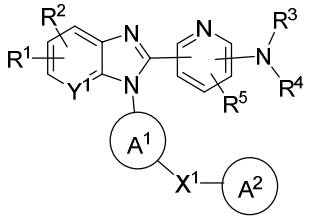
overgrowth of skin, connective tissue, brain, and other tissues. Patients with this disease also have an increased risk of premature death due to vascular deformities.

[0009] New compounds that inhibit AKT1 are needed and would provide a medical benefit to patients suffering from disorders associated with AKT1 activity. The present invention addresses the foregoing needs and provides other related advantages.

SUMMARY

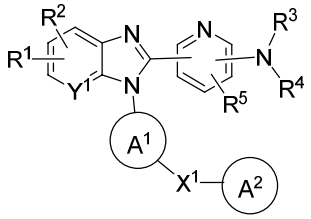
[0010] The disclosure provides aminopyridinyl imidazo[4,5-b]pyridine and related compounds, pharmaceutical compositions, and their use in treating disease, such as cancer. In particular, one example of the disclosure provides a collection of aminopyridinyl imidazo[4,5-b]pyridine and related compounds, such as a compound represented by Formula I:



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description. Further description of additional collections of aminopyridinyl imidazo[4,5-b]pyridine and related compounds are described in the detailed description. The compounds may be part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

[0010a] In one aspect, the present disclosure refers to a compound represented by Formula I:



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof; wherein:

R^1 is phenyl, a C_{3-6} monocyclic cycloalkyl, a 5-6 membered heteroaryl containing 1 or 2 heteroatoms selected from nitrogen, a 5-6 membered saturated heterocyclyl containing 1 or 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, C_{1-4} alkoxy or C_{1-6} alkyl, wherein the phenyl, cycloalkyl, heteroaryl, heterocyclyl, and alkoxy are each substituted with m occurrences of R^{12};

R^2, R^3, R^4, R^5, and R^9 are each independently selected from hydrogen, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^6 is halo or C_{1-4} alkyl;

R^7 is -(C_{0-4} alkylene)-CO_2H, -CO_2(C_{1-4} alkyl), $S(O)_2N(R^9)_2$ or -$C(O)N(R^9)_2$;

R^8 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, or halo;

R^{10} and R^{11} each represent independently for each occurrence hydrogen or C_{1-4} alkyl, or R^{10} and R^{11} are taken together with the nitrogen atom to which they are attached to form a 3-7 membered ring;

R^{12} represents independently for each occurrence halo, cyano, C_{1-4} alkoxy or C_{1-4} alkyl;

A^1 is phenylene or pyridinylene, each of which is substituted with 0, 1, or 2 occurrences of R^6;

A^2 is a C_{4-6} monocyclic cycloalkyl, C_{5-8} bridged or fused bicyclic cycloalkyl, dioxo-cyclohexyl, C_{7-10} spirocyclic saturated carbocyclyl, 7-10 membered spirocyclic saturated heterocyclyl containing 1 heteroatom selected from nitrogen or a 5-6 membered saturated heterocyclyl containing 1 or 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the cycloalkyl, carbocyclyl, and heterocyclyl are substituted with (i) 1 occurrence of R^7 and (ii) n occurrences of R^8;

X^1 is -N(R^9)C(O)-Ψ, -C(O)N(R^9)-Ψ, –(3-6 membered saturated heterocyclylene containing 1 or 2 heteroatoms selected from nitrogen)-C(O)-Ψ, -N(R^9)C(R^{10})(R^{11})-Ψ, -N(R^9)-Ψ, -C(O)-Ψ, -(C(R^{10})(R^{11}))$_p$-Ψ, –(3-6 membered saturated heterocyclylene containing 1 or 2 heteroatoms selected from nitrogen)-C(R^{10})(R^{11})-Ψ, -(C(R^{10})(R^{11}))$_p$-N(R^9)-Ψ, or a covalent bond; wherein Ψ is a bond to A^2, and wherein the 3-6 membered saturated heterocyclylene is substituted with 0, 1, or 2 occurrences of C_{1-4} alkyl;

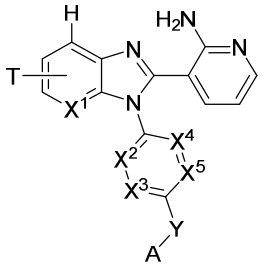
Y^1 is N or -C(H)-;

p is 1, 2, 3, 4, 5, or 6 and

m and n are independently 0, 1, 2, 3, or 4,

wherein when X^1 is a covalent bond, A^2 is not cyclobutyl.

[0010b] In one aspect, the present disclosure refers to a compound represented by Formula II:



(II)

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

T is hydrogen, halo, cyano, C(=O)NH_2, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-12} cycloalkyl, 3-12 membered heterocyclyl, C_{6-10} aryl, or 5-9 membered heteroaryl, wherein the C_{1-6} alkyl, C_{1-6} alkoxyl, C_{6-10} aryl, or 5-9 membered heteroaryl are optionally substituted with one or more occurrences of R^T;

R^T is independently for each occurrence halo, C_{1-6} alkoxyl, C_{1-6} alkyl, cyano, or NHC(=O)R^{T1};

R^{T1} is C_{6-10} aryl or C_{1-6} alkyl;

X^1 is N or CH;

X^2 and X^3 are independently for each occurrence N or CR^X;

X^4 and X^5 are CR^X;

R^X is independently for each occurrence hydrogen, C_{1-6} alkyl, or halo;

Y is absent, or Y is selected from the group consisting of –(C(R^{Y1})$_2$)$_q$-, -R^{Y2}C(R^{Y1})$_2$-*, -C(R^{Y1})$_2$$R^{Y2}$-*, -N$R^{Y1}$-, -(C($R^{Y1}$)$_2$)$_qNR^{Y1}$-*, -N$R^{Y1}$C($R^{Y1}$)$_2$-*, -$CH_2NR^{Y1}$(C=O)-*, -

(C=O)NR^{Y1}CH$_2$-*, -NR^{Y1}C(=O)-*, -C(=O)NR^{Y1}-*, -C(=O)-, -R^{Y2}C(=O)-*, and -C(=O)R^{Y2}-*, wherein * denotes an attachment to A;

R^{Y1} is independently for each occurrence hydrogen, C$_{1-6}$ alkyl, or C$_{1-6}$ haloalkyl;

R^{Y2} is 3-12 membered heterocyclyl, wherein the 3-12 membered heterocyclyl is optionally substituted with one or more occurrences of C$_{1-6}$ alkyl;

q is 1, 2, 3, 4,5 or 6;

A is C$_{3-12}$ cycloalkyl or 3-12 membered heterocyclyl, wherein the C$_{3-12}$ cycloalkyl or 3-12 membered heterocyclyl are substituted with one or more occurrences of R^{A};

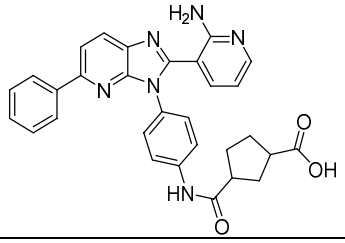
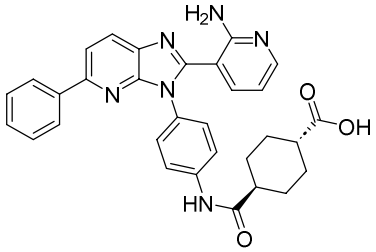
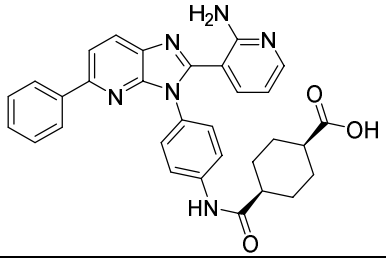
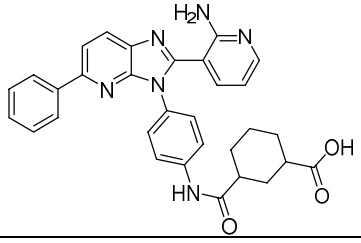
R^{A} is independently for each occurrence oxo, halo, C$_{1-6}$ alkyl, -(C$_{0-6}$ alkylene)-C(=O)OR^{A1}, C(=O)N(R^{A1})$_2$, NHC(=O)R^{A1}, NHC(=O)OR^{A1}, OC(=O)N(R^{A1})$_2$, S(=O)$_2$OR^{A1}, or S(=O)$_2$N(R^{A1})$_2$; and

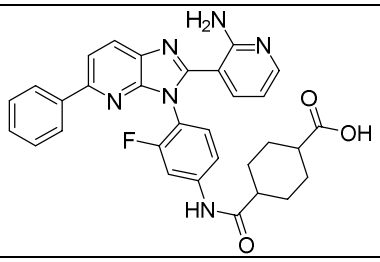
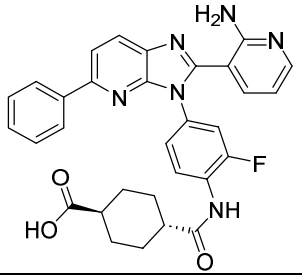
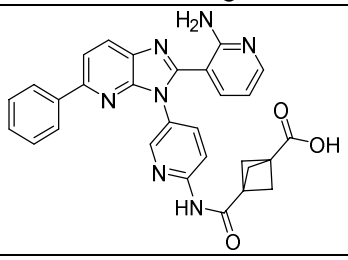
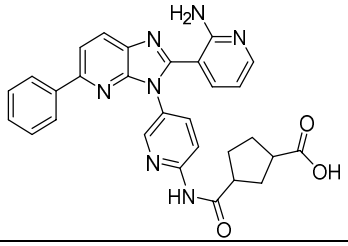
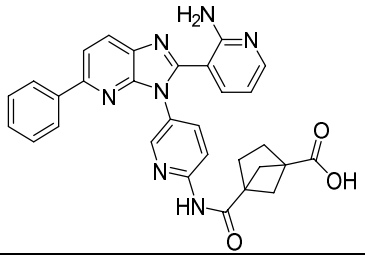
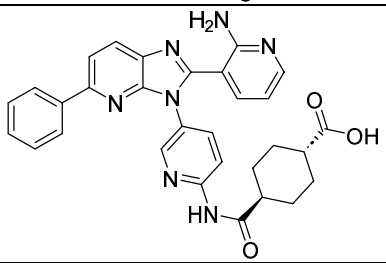
R^{A1} is independently for each occurrence hydrogen or C$_{1-6}$ alkyl,

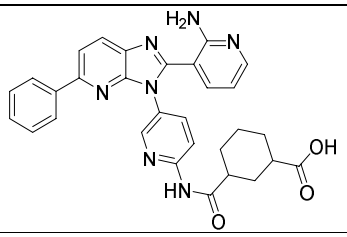
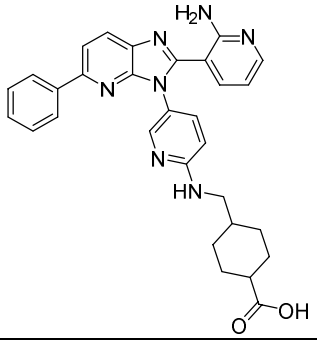
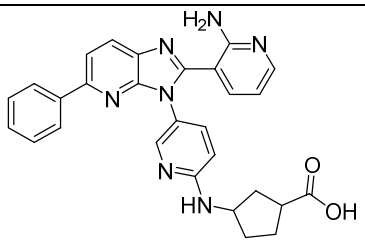
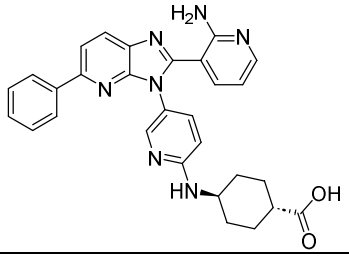
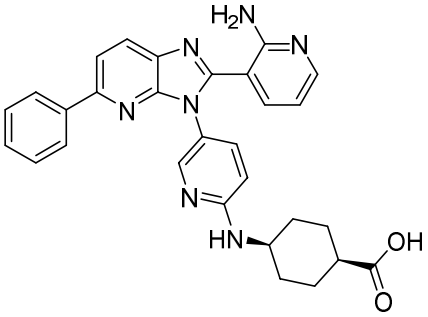
wherein when Y is absent, A is not cyclobutyl, azetidinyl, or oxetanyl.

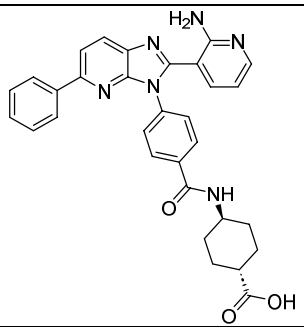
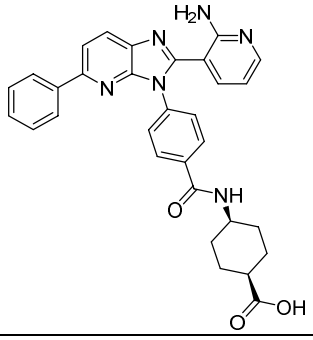
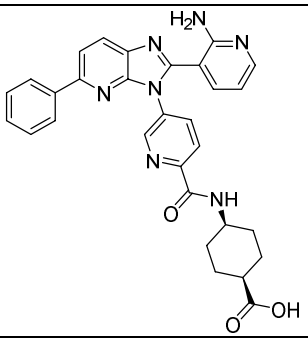
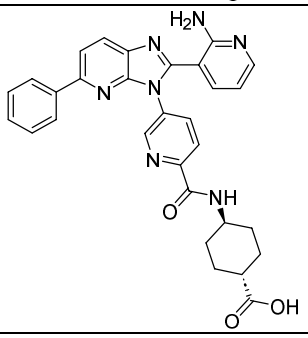
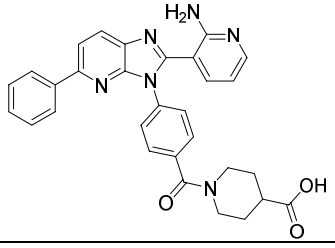
[0010c] In one aspect, the present disclosure refers to a compound in Table 1, or a stereoisomer or pharmaceutically acceptable salt thereof:

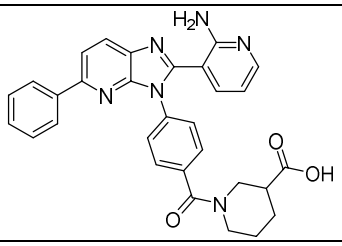
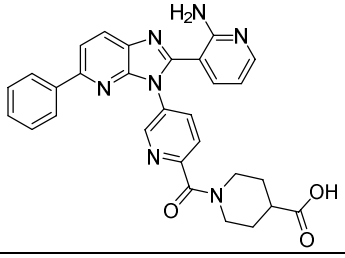
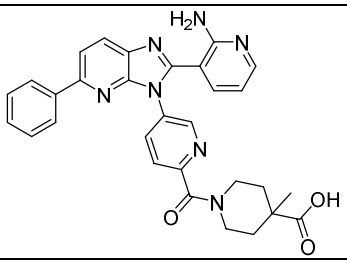
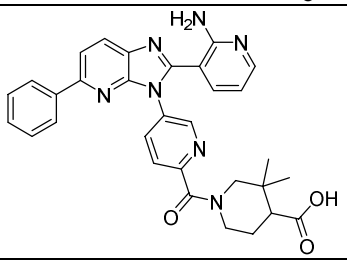
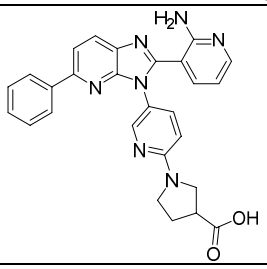
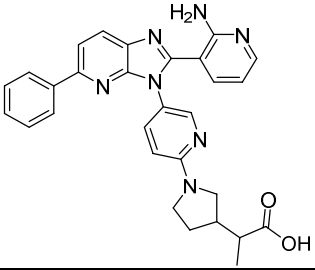
TABLE 1.

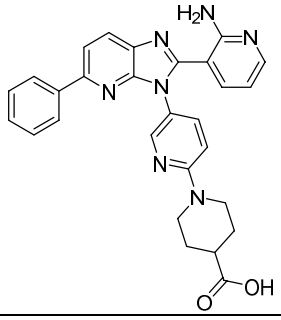
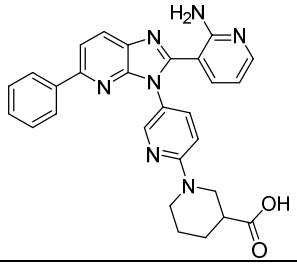
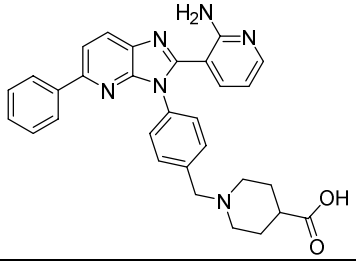
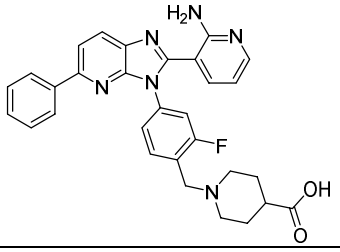
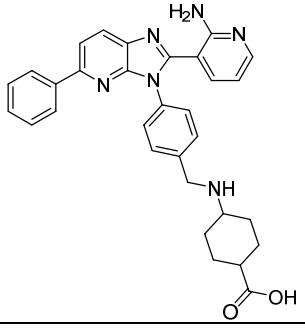
Compound No.	Chemical Structure
I-1	
I-2	
I-3	
I-4	

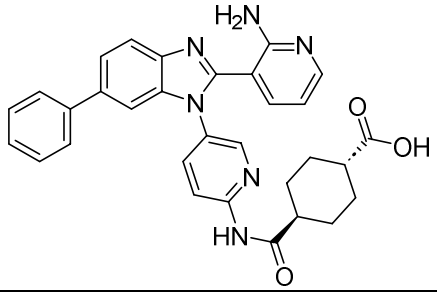
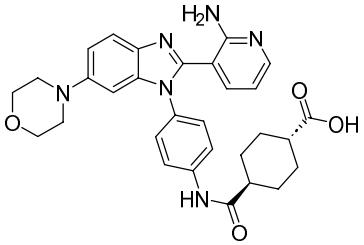
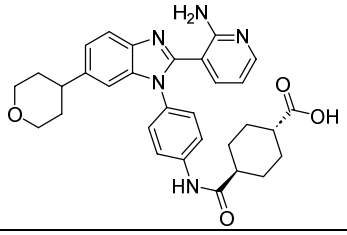
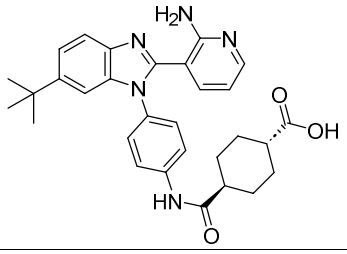
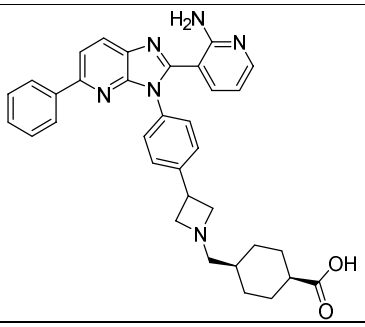
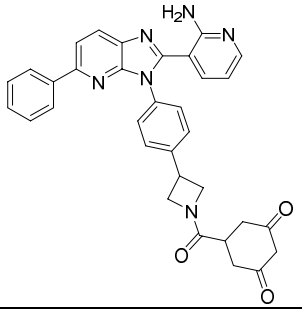
I-5	
I-6	
I-7	
I-8	
I-9	
I-10	

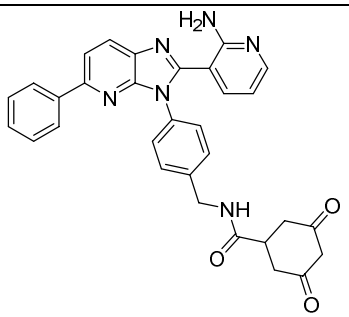
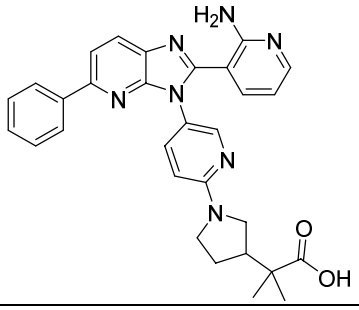
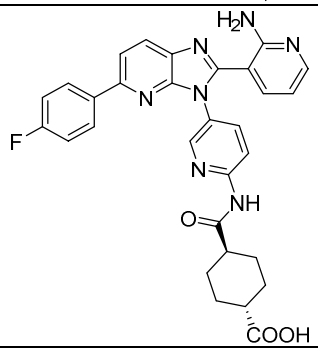
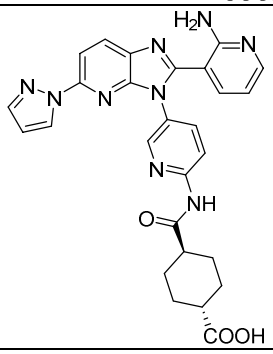
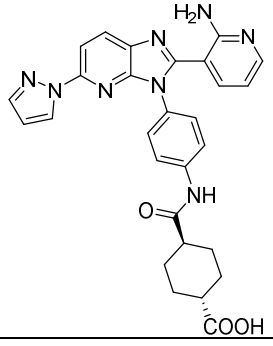
I-11	
I-12	
I-13	
I-14	
I-15	

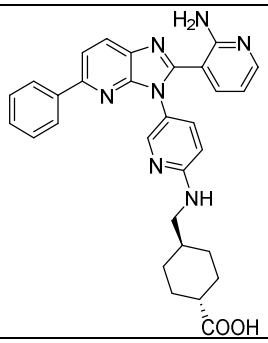
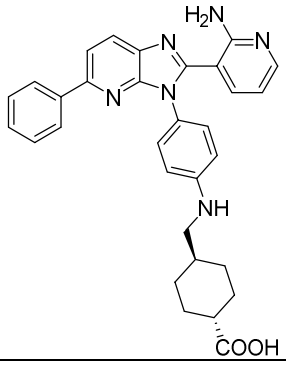
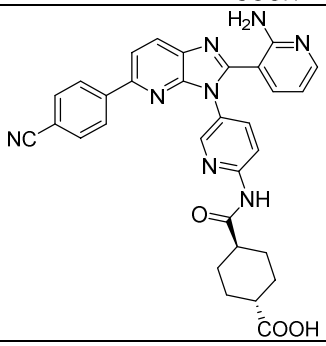
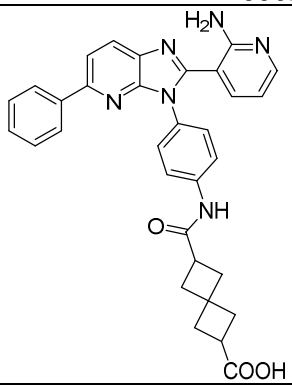
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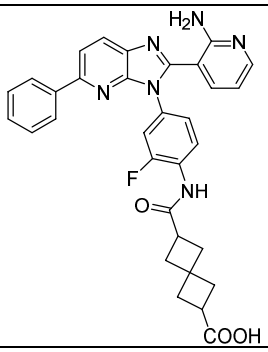
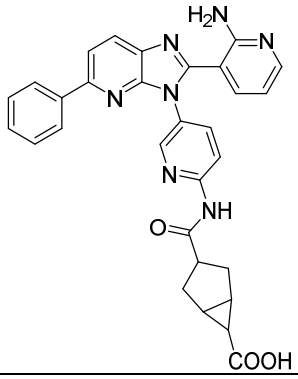
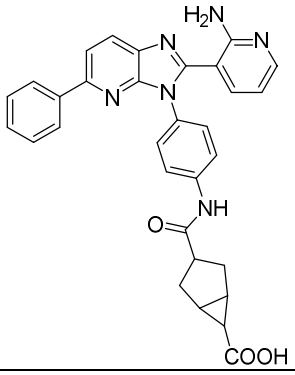
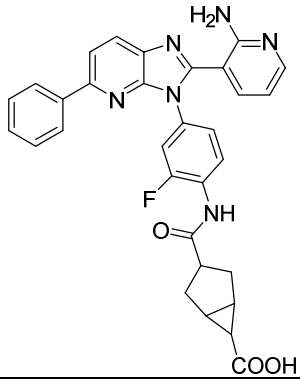
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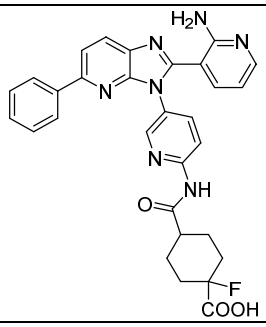
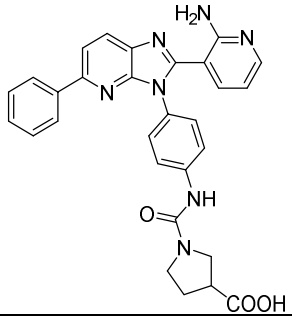
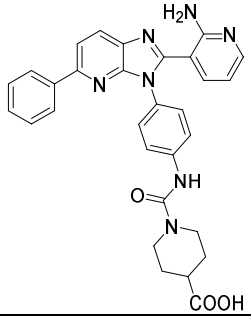
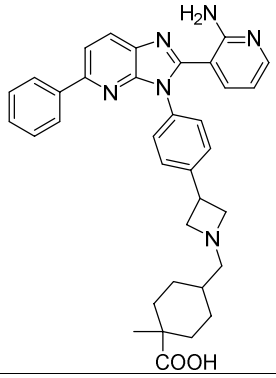
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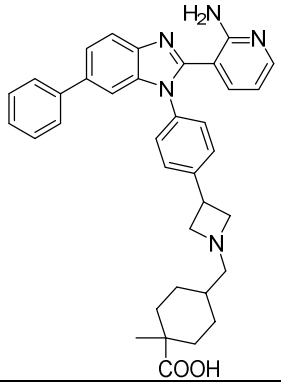
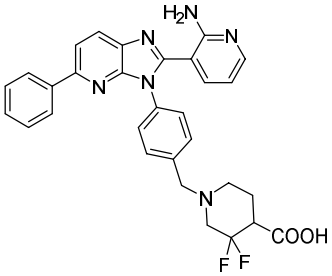
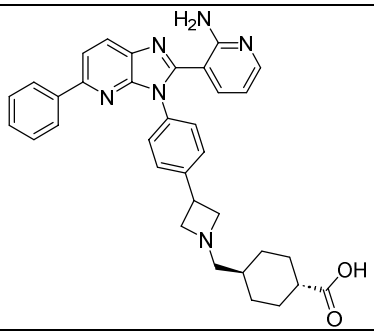
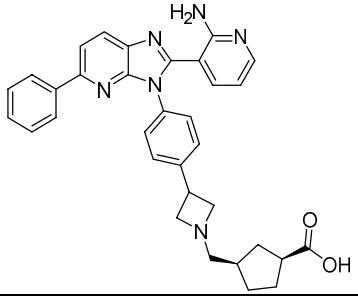
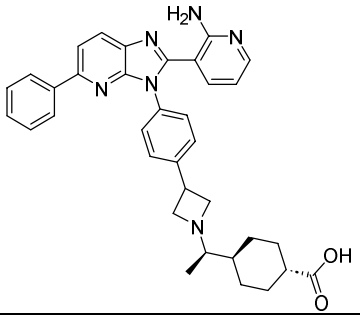
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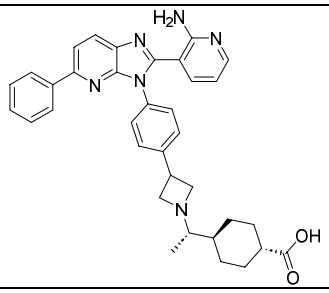
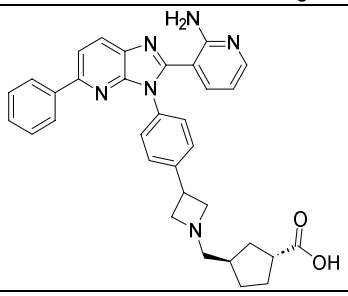
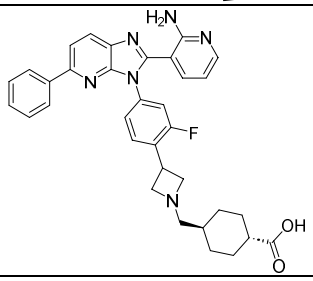
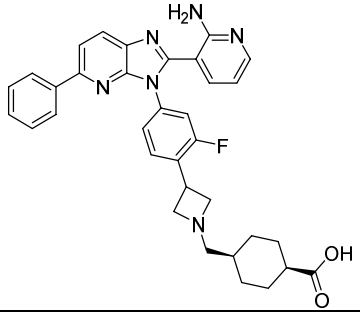
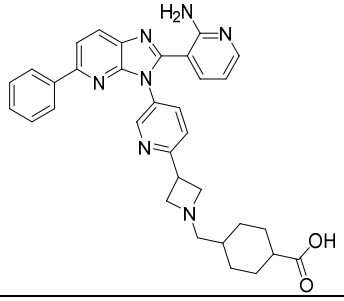
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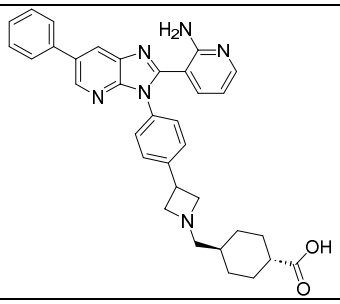
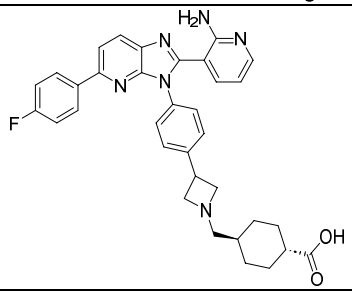
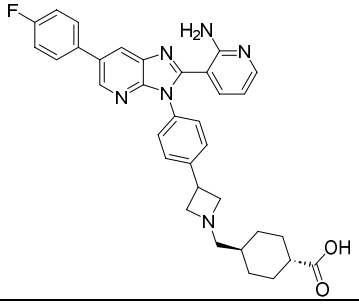
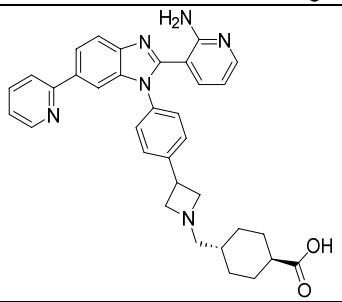
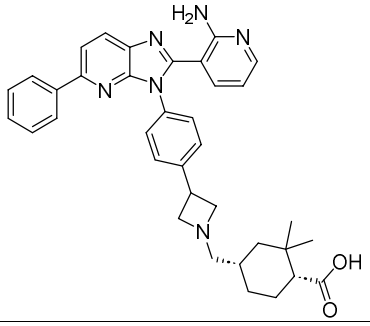
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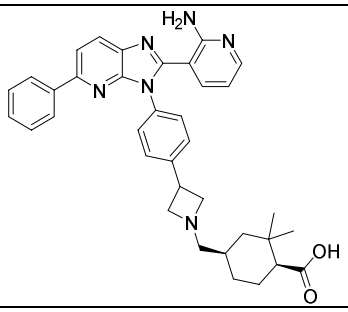
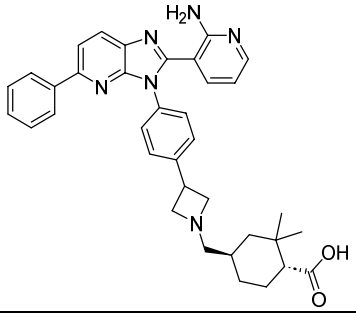
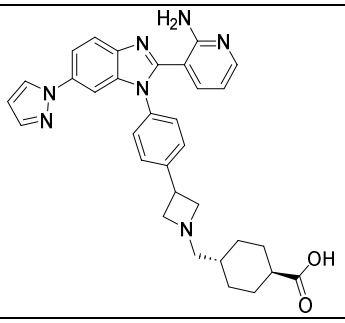
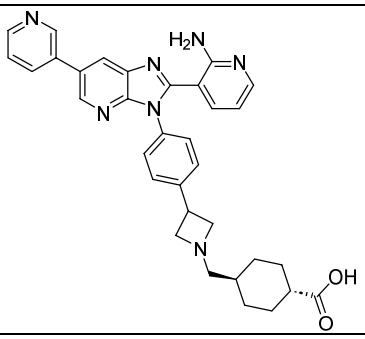
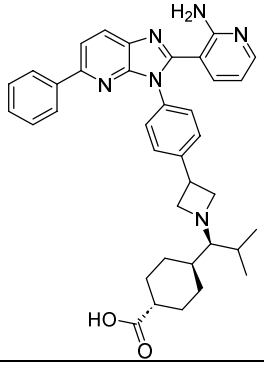
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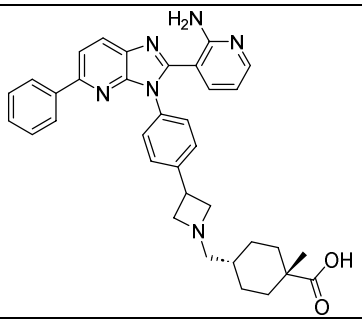
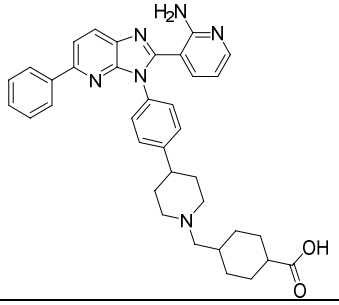
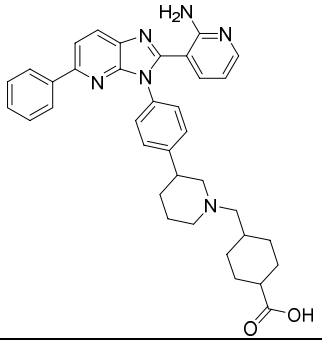
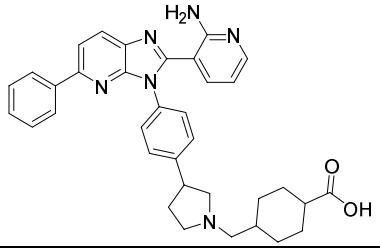
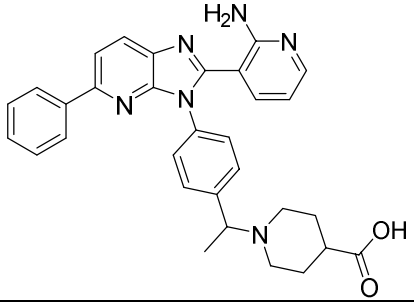
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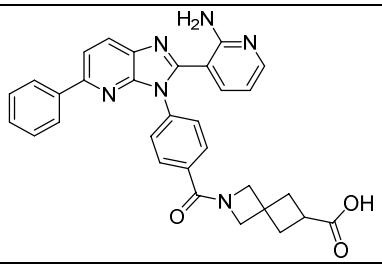
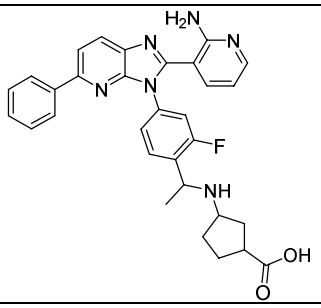
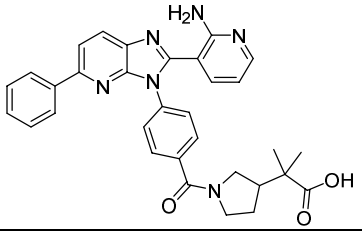
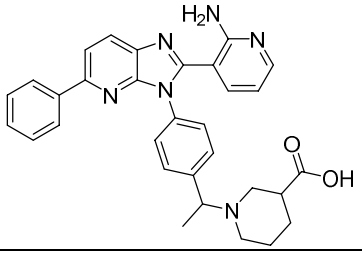
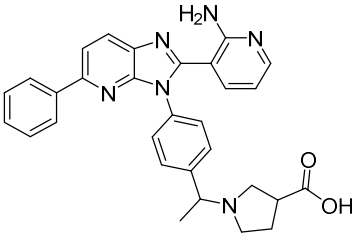
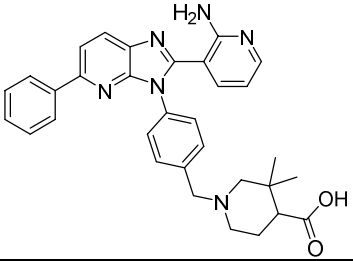
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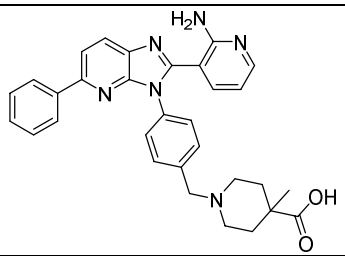
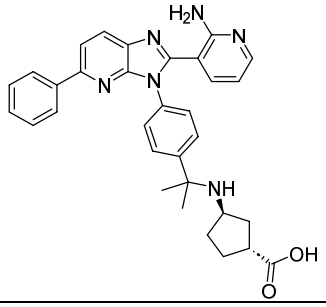
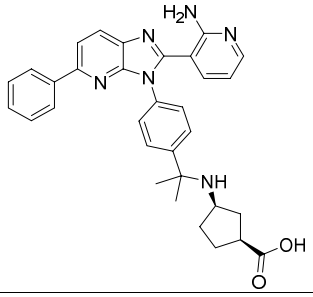
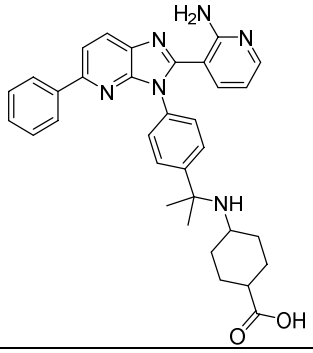
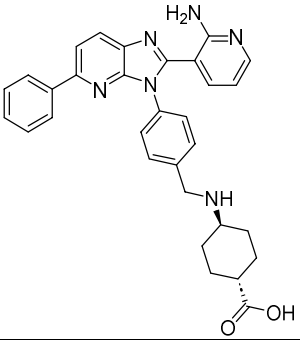
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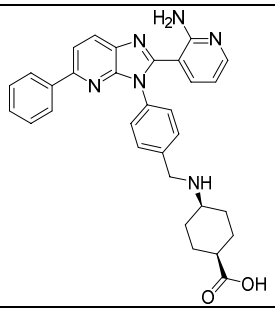
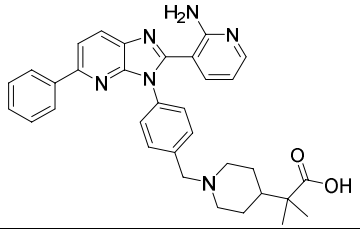
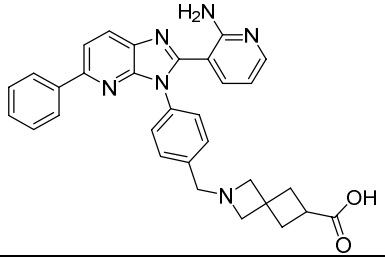
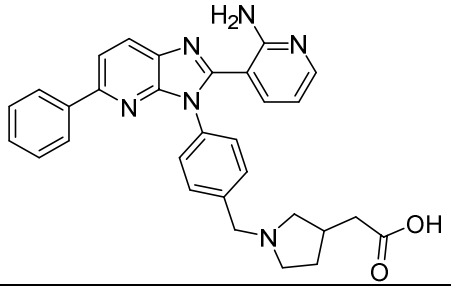
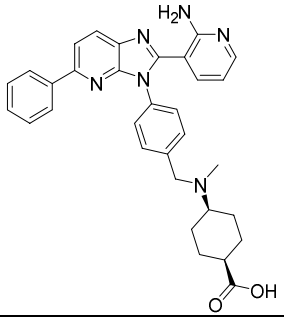
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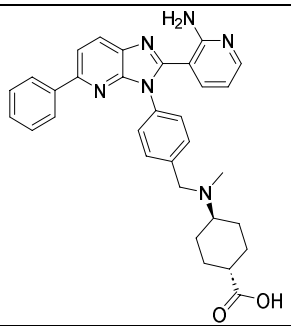
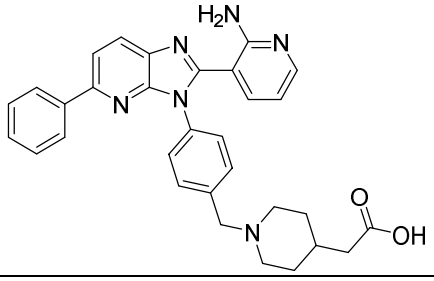
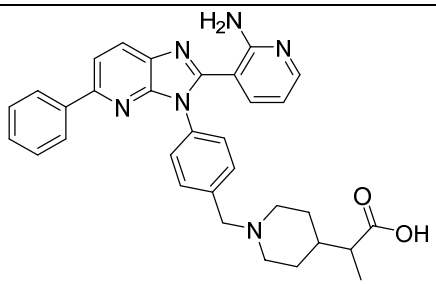
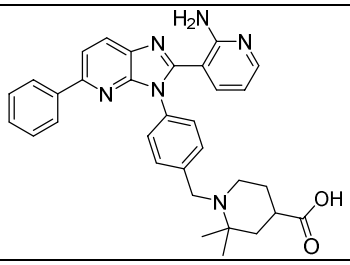
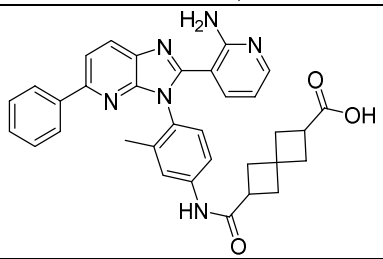
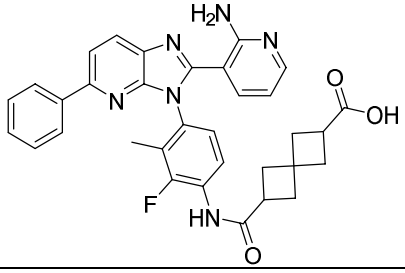
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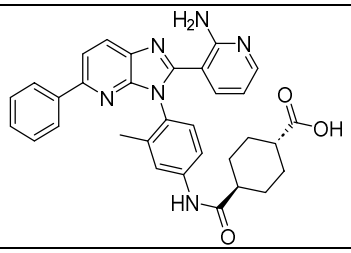
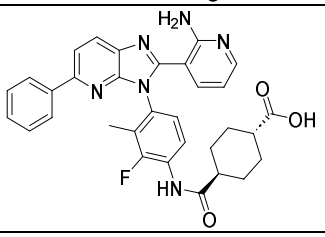
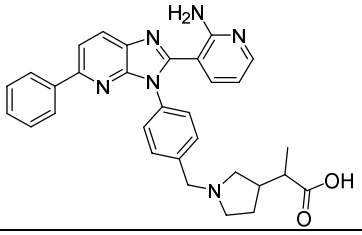
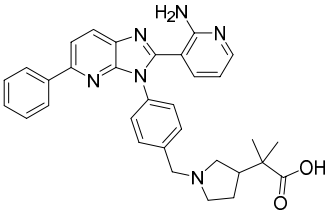
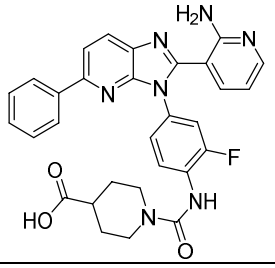
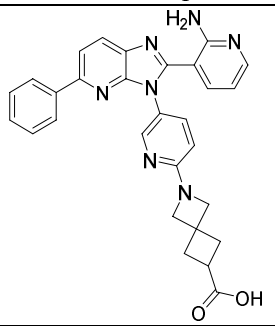
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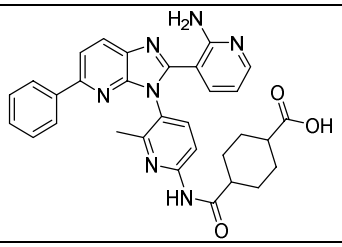
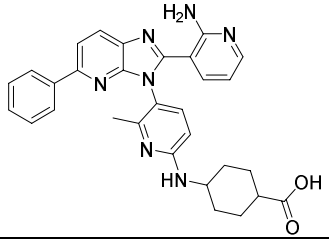
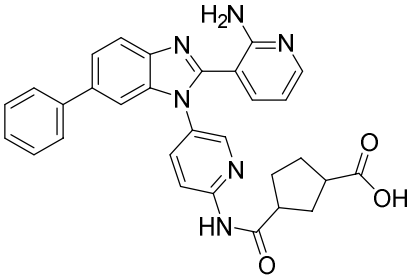
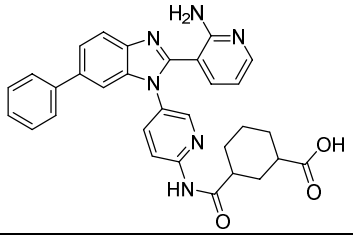
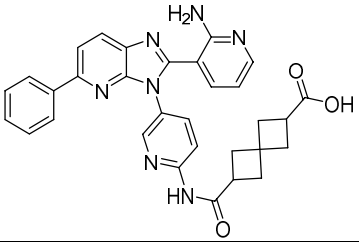
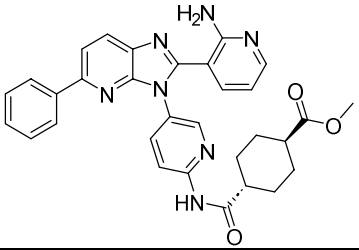
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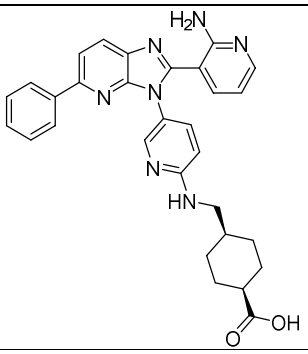
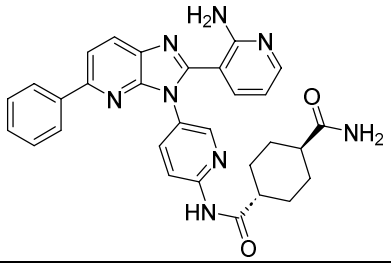
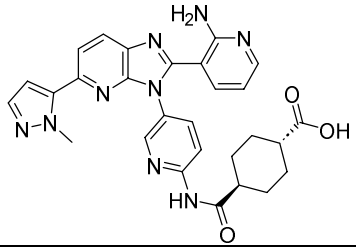
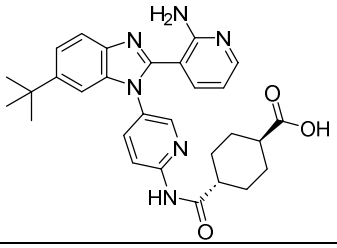
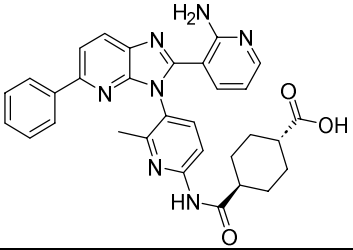
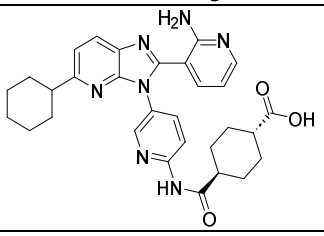
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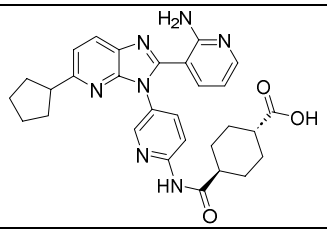
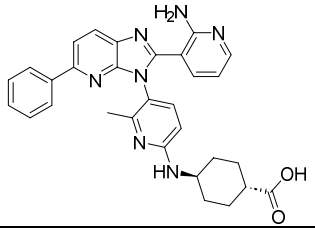
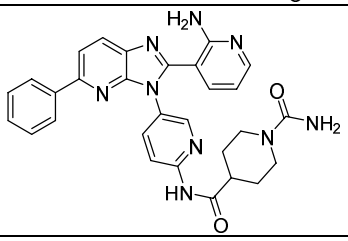
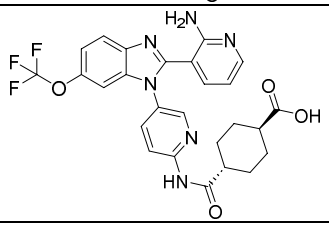
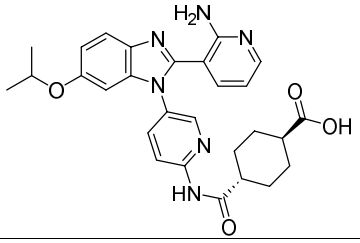
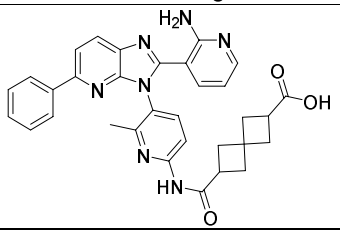
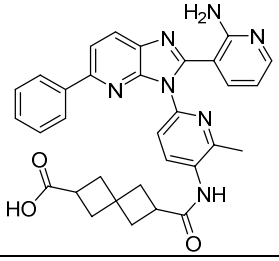
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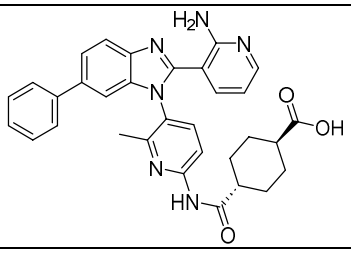
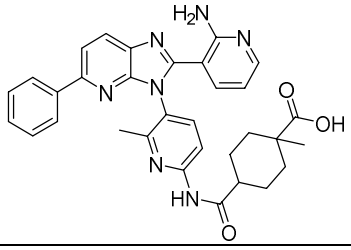
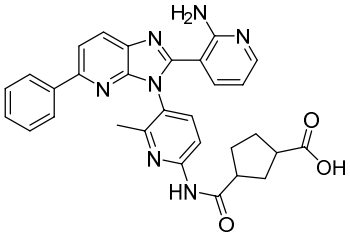
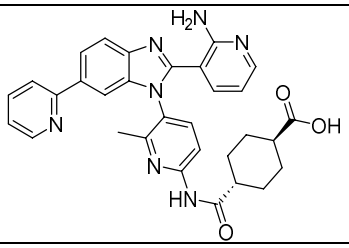
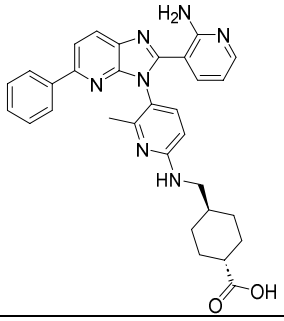
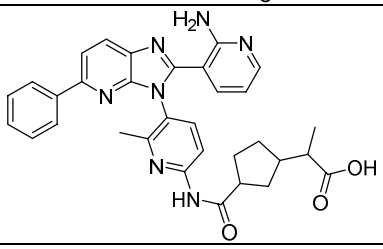
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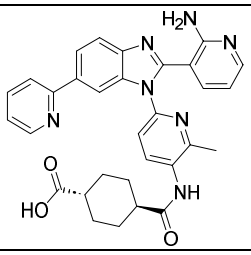
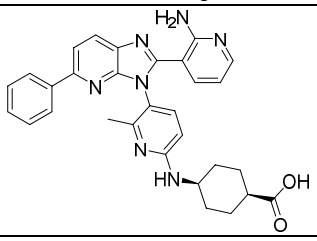
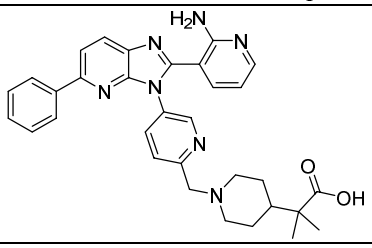
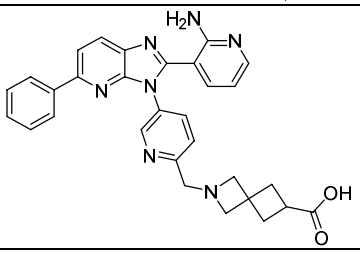
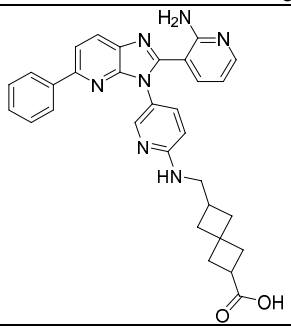
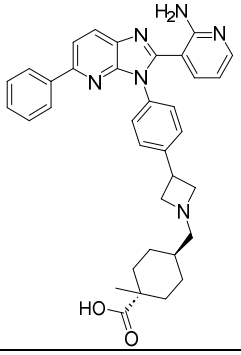
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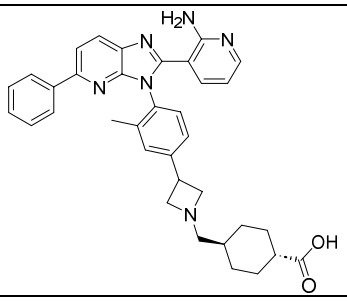
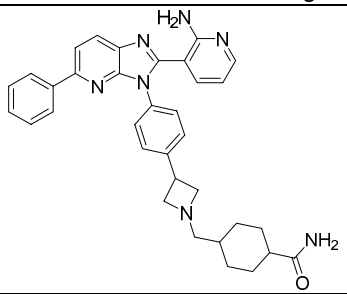
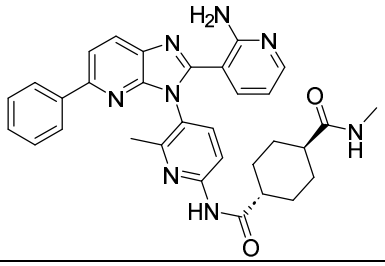
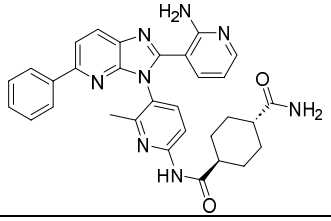
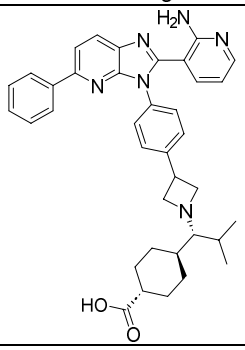
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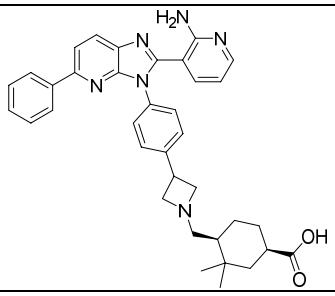
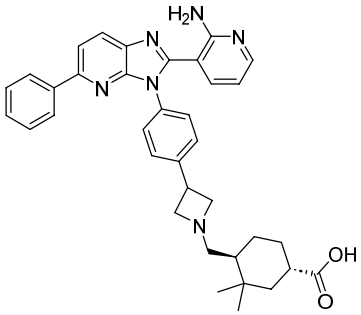
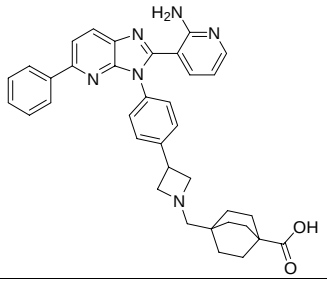
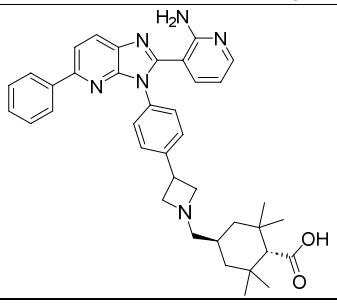
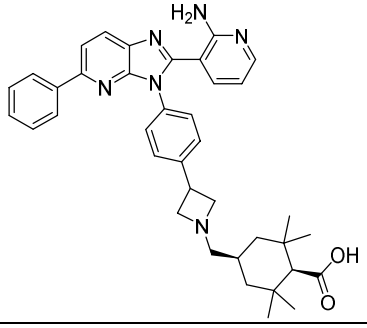
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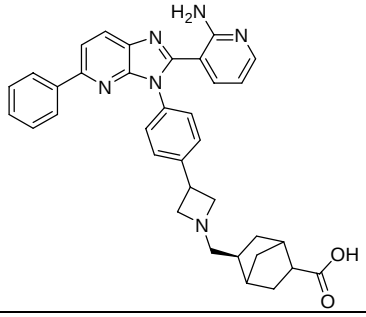
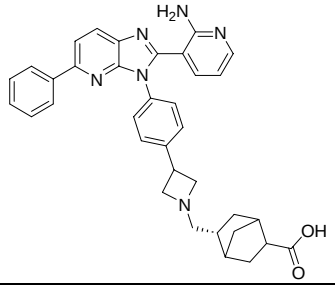
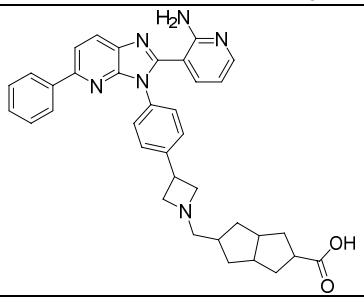
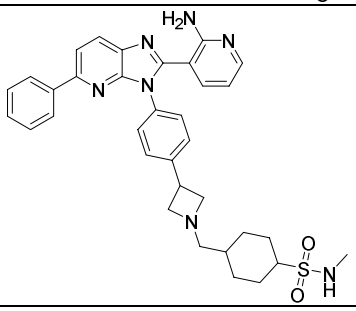
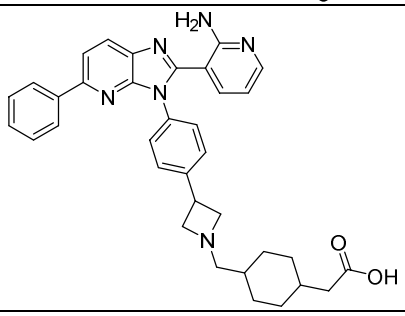
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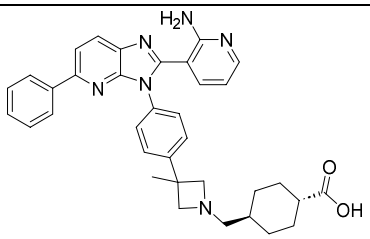
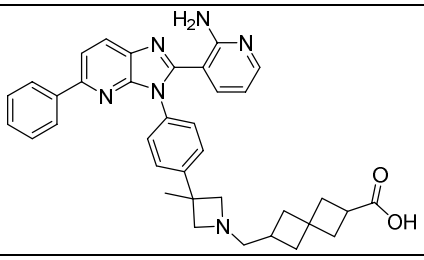
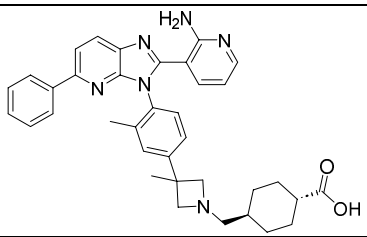
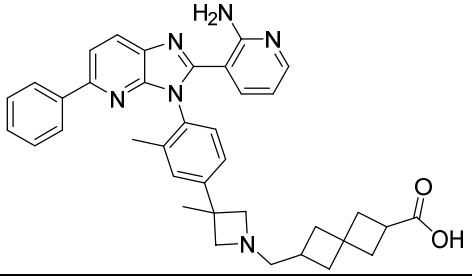
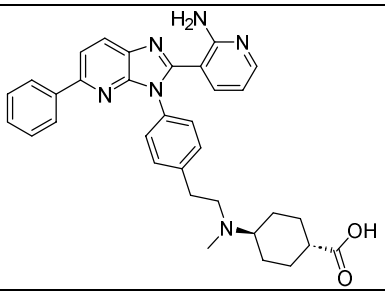
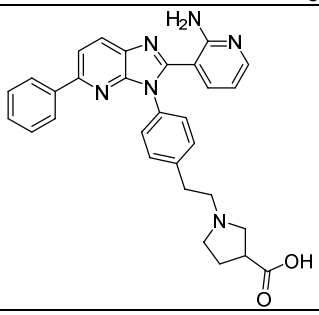
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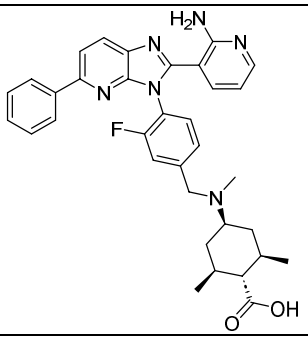
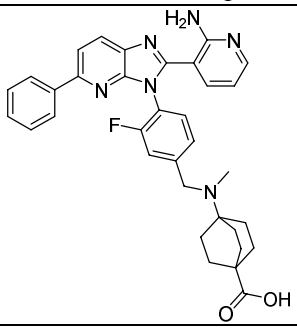
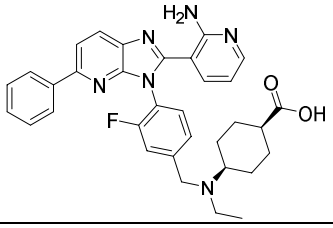
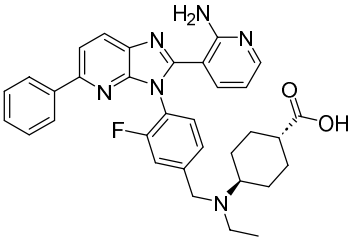
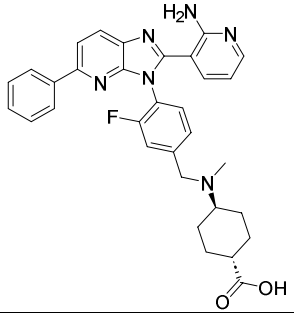
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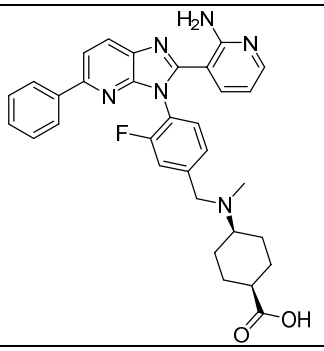
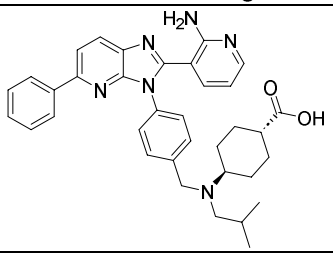
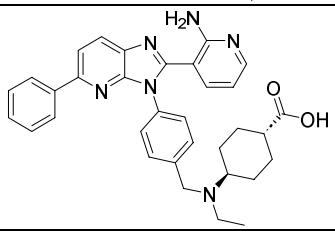
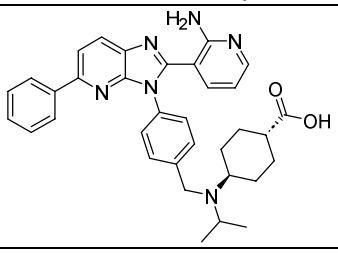
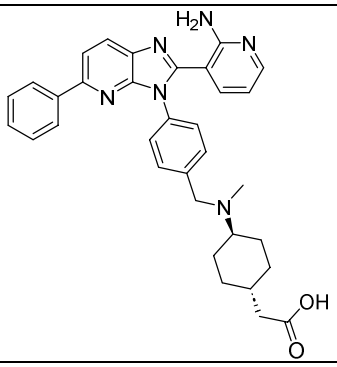
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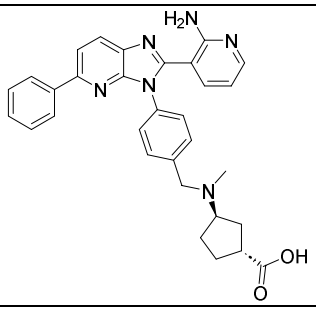
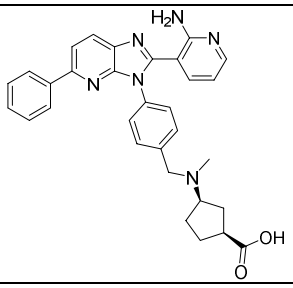
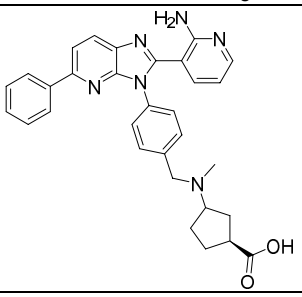
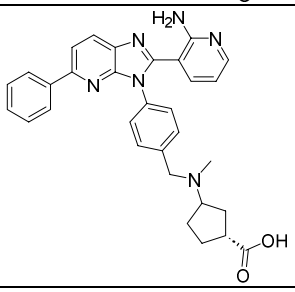
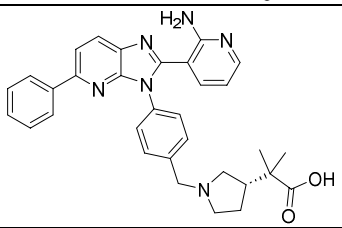
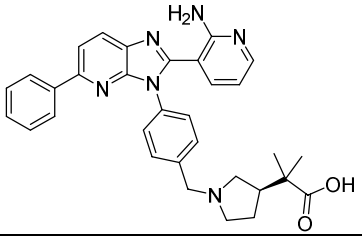
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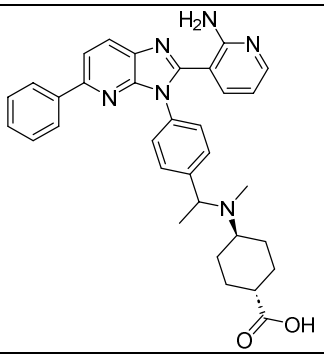
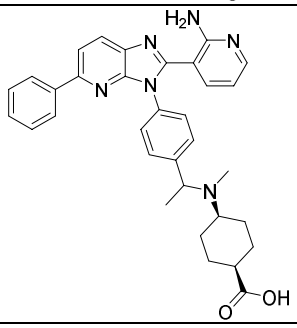
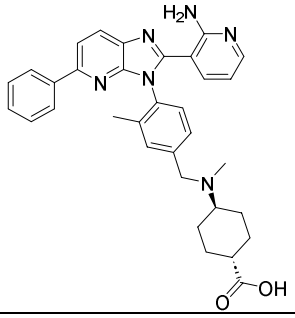
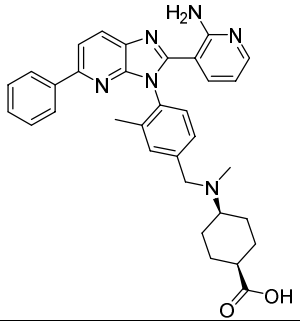
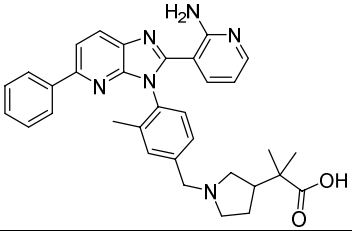
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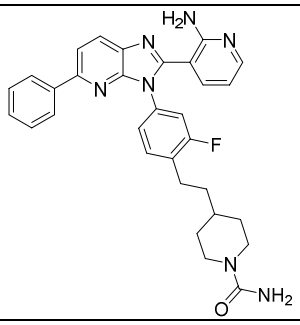
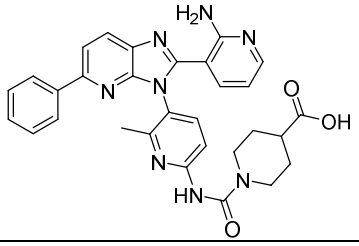
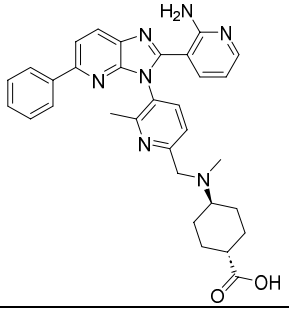
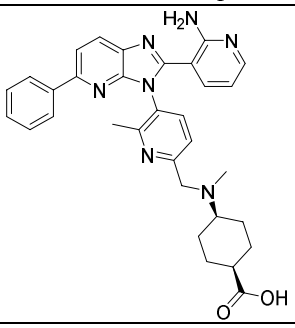
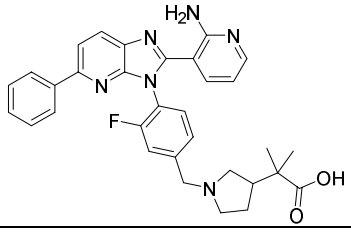
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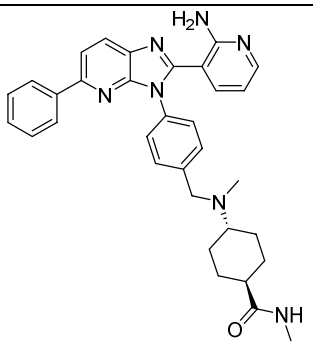
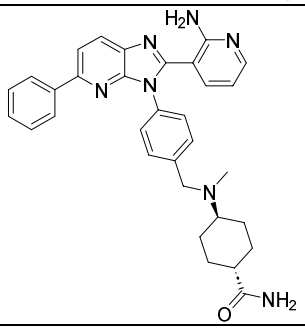
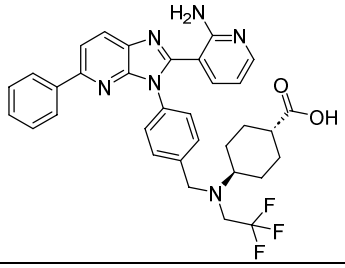
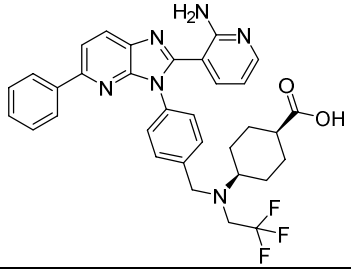
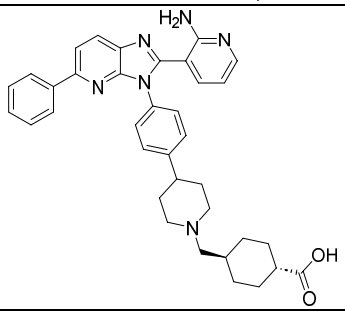
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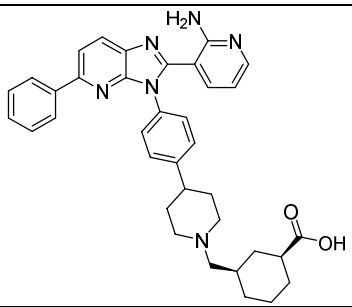
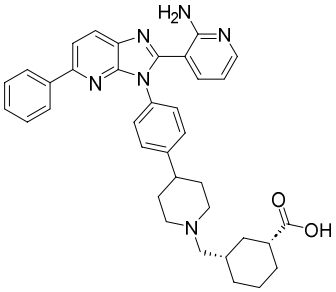
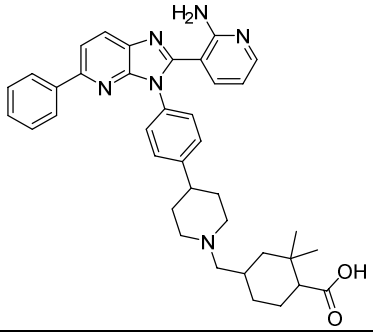
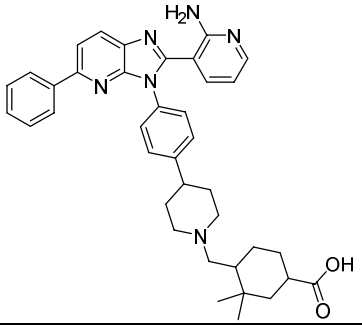
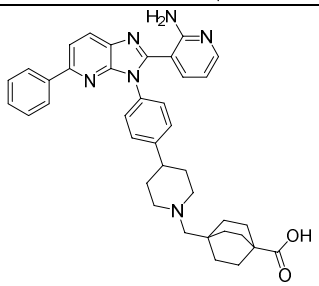
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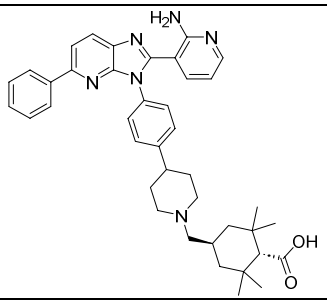
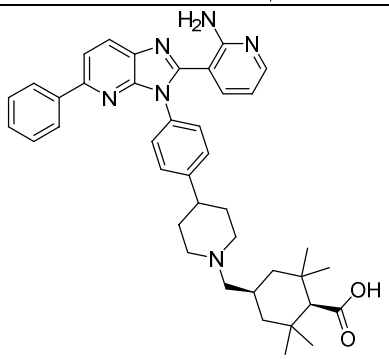
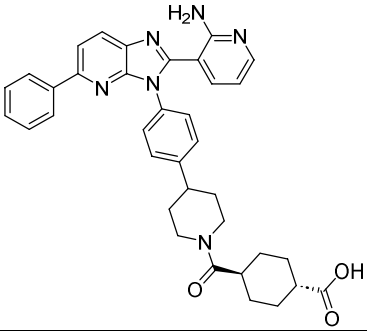
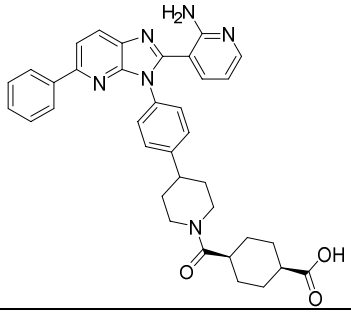
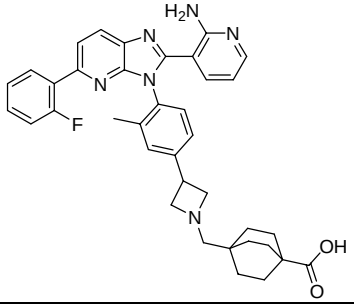
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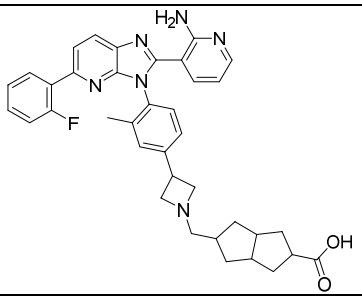
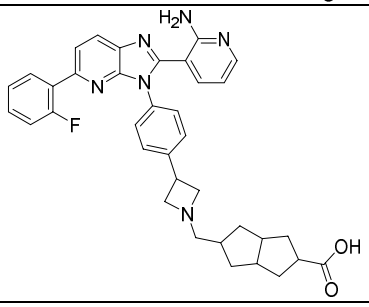
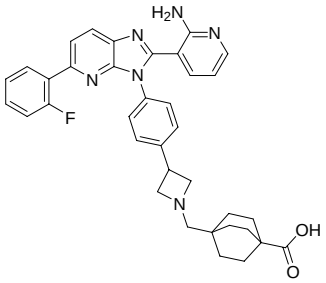
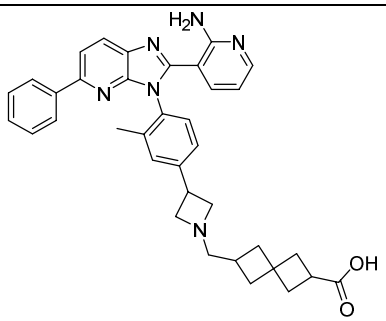
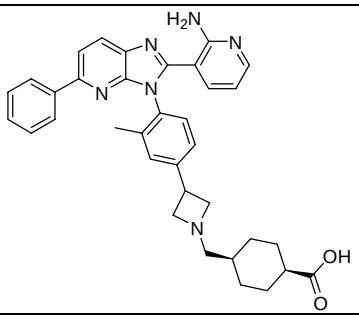
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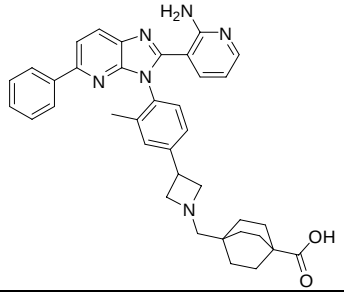
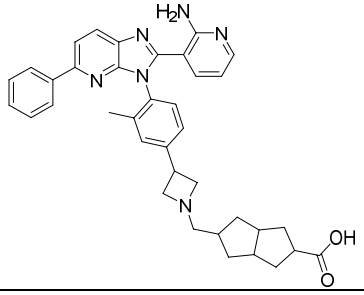
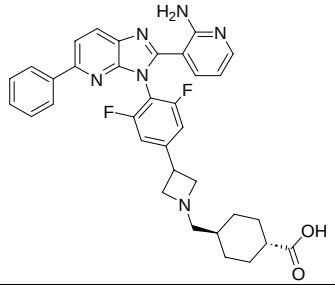
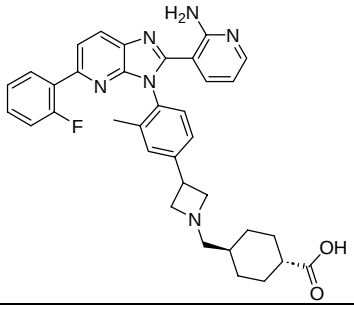
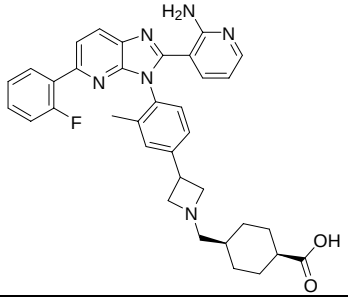
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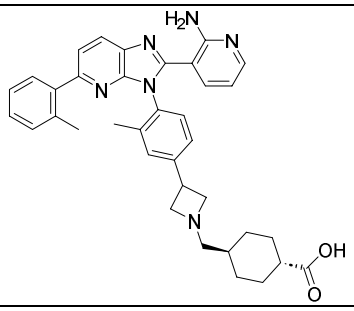
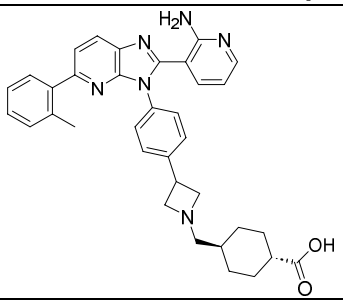
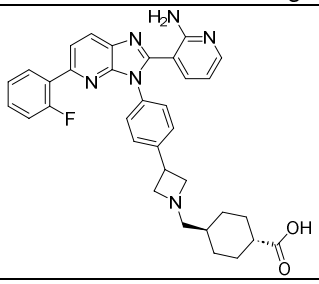
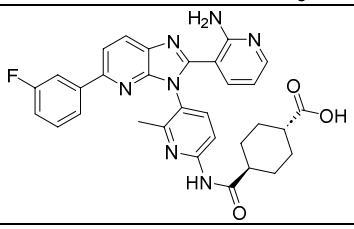
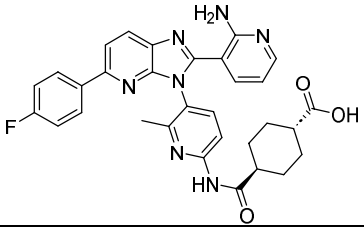
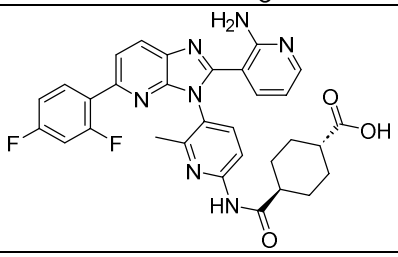
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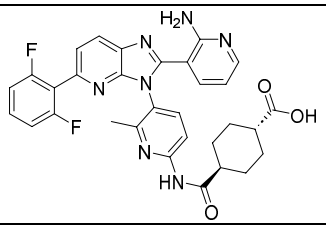
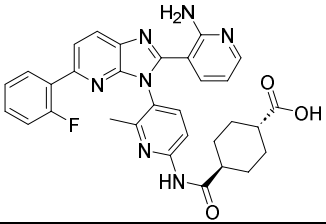
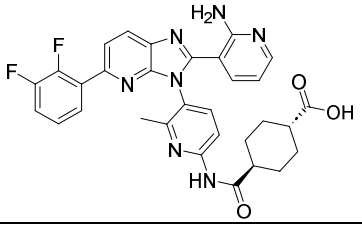
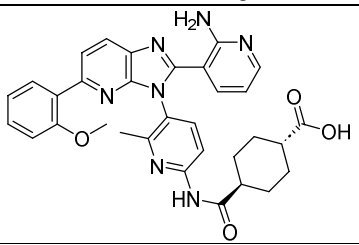
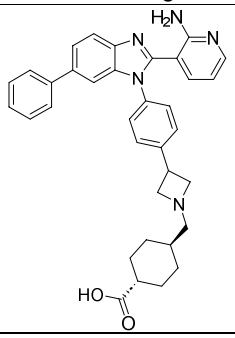
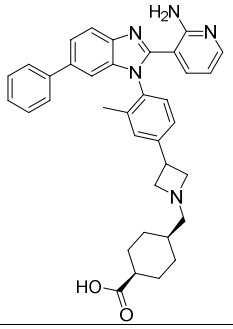
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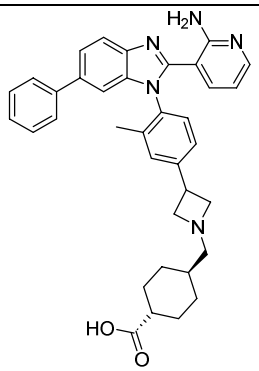
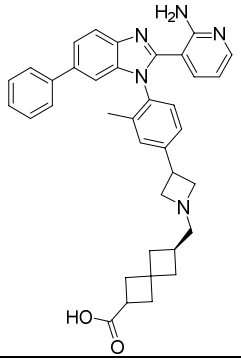
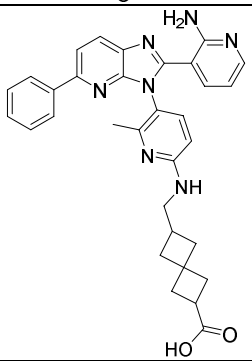
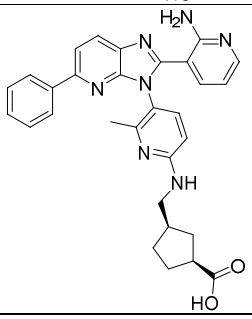
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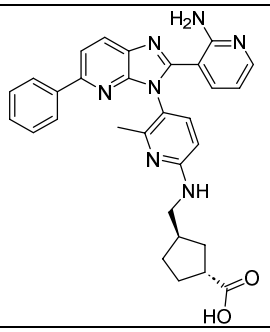
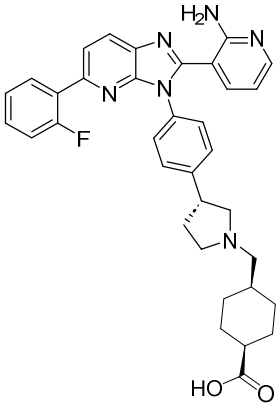
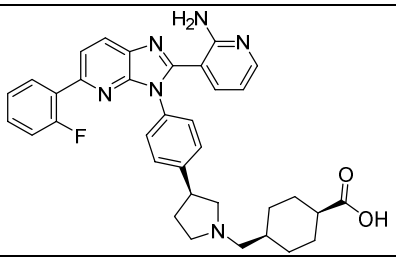
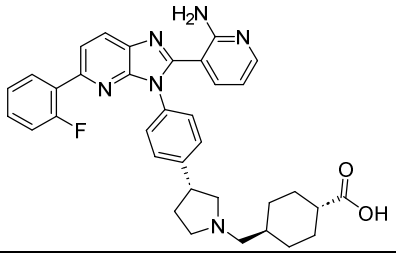
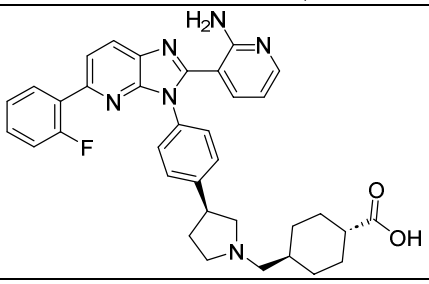
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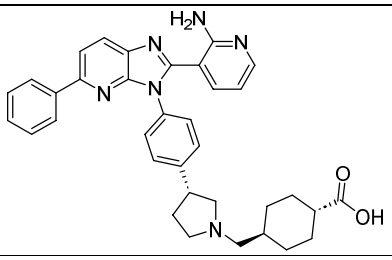
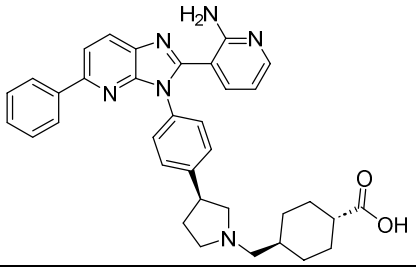
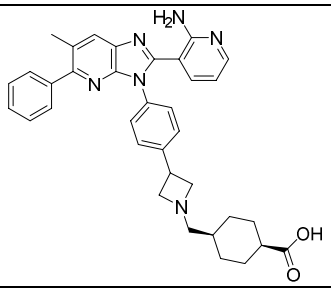
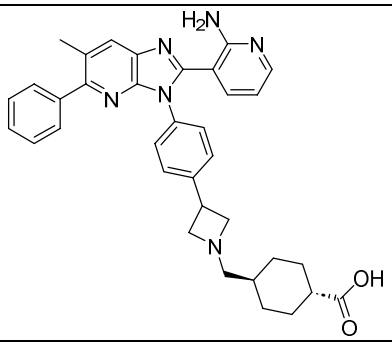
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[0010d] In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable carrier.

[0011] Another example of the disclosure provides a method of treating a disease or disorder associated with aberrant AKT1 signaling. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound described herein, such as a compound of Formula I, to treat the disease or disorder, as further described in the detailed description.

[0012] Another example of the disclosure provides a method of treating cancer. The method comprises administering to a subject in need thereof a therapeutically effective amount of a

compound described herein, such as a compound of Formula I, to treat the cancer, as further described in the detailed description. In certain examples, the cancer has a *AKT1* mutation.

[0012a] In one aspect, the present disclosure refers to use of compound disclosed herein in the manufacture of a medicament for treating cancer in a subject in need thereof.

[0013] A method of treating a disease or disorder associated with active PI3K signaling. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound described herein, such as a compound of Formula I, to treat the disease or disorder.

[0014] Another example of the disclosure provides a method inhibiting AKT1 activity. The method comprises contacting an AKT1 with an effective amount of a compound described herein, such as a compound of Formula I, to thereby inhibit the AKT1 activity, as further described in the detailed description.

DETAILED DESCRIPTION

[0015] The invention provides aminopyridinyl imidazo[4,5-b]pyridine and related compounds, pharmaceutical compositions, and their use in treating disease, such as cancer. The practice of the present invention employs, unless otherwise indicated, conventional techniques of organic chemistry, pharmacology, molecular biology (including recombinant techniques), cell biology, biochemistry, and immunology. Such techniques are explained in the literature, such as in "Comprehensive Organic Synthesis" (B.M. Trost & I. Fleming, eds., 1991-1992); "Handbook of experimental immunology" (D.M. Weir & C.C. Blackwell, eds.); "Current protocols in molecular biology" (F.M. Ausubel *et al.*, eds., 1987, and periodic updates); and "Current protocols in immunology" (J.E. Coligan *et al.*, eds., 1991), each of which is herein incorporated by reference in its entirety.

[0016] Various aspects of the invention are set forth below in sections; however, aspects of the invention described in one particular section are not to be limited to any particular section. Further, when a variable is not accompanied by a definition, the previous definition of the variable controls.

Definitions

[0017] Compounds of the present invention include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the