or more ring atom is a heteroatom such as, but not limited to, N, O, and S. Thus a heterocyclyl can be a cycloheteroalkyl, or a heteroaryl, or if polycyclic, any combination thereof. In some embodiments, heterocyclyl groups include 3 to about 20 ring members, whereas other such groups have 3 to about 15 ring members. A heterocyclyl group designated as a C₂-heterocyclyl can be a 5-ring with two carbon atoms and three heteroatoms, a 6-ring with two carbon atoms and four heteroatoms and so forth. Likewise a C₄-heterocyclyl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms. Ring sizes can also be expressed by the total number of atoms in the ring, e.g., a 3- to 10-membered heterocyclyl group, counting both carbon and non-carbon ring atoms. A

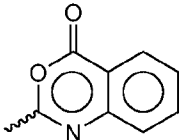
heterocyclyl ring can also include one or more double bonds. A heteroaryl ring is an embodiment of a heterocyclyl group. The term “heterocyclyl group” includes fused ring species including those comprising fused aromatic and non-aromatic groups. For example, a dioxolanyl ring and a benzodioxolanyl ring system (methylenedioxyphenyl ring system) are both heterocyclyl groups within the meaning herein. The term also includes polycyclic, e.g., bicyclo- and tricyclo- ring systems containing one or more heteroatom such as, but not limited to, quinuclidyl. Heterocyclyl groups can be unsubstituted, or can be substituted.

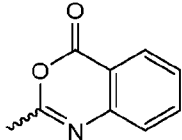
Heteroaryl groups are heterocyclic aromatic ring compounds containing 5 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S; for instance, heteroaryl rings can have 5 to about 8-12 ring members. A heteroaryl group is a variety of a heterocyclyl group that possesses an aromatic electronic structure, which is a multiply-unsaturated cyclic system that contains $4n+2$ π electrons wherein n is an integer. A heteroaryl group designated as a C_2 -heteroaryl can be a 5-ring (i.e., a 5-membered ring) with two carbon atoms and three heteroatoms, a 6-ring (i.e., a 6-membered ring) with two carbon atoms and four heteroatoms and so forth. Likewise a C_4 -heteroaryl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms.

Examples of heteroaryl ring systems described herein include structural unit of

formula , an imidazolyl-pyridazine, which it is understood can also be

portrayed as . Another heteroaryl ring system described here is of

formula , which it is understood can also be portrayed as

. Similarly, other aryl (e.g., phenyl) and heteroaryl (e.g., pyridyl) ring systems described herein can be written either with the explicit double bonds, or with the aryl “circle” nomenclature, but the meanings are the same.

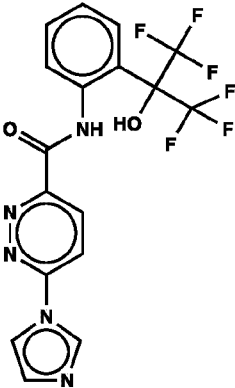
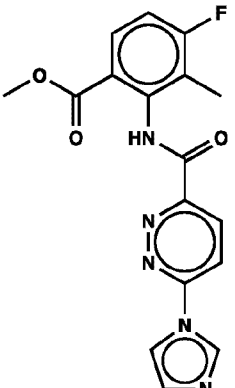
Cycloalkyl groups are groups containing one or more carbocyclic ring including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In some embodiments, the cycloalkyl group can have 3 to about 8-12 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to

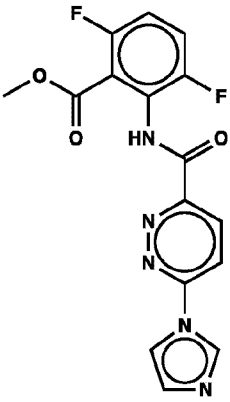
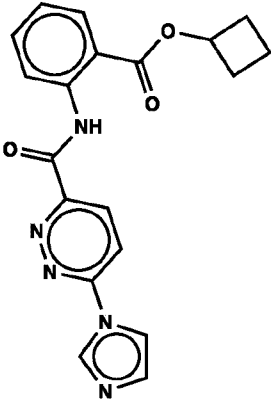
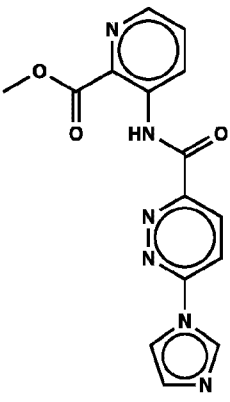
4, 5, 6, or 7. Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalanyl, and the like. Cycloalkyl groups also include rings that are substituted with straight or branched chain alkyl groups as defined above.

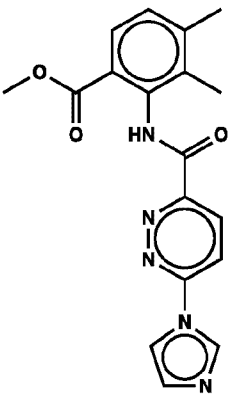
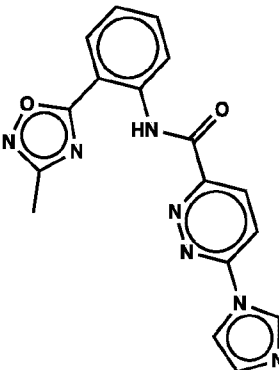
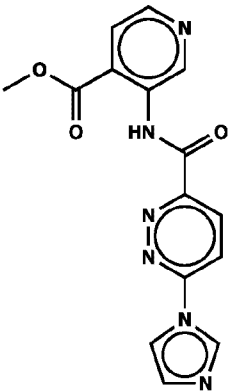
Cycloalkenyl groups include cycloalkyl groups having at least one double bond between 2 carbons. Thus for example, cycloalkenyl groups include but are not limited to cyclohexenyl, cyclopentenyl, and cyclohexadienyl groups. Cycloalkenyl groups can have from 3 to about 8-12 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 5, 6, or 7. Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalanyl, and the like, provided they include at least one double bond within a ring. Cycloalkenyl groups also include rings that are substituted with straight or branched chain alkyl groups as defined above.

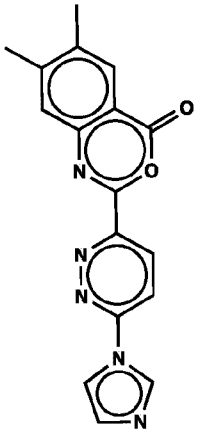
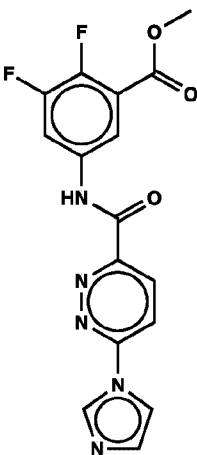
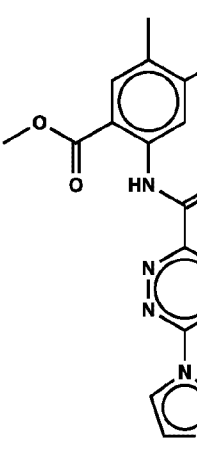
Heterocyclyl groups or the term "heterocyclyl" includes aromatic and non-aromatic ring compounds containing 3 or more ring members, of which one or more ring atom is a heteroatom such as, but not limited to, N, O, and S. Thus a heterocyclyl can be a cycloheteroalkyl, or a heteroaryl, or if polycyclic, any combination thereof. In some embodiments, heterocyclyl groups include 3 to about 20 ring members, whereas other such groups have 3 to about 15 ring members. A heterocyclyl group designated as a C₂-heterocyclyl can be a 5-ring with two carbon atoms and three heteroatoms, a 6-ring with two carbon atoms and four heteroatoms and so forth. Likewise a C₄-heterocyclyl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms. Ring sizes can also be expressed by the total number of atoms in the ring, e.g., a 3- to 10-membered heterocyclyl group, counting both carbon and non-carbon ring atoms. A heterocyclyl ring can also include one or more double bonds. A heteroaryl ring is an embodiment of a heterocyclyl group. The term "heterocyclyl group" includes fused ring species including those comprising fused aromatic and non-aromatic groups. For example, a dioxolanyl ring and a benzodioxolanyl ring system (methylenedioxyphenyl ring system) are both heterocyclyl groups within the meaning herein. The term also includes polycyclic, e.g., bicyclo- and tricyclo- ring systems containing one or more heteroatom such as, but not limited to, quinuclidyl.

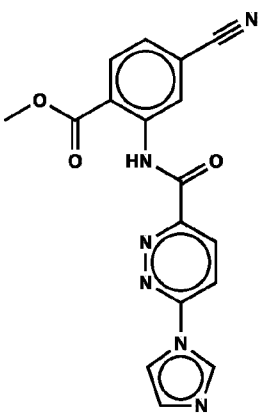
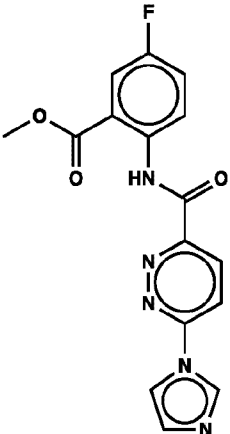
Table 1: Structures, bioactivities, and supporting structural data

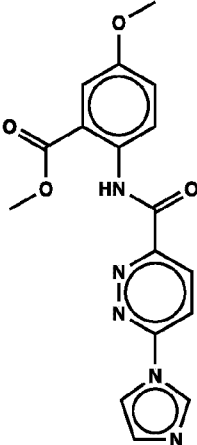
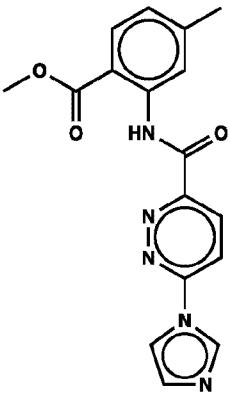
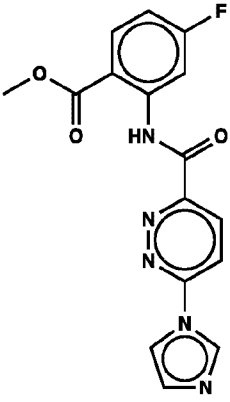
	Structure	ISG-LUC activation assay (EC50) [nM]	ISG-LUC activation assay (EC50) (Comment)	Analytical Data
1		592.8	++++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.24 (s, 1H), 10.40 (s, 1H), 8.87 (s, 1H), 8.70 (d, <i>J</i> = 8.4 Hz, 1H), 8.59 (d, <i>J</i> = 9.2 Hz, 1H), 8.49 (d, <i>J</i> = 9.1 Hz, 1H), 8.23 (s, 1H), 7.75 – 7.48 (m, 2H), 7.39 – 7.28 (m, 2H). MS-ESI: <i>m/z</i> 432.3 observed (M+H) ⁺
2		4686	++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.17 (s, 1H), 9.38 (s, 1H), 8.63 – 8.50 (m, 2H), 8.41 (s, 1H), 7.83 (dd, <i>J</i> = 8.8, 6.2 Hz, 1H), 7.60 (s, 1H), 7.39 – 7.24 (m, 1H), 3.72 (s, 5H), 2.20 (s, 3H). MS-ESI: <i>m/z</i> 356.32 observed (M+H) ⁺

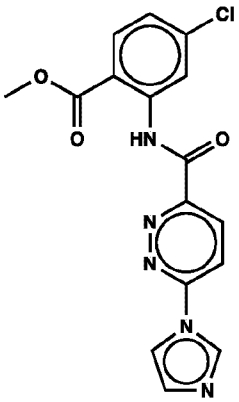
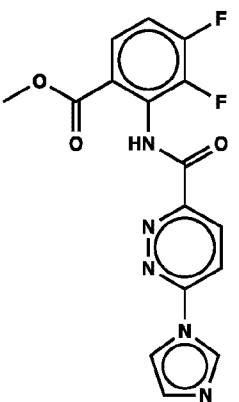
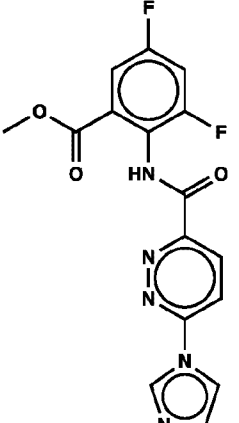
3		10187	++	¹H NMR (400 MHz, DMSO-d₆) δ 11.19 (s, 1H), 9.50 (s, 1H), 8.69 – 8.50 (m, 2H), 8.45 (d, J = 1.7 Hz, 1H), 7.74 – 7.58 (m, 2H), 7.58 – 7.32 (m, 1H), 3.78 (s, 3H). MS-ESI: <i>m/z</i> 360.27 observed (M+H)⁺
4		2067	++	MS-ESI: <i>m/z</i> 364.29 observed (M+H)⁺
5		1243	++	MS-ESI: <i>m/z</i> 325.3 observed (M+H)⁺

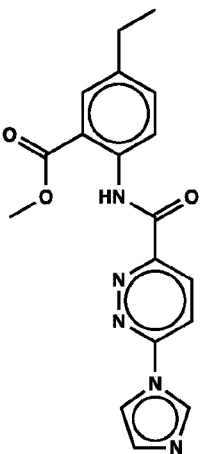
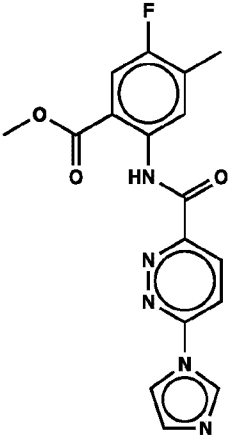
6		~ 2759	++	MS-ESI: <i>m/z</i> 352.3 observed (M+H) ⁺
7		>50000	++	MS-ESI: <i>m/z</i> 348.41 observed (M+H) ⁺
8		2571	++	MS-ESI: <i>m/z</i> 325.36 observed (M+H) ⁺

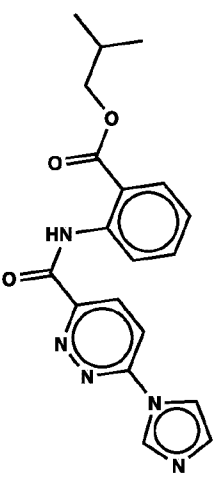
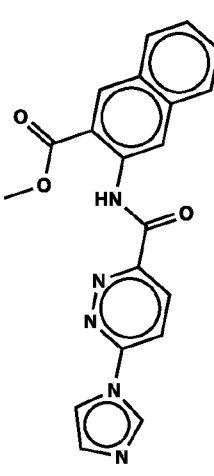
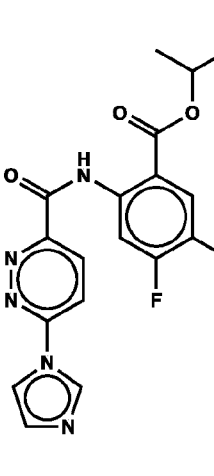
9		163.1	++++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.79 (s, 1H), 8.63 (d, <i>J</i> = 9.2 Hz, 1H), 8.42 (d, <i>J</i> = 9.2 Hz, 1H), 8.20 (s, 1H), 8.00 (s, 1H), 7.64 (s, 1H), 7.27 (s, 1H), 2.44 (s, 3H), 2.42 (s, 3H). MS-ESI: <i>m/z</i> 320.47 observed (M+H) ⁺
10		467.7	++++	MS-ESI: <i>m/z</i> 360.04 observed (M+H) ⁺
11		103.4	++++	MS-ESI: <i>m/z</i> 352.3 observed (M+H) ⁺

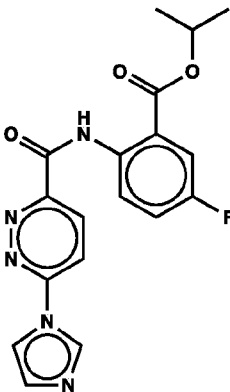
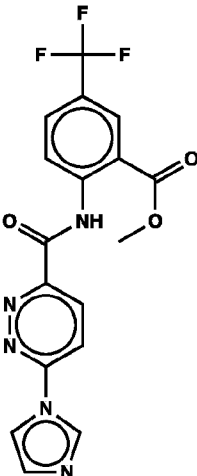
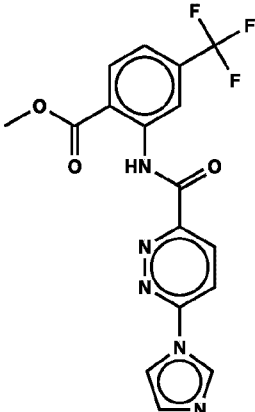
12		159	++++	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 13.05 (s, 1H), 9.33 (s, 1H), 9.14 (d, <i>J</i> = 1.6 Hz, 1H), 8.66 (d, <i>J</i> = 9.2 Hz, 1H), 8.55 (d, <i>J</i> = 9.2 Hz, 1H), 8.48 – 8.34 (m, 1H), 8.24 (d, <i>J</i> = 8.2 Hz, 1H), 7.77 (dd, <i>J</i> = 8.2, 1.7 Hz, 1H), 7.54 (s, 1H), 3.98 (s, 3H). MS-ESI: <i>m/z</i> 349.28 observed (M+H)⁺
13		248.7	++++	MS-ESI: <i>m/z</i> 342.25 observed (M+H)⁺

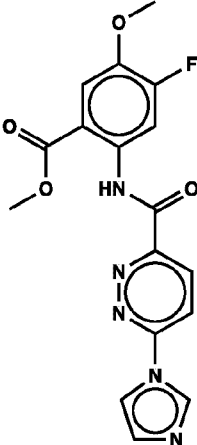
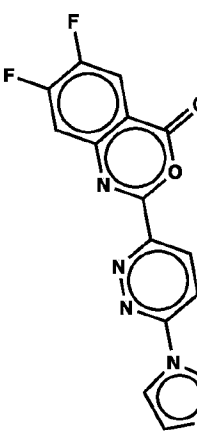
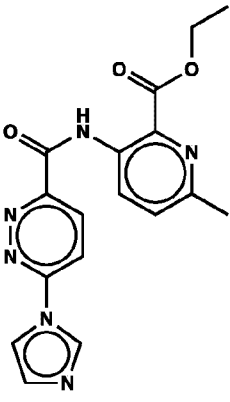
14		288.1	++++	MS-ESI: <i>m/z</i> 354.31 observed (M+H) ⁺
15		294.3	++++	MS-ESI: <i>m/z</i> 338.36 observed (M+H) ⁺
16		684.2	++++	MS-ESI: <i>m/z</i> 342.25 observed (M+H) ⁺

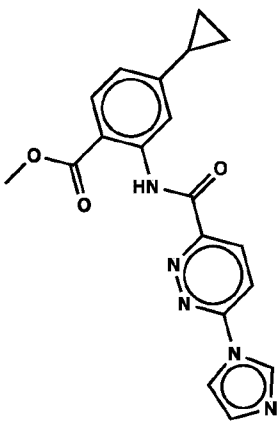
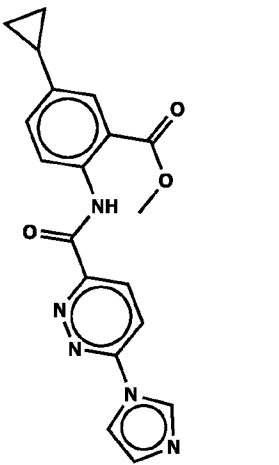
17		311.9	++++	MS-ESI: <i>m/z</i> 358.2 observed (M+H) ⁺
18		568.1	++++	¹H NMR (400 MHz, DMSO-d₆) δ 11.30 (s, 1H), 9.33 (s, 1H), 8.60 (d, J = 9.1 Hz, 1H), 8.53 (d, J = 9.1 Hz, 1H), 8.39 (s, 1H), 7.88 – 7.77 (m, 1H), 7.65 – 7.50 (m, 2H), 3.78 (s, 4H). MS-ESI: <i>m/z</i> 360.21 observed (M+H)⁺
19		817.3	++++	¹H NMR (400 MHz, DMSO-d₆) δ 11.06 (s, 1H), 9.42 (s, 1H), 8.59 (d, J = 9.1 Hz, 1H), 8.53 (d, J = 9.1 Hz, 1H), 8.41 (s, 1H), 7.82 – 7.72 (m, 1H), 7.68 – 7.50 (m, 2H), 3.77 (s, 3H). MS-ESI: <i>m/z</i> 360.21 observed (M+H)⁺

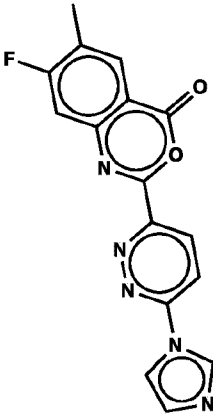
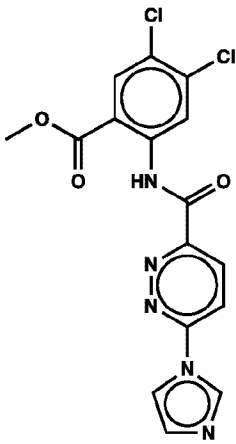
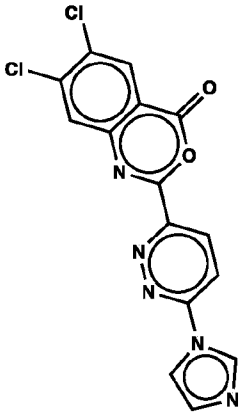
20		418.1	++++	¹H NMR (400 MHz, DMSO-d₆) δ 12.98 (s, 1H), 9.33 (s, 1H), 8.76 (d, J = 8.6 Hz, 1H), 8.62 (d, J = 9.1 Hz, 1H), 8.53 (d, J = 9.2 Hz, 1H), 8.41 (d, J = 1.6 Hz, 1H), 7.93 (d, J = 2.2 Hz, 1H), 7.61 (dd, J = 8.6, 2.2 Hz, 1H), 7.54 (s, 1H), 3.95 (s, 3H), 2.67 (q, J = 7.6 Hz, 2H), 1.21 (t, J = 7.6 Hz, 3H). MS-ESI: <i>m/z</i> 352.3 observed (M+H)⁺
21		90.36	++++	MS-ESI: <i>m/z</i> 356.25 observed (M+H)⁺

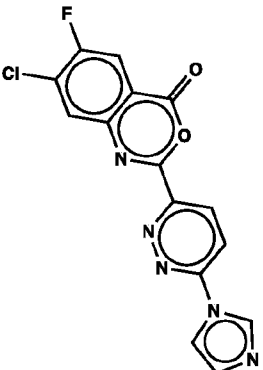
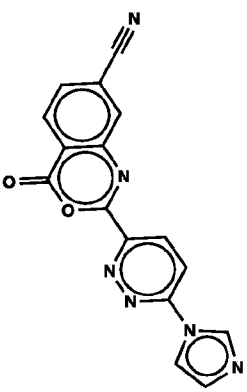
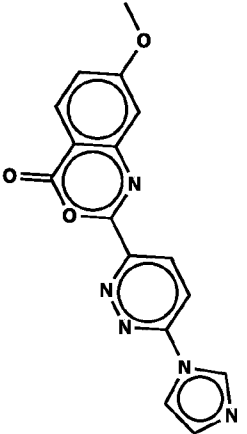
22		895.2	++++	MS-ESI: <i>m/z</i> 366.3 observed (M+H) ⁺
23		56.12	++++	MS-ESI: <i>m/z</i> 374.28 observed (M+H) ⁺
24		736.1	++++	MS-ESI: <i>m/z</i> 388.28 observed (M+H) ⁺

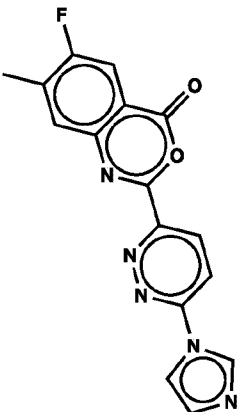
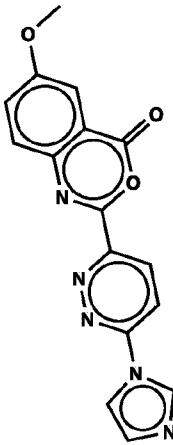
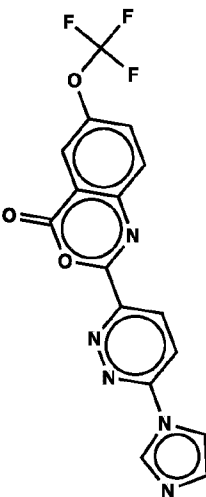
25		804.5	+++++	MS-ESI: <i>m/z</i> 370.26 observed (M+H) ⁺
26		114	+++++	MS-ESI: <i>m/z</i> 392.37 observed (M+H) ⁺
27		136.1	+++++	MS-ESI: <i>m/z</i> 392.37 observed (M+H) ⁺

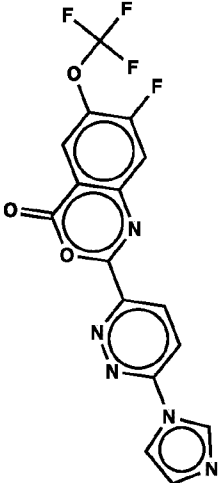
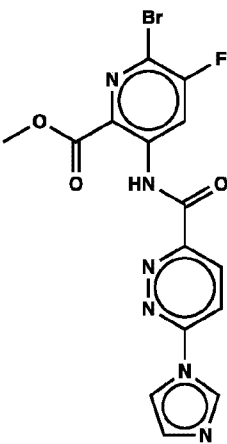
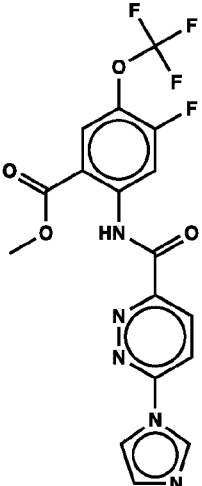
28		95.82	++++	MS-ESI: <i>m/z</i> 372.33 observed (M+H) ⁺
29		140	++++	MS-ESI: <i>m/z</i> 328.45 observed (M+H) ⁺
30		148.9	++++	MS-ESI: <i>m/z</i> 353.44 observed (M+H) ⁺

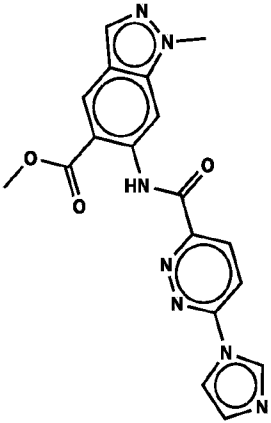
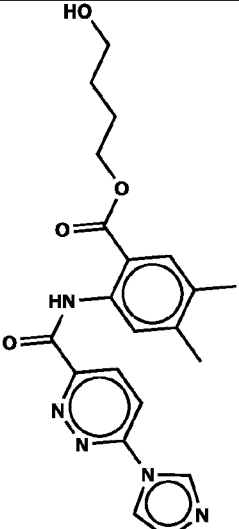
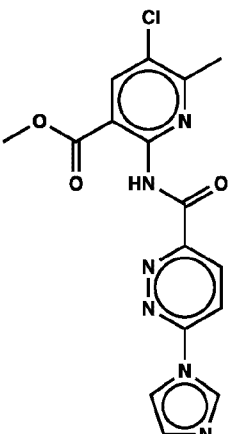
31		206.4	++++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.07 (s, 1H), 8.84 (t, <i>J</i> = 1.1 Hz, 1H), 8.62 (d, <i>J</i> = 1.8 Hz, 1H), 8.55 (d, <i>J</i> = 9.1 Hz, 1H), 8.48 (d, <i>J</i> = 9.1 Hz, 1H), 8.27 – 8.21 (m, 1H), 7.97 (d, <i>J</i> = 8.3 Hz, 1H), 7.32 – 7.24 (m, 1H), 7.01 (dd, <i>J</i> = 8.3, 1.9 Hz, 1H), 3.93 (s, 3H), 2.11 – 2.01 (m, 1H), 1.18 – 1.07 (m, 2H), 0.85 – 0.77 (m, 2H). MS-ESI: <i>m/z</i> 364.49 observed (M+H) ⁺
32		358.8	++++	MS-ESI: <i>m/z</i> 364.49 observed (M+H) ⁺

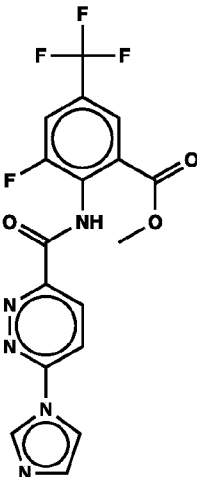
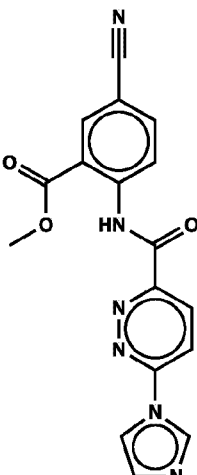
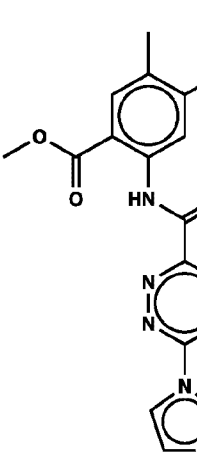
33		<19.53	++++	MS-ESI: <i>m/z</i> 324.49 observed (M+H) ⁺
34		72.61	++++	MS-ESI: <i>m/z</i> 392.43 observed (M+H) ⁺
35		61.67	++++	MS-ESI: <i>m/z</i> 360.47 observed (M+H) ⁺

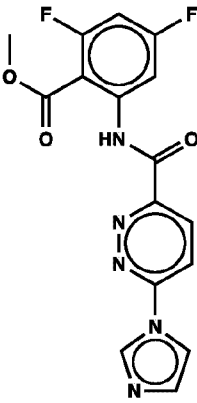
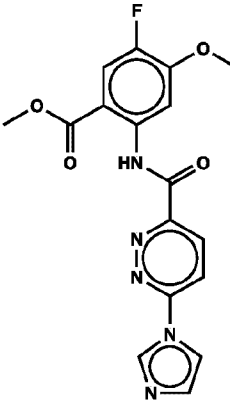
36		40.35	++++	MS-ESI: <i>m/z</i> 344.46 observed (M+H) ⁺
37		165.8	++++	¹H NMR (400 MHz, DMSO-d₆) δ 8.82 (s, 1H), 8.67 (d, <i>J</i> = 9.3 Hz, 1H), 8.47 (d, <i>J</i> = 9.2 Hz, 1H), 8.40 – 8.35 (m, 2H), 8.25 – 8.21 (m, 1H), 8.11 (dd, <i>J</i> = 8.2, 1.5 Hz, 1H), 7.28 (s, 1H). MS-ESI: <i>m/z</i> 317.46 observed (M+H)⁺
38		484.9	++++	MS-ESI: <i>m/z</i> 322.11 observed (M+H) ⁺

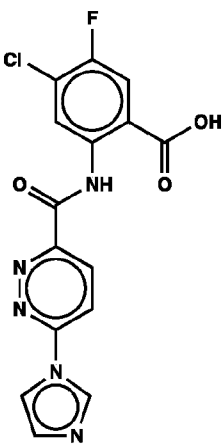
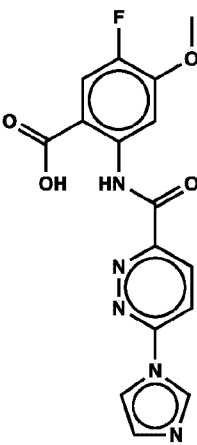
39		30.81	++++	MS-ESI: <i>m/z</i> 324.12 observed (M+H) ⁺
40		684.1	++++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.65 (d, <i>J</i> = 9.2 Hz, 1H), 8.42 (d, <i>J</i> = 9.3 Hz, 1H), 8.20 (t, <i>J</i> = 1.4 Hz, 1H), 7.80 (d, <i>J</i> = 8.4 Hz, 1H), 7.67 – 7.56 (m, 2H), 7.27 (dd, <i>J</i> = 1.5, 0.8 Hz, 1H), 3.95 (s, 3H). MS-ESI: <i>m/z</i> 322.11 observed (M+H) ⁺
41		176.2	++++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.87 – 8.80 (m, 1H), 8.71 (d, <i>J</i> = 9.2 Hz, 1H), 8.46 (d, <i>J</i> = 9.3 Hz, 1H), 8.27 – 8.19 (m, 1H), 8.19 – 8.11 (m, 1H), 8.10 – 8.02 (m, 1H), 7.98 (d, <i>J</i> = 8.8 Hz, 1H), 7.34 – 7.24 (m, 1H). MS-ESI: <i>m/z</i> 376.05 observed (M+H) ⁺

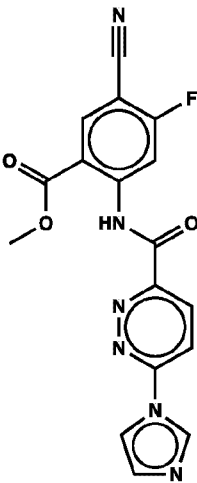
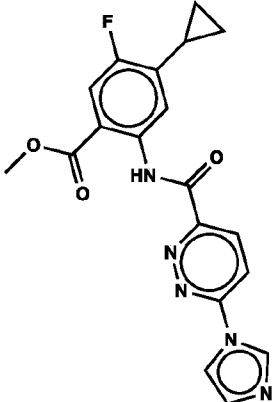
42		373.3	++++	MS-ESI: <i>m/z</i> 394.07 observed (M+H) ⁺
43		142.4	++++	MS-ESI: <i>m/z</i> 423.01 observed (M+H) ⁺
44		573.3	++++	MS-ESI: <i>m/z</i> 426.09 observed (M+H) ⁺

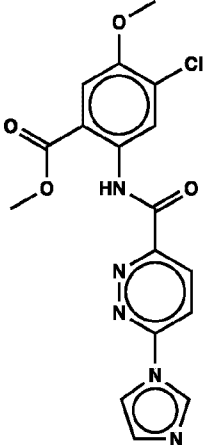
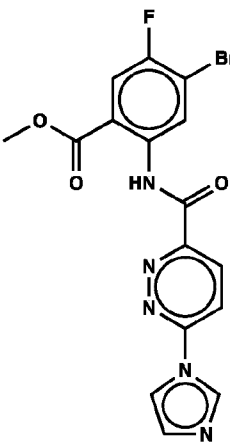
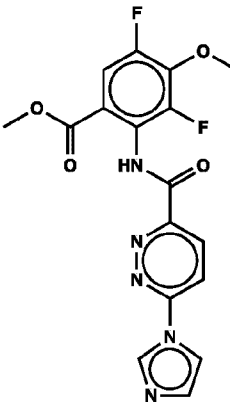
45		125.9	++++	MS-ESI: <i>m/z</i> 378.12 observed (M+H) ⁺
46		418.1	++++	MS-ESI: <i>m/z</i> 410.15 observed (M+H) ⁺
47		281.7	++++	MS-ESI: <i>m/z</i> 373.1 observed (M+H) ⁺

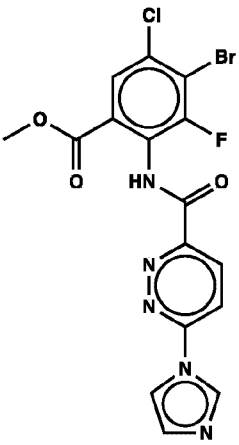
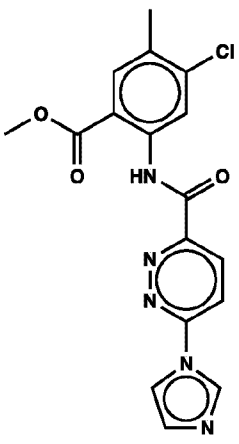
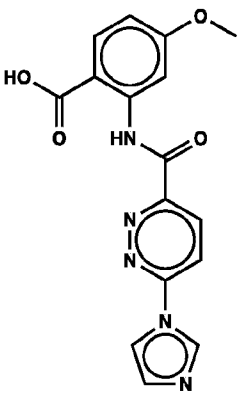
48		474.8	++++	MS-ESI: <i>m/z</i> 410.15 observed (M+H) ⁺
49		587.7	++++	MS-ESI: <i>m/z</i> 349.11 observed (M+H) ⁺
50		145	++++	MS-ESI: <i>m/z</i> 356.15 observed (M+H) ⁺

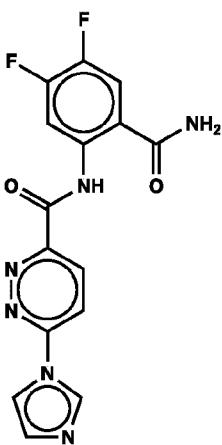
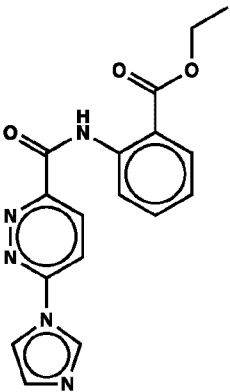
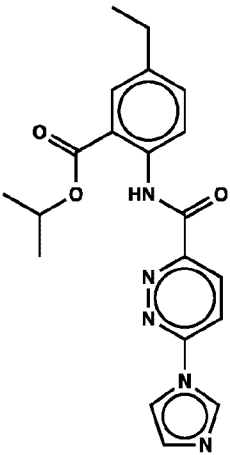
51		198.4	++++	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 12.65 (s, 1H), 9.16 (s, 1H), 8.61 (d, <i>J</i> = 9.1 Hz, 1H), 8.52 (d, <i>J</i> = 9.2 Hz, 1H), 8.41 – 8.27 (m, 2H), 7.45 (s, 1H), 7.29 (ddd, <i>J</i> = 11.6, 9.0, 2.6 Hz, 1H), 3.94 (s, 3H). MS-ESI: <i>m/z</i> 360.17 observed (M+H)⁺
52		74.45	++++	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 13.16 (s, 1H), 8.83 (t, <i>J</i> = 1.1 Hz, 1H), 8.76 (d, <i>J</i> = 8.2 Hz, 1H), 8.55 (d, <i>J</i> = 9.0 Hz, 1H), 8.48 (d, <i>J</i> = 9.2 Hz, 1H), 8.23 (t, <i>J</i> = 1.5 Hz, 1H), 7.84 (d, <i>J</i> = 12.1 Hz, 1H), 7.30 – 7.25 (m, 1H), 3.99 (s, 3H), 3.92 (s, 3H). MS-ESI: <i>m/z</i> 372.1 observed (M+H)⁺

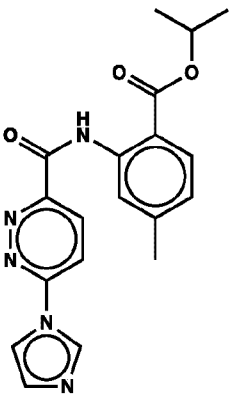
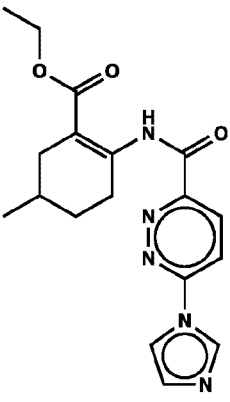
53		~624.6	++++	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 15.98 (s, 1H), 8.94 (d, <i>J</i> = 7.1 Hz, 1H), 8.80 (t, <i>J</i> = 1.1 Hz, 1H), 8.46 (d, <i>J</i> = 9.2 Hz, 1H), 8.41 (d, <i>J</i> = 9.2 Hz, 1H), 8.21 (t, <i>J</i> = 1.4 Hz, 1H), 7.88 (d, <i>J</i> = 10.3 Hz, 1H), 7.29 – 7.23 (m, 1H). MS-ESI: <i>m/z</i> 362.41 observed (M+H)⁺
54		247.8	++++	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 13.34 (s, 1H), 8.82 (s, 1H), 8.77 (d, <i>J</i> = 8.1 Hz, 1H), 8.55 (d, <i>J</i> = 9.1 Hz, 1H), 8.47 (d, <i>J</i> = 9.1 Hz, 1H), 8.22 (t, <i>J</i> = 1.5 Hz, 1H), 7.82 (d, <i>J</i> = 12.1 Hz, 1H), 7.30 – 7.24 (m, 1H), 3.97 (s, 3H); (carboxylic acid proton not located) MS-ESI: <i>m/z</i> 358.47 observed (M+H)⁺

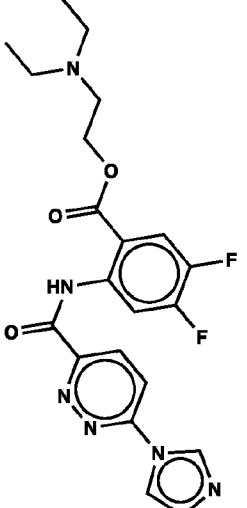
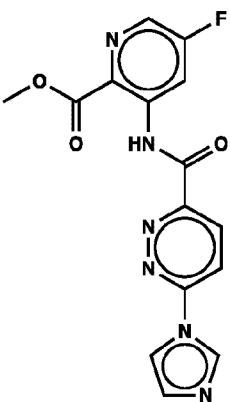
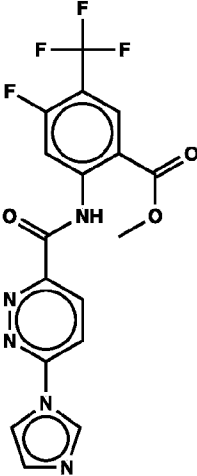
55		221.1	++++	MS-ESI: <i>m/z</i> 367.5 observed (M+H) ⁺
56		301.7	++++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.90 (s, 1H), 8.83 (s, 1H), 8.55 (d, <i>J</i> = 9.1 Hz, 1H), 8.52 – 8.43 (m, 2H), 8.27 – 8.20 (m, 1H), 7.77 (d, <i>J</i> = 10.8 Hz, 1H), 7.28 (dd, <i>J</i> = 1.5, 0.9 Hz, 1H), 3.94 (s, 3H), 2.19 (td, <i>J</i> = 8.5, 4.4 Hz, 1H), 1.22 – 1.14 (m, 2H), 0.90 – 0.78 (m, 2H). MS-ESI: <i>m/z</i> 382.51 observed (M+H) ⁺

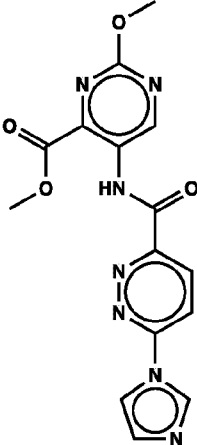
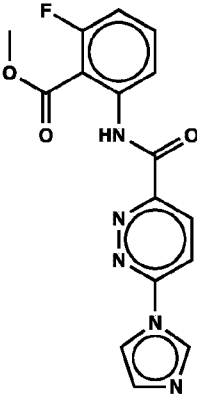
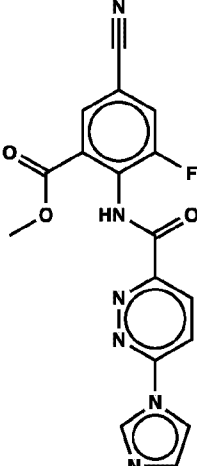
57		< 19.53	++++	MS-ESI: <i>m/z</i> 388.41 observed (M+H) ⁺
58		60.58	++++	MS-ESI: <i>m/z</i> 422.25 observed (M+H) ⁺
59		779.9	++++	MS-ESI: <i>m/z</i> 390.42 observed (M+H) ⁺

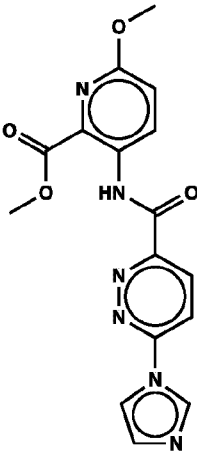
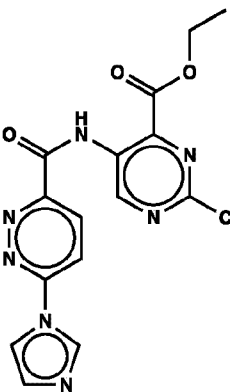
60		62.25	++++	MS-ESI: <i>m/z</i> 456.22 observed (M+H) ⁺
61		124	++++	MS-ESI: <i>m/z</i> 372.42 observed (M+H) ⁺
62		1457	+++	MS-ESI: <i>m/z</i> 340.14 observed (M+H) ⁺

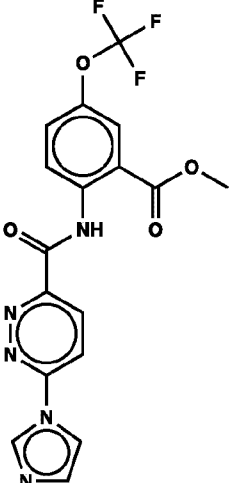
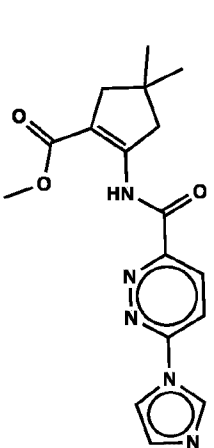
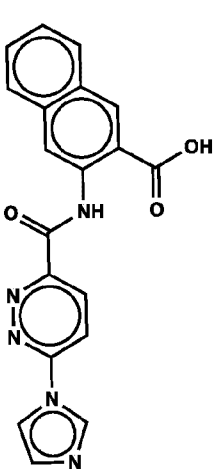
63		2638	+++	MS-ESI: <i>m/z</i> 345.47 observed (M+H) ⁺
64		926.2	+++	MS-ESI: <i>m/z</i> 338.3 observed (M+H) ⁺
65		1156	+++	MS-ESI: <i>m/z</i> 380.31 observed (M+H) ⁺

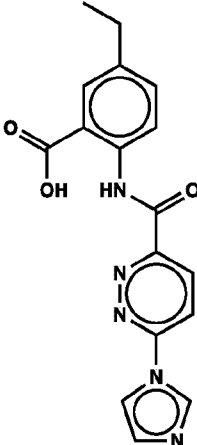
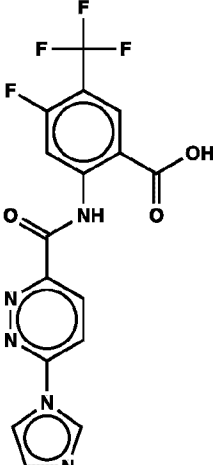
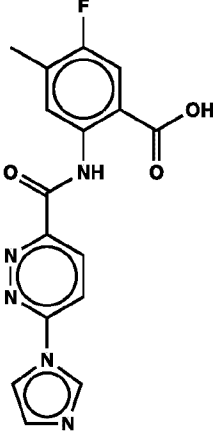
66		517.7	+++	MS-ESI: <i>m/z</i> 366.3 observed (M+H) ⁺
67		2953	+++	¹H NMR (400 MHz, Methanol-d₄) δ 13.49 (s, 1H), 9.26 (s, 1H), 8.52 (d, J = 9.2 Hz, 1H), 8.38 – 8.27 (m, 2H), 7.52 (s, 1H), 4.27 (q, J = 7.2 Hz, 2H), 3.12 – 2.98 (m, 1H), 2.69 – 2.56 (m, 1H), 2.02 – 1.83 (m, 2H), 1.78 – 1.64 (m, 1H), 1.40 – 1.25 (m, 5H), 1.06 (d, J = 6.5 Hz, 3H). MS-ESI: <i>m/z</i> 356.59 observed (M+H)⁺

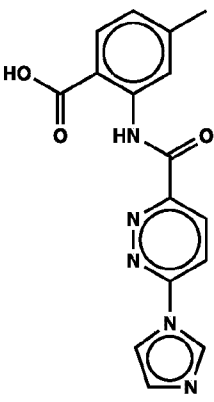
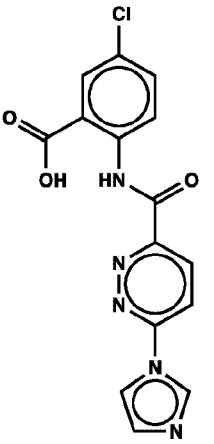
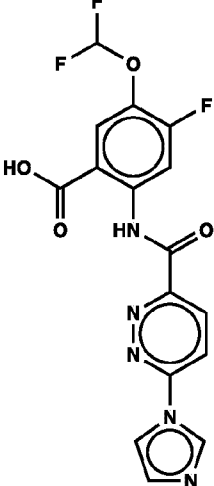
68		1808	+++	MS-ESI: <i>m/z</i> 445.43 observed (M+H) ⁺
69		2786	+++	MS-ESI: <i>m/z</i> 343.52 observed (M+H) ⁺
70		1719	+++	MS-ESI: <i>m/z</i> 410.09 observed (M+H) ⁺

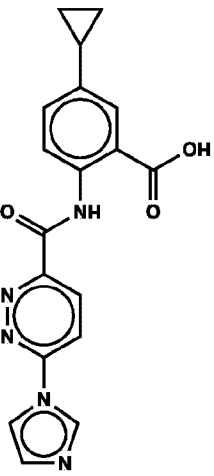
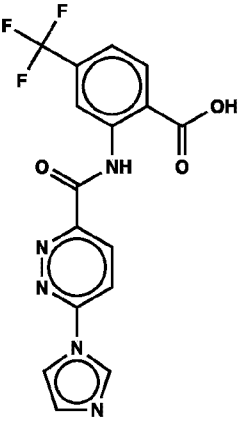
71		1658	+++	MS-ESI: m/z 356.15 observed ($M+H$) ⁺
72		1670	+++	¹ H NMR (400 MHz, DMSO- d_6) δ 12.23 (s, 1H), 9.13 (s, 1H), 8.59 (d, J = 9.1 Hz, 1H), 8.51 (d, J = 9.2 Hz, 1H), 8.40 – 8.26 (m, 2H), 7.73 (td, J = 8.4, 6.2 Hz, 1H), 7.44 (s, 1H), 7.26 – 7.17 (m, 1H), 3.92 (s, 3H). MS-ESI: m/z 342.15 observed ($M+H$) ⁺
73		2370	+++	MS-ESI: m/z 367.1 observed ($M+H$) ⁺

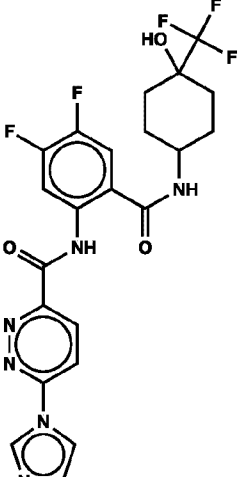
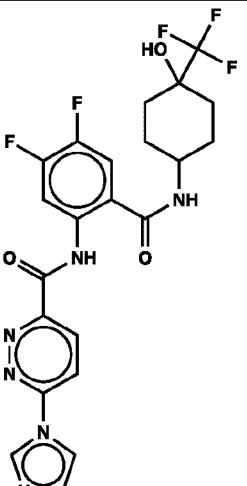
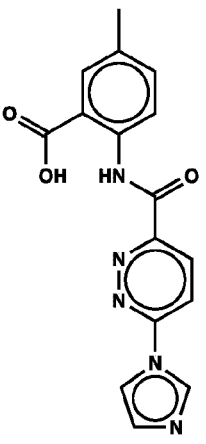
74		1355	+++	¹H NMR (400 MHz, DMSO-d₆) δ 12.67 (s, 1H), 9.04 (d, J = 9.2 Hz, 1H), 8.88 – 8.79 (m, 1H), 8.55 (d, J = 9.1 Hz, 1H), 8.47 (d, J = 9.2 Hz, 1H), 8.27 – 8.19 (m, 1H), 7.30 – 7.23 (m, 2H), 5.76 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H). MS-ESI: <i>m/z</i> 355.14 observed (M+H)⁺
75		1261	+++	¹H NMR (400 MHz, DMSO-d₆) δ 12.47 (s, 1H), 9.94 (s, 1H), 8.91 – 8.80 (m, 1H), 8.60 (d, J = 9.1 Hz, 1H), 8.50 (d, J = 9.1 Hz, 1H), 8.30 – 8.18 (m, 1H), 7.33 – 7.19 (m, 1H), 4.46 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H). MS-ESI: <i>m/z</i> 374.1 observed (M+H)⁺

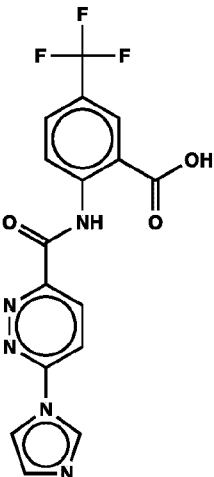
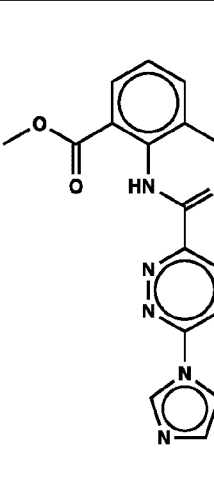
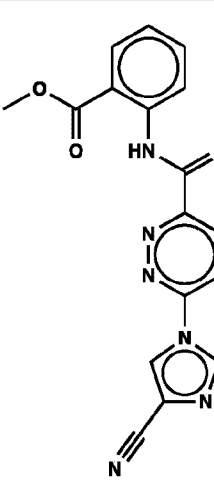
76		572.9	+++	MS-ESI: <i>m/z</i> 408.38 observed (M+H) ⁺
77		>50000	++	MS-ESI: <i>m/z</i> 342.21 observed (M+H) ⁺
78		4440	++	MS-ESI: <i>m/z</i> 360.33 observed (M+H) ⁺

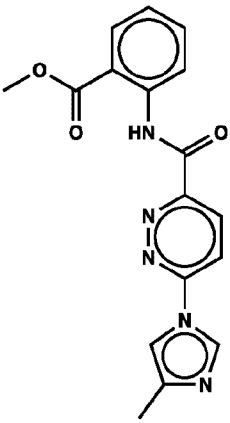
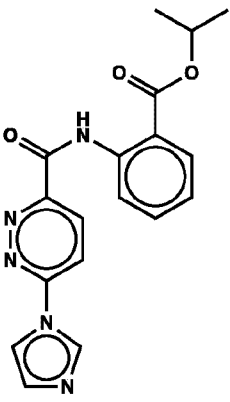
79		>20000	++	MS-ESI: <i>m/z</i> 338.5 observed (M+H) ⁺
80		3974	++	MS-ESI: <i>m/z</i> 396.08 observed (M+H) ⁺
81		2736	++	MS-ESI: <i>m/z</i> 342.15 observed (M+H) ⁺

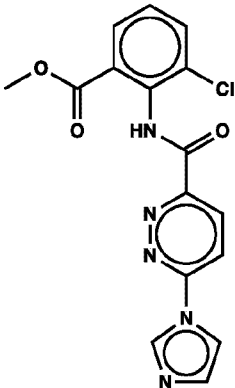
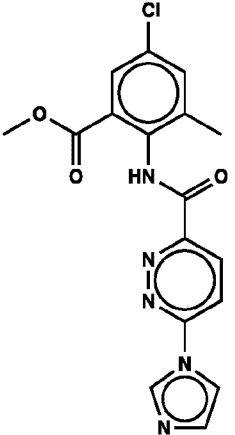
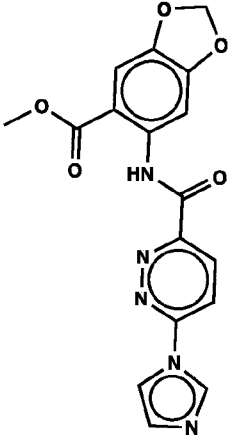
82		6390	++	MS-ESI: m/z 324.12 observed (M+H) ⁺
83		>20000	++	MS-ESI: m/z 344.02 observed (M+H) ⁺
84		8593	++	MS-ESI: m/z 394.07 observed (M+H) ⁺

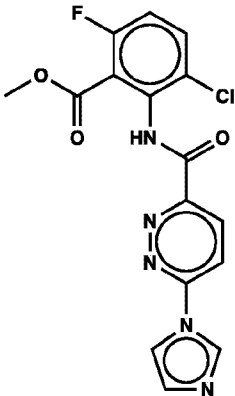
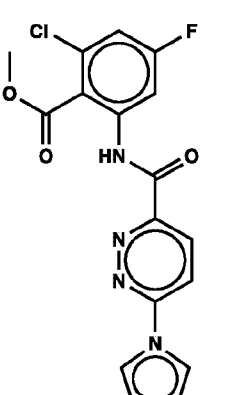
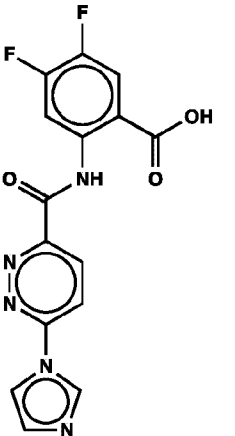
85		~16556	++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 15.90 (s, 1H), 8.79 (app t, <i>J</i> = 1.1 Hz, 1H), 8.60 (d, <i>J</i> = 8.5 Hz, 1H), 8.45 (d, <i>J</i> = 9.1 Hz, 1H), 8.39 (d, <i>J</i> = 9.1 Hz, 1H), 8.21 (app t, <i>J</i> = 1.5 Hz, 1H), 7.74 (d, <i>J</i> = 2.4 Hz, 1H), 7.26 (s, 1H), 7.06 (dd, <i>J</i> = 8.4, 2.4 Hz, 1H), 1.96 – 1.79 (m, 1H), 0.97 – 0.88 (m, 2H), 0.66 – 0.59 (m, 2H). MS-ESI: <i>m/z</i> 350.5 observed (M+H) ⁺
86		10341	++	MS-ESI: <i>m/z</i> 378.12 observed (M+H) ⁺

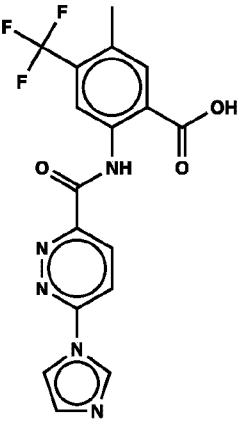
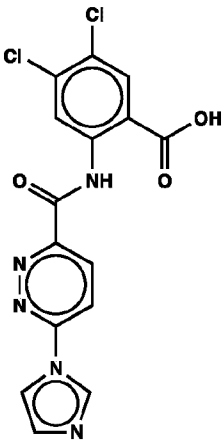
87		>20000	++	MS-ESI: <i>m/z</i> 511.23 observed (M+H) ⁺
88		5244	++	MS-ESI: <i>m/z</i> 511.23 observed (M+H) ⁺
89		>20000	++	MS-ESI: <i>m/z</i> 324.12 observed (M+H) ⁺

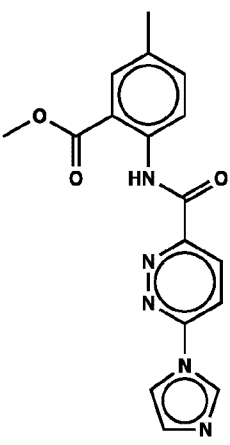
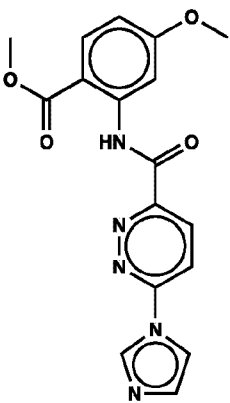
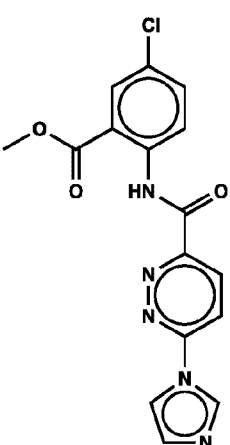
90		>20000	++	MS-ESI: <i>m/z</i> 378.06 observed (M+H) ⁺
91		~5073	++	MS-ESI: <i>m/z</i> 338.3 observed (M+H) ⁺
92		~ 5256	++	MS-ESI: <i>m/z</i> 349.1 observed (M+H) ⁺

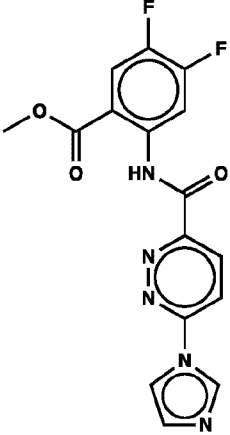
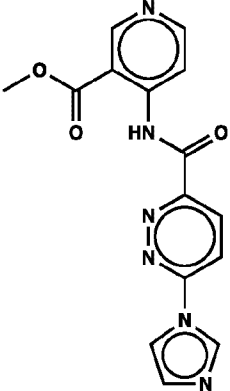
93		>20000	++	MS-ESI: m/z 338.3 observed (M+H) ⁺
95		1701	++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.04 (s, 1H), 9.16 (s, 1H), 8.84 (d, J = 8.4 Hz, 1H), 8.61 (d, J = 9.1 Hz, 1H), 8.51 (d, J = 9.1 Hz, 1H), 8.35 (d, J = 1.5 Hz, 1H), 8.10 (dd, J = 8.0, 1.6 Hz, 1H), 7.78 – 7.71 (m, 1H), 7.46 (s, 1H), 7.37 – 7.26 (m, 1H), 5.27 (p, J = 6.2 Hz, 1H), 1.39 (d, J = 6.2 Hz, 7H). MS-ESI: m/z 352.3 observed (M+H) ⁺

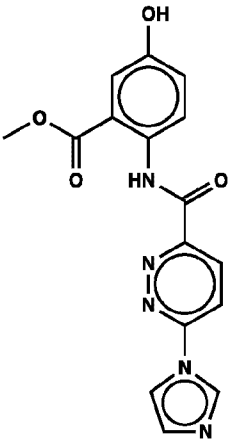
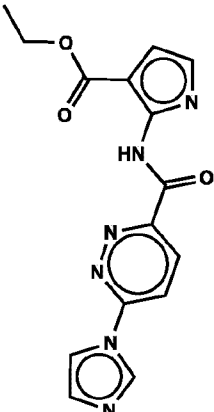
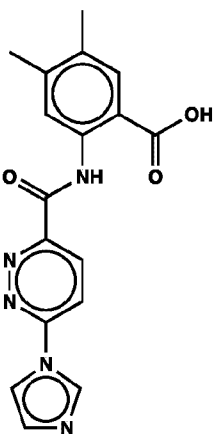
96		21070	++	¹H NMR (400 MHz, DMSO-d₆) δ 11.07 (s, 1H), 9.49 (s, 1H), 8.60 (d, J = 9.1 Hz, 1H), 8.54 (d, J = 9.1 Hz, 1H), 8.44 (s, 1H), 7.86 (dd, J = 8.0, 2.6 Hz, 2H), 7.66 (s, 1H), 7.59 – 7.47 (m, 1H), 3.73 (s, 3H). MS-ESI: <i>m/z</i> 358.2 observed (M+H)⁺
97		~ 2485	++	¹H NMR (400 MHz, DMSO-d₆) δ 10.97 (s, 1H), 9.31 (s, 1H), 8.59 – 8.46 (m, 2H), 8.38 (s, 1H), 7.71 (s, 2H), 7.56 (s, 1H), 3.72 (s, 5H), 2.32 (s, 4H). MS-ESI: <i>m/z</i> 372.27 observed (M+H)⁺
98		2678	++	¹H NMR (400 MHz, DMSO-d₆) δ 13.26 (s, 1H), 9.33 (s, 1H), 8.62 (d, J = 9.2 Hz, 1H), 8.53 (d, J = 9.1 Hz, 1H), 8.46 (s, 1H), 8.42 (s, 1H), 7.57 – 7.50 (m, 2H), 6.20 (s, 2H), 3.91 (s, 3H). MS-ESI: <i>m/z</i> 368.25 observed (M+H)⁺

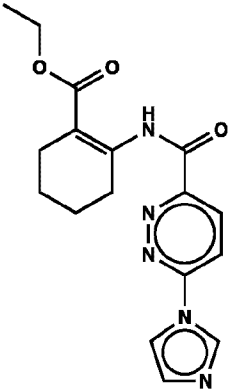
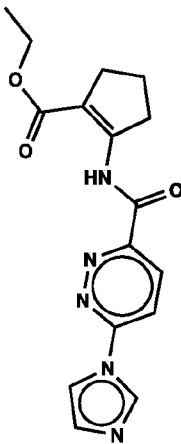
99		11919	++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.19 (s, 1H), 9.44 (s, 1H), 8.63 – 8.52 (m, 2H), 8.43 (s, 1H), 7.87 (dd, <i>J</i> = 9.2, 5.4 Hz, 1H), 7.63 (s, 1H), 7.47 (t, <i>J</i> = 9.1 Hz, 1H), 3.76 (s, 4H). MS-ESI: <i>m/z</i> 376.22 observed (M+H) ⁺
100		10199	++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.45 (s, 1H), 9.06 (s, 1H), 8.56 (d, <i>J</i> = 9.2 Hz, 1H), 8.49 (d, <i>J</i> = 9.1 Hz, 1H), 8.30 (s, 1H), 8.01 – 7.97 (m, 1H), 7.52 (dd, <i>J</i> = 8.4, 2.5 Hz, 1H), 7.41 (s, 1H), 3.90 (s, 3H). MS-ESI: <i>m/z</i> 376.22 observed (M+H) ⁺
101		731.3	++++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 16.11 (s, 1H), 8.79 (s, 1H), 8.74 (dd, <i>J</i> = 13.8, 7.7 Hz, 1H), 8.47 (d, <i>J</i> = 9.1 Hz, 1H), 8.40 (d, <i>J</i> = 9.2 Hz, 1H), 8.21 (t, <i>J</i> = 1.5 Hz, 1H), 7.92 (dd, <i>J</i> = 11.9, 9.8 Hz, 1H), 7.26 (d, <i>J</i> = 1.4 Hz, 1H). MS-ESI: <i>m/z</i>

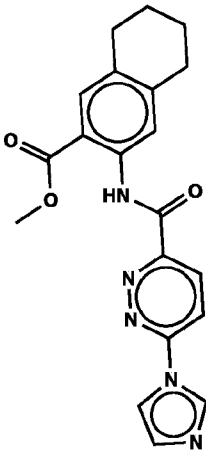
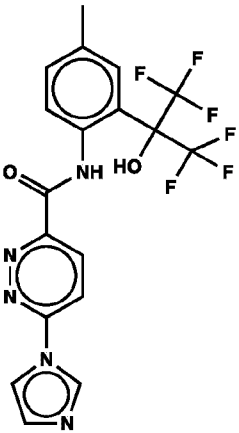
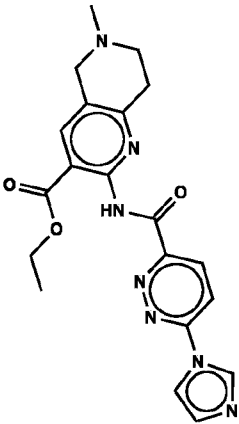
				346.1 observed (M+H) ⁺
102		12059	++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 15.91 (s, 1H), 9.13 (s, 1H), 8.80 (s, 1H), 8.46 (d, <i>J</i> = 9.2 Hz, 1H), 8.41 (d, <i>J</i> = 9.2 Hz, 1H), 8.25 – 8.16 (m, 1H), 8.03 (s, 1H), 7.26 (s, 1H), 2.44 – 2.37 (m, 3H). MS-ESI: <i>m/z</i> 392.44 observed (M+H) ⁺
103		451.3	++++	MS-ESI: <i>m/z</i> 378.06 observed (M+H) ⁺

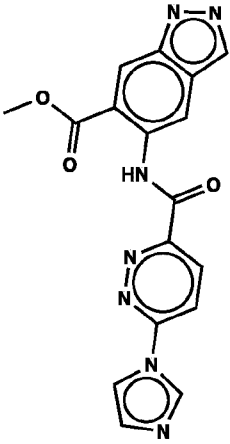
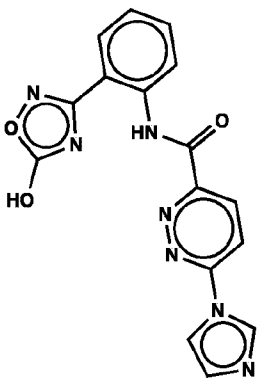
104		425.8	++++	MS-ESI: m/z 338.3 observed ($M+H$) ⁺
105		192.5	++++	¹ H NMR (400 MHz, DMSO- d_6) δ 13.26 (s, 1H), 9.39 (s, 1H), 8.63 (d, J = 9.1 Hz, 1H), 8.58 – 8.48 (m, 2H), 8.43 (d, J = 1.6 Hz, 1H), 8.07 (d, J = 8.9 Hz, 1H), 7.58 (s, 1H), 6.88 (dd, J = 8.9, 2.6 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H). MS-ESI: m/z 354.24 observed ($M+H$) ⁺
106		345.9	++++	¹ H NMR (400 MHz, DMSO- d_6) δ 13.00 (s, 1H), 9.51 (s, 1H), 8.84 (d, J = 9.0 Hz, 1H), 8.65 (d, J = 9.2 Hz, 1H), 8.56 (d, J = 9.2 Hz, 1H), 8.47 (d, J = 1.7 Hz, 1H), 8.04 (d, J = 2.7 Hz, 1H), 7.83 (dd, J = 9.0, 2.7 Hz, 1H), 7.63 (d, J = 1.7 Hz, 1H), 3.96 (s,

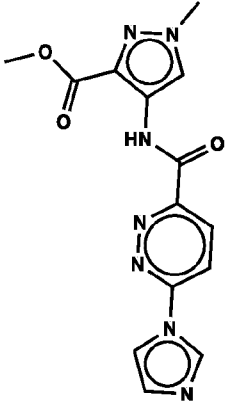
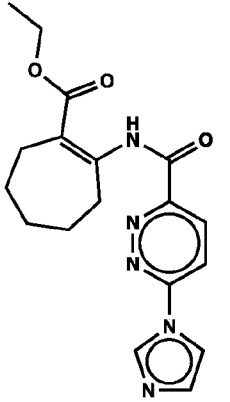
				4H). MS-ESI: <i>m/z</i> 358.2 observed (M+H) ⁺
107		414.8	++++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.08 (s, 1H), 9.26 (s, 1H), 8.83 (dd, <i>J</i> = 13.5, 7.5 Hz, 1H), 8.61 (d, <i>J</i> = 9.2 Hz, 1H), 8.52 (d, <i>J</i> = 9.2 Hz, 1H), 8.39 – 8.36 (m, 1H), 8.09 (dd, <i>J</i> = 11.2, 9.0 Hz, 1H), 7.50 (s, 1H), 3.95 (s, 3H). MS-ESI: <i>m/z</i> 360.21 observed (M+H) ⁺
108		334.6	++	MS-ESI: <i>m/z</i> 325.36 observed (M+H) ⁺

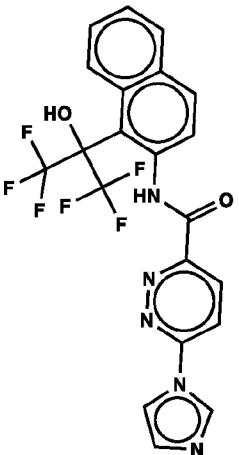
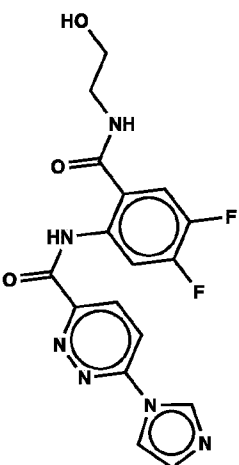
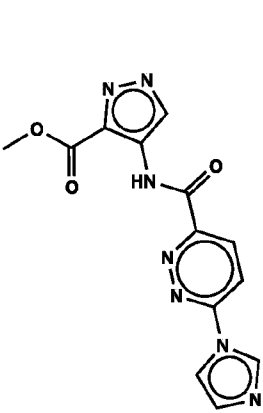
109		8945	++	MS-ESI: m/z 340.44 observed ($M+H$) ⁺
110		16896	++	MS-ESI: m/z 327.44 observed ($M+H$) ⁺
111		7248	++	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.79 (d, J = 1.1 Hz, 1H), 8.57 (s, 1H), 8.45 (d, J = 9.1 Hz, 1H), 8.40 (d, J = 9.2 Hz, 1H), 8.20 (t, J = 1.4 Hz, 1H), 7.80 (s, 1H), 7.26 (t, J = 1.3 Hz, 1H), 2.26 (s, 3H), 2.21 (s, 3H). MS-ESI: m/z 338.19 observed ($M+H$) ⁺

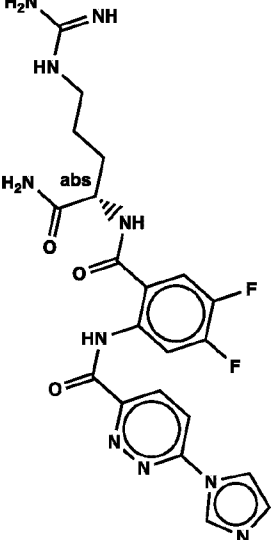
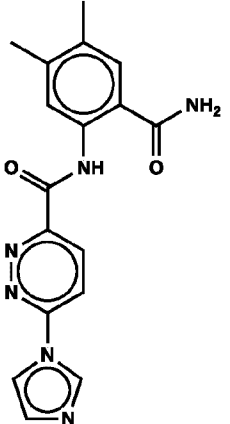
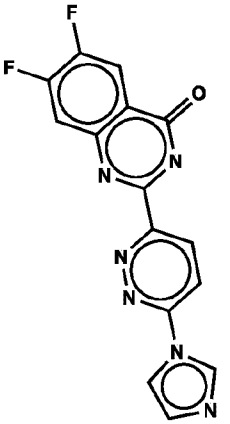
112		1504	++	¹H NMR (400 MHz, Methanol-d₄) δ 13.48 (s, 1H), 9.23 (s, 1H), 8.52 (d, J = 9.2 Hz, 1H), 8.37 – 8.24 (m, 2H), 7.51 (s, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.21 – 3.11 (m, 2H), 2.51 – 2.39 (m, 2H), 1.82 – 1.64 (m, 4H), 1.34 (t, J = 7.1 Hz, 4H). MS-ESI: <i>m/z</i> 342.45 observed (M+H)⁺
113		18734	++	MS-ESI: <i>m/z</i> 328.51 observed (M+H)⁺

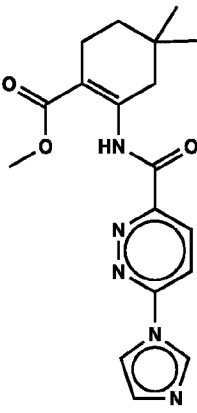
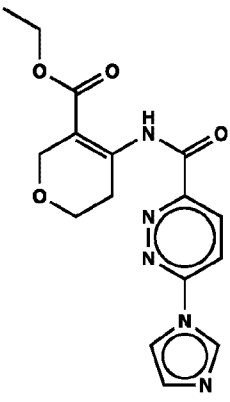
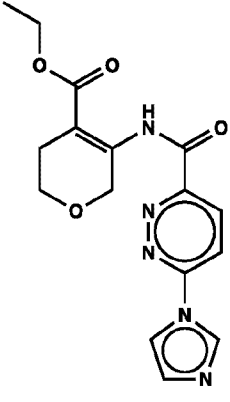
114		4345	++	¹H NMR (400 MHz, Methanol-d₄) δ 13.11 (s, 1H), 9.75 (s, 1H), 8.66 (d, J = 9.2 Hz, 1H), 8.61 (s, 1H), 8.49 (s, 1H), 8.44 (d, J = 9.1 Hz, 1H), 7.85 (s, 1H), 7.76 (s, 1H), 3.97 (s, 3H), 2.88 (s, 2H), 2.79 (s, 2H), 1.92 – 1.81 (m, 4H). MS-ESI: <i>m/z</i> 378.56 observed (M+H)⁺
115		7363	++	MS-ESI: <i>m/z</i> 446.37 observed (M+H)⁺
116		3464	++	¹H NMR (400 MHz, Methanol-d₄) δ 9.27 (s, 1H), 8.66 (d, J = 9.1 Hz, 1H), 8.44 – 8.37 (m, 2H), 8.32 (s, 1H), 7.53 (s, 1H), 4.69 – 4.37 (m, 4H), 3.92 – 3.64 (m, 2H), 3.41 (t, J = 6.4 Hz, 2H), 3.13 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H).

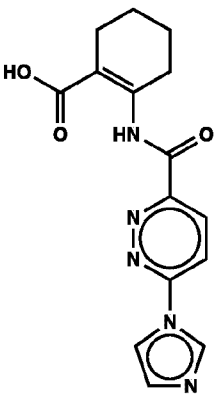
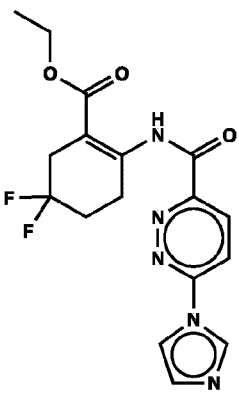
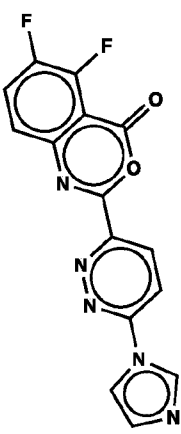
				MS-ESI: m/z 408.45 observed ($M+H$) ⁺
117		~2574	++	MS-ESI: m/z 364.43 observed ($M+H$) ⁺
118		3967	++	¹ H NMR (400 MHz, Methanol-d ₄) δ 13.51 (s, 1H), 10.06 (s, 1H), 8.95 (d, J = 7.9 Hz, 1H), 8.73 (d, J = 9.1 Hz, 1H), 8.63 – 8.58 (m, 1H), 8.50 (d, J = 9.1 Hz, 1H), 8.20 (dd, J = 7.9, 1.6 Hz, 1H), 7.92 (dd, J = 2.2, 1.3 Hz, 1H), 7.73 – 7.64 (m, 1H), 7.31 – 7.23 (m, 1H).

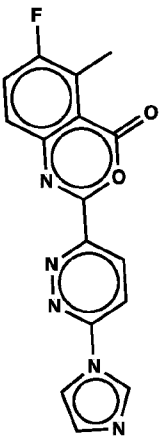
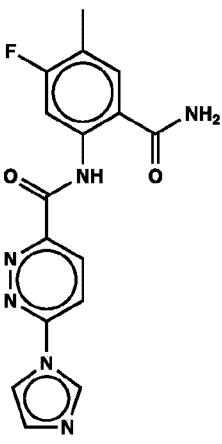
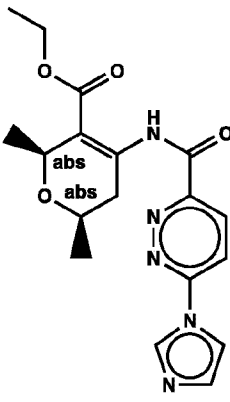
				MS-ESI: <i>m/z</i> 350.49 observed (M+H) ⁺
119		5892	++	MS-ESI: <i>m/z</i> 328.51 observed (M+H) ⁺
120		>50000	++	MS-ESI: <i>m/z</i> 356.59 observed (M+H) ⁺

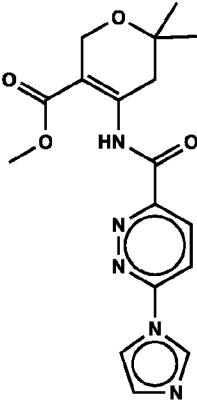
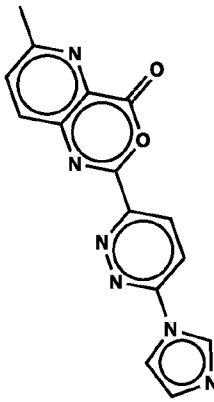
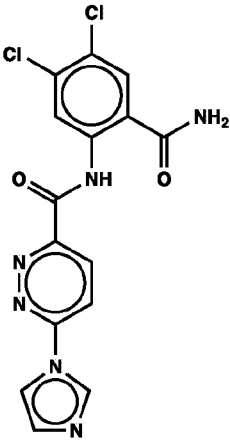
121		1832	++	MS-ESI: <i>m/z</i> 482.49 observed (M+H) ⁺
122		7955	++	MS-ESI: <i>m/z</i> 389.49 observed (M+H) ⁺
123		2993	++	MS-ESI: <i>m/z</i> 314.44 observed (M+H) ⁺

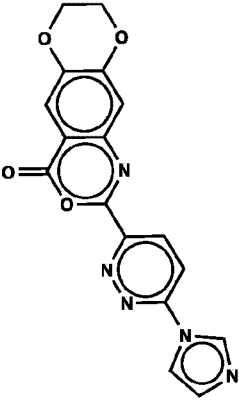
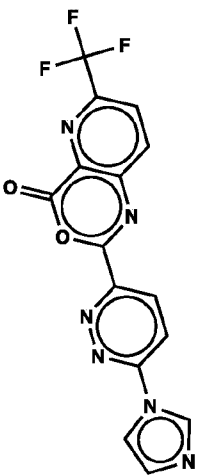
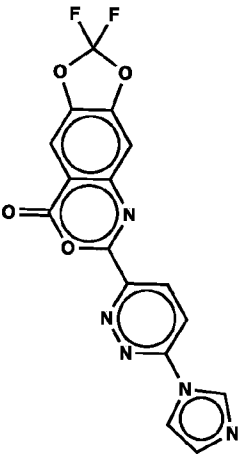
124		8078	++	MS-ESI: m/z 501.58 observed (M+H) ⁺
125		9617	++	MS-ESI: m/z 337.49 observed (M+H) ⁺
126		1120	++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.96 (s, 1H), 9.00 (s, 1H), 8.73 (dd, J = 9.3, 1.1 Hz, 1H), 8.50 (d, J = 9.3 Hz, 1H), 8.26 (d, J = 1.9 Hz, 1H), 8.15 (dd, J = 10.3, 8.6 Hz, 1H), 7.93 (dd, J = 11.2, 7.2 Hz, 1H), 7.39 (s, 1H). MS-ESI: m/z 327.44 observed (M+H) ⁺

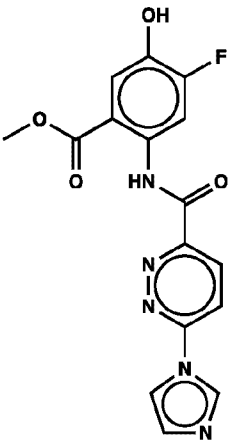
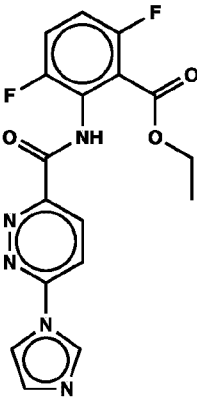
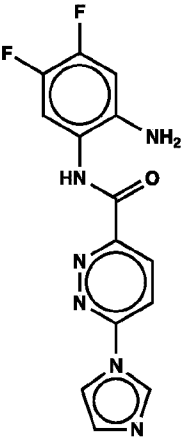
127		7299	++	MS-ESI: <i>m/z</i> 356.59 observed (M+H) ⁺
128		4349	++	MS-ESI: <i>m/z</i> 344.53 observed (M+H) ⁺
129		10683	++	MS-ESI: <i>m/z</i> 344.53 observed (M+H) ⁺

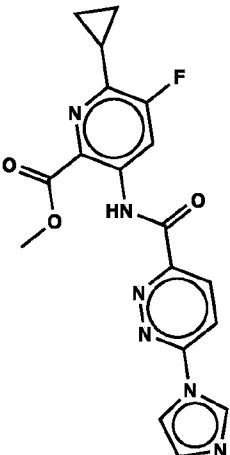
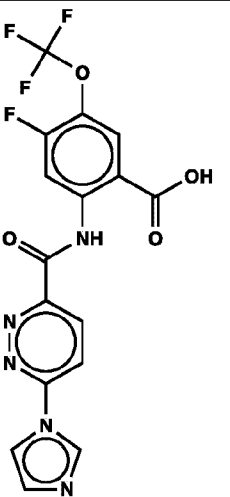
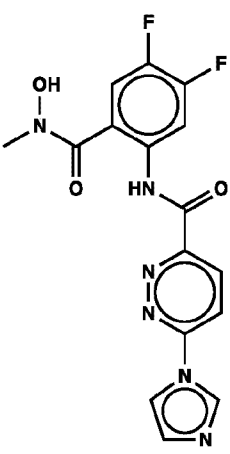
130		14770	++	MS-ESI: <i>m/z</i> 314.51 observed (M+H) ⁺
131		3479	++	MS-ESI: <i>m/z</i> 378.5 observed (M+H) ⁺
132		4284	++	MS-ESI: <i>m/z</i> 328.45 observed (M+H) ⁺

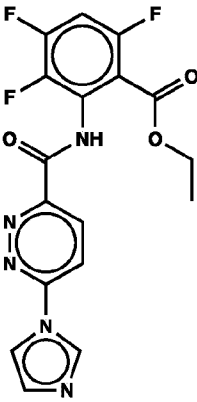
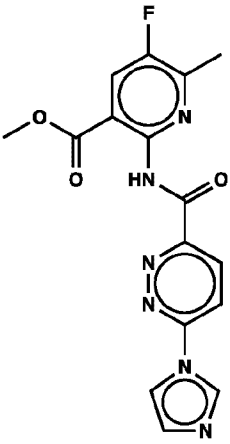
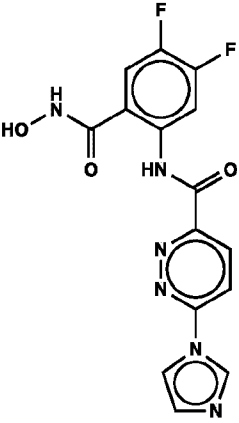
133		4173	++	MS-ESI: <i>m/z</i> 324.49 observed (M+H) ⁺
134		>50000	++	MS-ESI: <i>m/z</i> 341.51 observed (M+H) ⁺
135		12331	++	MS-ESI: <i>m/z</i> 372.53 observed (M+H) ⁺

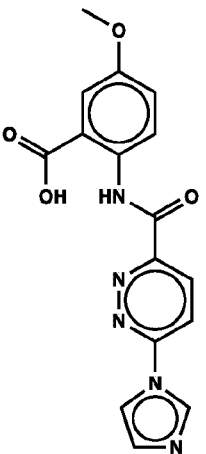
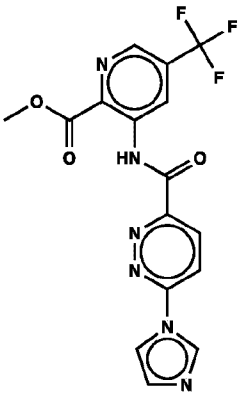
136		8844	++	MS-ESI: <i>m/z</i> 358.6 observed (M+H) ⁺
137		9328	++	MS-ESI: <i>m/z</i> 307.54 observed (M+H) ⁺
138		>50000	++	MS-ESI: <i>m/z</i> 377.49 observed (M+H) ⁺

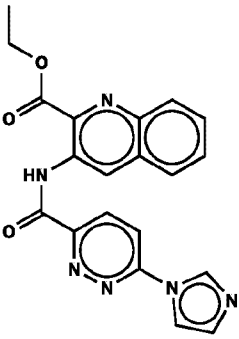
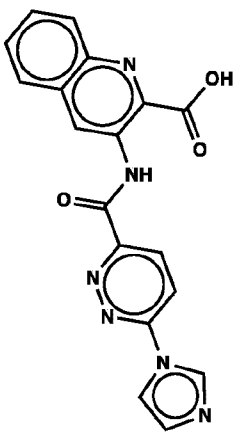
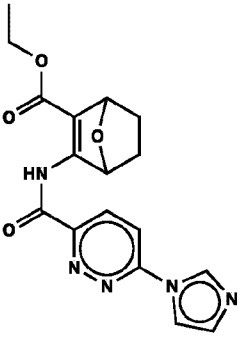
139		2518	++	MS-ESI: <i>m/z</i> 350.56 observed (M+H) ⁺
140		~25059	++	MS-ESI: <i>m/z</i> 361.5 observed (M+H) ⁺
141		>50000	++	MS-ESI: <i>m/z</i> 372.1 observed (M+H) ⁺

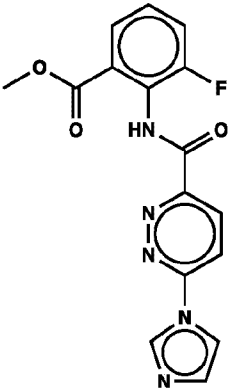
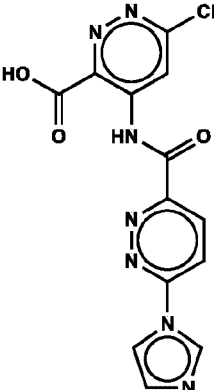
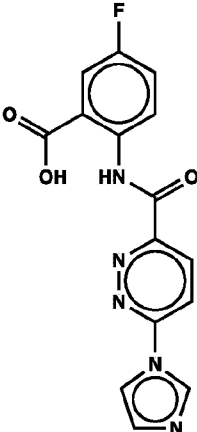
142		>50000	++	MS-ESI: <i>m/z</i> 358.16 observed (M+H) ⁺
143		9714	++	MS-ESI: <i>m/z</i> 374.1 observed (M+H) ⁺
144		>50000	++	MS-ESI: <i>m/z</i> 317.16 observed (M+H) ⁺

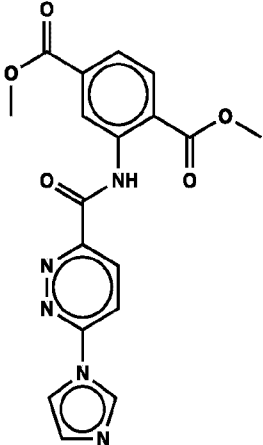
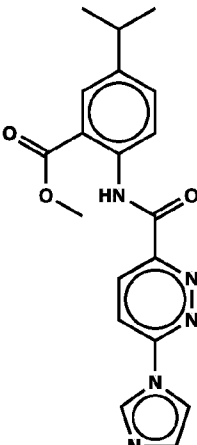
145		1583	++	MS-ESI: <i>m/z</i> 383.15 observed (M+H) ⁺
146		2178	++	MS-ESI: <i>m/z</i> 412.09 observed (M+H) ⁺
147		5245	++	MS-ESI: <i>m/z</i> 375.11 observed (M+H) ⁺

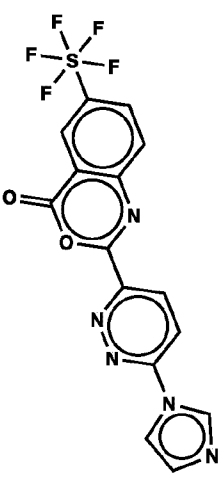
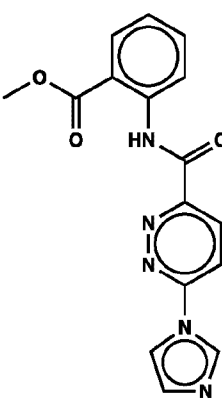
148		3677	++	MS-ESI: <i>m/z</i> 392.19 observed (M+H) ⁺
149		30053	++	MS-ESI: <i>m/z</i> 357.15 observed (M+H) ⁺
150		12167	++	MS-ESI: <i>m/z</i> 361.11 observed (M+H) ⁺

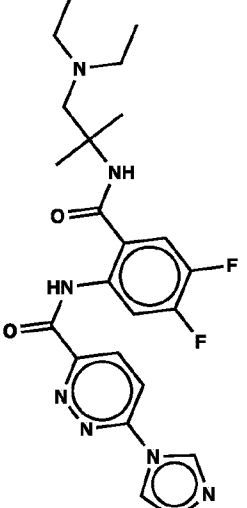
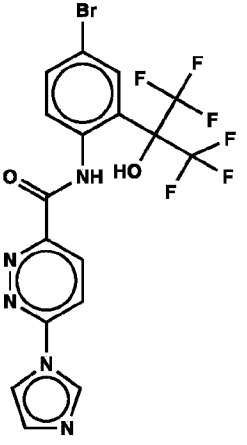
151		7761	++	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 15.68 (s, 1H), 8.78 (t, <i>J</i> = 1.1 Hz, 1H), 8.66 (d, <i>J</i> = 8.9 Hz, 1H), 8.44 (d, <i>J</i> = 9.1 Hz, 1H), 8.39 (d, <i>J</i> = 9.2 Hz, 1H), 8.20 (app t, <i>J</i> = 1.5 Hz, 1H), 7.61 (d, <i>J</i> = 3.2 Hz, 1H), 7.26 (dd, <i>J</i> = 1.5, 0.9 Hz, 1H), 6.92 (dd, <i>J</i> = 9.0, 3.2 Hz, 1H), 3.75 (s, 3H). MS-ESI: <i>m/z</i> 340.4 observed (M+H)⁺
152		~1266	++	¹H NMR (400 MHz, Methanol-<i>d</i>₄) δ 9.71 (s, 1H), 9.28 (s, 1H), 8.74 (s, 1H), 8.67 (d, <i>J</i> = 9.1 Hz, 1H), 8.41 (d, <i>J</i> = 9.1 Hz, 1H), 8.33 (s, 1H), 7.53 (s, 1H), 4.11 (s, 3H). MS-ESI: <i>m/z</i> 393.13 observed (M+H)⁺

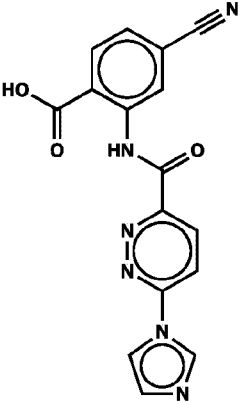
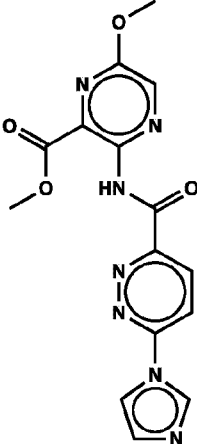
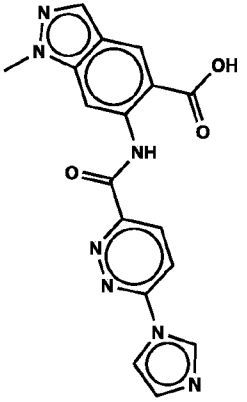
153		42.99	+++	MS-ESI: m/z 389.18 observed (M+H) ⁺
154		~10383	++	MS-ESI: m/z 361 observed (M+H) ⁺
155		>50000	++	MS-ESI: m/z 356.15 observed (M+H) ⁺

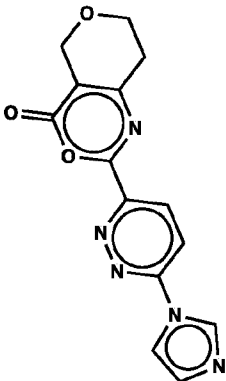
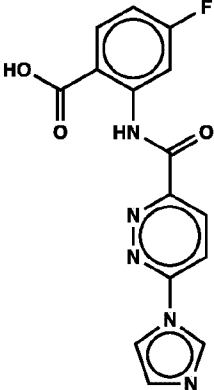
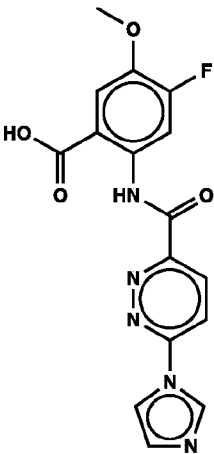
156		>50000	++	MS-ESI: <i>m/z</i> 342.15 observed (M+H) ⁺
157		>50000	++	MS-ESI: <i>m/z</i> 346.17 observed (M+H) ⁺
158		>20000	++	MS-ESI: <i>m/z</i> 328.08 observed (M+H) ⁺

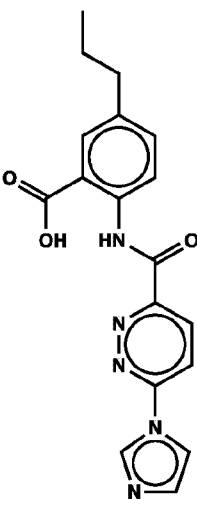
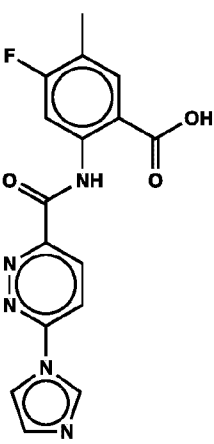
159		>20000	++	MS-ESI: <i>m/z</i> 382.14 observed (M+H) ⁺
160		3842	++	¹H NMR (400 MHz, DMSO-d₆) δ 12.96 (s, 1H), 8.85 – 8.82 (m, 1H), 8.77 (d, J = 8.6 Hz, 1H), 8.55 (d, J = 9.1 Hz, 1H), 8.47 (d, J = 9.2 Hz, 1H), 8.28 – 8.18 (m, 1H), 7.94 (d, J = 2.3 Hz, 1H), 7.66 (dd, J = 8.7, 2.3 Hz, 1H), 7.27 (t, J = 1.2 Hz, 1H), 3.95 (s, 3H), 2.97 (dt, J = 13.3, 6.6 Hz, 1H), 1.24 (d, J = 6.9 Hz, 6H). MS-ESI: <i>m/z</i> 366.2 observed (M+H)⁺

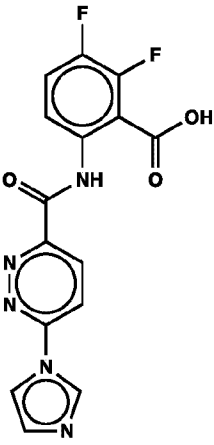
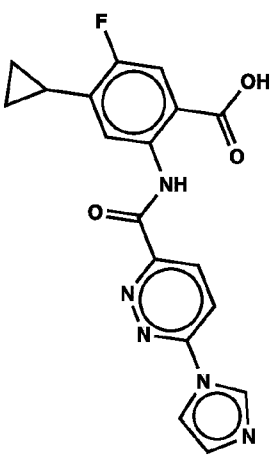
161		>20000	++	MS-ESI: <i>m/z</i> 418.05 observed (M+H) ⁺
162		956.4	+++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.08 (s, 1H), 9.39 (s, 1H), 8.86 (d, <i>J</i> = 8.4 Hz, 1H), 8.65 (d, <i>J</i> = 9.1 Hz, 1H), 8.55 (d, <i>J</i> = 9.1 Hz, 1H), 8.44 (s, 1H), 8.11 (d, <i>J</i> = 7.9 Hz, 1H), 7.77 (app t, <i>J</i> = 7.9 Hz, 1H), 7.58 (s, 1H), 7.32 (app t, <i>J</i> = 7.6 Hz, 1H), 3.96 (s, 3H). MS-ESI: <i>m/z</i> 324.27 observed (M+H) ⁺

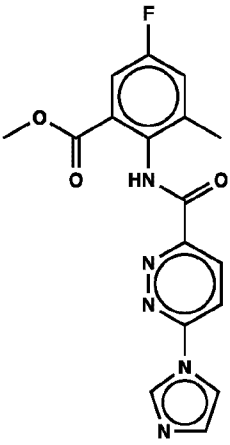
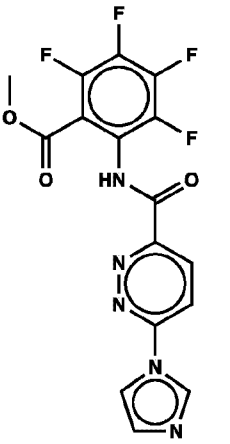
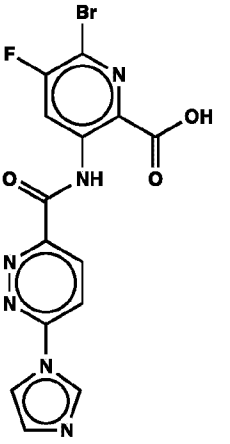
163		16559	++	MS-ESI: m/z 472.18 observed ($M+H$) ⁺
164		>20000	++	¹H NMR (400 MHz, DMSO-d_6) δ 12.27 (s, 1H), 10.77 (s, 1H), 9.01 (s, 1H), 8.71 (d, J = 9.0 Hz, 1H), 8.61 (d, J = 9.1 Hz, 1H), 8.51 (d, J = 9.1 Hz, 1H), 8.27 (d, J = 1.5 Hz, 1H), 7.89 (dd, J = 9.0, 2.2 Hz, 1H), 7.61 (d, J = 2.2 Hz, 1H), 7.39 (s, 1H). MS-ESI: m/z 511.97 observed ($M+H$)⁺

165		4086	++	MS-ESI: <i>m/z</i> 335.11 observed (M+H) ⁺
166		12093	++	MS-ESI: <i>m/z</i> 356.08 observed (M+H) ⁺
167		14939	++	MS-ESI: <i>m/z</i> 364.12 observed (M+H) ⁺

168		11265	++	MS-ESI: <i>m/z</i> 298.2 observed (M+H) ⁺
169		12637	++	MS-ESI: <i>m/z</i> 328.47 observed (M+H) ⁺
170		10950	++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.18 (s, 1H), 9.05 (s, 1H), 8.74 (d, <i>J</i> = 14.1 Hz, 1H), 8.58 (d, <i>J</i> = 9.1 Hz, 1H), 8.49 (d, <i>J</i> = 9.2 Hz, 1H), 8.30 (s, 1H), 7.77 (d, <i>J</i> = 9.6 Hz, 1H), 7.40 (s, 1H), 3.91 (s, 3H); (carboxylic acid proton not located) MS-ESI: <i>m/z</i> 358.48 observed (M+H) ⁺

171		>20000	++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 15.92 (s, 1H), 8.79 (app t, <i>J</i> = 1.1 Hz, 1H), 8.62 (d, <i>J</i> = 8.3 Hz, 1H), 8.45 (d, <i>J</i> = 9.2 Hz, 1H), 8.40 (d, <i>J</i> = 9.2 Hz, 1H), 8.21 (app t, <i>J</i> = 1.4 Hz, 1H), 7.86 (d, <i>J</i> = 2.3 Hz, 1H), 7.26 (dd, <i>J</i> = 1.5, 0.9 Hz, 1H), 7.15 (dd, <i>J</i> = 8.4, 2.3 Hz, 1H), 2.57 – 2.52 (m, 2H), 1.60 (h, <i>J</i> = 7.2 Hz, 2H), 0.91 (t, <i>J</i> = 7.3 Hz, 3H) MS-ESI: <i>m/z</i> 352.5 observed (M+H) ⁺
172		1010	++	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 16.22 (s, 1H), 8.80 (app t, <i>J</i> = 1.1 Hz, 1H), 8.53 – 8.43 (m, 2H), 8.40 (d, <i>J</i> = 9.1 Hz, 1H), 8.21 (app t, <i>J</i> = 1.4 Hz, 1H), 7.94 (d, <i>J</i> = 9.8 Hz, 1H), 7.26 (s, 1H), 2.21 (s, 3H). MS-ESI: <i>m/z</i> 342.11 (M+H) ⁺

173		> 20000	++	MS-ESI: <i>m/z</i> 346.45 observed (M+H) ⁺
174		10042	++	¹H NMR (400 MHz, DMSO-d₆) δ 15.84 (s, 1H), 8.83 – 8.76 (m, 1H), 8.50 – 8.37 (m, 3H), 8.24 – 8.18 (m, 1H), 7.66 (d, J = 11.4 Hz, 1H), 7.26 (dd, J = 1.6, 0.9 Hz, 1H), 2.08 (td, J = 8.4, 4.3 Hz, 1H), 1.10 – 0.97 (m, 2H), 0.80 – 0.68 (m, 2H). MS-ESI: <i>m/z</i> 368.51 observed (M+H)⁺

175		~ 2811	++	MS-ESI: <i>m/z</i> 356.46 observed (M+H) ⁺
176		~ 2484	++	MS-ESI: <i>m/z</i> 396.36 observed (M+H) ⁺
177		>20000	+	MS-ESI: <i>m/z</i> 409.01 mCLF203 observed (M+H) ⁺

Activity score based on potency and efficacy data	
Score	Interpretation
++	Active but less potent & efficacious than reference compound; EC₅₀ > 1000 nM
+++	Comparable activity to reference compound; EC₅₀ < 3000 nM
++++	More potent and/or efficacious than reference compound; EC₅₀ < 900 nM

Related documents

[1] Corrales L, Glickman LH, McWhirter SM, Kanne DB, Sivick KE, Katibah GE, Woo SR, Lemmens E, Banda T, Leong JJ, Metchette K, Dubensky TW Jr, Gajewski TF. (2015) Direct Activation of STING in the Tumor Microenvironment Leads to Potent and Systemic Tumor Regression and Immunity. *Cell Rep.* 11: 1018-30.

[2] Deng, L. et al. (2014) STING-Dependent Cytosolic DNA Sensing Promotes Radiation-Induced Type I Interferon-Dependent Antitumor Immunity in Immunogenic Tumors, *Immunity.* 41: 843.

[3] Corrales L, Matson V, Flood B, Spranger S, Gajewski TF. (2017) Innate immune signaling and regulation in cancer immunotherapy. *Cell Res.* 27: 96-108.

[4] Corrales L, McWhirter SM, Dubensky TW Jr, Gajewski TF. (2016) The host STING pathway at the interface of cancer and immunity. *J Clin Invest.* 126: 2404-11.

With respect to combination therapies comprising administration of a compound of the invention and an immune-checkpoint targeting drug, or as combination therapies for the potentiation of ionizing radiation-based and existing chemotherapies therapeutic approaches, such as DNA-damage-based chemotherapies, we believe that the STING agonists of the invention can complement and potentiate the effects of these known therapeutic approaches. This is based on recent papers indicating the critical role of STING-dependent micronuclei-mediated tumor clearance using these approaches, see for example:

[5] Mackenzie, K.F., et al, (2017), cGAS surveillance of micronuclei links genome instability to innate immunity, *Nature*, 548, 461.

[6] Wang, W. et al., (2016), Effector T Cells Abrogate Stroma-Mediated Chemoresistance in Ovarian Cancer, *Cell*, 165, 1092–1105.

[7] Charlotte E. Ariyan, et al., January 16, 2018; DOI: 10.1158/2326-6066, Robust antitumor responses result from local chemotherapy and CTLA-4 blockade, cancerimmunolres.aacrjournals.org on January 31, 2018.

[8] Chung Kil Song, et al., *www.moleculartherapy.org* vol. 15 no. 8 aug. 2007, Chemotherapy Enhances CD8+ T Cell-mediated Antitumor Immunity Induced by Vaccination With Vaccinia Virus.

Compounds of the invention can be used in therapeutic combinations with administration of an effective dose of an immune-checkpoint targeting drug. For example, the immune-checkpoint targeting drug can be an anti-PD-L1 antibody, anti-PD-1 antibody, anti-CTLA-4 antibody, or an anti-4-1BB antibody. See, for example:

[9] Ager, CR, et al., (2017) *Cancer Immunol Res*; 5(8), 676.

[10] Fu, J. et al. (2015) *Sci Transl Med*. 2015 April 15; 7(283): 283ra52.

doi:10.1126/scitranslmed.aaa4306.

[11] Wang, H., et al. (2017) *PNAS* | February 14, 2017 | vol. 114 | no. 7 | 1637–1642.

EXAMPLES

Tissue culture

Wild-type (cat. no. thpl-isg) and STING KO (cat. no. thpd-kostg) THP-1-Lucia ISG cells were purchased from Invivogen and maintained in growth media consisting of RPMI 1640, 2mM L-glutamine, 25 mM HEPES, 10% heat-inactivated fetal bovine serum (FBS), 1,000 units/ml penicillin, 1,000 µg/ml streptomycin, 0.25 µg/ml Amphotericin B, and 100 µg/ml zeocin unless otherwise stated.

Type 1 interferon stimuli

Poly(dA:dT) and 2'3'-cGAMP were purchased from invivogen and resuspended according to manufacturer's instructions.

ISRE-luciferase assay

THP-1 Lucia ISG cells were resuspended in low-serum growth media (2% FBS) at a density of 5×10^5 cells/ml and treated with test article or vehicle (DMSO). 50 µL of cells were seeded into each well of a 384-well white greiner plates and incubated for 24 hours. To evaluate expression of the luciferase reporter, 30 µl of Quanti-luc (Invivogen) detection reagent was added to each well and luminescence was read using an Envision plate reader (Perkin Elmer) set with an integration time of 0.1 seconds.

Viability assay

Cells were resuspended in low-serum growth media at a density of 5×10^5 cells/ml and treated with test article or vehicle (DMSO). 50 µL of cells were seeded into each well of a 384-well white greiner plates and incubated for 24 hours. To evaluate expression of the luciferase reporter, 30 µl of CellTiter-Glo (Promega) detection reagent was added to each well and luminescence was detected using an Envision Plate Reader set with an integration time of 0.1 seconds.

Western Blot

Cells were solubilized in 1X protein lysis buffer (25 mM HEPES, pH 7.4, 300 mM NaCl, 1.5 mM MgCl₂, 1 mM EGTA, 1% P-40, 1% sodium deoxycholate, 2.5 mM sodium pyrophosphate, 1 mM glycerophosphate) with freshly added protease and phosphatase inhibitors (Cell Signaling). Western blotting was performed using Bolt™ 4-12% Bis-Tris gels and Bolt™ mini transfer system following the manufacturer's instructions (ThermoFisher Scientific). STING and γ -tubulin antibodies were purchased from Cell Signaling diluted in 5% BSA, 1X TBS-T buffer (Table 3). Anti-rabbit HRP antibody was diluted in 5% non-fat dried milk, 1X TBS-T buffer and luminescence signal was imaged using a ChemiDoc Imager (BioRad).

Semi-quantitative real-time PCR (qPCR)

THP-1 cells were resuspended in low-serum growth media at a density of 5×10^5 cells/ml and treated with test article or vehicle (DMSO). 2.5 mL of cells were seeded into each well of a 6-well plate and incubated for 24 hours. RNA was isolated using an RNeasy Plus Mini Kit (Qiagen) and 1 μ g of purified RNA was reverse-transcribed into cDNA (VILO, cat. no. 11755050, ThermoFisher Scientific). Gene expression was assessed using Taqman primers and probes listed in Table 4 with the Taqman Universal Mix II (cat. no. 4440038, ThermoFisher) following manufacturer's instructions. Gene expression was normalized using the double delta Ct method and was reported as fold change in expression.

STING Thermal Shift Assay (TSA)

The c-terminal domains (CTD) of human and mouse STING were expressed and purified as detailed previously (Ouyang et al., 2012). Test article or vehicle controls were added to diluted STING protein (0.22 mg/ml) in 1X Protein Thermal Shift Buffer provided in the Protein Thermal Shift Dye Kit (cat # 4461146, ThermoFisher Scientific). Thermal Shift dye was added and mixed prior to performing a melt curve following parameters outlined for the Dye kit. Melt temperatures (T_m) were calculated using the Derivative method using Protein Thermal Shift Software v1.3 (cat # 4466038, ThermoFisher Scientific).

Table 2: Cell Signaling Antibodies

Protein target	Cat. No.	Dilution
STING	13647	1:1000
γ -tubulin	5886	1:3000
Rabbit IgG	7074	1:3000

Table 3: ThermoFisher Scientific Taqman Primers/Probe

Gene Symbol	Species	Cat. No.	Dye
IFNB1	human	Hs01077958_s1	FAM

CXCL10	human	Hs00171042_m1	FAM
IFIT3	human	Hs01922752_s1	FAM
B2M	human	Hs00187842_m1	VIC

Ouyang, S., Song, X., Wang, Y., Ru, H., Shaw, N., Jiang, Y., Niu, F., Zhu, Y., Qiu, W., Parvatiyar, K., *et al.* (2012). Structural analysis of the STING adaptor protein reveals a hydrophobic dimer interface and mode of cyclic di-GMP binding. *Immunity* 36, 1073-1086.

Compounds useful for carrying out a method of the invention can be prepared according to the following procedures in conjunction with ordinary knowledge and skill in organic synthesis, substituting appropriate reagents as apparent to the practitioner.

Experimental Procedures

Abbreviations

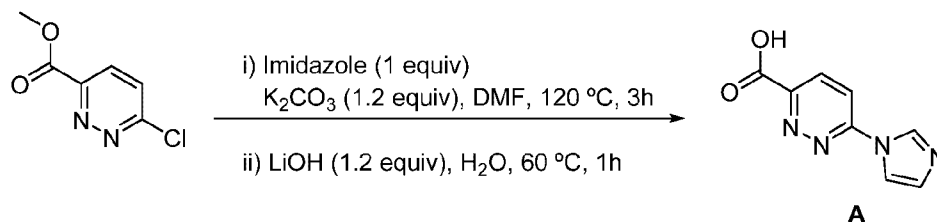
The following abbreviations are used: tetrahydrofuran (THF), dichloromethane (DCM), *N,N*-dimethylformamide (DMF), dimethylacetamide (DMA), dimethylsulfoxide (DMSO), trifluoroacetic acid (TFA), triethylamine (TEA), diisopropylethylamine (DIPEA), (1-Cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate, N-[(dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide (HATU).

General Examples for the Preparation of Compounds of the Invention

The starting materials and intermediates for the compounds of this invention may be prepared by the application or adaptation of the methods described below, their obvious chemical equivalents, or, for example, as described in literature such as *The Science of Synthesis*, Volumes 1-8. Editors E. M. Carreira et al. Thieme publishers (2001-2008). Details of reagent and reaction options are also available by structure and reaction searches using commercial computer search engines such as Scifinder (www.cas.org) or Reaxys (www.reaxys.com).

PART I: PREPARATION OF INTERMEDIATES

Scheme 1: Synthesis of intermediate-A:



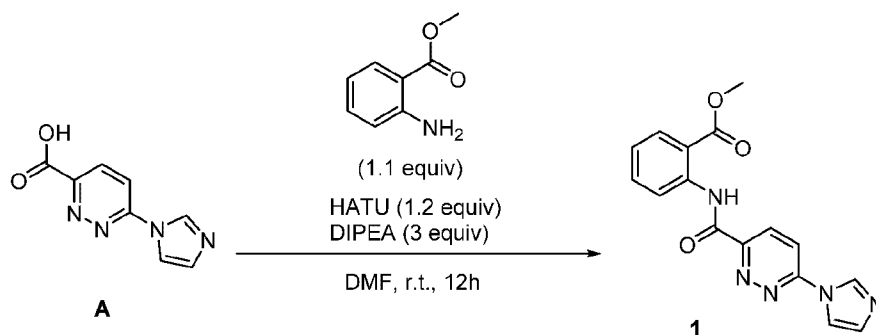
6-(1H-imidazol-1-yl)pyridazine-3-carboxylic acid, A: To a suspension of methyl 6-chloropyridazine-3-carboxylate (1 g, 5.8 mmol) and imidazole (400 mg, 5.8 mmol) in dry DMF (10 mL), was added K_2CO_3 (950 mg, 6.8 mmol) and the reaction mixture was stirred at 120 °C for 3h. The reaction was monitored by LCMS. After complete conversion to methyl 6-(1H-imidazol-1-yl)pyridazine-3-carboxylate, 2.5 M aq. LiOH (2.8 mL, 6.96 mmol) was added to the reaction mixture and stirred at 60 °C for 1h. The reaction was monitored by LCMS. After completion of the reaction, the reaction mixture was acidified with aq. 1 M HCl and the resulting precipitate was filtered and washed with water, to obtain the acid **A** (720 mg) as an off-white solid which was used in the next step without further purification. LC-MS (ESI+): m/z 191.0 $[M+H]^+$.

PART II: PREPARATION OF EXAMPLE COMPOUNDS

All compounds were prepared using the procedures exemplified below.

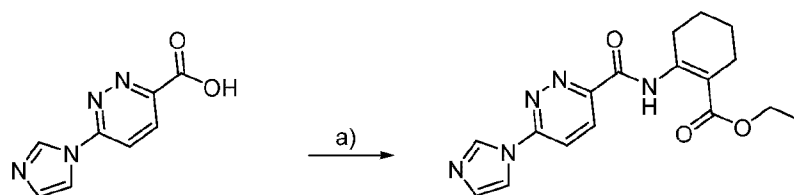
Example 1

Scheme 2: Synthesis of Compound 1:



methyl 2-(6-(1H-imidazol-1-yl)pyridazine-3-carboxamido)benzoate, 1: Intermediate A (190 mg, 1 mmol), methyl 2-aminobenzoate (166 mg, 1.1 mmol), HATU (456 mg, 1.2 mmol) and DIPEA (0.52 mL, 3 mmol) were dissolved in DMF (5 mL) and stirred at room temperature overnight. After the completion of reaction, solvent was evaporated under reduced pressure and the resulting crude material was purified by silica-gel column chromatography using 2-5% MeOH in DCM to obtain the compound **1** as an off-white solid (226 mg). LC-MS (ESI+): m/z 324.27 $[M+H]^+$.

Scheme 3

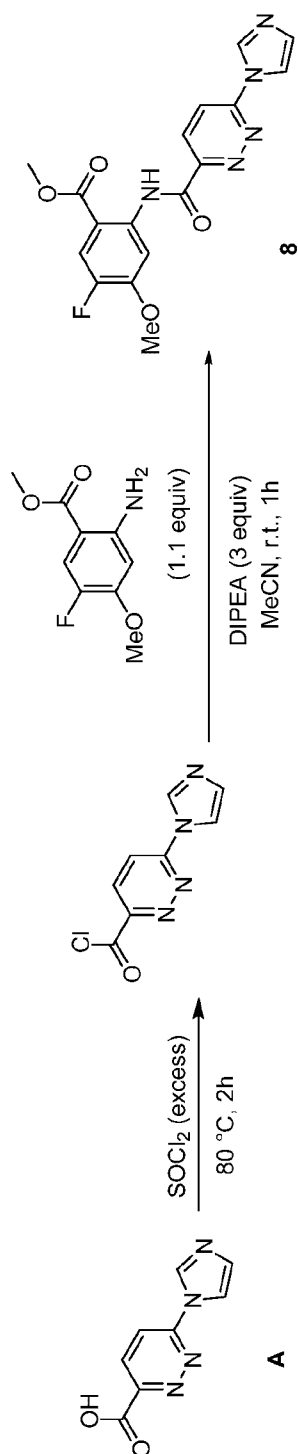


^aReagents and conditions: a) thionyl chloride, reflux, 3h; ethyl 2-aminocyclohex-1-ene-1-carboxylate, DIPEA, acetonitrile, rt, 30 min

Ethyl 2-(6-(1H-imidazol-1-yl)pyridazine-3-carboxamido)cyclohex-1-ene-1-carboxylate:

6-(1H-imidazol-1-yl)pyridazine-3-carboxylic acid (19 mg, 0.1 mmol) was dissolved in 0.3 mL of thionyl chloride and the mixture was heated under reflux for 3h. Then, the excess thionyl was removed under vacuum. The solid was dissolved in 0.5 mL of anhydrous acetonitrile and a solution of ethyl 2-aminocyclohex-1-ene-1-carboxylate (16.9 mg, 0.1 mmol) and DIPEA (26.1 μ L, 0.15 mmol) in 0.5 mL of anhydrous acetonitrile was added at room temperature. After stirring for 30 minutes, the crude mixture was filtered and purified by prep-HPLC to give the product (6.8 mg, 20 % yield).

Scheme 4: Synthesis of Compound 8:

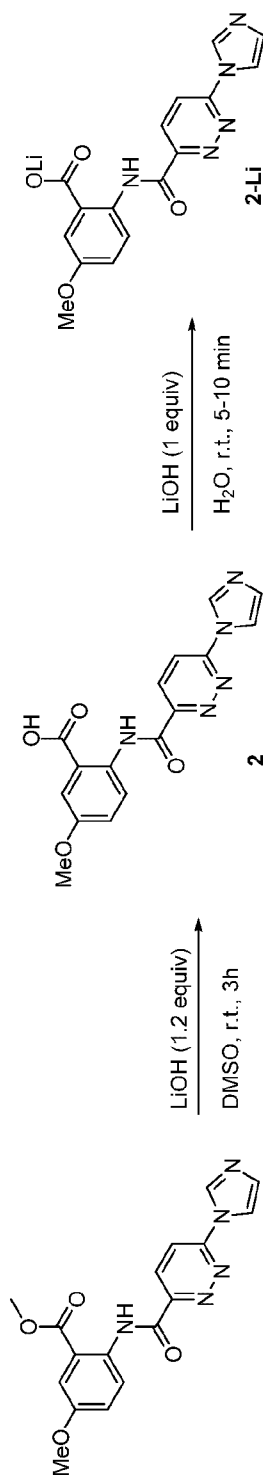


methyl 2-(6-(1H-imidazol-1-yl)pyridazine-3-carboxamido)-5-fluoro-4-methoxybenzoate,
8: Intermediate **A** (190 mg, 1 mmol) was stirred in the presence of SOCl_2 (5 mL) at 80°C for 2h. The volatiles were then removed followed by the addition of a solution of the methyl 2-

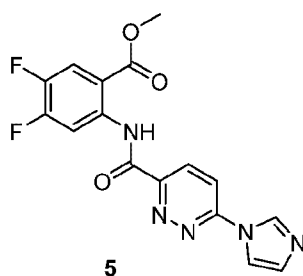
amino-5-fluoro-4-methoxybenzoate (219 mg, 1.1 mmol) and DIPEA (0.52 mL, 3 mmol) in acetonitrile (5 mL). The resulting reaction mixture was stirred at room temperature for 1h. The reaction was monitored by LCMS. After the completion of reaction, solvent was removed, and the resulting crude material was purified by silica-gel column chromatography using 2-5% MeOH in DCM to obtain the compound **8** as an off white solid (223 mg). LC-MS (ESI+): m/z 372.1 $[M+H]^+$.

Example 2-Li

Scheme 5: Synthesis of Compound 2-Li

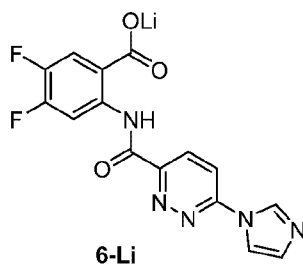


lithium 2-(6-(1H-imidazol-1-yl)pyridazine-3-carboxamido)-5-methoxybenzoate, 2-Li:
 methyl 2-(6-(1H-imidazol-1-yl)pyridazine-3-carboxamido)-5-methoxybenzoate was prepared by using the procedure followed for the compound **1** (Scheme C). The resulting ester (20 mg, 0.057 mmol) was dissolved in DMSO (0.8 mL) and then aq. 0.1M LiOH (0.68 mL, 1.2 mmol) was added followed by stirring at room temperature until completion of the reaction (~3 h). The reaction was monitored by LCMS. Then, the reaction mixture was acidified with 1M HCl via dropwise addition to generate the desired acid. The obtained precipitate was isolated and washed with water to give acid **2** as an off-white solid. LC-MS (ESI+): m/z 340.4 $[M+H]^+$. Acid **2** (10.2 mg, 0.03 mmol) was further suspended in 2.5 mL of water (0.25 mL/mg) and sonicated for 20 min to prepare a homogenous suspension. Thereafter, 1M LiOH (30 μ L, 0.03 mmol) was added to obtain a clear solution of the lithium salt, which was then filtered to remove any insoluble particles. The resulting solution was lyophilized to obtain the corresponding lithium salt **2-Li**. LC-MS (ESI+): m/z 340.4 $[M+H]^+$.



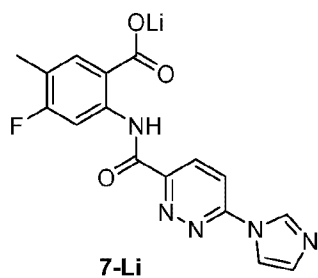
methyl 2-(6-(1H-imidazol-1-yl)pyridazine-3-carboxamido)-4,5-difluorobenzoate, 5:
 Compound **5** was prepared by using the procedure followed for the compound **1** (Scheme C). LC-MS (ESI+): m/z 360.21 $[M+H]^+$.

Example 6-Li



lithium 2-(6-(1H-imidazol-1-yl)pyridazine-3-carboxamido)-4,5-difluorobenzoate, 6-Li:
 Compound **6-Li** was prepared by using the procedure followed for the compound **2-Li** (Scheme D). LC-MS (ESI+): m/z 346.1 $[M+H]^+$.

Example 7-Li



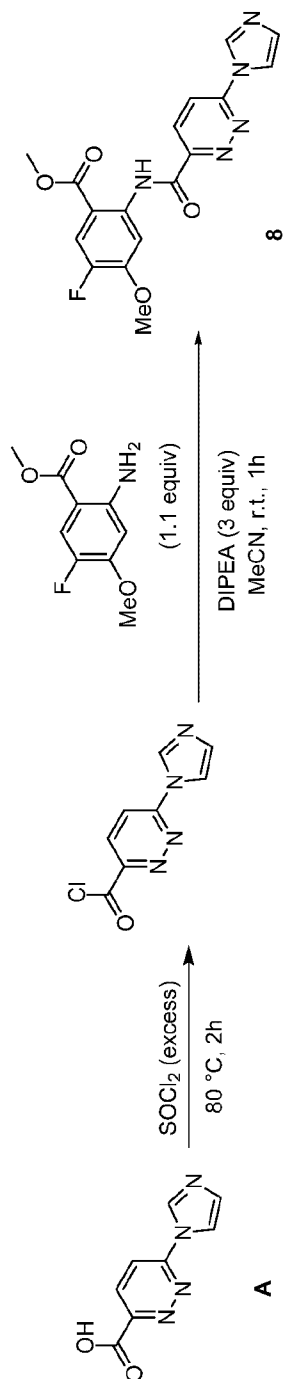
lithium 2-(6-(1H-imidazol-1-yl)pyridazine-3-carboxamido)-4-fluoro-5-methylbenzoate, 7-

Li: Compound 7-Li was prepared by using the procedure followed for the compound 2-Li

(Scheme D). LC-MS (ESI⁺): *m/z* 342.11 [M+H]⁺.

Example 8

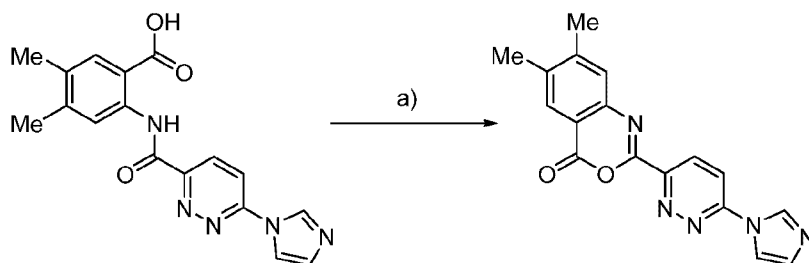
Scheme F: Synthesis of Compound 8:



methyl 2-(6-(1H-imidazol-1-yl)pyridazine-3-carboxamido)-5-fluoro-4-methoxybenzoate, 8: Intermediate A (190 mg, 1 mmol) was stirred in the presence of SOCl_2 (5 mL) at 80°C for 2 h. The volatiles were then removed followed by the addition of a solution of the methyl 2-amino-5-fluoro-4-methoxybenzoate (219 mg, 1.1 mmol) and DIPEA (0.52 mL, 3 mmol) in

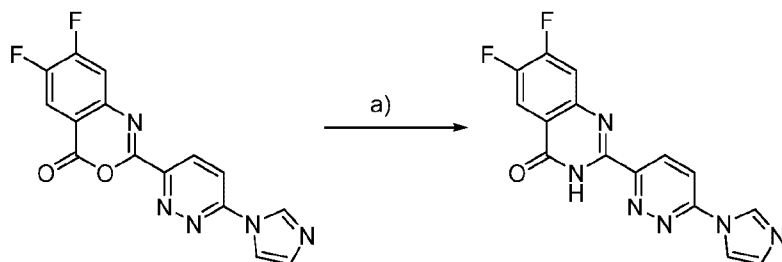
acetonitrile (5 mL). The resulting reaction mixture was stirred at room temperature for 1h. The reaction was monitored by LCMS. After the completion of reaction, solvent was removed, and the resulting crude material was purified by silica-gel column chromatography using 2-5% MeOH in DCM to obtain the compound **8** as an off white solid (223 mg). LC-MS (ESI+): m/z 372.1 $[M+H]^+$.

Scheme G: Synthesis of Dimethyl Oxazinone Compound



^aReagents and conditions: a) thionyl chloride, reflux, 3h; DIPEA, acetonitrile, rt, 30 min
2-(6-(1H-imidazol-1-yl)pyridazin-3-yl)-6,7-dimethyl-4H-benzo[d][1,3]oxazin-4-one: 2-(6-(1H-imidazol-1-yl)pyridazine-3-carboxamido)-4,5-dimethylbenzoic acid (33.7 mg, 0.1 mmol) was dissolved in 0.3 mL of thionyl chloride and the mixture was heated under reflux for 3h. Then, the excess thionyl was removed under vacuum. The solid was dissolved in 0.5 mL of anhydrous acetonitrile and a solution of DIPEA (26.1 μ L, 0.15 mmol) in 0.5 mL of anhydrous acetonitrile was added at room temperature. After stirring for 30 minutes, the obtained precipitate was isolated and washed with acetonitrile to give the product (26.2 mg, 82 % yield).

Scheme H: Synthesis of Difluoro Oxazinone Compound



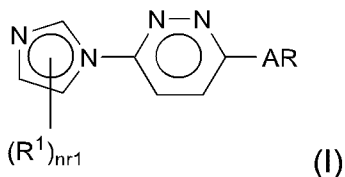
^aReagents and conditions: a) formamide, microwave, 200°C
2-(6-(1H-imidazol-1-yl)pyridazin-3-yl)-6,7-difluoro-4H-benzo[d][1,3]oxazin-4-one: A solution of 2-(6-(1H-imidazol-1-yl)pyridazin-3-yl)-6,7-difluoro-4H-benzo[d][1,3]oxazin-4-one (32.7mg, 0.1 mmol) in 2mL of formamide was placed in 10 mL microwave vial which was sealed and irradiated at a temperature of 200 °C for 15 min. The reaction was monitored by LCMS. After

the completion of reaction, 4 mL of methanol was added and the crude mixture was filtered and purified by prep-HPLC to give the product (13.0 mg, 40% yield).

While the invention has been described and exemplified in sufficient detail for those skilled in this art to make and use it, various alternatives, modifications, and improvements will be apparent to those skilled in the art without departing from the spirit and scope of the claims.

CLAIMS:

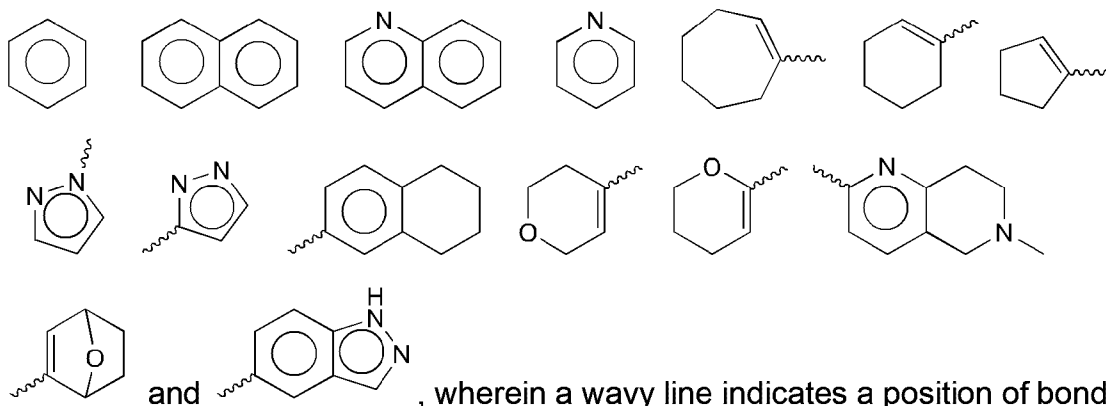
1. Use of a compound of formula (I) for stimulating expression of interferon genes in a patient:



wherein each R¹ is independently (C1-C4)alkyl, or CN, nr1 is 0, 1, 2, or 3, provided that each R¹ is bonded to a carbon atom; and,

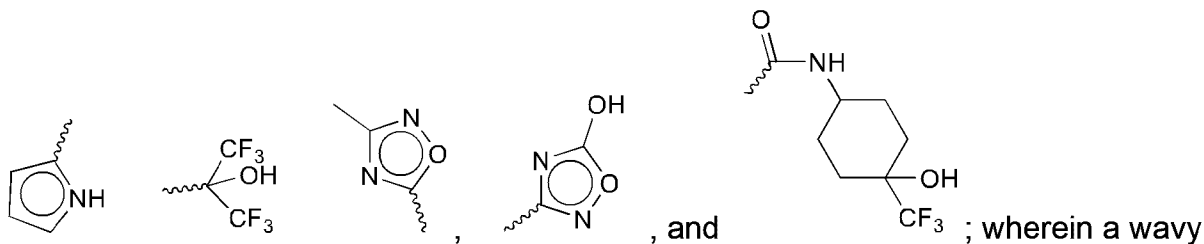
AR is a group of formula -C(=O)N(R)Ar¹; R is H or (C1-C4)alkyl;

wherein Ar¹ is chosen from the group consisting of:



wherein any Ar¹ is substituted with nr2 independently selected R² groups chosen from the group consisting of:

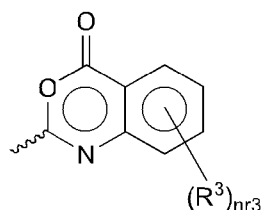
-(C1-C4)-alkyl, -(C1-C4)-alkylO, -(C1-C4)-alkylOC(O), -CN, -halo, -(C3-C7)cycloalkyl, -(C1-C4)-alkOC(O), -COOH, (C3-C7)-cycloalkylOC(O), -SF₅, -methylenedioxy, -difluoromethylenedioxy, -ethylenedioxy, -CF₃, -OCF₃, -C(O)NH₂, -C(O)NH(CH₂)₂OH, -CH₂OH, -NR₂, -CONH-arginine, -C(O)O(CH₂)₂NR₂,



line indicates a position of bonding; and, nr2 = 0, 1, 2, or 3;

or,

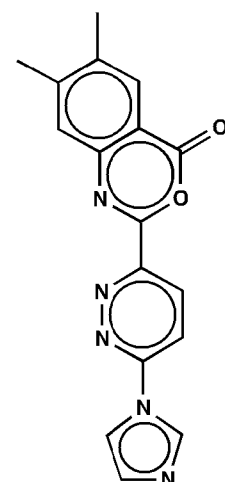
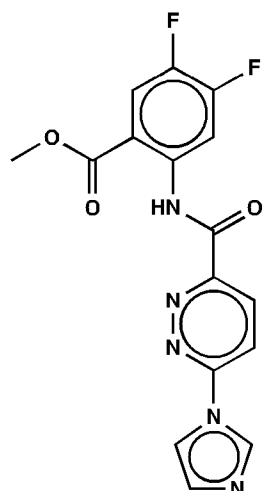
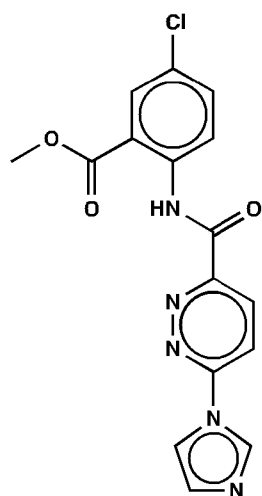
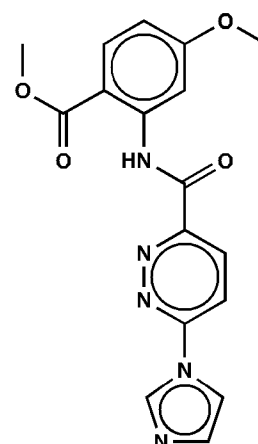
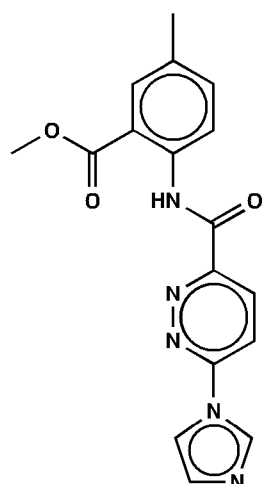
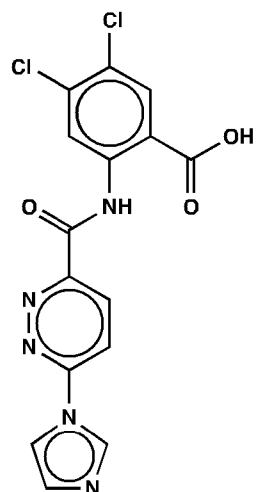
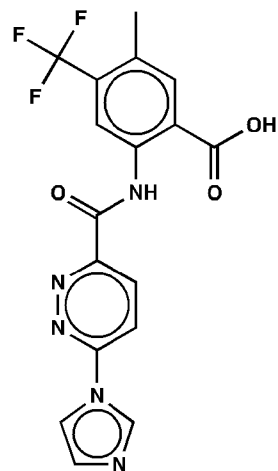
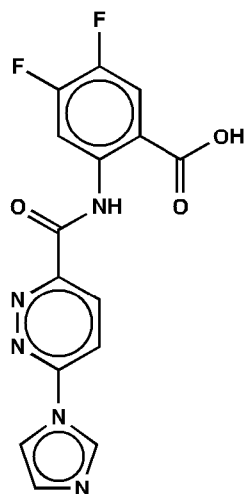
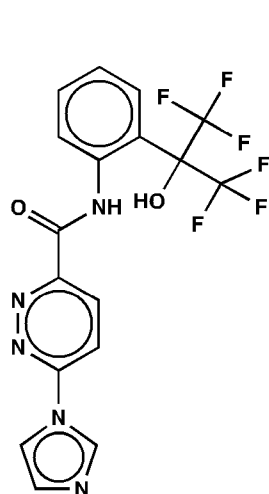
AR is a group of formula

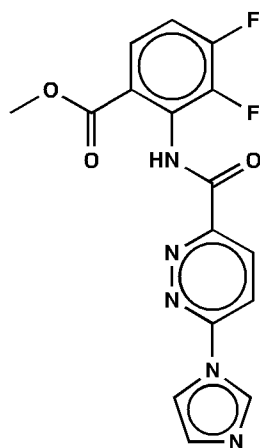
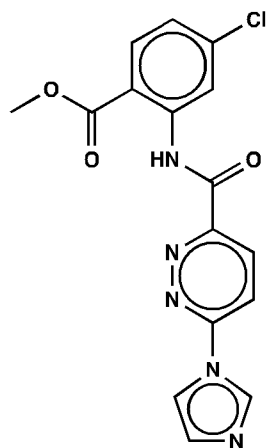
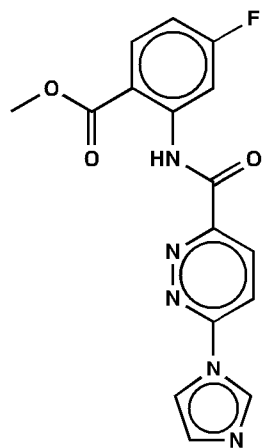
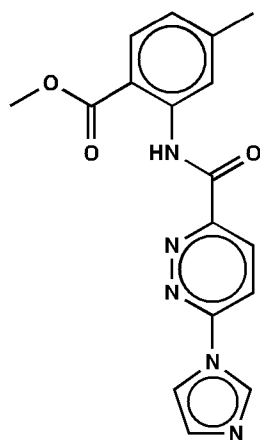
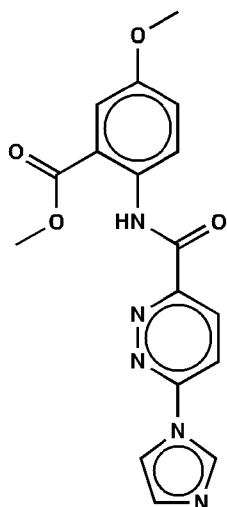
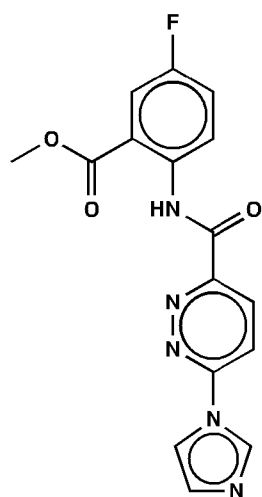
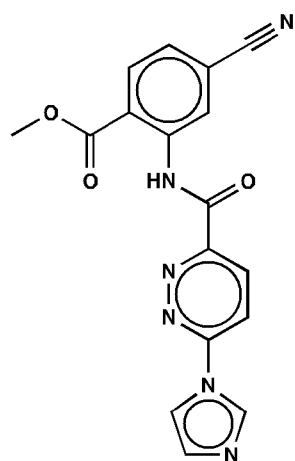
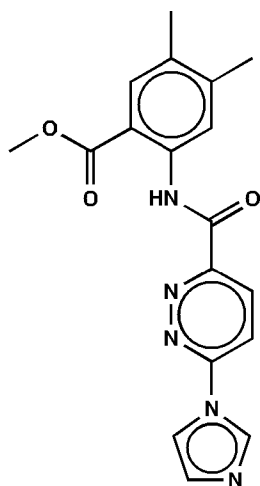
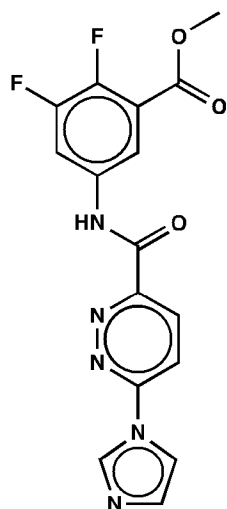


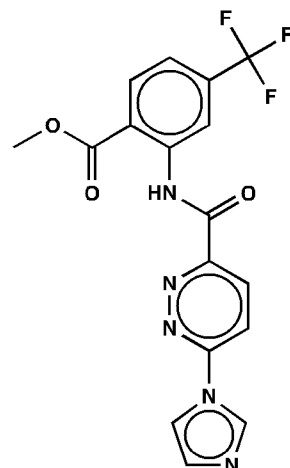
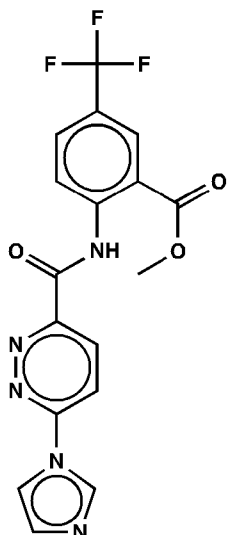
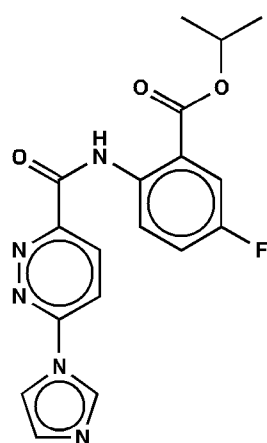
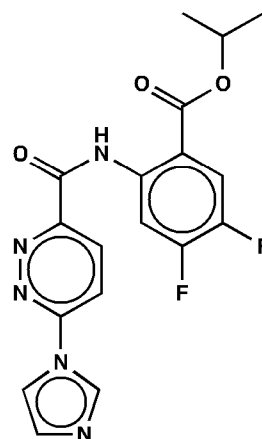
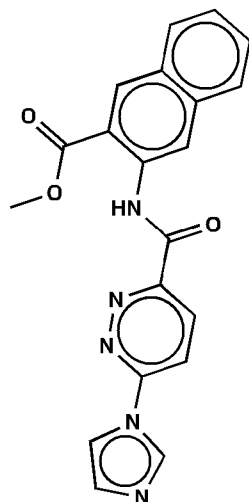
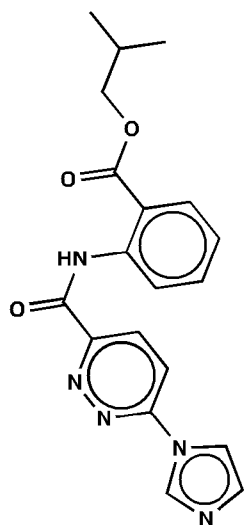
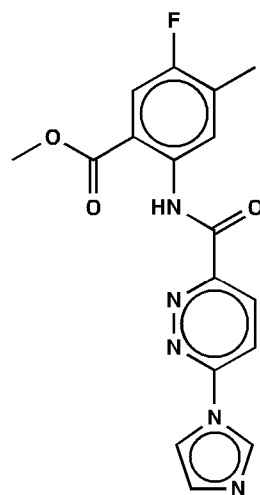
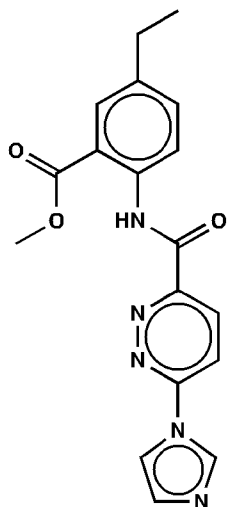
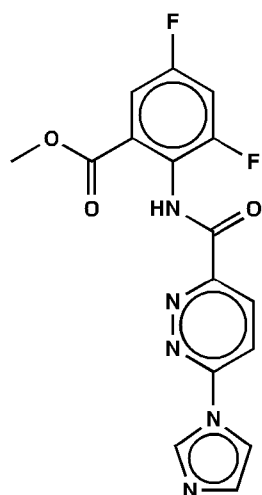
wherein R^3 is selected from the group consisting of

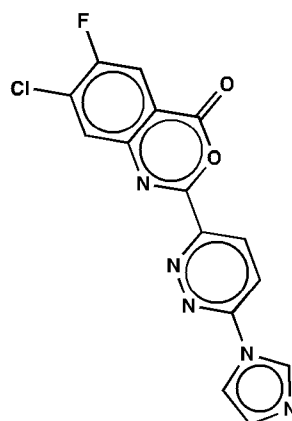
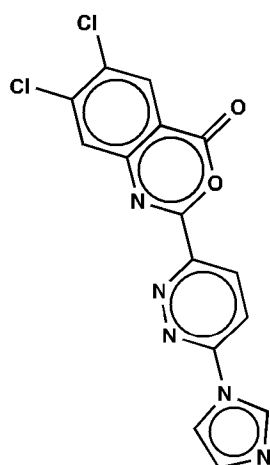
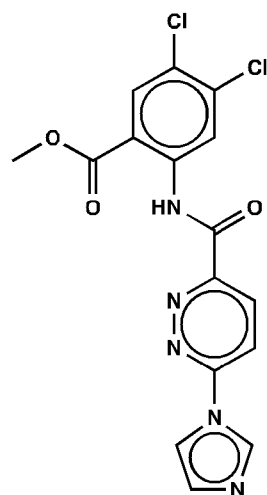
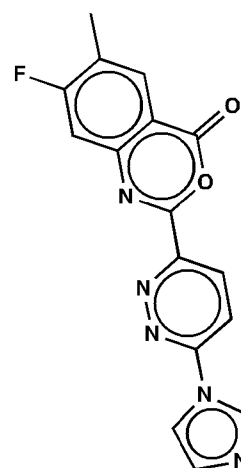
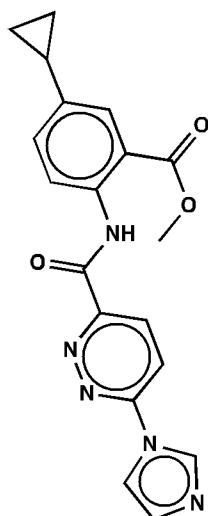
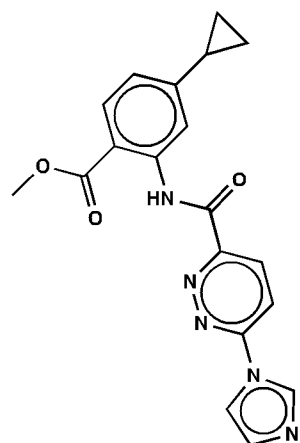
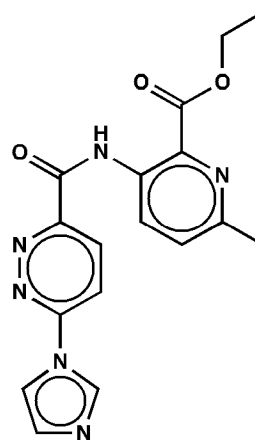
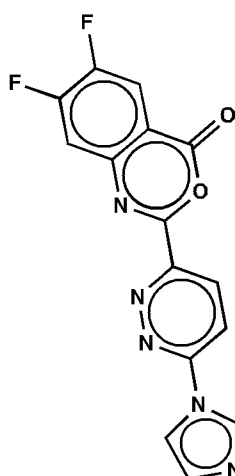
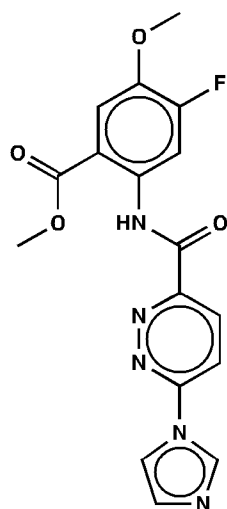
(C1-C4)-alkyl, (C1-C4)-alkylo, (C1-C4)-alkyloC(O), CN, halo, (C3-C7)cycloalkyl, (C1-C4)-alkOC(O), COOH, (C3-C7)-cycloalkyloC(O), $-SF_5$, methylenedioxy, difluoromethylenedioxy, ethylenedioxy, CF_3 , $-OCF_3$, $CONH_2$, $CONH(CH_2)_2OH$, CH_2OH , NR_2 , $CONH$ -arginine, and $C(O)O(CH_2)_2NR_2$; and $nr3 = 0, 1, 2, \text{ or } 3$;
or a pharmaceutically acceptable salt thereof.

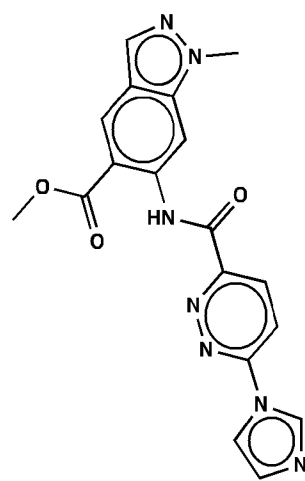
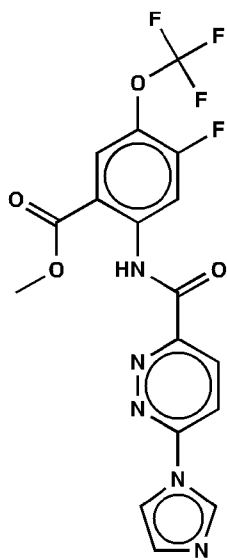
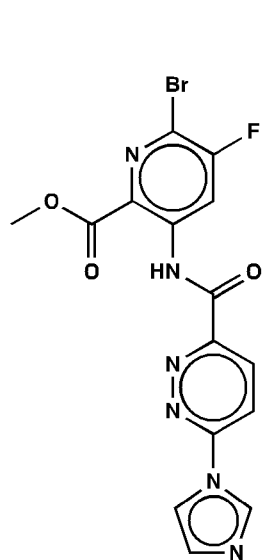
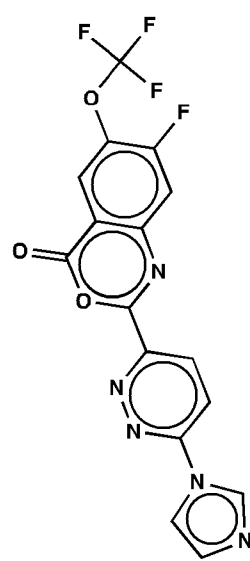
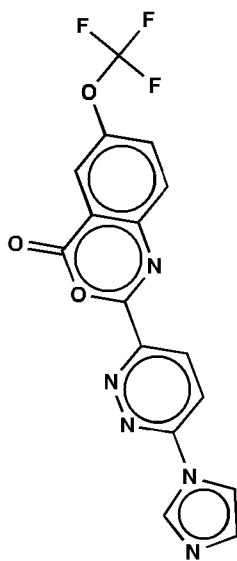
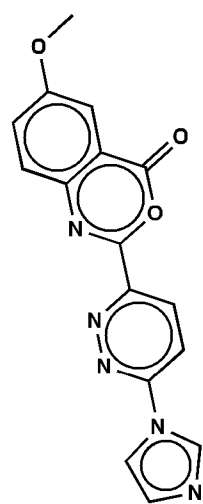
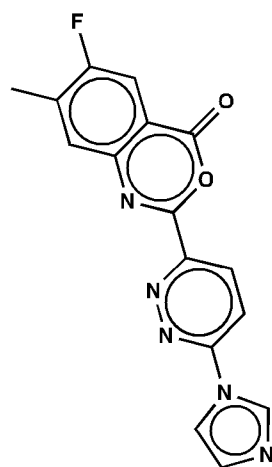
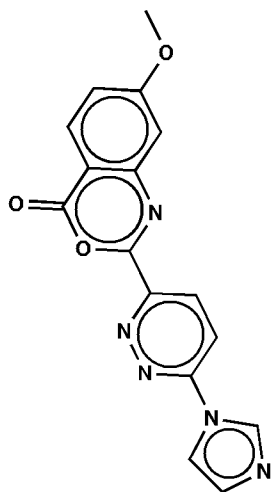
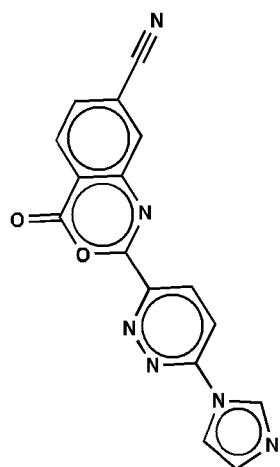
2. The use of claim 1, wherein the compound is for oral or intratumoral administration, or both.
3. The use of claim 1, wherein the compound is an antibody-drug conjugate, or in a liposomal formulation.
4. The use of claim 1, further comprising use of an effective dose of an immune-checkpoint targeting drug.
5. The use of claim 4, wherein the immune-checkpoint targeting drug comprises an anti-PD-L1 antibody, anti-PD-1 antibody, anti-CTLA-4 antibody, or an anti-4-1BB antibody.
6. The method of claim 1, further comprising use of ionizing radiation or anticancer drugs.
7. The use of claim 1, wherein the compound is any one of the following formulae:

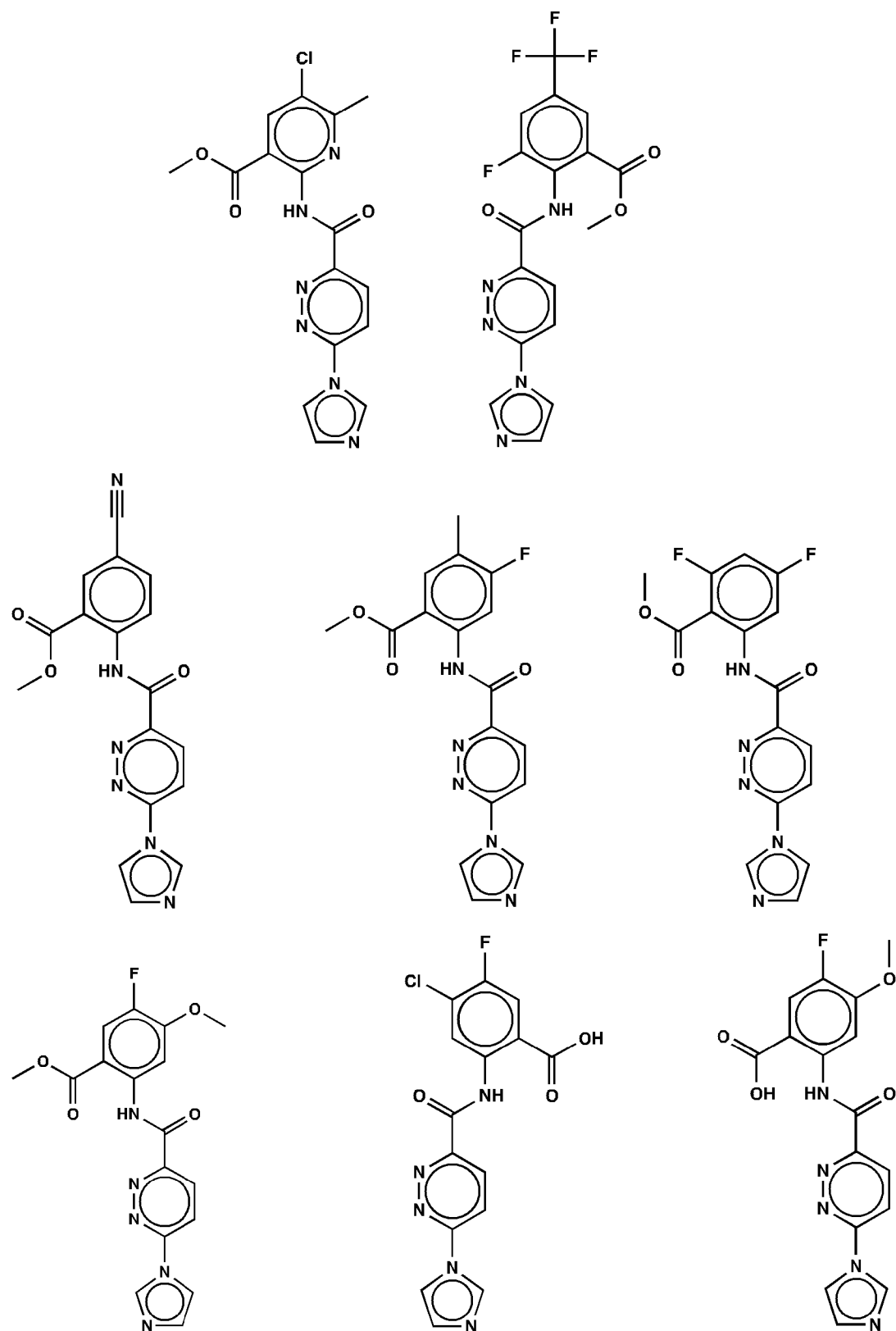


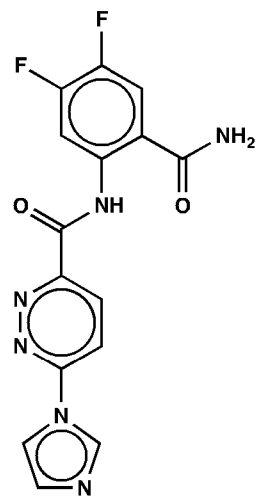
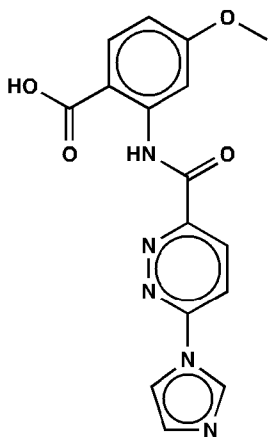
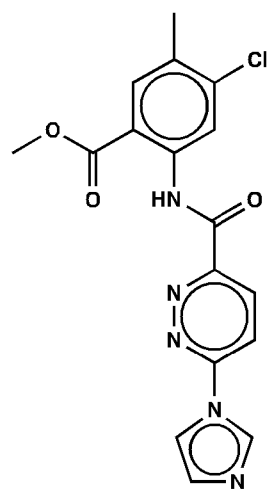
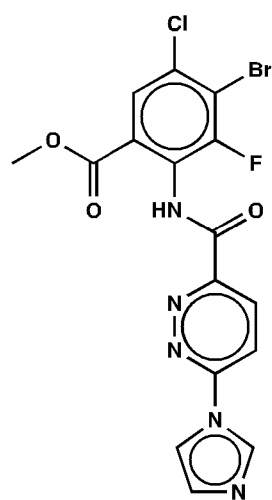
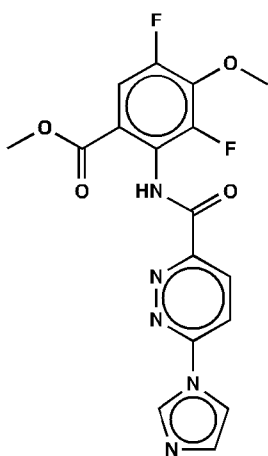
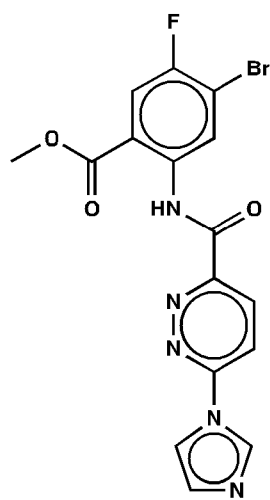
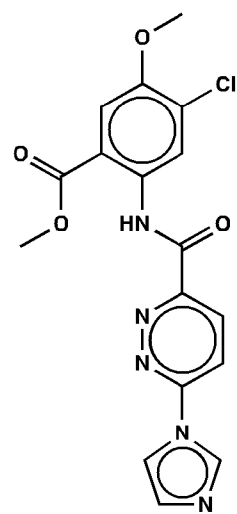
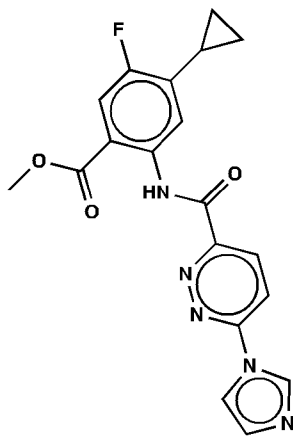
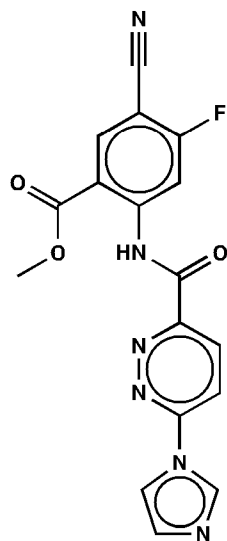


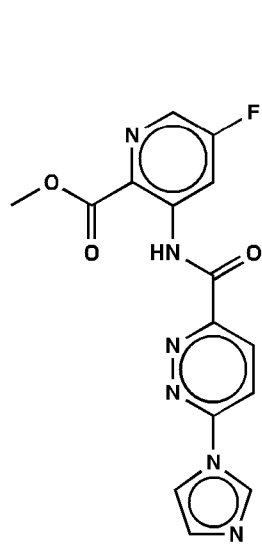
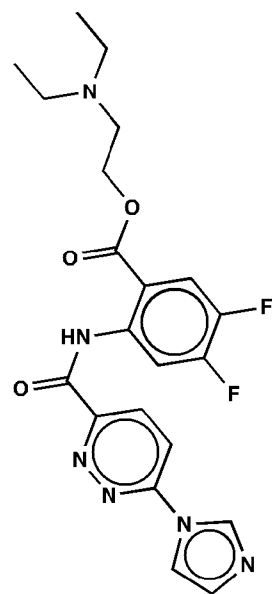
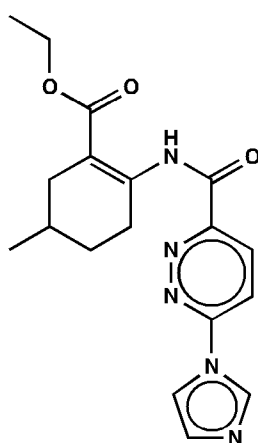
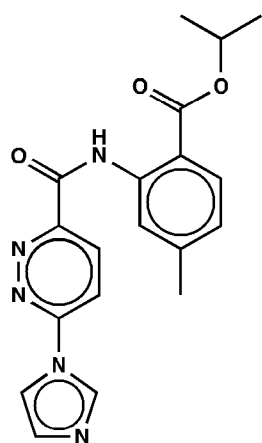
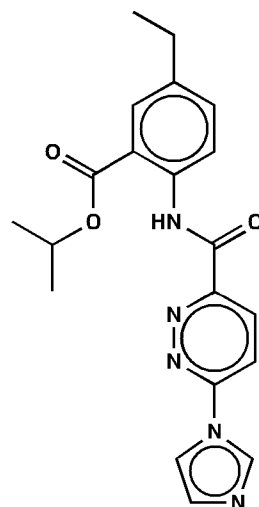
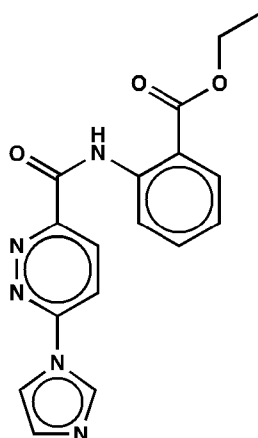
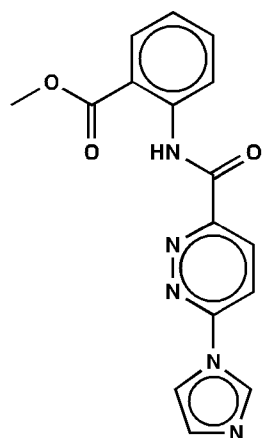




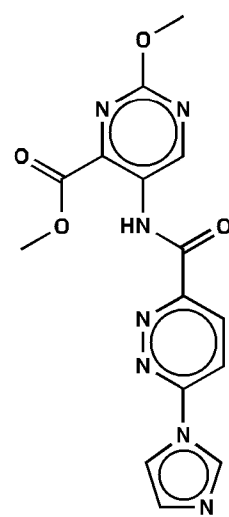
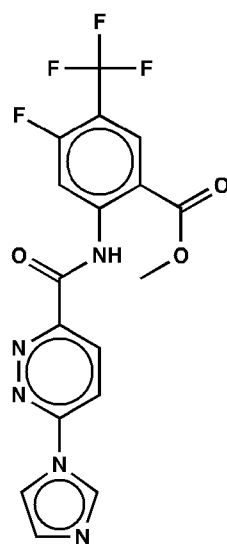


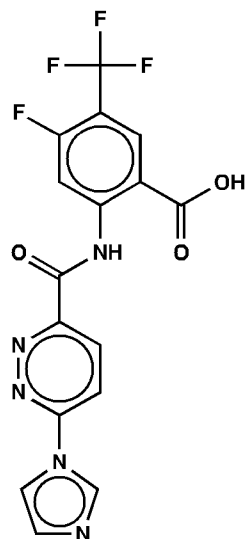
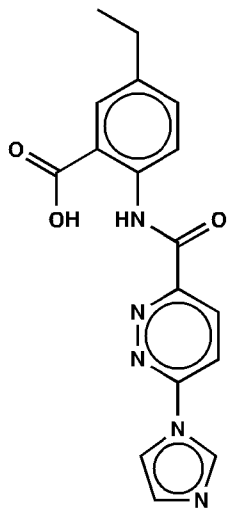
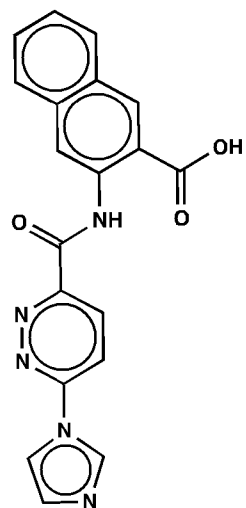
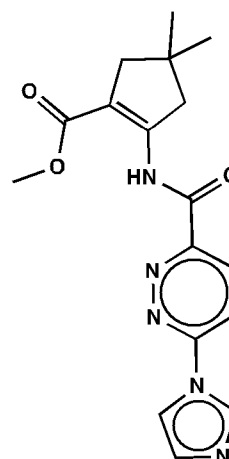
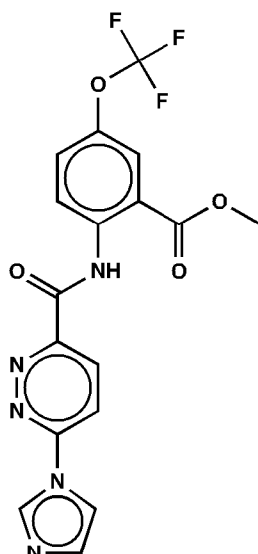
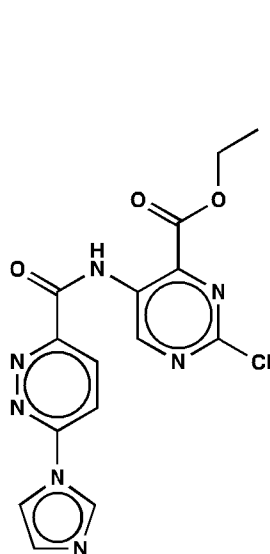
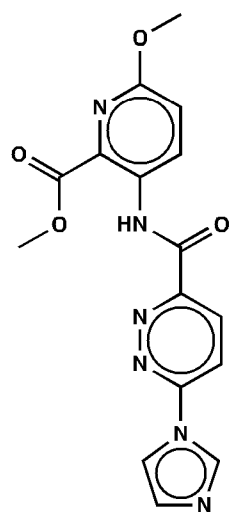
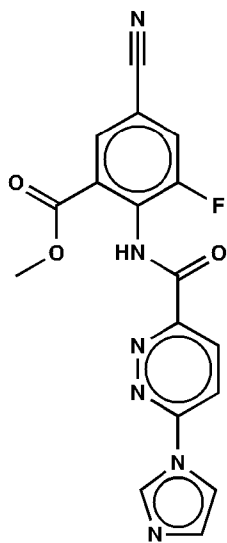
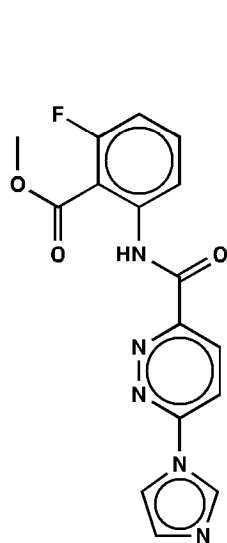


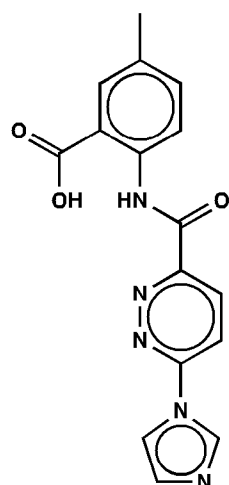
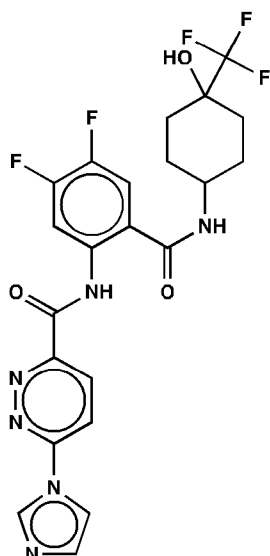
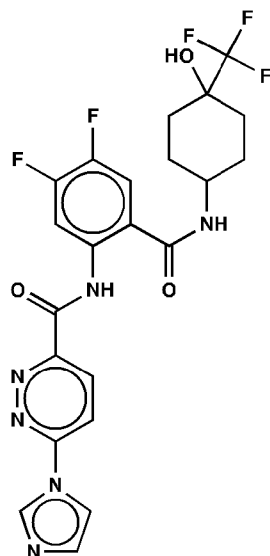
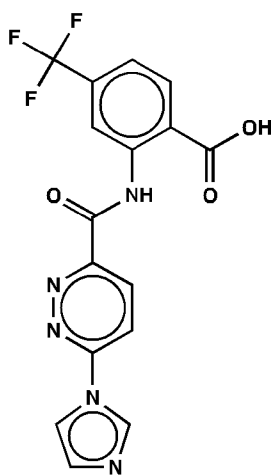
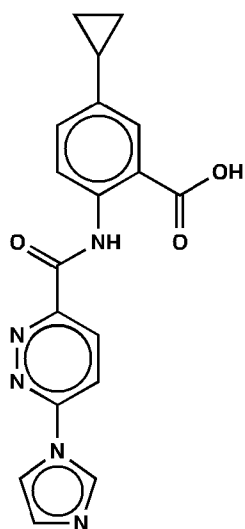
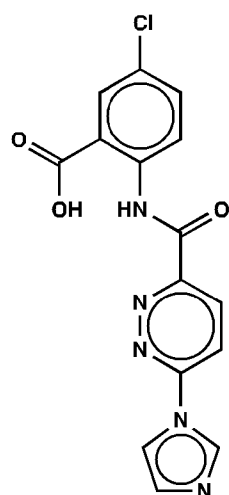
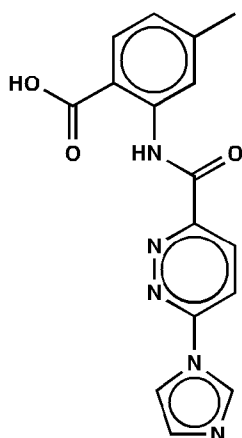
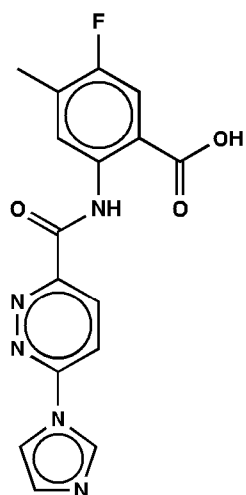


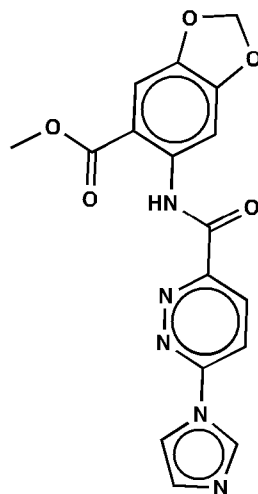
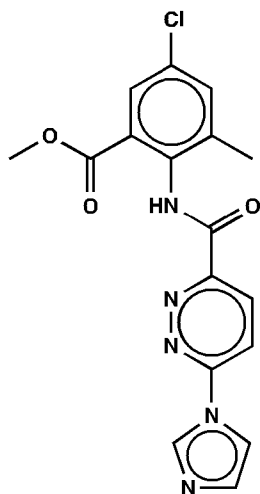
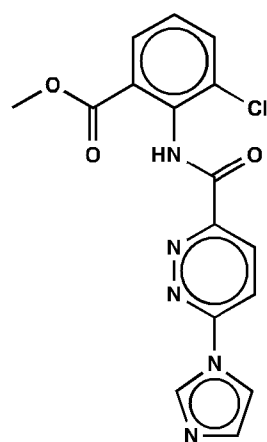
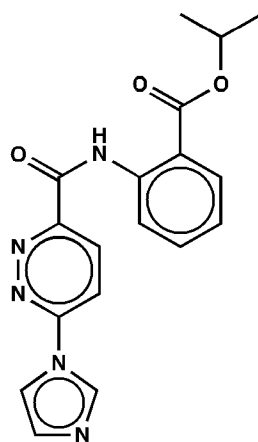
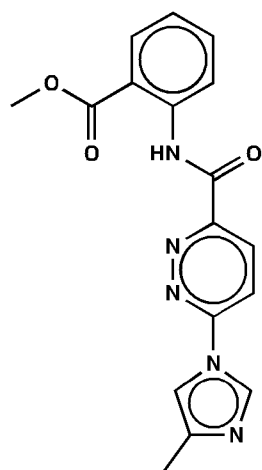
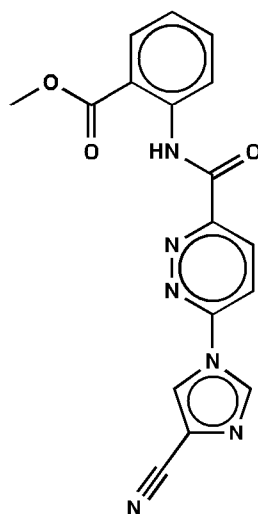
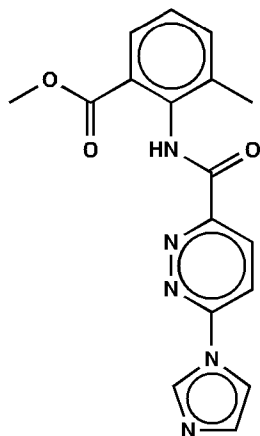
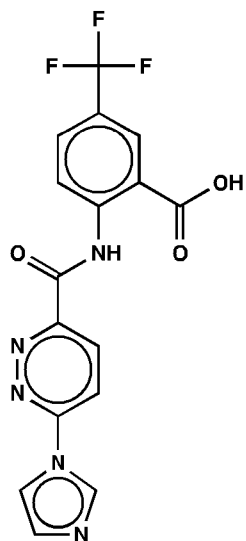


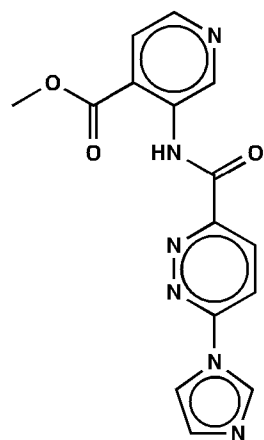
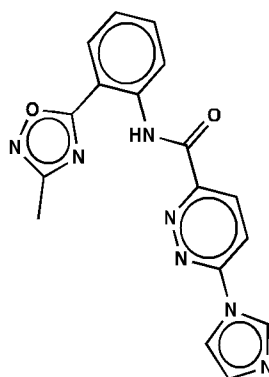
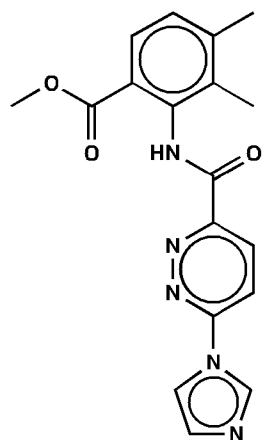
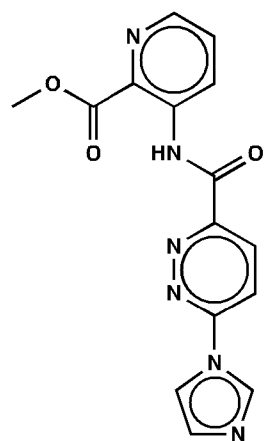
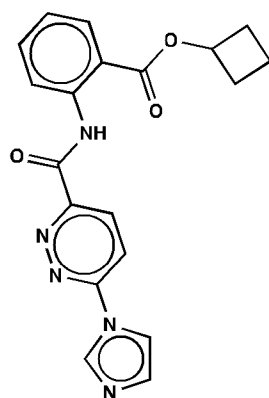
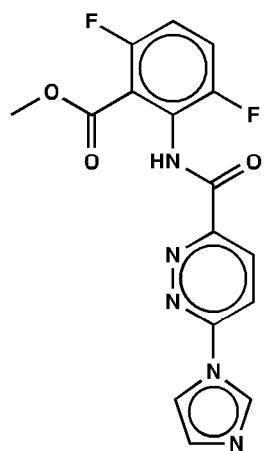
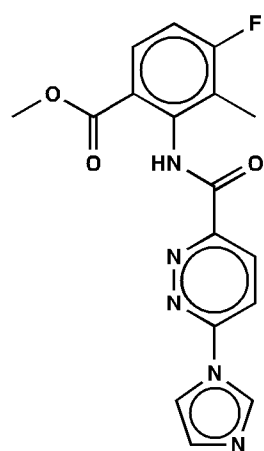
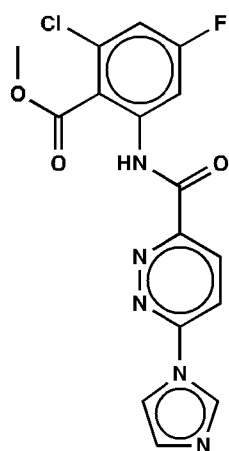
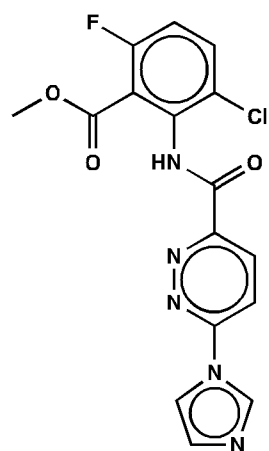
70

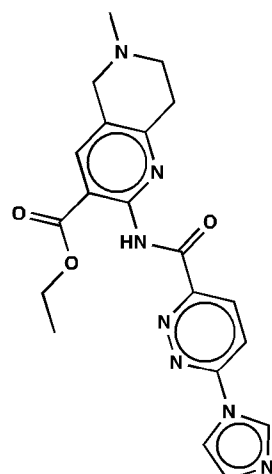
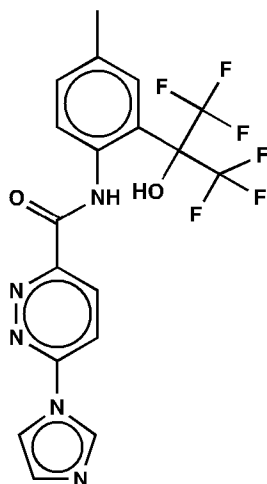
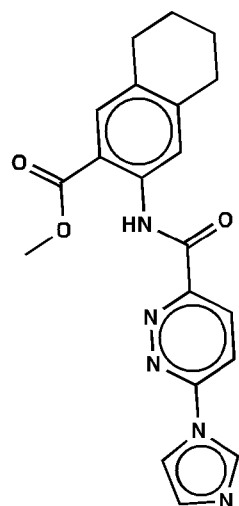
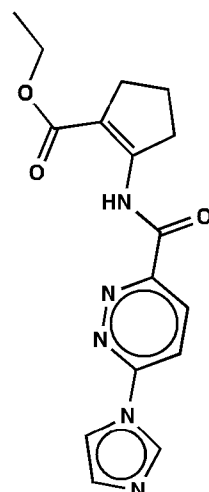
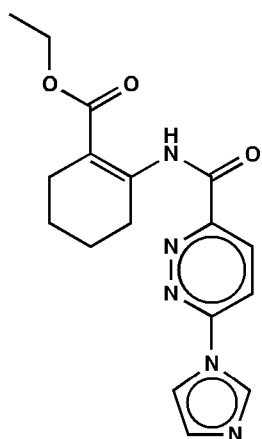
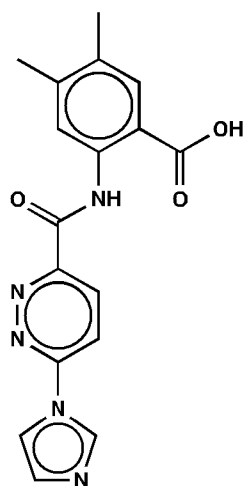
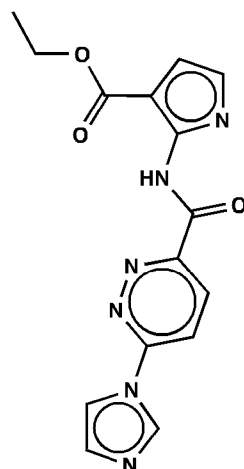
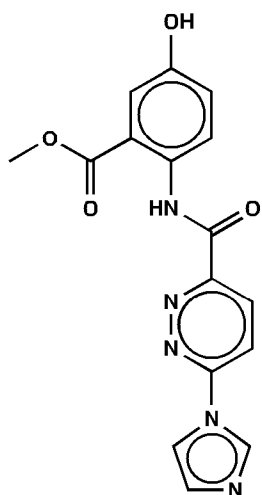
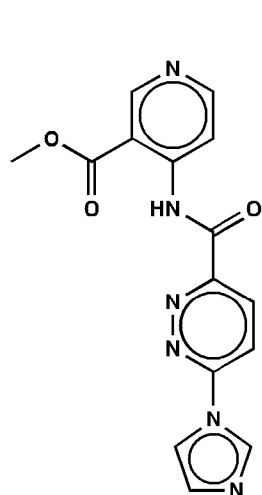


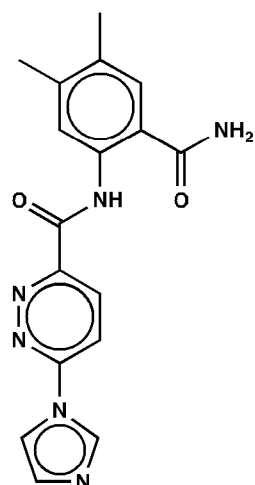
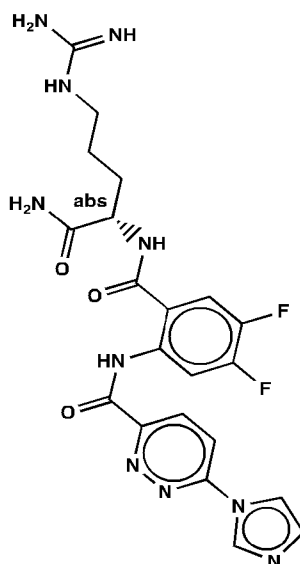
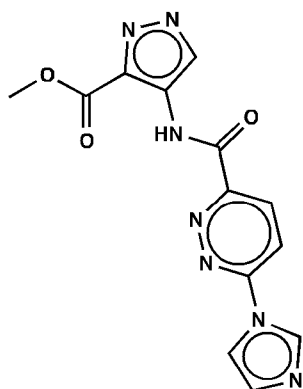
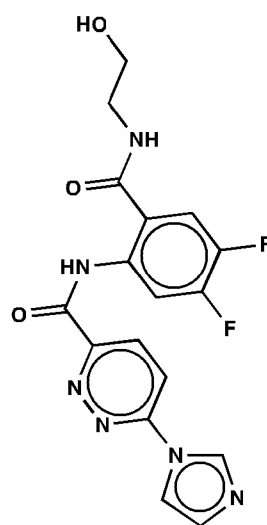
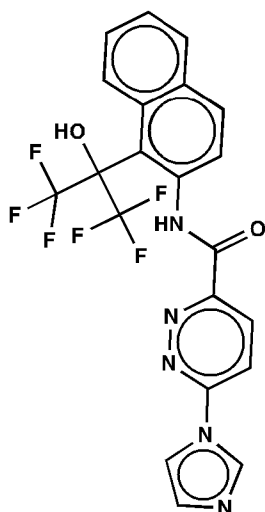
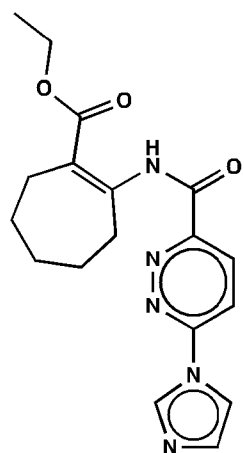
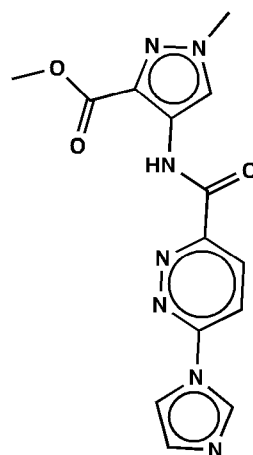
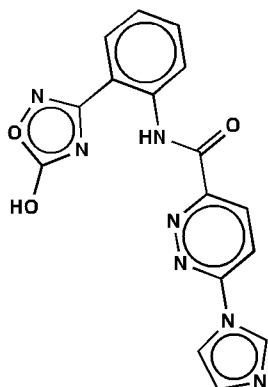
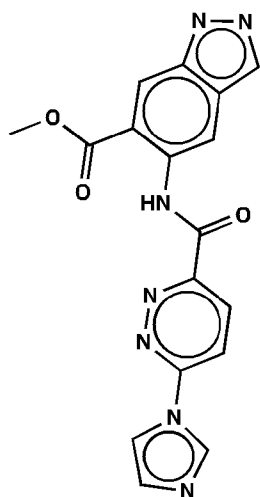


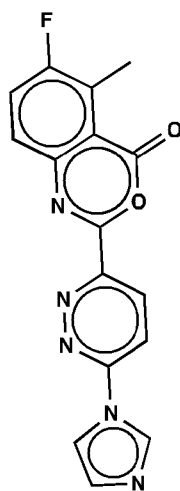
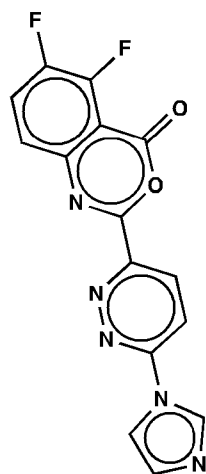
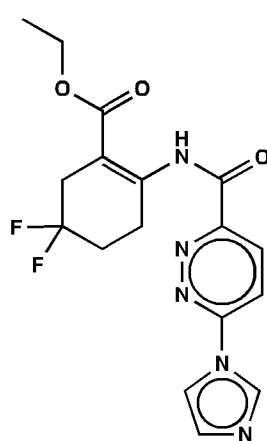
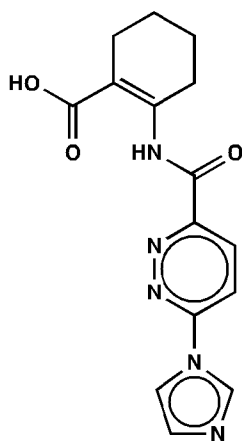
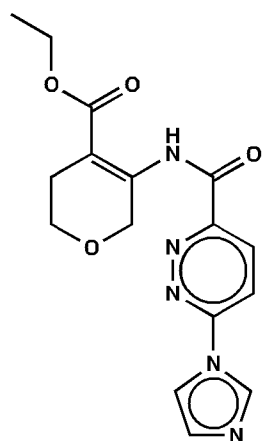
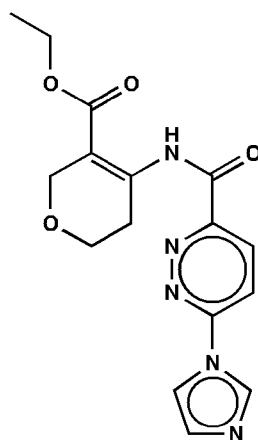
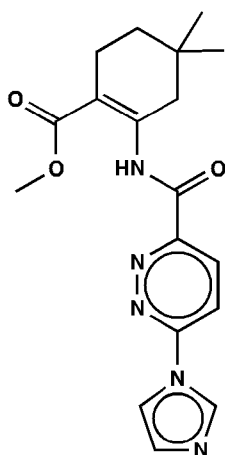
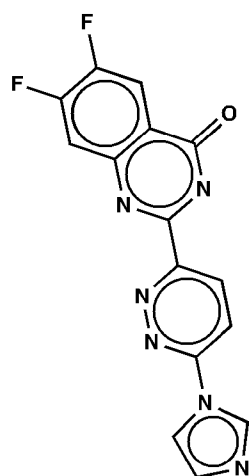


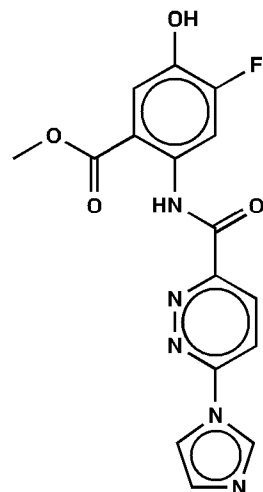
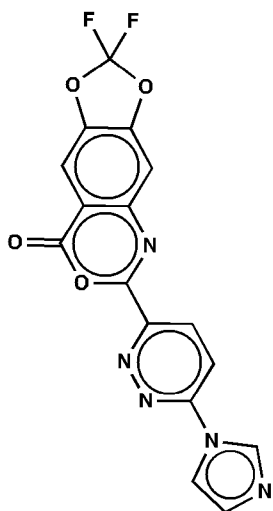
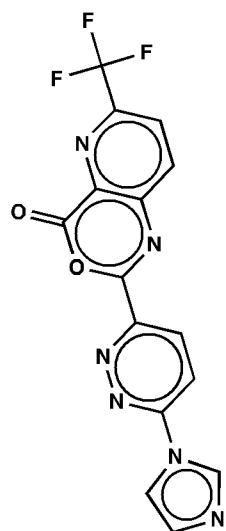
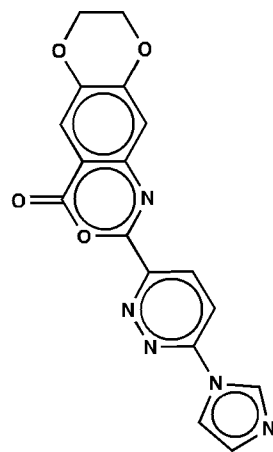
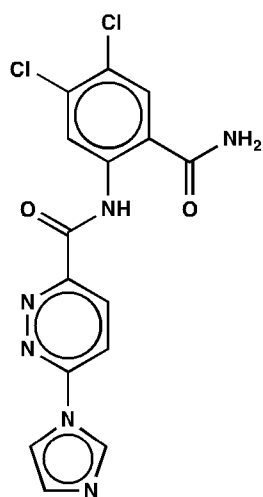
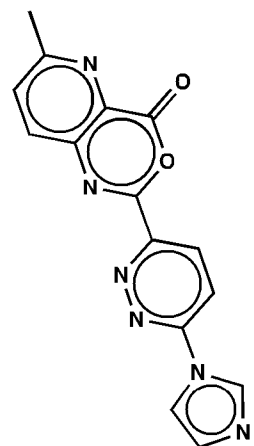
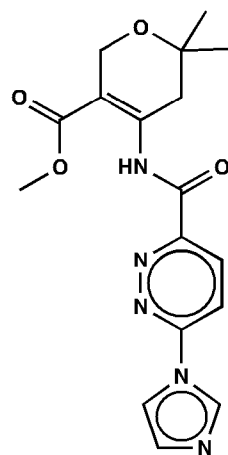
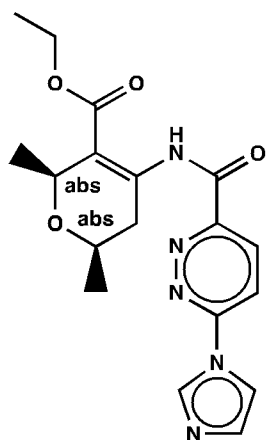
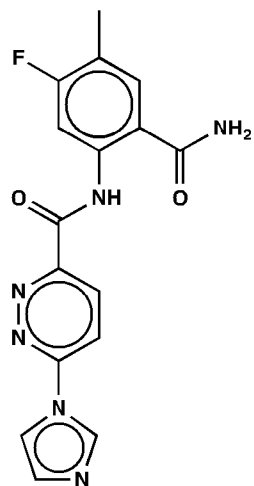


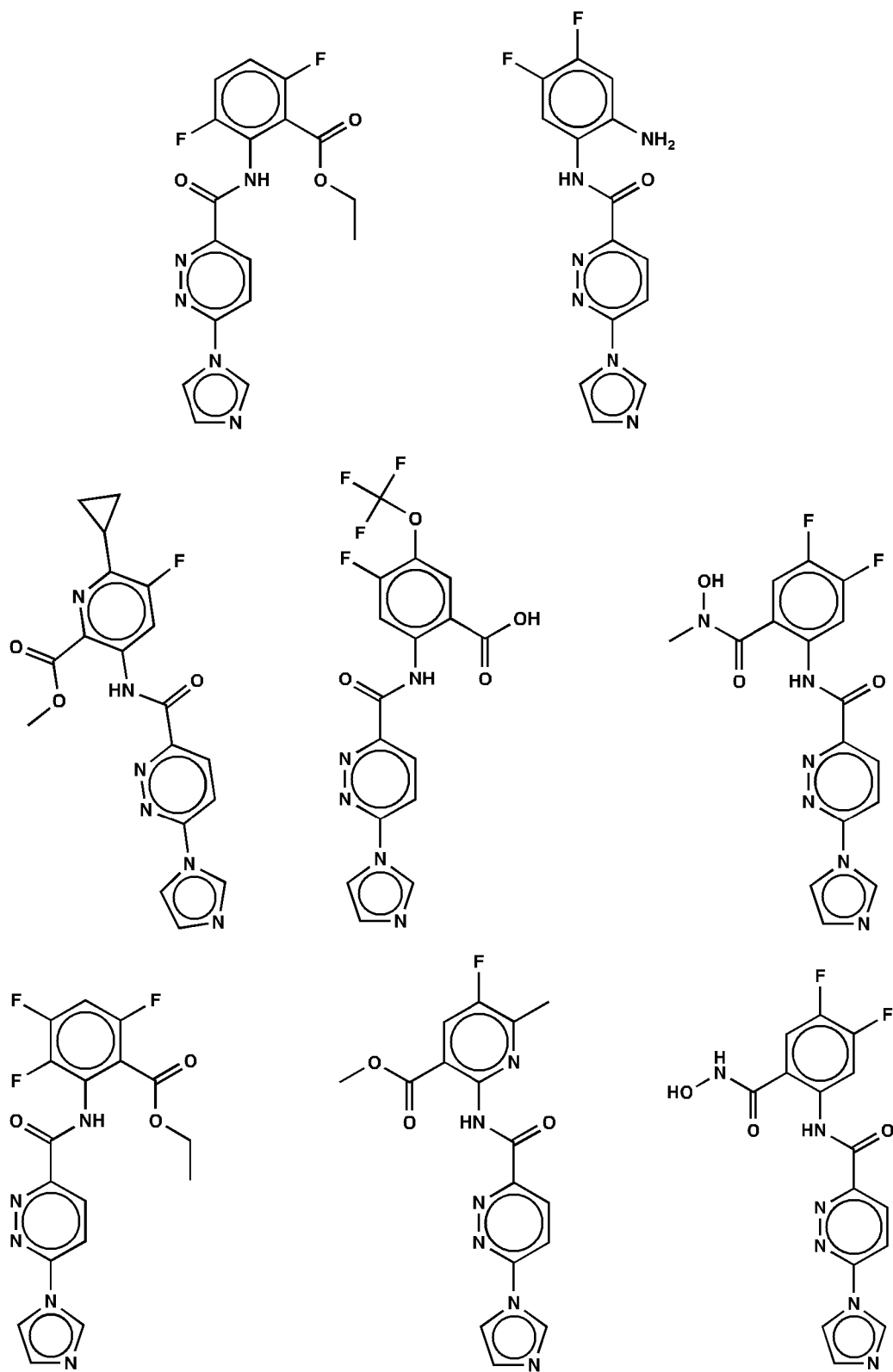


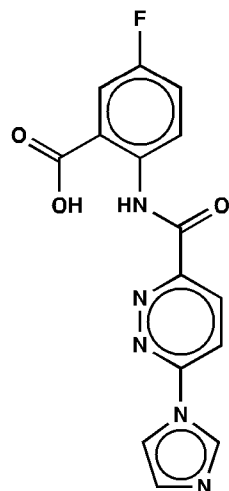
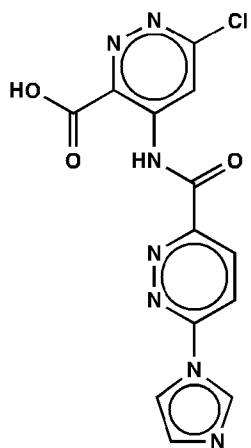
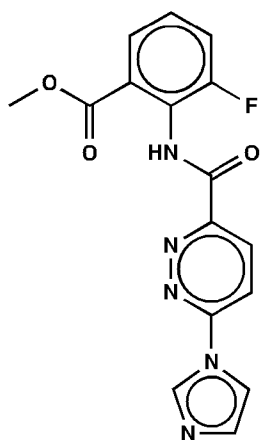
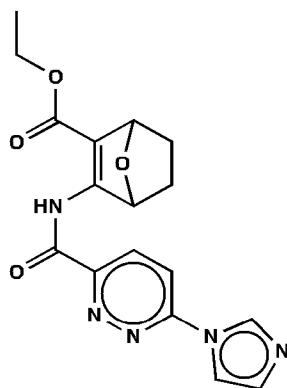
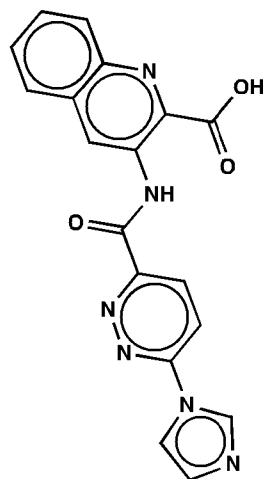
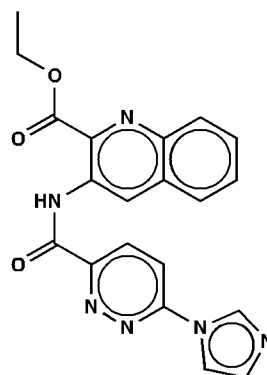
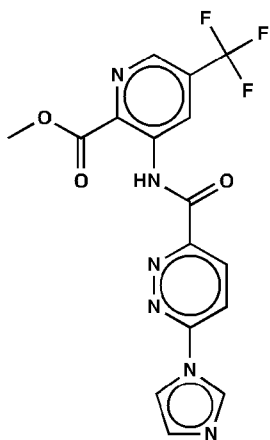
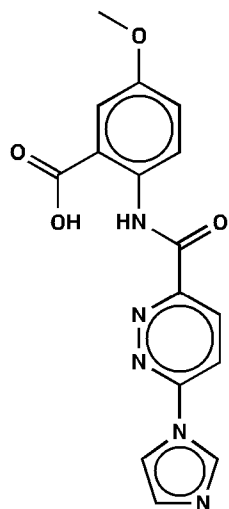


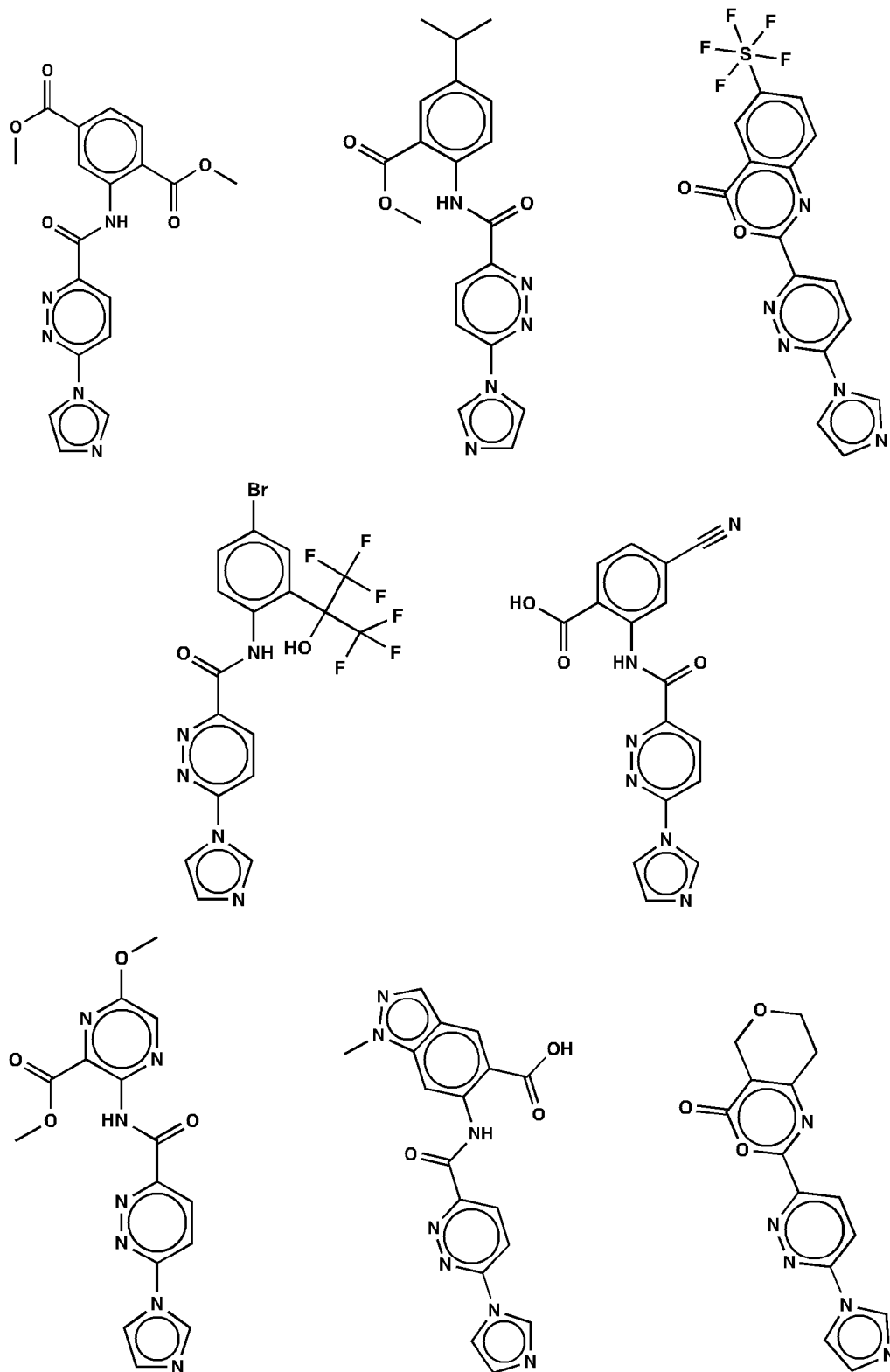


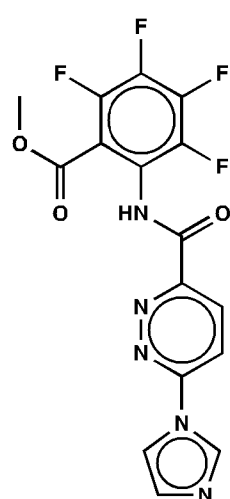
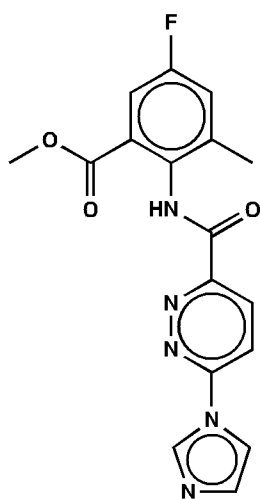
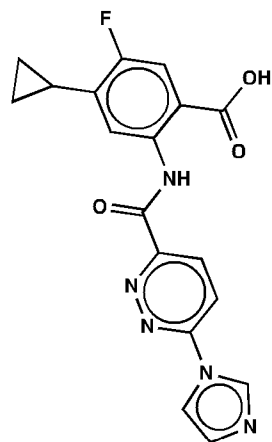
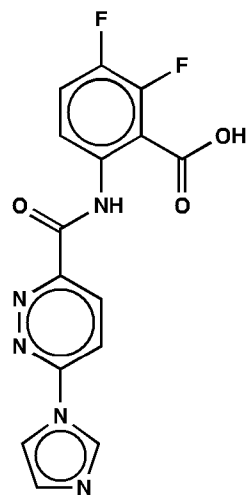
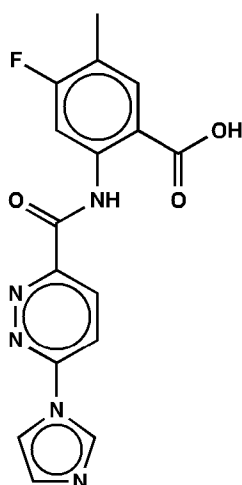
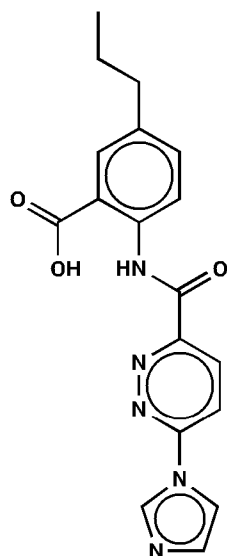
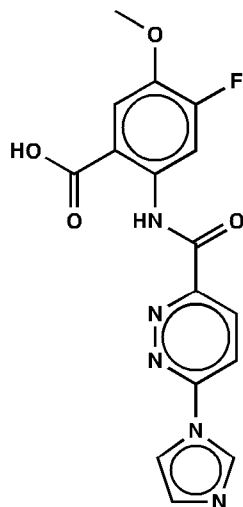
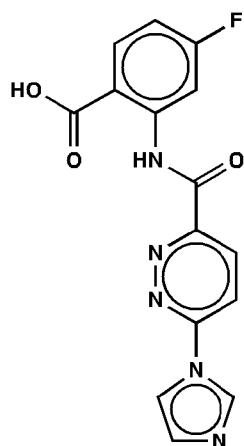


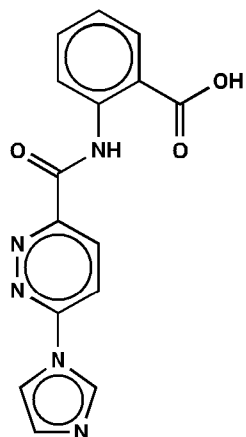






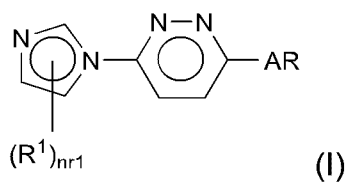






or a pharmaceutically acceptable salt thereof.

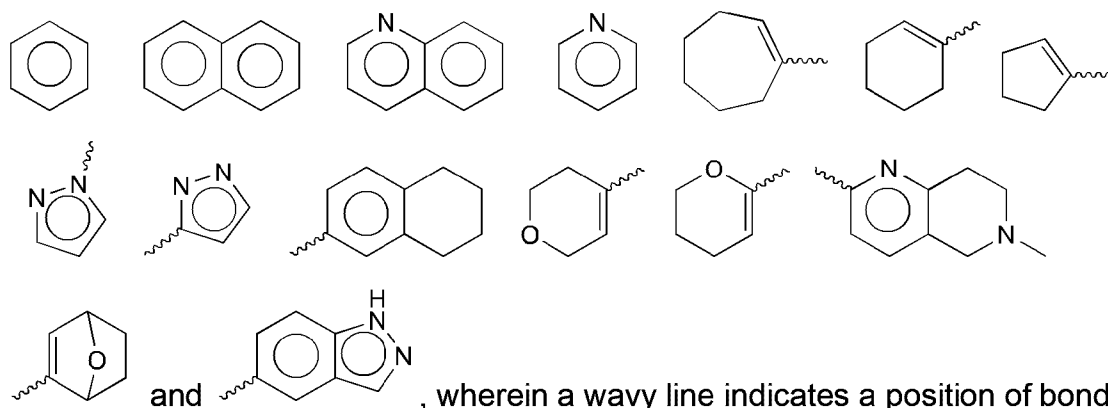
8. Use of a compound of formula (I) for treating a tumor in a patient:



wherein each R¹ is independently (C1-C4)alkyl, or CN, nr1 is 0, 1, 2, or 3, provided that each R¹ is bonded to a carbon atom; and,

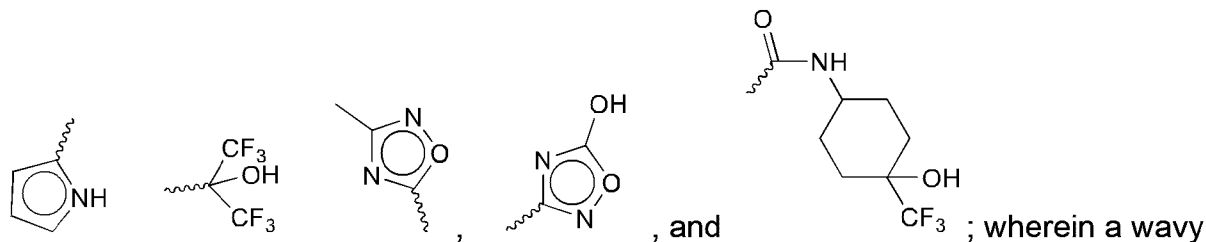
AR is a group of formula -C(=O)N(R)Ar¹; R is H or (C1-C4)alkyl;

wherein Ar¹ is chosen from the group consisting of:



wherein any Ar¹ is substituted with nr2 independently selected R² groups chosen from the group consisting of :

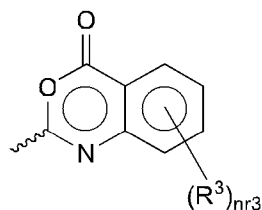
-(C1-C4)-alkyl, -(C1-C4)-alkylO, -(C1-C4)-alkyloc(O), -CN, -halo, -(C3-C7)cycloalkyl, -(C1-C4)-alkOC(O), -COOH, (C3-C7)-cycloalkyloc(O), -SF₅, -methylenedioxy, -difluoromethylenedioxy, -ethylenedioxy, -CF₃, -OCF₃, -C(O)NH₂, -C(O)NH(CH₂)₂OH, -CH₂OH, -NR₂, -CONH-arginine, -C(O)O(CH₂)₂NR₂,



line indicates a position of bonding; and, nr2 = 0, 1, 2, or 3;

or,

AR is a group of formula



wherein R³ is selected from the group consisting of

(C1-C4)-alkyl, (C1-C4)-alkylO, (C1-C4)-alkyloc(O), CN, halo, (C3-C7)cycloalkyl, (C1-C4)-alkOC(O), COOH, (C3-C7)-cycloalkyloc(O), -SF₅, methylenedioxy, difluoromethylenedioxy, ethylenedioxy, CF₃, -OCF₃, CONH₂, CONH(CH₂)₂OH, CH₂OH, NR₂, CONH-arginine, and C(O)O(CH₂)₂NR₂; and nr3 = 0, 1, 2, or 3; or a pharmaceutically acceptable salt thereof.

9. The use of claim 8, wherein the compound is for oral or intratumoral administration, or both.

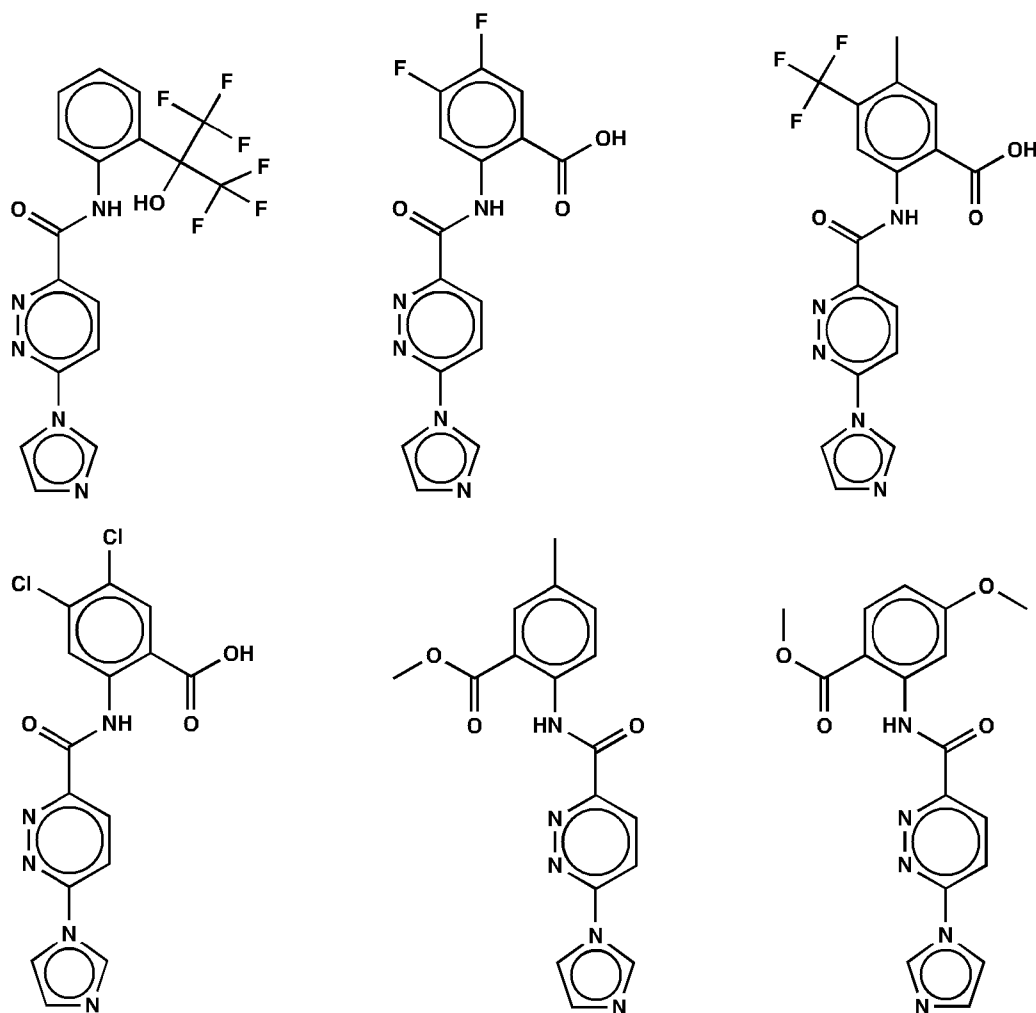
10. The use of claim 8, wherein the compound is an antibody-drug conjugate, or in a liposomal formulation.

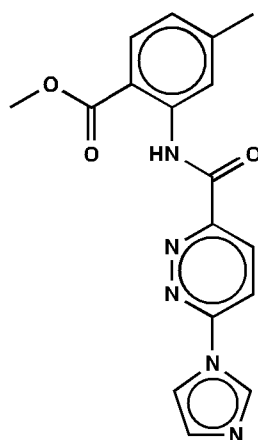
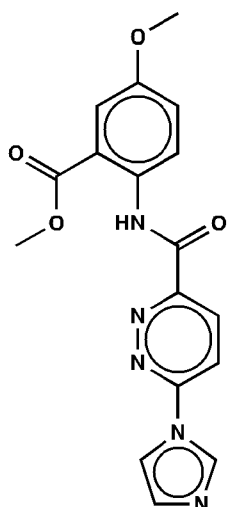
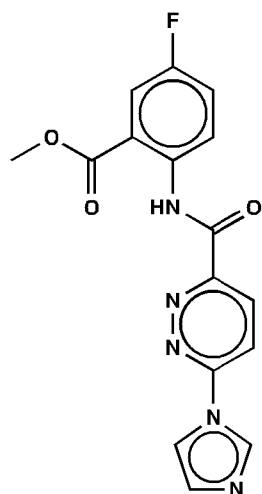
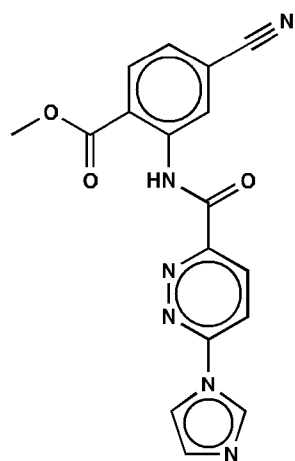
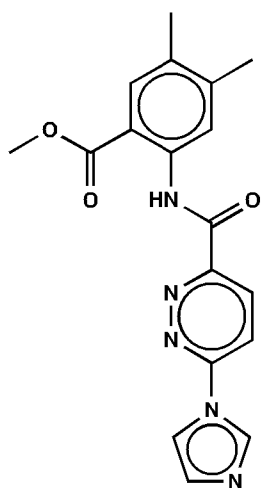
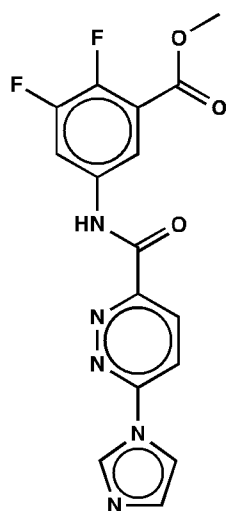
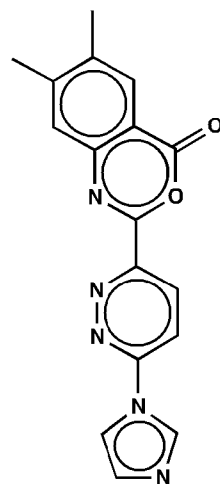
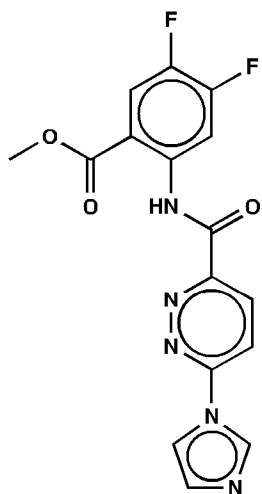
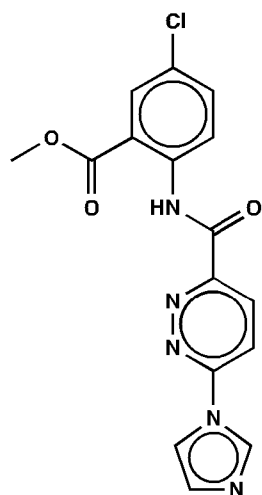
11. The use of claim 8, further comprising use of an effective dose of an immune-checkpoint targeting drug.

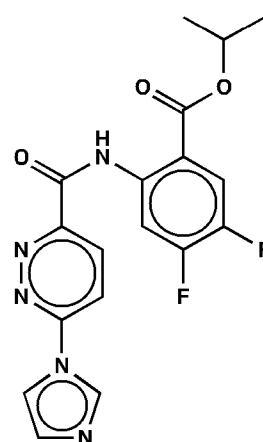
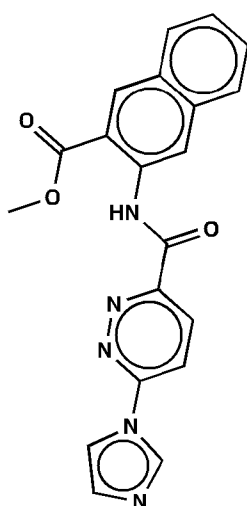
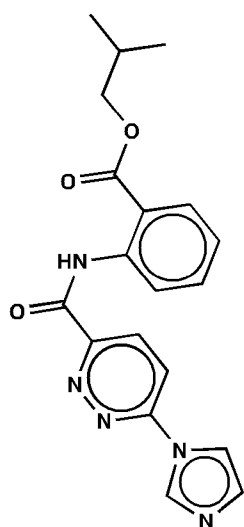
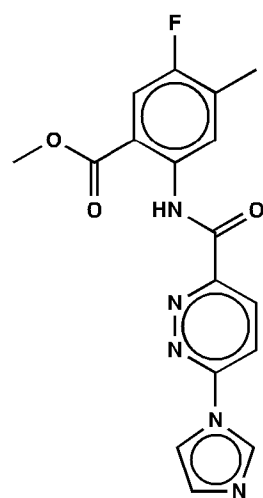
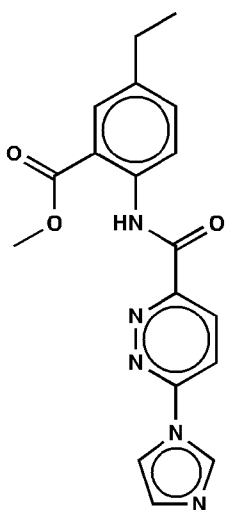
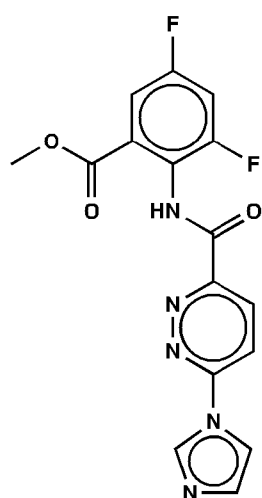
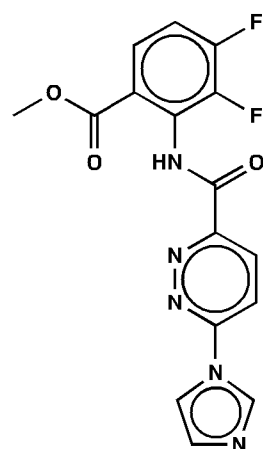
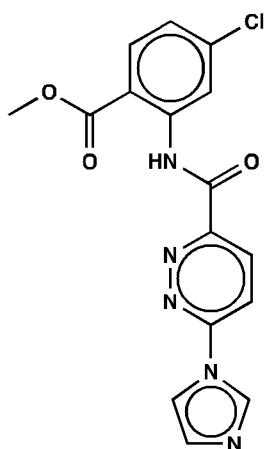
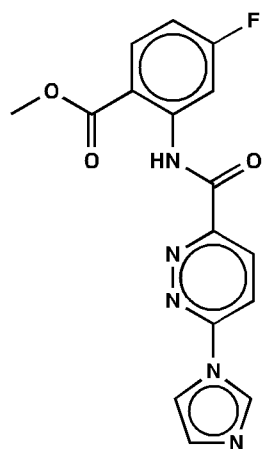
12. The use of claim 11, wherein the immune-checkpoint targeting drug comprises an anti-PD-L1 antibody, anti-PD-1 antibody, anti-CTLA-4 antibody, or an anti-4-1BB antibody.

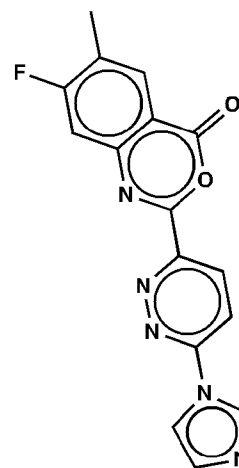
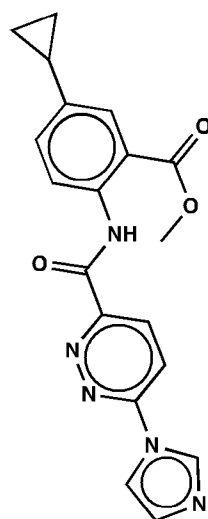
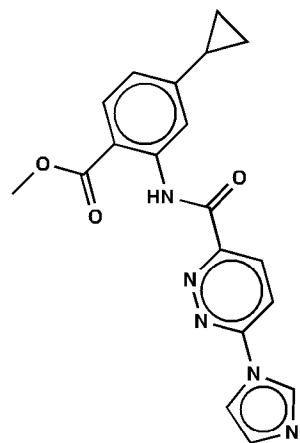
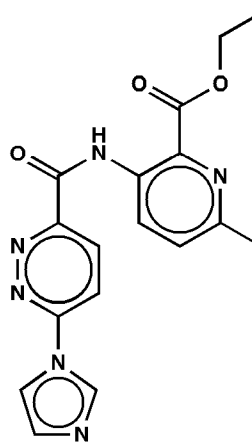
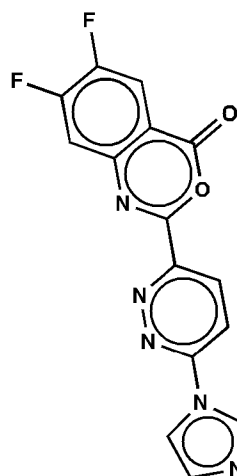
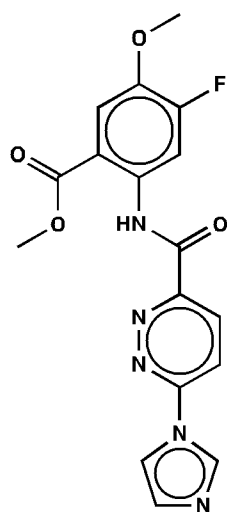
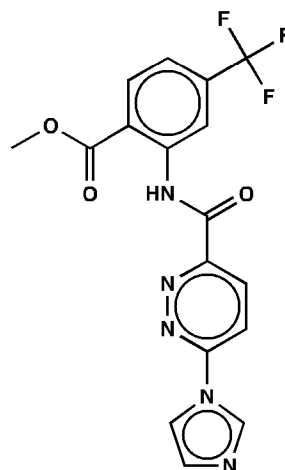
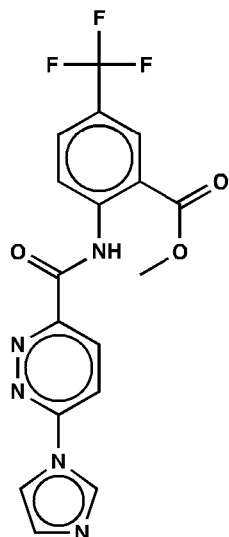
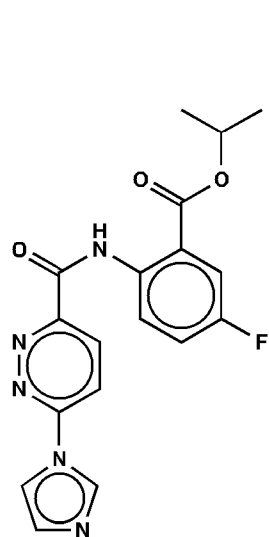
13. The use of claim 8, further comprising use of ionizing radiation or anticancer drugs.

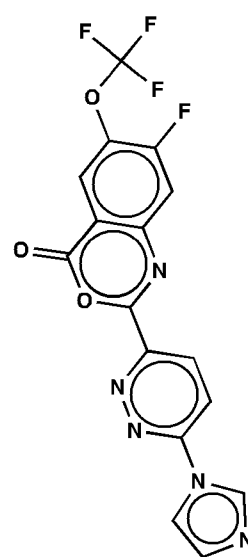
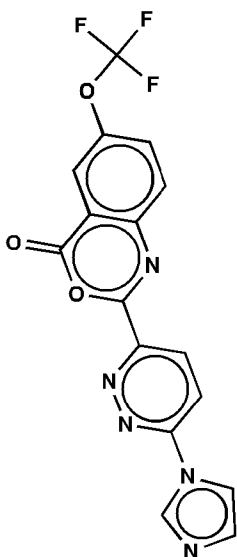
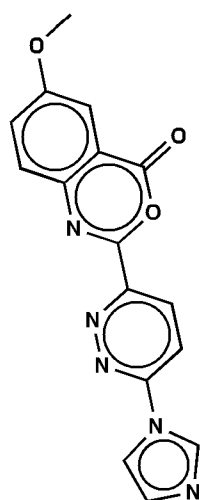
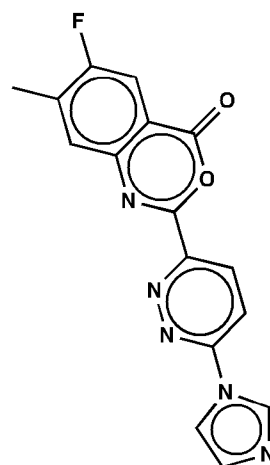
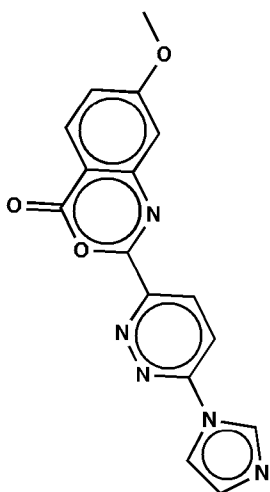
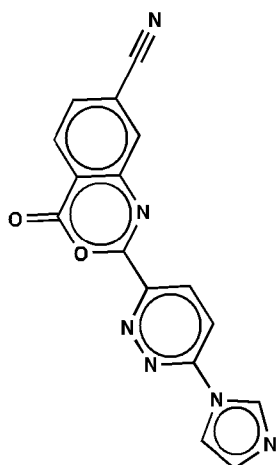
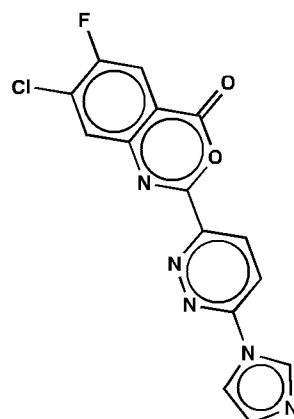
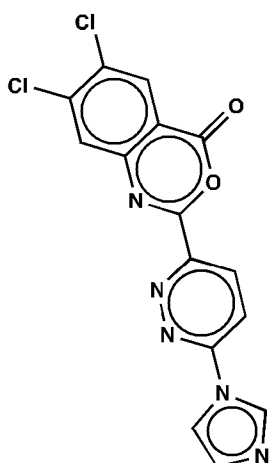
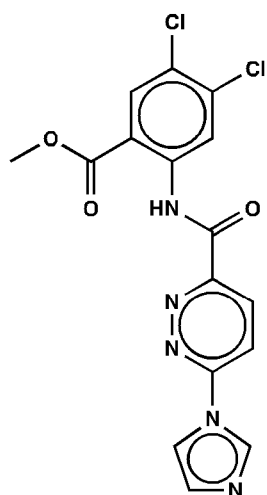
14. The use of claim 8, wherein the compound is any one of the following formulae:

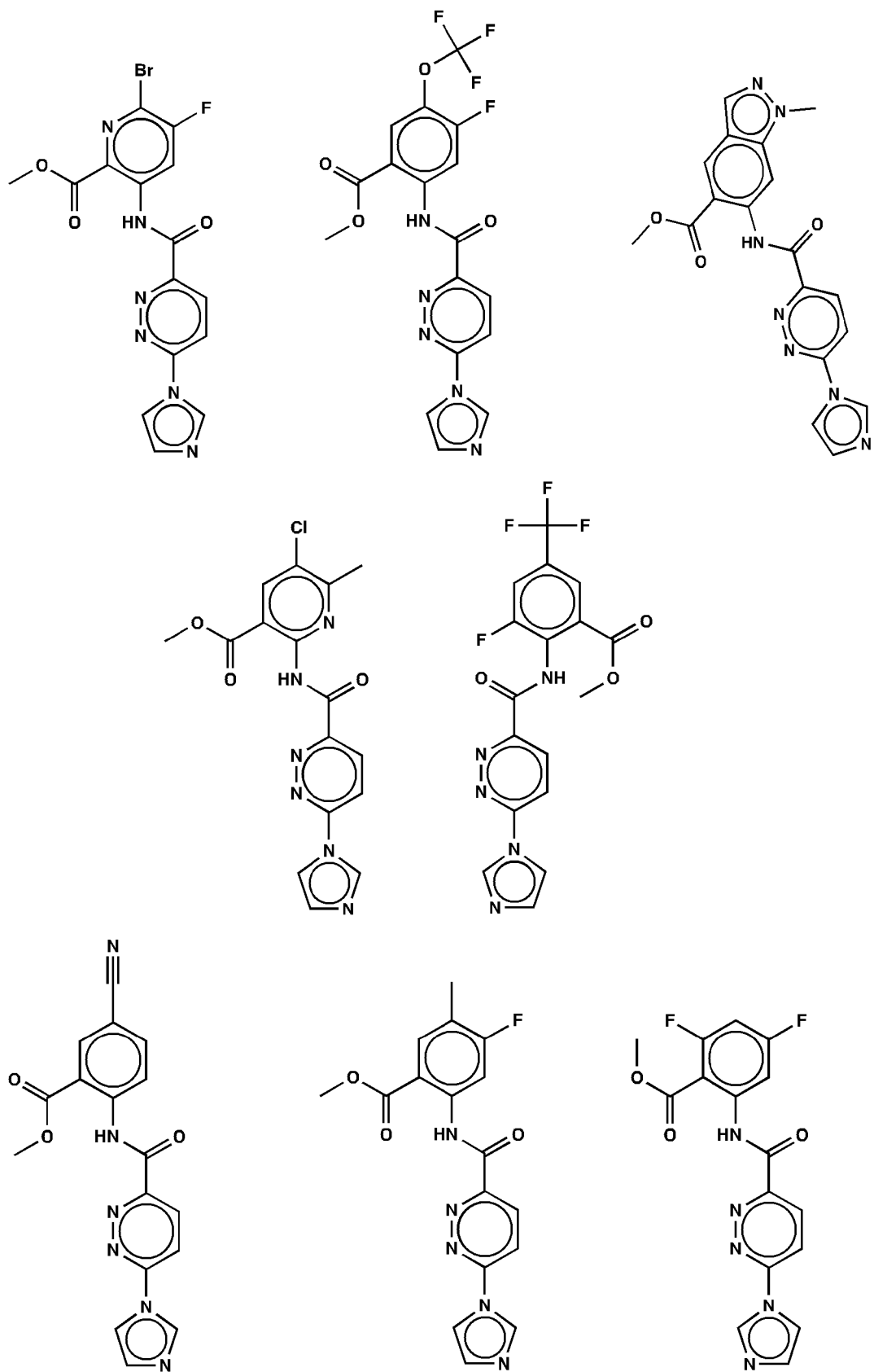


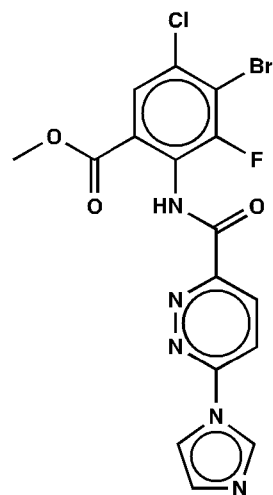
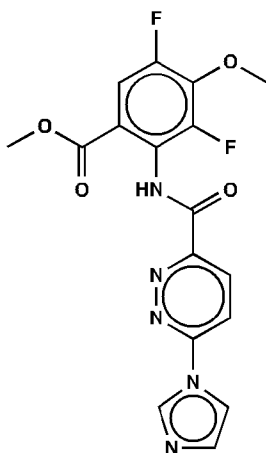
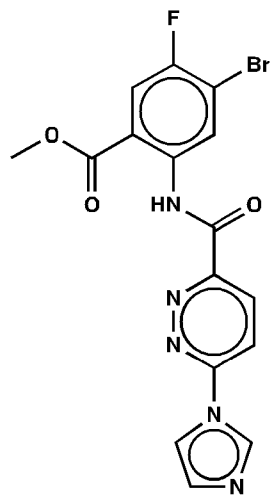
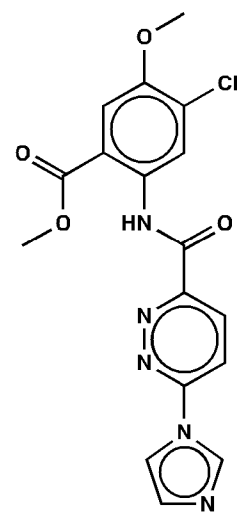
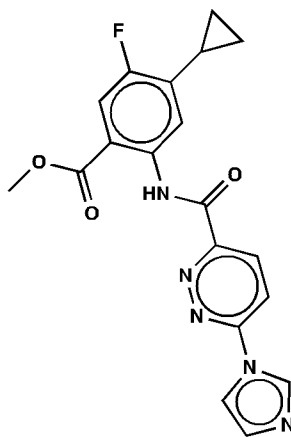
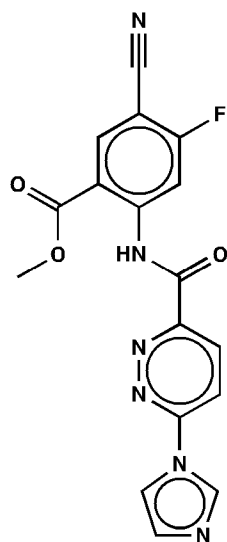
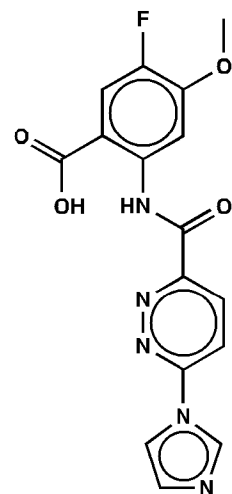
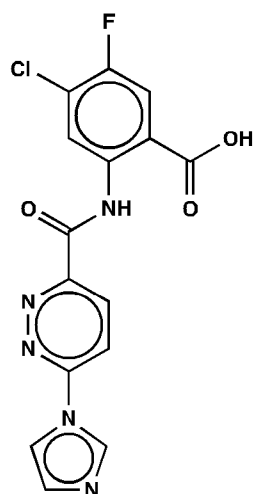
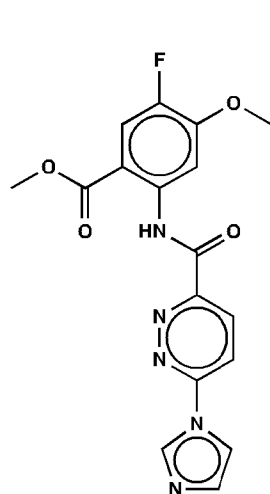


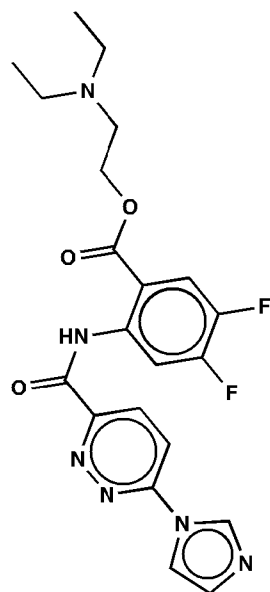
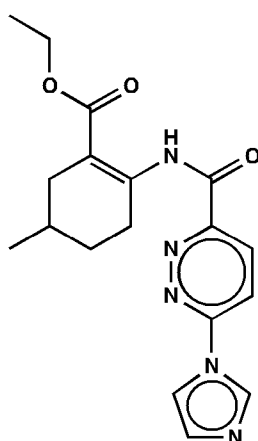
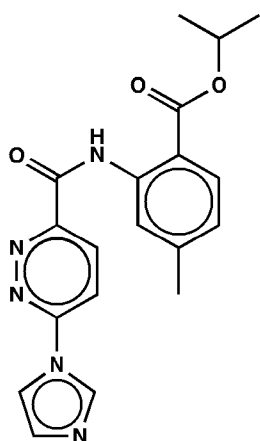
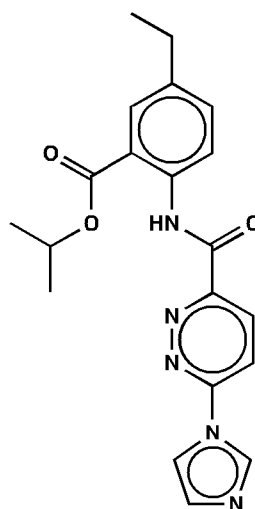
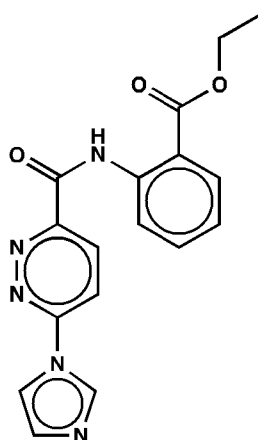
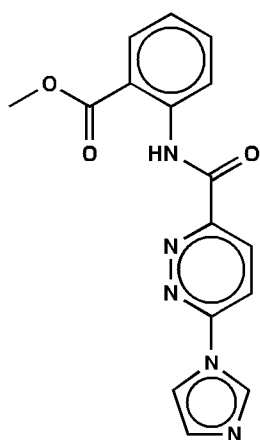
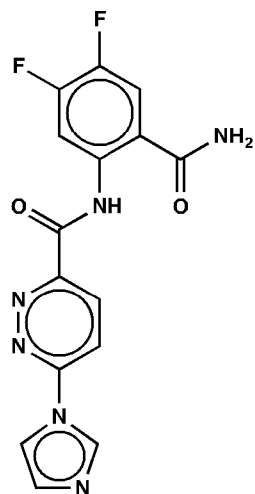
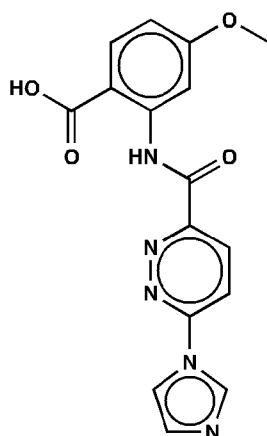
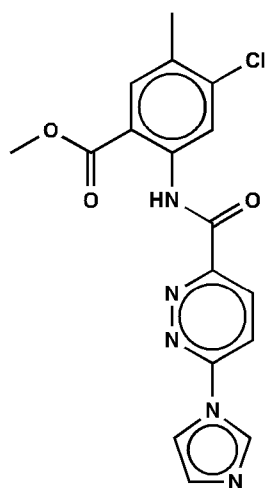


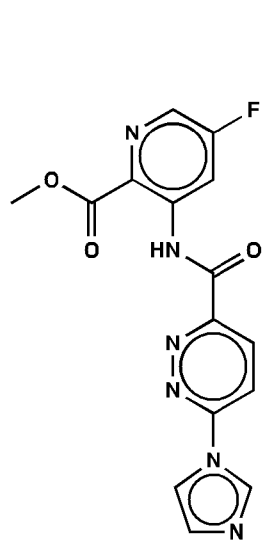




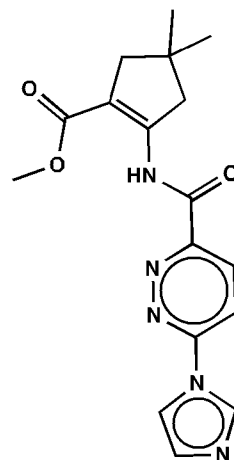
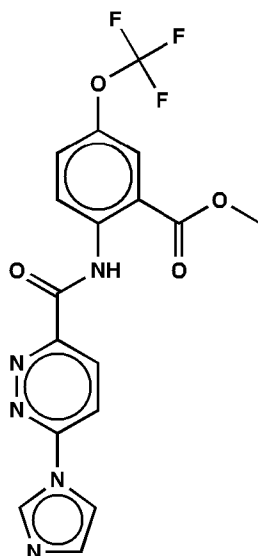
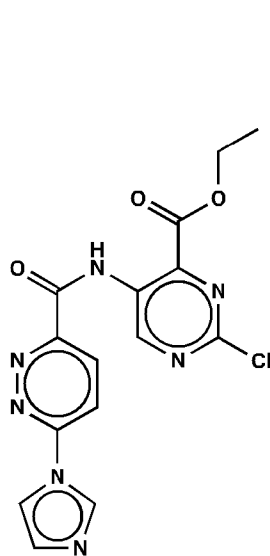
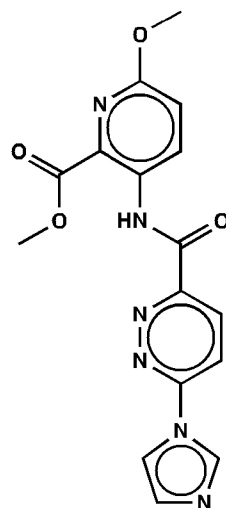
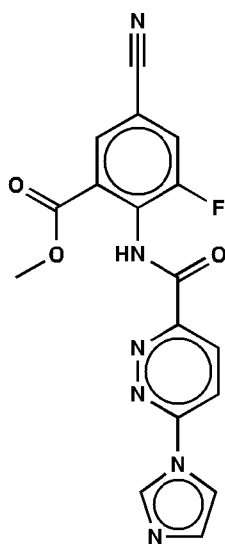
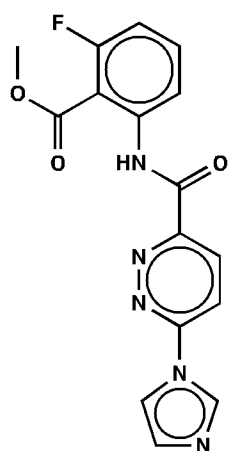
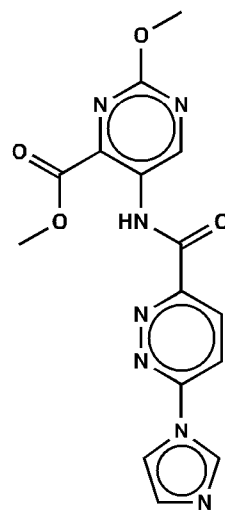
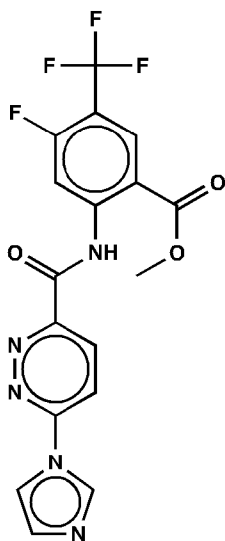


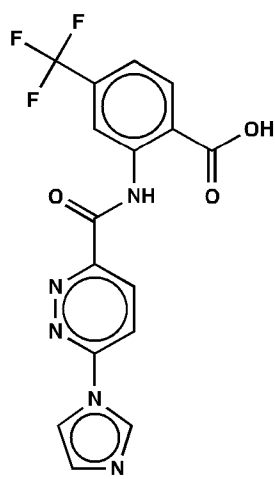
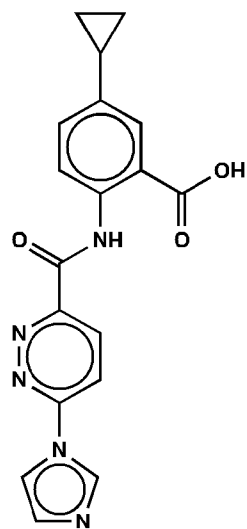
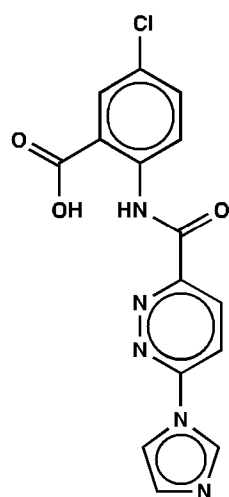
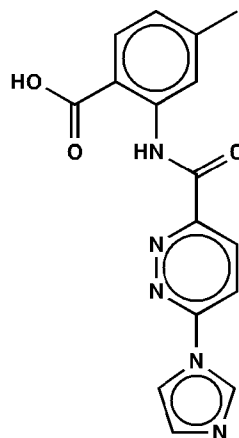
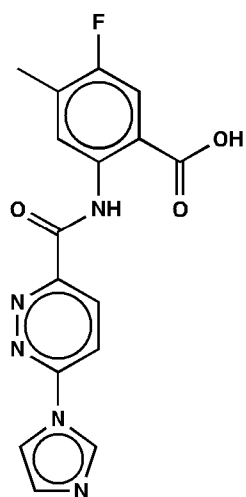
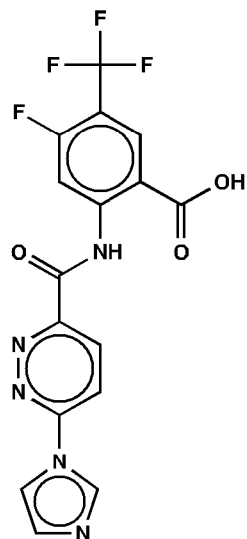
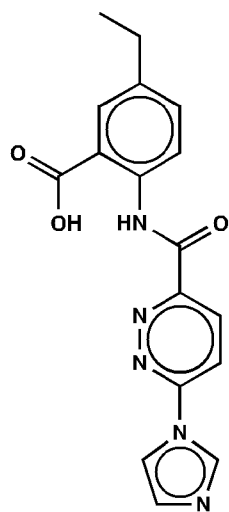
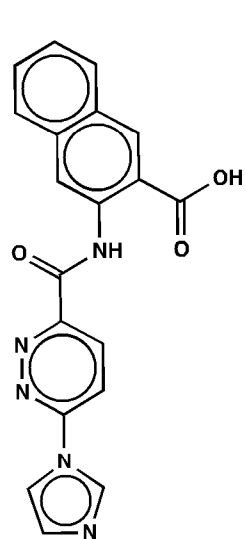


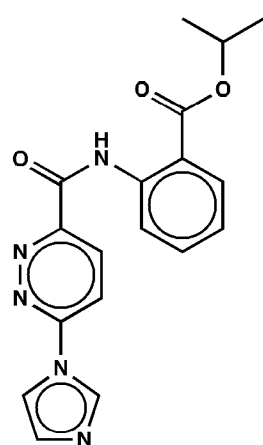
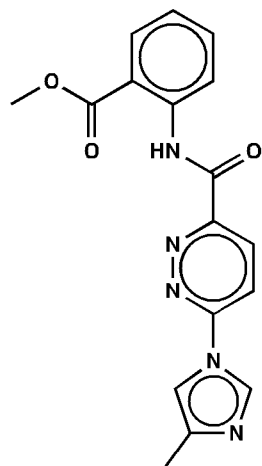
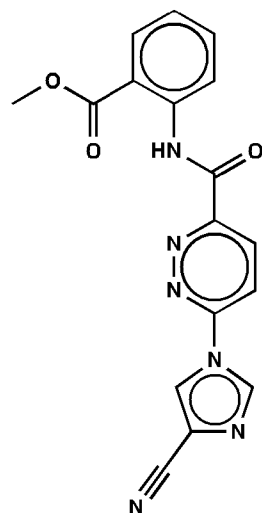
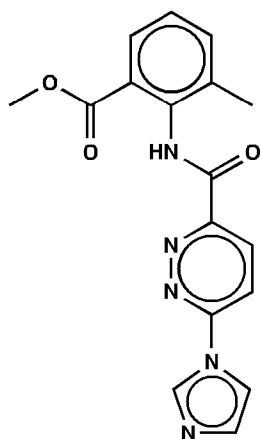
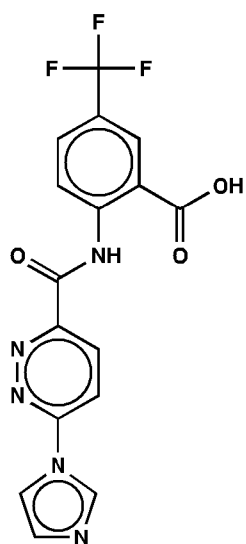
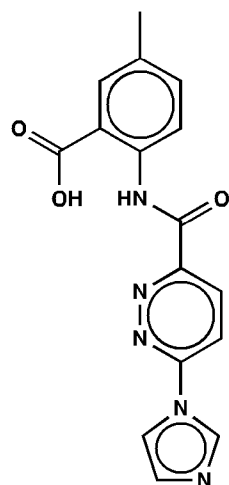
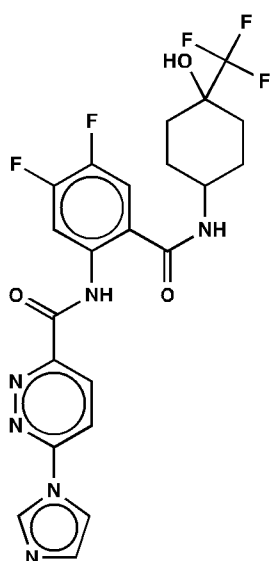
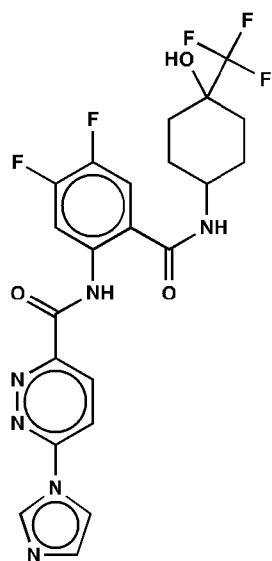


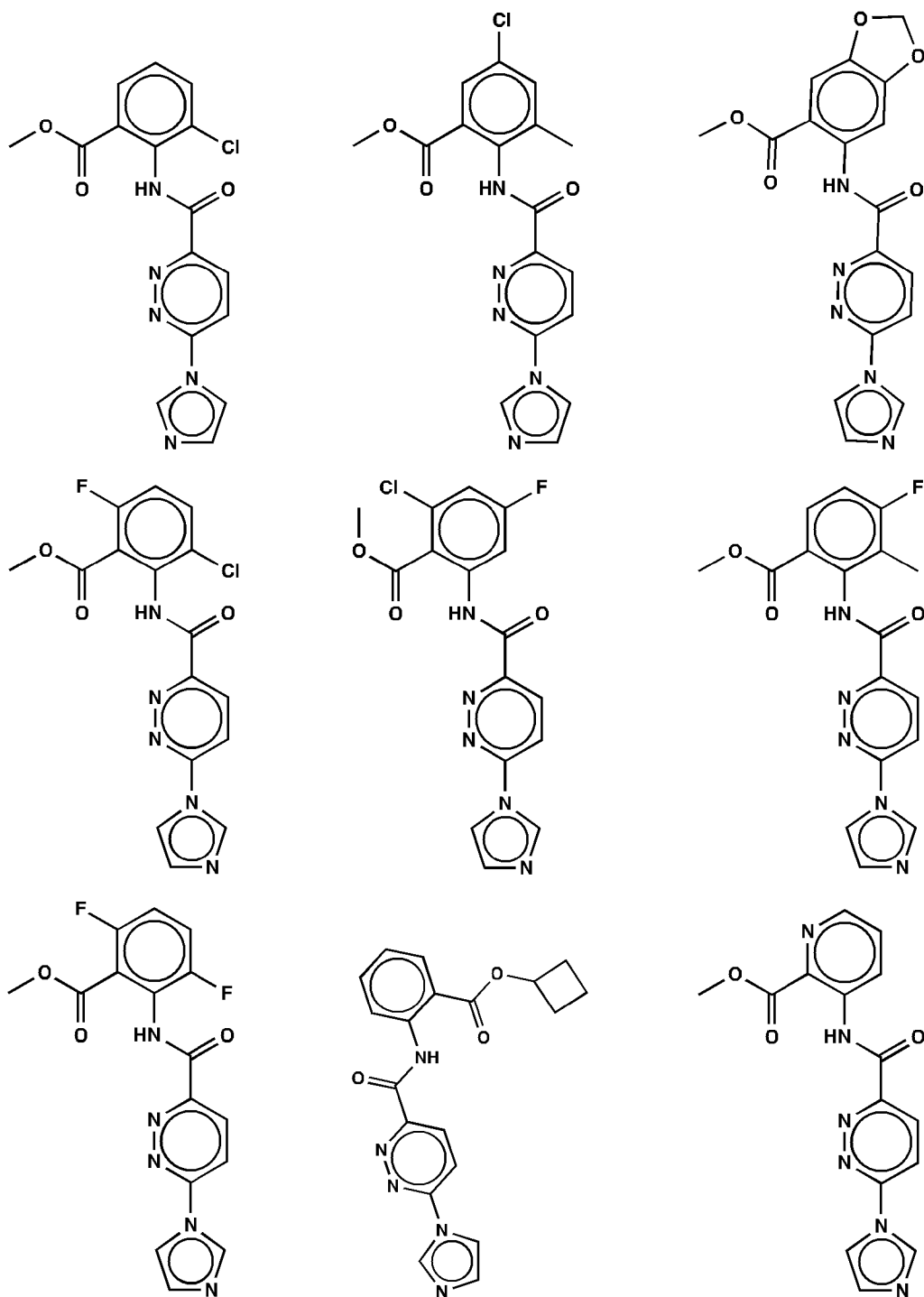


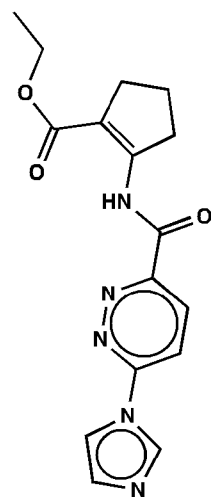
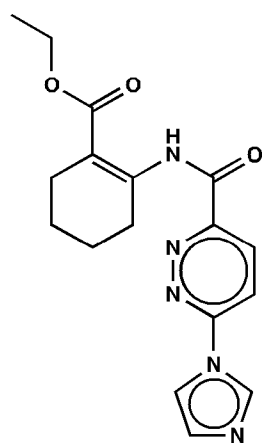
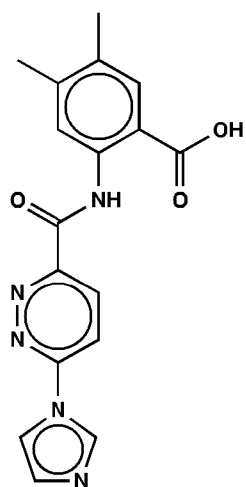
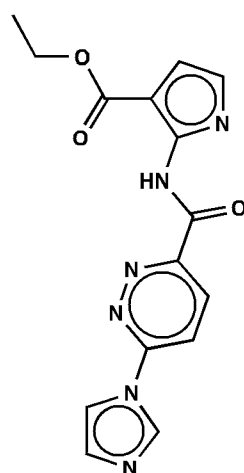
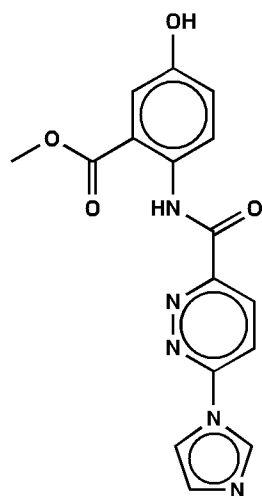
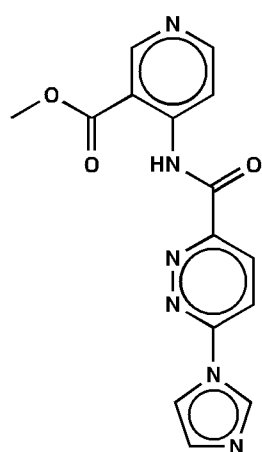
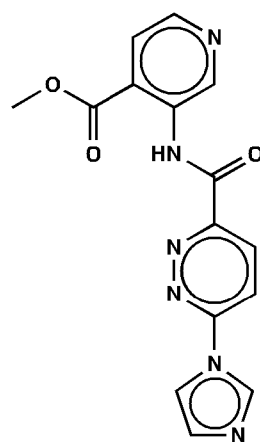
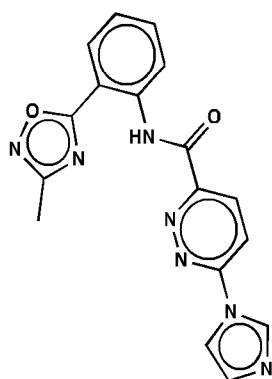
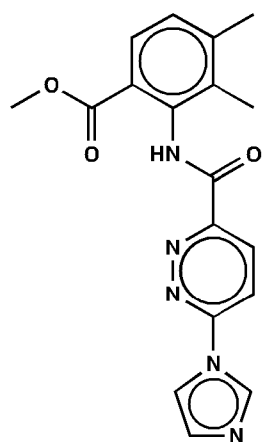
70

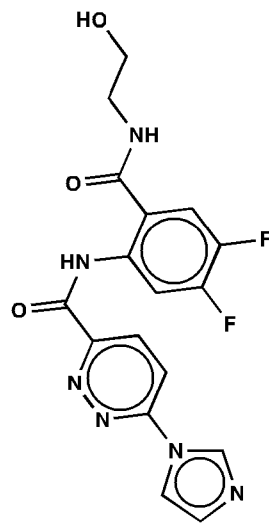
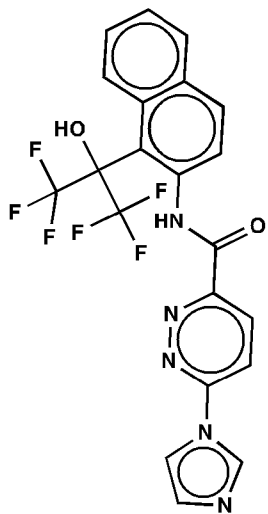
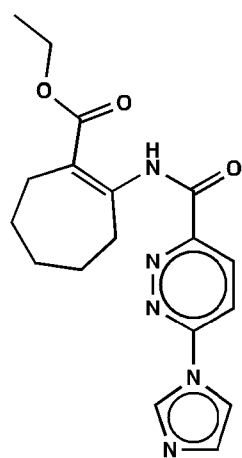
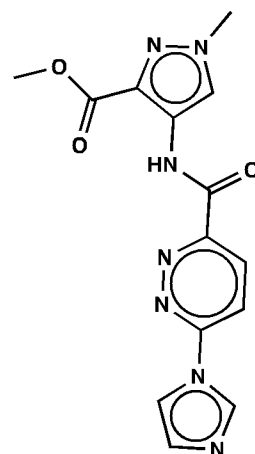
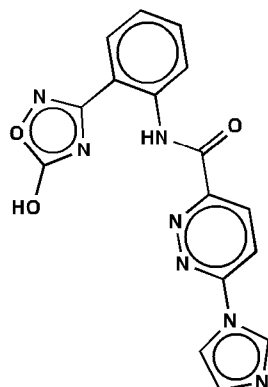
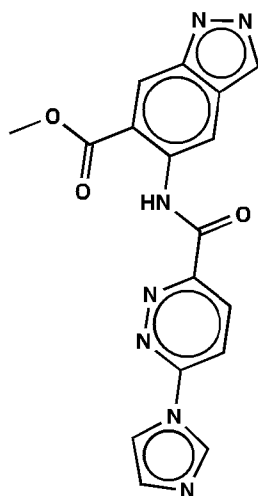
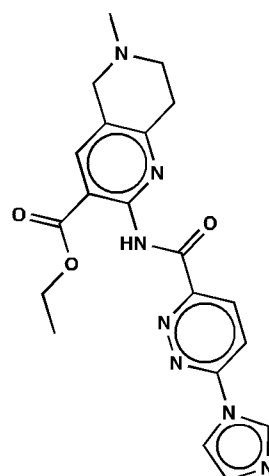
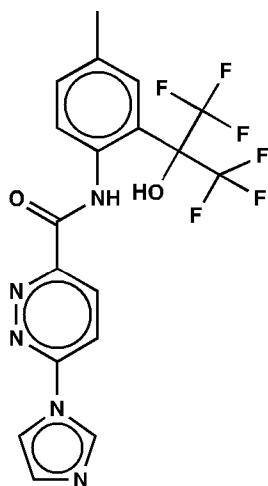
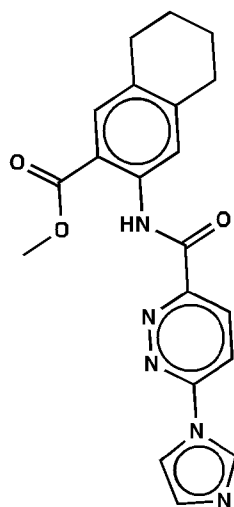


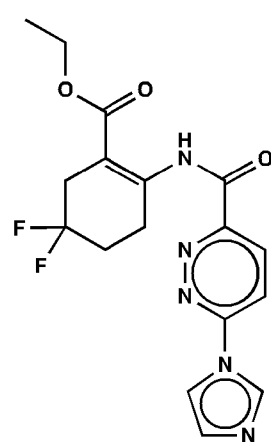
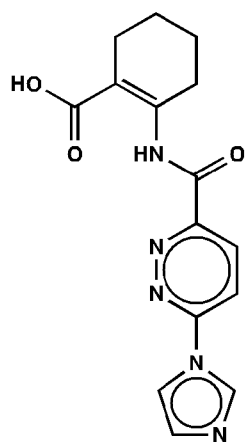
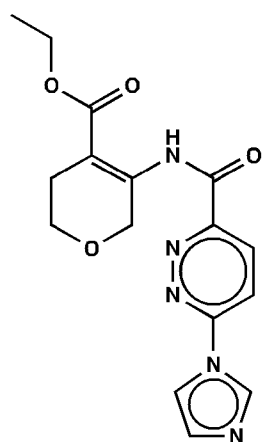
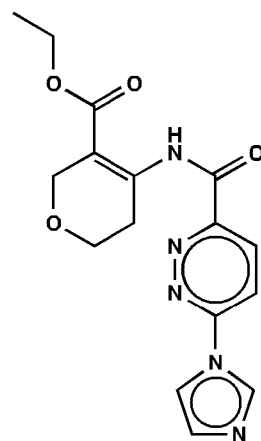
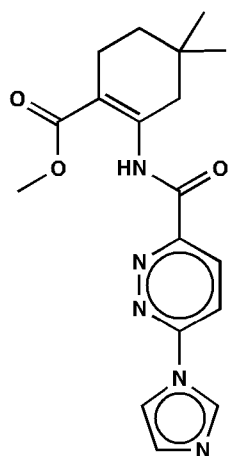
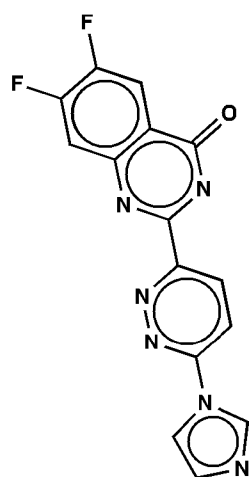
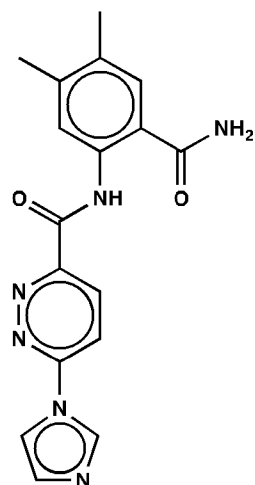
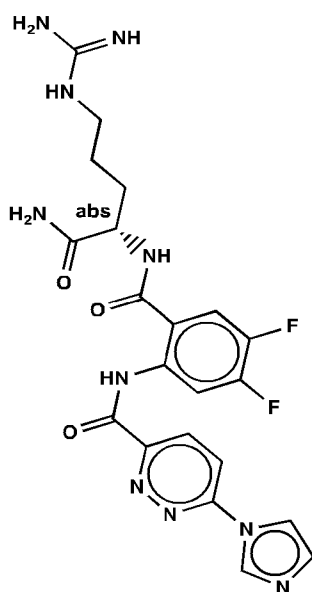
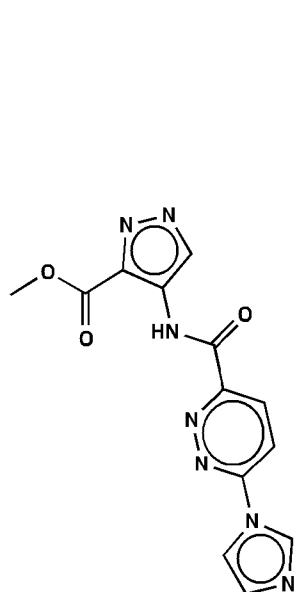


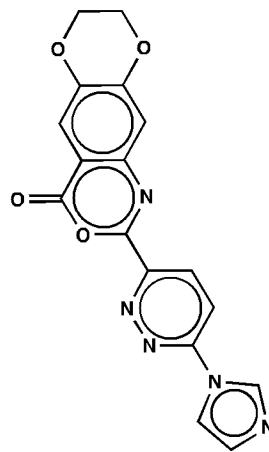
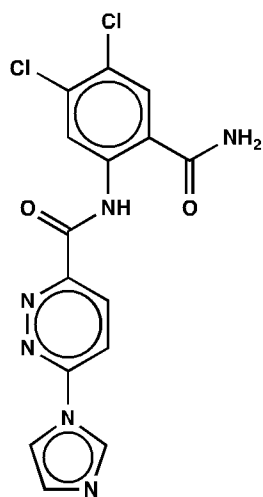
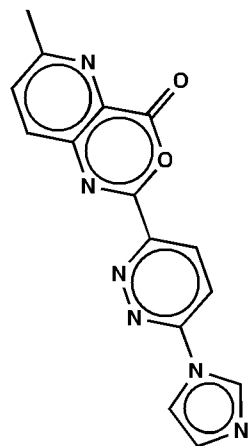
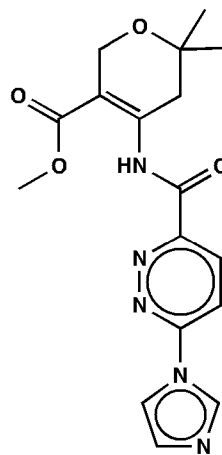
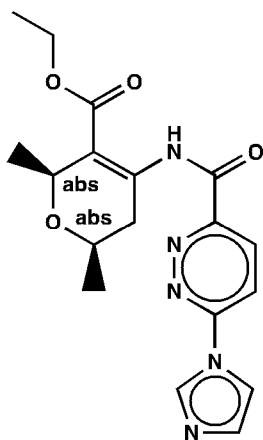
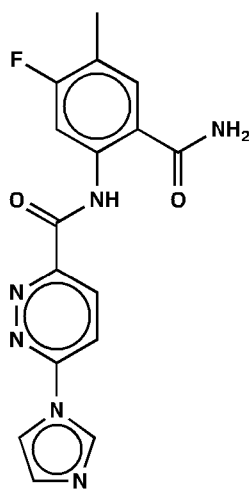
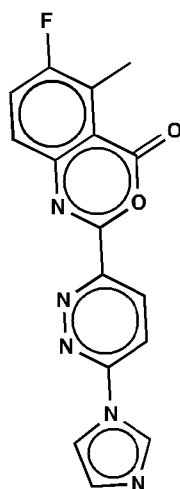
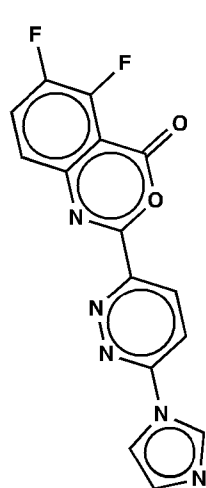


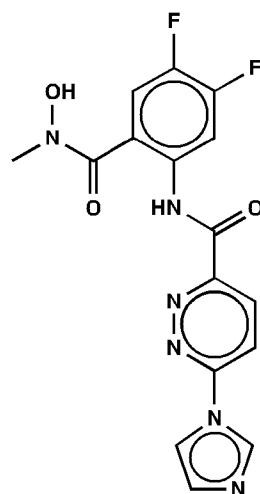
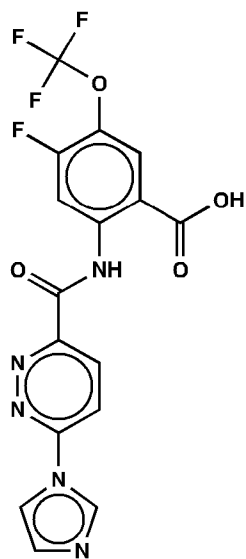
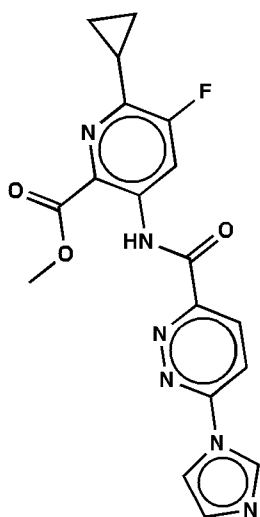
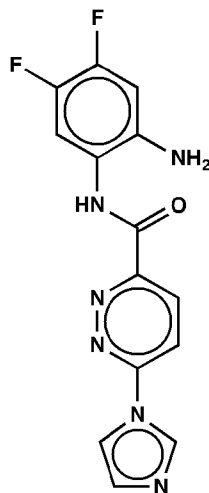
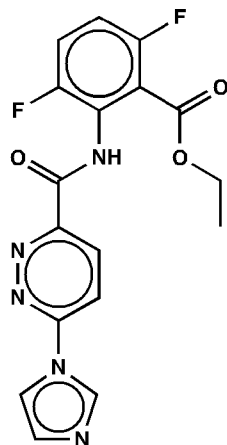
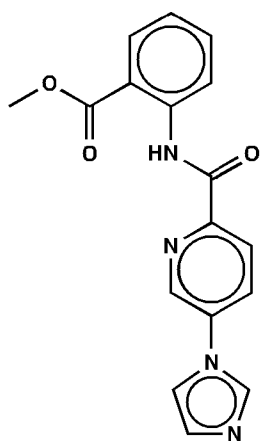
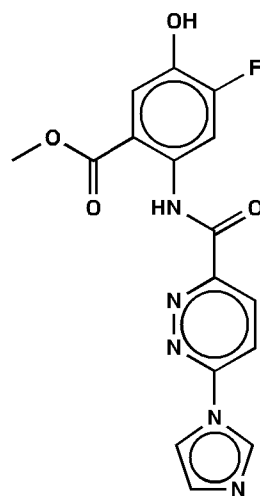
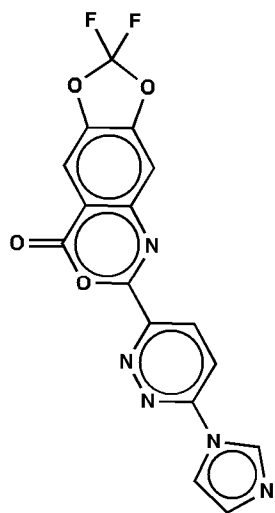
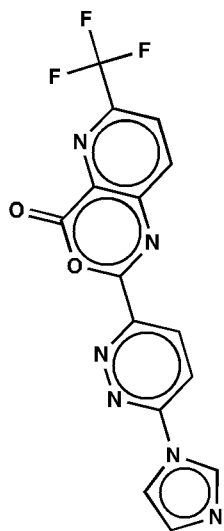


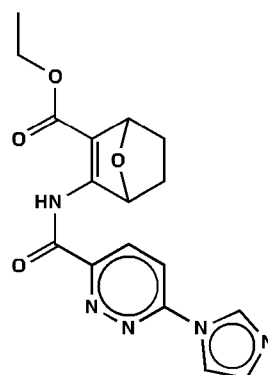
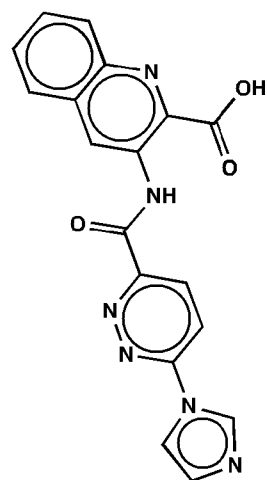
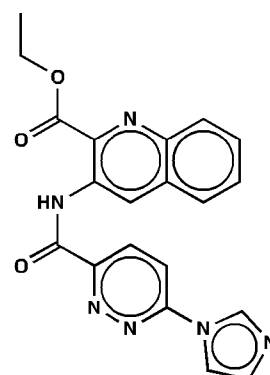
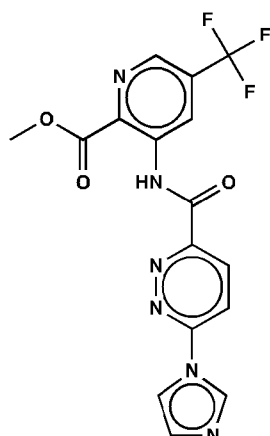
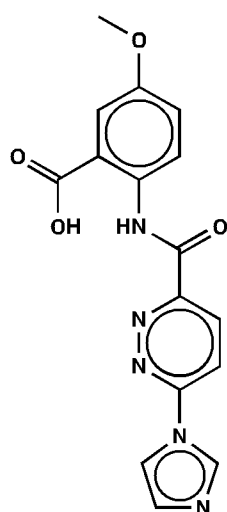
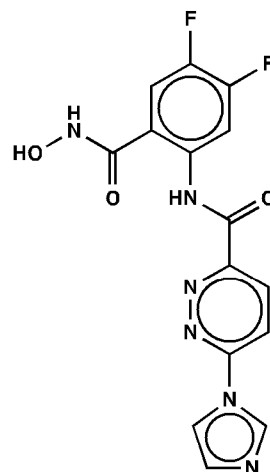
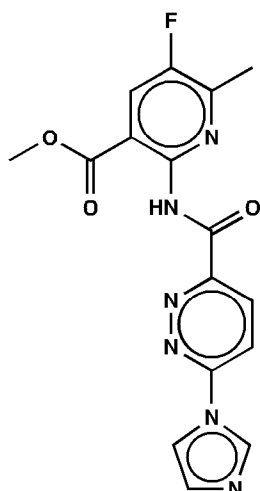
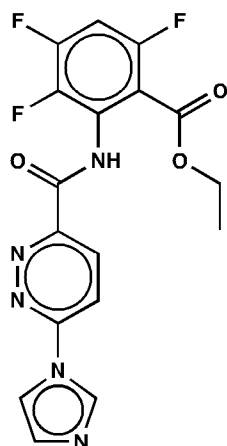


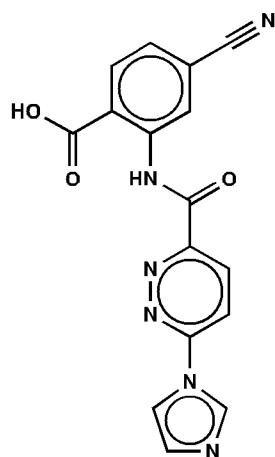
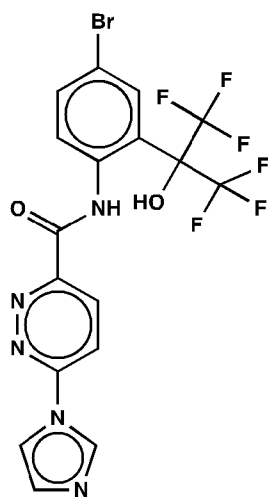
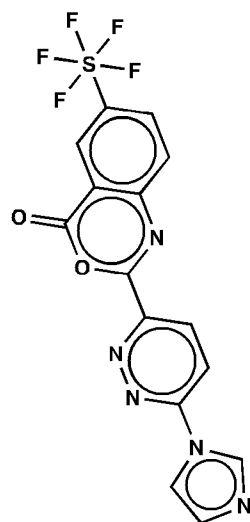
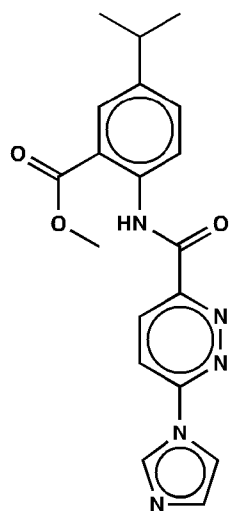
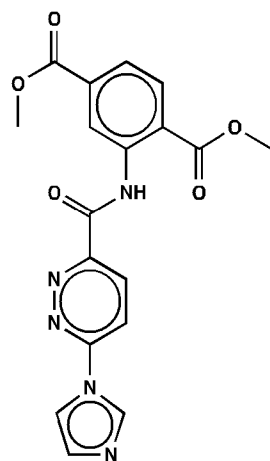
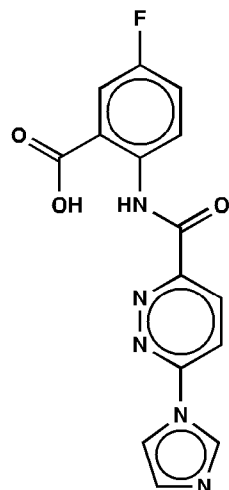
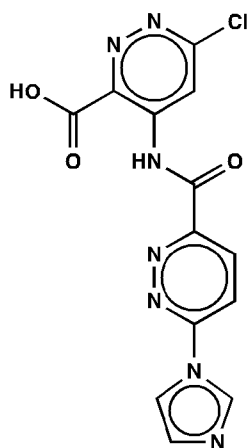
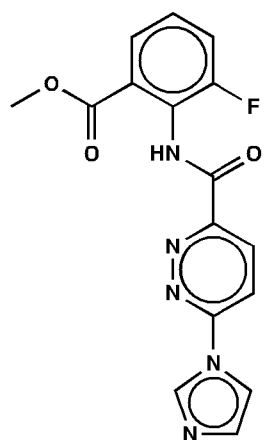


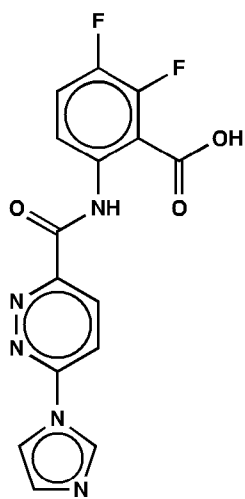
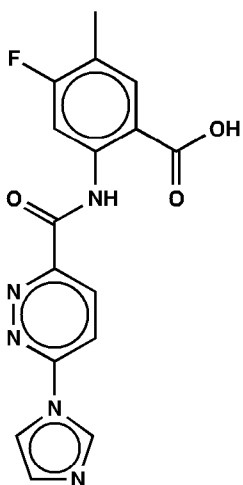
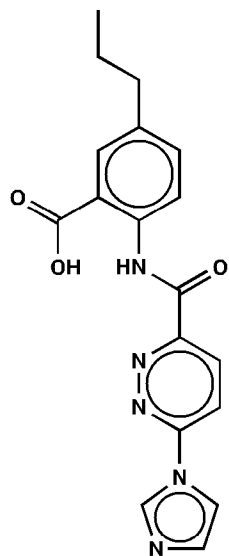
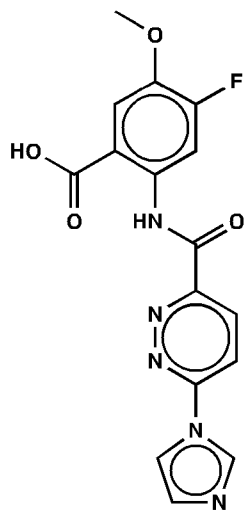
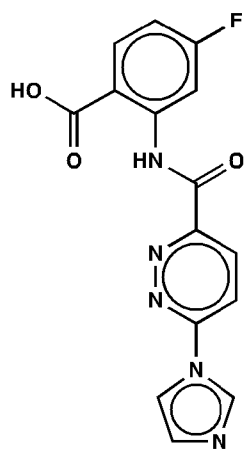
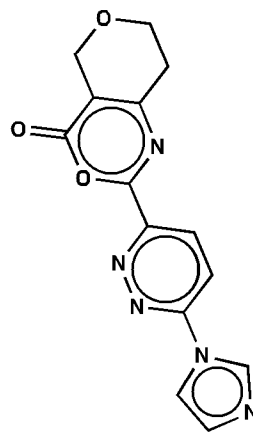
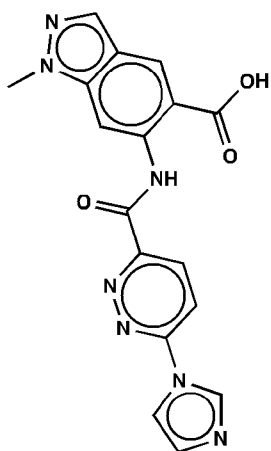
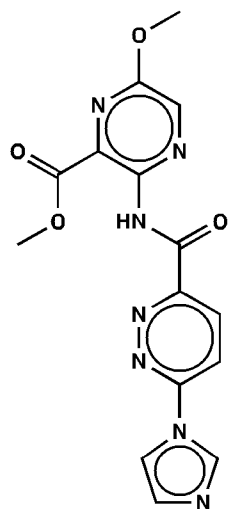


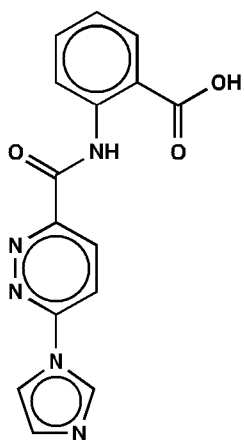
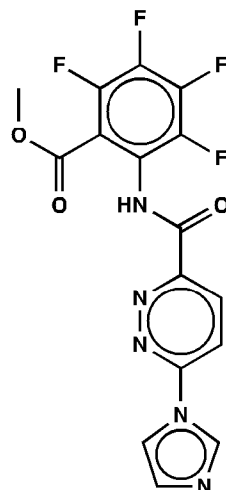
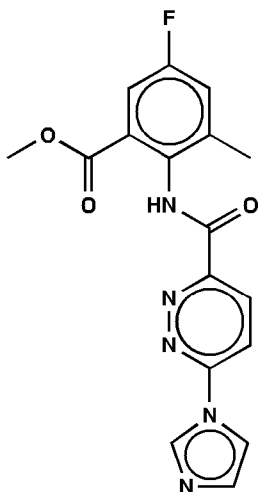
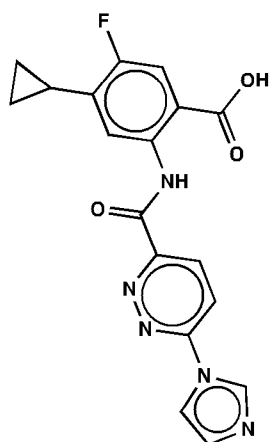






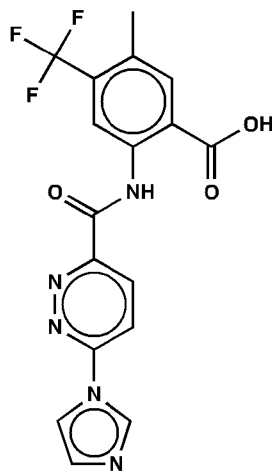
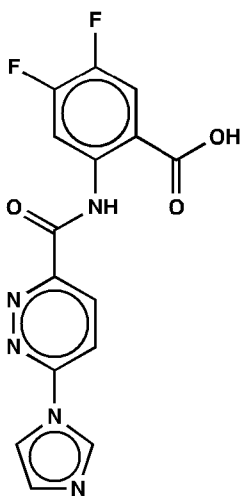
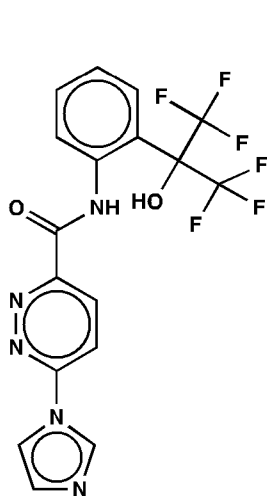


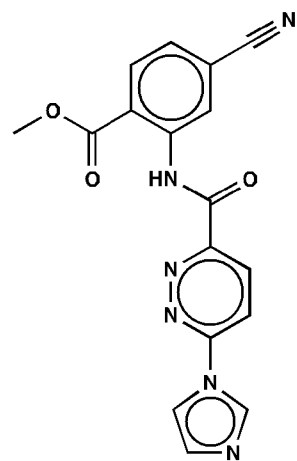
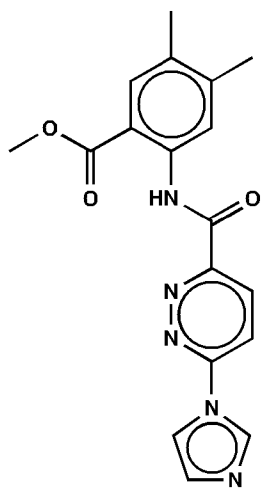
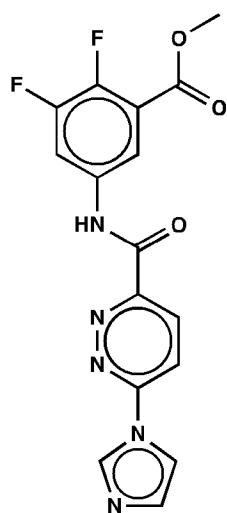
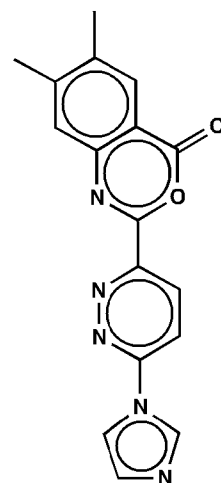
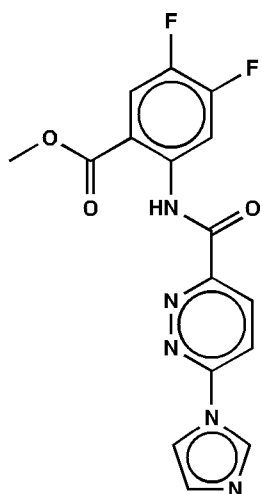
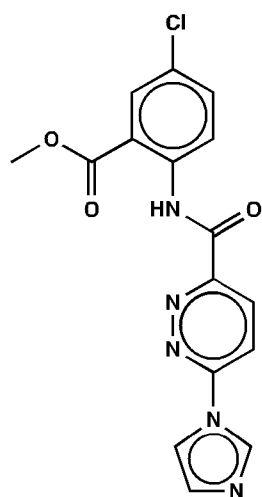
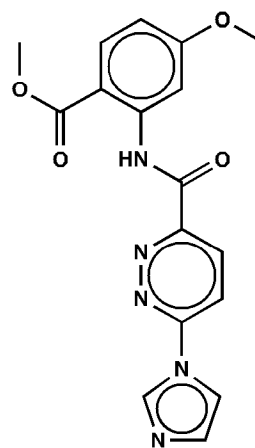
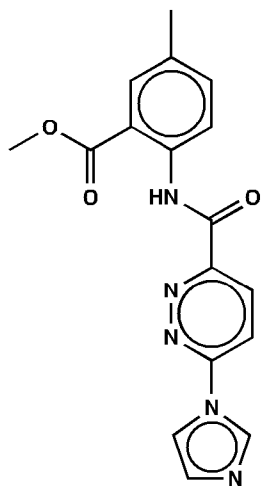
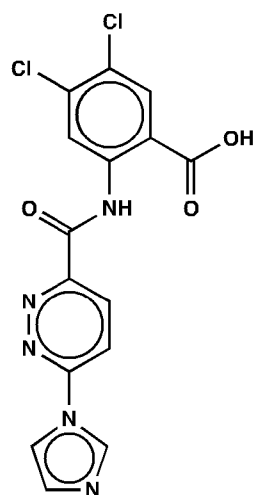


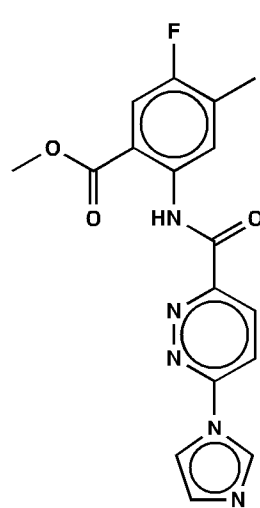
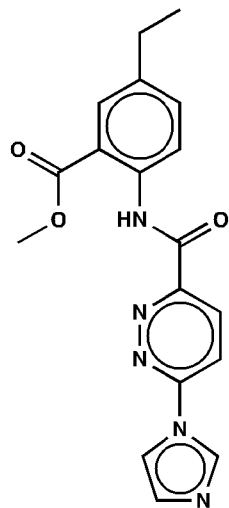
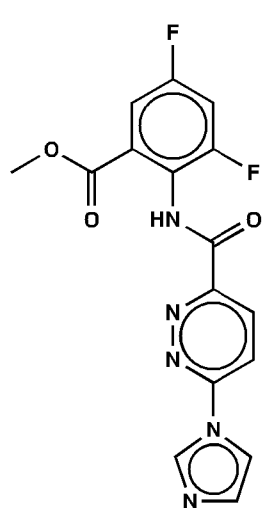
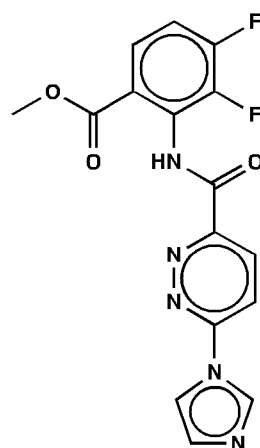
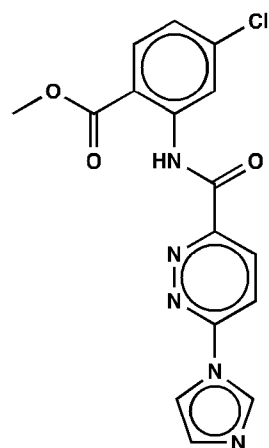
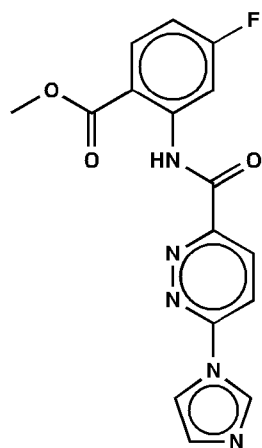
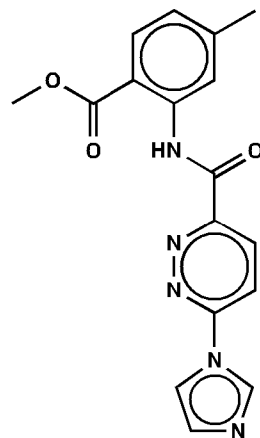
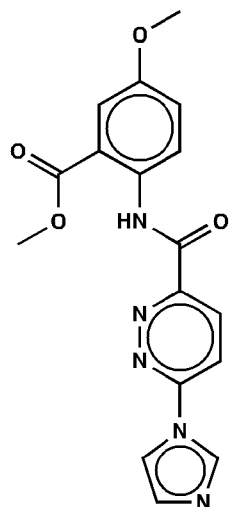
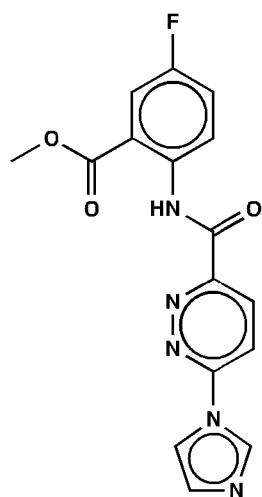


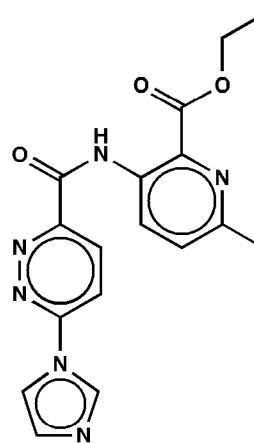
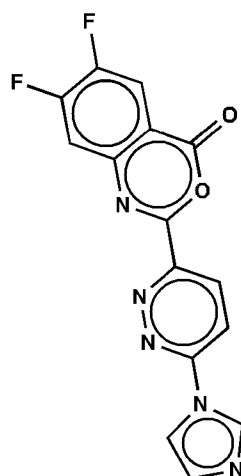
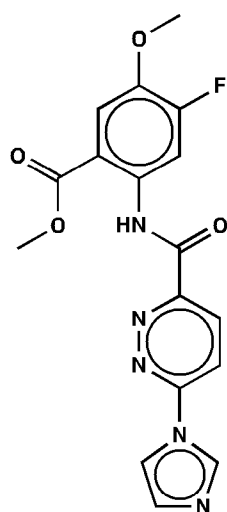
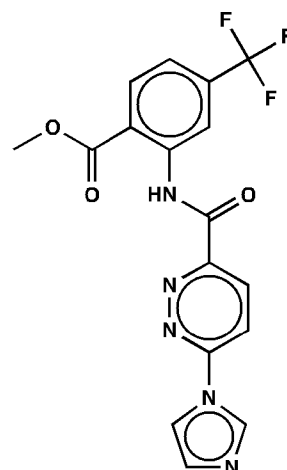
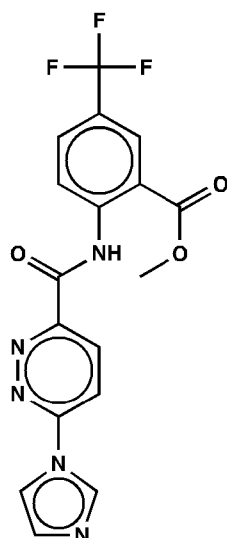
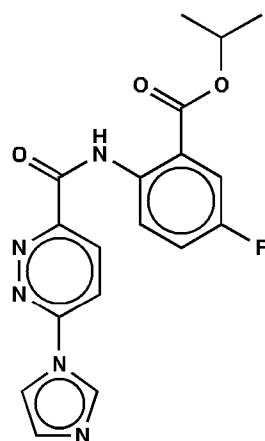
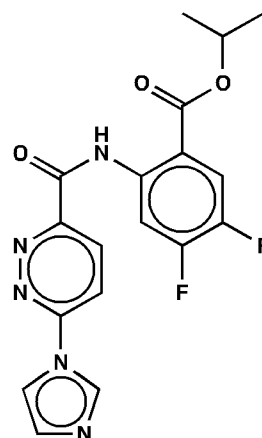
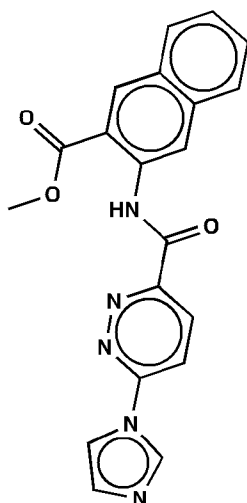
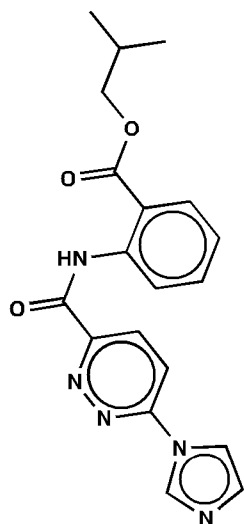
or a pharmaceutically acceptable salt thereof.

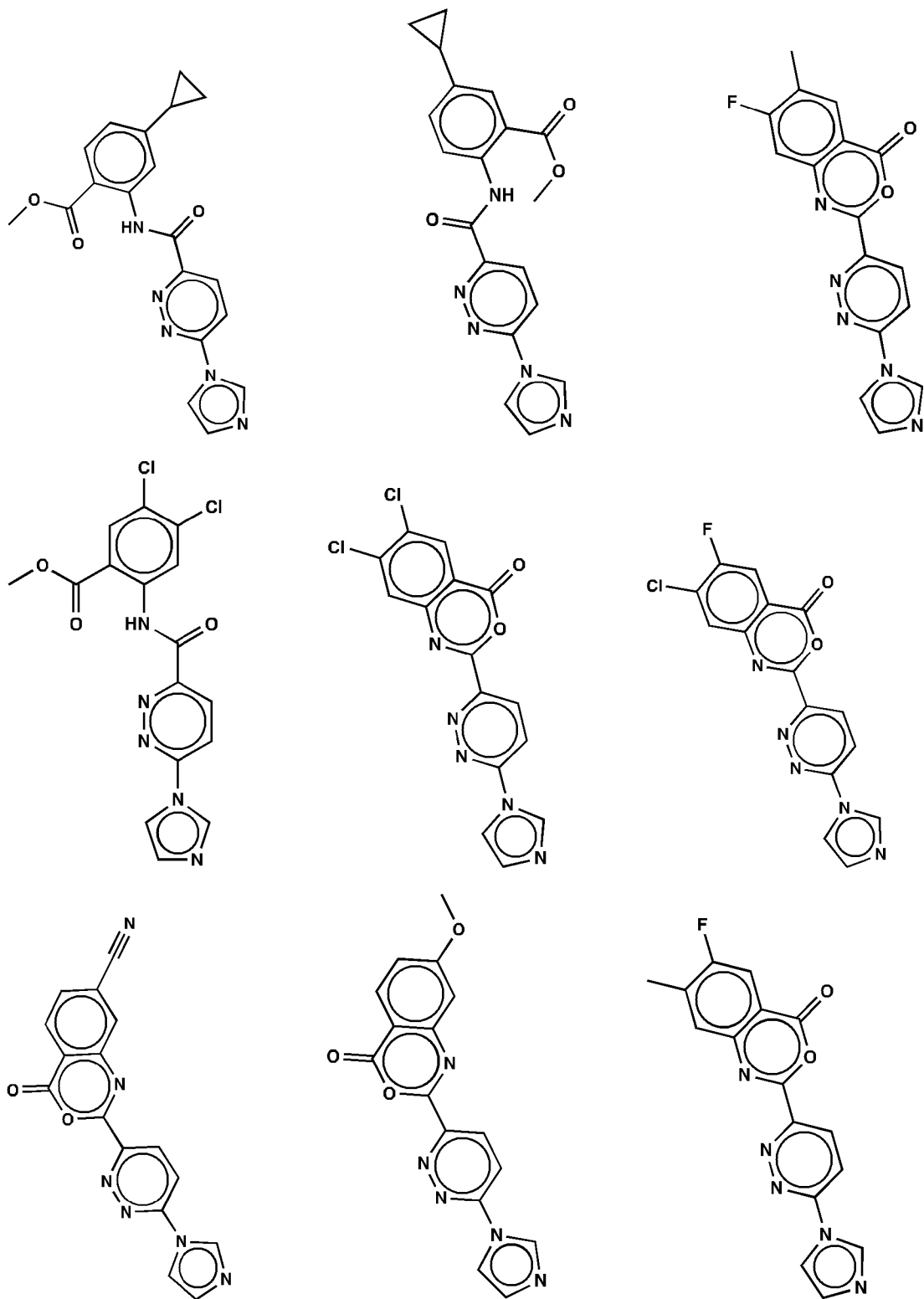
15. A compound of any one of the following formulae:

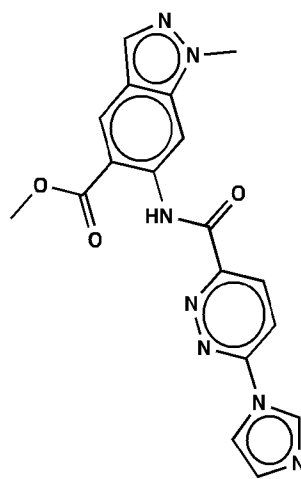
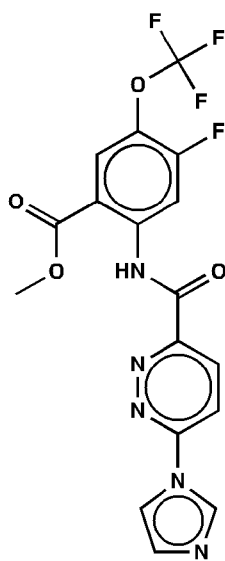
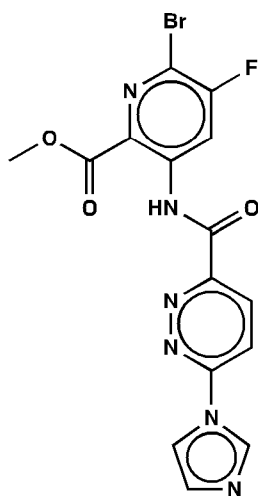
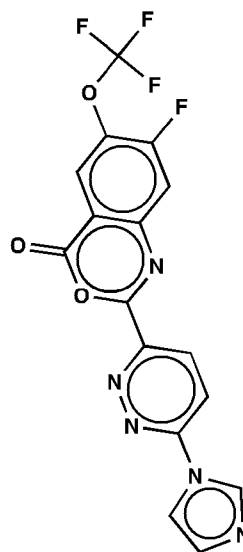
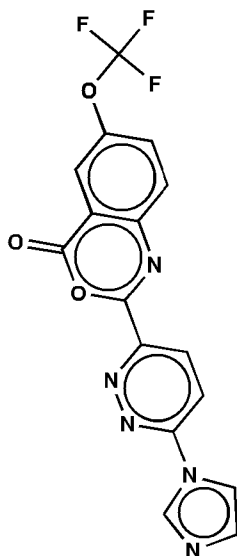
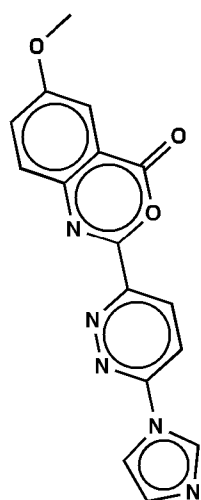


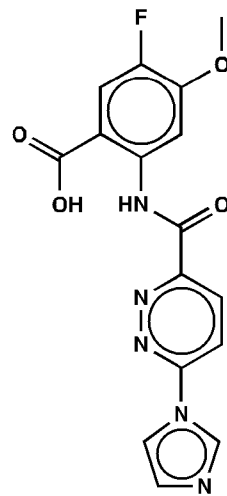
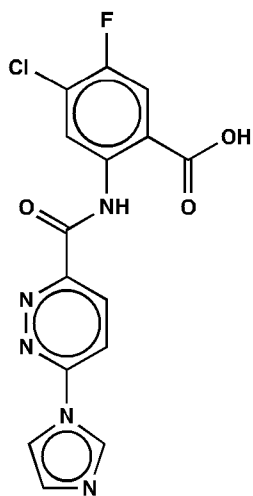
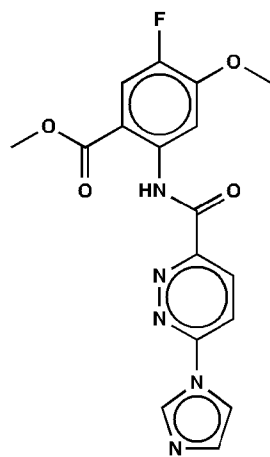
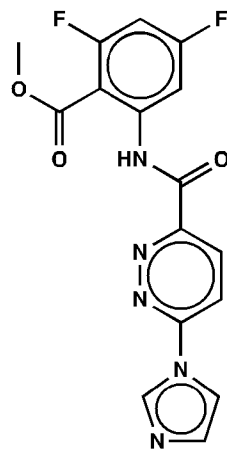
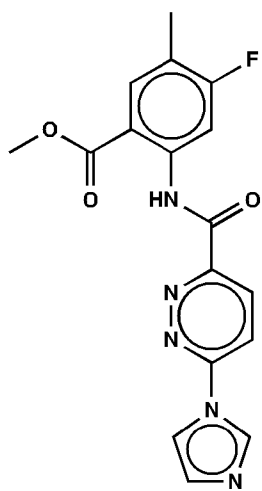
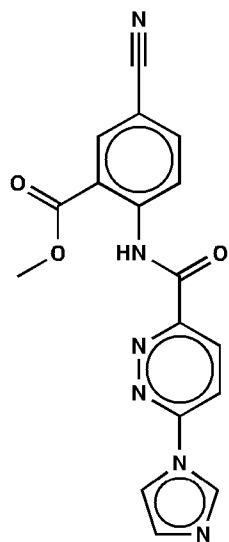
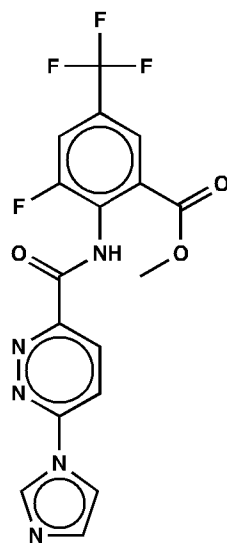
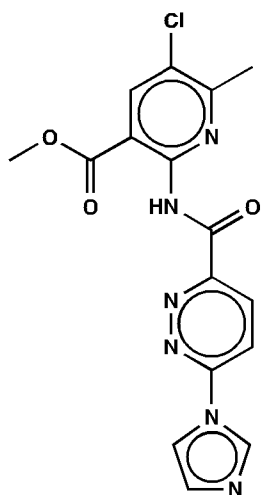
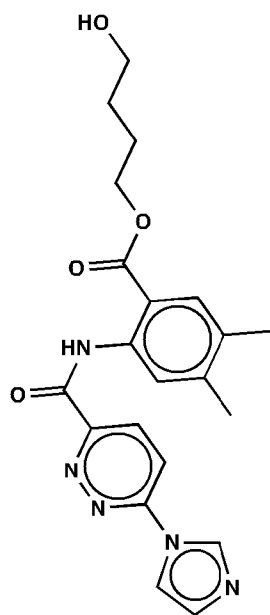


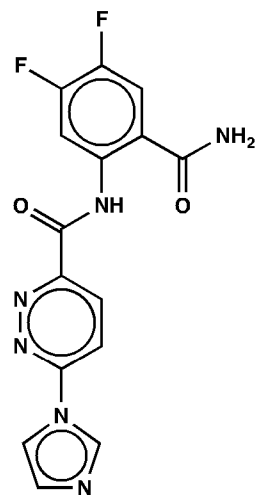
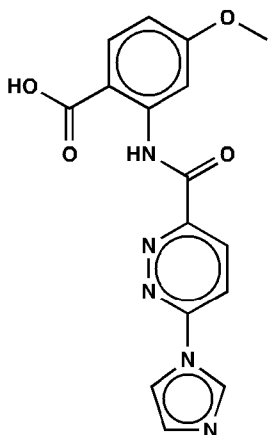
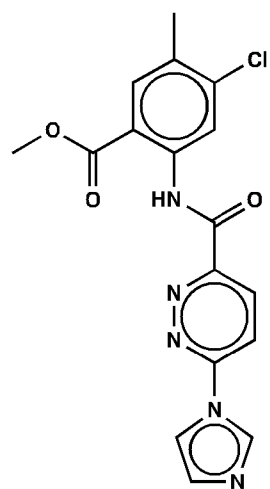
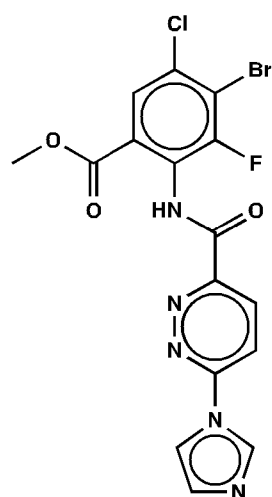
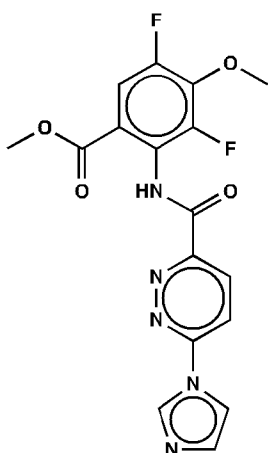
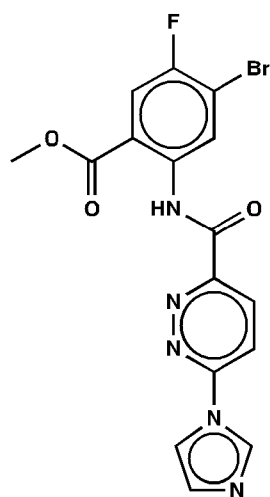
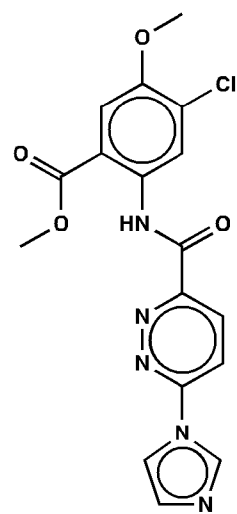
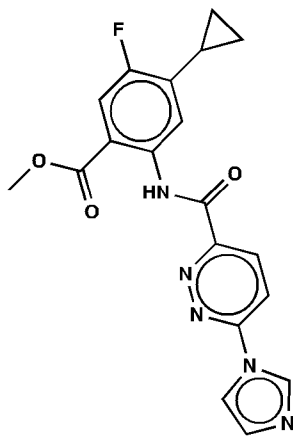
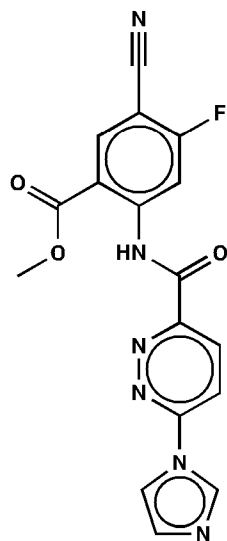


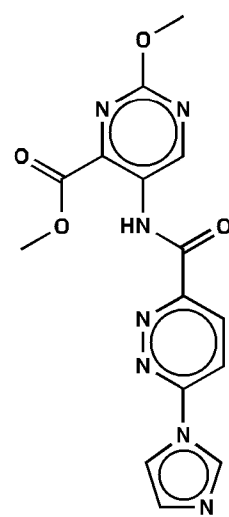
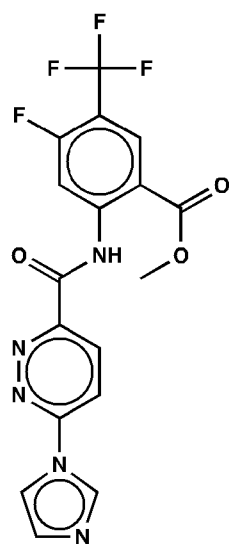
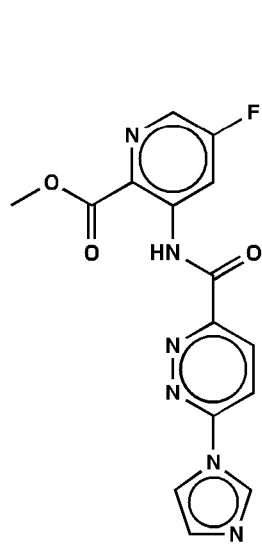
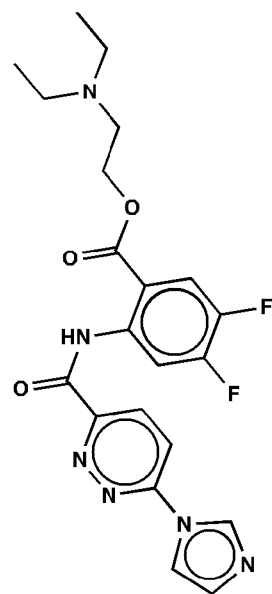
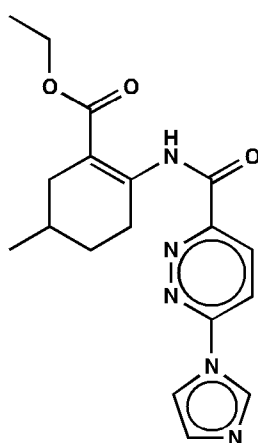
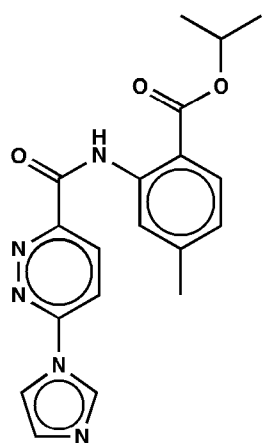
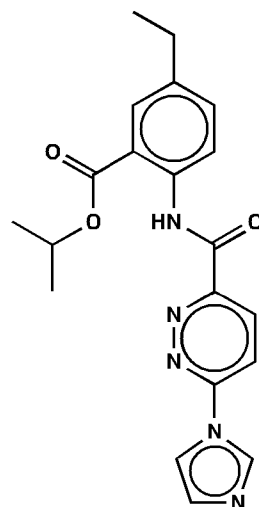
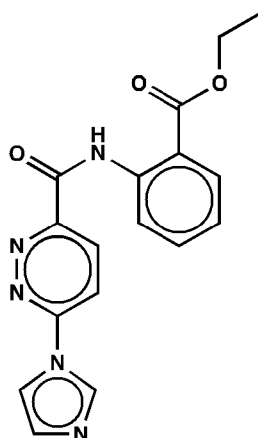
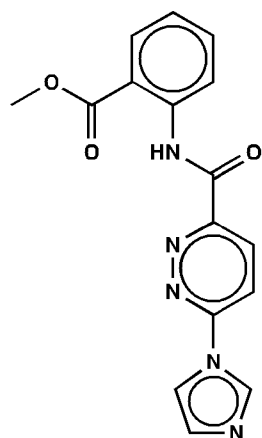




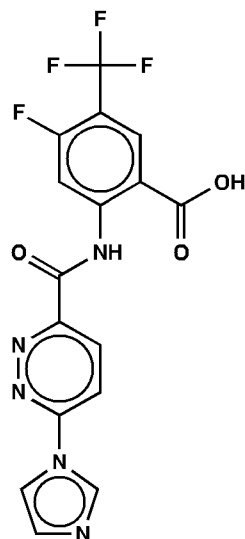
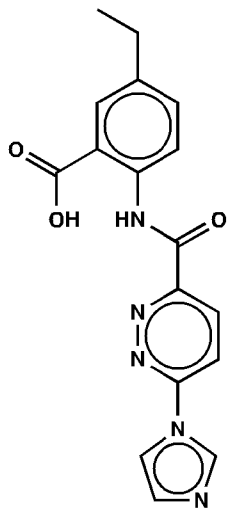
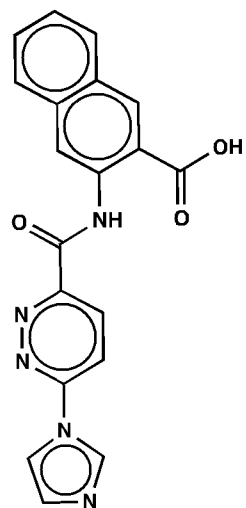
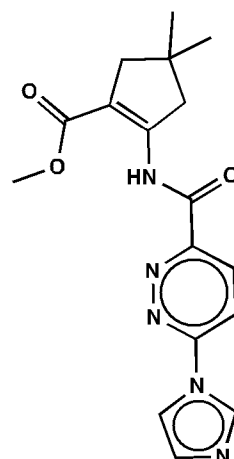
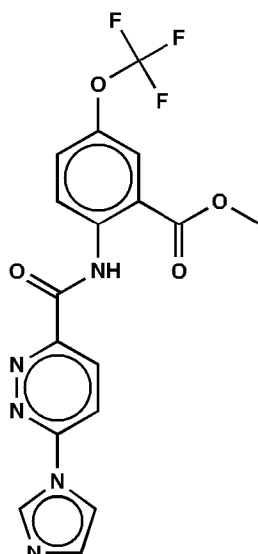
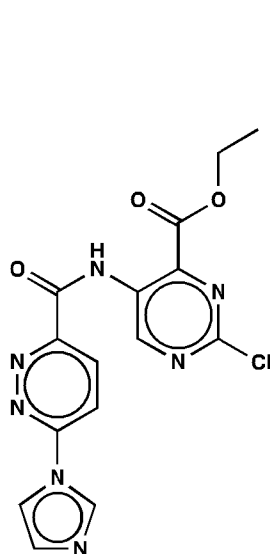
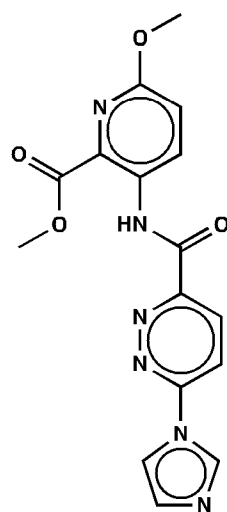
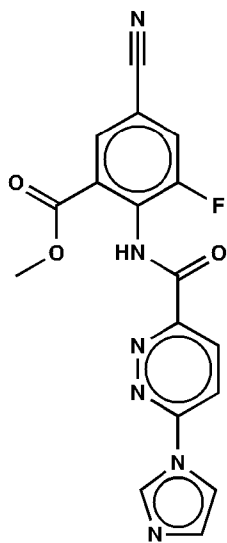
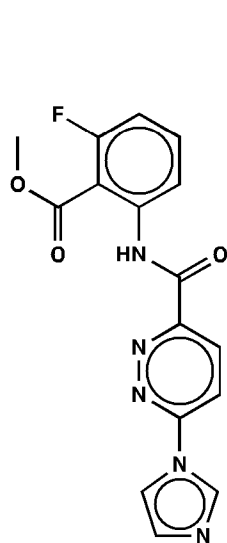


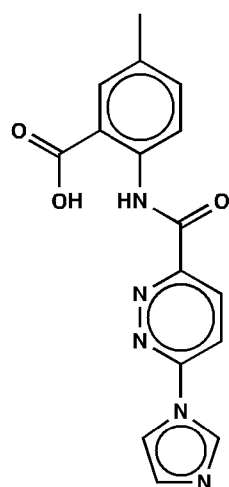
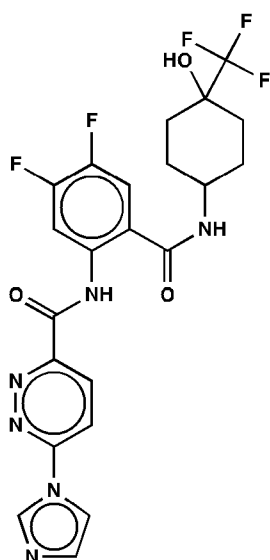
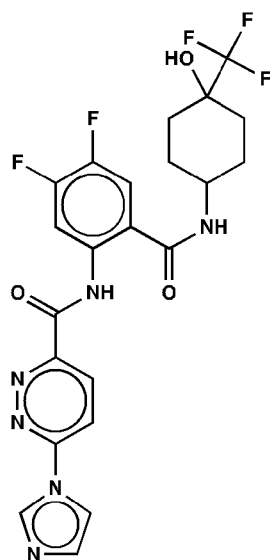
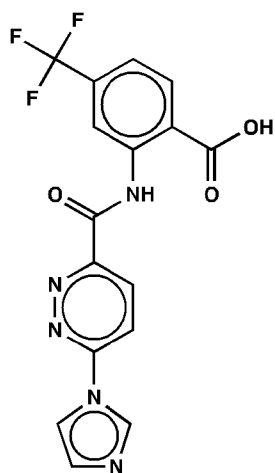
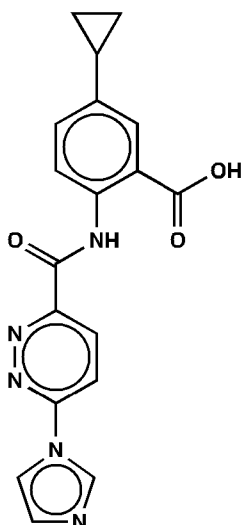
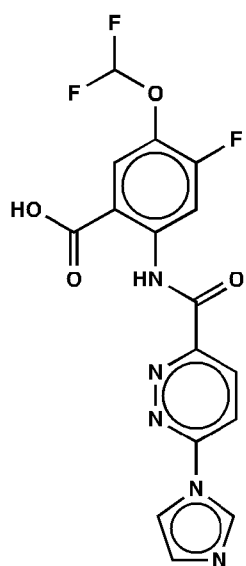
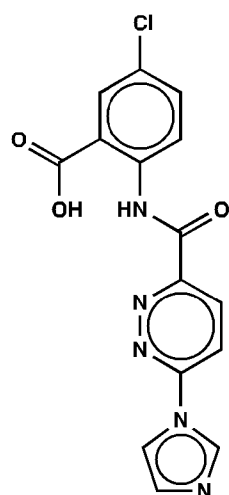
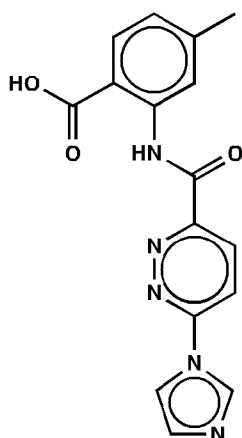
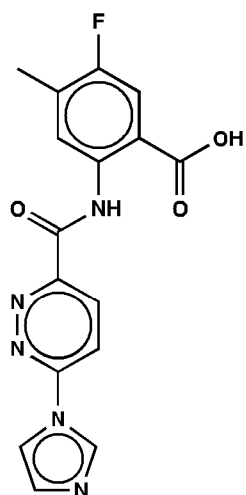


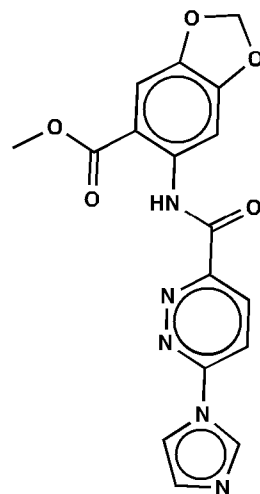
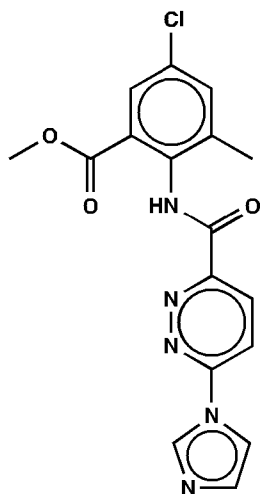
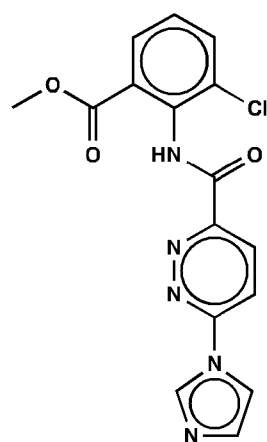
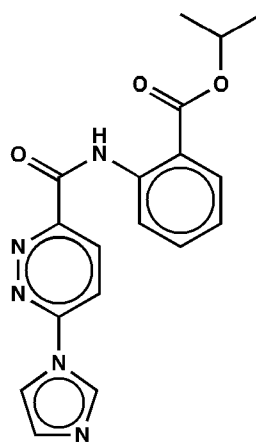
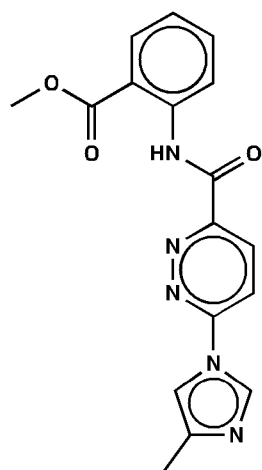
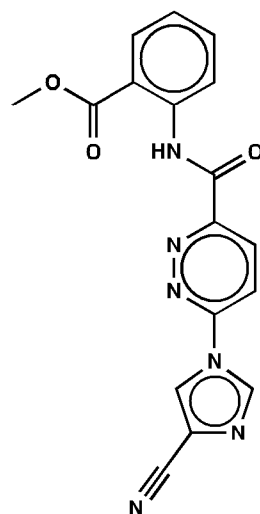
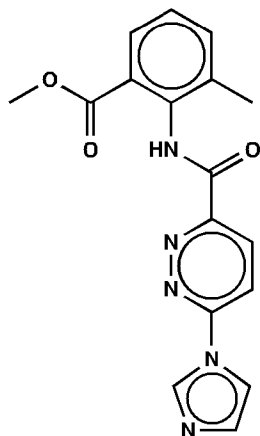
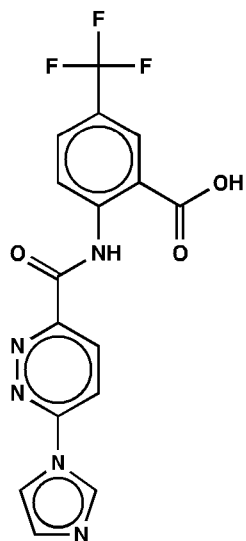


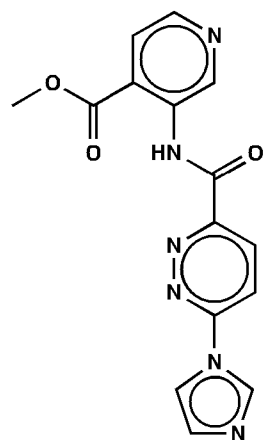
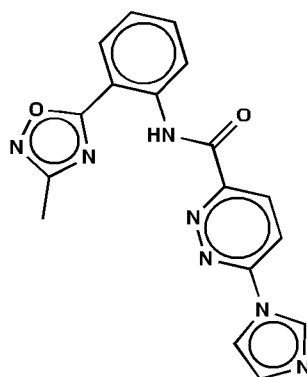
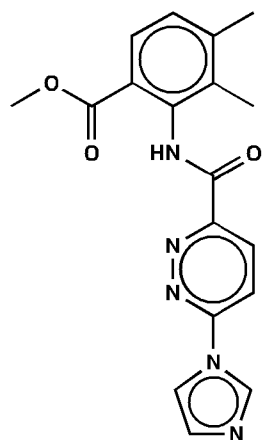
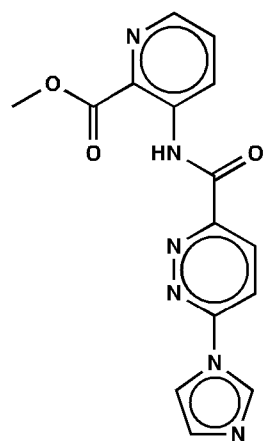
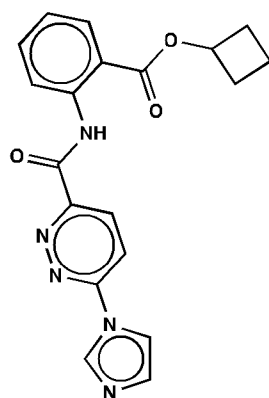
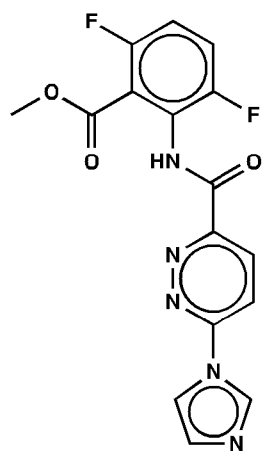
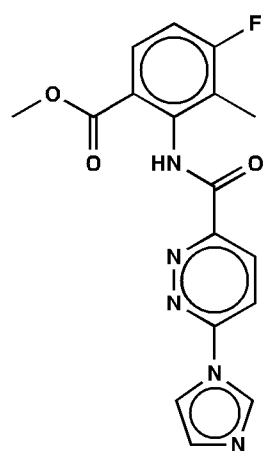
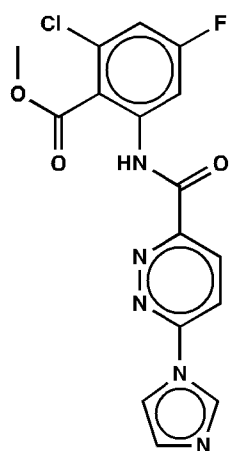
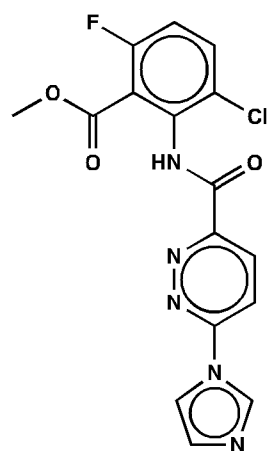


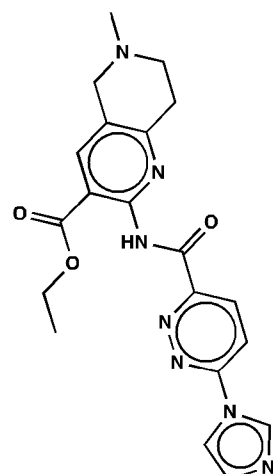
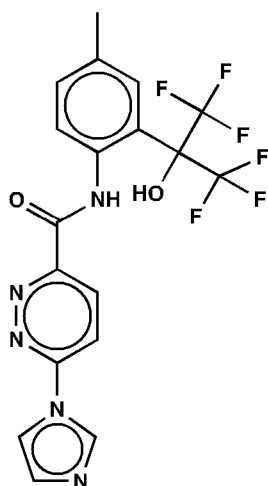
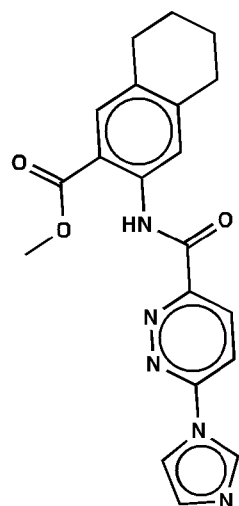
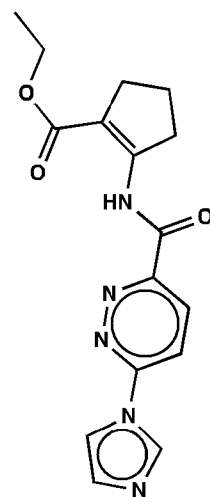
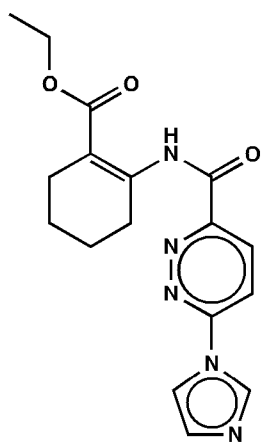
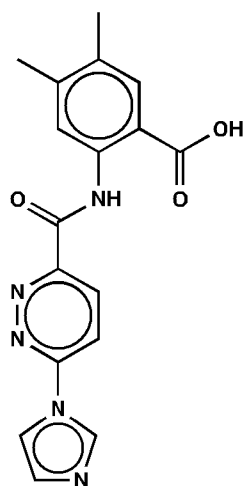
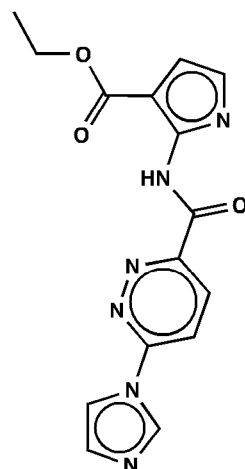
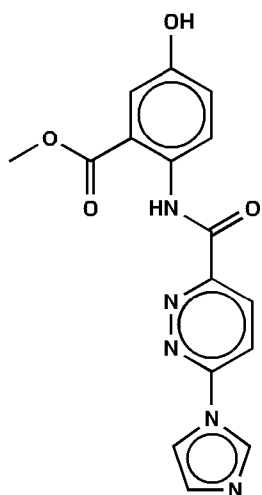
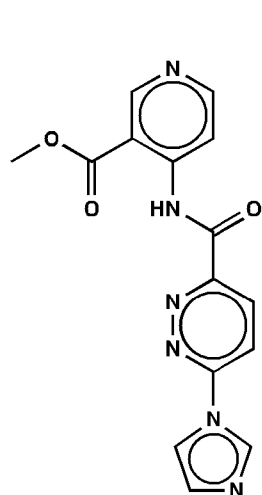
70

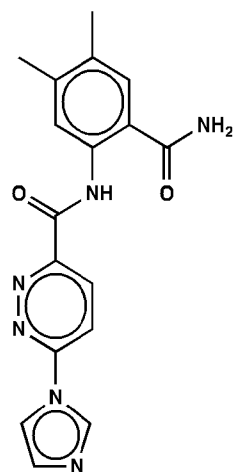
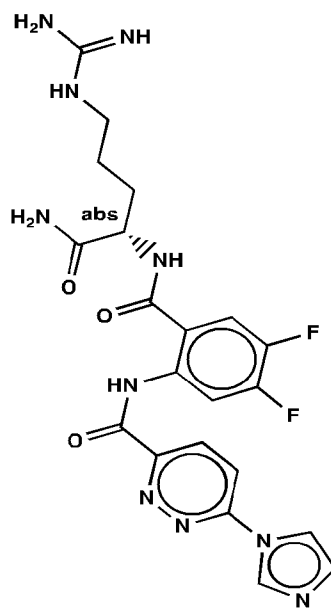
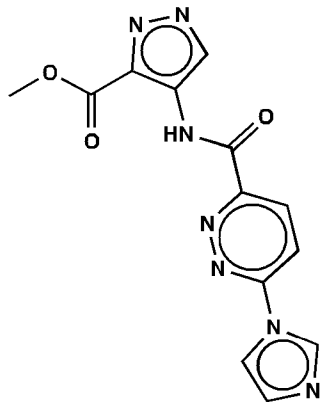
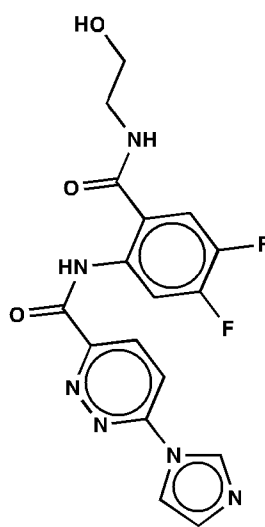
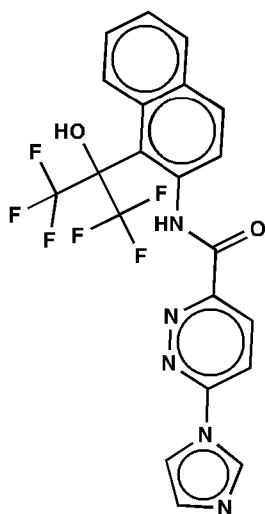
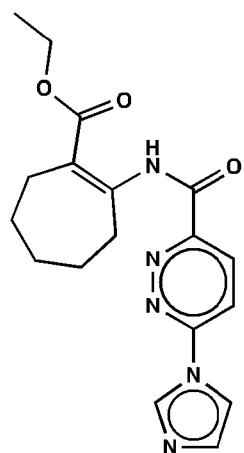
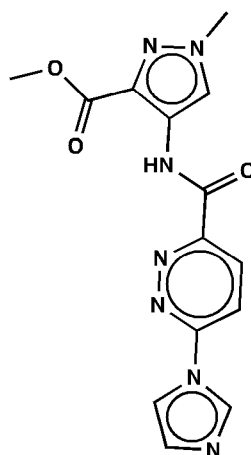
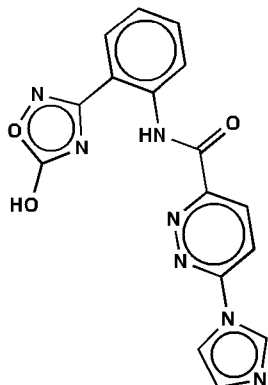
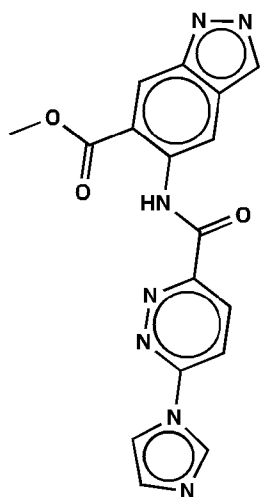


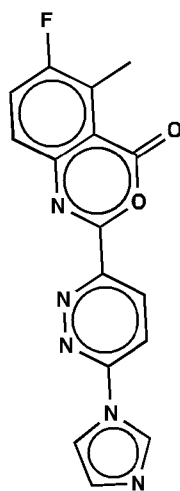
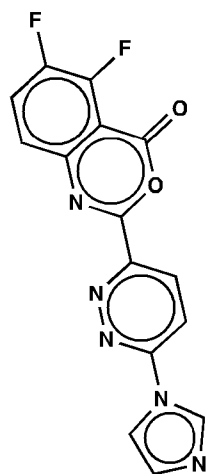
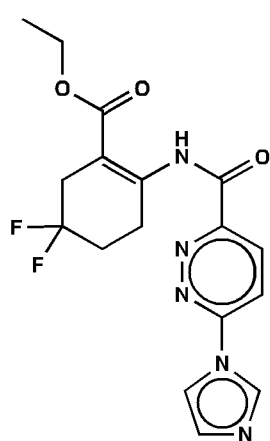
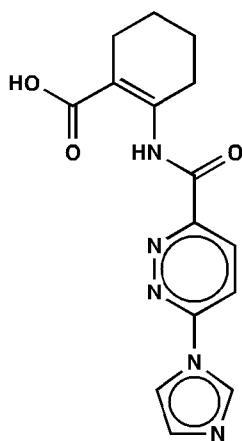
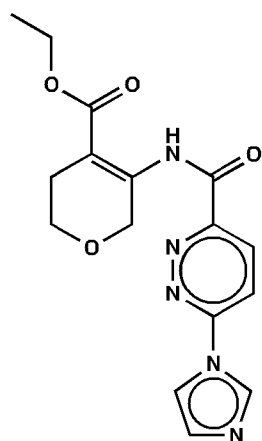
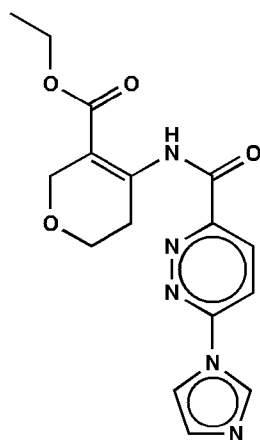
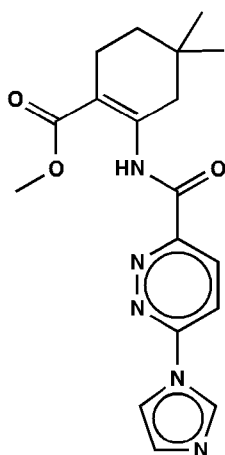
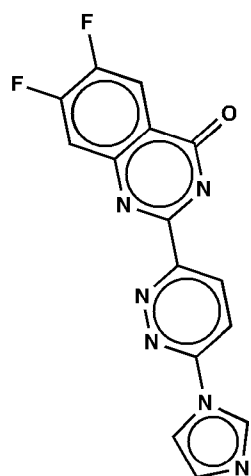


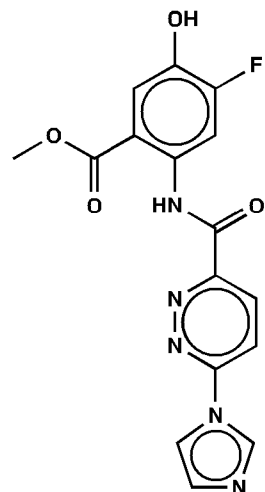
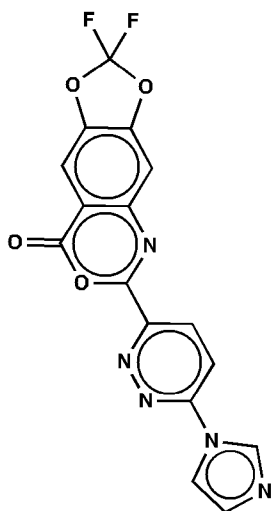
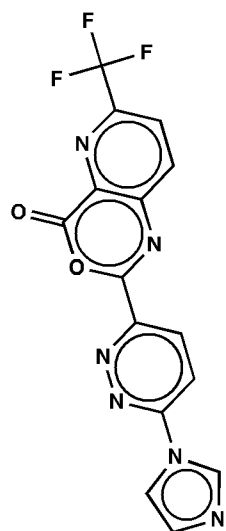
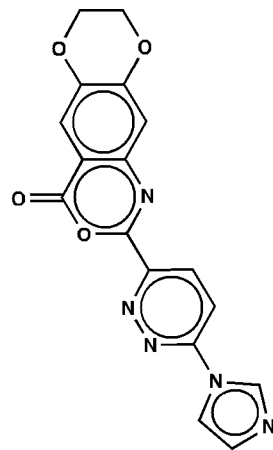
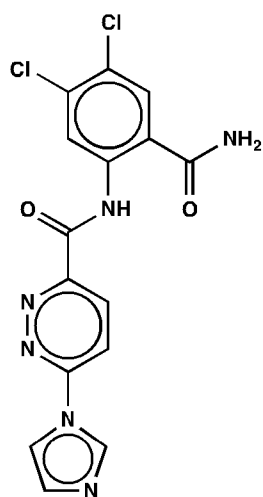
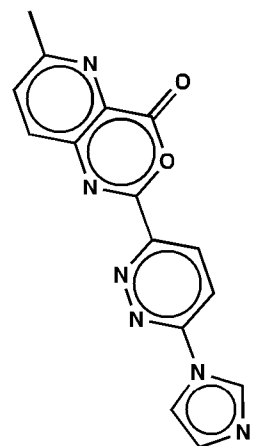
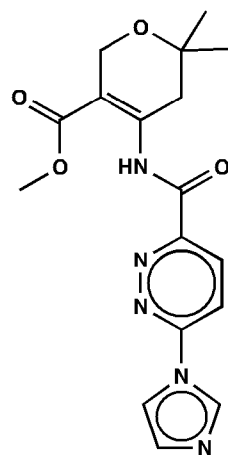
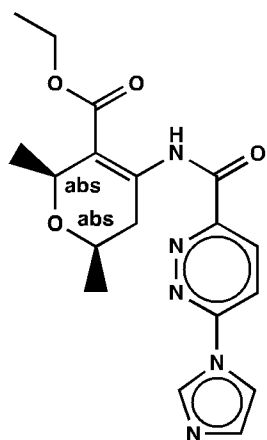
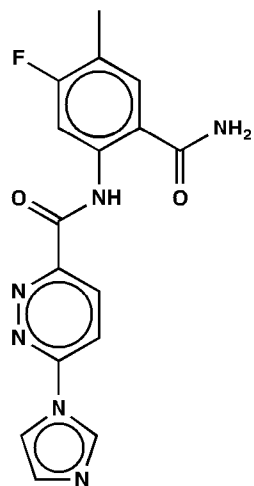


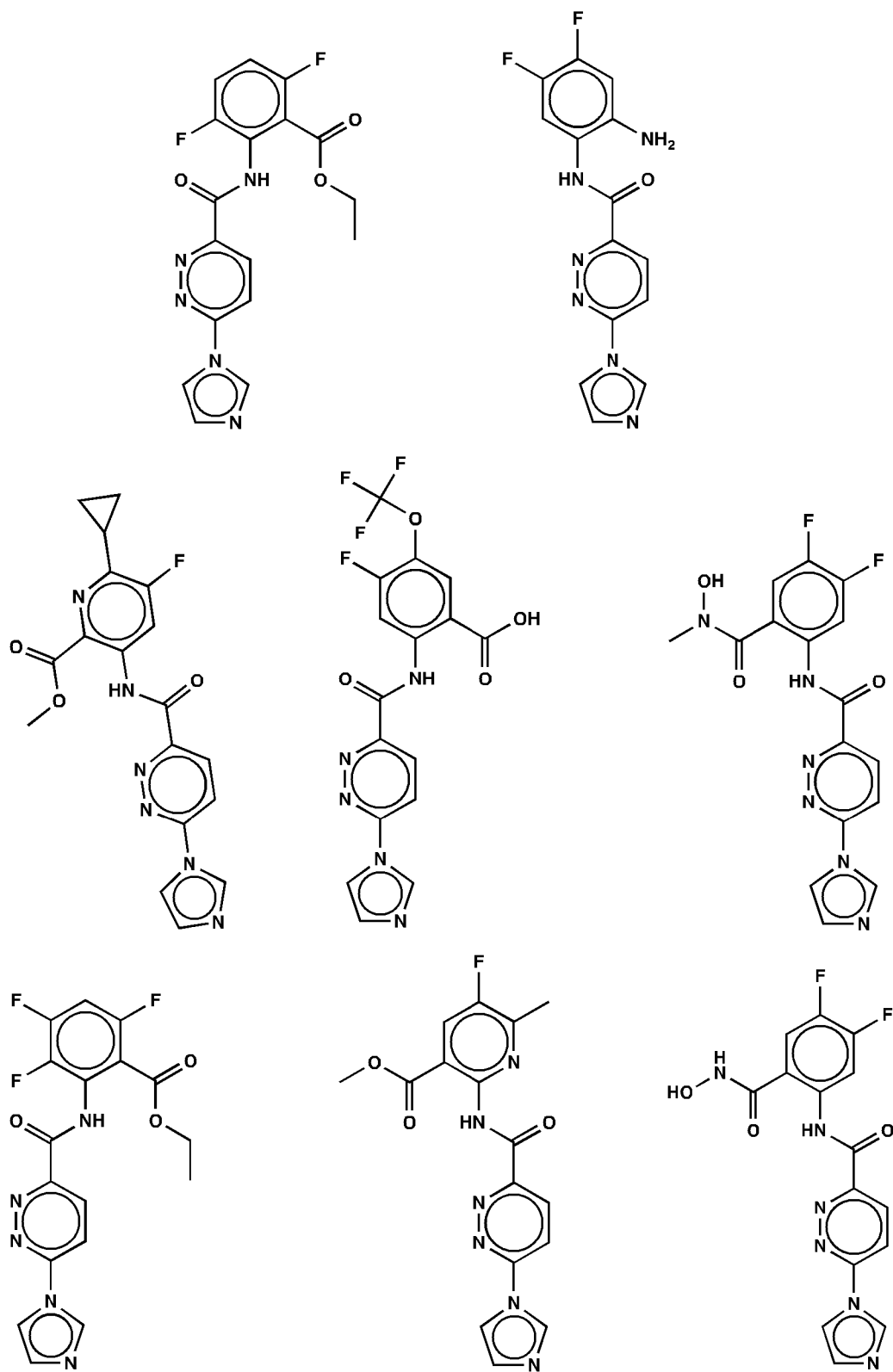


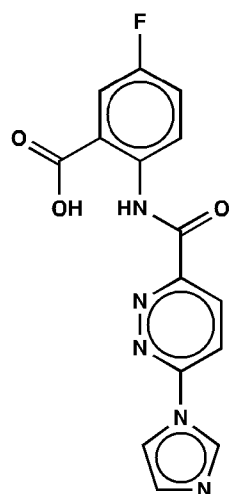
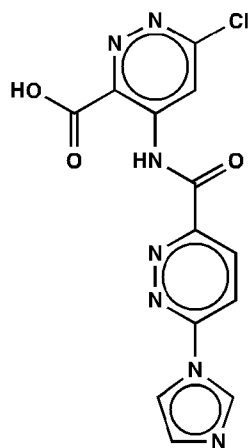
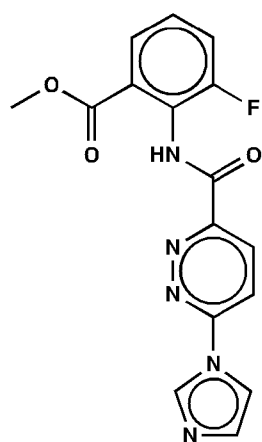
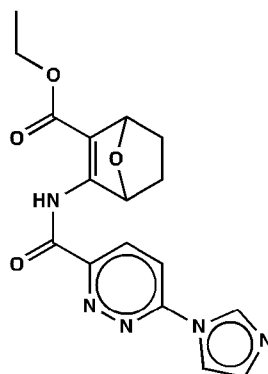
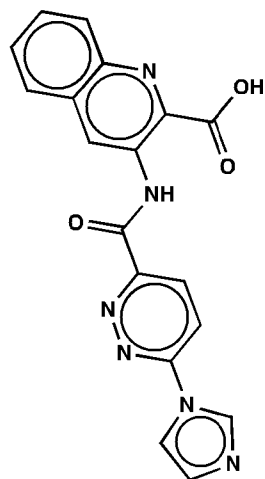
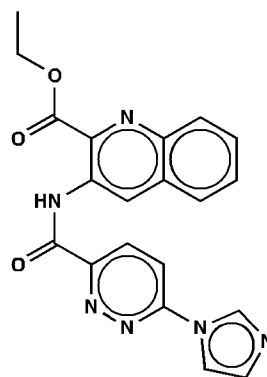
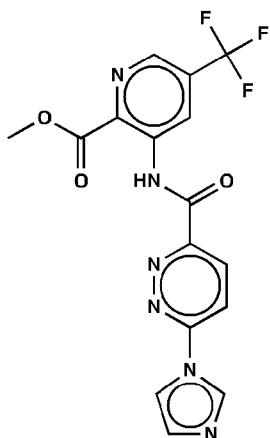
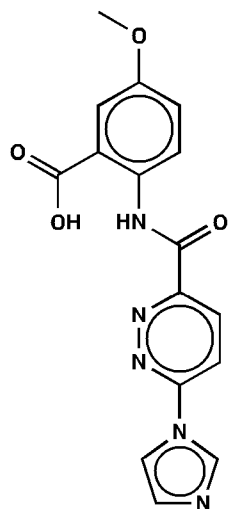


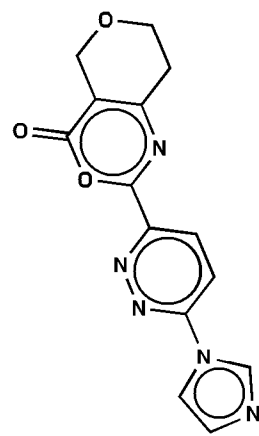
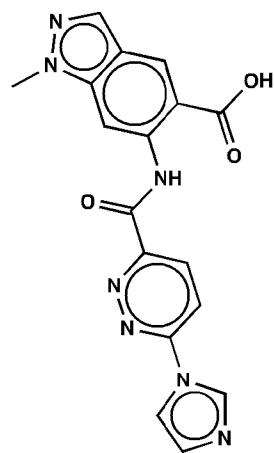
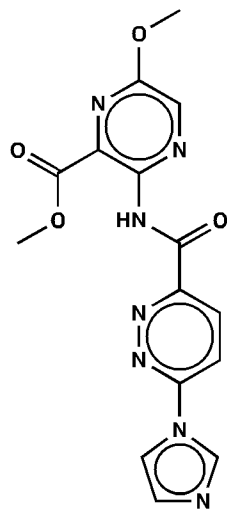
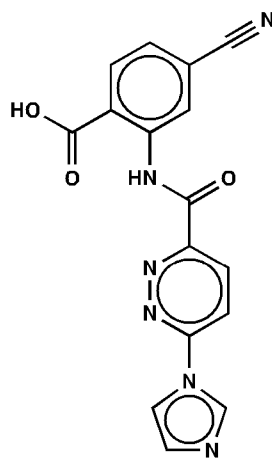
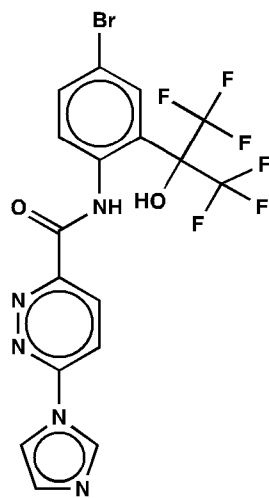
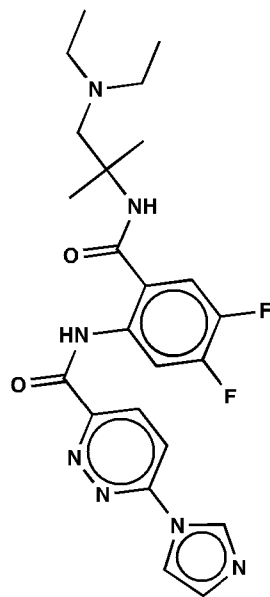
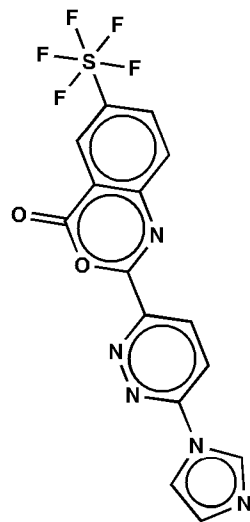
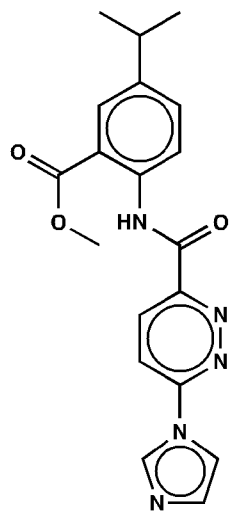
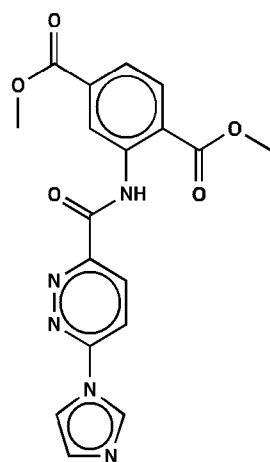


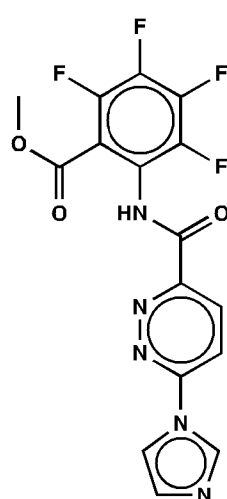
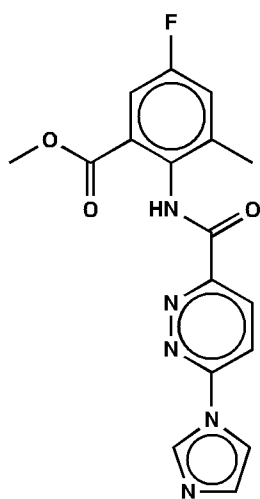
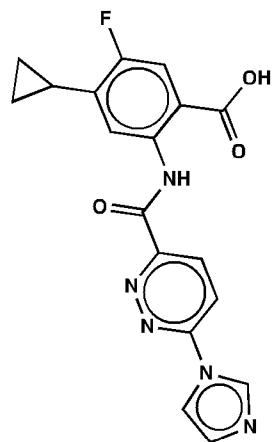
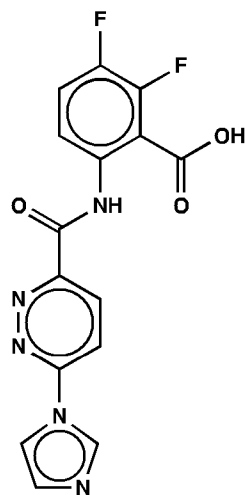
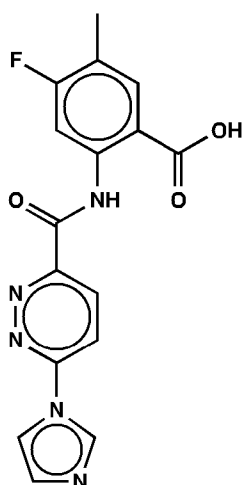
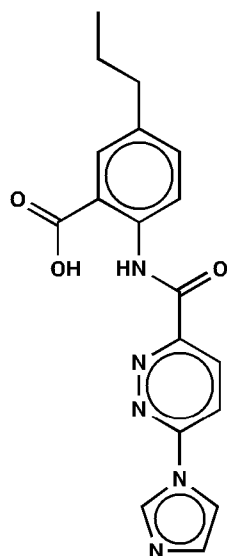
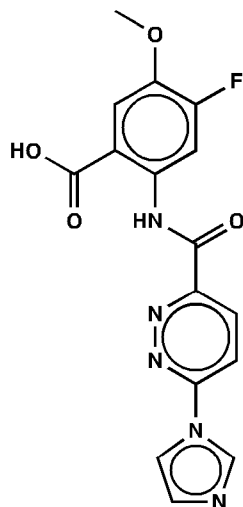
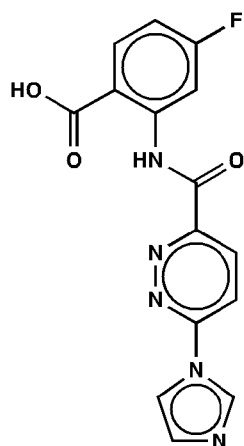


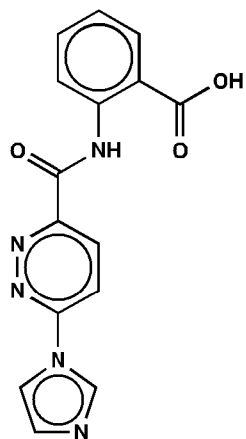












or a pharmaceutically acceptable salt thereof.

FIGURES

Fig. 1

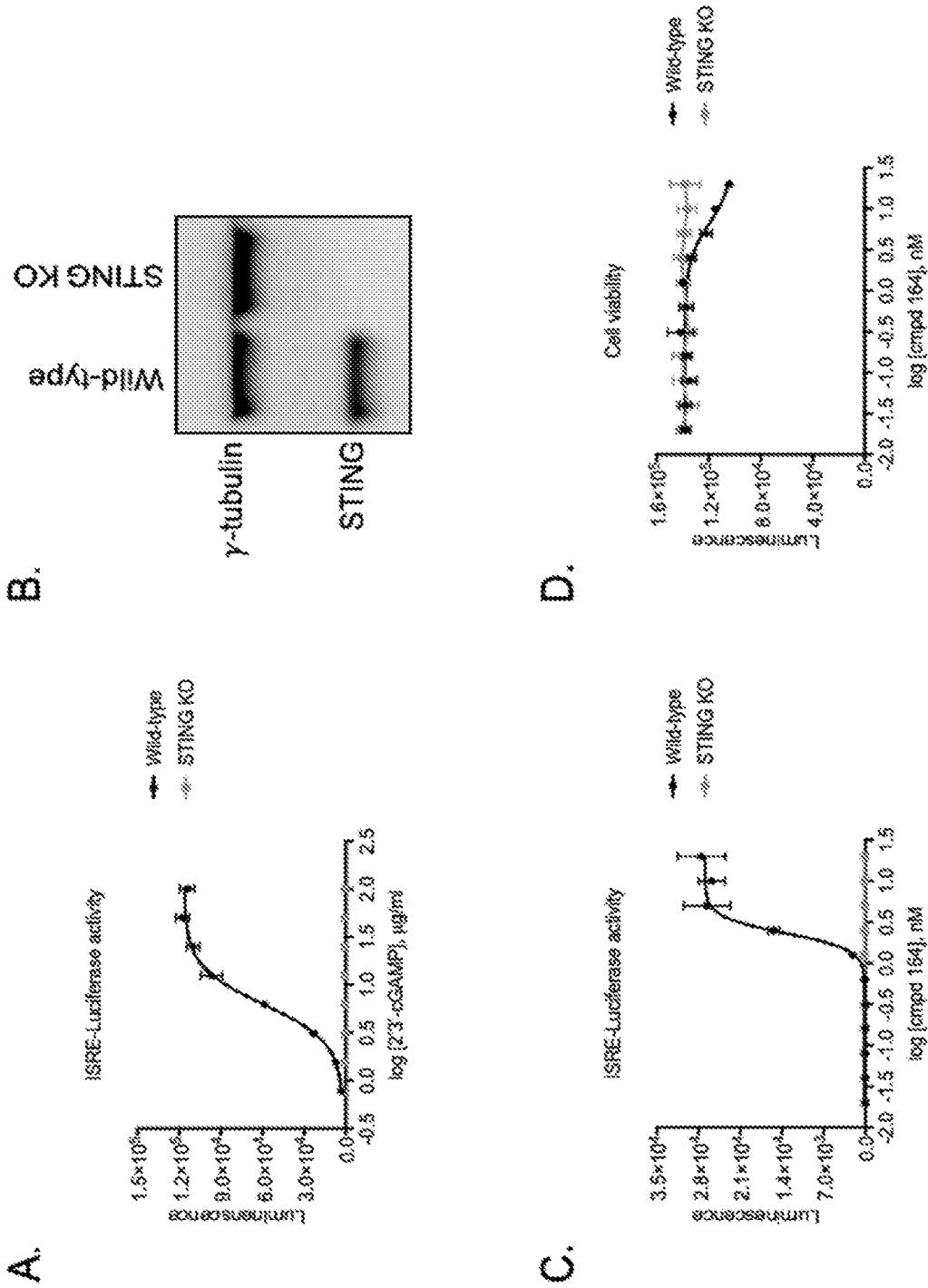


Fig. 2

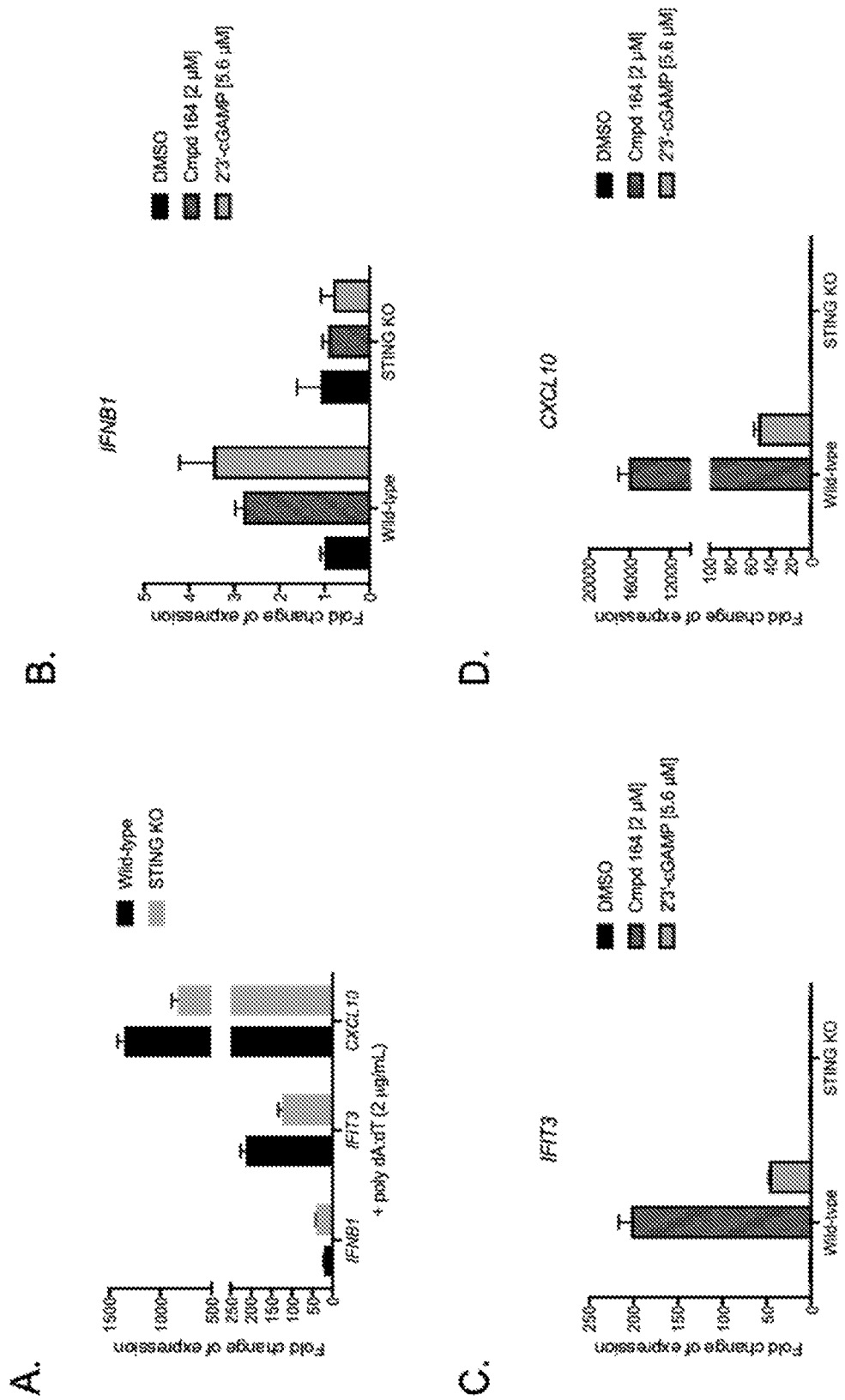
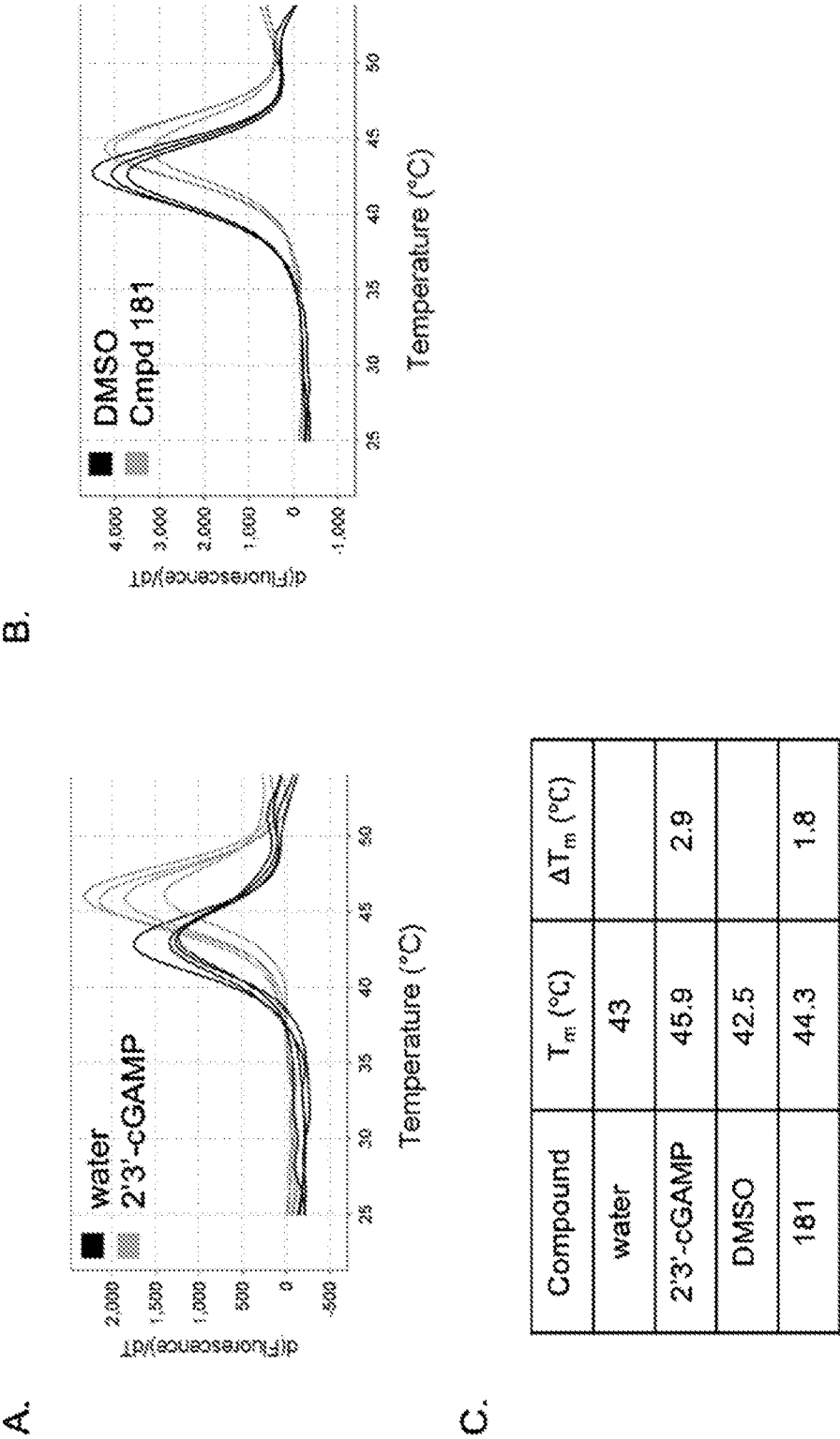
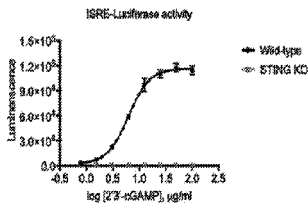


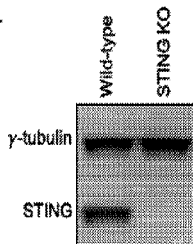
Fig. 3



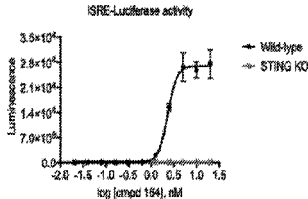
A.



B.



C.



D.

