



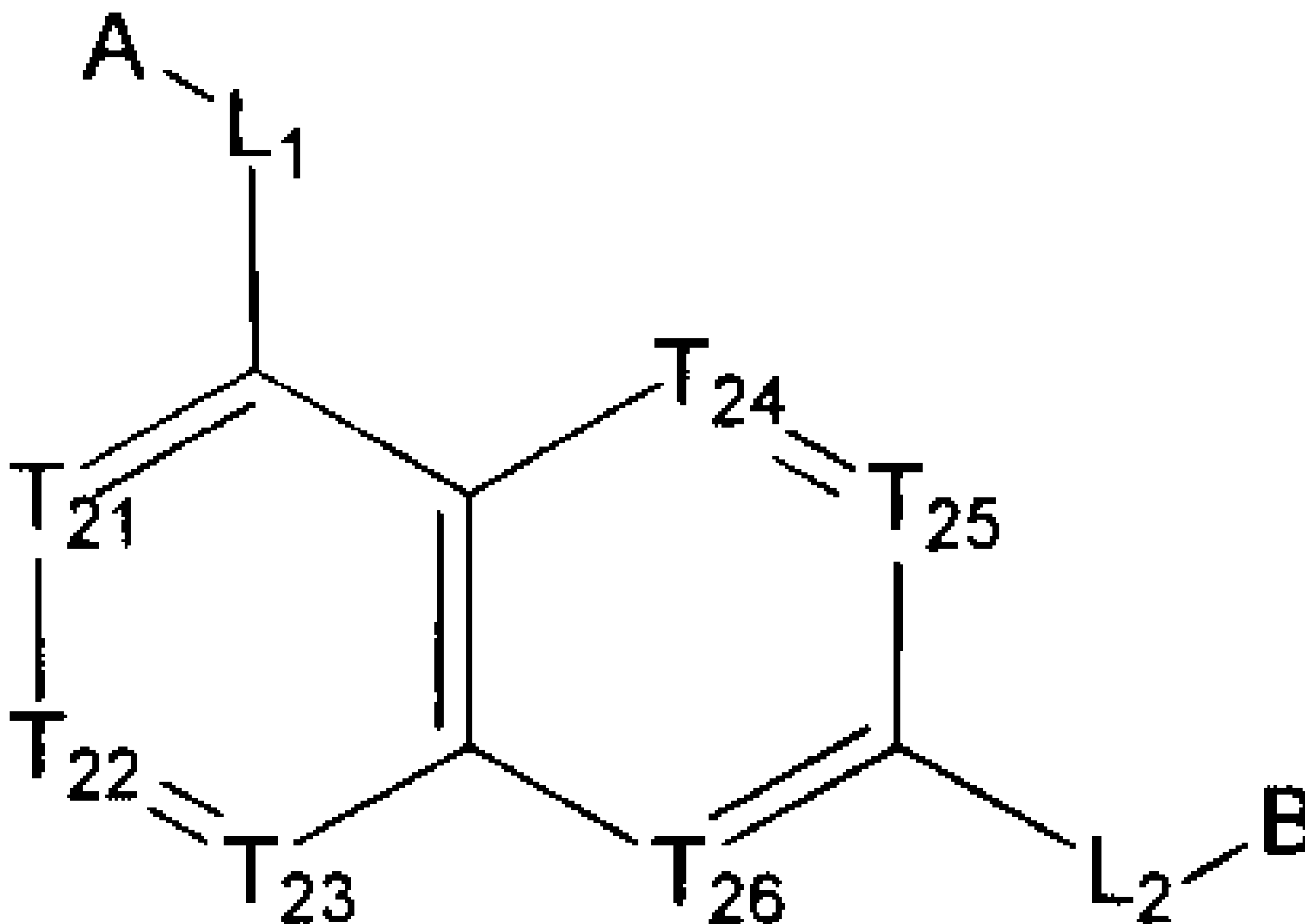
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(54) **Titre : DERIVES DE QUINOLEINE COMME INHIBITEURS DE SMO**

(54) **Title: QUINOLINE DERIVATIVES AS SMO INHIBITORS**



(57) **Abrégé/Abstract:**

Disclosed are quinoline derivatives as hedgehog pathway inhibitors, especially as SMO inhibitors. Compounds of the present invention can be used in treating diseases relating to hedgehog pathway including cancer.

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Abstract

Disclosed are quinoline derivatives as hedgehog pathway inhibitors, especially as SMO inhibitors. Compounds of the present invention can be used in treating diseases relating to hedgehog pathway including cancer.

Quinoline Derivatives as SMO Inhibitors

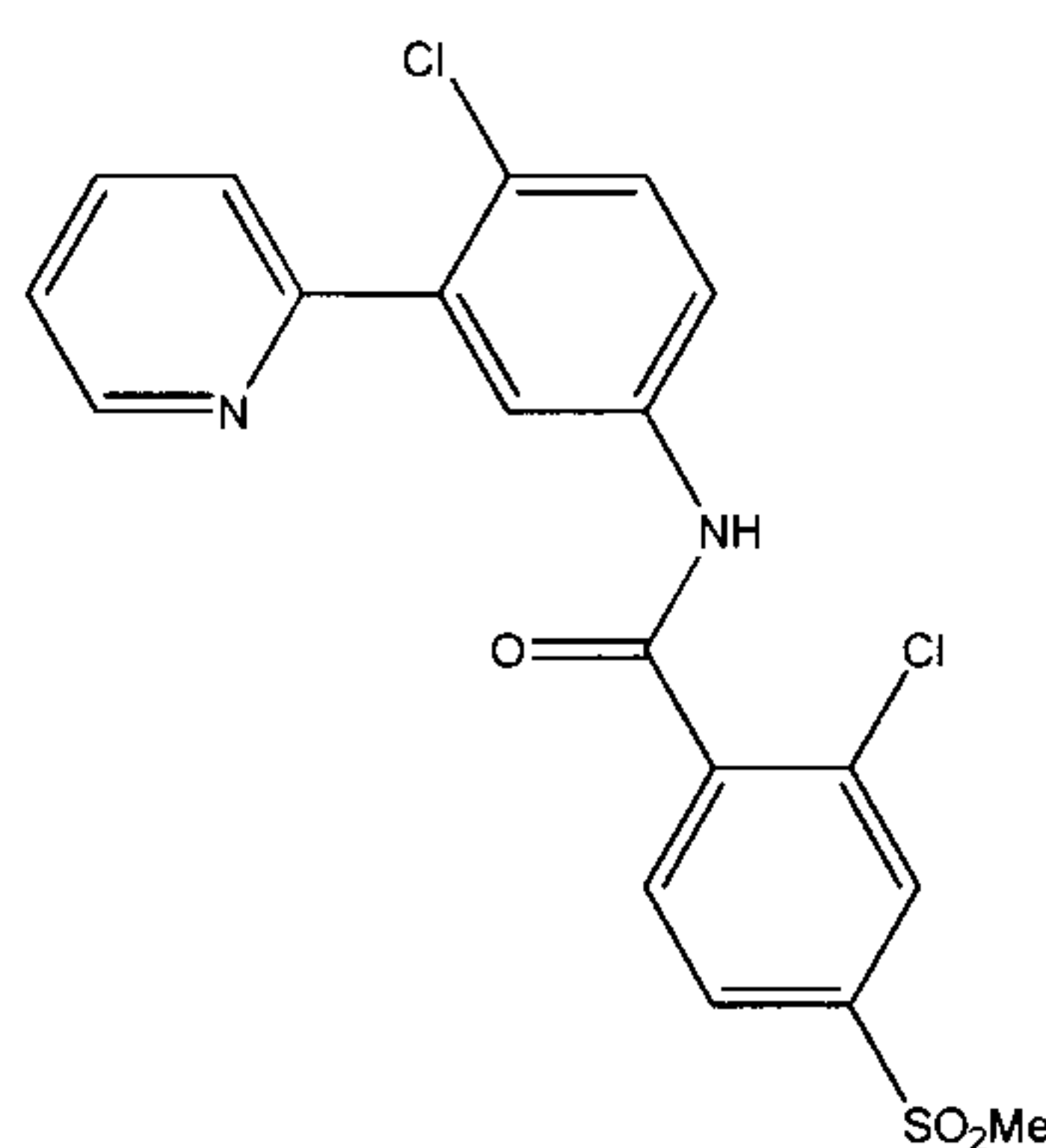
Field of invention

[1] The present invention relates to a series of quinoline derivatives, as hedgehog pathway inhibitors, especially as SMO inhibitors, compounds of the present invention can be used in treating diseases relating to hedgehog pathway including cancer.

Prior arts

[2] Hedgehog proteins are secreted signal proteins originally found in drosophila, they are highly hydrophobic proteins and play a critical role in embryonic development. Three types of homologous hedgehog proteins have already been identified in humans, which are sonic hedgehog (Shh), Indian hedgehog (Ihh) and Desert hedgehog (Dhh) respectively. Thereinto, Shh is not only essential for embryonic development and there are a lot of evidence showing that it also plays an important role in the carcinogenesis mechanism of some cancers including basal cell carcinoma and so on. (Caro, I. and J. A. Low, Clin Cancer Res, 2010. 16 (13): 3335-9). *In vivo* Shh synthesizes a precursor protein with a molecular weight of 45 kDa, produces a N-terminal fragment with a molecular weight of 20 kDa by self-excision, the N-terminal fragment is of all the known biological activities *in vivo*, including activating an intracellular hedgehog signaling pathway whose key members embraces patched (PTCH), GPCRs-like receptors oncogene smoothened (SMO) and transcription factor Gli, etc.. (Bale, A. E. and K. P. Yu, Hum Mol Genet, 2001. 10 (7): 757-62). Analysis results of the variation in basal cell carcinoma hedgehog signaling pathway show that most of the variation occurs in PTCH-1 and SMO. (Von Hoff, D. D., et al., N Engl J Med, 2009. 361 (12): 1164-72). PTCH-1 is a membrane protein with a 12-transmembrane structure, which is a direct receptor of Shh. In the absence of Shh, PTCH-1 interacts with SMO, which is a 7-transmembrane protein, to inhibit the biological activity of SMO. The binding of Shh and PTCH-1 leads to a removal of PTCH-1 from SMO thereby making SMO loose from being inhibited. Gli transcription factor is controlled by SMO which is as a switch of gene transcription and whose key members include Gli1, Gli2 and Gli3. The whole hedgehog pathway plays an important role in normal embryonic development. Disrupting this signaling pathway will cause serious malformation, the natural teratogenic compound cyclopamine is an example which is a hedgehog inhibitor. Usually, the concentration of hedgehog protein in an adult human body is very low. In the case of low hedgehog protein concentration, PTCH-1 binds to SMO thereby inhibiting the biological activity of SMO, so that the whole pathway is inactive or of very low activity. When the cells secrete hedgehog protein, the binding of hedgehog to the PTCH-1 receptor leads to its removal from SMO, thereby losing inhibition effect on SMO. SMO further activates transcription factor Gli-1 to regulate gene transcription and cell growth. Increasing evidence indicates that the majority of the basal cell carcinoma is caused by overhigh hedgehog signaling pathway activity led by mutations or other causes. Thus, inhibiting the overhigh

activity of hedgehog signaling pathway can inhibit the growth of cancer cells so as to achieve the treatment of basal cell carcinoma or other cancers caused by the same mechanism. The evidence that SMO's constitutive activation leads to cancer (e.g. BCC) as well as relieving the inhibition from Ptch makes SMO cause cancer illustrates the use of SMO antagonist as therapeutic agents in the treatment of the diseases (Stone, et al., (1996) Nature 384: 129). A series of scientific and clinical trials show that hedgehog inhibitors are effective in the treatment of many cancers. The latest clinical trial data show that hedgehog inhibitor GDC-0449 is effective in the treatment of basal cell carcinoma and medullary cell carcinoma (LorussoPM. et al. Clin Cancer Res. 2011; 17 (8): 2502-11), which was licensed by FDA in January 2012, and the other cancers cause by the same mechanism, such as basal cell nevus syndrome (BCNS) (Goldberg LH. et al. Arch Dermatol. 2011 Mar 21.). Biochemical studies show that the inhibition position of GDC-0449 locates on SMO, inhibiting the activity of SMO means inhibiting the activity of the whole hedgehog pathway, so as to achieve the purpose of anti-cancer. In addition to the two types of cancers, basal cell carcinoma and medullary cell carcinoma, there are many other cancers related to the ultra-high activity of hedgehog signaling pathway, including pancreatic cancer, stomach cancer, colorectal cancer, ovarian cancer and prostate cancer, and part of leukemia etc. (De Smaele E. et al. Curr Opin Investig Drugs. 2010; 11(6): 707-18). Thus, there is a promising prospect of developing hedgehog inhibitors as novel anticancer drugs.

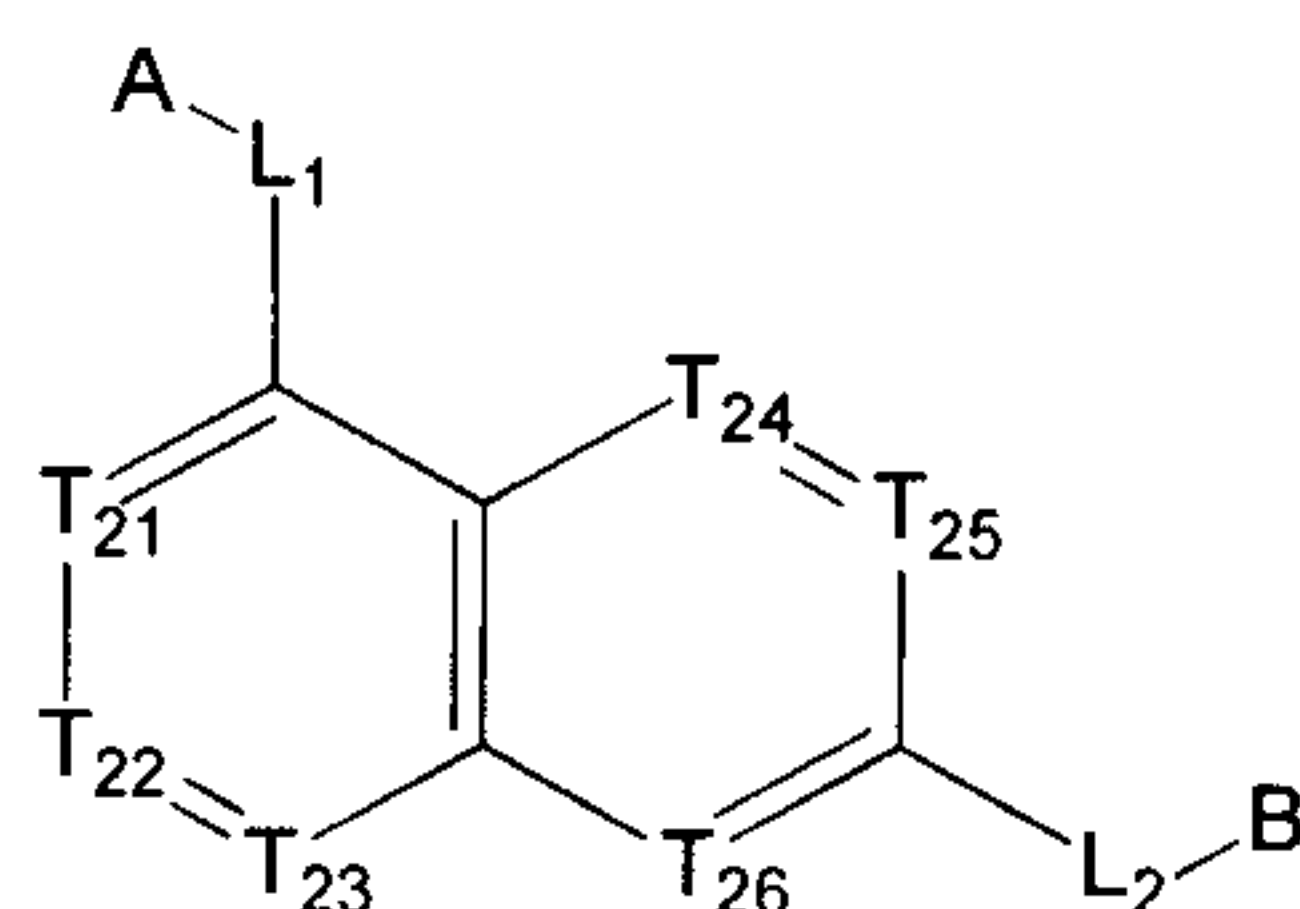


GDC-0449

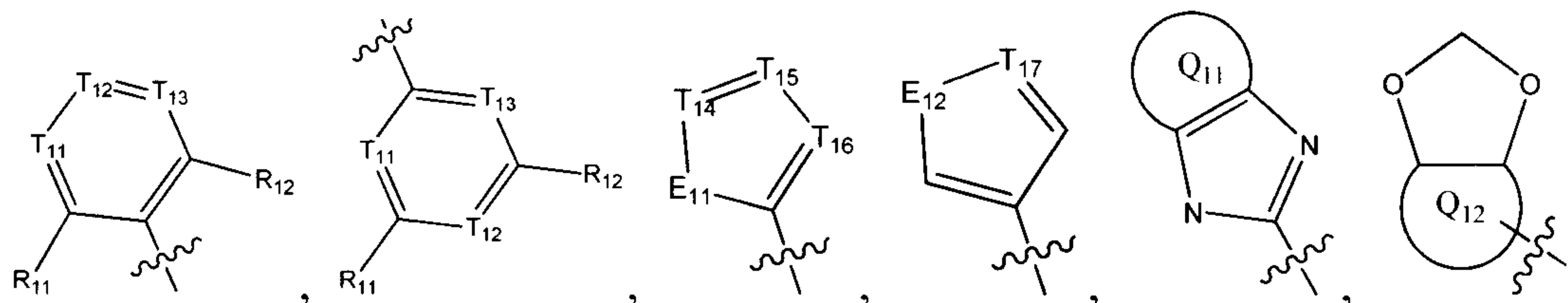
[3] Although there are some SMO inhibitors in the prior art, it still need to be further improved in the aspects of activity, solubility, pharmacokinetics, druggability and so on.

Content of the present invention

[4] The aim of the present invention is to provide a compound represented by formula (I) or a pharmaceutically acceptable salt thereof,



[5] wherein, A is selected from



$(R_{20})_3C-E_{13}-$;

[6] each of T_{11-17} is independently selected from N, C(R_{13});

[7] each of E_{11-13} , L_1 , L_2 is independently selected from $N(R_{14})$, $C(=O)N(R_{15})$, $S(=O)_2N(R_{16})$, $C=N(R_{17})$, $C(R_{18})(R_{19})$, S, $C(=O)O$, $C(=O)$, $C=S$, $S(=O)$ or $S(=O)_2$;

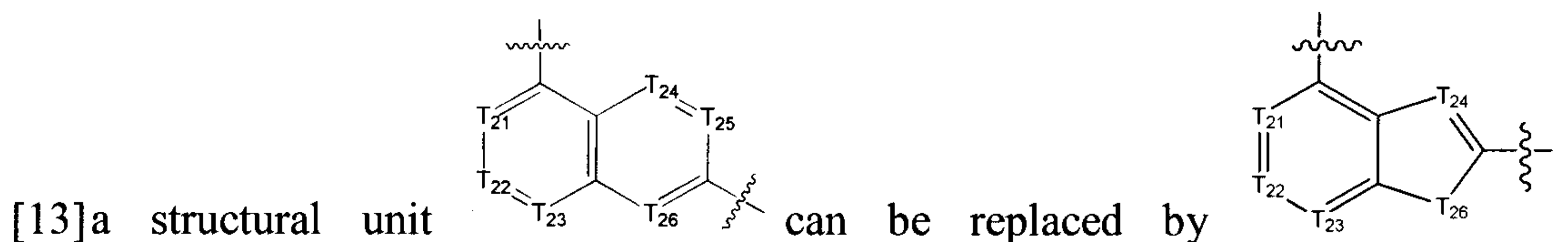
[8] each of L_1 , L_2 can also be independently selected from a single bond;

[9] each of R_{11-13} , R_{18-19} is independently selected from H, F, Cl, Br, I, CN, OH, SH, NH_2 , an optionally R_{01} -substituted C_{1-6} alkyl or heteroalkyl or alkyl-heteroatom group or heteroalkyl-heteroatom group, an optionally R_{02} -substituted C_{3-8} cyclic group or heterocyclic group or cycle-heteroatom group or heterocycle -heteroatom group; preferably selected from a methyl, a trifluoromethyl, a trifluoromethoxy, F, Cl, Br, I, CN, a methylaminocarbonyl, a methylsulfonyl, a trifluoromethylsulfonyl, a trifluoromethoxy, a cyclopropyl, a morpholiny sulfonyl, a 2-imidazolyl, a dimethylamino, a *n*-, or *iso*-propyl;

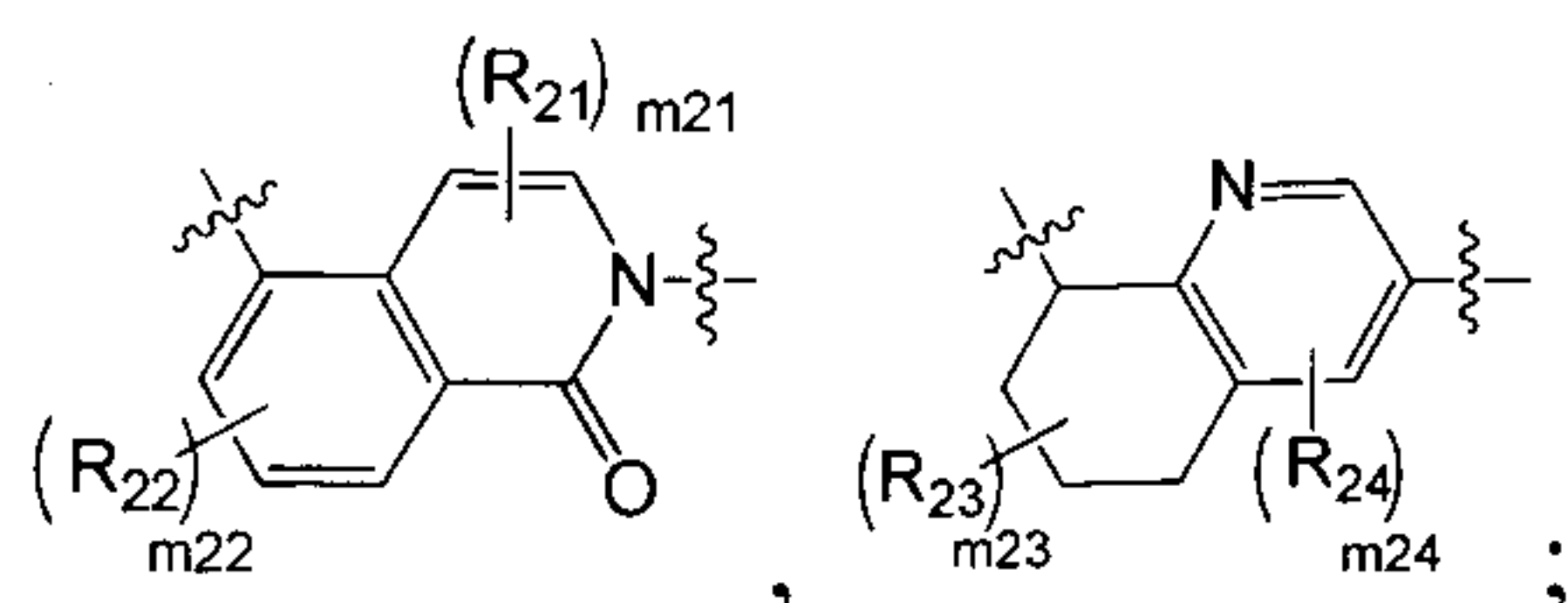
[10] each of R_{14-17} is independently selected from H, an optionally R_{01} -substituted C_{1-6} alkyl or C_{3-6} cycloalkyl;

[11] R_{20} is selected from H, F, Cl, Br, I, CN, OH, SH, NH_2 , a methoxy, a methylamino, a dimethylamino;

[12] each of Q_{11-12} is independently selected from a phenyl, a pyridyl, a thienyl, a furyl;

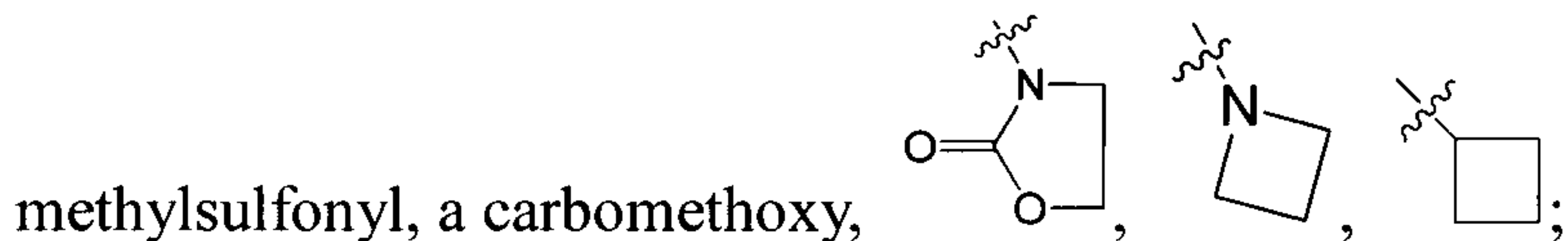


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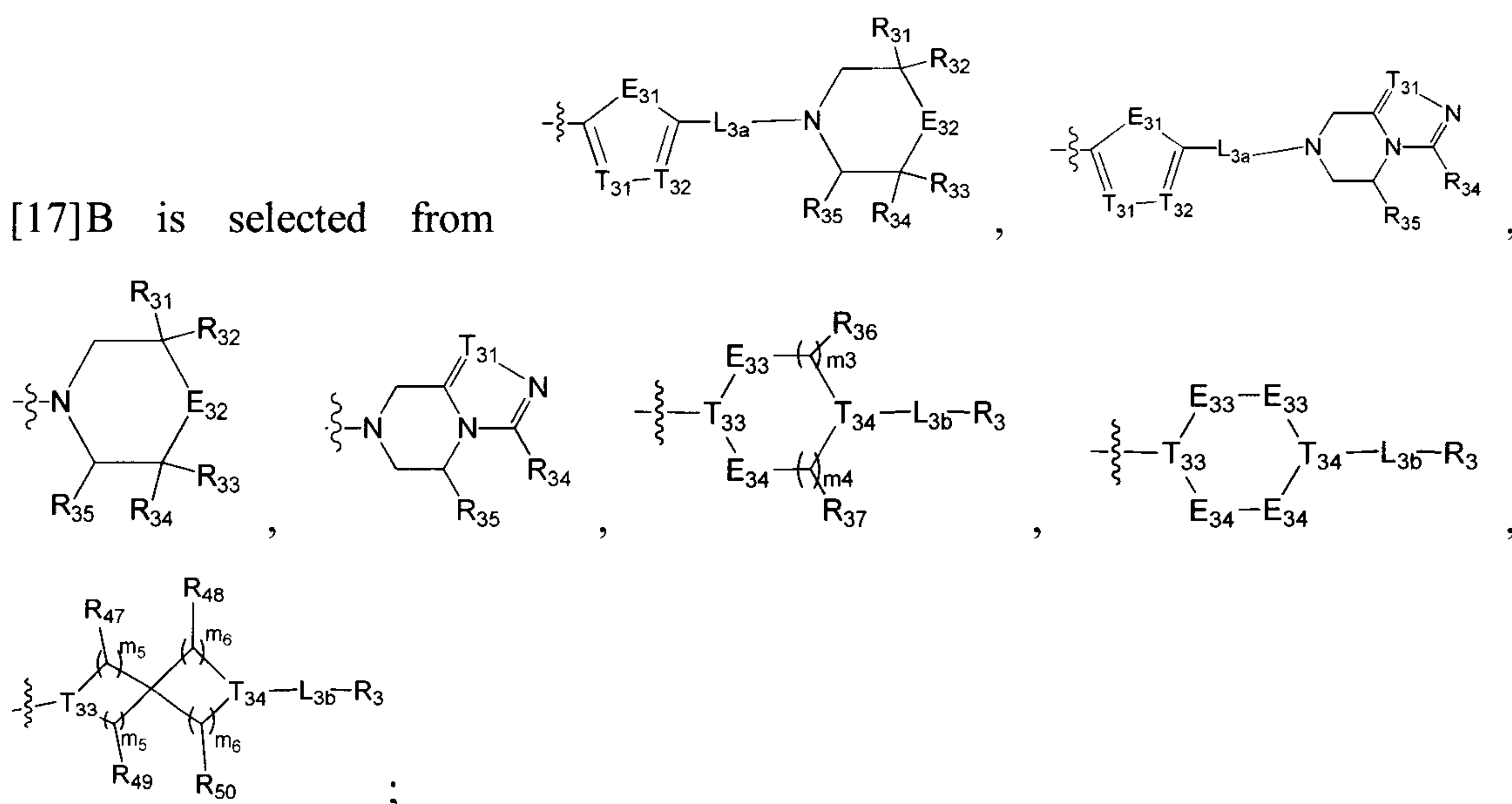


[14]each of T_{21-26} is independently selected from N, C(R_{25}); T_{25} can also be selected from $N^{\oplus}(R_{25})$;

[15]each of R_{21-25} is independently selected from H, F, Cl, Br, I, CN, OH, SH, NH_2 , an optionally R_{01} -substituted C_{1-6} alkyl or heteroalkyl or alkyl-heteroatom group or heteroalkyl-heteroatom group, an optionally R_{02} -substituted C_{3-8} cyclic group or heterocyclic group or cycle -heteroatom group or heterocycle-heteroatom group; preferably selected from F, Cl, Br, I, CN, OH, a methyl, an ethyl, an isopropyl, a methoxy, a trifluoromethyl, a difluoromethoxy, a *n*-, or *iso*-propoxy, a cyclopropyl, a formamido, a methanesulfonylamino, a dimethylamino, a dimethylaminoethoxy, a



[16]each of m_{21-24} is independently selected from 0,1 or 2;



[18] R_3 is selected from

H, an optionally R_{01} -substituted C_{1-6} alkyl or heteroalkyl or alkyl-heteroatom group or heteroalkyl-heteroatom group, an optionally R_{02} -substituted C_{3-8} cyclic group or heterocyclic group or cycle-heteroatom group or heterocycle-heteroatom group;

[19]each of E_{31-38} , L_{3a} , L_{3b} is independently selected from $N(R_{40})$, $N(R_{40})(CH_2)_{1-3}$,

$C(=O)N(R_{40})(CH_2)_{1-3}$, $C(=O)N(R_{41})$, $S(=O)_2N(R_{42})$, $C=N(R_{43})$, $C(R_{44})(R_{45})$, S , $C(=O)O$, $C(=O)$, $C=S$, $S(=O)$, $S(=O)_2$, O or $C(=O)C(R_{44})(R_{45})$;

[20] each of L_{3a} , L_{3b} can also be independently selected from a single bond or a C_{1-5} alkyl;

[21] each of E_{31} , E_{35} can also be independently selected from $-T_{39}=T_{40}-$;

[22] each of T_{31-40} is independently selected from N , $C(R_{46})$;

[23] each of R_{40-43} is independently selected from H , an optionally R_{01} -substituted C_{1-6} alkyl or C_{3-6} cycloalkyl, an optionally R_{01} -substituted C_{1-6} alkyl acyl or C_{3-6} cycloalkyl acyl, an optionally R_{01} -substituted C_{1-6} alkyl sulfonyl or C_{3-6} cycloalkyl sulfonyl, an optionally R_{01} -substituted 5-6 membered aryl acyl, an optionally R_{01} -substituted 5-6 membered heteroaryl acyl, an optionally R_{01} -substituted 5-6 membered aryl sulfonyl, an optionally R_{01} -substituted C_{1-6} alkyoxycarbonyl, an optionally R_{01} -substituted C_{1-6} alkyl amino carbonyl;

[24] each of R_{31-49} , R_{44-50} is independently selected from H , F , Cl , Br , I , CN , OH , SH , NH_2 , $C(=O)OH$, an optionally R_{01} -substituted C_{1-6} alkyl or heteroalkyl or alkyl-heteroatom group or heteroalkyl-heteroatom group, an optionally R_{02} -substituted C_{0-3} alkyl- C_{3-8} cyclic group or heterocyclic group or cycle-heteroatom group or heterocycle-heteroatom group;

[25] each of R_{01} , R_{02} is independently selected from F , Cl , Br , I , CN , OH , SH , NH_2 , R_{03} ;

[26] R_{03} is selected from a C_{1-6} alkyl amino, a $di(C_{1-6} \text{ alkyl})$ amino, a C_{1-6} alkoxy, a C_{3-8} cycloalkyl amino, a C_{3-8} heterocycloalkyl amino, a C_{3-8} cycloalkoxy;

[27] the heteroatom or the heteroatom group is independently selected from $C(=O)NR_{04}$, $N(R_{05})$, $C=N(R_{06})$, O , S , $C(=O)O$, $C(=O)$, $C=S$, $S(=O)$, $S(=O)_2$ and/ or $S(=O)_2N(R_{07})$;

[28] each of R_{04-07} is independently selected from H , R_{08} ;

[29] R_{08} is selected from a C_{1-6} alkyl or a C_{3-8} cycloalkyl;

[30] R_{03} , R_{08} are optionally substituted by R_{001} , R_{001} is selected from OH , $N(CH_3)_2$, $NH(CH_3)$, NH_2 , F , Cl , Br , I , CN , a methyl, a methoxy;

[31] a number of R_{01} , R_{02} , R_{001} , the heteroatom or the heteroatom group is independently selected from 0, 1, 2, or 3;

[32] each of m_3 , m_4 is independently selected from 0 or 1, when m_3 or m_4 is selected from 0, the corresponding structural unit represents a single bond just for the linkage;

[33] each of m_5 , m_6 is independently selected from 1 or 2;

[34] optionally, R_{31} and R_{32} , R_{31} and R_{33} , R_{31} and R_{35} , E_{33} and E_{34} form a linking bond $(CH_2)_{1-6}$ together, preferably $(CH_2)_2$, $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$;

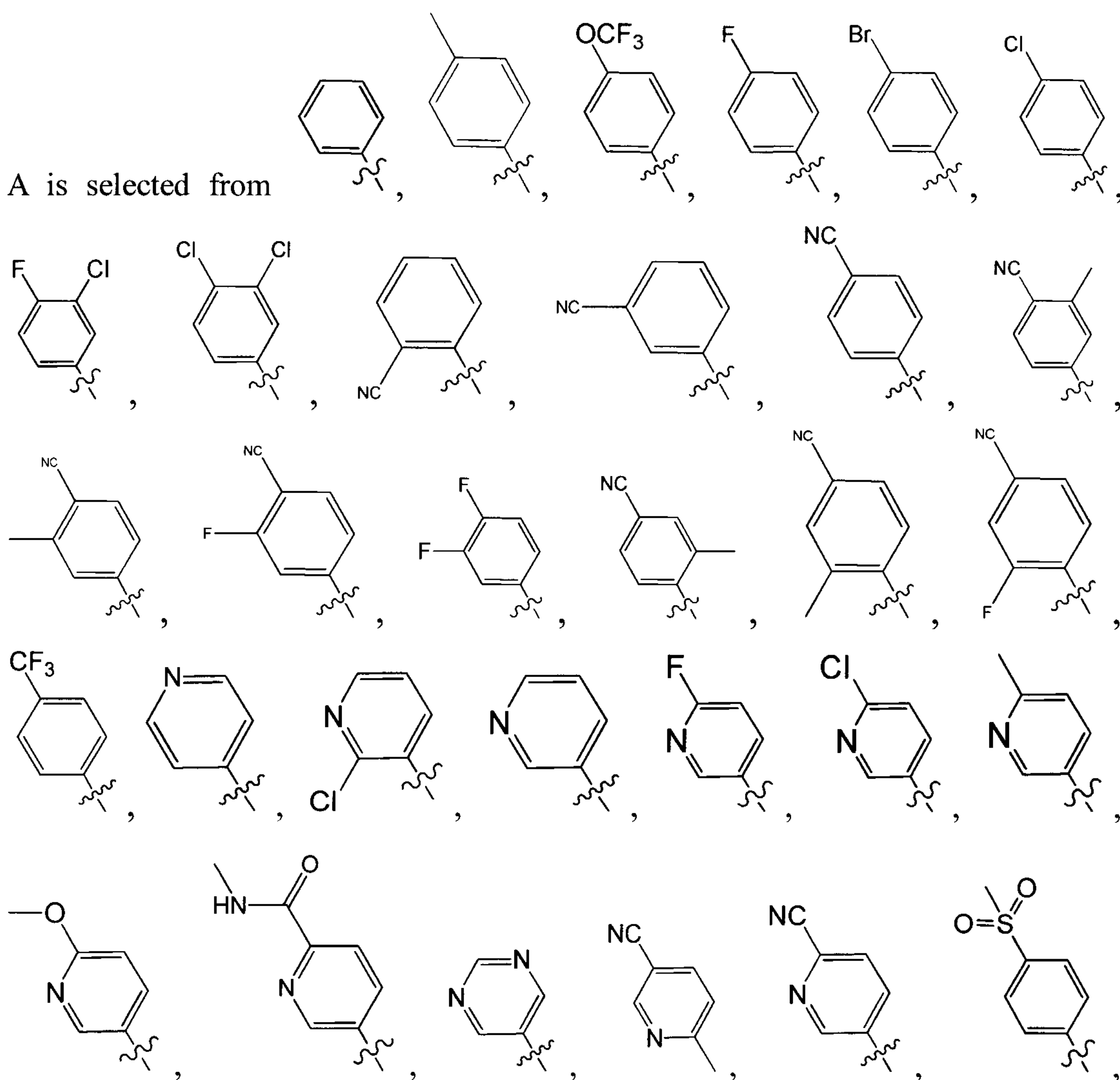
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[35]optionally, R_{32} and R_{32} connect with each other to form a 5-membered carbocyclic ring or a heterocyclic ring;

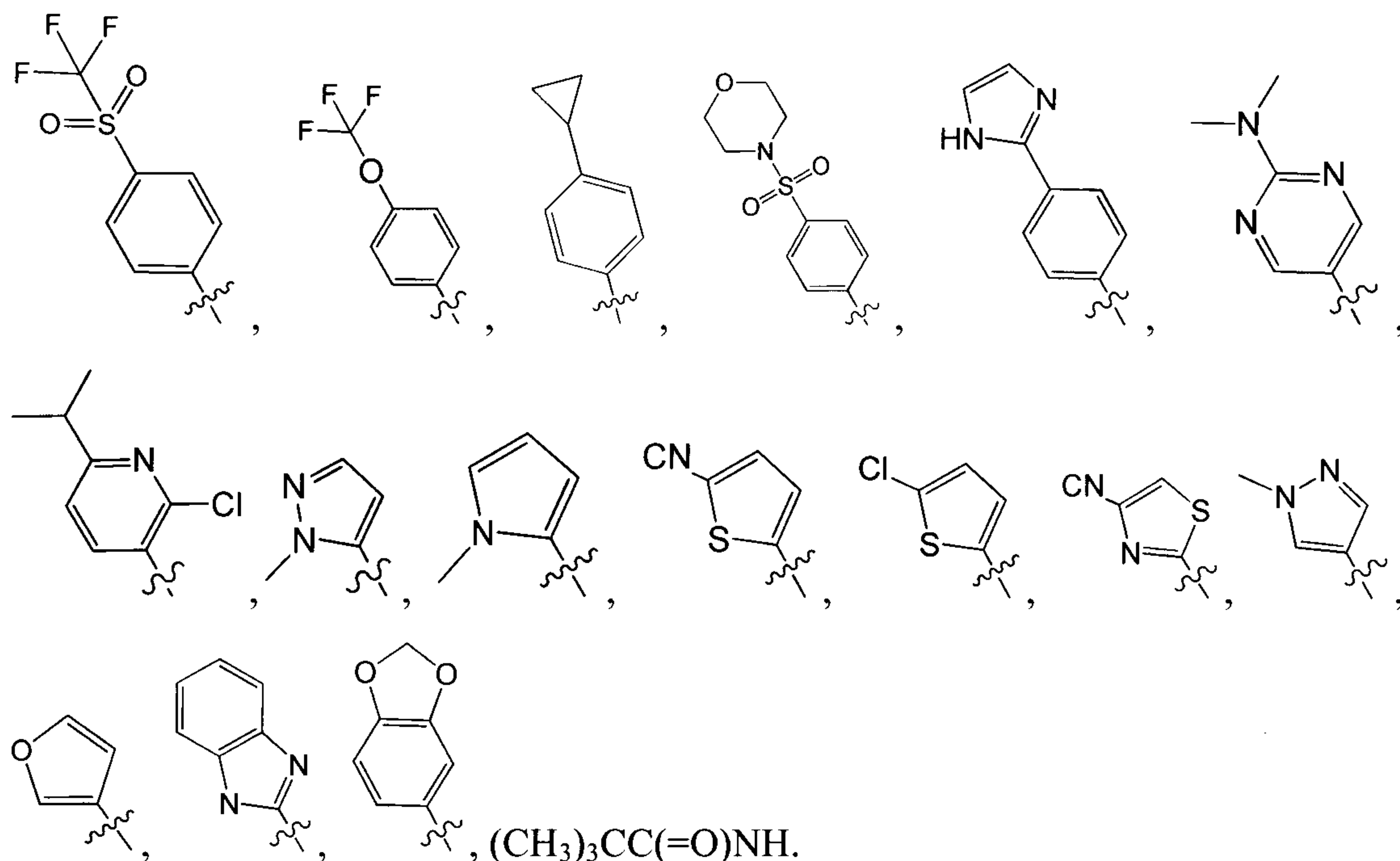
[36]optionally, when E_{32} is selected from $N(R_{40})$ or O, R_{31} and R_{34} present a *cis*-arrangement; when E_{32} is selected from $C(R_{43})(R_{44})$, R_{31} and R_{34} present a *trans*-arrangement; when T_{34} is selected from N, R_{36} and R_{37} present a *cis*-arrangement; when T_{34} is selected from $C(R_{45})$, R_{36} and R_{37} present a *trans*-arrangement;

[37]preferably, the C_{3-8} cyclic group or heterocyclic group or cycle-heteroatom group or heterocycle-heteroatom group is selected from a phenyl, a pyridyl, a thienyl, a furyl, an imidazolyl, an oxazolyl, a thiazolyl, an isothiazolyl.

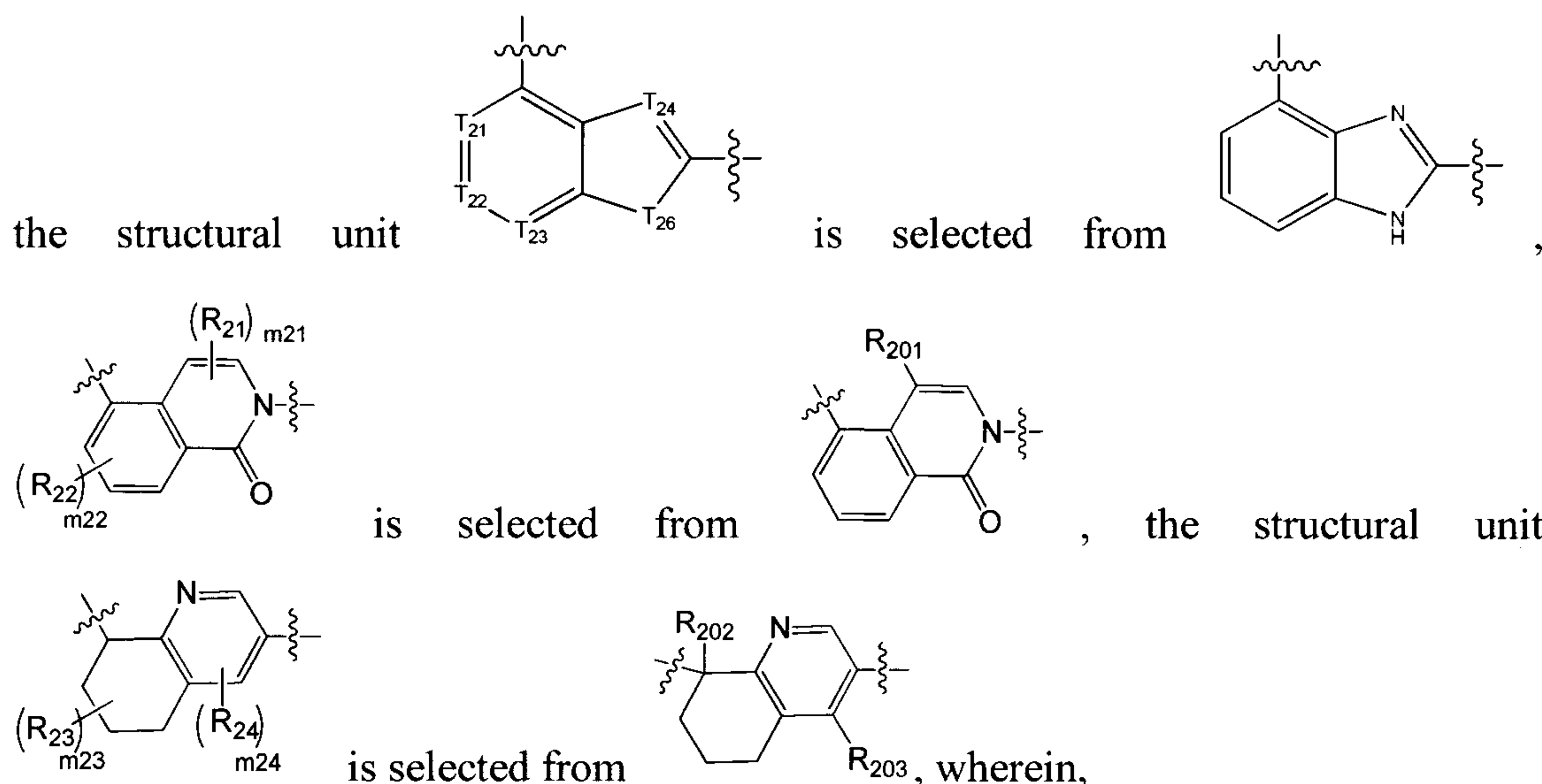
[38]preferably, the compound or the pharmaceutically acceptable salt thereof, wherein



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[39] optionally, the compound or the pharmaceutically acceptable salt thereof, wherein



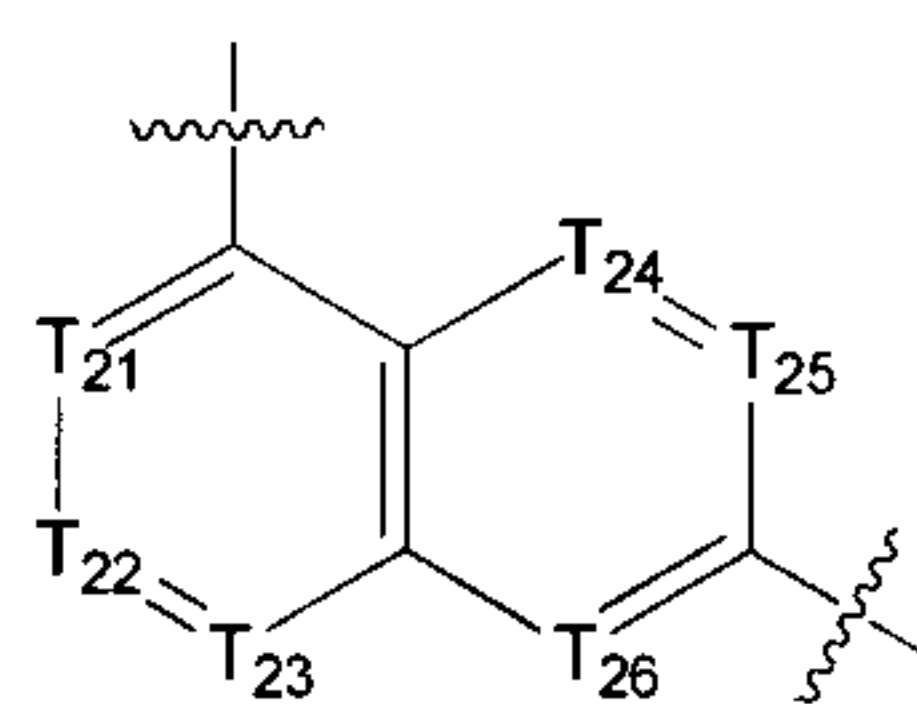
[40] each of R₂₀₁, R₂₀₂, R₂₀₃ is independently selected from H, F, Cl, Br, I, CN, OH, SH, NH₂, an optionally R₀₁-substituted C₁₋₆ alkyl or heteroalkyl or alkyl-heteroatom group or heteroalkyl-heteroatom group, an optionally R₀₂-substituted C₃₋₈ cyclic group or heterocyclic group or cycle-heteroatom group or heterocycle-heteroatom group;

[41] preferably, R₂₀₁ is selected from a methyl, F, Cl, Br, I; each of R₂₀₂, R₂₀₃ is independently selected from a C₁₋₆ alkoxy, more preferably a methoxy.

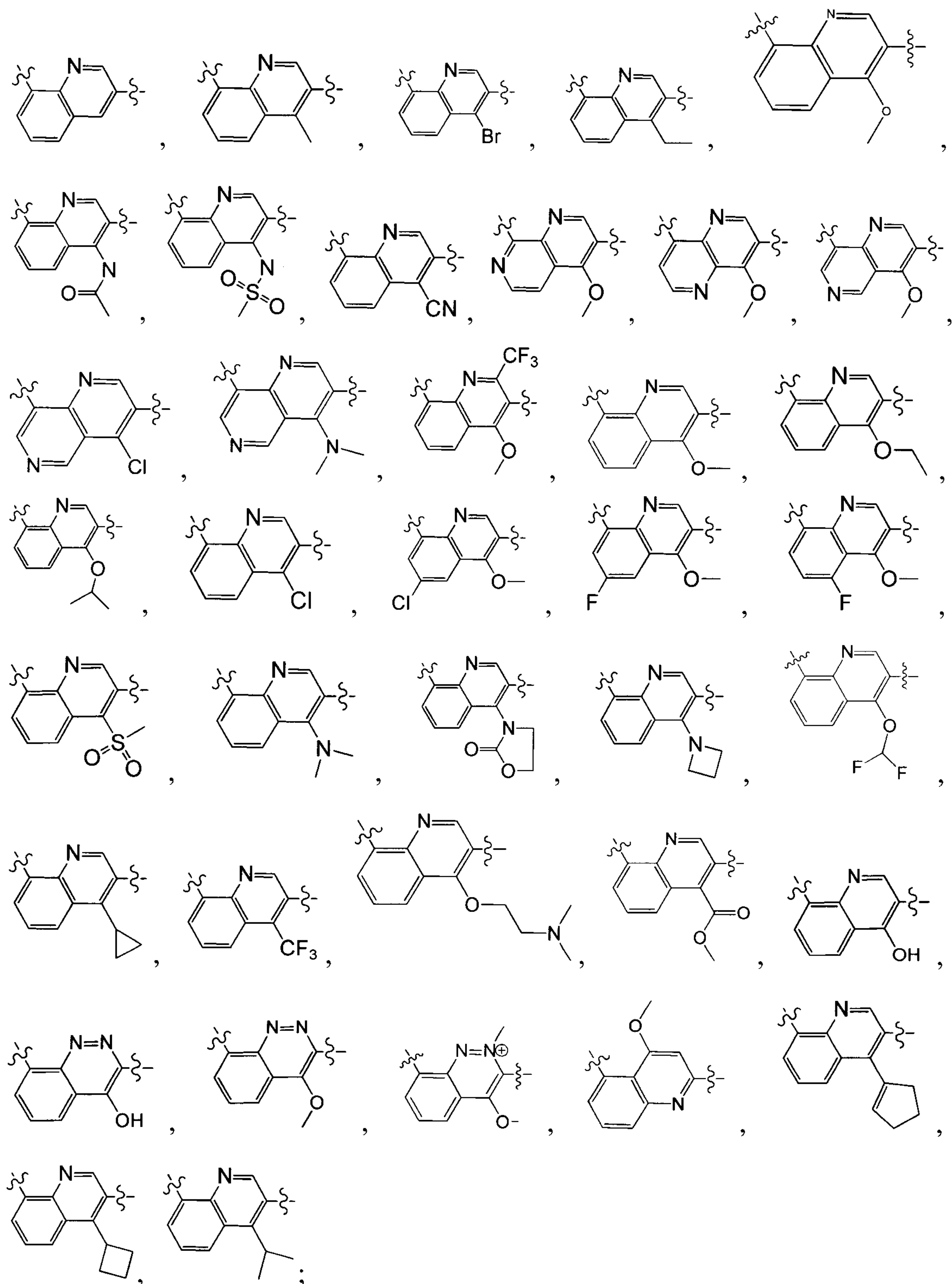
[42] Preferably, the compound or the pharmaceutically acceptable salt thereof,

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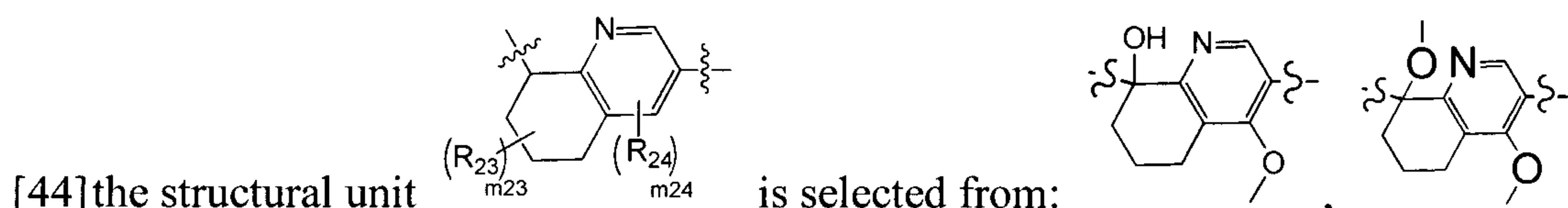
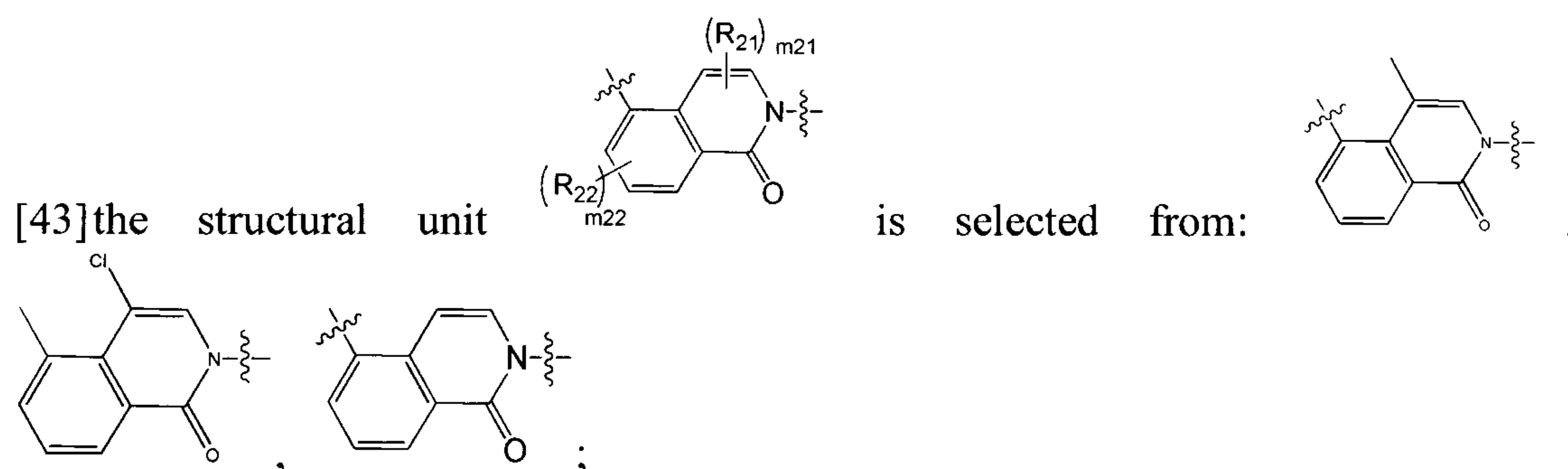
wherein the structural unit



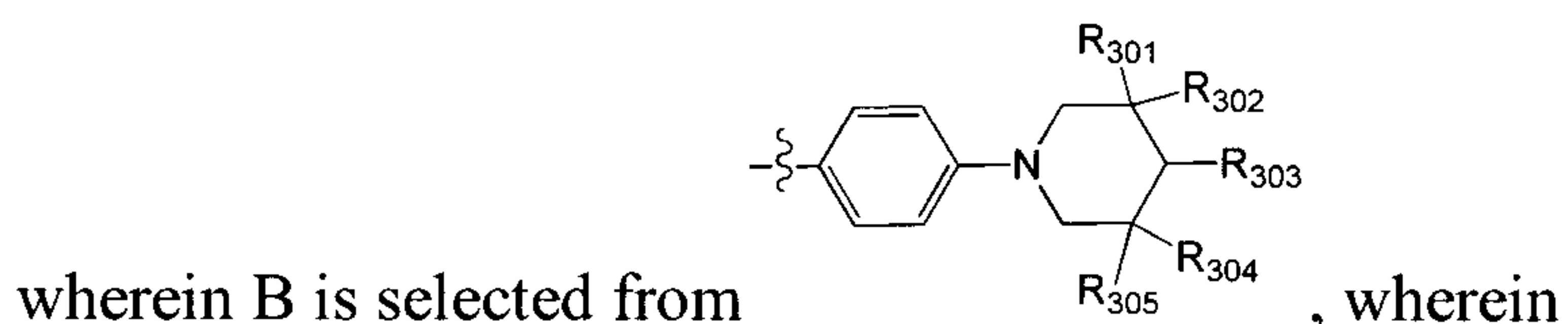
is selected from:



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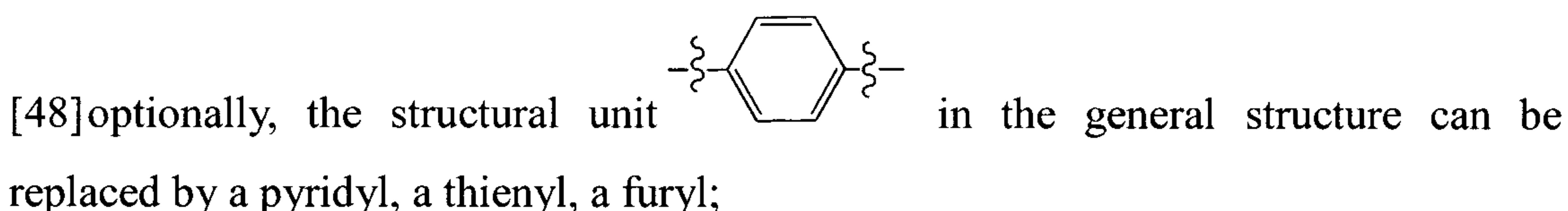


[45]Preferably, the compound or the pharmaceutically acceptable salt thereof,



[46]each of $R_{301-305}$ is independently selected from H, OH, NH_2 , F, Cl, Br, I, CN, an optionally R_{3001} -substituted C_{1-3} alkyl or alkoxy or alkyl amino or cyclopropyl;

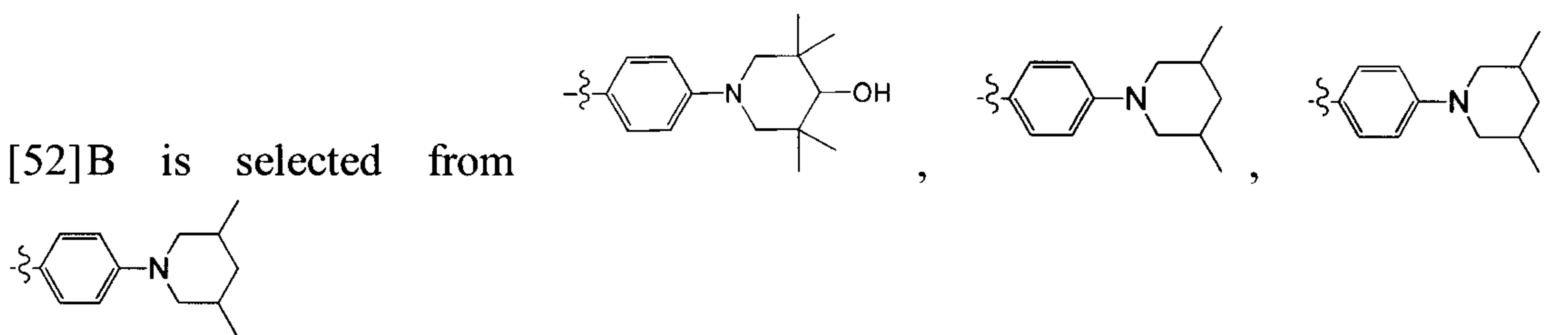
[47] R_{3001} is selected from OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2 , F, Cl, Br, I, CN, a methyl, a methoxy, the number of R_{3001} is selected from 1, 2 or 3;



[49]optionally,

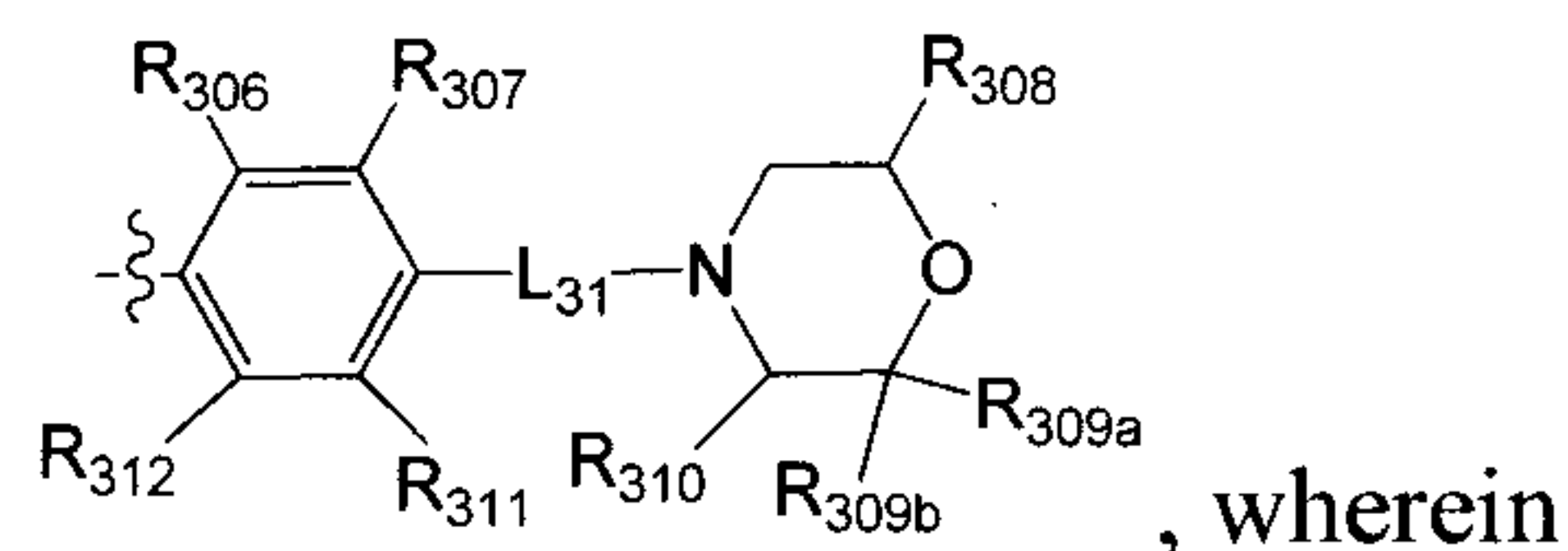
[50]each of $R_{301-305}$ is independently selected from a methyl, H, OH, NH_2 , F, Cl, Br, I, CN;

[51]further optionally,



[53]optionally, the compound or the pharmaceutically acceptable salt thereof, wherein B is selected from

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[54] each of $R_{306-308}$, R_{309a} , R_{309b} , $R_{310-312}$ is independently selected from H, OH, NH_2 , F, Cl, Br, I, CN, an optionally R_{3001} -substituted C_{1-3} alkyl or alkoxy or alkyl amino or cyclopropyl;

[55] R_{3001} is selected from OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2 , F, Cl, Br, I, CN, a methyl, a methoxy, the number of R_{3001} is selected from 1, 2 or 3;

[56] L_{31} is selected from a single bond, $R_{3002}N(R_{3003})R_{3004}$, O, S, $C(=O)O$, $C(=O)$, $C=S$, $S(=O)$ and/or $S(=O)_2$, R_{3002} is selected from a single bond or $C(=O)$;

[57] R_{3003} is selected from H, a C_{1-3} alkyl or a cyclopropyl;

[58] R_{3004} is selected from $(CH_2)_{0-3}$;

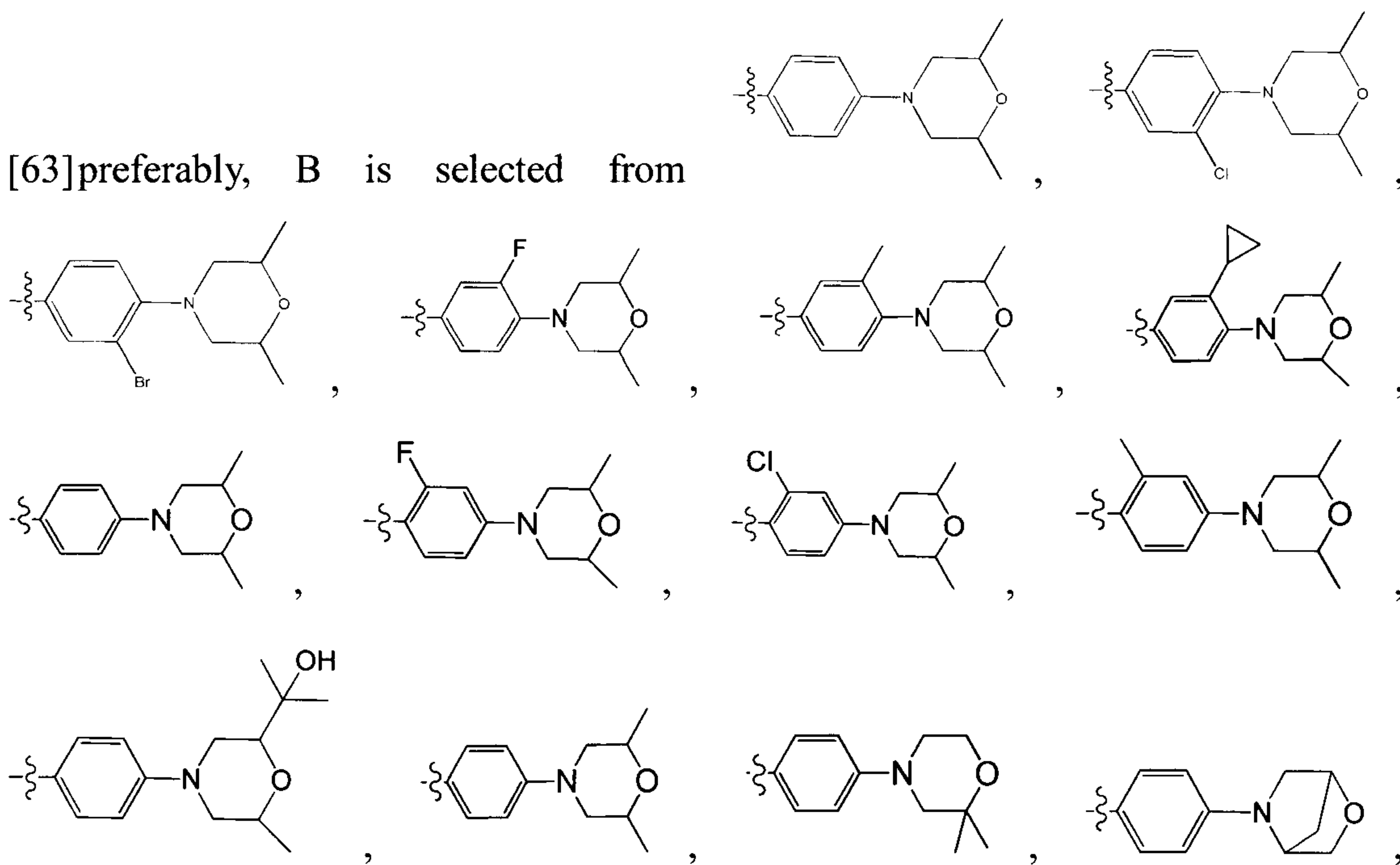
[59] optionally, R_{308} and R_{309a} , R_{308} and R_{310} form a linking bond $(CH_2)_{1-3}$ together;

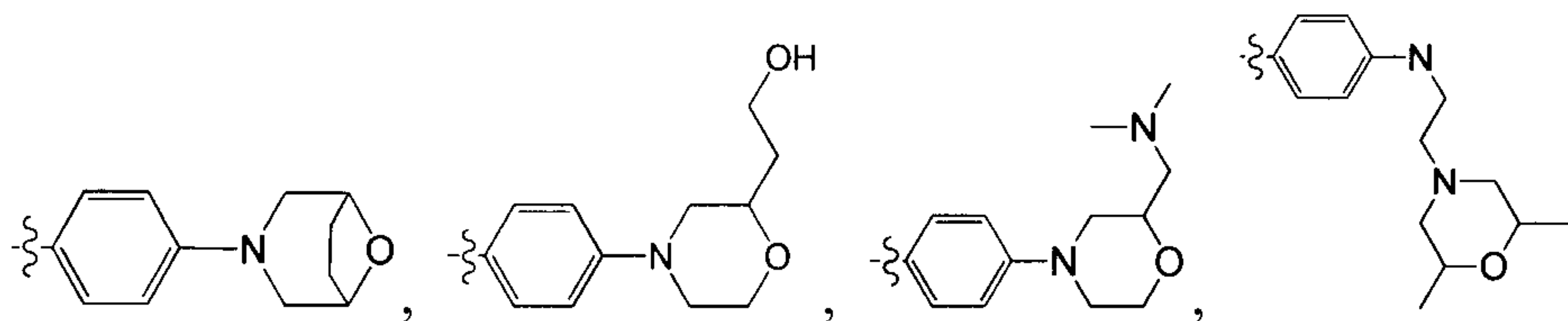
[60] preferably, the R_{308} and R_{310} form a linking bond CH_2 together, R_{308} and R_{309a} form a linking bond CH_2CH_2 together.

[61] preferably, each of $R_{306-308}$, R_{309a} , R_{309b} , $R_{310-312}$ is independently selected from a methyl, a cyclopropyl, $C(CH_3)_2(OH)$, CH_2CH_2OH , $CH_2N(CH_3)_2$, H, OH, NH_2 , F, Cl, Br, I, CN.

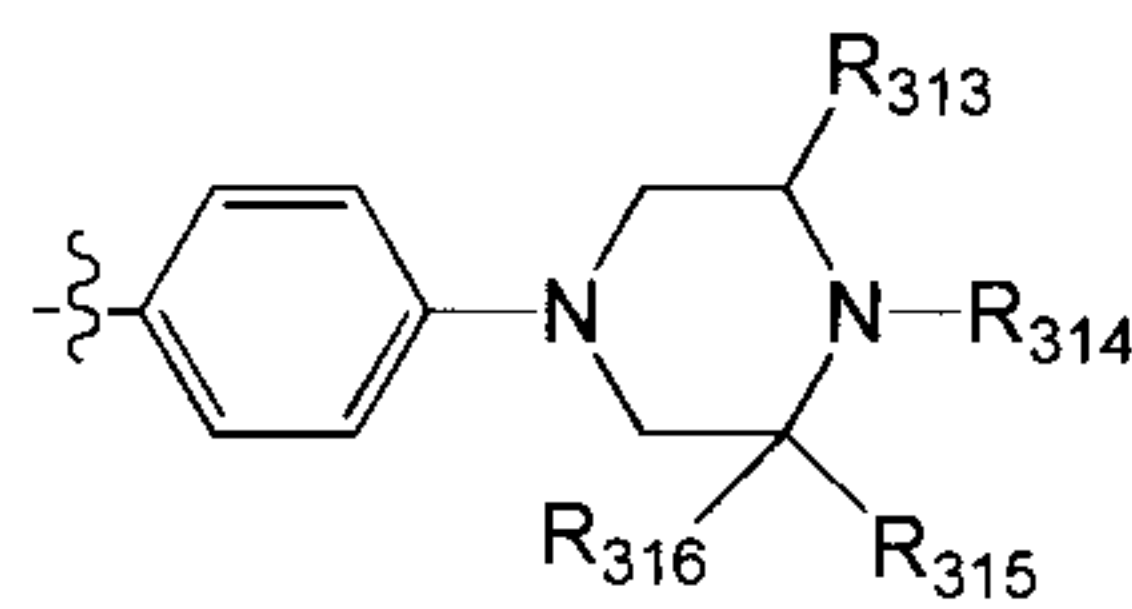
[62] preferably, L_{31} is selected from a single bond, $NHCH_2CH_2$;

[63] preferably, B is selected from





[64]preferably, the compound or the pharmaceutically acceptable salt thereof, wherein

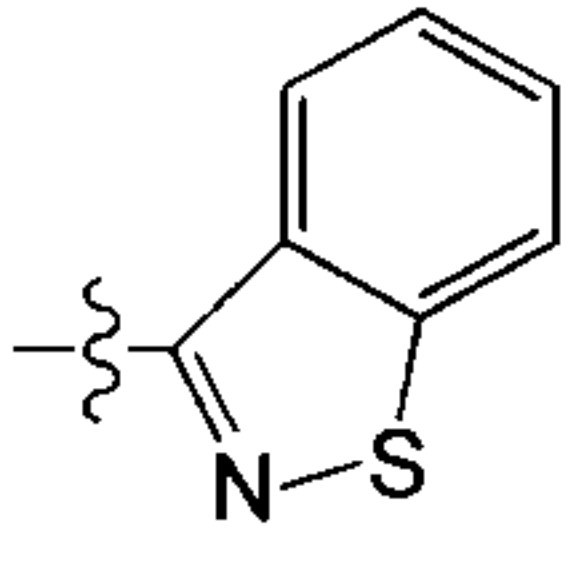


B is selected from

, wherein

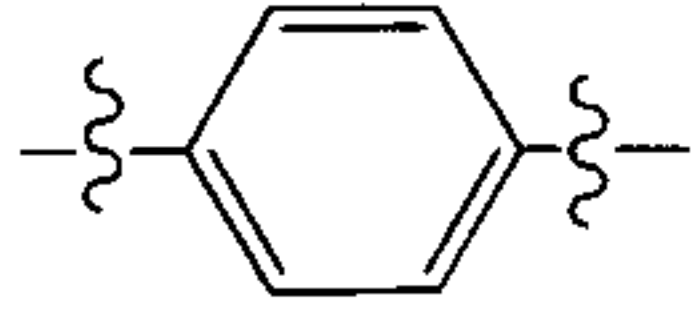
each of R_{313} , R_{315} , R_{316} is independently selected from H, OH, NH_2 , F, Cl, Br, I, CN, an optionally R_{3001} -substituted C_{1-3} alkyl or alkoxy or alkyl amino or cyclopropyl;

[65] R_{314} is selected from H, OH, NH_2 , F, Cl, Br, I, CN, an optionally R_{3001} -substituted

C_{1-3} alkyl or alkoxy or alkyl amino or cyclopropyl, $(CH_2)_{0-3}R_{3005}$, , wherein R_{3005} is optionally substituted by R_{3001} ;

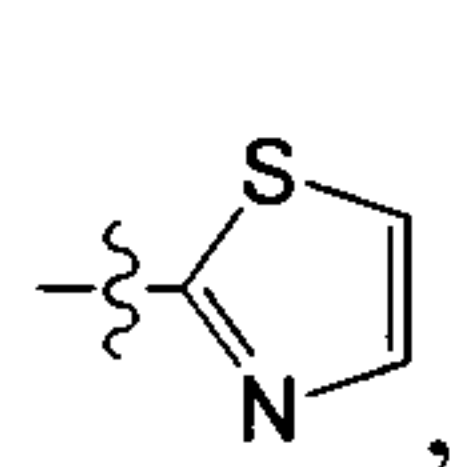
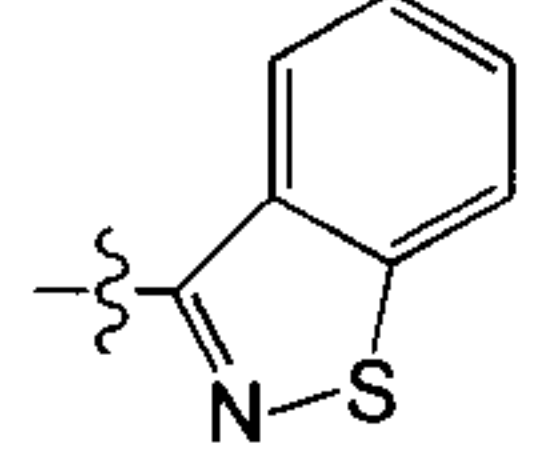
[66] R_{3005} is selected from a C_{3-6} cycloalkyl, a phenyl, a pyridyl, a thienyl, a furyl, an imidazolyl, an oxazolyl, a thiazolyl, an isothiazolyl, each of the above-mentioned group is optionally fused with a benzene ring;

[67] R_{3001} is selected from OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2 , F, Cl, Br, I, CN, a methyl, a methoxy, the number of R_{3001} is selected from 1, 2 or 3;

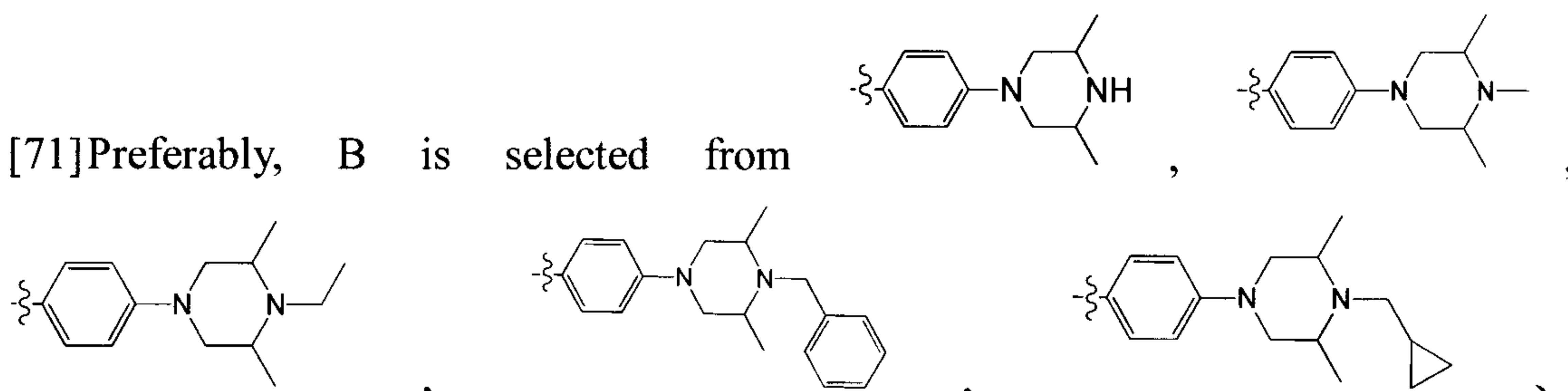
[68]optionally, the  in the general structure can be replaced by a pyridyl, a thienyl, a furyl, an imidazolyl, an oxazolyl, a thiazolyl, an isothiazolyl.

[69]Preferably, each of R_{313} , R_{315} , R_{316} is independently selected from H, a methyl;

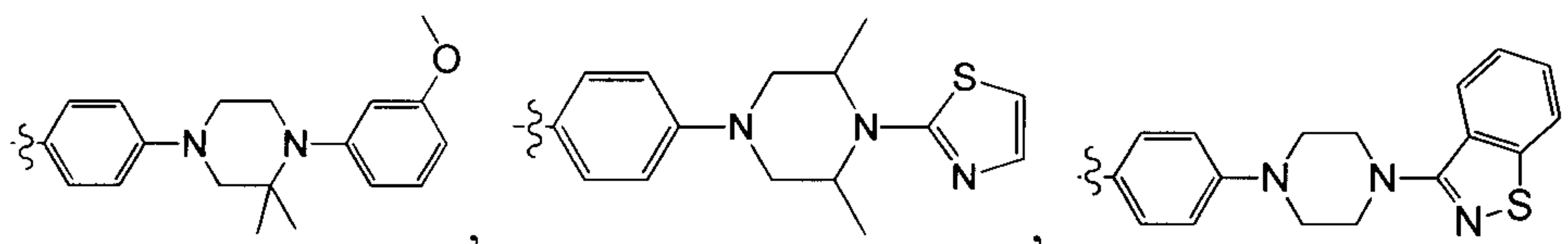
[70]preferably, R_{314} is selected from H, a methyl, an ethyl, a phenyl methylene, a

cyclopropyl methylene, a methoxyphenyl, , .

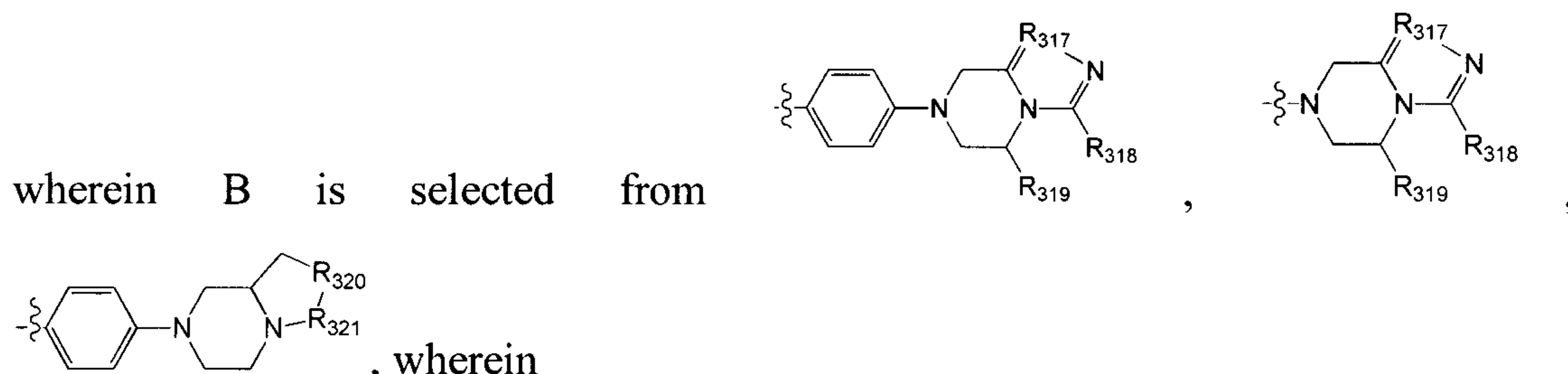
[71]Preferably, B is selected from



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[72] Preferably, the compound or the pharmaceutically acceptable salt thereof,



[73] R_{317} is selected from CR_{3006} or N;

[74] each of R_{318} , R_{319} , $R_{3006-3008}$ is independently selected from H, OH, NH_2 , F, Cl, Br, I, CN, an optionally R_{3001} -substituted C_{1-3} alkyl or alkoxy or alkyl amino or cyclopropyl;

[75] each of $R_{320-321}$ is independently selected from $C(R_{3007})(R_{3008})$, O, $CON(R_{3009})$, $N(R_{3010})$, $C=N(R_{3011})$, S, $C(=O)O$, $C(=O)$, $C=S$, $S(=O)$ and/or $S(=O)_2$;

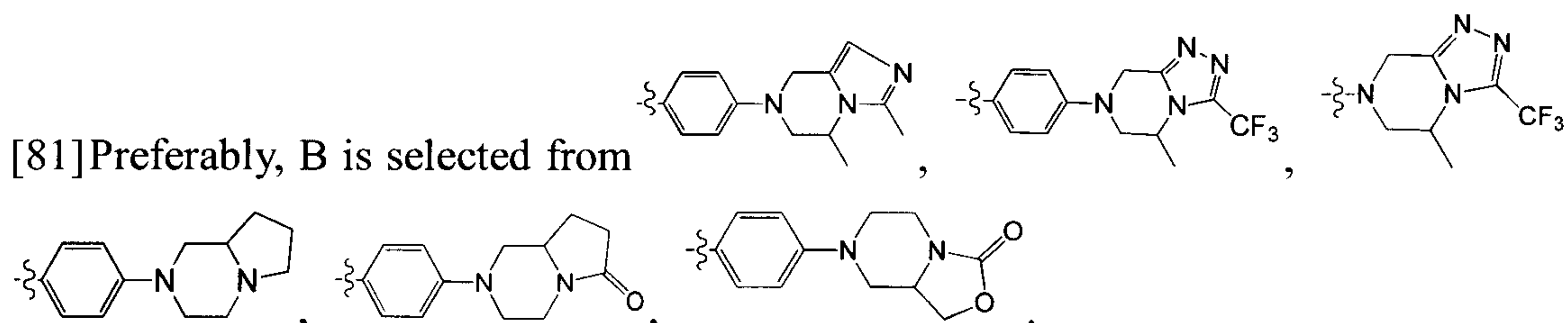
[76] each of $R_{3009-3011}$ is independently selected from H, an optionally R_{3001} -substituted C_{1-3} alkyl or cyclopropyl;

[77] R_{3001} is selected from OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2 , F, Cl, Br, I, CN, a methyl, a methoxyl, the number of R_{3001} is selected from 1, 2 or 3;

[78] optionally, the  in the general structure can be replaced by a pyridyl, a thienyl, a furyl, an imidazolyl, an oxazolyl, a thiazolyl, an isothiazolyl.

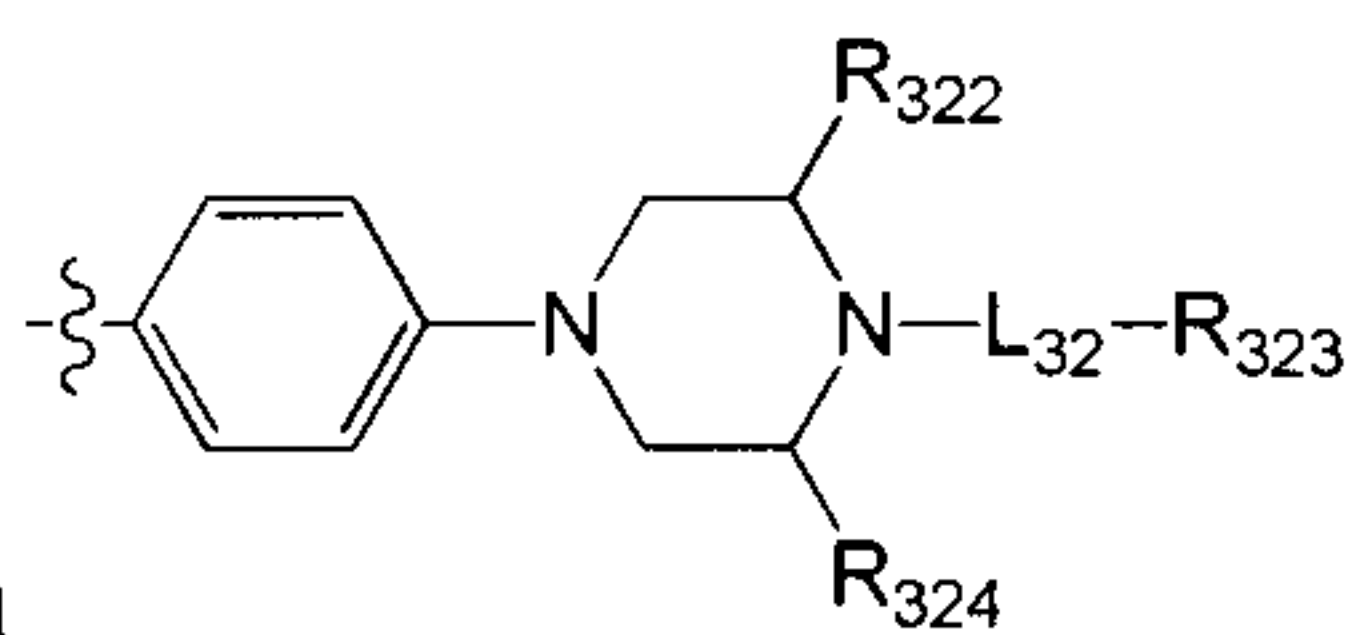
[79] Preferably, R_{317} is selected from CR_{3006} or N; each of R_{3006} , R_{318} , R_{319} is selected from a methyl, a trifluoromethyl;

[80] each of $R_{320-321}$ is independently selected from CH_2 , O, $C(=O)$.



[82] Preferably, the compound or the pharmaceutically acceptable salt thereof,

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wherein B is selected from

[83] wherein,

[84] L₃₂ is selected from C(R₃₀₀₇)(R₃₀₀₈), O, CON(R₃₀₀₉), N(R₃₀₁₀), C=N (R₃₀₁₁), S, C(=O)O, C(=O), C=S, S(=O) and/or S(=O)₂;

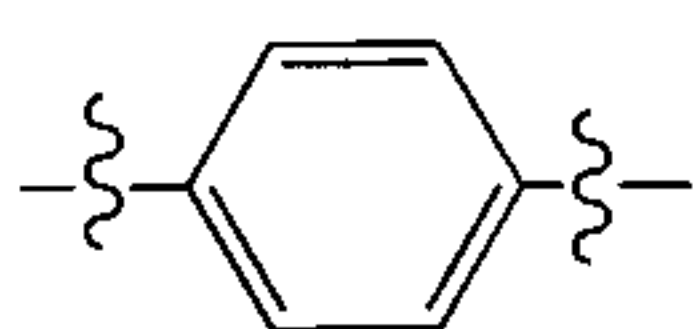
[85] R₃₂₃ is selected from a C₁₋₆ alkyl, a C₃₋₆ cycloalkyl, a phenyl, a pyridyl, an imidazolyl, a thienyl, a furyl, an oxazolyl, a thiazolyl, an isothiazolyl, each of the above-mentioned group is optionally substituted by R₃₀₁₂;

[86] each of R₃₂₂, R₃₂₄, R₃₀₀₇, R₃₀₀₈, R₃₀₁₂ is independently selected from H, OH, NH₂, F, Cl, Br, I, CN, an optionally R₃₀₀₁-substituted C₁₋₃ alkyl or alkoxy or alkyl amino or cyclopropyl;

[87] each of R₃₀₀₉₋₃₀₁₁ is independently selected from H, an optionally R₃₀₀₁-substituted C₁₋₃ alkyl or cyclopropyl;

[88] R₃₀₀₁ is selected from OH, N(CH₃)₂, NH(CH₃), NH₂, F, Cl, Br, I, CN, a methyl, a methoxy;

[89] the number of each of R₃₀₀₁, R₃₀₁₂ is selected from 1, 2 or 3.

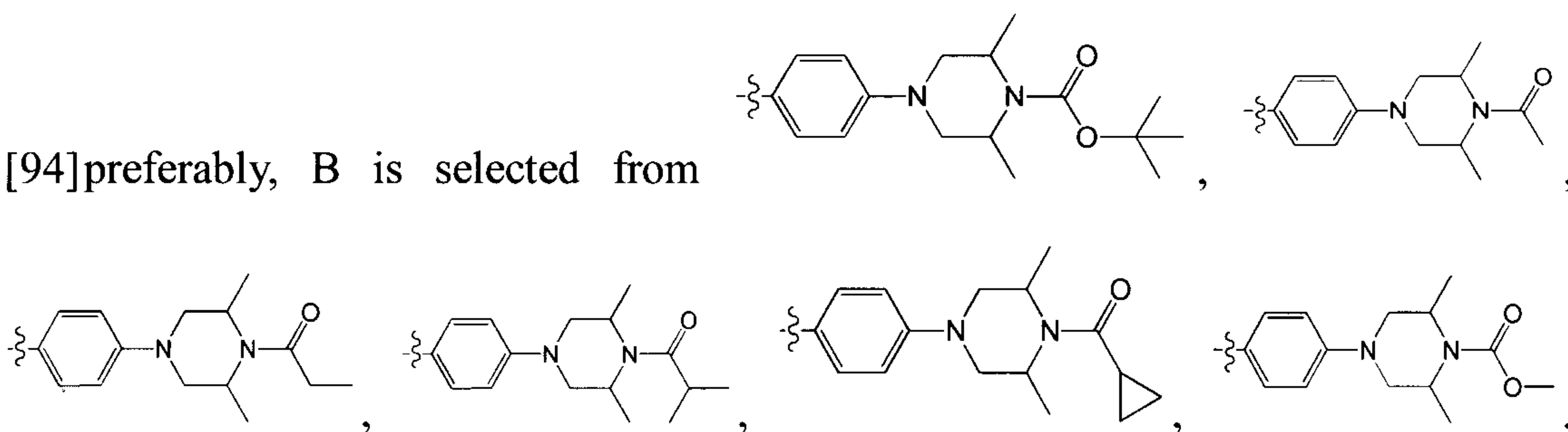
[90] Optionally, the  in the general structure can be replaced by a pyridyl, a thienyl, a furyl, an imidazolyl, an oxazolyl, a thiazolyl, an isothiazolyl.

[91] Preferably, each of R₃₂₂, R₃₂₄ is independently selected from H, a methyl, a phenyl, C(CH₃)₂OH.

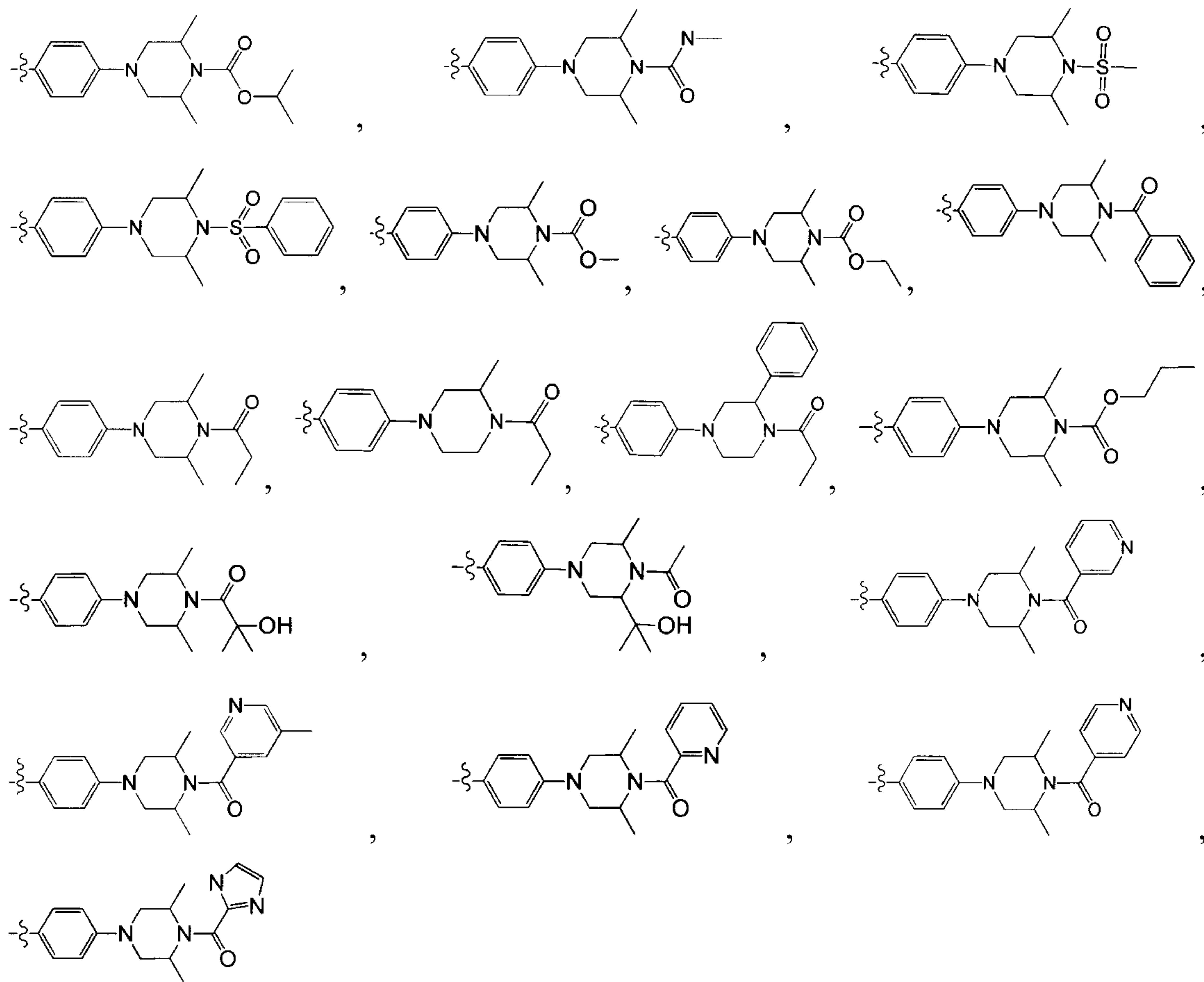
[92] Preferably, L₃₂ is selected from C(=O), S(=O)₂;

[93] preferably, R₃₂₃ is selected from a *tert*-butoxy, a methyl, a methoxy, an ethyl, an ethoxy, an propoxy, an isopropyl, a *n*-propyl, an isopropoxy, a cyclopropyl, a methylamino, a phenyl, a pyridyl, a 3-methyl pyridyl, an imidazolyl, C(CH₃)₂OH;

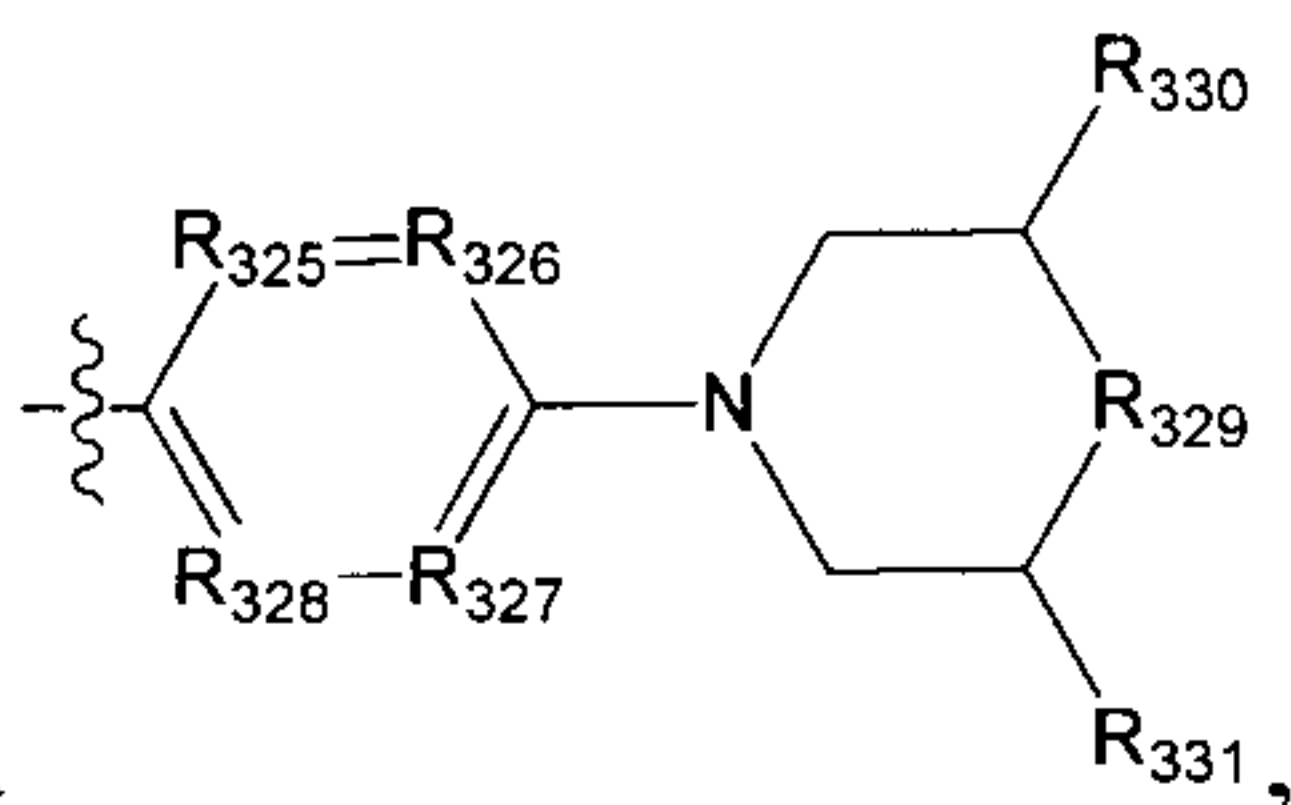
[94] preferably, B is selected from



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[95] Preferably, the compound or the pharmaceutically acceptable salt thereof,



wherein B is selected from

[96] wherein,

[97] one or two of R₃₂₅₋₃₂₈ is selected from N, the rest are selected from C(R₃₀₁₃);

[98] R₃₂₉ is selected from N(R₃₀₁₄), O, C(R₃₀₁₅)(R₃₀₁₆), CON(R₃₀₁₇), N(R₃₀₁₈), C=N(R₃₀₁₉), S, C(=O)O, C(=O), C=S, S(=O) and/or S(=O)₂;

[99] R₃₀₁₄ is selected from C(=O)R₃₀₂₀, S(=O)₂R₃₀₂₀, a thiazolyl, an isothiazolyl, a phenyl, a pyridyl, an imidazolyl, a thienyl, a furyl, an oxazolyl;

[100] R₃₀₂₀ is selected from an optionally R₃₀₀₁-substituted C₁₋₃ alkyl or alkoxy;

[101] each of R₃₀₁₃, R₃₀₁₅, R₃₀₁₆, R₃₃₀₋₃₃₁ is independently selected from H, OH, NH₂, F, Cl, Br, I, CN, C(=O)OH, an optionally R₃₀₀₁-substituted C₁₋₃ alkyl or alkoxy or alkyl amino or cyclopropyl;

[102] each of R₃₀₁₇₋₃₀₁₉ is independently selected from H, an optionally R₃₀₀₁-substituted C₁₋₃ alkyl or cyclopropyl;

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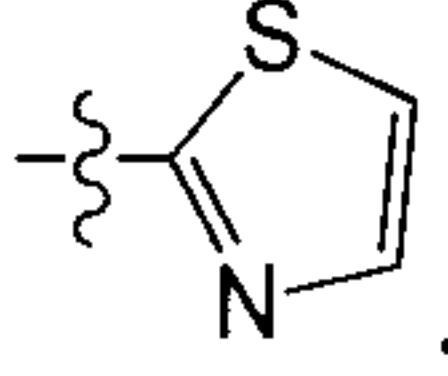
[103] R_{3001} is selected from OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2 , F, Cl, Br, I, CN, a methyl, a methoxy, the number of R_{3001} is selected from 1, 2 or 3;

[104] optionally, R_{330} and R_{331} form a linking bond $(CH_2)_{1-3}$ together;

[105] optionally, when R_{329} is selected from $N(R_{3014})$ or O, R_{330} and R_{331} present a *cis*-arrangement; when R_{329} is selected from $C(R_{3015})(R_{3016})$, R_{330} and R_{331} present a *trans*-arrangement;

[106] preferably, one or two of $R_{325-328}$ is selected from N, the rest are selected from CH, $CC(=O)OH$ or CCH_3 .

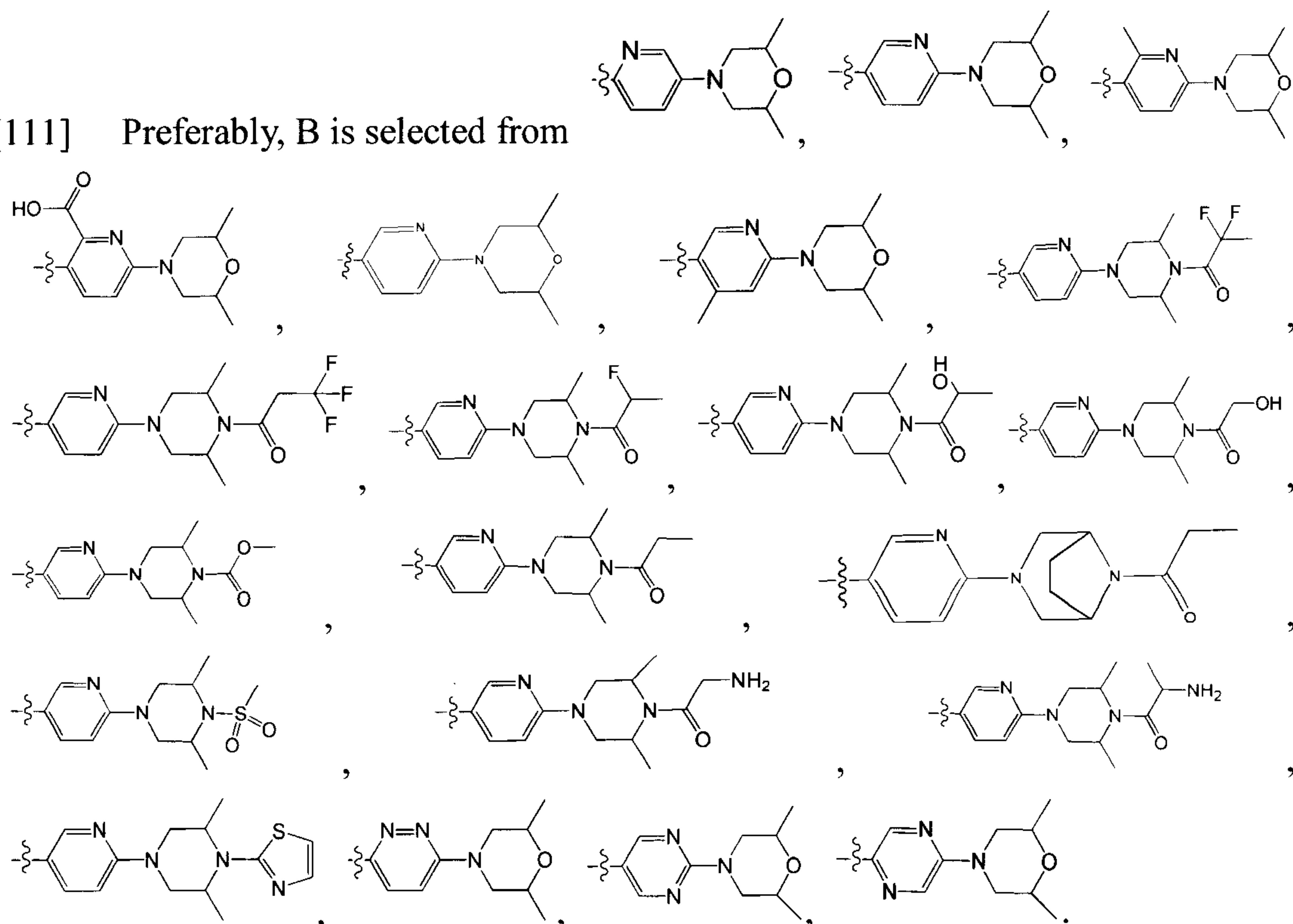
[107] Preferably, R_{329} is selected from $N(R_{3014})$, O.

[108] Preferably, R_{3014} is selected from $C(=O)R_{3020}$, .

[109] Preferably, R_{3020} is selected from $C(CH_3)(F)_2$, CH_3 , CF_3 , CH_2CH_3 , CH_2CF_3 , $CH(F)(CH_3)$, $CH(OH)(CH_3)$, $CH_2(OH)$, $CH(NH_2)(CH_3)$, a methoxy, an ethoxy, an amino methyl.

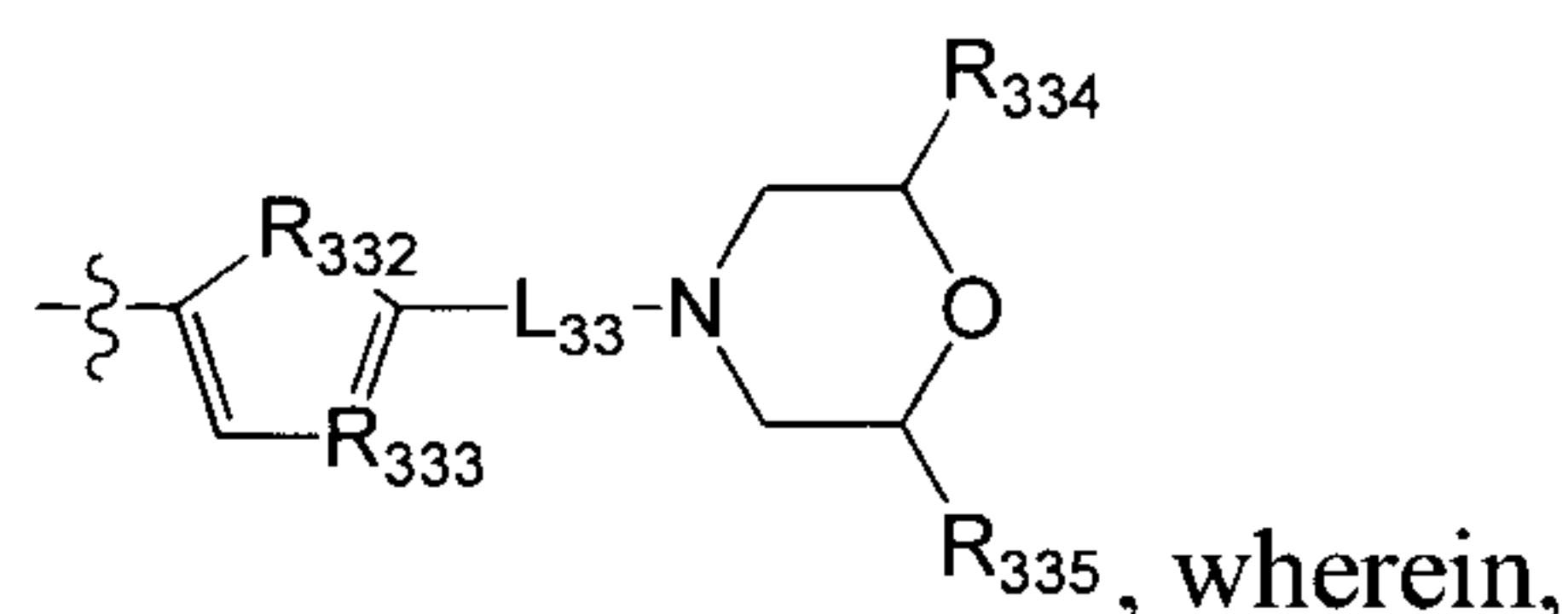
[110] Preferably, $R_{330-331}$ is selected from a methyl.

[111] Preferably, B is selected from



[112] Preferably, the compound or the pharmaceutically acceptable salt thereof, wherein B is selected from

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[113] R_{332} is selected from S, N(R_{3021}), O, C(R_{3022})(R_{3023}), CON(R_{3024}), N(R_{3025}), C=N(R_{3026}), S, C(=O)O, C(=O), C=S, S(=O) and/or S(=O)₂;

[114] L_{33} is selected from a single bond, C(=O), S, O, C(R_{3022})(R_{3023}), CON(R_{3024}), N(R_{3025}), C=N(R_{3026}), S, C(=O)O, C=S, S(=O) and/or S(=O)₂;

[115] R_{333} is selected from N, C(R_{3027});

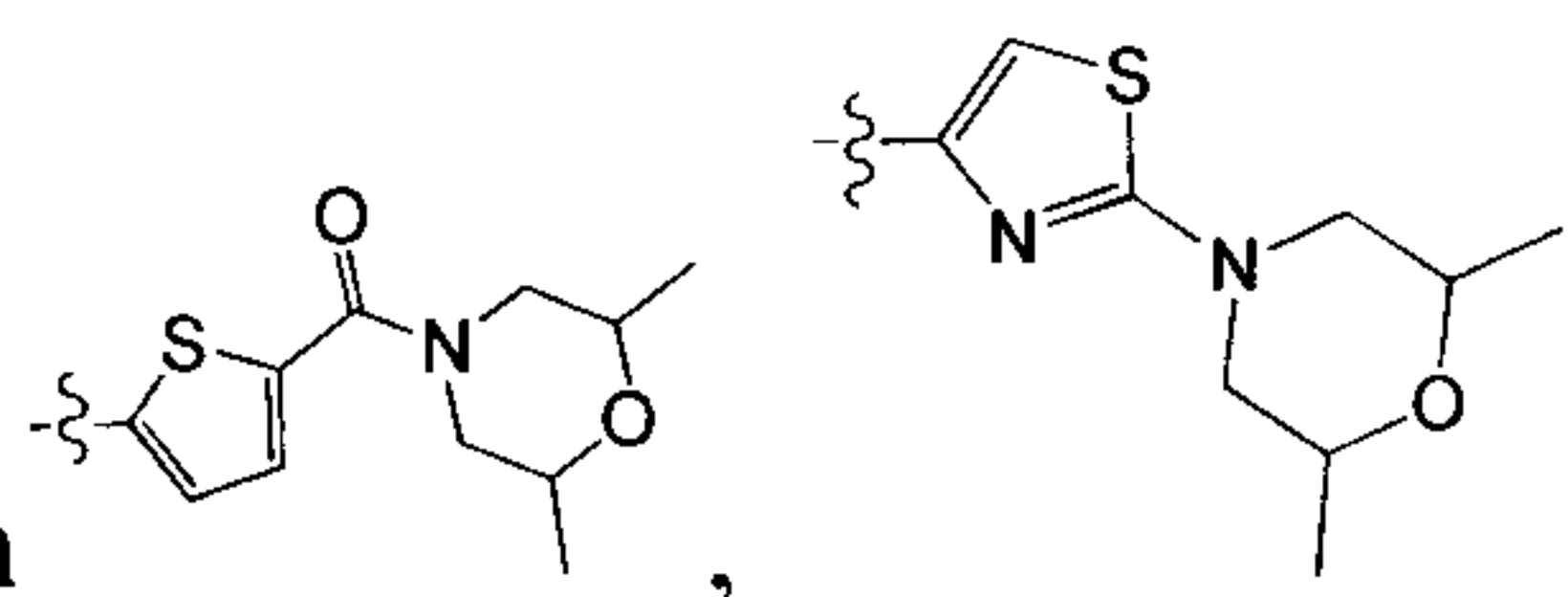
[116] each of R_{3027} , R_{334} , R_{335} , R_{3022} , R_{3023} is independently selected from H, OH, NH₂, F, Cl, Br, I, CN, an optionally R_{3001} -substituted C₁₋₃ alkyl or alkoxy or alkyl amino or cyclopropyl;

[117] each of R_{3021} , $R_{3024-3026}$ is independently selected from H, an optionally R_{3001} -substituted C₁₋₃ alkyl or cyclopropyl;

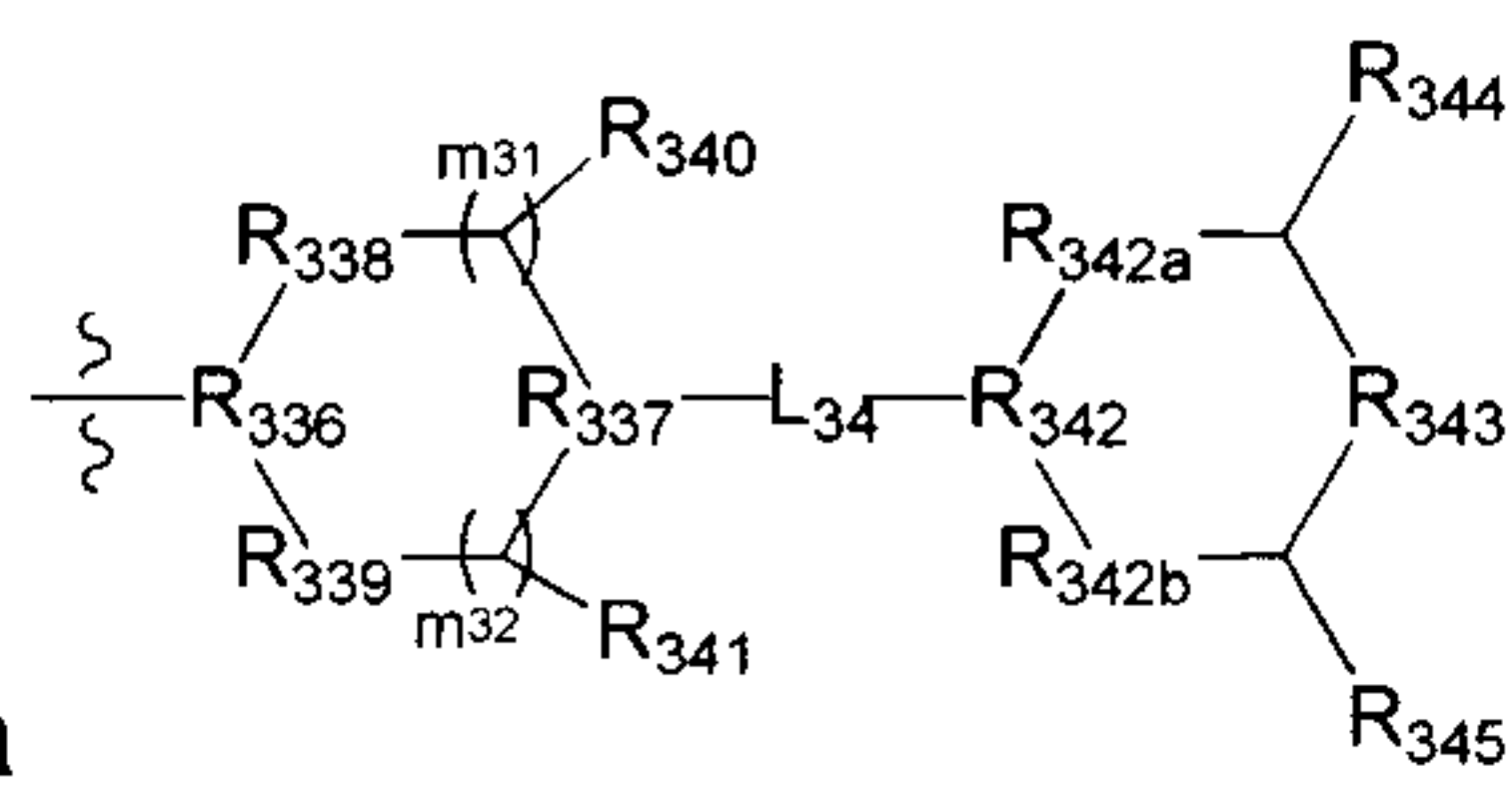
[118] R_{3001} is selected from OH, N(CH₃)₂, NH(CH₃), NH₂, F, Cl, Br, I, CN, a methyl, a methoxy, the number of R_{3001} is selected from 1, 2 or 3;

[119] preferably, R_{332} is selected from S, R_{333} is selected from N or CH, L_{33} is selected from a single bond, C(=O), each of R_{334} , R_{335} is selected from a methyl.

[120] Preferably, B is selected from



[121] Preferably, the compound or the pharmaceutically acceptable salt thereof,



wherein B is selected from

[122] each of R_{336} , R_{337} , R_{342} is independently selected from N or C(R_{3028});

[123] each of R_{338} , R_{339} is selected from C(R_{3029})(R_{3030}), optionally R_{338} and R_{339} connect to the same (CH₂)₁₋₃ together to form a ring;

[124] each of m_{31} , m_{32} is independently selected from 0 or 1;

[125] each of R_{342a} , R_{342b} , R_{343} , L_{34} is independently selected from a single bond, C(=O)N(R_{3031}), C(=O)C(R_{3032})(R_{3033}), C(R_{3034})(R_{3035}), CON(R_{3036}), N(R_{3037}), C=N(R_{3038}), O, S, C(=O)O, C(=O), C=S, S(=O) and/or S(=O)₂;

[127] each of R₃₄₀, R₃₄₁, R₃₄₄, R₃₄₅, R₃₀₂₈, R₃₀₂₉, R₃₀₃₀, R₃₀₃₂₋₃₀₃₅ is independently selected from H, OH, NH₂, F, Cl, Br, I, CN, an optionally R₃₀₀₁-substituted C₁₋₃ alkyl or alkoxy or alkyl amino or cyclopropyl;

[128] each of R₃₀₃₁, R₃₀₃₆₋₃₀₃₈ is independently selected from H, an optionally R₃₀₀₁-substituted C₁₋₃ alkyl or cyclopropyl;

[129] R₃₀₀₁ is selected from OH, N(CH₃)₂, NH(CH₃), NH₂, F, Cl, Br, I, CN, a methyl, a methoxy, the number of R₃₀₀₁ is selected from 1, 2 or 3;

[130] preferably, each of R₃₃₆, R₃₃₇, R₃₄₂ is independently selected from N or CH.

[131] Preferably, each of R₃₃₈, R₃₃₉ is independently selected from CH₂, optionally R₃₃₈ and R₃₃₉ connect to the same CH₂CH₂ together to form a ring.

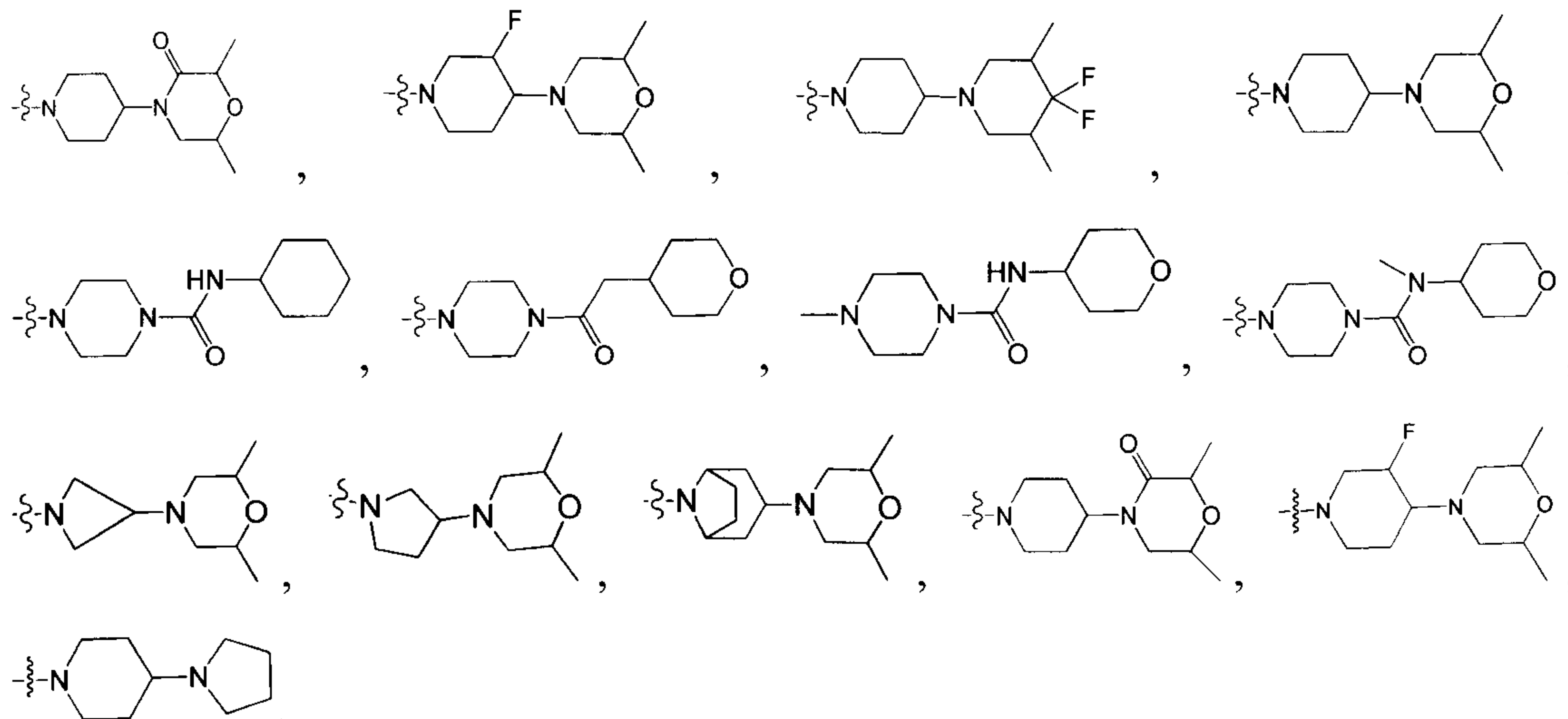
[132] Preferably, each of m_{31} , m_{32} is independently selected from 0 or 1.

[133] Preferably, L₃₄ is independently selected from a single bond, C(=O)NH, C(=O)N(CH₃), C(=O)CH₂.

[134] Preferably, each of R₃₄₀, R₃₄₁, R₃₄₄, R₃₄₅ is independently selected from H or a methyl.

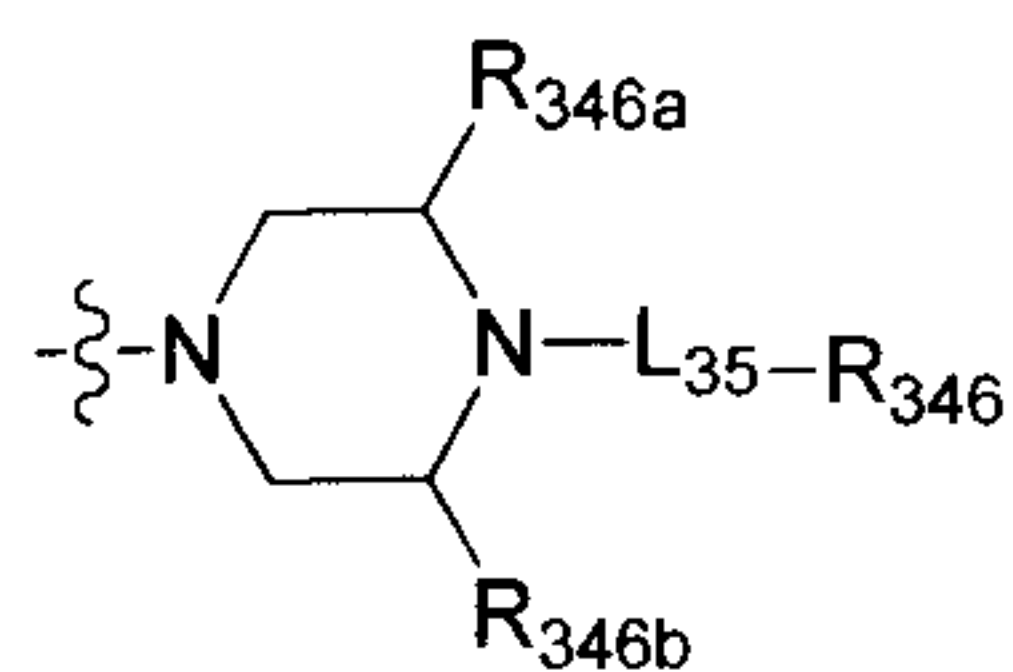
[135] Preferably, each of R_{342a}, R_{342b} is selected from C(=O) or CH₂.

The image shows two chemical structures separated by a comma. The structure on the left is 1,3-dimethyl-2-(4-sulfonylphenyl)azepane, which consists of a seven-membered azepane ring with methyl groups at positions 1 and 3, and a 4-sulfonylphenyl group at position 2. The structure on the right is 1,3-dimethyl-2-(4-sulfonylphenyl)piperazine, which consists of a six-membered piperazine ring with methyl groups at positions 1 and 3, and a 4-sulfonylphenyl group at position 2.



[137] Preferably, the compound or the pharmaceutically acceptable salt thereof,

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wherein B is selected from , wherein

[138] L_{35} is independently selected from a single bond, $C(=O)N(R_{3031})$, $C(=O)C(R_{3032})(R_{3033})$, $C(R_{3034})(R_{3035})$, $N(R_{3037})$, $C=N(R_{3038})$, O, S, $C(=O)O$, $C(=O)$, $C=S$, $S(=O)$ and/or $S(=O)_2$;

[139] L_{35} can also be selected from a single bond;

[140] each of $R_{3032-3035}$ is independently selected from H, OH, NH_2 , F, Cl, Br, I, CN, an optionally R_{3001} -substituted C_{1-3} alkyl or alkoxy or alkyl amino or cyclopropyl;

[141] each of R_{346} , R_{346a} , R_{346b} is independently selected from H, an optionally R_{3001} -substituted C_{1-3} alkyl or alkoxy or alkyl acyl or alkyl sulfonyl or alkyl amino or cyclopropyl, an optionally R_{3001} -substituted cyclopropyl acyl or cyclopropyl sulfonyl;

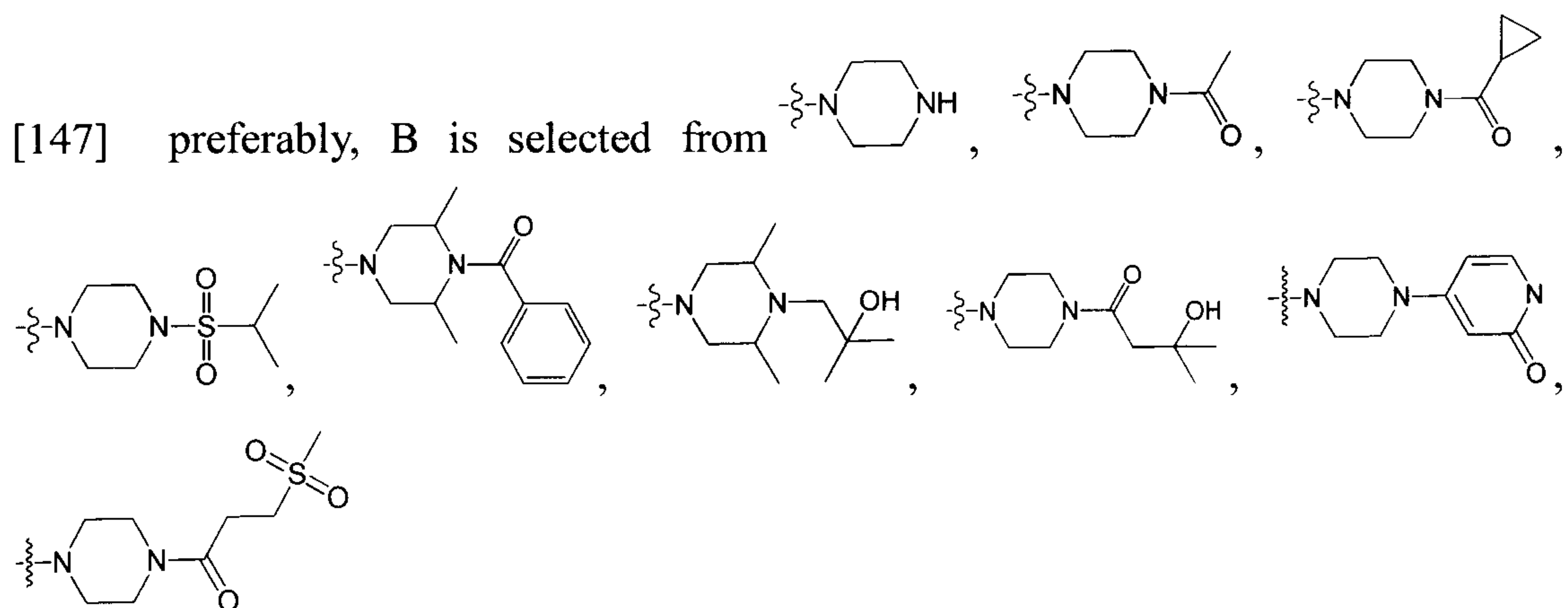
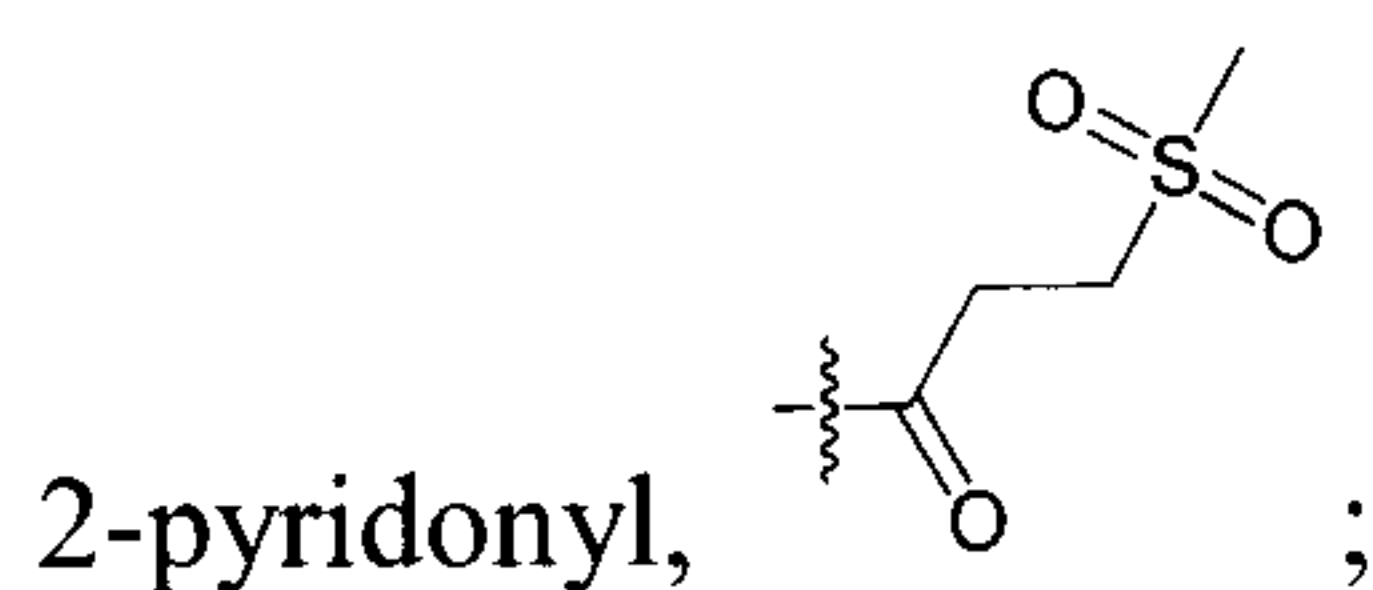
[142] R_{346} can also be selected from a phenyl, a pyridyl, an imidazolyl, a thienyl, a furyl, an oxazolyl, a thiazolyl, an isothiazolyl, a pyrrolidyl, a 2-pyridonyl;

[143] each of R_{3031} , R_{3037} , R_{3038} is independently selected from H, an optionally R_{3001} -substituted C_{1-3} alkyl or cyclopropyl;

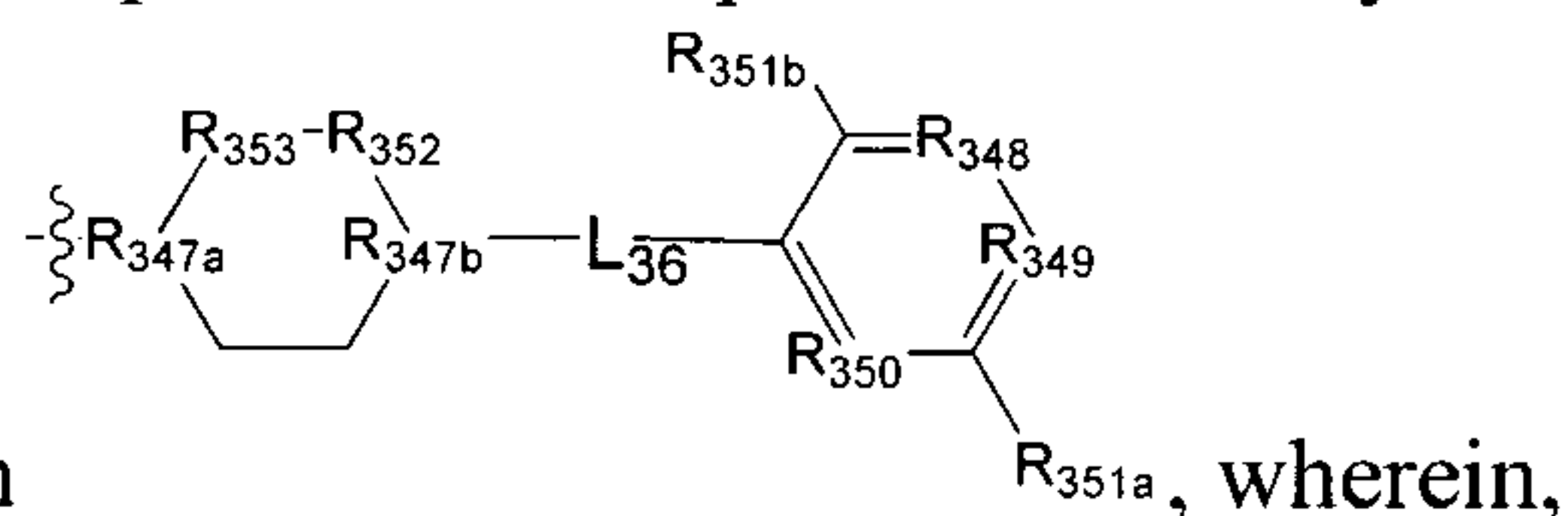
[144] R_{3001} is selected from OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2 , F, Cl, Br, I, CN, $-S(=O)CH_3$, $-S(=O)_2CH_3$, a methyl, a methoxy, the number of R_{3001} is selected from 1, 2 or 3;

[145] preferably, L_{35} is selected from a single bond, $C(=O)$, CH_2 ;

[146] preferably, R_{346} is selected from H, a methyl, a phenyl, $C(CH_3)_2(OH)$, $CH_2C(CH_3)_2(OH)$, a cyclopropyl acyl, an isopropyl sulfonyl, a pyrrolidyl, a



[148] Preferably, the compound or the pharmaceutically acceptable salt thereof,



wherein B is selected from

[149] each of R_{347a} , R_{347b} is independently selected from N or $C(R_{3028})$;

[150] none, one or two of $R_{348-350}$ is selected from N, the rest are selected from $C(R_{3039})$;

[151] each of R_{352} , R_{353} , L_{36} is independently selected from a single bond, $-C(=O)N(R_{3031})-$, $-C(=O)C(R_{3032})(R_{3033})-$, $C(R_{3034})(R_{3035})$, $CON(R_{3036})$, $N(R_{3037})$, $C=N(R_{3038})$, O, S, $C(=O)O$, $C(=O)$, $C=S$, $S(=O)$ and /or $S(=O)_2$;

[152] L_{36} can also be selected from a single bond;

[153] each of R_{3028} , $R_{3032-3035}$, R_{3039} , R_{351a} , R_{351b} is independently selected from H, OH, NH_2 , F, Cl, Br, I, CN, an optionally R_{3001} -substituted C_{1-3} alkyl or alkoxy or alkyl amino or cyclopropyl;

[154] each of R_{3031} , $R_{3036-3038}$ is independently selected from H, an optionally R_{3001} -substituted C_{1-3} alkyl or cyclopropyl;

[155] R_{3001} is selected from OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2 , F, Cl, Br, I, CN, a methyl, a methoxy, the number of R_{3001} is selected from 1, 2 or 3; preferably, L_{36} is selected from a single bond, $C(=O)NH$, $C(=O)CH_2$.

[156] Preferably, R_{347a} , R_{347b} is independently selected from N, CH or $C(OH)$.

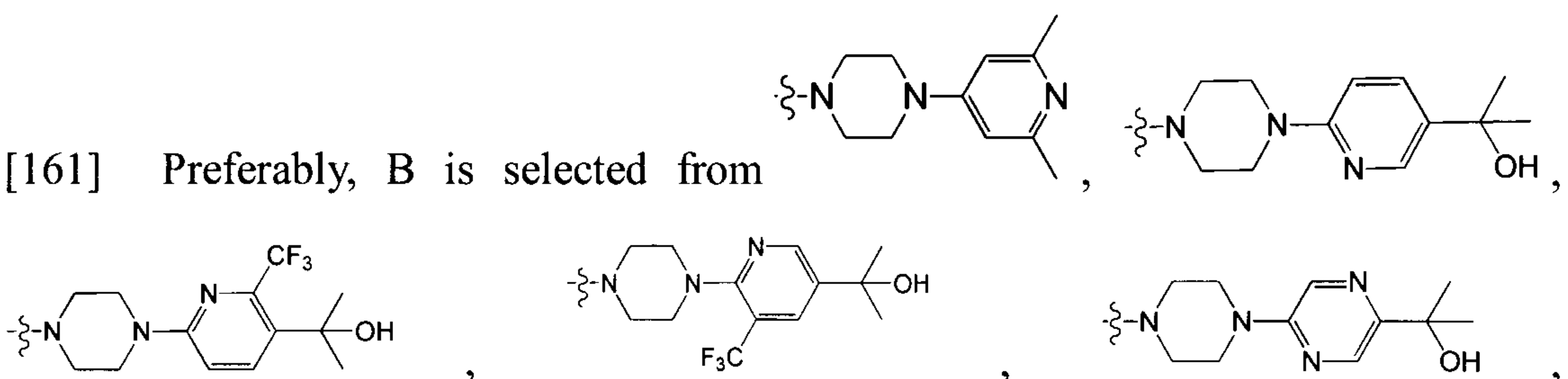
[157] Preferably, none, one or two of $R_{348-350}$ is selected from N, the rest are selected from $C(R_{3039})$.

[158] Preferably, R_{3039} is selected from H, a methyl, a trifluoromethyl, $C(CH_3)_2(OH)$.

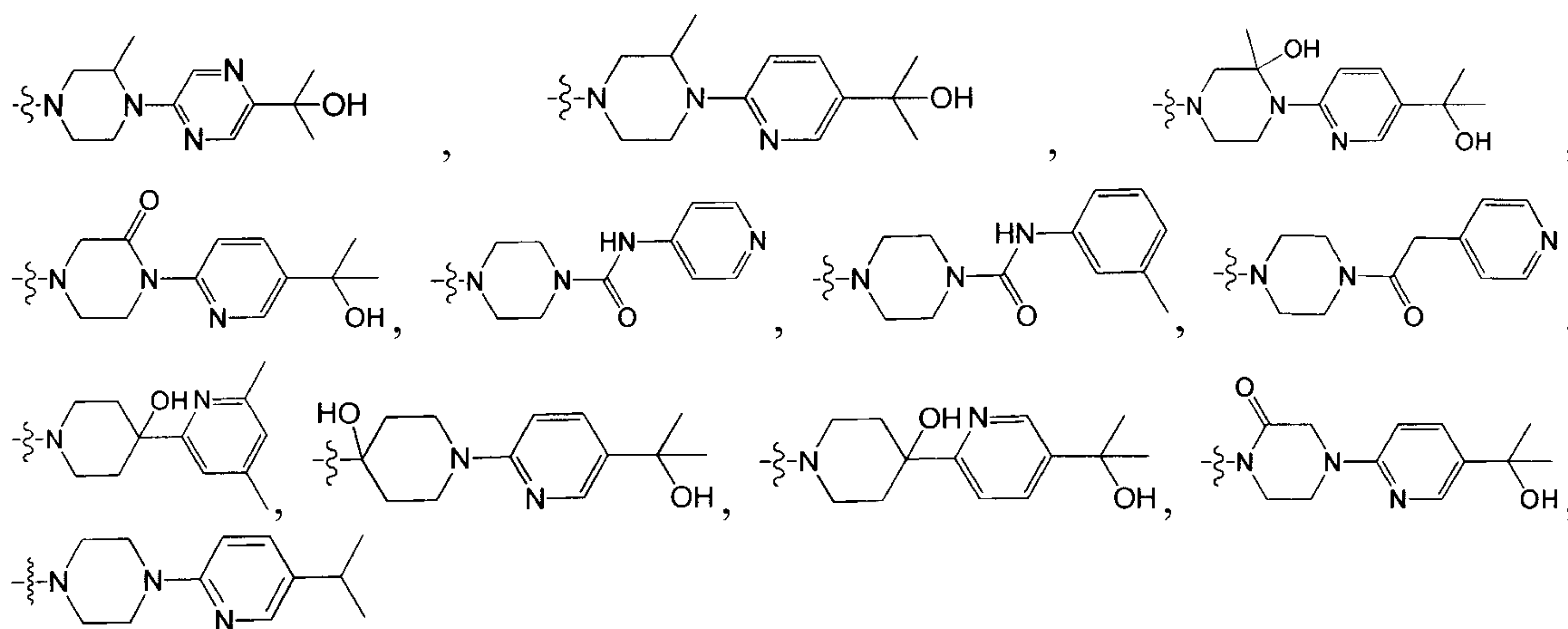
[159] Preferably, each of R_{351a} , R_{351b} is independently selected from H, a methyl, a trifluoromethyl, an isopropyl.

[160] Preferably, each of R_{352} , R_{353} is independently selected from $C(=O)$, $C(CH_3)(OH)$.

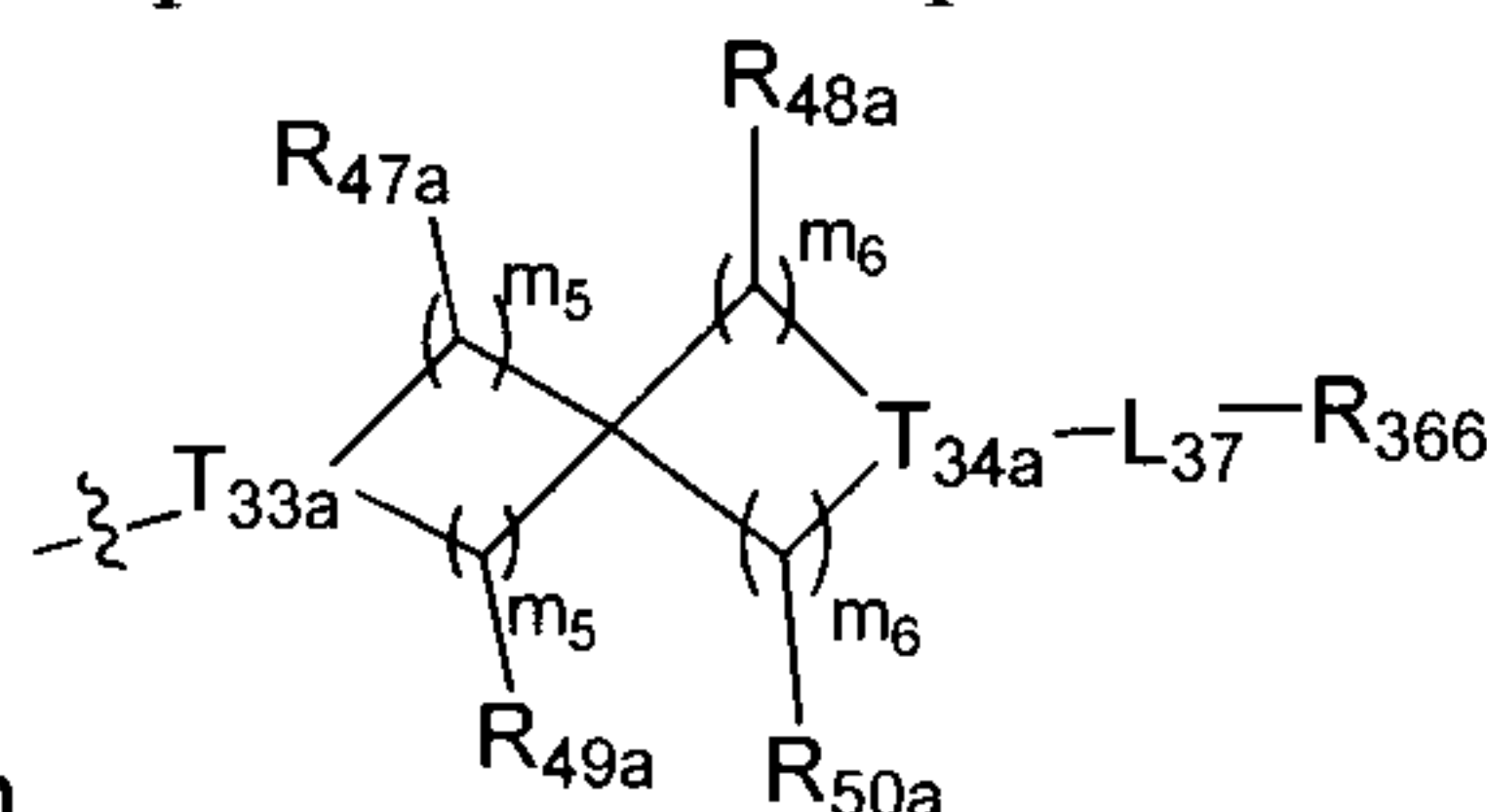
[161] Preferably, B is selected from



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[162] Preferably, the compound or the pharmaceutically acceptable salt thereof,



wherein B is selected from

, wherein

[163] each of T_{33a}, T_{34a} is independently selected from N, CH or C(R₄₀₀₁);

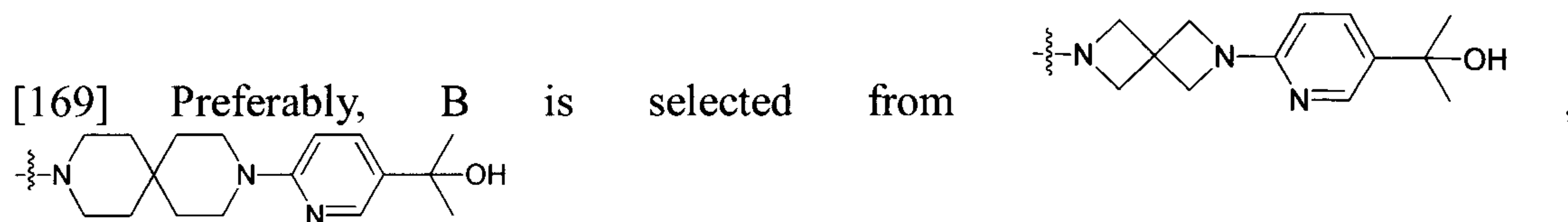
[164] L₃₇ is independently selected from a single bond, a C₁₋₃ alkyl, O, S, C(=O), C=S, S(=O) and/or S(=O)₂;

[165] each of R₃₆₆, R_{47a}, R_{48a}, R_{49a}, R_{50a} is independently selected from H, an optionally R₄₀₀₁-substituted C₁₋₃ alkyl or alkoxy or alkyl acyl or alkyl sulfonyl or alkyl amino or cyclopropyl, an optionally R₄₀₀₁-substituted cyclopropyl acyl or cyclopropyl sulfonyl;

[166] R₃₆₆ can also be selected from the group consisting of a phenyl, a pyridyl, an imidazolyl, a thienyl, a furyl, an oxazolyl, a thiazolyl and an isothiazolyl which is optionally substituted by R₄₀₀₁;

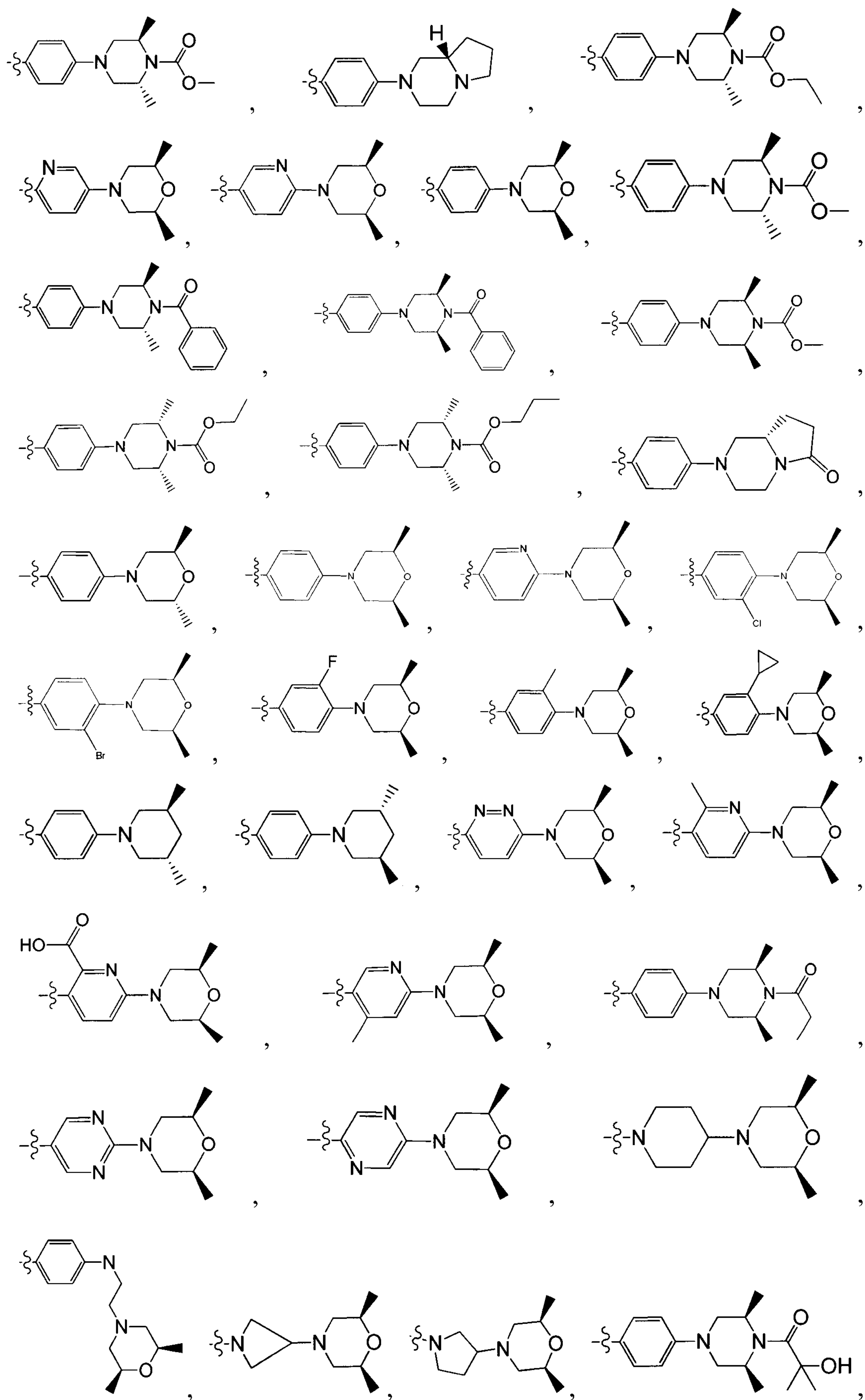
[167] R₄₀₀₁ is selected from OH, N(CH₃)₂, NH(CH₃), NH₂, C(CH₃)₂(OH), F, Cl, Br, I, CN, a methyl, a methoxy, the number of R₄₀₀₁ is selected from 1, 2 or 3;

[168] preferably, L₃₇ is selected from a single bond, C(=O), CH₂.



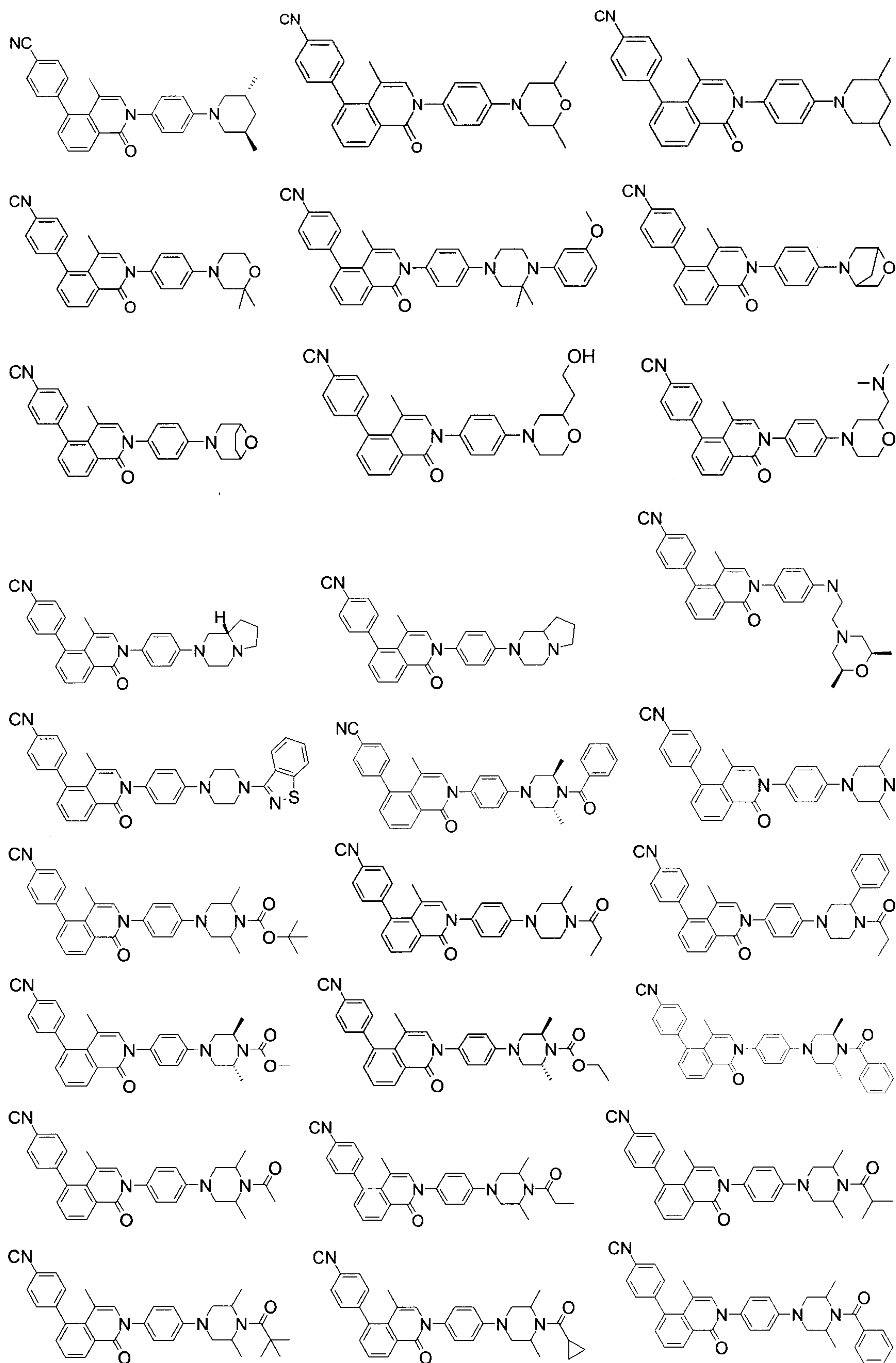
[170] Preferably, the compound or the pharmaceutically acceptable salt thereof, wherein B is selected from the group consisting of

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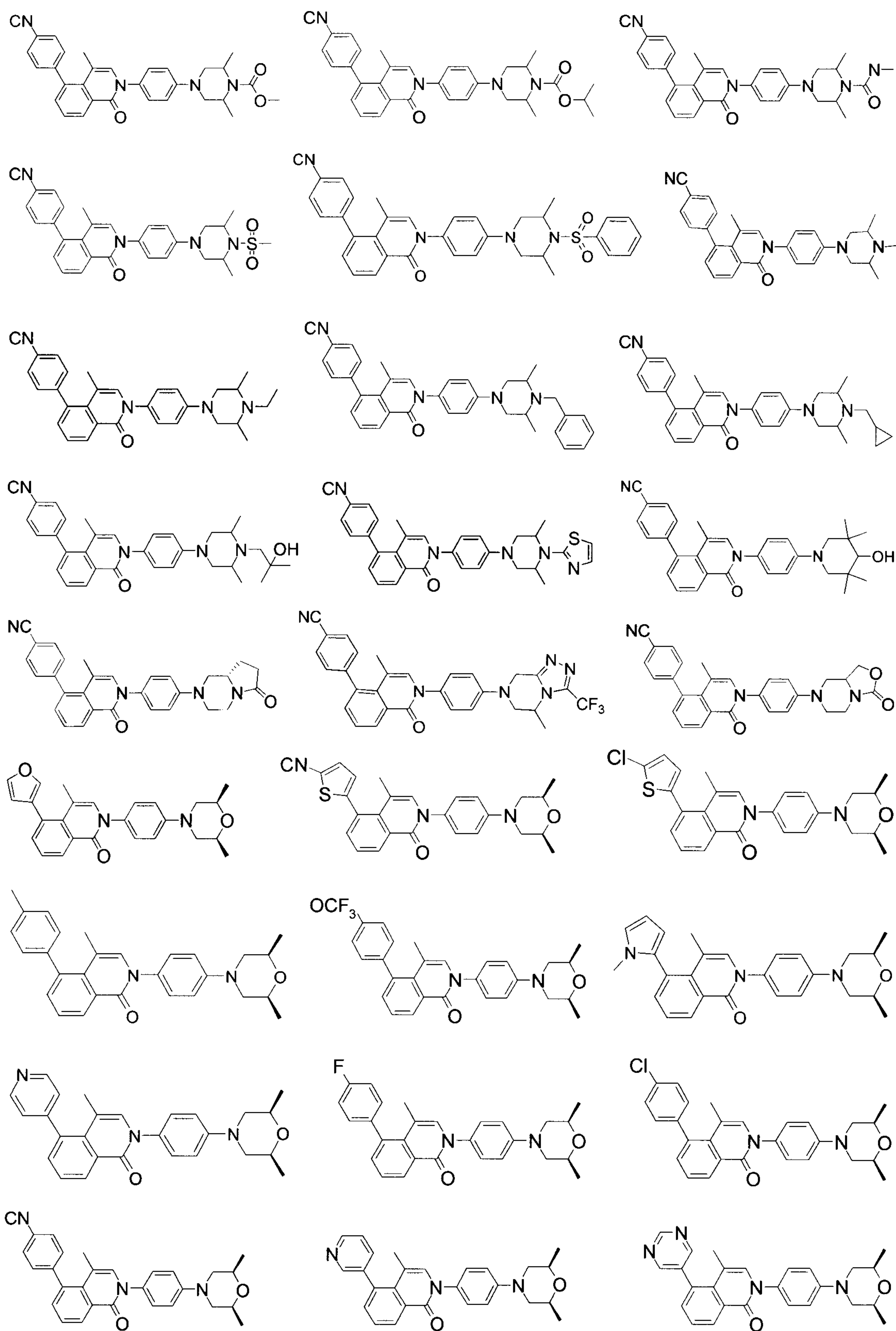


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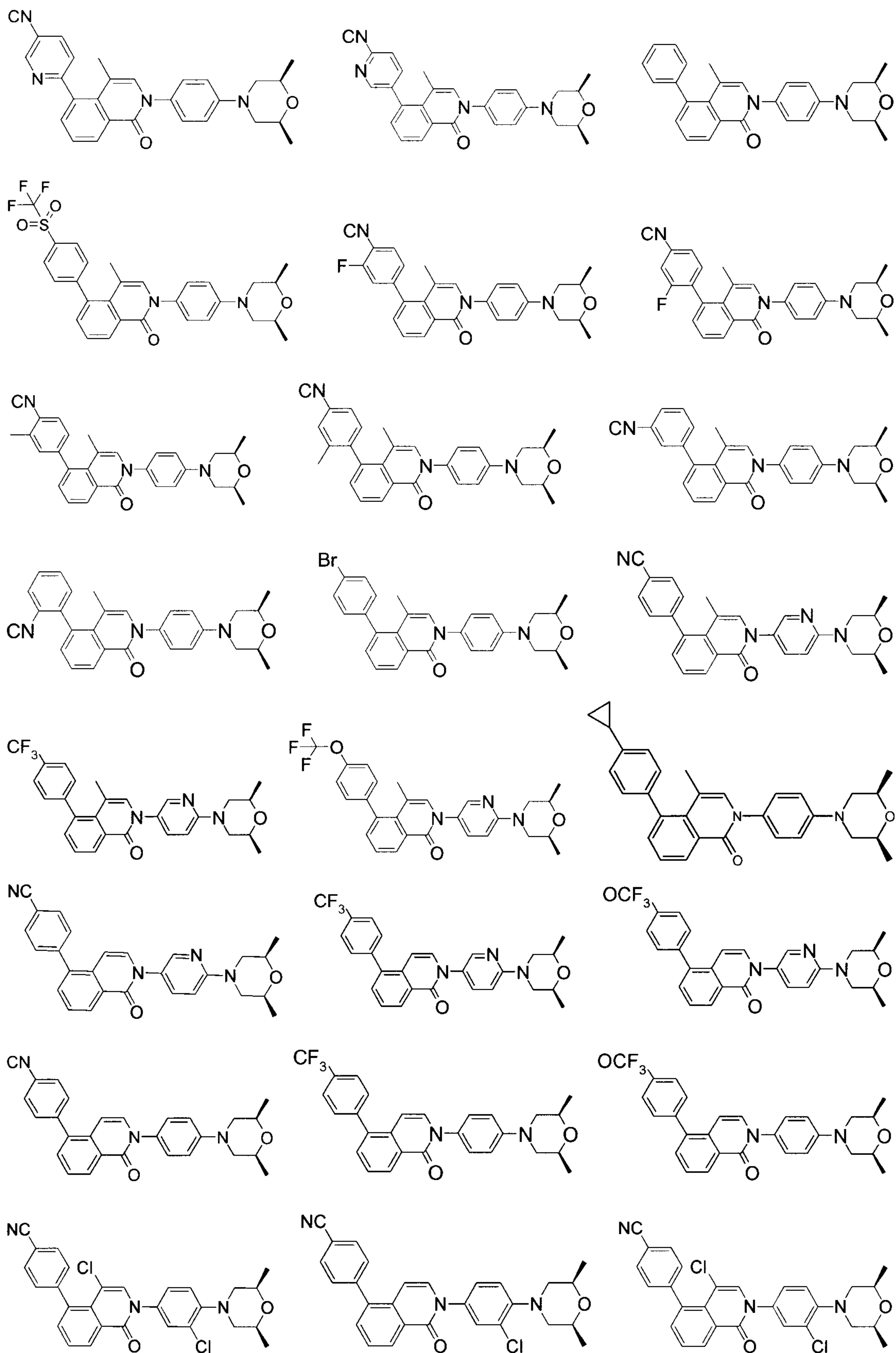
selected from the group consisting of



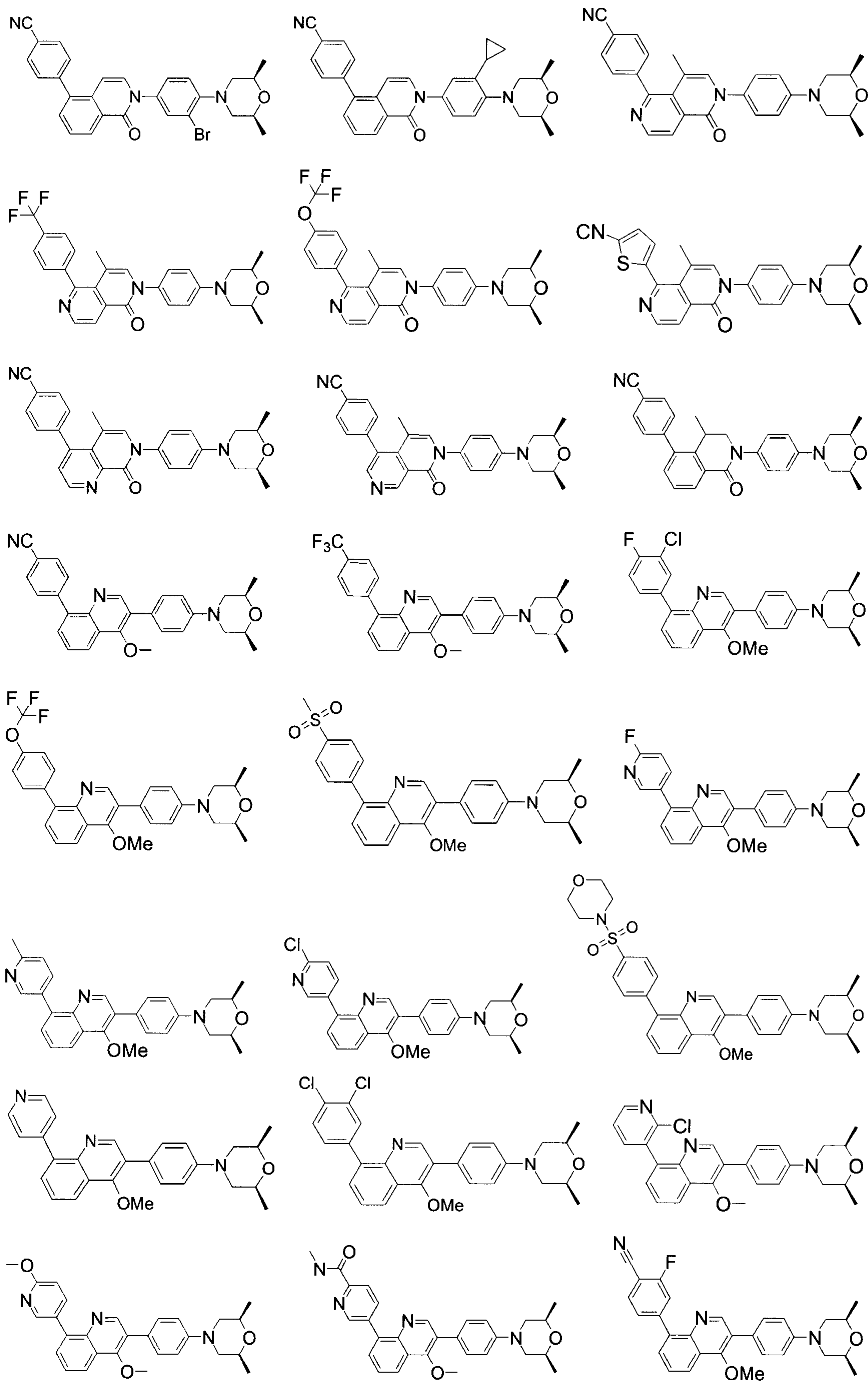
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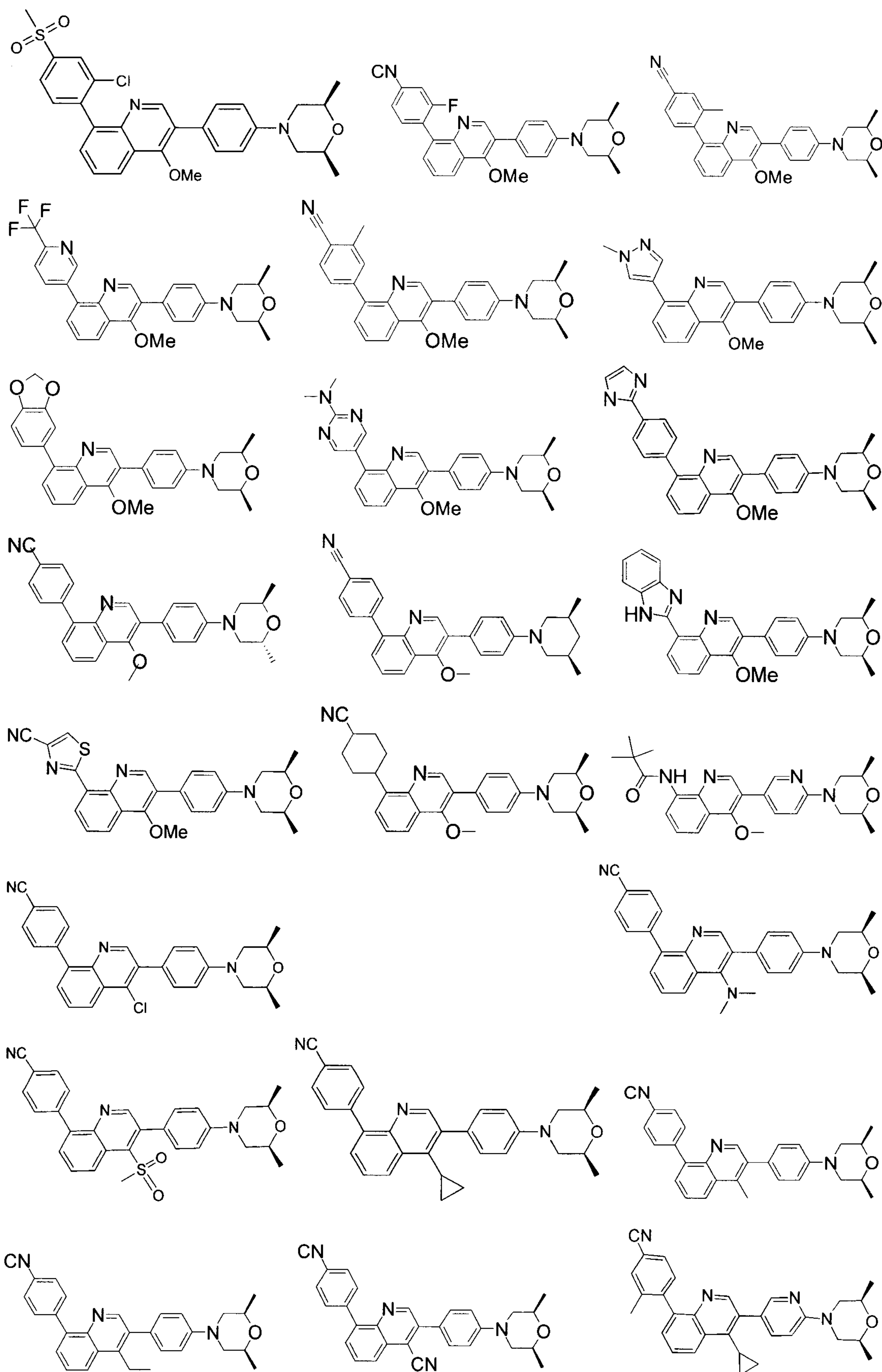


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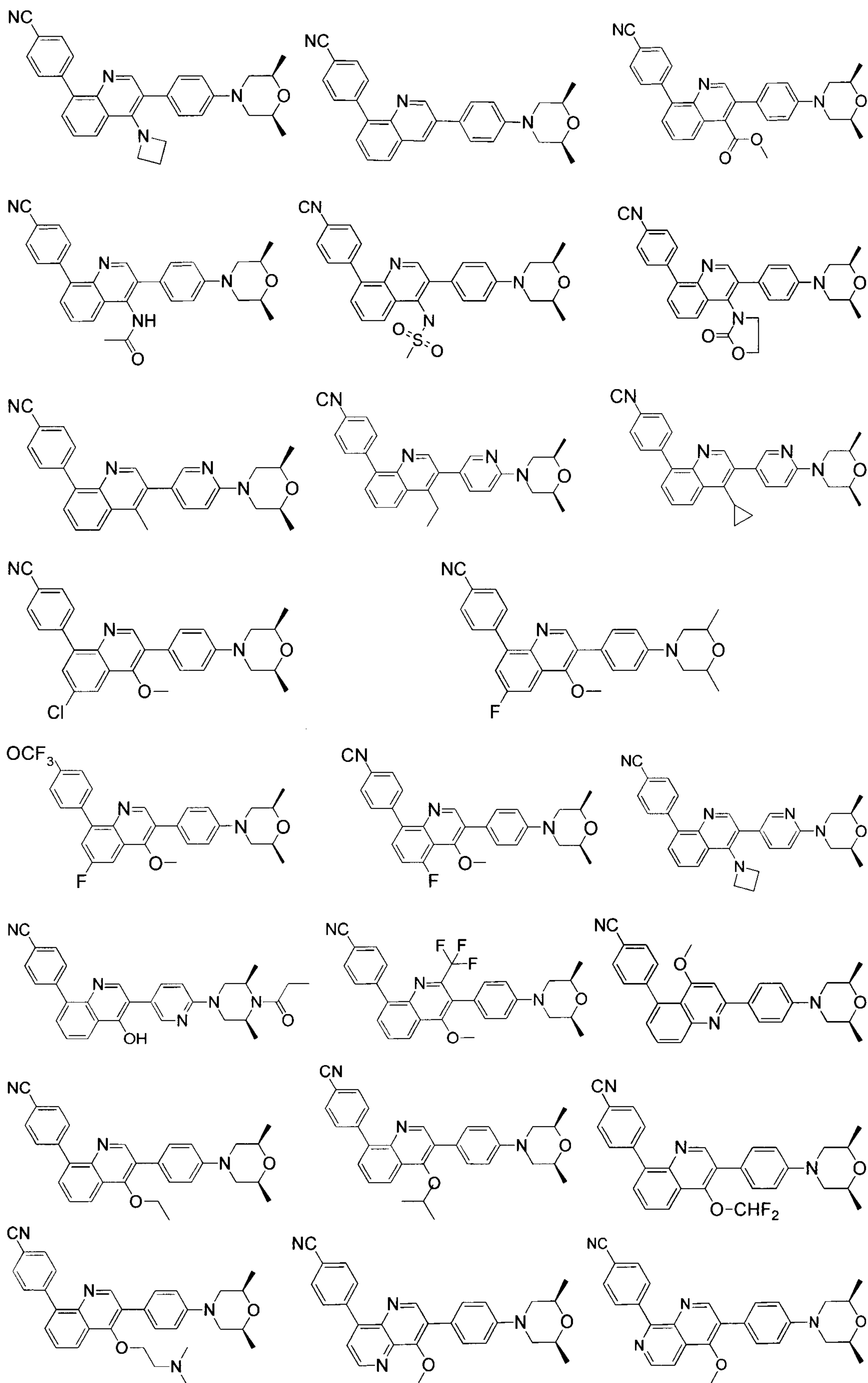


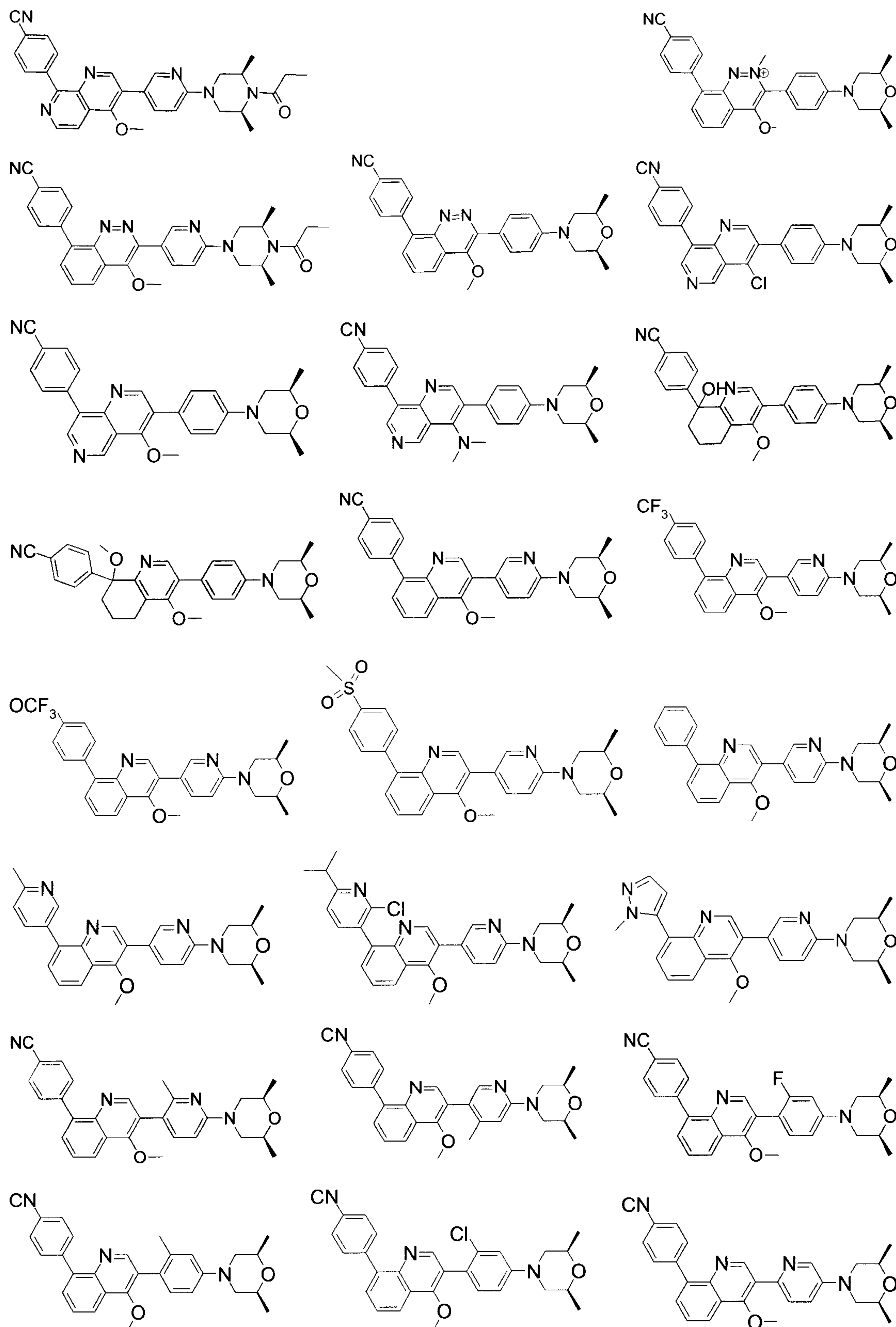
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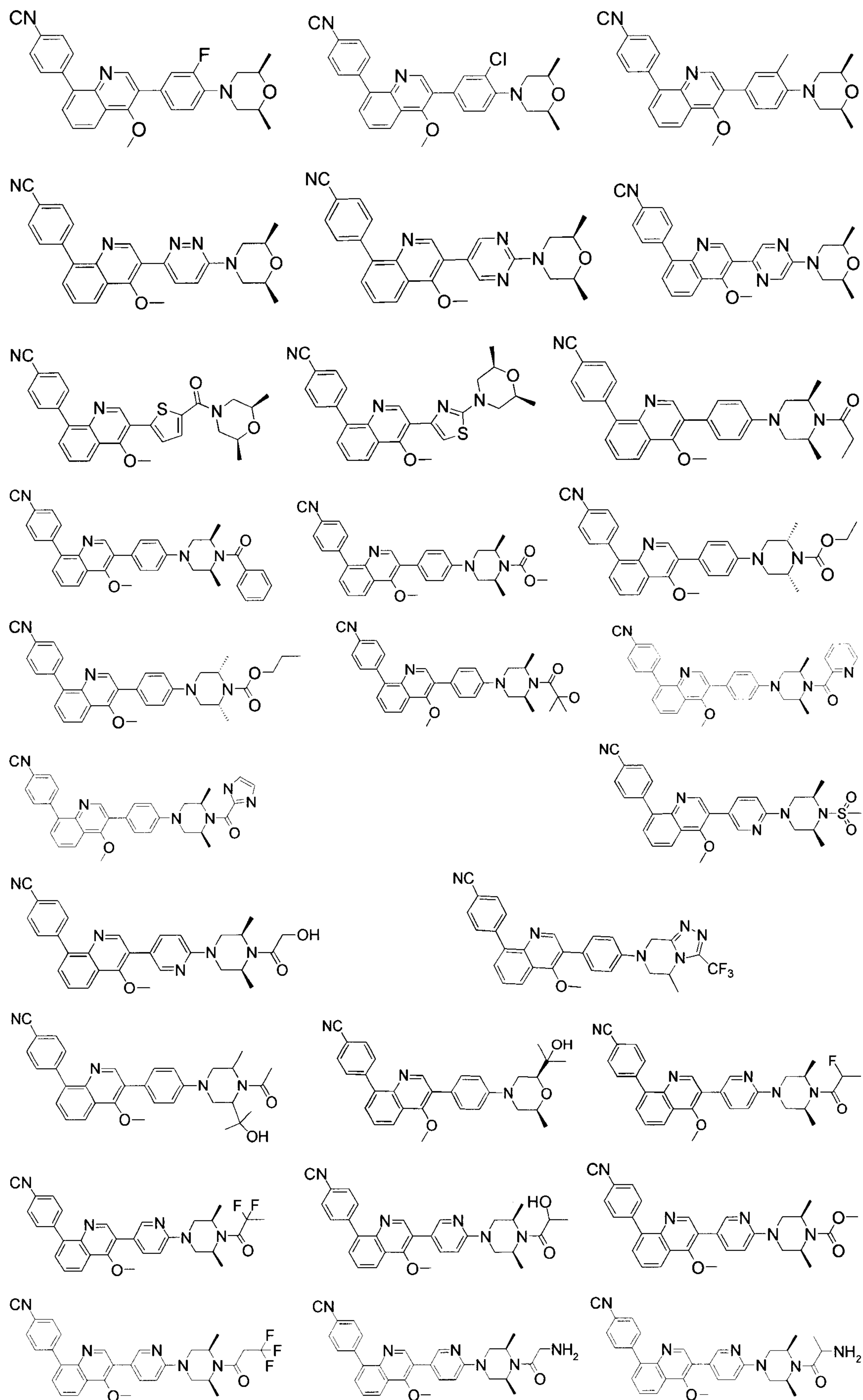


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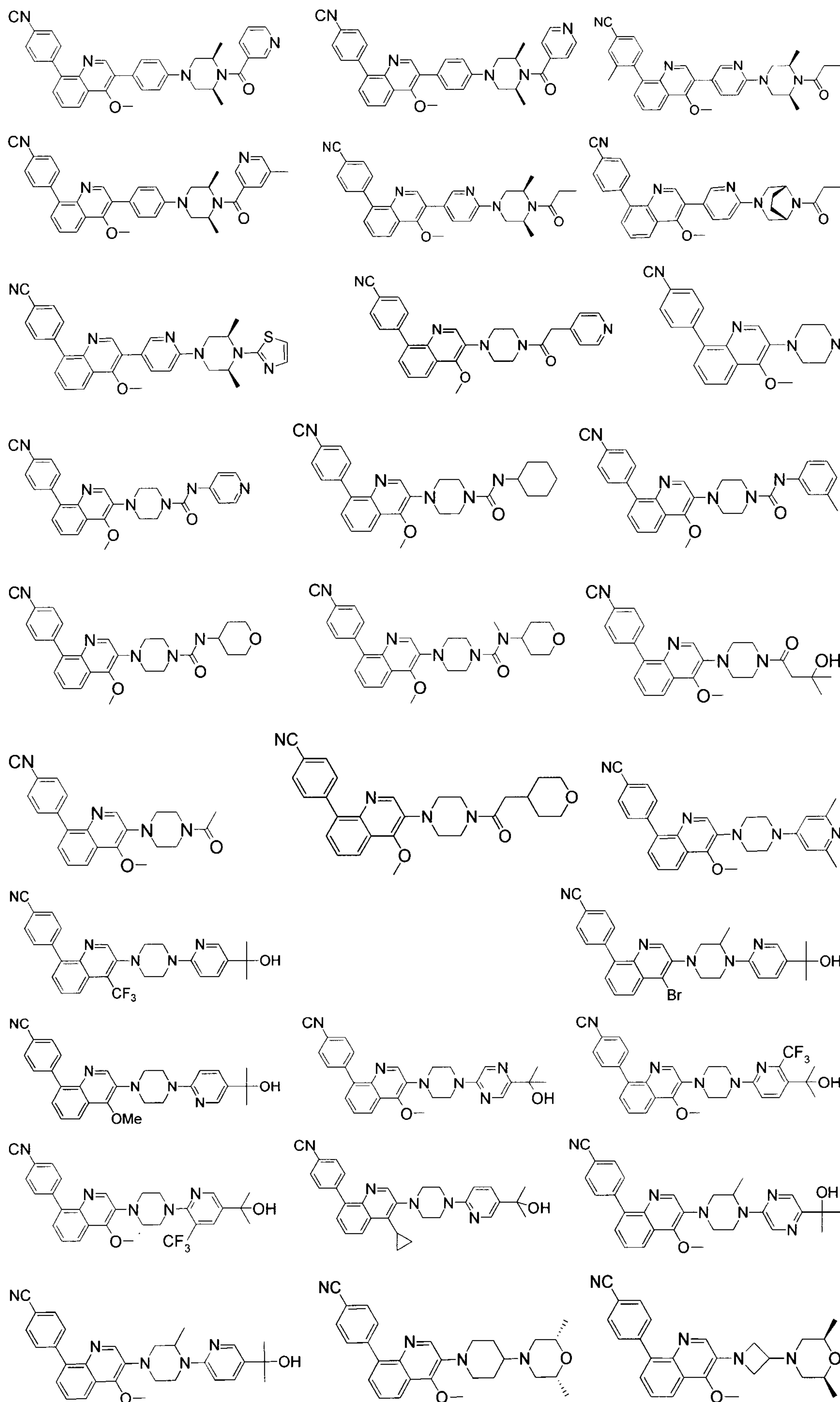




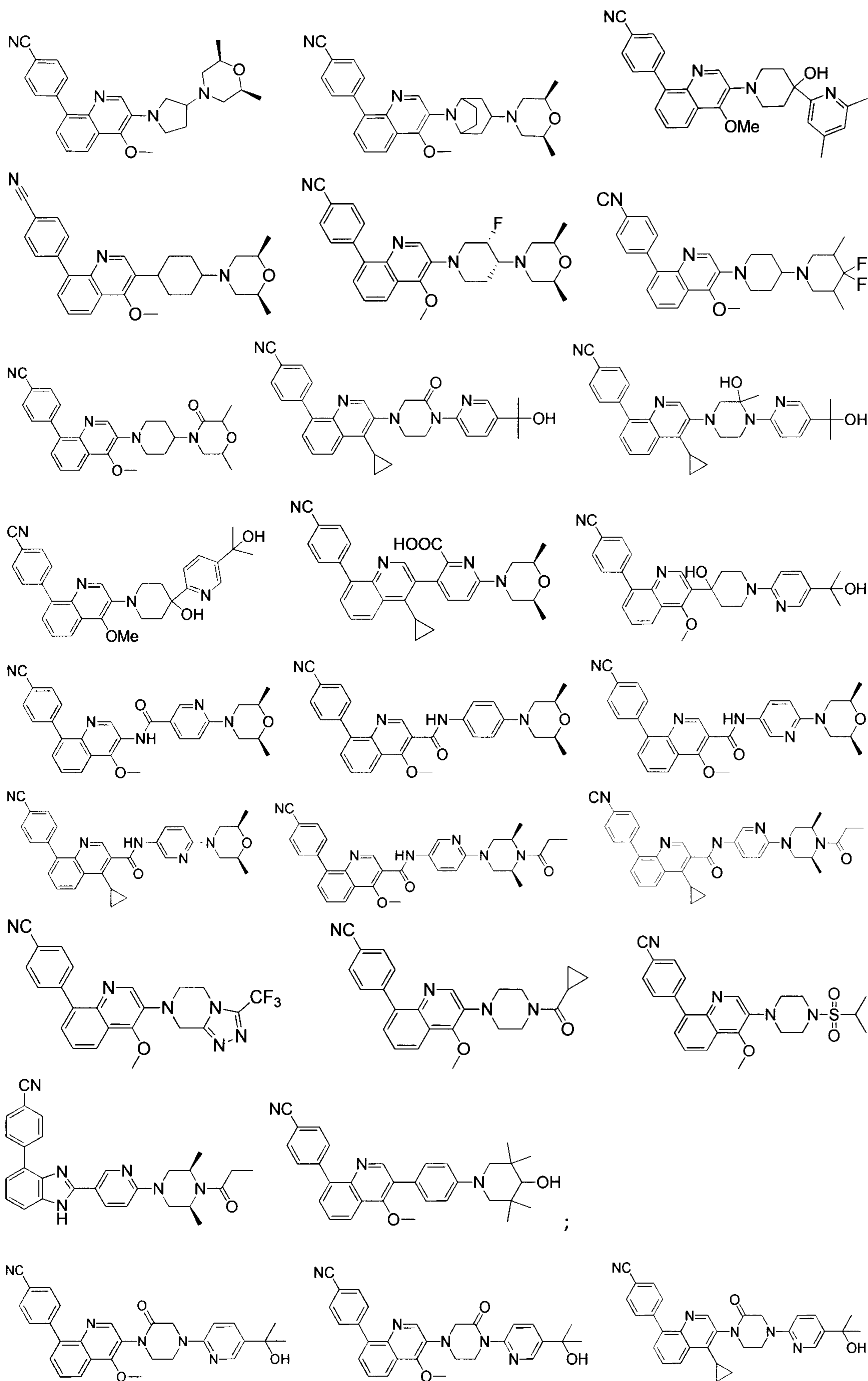
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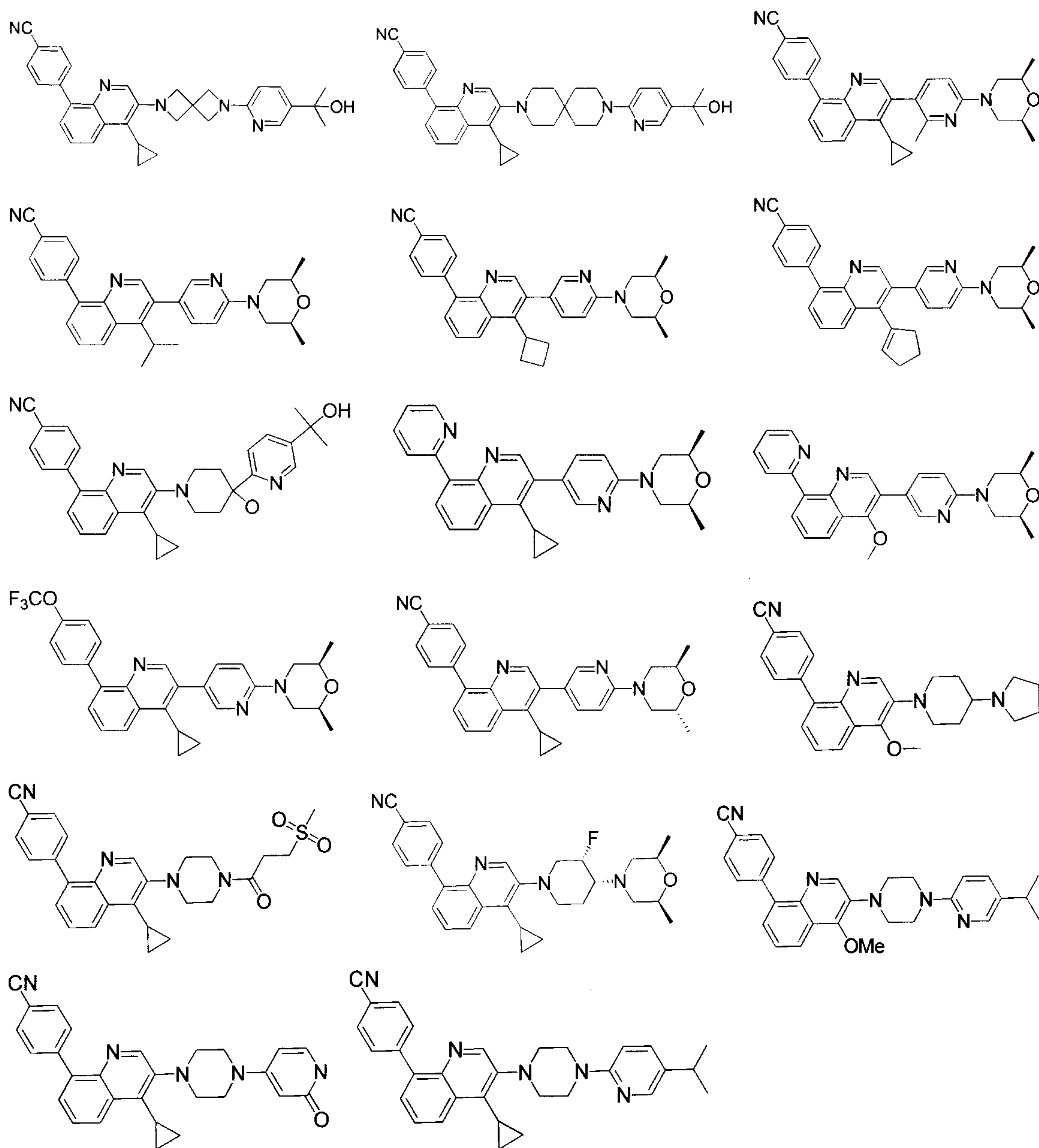


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[172] The term “pharmaceutically acceptable salt” refers to the salt of the compound of the present invention, which is prepared by the compound with specific substituent discovered by the present invention and relatively non-toxic acid or alkali. When the compound of the present invention contains a relatively acidic functional group, an alkali-addition salt can be obtained by contacting the compound in a neutral form with sufficient amount of alkali in a pure solution or suitable inert solvent. The pharmaceutically acceptable alkali-addition salt includes the salt of sodium, potassium, calcium, ammonium, organic ammonia or magnesium or the like. When the compound of the present invention contains a relatively alkaline functional group, an acid-addition salt can be obtained by contacting the compound in a neutral form with sufficient amount of acid in a pure solution or suitable inert solvent. Examples of the pharmaceutically acceptable acid-addition salt include a salt of inorganic acid, the inorganic acid includes such as hydrochloric acid, hydrobromic acid, nitric acid, carbonic acid, bicarbonate, phosphoric acid, hydrogen phosphate, dihydrogen

phosphate, sulfuric acid, hydrogen sulfate, hydriodic acid, phosphorous acid etc; and salt of organic acid, the organic acid includes such as acetic acid, propionic acid, isobutyric acid, maleic acid, malonic acid, benzoic acid, succinic acid, suberic acid, fumaric acid, lactic acid, mandelic acid, phthalic acid, phenylsulfonic acid, *p*-toluene sulfonic acid, citric acid, tartaric acid, methylsulfonic acid and the like; and also includes salt of amino acid (e.g. arginine etc.), and salt of organic acid such as glucuronic acid and the like (see Berge et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science 66: 1-19 (1977)). Some specific compound of the present invention contains both alkaline and acidic functional groups so as to be transformed to be any alkali-addition or acid-addition salt.

[173] Preferably, the neutral form of a compound is regenerated by contacting a salt with a base or an acid in a conventional manner and then separating the parent compound. The difference between a parent form of a compound and the various salt forms lies in some physical properties, such as that the solubility in a polar solvent is different.

[174] The "pharmaceutically acceptable salt" in the present invention is the derivatives of the compound of the present invention, wherein, the parent compound is modified by salifying with an acid or an alkali. Examples of the pharmaceutically acceptable salt include but not limited to: an inorganic acid or organic acid salt of an alkali such as amine, an alkali metal or organic salt of acid radical such as carboxylic acid and so on. The pharmaceutically acceptable salt includes conventionally non-toxic salts or quaternary ammonium salts of the parent compound, such as a salt formed by a non-toxic inorganic acid or organic acid. The conventionally non-toxic salt includes but not limited to those salts derived from inorganic acids and organic acids, the inorganic acids or organic acids are selected from 2-acetoxybenzoic acid, 2-isethionic acid, acetic acid, ascorbic acid, phenylsulfonic acid, benzoic acid, bicarbonate, carbonic acid, citric acid, edetic acid, ethanedisulfonic acid, ethanesulfonic acid, fumaric acid, glucoheptose, gluconic acid, glutamic acid, glycolic acid, hydrobromic acid, hydrochloric acid, hydriodate, hydroxyl, hydroxynaphthoic, isethionic acid, lactic acid, lactose, dodecanesulfonic acid, maleic acid, malic acid, mandelic acid, methanesulfonic acid, nitric acid, oxalic acid, pamoic acid, pantothenic acid, phenylacetic acid, phosphoric acid, polygalacturonan, propionic acid, salicylic acid, stearic acid, folinate acid, succinic acid, aminosulfonic acid, sulfanilic acid, sulphuric acid, tannic acid, tartaric acid and *p*-toluene sulfonic acid.

[175] The pharmaceutically acceptable salt of the present invention can be prepared by a conventional method with a parent compound containing an acidic or alkaline group. Generally, the preparation method of the salt comprises that in water or an organic solvent or the mixture of water and organic solvent, reacting these compounds in forms of free acids or alkalis with stoichiometric amount of proper alkalis or acids. In general, preferably choose non-aqueous media such as ether, ethyl acetate, ethanol, isopropanol or acetonitrile and so on.

[176] Except for the form of salt, there is a form of prodrug for the compound in

the present invention. The prodrug of the compound described in the present invention is easily transformed to be the compound of the present invention via chemical changes under physiological conditions. Besides, the prodrug can be transformed to be the compound of the present invention via chemical or biochemical method in vivo environment.

[177] Some compounds of the present invention can exist in the form of non-solvate or solvate forms, including hydrate forms. In general, the solvate form is similar to the non-solvate form, both of which are included within the scope of the present invention. Some compounds of the present invention can exist in polycrystalline or amorphous form.

[178] Some compounds of the present invention can contain asymmetric carbon atoms (optical center) or double bonds. The racemic isomers, diastereomers, geometric isomers and single isomers are included within the scope of the present invention.

[179] Unless otherwise specified, the term "substituted" refers to one or more hydrogen atoms in a specific atom optionally substituted by a substituent, including a deuterium and a variant of hydrogen, as long as the valence state of the specific atom is normal and the compound obtained after substitution is stable. When the substituent is a ketone group (i.e. =O), it means that two hydrogen atoms are substituted. A substitution of ketone group does not occur in an aryl. The term "optionally substituted" means that it may be substituted or not be substituted, unless otherwise specified, the type and number of substituents can be arbitrary under the premise of stability available in chemistry.

[180] Unless otherwise specified, when any parameter (e.g. R) shows an occurrence for more than one time in the composition or structure of the compound, the definition of each occurrence is independent. Therefore, for example, if a group is substituted by 0~2 of R, the group may optionally be substituted by at most two R, and R has an independent option in each case. In addition, the combination of substituents and/or their variants is allowed only if such a combination will lead to a stable compound.

[181] When one parameter therein is selected from a single bond, it means that the two groups the parameter connects to connect to each other directly, for example when the L in A-L-Z refers a single bond, it means that the structure actually is A-Z.

[182] Unless otherwise specified, when bonds of a substituent can be crossly connected to two atoms of a ring, the substituent can be bonded to arbitrary atoms in the ring. When it does not specify through which atom contained in the listed substituent is it connected to the general structure formula including the compound that is not specifically mentioned, the substituent can be bonded through any of its atoms. The combination of substituents and/or their variants is allowed only if such a combination will lead to a stable compound.

[183] Unless otherwise specified, the term "hydrocarbon group" or its specific concept (such as alkyl, alkenyl, alkynyl, phenyl, etc.) itself or as a part of another substituent represents a linear, branched or cyclic hydrocarbon group or a combination thereof, which can be fully saturated, monocyclic or polycyclic unsaturated, can be monosubstituted, disubstituted or polysubstituted, can be univalent (such as methyl), bivalent (such as methylene) or multivalent (such as methenyl), can include bivalent or multivalent atomic groups, with a specified number of carbon atoms (such as that C₁-C₁₀ refers to having 1~10 carbon atoms). The term "alkyl" includes an aliphatic hydrocarbon group and aromatic hydrocarbon group, the aliphatic hydrocarbon group includes linear and cyclic structures, specifically includes but not limited to alkyl, alkenyl and alkynyl, the aromatic hydrocarbon group includes but not limited to 6- to 12-membered aromatic hydrocarbon group such as benzene, naphthalene and the like. In some embodiments, the term "alkyl" refers to linear or branched or cyclic groups or their combination, which can be completely saturated, monocyclic or polycyclic unsaturated, can include divalent and polyvalent groups. Examples of saturated hydrocarbon groups include but not limited to homologues or isomers of methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *tert*-butyl, *iso*-butyl, *sec*-butyl, *iso*-butyl, cyclohexyl, (cyclohexyl) methyl, cyclopropyl methyl, and *n*-amyl, *n*-hexyl, *n*-heptyl, *n*-octyl and the like. Unsaturated alkyl has one or more double or triple bond, examples of which includes but not limited to vinyl, 2-propenyl, butenyl, crotyl, 2-isopentenyl, 2-butadienyl, 2,4-(pentadienyl), 3-(1,4-pentadienyl), acetenyl, 1- and 3-propinyl, 3-butylnyl, and more advanced homologues and isomers.

[184] Unless otherwise specified, the terms "heterohydrocarbon group", "heterocycle group", "hydrocarbon-heteroatom group", "cycle-heteroatom group", "heterohydrocarbon-heteroatom group", "heterocycle-heteroatom group" refer that a heteroatom or a heteroatom group is contained on a specified group, the heteroatom or heteroatom group include but not limited to N, NH, a substituted or protected NH, O, S, S(=O), S(=O)₂, C(=O), C(=O)O, for a ring system, a heteroatom or a heteroatom group can be located in internal position or external position of the ring system (e.g. cyclopropyl sulfonyl, cyclopropyl acyl), wherein, the "heterohydrocarbon group", "heterocycle group" are connected with the rest part of the molecule through a carbon atom, that is, the heteroatom can be located in any position of the group (excluding the position where hydrocarbon group is attached to the rest part of the molecule); the "hydrocarbon-heteroatom group", "cycle-heteroatom group" are connected with the rest part of the molecule through a heteroatom, that is, the heteroatom is located in the position where the group is attached to the rest part of the molecule); the "heterohydrocarbon-heteroatom group", "heterocycle-heteroatom group" are connected with the rest part of the molecule through a heteroatom, wherein the heteroatom can be located in any position of the group (including the position where hydrocarbon group is attached to the rest part of the molecule).

[185] Unless otherwise specified, the term "heterohydrocarbon group" or its specific concepts (such as heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl, etc.) itself or the term combining with another term refers to a stable linear, branched or

cyclic hydrocarbon group or their combinations, which consists of a certain number of carbon atoms and at least one heteroatom. In some embodiments, the term "heterohydrocarbon group" or its specific concepts (such as heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl, etc.) itself or the term combining with another term refers to a stable linear, branched hydrocarbon group or their combinations, which consists of a certain number of carbon atoms and at least one heteroatom. In a typical embodiment, the heteroatom is selected from the group consisting of B, O, N and S, in which the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom is optionally quaternized. Heteroatoms B, O, N and S can be located in any internal position of the heterohydrocarbon group (excluding the position where hydrocarbon group is attached to the rest part of the molecule). Examples include but not limited to $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-$, $-\text{S}(\text{O})-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})_2-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{CH}=\text{N}-\text{OCH}_3$ and $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$. At most two heteroatoms are adjacent, such as $-\text{CH}_2-\text{NH}-\text{OCH}_3$.

[186] Unless otherwise specified, the terms "alkoxy", "alkyl amino" and alkylthio" (or thioalkoxy) are the idiomatic expressions, which refers to the alkyl group is attached to the rest of molecule through an oxygen, an amino, or a sulfur atom, respectively.

[187] Unless otherwise specified, the term "cyclohydrocarbon group", "heterocyclo hydrocarbon group", "cyclohydrocarbon-heteroatom group" or its specific concepts (such as aryl, heteroaryl, aryl heteroatom group, cycloalkyl, heterocycloalkyl, cycloalkyl heteroatom group, cycloalkenyl, heterocycloalkenyl, cycloalkenyl heteroatom group, cycloalkynyl, heterocycloalkynyl, cycloalkynyl heteroatom group, etc.) itself or the term combining with other terms respectively refers to a cyclic "hydrocarbon group", "heterohydrocarbon group" or "hydrocarbon heteroatom group". Examples of the cycloalkyl include but not limited to cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, etc.. Unrestricted examples of the heterocyclic group include 1-(1,2,5,6-tetrahydropyridinyl), 1-piperidyl, 2-piperidyl, 3-piperidyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuranylidol-3-yl, tetrahydrothiophene-2-yl, tetrahydrothiophene-3-yl, 1-piperazinyl and 2-piperazinyl.

[188] Unless otherwise specified, the term "halogenated" or "halogen" itself or as a part of another substituent refers to fluorine, chlorine, bromine or iodine atom. In addition, the term "halogenated alkyl" is intended to include monohalogenated alkyl and polyhalogenated alkyl. For example, the term "halogenated (C_1-C_4) alkyl" is intended to include but not limited to trifluoromethyl, 2, 2, 2-trifluoroethyl, 4-chlorobutyl and 3-bromopropyl, etc..

[189] Unless otherwise specified, the term "aryl" refers to a polyunsaturated aromatic hydrocarbon substituent, which can be monosubstituted, disubstituted or multisubstituted, it can be monocyclic or polycyclic (preferably 1 to 3 rings), they fuse together or connect by a covalent linkage. The term "heteroaryl" refers to an

aryl (or ring) containing 1 to 4 heteroatoms. In an exemplary embodiment, the heteroatom is selected from the group consisting of B, N, O, and S, in which the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom is optionally quaternized. The heteroaryl group can be connected to the rest part of the molecule *via* a heteroatom. Unrestricted examples of an aryl or a heteroaryl include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-benzothiazolyl, purinyl, 2-benzoimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalyl, 5-quinoxalyl, 3-quinolyl and 6-quinolyl. Any one of the substituents in the aryl and heteroaryl ring system is selected from the acceptable substituents described below.

[190] Unless otherwise specified, for the sake of brevity, when used in combination with other terms (e.g. aryloxy, arylthio, aralkyl), the aryl includes the definition of aryl and heteroaryl ring defined above. Therefore, the term "aralkyl" is intended to include the groups that aryl attached to alkyl (e.g. benzyl, phenyl ethyl, pyridyl methyl), including those alkyls wherein carbon atoms (such as methylene) has been replaced by such as oxygen atoms, such as phenoxy methyl, 2-pyridyloxymethyl-3-(1-naphthoxy)propyl, etc..

[191] Unless otherwise specified, the "ring" refers to substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. The ring includes a fused ring. A number of the atoms in the ring is usually defined as the member of the ring, for example, "5- to 7-membered ring" is a ring looped with 5 to 7 atoms. Unless otherwise specified, the ring optionally contains 1 to 3 of heteroatoms. Therefore, "5- to 7-membered ring" includes, for example, phenyl pyridine and piperidinyl; on the other hand, the term "5- to 7-membered heterocycloalkyl ring" includes pyridyl and piperidinyl, but does not include phenyl. The term "ring" also includes a ring system containing at least one ring, wherein each ring is of the above definition independently.

[192] Unless otherwise specified, the term "heteroatom" includes atoms except carbon (C) and hydrogen (H), such as including oxygen (O), nitrogen (N), sulfur (S), silicon (Si), germanium (Ge), aluminum (Al) and boron (B) etc..

[193] Unless otherwise specified, the term "leaving group" refers to a functional group or atom which can be replaced by another functional group or atom through a substitution reaction (e.g., nucleophilic substitution reaction). For example, representative leaving groups include triflate; chlorine, bromine, iodine; sulfonate, such as mesylate, tosylate, *p*-bromobenzene sulfonate, *p*-tosylate etc.; acyloxy, such as acetoxy, trifluoroacetoxy and so on.

[194] Unless otherwise specified, the term "protecting group" includes but not

limited to “the protecting group of an amino”, “the protecting group of a hydroxyl”, or “the protecting group of a mercapto”. The term “the protecting group of an amino” refers to a protecting group that is suitable for preventing side reactions which occur at the nitrogen atom of an amino group. A representative protecting group of an amino includes but not limited to: formyl; acyl, such as alkanoyl (such as acetyl, trichloroacetyl or trifluoroacetyl); alkoxycarbonyl, such as tert-butoxycarbonyl (Boc); aryl methoxycarbonyl, such as benzyloxycarbonyl (Cbz) and 9-fluorenylmethoxycarbonyl (Fmoc); aryl methyl, such as benzyl (Bn), triphenyl methyl (Tr), 1,1-bis-(4'-methoxyphenyl) methyl; silyl, such as trimethylsilyl (TMS) and tert-butyldimethylsilyl (TBS) and etc.. The term “the protecting group of a hydroxyl” refers to a protecting group that is suitable for preventing side reactions of a hydroxyl group. A representative protecting group of a hydroxyl includes but not limited to: alkyl, such as methyl, ethyl, and tert-butyl; acyl, such as alkanoyl (such as acetyl); aryl methyl, such as benzyl (Bn), *p*-methoxybenzyl (PMB), 9-fluorenylmethyl (Fm) and diphenylmethyl (diphenylmethyl, DPM); silyl, such as trimethylsilyl (TMS) and tert-butyldimethylsilyl (TBS) and etc..

[195] Unless otherwise specified, examples of halogenated alkyl include but not limited to: trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. The alkoxyl represents that the alkyl group with a specific number of carbon atoms is connected by an oxygen bridge. The C₁₋₆ alkoxyl includes C₁, C₂, C₃, C₄, C₅ and C₆ alkoxyl. Examples of alkoxyl include but not limited to: methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *sec*-butoxy, *tert*-butoxy, *n*-pentyloxy and *S*-pentyloxy. The “cycloalkyl” includes saturated cyclic group, such as cyclopropyl, cyclobutyl or cyclopentyl. The 3- to 7-membered cycloalkyl includes C₃, C₄, C₅, C₆ and C₇ cycloalkyl. The “alkenyl” includes linear or branched hydrocarbon chain, wherein any stable sites on the chain exist one or more C-C double bonds, such as vinyl and propenyl.

[196] Unless otherwise specified, the term “halo” or “halogen” refers to fluorine, chlorine, bromine and iodine.

[197] Unless otherwise specified, the term “heterocycle” or “heterocyclic group” refers to a stable monocyclic, bicyclic or bicyclic hetero-ring, they can be saturated, partially unsaturated or unsaturated (aromatic), they contain carbon atoms and 1, 2, 3 or 4 of heteroatom in the ring which is independently selected from the group consisting of N, O and S, wherein any of the heterocycle can be fused to a benzene ring to form a bicyclic ring.

[198] Unless otherwise specified, examples of heterocyclic compound include but not limited to: acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzomercaptofuranyl, benzomercaptophenyl, benzoxazolyl, benzoxazolinyl, benzothiazolyl, benzotriazolyl, benzotetrazolyl, benzoisoxazolyl, benzoisothiazolyl, benzoimidazolinyl, carbazolyl, 4*aH*-carbazolyl, carbolinyl, chromanyl, chromene, cinnolinyl, decahydroquinolyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl,

imidazolyl, 1*H*-indazolyl, indoalkenyl, indolynyl, indolizynyl, indolyl, 3*H*-indolyl, isatino group, isobenzofuranyl, pyran, isoindolyl, isoindolynyl, isoindolyl, indolyl, isoquinolyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholynyl, naphthyridynyl, octahydroisoquinolyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidynyl, oxazolyl, isooxazolyl, hydroxyl indyl, pyrimidyl, phenanthridynyl, phenanthrolinyl, phenazine, phenothiazine, benzopurynyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidyl, oxopiperidynyl, 4-oxopiperidynyl, piperonyl, pteridyl, purynyl, pyranyl, pyrazynyl, pyrazolidynyl, pyrazolynyl, pyrazolyl, pyridazinyl, oxazolopyridine, pyridinoimidazole, pyridinothiazole, pyridyl, pyrimidyl, pyrrolidinyl, pyrrolinyl, 2*H*-pyrrolyl, pyrrolyl, pyrazolyl, quinazolynyl, quinolyl, 4*H*-quinolizynyl, quinoxalinyl, quinuclidynyl, tetrahydrofuryl, tetrahydroisoquinolynyl, tetrahydroquinolynyl, tetrazolyl, 6*H*-1,2,5-thiadiazynyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazyl, isothiazolylthienyl, thienyl, thiophenoxazolyl, thiophenothiazolyl, thiophenoimidazolyl, thienyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl. Fused ring and spiro ring compound are also included. Unless otherwise specified, the compound of the present invention can be prepared through many synthetic methods which are well-known to the person skilled in the art, including the specific embodiments listed below and its combination with other chemical synthetic methods and the equivalent alternative methods which are known to the person skilled in the art, the preferred embodiments include but not limited to the embodiments of the present invention.

[199] Unless otherwise specified, the solvents used in the present invention are commercially available.

[200] Unless otherwise specified, the present invention adopts the following abbreviations: aq represents water; HATU represents 2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate; EDC represents *N*-(3-dimethylaminopropyl)-*N'*-ethyl carbodiimide hydrochloride; m-CPBA represents m-chloroperbenzoic acid; eq represents equivalent, equal-quantitative; CDI represents carbonyl diimidazole; DCM represents dichloromethane; PE represents petroleum ether; DIAD represents diisopropyl azodicarboxylate; DMF represents *N,N*-dimethylformamide; DMSO represents dimethylsulfoxide; EtOAc represents ethyl acetate; EtOH represents ethanol; MeOH represents methanol; Cbz represents benzyloxycarbonyl, a protecting group of an amino; Boc represents tert-butoxycarbonyl, a protecting group of an amine; HOAc represents acetic acid; NaCNBH₃ represents sodium cyanoborohydride; r.t. represents room temperature; O/N represents overnight; THF represents tetrahydrofuran; Boc₂O represents di-tert-butyl dicarbonate; TFA represents trifluoroacetic acid; DIPEA represents diisopropylethylamine; SOCl₂ represents thionyl chloride; CS₂ represents carbon disulfide; TsOH represents *p*-toluene sulfonic acid; NFSI represents *N*-fluorobenzenesulfonimide; NCS represents *N*-chlorosuccinimide; *n*-Bu₄NF represents tetrabutylammonium fluoride; iPrOH represents 2-propanol; mp represents melting point.

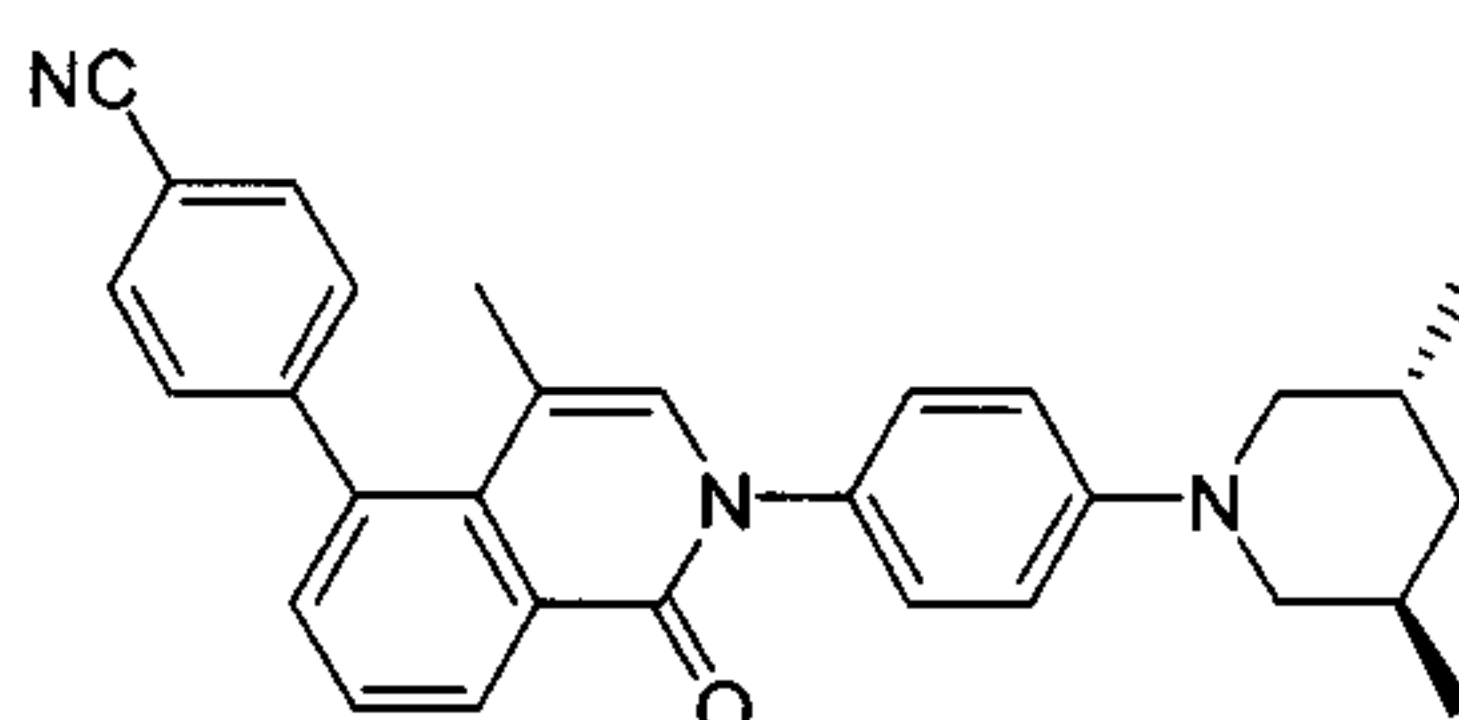
[201] Unless otherwise specified, compounds are named by manual work or software ChemDraw®, commercially available compounds are named in accordance with suppliers' catalogue.

[202] Compared to the prior art, the compounds of the present invention are effective, lower-toxic, and make great and even incredible progresses on the aspects of activity, half-life, solubility and pharmacokinetics etc., which are more suitable for the pharmaceutical industry.

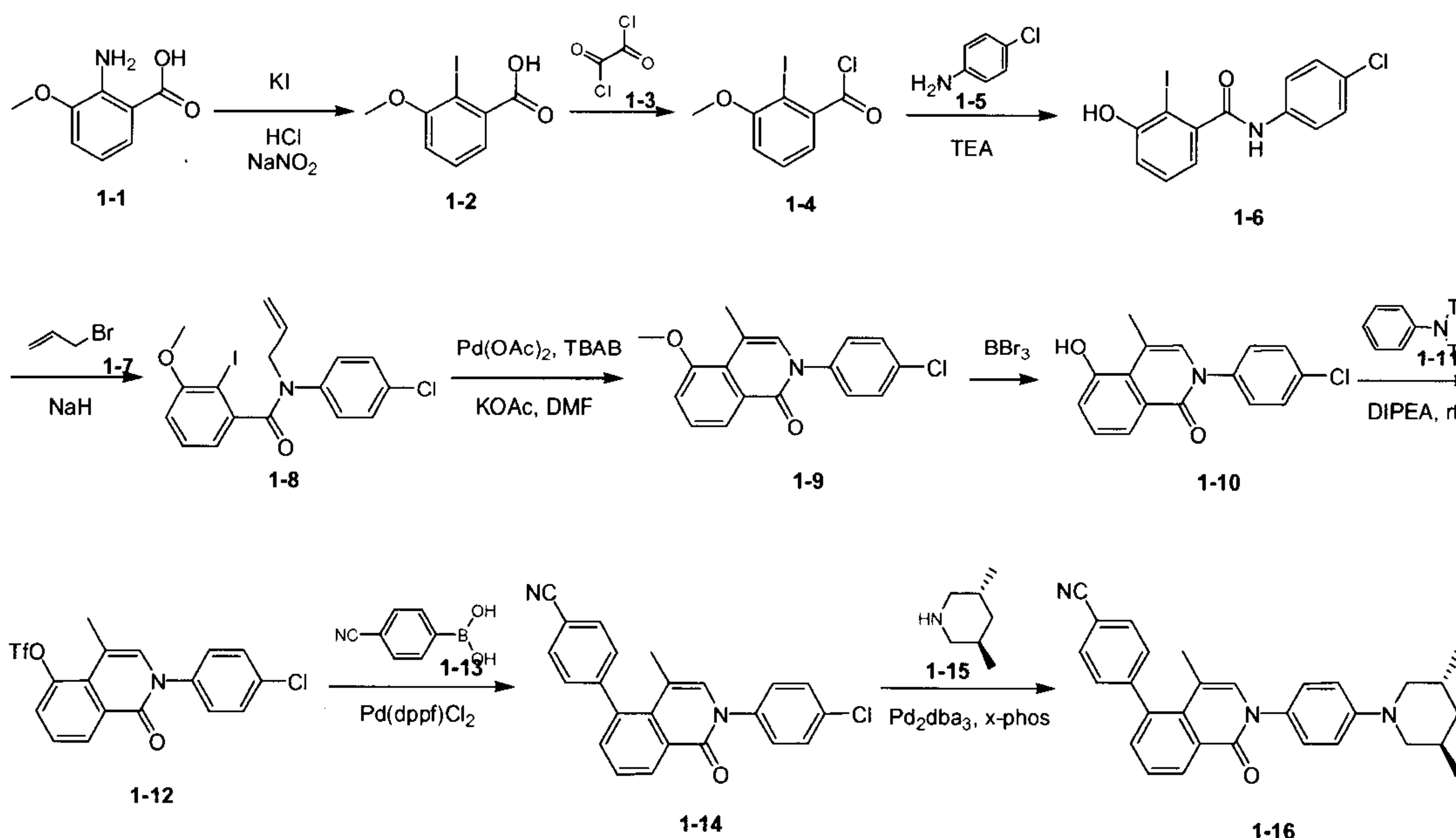
Detailed description of the preferred embodiment

[203] The following examples further illustrate the present invention, but it does not mean any unfavorable limitation to the present invention. The application has already described the present invention in details, in which the embodiments also have been disclosed, it is obvious for the person skilled in the art to vary and improve the embodiments of the present invention without departing from the spirit and scope of the present invention.

Embodiment 1



4-(2-(4-((3R,5R)-3,5-dimethylpiperidin-1-yl)phenyl)-4-methyl-1-oxo-1,2-dihydroisoquinolin-5-yl)benzonitrile



[204] Step 1: Compound 1-1(60 g, 0.36 mol) was dissolved in a solution of

ice-water (900 mL), acetone (300 mL) and HCl aqueous solution (180 mL, 2.23 mol), then the mixture was added dropwise into an aqueous solution (360 mL) of sodium nitrite (50 g, 0.72 mol) slowly when the temperature was kept at 0-10 °C. After stirring for 2 h, solid of potassium iodide (120 g, 0.72 mol) was added directly, and the temperature was kept at 7-10 °C for 30 min. The reaction mixture was heated to 80-90°C until purple gas disappeared, and then cooled to room temperature. The reaction mixture was filtrated to deliver the compound 1-2 (85 g, yield 85%) as yellow solid. **MS ESI** calcd for C₈H₇IO₃ [M+H]⁺ 279, found 279.

[205] Step 2: Compound 1-2 (34.5 g, 0.12 mol) was dissolved in DCM (300 mL), DMF (0.1 mL) was added, and then compound 1-3 (12 mL, 0.135 mol) was added dropwise, the reaction mixture was stirred for 1 h to deliver the compound 1-4 as yellow oil. The crude product was used for the next step directly. **MS ESI** calcd for C₈H₆ClIO₂ [M+H]⁺ 297, found 297.

[206] Step 3: Compound 1-5 (15 g, 0.12 mol) was dissolved in DCM (150 mL), then DIPEA (77 g, 0.6 mol) was added, the reaction mixture was stirred at room temperature for 5 min. Compound 1-4 (46 g, 0.12 mol) was dissolved in DCM (300 mL), and was added dropwise into the reaction mixture at 0 °C. After 3 h, the reaction was complete as detected by TLC (PE: EtOAc= 3:1), the reaction mixture was poured into water and extracted with DCM. The organic phase was washed with brines, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE: EtOAc=3:1) to deliver the target compound 1-6 (38 g, yield 75%) as yellow solid. **MS ESI** calcd for C₁₃H₉ClINO₂ [M+H]⁺ 374, found 374.

[207] Step 4: NaH (4.8 g, 0.2 mol) was added into a solution of compound 1-6 (38 g, 0.1 mol) in DMF (400 mL), the reaction mixture was added compound 1-7(24 g, 0.2 mol) and stirred at 0 °C for 2 h. After the reaction was complete as detected by LC-MS, the reaction mixture was poured into water slowly and extracted with EtOAc. The organic phase was washed with brines, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE: EtOAc=5:1) to deliver the target compound 1-8 (29 g, yield 69%) as yellow oil. **MS ESI** calcd for C₁₇H₁₅ClINO₂ [M+H]⁺ 428, found 428.

[208] Step 5: Compound 1-8 (28 g, 66 mmol), tetrabutyl ammonium bromide (53 g, 165 mmol), KOAc (9.7 g, 0.1 mol) and Pd(OAc)₂ (1.48 g, 6.6 mmol) were dissolved in DMF (250 mL), the reaction mixture was stirred at 100 °C for 16 h. The reaction was complete as detected by TLC (PE: EtOAc= 3:1). The reaction mixture was quenched with water and extracted with EtOAc. The organic phase was washed with brines, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by recrystallization to deliver the compound 1-9 as white solid (16 g, yield 81%). **MS ESI** calcd for C₁₇H₁₄ClINO₂ [M+H]⁺ 300, found 300.

[209] Step 6: BBr₃ (12.5 mL, 0.134 mol) was dripped into a solution of compound

1-9 (16 g, 0.054 mol) in DCM (150 mL) at 0 °C, the reaction mixture was stirred at room temperature for 16 h. The reaction was detected by TLC (PE: EtOAc= 3:1). The reaction mixture was quenched with saturated sodium carbonate solution and filtrated to deliver the compound 1-10 as white solid (13 g, yield 84%). **MS ESI** calcd for $C_{16}H_{12}ClNO_2$ $[M+H]^+$ 286, found 286.

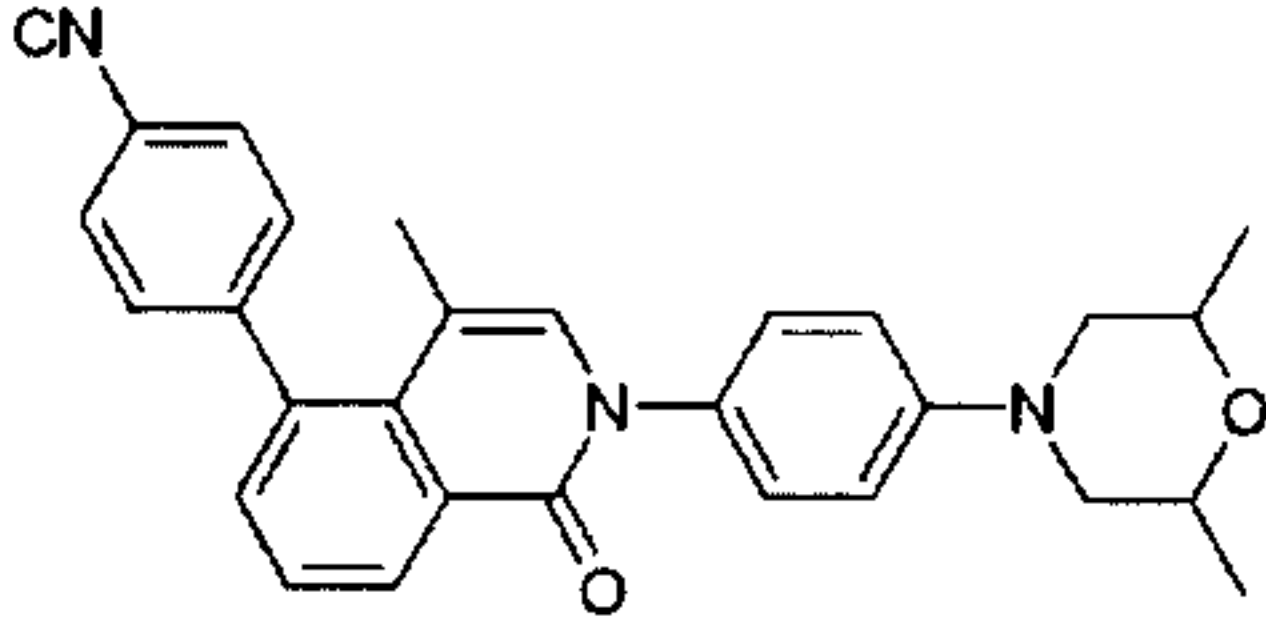
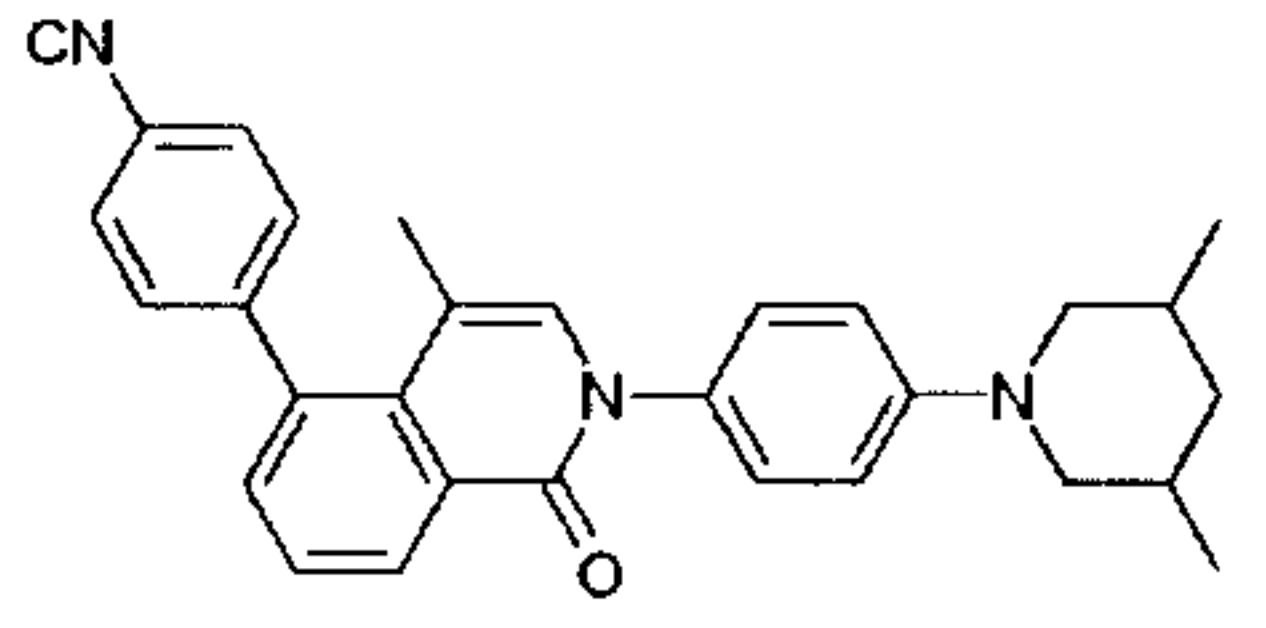
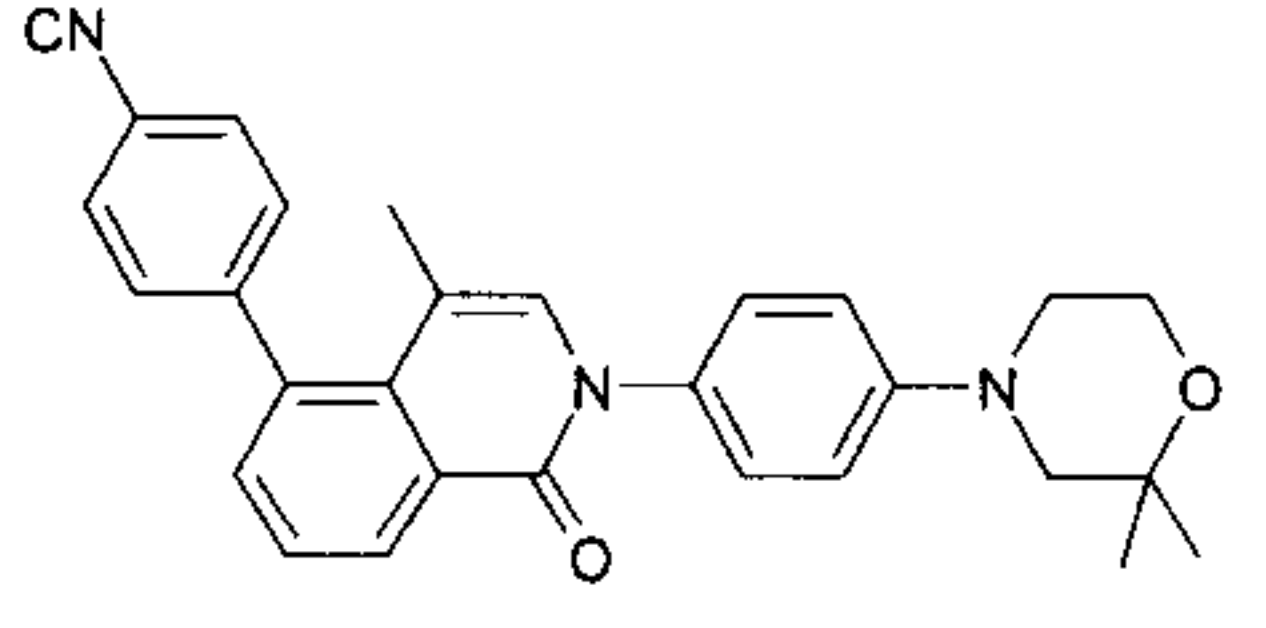
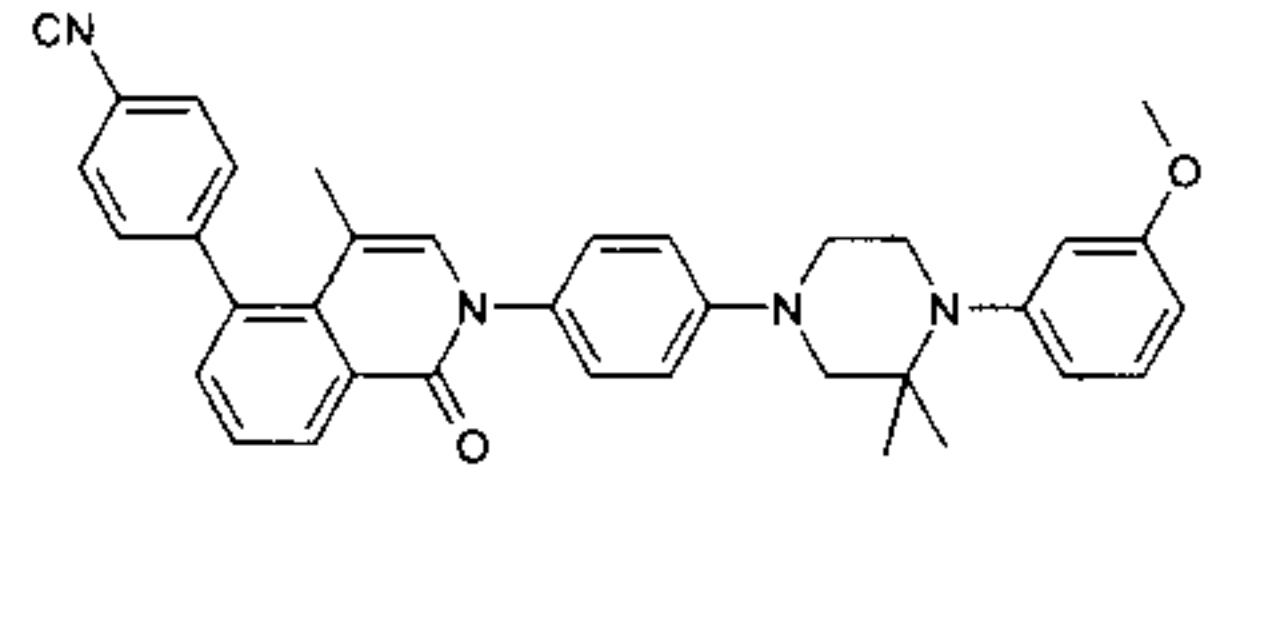
[210] Step 7: DIPEA (4.5 g, 35 mmol) and compound 1-11(9.4 g, 26 mmol) were added into a solution of compound 1-10 (5 g, 17.5 mmol) in THF (50 mL), the reaction mixture was stirred at room temperature for 16 h. The reaction was detected by TLC (PE: EtOAc= 2:1). The reaction mixture was poured into water, and extracted with EtOAc, the organic phase was washed with brines, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE: EtOAc=5:1) to deliver the compound 1-12 as yellow oil (3.6 g, yield 50%). **MS ESI** calcd for $C_{17}H_{11}ClF_3NO_4S$ $[M+H]^+$ 418, found 418.

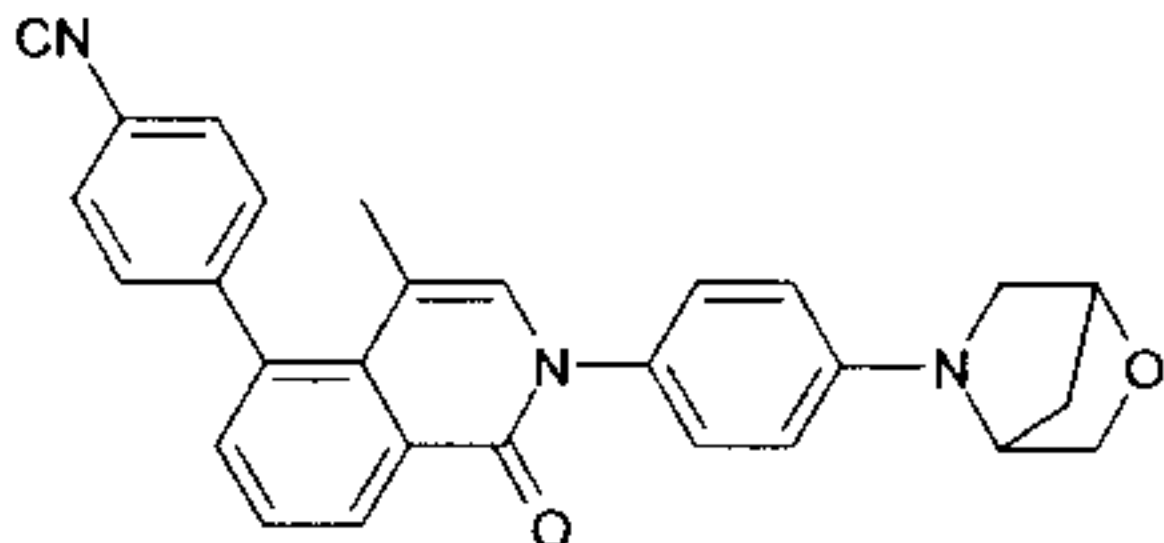
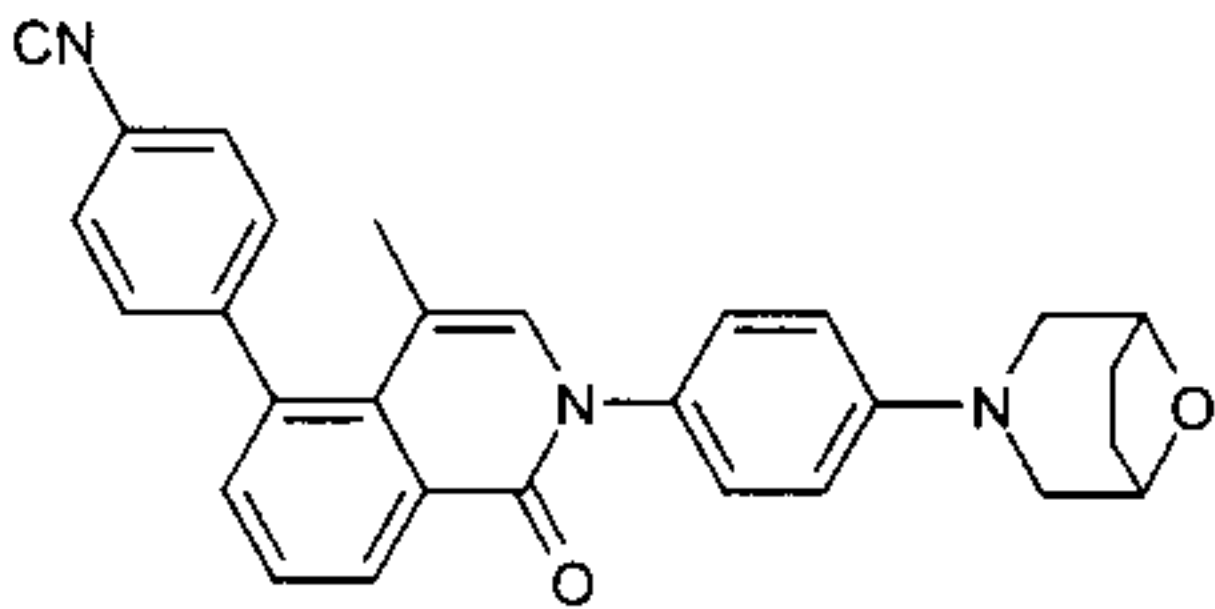
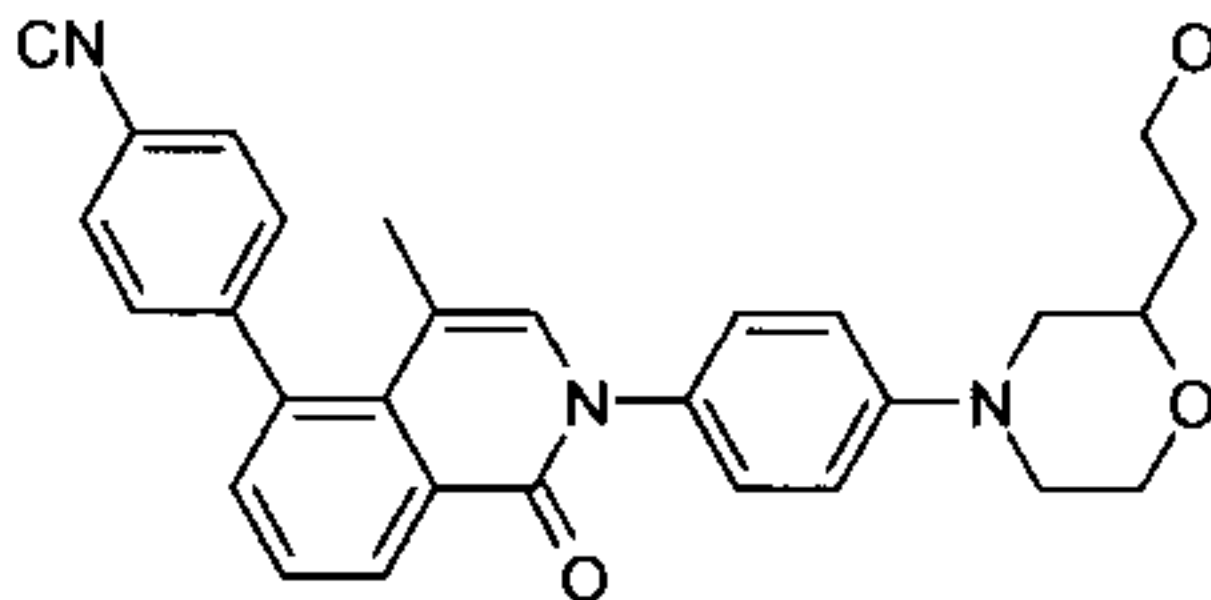
[211] Step 8: Compound 1-12 (3.6 g, 8.6 mmol), compound 1-13 (1.7 g, 12 mmol), $Pd(dppf)Cl_2$ (630 mg, 0.86 mmol) and sodium carbonate (2.1 g, 19.8 mmol) were dissolved in dioxane/ H_2O (48 mL), the reaction mixture was stirred at 110°C and refluxed for 16 h. The reaction was detected by TLC (PE: EtOAc= 3:1). The reaction mixture was poured into water, and filtrated to collect the residue, the crude product was purified by silica gel column chromatography (PE: EtOAc=5:1) to deliver the compound 1-14 as white solid (1.5 g, yield 50%). **MS ESI** calcd for $C_{23}H_{15}ClN_2O$ $[M+H]^+$ 371, found 371.

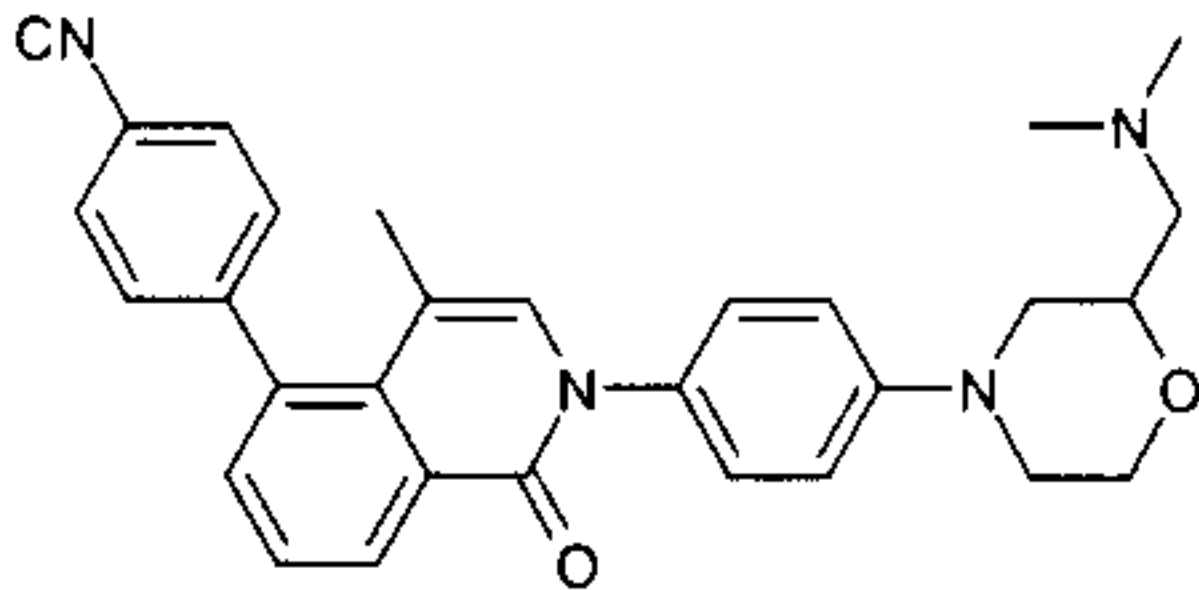
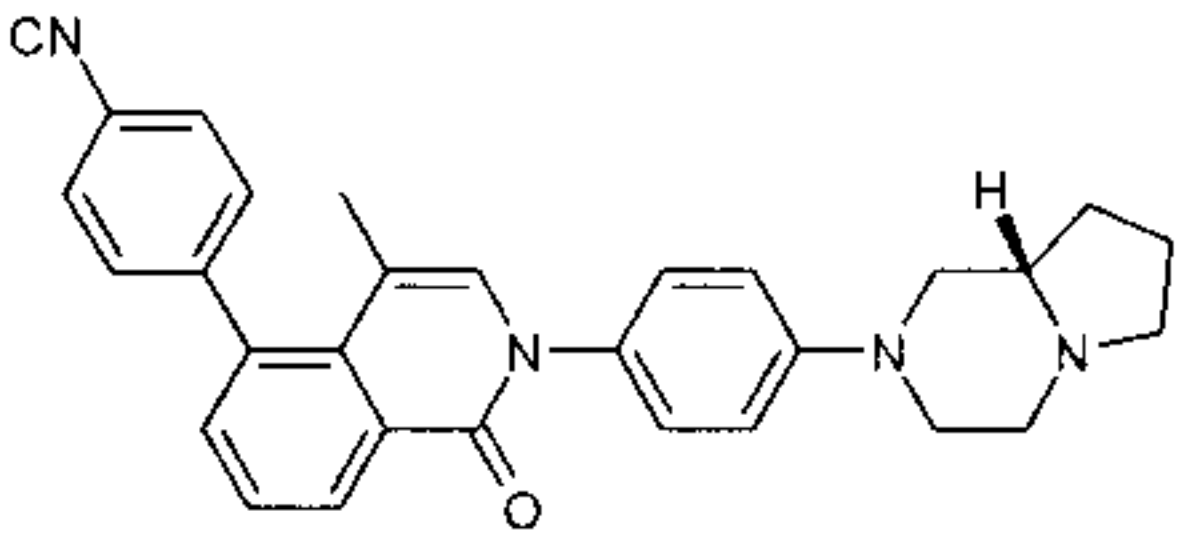
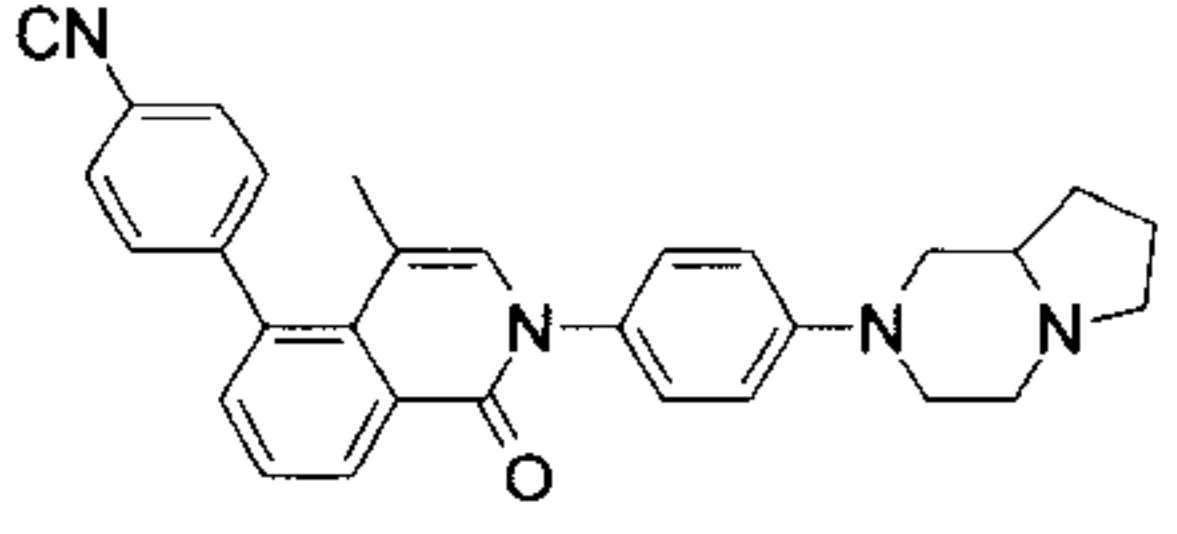
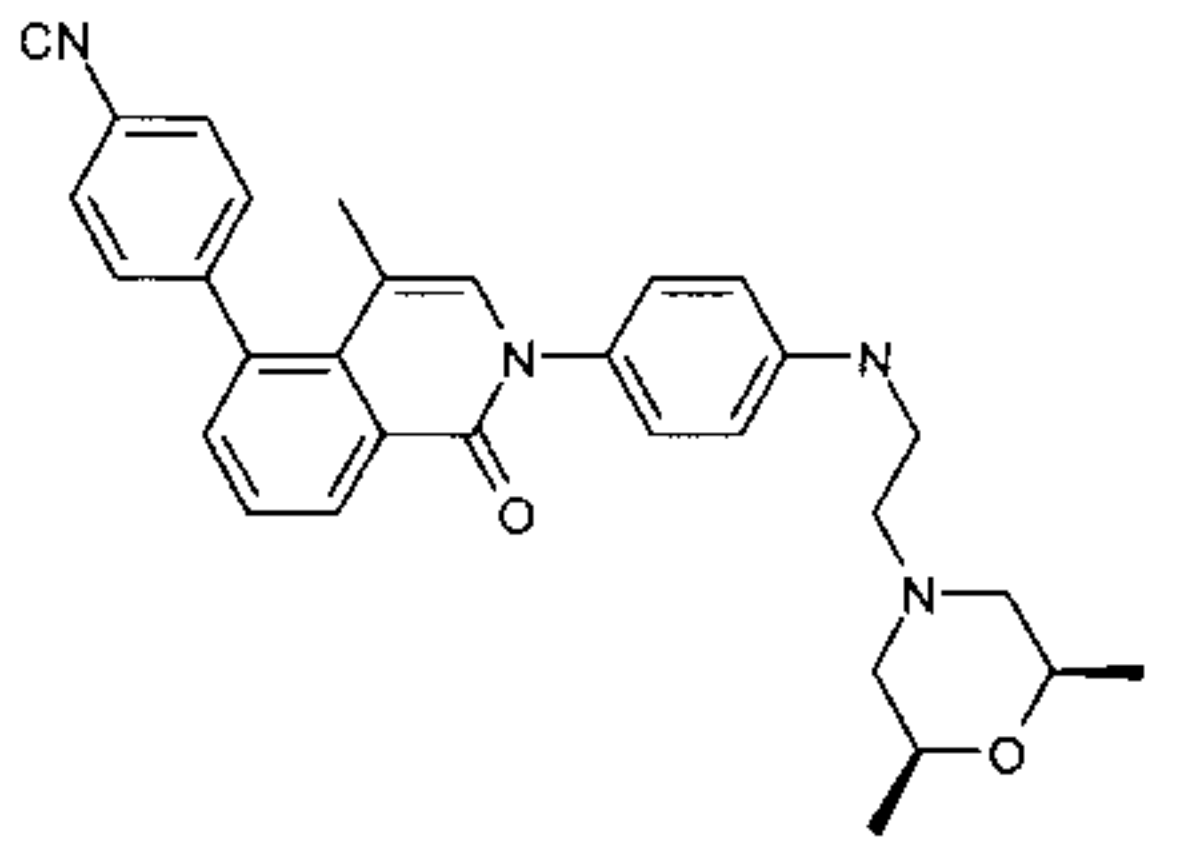
[212] Step 9: Under nitrogen gas atmosphere, compound 1-14 (100 mg, 0.27 mmol), compound 1-15 (46 mg, 0.40 mmol), $Pd_2(dba)_3$ (25 mg, 0.03 mmol), Xantphos (26 mg, 0.06 mmol) and potassium *tert*-butoxide (61 mg, 0.54 mmol) were dissolved in toluene (10 mL), the reaction mixture was refluxing at 120 °C and stirred for 2h. Then, the reaction mixture was filtrated with diatomite, concentrated by a rotary evaporator to remove the solvent, extracted with EtOAc (50 mL) and H_2O (20 mL), washed with brines, and dried over anhydrous sodium sulfate. After concentrated under reduced pressure, the residue was purified by preparative HPLC to deliver the title compound as white solid. **^1H NMR** (400 MHz, $CDCl_3$) δ 8.65 (d, J = 7.2 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.50-7.35 (m, 4H), 7.23 (d, J = 8.4 Hz, 2H), 6.93 (t, J = 8.8 Hz, 3H), 3.20 (dd, J = 3.2 Hz, J = 12.0 Hz, 2H), 2.85 (dd, J = 2.4 Hz, J = 11.6 Hz, 2H), 2.02 (dd, J = 5.6 Hz, J = 9.2 Hz, 2H), 1.56 (s, 3H), 1.45 (t, J = 6.0 Hz, 2H), 1.01 (d, J = 6.8 Hz, 6H). **MS ESI** calcd for $C_{30}H_{29}N_3O$ $[M+H]^+$ 448, found 448.

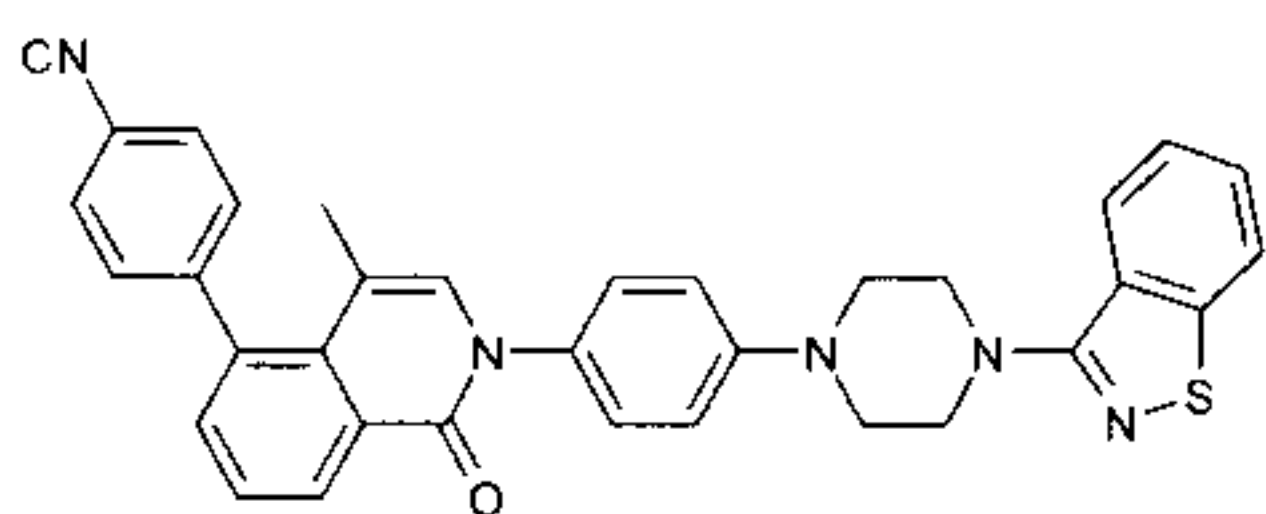
[213] The compounds listed in table 1 can be synthesized by compound 1-14 and corresponding amines.

Embod	Structure	NMR
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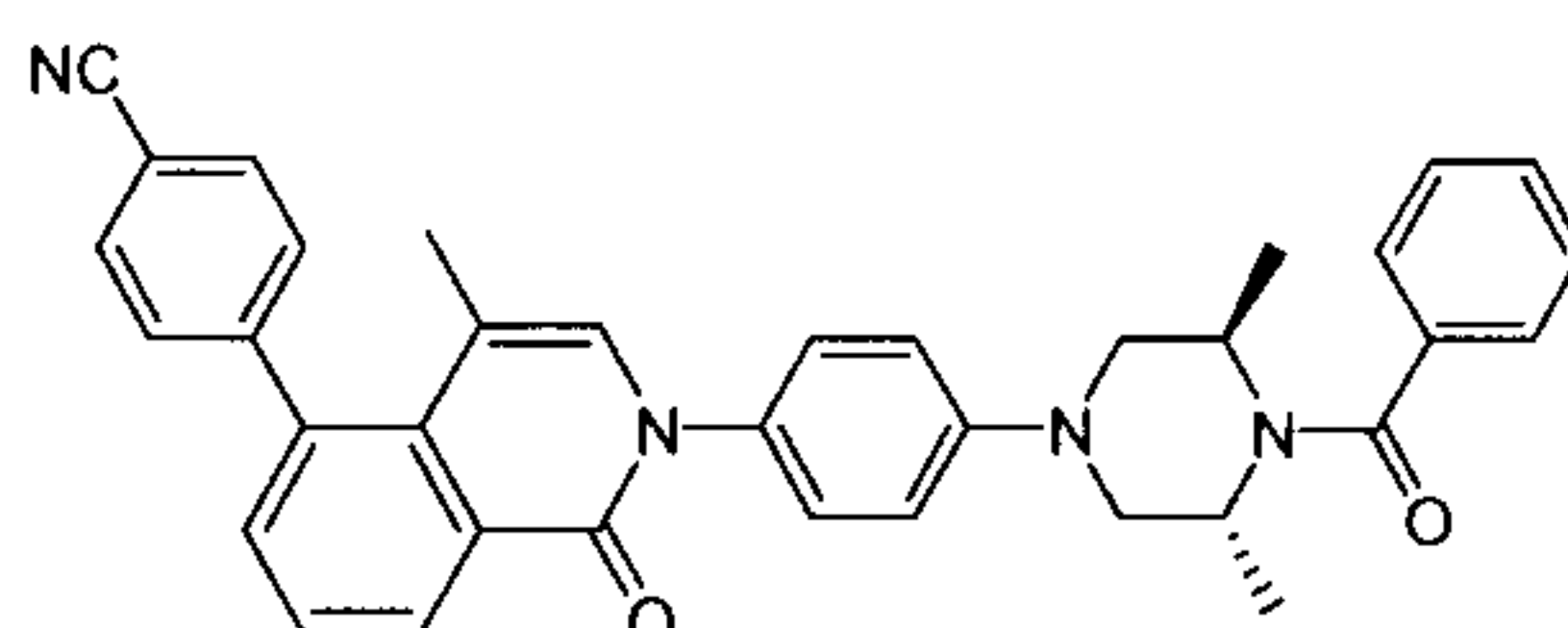
iment		
2		¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.41 (d, <i>J</i> = 7.6 Hz, 1H), 7.87 (d, <i>J</i> = 8.0 Hz, 2H), 7.58-7.49 (m, 4H), 7.26 (d, <i>J</i> = 8.8 Hz, 2H), 7.17 (s, 1H), 7.01 (d, <i>J</i> = 9.2 Hz, 2H), 3.69-3.60 (m, 4H), 2.26 (t, <i>J</i> = 10.8 Hz, 2H), 1.49 (s, 3H), 1.13 (d, <i>J</i> = 5.6 Hz, 6H). MS ESI calcd for C₂₉H₂₇N₃O₂ [M+H]⁺ 450, found 450.
3		¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.41 (d, <i>J</i> = 6.4 Hz, 1H), 7.87 (d, <i>J</i> = 8.4 Hz, 2H), 7.57-7.48 (m, 4H), 7.21 (d, <i>J</i> = 8.8 Hz, 2H), 7.17 (s, 1H), 6.98 (d, <i>J</i> = 9.2 Hz, 2H), 3.69 (d, <i>J</i> = 11.6 Hz, 2H), 2.20 (t, <i>J</i> = 12.0 Hz, 2H), 1.75-1.64 (m, 3H), 1.49 (s, 3H), 0.87 (d, <i>J</i> = 6.8 Hz, 6H), 0.74-0.67 (m, 1H). MS ESI calcd for C₃₀H₂₉N₃O [M+H]⁺ 448, found 448.
4		¹H NMR (400 MHz, CDCl₃) δ 8.67 (d, <i>J</i> = 7.6 Hz, 1H), 7.72 (d, <i>J</i> = 8.0 Hz, 2H), 7.57-7.47 (m, 4H), 7.31 (d, <i>J</i> = 8.8 Hz, 2H), 7.00 (d, <i>J</i> = 8.8 Hz, 2H), 6.95 (s, 1H), 3.93 (t, <i>J</i> = 4.8 Hz, 2H), 3.03 (s, 2H), 1.61 (s, 3H), 1.36 (s, 6H). MS ESI calcd for C₂₉H₂₇N₃O₂ [M+H]⁺ 450, found 450.
5		¹H NMR (400 MHz, CDCl₃) δ 8.67 (d, <i>J</i> = 8.0 Hz, 1H), 7.72 (d, <i>J</i> = 7.6 Hz, 2H), 7.55-7.40 (m, 4H), 7.36 (d, <i>J</i> = 8.8 Hz, 3H), 7.23 (s, 1H), 7.05-7.02 (m, 4H), 6.93 (s, 1H), 3.81 (brs, 3H), 3.73 (brs, 4H), 3.59 (s, 2H), 1.60 (s, 3H),

		1.47 (s, 6H). MS ESI calcd for C ₃₆ H ₃₄ N ₄ O ₂ [M+H] ⁺ 555, found 555.
6		¹ H NMR (400 MHz, CDCl ₃) δ 8.67 (d, <i>J</i> = 7.6 Hz, 1H), 7.72 (d, <i>J</i> = 8.0 Hz, 2H), 7.58 (t, <i>J</i> = 7.6 Hz, 1H), 7.49 (t, <i>J</i> = 4.4 Hz, 3H), 7.25 (d, <i>J</i> = 7.6 Hz, 2H), 6.97 (s, 1H), 6.67 (d, <i>J</i> = 9.2 Hz, 2H), 4.72 (s, 1H), 4.47 (s, 1H), 3.94 (dd, <i>J</i> = 24.8 Hz, <i>J</i> = 7.2 Hz 2H), 3.59 (d, <i>J</i> = 8.8 Hz, 1H), 3.23 (d, <i>J</i> = 9.2 Hz, 1H), 2.05 (dd, <i>J</i> = 24.4 Hz, <i>J</i> = 9.6 Hz, 2H), 1.62 (s, 3H). MS ESI calcd for C ₂₈ H ₂₃ N ₃ O ₂ [M+H] ⁺ 434, found 434.
7		¹ H NMR (400 MHz, CDCl ₃) δ 8.67 (d, <i>J</i> = 7.6 Hz, 1H), 7.72 (d, <i>J</i> = 7.6 Hz, 1H), 7.57 (t, <i>J</i> = 7.6 Hz, 1H), 7.48 (d, <i>J</i> = 7.6 Hz, 3H), 7.28 (d, <i>J</i> = 9.2 Hz, 2H), 6.95 (s, 1H), 6.88 (d, <i>J</i> = 8.4 Hz, 2H), 4.53 (s, 2H), 3.38 (d, <i>J</i> = 11.2 Hz, 2H), 3.08 (d, <i>J</i> = 11.2 Hz, 2H), 2.01-1.94 (m, 4H), 1.61 (s, 3H). MS ESI calcd for C ₂₉ H ₂₅ N ₃ O ₂ [M+H] ⁺ 448, found 448.
8		¹ H NMR (400 MHz, CDCl ₃) δ 8.66 (d, <i>J</i> = 8.0 Hz, 1H), 7.72 (d, <i>J</i> = 8.0 Hz, 2H), 7.58-7.41 (m, 6H), 7.23 (d, <i>J</i> = 8.8 Hz, 2H), 6.94 (s, 1H), 4.12-3.79 (m, 5H), 3.60 (dd, <i>J</i> = 24.8 Hz, <i>J</i> = 12.0 Hz, 2H), 3.09 (t, <i>J</i> = 3.2 Hz, 1H), 2.86 (t, <i>J</i> = 10.8 Hz, 1H), 1.88-1.75 (m, 2H), 1.62 (s, 3H). MS ESI calcd for C ₂₈ H ₂₅ N ₃ O ₃ [M+H] ⁺ 452, found 452.

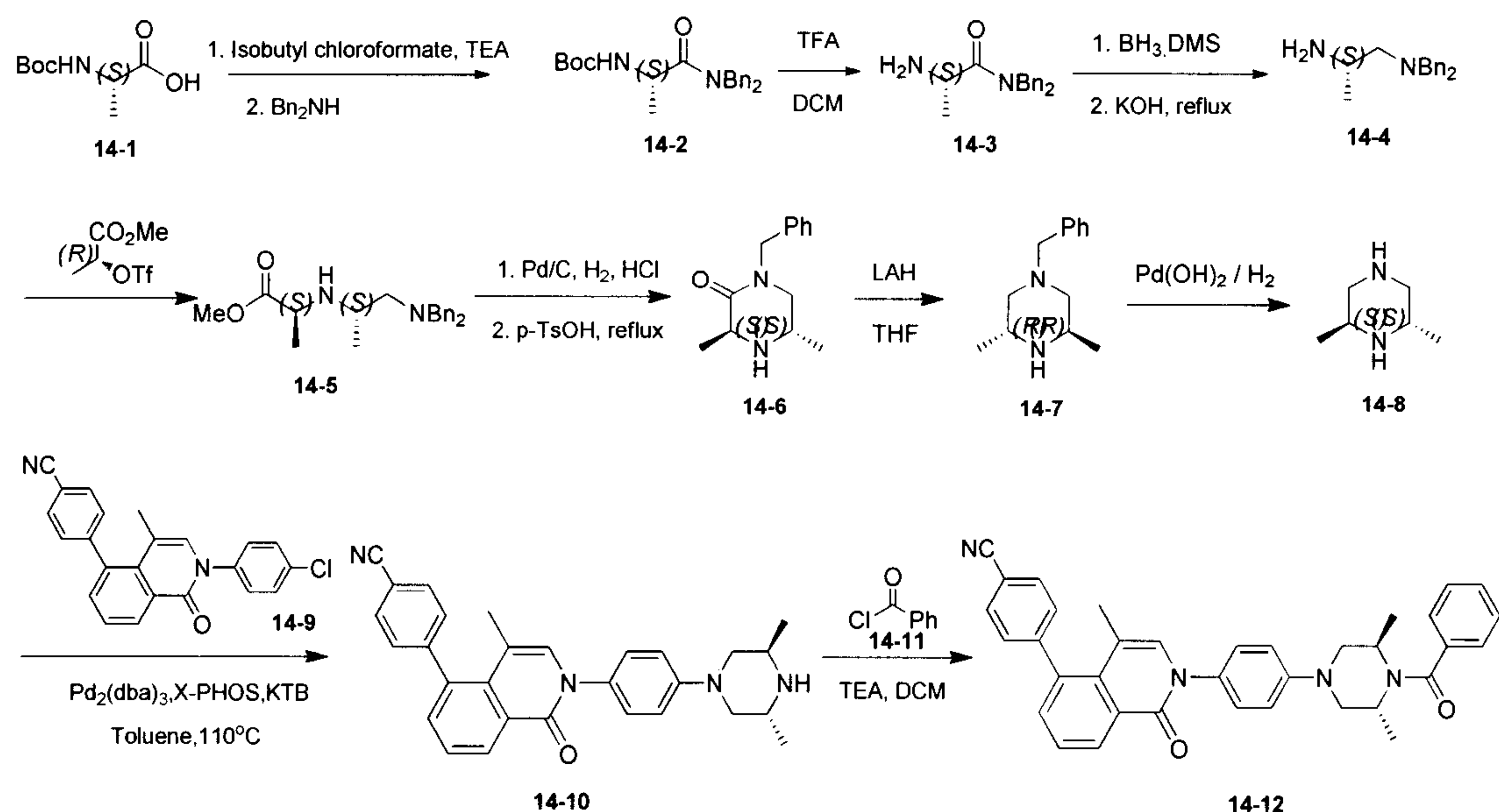
9		¹H NMR (400 MHz, CDCl ₃) δ 8.65 (d, <i>J</i> = 7.6 Hz, 1H), 7.71 (d, <i>J</i> = 8.0 Hz, 2H), 7.56-7.43 (m, 4H), 7.33 (d, <i>J</i> = 8.4 Hz, 2H), 6.98 (d, <i>J</i> = 8.8 Hz, 2H), 6.92 (s, 1H), 4.20 (t, <i>J</i> = 21.6 Hz, 1H), 4.04 (d, <i>J</i> = 11.2 Hz, 1H), 3.82 (t, <i>J</i> = 10.4 Hz, 1H), 3.57 (d, <i>J</i> = 11.6 Hz, 1H), 3.46 (d, <i>J</i> = 12.0 Hz, 1H), 3.32 (d, <i>J</i> = 13.2 Hz, 1H), 3.09-2.85 (m, 8H), 2.60 (t, <i>J</i> = 10.8 Hz, 1H), 1.59 (s, 3H). MS ESI calcd for C ₃₀ H ₃₀ N ₄ O ₂ [M+H] ⁺ 479, found 479.
10		¹H NMR (400 MHz, CDCl ₃) δ 8.65 (d, <i>J</i> = 8.0 Hz, 1H), 7.71 (d, <i>J</i> = 7.6 Hz, 2H), 7.54 (t, <i>J</i> = 8.0 Hz, 1H), 7.47 (d, <i>J</i> = 7.6 Hz, 3H), 7.35 (d, <i>J</i> = 8.4 Hz, 2H), 6.91 (s, 1H), 7.01 (dd, <i>J</i> = 21.6 Hz, <i>J</i> = 8.4 Hz, 2H), 3.95-3.32 (m, 7H), 3.27-3.07 (m, 1H), 3.02-2.72 (m, 1H), 2.37-2.05 (m, 14H), 1.60 (s, 3H). MS ESI calcd for C ₃₀ H ₂₈ N ₄ O [M+H] ⁺ 461, found 461.
11		¹H NMR (400 MHz, CDCl ₃) δ 8.65 (d, <i>J</i> = 7.2 Hz, 1H), 7.71 (d, <i>J</i> = 7.6 Hz, 2H), 7.51-7.58 (m, 1H), 7.40-7.50 (m, 3H), 7.35 (d, <i>J</i> = 8.8 Hz, 2H), 6.99 (dd, <i>J</i> = 8.4 Hz, <i>J</i> = 21.6 Hz, 2H), 6.91 (s, 1H), 3.33-4.15 (m, 5H), 2.90-3.30 (m, 4H), 2.05-2.40 (m, 4H), 1.59 (s, 3H). MS ESI calcd for C ₃₀ H ₂₈ N ₄ O [M+H] ⁺ 461, found 461.
12		¹H NMR (400 MHz, CDCl ₃) δ 8.64 (d, <i>J</i> = 7.2 Hz, 1H), 7.71 (d, <i>J</i> = 8.4 Hz, 2H), 7.56-7.46 (m, 4H), 7.21 (d, <i>J</i> = 8.8 Hz, 2H), 6.92 (s, 1H),

		6.67 (d, $J = 8.4$ Hz, 2H), 4.09-4.05 (m, 2H), 3.60 (t, $J = 4.8$ Hz, 2H), 3.52 (d, $J = 11.6$ Hz, 2H), 3.28 (brs, 2H), 2.44 (t, $J = 11.2$ Hz, 2H), 1.59 (s, 3H), 1.24 (d, $J = 6.0$ Hz, 6H). MS ESI calcd for $C_{31}H_{32}N_4O_2$ $[M+H]^+$ 493, found 493.
13		^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, $J = 8.0$ Hz, 1H), 7.94 (d, $J = 8.0$ Hz, 1H), 7.86 (d, $J = 8.0$ Hz, 1H), 7.73 (d, $J = 8.4$ Hz, 2H), 7.58-7.44 (m, 8H), 7.34 (d, $J = 8.4$ Hz, 2H), 6.96 (s, 1H), 3.94-3.84 (m, 4H), 3.64-3.58 (m, 4H), 1.62 (s, 3H). MS ESI calcd for $C_{34}H_{27}N_5OS$ $[M+H]^+$ 554, found 554.

Embodiment 14



4-(2-(4-((3R,5R)-4-benzoyl-3,5-dimethylpiperazin-1-yl)phenyl)-4-methyl-1-oxo-1,2-dihydroisoquinolin-5-yl)benzonitrile



[214] Step 1: Compound 14-1 (75 g, 0.4 mol) and TEA (60 mL, 0.45 mol) was dissolved in THF (500 mL) and cooled to -30°C , a solution of isobutyl chloroformate (54 mL, 0.42 mol) in THF (100 mL) was added dropwise and the resulting mixture was stirred at -30°C for 0.5 h, and then warmed to room temperature, stirred for further 5 h. The reaction mixture was cooled to 0°C again, Bn_2NH (88 mL, 0.43 mol) and TEA (70 mL, 500 mmol) were dissolved in THF (100 mL) and added dropwise, the reaction mixture was stirred at room temperature for 10 h. The reaction was detected by LC-MS. The reaction mixture was poured into water, and extracted with EtOAc. The organic phase was washed with brines, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to deliver the compound 14-2 as white solid (84 g, yield 60%). **MS ESI** calcd for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 369, found 369.

[215] Step 2: TFA (120 mL) was added into a solution of compound 14-2 (53 g, 0.15 mol) in DCM (450 mL), the reaction mixture was stirred at room temperature for 5h. The reaction was detected by TLC (PE: EtOAc=5:1). The reaction mixture was poured into water, sodium bicarbonate was added to adjust pH to more than 7, and extracted with DCM. The organic phase was washed with brines, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to deliver the compound 14-3 as yellow oil (38 g, yield 98%). **MS ESI** calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 269, found 269.

[216] Step 3: Borane-methyl sulfide (98 mL, 0.98 mol) was added into a solution of compound 14-3 (38 g, 0.14 mol) in THF (400 mL), the reaction mixture was stirred at room temperature for 48 h. The reaction was detected by LC-MS. The reaction mixture was quenched with hydrochloric acid, and adjusted to pH to more than 7 with NaOH aqueous solution, and then KOH (100 g) was added, the mixture was heated to reflux for 24 h. The reaction mixture was extracted with EtOAc, the organic phase was washed with brines, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (DCM: MeOH =10:1) to deliver the compound 14-4 as white solid (25 g, yield 69%). **MS ESI** calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2$ $[\text{M}+\text{H}]^+$ 255, found 255.

[217] Step 4: A solution of compound 14-4 (25 g, 98.4 mmol) and TEA (15.9 g, 157.44 mmol) in DCM (150 mL) was added into a solution of 2-trifluoromethanesulfonyloxy methyl propionate (27.9 g, 118.1 mmol) in DCM (100 mL) at 0°C , the reaction mixture was stirred at 0°C for 2h and at room temperature for 2 h. The reaction was detected by LC-MS, and poured into DCM and NaHCO_3 . The reaction mixture was extracted with DCM, the organic phase was washed with saturated brines, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc) to deliver the compound 14-5 as yellow oil (13.5 g, yield 40%). **MS ESI** calcd for $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 341, found 341.

[218] Step 5: Compound 14-5 (12 g, 35.2 mmol), hydrochloric acid (36%) (5 mL) and Pd/C (2.5 g) were dissolved in EtOH (100 mL), the reaction mixture was reacted

under 40psi for 2h. The reaction mixture was filtrated, the filtrate was concentrated. The residue was dissolved in EtOH (100 mL), *p*-toluene-sulfonic acid (2 g) was added, the reaction mixture was stirred at 90 °C and refluxed for 16h. The reaction was detected by LC-MS, the reaction mixture was concentrated under reduced pressure, DCM and NaHCO₃ were added. The reaction mixture was extracted with DCM, the organic phase was washed with brines, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to deliver compound 14-6 as yellow solid (6 g, yield 78%). **MS ESI** calcd for C₁₃H₁₈N₂O [M+H]⁺ 219, found 219.

[219] Step 6: Compound 14-6 (5.5 g, 25.2 mmol) was added into a solution of LAH (2.9 g, 75.6 mmol) in THF (50 mL) in portions, the reaction mixture was stirred at room temperature for 0.5 h, then heated to 70 °C and stirred for 6 h. The reaction was detected by LC-MS. The reaction system was quenched with H₂O (2.9 mL), 15% NaOH (2.9 mL) and H₂O (8.8 mL). The reaction mixture was stirred for 0.5 h, the solid was filtrated and washed with THF. The filtrate was dried over anhydrous sodium sulfate and concentrated under reduced pressure to deliver compound 14-7 as yellow solid (4.9 g, 96%). **MS ESI** calcd for C₁₃H₂₀N₂ [M+H]⁺ 205, found 205.

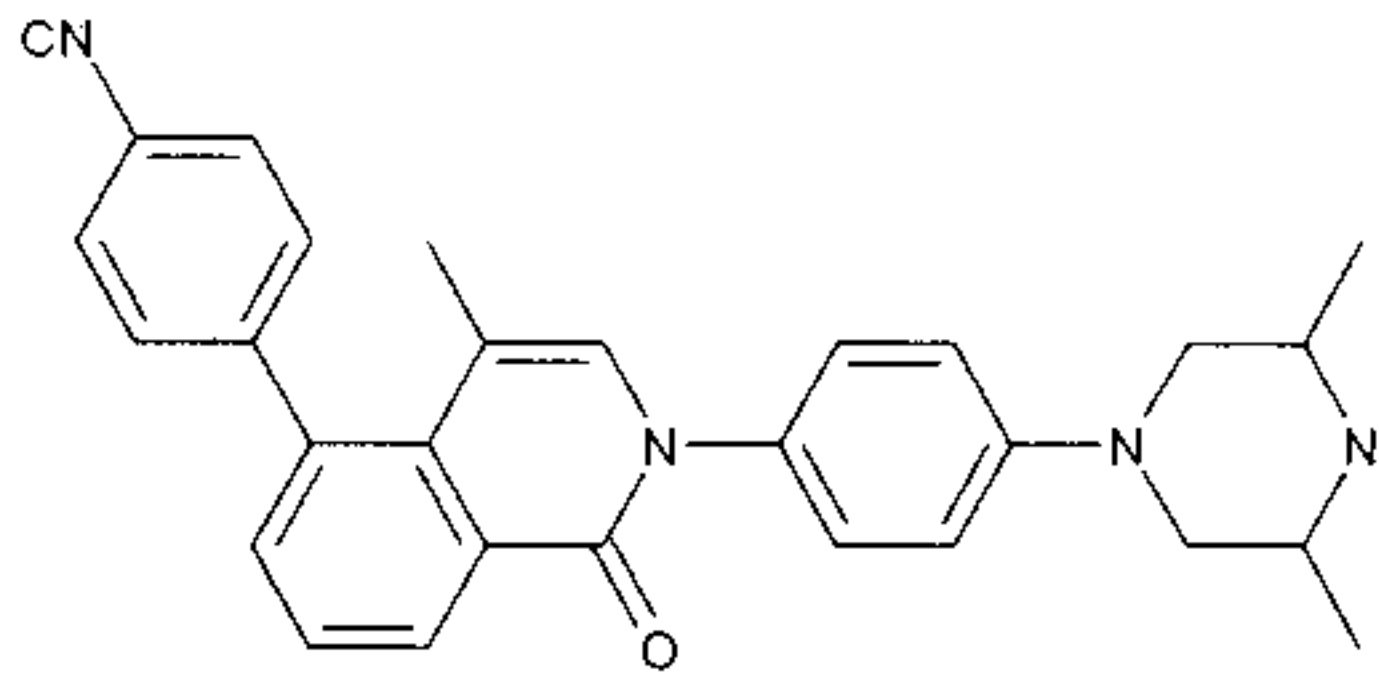
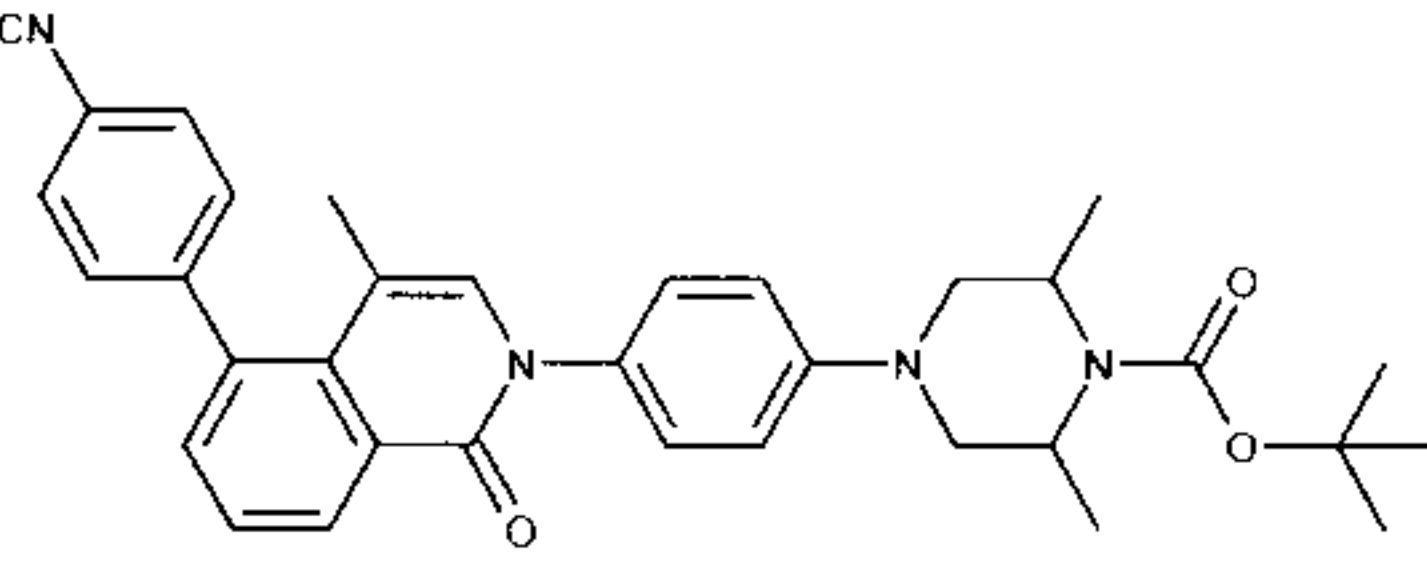
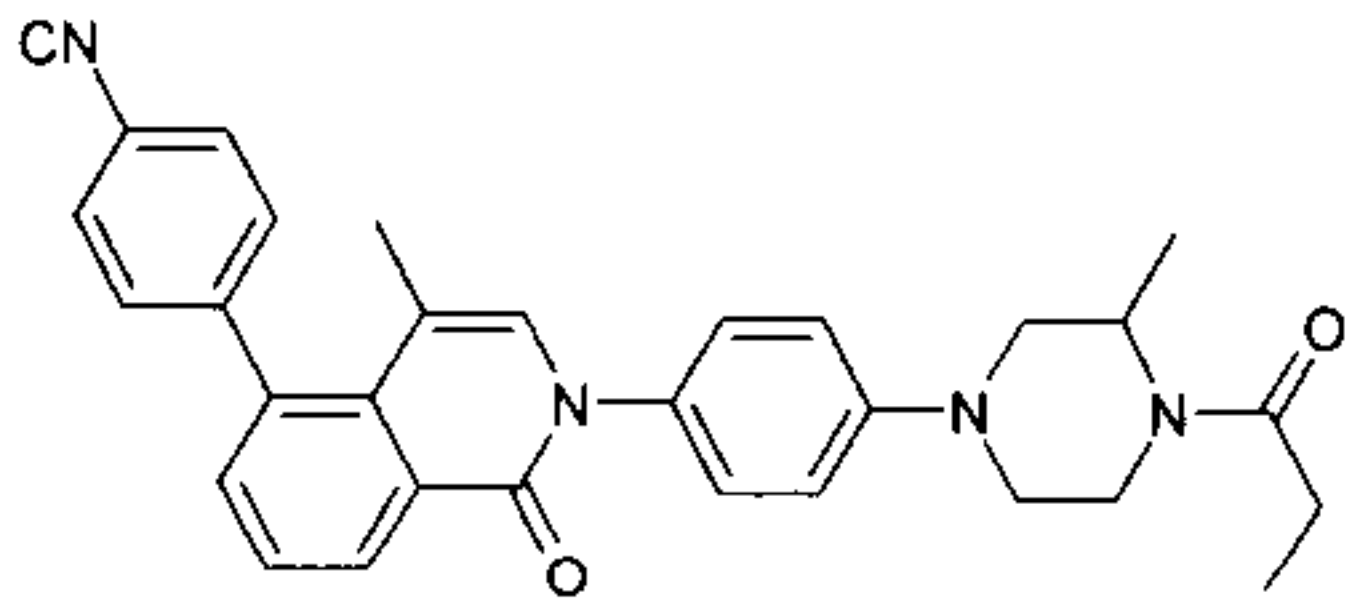
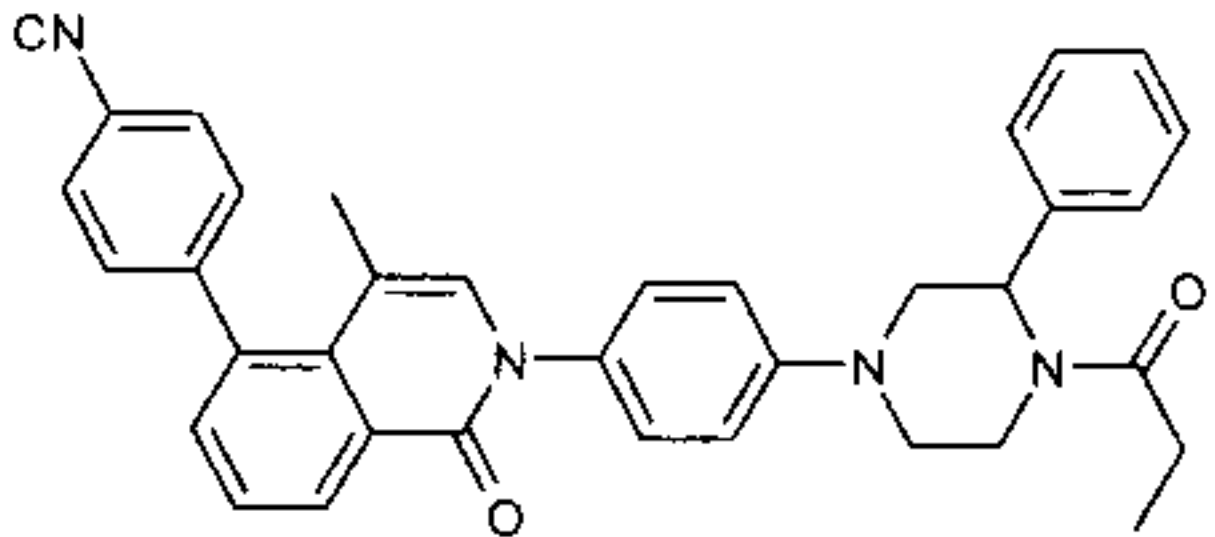
[220] Step 7: Compound 14-7 (2 g, 9.8 mmol) and Pd(OH)₂/C (0.9 g) were dissolved in MeOH (20 mL), the reaction mixture was reacted under 35psi for 24 h. The reaction mixture was filtrated, the filtrate was concentrated under reduced pressure to deliver compound 14-8 as colorless oil (1 g, yield 91%). **MS ESI** calcd for C₆H₁₄N₂ [M+H]⁺ 115, found 115.

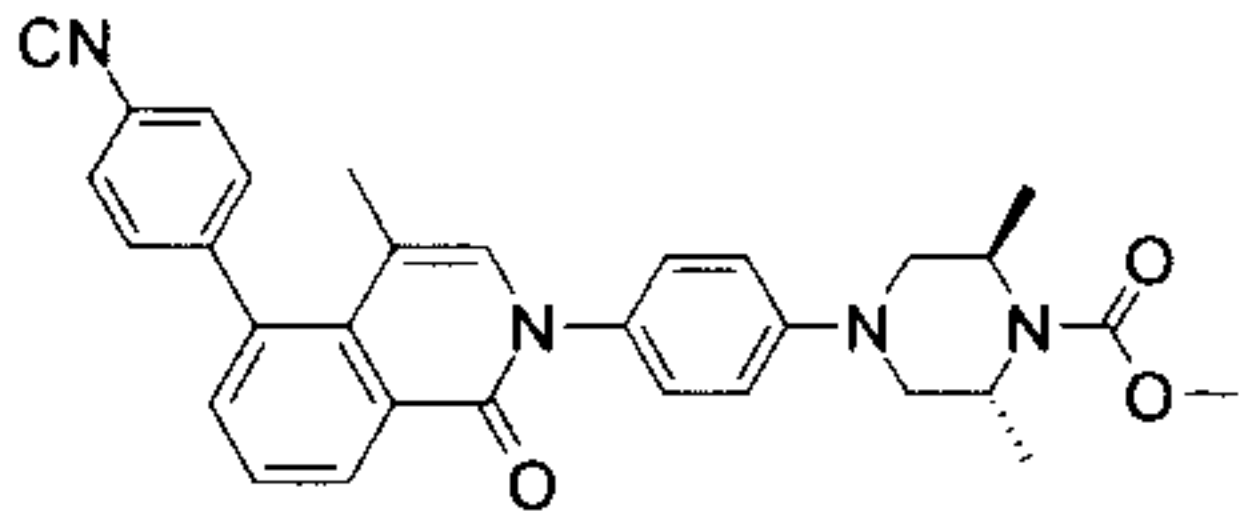
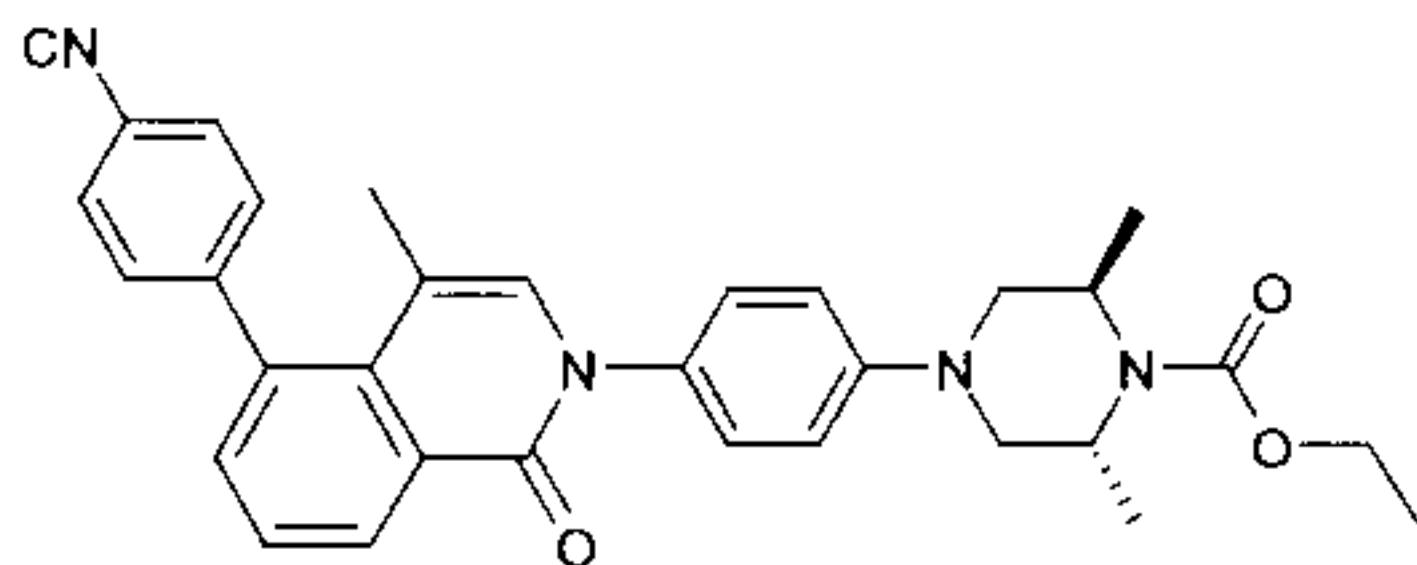
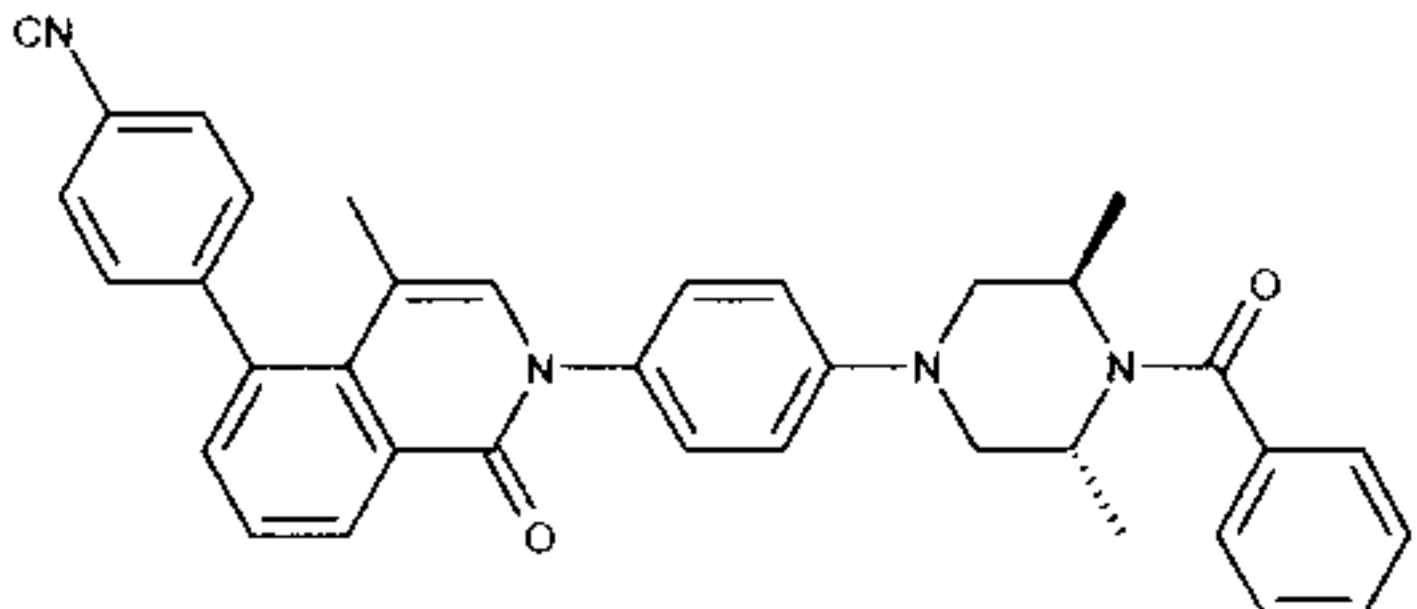
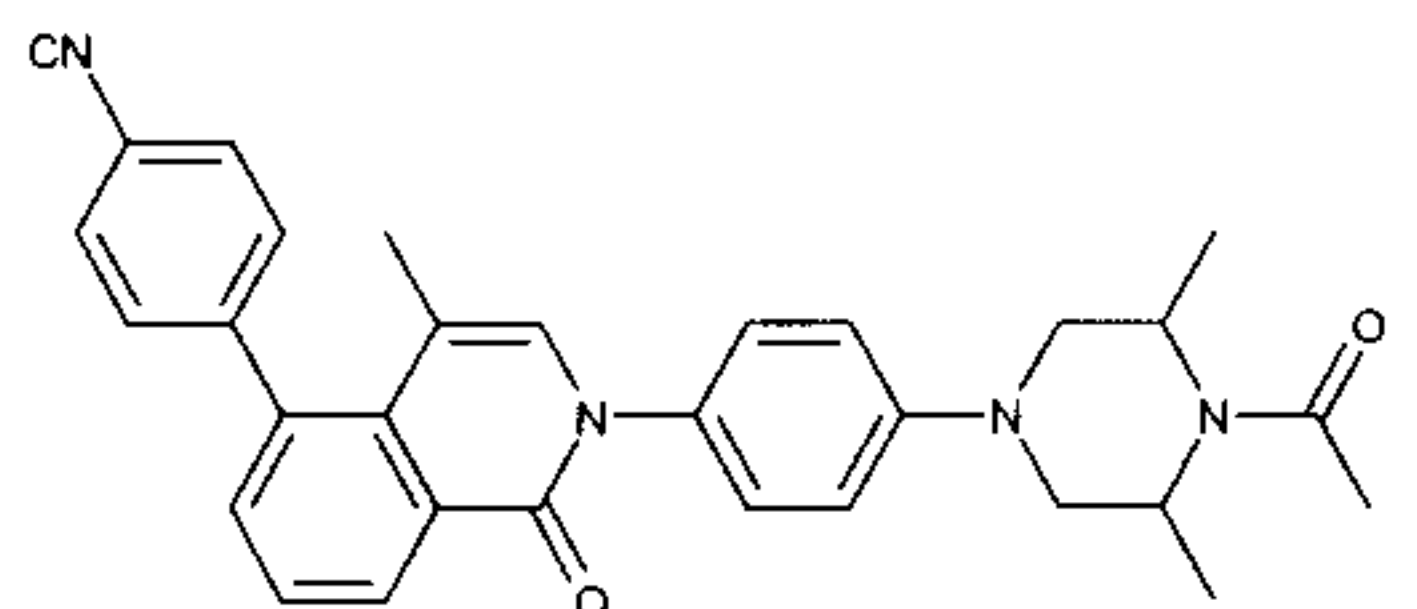
[221] Step 8: Compound 14-10 was prepared according to the above-mentioned method, as yellow solid (600 mg, yield 84%). **MS ESI** calcd for C₂₉H₂₈N₄O [M+H]⁺ 449, found 449.

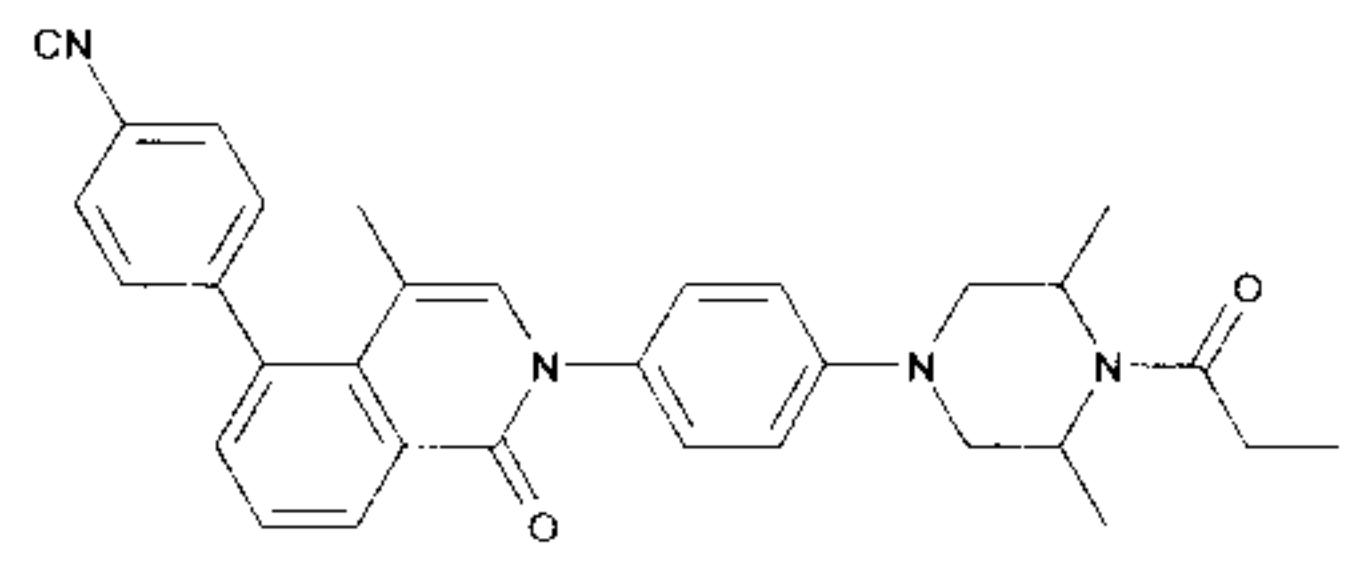
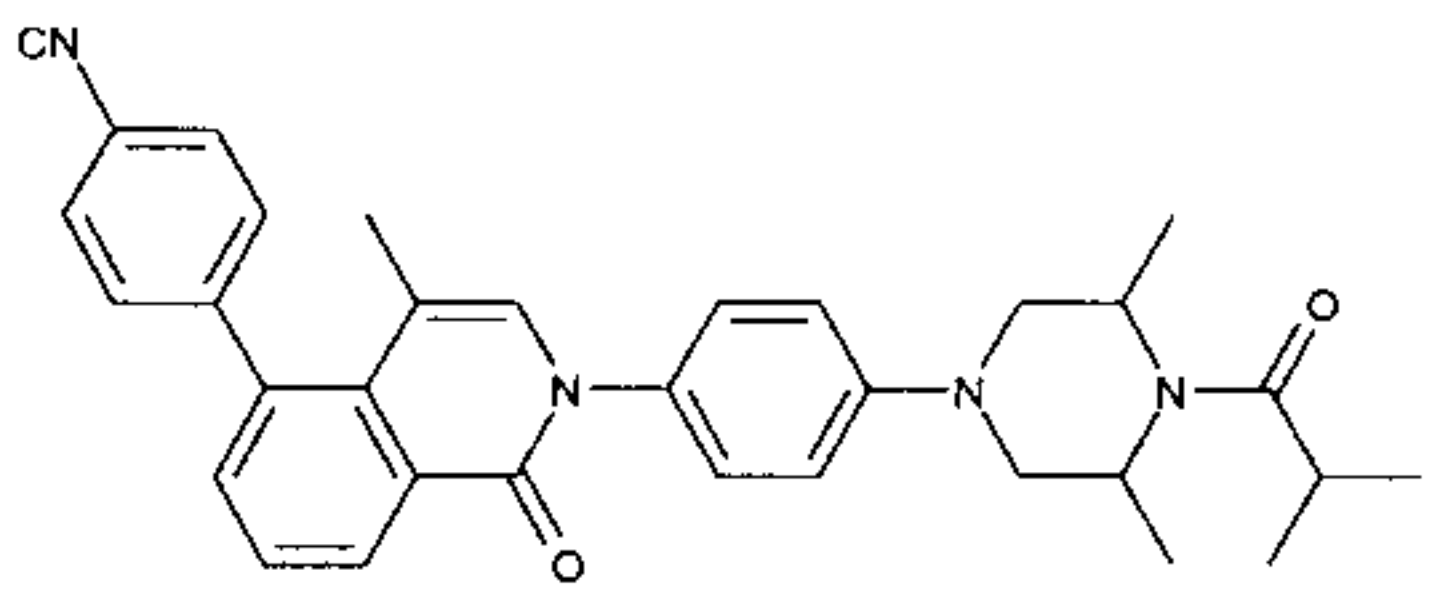
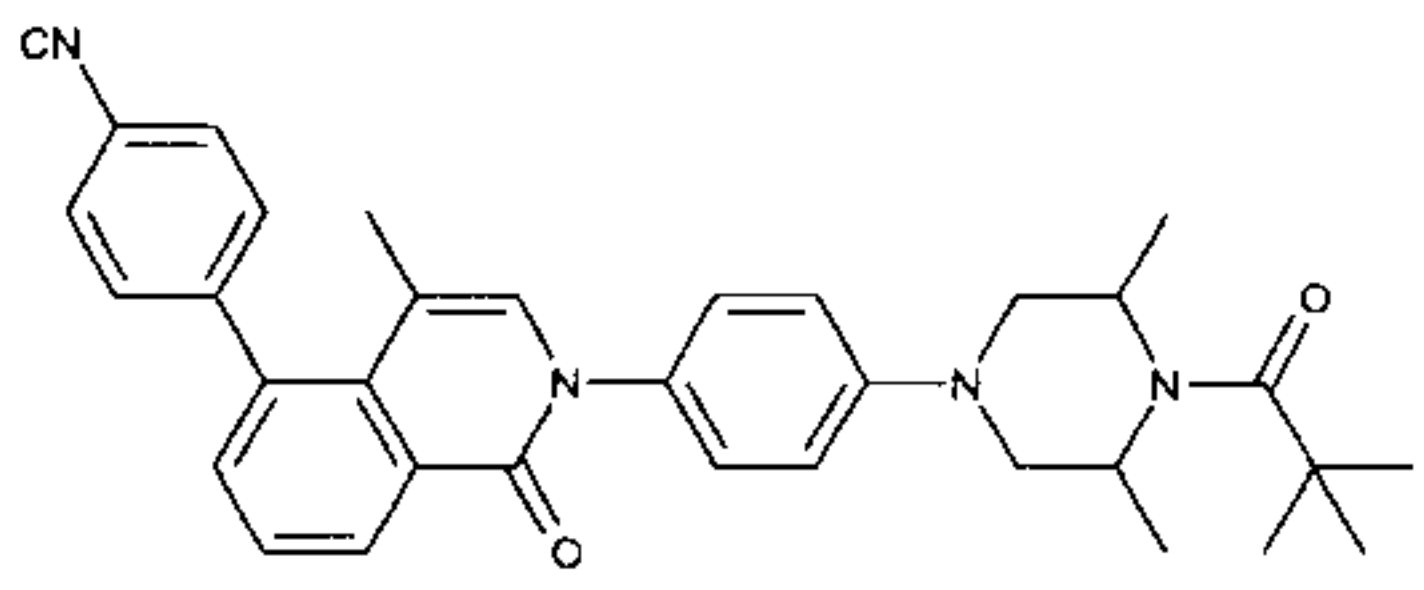
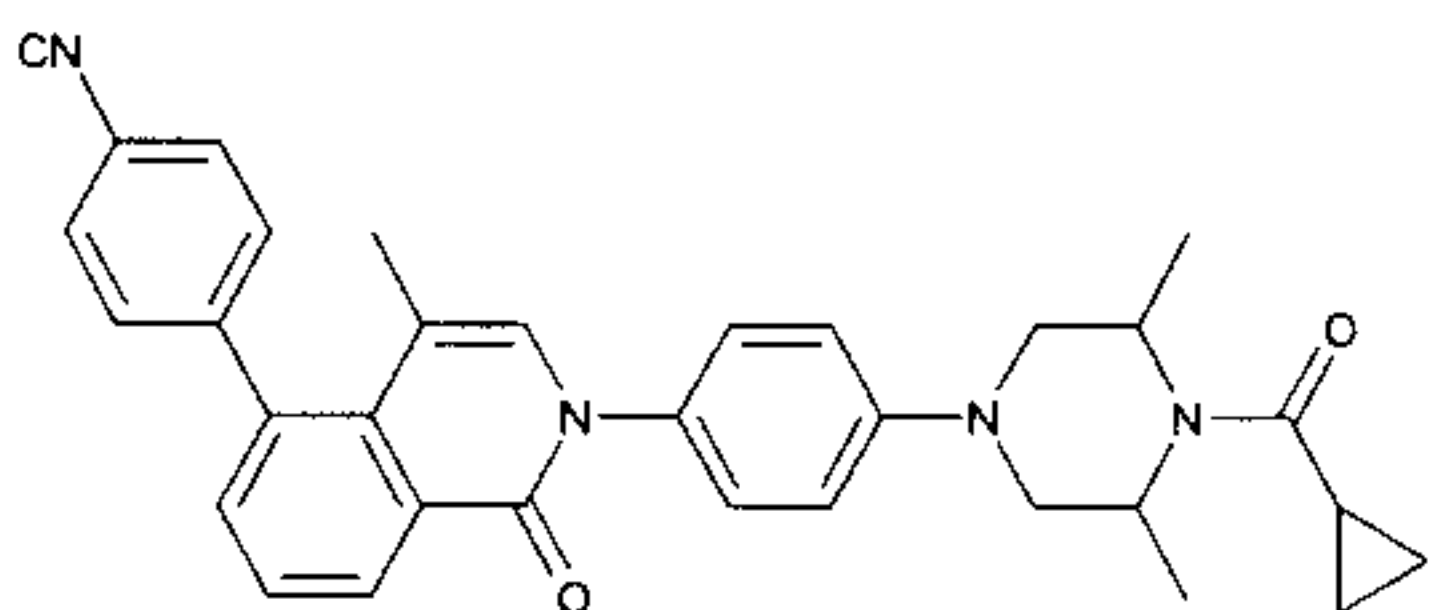
[222] Step 9: Compound 14-11 (93 mg, 0.66 mmol) was added into a solution of compound 14-10 (150 mg, 0.33 mmol) and TEA (100 mg, 0.99 mmol) in DCM (5 mL), the reaction mixture was stirred at room temperature for 5h. The reaction was detected by LC-MS. The crude product was purified by preparative HPLC to deliver the title compound as white solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.68 (d, *J* = 7.6Hz, 1H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.67-7.39 (m, 8H), 7.28 (t, *J* = 8.0 Hz, 3H), 6.96 (s, 1H), 6.74 (d, *J* = 8.4 Hz, 2H), 4.25 (brs, 2H), 3.85 (d, *J* = 10.4 Hz, 2H), 3.40 (d, *J* = 11.2 Hz, 2H), 1.61 (s, 3H), 1.31 (brs, 6H). **MS ESI** calcd for C₃₆H₃₂N₄O₂ [M+H]⁺ 553, found 553.

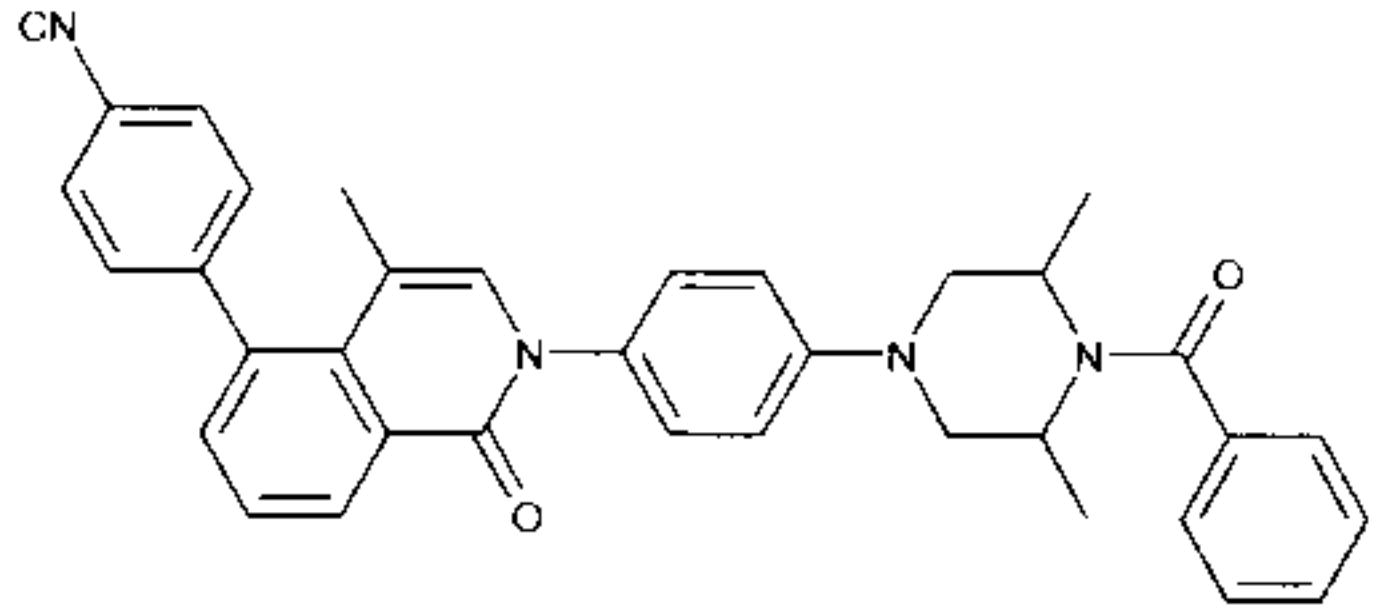
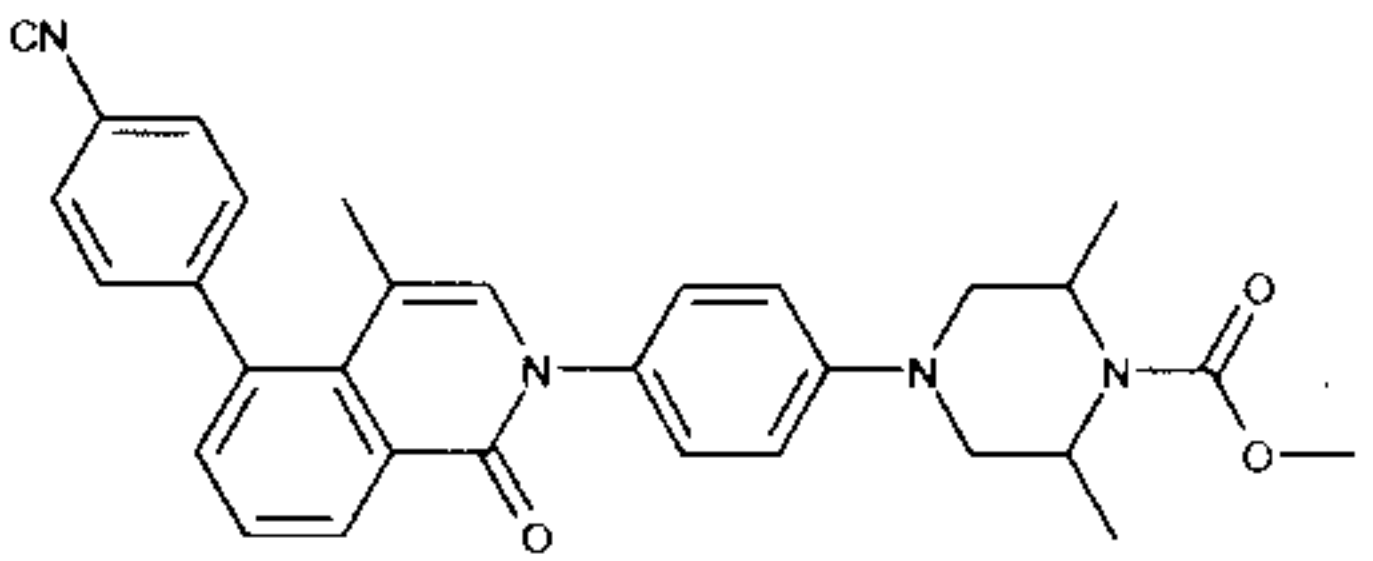
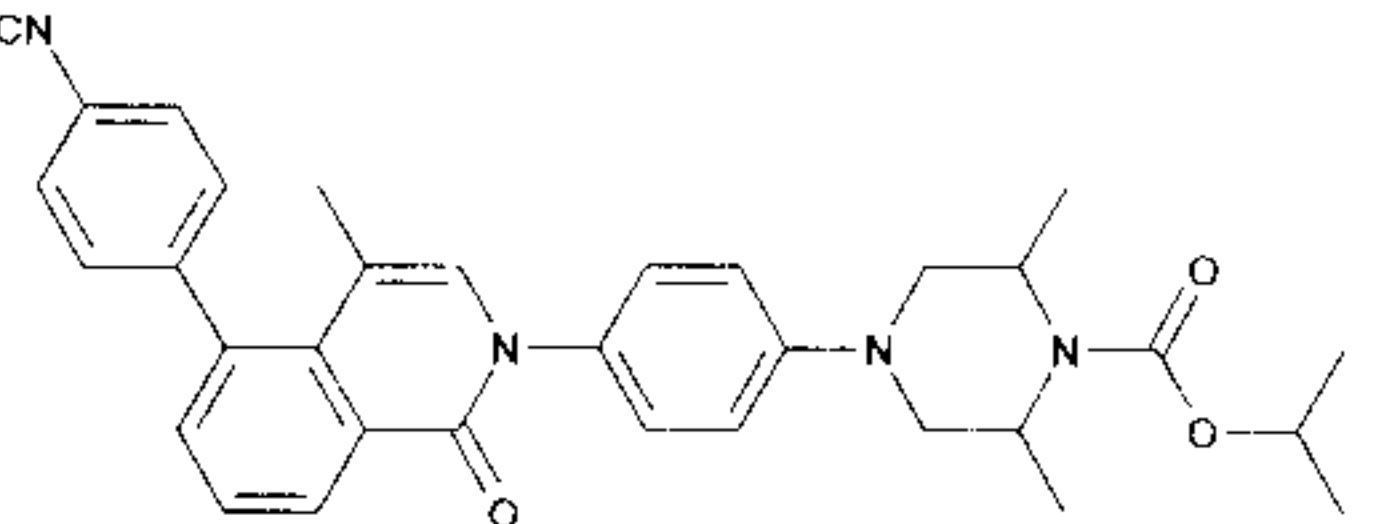
[223] The compounds listed in table 2 can be synthesized by compound 14-10 and corresponding acyl chlorides and sulfonyl chlorides.

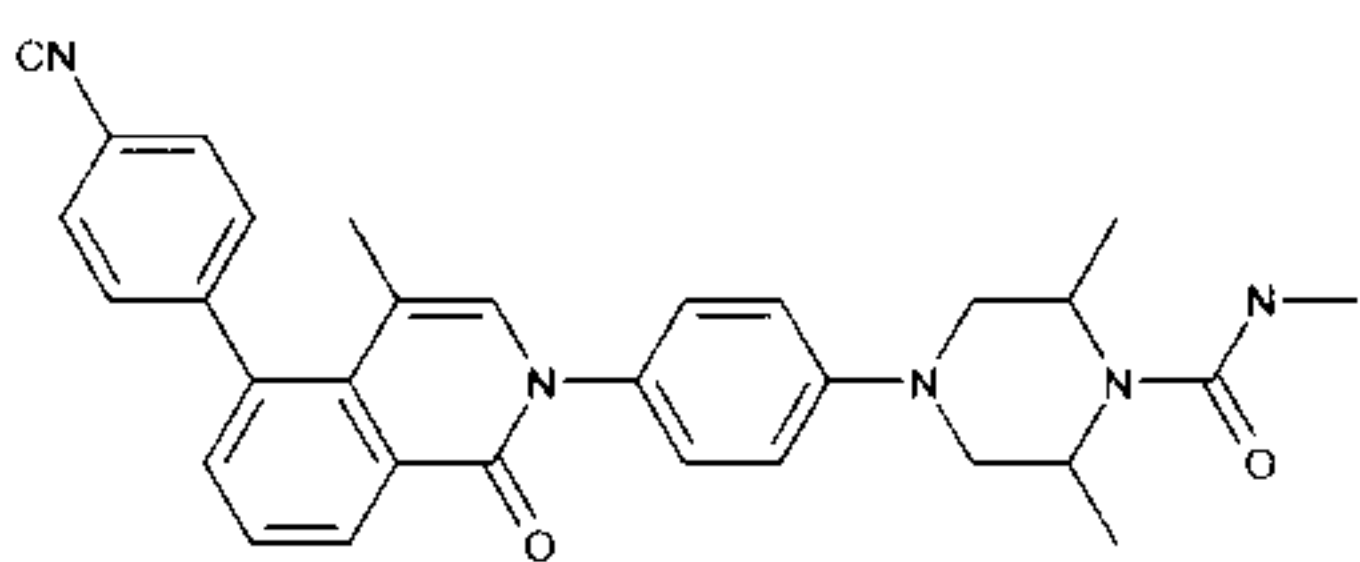
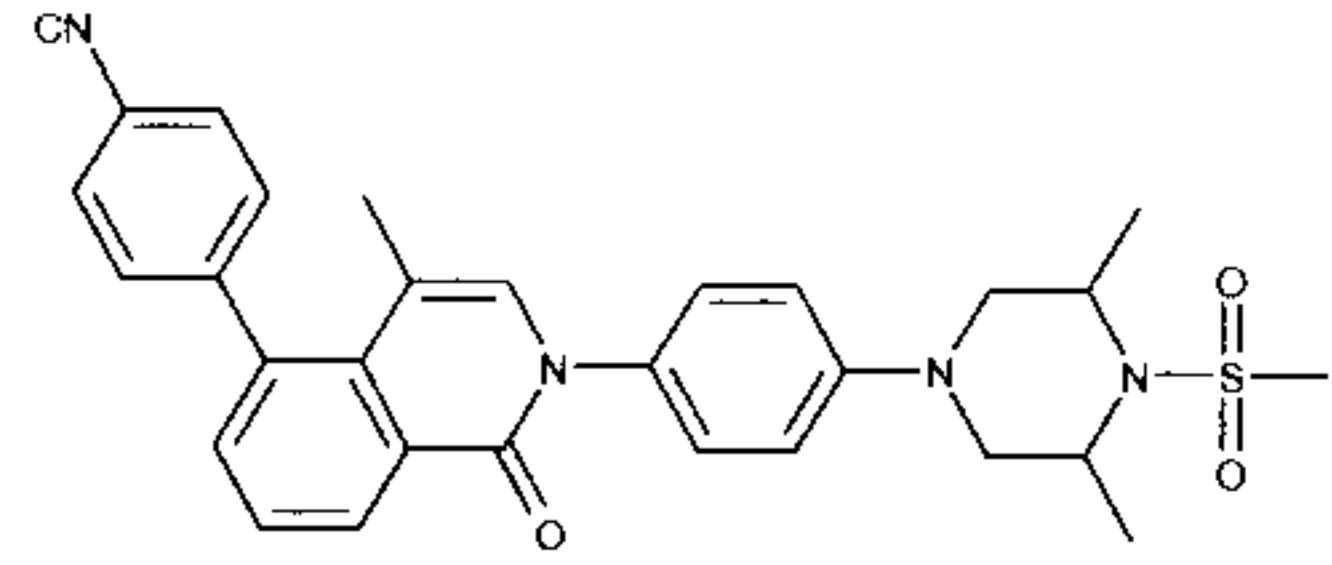
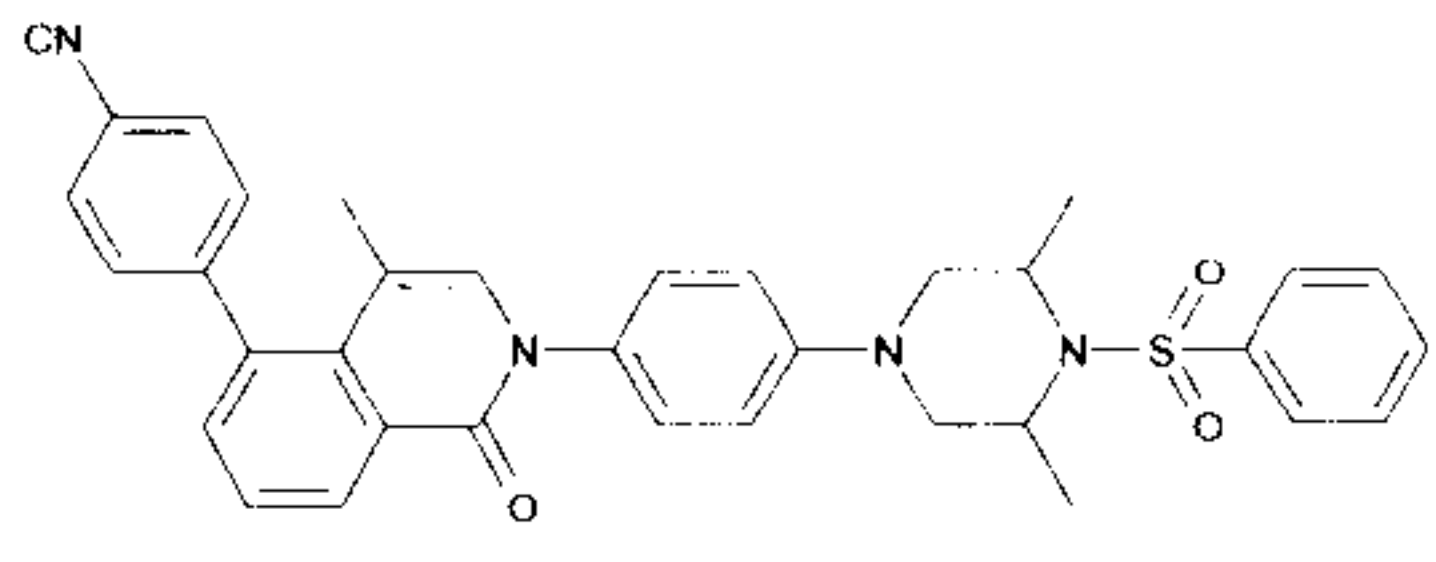
Embodiment	Structure	NMR
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15		¹H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.04 (d, <i>J</i> = 8.4 Hz, 1H), 8.41 (d, <i>J</i> = 8.0 Hz, 2H), 7.89 (d, <i>J</i> = 8.4 Hz, 2H), 7.58-7.50 (m, 4H), 7.32 (d, <i>J</i> = 8.4 Hz, 2H), 7.17 (s, 1H), 7.11 (d, <i>J</i> = 8.8 Hz, 2H), 3.93 (d, <i>J</i> = 12.8 Hz, 2H), 3.41-3.26 (brs, 2H), 2.65 (t, <i>J</i> = 12.8 Hz, 2H), 1.50 (s, 3H), 1.26 (d, <i>J</i> = 6.4 Hz, 6H). MS ESI calcd for C ₂₉ H ₂₈ N ₄ O [M+H] ⁺ 449, found 449.
16		¹H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.41 (d, <i>J</i> = 7.2 Hz, 1H), 7.87 (d, <i>J</i> = 7.6 Hz, 2H), 7.55-7.48 (m, 4H), 7.26 (d, <i>J</i> = 8.0 Hz, 2H), 7.18 (s, 1H), 7.02 (d, <i>J</i> = 8.0 Hz, 2H), 4.08 (brs, 2H), 3.55 (d, <i>J</i> = 12.0 Hz, 2H), 2.82 (d, <i>J</i> = 9.2 Hz, 2H), 1.48 (s, 3H), 1.39 (s, 9H), 1.22 (d, <i>J</i> = 6.0 Hz, 6H). MS ESI calcd for C ₃₄ H ₃₆ N ₄ O ₃ [M+H] ⁺ 549, found 549.
17		¹H NMR (400 MHz, CDCl ₃) δ 8.66 (d, <i>J</i> = 7.6 Hz, 1H), 7.01 (d, <i>J</i> = 8.0 Hz, 2H), 7.56-7.61 (m, 1H), 7.38-7.53 (m, 3H), 7.30 (d, <i>J</i> = 9.2 Hz, 2H), 6.96 (t, <i>J</i> = 8.8 Hz, 3H), 4.10-4.95 (m, 2H), 3.42-3.88 (m, 3H), 2.72-3.25 (m, 2H), 2.35-2.50 (m, 2H), 1.60 (s, 3H), 1.25-1.45 (m, 3H), 1.19 (t, <i>J</i> = 6.8 Hz, 3H). MS ESI calcd for C ₃₁ H ₃₀ N ₄ O ₂ [M+H] ⁺ 491, found 491.
18		¹H NMR (400 MHz, CDCl ₃) δ 8.66 (d, <i>J</i> = 6.8 Hz, 1H), 7.71 (d, <i>J</i> = 8.4 Hz, 2H), 7.59-7.27 (m, 11H), 7.07-6.93 (m, 3H), 3.72-3.23 (m, 7H), 2.54-2.42 (m, 2H), 1.60 (s, 3H),

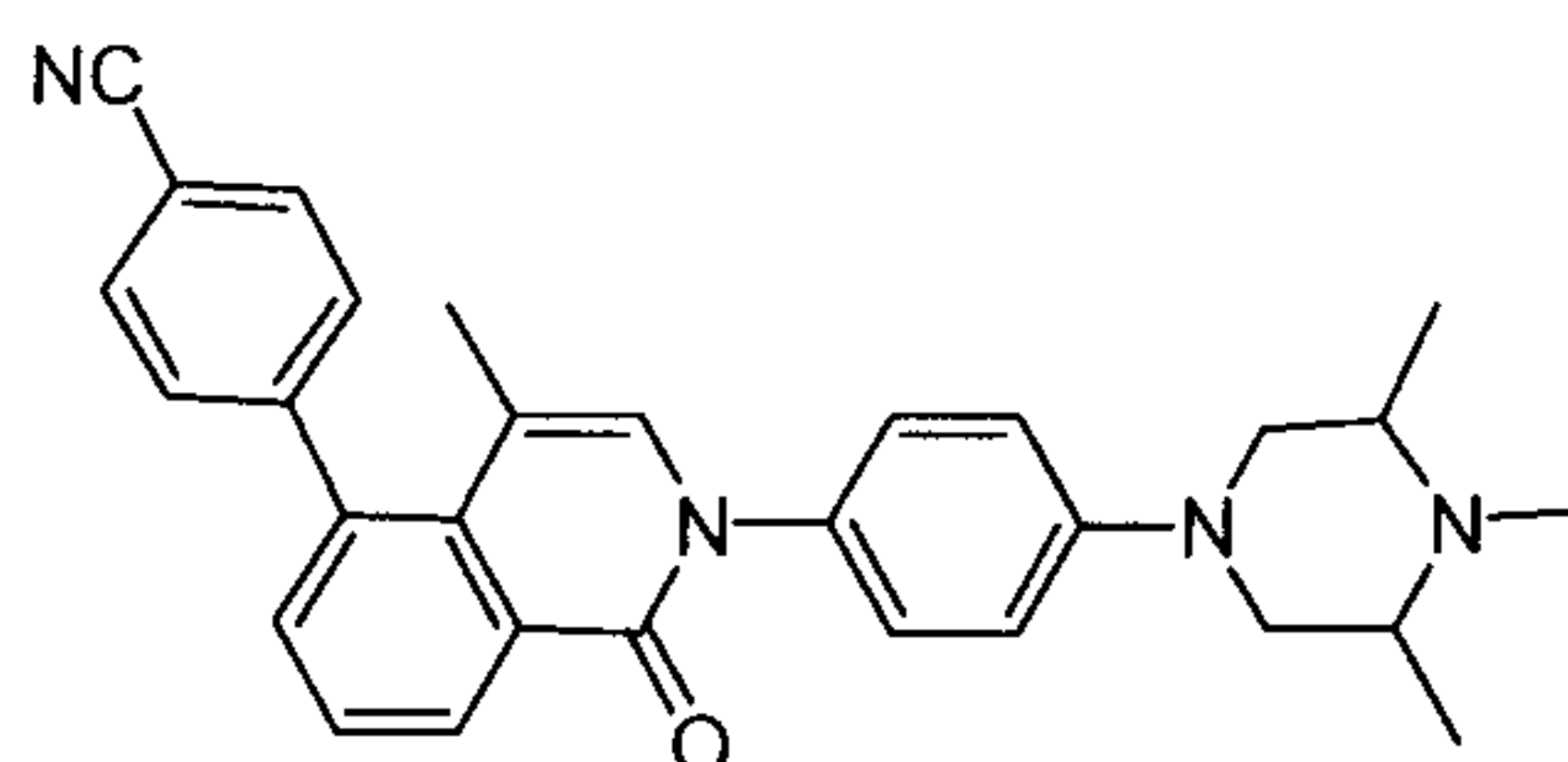
		1.43-1.08 (m, 3H). MS ESI calcd for $C_{36}H_{32}N_4O_2$ $[M+H]^+$ 553, found 553.
19		^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.53-7.45 (m, 4H), 7.31-7.25 (m, 2H), 6.94 (s, 1H), 6.723 (d, J = 8.8 Hz, 2H), 4.26 (brs, 2H), 3.79-3.75 (m, 5H), 3.37 (d, J = 11.6 Hz, 2H), 1.58 (s, 3H), 1.42-1.23 (m, 6H). MS ESI calcd for $C_{31}H_{30}N_4O_3$ $[M+H]^+$ 507, found 507.
20		^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 7.6 Hz, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.58 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 8.0 Hz, 3H), 7.28 (d, J = 9.2 Hz, 2H), 6.98 (s, 1H), 6.72 (d, J = 8.8 Hz, 2H), 4.27-4.18 (m, 4H), 3.80-3.76 (m, 2H), 3.37 (d, J = 11.6 Hz, 2H), 1.61 (s, 3H), 1.32-1.27 (m, 9H). MS ESI calcd for $C_{32}H_{32}N_4O_3$ $[M+H]^+$ 521, found 521.
21		^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 7.6 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.49-7.39 (m, 10H), 7.29 (d, J = 8.4 Hz, 2H), 6.97 (s, 1H), 6.74 (d, J = 8.8 Hz, 1H), 4.01 (brs, 2H), 3.87-3.78 (m, 2H), 3.46-3.38 (m, 2H), 1.61 (s, 3H), 1.37-1.23 (brs, 6H). MS ESI calcd for $C_{36}H_{32}N_4O_2$ $[M+H]^+$ 553, found 553.
22		^1H NMR (400 MHz, $DMSO-d_6$) δ 8.42 (d, J = 7.2 Hz, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.59-7.49 (m, 4H), 7.28 (d, J = 8.4 Hz, 2H), 7.19 (s, 1H), 6.05 (d, J = 8.8 Hz, 2H), 3.59 (d, J = 12.0 Hz, 4H), 2.83 (brs, 2H), 2.04 (s, 3H),

		1.50 (s, 3H), 1.26 (brs, 6H). MS ESI calcd for $C_{31}H_{30}N_4O_2$ $[M+H]^+$ 491, found 491.
23		^1H NMR (400 MHz, DMSO- d_6) δ 8.44 (d, J = 6.4 Hz, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.60-7.51 (m, 4H), 7.29 (d, J = 8.8 Hz, 2H), 7.21 (s, 1H), 7.06 (d, J = 8.4 Hz, 2H), 3.97 (brs, 4H), 3.61 (d, J = 12.0 Hz, 2H), 2.85 (brs, 2H), 1.51 (s, 3H), 1.28 (brs, 6H), 1.01 (t, J = 7.2 Hz, 3H). MS ESI calcd for $C_{32}H_{32}N_4O_2$ $[M+H]^+$ 505, found 505.
24		^1H NMR (400 MHz, DMSO- d_6) δ 8.43 (d, J = 6.4 Hz, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.61-7.51 (m, 4H), 7.30 (d, J = 8.8 Hz, 2H), 7.21 (s, 1H), 7.07 (d, J = 8.8 Hz, 2H), 3.85-3.52 (m, 4H), 2.86-2.81 (m, 3H), 1.51 (s, 3H), 1.42-1.17 (m, 6H), 1.03 (d, J = 6.4 Hz, 6H). MS ESI calcd for $C_{33}H_{34}N_4O_2$ $[M+H]^+$ 519, found 519.
25		^1H NMR (400 MHz, DMSO- d_6) δ 8.43 (d, J = 7.6 Hz, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.60-7.51 (m, 4H), 7.30 (d, J = 8.4 Hz, 2H), 7.21 (s, 1H), 7.03 (d, J = 8.8 Hz, 2H), 4.52 (brs, 2H), 3.55 (d, J = 11.6 Hz, 2H), 2.86 (d, J = 11.6 Hz, 2H), 1.51 (s, 3H), 1.32 (d, J = 6.0 Hz, 6H), 1.23 (s, 9H). MS ESI calcd for $C_{34}H_{36}N_4O_2$ $[M+H]^+$ 533, found 533.
26		^1H NMR (400 MHz, DMSO- d_6) δ 8.44 (d, J = 6.8 Hz, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.61-7.51 (m, 4H), 7.30 (d, J = 9.2 Hz, 2H),

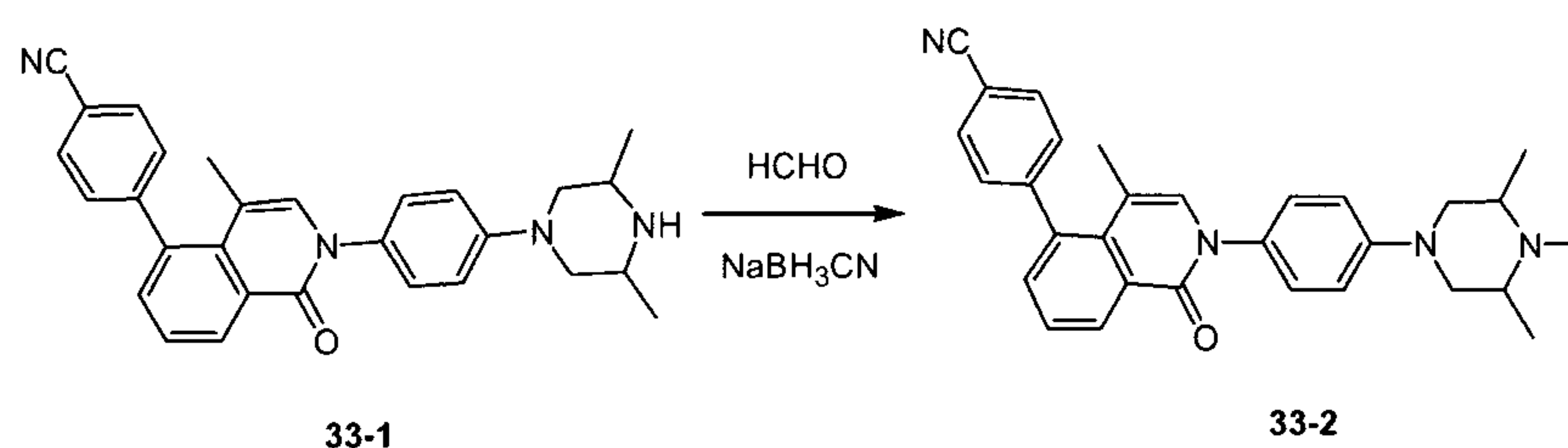
		7.21 (s, 1H), 7.8 (d, $J = 9.2$ Hz, 2H), 4.56-4.47 (m, 2H), 3.67 (brs, 2H), 2.92-2.84 (m, 2H), 2.28-1.93 (m, 1H), 1.51 (s, 3H), 1.31 (brs, 6H), 0.76-0.72 (m, 4H). MS ESI calcd for $C_{33}H_{32}N_4O_2$ $[M+H]^+$ 517, found 517.
27		^1H NMR (400 MHz, DMSO- d_6) δ 8.43 (d, $J = 7.2$ Hz, 1H), 7.90 (d, $J = 8.0$ Hz, 2H), 7.91-7.39 (m, 9H), 7.29 (d, $J = 8.8$ Hz, 2H), 7.21 (s, 1H), 7.04 (d, $J = 9.2$ Hz, 2H), 4.02 (brs, 2H), 3.61 (d, $J = 12.0$ Hz, 2H), 2.97-2.93 (m, 2H), 1.51 (s, 3H), 1.32 (d, $J = 6.0$ Hz, 6H). MS ESI calcd for $C_{36}H_{32}N_4O_2$ $[M+H]^+$ 553, found 553.
28		^1H NMR (400 MHz, MeOD) δ 8.54 (d, $J = 6.4$ Hz, 1H), 7.79 (d, $J = 8.4$ Hz, 2H), 7.62-7.53 (m, 4H), 7.30 (d, $J = 9.2$ Hz, 2H), 7.10 (d, $J = 8.4$ Hz, 3H), 4.28 (t, $J = 5.6$ Hz, 2H), 3.72 (s, 3H), 3.58 (d, $J = 12.8$ Hz, 2H), 2.95-2.91 (m, 2H), 1.63 (s, 3H), 1.36 (d, $J = 6.4$ Hz, 6H). MS ESI calcd for $C_{31}H_{30}N_4O_3$ $[M+H]^+$ 507, found 507.
29		^1H NMR (400 MHz, MeOD) δ 8.53 (d, $J = 6.8$ Hz, 1H), 7.79 (d, $J = 8.4$ Hz, 2H), 7.61-7.53 (m, 4H), 7.28 (d, $J = 8.8$ Hz, 2H), 7.09 (d, $J = 9.2$ Hz, 3H), 4.95-4.88 (m, 1H), 4.27 (t, $J = 5.2$ Hz, 2H), 3.57 (d, $J = 12.0$ Hz, 2H), 2.92 (dd, $J = 12.4$ Hz, $J = 4.0$ Hz, 2H), 1.62 (s, 3H), 1.35 (d, $J = 6.8$ Hz, 6H), 1.26 (d, $J = 6.0$ Hz, 6H). MS ESI calcd for $C_{33}H_{34}N_4O_3$ $[M+H]^+$ 535,

		found 535.
30		¹H NMR (400 MHz, MeOD) δ 8.53 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.61-7.52 (m, 4H), 7.28 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.0 Hz, 3H), 4.19-4.16 (m, 2H), 3.58 (d, J = 12.0 Hz, 2H), 2.91 (dd, J = 12.0 Hz, J = 3.6 Hz, 2H), 2.75 (s, 3H), 1.62 (s, 3H), 1.33 (d, J = 6.8 Hz, 6H). MS ESI calcd for $C_{31}H_{31}N_5O_2$ $[M+H]^+$ 506, found 506.
31		¹H NMR (400 MHz, MeOD) δ 8.53 (d, J = 6.8 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.61-7.53 (m, 4H), 7.29 (d, J = 8.0 Hz, 2H), 7.10-7.07 (m, 3H), 5.00 (brs, 1H), 4.14 (brs, 2H), 3.54 (t, J = 8.0 Hz, 2H), 3.20 (s, 1H), 3.12 (d, J = 3.6 Hz, 1H), 3.01 (dd, J = 12.4 Hz, J = 4.0 Hz, 1H), 2.94 (s, 1H), 1.62 (s, 3H), 1.48 (t, J = 8.0 Hz, 6H). MS ESI calcd for $C_{30}H_{30}N_4O_3S$ $[M+H]^+$ 527, found 527.
32		¹H NMR (400 MHz, MeOD) δ 8.52 (d, J = 6.8 Hz, 1H), 7.88 (d, J = 7.2 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.58-7.52 (m, 7H), 7.24 (d, J = 8.8 Hz, 2H), 7.07 (s, 1H), 6.97 (d, J = 8.8 Hz, 2H), 4.25-4.15 (m, 2H), 3.43 (d, J = 12.4 Hz, 2H), 2.64-2.60 (m, 2H), 1.61 (s, 3H), 1.47 (d, J = 6.8 Hz, 6H). MS ESI calcd for $C_{35}H_{32}N_4O_3S$ $[M+H]^+$ 589, found 589.

Embodiment 33



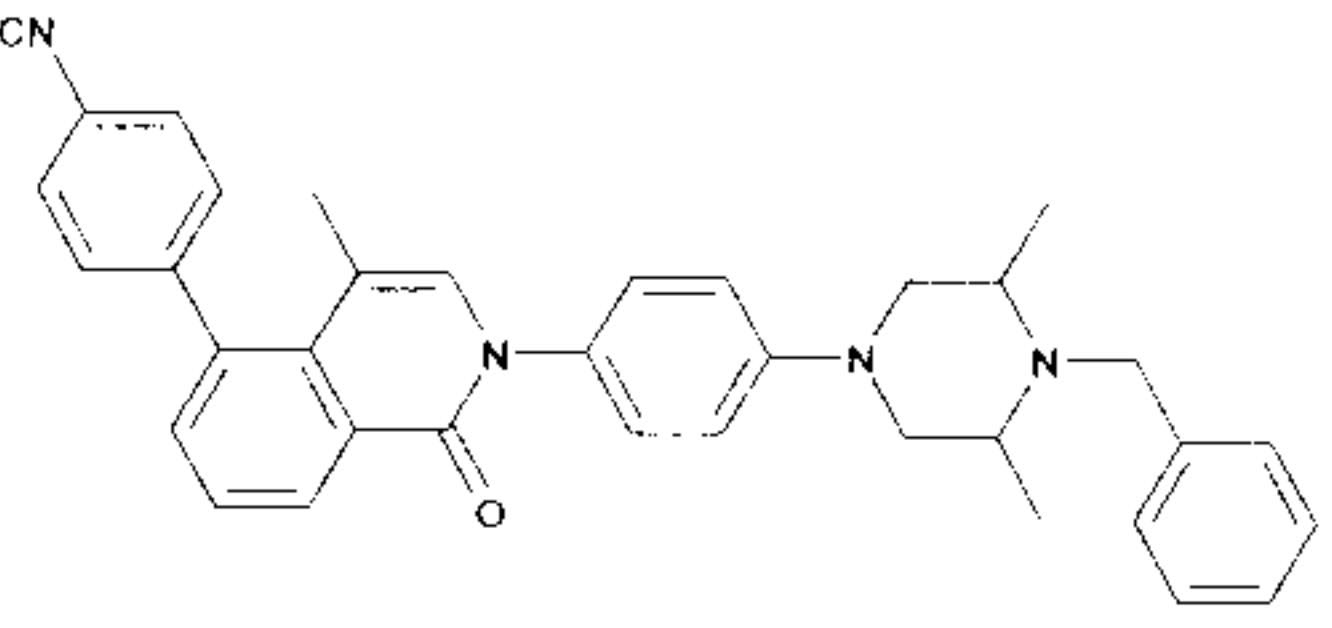
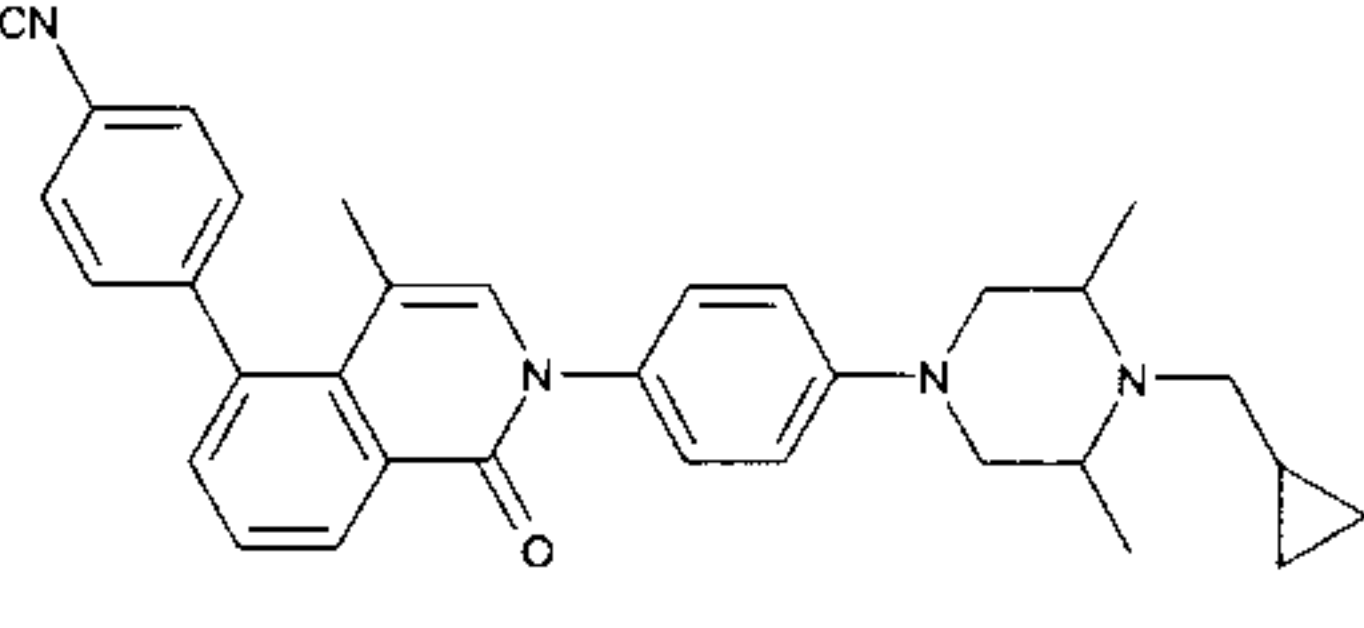
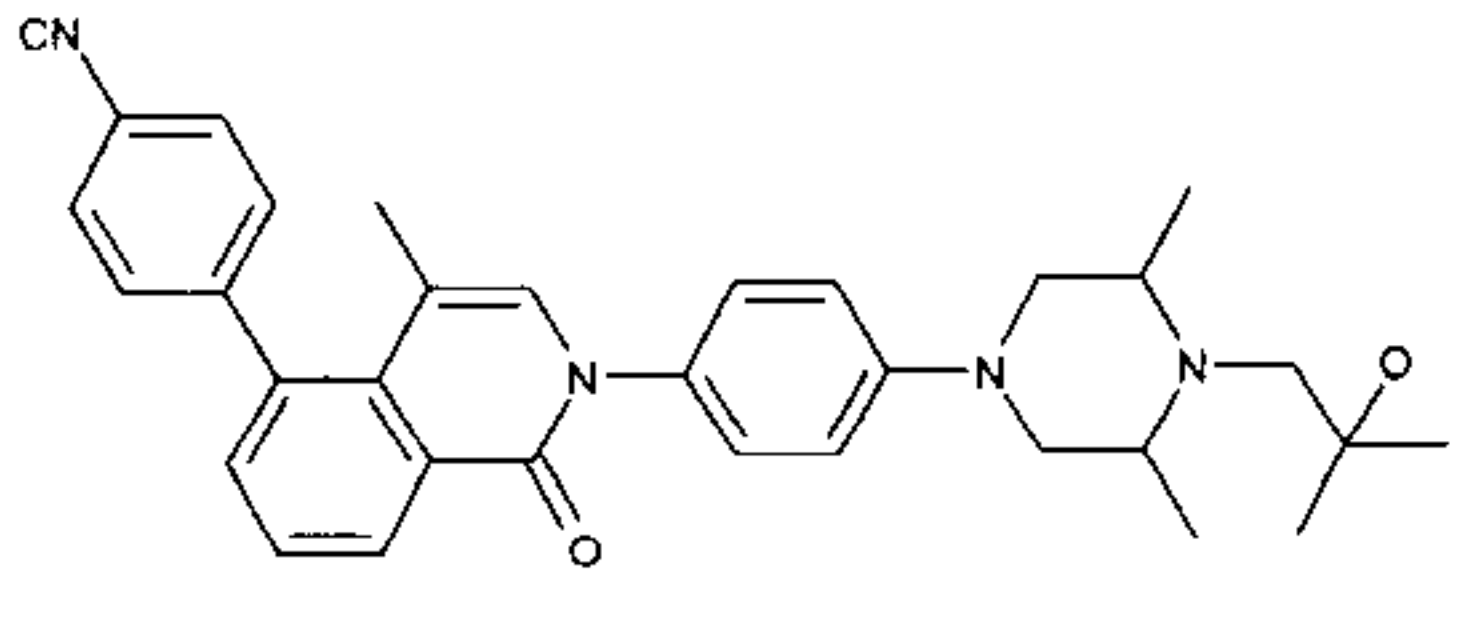
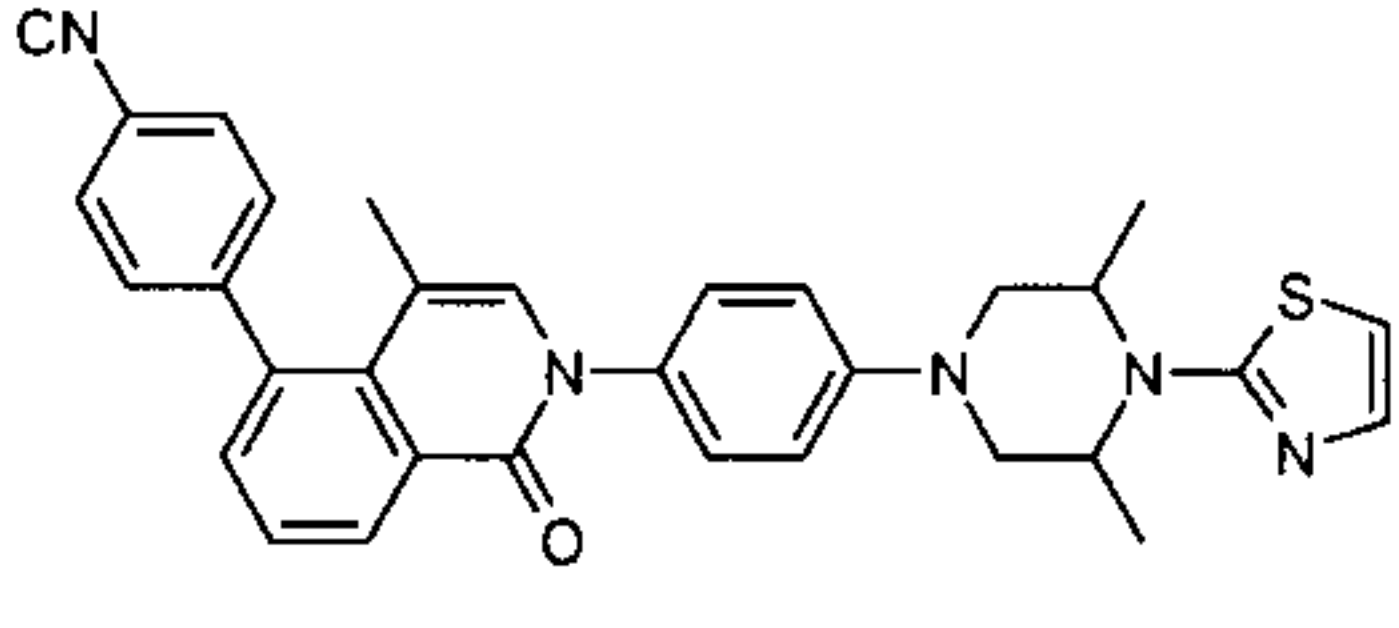
4-(4-methyl-1-oxo-2-(4-(3,4,5-trimethylpiperazin-1-yl)phenyl)-1,2-dihydroisoquinolin-5-yl)benzonitrile



[224] Compound 33-1 (200 mg, 0.45 mmol), formaldehyde (41 mg, 1.35 mmol) and NaBH₃CN (43 mg, 0.675 mmol) were dissolved in THF (5 mL), and the reaction mixture was stirred at room temperature for 16 h. The reaction was detected by LC-MS. The crude product was purified by preparative HPLC to deliver the title compound as white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.43 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.61-7.54 (m, 4H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.19 (s, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 4.01 (d, *J* = 12.8 Hz, 2H), 3.35 (d, *J* = 6.4 Hz, 2H), 2.85 (t, *J* = 12.4 Hz, 2H), 1.52 (s, 3H), 1.34 (d, *J* = 6.4 Hz, 6H), 1.19 (t, *J* = 6.4 Hz, 3H). MS ESI calcd for C₃₀H₃₀N₄O [M+H]⁺ 463, found 463.

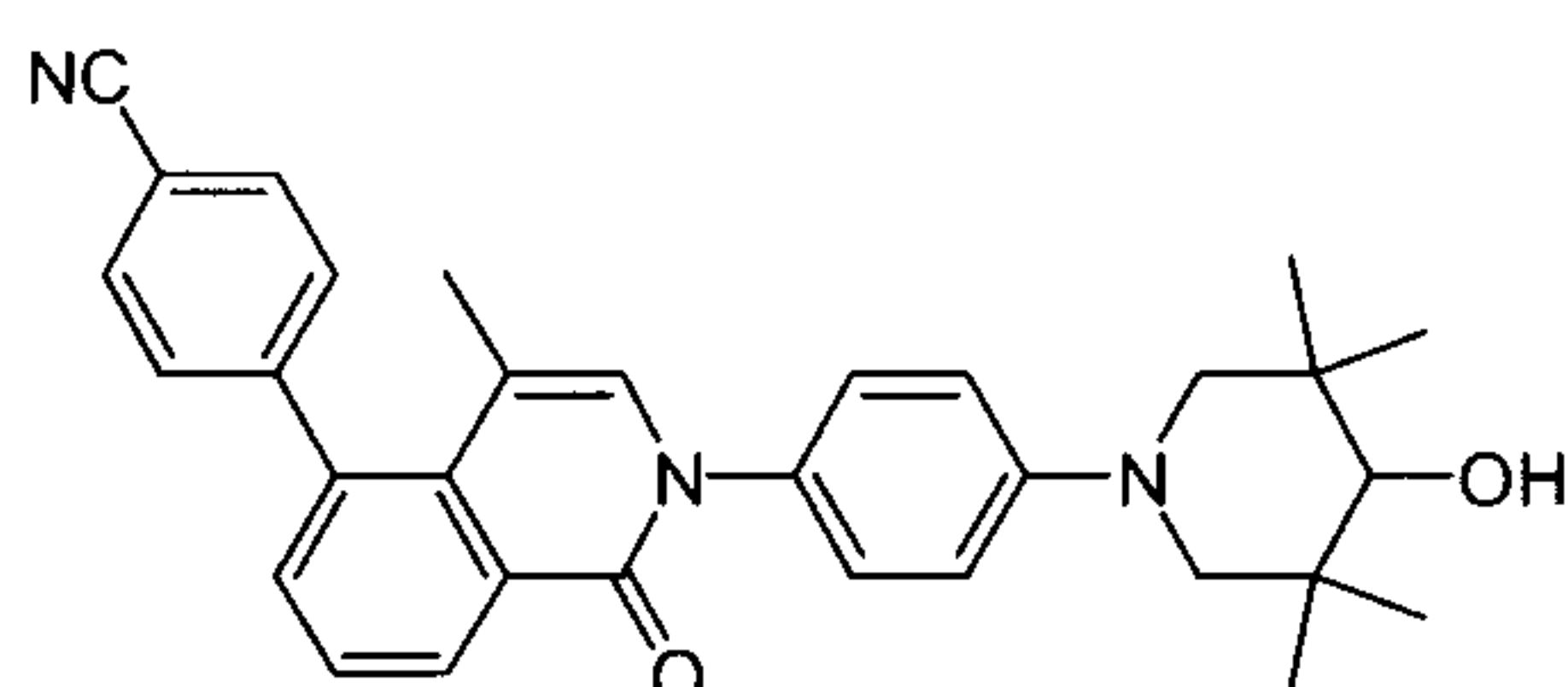
[225] The compounds listed in table 3 can be synthesized by compound 33-1 and corresponding aldehydes.

Embodi ment	Structure	NMR
34		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.43 (d, <i>J</i> = 8.0 Hz, 1H), 7.91 (d, <i>J</i> = 8.0 Hz, 2H), 7.561-7.54 (m, 4H), 7.35 (d, <i>J</i> = 8.8 Hz, 2H), 7.19 (s, 1H), 7.14 (d, <i>J</i> = 8.4 Hz, 2H), 4.02 (d, <i>J</i> = 12.8 Hz, 2H), 3.53-3.46 (m, 4H), 2.85 (t, <i>J</i> = 12.4 Hz, 2H), 1.52 (s, 3H), 1.34 (d, <i>J</i> = 6.4 Hz, 6H), 1.19 (t, <i>J</i> = 6.4 Hz, 3H). MS ESI calcd for C ₃₁ H ₃₂ N ₄ O [M+H] ⁺ 477, found 477.

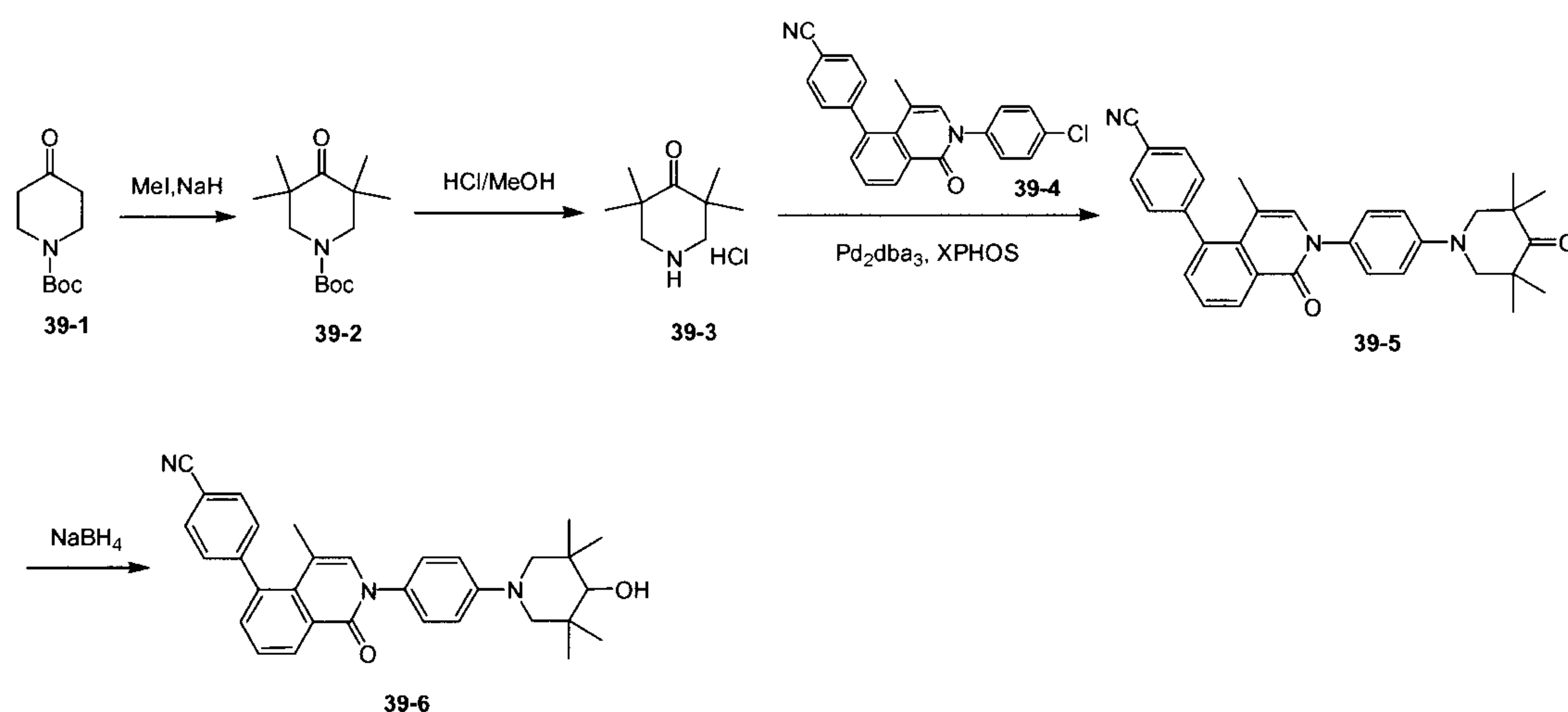
35		¹H NMR (400 MHz, CDCl ₃) δ 8.63 (d, <i>J</i> = 7.6 Hz, 1H), 7.70 (d, <i>J</i> = 8.0 Hz, 2H), 7.52-7.44 (m, 9H), 7.30 (d, <i>J</i> = 8.2 Hz, 2H), 6.93 (d, <i>J</i> = 8.4 Hz, 2H), 6.87 (s, 1H), 4.59 (s, 2H), 3.56 (d, <i>J</i> = 12.0 Hz, 2H), 3.43-3.31 (m, 4H), 1.78-1.67 (m, 4H), 1.57 (s, 3H). MS ESI calcd for C ₃₆ H ₃₄ N ₄ O [M+H] ⁺ 539, found 539.
36		¹H NMR (400 MHz, CDCl ₃) δ 8.59 (d, <i>J</i> = 7.6 Hz, 1H), 7.65 (d, <i>J</i> = 8.0 Hz, 2H), 7.55-7.42 (m, 4H), 7.29 (d, <i>J</i> = 8.8 Hz, 2H), 6.95 (d, <i>J</i> = 8.8 Hz, 2H), 6.85 (s, 1H), 3.69-3.56 (m, 4H), 3.46-3.31 (m, 2H), 3.29 (d, <i>J</i> = 7.2 Hz, 2H), 2.36 (brs, 1H), 1.46 (d, <i>J</i> = 6.0 Hz, 6H), 0.97-0.73 (m, 3H), 0.43-0.34 (m, 2H). MS ESI calcd for C ₃₃ H ₃₄ N ₄ O [M+H] ⁺ 503, found 503.
37		¹H NMR (400 MHz, CDCl ₃) δ 8.66 (d, <i>J</i> = 7.6 Hz, 1H), 7.72 (d, <i>J</i> = 7.6 Hz, 2H), 7.57-7.53 (m, 1H), 7.47 (d, <i>J</i> = 7.6 Hz, 3H), 7.36 (d, <i>J</i> = 6.4 Hz, 2H), 7.00 (d, <i>J</i> = 8.0 Hz, 2H), 6.92 (s, 1H), 4.02 (brs, 1H), 3.67-3.54 (m, 3H), 3.32 (brs, 1H), 3.20 (s, 1H), 3.17-2.85 (m, 3H), 2.67 (s, 5H), 1.60 (s, 3H), 1.43 (s, 6H). MS ESI calcd for C ₃₃ H ₃₆ N ₄ O ₂ [M+H] ⁺ 521, found 521.
38		¹H NMR (400 MHz, CDCl ₃) δ 8.91 (s, 1H), 8.67 (d, <i>J</i> = 6.8 Hz, 2H), 7.72 (d, <i>J</i> = 8.0 Hz, 2H), 7.58-7.54 (m, 2H), 7.48 (d, <i>J</i> = 7.6 Hz,

		3H), 7.36 (d, $J = 9.2$ Hz, 3H), 7.10 (d, $J = 8.8$ Hz, 2H), 6.94 (s, 1H), 3.62 (t, $J = 11.2$ Hz, 2H), 3.14-3.11 (m, 2H), 2.90 (t, $J = 10.0$ Hz, 2H), 2.17 (s, 1H), 1.61 (s, 3H), 1.02 (t, $J = 6.4$ Hz, 6H). MS ESI calcd for $C_{32}H_{29}N_5OS$ $[M+H]^+$ 532, found 532. Q?
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Embodiment 39



4-(2-(4-(4-hydroxy-3,3,5,5-tetramethylpiperidin-1-yl)phenyl)-4-methyl-1-oxo-1,2-dihydroisoquinolin-5-yl)benzonitrile



[226] Step 1: Compound 39-1 (4 g, 20 mmol) was dissolved in THF (50 mL), cooled to 0°C, NaH (6.4 g, 160 mmol) was added, and then the reaction mixture was stirred at room temperature for 0.5h, cooled to 0°C again, iodomethane (10 mL, 160 mmol) was added dropwise, then warmed to room temperature and stirred for further 2h. The reaction was detected by TLC, the reaction mixture was quenched with water and extracted with EtOAc, the organic phase was washed with brines, dried over anhydrous sodium sulfate and concentrated under reduced pressure to deliver the compound 39-2 as yellow solid (4.5 g, yield 88%). **MS ESI** calcd for $C_{14}H_{25}NO_3$ $[M+H]^+$ 256, found 256.

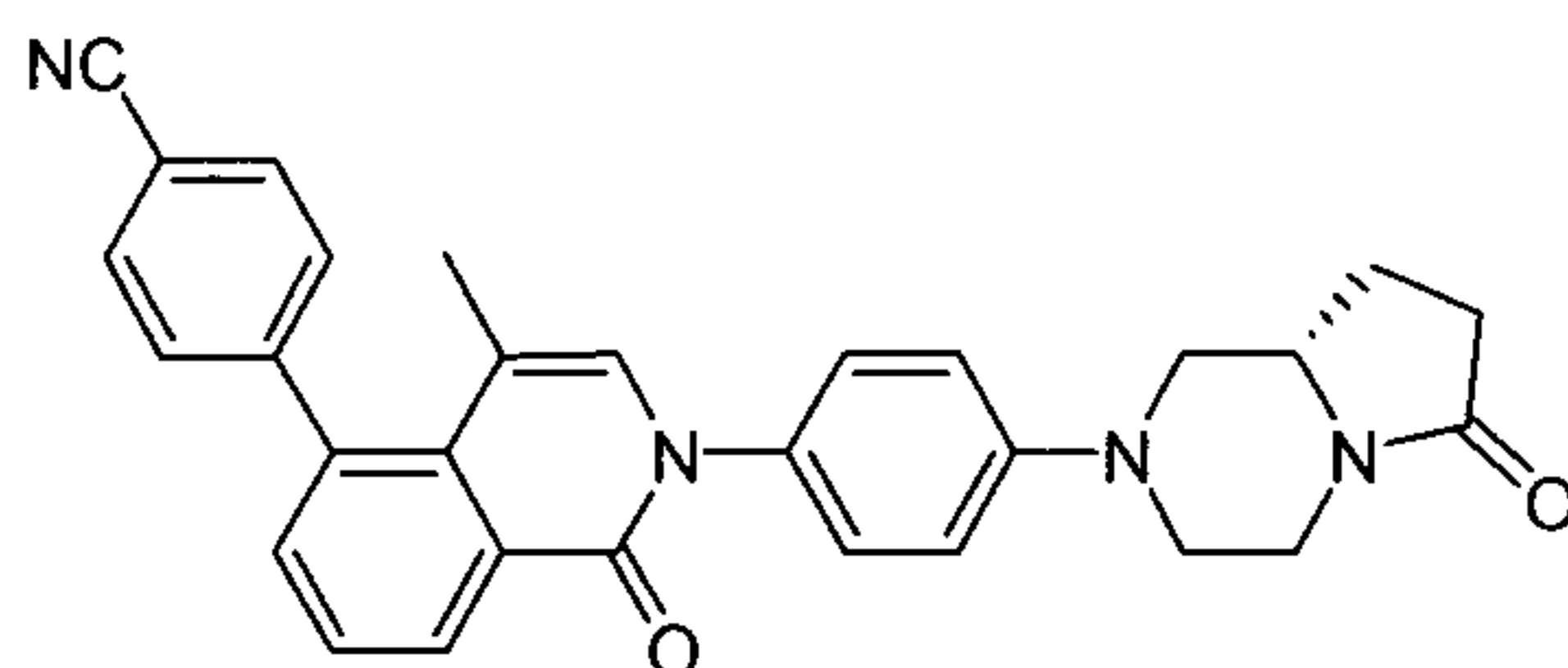
[227] Step 2: Compound 39-2 (410 mg, 1.6 mmol) was dissolved in hydrochloric

acid/methanol (10 mL) and stirred at room temperature for 2h. After the reaction was complete, the mixture was concentrated under reduced pressure to deliver compound 39-3 as yellow oil (330 mg, yield 86%). **MS ESI** calcd for $C_9H_{17}NO$ $[M+H]^+$ 156, found 156.

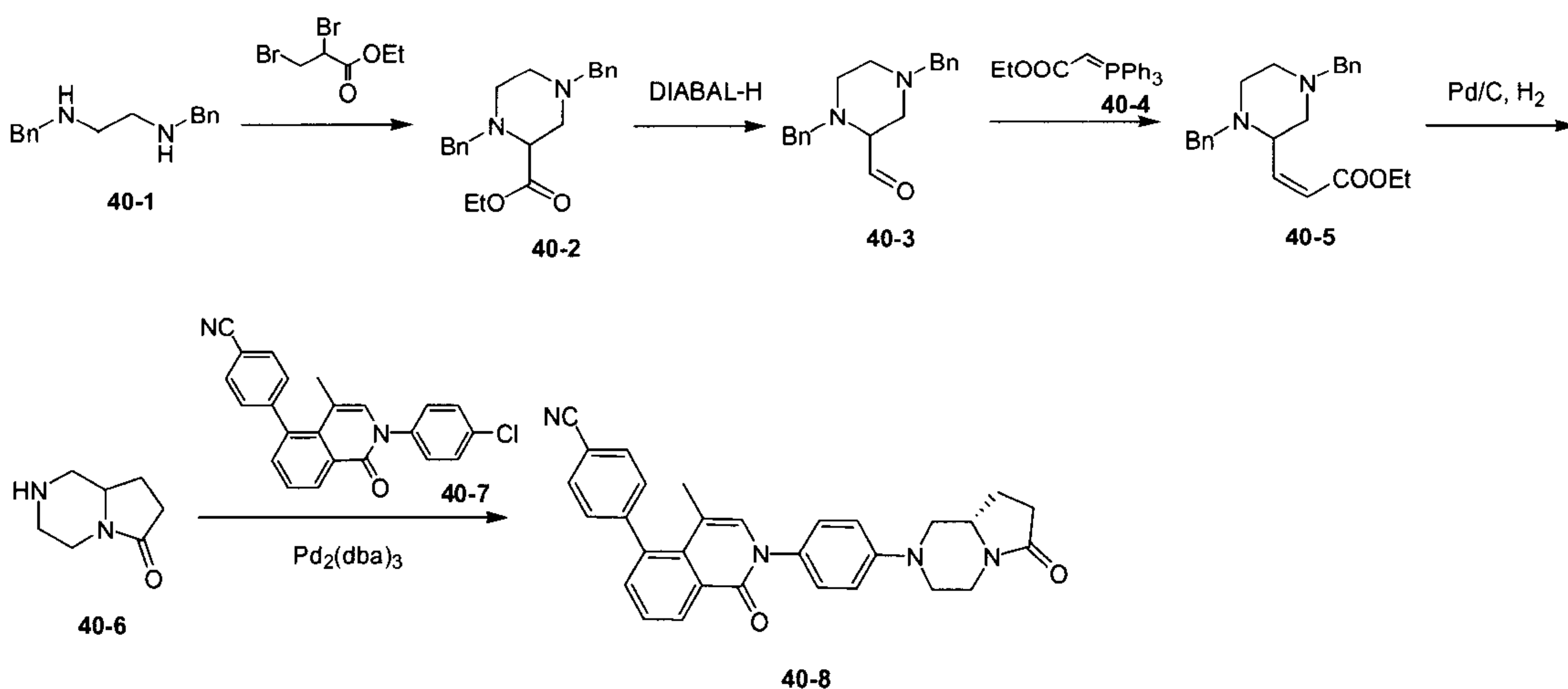
[228] Step 3: Compound 39-5 was prepared according to the above-mentioned method, as yellow solid (300 mg, yield 75%). **MS ESI** calcd for $C_{32}H_{31}N_3O_2$ $[M+H]^+$ 490, found 490.

[229] Step 4: Compound 39-5 (490 mg, 1 mmol) was dissolved in THF (10 mL), $NaBH_4$ (57 mg, 1.5 mmol) was added, then the mixture was stirred at room temperature for 0.5h. The reaction was detected by LC-MS, the residue was poured into H_2O , extracted with DCM. The organic phase was washed with brines, dried over anhydrous sodium sulfate and concentrated under reduced pressure to deliver the crude compound. The crude product was purified by preparative HPLC to deliver the title compound as white solid (64 mg, yield 13%). **^1H NMR** (400 MHz, $CDCl_3$) δ 8.69 (d, $J = 7.2$ Hz, 1H), 7.74 (d, $J = 7.6$ Hz, 2H), 7.60-7.45 (m, 4H), 7.27 (d, $J = 6.4$ Hz, 2H), 7.00-6.90 (m, 3H), 3.39 (d, $J = 12.0$ Hz, 2H), 3.12 (s, 1H), 2.60 (d, $J = 12.0$ Hz, 2H), 1.62 (s, 3H), 1.09 (s, 6H), 1.04 (s, 6H). **MS ESI** calcd for $C_{32}H_{33}N_3O_2$ $[M+H]^+$ 492, found 492.

Embodiment 40



(S)-4-(4-methyl-1-oxo-2-(4-(6-oxo-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)phenyl)-1,2-dihydroisoquinolin-5-yl)benzonitrile



[230] Step 1: Compound 40-1 (10 g, 4.20 mmol) and DIEA (10.8 g, 84 mmol) were

dissolved in toluene (200 mL) and cooled to 0 °C, ethyl 2,3-dibromopropionate (13.1 g, 50.4 mmol) was added, and then the reaction mixture was stirred at 100°C overnight. The reaction was detected by TLC. The reaction mixture was quenched with H₂O, extracted with EtOAc. The organic phase was washed with brines, dried over anhydrous sodium sulfate and concentrated under reduced pressure, the residue was purified by silica gel column chromatography (PE/EtOAc= 10/1) to deliver the compound 40-2 as yellow oil (8.5 g, yield 61%). **MS ESI** calcd for C₂₁H₂₆N₂O₂ [M+H]⁺ 339, found 339.

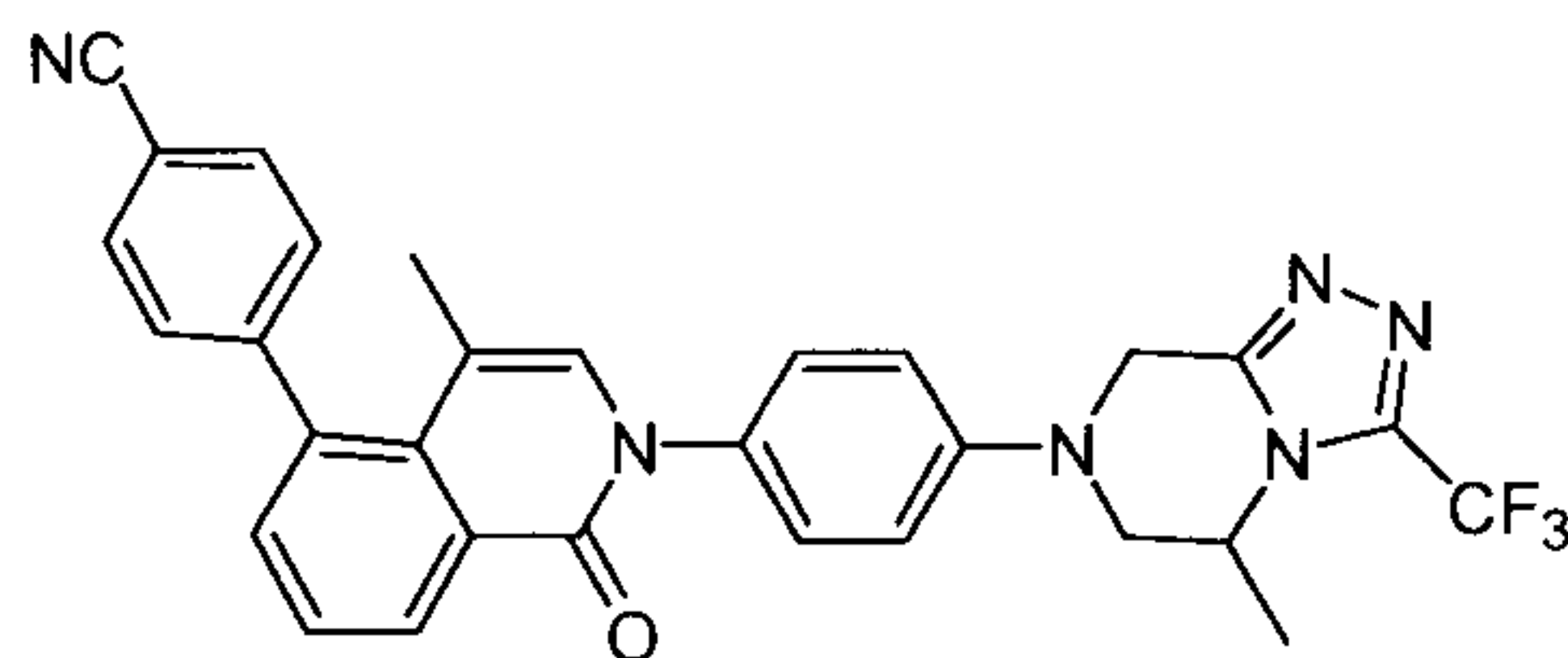
[231] Step 2: Under nitrogen gas atmosphere, DIBAL-H (45 mL, 45 mmol) was added into a solution of compound 40-2 (8.4 g, 24.85 mmol) in toluene (100 mL) at -78 °C, and stirred at -78°C for 1h. After the reaction was complete, 20% sodium hydroxide (30.7 mL) was added. The reaction mixture was warmed to room temperature and 20% sodium hydroxide aqueous solution (76.8 mL) was added. The reaction solution was extracted with EtOAc, and the organic phase was washed with brines, dried over anhydrous sodium sulfate and concentrated under reduced pressure to deliver compound 40-3 as yellow oil (7.4 g crude). **MS ESI** calcd for C₁₉H₂₂N₂O [M+H]⁺ 295, found 295.

[232] Step 3: Under nitrogen gas atmosphere, compound 40-3 (7.3 g, 24.75 mmol) was dissolved in toluene (100 mL), compound 40-4 (17.2 g, 49.50 mmol) was added, and the mixture was stirred at 80 °C overnight. The reaction was detected by LC-MS. The residue was poured into H₂O, extracted with EtOAc. The organic phase was washed with brines, dried over anhydrous sodium sulfate and concentrated under reduced pressure, the residue was purified by silica gel column chromatography (PE/EtOAc= 10/1 to 4/1) to deliver compound 40-5 as yellow oil (5.6 g, yield 62%). **MS ESI** calcd for C₂₃H₂₈N₂O₂ [M+H]⁺ 365, found 365.

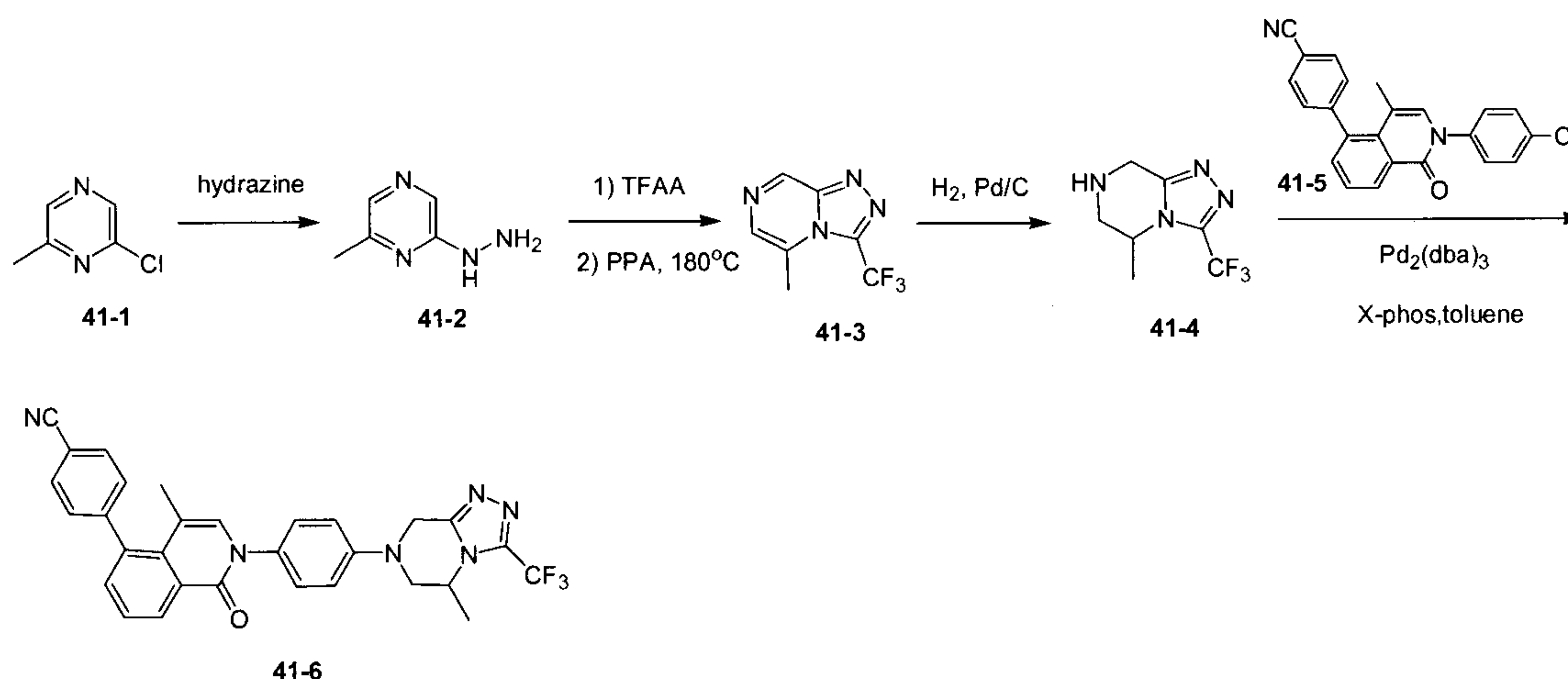
[233] Step 4: Pd/C (2.8 g, 10%) was added into a solution of compound 40-5 (5.6 g, 15.34 mmol) in ethanol (100 mL), the reaction mixture was heated to 70°C under 55psi and stirred overnight. The reaction was detected by TLC, and filtrated with diatomite, the filtrate was concentrated to deliver compound 40-6 as yellow oil (2 g, yield 71%). **MS ESI** calcd for C₇H₁₂N₂O [M+H]⁺ 141, found 141.

[234] Step 5: The title compound was prepared according to the above-mentioned method, as white solid (30 mg, yield 12%). ¹H NMR (400 MHz, CDCl₃) δ 8.66 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.42-7.58 (m, 4H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.94 (s, 1H), 4.13-4.18 (m, 1H), 3.76-3.90 (m, 2H), 2.69 (d, *J* = 12.0 Hz, 1H), 3.05-3.18 (m, 1H), 2.75-2.85 (m, 1H), 2.52-2.63 (m, 3H), 2.25-2.35 (m, 1H), 1.65-1.78 (m, 1H), 1.61 (s, 3H). **MS ESI** calcd for C₃₀H₂₆N₄O₂ [M+H]⁺ 475, found 475.

Embodiment 41



4-(4-methyl-2-(4-(5-methyl-3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)phenyl)-1-oxo-1,2-dihydroisoquinolin-5-yl)benzonitrile



[235] Step 1: Compound 41-1 (2.9 g, 22.75 mmol) was added into hydrazine hydrate (15 mL), the reaction mixture was subject to an preheated oil bath (50 °C), then warmed to 100°C above for 30 min. After cooled to room temperature, the reaction mixture was cooled to 0°C for 1 h. The residue was collected by filtration and dried to deliver compound 41-2 as white solid (1.6g, yield 58%). **MS ESI** calcd for C₅H₈N₄ [M+H]⁺ 125, found 125.

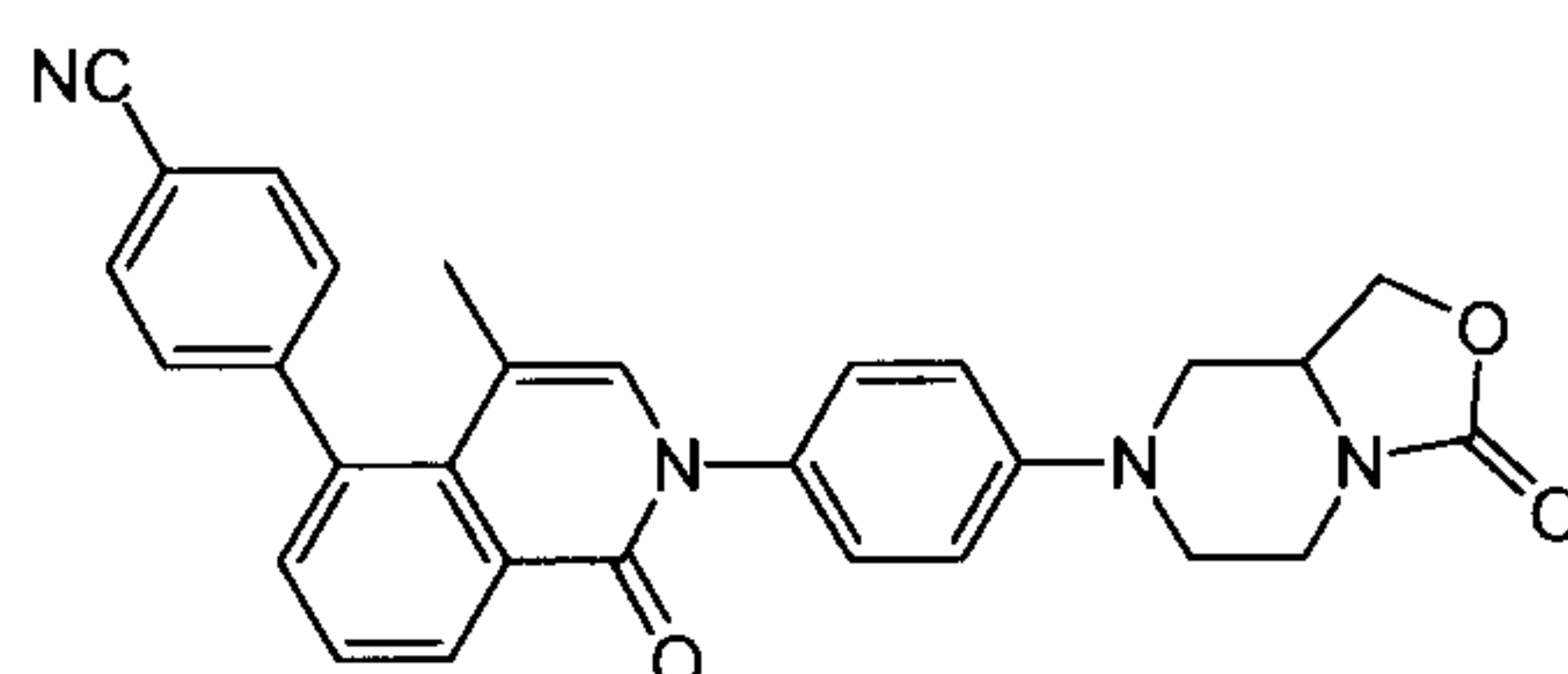
[236] Step 2: TFAA (35 mL) was added into compound 41-2 (1.6 g, 13.2 mmol) dropwise at 0 °C, the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to deliver yellow solid. Then PPA (40 mL) was added. The reaction mixture was heated to 120°C and stirred for 18h. The hot PPA solution was poured into ice water and neutralized with ammonia. The aqueous phase was extracted with EtOAc, the organic phase was washed with brines, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE: EtOAc= 1:1) to deliver compound 41-3 as yellow solid (2 g, yield 77%). **MS ESI** calcd for C₇H₅F₃N₄ [M+H]⁺ 203, found 203.

[237] Step 3: Compound 41-3 (2 g, 10 mmol) and Pd/C (1.1 g) were dissolved in EtOH (30 mL) and THF (15 mL), under hydrogen gas atmosphere, the reaction mixture was stirred at room temperature for 18h. The reaction mixture was filtrated and the filtrate was concentrated to deliver compound 41-4 as yellow oil (1.9 g, yield 90%). **MS ESI** calcd for C₇H₉F₃N₄ [M+H]⁺ 207, found 207.

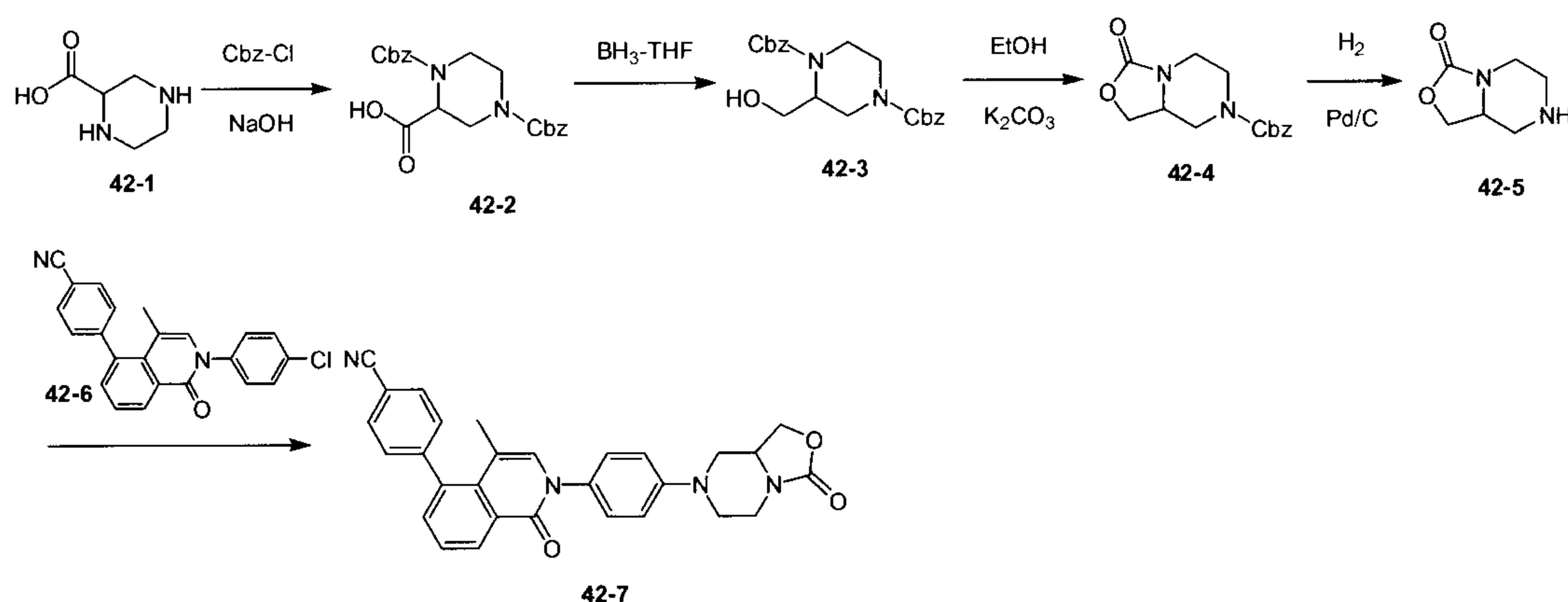
[238] Step 4: The title compound was prepared according to the above-mentioned

method, as white solid (25 mg, yield 6.8%). ¹H NMR (400 MHz, CDCl₃) δ 8.66 (d, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.45 (dd, *J* = 23.2 Hz, *J* = 8.0 Hz, 5H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.92 (s, 1H), , 4.91 (d, *J* = 16.0 Hz, 1H), 4.70 (brs, 1H), 4.44 (d, *J* = 16.0 Hz, 1H), 3.83 (d, *J* = 13.2 Hz, 1H), 3.53 (d, *J* = 10.8 Hz, 1H), 1.68 (d, *J* = 6.0 Hz, 3H), 1.59 (s, 3H). MS ESI calcd for C₃₀H₂₃F₃N₆O [M+H]⁺ 541, found 541.

Embodiment 42



4-(4-methyl-1-oxo-2-(4-(3-oxotetrahydro-1H-oxazolo[3,4-a]pyrazin-7(3H)-yl)phenyl)-1,2-dihydroisoquinolin-5-yl)benzonitrile



[239] Step 1: Compound 42-1 (17 g, 84 mmol) was dissolved in dioxane (340 mL) and H₂O (210 mL), the solution was adjust to pH>11 with sodium hydroxide aqueous solution (50%), CbzCl (24 mL, 168 mmol) was added, the reaction mixture was stirred for 2 h, and then poured into 1L H₂O. The aqueous phase was extracted with DCM, the organic phase was washed with brines, dried over anhydrous sodium sulfate and concentrated under reduced pressure to deliver compound 42-2 as colorless adhesive oil (18 g, 51%). MS ESI calcd for C₂₁H₂₂N₂O₆ [M+H]⁺ 399, found 399.

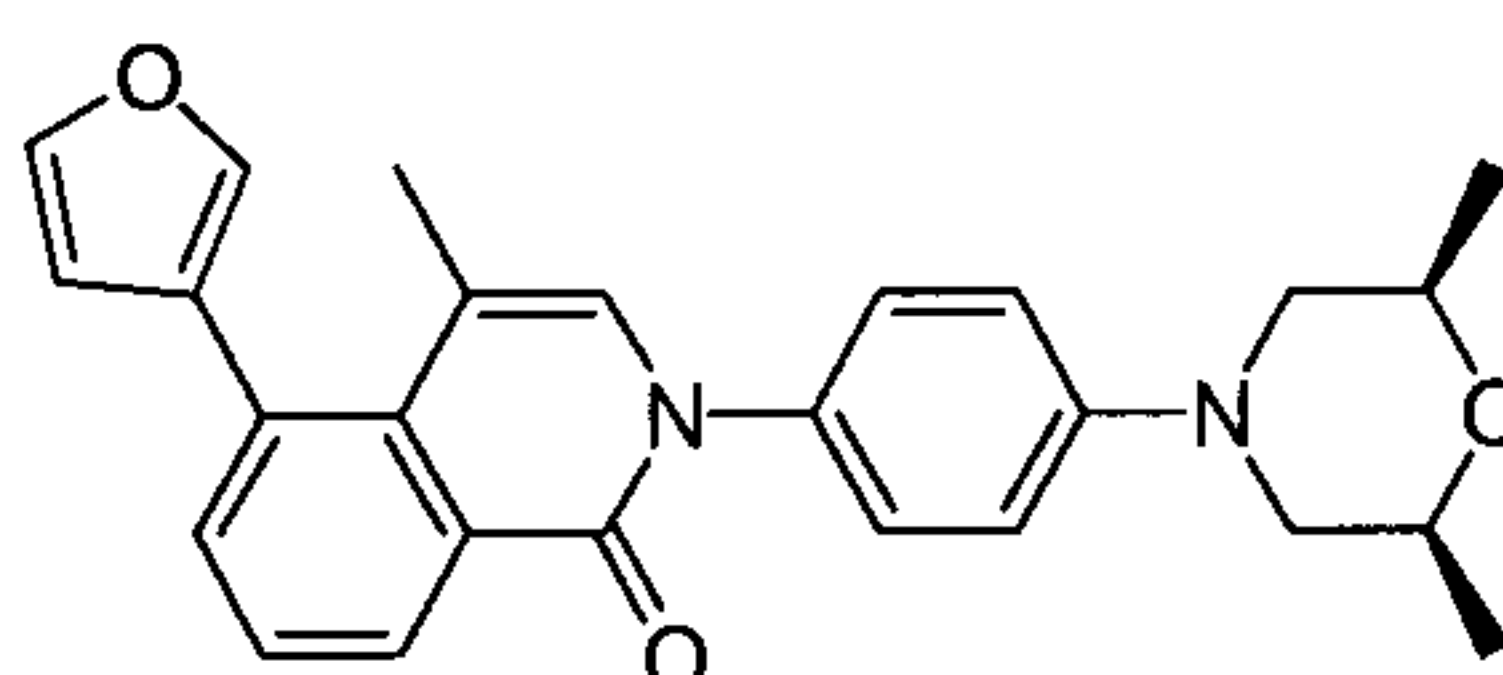
[240] Step 2: Compound 42-2 (14 g, 35 mmol) was dissolved in THF (150 mL), then BH₃-THF (70 mL, 70 mmol) was added dropwise, the reaction mixture was stirred at 50°C for 3h. After the reaction was complete as detected by LC-MS, MeOH was added slowly to quench the reation. When no gas was released, the reaction mixture was warmed to 50°C and stirred for 1h, and then concentrated under reduced pressure to deliver compound 42-3 as colorless oil (4 g, 30%). MS ESI calcd for C₂₁H₂₄N₂O₅ [M+H]⁺ 385, found 385.

[241] Step 3: Compound 42-3 (4 g, 10.4 mmol) and potassium carbonate (1.7 g, 12.5 mmol) were dissolved in EtOH (40 mL), the reaction mixture was stirred at 70°C overnight. After the reaction was complete as detected by LC-MS, the mixture was filtrated to remove the remained potassium carbonate. The filtrate was concentrated under reduced pressure, purified by silica gel column chromatography (PE: EtOAc= 1:1) to deliver compound 42-4 as yellow solid (2.2 g, 78%). **MS ESI** calcd for $C_{14}H_{16}N_2O_4$ $[M+H]^+$ 277, found 277.

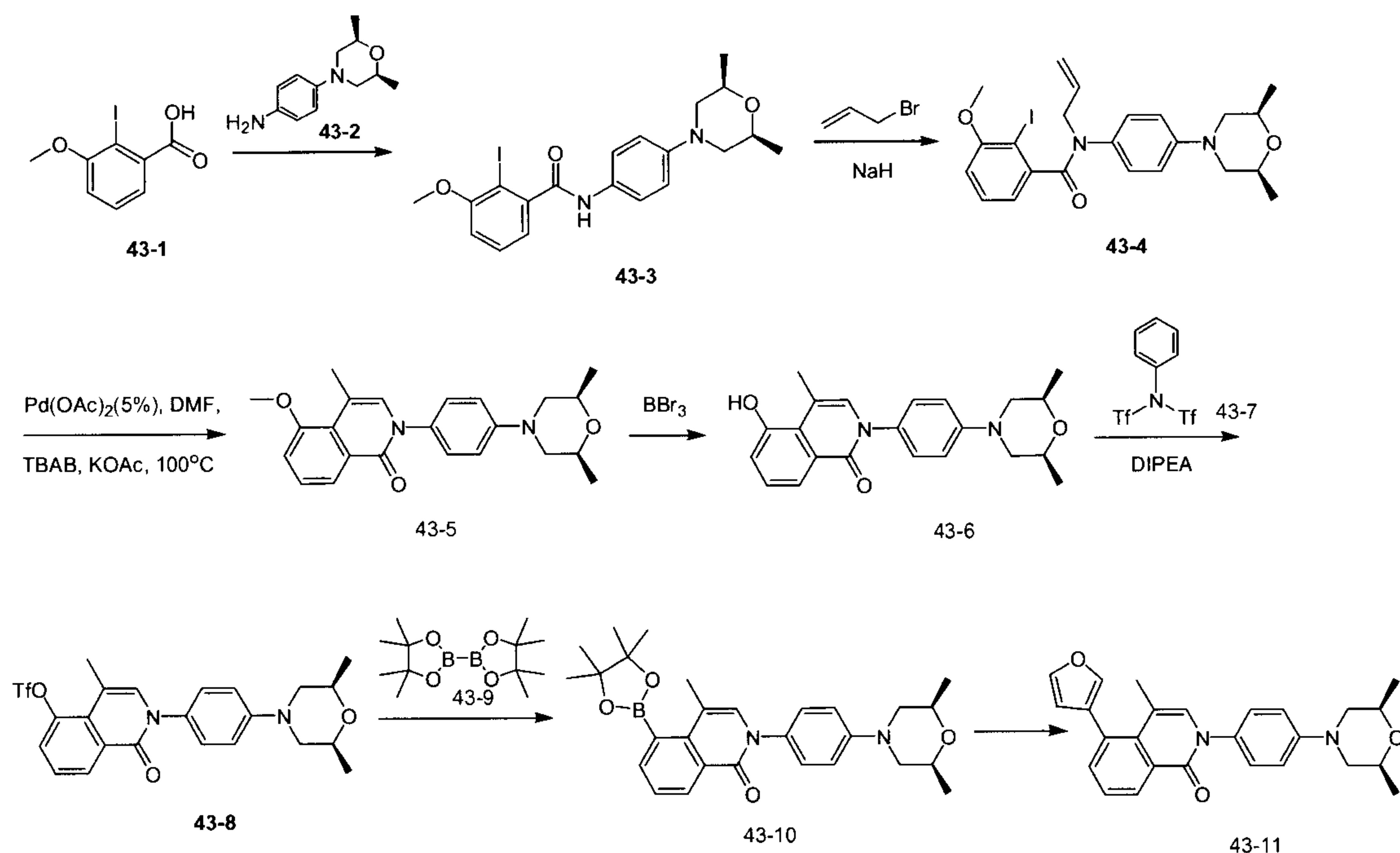
[242] Step 4: Pd/C (100 mg) was added into a solution of compound 42-4 (500 mg, 1.8 mmol) in MeOH (50 mL), under hydrogen gas atmosphere (40psi), the reaction mixture was stirred at room temperature for 12 h. Pd/C was removed by filtration, the filtrate was concentrated under reduced pressure to deliver compound 42-5 as yellow oil (240 mg, 95%). **MS ESI** calcd for $C_6H_{10}N_2O_2$ $[M+H]^+$ 143, found 143.

[243] Step 5: The title compound was prepared according to the above-mentioned method, as white solid (55 mg, yield 20%). **^1H NMR** (400 MHz, $CDCl_3$) δ 8.67 (d, J = 6.8 Hz, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.55 (t, J = 8.0 Hz, 1H), 7.48 (d, J = 7.6 Hz, 3H), 7.35 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 6.92 (s, 1H), 4.51 (t, J = 10.4 Hz, 1H), 4.04 (d, J = 5.6 Hz, 2H), 3.96 (d, J = 2.4 Hz, 1H), 3.71 (d, J = 12.0 Hz, 1H), 3.61 (d, J = 12.0 Hz, 1H), 3.37-3.22 (m, 1H), 2.94-2.78 (m, 1H), 2.76 (t, J = 10.04 Hz, 1H), 1.59 (s, 3H). **MS ESI** calcd for $C_{29}H_{24}N_4O_3$ $[M+H]^+$ 477, found 477.

Embodiment 43



2-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-5-(furan-3-yl)-4-methylisoquinolin-1(2H)-one



[244] Step 1: HATU (5.5 g, 40.86 mmol) was added into a solution of compound 43-1 (9.7 g, 34.9 mmol) in DMF (100 mL) at 0 °C. After stirring at room temperature for 30 min, DIEA (18 g, 69.8 mmol) and compound 43-2 (7.2 g, 34.9 mmol) was added at 0 °C, and then the reaction mixture was reacted at room temperature overnight. The reaction mixture was poured into H₂O, extracted with EtOAc. The organic phase was washed with H₂O, dried over anhydrous sodium sulfate, filtrated and concentrated. The residue was purified by silica gel column chromatography to deliver compound 43-3 (13 g, yield 80%) as white solid. **MS (ESI)** *m/z* (M+H)⁺ 467.

[245] Step 2: Under nitrogen gas atmosphere, NaH (1.34 g, 33.5 mmol), 3-bromo-1-propylene (6.8 g, 55.8 mmol) were added into a solution of compound 43-3 (13 g, 27.9 mmol) in DMF (100 mL) at 0 °C, and then the reaction mixture was reacted at room temperature overnight. The reaction mixture was poured into H₂O, extracted with EtOAc, the organic phase was washed with H₂O, dried over anhydrous sodium sulfate, filtrated and concentrated, the residue was purified by silica gel column chromatography to deliver compound 43-4 (12 g, yield 85.7%). **MS (ESI)** *m/z* (M+H)⁺ 507.

[246] Step 3: Compound 43-4 (11.1 g, 21.74 mmol), TBAB (17.50 g, 54.35 mmol), potassium acetate (3.2 g, 32.61 mmol), palladium acetate (487 mg, 2.17 mmol) were added into DMF (700 mL), heated to 100°C and stirred overnight. H₂O was added into the reaction mixture, EtOAc was used for extraction, the organic phase was washed with H₂O, dried over anhydrous sodium sulfate, filtrated and concentrated, the residue was purified by silica gel column chromatography to deliver compound 43-5 (4.5 g, yield 50%). **MS (ESI)** *m/z* (M+H)⁺ 379.

[247] Step 4: Boron tribromide (12.6 g, 4.7 mL) was added into a solution of

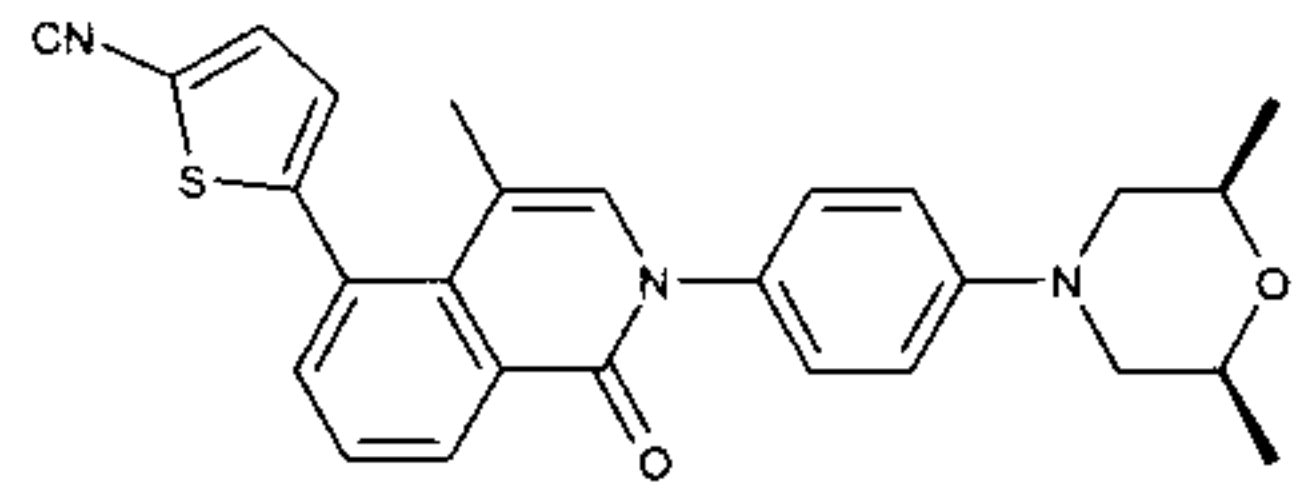
compound 43-5 (3.8 g, 10.05 mmol) in DCM (40 mL) at 0 °C, the reaction mixture was stirred at room temperature overnight, then quenched with saturated sodium carbonate solution, the mixture was filtrated to deliver compound 43-6 (1.9 g, yield 53%). **MS (ESI)** m/z (M+H)⁺ 365.

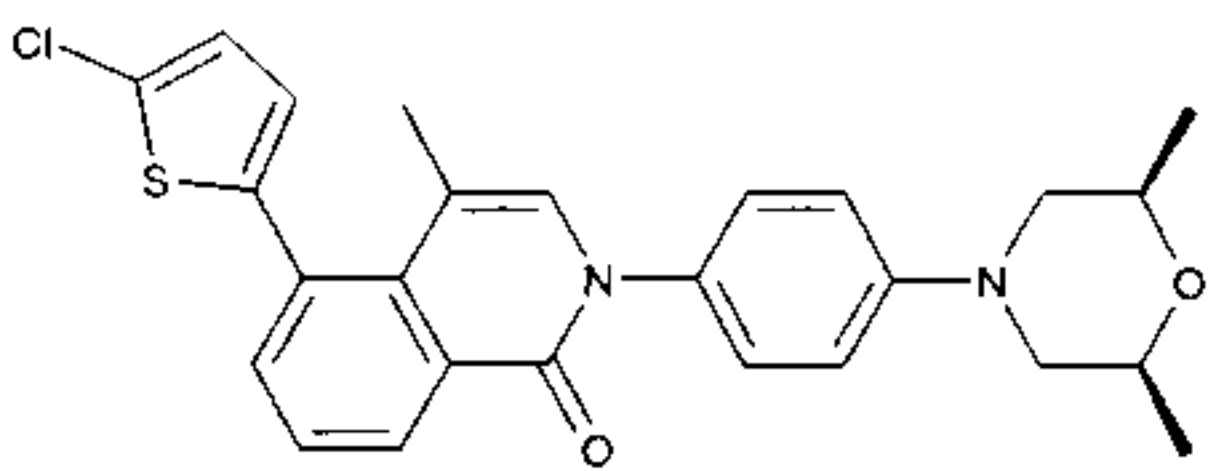
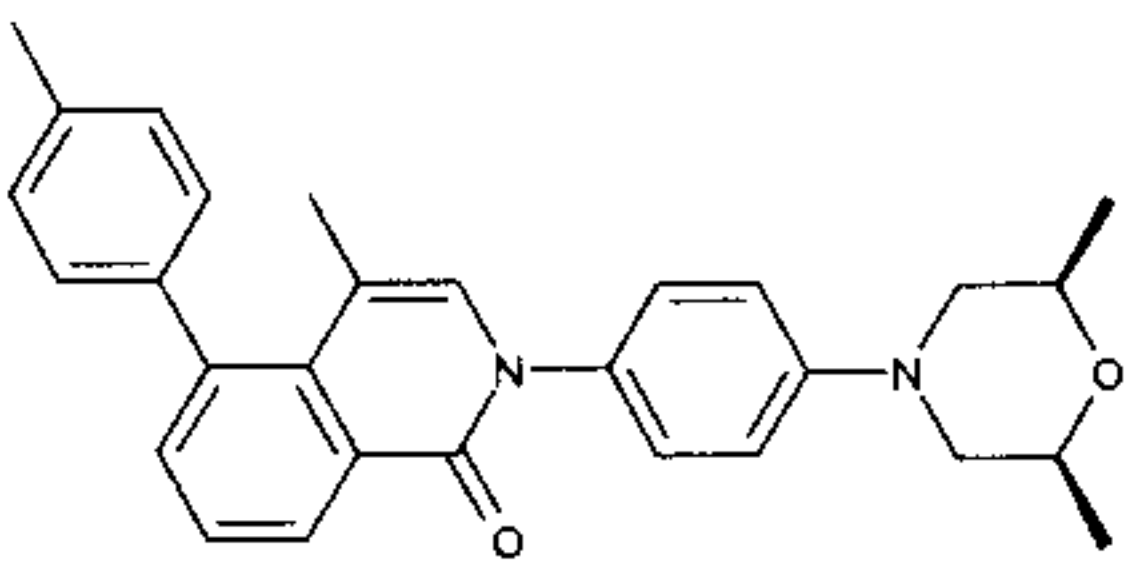
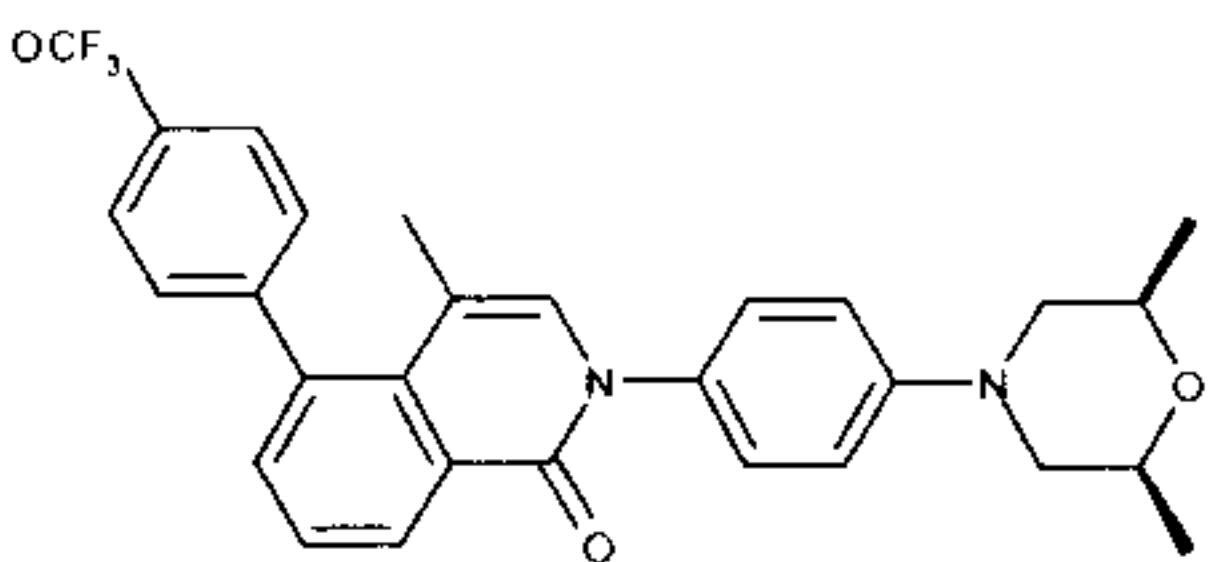
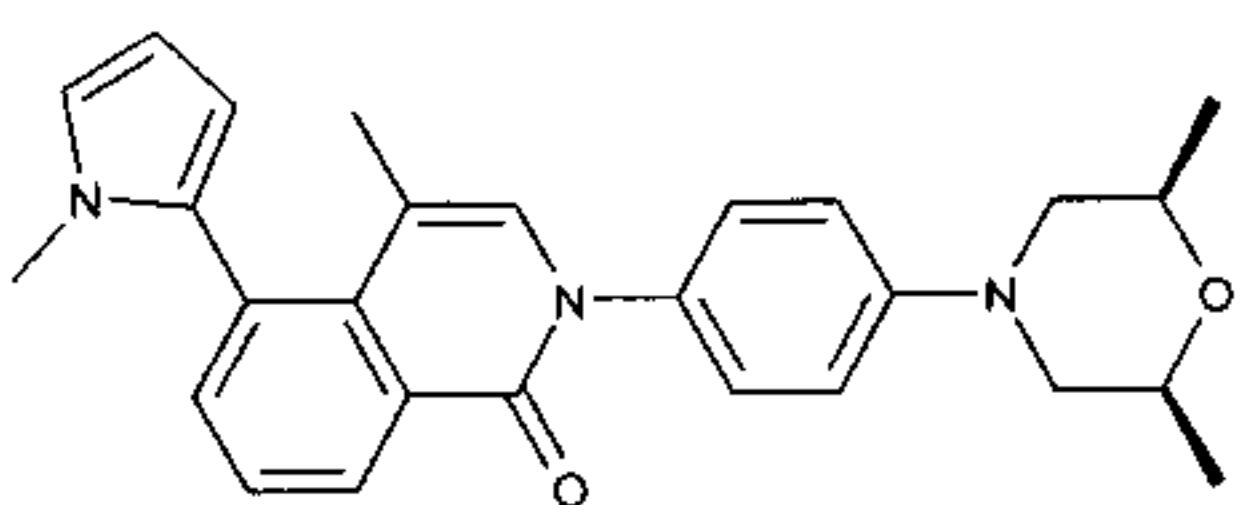
[248] Step 5: DIPEA (1.1 g, 8.24 mmol) and compound 43-7 (2.2 g, 6.18 mmol) were added into a solution of compound 43-6 (1.5 g, 4.12mmol) in DMF (60 mL), the reaction mixture reacted at room temperature overnight, and then concentrated under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography to deliver compound 43-8 (1.5 g, yield 75%). **MS (ESI)** m/z (M+H)⁺ 497.

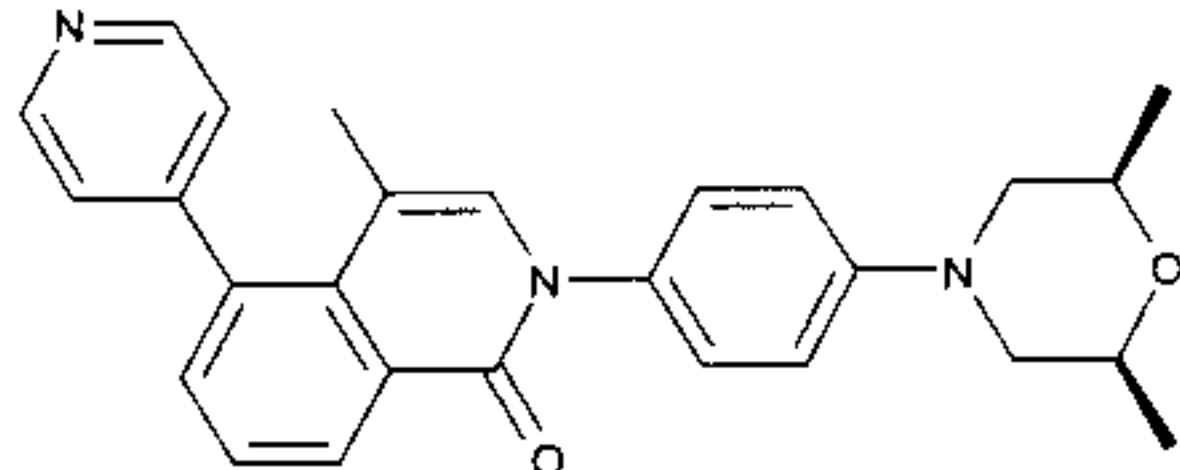
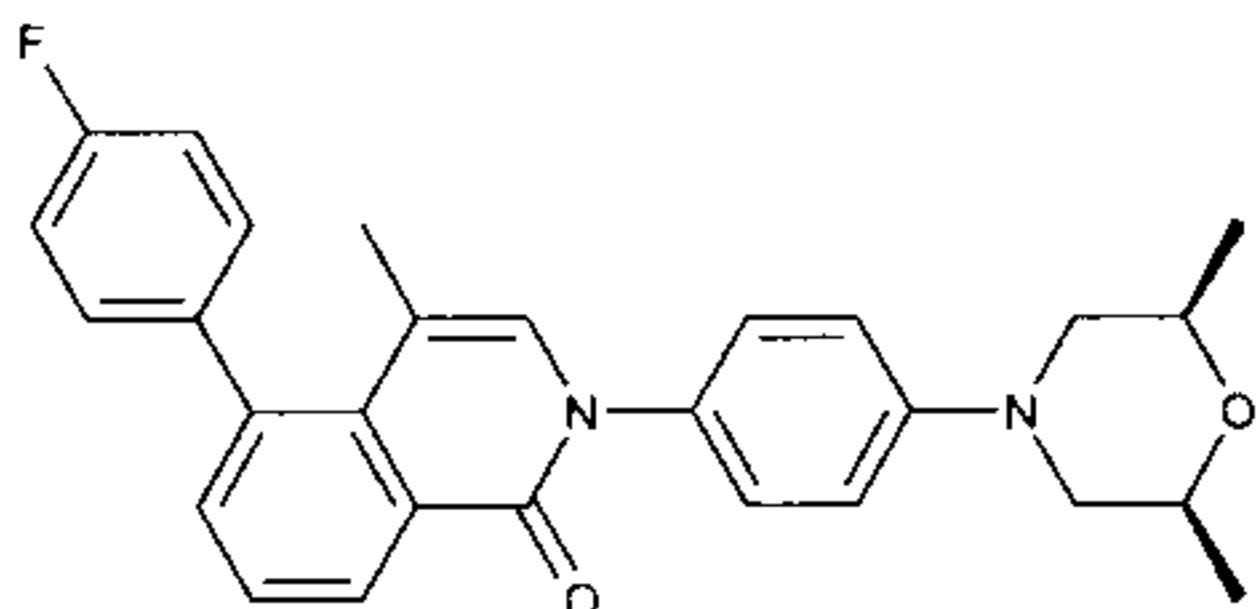
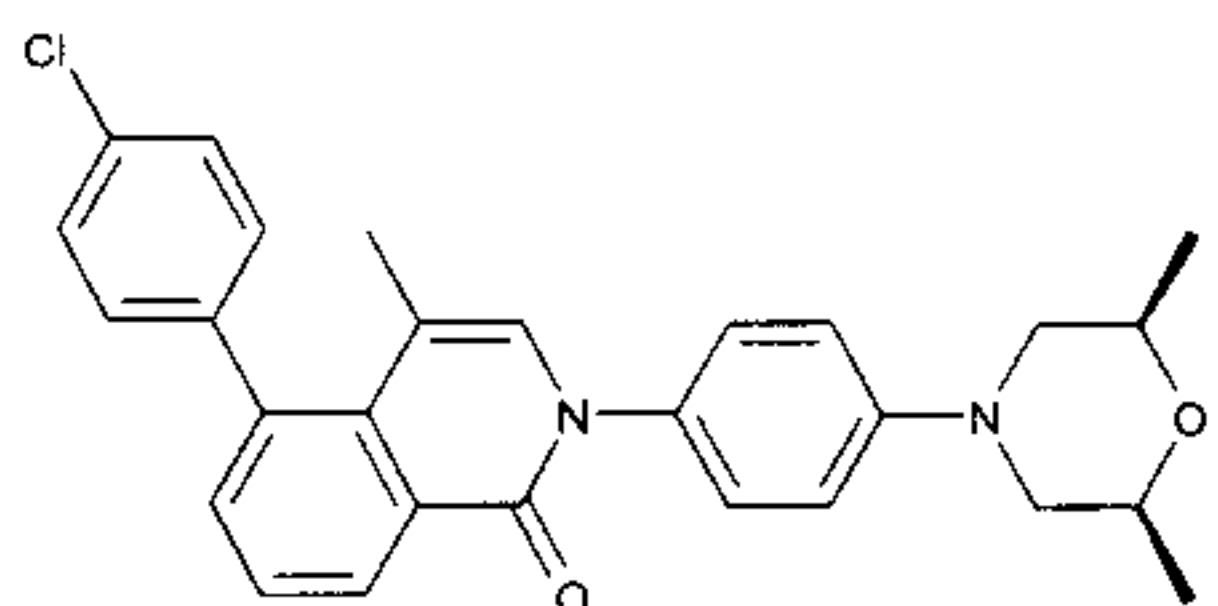
[249] Step 6: Compound 43-9 (508 mg, 2.0 mmol), Pd(dppf)Cl₂ (73 mg, 0.10 mmol) and potassium acetate (196 mg, 2.0 mmol) were added into a solution of compound 43-8 (496 mg, 1.0 mmol) in 1,4-dioxane. Under nitrogen gas atmosphere, the reaction mixture reacted at 110 °C overnight, and then the solvent was evaporated. The residue was purified by silica gel column chromatography to deliver compound 43-10 (270 mg, yield 60%). **MS (ESI)** m/z (M+H)⁺ 475.

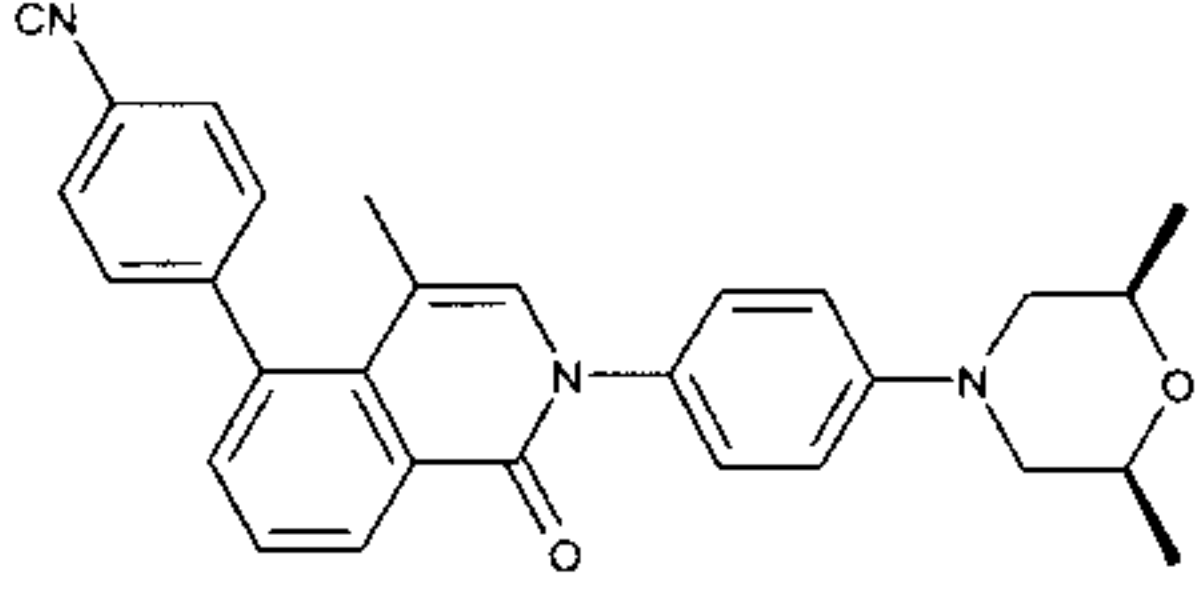
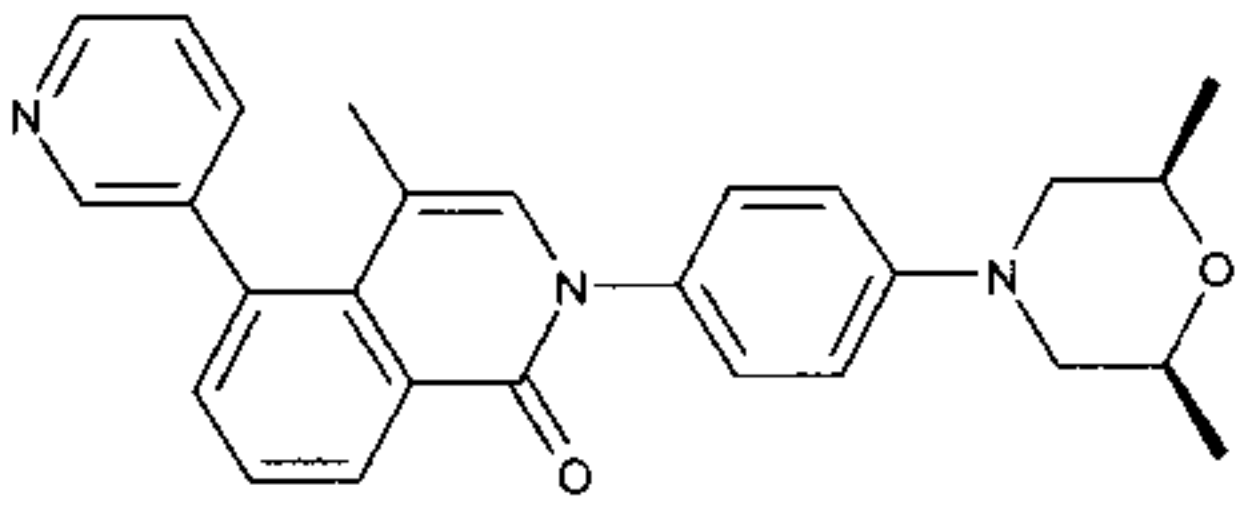
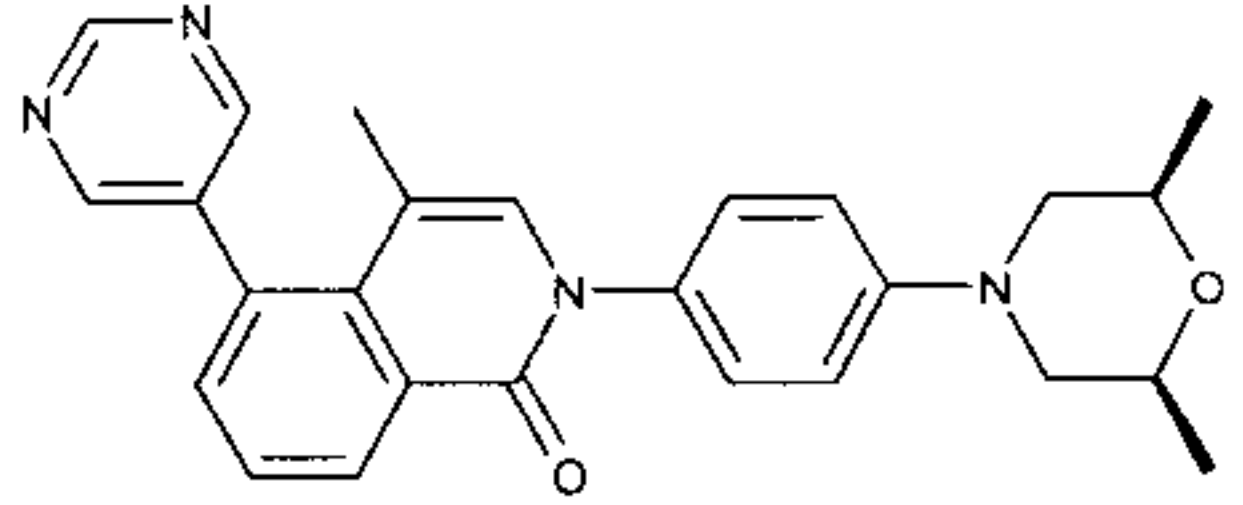
[250] Step 7: 3-furanboronic acid (24 mg, 1.5 eq), potassium phosphate (59 mg, 0.28 mmol) and Pd(dppf)Cl₂ (10 mg) were added into a solution of compound 43-10 (70 mg, 0.14 mmol) in DMF and H₂O (6 mL, 5:1), then the reaction mixture was refluxed overnight, H₂O was added into the reaction mixture, DCM was used to extract for 3 times, the organic phases were combined and washed with brines, dried over anhydrous sodium sulfate, filtrated and concentrated under reduced pressure, the residue was purified by preparative HPLC to deliver the title compound as light yellow solid. **¹H NMR** (400 MHz, Methanol-*d*₄) δ 8.57-8.59 (d, *J* =8.0 Hz, 1H) 7.55-7.60 (m, 4H) 7.33-7.35 (mz, 2H) 7.16-7.18 (d, *J* =8.4 Hz, 2H) 7.13 (s, 1H) 6.52 (s, 1H) 3.79-3.83 (d, *J* =14.4 Hz 2H) 3.60-3.63 (t, *J* =11.2 Hz, 2H) 2.50-2.56 (t, *J* =22.4 Hz ,2H) 1.97 (s, 3H) 1.24-1.25 (d, *J* =6.4 Hz ,6 H). **MS ESI** calcd for C₂₆H₂₆N₂O₃ [M+H]⁺ 416, found 416.

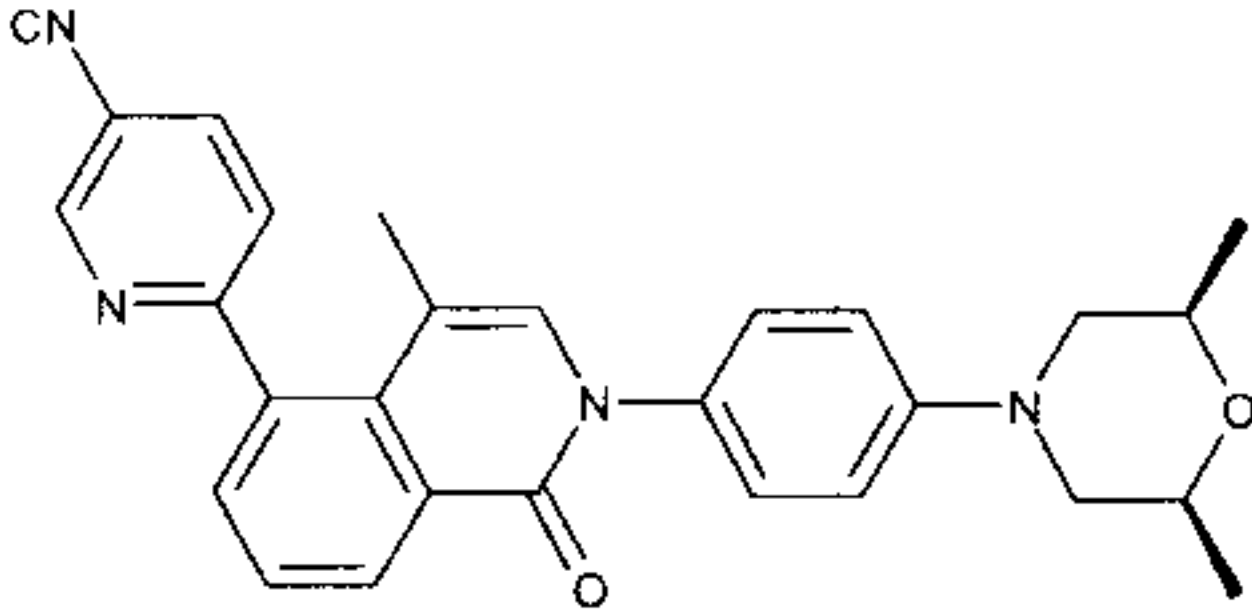
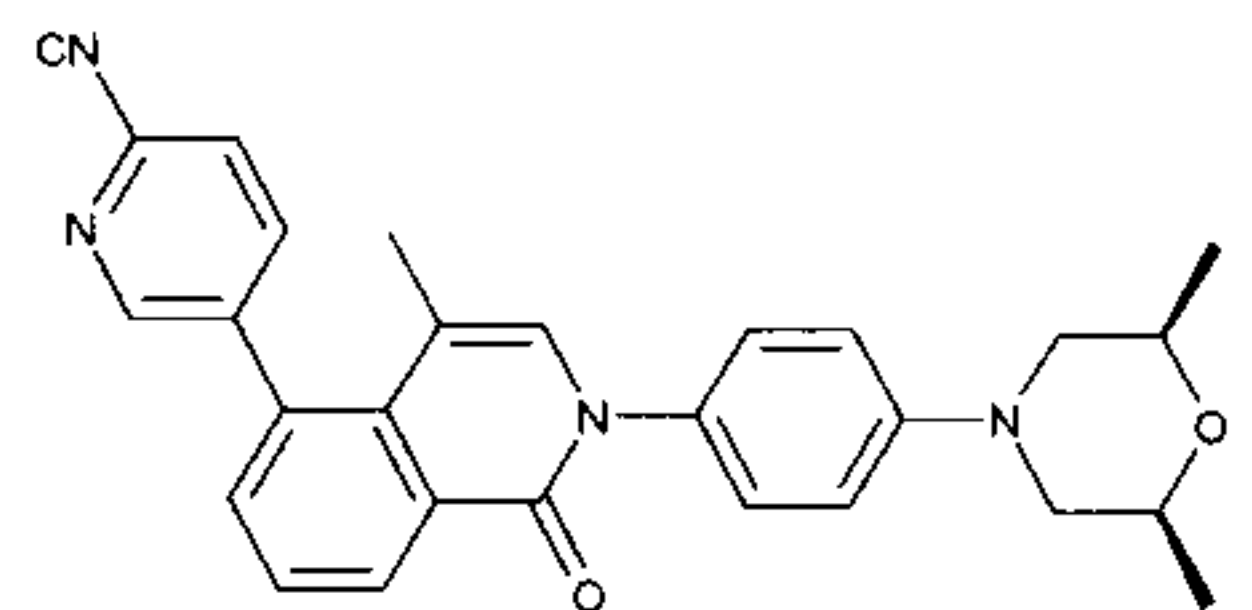
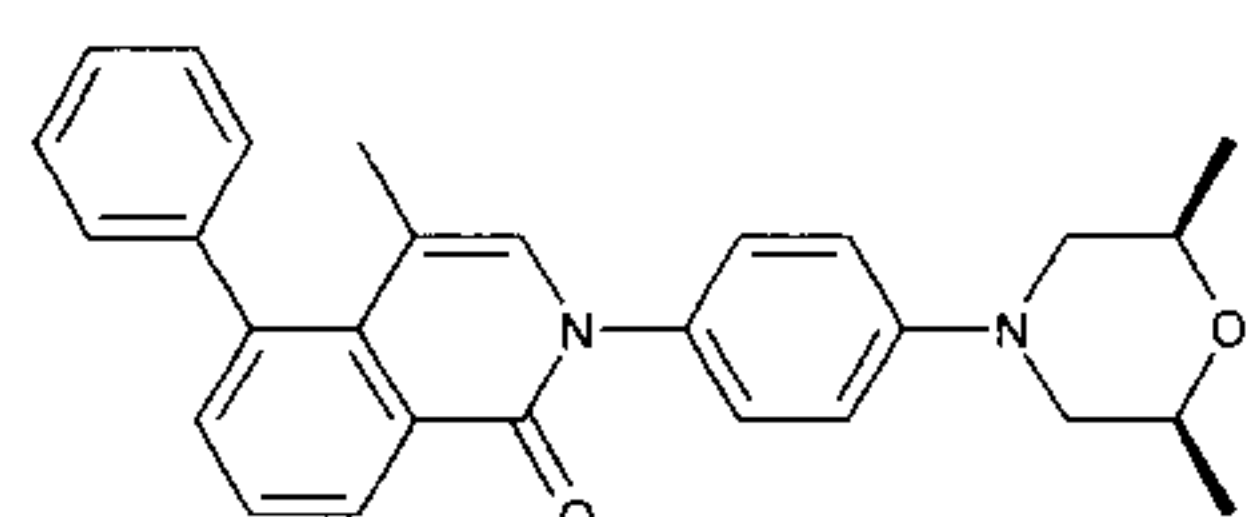
[251] The compounds listed in table 4 can be synthesized by compound 43-10 and corresponding boric acids.

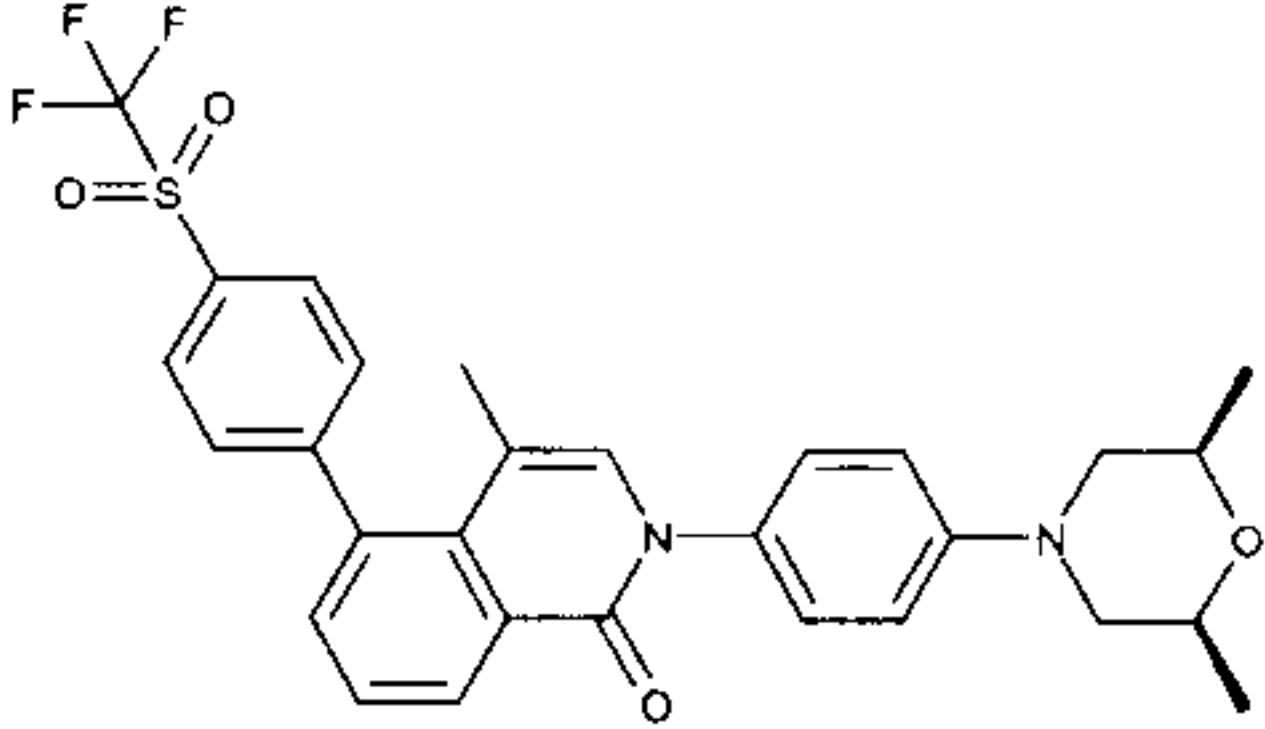
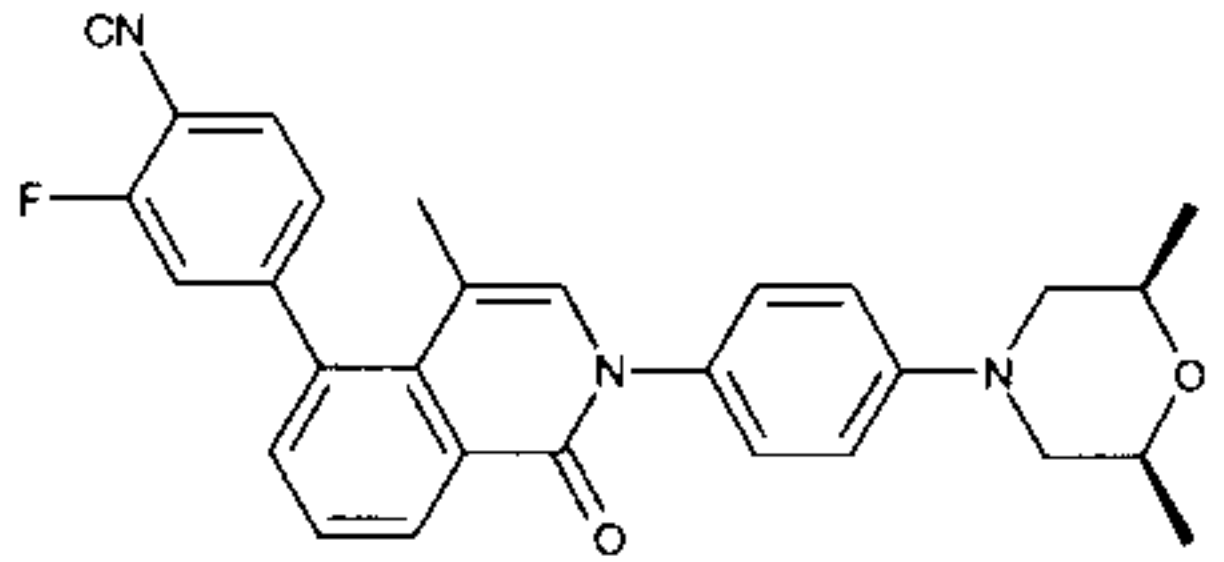
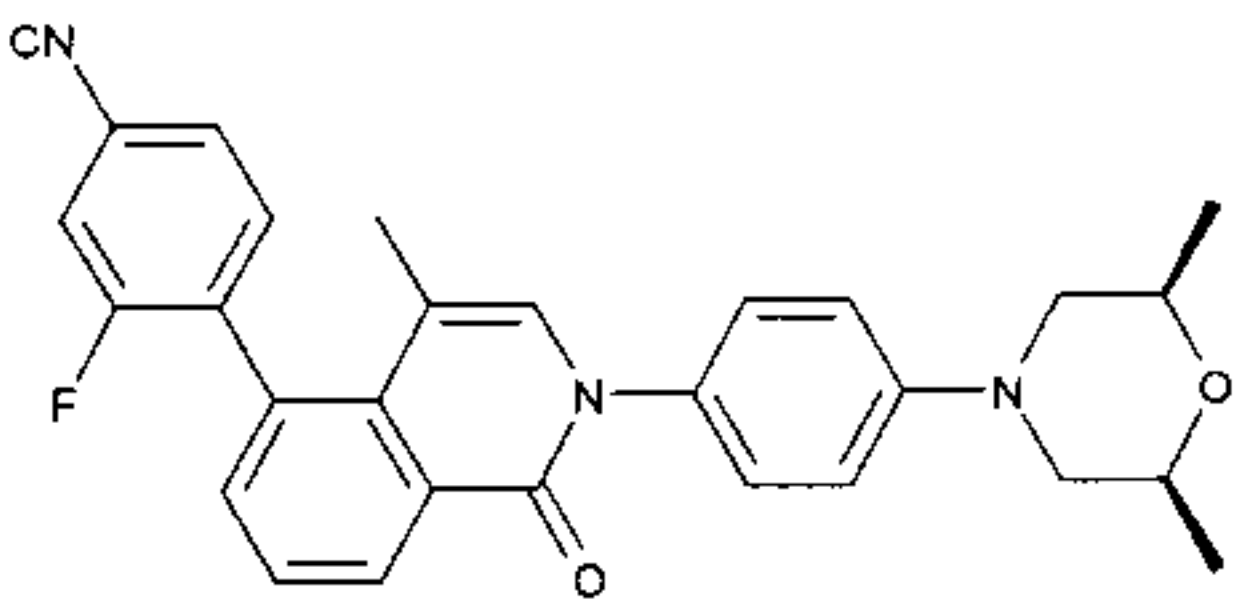
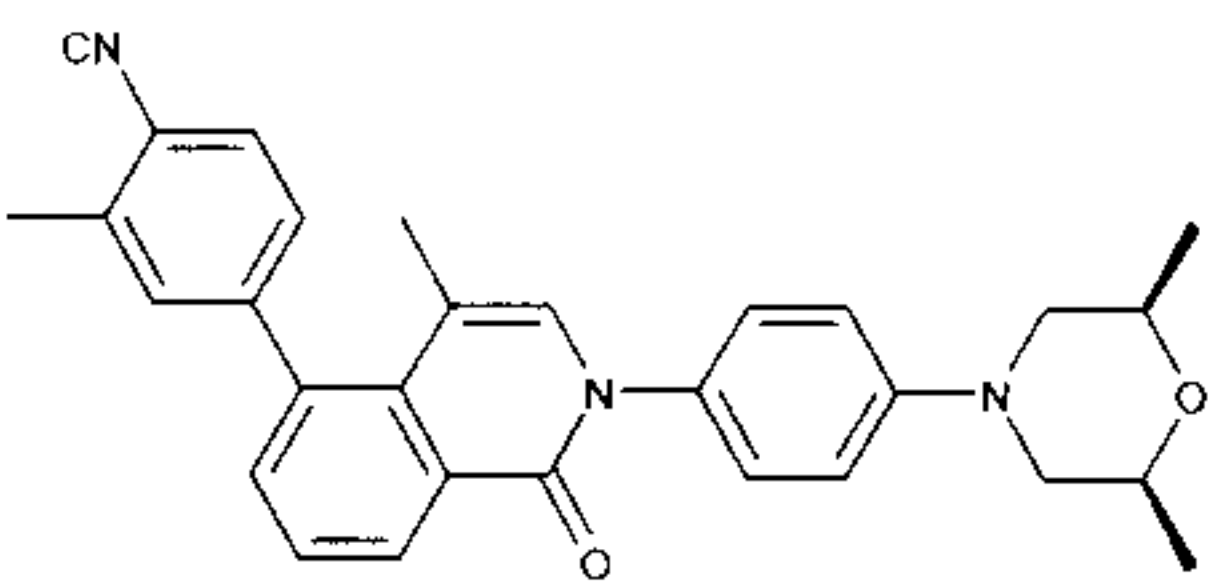
Embodiment	Structure	NMR
44		¹H NMR (400MHz, Methanol- <i>d</i> ₄) δ 8.57-8.59 (d, <i>J</i> =8.0 Hz, 1H) 7.72-7.76 (d d, <i>J</i> =8.0 Hz, 2H) 7.57-7.61 (t, <i>J</i> =16 Hz, 1H) 7.31-7.33 (t, <i>J</i> =9.2 Hz, 2H) 7.15-7.16 (d, <i>J</i> =3.6 Hz, 3H) 7.13 (s, 1H) 3.79-3.83 (d, <i>J</i> =14.4 Hz 2H) 3.59-3.62 (t, <i>J</i> =11.2 Hz, 2H) 2.43-2.49 (t, <i>J</i> =22.4 Hz,

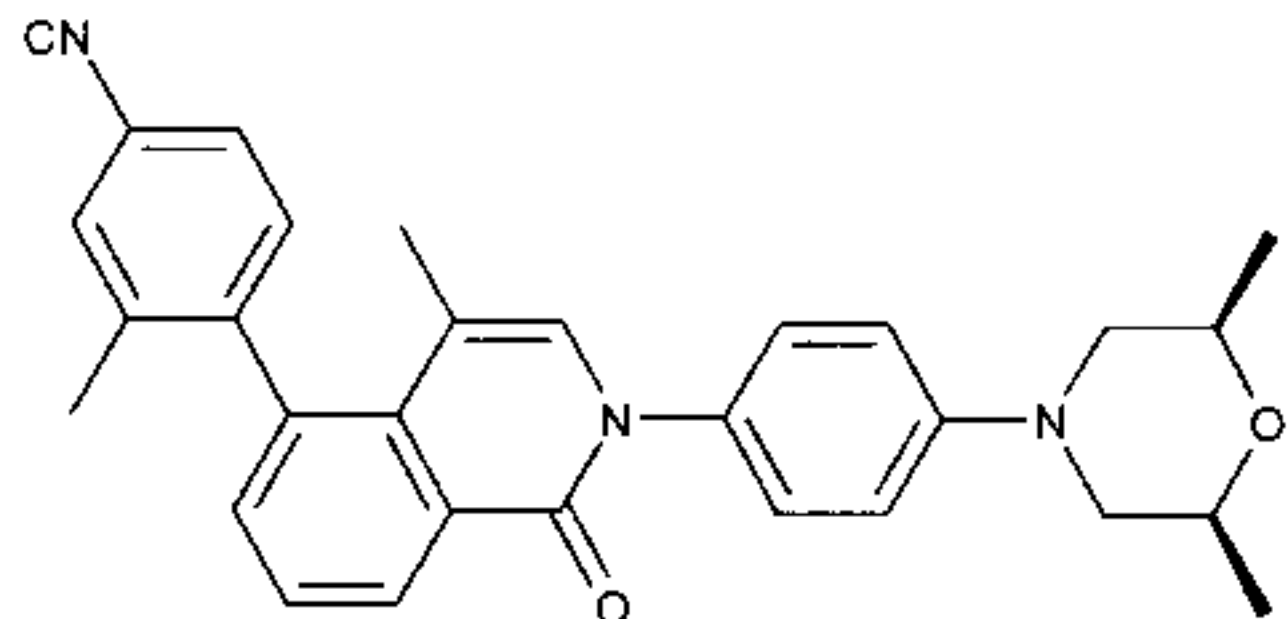
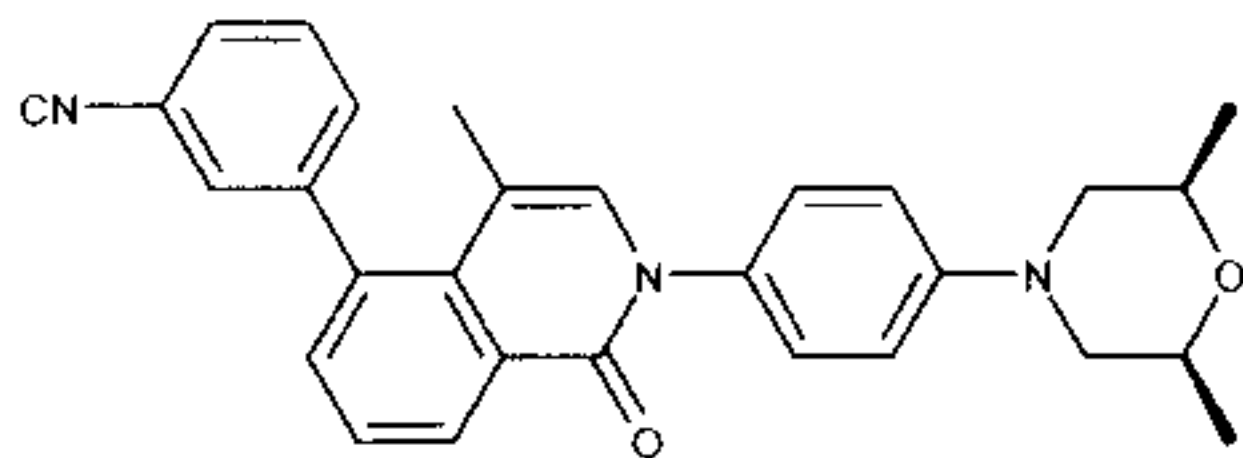
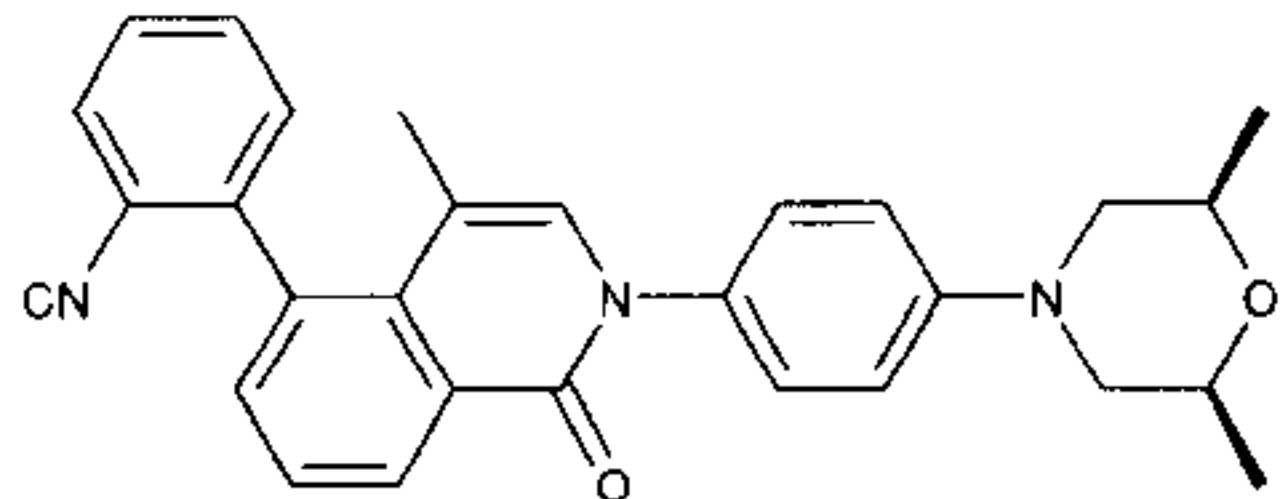
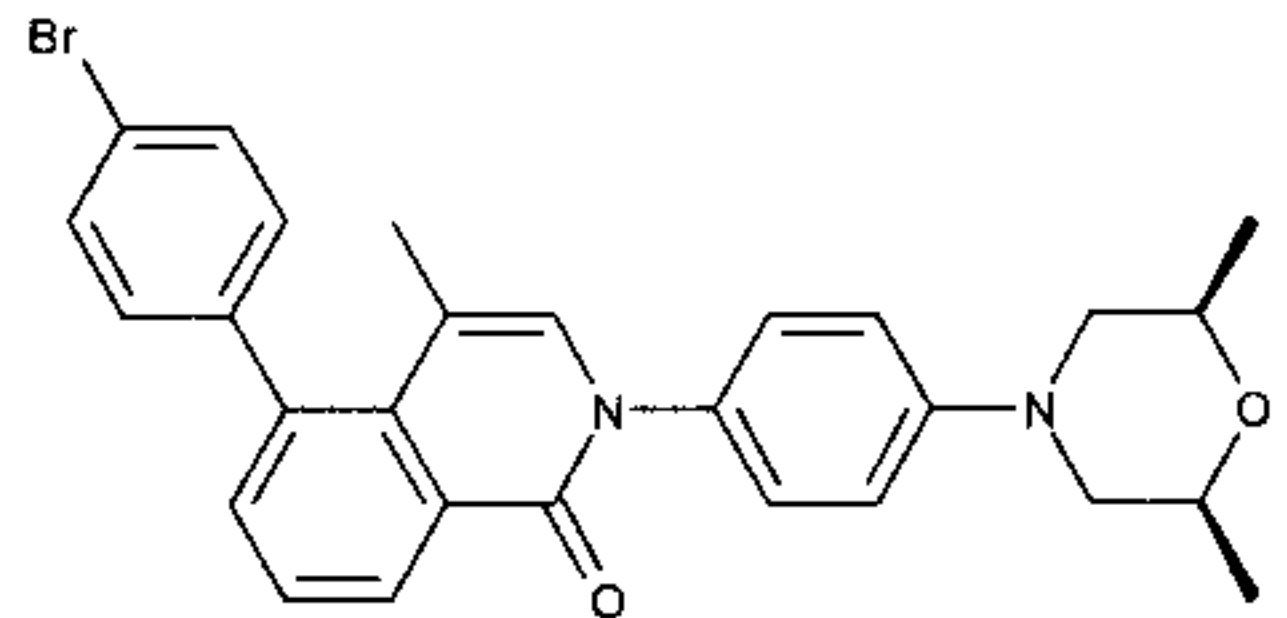
		2H) 1.85 (s, 3H) 1.22-1.24 (d, $J=6.4$ Hz ,6 H). MS ESI calcd for $C_{27}H_{25}N_3O_2S$ $[M+H]^+$ 456, found 456.
45		^1H NMR (400MHz, Methanol- d_4) δ 8.52-8.54 (d, $J=8.0$ Hz, 1H) 7.70-7.72 (d, $J=6.8$ Hz, 1H) 7.53-7.57 (t, $J=16$ Hz, 1H) 7.31-7.33 (t, $J=8.8$ Hz, 2H) 7.12-7.15 (d, $J=9.6$ Hz, 3H) 6.97-6.98 (d, $J=3.2$ Hz, 1H) 6.82-6.83 (d, $J=4.0$ Hz 1H) 3.79-3.83 (d, $J=12.0$ Hz 2H) 3.59-3.62 (t, $J=11.2$ Hz, 2H) 2.43-2.49 (t, $J=22.4$ Hz ,2H) 1.85 (s, 3H) 1.22-1.24 (d, $J=6.4$ Hz ,6 H). MS ESI calcd for $C_{26}H_{25}ClN_2O_2S$ $[M+H]^+$ 466, found 466.
46		^1H NMR (400MHz, DMSO- d_6) δ 8.41-8.43 (m, 1H), 7.80-7.82 (d, $J=7.2$ Hz, 2H) 7.58-7.63 (m, 4H), 7.30-7.32 (d, $J=7.2$ Hz, 2H), 7.21 (s, 1H) 7.05-7.07 (d, $J=8.8$ Hz, 2H) 3.66-3.69 (m, 1H), 2.28-2.34 (m, 4H), 1.54 (s, 3H), 1.18-1.19 (d, $J=5.6$ Hz ,6 H). MS ESI calcd for $C_{29}H_{27}F_3N_2O_2$ $[M+H]^+$ 493, found 493.
47		^1H NMR (400MHz, DMSO- d_6) δ 8.52-8.53 (m, 1H), 7.61-7.62 (d, $J=4.0$ Hz, 2H) 7.48-7.5 (m, 2H), 7.30-7.36 (m, 4H), 7.10-7.12 (m, 2H), 3.63-3.65 (m, 2H), 2.38-2.44 (m, 2H), 2.16-2.18 (m, 2H), 1.68 (s, 3H), 1.26-1.28 (d, $J=6.0$ Hz ,6 H). MS ESI calcd for $C_{29}H_{27}F_3N_2O_3$ $[M+H]^+$ 509, found 509.
48		^1H NMR (400MHz, DMSO- d_6) δ 8.57-8.59 (d, $J=6.8$ Hz, 1H), 7.56-7.57 (d, $J=6.0$ Hz, 1H),

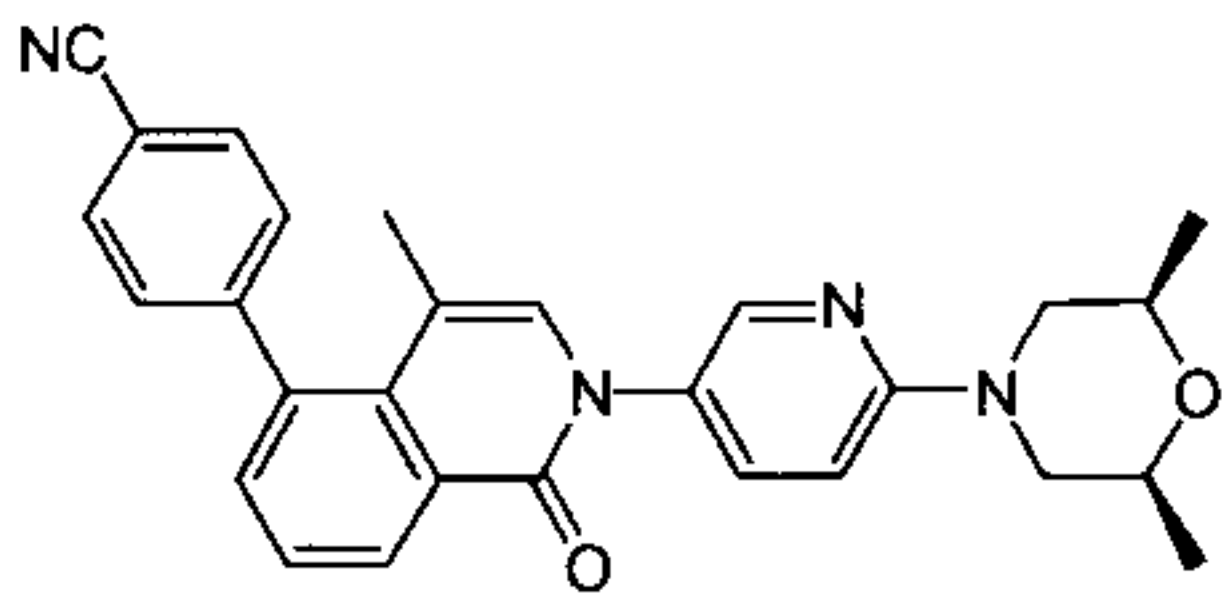
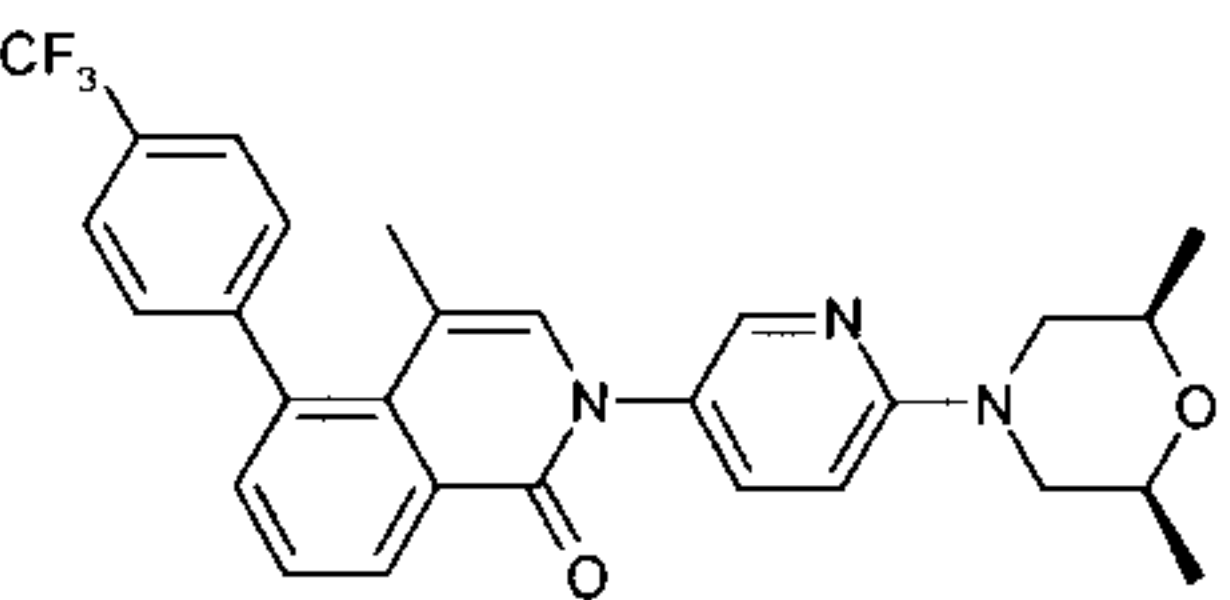
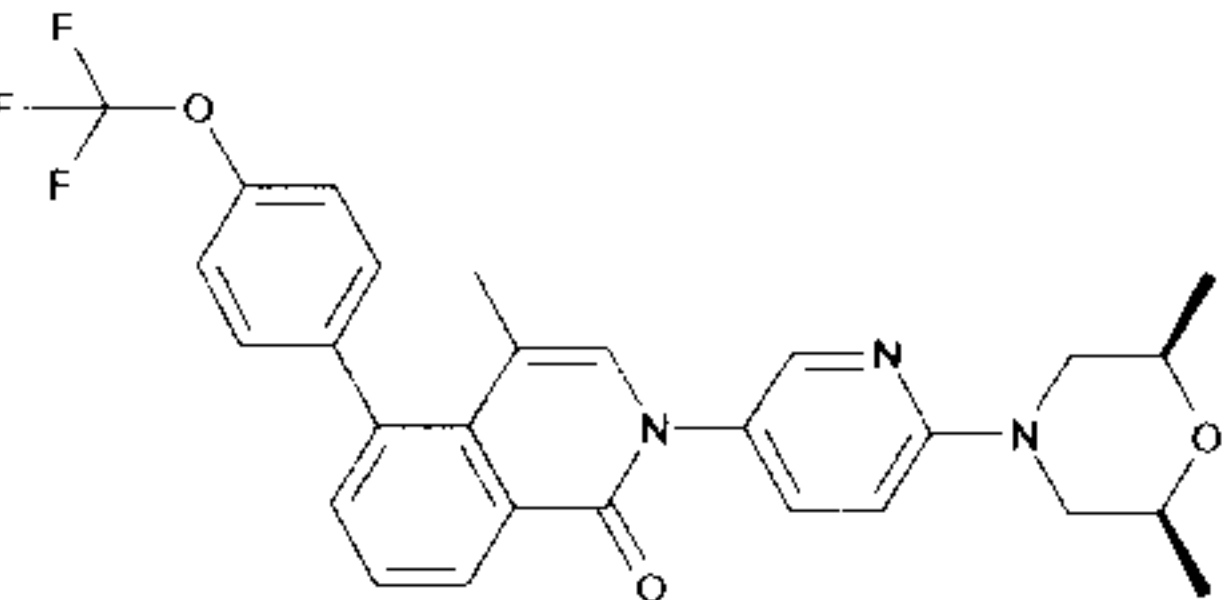
		7.45-7.46 (d, J =7.6 Hz, 1H), 7.24-7.26 (d, J =9.2 Hz, 2H), 6.86-6.92 (m, 3H), 6.64 (s, 1H), 6.07-6.16 (m, 2H), 3.73-3.75 (m, 2H), 3.41-3.44 (m, 2H), 3.21 (s, 3H), 2.38-2.43 (m, 2H), 1.54 (s, 3H), 1.18-1.20 (d, J =6.4 Hz ,6 H). MS ESI calcd for $C_{27}H_{29}N_3O_2$ $[M+H]^+$ 428, found 428.
49		^1H NMR (400MHz, DMSO- d_6) δ 8.64-8.65 (d, J =4.4 Hz, 2H), 8.46-8.48 (d, J =8.0 Hz, 1H), 7.60-7.64 (m, 2H), 7.53-7.55 (d, J =7.6 Hz, 2H), 7.44-7.45 (d, J =4.8 Hz, 2H), 7.31-7.33 (d, J =8.4 Hz, 2H), 7.23 (s, 1H), 7.06-7.08 (d, J =8.4 Hz, 1H), 3.66-3.75 (m, 4H), 2.29-2.35 (m, 2H), 1.61 (s, 3H), 1.18-1.20 (d, J =6.0 Hz ,6 H). MS ESI calcd for $C_{27}H_{27}N_3O_2$ $[M+H]^+$ 426, found 426.
50		^1H NMR (400MHz, DMSO- d_6) δ 8.37-8.39 (d, J =7.2 Hz, 1H), 7.49-7.53 (m, 2H), 7.34-7.35 (d, J =5.6 Hz, 2H), 7.20-7.27 (m, 4H), 7.13 (s, 1H), 7.00-7.02(d, J =7.6 Hz, 2H), 3.61-3.69 (m, 4H), 2.23-2.29 (m, 2H), 1.51 (s, 3H), 1.13-1.14 (d, J =6.0 Hz ,6 H). MS ESI calcd for $C_{28}H_{27}FN_2O_2$ $[M+H]^+$ 443, found 443.
51		^1H NMR (400MHz, DMSO- d_6) δ 8.39-8.41 (d, J =7.2 Hz, 1H), 7.49-7.55 (m, 3H), 7.35-7.37 (d, J =7.6 Hz, 2H), 7.27-7.29 (d, J =8.0 Hz, 2H), 7.16 (s, 1H), 7.02-7.04 (d, J =8.0 Hz, 2H), 3.62-3.69 (m, 4H), 2.25-2.30 (m, 2H), 1.55 (s, 3H), 1.15-1.16 (d, J =6.4 Hz ,6 H). MS ESI

		calcd for C ₂₈ H ₂₇ ClN ₂ O ₂ [M+H] ⁺ 460, found 460.
52		¹ H NMR (400MHz, DMSO- <i>d</i> ₆) δ 8.42-8.44 (d, <i>J</i> =7.6 Hz, 1H), 7.88-7.90 (d, <i>J</i> =8.0 Hz, 2H), 7.50-7.58 (m, 3H), 7.27-7.29 (d, <i>J</i> =8.4 Hz, 2H), 7.27-7.29 (d, <i>J</i> =8.0 Hz, 2H), 7.19 (s, 1H), 7.02-7.04 (d, <i>J</i> =8.0 Hz, 2H), 3.63-3.69 (m, 4H), 2.25-2.30 (m, 2H), 1.51 (s, 3H), 1.15-1.16 (d, <i>J</i> =6.0 Hz, 6 H). MS ESI calcd for C ₂₉ H ₂₇ N ₃ O ₂ [M+H] ⁺ 450, found 450.
53		¹ H NMR (400MHz, Methanol- <i>d</i> ₄) δ 8.88 (s, 1H) 8.84-8.85 (d, <i>J</i> =4.4 Hz, 1H) 8.59-8.62 (t, <i>J</i> =9.6 Hz, 1H) 8.44-8.46 (d, <i>J</i> =8.0 Hz, 1H) 7.97-8.00 (d d, <i>J</i> =6.0 Hz, 1H) 7.64-7.66 (d, <i>J</i> =4.8 Hz, 2H) 7.28-7.30 (d, <i>J</i> =8.4 Hz 2H) 7.17 (s, 1H) 7.08-7.10 (d, <i>J</i> =8.8 Hz 1H) 3.77-3.80 (d d, <i>J</i> =4.4 Hz 2H) 3.58-3.62 (t, <i>J</i> =11.6 Hz, 2H) 2.36-2.41 (t, <i>J</i> =22.4 Hz, 2H) 1.63 (s, 3H) 1.21-1.23 (d, <i>J</i> =5.6 Hz, 6 H). MS ESI calcd for C ₂₇ H ₂₇ N ₃ O ₂ [M+H] ⁺ 426, found 426.
54		¹ H NMR (400MHz, Methanol- <i>d</i> ₄) δ 9.21 (s, 1H) 8.42.-8.49 (m, 2H) 7.82-7.84 (t, <i>J</i> =8.0 Hz, 1H) 7.63-7.64 (d d, <i>J</i> =4.4 Hz, 2H) 7.30-7.32 (d, <i>J</i> =8.8 Hz, 2H) 7.24 (s, 1H) 7.05-7.07 (d, <i>J</i> =8.8 Hz, 2H) 3.81-3.85 (t, <i>J</i> =14.4 Hz 2H) 3.60-3.62 (d, <i>J</i> =11.6 Hz, 2H) 2.49-2.55 (t, <i>J</i> =22.8 Hz, 2H) 1.64 (s, 3H) 1.23-1.24 (d, <i>J</i> =6.0 Hz, 6 H). MS ESI calcd for C ₂₆ H ₂₆ N ₄ O ₂ [M+H] ⁺ 427, found 427.

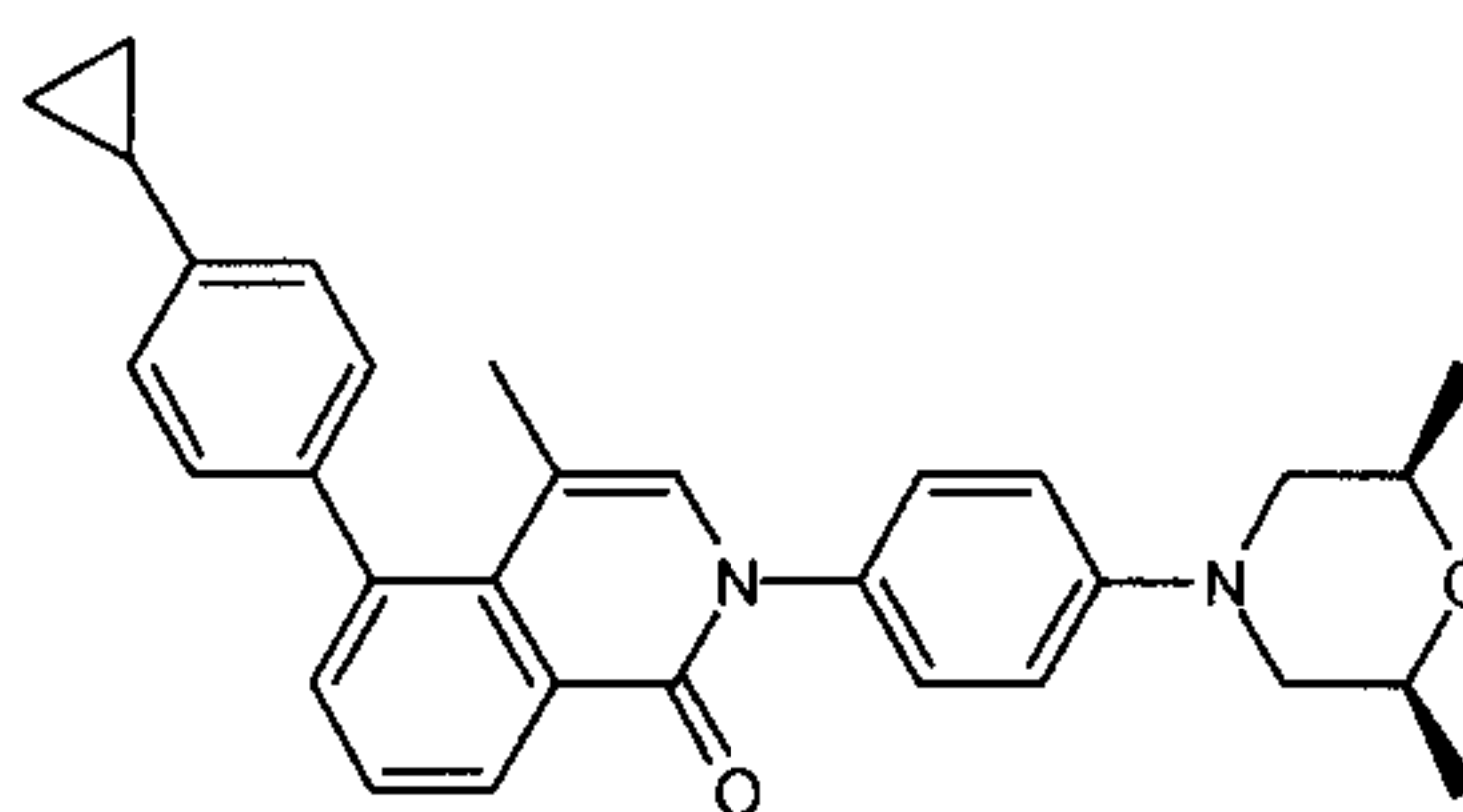
55		¹H NMR (400MHz, Methanol-<i>d</i>₄) δ 9.11 (s, 1H) 8.83 (s, 2H) 8.57-8.59 (t, <i>J</i> =6.8 Hz, 1H) 7.64-7.65 (t, <i>J</i> =6.4 Hz, 2H) 7.34-7.36 (d d, <i>J</i> =8.8 Hz, 2H) 7.16-7.20 (t, <i>J</i> =10.8 Hz, 3H) 3.81-3.85 (t, <i>J</i> =14.4 Hz 2H) 3.60-3.62 (d, <i>J</i> =11.6 Hz, 2H) 2.27-2.32 (t, <i>J</i> =22.0 Hz ,2H) 1.47 (s, 3H) 1.16-1.18 (d, <i>J</i> =6.0 Hz ,6 H). MS ESI calcd for C₂₈H₂₆N₄O₂ [M+H]⁺ 452, found 452.
56		¹H NMR (400MHz, Methanol-<i>d</i>₄) δ 8.72 (s, 1H) 8.56-8.58 (d, <i>J</i> =7.2 Hz, 1H) 7.94-8.02 (m, 2H) 7.59-7.63 (t, <i>J</i> =16.4 Hz, 2H) 7.31-7.33 (t, <i>J</i> =8.8 Hz, 2H) 7.12-7.15 (t, <i>J</i> =12 Hz, 3H) 3.80-3.84 (t, <i>J</i> =16.0 Hz 2H) 3.59-3.62 (d, <i>J</i> =11.6 Hz, 2H) 2.41-2.47 (t, <i>J</i> =22.8 Hz ,2H) 1.61 (s, 3H) 1.22-1.23 (d, <i>J</i> =6.4 Hz ,6 H). MS ESI calcd for C₂₈H₂₆N₄O₂ [M+H]⁺ 452, found 452.
57		¹H NMR (400MHz, Methanol-<i>d</i>₄) δ 8.48-8.50 (d d, <i>J</i> =3.6 Hz, 1H) 7.56-8.57 (d, <i>J</i> =4.0 Hz 2H) 7.38-7.40 (m, 5H) 7.31-7.33 (t, <i>J</i> =6.4 Hz, 2H) 7.23-7.25 (t, <i>J</i> =9.2 Hz, 2H) 7.05 (s, 1H) 3.84-3.87 (t, <i>J</i> =14.4 Hz 2H) 3.61-3.64 (d, <i>J</i> =11.6 Hz, 2H) 2.57-2.62 (t, <i>J</i> =22.4 Hz ,2H) 1.62 (s, 3H) 1.24-1.25 (d, <i>J</i> =6.4 Hz ,6 H). MS ESI calcd for C₂₈H₂₈N₂O₂ [M+H]⁺ 426, found 426.

58		¹H NMR (400MHz, Methanol- <i>d</i> ₄) δ 8.56 (s, 1H) 8.14 (s, 2H) 7.78-7.80 (d, <i>J</i> =5.6 Hz 2H) 7.61(s, 2H)7.32 (m, 2H) 7.13 (m, 3H) 3.84 (m, 2H) 3.61-3.64 (d, <i>J</i> =11.2 Hz, 2H) 2.44-2.49 (t, <i>J</i> =20.4 Hz ,2H) 1.60 (s, 3H) 1.23-1.24 (d, <i>J</i> =6.4 Hz ,6 H). MS ESI calcd for C ₂₉ H ₂₉ F ₃ N ₂ O ₄ S [M+H] ⁺ 559, found 559.
59		¹H NMR (400MHz, CDCl ₃) δ 8.67-8.69 (d, <i>J</i> =8.0 Hz 1H) 7.68-7.70 (m, 1H) 7.59-7.61 (m, 1H) 7.47-7.51 (m, 3H) 7.40-7.42 (d, <i>J</i> =8.4 Hz 2H) 7.25-7.27 (t, <i>J</i> =9.2 Hz 2H) 6.97(s, 1H) 3.61-3.64 (d, <i>J</i> =10.4 Hz, 2H) 2.75-2.80 (t, <i>J</i> =22.4 Hz ,2H) 1.68 (s, 3H) 1.30-1.31 (d, <i>J</i> =6.4 Hz ,6 H). MS ESI calcd for C ₂₉ H ₂₆ FN ₃ O ₂ [M+H] ⁺ 469, found 469.
60		¹H NMR (400MHz, CDCl ₃) δ 8.69-8.71 (d, <i>J</i> =7.6 Hz 1H) 7.54-7.58 (t, <i>J</i> =13.2 Hz 2H) 7.44-7.49 (d d, <i>J</i> =8.0 Hz 3H) 7.30-7.32 (d, <i>J</i> =8.8 Hz 3H) 6.95-6.99 (t, <i>J</i> =16.4 Hz 3H) 3.80-3.83 (d, <i>J</i> =14.0 Hz, 2H) 3.48-3.51 (d, <i>J</i> =11.6 Hz, 2H) 2.44-2.49 (t, <i>J</i> =22.0 Hz ,2H) 1.66 (s, 3H) 1.27-1.28 (d, <i>J</i> =6.4 Hz ,6 H). MS ESI calcd for C ₂₉ H ₂₆ FN ₃ O ₂ [M+H] ⁺ 469, found 469.
61		¹H NMR (400MHz, CDCl ₃) δ 8.65-8.67 (d, <i>J</i> =7.2 Hz 1H) 7.66-7.67 (d, <i>J</i> =3.6 Hz 1H) 7.56-7.57 (d, <i>J</i> =3.2 Hz 1H)7.49-7.51 (d, <i>J</i> =7.2 Hz 1H) 7.44-7.46 (d, <i>J</i> =7.6 Hz 2H) 7.33 (s, 1H) 6.94 (s, 1H) 3.99-4.01 (t, <i>J</i> =8.0 Hz, 2H)

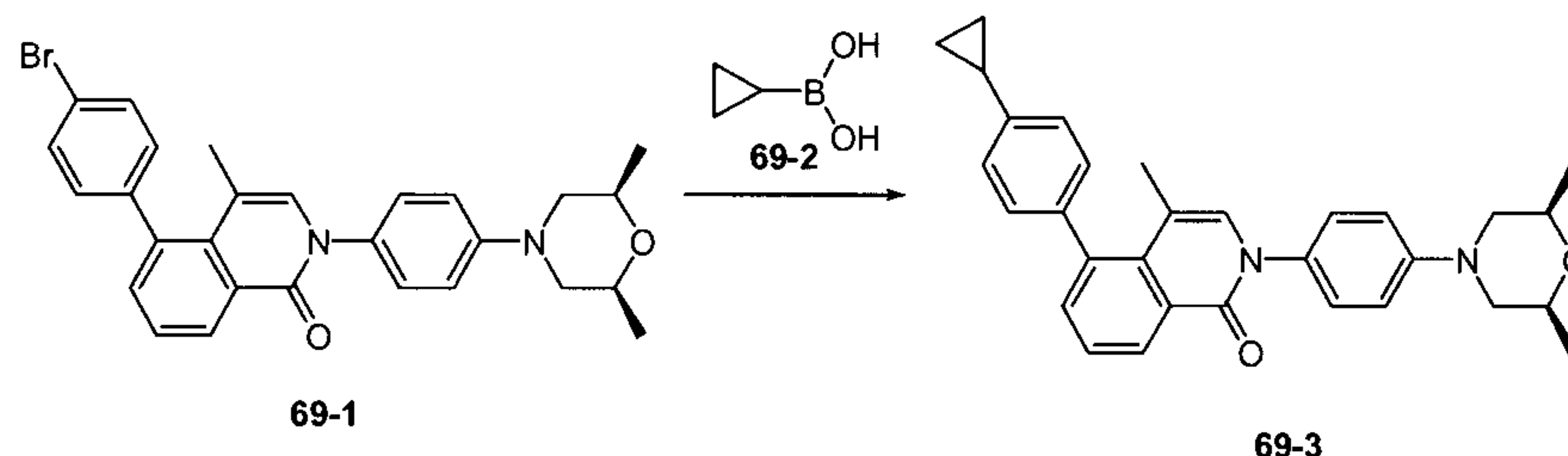
		3.57-3.60 (d, J =11.6 Hz, 2H) 2.67-2.72 (t, J =22.4 Hz ,2H) 1.64 (s, 3H) 1.30-1.31 (d, J =6.0 Hz ,6 H). MS ESI calcd for $C_{30}H_{29}N_3O_2$ $[M+H]^+$ 465, found 465.
62		^1H NMR (400MHz, $CDCl_3$) δ 8.66-8.68 (d, J =8.0 Hz 1H) 7.66-7.67 (m, 5H) 7.38-7.47 (m, 3H) 7.27 (s, 1H) 6.93 (s, 1H) 4.08-4.10 (t, J =8.0 Hz, 2H) 3.63-3.65 (d, J =11.6 Hz, 2H) 2.79-2.85 (t, J =22.0 Hz ,2H) 2.10 (s, 3H) 1.57 (s, 3H) 1.31-1.32 (d, J =6.0 Hz ,6 H). MS ESI calcd for $C_{30}H_{29}N_3O_2$ $[M+H]^+$ 465, found 465.
63		^1H NMR (400MHz, $CDCl_3$) δ 8.67-8.68 (d, J =7.2 Hz 1H) 7.50-7.71 (m, 6H) 7.38-7.40 (d, J =8.4 Hz 2H) 7.15-7.17 (d, J =8.8 Hz 2H) 6.94 (s, 1H) 3.91-3.95 (t, J =15.2 Hz, 2H) 3.53-3.55 (d, J =11.6 Hz, 2H) 2.57-2.62 (t, J =22.8 Hz ,2H) 1.60 (s, 3H) 1.28-1.30 (d, J =6.0 Hz ,6 H). MS ESI calcd for $C_{29}H_{27}N_3O_2$ $[M+H]^+$ 451, found 451.
64		^1H NMR (400MHz, $CDCl_3$) δ 8.70-8.72 (d, J =7.6 Hz 1H) 7.55-7.76 (m, 5H) 7.47-7.49 (t, J =8.8 Hz 3H) 7.32-7.34 (d, J =9.2 Hz 2H) 6.94 (s, 1H) 4.01-4.04 (t, J =14.8 Hz, 2H) 3.57-3.60 (d, J =11.6 Hz, 2H) 2.69-2.75 (m, 2H) 1.60 (s, 3H) 1.29-1.31 (d, J =6.0 Hz ,6 H). MS ESI calcd for $C_{29}H_{27}N_3O_2$ $[M+H]^+$ 451, found 451.
65		^1H NMR (400MHz, $CDCl_3$) δ 8.63-8.65 (d, J =6.0 Hz 1H) 7.52-7.57 (m, 4H) 7.41-7.43 (d, J =8.4 Hz 2H) 7.22-7.24 (d, J =8.4 Hz 4H) 6.92 (s,

		1H) 3.96-3.99 (t, J =14.4 Hz, 2H) 3.55-3.57 (d, J =11.2 Hz, 2H) 2.62-2.67 (t, J =22.4 Hz, 2H) 1.66 (s, 3H) 1.29-1.31 (d, J =6.4 Hz, 6H). MS ESI calcd for $C_{28}H_{27}BrN_2O_2$ $[M+H]^+$ 504, found 504.
66		^1H NMR (400 MHz, Methanol- d_4) δ 8.44 (d, J = 8.0 Hz, 1H), 8.08 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.61-7.41 (m, 5H), 7.03 (s, 1H), 6.85 (d, J = 8.8 Hz, 1H), 4.10 (d, J = 12.0 Hz, 2H), 3.71-3.15 (m, 2H), 2.44 (t, J = 12.0 Hz, 2H), 1.55 (s, 3H), 1.25-1.08 (m, 6H). MS ESI calcd for $C_{28}H_{26}N_4O_2$ $[M+H]^+$ 451, found 451.
67		^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 7.6 Hz, 1H), 8.28 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.75-7.41 (m, 6H), 6.93 (d, J = 9.2 Hz, 1H), 6.87 (s, 1H), 4.07 (d, J = 12.4 Hz, 2H), 3.80-3.61 (m, 2H), 2.84 (t, J = 12.0 Hz, 2H), 1.59 (s, 3H), 1.35-1.20 (m, 6H). MS ESI calcd for $C_{28}H_{26}F_3N_3O_2$ $[M+H]^+$ 494, found 494.
68		^1H NMR (400 MHz, Methanol- d_4) δ 8.53 (t, J = 4.8 Hz, 1H), 8.20 (s, 1H), 7.90 (d, J = 7.2 Hz, 1H), 7.61 (d, J = 4.0 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 9.6 Hz, 1H), 7.12 (s, 1H), 6.87 (s, 1H), 4.14 (d, J = 12.4 Hz, 2H), 3.81-3.71 (m, 2H), 2.73 (t, J = 12.0 Hz, 2H), 1.67 (s, 3H), 1.27 (d, J = 6.4 Hz, 6H). MS ESI calcd for $C_{28}H_{26}F_3N_3O_3$ $[M+H]^+$ 510, found 510.

Embodiment 69

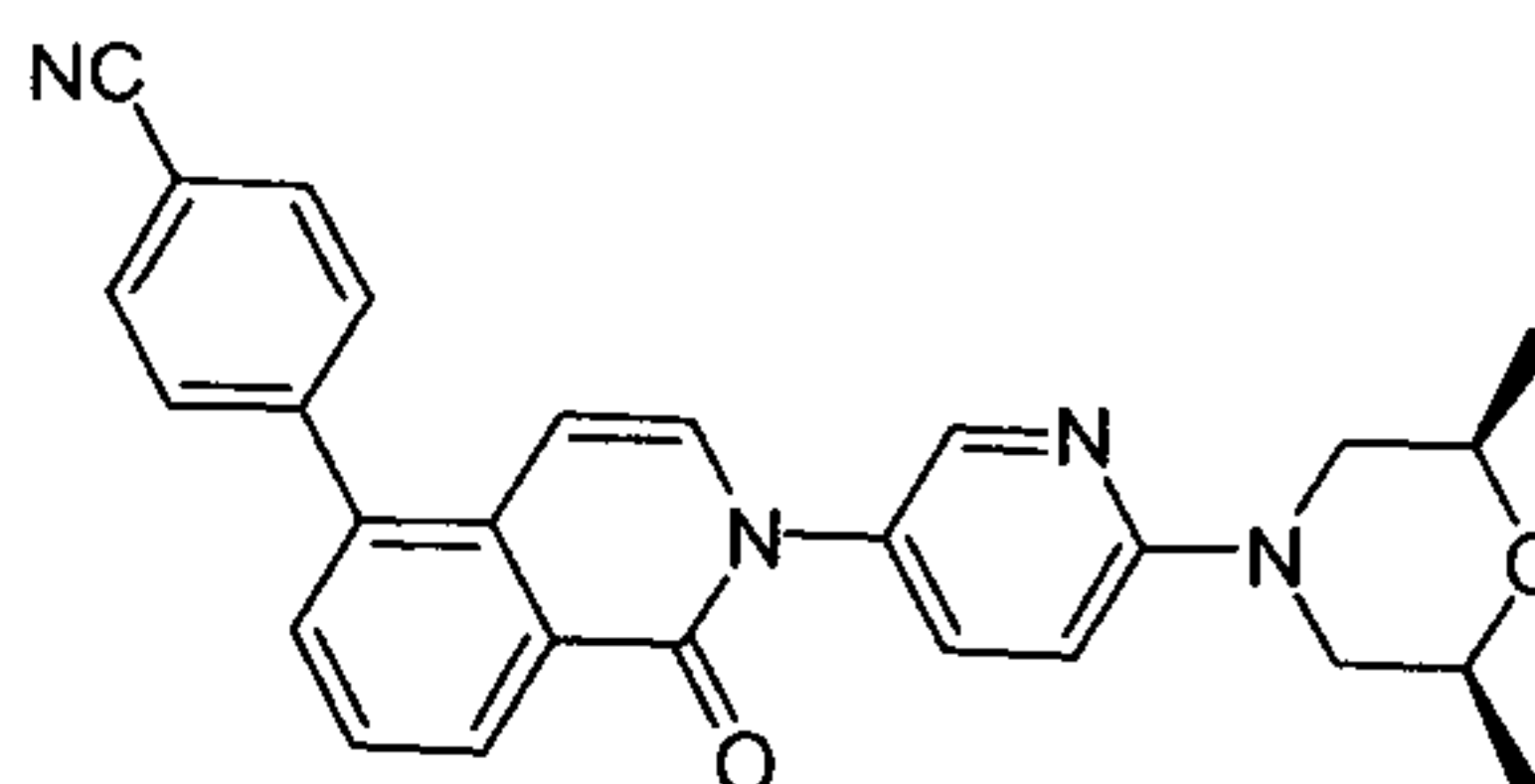


5-(4-cyclopropylphenyl)-2-(4-((2R,6S)-2,6-dimethylmorpholino)phenyl)-4-methylisoquinolin-1(2H)-one



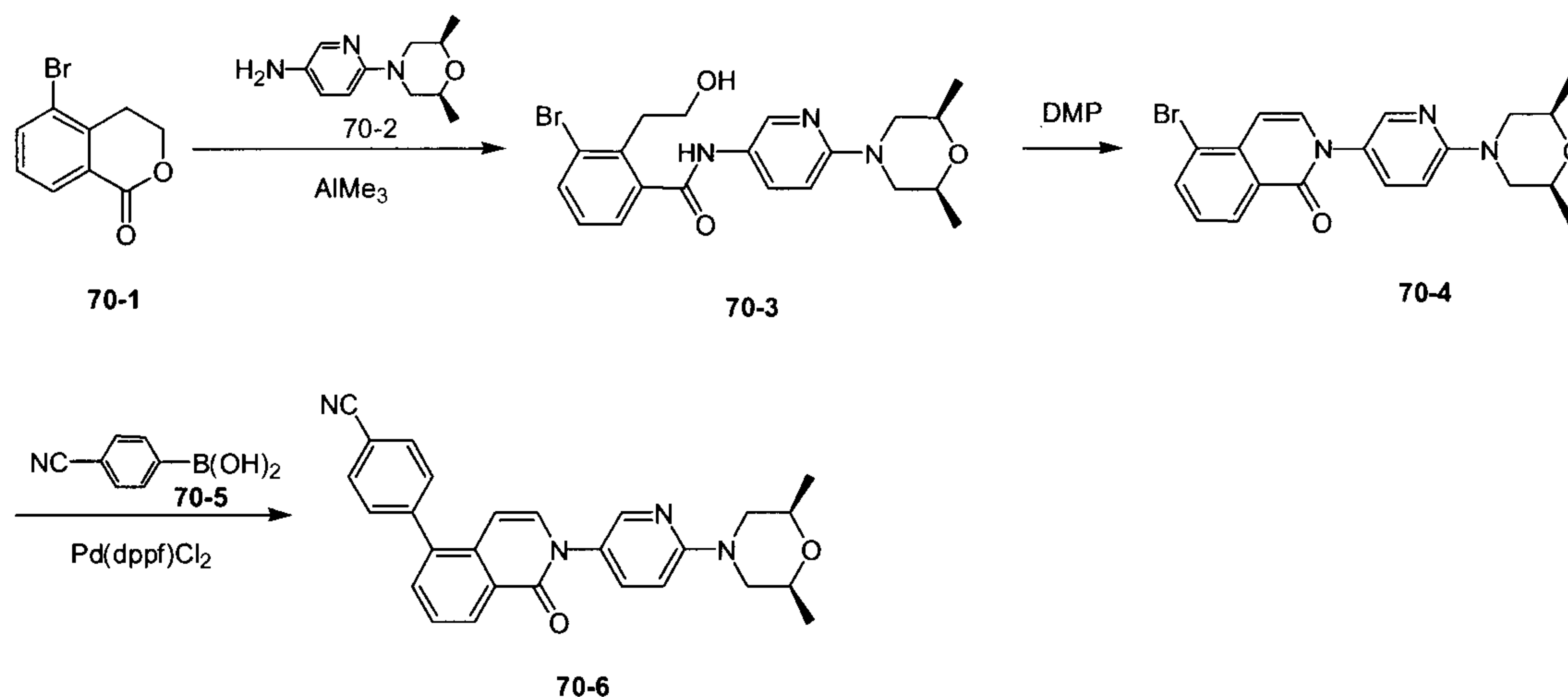
[252] Compound 69-1 (106 mg, 0.20 mmol), compound 69-2 (52 mg, 0.60 mmol), *n*-BuPAd₂ (6.5 mg, 0.02 mmol), palladium acetate (2.7 mg, 0.01 mmol) and cesium carbonate (197 mg, 0.6 mmol) were added into toluene/H₂O (5:1, 3 mL), and then under nitrogen gas atmosphere, the reaction mixture was stirred at 110°C for 2h. The reaction mixture was poured into H₂O, extracted with EtOAc (10 mL), the extraction liquid was washed with brines, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by preparative HPLC to deliver the title compound (20 mg, yield 15%) as yellow solid. ¹H NMR (400MHz, CDCl₃) δ 8.60-8.62 (t, *J* =9.6 Hz, 1H) 7.55-7.56 (d, *J* =3.6 Hz, 2H) 7.46-7.48 (d, *J* =8.4 Hz, 2H), 7.27-7.32 (m, 2H) 7.20-7.22 (d, *J* =8.0 Hz, 2H), 7.09-7.11 (d, *J* =8.0 Hz, 2H), 6.89 (s, 1H), 4.00-4.04 (t, *J* =14.4 Hz 2H) 3.57-3.60 (t, *J* =11.2 Hz, 2H) 2.68-2.73 (t, *J* =22.4 Hz, 2H), 1.96-1.98 (m, 1H), 1.66 (s, 3H), 1.30-1.31 (d, *J* =6.0 Hz, 6 H), 1.03-1.05 (m, 2H), 0.77-0.79 (m, 2H). MS ESI calcd for C₃₁H₃₂N₂O₂ [M+H]⁺ 465, found 465.

Embodiment 70



4-(2-(6-(2,6-dimethylmorpholino-4-yl)pyridin-3-yl)-1-oxo-1,2-dihydroisoquinolin-5-yl)benzonitrile

Our Ref.: P1650132CA

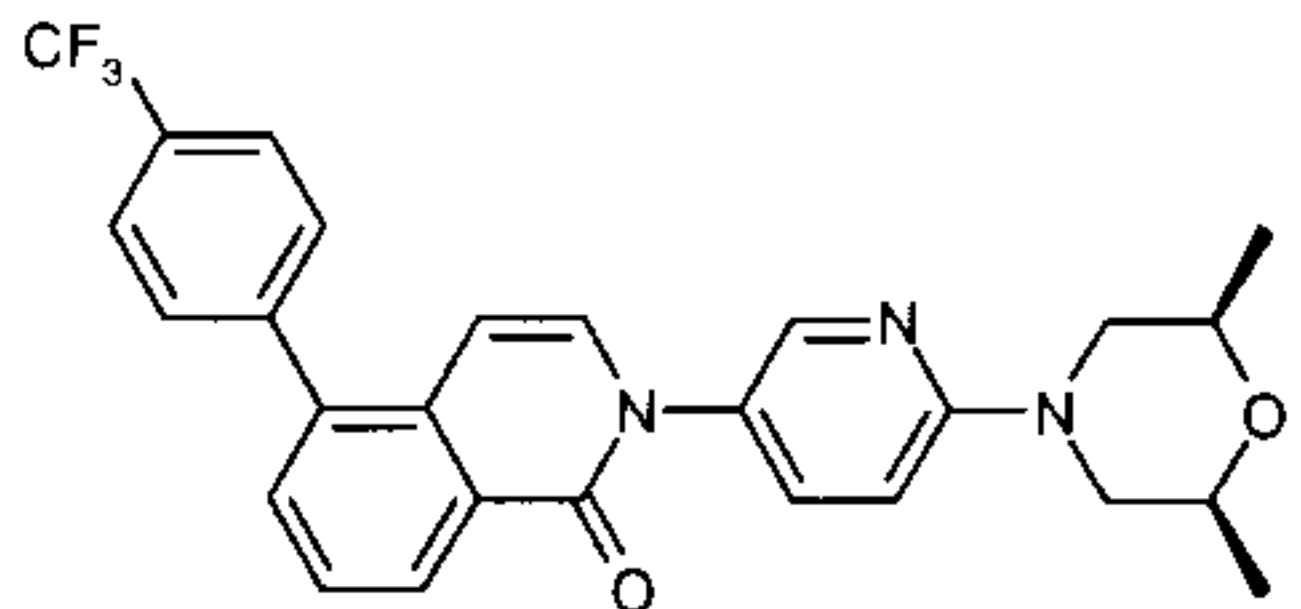
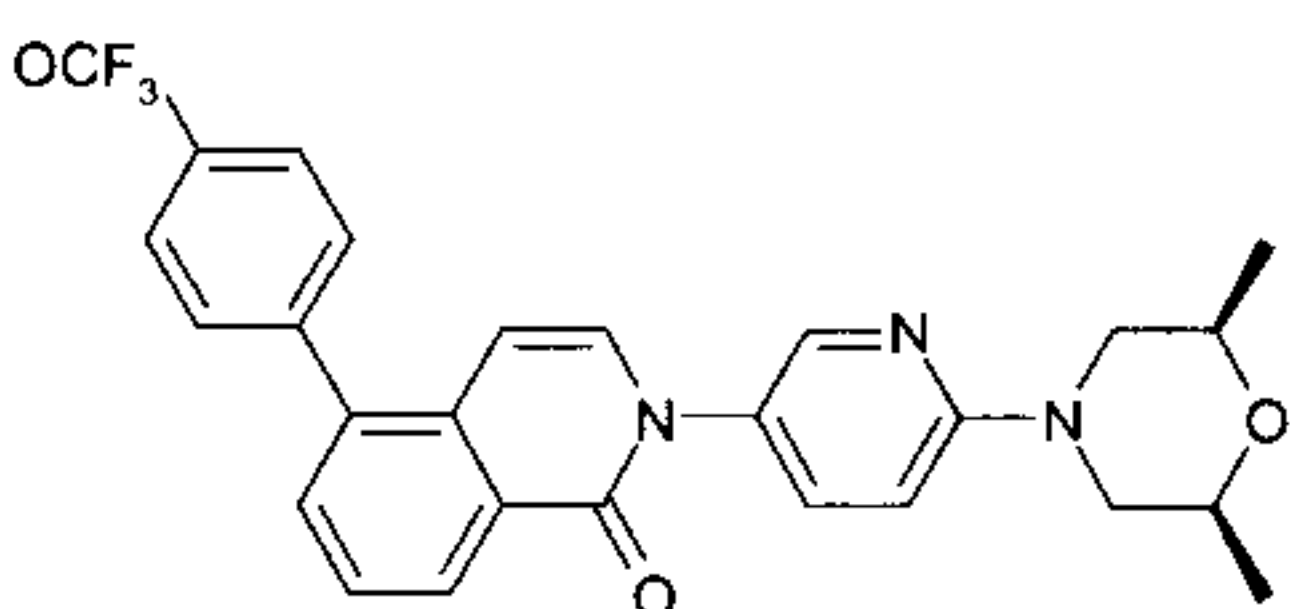
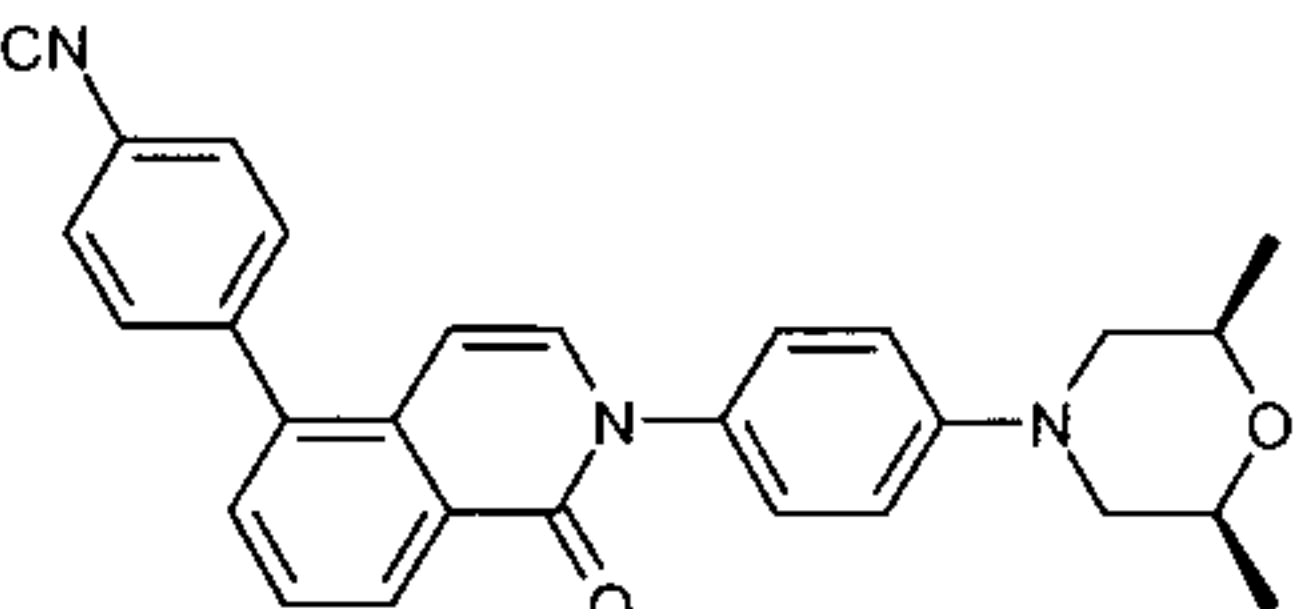


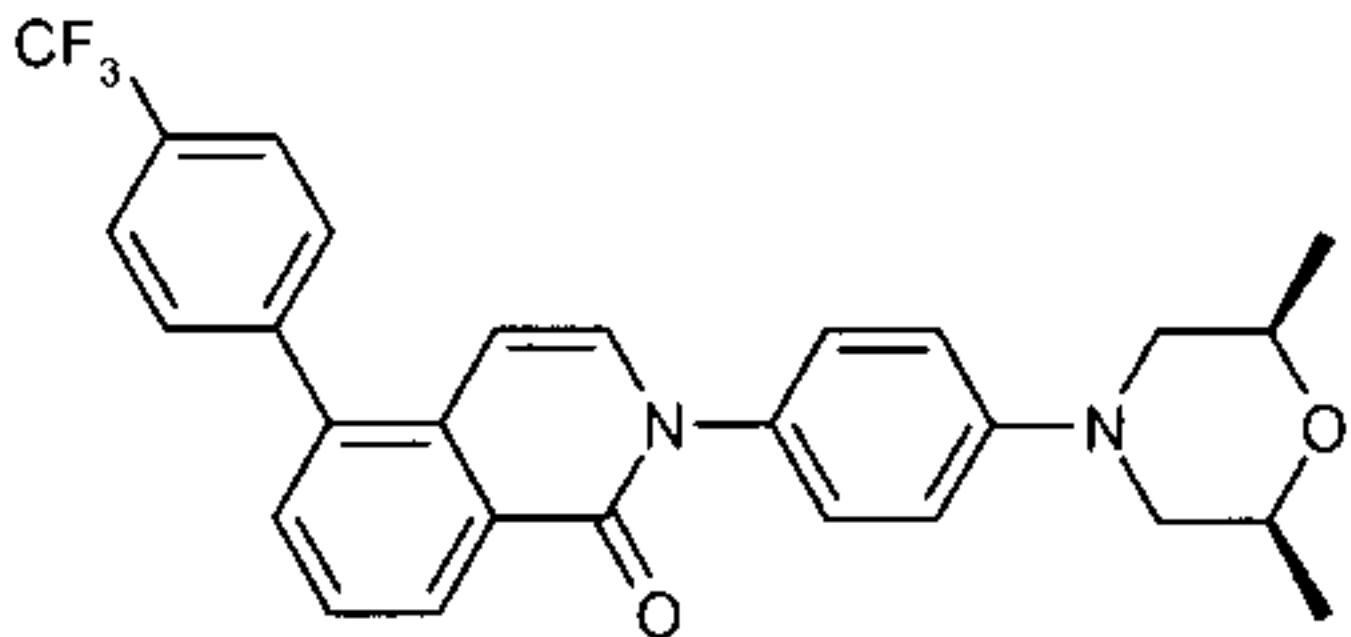
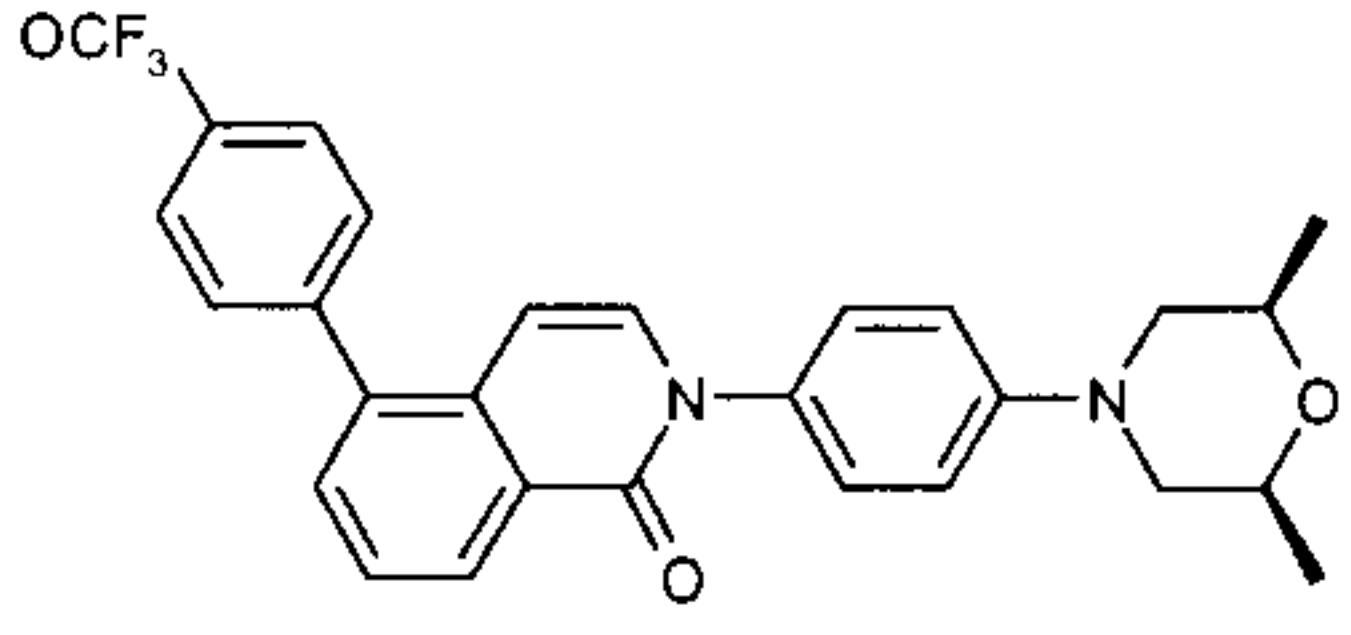
[253] Step 1: A solution of trimethyl aluminum (2 mol/L, 3.85 mL) in toluene was added into a solution of compound 70-2 in dry DCM (20 mL) at 0 °C, the reaction mixture was stirred at room temperature for 15 min. Then a solution of compound 70-1 (0.7 g, 3.1 mmol) in DCM (5 mL) was added dropwise, and the obtained solution was stirred at room temperature for 3h. After the reaction was complete as detected by LCMS, Rochelle salt solution was added. The obtained mixture was extracted with DCM, washed with brines, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc= 5:1) to deliver compound 70-3 (1.1 g, 85%) as yellow solid. **MS ESI** calcd for C₂₀H₂₄BrN₃O₃ [M+H]⁺ 435, found 435.

[254] Step 2: Dess-Martin periodinane (507 mg, 1.2 mmol) was added into a solution of compound 70-3 (434 mg, 1 mmol) in dry DCM (20 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight. Then the reaction mixture were quenched with saturated sodium thiosulfate aqueous solution and extracted with DCM, the organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc= 5:1) to deliver compound 70-4 (320 mg, 77%) as yellow solid. **MS ESI** calcd for C₂₀H₂₀BrN₃O₂ [M+H]⁺ 415, found 415.

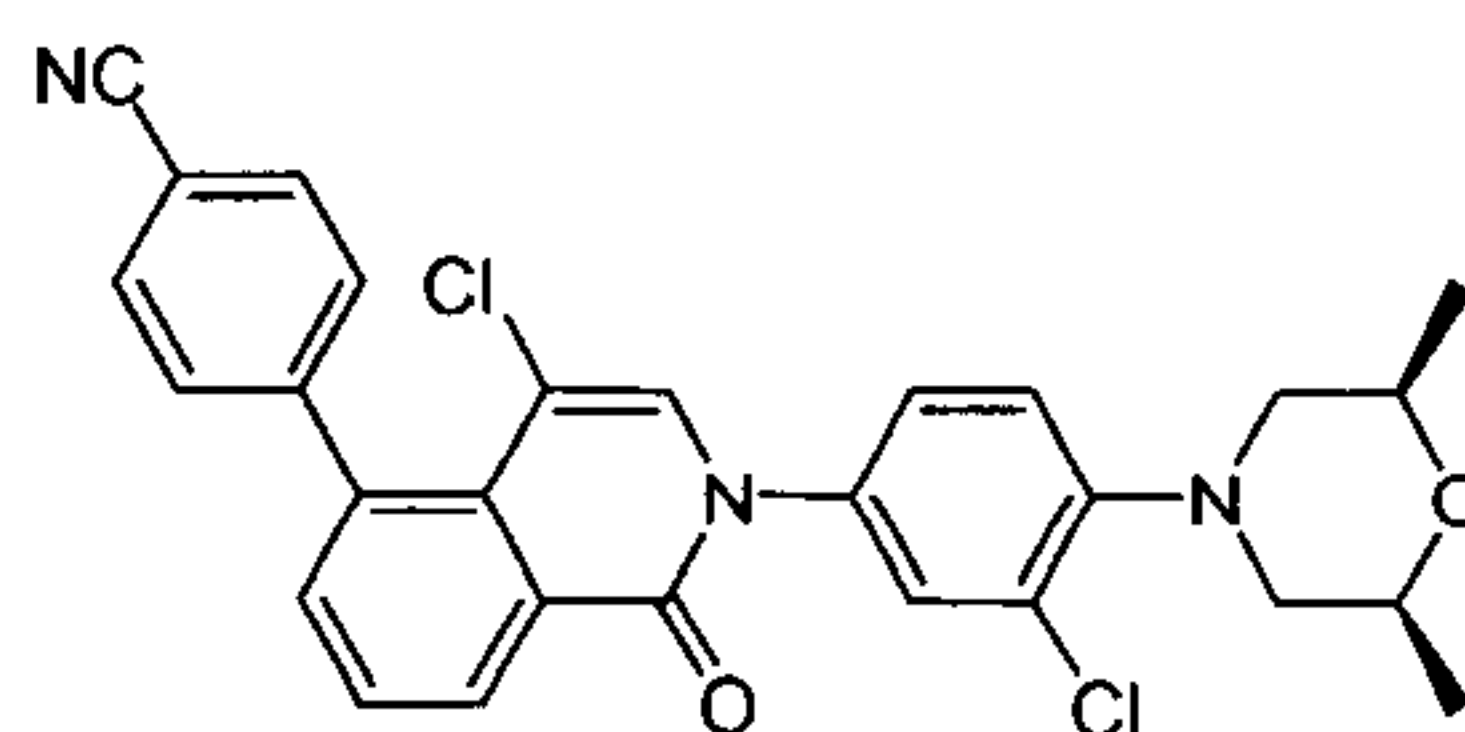
[255] Step 3: Under nitrogen gas atmosphere, compound 70-5 (53 mg, 0.36 mmol), sodium carbonate (51 mg, 0.48 mmol) and Pd(dppf)Cl₂ (18 mg, 0.024 mmol) were added into a solution of compound 70-4 (0.10 g, 0.24 mmol) in 1,4-dioxane (5 mL) and H₂O (1 mL). Then the reaction mixture was heated to reflux and stirred overnight. After the reaction was complete, the residue was purified by preparative HPLC to deliver the title compound (56 mg, 53%) as white solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.43 (d, *J* = 8.0 Hz, 1H), 8.18(d, *J* = 2.0 Hz, 1H), 7.90-7.82 (m, 3H), 7.75-7.61 (m, 4H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 6.60 (d, *J* = 7.6 Hz, 1H), 4.13 (d, *J* = 12.8 Hz, 2H), 3.75-3.71 (m, 2H), 2.68 (t, *J* = 12.0 Hz, 2H), 1.24 (d, *J* = 5.6 Hz, 6H). **MS ESI** calcd for C₂₇H₂₄N₄O₂ [M+H]⁺ 437, found 437.

[256] The compounds listed in table 5 can be synthesized by compound 70-4 and corresponding boric acids.

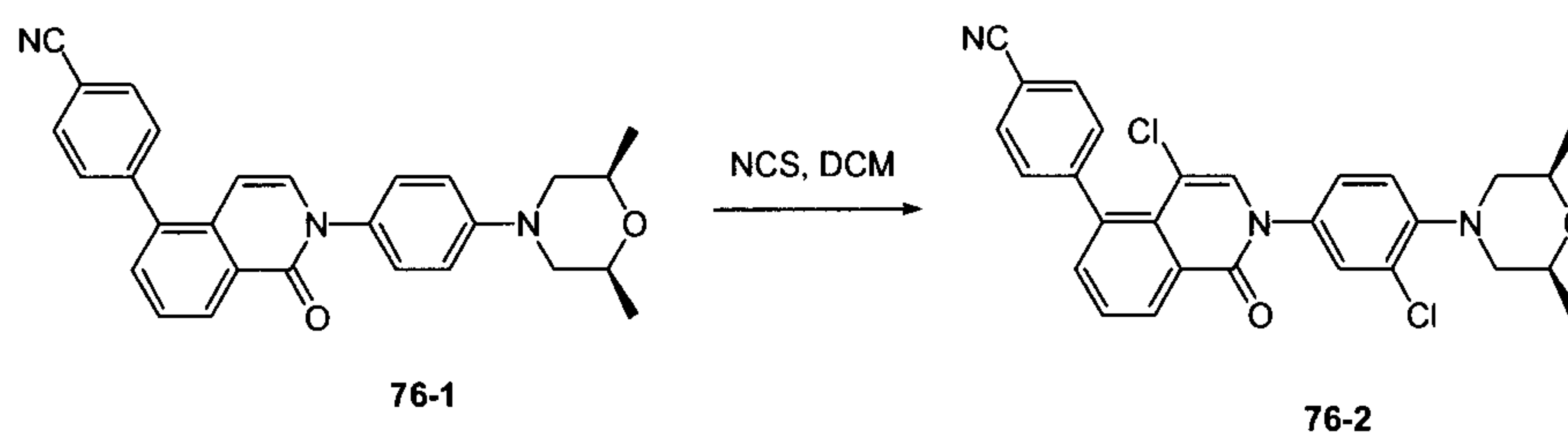
Embodiment	Structure	NMR
71		¹ H NMR (400 MHz, CDCl ₃) δ 8.42 (d, <i>J</i> = 8.0 Hz, 1H), 8.19(s, 1H), 7.90-7.80 (m, 3H), 7.75-7.60 (m, 3H), 7.32 (d, <i>J</i> = 8.0 Hz, 1H), 7.20 (d, <i>J</i> = 8.8 Hz, 1H), 6.61 (d, <i>J</i> = 7.6 Hz, 1H), 4.13 (d, <i>J</i> = 12.4 Hz, 2H), 3.75-3.71 (m, 2H), 2.71 (t, <i>J</i> = 12.0 Hz, 2H), 1.24 (d, <i>J</i> = 5.6 Hz, 6H). MS ESI calcd for C ₂₇ H ₂₄ F ₃ N ₃ O ₂ [M+H] ⁺ 480, found 480.
72		¹ H NMR (400 MHz, CDCl ₃) δ 8.40 (d, <i>J</i> = 8.0 Hz, 1H), 8.19(s, 1H), 7.92-7.82 (m, 1H), 7.70 (d, <i>J</i> = 8.0 Hz, 1H), 7.65-7.60 (m, 1H), 7.50 (d, <i>J</i> = 8.0 Hz, 2H), 7.43 (d, <i>J</i> = 8.0 Hz, 2H), 7.31 (d, <i>J</i> = 8.0 Hz, 1H), 7.21 (d, <i>J</i> = 8.8 Hz, 1H), 6.61 (d, <i>J</i> = 7.6 Hz, 1H), 4.11 (d, <i>J</i> = 12.4 Hz, 2H), 3.70-3.61 (m, 2H), 2.72 (t, <i>J</i> = 12.0 Hz, 2H), 1.22 (d, <i>J</i> = 5.6 Hz, 6H). MS ESI calcd for C ₂₇ H ₂₄ F ₃ N ₃ O ₃ [M+H] ⁺ 496, found 496.
73		¹ H NMR (400MHz, Methanol- <i>d</i> ₄) δ 8.42-8.44 (d, <i>J</i> = 8.0 Hz, 1H) 7.85-7.87 (m, 2H), 7.61-7.71 (m, 4H) 7.29-7.34 (m, 3H) 7.15-7.17 (d, <i>J</i> = 8.4 Hz, 2H), 6.56-6.58 (d, <i>J</i> = 8.0 Hz, 1H), 3.79-3.83 (t, <i>J</i> = 14.4 Hz, 2H) 3.58-3.61 (t, <i>J</i> = 11.6 Hz, 2H) 2.46-2.51 (t, <i>J</i> = 22.4 Hz, 2H), 1.21-1.23 (d, <i>J</i> = 6.4 Hz, 6H). MS ESI calcd for C ₂₈ H ₂₅ N ₃ O ₂ [M+H] ⁺ 436, found 436.

74		¹H NMR (400MHz, Methanol-<i>d</i>₄) δ 8.40-8.42 (d, <i>J</i> =8.0 Hz, 1H) 7.61-7.85 (m, 6H), 7.27-7.33 (d d, <i>J</i> =8.0 Hz, 3H) 7.13-7.15 (d, <i>J</i> =9.2 Hz, 2H), 6.56-6.58 (d, <i>J</i> =8.0 Hz, 1H), 3.79-3.83 (t, <i>J</i> =14.4 Hz 2H) 3.58-3.61 (t, <i>J</i> =11.6 Hz, 2H) 2.44-2.50 (t, <i>J</i> =22.0 Hz ,2H), 1.21-1.23 (d, <i>J</i> =6.0 Hz ,6 H). MS ESI calcd for C₂₈H₂₅F₃N₂O₂ [M+H]⁺ 479, found 479.
75		¹H NMR (400MHz, Methanol-<i>d</i>₄) δ 8.39-8.41 (d, <i>J</i> =8.4 Hz, 1H) 7.52-7.67 (m, 4H), 7.39-7.41 (m, <i>J</i> =8.0 Hz,2H) 7.28-7.33 (m, 3H), 7.12-7.15 (d, <i>J</i> =9.6 Hz, 2H), 6.59-6.61 (d, <i>J</i> =8.0 Hz, 1H), 3.78-3.82 (t, <i>J</i> =14.4 Hz 2H) 3.58-3.61 (t, <i>J</i> =11.6 Hz, 2H) 2.43-2.48 (t, <i>J</i> =22.4 Hz ,2H), 1.21-1.23 (d, <i>J</i> =6.4 Hz ,6 H). MS ESI calcd for C₂₈H₂₅F₃N₂O₃ [M+H]⁺ 495, found 495.

Embodiment 76



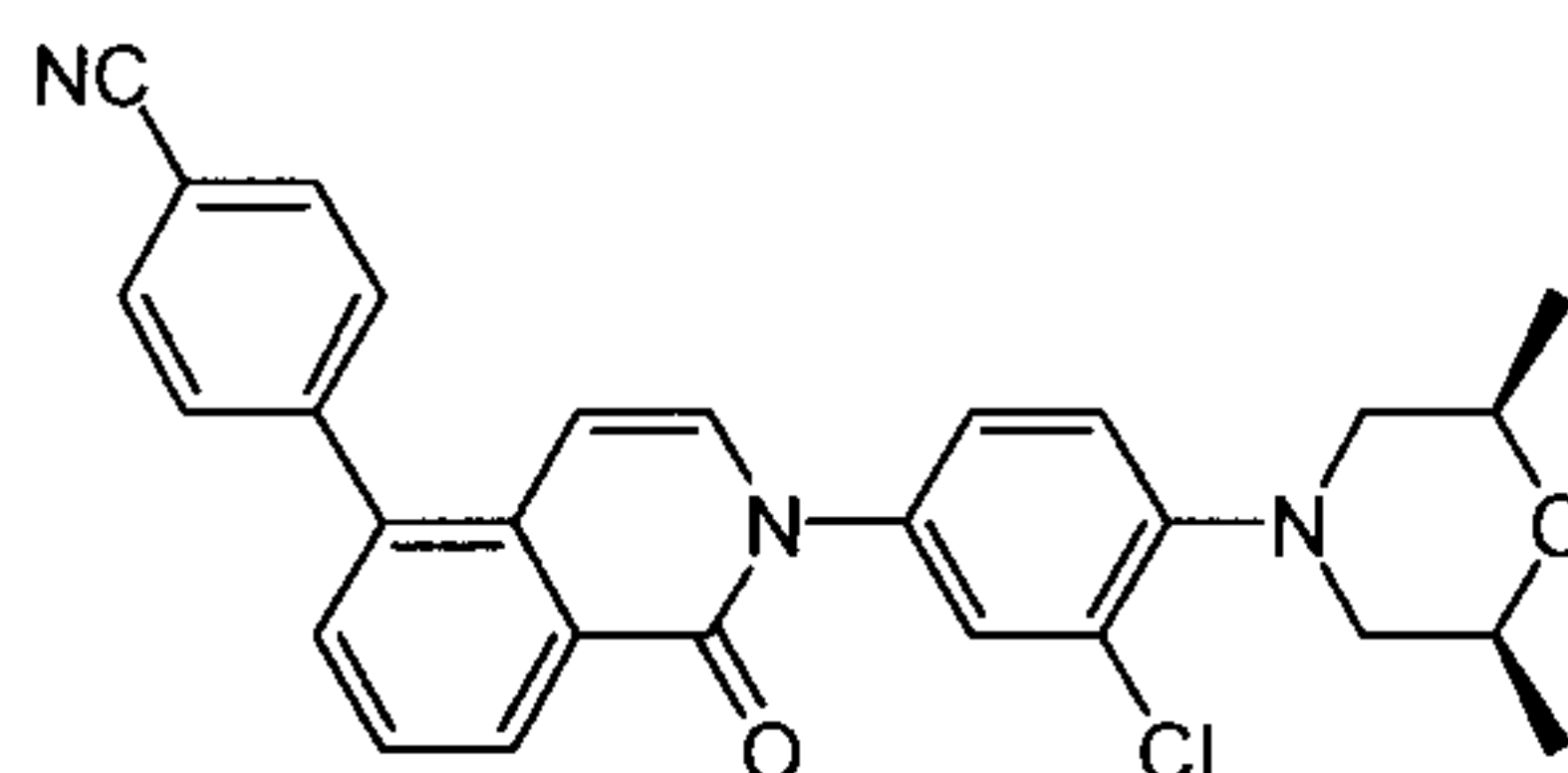
4-(4-chloro-2-(3-chloro-4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-1-oxo-1,2-dihydroisoquinolin-5-yl)benzonitrile



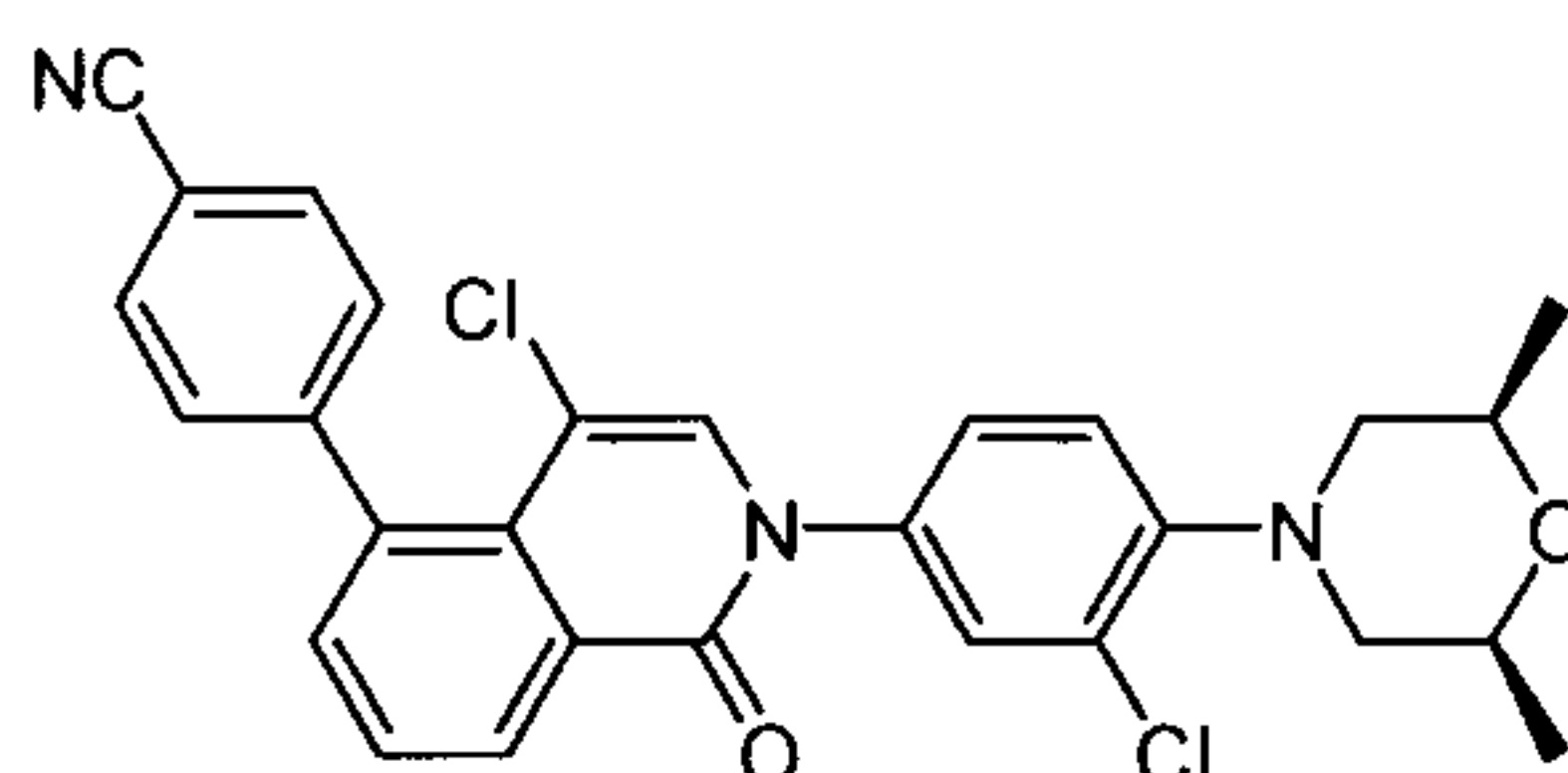
Our Ref.: P1650132CA

[257] NCS (48 mg, 0.36 mmol) was added into a solution of compound 76-1 (100 mg, 0.24 mmol) in dry DCM (10 mL). Then the reaction mixture was stirred at room temperature overnight. After the reaction was complete, the residue was purified by preparative HPLC to deliver the title compound as white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.65 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.50-7.68 (m, 2H), 7.40-7.49 (m, 3H), 7.27-7.35 (m, 2H), 7.12 (d, *J* = 8.0 Hz, 1H), 3.85-4.00 (m, 2H), 3.20-3.35 (m, 2H), 2.40-2.55 (m, 2H), 1.25 (s, 3H), 1.24 (s, 3H). MS ESI calcd for C₂₈H₂₇N₅O [M+H]⁺ 450, found 450.

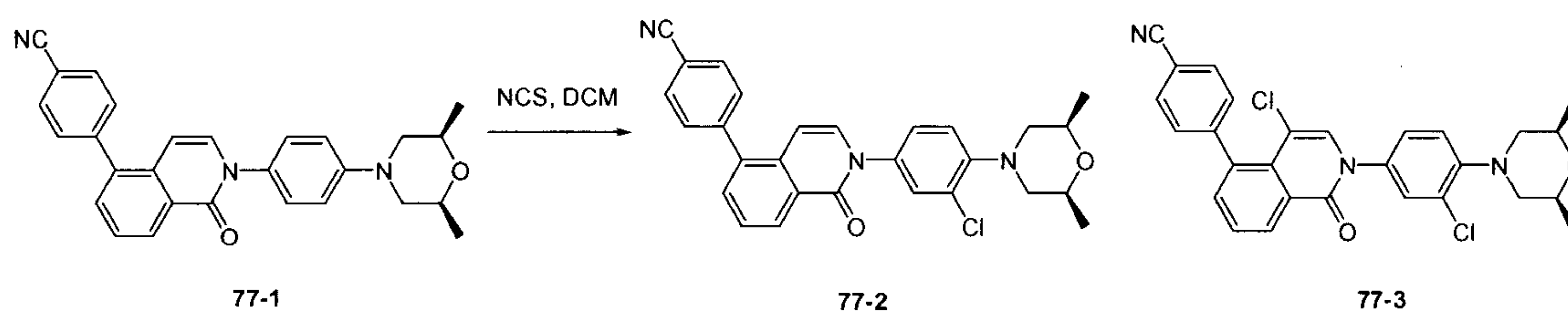
Embodiments 77, 78



4-(2-(3-chloro-4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-1-oxo-1,2-dihydroisoquinolin-5-yl)benzonitrile



4-(4-chloro-2-(3-chloro-4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-1-oxo-1,2-dihydroisoquinolin-5-yl)benzonitrile

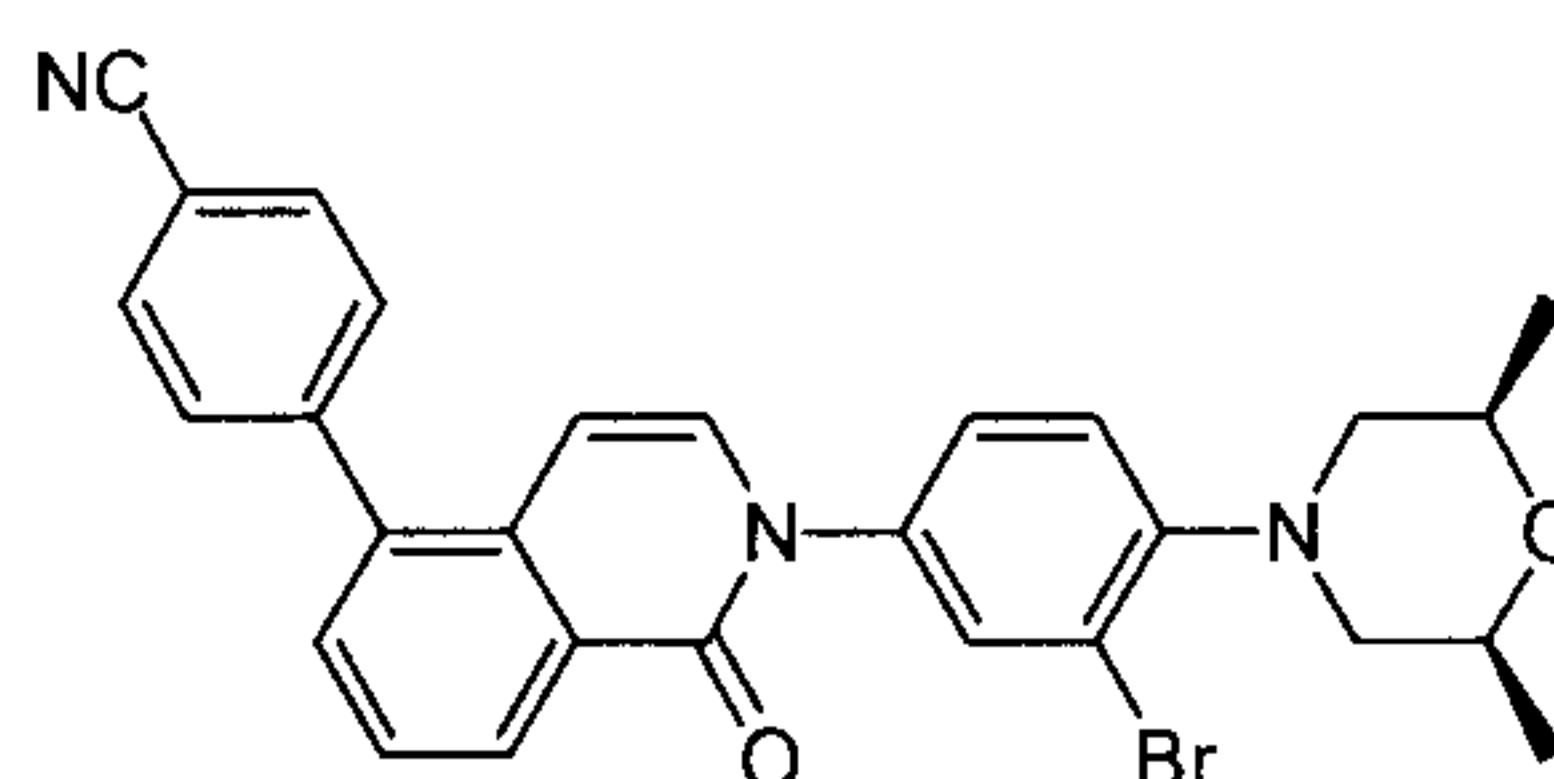


[258] NCS (48 mg, 0.36 mmol) was added into a solution of compound 77-1 (100 mg, 0.24 mmol) in DCM (10 mL) in portions, and then the reaction mixture was stirred at room temperature overnight and the solvent was evaporated, the residue was purified by preparative HPLC to deliver the title compound of embodiment 77 as yellow solid. ¹H NMR (400MHz, CDCl₃) δ 8.57-8.59 (d, *J* = 8.0 Hz, 1H) 7.80-7.82 (d, *J* = 8.0 Hz, 2H) 7.63-7.64 (t, *J* = 6.4 Hz, 2H), 7.56-7.58 (t, *J* = 8.0 Hz, 2H), 7.46 (s, 1H) 7.29-7.34 (m, 1H) 7.12-7.14 (d, *J* = 8.4 Hz, 2H), 6.52-6.54 (d, *J* = 8.0 Hz, 1H), 3.93-3.95 (t, *J* = 14.4 Hz, 2H) 3.27-3.30 (t, *J* = 10.8 Hz, 2H) 2.47-2.53 (t, *J* = 23.2 Hz, 2H), 1.24-1.26 (d, *J* = 6.0 Hz, 6 H). MS ESI calcd for C₂₈H₂₄ClN₃O₂ [M+H]⁺ 471, found 471. At the same time, the title compound of embodiment 78 was

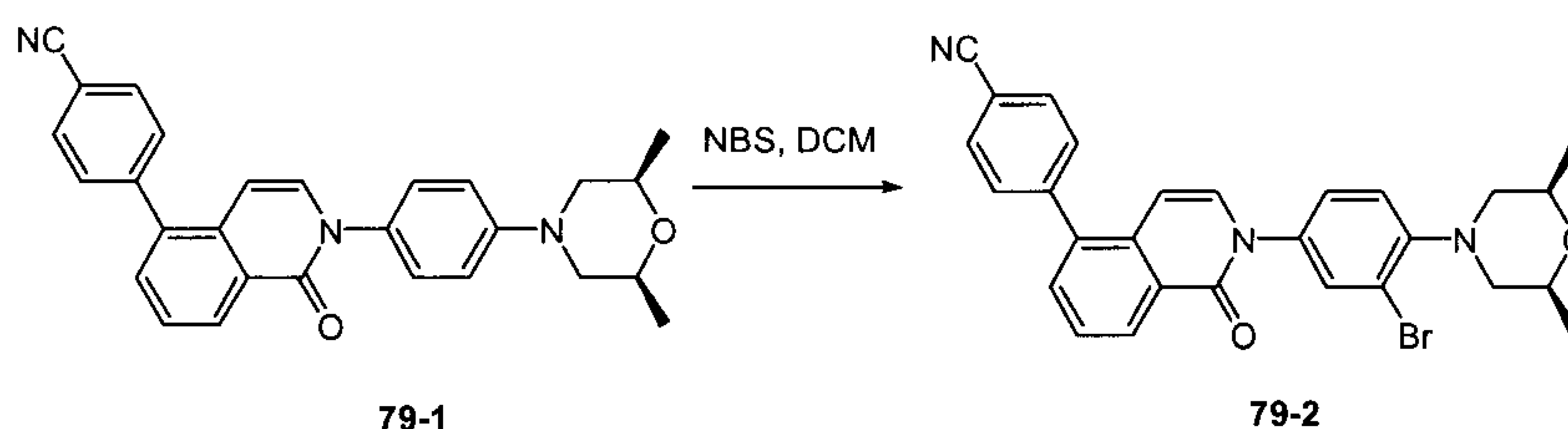
Our Ref.: P1650132CA

isolated as yellow solid. **¹H NMR** (400MHz, Methanol-*d*₄) δ 8.64-8.66 (d, *J* = 7.2 Hz, 1H) 7.57-7.71 (m, 4H), 7.44-7.47 (d d, *J* = 8.0 Hz, 3H) 7.31 (s, 1H), 7.11-7.13 (d, *J* = 8.0 Hz, 1H), 3.89-3.93 (t, *J* = 14.4 Hz 2H), 3.26-3.29 (t, *J* = 11.6 Hz, 2H) 2.44-2.50 (t, *J* = 21.6 Hz, 2H), 1.24-1.26 (d, *J* = 6.0 Hz, 6 H). **MS ESI** calcd for C₂₈H₂₃Cl₂N₃O₂ [M+H]⁺ 505, found 505.

Embodiment 79

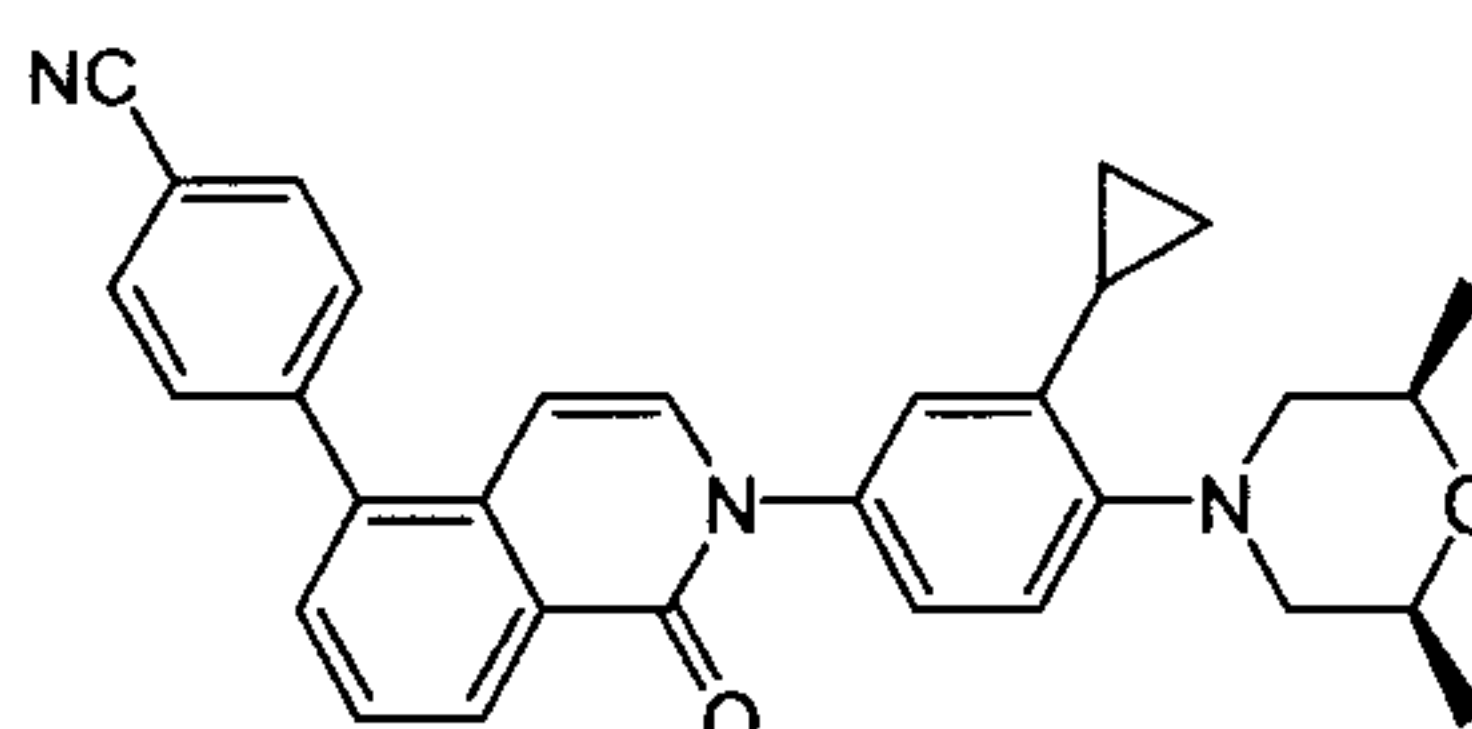


4-(2-(3-bromo-4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-1-oxo-1,2-dihydroisoquinolin-5-yl)benzonitrile



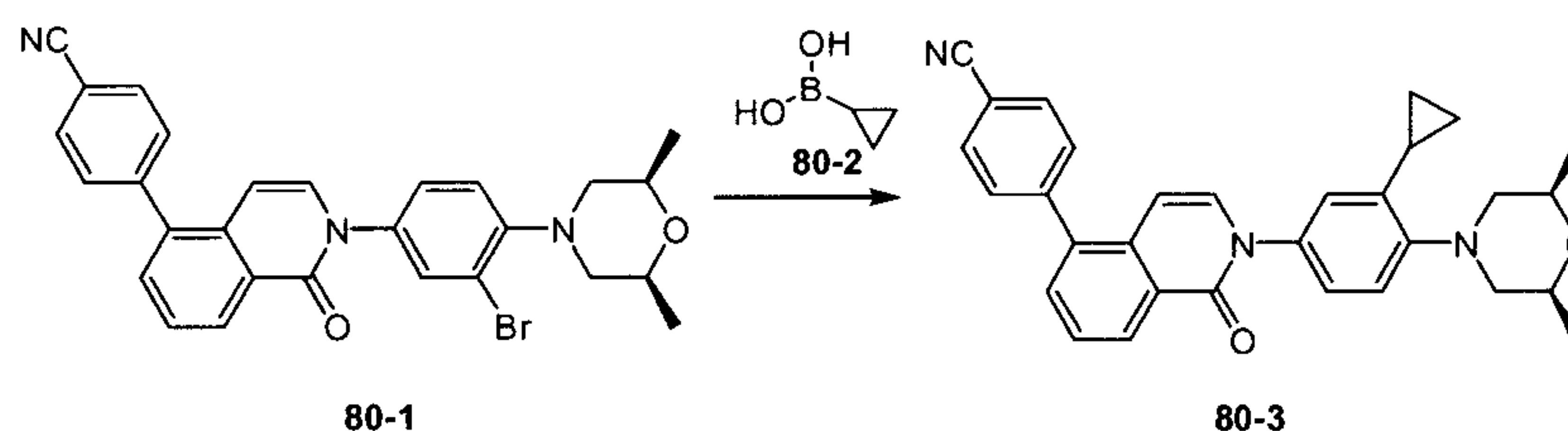
[259] NBS (43 mg, 0.24 mmol) was added into a solution of compound 79-1 (100 mg, 0.24 mmol) in DCM (10 mL) in portions, then the reaction mixture was stirred at room temperature overnight and the solvent was evaporated, the residue was purified by preparative HPLC to deliver the title compound (20 mg, yield 25%) as white solid. **¹H NMR** (400MHz, Methanol-*d*₄) δ 8.43-8.45 (d, *J* = 7.6 Hz, 1H) 7.87-7.89 (d, *J* = 8.4 Hz, 2H), 7.64-7.71 (m, 5H), 7.24-7.40 (m, 3H), 6.58-6.60 (d, *J* = 7.6 Hz, 2H), 3.87-3.91 (t, *J* = 14.4 Hz 2H), 2.42-2.47 (t, *J* = 22.4 Hz, 2H), 1.18-1.20 (d, *J* = 6.4 Hz, 6 H). **MS ESI** calcd for C₂₈H₂₄BrN₃O₂ [M+H]⁺ 515, found 515.

Embodiment 80



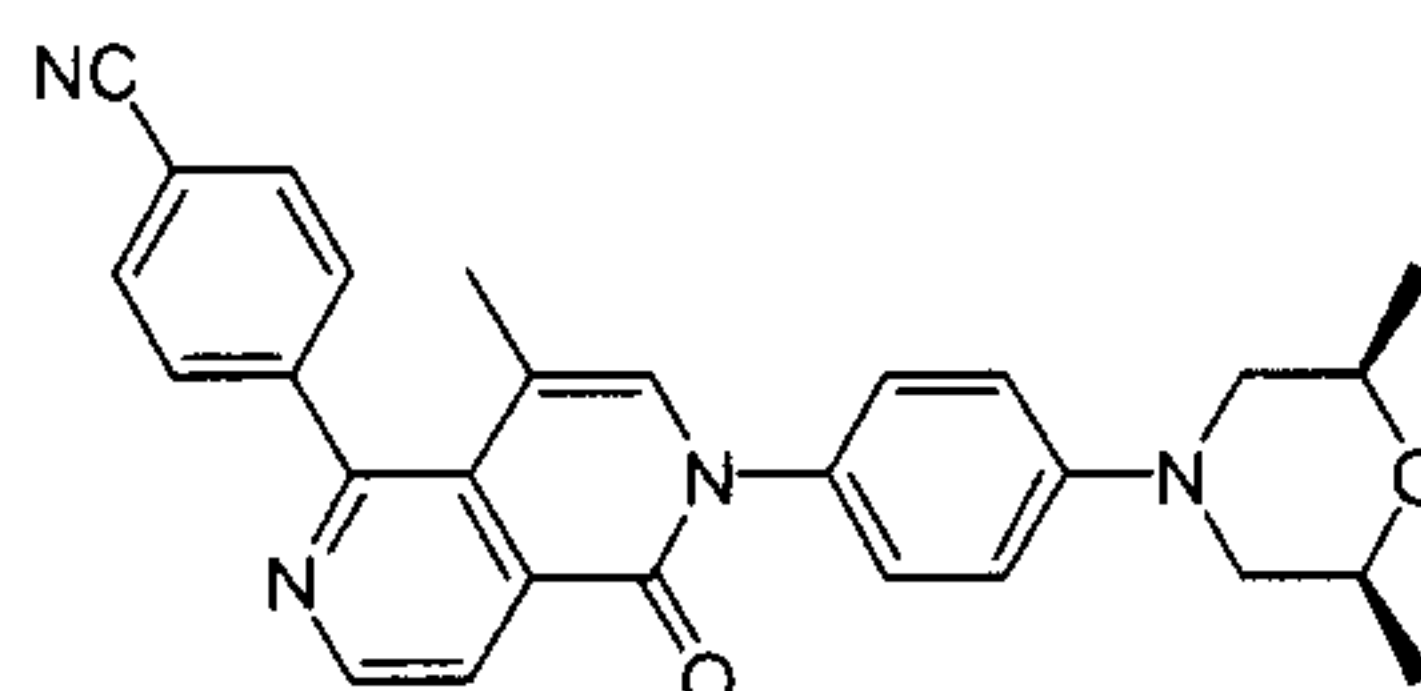
4-(2-(3-cyclopropyl-4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-1-oxo-1,2-dihydroisoquinolin-5-yl)benzonitrile

Our Ref.: P1650132CA

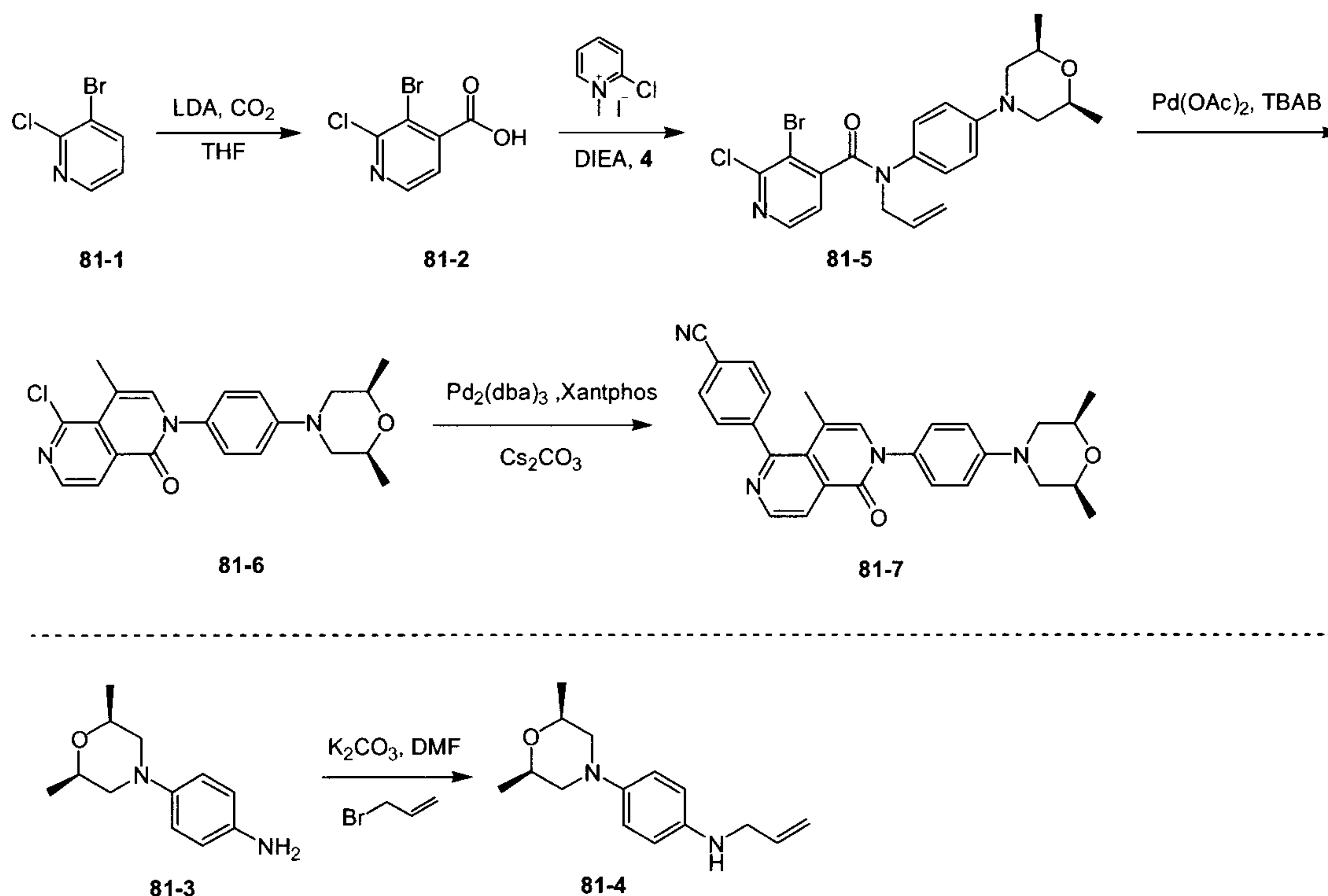


[260] Compound 80-1 (100 mg, 0.19 mmol), 80-2 (49 mg, 0.57 mmol), n-BuPAd₂ (7.2 mg, 0.02 mmol), palladium acetate (3 mg, 0.01 mmol) and cesium carbonate (187 mg, 0.57 mmol) were added into toluene/H₂O (5:1, 3 mL), then under nitrogen gas atmosphere, the reaction mixture was stirred at 110°C for 2h. The reaction mixture was poured into H₂O, extracted with EtOAc (10 mL), the extraction liquid was washed with brines, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by preparative HPLC to deliver the title compound (250 mg, yield 20%) as yellow solid. ¹H NMR (400MHz, CDCl₃) δ 8.57-8.59 (t, *J* =9.2 Hz, 1H) 7.80-7.82 (d, *J* =8.0 Hz, 2H) 7.57-7.63 (m, 4H), 7.11-7.18 (m, 3H) 6.83-6.84 (d, *J* =1.6 Hz, 1H), 6.50-6.52 (d, *J* =7.6 Hz, 1H), 3.94-3.98 (t, *J* =14.4 Hz 2H) 3.27-3.30 (t, *J* =10.8 Hz, 2H) 2.55-2.60 (t, *J* =21.6 Hz, 2H), 2.29-2.34 (m, 2H), 1.24-1.26 (d, *J* =6.4 Hz, 6 H), 1.03-1.05 (m, 2H), 0.75-0.76 (m, 2H). MS ESI calcd for C₃₁H₂₉N₃O₂ [M+H]⁺ 476, found 476.

Embodiment 81



4-(6-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-8-methyl-5-oxo-5,6-dihydro-2,6-naphthyridin-1-yl)benzonitrile



[261] Step 1: LDA (60 mL, 0.12 mol) was dripped into a solution of compound 81-1 (20 g, 0.1 mol) in THF (200 mL) at -78 °C, the reaction mixture was stirred at -78°C for 2h. The reaction mixture was poured into dry ice quickly. Then the mixture was stirred at room temperature for 30 min, and quenched with H₂O in the end. The aqueous phase was extracted with EtOAc. The combined organic phase was washed with brines, dried over sodium sulfate, and concentrated under reduced pressure to deliver compound 81-2 (10 g, yield 43%) as white-off solid. **MS ESI** calcd for C₆H₃BrClNO₂ [M+H]⁺ 236, found 236.

[262] Step 2: A mixture of compound 81-3 (5 g, 24.3 mmol), allyl bromide (2.1 g, 17 mmol) and K₂CO₃ (6.7 g, 48.6 mmol) was added into DMF (50 mL), the reaction mixture was stirred at 80°C for 5h. The reaction mixture was poured into H₂O. The aqueous phase was extracted with EtOAc. The combined organic phase was washed with brines, dried over sodium sulfate, and concentrated under reduced pressure. The obtained crude prduct was purified by silica gel chromatography (PE: EtOAc= 15:1) to deliver compound 81-4 (2.5 g, yield 42%) as brown solid. **MS ESI** calcd for C₁₅H₂₂N₂O [M+H]⁺ 247, found 247.

[263] Step 3: CMPI (2.2 g, 8.9 mmol) was added into a solution of compound 81-2 (2.1 g, 8.9 mmol), compound 81-4 (2.2 g, 8.9 mmol) and DIEA (2.3 g, 17.8 mmol) in acetonitrile (20 mL). The reaction mixture was stirred at room temperature for 16h. The crude product was used for the next step directly. **MS ESI** calcd for C₂₁H₂₃BrClN₃O₂ [M+H]⁺ 464, found 464.

[264] Step 4: Compound 81-5 (4.1 g, 8.9 mmol), tetra-butyl ammonium bromide (7.2 g, 22.3 mmol), palladium acetate (200 mg, 0.89 mmol) and TEA (2.7 g, 26.7 mmol) in acetonitrile (40 mL) were heated to reflux and stirred for 48h. The

reaction mixture was poured into H₂O. The aqueous phase was extracted with EtOAc. The combined organic phase was washed with brines, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (PE: EtOAc= 2:1) to deliver compound 81-6 (1 g, yield 30%) as brown solid. **MS ESI** calcd for C₂₁H₂₂ClN₃O₂ [M+H]⁺ 384, found 384.

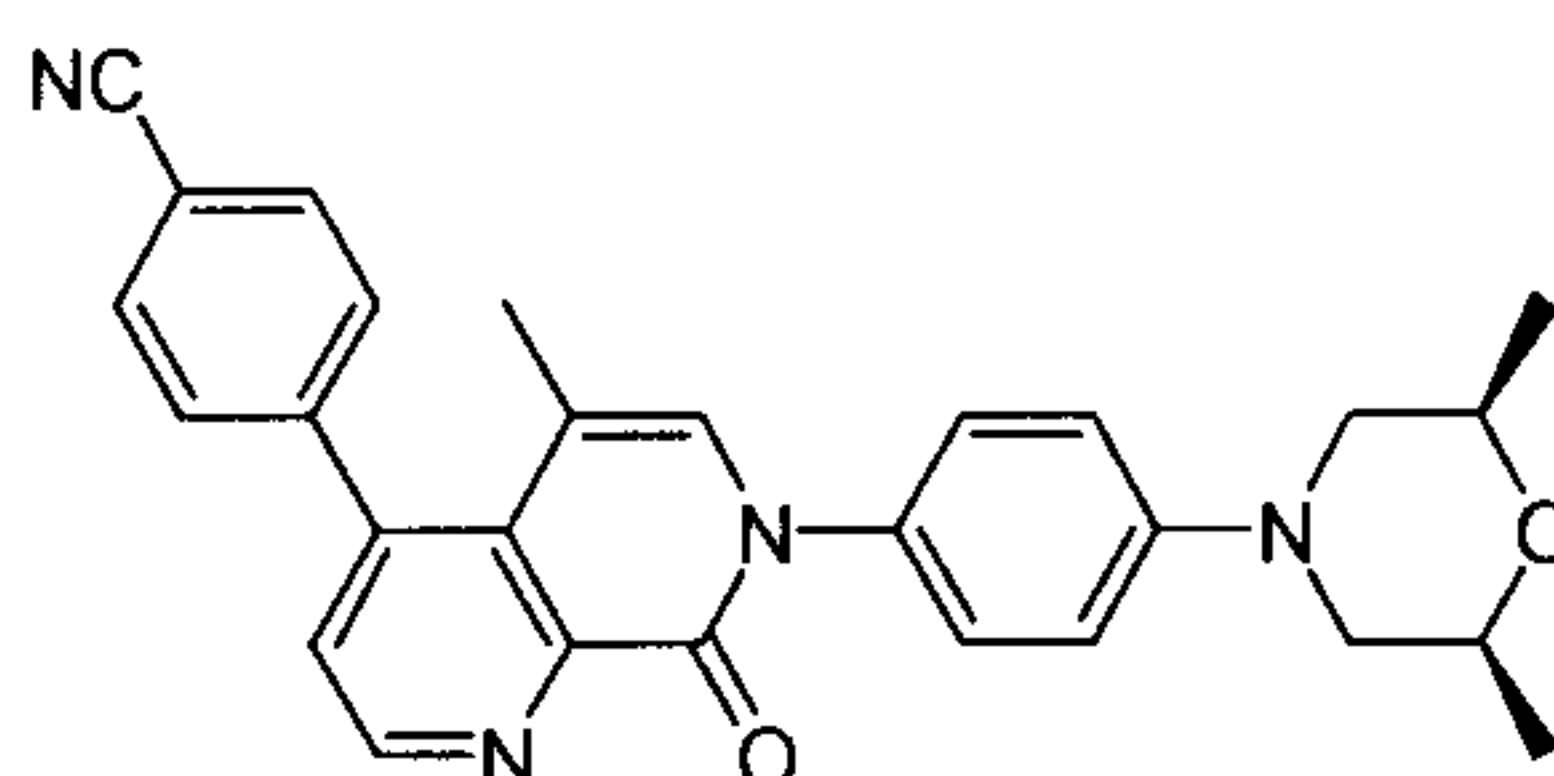
[265] Step 5: Compound 81-6 (100 mg, 0.26 mmol), 4-cyanophenyl boronic acid (45.6 mg, 0.31 mmol), Pd₂(dba)₃ (24 mg, 0.026 mmol), Xantphos (25 mg, 0.052 mmol) and cesium carbonate (171 mg, 0.52 mmol) were added into dioxane (5 mL) and the mixture was heated to reflux, then stirred for 16h. The crude product was purified by preparative HPLC to deliver the title compound as white solid. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 8.79 (d, *J*= 5.6 Hz, 1H), 7.77 (d, *J*= 8.0 Hz, 2H), 7.67 (d, *J*= 5.2 Hz, 1H), 7.61 (s, 1H), 7.54 (d, *J*= 8.0 Hz, 2H), 7.17 (d, *J*= 8.4 Hz, 2H), 6.97 (d, *J*= 8.8 Hz, 2H), 3.45-3.52 (m, 4H), 2.15-2.30 (m, 4H), 1.13 (s, 3H), 1.11 (s, 3H). **MS ESI** calcd for C₂₈H₂₆N₄O₂ [M+H]⁺ 451, found 451.

[266] The compounds listed in table 6 can be synthesized by compound 81-6 and corresponding boric acids.

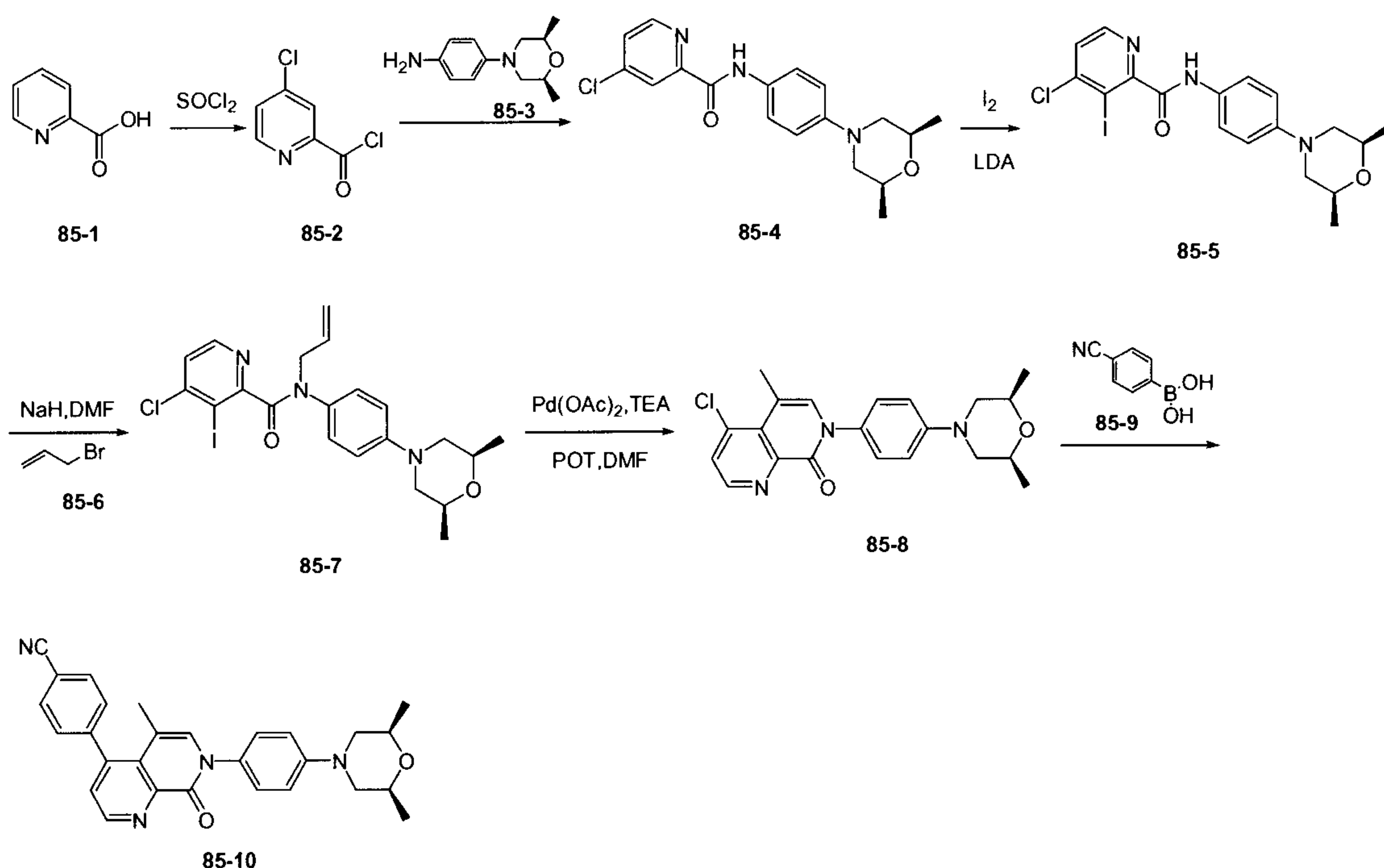
Embodiment	structure	NMR
82		¹H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.79 (d, <i>J</i> = 5.6 Hz, 1H), 7.64-7.63 (m, 3H), 7.52-7.62 (m, 3H), 7.17 (d, <i>J</i> = 8.8 Hz, 2H), 6.97 (d, <i>J</i> = 8.8 Hz, 2H), 3.40-3.50 (m, 4H), 2.15-2.35 (m, 5H), 1.20 (s, 3H), 1.13 (s, 3H). MS ESI calcd for C ₂₈ H ₂₆ F ₃ N ₃ O ₂ [M+H] ⁺ 494, found 494.
83		¹H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.77 (d, <i>J</i> = 5.6 Hz, 1H), 7.67 (d, <i>J</i> = 5.6 Hz, 1H), 7.62 (s, 1H), 7.50 (d, <i>J</i> = 8.0 Hz, 2H), 7.30 (d, <i>J</i> = 8.4 Hz, 2H), 7.18 (d, <i>J</i> = 8.4 Hz, 2H), 6.98 (d, <i>J</i> = 9.2 Hz, 2H), 3.40-3.50 (m, 4H), 2.15-2.33 (m, 5H), 1.13 (s, 3H), 1.11 (s, 3H). MS ESI calcd for C ₂₈ H ₂₆ F ₃ N ₃ O ₃ [M+H] ⁺ 510, found 510.
84		¹H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.75 (d, <i>J</i> = 5.2 Hz, 1H), 7.84 (d, <i>J</i> = 8.0 Hz, 1H), 7.58-7.70 (m, 3H), 7.25 (d, <i>J</i> = 9.2 Hz, 2H), 7.01 (d, <i>J</i> =

		8.8 Hz, 2H), 3.60-3.70 (m, 4H), 2.19-2.35 (m, 5H), 1.14 (s, 3H), 1.13 (s, 3H). MS ESI calcd for C ₂₆ H ₂₄ N ₄ O ₂ S [M+H] ⁺ 457, found 457.
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Embodiment 85



4-(7-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-5-methyl-8-oxo-7,8-dihydro-1,7-naphthyridin-4-yl)benzonitrile



[267] Step1: Compound 85-1 (4.3 g, 35 mmol), DMF (0.5 mL) and thionyl chloride (13 mL, 181 mmol) were stirred at 80°C for 12h. The reaction mixture was concentrated to dry under reduced pressure to deliver compound 85-2 (6.1 g, yield 100%) as brown solid. **MS ESI** calcd for C₆H₃Cl₂NO [M+H]⁺ 176, found 176.

[268] Step 2: Compound 85-2 (6.1 g, 35 mmol) was added into a solution of compound 85-3 (6 g, 29.1 mmol) in DCM (60 mL) at 0 °C. After the additon, the reaction mixture was stirred ar room temperature for 3h. The reaction mixture was poured into H₂O (200 mL), and the precipitate was collected by filtration. The filtrate cake was dissolved in EtOAc, dried over sodium sulfate, filtrated and concentrated to dry. In the end, the residue was purified by silica gel

chromatography (PE: EtOAc= 2:1) to deliver compound 85-4 (5.6 g, yield 56%) as white solid. **MS ESI** calcd for $C_{18}H_{20}ClN_3O_2$ $[M+H]^+$ 346, found 346.

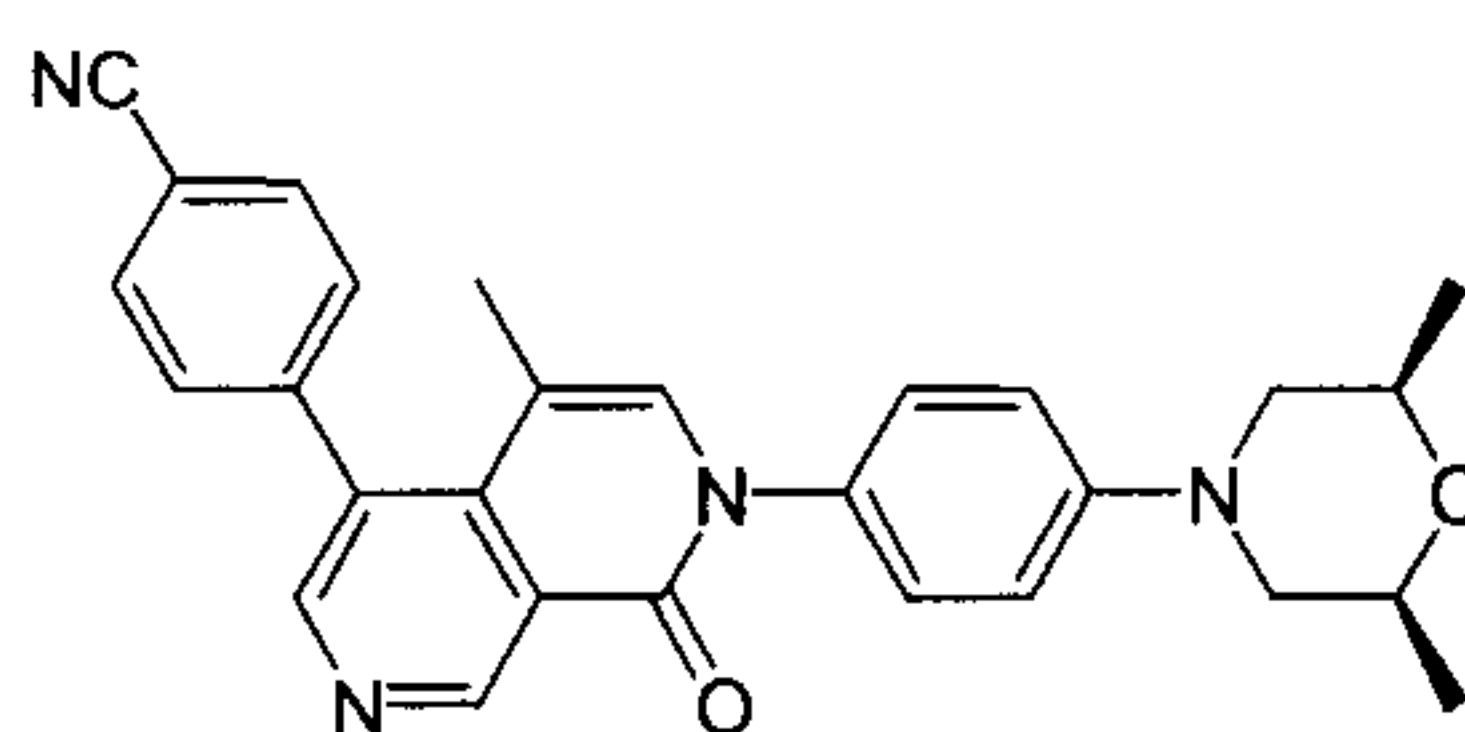
[269] Step 3: Under nitrogen gas atmosphere, LDA (22 mL, 43.5 mmol) was added into a solution of compound 85-4 (5 g, 14.5 mmol) in THF (20 mL) at $-78^{\circ}C$. After 30 min, a solution of I_2 (5.5 g, 22.7 mmol) in THF (20 mL) was added into the solution. The obtained reaction mixture was stirred at $-78^{\circ}C$ for further 2h. Then the reaction mixture was poured into H_2O , extracted with EtOAc, the organic phases were combined and washed with brines, dried over anhydrous sodium sulfate, filtrated and concentrated under reduced pressure. The residue was purified by silica gel chromatography (PE: EtOAc= 2:1) to deliver compound 85-5 (5 g, yield 74%) as yellow solid. **MS ESI** calcd for $C_{18}H_{19}ClN_3O_2$ $[M+H]^+$ 472, found 472.

[270] Step 4: NaH (848 mg, 21.2 mmol, containing 40% mineral oil) was added into a solution of compound 85-5 (5 g, 10.6 mmol) in DMF at $0^{\circ}C$. The reaction mixture was stirred under nitrogen gas atmosphere for 10 min. Compound 85-6 (2.56 g, 21.2 mmol) was added into the solution, and the obtained mixture was stirred at $0^{\circ}C$ for further 2h. Then the reaction mixture was poured into H_2O , extracted with EtOAc. The combined organic phase was washed with brines, dried over anhydrous sodium sulfate, filtrated and concentrated under reduced pressure to deliver compound 85-7 (5.3 g, yield 99%) as white solid. **MS ESI** calcd for $C_{21}H_{23}ClN_3O_2$ $[M+H]^+$ 512, found 512.

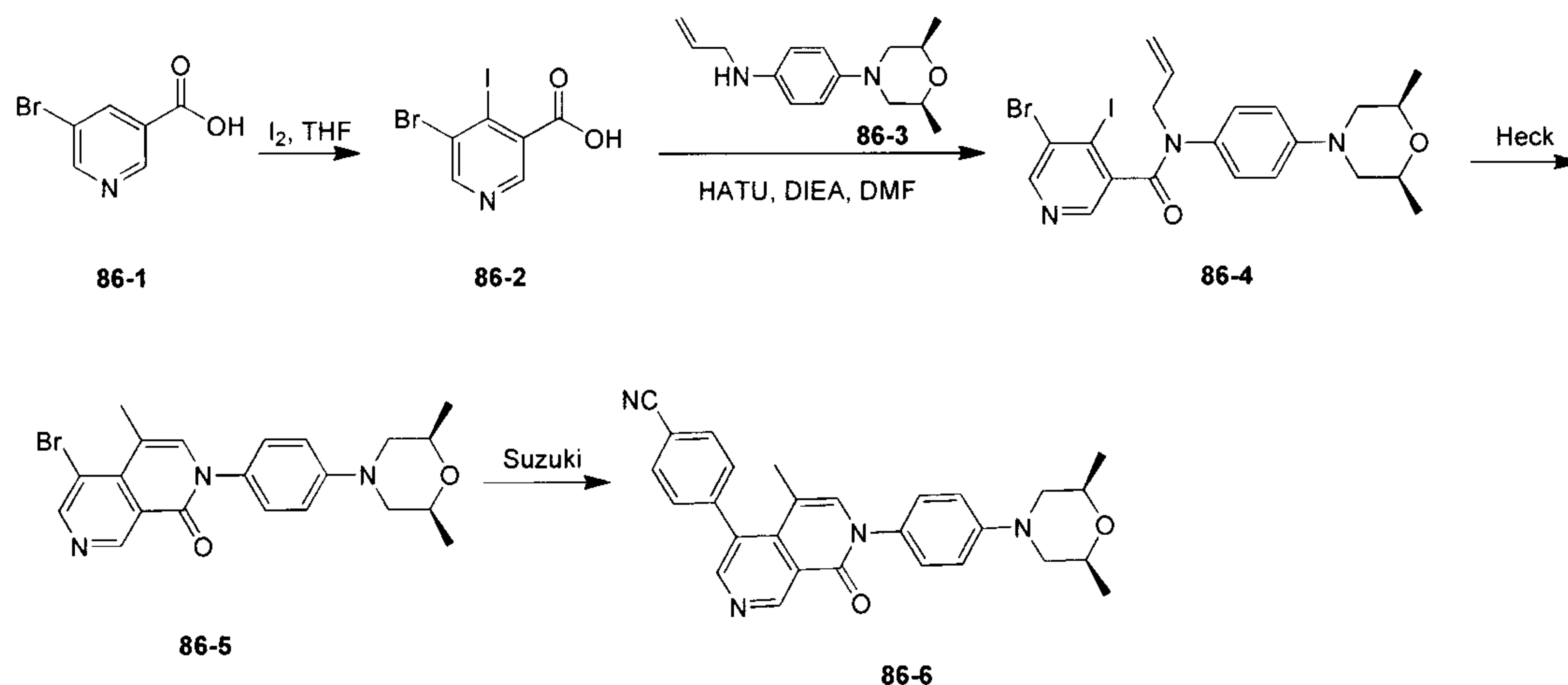
[271] Step 5: Compound 85-7 (5.4 g, 10.6 mmol), palladium acetate (237 mg, 1.06 mmol), TEA (2.1 g, 21.2 mmol) and POT (322 mg, 1.06 mmol) were added into DMF (40 mL) and the reaction mixture was stirred at $120^{\circ}C$ for 12h. The reaction mixture was poured into H_2O , extracted with EtOAc. The combined organic phase was washed with brines, dried over anhydrous sodium sulfate, filtrated and concentrated, finally purified by silica gel chromatography (PE: EtOAc= 1:1) to deliver compound 85-8 (3 g, yield 75%) as white-off solid. **MS ESI** calcd for $C_{21}H_{22}ClN_3O_2$ $[M+H]^+$ 384, found 384.

[272] Step 6: Compound 85-8 (300 mg, 0.78 mmol), compound 85-9 (160 mg, 1.09 mmol), K_3PO_4 (413 mg, 1.95 mmol), $Pd(dppf)Cl_2$ (57 mg, 0.078 mmol) were added into DMF (5 mL), and then under nitrogen gas atmosphere, the mixture was stirred at $120^{\circ}C$ for 12h. The reaction mixture was poured into H_2O , extracted with EtOAc. The combined organic phase was washed with brines, dried over anhydrous sodium sulfate, filtrated and concentrated, purified by preparative HPLC to deliver the title compound (75 mg, yield 21%) as white solid. **MS ESI** calcd for $C_{28}H_{26}N_4O_2$ $[M+H]^+$ 451, found 451.

Embodiment 86



4-(7-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-5-methyl-8-oxo-7,8-dihydro-2,7-naphthyridin-4-yl)benzonitrile



[273] Step 1: Under nitrogen gas atmosphere, *n*-butyl lithium (1.8 mL, 4.4 mmol) was added dropwise into a solution of 2,2,6,6-tetramethyl piperidine (0.81 mL, 4.8 mmol) in THF (10 mL) at -50°C . After 5 min, 5-bromonicotinic acid (0.40 g, 2.0 mmol) was added. After 30 min, a solution of I_2 (0.61 g, 2.4 mmol) in THF (5 mL) was added dropwise at -50°C . The obtained reaction mixture was stirred at -50°C for 2 h. The reaction mixture was quenched with H_2O (10 mL), the aqueous phase was separated and extracted with Et_2O (10 mL), then the aqueous phase was acidified with 1 M hydrochloric acid to $\text{pH} = 3$. The precipitate was filtrated and the filtrate cake was dried to deliver compound 86-2 as beige powder. **MS ESI** calcd for $\text{C}_6\text{H}_3\text{BrINO}_2$ $[\text{M}+\text{H}]^+$ 328, found 328.

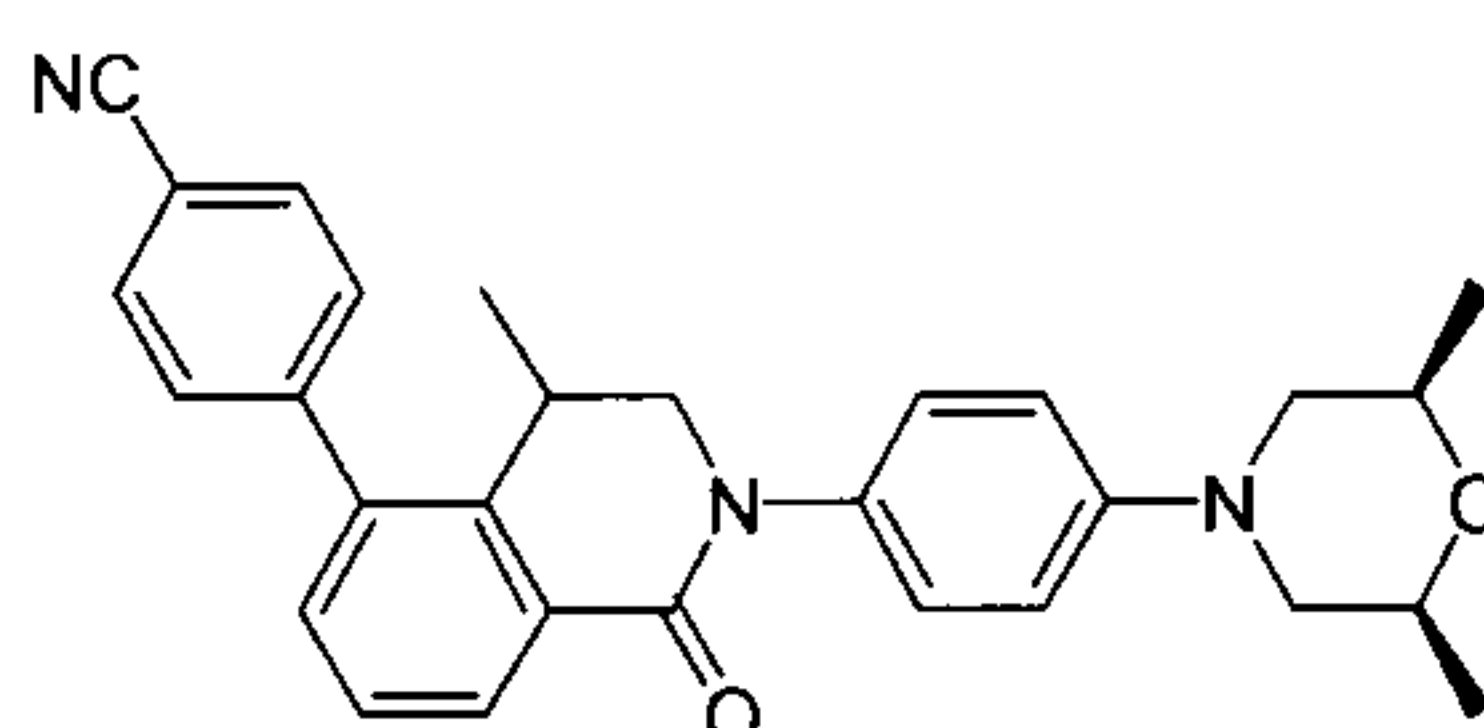
[274] Step 2: Compound 86-2 (650 mg, 25 mmol), compound 86-3 (500 mg, 2 mmol), HATU (770 mg, 2 mmol) and DIEA (2 mL) were added into DMF (10 mL), and the mixture was stirred at 20°C for 4h. The reaction mixture was poured into H_2O , and extracted with EtOAc. The combined organic phase was dried over sodium sulfate. After concentration, the residue was purified by silica gel chromatography to deliver compound 86-4 (yield 70%) as white-off solid. **MS ESI** calcd for $\text{C}_{21}\text{H}_{23}\text{BrIN}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 556, found 556.

[275] Step 3: Compound 86-5 as white solid was synthesized according to the method previously described. **MS ESI** calcd for $\text{C}_{21}\text{H}_{22}\text{BrN}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 428, found 428.

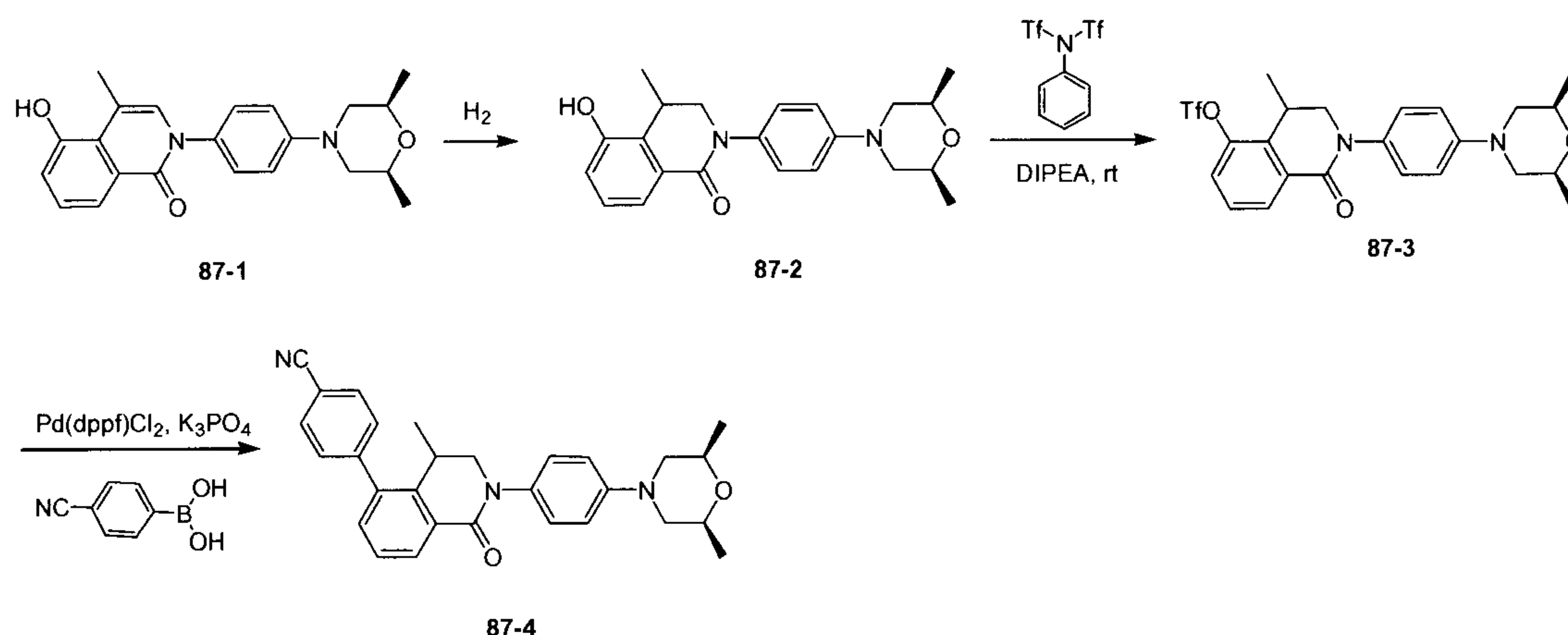
[276] Step 4: The title compound (yield 48%) as white solid was synthesized according to the method previously described. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.66

(s, 1H), 8.56 (s, 1H), 7.72 (d, $J = 8.4$ Hz, 2H), 7.44 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 8.4$ Hz, 2H), 6.95 (d, $J = 8.8$ Hz, 2H), 3.55-3.75 (m, 3H), 3.40-3.50 (m, 2H), 2.35-2.50 (m, 2H), 1.57 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H). **MS ESI** calcd for $C_{28}H_{26}N_4O_2$ $[M+H]^+$ 451, found 451.

Embodiment 87



4-(2-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-5-yl)benzonitrile

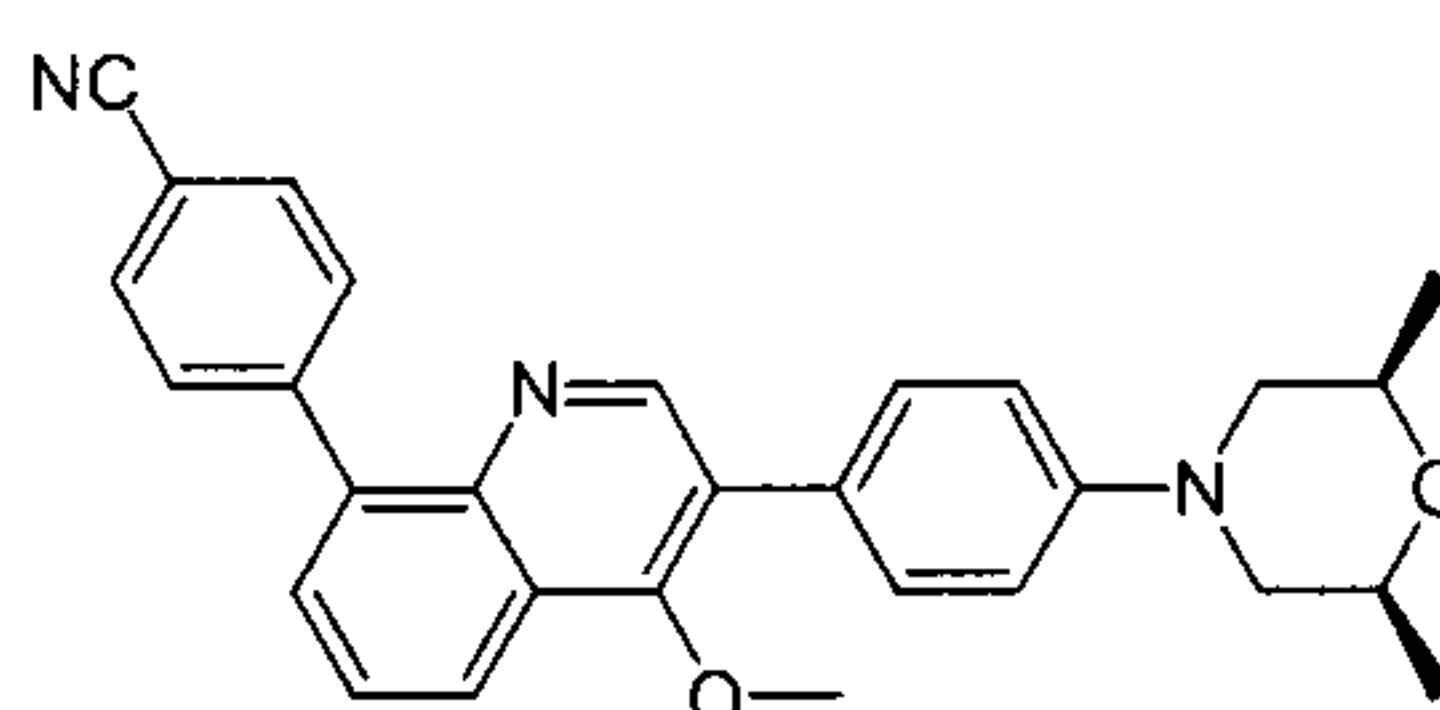


[277] Step 1: 10% Pd/C (50 mg, 50% wet) was added into a solution of compound 87-1 (500 mg, 1.37 mmol) in MeOH (50 mL). Then under a hydrogen gas pressure of 55 psi, the reaction mixture was stirred at 40°C for 48h. After the reaction was complete, the reaction mixture was filtrated with diatomite, and the filtrate was concentrated under reduced pressure to deliver compound 87-2 (400 mg, yield 80%) as white solid. **MS ESI** calcd for $C_{22}H_{26}N_2O_3$ $[M+H]^+$ 367, found 367.

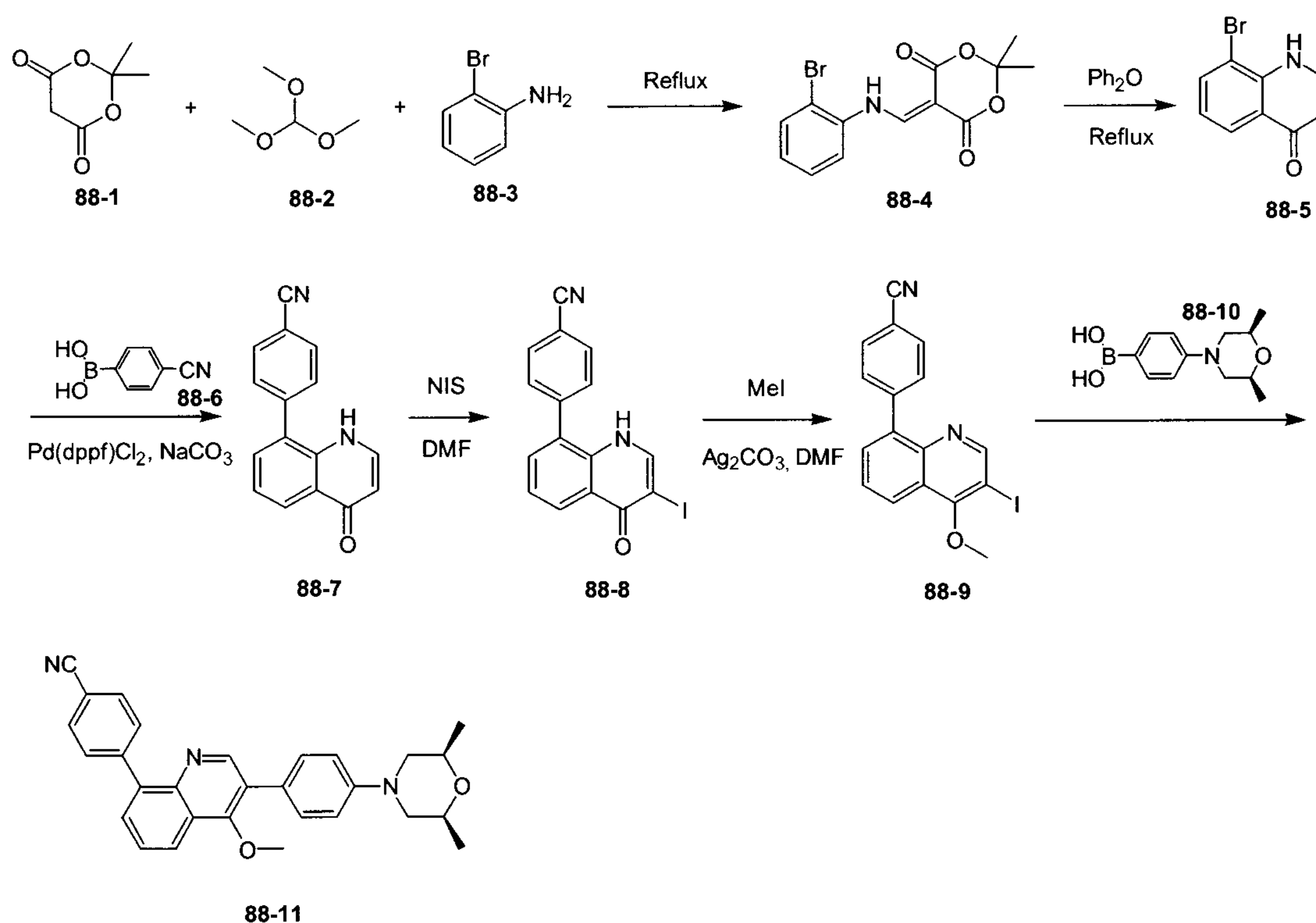
[278] Step 2: Compound 87-3 (150mg, yield 30%) as white-off solid was synthesized according to the method previously described. **MS ESI** calcd for $C_{22}H_{26}N_2O_3$ $[M+H]^+$ 499, found 499.

[279] Step 3: The title compound as white solid was synthesized according to the method previously described. **¹H NMR** (400 MHz, $CDCl_3$) δ 8.25 (d, $J = 7.6$ Hz, 1H), 7.78 (d, $J = 8.4$ Hz, 2H), 7.35-7.56 (m, 8H), 4.33 (dd, $J = 8.4, 3.6$ Hz, 1H), 4.06-4.16 (m, 2H), 3.50-3.57 (m, 3H), 3.07-3.16 (m, 1H), 2.75-2.85 (m, 2H), 1.31 (s, 3H), 1.30 (s, 3H), 1.24 (d, $J = 6.8$ Hz, 1H). **MS ESI** calcd for $C_{29}H_{29}N_3O_2$ $[M+H]^+$ 452, found 452.

Embodiment 88



4-(3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxyquinolin-8-yl)benzonitrile



[280] Step 1: Compound 88-1 (50 g, 350 mmol) was added into compound 88-2 (170 mL, 1 mol), then the reaction system was heated to reflux for 3 h. After the reaction system was cooled to room temperature, compound 88-3 (48 g, 280mmol) was added. The reaction mixture was stirred for 12 h, monitored by LC-MS until the reaction was complete. Then the system was concentrated, the residue was washed with MeOH, dried to deliver light yellow compound 88-4 (80 g, 90%). **MS ESI** calcd for $C_{13}H_{12}BrNO_4$ $[M+H]^+$ 326, found 326.

[281] Step 2: Compound 88-4 (80 g, 245 mmol) was dissolved in Ph_2O (560 mL), then the mixture was heated to reflux for 1h. After the reaction was complete as monitored by LC-MS, 560 mL *n*-hexane was added into the solution in portions to deliver the product. The product was washed with *n*-hexane, dried under reduced pressure to deliver compound 88-5 (48 g, 87%) as gray solid. **MS ESI** calcd for C_9H_6BrNO $[M+H]^+$ 225, found 225.

[282] Step 3: Compound 88-5 (20 g, 89 mmol), compound 88-6 (14.4 g, 98 mmol), $Pd(dppf)Cl_2$ (6.5 g, 8.9 mmol) and Na_2CO_3 (18.8 g, 178 mmol) were dissolved in DMF (200 mL), and 40 mL H_2O was added into the solution. The reaction system

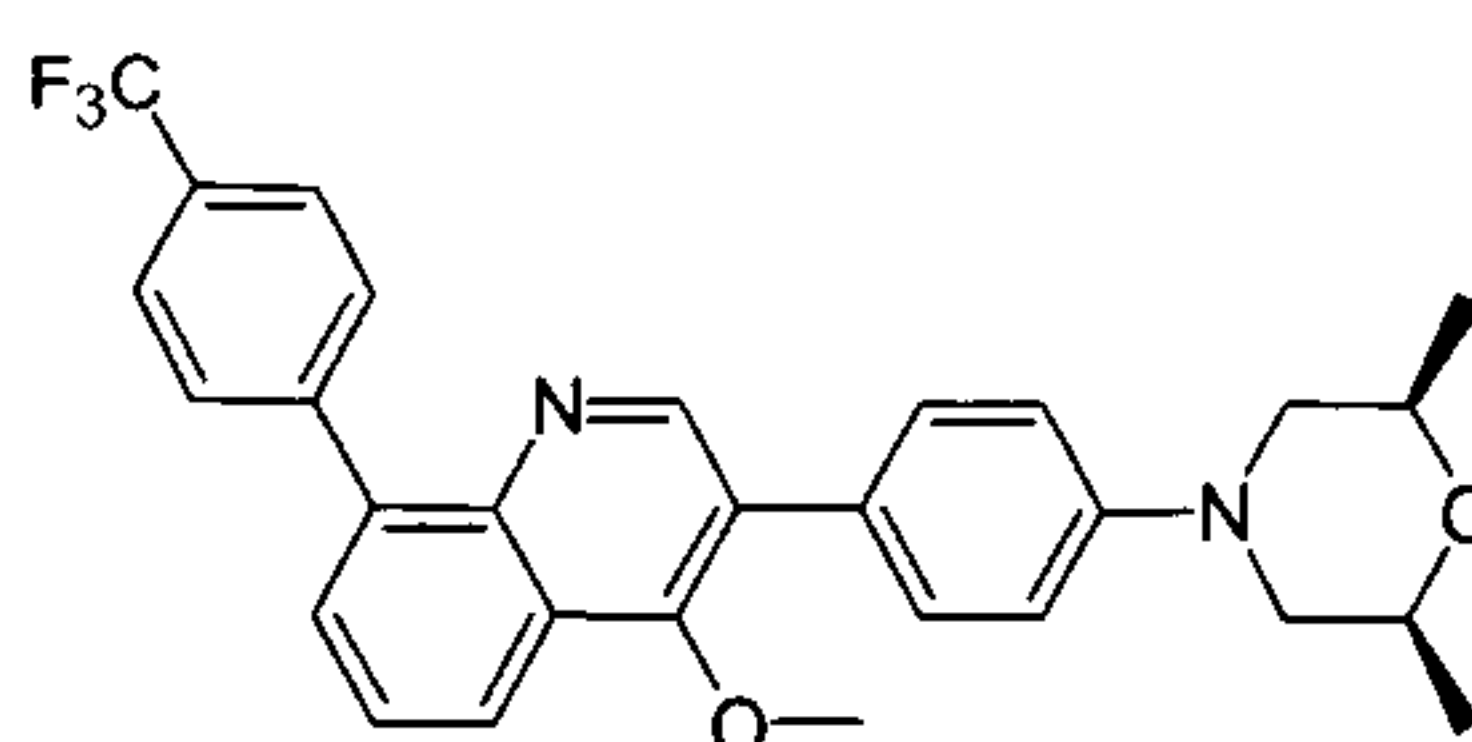
reacted at 90°C overnight. After the reaction was complete as monitored by LC-MS, the reaction system was poured into 500 mL H₂O, filtrated to deliver brown solid (19 g, 87%). **MS ESI** calcd for C₁₆H₁₀N₂O [M+H]⁺ 247, found 247.

[283] Step 4: NIS (17.4 g, 77.2 mmol) was added into a solution of 88-7 (19 g, 77.2 mmol) in DMF (200 mL) in portions. The reaction system was stirred at room temperature for 3h. The reaction was monitored by LC-MS and TLC until completion. The solution was poured into H₂O (500 mL), filtrated to deliver brown residue. The residue was washed with MeOH, and recrystallized with PE:EtOAc = 1:1 to deliver the target compound 88-8 (25 g, 87%) as brown solid. **MS ESI** calcd for C₁₆H₉IN₂O [M+H]⁺ 373, found 373.

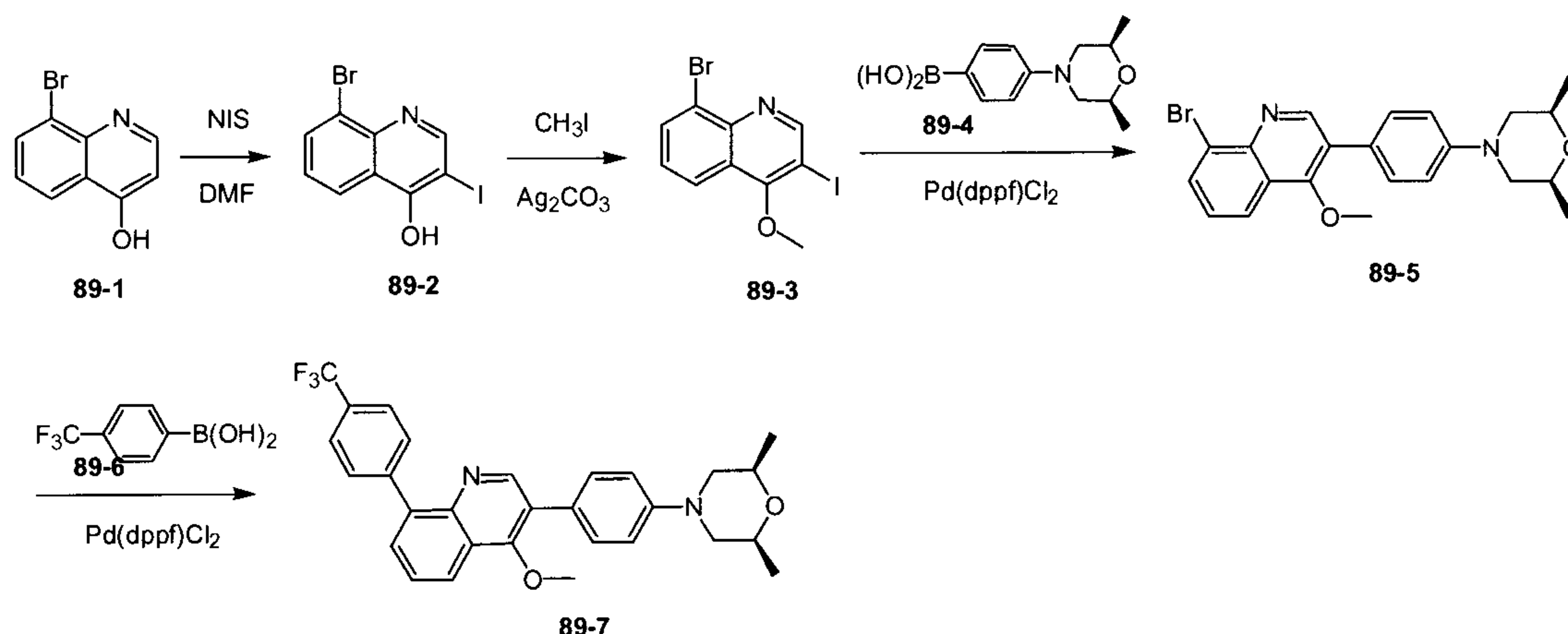
[284] Step 5: Compound 88-8 (15 g, 40.3 mmol) and Ag₂CO₃ (25 g, 80.6 mmol) were dissolved in DMF (150 mL). Then MeI (3.8 mL, 60.5 mmol) was added into the reaction system. The reaction was stirred at 80°C for 3h. The reaction was monitored by LC-MS until completion, the reaction mixture was added into H₂O and extracted with EtOAc. The organic phases were combined and washed with brines, dried over anhydrous sodium sulfate, filtrated and concentrated to dry. The crude product was purified by column chromatography (PE: EtOAc = 10:1) to deliver white compound 88-9 (3 g, 19%). **MS ESI** calcd for C₁₇H₁₁IN₂O [M+H]⁺ 387, found 387.

[285] Step 5: Compound 88-9 (200 mg, 0.52 mmol), compound 88-13 (246 mg, 1.04 mmol), Pd(dppf)Cl₂ (38 mg, 0.052 mmol) and Na₂CO₃ (110 mg, 1.04 mmol) were dissolved in THF (5 mL) and H₂O (1 mL). The mixture was stirred at 60°C overnight. The reaction was monitored by LC-MS until completion. The reaction system was extracted with EtOAc, the organic phases were combined and washed with brines, dried over anhydrous sodium sulfate, filtrated concentrated, the crude product was purified by preparative chromatography to deliver the title compound as light yellow solid (23 mg, yield 10%). **¹H NMR** (400 MHz, CDCl₃) δ 8.89 (s, 1H), 8.33-8.31 (m, 1H), 7.84-7.56 (m, 8H), 7.04 (d, *J* = 8.8Hz, 2H), 3.86-3.82 (m, 2H), 3.70 (s, 3H), 3.57 (d, *J* = 11.2Hz, 2H), 2.51 (t, *J* = 11.2Hz, 2H), 1.30 (d, *J* = 6.0Hz, 6H). **MS ESI** calcd for C₂₉H₂₇N₃O₂ [M+H]⁺ 450, found 450.

Embodiment 89



(2R,6S)-4-(4-(4-methoxy-8-(4-(trifluoromethyl)phenyl)quinolin-3-yl)phenyl)-2,6-dimethylmorpholine



[286] Step 1: NIS (3.8 g, 22 mmol) was added into a solution of compound 89-1 (4.9 g, 22 mmol) in DMF (40 mL) in portions. The reaction mixture was stirred at room temperature for 2h. After the reaction was complete as detected by LC-MS, the reaction mixture was poured into H₂O (500 mL). The product 89-2 was obtained by filtration (5.5 g, 71%) as brown solid. **MS ESI** calcd for C₉H₅BrINO [M+H]⁺ 350, found 350.

[287] Step 2: CH₃I (1.2 g, 8.7 mmol) was added into a solution of compound 89-2 (2.0 g, 5.8 mmol) and Ag₂CO₃ (2.4 g, 8.7 mmol) in DMF (20 mL). The reaction mixture was stirred at 60 °C for 2 h. After the reaction was complete as detected by LC-MS, the reaction mixture was poured into H₂O, then extracted with EtOAc (80×3 mL), the organic phase was dried over anhydrous sodium sulfate. After concentration, the crude product was further purified by column chromatography (PE: EtOAc=5:1) to deliver compound 89-3 (464 mg, 22%) as white solid. **MS ESI** calcd for C₁₀H₇BrINO [M+H]⁺ 364, found 364.

[288] Step 3: Compound 89-3 (1089 mg, 3 mmol), compound 89-4 (1050 mg, 3.3 mmol), Pd(dppf)Cl₂ (110 mg, 0.15 mmol) and Na₂CO₃ (636 mg, 6 mmol) were added into THF (20 mL) / H₂O (2 mL), under nitrogen gas atmosphere, the reaction mixture was stirred at 60°C overnight. After the reaction was complete, the mixture was filtrated, the filtrate was extracted with EtOAc, the organic phase was washed with brines, dried over anhydrous sodium sulfate, concentrated under reduced pressure to deliver crude product 4 (140 mg, 11%) as white solid. **MS ESI** calcd for C₂₂H₂₃BrN₂O₂ [M+H]⁺ 427, found 427.

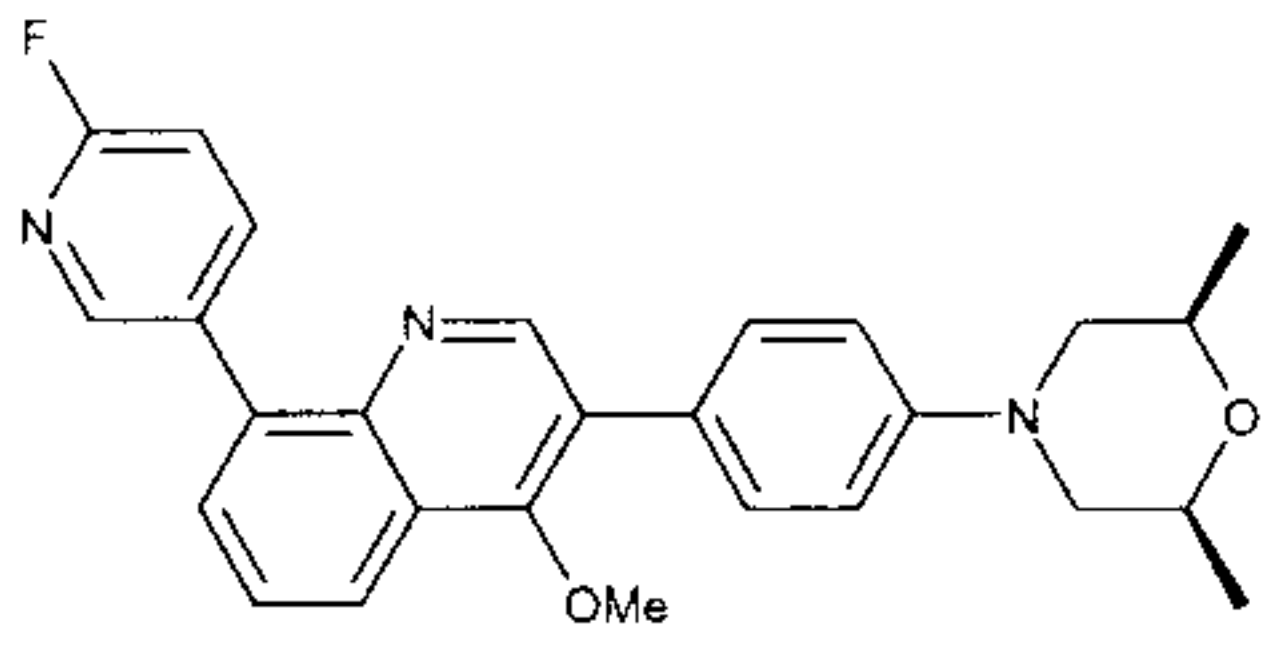
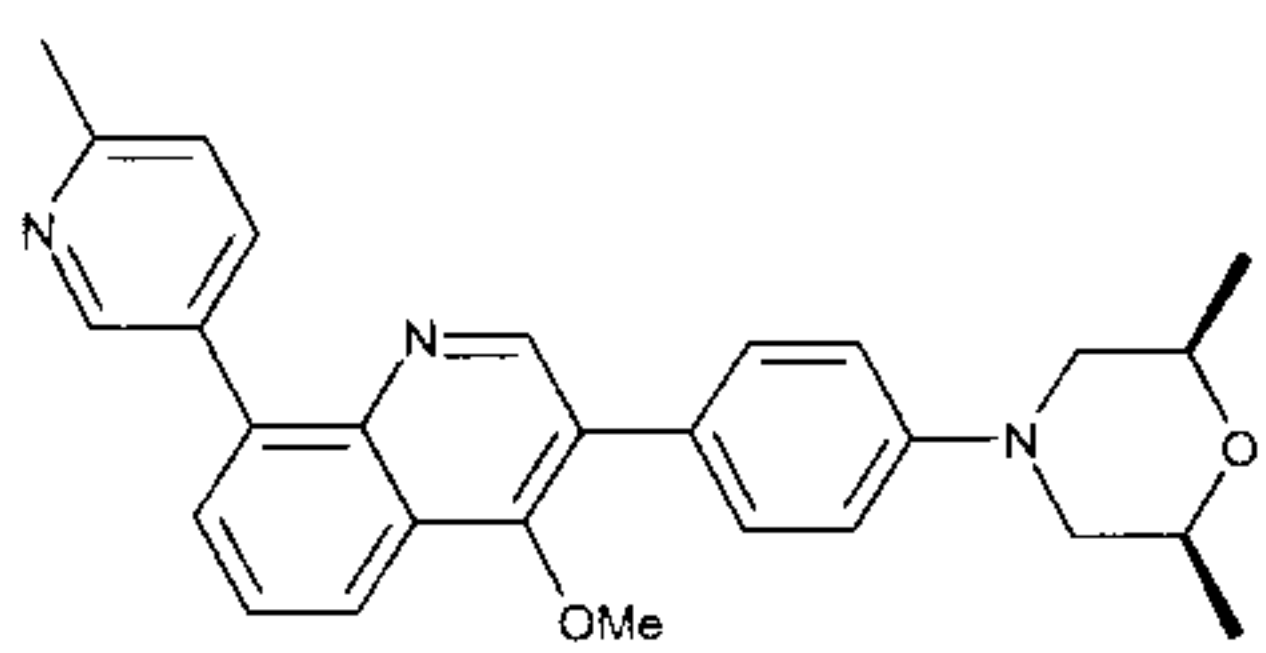
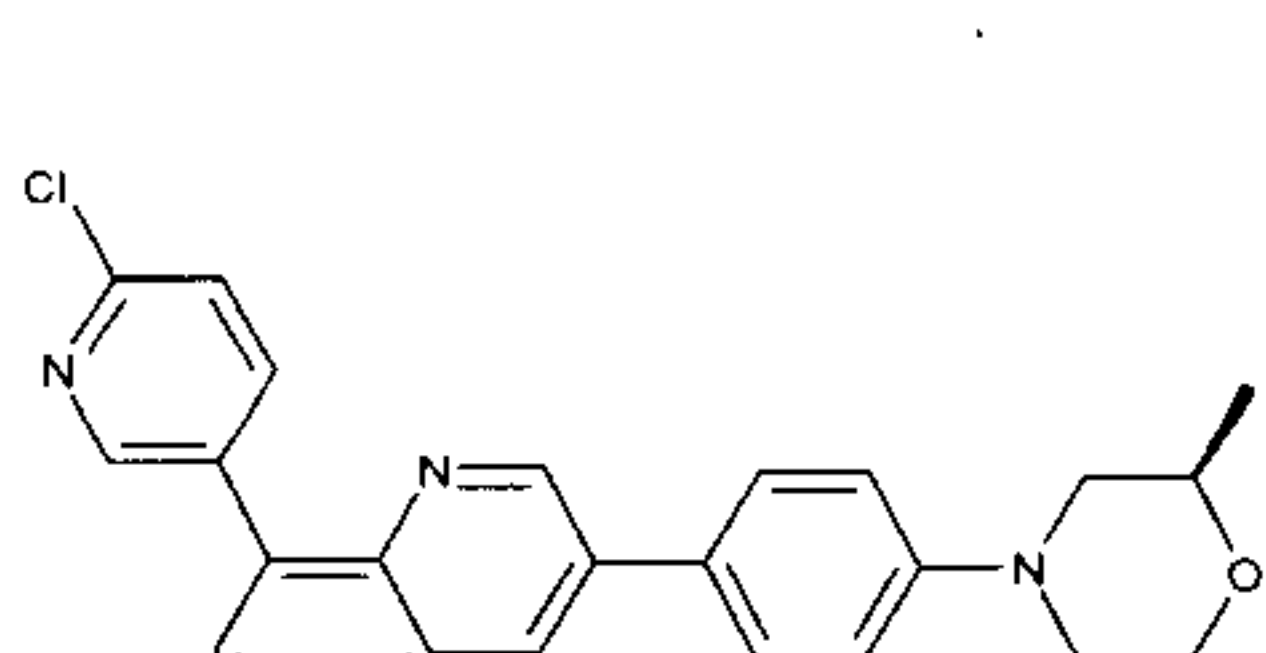
[289] Step 4: Compound 89-5 (70 mg, 0.16 mmol), compound 89-6 (46 mg, 0.24 mmol) were added into a solution of Pd(dppf)Cl₂ (15mg, 0.02 mmol), Na₂CO₃ (34mg, 0.32 mmol) in THF (10 mL) / H₂O (1 mL), under nitrogen gas atmosphere, the reaction mixture was stirred at 80°C overnight. After the reaction was complete, the mixture was filtrated, the filtrate was extracted with EtOAc, the organic phase was washed with brines, dried over anhydrous sodium sulfate, concentrated under reduced pressure to deliver the title compound (35 mg, 45%) as light yellow solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.91 (s, 1H), 8.32-8.30 (m, 1H), 7.83-7.57 (m, 8H), 7.04 (d, J= 8.8Hz, 2H), 3.84-3.83 (m, 2H), 3.71 (s, 3H), 3.57 (d, J= 11.2Hz, 2H), 2.51 (t, J=

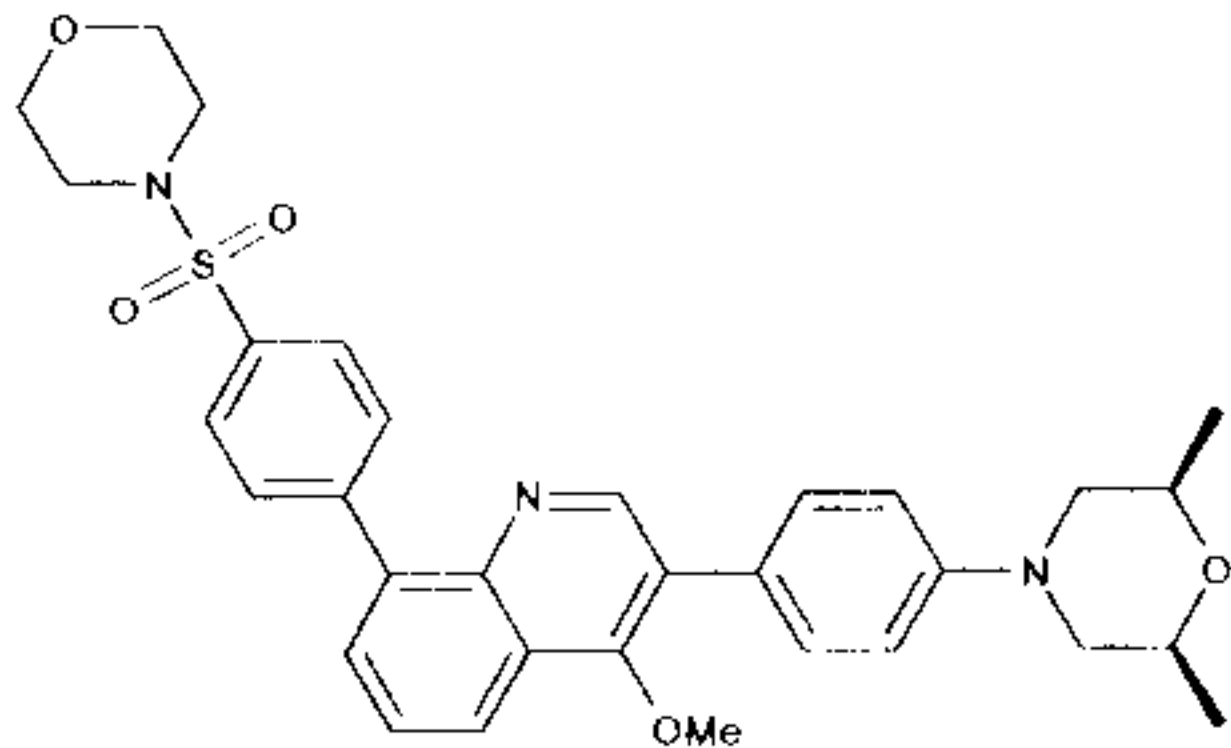
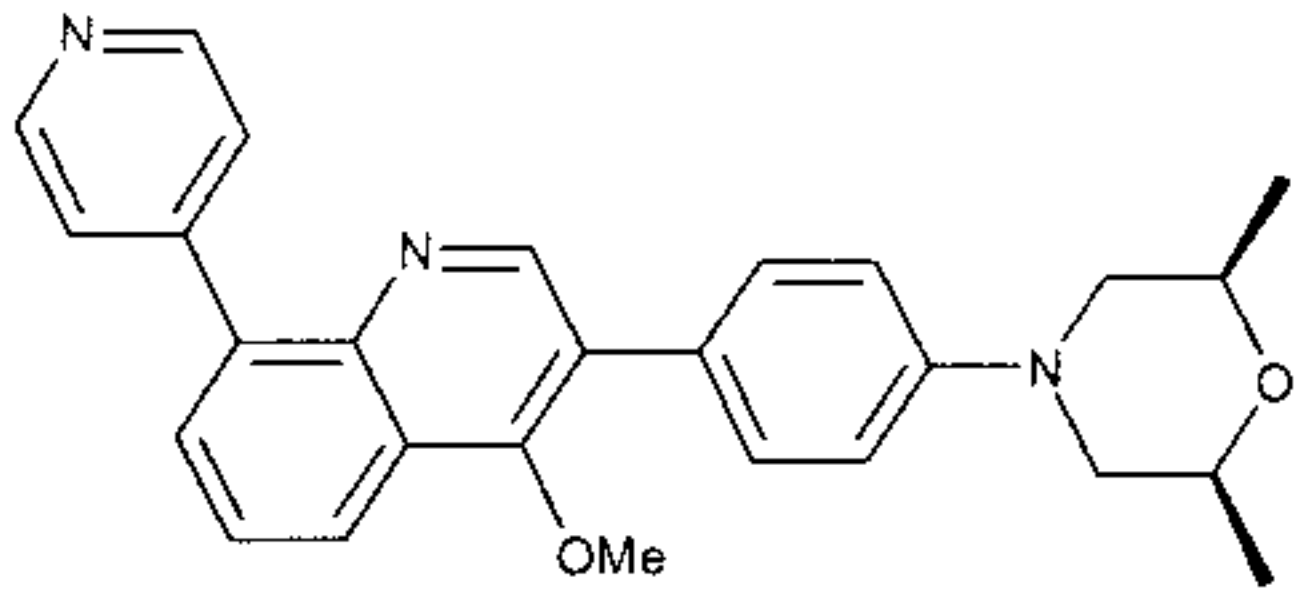
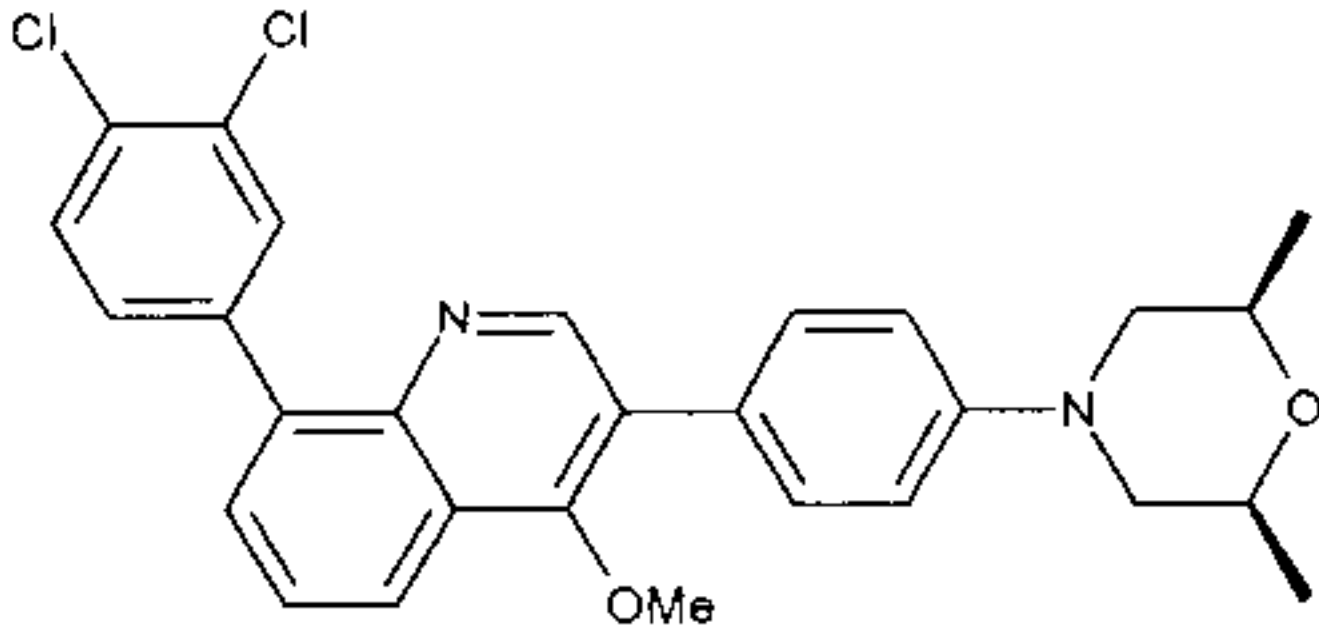
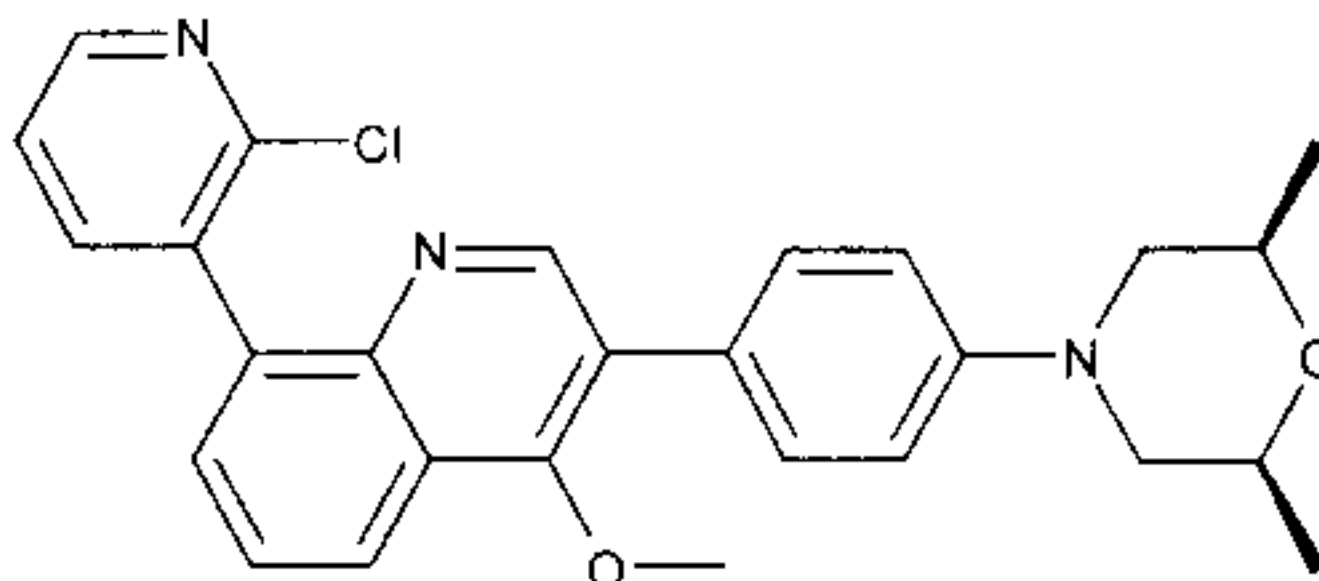
Our Ref.: P1650132CA

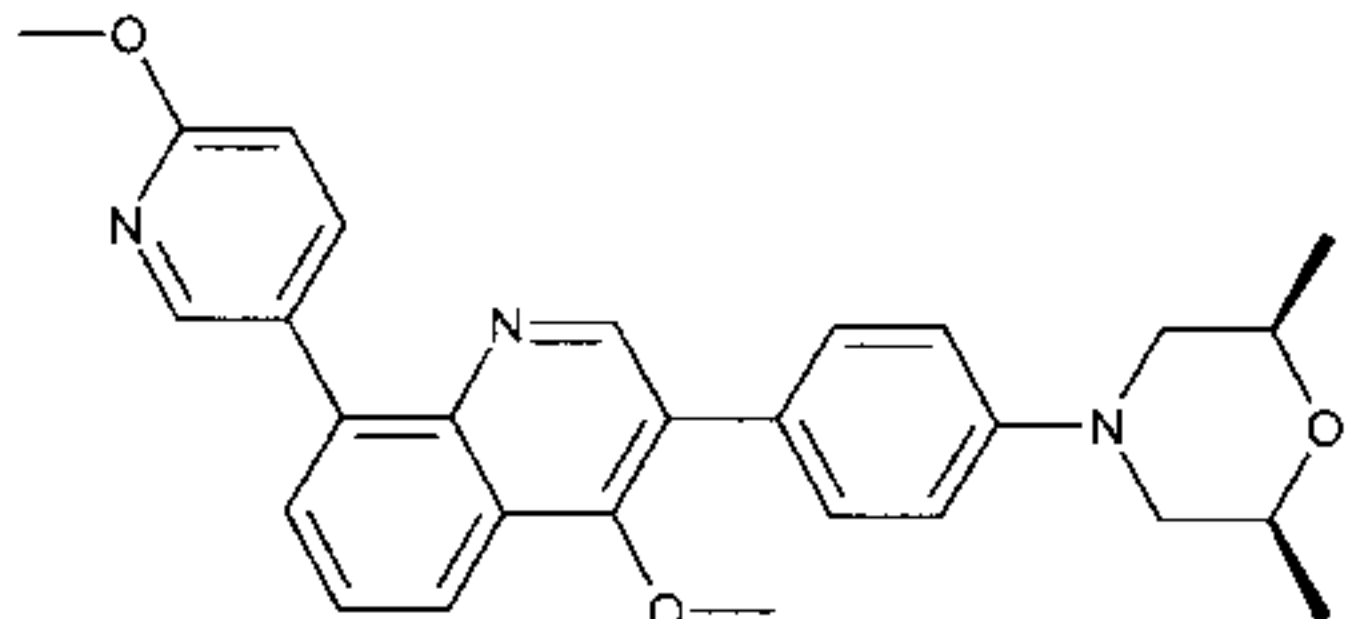
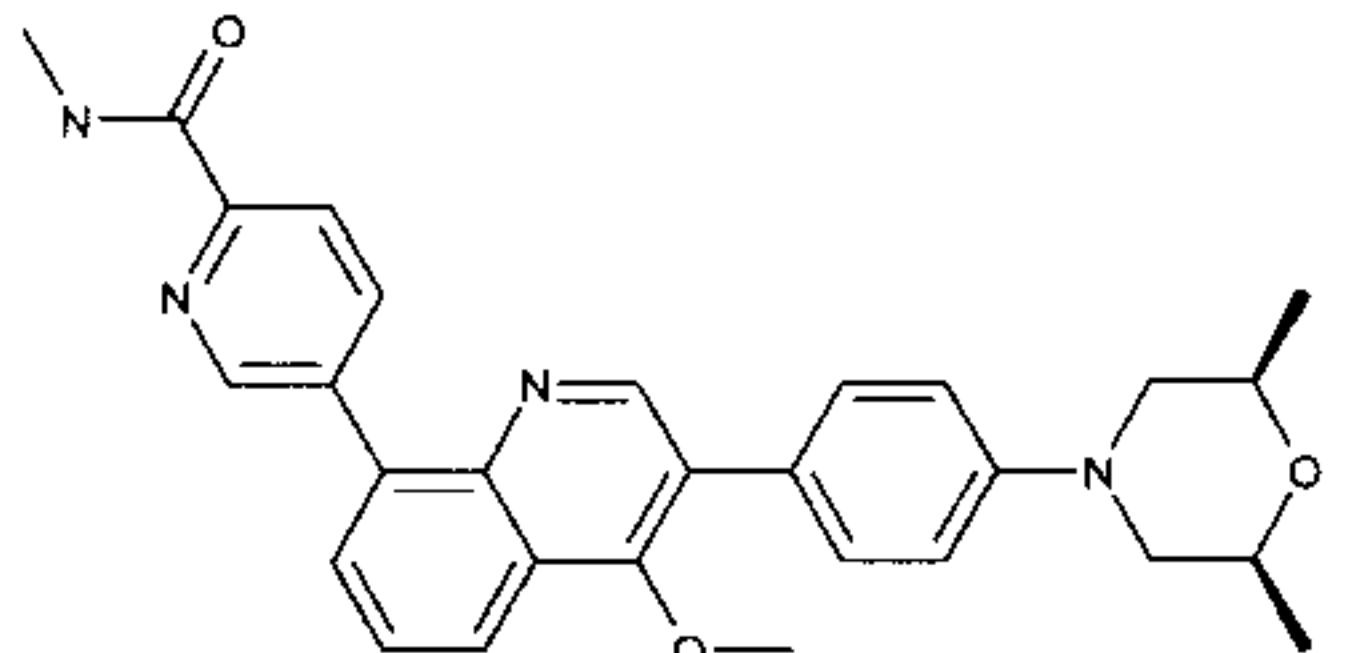
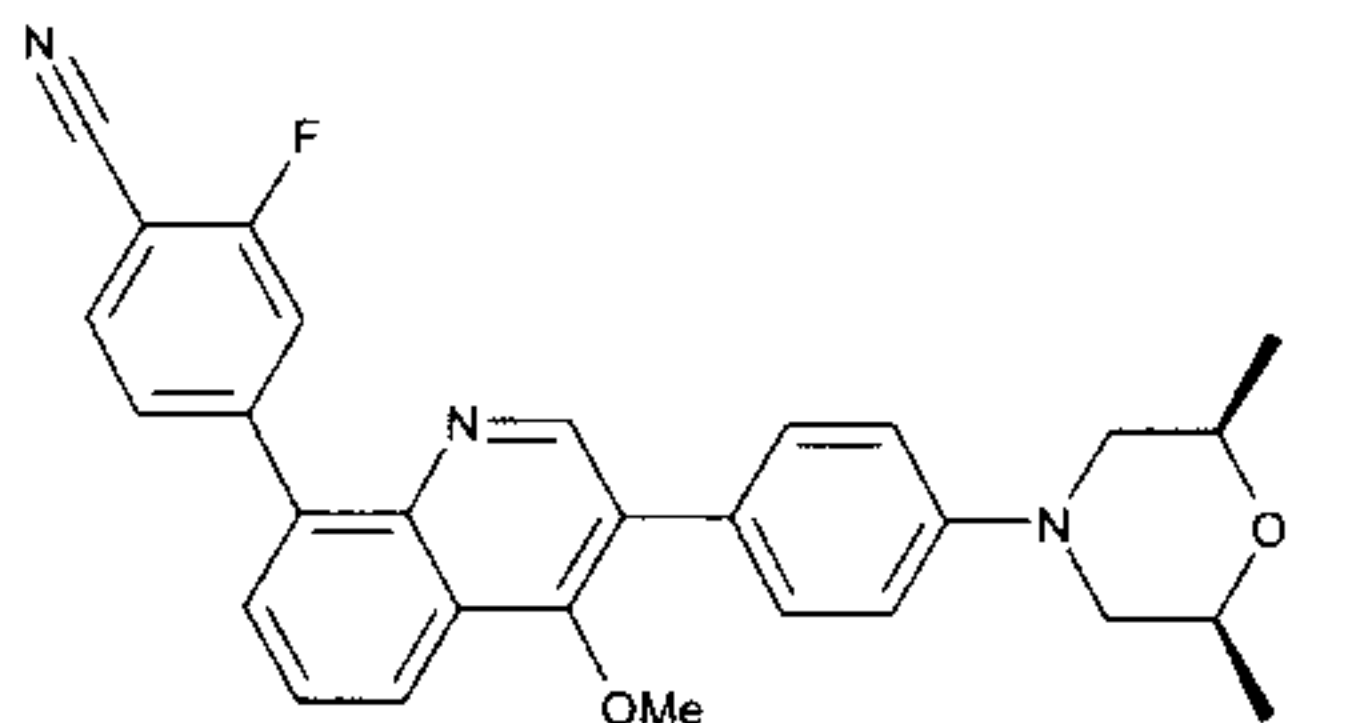
11.2Hz, 2H), 1.30 (d, J = 6.0Hz, 6H). **MS ESI** calcd for $C_{29}H_{27}F_3N_2O_2$ $[M+H]^+$ 493, found 493.

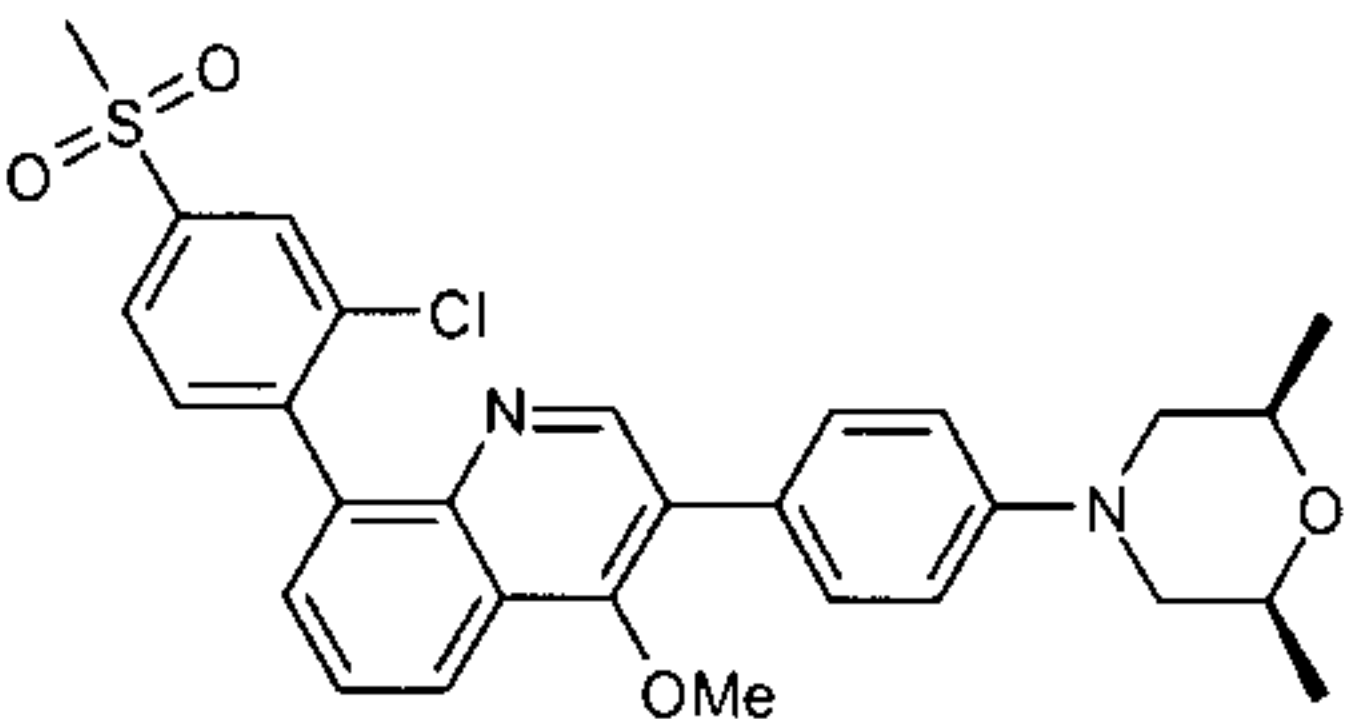
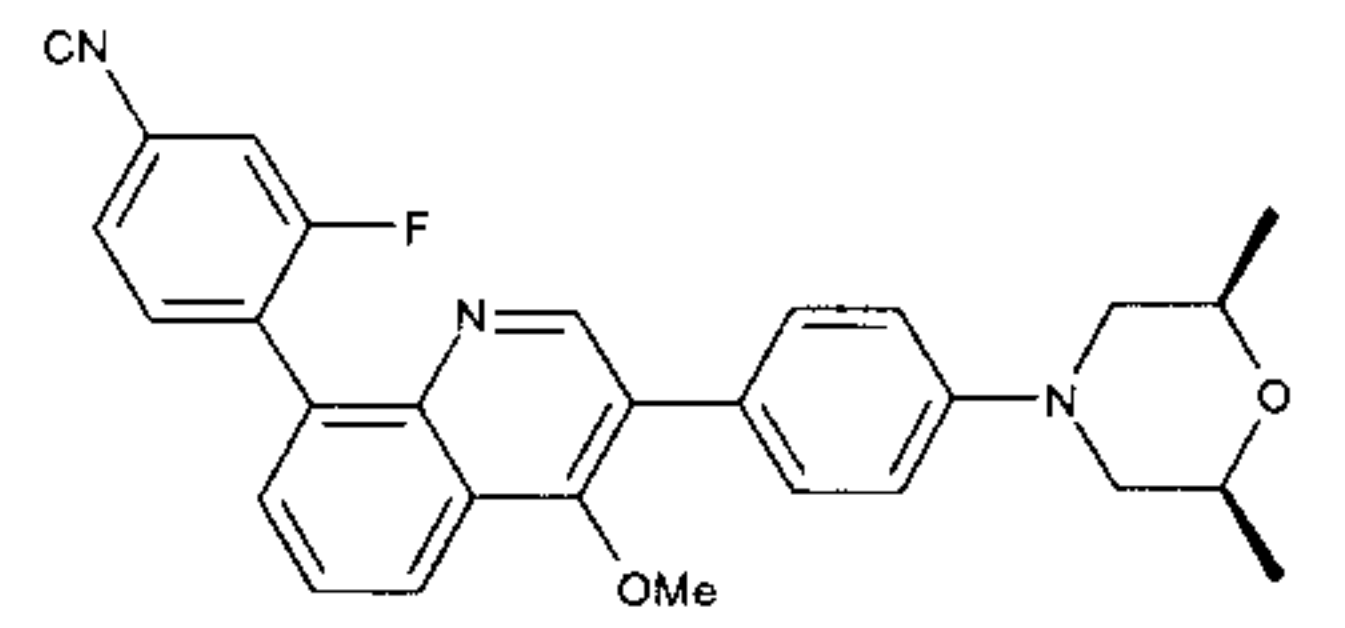
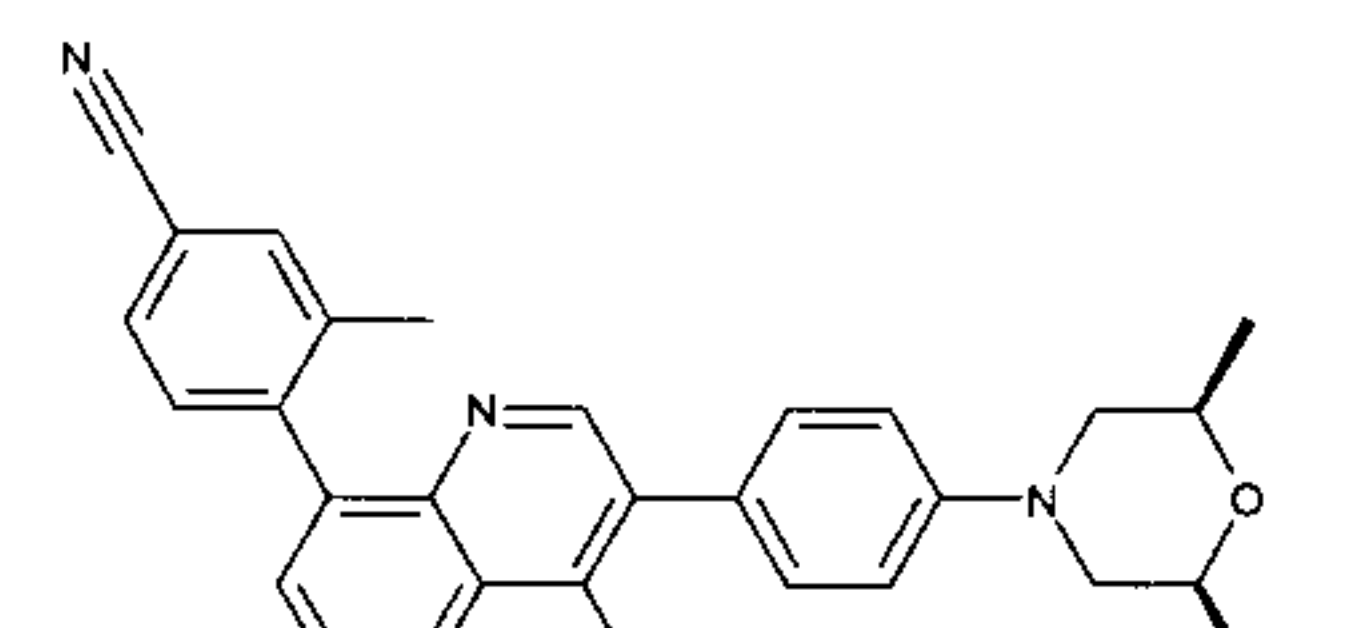
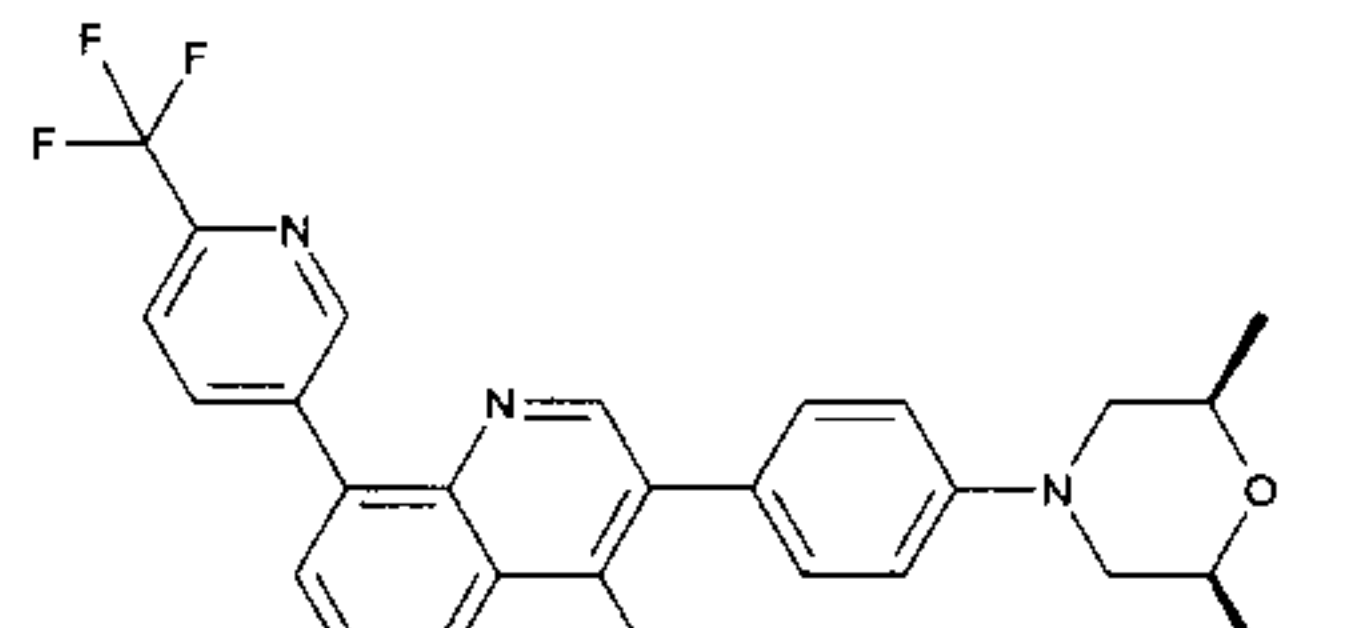
[290] The compounds listed in table 7 were synthesized by compound 89-5 and corresponding boric acids.

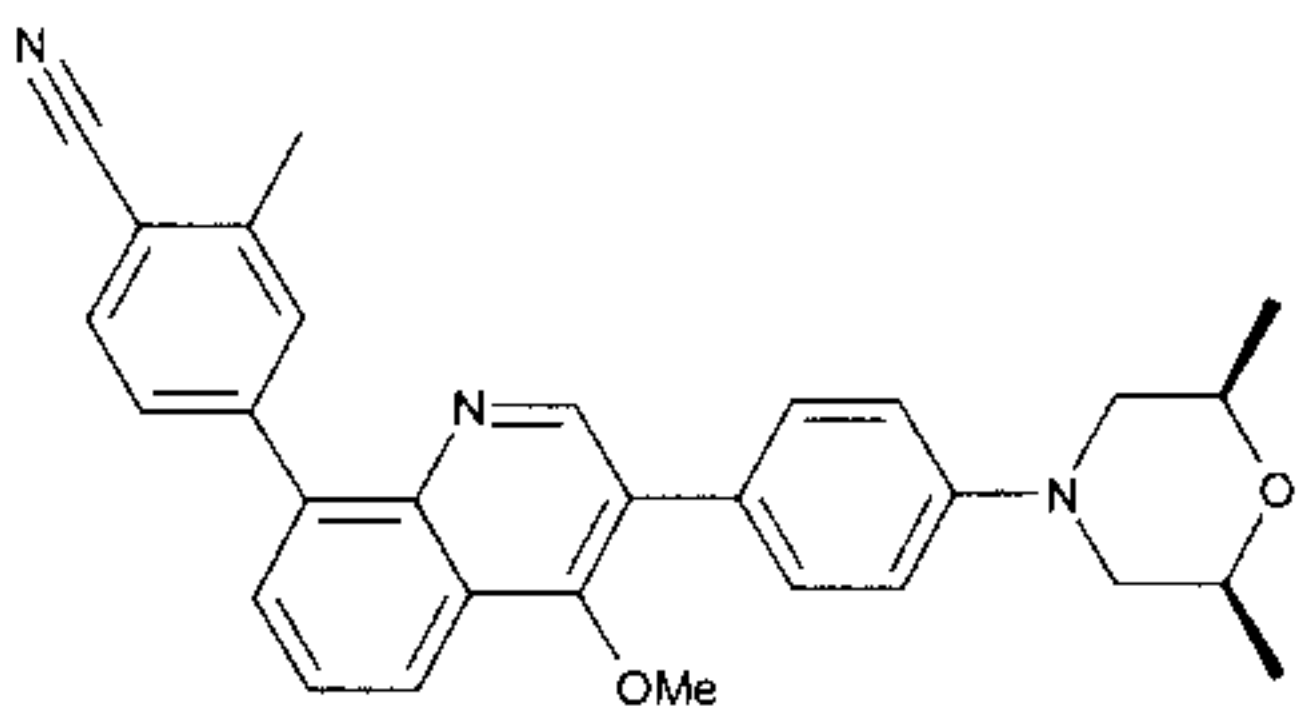
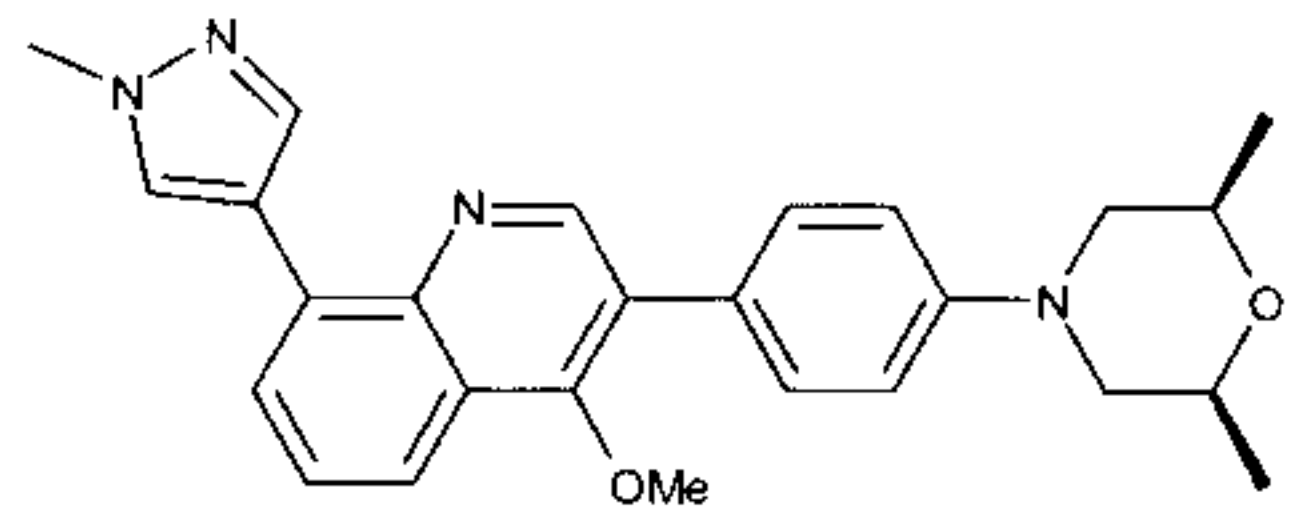
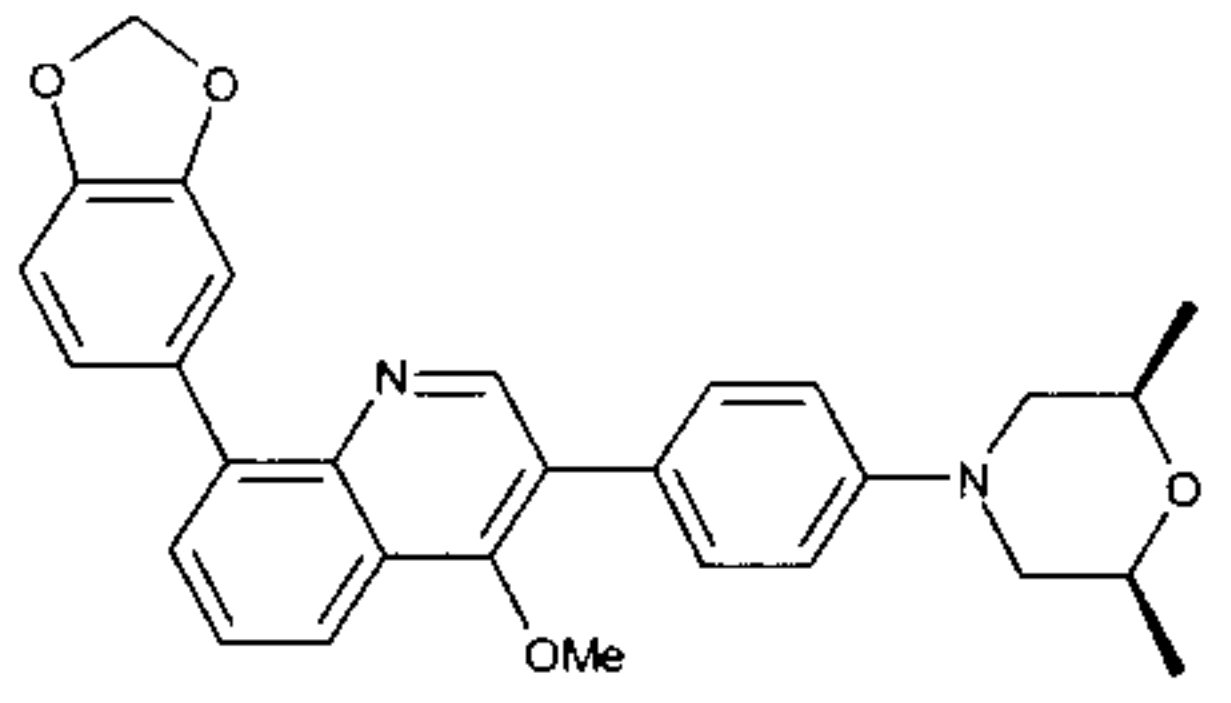
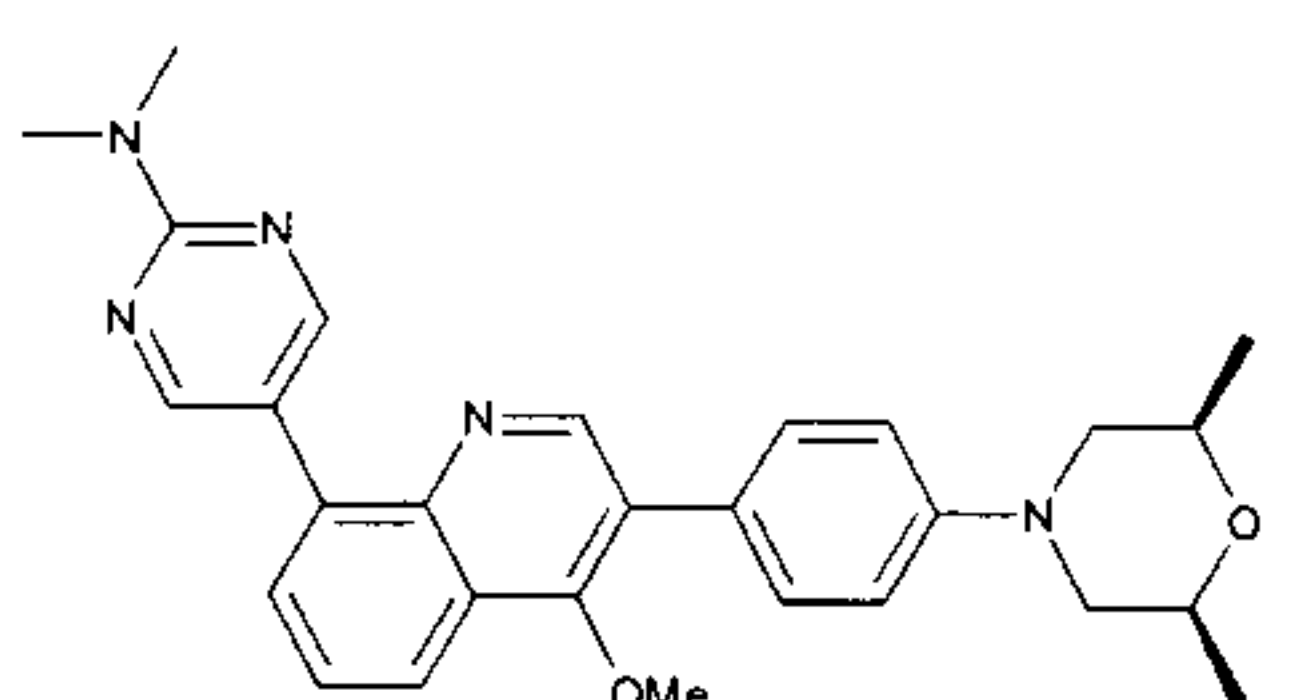
Embodiment	Structure	NMR
90		^1H NMR (400MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.30-8.28 (m, 1H), 7.80-7.58 (m, 6H), 7.24 (s, 1H), 7.06-7.03 (d, J = 12Hz, 2H), 3.87-3.83 (m, 2H), 3.71 (s, 3H), 3.60-3.57 (d, J = 12Hz, 2 H), 2.55-2.49 (m, 2H), 1.32-1.30 (d, J = 8Hz, 6H). MS ESI calcd for $C_{28}H_{26}ClFN_2O_2$ $[M+H]^+$ 477, found 477.
91		^1H NMR (400MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.30-8.28 (d, J = 8Hz, 1H), 7.77-7.60 (m, 6H), 7.58-7.34 (m, 2H), 7.06-7.03 (d, J = 12Hz, 2H), 3.87-3.85(d, J = 8Hz, 2 H), 3.71 (s, 3H), 3.60-3.57 (d, J = 12Hz, 2 H), 2.55-2.49 (m, 2H), 1.32-1.30 (d, J = 8Hz, 6H). MS ESI calcd for $C_{29}H_{27}F_3N_2O_3$ $[M+H]^+$ 509, found 509.
92		^1H NMR (400MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.36 (m, 1H), 8.09-8.07 (m, 2H), 7.96-7.94 (d, J =8.5Hz, 2H), 7.74-7.60 (m, 3H), 7.07-7.05 (d, J =8.8Hz, 2H), 3.88-3.84 (m, 2H), 3.74 (s, 2H), 3.61-3.58 (m, 2H), 3.15 (s, 3H), 2.56-2.50 (m, 2H) 1.32-1.31 (m, 6H). MS ESI calcd for $C_{28}H_{28}N_2O_3S$ $[M+H]^+$ 473, found 473.

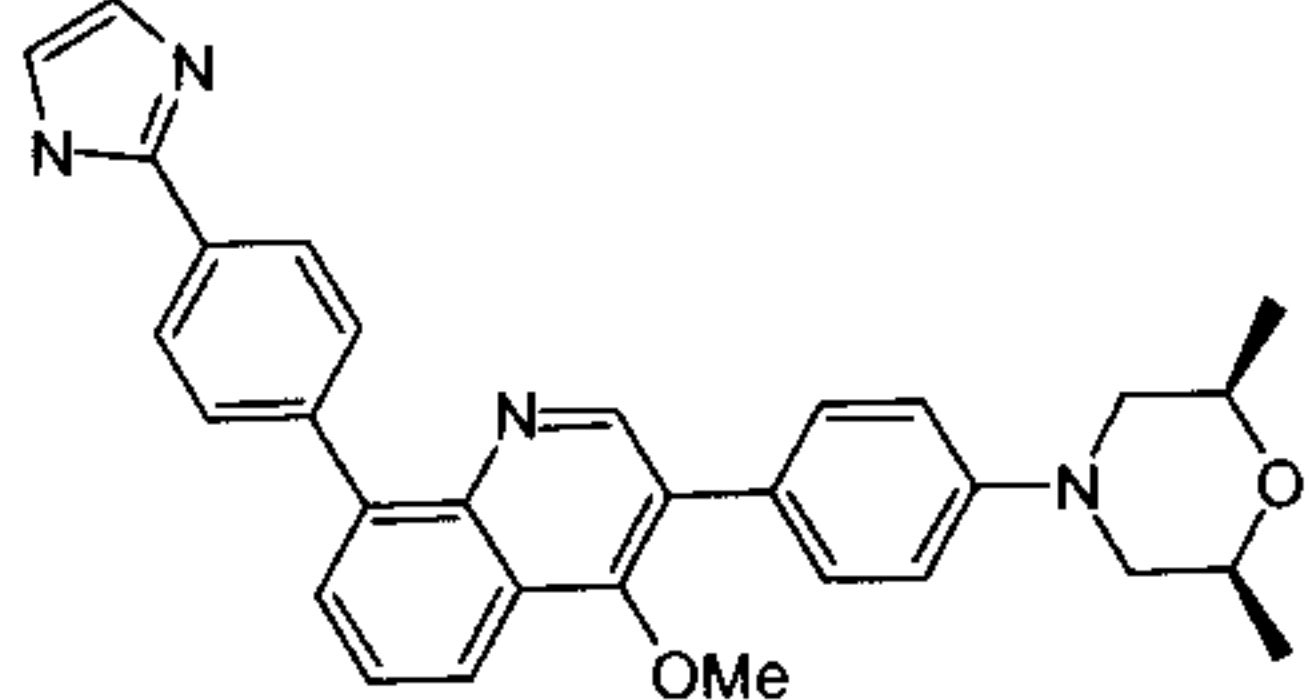
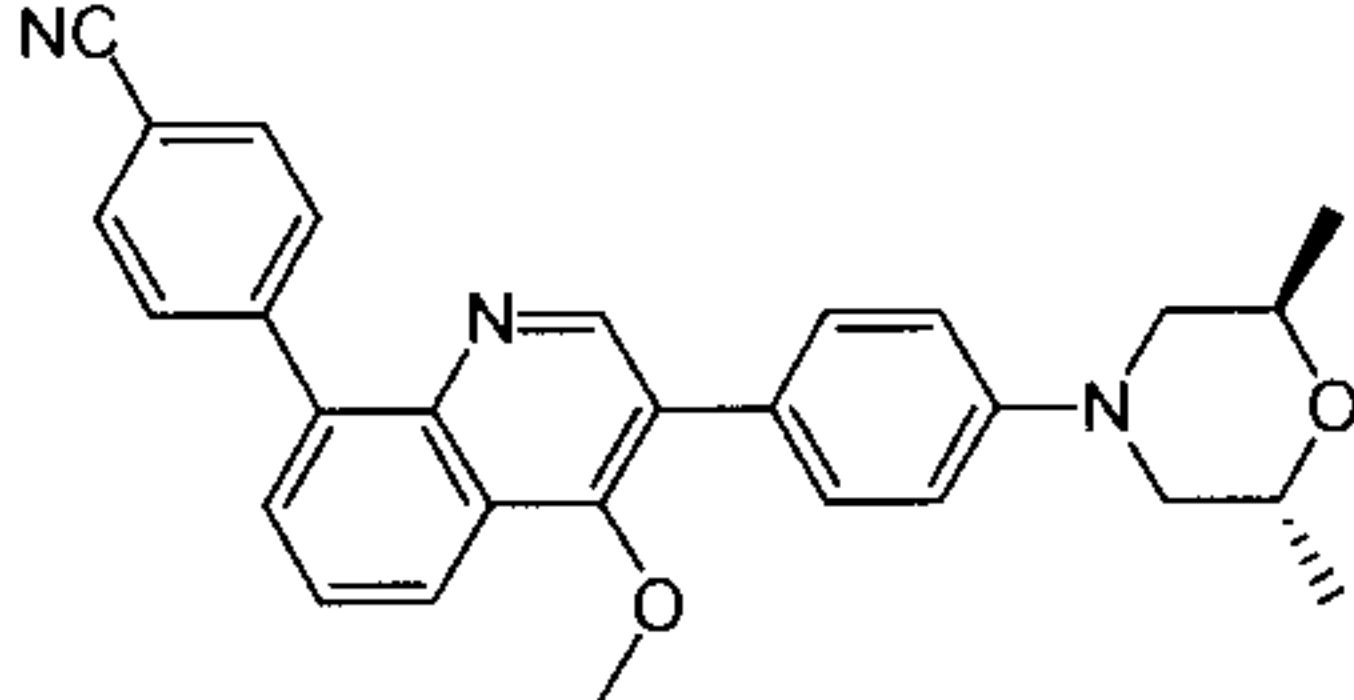
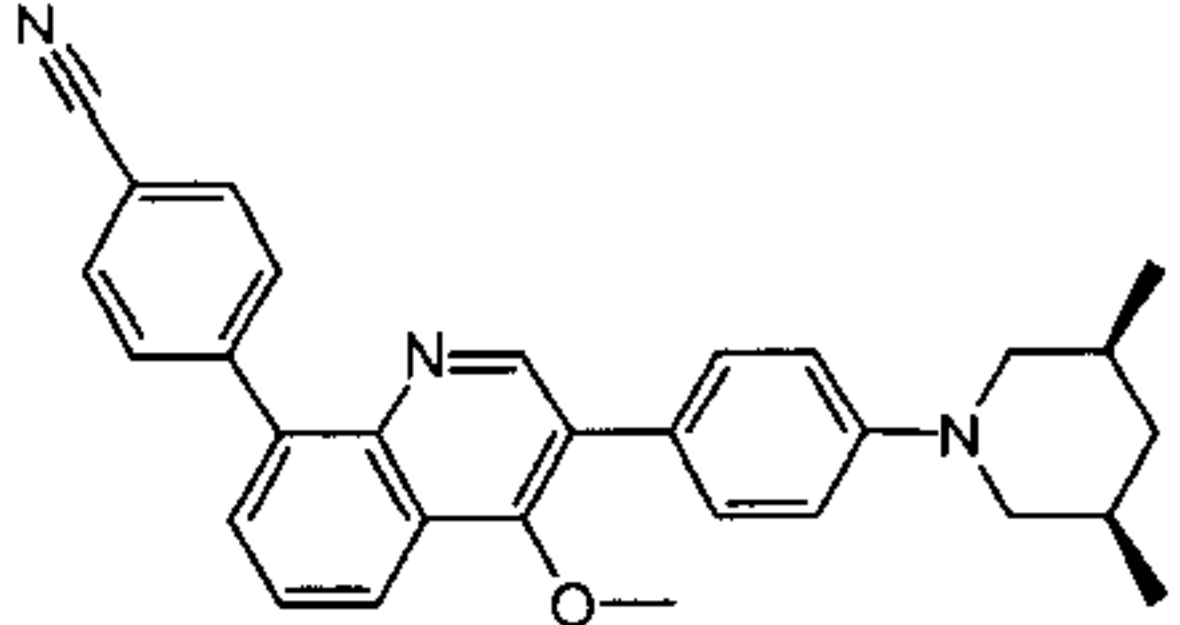
93		¹H NMR (400MHz, CDCl₃) δ 8.89 (s, 1H), 8.52 (d, <i>J</i>=2.0Hz, 1H), 8.32 (dd, <i>J</i>=1.4, 8.2Hz, 1H), 8.23 (dt, <i>J</i>=2.4, 8.1Hz, 1H), 7.75-7.69 (m, 1H), 7.68-7.62 (m, 1H), 7.59 (d, <i>J</i>=8.8Hz, 2H), 7.12-6.98 (m, 3H), 3.91-3.76 (m, 2H), 3.71 (s, 3H), 3.58 (d, <i>J</i>=11.0Hz, 2H), 2.52 (t, <i>J</i>=11.2Hz, 2H), 1.35-1.21 (m, 6H). MS ESI calcd for C₂₇H₂₆FN₃O₂ [M+H]⁺ 444, found 444.
94		¹H NMR (400MHz, CDCl₃) δ 8.91 (s, 1H), 8.83 (d, <i>J</i>=1.8Hz, 1H), 8.35-8.28 (m, 1H), 8.02 (dd, <i>J</i>=2.1, 7.9Hz, 1H), 7.73 (d, <i>J</i>=5.8Hz, 1H), 7.70-7.57 (m, 2H), 7.32 (d, <i>J</i>=8.0Hz, 1H), 7.06 (d, <i>J</i>=8.8Hz, 1H), 3.89-3.82 (m, 1H), 3.73 (s, 2H), 3.59 (d, <i>J</i>=10.8Hz, 1H), 2.67 (s, 2H), 2.53 (t, <i>J</i>=11.2Hz, 1H), 1.32 (d, <i>J</i>=6.3Hz, 6H). MS ESI calcd for C₂₈H₂₉N₃O₂ [M+H]⁺ 440, found 440.
95		¹H NMR (400MHz, CDCl₃) δ 8.89 (s, 1H), 8.70 (s, 1H), 8.34-8.32 (d, <i>J</i> = 7.9 Hz, 1H), 8.11-8.09 (d, <i>J</i> = 7.1 Hz, 1H), 7.72-7.71 (d, <i>J</i> = 5.7 Hz, 1H), 7.67-7.65 (d, <i>J</i> = 7.5 Hz, 1H), 7.59(s, 1H), 7.57 (s, 2H), 7.47-7.45 (d, <i>J</i> = 7.9 Hz, 1 H), 7.05-7.03(d, <i>J</i> = 7.5 Hz, 2H), 3.85 (s, 2H), 3.71(s, 3H), 3.59-3.57 (d, <i>J</i> = 11.5 Hz, 2H), 2.54-2.49 (t, 2H), 1.31-1.30 (d, <i>J</i> = 5.3 Hz, 6H). MS ESI calcd for C₂₇H₂₆ClN₃O₂ [M+H]⁺ 460, found 460.

96		¹H NMR (400MHz, CDCl₃) δ 8.91 (s, 1H), 8.35-8.32 (m, 1H), 7.94-7.87 (m, 4H), 7.73-7.71 (m, 1H), 7.86-7.64 (m, 1H), 7.60-7.58 (d, <i>J</i> = 8.5Hz, 2H), 7.06-7.04 (d, <i>J</i> = 8.5Hz, 2H), 3.85-3.79 (m, 6H), 3.72 (s, 3 H), 3.60-3.57 (d, <i>J</i> = 10.8Hz, 2H), 3.15-3.13 (m, 4H), 2.55-2.49 (m, 2H), 1.31-1.30 (d, <i>J</i> = 6.3Hz, 6H). MS ESI calcd for C₃₂H₃₅N₃O₅S [M+H]⁺ 574, found 574.
97		¹H NMR (400MHz, CDCl₃) δ 8.92-8.90 (d, <i>J</i> = 6.2Hz, 2H), 8.86 (s, 1H), 8.55-8.53 (m, 1H), 8.48-8.46 (d, <i>J</i> = 6.2Hz, 2H), 8.06-8.04 (d, <i>J</i> = 6.2Hz, 1H), 7.85-7.81 (m, 1H), 7.61-7.58 (d, <i>J</i> = 8.4Hz, 2H), 7.17-7.14 (d, <i>J</i> = 8.8Hz, 2H), 3.86-3.82 (m, 2H), 3.75 (s, 1H), 3.69-3.66 (d, <i>J</i> = 10.6Hz, 2H), 2.47-2.42 (t, 2H), 1.27-1.26 (m, 6H). MS ESI calcd for C₂₇H₂₇N₃O₂ [M+H]⁺ 426, found 426
98		¹H NMR (400MHz, CDCl₃) δ 8.91 (s, 1H), 8.30-8.28 (d, <i>J</i> = 8 Hz, 1H), 7.81 (s, 1H), 7.67-7.56 (m, 6H), 7.05-7.03 (d, <i>J</i> = 8Hz, 2H), 3.87-3.83 (m, 2H), 3.71 (s, 3H), 3.60-3.57 (d, <i>J</i> = 12Hz, 2H), 2.55-2.49 (m, 2H), 1.32-1.30 (d, <i>J</i> = 8Hz, 6H). MS ESI calcd for C₂₈H₂₆Cl₂N₂O₂ [M+H]⁺ 493, found 493.
99		¹H NMR (400MHz, CDCl₃) δ 8.87 (s, 1H), 8.50 (m, 1H), 8.37 (m, 1H), 7.82 (m, 1H), 7.68-7.58 (m, 3H), 7.40 (m, 1H), 7.05(d, <i>J</i>=8.8Hz, 2H) 3.88-3.84 (m, 2H), 3.74 (s, 2 H),

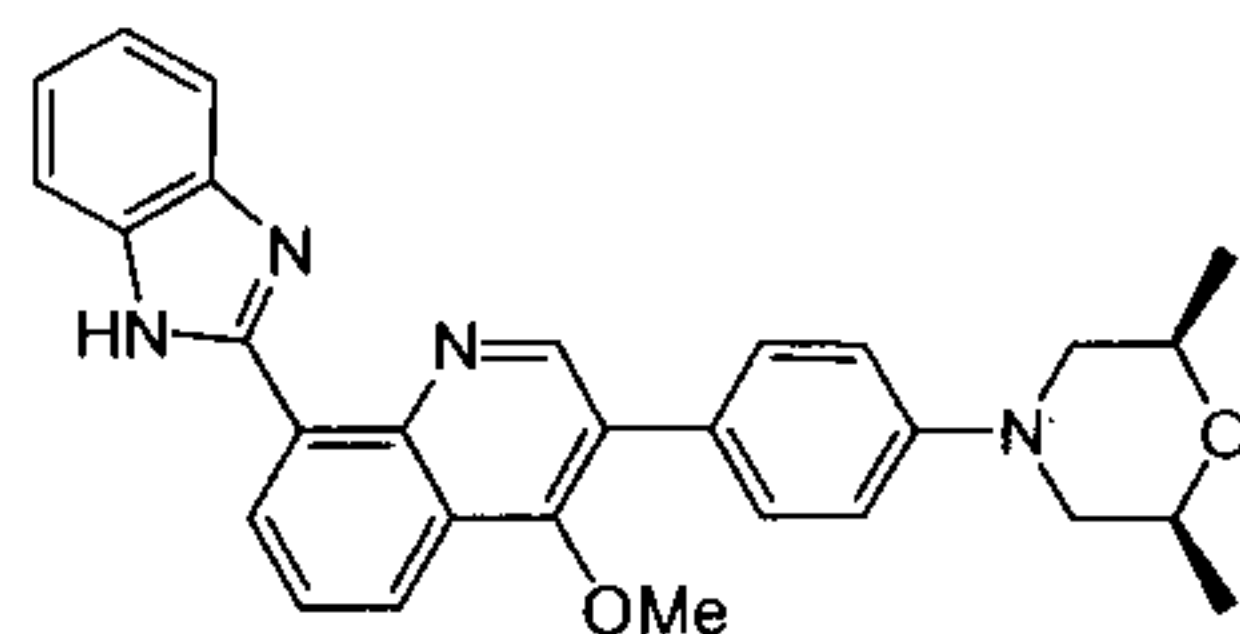
		3.61-3.58 (d, $J=10.5\text{Hz}$, 2H), 2.56-2.50 (m, 2H), 1.32-1.31 (m, 6H). MS ESI calcd for $\text{C}_{26}\text{H}_{24}\text{ClN}_3\text{O}$ $[\text{M}+\text{H}]^+$ 430, found 430.
100		^1H NMR (400MHz, CDCl_3) δ 8.90 (s, 1H), 8.50 (d, $J=2.0\text{Hz}$, 1H), 8.27 (d, $J=8.3\text{ Hz}$, 1H), 8.03 (dd, $J=2.0, 8.5\text{Hz}$, 1H), 7.73-7.67 (m, 1H), 7.67-7.54 (m, 3H), 7.04 (d, $J=8.8\text{Hz}$, 2H), 6.89 (d, $J=8.5\text{Hz}$, 1H), 4.03 (s, 3H), 3.86 (d, $J=7.8\text{Hz}$, 2H), 3.71 (s, 3H), 3.58 (d, $J=11.5\text{Hz}$, 2H), 2.52 (t, $J = 11.2\text{Hz}$, 2H), 1.31 (d, $J=6.3\text{Hz}$, 6H). MS ESI calcd for $\text{C}_{28}\text{H}_{29}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$ 456, found 456.
101		^1H NMR (400MHz, CDCl_3) δ 8.95-8.86 (m, 2H), 8.34 (dd, $J=4.6, 7.7\text{Hz}$, 2H), 8.22 (dd, $J=1.6, 7.9\text{Hz}$, 1H), 8.10 (d, $J=4.5\text{Hz}$, 1H), 7.75 (d, $J=6.3\text{Hz}$, 1H), 7.71-7.64 (m, 1H), 7.59 (d, $J=8.8\text{Hz}$, 2H), 7.05 (d, $J=8.8\text{Hz}$, 2H), 3.93-3.78 (m, 2H), 3.72 (s, 3H), 3.58 (d, $J=11.3\text{Hz}$, 2H), 3.09 (d, $J=5.0\text{Hz}$, 3H), 2.52 (t, $J=11.0\text{Hz}$, 2H), 1.31 (d, $J=6.3\text{Hz}$, 6H). MS ESI calcd for $\text{C}_{29}\text{H}_{30}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]^+$ 483, found 483.
102		^1H NMR (400MHz, CDCl_3) δ 8.89 (s, 1H), 8.36-8.33 (d, $J = 12\text{Hz}$, 1H), 7.72-7.60 (m, 7H), 7.04-7.02 (d, $J = 8\text{Hz}$, 2H), 3.86-3.82 (m, 2H), 3.75 (s, 3H), 3.59-3.56 (d, $J = 12\text{Hz}$, 2H), 2.54-2.49 (m, 2H), 1.31-1.29 (d, $J = 8\text{Hz}$, 6H). MS ESI calcd for $\text{C}_{29}\text{H}_{26}\text{FN}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 468, found 468.

103		¹H NMR (400MHz, CDCl₃) δ 8.87 (s, 1H), 8.38 (m, 1H), 8.14 (m, 1H), 7.95 (m, 1H), 7.68-7.58 (m, 5H), 7.06-7.04(m, 2H), 3.85 (s, 1H), 3.74 (s, 3 H), 3.60-3.57 (m, 2H), 2.55-2.50 (m, 6H), 1.32-1.27 (m, 6H). MS ESI calcd for C₂₉H₂₉ClN₂O₄S [M+H]⁺ 537, found 537.
104		¹H NMR (400MHz, CDCl₃) δ 8.861 (s, 1H) 8.38-8.36 (m, 1H) 7.68-7.51 (m, 7H) 7.05-7.03 (m, 2H) 3.86-3.83 (m, 2H) 3.72 (s, 3H) 3.59-3.56 (m, 2H) 2.54-2.49 (t, 2H) 1.31-1.29 (d, <i>J</i>=6.8Hz, 6H). MS ESI calcd for C₂₉H₂₆FN₃O₂ [M+H]⁺ 468, found 468.
105		¹H NMR (400MHz, CDCl₃) δ 8.90 (s, 1H), 8.34-8.32 (d, <i>J</i> = 8Hz, 1H), 7.63-7.53 (m, 6H), 7.42-7.40 (d, <i>J</i> = 8Hz, 1H), 7.04-7.02 (d, <i>J</i> = 8Hz, 2H), 3.84-3.82 (d, <i>J</i> = 8Hz, 2H), 3.72 (s, 3 H), 3.59-3.56 (d, <i>J</i> = 12Hz, 2H), 2.54-2.48 (m, 2H), 2.12 (s, 3 H), 1.31-1.29 (d, <i>J</i> = 8Hz, 6H). MS ESI calcd for C₃₀H₂₉N₃O₂ [M+H]⁺ 464, found 464.
106		¹H NMR (400MHz, CDCl₃) δ 9.06 (s, 1H) 8.89 (s, 1H) 8.38-8.36 (m, 1H) 8.30-8.28 (m, 1H) 7.68-7.51 (m, 7H) 7.05-7.03 (m, 2H) 3.86-3.83 (m, 2H) 3.72 (s, 3H) 3.59-3.56 (m, 2H) 2.54-2.49 (t, 2 H) 1.31-1.29 (d, <i>J</i>=6.8Hz, 6H). MS ESI calcd for C₂₈H₂₆F₃N₃O₂ [M+H]⁺ 494, found 494.

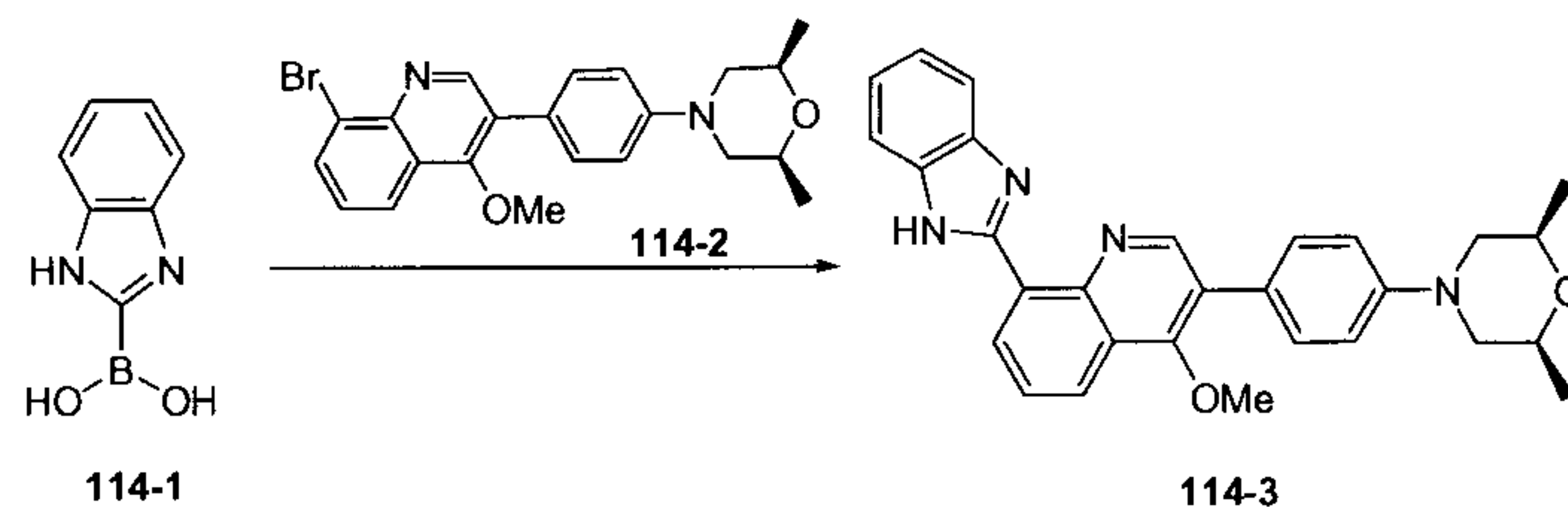
107		¹H NMR (400MHz, CDCl ₃) δ 8.90 (s, 1H), 8.32-8.30 (m, 1H), 7.74-7.57 (m, 7H), 7.05-7.01 (m, 2H), 3.86-3.82 (m, 2H), 3.71 (s, 3H), 3.59-3.57 (m, 2H), 2.65 (s, 3H), 2.55-2.49 (m, 2H), 1.31-1.30 (m, 6 H). MS ESI calcd for C ₃₀ H ₂₉ N ₃ O ₂ [M+H] ⁺ 464, found 464.
108		¹H NMR (400MHz, CDCl ₃) δ 8.90 (s, 1H), 8.60 (s, 1H), 8.18 (s, 1H), 7.97-8.06 (m, 2H), 7.56-7.63 (m, 3H), 7.10 (d, <i>J</i> = 8.82Hz, 2H), 3.92 (s, 3H), 3.69 (d, <i>J</i> = 10.58Hz, 4H), 3.63 (s, 3 H), 2.32 (t, <i>J</i> = 11.47Hz, 2H), 1.17 (d, <i>J</i> = 5.73Hz, 6H). MS ESI calcd for C ₂₆ H ₂₈ N ₄ O ₂ [M+H] ⁺ 429, found 429.
109		¹H NMR (400MHz, CDCl ₃) δ 8.84 (s, 1H), 8.17 (dd, <i>J</i> = 8.38, 1.32Hz, 1H), 7.63-7.73 (m, 2H), 7.56 (d, <i>J</i> = 8.38Hz, 2H), 7.23 (d, <i>J</i> = 1.32Hz, 1H), 7.09 (d, <i>J</i> = 7.94Hz, 3H), 6.98-7.02 (m, 1H), 6.06 (s, 2H), 3.69 (d, <i>J</i> = 10.58Hz, 4H), 3.64 (s, 3H), 2.31 (t, <i>J</i> = 11.69Hz, 2H), 1.16 (d, <i>J</i> = 6.17Hz, 6H). MS ESI calcd for C ₂₉ H ₂₈ N ₂ O ₄ [M+H] ⁺ 469, found 469.
110		¹H NMR (400MHz, CDCl ₃) δ 8.84 (s, 1H), 8.69 (s, 2H), 8.17 (d, <i>J</i> =7.06Hz, 1H), 7.79 (d, <i>J</i> =5.73Hz, 1H), 7.65-7.72 (m, 1H), 7.56 (d, <i>J</i> =8.82Hz, 2H), 7.09 (d, <i>J</i> =8.82Hz, 2H), 3.69 (d, <i>J</i> =10.14Hz, 4H), 3.18 (s, 6H) 3.64 (s, 3H), 2.31 (t, <i>J</i> =11.47Hz, 2H), 1.16 (d, <i>J</i> =5.73Hz,

		6H). MS ESI calcd for $C_{28}H_{31}N_5O_2[M+H]^+$ 470, found 470.
111		^1H NMR (400MHz, $CDCl_3$) δ 8.92 (s, 1H) 8.30-8.28 (m, 1H) 7.87-7.74 (m, 2H) 7.73-7.72 (m, 3H) 7.64-7.58 (m, 3H) 7.15 (s, 2H) 7.05-7.03 (m, 2H) 3.86-3.83 (m, 2H) 3.73 (s, 3H) 3.69-3.56 (m, 2H) 2.54-2.49 (m, 2H) 1.31-1.29 (m, 6H). MS ESI calcd for $C_{31}H_{30}N_4O_2[M+H]^+$ 491, found 491.
112		^1H NMR (400MHz, $CDCl_3$) δ 8.84 (s, 1 H), 8.27 (d, $J=7.94$ Hz, 1 H), 7.88-7.96 (m, 2 H), 7.83-7.88 (m, 2 H), 7.77-7.82 (m, 1 H), 7.69-7.76 (m, 1 H), 7.55 (d, $J=8.82$ Hz, 2 H), 7.06 (d, $J=8.82$ Hz, 2 H), 4.06 (d, $J=3.09$ Hz, 2 H), 3.66 (s, 3 H), 3.27 (br. s., 2 H), 2.94 (dd, $J=11.69, 5.95$ Hz, 2 H), 1.20 (d, $J=6.17$ Hz, 6 H). MS ESI calcd for $C_{29}H_{27}N_3O_2[M+H]^+$ 450, found 450.
113		^1H NMR (400MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.31 (d, $J=4.0$ Hz, 1H), 7.85-7.78 (m, 4H), 7.68-7.66 (m, 2H), 7.64-7.54 (m, 2H), 7.07-7.05 (m, 2H), 3.76-3.72 (m, 5H), 2.35-2.29 (m, 2 H), 1.87-1.84 (m, 1H), 1.30-1.27 (m, 1H), 0.99-0.97 (m, 6H), 0.93-0.89 (m, 1H), 0.78-0.75 (m, 1H). MS ESI calcd for $C_{30}H_{29}N_3O$ $[M+H]^+$ 448, found 448.

Embodiment 114

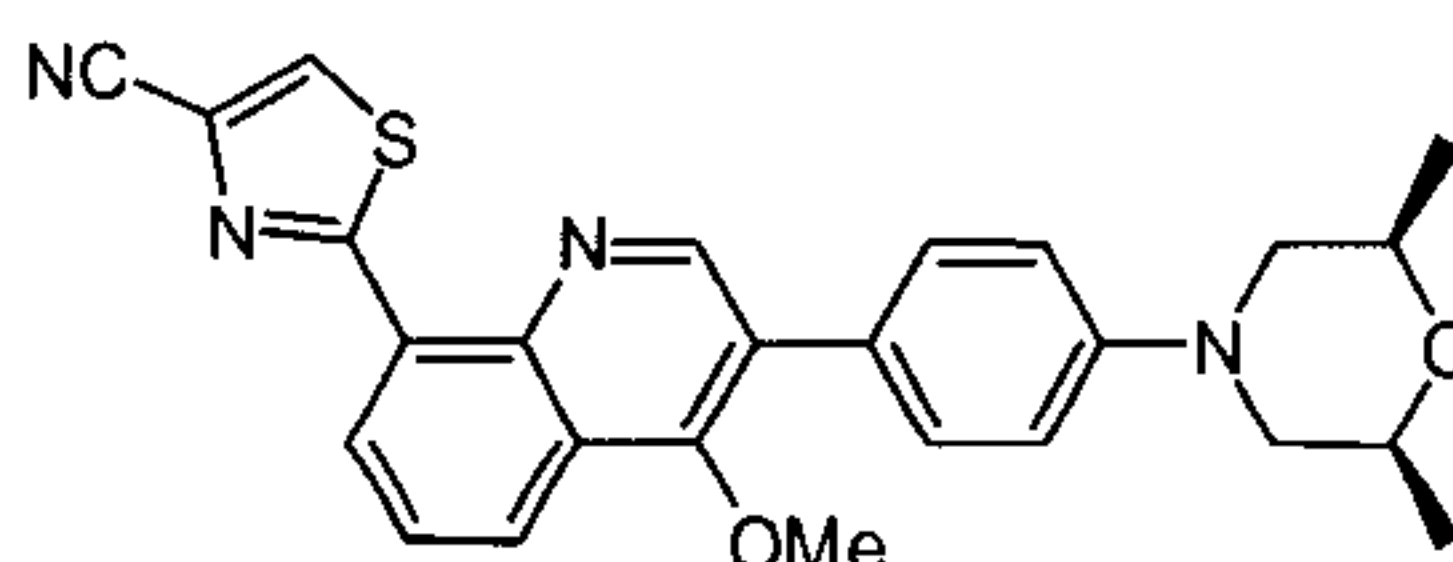


(2S,6R)-4-(4-(8-(1H-benzo[d]imidazol-2-yl)-4-methoxyquinolin-3-yl)phenyl)-2,6-dimethylmorpholine

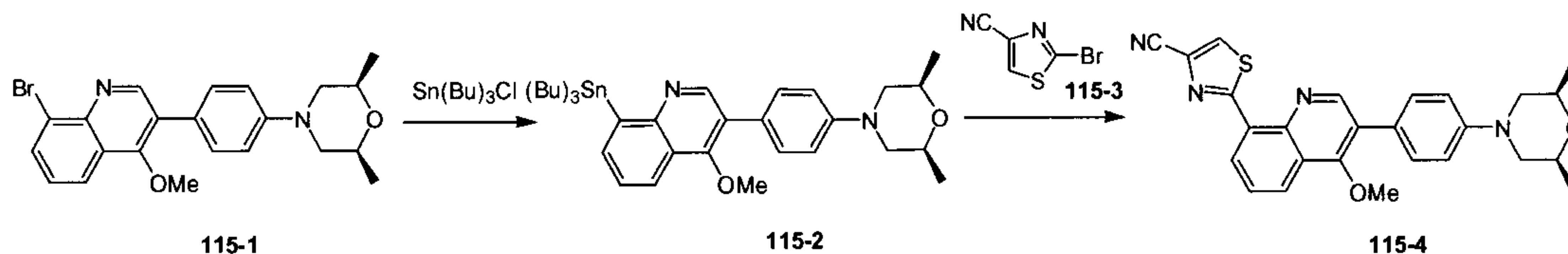


[291] A mixture of compound 114-1 (100 mg, 0.61 mmol), Pd(dppf)Cl₂ (23.1 mg, 0.061 mmol), compound 114-2 (263.5 mg, 0.61 mmol) and Na₂CO₃ (161 mg, 1.53 mmol) was added into dioxane (2 mL). Under nitrogen gas atmosphere, the obtained reaction mixture was heated to 120°C and stirred for 16h. The reaction mixture were poured into H₂O, extracted with EtOAc. The combined extraction liquid was washed with brines, dried over sodium sulfate and concentrated to dry, finally purified by column chromatography (PE:EtOAc = 3:1) to deliver the title compound (15 mg, yield 5.4%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 9.10-9.20 (m, 1H), 9.02 (s, 1H), 8.37 (d, *J* = 8.0 Hz, 1H), 7.65-7.80 (m, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.20-7.35 (m, 5H), 7.08 (d, *J* = 8.4 Hz, 1H), 3.80-3.92 (m, 2H), 3.74 (s, 3H), 3.55-3.62 (m, 2H), 2.50-2.60 (m, 2H), 1.20-1.40 (m, 6H). MS ESI calcd for C₂₉H₂₈N₄O₂ [M+H]⁺ 465, found 465.

Embodiment 115



2-(3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxyquinolin-8-yl)thiazole-4-carbonitrile

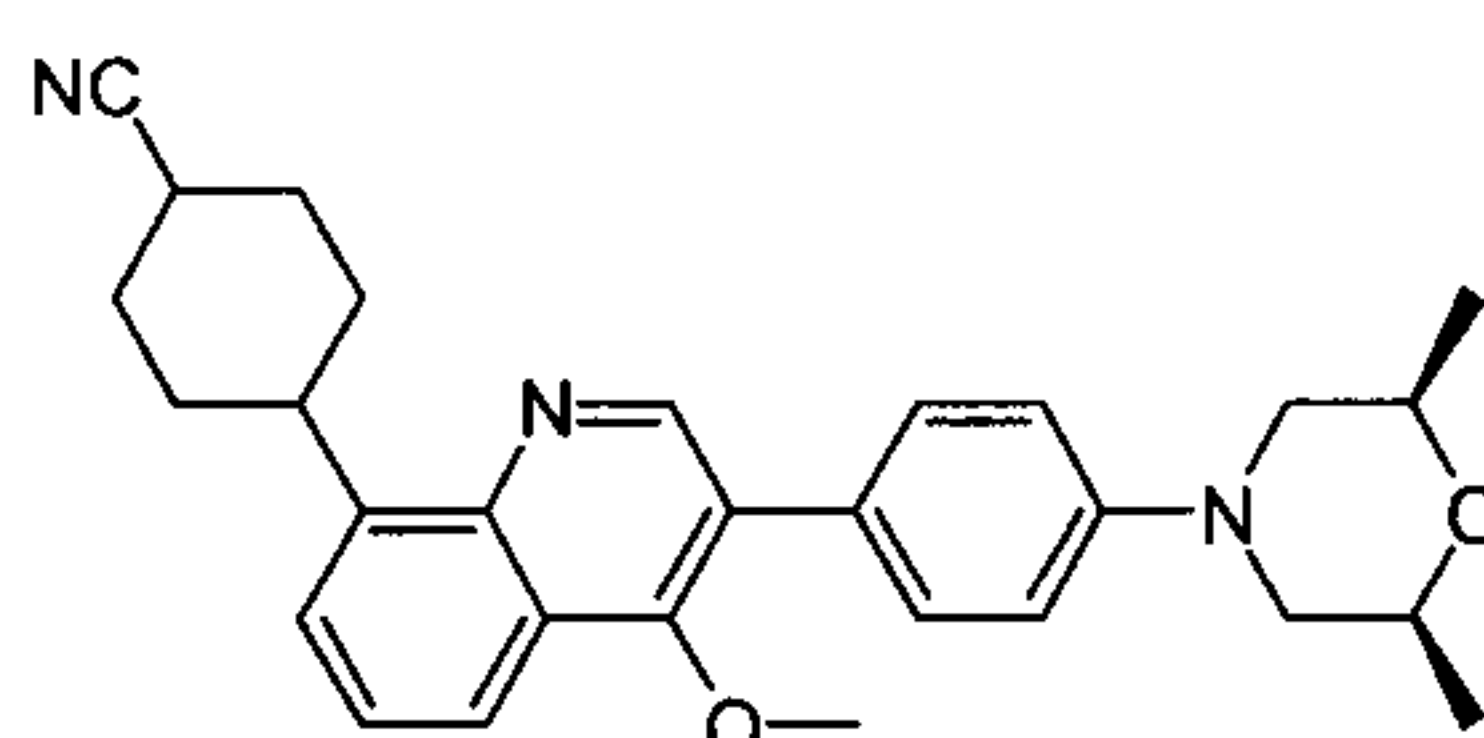


[292] Step 1: Under nitrogen gas atmosphere, ⁿBuLi (0.22mL, 0.552mmol) was added dropwise into a solution of compound 115-1 (200 mg, 0.46 mmol) in THF (10 mL) at -65 °C. After the addition, the reaction mixture was stirred at this

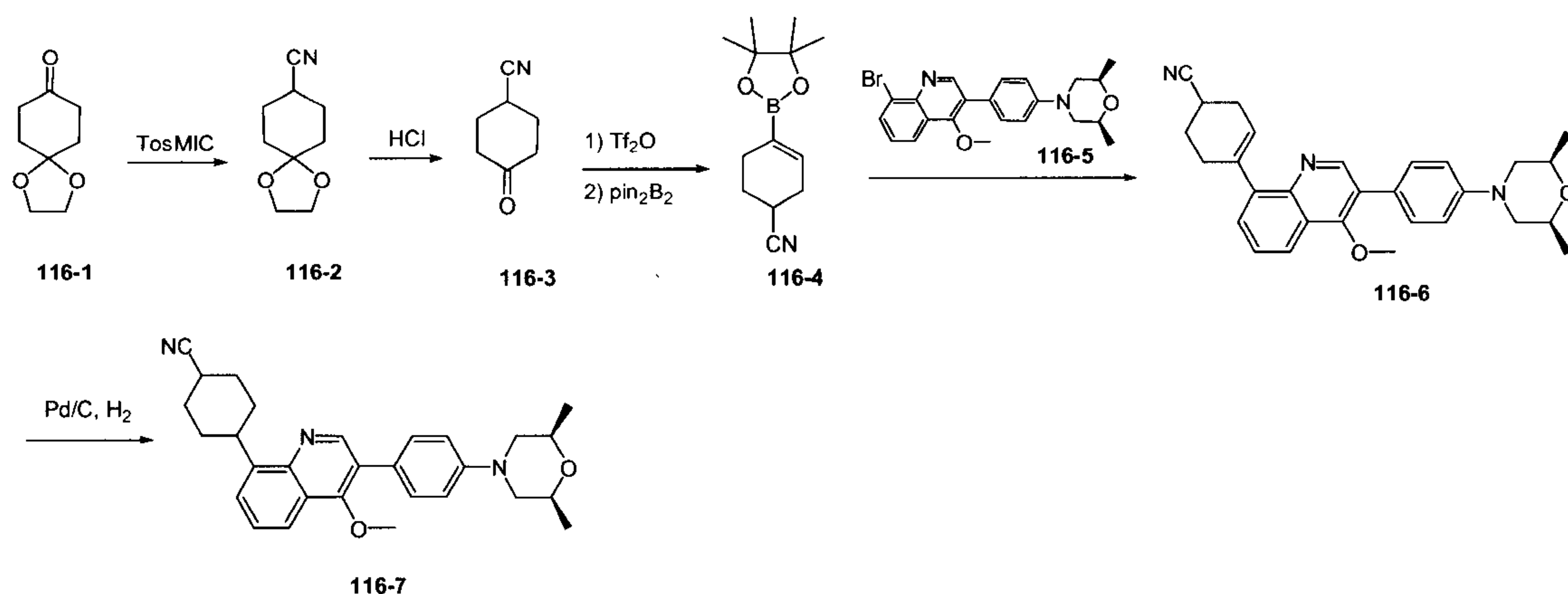
temperature for further 1h. Then SnBu_3Cl (150 mg, 0.46 mmol) was added into the solution. The reaction mixture was stirred at $-65\text{ }^\circ\text{C}$ for further 4 h. After the reaction was complete, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined extraction liquid was washed with brines, dried over sodium sulfate and concentrated to dry, finally purified by column chromatography (PE:EtOAc = 1:1) to deliver compound 115-2 (120 mg, yield 41%) as white solid. **MS ESI** calcd for $\text{C}_{34}\text{H}_{50}\text{N}_2\text{O}_2\text{Sn}$ $[\text{M}+\text{H}]^+$ 639, found 639.

[293] Step 2: Compound 115-2 (100 mg, 0.16 mmol), compound 115-3 (30 mg, 0.16 mmol), Na_2CO_3 (43 mg, 0.4 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (10 mg, 0.016 mmol) were added into dioxane (2 mL). Under nitrogen gas atmosphere, the reaction mixture was heated to 120°C and stirred for 16h. The reaction mixture was poured into H_2O , extracted with EtOAc. The combined extraction liquid was washed with brines, dried over sodium sulfate and concentrated to dry, finally purified by column chromatography (PE:EtOAc = 1:1) to deliver the title compound (25 mg, yield 34%) as white solid. **^1H NMR** (400 MHz, CDCl_3) δ 8.95 (s, 1H), 8.85 (d, $J=2.0$ Hz, 1H), 8.33 (d, $J=2.0$ Hz, 1H), 8.10 (s, 1H), 7.60-7.70 (m, 1H), 7.56 (d, $J=8.4$ Hz, 2H), 7.02 (d, $J=8.4$ Hz, 2H), 3.75-3.85 (m, 2H), 3.57 (s, 3H), 3.52-3.60 (m, 2H), 3.40-3.50 (m, 2H), 1.29 (s, 3H), 1.27 (s, 3H). **MS ESI** calcd for $\text{C}_{26}\text{H}_{24}\text{N}_4\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 457, found 457.

Embodiment 116



4-(3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxyquinolin-8-yl)
cyclohexane carbonitrile



[294] Step 1: *t*-BuOK (18.5 g, 165.2 mmol) was added into a solution of compound 116-1 (10 g, 64 mmol) and TosMIC (17.6 g, 90.27 mmol) in DME (10 mL) at $0\text{ }^\circ\text{C}$.

The reaction mixture was stirred at 0°C for 2h. After the reaction was complete, the reaction mixture was quenched with saturated NH₄Cl solution and extracted with EtOAc. The combined extraction liquid was washed with brines, dried over sodium sulfate and concentrated to dry, finally purified by column chromatography (PE:EtOAc = 1:1) to deliver 116-2 (6.7 g, yield 50%) as colorless oil.

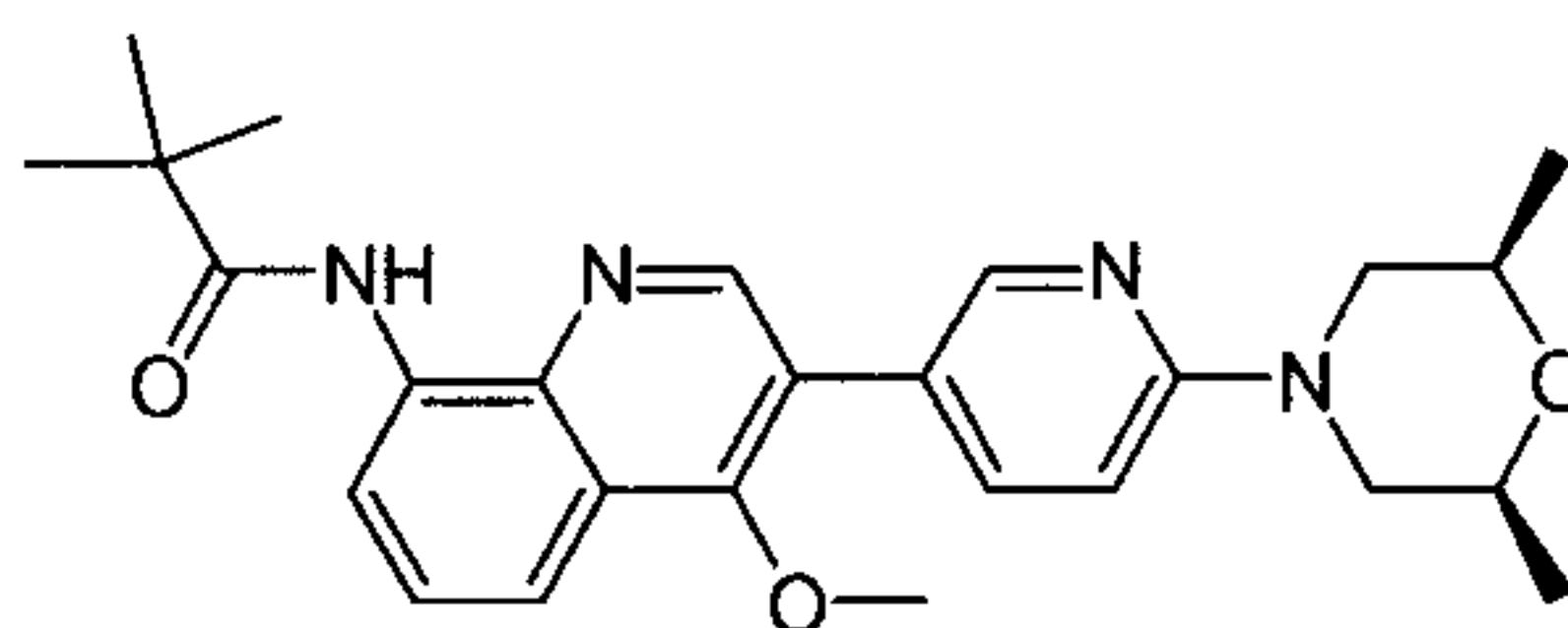
[295] Step 2: A mixture of compound 116-2 (3 g, 18 mmol) in *conc.* hydrochloric acid / H₂O (v/v = 1:1, 20 mL) was stirred at room temperature for 2h. The reaction mixture was adjusted to pH = 8 with NaOH, and extracted with EtOAc. The combined extraction liquid was washed with brines, dried over sodium sulfate and concentrated to dry, finally purified by column chromatography (PE:EtOAc = 1:1) to deliver compound 116-3 (1.5 g, yield 68%) as colorless oil.

[296] Step 3: LiHMDS (9.5 mL, 9.5 mmol) was added dropwise into a solution of compound 116-3 (1 g, 8 mmol) in THF (20 mL) at 0 °C. After the addition, the reaction mixture was stirred for further 30min. Then PhN(SO₂CF₃) (3.6 g, 8.6 mmol) was added into the solution. The obtained mixture was stirred at 25°C for 6h, finally quenched with H₂O and extracted with EtOAc. The combined extraction liquid was washed with brines, dried over sodium sulfate and concentrated to dry to deliver sulfonate as yellow oil. The obtained sulfonate, Pd(dppf)Cl₂ (80.4 mg, 0.11 mmol), bis(pinacolato)diboron (0.67 g, 2.6 mmol) and KOAc (0.65 g, 6.6 mmol) were added into dioxane (15 mL), under nitrogen gas atmosphere, the reaction mixture was heated to 100°C and stirred for 18h. The reaction mixture was poured into H₂O, extracted with EtOAc. The combined extraction liquid was washed with brines, dried over sodium sulfate and concentrated to dry, finally purified by column chromatography (PE:EtOAc = 5:1) to deliver compound 116-4 (0.5 g, yield 28%) as white solid.

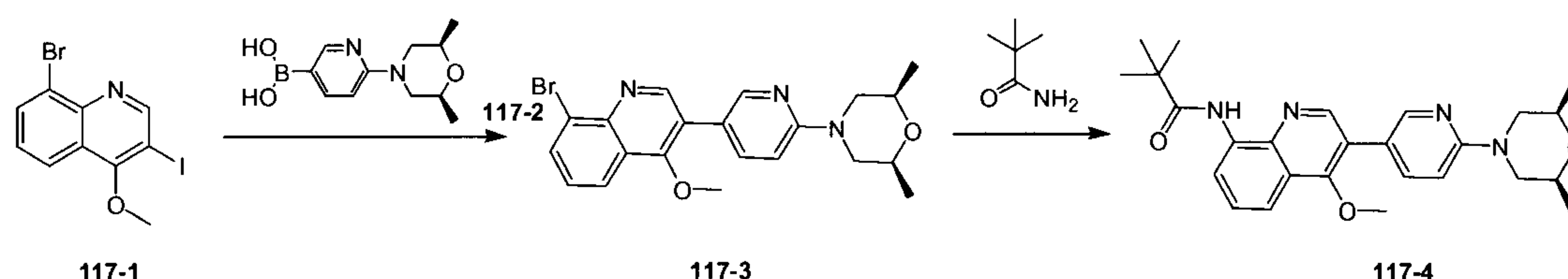
[297] Step 4: A mixture of Pd(dppf)Cl₂ (180.8 mg, 0.23 mmol), compound 116-4 (500 mg, 2.1 mmol), compound 116-5 (1 g, 2.3 mmol) and Na₂CO₃ (556 mg, 5.25 mmol) was added into dioxane (20 mL). Under nitrogen gas atmosphere, the obtained suspension was heated to 80°C and stirred for 4h. The reaction mixture was poured into H₂O, extracted with EtOAc. The combined extraction liquid was washed with brines, dried over sodium sulfate and concentrated to dry, finally purified by column chromatography (PE:EtOAc = 5:1) to deliver compound 116-6 (400 mg, yield 42%) as white solid. **MS ESI** calcd for C₂₉H₃₁N₃O₂ [M+H]⁺ 454, found 454.

[298] Step 5: Pd/C (100 mg, 10%) and compound 116-6 (100 mg, 0.22 mmol) were added into EtOAc (20 mL). Under hydrogen gas atmosphere provided by hydrogen balloon, the reaction mixture was stirred at room temperature for 50h. The reaction mixture was filtrated, the filtrate was concentrated to dry, finally purified by preparative HPLC to deliver the title compound (50 mg, yield 46%) as white solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.90 (s, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.50-7.65 (m, 6H), 7.06 (d, *J* = 8.8 Hz, 2H), 4.00-4.15 (m, 1H), 3.80-3.95 (m, 2H), 3.69 (s, 3H), 3.55-3.65 (m, 2H), 3.15-3.20 (m, 1H), 2.45-2.55 (m, 2H), 1.90-2.25 (m, 7H), 1.55-1.65 (m, 1H), 1.33 (s, 3H), 1.31 (s, 3H). **MS ESI** calcd for C₂₉H₃₃N₃O₂ [M+H]⁺ 456, found 456.

Embodiment 117



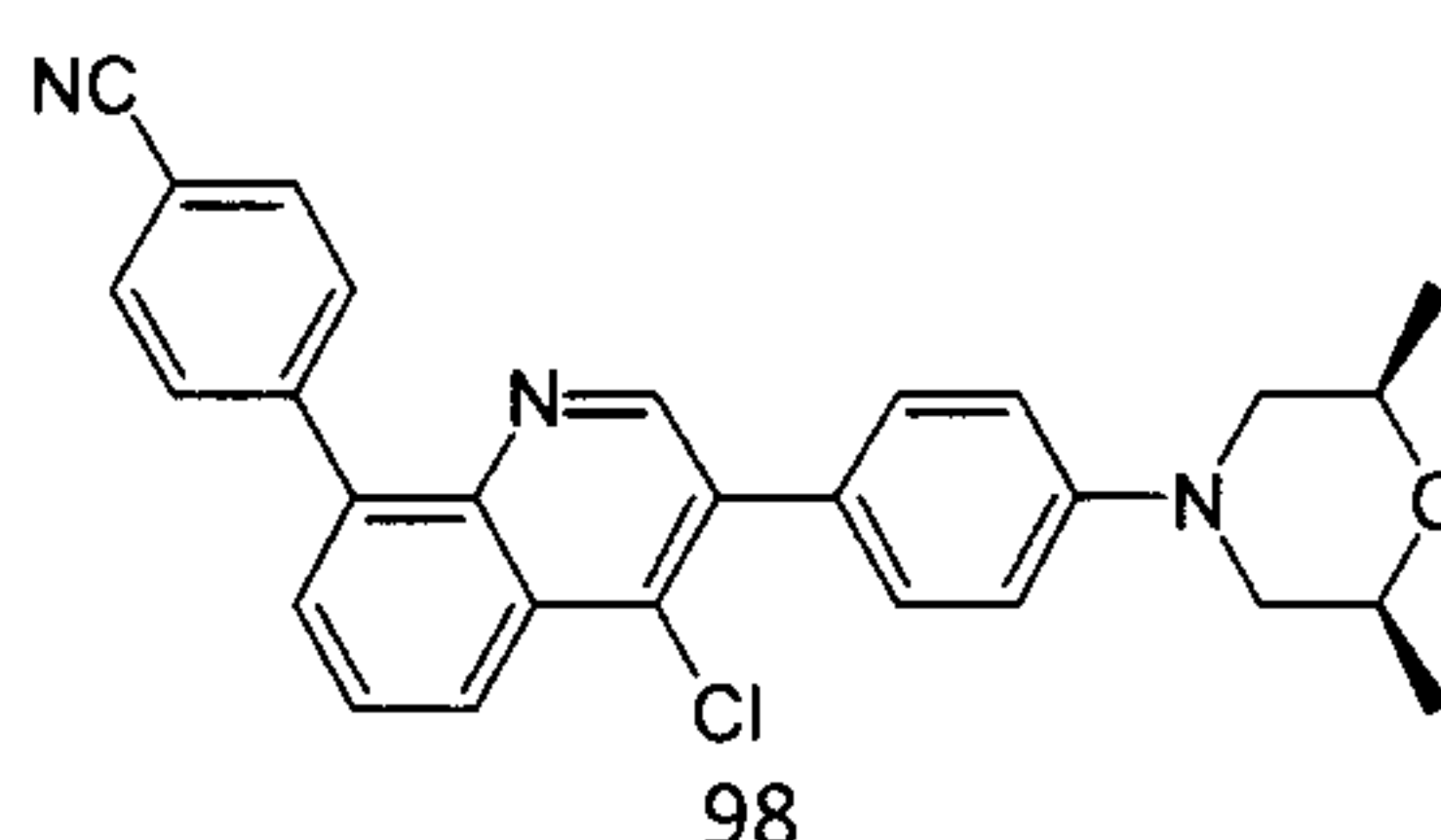
N-(3-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-4-methoxyquinolin-8-yl) pivalamide



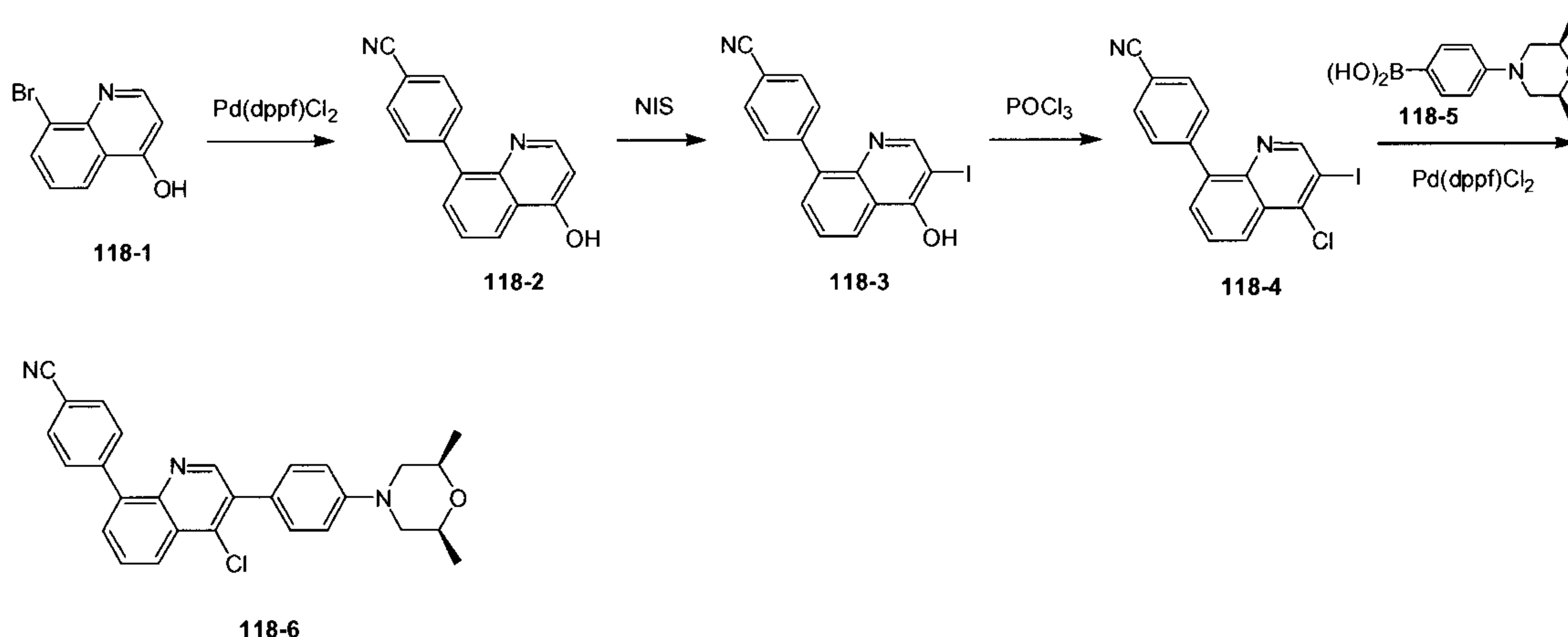
[299] Step 1: A mixture of Na_2CO_3 (430 mg, 4 mmol), compound 117-1 (730 mg, 2 mmol), compound 117-2 (480 mg, 2 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (150 mg, 0.2 mmol) was added into a mixed solvent of THF/DMF/ H_2O . Then the reaction mixture was heated to 80°C and stirred for 4h. The reaction mixture was poured into H_2O , extracted with EtOAc. The combined extraction liquid was dried over sodium sulfate and concentrated to dry, finally purified by column chromatography (PE:EtOAc= 5:1) to deliver compound 117-3 (430 mg, yield 50%) as brown solid. **MS ESI** calcd for $\text{C}_{21}\text{H}_{22}\text{BrN}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 428, found 428.

[300] Step 2: A mixture of compound 117-3 (130 mg, 0.3 mmol), trimethylacetamide (60 mg, 0.6 mmol), Cs_2CO_3 (190 mg, 0.6 mmol), $\text{Pd}_2(\text{dba})_3$ (30 mg, 0.03 mmol) and Xantphos (36 mg, 0.06 mmol) was added into dioxane (5 mL). Under nitrogen gas atmosphere, the reaction mixture was heated to 120°C and stirred for 4h. The reaction mixture was poured into H_2O , extracted with EtOAc. The combined extraction liquid was dried over sodium sulfate and concentrated to dry, finally purified by preparative HPLC to deliver the title compound (30 mg, yield 21%) as white solid. **^1H NMR** (400 MHz, CDCl_3) δ 10.23 (brs, 1H), 8.77 (d, $J=7.6$ Hz, 1H), 8.74 (s, 1H), 8.47 (d, $J=2.0$ Hz, 1H), 7.90-7.95 (m, 2H), 7.69-7.80 (m, 1H), 6.78 (d, $J=8.4$ Hz, 1H), 4.05-4.10 (m, 2H), 3.35-3.46 (m, 5H), 2.26-2.85 (m, 2H), 1.42 (s, 9H), 1.31 (s, 9H), 1.29 (s, 3H). **MS ESI** calcd for $\text{C}_{26}\text{H}_{32}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]^+$ 449, found 449.

Embodiment 118



4-(4-chloro-3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)quinolin-8-yl)benzonitrile



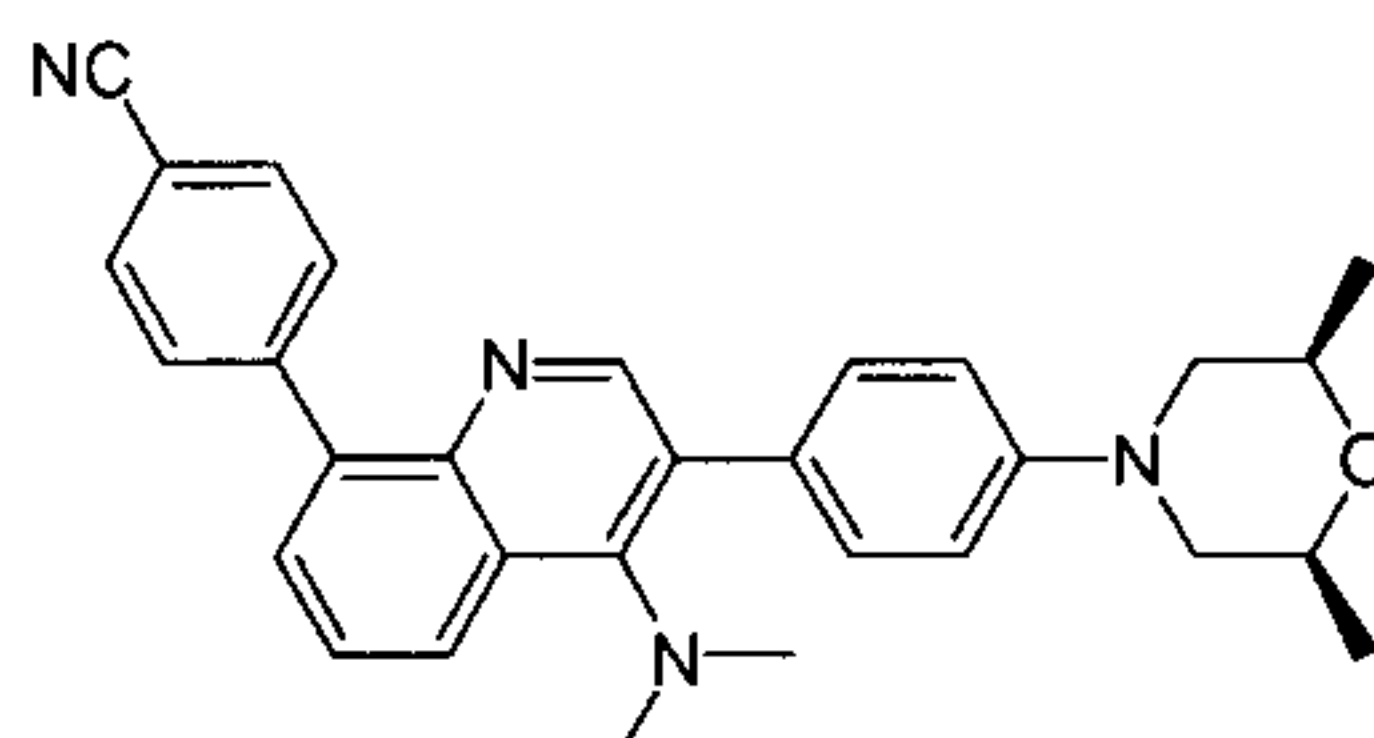
[301] Step 1: Pd(dppf)Cl₂ (1.6 g, 0.1 mmol), sodium carbonate (9.5 g, 89.23 mmol) and DMF / H₂O (100:20, 120 mL) were added into a suspension of compound 118-1 (10 g, 44.64 mmol), 4-cyanophenylboronic acid (7.2 g, 49.11 mmol). Under nitrogen gas atmosphere, the reaction mixture was stirred at 90°C overnight. After the reaction was complete as detected by LC-MS, the reaction mixture was poured into H₂O (500 mL). The product 2 was obtained after filtration as brown solid (10.8g, 98%). **MS ESI** calcd for C₁₆H₁₀N₂O [M+H]⁺ 247, found 247.

[302] Step 2: NIS (11.96 g, 53.17 mmol) was added into a solution of compound 118-2 (10.9 g, 44.31 mmol) in DMF(110 mL) in portions. The reaction mixture was stirred at room temperature for 3h. After the reaction was complete as detected by LC-MS and TLC, the reaction mixture was poured into H₂O (500 mL). The product was obtained after filtration as brown residue (14g and 85%). **MS ESI** calcd for C₁₆H₉IN₂O [M+H]⁺ 373, found 373.

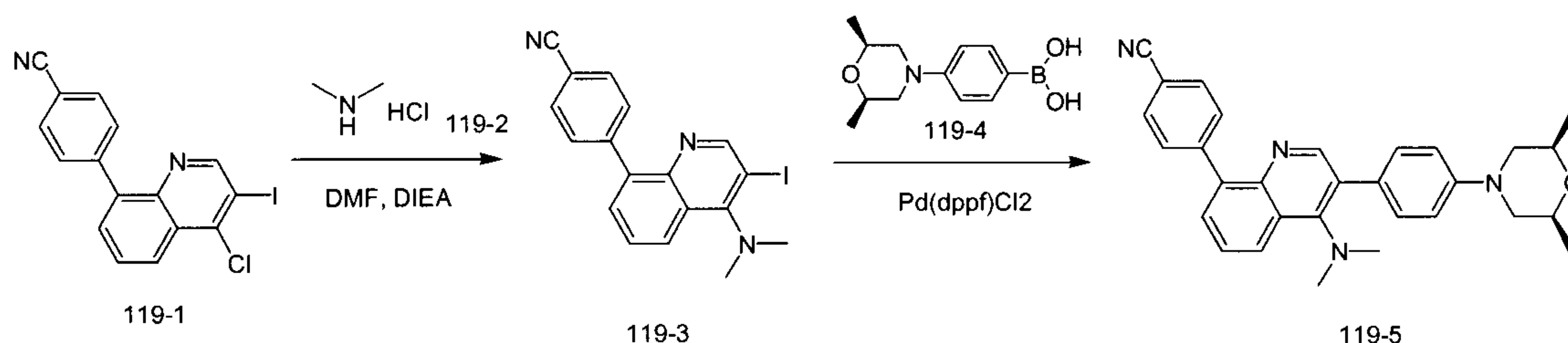
[303] Step 3: compound 118-3 (5 g, 13.4 mmol) was added into phosphorus oxychloride (20 mL). The reaction mixture was stirred at reflux for 3h. After the reaction was complete as detected by LC-MS, the reaction mixture was poured into H₂O (500 mL). The mixture was filtrated and dried under vacuum to deliver compound 4(5.2 g, 99%) as brown solid. **MS ESI** calcd for C₁₆H₈ClIN₂ [M+H]⁺ 391, found 391.

[304] Step 4: Compound 118-1 (200 mg, 0.5 mmol), compound 118-5 (176 mg, 0.75 mmol) were added into a suspension of Pd(dppf)Cl₂ (18 mg, 0.03 mmol), sodium carbonate (106 mg, 1.0 mmol) in THF/H₂O (10:1, 11 mL), then under nitrogen gas atmosphere, the reaction mixture was stirred at 90 deg.C overnight. The reaction was complete as detected by LC-MS. The mixture was purified by preparative HPLC to deliver the desired product as brown solid (40mg, 33%). **¹H NMR** (400 MHz, CDCl₃) δ 8.84 (s, 1H), 8.38-8.49 (m, 1H), 7.37-7.62 (m, 6H), 7.54 (d, 2H, *J* =8.0 Hz), 7.25 (d, 2H, *J* =8.4 Hz), 3.97 (t, 2H, *J* =7.6 Hz), 3.61 (d, 2H, *J* =11.6 Hz), 2.67 (t, 2H, *J* =11.6 Hz), 1.28 (d, 6H, *J* =6.4 Hz). **MS ESI** calcd for C₂₈H₂₄ClN₃O [M+H]⁺ 454, found 454.

Embodiment 119



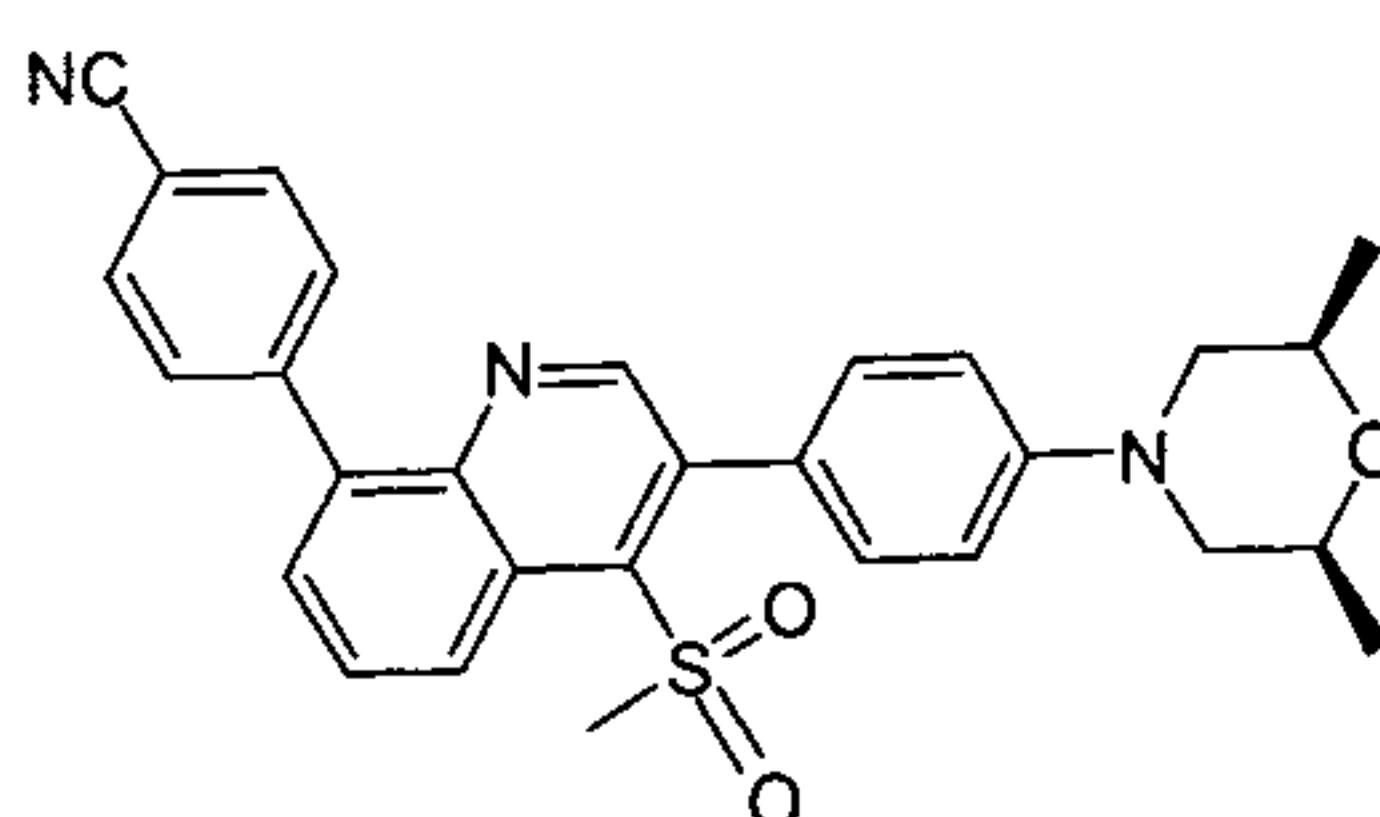
4-(4-(dimethylamino)-3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)quinolin-8-yl)benzonitrile



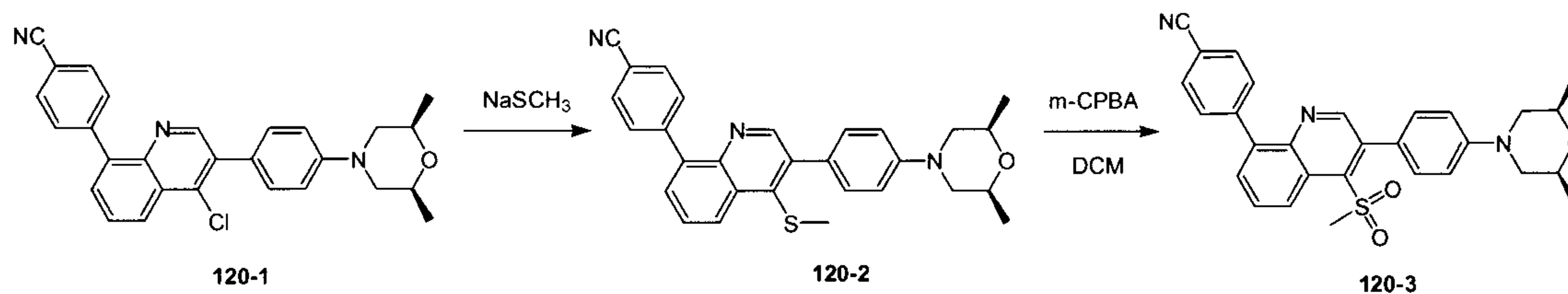
[305] Step 1: Compound 119-2 (1.1 g, 13 mmol) was added into a solution of compound 119-1 (500 mg, 1.3 mmol) in DMF (5 mL). DIEA (5 g, 39 mmol) was added. The reaction mixture was stirred at 120.deg.C. for 10h. Then the reaction mixture was poured into H₂O (50 mL), and extracted with EtOAc. The organic phase was dried over sodium sulfate and concentrated under reduced pressure to deliver the desired compound as white solid (100 mg, 20%). **MS ESI** calcd for C₁₈H₁₄IN₃ [M+H]⁺ 400, found 400.

[306] Step 2: Under nitrogen gas atmosphere, a mixture of compound 119-3 (18 mg, 0.03 mmol), sodium carbonate (100 mg, 0.25 mmol), compound 119-4 (88 mg, 0.37 mmol), Pd(dppf)Cl₂ (53 mg, 0.5 mmol) in THF/H₂O (11 mL, 10:1) was stirred at 90.deg.C overnight. After the reaction was complete as detected by LC-MS, the reaction mixture was purified by preparative HPLC to deliver the title compound (20 mg, 20%) as white solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.37 (s, 1H), 8.26 (t, 1H, *J* = 4.8 Hz), 7.80 (d, 2H, *J* = 6.8 Hz), 7.74 (d, 2H, *J* = 4.4 Hz), 7.59 (d, 2H, *J* = 7.2 Hz), 7.19 (d, 2H, *J* = 7.2 Hz), 7.05 (d, 2H, *J* = 8.0 Hz), 3.85 (t, 2H, *J* = 7.2 Hz), 3.12 (s, 6H), 2.53 (t, 2H, *J* = 11.2 Hz), 1.28 (d, 6H, *J* = 10.0 Hz). **MS ESI** calcd for C₃₀H₃₀N₄O [M+H]⁺ 463, found 463.

Embodiment 120



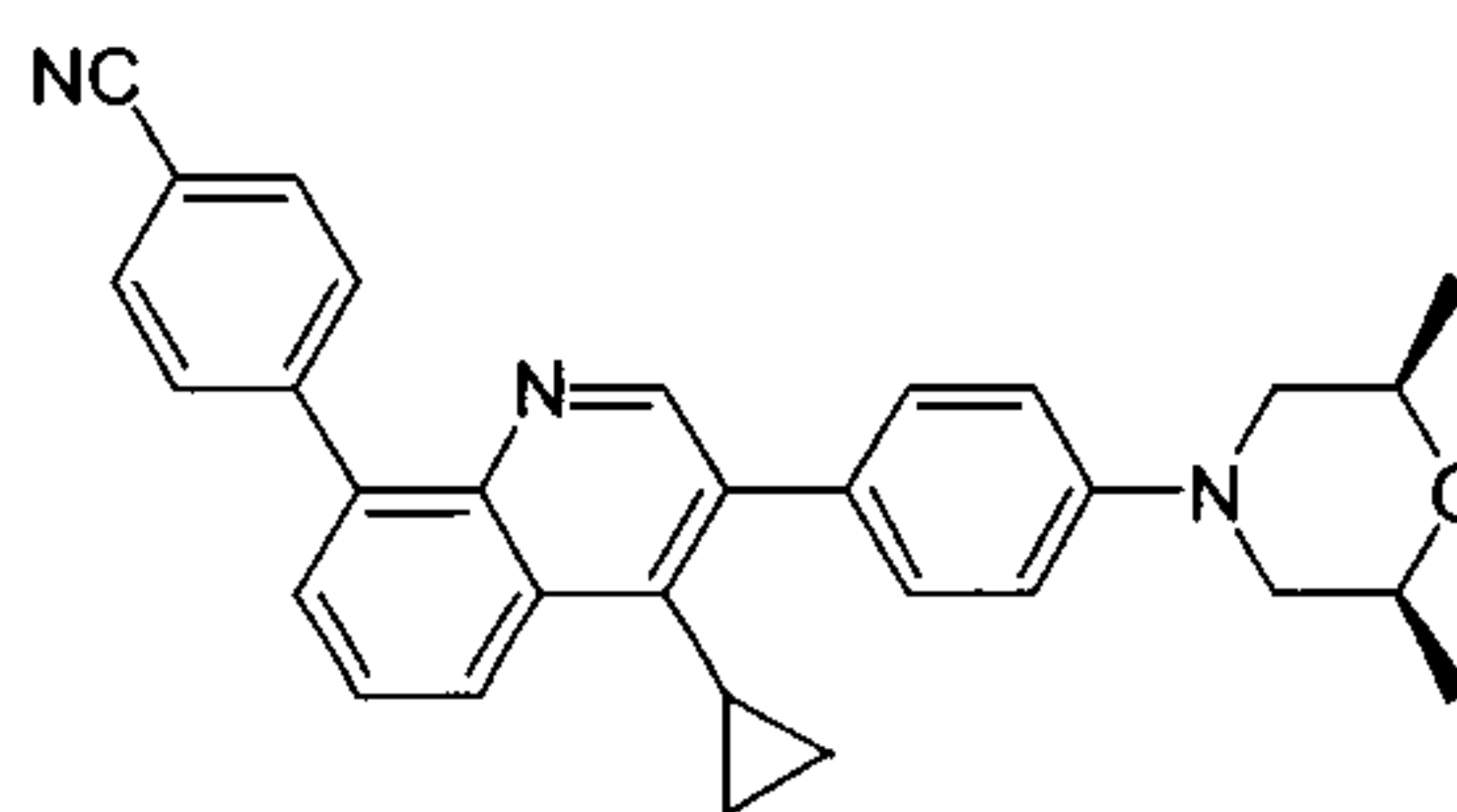
4-(3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-(methylsulfonyl)quinolin-8-yl) benzonitrile



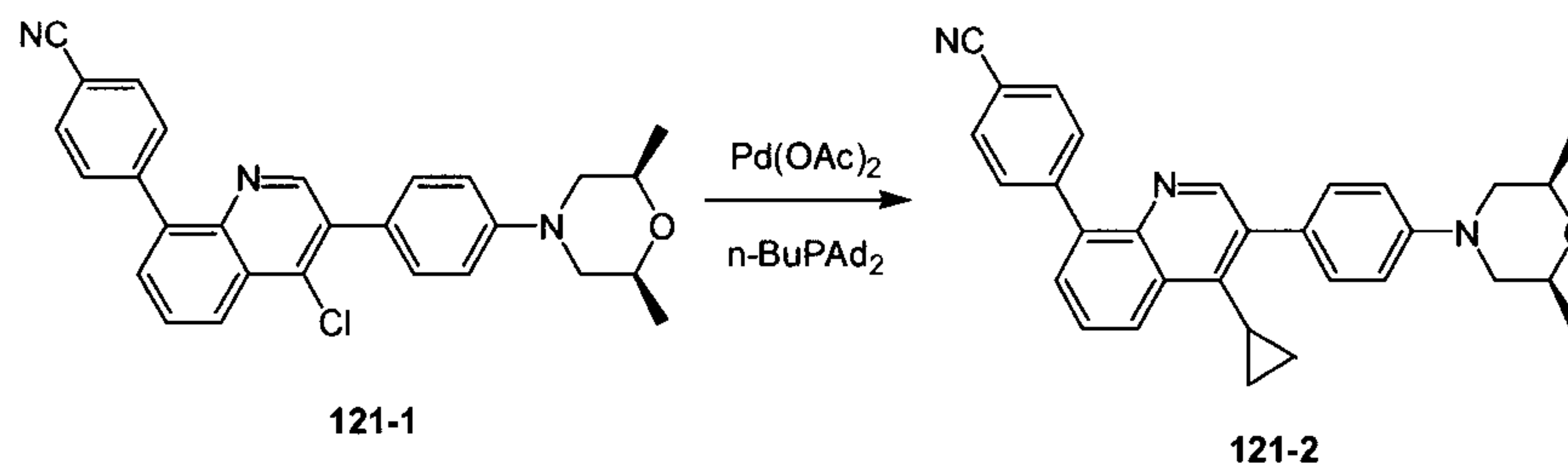
[307] Step 1: NaSCH₃ (31 mg, 0.44 mmol) was added into a solution of compound 120-1 (200 mg, 0.44 mmol) in DMF (5 mL). Then the reaction mixture was stirred at 60°C for 3h. After the reaction was complete as detected by LC-MS, the reaction mixture was poured into H₂O and extracted with EtOAc. The organic phase was dried over sodium sulfate and concentrated under vacuum to deliver the desired compound (200mg, 97.6%) as white solid. **MS ESI** calcd for C₂₉H₂₇N₃OS [M+H]⁺ 466, found 466.

[308] Step 2: *m*-chloroperbenzoic acid (186 mg, 1.08 mmol, 80%) was added into a solution of compound 120-2 (200 mg, 0.43 mmol) in DCM (20 mL). Then the reaction mixture was stirred at reflux overnight. After the reaction was complete as detected by LC-MS, the reaction mixture was poured into H₂O and extracted with DCM. The organic phase was dried over sodium sulfate and concentrated under vacuum, purified by preparative HPLC to deliver the desired product (120 mg, 55%) as white solid. **¹H NMR** (400 MHz, CDCl₃) δ 9.36 (d, 1H, *J*=8.0 Hz), 8.77 (s, 1H), 7.99 (d, 2H, *J*=8.4 Hz), 7.68-7.88 (m, 6H), 7.62 (d, 2H, *J*=8.4 Hz), 4.67 (s, 2H), 4.19 (d, 2H, *J*=14.0 Hz), 3.48 (dd, 2H, *J*=10.0 Hz, 22.0 Hz), 3.06 (s, 3H), 1.22-1.42 (m, 6H). **MS ESI** calcd for C₂₉H₂₇N₃O₃S [M+H]⁺ 498, found 498.

Embodiment 121



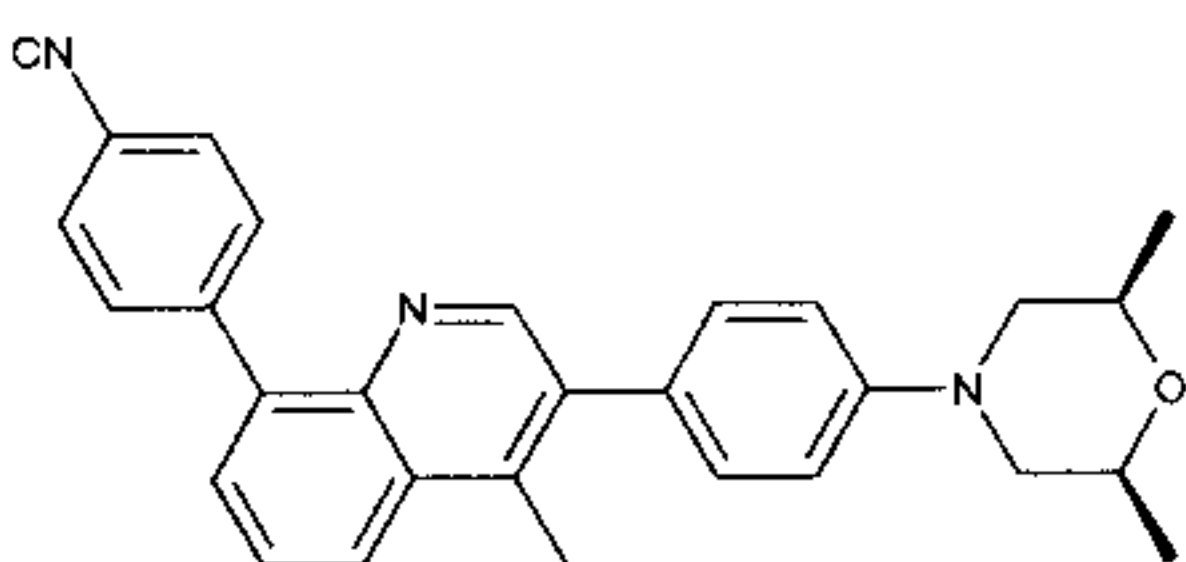
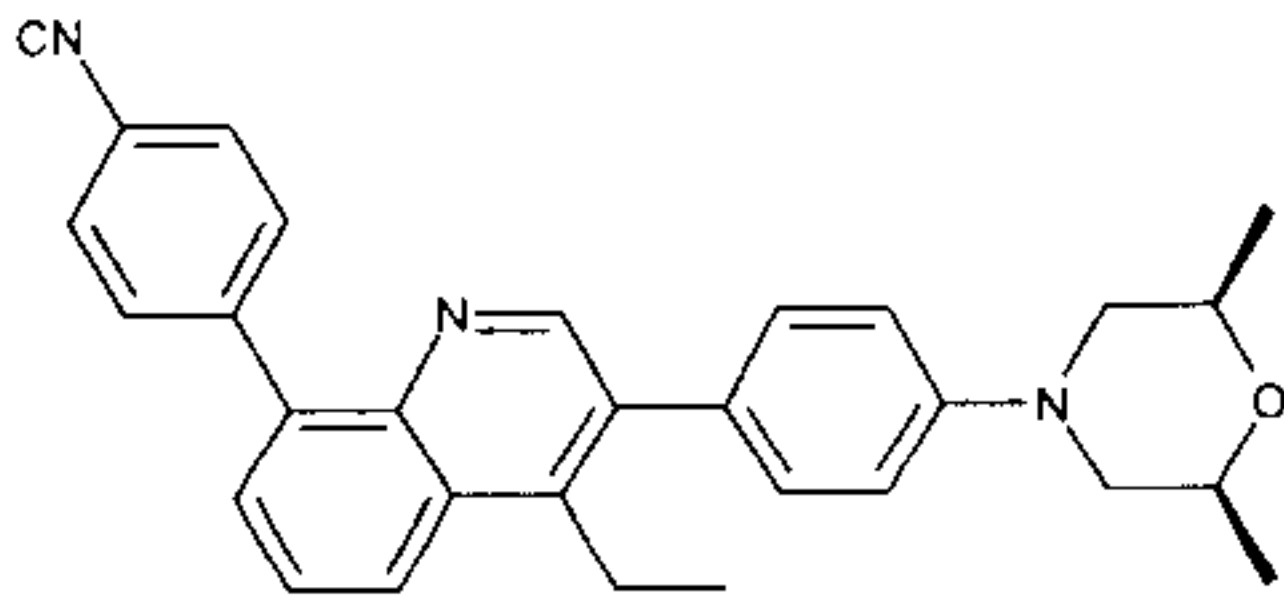
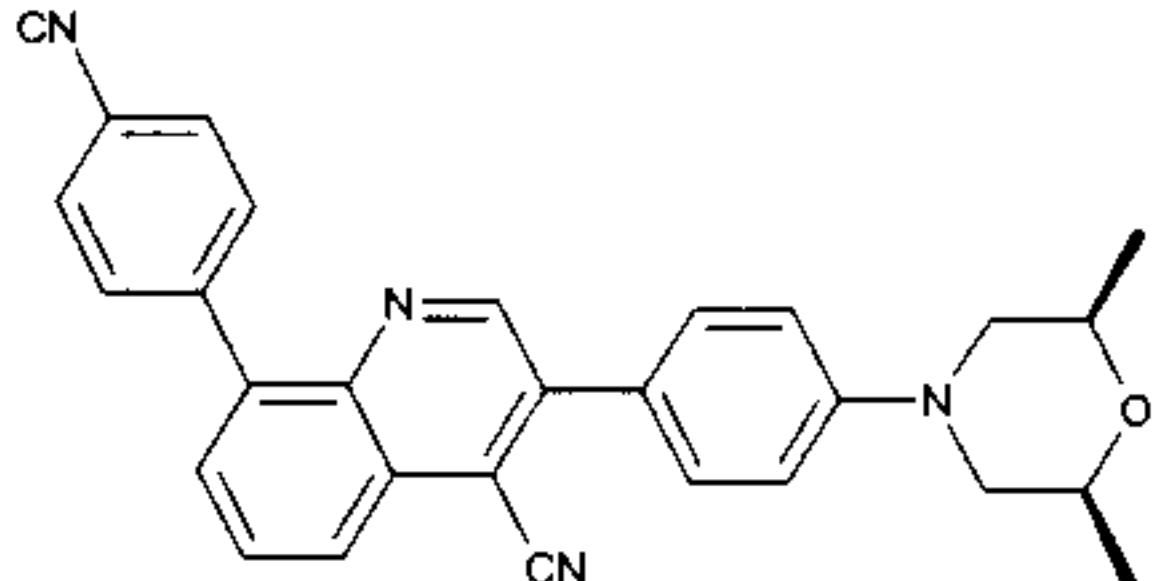
4-(4-cyclopropyl-3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)quinolin-8-yl) benzonitrile

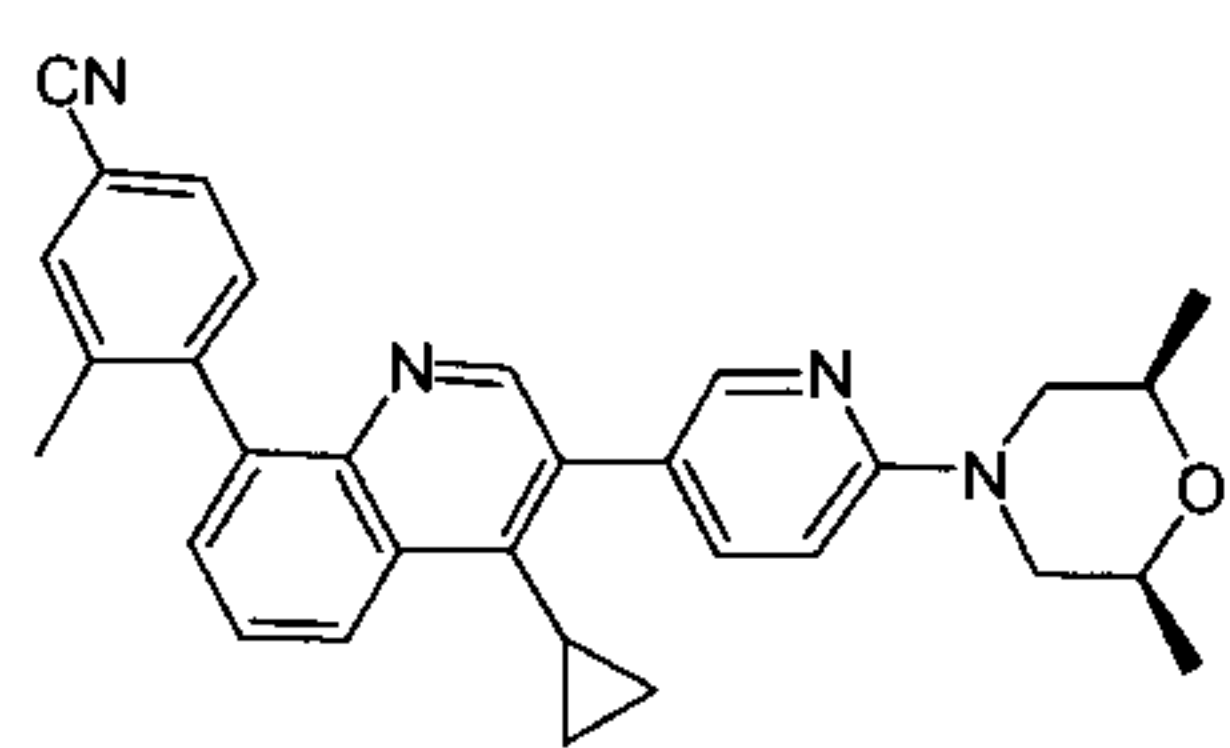


[309] Under nitrogen gas atmosphere, a mixture of compound 121-1 (100 mg, 0.22

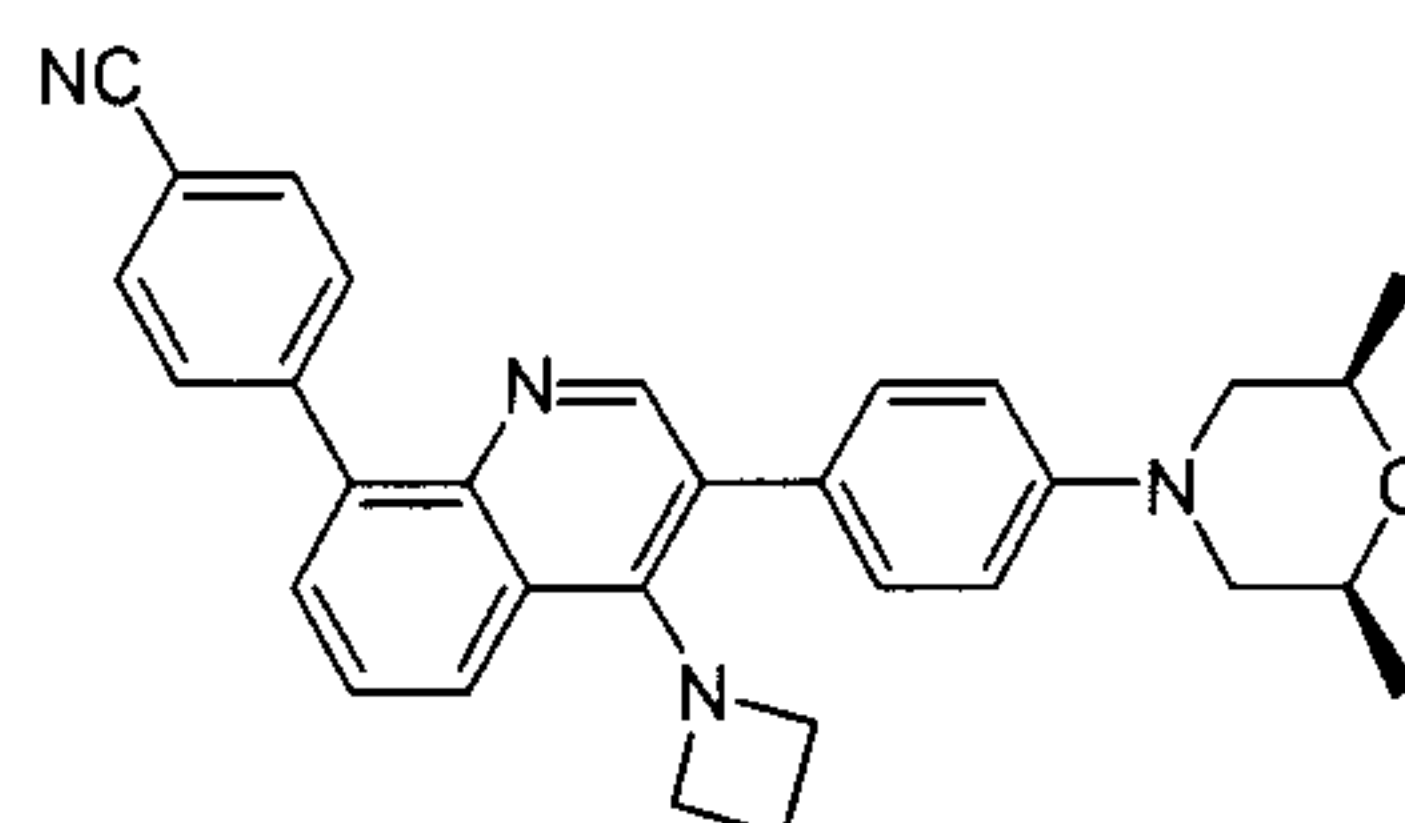
mmol), palladium acetate (4.5 mg, 0.02 mmol), n-BuPAd₂ (4.7 mg, 0.01 mmol), cesium carbonate (143 mg, 0.44 mmol) in toluene/H₂O (10:1, 11 mL) was stirred at 120 deg.C overnight. After the reaction was complete as detected by LC-MS, the reaction mixture was purified by preparative HPLC to deliver the desired product (50 mg, 42%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.80 (s, 1H), 8.70 (d, 1H, *J* = 8.4 Hz), 7.77 (t, 2H, *J* = 8.4 Hz), 7.65-7.75 (m, 3H), 7.50 (d, 2H, *J* = 8.0 Hz), 7.38 (d, 2H, *J* = 8.4 Hz), 7.04-7.13 (m, 2H), 3.85 (dd, 2H, *J* = 6.0 Hz, *J* = 8.0 Hz), 3.50 (d, 2H, *J* = 11.2 Hz), 2.56 (t, 2H, *J* = 11.2 Hz), 2.34 (t, 1H, *J* = 6.4 Hz), 1.18 (d, 6H, *J* = 6.0 Hz), 1.08 (d, 2H, *J* = 8.0 Hz), 0.33 (d, 2H, *J* = 5.6 Hz). MS ESI calcd for C₃₁H₂₉N₃O [M+H]⁺ 460, found 460.

[310] The compounds listed in table 8 were synthesized by compound 121-1 and corresponding boric acids.

Embodiment	Structure	NMR
122		¹ H NMR (400 MHz, CDCl ₃) δ 8.85 (s, 1H), 8.12-8.21 (m, 1H), 7.68-7.81 (m, 6H), 7.32 (d, 2H, <i>J</i> = 8.8 Hz), 7.08 (d, 2H, <i>J</i> = 8.4 Hz), 3.87 (t, 2H, <i>J</i> = 6.4 Hz), 3.57 (d, 2H, <i>J</i> = 10.8 Hz), 2.76 (s, 3H), 2.55 (t, 2H, <i>J</i> = 10.8 Hz), 1.30 (d, 6H, <i>J</i> = 6.4 Hz). MS ESI calcd for C ₂₉ H ₂₇ N ₃ O [M+H] ⁺ 434, found 434.
123		¹ H NMR (400 MHz, CDCl ₃) δ 8.82 (s, 1H), 8.24 (d, 1H, <i>J</i> = 10.8 Hz), 7.66-7.80 (m, 6H), 7.31 (d, 2H, <i>J</i> = 8.4 Hz), 7.11 (d, 2H, <i>J</i> = 8.8 Hz), 3.86 (t, 2H, <i>J</i> = 6.4 Hz), 3.58 (d, 2H, <i>J</i> = 11.2 Hz), 3.20 (d, 2H, <i>J</i> = 7.6 Hz), 2.58 (t, 2H, <i>J</i> = 11.2 Hz), 1.23-1.40 (m, 9H). MS ESI calcd for C ₃₀ H ₂₉ N ₃ O [M+H] ⁺ 448, found 448.
124		¹ H NMR (400 MHz, CDCl ₃) δ 9.13 (s, 1H), 8.35 (d, 1H, <i>J</i> = 6.0 Hz), 7.78-7.86 (m, 6H), 7.68 (d, 2H, <i>J</i> = 8.8 Hz), 7.08 (d, 2H, <i>J</i> = 8.8 Hz), 3.79 (t, 2H, <i>J</i> = 6.4 Hz), 3.62 (d, 2H, <i>J</i> = 10.8 Hz), 2.56 (t, 2H, <i>J</i> = 10.8 Hz), 1.30 (d, 6H, <i>J</i> = 6.0

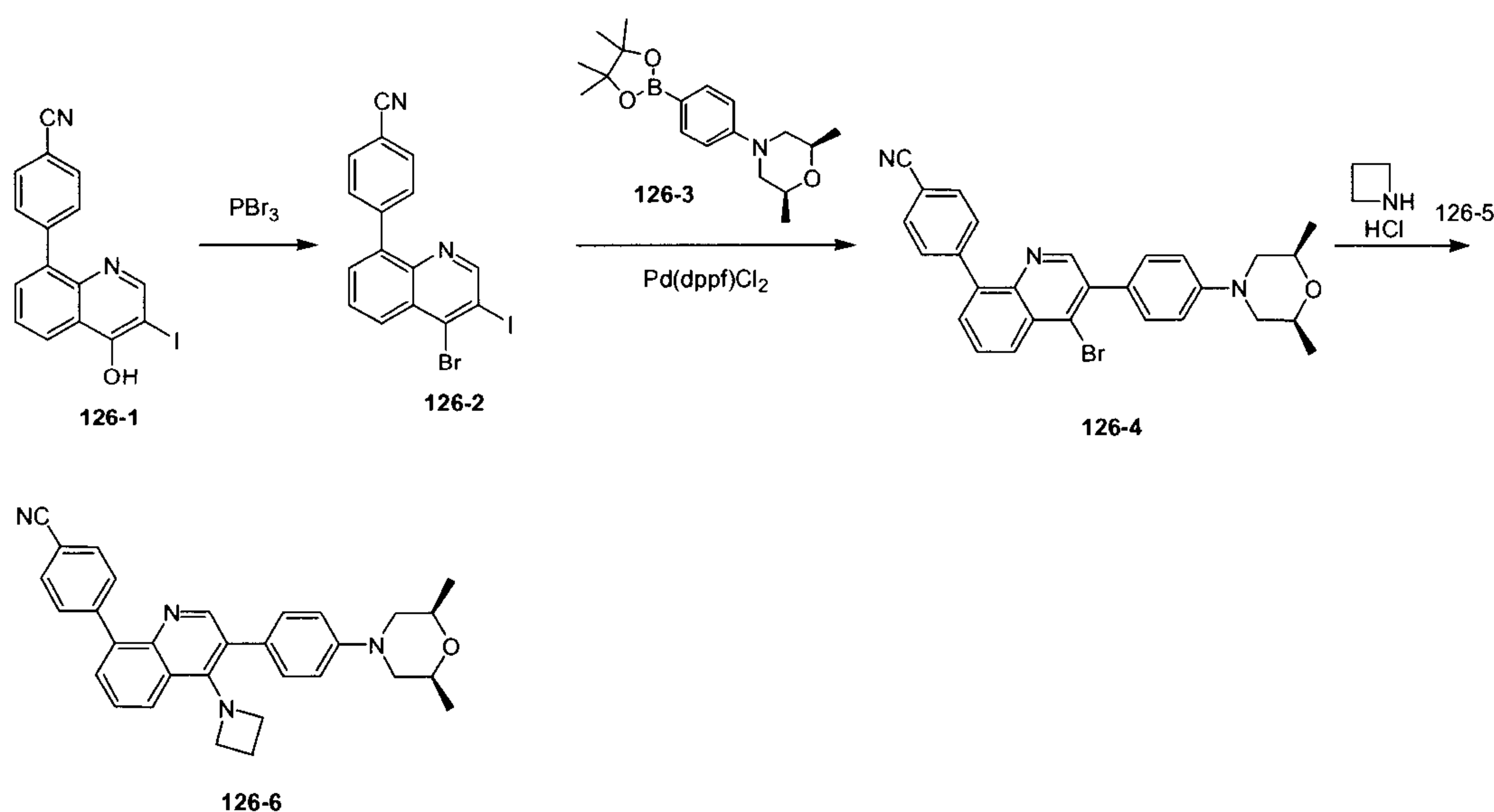
		Hz). MS ESI calcd for C ₂₉ H ₂₄ N ₄ O [M+H] ⁺ 445, found 445.
125		¹H NMR (400 MHz, CDCl ₃) δ 8.89 (s, 1H), 8.65-8.67 (d, <i>J</i> = 8.4 Hz, 1H), 8.38 (s, 1H), 7.53-7.70 (m, 5H) 7.39-7.41 (d, <i>J</i> = 7.6 Hz, 1H) 6.77-6.79 (d, <i>J</i> = 8.8 Hz, 1H) 4.14-4.17 (m, 2H), 3.79-3.81 (m, 2H) 2.61-2.67 (m, 2H) 2.32-2.34 (m, 1H) 2.24(s, 3H) 1.32-1.33 (d, <i>J</i> = 6.0 Hz 6H) 1.13-1.15 (m, 2H) 0.40-0.42 (m, 2H). MS ESI calcd for C ₃₁ H ₃₀ N ₄ O [M+H] ⁺ 475, found 475.

Embodiment 126



4-(4-(azetidin-1-yl)-3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)quinolin-8-yl)

benzonitrile

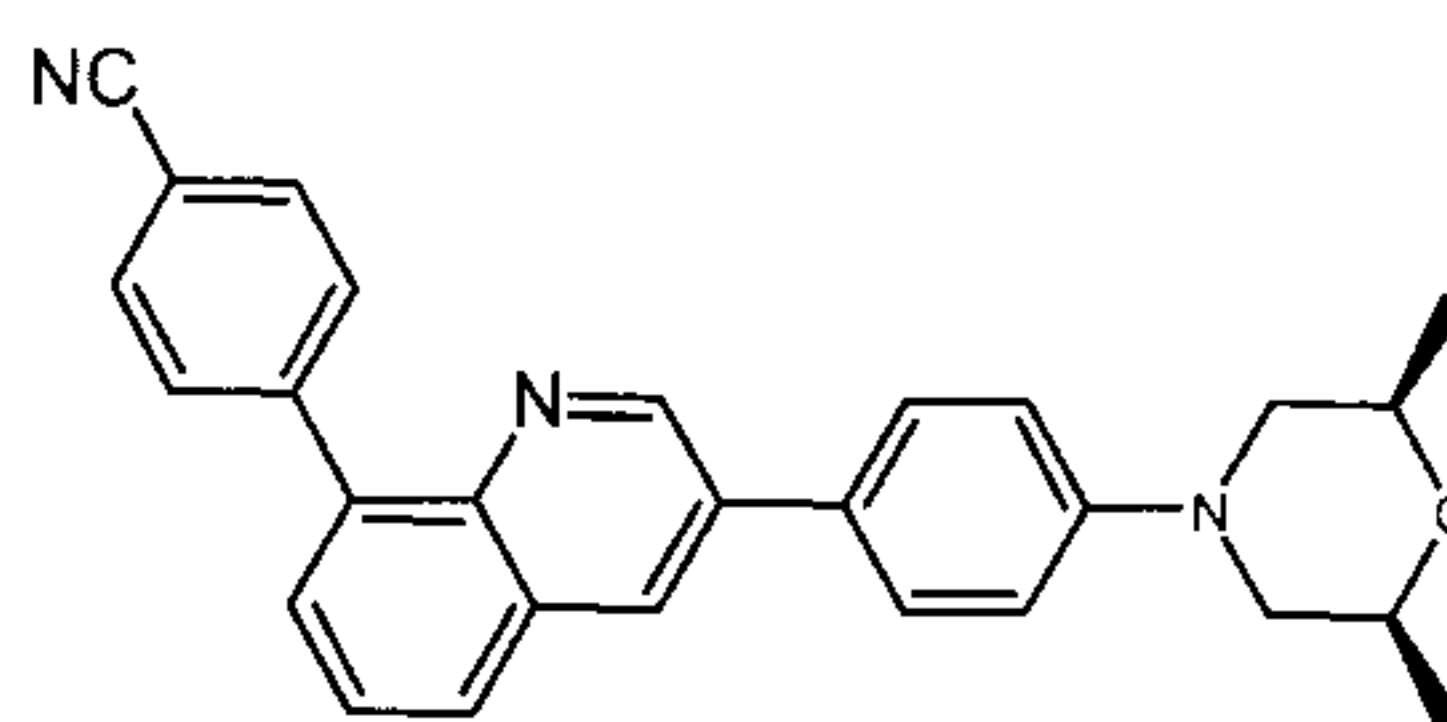


[311] Step 1: PBr₃ (26.0 g, 97 mmol) solution was added dropwise into a solution of compound 126-1 (24.0 g, 65 mmol) in DMF (320 mL). The reaction mixture was stirred at room temperature for 1h, and then filtrated to give the product 126-5 (26.0 g, yield 93%) as white solid. **MS ESI** calcd for C₁₆H₈BrIN₂ [M+H]⁺ 434, found 434.

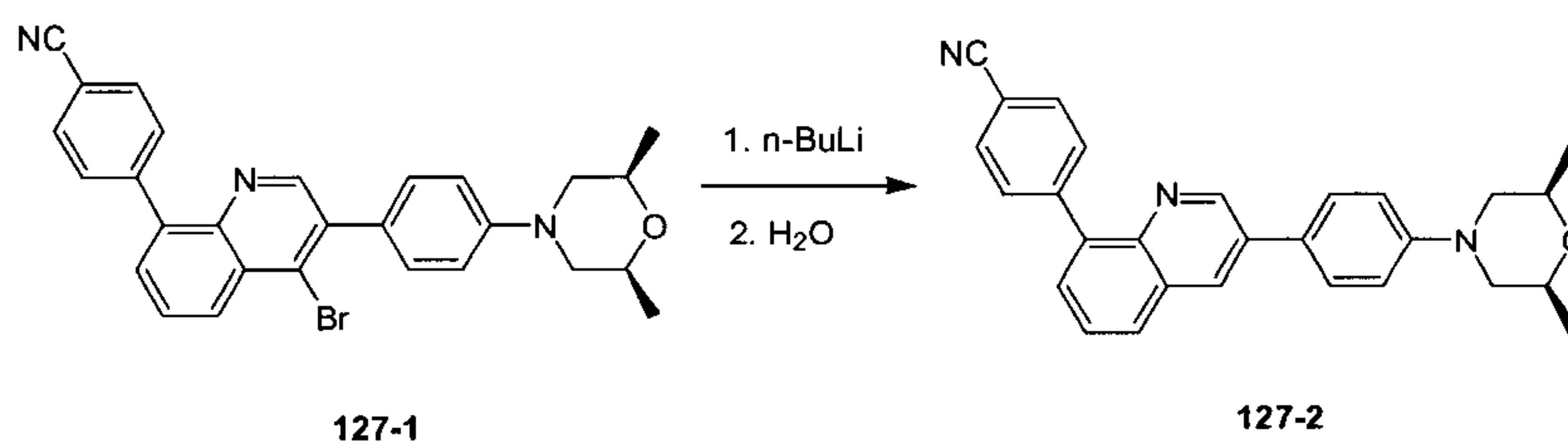
[312] Step 2: To a solution of compound 126-2 (11 g, 25 mmol), compound 126-3 (9 g, 28 mmol) and sodium carbonate (5.3 g, 50 mmol) in THF/H₂O (5:1, 180 mL), was added Pd(dppf)Cl₂ (1.83 g, 2.5 mmol). The reaction mixture was stirred at 66°C for 12h. The reaction was complete as detected by LCMS. Then the reaction mixture was poured into H₂O, extracted with EtOAc, dried over anhydrous sodium sulfate. The crude product 126- was purified by column chromatography to deliver compound 126-4 (9.3 g, yield 74%) as yellow solid. **MS ESI** calcd for C₂₈H₂₄BrN₃O [M+H]⁺ 498, found 498.

[313] Step 3: To a solution of compound 126-4 (100 mg, 0.2 mmol), compound 126-5 (37.6 mg, 0.4 mmol) and potassium *tert*-butoxide (112 mg, 1 mmol) in PhCH₃ (5 mL), were added Pd₂(dba)₃ (18.3 mg, 0.02 mmol) and Xantphos (19.1 mg, 0.04 mmol). The reaction mixture was heated to reflux for 12 h. The reaction was complete as detected by LCMS. Then the reaction mixture was poured into H₂O, extracted with ether (3×3 mL), the organic phase was dried over anhydrous sodium sulfate. After concentration, the residue was purified by preparative HPLC to deliver the title compound (yield 21%) as white solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.30 (brs, 1H), 8.00 (d, 1H, *J* = 8.0 Hz), 7.70-7.80 (m, 3H), 7.50-7.65 (m, 5H), 6.92 (d, 2H, *J* = 5.6 Hz), 3.79 (t, 3H, *J* = 8.0 Hz), 3.45-3.53 (m, 4H), 2.30-2.50 (m, 5H), 1.27 (d, 6H, *J* = 6.0 Hz). **MS ESI** calcd for C₃₁H₃₀N₄O [M+H]⁺ 475, found 475.

Embodiment 127

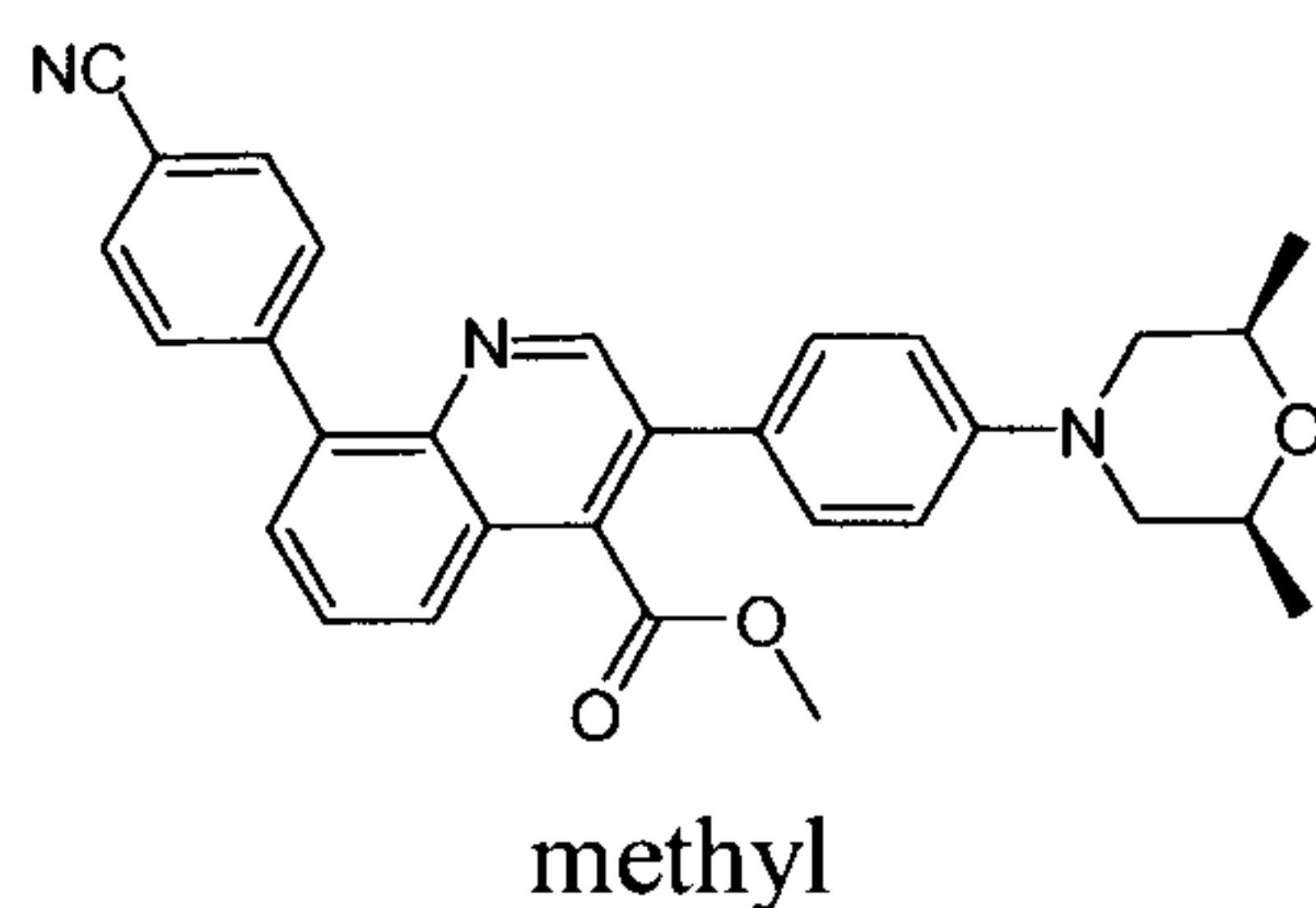


4-(3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)quinolin-8-yl)benzonitrile

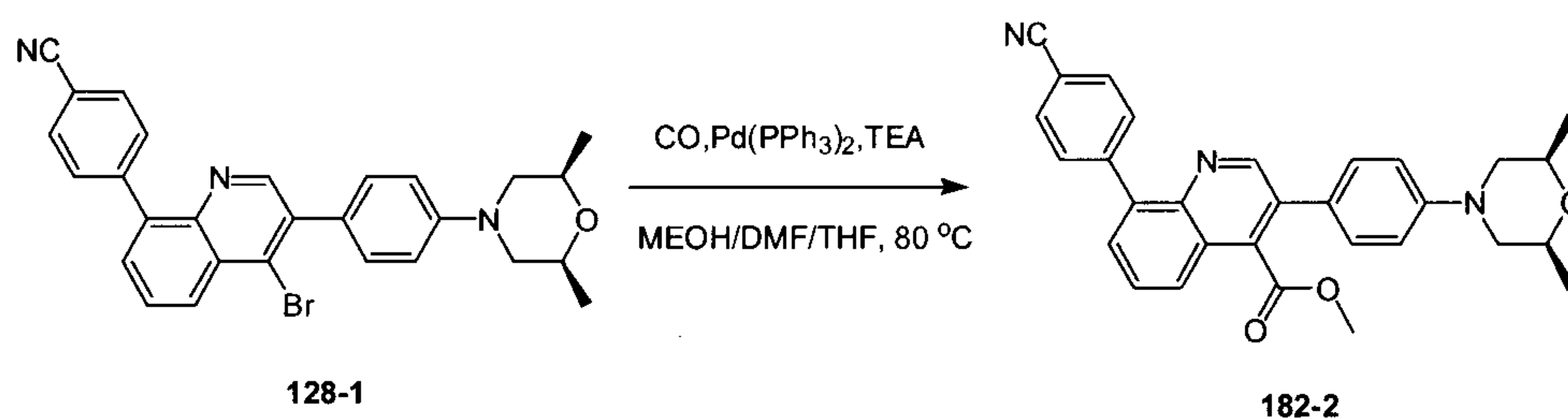


[314] *n*-BuLi (0.5 mmol, 0.2 mL) was added into a solution of compound 127-1 (150 mg, 0.3 mmol) in THF at -70 °C. The reaction mixture was poured into H₂O. The aqueous phase was extracted with EtOAc. The combined organic phase was washed with saturated brines, dried over anhydrous sodium sulfate, concentrated under reduced pressure. The crude product was purified by preparative HPLC to deliver the product (50 mg, yield: 50%) as white solid. **MS ESI** calcd for C₂₈H₂₅N₃O [M+H]⁺ 420, found 420.

Embodiment 128

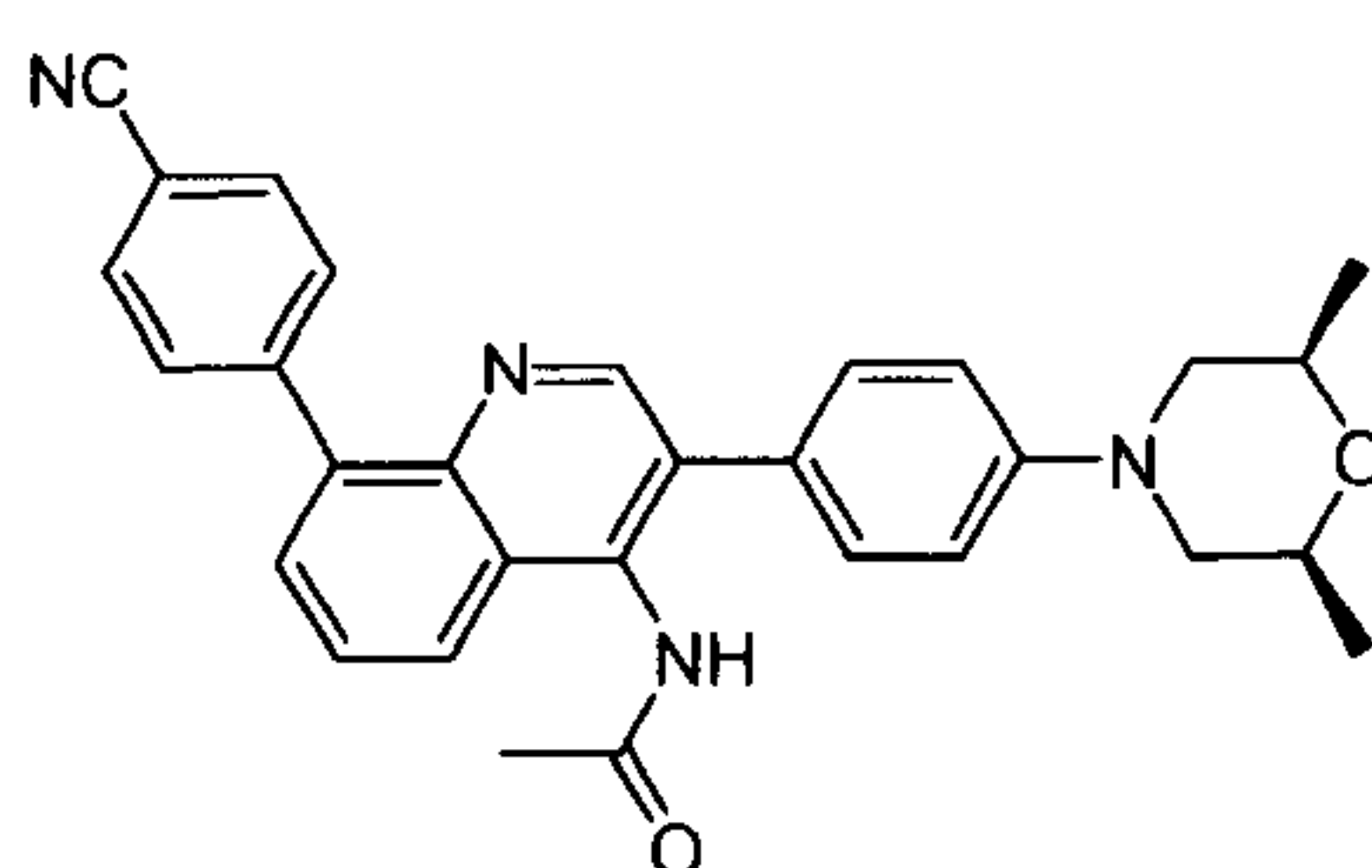


8-(4-cyanophenyl)-3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)quinoline-4-carboxylate

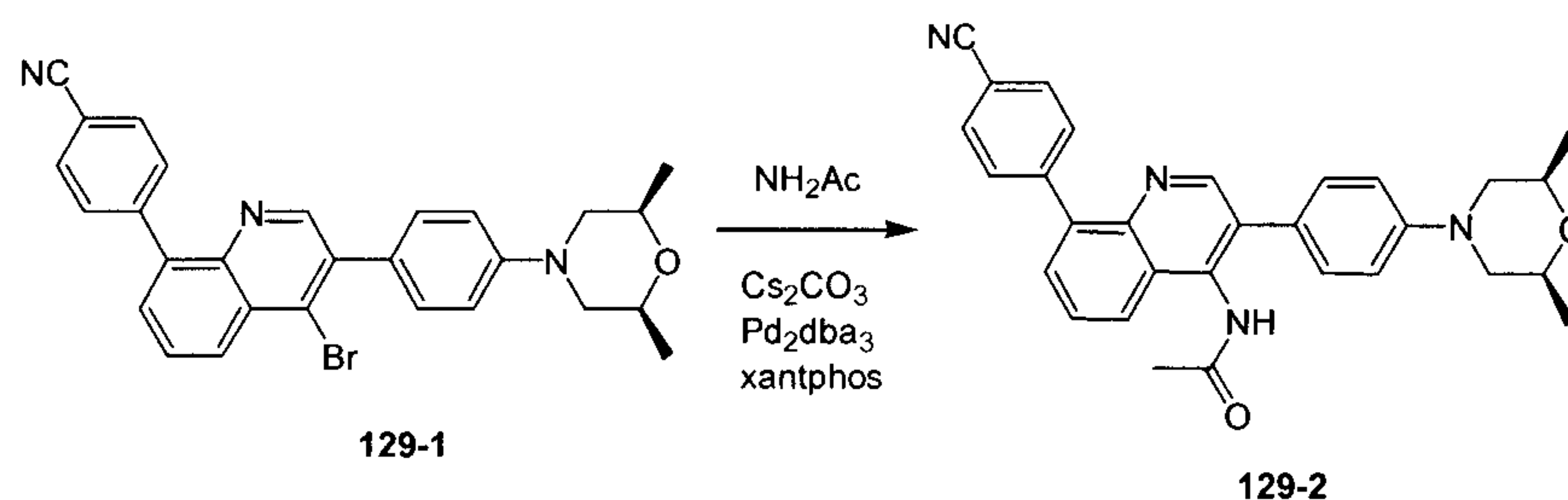


[315] $\text{Pd}(\text{PPh}_3)\text{Cl}_2$ (21 mg, 0.03 mmol) and TEA (303 mg, 3 mmol) were added into a solution of compound 128-1 (150 mg, 0.3 mmol) in methanol/DMF/THF(25/5/5 mL), under CO gas atmosphere with a pressure of 50psi, the reaction mixture was stirred at 70°C for 48h. After the reaction was complete as detected by LC-MS, the crude product was purified by preparative HPLC to deliver the title compound as white solid. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.00 (s, 1H), 7.95 (d, 1H, $J = 7.6$ Hz), 7.68-7.85 (m, 6H), 7.50 (d, 2H, $J = 8.8$ Hz), 7.27 (d, 2H, $J = 8.8$ Hz), 3.98 (d, 2H, $J = 6.4$ Hz), 3.86 (s, 3H), 3.62 (d, 2H, $J = 11.6$ Hz), 2.62-2.73 (m, 2H), 1.30 (d, 6H, $J = 6.0$ Hz). **MS ESI** calcd for $\text{C}_{30}\text{H}_{27}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$ 478, found 478.

Embodiment 129



N-(8-(4-cyanophenyl)-3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)quinolin-4-yl)acetamide



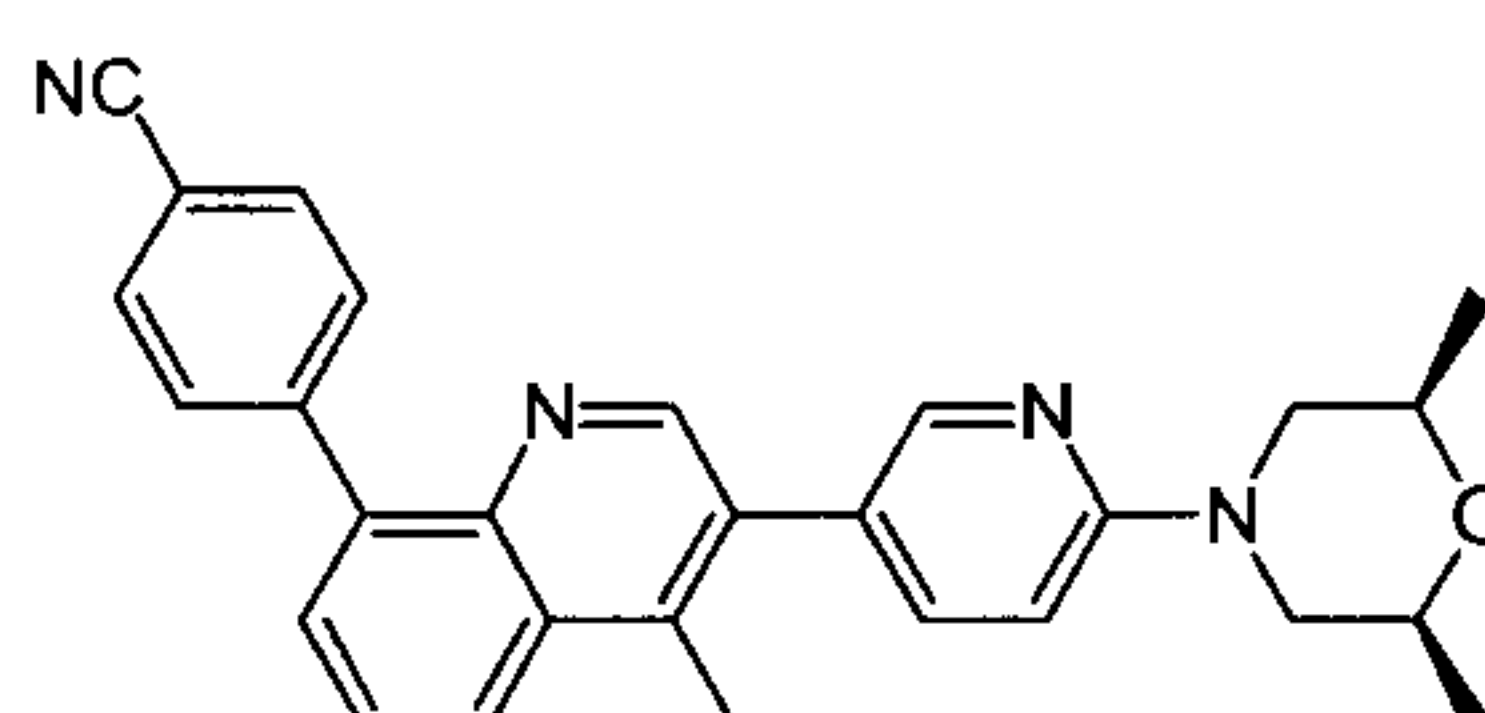
[316] Cesium carbonate (100 mg, 0.3 mmol), Pd₂dba₃ (9 mg, 0.01mmol) and Xantphos (12 mg, 0.02 mmol) were added into a solution of compound 129-1 (50 mg, 0.1 mmol) and NH₂Ac (30 mg, 0.5 mmol) in dioxane (5 mL). The reaction mixture was heated to reflux for 12 h. After the reaction was complete as detected by LC-MS, the reaction mixture was poured into H₂O, extracted with EtOAc, dried over anhydrous sodium sulfate and dissolved in DMF. The crude product was purified by preparative HPLC to deliver the title compound (21 mg, yield 44%) as yellow solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.93 (s, 1H), 8.00 (d, 1H, *J*=8.4 Hz), 7.65-7.80 (m, 6H), 7.37 (d, 2H, *J*=8.8 Hz), 7.10 (d, 2H, *J*=8.8 Hz), 3.87 (t, 2H, *J*=7.6 Hz), 3.58 (d, 2H, *J*=11.6 Hz), 3.56 (t, 2H, *J*=11.6 Hz), 2.22 (brs, 2H), 1.93 (s, 3H), 1.18 (d, 6H, *J*=6.0 Hz). **MS ESI** calcd for C₃₀H₂₈N₄O₂ [M+H]⁺ 477 found 477.

[317] The compounds listed in table 9 were synthesized by compound 129-1 and corresponding amides.

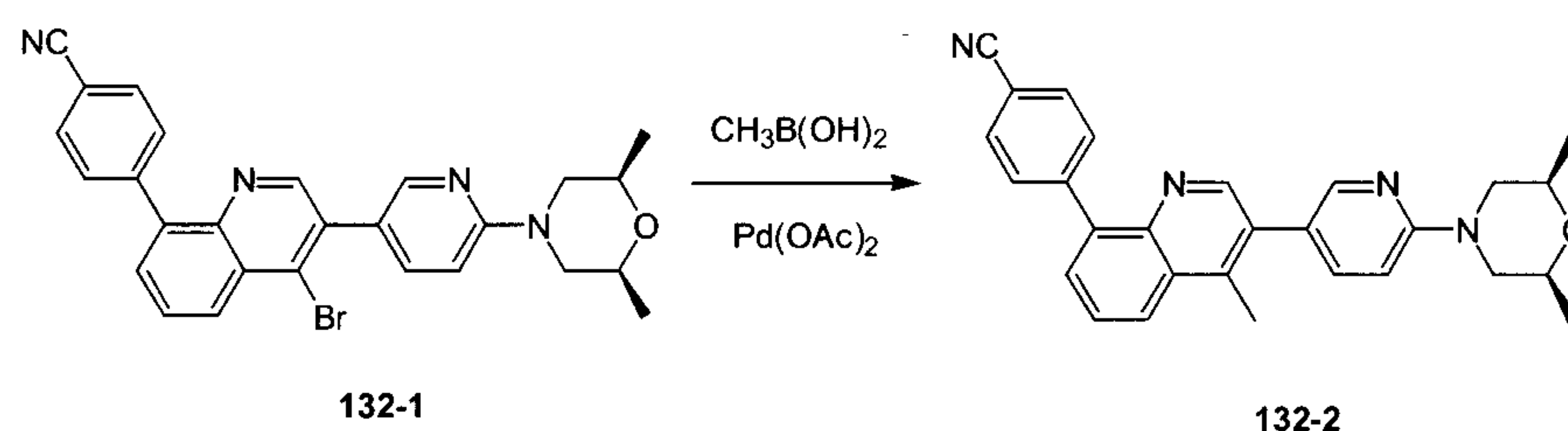
Embodi ment	Structure	NMR
130		¹H NMR (400 MHz, CDCl ₃) δ 8.92 (s, 1H), 8.40-8.48 (m, 1H), 7.72-7.82 (m, 6H), 7.41 (d, 2H, <i>J</i> =8.4 Hz), 7.10 (d, 2H, <i>J</i> =8.8 Hz), 6.78 (s, 1H), 3.86 (t, 2H, <i>J</i> =7.6 Hz), 3.56 (d, 2H, <i>J</i> =10.4 Hz), 2.45-2.55 (m, 5H), 1.28 (d, 6H, <i>J</i> =6.4 Hz). MS ESI calcd for C ₂₉ H ₂₈ N ₄ O ₃ S [M+H] ⁺ 513, found 513.
131		¹H NMR (400 MHz, CDCl ₃) δ 8.96 (s, 1H), 7.95-8.00 (m, 1H), 7.68-7.78 (m, 6H), 7.42 (d, 2H, <i>J</i> =8.4 Hz), 7.07 (d, 2H, <i>J</i> =7.2 Hz), 4.50-4.60 (m, 1H), 4.25-4.35 (m, 1H), 3.86 (brs, 2H), 3.65-3.75 (m, 1H), 3.56 (d, 2H, <i>J</i> =12.0 Hz), 3.40-3.50 (m, 1H), 3.53 (t, 2H, <i>J</i>

		=11.6 Hz), 1.29 (d, 6H, J =6.0 Hz). MS ESI calcd for $C_{31}H_{28}N_4O_3$ $[M+H]^+$ 505, found 505.
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Embodiment 132



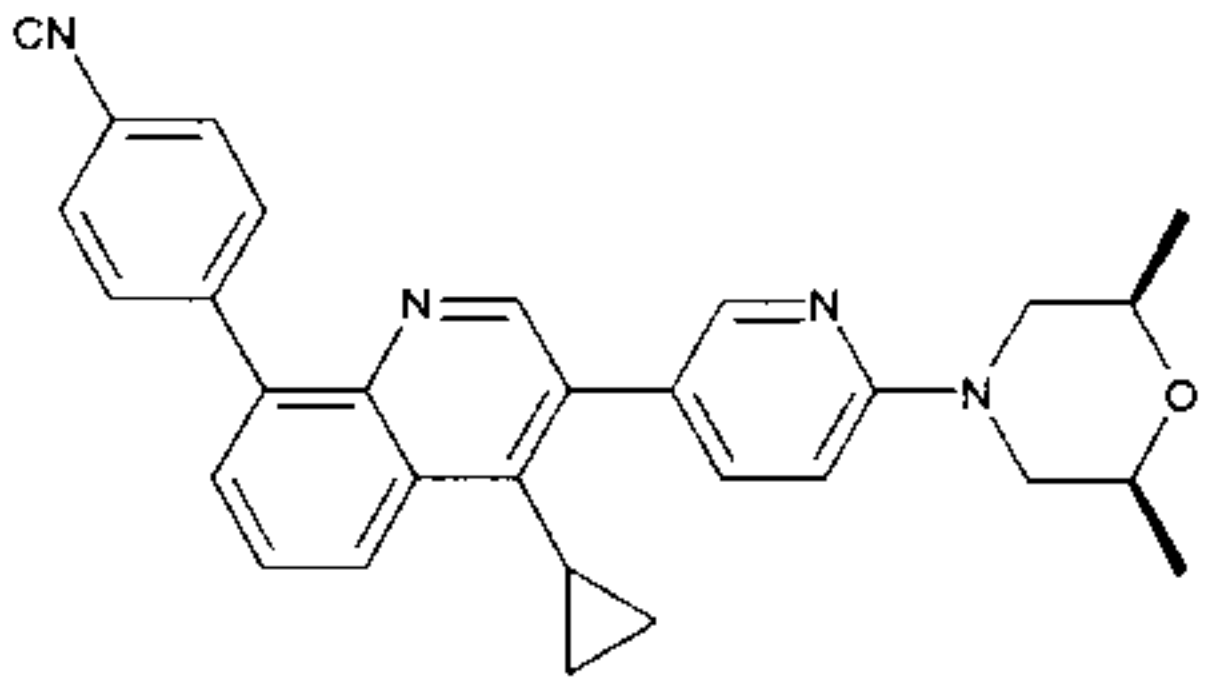
4-(3-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-4-methylquinolin-8-yl)
benzonitrile



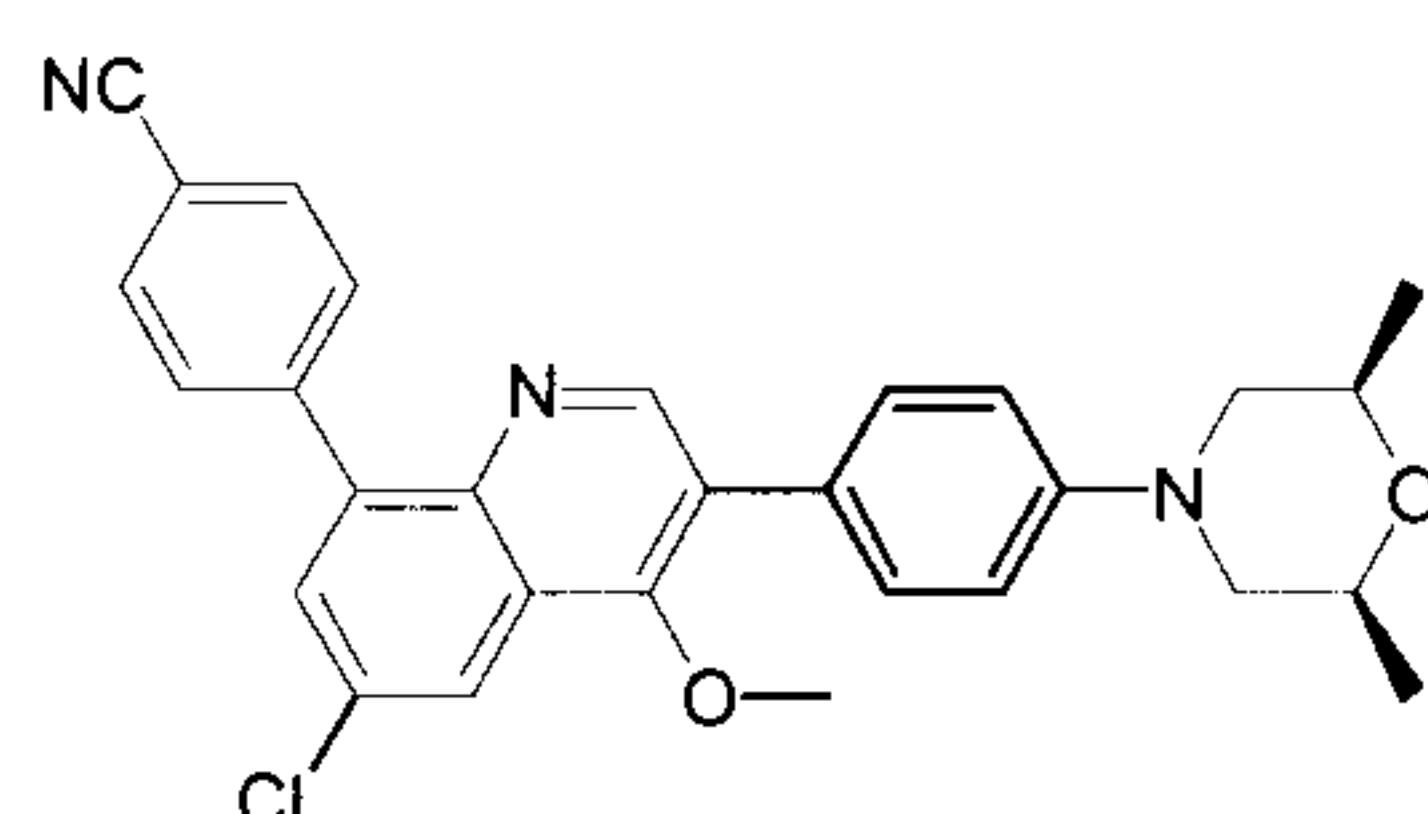
[318] A mixture of *n*-BuPAd₂ (20 mg, 0.04 mmol), palladium acetate (5 mg, 0.02 mmol) and cesium carbonate (130 mg, 0.4 mmol) was added into a solution of compound 132-1 (100 mg, 0.2 mmol) and CH₃B(OH)₂ (120 mg, 2 mmol) in Toluene/H₂O (3 mL / 1 mL), then the reaction mixture was stirred at 110°C overnight. After poured into H₂O, the mixture was extracted with EtOAc, dried over sodium sulfate, concentrated to deliver the crude product which was purified by preparative HPLC to deliver the title compound (30 mg, yield 30%) as yellow solid. **MS ESI** calcd for $C_{28}H_{26}N_4O$ $[M+H]^+$ 435 found 435.

[319] The compounds listed in table 10 were synthesized by compound 132-1 and corresponding boric acids.

Embodiment	structure	NMR
133		¹ H NMR (400 MHz, CDCl ₃) δ 8.70 (s, 1H), 8.29 (s, 1H), 8.20 (dd, 1H, J =2.8 Hz, J =6.8 Hz), 7.65-7.80 (m, 7H), 6.93 (d, 1H, J =8.0 Hz), 4.15 (d, 2H, J =12.8 Hz), 3.70-3.83 (m, 2H), 3.11 (d, 2H, J =7.6 Hz), 2.82 (t, 2H, J =11.2 Hz), 1.25-1.38 (m, 9H). MS ESI calcd for $C_{29}H_{28}N_4O$ $[M+H]^+$ 449, found 449.

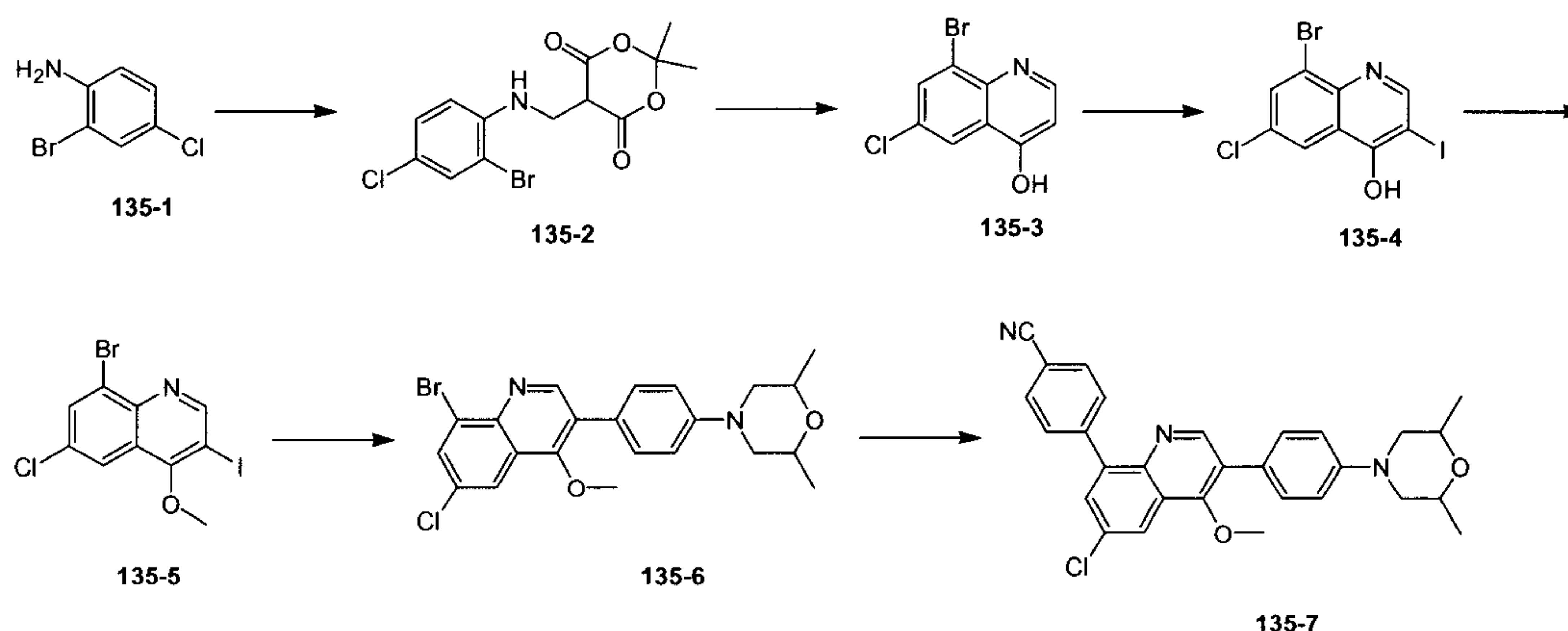
134		¹H NMR (400MHz, CDCl₃) 8.83 (s, 1H), 8.65-8.66 (d, <i>J</i>=5.2 Hz, 1H), 8.37-8.38 (d, <i>J</i>=2.8 Hz, 1H), 7.77-7.82 (d d, <i>J</i> =8.0 Hz, 4H), 7.67-7.70 (d d, <i>J</i>=3.6 Hz, 3H), 6.76-6.78 (d, <i>J</i> =8.8 Hz, 1H), 4.13-4.16 (d, <i>J</i> =11.6 Hz 2H), 3.77-3.81 (m, 2H), 2.61-2.66 (t, <i>J</i> =22.8 Hz 2H), 2.31-2.33 (m, 1H), 1.31-1.33 (d, <i>J</i> =6.8 Hz 6H), 1.11-1.13 (m, 2H), 0.38-0.39 (m, 2H). MS ESI calcd for C₃₀H₂₈N₄O [M+H]⁺ 461, found 461.
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Embodiment 135



4-(6-chloro-3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxyquinolin-8-yl)

benzonitrile



[320] Step 1: A mixture of 2,2-dimethyl-1,3-dioxane-4,6-dione (19.2 g, 133 mmol) and trimethoxymethane (70 mL, 680 mmol) was refluxed for 2.5h, then the compound 135-1 (20 g, 97 mmol) was added into the solution at 100°C and stirred overnight, the solid was collected after filtration to give compound 135-2 (35.6 g, yield 98%) as yellow solid. **MS ESI** calcd for C₁₃H₁₃BrClNO₄ [M+H]⁺ 362, found 362.

[321] Step 2: A mixture of compound 135-2 (35.6 g, 100 mmol) and compound 135-Ph₂O (170 g, 1 mol) was heated to 250°C for 0.5h, then cooled to room temperature, the solid was collected after filtration to give the product as brown solid

(12.2g, yield 48%). **MS ESI** calcd for $C_9H_5BrClNO$ $[M+H]^+$ 258, found 258.

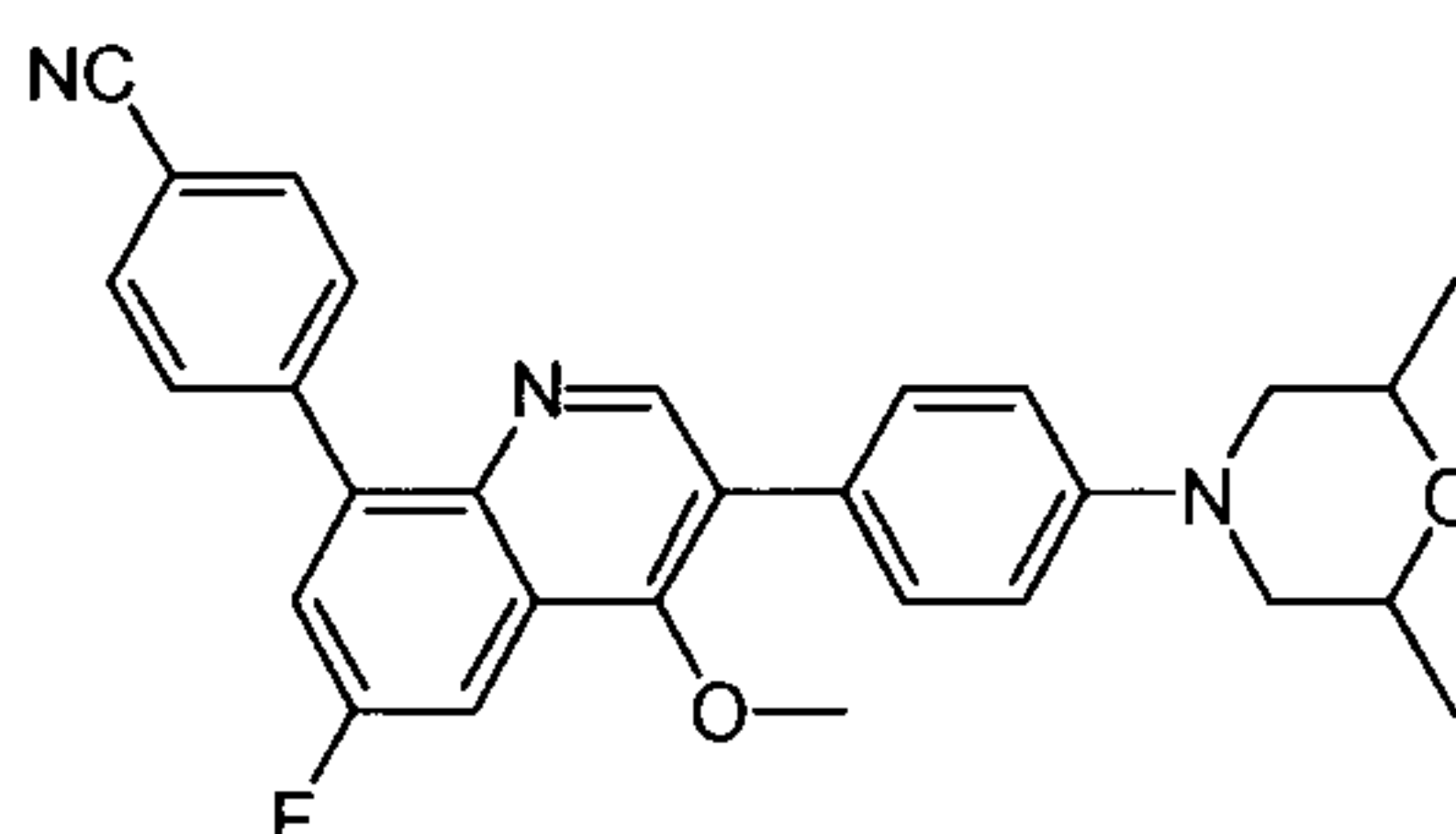
[322] Step 3: To a solution of compound 135-3 (3.56 g, 14 mmol) and NIS (3.1 g, 14 mmol) in DMF (10 mL), the mixture was stirred at room temperature for 2h, the solid was collected after filtration to give 4.2 g product as yellow solid (yield 80%). **MS ESI** calcd for $C_9H_4BrClINO$ $[M+H]^+$ 384, found 384.

[323] Step 4: MeI (2.0 g, 14 mmol) and Ag_2CO_3 (6.6 g, 24 mmol) were added into a solution of compound 135-4 (4.5 g, 12 mmol) in DMF (20 mL), then the mixture was stirred at 70°C for 2h, after filtration, the mixture was extracted with EtOAc, dried over sodium sulfate, concentrated to deliver 4.8g crude product, which was purified by column chromatography to deliver 2.2g product as red solid (yield 47%). **MS ESI** calcd for $C_{10}H_6BrClINO$ $[M+H]^+$ 397, found 397.

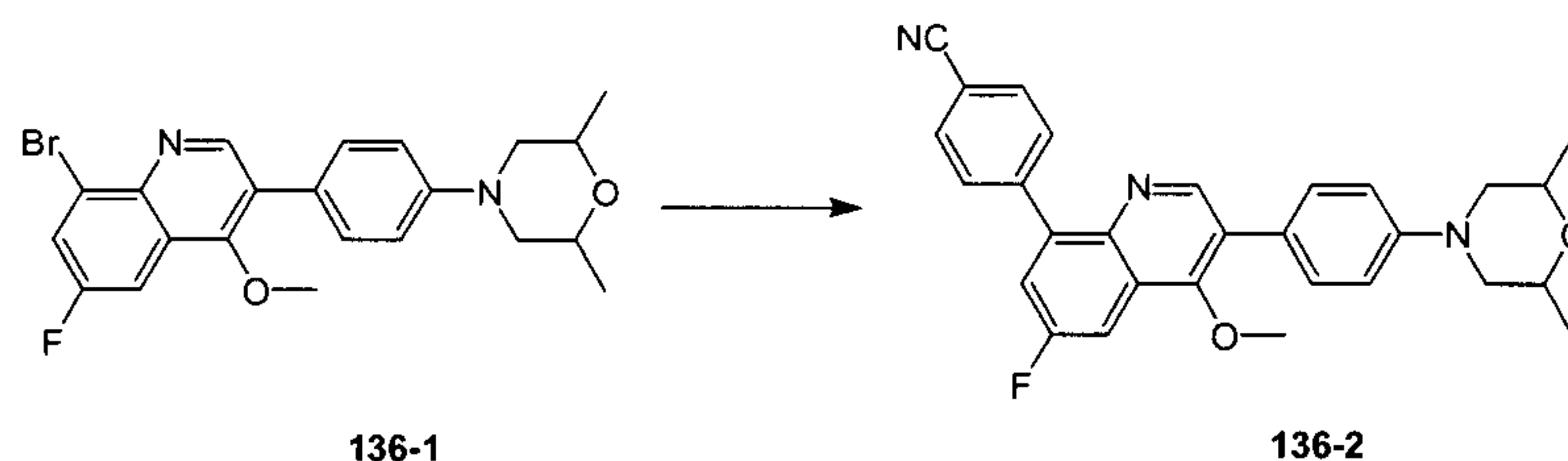
[324] Step 5: $Pd(dppf)Cl_2$ (40 mg, 0.05 mmol) and sodium carbonate (107 mg, 1.0 mmol) were added into a solution of compound 135-5 (200 mg, 0.5 mmol) and 2,6-dimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine (160 mg, 0.5 mmol) in THF/ H_2O (6 mL, 5:1). The reaction mixture was stirred at 70°C overnight, then poured into H_2O , the mixture was extracted with EtOAc, dried over sodium sulfate, concentrated to deliver compound 135-6 as yellow solid (200mg, yield 40%). **MS ESI** calcd for $C_{22}H_{22}BrClN_2O_2$ $[M+H]^+$ 461, found 461.

[325] Step 6: $Pd(dppf)Cl_2$ (37 mg, 0.05 mmol) and sodium carbonate (92 mg, 0.86 mmol) were added into a solution of compound 135-6 (200 mg, 0.43 mmol) and 4-cyanophenylboronic acid (63.7 mg, 0.43 mmol) in THF/ H_2O (6 mL, 5:1). After stirred at 70°C for 3h, the mixture was poured into H_2O , extracted with EtOAc, dried over sodium sulfate, concentrated to deliver the crude product which was purified by preparative HPLC to deliver the title compound (55 mg, yield 26%) as yellow solid. **^1H NMR** (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.27 (d, 1H, $J=2.4$ Hz), 7.78 (dd, 4H, $J=8.4$ Hz, $J=10.8$ Hz), 7.63 (d, 1H, $J=2.0$ Hz), 7.54 (d, 2H, $J=8.8$ Hz), 7.02 (d, 2H, $J=8.4$ Hz), 3.75-3.85 (m, 2H), 3.68 (s, 3H), 3.56 (d, 2H, $J=10.8$ Hz), 2.50 (t, 2H, $J=11.2$ Hz), 1.28 (d, 6H, $J=6.4$ Hz). **MS ESI** calcd for $C_{29}H_{26}ClN_3O_2$ $[M+H]^+$ 484, found 484.

Embodiment 136



4-(3-(4-(2,6-dimethylmorpholino)phenyl)-6-fluoro-4-methoxyquinolin-8-yl)
benzonitrile



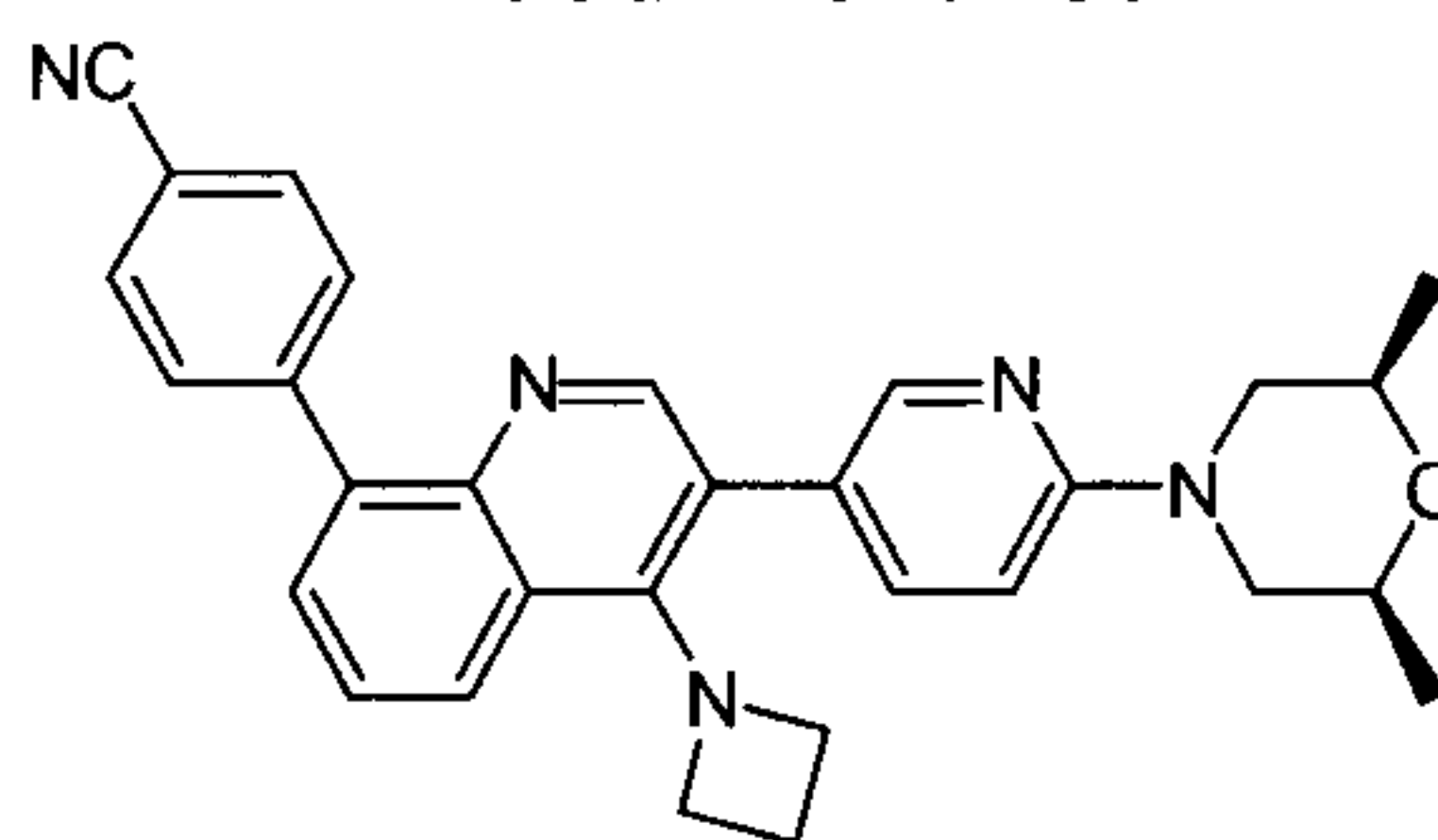
[326] Pd(dppf)Cl₂ (33 mg, 0.045 mmol) and sodium carbonate (96 mg, 0.9 mmol) were added into a solution of compound 136-1 (200 mg, 0.45 mmol) and 4-cyanophenylboronic acid (66 mg, 0.45 mmol) in THF/H₂O (6 mL, 5:1). The reaction mixture was stirred at 70°C overnight, then poured into H₂O, extracted with EtOAc, dried over sodium sulfate, concentrated to deliver the crude product which was purified by preparative HPLC to deliver the title compound (45 mg, yield 21.4%) as yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.82 (s, 1H), 7.65-7.70 (m, 1H), 7.70-7.80 (m, 4H), 7.50-7.60 (m, 2H), 7.47 (dd, 1H, *J*=2.8 Hz, *J*=8.8 Hz), 7.03 (brs, 2H), 3.85 (brs, 2H), 3.68 (s, 3H), 3.56 (d, 2H, *J*=10.8 Hz), 2.53 (t, 2H, *J*=10.4 Hz), 1.29 (d, 6H, *J*=6.4 Hz). MS ESI calcd for C₂₉H₂₆FN₃O₂ [M+H]⁺ 468 found 468.

[327] The compounds listed in table 11 were synthesized by compound 136-1 and corresponding boric acids.

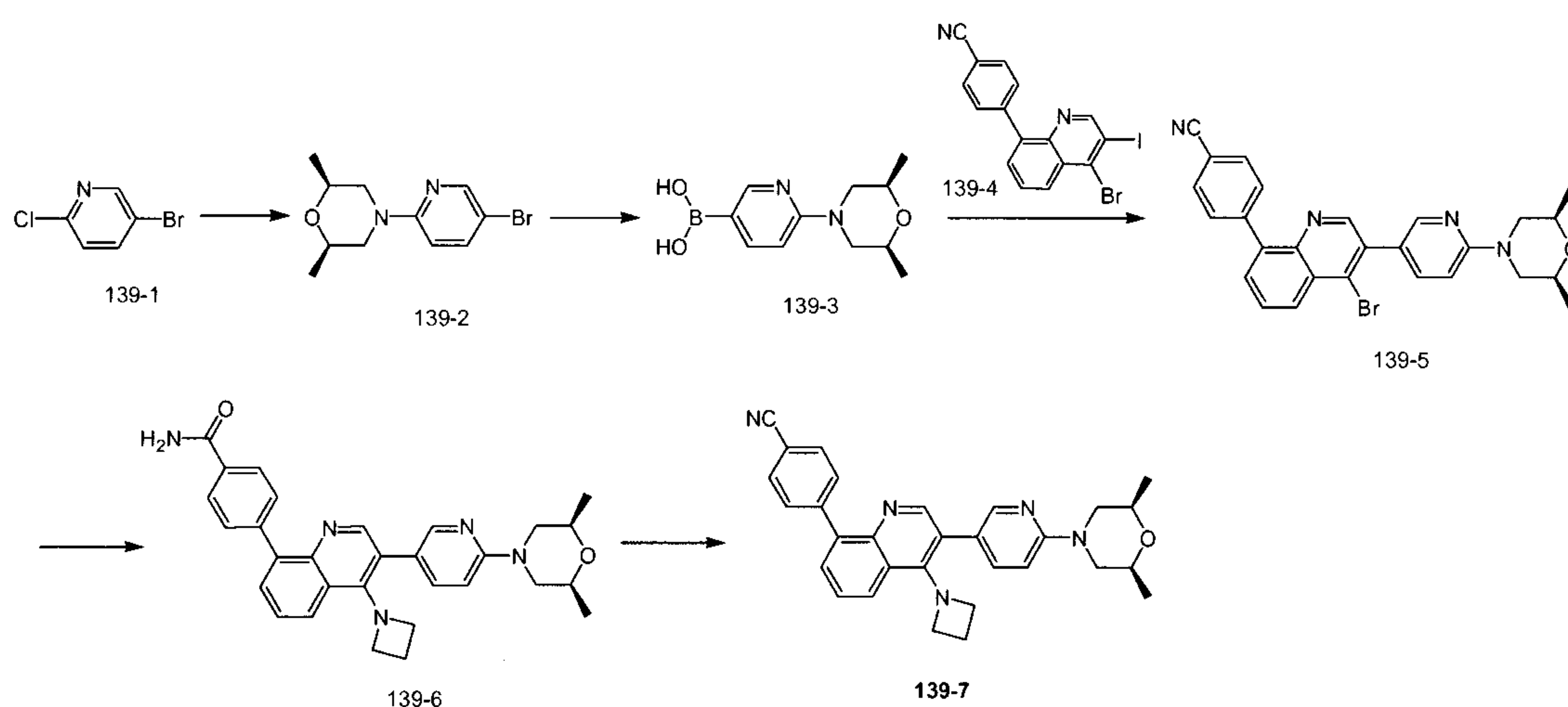
Embodiment	Structure	NMR
137		¹ H NMR (400 MHz, CDCl ₃) δ 8.73 (s, 1H), 7.70-7.75 (m, 1H), 7.61 (d, 2H, <i>J</i> =8.8 Hz), 7.45 (d, 2H, <i>J</i> =8.4 Hz), 7.35 (dd, 1H, <i>J</i> =2.8 Hz, <i>J</i> =9.2 Hz), 7.22 (d, 2H, <i>J</i> =8.0 Hz), 6.85-7.00 (m, 2H), 3.65-3.80 (m, 2H), 3.56 (s, 3H), 3.40-3.45 (m, 2H), 2.35-2.45 (m, 2H), 1.17 (d, 6H, <i>J</i> =6.0 Hz). MS ESI calcd for C ₂₉ H ₂₆ F ₄ N ₂ O ₃ [M+H] ⁺ 527, found 527.
138		¹ H NMR (400 MHz, CDCl ₃) δ 8.83 (s, 1H), 7.85-7.90 (m, 1H), 7.72-7.78 (m, 4H), 7.50-7.58 (m, 2H), 7.47 (dd, 1H, <i>J</i> =2.8 Hz, <i>J</i> =8.8 Hz), 7.05 (m, 2H), 3.75-3.90 (m, 2H), 3.69 (s, 3H), 3.56 (d, 2H, <i>J</i> =10.8 Hz), 2.53 (t, 2H, <i>J</i> =10.4 Hz), 1.29 (d, 6H, <i>J</i> =6.4 Hz). MS ESI calcd

	for C ₂₉ H ₂₆ FN ₃ O ₂ [M+H] ⁺ 468, found 468.
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Embodiment 139



4-(4-(azetidin-1-yl)-3-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)quinolin-8-yl)benzonitrile



[328] Step 1: 2,6-dimethylmorpholine (18 g, 0.15 mol) and K₂CO₃ (27.6 g, 0.2 mol) were added into a solution of compound 139-1 (19.2 g, 0.1 mol) in DMF (200 mL), the reaction mixture as stirred at 120°C for 4h. After poured into H₂O, the reaction mixture was extracted with EtOAc, dried oversodium sulfate, concentrated to deliver the crude product which was purified by column chromatography (EtOAc: PE =1:5 to 1:1) to deliver compound 139-2 (15.4 g, yield 57%) as yellow solid. **MS ESI** calcd for C₁₁H₁₅BrN₂O [M+H]⁺ 271, found 271.

[329] Step 2: Pd(dppf)Cl₂ (732 mg, 1 mmol) and AcOK (4.0 g, 40 mmol) were added into a solution of compound 139-2 (5.4 g, 20 mmol) and bis(pinacolato)diboron (7.6 g, 30 mmol) in 1,4-dioxane (100 mL), the mixture was stirred at 120°C for 6h. Then the solvent was removed, the residue was purified by column chromatography (EtOAc: PE =1:10 to 1:2) to deliver compound 139-3 (5.0 g, yield 98%) as white solid. **MS ESI** calcd for C₁₁H₁₇BN₂O₃ [M+H]⁺ 237, found 237.

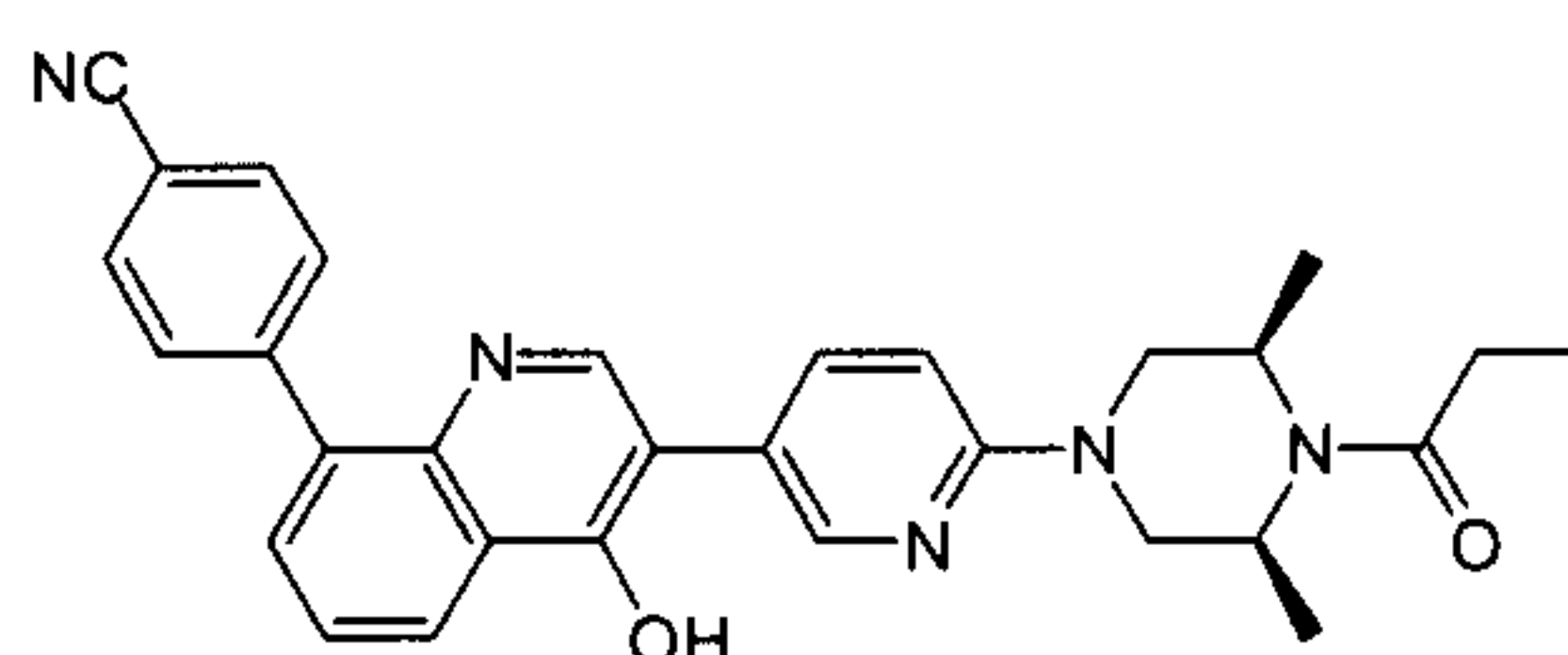
[330] Step 3: A mixture of sodium carbonate (214 mg, 4 mmol) was added into a solution of compound 139-3 (236 mg, 0.7 mmol) and compound 139-4 (300 mg, 2 mmol) in DMF/H₂O/THF (14:1:5 mL), and the mixture was stirred at -80°C for 2h. After poured in H₂O, the reaction mixture was extracted with EtOAc, dried over sodium sulfate, concentrated to deliver the crude product which was purified by

column chromatography (PE: EtOAc=5: 1) to deliver compound 139-5 (200mg, yield 57%) as white solid. **MS ESI** calcd for $C_{27}H_{23}BrN_4O$ $[M+H]^+$ 499, found 499.

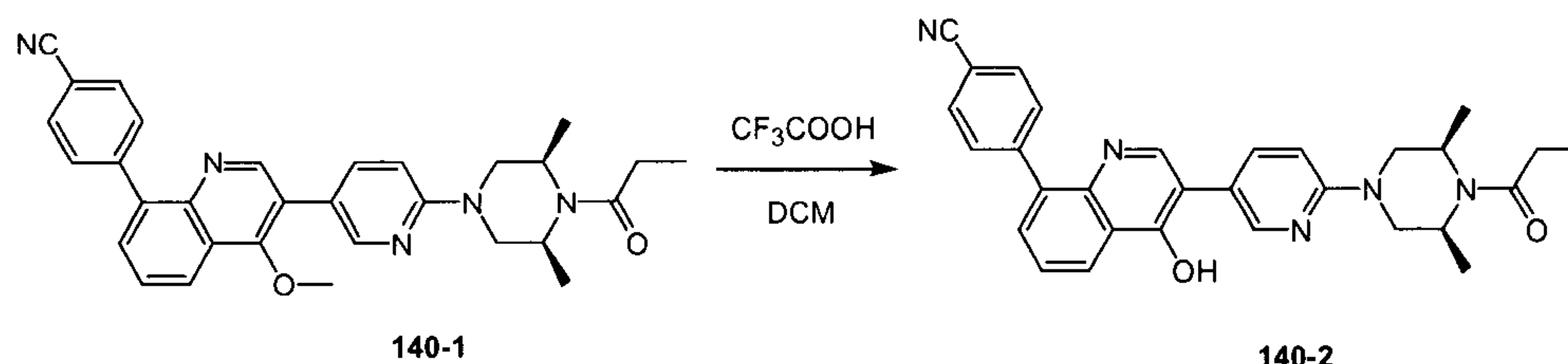
[331] Step 4: Xantphos (350 mg, 0.6 mmol), $Pd_2(dba)_3$ (275 mg, 0.3 mmol) and potassium *tert*-butoxide (1.3 g, 12 mmol) were added into a solution of compound 139-2 (1.5 g, 3 mmol) and azetidine (560 mg, 6 mmol) in toluene (20 mL), the reaction mixture was stirred at 110°C for 3h. After poured in H_2O , the reaction mixture was extracted with EtOAc, dried over sodium sulfate, concentrated to deliver the crude product which was purified by column chromatography to deliver the desired product compound 139-6 as yellow solid (500mg, yield 30%). **MS ESI** calcd for $C_{30}H_{31}N_5O_2$ $[M+H]^+$ 494, found 494.

[332] Step 5: TFAA (4 mL) and DIPEA (4 mL) were added into a solution of compound 139-6 (1.5 g, 3 mmol) in DCM (20 mL), the reaction mixture was stirred at room temperature for 30min, then poured in H_2O , extracted with EtOAc, dried over sodium sulfate, concentrated to deliver the crude product which was transferred to be purified by preparative HPLC to deliver the title compound as yellow solid (500mg, yield 30%). **^1H NMR** (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.19 (s, 1H), 8.05 (d, 1H, $J=8.0$ Hz), 7.93 (brs, 1H), 7.80 (d, 2H, $J=7.6$ Hz), 7.50-7.70 (m, 4H), 6.98 (brs, 1H), 4.70 (brs, 3H), 4.17 (d, 3H, $J=12.4$ Hz), 3.65-3.80 (m, 2H), 2.78 (t, 2H, $J=11.6$ Hz), 2.47 (brs, 2H), 1.30 (d, 6H, $J=6.0$ Hz). **MS ESI** calcd for $C_{30}H_{29}N_5O$ $[M+H]^+$ 476 found 476.

Embodiment 140



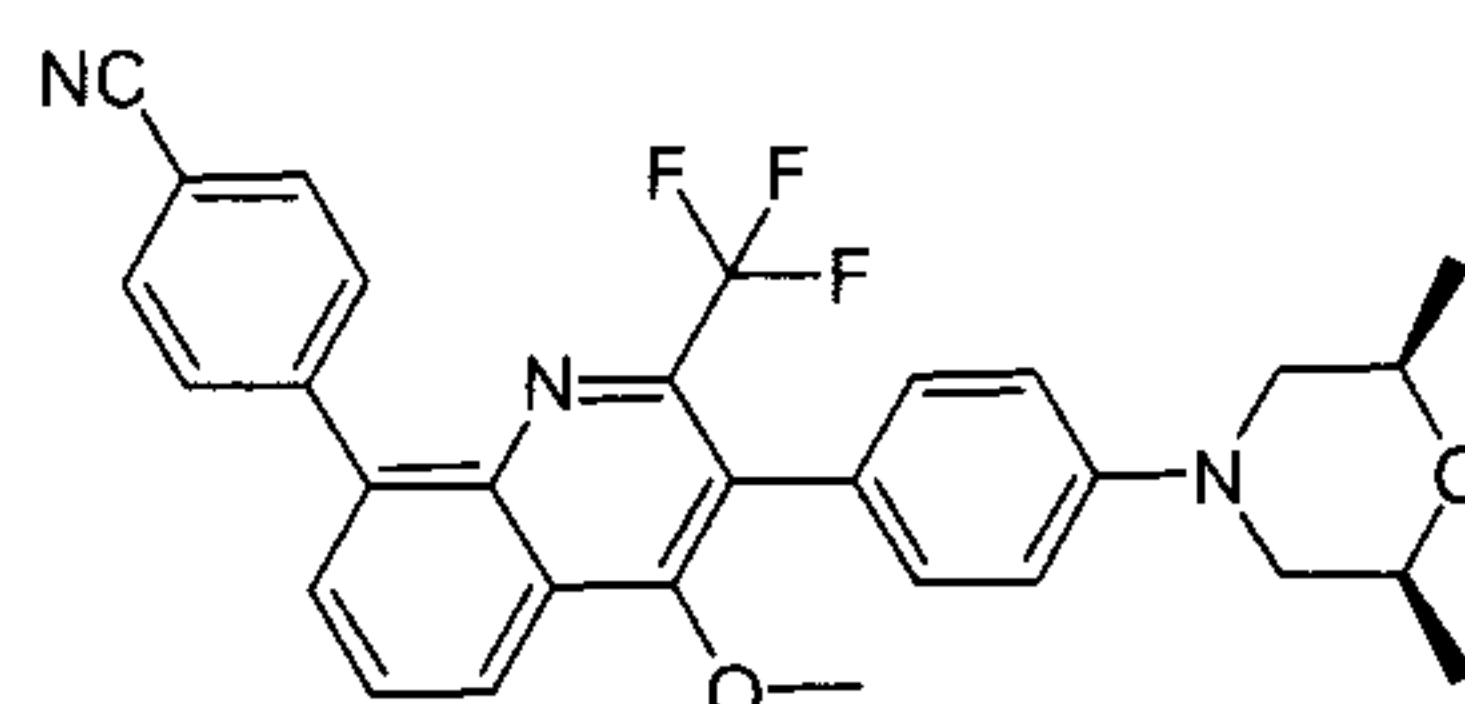
4-(3-(6-((3S,5R)-3,5-dimethyl-4-propionylpiperazin-1-yl)pyridin-3-yl)-4-hydroxyquinolin-8-yl)benzonitrile



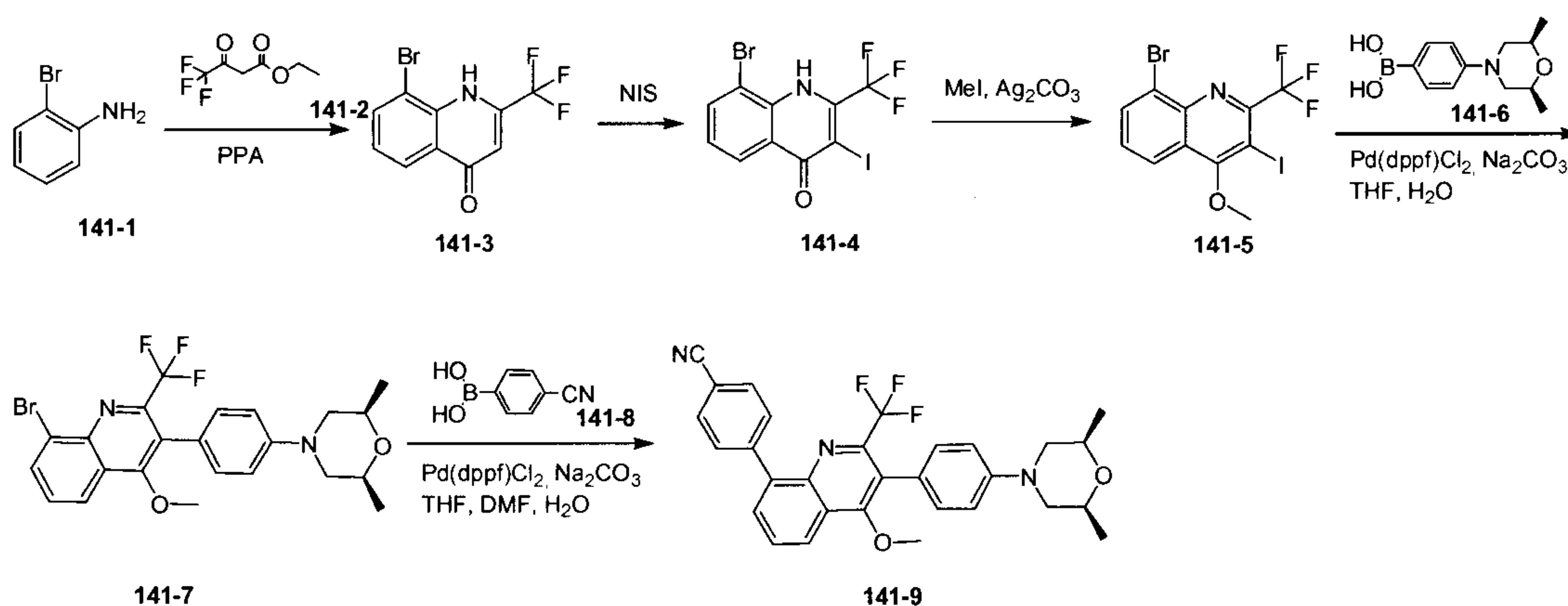
[333] CF_3COOH (114 mg, 1 mmol) was added into a solution of compound 140-1 (100 mg, 0.2 mmol) in DCM (5 mL). The reaction mixture was stirred at 50°C for 2h, the reaction was complete as detected by LC-MS. The reaction mixture was poured in H_2O , extracted with EtOAc (30×3 mL), the organic phase was dried over sodium sulfate. After concentration, the residue was purified by preparative HPLC to deliver the title compound (30mg) as white solid product. **MS ESI** calcd for

$C_{30}H_{29}N_5O_2$ $[M+H]^+$ 492 found 492.

Embodiment 141



4-(3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxy-2-(trifluoromethyl)quinolin-8-yl)benzonitrile



[334] Step 1: Compound 141-1 (10 g, 58.5 mmol) was added dropwise into a mixture of compound 140-2 (10.7 g, 58.5 mmol) and PPA (40 g) at 100°C, the period of addition was no less than 15 min. After the addition, the reaction mixture was heated to 150°C and stirred for 12 h. After cooling, the reaction mixture was diluted with sodium hydroxide (160 mL, 10 wt.%). The obtained precipitate was filtrated, the filtrate was acidified with *conc.* hydrochloric acid. The obtained precipitate was filtrated, recrystallized with ethanol to deliver compound 141-3 (10.5 g, yield 62%) as white solid. **MS ESI** calcd for $C_{10}H_5BrF_3NO$ $[M+H]^+$ 292, found 292.

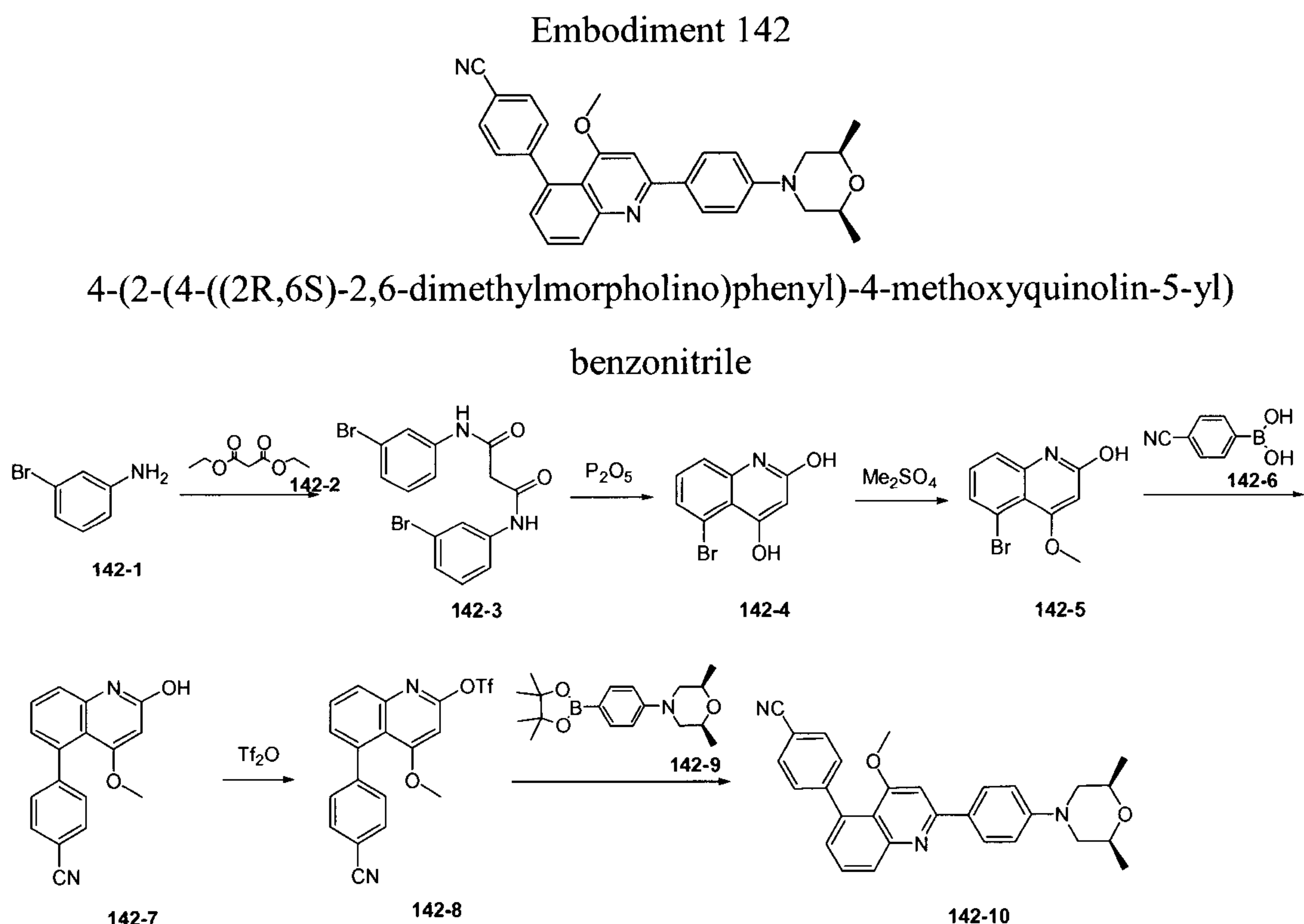
[335] Step 2: NIS (8.1 g, 36 mmol) was added into a solution of compound 141-3 (10.5 g, 36 mmol) in DMF (100 mL) in portions. The reaction mixture was stirred at room temperature for 1 h. Then the reaction mixture was poured into H_2O (1 L) and filtrated, the filtrate cake was dissolved in EtOAc, dried over sodium sulfate, concentrated to deliver compound 141-4 (14.3 g, yield 95%) as yellow solid. **MS ESI** calcd for $C_{10}H_4BrF_3INO$ $[M+H]^+$ 418, found 418.

[336] Step 3: MeI (0.22 mL, 3.6 mmol) was added dropwise into a suspension of compound 141-4 (1 g, 2.4 mmol) and Ag_2CO_3 (1.5 g, 4.8 mmol) in toluene (10 mL). Then the reaction mixture was stirred at 70°C for 2 h. The reaction mixture was poured into H_2O , extracted with EtOAc. The combined extraction liquid was washed with brines, dried over Na_2SO_4 and concentrated to dry, finally purified by column chromatography (PE:EtOAc = 10:1) to deliver compound 141-5 (550 mg, yield 55%) as yellow-brown solid. **MS ESI** calcd for $C_{11}H_6BrF_3INO$ $[M+H]^+$ 432,

found 432.

[337] Step 4: A mixture of compound 141-5 (550 mg, 1.27 mmol), compound 140-6 (299 mg, 1.27 mmol), Pd(dppf)Cl₂ (93 mg, 0.127 mmol) and Na₂CO₃ (269 mg, 2.54 mmol) was added into a mixed solvent of THF (5 mL) and H₂O (1 mL), under nitrogen gas atmosphere, the reaction mixture was heated to 60 °C and stirred overnight. The reaction mixture was poured into H₂O, extracted with EtOAc. The combined extraction liquid was washed with brines, dried over Na₂SO₄ and concentrated to dry to deliver compound 141-7 (170 mg, yield 27%) as yellow-brown solid. **MS ESI** calcd for C₂₃H₂₂BrF₃N₂O₂ [M+H]⁺ 495, found 495.

[338] Step 5: A mixture of compound 141-7 (170 mg, 0.34 mmol), compound 140-8 (60.6 mg, 0.41 mmol), Pd(dppf)Cl₂ (25 mg, 0.034 mmol) and Na₂CO₃ (72 mg, 0.68 mmol) was added into a mixed solvent of THF (10 mL), DMF(2 mL) and H₂O (2 mL), under nitrogen gas atmosphere, the reaction mixture was heated to 110°C and stirred overnight. The organic phase was separated and washed with brines, dried over Na₂SO₄ and concentrated to dry, finally purified by preparative HPLC to deliver the title compound (60 mg, yield 34%) as white solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.26 (d, *J*= 8.0 Hz, 1H), 7.82-7.95 (m, 3H), 7.70-7.80 (m, 3H), 7.35-7.50 (m, 4H), 3.95-4.20 (m, 3H), 3.65-3.80 (m, 2H), 3.63 (s, 3H), 2.76-2.90 (m, 2H), 1.33 (s, 3H), 1.32 (s, 3H). **MS ESI** calcd for C₃₀H₂₆F₃N₃O₂ [M+H]⁺ 518, found 518.



[339] Step 1: Compound 142-1 (3.0 g, 17.4 mmol) and compound 142-2 (1.4 g, 8.7 mmol) were heated to 180°C under microwave and stirred for 3h. After cooling, the

obtained solid was washed with EtOAc to deliver compound 142-3 (2.4 g, yield 22.2%) as yellow-brown solid. **MS ESI** calcd for $C_{15}H_{12}Br_2N_2O_2$ $[M+H]^+$ 411, found 411.

[340] Step 2: A solution of compound 142-3 (3.5 g, 8.46 mmol) and P_2O_5 (2.4 g, 16.9 mmol) in CH_3SO_3H (15 mL) was heated to 160°C and stirred for 3h. The reaction mixture was poured into ice. The solid obtained from filtration was washed with H_2O . Then the solid was dissolved into 1 M NaOH solution. The undissolved substance was filtrated. The aqueous phase was adjusted to pH to 3 with *conc.* hydrochloric acid. The precipitate was filtrated and washed with small amounts of H_2O , finally dried under reduced pressure to deliver compound 142-4 (1.85 g, yield 91%) as white solid. **MS ESI** calcd for $C_9H_6BrNO_2$ $[M+H]^+$ 240, found 240.

[341] Step 3: A mixture of compound 142-4 (1.84 g, 7.62 mmol) and K_2CO_3 (2.11 g, 15.24 mmol) was added into acetone (300 mL). Dimethyl sulfate (1.152 g, 9.15 mmol) was added dropwise into the mixture while stirring at room temperature. After addition, the reaction mixture was heated to 50°C and stirred for 2h. The reaction mixture was concentrated to dry, then adjusted to pH to 4 with 1 M HCl aqueous solution. The precipitate was filtrated and washed with *n*-hexane to deliver a mixture of compound 142-5 (0.84 g, yield 43%). The mixture was purified by preparative HPLC to deliver compound 142-5 (420 mg) as white solid. **MS ESI** calcd for $C_{10}H_8BrNO_2$ $[M+H]^+$ 254, found 254.

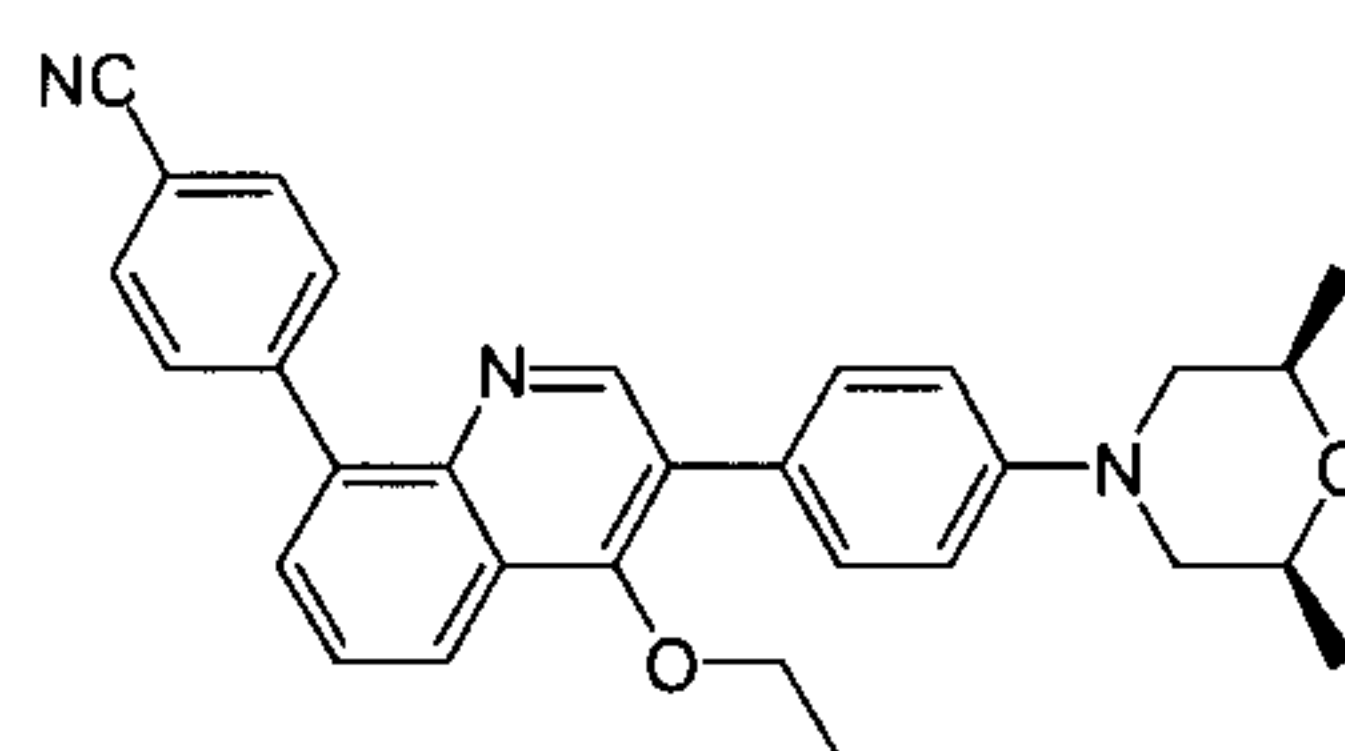
[342] Step 4: A mixture of compound 142-5 (300 mg, 1.18 mmol), compound 142-6 (208 mg, 1.41 mmol), Na_2CO_3 (313 mg, 2.95 mmol) and $Pd(dppf)Cl_2$ (86 mg, 0.118 mmol) was added into a mixed solvent of CH_3CN (5 mL) and H_2O (1 mL). Then under nitrogen gas atmosphere, the reaction mixture was heated to 80°C and stirred for 8h. The reactants was filtrated, the filtrate was concentrated to dry, finally purified by column chromatography to deliver compound 142-7 (223 mg, yield 69%) as yellow-brown solid. **MS ESI** calcd for $C_{17}H_{12}N_2O_2$ $[M+H]^+$ 277, found 277.

[343] Step 5: Trifluoromethanesulfonic anhydride (644 mg, 2.28 mmol) was added dropwise into a solution of compound 142-7 (350 mg, 1.27 mmol) and pyridine (201 mg, 2.54 mmol) in DCM (15 mL). Then the reaction mixture was stirred overnight. The reaction mixture was concentrated to dry, finally purified by column chromatography to deliver compound 142-8 (254 mg, yield 49%) as white solid. **MS ESI** calcd for $C_{18}H_{11}F_3N_2O_4S$ $[M+H]^+$ 409, found 409.

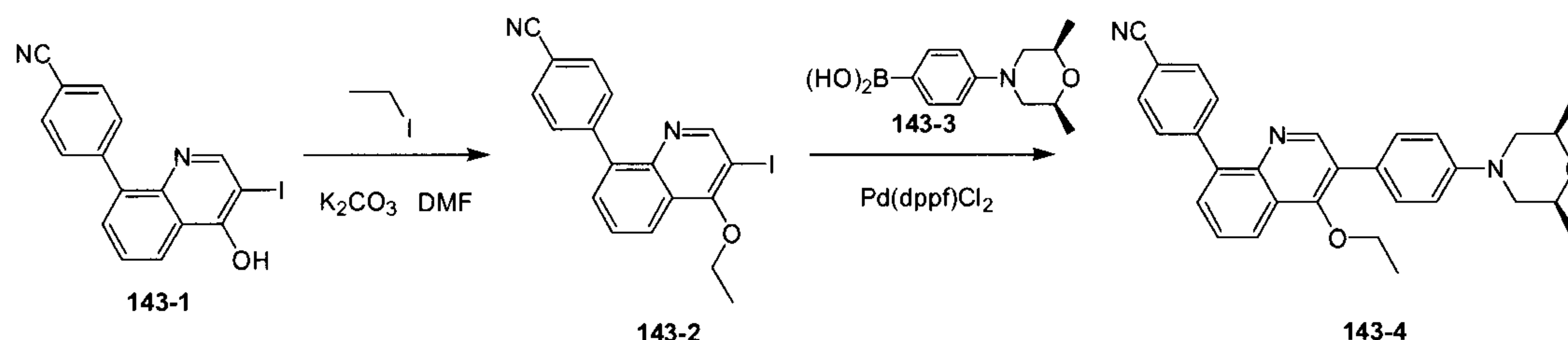
[344] Step 6: A mixture of compound 142-8 (100 mg, 0.245 mmol), compound 142-9 (116 mg, 0.367 mmol), Na_2CO_3 (78 mg, 0.735 mmol) and $Pd(dppf)Cl_2$ (36 mg, 0.049 mmol) was added into a mixed solvent of CH_3CN (5 mL) and H_2O (1 mL). Under nitrogen gas atmosphere, the reaction mixture was heated to 80°C and stirred for 3h. The reactants was filtrated, the filtrate was concentrated to dry, finally purified by preparative HPLC to deliver the title compound (95 mg, yield 86%) as white solid. **^1H NMR** (400 MHz, $CDCl_3$) δ 8.18 (d, J = 7.6 Hz, 1H), 8.09 (d, J = 8.8 Hz, 2H), 7.62-7.72 (m, 3H), 7.40-7.50 (m, 2H), 7.19 (d, J = 6.4 Hz, 1H), 7.09 (s, 1H),

7.03 (d, J = 8.8 Hz, 2H), 3.75-3.83 (m, 2H), 3.65 (s, 3H), 3.55-3.64 (m, 2H), 2.45-2.57 (m, 2H), 1.25-1.30 (m, 6H). **MS ESI** calcd for $C_{29}H_{27}N_3O_2$ $[M+H]^+$ 450, found 450.

Embodiment 143



4-(3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-ethoxyquinolin-8-yl)benzonitrile

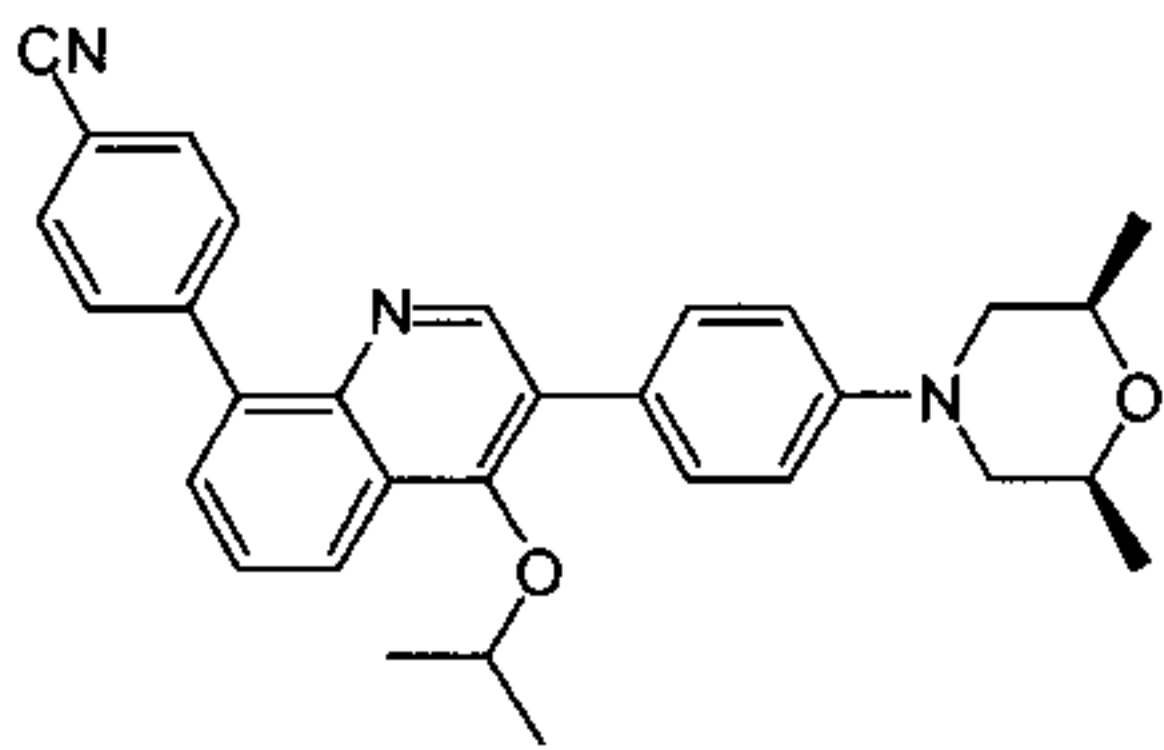
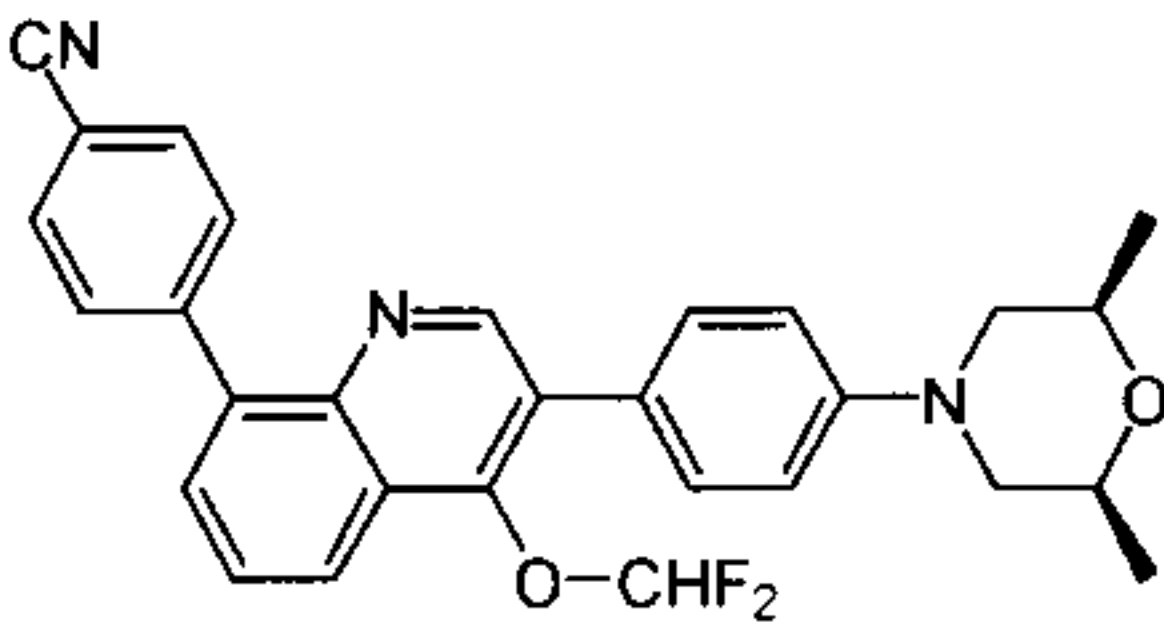
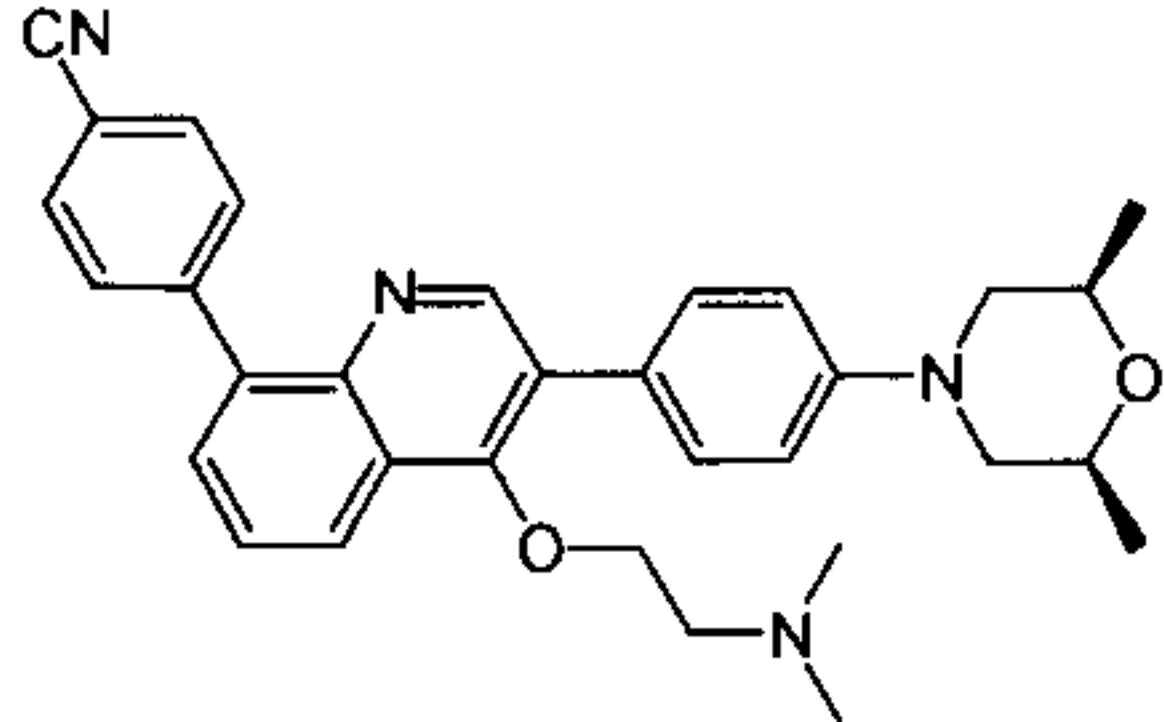


[345] Step 1: K_2CO_3 (745 mg, 5.4 mmol) and ethyl iodide were added into a solution of compound 143-1 in DMF (20 mL), the reaction mixture was stirred at $90^\circ C$ for 2h. After the reaction was complete, H_2O was added, then the reaction mixture was extracted with EtOAc. The combined organic phase was washed with brines, dried over Na_2SO_4 , and concentrated under vacuum to deliver the desired compound 2 (0.9g, 83%) as solid. **MS ESI** calcd for $C_{18}H_{13}IN_2O$ $[M+H]^+$ 401, found 401.

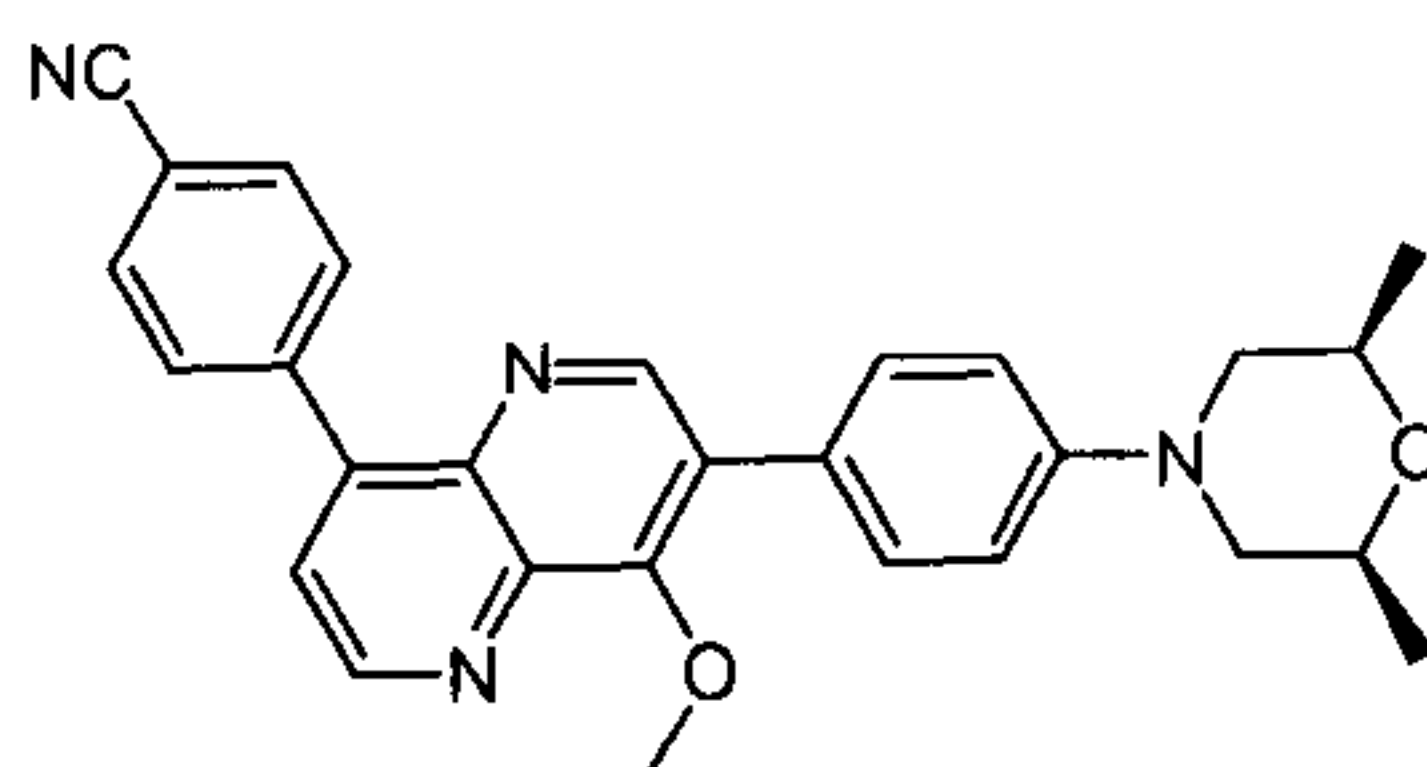
[346] Step 2: Compound 143-2 (200 mg, 0.5 mmol), compound 143-3 (176 mg, 0.74 mmol), $Pd(dppf)Cl_2$ (36 mg, 0.05 mmol) and Na_2CO_3 (106mg, 1 mmol) were suspended in a mixed solvent of THF/ H_2O (10:1, 11 mL), then under nitrogen gas atmosphere, the reaction mixture was stirred at $90^\circ C$ for 12h. After cooling, the reaction mixture was diluted with EtOAc, then washed with brines, dried over Na_2SO_4 , concentrated under reduced pressure, the residue was purified by RP-HPLC (acetonitrile/ H_2O with 0.05% ammonium hydroxide modifier) to deliver the title compound (150mg, 70%) as white solid. **^1H NMR** (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.51-8.49 (m, 1H), 7.82 (s, 4H), 7.64 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 7.6 Hz, 2H), 7.08 (d, J = 7.6 Hz, 2H), 4.08-4.03 (m, 2H), 3.86 (br. s., 2H), 3.58 (d, J = 12 Hz, 2H), 2.56 (t, J = 11.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H), 1.0 (d, J = 6.4 Hz, 6H). **MS ESI** calcd for $C_{30}H_{29}N_3O_2$ $[M+H]^+$ 464, found 464.

[347] The compounds listed in table 12 were synthesized by compound 143-1 and corresponding haloalkanes.

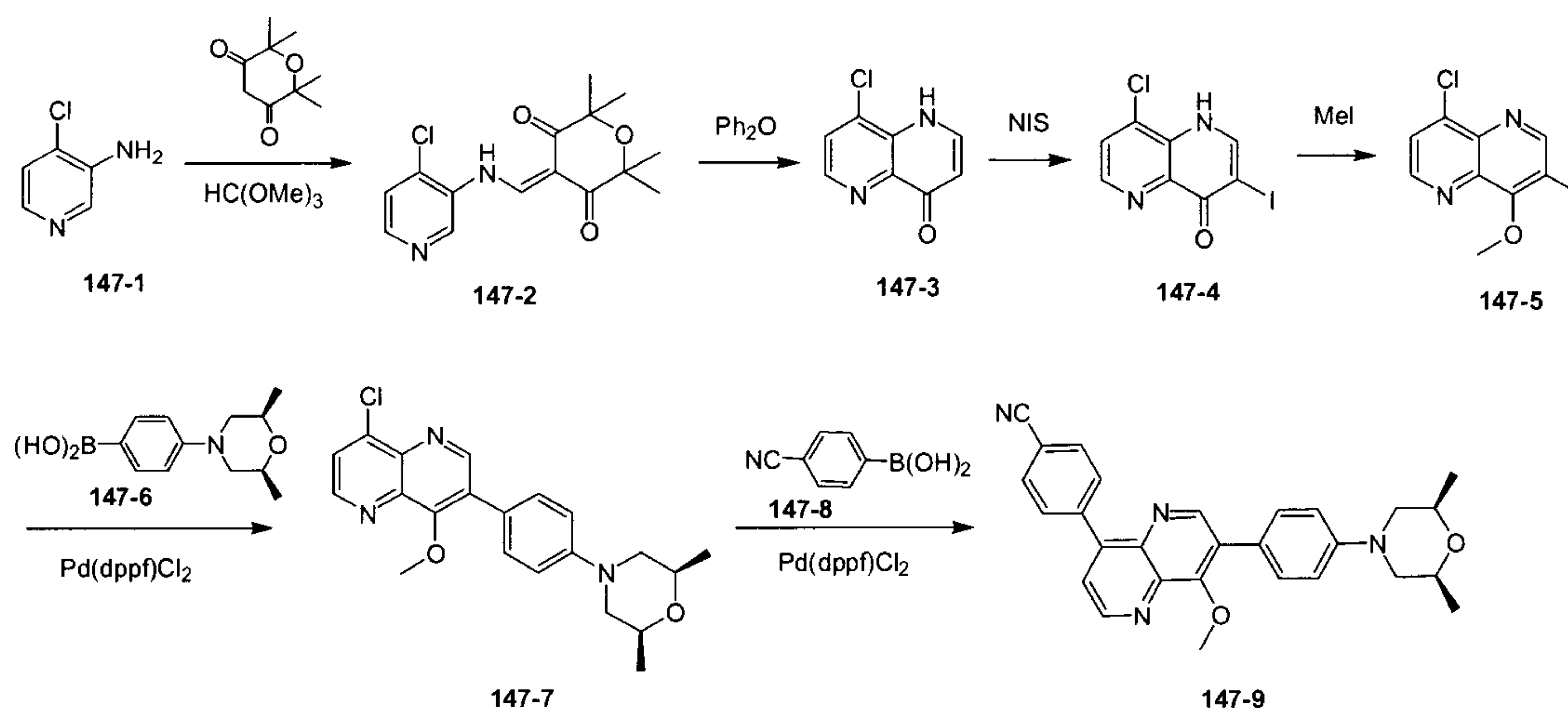
Embodiment	Structure	NMR
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144		¹H NMR (400 MHz, CDCl ₃) δ 8.88 (s, 1H), 8.52(dd, <i>J</i> = 7.2, 2.4 Hz, 1H), 7.87-7.82 (m, 4H), 7.63 (d, <i>J</i> = 8 Hz, 2H), 7.52 (d, <i>J</i> = 8.8 Hz, 2H), 7.09 (d, <i>J</i> = 8.8 Hz, 2H), 4.61-4.57 (m, 1H), 3.88-3.84 (m, 2H), 3.58 (d, <i>J</i> = 11.6 Hz, 2H), 2.57 (t, <i>J</i> = 10.8 Hz, 2H), 1.31-1.23 (m, 12H). MS ESI calcd for C ₃₁ H ₃₁ N ₃ O ₂ [M+H] ⁺ 478, found 478.
145		¹H NMR (400 MHz, CDCl ₃) δ 8.43 (d, <i>J</i> =7.83 Hz, 1H), 7.92 (d, <i>J</i> =7.83 Hz, 3H), 7.70 (d, <i>J</i> =8.2 Hz, 3H), 7.66-7.58 (m, 2H), 7.55-7.48 (m, 2H), 7.38-7.18 (m, 1H), 2.74 (br. s., 1 H), 1.25 (d, <i>J</i> = 6.3 Hz, 6H). MS ESI calcd for C ₂₉ H ₂₅ F ₂ N ₃ O ₂ [M+H] ⁺ 486, found 486.
146		¹H NMR (400 MHz, CDCl ₃) δ 8.88 (s, 1H), 8.32 (s, 1H), 7.77 (d, <i>J</i> = 6.8 Hz, 6H), 7.52 (d, <i>J</i> = 6 Hz, 2H), 7.12 (d, <i>J</i> = 6.8 Hz, 2H), 4.19 (s, 2H), 3.88 (s, 2H), 3.58 (d, <i>J</i> = 11.2 Hz, 2H), 3.56 (s, 2H), 2.91 (s, 6 H), 2.57 (t, <i>J</i> = 10.4 Hz, 2H), 1.30 (d, <i>J</i> = 5.6 Hz, 6H). MS ESI calcd for C ₃₂ H ₃₄ N ₄ O ₂ [M+H] ⁺ 507, found 507.

Embodiment 147



4-(7-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-8-methoxy-1,5-naphthyridin-4-yl)
benzonitrile



[348] Step 1: 2,2,6,6-tetramethyl-2H-pyran-3,5(4H,6H)-dione (13.8g, 96mmol) was added into HC(OMe)_3 (50 mL, 288mmol). After the mixture was stirred at 80°C for 3h, compound 147-1 (10g, 76.9mmol) was added, the mixture was stirred for further 5h. After detected by LC-MS, the mixture was concentrated under reduced pressure, the crude product was washed with MeOH to deliver compound 147-2 (15 g, yield 57%). **MS ESI** calcd for $\text{C}_{15}\text{H}_{17}\text{ClN}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 309, found 309.

[349] Step 2: Compound 147-2 (13 g, 46 mmol) was added into preheated Ph_2O (250 °C) (500 mL) in portions. After stirred for 5min, the mixture was detected by LC-MS. After the reaction mixture was cooled to room temperature, petroleum ether was added to filtrate, the filtrate was concentrated under reduced pressure to deliver compound 147-3 (4 g, yield 48%). **MS ESI** calcd for $\text{C}_8\text{H}_5\text{ClN}_2\text{O}$ $[\text{M}+\text{H}]^+$ 309, found 309.

[350] Step 3: A solution of compound 147-3 (3 g, 16.7 mmol) and NIS (4.1 g, 18.3 mmol) in DMF (20 mL) was stirred at room temperature for 16h. The reaction mixture was filtrated, and the filtrate was concentrated under reduce pressure to deliver 147-4 (2.5g, yield 49%). **MS ESI** calcd for $\text{C}_8\text{H}_4\text{ClIN}_2\text{O}$ $[\text{M}+\text{H}]^+$ 307, found 307.

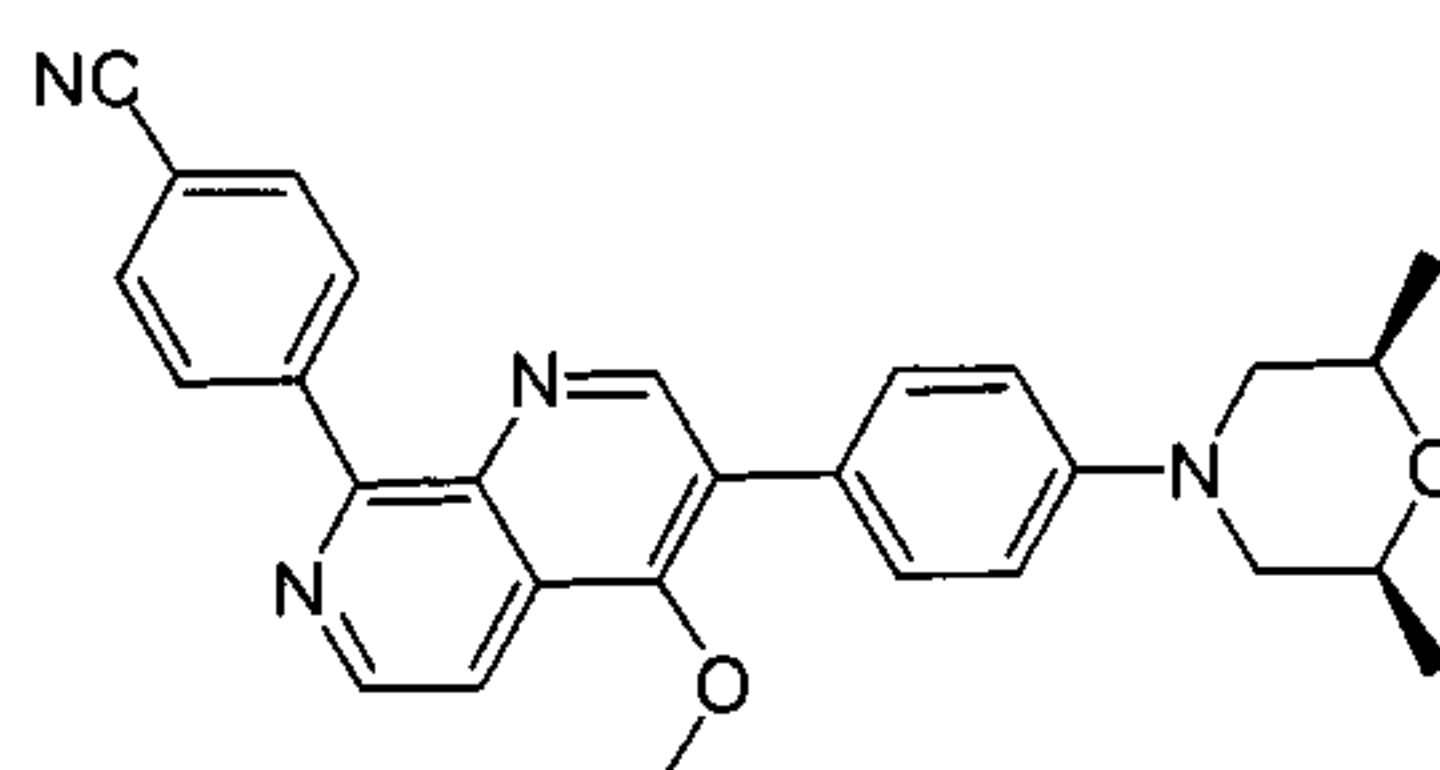
[351] Step 4: A solution of compound 147-4 (2.5 g , 8.2 mmol), MeI (1.75 g , 12.3 mmol) and Ag_2CO_3 (4.5 g, 16.4 mmol) in DMF (20 mL) was stirred at 90°C for 3h. The reaction mixture was detected by LC-MS. The mixture was poured into H_2O , the aqueous phase was extracted with EtOAc. The combined organic phase was washed with brines, dried over Na_2SO_4 , concentrated under reduced pressure. The crude product was purified by silica gel chromatography (PE: EtOAc= 10:1) to deliver compound 147-5 (300 mg, yield 12%). **MS ESI** calcd for $\text{C}_9\text{H}_6\text{ClIN}_2\text{O}$ $[\text{M}+\text{H}]^+$ 321, found 321.

[352] Step 5: Compound 147-5 (320 mg,1 mmol), compound 147-6 (350 mg, 1.1 mmol), Pd(dppf)Cl_2 (74 mg, 0.1 mmol) and Na_2CO_3 (212 mg, 2 mmol) were dissolved in a mixed solvent of THF/ H_2O (10:2 mL), and stirred at 70°C for 16h. The reaction mixture was detected by LC-MS. The mixture was poured into H_2O , the aqueous phase was extracted with EtOAc. The combined organic phase was

washed with brines, dried over Na_2SO_4 , concentrated under reduced pressure. The crude product was purified by silica gel chromatography (PE: EtOAc= 2:1) to deliver compound 147-7 (200 mg, yield 52%). **MS ESI** calcd for $\text{C}_{21}\text{H}_{22}\text{ClN}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 384, found 384.

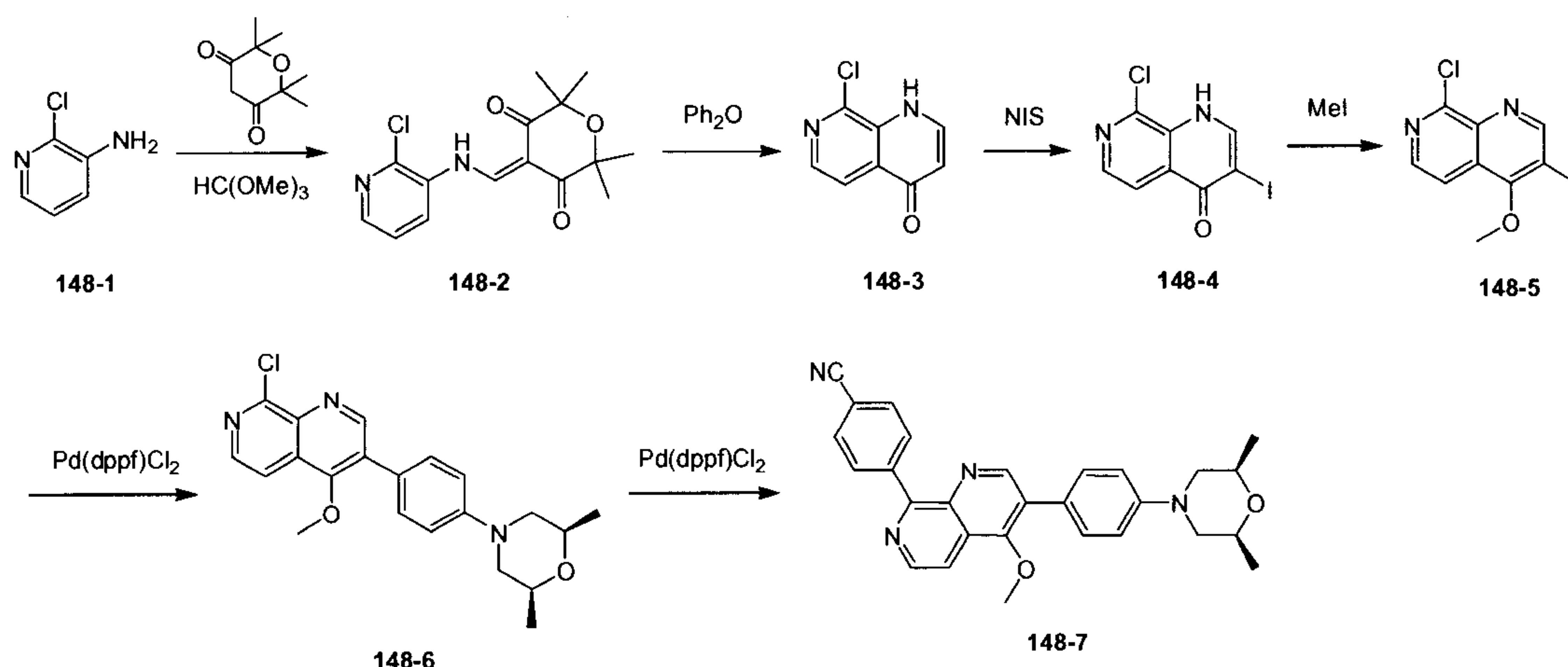
[353] Step 6: Compound 147-7 (200 mg, 0.52 mmol), compound 147-8 (84 mg, 0.57 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (38 mg, 0.052 mmol) and Na_2CO_3 (110 mg, 1.04 mmol) were dissolved in a mixed solvent of THF/ H_2O /DMF (10:2:2 mL), and the mixture was stirred at 90°C for 4h. The reaction mixture was detected by LC-MS. The mixture was poured into H_2O , the aqueous phase was extracted with EtOAc. The combined organic phase was dried over Na_2SO_4 , concentrated under reduced pressure. The crude product was purified by preparative HPLC to deliver the title compound (80 mg, yield 34%) as white solid. **^1H NMR** (400 MHz, CDCl_3) δ 9.05 (d, $J= 4.8$ Hz, 1H), 8.95 (s, 1H), 7.89-7.81 (m, 4H), 7.59 (t, $J= 4.4$ Hz, 3H), 7.04 (d, $J= 8.8$ Hz, 2H), , 4.09 (s, 3H), 3.85-3.82 (m, 2H), 3.58 (d, $J= 11.2$ Hz, 2H), 2.51 (t, $J= 11.2$ Hz, 2H), 1.30-1.25 (m, 6H). **MS ESI** calcd for $\text{C}_{28}\text{H}_{26}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ 451, found 451.

Embodiment 148



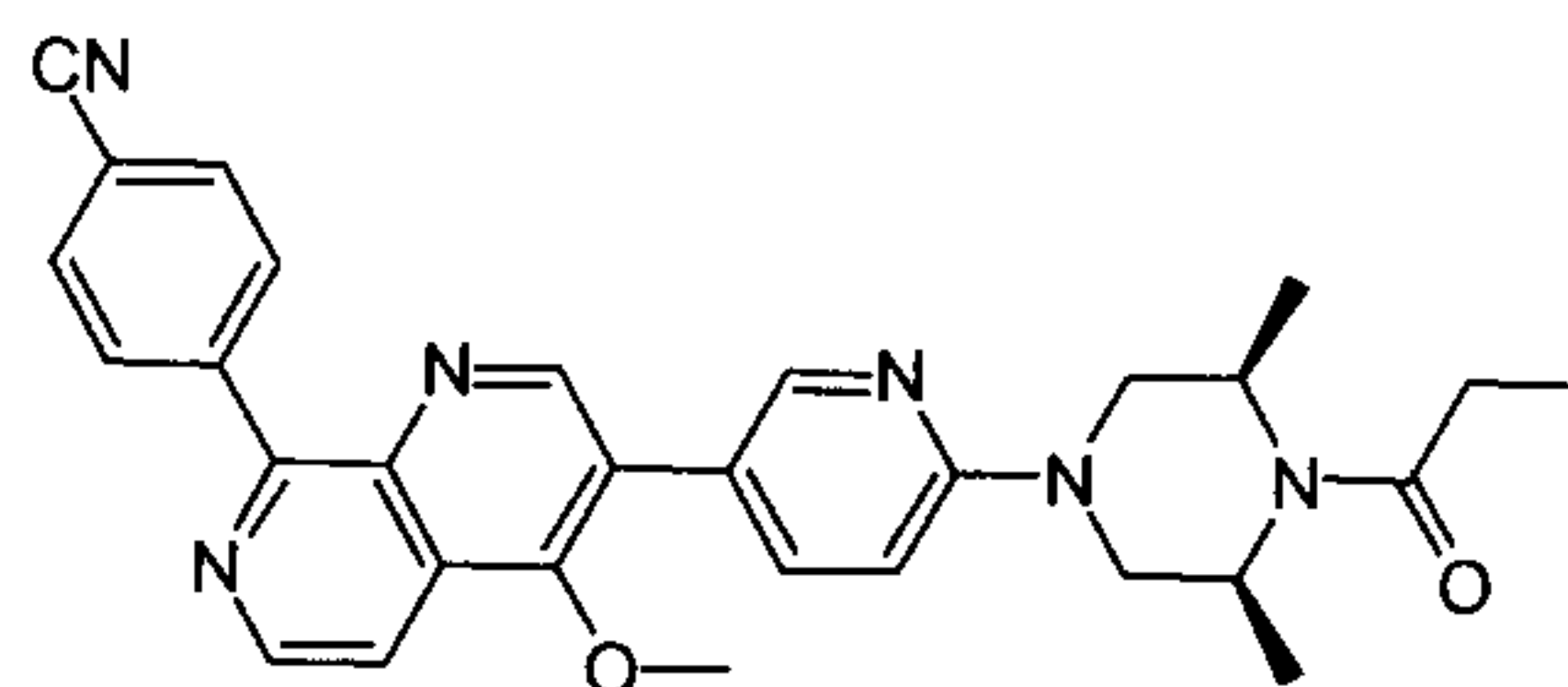
4-(3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxy-1,7-naphthyridin-8-yl)

benzonitrile



[354] The title compound was synthesized according to the above-mentioned method as white solid. **^1H NMR** (400 MHz, CDCl_3) δ 9.05 (s, 1H), 8.82 (d, $J= 5.2$ Hz, 1H), 8.32 (d, $J= 5.6$ Hz, 1H), 8.14 (d, $J= 7.6$ Hz, 2H), 7.87 (d, $J= 8$ Hz, 2H), 7.62 (d, $J= 8$ Hz, 2H), 7.16 (d, $J= 8$ Hz, 2H), 3.89 (s, 2H), 3.77 (s, 3H), 3.62 (d, $J= 12$ Hz, 2H), 2.61 (d, $J= 10.8$ Hz, 2H), 1.31 (d, $J= 6$ Hz, 6H). **MS ESI** calcd for $\text{C}_{28}\text{H}_{26}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ 451, found 451.

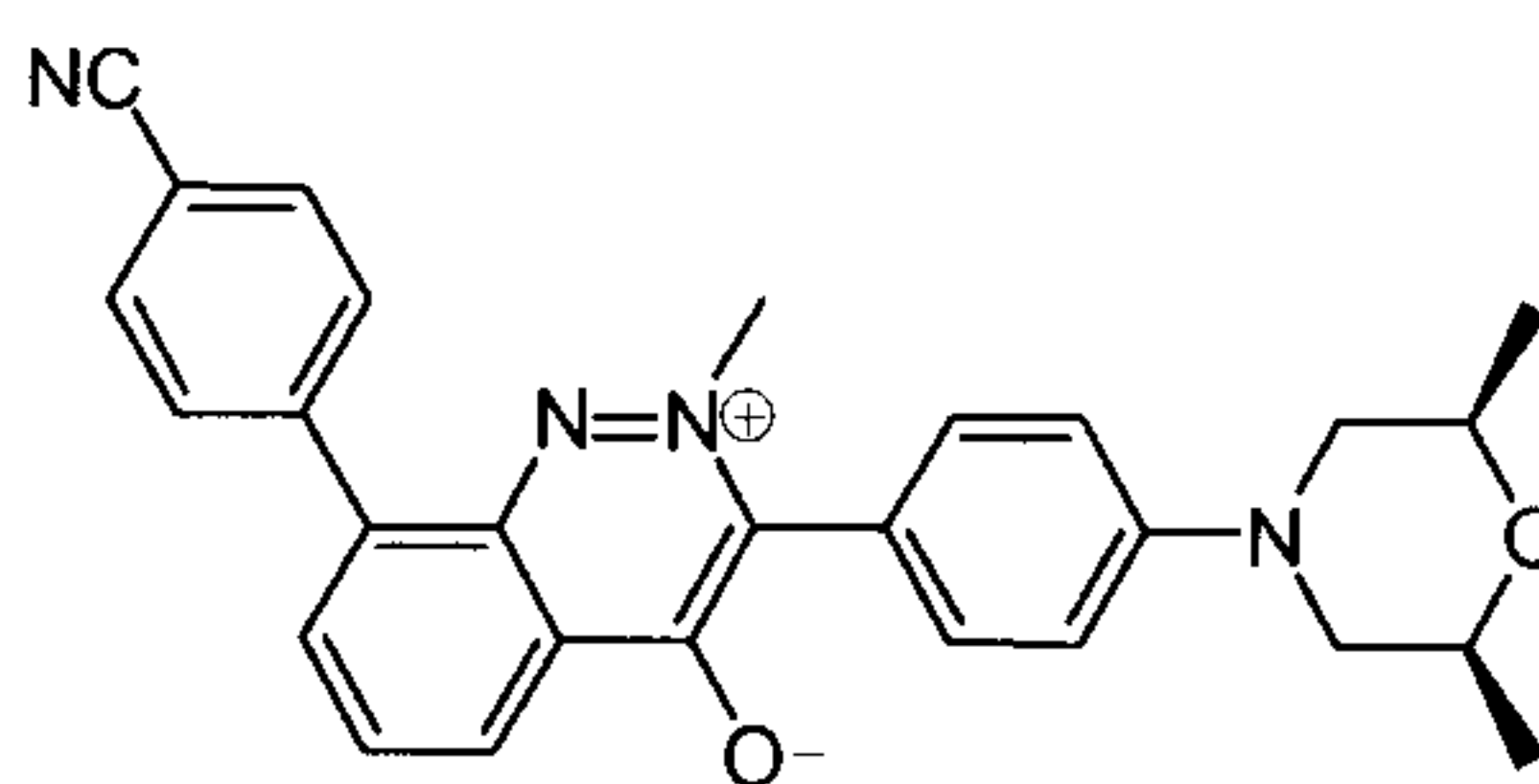
Embodiment 149



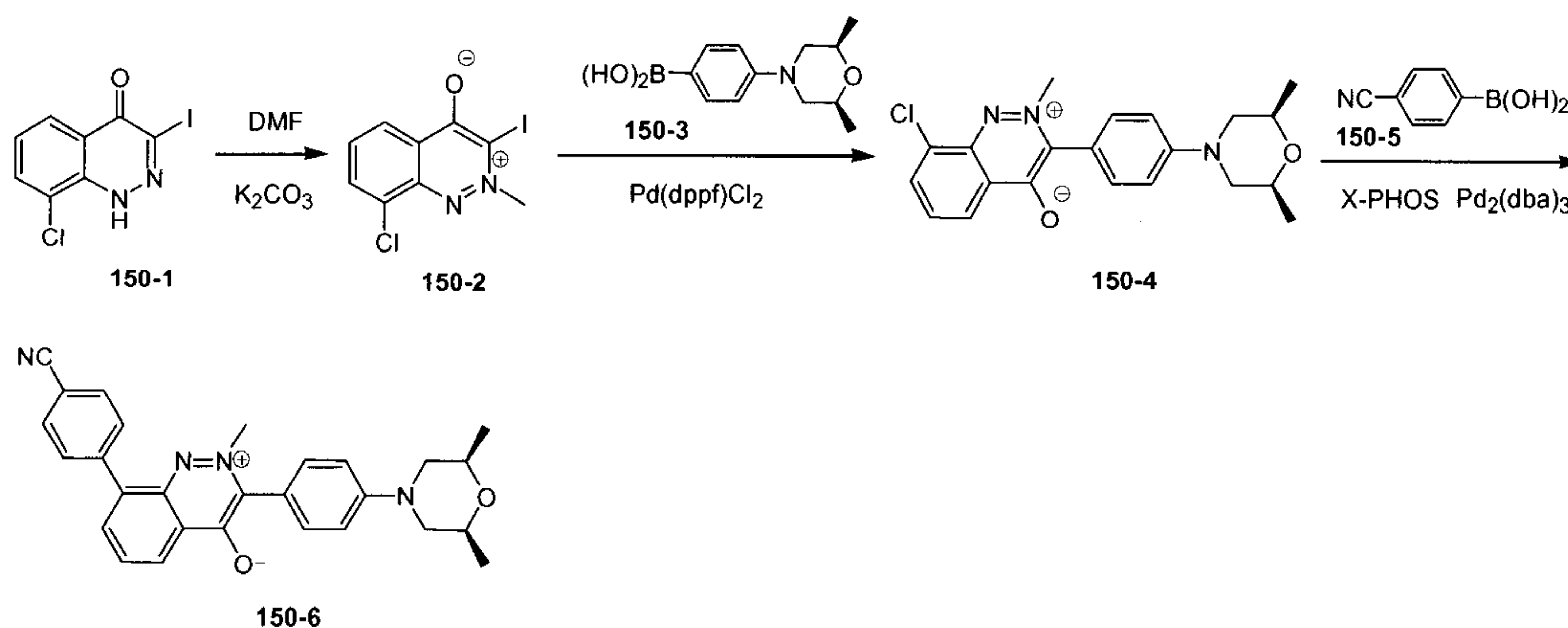
4-(3-(6-((3S,5R)-3,5-dimethyl-4-propionylpiperazin-1-yl)pyridin-3-yl)-4-methoxy-1,7-naphthyridin-8-yl)benzonitrile

[355] The title compound was synthesized according to the above-mentioned method as white solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 8.96 (s, 1H), 8.69 (d, *J* = 5.6 Hz, 1H), 8.46 (d, *J* = 2.4 Hz, 1H), 8.18 (dd, *J* = 11.6, 8.4 Hz, 3H), 7.95 (dd, *J* = 8.8, 2.4 Hz, 2H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 1H), 4.31-4.42 (m, 3H), 3.81 (s, 3H), 3.16 (d, *J* = 11.6 Hz, 2H), 2.50 (m, 2H), 1.31 (s, 6H), 1.15 (t, *J* = 7.6 Hz, 3H). MS ESI calcd for C₃₀H₃₀N₆O₂ [M+H]⁺ 507, found 507.

Embodiment 150



8-(4-cyanophenyl)-3-(4-((2R,6S)-2,6-dimethylmorpholino)phenyl)-2-methylcinnolin-2-ium-4-olate



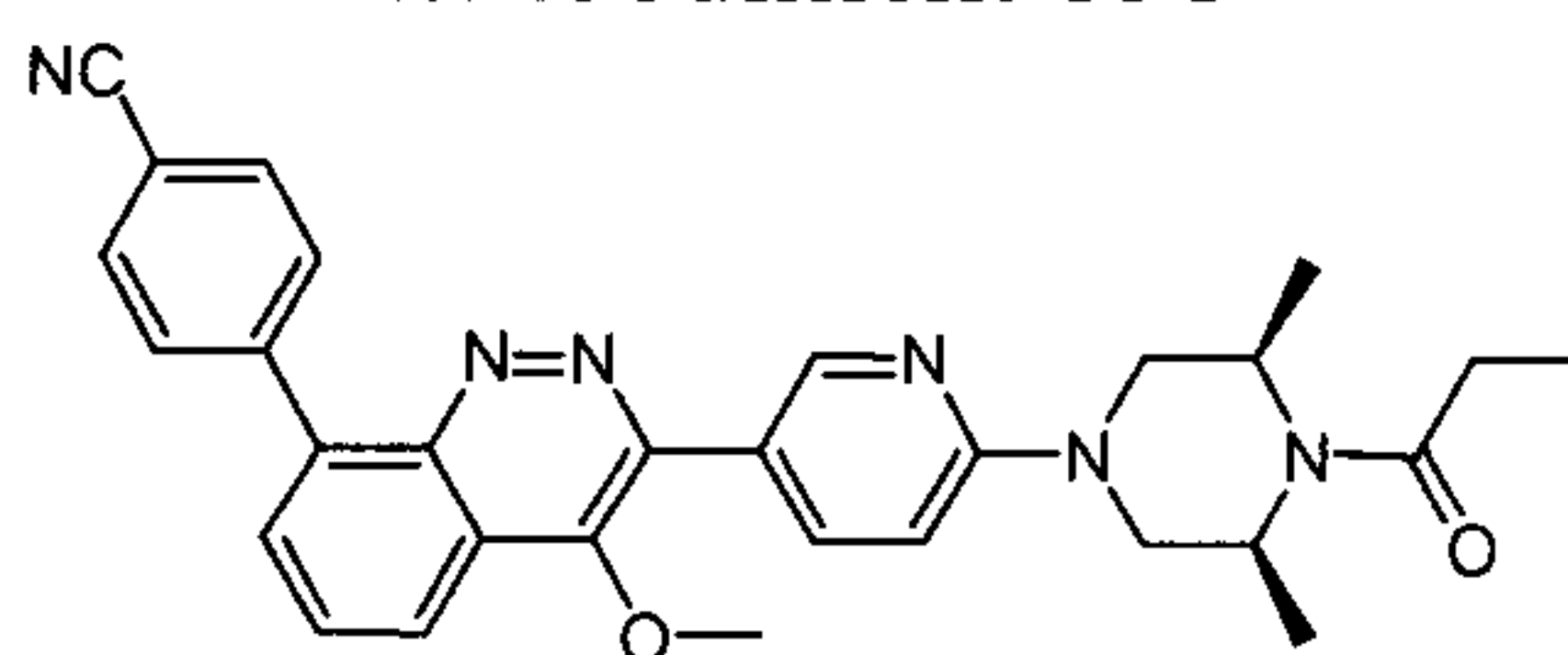
[356] Step 1: K₂CO₃ (1.9 g, 13.7 mmol) and methyl iodide were added into a solution of compound 150-1 (2.3 g, 6.84 mmol) in DMF (20 mL). The reaction mixture was stirred at 90°C for 4h. After the reaction was complete as detected by LC-MS, H₂O was added and then the reaction mixture was extracted with EtOAc.

The combined organic phase was washed with brines, dried over Na₂SO₄, and concentrated under vacuum. The residue was purified by silica gel chromatography (PE / EtOAc= 3:1) to deliver the desired compound 2 (1.5 g, 68%) as solid. **MS ESI** calcd for C₉H₆ClIN₂O [M+H]⁺ 321, found 321.

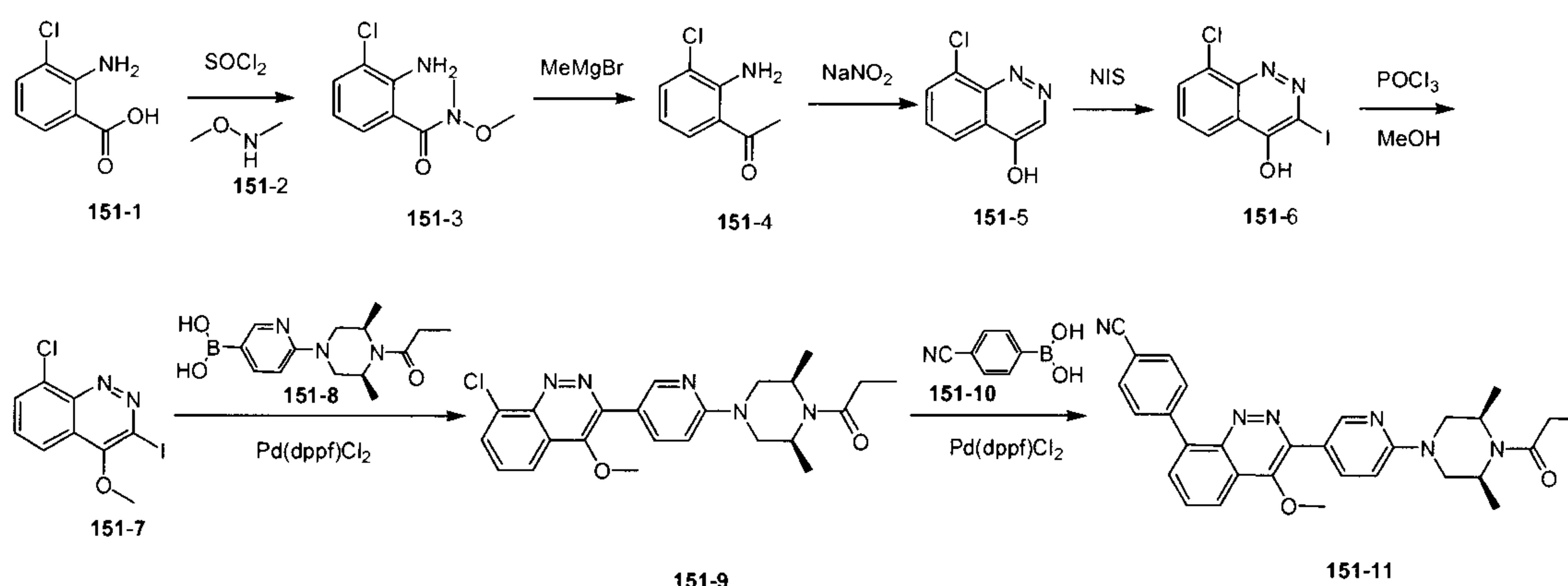
[357] Step 2: Compound 150-2 (321 mg, 1mmol), compound 150-3 (282 mg, 1.2 mmol), Pd(dppf)Cl₂ (73.2 mg, 0.1 mmol) and Na₂CO₃ (212 mg, 2 mmol) were suspended in a mixed solvent of THF/H₂O (10:1 mL), under nitrogen gas atmosphere, the reaction mixture was stirred at 90°C overnight. After the reaction was complete as detected by LC-MS, H₂O was added and then the reaction mixture was extracted with EtOAc. The combined organic phase was washed with brines, dried over Na₂SO₄, and concentrated under vacuum to deliver the crude product 4 (320 mg, 83.6%). **MS ESI** calcd for C₂₁H₂₂ClN₃O₂ [M+H]⁺ 384, found 384.

[358] Step 3: Compound 150-4 (320 mg, 0.84 mmol), compound 150-5 (184 mg, 1.25 mmol), Pd₂(dba)₃ (77 mg, 0.08 mmol), Xantphos (86 mg, 0.16 mmol) and Na₂CO₃ (178 mg, 1.68 mmol) were suspended in a mixed solvent of 1,4-dioxane/H₂O (10:1 mL), under nitrogen gas atmosphere, the reaction mixture was heated to 120°C and refluxed for 3h. After the reaction was complete, the mixture was filtrated with diatomite, the filtrate was evaporated, extracted with EtOAc. The combined EtOAc phase was washed with brines, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by preparative HPLC to deliver the title compound (80 mg, 20%). **¹H NMR** (400 MHz, CDCl₃) δ 8.48 (d, *J*= 8 Hz, 1H), 7.80-7.69 (m, 6H), 7.89-7.81 (m, 4H), 7.36 (d, *J*= 8.8 Hz, 2H), 7.15 (d, *J*= 8.4 Hz, 2H), 4.19 (s, 3H), 3.90-3.86 (m, 2H), 3.60 (d, *J*= 11.6 Hz, 2H), 2.61 (t, *J*= 10.8 Hz, 2H), 1.29 (d, *J*= 6.4 Hz, 6H). **MS ESI** calcd for C₂₈H₂₆N₄O₂ [M+H]⁺ 451, found 451.

Embodiment 151



4-(3-(6-(3,5-dimethyl-4-propionylpiperazin-1-yl)pyridin-3-yl)-4-methoxycinnolin-8-yl)benzonitrile



[359] Step 1: Compound 151-1 (51 g, 0.3 mol), thionyl chloride (200 mL) were heated to reflux for 2h, then thionyl chloride was evaporated, the residue was dissolved in DCM, a solution of compound 151-2 (42.3 g, 0.45 mol), DIPEA (116 g, 0.9 mol) in DCM was added, the reaction mixture reacted at room temperature for 1h, then poured into H₂O, the mixture was washed with H₂O and brines respectively, the organic phase was dried and concentrated, the residue was purified by column chromatography to deliver compound 151-3 (26 g, yield 40%) as yellow oil. **MS ESI** calcd for C₉H₁₁ClN₂O₂ [M+H]⁺ 215, found 215.

[360] Step 2: Compound 151-3 (26 g, 0.12 mol) was dissolved in THF (300 mL), MeMgBr (120 mL, 3M in Et₂O) was added slowly into the solution at 0 °C. After the addition, the reaction mixture was kept at 0°C for 2h, and then poured into ammonium chloride aqueous solution, extracted with EtOAc, the extraction liquid was washed with brines, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by column chromatography to deliver compound 151-4 (10.5 g, yield 51.4%) as yellow solid. **MS ESI** calcd for C₈H₈ClNO [M+H]⁺ 169, found 169.

[361] Step 3: Compound 151-4 (1.69 g, 10 mmol) was added into H₂O (10 mL), *conc.* hydrochloric acid (17 mL) was added at 0 °C, then a solution of sodium nitrite (2.1 g, 30 mmol) in H₂O (10 mL) was added dropwise at -5 to 0 °C. After the addition, the reaction mixture reacted at 0°C for 1h, then heated to 80°C and reacted for 6h, then cooled in an ice bath. The mixture was filtrated, dried to deliver 1.2g compound 151-5, yield 67% as yellow solid. **MS ESI** calcd for C₈H₅ClN₂O [M+H]⁺ 181, found 181.

[362] Step 4: NIS (1.5 g, 0.67 mmol) was added into a solution of compound 151-5 (1.2 g, 0.67 mmol) in DMF (10 mL), the reaction mixture was stirred at room temperature for 2h, the the solution was poured into H₂O, filtrated, the filtrate cake was dried to deliver 1.5g compound 151-6, yield 75% as yellow solid. **MS ESI** calcd for C₈H₄ClIN₂O [M+H]⁺ 307, found 307.

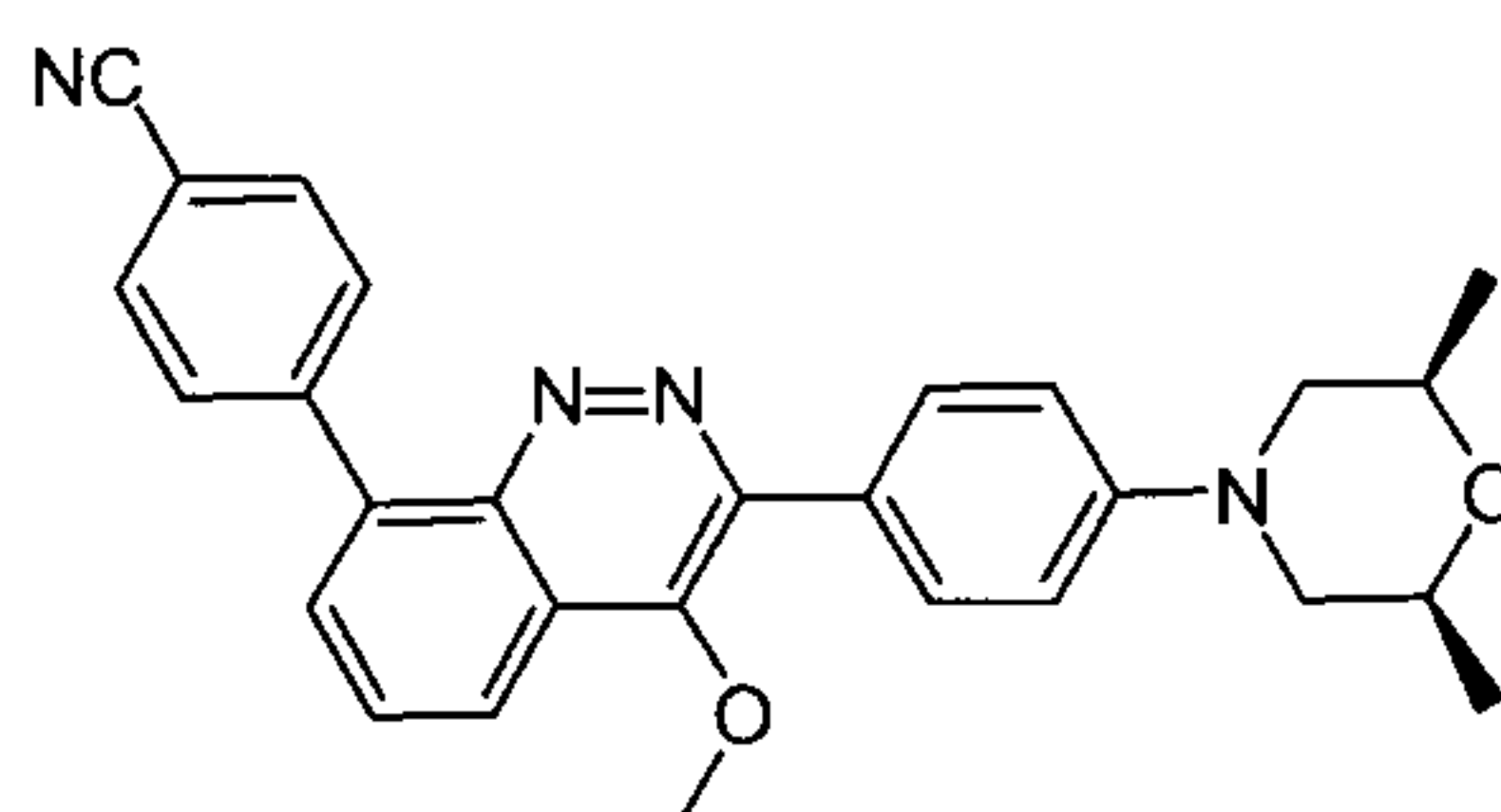
[363] Step 5: Compound 151-6 (1.2 g, 0.67 mmol), phosphorus oxychloride (5 mL) were heated to 120°C and stirred for 2h, then the reaction mixture was cooled and poured into methanol, H₂O and EtOAc were added respectively, the organic phase

was separated, dried and concentrated to deliver 1.0g compound 151-7, yield 62.5% as yellow solid. **MS ESI** calcd for $C_9H_6ClIN_2O$ $[M+H]^+$ 321, found 321.

[364] Step 6: Compound 151-7 (320 mg, 1.0 mmol), compound 151-8 (292 mg, 1.0 mmol), $Pd(dppf)Cl_2$ (73 mg, 0.1 mmol) and sodium carbonate (212 mg, 2.0 mmol) were added into a solution of THF/ H_2O /DMF (10:1:1, 12 mL), under nitrogen gas atmosphere, the reaction mixture was stirred at 80°C overnight. The mixture was filtrated with diatomite, the filtrate was washed with H_2O (10 mL) and extracted with EtOAc (20 mL), the extraction liquid was washed with brines, and dried over anhydrous sodium sulfate, concentrated under vacuum. The residue was purified by column chromatography to deliver compound 151-9 (200 mg, yield 68%) as yellow solid. **MS ESI** calcd for $C_{23}H_{26}ClN_5O_2$ $[M+H]^+$ 441, found 441.

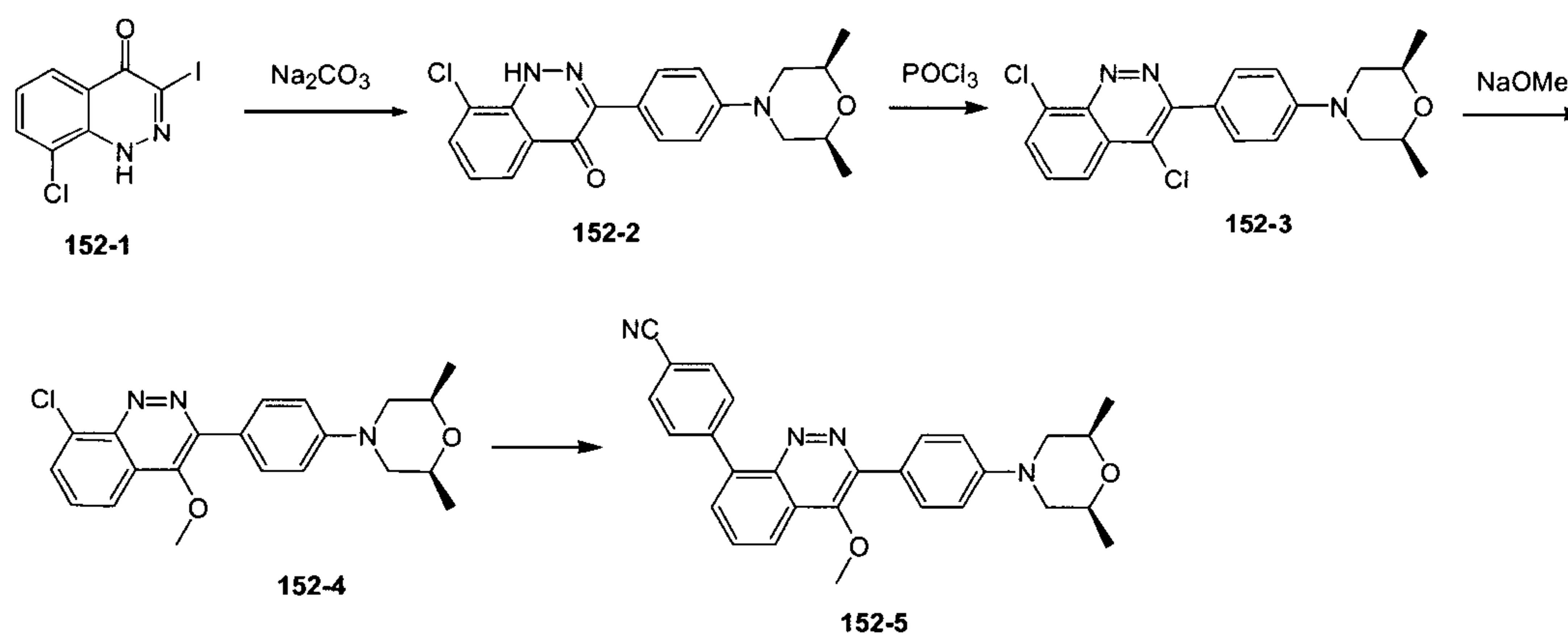
[365] Step 7: The title compound (10 mg, yield 9%) was synthesized according to the above-mentioned method as white solid. **^1H NMR** (400 MHz, $CDCl_3$) δ 9.04-9.05(d, J = 2.0 Hz, 1H), 8.42-8.43(d, J = 6.8 Hz, 1H), 8.28-8.30 (d, J = 8.8 Hz, 1H), 7.91-7.93 (d, J = 8.4 Hz, 2H), 7.55-7.85 (m, 4H) 6.86-6.88 (d, J = 8.8 Hz, 1H) 4.08-4.13 (m, 2H), 3.90(s, 3H) 3.17-3.21 (d d, J = 4.0 Hz 2H), 2.25-2.28 (m, 2H) 2.03-2.06 (m, 1H) 1.19-1.28 (m, 9H) 0.98-0.99 (d, J = 6.4 Hz 2H). **MS ESI** calcd for $C_{30}H_{30}N_6O_2$ $[M+H]^+$ 507, found 507.

Embodiment 152



4-(3-(4-((2R,6S)-2,6-dimethylmorpholino)phenyl)-4-methoxycinnolin-8-yl)

benzonitrile



[366] Step 1: Compound 152-1 (1.2 g, 4 mmol), sodium carbonate (4.3 g, 40.2 mmol), $Pd(dppf)Cl_2$ (200 mg, 02 mmol) were added into a solution of 4-((2R,6S)-2,6-dimethylmorpholinyl)benzoboric acid (1.15 g, 5 mmol) in a mixed

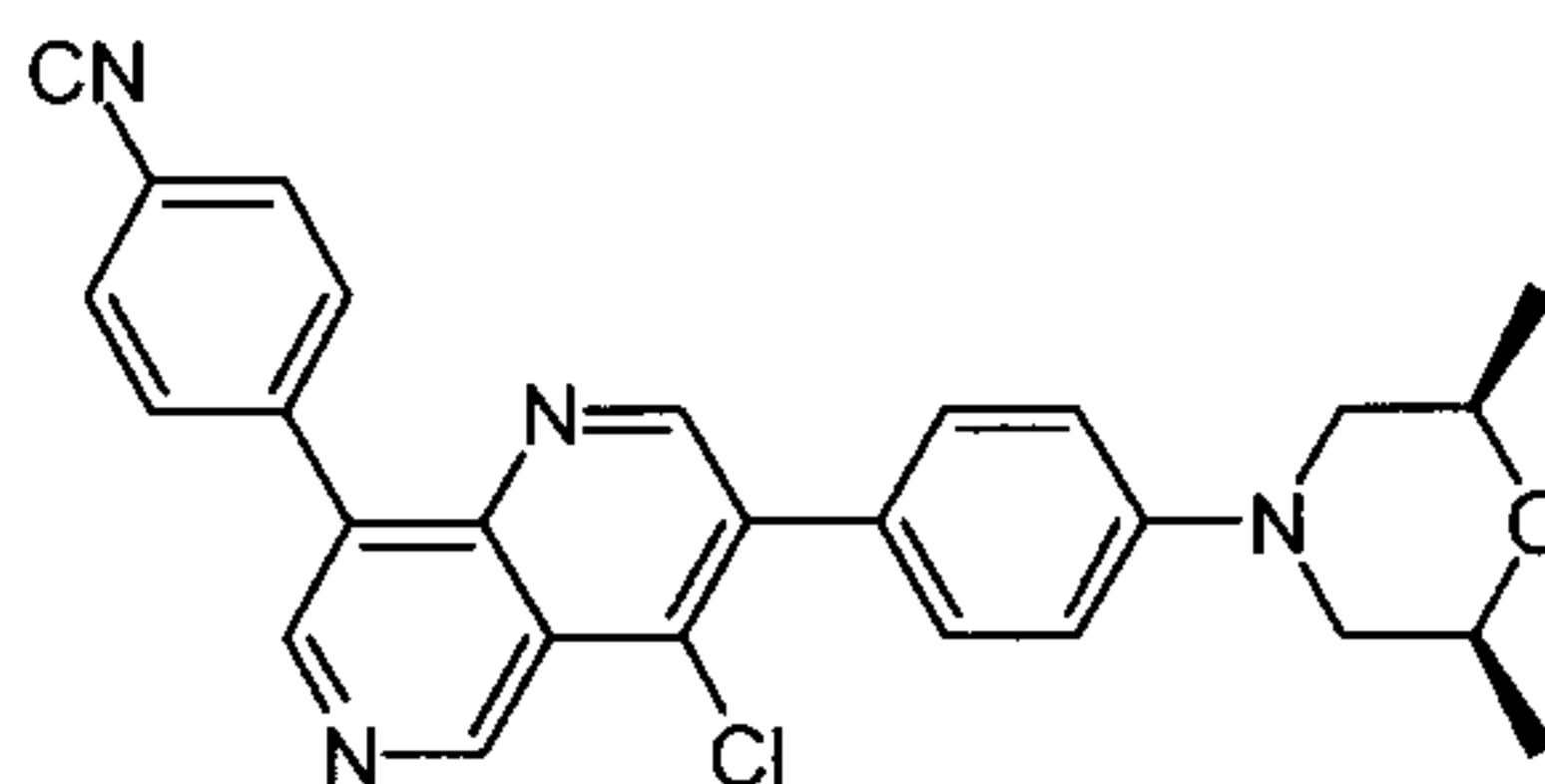
solvent of THF/H₂O (20:4 mL), and stirred at 70°C overnight. After the reaction was complete as detected by LC-MS, H₂O was added, then extracted with EtOAc. The combined organic phase was washed with brines, dried over sodium sulfate, concentrated under vacuum. The residue was purified by silica gel chromatography (PE: EtOAc = 5:1-2:1) to deliver compound 152-2 (0.62 g, yield 44%). **MS ESI** calcd for C₂₀H₂₀ClN₃O₂ [M+H]⁺ 370, found 370.

[367] Step 2: A solution of compound 152-2 (3.7 g, 10 mmol) in POCl₃ (35 mL) was heated at 110°C for 6h. The solvent was removed under vacuum. The residue was quenched with H₂O. The solution was partitioned between EtOAc and H₂O, the organic phase were combined, washed with brines, dried over anhydrous sodium sulfate, filtrated and concentrated under vacuum. The residue was purified by silica gel chromatography (PE:EtOAc = 2:1) to deliver compound 152-3 (0.78 g, yield 21%). **MS ESI** calcd for C₂₀H₁₉Cl₂N₃O [M+H]⁺ 389, found 389.

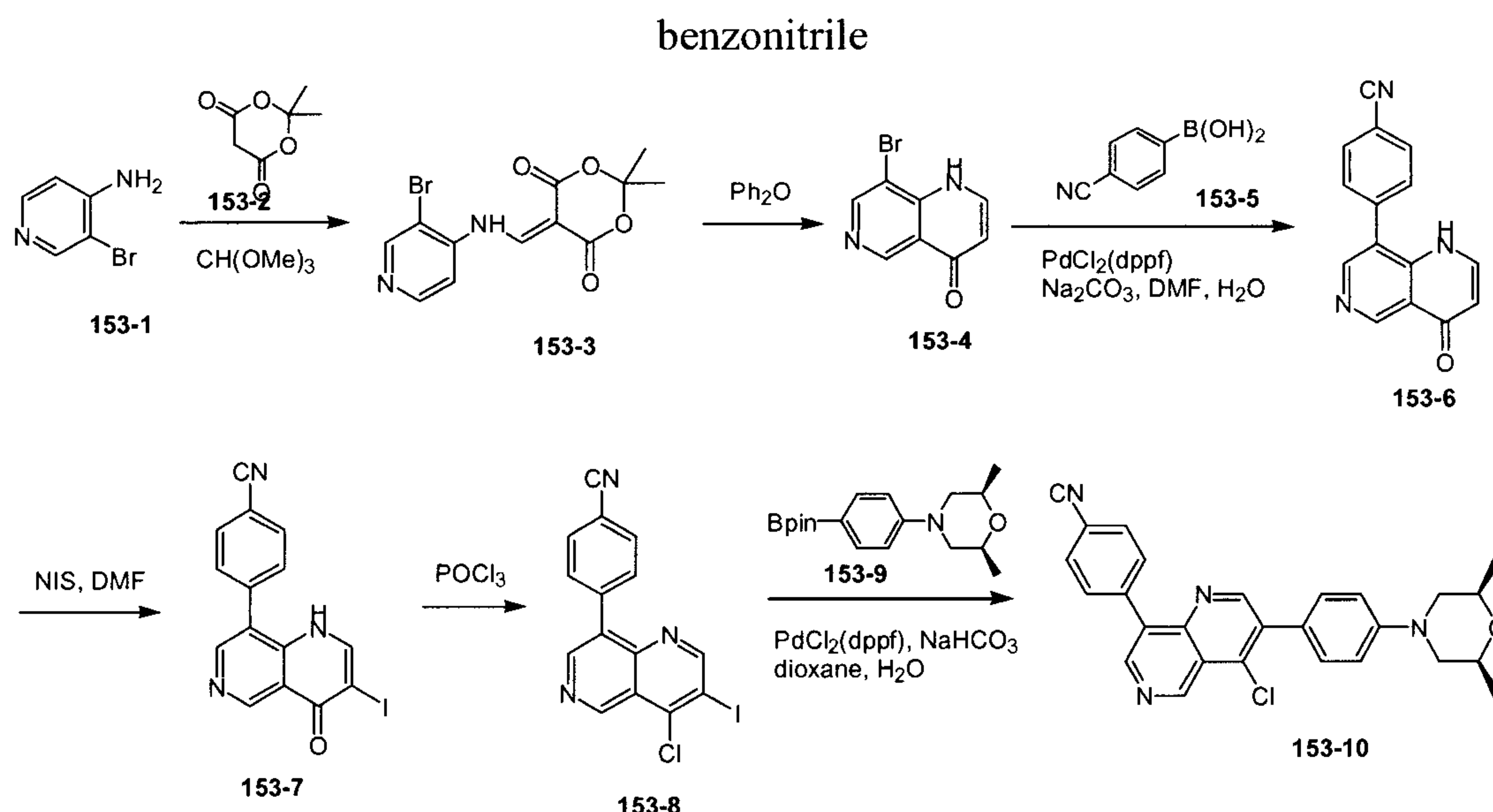
[368] Step 3: NaOMe (0.055 g, 1 mmol) was added into a solution of compound 152-3 (0.19 g, 0.5 mmol) in MeOH (10 mL) at -10 °C in 10 min in portions. The reaction mixture was stirred at 20°C for 1h, then stirred at 50°C for 3h. After the reaction was complete, H₂O (100 mL) was added, then the reaction mixture was extracted with EtOAc. The combined organic phase was washed with brines, dried over sodium sulfate, and concentrated under vacuum to deliver compound 152-4 (0.11g, 58%) as brown solid which was used in the nest step directly. **MS ESI** calcd for C₂₁H₂₂ClN₃O₂ [M+H]⁺ 384, found 384.

[369] Step 4: Compound 152-4 (40 mg, 0.1 mmol), 4-cyanophenyl boronic acid (30 mg, 0.2 mmol), Pd₂(dba)₃ (9 mg, 0.01 mmol), Xantphos (10 mg, 0.02 mmol) and sodium carbonate (4.3 g, 40.2 mmol) were dissolved in a mixed solvent of dioxane/H₂O (5:1 mL), under nitrogen gas atmosphere, the reaction mixture was stirred at 110°C for 6h. The mixture was diluted with H₂O (10 mL), extracted with EtOAc. The combined organic phase was washed with brines, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by preparative HPLC to deliver the title compound as white solid (yield 32%). **¹H NMR** (400 MHz, CDCl₃) δ 8.23 (d, *J*= 8 Hz, 1H), 8.06 (d, *J*= 8.4 Hz, 2H), 7.85 (d, *J*= 8 Hz, 2H), 7.77-7.69 (m, 4H), 6.99 (d, *J*= 8.8 Hz, 2H), 3.74 (s, 5H), 3.57 (d, *J*= 12 Hz, 2H), 2.47 (t, *J*= 10.8 Hz, 2H), 1.23 (d, *J*= 6.4 Hz, 6H). **MS ESI** calcd for C₂₈H₂₆N₄O₂ [M+H]⁺ 451, found 451.

Embodiment 153



4-(4-chloro-3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-1,6-naphthyridin-8-yl)



[370] Step 1: A solution of compound 153-2 (21 g, 0.146 mol) in $\text{CH}(\text{OMe})_3$ (50 mL) was stirred at 60°C for 0.5h. The reaction mixture was cooled to room temperature, compound 153-1 (21.05 g, 0.122 mol) was added. The mixture was refluxed at 100°C for 2h. TLC (PE:EtOAc = 1:1) showed that the starting material was completely consumed. The reaction mixture was cooled to 0°C and filtrated. The filtrate cake was grinded with MeOH to deliver compound 153-2 (24 g, 62%) as dark-yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.48 (brs, 1 H), 8.96-8.81 (m, 1H), 8.77 (s, 1H), 8.51 (d, $J=5.29$ Hz, 1H), 7.90 (d, $J=5.29$ Hz, 1 H), 7.37 (t, $J=7.9$ Hz, 1H), 7.15-6.90 (m, 1 H), 1.68 (s, 6 H). **MS ESI** calcd for $\text{C}_{12}\text{H}_{11}\text{BrN}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 326, 328, found 326, 328.

[371] Step 2: A solution of compound 153-2 (0.4 g, 1.223 mol) in Ph_2O (3 mL) was refluxed at 220°C for 0.5h. TLC showed that the starting material was completely consumed. The reaction mixture was cooled to room temperature and hexane was added. The mixture was filtrated, and the filtrate cake was washed with hexane to deliver compound 153-4 (200 mg, 72%) as dark-yellow solid. **MS ESI** calcd for $\text{C}_8\text{H}_5\text{BrN}_2\text{O}$ $[\text{M}+\text{H}]^+$ 224 and 226, found 224 and 226.

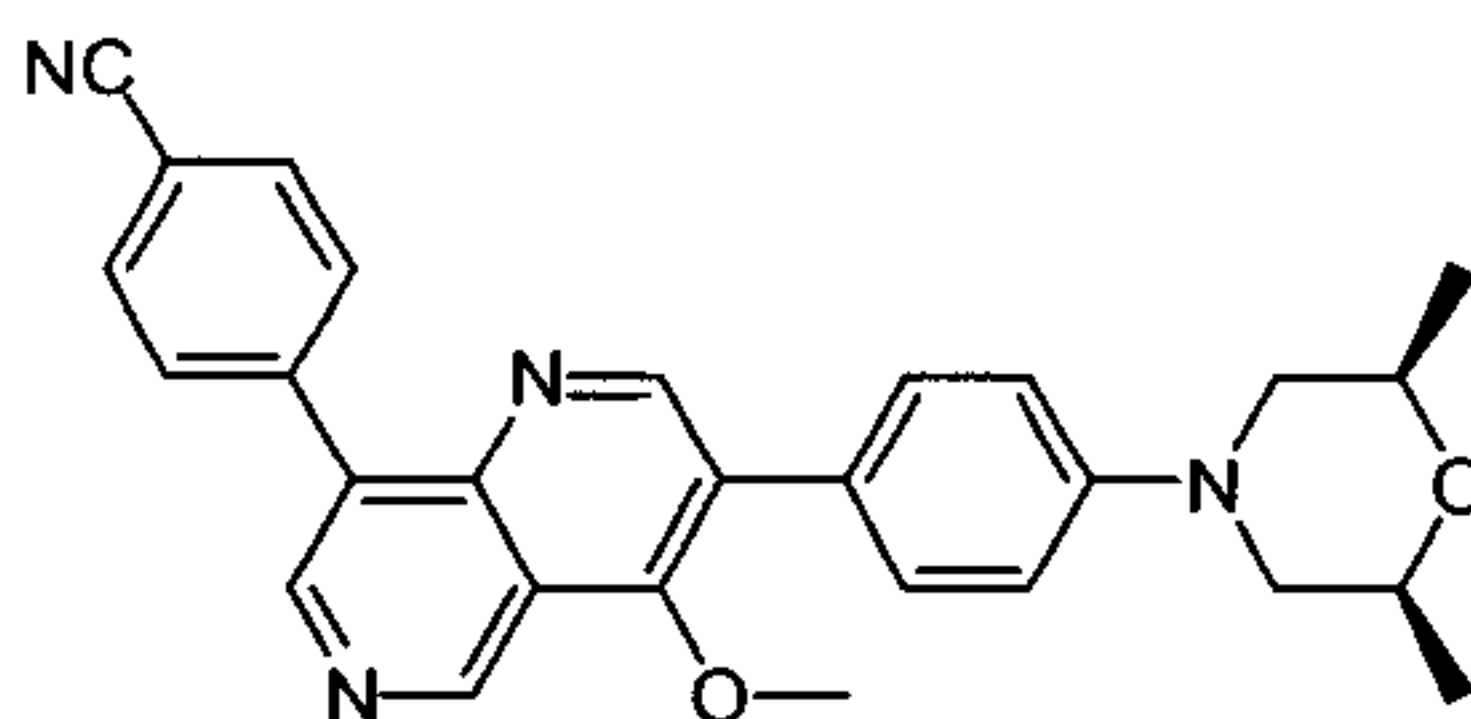
[372] Step 3: Sodium carbonate (780 mg, 7.365 mmol) was added into a solution of compound 153-4 (550 mg, 2.455 mmol) and compound 153-5 (397 mg, 2.701 mmol) (397 mg, 2.701 mmol) in a mixed solvent of DMF (5 mL) and H_2O (1 mL) at room temperature. The reaction mixture was swept with nitrogen gas for 3 times, $\text{PdCl}_2(\text{dppf})$ (90 mg, 0.123 mmol) was added. Then the reaction mixture was swept with nitrogen gas for 3 times again and stirred at reflux overnight. TLC (EtOAc) showed that the starting material was completely consumed. The reaction mixture was filtrated with diatomite mat. The filtrate was concentrated to dry to deliver the crude product which was purified by silica gel chromatography (EtOAc:MeOH = 100: 4) to deliver compound 153-6 (310 mg, 35%) as beige solid. **MS ESI** calcd for $\text{C}_{15}\text{H}_9\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$ 248, found 248.

[373] Step 4: NIS (200 mg, 0.887 mmol) was added into a solution of compound 153-6 (210 mg, 0.85 mmol) in DMF (2 mL) in portions at 0°C. The reaction mixture was stirred at room temperature overnight. TLC (EtOAc) showed that most of the starting material was consumed. The reaction mixture was filtrated, the filtrate was concentrated to deliver compound 153-7 (250 mg, 79%) as white sold. **MS ESI** calcd for C₁₅H₈IN₃O [M+H]⁺ 374, found 374.

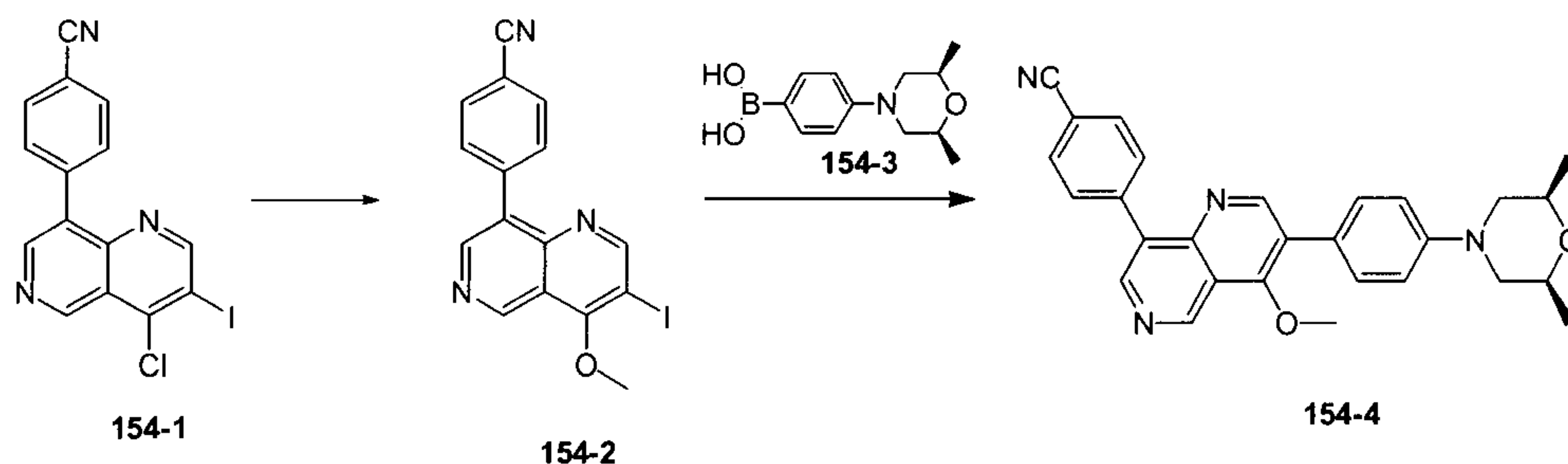
[374] Step 5: A solution of compound 153-7 (310 mg, 0.831 mmol) in POCl₃ (10 mL) was stirred at reflux for 4h. TLC showed that the starting material was completely consumed. The reaction mixture was concentrated to dry and diluted with EtOAc. The obtained solution was basified with NaHCO₃ (aq) at 0°C. The mixture was partitioned between EtOAc and H₂O. The organic phase was concentrated to dry to deliver a crude product which was purified by silica gel chromatography (PE:EtOAc= 1:1) to deliver compound 153-8 (290 mg, 90%) as white solid. **MS ESI** calcd for C₁₅H₇ClIN₃ [M+H]⁺ 392, found 392.

[375] Step 6: Compound 153-8 (27 mg, 0.691 mmol) and compound 153-9 (262 mg, 0.828 mmol) were dissolved in a mixed solvent of dioxane (3 mL) and H₂O (0.6 mL), sodium bicarbonate (145 mg, 1.727 mmol) was added. The reaction mixture was swept with nitrogen gas for 3 times, Pd (dppf)Cl₂ (50 mg, 0.069 mmol) was added, then the reaction mixture was swept with nitrogen gas for 3 times again, and stirred at 80°C for 2h. TLC (PE:EtOAc = 3:1) showed that the starting material was completely consumed. The reaction mixture was filtrated with diatomite mat. The filtrate was concentrated to dry to deliver a crude product which was purified by silica gel chromatography (PE: EtOAc= 2:1) to deliver the title compound (120 mg, 30%) as yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 9.85 (s, 1 H), 9.08 (s, 1 H), 8.87 (s, 1 H), 7.90-7.83 (m, 5 H), 7.52 (d, *J*=8.53 Hz, 2 H), 7.09 (d, *J*=7.78 Hz, 2 H), 3.87 (br. s., 2 H), 3.62 (d, *J*=11.29 Hz, 2 H), 2.57 (t, *J*=11.17 Hz, 2 H), 1.32 (d, *J*=6.27 Hz, 6 H). **MS ESI** calcd for C₂₇H₂₃ClN₄O [M+H]⁺ 455, found 455.

Embodiment 154



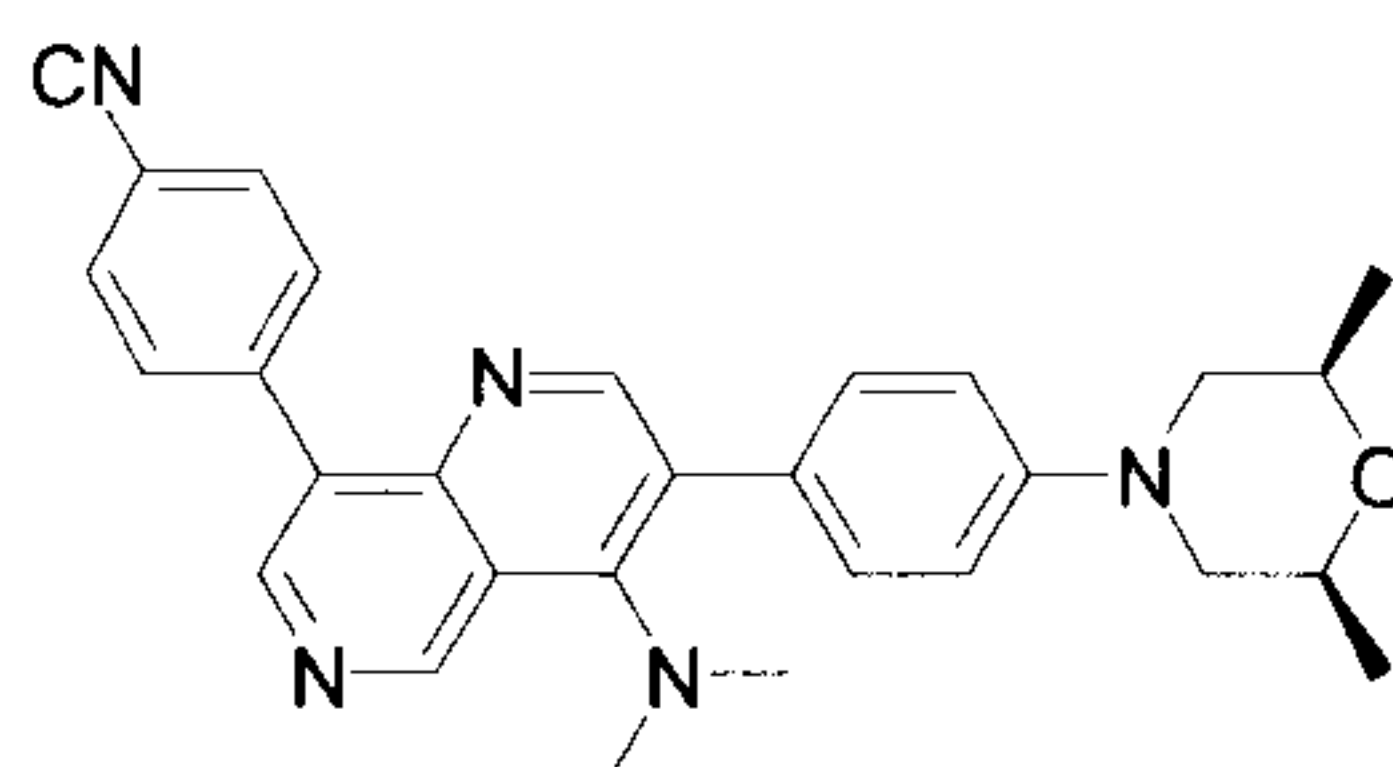
4-(3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxyquinolin-8-yl)benzonitrile



[376] Step 1: NaOMe (32 mg, 6 mmol) was added into a solution of compound 154-1 (120 mg, 3 mmol) in MeOH (15 mL), and the mixture was stirred at 45°C for 16h. After LC-MS showed that the starting material was completely consumed, the solution was concentrated under vacuum and partitioned between EtOAc and H₂O. The organic phase was combined and washed with brines, dried over anhydrous sodium sulfate, filtrated and concentrated under reduced pressure to deliver compound 154-2 (0.1 g, 83%) as white solid. **MS ESI** calcd for C₁₆H₁₀IN₃O [M+H]⁺ 387, found 387.

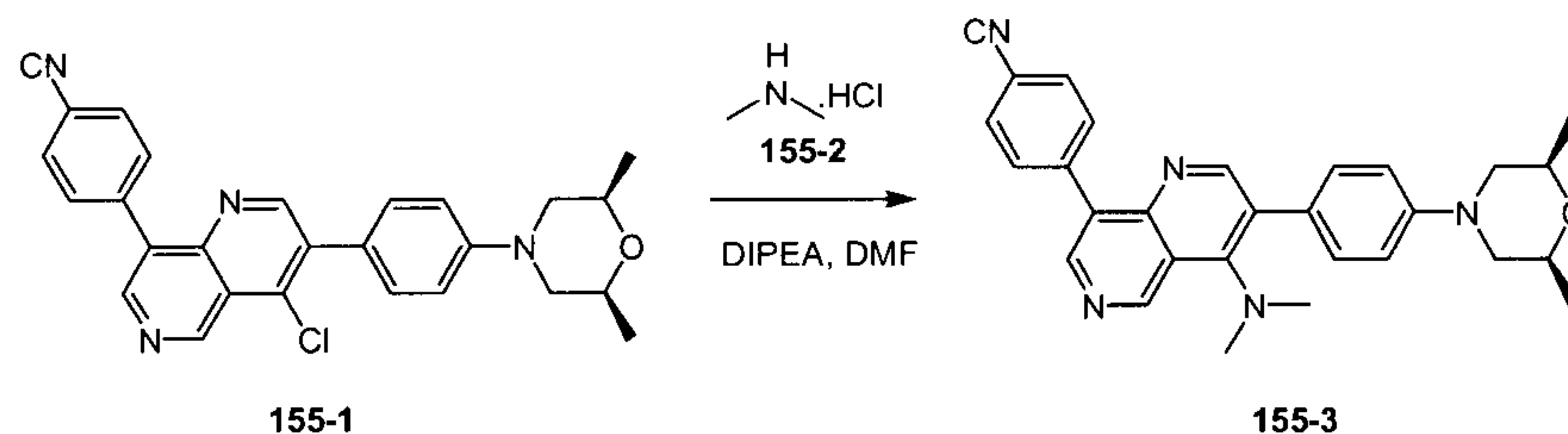
[377] Step 2: Compound 154-2 (100 mg, 0.28 mmol), compound 154-3 (91 mg, 0.39 mmol), Pd(dppf)Cl₂ (22 mg, 0.032 mmol) and sodium carbonate (45 mg, 0.52 mmol) were dissolved in a mixed solvent of THF (20 mL) and H₂O (3 mL), and the mixture was stirred at 80°C overnight. After LC-MS showed that the starting material was completely consumed, the solution was partitioned between EtOAc and H₂O. The organic phases were combined and washed with brines, dried over anhydrous sodium sulfate, filtrated and concentrated under vacuum. The residue was purified by preparative HPLC to deliver the title compound (30 mg, 25%). **¹H NMR** (400 MHz, CDCl₃) δ 9.71 (s, 1H), 9.03 (s, 1H), 8.76 (s, 1H), 7.87 (d, *J* = 8 Hz, 2H), 7.81 (d, *J* = 8 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 3.86 – 3.82 (m, 5H), 3.59 (d, *J* = 10.8 Hz, 2H), 2.52 (t, *J* = 11.2 Hz, 2H), 1.30 (d, *J* = 6.4 Hz, 6H). **MS ESI** calcd for C₂₈H₂₆N₄O₂ [M+H]⁺ 451, found 451.

Embodiment 155



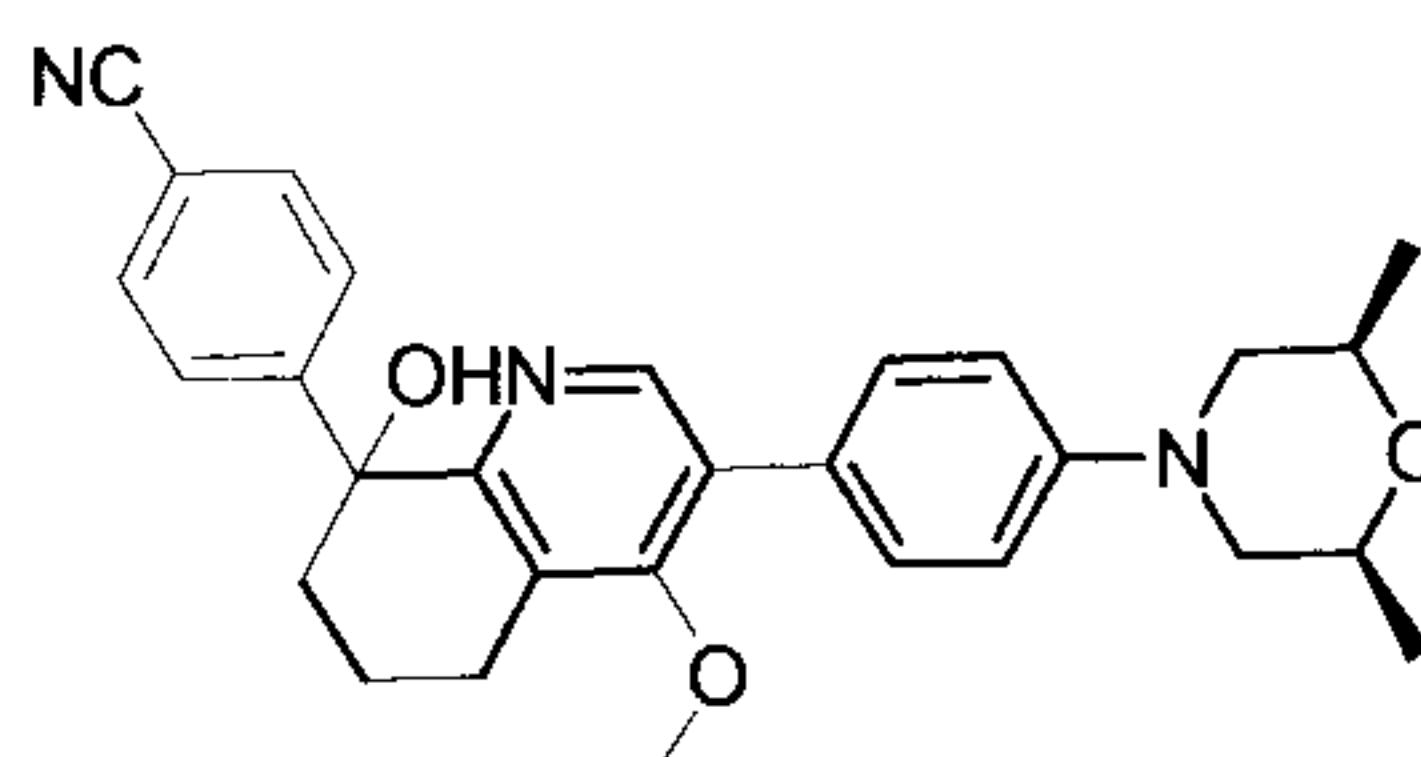
4-(4-(dimethylamino)-3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-1,6-naphthyridin-8-yl)benzonitrile

Our Ref.: P1650132CA

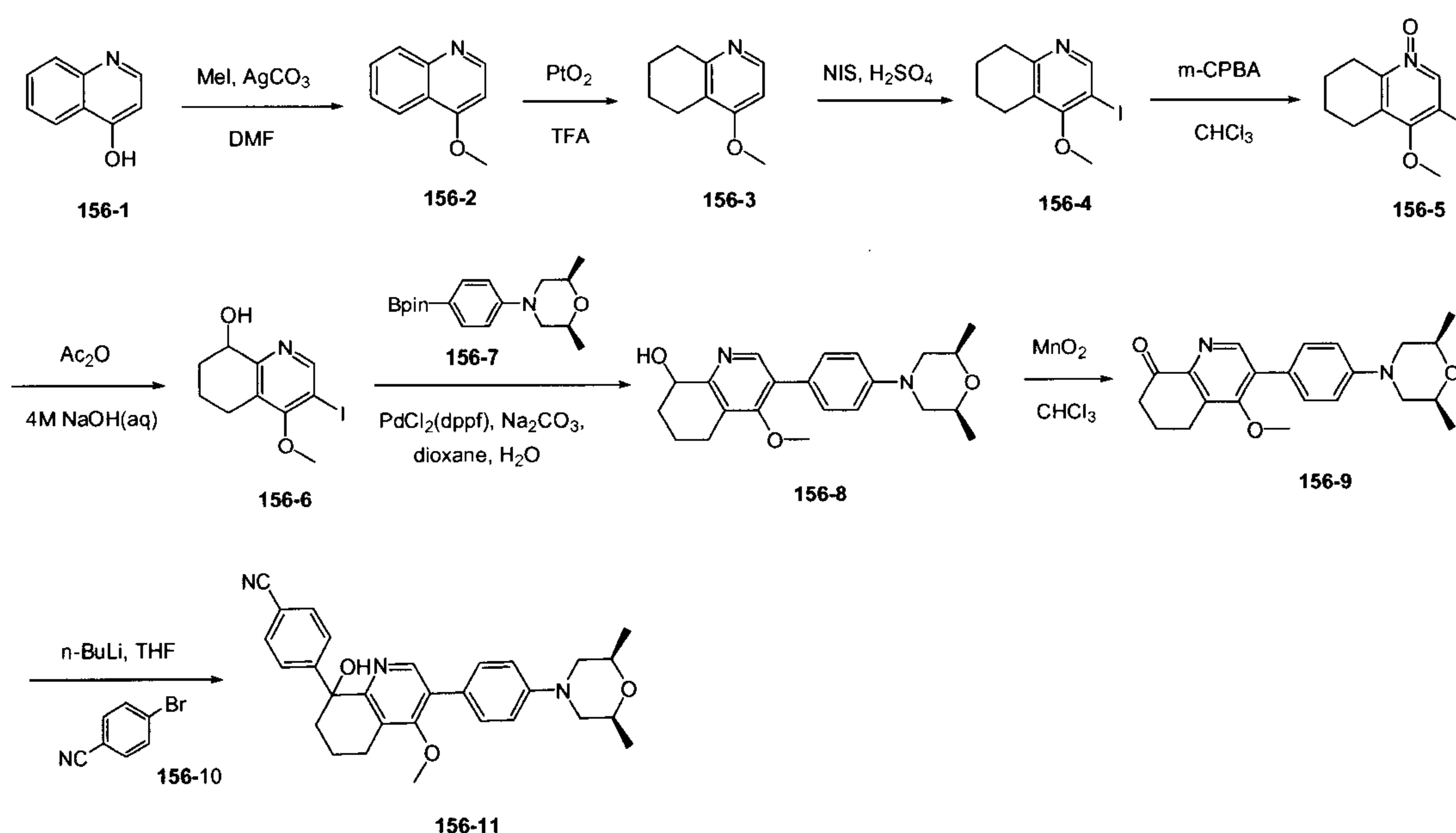


[378] Compound 155-2 (146 mg, 1.79 mmol) and DIPEA (282 mg, 2.186 mmol) were added into a solution of compound 155-1 (80 mg, 0.176 mmol) in DMF (2 mL). The mixture was stirred at 120°C overnight. TLC (PE:EtOAc = 1:1) showed that the starting material was completely consumed. The mixture was concentrated to give a crude product which was purified by silica gel chromatography (PE:EtOAc = 1:1) to deliver the title compound (35 mg, 43%) as yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 9.62 (br. s., 1 H), 8.77 (s, 1 H), 8.61 (s, 1 H), 7.91 (d, *J*=7.06 Hz, 2 H), 7.84-7.69 (m, 5 H), 7.40 (d, *J*=7.06 Hz, 2 H), 4.58 (br. s., 2 H), 3.51 (d, *J*=11.47 Hz, 2 H), 3.01 (s, 6 H), 2.91 (t, *J*=11.25 Hz, 2 H), 2.55 (s, 1 H), 1.94 (s, 1 H), 1.25 (d, *J*=6.62 Hz, 6 H). MS ESI calcd for C₂₉H₂₉N₅O [M+H]⁺ 464, found 464.

Embodiment 156



4-(3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-8-hydroxy-4-methoxy-5,6,7,8-tetrahydroquinolin-8-yl)benzonitrile



[379] Step 1: Ag₂CO₃ (55.55 g, 0.201 mol) was added into a solution of compound

156-1 (14.62 g, 0.101 mol) in DMF (150 mL). The reaction mixture was swept with nitrogen gas and MeI (12.88 g, 0.091 mol) was added. Then the reaction mixture was stirred at 80°C overnight. TLC (EtOAc) showed that the starting material was completely consumed. The mixture was filtrated, the filtrate was partitioned between EtOAc and H₂O. The organic phase was concentrated to give a crude product which was purified by silica gel chromatography (PE:EtOAc = 2:1) to deliver compound 156-2 (10 g, 56%) as colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.72 (d, *J*=3.53 Hz, 1 H), 8.17 (d, *J*=7.94 Hz, 1 H), 8.02 (d, *J*=8.38 Hz, 1 H), 7.71-7.62 (m, 1 H), 7.52-7.42 (m, 1 H), 6.75-6.59 (m, 1 H), 3.99 (d, *J*=1.76 Hz, 4 H). **MS ESI** calcd for C₁₀H₉NO [M+H]⁺ 160, found 160.

[380] Step 2: Under nitrogen gas atmosphere, PtO₂ (1 g) was added into a solution of compound 156-2 (5 g, 0.031 mol) in TFA (45 mL). The mixture was stirred under a hydrogen gas pressure of 50 psi at room temperature. TLC (PE:EtOAc = 1:1) showed that the starting material was completely consumed. The mixture was filtrated, the filtrate was concentrated under vacuum. The residue was dissolved into H₂O, basified to pH=9 with 8 N NaOH (aq.) at 0 °C, the aqueous phase was extracted with DCM, the organic phase was washed with brines, dried over anhydrous sodium sulfate and concentrated to deliver compound 156-3 (4 g, 80%) as yellow oil, which was used in the next step directly. ¹H NMR (400 MHz, CDCl₃) δ 8.18 (d, *J*=5.73 Hz, 1H), 6.50 (d, *J*=5.73 Hz, 1H), 3.75 (s, 3H), 2.78 (t, *J*=6.17 Hz, 2H), 2.53 (t, *J*=6.17 Hz, 2H), 1.79-1.62 (m, 5H). **MS ESI** calcd for C₁₀H₁₃NO [M+H]⁺ 164, found 164.

[381] Step 3: NIS (9.6 g, 0.043 mol) was added into a solution of compound 156-3 (5.8 g, 0.0356 mol) in sulphuric acid (30 mL) at 0°C in portions, the mixture was stirred at room temperature for 0.5h, then heated to 60°C and stirred for 2h. TLC (PE:EtOAc = 1:1) showed that the starting material was completely consumed. The mixture was poured into ice-water, and basified to pH = 9 with 8 N NaOH (aq). Then the aqueous phase was extracted with DCM. The organic phase was washed with sat. NaHCO₃ (aq) and brines, concentrated to deliver a crude product, which was purified by silica gel chromatography (PE:EtOAc = 15:1) to deliver compound 156-4 (sat. NaHCO₃ (aq) as brown solid. ¹H NMR (400 MHz, CDCl₃) δ 8.55 (brs, 1H), 3.80-3.73 (m, 2H), 2.84-2.77 (m, 2H), 2.76-2.70 (m, 2H), 1.85-1.69 (m, 4H). **MS ESI** calcd for C₁₀H₁₂INO [M+H]⁺ 290, found 290.

[382] Step 4: *m*-CPBA (2.6 g, 0.015 mol) was added into a solution of compound 156-4 (1.44 g, 0.005 mol) in CHCl₃ (10 mL) at 0°C in portions, the mixture was stirred at 40°C for 2h. The mixture was quenched with H₂O, adjusted to pH to 14 with 8 N NaOH (aq). Then the aqueous phase was extracted with DCM. The organic phase was washed with sat. NaHCO₃ (aq) and brines, concentrated to deliver compound 156-5 (1.3 g, 88%) as yellow solid, which was used for the next step directly. **MS ESI** calcd for C₁₀H₁₂INO₂ [M+H]⁺ 306, found 306.

[383] Step 5: A solution of compound 156-5 (1.3 g, 0.0043 mmol) in Ac₂O (6 mL) was stirred at 90°C for 2h. The mixture was concentrated and 4 N NaOH (aq) (4.3 mL, 0.017 mol) was added. The mixture was stirred at 80°C for 2h. Then the

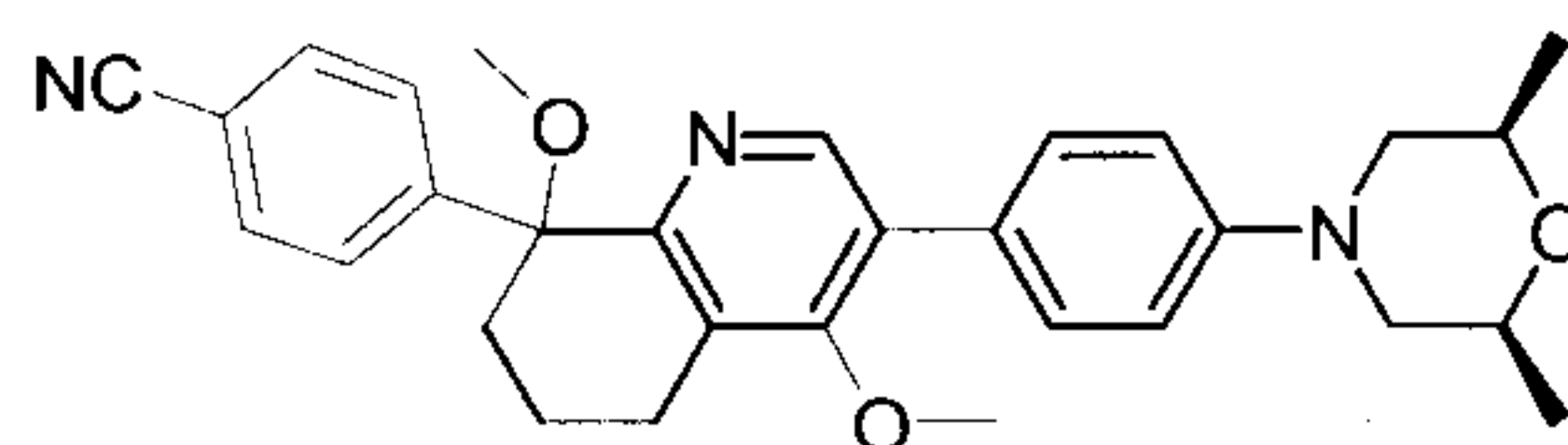
aqueous phase was extracted with DCM. The organic phase was concentrated to deliver a crude product, which was purified by silica gel chromatography (PE:EtOAc= 3:1) to deliver compound 156-6 (0.82 g, 33%) as yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 8.61 (s, 1H), 4.59 (brs, 1 H), 3.79 (s, 3H), 3.67 (br. s., 1H), 2.77 (br. s., 2H), 2.19 (br. s., 1H), 1.94 (br. s., 1H), 1.71 (br. s., 2H). **MS ESI** calcd for $\text{C}_{10}\text{H}_{12}\text{INO}_2$ $[\text{M}+\text{H}]^+$ 306, found 306.

[384] Step 6: Sodium carbonate (0.69 g, 0.0065 mol) was added into a solution of compound 156-6 (0.8 g, 0.0026 mol) and compound 156-7 in a mixed solvent of dioxane (8 mL) and H_2O (2 mL). The mixture was swept with nitrogen gas and Pd (dppf) Cl_2 (0.19 g, 0.26 mmol) was added. Then the mixture was stirred at 100°C and refluxed for 2h. The mixture was filtrated with diatomite mat, the filtrate was concentrated to give a crude product, which was purified by silica gel chromatography (PE:EtOAc= 1:2) to deliver compound 156-8 (0.66 g, 68%) as yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 8.28 (s, 1 H), 7.37 (d, $J=8.82$ Hz, 2H), 6.91 (d, $J=8.82$ Hz, 2H), 4.65 (t, $J=6.84$ Hz, 1H), 3.88 (s, 1H), 3.79-3.68 (m, 2H), 3.47 (d, $J=11.03$ Hz, 2H), 3.39 (s, 3H), 2.82-2.63 (m, 2H), 2.41 (t, $J=11.03$ Hz, 2H), 2.27-2.14 (m, 1H), 2.01-1.91 (m, 1H), 1.73 (t, $J=8.16$ Hz, 2H), 1.22 (d, $J=6.17$ Hz, 7H). **MS ESI** calcd for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 369, found 369.

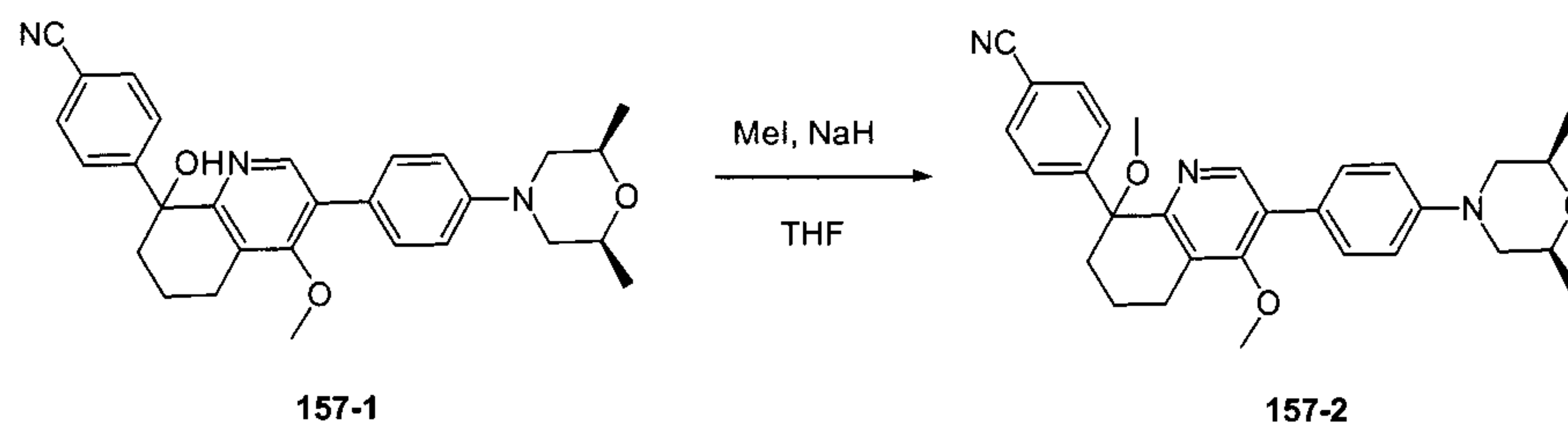
[385] Step 7: MnO_2 (1.56 g, 0.018 mol) was added into a solution of compound 156-8 (0.66 g, 0.0018 mol) in CHCl_3 (10 mL). The mixture was stirred at reflux overnight. The mixture was filtrated with diatomite mat, the filtrate was concentrated to give a crude product, which was purified by silica gel chromatography (PE:EtOAc= 1:2) to deliver compound 156-9 (0.57 g, 86%) as yellow solid. **MS ESI** calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 367, found 367.

[386] Step 8: Under nitrogen gas atmosphere, n-BuLi (0.3 mL, 0.75 mmol) was added dropwise into a solution of compound 156-10 (124 mg, 0.682 mmol) in THF (2 mL) at -65°C . The mixture was stirred at -65°C for 0.5h, then a solution of compound 156-9 (200 mg, 0.546 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at -65°C for 1h, and stirred at 0°C for another 1h. TLC showed that the starting material was completely consumed. The reaction mixture was quenched with sat. NaHCO_3 (aq) and diluted with EtOAc. The organic phase was concentrated to give a crude product, which was purified by silica gel chromatography (PE:EtOAc= 3:1) to deliver the title compound (65 mg, 30%) as yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 8.28 (s, 1H), 7.51 (d, $J=8.38$ Hz, 2H), 7.39 (d, $J=8.82$ Hz, 2H), 7.27 (d, $J=8.38$ Hz, 2H), 6.92 (d, $J=8.82$ Hz, 2H), 4.08 (s, 1H), 3.76 (ddd, $J=10.14, 6.17, 2.21$ Hz, 2H), 3.49 (s, 1 H), 3.46 (s, 4H), 2.91-2.74 (m, 2H), 2.42 (t, $J=11.25$ Hz, 2H), 2.21-2.11 (m, 2H), 1.85 (brs, 1H), 1.55 (brs, 1H), 1.22 (d, $J=6.17$ Hz, 6H). **MS ESI** calcd for $\text{C}_{29}\text{H}_{31}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$ 470, found 470.

Embodiment 157

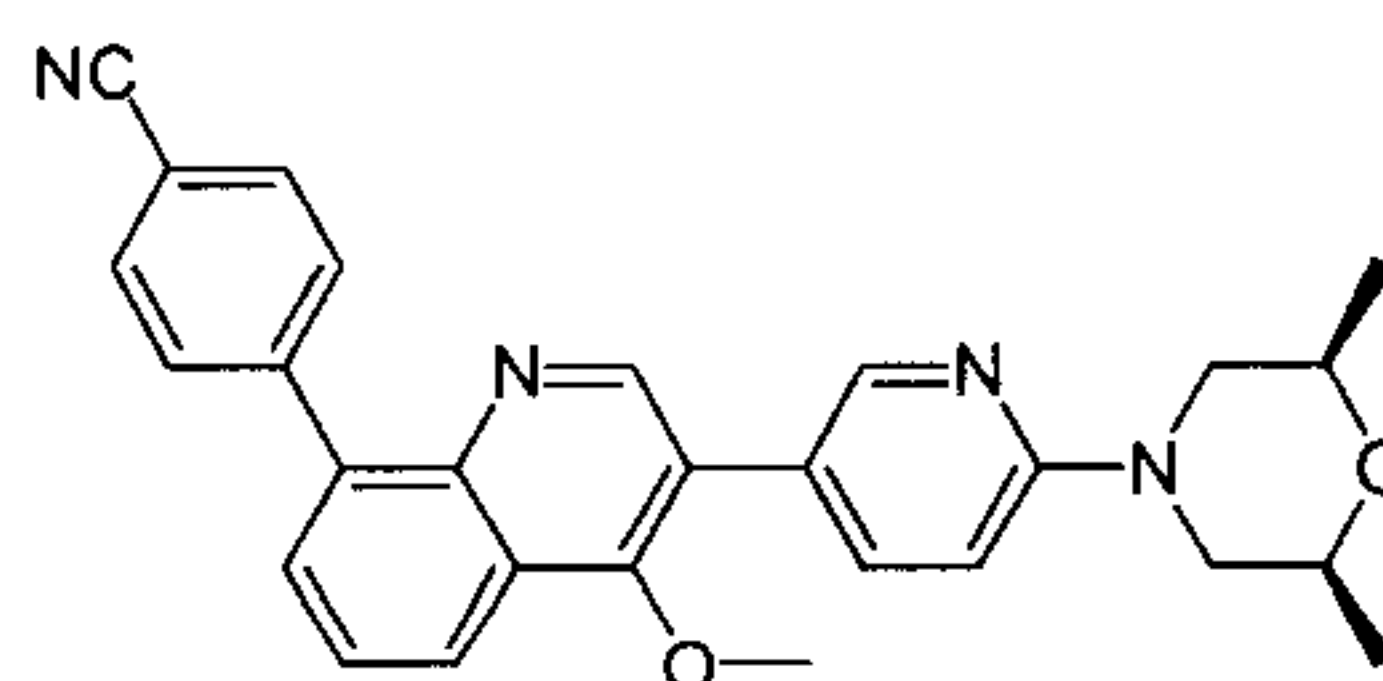


4-(3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4,8-dimethoxy-5,6,7,8-tetrahydroquinolin-8-yl)benzonitrile



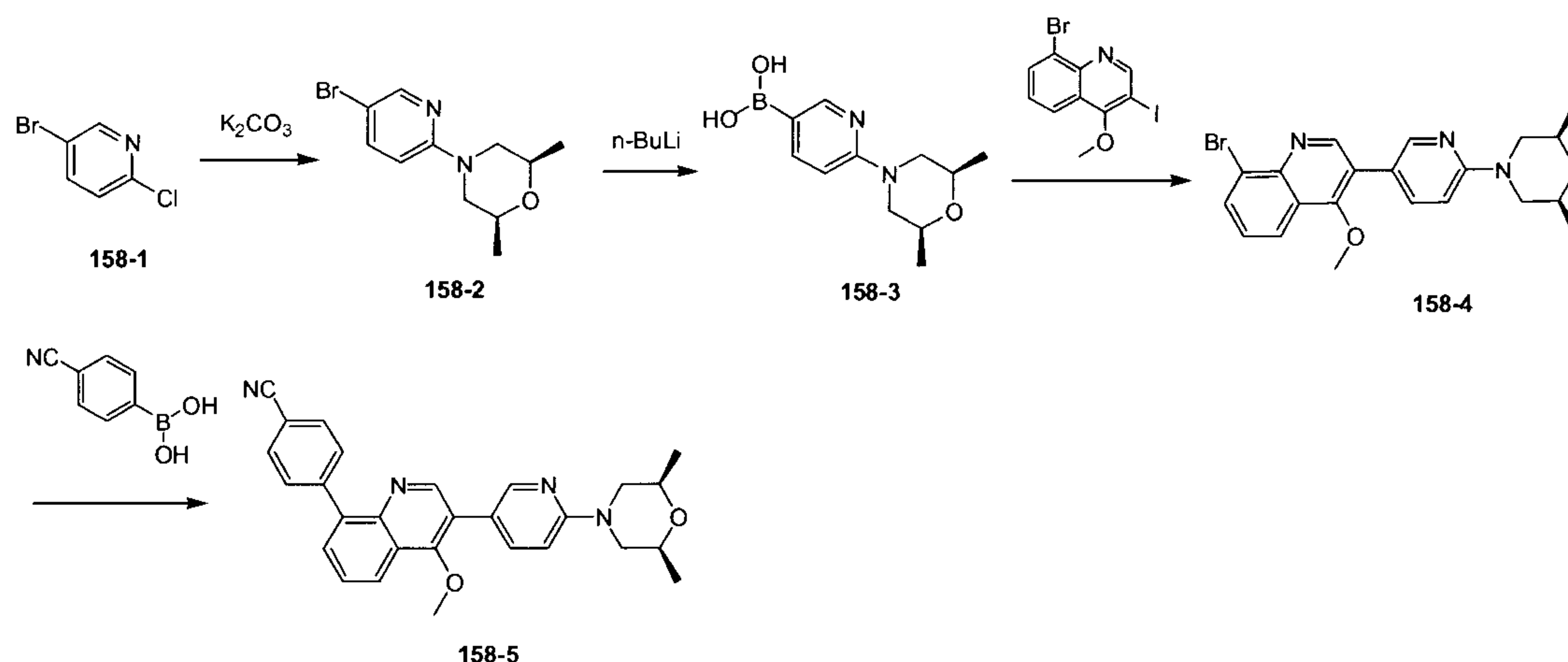
[387] NaH (27.3 mg, 0.682 mmol) was added into a solution of compound 157-1 (80 mg, 0.171 mmol) in THF (3 mL) at 0 °C, the suspension was stirred at 0 °C for 10 min. A solution of MeI (29 mg, 0.204 mmol) in THF (1 mL) was added. The mixture was stirred at room temperature overnight. TLC showed that compound 157-1 was completely consumed. The mixture was concentrated to give a crude product which was purified by pre TLC (PE:EtOAc= 3:1) to deliver the title compound (40 mg, 40%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.43 (s, 1 H), 7.63 (d, *J*=8.28 Hz, 2 H), 7.56-7.49 (m, 2 H), 7.41 (d, *J*=8.28 Hz, 2 H), 7.02 (d, *J*=8.78 Hz, 2 H), 3.90-3.79 (m, 2 H), 3.59 (br. s., 1 H), 3.57-3.51 (m, 4 H), 3.27 (s, 3 H), 3.10-3.00 (m, 1 H), 2.87-2.76 (m, 1 H), 2.51 (t, *J*=11.17 Hz, 2 H), 2.33 (dd, *J*=13.30, 4.02 Hz, 1 H), 2.14 (br. s., 1 H), 2.00-1.90 (m, 1 H), 1.84 (d, *J*=6.78 Hz, 1 H), 1.31 (d, *J*=6.27 Hz, 6 H). MS ESI calcd for C₃₀H₃₃N₃O₃ [M+H]⁺ 484, found 484.

Embodiment 158



4-(3-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-4-methoxyquinolin-8-yl)benzonitrile

Our Ref.: P1650132CA



[388] Step 1: (2S, 6R)-2,6-dimethylmorpholine (4.0 g, 34.8 mmol) and potassium carbonate (8.0 g, 58 mmol) were added into a solution of 5-bromo-2-chloro-pyridine (5.0 g, 26.2 mmol) in DMF (18 mL). The reaction mixture was stirred at 90°C for 6h and filtrated, the filtrate cake was washed with EtOAc. The filtrate was concentrated, the crude product was purified by silica gel column chromatography to deliver compound 158-2 (6 g, yield 84.9%) as yellow oil. **MS ESI** calcd for $C_{11}H_{15}BrN_2O$ $[M+H]^+$ 271, found 271.

[389] Step 2: *n*-BuLi (8.3 mL, 20.6 mmol) was added into a solution of compound 158-2 (3.7 g, 13.7 mmol) in THF (30 mL), under nitrogen gas atmosphere, the reaction mixture was stirred at -78°C for 30min. Triisopropyl borate (7.8 g, 41.2 mmol) was added into the reaction mixture, then stirred at -78°C for 3h. The mixture was poured into H₂O, extracted with EtOAc, dried over sodium sulfate and filtrated, concentrated under reduced pressure, the residue was purified by silica gel column chromatography to deliver compound 158-3 (1.3g, yield 40.2%) as brown solid. **MS ESI** calcd for $C_{11}H_{17}BN_2O_3$ $[M+H]^+$ 237, found 237.

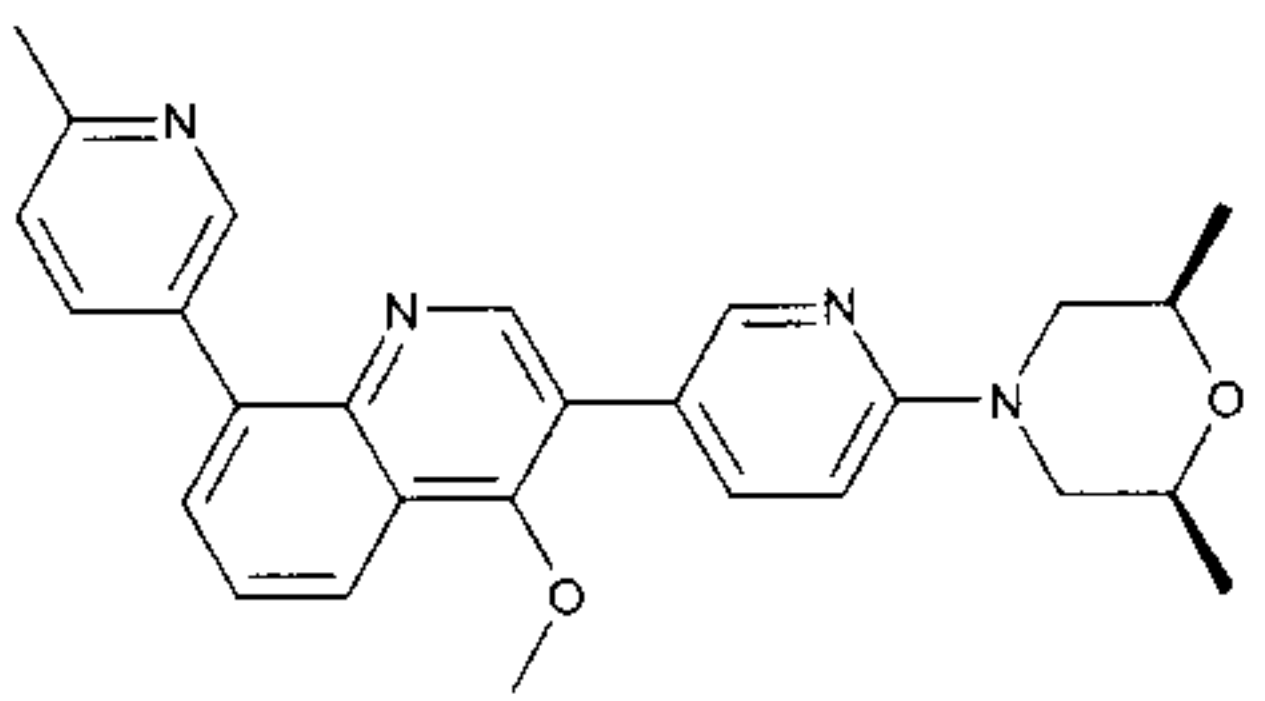
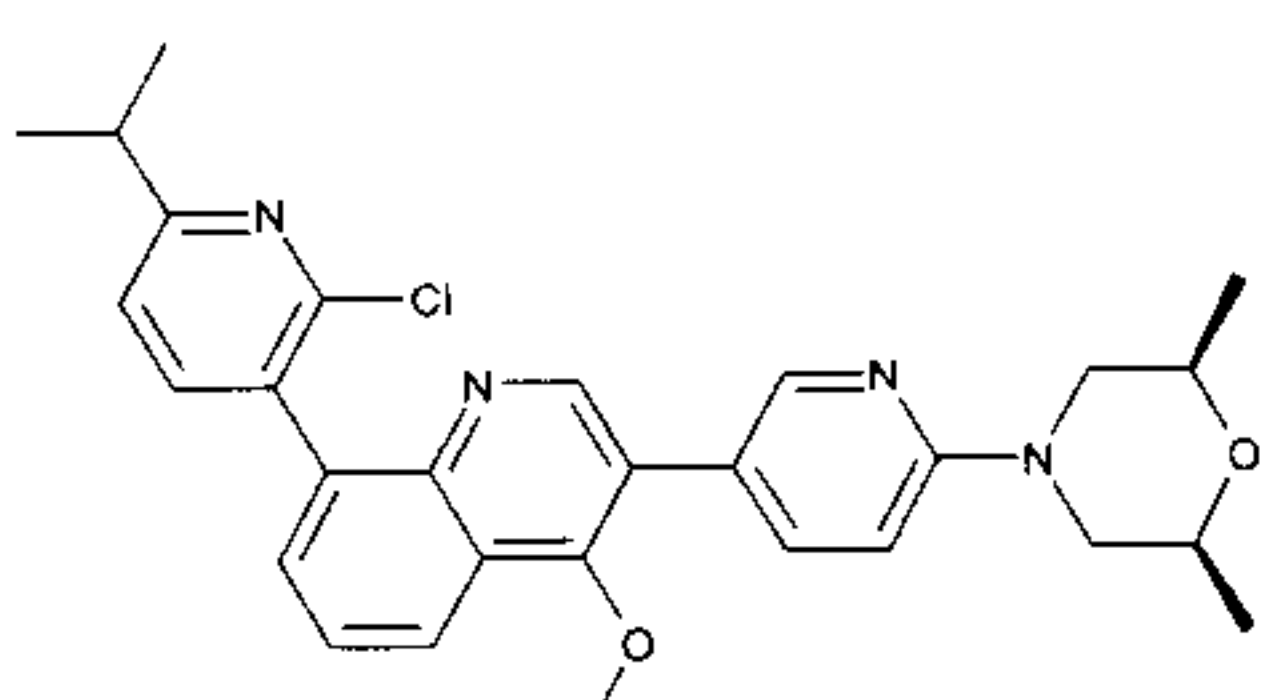
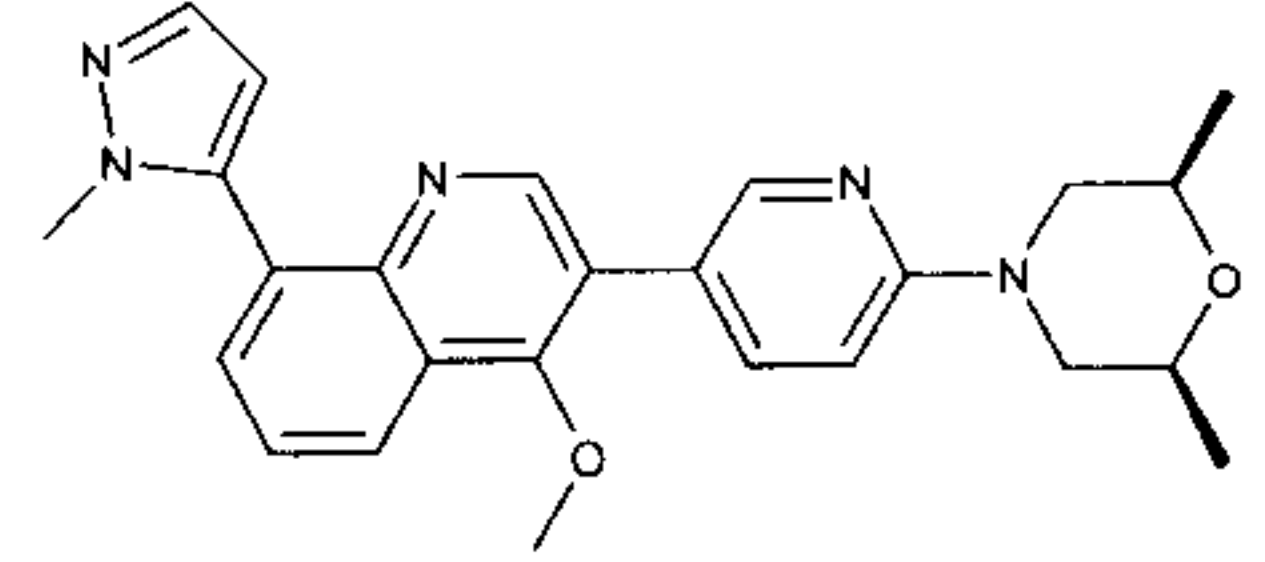
[390] Step 3: Compound 158-3 (324 mg, 1.37 mmol), Pd(dppf)Cl₂ (100.3 mg, 1.37 mmol) and sodium carbonate (290 mg, 2.74 mmol) were added into a solution of 8-bromo-3-iodo-4-methoxyquinoline (500 mg, 1.37 mmol) in a mixed solvent of THF (4 mL), H₂O (1 mL) and DMF (1 mL), the reaction mixture was stirred at 60°C for 3h. Then the reaction mixture was poured into H₂O, extracted with EtOAc, dried over anhydrous sodium sulfate, filtrated and concentrated under reduced pressure to deliver a crude product 158-4 (400mg, yield 68.4%) as brown solid. **MS ESI** calcd for $C_{21}H_{22}BrN_3O_2$ $[M+H]^+$ 428, found 428.

[391] Step 4: 4-cyanophenylboronic acid (206 mg, 1.4 mmol), Pd(dppf)Cl₂ (34 mg, 0.0466 mmol) and sodium carbonate (100 mg, 0.932 mmol) were added into a solution of compound 158-4 (200 mg, 0.466 mmol) in a mixed solvent of THF (3 mL), H₂O (0.5 mL) and DMF (0.5 mL). The reaction mixture was stirred at 70°C for 4h. Then the mixture was poured into H₂O and extracted with EtOAc, the organic phase was dried over anhydrous sodium sulfate, filtrated and concentrated under reduced pressure, the crude product was purified by preparative HPLC to deliver the title compound (100 mg, yield 47.8%) as white solid. **¹H NMR** (400MHz, CDCl₃) δ 8.89

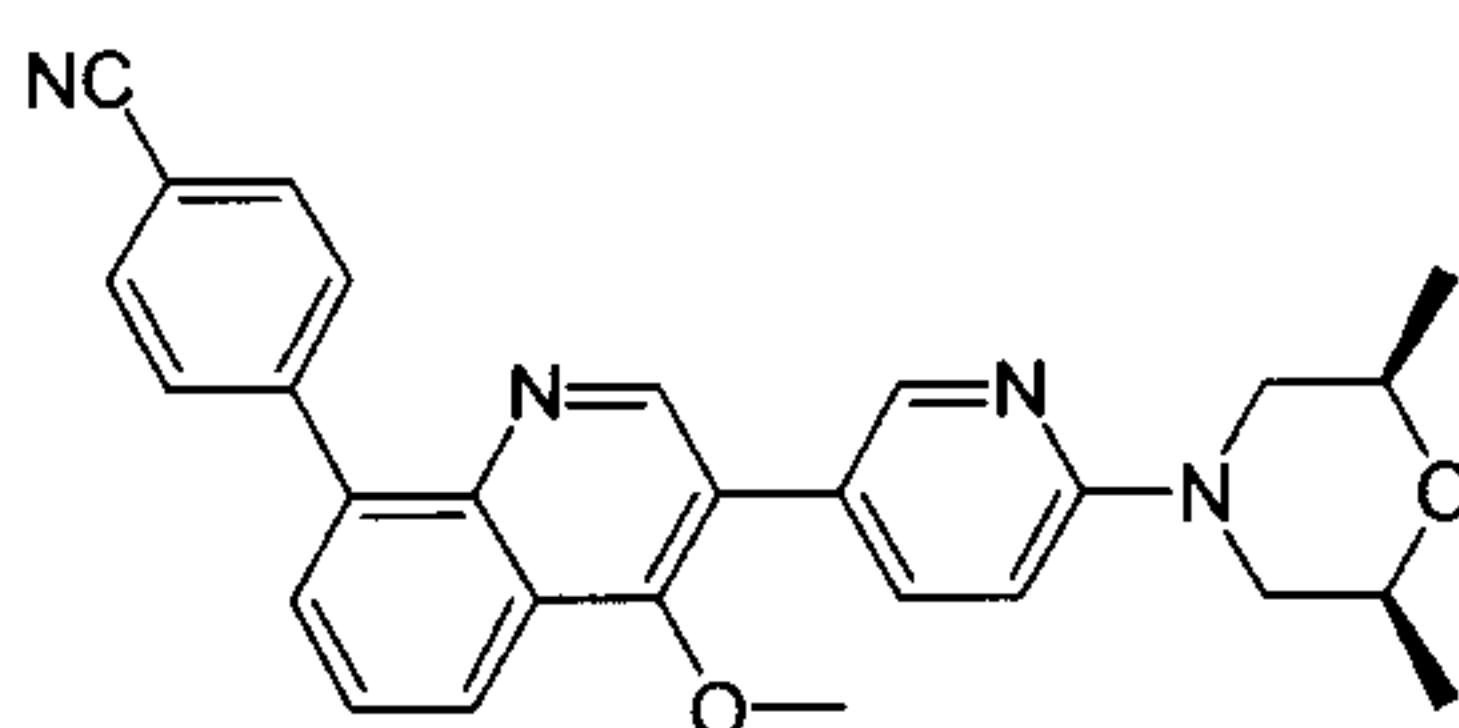
(s, 1H), 8.50 (s, 1H), 8.31(d, $J=7.2$ Hz, 1H), 7.78-7.87 (m, 5H), 7.66-7.71 (m, 2H), 6.78 (d, $J=8.8$ Hz, 1H), 4.15 (d, $J=12$ Hz, 2H), 3.76 (s, 5H), 2.63 (t, $J=11.6$ Hz, 2H), 1.31 (d, $J=6.4$ Hz, 7H). **MS ESI** calcd for $C_{28}H_{26}N_4O_2$ $[M+H]^+$ 451, found 451.

[392] The compounds listed in table 13 were synthesized by compound 158-4 and corresponding boric acids.

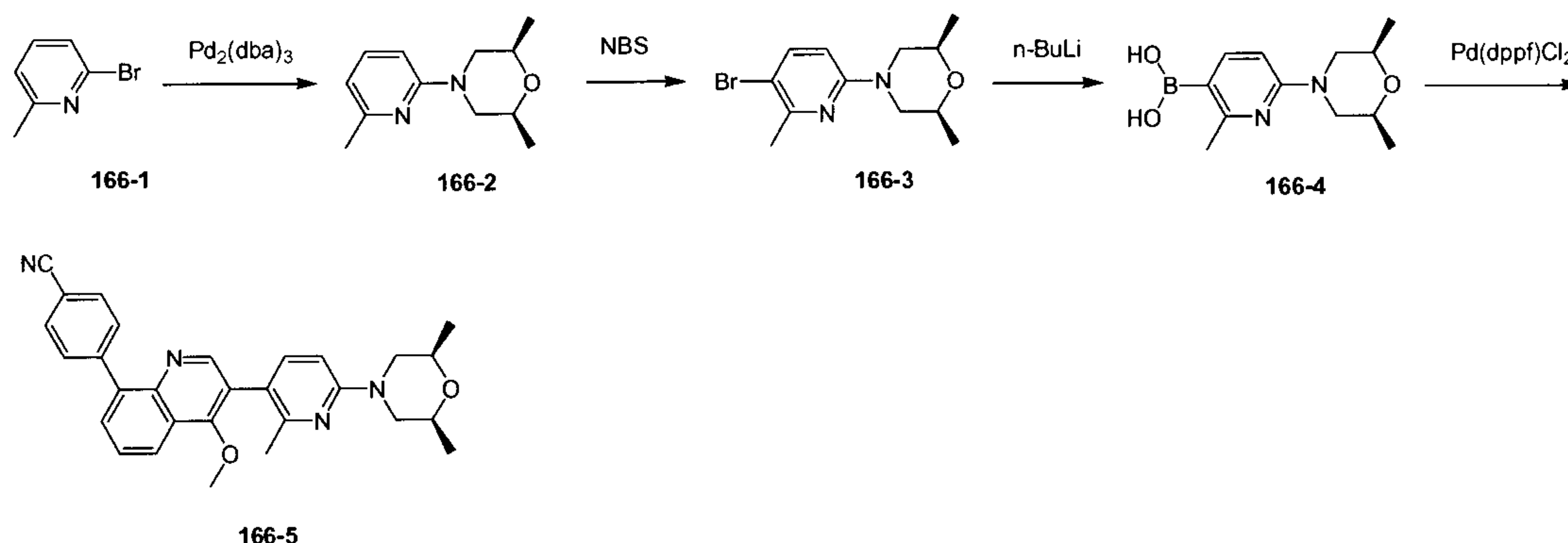
Embodiment	Structure	NMR
159		^1H NMR (400MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.49 (s, 1H), 8.27(d, $J=6.8$ Hz, 1H), 7.65-7.81 (m, 7H), 6.78 (d, $J=8.8$ Hz, 1H), 4.15 (d, $J=12.4$ Hz, 2H), 3.75 (s, 5H), 2.63 (t, $J=11.6$ Hz, 2H), 1.29 (d, $J=6.4$ Hz, 7H). MS ESI calcd for $C_{28}H_{26}F_3N_3O_2$ $[M+H]^+$ 494, found 494.
160		^1H NMR (400MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.49 (s, 1H), 8.24(d, $J=8.0$ Hz, 1H), 7.61-7.85 (m, 5H), 7.32-7.34 (m, 2H), 6.78 (d, $J=8.4$ Hz, 1H), 4.15 (d, $J=12.4$ Hz, 2H), 3.75 (s, 5H), 2.63 (t, $J=11.4$ Hz, 2H), 1.29 (d, $J=6.4$ Hz, 7H). MS ESI calcd for $C_{28}H_{26}F_3N_3O_3$ $[M+H]^+$ 510, found 510.
161		^1H NMR (400MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.50 (s, 1H), 8.30(d, $J=8.4$ Hz, 1H), 8.05-8.07 (m, 2H), 7.89-7.92 (m, 3H), 7.67-7.75 (m, 3H), 3.77 (s, 6H), 3.12 (s, 4H), 1.30 (d, $J=6.4$ Hz, 9H). MS ESI calcd for $C_{28}H_{29}N_3O_4S$ $[M+H]^+$ 504, found 504.
162		^1H NMR (400MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.50 (s, 1H), 8.31(d, $J=7.2$ Hz, 1H), 7.75-7.87 (m, 1H), 7.75-7.87 (m, 4H), 7.61-7.65 (m,

		3H), 7.34-7.44 (m, 3H), 6.70 (d, $J = 9.2$ Hz, 1H), 4.15 (d, $J = 12$ Hz, 2H), 3.68 (s, 5H), 2.53 (t, $J = 11.6$ Hz, 2H), 1.23 (d, $J = 6.0$ Hz, 6H). MS ESI calcd for $C_{27}H_{27}N_3O_2$ $[M+H]^+$ 426, found 426.
163		^1H NMR (400MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.80 (s, 1H), 8.50 (s, 1H), 8.25-8.28 (m, 1H), 8.02-8.05 (m, 1H), 7.84-7.86 (m, 1H), 7.66-7.71 (m, 3H), 7.29-7.31 (m, 1H), 6.78 (d, $J = 8.8$ Hz, 1H), 4.15 (d, $J = 11.6$ Hz, 2H), 3.76 (s, 5H), 2.59-2.65 (m, 5H), 1.29 (d, $J = 6.4$ Hz, 6H). MS ESI calcd for $C_{27}H_{28}N_4O_2$ $[M+H]^+$ 441, found 441.
164		^1H NMR (400MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.48 (s, 1H), 8.30 (d, $J = 8.0$ Hz, 1H), 7.83-7.85 (m, 1H), 7.62-7.71 (m, 3H), 7.23-7.25 (m, 1H), 6.78 (d, $J = 8.8$ Hz, 1H), 4.13 (d, $J = 12$ Hz, 2H), 3.76 (s, 5H), 3.14 (t, $J = 7.0$ Hz, 1H), 2.61 (t, $J = 11.6$ Hz, 2H), 1.31 (d, $J = 6.8$ Hz, 6H), 1.28 (d, $J = 6.4$ Hz, 6H). MS ESI calcd for $C_{29}H_{31}ClN_4O_2$ $[M+H]^+$ 503, found 503.
165		^1H NMR (400MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.42 (s, 1H), 8.25-8.27 (m, 1H), 7.76-7.77 (m, 1H), 7.55-7.64 (m, 3H), 6.70 (d, $J = 8.8$ Hz, 1H), 6.35 (s, 1H), 4.10 (d, $J = 11.6$ Hz, 2H), 3.68-3.75 (m, 8H), 2.56 (t, $J = 11.8$ Hz, 2H), 1.23 (d, $J = 6.0$ Hz, 7H). MS ESI calcd for $C_{25}H_{27}N_5O_2$ $[M+H]^+$ 430, found 430.

Embodiment 166



4-(3-(6-((2*S*,6*R*)-2,6-dimethylmorpholino)-2-methylpyridin-3-yl)-4-methoxyquinolin-8-yl)benzonitrile



[393] Step 1: Xantphos (1.7g, 3.48mmol), (2*S*,6*R*)-2,6-dimethylmorpholine (6 g, 52.2 mmol), potassium *tert*-butoxide (3.9 g, 34.8 mmol), Pd₂(dba)₃ (1.6 g, 1.74 mmol) were added into a solution of 2-bromo-6-methyl pyridine (3 g, 17.4 mmol) in toluene (50 mL) respectively. The reaction mixture was stirred at 110°C for 2h, then poured into H₂O, extracted with EtOAc (50 mL×3), the organic phase was washed with brines, filtrated and dried over sodium sulfate. After concentration, the residue was purified by silica gel column chromatography to deliver compound 166-2 (2.4 g, yield 66.7%) as white solid. **MS ESI** calcd for C₁₂H₁₈N₂O [M+H]⁺ 207, found 207.

[394] Step 2: NBS (1.65g, 9.3mmol) was added into a solution of compound 166-2 (2.4 g, 11.6 mmol) in DMF (30 mL). The reaction mixture was stirred at room temperature for 6h, poured into H₂O, extracted with EtOAc (30×3 mL), the organic phase was dried over sodium sulfate, after concentration, the crude product was purified by silica gel column chromatography to deliver compound 166-3 (0.86 g, yield 25.9%) as white solid. **MS ESI** calcd for C₁₂H₁₇BrN₂O [M+H]⁺ 285, found 285.

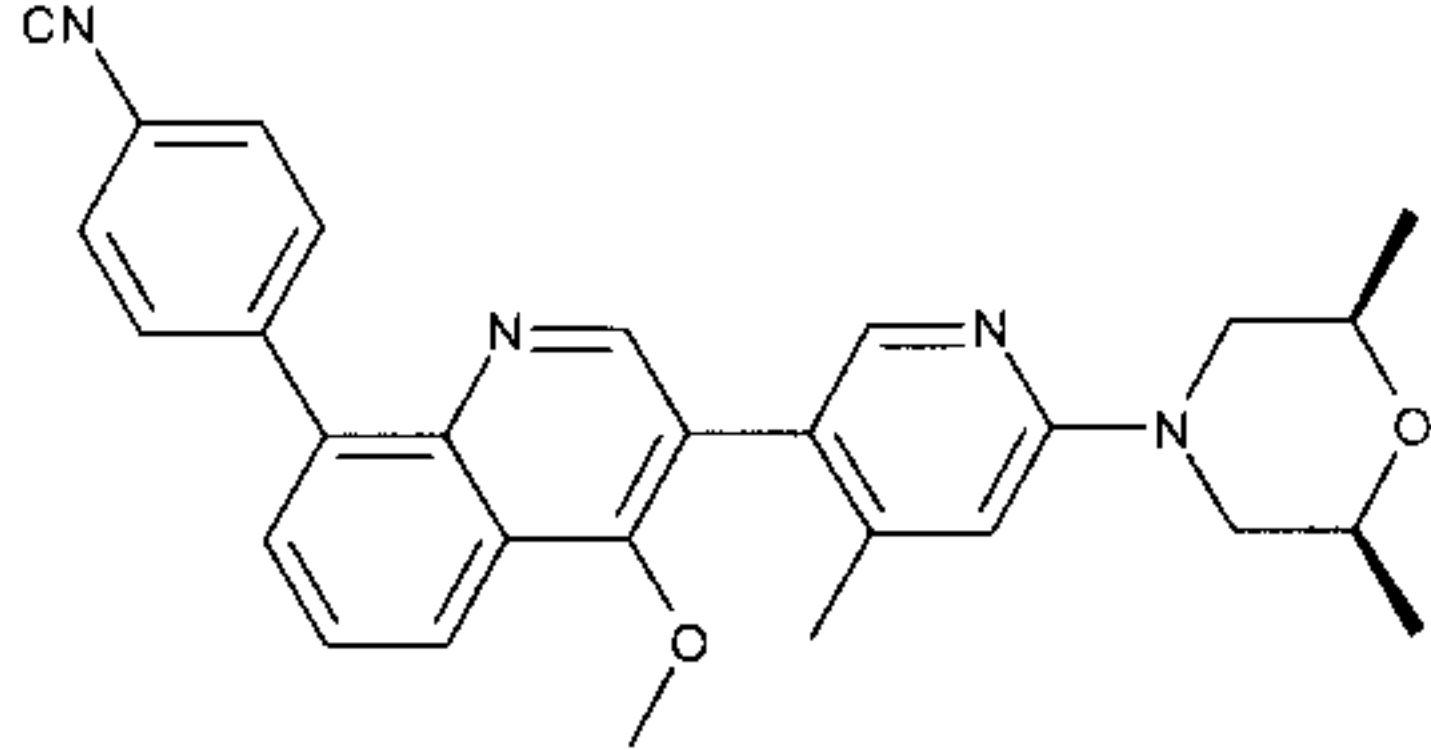
[395] Step 3: A solution of *n*-BuLi (1.8 mL, 4.5 mmol) was added into a solution of compound 166-3 (0.86 g, 3 mmol) in THF (20 mL) at -78°C. The reaction mixture was stirred at -78°C for 30min. Then triisopropyl borate (846 mg, 4.5 mmol) was added. Then the reaction mixture was poured into H₂O, extracted with EtOAc (50 mL×3), the organic phase was dried over sodium sulfate, filtrated and concentrated to deliver a crude product 166-4 (375 mg) as white solid. **MS ESI** calcd for C₁₂H₁₉BN₂O₃ [M+H]⁺ 251, found 251.

[396] Step 4: (6-((2*S*,6*R*)-2,6-dimethylmorpholino)-2-methylpyridin-3-yl)boric acid (375 mg, 1.5 mmol), 4-(3-bromo-4-methoxyquinolin-8-yl)benzonitrile (340 mg,

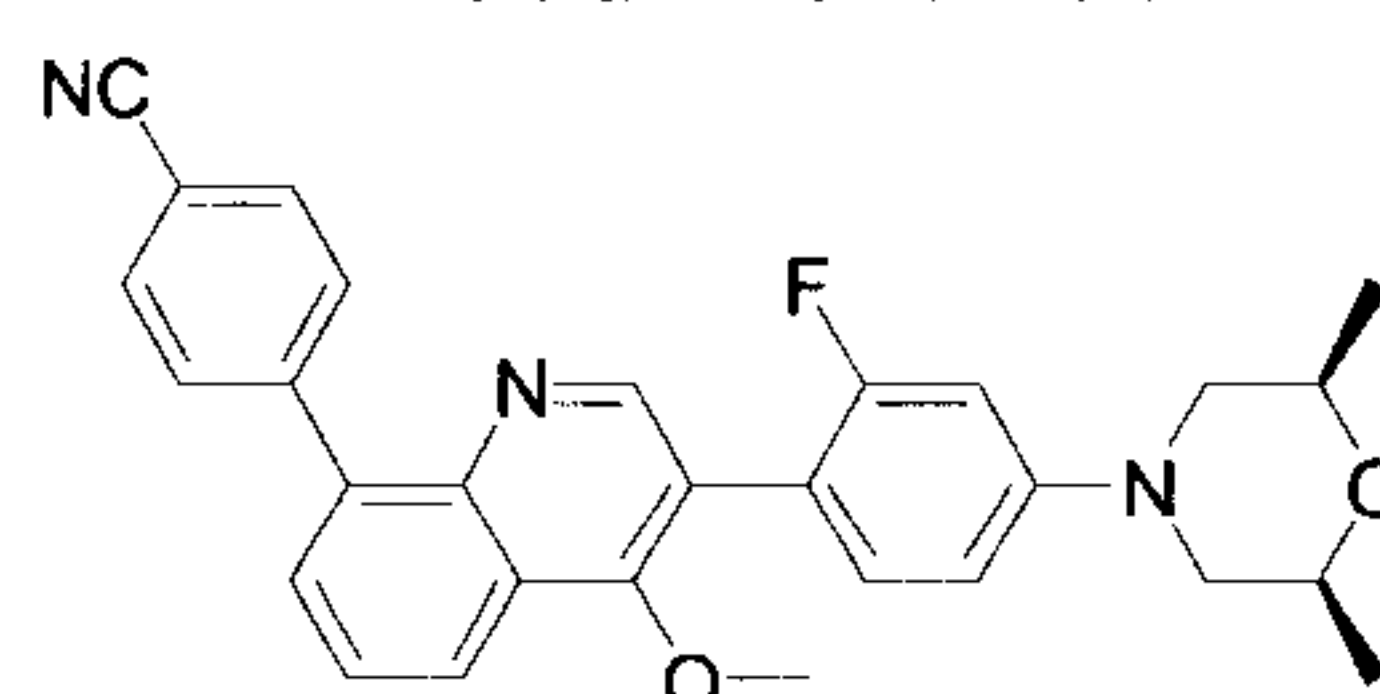
Our Ref.: P1650132CA

1 mmol) and sodium carbonate (212 mg, 2 mmol) were dissolved in DMF (3 mL), H₂O (3 mL) and THF (15 mL), Pd(dppf)Cl₂ (73 mg, 0.1 mmol) was added into the solution, then the reaction mixture was stirred at 70°C for 2h. Then the reaction mixture was poured into H₂O, extracted with EtOAc, the organic phase was washed with brines, dried over sodium sulfate. The crude product was purified by preparative HPLC to deliver the title compound (55 mg, yield 8%) as white solid. **¹H NMR** (400MHz, CDCl₃) δ 8.64 (s, 1H), 8.29 (d, *J*=8.0 Hz, 1H), 7.93-7.95(m, 2H), 7.84-7.89 (m, 3H), 7.52-7.54 (m, 1H), 7.45-7.50 (m, 1H), 6.82 (d, *J*=8.4 Hz, 1H), 4.23 (d, *J*=12 Hz, 2H), 3.63-3.65 (m, 5H), 2.62-2.66 (m, 2H), 2.22(s, 2H), 1.19 (d, *J*=6.0 Hz, 7H). **MS ESI** calcd for C₂₉H₂₈N₄O₂ [M+H]⁺ 465, found 465.

[397] The compound listed in table 14 was synthesized by corresponding aryl halide.

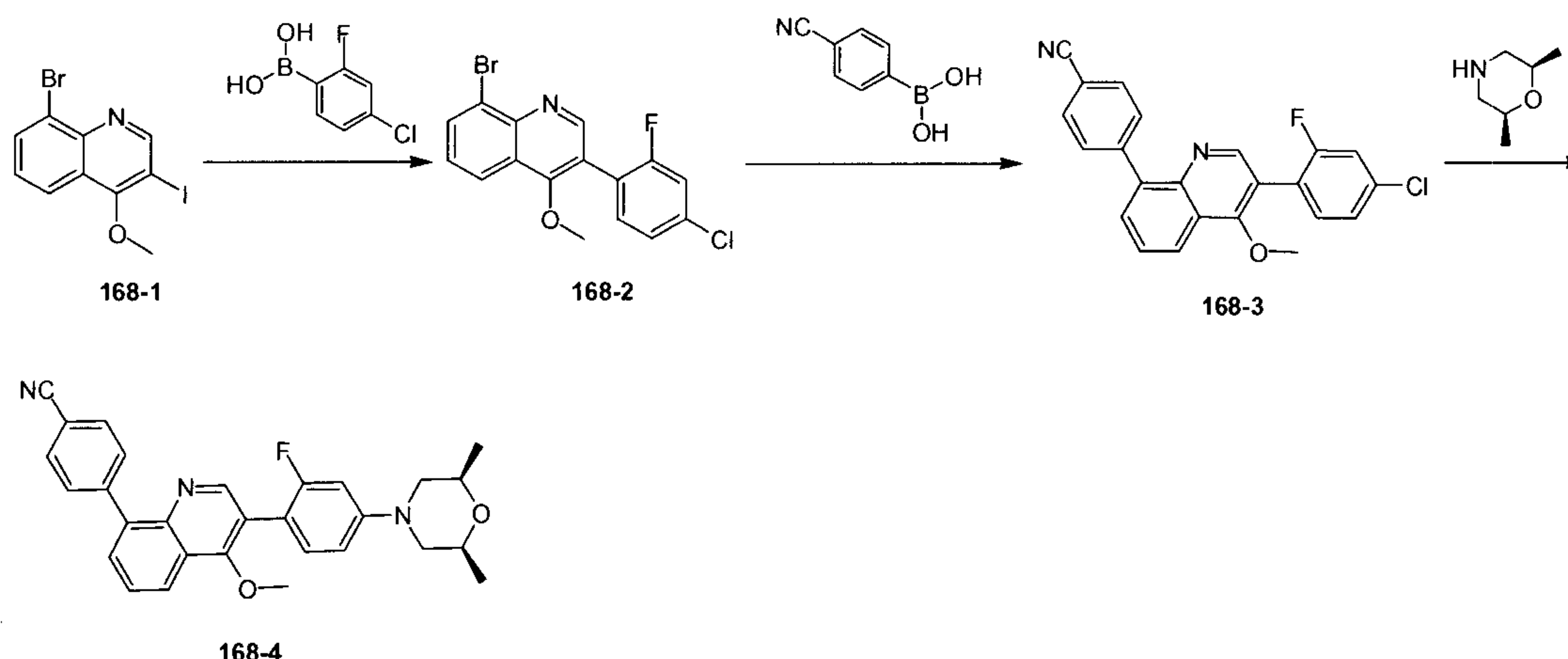
Embodiment	Structure	NMR
167		¹H NMR (400MHz, CDCl ₃) δ 8.64 (s, 1H), 8.32 (d, <i>J</i> =8.0 Hz, 1H), 8.12(s, 1H), 7.65-7.84(m, 6H), 6.64 (s, 1H), 4.15 (d, <i>J</i> =12.8 Hz, 2H), 3.74-3.78 (m, 2H), 3.68 (s, 3H), 2.61 (s, 1H), 2.18(s, 3H), 1.29 (d, <i>J</i> =6.0 Hz, 6H). MS ESI calcd for C ₂₉ H ₂₈ N ₄ O ₂ [M+H] ⁺ 465, found 465.

Embodiment 168



4-(3-(4-((2*S*,6*R*)-2,6-dimethylmorpholino)-2-fluorophenyl)-4-methoxyquinolin-8-yl) benzonitrile

Our Ref.: P1650132CA



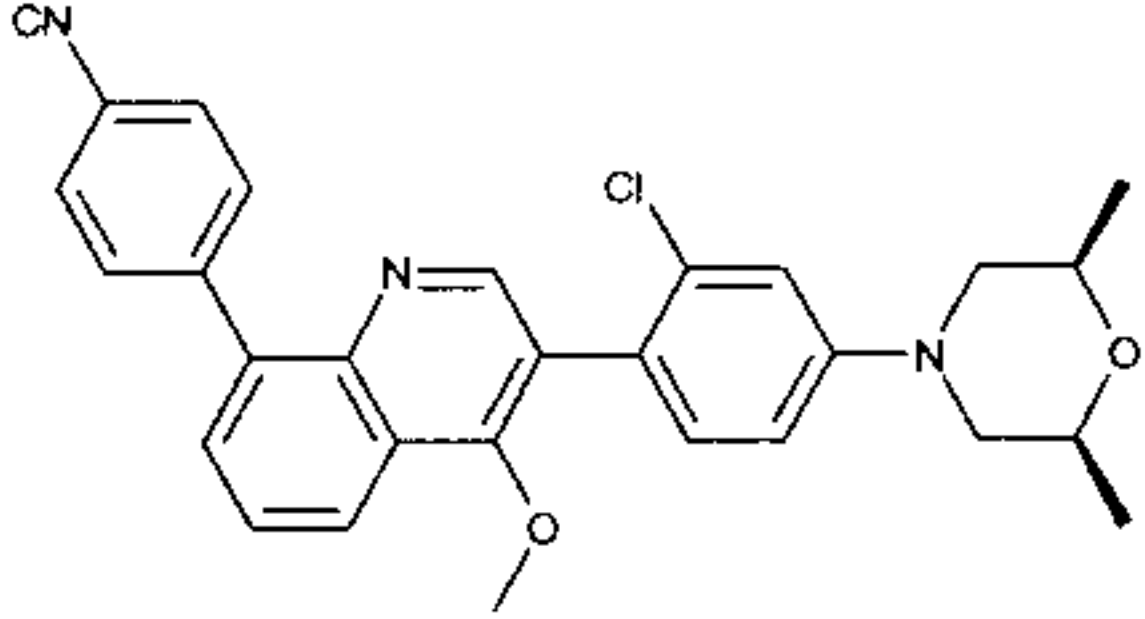
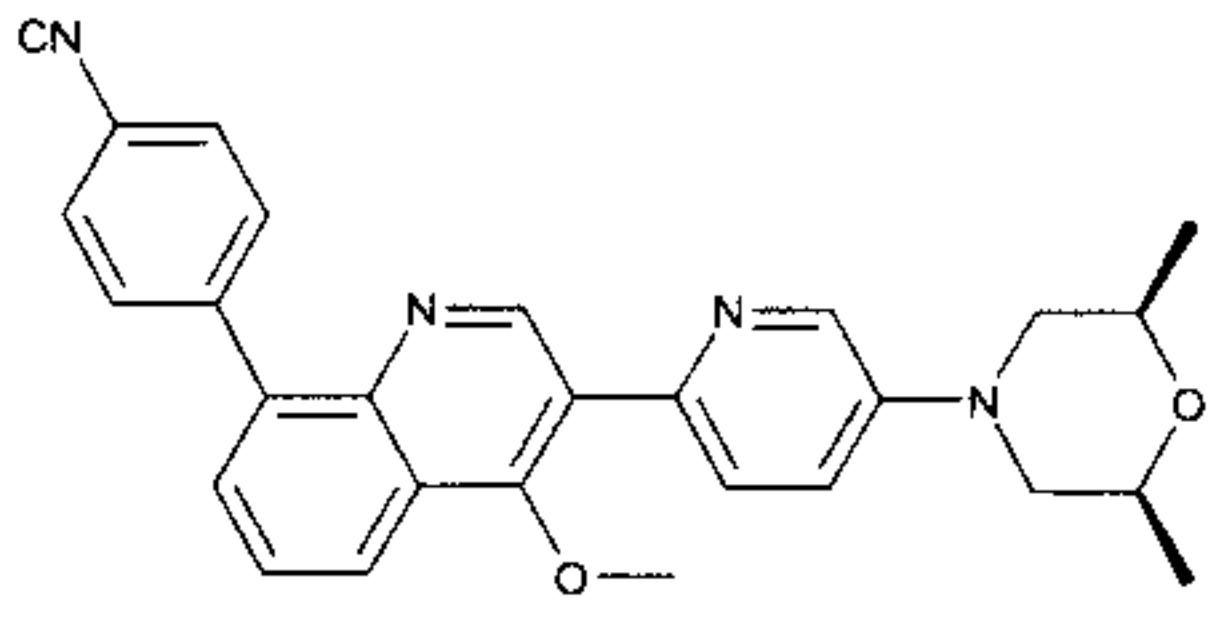
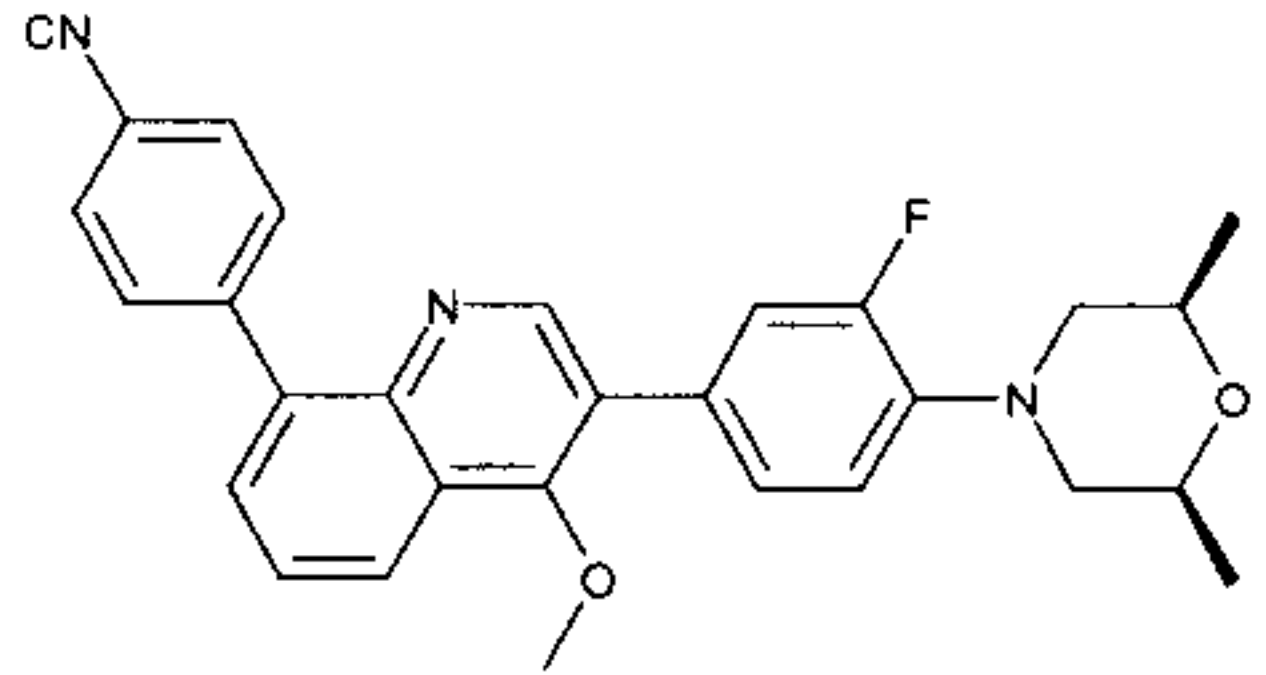
[398] Step 1: (4-chloro-2-fluorophenyl)boric acid (0.87 g, 5 mmol) was added into a solution of compound 168-1 (1.8 g, 5 mmol) in THF/H₂O/DMF (15/3/3 mL), Pd(dppf)Cl₂ (350 mg, 0.5 mmol) and sodium carbonate (1.1 g, 10 mmol) were added at room temperature. The reaction mixture was stirred at 70°C for 4h. The reaction mixture was poured into H₂O, extracted with EtOAc, the organic phase was dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography eluting with PE/EtOAc (15/1) to deliver compound 168-2 (1.158 g, yield 63.3%) as brown solid. **MS ESI** calcd for C₁₆H₁₀BrClFNO [M+H]⁺ 366, found 366.

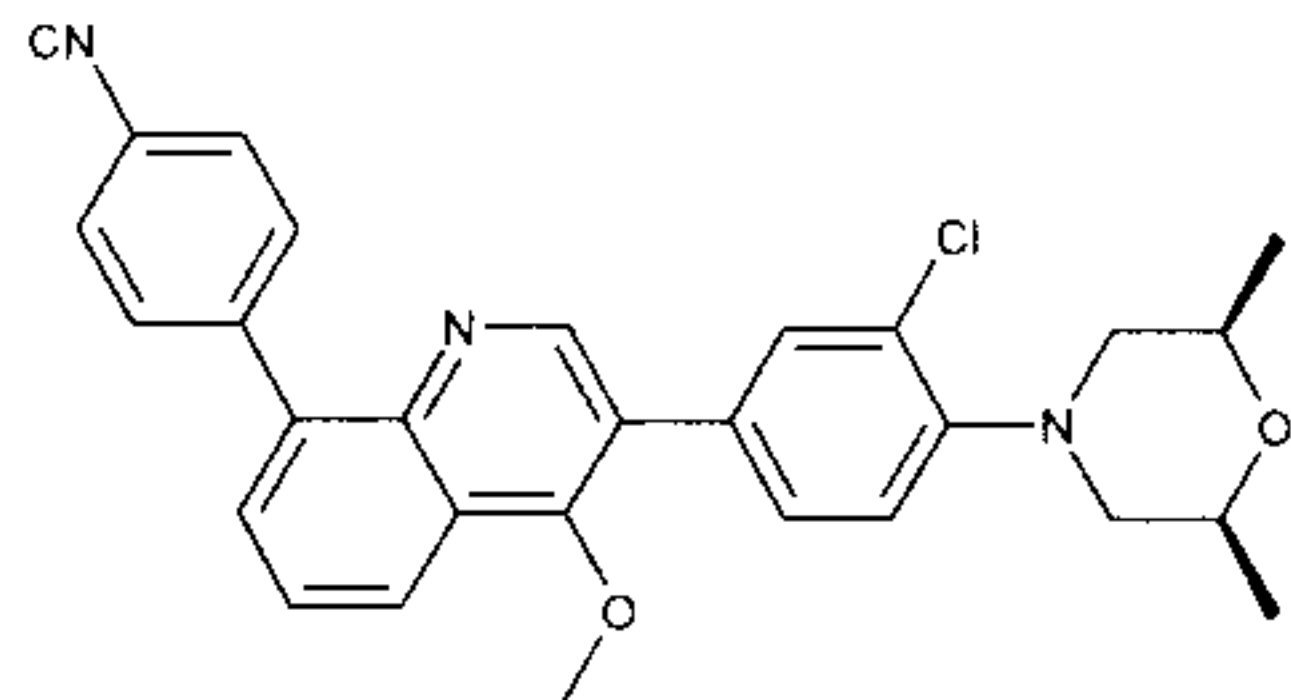
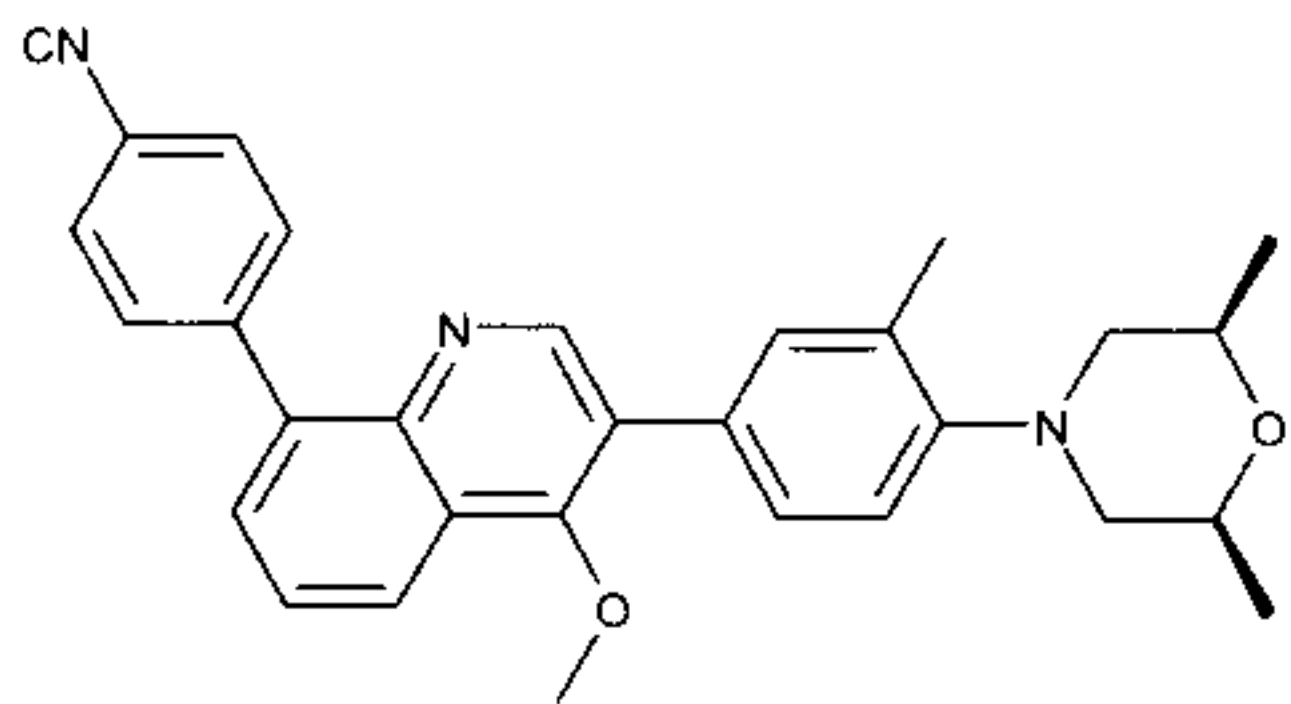
[399] Step 2: 4-cyanophenylboric acid (0.2 g, 1.4 mmol), Pd(dppf)Cl₂ (73 mg, 0.1 mmol) and sodium carbonate (0.4 g) were added into a solution of compound 168-2 (0.4 g, 1 mmol) in THF/H₂O/DMF (5/1/1 mL) at room temperature. The reaction was stirred at 70°C for 5h. The reaction mixture was poured into H₂O, extracted with EtOAc, the organic phase was dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography eluting with PE/EtOAc (10/1) to deliver compound 168-3 (158 mg, yield 43.2%) as brown solid. **MS ESI** calcd for C₂₃H₁₄ClFN₂O [M+H]⁺ 389, found 389.

[400] Step 3: The title compound (100 mg, yield 55.6%) was synthesized according to the above-mentioned method as white solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.78 (s, 1H), 8.34 (d, *J* = 6.8 Hz, 1H), 7.85-7.60 (m, 6H), 7.37 (t, *J* = 6.4 Hz, 1H), 6.82-6.71 (m, 2H), 3.90-3.75 (m, 2H), 3.75 (s, 3H), 2.53 (t, *J* = 11.2 Hz, 2H), 1.31 (d, *J* = 6.8 Hz, 6H). **MS ESI** calcd for C₂₉H₂₆FN₃O₂ [M+H]⁺ 468, found 468.

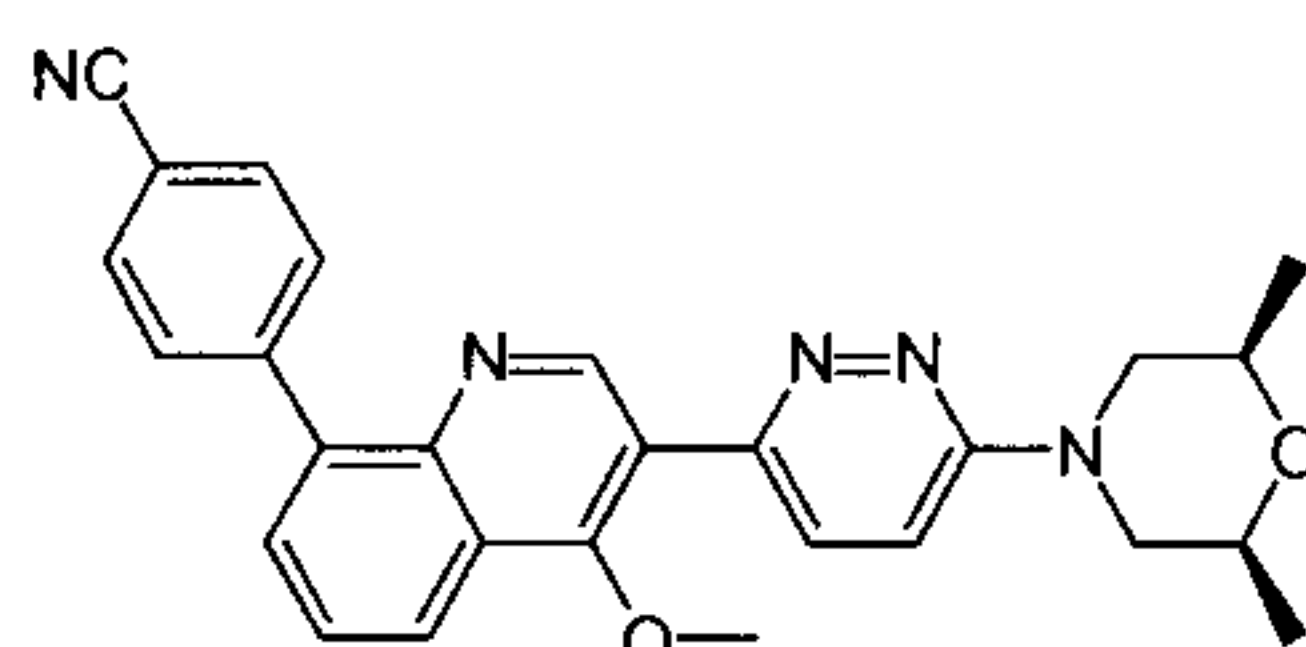
[401] The compounds listed in table 15 were synthesized by compound 168-1 and corresponding boric acids.

Embodiment	Structure	NMR
169		¹H NMR (400 MHz, CDCl ₃) δ 8.66 (s, 1H), 8.35 (d, <i>J</i> = 7.6 Hz, 1H), 7.85-7.60 (m, 6H),

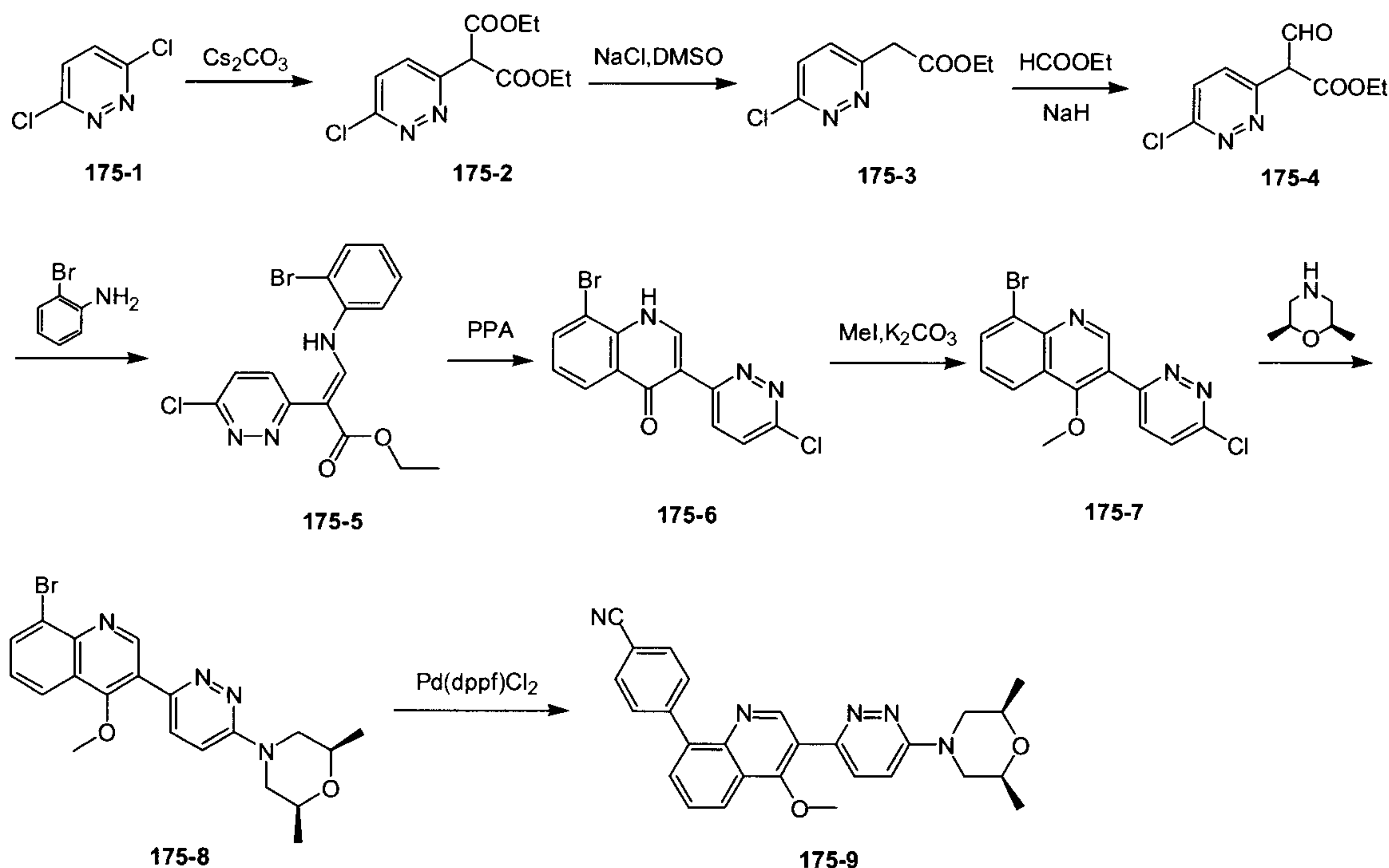
		7.21 (d, J = 8.0 Hz, 1H), 6.90-6.80 (m, 2H), 3.65-3.50 (m, 5H), 2.49 (t, J = 11.2 Hz, 2H), 2.20 (s, 3H), 1.29 (d, J = 6.4 Hz, 6H). MS ESI calcd for $C_{30}H_{29}N_3O_2$ $[M+H]^+$ 464, found 464.
170		^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.36-8.34 (m, 1H), 7.79-7.77 (m, 2H), 7.73-7.62 (m, 2H), 7.30-7.28 (m, 2H), 7.04-7.03 (m, 1H), 6.92-6.89 (m, 1H), 3.83-3.81 (m, 1H), 3.70 (s, 3H), 3.55-3.52 (m, 2H), 2.55-2.50 (m, 2H), 1.30 (d, 6H). MS ESI calcd for $C_{29}H_{26}ClN_3O_2$ $[M+H]^+$ 484, found 484.
171		^1H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.45 (d, J = 2.8 Hz, 1H), 8.40-8.30 (m, 1H), 7.37 (t, J = 6.4 Hz, 1H), 7.85-7.60 (m, 7H), 7.35-7.25 (m, 1H), 3.90-3.75 (m, 5H), 3.62-3.50 (m, 2H), 2.53 (t, J = 11.2 Hz, 2H), 1.30 (d, J = 6.0 Hz, 6H). MS ESI calcd for $C_{28}H_{26}N_4O_2$ $[M+H]^+$ 451, found 451.
172		^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.32 (d, J = 8.4 Hz, 1H), 7.85-7.60 (m, 5H), 7.40-7.30 (m, 3H), 7.10-7.00 (m, 1H), 3.95-3.85 (m, 2H), 3.89 (s, 3H), 3.42-3.30 (m, 2H), 2.53 (t, J = 11.2 Hz, 2H), 1.25 (d, J = 6.4 Hz, 6H). MS ESI calcd for $C_{29}H_{26}FN_3O_2$ $[M+H]^+$ 468, found 468.

173		¹H NMR (400 MHz, CDCl₃) δ 8.74 (s, 1H), 8.25-8.15 (m, 1H), 7.75-7.50 (m, 7H), 7.40-7.33 (m, 1H), 7.10-7.00 (m, 1H), 3.90-3.875 (m, 2H), 3.61 (s, 3H), 3.25-3.15 (m, 2H), 2.39 (t, <i>J</i> = 11.2 Hz, 2H), 1.13 (d, <i>J</i> = 6.4 Hz, 6H). MS ESI calcd for C₂₉H₂₆ClN₃O₂ [M+H]⁺ 484, found 484.
174		¹H NMR (400 MHz, CDCl₃) δ 8.34 (d, <i>J</i> = 8.4 Hz, 1H), 7.85-7.60 (m, 7H), 7.50-7.40 (m, 2H), 7.12-7.05 (m, 1H), 3.95-3.85 (m, 2H), 3.72 (s, 3H), 3.03 (d, <i>J</i> = 11.6 Hz, 2H), 2.51 (t, <i>J</i> = 10.8 Hz, 2H), 2.39 (s, 3H), 1.24 (d, <i>J</i> = 6.4 Hz, 6H). MS ESI calcd for C₃₀H₂₉N₃O₂ [M+H]⁺ 464, found 464.

Embodiment 175



4-(3-(6-((2*S*,6*R*)-2,6-dimethylmorpholino)pyridazin-3-yl)-4-methoxyquinolin-8-yl)
benzonitrile



[402] Step 1: Cesium carbonate (176 g, 540 mmol) was added into a solution of compound 175-1 (40 g, 270 mmol) and diethyl malonate (61 mL, 410 mmol) in DMSO (80 mL) at room temperature. The reaction mixture was stirred at 110 °C for 1h. The reaction mixture was poured into H₂O, extracted with EtOAc. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (PE:EtOAc= 10:1) to deliver compound 175-2 (52 g, yield 71%) as colorless oil. **MS ESI** calcd for C₁₁H₁₃ClN₂O₄ [M+H]⁺ 273, found 273.

[403] Step 2: Compound 2 (52 g, 190 mmol), NaCl (45 g, 760 mmol) and H₂O (5 mL) were added into DMSO (300 mL), the reaction mixture was stirred at 150 to 160°C for 2h. The reaction mixture was poured into H₂O, extracted with EtOAc. The organic phase was concentrated under reduced pressure. The crude product was purified by silica gel chromatography (PE:EtOAc= 5:1) to deliver compound 175-3 (30 g, yield 79%) as colorless oil. **MS ESI** calcd for C₈H₉ClN₂O₂ [M+H]⁺ 201, found 201.

[404] Step 3: Under nitrogen gas atmosphere, NaH (8.4 g, 350 mmol) was added into a solution of compound 175-3 (20 g, 100 mmol) in HCO₂Et (200 mL) at 0°C. The reaction mixture was stirred at room temperature for 2h. Then the reaction mixture was poured into 5% HCl aqueous solution, extracted with EtOAc. The organic phase was washed with Na₂CO₃ aqueous solution and dried over sodium sulfate. The crude product was purified by silica gel chromatography (PE:EtOAc= 8:1) to deliver compound 175-4 (6 g, yield 26%) as colorless oil. **ESI** calcd for C₉H₉ClN₂O₃ [M+H]⁺ 229, found 229.

[405] Step 4: A solution of compound 175-4 (5 g, 22 mmol) and 2-bromophenylamine (3.8 g, 22 mmol) in EtOH (100 mL) was stirred at 70°C for 20h.

The reaction mixture was cooled to room temperature. The crude product was collected by filtration to deliver compound 175-5 (5 g, yield 57%) as yellow solid. **MS ESI** calcd for $C_{15}H_{13}BrClN_3O_2$ $[M+H]^+$ 382, found 382.

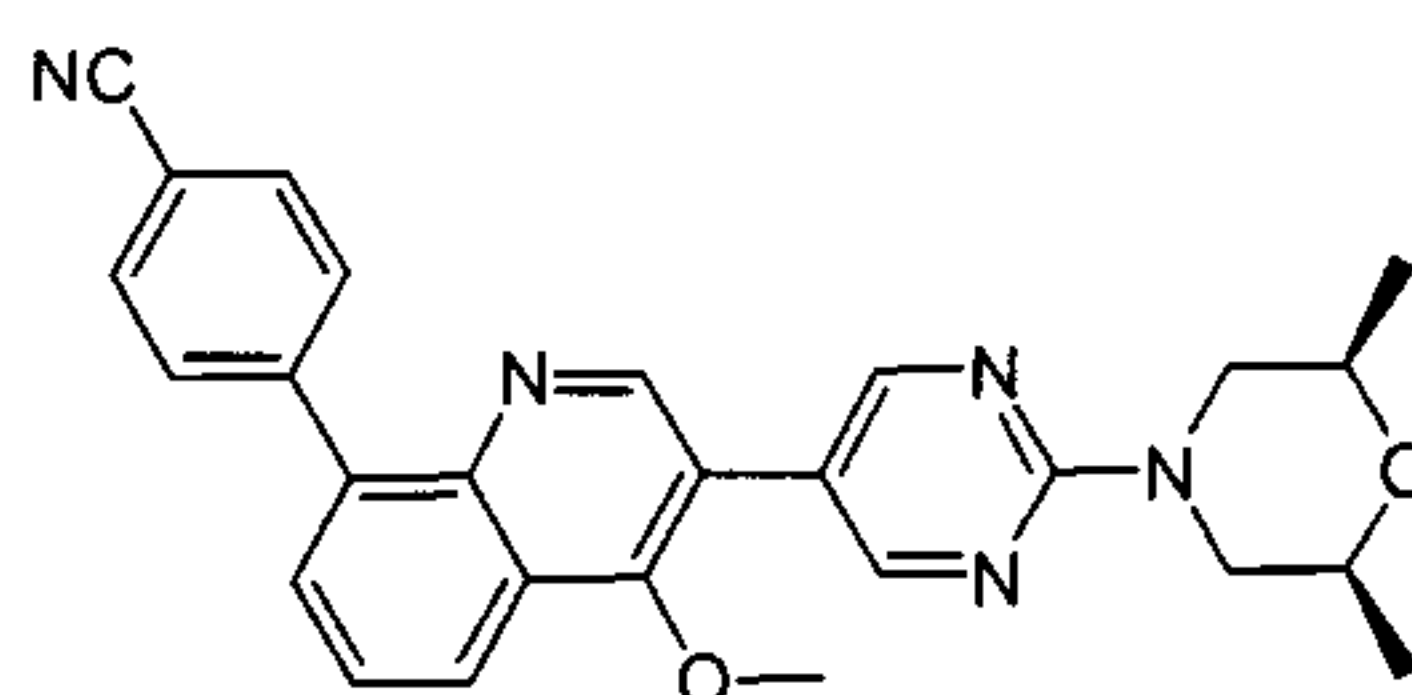
[406] Step 5: Compound 175-5 (4.4 g, 11.5 mmol) was dissolved in PPA (50 mL). The reaction mixture was stirred at room temperature for 12h. The reaction mixture was poured into ice water. The product was collected by filtration to deliver compound 175-6 (3 g, yield 77%) as yellow solid. **MS ESI** calcd for $C_{13}H_7BrClN_3O$ $[M+H]^+$ 335, found 335.

[407] Step 6: A solution of compound 175-6 (1.4 g, 4.2 mmol), CH_3I (887 mg, 6.2 mmol) and Ag_2CO_3 (2.3 g, 8.4 mmol) in DMF (20 mL) was stirred at 70°C for 4h. The reaction mixture was poured into H_2O , extracted with DCM. The organic phase was washed with brines, dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (PE: EtOAc= 1:1) to deliver compound 175-7 (540 mg, yield 37%) as yellow solid. **MS ESI** calcd for $C_{14}H_9BrClN_3O$ $[M+H]^+$ 350, calcd for 350.

[408] Step 7: A solution of compound 175-7 (540 mg, 1.55 mmol) in (2*S*,6*R*)-2,6-dimethylmorpholine (1 mL) was stirred at 120°C for 2h. The reaction mixture was poured into H_2O , extracted with DCM. The combined organic phase was washed with brines, dried over sodium sulfate and concentrated under reduced pressure to deliver compound 175-8 (663 mg, 100%) as yellow solid. The crude product was used in the next step directly without further purification. **MS ESI** calcd for $C_{20}H_{21}BrN_4O_2$ $[M+H]^+$ 429, found 429.

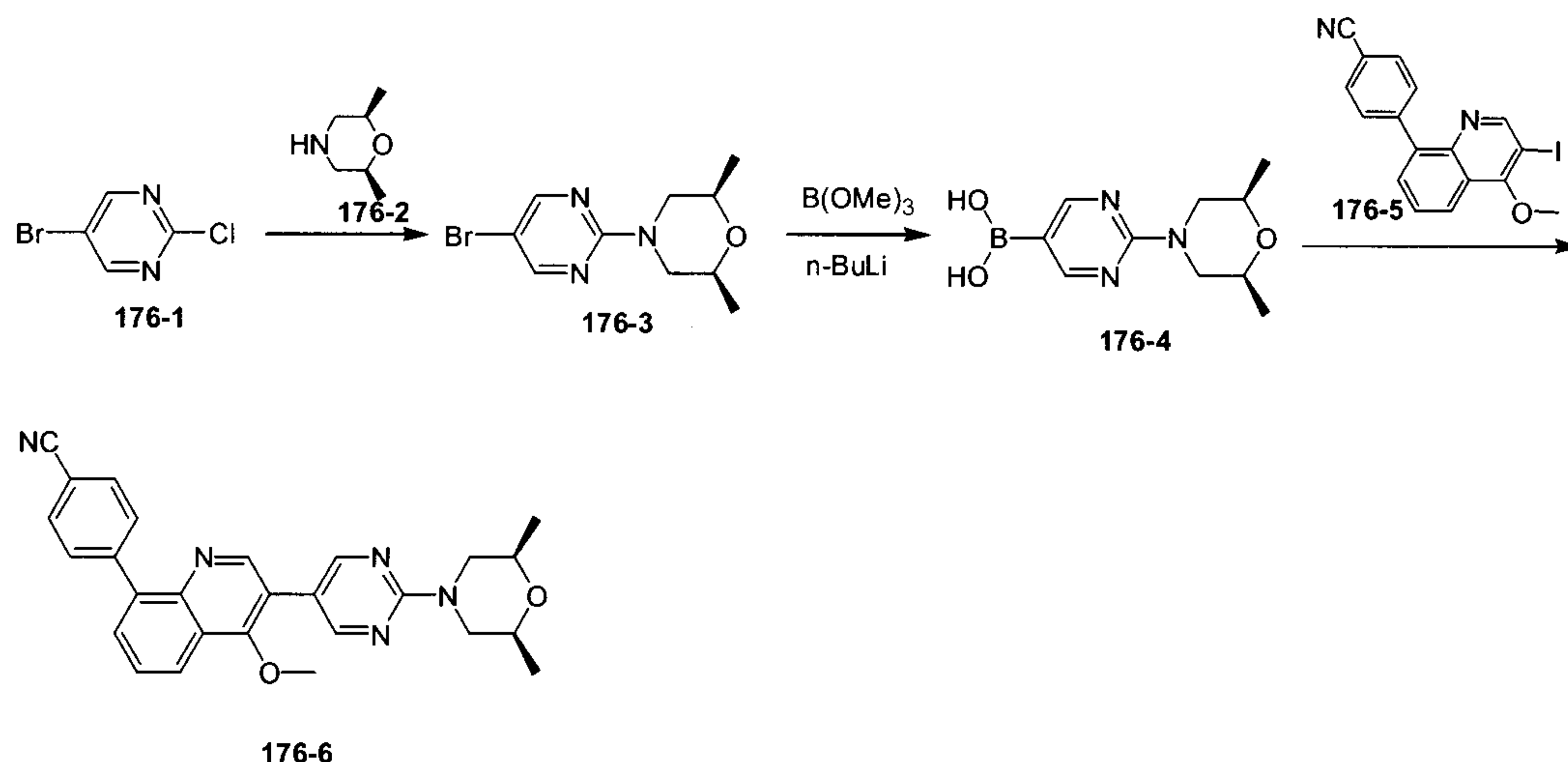
[409] Step 8: A solution of $Pd(dppf)Cl_2$ (117 mg, 0.16 mmol) and sodium carbonate (329 mg, 3.1 mmol) in THF/ H_2O /DMF(10/2/2) was added into a solution of compound 175-8 (663 mg, 1.55 mmol), 4-cyanophenyl boric acid (251 mg, 1.7 mmol), stirred at 90°C for 3h. The reaction mixture was filtrated, and partitioned between EtOAc and H_2O , the organic phase was dried and concentrated. The crude product was purified by preparative HPLC to deliver the title compound (90 mg, yield 13%) as yellow solid. **^1H NMR** (400 MHz, Methanol- d_4) δ 8.96 (s, 1H), 8.65 (d, J = 9.6 Hz, 1H), 8.56 (d, J = 10.0 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.81-7.61 (m, 6H), 4.29 (d, J = 12.8 Hz, 2H), 3.81-3.71 (m, 2H), 3.30 (s, 3H), 2.81 (t, J = 12.0 Hz, 2H), 1.28 (d, J = 5.6 Hz, 6H). **MS ESI** calcd for $C_{27}H_{25}N_5O_2$ $[M+H]^+$ 452, found 452.

Embodiment 176



4-(3-(2-((2*S*,6*R*)-2,6-dimethylmorpholino)pyrimidin-5-yl)-4-methoxyquinolin-8-yl)

benzonitrile



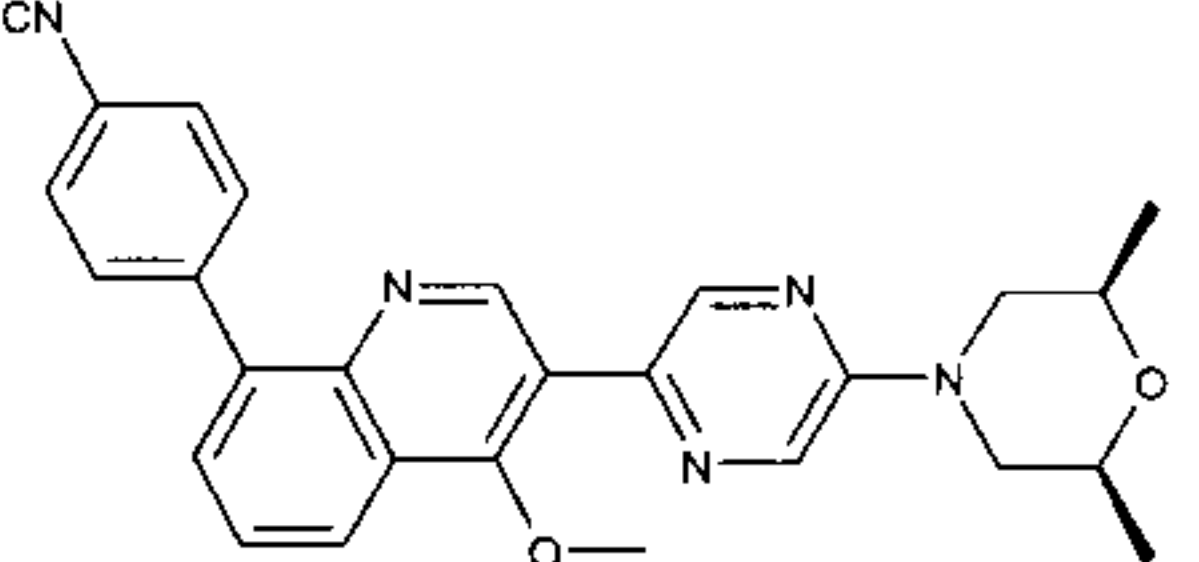
[410] Step 1: Compound 176-1 (3 g, 15.5 mmol) was dissolved in compound 176-2 (1.8 g, 15.5 mmol), then stirred for 2h at 100°C. The solution was partitioned between EtOAc and H₂O, the organic phase was washed with brines, dried over anhydrous sodium sulfate, filtrated and concentrated under reduced pressure to deliver compound 176-3 (3.1 g, 74%) as white solid. **MS ESI** calcd for C₁₀H₁₄BrN₃O [M+H]⁺ 272, found 272.

[411] Step 2: Compound 176-3 (4.2 g, 15.4 mmol) was dissolved in THF (40 mL), $n\text{-BuLi}$ (9.2 mL, 23.1 mmol) was added dropwise into the solution at -78°C. The mixture was stirred for 30 min, then B(OMe)_3 (4.8 g, 46.2 mmol) was added dropwise. Then the reaction mixture was warmed to 0°C and stirred for 3h. The reaction mixture was partitioned between EtOAc and H₂O, the organic phase was separated, combined, washed with brines, dried over anhydrous sodium sulfate, filtrated and concentrated to deliver compound 176-4 (2.6 g, 72%) as brown solid. **MS ESI** calcd for C₁₀H₁₆BN₃O₃ [M+H]⁺ 237, found 237.

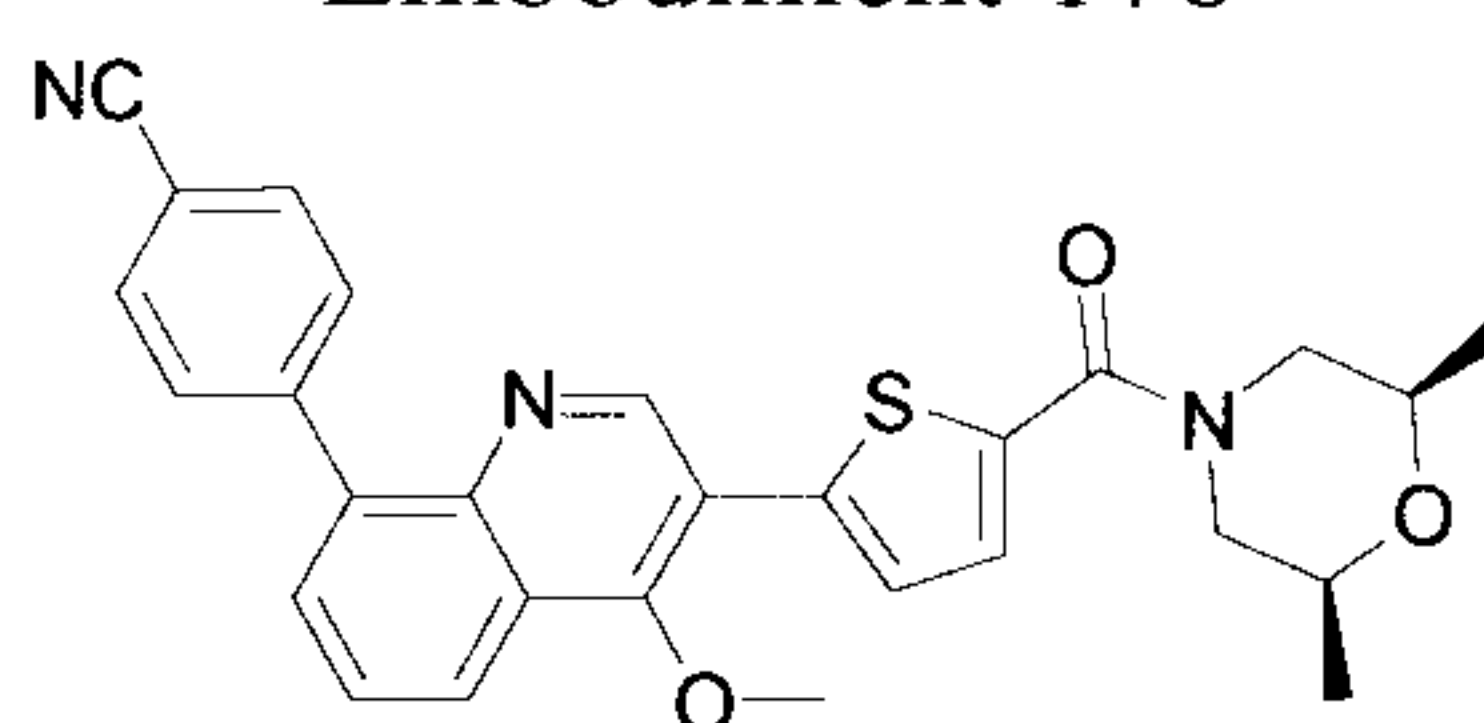
[412] Step 3: The title compound was synthesized according to the above-mentioned method (23 mg, 10%) as brown solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.83 (s, 1H), 8.65 (s, 2H), 8.27 (d, J = 7.2 Hz, 1H), 7.85-7.60 (m, 6H), 4.63 (d, J = 12.8 Hz, 2H), 3.80 (s, 3H), 3.75-3.61 (m, 2H), 2.68 (t, J = 12.0 Hz, 2H), 1.27 (d, J = 6.0 Hz, 6H). **MS ESI** calcd for C₂₇H₂₅N₅O₂ [M+H]⁺ 452, found 452.

[413] The compound listed in table 16 was synthesized by corresponding aryl halide.

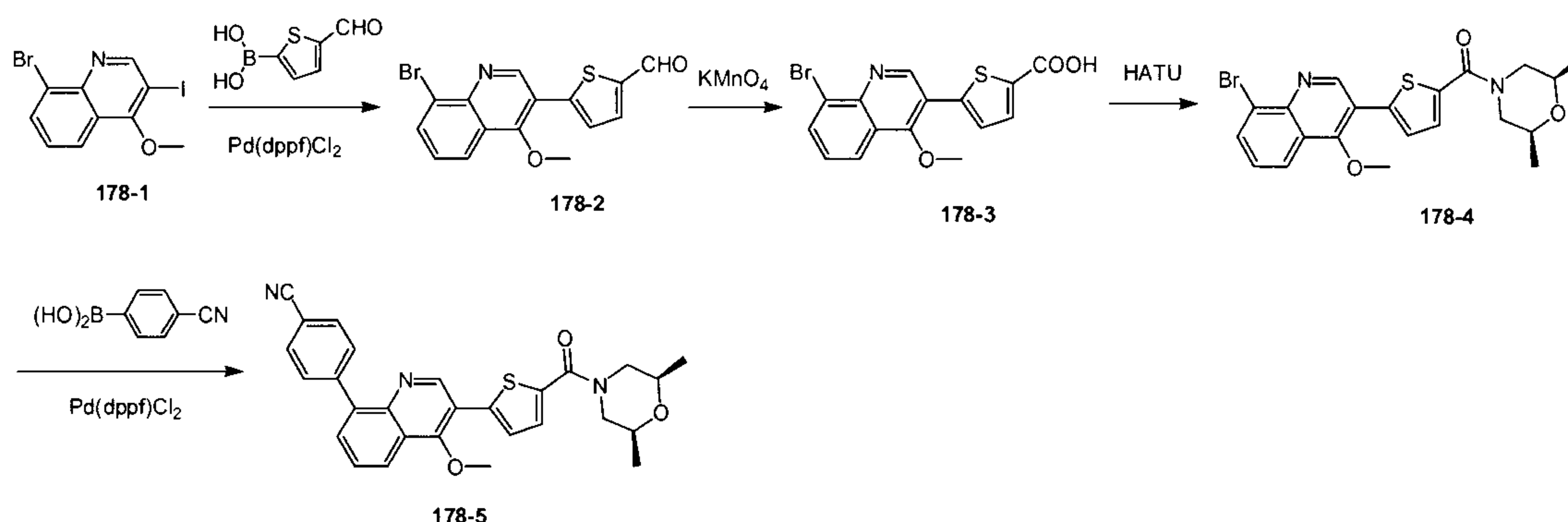
Embodiment	Structure	LC-MS & NMR
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177		¹H NMR (400 MHz, CDCl₃) δ 9.24 (s, 1H), 8.74 (s, 1H), 8.35-8.20 (m, 2H), 7.85-7.60 (m, 6H), 4.17 (d, <i>J</i>= 12.4 Hz, 2H), 3.85 (s, 3H), 3.46 (s, 2H), 2.68 (t, <i>J</i>= 12.0 Hz, 2H), 1.29 (d, <i>J</i>= 6.4 Hz, 6H). MS ESI calcd for C₂₇H₂₅N₅O₂ [M+H]⁺ 452, found 452.
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Embodiment 178



4-(3-(5-((2*S*,6*R*)-2,6-dimethylmorpholine-4-carbonyl)thiophen-2-yl)-4-methoxyquinolin-8-yl)benzonitrile



[414] Step 1: Pd(dppf)Cl₂ (102 mg, 0.14 mmol) was added into a solution of compound 178-1 (500 mg, 1.4 mmol), (5-formylthiophene-2-yl)boric acid (270 mg, 1.7 mmol) and sodium carbonate (300 mg, 2.8 mmol) in DMF (2 mL)/ H₂O (2 mL)/ THF(10 mL). The mixture was stirred at 70°C for 2h. The mixture was poured into H₂O, extracted with EtOAc, the organic phase was washed with brines, dried over sodium sulfate, concentrated. The residue was purified by column chromatography (PE/EtOAc= 5:1) to deliver compound 178-2 (438 mg, 91.6%) as brown solid. **MS ESI** calcd for C₁₅H₁₀BrNO₂S [M+H]⁺ 348, found 348.

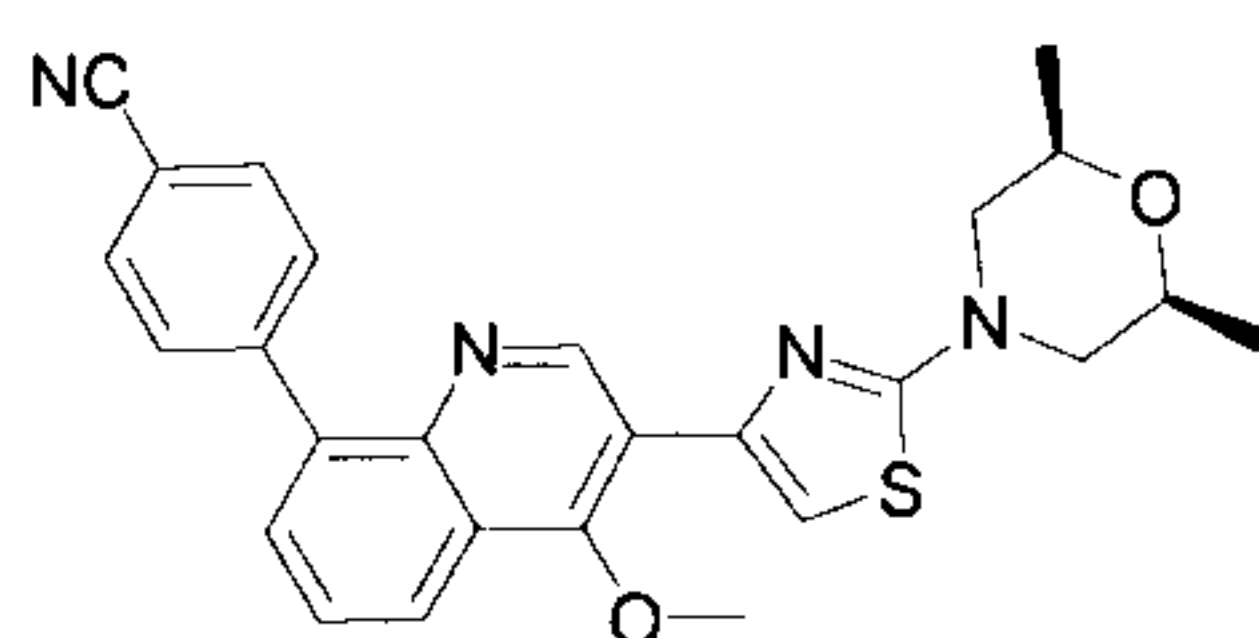
[415] Step 2: Sodium dihydrogen phosphate (300 mg, 2.5 mmol) was added into a solution of compound 178-2 (438 mg, 1.25 mmol) and potassium hypermanganate (200 mg, 1.25 mmol) in acetone (15 mL). The mixture was stirred at room temperature for 4h. The brown MnO₂ precipitate was filtrated, acetone was removed under vacuum, the mixture was acidified with 1 N HCl and extracted with EtOAc. The organic phase was dried over anhydrous sodium sulfate, concentrated to deliver compound 178-3 (350 mg, 76.4%) as brown solid. **MS ESI** calcd for

$C_{15}H_{10}BrNO_3S$ $[M+H]^+$ 364, found 364.

[416] Step 3: To a solution of compound 178-3 (350 mg, 1 mmol), HATU (384 mg, 1 mmol) and (2S, 6R)-2,6-dimethylmorpholine (138 mg, 1.2 mmol) in DMF (10 mL) was added DIPA (387 mg, 3 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was poured into H_2O , extracted with EtOAc, the organic phase was dried over sodium sulfate and concentrated. The residue was purified by column chromatography (PE/EtOAc = 2:1) to deliver compound 178-4 (265 mg, 59.8%) as brown solid. **MS ESI** calcd for $C_{21}H_{21}BrN_2O_3S$ $[M+H]^+$ 461, found 461.

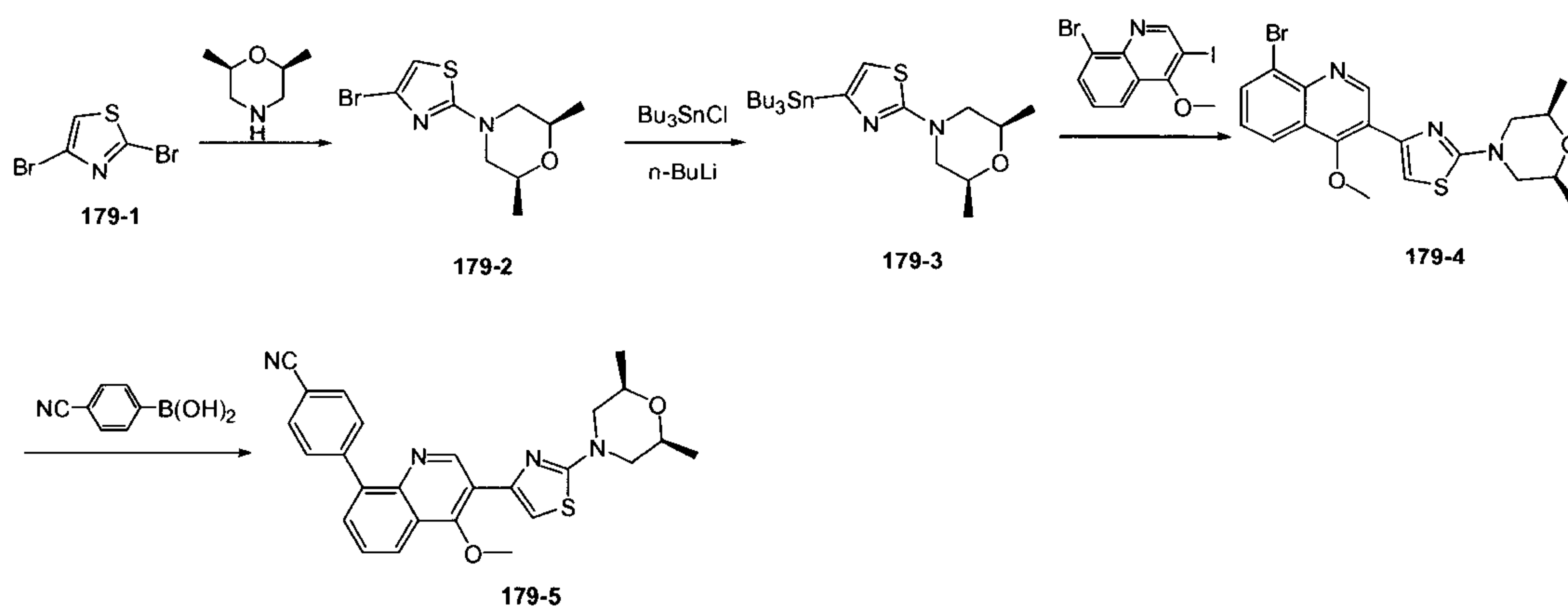
[417] Step 4: $Pd(dppf)Cl_2$ (45 mg, 0.06 mmol) was added into a solution of compound 178-4 (265 mg, 0.6 mmol), 4-cyanophenylboric acid (106 mg, 0.72 mmol) and sodium carbonate (127 mg, 1.2 mmol) in DMF (2 mL)/ H_2O (solvent 2 mL)/ THF (10 mL). The mixture was stirred at $70^\circ C$ for 2h. The reaction mixture was poured into H_2O , extracted with EtOAc, the organic phase was washed with brines, dried over sodium sulfate and concentrated. The residue was purified by preparative HPLC to deliver the title compound (32 mg, yield 11%) as white solid. **^1H NMR** (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.26-8.24 (m, 1H), 7.83-7.78 (m, 4H), 7.74-7.68 (m, 2H), 7.56-7.55 (m, 1H), 7.35-7.34 (m, 1H), 4.03 (s, 3H), 3.67 (s, 1H), 1.24 (d, 6H). **MS ESI** calcd for $C_{28}H_{25}N_3O_3S$ $[M+H]^+$ 484, found 484.

Embodiment 179



4-(3-(2-(2,6-dimethylmorpholin-4-yl)thiazol-4-yl)-4-methoxyquinolin-8-yl)

benzonitrile



[418] Step 1: K_2CO_3 (5.7 g, 41 mmol) was added into a solution of compound 179-1 (5.0 g, 20.5 mmol) and (2S, 6R)-2, 6-dimethylmorpholine (3.55 g, 30.9 mmol) in DMF (60 mL). The mixture was stirred at $70^\circ C$ overnight. The reaction mixture

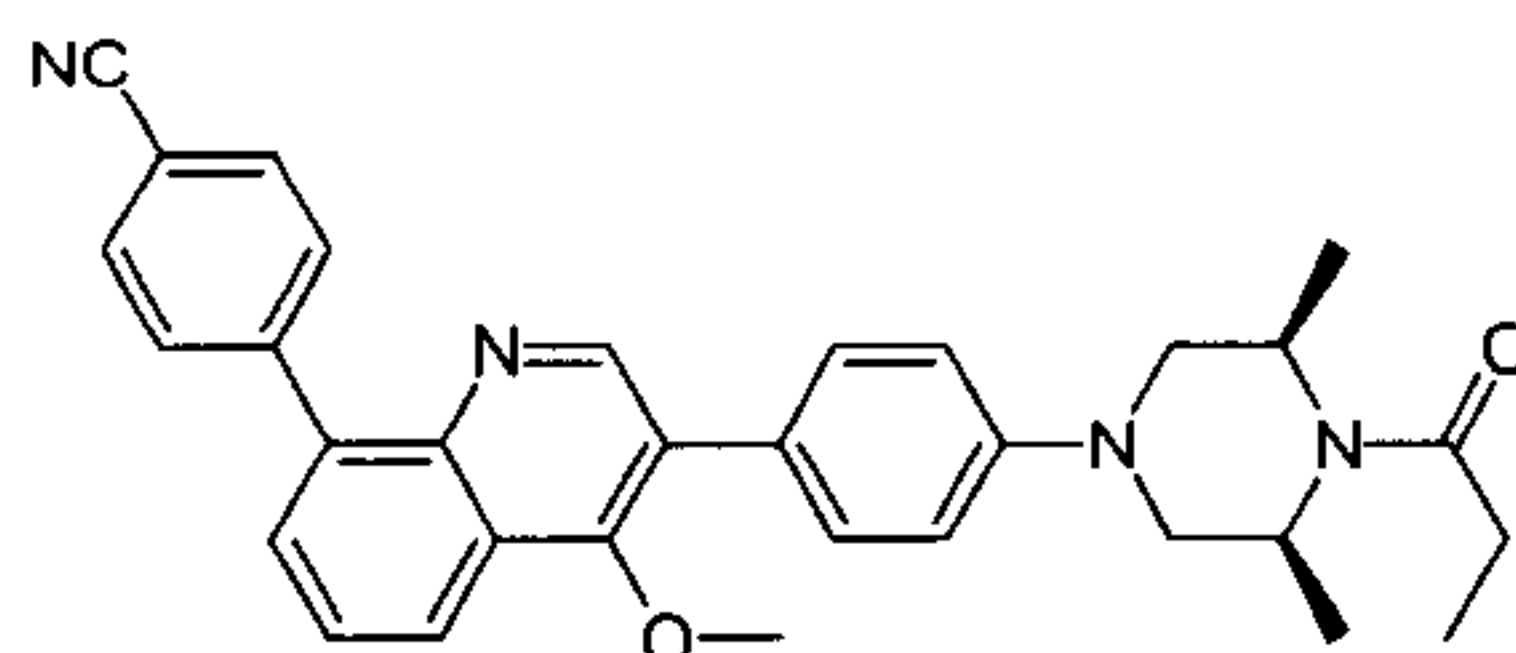
was cooled to room temperature, then poured into H₂O, extracted with EtOAc, dried over sodium sulfate and concentrated. The residue was purified by column chromatography to deliver compound 179-2 (5.56 g, yield 99%) as yellow oil. **MS ESI** calcd for C₉H₁₃BrN₂OS [M+H]⁺ 277, found 277.

[419] Step 2: *n*-BuLi (0.8 mL, 2.5M in THF solution) was added into a solution of compound 179-2 (500 mg, 1.8 mmol) in THF (10 mL) at -78°C, the mixture was stirred at -78°C for 1h, then SnBu₃Cl (650 mg, 2 mmol) was added at -78°C and stirred at -78°C for 1h. The reaction mixture was poured into H₂O, extracted with EtOAc, dried over sodium sulfate, concentrated to deliver compound 179-3 (0.7 g, yield 79%) as colorless oil. **MS ESI** calcd for C₂₁H₄₀N₂OSSn [M+H]⁺ 489, found 489.

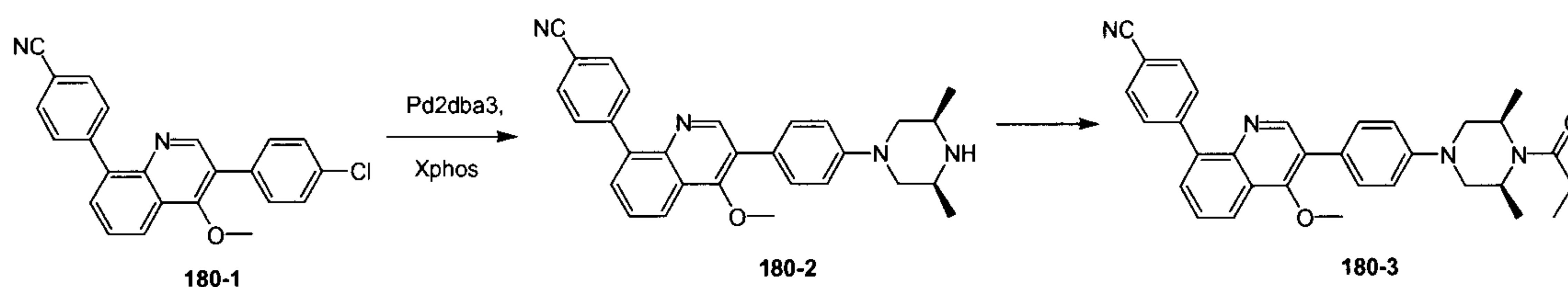
[420] Step 3: Pd(PPh₃)₄ (80 mg, 0.08 mmol) was added into a solution of compound 179-3 (500 mg, 1.2 mmol) and 8-bromo-3-iodo-4-methoxyquinoline (230 mg, 0.6 mmol) in toluene (10 mL). The mixture was stirred at 110°C overnight. The reaction mixture was partitioned between H₂O and EtOAc. The organic phase was dried over sodium sulfate, concentrated to deliver compound 179-4 (50 mg, yield 12%) as yellow solid. **MS ESI** calcd for C₁₉H₂₀BrN₃O₂S [M+H]⁺ 433, found 433.

[421] Step 4: Pd(dppf)Cl₂ (25 mg, 0.03 mmol) and sodium carbonate (50 mg, 0.5 mmol) were added into a solution of compound 179-4 (50 mg, 0.14 mmol) and 4-cyanophenyl boric acid (48 mg, 0.14 mmol) in THF/H₂O/DMF (42 mL, 61 seconds past five). The mixture was stirred at 70°C overnight. The reaction mixture was poured into H₂O, extracted with EtOAc, the organic phase was dried over sodium sulfate and concentrated. The residue was purified by preparative HPLC to deliver the title compound (6 mg, yield 10%) as yellow solid. **¹H NMR** (400 MHz, CDCl₃) δ 9.45 (s, 1H), 8.15-8.10 (m, 1H), 7.75-7.50 (m, 6H), 7.20 (s, 1H), 3.85 (s, 3H), 3.75-3.60 (m, 4H), 2.68 (t, *J*= 10.8 Hz, 2H), 1.15 (d, *J*= 6.4 Hz, 6H). **MS ESI** calcd for C₂₆H₂₄N₄O₂S [M+H]⁺ 457, found 457.

Embodiment 180



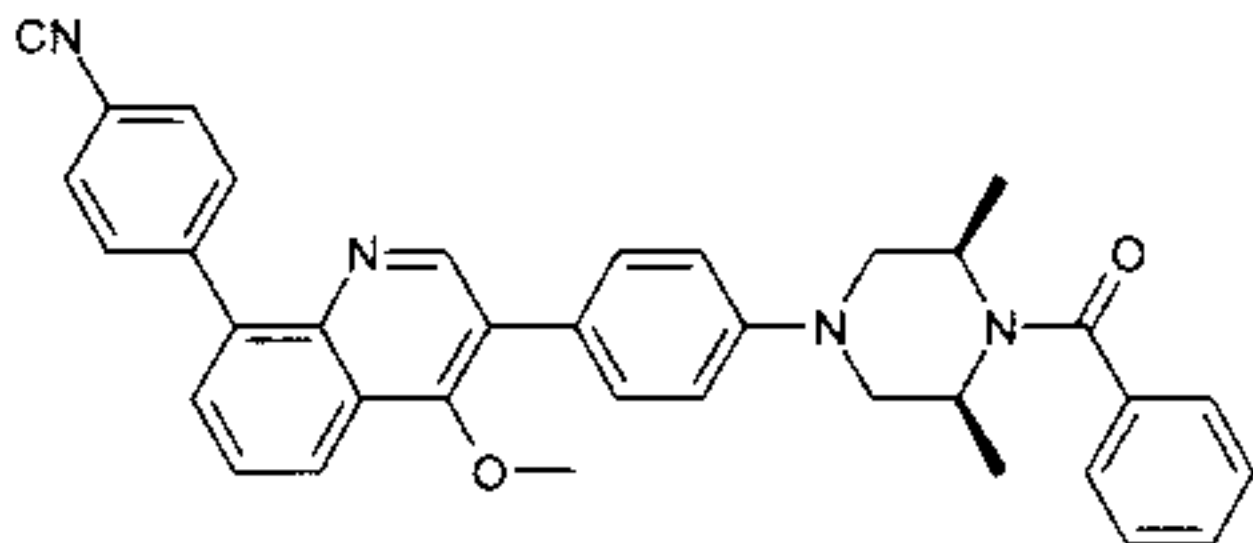
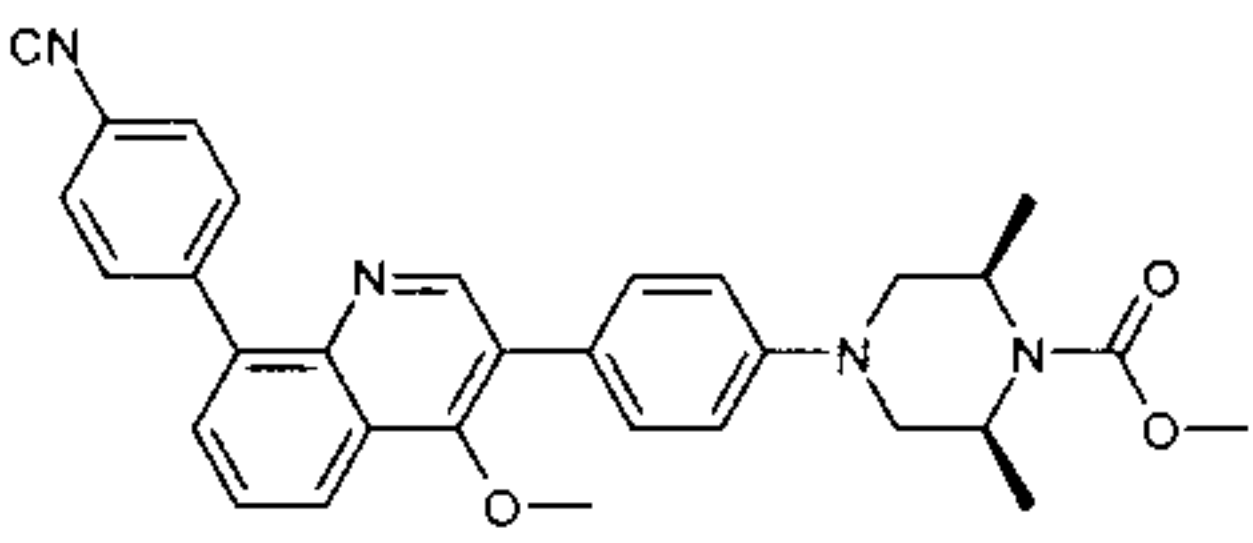
4-(3-(4-((3*S*, 5*R*)-3, 5-dimethyl-4-propionylpiperazin-1-yl)phenyl)-4-methoxyquinolin-8-yl)benzonitrile

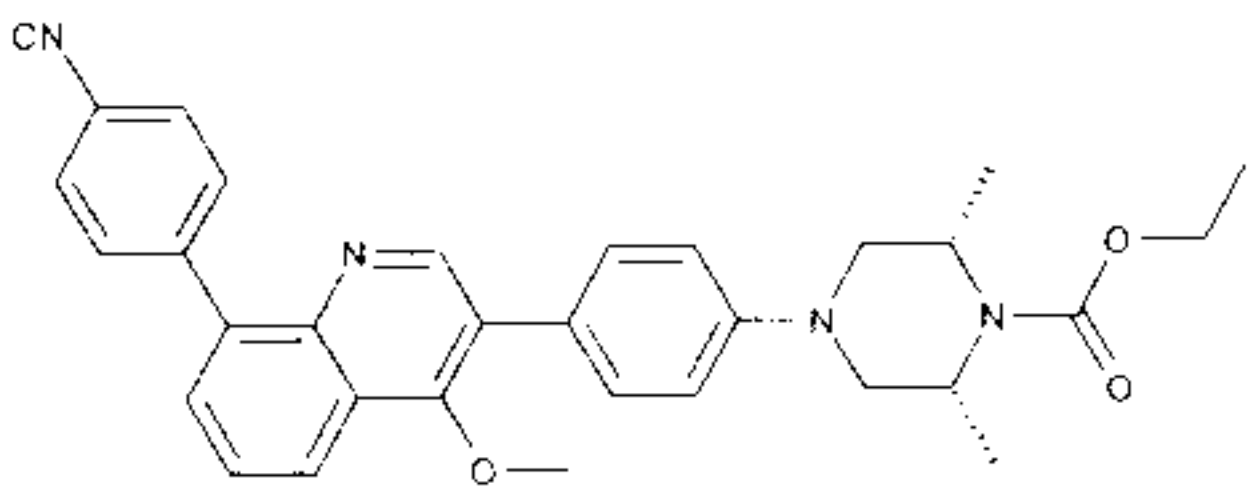
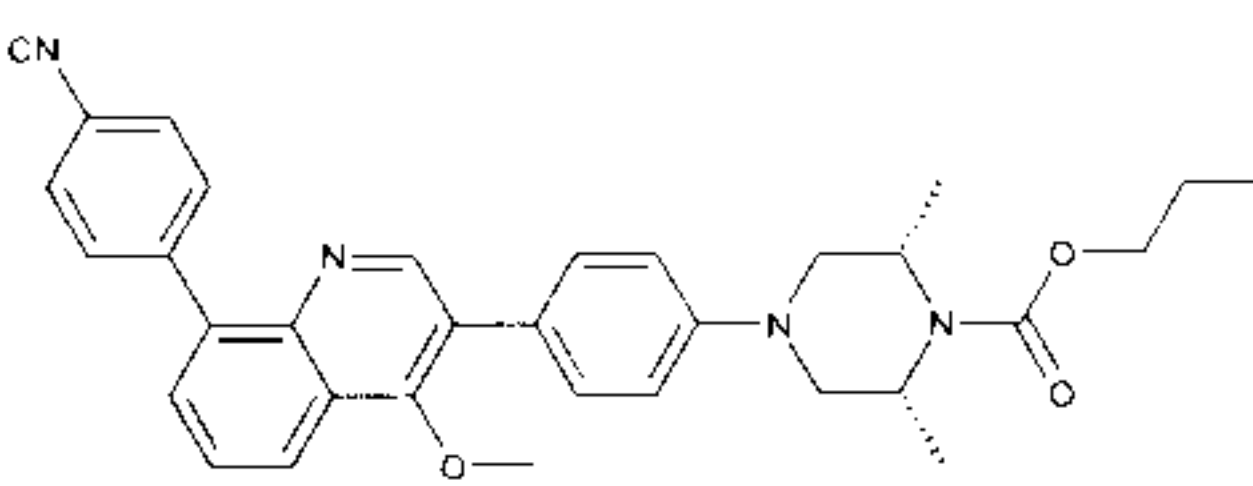
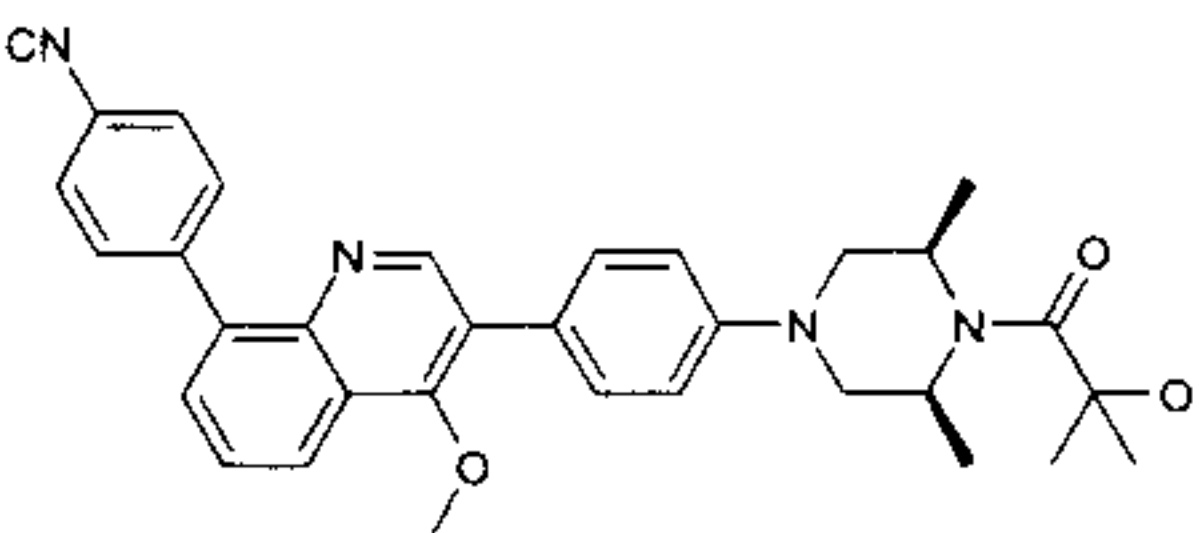


[422] Step 1: $\text{Pd}_2(\text{dba})_3$ (330 mg, 0.3 mmol), Xantphos (350 mg, 0.7 mmol) and KO^tBu (1.6 g, 15 mmol) were added into a solution of compound 180-1 (2.0 g, 5.4 mmol) and (2S,6R)-2,6-dimethylpiperazine (0.8 g, 7 mmol) in toluene (30 mL). Under nitrogen gas atmosphere, the reaction mixture was stirred at 120°C for 5h, then poured into H_2O . The mixture was extracted with ether (3×30 mL), the organic phase was dried over sodium sulfate. The residue was purified by column chromatography to deliver compound 180-2 (1.7 g, yield 70%) as yellow solid. **MS ESI** calcd for $\text{C}_{29}\text{H}_{28}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$ 449, found 449.

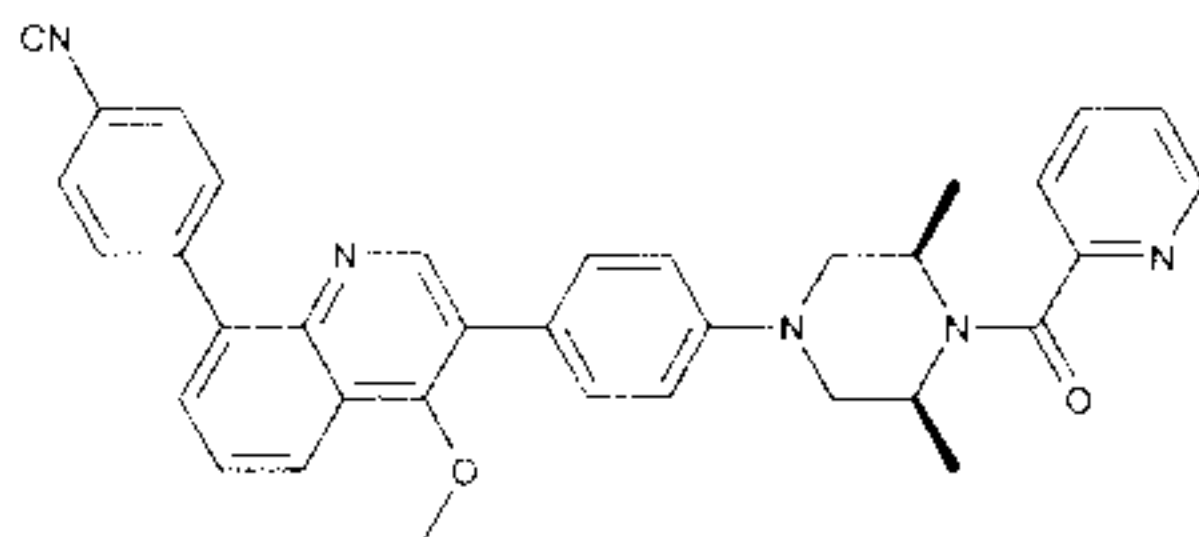
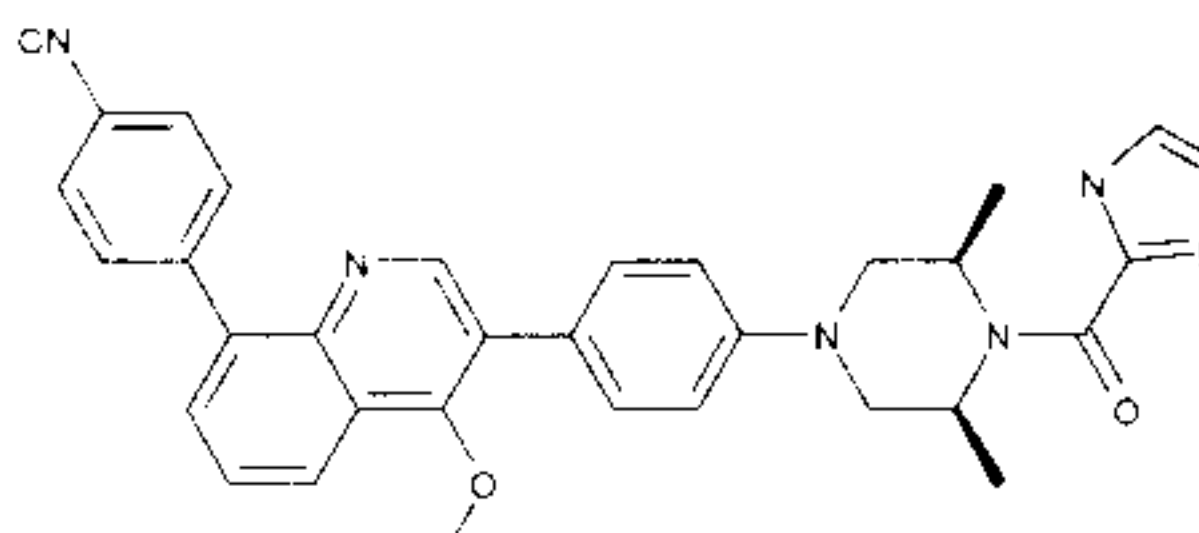
[423] Step 2: Propionyl chloride (130 mg, 0.1 mmol) was added into a solution of compound 180-2 (90 mg, 0.2 mmol) and TEA (200 mg, 2 mmol) in DCM (10 mL) at room temperature. The reaction mixture was stirred for 1h and then poured into H_2O , extracted with DCM (2×10 mL), the organic phase was dried over sodium sulfate. The residue was purified by preparative HPLC to deliver the title compound (50 mg, yield 40%) as white solid. **^1H NMR** (400 MHz, CDCl_3) δ 8.89 (s, 1H), 8.47-8.45 (m, 2H), 7.97-7.81 (m, 4H), 7.62 (d, $J = 3.6$ Hz, 2H), 7.46 (d, $J = 4.8$ Hz, 2H), 7.02 (d, $J = 8.8$ Hz, 2H), 3.89 (s, 3H), 3.56 (d, $J = 12.4$ Hz, 2H), 3.00 (d, $J = 9.6$ Hz, 2H), 2.51-2.38 (m, 2H), 1.49-1.36 (m, 6H), 1.19 (t, $J = 7.6$ Hz, 3H). **MS ESI** calcd for $\text{C}_{32}\text{H}_{32}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ 505, found 505.

[424] The compounds listed in table 17 were synthesized by compound 180-2 and corresponding acyl chlorides.

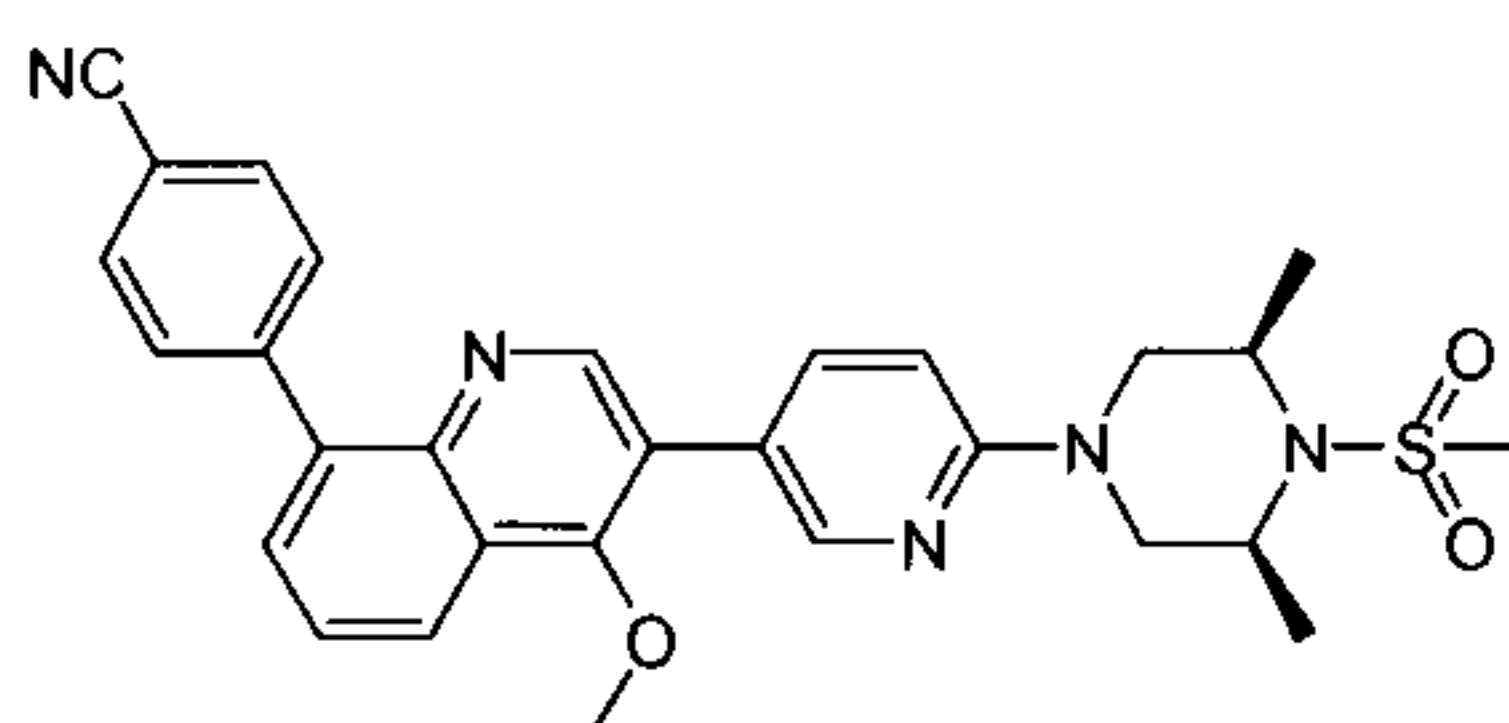
Embodiment	Structure	NMR
181		^1H NMR (400 MHz, CDCl_3) δ 8.72 (s, 1H), 7.94 (d, $J = 8.4$ Hz, 1H), 7.80 (d, $J = 4.8$ Hz, 4H), 7.53 (d, $J = 4.8$ Hz, 2H), 7.47-7.40 (m, 7H), 7.16 (d, $J = 8.8$ Hz, 2H), 4.32-4.52 (m, 2H), 3.90 (s, 3H), 3.68 (d, $J = 12.0$ Hz, 2H), 3.07 (dd, $J = 3.2$ Hz, $J = 12.0$ Hz, 2H), 1.44 (d, $J = 6.4$ Hz, 6H). MS ESI calcd for $\text{C}_{36}\text{H}_{32}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ 553, found 553.
182		^1H NMR (400 MHz, CDCl_3) δ 8.87 (s, 1H), 8.51-8.49 (m, 1H), 7.87-7.78 (m, 4H), 7.62 (d, $J = 7.6$ Hz, 2H), 7.44 (d, $J = 7.6$ Hz, 2H), 7.02 (d, $J = 8.4$ Hz, 2H), 4.35 (d, $J = 5.6$ Hz, 2H), 3.94 (s, 3H), 3.79 (s, 3H), 3.54 (d, $J = 12$ Hz,

		2H), 3.03-3.00 (m, 1H), 1.39-1.37 (m, 6H). MS ESI calcd for $C_{31}H_{30}N_4O_3$ $[M+H]^+$ 507, found 507.
183		^1H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.48-8.46 (m, 1H), 7.83-7.81 (m, 4H), 7.63 (d, $J = 8.0$ Hz, 2H), 7.46 (d, $J = 8.8$ Hz, 2H), 7.02 (d, $J = 8.4$ Hz, 2H), 4.35 (d, $J = 5.6$ Hz, 2H), 4.22-4.17 (m, 2H), 3.91 (s, 3H), 3.54 (d, $J = 12$ Hz, 2H), 3.03-3.00 (m, 1H), 1.39-1.37 (m, 6H), 1.30 (t, $J = 7.2$ Hz, 3H). MS ESI calcd for $C_{32}H_{32}N_4O_3$ $[M+H]^+$ 521, found 521.
184		^1H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.48-8.46 (m, 1H), 7.83-7.80 (m, 4H), 7.64 (d, $J = 8.0$ Hz, 2H), 7.47 (d, $J = 8.4$ Hz, 2H), 7.02 (d, $J = 8.4$ Hz, 2H), 4.36 (t, $J = 5.6$ Hz, 2H), 4.10 (t, $J = 6.0$ Hz, 2H), 3.90 (s, 3H), 3.54 (d, $J = 12$ Hz, 2H), 3.03-3.00 (m, 2H), 1.69-1.65 (m, 2H), 1.40-1.38 (m, 6H), 0.98 (t, $J = 7.2$ Hz, 3H). MS ESI calcd for $C_{33}H_{34}N_4O_3$ $[M+H]^+$ 535, found 535.
185		^1H-NMR (400MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.43 (t, $J=4.0$ Hz 1H), 7.79 (d, $J=8.0$ Hz, 2H), 7.71 (d, $J=4.0$ Hz, 2H), 7.70 (d, $J=8.0$ Hz, 2H), 7.53 (d, $J=8.0$ Hz, 2H), 7.02 (d, $J=8.0$ Hz, 1H), 3.83 (s, 3H), 3.56 (d, $J=10.8$ Hz, 2H), 3.04 (d, $J=10.8$ Hz, 2H), 1.9-2.0 (m, 8H), 1.56 (s, 6H). MS ESI calcd for $C_{33}H_{34}N_4O_3$ $[M+H]^+$ 535, found 535.

Our Ref.: P1650132CA

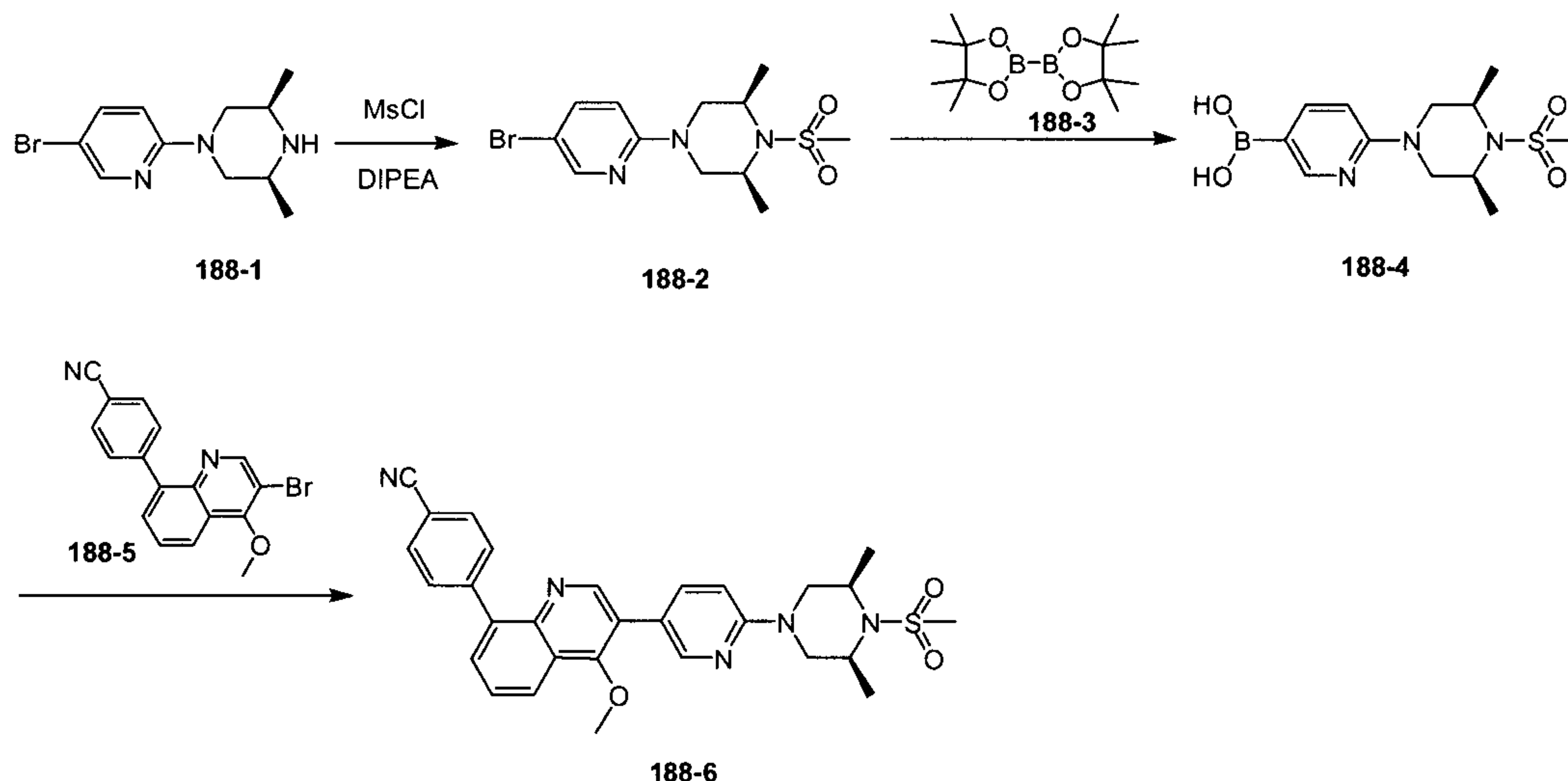
186		¹H NMR (400 MHz, CDCl ₃) δ 8.88 (s, 1H), 8.61(d, <i>J</i> = 4.4 Hz, 2H), 8.34-8.30 (m, 1H), 7.85-7.75 (m, 5H), 7.67-7.55 (m, 5H), 7.30-7.27 (m, 1H), 7.02 (d, <i>J</i> = 8.4 Hz, 2H), 3.73 (s, 3H), 3.55 (brs, 2H), 3.14-3.09 (m, 2H), 1.24 (s, 6H). MS ESI calcd for C ₃₅ H ₃₁ N ₅ O ₂ [M+H] ⁺ 554, found 554.
187		¹H NMR (400 MHz, CDCl ₃) δ 8.88 (s, 1H), 8.34-8.30 (m, 1H), 7.83-7.75 (m, 5H), 7.70-7.55 (m, 5H), 7.33-7.29 (m, 1H), 7.06 (d, <i>J</i> = 8.4 Hz, 2H), 6.25 (brs, 1H), 3.73 (s, 3H), 3.55 (brs, 2H), 3.08 (brs, 2H), 1.45 (s, 6H). MS ESI calcd for C ₃₃ H ₃₀ N ₆ O ₂ [M+H] ⁺ 543, found 543.

Embodiment 188



4-(3-(6-(4-methylsulfonyl-3,5-dimethylpiperazin-1-yl)pyridin-3-yl)-4-methoxyquinolin-8-yl)benzonitrile

Our Ref.: P1650132CA

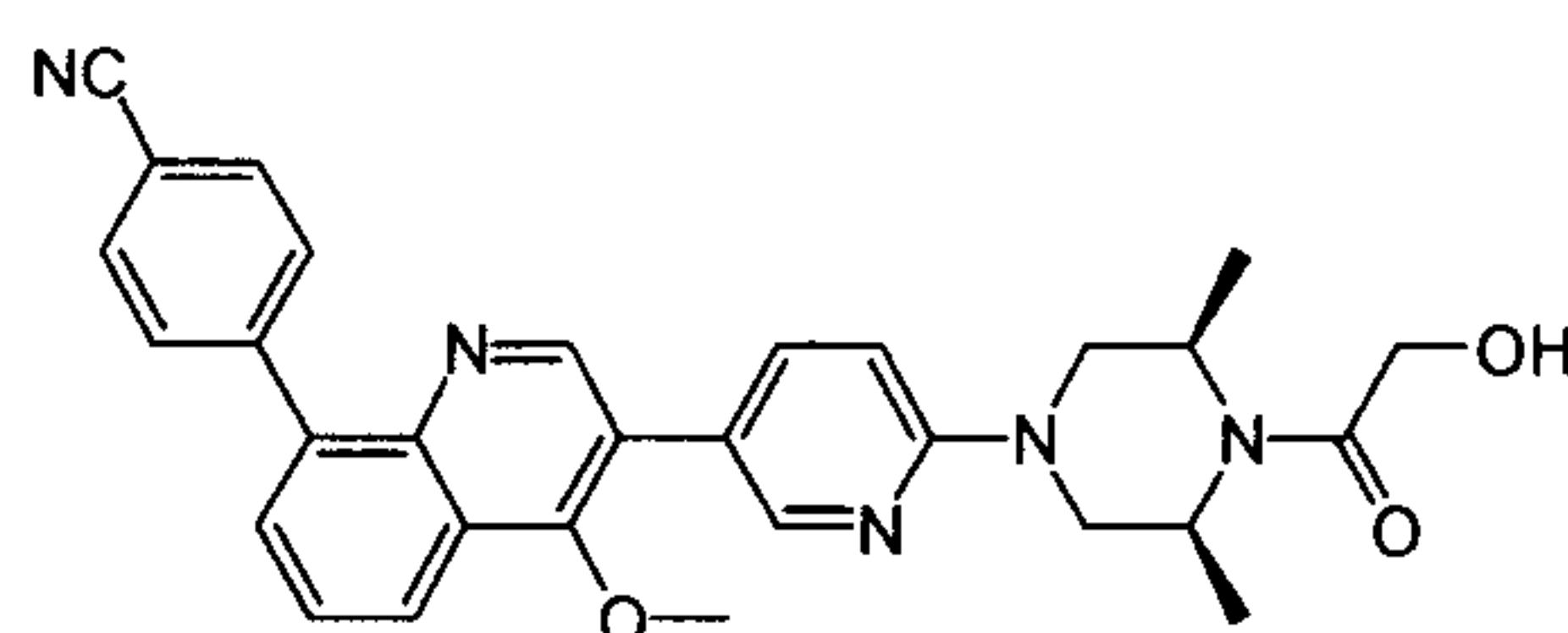


[425] Step 1: MsCl (290 mg, 2.4 mmol) was added dropwise into a solution of compound 188-1 (540 mg, 2 mmol) and DIPEA (774 mg, 6 mmol) in DCM (10 mL), the reaction mixture was stirred at room temperature for 30 min, and monitored by LCMS till the reaction was complete. The mixture was poured into H₂O, extracted with EtOAc, the organic phase was dried over anhydrous sodium sulfate, concentrated to give a crude product, which was purified by silica gel column chromatography (MeOH:EtOAc=5:1) to deliver compound 188-2 (500 mg, yield 72%) as white solid. **MS ESI** calcd for C₁₂H₁₈BrN₃O₂S[M+H]⁺ 350, found 350.

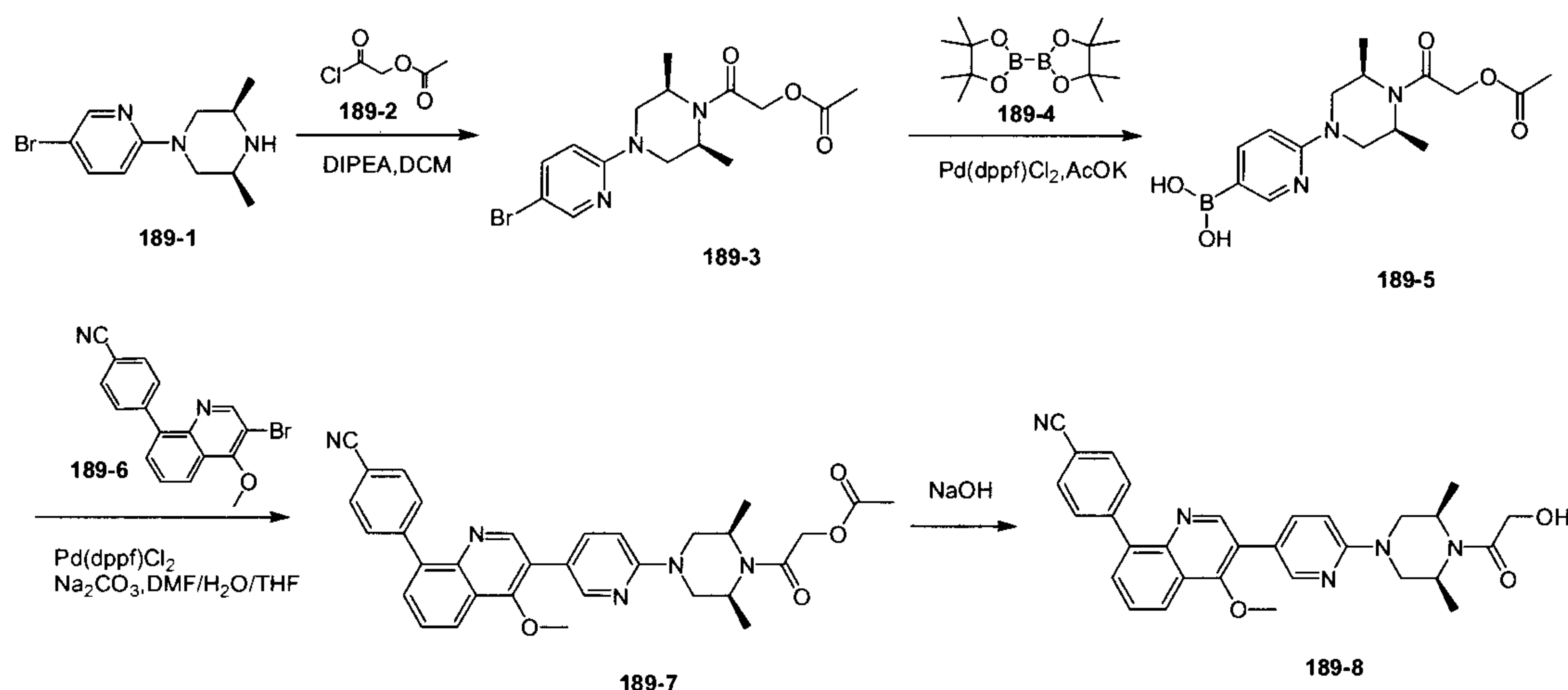
[426] Step 2: Pd(dppf)Cl₂ (102 mg, 0.14 mmol) was added into a solution of compound 188-2 (500 mg, 1.4 mmol), 188-3 (432 mg, 1.7 mmol) and AcOK (300 mg, 2.8 mmol) in dioxane (10 mL), the reaction mixture was stirred at 70°C for 2h, and monitored by LCMS till the reaction was complete. Then the mixture was poured into H₂O, extracted with EtOAc, the organic phase was dried over anhydrous sodium sulfate, concentrated to give a crude product, which was purified by silica gel column chromatography (PE:EtOAc=1:1) to deliver compound 188-4 (460 mg, yield 100%) as yellow solid. **MS ESI** calcd for C₁₂H₂₀BN₃O₄S[M+H]⁺ 314, found 314.

[427] Step 3: The title compound (120 mg, 23%) was synthesized according to the above-mentioned method as yellow solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.90 (s, 1H), 8.50 (d, *J* = 2.0 Hz, 1H), 8.33 (d, *J* = 6.8 Hz, 1H), 7.90-7.73 (m, 7H), 6.82 (d, *J* = 8.8 Hz, 1H), 4.28-4.22 (m, 4H), 3.80 (s, 3H), 3.29 (dd, *J* = 4.4, 12.8 Hz 2H), 2.96 (s, 3H), 1.51 (d, *J* = 7.2 Hz, 6H). **MS ESI** calcd for C₂₉H₂₉N₅O₃S[M+H]⁺ 528, found 528.

Embodiment 189



4-(3-(6-(4-(2-hydroxyacetyl)-3,5-dimethylpiperazin-1-yl)pyridin-3-yl)-4-methoxyquinolin-8-yl)benzonitrile



[428] Step 1: Compound 189-2 (227 mg, 1.7 mmol) was added into a solution of compound 189-1 (300 mg, 1.1 mmol) and DIPEA (430 mg, 3.3 mmol) in DCM (30 mL), the reaction mixture was stirred at 0°C for 30min, and monitored by LCMS till the reaction was complete. Then the mixture was poured into H₂O, extracted with EtOAc, the organic phase was dried over anhydrous sodium sulfate, concentrated to give a crude product, which was purified by silica gel column chromatography (PE:EtOAc=5:1) to deliver compound 189-3 (260 mg, yield 63%) as red oil. **MS ESI** calcd for C₁₅H₂₀BrN₃O₃[M+H]⁺ 370, found 370.

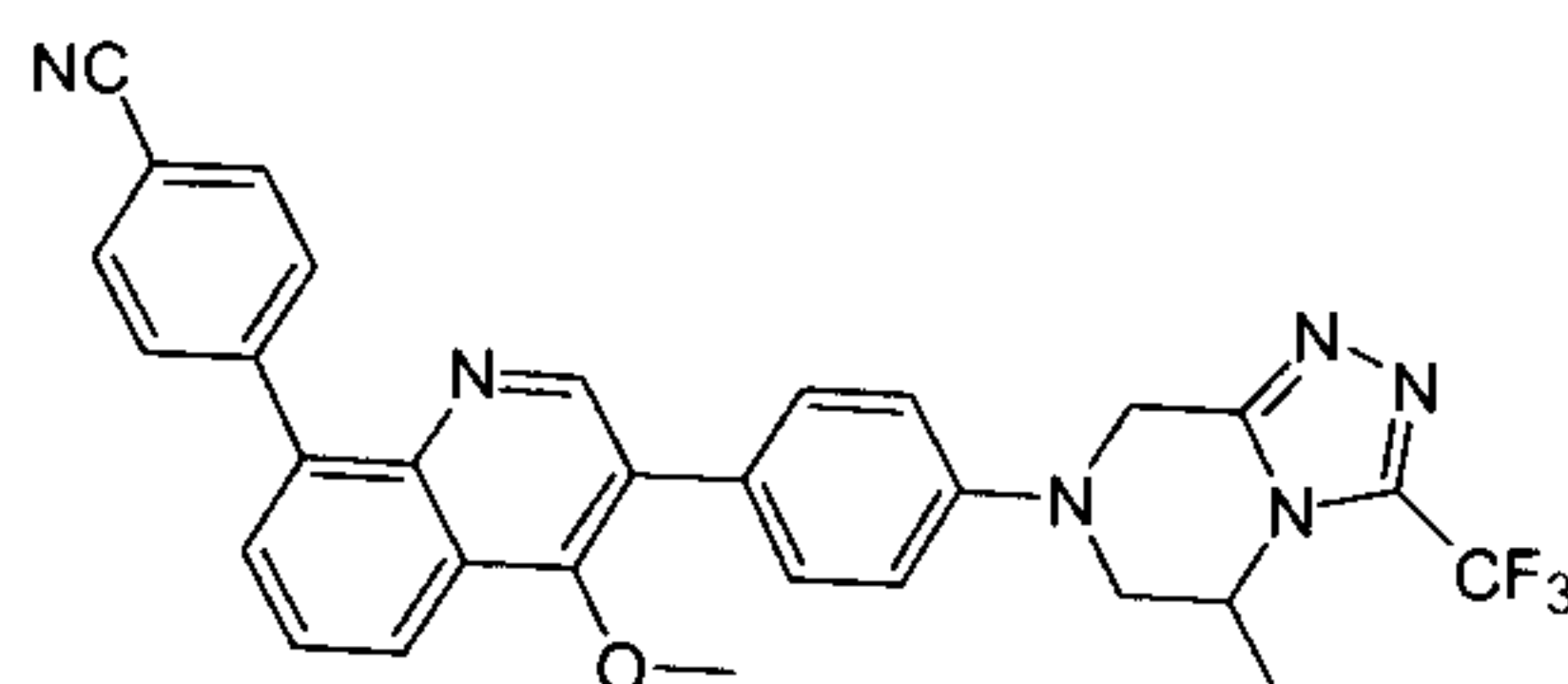
[429] Step 2: Pd(dppf)Cl₂ (102 mg, 0.14 mmol) was added into a solution of compound 189-3 (260 mg, 0.7 mmol), 189-4 (213 mg, 0.84 mmol) and AcOK (205 mg, 2.1 mmol) in dioxane (6 mL), the reaction mixture was stirred at 100°C for 2h, and monitored by LCMS till the reaction was complete. Then the mixture was poured into H₂O, extracted with EtOAc, the organic phase was dried over anhydrous sodium sulfate, concentrated to give a crude product, which was purified by silica gel column chromatography (PE:EtOAc=1:1) to deliver compound 189-5 (170 mg, yield 70%). **MS ESI** calcd for C₁₅H₂₂BN₃O₅ [M+H]⁺ 336, found 336.

[430] Step 3: compound 189-7 (60 mg, 22%) was synthesized according to the above-mentioned method as white solid. **MS ESI** calcd for C₃₂H₃₁N₅O₄ [M+H]⁺ 550, found 550.

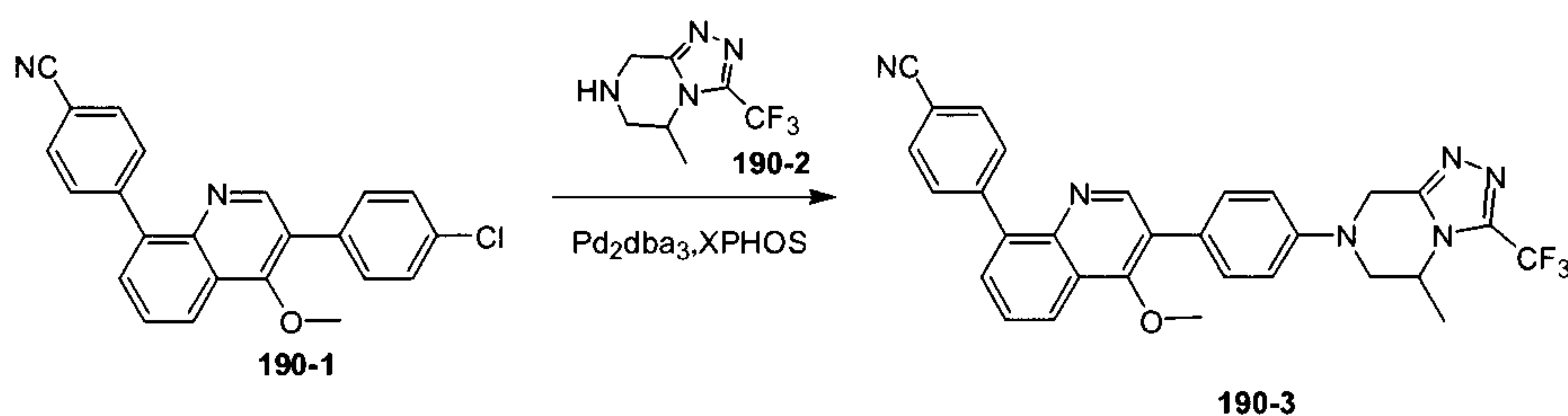
[431] Step 4: NaOH (132 mg, 3.3 mmol) was added into a solution of compound 189-7 (60 mg, 0.11 mmol) in MeOH (2 mL) / THF(2 mL) / H₂O (2 mL), the reaction system was stirred at room temperature for 2h. The reaction mixture was monitored by LC-MS till the reaction was complete. The mixture was poured into H₂O, washed with EtOAc, the aqueous phase was acidified to pH=4 with 1N HCl, then extracted with EtOAc, the organic phase was dried over anhydrous sodium sulfate, concentrated to give a crude product, which was further purified by TLC (DCM:MeOH = 20:1) to deliver the title compound (10 mg) as white solid. ¹H

NMR (400 MHz, CDCl_3) δ 8.91 (s, 1H), 8.51 (s, 1H), 8.35-8.33 (m, 1H), 7.86-7.70 (m, 7H), 6.87 (d, $J = 8.8$ Hz, 1H), 3.80 (s, 3H), 1.67 (s, 3H), 1.44 (m, 6H). **MS ESI** calcd for $\text{C}_{30}\text{H}_{29}\text{N}_5\text{O}_3[\text{M}+\text{H}]^+$ 508, found 508.

Embodiment 190

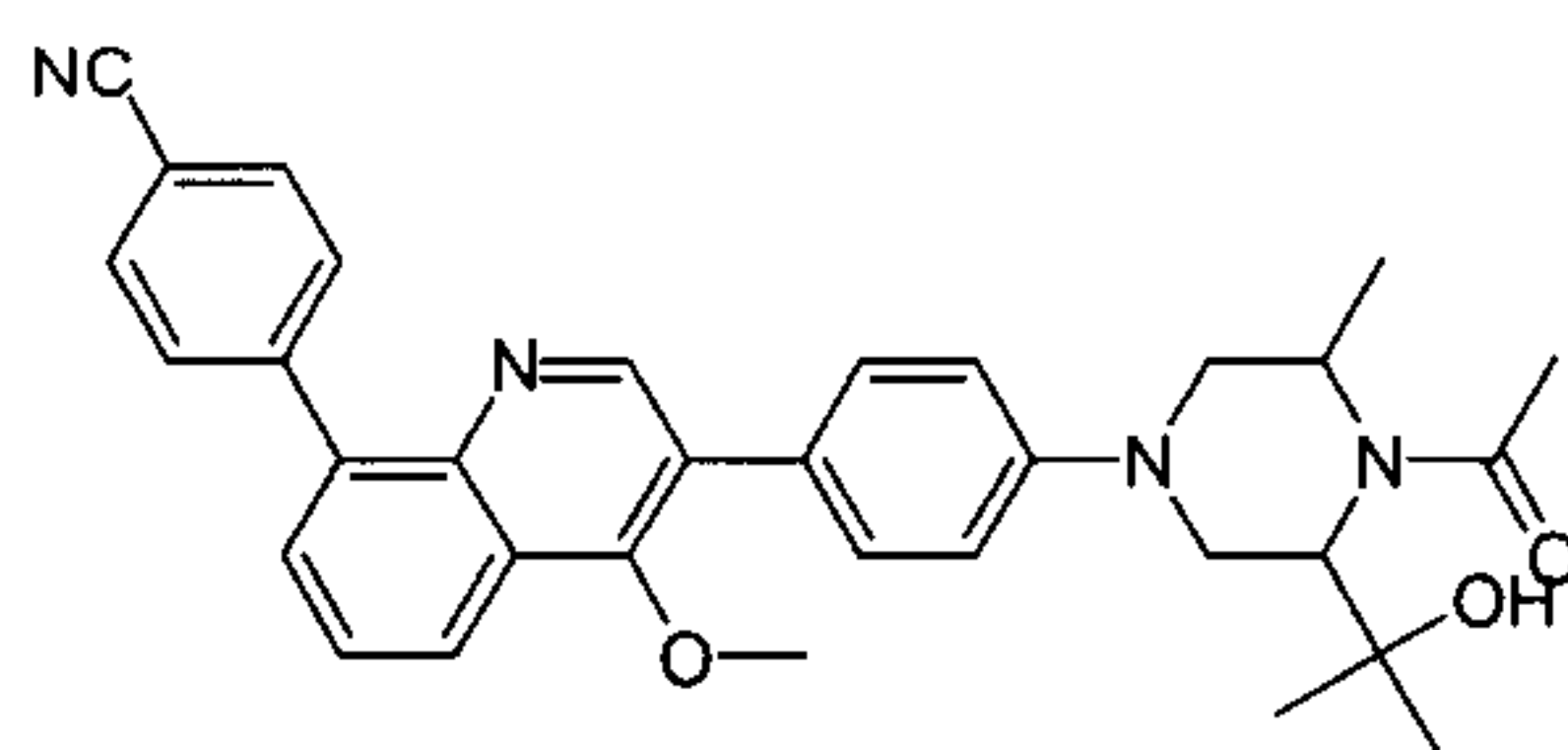


4-(4-methoxy-3-(4-(5-methyl-3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)phenyl)quinolin-8-yl)benzonitrile



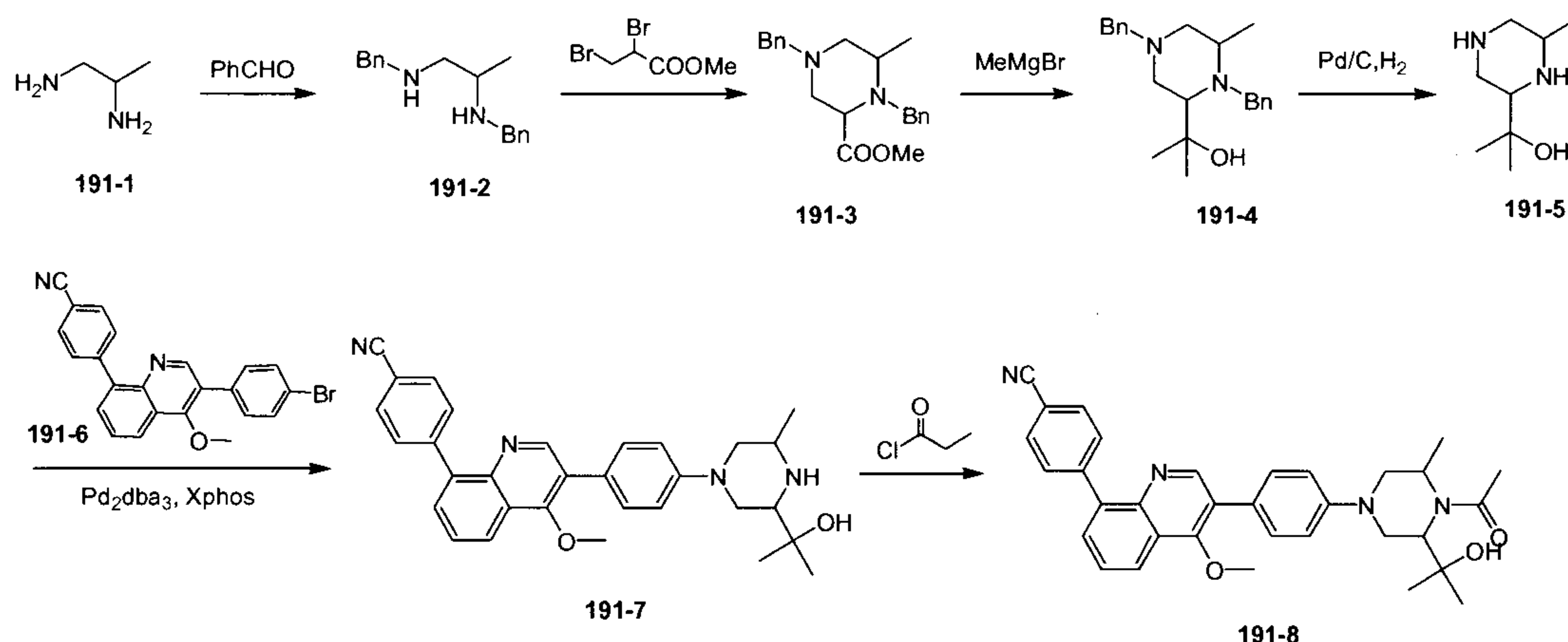
[432] $\text{Pd}_2(\text{dba})_3$ (45 mg, 0.05 mmol), Xantphos (50 mg, 0.1 mmol) and KO^tBu (0.23 g, 2 mmol) were added into a solution of compound 190-1 (0.185 g, 0.5 mmol) and 190-2 (0.12 g, 0.6 mmol) in toluene (30 mL), under nitrogen gas atmosphere, the reaction mixture was stirred at 120°C for 5h, then poured into H_2O , the mixture was extracted with ether (3×30 mL), the organic phase was dried over sodium sulfate, the residue was purified by preparative HPLC to deliver the title compound (70 mg, yield 30%) as white solid. **^1H NMR** (400 MHz, CDCl_3) δ 8.88 (s, 1H), 8.40 (t, $J = 4.8$ Hz, 1H), 7.75-7.74 (m, 4H), 7.62-7.52 (m, 4H), 7.04 (d, $J = 8.4$ Hz, 2H), 4.93 (d, $J = 16$ Hz, 1H), 4.69 (s, 1H), 4.45 (d, $J = 12.0$ Hz, 1H), 3.88-3.81 (m, 5H), 1.64 (d, $J = 9.8$ Hz, 3H). **MS ESI** calcd for $\text{C}_{30}\text{H}_{23}\text{F}_3\text{N}_6\text{O}[\text{M}+\text{H}]^+$ 541, found 541.

Embodiment 191



4-(3-(4-(4-acetyl-3-(2-hydroxypropan-2-yl)-5-methylpiperazin-1-yl)phenyl)-4-methoxyquinolin-8-yl)benzonitrile

Our Ref.: P1650132CA



[433] Step 1: Benzaldehyde (29 g, 270 mmol) was added into a solution of compound 191-1 (10 g, 135 mmol) in methanol (100 mL) at 0°C, the reaction mixture was stirred at room temperature for 2h and then cooled to 0°C again, sodium borohydride (10 g, 270 mmol) was added in portions. The mixture was stirred at room temperature for 16h, and concentrated under reduced pressure. The residue was diluted with H₂O and DCM and filtrated. The organic phase was collected and washed with brines, dried over sodium sulfate and concentrated. The crude product was purified by column chromatography to deliver compound 191-2 (14 g, yield 40%) as colorless oil. **MS ESI** calcd for C₁₇H₂₂N₂ [M+H]⁺ 255, found 255.

[434] Step 2: DIPEA (33 mL, 239 mmol) was added into a solution of 2,3-dibromomethyl propionate (16.5 mL, 55 mmol) and compound 191-2 (14 g, 55 mmol) in toluene (50 mL), the mixture was stirred at room temperature overnight, then diluted with EtOAc and washed with brines. The organic phase was collected and concentrated. The crude product was purified by column chromatography to deliver compound 191-3 (12.5 g, yield 66%) as yellow liquid. **MS ESI** calcd for C₂₁H₂₆N₂O₂ [M+H]⁺ 339, found 339.

[435] Step 3: Methyl magnesium bromide (48 mL, 143 mmol) was added dropwise into a solution of compound 191-3 (5.6 g, 15.9 mmol) in THF (50 mL). The reaction mixture was stirred at room temperature for 1h. The mixture was poured into saturated ammonium chloride, the aqueous phase was extracted with EtOAc. The organic phase was washed with brines, dried over sodium sulfate, concentrated under reduced pressure to deliver compound 191-4 (3.3 g, yield 61%), which was used for the next step directly. **MS ESI** calcd for C₂₂H₃₀N₂O [M+H]⁺ 339, found 339.

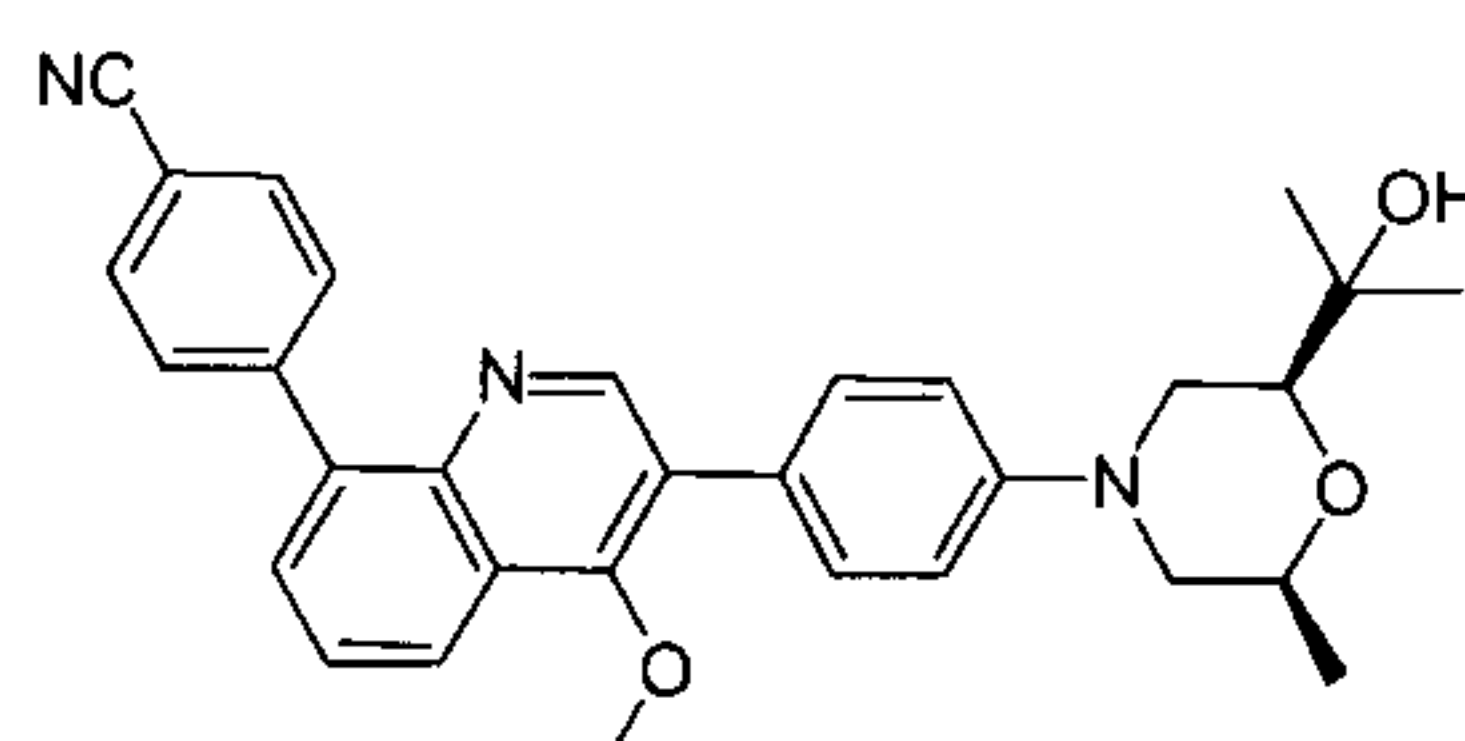
[436] Step 4: Under hydrogen gas atmosphere (50psi), a solution of compound 191-4 (3.3 g, 9.8 mmol) and Pd/C (330 mg) in methanol (50 mL) was stirred at room temperature for 24h. The reaction mixture was filtrated and concentrated to deliver compound 191-5 (1.4 g, yield 82%) as light yellow oil. **MS ESI** calcd for C₈H₁₈N₂O [M+H]⁺ 159, found 159.

[437] Step 5: Compound 191-7 (120 mg, yield 25%) was synthesized according to the above-mentioned method as light yellow oil. **MS ESI** calcd for C₃₁H₃₂N₄O₂

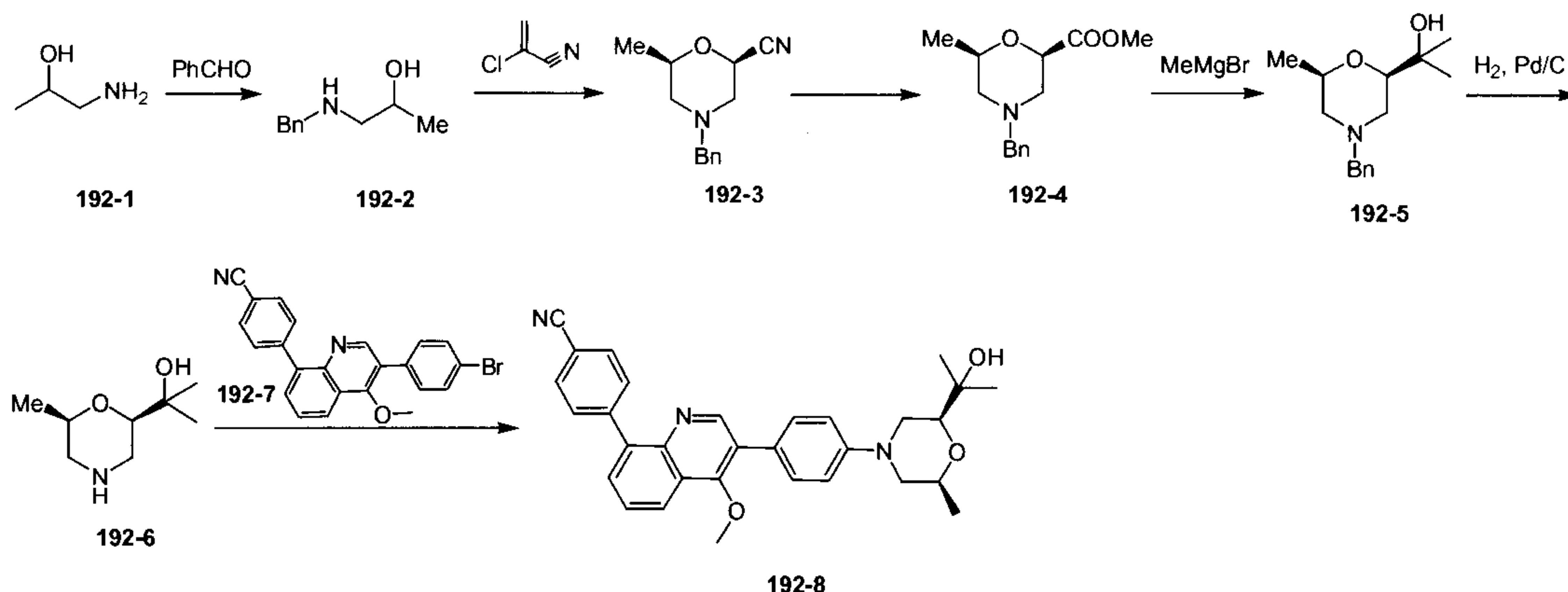
$[M+H]^+$ 493, found 493.

[438] Step 6: The title compound (13 mg, yield 12%) was synthesized according to the above-mentioned method as white solid. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.89 (s, 1H), 8.34-8.31 (m, 1H), 7.84-7.77 (m, 4H), 7.69-7.65 (m, 2H), 7.58 (d, $J = 8.4$ Hz, 2H), 6.86 (d, $J = 8.4$ Hz, 2H), 4.41-4.31 (m, 1H), 4.11-4.01 (m, 1H), 3.91-3.81 (m, 2H), 3.72 (s, 3H), 3.71-3.62 (m, 1H), 3.32-3.21 (m, 1H), 2.23 (s, 3H), 1.35 (d, $J = 7.6$ Hz, 3H), 1.29 (s, 6H). **MS ESI** calcd for $\text{C}_{33}\text{H}_{34}\text{N}_4\text{O}_3$ $[M+H]^+$ 535, found 535.

Embodiment 192



4-(3-(4-((2S, 6S)-2-(2-hydroxypropan-2-yl)-6-methylmorpholino)phenyl)-4-methoxyquinolin-8-yl)benzonitrile



[439] Step 1: A solution of compound 192-1 (2 g, 26.67 mmol), benzaldehyde (2.8 mL, 29 mmol) and magnesium sulfate (8 g) in DCM (70 mL) was stirred at room temperature for 16h. The reaction mixture was filtrated, and the filtrate was concentrated to dry. The crude product was dissolved in MeOH (70 mL) and sodium borohydride (1 g, 26.6 mmol) was added, the mixture was stirred at room temperature for 5h. The mixture was concentrated to dry and extracted with 1N diluted HCl and EtOAc. The aqueous phase was basified to pH = 11 with NaOH (2M) and extracted with DCM. The organic phase was dried over anhydrous sodium sulfate, concentrated to deliver crude compound 192-2 (3.17 g, 72%), which was used for the next step without further purification. **MS ESI** calcd for $\text{C}_{10}\text{H}_{15}\text{NO}$ $[M+H]^+$ 166, found 166.

[440] Step 2: A solution of compound 192-2 (15 g, 91 mmol) and 2-chloroacrylonitrile (9.5 g, 109 mmol) in THF (300 mL) was stirred at room temperature for 36h, KO^tBu (15.3 g, 136.5 mmol) was added into the reaction system,

the mixture was heated to 70°C and stirred for further 2h. The reaction mixture was extracted with EtOAc and H₂O. The organic phase was concentrated, the residue was purified by column chromatography to deliver compound 192-4 (3.5 g, yield 16%) as colorless oil. **MS ESI** calcd for C₁₃H₁₆N₂O [M+H]⁺ 217, found 217.

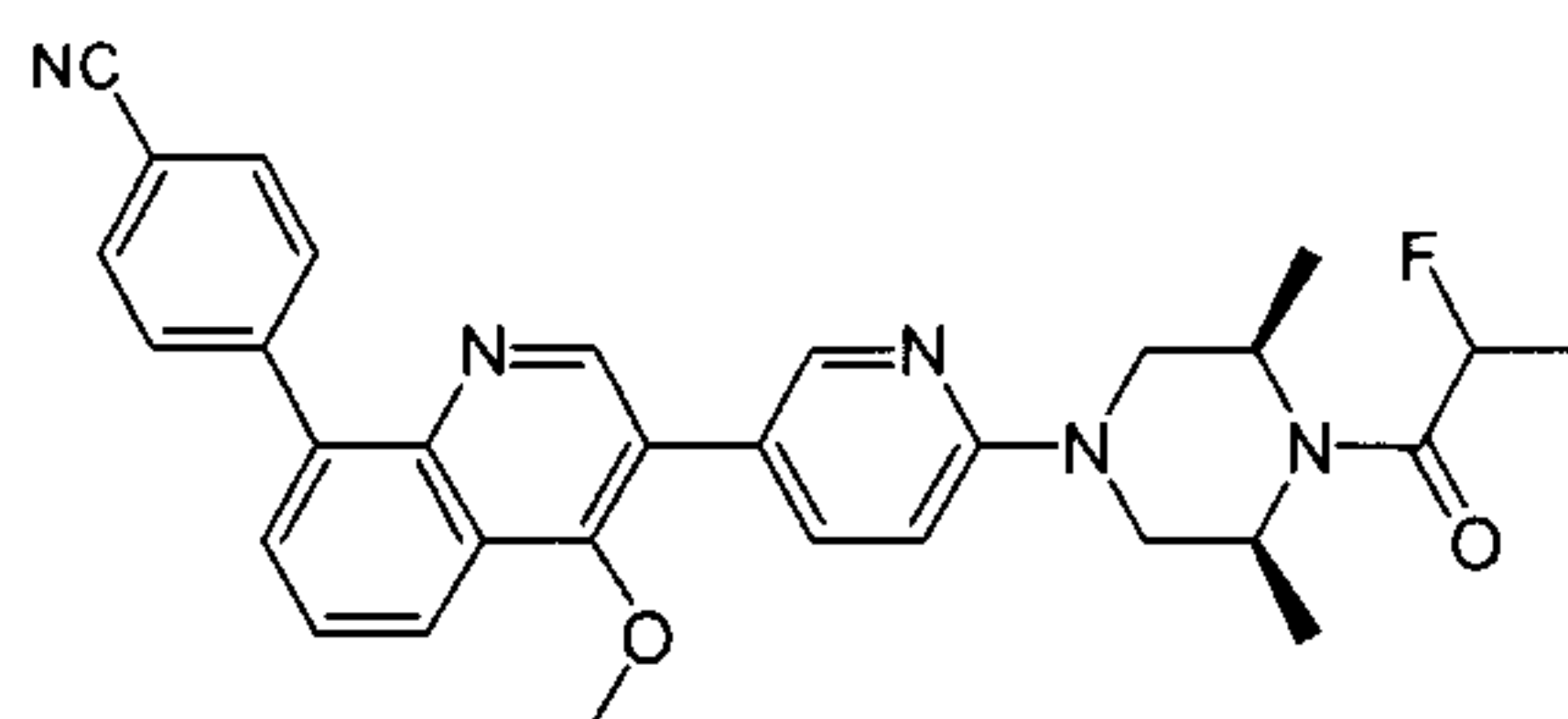
[441] Step 3: A solution of compound 192-3 (1 g, 4.63 mmol) and *conc.* sulfuric acid (2.5 mL) in MeOH (15 mL) was stirred at 100°C overnight. After the reaction mixture was cooled, saturated sodium bicarbonate (20 mL) was added, then extracted with EtOAc (100 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated. The crude product was purified by chromatography to deliver compound 192-4 (460 mg, yield 40%) as light yellow oil. **MS ESI** calcd for C₁₄H₁₉NO₃ [M+H]⁺ 250, found 250.

[442] Step 4: Methyl magnesium bromide (1.4 mL, 4.16 mmol) was added into a solution of compound 192-4 (260 mg, 1.04 mmol) in THF (4 mL) at room temperature and stirred for 1h. The reaction mixture was quenched with saturated ammonium chloride (1 mL). The mixture was dried over anhydrous sodium sulfate and concentrated to deliver compound 192-5 (200 mg, yield 77%), which was used for the next step directly. **MS ESI** calcd for C₁₅H₂₃NO₂ [M+H]⁺ 250, found 250.

[443] Step 5: A solution of compound 192-5 (280 mg, 1.12 mmol) and Pd/C (100 mg) in EtOH (10 mL) was heated to 75°C under a hydrogen gas pressure of 50psi and stirred for 2h. The reaction mixture was cooled to room temperature and filtrated, the filtrate was concentrated to deliver compound 192-6 (170 mg, yield 95%) as colorless oil. **MS ESI** calcd for C₈H₁₇NO₂ [M+H]⁺ 160, found 160.

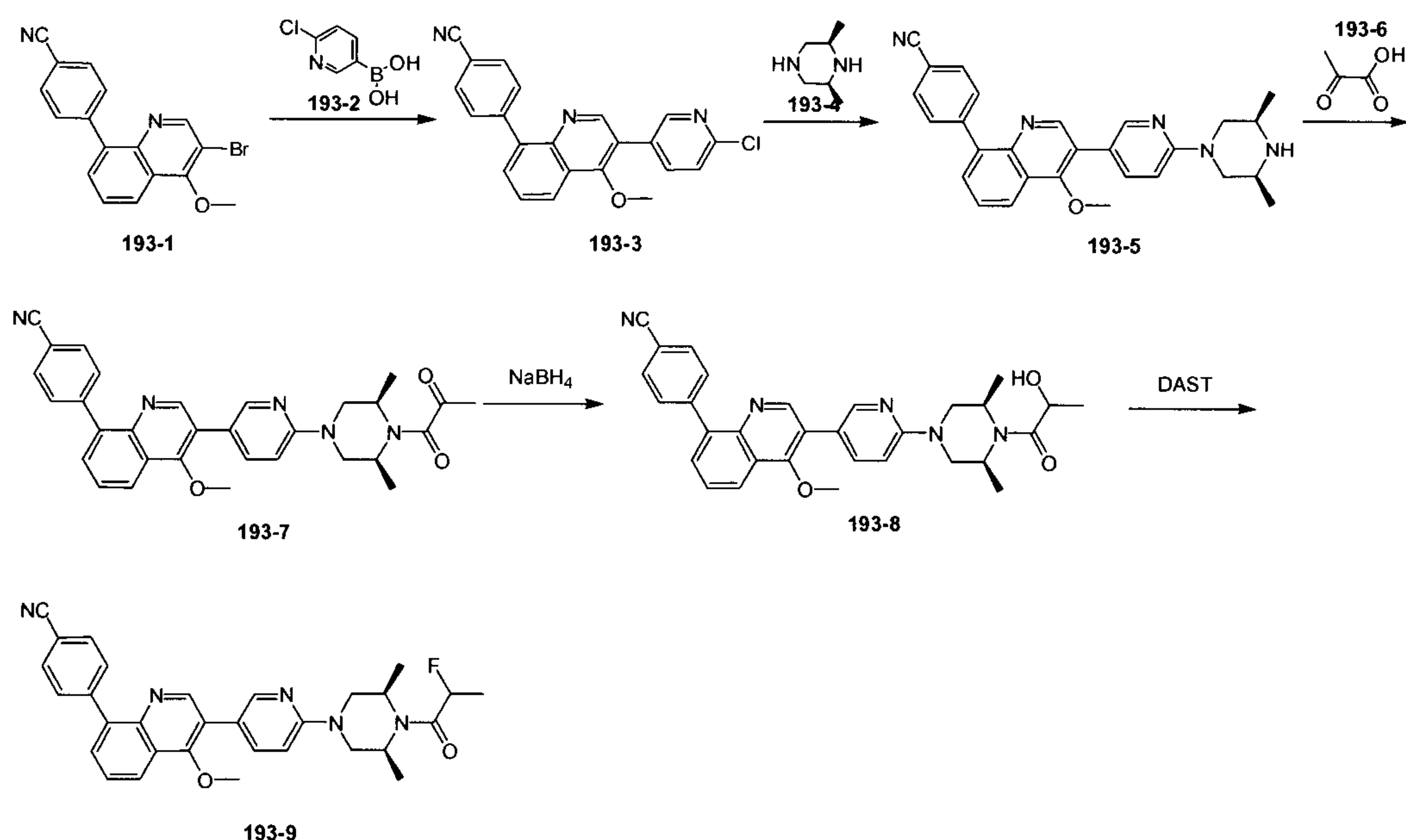
[444] Step 6: The title compound (50 mg, yield 28%) was synthesized according to the above-mentioned method as white solid. ¹H NMR (400MHz, CDCl₃) δ ppm 8.90 (s, 1H) 8.36-8.32 (m, 1H) 7.85-7.78 (m, 4H) 7.70-7.65 (m, 2H) 7.60-7.58 (d, *J*=8, 2H) 7.07-7.05 (d, *J*=8, 2H) 3.87-3.76(m, 1H) 3.72 (s, 3H) 3.642-3.52 (m, 3H) 2.73-2.68 (m, 1H) 2.55-2.49(m, 2H) 1.32-1.28 (m, 9H). **MS ESI** calcd for C₃₁H₃₁N₃O₃ [M+H]⁺ 494, found 494.

Embodiment 193



4-(3-(6-((3*S*, 5*R*)-4-(2-fluoropropanoyl)-3, 5-dimethylpiperazin-1-yl)pyridin-3-yl)-4-methoxyquinolin-8-yl)benzonitrile

Our Ref.: P1650132CA



[445] Step 1: Under nitrogen gas atmosphere, Pd (dppf)Cl₂ (1.7 g, 2 mmol) was added into a solution of compound 193-1 (8.0 g, 23.6 mmol), compound 193-2 (4.5 g, 28.3 mmol) and sodium carbonate (6.3 g, 59 mmol) in THF (160 mL) and H₂O (32 mL). The reaction mixture was heated to 80°C and stirred for 16h. The reaction mixture was cooled and extracted with EtOAc, the organic phase was dried over sodium sulfate and concentrated, the residue was purified by column chromatography to deliver pure compound 193-3 (8.51 g, yield 97%) as yellow solid. **MS ESI** calcd for C₂₂H₁₄ClN₃O [M+H]⁺ 372, found 372.

[446] Step 2: Under nitrogen gas atmosphere, Pd₂(dba)₃ (2.1 g, 2.3 mmol) was added into a solution of compound 193-3 (8.51 g, 23 mmol), compound 193-4 (2.88 g, 25 mmol), NaO^tBu (5.51 g, 57 mmol) and Xantphos (2.65 g, 4.6 mmol) in toluene (100 mL). The reaction mixture was heated to 130°C for 16h. The mixture was cooled, and extracted with EtOAc, the organic phase was dried over sodium sulfate and concentrated, the residue was purified by column chromatography to deliver compound 193-5 (4 g, yield 39%) as yellow solid. **MS ESI** calcd for C₂₈H₂₇N₅O [M+H]⁺ 450, found 450.

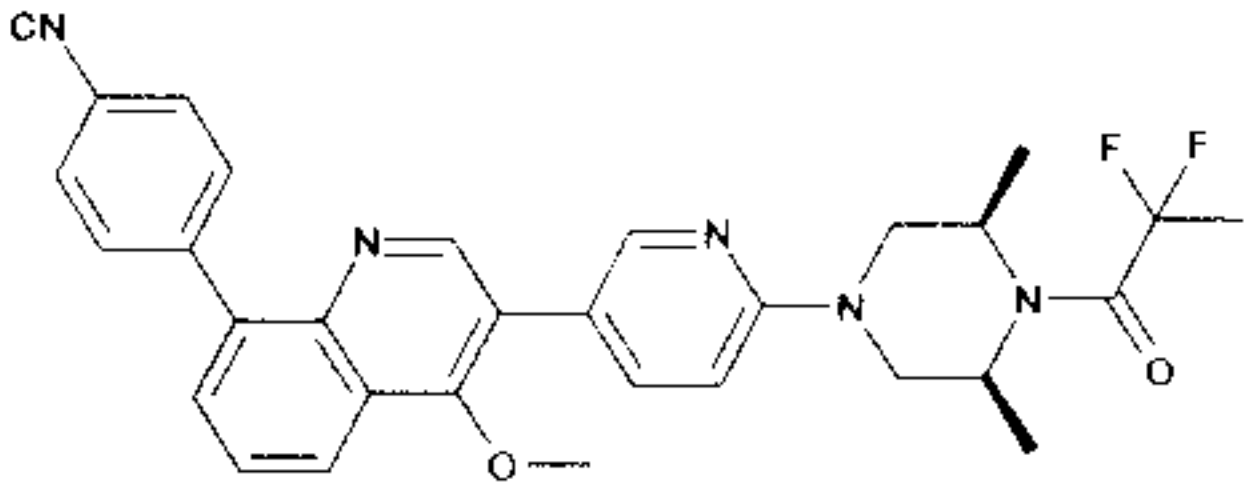
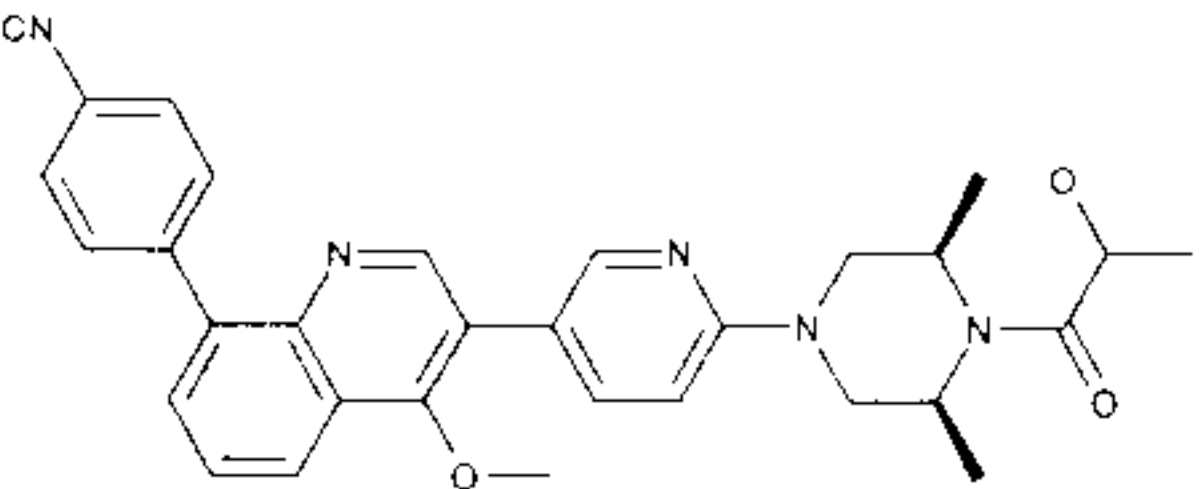
[447] Step 3: Compound 193-6 (294 mg, 3.34 mmol) and pyridine (440 mg, 5.57 mmol) were added into a solution of compound 193-5 (1 g, 2.23 mmol) and HATU (1.35 g, 3.56 mmol) in DCM (15 mL), the reaction mixture was stirred at reflux overnight. The residue was extracted with EtOAc and H₂O, the organic phase was dried over sodium sulfate and concentrated, the crude product was purified by column chromatography to deliver compound 193-7 (226 mg, yield 20%) as light yellow solid. **MS ESI** calcd for C₃₁H₂₉N₅O₃ [M+H]⁺ 520, found 520.

[448] Step 4: NaBH₄ (33 mg, 0.87 mmol) was added into a solution of compound 193-7 (226 mg, 0.44 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 1h, quenched with H₂O (2 drops). The mixture was dried over sodium sulfate and concentrated to dry. The residue was purified by preparative

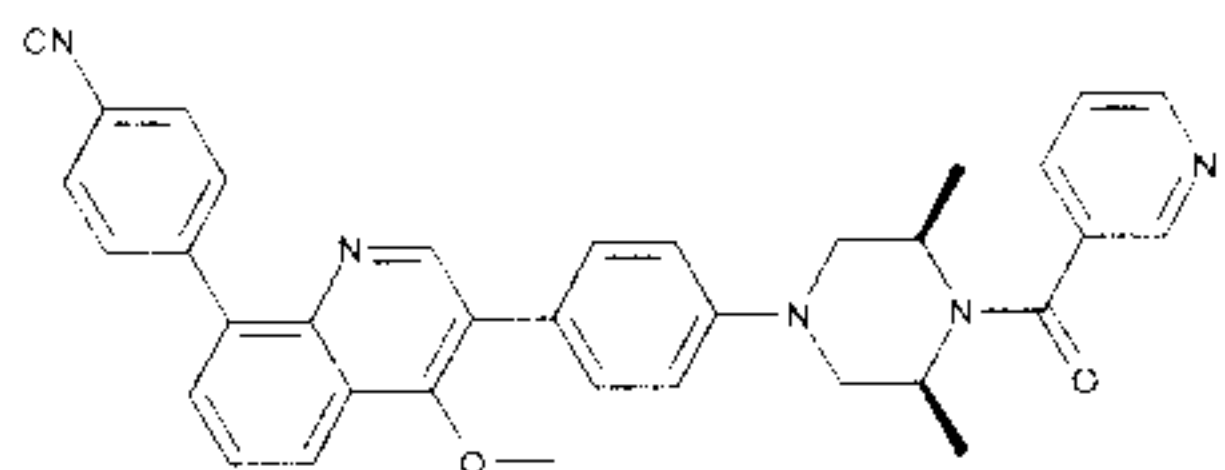
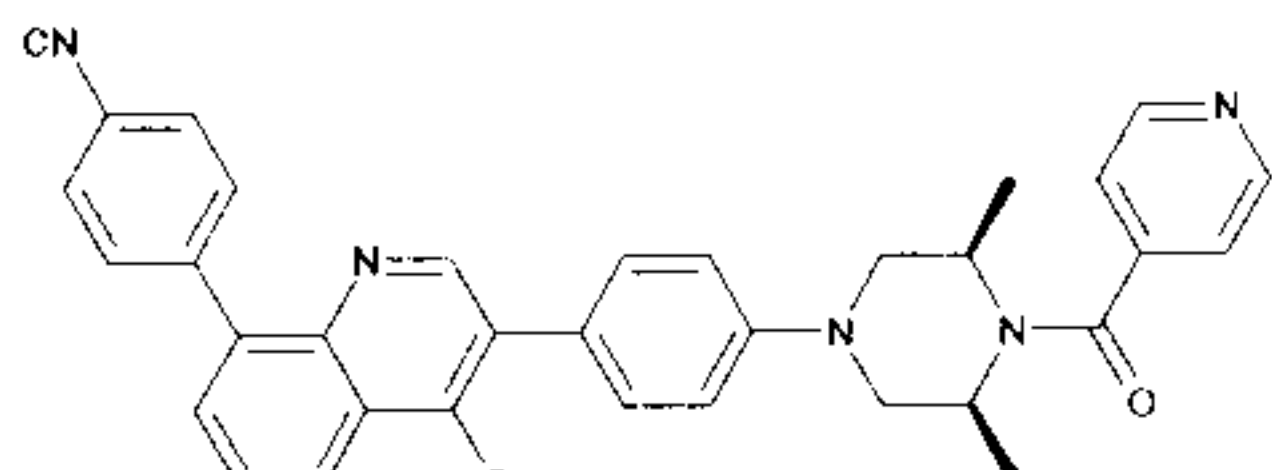
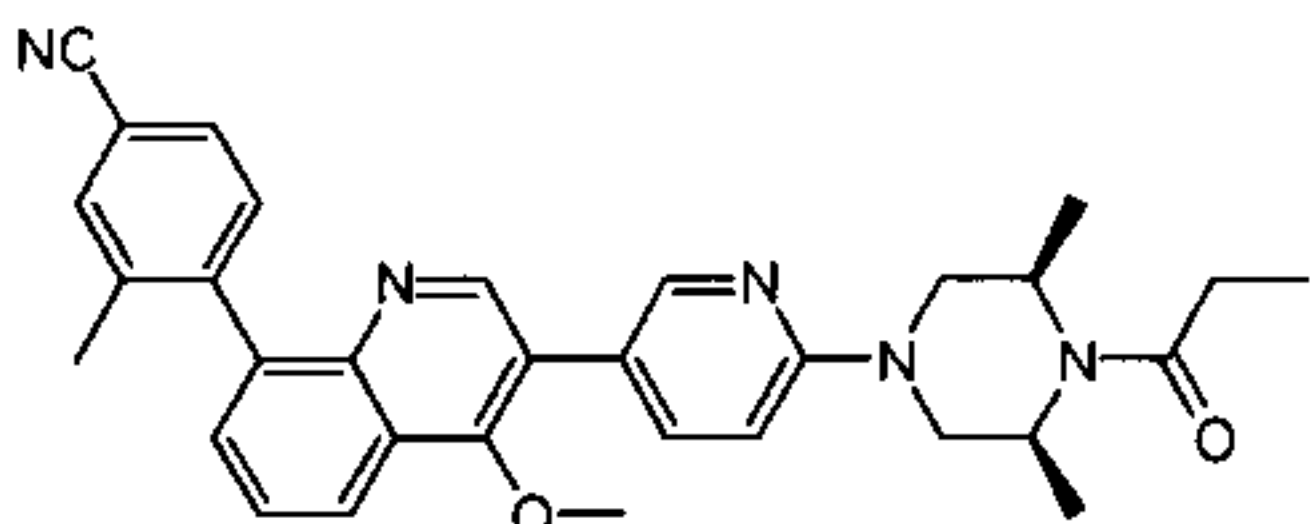
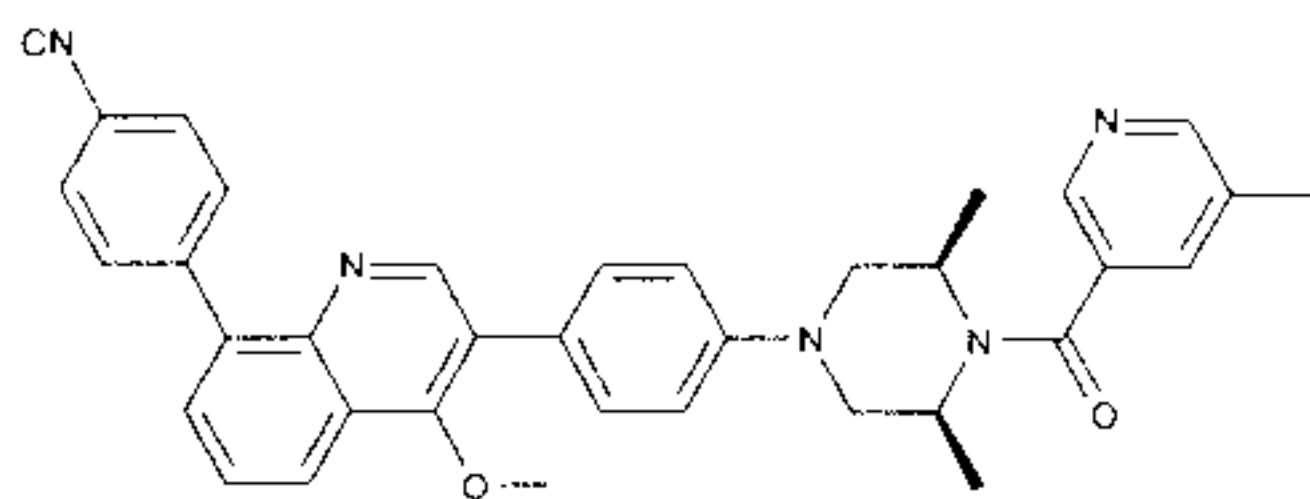
HPLC to deliver compound 193-8 (220 mg, yield 97%) as white solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.90 (s, 1H), 8.50 (d, *J*=4.0 Hz, 1H), 8.31 (s, 1H), 7.90-7.79 (m, 5H), 7.72-7.68 (m, 2H), 6.87-6.85 (d, *J*=8.0 Hz, 1H), 4.75-4.74 (m, 1H), 4.46-4.43(m, 2H), 4.22-4.19(m, 1H), 4.02-4.00(m, 1H), 3.83-3.81(m, 1H), 3.79 (s, 3H), 3.20-3.12 (m, 2H), 1.53-1.47(m, 3H), 1.43-1.40(m, 6H). **MS ESI** calcd for C₃₁H₃₁N₅O₃ [M+H]⁺ 522, found 522.

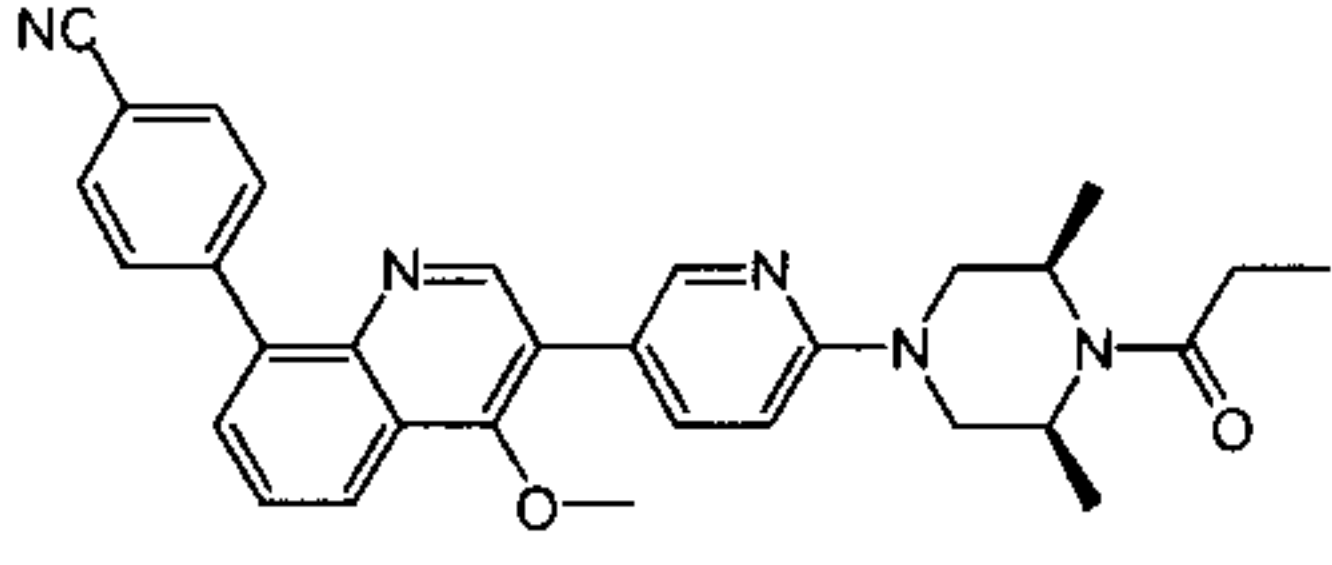
[449] Step 5: DAST (740 mg, 4.6 mmol) was added into a solution of compound 193-8 (120 mg, 0.23 mmol) in DCM (10 mL) at 0°C. The reaction mixture was stirred at room temperature for 1h, the mixture was diluted with DCM and washed with saturated sodium bicarbonate for 3 times, the organic phase was dried and concentrated, the residue was purified by preparative TLC to deliver the title compound (41 mg, yield 33%) as white solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.94 (s, 1H), 8.55 (s, 1H), 8.37 (d, *J*=8.0 Hz, 1H), 7.94-7.83 (m, 5H), 7.76-7.72 (m, 2H), 6.90 (d, *J*=8.4 Hz, 1H), 5.46-5.35 (m, 1H), 4.84 (brs, 1H), 4.51-4.21 (m, 3H), 3.83 (s, 3H), 3.36-3.19 (m, 2H), 1.72-1.64 (m, 3H), 1.53-1.45 (m, 6 H). **MS ESI** calcd for C₃₁H₃₀FN₅O₂ [M+H]⁺ 524, found 524.

[450] The compounds listed in table 18 were synthesized by compound 193-5 and corresponding acids.

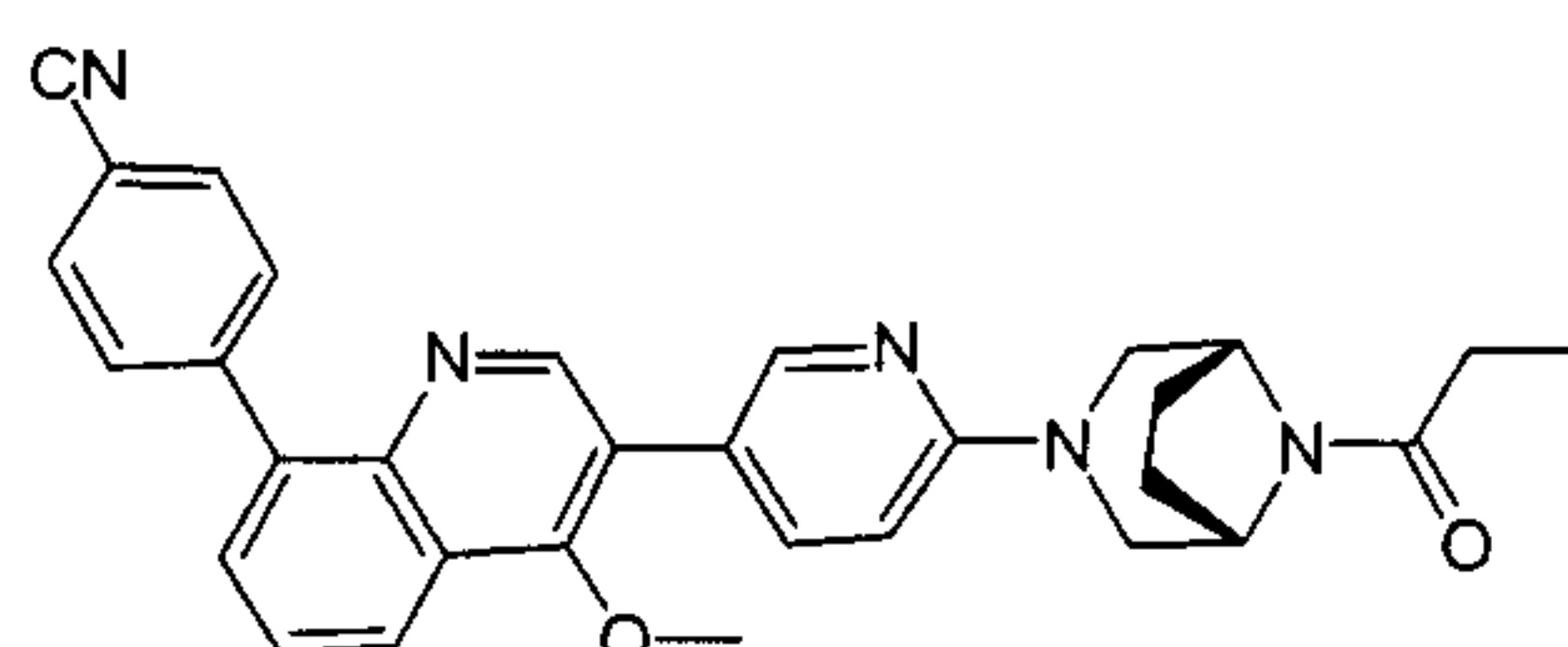
Embodiment	Structure	NMR
194		¹H NMR (400 MHz, CDCl ₃) δ 8.90 (s, 1H), 8.53-8.49 (m, 1H), 8.32 (d, <i>J</i> = 8.0 Hz, 1H), 7.89-7.79 (m, 5H), 7.72-7.68 (m, 2H), 6.83 (d, <i>J</i> = 8.0 Hz, 1H), 4.70 (s, 2H), 4.27-4.21 (m, 2H), 3.78(s, 3H), 3.35-3.20 (m, 2H), 1.95-1.85(m, 3H), 1.49(d, <i>J</i> = 6.4 Hz, 3H), 1.41(d, <i>J</i> = 6.4 Hz, 3H). MS ESI calcd for C ₃₁ H ₂₉ F ₂ N ₅ O ₂ [M+H] ⁺ 542, found 542.
195		¹H NMR (400 MHz, CDCl ₃) δ 8.90 (s, 1H), 8.50 (d, <i>J</i> =4.0 Hz, 1H), 8.31 (s, 1H), 7.90-7.79 (m, 5H), 7.72-7.68 (m, 2H), 6.87-6.85 (d, <i>J</i> =8.0 Hz, 1H), 4.75-4.74 (m, 1H), 4.46-4.43(m, 2H), 4.22-4.19(m, 1H), 4.02-4.00(m, 1H), 3.83-3.81(m, 1H), 3.79 (s, 3H), 3.20-3.12 (m,

		2H), 1.53-1.47(m, 3H), 1.43-1.40(m, 6H). MS ESI calcd for $C_{31}H_{31}N_5O_3$ $[M+H]^+$ 522, found 522.
196		^1H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.50 (d, $J=4.0$ Hz, 1H), 8.33 (d, $J=8.0$ Hz, 1H), 7.85-7.75 (m, 5H) 7.71-7.67 (m, 2H) 6.82 (d, $J=8.4$ Hz, 1H), 4.40-4.37 (m, 2H), 4.23-4.20(m, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 3.22-3.17(m, 2H) 1.36 (d, $J=6.8$ Hz, 6H). MS ESI calcd for $C_{30}H_{29}N_5O_3$ $[M+H]^+$ 508, found 508.
197		^1H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.50 (s, 1H), 8.33 (d, $J=8.0$ Hz, 1H), 7.90-7.78 (m, 5H), 7.74-7.66 (m, 2H), 6.85 (d, $J=8.4$ Hz, 1H), 3.79 (s, 1H), 3.21-3.16 (m, 2H), 1.43-1.26 (brs, 6 H). MS ESI calcd for $C_{31}H_{28}F_3N_5O_2$ $[M+H]^+$ 560, found 560.
198		^1H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.48 (s, 1H), 8.30 (d, $J = 8.0$ Hz, 1H), 7.87-7.77 (m, 5H), 7.72-7.64 (m, 2H), 6.83 (d, $J = 8.4$ Hz, 1H), 3.77 (s, 3H), 3.20-3.17 (m, 2H), 1.36 (brs, 6 H). MS ESI calcd for $C_{30}H_{30}N_6O_2$ $[M+H]^+$ 507, found 507.
199		^1H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.49 (s, 1H), 8.38 (d, $J = 8.0$ Hz, 1 H), 7.98 (d, $J = 6.8$ Hz, 1 H), 7.87-7.74 (m, 6 H), 7.11 (d, $J = 8.8$ Hz, 1 H), 4.65-4.30 (m, 4H), 3.81 (s, 1H), 3.25-3.16 (m, 2H), 1.56-1.47 (m, 6 H), 1.39 (d, $J = 6.8$ Hz, 3 H). MS ESI calcd for $C_{31}H_{32}N_6O_2$ $[M+H]^+$ 521, found 521.

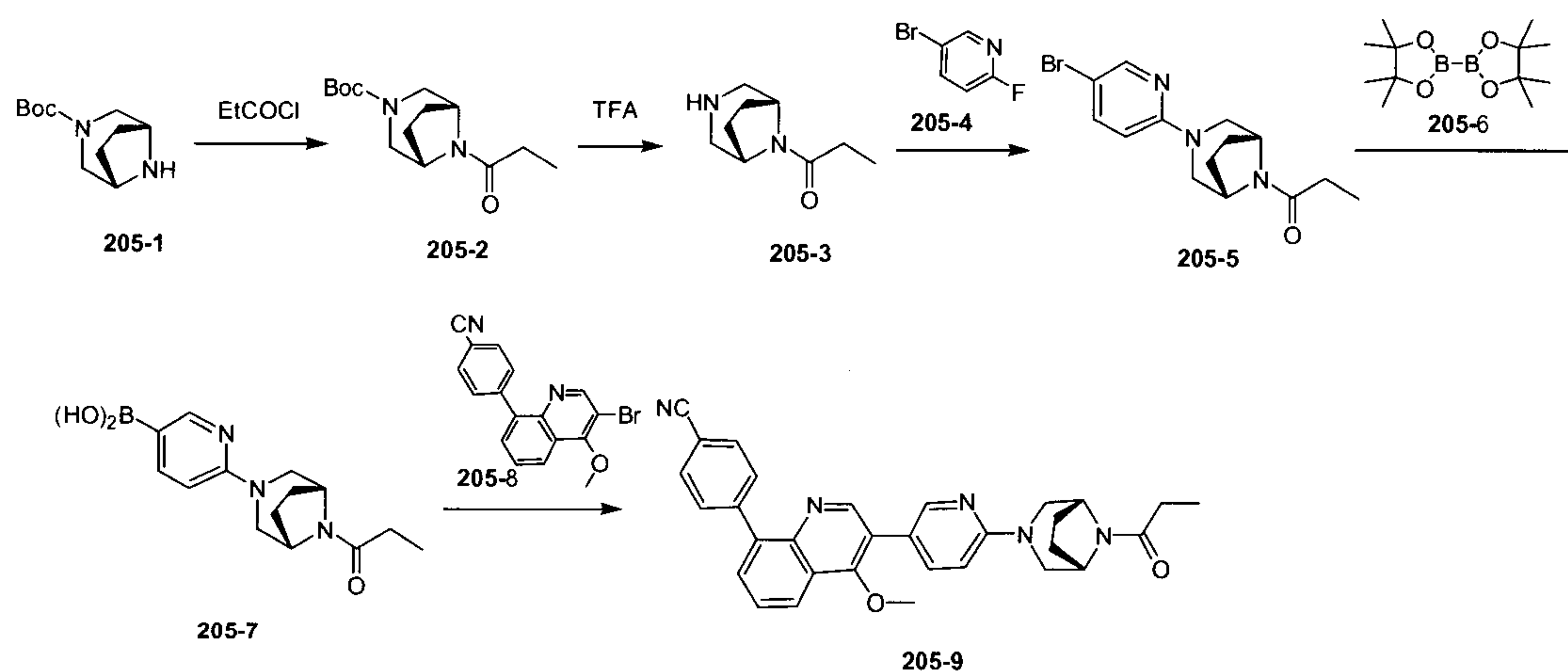
200		¹H NMR (400 MHz, CDCl ₃) δ 8.88 (s, 1H), 8.69 (s, 1H), 8.38 (d, <i>J</i> = 8.0 Hz, 1 H), 7.87-7.74 (m, 5 H), 7.70-7.54 (m, 4 H), 7.45-7.40 (m, 1 H), 7.04 (d, <i>J</i> = 8.4 Hz, 2 H), 4.49 (brs, 2H), 3.71 (s, 3H), 3.59-3.51 (m, 2H), 3.21-3.11 (m, 2H), 1.26 (d, <i>J</i> = 6.8 Hz, 6 H). MS ESI calcd for C ₃₅ H ₃₁ N ₅ O ₂ [M+H] ⁺ 554, found 554.
201		¹H NMR (400 MHz, CDCl ₃) δ 8.90 (s, 1H), 8.79-8.77 (m, 2H), 8.34 (d, <i>J</i> = 8.0 Hz, 1 H), 7.87-7.75 (m, 5 H), 7.70-7.55 (m, 4 H), 7.35-7.33 (m, 2 H), 7.06 (d, <i>J</i> = 8.4 Hz, 2 H), 3.76 (s, 3H), 3.59-3.56 (m, 2H), 3.11-3.01 (m, 2H), 1.52 (d, <i>J</i> = 6.8 Hz, 6 H). MS ESI calcd for C ₃₅ H ₃₁ N ₅ O ₂ [M+H] ⁺ 554, found 554.
202		¹H NMR (400 MHz, CDCl ₃) δ 8.83 (s, 1H), 8.47 (s, 1H), 8.30-8.32 (d, <i>J</i> = 7.6 Hz, 1H), 7.83-7.84 (d, <i>J</i> = 2.0 Hz, 1H), 7.53-7.65 (m, 4H) 7.39-7.40 (d, <i>J</i> = 7.2 Hz, 1H) 6.81-6.83 (d, <i>J</i> = 8.8 Hz, 1H) 4.65-4.85 (m, 2H), 4.08-4.18 (m, 2H) 3.79(s, 3H) 3.12-3.16 (d d, <i>J</i> = 4.0 Hz 2H), 2.41-2.43 (m, 2H) 2.12(s, 3H) 1.37-1.38 (d, <i>J</i> = 6.0 Hz 6H) 1.19-1.26 (m, 3H). MS ESI calcd for C ₃₂ H ₃₃ N ₅ O ₂ [M+H] ⁺ 520, found 520.
203		¹H NMR (400 MHz, CDCl ₃) δ 8.89 (s, 1H), 8.59-8.56 (m, 2H), 8.36 (d, <i>J</i> = 8.0 Hz, 1 H), 7.87-7.75 (m, 4 H), 7.70-7.58 (m, 5 H), 7.05 (d, <i>J</i> = 8.4 Hz, 2 H), 4.50 (brs, 2H), 3.74 (s, 3H), 3.59-3.54 (m, 2H), 3.13-3.00 (m, 2H), 2.41 (s, 3H), 1.51 (d, <i>J</i> = 6.8 Hz, 6 H). MS ESI calcd

		for C ₃₆ H ₃₃ N ₅ O ₂ [M+H] ⁺ 568, found 568.
204		¹ H NMR (400MHz, CDCl ₃) δ 8.89 (s, 1H), 8.48 (d, <i>J</i> =8.0 Hz, 1H), 8.30-8.33 (m, 1H), 7.78-7.85 (m, 5H), 7.67-7.71 (m, 2H), 6.83 (d, <i>J</i> =8.8 Hz, 1H), 4.85-4.80 (m, 2H), 4.15-4.10 (m, 2H), 3.78 (s, 3H), 3.13-3.17 (m, 2H), 2.46-2.41 (m, 2H), 1.38 (s, 6H), 1.21 (d, <i>J</i> =7.4 Hz, 3H). MS ESI calcd for C ₃₁ H ₃₁ N ₅ O ₂ [M+H] ⁺ 506, found 506.

Embodiment 205



4-(4-methoxy-3-(6-(8-propionyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)quinolin-8-yl)benzonitrile



[451] Step 1: K₂CO₃ (27.6 g, 0.2 mol) was added into a solution of compound 205-1 (100 mg, 0.47 mmol), propionyl chloride (87 mg, 0.94 mmol) in DCM (3 mL), after the reaction mixture was stirred at room temperature for 1h, the mixture was filtrated, the filtrate was concentrated to deliver 120 mg compound 205-2 as yellow oil (95%).

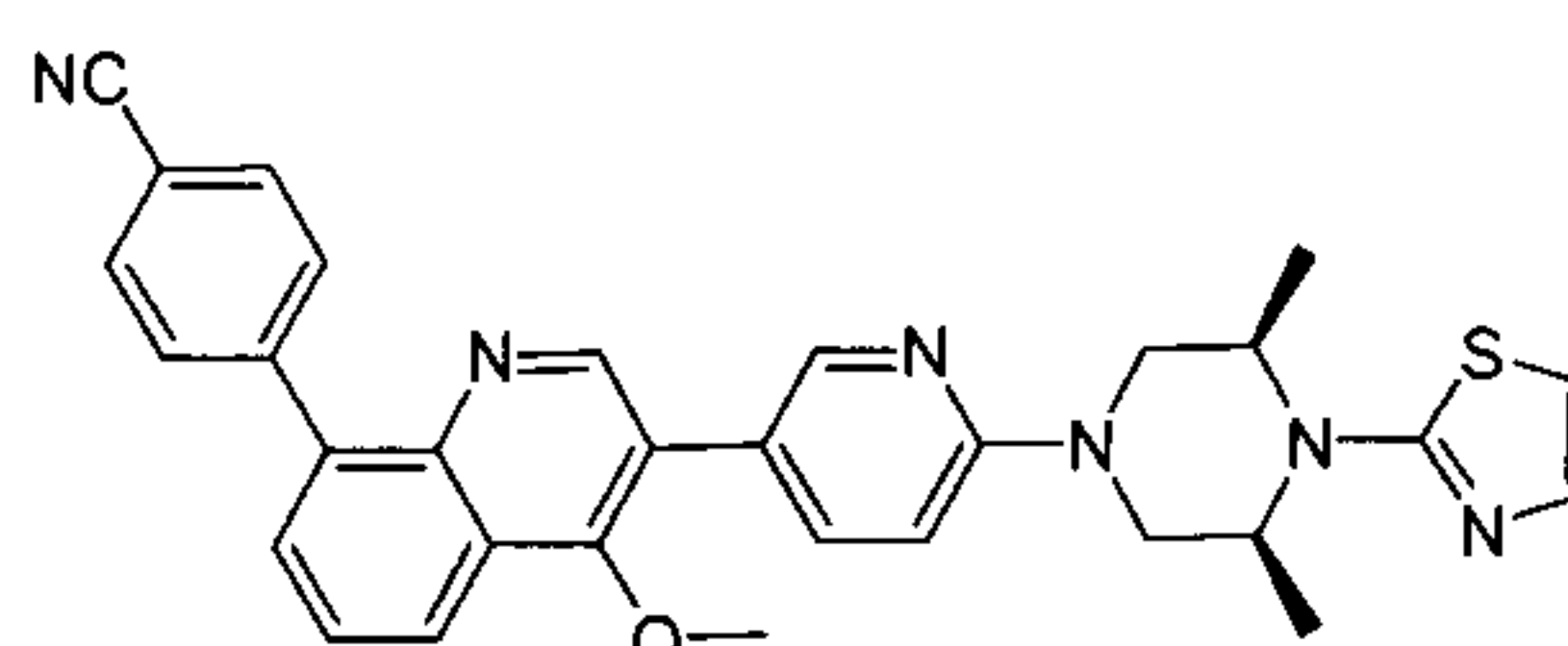
[452] Step 2: CF₃COOH (3 mL) was added dropwise into a solution of compound 205-2 (120 mg, 0.47 mmol) in DCM (6 mL), after the addtion, the reaction mixture was stirred at room temperature for 1h, then the solvent was evaporated to deliver 80 mg compound 205-3 as brown oil, yield 95%.

[453] Step 3: K_2CO_3 (100 mg, 0.8 mmol) was added into a solution of compound 205-3 (70 mg, 0.4 mmol) and compound 205-4 (73 mg, 0.4 mmol) in DMF (2 mL), then the mixture was stirred at 120°C for 2h, after cooling, the reaction mixture was poured into H_2O , and extracted with EtOAc (10 mL), the extraction liquid was washed with brines, dried over anhydrous sodium sulfate and concentrated under vacuum to deliver 40 mg compound 205-5 as white solid, yield 31%. **MS ESI** calcd for $C_{14}H_{18}BrN_3O$ $[M+H]^+$ 325, found 325.

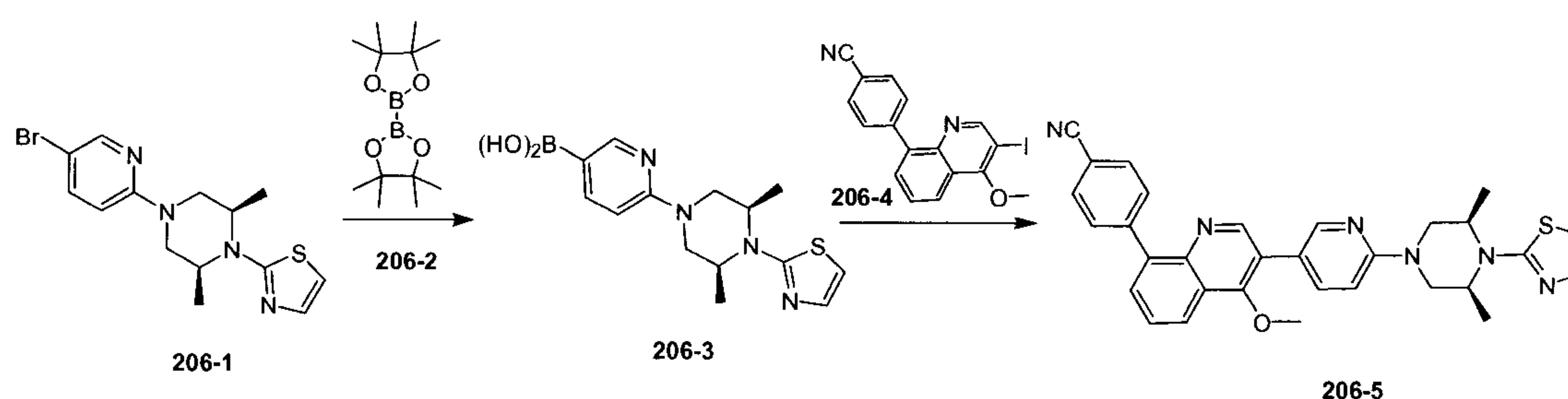
[454] Step 4: Compound 205-5 (33 mg, 0.1 mmol), compound 205-6 (50 mg, 0.2 mmol), $Pd(dppf)Cl_2$ (8 mg, 0.01 mmol) and potassium acetate (20 mg, 0.2 mmol) were added into 1,4-dioxane (2 mL), under nitrogen gas atmosphere, the reaction mixture was stirred at 110°C for 2h. The mixture was filtrated with diatomite, the filtrate was concentrated under vacuum. The residue was purified by column chromatography to deliver compound 205-7 (20 mg, yield 95%) as white solid. **MS ESI** calcd for $C_{14}H_{20}BN_3O_3$ $[M+H]^+$ 290, found 290.

[455] Step 5: The title compound (10 mg, yield 20%) was synthesized according to the above-mentioned method as white solid. **^1H NMR** (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.49-8.50 (d, $J=2.4$ Hz, 1H), 8.31-8.33 (m, 1H) 7.78-7.86 (m, 5H) 7.68-7.72 (m, 2H) 6.73-6.75 (d, $J=8.8$ Hz, 1H) 4.93-4.95 (d, $J=5.2$ Hz, 2H), 4.36-4.38 (d, $J=6.0$ Hz, 2H), 4.24-4.27 (m, 2H) 3.92-3.94 (m, 2H) 3.78(s, 3H) 3.12-3.25 (d d, $J=10.8$ Hz 2H) 2.38-2.47 (m, 2H) 1.95-2.03 (m, 4H) 1.22-1.25 (t, $J=14.8$ Hz 3H). **MS ESI** calcd for $C_{31}H_{29}N_5O_2$ $[M+H]^+$ 504, found 504.

Embodiment 206



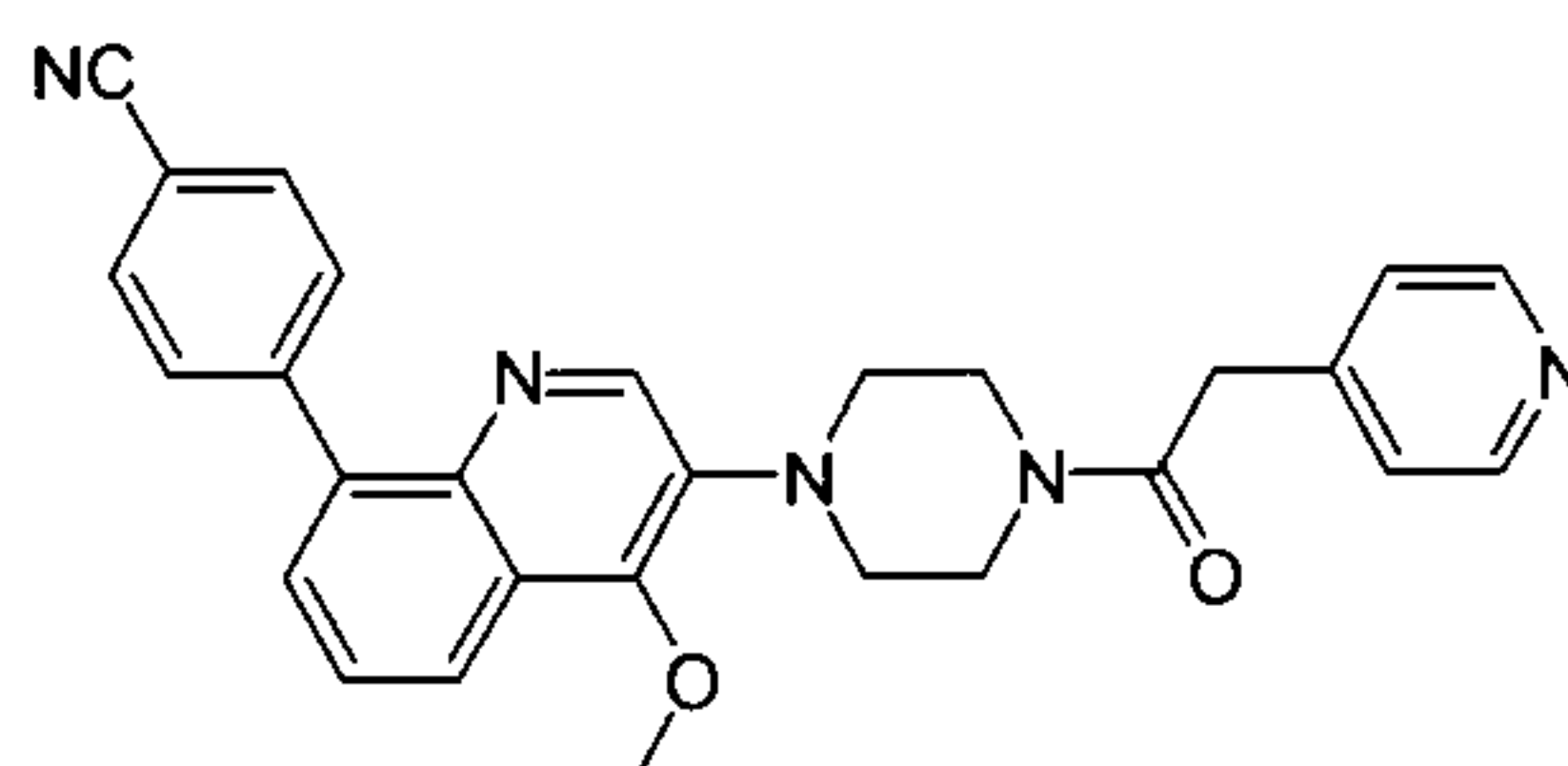
4-(3-(6-((3*S*,5*R*)-3,5-dimethyl-4-(thiazol-2-yl)piperazin-1-yl)pyridin-3-yl)-4-methoxyquinolin-8-yl)benzonitrile



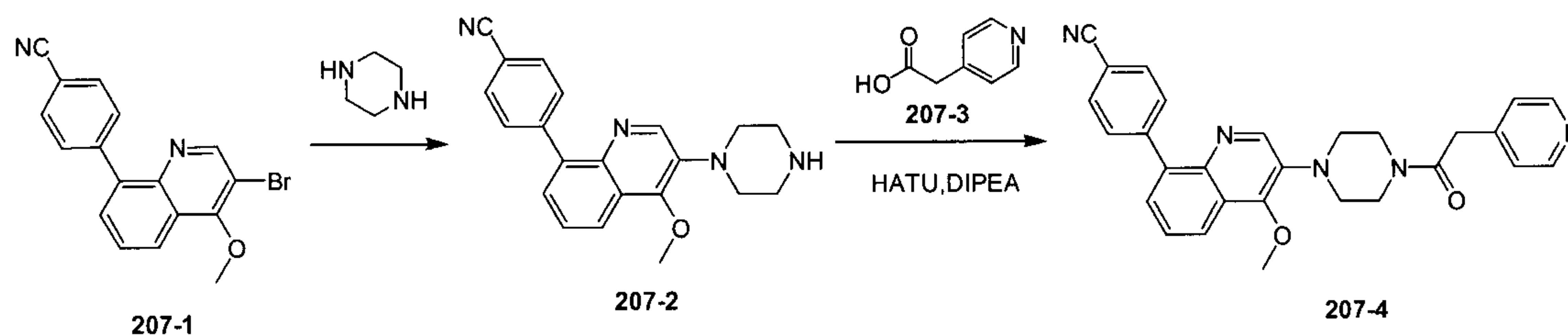
[456] Step 1: Under nitrogen gas atmosphere, $Pd(dppf)_2Cl_2$ (50 mg, 0.07 mmol) and KOAc (150 mg, 1.42 mmol) were added into a solution of compound 206-1 (250 mg, 0.71 mmol) and compound 206-2 (216 mg, 0.85 mmol) in dioxane (5 mL). The reaction mixture was stirred at 120°C for 4h, and used for the next step directly.

[457] Step 2: The title compound (30 mg, yield 12%) was synthesized according to the above-mentioned method as white solid. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.86 (s, 1H), 8.49 (s, 1H), 8.33 (d, $J = 8.0$ Hz, 1 H), 7.85-7.55 (m, 7 H), 7.23 (d, $J = 4.0$ Hz, 1 H), 6.87 (d, $J = 8.8$ Hz, 1 H), 6.57 (d, $J = 4.0$ Hz, 1 H), 4.33-4.28 (m, 4H), 3.78 (s, 3H), 3.35-3.30 (m, 2H), 1.43 (d, $J = 6.8$ Hz, 6 H). **MS ESI** calcd for $\text{C}_{31}\text{H}_{28}\text{N}_6\text{OS}$ $[\text{M}+\text{H}]^+$ 533, found 533.

Embodiment 207



4-(4-methoxy-3-(4-(2-(pyridin-4-yl)acetyl)piperazin-1-yl)quinolin-8-yl)benzonitrile

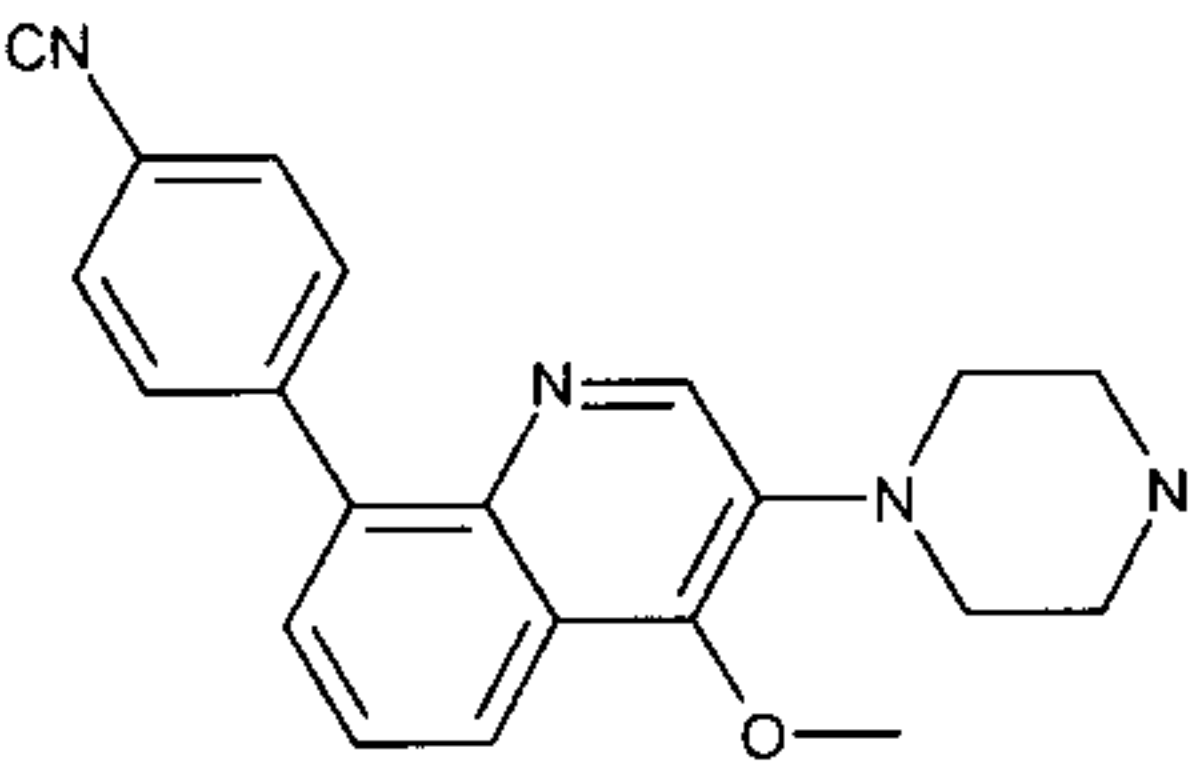
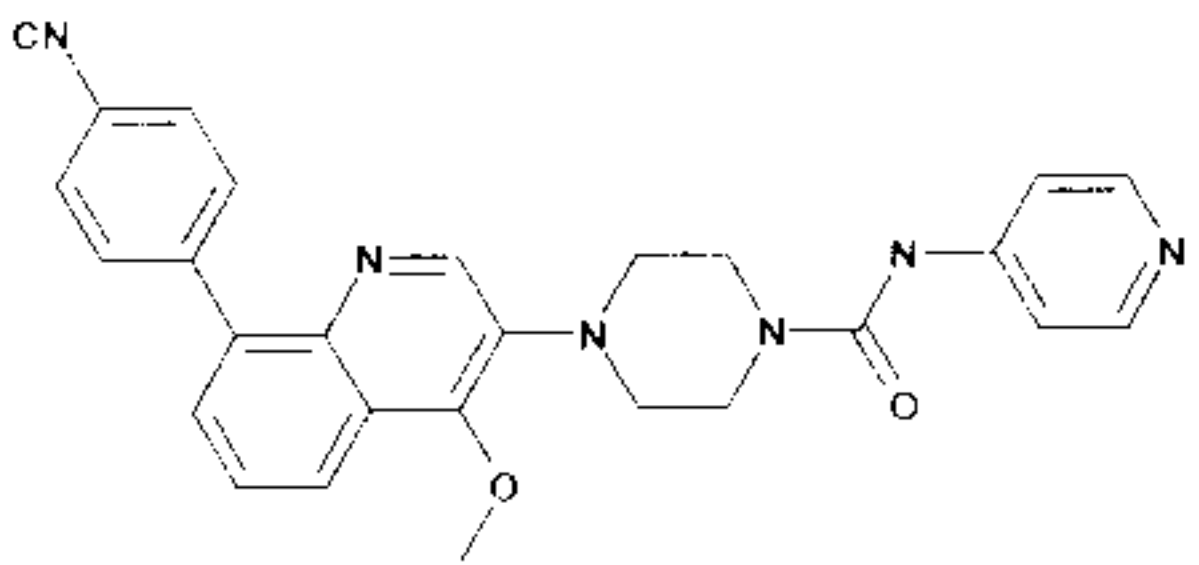
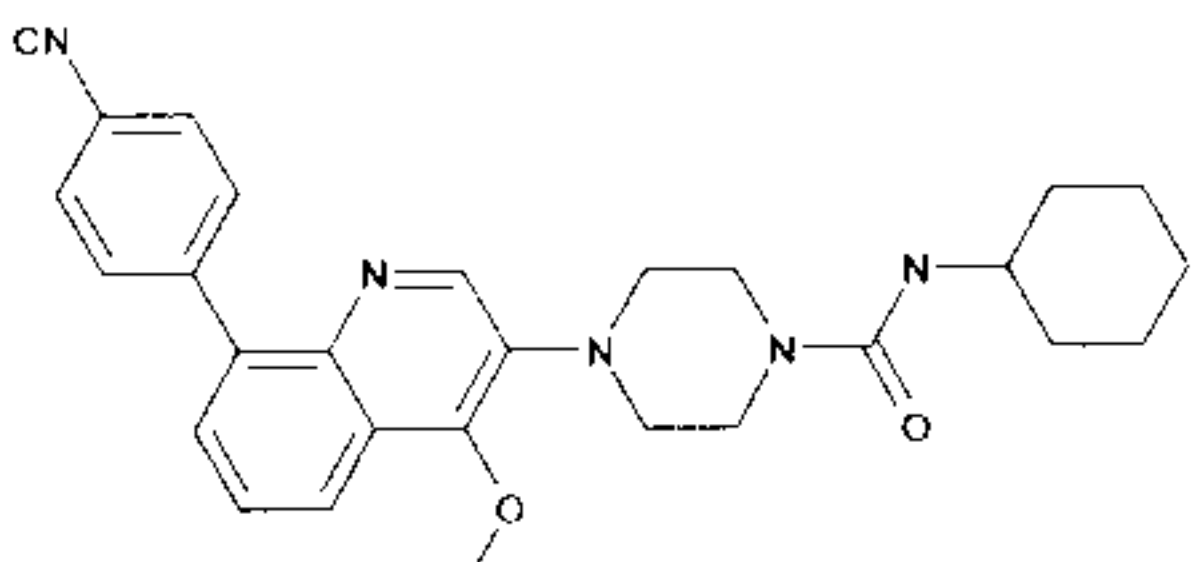
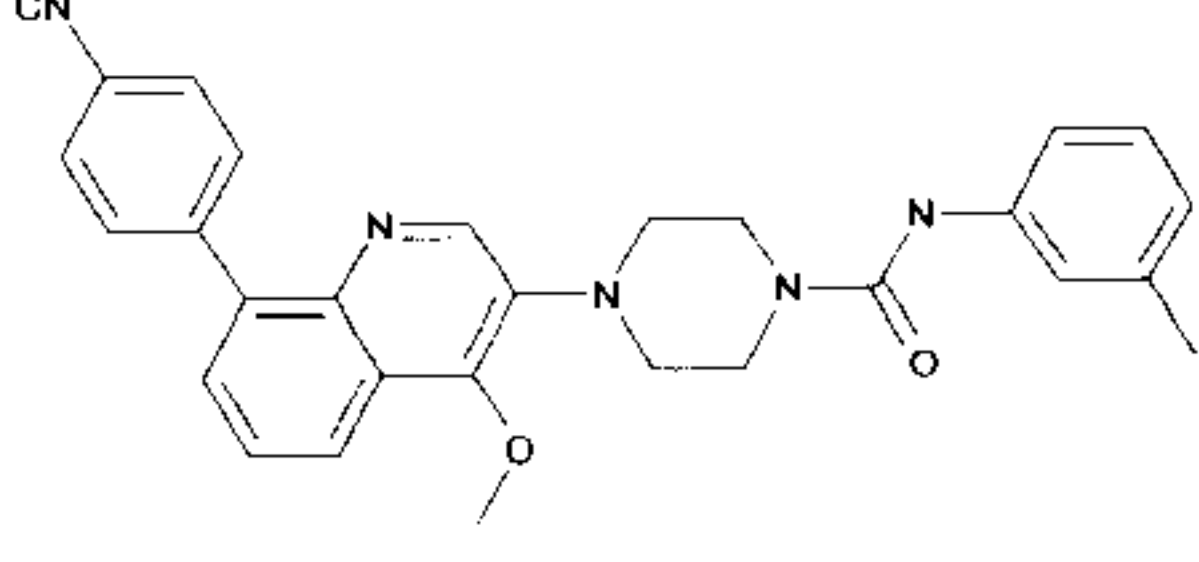
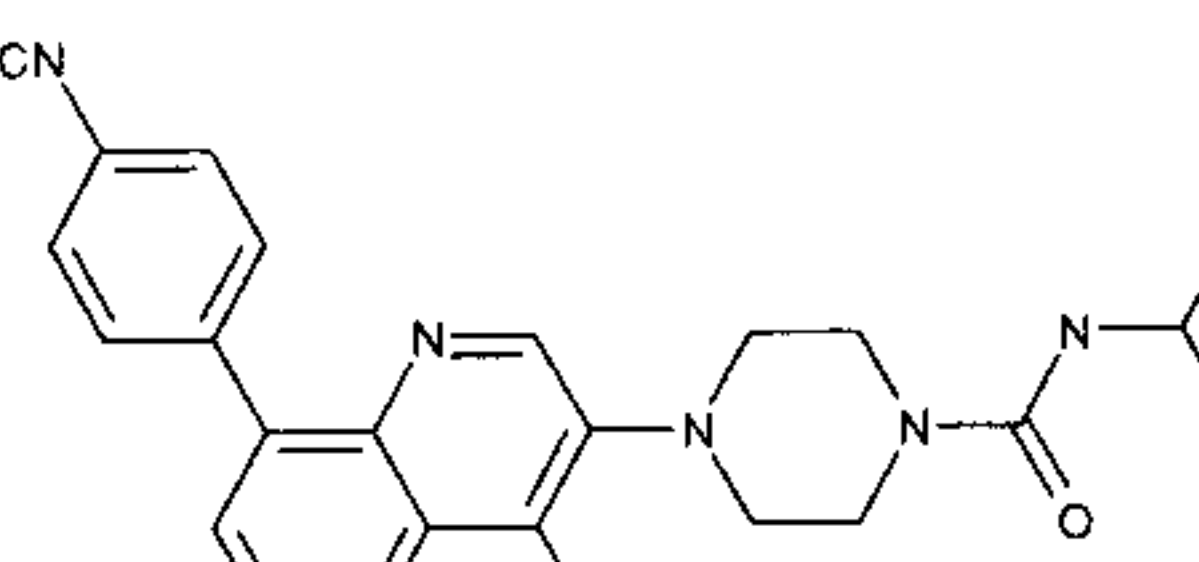


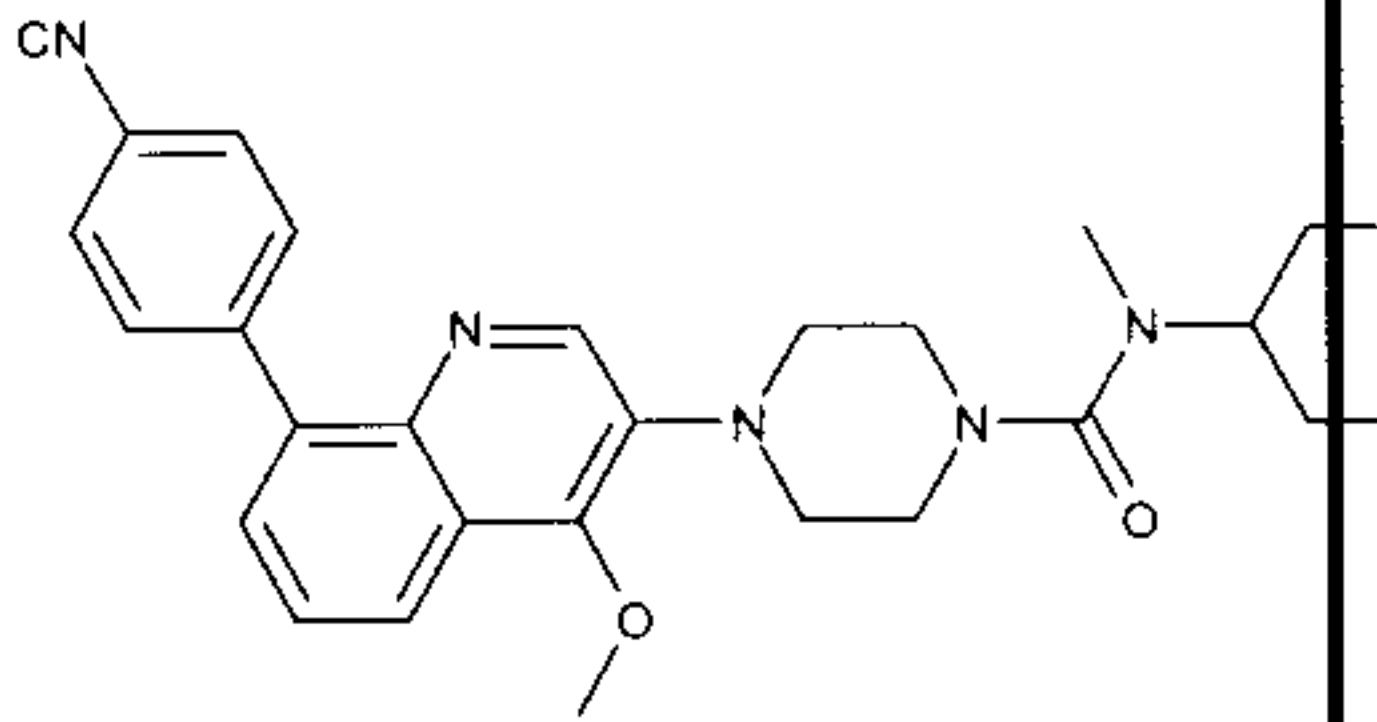
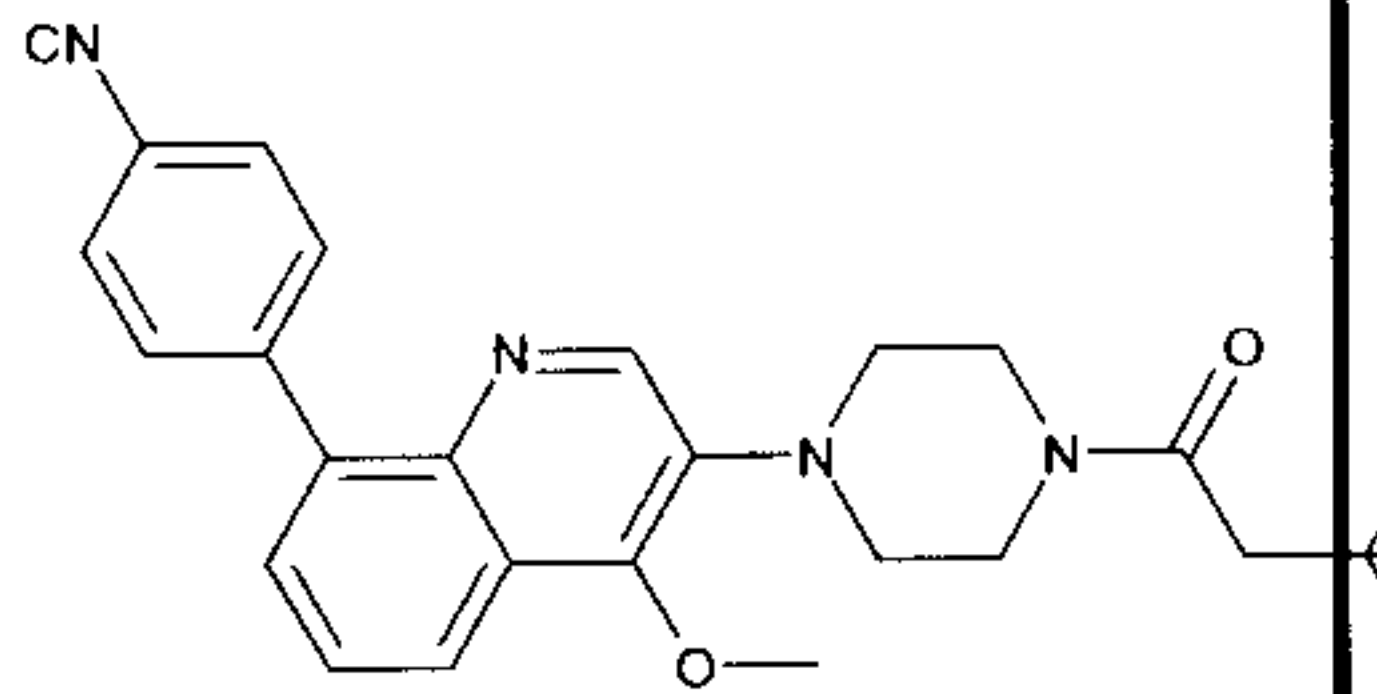
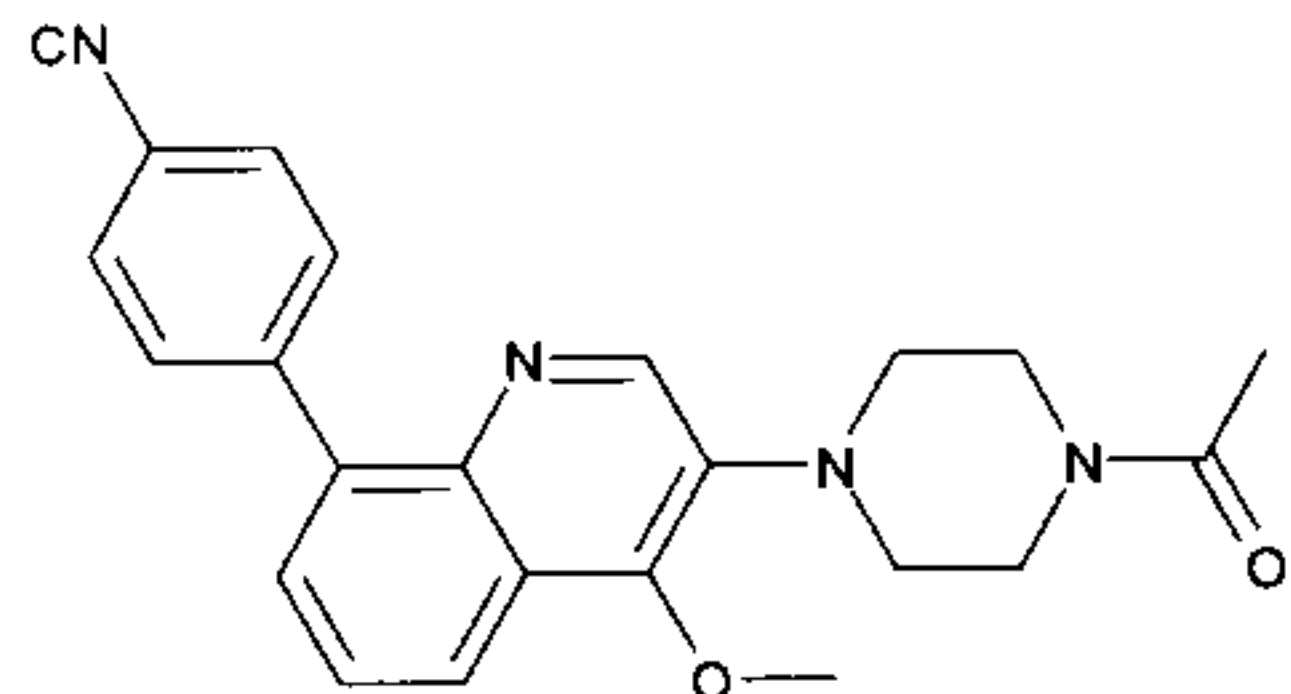
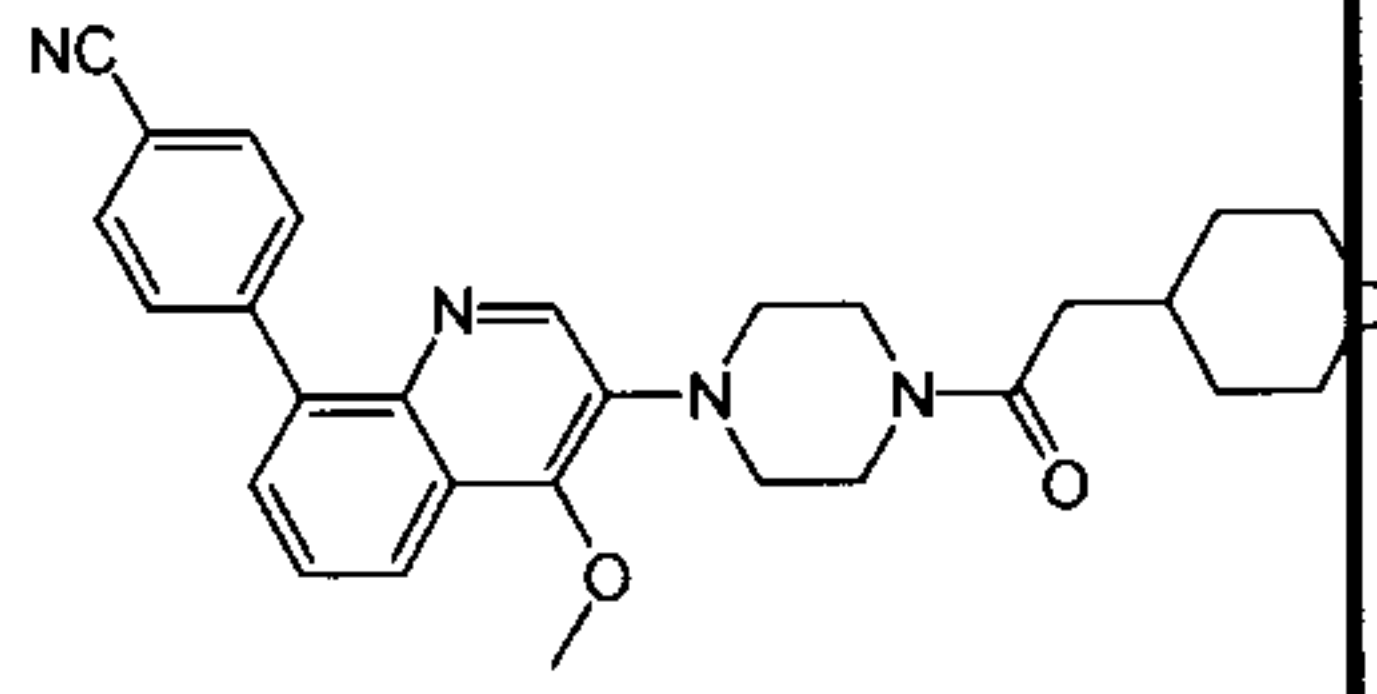
[458] Step 1: Under nitrogen gas atmosphere, sodium *tert*-butoxide (900 mg, 9 mmol), $\text{Pd}_2(\text{dba})_3$ (270 mg, 0.3 mmol) and Xantphos (350 mg, 0.6 mmol) were added into a solution of compound 207-1 (1 g, 3 mmol) and piperazine (270 mg, 3 mmol) in toluene (15 mL). The reaction mixture was stirred at 130°C for 3h. The mixture was concentrated under vacuum, the crude product was purified by column chromatography (EtOAc/methanol = 1:1) to deliver compound 207-2 (420 mg, yield 42%) as yellow solid. **MS ESI** calcd for $\text{C}_{21}\text{H}_{20}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$ 345, found 345.

[459] Step 2: DIPEA (260 mg, 2 mmol) and HATU (380 mg, 1 mmol) were added into a solution of compound 207-2 (69 mg, 0.2 mmol), compound 207-3 (144 mg, 1 mmol) in DMF. The mixture was stirred at room temperature for 30min, purified by preparative HPLC to deliver the title compound (20 mg, 21%) as white solid. $^1\text{H NMR}$ (400MHz, CDCl_3) δ 8.68 (s, 1H), 8.59 (d, $J = 8.0$ Hz, 2H), 7.75-7.73 (m, 4H), 7.61-7.59 (m, 2H), 7.24-7.22 (m, 2H), 4.09(s, 3H), 3.88-3.85 (m, 2 H), 3.80 (s, 2 H), 3.68-3.65 (m, 2 H), 3.28-3.25 (m, 2 H), 3.18-3.15 (m, 2 H). **MS ESI** calcd for $\text{C}_{28}\text{H}_{25}\text{N}_5\text{O}_2$ $[\text{M}+\text{H}]^+$ 464, found 464.

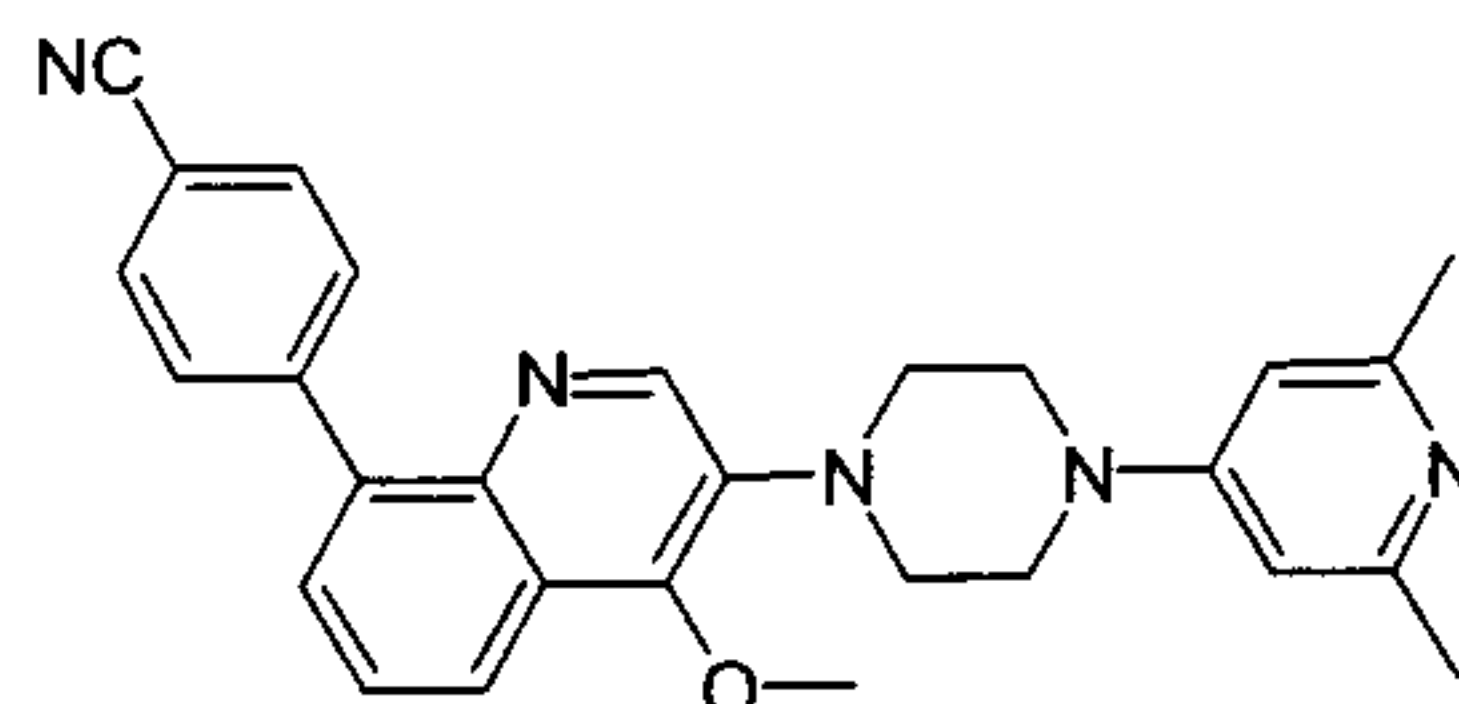
[460] The compounds listed in table 19 were synthesized by compound 207-2 and corresponding acids.

Embodiment	Structure	NMR
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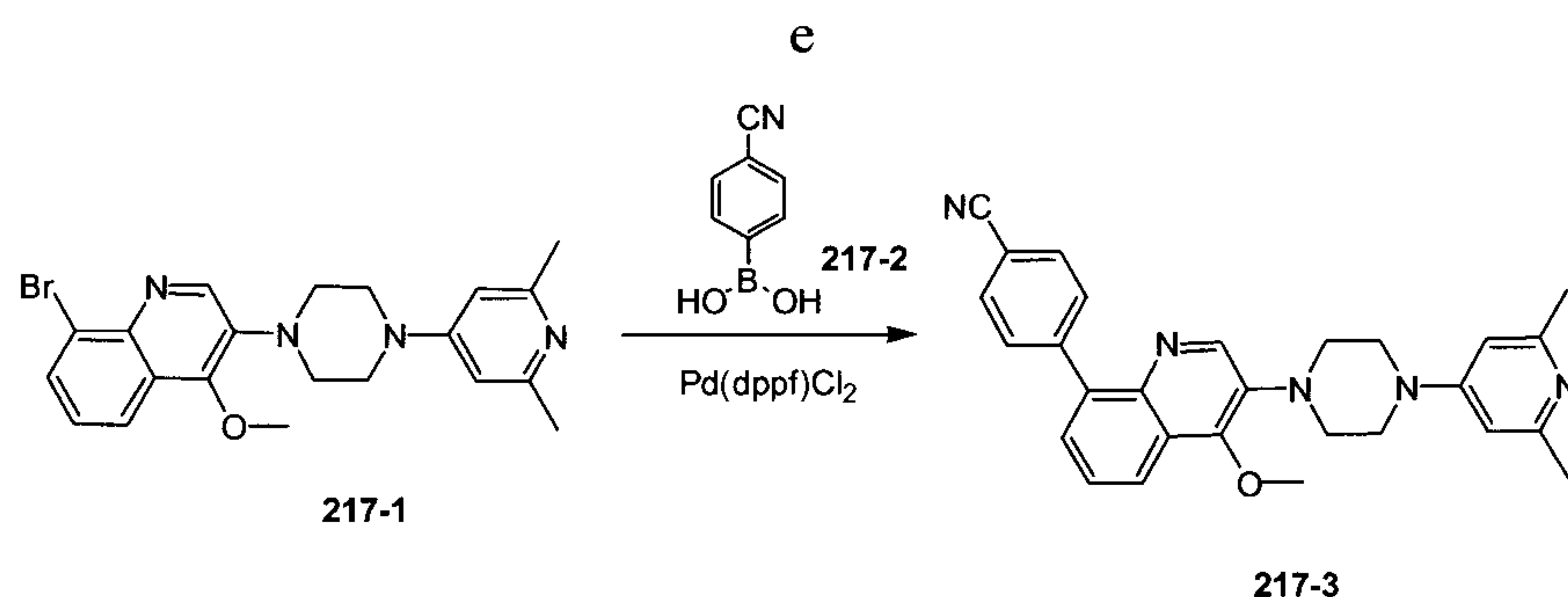
208		¹H NMR (400MHz, CDCl ₃) δ 8.74 (s, 1H), 8.20-8.17 (m, 1H), 7.76-7.73 (m, 4H), 7.58-7.54 (m, 2H), 4.11 (s, 3 H), 3.23 (t, <i>J</i> =4.4Hz, 4H), 3.10 (t, <i>J</i> =4.4Hz, 4H). MS ESI calcd for C ₂₁ H ₂₀ N ₄ O [M+H] ⁺ 345, found 345.
209		¹H NMR (400MHz, CDCl ₃) δ 8.73 (s, 1H), 8.51 (d, <i>J</i> = 8.0 Hz, 2H), 8.38 (d, <i>J</i> = 8.0 Hz, 1H), 8.01 (d, <i>J</i> = 8.0 Hz, 2H), 7.89 (d, <i>J</i> = 8.4 Hz, 2H), 7.80-7.74 (m, 4H), 4.36 (s, 3 H), 3.91 (t, <i>J</i> = 4.4 Hz, 4 H), 3.37 (t, <i>J</i> = 4.4 Hz, 4 H). MS ESI calcd for C ₂₇ H ₂₄ N ₆ O ₂ [M+H] ⁺ 465, found 465.
210		¹H NMR (400MHz, MeOD) δ 8.67 (s, 1H), 8.44-8.42 (m, 1H), 7.92 (d, <i>J</i> = 8.0 Hz, 2H), 7.84 (d, <i>J</i> = 8.0 Hz, 2H), 7.81-7.74 (m, 2H), 4.40 (s, 3 H), 3.66 (t, <i>J</i> = 4.4 Hz, 4 H), 3.29 (t, <i>J</i> = 4.4 Hz, 4 H), 1.97-1.91 (m, 2 H), 1.76-1.69 (m, 2 H), 1.60-1.50 (m, 1H), 0.91-0.67(m, 6 H). MS ESI calcd for C ₂₈ H ₃₁ N ₅ O ₂ [M+H] ⁺ 470, found 470.
211		¹H NMR (400MHz, MeOD) δ 8.74 (s, 1H), 8.54-8.52 (m, 1H), 8.00 (d, <i>J</i> = 8.0 Hz, 2H), 7.92 (d, <i>J</i> = 8.0 Hz, 2H), 7.81-7.74 (m, 2H), 7.23 (s, 1H), 7.17 (d, <i>J</i> = 8.4 Hz, 2H), 6.91-6.88 (m, 1H), 4.52 (s, 3 H), 3.84 (t, <i>J</i> = 4.4 Hz, 4 H), 3.29 (t, <i>J</i> = 4.4 Hz, 4 H), 2.32(s, 3 H). MS ESI calcd for C ₂₉ H ₂₇ N ₅ O ₂ [M+H] ⁺ 478, found 478.
212		¹H NMR (400MHz, CDCl ₃) δ 8.72 (s, 1H), 8.21 (d, <i>J</i> = 8.0 Hz, 2H), 7.78-7.73 (m, 4H), 7.59-7.53 (m, 2H), 4.38-4.36 (m, 1H), 4.09(s, 3H), 3.98-3.85(m, 3 H), 3.65-3.55(m, 6 H),

		3.39-3.30(m, 4 H), 1.97-1.94(m, 2 H) , 1.47-1.44(m, 2 H). MS ESI calcd for $C_{27}H_{29}N_5O_3$ $[M+H]^+$ 472, found 472.
213		^1H NMR (400MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.16 (d, $J= 8.0$ Hz, 2H), 7.73-7.70 (m, 4H), 7.57-7.51 (m, 2H), 4.01 (s, 3H), 3.99-3.89 (m, 3 H), 3.47-3.41 (m, 6 H), 3.30-3.27 (m, 4 H), 3.22 (s, 3H), 1.85-1.77 (m, 2 H) , 1.67-1.54 (m, 2 H). MS ESI calcd for $C_{28}H_{31}N_5O_3$ $[M+H]^+$ 486, found 486.
214		^1H NMR (400MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.20-8.17 (m, 1H), 7.76-7.70 (m, 4H), 7.59-7.56 (m, 2H), 5.02 (brs, 1H), 4.14 (s, 3 H), 3.87-3.85 (m, 2H), 3.76-3.68 (m, 2 H), 3.27-3.241 (m, 4 H), 2.51 (s, 2H), 1.37 (s, 6H). MS ESI calcd for $C_{26}H_{28}N_4O_3$ $[M+H]^+$ 445, found 445.
215		^1H NMR (400MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.21-8.18 (m, 1H), 7.78-7.74 (m, 4H), 7.59-7.56 (m, 2H), 4.11 (s, 3 H), 3.85-3.83 (m, 2H), 3.69-3.67 (m, 2H), 3.29-3.25 (m, 4H), 2.16 (s, 2 H). MS ESI calcd for $C_{23}H_{22}N_4O_2$ $[M+H]^+$ 387, found 387.
216		^1H NMR (400MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.11-8.16 (m, 1H), 7.52-7.68(m, 4H), 7.52-7.56(m, 2H), 4.06(s, 3H), 3.88-3.91 (m, 2H), 3.80 (s, 2H), 3.65 (s, 2H), 2.25-2.27 (m, 2H), 2.05-2.07(m, 1H), 1.63-1.66 (m, 2H), 1.27-1.34(m, 2H). MS ESI calcd for $C_{28}H_{30}N_4O_3$ $[M+H]^+$ 471, found 471.

Embodiment 217

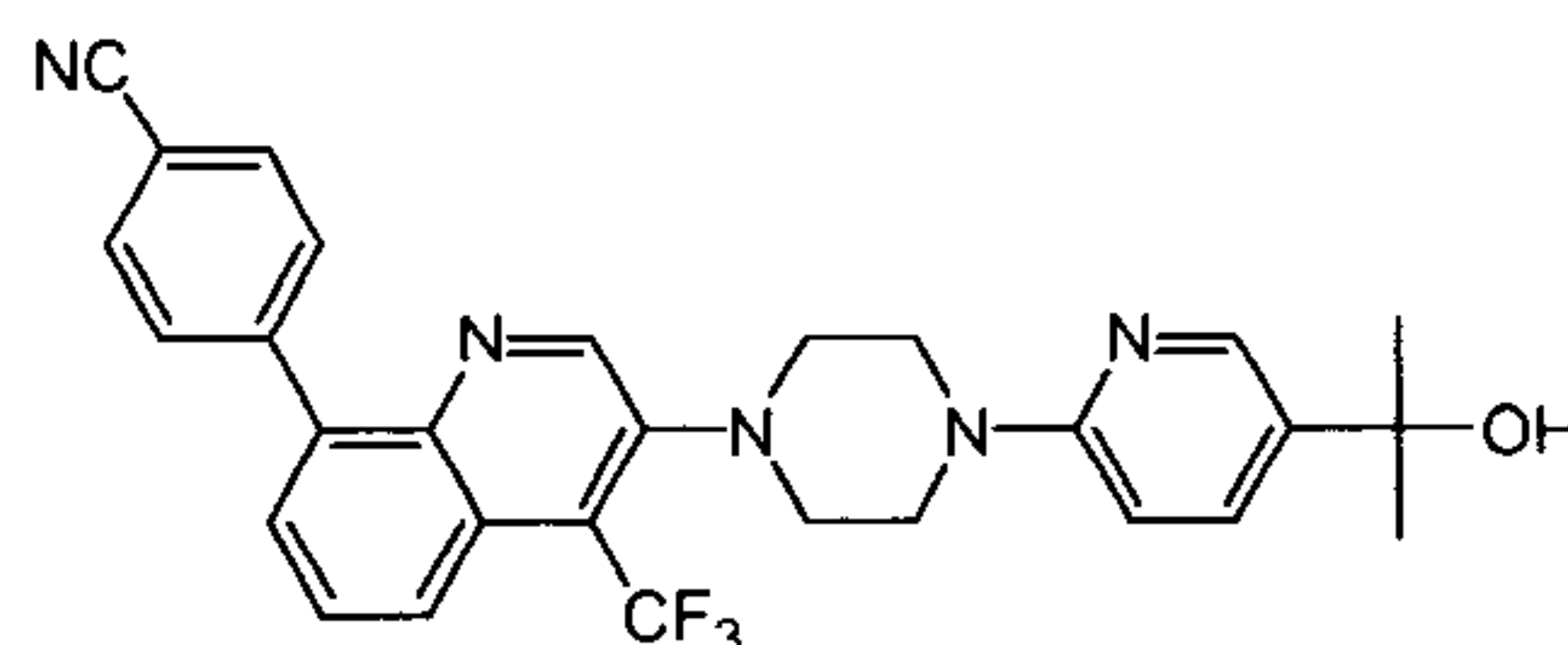


4-(3-(4-(2,6-dimethylpyridin-4-yl)piperazin-1-yl)-4-methoxyquinolin-8-yl)benzonitril



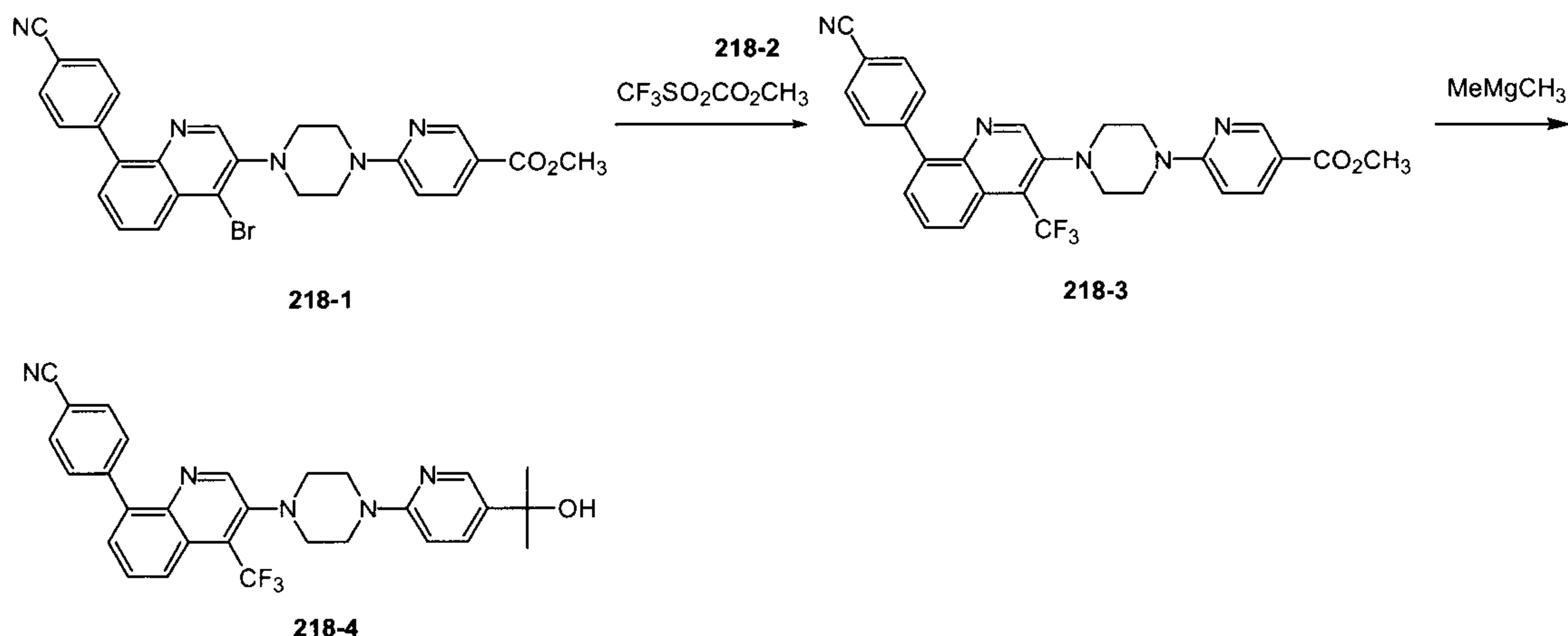
[461] Compound 217-1 (490 mg, 1.1 mmol), compound 217-2 (253 mg, 1.7 mmol), Pd(dppf)Cl₂ (81 mg, 0.11 mmol) and Na₂CO₃ (233 mg, 2.2 mmol) were added into THF/H₂O (10:1, 11 mL), under nitrogen gas atmosphere, the mixture was stirred at 80°C overnight. The mixture was filtrated with diatomite, the filtrate was washed with H₂O (50 mL) and extracted with EtOAc (100 mL), the extraction liquid was washed with brines and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by preparative HPLC to deliver the title compound (200 mg, yield 45%) as white solid. ¹H NMR (400MHz, CDCl₃) δ 8.93 (s, 1H), 8.31 (d, *J*= 8.0 Hz, 1H), 7.76-7.74 (m, 6H), 7.48-7.38 (m, 1H), 6.60 (s, 2H), 4.27 (s, 3H), 3.83 (s, 4H), 3.41 (s, 4H), 2.51 (s, 6H). MS ESI calcd for C₂₈H₂₇N₅O [M+H]⁺ 450, found 450.

Embodiment 218



4-(3-(4-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)piperazin-1-yl)-4-(trifluoromethyl)quinolin-8-yl)benzonitrile

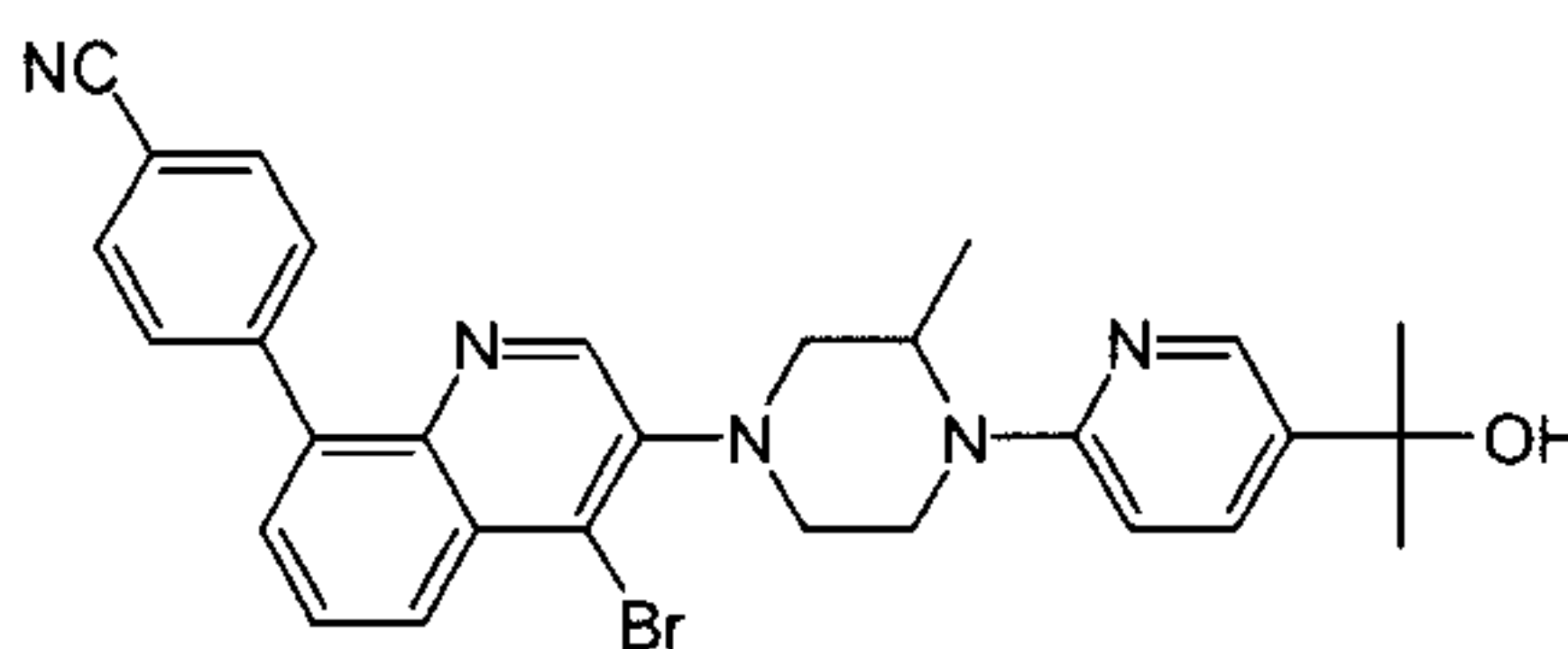
Our Ref.: P1650132CA



[462] Step 1: CuI (155 mg, 0.82 mmol) and KF (32 mg, 0.55 mmol) were added into a solution of compound 218-1 (300 mg, 0.55 mmol) and compound 218-2 (210 mg, 1.1 mmol) in DMF (10 mL). The suspension was stirred at 110°C for 3h, then poured into H₂O, extracted with EtOAc, dried over sodium sulfate and concentrated. The crude product was purified by column chromatography to deliver compound 218-3 as yellow solid (200 mg, yield 70%). **MS ESI** calcd for C₂₈H₂₂F₃N₅O₂ [M+H]⁺ 518, found 518.

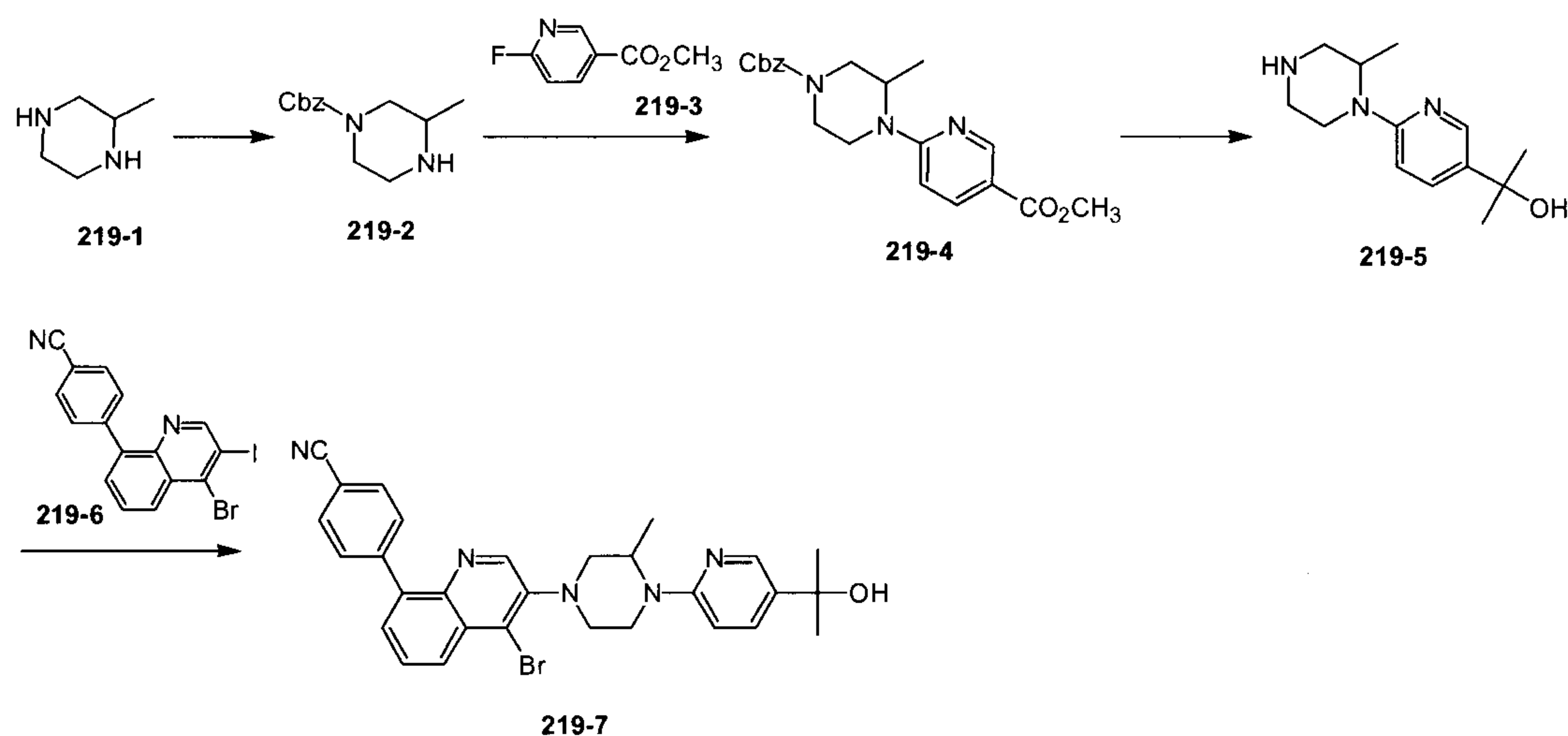
[463] Step 2: MeMgBr solution (3 M, 0.13 mL, 0.38 mmol) was added into a solution of compound 218-3 (200 mg, 0.38 mmol) in THF (20 mL) at 0°C. The mixture was stirred at 0°C for 2h, then poured into saturated ammonium chloride, extracted with EtOAc, dried over sodium sulfate and concentrated. The crude product was purified by preparative HPLC to deliver the title compound (30 mg, yield 15%) as yellow solid. **¹H NMR** (400MHz, CDCl₃) δ 8.96 (s, 1H), 8.36 (s, 1H), 8.22 (d, *J*= 8.0 Hz, 1H), 7.75-7.53 (m, 7H), 6.75-6.70 (m, 1H), 3.77 (t, *J*= 4.4 Hz, 4 H), 3.40 (t, *J*= 4.4 Hz, 4 H), 1.56(s, 6H). **MS ESI** calcd for C₂₉H₂₆F₃N₅O [M+H]⁺ 518, found 518.

Embodiment 219



4-(4-bromo-3-(4-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)-3-methylpiperazin-1-yl)
quinolin-8-yl)benzonitrile

Our Ref.: P1650132CA



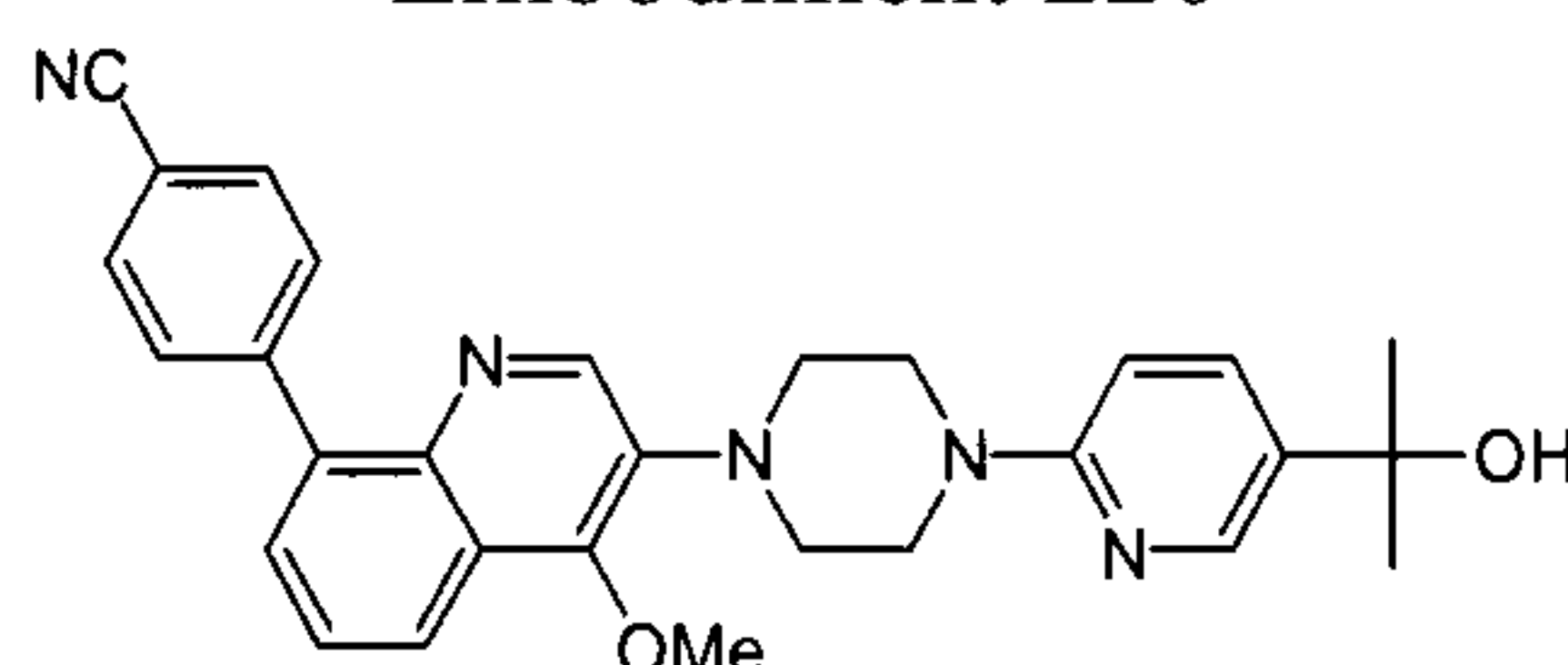
[464] Step 1: CbzCl (17 g, 0.1 mol) was added into a solution of compound 219-1 (30 g, 0.3 mol) and DIPEA (40 g, 0.3 mol) in DCM (200 mL) at 0°C, then the mixture was stirred at room temperature for 3h and the solvent was removed, the crude product was purified by column chromatography to deliver compound 2 (11 g, yield 47%) as yellow oil. **MS ESI** calcd for C₁₃H₁₈N₂O₂ [M+H]⁺ 235, found 235.

[465] Step 2: K₂CO₃ (4 g, 0.029mol) was added into a solution of compound 219-2 (2.25 g, 14.5 mmol) and compound 219-3 (3.41 g, 14.5 mmol) in DMF (10 mL). The mixture was stirred at 160°C for 4h, then poured into H₂O. The mixture was extracted with EtOAc, dried over anhydrous sodium sulfate and concentrated, the crude product was purified by column chromatography to deliver compound 219-4 (2.8 g, yield 52%). **MS ESI** calcd for C₂₀H₂₃N₃O₄ [M+H]⁺ 370, found 370.

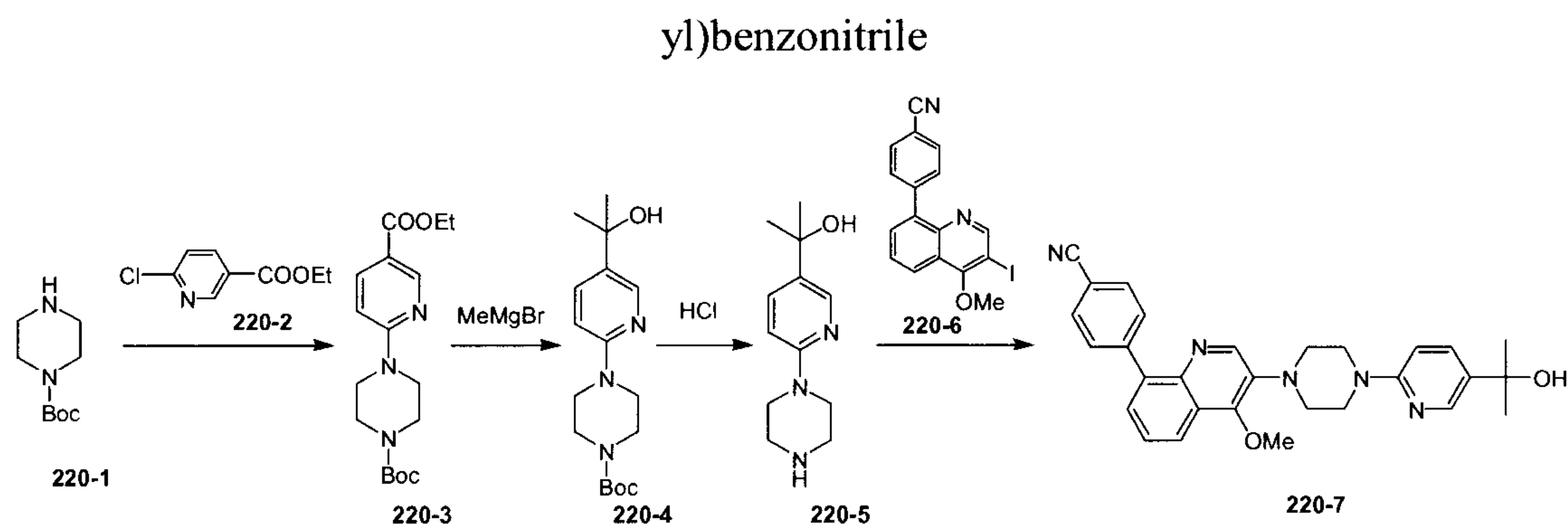
[466] Step 3: MeMgBr solution (3.3 mL, 11 mmol) was added slowly into a solution of compound 219-4 (370 mg, 1 mmol) in THF (10 mL) at 0°C. The mixture was stirred at 0°C for 1h, then heated to 80°C and stirred for 2h, then poured into a saturated ammonium chloride solution, the mixture was extracted with EtOAc, dried over anhydrous sodium sulfate and concentrated to deliver compound 219-5 (100 mg, yield 42%) as white solid. **MS ESI** calcd for C₁₃H₂₁N₃O [M+H]⁺ 236, found 236.

[467] Step 4: The title compound (120 mg, yield 23%) was synthesized according to the above-mentioned method as white solid. **¹H NMR** (400MHz, CDCl₃) δ 8.74 (s, 1H), 8.39-8.34 (m, 2H), 7.76-7.63 (m, 5H), 6.67-6.61 (m, 1H), 4.65 (brs, 1H), 4.22-4.19 (m, 1H), 3.62-3.32 (m, 4 H), 3.20-3.01 (m, 4 H), 1.60 (s, 6H), 1.47 (d, *J*=6.4 Hz, 3H). **MS ESI** calcd for C₂₉H₂₈BrN₅O [M+H]⁺ 542, found 542.

Embodiment 220



4-(3-(4-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)piperazin-1-yl)-4-methoxyquinolin-8-



[468] Step 1: A solution of compound 220-1 (5 g, 36.9 mmol), compound 220-2 (5.34 g, 28.8 mmol) and DIPEA (7mL, 40 mmol) in DME (30 mL) was heated to 130°C overnight in an autoclave. The mixture was diluted with EtOAc (200 mL), washed with 10% NaOH aqueous solution twice, citric acid and brines once respectively. The organic phase was dried over sodium sulfate and concentrated, the crude product was purified by silica gel column chromatography to deliver compound 220-3 (7.7 g, yield 85%) as yellow solid. ¹H NMR (400MHz, CDCl₃) δ 8.81 (s, 1H) 8.04 (d, *J*=12.0 Hz, 1H) 6.59 (d, *J*=8.0 Hz, 1H) 4.37-4.31 (m, 2H) 3.70-3.67 (m, 4H) 3.56-3.54 (m, 4H) 1.49 (s, 9H) 1.39-1.36 (m, 3 H). MS ESI calcd for C₁₇H₂₅N₃O₄ [M+H]⁺ 336, found 336.

[469] Step 2: MeMgBr solution (24 mL, 71.6 mmol) was added dropwise into a solution of compound 220-3 (6 g, 17.9 mmol) in THF (80 mL) and the mixture was stirred at room temperature for 3h. The reaction mixture was quenched with saturated ammonium chloride (10 mL) and extracted with EtOAc (200 mL). The organic phase was dried over sodium sulfate and concentrated. The crude product was purified by column chromatography to deliver pure compound 220-4 (4.3 g, yield 74%) as yellow solid. ¹H NMR (400MHz, CDCl₃) δ 8.30 (s, 1H) 7.68-7.60 (m, 1H) 6.64 (d, *J*= 8.0 Hz, 1H) 3.54-3.52 (m, 8H) 1.57 (s, 6H) 1.49 (s, 9H). MS ESI calcd for C₁₇H₂₇N₃O₃ [M+H]⁺ 322, found 322.

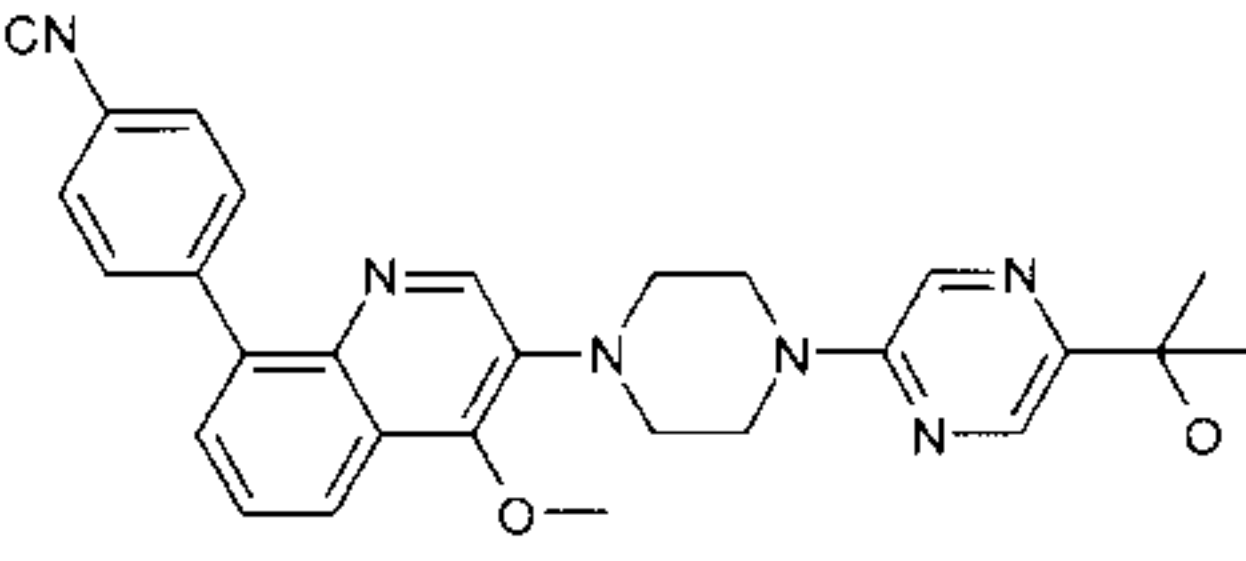
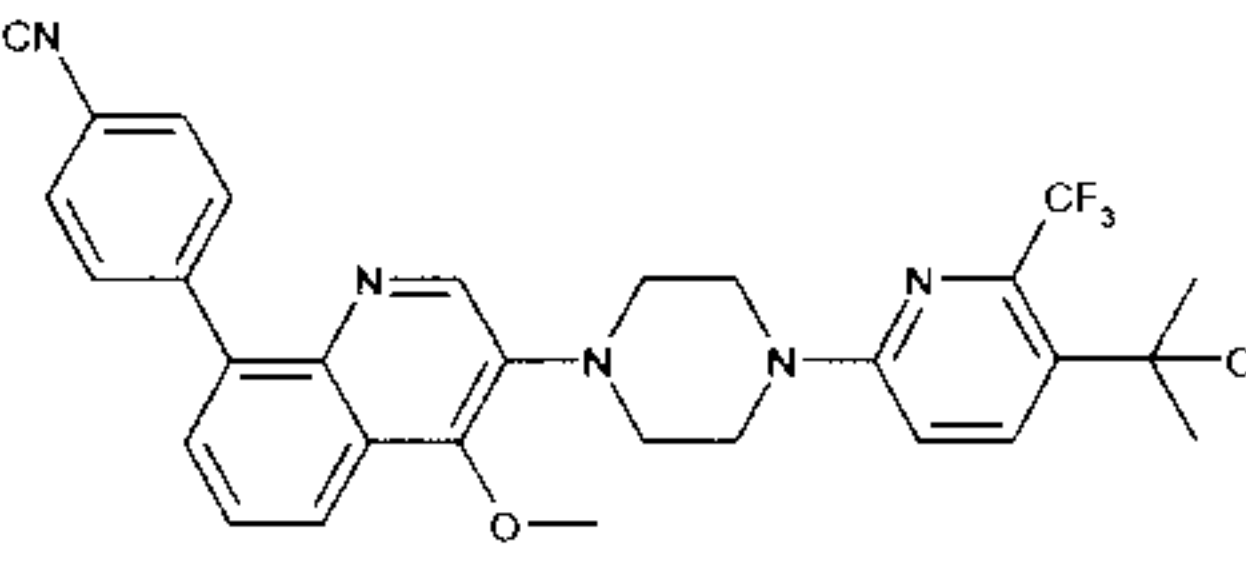
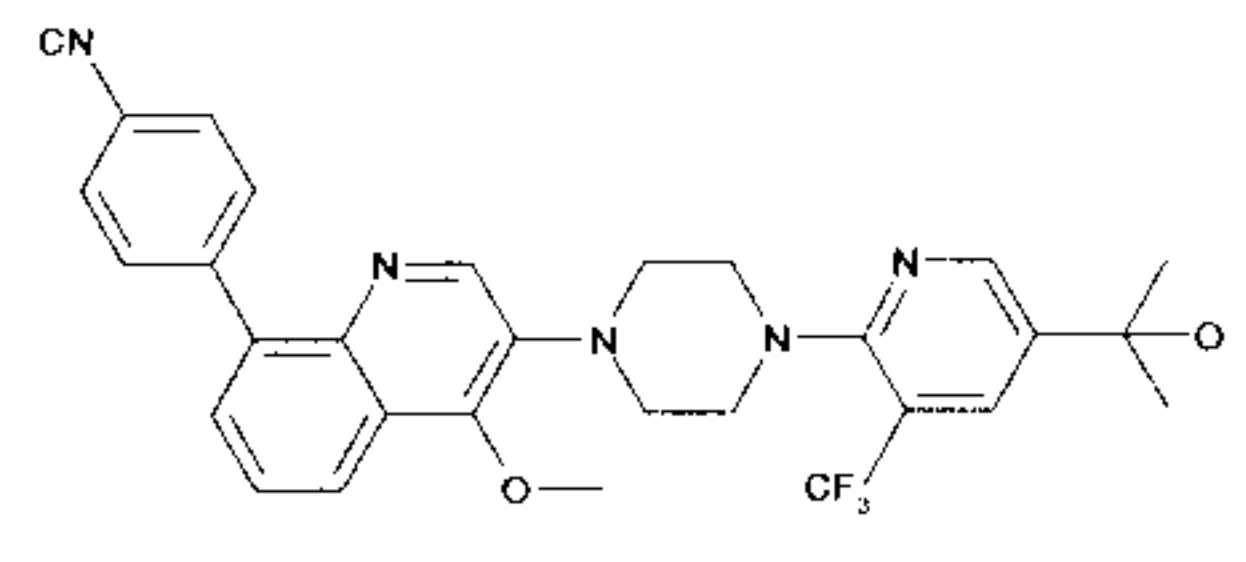
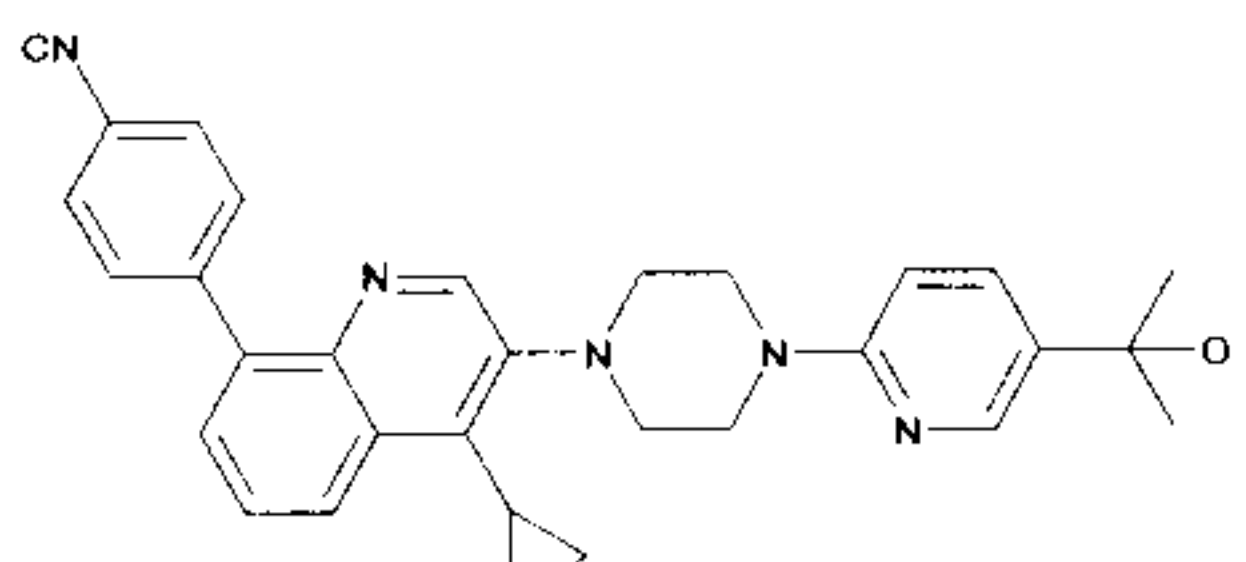
[470] Step 3: CF₃COOH (15 mL) was added into a solution of compound 220-4 (3 g, 9.33 mmol) in DCM (30 mL). Then the mixture was stirred at room temperature for 30min. NaOH (6 M) was added to basify the mixture to pH = 9, then the mixture was extracted with CHCl₃ for 3 times. The combined organic phase was dried over sodium sulfate and concentrated. The crude product was purified by column chromatography to deliver compound 220-5 (1.6 g, yield 75%) as light yellow solid. ¹H NMR (400MHz, CDCl₃) δ 8.22 (s, 1H) 7.71-7.68 (m, 1H) 6.80-6.75 (m, 1H) 3.47-3.40 (m, 4H) 2.94-2.88 (m, 4H), 1.51 (s, 6H). MS ESI calcd for C₁₂H₁₉N₃O [M+H]⁺ 222, found 222.

[471] Step 4: The title compound (21 mg, yield 11%) was synthesized according to the above-mentioned method as white solid. ¹H NMR (400MHz, CDCl₃) δ 8.79 (s, 1H) 8.36-8.35 (m, 1H) 8.24-8.22 (m, 1H) 7.81-7.78 (m, 4H) 7.76-7.70 (m, 1H) 7.60-7.59 (m, 2H) 6.75-6.73 (m, 1H) 4.16 (s, 3H) 3.78-3.76(m, 4H) 3.42-3.39(m, 4H)

Our Ref.: P1650132CA

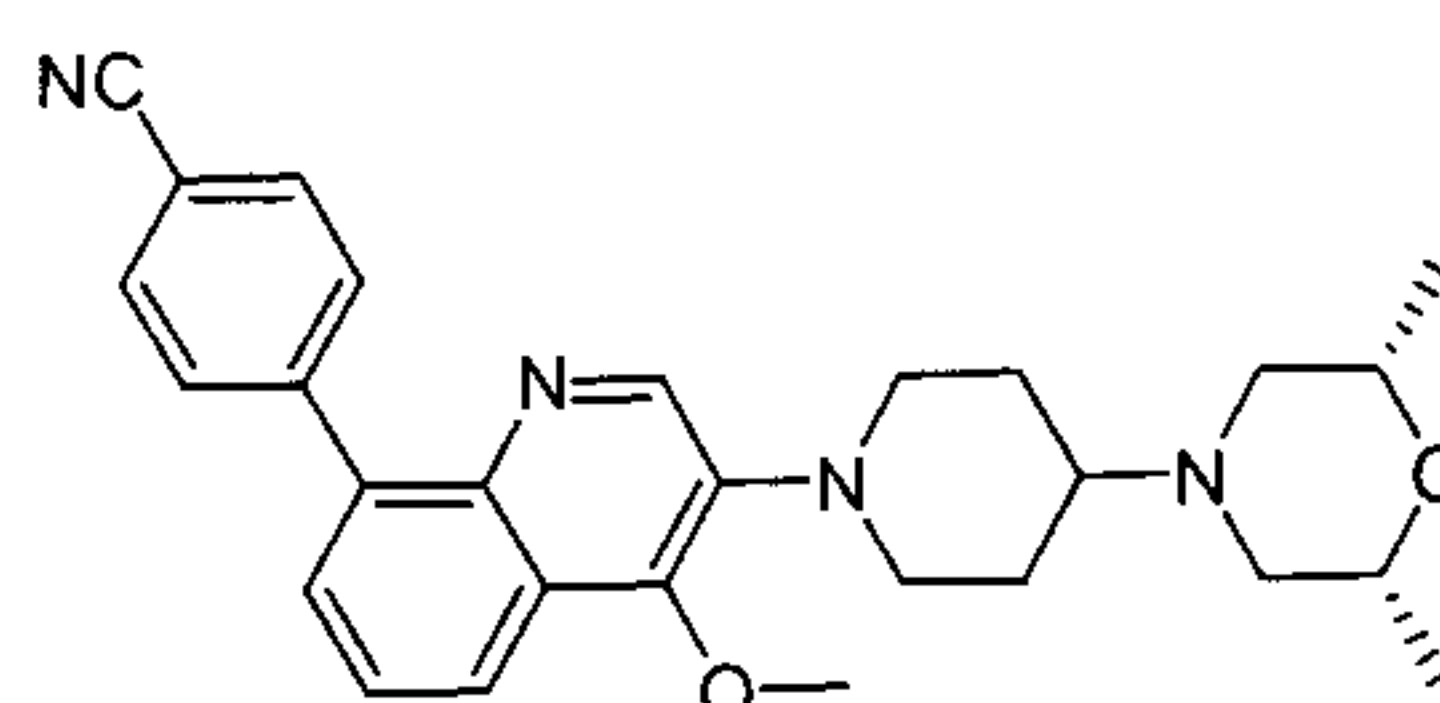
1.67 (s, 1H) 1.60 (s, 6H). **MS ESI** calcd for $C_{29}H_{29}N_5O_2$ $[M+H]^+$ 480, found 480.

[472] The compounds listed in table 20 were synthesized by compound 220-6 and corresponding amines.

Embodiment	Structure	NMR
221		^1H NMR (400MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.81 (s, 1H), 8.43 (d, $J=8.0$ Hz, 1H), 8.16 (s, 1H), 7.81-7.64 (m, 6H), 4.32 (s, 3 H), 4.01 (s, 4 H), 3.41 (s, 4 H), 2.62 (s, 6 H). MS ESI calcd for $C_{28}H_{28}N_6O_2$ $[M+H]^+$ 481, found 481.
222		^1H NMR (400MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.31-8.17 (m, 2H), 7.91-7.80 (m, 4H), 7.58 (d, $J=8.0$ Hz, 2H), 6.81 (d, $J=8.0$ Hz, 1H), 4.14 (s, 3 H), 3.80 (s, 4 H), 3.34 (s, 4 H), 1.65 (s, 6 H). MS ESI calcd for $C_{30}H_{28}F_3N_5O_2$ $[M+H]^+$ 548, found 548.
223		^1H NMR (400MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.50 (s, 1H), 8.21-8.17 (m, 1H), 8.00 (s, 1H), 7.75-7.60 (m, 4H), 7.52-7.48 (m, 2H), 4.07 (s, 3 H), 3.57-3.41 (m, 8 H), 1.55 (s, 6 H). MS ESI calcd for $C_{30}H_{28}F_3N_5O_2$ $[M+H]^+$ 548, found 548.
224		^1H NMR (400MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.52 (d, $J=8.0$ Hz, 1H), 8.35 (d, $J=7.2$ Hz, 1H), 7.62-7.53 (m, 7H), 6.75 (d, $J=8.0$ Hz, 1H), 3.75 (t, $J=4.4$ Hz, 4 H), 3.41 (t, $J=4.4$ Hz, 4 H), 2.07-2.01 (m, 1H), 1.97-1.91 (m, 2H), 1.59 (s, 6H), 1.42-1.35 (m, 2H). MS ESI calcd for $C_{31}H_{31}N_5O$ $[M+H]^+$ 490, found 490.

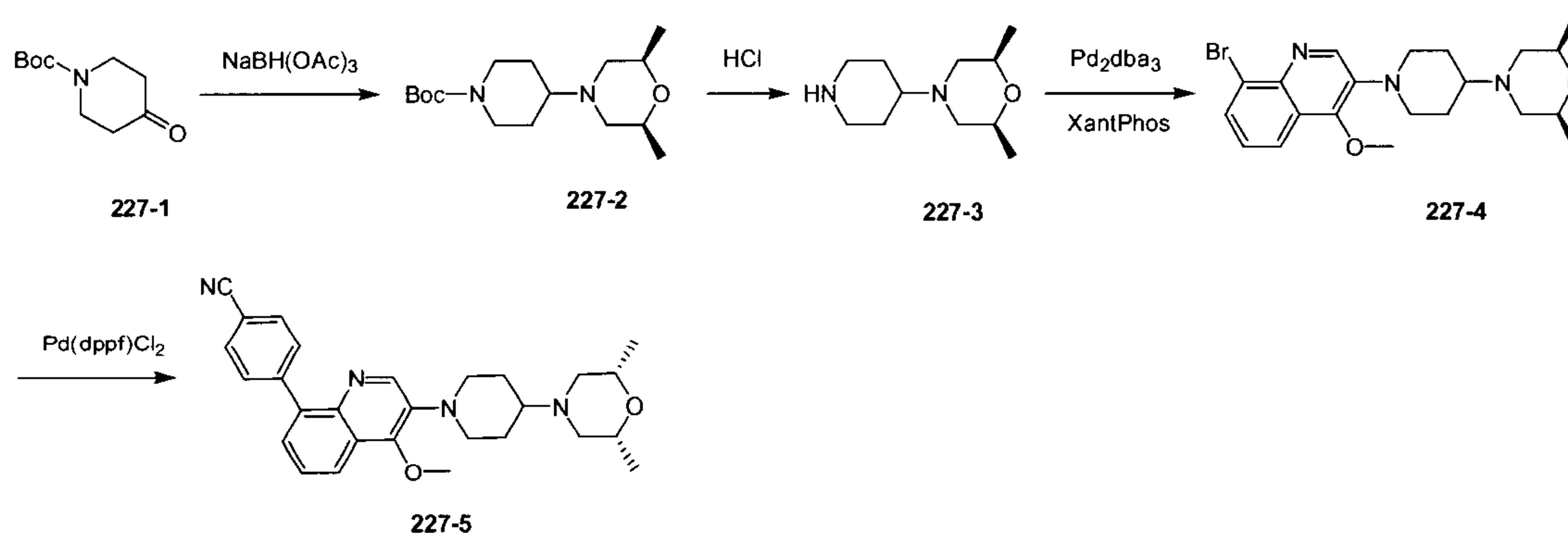
225		MS ESI calcd for C ₂₉ H ₃₀ N ₆ O ₂ [M+H] ⁺ 495, found 495.
226		¹H NMR (400 MHz, CDCl ₃) δ 8.72 (s, 1H), 8.35 (s, 1H), 8.27-8.25 (m, 1H), 7.81-7.64 (m, 5H), 7.61-7.57 (m, 2H), 6.77-6.72 (m, 1H), 4.68 (brs, 1H), 4.22-4.18 (m, 1H), 4.14(s, 3H), 3.72-3.70 (m, 1H), 3.63-3.61 (m, 1H), 3.50-3.48 (m, 1H), 3.30-3.28 (m, 1H), 3.02-2.99 (m, 1H), 1.59 (s, 6 H), 1.35 (d, <i>J</i> = 6.0 Hz, 3H). MS ESI calcd for C ₃₀ H ₃₁ N ₅ O ₂ [M+H] ⁺ 494, found 494.

Embodiment 227



4-(3-(4-(2,6-dimethylmorpholino)piperidin-1-yl)-4-methoxyquinolin-8-yl)

benzonitrile



[473] Step 1: A solution of compound 227-1 (2.0 g, 10 mmol) and *cis*-2,6-dimethyl morpholine (1.25 g, 11 mmol) in DCM (40 mL) was stirred at 0°C for 1h, then sodium triacetoxyborohydride (5.3 g, 25 mmol) was added at 20°C and the mixture was stirred at 20°C for 5h. Then the reaction mixture was quenched with saturated sodium carbonate aqueous solution, extracted with DCM (30×2 mL). The organic phases were combined and dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc= 5:1-1:1) to deliver compound 227-2 (1.5 g, 50%) as white solid. **MS**

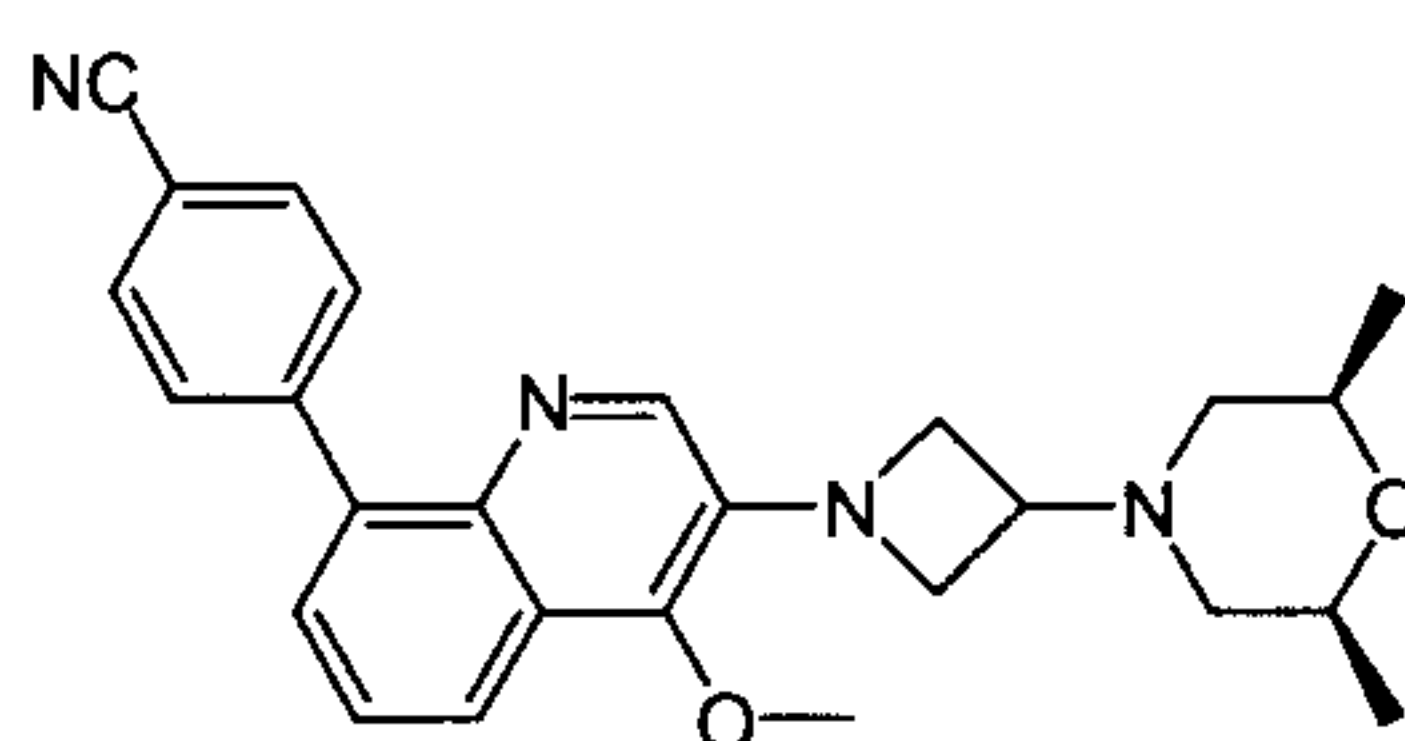
ESI calcd for $C_{16}H_{30}N_2O_3$ $[M+H]^+$ 299, found 299.

[474] Step 2: HCl (4 M methanol solution, 10 mL) was added into a solution of compound 227-2 (3.0 g, 10 mmol) in methanol (20 mL). The obtained solution was stirred at 20°C for 4h, then concentrated under reduced pressure. The obtained yellow solid was used for the next step directly without further purification (1.9 g, 99%). **MS ESI** calcd for $C_{11}H_{22}N_2O$ $[M+H]^+$ 199, found 199.

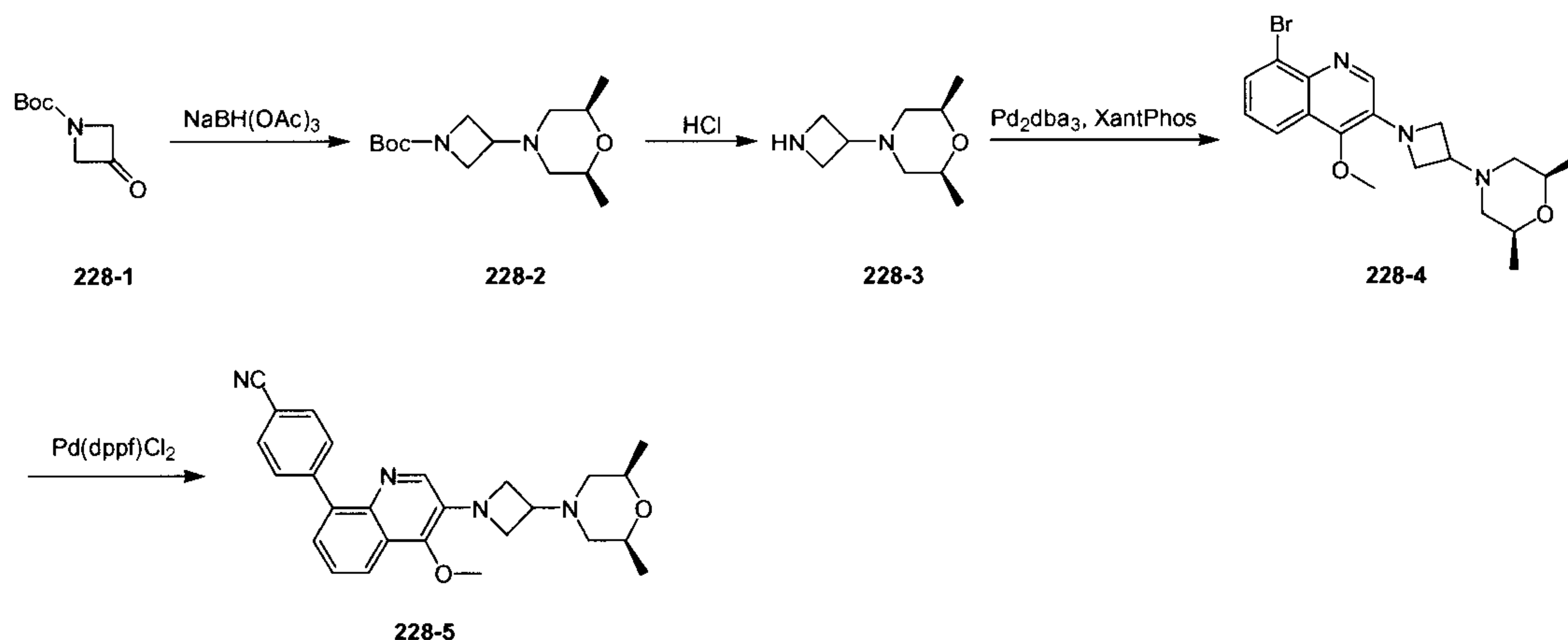
[475] Step 3: Under nitrogen gas atmosphere, $Pd_2(dba)_3$ (180 mg, 0.2 mmol), Xantphos (290 mg, 0.5 mmol) and sodium *tert*-butoxide (1.0 g, 10 mmol) were added into a solution of compound 227-3 (1.0 g, 5.0 mmol) and 8-bromo-3-iodo-4-methoxyquinoline (1.4 g, 4 mmol) in toluene (30 mL), the reaction mixture was stirred at 120°C for 5h, then poured into H_2O , and extracted with ether (3×3 mL), the organic phases were combined and dried over sodium sulfate and concentrated under reduced pressure, the residue was purified by silica gel column chromatography (PE/EtOAc= 1:1-1:2) to deliver compound 227-4 (0.36 g, 50%) as yellow solid. **MS ESI** calcd for $C_{21}H_{28}BrN_3O_2$ $[M+H]^+$ 435, found 435.

[476] Step 4: The title compound (0.1 g, 40%) was synthesized according to the above-mentioned method as white solid. **^1H NMR** (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.23-8.15 (m, 1H), 7.79-7.74 (m, 4H), 7.58-7.46 (m, 2H), 4.11 (s, 3H), 3.72-3.65 (m, 4H), 2.90-2.84 (m, 4H), 2.35-2.28 (m, 1H), 2.20-2.10 (m, 2H), 1.90-1.80 (m, 2H), 1.77-1.67 (m, 2H), 1.21 (d, J = 5.6 Hz, 6H). **MS ESI** calcd for $C_{28}H_{32}N_4O_2$ $[M+H]^+$ 457, found 457.

Embodiment 228



4-(3-(3-(2,6-dimethylmorpholino-4-yl)azetidin-1-yl)-4-methoxyquinolin-8-yl)
benzonitrile

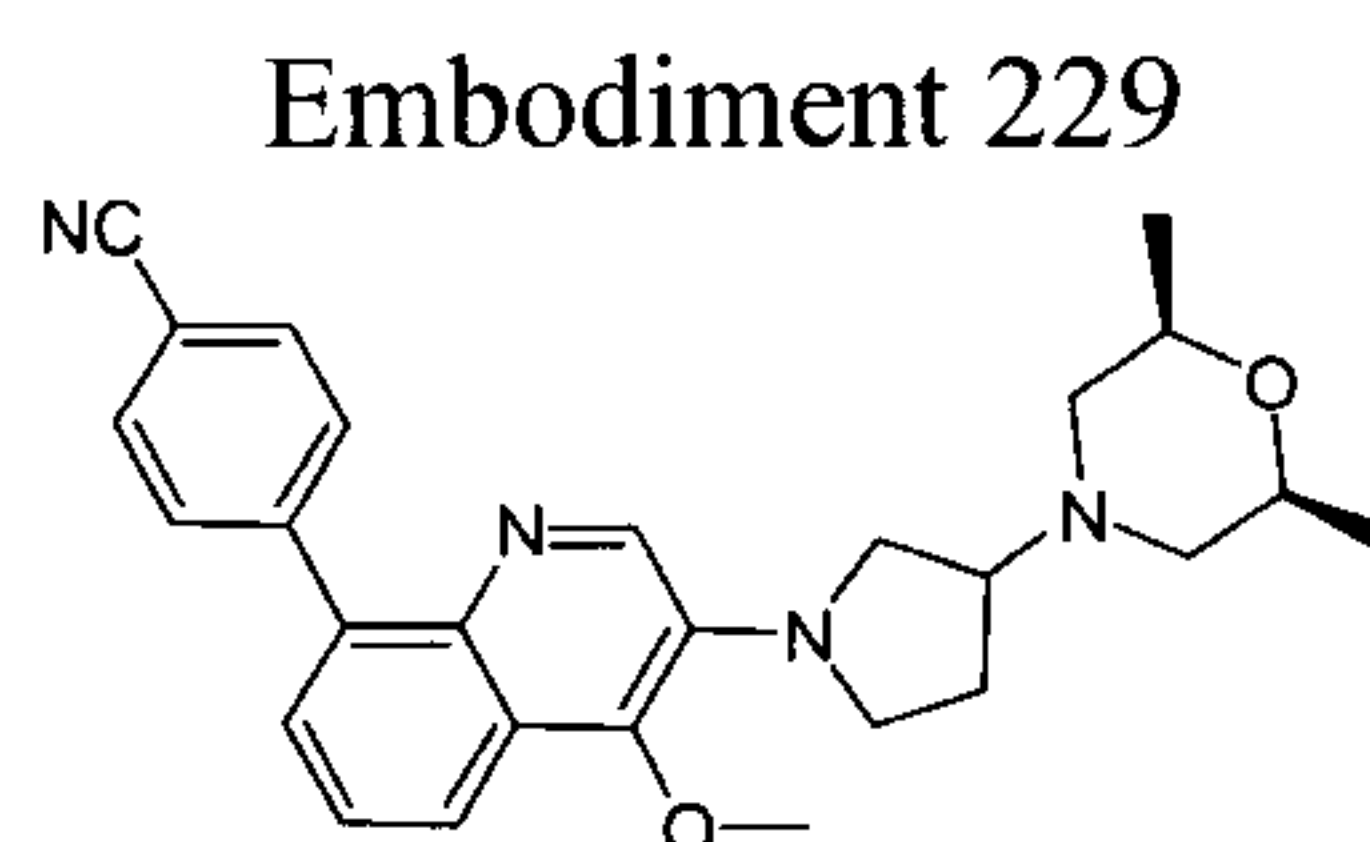


[477] Step 1: A solution of compound 228-1 (1.7 g, 10 mmol) and *cis*-2,6-dimethylmorpholine (1.4 g, 12 mmol) in DCM (30 mL) was stirred at 0°C for 1h, then sodium triacetoxyborohydride (6.0 g, 30 mmol) was added at 20°C and the mixture was stirred at 20°C for 5h. Then the reaction mixture was quenched with saturated sodium carbonate aqueous solution, extracted with DCM (30×2 mL). The organic phases were combined and dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc= 5:1-1:1) to deliver compound 228-2 (1.8 g, 67%) as white solid. **MS ESI** calcd for C₁₄H₂₆N₂O₃ [M+H]⁺ 271, found 271.

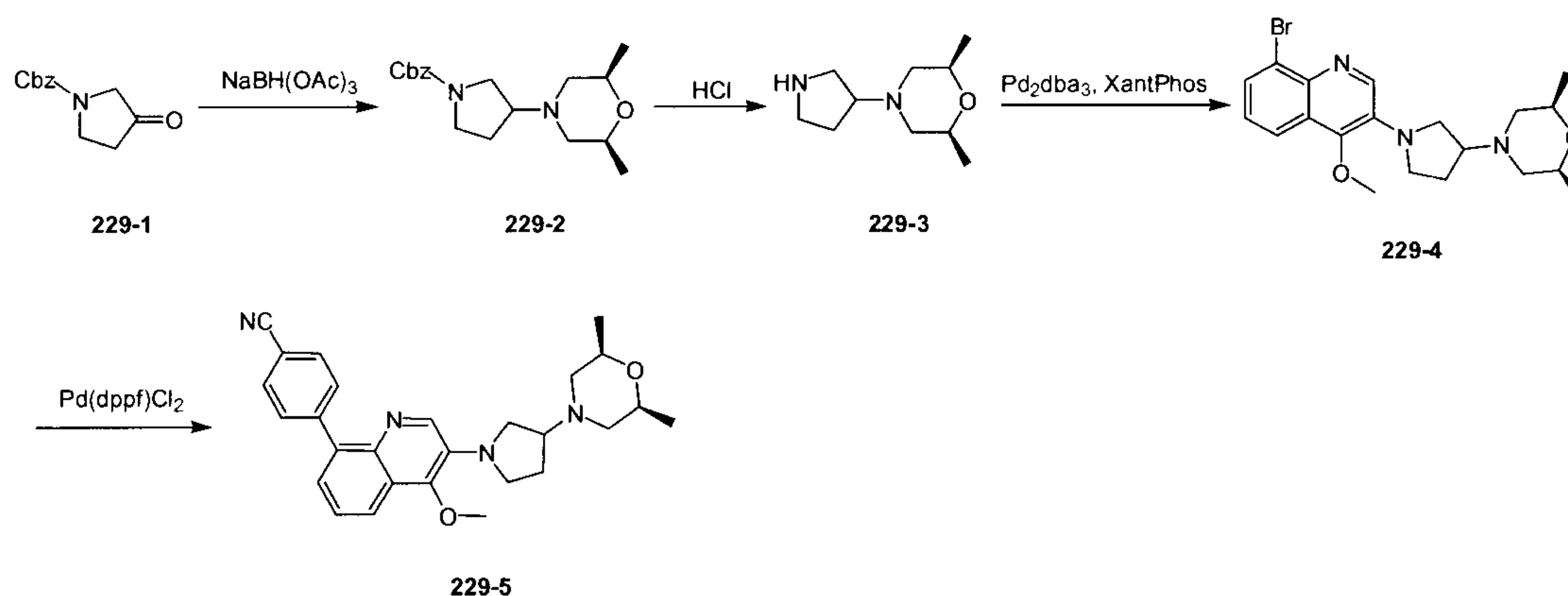
[478] Step 2: HCl (4 M methanol solution, 10 mL) was added into a solution of compound 228-2 (2.6 g, 10 mmol) in methanol (20 mL). The obtained solution was stirred at 20°C for 4h, then concentrated under reduced pressure. The obtained yellow solid was used for the next step directly without further purification (1.6 g, 99%). **MS ESI** calcd for C₉H₁₈N₂O [M+H]⁺ 171, found 171.

[479] Step 3: Under nitrogen gas atmosphere, Pd₂(dba)₃ (90 mg, 0.1 mmol), Xantphos (120 mg, 0.2 mmol) and sodium *tert*-butoxide (0.6 g, 6 mmol) were added into a solution of compound 228-3 (1.1 g, 3 mmol) and 8-bromo-3-iodo-4-methoxyquinoline (0.55 g, 3.3 mmol) in toluene (10 mL), the reaction mixture was stirred at 120°C for 5h, then poured into H₂O, and extracted with ether (3×3 mL), the organic phases were combined and dried over anhydrous sodium sulfate and concentrated under reduced pressure, the residue was purified by silica gel column chromatography (PE/EtOAc= 1:1-1:2) to deliver compound 228-4 (0.57 g, 47%) as yellow solid. **MS ESI** calcd for C₁₉H₂₄BrN₃O₂ [M+H]⁺ 407, found 407.

[480] Step 4: The title compound (0.045 g, 10%) was synthesized according to the above-mentioned method as white solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.50 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.80-7.65 (m, 6H), 4.56 (brs, 2H), 4.41 (brs, 2H), 4.06 (brs, 2H), 3.94 (s, 3H), 3.91 (brs, 1H), 3.49 (d, *J* = 7.6 Hz, 2H), 2.34 (t, *J* = 11.6 Hz, 2H), 1.26 (d, *J* = 6.0 Hz, 6H). **MS ESI** calcd for C₂₆H₂₈N₄O₂ [M+H]⁺ 429, found 429.



4-(3-(3-(2,6-dimethylmorpholino)pyrrolidin-1-yl)-4-methoxyquinolin-8-yl)
benzonitrile

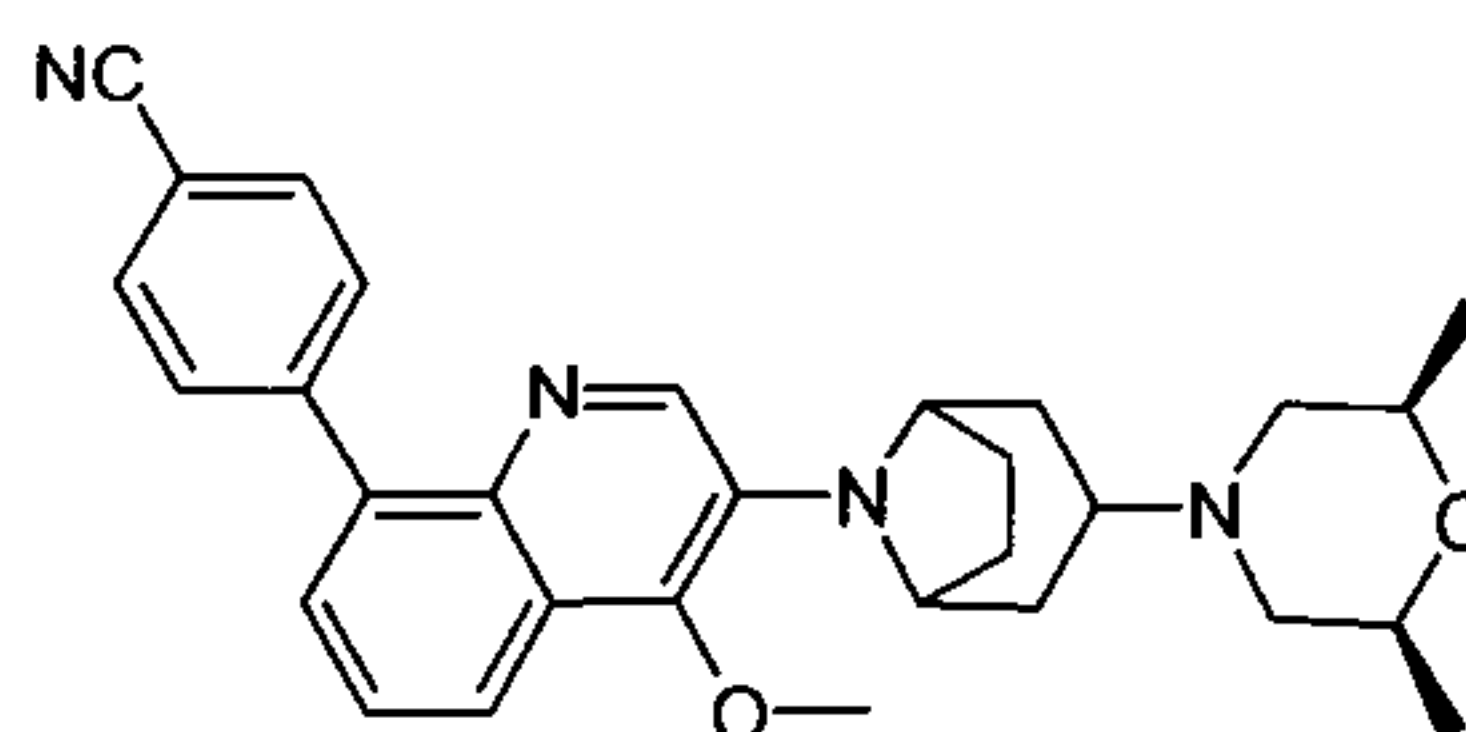


[481] Step 1: A solution of compound 229-1 (2.0 g, 10 mmol) and *cis*-2,6-dimethyl morpholine (1.25 g, 11 mmol) in DCM (40 mL) was stirred at 0°C for 1h, then sodium triacetoxyborohydride (6.0 g, 30 mmol) was added at 20°C and the mixture was stirred at 20°C for 5h. Then the reaction mixture was quenched with saturated sodium carbonate aqueous solution, extracted with DCM (30×2 mL). The organic phases were combined and dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc= 5:1-1:1) to deliver compound 229-2 (1.5 g, 60%) as white solid. **MS ESI** calcd for C₁₈H₂₆N₂O₃ [M+H]⁺ 319, found 319.

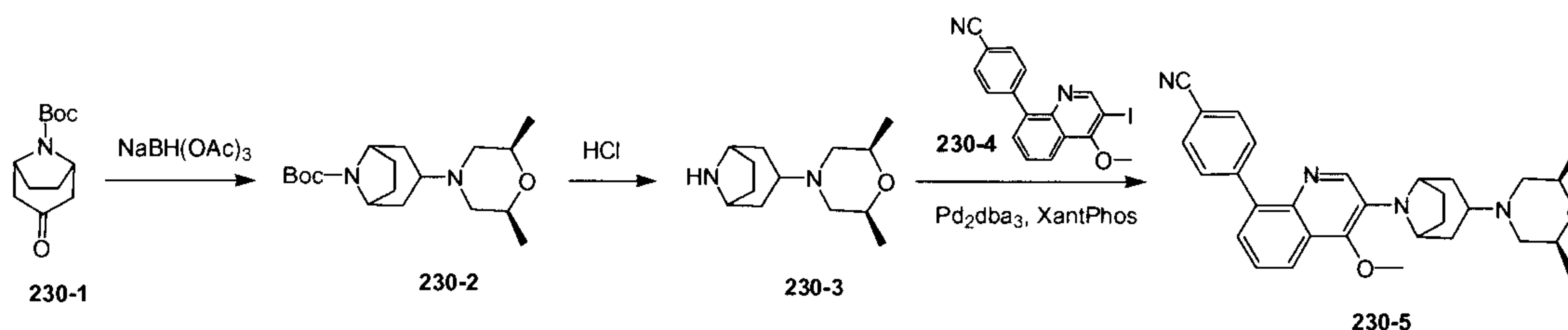
[482] Step 2: Pd/C (100 mg) was added into a solution of compound 229-2 (0.65 g, 2 mmol) in methanol (10 mL) and the mixture was hydrogenated under 30 psi at 20°C for 4h. Then the mixture was filtrated and concentrated under reduced pressure. The obtained yellow solid was used for the next step directly without further purification (0.37 g, 99%). **MS ESI** calcd for C₁₀H₂₀N₂O [M+H]⁺ 185, found 185.

[483] Step 3: Under nitrogen gas atmosphere, Pd₂(dba)₃ (90 mg, 0.1 mmol), Xantphos (120 mg, 0.2 mmol) and sodium *tert*-butoxide (0.4 g, 3 mmol) were added into a solution of compound 229-3 (0.4 g, 1.1 mmol) and 8-bromo-3-iodo-4-methoxyquinoline (0.2 g, 1.1 mmol) in toluene (10 mL), the reaction mixture was stirred at 120°C for 5h, then poured into H₂O, and extracted with ether (3×3 mL), the organic phases were combined and dried over sodium sulfate and concentrated under reduced pressure, the residue was purified by silica gel column chromatography (PE/EtOAc= 1:1-1:2) to deliver compound 229-4 (0.36 g, 42%) as yellow solid. **MS ESI** calcd for C₂₀H₂₆BrN₃O₂ [M+H]⁺ 421, found 421.

[484] Step 4: The title compound (0.13 g, 60%) was synthesized according to the above-mentioned method as white solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.68 (s, 1H), 8.14-8.12 (m, 1H), 7.72-7.65 (m, 4H), 7.49-7.47 (m, 2H), 4.04 (s, 3H), 3.64-3.60 (m, 4H), 2.82-2.78 (m, 4H), 2.24-2.20 (m, 1H), 2.00-1.92 (m, 2H), 1.86-1.72 (m, 2H), 1.68-1.56 (m, 2H), 1.16 (d, *J* = 6.0 Hz, 6H). **MS ESI** calcd for C₂₇H₃₀N₄O₂ [M+H]⁺ 443, found 443.



4-(3-(3-(2,6-dimethylmorpholino-4-yl)-8-azabicyclo[3.2.1]octan-8-yl)-4-methoxyquinolin-8-yl)benzonitrile

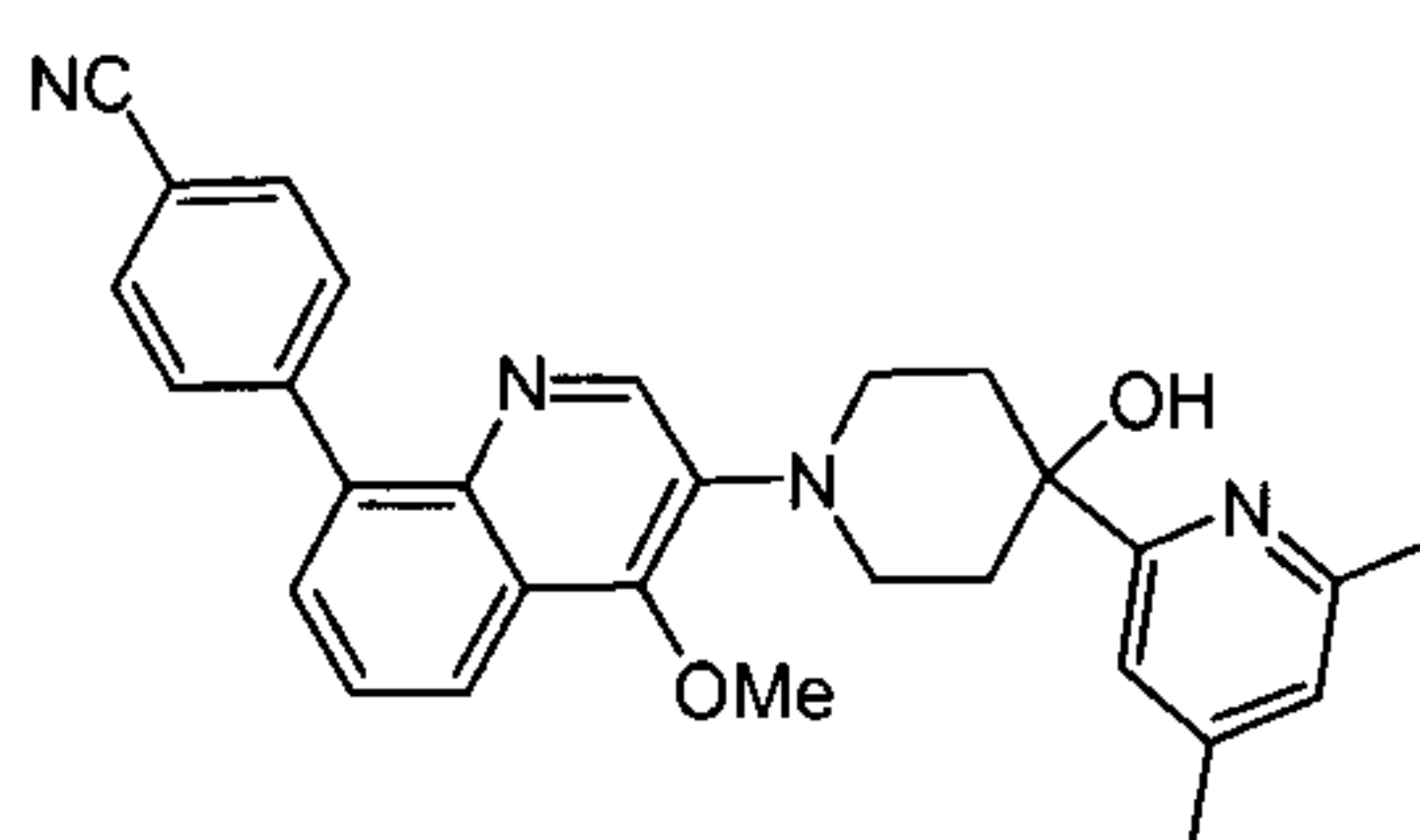


[485] Step 1: Sodium triacetoxyborohydride (6.3 g, 30 mmol) was added into a solution of compound 230-1 (4.5 g, 20 mmol) and *cis*-2,6-dimethyl morpholine (2.5 g, 22 mmol) in DCM (60 mL) at 0°C and the mixture was stirred at 25°C for 12h. Then the mixture was poured into H₂O, and extracted with EtOAc. The organic phases were combined, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc=10:1) to deliver compound 230-2 (1.1 g, 17%) as white solid. **MS ESI** calcd for C₁₈H₃₂N₂O₃ [M+H]⁺ 325, found 325.

[486] Step 2: HCl (4 M methanol solution, 10 mL) was added into a solution of compound 230-2 (324 mg, 1 mmol) in methanol (5 mL). The obtained solution was stirred at 25°C for 2h, then concentrated under reduced pressure. The obtained yellow solid was used for the next step directly without further purification (224 mg, 100%). **MS ESI** calcd for C₁₃H₂₄N₂O [M+H]⁺ 225, found 225.

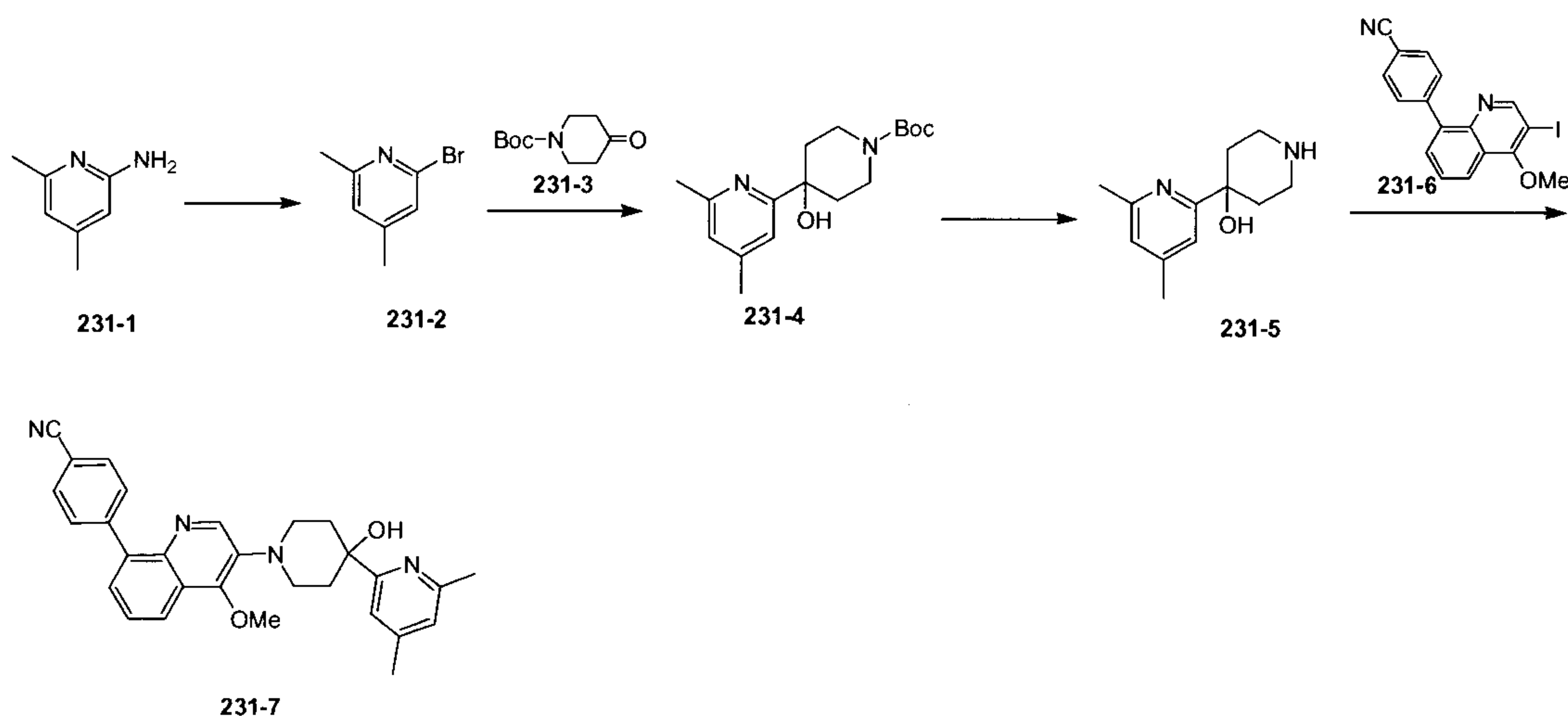
[487] Step 3: The title compound (40 mg, 8.3%) was synthesized according to the above-mentioned method as white solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.71 (s, 1H), 8.24-8.21 (m, 1H), 7.82-7.75 (m, 4H), 7.59-7.57 (m, 2H), 4.75-4.60 (m, 2H), 3.97(s, 3H), 3.74-3.68 (m, 3H), 3.52 (d, *J* = 12.0 Hz, 2H), 2.62-2.50 (m, 2H), 2.20-2.18 (m, 4H), 2.00-1.89 (m, 2H), 1.21 (d, *J* = 6.4 Hz, 6H). **MS ESI** calcd for C₃₀H₃₄N₄O₂ [M+H]⁺ 483, found 483.

Embodiment 231



4-(3-(4'-hydroxy-4,6-dimethyl-3',4',5',6'-tetrahydro-2'H-[2,4']

bipyridyl-1'-yl)-4-methoxyquinolin-8-yl) benzonitrile



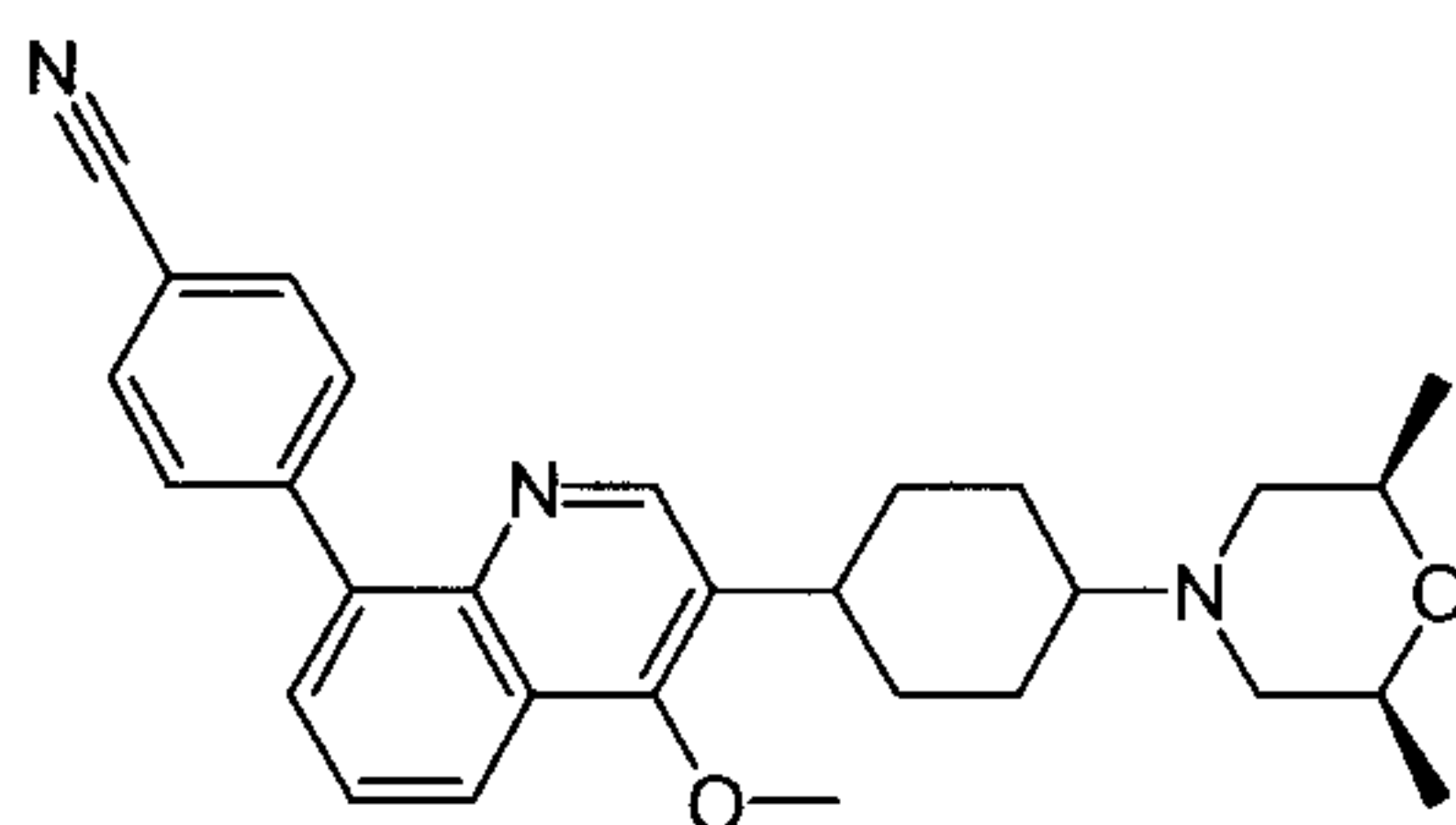
[488] Step 1: Br_2 (36.8 g, 0.23 mmol) was added into a solution of compound 231-1 (10 g, 82 mmol) in HBr (41 mL), and the mixture was stirred at -10°C for 10 min. Then NaNO_2 (14.1 g, 210 mmol) was added while the reaction temperature was kept no more than 0°C . The reaction mixture was stirred for 30 min. Then NaOH solution (35 g dissolved in 35 mL H_2O) was added, and the mixture was extracted with EtOAc . The organic phases were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($\text{PE}/\text{EtOAc}=10:1$) to deliver compound 231-2 (3.36 g, 22%) as light yellow oil. **MS ESI** calcd for $\text{C}_7\text{H}_8\text{BrN}$ $[\text{M}+\text{H}]^+$ 187, found 187.

[489] Step 2: $n\text{-BuLi}$ (8 mL, 19.91 mmol) was added into a solution of compound 231-2 (3.36 g, 18.1 mmol) in THF (70 mL) at -70°C and stirred for 1h. Then compound 231-3 (4.32 g, 21.71 mmol) was added at -70°C . The reaction mixture was warmed to room temperature slowly and stirred at room temperature for 2h. Then the reaction mixture was quenched with saturated ammonium chloride aqueous solution (2 mL) and extracted with EtOAc (200 mL). The organic phases were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($\text{PE}/\text{EtOAc}=5:1$) to deliver compound 231-4 (3.11 g, 56%) as light yellow oil. **MS ESI** calcd for $\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 307, found 307.

[490] Step 3: CF_3COOH (6 mL) was added dropwise into a solution of compound 231-4 (2 g, 6.5 mL) in DCM (30 mL). The reaction mixture was stirred at room temperature for 30 min. Then the reaction mixture was basified with 6 N NaOH to $\text{pH}=9$, extracted with CHCl_3 (70×3 mL). The organic phases were combined, dried over sodium sulfate and concentrated under reduced pressure to deliver crude compound 231-5 (1.197 g, 89%) as yellow solid, which was used for the next step directly without further purification. **MS ESI** calcd for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 207, found 207.

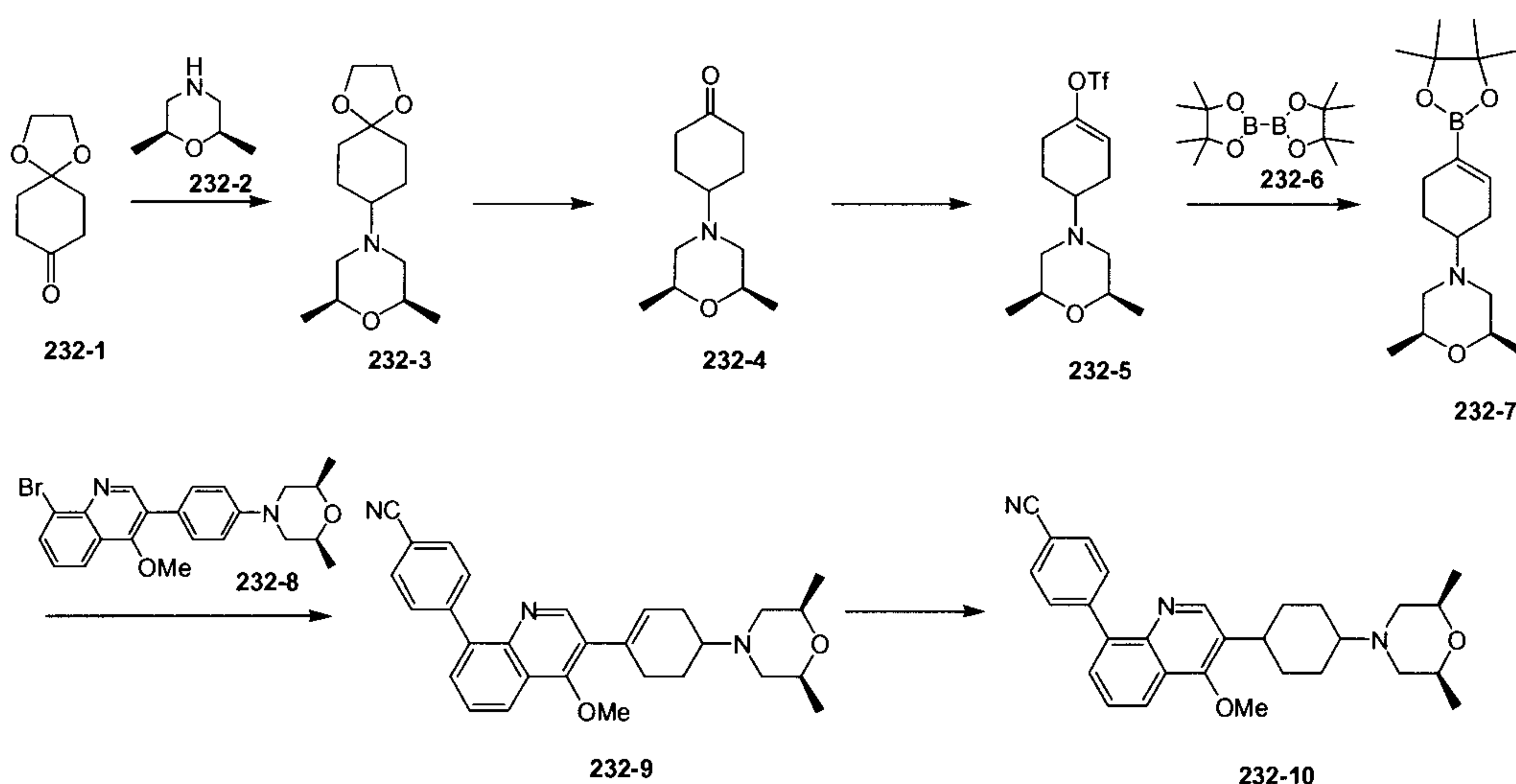
[491] Step 4: The title compound (18 mg, 9.5%) was synthesized according to the above-mentioned method as white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.89 (s, 1H), 8.24-8.21 (m, 1H), 7.83-7.76 (m, 4H), 7.60-7.56 (m, 2H), 7.01 (s, 1H), 6.94 (s, 1H), 5.74 (s, 1H), 4.19 (s, 3H), 3.63-3.49 (m, 4H), 2.54 (s, 3H), 2.37 (s, 3H), 2.28-2.21 (m, 2H), 1.79-1.76 (m, 2H). MS ESI calcd for C₂₉H₂₈N₄O₂ [M+H]⁺ 465, found 465.

Embodiment 232



4-(3-(4-(2,6-dimethylmorpholino-4-yl)cyclohexyl)-4-methoxyquinolin-8-yl)

benzonitrile



[492] Step 1: Sodium triacetoxyborohydride (54.3 g, 0.26 mol) was added into a solution of compound 232-1 (20 g, 0.13 mol), *cis*-2,6-dimethyl morpholine (14.74 g, 0.13 mol) and acetic acid (7.69 mg, 0.13 mol) in 1,2-dichloroethane (400 mL) at 0°C and the mixture was stirred at 25°C for 16h. Then 10% NaOH aqueous solution (200 mL) was slowly added dropwise (in 20 min) to quench the reaction, then the mixture was extracted with EtOAc. The organic phases were combined, dried over sodium sulfate and concentrated under reduced pressure to deliver compound 232-3 (30 g, 92%) as white solid. MS ESI calcd for C₁₄H₂₅NO₃ [M+H]⁺ 256, found 256.

[493] Step 2: 7 N HCl aqueous solution (40 mL) was added into a solution of compound 232-3 (10 g, 39.2 mmol) in THF (200 mL), and the mixture was stirred at 25°C for 16h. Then 2 N NaOH aqueous solution (500 mL) was added to quench the reaction, then the mixture was extracted with EtOAc (1X) and DCM (3X). The organic phases were combined, dried over sodium sulfate and concentrated under

reduced pressure to deliver crude compound 232-4 (8 g, 96%) as white solid. **MS ESI** calcd for $C_{21}H_{12}NO_2$ $[M+H]^+$ 212, found 212.

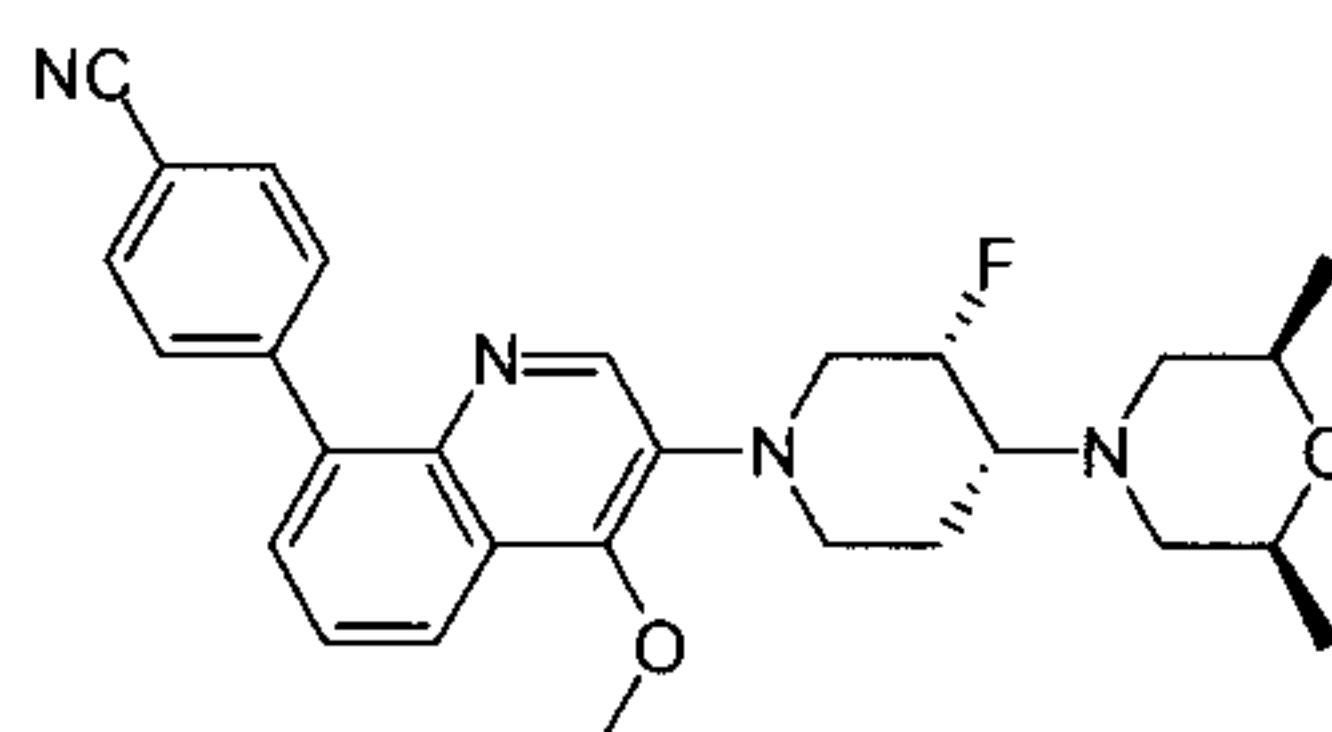
[494] Step 3: LiHMDS (17 mL, 17 mmol) was added into a solution of compound 232-4 (3 g, 14.2 mmol) in THF (50 mL) at 0°C, then the reaction mixture was stirred for 30 min. Then N,N-bis(trifluoromethylsulfonyl)aniline (5.58 g, 15.6 mmol) was added, and the reaction mixture was stirred at 25°C for 6h. The reaction mixture was poured into H₂O and extracted with EtOAc. The organic phases were combined, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc = 5:1) to deliver compound 232-5 (2.3 g, 47%) as white solid. **MS ESI** calcd for $C_{13}H_{20}F_3NO_4S$ $[M+H]^+$ 344, found 344.

[495] Step 4: Under nitrogen gas atmosphere, Pd(dppf)Cl₂ (0.4 mg, 0.11 mmol) and KOAc (0.65 g, 6.6 mmol) were added into a solution of compound 232-5 (0.76 g, 2.2 mmol) and compound 232-6 (0.67 g, 2.6 mmol) in 1,4-dioxane (15 mL). The reaction mixture was stirred at 100°C for 15h, then poured into H₂O and extracted with EtOAc (50×2 mL). The organic phases were combined, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc = 5:1) to deliver compound 232-7 (0.35 g, 49%) as yellow solid. **MS ESI** calcd for $C_{18}H_{32}BNO_3$ $[M+H]^+$ 322, found 322.

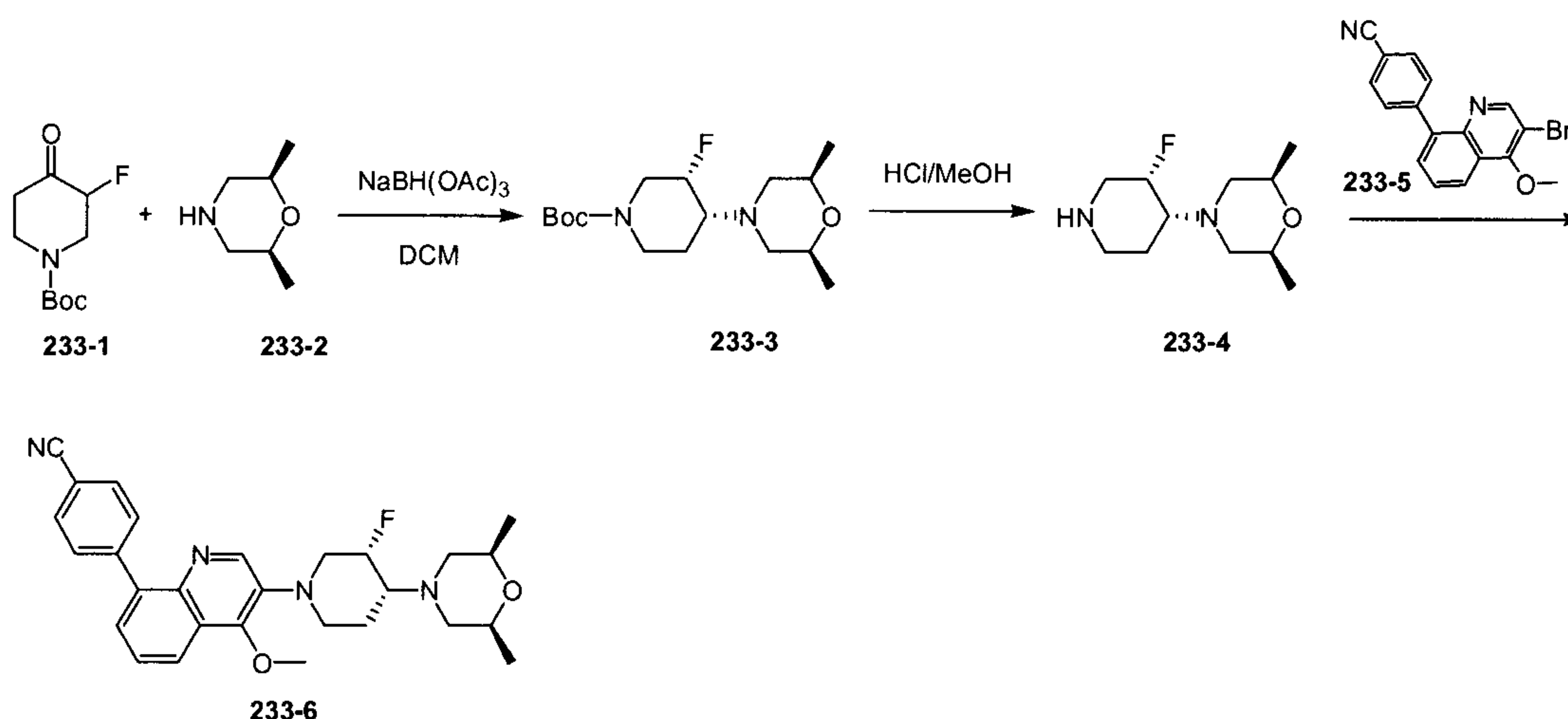
[496] Step 5: Under nitrogen gas atmosphere, Pd(dppf)Cl₂ (113.8 mg, 0.16 mmol) and Na₂CO₃ (412 mg, 3.89 mmol) were added into a solution of compound 232-7 (600 mg, 1.87 mmol) and compound 232-8 (601 mg, 1.56 mmol) in THF (10 mL) and H₂O (2 mL). The reaction mixture was stirred at 80°C for 4h, then extracted with EtOAc (50×2 mL). The organic phases were combined, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc = 5:1) to deliver compound 232-7 (400 mg, 48%) as white solid. **MS ESI** calcd for $C_{29}H_{31}N_3O_2$ $[M+H]^+$ 454, found 454.

[497] Step 6: Pd/C (100 mg) was added into a solution of compound 232-9 (100 mg, 0.22 mmol) in EtOAc (20 mL), and the reaction mixture was hydrogenated under hydrogen balloon at 20°C for 50h. Then the mixture was filtrated and concentrated under reduced pressure. The obtained yellow solid was purified by preparative HPLC to deliver the title compound (27 mg, 54%) as white solid. **¹H NMR** (400 MHz, DMSO) δ 8.99 (s, 1H), 8.17-8.15 (*J* = 8 Hz, d, 1H), 7.94-7.92 (d, *J* = 12 Hz, 2H), 7.85-7.83 (d, *J* = 8 Hz, 2H), 7.80-7.78 (*J* = 8 Hz, d, 1H), 7.74-7.72 (*J* = 8 Hz, d, 1H), 3.98 (s, 3H) 3.54 (s, 2H), 3.18-3.17 (*J* = 4 Hz, d, 1H), 3.54 (s, 1H), 2.76-2.74 (*J* = 8 Hz, d, 2H), 1.95-1.71 (m, 8H), 1.49-1.44 (m, 2H), 1.07-1.05 (*J* = 8 Hz, d, 6H). **MS ESI** calcd for $C_{29}H_{33}N_3O_2$ $[M+H]^+$ 465, found 465.

Embodiment 233



4-(3-(4-(2,6-dimethylmorpholino-4-yl)-3-fluoropiperidin-1-yl)-4-methoxyquinolin-8-yl)benzonitrile

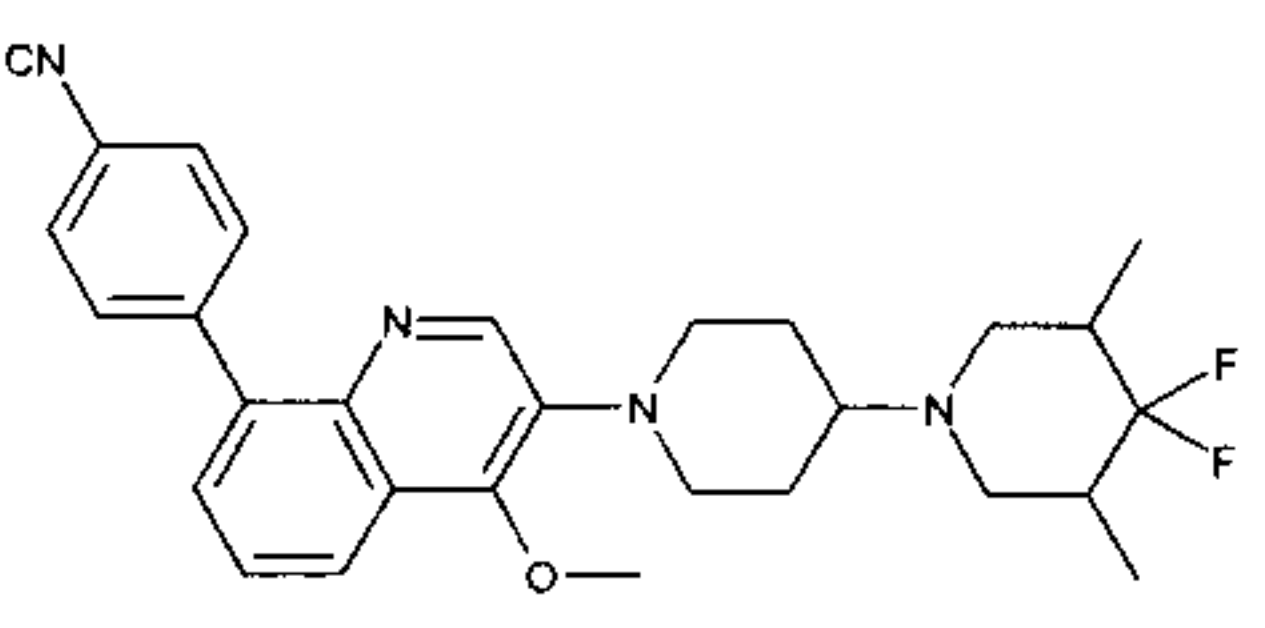


[498] Step 1: A solution of compound 1 (3.0 g, 13.8 mmol) and *cis*-2,6-dimethyl morpholine (1.7 g, 15.2 mmol) in DCM (15 mL) was stirred at 20°C for 0.5h, then sodium triacetoxyborohydride (4.4 g, 20.7 mmol) was added at 20°C and the reaction mixture was stirred at 20°C for 15h. Then the reaction mixture was quenched with saturated sodium carbonate aqueous solution (50 mL), extracted with DCM (50 mL). The organic phases were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc =8:1-1:1) to deliver compound 233-3 (1.2 g, 27%) as white solid. **MS ESI** calcd for C₁₆H₂₉FN₂O₃ [M+H]⁺ 317, found 317.

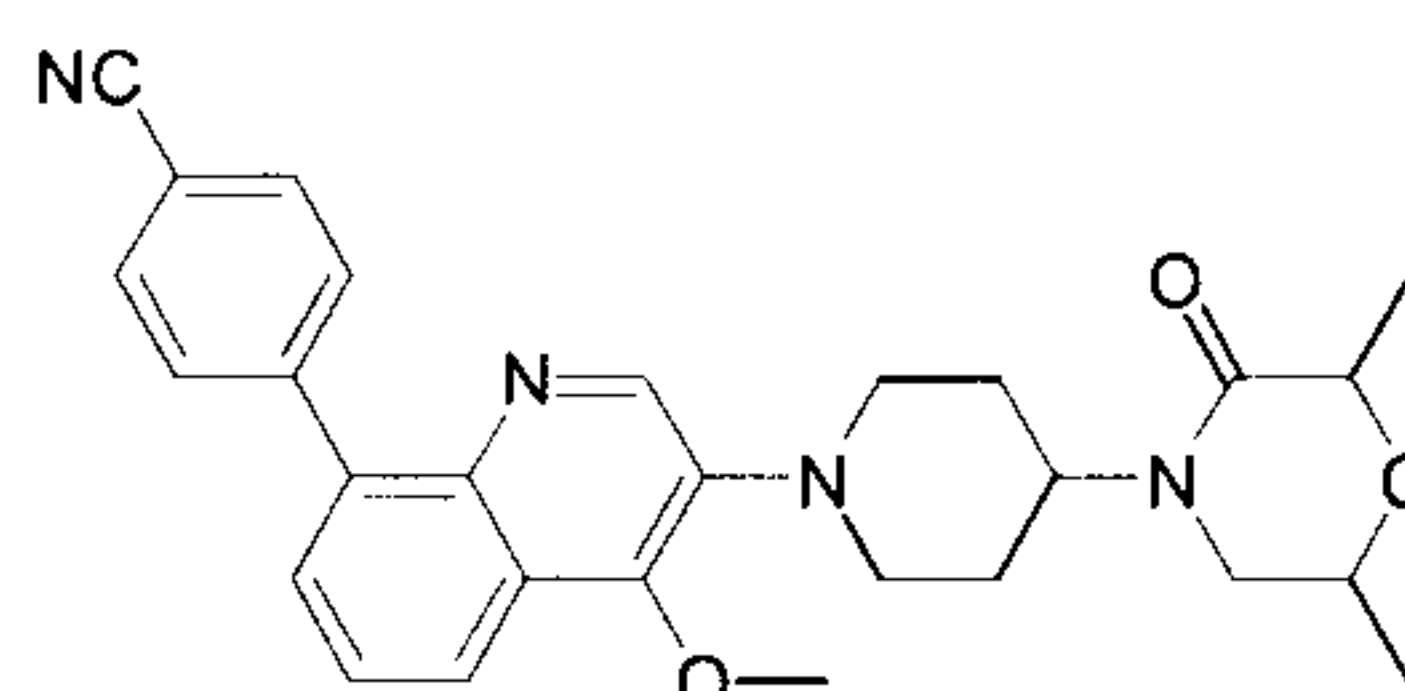
[499] Step 2: HCl (4 M methanol solution, 60 mL) was added into a solution of compound 233-3 (1.2 g, 3.8 mmol) in methanol (10 mL). The obtained solution was stirred at 20°C for 0.5h, then concentrated under reduced pressure. The obtained yellow solid was used for the next step directly without further purification (0.6 g, 75%). **MS ESI** calcd for C₁₁H₂₁FN₂O [M+H]⁺ 217, found 217.

[500] Step 3: The title compound (27 mg, 15%) was synthesized according to the above-mentioned method as white solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.73 (s, 1H), 8.24-8.21 (m, 1H), 7.80-7.75 (m, 4H), 7.59-7.58 (d, *J* =4 Hz, 2H), 4.15 (s, 3H), 4.03-4.00 (m, 1H), 3.74-3.71 (m, 3H), 3.07-2.92(m, 4H), 2.25-1.94(m, 6H), 1.21-1.19 (d, *J*=8 Hz, 6H). **MS ESI** calcd for C₂₈H₃₁FN₄O₂ [M+H]⁺ 475, found 475.

[501] The compound listed in table 21 was synthesized by compound 233-5 and corresponding amine.

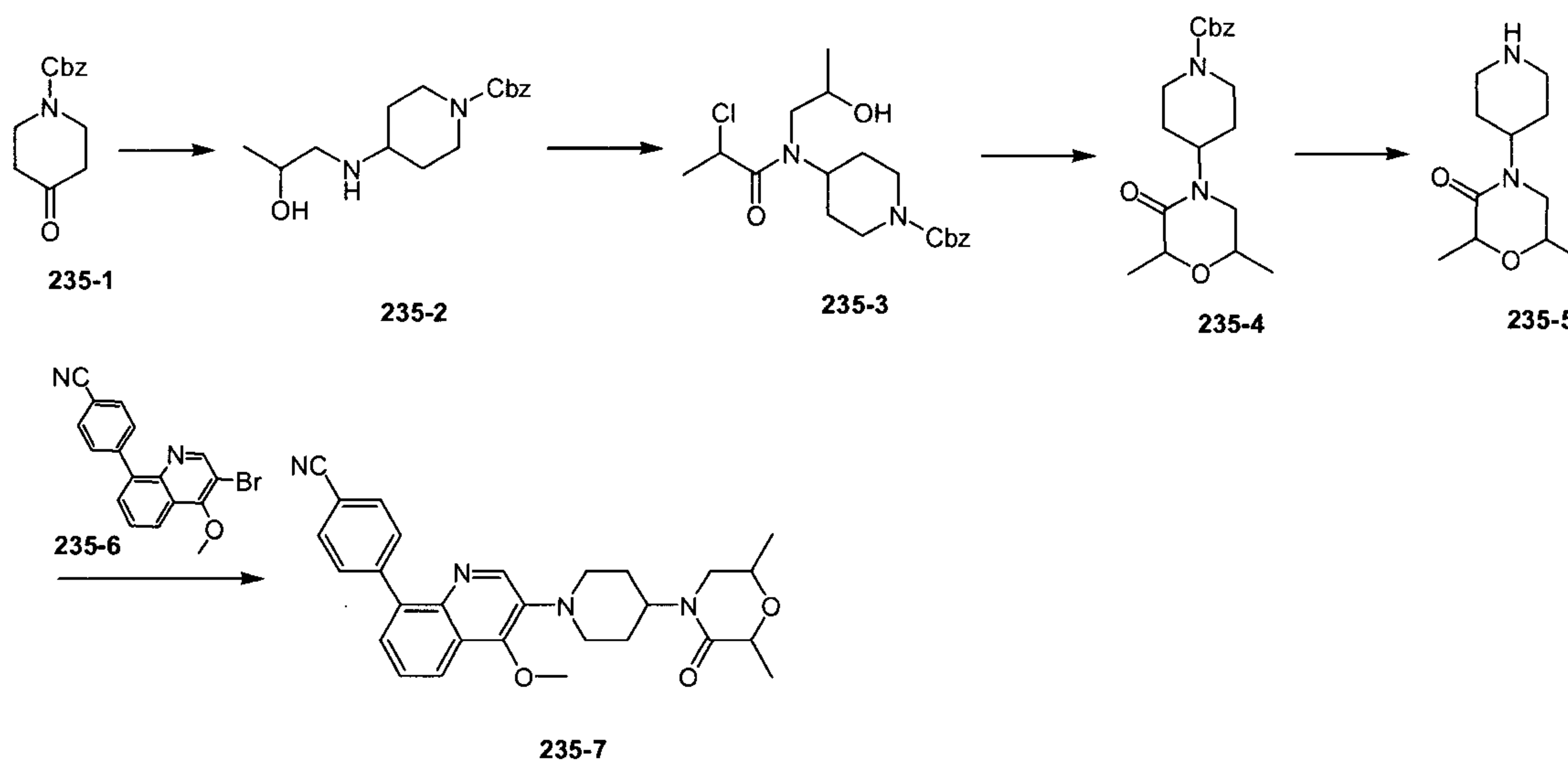
Embodiment	structure	NMR
234		¹ H NMR (400 MHz, CDCl ₃) δ ppm 8.76 (s, 1H) 8.23-8.19 (m, 1H) 7.81-7.77 (m, 4H) 7.58-7.56 (m, 2H) 4.12 (s, 3H) 3.72-3.69 (m, 2H) 2.90-2.85 (m, 4H) 2.49-2.24(m, 1H) 2.21-1.98(m, 6H) 1.78-1.74 (m, 2H) 1.05-1.03 (d, <i>j</i> =8, 6H).

Embodiment 235



4-(3-(4-(2,6-dimethyl-3-oxo-morpholino-4-yl)piperidin-1-yl)-4-methoxyquinolin-8-yl)

benzonitrile



[502] Step 1: A solution of compound 235-1 (15 g, 64 mmol), compound 235-A (12 mL, 192 mmol) and acetic acid (11.04 mL, 192 mmol) in methanol (200 mL) was stirred at 20°C for 1h, then NaBH₃CN (12.11 g, 192 mmol) was added in a whole and the mixture was stirred at 25°C overnight. After the reaction was complete as detected by LCMS, the reaction mixture was extracted with DCM and washed with saturated sodium bicarbonate aqueous solution. The organic phases were combined, dried over sodium sulfate and concentrated under reduced pressure to deliver compound 235-2 (15.6 g, 83%) as yellow oil. MS ESI calcd for C₁₆H₂₄N₂O₃

$[M+H]^+$ 293, found 293.

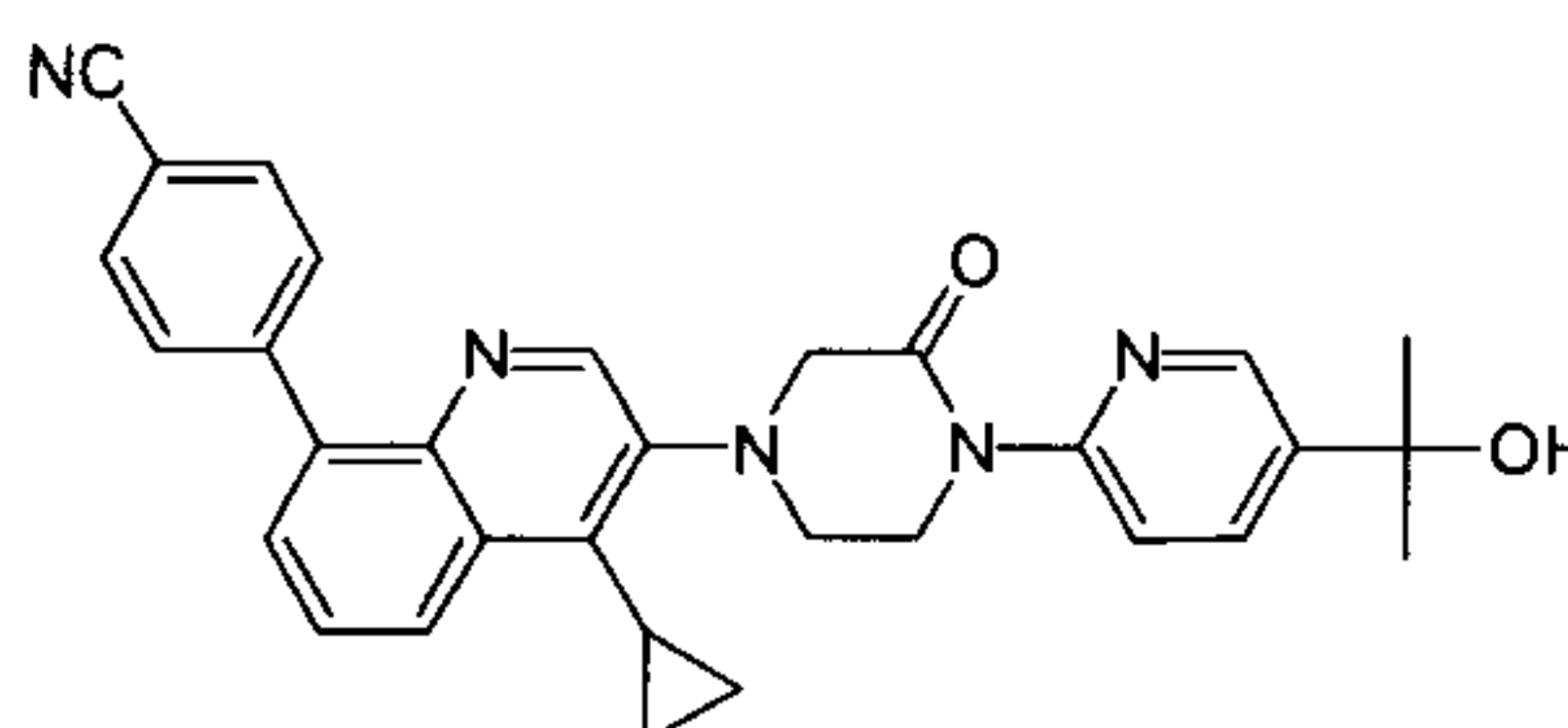
[503] Step 2: TEA (0.7 g, 7 mmol) and compound 235-B (0.59 g, 4.65 mmol) were added into a solution of compound 235-2 (1.36 g, 4.65 mmol) in DCM (20 mL), the mixture was stirred at room temperature for 2h. After the reaction was complete as detected by LCMS, the reaction mixture was extracted with DCM. The organic phases were combined, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc= 5:1) to deliver compound 235-3 (1.2 g, 67.4%) as yellow oil. **MS ESI** calcd for $C_{19}H_{27}ClN_2O_4$ $[M+H]^+$ 383, found 383.

[504] Step 3: Potassium *tert*-butoxide (225 mg, 2 mmol) was added into a solution of compound 235-3 (760 mg, 2 mmol) in THF (10 mL), the mixture was stirred at room temperature for 2h. After the reaction was complete as detected by LCMS, the reaction mixture was extracted with EtOAc. The organic phases were combined, dried over sodium sulfate and concentrated under reduced pressure to deliver compound 235-4 (500 mg, 70%) as yellow oil. **MS ESI** calcd for $C_{19}H_{26}N_2O_4$ $[M+H]^+$ 347, found 347.

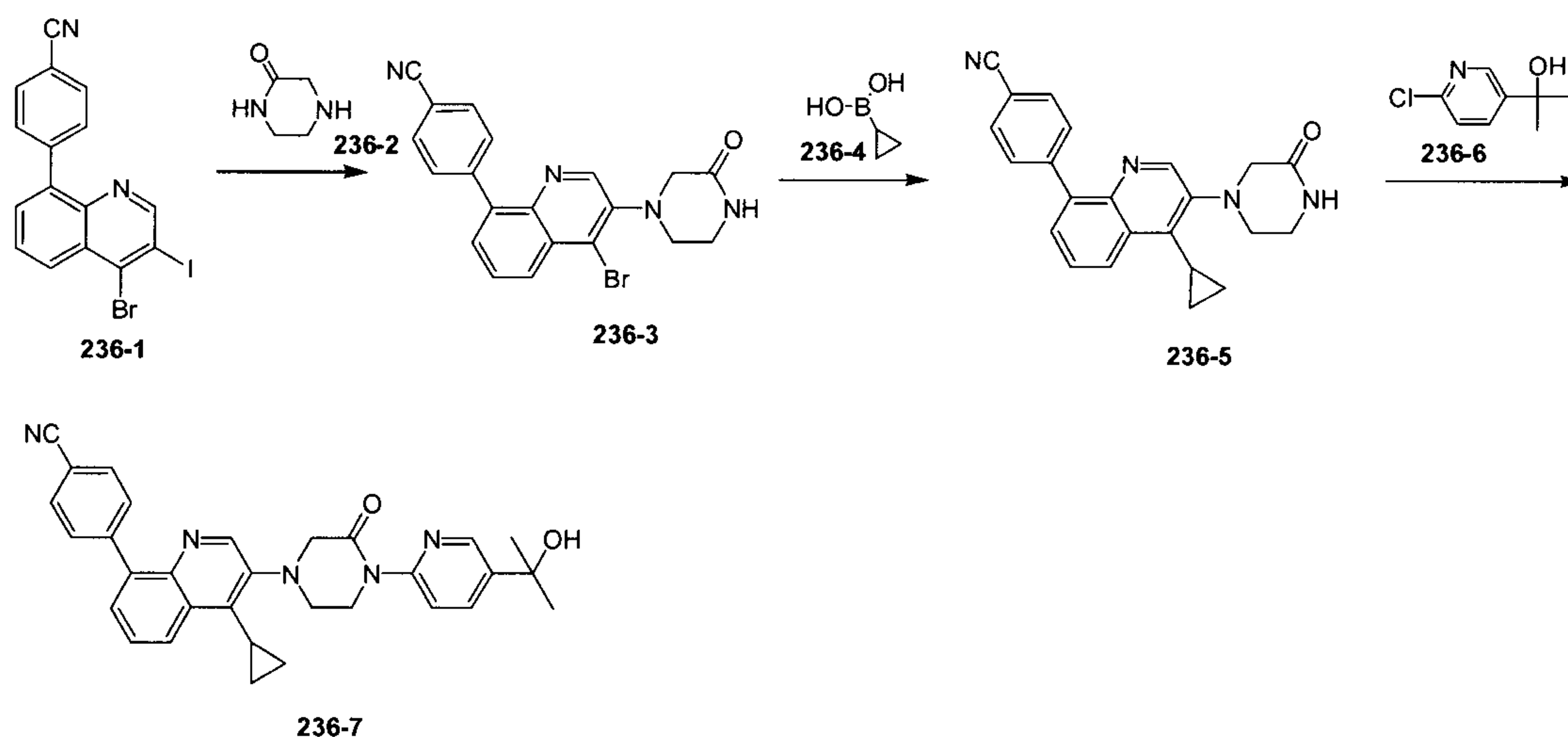
[505] Step 4: Pd/C (300 mg) was added into a solution of compound 235-4 (3.0 g, 8.6 mmol) in methanol (10 mL), and the mixture was hydrogenated under 40psi at room temperature overnight. Then the mixture was filtrated and concentrated under reduced pressure. The obtained colorless oil was used for the next step directly without further purification (1.3 g, 71%). **MS ESI** calcd for $C_{11}H_{20}N_2O_2$ $[M+H]^+$ 213, found 213.

[506] Step 5: The title compound (20 mg, 1.8%) was synthesized according to the above-mentioned method as yellow solid. **^1H NMR** (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.35-8.32 (m, 1H), 7.83-7.72 (m, 4H), 7.59-7.57 (m, 2H), 4.55-4.50 (m, 1H), 4.49-4.45 (m, 1H), 4.32(s, 3H), 4.15-4.02 (m, 2H), 3.75-3.52 (m, 2H), 3.22-3.02 (m, 4H), 2.15-2.07 (m, 2H), 2.05-1.92 (m, 2H), 1.48 (d, $J = 7.2$ Hz, 3H). **MS ESI** calcd for $C_{28}H_{30}N_4O_3$ $[M+H]^+$ 471, found 471.

Embodiment 236



4-(4-cyclopropyl-3-(4-(5-(1-hydroxy-1-methyl-ethyl)pyridin-2-yl)-3-oxo-piperazin-1-yl)quinolin-8-yl)benzonitrile

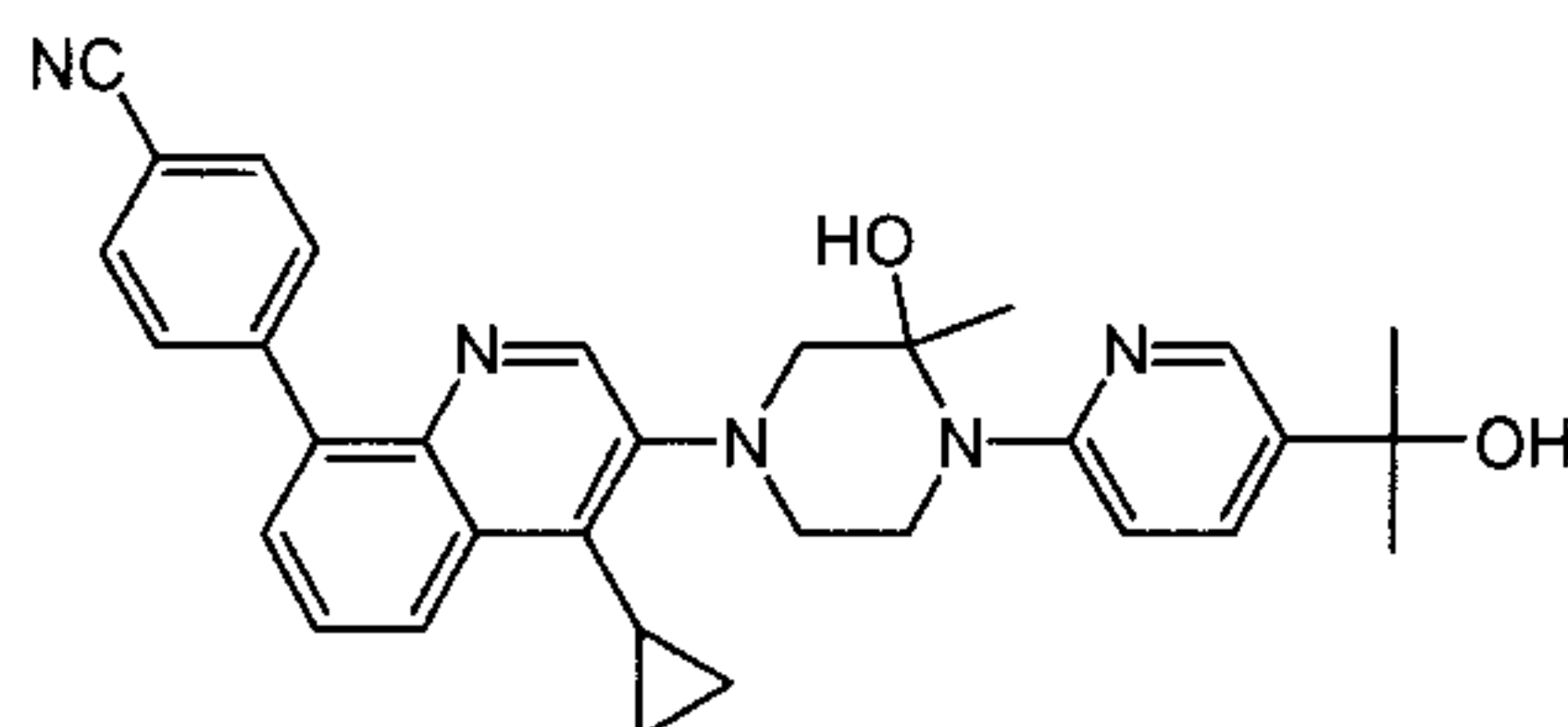


[507] Step 1: Compound 236-1 (4.35 g, 10 mmol), compound 236-2 (1.0 g, 10 mmol), $\text{Pd}_2(\text{dba})_3$ (920 mg, 1.0 mmol), Xantphos (1.15 g, 2.0 mmol) and sodium *tert*-butoxide (2.0 g, 20 mmol) were added into toluene (30 mL), under nitrogen gas atmosphere, the reaction mixture was stirred at 120°C for 2h. The mixture was poured into H_2O , extracted with EtOAc (100 mL), the extraction liquid was washed with brines, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to deliver 1.5 g compound 236-3, yield 37.5%, as yellow solid. **MS ESI** calcd for $\text{C}_{20}\text{H}_{15}\text{BrN}_4\text{O}$ $[\text{M}+\text{H}]^+$ 407, found 407.

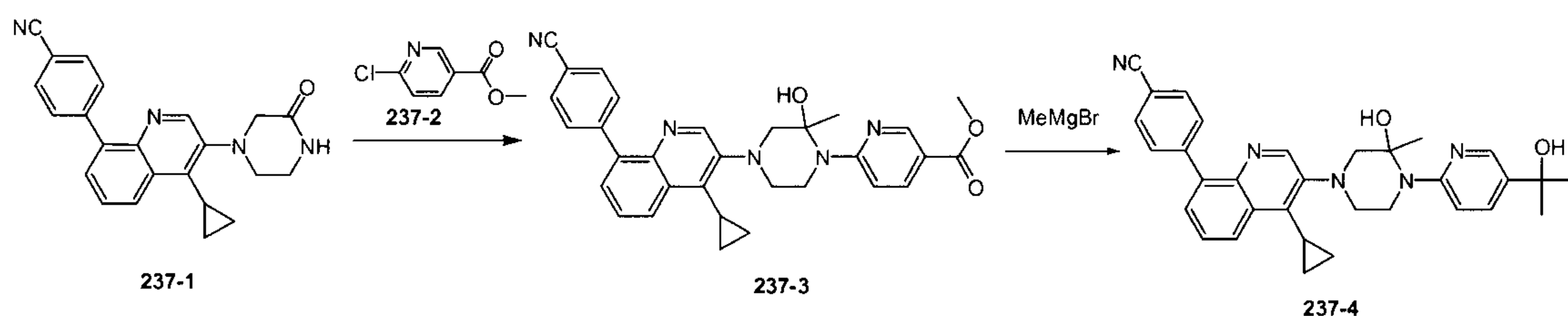
[508] Step 2: Compound 236-3 (407 mg, 1.0 mmol), compound 236-4 (870 mg, 10 mmol), *n*-BuPAd₂ (71 mg, 0.2 mmol), palladium acetate (23 mg, 0.1 mmol) and cesium carbonate (650 mg, 2.0 mmol) were added into toluene/ H_2O (5:1, 12 mL), under nitrogen gas atmosphere, the reaction mixture was stirred at 110°C for 2h. The mixture was poured into H_2O , extracted with EtOAc (50 mL), the extraction liquid was washed with brines, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to deliver 230 mg compound 236-5, yield 64%, as yellow solid. **MS ESI** calcd for $\text{C}_{23}\text{H}_{20}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$ 369, found 369.

[509] Step 3: Compound 236-5 (185 mg, 0.5 mmol), compound 236-6 (86 mg, 0.5 mmol), $\text{Pd}_2(\text{dba})_3$ (46 mg, 0.05 mmol), Xantphos (57.7 mg, 0.1 mmol) and cesium carbonate (325 mg, 1.0 mmol) were added into toluene (10 mL), under nitrogen gas atmosphere, the reaction mixture was stirred at 120°C for 2h. The mixture was poured into H_2O , extracted with EtOAc (100 mL), the extraction liquid was washed with brines, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative HPLC to deliver the title compound (80 mg, yield 32%) as white solid. **^1H NMR** (400 MHz, CDCl_3) δ 8.78(s, 1H), 8.61-8.62(d, J = 2.0 Hz, 1H), 8.53-8.55 (d, J =7.6 Hz, 1H), 8.01-8.04 (d, J = 8.4 Hz, 1H), 7.78-7.80 (m, 4H) 7.61-7.67 (m, 2H) 4.26-4.28 (t, J =10.4 Hz 2H), 4.23(s, 2H) 3.74-3.76 (t, J = 10.8 Hz 2H), 2.11-2.15 (m, 1H) δ 1.65(s, 6H), 1.34-1.37 (m, 2H) 0.98-1.00 (d, J = 6.4 Hz 2H). **MS ESI** calcd for $\text{C}_{31}\text{H}_{29}\text{N}_5\text{O}_2$ $[\text{M}+\text{H}]^+$ 504, found 504.

Embodiment 237



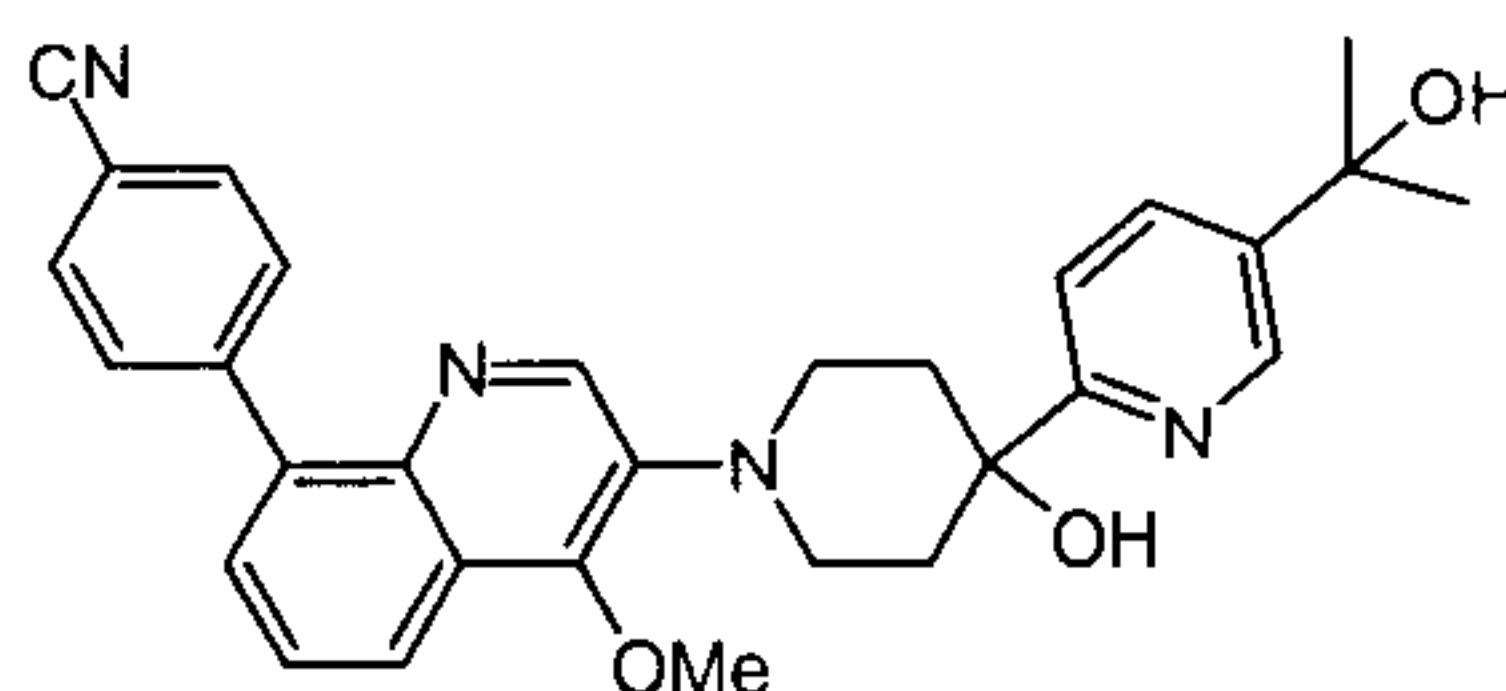
4-(4-cyclopropyl-3-(3-hydroxy-4-(5-(1-hydroxy-1-methyl-ethyl)pyridin-2-yl)-3-methylpiperazin-1-yl)quinolin-8-yl)benzonitrile



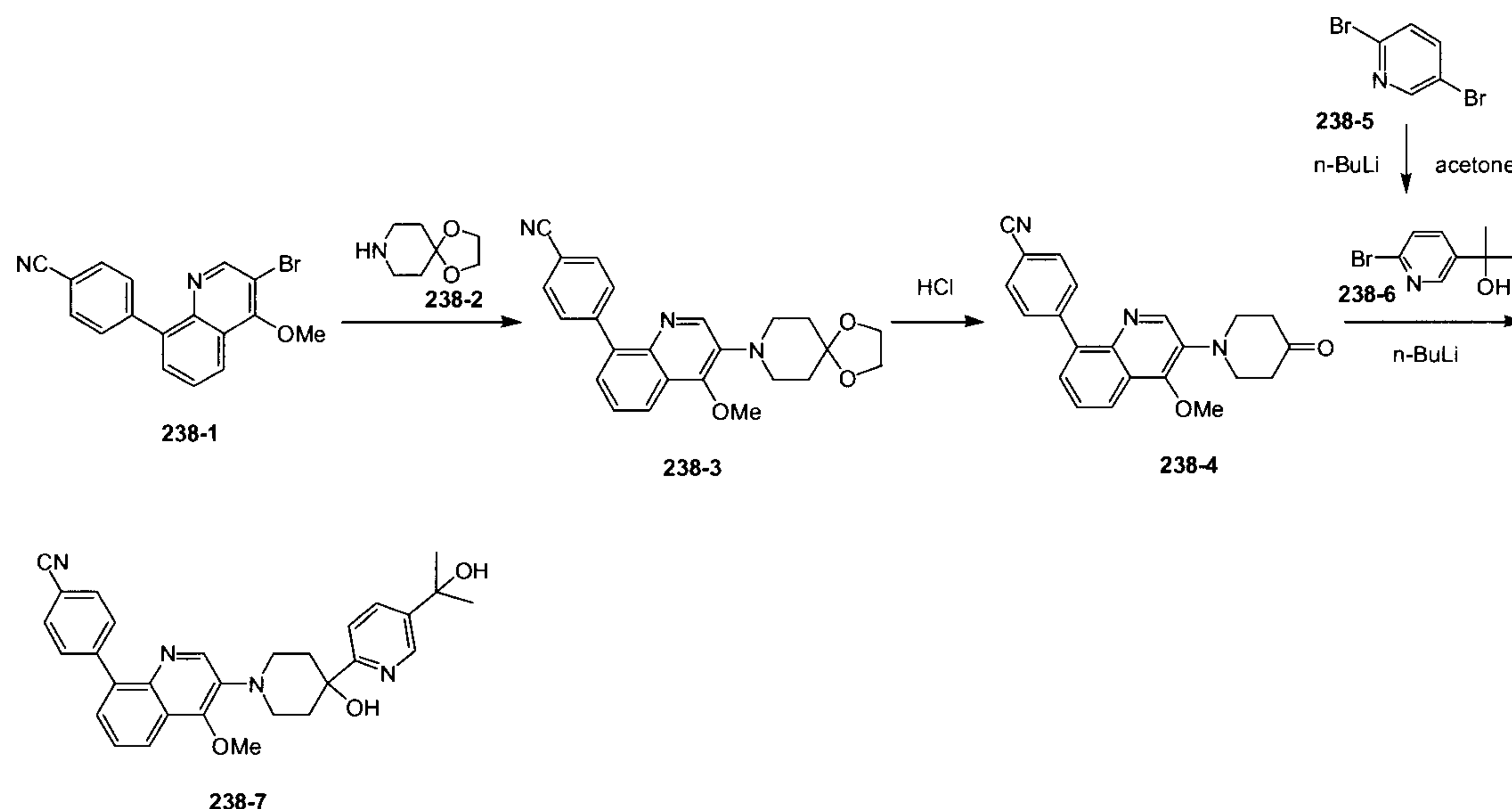
[510] Step 1: Compound 237-1 (150 mg, 0.4 mmol), compound 237-2 (70 mg, 0.4 mmol), $\text{Pd}_2(\text{dba})_3$ (37 mg, 0.04 mmol), Xantphos (45 mg, 0.08 mmol) and cesium carbonate (260 mg, 0.8 mmol) were added into toluene (2 mL), under nitrogen gas atmosphere, the reaction mixture was stirred at 120°C for 2h. The mixture was poured into H_2O , extracted with EtOAc (10 mL), the extraction liquid was washed with brines, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column chromatography to deliver 80 mg compound 237-3, yield 39% as yellow solid. **MS ESI** calcd for $\text{C}_{30}\text{H}_{25}\text{N}_5\text{O}_3$ $[\text{M}+\text{H}]^+$ 504, found 504.

[511] Step 2: Compound 237-3 (50 mg, 0.1 mmol) was dissolved in THF (5 mL), methyl magnesium bromide (0.1 mL, 3 M in Et_2O) was added slowly into the solution at -76°C, stirred at this temperature for 1h, the reaction mixture was poured into an ammonium chloride aqueous solution, extracted with EtOAc (10 mL), the extraction liquid was washed with brines, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by preparative HPLC to deliver the title compound (10 mg, yield 20%) as white solid. **^1H NMR** (400 MHz, CDCl_3) δ 8.76(s, 1H), 8.66(s, 1H), 8.38-8.39(d, J = 6.4 Hz, 1H), 7.83-7.85 (d d, J = 2.0 Hz, 1H), 7.80-7.83 (m, 4H) 7.54-7.57 (m, 2H) 6.25-6.33 (m, 2H) 4.29 (s, 2H), 3.84(s, 3H) 3.72-3.75 (t, J = 11.2 Hz 2H), 3.47-3.49(d, J = 6.8 Hz, 2H), 2.16 (s, 6H) 1.92-1.95(m, 1H), 1.22-1.26 (m, 2H) 0.75-0.79 (m, 2H). **MS ESI** calcd for $\text{C}_{32}\text{H}_{33}\text{N}_5\text{O}_2$ $[\text{M}+\text{H}]^+$ 520, found 520.

Embodiment 238



4-(3-(4-hydroxy-4-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)piperidin-1-yl)-4-methoxyquinolin-8-yl)benzonitrile



[512] Step 1: Compound 238-2 (930 mg, 6.5 mmol) and sodium *tert*-butoxide (1.9 g, 19.5 mmol) were added into a solution of compound 238-1 (2.64 g, 7.8 mmol) in toluene (70 mL), then under nitrogen gas atmosphere, Pd₂(dba)₃ (595 mg, 0.65 mmol) and Xantphos (750 mg, 1.3 mmol) were added, the reaction mixture was heated to 100°C and stirred for 3 h. The solvent was evaporated, H₂O (100 mL) was added, the mixture was extracted with EtOAc (50 mL x 3). The organic phase was washed with brines, dried over sodium sulfate and concentrated to give a crude product. The crude product was purified by silica gel column chromatography (PE/EtOAc= 5/1) to deliver compound 238-3 (1 g crude) as yellow solid. **MS ESI** calcd for C₂₄H₂₃N₃O₃ [M+H]⁺ 402, found 402.

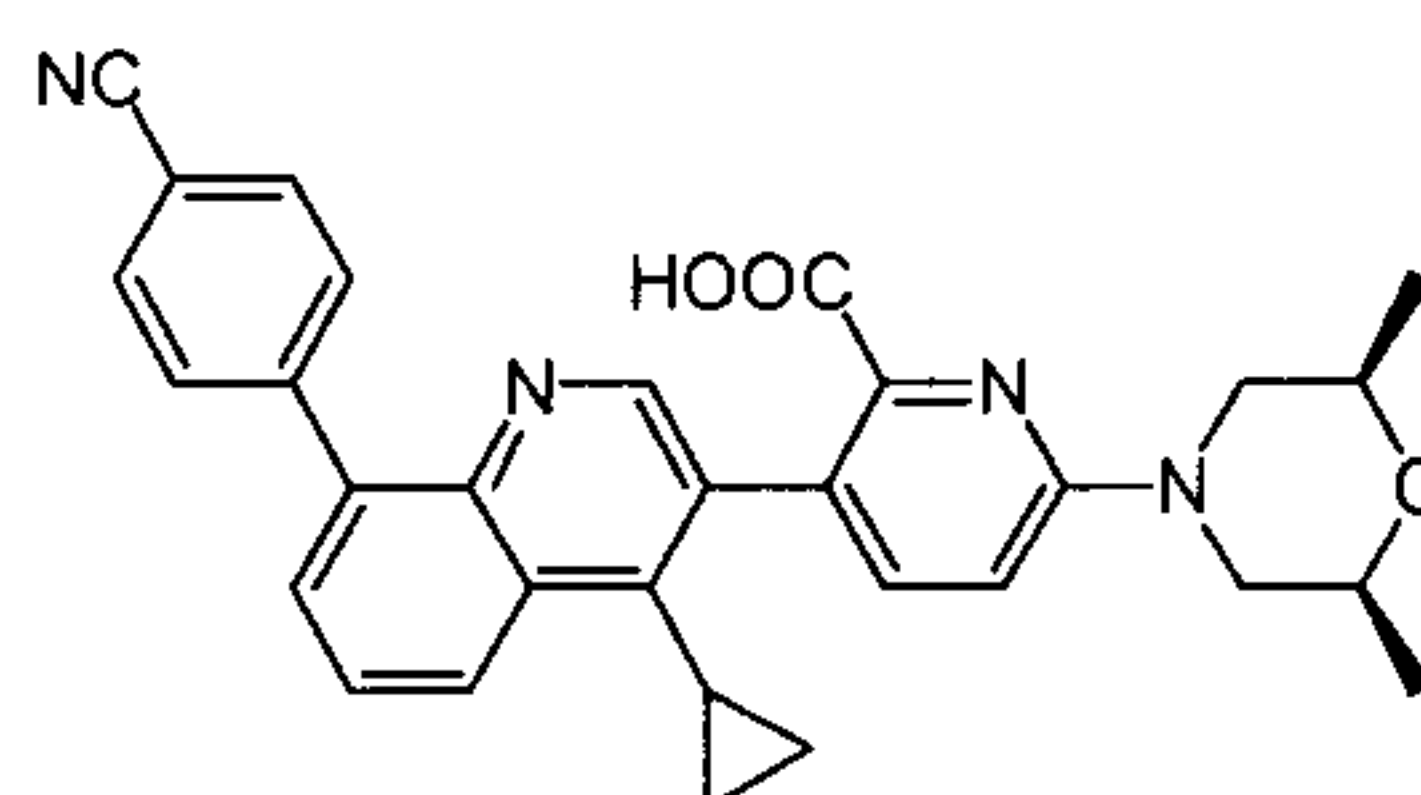
[513] Step 2: 2 N HCl (15 mL) was added into a solution of compound 238-3 (1 g crude, 2.5 mmol) in THF (15 mL), the reaction mixture was stirred at room temperature for h. The mixture was quenched with 2 N NaOH aqueous solution, and adjusted to pH = 7 to 8. H₂O (20 mL) was added, the mixture was extracted with EtOAc (20 mL x 2). The organic phase was washed with brines, dried over sodium sulfate and concentrated to deliver compound 238-4 (380 mg crude) as yellow oil. **MS ESI** calcd for C₂₂H₁₉N₃O₂ [M+H]⁺ 358, found 358.

[514] Step 3: Compound 238-5 was dissolved in THF (150 mL), cooled to -70°C, *n*-BuLi (5 mL, 12.5 mmol) was added dropwise, after reacting for 30 min, acetone (2 mL, 20 mmol) was added dropwise, then the reaction mixture was stirred at -70°C for 1h. The reaction mixture was quenched with saturated ammonium chloride solution, H₂O (30 mL) was added, then extracted with EtOAc (30 mL x 3). The organic phase

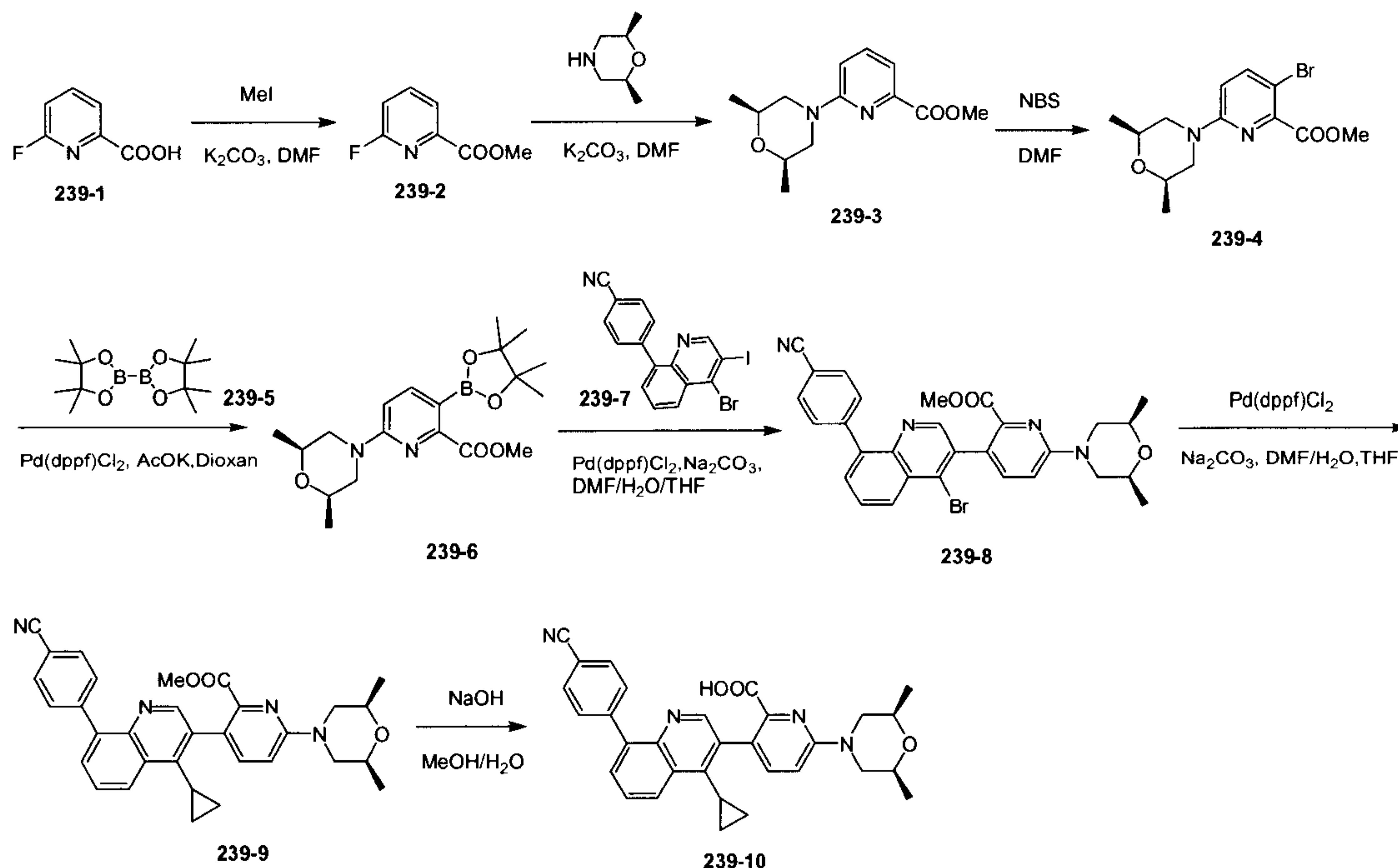
was washed with brines, dried over sodium sulfate and concentrated to give a crude product. The crude product was purified by column chromatography (PE/EtOAc=3/1) to deliver compound 238-6 (462 mg, 17.1%) as white solid. **MS ESI** calcd for $C_8H_{10}BrNO$ $[M+H]^+$ 216, found 216.

[515] Step 4: Compound 238-6 (30 mg, 0.14 mmol) was dissolved in THF (5 mL), the mixture was cooled to -70°C , *n*-BuLi (0.12 mL, 0.31 mmol) was added dropwise, after reacting for 30 min, compound 238-4 (50 mg crude, 0.14 mmol) in THF (2 mL) was added dropwise, the reaction mixture was stirred at -70°C for 1h. The reaction mixture was quenched with saturated ammonium chloride solution, H_2O (10 mL) was added, then extracted with EtOAc (20 mL). The organic phase was washed with brines, dried over sodium sulfate and concentrated to give a crude product. The crude product was purified by prep-HPLC to deliver the title compound (3 mg, 4.3%) as yellow solid. **MS ESI** calcd for $C_{30}H_{30}N_4O_3$ $[M+H]^+$ 495, found 495.

Embodiment 239



3-(8-(4-cyanophenyl)-4-cyclopropylquinolin-3-yl)-6-(2,6-dimethylmorpholino-4-yl)pyridin-2-carboxylic acid



[516] Step 1: Compound 239-1 (5 g, 35 mmol) and K_2CO_3 (10 g, 70 mmol) were added into a solution of MeI (5 g, 35 mmol) in DMF (40 mL), the reaction mixture was stirred at 60°C for 2h, the reaction was monitored by LCMS till completion.

Then 2,6-dimethylmorpholine (6.1 g, 53 mmol) was added into the reaction system, then the mixture was stirred at 110°C for 2h, after the reaction was complete as detected by TLC, the mixture was poured into H₂O and extracted with EtOAc, the organic phase was dried over anhydrous sodium sulfate and concentrated to deliver a crude product. The crude product was purified by silica gel column chromatography (MeOH:EtOAc=5:1) to deliver compound 239-3 (3.5 g, yield 40%) as oil. **MS ESI** calcd for C₁₃H₁₈N₂O₃[M+H]⁺ 251, found 251.

[517] Step 2: NBS (1.6 g, 9 mmol) was added slowly into a solution of compound 239-3 (5 g, 35 mmol) in DMF (15 mL), the reaction mixture was stirred at room temperature for 6h, and the reaction was monitored by LCMS till completion. Then the mixture was poured into H₂O, and extracted with EtOAc (100×3 mL), the organic phase was dried over anhydrous sodium sulfate and concentrated to deliver a crude product. The crude product was purified by silica gel column chromatography (PE:EtOAc=5:1) to deliver compound 239-4 (3 g, yield 91%) as white solid. **MS ESI** calcd for C₁₃H₁₇BrN₂O₃[M+H]⁺ 329, found 329.

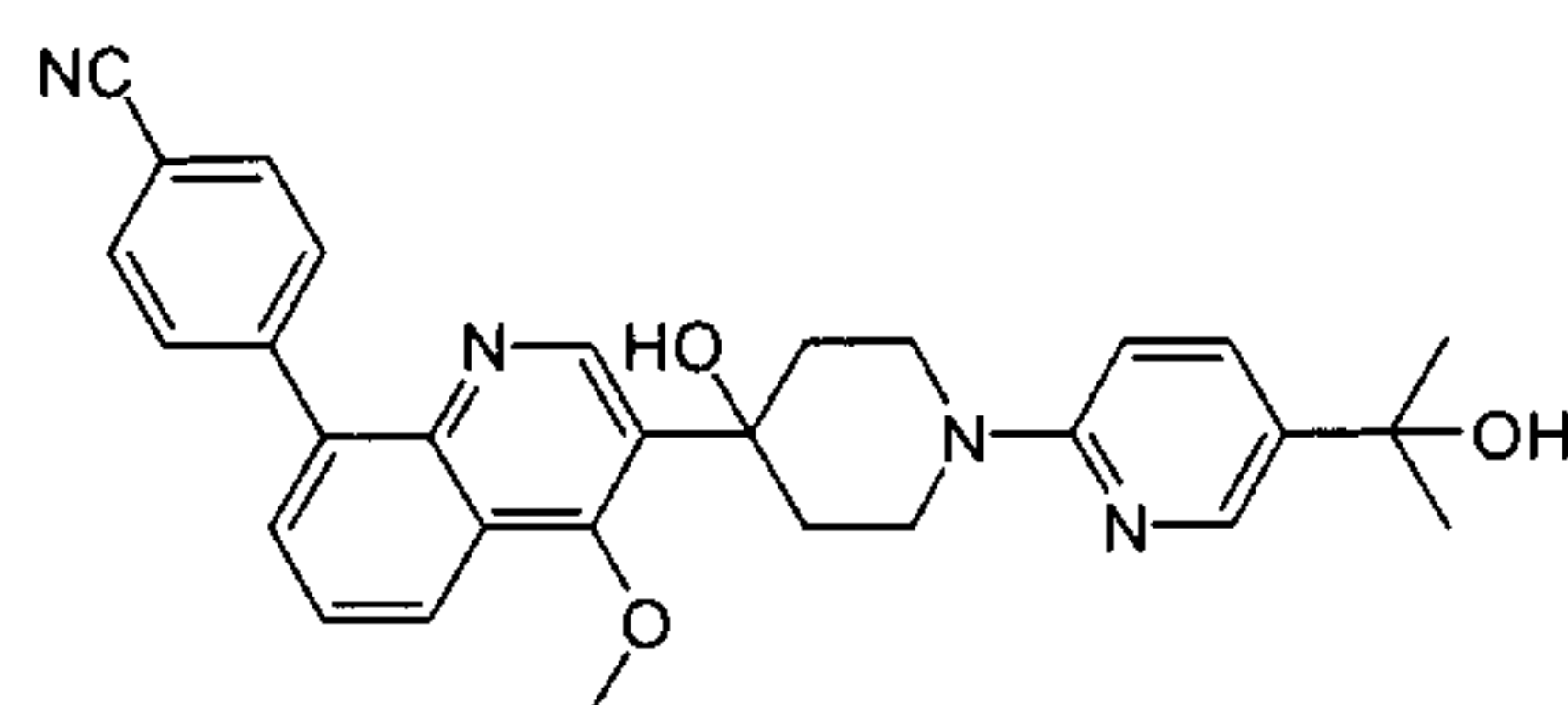
[518] Step 3: Compound 239-4 (2 g, 6 mmol), compound 239-5 (1.82 g, 7.2 mmol) and KOAc (1.2 g, 12 mmol) were dissolved in dioxane (50 mL), then under nitrogen gas atmosphere, Pd(dppf)Cl₂ (440 mg, 0.6 mmol) was added, the reaction mixture was stirred at 120°C for 3h. After the reaction was complete, the mixture was poured into H₂O, and extracted with EtOAc. The organic phase was dried over anhydrous sodium sulfate and concentrated to deliver a crude product. The crude product was purified by silica gel column chromatography (PE:EtOAc=5:1) to deliver compound 239-6 (1.3 g, 60%) as yellow solid. **MS ESI** calcd for C₁₉H₂₉BN₂O₅[M+H]⁺ 377, found 377.

[519] Step 4: Compound 239-7 (1.74 g, 4 mmol), compound 239-6 (1.5 g, 4 mmol), and Na₂CO₃ (848 mg, 8 mmol) were dissolved in DMF (2 mL) / H₂O (2 mL) / THF (10 mL), then Pd(dppf)Cl₂ (293 mg, 0.4 mmol) was added into the solution. The reaction system reacted at 70°C overnight. After the reaction was complete as detected by LC-MS. The mixture was poured into H₂O, and extracted with EtOAc. The organic phase was dried over anhydrous sodium sulfate and concentrated to deliver a crude product. The crude product was purified by silica gel column chromatography (PE:EtOAc=2:1) to deliver compound 239-8 (474 mg, 21%) as red solid. **MS ESI** calcd for C₂₉H₂₅BrN₄O₃[M+H]⁺ 557, found 557.

[520] Step 5: Compound 239-8 (474 mg, 0.85 mmol), cyclopropyl boric acid (731 mg, 8.5 mmol) and Na₂CO₃ (180 mg, 1.7 mmol) were dissolved in DMF (2 mL) / H₂O (2 mL) / THF (10 mL), then Pd(dppf)Cl₂ (73 mg, 0.1 mmol) was added into the solution. The reaction system was reacted at 70°C overnight. After the reaction was complete as detected by LC-MS. The mixture was poured into H₂O, and extracted with EtOAc. The organic phase was dried over anhydrous sodium sulfate and concentrated to deliver a crude product. The crude product was purified by silica gel column chromatography (PE:EtOAc=2:1) to deliver compound 239-9 (200 mg, 21%) as red solid. **MS ESI** calcd for C₃₂H₃₀N₄O₃[M+H]⁺ 519, found 519.

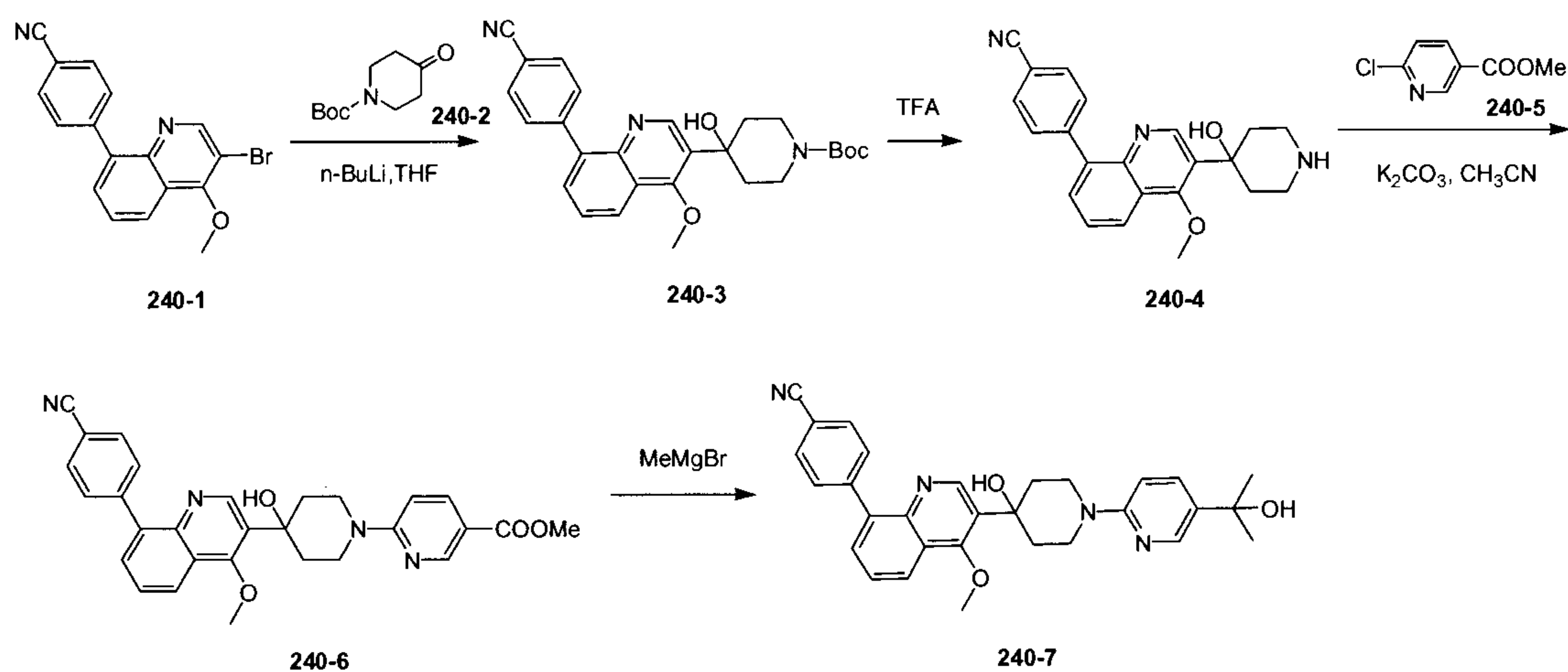
[521] Step 6: NaOH (80 mg, 2 mmol) was added into a solution of compound 239-9 (200 mg, 0.4 mmol) in MeOH (5 mL) / H₂O (1 mL), the reaction system reacted at room temperature overnight. After the reaction was complete as detected by LC-MS, the crude product was purified by HPLC to deliver the title compound (30 mg, 15%) as yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.77 (d, *J* = 8.4Hz, 1H), 7.86-7.82 (m, 5H), 7.76-7.06 (m, 3H), 7.07 (d, *J* = 8.4Hz, 1H), 4.10 (d, *J* = 12.0 Hz, 2H), 3.81 (m, 2H), 2.76 (m, 2H), 2.32 (m, 2H), 1.37 (d, *J* = 6.0Hz, 6H), 1.08 (m, 2H), 0.49 (d, *J* = 5.2Hz, 2H), MS ESI calcd for C₃₁H₂₈N₄O₃[M+H]⁺ 505, found 505.

Embodiment 240



4-(3-(4-hydroxy-5'-(1-hydroxy-1-methyl-ethyl)-3,4,5,6-tetrahydro-2H-[1,2']

bipyridyl-4-yl)4-methoxyquinolin-8-yl)benzonitrile



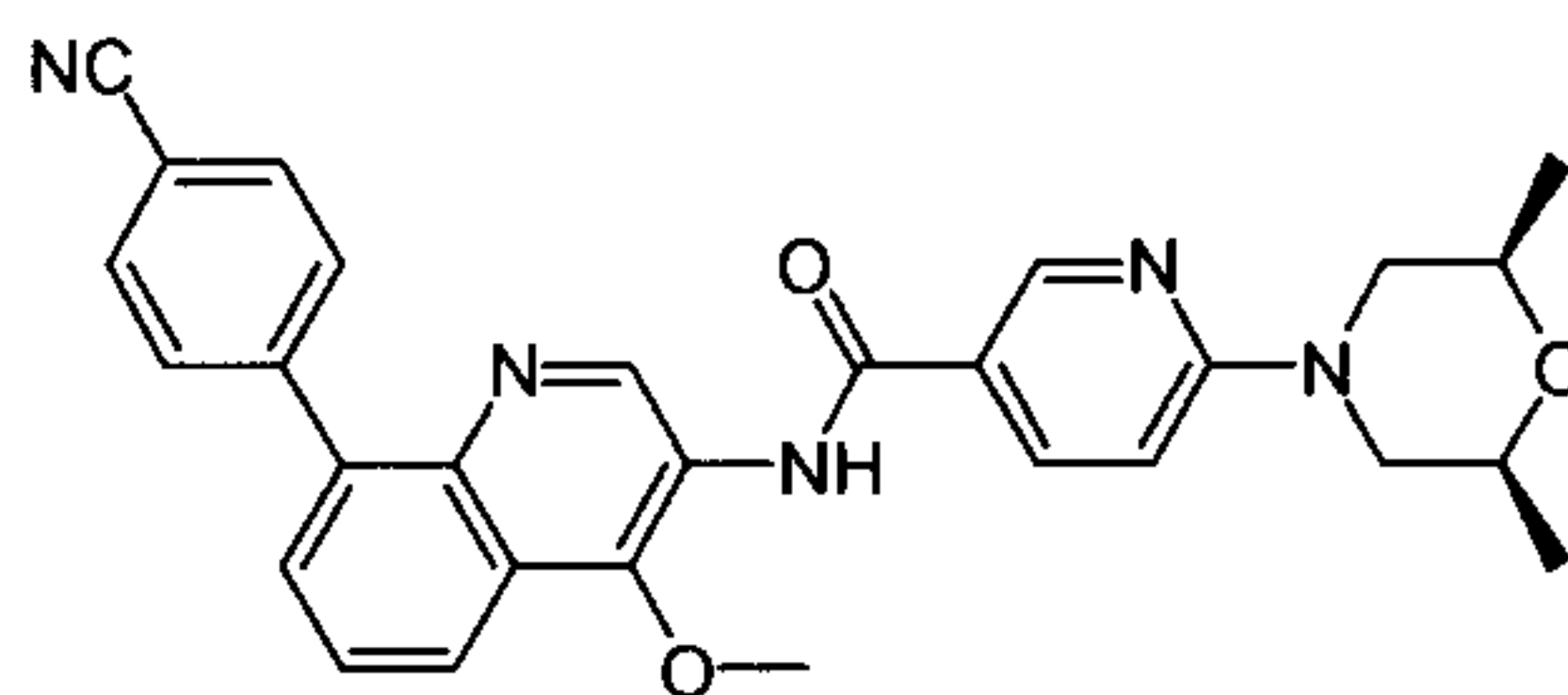
[522] Step 1: *n*-BuLi (2.5 M, 1.25 mmol) was added slowly into a solution of compound 240-1 (170 mg, 0.5 mmol) in THF (10 mL) at -78°C, the reaction mixture was stirred at -78°C for 0.5h, then 2 (100 mg, 0.5 mmol) was added into the reaction system, the mixture was stirred at -78°C for 2h, after the reaction was complete as detected by TLC, the mixture was poured into NH₄Cl (aq), extracted with EtOAc, the organic phase was dried over anhydrous sodium sulfate and concentrated to deliver a crude product. The crude product was purified by silica gel column chromatography (MeOH:EtOAc=2:1) to deliver compound 240-3 (100 mg, yield 33%) as oil. MS ESI calcd for C₂₇H₂₉N₃O₄[M+H]⁺ 460, found 460.

[523] Step 2: CF₃COOH (2 mL) was added into a solution of compound 240-3 (400 mg, 0.9 mmol) in DCM (4 mL), the reaction mixture was stirred at room temperature for 1h, the reaction was monitored by TLC till completion. Then the solvent was evaporated to dry, the crude product was used for the next step directly.

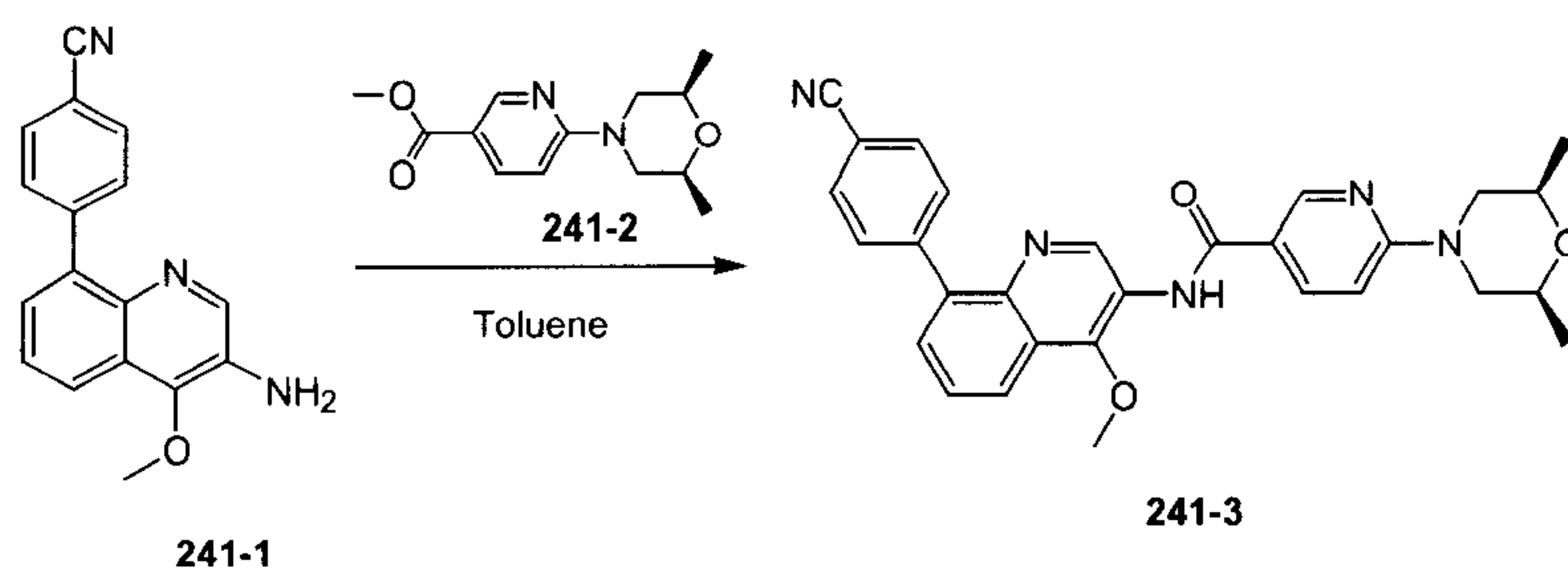
[524] Step 3: Compound 240-4 (250 mg, 0.7 mmol), K_2CO_3 (292 mg, 2.1 mmol) were dissolved in ACN (10 mL), then 240-5 (120 mg, 0.7 mmol) was added, the reaction mixture was stirred at 100°C for 8h. After the reaction was complete as detected by LCMS, the filtrate was concentrated to give a crude product. The crude product was purified by silica gel column chromatography (PE:EtOAc=1:1) to deliver compound 240-6 (200 mg, 58%) as white solid. **MS ESI** calcd for $C_{29}H_{26}N_4O_4[M+H]^+$ 495, found 495.

[525] Step 4: MeMgBr (1 mL, 3.0 mmol) was added dropwise slowly into a solution of compound 240-6 (200 mg, 0.4 mmol) in THF (10 mL) at room temperature, the reaction mixture was stirred at room temperature for 30 min. After the reaction was complete as detected by LC-MS. The mixture was poured into NH_4Cl (aq), and extracted with EtOAc (100×3 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated to deliver a crude product. The crude product was purified by HPLC to deliver the title compound (25 mg, 13%) as yellow solid. **^1H NMR** (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.35 (d, $J = 3.2$ Hz, 1H), 8.15 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.79 (s, 4H), 7.74-7.68 (m, 3H), 6.76 (d, $J = 7.2$ Hz, 1H), 4.29-4.26 (m, 2H), 4.20 (s, 3H), 3.86 (s, 1H), 3.51 (t, $J = 12$ Hz, 2H), 2.40-2.33 (m, 2H), 2.09-2.03 (m, 2H), 1.61 (s, 6H). **MS ESI** calcd for $C_{30}H_{30}N_4O_3[M+H]^+$ 495, found 495.

Embodiment 241



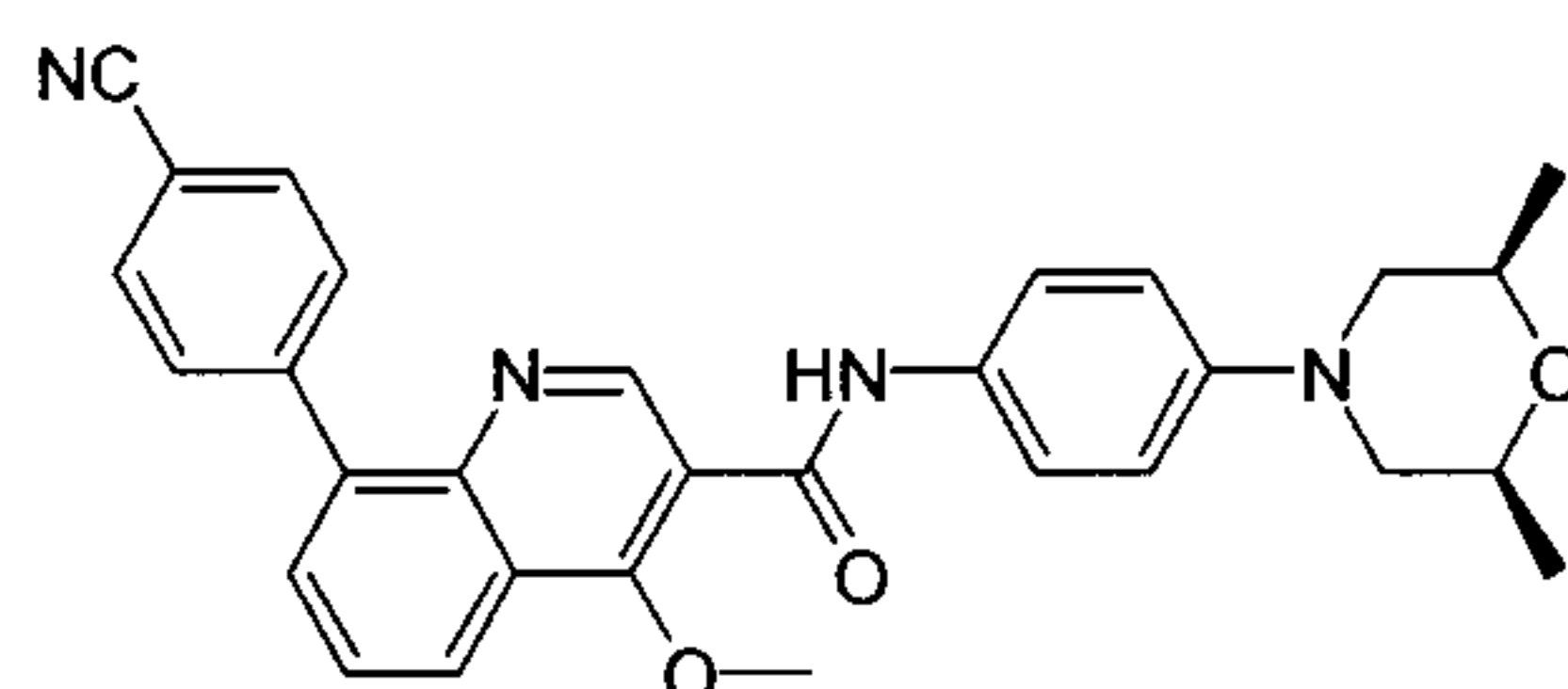
N-(8-(4-cyanophenyl)-4-methoxyquinolin-3-yl)-6-(2,6-dimethylmorpholino-4-yl)
nicotinamide



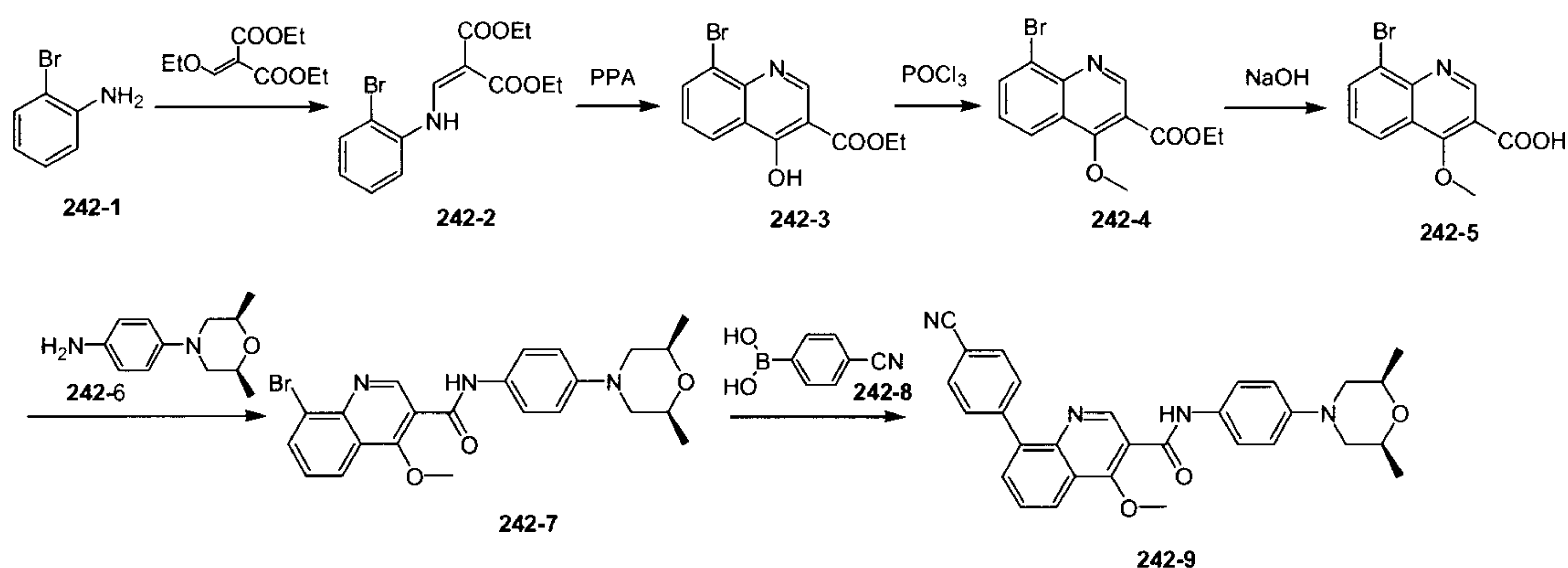
[526] Compound 241-1 (100 mg, 0.36 mmol), compound 241-2 (100 mg, 0.4 mmol), trimethyl aluminum solution (0.9 mL, 0.9 mmol) were dissolved in toluene (2 mL), the reaction mixture was stirred at 80 °C for 12h. The reaction mixture was cooled to room temperature, H_2O was added, the solution was extracted with EtOAc (50 mL×2), the organic phase was washed with H_2O , brines respectively, dried over anhydrous sodium sulfate, filtrated and concentrated under reduced pressure, the

crude product was purified by silica gel column chromatography to deliver the title compound (80 mg, yield 44%) as white solid. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.89 (s, 1H), 8.84 (s, 1H), 8.33-8.36(d, $J = 8.4$ Hz, 1 H), 8.17 (d, $J = 8.8$ Hz, 1 H), 7.71-7.85 (m, 5 H), 6.94 (d, $J = 9.2$ Hz, 1 H), 5.51 (s, 1H), 4.35 (d, $J = 13.2$ Hz, 2 H), 4.16 (s, 3 H), 2.66 (t, $J = 12.8$ Hz, 2 H), 1.28 (d, $J = 6.4$ Hz, 6 H). **MS ESI** calcd for $\text{C}_{29}\text{H}_{27}\text{N}_5\text{O}_3$ $[\text{M}+\text{H}]^+$ 494, found 494.

Embodiment 242



8-(4-cyanophenyl)-N-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxyquinoline-3-carboxamide



[527] Step 1: (Diethyl ethoxymethylene)malonate (13 g, 60 mmol), 2-bromoaniline (10.3 g, 60 mmol) were mixed and stirred at 100°C for 2h. After cooled to room temperature, the reaction mixture was poured into methanol, recrystallized with methanol to deliver compound 242-2 (14.5 g, yield 70.7%) as yellow solid. **MS ESI** calcd for $\text{C}_{14}\text{H}_{16}\text{BrNO}_4$ $[\text{M}+\text{H}]^+$ 342, found 342.

[528] Step 2: Compound 242-2 (10 g, 29.2 mmol) in Ph_2O (100 mL) was stirred at reflux for 30 min, then cooled to room temperature, hexane was added, the mixture was filtrated to deliver compound 242-3 (2.8 g, yield 32.6%) as brown solid. **MS ESI** calcd for $\text{C}_{12}\text{H}_{10}\text{BrNO}_3$ $[\text{M}+\text{H}]^+$ 295, found 295.

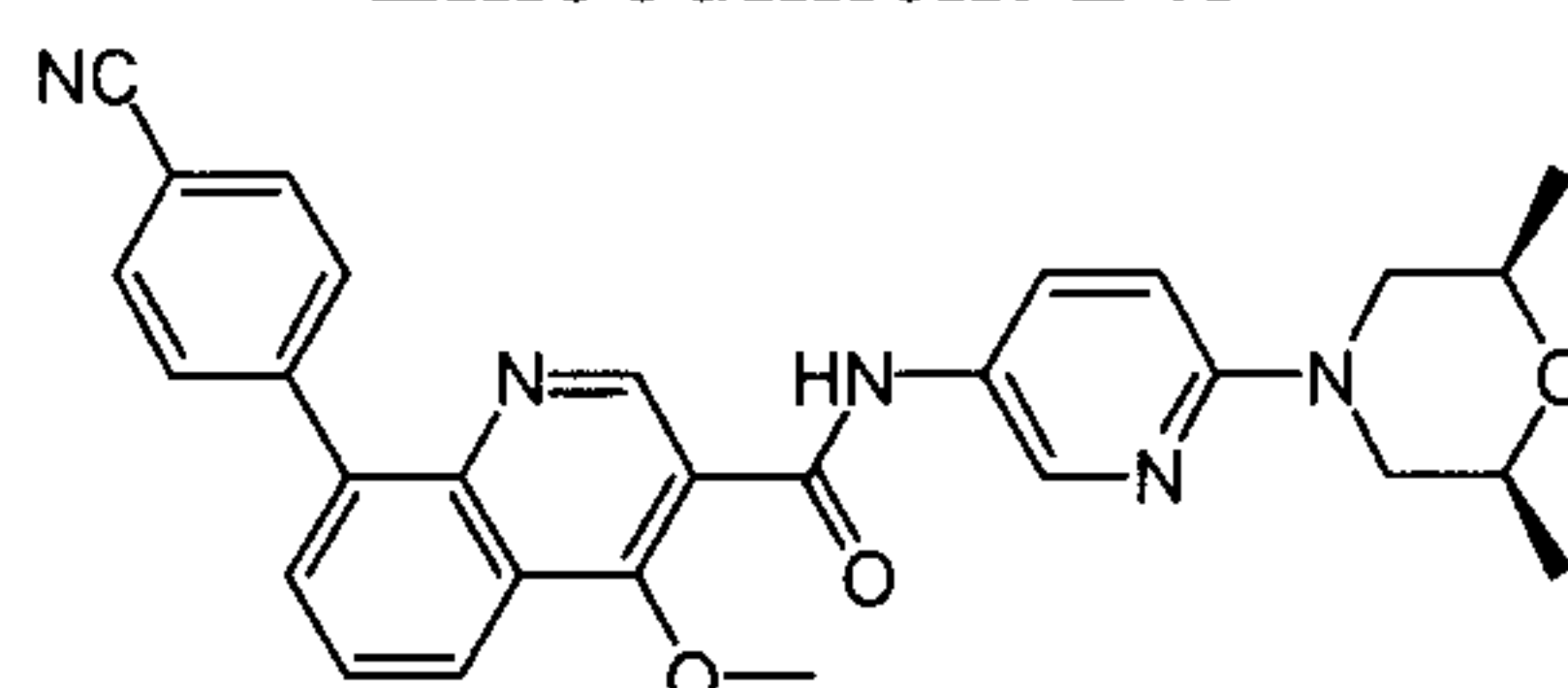
[529] Step 3: Compound 242-3 (500 mg, 1.7 mmol) was dissolved in POCl_3 (4 mL), and the mixture was stirred at 110°C for 1h. Then the reaction mixture was poured into methanol and sodium carbonate aqueous solution was added. The mixture was extracted with EtOAc, dried over over anhydrous sodium sulfate, filtrated and concentrated under vacuum to deliver compound 242-4 (400 mg, yield 76%) as brown solid. **MS ESI** calcd for $\text{C}_{13}\text{H}_{12}\text{BrNO}_3$ $[\text{M}+\text{H}]^+$ 310, found 310.

[530] Step 4: Compound 242-4 (527 mg, 1.7 mmol) was dissolved in methanol (5 mL), H₂O (1 mL), NaOH (340 mg, 8.5 mmol) was added, the reaction mixture was stirred at room temperature for 5h. Then the mixture was poured into H₂O, then HCl solution was added to adjust pH = 7, the mixture was extracted with EtOAc, dried over sodium sulfate, filtrated and concentrated under vacuum to deliver compound 242-5 (478 mg, yield 99%) as yellow solid. **MS ESI** calcd for C₁₁H₈BrNO₃ [M+H]⁺ 282, found 282.

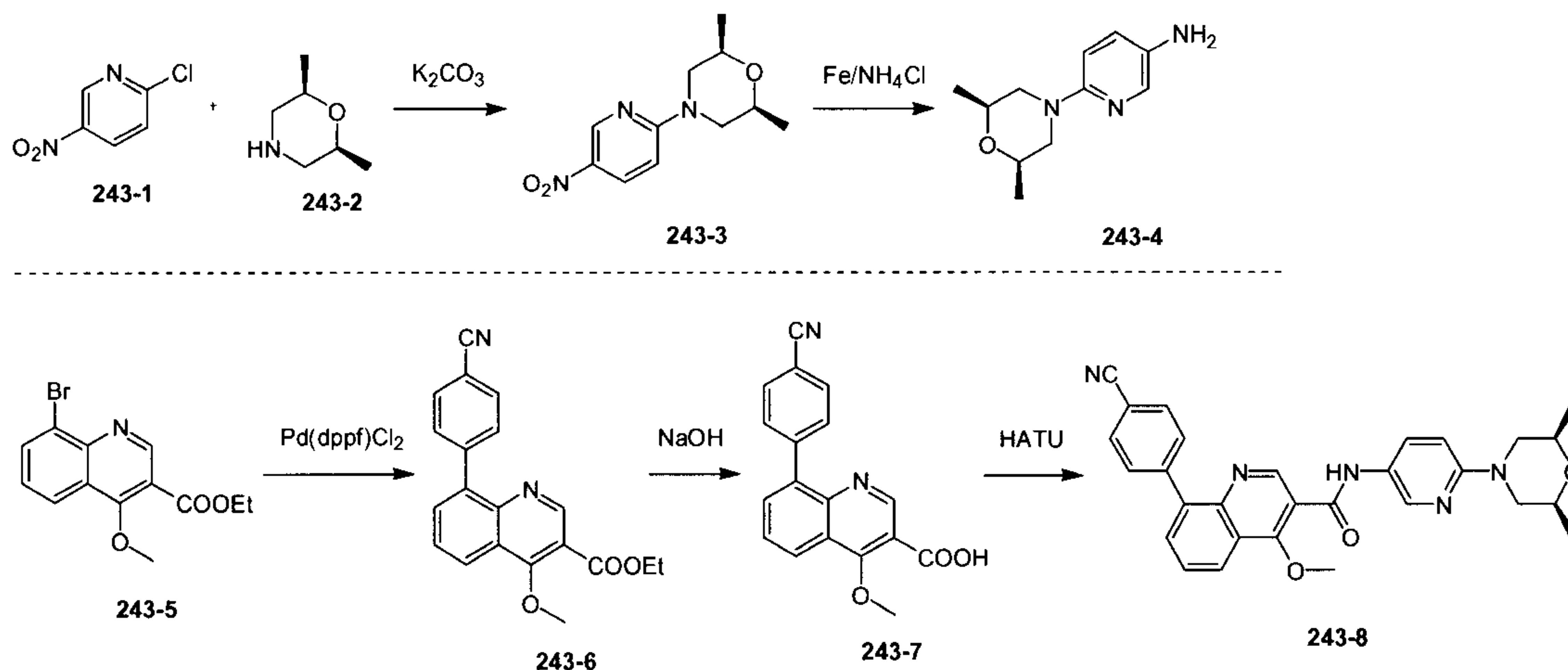
[531] Step 5: Compound 242-5 (478 mg, 1.7 mmol), 4-((2S,6R)-2,6-dimethylmorpholino)aniline 6 (525 mg, 2.55 mmol), TEA (515 mg, 5.1 mmol) were dissolved in DMF (5 mL), HATU (980 mg, 2.55 mmol) was added, the reaction mixture was stirred at room temperature for 2h. Then the reaction mixture was poured into H₂O, extracted with EtOAc, the organic phase was dried over sodium sulfate, filtrated and concentrated under vacuum, the residue was purified by silica gel column chromatography to deliver compound 242-7 (400 mg, yield 50%) as yellow solid. **MS ESI** calcd for C₂₃H₂₄BrN₃O₃ [M+H]⁺ 470, found 470.

[532] Step 6: The title compound (100 mg, yield 32%) was synthesized according to the above-mentioned method as white solid. **¹H NMR** (400MHz, CDCl₃) δ 9.49 (s, 1H), 9.23 (s, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 7.74-7.84(m, 7H), 7.65-7.67(m, 2H), 7.02 (s, 1H), 4.21 (s, 3H), 3.90 (s, 1H), 3.44-3.49 (m, 3H), 2.48 (s, 2H), 1.28 (d, *J* = 6.0 Hz, 6H). **MS ESI** calcd for C₃₀H₂₈N₄O₃ [M+H]⁺ 493, found 493.

Embodiment 243



8-(4-cyanophenyl)-N-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-4-methoxyquinoline-3-carboxamide



[533] Step 1: Compound 2-chloro-5-nitropyridine (5 g, 32 mmol) and K_2CO_3 (8.8 g, 64 mmol) were dissolved in MeCN (40 mL), (2S,6R)-2,6-dimethylmorpholine (4.4 g, 38.4 mmol) was added. The reaction mixture was stirred at 110°C for 2h. Then the reaction mixture was filtrated, the filtrate was concentrated to deliver compound 243-3 (7.3 g) as yellow solid. **MS ESI** calcd for $C_{11}H_{15}N_3O_3$ $[M+H]^+$ 238, found 238.

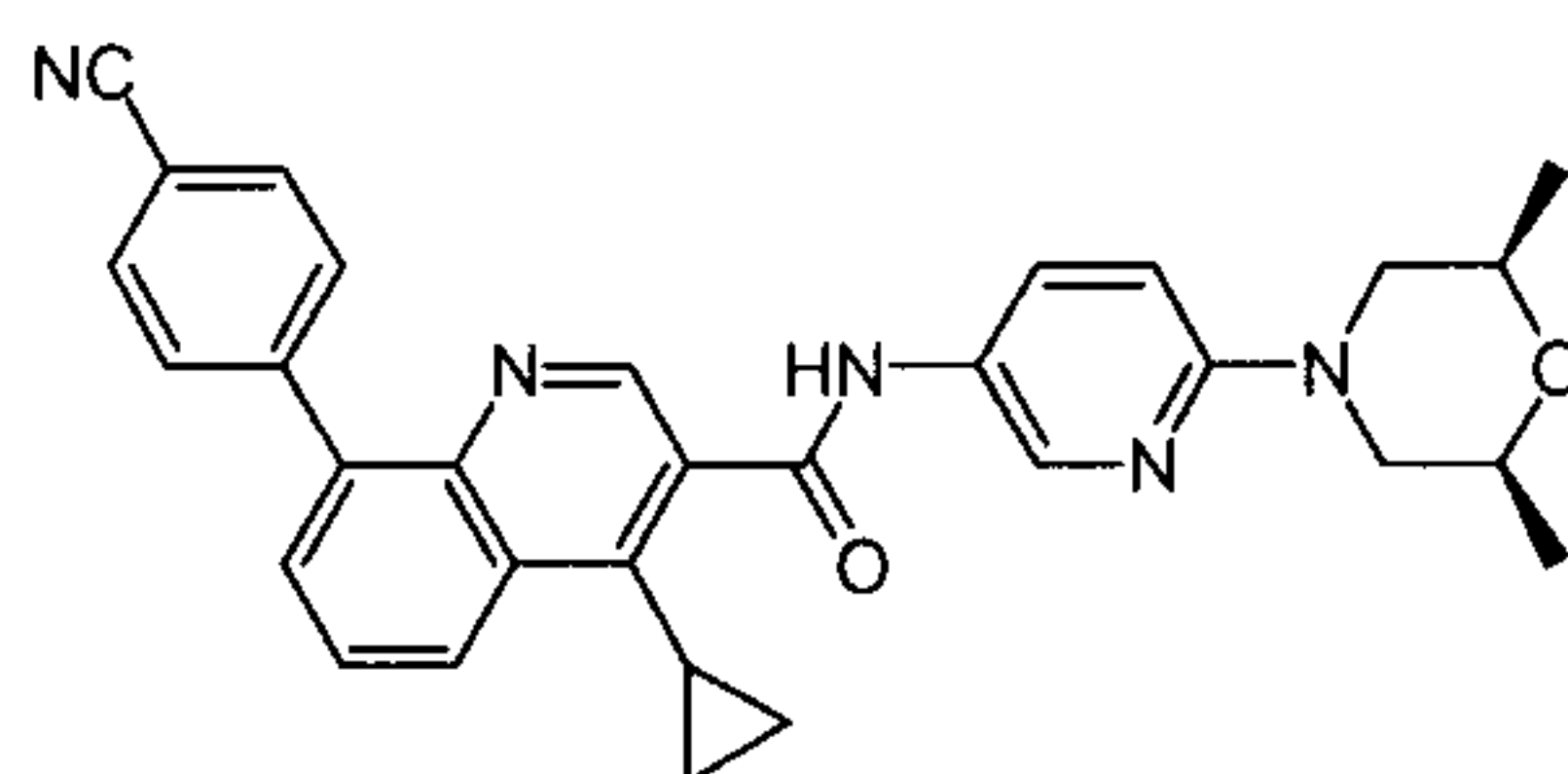
[534] Step 2: Compound 243-3 (7.3 g, 31 mmol) and ammonium chloride (16.7 g, 310 mmol) were dissolved in MeOH (80 mL) and H_2O (80 mL), iron powder (20.8 g, 372 mmol) was added. The reaction mixture was stirred at 80°C for 3h. Then the mixture was filtrated, the filtrate was concentrated, the residue was dissolved in acetone, filtrated and concentrated under vacuum, the crude product was purified by silica gel column chromatography to deliver compound 243-4 (800 mg) as brown solid. **MS ESI** calcd for $C_{11}H_{17}N_3O$ $[M+H]^+$ 208, found 208.

[535] Step 3: 4-cyanophenyl boric acid (1.8 g, 12 mmol), compound 243-4 (3.1 g, 10 mmol) and sodium carbonate (2.1 g, 20 mmol) were dissolved in DMF (5 mL), H_2O (5 mL) and THF (25 mL), $Pd(dppf)Cl_2$ (732 mg, 1 mmol) was added. The reaction mixture was stirred at 70°C for 2h. Then the mixture was poured into H_2O , extracted with EtOAc, the organic phase was washed with brines, dried over over sodium sulfate, filtrated and concentrated, the residue was purified by silica gel column chromatography to deliver compound 243-6 (2.8 g) as white solid. **MS ESI** calcd for $C_{20}H_{16}N_2O_3$ $[M+H]^+$ 333, found 333.

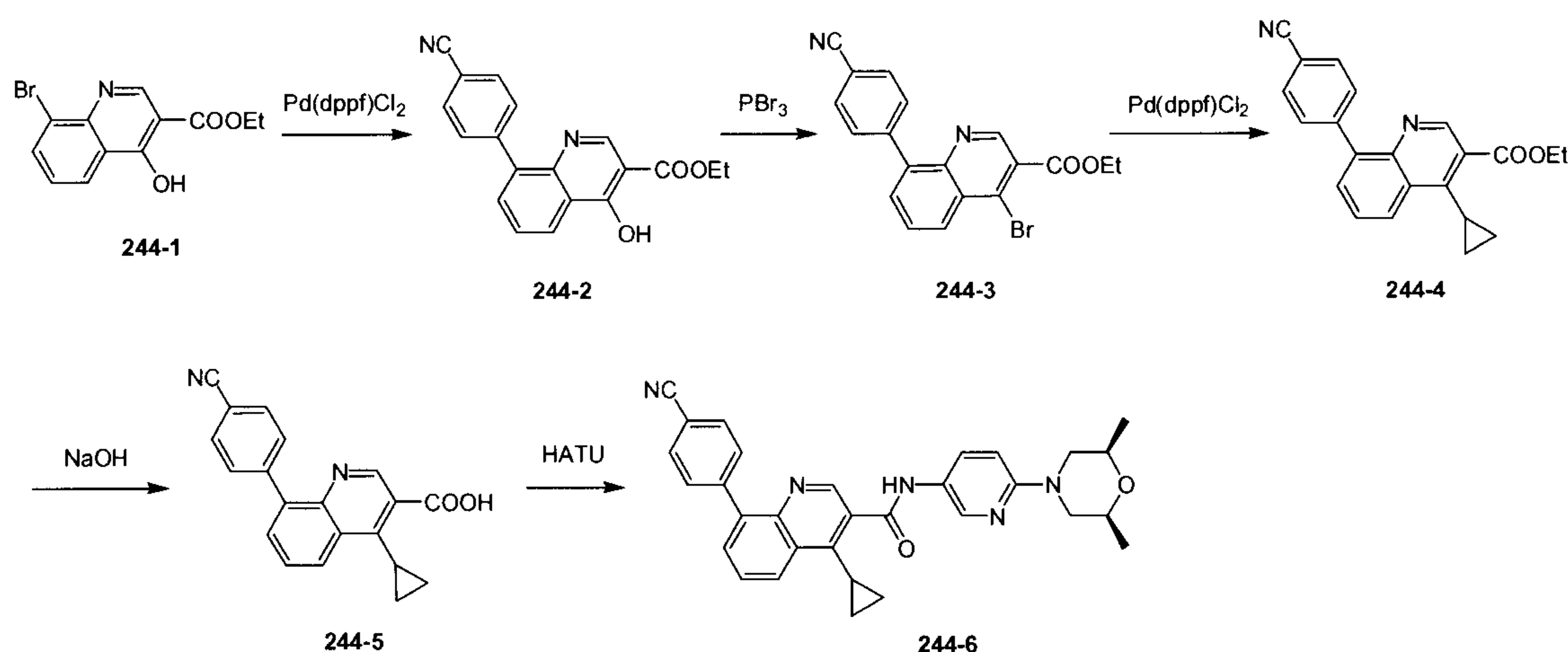
[536] Step 4: Compound 243-6 (1.8 g, 5.4 mmol) was dissolved in MeOH (10 mL) and H_2O (4mL), NaOH (1 g, 27 mmol) was added, the reaction mixture was stirred at room temperature for 2h. Then the mixture was poured into H_2O , extracted with EtOAc, the aqueous phase was acidified to pH = 4 with 1 N hydrochloric acid, and then extracted with EtOAc, the organic phase was washed with brines, dried over over sodium sulfate, filtrated and concentrated under reduced pressure to deliver compound 243-7 (580 mg) as white solid. **MS ESI** calcd for $C_{18}H_{12}N_2O_3$ $[M+H]^+$ 305, found 305.

[537] Step 5: Compound 243-7 (200 mg, 0.65 mmol), HATU (494 mg, 1.3 mmol) and compound 243-4 (136 mg, 0.65 mmol) were dissolved in DMF (5 mL), DIPEA (387 mg, 3 mmol) was added. The reaction mixture was stirred at room temperature overnight, the reaction mixture was purified by preparative HPLC to deliver the title compound (100 mg) as white solid. **^1H NMR** (400MHz, $CDCl_3$) δ 9.49 (s, 1H), 9.23 (s, 1H), 8.27-8.30 (m, 3H), 7.73-7.85(m, 7H), 6.73-6.75(m, 1H), 4.21 (s, 3H), 4.05-4.08 (m, 2H), 3.74-3.79 (m, 2H), 2.56-2.61 (m, 2H), 1.29 (d, J =6.0 Hz, 6H). **MS ESI** calcd for $C_{29}H_{27}N_5O_3$ $[M+H]^+$ 494, found 494.

Embodiment 244



8-(4-cyanophenyl)-4-cyclopropyl-N-(6-((2*S*,6*R*)-2,6-dimethylmorpholino)pyridin-3-yl)quinoline-3-carboxamide



[538] Step 1: 4-cyanophenyl boric acid (2 g, 14.4 mmol), ethyl-8-bromo-4-hydroxyquinolyl-3-carboxylic acid ethyl ester (3.5 g, 12 mmol) and sodium carbonate (2.5 g, 24 mmol) were dissolved in DMF (5 mL), H₂O (5 mL) and THF (25 mL), Pd(dppf)Cl₂ (878 mg, 1.2 mmol) was added. The reaction mixture was stirred at 70°C for 2h. Then the mixture was poured into H₂O, filtrated to deliver compound 244-2 (3.2 g) as brown solid. **MS ESI** calcd for C₁₉H₁₄N₂O₃ [M+H]⁺ 319, found 319.

[539] Step 2: Compound 244-2 (3.2 g, 10 mmol) was dissolved in DMF (40 mL), PBr₃ (4 mL, 10 M) was added, the reaction mixture was stirred at room temperature for 1h. Then the mixture was poured into H₂O, the solid was filtrated and washed with H₂O, dried in the air to deliver compound 244-3 (3.0 g) as brown solid. **MS ESI** calcd for C₁₉H₁₃BrN₂O₂ [M+H]⁺ 381, founs 381.

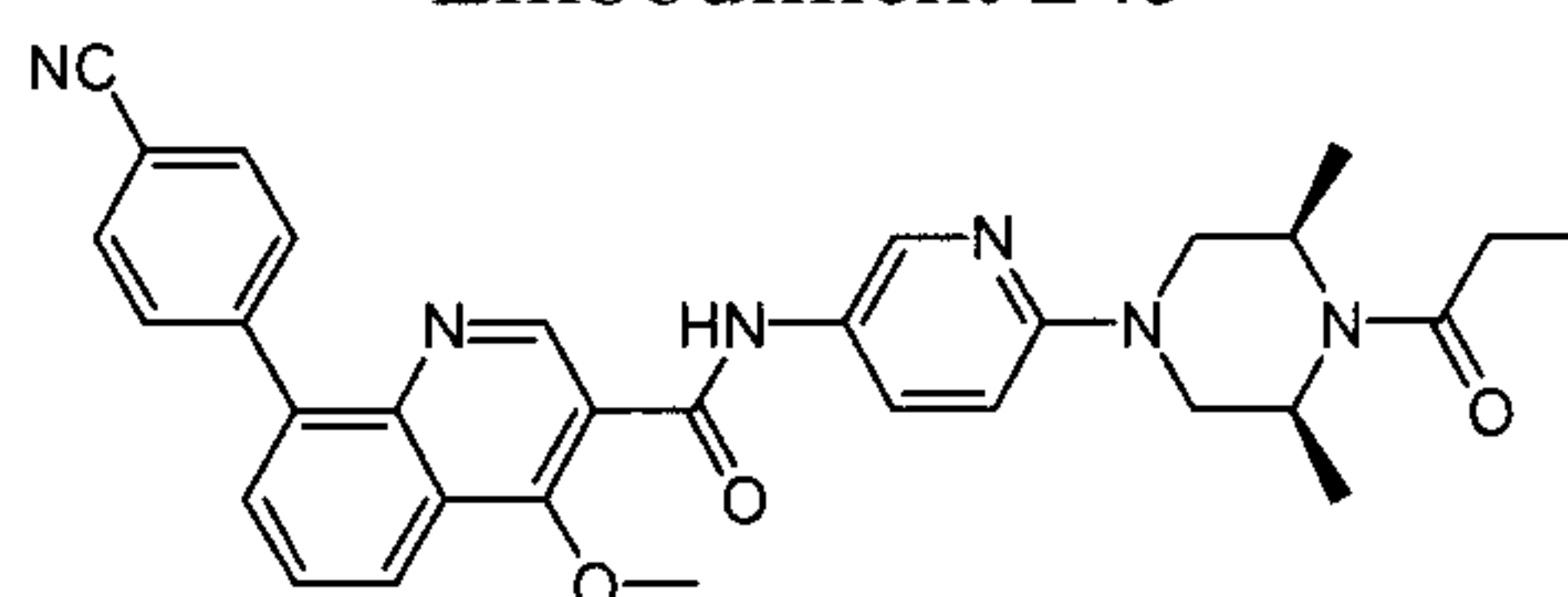
[540] Step 3: Cyclopropyl boric acid (6.7 g, 78 mmol), compound 244-3 (3.0 g, 7.8 mmol) and sodium carbonate (1.7 g, 15.6 mmol) were dissolved in DMF (5 mL), H₂O (5 mL) and THF (25 mL), Pd(dppf)Cl₂ (571 mg, 0.78 mmol) was added. The reaction mixture was stirred at 70°C for 2h. Then the mixture was poured into H₂O, extracted with EtOAc, the organic phase was washed with brines, dried over sodium sulfate, filtrated and concentrated under reduced pressure, the crude was purified by silica gel column chromatography to deliver compound 244-4 (1.8 g) as yellow solid. **MS ESI** calcd for C₂₂H₁₈N₂O₂ [M+H]⁺ 343, found 343.

[541] Step 4: Compound 244-4 (1.8 g, 5.4 mmol) was dissolved in MeOH (10 mL) and H₂O (4 mL), NaOH (1 g, 27 mmol) was added. The reaction mixture was stirred at room temperature for 2h. Then the mixture was poured into H₂O, extracted with

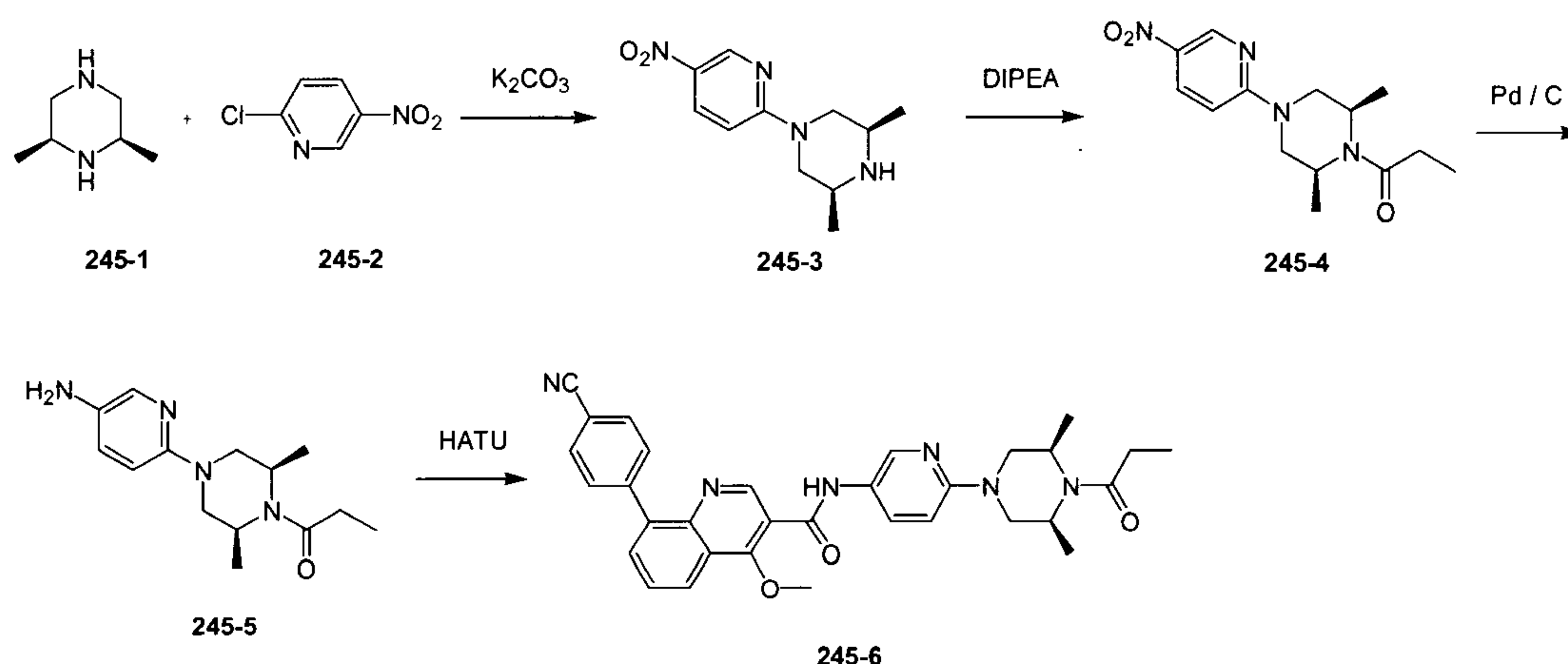
EtOAc, the aqueous phase was acidified with 1N HCl solution, extracted with EtOAc, the organic phase was washed with brines, dried over sodium sulfate, filtrated and concentrated under reduced pressure to deliver compound 244-5 (570 mg) as yellow solid. **MS ESI** calcd for $C_{20}H_{14}N_2O_2$ $[M+H]^+$ 315, found 315.

[542] Step 5: Compound 244-5 (200 mg, 0.65 mmol), HATU (494 mg, 1.3 mmol) and 6-((2S,6R)-2,6-dimethylmorpholino)pyridine-3-amine (136 mg, 0.65 mmol) were dissolved in DMF (5 mL), DIPEA (387 mg, 3 mmol) was added. The reaction mixture was stirred at room temperature overnight, purified by preparative HPLC (100 mg) to deliver the title compound as white solid. **^1H NMR** (400MHz, $CDCl_3$) δ 10.2 (s, 1H), 8.95 (s, 1H), 8.61-8.74 (m, 3H), 7.75-7.78(m, 4H), 7.63-7.65(m, 2H), 7.08(d, J =9.2 Hz, 1H), 4.04 (d, J =13.2 Hz, 2H), 3.74 (s, 2H), 2.83-2.89 (m, 2H), 2.64 (s, 1H), 1.27 (d, J =6.0 Hz, 8H), 0.72-0.73(m,1H). **MS ESI** calcd for $C_{31}H_{29}N_5O_2$ $[M+H]^+$ 504, found 504.

Embodiment 245



8-(4-cyanophenyl)-N-(6-((3S,5R)-3,5-dimethyl-4-propionylpiperazin-1-yl)pyridin-3-yl)-4-methoxyquinoline-3-carboxamide



[543] Step 1: 2-chloro-5-nitropyridine (5 g, 32 mmol) and K_2CO_3 (8.8 g, 64 mmol) were dissolved in acetonitrile (40 mL), compound 245-1 (4.3 g, 38.4 mmol) was added. The reaction mixture was stirred at 80°C for 1h, then the reaction mixture was filtrated, concentrated to deliver compound 245-3 (4.5 g) as yellow solid. **MS ESI** calcd for $C_{11}H_{16}N_4O_2$ $[M+H]^+$ 237, found 237.

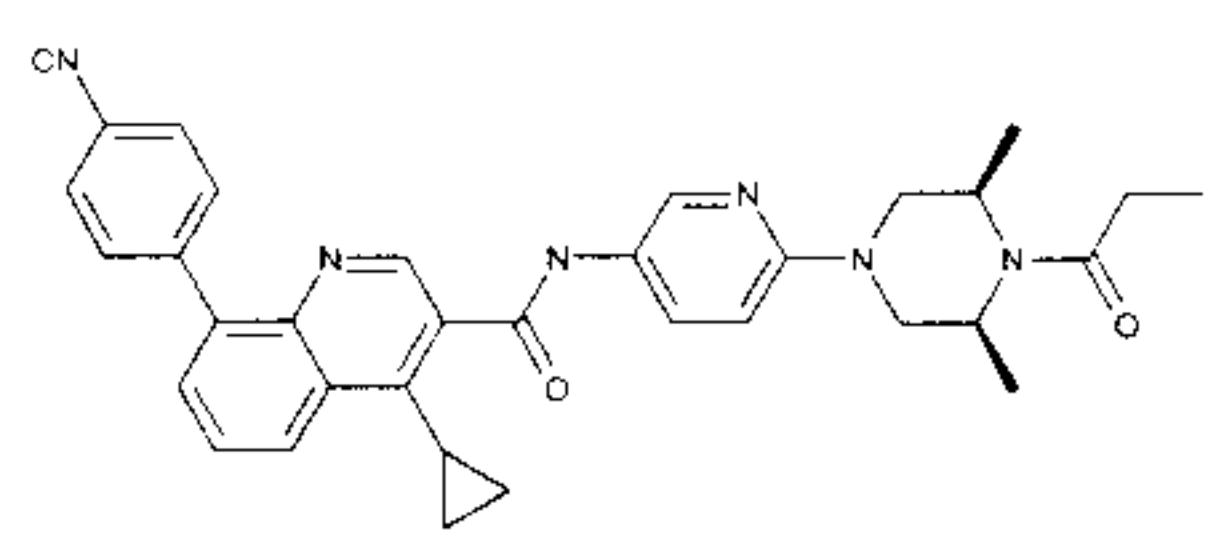
[544] Step 2: Compound 245-3 (4.5 g, 19 mmol) and DIPEA (7.4 g, 57 mmol) in DCM (40 mL), propionyl chloride (2.2 g, 23 mmol) was added. The reaction mixture was stirred at 0°C for 30min. Then the reaction mixture was poured into

H₂O, extracted with EtOAc, the organic phase was washed with brines, dried over sodium sulfate, filtrated and concentrated under reduced pressure to deliver compound 245-4 (3.2 g) as yellow solid. **MS ESI** calcd for C₁₄H₂₀N₄O₃ [M+H]⁺ 293, found 293.

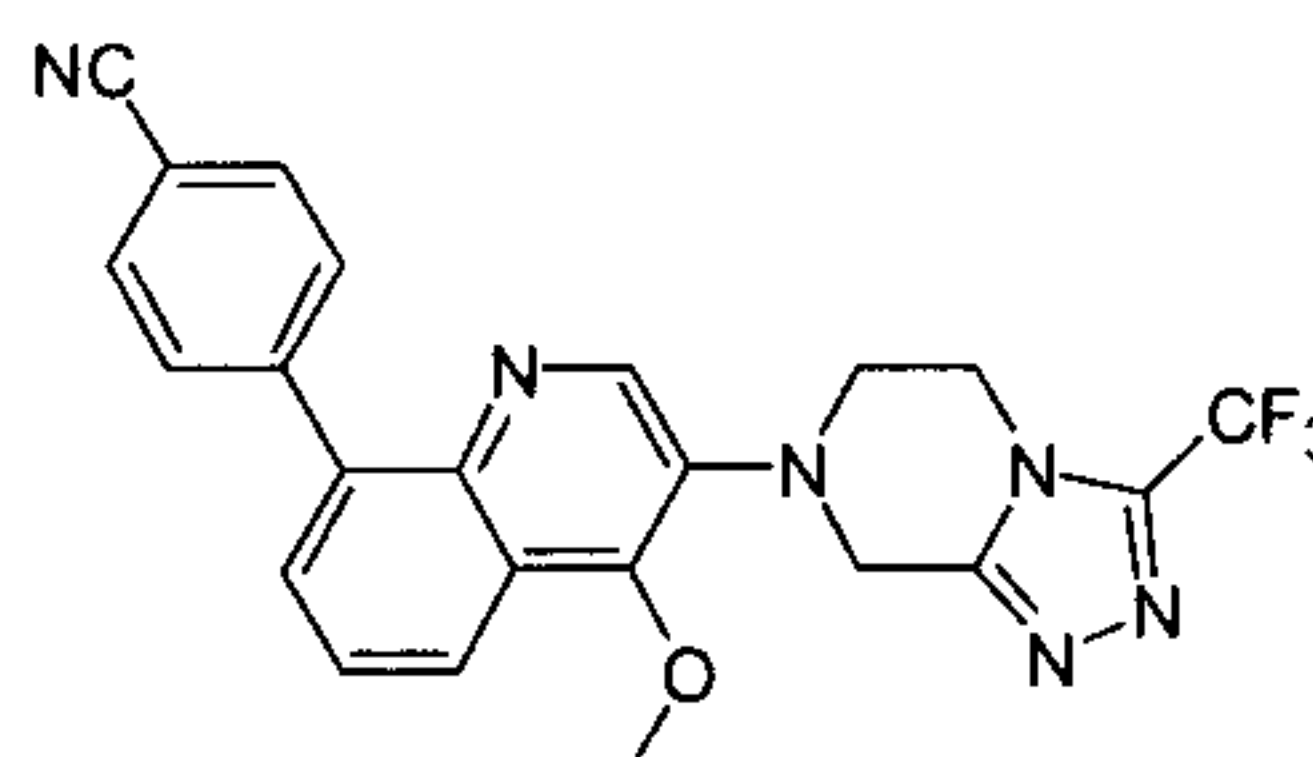
[545] Step 3: Compound 245-4 (3.2 g, 11 mmol) and Pd/C (0.32 g) were dissolved in methanol (500 mL), the reaction mixture was stirred at room temperature under a hydrogen gas pressure of 40psi overnight. Then the reaction mixture was filtrated, the solvent was concentrated under reduced pressure to deliver crude compound 245-5 (800 mg) as red oil. **MS ESI** calcd for C₁₄H₂₂N₄O [M+H]⁺ 263, found 263.

[546] Step 4: A solution of 8-(4-cyanophenyl)-4-methoxyquinoline-3-carboxylic acid (100 mg, 0.33 mmol), HATU (251 mg, 0.66 mmol) and compound 245-5 (86 mg, 0.33 mmol) were dissolved in DMF (5 mL), DIPEA (86 mg, 0.33 mmol) was added. After stirred at room temperature overnight, the reaction mixture was purified by HPLC to deliver the title compound (80 mg) as white solid. **¹H NMR** (400MHz, CDCl₃) δ 9.47 (s, 1H), 9.24 (s, 1H), 8.26-8.28 (m, 3H), 7.72-7.84(m, 6H), 6.77(d, *J* =9.2 Hz, 1H), 4.21 (s, 3H), 3.05-3.10 (m, 2H), 1.34 (s, 6H), 1.19(t, *J* =7.4 Hz, 1H). **MS ESI** calcd for C₃₂H₃₂N₆O₃ [M+H]⁺ 548, found 548.

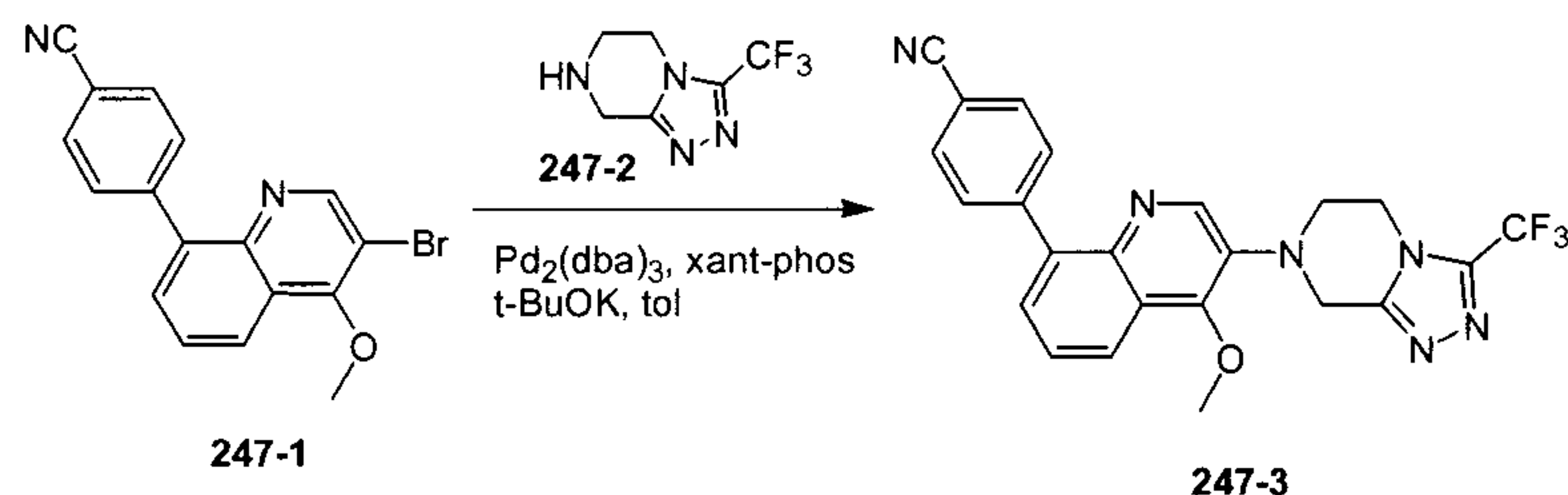
[547] The compound listed in table 22 was synthesized by compound 245-5 and corresponding acid.

Embodiment	structure	NMR
246		¹H NMR (400MHz, CDCl ₃) δ 10.02 (s, 1H), 8.93 (s, 1H), 8.60-8.70 (m, 3H), 7.74-7.78(m, 4H), 7.63-7.65(m, 2H), 7.10(d, <i>J</i> =9.6 Hz, 1H), 3.78-3.80 (m, 2H), 2.55 (s, 1H), 1.15-1.35 (m, 12H), 0.72-0.74 (m, 2H). MS ESI calcd for C ₃₄ H ₃₄ N ₆ O ₂ [M+H] ⁺ 559, found 559.

Embodiment 247

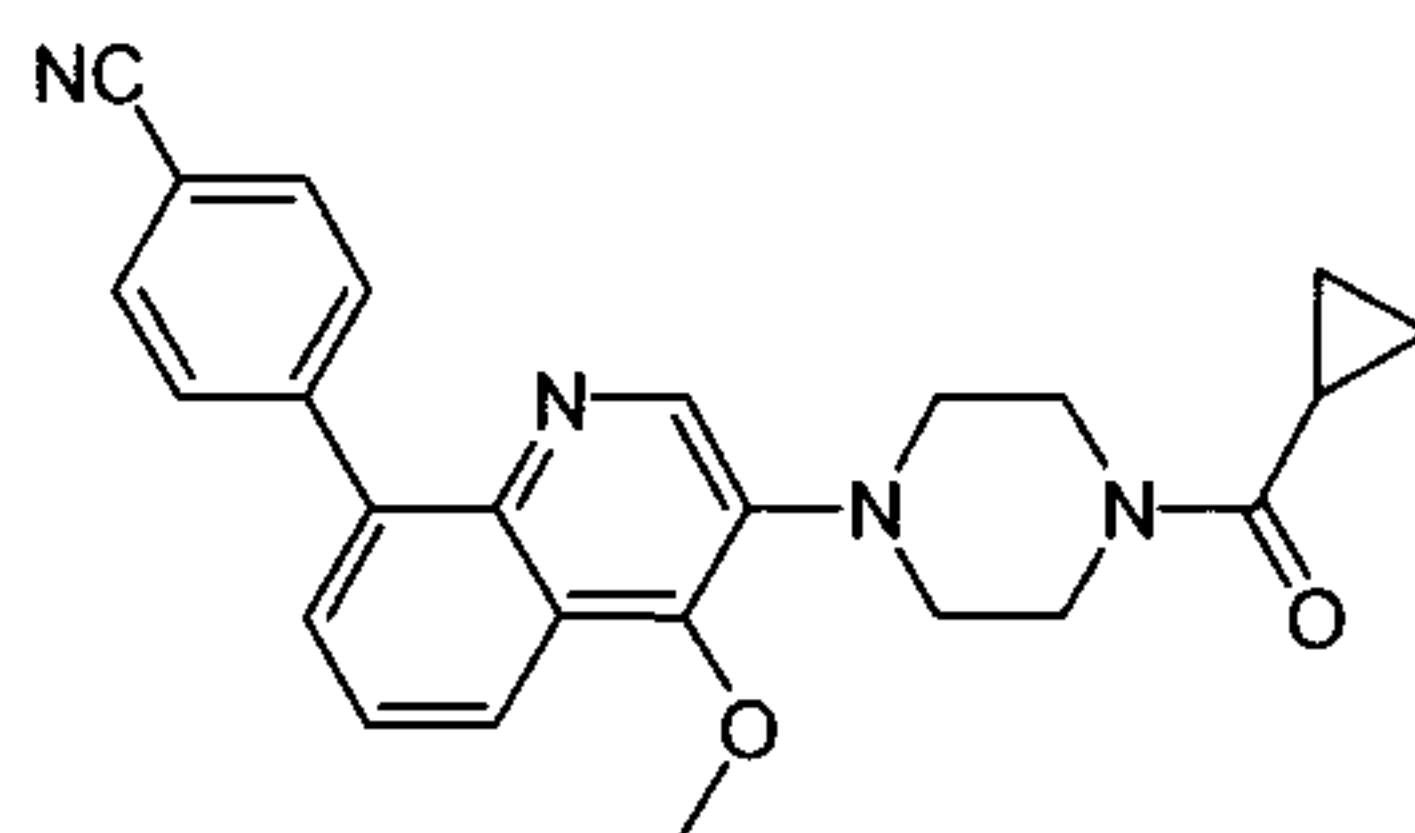


4-(4-methoxy-3-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)quinolin-8-yl)benzonitrile

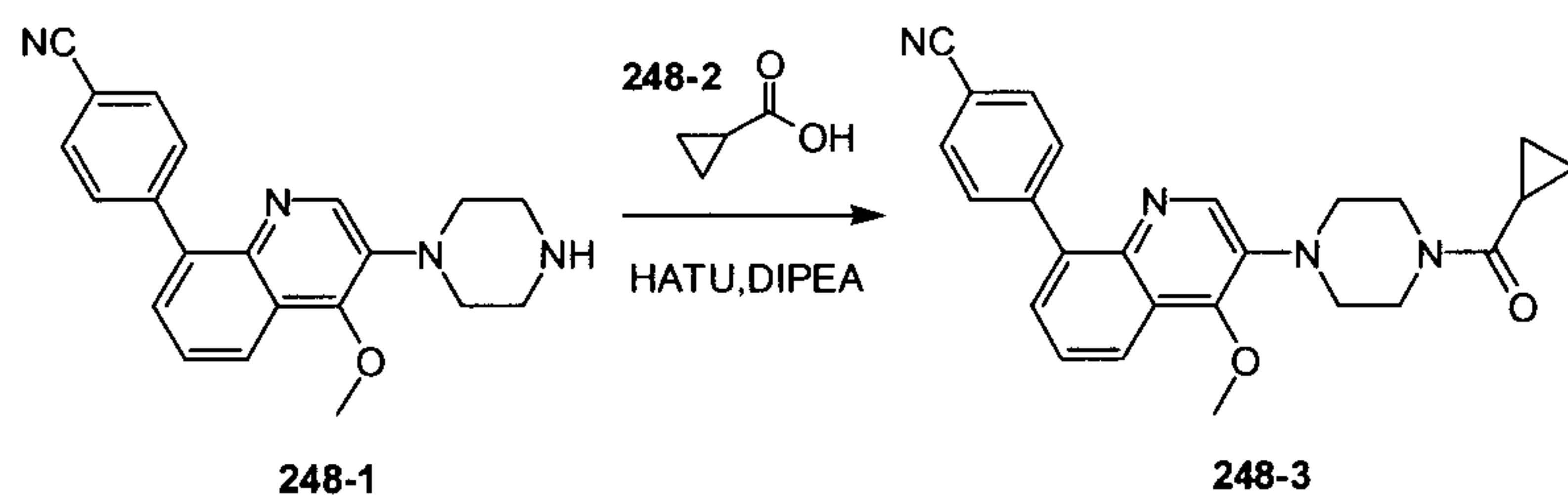


[548] Compound 247-1 (339 mg, 1 mmol), Xantphos (115 mg, 0.2 mmol), 247-2 (192 mg, 1 mmol) and *t*-BuONa (200 mg, 2 mmol) were dissolved in toluene (10 mL), then under nitrogen gas atmosphere, $\text{Pd}_2(\text{dba})_3$ (92 mg, 0.1 mmol) was added, the reaction mixture was stirred at 110°C for 2h. After the reaction was complete, the mixture was poured into H_2O , extracted with EtOAc. The organic phase was dried over anhydrous sodium sulfate, concentrated to give a crude product. The crude product was purified by HPLC to deliver the title compound (30 mg, 7%) as yellow solid. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.48(s, 1H), 8.45 (d, $J = 8.0$ Hz, 1H), 7.87 (m, 4H), 7.66 (m, 2H), 4.98 (s, 1H), 4.45-4.39 (m, 5H), 4.02 (s, 2H). **MS ESI** calcd for $\text{C}_{23}\text{H}_{17}\text{F}_3\text{N}_6\text{O}[\text{M}+\text{H}]^+$ 451, found 451.

Embodiment 248

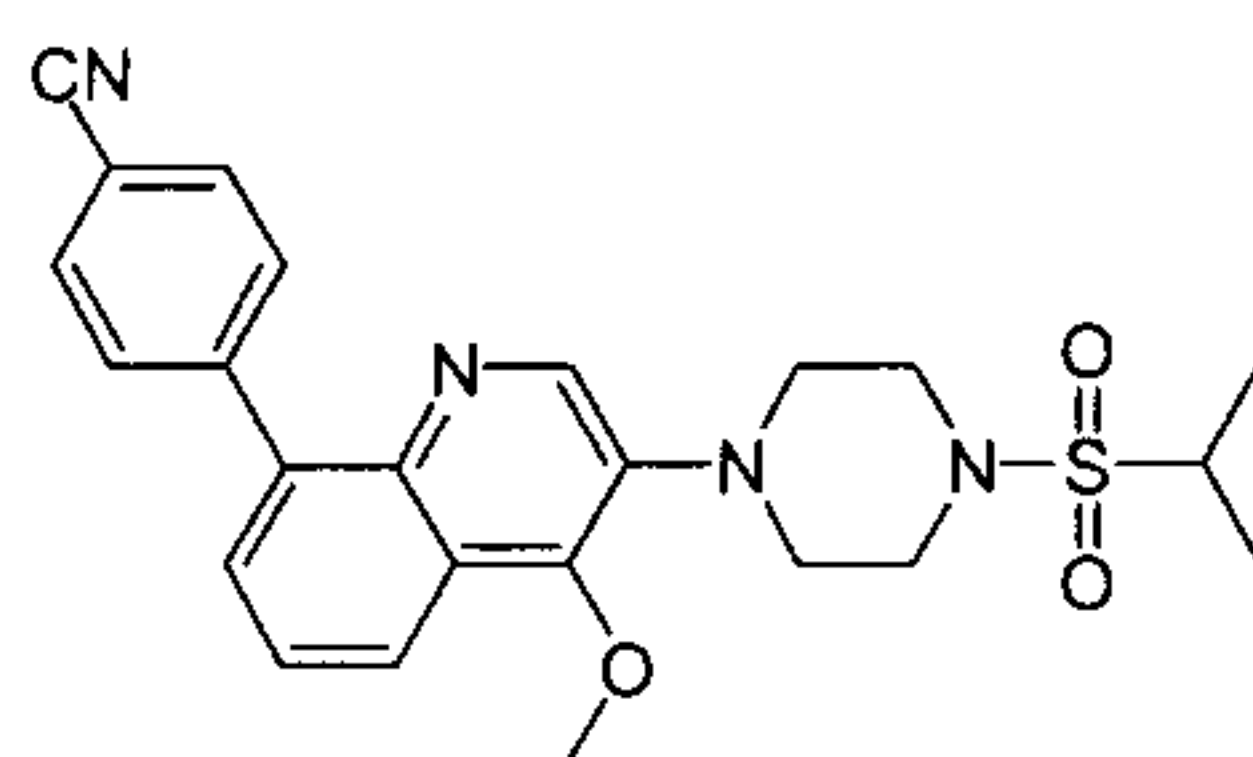


4-(3-(4-cyclopropanecarbonylpiperazin-1-yl)-4-methoxyquinolin-8-yl)benzonitrile

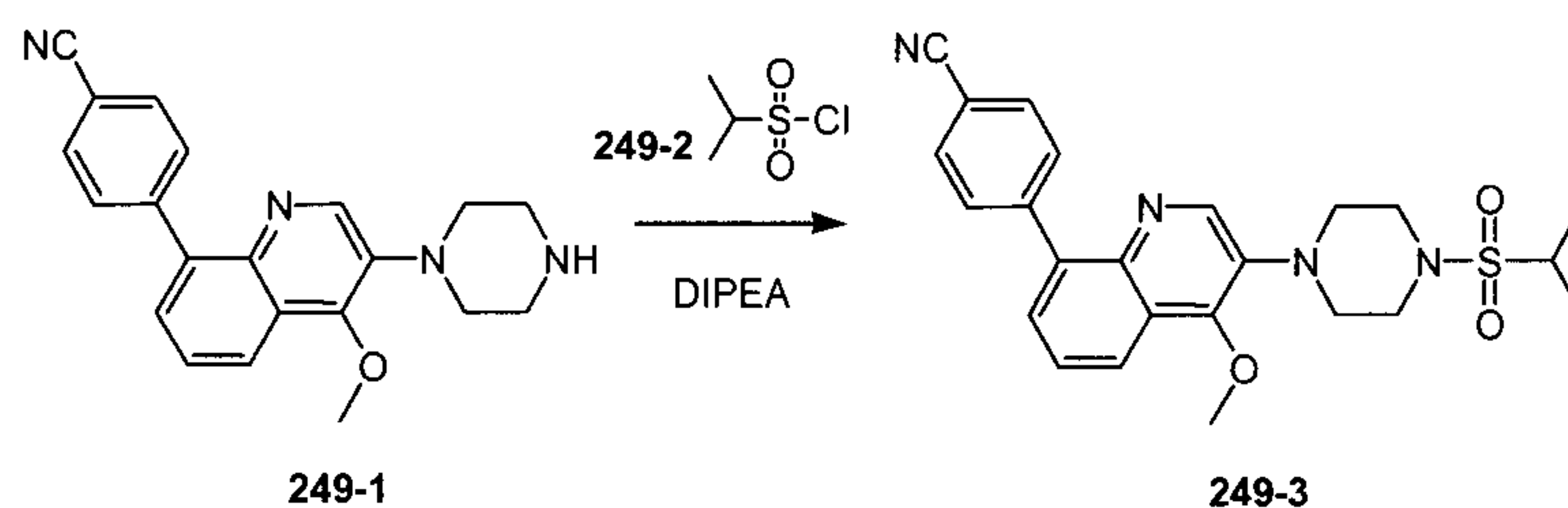


[549] Compound 248-1 (172 mg, 0.5 mmol), HATU (380 mg, 1 mmol) and 248-2 (86 mg, 1 mmol) were dissolved in DMF (4 mL), then DIPEA (194 mg, 1.5 mmol) was added, the reaction mixture was stirred at room temperature overnight. The reaction mixture was monitored by LCMS till completion. The reaction system was purified by HPLC to deliver the title compound (40 mg, 20%) as yellow solid. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.76 (s, 1H), 8.4 (t, $J = 4.8$ Hz, 1H), 7.82-7.79 (m, 4H), 7.63-7.59 (m, 2H), 4.16 (s, 3H), 3.92 (m, 4H), 3.33-3.30 (m, 4H), 1.85-1.80 (m, 1H), 1.08-1.05 (m, 2H), 0.86-0.83 (m, 2H). **MS ESI** calcd for $\text{C}_{25}\text{H}_{24}\text{N}_4\text{O}_2[\text{M}+\text{H}]^+$ 413, found 413.

Embodiment 249

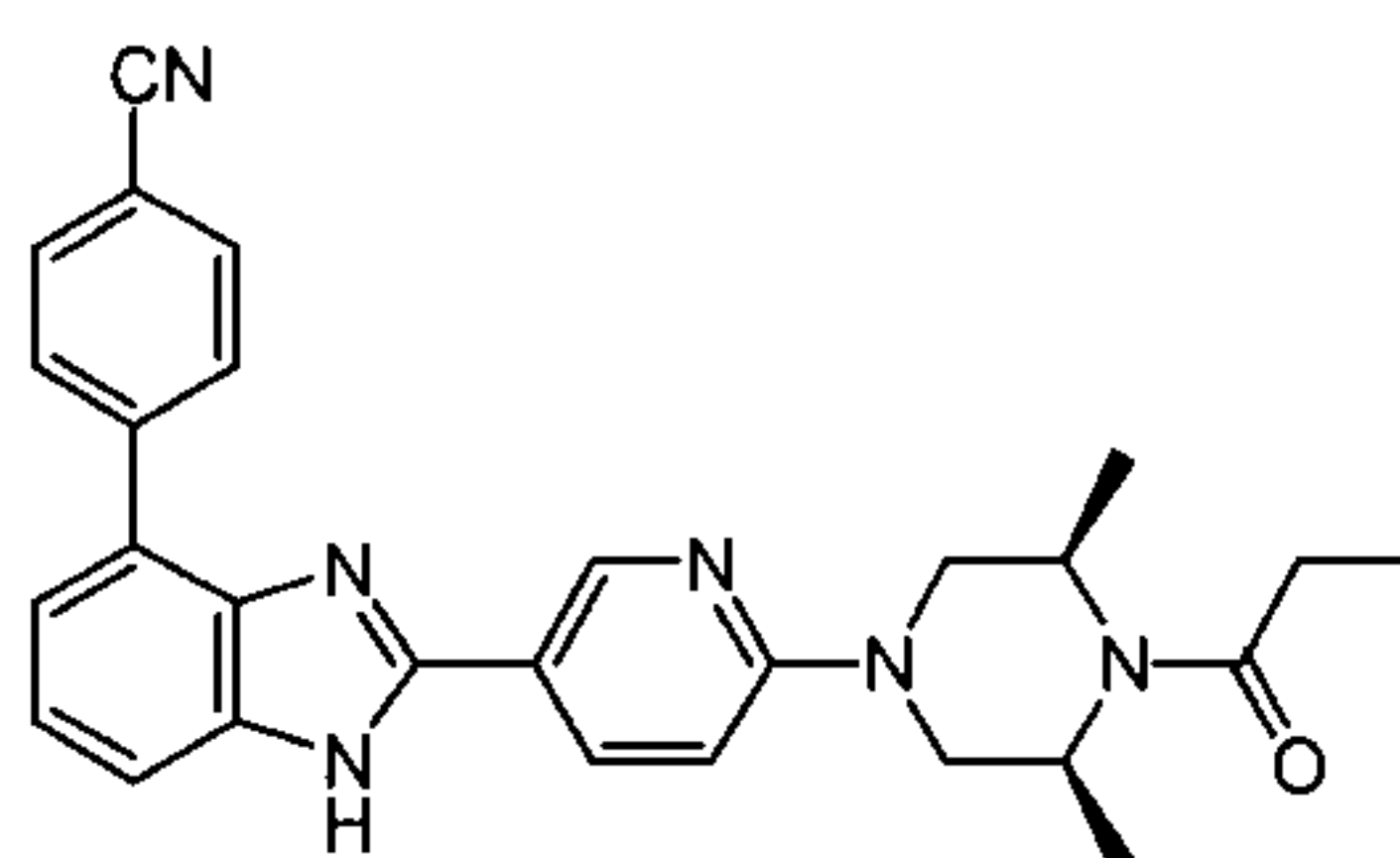


4-(4-methoxy-3-(4-(propane-2-sulfonyl)piperazin-1-yl)-quinolin-8-yl)benzonitrile



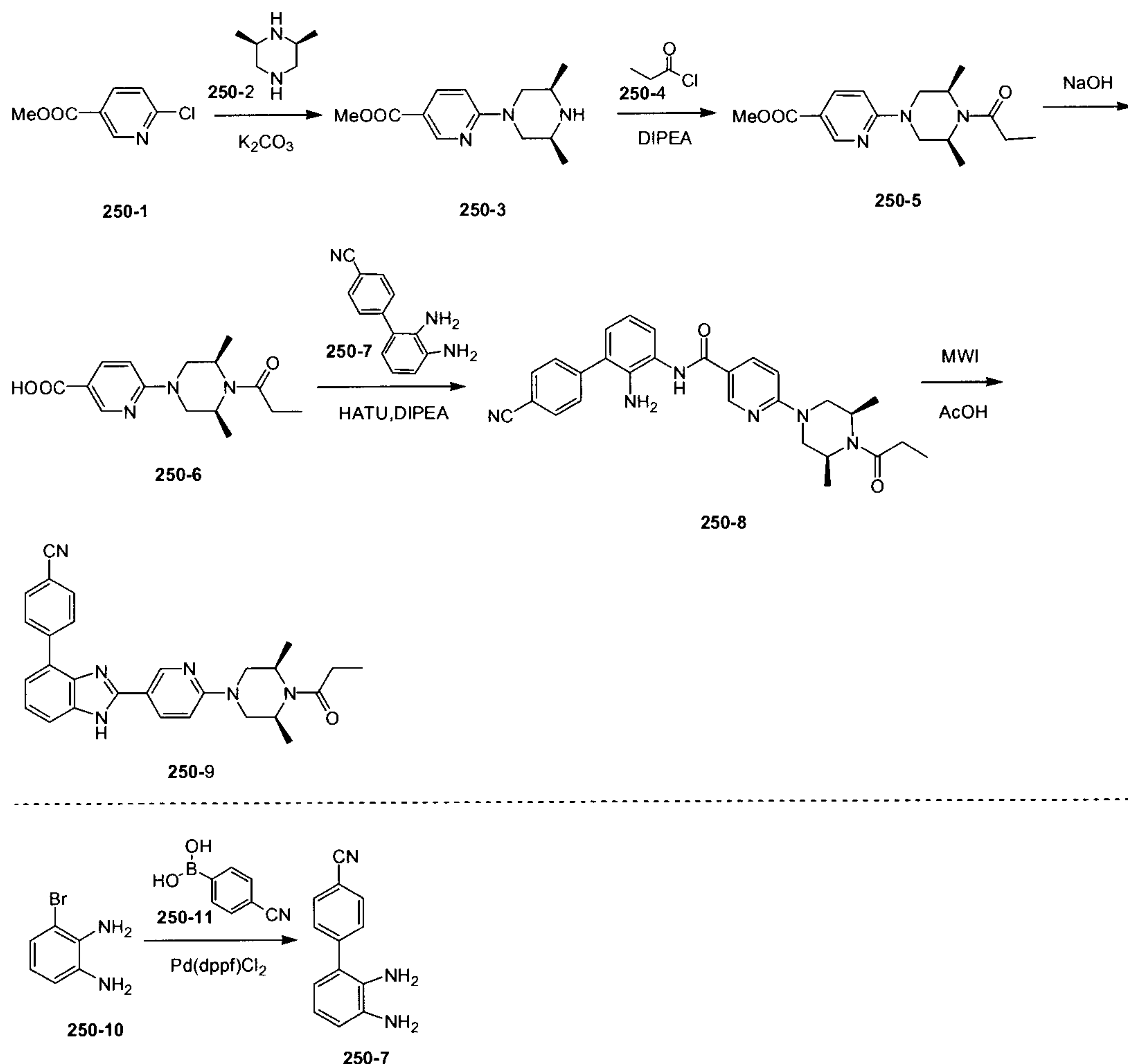
[550] Compound 249-1 (172 mg, 0.5 mmol) and DIPEA (194 mg, 1.5 mmol) were dissolved in DCM (5 mL), then 2 (142 mg, 1 mmol) was added, the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was monitored by LCMS till completion. The reaction mixture was poured into H₂O, extracted with EtOAc. The organic phase was dried over anhydrous sodium sulfate, concentrated to give a crude product. The crude product was purified by HPLC to deliver the title compound (20 mg, 10%) as yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.75 (s, 1H), 8.22 (dd, *J* = 4.4, 5.6 Hz, 1H), 7.82-7.77 (m, 4H), 7.63-7.61 (m, 2H), 4.13 (s, 3H), 3.62-3.60 (m, 4H), 3.33-3.30 (m, 4H), 3.31-3.26 (m, 1H), 1.43 (d, *J* = 7.2 Hz, 6H). MS ESI calcd for C₂₄H₂₆N₄O₃S[M+H]⁺ 451, found 451.

Embodiment 250



4-(2-(6-(3,5-dimethyl-4-propionylpiperazin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-4-yl)benzonitrile

Our Ref.: P1650132CA



[551] Step 1: Compound 250-2 (1.14 g, 10 mmol) was added into a solution of compound 250-1 (1.71 g, 10 mmol) and K_2CO_3 (2.78 g, 20 mmol) in DMF (20 mL), the reaction mixture was stirred at 110°C for 2h, monitored by LCMS till completion. Then the mixture was poured into H_2O , extracted with EtOAc, the organic phase was dried over anhydrous sodium sulfate, concentrated to give a crude product. The crude product was purified by silica gel column chromatography (PE:EtOAc=1:1) to deliver compound 250-3 (2.3 g, yield 92%) as oil. **MS ESI** calcd for $C_{13}H_{19}N_3O_2[M+H]^+$ 250, found 250.

[552] Step 2: 250-4 (1.0 g, 10.8 mmol) was added slowly into a solution of compound 250-3 (2.3 g, 9 mmol) and DIPEA (2.3 g, 18 mmol) in DCM (30 mL), the reaction mixture was stirred at 0°C for 30min, monitored by LCMS till completion. Then the mixture was poured into H_2O , extracted with EtOAc (100×3 mL), the organic phase was dried over anhydrous sodium sulfate, concentrated to deliver crude product 250-5 (2.5 g, yield 91%). **MS ESI** calcd for $C_{16}H_{23}N_3O_3[M+H]^+$ 306, found 306.

[553] Step 3: NaOH (1.28 g, 32 mmol) was added into a solution of compound 250-5 (2.5 g, 8 mmol) in MeOH (10 mL) / H_2O (2 mL), the reaction mixture was stirred at 40°C for 1h. After the reaction was complete, the mixture was poured into H_2O , washed with EtOAc, the aqueous phase was acidified to pH=4 with 1 N HCl

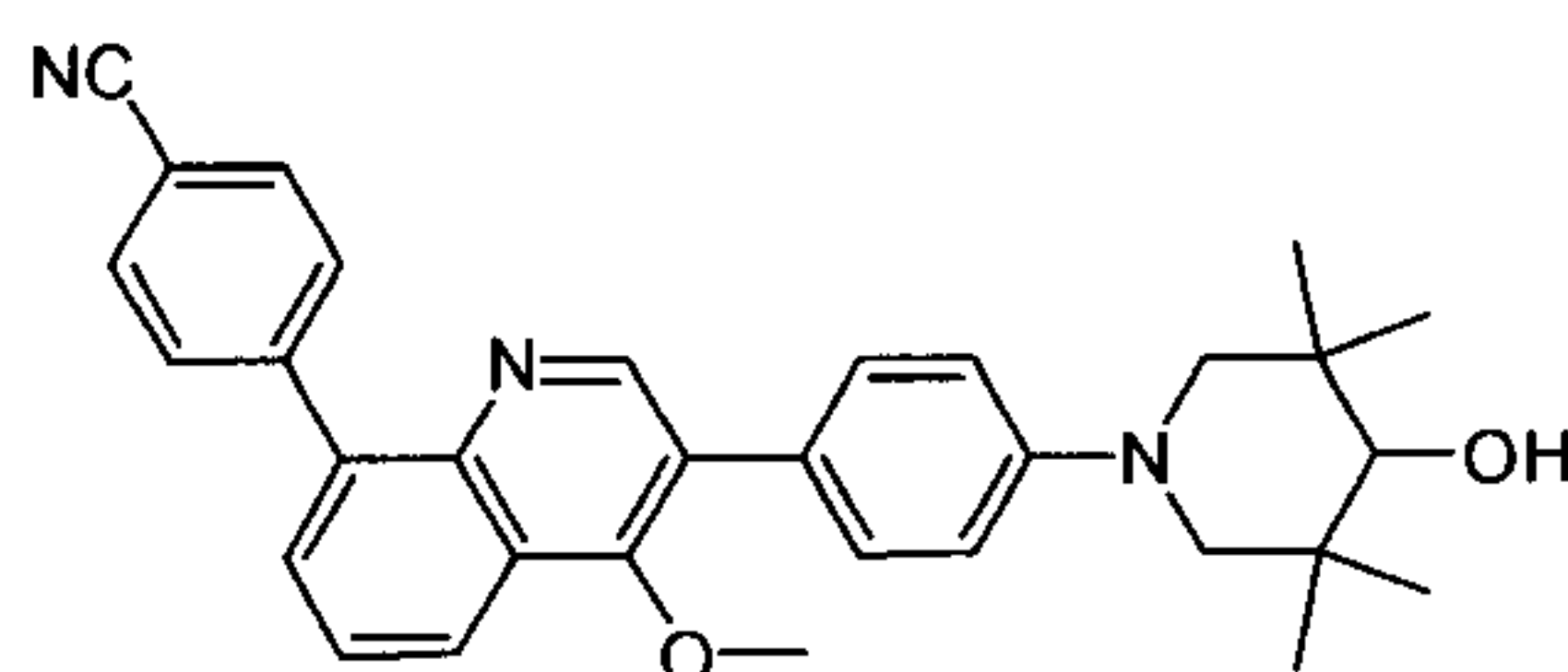
solution, then extracted with EtOAc, the organic phase was dried over anhydrous sodium sulfate, concentrated to deliver crude product 250-6 (1 g, 43%). The crude product was used for the next step directly.

[554] Step 4: Compound 250-10 (374 mg, 2 mmol), compound 250-11 (294 mg, 2 mmol) and Na_2CO_3 (424 mg, 4 mmol) were dissolved in DMF (2 mL) / H_2O (2 mL) / THF (10 mL), then $\text{Pd}(\text{dppf})\text{Cl}_2$ (146 mg, 0.2 mmol) was added into the solution. The reaction system was stirred at 70°C overnight, monitored by LC-MS till completion. The mixture was poured into H_2O , extracted with EtOAc. The organic phase was dried over anhydrous sodium sulfate, concentrated to give a crude product. The crude product was purified by silica gel column chromatography (PE:EtOAc=1:1) to deliver compound 250-7 (200 mg, 50%) as red solid. **MS ESI** calcd for $\text{C}_{13}\text{H}_{11}\text{N}_3[\text{M}+\text{H}]^+$ 210, found 210.

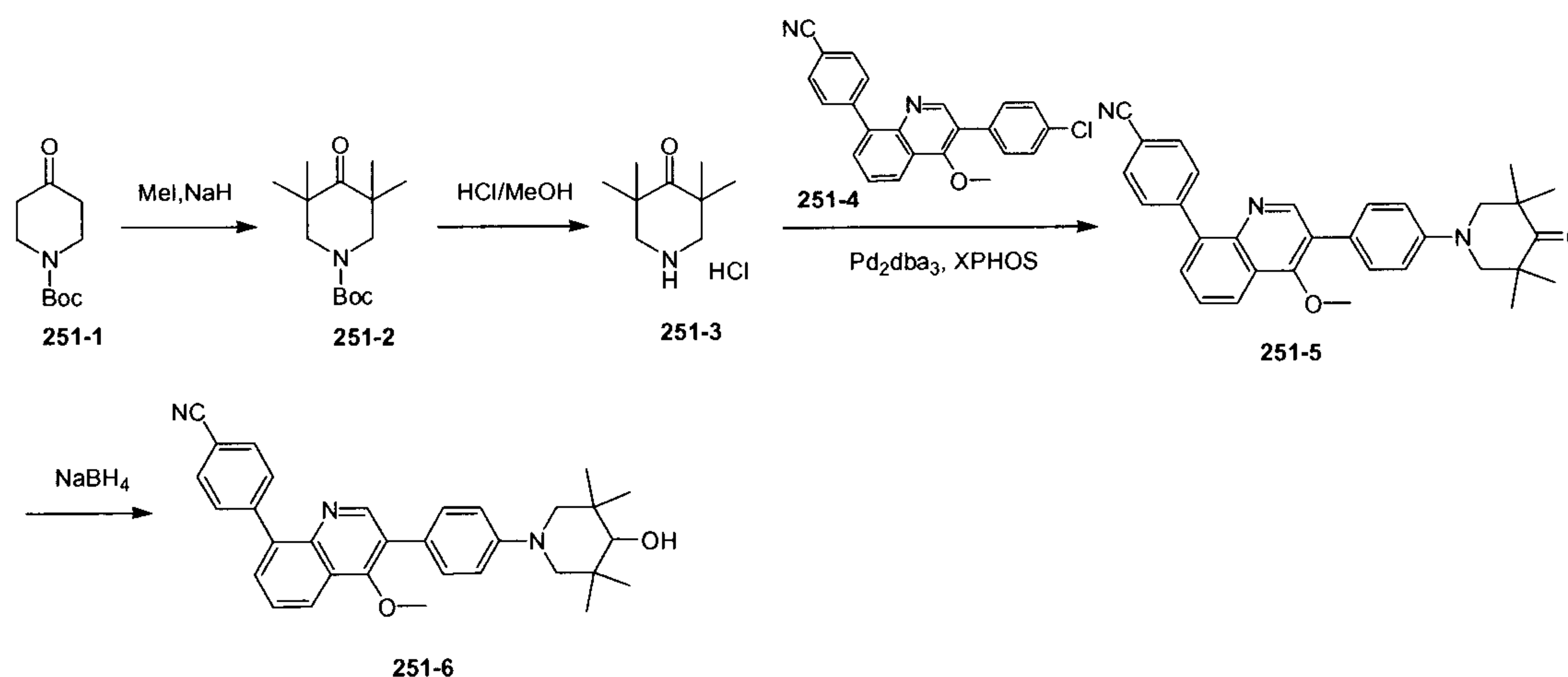
[555] Step 5: Compound 250-7 (200 mg, 1 mmol), HATU (760 mg, 2 mmol) and 250-6 (291 mg, 1 mmol) were dissolved in DMF (10 mL), then DIPEA (387 mg, 3 mmol) was added into the solution. The reaction system was stirred at room temperature for 1h, monitored by LC-MS till completion. The mixture was poured into H_2O , extracted with EtOAc. The organic phase was dried over anhydrous sodium sulfate, concentrated to give a crude product. The crude product was purified by silica gel column chromatography (PE:EtOAc=1:1) to deliver compound 250-5 (200 mg, 42%) as brown solid. **MS ESI** calcd for $\text{C}_{28}\text{H}_{30}\text{N}_6\text{O}_2[\text{M}+\text{H}]^+$ 483, found 483.

[556] Step 6: Compound 250-5 (80 mg, 0.16 mmol) was dissolved in AcOH (2 mL), the reaction system reacted under microwave at 180°C for 40min. The reaction mixture was monitored by LC-MS till completion. The crude product was purified by HPLC to deliver the title compound (10 mg, 14%) as yellow solid. **^1H NMR** (400 MHz, CDCl_3) δ 8.83-8.82 (m, 1H), 8.30-8.26 (m, 3H), 7.78-7.62 (m, 3H), 7.52-7.32 (m, 2H), 6.79-6.75 (m, 1H), 3.23-3.18 (m, 2H), 1.67 (s, 3H), 1.34 (s, 6H), 1.22 (t, $J = 7.6$ Hz, 3H). **MS ESI** calcd for $\text{C}_{28}\text{H}_{28}\text{N}_6\text{O}[\text{M}+\text{H}]^+$ 465, found 465.

Embodiment 251



4-(2-(6-(3,5-dimethyl-4-propionylpiperazin-1-yl)pyridin-3-yl)-1H-benzimidazole-4-yl)benzonitrile



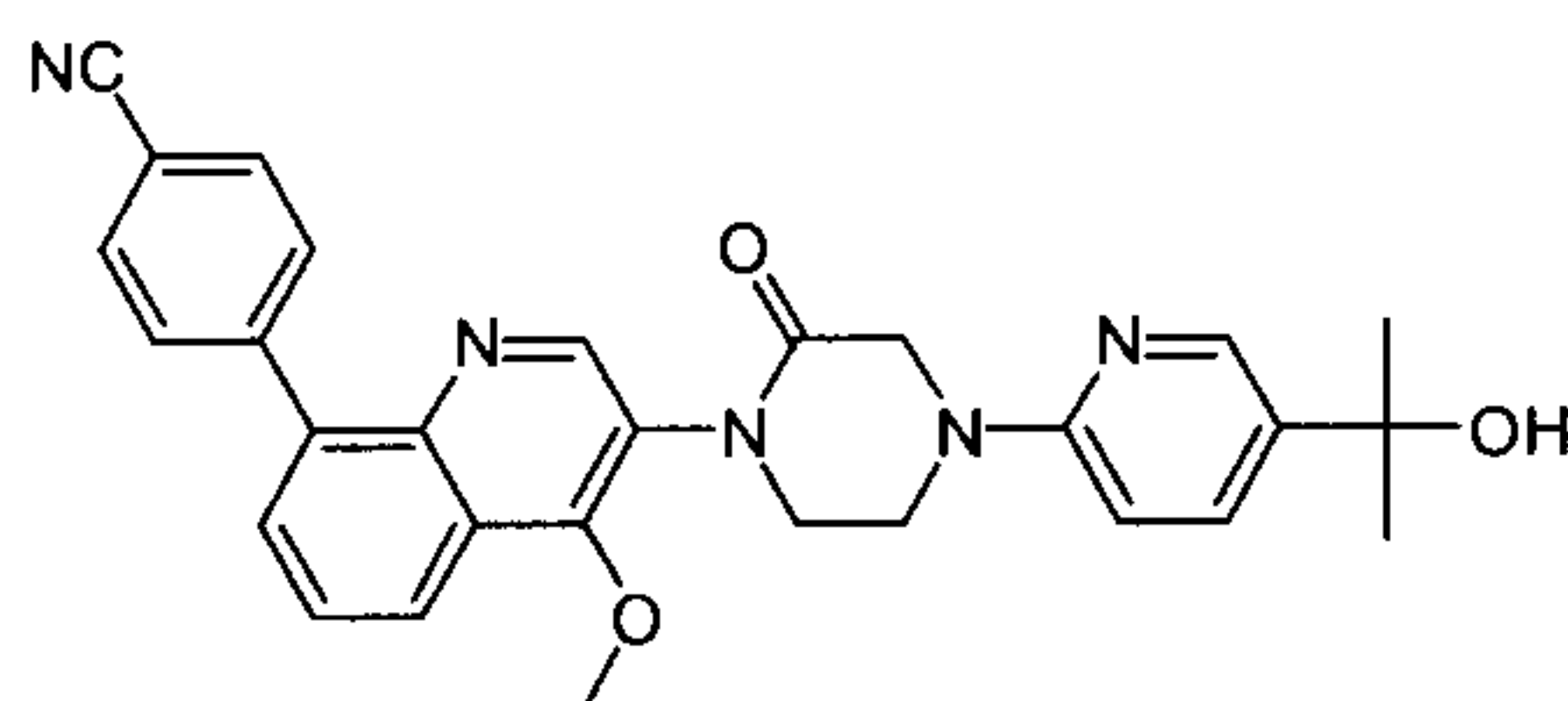
[557] Step 1: Under an ice bath, NaH (6.4 g, 160 mmol) was added into a solution of compound 251-1 (4 g, 20 mmol) in THF (50 mL). The reaction mixture was stirred at room temperature for 0.5h, then cooled to 0°C again, MeI (10 mL, 160 mmol) was added dropwise. Then the reaction mixture was warmed to room temperature and stirred for another 2h. The reaction was detected by TLC. The mixture was quenched with H_2O . The aqueous phase was extracted with EtOAc . The combined organic phase was washed with saturated sodium chloride solution, dried over sodium sulfate, concentrated under reduced pressure to deliver the desired product 251-2 (4.5g, 88%). **MS ESI** calcd for $\text{C}_{14}\text{H}_{25}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 256, found 256.

[558] Step 2: Compound 251-2 (410 mg, 1.6 mmol) was dissolved in $\text{HCl}/\text{methanol}$ (4 M, 10 mL), and stirred at room temperature for 2h. After the reaction was complete, the reaction mixture was concentrated under reduced pressure to deliver the desired product 251-3 (330 mg, 86%). **MS ESI** calcd for $\text{C}_9\text{H}_{17}\text{NO}$ $[\text{M}+\text{H}]^+$ 156, found 156.

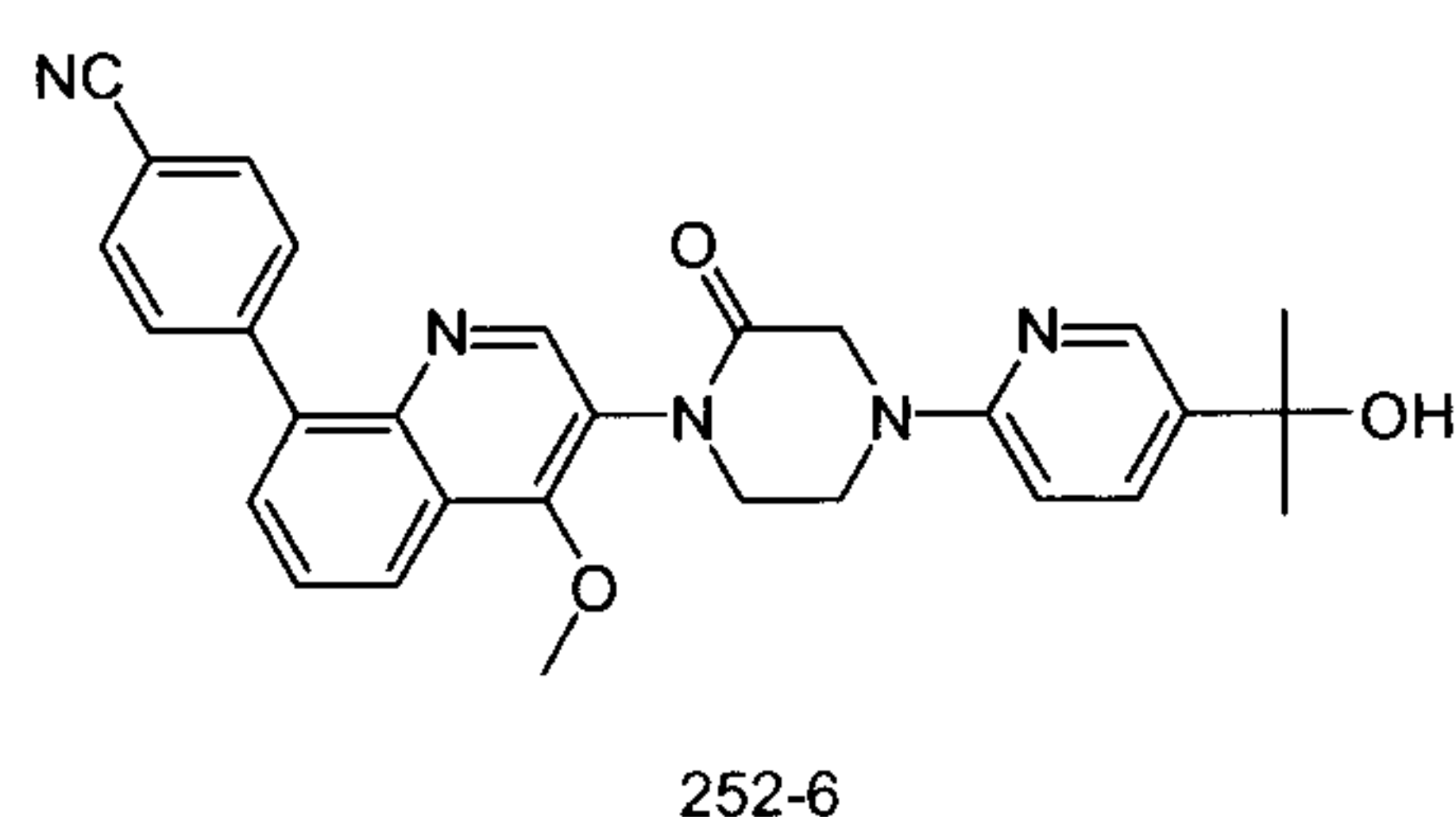
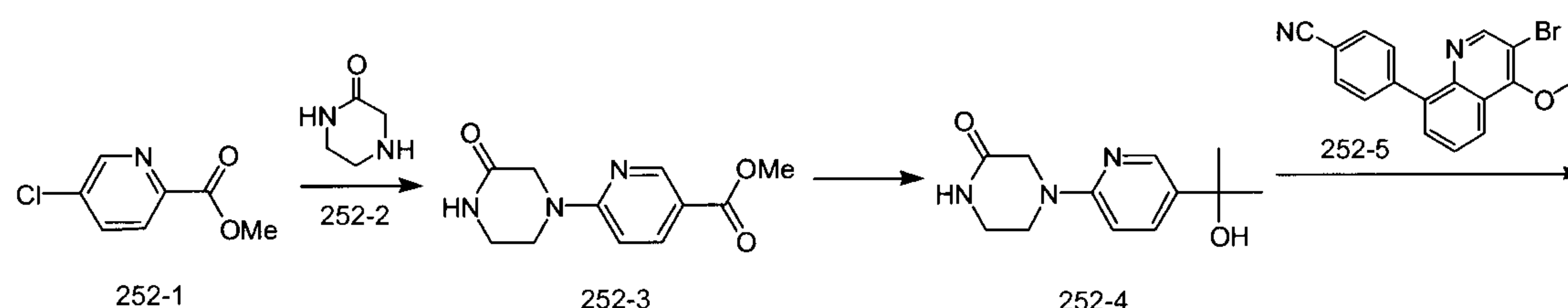
[559] Step 3: Compound 251-5 (300 mg, yield 75%) was synthesized as mentioned before. **MS ESI** calcd for $\text{C}_{32}\text{H}_{31}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 490, found 490.

[560] Step 4: NaBH_4 (57 mg, 1.5 mmol) was added into a solution of compound 251-5 (490 mg, 1 mmol) in THF (10 mL), then stirred at room temperature for 0.5h. After the reaction was complete as detected by LC-MS, the residue was poured into H_2O . The aqueous phase was extracted with DCM. The combined organic phase was washed with saturated sodium chloride solution, dried over sodium sulfate and concentrated. The crude product was purified by preparative HPLC to deliver the title compound (64 mg, yield 13%) as white solid. ^1H NMR (400 MHz, CDCl_3) δ 8.93 (s, 1H), 8.47-8.44 (m, 1H), 7.83-7.78 (m, 4H), 7.66 (d, $J=7.6$ Hz, 2H), 7.43 (d, $J=8.4$ Hz, 2H), 7.00 (d, $J=8.8$ Hz, 2H), 3.88 (s, 3H), 3.47 (d, $J=12.4$ Hz, 2H), 3.12 (s, 1H), 2.64 (s, 2H), 1.08 (s, 6H), 1.05 (s, 6H).

Embodiment 252



4-(3-(4-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)-2-oxopiperazin-1-yl)-4-methoxy
quinolin-8-yl)benzonitrile



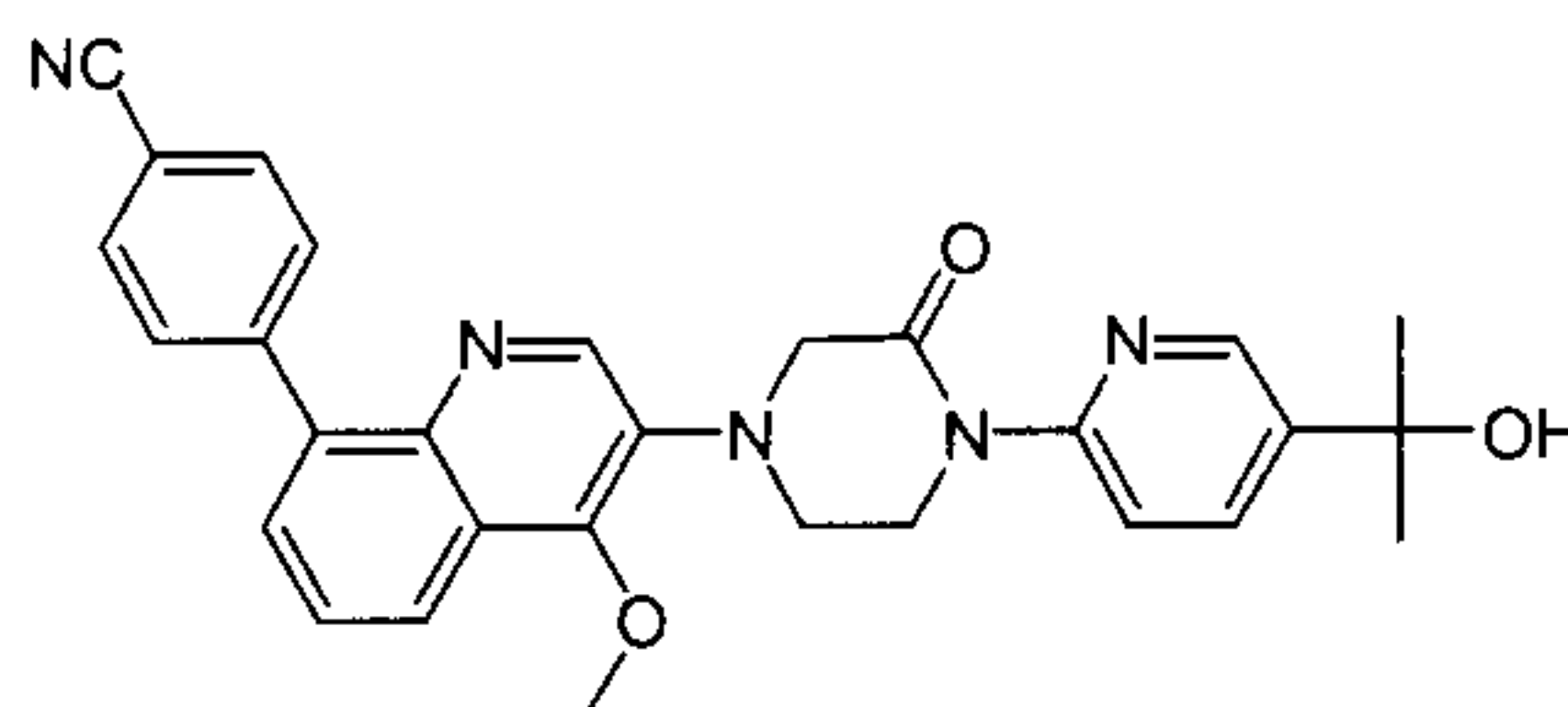
[561] Step 1: K_2CO_3 (13.8 g, 0.1 mol) was added into a solution of compound 252-1 (8.6 g, 50 mmol) and 252-2 (5 g, 50 mmol) in DMF (50 mL), then the mixture was stirred at 120°C overnight. The mixture was cooled and poured into H_2O . The precipitate was collected after filtration, washed with H_2O and methanol to deliver 6-(3-oxopiperazin-1-yl)nicotinic acid methyl ester (8.5 g, yield 72.6%) as yellow solid. **MS ESI** calcd for $C_{11}H_{13}N_3O_3$ $[M+H]^+$ 236, found 236.

[562] Step 2: At -78°C, MeMgBr (3 mL, 3 M in THF, 9 mmol) was added into a solution of 252-3 (708 mg, 3 mmol) in THF (50 mL). The mixture was stirred at room temperature for 1h and poured into saturated NH_4Cl solution. The mixture was extracted with EtOAc, dried over sodium sulfate, concentrated to deliver 252-4 (260 mg, yield 37%) as yellow solid. **MS ESI** calcd for $C_{12}H_{17}N_3O_2$ $[M+H]^+$ 236, found 236.

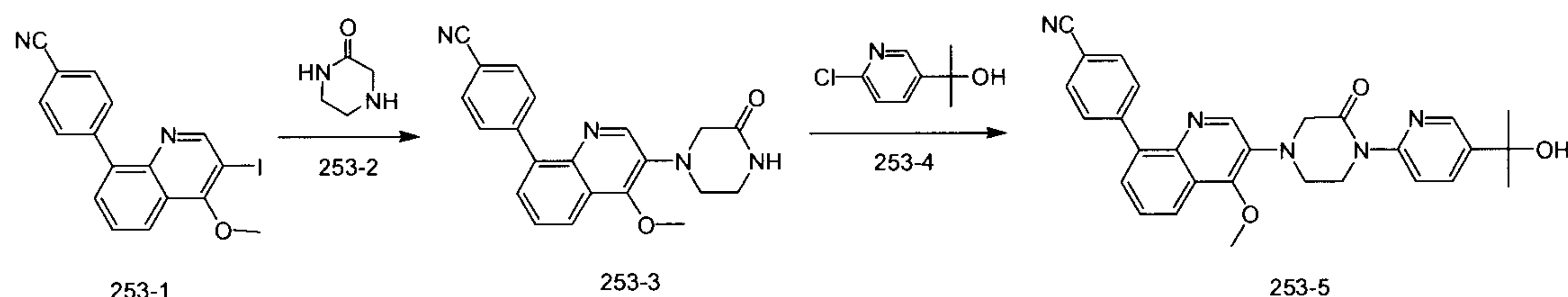
[563] Step 3: Under nitrogen gas atmosphere, N1,N1,N3,N3-tetramethylpropane-1,3-diamine (3 mg, 0.03 mmol), CuI (4 mg, 0.02 mmol) and K_2CO_3 (70 mg, 0.6 mmol) were added into a solution of compound 252-4 (100 mg, 0.3 mmol) and 252-5 (72 mg, 0.3 mmol) in toluene (5 mL). The reaction mixture was stirred at 120°C overnight. After poured into H_2O , the mixture was extracted with EtOAc twice. The organic phase was dried over sodium sulfate and concentrated. The concentration was purified by preparative HPLC to deliver the title compound (10 mg, yield 7%) as yellow solid. **MS ESI** calcd for $C_{29}H_{27}N_5O_3$ $[M+H]^+$ 494, found 494. **^1H NMR** (400 MHz, $CDCl_3$) δ ppm 8.69 (s, 1 H), 8.39-8.40 (d, $J=2.0$ Hz, 1 H), 8.27 (m, 1 H), 7.67-7.80 (m, 7 H), 6.69-6.71 (d, $J=8.8$ Hz, 1H),

4.39 (s, 2 H), 4.15-4.18 (m, 2 H), 4.11 (s, 3 H), 3.88 (s, 2 H), 1.62 (m, 6 H).

Embodiment 253



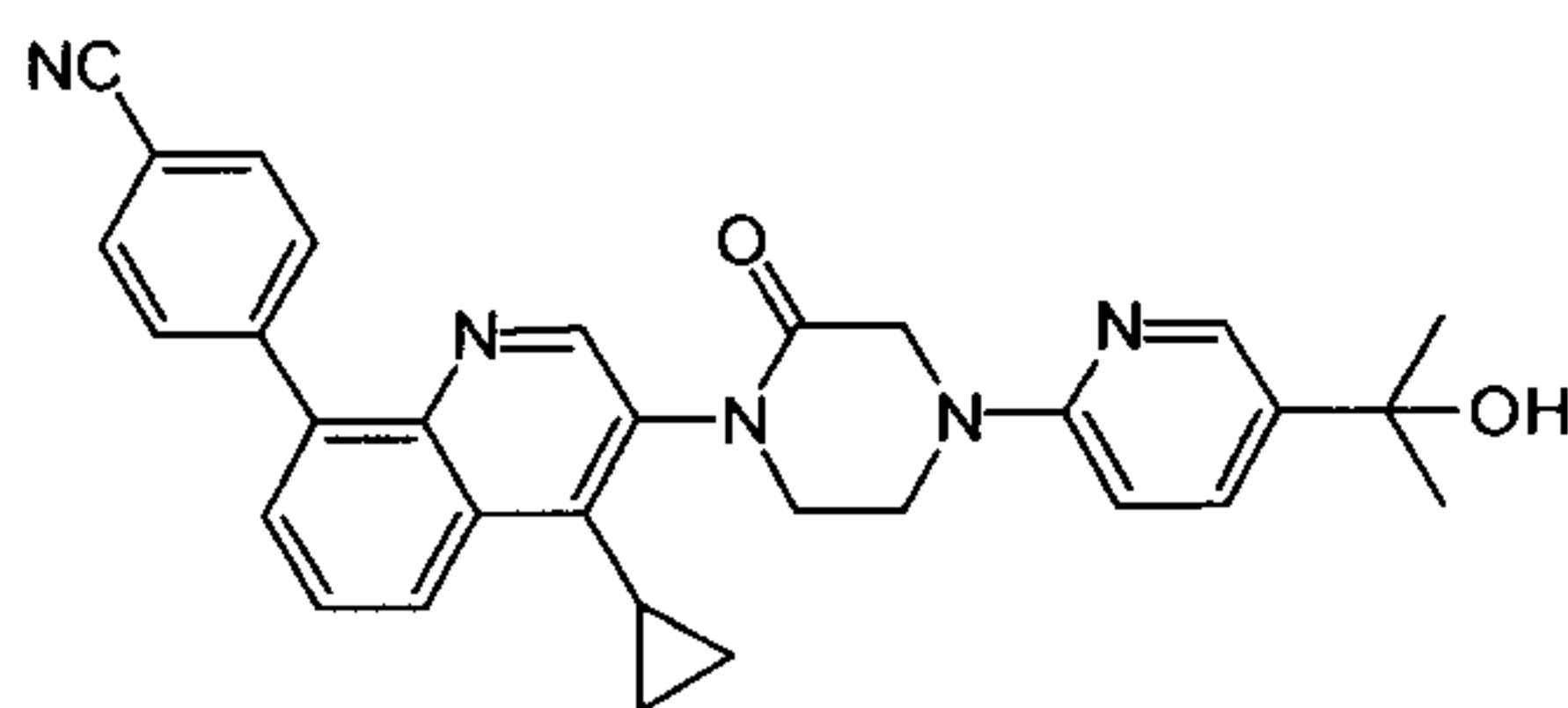
4-(3-(4-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)-3-oxopiperazin-1-yl)-4-methoxyquinolin-8-yl)benzonitrile



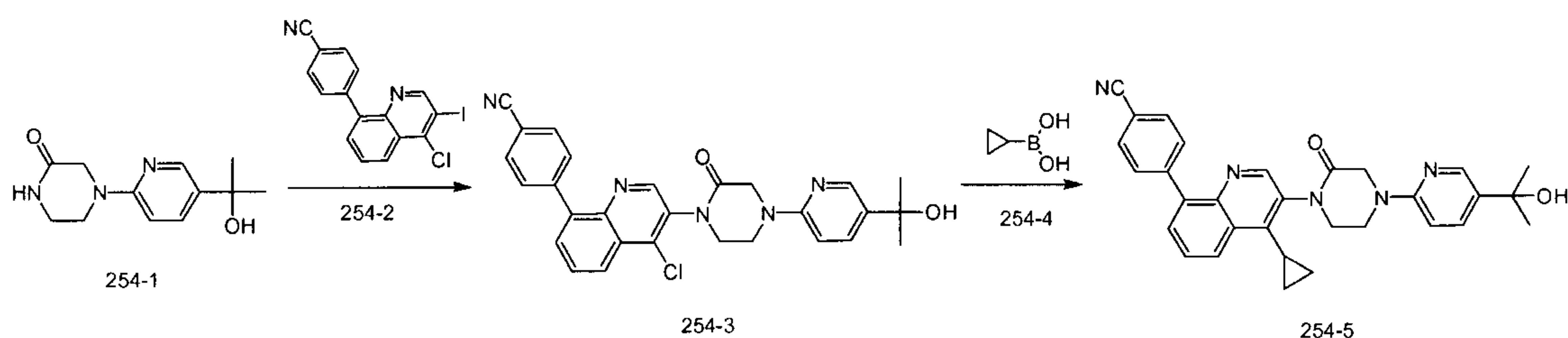
[564] Step 1: Under nitrogen gas atmosphere, $\text{Pd}_2(\text{dba})_3$ (184 mg, 0.2 mmol), Xantphos (240 mg, 0.4 mmol) and cesium carbonate (1.3 g, 4 mmol) were added into a solution of compound 253-1 (768 mg, 2 mmol) and 253-2 (200 mg, 2 mmol) in toluene (10 mL). The mixture was stirred at 120°C overnight. After poured into H_2O , the mixture was extracted with EtOAc twice. The organic phase was dried over sodium sulfate and concentrated. The concentration was purified by silica gel column chromatography (PE/EtOAc 1:1) to deliver 253-3 (300 mg, yield 44%) as yellow solid. **MS ESI** calcd for $\text{C}_{21}\text{H}_{18}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ 359, found 359.

[565] Step 2: 253-3 (180 mg, 0.5 mmol) and 253-4 (86 mg, 0.5 mmol) were added into toluene (5 mL), $\text{Pd}_2(\text{dba})_3$ (46 mg, 0.05 mmol), Xantphos (57.7 mg, 0.1 mmol) and cesium carbonate (325 mg, 1 mmol) were added into the obtained solution under nitrogen gas atmosphere. The mixture was stirred at 120°C overnight. After poured into H_2O , the mixture was extracted with EtOAc twice. The organic phase was dried over sodium sulfate and concentrated. The residue was purified by preparative HPLC to deliver the target product (80 mg, yield 12%) as yellow solid. **MS ESI** calcd for $\text{C}_{29}\text{H}_{27}\text{N}_5\text{O}_3$ $[\text{M}+\text{H}]^+$ 494, found 494. **^1H NMR** (400 MHz, CDCl_3) δ ppm 8.69 (s, 1 H), 8.39-8.40 (d, $J=2.0\text{ Hz}$, 1 H), 8.27(m, 1 H), 7.67-7.80 (m, 7 H), 6.69-6.71 (d, $J=8.8\text{ Hz}$, 1 H), 4.39 (s, 2 H), 4.15-4.18 (m, 2 H), 4.11 (s, 3 H), 3.88 (s, 2 H), 1.64 (m, 6 H).

Embodiment 254



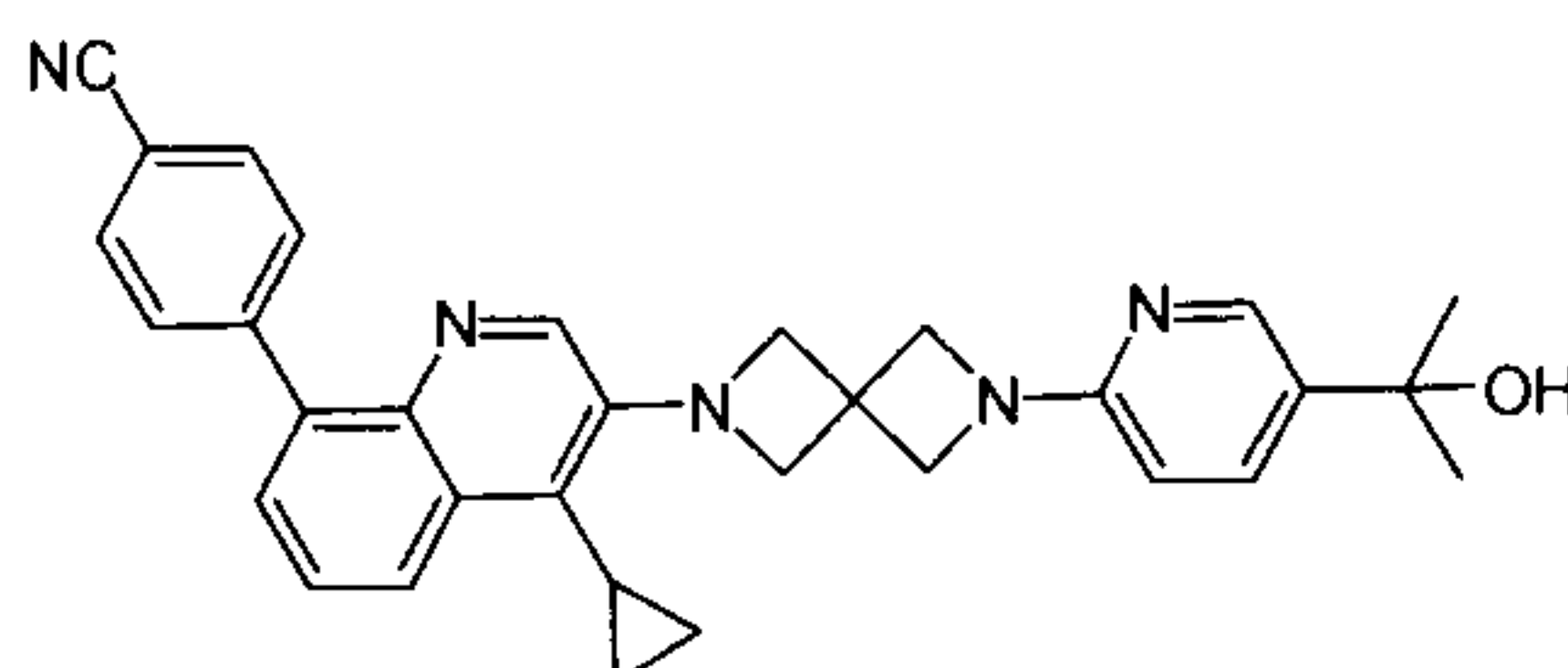
4-(4-cyclopropyl-3-(4-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)-2-oxopiperazin-1-yl)-quinolin-8-yl)benzonitrile



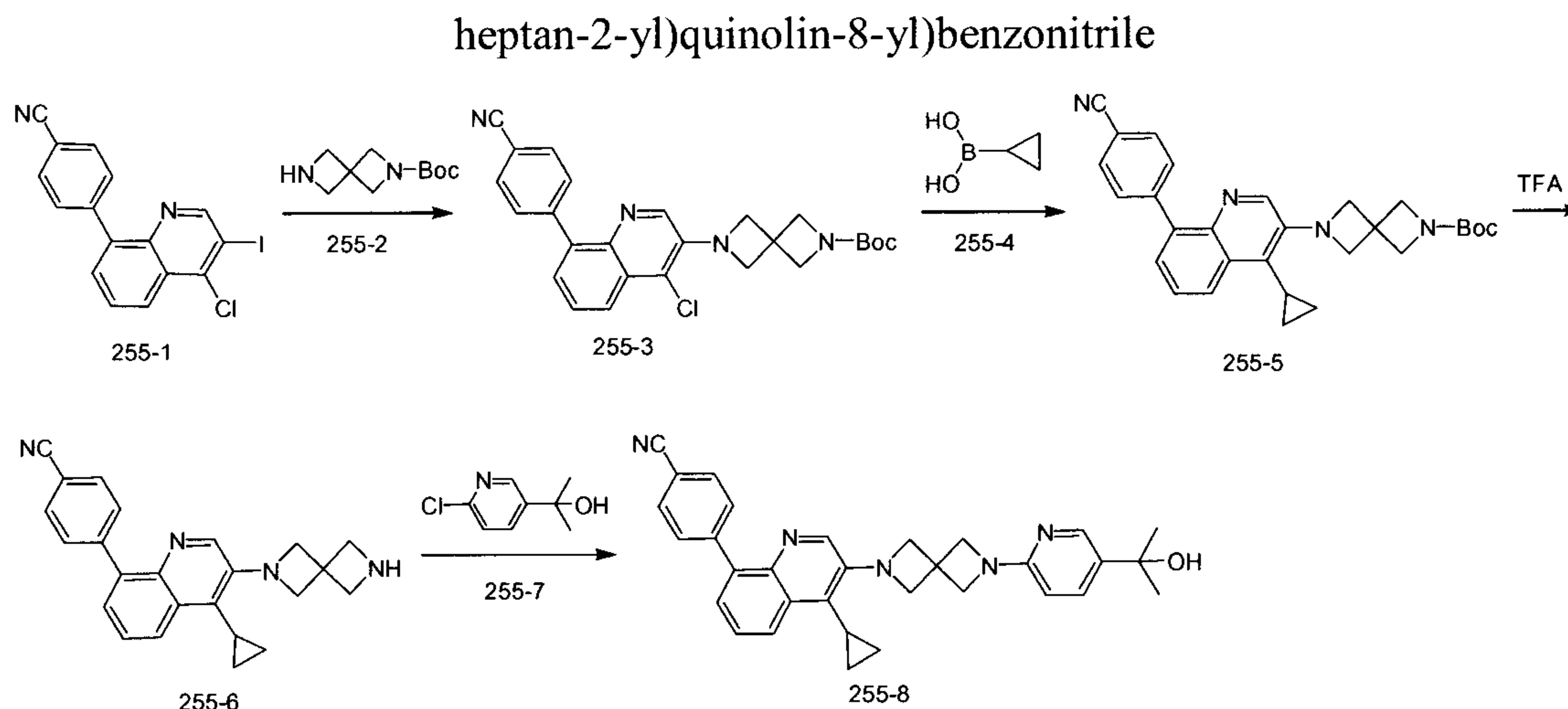
[566] Step 1: 254-1 (472 mg, 2 mmol) and 254-2 (780 mg, 2 mmol), $\text{Pd}_2(\text{dba})_3$ (180 mg, 0.2 mmol), Xantphos (240 mg, 0.4 mmol) and cesium carbonate (1.3 mg, 4 mmol) were added into toluene (20 mL). The mixture was stirred at 120°C overnight under nitrogen gas atmosphere. After poured into H_2O , the mixture was extracted with EtOAc twice. The organic phase was dried over sodium sulfate and concentrated. The concentration was purified by silica gel column chromatography (PE:EtOAc=1:1) to deliver compound 254-3 (520 mg, yield 52%) as yellow solid. **MS ESI** calcd for $\text{C}_{28}\text{H}_{24}\text{ClN}_5\text{O}_2$ $[\text{M}+\text{H}]^+$ 498, found 498.

[567] Step 2: 254-3 (150 mg, 0.3 mmol) and cyclopropyl boric acid (262 mg, 3 mmol), *n*-BuPAD (22 mg, 0.06 mmol), $\text{Pd}(\text{OAc})_2$ (7 mg, 0.03 mmol) and cesium carbonate (195 mg, 0.6 mmol) were added into toluene/ H_2O (5 mL/1 mL). The mixture was stirred at 120°C overnight under nitrogen gas atmosphere. After poured into H_2O , the mixture was extracted with EtOAc twice. The organic phase was dried over sodium sulfate and concentrated. The residue was purified by preparative HPLC to deliver the target compound (50 mg, yield 33%) as yellow solid. **MS ESI** calcd for $\text{C}_{31}\text{H}_{29}\text{N}_5\text{O}_2$ $[\text{M}+\text{H}]^+$ 504, found 504. **^1H NMR**(400 MHz, CDCl_3) δ ppm 8.71 (s, 1 H), 8.59-8.61 (d, $J=8.0$ Hz, 1 H), 8.39 (dd, $J=2.0$ Hz, 1 H), 7.68-7.78 (m, 7H), 6.69-6.71(d, $J=8.8$ Hz, 1H), 4.31-4.65(m, 2H), 4.12-4.23(m, 2H), 3.91-3.96(m, 2H), 2.13(m, 1 H), 1.62 (s, 6H), 1.18-1.24(m, 2H), 0.84(m, 1H), 0.64(m, 1H).

Embodiment 255



4-(4-cyclopropyl-3-(6-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)-2,6-diazaspiro[3.3]



[568] Step 1: $\text{Pd}_2(\text{dba})_3$ (92 mg, 0.1 mmol), Xantphos (120 mg, 0.2 mmol) and cesium carbonate (650 mg, 2 mmol) were added into a solution of 255-1 (390 mg, 1 mmol) and 255-2 (299 mg, 1 mmol) in toluene (10 mL). Under nitrogen gas atmosphere, the mixture was stirred at 120°C overnight. After poured into H_2O , the mixture was extracted with EtOAc twice. The organic phase was dried over anhydrous sodium sulfate and concentrated. The concentration was purified by silica gel column chromatography (PE/ EtOAc =1:1) to deliver 255-3 (400 mg, yield 87%) as yellow solid. **MS ESI** calcd for $\text{C}_{26}\text{H}_{25}\text{ClN}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ 461, found 461.

[569] Step 2: 255-3 (400 mg, 0.87 mmol) and cyclopropyl boric acid (378 mg, 4.35 mmol), *n*-BuPAd (62 mg, 0.174 mmol), $\text{Pd}(\text{OAc})_2$ (20 mg, 0.09 mmol) and cesium carbonate (565 mg, 1.74 mmol) were added into toluene/ H_2O (10 mL/1 mL). Under nitrogen gas atmosphere, the mixture was stirred at 120°C overnight. After poured into H_2O , the mixture was extracted with EtOAc twice. The organic phase was dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/ EtOAc =3:1) to deliver 255-5 (400 mg, yield 98%) as yellow solid. **MS ESI** calcd for $\text{C}_{29}\text{H}_{30}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ 467, found 467.

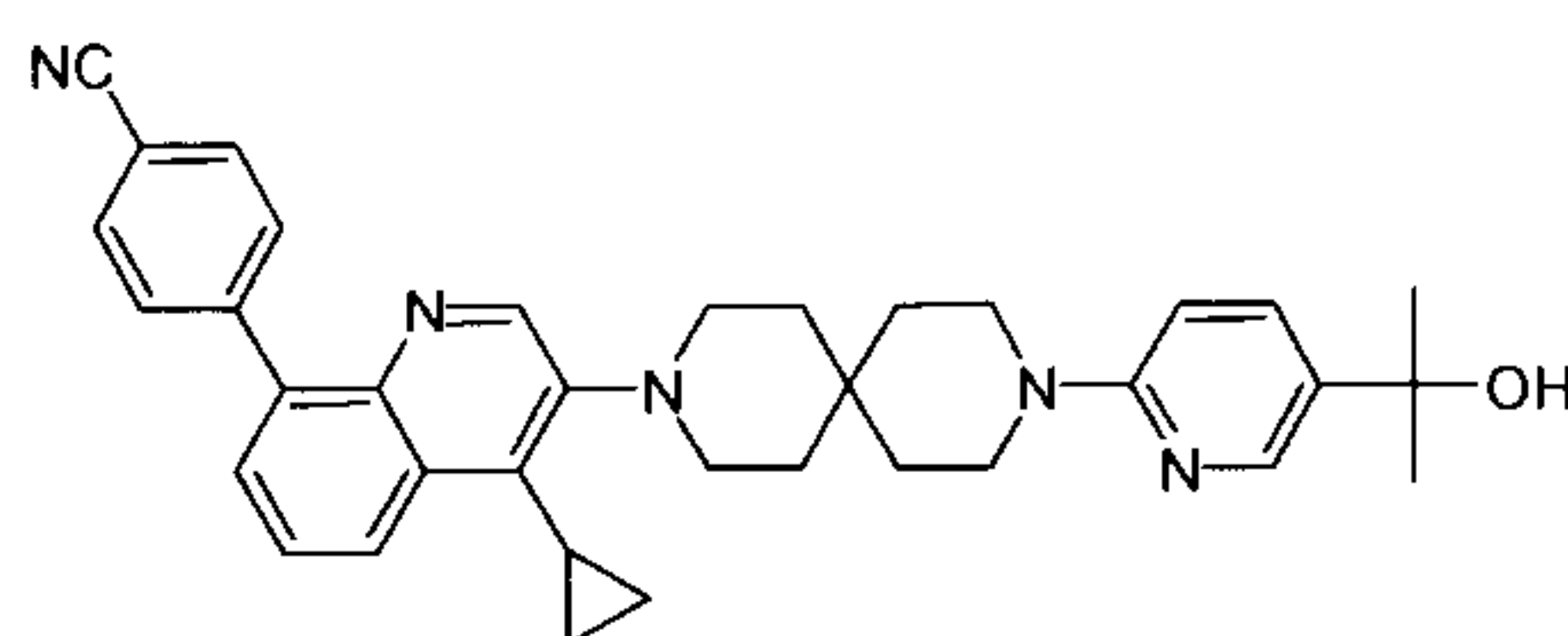
[570] Step 3: 255-5 (400 mg, 0.87 mmol) was dissolved in DCM (10 mL) and TFA (5 mL) was added, the mixture was stirred at room temperature for 2h. The mixture was concentrated and dried to deliver compound 255-6 (300 mg, yield 94%) as yellow oil. **MS ESI** calcd for $\text{C}_{24}\text{H}_{22}\text{N}_4$ $[\text{M}+\text{H}]^+$ 367, found 367.

[571] Step 4: 255-6 (184 mg, 0.5 mmol) and 255-7 (86 mg, 0.5 mmol), $\text{Pd}_2(\text{dba})_3$ (46 mg, 0.05 mmol), Xantphos (57.7 mg, 0.1 mmol) and cesium carbonate (325 mg, 1 mmol) were added in toluene (5 mL). Under nitrogen gas atmosphere, the mixture was stirred at 120°C overnight. After poured into H_2O , the mixture was extracted with EtOAc twice. The organic phase was dried over sodium sulfate and concentrated. The residue was purified by preparative HPLC to deliver the target compound (30 mg, yield 12%) as yellow solid. **MS ESI** calcd for $\text{C}_{32}\text{H}_{31}\text{N}_5\text{O}$ $[\text{M}+\text{H}]^+$ 502, found 502. **^1H NMR**(400 MHz, CDCl_3) δ ppm 8.30-8.38 (m, 3H), 7.70-7.77 (m, 4H), 7.68 (d, $J=2.0$ Hz, 1H), 7.56-7.58 (d, $J=8.4$ Hz, 1H), 6.35-6.37 (d,

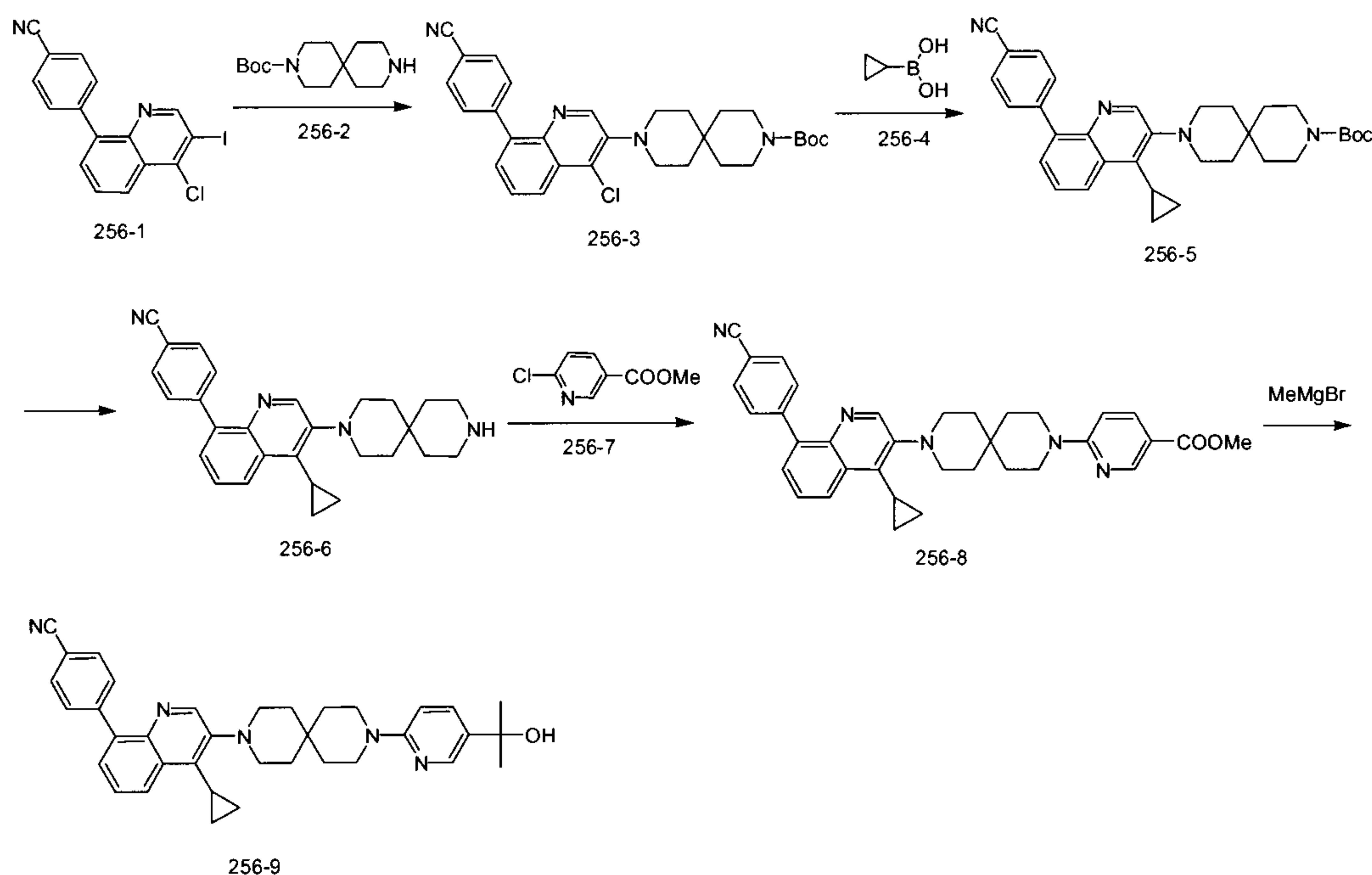
Our Ref.: P1650132CA

$J=8.8$ Hz, 1H), 4.37-4.40 (m, 4H), 4.11-4.13 (m, 4H), 2.05-2.07 (m, 1H), 1.59 (s, 6H), 1.23-1.27 (m, 2H), 0.78-0.79 (m, 2H)

Embodiment 256



4-(4-cyclopropyl-3-(9-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)quinolin-8-yl)benzonitrile



[572] Step 1: 256-1 (780.00 mg, 2.0 mmol) and 256-2 (507.96 mg, 2.0 mmol) were dissolved in toluene (20 mL), under nitrogen gas atmosphere, $\text{Pd}_2(\text{dba})_3$ (115.00 mg, 200.00 μmol) was added. The mixture was stirred at room temperature for 10 min, then heated to 110°C and reacted for 3h. After cooled to room temperature, the mixture was poured into H_2O (200 mL) and stirred for 20min. Then the mixture was extracted with EtOAc (400 mL*3). The combined organic phase was washed with H_2O and brines (200 mL*2) respectively, dried over sodium sulfate, filtrated and concentrated under reduced pressure. The residue was purified by thin layer chromatography (PE/ EtOAc extract part=5:1) to deliver 256-3 (100 mg, yield 9.67%) as yellow solid. **MS ESI** calcd for $\text{C}_{30}\text{H}_{33}\text{ClN}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ 517, found 517.

[573] Step 2: 256-3 (100 mg, 193.4 μmol), cyclopropyl boric acid (83.07 mg, 967 μmol) were dissolved in toluene (10 mL), under nitrogen gas atmosphere, $\text{Pd}(\text{OAc})_2$ (0.20 mg, 38.68 μmol) was added. The mixture was stirred at room temperature for 10min, then heated to 110°C and reacted for 1h. After cooled to room temperature,

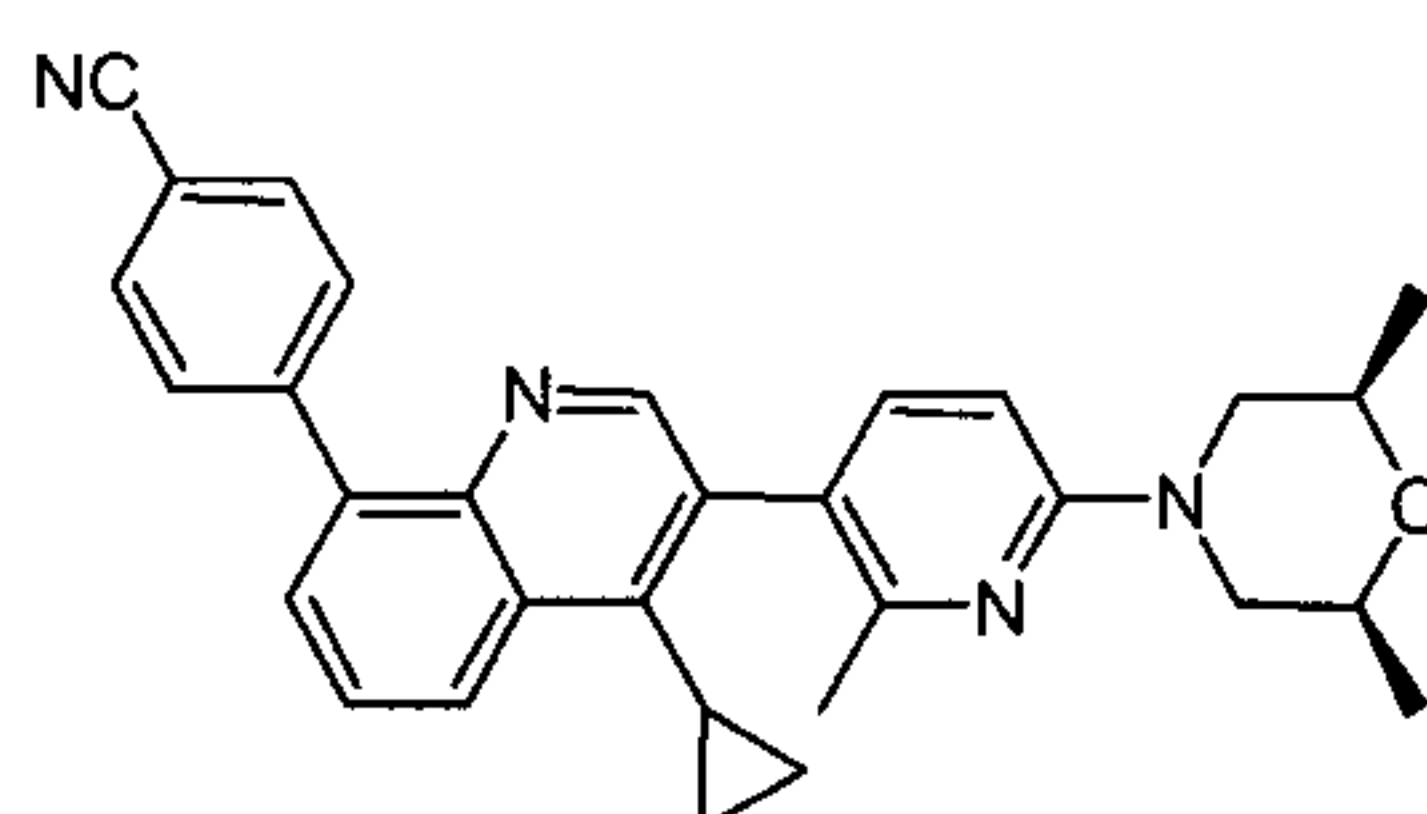
the mixture was poured into H₂O (50 mL) and stirred for 20 min. Then the mixture was extracted with EtOAc (100mL*3). The combined organic phase was washed with H₂O and brines (50 mL*2), dried over anhydrous sodium sulfate, filtrated and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/ EtOAc=5:1) to deliver 256-5 (80.00 mg, yield 79.14%) as yellow solid. **MS ESI** calcd for C₃₃H₃₈N₄O₂ [M+H]⁺ 523, found 523.

[574] Step 3: 256-5 (80 mg, 153.06 μmol) was dissolved in DCM (5 mL) and HCl/EtOAc (4 M, 2 mL) was added. Then the mixture was stirred at room temperature for 2h. The crude product 256-6 obtained after concentration was used for the next step directly. **MS ESI** calcd for C₂₈H₃₀N₄ [M + H]⁺ 423, found 423.

[575] Step 4: 256-6 (50 mg, 118.33 μmol) and 256-7 (24.36 mg, 142 μmol) were dissolved in acetonitrile (5 mL) and K₂CO₃ (163.54 mg, 1.18 mmol) was added. The mixture was stirred at room temperature for 10 min, then heated to 80°C for 12h. After cooled to room temperature, the mixture was poured into H₂O (50 mL) and stirred for 20 min, the obtained mixture was extracted with EtOAc (50 mL*3). The organic phases were combined and washed with brines (50 mL), dried over anhydrous sodium sulfate, filtrated and concentrated under vacuum. The residue was purified by thin layer chromatography (PE/EtOAc=5:1) to deliver 256-8 (30 mg, yield 45.46%) as yellow solid. **MS ESI** calcd for C₃₅H₃₅N₅O₂ [M+H]⁺ 558, found 558.

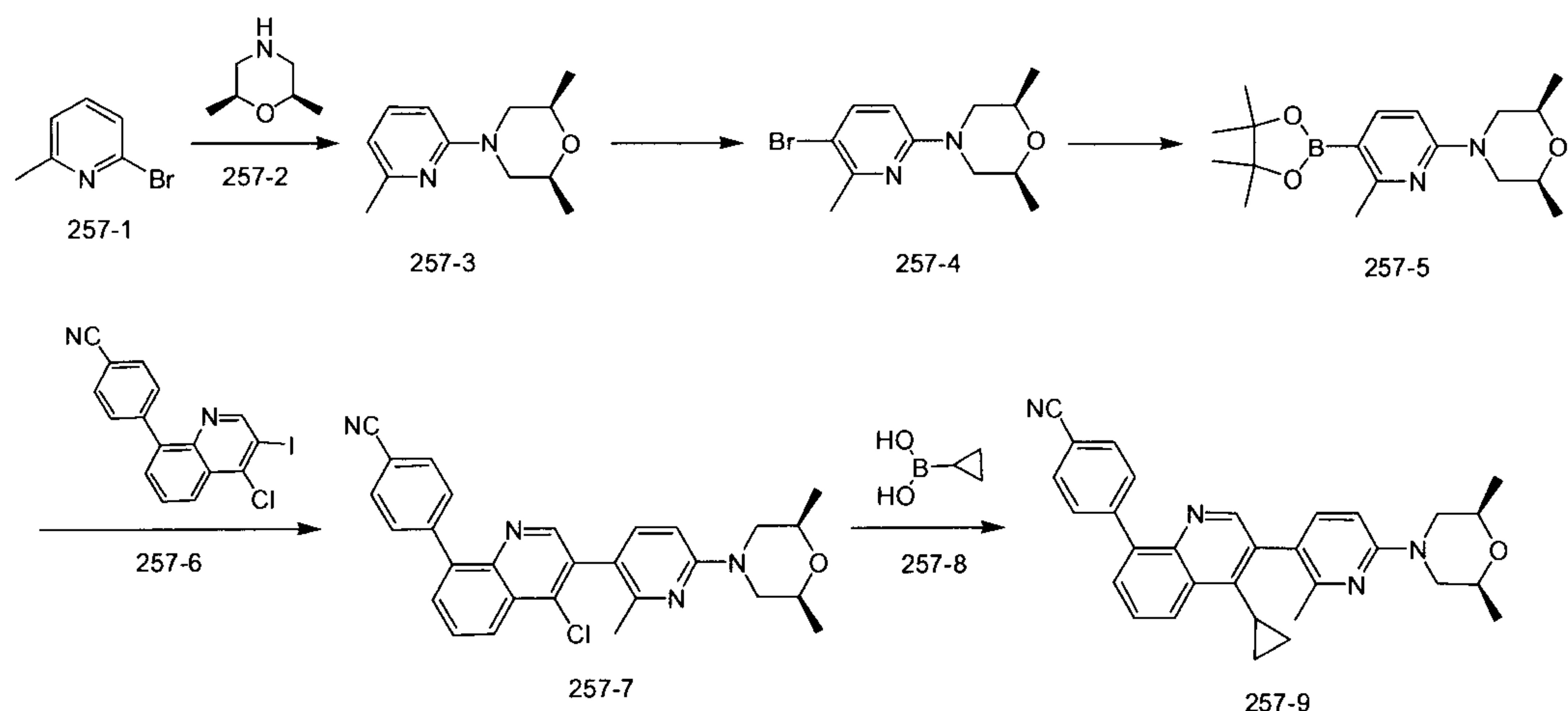
[576] Step 5: 256-8 (30 mg, 53.79 μmol) was dissolved in THF (5 mL), methyl magnesium bromide (32.07 mg, 268.95 μmol) was added dropwise at room temperature. The mixture was stirred at room temperature for 1h, then poured into ammonium chloride aqueous solution (50 mL), stirred for 20 min, the obtained mixture was extracted with EtOAc (50 mL*3). The organic phases were combined and washed with brines (20 mL), dried over anhydrous sodium sulfate, filtrated and concentrated under vacuum. The residue was purified by preparative HPLC to deliver the target compound (2 mg, yield 6.67%) as yellow solid. **MS ESI** calcd for C₃₆H₃₉N₅O [M+H]⁺ 558, found 558. **¹HNMR** (400MHz, METHANOL-d₄) δ ppm 8.76 (s, 1H), 8.49 (d, *J*= 8 Hz, 1H), 8.31 (d, *J*= 2.0 Hz, 1H), 7.76 (s, 4H), 7.66 (t, *J*= 6.4 Hz, 1H), 7.51-7.58 (m, 2H), 3.50-3.58 (m, 4H), 3.25-3.29 (m, 4H), 2.01-2.05 (m, 2H), 1.63 (s, 6H), 1.23-1.26 (m, 2H).

Embodiment 257



4-(4-cyclopropyl-3-(6-((2*S*,6*R*)-2,6-dimethylmorpholino)-2-methylpyridin-3-yl)
quinolin-8-yl)benzonitrile

Our Ref.: P1650132CA



[577] Step 1: 257-1 (10 g, 58.13 mmol), 257-2 (8.03 g, 69.76 mmol), $\text{Pd}_2(\text{dba})_3$ (53.23 g, 58.13 mmol), Xantphos (33.64 g, 58.13 mmol) and potassium *tert*-butoxide (6.52 g, 58.13 mmol) were mixed in toluene (40 mL), degassing and swept with nitrogen gas for 3 times. Under nitrogen gas atmosphere, the mixture was stirred at 110°C for 12 h. The reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (100 mL*3). The organic phases were combined and washed with brines (20 mL), dried over anhydrous sodium sulfate, filtrated and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc=10:1) to deliver compound 257-3 (8 g, yield 66.72%) as yellow oil. **MS ESI** calcd for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 207, found 207.

[578] Step 2: 257-3 (11.40 g, 55.26 mmol) was dissolved in DMF (20 mL), NBS (9.34 g, 52.50 mmol) was added. The mixture was stirred at 25°C for 0.5h, diluted with H_2O (100 mL), then extracted with EtOAc (100 mL*3). The combined organic phase was washed with brines (100 mL), dried over anhydrous sodium sulfate, filtrated and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc=10:1) to deliver compound 257-4 (12 g, yield 76.15%) as white solid. **MS ESI** calcd for $\text{C}_{12}\text{H}_{17}\text{BrN}_2\text{O}$ $[\text{M}+\text{H}]^+$ 285, found 285.

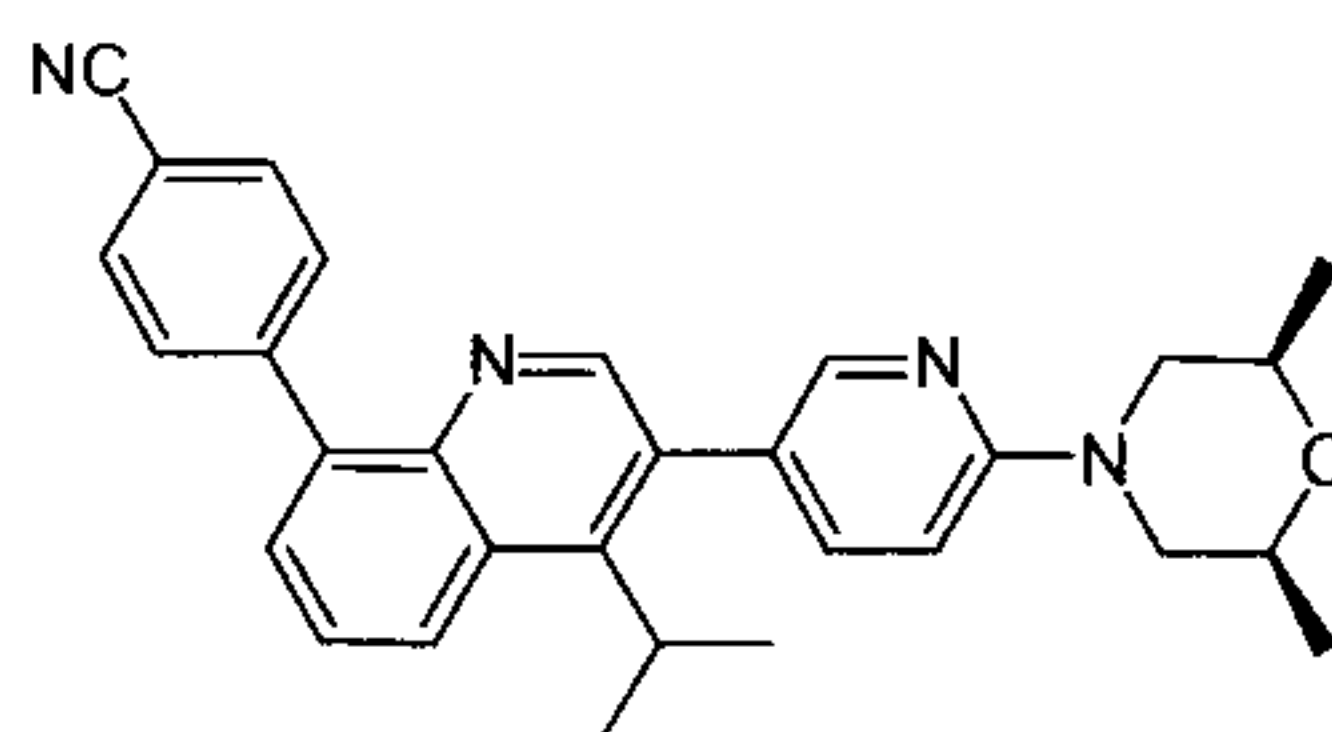
[579] Step 3: 257-4 (16 g, 56.10 mmol), bis(pinacolato)diboron (21.37 g, 84.15 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (2.05 g, 2.81 mmol) and KOAc (11.01 g, 112.20 mmol) were mixed in dioxane (50 mL). Under nitrogen gas atmosphere, the mixture was stirred at 100°C for 2h. The reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (100 mL*3). The organic phase was combined and washed with brines (20 mL), dried over sodium sulfate, filtrated and concentrated. The residue was purified by silica gel column chromatography (PE/ EtOAc = 10:1) to deliver compound 257-5 (10 g, yield 53.65%) as white solid. **MS ESI** calcd for $\text{C}_{18}\text{H}_{29}\text{BN}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 333, found 333.

[580] Step 4: $\text{Pd}(\text{dppf})\text{Cl}_2$ (561.95 mg, 768 μmol) and Na_2CO_3 (3.26 g, 30.72 mmol) were added into a solution of 257-6 (6 g, 15.36 mmol) and 257-5 (7.65 g, 23.04 mmol) in DMF (5 mL)/ H_2O (5 mL)/THF (25 mL). The mixture was stirred at 70°C for 2h. The reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (100

mL*3). The combined organic phase was washed with brines (20 mL), dried over sodium sulfate, filtrated and concentrated under reduced pressure. The residue was purified by column chromatography (PE/ EtOAc=5:1) to deliver 257-7(3 g, yield 41.65%) as yellow solid. **MS ESI** calcd for $C_{28}H_{25}ClN_4O$ $[M+H]^+$ 469, found 469.

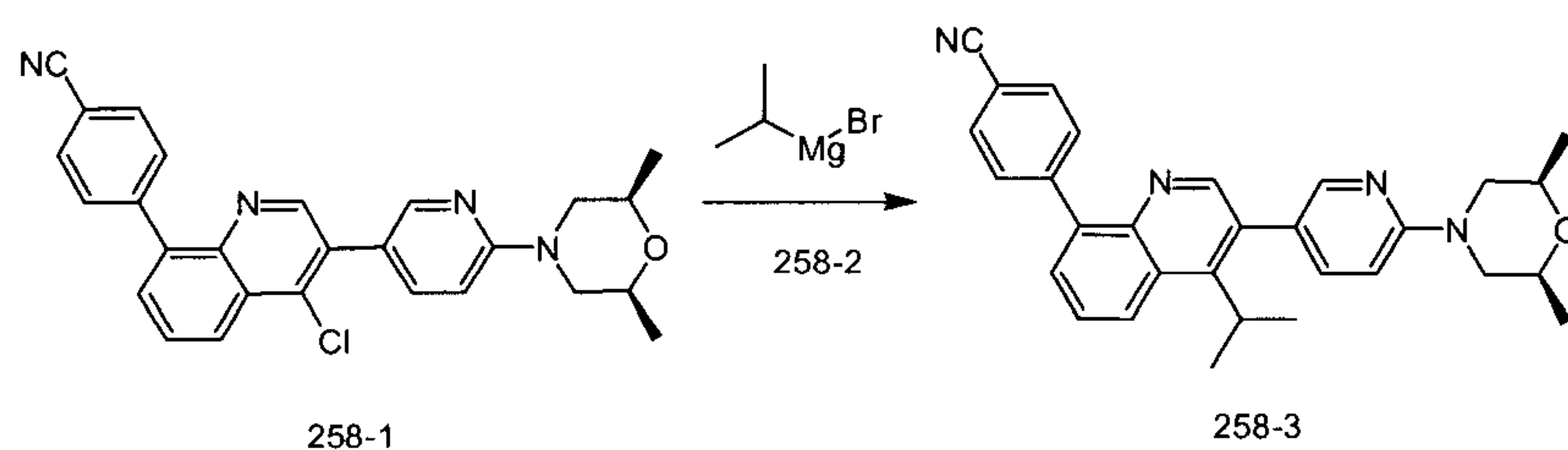
[581] Step 5: Bis(adamantyl) butyl phosphine (229.47 mg, 640 μ mol), Cs_2CO_3 (2.09 g, 6.40 mmol) and $Pd(OAc)_2$ (71.84 mg, 320 μ mol) were added into a solution of 257-7 (1.50 g, 3.20 mmol) and cyclopropyl boric acid (1.37 g, 16 mmol) in toluene (15 mL). The mixture was stirred at 110°C for 2h. The reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (100 mL*3). The combined organic phase was washed with brines (20 mL), dried over sodium sulfate, filtrated and concentrated. The residue was purified by column chromatography (PE/EtOAc =10:1) to deliver the target product (1 g, yield 65.85%) as light red solid. **MS ESI** calcd for $C_{31}H_{30}N_4O$ $[M+H]^+$ 475, found 475. **^1H NMR** (400MHz, $CDCl_3$) δ ppm 8.69 (s, 1H), 8.64 (dd, J = 3.0, 6.5 Hz, 1H), 7.74 - 7.90 (m, 4H), 7.67 - 7.72 (m, 2H), 7.35 (d, J = 8.5 Hz, 1H), 6.58 (d, J = 8.5 Hz, 1H), 4.06 - 4.26 (m, 2H), 3.69 - 3.79 (m, 2H), 2.58 (t, J = 11.5 Hz, 2H), 2.29 (s, 3H), 2.09 - 2.21 (m, 1H), 1.31 (d, J = 6.5 Hz, 6H), 0.99 (q, J = 5.3, 8.6 Hz, 2H), 0.27 - 0.54 (m, 2H).

Embodiment 258



4-(3-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-4-isopropylquinolin-8-yl)

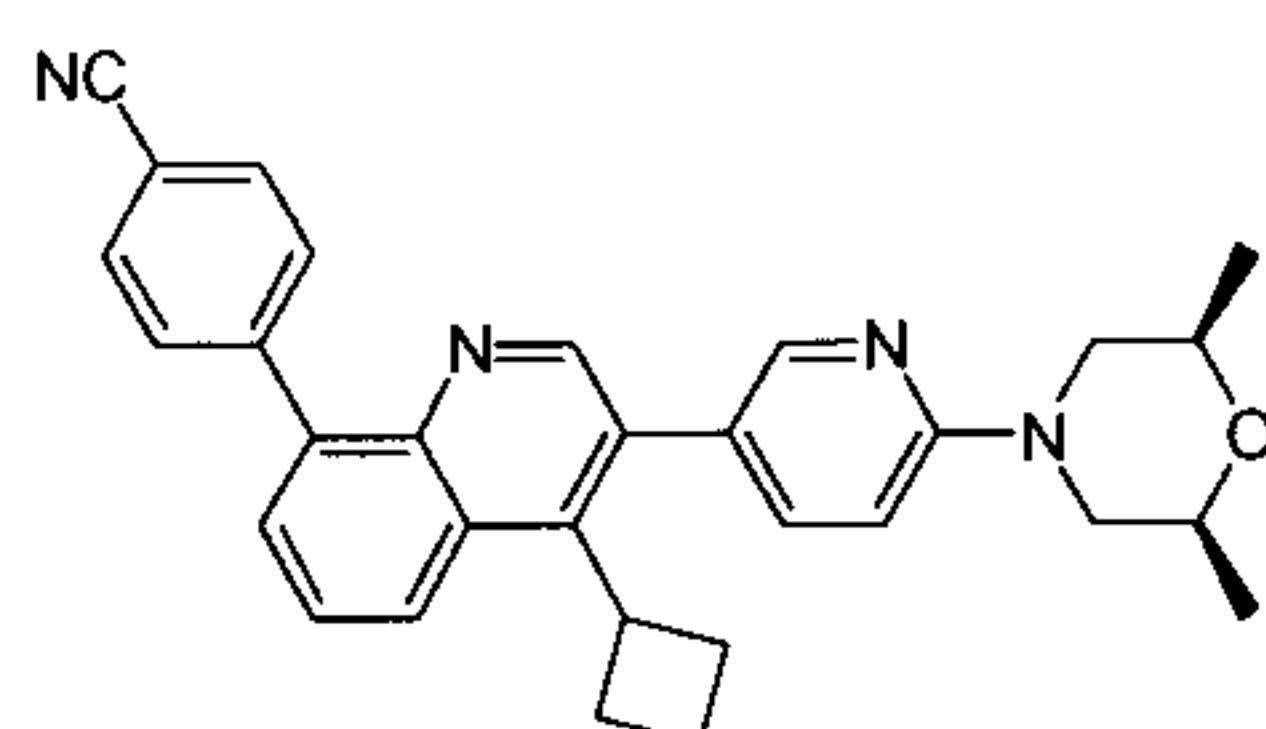
benzonitrile



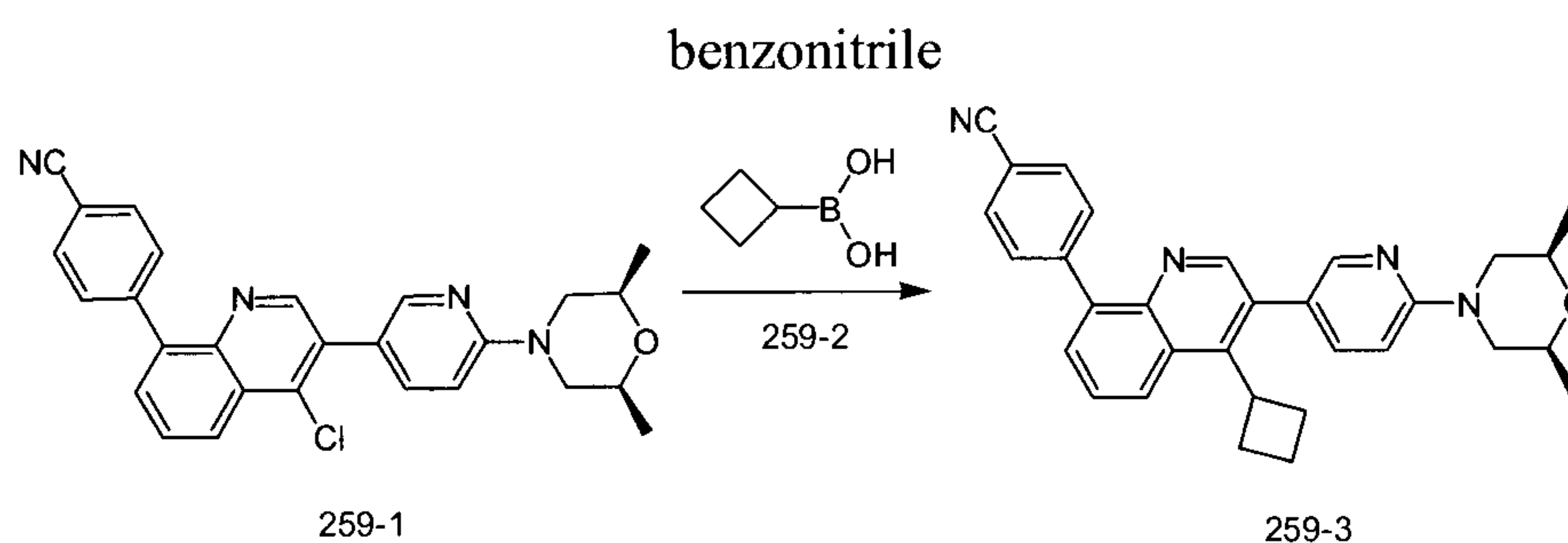
[582] 258-1 (227.48 mg, 500 μ mol) was dissolved in THF (4 mL) and NMP (1 mL), then at -40°C isopropyl magnesium bromide (73.65 mg, 500 μ mol) was added dropwise. The reaction mixture was warmed to 0°C and stirred for 10 min, then room temperature for 2h. The reaction mixture was quenched with ice slowly, then extracted with EtOAc (5 mL*3). The organic phases were combined and washed with brines (100 mL), dried over anhydrous sodium sulfate, filtrated and concentrated. The residue was purified by HPLC to deliver the target compound (20 mg, yield 8.79%) as white solid. **MS ESI** calcd for $C_{30}H_{30}N_4O$ $[M+H]^+$ 463, found 463. **^1H NMR** (400 MHz, $CHLOROFORM-d$) δ ppm 8.68 (s, 1 H), 8.46-8.48 (t, J = 5.02

Hz, 1 H), 8.22 (s, 1 H), 7.73 - 7.82 (m, 7 H), 7.06-7.08 (d, $J=9.2$ Hz, 1 H), 4.13-4.16 (m, 2 H), 3.81-3.84 (m, 2 H), 3.65 (m, 1 H), 2.91-2.97 (m, 2 H), 1.60 - 1.62 (d, $J=7.2$ Hz, 6 H), 1.33-1.35 (d, $J=6.0$ Hz, 6 H).

Embodiment 259

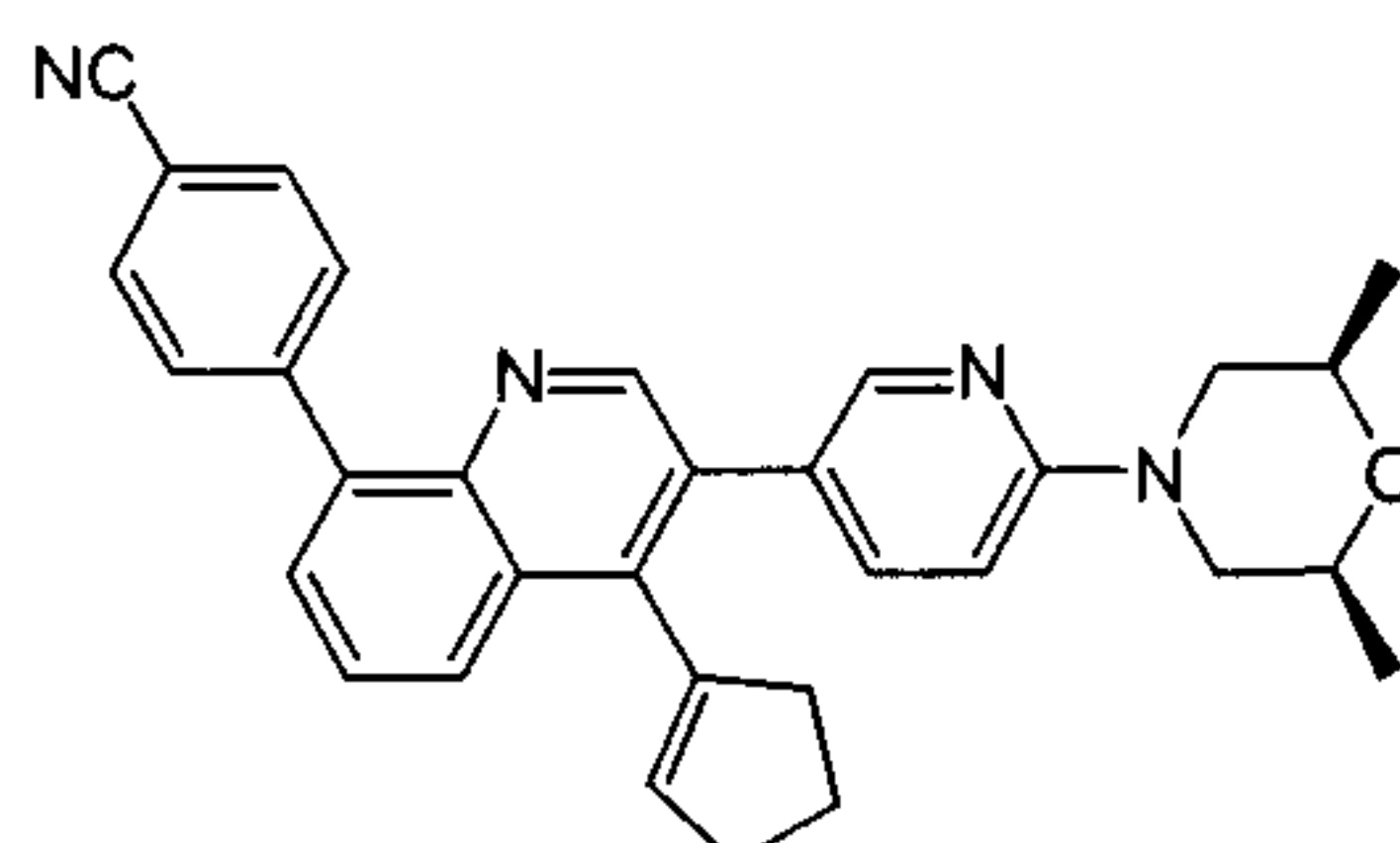


4-(4-cyclobutyl-3-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)quinolin-8-yl)



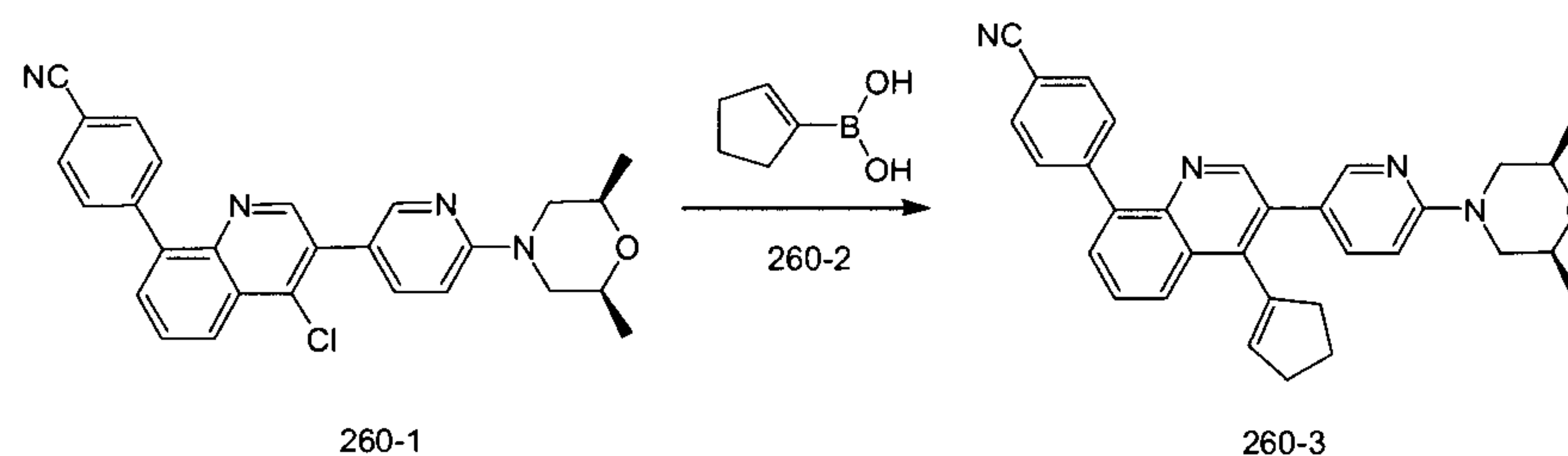
[583] Pd(dppf)Cl₂ (36.59 mg, 50 μmol) and Na₂CO₃ (105.99 mg, 1 mmol) were added into a solution of 259-1 (227.48 mg, 500 μmol), cyclobutyl boric acid (99.92 mg, 1 mmol) in THF / H₂O (2 mL). Under nitrogen gas atmosphere, the mixture was heated to 80°C and reacted for 2h, then poured into H₂O (10 mL). The reaction mixture was extracted with EtOAc (10 mL*3). The organic phase was washed with brines (30 mL), dried over anhydrous MgSO₄, concentrated under vacuum. The residue was purified by prep-HPLC to deliver the target product (50 mg, yield 21.07%). **MS ESI** calcd for C₃₁H₃₀N₄O [M+H]⁺ 475, found 475. **¹H NMR** (400 MHz, CHLOROFORM-d) δ ppm 8.70 (s, 1 H), 8.09 - 8.23 (m, 2 H), 7.79 (d, $J=3.01$ Hz, 4 H), 7.58 - 7.71 (m, 2 H), 7.46 - 7.57 (m, 1 H), 6.63 - 6.84 (m, 1 H), 4.26 - 4.50 (m, 1 H), 4.12 (d, $J=12.55$ Hz, 2 H), 3.76 (d, $J=6.53$ Hz, 2 H), 2.54 - 2.69 (m, 2 H), 2.37 (d, $J=8.53$ Hz, 2 H), 1.84 - 2.15 (m, 4 H), 1.65 - 1.78 (m, 1 H), 1.17 - 1.38 (m, 8 H).

Embodiment 260



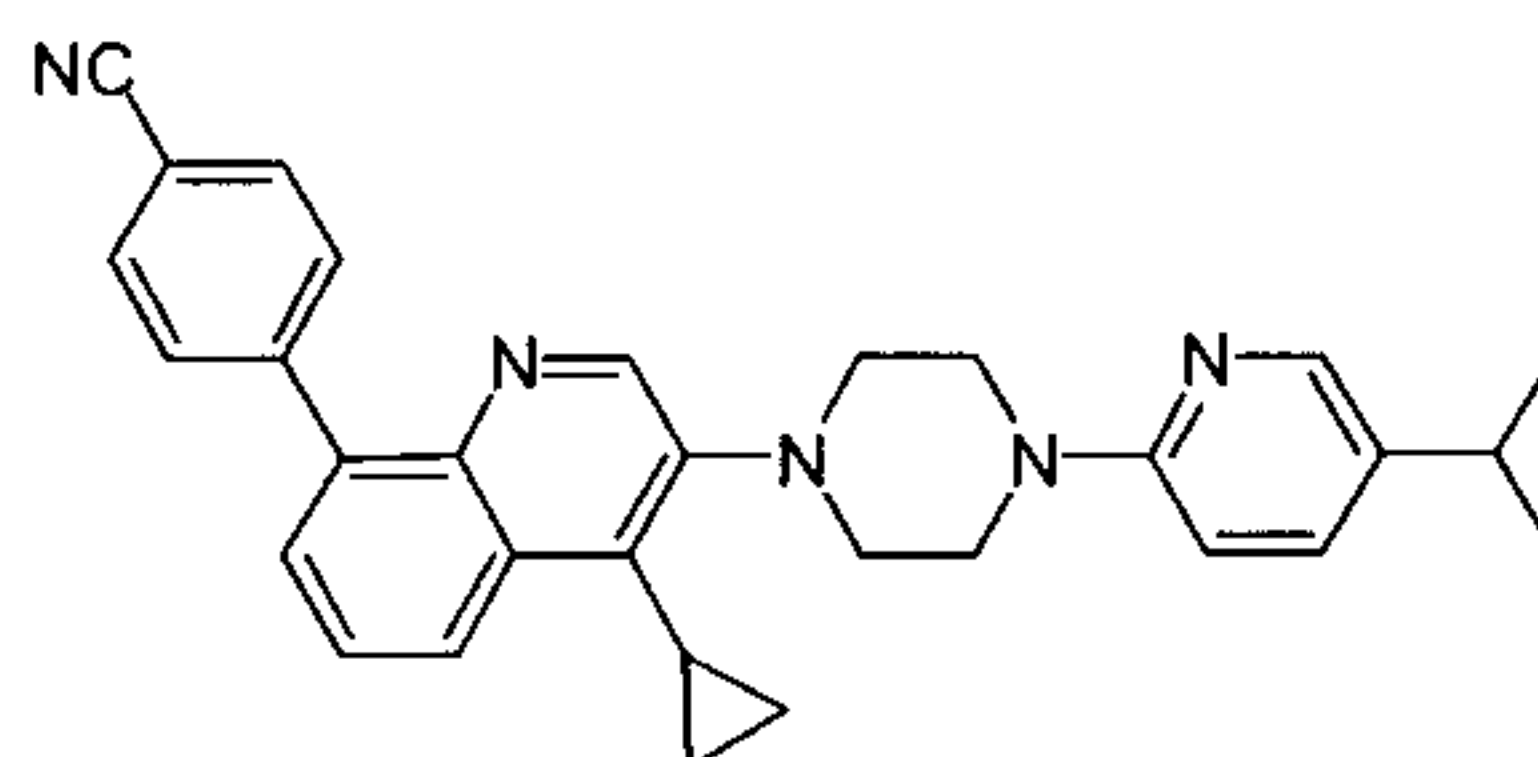
4-(4-(1-cyclopenten-1-yl)-6-(3-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)quinolin-8-yl)benzonitrile

Our Ref.: P1650132CA

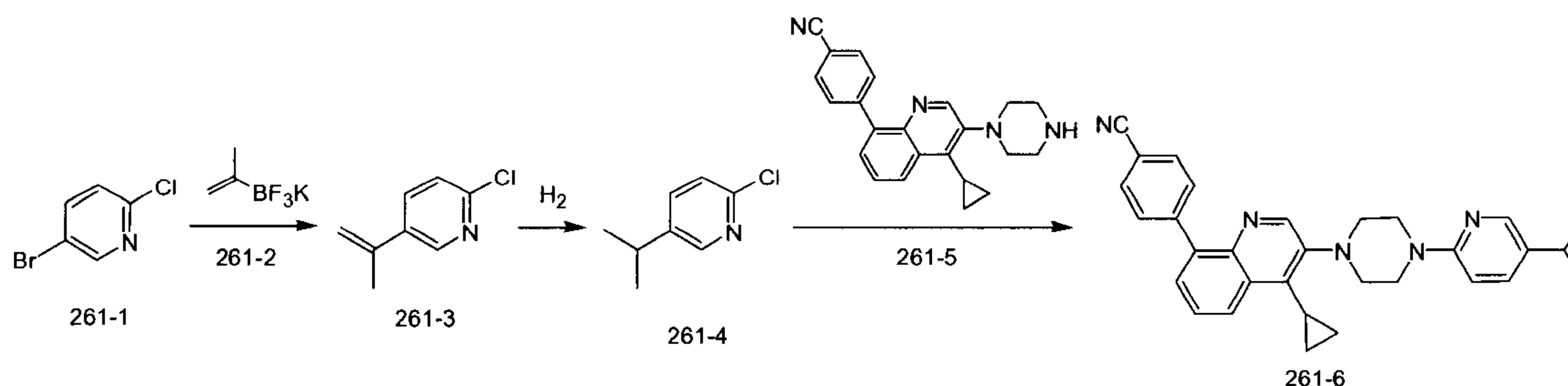


[584] Pd(dppf)Cl_2 (80.49 mg, 110 μmol) and Na_2CO_3 (233.18 mg, 2.20 mmol) were added into a solution of 260-1 (500 mg, 1.10 mmol), 260-2 (256.19 mg, 1.32 mmol) in THF (10 mL). Under nitrogen gas atmosphere, the mixture was heated to 80°C and reacted for 2h. The reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (10 mL*3). The organic phase was washed with brines (10 mL), dried over anhydrous magnesium sulfate and concentrated under vacuum. The residue was purified by column chromatography to deliver the target compound (450 mg, yield 84.07%) as yellow solid. **MS ESI** calcd for $\text{C}_{32}\text{H}_{30}\text{N}_4\text{O}$ $[\text{M} + \text{H}]^+$ 487, found 487. **$^1\text{H NMR}$** (400 MHz, CHLOROFORM-d) δ ppm 8.78 - 8.91 (m, 1 H), 8.31 (d, $J = 2.26$ Hz, 1 H), 8.13 (dd, $J = 8.28, 1.25$ Hz, 1 H), 7.74 - 7.88 (m, 5 H), 7.60 - 7.73 (m, 2 H), 6.72 (d, $J = 8.78$ Hz, 1 H), 5.96 (s, 1 H), 4.05 - 4.29 (m, 2 H), 3.72 - 3.90 (m, 2 H), 2.64 (d, $J = 10.54$ Hz, 4 H), 2.32 - 2.47 (m, 1 H), 2.01 (t, $J = 7.28$ Hz, 2 H), 1.32 (d, $J = 6.27$ Hz, 6 H).

Embodiment 261



4-(4-((4-cyclopropyl-35-isopropylpyridin-2-yl)-3-)-quinolin-8-yl)benzonitrile



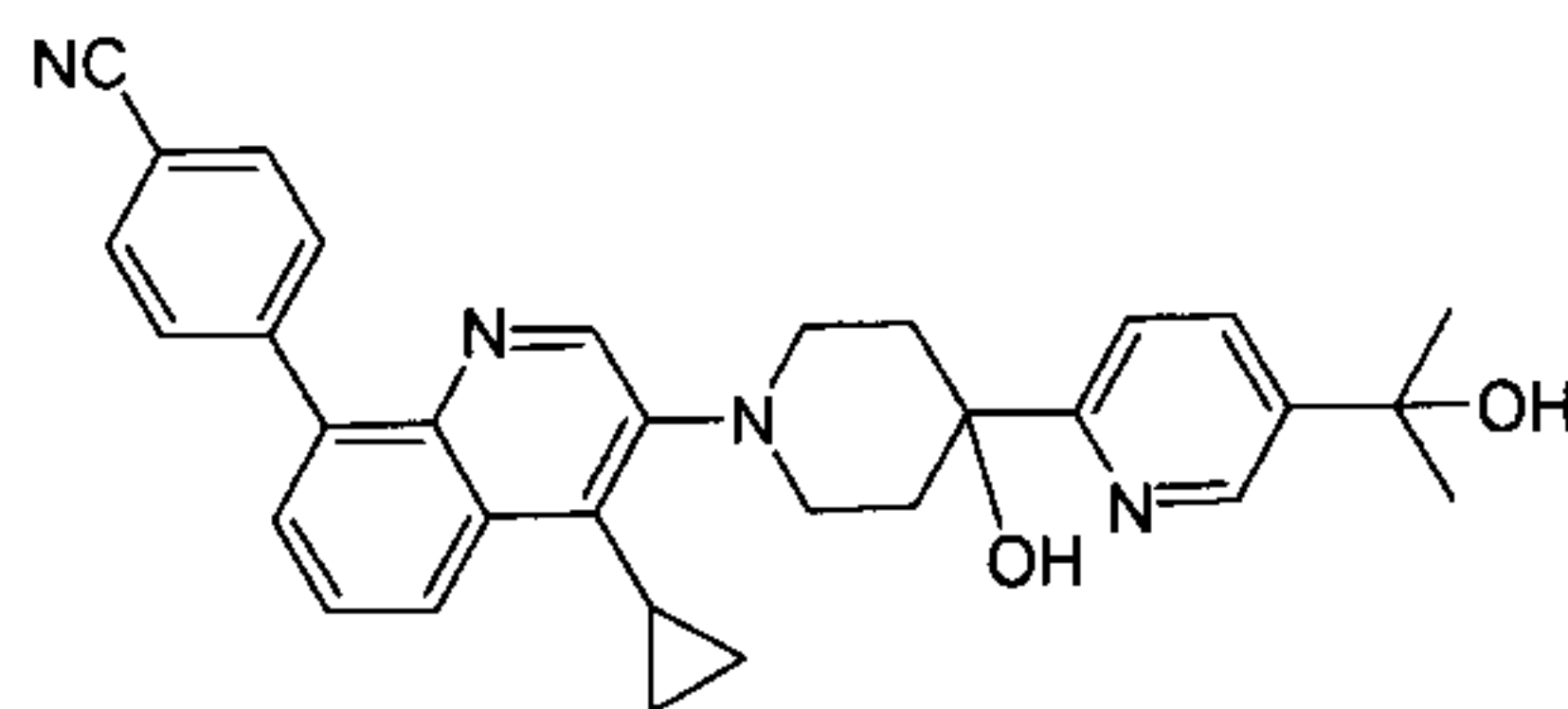
[585] Step 1: Under nitrogen gas atmosphere, Pd(dppf)Cl_2 (1.14 g, 1.56 mmol, 0.10 eq) was added into a mixture of 261-1 (3 g, 15.59 mmol, 1 eq), sodium carbonate (3.30 g, 31.18 mmol, 2 eq) and 261-2 (2.77 g, 18.71 mmol, 1.20 eq) in DMF (2 mL)/ H_2O (2 mL)/ THF (10 mL). The mixture was stirred at 70°C for 12h, poured into H_2O (150 mL). The obtained mixture was extracted with EtOAc (100*3). The combined organic phase was washed with brines (150 mL), dried over anhydrous sodium sulfate, filtrated and concentrated under vacuum. The residue was purified

by column chromatography (PE/EtOAc=20:1) to deliver 261-3 (1.50 g, yield 62.60%) as colorless oil. **MS ESI** calcd for C_8H_8ClN $[M+H]^+$ 154, found 154.

[586] Step 2: 261-3 (1.50 g, 9.76 mmol, 1 eq) was dissolved in ethanol (30 mL), under nitrogen gas atmosphere, PtO_2 (2.22 g, 9.76 mmol, 1 eq) (10%, 0.15 g) was added. The suspension was degassed under vacuum and swept by hydrogen gas for 3 times. The mixture was stirred at 25 °C for 4 h under H_2 (30 psi). The reaction mixture was filtrated, the filtrate was concentrated. The crude product was used for the next step directly. **MS ESI** calcd for $C_8H_{10}ClN$ $[M+H]^+$ 156, found 156.

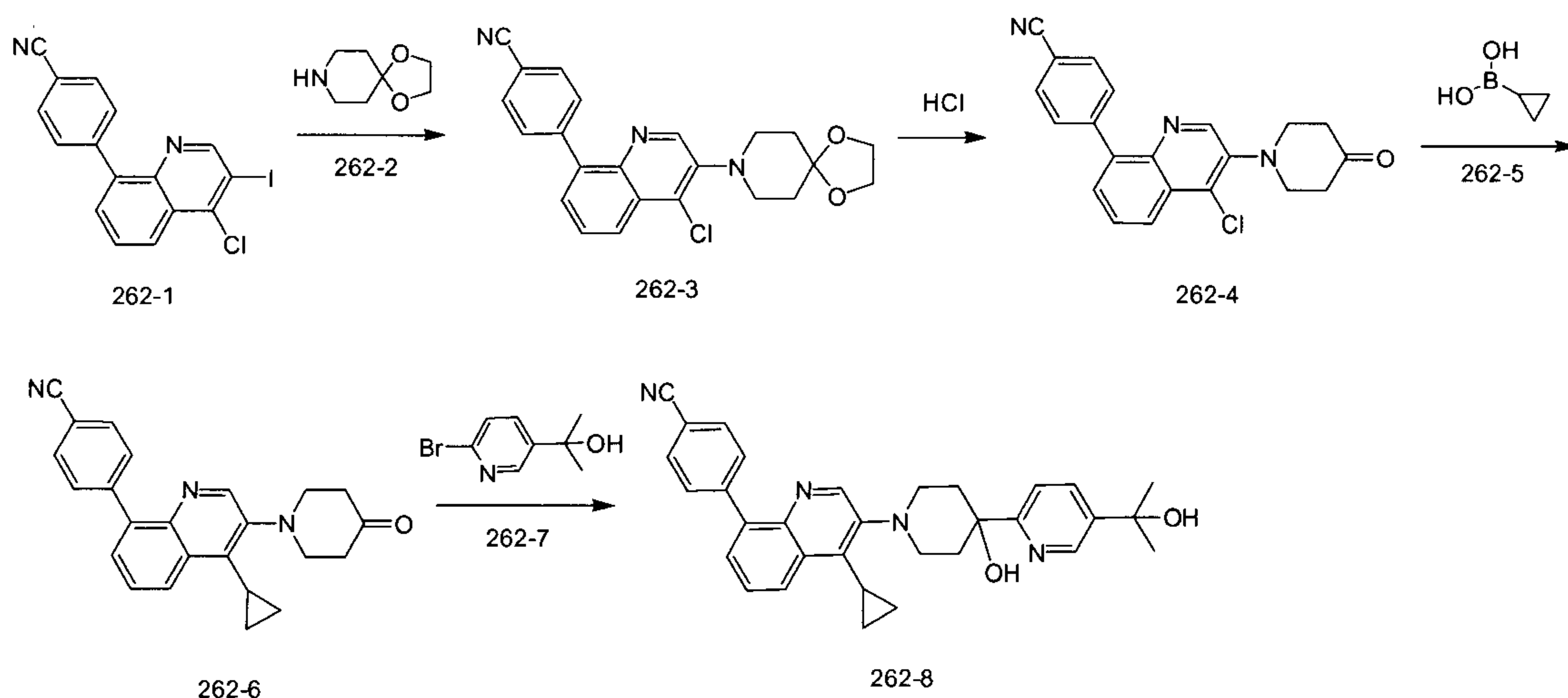
[587] Step 3: A mixture of 261-5 (100 mg, 282.13 μ mol, 1 eq), cesium carbonate (183.85 mg, 564.26 μ mol, 2 eq), Xantphos(32.65 mg, 56.43 μ mol, 0.20 eq) and 261-4 (65.86 mg, 423.20 μ mol, 1.50 eq) was dissolved in toluene (10 mL), under nitrogen gas atmosphere, $Pd_2(dba)_3$ (25.84 mg, 28.21 mmol, 0.10 eq) was added. The mixture was stirred at 110 °C for 2h, poured into H_2O (100 mL). The obtained mixture was extracted with EtOAc (100 mL $\times$ 3). The organic phases were combined and washed with brines (100 mL), dried over anhydrous sodium sulfate, filtrated and concentrated under vacuum. The residue was purified (acid) by HPLC to deliver the target compound (20 mg, yield 14.97%) as yellow solid. **MS ESI** calcd for $C_{31}H_{31}N_5$ $[M+H]^+$ 474, found 474. **^1H NMR** (400MHz, METHANOL- d_4) δ ppm 8.86 (d, $J= 8.3$ Hz, 1H), 8.73 (s, 1H), 8.14 (dd, $J= 2.0, 9.3$ Hz, 1H), 7.95 - 8.03 (m, 3H), 7.75 - 7.91 (m, 4H), 7.52 (d, $J= 9.5$ Hz, 1H), 4.04 (brs, 4H), 3.64 (brs, 4H), 1.59 (d, $J= 7.3$ Hz, 2H), 1.32 (d, $J= 7.0$ Hz, 7H), 1.10 (d, $J= 4.8$ Hz, 2H).

Embodiment 262



4-(4-cyclopropyl-3-(4-hydroxy-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)piperidin-1-yl)
quinolin-8-yl benzonitrile

Our Ref.: P1650132CA



[588] Step 1: Under nitrogen gas atmosphere, $\text{Pd}_2(\text{dba})_3$ (234.42 mg, 256 μmol , 0.10 eq) was added into a mixture of 262-1 (1 g, 2.56 mmol, 1 eq), Xantphos (296.25 mg, 512 μmol , 0.20 eq), cesium carbonate (1.67 g, 5.12 mmol, 2 eq) and 262-2 (439.85 mg, 3.07 mmol, 1.20 eq) in toluene (20 mL). The mixture was stirred at 110°C for 2h, poured into H_2O (150 mL). The obtained mixture was extracted with EtOAc (400 mL $\times$ 3). The organic phases were combined and washed with brines (200 mL), dried over anhydrous sodium sulfate, filtrated and concentrated under vacuum. The residue was purified by column chromatography (PE/EtOAc=3:1) to deliver compound 262-3 (800 mg, yield 76.99%) as yellow solid. **MS ESI** calcd for $\text{C}_{23}\text{H}_{20}\text{ClN}_3\text{O}_2$ $[\text{M} + \text{H}]^+$ 406, found 406.

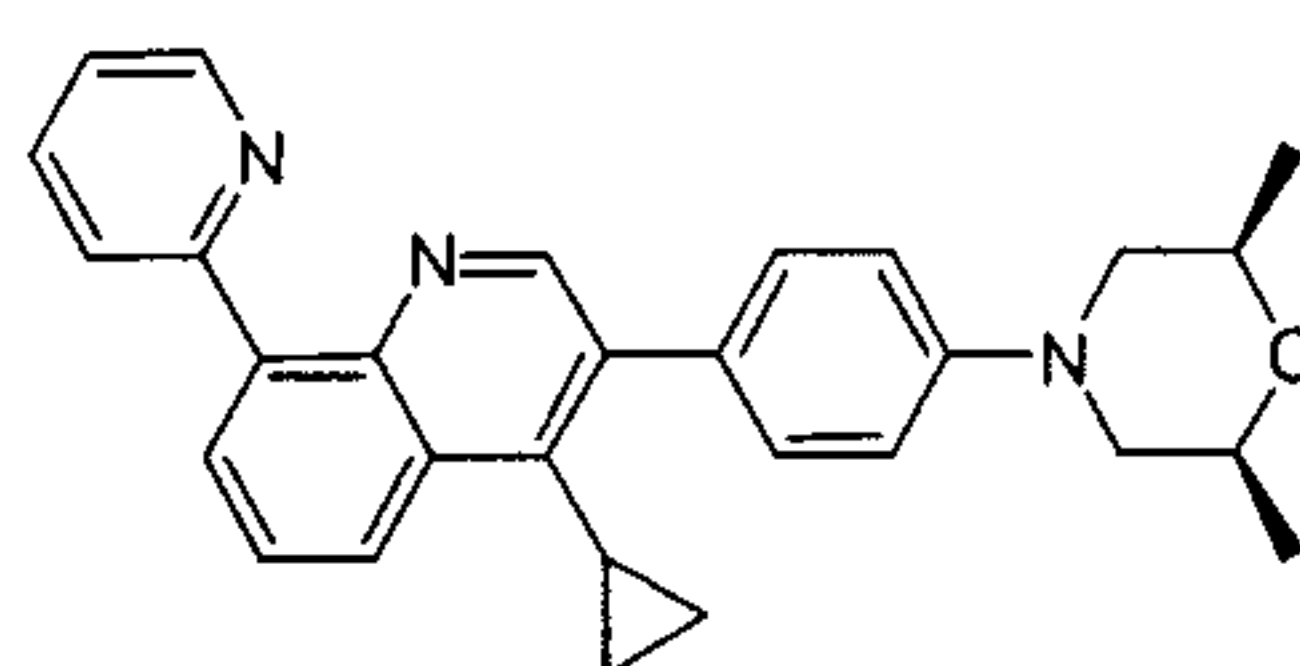
[589] Step 2: 262-3 (400 mg, 985.51 μmol , 1 eq) was dissolved in THF (10 mL) and HCl solution (4 M EtOAc, 2 mL) was added. The reaction mixture was stirred at room temperature for 12 h, then heated to 45°C and stirred for another 1h. The mixture was poured into H_2O (150 mL) and extracted with EtOAc (400 mL $\times$ 3). The organic phases were combined and washed with brines (20 mL), dried over anhydrous sodium sulfate, filtrated and concentrated under vacuum. The residue was purified by column chromatography (PE/EtOAc=2:1) to deliver 262-4 (320 mg, yield 89.74%) as white solid. **MS ESI** calcd for $\text{C}_{22}\text{H}_{19}\text{N}_3\text{O}_2$ $[\text{M} + \text{H}]^+$ 358, found 358.

[590] Step 3: Under nitrogen gas atmosphere, bis(adamantyl)butyl phosphine (79.27 mg, 221.10 μmol) was added into a mixture of 262-4 (200 mg, 552.76 μmol , 1 eq) and 262-5 (237.41 mg, 2.76 mmol, 5 eq) in toluene (10 mL). The mixture was stirred at 110°C for 2h, poured into H_2O (150 mL). The obtained mixture was extracted with EtOA (400 mL $\times$ 3). The organic phases were combined and washed with brines (200 mL), dried over anhydrous sodium sulfate, filtrated, and concentrated under vacuum. The residue was purified by column chromatography (PE/EtOAc=2:1) to deliver 262-6 (150 mg, yield 73.85%) as white solid. **MS ESI** calcd for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}$ $[\text{M} + \text{H}]^+$ 368, found 368.

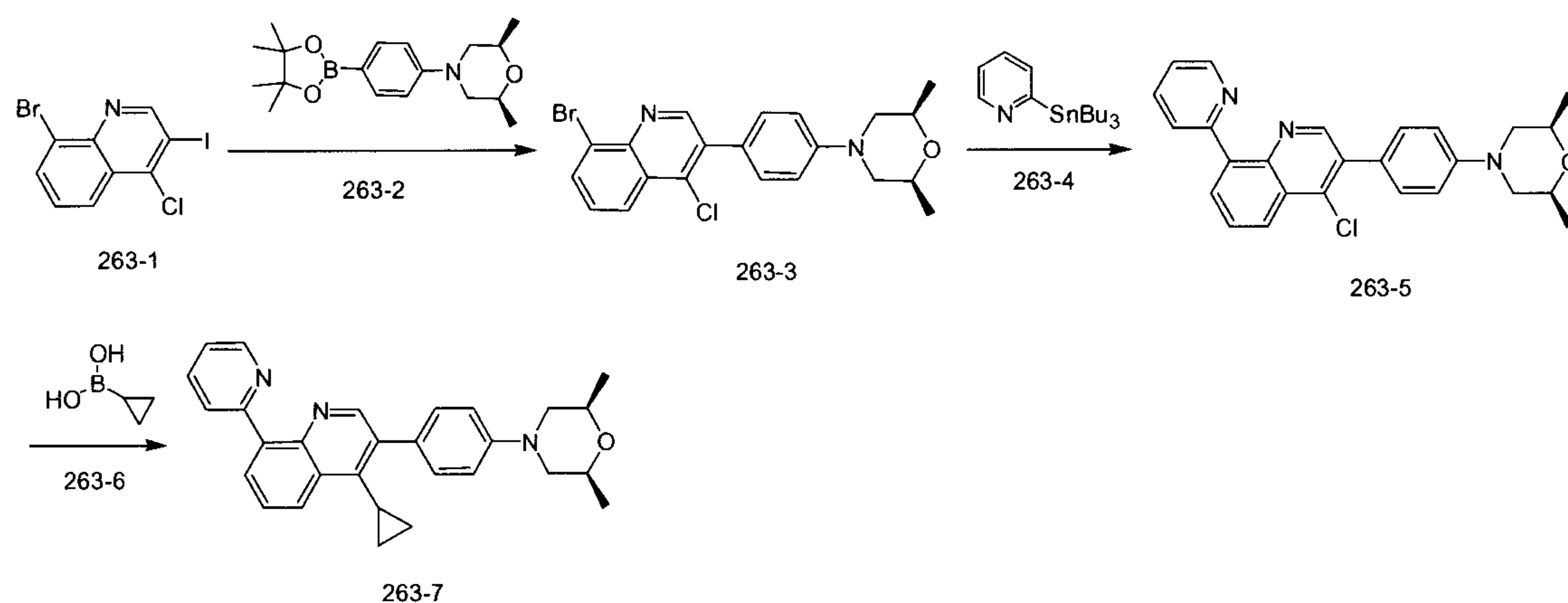
[591] Step 4: Under nitrogen gas atmosphere, *n*-BuLi (52.30 mg, 816.45 μmol , 3 eq) was added dropwise into a solution of 262-7 (70.56 mg, 326.58 μmol , 1.20 eq) dissolved in THF (5 mL) at -78°C. After 1h, 262-6 (100 mg, 272.15 μmol , 1 eq) was

added into the mixture, and the mixture was stirred at -78°C for further 1h. The mixture was warmed to 25°C , poured into saturated NH_4Cl solution (50 mL), then stirred for 20 min, the obtained mixture was extracted with EtOAc (100 mL $\times$ 3). The organic phases were combined and washed with brines (50 mL), dried over anhydrous sodium sulfate, filtrated, and concentrated under vacuum. The residue was purified by HPLC to deliver the target compound (3 mg, yield 2.18%) as yellow solid. **MS ESI** calcd for $\text{C}_{32}\text{H}_{32}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ 505, found 505. **^1H NMR** (400MHz, CDCl_3) δ ppm 8.56-9.23 (m, 2H), 7.53 - 7.95 (m, 10H), 3.68 (brs., 4H), 2.21 (brs, 1H), 1.58 (brs, 11H), 1.06 (brs., 2H).

Embodiment 263



(2*S*,6*R*)-4-(5-(4-(8-cyclopropyl-2-pyridinyl)quinolin-3-yl)pyridin-2-yl)-2,6-dimethylmorpholine



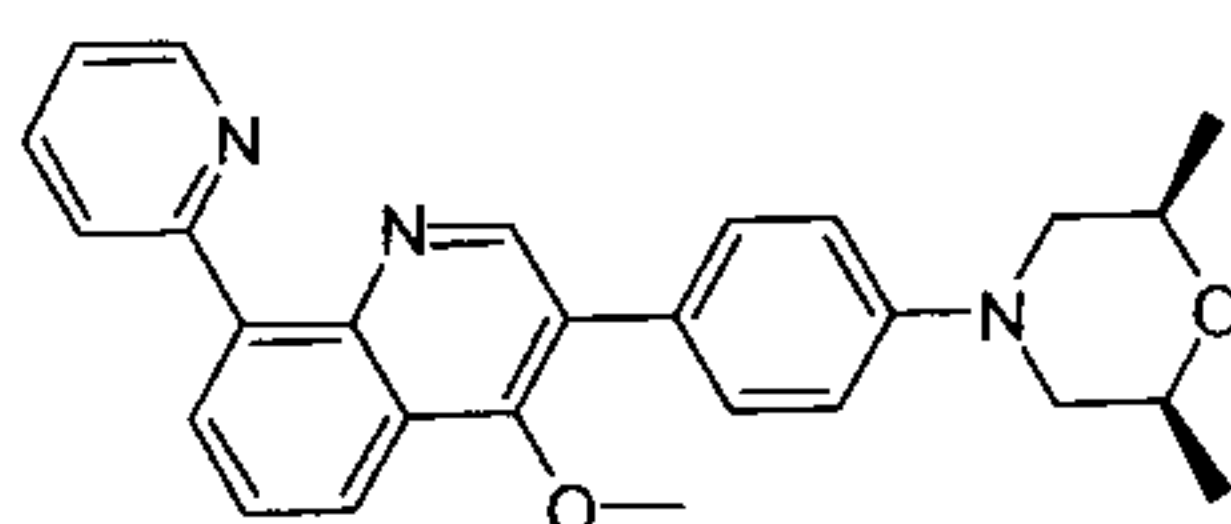
[592] Step 1: 263-1 (266.27 mg, 722.77 μmol , 1 eq) and 263-2 (230 mg, 722.77 μmol , 1 eq) were dissolved in DMF (2 mL) / THF (2 mL). Under nitrogen gas atmosphere, $\text{Pd}(\text{dppf})\text{Cl}_2$ (52.89 mg, 72.28 μmol , 0.10 eq) was added into the reaction system. The mixture was stirred at 70°C for 2h, poured into H_2O (100 mL). The mixture was extracted with EtOAc (200 mL $\times$ 3). The organic phases were combined and washed with brines (100 mL), dried over anhydrous sodium sulfate, filtrated, and concentrated under vacuum. The residue was purified by column chromatography (PE/EtOAc=5:1) to deliver 263-3 (270 mg, yield 86.33%) as white solid. **MS ESI** calcd for $\text{C}_{21}\text{H}_{20}\text{BrClN}_2\text{O}$ $[\text{M}+\text{H}]^+$ 431, found 431.

[593] Step 2: Under nitrogen gas atmosphere, $\text{Pd}(\text{PPh}_3)_4$ (72.10 mg, 62.39 μmol , 0.10 eq) was added in a solution of 263-3 (270 mg, 623.93 μmol , 1 eq) and 263-4 (229.69 mg, 623.93 μmol , 1 eq) in toluene (10 mL). The mixture was stirred at 110°C for 2h, poured into H_2O (50 mL). The mixture was extracted with EtOAc

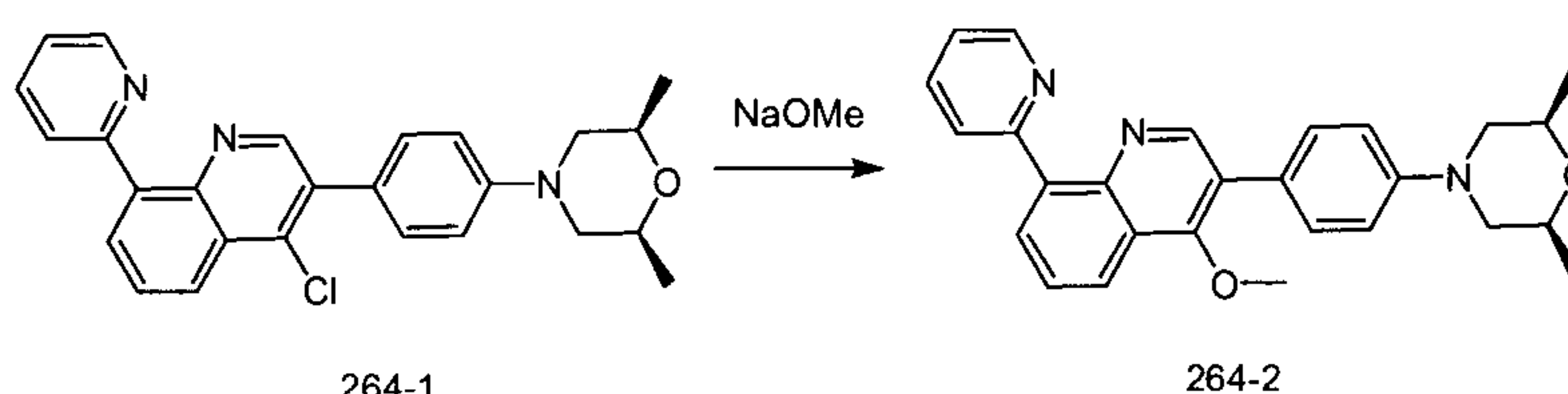
(100 mL×3). The organic phases were combined and washed with brines (50 mL), dried over anhydrous sodium sulfate, filtrated and concentrated under vacuum. The residue was purified by column chromatography (PE/EtOAc=2:1) to deliver 263-5 (120 mg, yield 44.63%) as white solid. **MS ESI** calcd for C₂₆H₂₄ClN₃O [M+H]⁺ 430, found 430.

[594] Step 3: Under nitrogen gas atmosphere, Pd(OAc)₂ and bis(adamantyl) butyl phosphine (66.56 mg, 185.65 μmol, 1 eq) were added into a solution of 263-5 (80 mg, 185.65 μmol, 1 eq) and cyclopropyl boric acid (159.47 mg, 1.86 mmol, 10 eq) in toluene (5 mL). The mixture was stirred at 110°C for 2h, then poured into H₂O (50 mL). The mixture was extracted with EtOAc (100 mL×3). The organic phases were combined and washed with brines (50 mL), dried over anhydrous sodium sulfate, filtrated, and concentrated under vacuum. The residue was purified by HPLC to deliver the target compound (15 mg, yield 18.51%) as white solid. **MS ESI** calcd for C₂₉H₂₉N₃O [M+H]⁺ 436, found 436. **¹H NMR** (400MHz, METHANOL-*d*₄) δ ppm 9.14 (s, 1H), 9.03 - 9.13 (m, 2H), 8.75 - 8.81 (m, 1H), 8.65 - 8.72 (m, 2H), 8.41 - 8.51 (m, 1H), 8.35 (s, 1H), 8.03 - 8.11 (m, 2H), 7.68 (d, *J*= 9.5 Hz, 1H), 4.19 - 4.29 (m, 2H), 3.89 (dd, *J*= 6.3, 8.5 Hz, 2H), 3.04 (dd, *J*= 11.2, 12.4 Hz, 2H), 2.57 - 2.75 (m, 1H), 1.28 - 1.37 (m, 8H), 0.52 (q, *J*= 5.5 Hz, 2H).

Embodiment 264

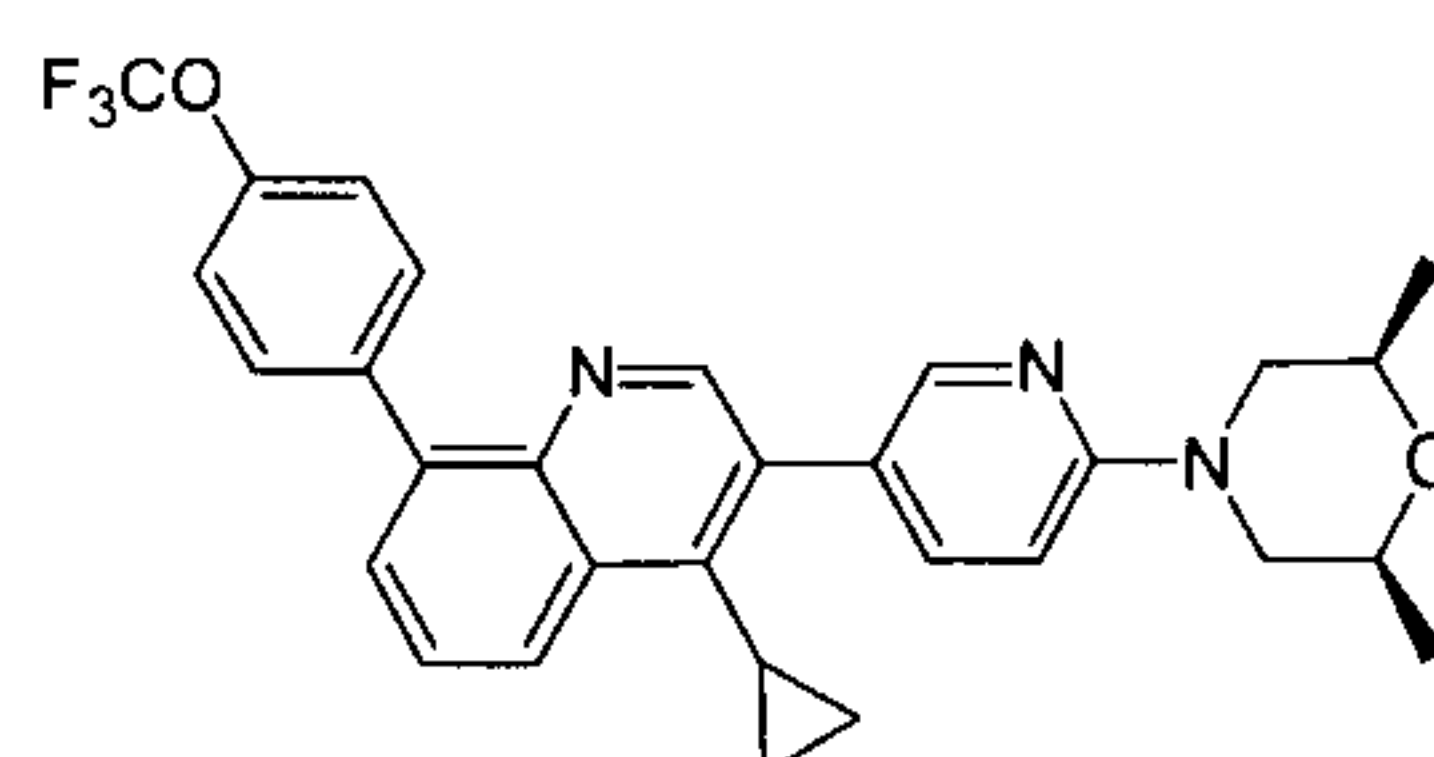


(2*S*,6*R*)-4-(5-(4-methoxy-8-(pyridin-2-yl)quinolin-3-yl)pyridin-2-yl)-2,6-dimethylmorpholine

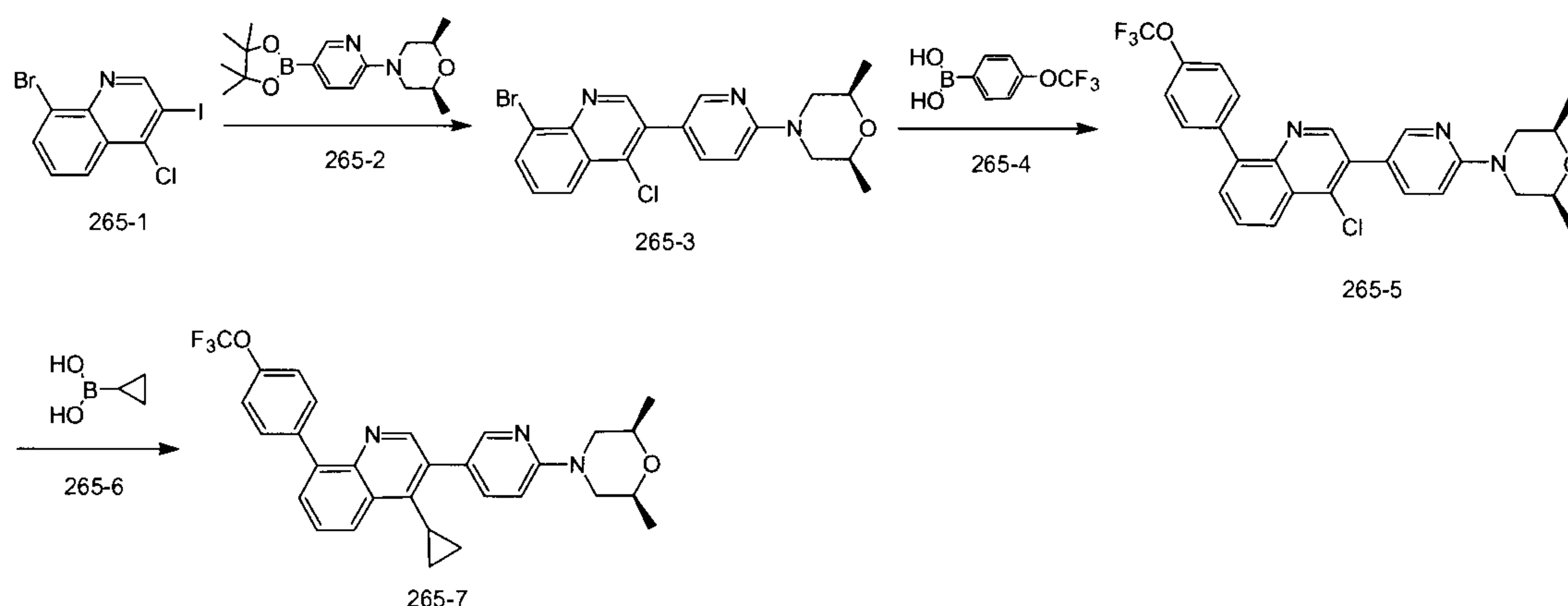


[595] 264-1 (40 mg, 92.82 μmol) was dissolved in methanol (5 mL), then NaOMe (50.14 mg, 928.20 μmol) was added. The mixture was stirred at 25°C for 48h, quenched with H₂O. After concentration, the residue was purified by prep-HPLC to deliver the target compound (3 mg, yield 7.58%) as white solid. **MS ESI** calcd for C₂₇H₂₇N₃O₂ [M+H]⁺ 426, found 426. **¹H NMR** (400MHz, CDCl₃) δ ppm 8.91 (s, 1H), 8.79 (d, *J*= 4.5 Hz, 1H), 8.51 (d, *J*= 2.0 Hz, 1H), 8.31 (d, *J*= 8.5 Hz, 1H), 8.08 (dd, *J*= 7.3, 13.8 Hz, 2H), 7.79 - 7.90 (m, 2H), 7.70 (t, *J*= 7.8 Hz, 1H), 7.28 - 7.36 (m, 1H), 6.79 (d, *J*= 9.0 Hz, 1H), 4.16 (d, *J*= 12.0 Hz, 2H), 3.68 - 3.84 (m, 5H), 2.63 (t, *J*= 11.8 Hz, 2H), 1.31 (d, *J*= 6.0 Hz, 6H).

Embodiment 265



(2*S*,6*R*)-4-(5-(4-cyclopropyl-8-(4-(trifluoromethoxy)phenyl)quinolin-3-yl)pyridin-2-yl)-2,6-dimethylmorpholine



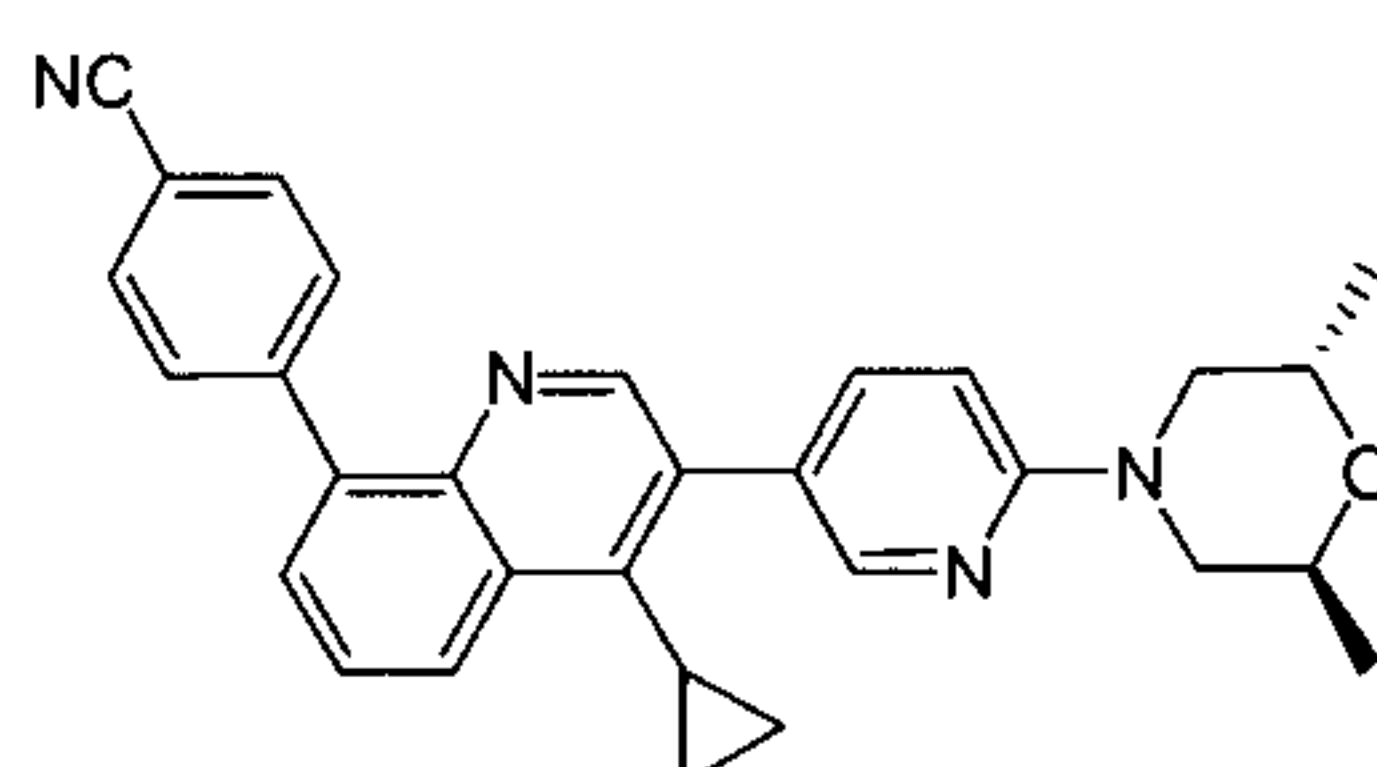
[596] Step 1: Under nitrogen gas atmosphere, a mixture of 265-1 (500 mg, 1.36 mmol, 1 eq), 265-2 (431.89 mg, 1.36 mmol, 1 eq), Pd(dppf)Cl₂ (99.51 mg, 136 μmol, 0.10 eq) and Na₂CO₃ (288.29 mg, 2.72 mmol, 2 eq) in THF (10 mL) was heated to 80°C and reacted for 2h. The reaction mixture was poured into H₂O (10 mL). The mixture was extracted with EtOAc twice. The organic phase was washed with brines (10 mL), dried over anhydrous MgSO₄, concentrated under vacuum. The residue was purified by column chromatography (PE/EtOAc=3:1) to deliver 265-3 (500 mg, yield 84.96%) as yellow solid. **MS ESI** calcd for C₂₀H₁₉BrClN₃O [M+H]⁺ 432, found 432.

[597] Step 2: Under nitrogen gas atmosphere, a mixture of 265-3 (500 mg, 1.16 mmol, 1 eq), 265-4 (237.94 mg, 1.16 mmol, 1 eq), Pd(dppf)Cl₂ (84.88 mg, 116 μmol, 0.10 eq) and Na₂CO₃ (245.90 mg, 2.32 mmol, 2 eq) in THF (10 mL) and H₂O (2 mL) were heated to 80°C and reacted for 2h. The reaction mixture was poured into H₂O (10 mL), extracted with EtOAc (10 mL×3). The organic phase was washed with brines (10 mL), dried over anhydrous MgSO₄ and concentrated under vacuum. The residue was purified by column chromatography (PE/EtOAc=3:1) to deliver 265-5 (560 mg, 1.09 mmol, 93.93% yield) as yellow solid. **MS ESI** calcd for C₂₇H₂₃ClF₃N₃O₂ [M+H]⁺ 514, found 514.

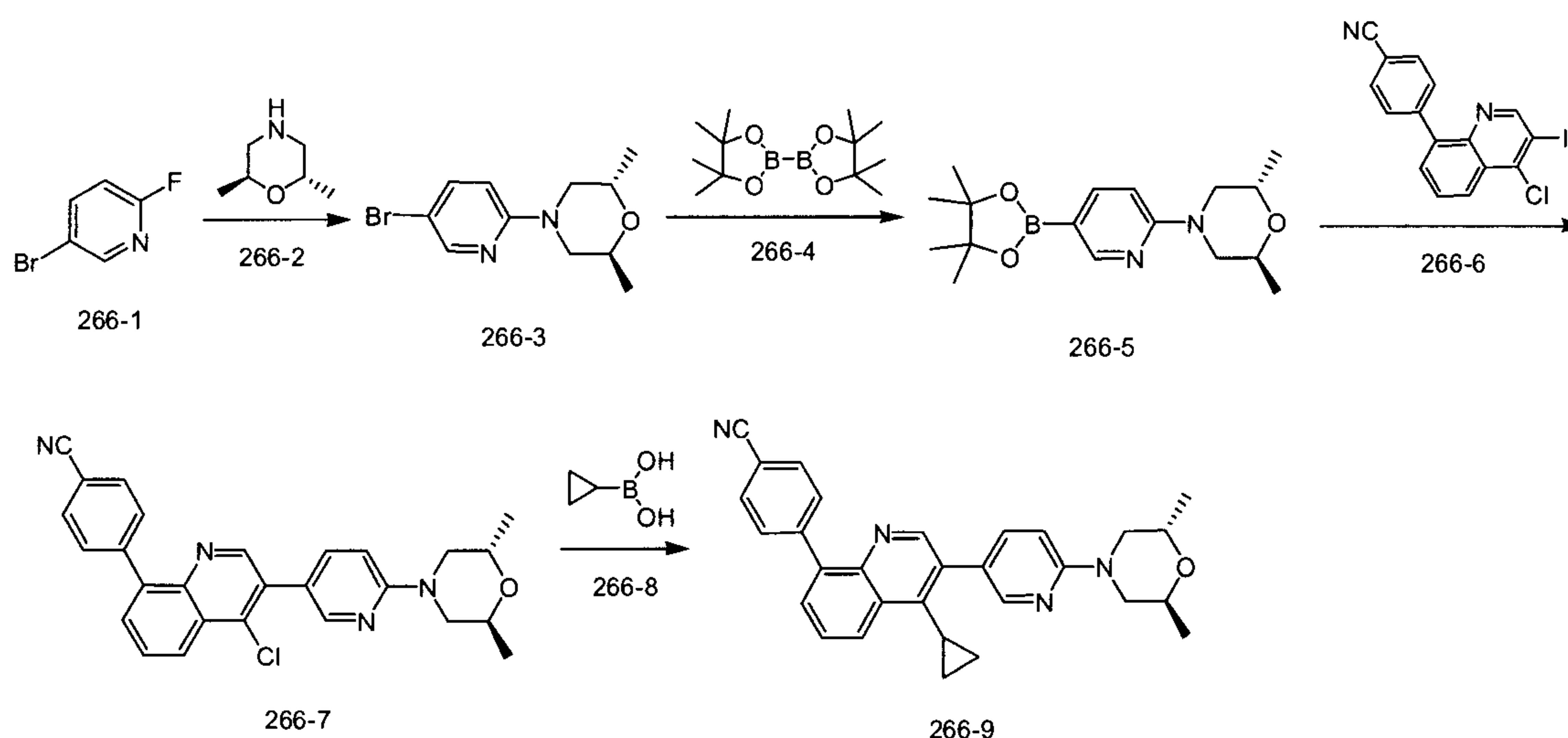
[598] Step 3: Under nitrogen gas atmosphere, a mixture of 265-5 (100 mg, 194.58 μmol, 1 eq), cyclopropyl boric acid (83.57 mg, 972.90 μmol, 5 eq), Pd(OAc)₂ (4.37 mg, 19.46 μmol, 0.10 eq) and bis(adamantyl)butyl phosphine (13.95 mg, 38.92 μmol, 0.20 eq) in toluene (5 mL) was heated to 120°C and reacted for 2h. The reaction mixture was poured into H₂O (10 mL), extracted with EtOAc (10 mL×3). The organic phase was washed with brines (10 mL), dried over anhydrous Na₂SO₄ and

concentrated under vacuum. The residue was purified by preparative HPLC (TFA) to deliver the target compound (60 mg, yield 59.35%) as white solid. **MS ESI** calcd for $C_{30}H_{28}F_3N_3O_2$ $[M + H]^+$ 520, found 520. **^1H NMR** (400 MHz, CHLOROFORM- d) δ ppm 8.87 (s, 1 H), 8.63 (dd, $J = 7.28, 2.51$ Hz, 1 H), 8.40 (d, $J = 2.26$ Hz, 1 H), 7.63 - 7.80 (m, 5 H), 7.36 (d, $J = 8.28$ Hz, 2 H), 6.79 (d, $J = 8.78$ Hz, 1 H), 4.17 (d, $J = 11.29$ Hz, 2 H), 3.81 (dd, $J = 4.02, 2.26$ Hz, 2 H), 2.65 (dd, $J = 12.42, 10.92$ Hz, 2 H), 2.34 (s, 1 H), 1.33 (d, $J = 6.27$ Hz, 6 H), 1.13 (d, $J = 7.53$ Hz, 2 H), 0.41 (d, $J = 5.02$ Hz, 2 H).

Embodiment 266



4-(4-cyclopropyl-3-(6-((2*S*,6*S*)-2,6-dimethylmorpholino)pyridin-3-yl)quinolin-8-yl)
benzonitrile



[599] Step 1: 266-1 (600 mg, 3.41 mmol, 1 eq) and 266-2 (471.28 mg, 4.09 mmol, 1.20 eq) were dissolved in acetonitrile (10 mL), then K_2CO_3 (942.59 mg, 6.82 mmol, 2 eq) was added. The mixture was stirred at 80°C for 24h. The mixture was cooled, filtrated and concentrated. The residue was purified by column chromatography (PE/EtOAc=10:1) to deliver 266-3 (450 mg, yield 48.67%) as white solid. **MS ESI** calcd for $C_{11}H_{15}BrN_2O$ $[M+H]^+$ 271, found 271.

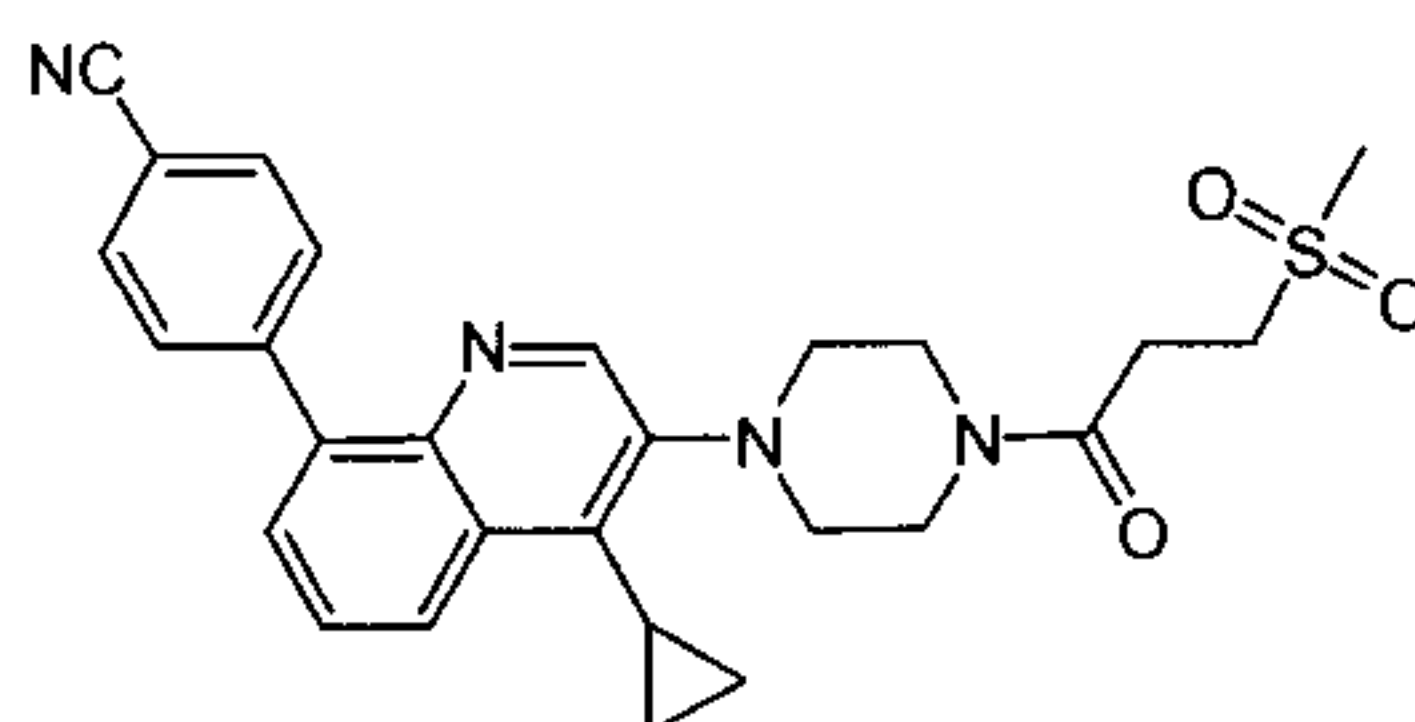
[600] Step 2: Under nitrogen gas atmosphere, $Pd(dppf)Cl_2$ (121.46 mg, 166 μ mol, 0.10 eq) was added into a solution of 266-3 (450 mg, 1.66 mmol, 1 eq), KOAc (325.82 mg, 3.32 mmol, 2 eq) and 266-4 (843.08 mg, 3.32 mmol, 2 eq) in dioxane (10 mL). The mixture was stirred at 80°C for 2h, poured into H_2O (100 mL). The mixture was extracted with EtOAc (100 $\times$ 3). The organic phases were combined and

washed with brines (100 mL), dried over anhydrous sodium sulfate, filtrated, and concentrated under vacuum. The residue was purified by column chromatography (PE/EtOAc=5:1) to deliver 266-5 (200 mg, yield 37.86%) as yellow solid. **MS ESI** calcd for $C_{17}H_{27}BN_2O_3$ $[M+H]^+$ 319, found 319.

[601] Step 3: 266-6 (200 mg, 512.03 μ mol, 1 eq) and 266-5 (195.53 mg, 614.44 μ mol, 1.20 eq) were dissolved in DMF (2 mL)/H₂O (2 mL)/ THF (10 mL), under nitrogen gas atmosphere, Pd(dppf)Cl₂ (37.47 mg, 51.20 μ mol, 0.10 eq) was added. The mixture was stirred at 70°C for 2h, poured into H₂O (150 mL). The mixture was extracted with EtOAc (150 mL×3). The organic phases were combined and washed with brines (100 mL), dried over anhydrous sodium sulfate, filtrated and concentrated under vacuum. The residue was purified by column chromatography (PE/EtOAc=5:1) to deliver 266-7 (150 mg, yield 64.39%) as yellow solid. **MS ESI** calcd for $C_{27}H_{23}ClN_4O$ $[M+H]^+$ 455, found 455.

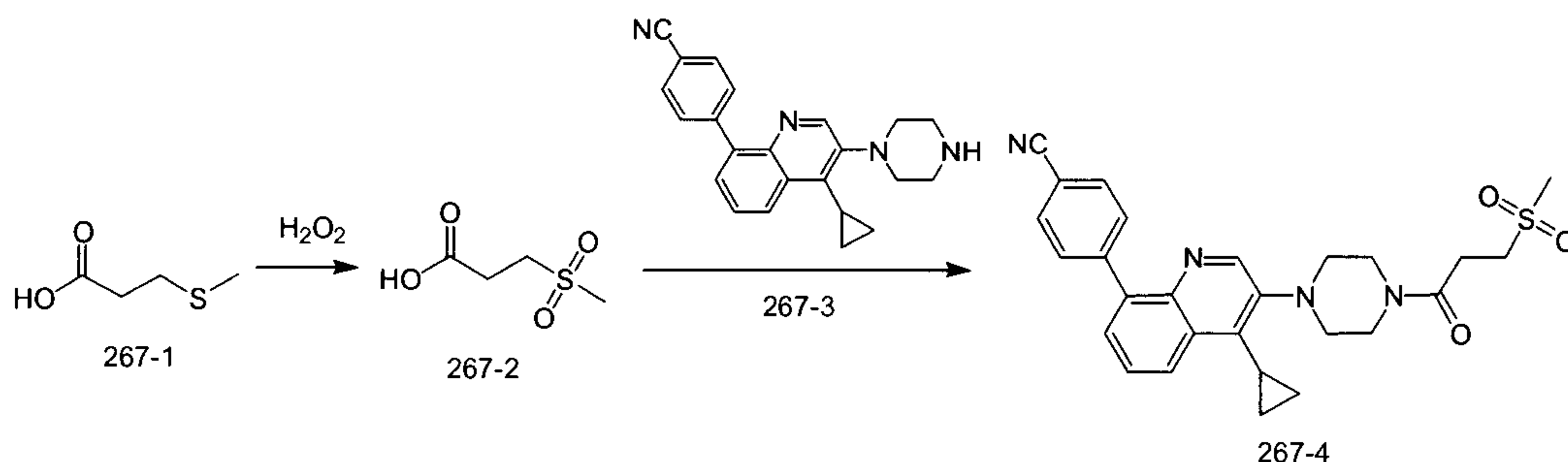
[602] Step 4: 266-7 (150 mg, 329.71 μ mol, 1 eq), cesium carbonate (214.85 mg, 659.42 μ mol, 2 eq), bis(adamantyl)butyl phosphine (118.21 mg, 329.71 μ mol, 1 eq) and cyclopropyl boric acid (141.61 mg, 1.65 mmol, 5 eq) were dissolved in toluene (10 mL), under nitrogen gas atmosphere, Pd(OAc)₂ (37.01 mg, 164.86 μ mol, 0.50 eq) was added. The mixture was stirred at 110°C for 2h, poured into H₂O (100 mL). The obtained mixture was extracted with EtOAc (100 mL×3). The organic phases were combined and washed with brines (100 mL), dried over anhydrous sodium sulfate, filtrated, and concentrated under vacuum. The residue was purified by HPLC (acid) to deliver 266-9 (50 mg, yield 32.93%) as yellow solid. **MS ESI** calcd for $C_{30}H_{28}N_4O$ $[M+H]^+$ 461, found 461. **¹H NMR** (CDCl₃, 400MHz): δ ppm 8.83 (s, 1H), 8.65 (t, J = 4.8 Hz, 1H), 8.36 (s, 1H), 7.74-7.85 (m, 4H), 7.64-7.73 (m, 3H), 6.74 (d, J = 9.0 Hz, 1H), 4.20 (td, J = 6.3, 3.5 Hz, 2H), 3.78 (d, J = 3.0 Hz, 1H), 3.69-3.74 (m, 1H), 3.33 (dd, J = 12.5, 6.5 Hz, 2H), 2.28-2.41 (m, 1H), 1.33 (d, J = 6.5 Hz, 6H), 1.13 (d, J = 8.0 Hz, 2H), 0.39 (q, J = 5.5 Hz, 2H).

Embodiment 267



4-(4-cyclopropyl-3-(4-(3-(methylsulfonyl)-3-propanoyl))quinolin-8-yl) benzonitrile

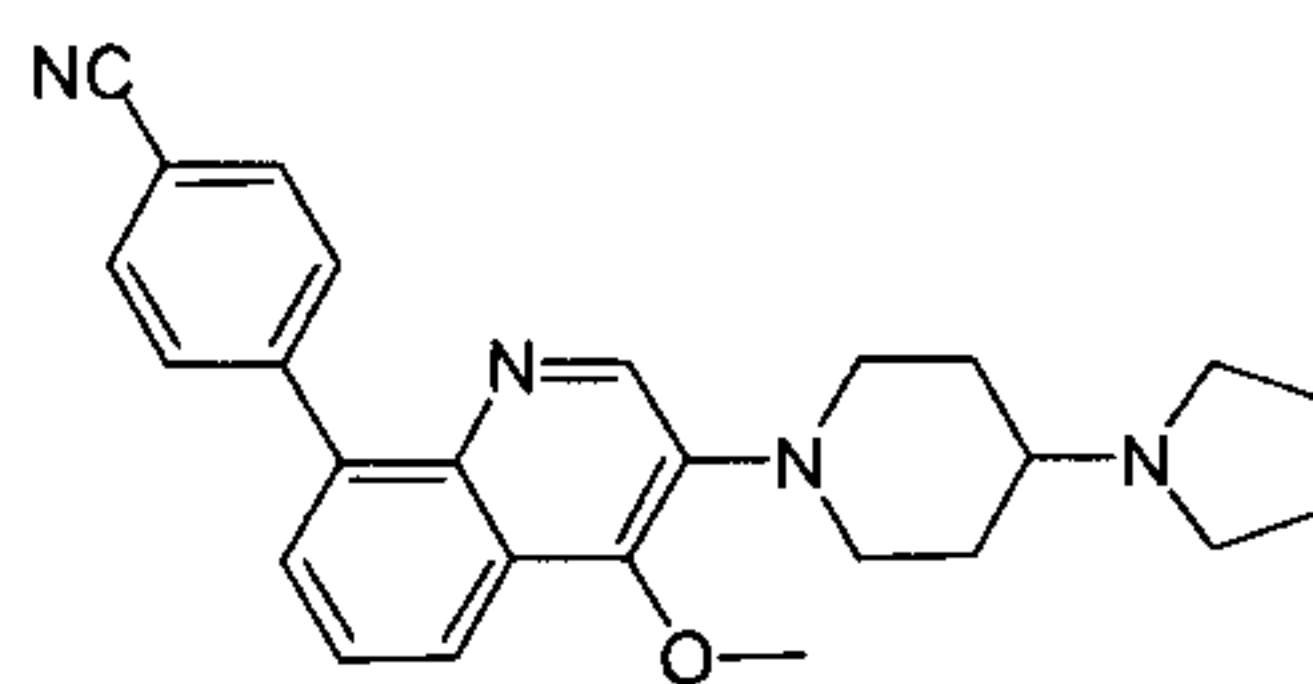
Our Ref.: P1650132CA



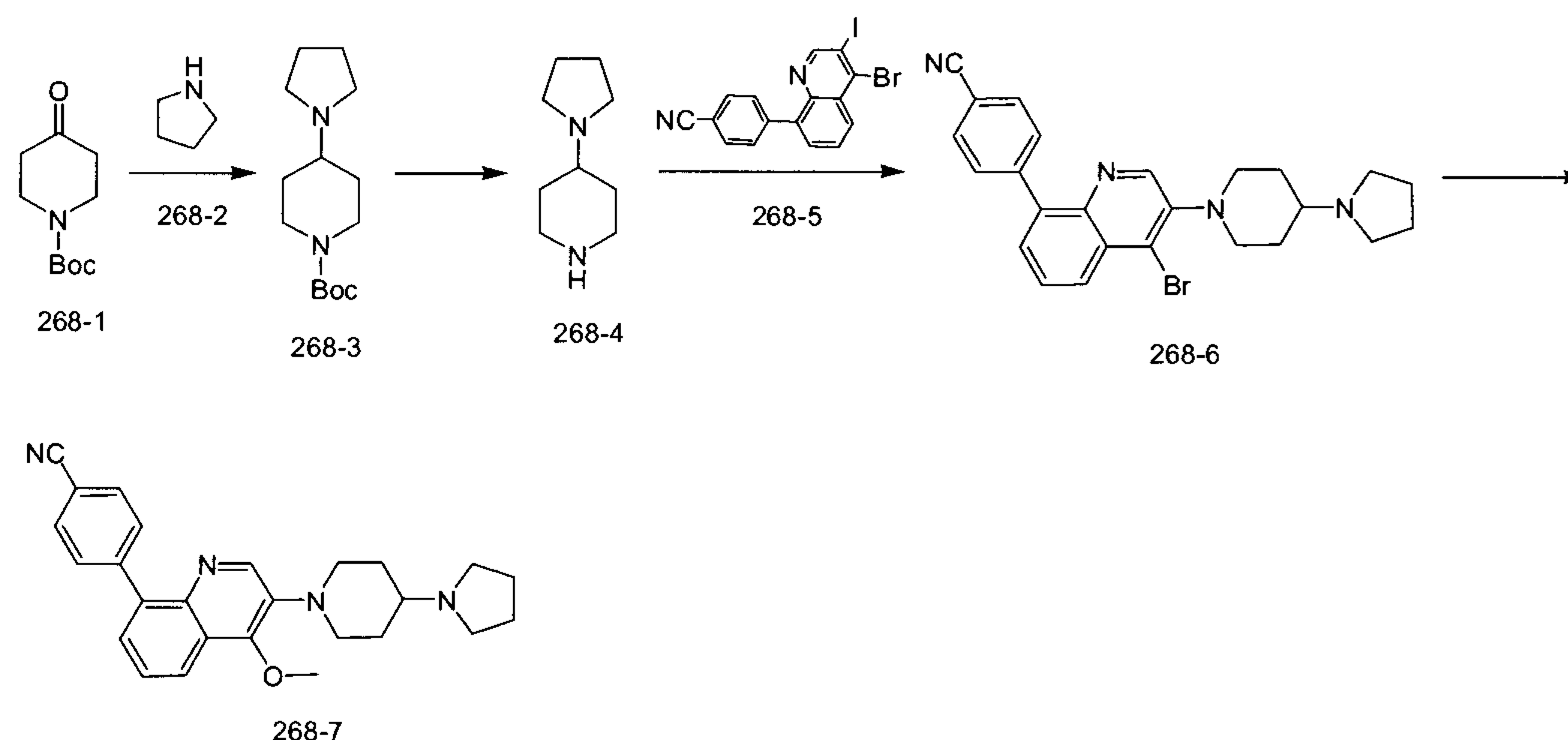
[603] Step 1: 267-1 (3 g, 24.96 mmol, 1 eq) was dissolved in acetic anhydride (20 mL)/acetic acid (20 mL), H₂O₂ (40%, 2 mL) was added. The mixture was stirred at 25°C for 12h. After filtration, the filtrate was concentrated to deliver 267-2 (3 g, yield 78.99%) as white solid. **MS ESI** calcd for C₂₅H₂₅ClN₄O₂ [M+H]⁺ 449, found 153.

[604] Step 2: 267-3 (1.08 g, 3.05 mmol, 1 eq) and 267-2 (556.94 mg, 3.66 mmol, 1.20 eq) were dissolved in DMF (10 mL), HATU (2.32 g, 6.10 mmol, 2 eq) and DIEA (1.18 g, 9.15 mmol, 3 eq) were added. The mixture was stirred at 25°C for 0.5h, then the mixture was partitioned between H₂O (100 mL) and EtOAc (100 mL). The EtOAc phase was washed with brines (30×3), dried over Na₂SO₄, filtrated and concentrated. The residue was purified by column chromatography (PE/EtOAc=3:1) to deliver the target compound (800 mg, yield 53.68%) as yellow solid. **MS ESI** calcd for C₂₇H₂₈N₄O₃S [M+H]⁺ 489, found 489. **¹H NMR** (400MHz, CDCl₃) δ ppm 8.69 (s, 1H), 8.51 (d, *J*=8.5 Hz, 1H), 7.76 (s, 4H), 7.56 - 7.63 (m, 2H), 3.88 (brs, 2H), 3.74 (brs, 2H), 3.48 (t, *J*=7.0 Hz, 2H), 3.18 - 3.36 (m, 4H), 3.01 (s, 3H), 2.99 (d, *J*=7.5 Hz, 2H), 2.00 - 2.16 (m, 1H), 1.32 (d, *J*=8.0 Hz, 2H), 0.98 (d, *J*=4.5 Hz, 2H).

Embodiment 268



4-(4-methoxy-3-(4-(pyrrolidin-1-yl)piperidin-1-yl)quinolin-8-yl)benzonitrile



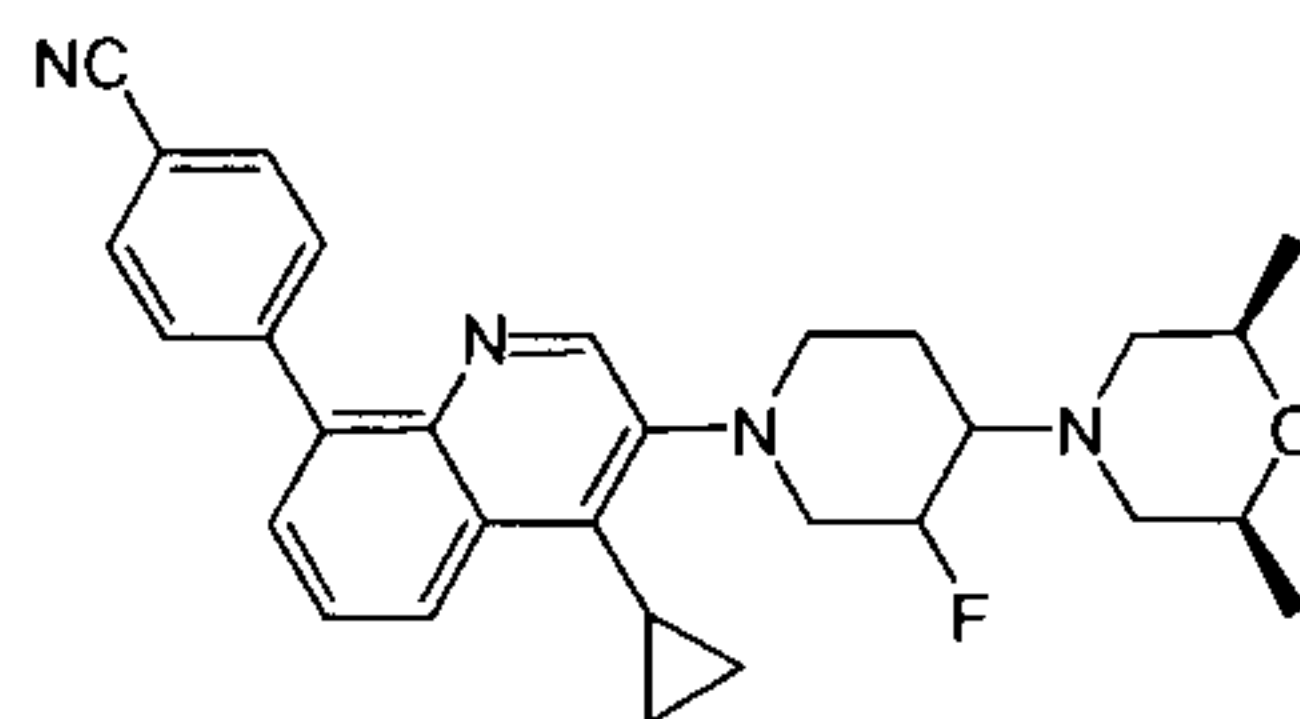
[605] Step 1: 268-1 (10 g, 50.19 mmol, 1 eq) and pyrrolidine (3.57 g, 50.19 mmol, 1 eq) were dissolved in DCM (100 mL) and $\text{NaBH}(\text{OAc})_3$ (15.96 g, 75.29 mmol, 1.50 eq) and acetic acid (1.05 g, 17.49 mmol) were added. The mixture was stirred at 25°C for 16h, poured into ice-water (W/W=1/1) (100 mL) and stirred for 10 min. The mixture was extracted with DCM (100 mL $\times$ 3). The organic phases were combined and washed with brines (100 mL), dried over anhydrous sodium sulfate, filtrated, and concentrated under vacuum. The residue was purified by silica gel column chromatography (PE/EtOAc=5:1 to 1:1) to deliver 268-3 (8.50 g, yield 66.58%) as yellow solid. **MS ESI** calcd for $\text{C}_{14}\text{H}_{26}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 255, found 255.

[606] Step 2: 268-3 (8.50 g, 33.42 mmol, 1 eq) was dissolved in DCM (50 mL) and TFA (50 mL) was added. The obtained compound was stirred at 25°C for 5h, concentrated and dried to deliver crude product 268-4 as yellow oil, which was used for the next step directly without further purification. **MS ESI** calcd for $\text{C}_9\text{H}_{18}\text{N}_2$ $[\text{M}+\text{H}]^+$ 155, found 155.

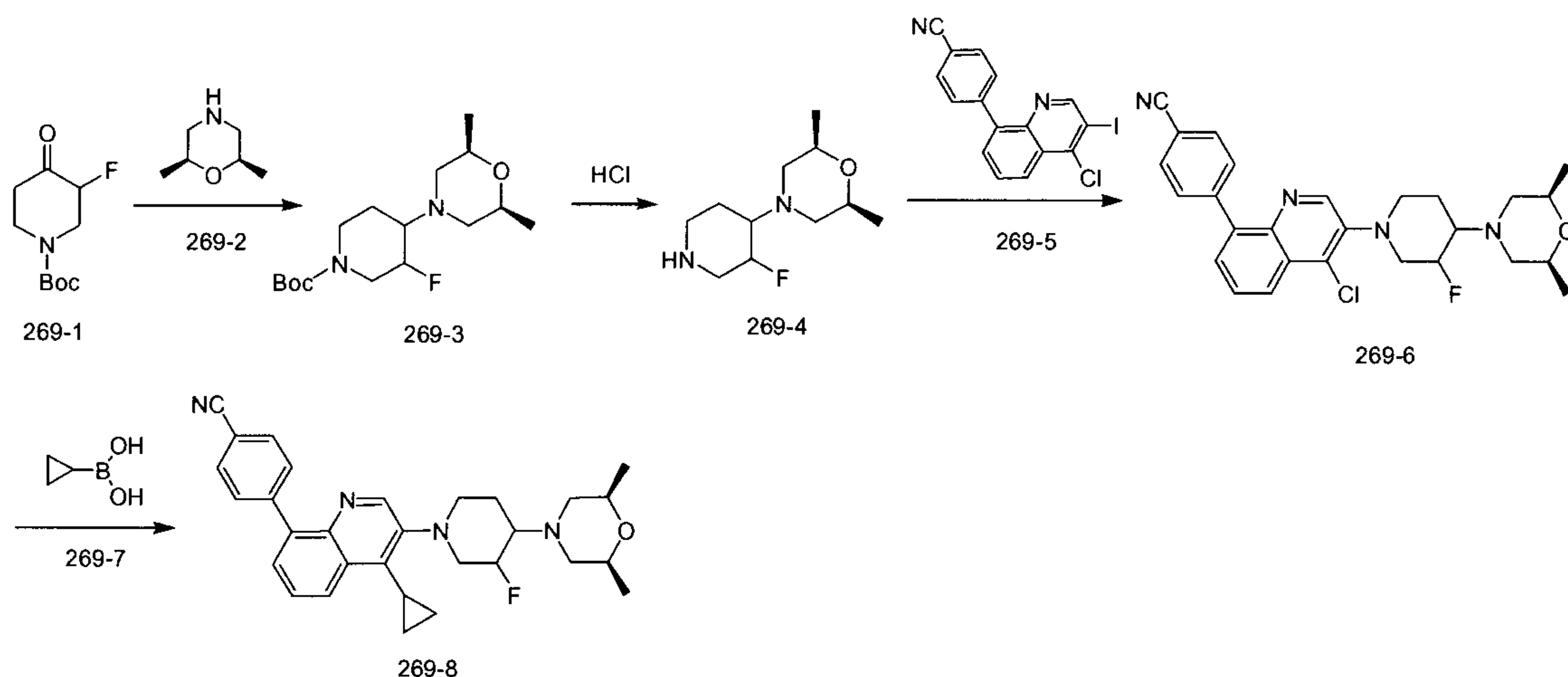
[607] Step 3: 268-5 (500 mg, 1.15 mmol, 1 eq) and 268-4 (308.31 mg, 1.15 mmol, 1 eq) were dissolved in toluene (10 mL), Xantphos (133 mg, 229.85 μmol , 0.20 eq), $\text{Pd}_2(\text{dba})_3$ (105.24 mg, 114.93 μmol , 0.10 eq), and cesium carbonate (1.50 g, 4.60 mmol, 4 eq) were added. The mixture was stirred at 120°C for 2h, cooled to 60°C and concentrated. The concentrate was purified by silica gel column chromatography (PE/EtOAc=10:1 to 1:1) to deliver 268-6 (220 mg, yield 41.46%) as yellow solid. **MS ESI** calcd for $\text{C}_{25}\text{H}_{25}\text{BrN}_4$ $[\text{M}+\text{H}]^+$ 461, found 461.

[608] Step 4: KOMe (7.60 mg, 108.37 μmol , 1 eq) was added into a solution of 268-6 (50 mg, 108.37 μmol , 1 eq) in DMF (2 mL) in portions. The compound was stirred at 25°C for 2h and concentrated under vacuum. The residue was purified by HPLC (TFA) to deliver the target compound (10 mg, yield 22.37%) as yellow solid. **MS ESI** calcd for $\text{C}_{26}\text{H}_{28}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$ 413, found 413. **^1H NMR** (400 MHz, CHLOROFORM-d) δ ppm 9.07 (brs, 1 H), 2.13 Hz, 1 H), 8.36 (d, $J=7.65, 7.82$ (d, $J=8.03$ Hz, 2 H), 7.71 - 7.78 (m, 2 H), 7.65 (d, $J=7.78$ Hz, 2 H), 4.34 (s, 3 H), 3.86 - 4.05 (m, 3 H), 3.57 - 3.72 (m, 2 H), 2.95 - 3.16 (m, 5 H), 2.05 - 2.43 (m, 9 H).

Embodiment 269



4-(4-cyclopropyl-3-((3S,4R)-4-((2S,6R)-2,6-dimethylmorpholino)-3-fluoro
piperidin-1-yl)quinolin-8-yl)benzonitrile



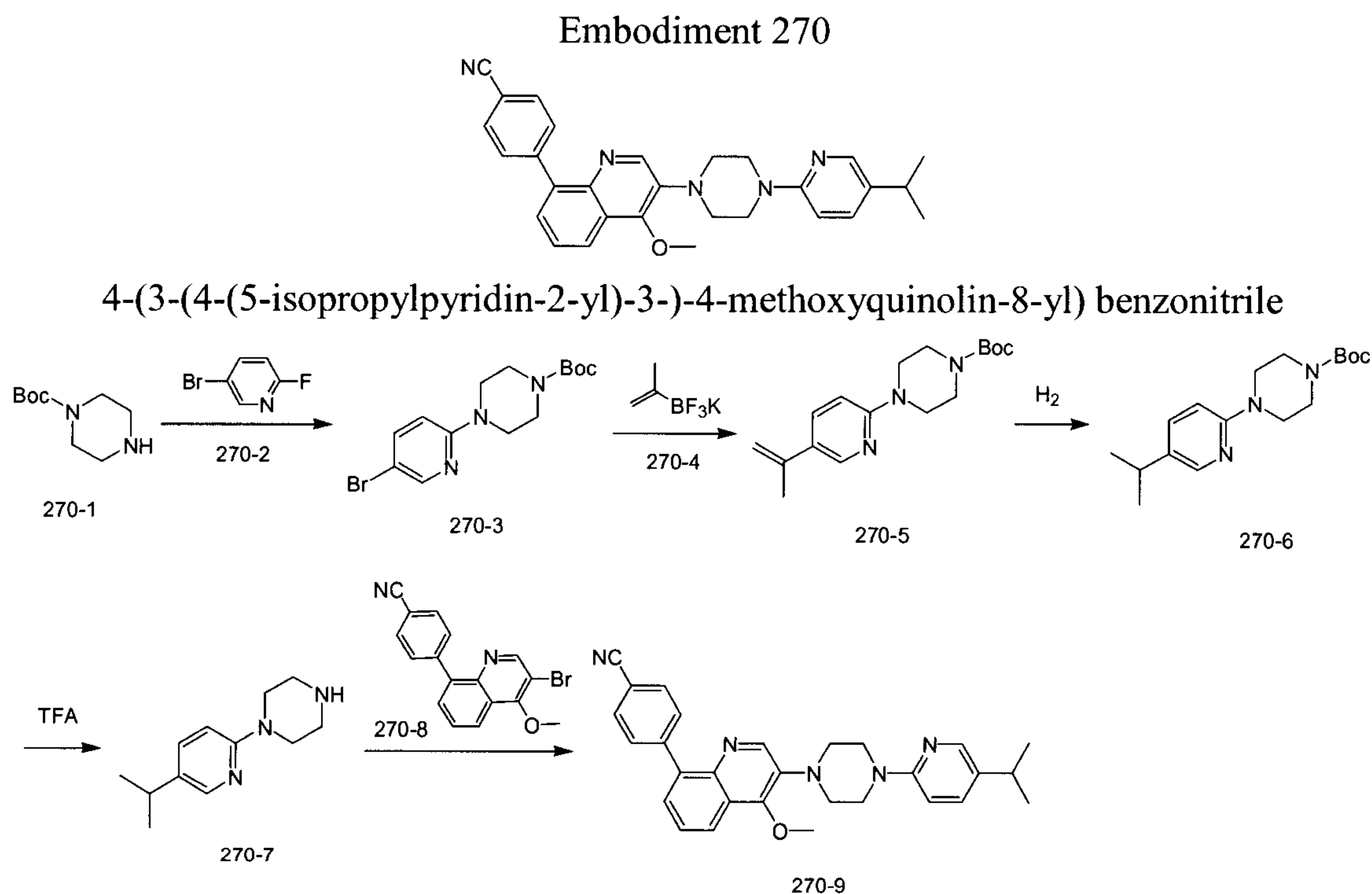
[609] Step 1: 269-1 (3g, 1.00 mmol) and 269-2 (1.91 g, 1.20 mmol) were dissolved in DCM (15 mL) and stirred at room temperature for 0.5h, then NaBH(OAc)₃ (4.39g, 16.57 mmol) was added, the mixture was stirred for 17h. The mixture was poured into H₂O (100 mL), extracted with DCM (150 mL*3). The organic phase was washed with brines (150 mL), dried over Na₂SO₄, filtrated and concentrated under vacuum. The residue was purified by silica gel column chromatography (PE/EtOAc=10:1 to 2:1) to deliver 269-3 (2g, yield 45.77%) as colorless oil. **MS ESI** calcd for C₁₆H₂₉FN₂O₃ [M+H]⁺ 317, found 317.

[610] Step 2: 269-3 (720 mg, 2.28 mmol) was dissolved in DCM (10 mL) and HCl/dioxane (4 M, 2 mL) was added. The mixture was stirred at room temperature for 30 min. After concentration, 269-4 was obtained, which was used for the next step directly. **MS ESI** calcd for C₁₁H₂₁FN₂O [M + H]⁺ 217, found 217.

[611] Step 3: 269-5 (700 mg, 1.79 mmol), Xantphos (207.15 mg, 358.00 μmol), Cs₂CO₃ (2.33 g, 7.16 mmol) and 269-4 (464.5 mg, 2.15 mmol) were dissolved in toluene (15 mL) and Pd₂(dba)₃ (163.91 mg, 179 μmol) was added. The mixture was stirred at 110°C for 2h, then poured into H₂O (150 mL). The mixture was extracted with EtOAc (200 mL*3). The organic phase was washed with brines (200 mL), dried over anhydrous sodium sulfate, filtrated and concentrated. The residue was purified by column chromatography (PE/EtOAc=8:1 to 1:1) to deliver 269-3 (200 mg, yield 23.33%) as white solid. **MS ESI** calcd for C₂₇H₂₈ClFN₄O [M+H]⁺ 479, found

479.

[612] Step 4: 269-6 (50 mg, 104.39 μ mol), cesium carbonate (68.02 mg, 208.78 μ mol), bis(adamantyl)butyl phosphine (37.43 mg, 104.39 μ mol) and 269-7 (44.84 mg, 521.955 μ mol) were dissolved in toluene (3 mL), Pd(OAc)₂ (11.72 mg, 52.20 μ mol) was added. The mixture was stirred at 110°C for 2h, then poured into H₂O (50 mL). The mixture was extracted with EtOAc (20 mL*3). The organic phase was washed with brines (50 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by HPLC to deliver compound (2 mg, yield 3.95%) as yellow solid. **MS ESI** calcd for C₃₀H₃₃FN₄O [M+H]⁺ 485, found 485. **¹HNMR** (400MHz, CDCl₃) δ ppm 8.72 (s, 1H), 8.51 (d, *J*= 7.8 Hz, 1H), 7.77 (s, 5H), 7.56 - 7.62 (m, 2H), 3.73 - 3.91 (m, 4H), 3.17 - 3.23 (m, 1H), 2.95 - 3.12 (m, 3H), 2.28 - 2.48 (m, 2H), 1.98 - 2.17 (m, 4H), 1.91 (d, *J*= 9.8 Hz, 1H), 1.22 (d, *J*= 6.0 Hz, 7H), 0.90 (t, *J*= 6.7 Hz, 3H).



[613] Step 1: K₂CO₃ (2.76 g, 20 mmol) was added into a mixture of 270-2 (1.76 g, 10 mmol) and 270-1 (2.24 g, 12 mmol) in DMF (20 mL). The mixture was stirred at 110°C for 12h, poured into H₂O (100 mL). The obtained mixture was extracted with EtOAc (150 mL×3). The organic phases were combined and washed with brines (150 mL), dried over anhydrous sodium sulfate, filtrated, and concentrated under vacuum. The residue was purified by column chromatography (PE/EtOAc=7:1) to deliver 270-3 (3 g, yield 87.66%) as colorless oil. **MS ESI** calcd for C₁₄H₂OBrN₃O₂ [M+H]⁺ 342, found 342.

[614] Step 2: 270-3 (1.70 g, 4.97 mmol), Na₂CO₃ (1.05 g, 9.94 mmol) and potassium isopropenyl trifluoroborate (1.49 g, 9.94 mmol) were dissolved in DMF (2

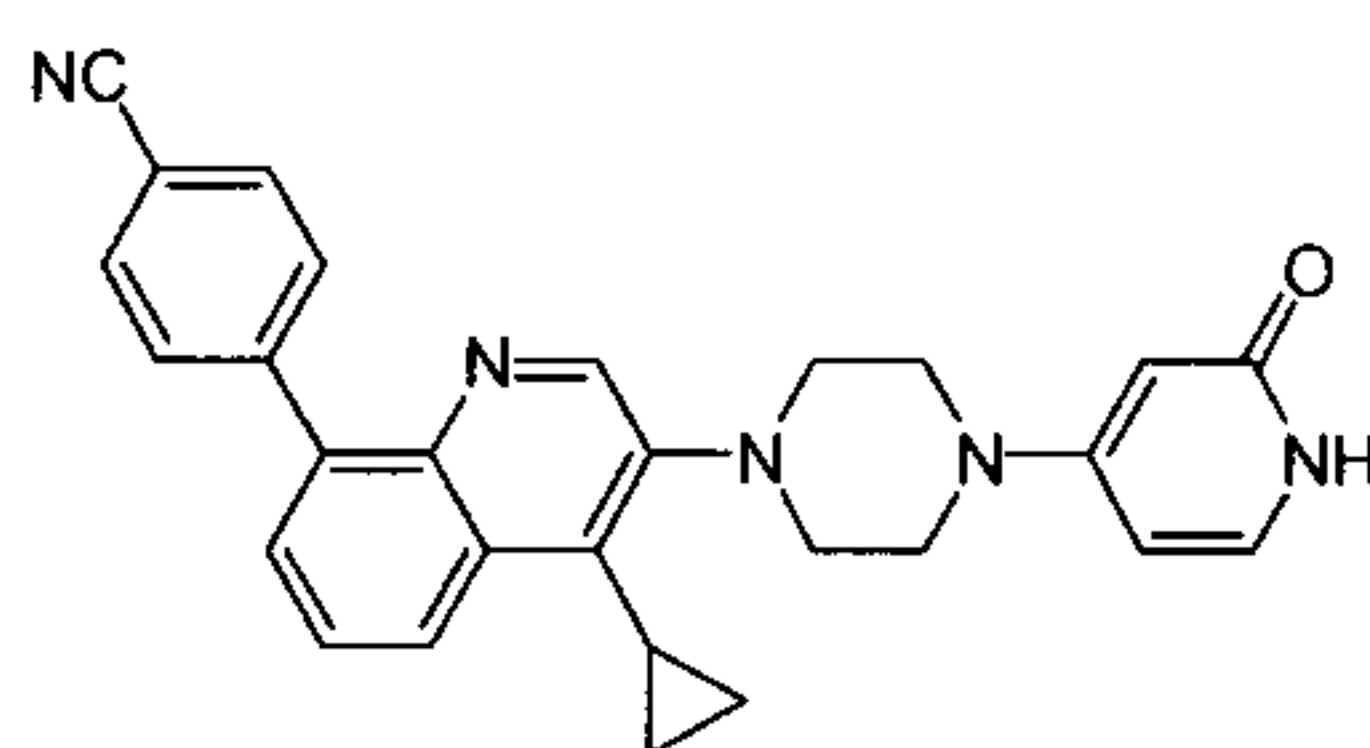
mL), under nitrogen gas atmosphere, Pd(dppf)Cl₂ (363.65 mg, 497 μmol) was added. The mixture was stirred at 70°C for 2h, then poured into H₂O (150 mL). The obtained mixture was extracted with EtOAc (150 mL×3). The organic phases were combined and washed with brines (150 mL), dried over anhydrous sodium sulfate, filtrated and concentrated under vacuum. The residue was purified by column chromatography (PE/EtOAc=10:1) to deliver 270-5 (1 g, yield 66.32%) as colorless oil. **MS ESI** calcd for C₁₇H₂₅N₃O₂ [M+H]⁺ 304, found 304.

[615] Step 3: 270-5 (1 g, 3.30 mmol) was dissolved in methanol (30 mL)/EtOAc (30 mL) and Pd(OH)₂/C (10%, 0.1 g) was added. The suspension was degassed and swept with hydrogen gas for 3 times. The mixture was stirred at 25°C for 2h under H₂ (40psi). TLC showed that the starting material was completely consumed. The mixture was filtrated, the filtrate was concentrated. The crude product was used for the next step directly. **MS ESI** calcd for C₁₇H₂₇N₃O₂ [M+H]⁺ 306, found 306.

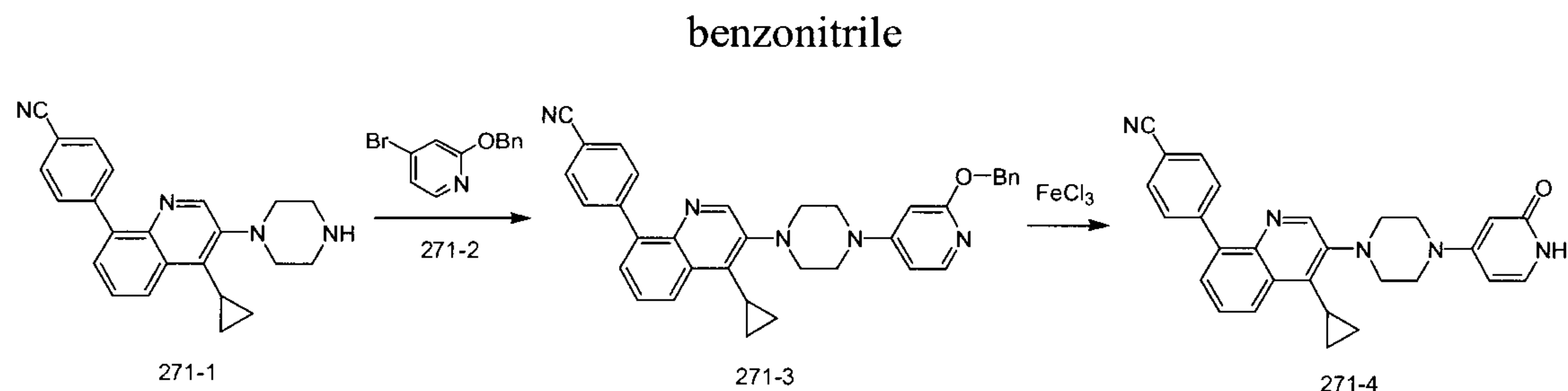
[616] Step 4: 270-6 (500 mg, 1.64 mmol) was dissolved in DCM (5 mL) and TFA (2.43 g, 21.32 mmol) was added in portions. The mixture was stirred for 30 min and concentrated. The residue was poured into saturated Na₂CO₃ solution (100 mL). The obtained mixture was extracted with EtOAc (100 mL×3). The organic phases were combined and washed with brines (100 mL), dried over anhydrous sodium sulfate, filtrated, and concentrated under vacuum. The crude product was used for the next step directly. **MS ESI** calcd for C₁₂H₁₉N₃ [M + H]⁺ 206, found 206.

[617] Step 5: Under nitrogen gas atmosphere, Pd₂(dba)₃ (40.50 mg, 44.22 μmol, 0.10 eq) was added into a solution of 270-8 (150 mg, 442.23 μmol, 1 eq), cesium carbonate (288.17 mg, 884.46 μmol, 2 eq), Xantphos (51.18 mg, 88.45 μmol, 0.20 eq) and 270-7 (108.95 mg, 530.68 μmol, 1.20 eq) in toluene(10 mL). The mixture was stirred at 110°C for 2h, poured into H₂O (100 mL). The obtained mixture was extracted with EtOAc (150 mL×3). The organic phases were combined and washed with brines (100 mL), dried over anhydrous sodium sulfate, filtrated, and concentrated under vacuum. The residue was purified by HPLC (acid) to deliver the target product (50 mg, yield 24.39%) as yellow solid. **MS ESI** calcd for C₂₉H₂₉N₅O [M+H]⁺ 464, found 464. ¹H NMR (400MHz, CDCl₃) δ ppm 8.79 (s, 1H), 8.16 - 8.27 (m, 1H), 8.05 - 8.14 (m, 1H), 7.74 - 7.82 (m, 4H), 7.53 - 7.64 (m, 2H), 7.35 - 7.45 (m, 1H), 6.72 (dd, J= 6.3, 8.3 Hz, 1H), 4.15 (s, 3H), 3.7₂ (d, J= 4.0 Hz, 4H), 3.34 - 3.44 (m, 4H), 2.49 (t, J= 7.5 Hz, 1H), 1.21 - 1.31 (m, 5H).

Embodiment 271



4-(4-cyclopropyl-3-(4-(2-oxo-1,2-dihydropyridin-4-yl)piperazin-1-yl)quinolin-8-yl)



[618] Step 1: Under nitrogen gas atmosphere, $\text{Pd}_2(\text{dba})_3$ (38.75 mg, 42.32 μmol) was added into a mixture of 271-1 (150 mg, 423.19 μmol), sodium tert-butoxide (81.34 mg, 846.38 μmol), Xantphos (48.97 mg, 84.64 μmol) and 271-2 (134.13 mg, 507.83 μmol) in toluene (10 mL). The mixture was stirred at 110°C for 2h, poured into H_2O (150 mL). The obtained mixture was extracted with EtOAc (100 $\times$ 3). The organic phases were combined and washed with brines (100 mL), dried over anhydrous sodium sulfate, filtrated, and concentrated under vacuum. The residue was purified by column chromatography (PE/EtOAc=3:1) to deliver 271-3 (150 mg, yield 65.93%) as yellow solid. **MS ESI** calcd for $\text{C}_{35}\text{H}_{31}\text{N}_5\text{O}$ $[\text{M}+\text{H}]^+$ 538, found 538.

[619] Step 2: FeCl_3 (452.52 mg, 2.79 mmol) was added into a mixture of 271-3 (150 mg, 278.99 μmol) in DCM (10 mL) in portions. The reaction mixture was stirred at room temperature for 60 min, then filtrated, extracted with EtOAc (100 mL $\times$ 3). The organic phases were combined and washed with brines (100 mL), dried over anhydrous sodium sulfate, filtrated, and concentrated under vacuum. The residue was purified by preparative HPLC (acid) to deliver the target compound (50 mg, yield 40.05%) as yellow solid. **MS ESI** calcd for $\text{C}_{28}\text{H}_{25}\text{N}_5\text{O}$ $[\text{M}+\text{H}]^+$ 448, found 448. **^1H NMR** (400MHz, METHANOL- d_4) δ ppm 8.77 (d, J = 7.8 Hz, 1H), 8.67 (s, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.82 - 7.89 (m, 1H), 7.76 - 7.83 (m, 3H), 7.72 (d, J = 7.5 Hz, 1H), 6.86 (d, J = 5.5 Hz, 1H), 6.25 (d, J = 2.3 Hz, 1H), 3.91 (brs., 4H), 3.55 (d, J = 4.8 Hz, 4H), 1.52 (brs, 1H), 0.99 – 1.09 (m, 2H), 0.13 (brs, 2H).

[620] Experiment 1: Assay *in vitro*

[621] Experimental objective:

[622] The luciferase (Gli-Luc) reporter gene with Gli response element was transfected into C3H10T1/2 cells, under Shh-N stimulation conditions, determine the Hedgehog signaling pathway inhibitors through the detection of gene expression in cell activity report. In this study, we evaluated the inhibitory effects of compounds on Hedgehog signaling pathway in the IC50 value of the compound as an index.

[623] Experimental materials:

Cell lines: C3H10T1/2/Gli-Luc stable cell line

C3H10T1/2/Gli-Luc Cell culture medium (DMEM/high glucose HyClone, #SH30022.01B; 10% serum Hyclone, #SV30087; 0.4% Hygromycin B Roche,

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#13398200)

0.25% Trypsin-EDTA (Gibco, #25200)

PBS (KH₂PO₄ 0.24g, Na₂HPO₄ 1.44g, NaCl 8.0g, KCl 0.2g, H₂O added to 1 L and adjusted to PH 7.4)

Shh-N, HEK293/SHH-N stable cell culture supernatant

Lysates (Promega, # E1531)

Reaction solution (Promega, # E1501)

384-well plate, Greiner #781074

96-well culture plate, Greiner # 655180

96-well microhole plate, Bi Yuntian #FPT019

CO₂ incubator, Thermo #3423

Clean bench, AIRTECH #A10051560

Inverted microscope, Nikon #TS100

Centrifuge, Xiangyi #L530

Therom VarioSkan Flash Multifunctional reading instrument

[624] Experimental procedure and method:

Inoculate the logarithmic growth phase of C3H10T1/2/Gli-Luc cells into a 96-well culture plate with 20000 cells per well, cells were cultured in a 37°C, 5% CO₂ incubator overnight. The next day, the compounds were diluted in the following ways: the positive compound GDC0449 (1 mM) and the compounds (1 mM) to be measured were serially diluted to 7 concentrations by DMSO according to 1:3 and 1:10 respectively, the eighth is for DMSO control, and then diluted with fresh medium 100 times. The medium of the cells cultured overnight was removed, 80 µL fresh culture medium was added per well, then 20 µL gradiently diluted positive compound and compounds to be measured and 100 µL 30 nM Shh-N containing conditioned medium were added, each concentration repeated 2 wells, at the same time, positive and negative reference well were set (i.e. Shh Ctrl: 80 µL fresh medium+20 µL 1% DMSO containing medium+100 µL 30 nM Shh-N containing conditioned medium; Unstimulated Ctrl: 180 µL fresh medium+20 µL 1% DMSO containing medium), cells were cultured in the incubator for further 24 h.

Intracellular luciferase activity detection: take the cells out of 96-well plate, discard the culture medium, the cells were washed with PBS twice, then each well added with 20 µL lysate (Promega E1531), oscillate pyrolysis at room temperature for 30 min. 5 µL cell lysates were transferred to 384-well plate (Greiner 781074), then each well was added with 25 µL luciferase reaction liquid (Promega E1501), after rapid mixed, immediately placed into the VarioSkan Flash multi-function reading instrument to read the relative light units (RLU) value.

Data analysis: using Prism's GraphPad 5 for data analysis. RLU reading to the logarithmic mapping of compound concentration on behalf of luciferase activity, and then curve fitting using the following equation to give IC₅₀ value, $Y (RLU) = \text{minimum} + (\text{maximum} - \text{minimum}) / (1 + 10^{(\log \text{ of compound concentration} - \text{LogIC}_{50}))$.

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Table 1. IC₅₀ of the inhibitory activities of compounds on the hedgehog pathway or inhibition rates of compounds at a certain concentration

Compounds obtained in Embodiments	biological activity
Embodiment 1	C
Embodiment 2	C
Embodiment 3	C
Embodiment 4	C
Embodiment 5	C
Embodiment 6	D
Embodiment 7	D
Embodiment 8	C
Embodiment 9	E
Embodiment 10	C
Embodiment 11	C
Embodiment 12	D
Embodiment 13	C
Embodiment 14	B
Embodiment 15	C
Embodiment 16	C
Embodiment 17	B
Embodiment 18	C
Embodiment 19	C
Embodiment 20	C
Embodiment 21	C
Embodiment 22	B
Embodiment 23	A
Embodiment 24	B
Embodiment 25	B
Embodiment 26	B

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Embodiment 27	A
Embodiment 28	A
Embodiment 29	C
Embodiment 30	C
Embodiment 31	C
Embodiment 32	C
Embodiment 33	C
Embodiment 34	C
Embodiment 35	C
Embodiment 36	C
Embodiment 37	C
Embodiment 38	A
Embodiment 39	A
Embodiment 40	A
Embodiment 41	A
Embodiment 42	C
Embodiment 43	E
Embodiment 44	D
Embodiment 45	E
Embodiment 46	C
Embodiment 47	E
Embodiment 48	E
Embodiment 49	D
Embodiment 50	D
Embodiment 51	C
Embodiment 52	C
Embodiment 53	D
Embodiment 54	E
Embodiment 55	E

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Embodiment 56	D
Embodiment 57	D
Embodiment 58	E
Embodiment 59	D
Embodiment 60	C
Embodiment 61	C
Embodiment 62	C
Embodiment 63	E
Embodiment 64	D
Embodiment 65	D
Embodiment 66	D
Embodiment 67	D
Embodiment 68	E
Embodiment 69	D
Embodiment 70	D
Embodiment 71	E
Embodiment 72	E
Embodiment 73	D
Embodiment 74	E
Embodiment 75	E
Embodiment 76	C
Embodiment 77	D
Embodiment 78	C
Embodiment 79	D
Embodiment 80	E
Embodiment 81	E
Embodiment 82	E
Embodiment 83	E
Embodiment 84	E

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Embodiment 85	D
Embodiment 86	D
Embodiment 87	C
Embodiment 88	A
Embodiment 89	A
Embodiment 90	B
Embodiment 91	A
Embodiment 92	A
Embodiment 93	A
Embodiment 94	A
Embodiment 95	A
Embodiment 96	C
Embodiment 97	C
Embodiment 98	A
Embodiment 99	A
Embodiment 100	C
Embodiment 101	C
Embodiment 102	B
Embodiment 103	B
Embodiment 104	A
Embodiment 105	A
Embodiment 106	B
Embodiment 107	A
Embodiment 108	C
Embodiment 109	B
Embodiment 110	C
Embodiment 111	C
Embodiment 112	A
Embodiment 113	A

Our Ref.: P1650132CA

Embodiment 114	E
Embodiment 115	E
Embodiment 116	C
Embodiment 117	E
Embodiment 118	B
Embodiment 119	B
Embodiment 120	D
Embodiment 121	A
Embodiment 122	B
Embodiment 123	A
Embodiment 124	B
Embodiment 125	A
Embodiment 126	C
Embodiment 127	C
Embodiment 128	D
Embodiment 129	B
Embodiment 130	D
Embodiment 131	E
Embodiment 132	A
Embodiment 133	A
Embodiment 134	A
Embodiment 135	C
Embodiment 136	B
Embodiment 137	C
Embodiment 138	A
Embodiment 139	B
Embodiment 140	D
Embodiment 141	C
Embodiment 142	D

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Embodiment 143	A
Embodiment 144	C
Embodiment 145	A
Embodiment 146	D
Embodiment 147	C
Embodiment 148	B
Embodiment 149	A
Embodiment 150	D
Embodiment 151	A
Embodiment 152	A
Embodiment 153	C
Embodiment 154	A
Embodiment 155	C
Embodiment 156	D
Embodiment 157	E
Embodiment 158	A
Embodiment 159	A
Embodiment 160	A
Embodiment 161	A
Embodiment 162	A
Embodiment 163	C
Embodiment 164	C
Embodiment 165	C
Embodiment 166	A
Embodiment 167	A
Embodiment 168	A
Embodiment 169	A
Embodiment 170	A
Embodiment 171	A

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Embodiment 172	A
Embodiment 173	C
Embodiment 174	C
Embodiment 175	C
Embodiment 176	A
Embodiment 177	A
Embodiment 178	C
Embodiment 179	D
Embodiment 180	A
Embodiment 181	A
Embodiment 182	A
Embodiment 183	B
Embodiment 184	B
Embodiment 185	C
Embodiment 186	A
Embodiment 187	A
Embodiment 188	A
Embodiment 189	A
Embodiment 190	A
Embodiment 191	A
Embodiment 192	A
Embodiment 193	C
Embodiment 194	A
Embodiment 195	B
Embodiment 196	C
Embodiment 197	D
Embodiment 198	B
Embodiment 199	C
Embodiment 200	A

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Embodiment 201	A
Embodiment 202	A
Embodiment 203	A
Embodiment 204	A
Embodiment 205	B
Embodiment 206	A
Embodiment 207	C
Embodiment 208	C
Embodiment 209	A
Embodiment 210	A
Embodiment 211	A
Embodiment 212	A
Embodiment 213	A
Embodiment 214	A
Embodiment 215	C
Embodiment 216	C
Embodiment 217	C
Embodiment 218	A
Embodiment 219	A
Embodiment 220	A
Embodiment 221	A
Embodiment 222	A
Embodiment 223	C
Embodiment 224	A
Embodiment 225	A
Embodiment 226	A
Embodiment 227	A
Embodiment 228	C
Embodiment 229	C

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Embodiment 230	C
Embodiment 231	A
Embodiment 232	C
Embodiment 233	A
Embodiment 234	A
Embodiment 235	A
Embodiment 236	A
Embodiment 237	C
Embodiment 238	A
Embodiment 239	C
Embodiment 240	C
Embodiment 241	C
Embodiment 242	A
Embodiment 243	A
Embodiment 244	A
Embodiment 245	C
Embodiment 246	A
Embodiment 247	C
Embodiment 248	A
Embodiment 249	A
Embodiment 250	C
Embodiment 251	A
Embodiment 252	C
Embodiment 253	C
Embodiment 254	A
Embodiment 255	C
Embodiment 256	C
Embodiment 257	A
Embodiment 258	C

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Embodiment 259	B
Embodiment 260	C
Embodiment 261	C
Embodiment 262	A
Embodiment 263	A
Embodiment 264	A
Embodiment 265	B
Embodiment 266	A
Embodiment 267	A
Embodiment 268	C
Embodiment 269	A
Embodiment 270	B
Embodiment 271	C

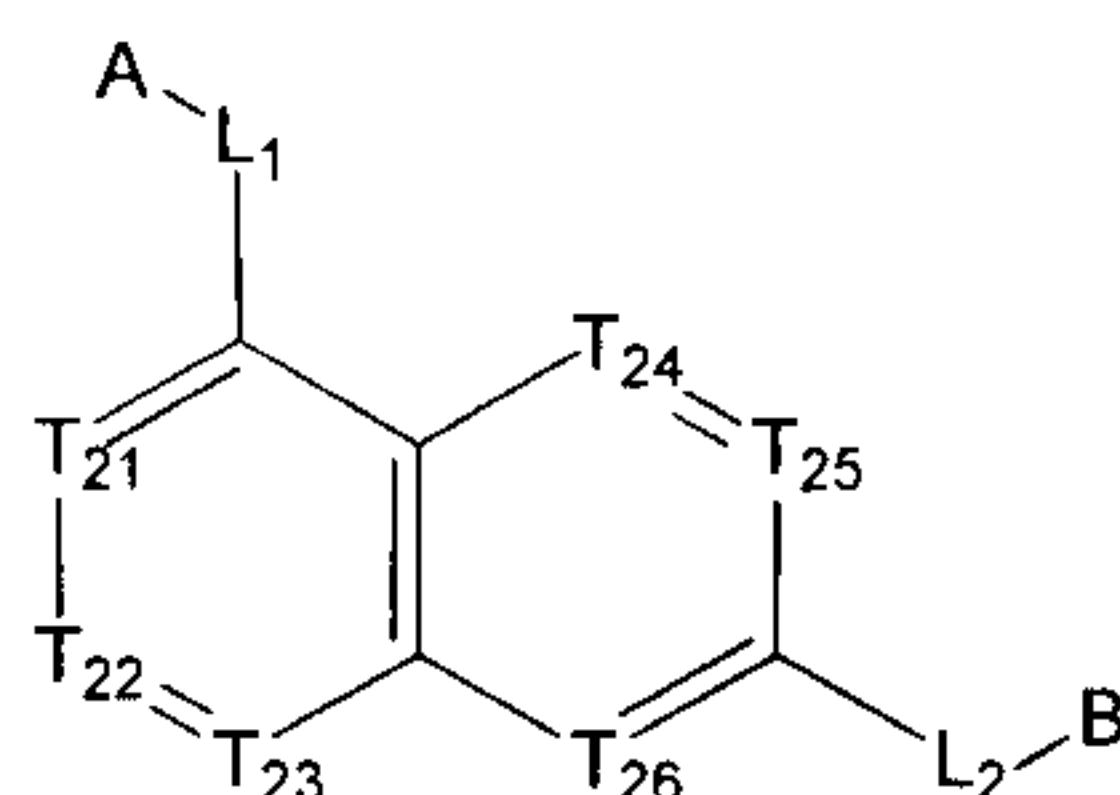
Note: $A \leq 50 \text{ nM}$; $50 \text{ nM} < B \leq 100 \text{ nM}$; $100 \text{ nM} < C \leq 500 \text{ nM}$; $500 \text{ nM} < D \leq 1000 \text{ nM}$; $1000 \text{ nM} < E \leq 5000 \text{ nM}$.

Conclusion: the compounds of the present invention have significant inhibition effect on the hedgehog pathway.

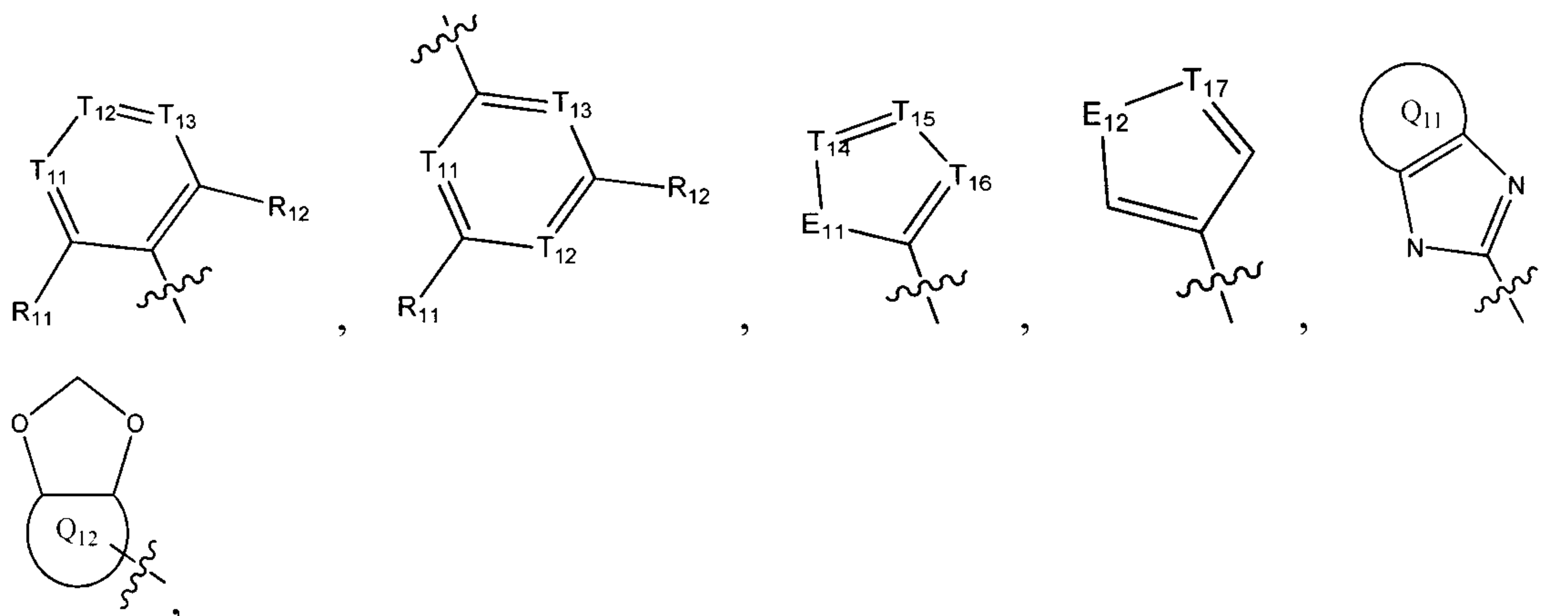
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What is claimed is:

1. A compound represented by formula (I), or a pharmaceutically acceptable salt thereof,



wherein, A is selected from



(R₂₀)₃C-E₁₃-;

each of T₁₁₋₁₇ is independently selected from N, C(R₁₃);

each of E₁₁₋₁₃, L₁, L₂ is independently selected from N(R₁₄), C(=O)N(R₁₅), S(=O)₂N(R₁₆), C=N(R₁₇), C(R₁₈)(R₁₉), S, C(=O)O, C(=O), C=S, S(=O) or S(=O)₂;

each of L₁, L₂ can also be independently selected from a single bond;

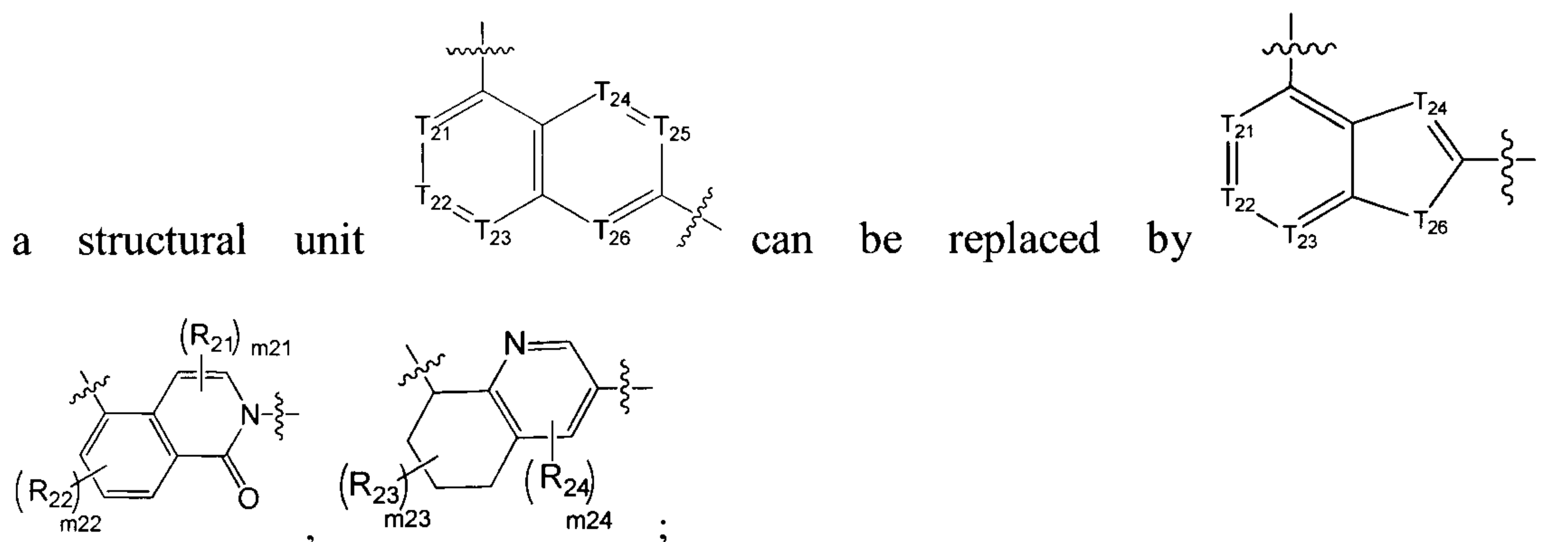
each of R₁₁₋₁₃, R₁₈₋₁₉ is independently selected from H, F, Cl, Br, I, CN, OH, SH, NH₂, an optionally R₀₁-substituted C₁₋₆ alkyl or heteroalkyl or alkyl-heteroatom group or heteroalkyl-heteroatom group, an optionally R₀₂-substituted C₃₋₈ cyclic group or heterocyclic group or cycle-heteroatom group or heterocycle-heteroatom group]; or selected from a methyl, a trifluoromethyl, a trifluoromethoxy, F, Cl, Br, I, CN, a methylamino carbonyl, a methylsulfonyl, a trifluoromethylsulfonyl, a trifluoromethoxy, a cyclopropyl, a morpholinylsulfonyl, a 2-imidazolyl, a dimethylamino, a *n*-, or *iso*-propyl;

each of R₁₄₋₁₇ is independently selected from H, an optionally R₀₁-substituted C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

R₂₀ is selected from H, F, Cl, Br, I, CN, OH, SH, NH₂, a methoxy, a methylamino, a dimethylamino;

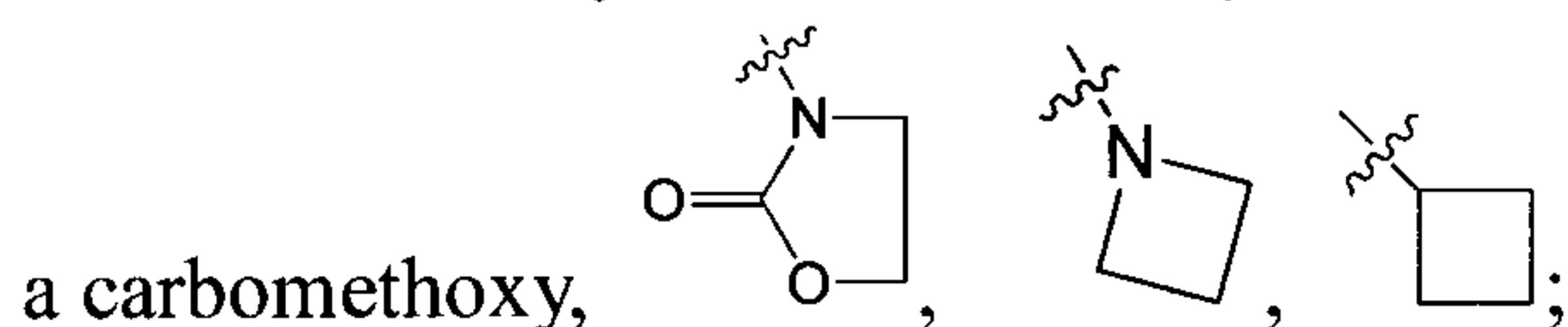
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each of Q_{11-12} is independently selected from a phenyl, a pyridyl, a thienyl, a furyl;

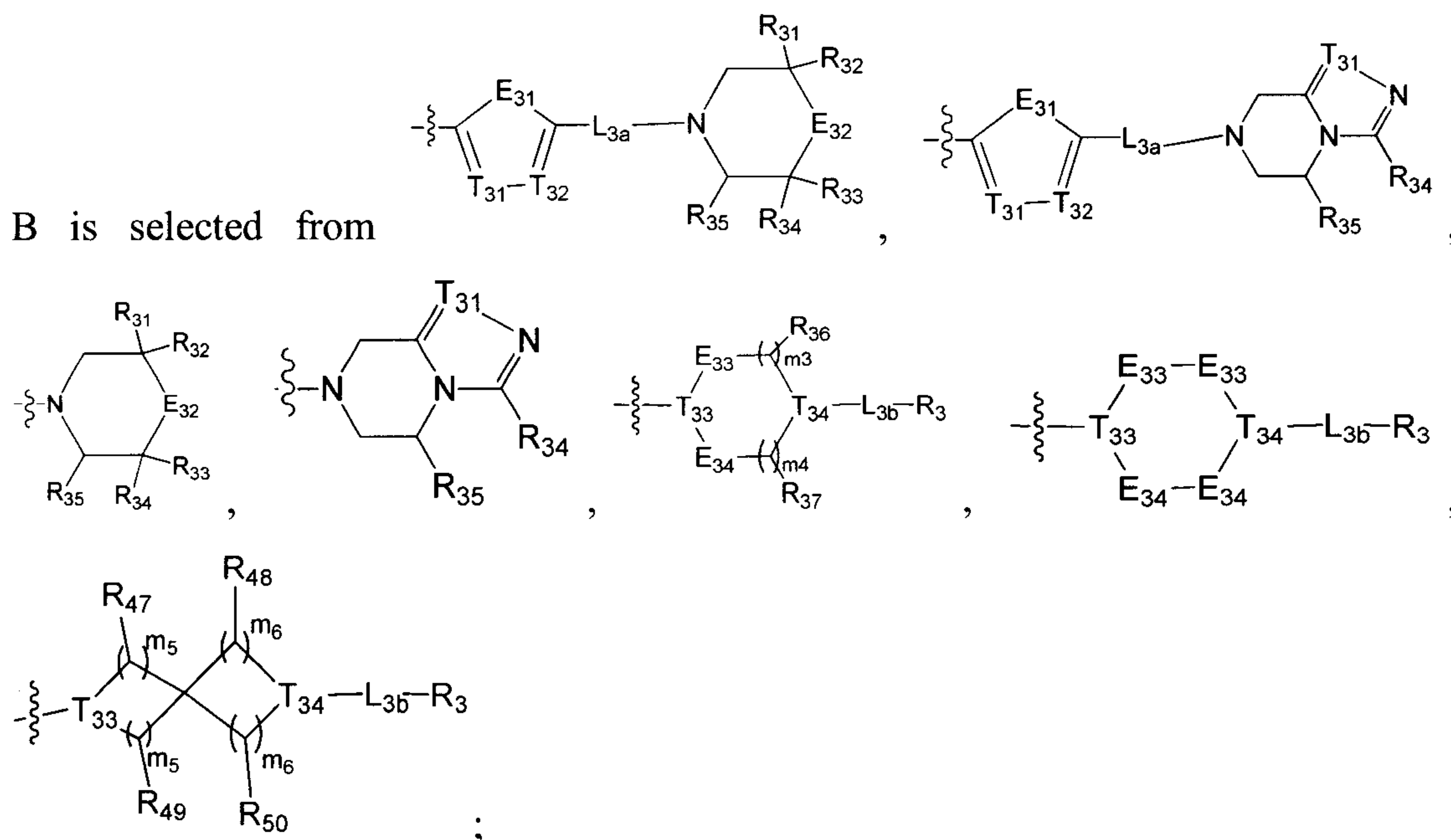


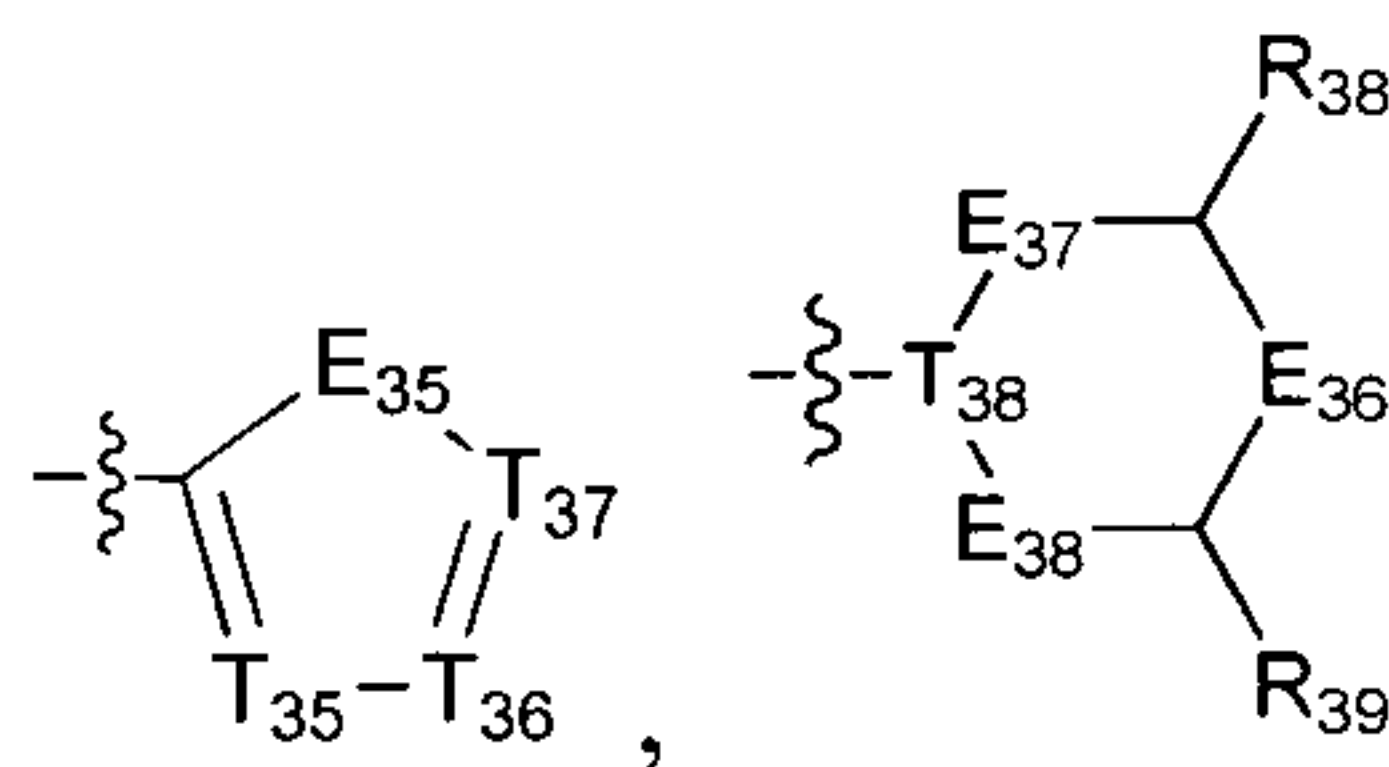
each of T_{21-26} is independently selected from N, $C(R_{25})$; also T_{25} can be selected from $N^+(R_{25})$;

each of R_{21-25} is independently selected from H, F, Cl, Br, I, CN, OH, SH, NH_2 , an optionally R_{01} -substituted C_{1-6} alkyl or heteroalkyl or alkyl-heteroatom group or heteroalkyl-heteroatom group, an optionally R_{02} -substituted C_{3-8} cyclic group or heterocyclic group or cycle -heteroatom group or heterocycle-heteroatom group; or selected from F, Cl, Br, I, CN, OH, a methyl, an ethyl, an isopropyl, a methoxy, a trifluoromethyl, a difluoromethoxy, a *n*-, or *iso*-propoxy, a cyclopropyl, a formamido, a methanesulfonylamino, a dimethylamino, a dimethylaminoethoxy, a methysulfonyl,



each of m_{21-24} is independently selected from 0, 1 or 2;





R_3 is selected from $T_{35}-T_{36}$, $T_{38}-T_{39}$, H, an optionally R_{01} -substituted C_{1-6} alkyl or heteroalkyl or alkyl-heteroatom group or heteroalkyl-heteroatom group, an optionally R_{02} -substituted C_{3-8} cyclic group or heterocyclic group or cycle-heteroatom group or heterocycle-heteroatom group;

each of E_{31-38} , L_{3a} , L_{3b} is independently selected from $N(R_{40})$, $N(R_{40})(CH_2)_{1-3}$, $C(=O)N(R_{40})(CH_2)_{1-3}$, $C(=O)N(R_{41})$, $S(=O)_2 N(R_{42})$, $C=N(R_{43})$, $C(R_{44})(R_{45})$, S , $C(=O)O$, $C(=O)$, $C=S$, $S(=O)$, $S(=O)_2$, O or $C(=O)C(R_{44})(R_{45})$;

each of L_{3a} , L_{3b} can also be independently selected from a single bond or C_{1-5} alkyl;

each of E_{31} , E_{35} can also be independently selected from $-T_{39}=T_{40}-$;

each of T_{31-40} is independently selected from N , $C(R_{46})$;

each of R_{40-43} is independently selected from H, an optionally R_{01} -substituted C_{1-6} alkyl or C_{3-6} cycloalkyl, an optionally R_{01} -substituted C_{1-6} alkyl acyl or C_{3-6} cycloalkyl acyl, an optionally R_{01} -substituted C_{1-6} alkyl sulfonyl or C_{3-6} cycloalkyl sulfonyl, an optionally R_{01} -substituted 5-6 membered aryl acyl, an optionally R_{01} -substituted 5-6 membered heteroaryl acyl, an optionally R_{01} -substituted 5-6 membered aryl sulfonyl, an optionally R_{01} -substituted C_{1-6} alkyoxycarbonyl, an optionally R_{01} -substituted C_{1-6} alkyl amino carbonyl;

each of R_{31-49} , R_{44-50} is independently selected from H, F, Cl, Br, I, CN, OH, SH, NH_2 , $C(=O)OH$, an optionally R_{01} -substituted C_{1-6} alkyl or heteroalkyl or alkyl-heteroatom group or heteroalkyl-heteroatom group, an optionally R_{02} -substituted C_{0-3} alkyl- C_{3-8} cyclic group or heterocyclic group or cycle-heteroatom group or heterocycle-heteroatom group;

each of R_{01} , R_{02} is independently selected from F, Cl, Br, I, CN, OH, SH, NH_2 , R_{03} ;

R_{03} is selected from a C_{1-6} alkyl amino, a di(C_{1-6} alkyl)amino, a C_{1-6} alkoxy, a C_{3-8} cycloalkyl amino, a C_{3-8} heterocycloalkyl amino, a C_{3-8} cycloalkoxy;

the heteroatom or the heteroatom group is independently selected from $C(=O)NR_{04}$, $N(R_{05})$, $C=N(R_{06})$, O , S , $C(=O)O$, $C(=O)$, $C=S$, $S(=O)$, $S(=O)_2$ and/ or $S(=O)_2 N(R_{07})$;

each of R_{04-07} is independently selected from H, R_{08} ;

R_{08} is selected from a C_{1-6} alkyl or a C_{3-8} cycloalkyl;

R_{03} , R_{08} are optionally substituted by R_{001} , R_{001} is selected from OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2 , F, Cl, Br, I, CN, a methyl, a methoxy;

a number of R_{01} , R_{02} , R_{001} , the heteroatom or the heteroatom group is independently selected from 0, 1, 2, or 3;

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each of m_3 , m_4 is independently selected from 0 or 1, when m_3 or m_4 is selected from 0, the corresponding structural unit represents a single bond just for the linkage;

each of m_5 , m_6 is independently selected from 1 or 2;

or, R_{31} and R_{32} , R_{31} and R_{33} , R_{31} and R_{35} , E_{33} and E_{34} form a linking bond $(CH_2)_{1-6}$ together, or $(CH_2)_2$, $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$;

or, R_{32} and R_{32} connect with each other to form a 5-membered carbocyclic ring or a heterocyclic ring;

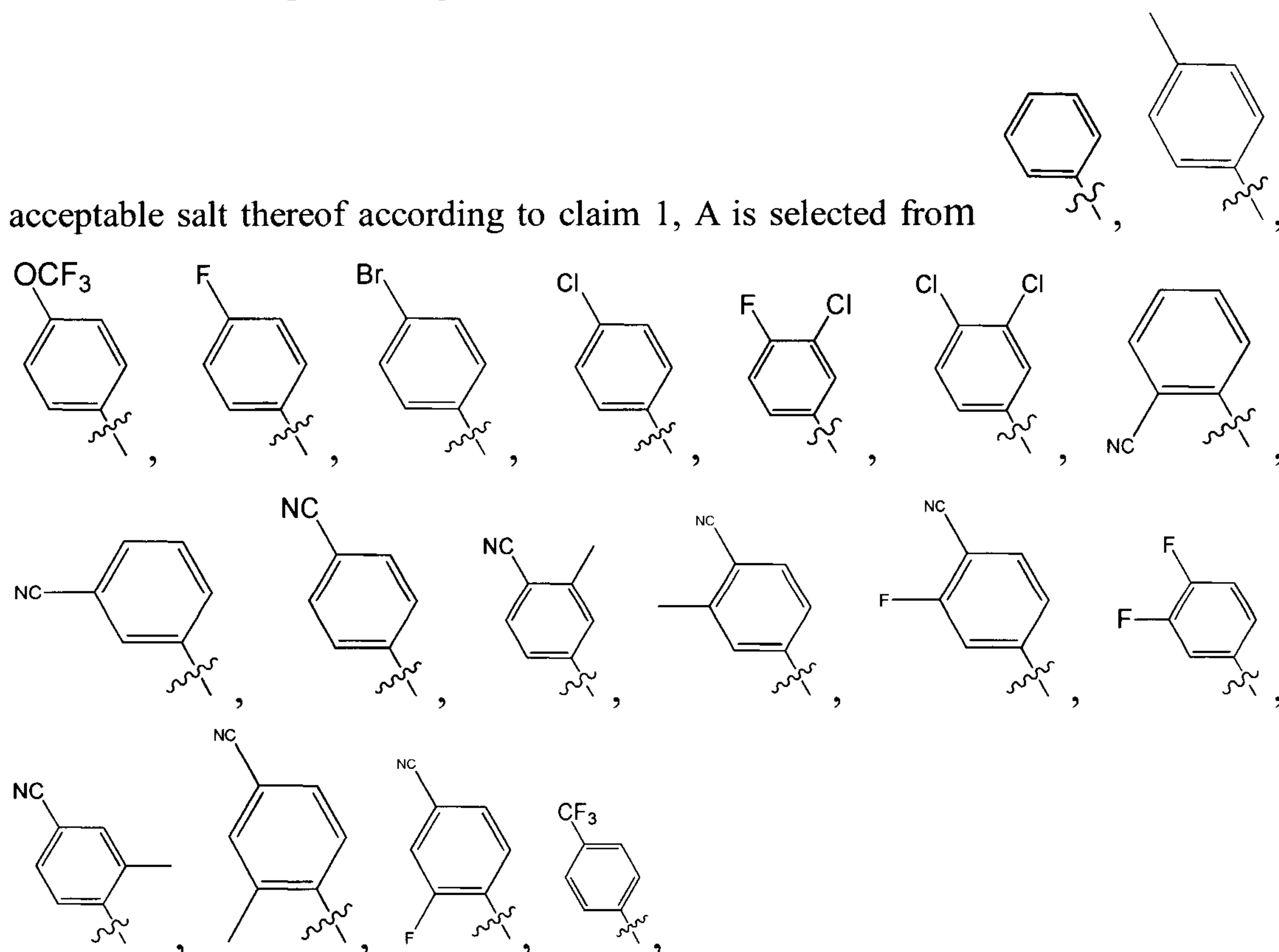
or, when E_{32} is selected from $N(R_{40})$ or O , R_{31} and R_{34} present a *cis*-arrangement; when E_{32} is selected from $C(R_{43})(R_{44})$, R_{31} and R_{34} present a *trans*-arrangement; when T_{34} is selected from N , R_{36} and R_{37} present a *cis*-arrangement; when T_{34} is selected from $C(R_{45})$, R_{36} and R_{37} present a *trans*-arrangement;

preferably,

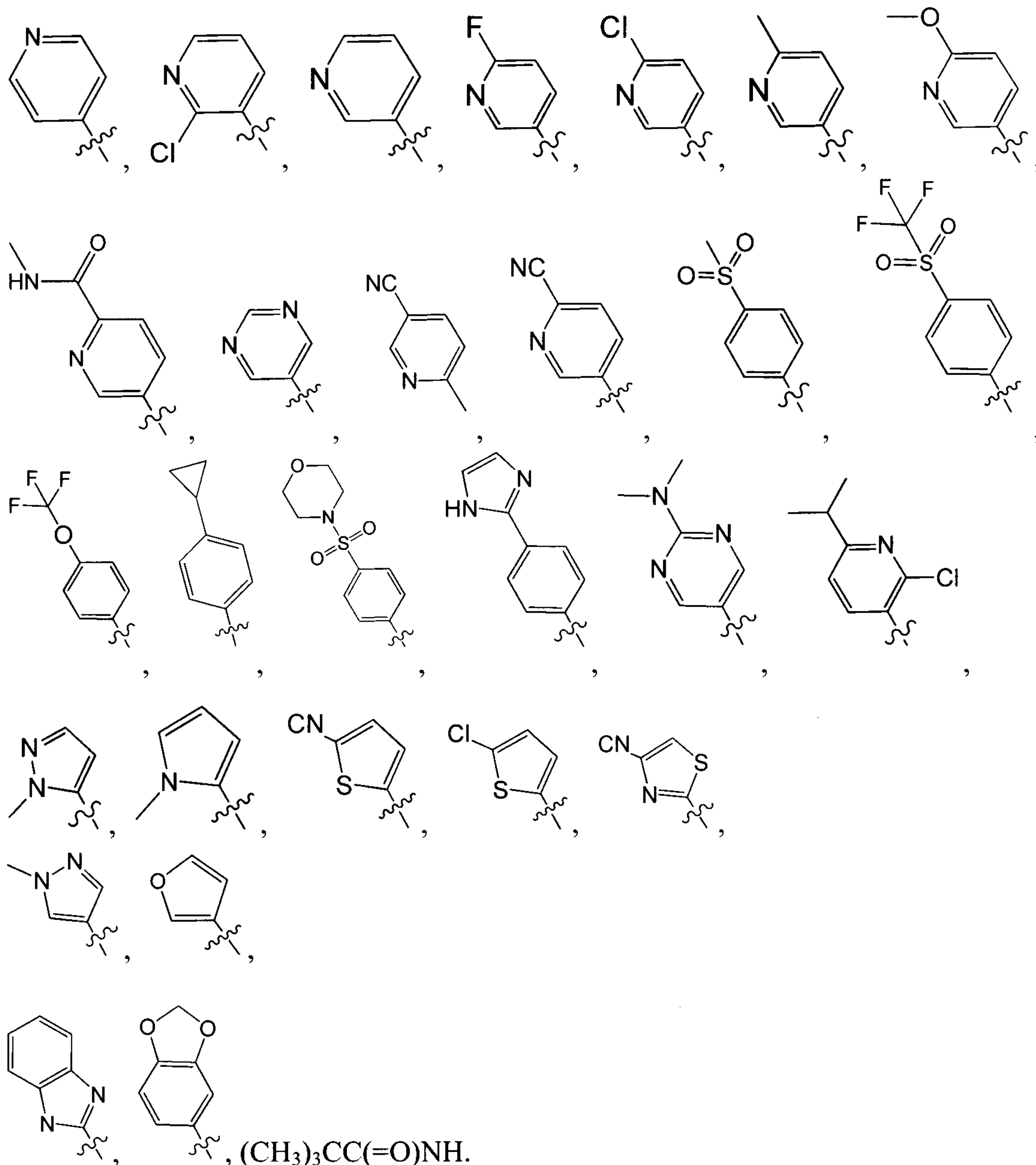
the C_{3-8} cyclic group or heterocyclic group or cycle-heteroatom group or heterocycle-heteroatom group is selected from a phenyl, a pyridyl, a thienyl, a furyl, an imidazolyl, an oxazolyl, a thiazolyl, an isothiazolyl.

2. The compound represented by formula (I), or the pharmaceutically

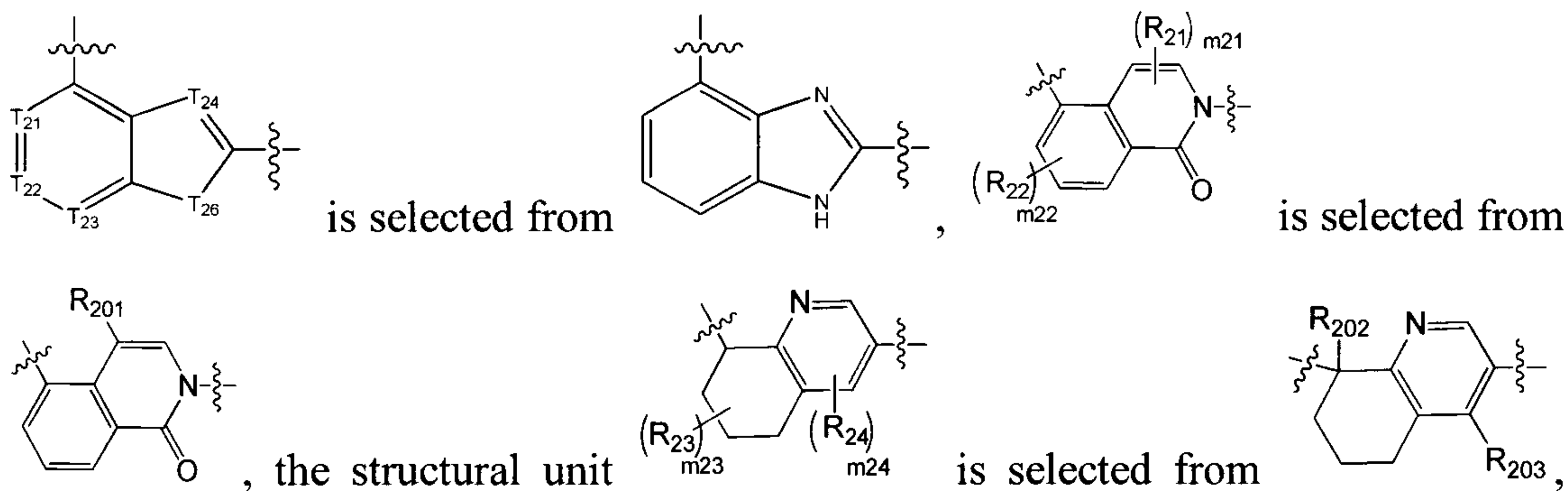
acceptable salt thereof according to claim 1, A is selected from



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3. The compound represented by formula (I), or the pharmaceutically acceptable salt thereof according to claim 1, wherein the structural unit

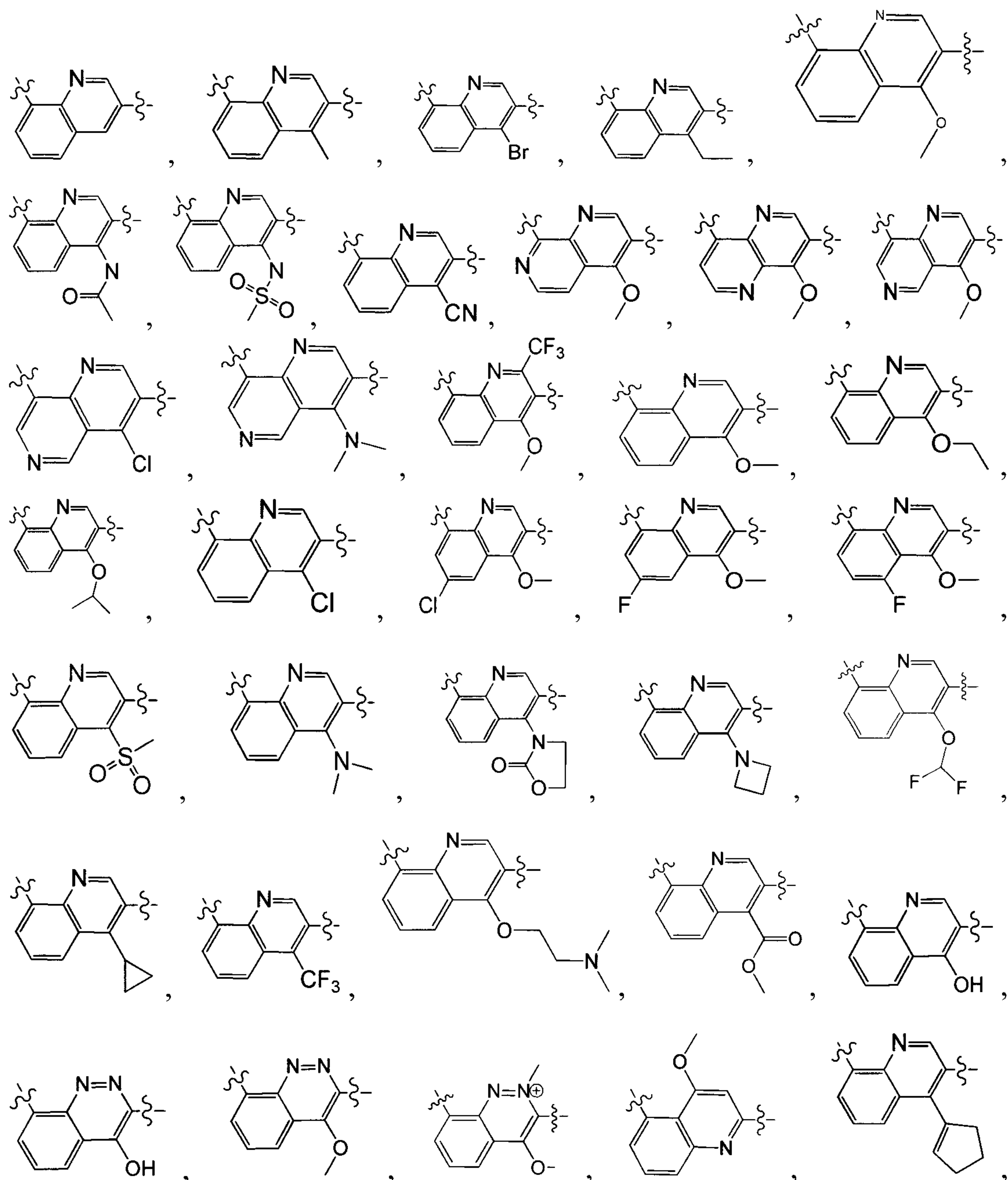


wherein,

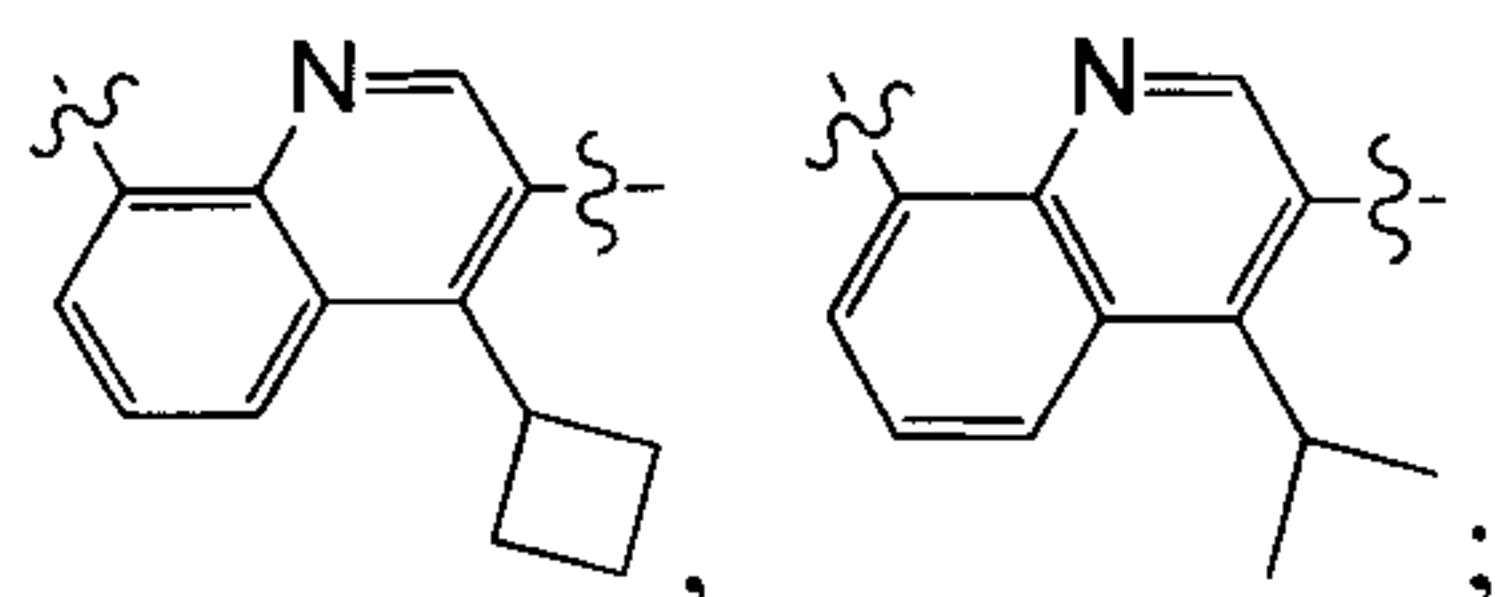
each of R₂₀₁, R₂₀₂, R₂₀₃ is independently selected from H, F, Cl, Br, I, CN, OH, SH,

or, R₂₀₁ is selected from methyl, F, Cl, Br, I; each of R₂₀₂, R₂₀₃ is independently selected from a C₁₋₆ alkoxy, or a methoxy.

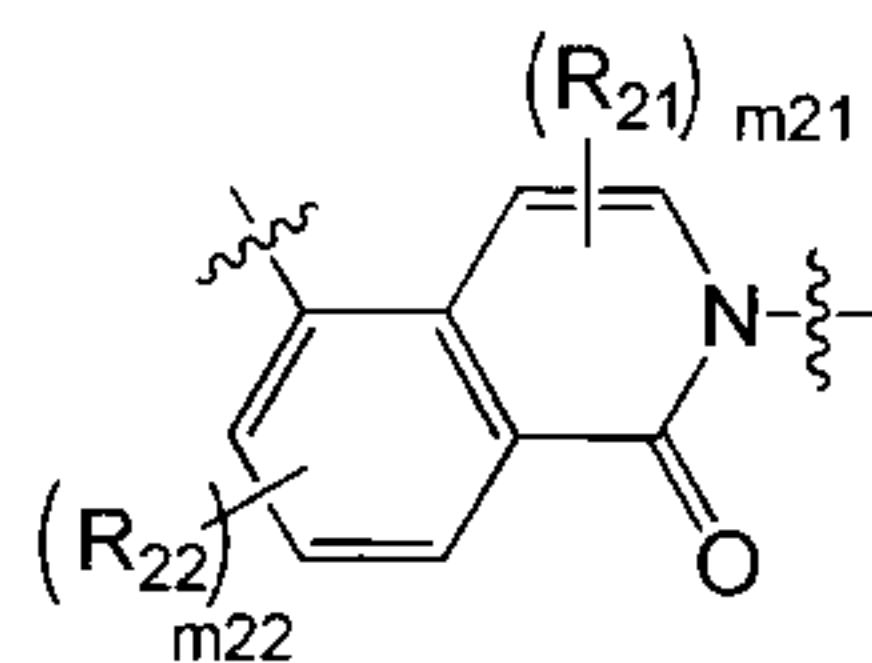
is selected from:



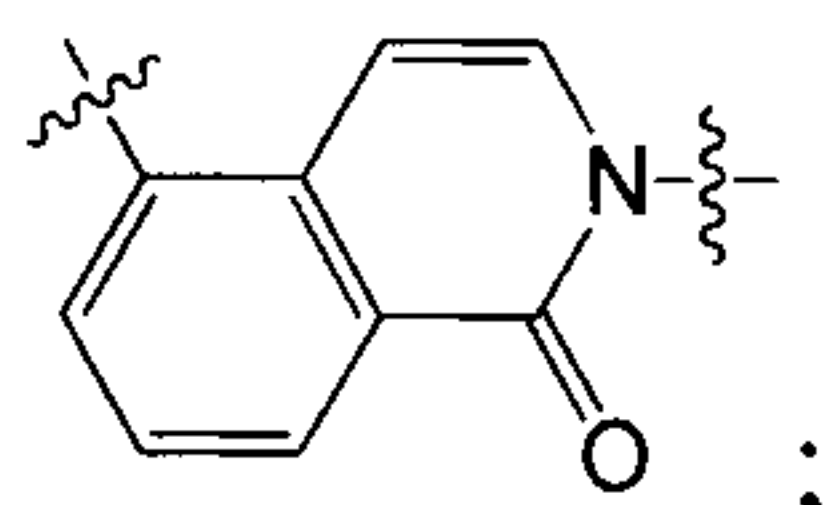
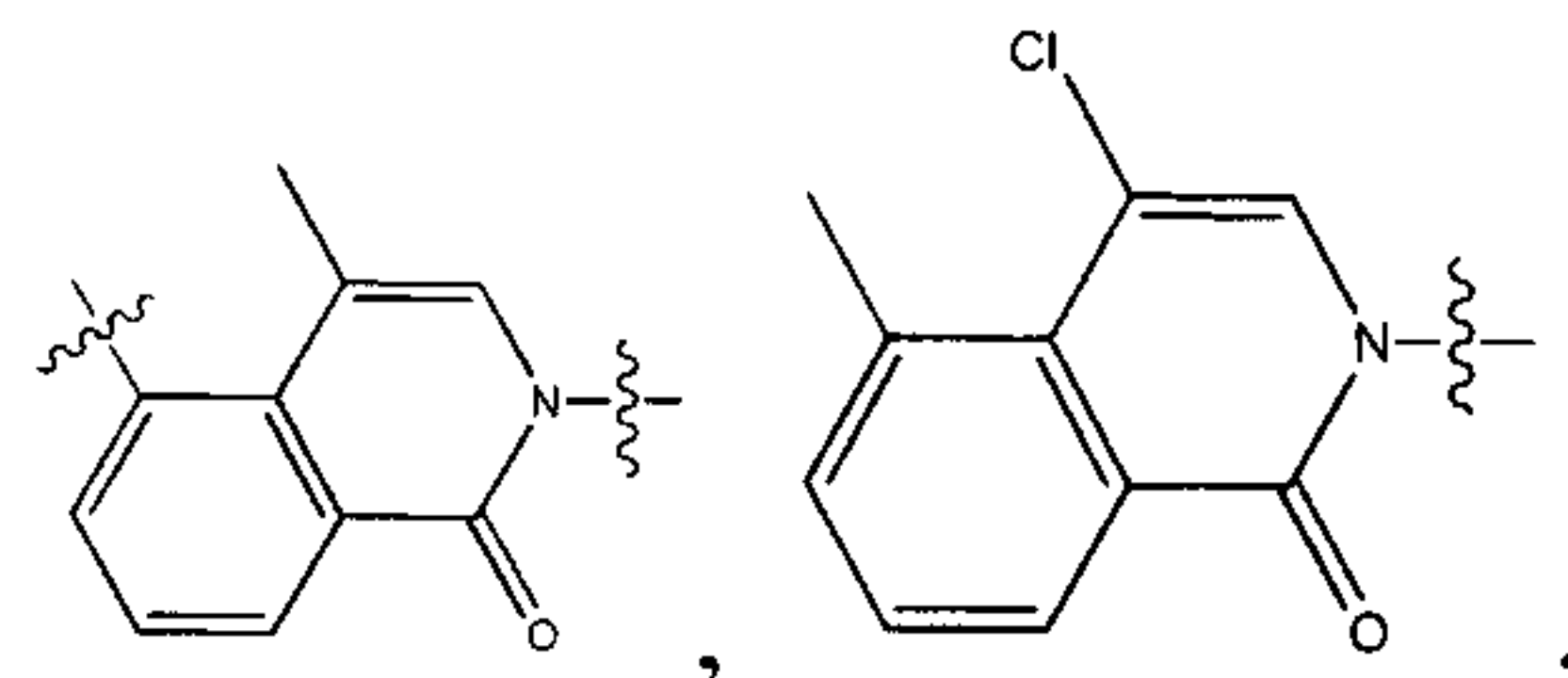
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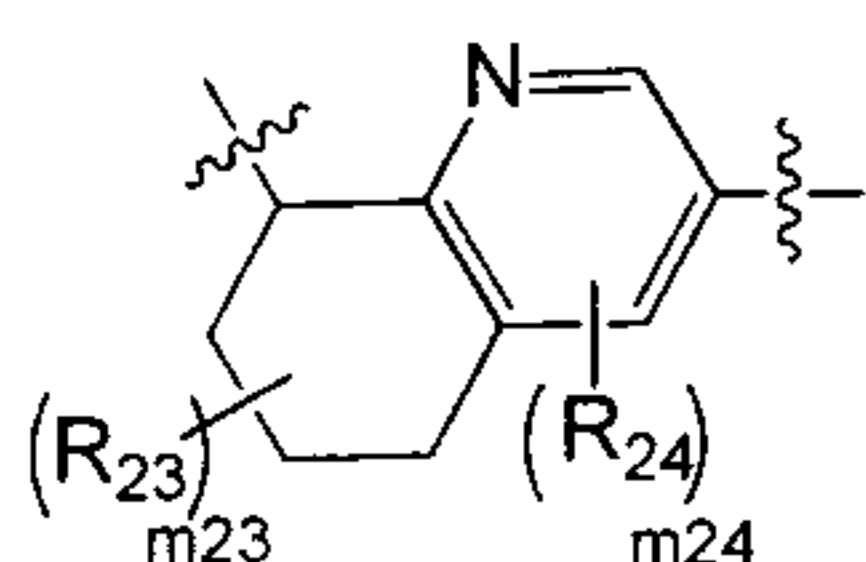
the structural unit



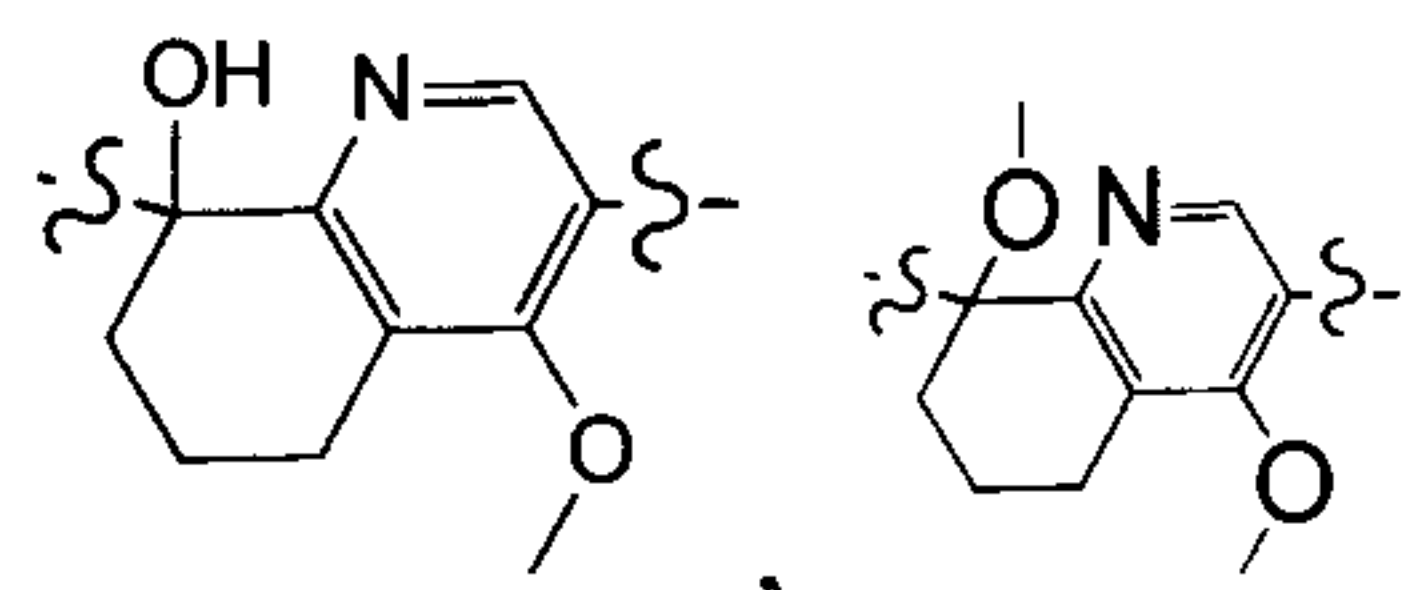
is selected from:



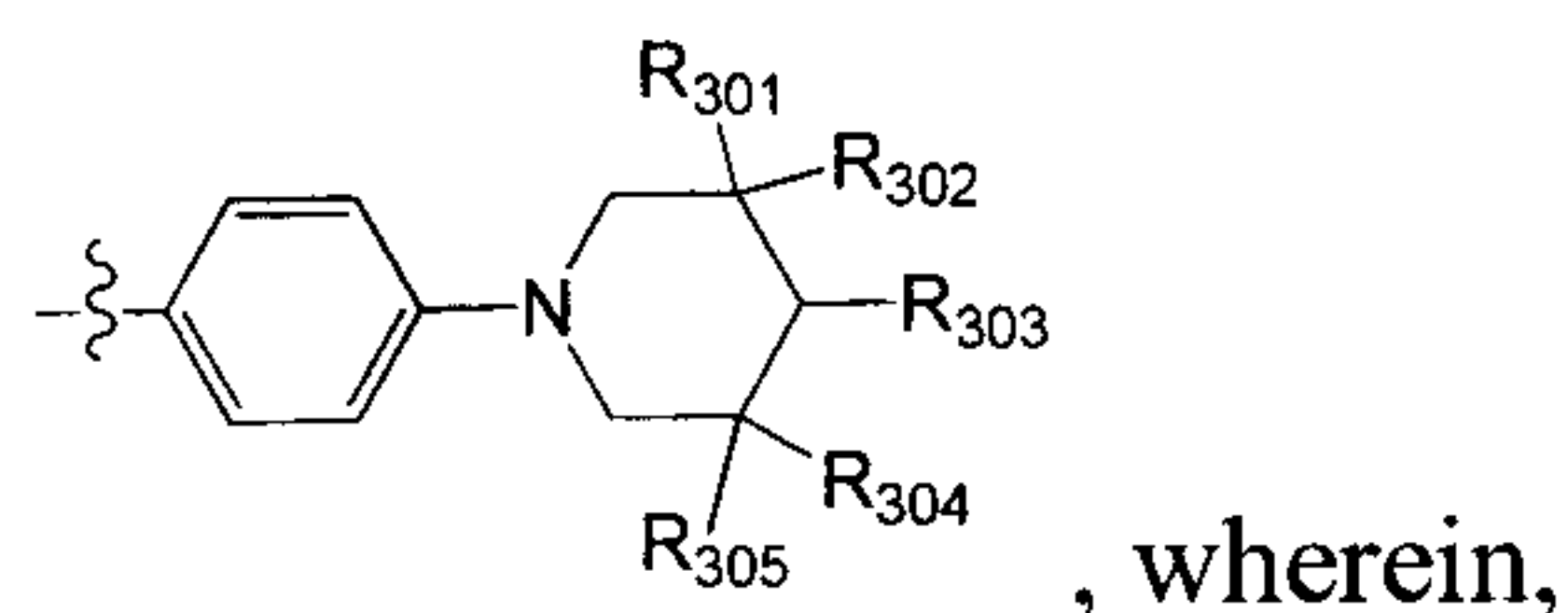
the structural unit



is selected from:



5. The compound represented by formula (I), or the pharmaceutically acceptable salt thereof according to claim 1, wherein B is selected from

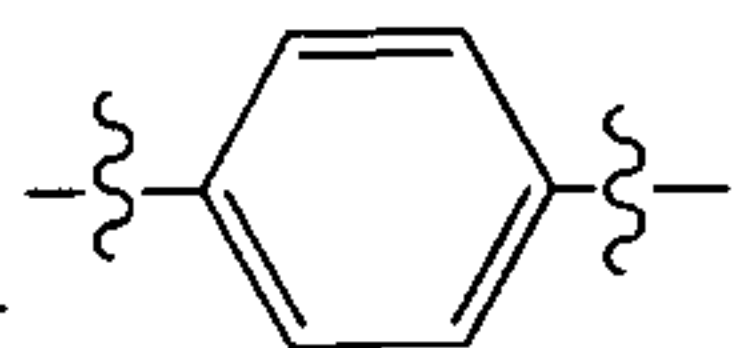


, wherein,

each of $R_{301-305}$ is independently selected from H, OH, NH_2 , F, Cl, Br, I, CN, an optionally R_{3001} -substituted C_{1-3} alkyl or alkoxy or alkyl amino or cyclopropyl;

R_{3001} is selected from OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2 , F, Cl, Br, I, CN, a methyl, a methoxy, the number of R_{3001} is selected from 1, 2 or 3;

or, the structural unit



in the general structure can be replaced by a

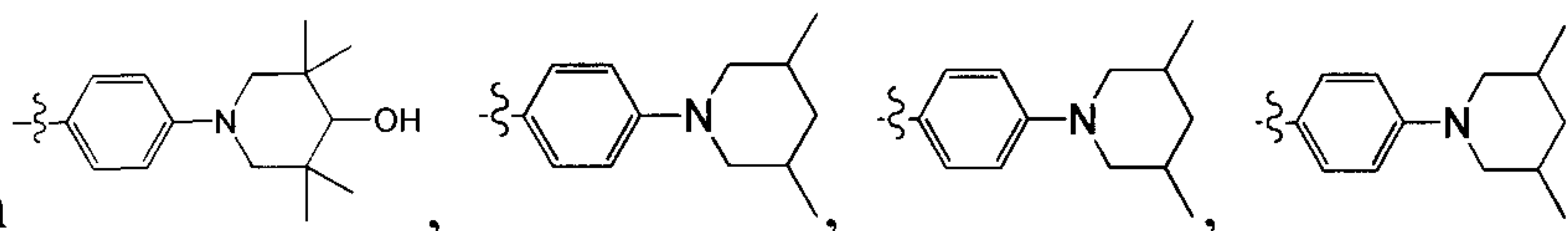
pyridyl, a thienyl, a furyl;

or,

each of $R_{301-305}$ is independently selected from a methyl, H, OH, NH_2 , F, Cl, Br, I, CN;

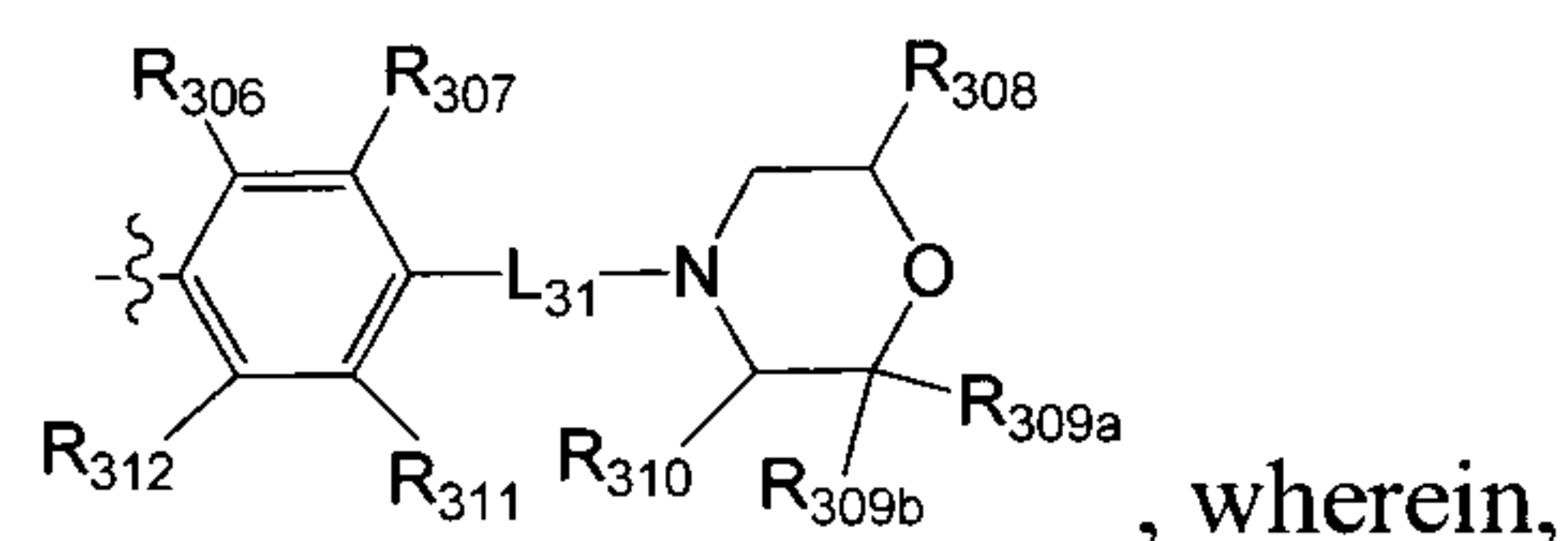
or,

B is selected from



6. The compound represented by formula (I), or the pharmaceutically acceptable salt thereof according to claim 1, wherein, B is selected from

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each of $R_{306-308}$, R_{309a} , R_{309b} , $R_{310-312}$ is independently selected from H, OH, NH_2 , F, Cl, Br, I, CN, an optionally R_{3001} -substituted C_{1-3} alkyl or alkoxy or alkyl amino or cyclopropyl;

R_{3001} is selected from OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2 , F, Cl, Br, I, CN, a methyl, a methoxy, the number of R_{3001} is selected from 1, 2 or 3;

L_{31} is selected from a single bond, $R_{3002}N(R_{3003})R_{3004}$, O, S, $C(=O)O$, $C(=O)$, $C=S$, $S(=O)$ and/or $S(=O)_2$, R_{3002} is selected from a single bond or $C(=O)$;

R_{3003} is selected from H, a C_{1-3} alkyl or a cyclopropyl;

R_{3004} is selected from $(CH_2)_{0-3}$;

or, R_{308} and R_{309a} , R_{308} and R_{310} form a linking bond $(CH_2)_{1-3}$ together;

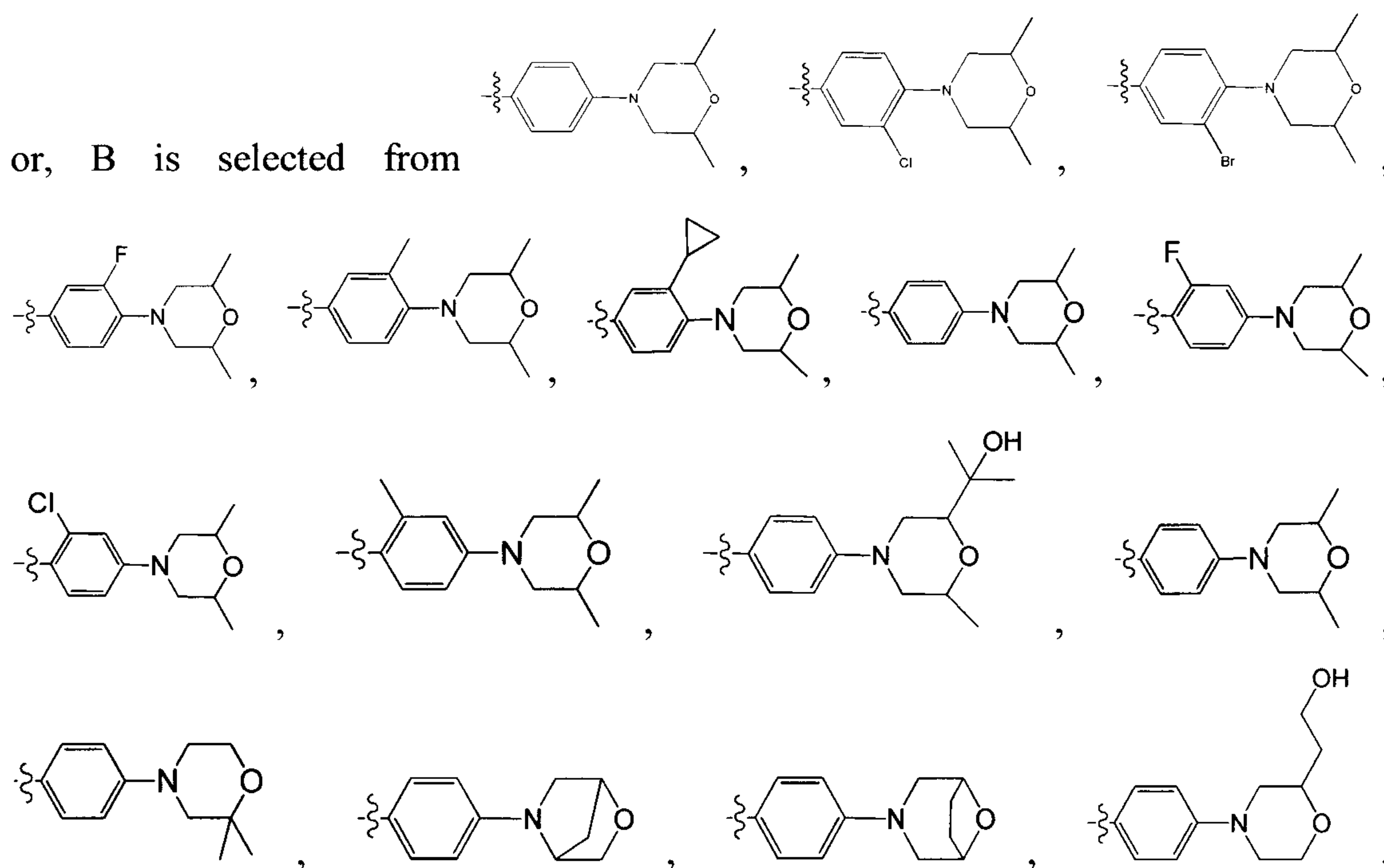
or,

the R_{308} and R_{310} form a linking bond CH_2 together, R_{308} and R_{309a} form a linking bond CH_2CH_2 together;

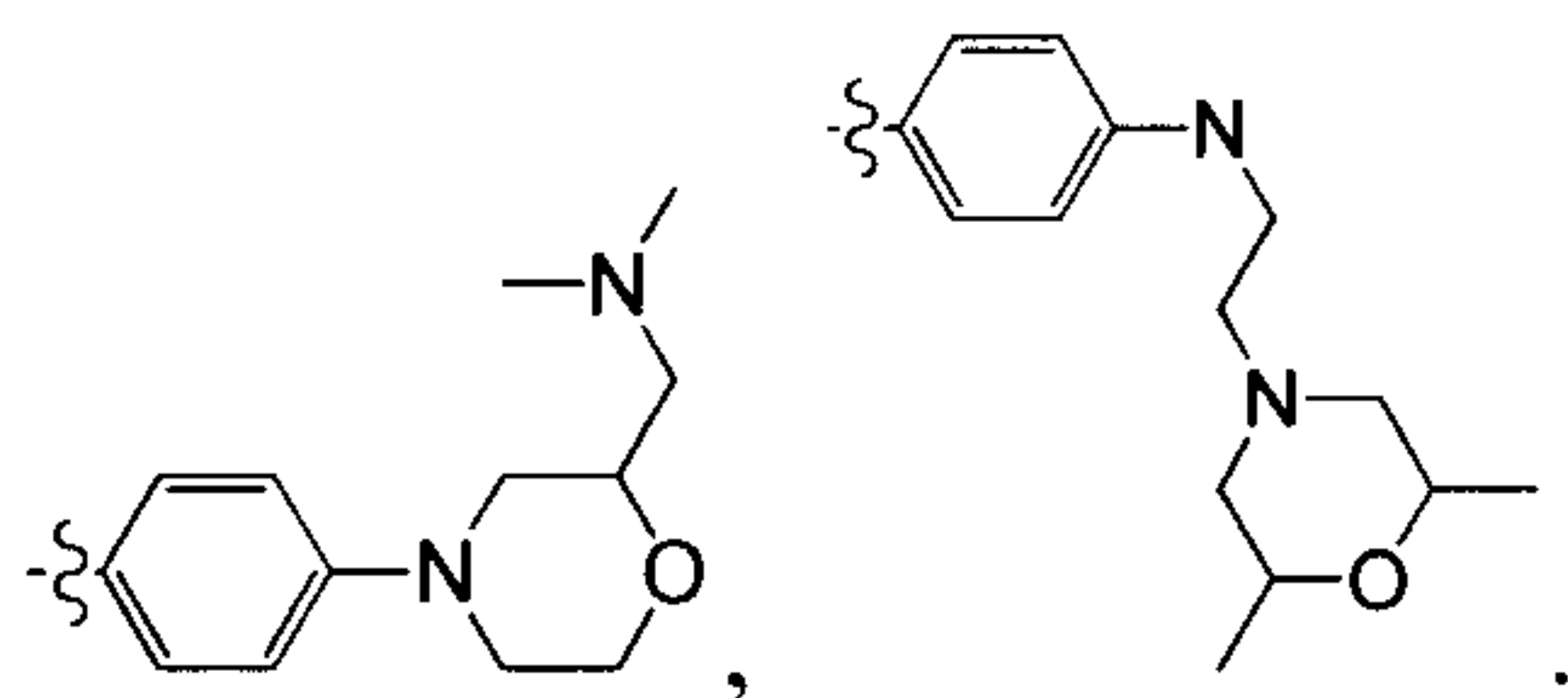
or, each of $R_{306-308}$, R_{309a} , R_{309b} , $R_{310-312}$ is independently selected from a methyl, a cyclopropyl, $C(CH_3)_2(OH)$, CH_2CH_2OH , $CH_2N(CH_3)_2$, H, OH, NH_2 , F, Cl, Br, I, CN;

L_{31} is selected from a single bond, $NHCH_2CH_2$;

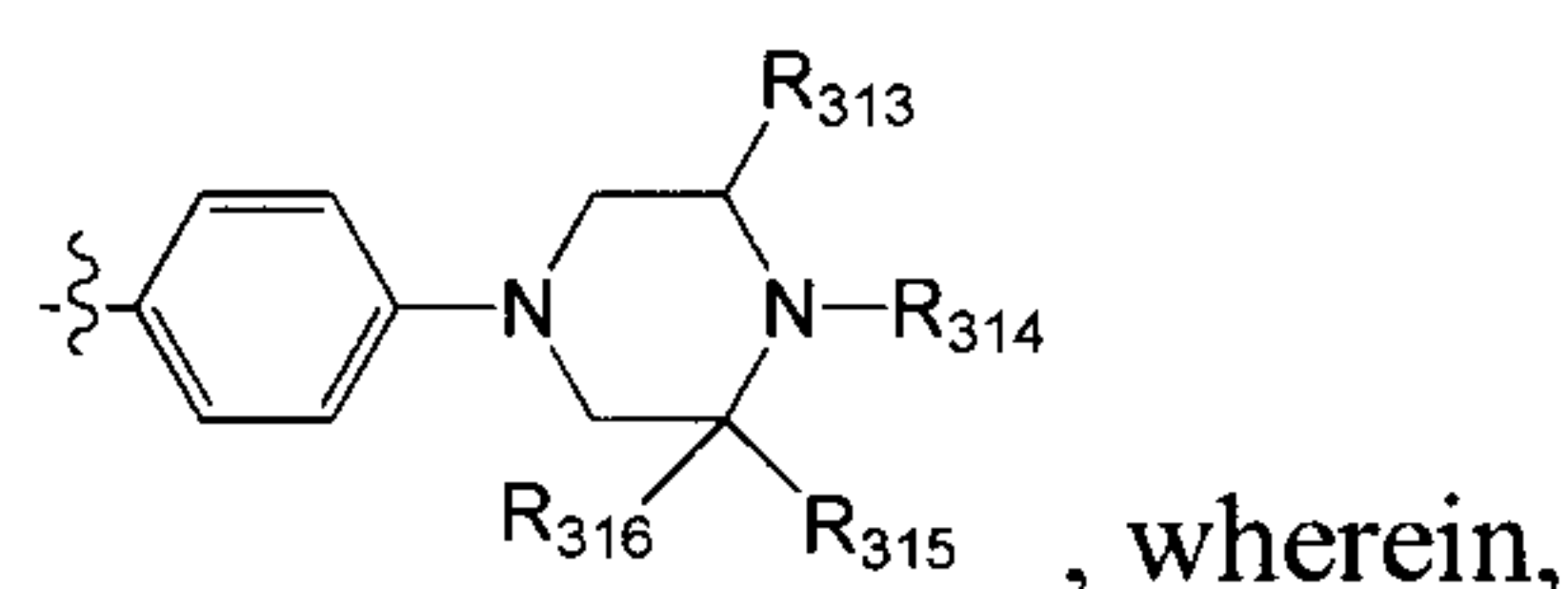
or, B is selected from



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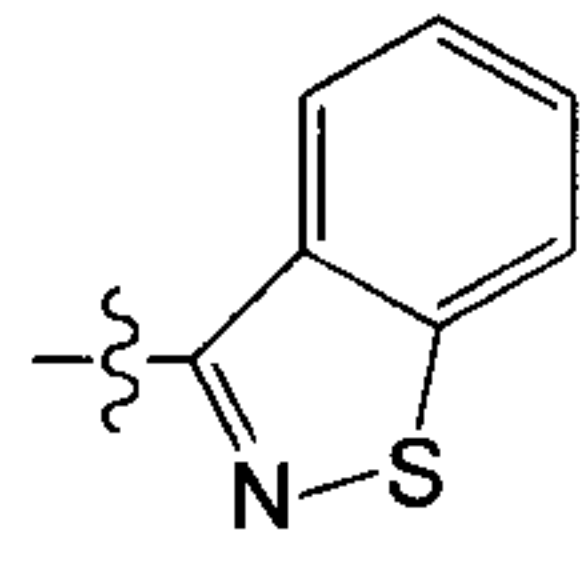


7. The compound represented by formula (I), or the pharmaceutically acceptable salt thereof according to claim 1, wherein, B is selected from



each of R_{313} , R_{315} , R_{316} is independently selected from H, OH, NH_2 , F, Cl, Br, I, CN, an optionally R_{3001} -substituted C_{1-3} alkyl or alkoxy or alkyl amino or cyclopropyl;

R_{314} is selected from H, OH, NH_2 , F, Cl, Br, I, CN, an optionally R_{3001} -substituted C_{1-3}

alkyl or alkoxy or alkyl amino or cyclopropyl, $(CH_2)_{0-3}R_{3005}$, , wherein R_{3005} is optionally substituted by R_{3001} ;

R_{3005} is selected from a C_{3-6} cycloalkyl, a phenyl, a pyridyl, a thienyl, a furyl, an imidazolyl, an oxazolyl, a thiazolyl, an isothiazolyl, each of the above-mentioned group is optionally fused with a benzene ring;

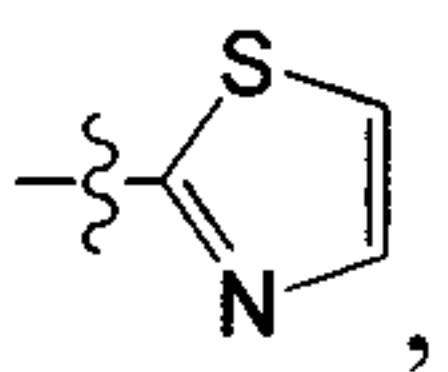
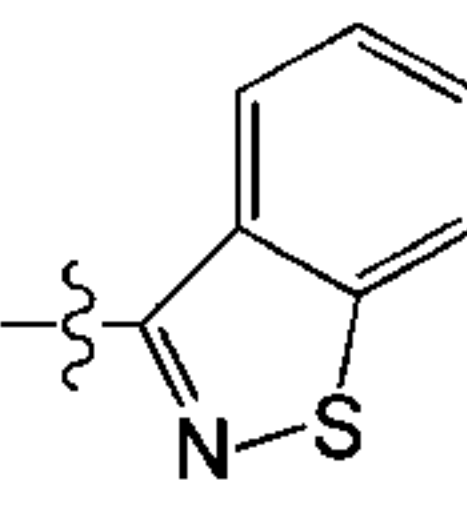
R_{3001} is selected from OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2 , F, Cl, Br, I, CN, a methyl, a methoxy, the number of R_{3001} is selected from 1, 2 or 3;

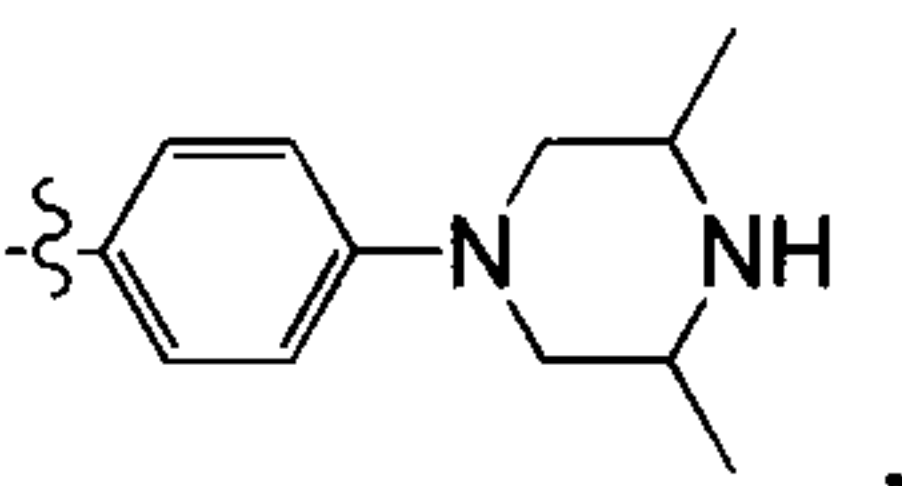
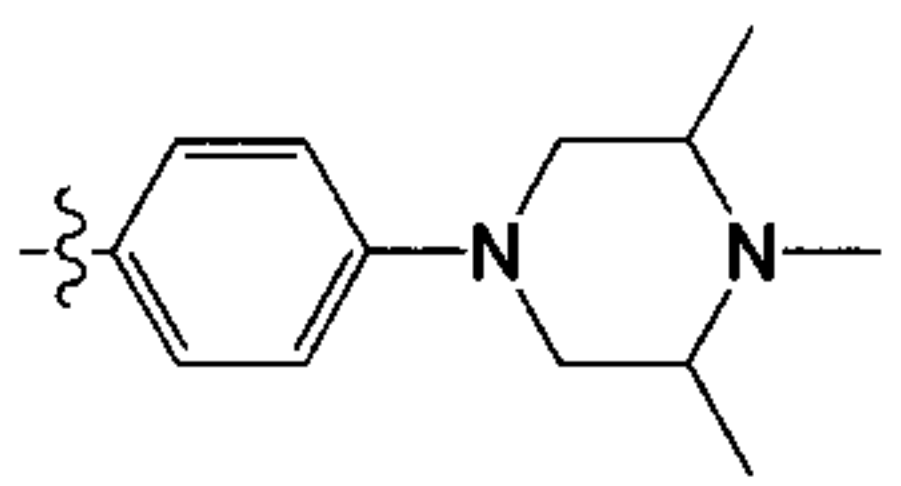
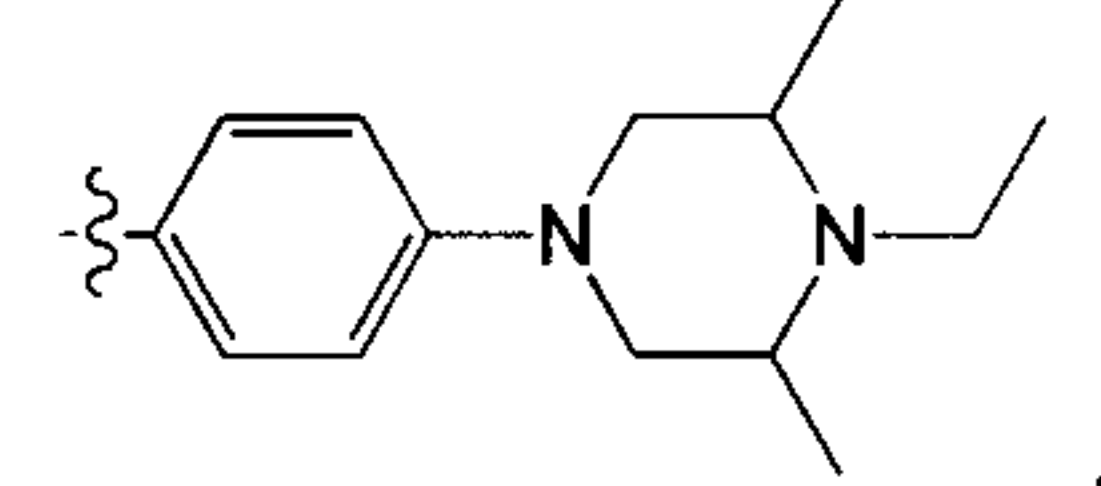
or, the  in the general structure can be replaced by a pyridyl, a thienyl, a furyl, an imidazolyl, an oxazolyl, a thiazolyl, an isothiazolyl;

or,

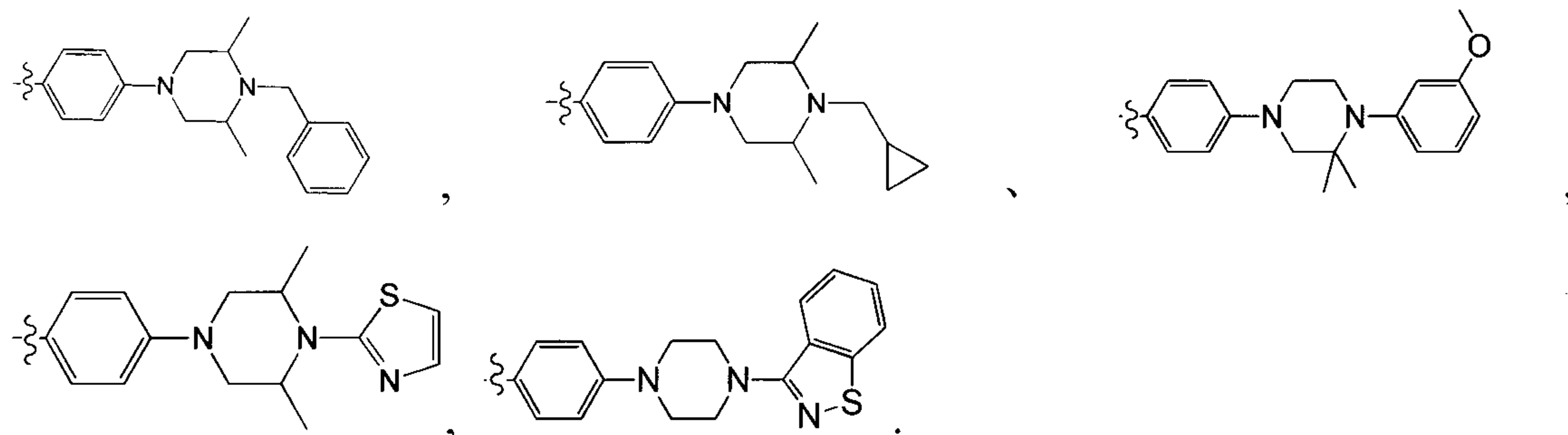
each of R_{313} , R_{315} , R_{316} is independently selected from H, a methyl;

R_{314} is selected from H, a methyl, an ethyl, a phenyl methylene, a cyclopropyl

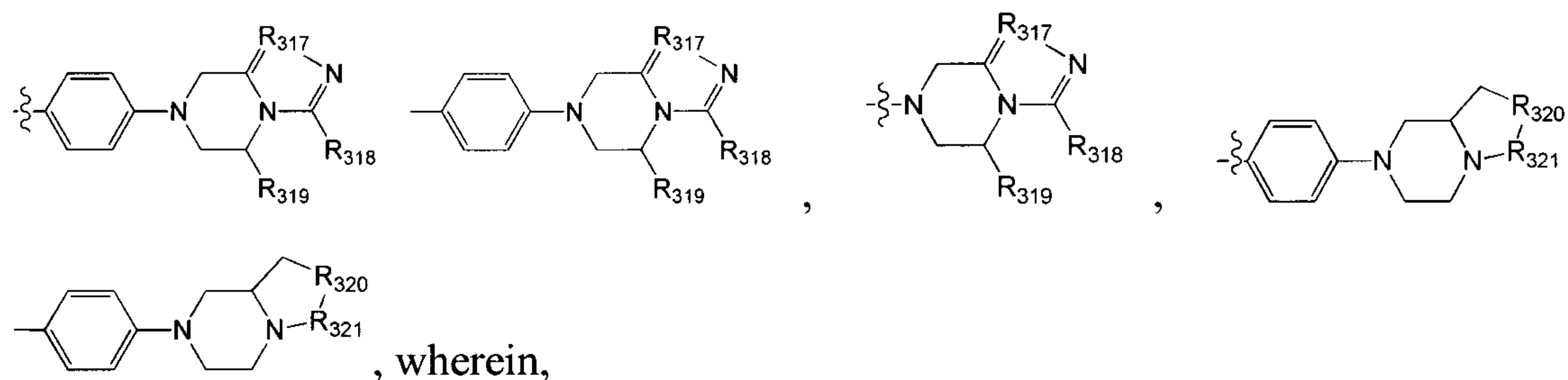
methylene, a methoxyphenyl, ,  ;

or, B is selected from , , ,

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8. The compound represented by formula (I), or the pharmaceutically acceptable salt thereof according to claim 1, wherein B is selected from



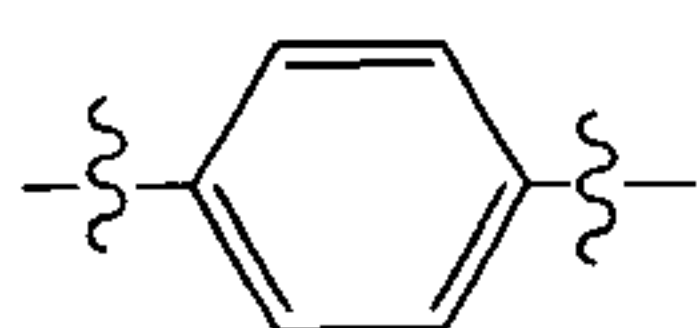
R_{317} is selected from CR_{3006} or N;

each of R_{318} , R_{319} , $R_{3006-3008}$ is independently selected from H, OH, NH_2 , F, Cl, Br, I, CN, an optionally R_{3001} -substituted C_{1-3} alkyl or alkoxy or alkyl amino or cyclopropyl;

each of $R_{320-321}$ is independently selected from $C(R_{3007})(R_{3008})$, O, $CON(R_{3009})$, $N(R_{3010})$, $C=N(R_{3011})$, S, $C(=O)O$, $C(=O)$, $C=S$, $S(=O)$ and/or $S(=O)_2$;

each of $R_{3009-3011}$ is independently selected from H, an optionally R_{3001} -substituted C_{1-3} alkyl or cyclopropyl;

R_{3001} is selected from OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2 , F, Cl, Br, I, CN, a methyl, a methoxyl, the number of R_{3001} is selected from 1, 2 or 3;

or, the  in the general structure can be replaced by a pyridyl, a thienyl, a furyl, an imidazolyl, an oxazolyl, a thiazolyl, an isothiazolyl;

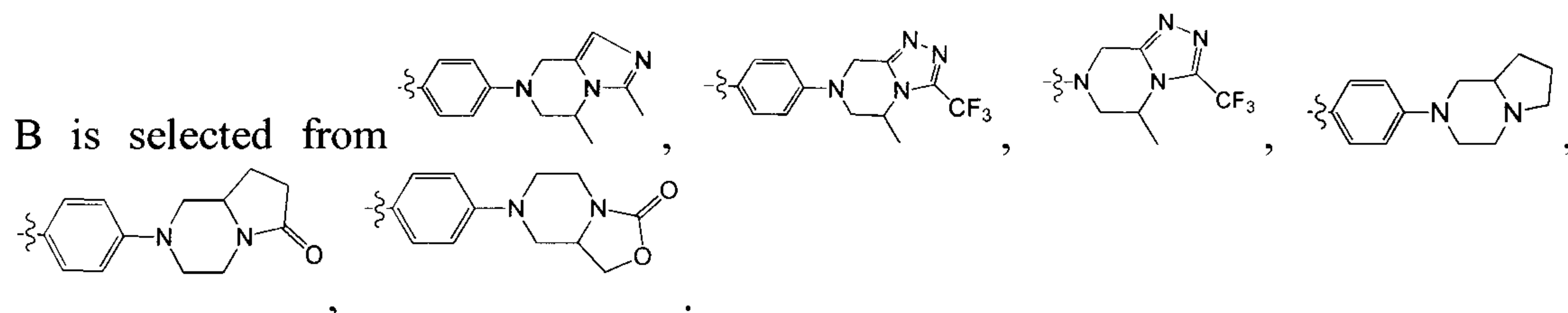
or,

R_{317} is selected from CR_{3006} or N; each of R_{3006} , R_{318} , R_{319} is selected from a methyl, a trifluoromethyl;

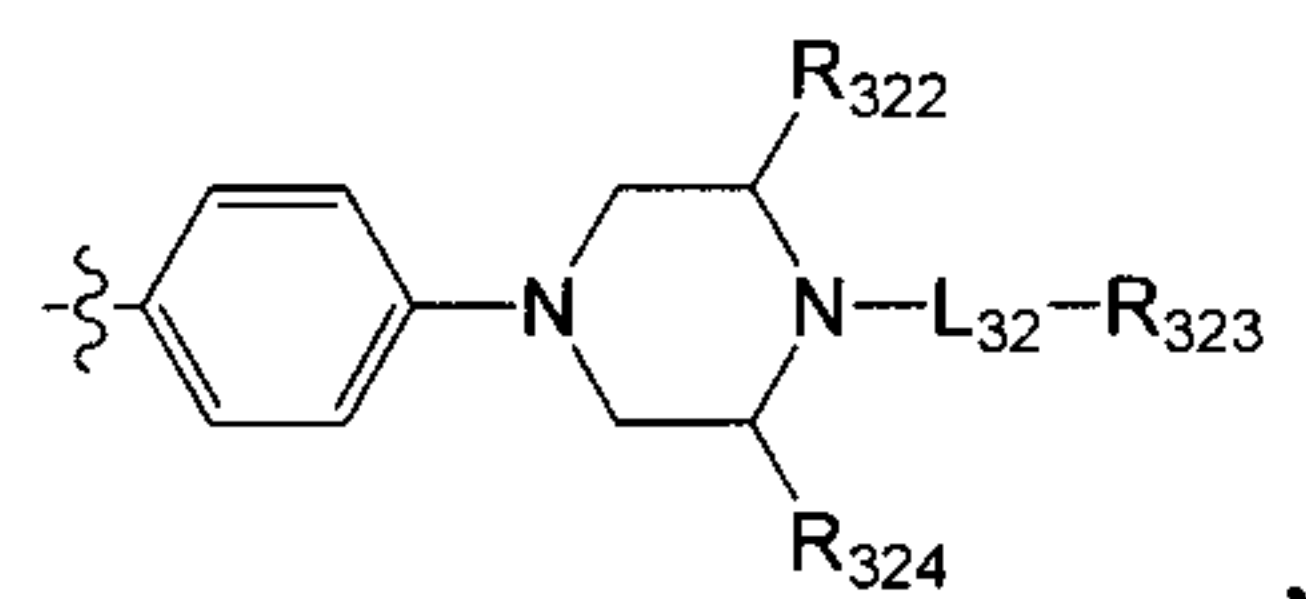
each of $R_{320-321}$ is independently selected from CH_2 , O, $C(=O)$;

or,

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9. The compound represented by formula (I), or the pharmaceutically acceptable salt thereof according to claim 1, wherein B is selected from



wherein,

L_{32} is selected from $C(R_{3007})(R_{3008})$, O, $CON(R_{3009})$, $N(R_{3010})$, $C=N(R_{3011})$, S, $C(=O)O$, $C(=O)$, $C=S$, $S(=O)$ and/or $S(=O)_2$;

R_{323} is selected from a C_{1-6} alkyl, a C_{3-6} cycloalkyl, a phenyl, a pyridyl, an imidazolyl, a thienyl, a furyl, an oxazolyl, a thiazolyl, an isothiazolyl, each of the above-mentioned group is optionally substituted by R_{3012} ;

each of R_{322} , R_{324} , R_{3007} , R_{3008} , R_{3012} is independently selected from H, OH, NH_2 , F, Cl, Br, I, CN, an optionally R_{3001} -substituted C_{1-3} alkyl or alkoxy or alkyl amino or cyclopropyl;

each of $R_{3009-3011}$ is independently selected from H, an optionally R_{3001} -substituted C_{1-3} alkyl or cyclopropyl;

R_{3001} is selected from OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2 , F, Cl, Br, I, CN, a methyl, a methoxy;

the number of each of R_{3001} , R_{3012} is selected from 1, 2 or 3;

or, the  in the general structure can be replaced by a pyridyl, a thienyl, a furyl, an imidazolyl, an oxazolyl, a thiazolyl, an isothiazolyl;

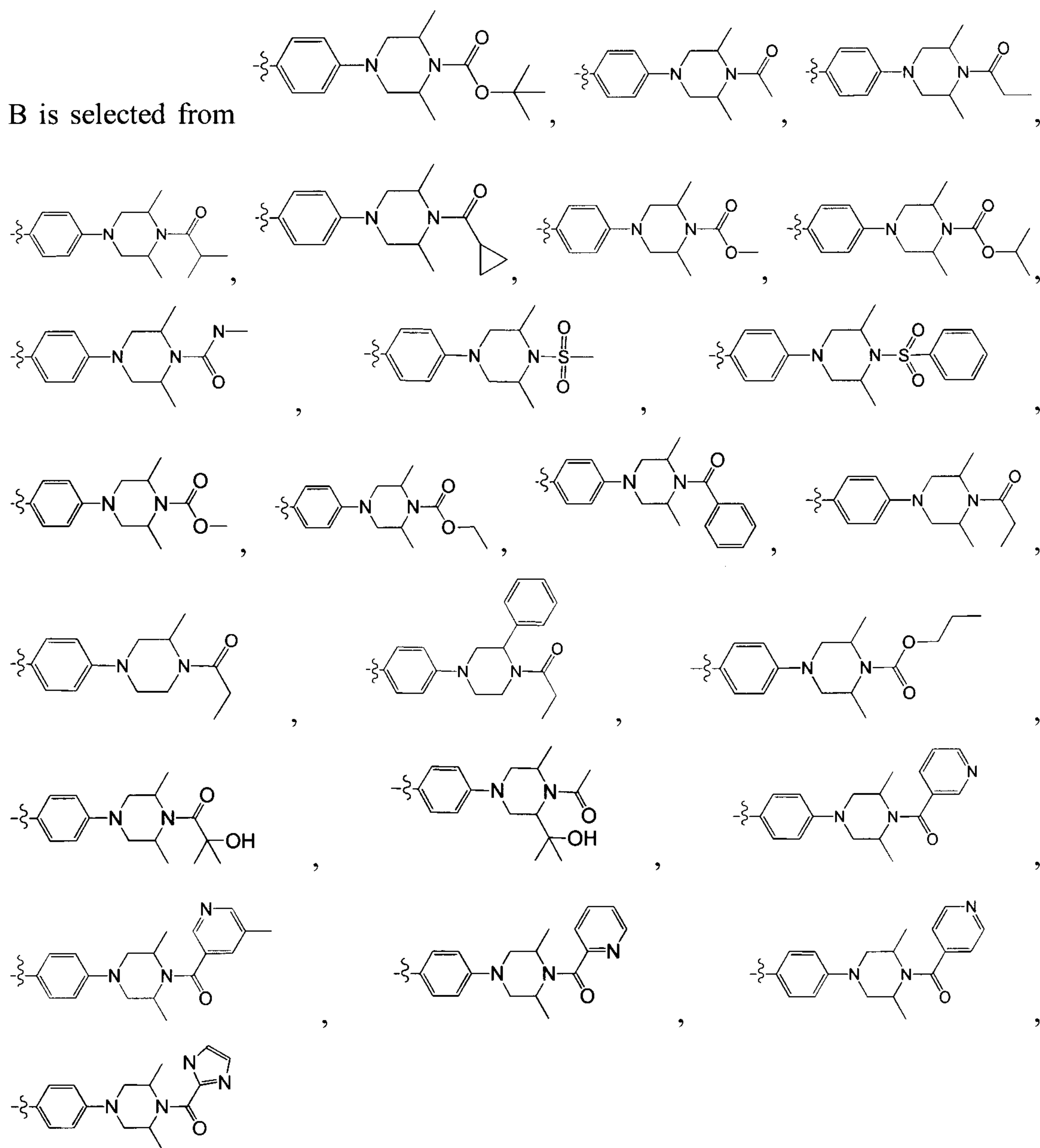
or,

each of R_{322} , R_{324} is independently selected from H, a methyl, a phenyl, $C(CH_3)_2OH$;

L_{32} is selected from $C(=O)$, $S(=O)_2$;

or, R_{323} is selected from a *tert*-butoxy, a methyl, a methoxy, an ethyl, an ethoxy, an propoxy, an isopropyl, a *n*-propyl, an isopropoxy, a cyclopropyl, a methylamino, a phenyl, a pyridyl, a 3-methyl pyridyl, an imidazolyl, $C(CH_3)_2OH$;

B is selected from



The structure shows a benzene ring with substituents R_{325} , R_{326} , R_{328} , and R_{327} . The benzene ring is connected to a piperidine ring at the nitrogen atom. The piperidine ring has substituents R_{330} , R_{329} , and R_{331} .

R₃₂₉ is selected from N(R₃₀₁₄), O, C(R₃₀₁₅)(R₃₀₁₆), CON(R₃₀₁₇), N(R₃₀₁₈), C=N (R₃₀₁₉),

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S, C(=O)O, C(=O), C=S, S(=O) and/or S(=O)₂;

R₃₀₁₄ is selected from C(=O)R₃₀₂₀, S(=O)₂R₃₀₂₀, a thiazolyl, an isothiazolyl, a phenyl, a pyridyl, an imidazolyl, a thienyl, a furyl, an oxazolyl

R₃₀₂₀ is selected from an optionally R₃₀₀₁-substituted C₁₋₃ alkyl or alkoxy;

each of R₃₀₁₃, R₃₀₁₅, R₃₀₁₆, R₃₃₀₋₃₃₁ is independently selected from H, OH, NH₂, F, Cl, Br, I, CN, C(=O)OH, an optionally R₃₀₀₁-substituted C₁₋₃ alkyl or alkoxy or alkyl amino or cyclopropyl;

each of R₃₀₁₇₋₃₀₁₉ is independently selected from H, an optionally R₃₀₀₁-substituted C₁₋₃ alkyl or cyclopropyl;

R₃₀₀₁ is selected from OH, N(CH₃)₂, NH(CH₃), NH₂, F, Cl, Br, I, CN, a methyl, a methoxy, the number of R₃₀₀₁ is selected from 1, 2 or 3;

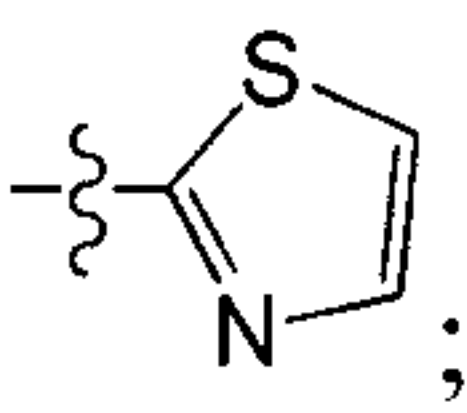
or, R₃₃₀ and R₃₃₁ form a linking bond (CH₂)₁₋₃ together;

or, when R₃₂₉ is selected from N(R₃₀₁₄) or O, R₃₃₀ and R₃₃₁ present a *cis*-arrangement; when R₃₂₉ is selected from C(R₃₀₁₅)(R₃₀₁₆), R₃₃₀ and R₃₃₁ present a *trans*-arrangement;

or,

one or two of R₃₂₅₋₃₂₈ is selected from N, the rest are selected from CH, CC(=O)OH or CCH₃;

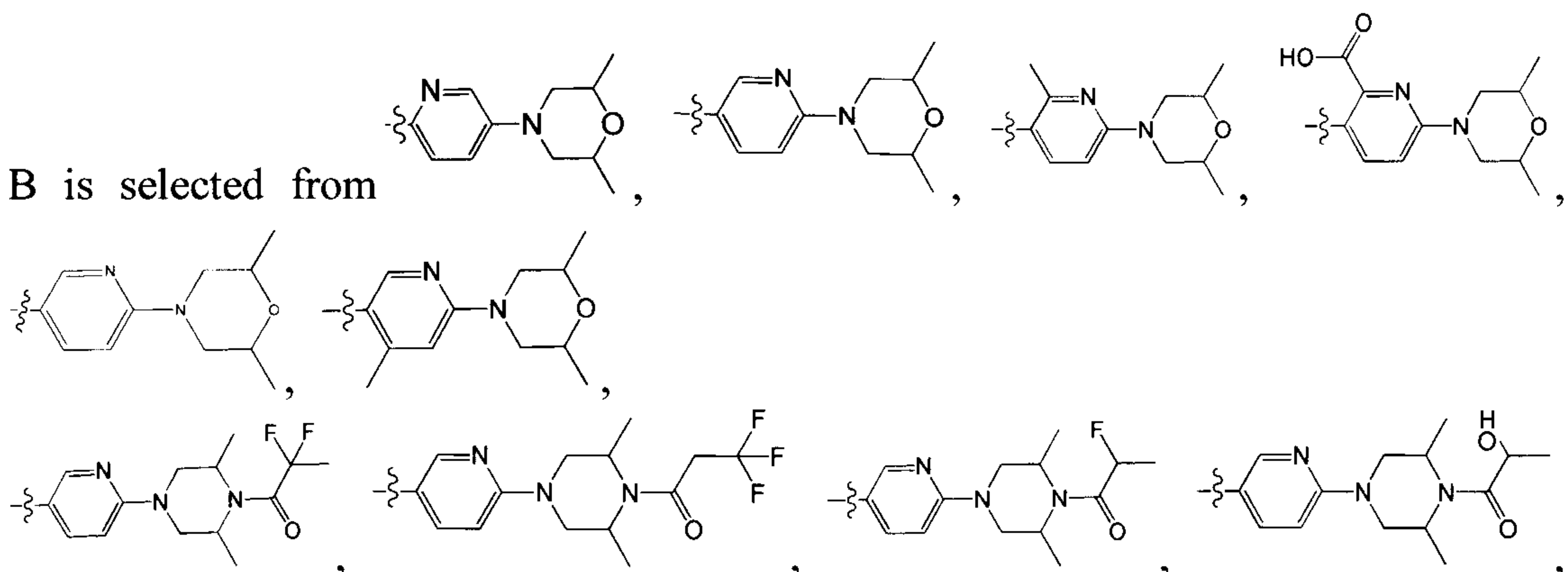
R₃₂₉ is selected from N(R₃₀₁₄), O;

R₃₀₁₄ is selected from C(=O)R₃₀₂₀, ;

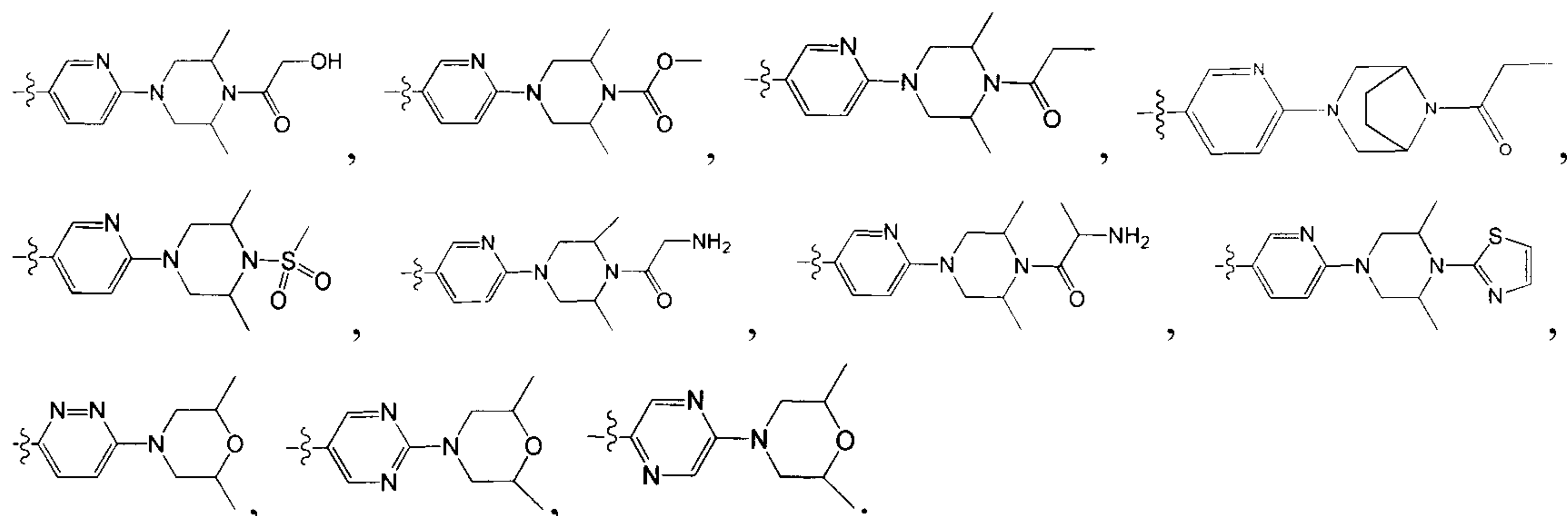
R₃₀₂₀ is selected from C(CH₃)(F)₂, CH₃, CF₃, CH₂CH₃, CH₂CF₃, CH(F)(CH₃), CH(OH)(CH₃), CH₂(OH), CH(NH₂)(CH₃), a methoxy, an ethoxy, an amino methyl;

R₃₃₀₋₃₃₁ is selected from a methyl;

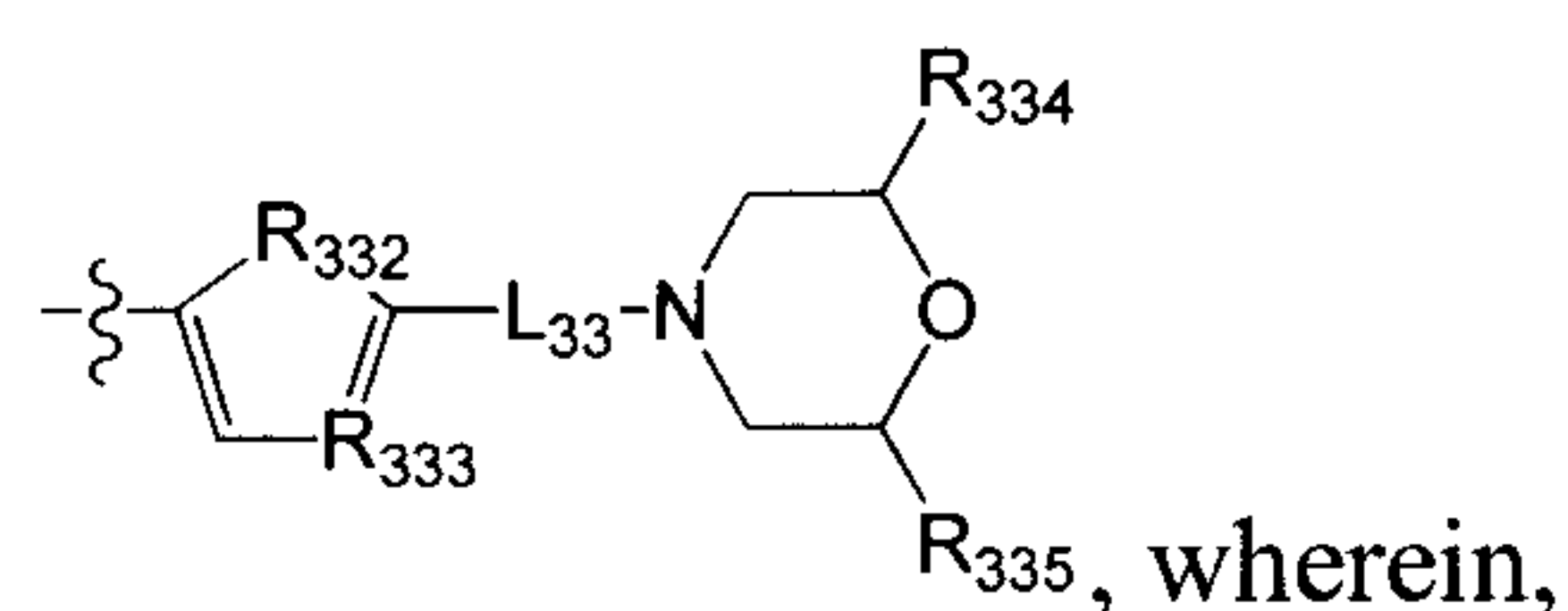
or,



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11. The compound represented by formula (I), or the pharmaceutically acceptable salt thereof according to claim 1, wherein B is selected from



R₃₃₂ is selected from S, N(R₃₀₂₁), O, C(R₃₀₂₂)(R₃₀₂₃), CON(R₃₀₂₄), N(R₃₀₂₅), C=N(R₃₀₂₆), S, C(=O)O, C(=O), C=S, S(=O) and/or S(=O)₂;

L₃₃ is selected from a single bond, C(=O), S, O, C(R₃₀₂₂)(R₃₀₂₃), CON(R₃₀₂₄), N(R₃₀₂₅), C=N(R₃₀₂₆), S, C(=O)O, C=S, S(=O) and/or S(=O)₂;

R₃₃₃ is selected from N, C(R₃₀₂₇);

each of R₃₀₂₇, R₃₃₄, R₃₃₅, R₃₀₂₂, R₃₀₂₃ is independently selected from H, OH, NH₂, F, Cl, Br, I, CN, an optionally R₃₀₀₁-substituted C₁₋₃ alkyl or alkoxy or alkyl amino or cyclopropyl;

each of R₃₀₂₁, R₃₀₂₄₋₃₀₂₆ is independently selected from H, an optionally R₃₀₀₁-substituted C₁₋₃ alkyl or cyclopropyl;

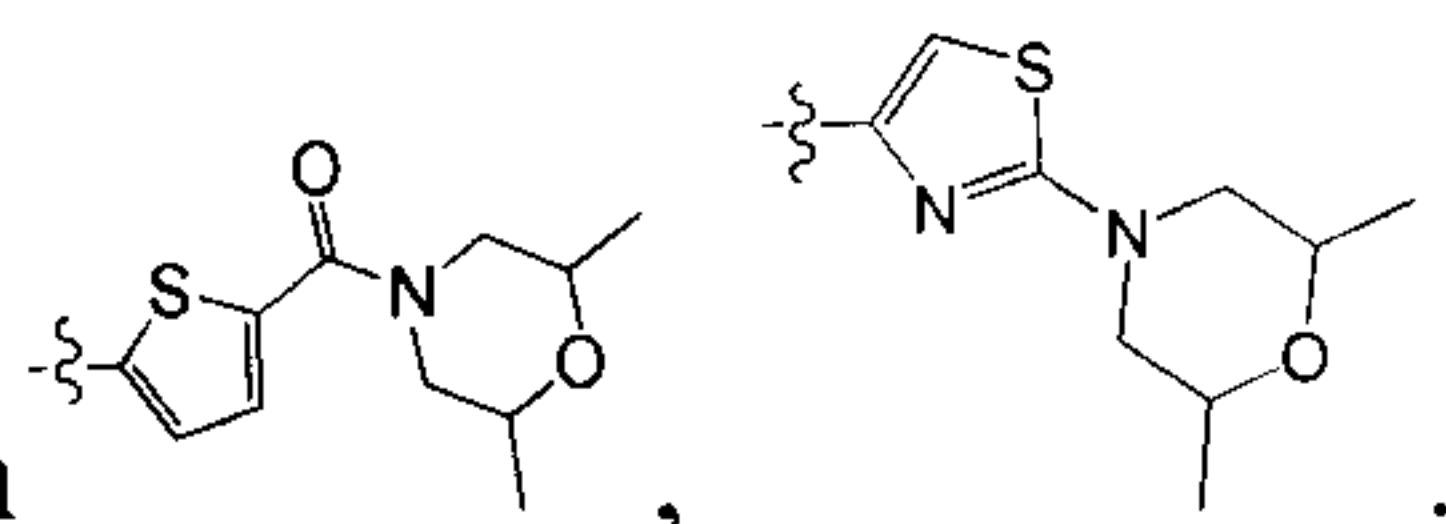
R₃₀₀₁ is selected from OH, N(CH₃)₂, NH(CH₃), NH₂, F, Cl, Br, I, CN, a methyl, a methoxy, the number of R₃₀₀₁ is selected from 1, 2 or 3;

or,

R₃₃₂ is selected from S, R₃₃₃ is selected from N or CH, L₃₃ is selected from a single bond, C(=O), each of R₃₃₄, R₃₃₅ is selected from a methyl;

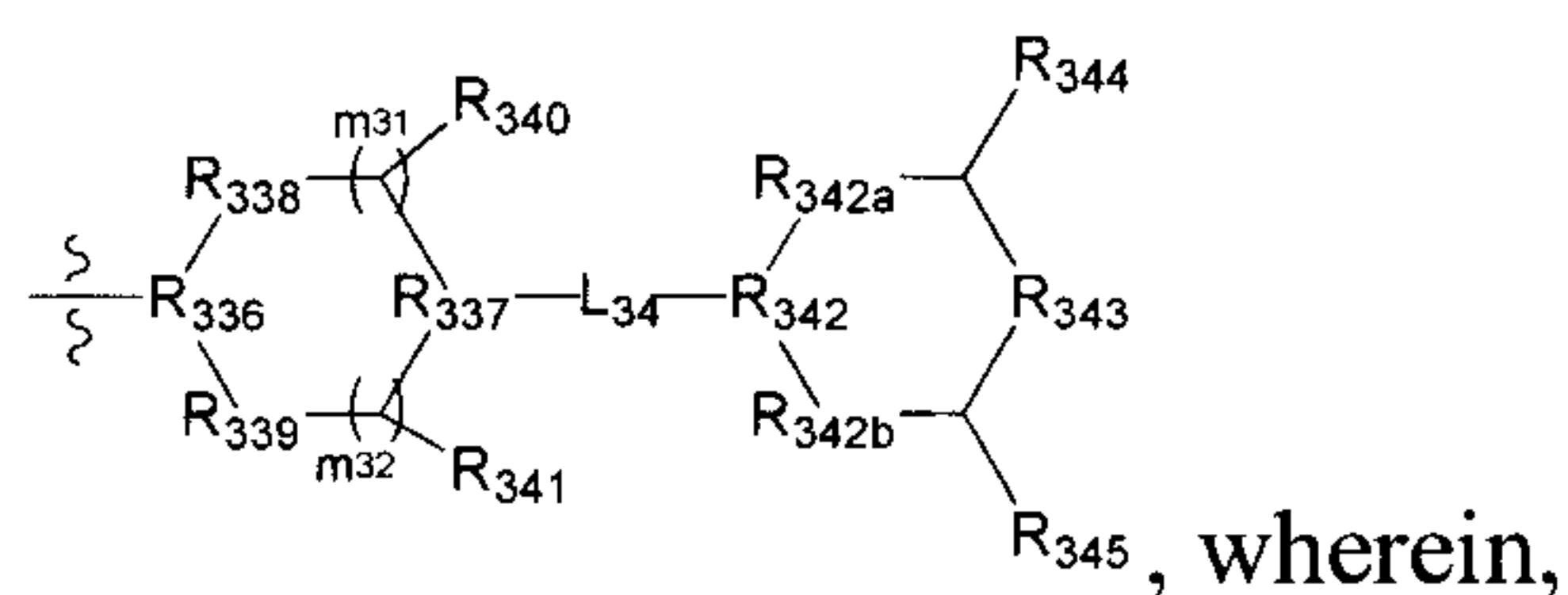
or,

B is selected from



12. The compound represented by formula (I), or the pharmaceutically acceptable salt thereof according to claim 1, wherein B is selected from

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each of R_{336} , R_{337} , R_{342} is independently selected from N or $C(R_{3028})$;

each of R_{338} , R_{339} is selected from $C(R_{3029})$ (R_{3030}), or R_{338} and R_{339} connect to the same $(CH_2)_{1-3}$ together to form a ring;

each of m_{31} , m_{32} is independently selected from 0 or 1;

each of R_{342a} , R_{342b} , R_{343} , L_{34} is independently selected from a single bond, $C(=O)N(R_{3031})$, $C(=O)C(R_{3032})(R_{3033})$, $C(R_{3034})(R_{3035})$, $CON(R_{3036})$, $N(R_{3037})$, $C=N(R_{3038})$, O, S, $C(=O)O$, $C(=O)$, $C=S$, $S(=O)$ and/or $S(=O)_2$;

L_{34} can also be selected from a single bond;

each of R_{340} , R_{341} , R_{344} , R_{345} , R_{3028} , R_{3029} , R_{3030} , $R_{3032-3035}$ is independently selected from H, OH, NH_2 , F, Cl, Br, I, CN, an optionally R_{3001} -substituted C_{1-3} alkyl or alkoxy or alkyl amino or cyclopropyl;

each of R_{3031} , $R_{3036-3038}$ is independently selected from H, an optionally R_{3001} -substituted C_{1-3} alkyl or cyclopropyl;

R_{3001} is selected from OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2 , F, Cl, Br, I, CN, a methyl, a methoxy, the number of R_{3001} is selected from 1, 2 or 3;

or,

each of R_{336} , R_{337} , R_{342} is independently selected from N or CH;

each of R_{338} , R_{339} is independently selected from CH_2 , or R_{338} and R_{339} connect to the same CH_2CH_2 together to form a ring;

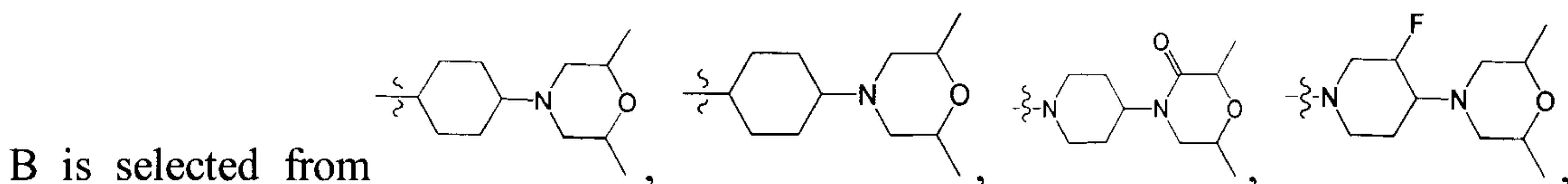
each of m_{31} , m_{32} is independently selected from 0 or 1;

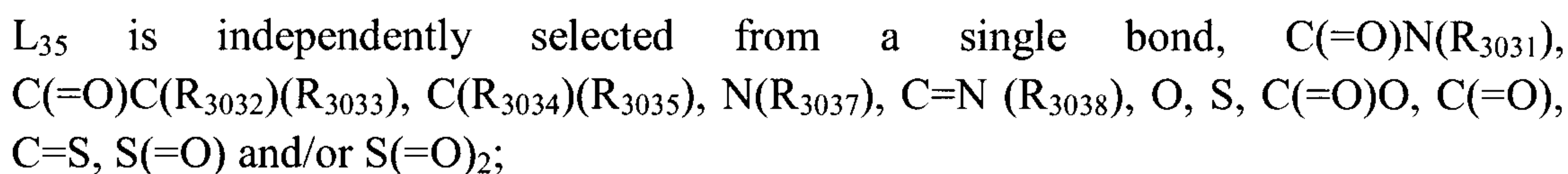
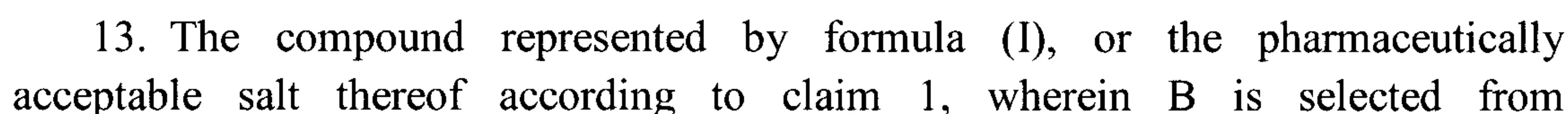
L_{34} is independently selected from a single bond, $C(=O)NH$, $C(=O)N(CH_3)$, $C(=O)CH_2$;

each of R_{340} , R_{341} , R_{344} , R_{345} is independently selected from H or a methyl;

each of R_{342a} , R_{342b} is independently selected from $C(=O)$ or CH_2 ;

or,





each of R₃₄₆, R_{346a}, R_{346b} is independently selected from H, an optionally R₃₀₀₁-substituted C₁₋₃ alkyl or alkoxy or alkyl acyl or alkyl sulfonyl or alkyl amino or cyclopropyl, an optionally R₃₀₀₁-substituted cyclopropyl acyl or cyclopropyl sulfonyl;

R₃₄₆ can also be selected from a phenyl, a pyridyl, an imidazolyl, a thienyl, a furyl, an oxazolyl, a thiazolyl, an isothiazolyl, a pyrrolidyl, a 2-pyridonyl;

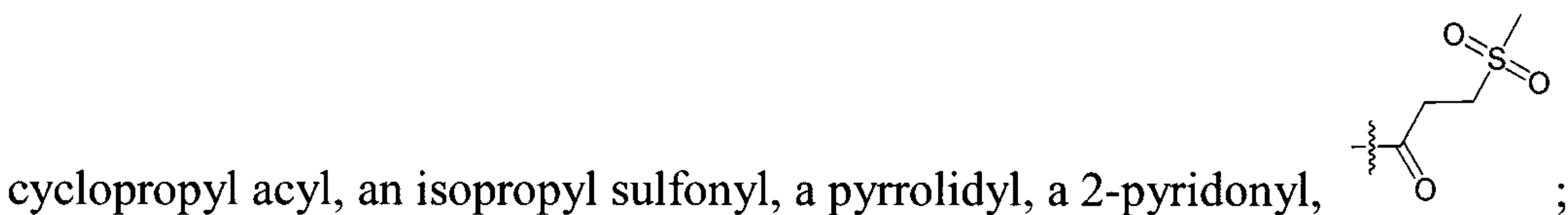
each of R₃₀₃₁, R₃₀₃₇, R₃₀₃₈ is independently selected from H, an optionally R₃₀₀₁-substituted C₁₋₃ alkyl or cyclopropyl;

R₃₀₀₁ is selected from OH, N(CH₃)₂, NH(CH₃), NH₂, F, Cl, Br, I, CN, -S(=O)CH₃, -S(=O)₂CH₃, a methyl, a methoxy, the number of R₃₀₀₁ is selected from 1, 2 or 3;

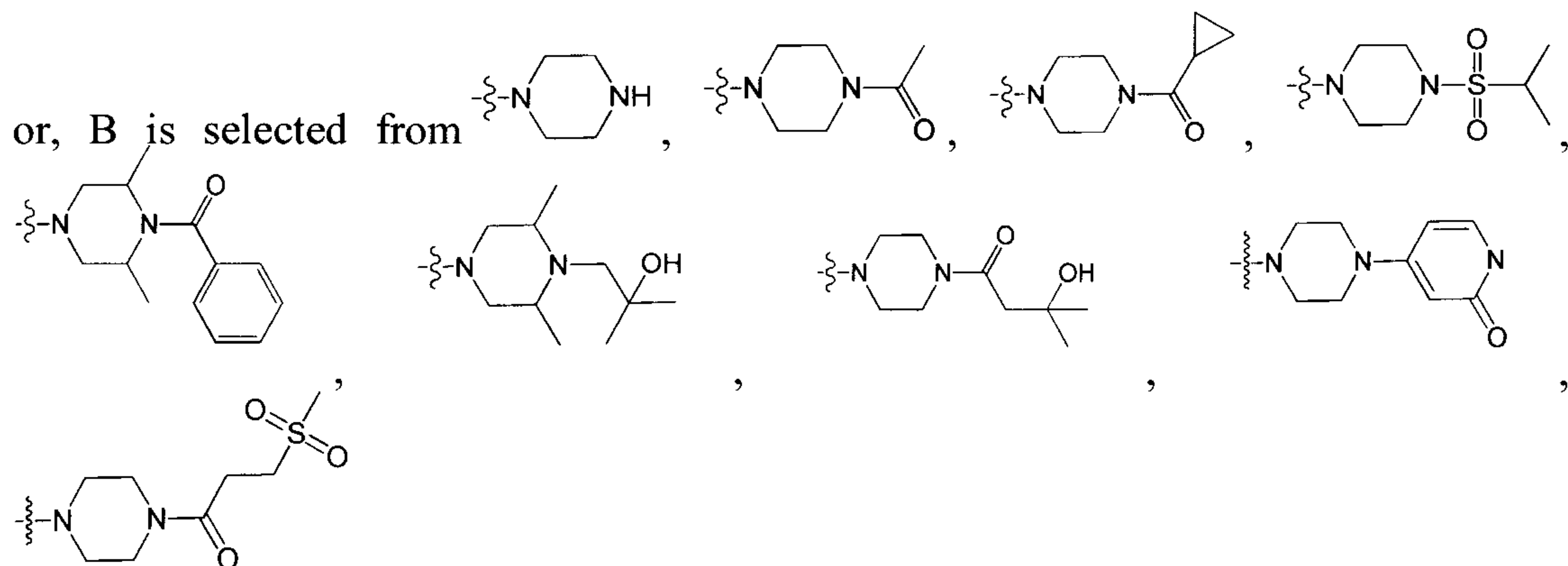
or,

L₃₅ is selected from a single bond, C(=O), CH₂;

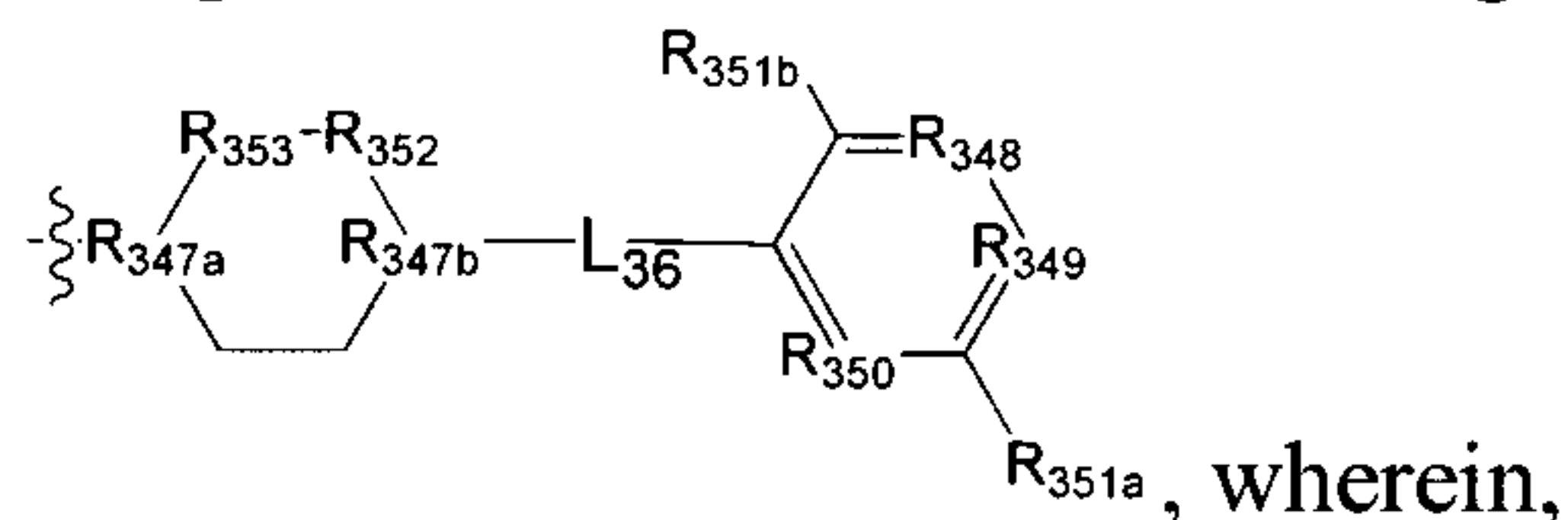
or, R₃₄₆ is selected from H, a methyl, a phenyl, C(CH₃)₂(OH), CH₂C(CH₃)₂(OH), a



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14. The compound represented by formula (I), or the pharmaceutically acceptable salt thereof according to claim 1, wherein B is selected from



each of R_{347a} , R_{347b} is independently selected from N or $C(R_{3028})$;

none, one or two of $R_{348-350}$ is selected from N, the rest are selected from $C(R_{3039})$;

each of R_{352} , R_{353} , L_{36} is independently selected from a single bond, $-C(=O)N(R_{3031})-$, $-C(=O)C(R_{3032})(R_{3033})-$, $C(R_{3034})(R_{3035})$, $CON(R_{3036})$, $N(R_{3037})$, $C=N(R_{3038})$, O, S, $C(=O)O$, $C(=O)$, $C=S$, $S(=O)$ and /or $S(=O)_2$;

L_{36} can also be selected from a single bond;

each of R_{3028} , $R_{3032-3035}$, R_{3039} , R_{351a} , R_{351b} is independently selected from H, OH, NH_2 , F, Cl, Br, I, CN, an optionally R_{3001} -substituted C_{1-3} alkyl or alkoxy or alkyl amino or cyclopropyl;

each of R_{3031} , $R_{3036-3038}$ is independently selected from H, an optionally R_{3001} -substituted C_{1-3} alkyl or cyclopropyl;

R_{3001} is selected from OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2 , F, Cl, Br, I, CN, a methyl, a methoxy, the number of R_{3001} is selected from 1, 2 or 3;

or,

L_{36} is selected from a single bond, $C(=O)NH$, $C(=O)CH_2$;

each of R_{347a} , R_{347b} is independently selected from N, CH or $C(OH)$;

none, one or two of $R_{348-350}$ is selected from N, the rest are selected from $C(R_{3039})$;

R_{3039} is selected from H, a methyl, a trifluoromethyl, $C(CH_3)_2(OH)$;

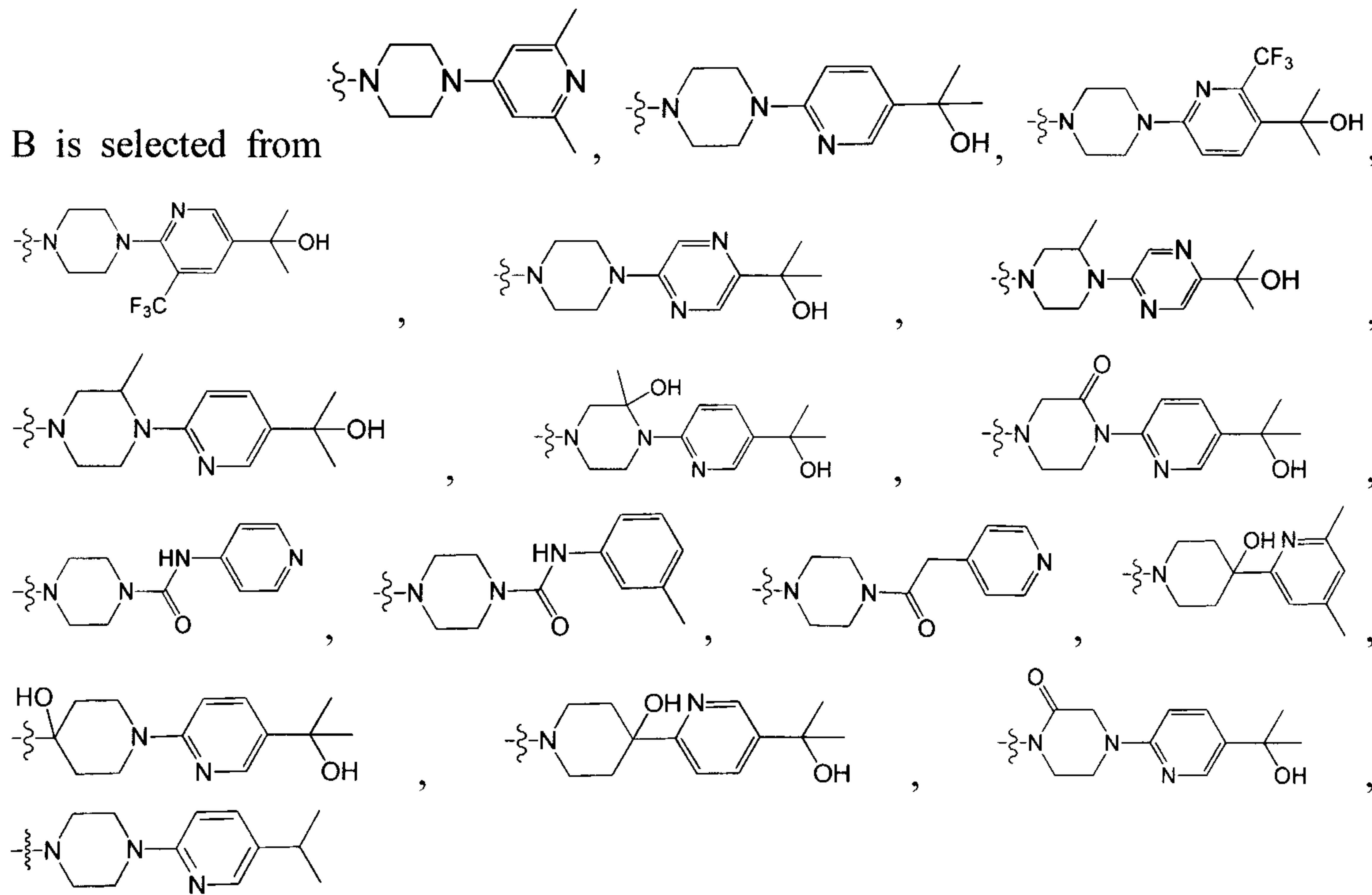
each of R_{351a} , R_{351b} is independently selected from H, a methyl, a trifluoromethyl, an

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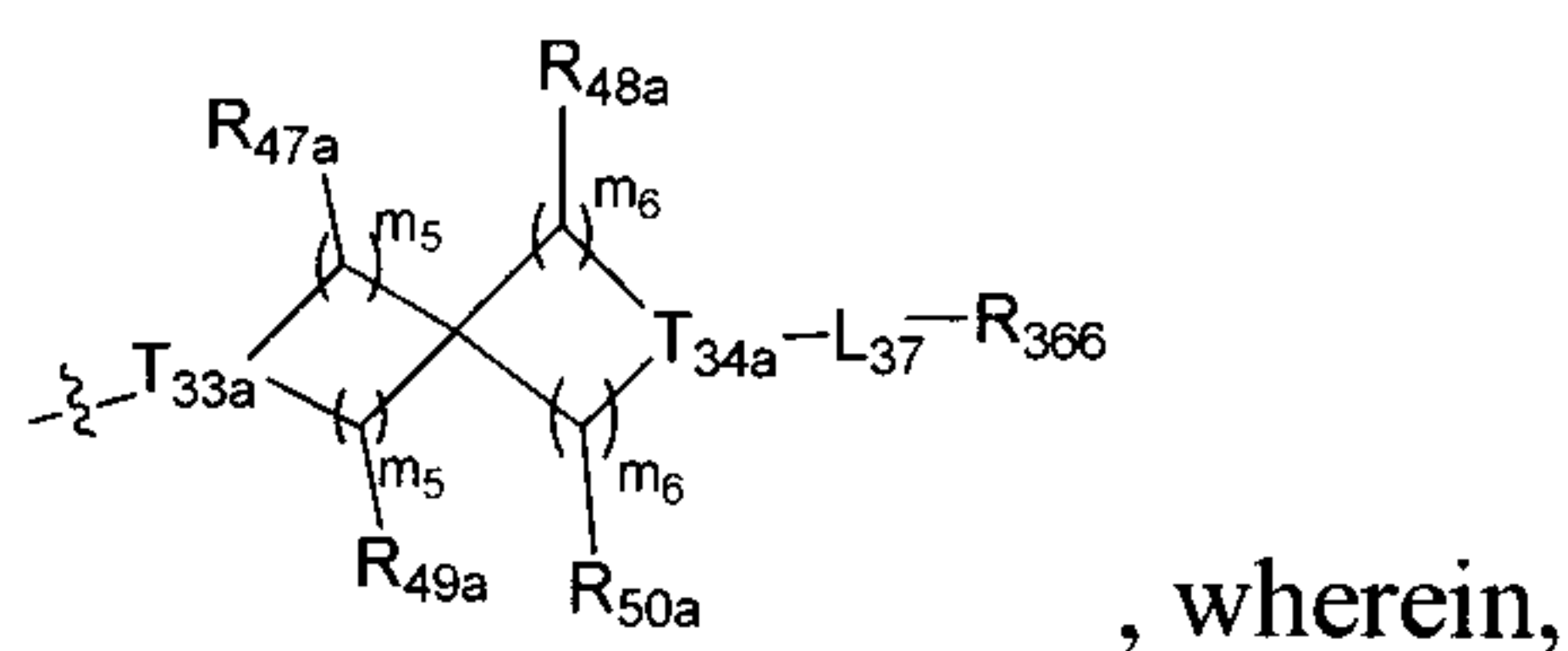
isopropyl;

each R_{352} , R_{353} is independently selected from $C(=O)$, $C(CH_3)(OH)$;

or,



15. The compound represented by formula (I), or the pharmaceutically acceptable salt thereof according to claim 1, wherein B is selected from



each of T_{33a} , T_{34a} is independently selected from N, CH or $C(R_{4001})$

L_{37} is independently selected from a single bond, a C_{1-3} alkyl, O, S, $C(=O)$, $C=S$, $S(=O)$ and/or $S(=O)_2$;

each of R_{366} , R_{47a} , R_{48a} , R_{49a} , R_{50a} is independently selected from H, an optionally R_{4001} -substituted C_{1-3} alkyl or alkoxy or alkyl acyl or alkyl sulfonyl or alkyl amino or cyclopropyl, an optionally R_{4001} -substituted cyclopropyl acyl or cyclopropyl sulfonyl;

R_{366} can also be selected from the group consisting of a phenyl, a pyridyl, an imidazolyl, a thienyl, a furyl, an oxazolyl, a thiazolyl and an isothiazolyl which is optionally substituted by R_{4001} ;

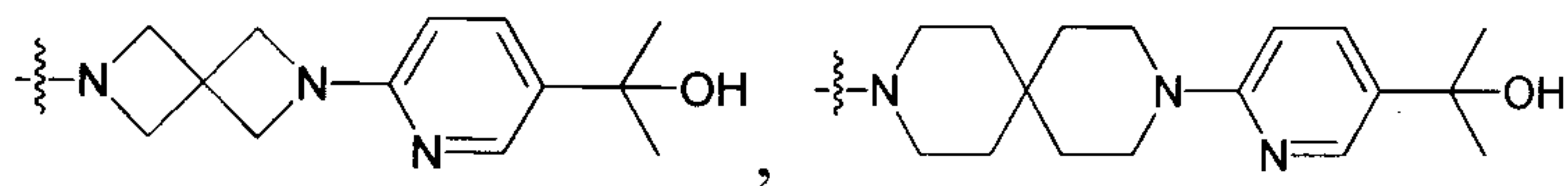
R_{4001} is selected from OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2 , $C(CH_3)_2(OH)$, F, Cl, Br, I, CN, a methyl, a methoxy, the number of R_{4001} is selected from 1, 2 or 3;

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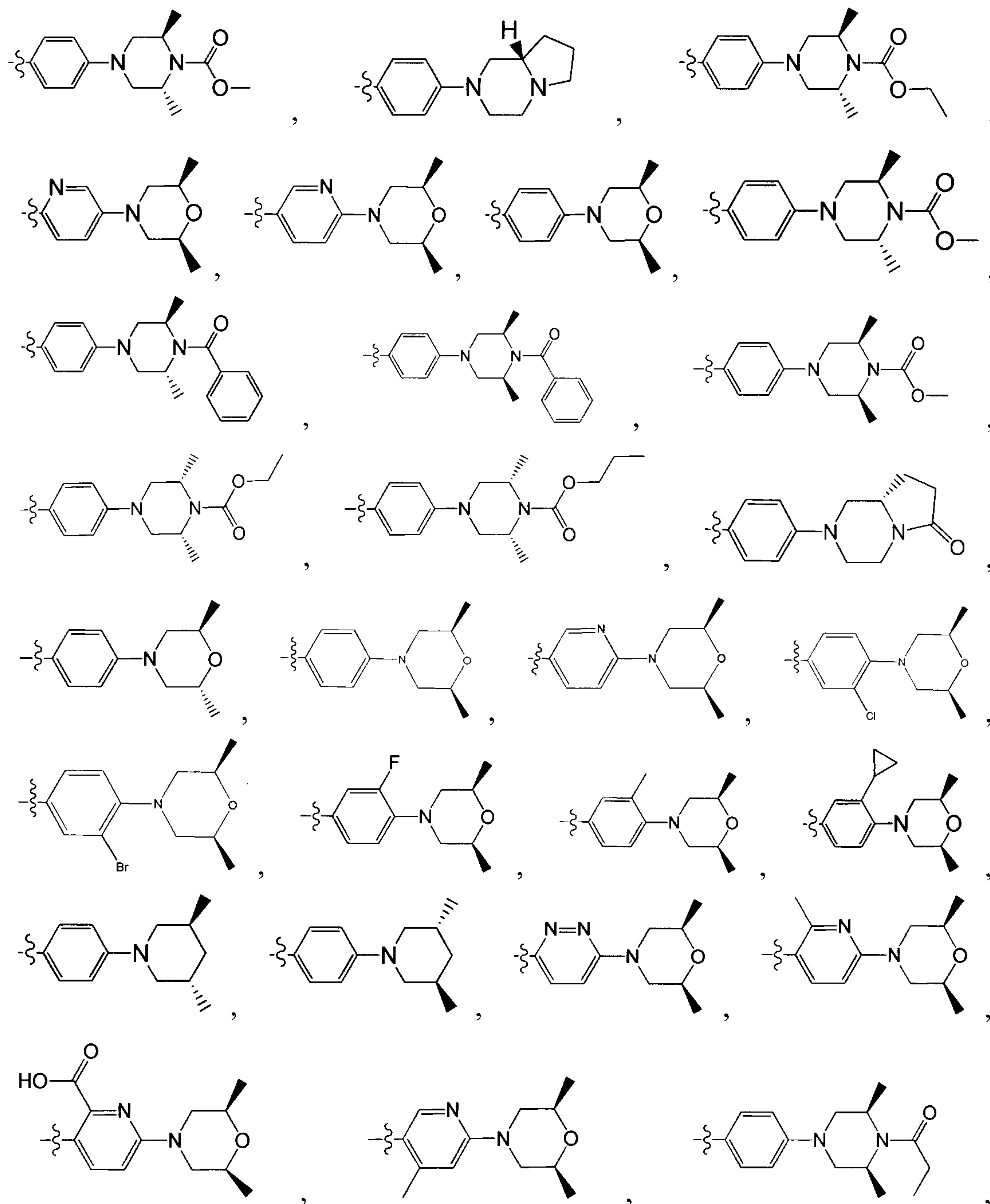
or,

 L_{37} is selected from a single bond, C(=O), CH₂;

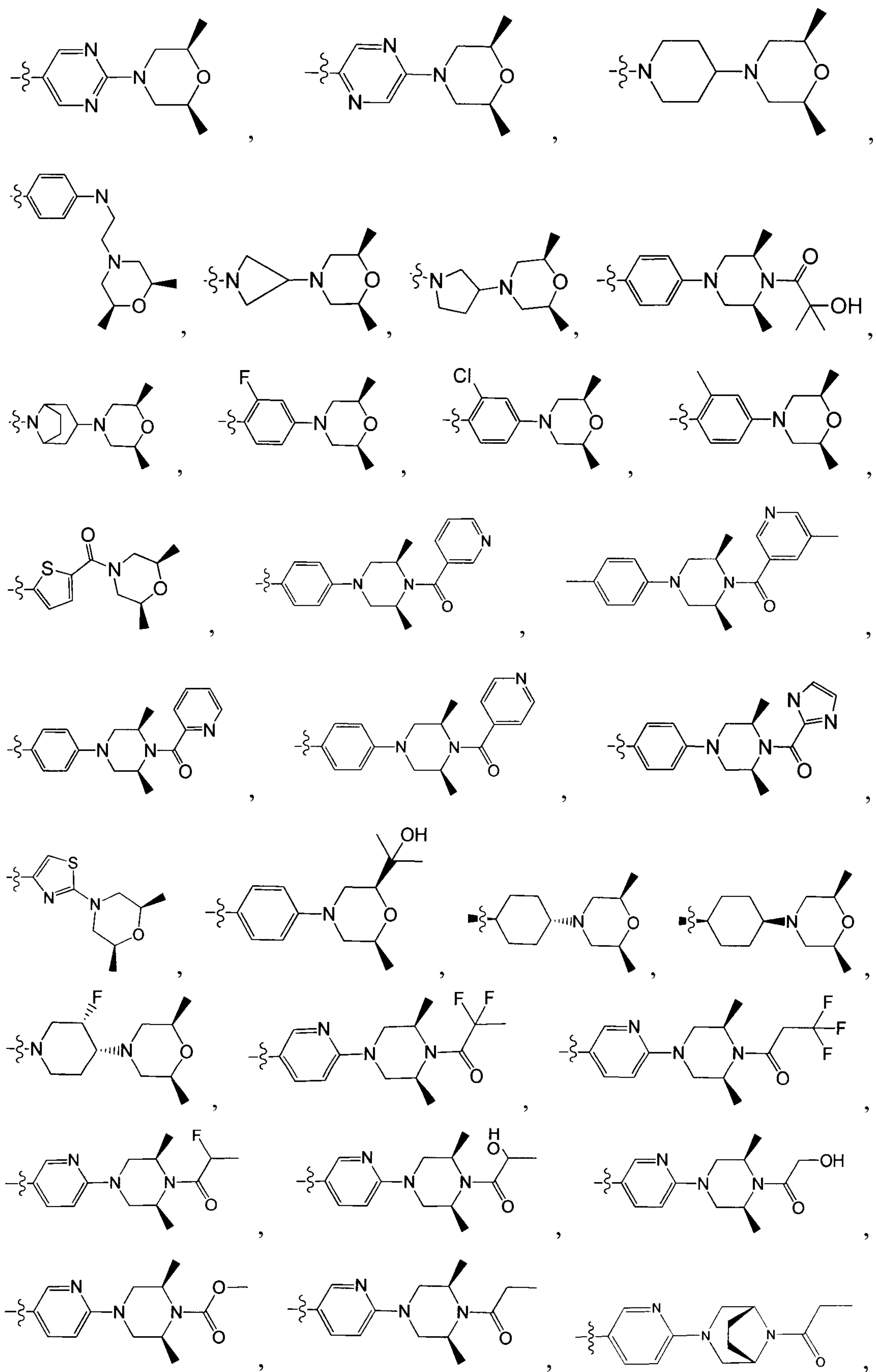
or, B is selected from



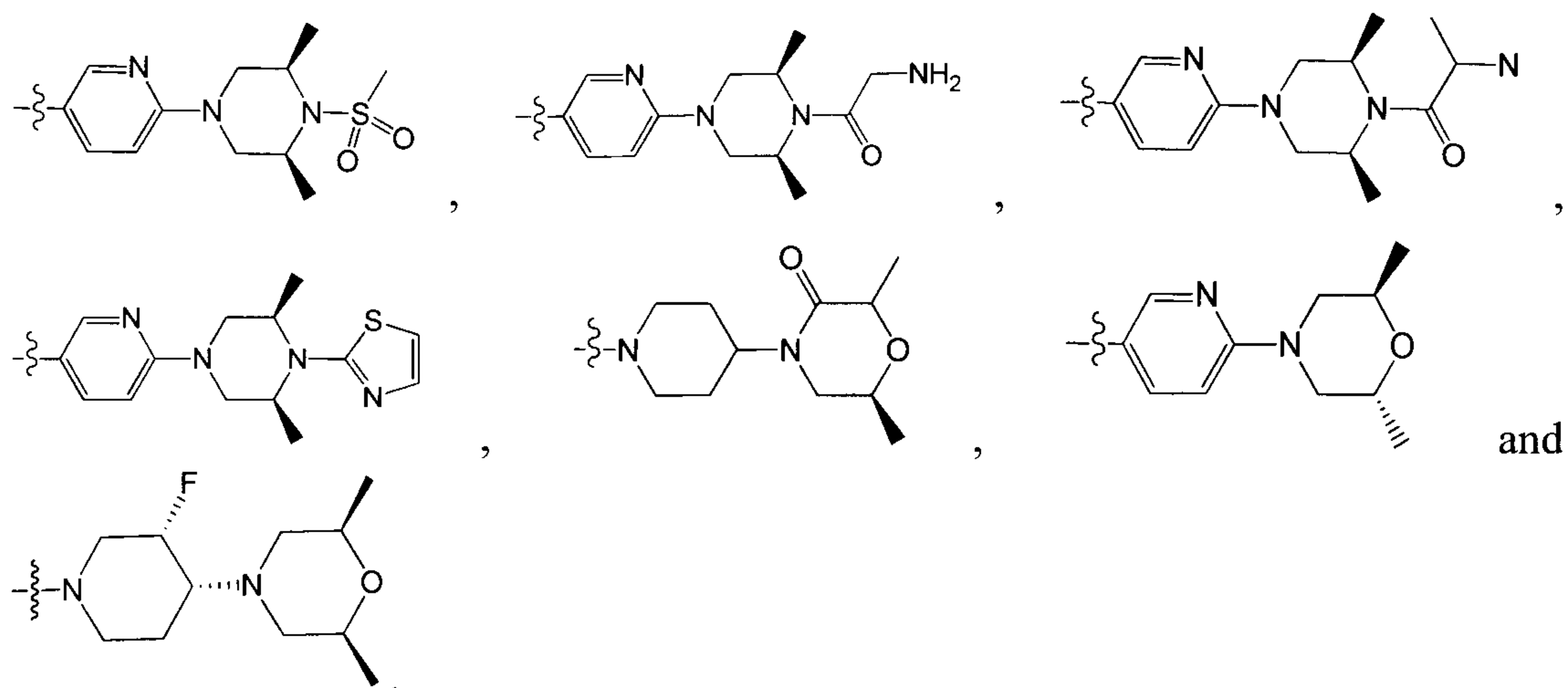
16. The compound represented by formula (I), or the pharmaceutically acceptable salt thereof according to claim 1, wherein B is selected from the group consisting of



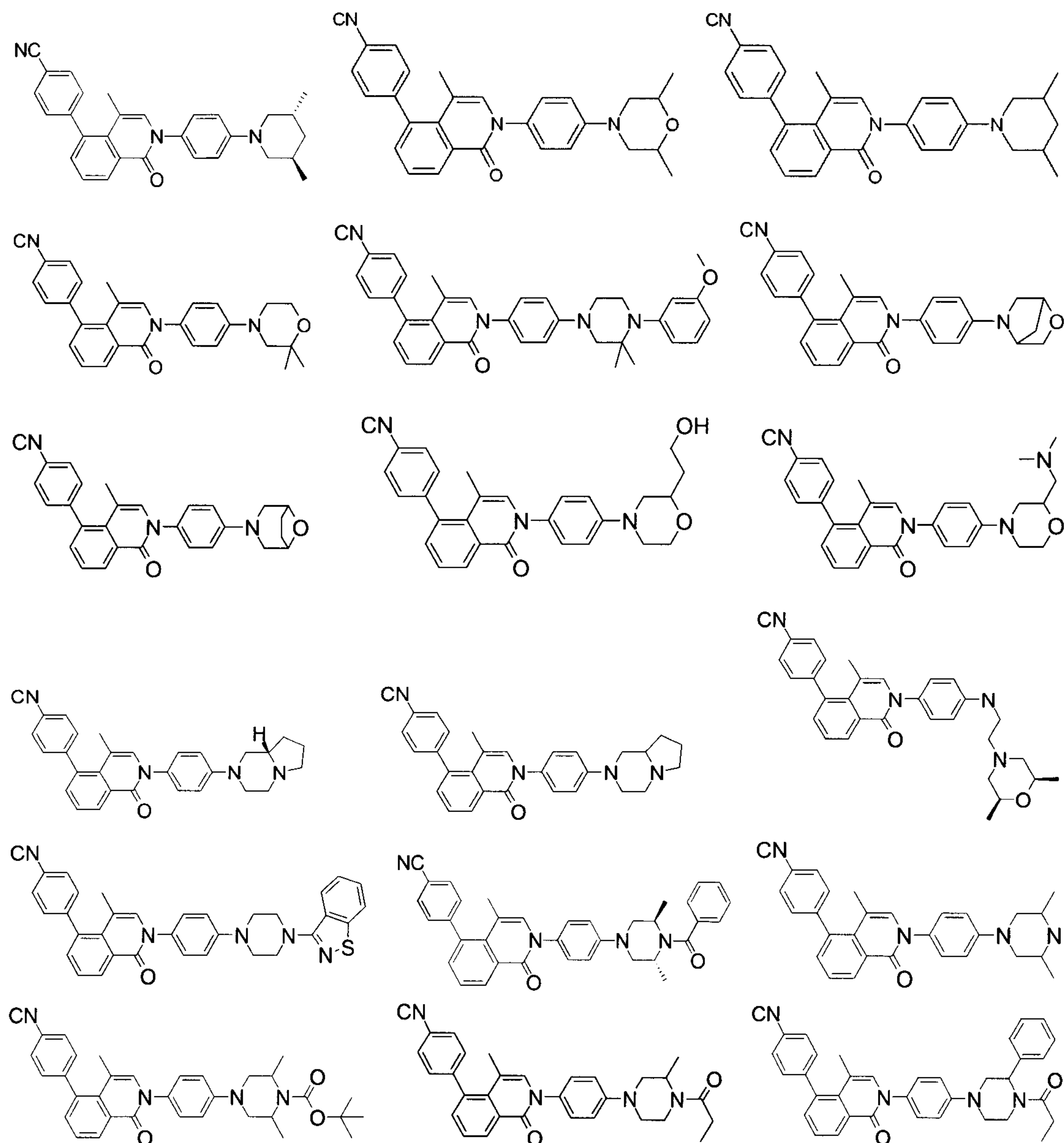
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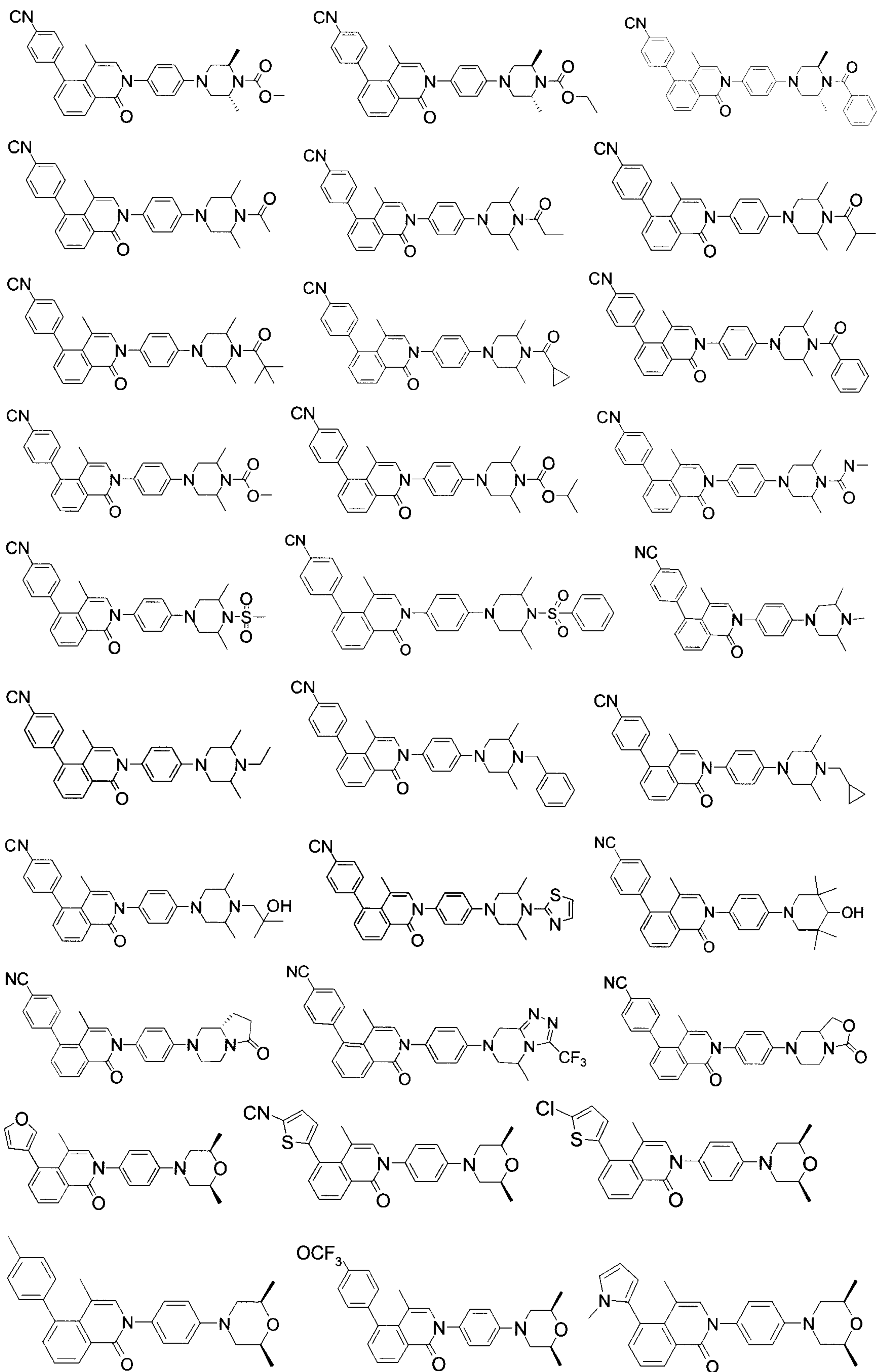
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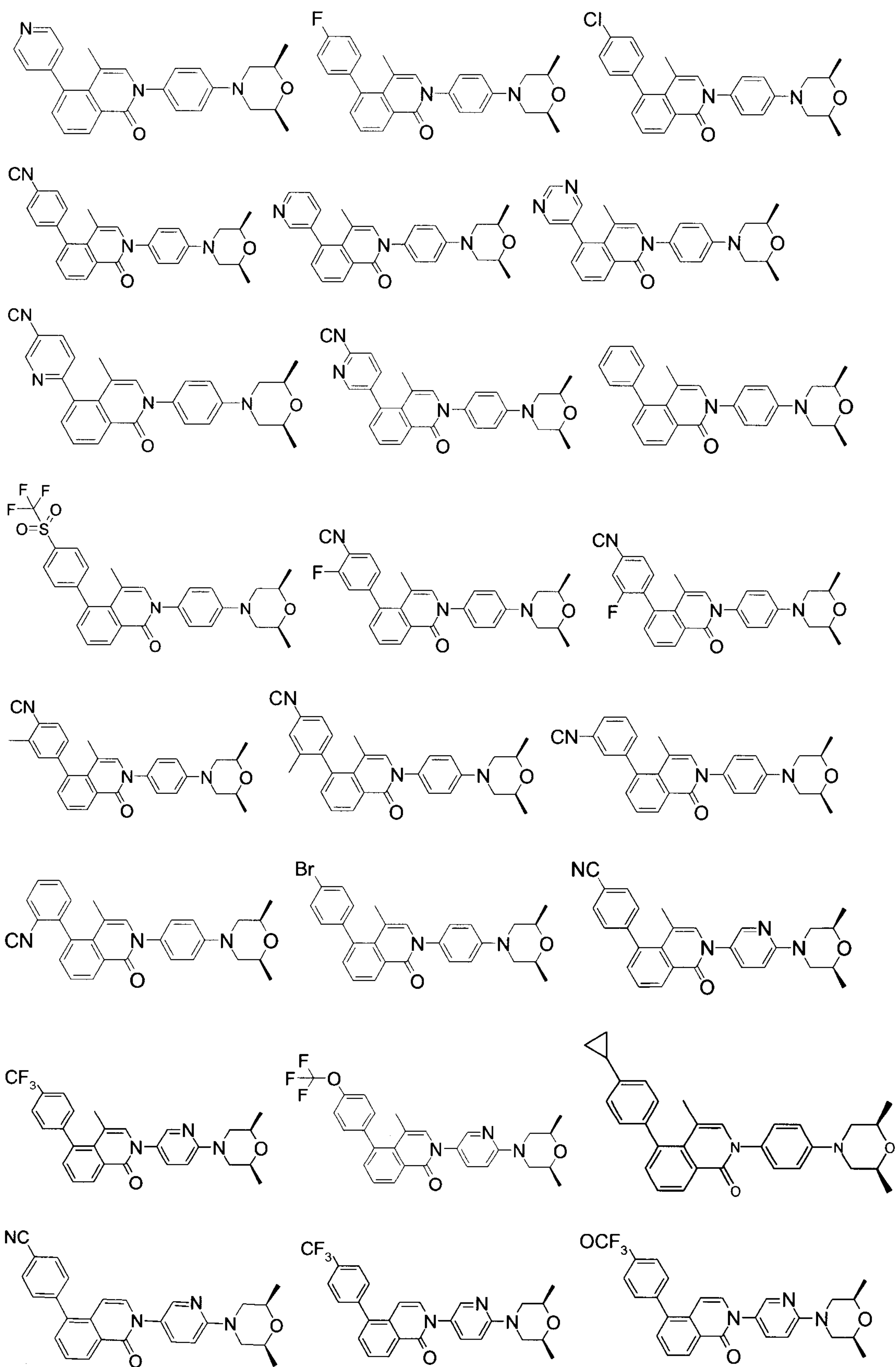


17. The compound represented by formula (I), or the pharmaceutically acceptable salt thereof according to claim 1, which is selected from the group consisting of

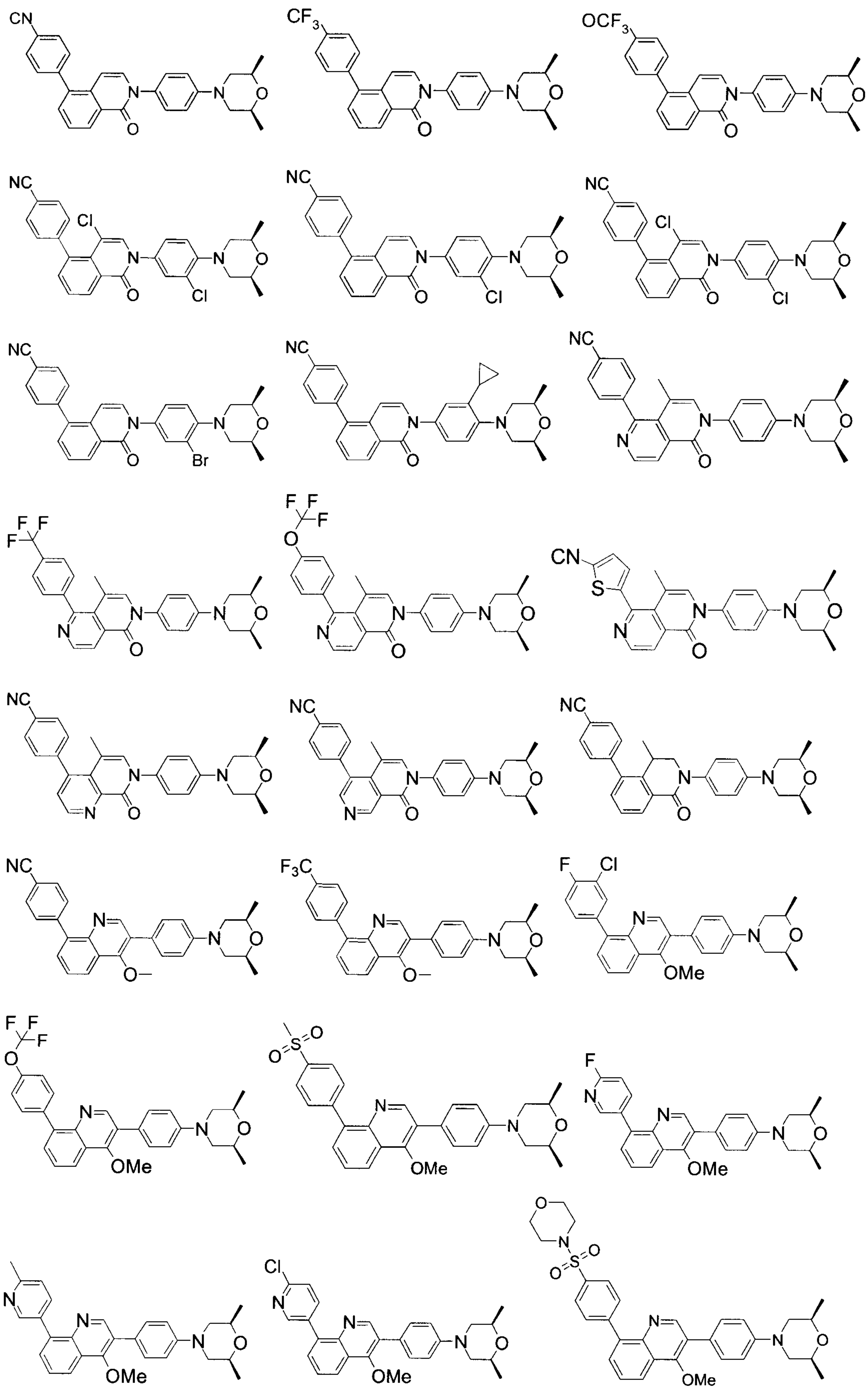


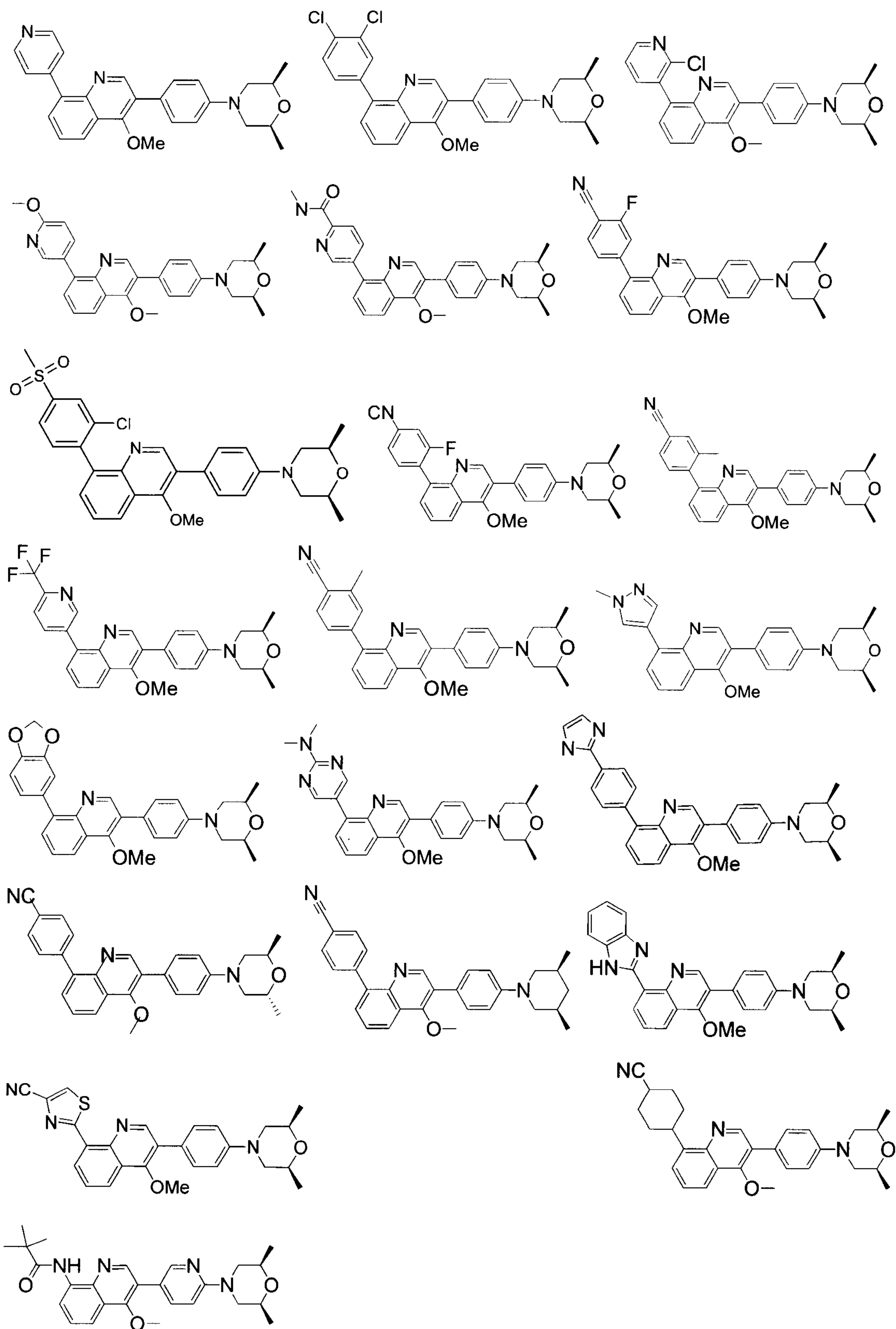
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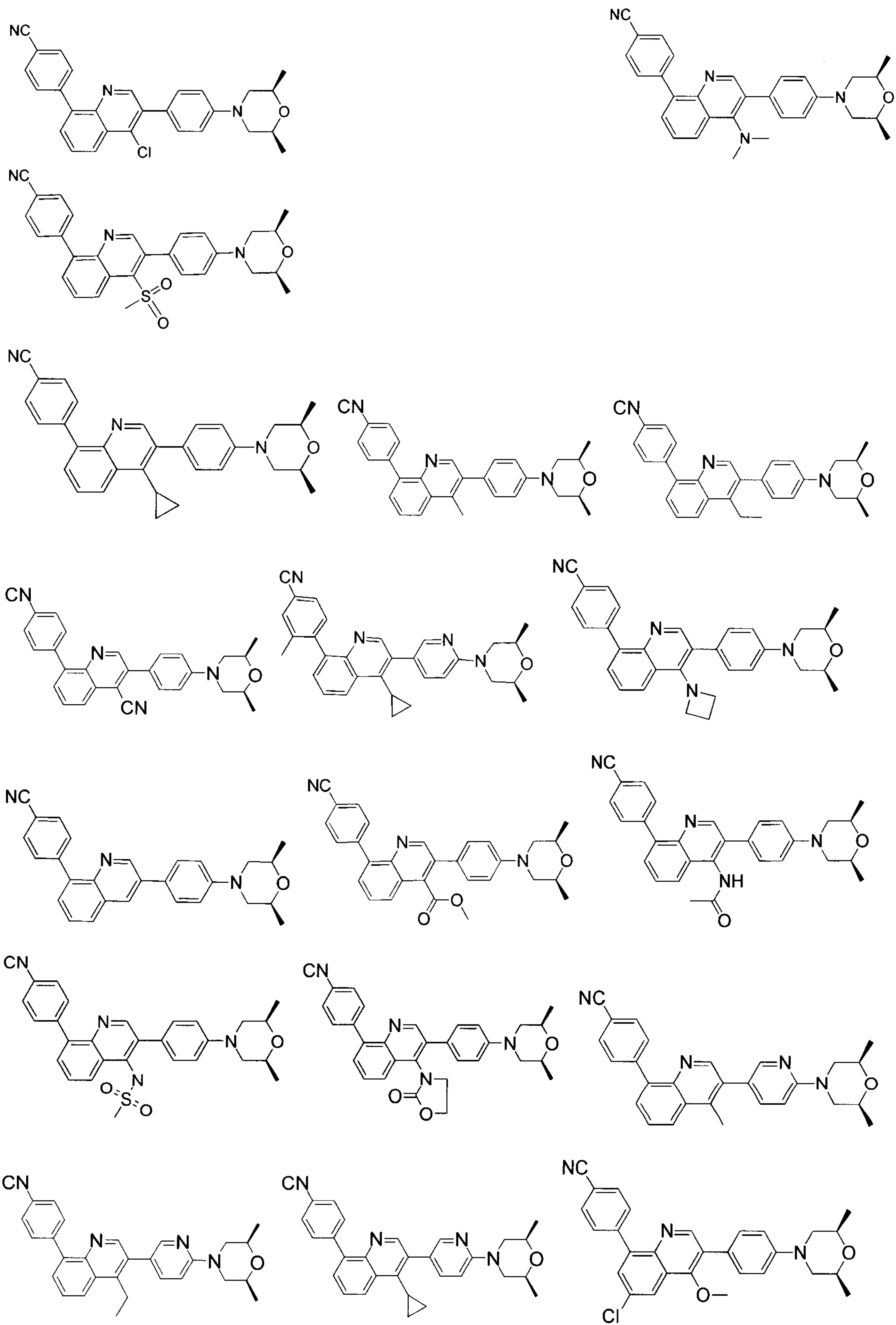


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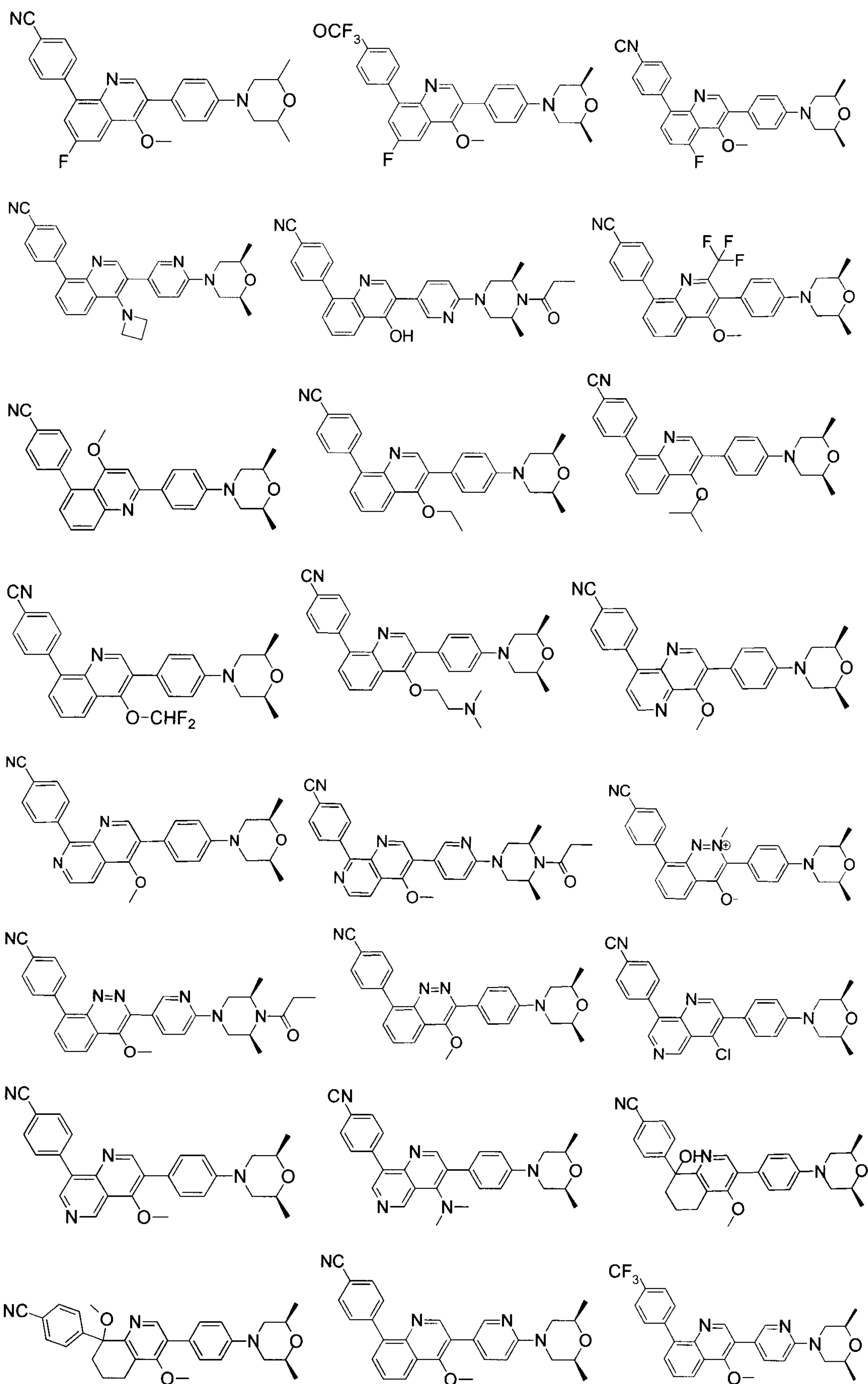




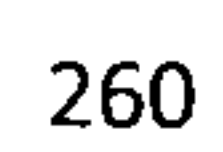
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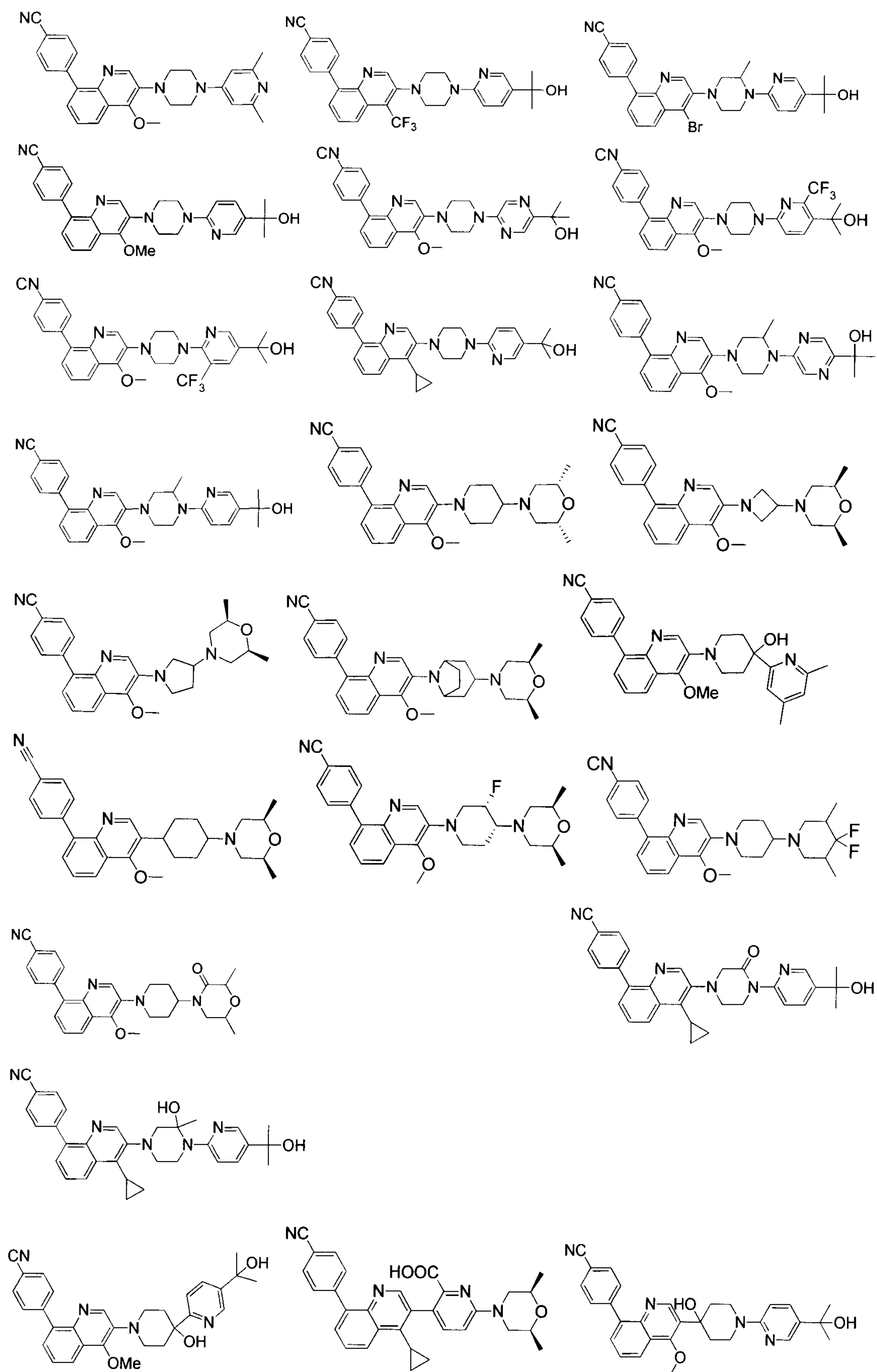


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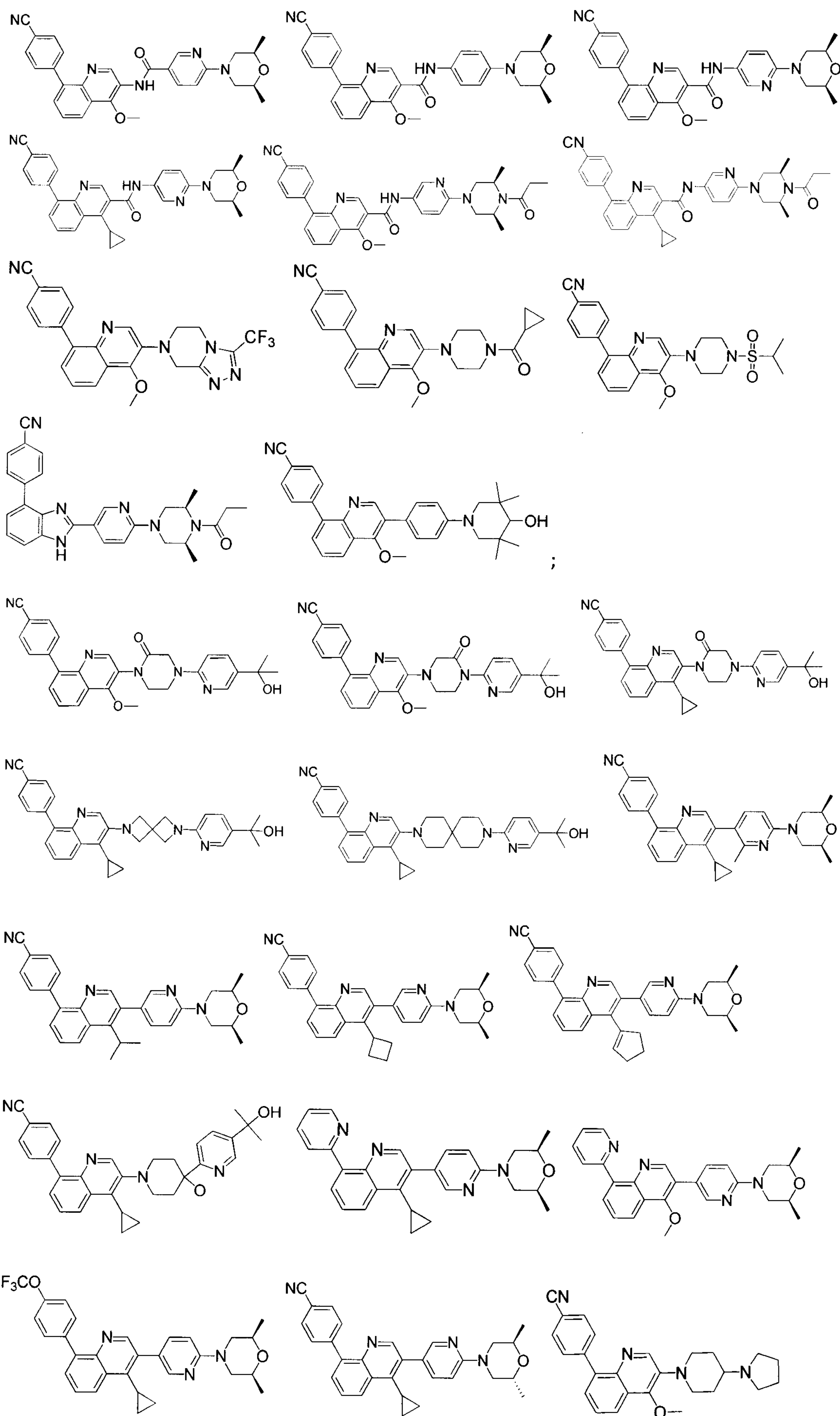








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