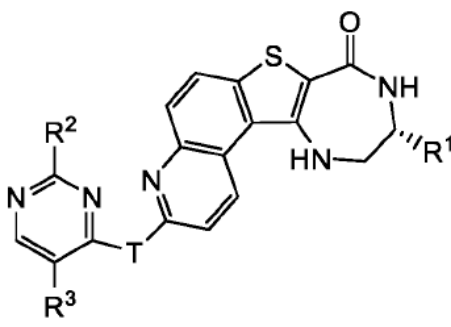


EMBO. 17:4426-4441 (1998); Shi et al., Biol. Chem. 383:1519-1536 (2002); Staklatvala., Curr. Opin. Pharmacol. 4:372-377 (2004), and Shiroto et al., J. Mol. Cardiol. 38:93-97 (2005)).

[0006] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events as described above. These diseases include, but are not limited to, autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, Alzheimer's disease, and hormone-related diseases. Accordingly, there remains a need to find protein kinase inhibitors useful as therapeutic agents.

SUMMARY OF THE INVENTION

[0006a] In a first aspect of the present disclosure, there is provided a compound of formula **III**:



III

or a pharmaceutically acceptable salt thereof, wherein:

T is a bivalent moiety selected from -N(R)-, -O-, or -S-;

each R is independently hydrogen or an optionally substituted C₁₋₆ aliphatic, or:

two R groups on the same nitrogen are taken together with the nitrogen to form a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms selected from nitrogen, oxygen, or sulfur;

R¹ is R or -(CH₂)_pR^x;

p is 0, 1, 2, or 3;

R^x is -CN, -NO₂, halogen, -OR, -SR, -N(R)₂, -C(O)N(R)₂, -C(O)OR, -C(O)R, -N(R)C(O)R, -SO₂N(R)₂, or -N(R)SO₂;

R² is halogen, -CN, -SR^y, -S(O)R^y, -SO₂R^y, -OSO₂R^y, -OC(O)R^y, or -OP(O)₂OR^y;

each R^y is independently selected from optionally substituted C₁₋₆ aliphatic or optionally substituted phenyl;

R³ is hydrogen, optionally substituted C₁₋₆ aliphatic, -CN, -NO₂, halogen, -OR, -N(R)₂, -C(O)N(R)₂, -C(O)OR, -Cy, -C(O)N(R)-Cy, -C(O)-Cy, -O-Cy, -O-(CH₂)_n-Cy, -(CH₂)_n-OCy, -(CH₂)_mN(R)₂, -(CH₂)_mOR, -N(R)-Cy, -N(R)-(CH₂)_n-Cy, -(CH₂)_n-N(R)-Cy, or -(CH₂)_mCy;

each of m and n is independently 0-4; and

each Cy is independently an optionally substituted ring selected from a 3-9 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 3-9 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, phenyl, a 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 7-12 membered saturated or partially unsaturated fused or bridged bicyclic carbocyclic ring, or a 6-12 membered saturated or partially unsaturated fused or bridged bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

wherein:

a substituent on an optionally substituted carbon atom of an optionally substituted group is independently selected from:

- (i) halogen; -(CH₂)₀₋₄R^o; -(CH₂)₀₋₄OR^o; -O(CH₂)₀₋₄R^o, -O-(CH₂)₀₋₄C(O)OR^o; -(CH₂)₀₋₄CH(OR^o)₂; -(CH₂)₀₋₄SR^o; -(CH₂)₀₋₄Ph, which are may be substituted with R^o; -(CH₂)₀₋₄(CH₂)₀₋₁Ph which may be substituted with R^o; -CH=CHPh, which may be substituted with R^o; -(CH₂)₀₋₄O(CH₂)₀₋₁-pyridyl which may be substituted with R^o; -NO₂; -CN; -N₃; -(CH₂)₀₋₄N(R^o)₂; -(CH₂)₀₋₄N(R^o)C(O)R^o; -N(R^o)C(S)R^o; -(CH₂)₀₋₄N(R^o)C(O)NR^o₂; -N(R^o)C(S)NR^o₂; -(CH₂)₀₋₄N(R^o)C(O)OR^o; -N(R^o)N(R^o)C(O)R^o; -N(R^o)N(R^o)C(O)NR^o₂; -N(R^o)N(R^o)C(O)OR^o; -(CH₂)₀₋₄C(O)R^o; -C(S)R^o; -(CH₂)₀₋₄C(O)OR^o; -(CH₂)₀₋₄C(O)SR^o; -(CH₂)₀₋₄C(O)OSiR^o₃; -(CH₂)₀₋₄OC(O)R^o; -OC(O)(CH₂)₀₋₄SR^o; -(CH₂)₀₋₄SC(O)R^o; -(CH₂)₀₋₄C(O)NR^o₂; -C(S)NR^o₂; -C(S)SR^o; -SC(S)SR^o, -(CH₂)₀₋₄OC(O)NR^o₂; -C(O)N(OR^o)R^o; -C(O)C(O)R^o; -C(O)CH₂C(O)R^o; -C(NOR^o)R^o; -(CH₂)₀₋₄SSR^o; -(CH₂)₀₋₄S(O)₂R^o; -(CH₂)₀₋₄S(O)₂OR^o; -(CH₂)₀₋₄OS(O)₂R^o; -S(O)₂NR^o₂; -(CH₂)₀₋₄S(O)R^o; -N(R^o)S(O)₂NR^o₂; -N(R^o)S(O)₂R^o; -N(OR^o)R^o; -C(NH)NR^o₂; -P(O)₂R^o;

-P(O)R[°]₂; -OP(O)R[°]₂; -OP(O)(OR[°])₂; SiR[°]₃; —(C₁₋₄ straight or branched alkylene)O-N(R[°])₂; or -(C₁₋₄ straight or branched alkylene)C(O)O-N(R[°])₂;

each R[°] is independently hydrogen, C₁₋₆ aliphatic, -CH₂Ph, -O(CH₂)₀₋₁Ph, -CH₂-(5-6 membered heteroaryl ring), or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R[°], taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein each R[°] (or the ring formed by taking two independent occurrences of R[°] together with their intervening atoms), may be independently substituted with:

(a) halogen, -(CH₂)₀₋₂R[•], -(haloR[•]), -(CH₂)₀₋₂OH, -(CH₂)₀₋₂OR[•], -(CH₂)₀₋₂CH(OR[•])₂; -O(haloR[•]), -CN, -N₃, -(CH₂)₀₋₂C(O)R[•], -(CH₂)₀₋₂C(O)OH, -(CH₂)₀₋₂C(O)OR[•], -(CH₂)₀₋₂SR[•], -(CH₂)₀₋₂SH, -(CH₂)₀₋₂NH₂, -(CH₂)₀₋₂NHR[•], -(CH₂)₀₋₂NR[•]₂, -NO₂, -SiR[•]₃, -OSiR[•]₃, -C(O)SR[•], -(C₁₋₄ straight or branched alkylene)C(O)OR[•], or -SSR[•];

each R[•] is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently selected from C₁₋₄ aliphatic, -CH₂Ph, -O(CH₂)₀₋₁Ph, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

(b) =O or =S; or;

(ii) =O, =S, =NNR^{*}₂, =NNHC(O)R^{*}, =NNHC(O)OR^{*}, =NNHS(O)₂R^{*}, =NR^{*}, =NOR^{*}, -O(C(R^{*}₂))₂₋₃O-, or -S(C(R^{*}₂))₂₋₃S-; or a substituent on optionally substituted vicinal carbon atoms of an optionally substituted group is independently selected from -O(CR^{*}₂)₂₋₃O-;

wherein each R^{*} is independently selected from hydrogen, C₁₋₆ aliphatic, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein substituents on the aliphatic group of R* are independently selected from halogen, -R[•], -(haloR[•]), -OH, -OR[•], -O(haloR[•]), -CN, -C(O)OH, -C(O)OR[•], -NH₂, -NHR[•], -NR[•]₂, or -NO₂;

each R[•] is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently selected from C₁₋₄ aliphatic, -CH₂Ph, -O(CH₂)₀₋₁Ph, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

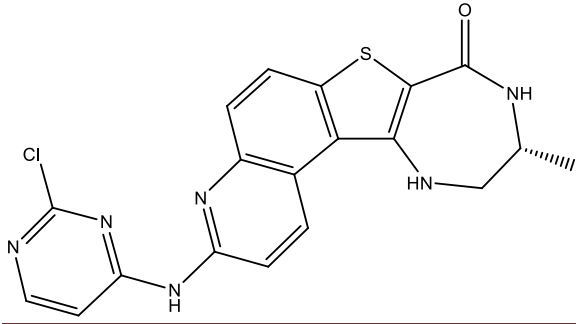
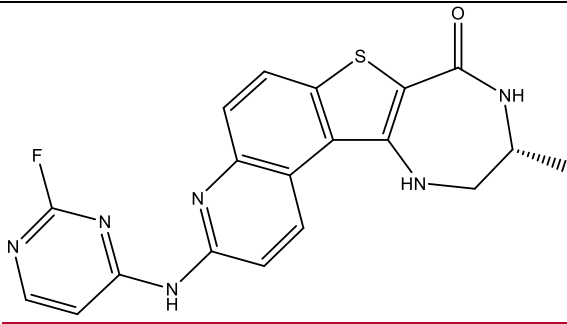
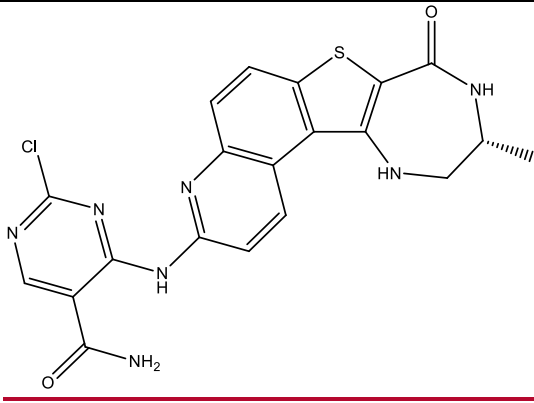
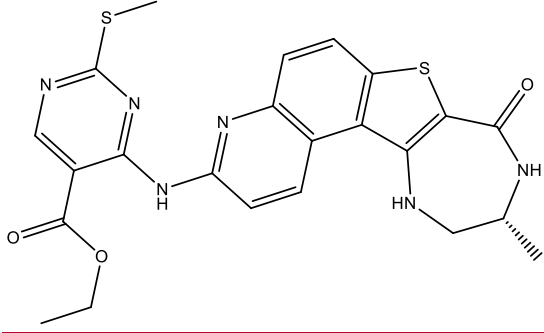
a substituent on an optionally substituted nitrogen atom of an optionally substituted group is independently selected from -R[†], -NR[†]₂, -C(O)R[†], -C(O)OR[†], -C(O)C(O)R[†], -C(O)CH₂C(O)R[†], -S(O)₂R[†], -S(O)₂NR[†]₂, -C(S)NR[†]₂, -C(NH)NR[†]₂, or -N(R[†])S(O)₂R[†];

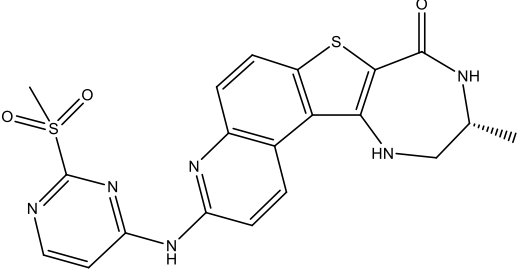
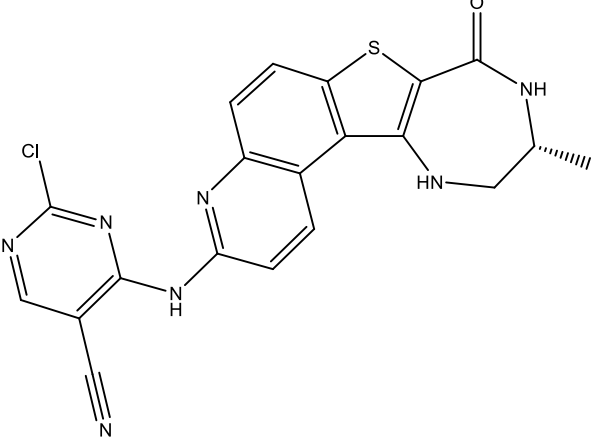
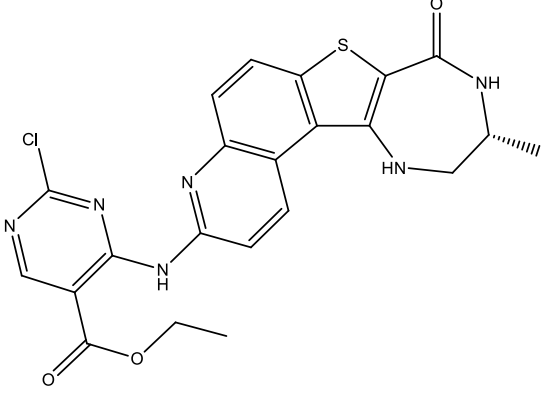
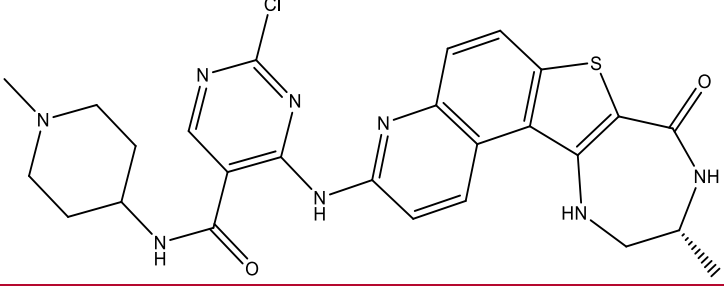
wherein each R[†] is independently hydrogen, C₁₋₆ aliphatic, unsubstituted -OPh, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or two independent occurrences of R[†], taken together with their intervening atom(s) form an unsubstituted 3-12-membered saturated, partially unsaturated, or aryl mono-or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

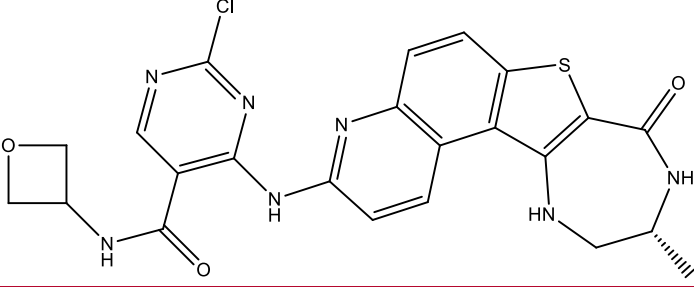
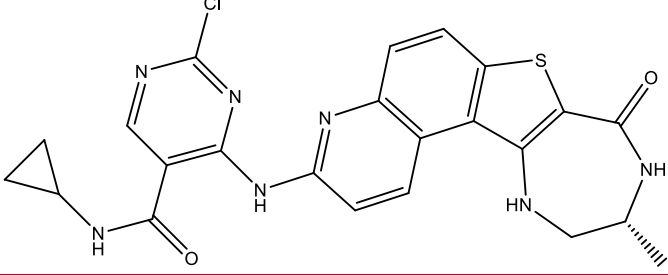
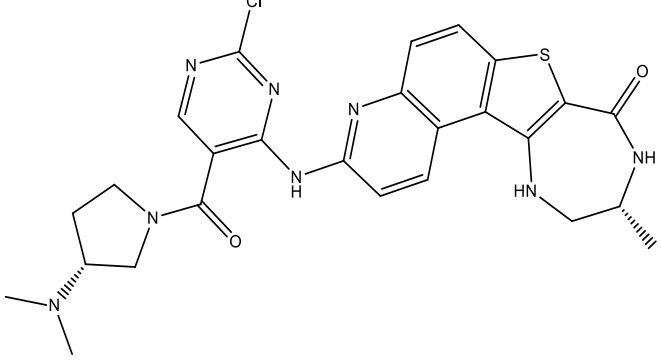
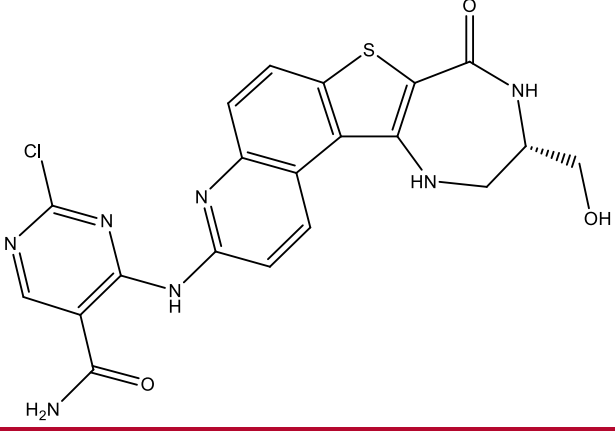
wherein substituents on the aliphatic group of R[†] are independently selected from -R[•], -(haloR[•]), -OH, -OR[•], -O(haloR[•]), -CN, -C(O)OH, -C(O)OR[•], -NH₂, -NHR[•], -NR[•]₂, or -NO₂; and

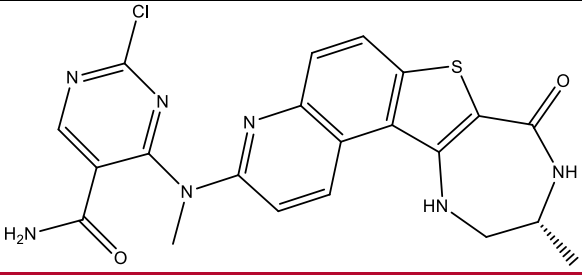
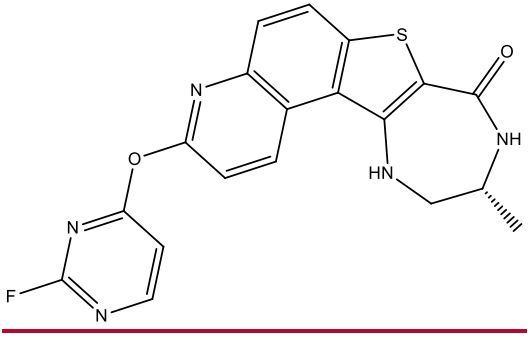
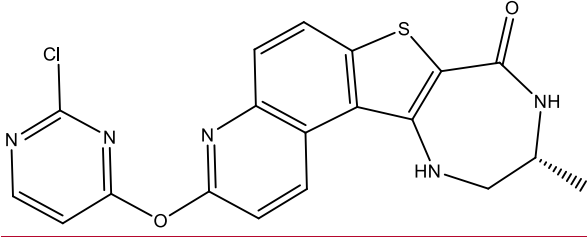
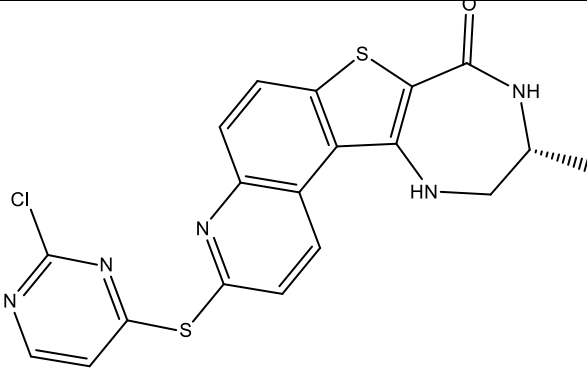
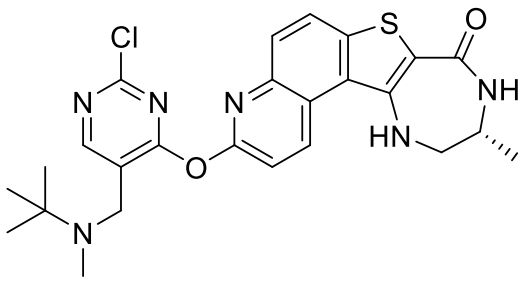
each R[•] is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C₁₋₄ aliphatic, -CH₂Ph, -O(CH₂)₀₋₁Ph, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

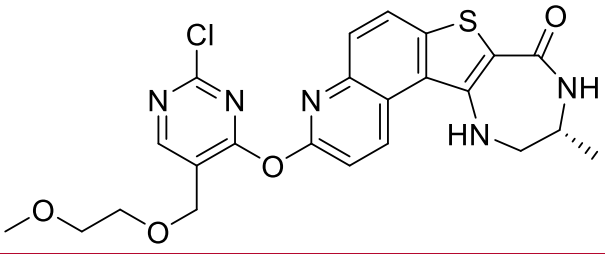
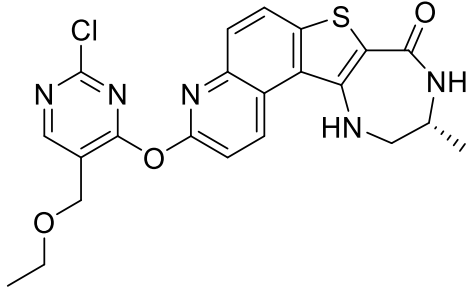
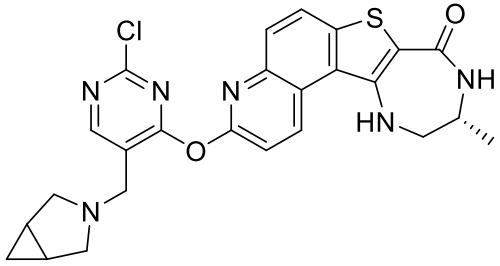
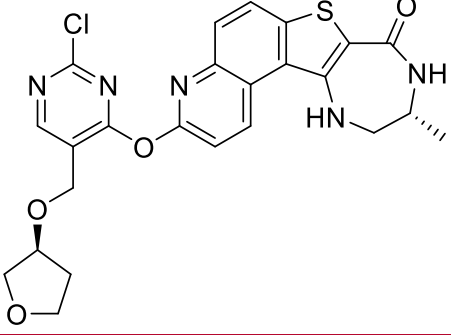
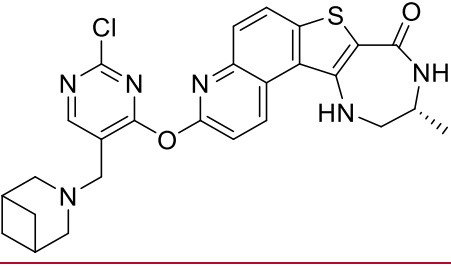
[0006b] In another aspect of the present disclosure, there is provided a compound selected from:

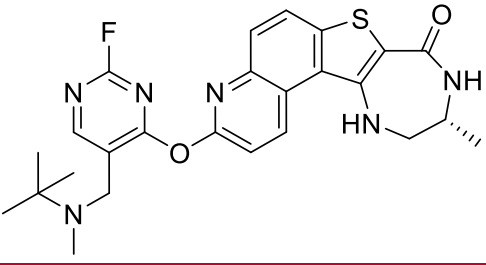
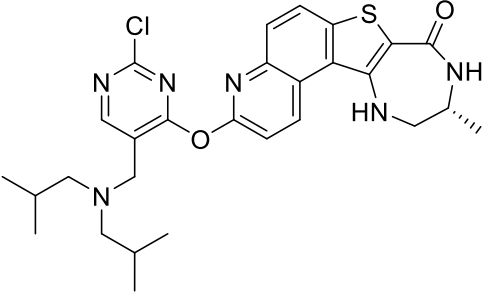
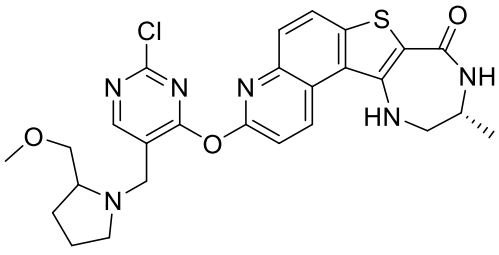
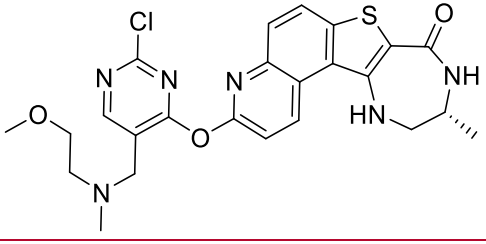
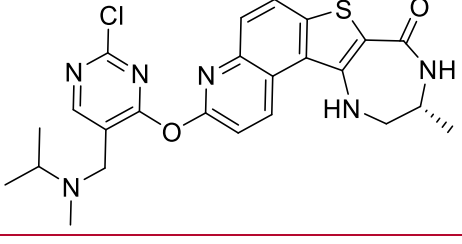
<u>Compound #</u>	<u>Structure</u>
<u>I-5</u>	 <chem>Clc1nc(Nc2nc3cc4c(cc3n2)sc5c4c[nH]c(=O)[nH]5C)ccc1N</chem>
<u>I-8</u>	 <chem>Fc1nc(Nc2nc3cc4c(cc3n2)sc5c4c[nH]c(=O)[nH]5C)ccc1N</chem>
<u>I-9</u>	 <chem>NC(=O)c1nc(Nc2nc3cc4c(cc3n2)sc5c4c[nH]c(=O)[nH]5C)nc(Cl)c1N</chem>
<u>I-12</u>	 <chem>CCOC(=O)Nc1cc(Nc2nc3cc4c(cc3n2)sc5c4c[nH]c(=O)[nH]5C)nc(SC)n1</chem>

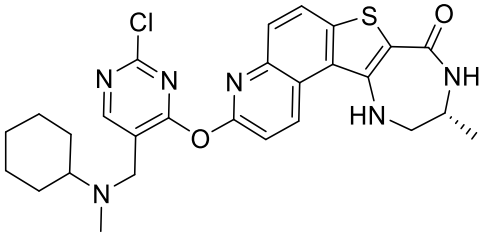
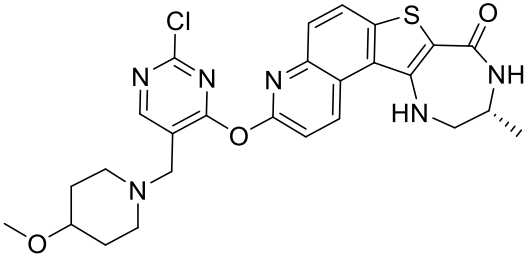
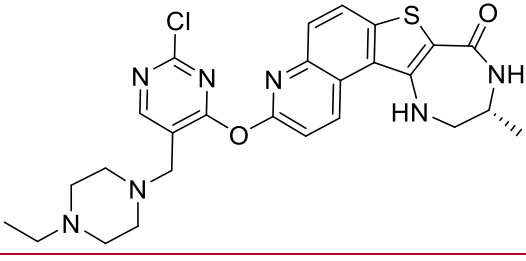
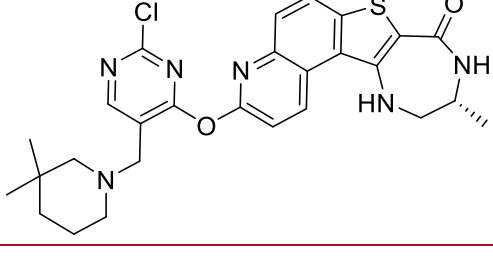
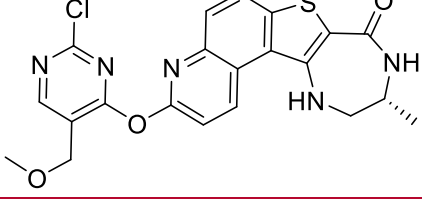
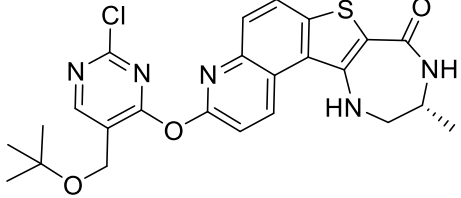
Compound #	Structure
<u>I-14</u>	
<u>I-16</u>	
<u>I-18</u>	
<u>I-19</u>	

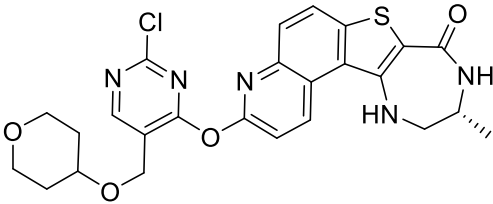
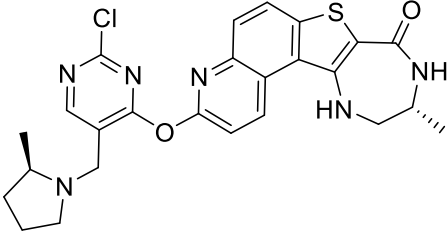
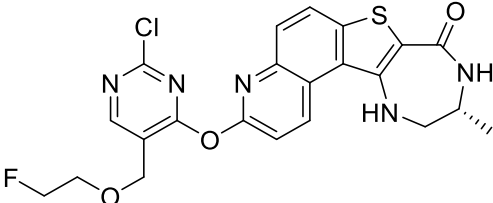
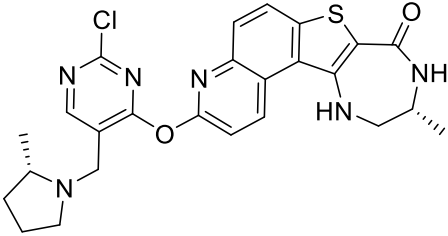
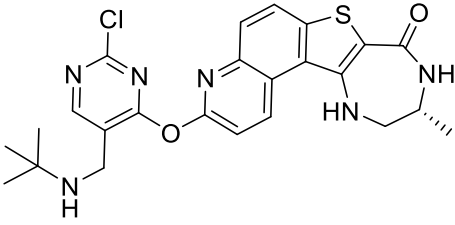
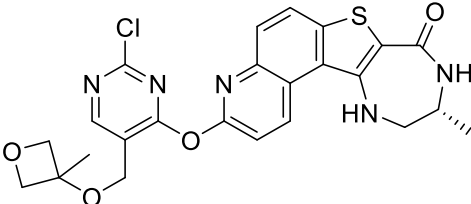
Compound #	Structure
<u>I-20</u>	
<u>I-21</u>	
<u>I-24</u>	
<u>I-30</u>	

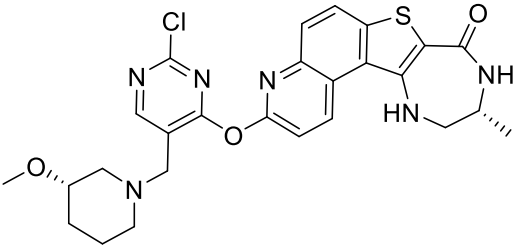
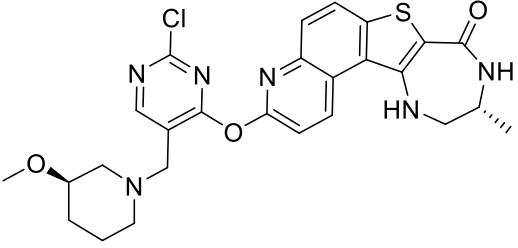
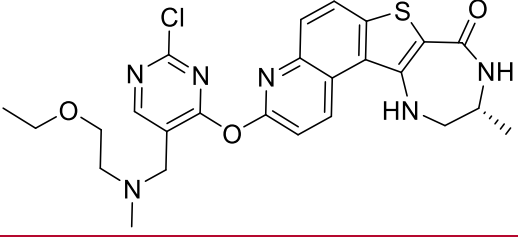
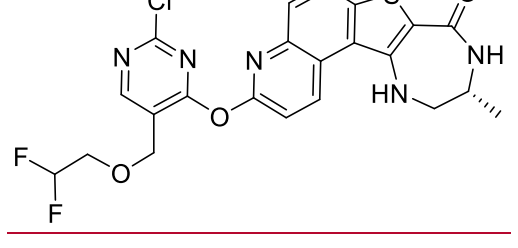
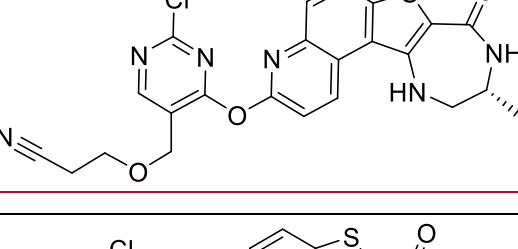
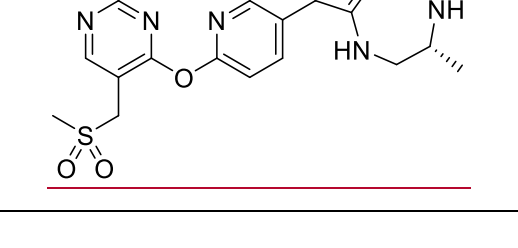
Compound #	Structure
<u>I-34</u>	
<u>I-52</u>	
<u>I-53</u>	
<u>I-72</u>	
<u>I-80</u>	

<u>Compound #</u>	<u>Structure</u>
<u>I-81</u>	
<u>I-82</u>	
<u>I-83</u>	
<u>I-84</u>	
<u>I-85</u>	

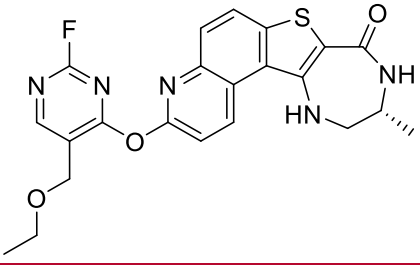
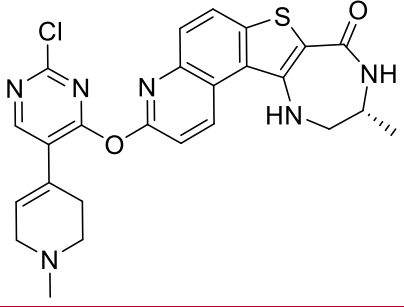
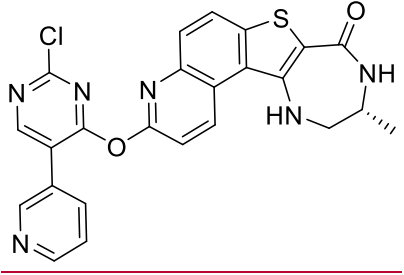
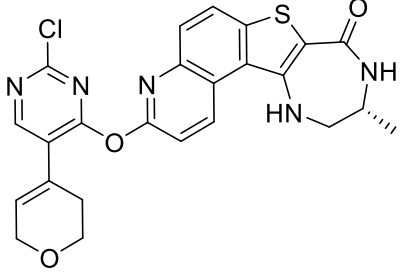
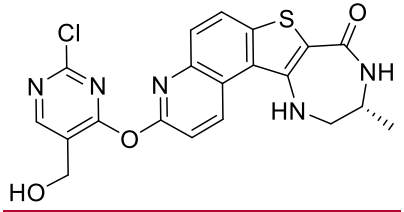
<u>Compound #</u>	<u>Structure</u>
<u>I-87</u>	
<u>I-88</u>	
<u>I-89</u>	
<u>I-90</u>	
<u>I-91</u>	

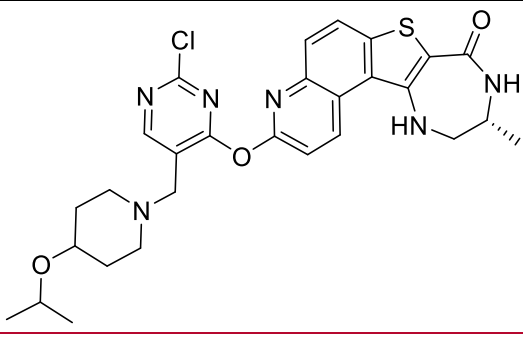
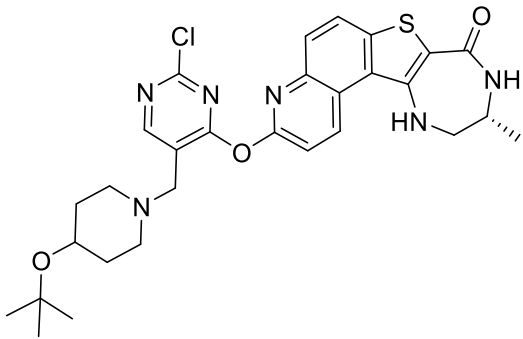
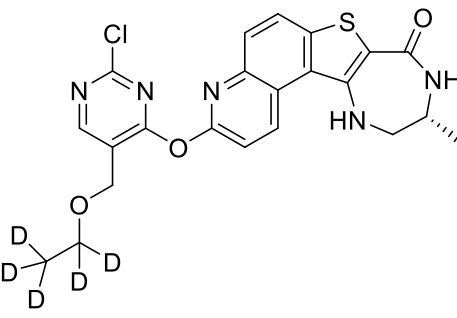
Compound #	Structure
<u>I-92</u>	
<u>I-93</u>	
<u>I-94</u>	
<u>I-95</u>	
<u>I-96</u>	
<u>I-97</u>	

<u>Compound #</u>	<u>Structure</u>
<u>I-98</u>	
<u>I-99</u>	
<u>I-100</u>	
<u>I-101</u>	
<u>I-102</u>	
<u>I-103</u>	

<u>Compound #</u>	<u>Structure</u>
<u>I-106</u>	
<u>I-107</u>	
<u>I-108</u>	
<u>I-110</u>	
<u>I-111</u>	
<u>I-112</u>	

<u>Compound #</u>	<u>Structure</u>
<u>I-113</u>	
<u>I-114</u>	
<u>I-115</u>	
<u>I-116</u>	
<u>I-120</u>	

<u>Compound #</u>	<u>Structure</u>
<u>I-121</u>	
<u>I-122</u>	
<u>I-123</u>	
<u>I-124</u>	
<u>I-127</u>	

<u>Compound #</u>	<u>Structure</u>
<u>I-133</u>	
<u>I-134</u>	
<u>I-135</u>	

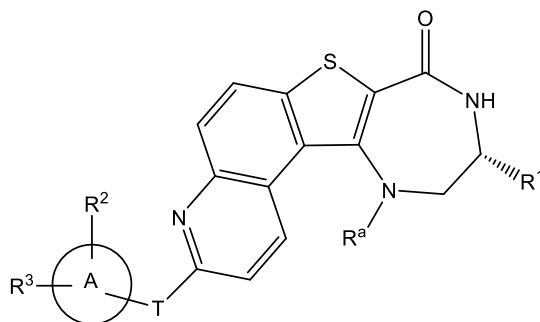
or a pharmaceutically acceptable salt thereof.

[0006c] In yet another aspect of the present disclosure, there is provided a pharmaceutically acceptable composition comprising the compound as disclosed herein and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0006d] In a further aspect of the present disclosure, there is provided a use of a composition as disclosed herein in the manufacture of a medicament for treating an MK2-mediated disease or disorder in a patient in need thereof, wherein the MK2-mediated disease or disorder is an autoimmune disorder, chronic or acute inflammatory disorder, an auto-inflammatory disorder, a fibrotic disorder, a metabolic disorder, a neoplasia, or a cardiovascular or cerebrovascular disorder.

[0006e] In another aspect of the present disclosure, there is provided a composition as disclosed herein, for use in therapy.

[0007] It has now been found that compounds of this ~~invention~~present disclosure, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of MK2. Such compounds have general formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, T, R^a, R¹, R², and R³, with respect to the formula **I** above, is as defined and described in ~~embodiments~~examples herein.

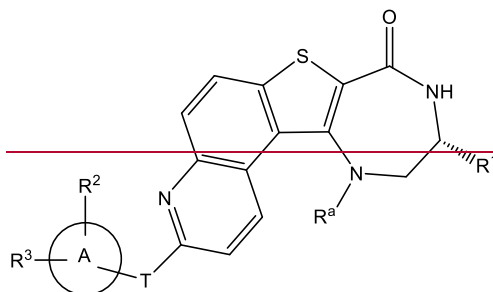
[0008] Compounds of the present ~~invention~~disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with abnormal cellular responses triggered by protein kinase-mediated events. Such diseases, disorders, or conditions include those described herein.

[0009] Compounds provided by this ~~invention~~present disclosure are also useful for the study of kinases in biological and pathological phenomena; the study of intracellular signal transduction pathways mediated by such kinases; and the comparative evaluation of new kinase inhibitors.

CLAIMS

We claim:

~~1. A compound of formula I':~~



I'

~~or a pharmaceutically acceptable salt thereof, wherein:~~

~~Ring A is phenyl or a 5-6 membered monocyclic heteroaryl ring having 1-3 nitrogens, or a 8-14 membered bridged or fused bicyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;~~

~~T is a bivalent moiety selected from by N(R), O, S, S(O), SO₂, C(S), Si(R⁴)₂, P(R⁵), P(O)₂, or a bivalent saturated straight or branched 1-3 membered hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with oxo or OR;~~

~~each R is independently hydrogen or an optionally substituted C₁₋₆ aliphatic, or:~~

~~two R groups on the same nitrogen are taken together with the nitrogen to form a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms selected from nitrogen, oxygen, or sulfur;~~

~~R^a is hydrogen or an optionally substituted C₁₋₆ aliphatic;~~

~~R¹ is R or (CH₂)_pR^{*};~~

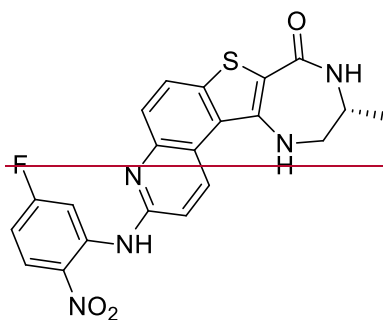
~~p is 0, 1, 2, or 3;~~

~~R^{*} is CN, NO₂, halogen, OR, SR, N(R)₂, C(O)N(R)₂, C(O)OR, C(O)R, N(R)C(O)R, SO₂N(R)₂, or N(R)SO₂;~~

~~R² is halogen, CN, SR^{*}, S(O)R^{*}, SO₂R^{*}, OSO₂R^{*}, OC(O)R^{*}, or OP(O)₂OR^{*};~~

~~each R^{*} is independently selected from optionally substituted C₁₋₆ aliphatic or optionally substituted phenyl;~~

R^2 is hydrogen, optionally substituted C_{1-6} aliphatic, CN , NO_2 , halogen, OR , $N(R)_2$, $C(O)N(R)_2$, $C(O)OR$, Cy , $C(O)N(R)Cy$, $C(O)Cy$, OCy , $O(CH_2)_nCy$, $(CH_2)_nOCy$, $(CH_2)_mN(R)_2$, $(CH_2)_mOR$, $N(R)Cy$, $N(R)(CH_2)_nCy$, $(CH_2)_nN(R)Cy$, or $(CH_2)_mCy$;
each R^4 is independently hydrogen, OR , C_{1-6} aliphatic, phenyl, a or 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;
each R^5 is independently OR , C_{1-6} aliphatic, phenyl, or a 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;
each of m and n is independently 0-4; and
each Cy is independently an optionally substituted ring selected from a 3-9 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 3-9 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, phenyl, a 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 7-12 membered saturated or partially unsaturated fused or bridged bicyclic carbocyclic ring, or a 6-12 membered saturated or partially unsaturated fused or bridged bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur
wherein said compound is other than:

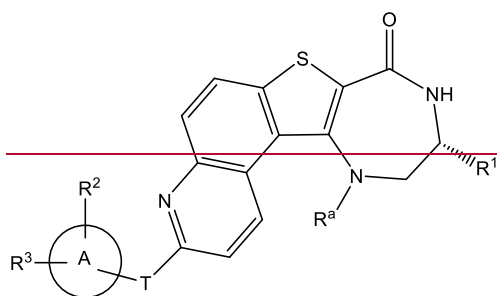


2. The compound according to claim 1, wherein T is $N(R)$, O , or S .
3. The compound according to claim 2, wherein T is NH or O .
4. The compound according to claim 3, wherein T is NH .
5. The compound according to claim 1, wherein R^1 is R , CH_2OR , or $CH_2N(R)_2$.

6. ~~The compound according to claim 1, wherein R^1 is methyl, CH_2OCH_3 , or CH_2NH_2 .~~

7. ~~The compound according to claim 6, wherein R^1 is methyl.~~

8. ~~The compound according to claim 1, of formula I,~~



I

~~or a pharmaceutically acceptable salt thereof, wherein:~~

~~Ring A is phenyl or a 5-6 membered heteroaryl ring having 1-3 nitrogens;~~

~~T is a bivalent moiety selected from by $N(R)$, O , S , $S(O)$, SO_2 , $C(S)$, $Si(R^4)_2$, $P(R^5)$, $P(O)_2$, or a bivalent saturated straight or branched 1-3 membered hydrocarbon chain,~~

~~wherein the hydrocarbon chain is optionally substituted with oxo or OR ;~~

~~each R is independently hydrogen or an optionally substituted C_{1-6} aliphatic, or:~~

~~two R groups on the same nitrogen are taken together with the nitrogen to form a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms selected from nitrogen, oxygen, or sulfur;~~

~~R^a is hydrogen or an optionally substituted C_{1-6} aliphatic;~~

~~R^1 is R or $(CH_2)_pR^*$;~~

~~p is 0, 1, 2, or 3;~~

~~R^* is CN , NO_2 , halogen, OR , SR , $N(R)_2$, $C(O)N(R)_2$, $C(O)OR$, $C(O)R$, $N(R)C(O)R$, $SO_2N(R)_2$, or $N(R)SO_2$;~~

~~R^2 is halogen, CN , SR^* , $S(O)R^*$, SO_2R^* , OSO_2R^* , $OC(O)R^*$, or $OP(O)_2OR^*$;~~

~~each R^* is independently selected from optionally substituted C_{1-6} aliphatic or optionally substituted phenyl;~~

~~R³ is hydrogen, optionally substituted C₁₋₆ aliphatic, CN, NO₂, halogen, OR, N(R)₂, C(O)N(R)₂, C(O)OR, Cy, C(O)N(R) Cy, C(O) Cy, O Cy, O (CH₂)_n Cy, (CH₂)_n O Cy, N(R) Cy, N(R) (CH₂)_n Cy, (CH₂)_n N(R) Cy, or (CH₂)_m Cy;~~

~~each R⁴ is independently hydrogen, OR, C₁₋₆ aliphatic, phenyl, or a 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;~~

~~each R⁵ is independently OR, C₁₋₆ aliphatic, phenyl, or a 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;~~

~~each of m and n is independently 0-4; and~~

~~each Cy is independently an optionally substituted ring selected from a 3-9 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 3-9 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, phenyl, a 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 7-12 membered saturated or partially unsaturated fused or bridged bicyclic carbocyclic ring, or a 7-12 membered saturated or partially unsaturated fused or bridged bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.~~

~~9. —The compound according to claim 1, wherein Ring A is phenyl and R³ is selected from CN, NO₂, halogen, C(O)N(R)₂, C(O)OR, Cy, C(O)N(R) Cy, or C(O) Cy.~~

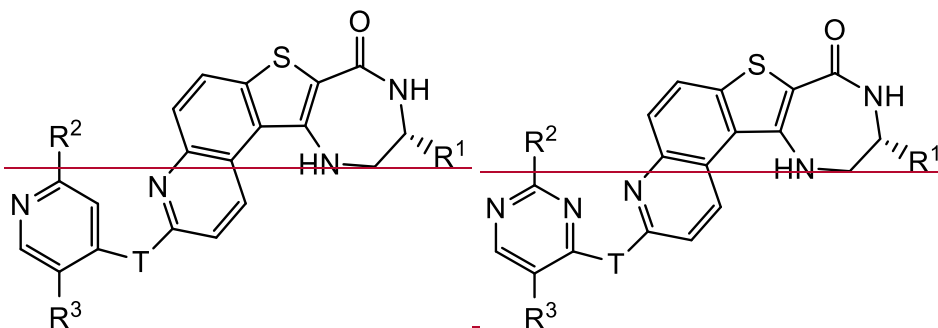
~~10. —The compound according to claim 9, wherein Ring A is phenyl and R³ is selected from CN, NO₂, or halogen.~~

~~11. —The compound according to claim 10, wherein Ring A is phenyl and R³ is selected from CN or halogen.~~

~~12. —The compound according to claim 1, wherein Ring A is a 6-membered heteroaryl ring having 1-3 nitrogens.~~

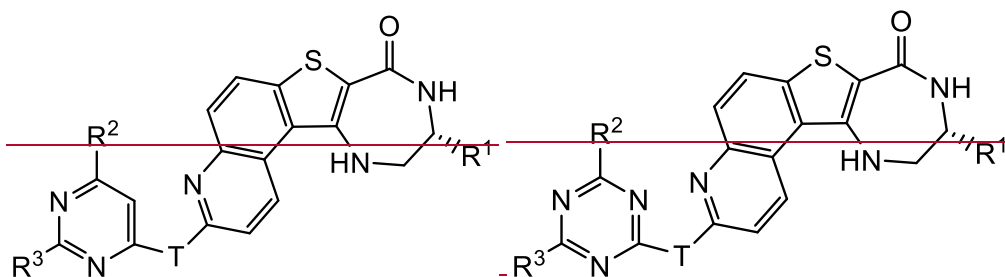
~~13. —The compound according to claim 12, wherein Ring A is pyridyl, pyrimidinyl, pyridazinyl, or triazinyl.~~

14. ~~The compound according to claim 13, wherein said compound is any one of formula **II**, **III**, **IV**, **V**, or **VI**:~~



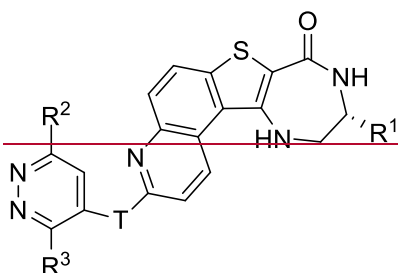
II

III



IV

V



VI

~~or a pharmaceutically acceptable salt thereof.~~

15. ~~The compound according to claim 1, wherein R^2 is halogen.~~

16. ~~The compound according to claim 15, wherein R^2 is fluoro or chloro.~~

17. ~~The compound according to claim 1, wherein R^2 is SR^* or SO_2R^* .~~

18. ~~The compound according to claim 15, wherein R^2 is SCH_3 or SO_2CH_3 .~~
19. ~~The compound according to claim 12, wherein R^3 is R, wherein R is hydrogen.~~
20. ~~The compound according to claim 12, wherein R^3 is R, wherein R is optionally substituted C_{1-6} -aliphatic.~~
21. ~~The compound according to claim 20, wherein R^3 is selected from CH_2OH , CH_2OCH_3 and CH_3 .~~
22. ~~The compound according to claim 12, wherein R^3 is OR .~~
23. ~~The compound according to claim 22, wherein R^3 is selected from $\text{O}(\text{CH}_2)_2\text{OCH}_3$, $\text{O}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$, and OCH_3 .~~
24. ~~The compound according to claim 1, wherein R^3 is halogen, CN , NO_2 , $\text{C}(\text{O})\text{N}(\text{R})_2$, or $\text{C}(\text{O})\text{OR}$.~~
25. ~~The compound according to claim 24, wherein R^3 is halogen, CN , or NO_2 .~~
26. ~~The compound according to claim 24, wherein R^3 is $\text{C}(\text{O})\text{N}(\text{R})_2$, or $\text{C}(\text{O})\text{OR}$.~~
27. ~~The compound according to claim 26, wherein R^3 is selected from $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{OCH}_2\text{CH}_3$, and $\text{OC}(\text{O})\text{CH}_3$.~~
28. ~~The compound according to claim 12, wherein R^3 is Cy , $(\text{CH}_2)_n\text{Cy}$, $\text{C}(\text{O})\text{N}(\text{R})\text{Cy}$, $\text{C}(\text{O})\text{Cy}$, OR , OCy , $\text{N}(\text{R})\text{Cy}$, $\text{N}(\text{R})(\text{CH}_2)_n\text{Cy}$, $(\text{CH}_2)_n\text{N}(\text{R})\text{Cy}$, or $\text{O}(\text{CH}_2)_n\text{Cy}$.~~

~~29.—The compound according to claim 28, wherein each Cy is independently an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring.~~

~~30.—The compound according to claim 28, wherein each Cy is independently an optionally substituted ring selected from a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.~~

~~31.—The compound according to claim 30, wherein each Cy is independently an optionally substituted ring selected from oxetanyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl, piperazinyl, and morpholinyl.~~

~~32.—A pharmaceutically acceptable composition comprising the compound according to claim 1 and a pharmaceutically acceptable carrier, adjuvant, or vehicle.~~

~~33.—A method for inhibiting MK2 kinase, or a mutant thereof, activity in a biological sample comprising the step of contacting said biological sample with a compound according to claim 1.~~

~~34.—A method for inhibiting MK2 kinase, or a mutant thereof, activity in a patient comprising the step of administering to said patient the composition according to claim 32.~~

~~35.—The method according to claim 34, wherein the MK2 kinase, or a mutant thereof, activity is inhibited irreversibly.~~

~~36.—The method according to claim 35, wherein the MK2 kinase, or a mutant thereof, activity is inhibited irreversibly by covalently modifying Cys140 of MK2.~~

~~37. — A method for treating an MK2-mediated disease or disorder in a patient in need thereof, comprising the step of administering to said patient the composition according to claim 32.~~

~~38. — The method according to claim 37, wherein the MK2-mediated disease or disorder is an autoimmune disorder, chronic or acute inflammatory disorder, an auto-inflammatory disorder, a fibrotic disorder, a metabolic disorder, a neoplasia, or a cardiovascular or cerebrovascular disorder.~~

~~39. — The method according to claim 38, wherein the MK2-mediated disease or disorder is an autoimmune disorder, chronic or acute inflammatory disorder, or an auto-inflammatory disorder.~~

~~40. — The method according to claim 39, wherein the autoimmune disorder, chronic or acute inflammatory disorder, and/or auto-inflammatory disorder is selected from the group consisting of inflammatory bowel diseases, ulcerative colitis, Crohn's disease, multiple sclerosis, psoriasis, arthritis, rheumatoid arthritis, osteoarthritis, juvenile arthritis, psoriatic arthritis, reactive arthritis, ankylosing spondylitis, cryopyrin-associated periodic syndromes, Muckle-Wells syndrome, familial cold auto-inflammatory syndrome, neonatal-onset multisystem inflammatory disease, TNF-receptor-associated periodic syndrome, acute and chronic pancreatitis, atherosclerosis, gout, ankylosing spondylitis, fibrotic disorders, hepatic fibrosis, idiopathic pulmonary fibrosis, nephropathy, sarcoidosis, scleroderma, anaphylaxis, diabetes, diabetes mellitus type 1, diabetes mellitus type 2, diabetic retinopathy, Still's disease, vasculitis, sarcoidosis, pulmonary inflammation, acute respiratory distress syndrome, wet and dry age-related macular degeneration, autoimmune hemolytic syndromes, autoimmune and inflammatory hepatitis, autoimmune neuropathy, autoimmune ovarian failure, autoimmune orchitis, autoimmune thrombocytopenia, silicone implant-associated autoimmune disease, Sjogren's syndrome, familial Mediterranean fever, systemic lupus erythematosus, vasculitis syndromes, temporal, Takayasu's and giant cell arteritis, Behçet's disease, Wegener's granulomatosis, vitiligo, secondary hematologic manifestation of autoimmune diseases, anemias, drug-induced autoimmunity, Hashimoto's thyroiditis, hypophysitis, idiopathic thrombocytic purpura, metal-~~

~~induced autoimmunity, myasthenia gravis, pemphigus, autoimmune deafness, Meniere's disease, Goodpasture's syndrome, Graves' disease, HW related autoimmune syndromes, Gullain Barre disease, Addison's disease, anti-phospholipid syndrome, asthma, atopic dermatitis, Celiac disease, Cushing's syndrome, dermatomyositis, idiopathic adrenal atrophy, idiopathic thrombocytopenia, Kawasaki syndrome, Lambert-Eaton Syndrome, pernicious anemia, pollinosis, polyarteritis nodosa, primary biliary cirrhosis, primary sclerosing cholangitis, Raynaud's, Reiter's Syndrome, relapsing polychondritis, Schmidt's syndrome, thyrotoxicosis, sepsis, septic shock, endotoxic shock, exotoxin-induced toxic shock, gram-negative sepsis, toxic shock syndrome, glomerulonephritis, peritonitis, interstitial cystitis, hyperoxia-induced inflammations, chronic obstructive pulmonary disease (COPD), vasculitis, graft vs. host reaction, graft vs. host disease, allograft rejections, acute allograft rejection, chronic allograft rejection, early transplantation rejection, acute allograft rejection, reperfusion injury, pain, acute pain, chronic pain, neuropathic pain, fibromyalgia, chronic infections, meningitis, encephalitis, myocarditis, gingivitis, post-surgical trauma, tissue injury, traumatic brain injury, enterocolitis, sinusitis, uveitis, ocular inflammation, optic neuritis, gastric ulcers, esophagitis, peritonitis, periodontitis, dermatomyositis, gastritis, myositis, polymyalgia, pneumonia and bronchitis.~~

~~41.—The method according to claim 38, wherein the MK2-mediated disease or disorder is a fibrotic disorder.~~

~~42.—The method according to claim 41, wherein the fibrotic disorder is selected from the group consisting of systemic sclerosis/scleroderma, lupus nephritis, connective tissue disease, wound healing, surgical scarring, spinal cord injury, CNS scarring, acute lung injury, pulmonary fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, acute lung injury, drug-induced lung injury, glomerulonephritis, chronic kidney disease, diabetic nephropathy, hypertension-induced nephropathy, alimentary tract or gastrointestinal fibrosis, renal fibrosis, hepatic or biliary fibrosis, liver fibrosis, nonalcoholic steatohepatitis, hepatitis C, hepatocellular carcinoma, cirrhosis, primary biliary cirrhosis, cirrhosis due to fatty liver disease, cirrhosis due to alcoholic fatty liver disease, cirrhosis due to nonalcoholic steatosis/non-alcoholic fatty liver disease, radiation-induced fibrosis, head and neck fibrosis, gastrointestinal fibrosis, pulmonary fibrosis,~~

~~primary sclerosing cholangitis, restenosis, cardiac fibrosis, endomyocardial fibrosis, atrial fibrosis, ocular scarring, fibrosclerosis, fibrotic cancers, fibroids, fibroma, fibroadenomas, fibrosarcomas, transplant arteriopathy, keloid, mediastinal fibrosis, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis, and nephrogenic systemic fibrosis.~~

~~43. The method according to claim 38, wherein the MK2-mediated disease or disorder is a metabolic disorder.~~

~~44. The method according to claim 43, wherein the metabolic disorder is selected from the group consisting of obesity, steroid resistance, glucose intolerance, and metabolic syndrome.~~

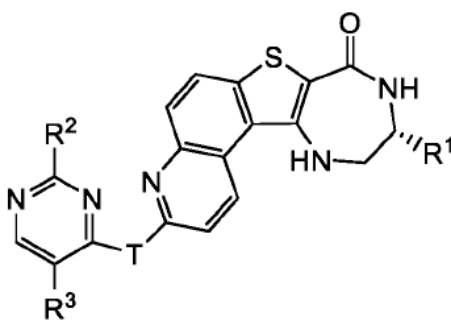
~~45. The method according to claim 38, wherein the MK2-mediated disease or disorder is a neoplasia.~~

~~46. The method according to claim 45, wherein the neoplasia is selected from the group consisting of angiogenesis disorders, multiple myeloma, leukemias, acute lymphocytic leukemia, acute and chronic myelogenous leukemia, chronic lymphocytic leukemia, acute lymphoblastic leukemia, promyelocytic leukemia, lymphomas, B-cell lymphoma, T-cell lymphoma, mantle cell lymphoma, hairy cell lymphoma, Burkitt's lymphoma, mast cell tumors, Hodgkin's disease, non-Hodgkin's disease, myelodysplastic syndrome, fibrosarcoma, rhabdomyosarcoma; astrocytoma, neuroblastoma, glioma, schwannomas, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentosum, keratoanthoma, thyroid follicular cancer, Kaposi's sarcoma, melanoma, teratoma, rhabdomyosarcoma, metastatic and bone disorders, cancer of the bone, mouth/pharynx, esophagus, larynx, stomach, intestine, colon, rectum, lung, , liver, pancreas, nerve, brain, , head and neck, throat, ovary, uterus, prostate, testis, bladder, kidney, breast, gall bladder, cervix, thyroid, prostate, and skin, non-small cell lung cancer, small cell lung cancer, glioma, and glioblastoma multiforme.~~

~~47. The method according to claim 38 wherein the MK2-mediated disease or disorder is a cardiovascular or cerebrovascular disorder.~~

48. ~~The method according to claim 47, wherein the cardiovascular or cerebrovascular disorder is selected from the group consisting of atherosclerosis, restenosis of an atherosclerotic coronary artery, acute coronary syndrome, myocardial infarction, cardiac allograft vasculopathy, stroke, central nervous system disorders with an inflammatory or apoptotic component, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, neuronal ischemia and peripheral neuropathy.~~

1. A compound of formula III:



III

or a pharmaceutically acceptable salt thereof, wherein:

T is a bivalent moiety selected from -N(R)-, -O-, or -S-;

each R is independently hydrogen or an optionally substituted C₁₋₆ aliphatic, or:

two R groups on the same nitrogen are taken together with the nitrogen to form a 3-7
membered saturated or partially unsaturated heterocyclic ring having 1-3
heteroatoms selected from nitrogen, oxygen, or sulfur;

R¹ is R or -(CH₂)_pR^x;

p is 0, 1, 2, or 3;

R^x is -CN, -NO₂, halogen, -OR, -SR, -N(R)₂, -C(O)N(R)₂, -C(O)OR, -C(O)R,
-N(R)C(O)R, -SO₂N(R)₂, or -N(R)SO₂;

R² is halogen, -CN, -SR^y, -S(O)R^y, -SO₂R^y, -OSO₂R^y, -OC(O)R^y, or -OP(O)₂OR^y;

each R^y is independently selected from optionally substituted C₁₋₆ aliphatic or optionally
substituted phenyl;

R³ is hydrogen, optionally substituted C₁₋₆ aliphatic, -CN, -NO₂, halogen, -OR, -N(R)₂,
-C(O)N(R)₂, -C(O)OR, -Cy, -C(O)N(R)-Cy, -C(O)-Cy, -O-Cy, -O-(CH₂)_n-Cy,

-(CH₂)_n-OCy, -(CH₂)_mN(R)₂, -(CH₂)_mOR, -N(R)-Cy, -N(R)-(CH₂)_n-Cy,
-(CH₂)_n-N(R)-Cy, or -(CH₂)_mCy;

each of m and n is independently 0-4; and

each Cy is independently an optionally substituted ring selected from a 3-9 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 3-9 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, phenyl, a 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 7-12 membered saturated or partially unsaturated fused or bridged bicyclic carbocyclic ring, or a 6-12 membered saturated or partially unsaturated fused or bridged bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

wherein:

a substituent on an optionally substituted carbon atom of an optionally substituted group is independently selected from:

- (i) halogen; -(CH₂)₀₋₄R[°]; -(CH₂)₀₋₄OR[°]; -O(CH₂)₀₋₄R[°], -O-(CH₂)₀₋₄C(O)OR[°];
-(CH₂)₀₋₄CH(OR[°])₂; -(CH₂)₀₋₄SR[°]; -(CH₂)₀₋₄Ph, which are may be substituted with R[°]; -(CH₂)₀₋₄(CH₂)₀₋₁Ph which may be substituted with R[°]; -CH=CHPh, which may be substituted with R[°]; -(CH₂)₀₋₄O(CH₂)₀₋₁-pyridyl which may be substituted with R[°]; -NO₂; -CN; -N₃; -(CH₂)₀₋₄N(R[°])₂; -(CH₂)₀₋₄N(R[°])C(O)R[°];
-N(R[°])C(S)R[°]; -(CH₂)₀₋₄N(R[°])C(O)NR[°]₂; -N(R[°])C(S)NR[°]₂;
-(CH₂)₀₋₄N(R[°])C(O)OR[°]; -N(R[°])N(R[°])C(O)R[°]; -N(R[°])N(R[°])C(O)NR[°]₂;
-N(R[°])N(R[°])C(O)OR[°]; -(CH₂)₀₋₄C(O)R[°]; -C(S)R[°]; -(CH₂)₀₋₄C(O)OR[°];
-(CH₂)₀₋₄C(O)SR[°]; -(CH₂)₀₋₄C(O)OSiR[°]₃; -(CH₂)₀₋₄OC(O)R[°];
-OC(O)(CH₂)₀₋₄SR[°]; -(CH₂)₀₋₄SC(O)R[°]; -(CH₂)₀₋₄C(O)NR[°]₂; -C(S)NR[°]₂;
-C(S)SR[°]; -SC(S)SR[°]; -(CH₂)₀₋₄OC(O)NR[°]₂; -C(O)N(OR[°])R[°]; -C(O)C(O)R[°];
-C(O)CH₂C(O)R[°]; -C(NOR[°])R[°]; -(CH₂)₀₋₄SSR[°]; -(CH₂)₀₋₄S(O)₂R[°];
-(CH₂)₀₋₄S(O)₂OR[°]; -(CH₂)₀₋₄OS(O)₂R[°]; -S(O)₂NR[°]₂; -(CH₂)₀₋₄S(O)R[°];
-N(R[°])S(O)₂NR[°]₂; -N(R[°])S(O)₂R[°]; -N(OR[°])R[°]; -C(NH)NR[°]₂; -P(O)₂R[°];
-P(O)R[°]₂; -OP(O)R[°]₂; -OP(O)(OR[°])₂; SiR[°]₃; —(C₁₋₄ straight or branched alkylene)O-N(R[°])₂; or -(C₁₋₄ straight or branched alkylene)C(O)O-N(R[°])₂;

each R° is independently hydrogen, C₁₋₆ aliphatic, -CH₂Ph, -O(CH₂)₀₋₁Ph, -CH₂-(5-6 membered heteroaryl ring), or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein each R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), may be independently substituted with:

(a) halogen, -(CH₂)₀₋₂R°, -(haloR°), -(CH₂)₀₋₂OH, -(CH₂)₀₋₂OR°, -(CH₂)₀₋₂CH(OR°)₂; -O(haloR°), -CN, -N₃, -(CH₂)₀₋₂C(O)R°, -(CH₂)₀₋₂C(O)OH, -(CH₂)₀₋₂C(O)OR°, -(CH₂)₀₋₂SR°, -(CH₂)₀₋₂SH, -(CH₂)₀₋₂NH₂, -(CH₂)₀₋₂NHR°, -(CH₂)₀₋₂NR°₂, -NO₂, -SiR°₃, -OSiR°₃, -C(O)SR°, -(C₁₋₄ straight or branched alkylene)C(O)OR°, or -SSR°;

each R° is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently selected from C₁₋₄ aliphatic, -CH₂Ph, -O(CH₂)₀₋₁Ph, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

(b) =O or =S; or;

(ii) =O, =S, =NNR*₂, =NNHC(O)R*, =NNHC(O)OR*, =NNHS(O)₂R*, =NR*, =NOR*, -O(C(R*₂))₂₋₃O-, or -S(C(R*₂))₂₋₃S-; or a substituent on optionally substituted vicinal carbon atoms of an optionally substituted group is independently selected from -O(CR*₂)₂₋₃O-;

wherein each R* is independently selected from hydrogen, C₁₋₆ aliphatic, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein substituents on the aliphatic group of R* are independently selected from halogen, -R°, -(haloR°), -OH, -OR°, -O(haloR°), -CN, -C(O)OH, -C(O)OR°, -NH₂, -NHR°, -NR°₂, or -NO₂;

each R[•] is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently selected from C₁₋₄ aliphatic, -CH₂Ph, -O(CH₂)₀₋₁Ph, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

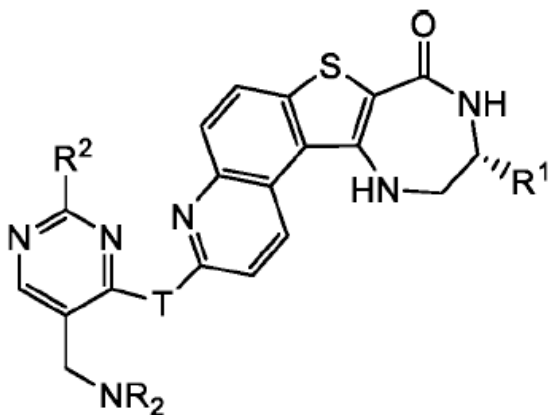
a substituent on an optionally substituted nitrogen atom of an optionally substituted group is independently selected from -R[†], -NR[†]₂, -C(O)R[†], -C(O)OR[†], -C(O)C(O)R[†], -C(O)CH₂C(O)R[†], -S(O)₂R[†], -S(O)₂NR[†]₂, -C(S)NR[†]₂, -C(NH)NR[†]₂, or -N(R[†])S(O)₂R[†];

wherein each R[†] is independently hydrogen, C₁₋₆ aliphatic, unsubstituted -OPh, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or two independent occurrences of R[†], taken together with their intervening atom(s) form an unsubstituted 3-12-membered saturated, partially unsaturated, or aryl mono-or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

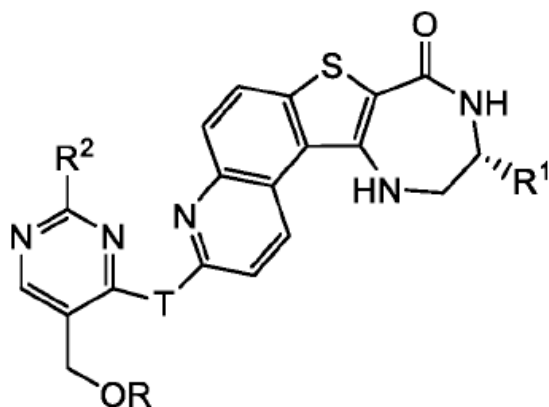
wherein substituents on the aliphatic group of R[†] are independently selected from -R[•], - (haloR[•]), -OH, -OR[•], -O(haloR[•]), -CN, -C(O)OH, -C(O)OR[•], -NH₂, -NHR[•], -NR[•]₂, or -NO₂; and

each R[•] is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C₁₋₄ aliphatic, -CH₂Ph, -O(CH₂)₀₋₁Ph, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

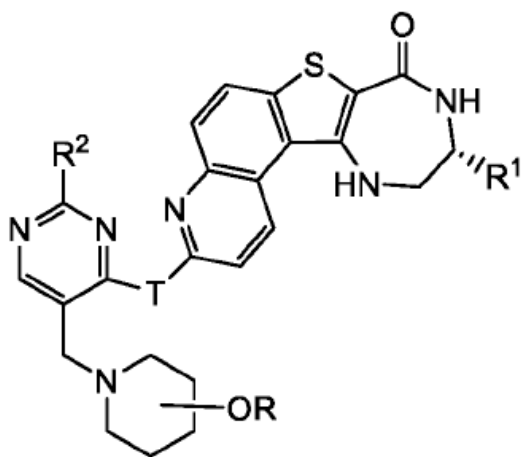
2. The compound according to claim 1, wherein said compound is any one of formula XVI, XX, XXII, or XXIII:



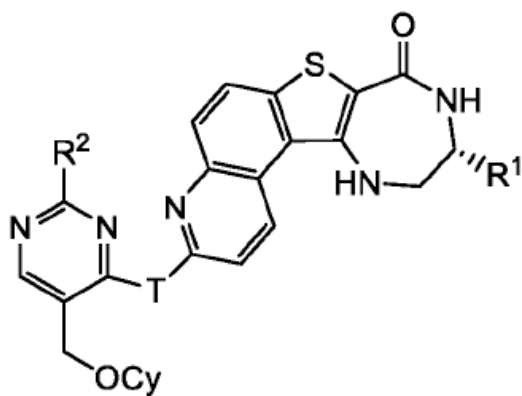
XVI



XX



XXII



XXIII

or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1 or 2, wherein R² is halogen.

4. The compound according to claim 3, wherein R² is chloro.

5. The compound according to claim 1, wherein R³ is optionally substituted C₁₋₆ aliphatic.

6. The compound according to claim 5, wherein R³ is C₁₋₆ aliphatic substituted with -(CH₂)₀₋₄OR^o, wherein R^o is C₁₋₆ aliphatic.

7. The compound according to claim 5, wherein R^3 is C_{1-6} aliphatic substituted with $-(CH_2)_{0-4}OR^\circ$, wherein R° is hydrogen or C_{1-6} aliphatic optionally substituted with halogen, $-CN$, or $-(CH_2)_{0-2}OR^\bullet$, wherein $R^\bullet$ is C_{1-4} aliphatic.

8. The compound according to claim 5, wherein R^3 is C_{1-6} aliphatic substituted with $-(CH_2)_{0-4}N(R^\circ)_2$, wherein each R° is independently hydrogen or C_{1-6} aliphatic optionally substituted with $-(CH_2)_{0-2}OR^\bullet$, wherein $R^\bullet$ is C_{1-4} aliphatic.

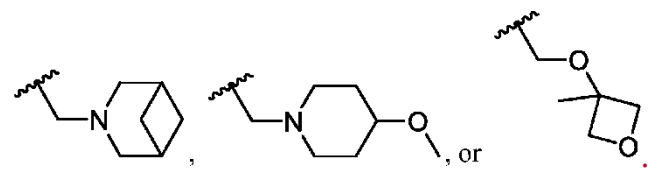
9. The compound according to claim 1, wherein R^3 is $-(CH_2)_mOR$.

10. The compound according to claim 9, wherein R^3 is $-CH_2OR$, wherein R is optionally substituted C_{1-6} aliphatic.

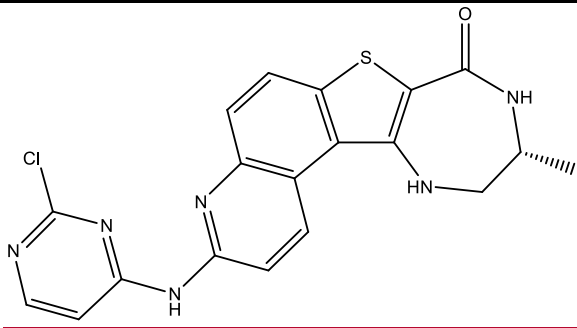
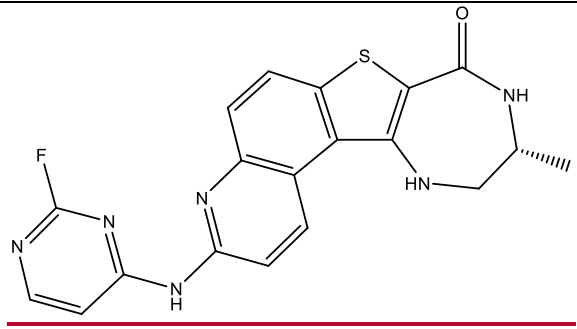
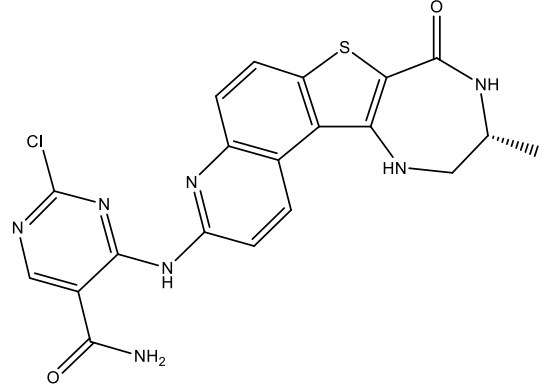
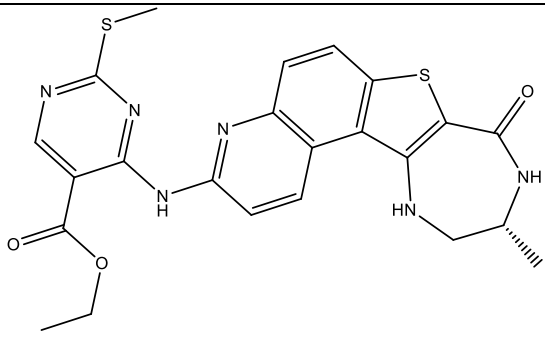
11. The compound according to claim 10, wherein R is C_{1-6} aliphatic substituted with oxo, halogen, $-CN$, $-(CH_2)_{0-4}R^\circ$, $-(CH_2)_{0-4}OR^\circ$, or $-(CH_2)_{0-4}S(O)_2R^\circ$, wherein R° is C_{1-6} aliphatic.

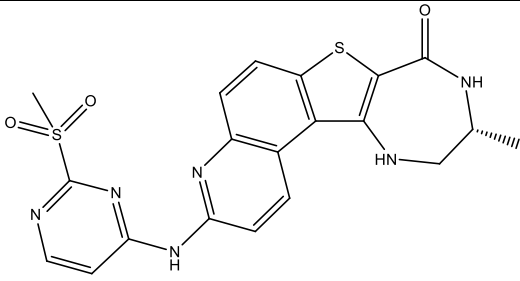
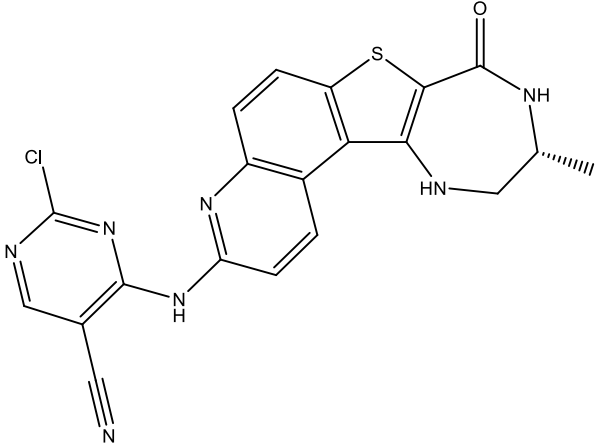
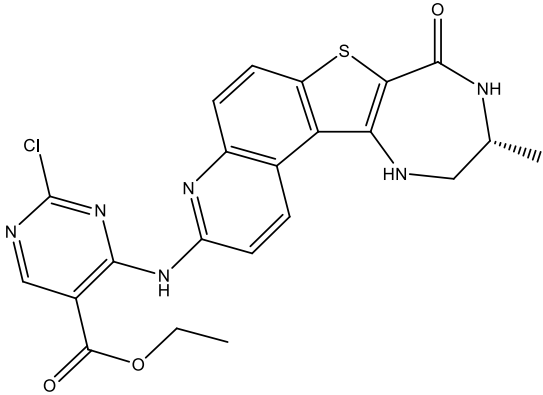
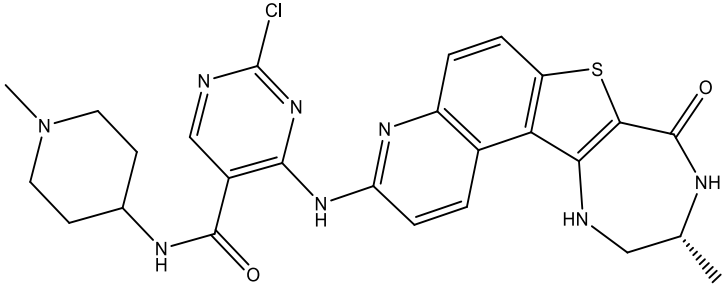
12. The compound according to claim 10, wherein R is ethyl substituted with oxo, halogen, $-CN$, $-(CH_2)_{0-4}R^\circ$, $-(CH_2)_{0-4}OR^\circ$, or $-(CH_2)_{0-4}S(O)_2R^\circ$, wherein R° is C_{1-6} aliphatic.

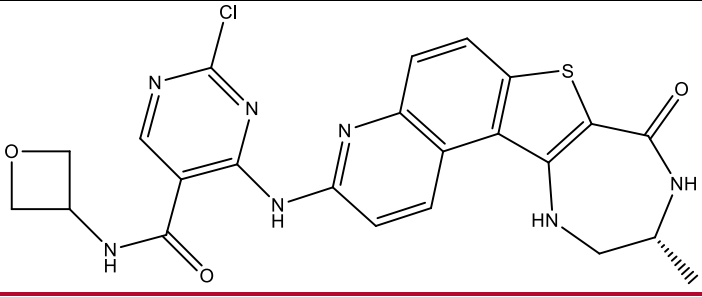
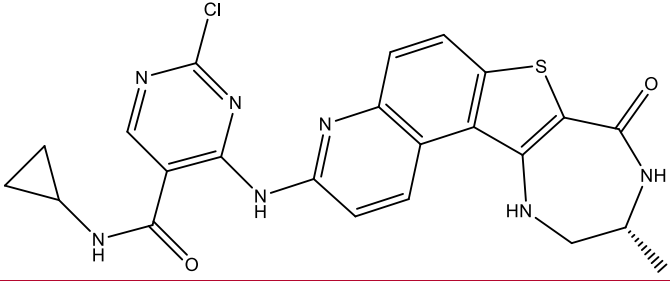
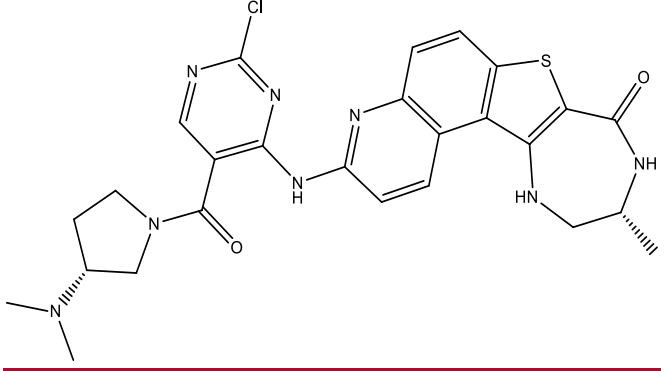
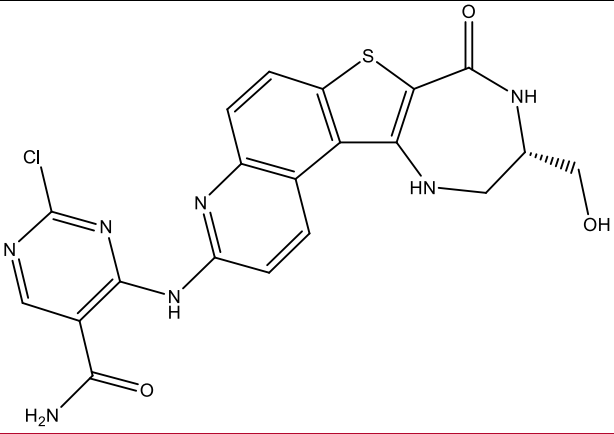
13. The compound according to claim 1, wherein R^3 is $-CH_2OCH_2CH_3$, $-CH_2OCH_2CH_2F$,

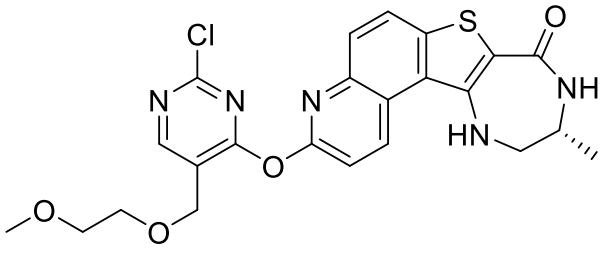
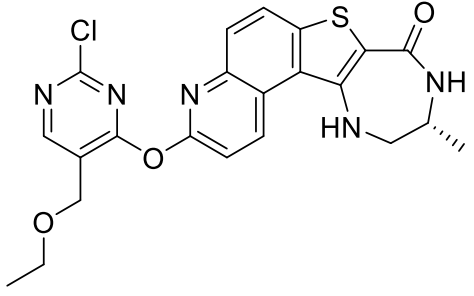
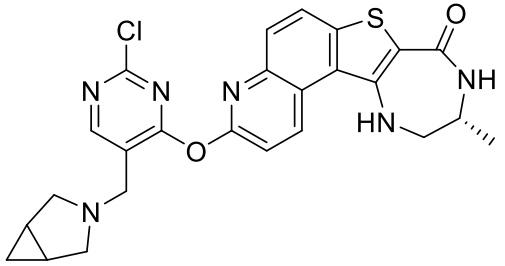
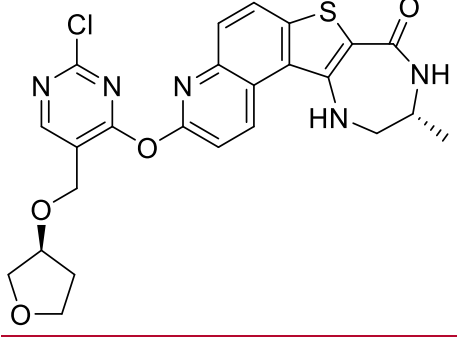
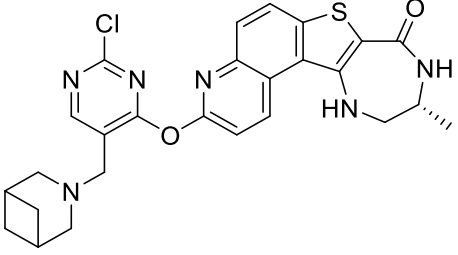


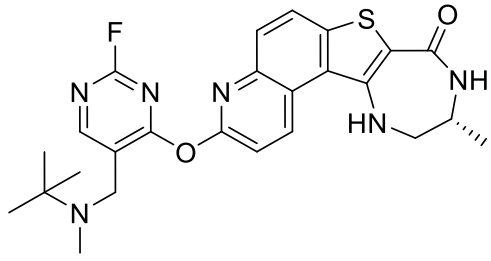
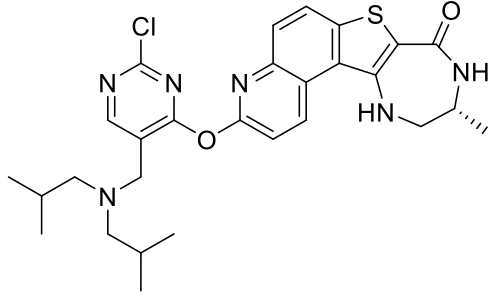
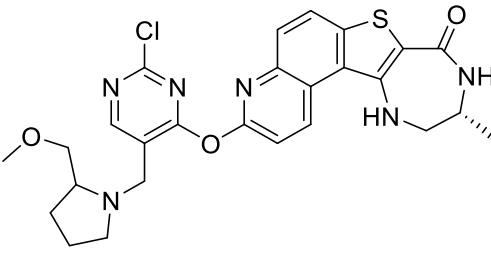
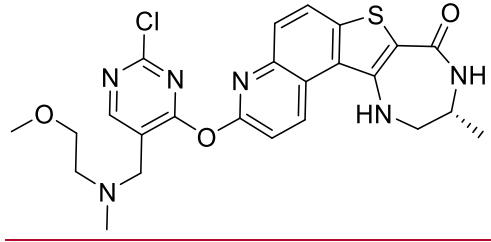
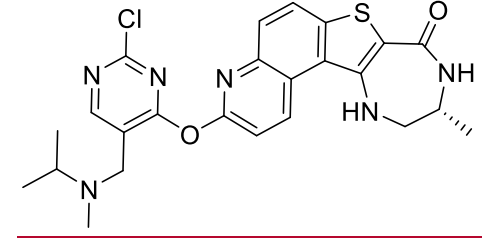
14. A compound selected from:

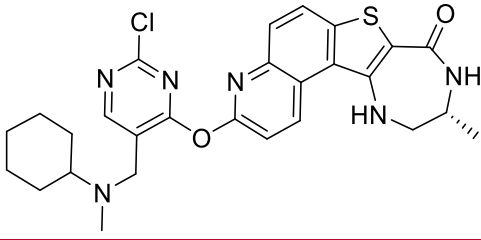
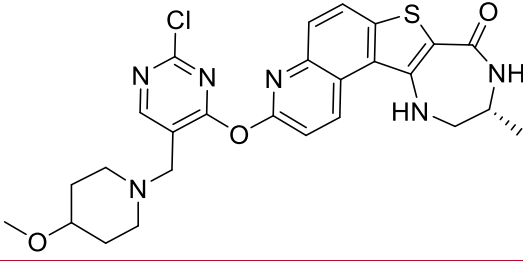
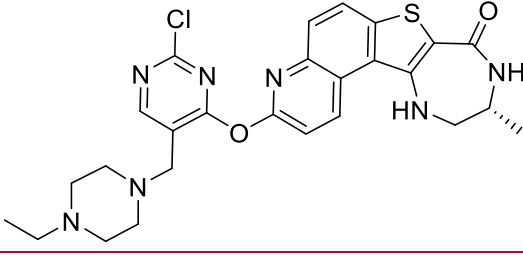
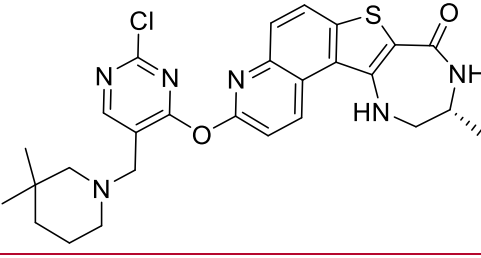
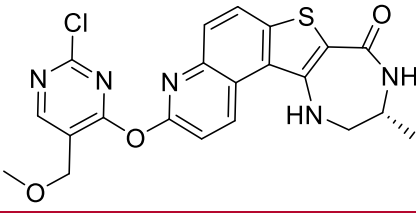
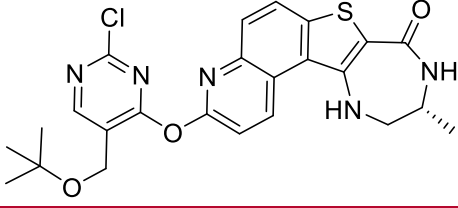
<u>Compound #</u>	<u>Structure</u>
<u>I-5</u>	
<u>I-8</u>	
<u>I-9</u>	
<u>I-12</u>	

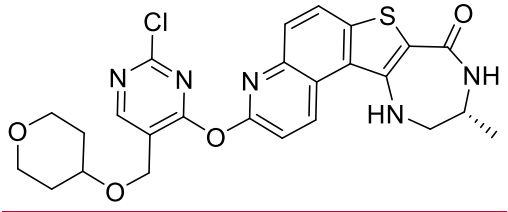
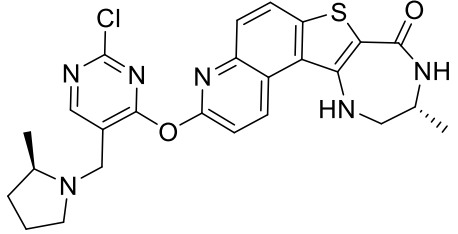
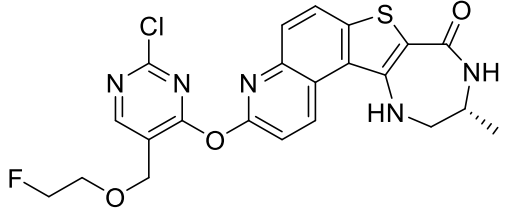
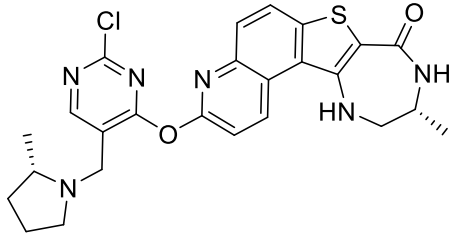
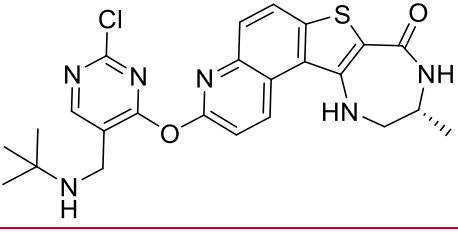
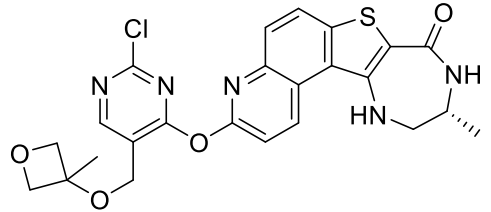
<u>Compound #</u>	<u>Structure</u>
<u>I-14</u>	
<u>I-16</u>	
<u>I-18</u>	
<u>I-19</u>	

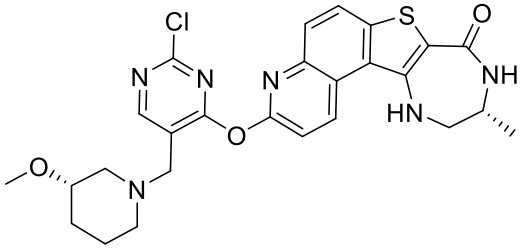
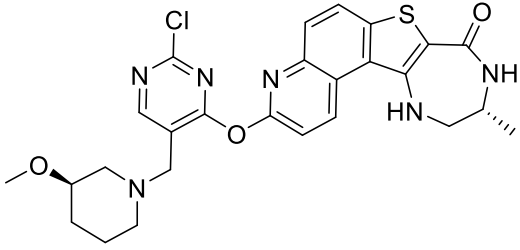
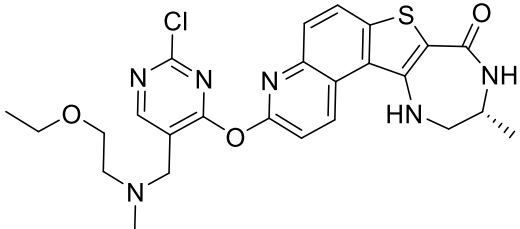
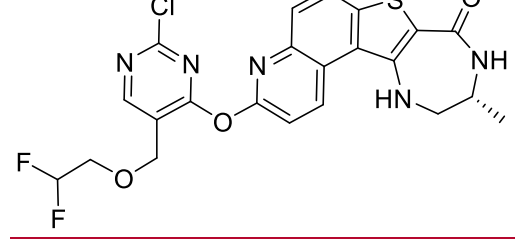
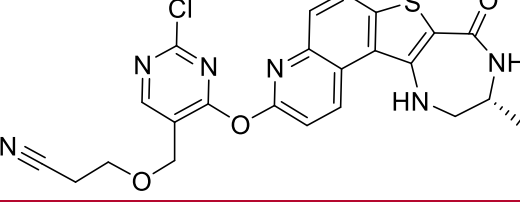
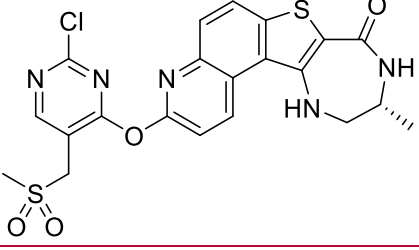
<u>Compound #</u>	<u>Structure</u>
<u>I-20</u>	
<u>I-21</u>	
<u>I-24</u>	
<u>I-30</u>	

<u>Compound #</u>	<u>Structure</u>
<u>I-81</u>	
<u>I-82</u>	
<u>I-83</u>	
<u>I-84</u>	
<u>I-85</u>	

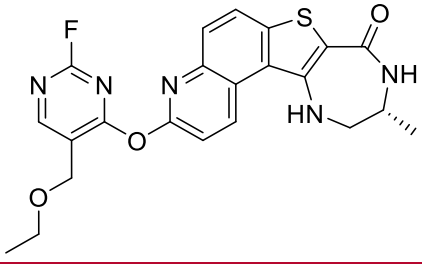
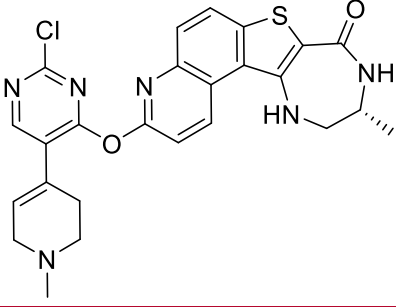
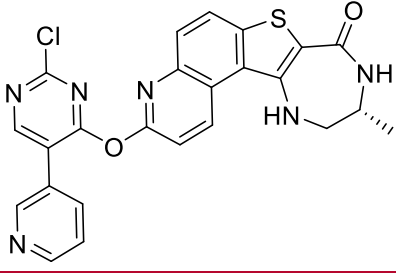
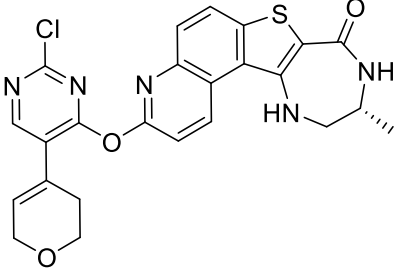
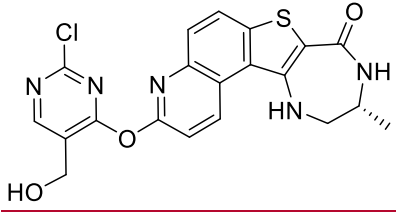
<u>Compound #</u>	<u>Structure</u>
<u>I-87</u>	
<u>I-88</u>	
<u>I-89</u>	
<u>I-90</u>	
<u>I-91</u>	

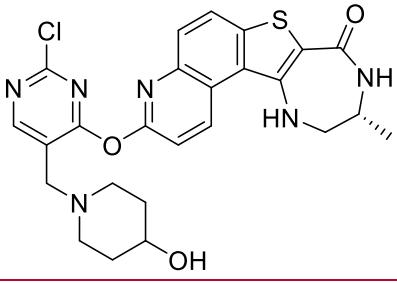
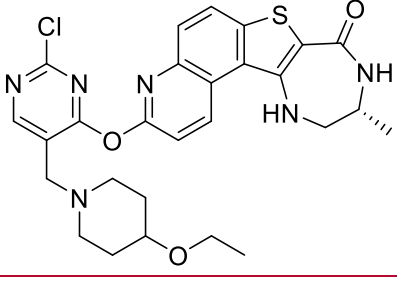
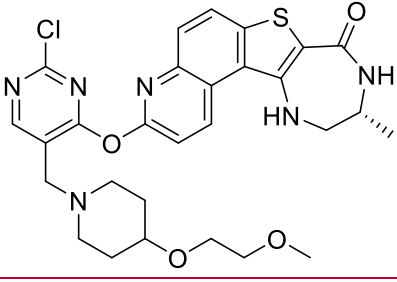
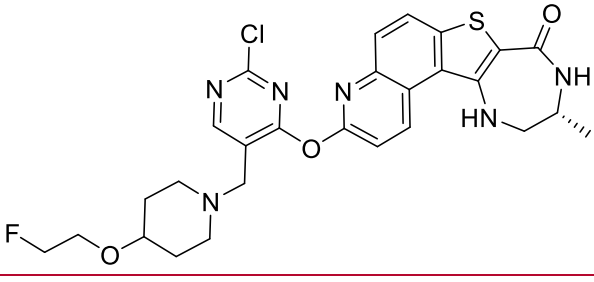
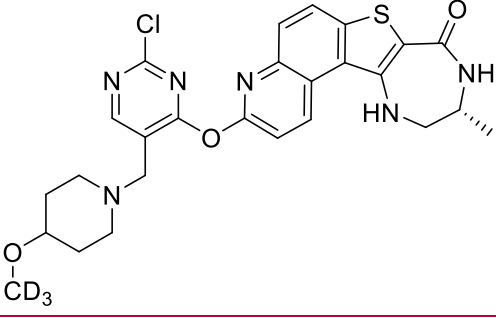
Compound #	Structure
<u>I-92</u>	
<u>I-93</u>	
<u>I-94</u>	
<u>I-95</u>	
<u>I-96</u>	
<u>I-97</u>	

<u>Compound #</u>	<u>Structure</u>
<u>I-98</u>	
<u>I-99</u>	
<u>I-100</u>	
<u>I-101</u>	
<u>I-102</u>	
<u>I-103</u>	

<u>Compound #</u>	<u>Structure</u>
<u>I-106</u>	
<u>I-107</u>	
<u>I-108</u>	
<u>I-110</u>	
<u>I-111</u>	
<u>I-112</u>	

<u>Compound #</u>	<u>Structure</u>
<u>I-113</u>	
<u>I-114</u>	
<u>I-115</u>	
<u>I-116</u>	
<u>I-120</u>	

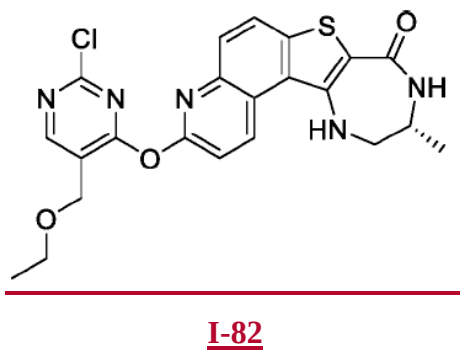
<u>Compound #</u>	<u>Structure</u>
<u>I-121</u>	
<u>I-122</u>	
<u>I-123</u>	
<u>I-124</u>	
<u>I-127</u>	

<u>Compound #</u>	<u>Structure</u>
<u>I-128</u>	
<u>I-129</u>	
<u>I-130</u>	
<u>I-131</u>	
<u>I-132</u>	

<u>Compound #</u>	<u>Structure</u>
<u>I-133</u>	
<u>I-134</u>	
<u>I-135</u>	

or a pharmaceutically acceptable salt thereof.

15. The compound according to claim 1, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

16. A pharmaceutically acceptable composition comprising the compound according to any one of claims 1-14 and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

17. A pharmaceutically acceptable composition comprising the compound according to claim 15 and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

18. Use of a composition according to claim 16 or 17 in the manufacture of a medicament for treating an MK2-mediated disease or disorder in a patient in need thereof, wherein the MK2-mediated disease or disorder is an autoimmune disorder, chronic or acute inflammatory disorder, an auto-inflammatory disorder, a fibrotic disorder, a metabolic disorder, a neoplasia, or a cardiovascular or cerebrovascular disorder.

19. The use according to claim 18, wherein

(i) the MK2-mediated disease or disorder is an autoimmune disorder, chronic or acute inflammatory disorder, and/or auto-inflammatory disorder is selected from the group consisting of inflammatory bowel diseases, ulcerative colitis, Crohn's disease, multiple sclerosis, psoriasis, arthritis, rheumatoid arthritis, osteoarthritis, juvenile arthritis, psoriatic arthritis, reactive arthritis, ankylosing spondylitis, cryopyrin associated periodic syndromes, Muckle-Wells syndrome, familial cold auto-inflammatory syndrome, neonatal-onset multisystem inflammatory disease, TNF receptor associated periodic syndrome, acute and chronic pancreatitis, atherosclerosis, gout, ankylosing spondylitis, fibrotic disorders, hepatic fibrosis, idiopathic pulmonary fibrosis, nephropathy, sarcoidosis, scleroderma, anaphylaxis, diabetes, diabetes mellitus type 1, diabetes mellitus type 2, diabetic retinopathy, Still's disease, vasculitis, sarcoidosis, pulmonary inflammation, acute respiratory distress syndrome, wet and dry age-related macular degeneration, autoimmune hemolytic syndromes, autoimmune and inflammatory hepatitis, autoimmune neuropathy, autoimmune ovarian failure, autoimmune orchitis, autoimmune thrombocytopenia, silicone implant associated autoimmune disease, Sjogren's syndrome, familial Mediterranean fever, systemic lupus erythematosus, vasculitis syndromes, temporal, Takayasu's and giant cell arteritis, Behçet's disease, Wegener's granulomatosis, vitiligo, secondary hematologic manifestation of autoimmune diseases, anemias, drug-induced autoimmunity, Hashimoto's thyroiditis, hypophysitis, idiopathic

thrombocytic pupura, metal-induced autoimmunity, myasthenia gravis, pemphigus, autoimmune deafness, Meniere's disease, Goodpasture's syndrome, Graves' disease, HW-related autoimmune syndromes, Gullain-Barre disease, Addison's disease, anti-phospholipid syndrome, asthma, atopic dermatitis, Celiac disease, Cushing's syndrome, dermatomyositis, idiopathic adrenal atrophy, idiopathic thrombocytopenia, Kawasaki syndrome, Lambert-Eaton Syndrome, pernicious anemia, pollinosis, polyarteritis nodosa, primary biliary cirrhosis, primary sclerosing cholangitis, Raynaud's, Reiter's Syndrome, relapsing polychondritis, Schmidt's syndrome, thyrotoxicosis, sepsis, septic shock, endotoxic shock, exotoxin-induced toxic shock, gram negative sepsis, toxic shock syndrome, glomerulonephritis, peritonitis, interstitial cystitis, hyperoxia-induced inflammations, chronic obstructive pulmonary disease (COPD), vasculitis, graft vs. host reaction, graft vs. host disease, allograft rejections, acute allograft rejection, chronic allograft rejection, early transplantation rejection, acute allograft rejection, reperfusion injury, pain, acute pain, chronic pain, neuropathic pain, fibromyalgia, chronic infections, meningitis, encephalitis, myocarditis, gingivitis, post surgical trauma, tissue injury, traumatic brain injury, enterocolitis, sinusitis, uveitis, ocular inflammation, optic neuritis, gastric ulcers, esophagitis, peritonitis, periodontitis, dermatomyositis, gastritis, myositis, polymyalgia, pneumonia and bronchitis; or

(ii) the MK2-mediated disease or disorder is a fibrotic disorder is selected from the group consisting of systemic sclerosis/scleroderma, lupus nephritis, connective tissue disease, wound healing, surgical scarring, spinal cord injury, CNS scarring, acute lung injury, pulmonary fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, acute lung injury, drug-induced lung injury, glomerulonephritis, chronic kidney disease, diabetic nephropathy, hypertension-induced nephropathy, alimentary track or gastrointestinal fibrosis, renal fibrosis, hepatic or biliary fibrosis, liver fibrosis, nonalcoholic steatohepatitis, hepatitis C, hepatocellular carcinoma, cirrhosis, primary biliary cirrhosis, cirrhosis due to fatty liver disease cirrhosis due to alcoholic fatty liver disease, cirrhosis due to nonalcoholic steatosis/non-alcoholic fatty liver disease, radiation-induced fibrosis head and neck fibrosis, gastrointestinal fibrosis, pulmonary fibrosis, primary sclerosing cholangitis, restenosis, cardiac fibrosis, endomyocardial fibrosis, atrial fibrosis, opthalmic scarring, fibrosclerosis, fibrotic cancers, fibroids, fibroma, fibroadenomas, fibrosarcomas, transplant arteriopathy, keloid, mediastinal fibrosis, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis, and nephrogenic systemic fibrosis; or

- (iii) the MK2-mediated disease or disorder is a metabolic disorder is selected from the group consisting of obesity, steroid-resistance, glucose intolerance, and metabolic syndrome; or
- (iv) the MK2-mediated disease or disorder is a neoplasia is selected from the group consisting of angiogenesis disorders, multiple myeloma, leukemias, acute lymphocytic leukemia, acute and chronic myelogenous leukemia, chronic lymphocytic leukemia, acute lymphoblastic leukemia, promyelocytic leukemia, lymphomas, B-cell lymphoma, T-cell lymphoma, mantle cell lymphoma, hairy cell lymphoma, Burkitt's lymphoma, mast cell tumors, Hodgkin's disease, non-Hodgkin's disease, myelodysplastic syndrome, fibrosarcoma, rhabdomyosarcoma; astrocytoma, neuroblastoma, glioma, schwannomas, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentosum, keratocanthoma, thyroid follicular cancer, Kaposi's sarcoma, melanoma, teratoma, rhabdomyosarcoma, metastatic and bone disorders, cancer of the bone, mouth/pharynx, esophagus, larynx, stomach, intestine, colon, rectum, lung, , liver, pancreas, nerve, brain, , head and neck, throat, ovary, uterus, prostate, testis, bladder, kidney, breast, gall bladder, cervix, thyroid, prostate, and skin, non-small cell lung cancer, small cell lung cancer, glioma, and glioblastoma multiforme; or
- (v) the MK2-mediated disease or disorder is a cardiovascular or cerebrovascular disorder is selected from the group consisting of atherosclerosis, restenosis of an atherosclerotic coronary artery, acute coronary syndrome, myocardial infarction, cardiac-allograft vasculopathy, stroke, central nervous system disorders with an inflammatory or apoptotic component, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, neuronal ischemia and peripheral neuropathy.

20. The use according to claim 19, wherein the MK2-mediated disease or disorder is psoriasis.

21. The use according to claim 19, wherein the MK2-mediated disease or disorder is rheumatoid arthritis.

22. The use according to claim 19, wherein the MK2-mediated disease or disorder is psoriatic arthritis.

23. The use according to claim 19, wherein the MK2-mediated disease or disorder is ankylosing spondylitis.

24. A composition according to claim 16 or 17, for use in therapy.