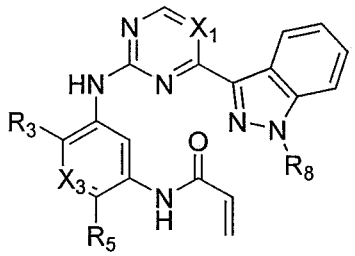
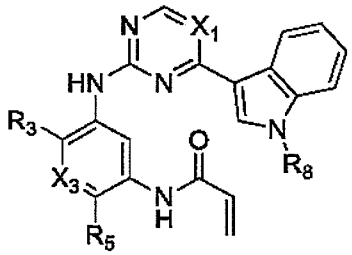
[35] Formula I includes a compound of Formula Bi:



Formula Bi

[35a] In one aspect, provided herein is a compound of Formula Bf:



Formula Bf

or a pharmaceutically acceptable form thereof, wherein:

X_1 is CR_1;

X_3 is CR_4;

R_1 is selected from amido and ester, which is substituted with 0, 1, 2, or 3 R_{12};

R_3, and R_4 are each independently selected from H, alkyl, alkoxy, halo, CN, and NO_2, each of which is substituted with 0, 1, 2, or 3 R_{12};

R_5 is selected from H, alkyl, alkenyl, alkynyl, $-NR_{10}R_{11}$, $-OR_{11}$, and $-SR_{11}$, each of which is independently substituted with 0, 1, 2, or 3 R_{12}; or when R_5 is $-NR_{10}R_{11}$, then R_{10} and R_{11} can be taken together with the nitrogen atom to which they are attached to form a heterocyclyl or heteroaryl group, each of which is substituted with 0, 1, 2, or 3 R_{12};

R_4 and R_5 can be taken together with the carbon atoms to which they are attached to form a cycloalkyl, heterocyclyl, aryl, or heteroaryl group, each of which is independently substituted with 0, 1, 2, or 3 R_{12};

R_8 is selected from H, acyl, alkyl, cycloalkyl, amido, amino, carbamate, carbonyl, and urea, each of which is substituted with 0, 1, 2, or 3 R_{12};

each R_{10} and R_{11} are independently selected from H, acyl, alkyl, carbonyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, each of which is independently substituted with 0, 1, 2, or 3 R_{12}; and

each R_{12} is independently selected from acyl, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, alkoxycarbonyl, amido, amino, carbonate, carbamate, carbonyl, ester, halo, CN, NO_2, hydroxyl, phosphate, phosphonate, phosphinate, phosphine oxide, thio, alkylthio, arylthio, thiocarbonyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl.

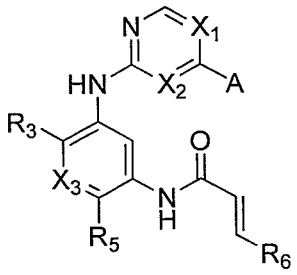
[35b] In one aspect, provided herein is a compound as disclosed herein, or a pharmaceutically acceptable form thereof for use in therapy.

[35c] In one aspect, provided herein is a use of a compound as disclosed herein, or a pharmaceutically acceptable form thereof in the manufacture of a medicament for treating a cancer, which is associated with one or more insertion or deletion mutations in the exon 20 domain of EGFR or HER2.

[36] A method is also disclosed herein for treating cancer associated with one or more insertion or deletion mutations in the exon 20 domain of EGFR or of HER2, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formula I.

[37] A composition (e.g., a pharmaceutical composition) is also disclosed comprising a compound as described herein and one or more pharmaceutically acceptable excipients. In some embodiments, provided herein is a method of inhibiting exon 20 mutant EGFR, comprising contacting the exon 20 mutant EGFR with an effective amount of a compound or pharmaceutical composition as described herein. In some embodiments, a method is provided for inhibiting exon 20 mutant EGFR wherein said exon 20 mutant EGFR is present in a cell. This inhibition can be selective for exon 20 mutant EGFR over wild type. In other aspects, the inhibition can take place in a subject suffering from a disorder selected from various cancers, such as but not limited to, NSCLC, colorectal cancer, pancreatic cancer, and head and neck cancers. In some embodiments, a second therapeutic agent can be administered to the subject.

[38] In one aspect, provided herein are compounds of Formula I:

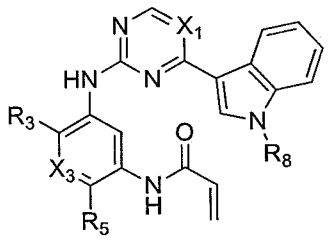


Formula I

wherein:

WHAT IS CLAIMED IS:

1. A compound of Formula Bf:



Formula Bf

or a pharmaceutically acceptable form thereof, wherein:

X_1 is CR_1;

X_3 is CR_4;

R_1 is selected from amido and ester, which is substituted with 0, 1, 2, or 3 R_{12};

R_3, and R_4 are each independently selected from H, alkyl, alkoxy, halo, CN, and NO_2, each of which is substituted with 0, 1, 2, or 3 R_{12};

R_5 is selected from H, alkyl, alkenyl, alkynyl, $-NR_{10}R_{11}$, $-OR_{11}$, and $-SR_{11}$, each of which is independently substituted with 0, 1, 2, or 3 R_{12}; or when R_5 is $-NR_{10}R_{11}$, then R_{10} and R_{11} can be taken together with the nitrogen atom to which they are attached to form a heterocyclyl or heteroaryl group, each of which is substituted with 0, 1, 2, or 3 R_{12};

R_4 and R_5 can be taken together with the carbon atoms to which they are attached to form a cycloalkyl, heterocyclyl, aryl, or heteroaryl group, each of which is independently substituted with 0, 1, 2, or 3 R_{12};

R_8 is selected from H, acyl, alkyl, cycloalkyl, amido, amino, carbamate, carbonyl, and urea, each of which is substituted with 0, 1, 2, or 3 R_{12};

each R_{10} and R_{11} are independently selected from H, acyl, alkyl, carbonyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, each of which is independently substituted with 0, 1, 2, or 3 R_{12}; anda

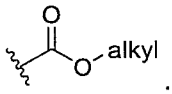
each R_{12} is independently selected from acyl, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, alkoxycarbonyl, amido, amino, carbonate, carbamate, carbonyl, ester, halo, CN, NO_2, hydroxyl,

phosphate, phosphonate, phosphinate, phosphine oxide, thio, alkylthio, arylthio, thiocarbonyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl.

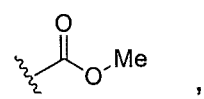
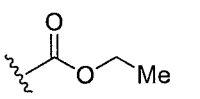
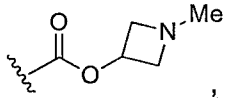
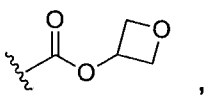
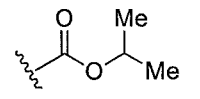
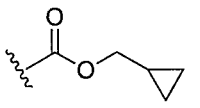
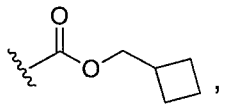
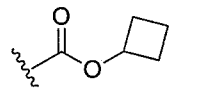
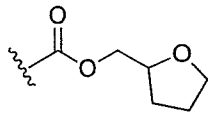
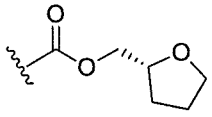
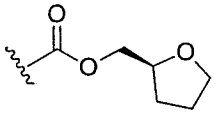
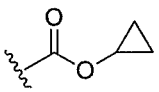
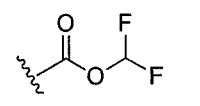
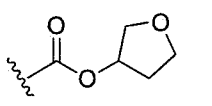
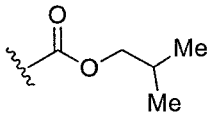
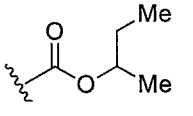
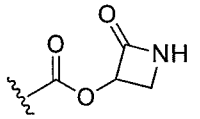
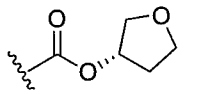
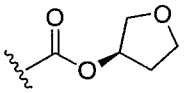
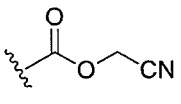
2. The compound or pharmaceutically acceptable form according to claim 1, wherein X_1 is CR_1; and R_1 is ester.

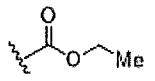
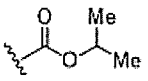
3. The compound or pharmaceutically acceptable form according to claim 1 or 2, wherein X_3 is CR_4, and R_4 is H.

4. The compound or pharmaceutically acceptable form according to claim 2, wherein R_1 is



5. The compound or pharmaceutically acceptable form according to claim 1, 2, or 3, wherein the ester is selected from


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6. The compound or pharmaceutically acceptable form according to claim 4, wherein R_1 is  , and  .

7. The compound or pharmaceutically acceptable form according to claim 1, 2, or 3, wherein R_3 is selected from H and alkoxy.

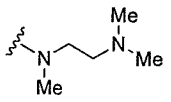
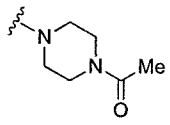
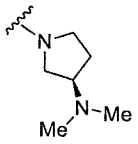
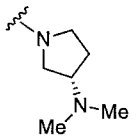
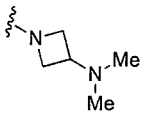
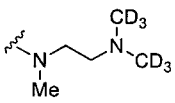
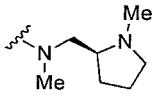
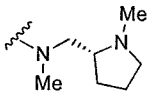
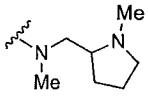
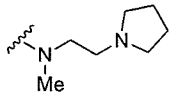
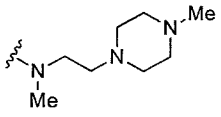
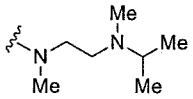
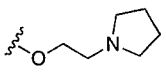
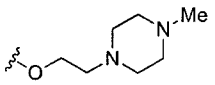
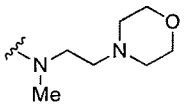
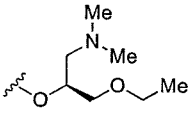
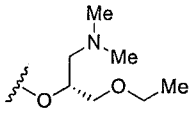
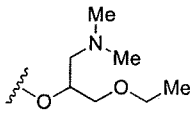
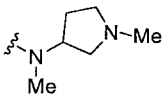
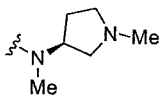
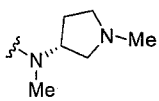
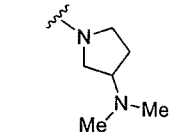
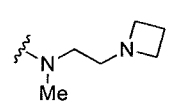
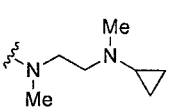
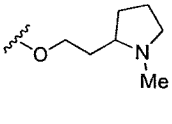
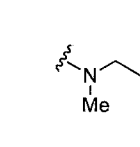
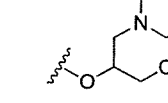
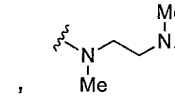
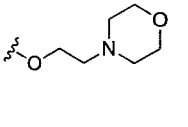
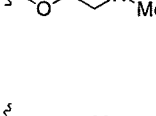
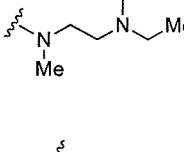
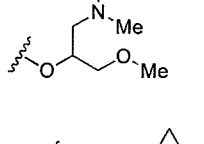
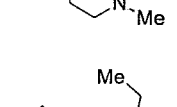
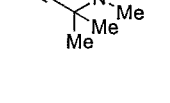
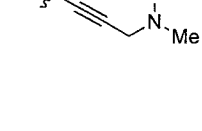
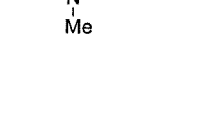
8. The compound or pharmaceutically acceptable form according to claim 7, wherein the alkoxy is –OMe.

9. The compound or pharmaceutically acceptable form according to claim 1, 2, or 3, wherein R_5 is –$NR_{10}R_{11}$, R_{10} is alkyl, R_{11} is alkyl substituted with 1 or 2 R_{12}, and R_{12} is amino or heterocyclyl.

10. The compound or pharmaceutically acceptable form according to claim 1, 2, or 3, wherein R_5 is –$NR_{10}R_{11}$, and R_{10} and R_{11} are taken together with the nitrogen atom to which they are attached to form a heterocyclyl or heteroaryl group, substituted with 0 or 1 R_{12}.

11. The compound or pharmaceutically acceptable form according to claim 1, 2, or 3, wherein R_5 is –OR_{11}, R_{11} is alkyl substituted with 0, 1 or 2 R_{12}, and each R_{12} is independently selected from heterocyclyl, heterocyclylalkyl, alkoxyalkyl, and aminoalkyl.

12. The compound or pharmaceutically acceptable form according to claim 1, 2, or 3, wherein R_5 is selected from


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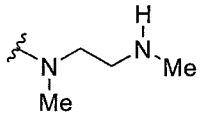
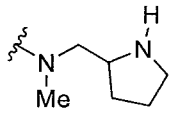
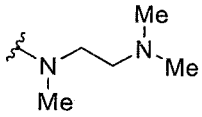
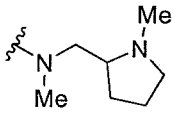
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13. The compound or pharmaceutically acceptable form according to claim 1, 2, or 3, wherein R_5 is selected from  ,  ,  and  .

14. The compound or pharmaceutically acceptable form according to claim 1, wherein:

X_1 is CR_1;

X_3 is CR_4;

R_1 is ester;

R_3 is alkoxy;

R_4 is H;

R_5 is $-NR_{10}R_{11}$;

R_8 is selected from H and alkyl;

R_{10} is alkyl; and

R_{11} is alkyl substituted with one R_{12}, and R_{12} is substituted with amino or heterocyclyl.

15. The compound or pharmaceutically acceptable form according to claim 1, wherein:

X_1 is CR_1;

X_3 is CR_4;

R_1 is ester;

R_3 is alkoxy;

R_4 is H;

R_5 is selected from H, alkynyl, $-NR_{10}R_{11}$, and $-OR_{11}$, each of which is independently substituted with 0, 1, or 2 R_{12}, and R_{12} is amino, alkoxy, or heterocyclyl; or when R_5 is $-NR_{10}R_{11}$, then R_{10} and R_{11} can be taken together with the nitrogen atom to which they are attached to form a heterocyclyl or heteroaryl group, each of which is substituted with 1 R_{12}, and R_{12} is alkyl or amino;

R_8 is alkyl; and

R_{10} and R_{11} are each independently alkyl, each of which is independently substituted with 0, 1, or 2 R_{12}, and R_{12} is amino, alkoxy, or heterocyclyl.

16. The compound or pharmaceutically acceptable form according to claim 1, wherein the compound of Formula Bf is a compound selected from:

Sec-butyl 2-((5-acrylamido-4-((2-(dimethylamino)ethyl)(methyl)amino)-2-methoxyphenyl)amino)-4-(1-methyl-1H-indol-3-yl)pyrimidine-5-carboxylate;

Isobutyl 2-((5-acrylamido-4-((2-(dimethylamino)ethyl)(methyl)amino)-2-methoxyphenyl)amino)-4-(1-methyl-1H-indol-3-yl)pyrimidine-5-carboxylate;

Cyclopropylmethyl 2-((5-acrylamido-4-((2-(dimethylamino)ethyl)(methyl)amino)-2-methoxyphenyl)amino)-4-(1-methyl-1H-indol-3-yl)pyrimidine-5-carboxylate;

Cyclobutyl 2-((5-acrylamido-4-((2-(dimethylamino)ethyl)(methyl)amino)-2-methoxyphenyl)amino)-4-(1-methyl-1H-indol-3-yl)pyrimidine-5-carboxylate;

Methyl 2-((5-acrylamido-4-((2-(dimethylamino)ethyl)(methyl)amino)-2-methoxyphenyl)amino)-4-(1-methyl-1H-indol-3-yl)pyrimidine-5-carboxylate;

Oxetan-3-yl 2-((5-acrylamido-4-((2-(dimethylamino)ethyl)(methyl)amino)-2-methoxyphenyl)amino)-4-(1-methyl-1H-indol-3-yl)pyrimidine-5-carboxylate;

Isopropyl 2-((5-acrylamido-2-methoxy-4-(methyl((1-methylpyrrolidin-2-yl)methyl)amino)phenyl)amino)-4-(1-methyl-1H-indol-3-yl)pyrimidine-5-carboxylate;

Ethyl 2-((5-acrylamido-4-((2-(dimethylamino)ethyl)(methyl)amino)-2-methoxyphenyl)amino)-4-(1-methyl-1H-indol-3-yl)pyrimidine-5-carboxylate;

Isopropyl 2-((5-acrylamido-4-((2-(dimethylamino)ethyl)(methyl)amino)-2-methoxyphenyl)amino)-4-(1-methyl-1H-indol-3-yl)pyrimidine-5-carboxylate;

N-(2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxy-5-((4-(1-methyl-1H-indol-3-yl)-5-pivalamidopyrimidin-2-yl)amino)phenyl)acrylamide;

Isopropyl 2-((5-acrylamido-2-methoxy-4-(methyl(2-(methylamino)ethyl)-amino)phenyl)amino)-4-(1-methyl-1H-indol-3-yl)pyrimidine-5-carboxylate;

N-(2-((2-(dimethylamino)ethyl)(methyl)-amino)-4-methoxy-5-((4-(1-methyl-1H-indol-3-yl)-5-(N-methylisobutyramido)-pyrimidin-2-yl)amino)phenyl)acrylamide;

N-(2-((2-(dimethylamino)ethyl)(methyl)amino)-5-((5-isobutyramido-4-(1-methyl-1H-indol-3-yl)pyrimidin-2-yl)amino)-4-methoxyphenyl)acrylamide;

Isopropyl 2-((5-acrylamido-4-((2-(dimethylamino)ethyl)(methyl)amino)-2-methoxyphenyl)amino)-4-(1H-indol-3-yl)pyrimidine-5-carboxylate;

Methyl 2-((5-acrylamido-2-methoxy-4-(methyl((1-methylpyrrolidin-2-yl)methyl)amino)phenyl)amino)-4-(1-methyl-1H-indol-3-yl)pyrimidine-5-carboxylate;

Isopropyl (*R*)-2-((5-acrylamido-2-methoxy-4-(methyl((1-methylpyrrolidin-2-yl)methyl)amino)phenyl)amino)-4-(1*H*-indol-3-yl)pyrimidine-5-carboxylate;

Ethyl (*R*)-2-((5-acrylamido-2-methoxy-4-(methyl((1-methylpyrrolidin-2-yl)methyl)amino)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylate;

Isopropyl 2-((5-acrylamido-4-(2-(dimethylamino)ethoxy)-2-methoxyphenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylate;

Methyl 2-((5-acrylamido-4-(3-(dimethylamino)prop-1-yn-1-yl)-2-methoxyphenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylate;

Methyl 2-((5-acrylamido-4-(3-(dimethylamino)propyl)-2-methoxyphenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylate;

Methyl 2-((5-acrylamido-4-((2-(dimethylamino)ethyl)(methyl)amino)-2-methoxyphenyl)amino)-4-(1-(dimethylamino)-1H-indol-3-yl)pyrimidine-5-carboxylate;

Isopropyl 2-((5-acrylamido-4-((2-(dimethylamino)ethyl)(methyl)amino)-2-methoxyphenyl)amino)-4-(1-ethyl-1H-indol-3-yl)pyrimidine-5-carboxylate;

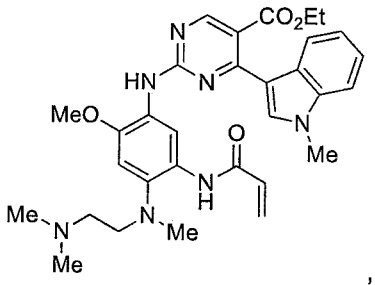
Isopropyl 4-(1-acetyl-1H-indol-3-yl)-2-((5-acrylamido-4-((2-(dimethylamino)ethyl)(methyl)amino)-2-methoxyphenyl)amino)pyrimidine-5-carboxylate;

Isopropyl 2-((5-acrylamido-4-((2-(dimethylamino)ethyl)(methyl)amino)-2-methoxyphenyl)amino)-4-(1-cyclopropyl-1H-indol-3-yl)pyrimidine-5-carboxylate; and

N-(2,4-dimethoxy-5-((4-(1-methyl-1H-indol-3-yl)-5-pivalamidopyrimidin-2-yl)amino)phenyl)acrylamide;

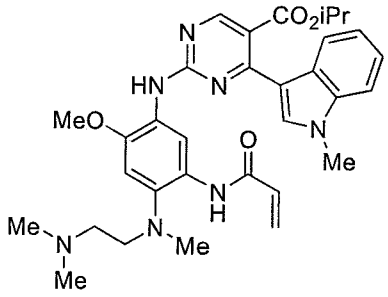
or a pharmaceutically acceptable form thereof.

17. The compound according to claim 1, wherein the compound of Formula Bf is:



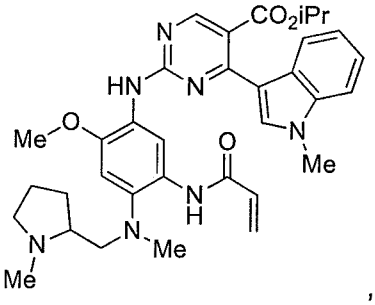
, or a pharmaceutically acceptable form thereof.

18. The compound according to claim 1, wherein the compound of Formula Bf is:



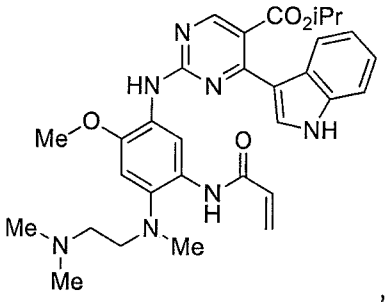
, or a pharmaceutically acceptable form thereof.

19. The compound according to claim 1, wherein the compound of Formula Bf is:



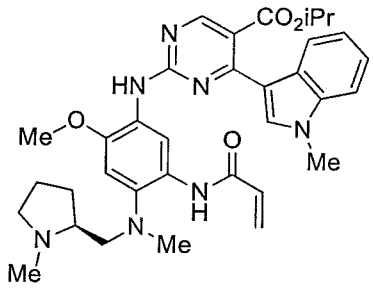
, or a pharmaceutically acceptable form thereof.

20. The compound according to claim 1, wherein the compound of Formula Bf is:



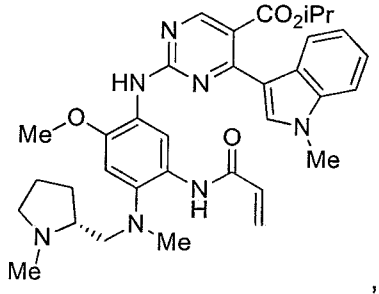
, or a pharmaceutically acceptable form thereof.

21. The compound according to claim 1, wherein the compound of Formula Bf is:



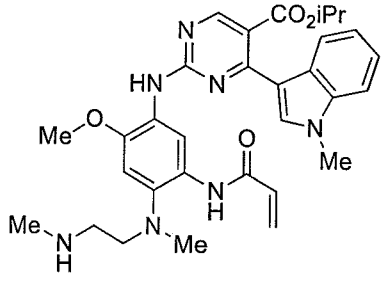
, or a pharmaceutically acceptable form thereof.

22. The compound according to claim 1, wherein the compound of Formula Bf is:



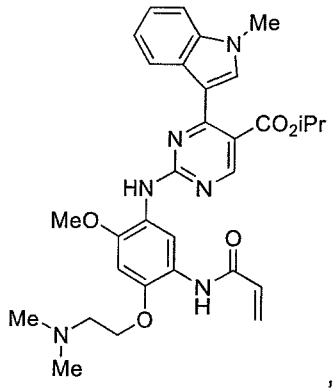
, or a pharmaceutically acceptable form thereof.

23. The compound according to claim 1, wherein the compound of Formula Bf is:



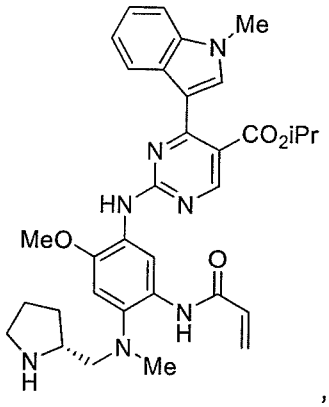
, or a pharmaceutically acceptable form thereof.

24. The compound according to claim 1, wherein the compound of Formula Bf is:



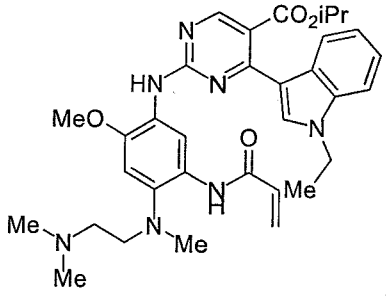
, or a pharmaceutically acceptable form thereof.

25. The compound according to claim 1, wherein the compound of Formula Bf is:



, or a pharmaceutically acceptable form thereof.

26. The compound according to claim 1, wherein the compound of Formula Bf is:



, or a pharmaceutically acceptable form thereof.

27. A pharmaceutical composition comprising a compound or pharmaceutically acceptable form of any one of claims 1-26, and a pharmaceutically acceptable carrier, diluent, or vehicle.

28. The compound according to any one of claims 1-26, or a pharmaceutically acceptable form thereof for use in therapy.

29. Use of a compound according to any one of claims 1-26, or a pharmaceutically acceptable form thereof in the manufacture of a medicament for treating a cancer, which is associated with one or more insertion or deletion mutations in the exon 20 domain of EGFR or HER2.

30. The use of claim 29, wherein the cancer is lung cancer, colorectal cancer, pancreatic cancer, head and neck cancers, breast cancer, ovarian cancer, uterine cancer, or stomach cancer.

31. The use of claim 29, wherein the cancer is non-small cell lung cancer (NSCLC).