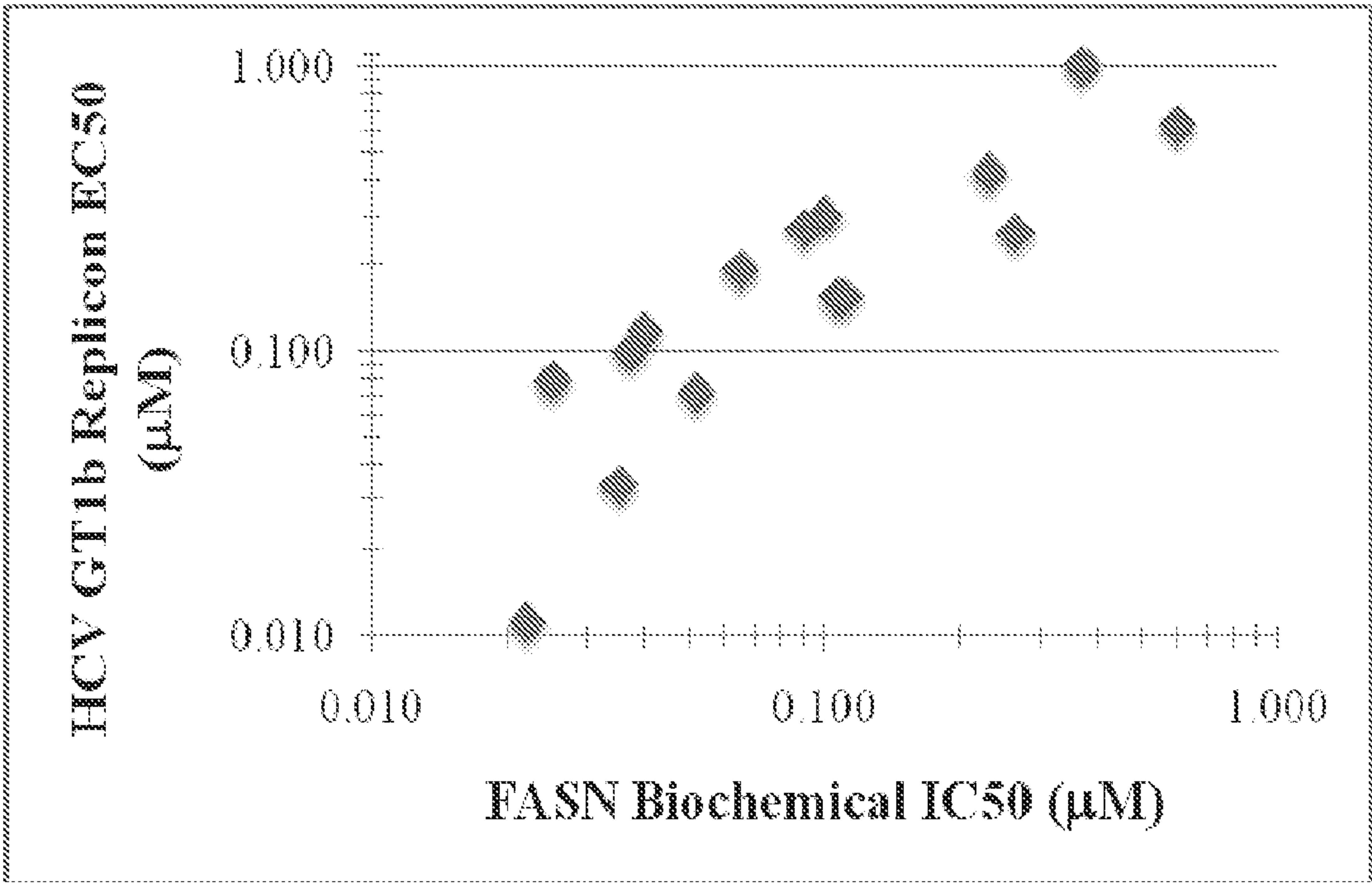




(86) Date de dépôt PCT/PCT Filing Date: 2012/03/08 (87) Date publication PCT/PCT Publication Date: 2012/09/13 (45) Date de délivrance/Issue Date: 2019/07/23 (85) Entrée phase nationale/National Entry: 2013/09/04 (86) N° demande PCT/PCT Application No.: US 2012/028309 (87) N° publication PCT/PCT Publication No.: 2012/122391 (30) Priorités/Priorities: 2011/03/08 (US61/450,482); 2011/03/08 (US61/450,561); 2011/07/16 (US61/508,611); 2012/01/11 (US61/585,642)	(51) Cl.Int./Int.Cl. <i>C07D 405/12</i> (2006.01), <i>A61K 31/445</i> (2006.01), <i>A61K 31/4525</i> (2006.01), <i>A61K 31/454</i> (2006.01), <i>A61K 31/4545</i> (2006.01), <i>A61K 31/55</i> (2006.01), <i>A61P 3/06</i> (2006.01), <i>A61P 31/14</i> (2006.01), <i>A61P 35/00</i> (2006.01), <i>C07D 211/34</i> (2006.01), <i>C07D 401/10</i> (2006.01), <i>C07D 487/04</i> (2006.01) (72) Inventeurs/Inventors: OSLOB, JOHAN D., US; MCDOWELL, ROBERT S., US; JOHNSON, RUSSELL, US; YANG, HANBIAO, US; ... (73) Propriétaire/Owner:
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(54) **Titre :** MODULATEURS HETEROCYCLIQUES DE LA SYNTHÈSE DES LIPIDES
(54) **Title:** HETEROCYCLIC MODULATORS OF LIPID SYNTHESIS



(57) **Abrégé/Abstract:**
Compounds that are fatty acid synthesis modulators are provided. The compounds may be used to treat disorders characterized by dysregulation of the fatty acid synthase function by modulating the function and/or the fatty acid synthase pathway. Methods are provided for treating such disorders including viral infections, such as hepatitis C infection, cancer and metabolic disorders.

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

(19) World Intellectual Property

Organization

International Bureau



WIPO | PCT



(10) International Publication Number

WO 2012/122391 A1

(43) International Publication Date
13 September 2012 (13.09.2012)

(51) International Patent Classification:

A01N 43/58 (2006.01)

(21) International Application Number:

PCT/US2012/028309

(22) International Filing Date:

8 March 2012 (08.03.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/450,561	8 March 2011 (08.03.2011)	US
61/450,482	8 March 2011 (08.03.2011)	US
61/508,611	16 July 2011 (16.07.2011)	US
61/585,642	11 January 2012 (11.01.2012)	US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: HETEROCYCLIC MODULATORS OF LIPID SYNTHESIS

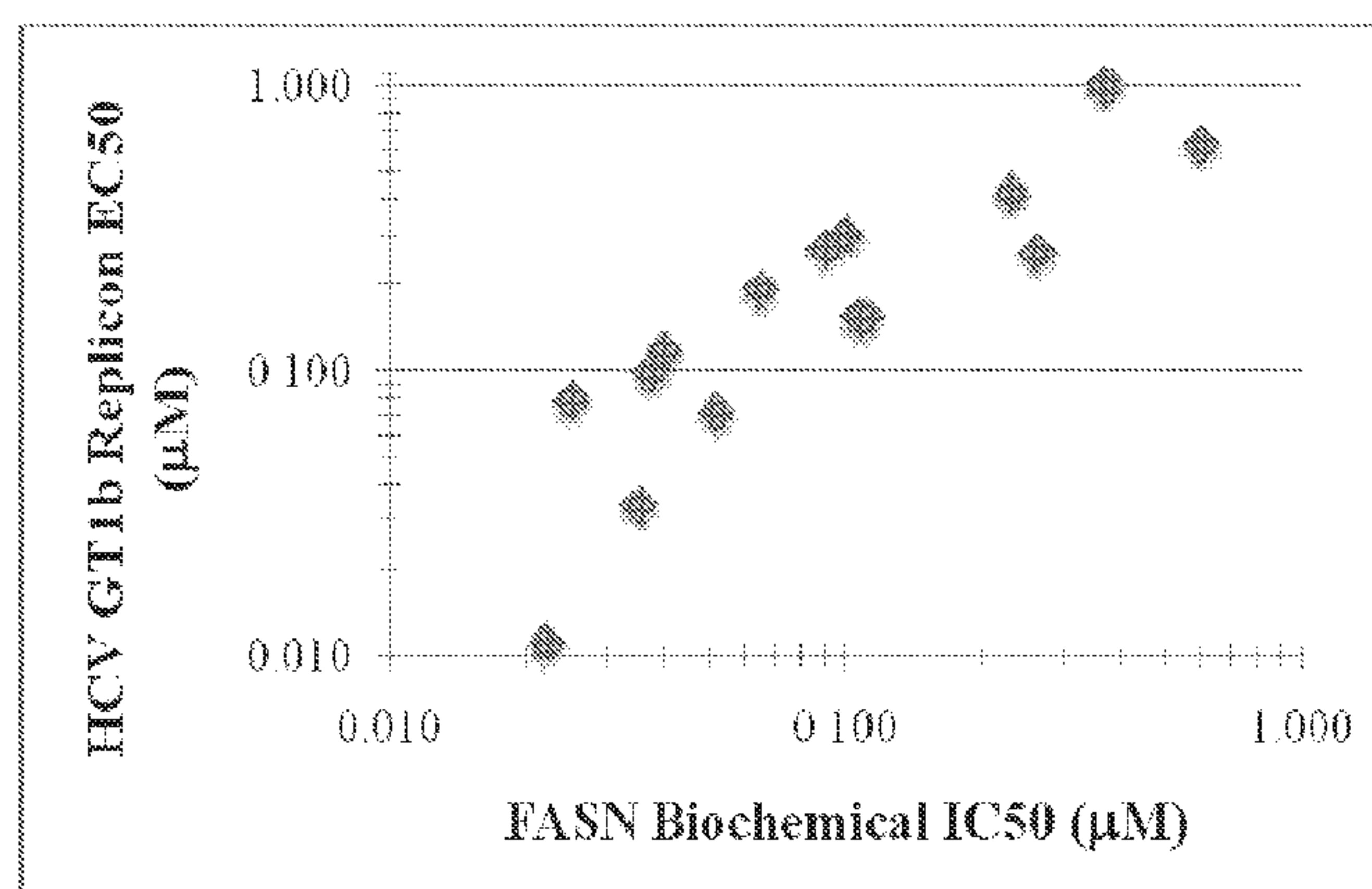


FIG. 1

(57) Abstract: Compounds that are fatty acid synthesis modulators are provided. The compounds may be used to treat disorders characterized by dysregulation of the fatty acid synthase function by modulating the function and/or the fatty acid synthase pathway. Methods are provided for treating such disorders including viral infections, such as hepatitis C infection, cancer and metabolic disorders.

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HETEROCYCLIC MODULATORS OF LIPID SYNTHESIS

[0001]

FIELD

[0002] The present disclosure relates generally to heterocyclic modulators of lipid synthesis and methods of use thereof. The present heterocyclic modulators of lipid synthesis can be used for the treatment of disorders characterized by dysregulation in the fatty acid synthase function in a subject by modulating the fatty acid synthase pathway and/or the fatty acid synthase function.

BACKGROUND

[0003] Viral disease is a significant health concern that threatens large segments of human populations. Some of the features related to viral infection which are of concern to health care professionals include its highly contagious nature (e.g., HIV, SARS, etc.) and high mutability. Some viruses are also oncogenic (such as HPV, EBV and HBV). While viruses are structurally amongst the simplest of organisms, they are regarded to be among the most difficult to control and present a formidable challenge for antiviral drug R&D.

[0004] Thus far, there have been a few antiviral drugs widely used in patients, such as Amantadine and Oseltamivir for influenza, Acyclovir for HSV-related infections, Ganciclovir for CMV infection, and multiple agents including co-formulated drugs (Efavirenz, emtricitabine, and tenofovir disoproxil fumarate) for AIDS treatments. These drugs possess a variety of undesirable neurological, metabolic and immunological side-effects. Therefore, development of new antiviral therapy has become a major focus of medical and pharmaceutical research and development.

[0005] Infection by hepatitis C virus (HCV) is a serious health issue. It is estimated that 170 million people worldwide are chronically infected with HCV. HCV infection can lead to chronic hepatitis, cirrhosis, liver failure and hepatocellular carcinoma. Chronic HCV infection is thus a major worldwide cause of liver-related premature mortality.

[0006] The present standard of care treatment regimen for HCV infection involves combination therapy with interferon-alpha and ribavirin, often with the addition of a direct-acting protease inhibitor (Telaprevir or Boceprevir). The treatment is cumbersome and sometimes has debilitating and severe side effects. For this reason, many patients are not

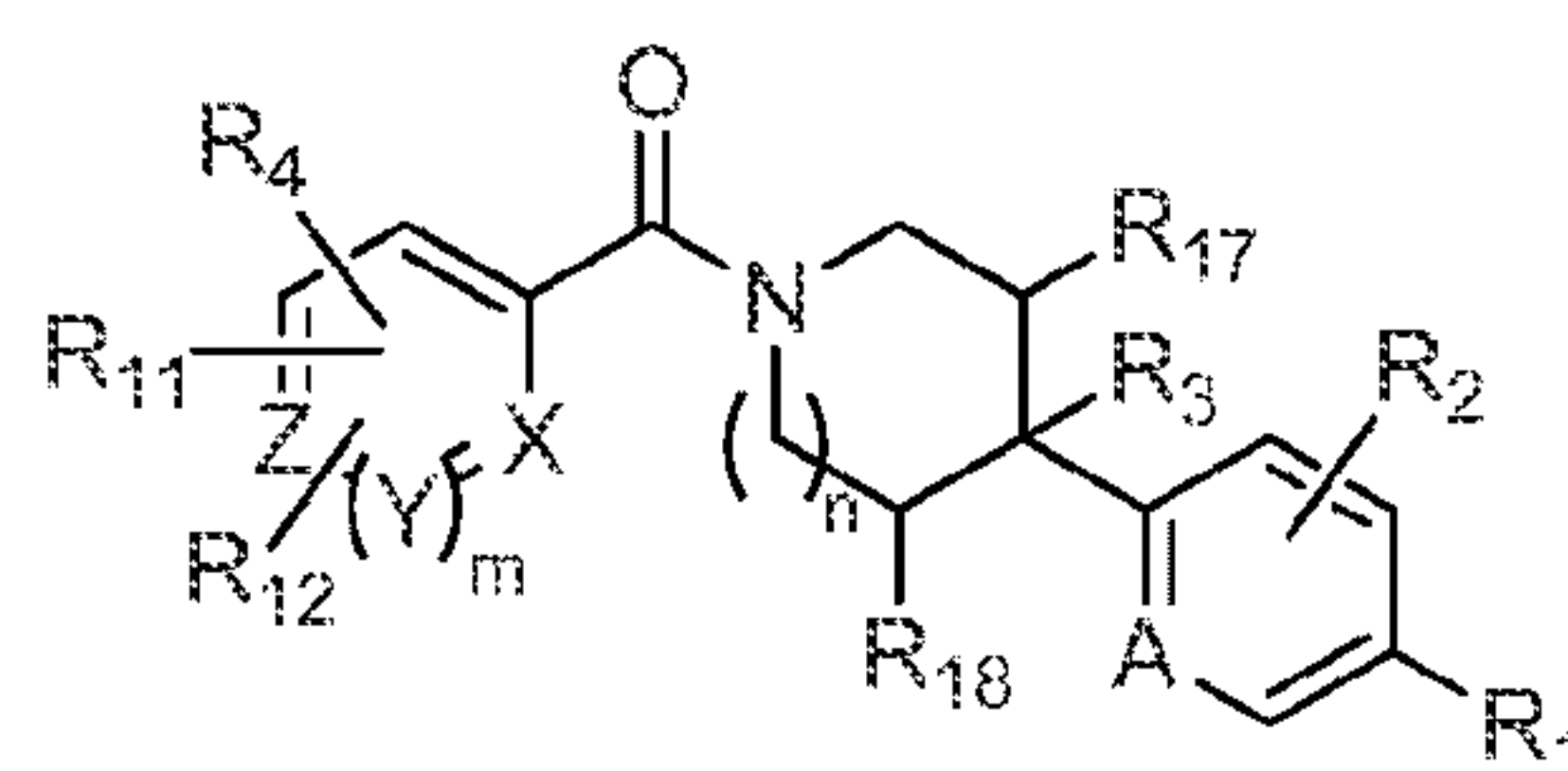
treated in early stages of the disease. Additionally, some patient populations do not durably respond to treatment. New and effective methods of treating HCV infection are urgently needed.

[0007] The dominant therapeutic approaches that are currently employed to treat cancer include surgical removal of primary tumors, tumor irradiation, and parenteral application of anti-mitotic cytotoxic agents. Unfortunately, only a relatively small cross-section of cancer patients have tumors that are “addicted” to a specific pathway, and can therefore be treated with newer targeted agents. The continued dominance of these long established therapies is mirrored by the lack of improvement in survival rates for most cancers. In addition to limited clinical success, devastating side effects accompany classic therapies. Both radiation- and cytotoxic-based therapies result in the destruction of rapidly dividing hematopoietic and intestinal epithelial cells leading to compromised immune function, anemia, and impaired nutrient absorption. Surgical intervention often results in a release of tumor cells into the circulation or lymph systems from which metastatic tumors can subsequently be established. Improved methods for the treatment of cancer are needed.

SUMMARY

[0008] The present disclosure addresses the deficiencies for antiviral and anticancer treatments by providing novel heterocyclic modulators of lipid synthesis having improved antiviral and anticancer activities.

[0009] In various aspects, the present disclosure provides for compounds of Structure (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X, Y, and Z are each independently CR or NR', wherein R is hydrogen or C₁₋₆ alkyl
and R' is hydrogen, C₁₋₆ alkyl, or absent;

A is CH or N;

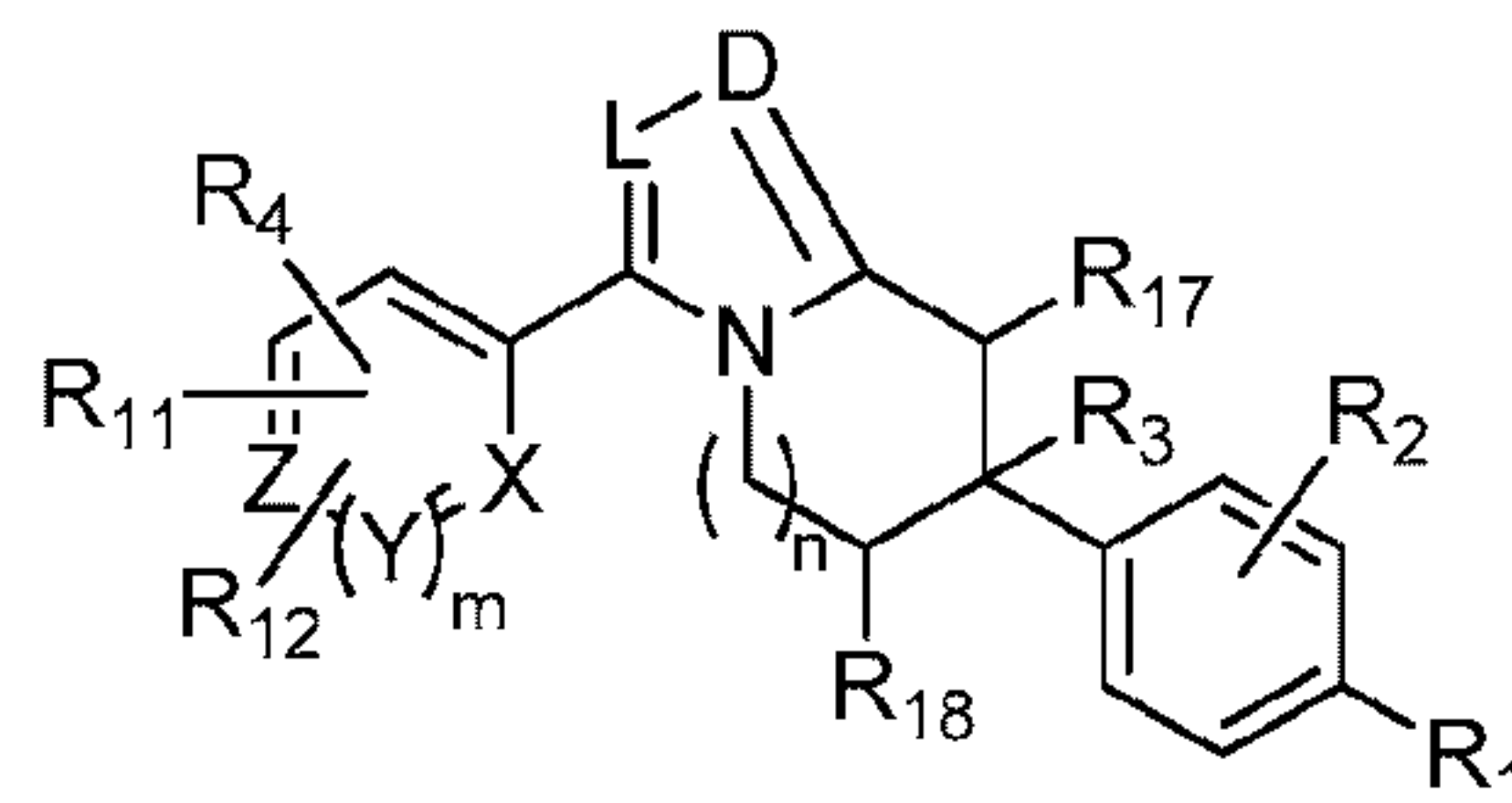
R₁ is hydrogen, cyano, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, -C(=O)N(R₁₃)(R₁₄),
-(CH₂)_qC(=O)N(R₁₃)(R₁₄), CF₃, -OCF₃, or -S(=O)₂R₂₀;

q is 0, 1, 2, 3, or 4;

R₂₀ is hydrogen or C₁₋₆ alkyl, C₁₋₆ alkoxy, or -N(R₁₃)(R₁₄);

- R_2 is hydrogen, halo, C_{1-6} alkoxy, C_{1-6} alkyl, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;
- R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;
- R_4 is hydrogen, heteroaryl, heterocyclyl, $-C(=O)N(R_5R_6)$, $-N(R_7)C(=O)R_8$, $-N(R_9R_{10})$, C_{1-6} alkyl, C_{1-6} alkoxy, $-S(=O)_2R_{20}$, or R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl;
- R_{11} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl, or R_{11} and R_{12} taken together with the atoms to which they are attached join together to form a heteroaryl;
- R_{12} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, or R_{11} and R_{12} taken together with the atoms to which they are attached join together to form a heteroaryl;
- R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{13} , and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;
- R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, or alkylamino;
- R_{17} and R_{18} are each independently hydrogen or alkyl or can optionally join together to form a bond;
- n is 1 or 2; and
- m is 0 or 1.

[0010] In various aspects, the present disclosure provides for compounds of Structure (II):



(II)

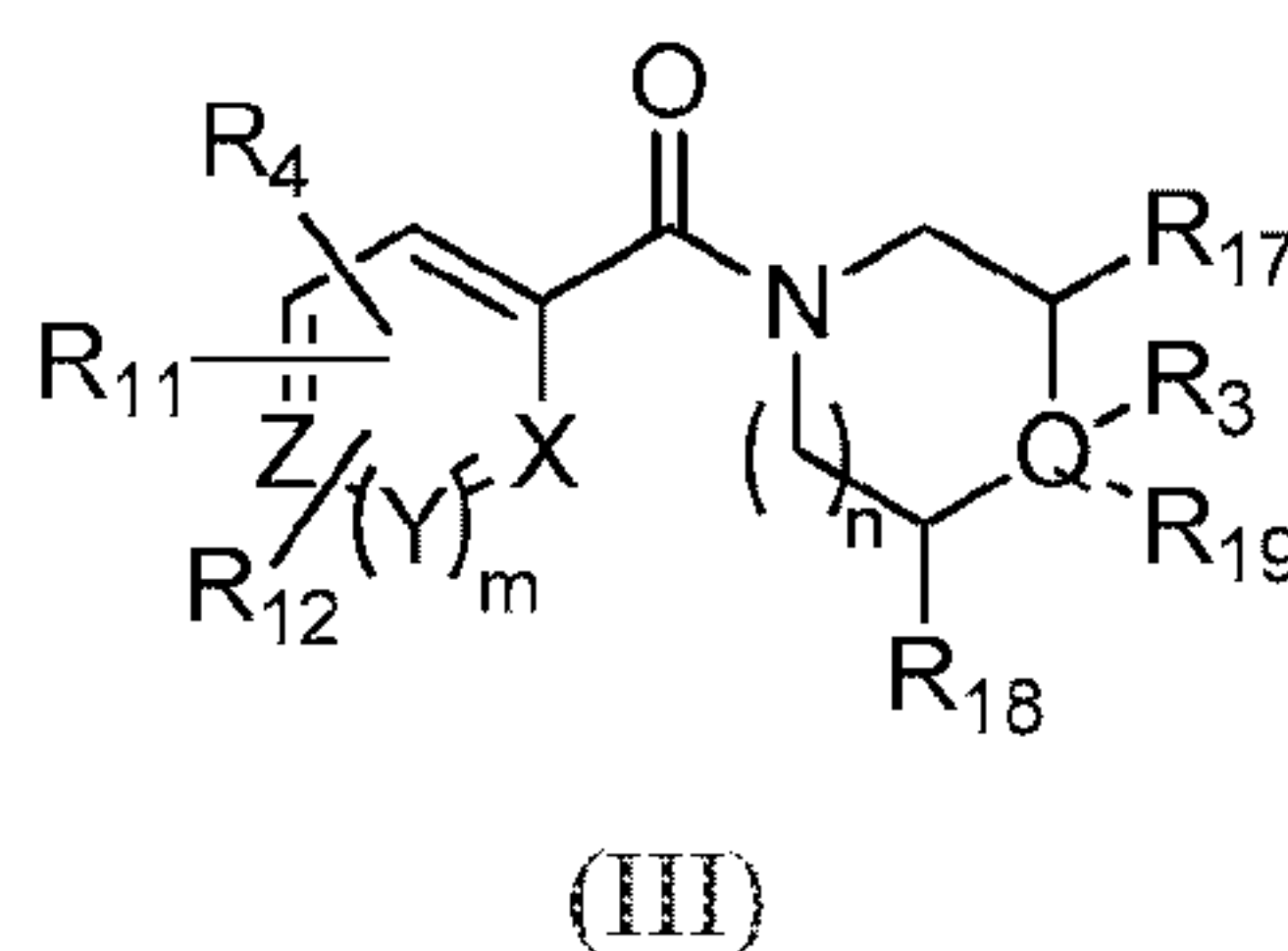
or a pharmaceutically acceptable salt thereof, wherein:

X, Y, and Z are each independently CR or NR', wherein R is hydrogen or C_{1-6} alkyl and R' is hydrogen, C_{1-6} alkyl, or absent;

L and D are each independently C or N;

- R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$, $-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;
 q is 0, 1, 2, 3, or 4;
 R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;
 R_2 is hydrogen, halo, C_{1-6} alkoxy, C_{1-6} alkyl, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;
 R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;
 R_4 is hydrogen, heteroaryl, heterocyclyl, $-C(=O)N(R_5R_6)$, $-N(R_7)C(=O)R_8$, $-N(R_9R_{10})$, C_{1-6} alkyl, C_{1-6} alkoxy, $-S(=O)_2R_{20}$, or R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl;
 R_{11} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl, or R_{11} and R_{12} taken together with the atoms to which they are attached join together to form a heteroaryl;
 R_{12} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, or R_{11} and R_{12} taken together with the atoms to which they are attached join together to form a heteroaryl;
 R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{13} , and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;
 R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, or alkylamino;
 R_{17} and R_{18} are each independently hydrogen or alkyl or can optionally join together to form a bond;
 n is 1 or 2; and
 m is 0 or 1.

[0011] In various aspects, the present disclosure provides for compounds of Structure (III):



or a pharmaceutically acceptable salt thereof, wherein:

X, Y, and Z are each independently CR or NR', wherein R is hydrogen or C₁₋₆ alkyl and R' is hydrogen, C₁₋₆ alkyl, or absent;

Q is C or N;

R₃ is hydrogen, hydroxyl, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, or if Q is N then R₃ is absent;

R₄ is hydrogen, heteroaryl, heterocyclyl, -C(=O)N(R₅R₆), -N(R₇)C(=O)R₈, -N(R₉R₁₀), C₁₋₆ alkyl, C₁₋₆ alkoxy, -S(=O)₂R₂₀, or R₄ and R₁₁ taken together with the atoms to which they are attached join together to form a heteroaryl;

R₁₁ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy, -N(R₁₃R₁₄), CF₃, -OCF₃, -S(=O)₂R₂₀, R₄ and R₁₁ taken together with the atoms to which they are attached join together to form a heteroaryl, or R₁₁ and R₁₂ taken together with the atoms to which they are attached join together to form a heteroaryl;

R₁₂ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy, -N(R₁₃R₁₄), CF₃, -OCF₃, -S(=O)₂R₂₀, or R₁₁ and R₁₂ taken together with the atoms to which they are attached join together to form a heteroaryl;

R₂₀ is hydrogen or C₁₋₆ alkyl, C₁₋₆ alkoxy, or -N(R₁₃)(R₁₄);

R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₃, and R₁₄ are each independently hydrogen, C₁₋₆ alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, -N(R₁₅R₁₆), or -S(=O)₂R₂₀;

R₁₅ and R₁₆ are each independently hydrogen, C₁₋₆ alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, or alkylamino;

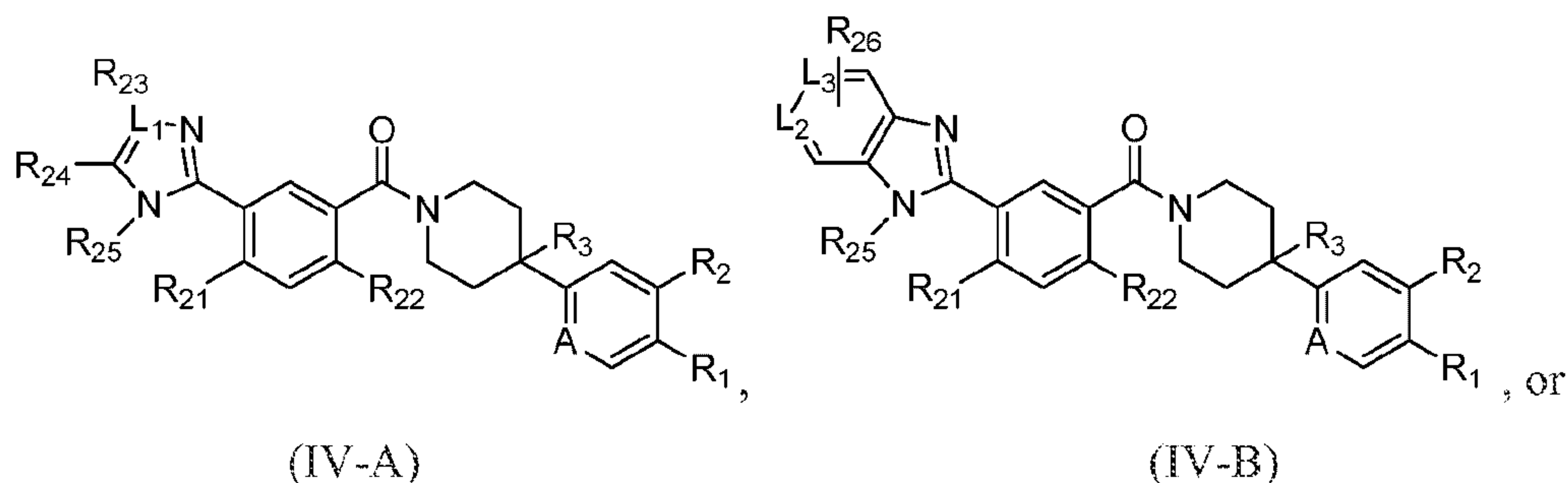
R₁₇ and R₁₈ are each independently hydrogen or alkyl or can optionally join together to form a bond;

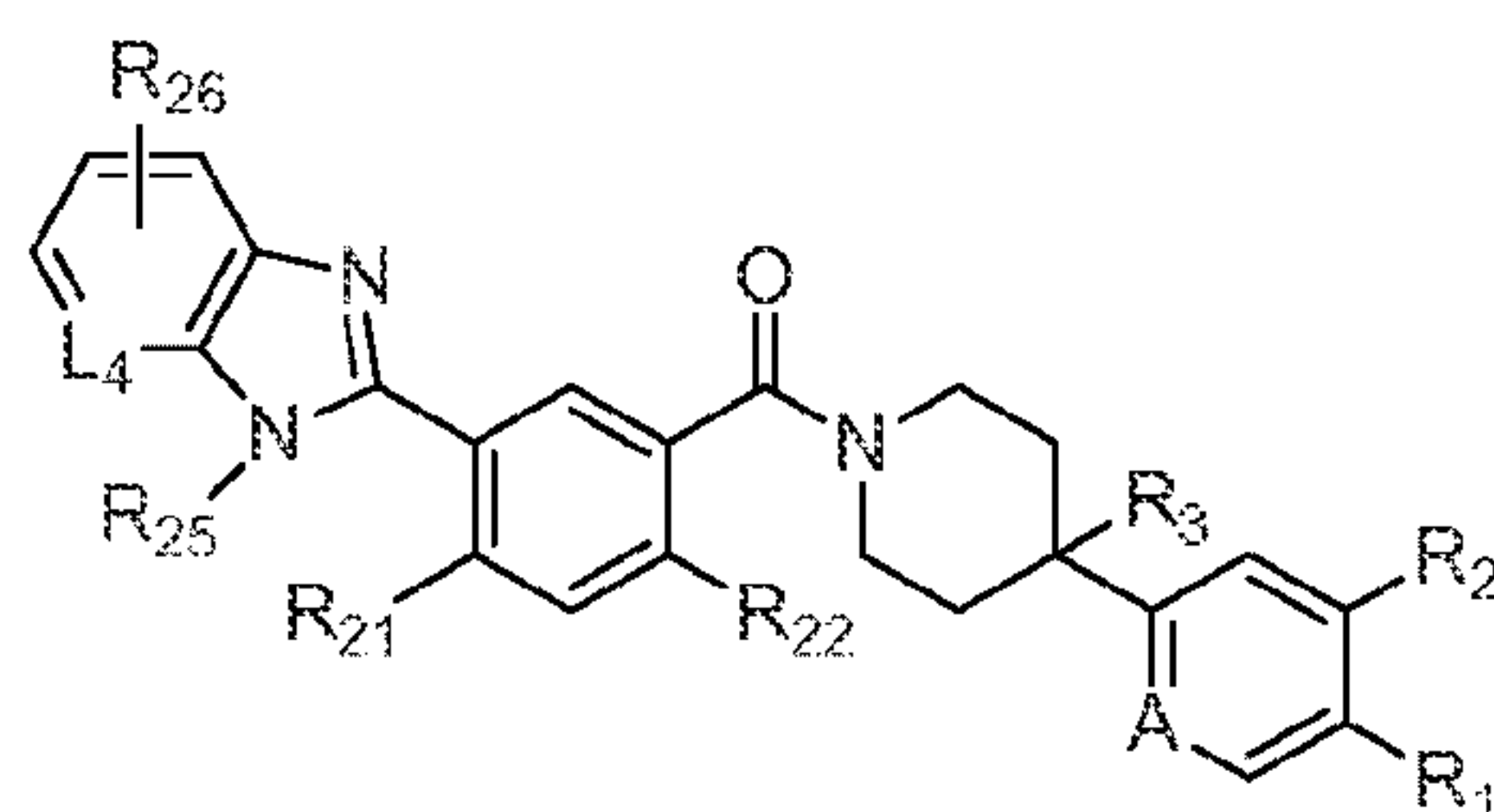
R₁₉ is aryl, heteroaryl, cycloalkyl, or heterocyclyl;

n is 0, 1, or 2; and

m is 0 or 1.

[0012] In various aspects, the present disclosure provides for compounds of Structures (IV-A), (IV-B), or (IV-C):





(IV-C)

or a pharmaceutically acceptable salt thereof, wherein:

L₁, L₂, L₃, L₄, and A are each independently CH or N;

R₁ is hydrogen, cyano, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, $-\text{C}(=\text{O})\text{N}(\text{R}_{13})(\text{R}_{14})$,

$-(\text{CH}_2)_q\text{C}(=\text{O})\text{N}(\text{R}_{13})(\text{R}_{14})$, CF₃, $-\text{OCF}_3$, or $-\text{S}(=\text{O})_2\text{R}_{20}$;

q is 0, 1, 2, 3, or 4;

R₂₀ is hydrogen or C₁₋₆ alkyl, C₁₋₆ alkoxy, or $-\text{N}(\text{R}_{13})(\text{R}_{14})$;

R₂ is hydrogen, halo, C₁₋₆ alkoxy, or C₁₋₆ alkyl;

R₃ is hydrogen, hydroxyl, halo, C₁₋₆ alkyl, or C₁₋₆ alkoxy;

R₂₁ and R₂₂ are each independently hydrogen, halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy,

CF₃, $-\text{OCF}_3$, or $-\text{S}(=\text{O})_2\text{R}_{20}$;

R₂₃ is hydrogen, $-\text{N}(\text{R}_{13})(\text{R}_{14})$, C₁₋₆ alkyl, C₁₋₆ alkoxy, is absent if L₁ is N, or R₂₃ and

R₂₄ taken together with the atoms to which they are attached join together to form a heterocyclyl, heteroaryl, or cycloalkyl;

R₂₄ is hydrogen, $-\text{N}(\text{R}_{13})(\text{R}_{14})$, C₁₋₆ alkyl, C₁₋₆ alkoxy, $-(\text{C}_{1-6} \text{ alkoxy})(\text{heterocyclyl})$,

heterocyclyl, or R₂₃ and R₂₄ taken together with the atoms to which they are attached join together to form a heterocyclyl, heteroaryl, or cycloalkyl;

R₂₆ is hydrogen, heteroaryl, heterocyclyl, $-\text{N}(\text{R}_{13})(\text{R}_{14})$, or $-\text{S}(=\text{O})_2\text{R}_{20}$;

R₁₃ and R₁₄ are each independently hydrogen, C₁₋₆ alkyl, cycloalkyl, aryl,

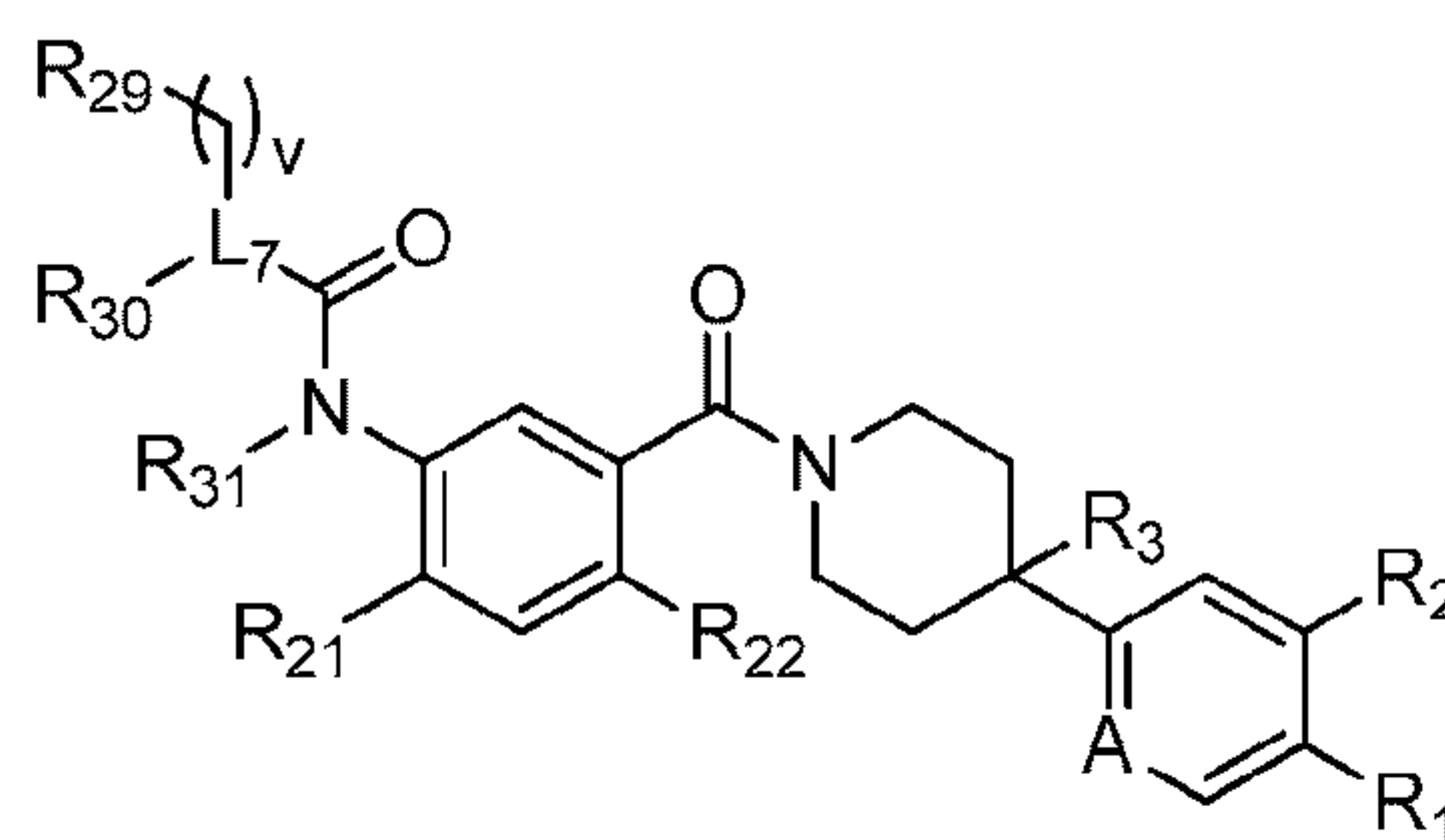
heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-\text{N}(\text{R}_{15}\text{R}_{16})$, or $-\text{S}(=\text{O})_2\text{R}_{20}$;

R₂₅ is hydrogen, C₁₋₆ alkyl, or C₁₋₆ alkoxy; and

R₁₅ and R₁₆ are each independently hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, cycloalkyl, aryl,

heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino.

[0013] In various aspects, the present disclosure provides for compounds of Structure (V):



(V)

or a pharmaceutically acceptable salt thereof, wherein:

L_7 is N or O, wherein R_{30} is absent if L_7 is O;

A is CH or N;

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$,

$-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

q is 0, 1, 2, 3, or 4;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_2 is hydrogen, halo, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_3 is halo, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{21} and R_{22} are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy,

CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

R_{29} and R_{30} are each independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxyalkyl,

heteroaryl, heterocyclyl, $-N(R_{15}R_{16})$, $-C(=O)R_{46}$, $-R_{48}C(=O)R_{47}$, or R_{29} and R_{30}

taken together with the atoms to which they are attached join together to form a

heteroaryl or heterocyclyl, wherein R_{30} is absent if L_7 is O;

R_{46} and R_{47} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl,

heterocyclyl, heteroaryl, hydroxyalkyl, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;

R_{48} is alkyl or is absent;

R_{31} is hydrogen, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{13} and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl,

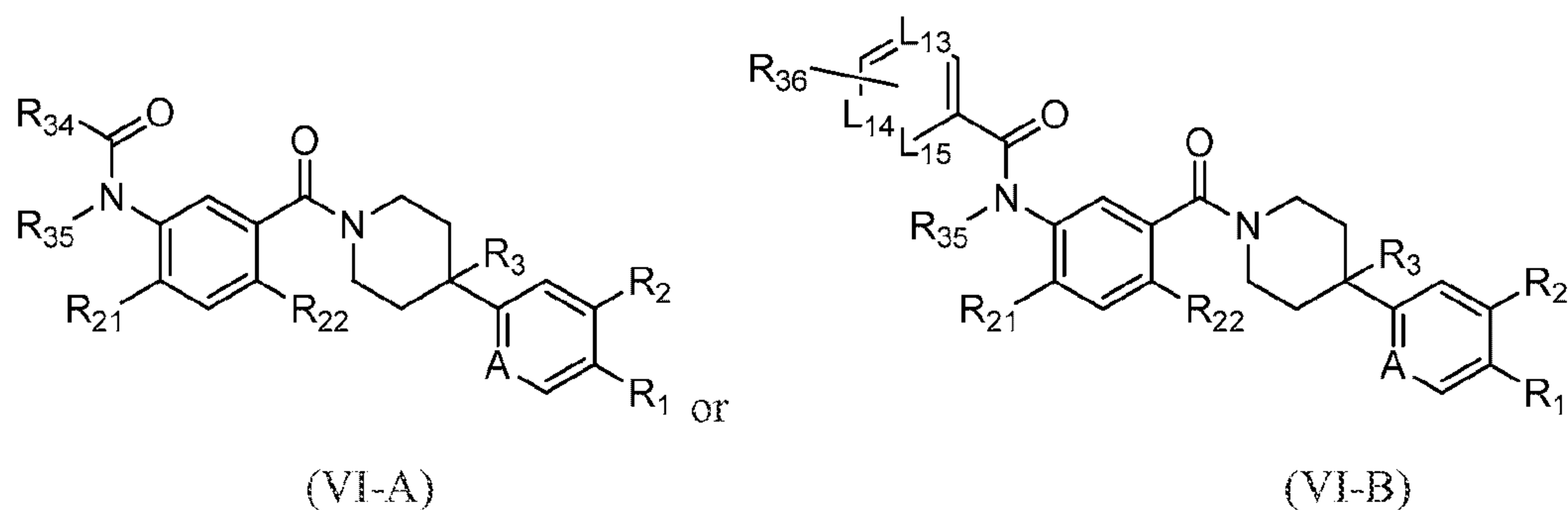
heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;

R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl,

heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino; and

v is 0 or 1.

[0014] In various aspects, the present disclosure provides for compounds of Structures (VI-A) or (VI-B):



or a pharmaceutically acceptable salt thereof, wherein:

L_{13} , L_{14} , L_{15} , and A are each independently CH or N;

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$,

$-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

q is 0, 1, 2, 3, or 4;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_2 is hydrogen, halo, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_3 is halo, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{21} and R_{22} are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy,

CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

R_{34} is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, cycloalkyl, hydroxyl, hydroxyalkyl, aryl, heterocyclyl, heteroaryl, alkylamino, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, or $-N(R_{15}R_{16})$;

R_{35} is hydrogen, C_{1-6} alkyl, or C_{1-6} alkoxy;

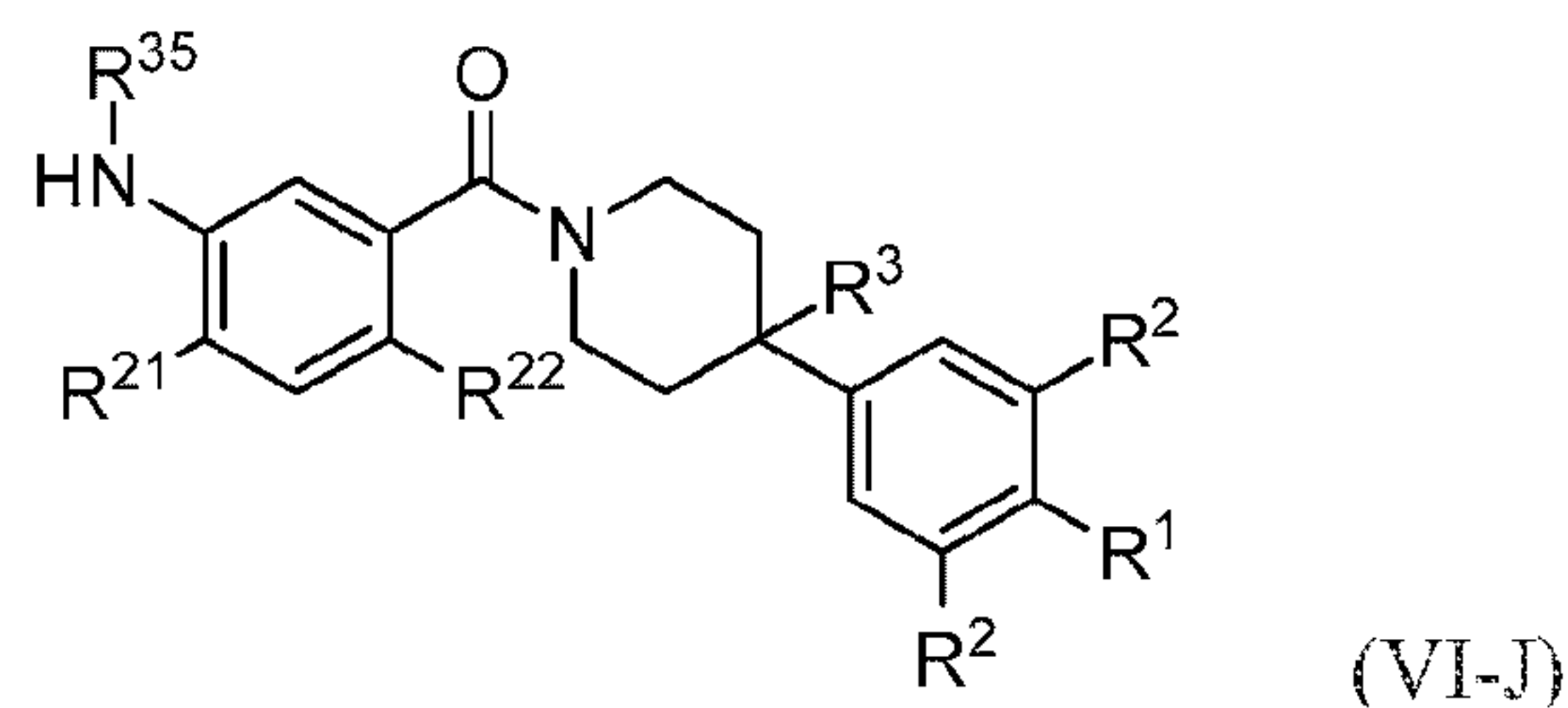
R_{36} is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{15}R_{16})$, heterocyclyl, or heteroaryl;

R_{13} and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;

and

R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino.

[0015] In various aspects, the present disclosure provides for compounds of Structure (VI-J):



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, -CN, halogen, C_1 - C_4 straight or branched alkyl, -O-(C_3 - C_5 cycloalkyl),
 -O-(C_1 - C_4 straight or branched alkyl) wherein:
 the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom; and
 when R^1 is not H, -CN or halogen, it is optionally substituted with one or more
 halogens;

each R^2 is independently H, halogen or C_1 - C_4 straight or branched alkyl;

R^3 is H, -OH, or halogen;

R^{21} is cyclobutyl, azetidin-1-yl, or cyclopropyl;

R^{22} is H, halogen, or C_1 - C_2 alkyl;

R^{35} is -C(O)- R^{351} , -C(O)-NHR³⁵¹, -C(O)-O- R^{351} or S(O)₂ R^{351} ; and

R^{351} is C_1 - C_6 straight or branched alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl.

[0016] In some aspects of Structure (VI-J), R^3 is H or halogen.

[0017] In some aspects of Structure (VI-J), R^1 is halogen, -CN or C_1 - C_2 haloalkyl.

[0018] In some aspects of Structure (VI-J), R^{22} is C_1 - C_2 alkyl.

[0019] In some aspects of Structure (VI-J), R^{21} is cyclobutyl and R^{22} is
 C_1 - C_2 alkyl.

[0020] In some aspects of Structure (VI-J), R^{21} is cyclobutyl.

[0021] In some aspects of Structure (VI-J), R^3 is H or F.

[0022] In some aspects of Structure (VI-J), R^1 is -CN.

[0023] In some aspects of Structure (VI-J), R^1 is -CF₃.

[0024] In some aspects of Structure (VI-J), R^{22} is H, methyl or ethyl.

[0025] In some aspects of Structure (VI-J), R^{22} is H.

[0026] In some aspects of Structure (VI-J), R^{22} is methyl.

[0027] In some aspects of Structure (VI-J), R^{35} is -C(O)-NHR³⁵¹.

[0028] In some aspects of Structure (VI-J), R^{351} is isopropyl, isobutyl, (R)-3-tetrahydrofuranyl, (S)-3-tetrahydrofuranyl, (R)-(tetrahydrofuran-2-yl)methyl, (S)-(tetrahydrofuran-2-yl)methyl, (R)-tetrahydro-2H-pyran-3-yl or (S)-tetrahydro-2H-pyran-3-yl.

[0029] In some aspects of Structure (VI-J), R^{351} is (R)-(tetrahydrofuran-2-yl)methyl or (S)-(tetrahydrofuran-2-yl)methyl.

[0030] In some aspects of Structure (VI-J), R^1 is -CN, each R^2 is hydrogen, R^3 is H or F, R^{21} is C_3 - C_4 cycloalkyl, R^{22} is H, R^{35} is -C(O)-NHR³⁵¹ where R^{351} is isopropyl, isobutyl, (R)-3-tetrahydrofuranyl, (S)-3-tetrahydrofuranyl, (R)-(tetrahydrofuran-2-yl)methyl, (S)-(tetrahydrofuran-2-yl)methyl, (R)-tetrahydro-2H-pyran-3-yl, or (S)-tetrahydro-2H-pyran-3-yl.

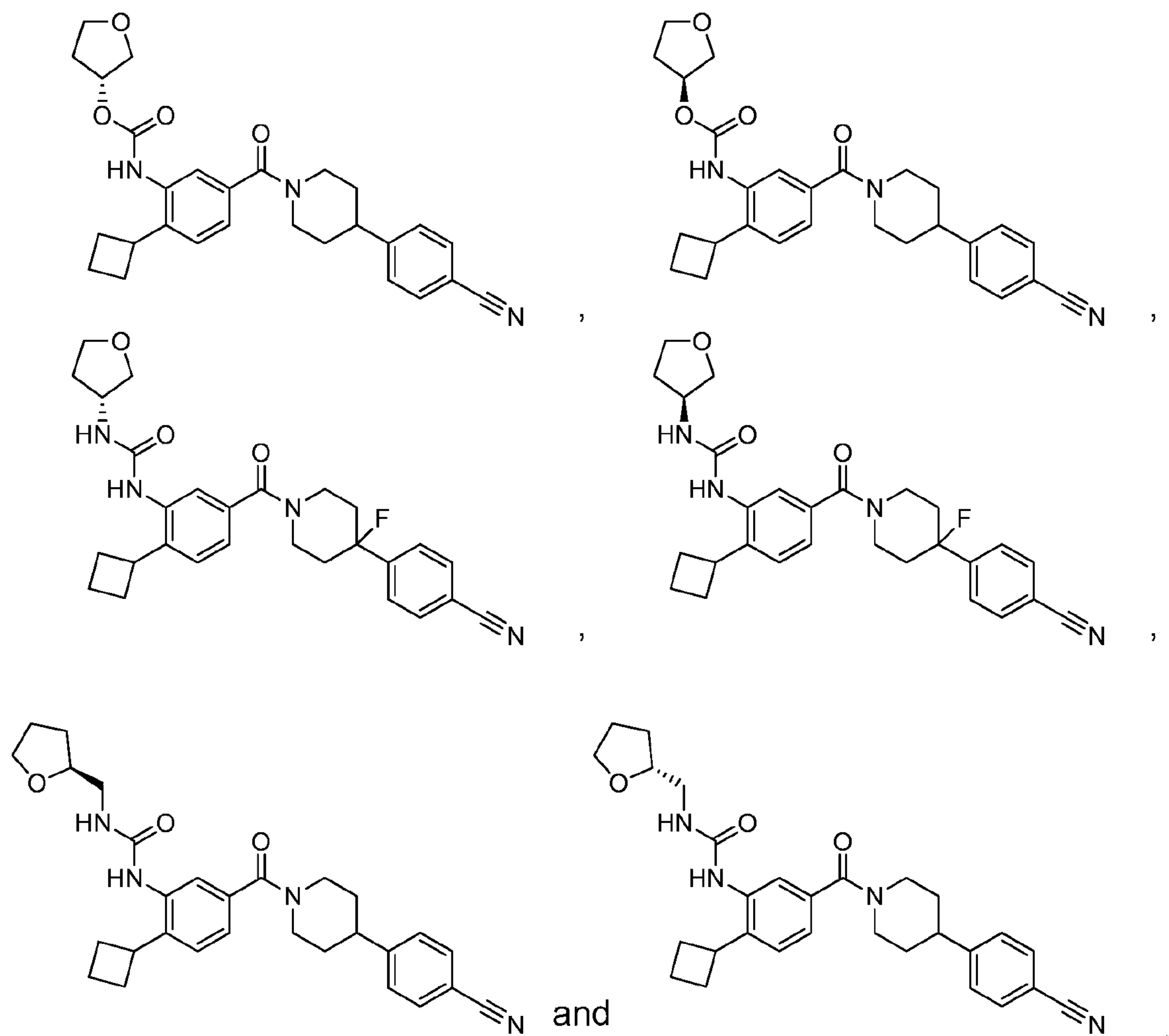
[0031] In some aspects of Structure (VI-J), R^{35} is -C(O)-O- R^{351} .

[0032] In some aspects of Structure (VI-J), R^{351} is isopropyl, isobutyl, (R)-3-tetrahydrofuranyl, (S)-3-tetrahydrofuranyl, (R)-(tetrahydrofuran-2-yl)methyl, (S)-(tetrahydrofuran-2-yl)methyl, (R)-tetrahydro-2*H*-pyran-3-yl, or (S)-tetrahydro-2*H*-pyran-3-yl.

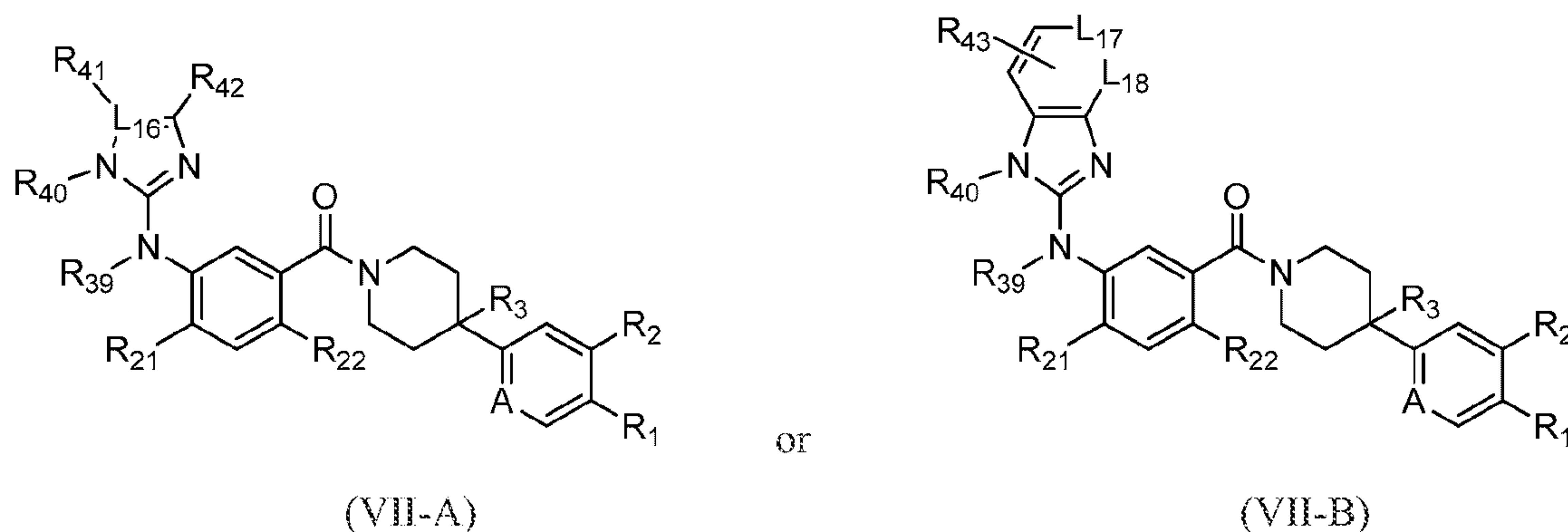
[0033] In some aspects of Structure (VI-J), R^1 is $-\text{CN}$, each R^2 is H, R^3 is H or F, R^{21} is C_3 - C_4 cycloalkyl, R^{22} is H, R^{35} is $-\text{C}(\text{O})-\text{O}-R^{351}$ where R^{351} is isopropyl, isobutyl, (R)-3-tetrahydrofuranyl, (S)-3-tetrahydrofuranyl, (R)-(tetrahydrofuran-2-yl)methyl, (S)-(tetrahydrofuran-2-yl)methyl, (R)-tetrahydro-2*H*-pyran-3-yl, or (S)-tetrahydro-2*H*-pyran-3-yl.

[0034] In some aspects of Structure (VI-J), R^{351} is (R)-3-tetrahydrofuranyl or (S)-3-tetrahydrofuranyl.

[0035] In some aspects of Structure (VI-J), compounds have a structure selected from the group consisting of:



[0036] In various aspects, the present disclosure provides for compounds of Structures (VII-A) or (VII-B):



or a pharmaceutically acceptable salt thereof, wherein:

L_{16} is C or N, wherein R_{41} is absent if L_{16} is N;

L_{17} , L_{18} , and A are each independently CH or N;

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$,
 $-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

q is 0, 1, 2, 3, or 4;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_2 is hydrogen, halo, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{21} and R_{22} are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy,
 CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

R_{40} , R_{42} , and R_{43} are each independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy,
 $-S(=O)_2R_{20}$, $-C(=O)R$, hydroxyalkyl, hydroxyl, $-N(R_{13}R_{14})$, or R_{41} and R_{42} taken
together with the atoms to which they are attached join together to form a
heteroaryl or heterocyclyl;

R_{41} is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-S(=O)_2R_{20}$, $-C(=O)R$, hydroxyalkyl,
hydroxyl, $-N(R_{13}R_{14})$, R_{41} is absent if L_{16} is N, or R_{41} and R_{42} taken together with
the atoms to which they are attached join together to form a heteroaryl or
heterocyclyl;

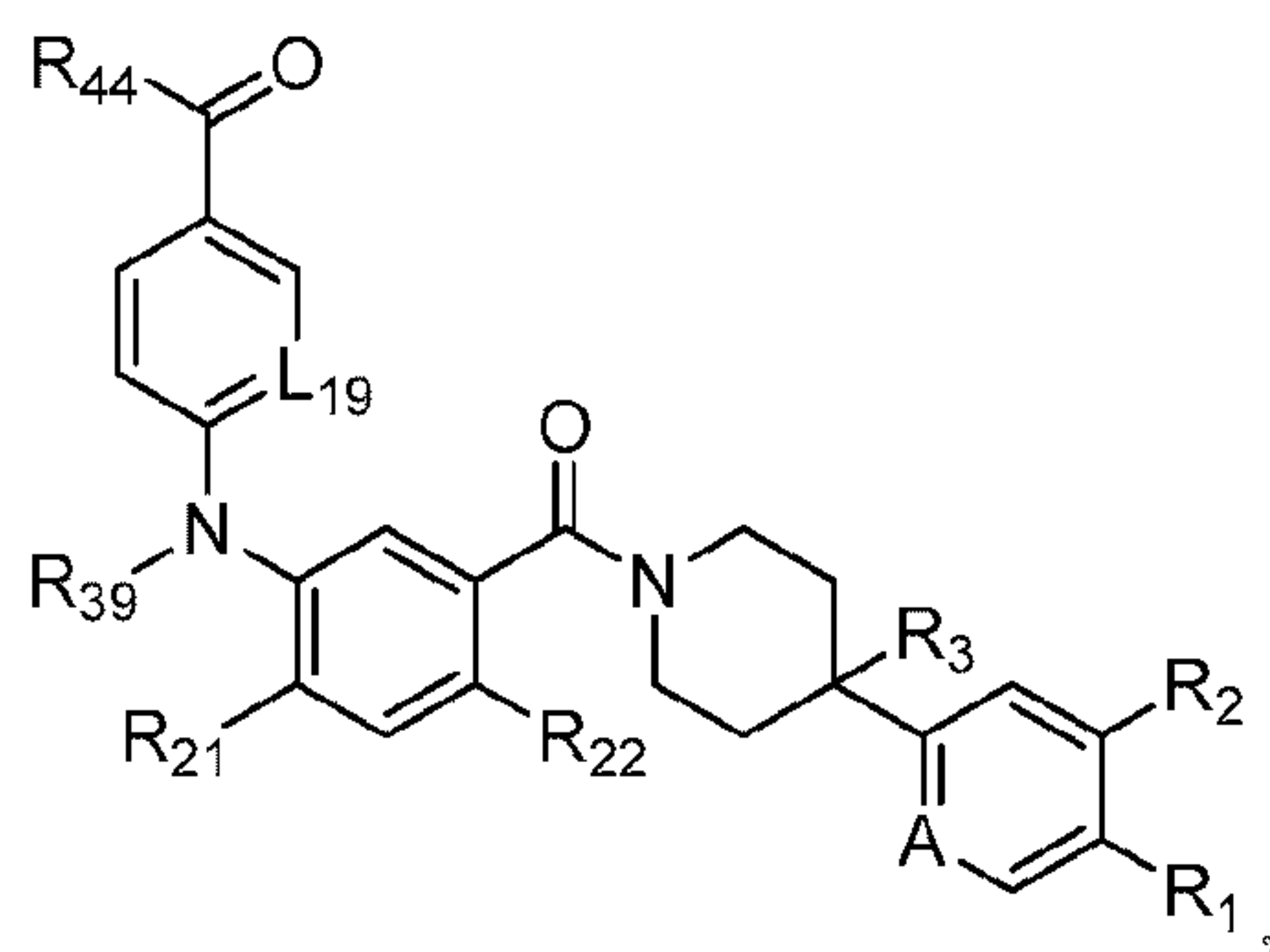
R is hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl,
 $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;

R_{39} is hydrogen, C_{1-6} alkyl, or C_{1-6} alkoxy;

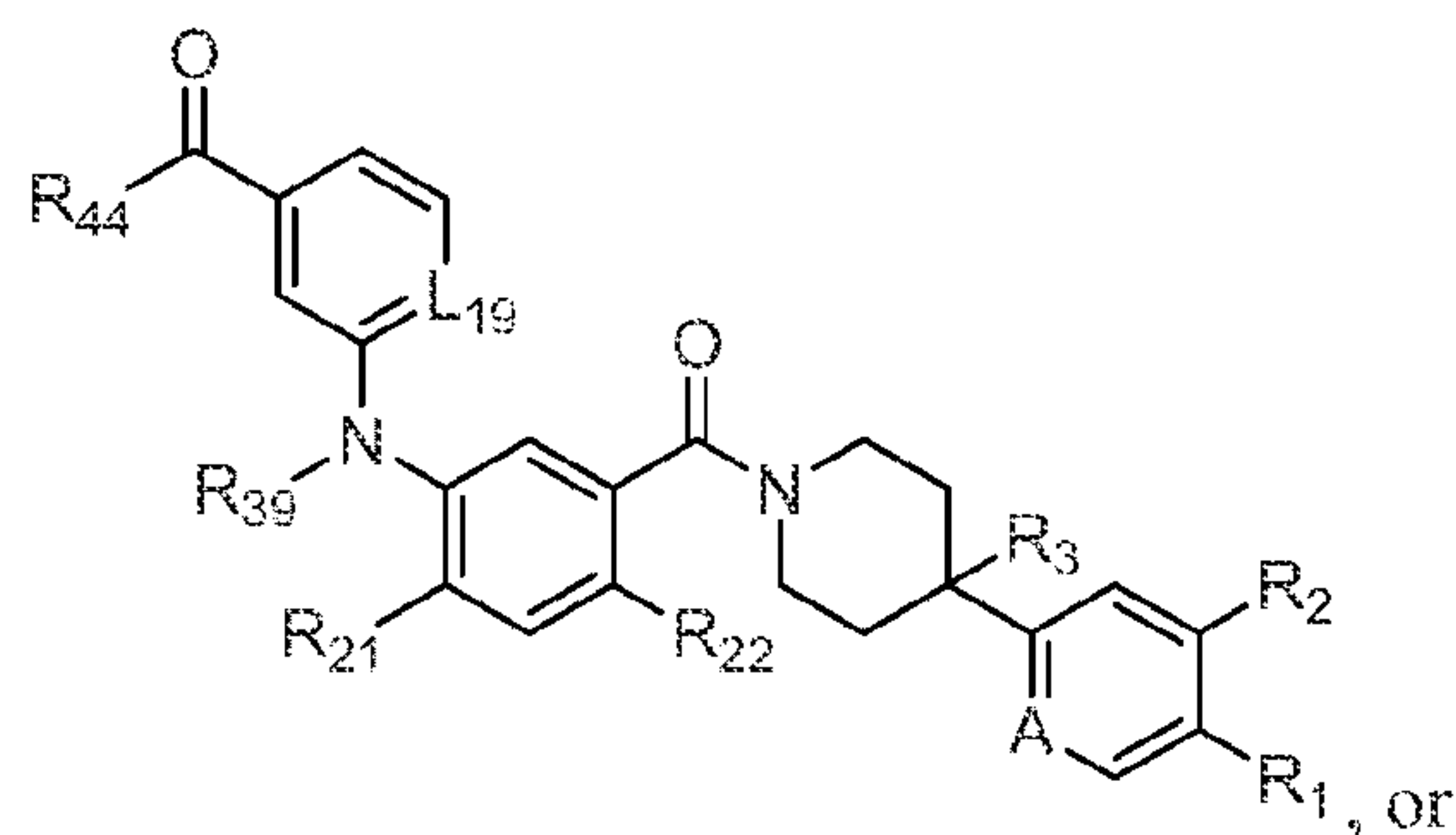
R_{13} and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$; and

R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino.

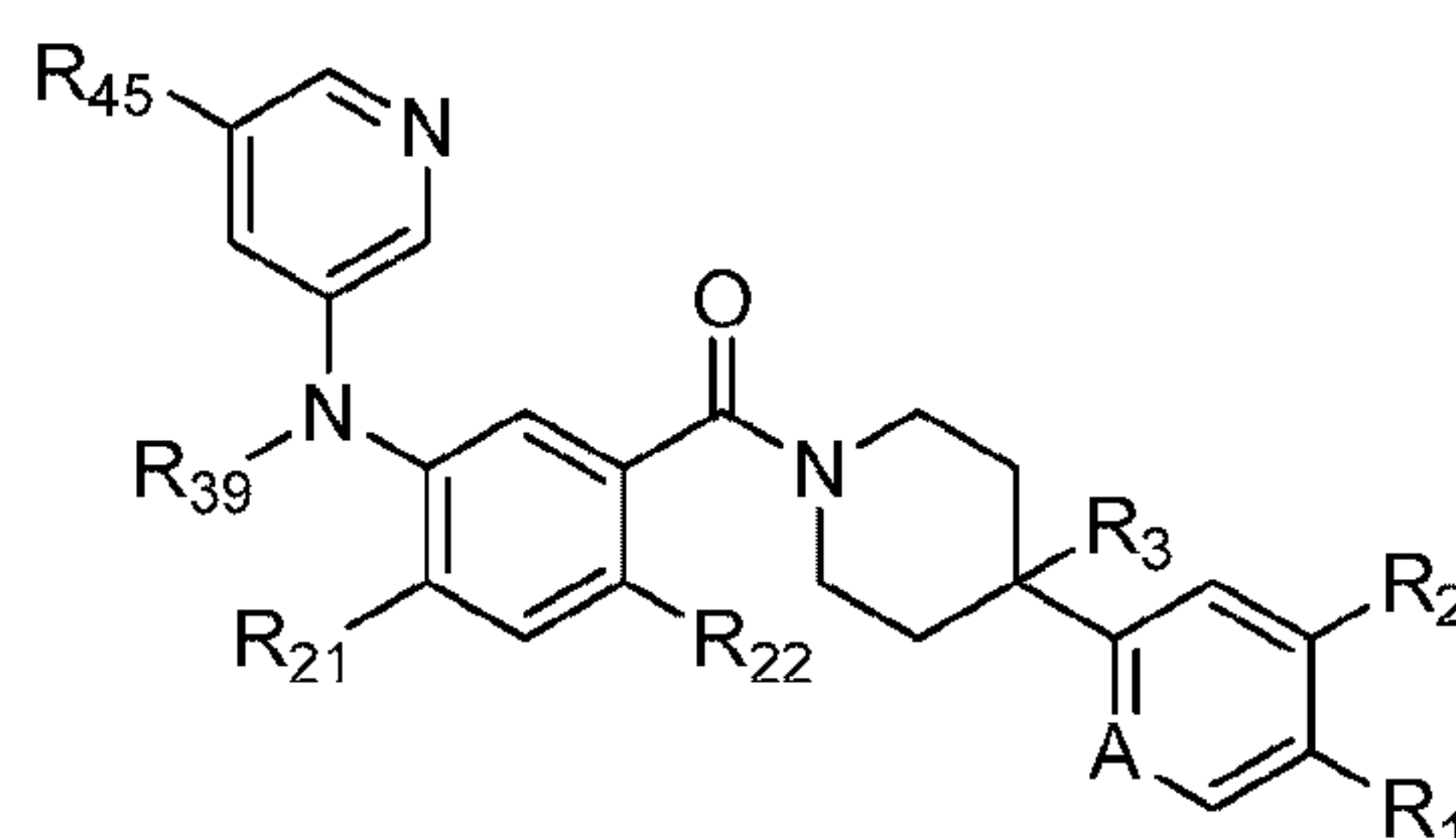
[0037] In various aspects, the present disclosure provides for compounds of Structures (VIII-A), (VIII-B), or (VIII-C):



(VIII-A)



(VIII-B)



(VIII-C)

or a pharmaceutically acceptable salt thereof, wherein:

L_{19} and A are each independently CH or N;

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$,

$-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

q is 0, 1, 2, 3, or 4;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_2 is hydrogen, halo, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{21} and R_{22} are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy,

CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

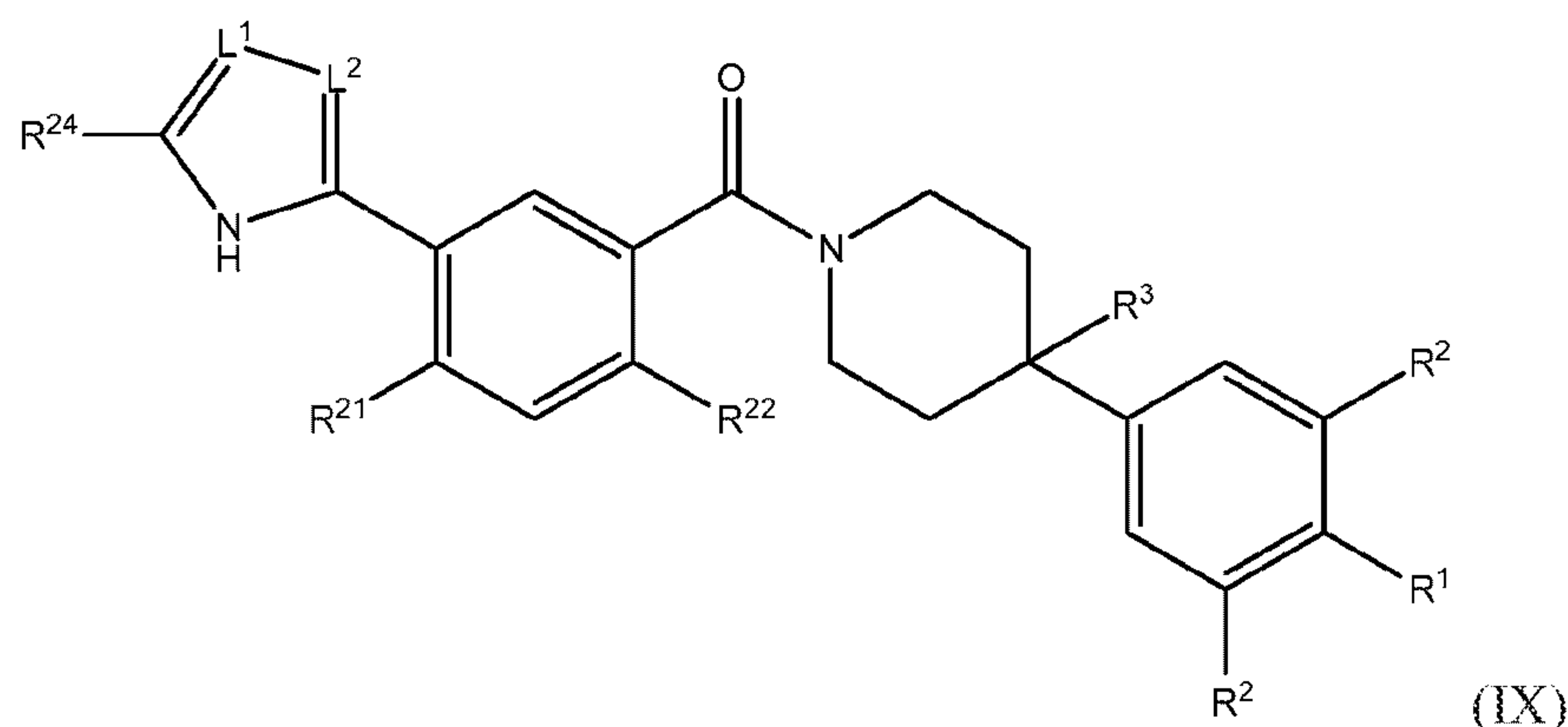
R_{39} is hydrogen, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{44} and R_{45} are each independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, cycloalkyl, hydroxyalkyl, aryl, heterocyclyl, heteroaryl, alkylamino, $-S(=O)_2R_{20}$, $-C(=O)R$, or $-N(R_{13}R_{14})$; and

R_{13} and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$; and

R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino.

[0038] In various aspects, compounds of Structure (IX) are provided:



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, -CN, halogen, C_1 - C_4 straight or branched alkyl, $-O-(C_3$ - C_5 cycloalkyl), $-O-(C_1$ - C_4 straight or branched alkyl) wherein:

C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom; and

when R^1 is not H, -CN or halogen, it is optionally substituted with one or more halogens;

each R^2 is independently hydrogen, halogen or C_1 - C_4 straight or branched alkyl;

R^3 is H, -OH, or halogen;

R^{21} is H, halogen, C_1 - C_4 straight or branched alkyl, C_3 - C_5 cycloalkyl wherein the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom;

R^{22} is H, halogen, or C_1 - C_2 alkyl;

R^{24} is H, C_1 - C_4 straight or branched alkyl, $-(C_1$ - C_4 alkyl) $_t$ -OH,

$-(C_1$ - C_4 alkyl) $_t$ -O $_t$ -(C_3 - C_5 cycloalkyl), or

$-(C_1$ - C_4 alkyl) $_t$ -O-(C_1 - C_4 straight or branched alkyl) wherein:

t is 0 or 1;

the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom;

L^1 is CR^{23} or N;

L^2 is CH or N;

at least one of L^1 or L^2 is N; and

R^{23} is H or C_1 - C_4 straight or branched alkyl.

[0039] In some aspects of Structure (IX), R^{24} is C_1 - C_4 straight or branched alkyl or $-(C_1$ - C_4 alkyl) $_t$ -O- $(C_1$ - C_4 straight or branched alkyl) wherein t is 0 or 1.

[0040] In some aspects of Structure (IX), R^{21} is halogen, C_1 - C_4 straight or branched alkyl, C_3 - C_5 cycloalkyl wherein the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom, $-S(O)_u$ -(C_1 - C_4 straight or branched alkyl) wherein u is 0 or 2, or $-S(O)_u$ -(C_3 - C_5 cycloalkyl) wherein u is 0 or 2;

[0041] In some aspects of Structure (IX), R^3 is H or halogen.

[0042] In some aspects of Structure (IX), R^1 is halogen, $-CN$ or C_1 - C_2 haloalkyl.

[0043] In some aspects of Structure (IX), both L^1 and L^2 are N.

[0044] In some aspects of Structure (IX), R^{21} is C_1 - C_2 alkyl or C_3 - C_5 cycloalkyl and R^{22} is C_1 - C_2 alkyl.

[0045] In some aspects of Structure (IX), R^{21} is C_3 - C_5 cycloalkyl and R^{22} is C_1 - C_2 alkyl.

[0046] In some aspects of Structure (IX), R^{24} is $-(C_1$ - C_2 alkyl) $_t$ -O- $(C_1$ - C_2 alkyl) wherein t is 0 or 1.

[0047] In some aspects of Structure (IX), R^{21} is C_3 - C_5 cycloalkyl, R^{22} is C_1 - C_2 alkyl and R^{24} is C_1 - C_2 alkyl.

[0048] In some aspects of Structure (IX), R^{21} is cyclobutyl, R^{22} is C_1 - C_2 alkyl and R^{24} is C_1 - C_2 alkyl.

[0049] In some aspects of Structure (IX), R^{21} is cyclobutyl.

[0050] In some aspects of Structure (IX), R^3 is H or F.

[0051] In some aspects of Structure (IX), R^1 is $-CN$.

[0052] In some aspects of Structure (IX), R^1 is $-CF_3$.

[0053] In some aspects of Structure (IX), R^{22} is H, methyl or ethyl.

[0054] In some aspects of Structure (IX), R^{22} is H.

[0055] In some aspects of Structure (IX), R^{22} is methyl.

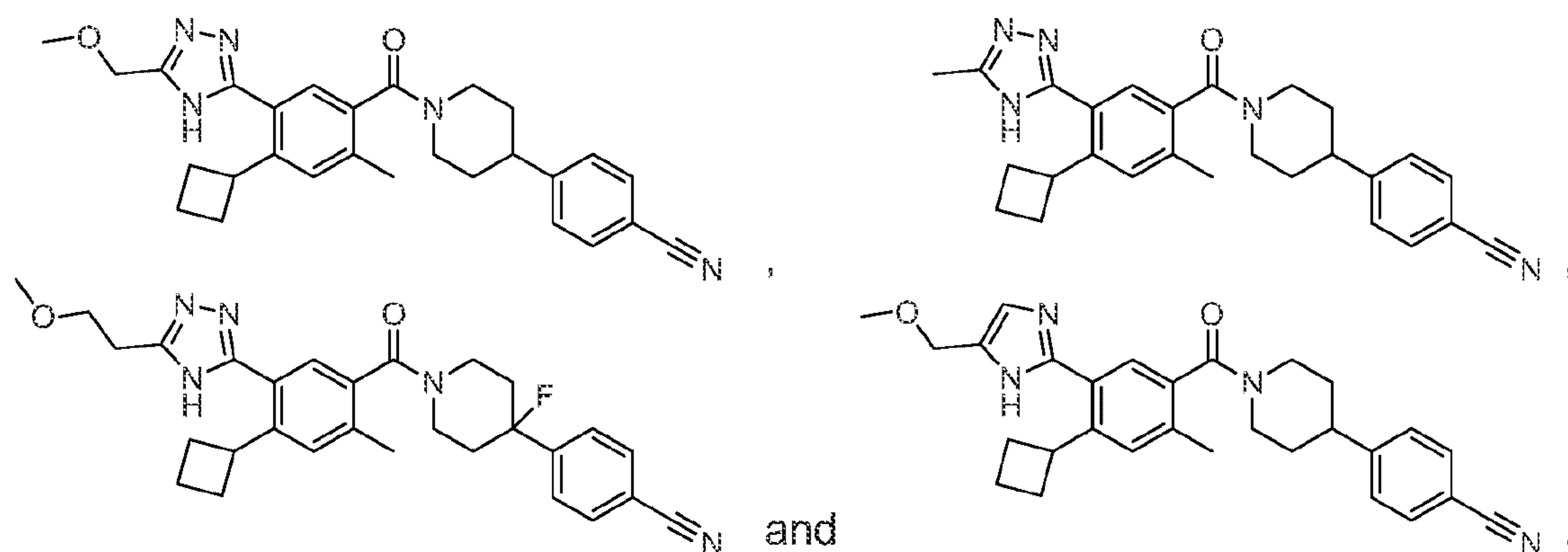
[0056] In some aspects of Structure (IX), R^1 is $-CN$, each R^2 is H, R^3 is H or F, R^{21} is C_3 - C_4 cycloalkyl, R^{22} is methyl, L^1 and L^2 are N, and R^{24} is methyl, ethyl, hydroxymethyl, methoxymethyl, 2-methoxyethyl.

[0057] In some aspects of Structure (IX), R^1 is $-CN$, each R^2 is H, R^3 is H or F, R^{21} is C_3 - C_4 cycloalkyl, R^{22} is methyl, L^1 and L^2 are N, and R^{24} is methoxy or ethoxy.

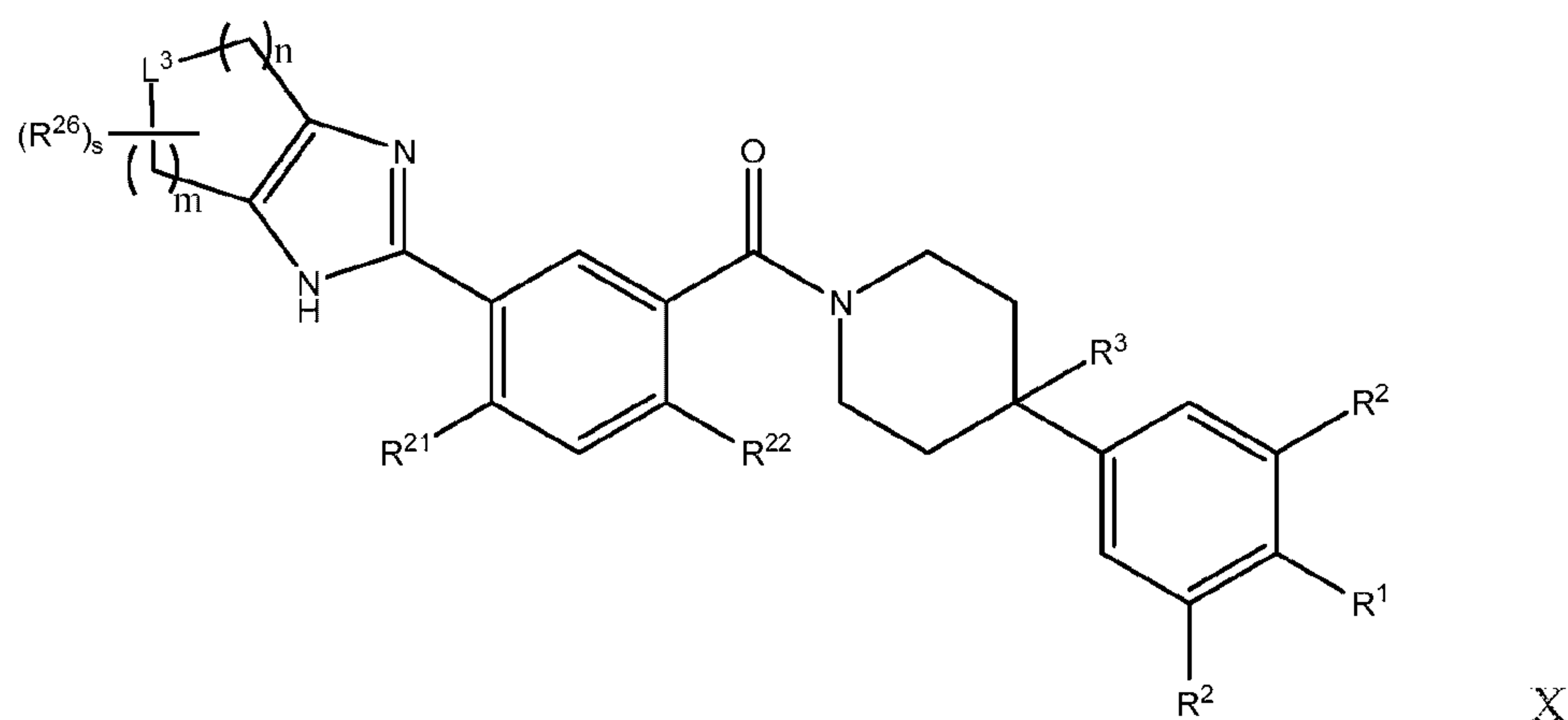
[0058] In some aspects of Structure (IX), R^1 is $-\text{CN}$, each R^2 is H, R^3 is H or F, R^{21} is C_3 - C_4 cycloalkyl, R^{22} is methyl, L^1 is CH, L^2 is N, and R^{24} is methyl, ethyl, hydroxymethyl, methoxymethyl, or 2-methoxyethyl.

[0059] In some aspects of Structure (IX), R^1 is $-\text{CN}$, each R^2 is H, R^3 is H or F, R^{21} is C_3 - C_4 cycloalkyl, R^{22} is methyl, L^1 is N, L^2 is CH, and R^{24} is methyl, ethyl, hydroxymethyl, methoxymethyl, or 2-methoxyethyl.

[0060] In some aspects of Structure (IX), compounds have a structure selected from the group consisting of:



[0061] In various aspects, compounds of Structure (X) are provided:



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, $-\text{CN}$, halogen, C_1 - C_4 straight or branched alkyl, $-\text{O}-(\text{C}_3$ - C_5 cycloalkyl),

$-\text{O}-(\text{C}_1$ - C_4 straight or branched alkyl) wherein:

the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom; and

when R^1 is not H, $-\text{CN}$ or halogen, it is optionally substituted with one or more halogens;

each R^2 is independently hydrogen, halogen or C_1 - C_4 straight or branched alkyl;

R^3 is H, $-\text{OH}$ or halogen;

L^3 is $C(R^{60})_2$, O or NR^{50} ;

each R^{60} is independently H, -OH, -CN, $-O_t-(C_3-C_5 \text{ cycloalkyl})$, $-O-(C_1-C_4 \text{ straight or branched alkyl})$, or $-C(O)-N(R^{601})_2$ wherein:

t is 0 or 1, and

the C_3-C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom;

each R^{50} is independently H, $-C(O)-O_t-(C_1-C_4 \text{ straight or branched alkyl})$,

$-C(O)-O_t-(C_3-C_5 \text{ cyclic alkyl})$, $-C_3-C_5$ cyclic alkyl optionally containing an oxygen or nitrogen heteroatom, $-C(O)-N(R^{501})_2$, C_1-C_4 straight or branched alkyl wherein:

t is 0 or 1, and

the C_3-C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom;

n is 1, 2 or 3;

m is 1 or 2;

R^{21} is H, halogen, C_1-C_4 straight or branched alkyl, C_3-C_5 cycloalkyl wherein the C_3-C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom

R^{22} is H, halogen, C_1-C_2 alkyl;

each R^{26} is independently -OH, -CN, halogen, C_1-C_4 straight or branched alkyl,

$-(C_1-C_4 \text{ alkyl})_t-O_t-(C_3-C_5 \text{ cycloalkyl})$, $-(C_1-C_4 \text{ alkyl})_t-O-(C_1-C_4 \text{ straight or branched alkyl})$, $-C(O)-O_t-(C_1-C_4 \text{ alkyl})$, or $-C(O)-N(R^{501})_2$ wherein:

t is 0 or 1, and

the C_3-C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom;

s is 0, 1 or 2;

each R^{601} and R^{501} is independently H or C_1-C_4 straight or branched alkyl; and

wherein two of R^{26} , R^{60} , R^{50} , R^{501} and R^{601} optionally join to form a ring wherein the two of R^{26} , R^{60} , R^{50} , R^{501} and R^{601} may be two R^{26} , two R^{60} , two R^{50} , two R^{501} or two R^{601} .

[0062] In some aspects of Structure (X), R^{21} is halogen, C_1-C_4 straight or branched alkyl or C_3-C_5 cycloalkyl.

[0063] In some aspects of Structure (X), R^3 is H or halogen.

[0064] In some aspects of Structure (X), R^1 is -CN or C_1-C_2 haloalkyl.

[0065] In some aspects of Structure (X), R^3 is H or F.

[0066] In some aspects of Structure (X), R^1 is -CN.

[0067] In some aspects of Structure (X), R^1 is $-CF_3$.

[0068] In some aspects of Structure (X), n is 1.

[0069] In some aspects of Structure (X), n is 2.

[0070] In some aspects of Structure (X), m is 1

[0071] In some aspects of Structure (X), m is 2.

[0072] In some aspects of Structure (X), R^{21} is C_1 - C_2 alkyl or C_3 - C_5 cycloalkyl and R^{22} is C_1 - C_2 alkyl.

[0073] In some aspects of Structure (X), R^{21} is C_3 - C_5 cycloalkyl and R^{22} is C_1 - C_2 alkyl.

[0074] In some aspects of Structure (X), n is 2, m is 1, L^3 is $-N-C(O)-O-(C_1-C_2 \text{ alkyl})$.

[0075] In some aspects of Structure (X), L^3 is NR^{50} ; R^{50} is C_1 - C_2 alkyl; R^{21} is cyclobutyl; R^{22} is H or methyl; R^3 is H; R^1 is $-CN$; m is 2 and n is 1 or 2.

[0076] In some aspects of Structure (X), n is 2, m is 1, L^3 is O and s is 0.

[0077] In some aspects of Structure (X), R^{22} is H, methyl or ethyl.

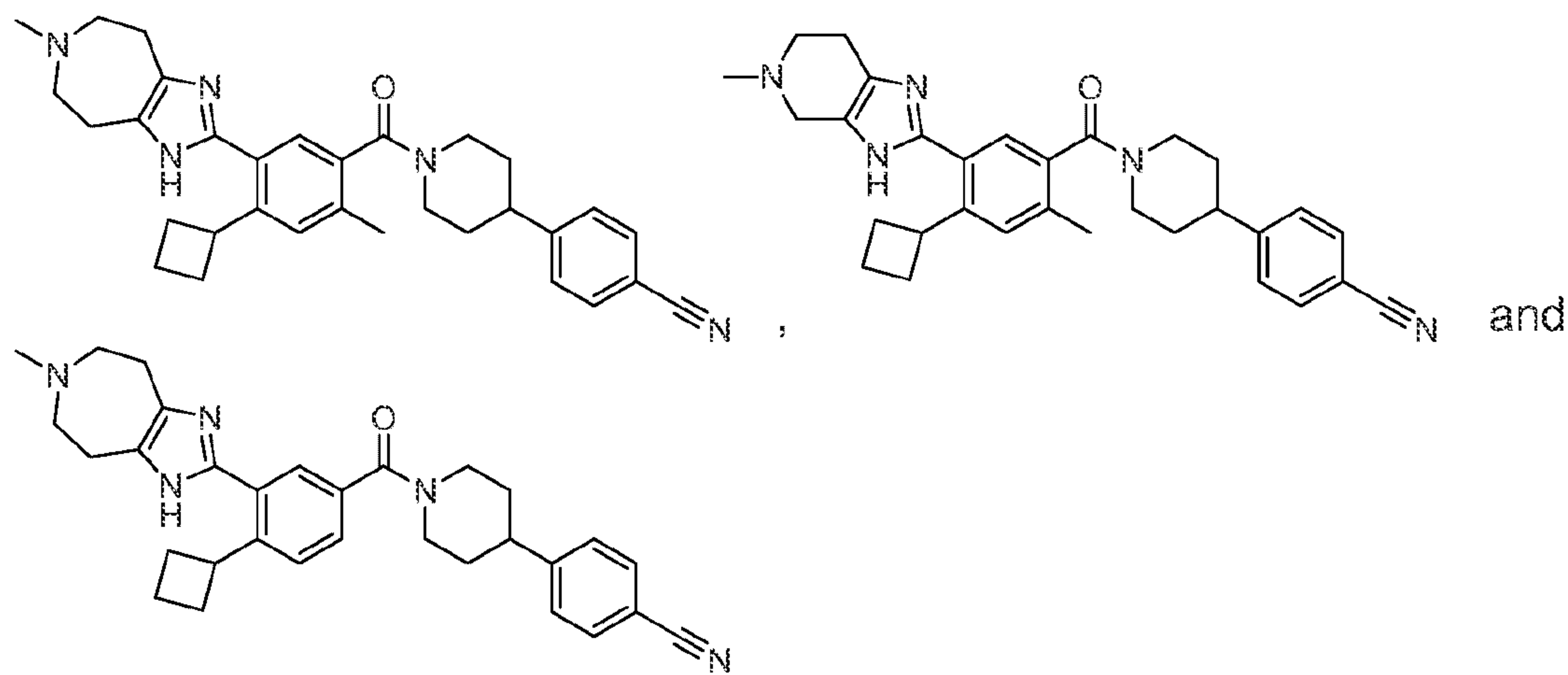
[0078] In some aspects of Structure (X), R^{22} is methyl.

[0079] In some aspects of Structure (X), R^{22} is H.

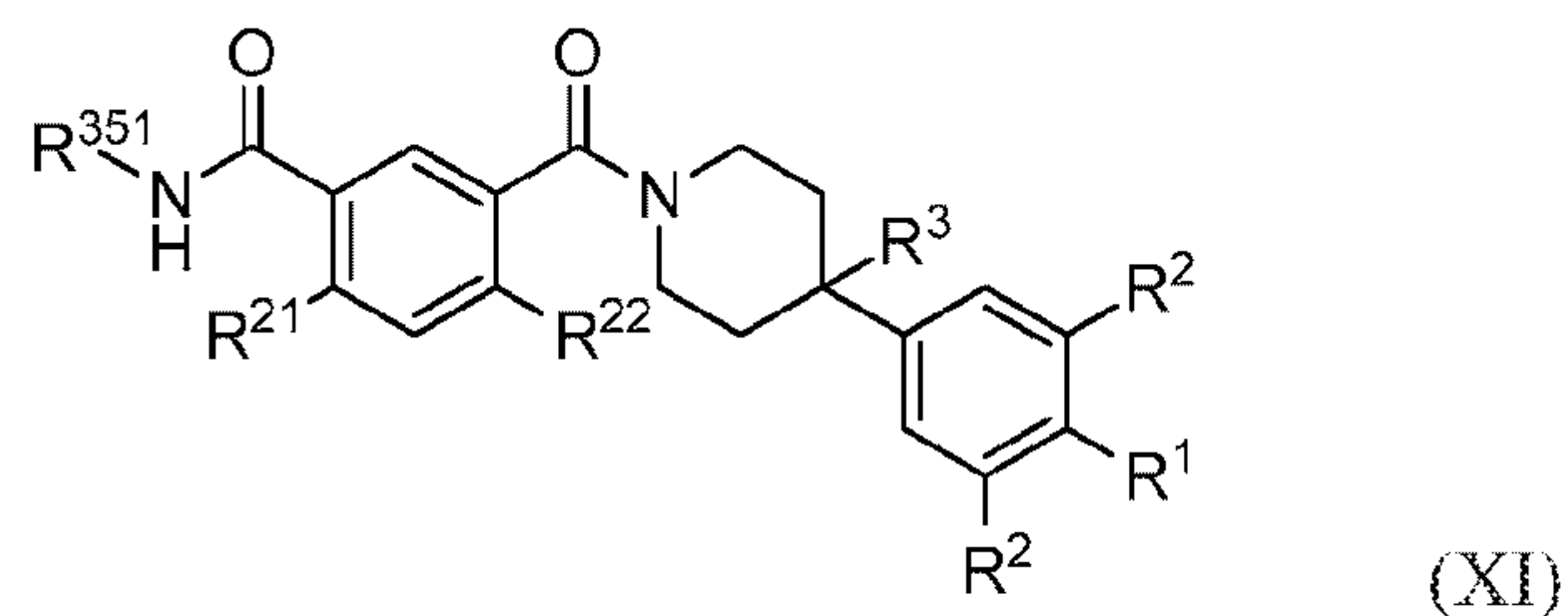
[0080] In some aspects of Structure (X), R^1 is $-CN$, each R^2 is H, R^3 is H or F, R^{21} is C_3 - C_4 cycloalkyl, R^{22} is methyl, n is 2 and L^3 is NR^{50} where R^{50} is methyl or ethyl.

[0081] In some aspects of Structure (X), R^1 is $-CN$, each R^2 is H, R^3 is H or F, R^{21} is C_3 - C_4 cycloalkyl, R^{22} is methyl, n is 2 and L^3 is O.

[0082] In some aspects of Structure (X), the compound has a structure selected from the group consisting of:



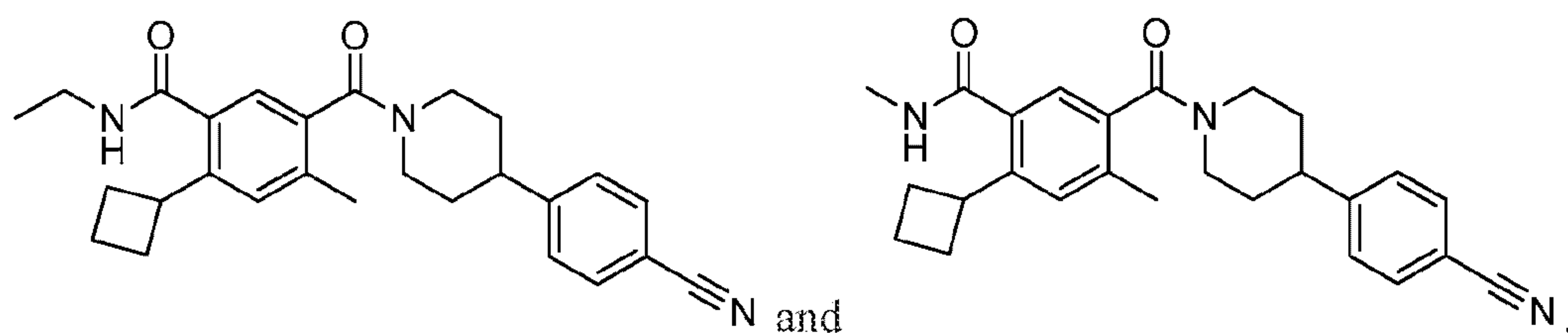
[0083] In various aspects, compounds of Structure (XI) are provided:



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, -CN, halogen, C_1 - C_4 straight or branched alkyl, -O-(C_3 - C_5 cycloalkyl), -O-(C_1 - C_4 straight or branched alkyl) wherein:
the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom; and
when R^1 is not H, -CN or halogen, it is optionally substituted with one or more halogens;
each R^2 is independently H, halogen or C_1 - C_4 straight or branched alkyl;
 R^3 is H, -OH, or halogen;
 R^{21} is cyclobutyl, azetidin-1-yl, or cyclopropyl;
 R^{22} is H, halogen, C_1 - C_2 alkyl; and
 R^{351} is C_1 - C_2 alkyl or C_2 -O-(C_1 or C_2 alkyl).

- [0084] In some aspects of Structure (XI), R^3 is H or halogen.
[0085] In some aspects of Structure (XI), R^1 is halogen, -CN or C_1 - C_2 haloalkyl.
[0086] In some aspects of Structure (XI), R^{21} is C_3 - C_4 cycloalkyl and R^{22} is C_1 - C_2 alkyl.
[0087] In some aspects of Structure (XI), R^{21} is cyclobutyl and R^{22} is C_1 - C_2 alkyl.
[0088] In some aspects of Structure (XI), R^{21} is cyclobutyl.
[0089] In some aspects of Structure (XI), R^3 is H or F.
[0090] In some aspects of Structure (XI), R^1 is -CN.
[0091] In some aspects of Structure (XI), R^1 is -CF₃.
[0092] In some aspects of Structure (XI), R^{22} is H, methyl or ethyl.
[0093] In some aspects of Structure (XI), R^{22} is H.
[0094] In some aspects of Structure (XI), R^{22} is methyl.
[0095] In some aspects of Structure (XI), R^1 is -CN, each R^2 is H, R^3 is H or F, R^{21} is cyclobutyl, R^{22} is methyl and R^{351} is methyl or ethyl.
[0096] In some aspects of Structure (XI), the compound has a structure selected from the group consisting of:



- [0097] In various aspects, the present disclosure provides pharmaceutical compositions comprising any one of the compounds of Structures (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X) or (XI) and a pharmaceutically acceptable carrier, excipient, or diluent.

[0098] In various aspects, the present disclosure provides methods of treating a condition characterized by dysregulation of a fatty acid synthase function in subject, the method comprising administering to the subject in need of such treatment an effective amount of a compound of any one of the Structures (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X) or (XI). In various aspects the condition characterized by dysregulation of the fatty acid synthase function is a viral infection or cancer. In various aspects the viral infection is treated using a compound of any one of the Structures (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X) or (XI) in combination with one or more additional antiviral treatments. In various aspects the cancer is treated using a compound of any one of the Structures (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X) or (XI) in combination with one or more additional cancer treatments. In various aspects, the viral infection is hepatitis C.

BRIEF DESCRIPTION OF THE DRAWINGS

[0099] FIG. 1 illustrates a correlation between FASN inhibition and HCV inhibition.

DETAILED DESCRIPTION

[0100] The present disclosure addresses the deficiencies in treating conditions characterized by dysregulation of the FASN function in a subject, such as viral infection, cancer and metabolic disorders, by providing novel heterocyclic modulators of lipid synthesis.

[0101] In certain aspects, the present disclosure provides compositions and methods for treatment of viral infections. In general, the compositions and methods for treatment of viral infections are directed toward modulation of the fatty acid synthesis pathway. The fatty acid synthesis pathway is involved in the replication of viruses into the host cells. The present invention embodies methods for the treatment of viral infection, such as hepatitis C infections, yellow fever infections, and human rhinovirus infections, or any virus that targets the fatty acid synthesis pathway.

[0102] In certain aspects, the present disclosure provides compositions and methods for the treatment of cancer. Fatty acid synthase is responsible for conversion of malonyl-CoA into long-chain fatty acids, which is an early reaction in fatty acid biosynthesis. Fatty acid synthase is overexpressed in many cancer cells. Without being bound by any particular theory, it is hypothesized that inhibition of fatty acid synthase expression or fatty acid synthase activity selectively suppresses proliferation and induces cell death of cancer cells, with little toxicity towards normal cells.

[0103] Further, the present disclosure provides compounds and methods for modulating host cell targets that are targeted by viruses. Such modulation of host cell targets can include either activation or inhibition of the host cell targets. Accordingly, compounds that modulate,

e.g., inhibit, the activity of a non-viral protein, e.g., a host cell protein, e.g., components of the fatty acid synthesis pathway, can be used as antiviral pharmaceutical agents.

Definitions

[0104] Chemical moieties referred to as univalent chemical moieties (e.g., alkyl, aryl, etc.) also encompass structurally permissible multivalent moieties, as understood by those skilled in the art. For example, while an “alkyl” moiety generally refers to a monovalent radical (e.g., CH_3CH_2-), in appropriate circumstances an “alkyl” moiety can also refer to a divalent radical (e.g., $-\text{CH}_2\text{CH}_2-$, which is equivalent to an “alkylene” group). Similarly, under circumstances where a divalent moiety is required, those skilled in the art will understand that the term “aryl” refers to the corresponding divalent arylene group.

[0105] All atoms are understood to have their normal number of valences for bond formation (e.g., 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the atom's oxidation state). On occasion a moiety can be defined, for example, as $(\text{A})_a\text{B}$, wherein a is 0 or 1. In such instances, when a is 0 the moiety is B and when a is 1 the moiety is AB.

[0106] Where a substituent can vary in the number of atoms or groups of the same kind (e.g., alkyl groups can be C_1 , C_2 , C_3 , etc.), the number of repeated atoms or groups can be represented by a range (e.g., $\text{C}_1\text{-C}_6$ alkyl) which includes each and every number in the range and any and all sub ranges. For example, $\text{C}_1\text{-C}_3$ alkyl includes C_1 , C_2 , C_3 , C_{1-2} , C_{1-3} , and C_{2-3} alkyl.

[0107] “Alkanoyl” refers to a carbonyl group with a lower alkyl group as a substituent.

[0108] “Alkylamino” refers to an amino group substituted by an alkyl group.

[0109] “Alkoxy” refers to an O-atom substituted by an alkyl group as defined herein, for example, methoxy [$-\text{OCH}_3$, a C_1 alkoxy]. The term “ C_{1-6} alkoxy” encompasses C_1 alkoxy, C_2 alkoxy, C_3 alkoxy, C_4 alkoxy, C_5 alkoxy, C_6 alkoxy, and any sub-range thereof.

[0110] “Alkoxy carbonyl” refers to a carbonyl group with an alkoxy group as a substituent.

[0111] “Alkyl,” “alkenyl,” and “alkynyl,” refer to optionally substituted, straight and branched chain aliphatic groups having from 1 to 30 carbon atoms, or preferably from 1 to 15 carbon atoms, or more preferably from 1 to 6 carbon atoms. Examples of alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, isobutyl, pentyl, hexyl, vinyl, allyl, isobutenyl, ethynyl, and propynyl. The term “heteroalkyl” as used herein contemplates an alkyl with one or more heteroatoms.

[0112] “Alkylene” refers to an optionally substituted divalent radical which is a branched or unbranched hydrocarbon fragment containing the specified number of carbon atoms, and having two points of attachment. An example is propylene [$-\text{CH}_2\text{CH}_2\text{CH}_2-$, a C_3 alkylene].

[0113] “Amino” refers to the group -NH_2 .

[0114] “Aryl” refers to optionally substituted aromatic groups which have at least one ring having a conjugated pi electron system and includes carbocyclic aryl, and biaryl groups, all of which can be optionally substituted. Phenyl and naphthyl groups are preferred carbocyclic aryl groups.

[0115] “Aralkyl” or “arylalkyl” refer to alkyl-substituted aryl groups. Examples of aralkyl groups include butylphenyl, propylphenyl, ethylphenyl, methylphenyl, 3,5-dimethylphenyl, tert-butylphenyl.

[0116] “Carbamoyl” as used herein contemplates a group of the structure $\text{---}\overset{\text{O}}{\parallel}\text{C---NR}^{\text{N}}_2$ where in R^{N} is selected from the group consisting of hydrogen, -OH , C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, sulfonyl, sulfonate and sulfonamide.

[0117] “Carbonyl” refers to a group of the structure $\text{---}\overset{\text{O}}{\parallel}\text{C---}$.

[0118] “Cycloalkyl” refers to an optionally substituted ring, which can be saturated or unsaturated and monocyclic, bicyclic, or tricyclic formed entirely from carbon atoms. An example of a cycloalkyl group is the cyclopentenyl group ($\text{C}_5\text{H}_7\text{---}$), which is a five carbon (C_5) unsaturated cycloalkyl group.

[0119] “Heterocycle” refers to an optionally substituted 5- to 7-membered cycloalkyl ring system containing 1, 2 or 3 heteroatoms, which can be the same or different, selected from N, O or S, and optionally containing one double bond.

[0120] “Halogen” refers to a chloro, bromo, fluoro or iodo atom radical. The term “halogen” also contemplates terms “halo” or “halide.”

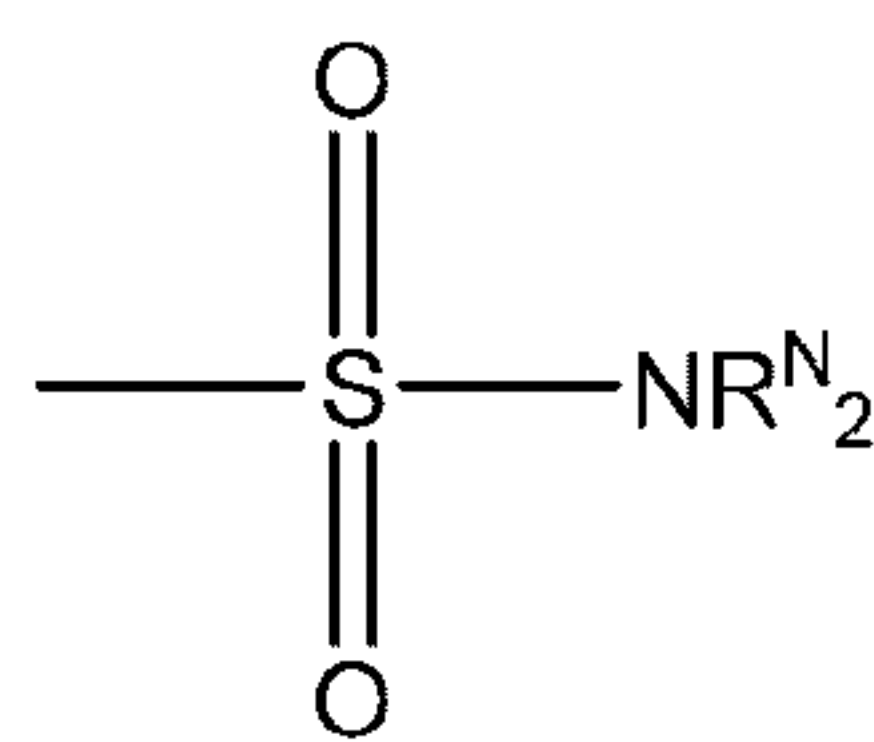
[0121] “Heteroatom” refers to a non-carbon atom, where boron, nitrogen, oxygen, sulfur and phosphorus are preferred heteroatoms, with nitrogen, oxygen and sulfur being particularly preferred heteroatoms in the compounds of the present disclosure.

[0122] “Heteroaryl” refers to optionally substituted aryl groups having from 1 to 9 carbon atoms and the remainder of the atoms are heteroatoms, and includes those heterocyclic systems described in “Handbook of Chemistry and Physics,” 49th edition, 1968, R. C. Weast, editor; The Chemical Rubber Co., Cleveland, Ohio. See particularly Section C, Rules for Naming Organic Compounds, B. Fundamental Heterocyclic Systems. Suitable heteroaryls

include thienyl, pyrrolyl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, pyranyl, tetrazolyl, pyrrolyl, pyrrolinyl, pyridazinyl, triazolyl, indolyl, isoindolyl, indoliziny, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl, oxadiazolyl, benzoxazolyl, benzoxadiazolyl, thiadiazolyl, benzothiazolyl, benzothiadiazolyl, and the like.

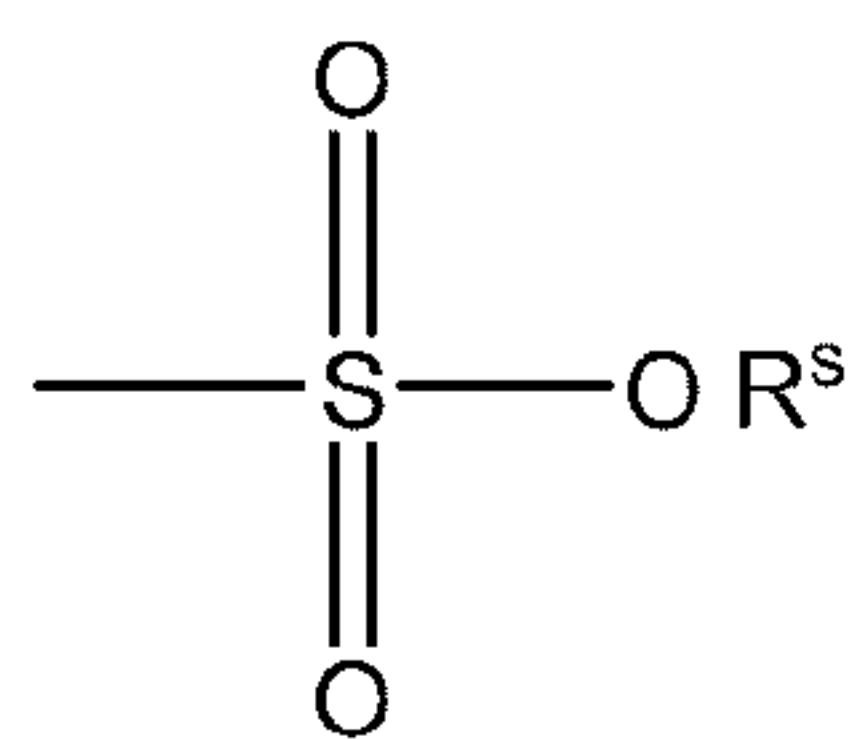
[0123] An “optionally substituted” moiety can be substituted with from one to four, or preferably from one to three, or more preferably one or two non-hydrogen substituents. Unless otherwise specified, when the substituent is on a carbon, it is selected from the group consisting of -OH, -CN, -NO₂, halogen, C₁ to C₁₂ alkyl, C₁ to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, none of which are further substituted. Unless otherwise specified, when the substituent is on a nitrogen, it is selected from the group consisting of C₁ to C₁₂ alkyl, C₁ to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, sulfonyl, sulfonate and sulfonamide none of which are further substituted.

[0124] The term “sulfonamide” as used herein contemplates a group having the structure



wherein R^N is selected from the group consisting of hydrogen, -OH, C₁ to C₁₂ alkyl, C₁ to C₁₂ heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

[0125] The term “sulfonate” as used herein contemplates a group having the structure



wherein R^S is selected from the group consisting of hydrogen, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkanoyl, or C₁-C₁₀ alkoxycarbonyl.

[0126] “Sulfonyl” as used herein alone or as part of another group, refers to an SO₂ group. The SO₂ moiety is optionally substituted.

[0127] Compounds of the present disclosure can exist as stereoisomers, wherein asymmetric or chiral centers are present. Stereoisomers are designated (R) or (S) depending on the configuration of substituents around the chiral carbon atom. The terms (R) and (S) used

herein are configurations as defined in IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem., (1976), 45: 13-30. The present disclosure contemplates various stereoisomers and mixtures thereof and are specifically included within the scope of the present disclosure. Stereoisomers include enantiomers, diastereomers, and mixtures of enantiomers or diastereomers. Individual stereoisomers of compounds of the present disclosure can be prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

[0128] Also, moieties disclosed herein which exist in multiple tautomeric forms include all such forms encompassed by a given tautomeric structure.

[0129] Individual atoms in the disclosed compounds may be any isotope of that element. For example hydrogen may be in the form of deuterium.

[0130] “Pharmaceutically acceptable” means approved or approvable by a regulatory agency of the Federal or state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly in humans. It can be material which is not biologically or otherwise undesirable, i.e., the material can be administered to an individual without causing any undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[0131] The term “pharmaceutically acceptable salt” of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include, for example, acid addition salts and base addition salts.

[0132] “Acid addition salts” according to the present disclosure, are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid,

benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like.

[0133] “Base addition salts” according to the present disclosure are formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base.

Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are often formed during the process of crystallization. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature can cause a single crystal form to dominate.

[0134] The term “treating” includes the administration of the compounds or agents of the present invention to a subject to prevent or delay, to alleviate, or to arrest or inhibit development of the symptoms or conditions associated with fatty acid synthase-associated disorders, e.g., tumor growth associated with cancer. A skilled medical practitioner will know how to use standard methods to determine whether a patient is suffering from a disease associated with activity of fatty acid synthase, e.g., by examining the patient and determining whether the patient is suffering from a disease known to be associated with fatty acid synthase activity or by assaying for fatty acid synthase levels in blood plasma or tissue of the individual suspected of suffering from fatty acid synthase associated disease and comparing fatty acid synthase levels in the blood plasma or tissue of the individual suspected of suffering from a fatty acid synthase associated disease fatty acid synthase levels in the blood plasma or tissue of a healthy individual. Increased securin levels are indicative of disease. Accordingly, the present invention provides, inter alia, methods of administering a compound

of the present invention to a subject and determining fatty acid synthase activity in the subject. Fatty acid synthase activity in the subject can be determined before and/or after administration of the compound.

[0135] A “therapeutically effective amount” or “pharmaceutically effective amount” means the amount that, when administered to a subject, produces effects for which it is administered. For example, a “therapeutically effective amount,” when administered to a subject to inhibit fatty acid synthase activity, is sufficient to inhibit fatty acid synthase activity. A “therapeutically effective amount,” when administered to a subject for treating a disease, is sufficient to effect treatment for that disease.

[0136] Except when noted, the terms “subject” or “patient” are used interchangeably and refer to mammals such as human patients and non-human primates, as well as experimental animals such as rabbits, rats, and mice, and other animals. Accordingly, the term “subject” or “patient” as used herein means any mammalian patient or subject to which the compounds of the invention can be administered. In an exemplary aspect of the present invention, to identify subject patients for treatment according to the methods of the invention, accepted screening methods are employed to determine risk factors associated with a targeted or suspected disease or condition or to determine the status of an existing disease or condition in a subject. These screening methods include, for example, conventional work-ups to determine risk factors that are associated with the targeted or suspected disease or condition. These and other routine methods allow the clinician to select patients in need of therapy using the methods and formulations of the present invention.

FASN Pathway Modulators

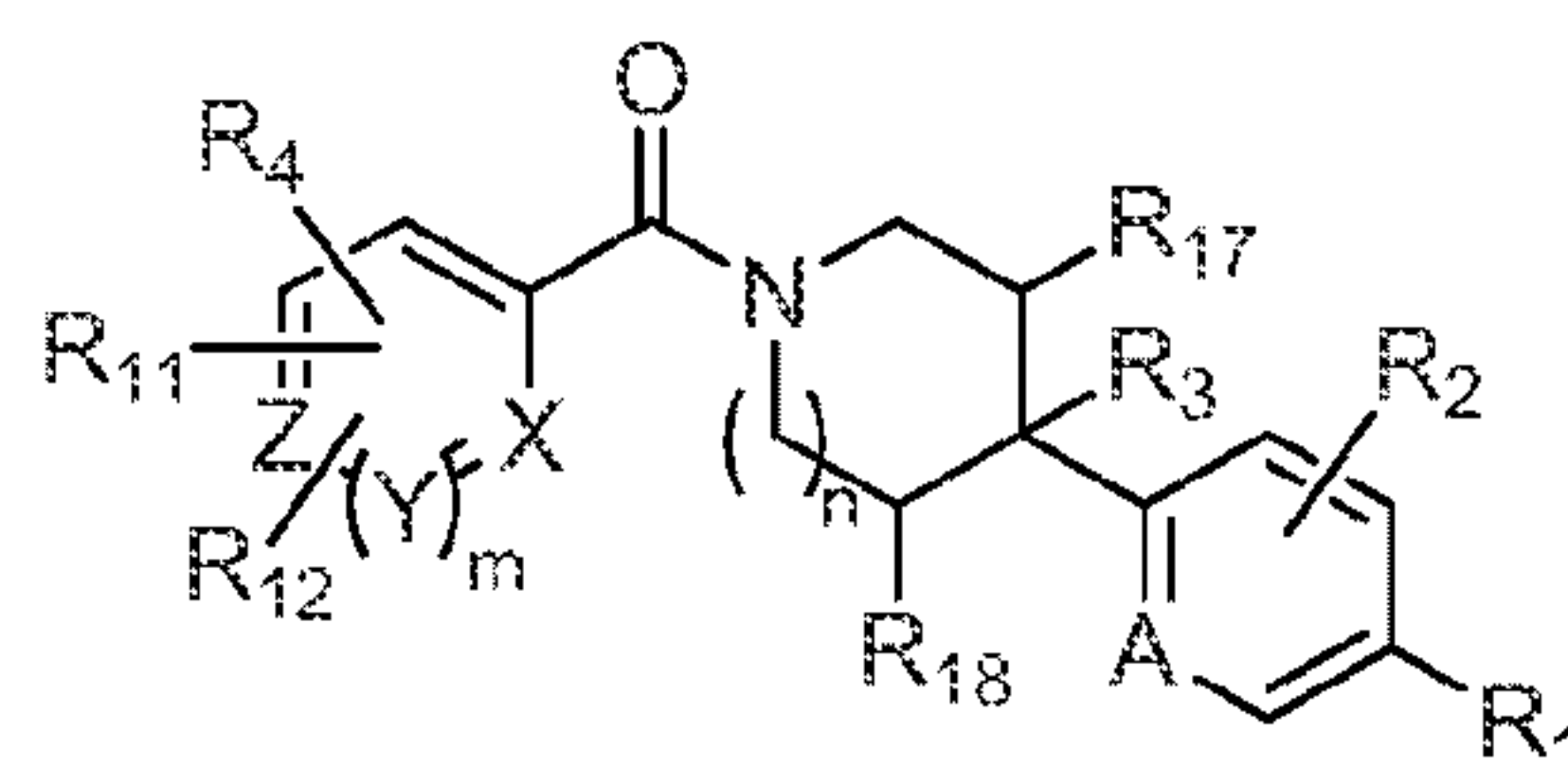
[0137] One aspect of the present disclosure includes a method of inhibiting viral infection or treating cancer by contacting a cell with an agent that modulates the fatty acid synthesis pathway. This method of inhibiting viral infection or treating cancer can be performed *in vitro* by contacting virally infected/cancerous cells with an agent that modulates the fatty acid synthesis pathway, or *in vivo* by administering an agent that modulates the fatty acid synthesis pathway to a subject infected with a virus/having cancer. In one aspect, an agent can be an inhibitor of the fatty acid synthesis pathway.

[0138] Examples of inhibitors of the fatty acid synthesis pathway that can be used in the methods and compositions of the present disclosure are described below.

Compounds of Structure (I)

[0139] In various aspects, the present disclosure provides for compounds of Structure (I):

26



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X, Y, and Z are each independently CR or NR', wherein R is hydrogen or C₁₋₆ alkyl
and R' is hydrogen, C₁₋₆ alkyl, or absent;

A is CH or N;

R₁ is hydrogen, cyano, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, -C(=O)N(R₁₃)(R₁₄),
-(CH₂)_qC(=O)N(R₁₃)(R₁₄), CF₃, -OCF₃, or -S(=O)₂R₂₀;

q is 0, 1, 2, 3, or 4;

R₂₀ is hydrogen or C₁₋₆ alkyl, C₁₋₆ alkoxy, or -N(R₁₃)(R₁₄);

R₂ is hydrogen, halo, C₁₋₆ alkoxy, C₁₋₆ alkyl, or R₂ and R₃ taken together with the
atoms to which they are attached form a 5-membered heterocyclyl;

R₃ is hydrogen, hydroxyl, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, or R₂ and R₃ taken together
with the atoms to which they are attached form a 5-membered heterocyclyl;

R₄ is hydrogen, heteroaryl, heterocyclyl, -C(=O)N(R₅R₆), -N(R₇)C(=O)R₈, -N(R₉R₁₀),
C₁₋₆ alkyl, C₁₋₆ alkoxy, -S(=O)₂R₂₀, or R₄ and R₁₁ taken together with the atoms to
which they are attached join together to form a heteroaryl;

R₁₁ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy, -N(R₁₃R₁₄), CF₃, -OCF₃,
-S(=O)₂R₂₀, R₄ and R₁₁ taken together with the atoms to which they are attached
join together to form a heteroaryl, or R₁₁ and R₁₂ taken together with the atoms to
which they are attached join together to form a heteroaryl;

R₁₂ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy, -N(R₁₃R₁₄), CF₃, -OCF₃,
-S(=O)₂R₂₀, or R₁₁ and R₁₂ taken together with the atoms to which they are
attached join together to form a heteroaryl;

R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₃, and R₁₄ are each independently hydrogen, C₁₋₆ alkyl,
cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, -N(R₁₅R₁₆),
or -S(=O)₂R₂₀;

R₁₅ and R₁₆ are each independently hydrogen, C₁₋₆ alkyl, cycloalkyl, aryl,
heterocyclyl, heteroaryl, or alkylamino;

R_{17} and R_{18} are each independently hydrogen or alkyl or can optionally join together to form a bond;

n is 1 or 2; and

m is 0 or 1.

[0140] In certain aspects of Structure (I), R_3 is F.

[0141] In certain aspects of Structure (I), A is CH.

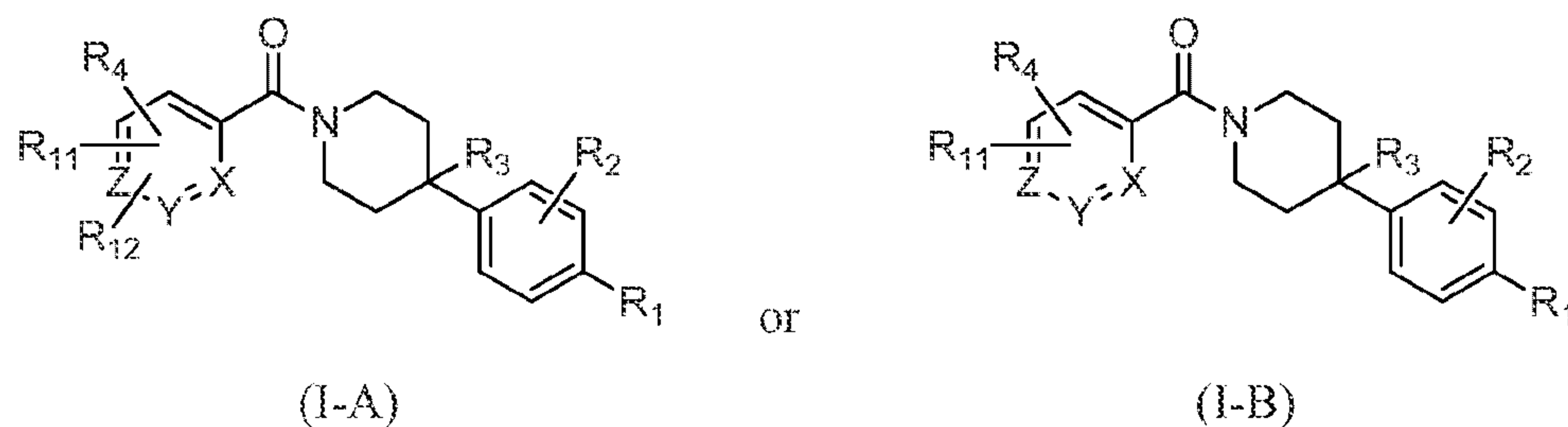
[0142] In certain aspects of Structure (I), A is N.

[0143] In certain aspects of Structure (I), X, Y, and Z are NR' .

[0144] In certain aspects of Structure (I), R_4 is heteroaryl, heterocyclyl, $-C(=O)N(R_5R_6)$, $-N(R_7)C(=O)R_8$, $-N(R_9R_{10})$, C_{1-6} alkyl, C_{1-6} alkoxy, or R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl.

[0145] In certain aspects of Structure (I), R_5 is hydrogen and R_6 is aryl or heteroaryl.

[0146] In certain aspects, the compounds of Structure (I) have one of the following Structures (I-A) or (I-B):



or a pharmaceutically acceptable salt thereof, wherein:

X, Y, and Z are each independently CR or NR' , wherein R is hydrogen or C_{1-6} alkyl and R' is hydrogen, C_{1-6} alkyl, or absent;

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$,

$-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

q is 0, 1, 2, 3, or 4;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_2 is hydrogen, halo, C_{1-6} alkoxy, C_{1-6} alkyl, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R_4 is hydrogen, heteroaryl, heterocyclyl, $-C(=O)N(R_5R_6)$, $-N(R_7)C(=O)R_8$, $-N(R_9R_{10})$, C_{1-6} alkyl, C_{1-6} alkoxy, $-S(=O)_2R_{20}$, or R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl;

R_{11} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl, or R_{11} and R_{12} taken together with the atoms to which they are attached join together to form a heteroaryl;

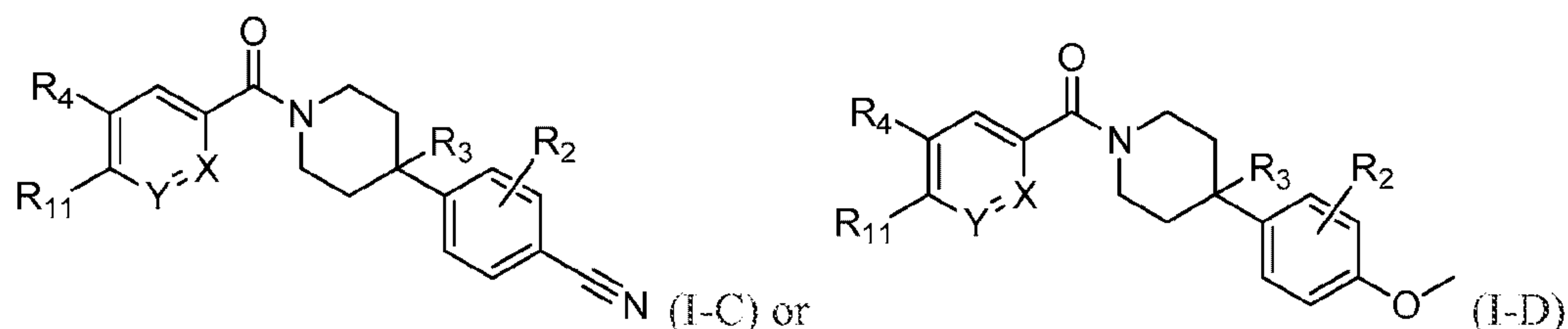
R_{12} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, or R_{11} and R_{12} taken together with the atoms to which they are attached join together to form a heteroaryl;

R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{13} , and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;

R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, or alkylamino; and

R_{17} and R_{18} are each independently hydrogen or alkyl or can optionally join together to form a bond.

[0147] In certain aspects, the compounds of Structure (I) have one of the following Structures (I-C) or (I-D):



or a pharmaceutically acceptable salt thereof, wherein:

X , Y , and Z are each independently CR or NR' , wherein R is hydrogen or C_{1-6} alkyl and R' is hydrogen, C_{1-6} alkyl, or absent;;

R_2 is hydrogen, halo, C_{1-6} alkoxy, C_{1-6} alkyl, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R_4 is hydrogen, heteroaryl, heterocyclyl, $-C(=O)N(R_5R_6)$, $-N(R_7)C(=O)R_8$, $-N(R_9R_{10})$, C_{1-6} alkyl, C_{1-6} alkoxy, $-S(=O)_2R_{20}$, or R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl;

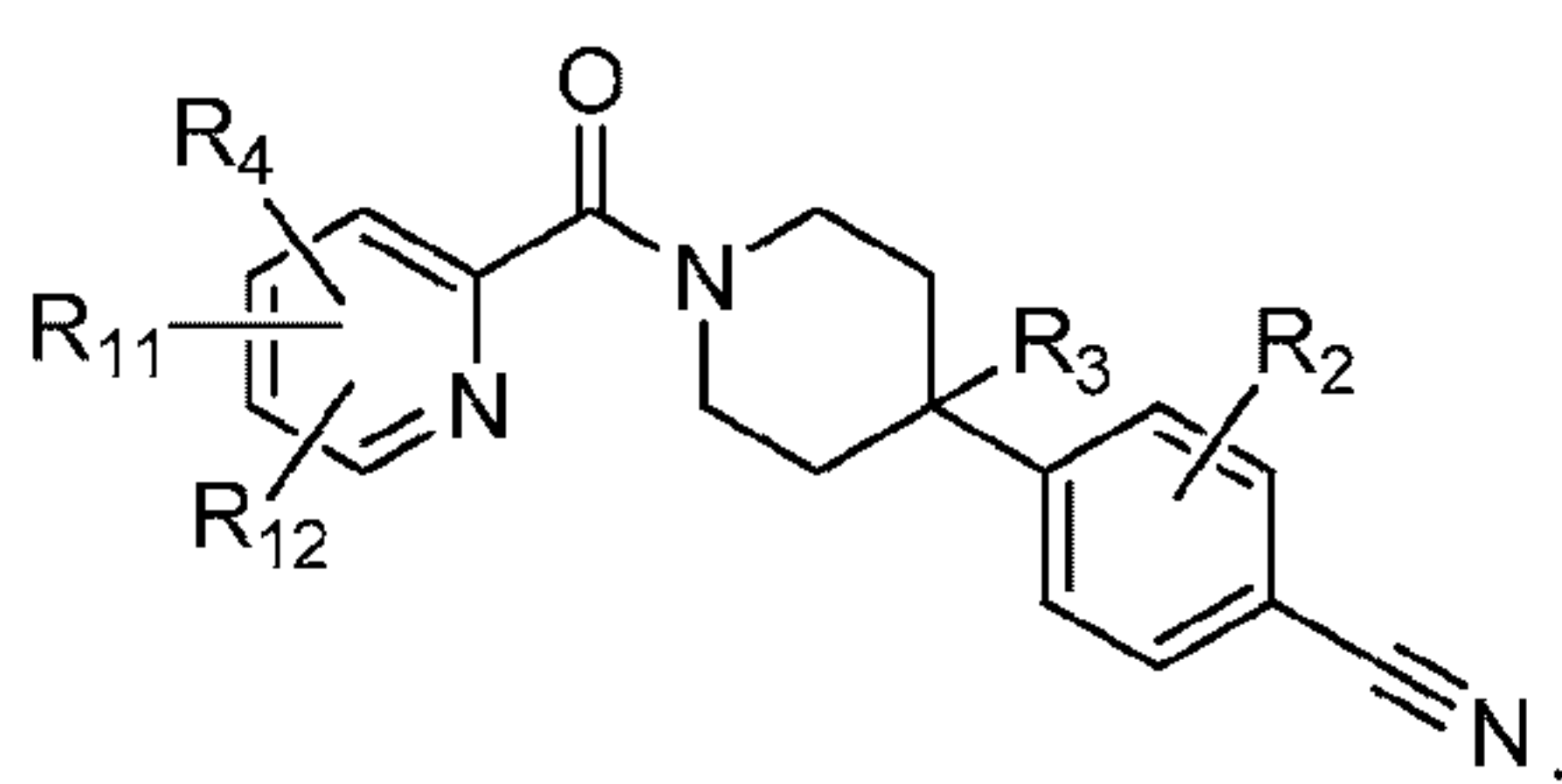
R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_{11} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, or R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl;

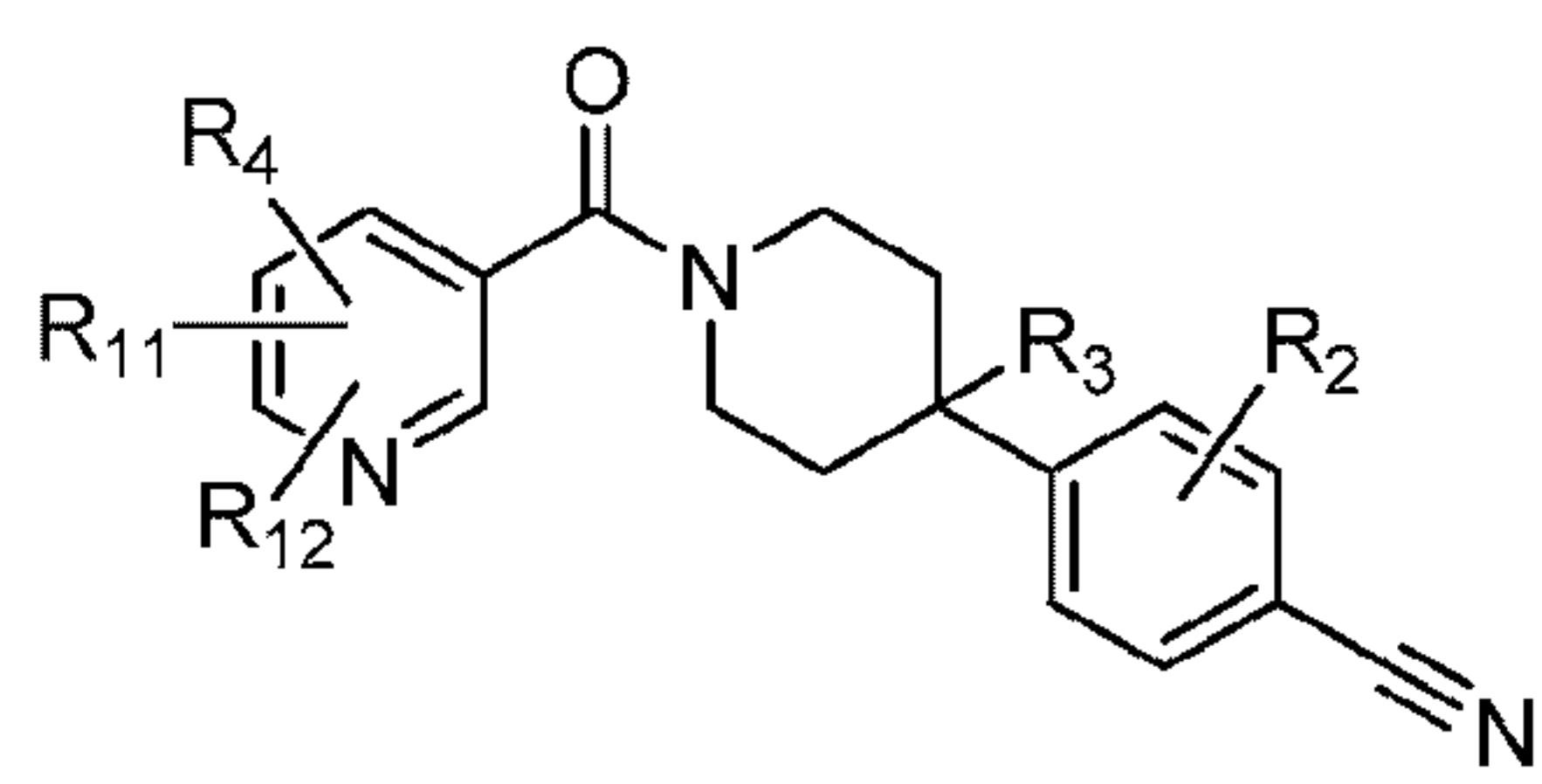
R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylamino, or $-N(R_{15}R_{16})$; and

R_{15} and R_{16} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, or alkylamino.

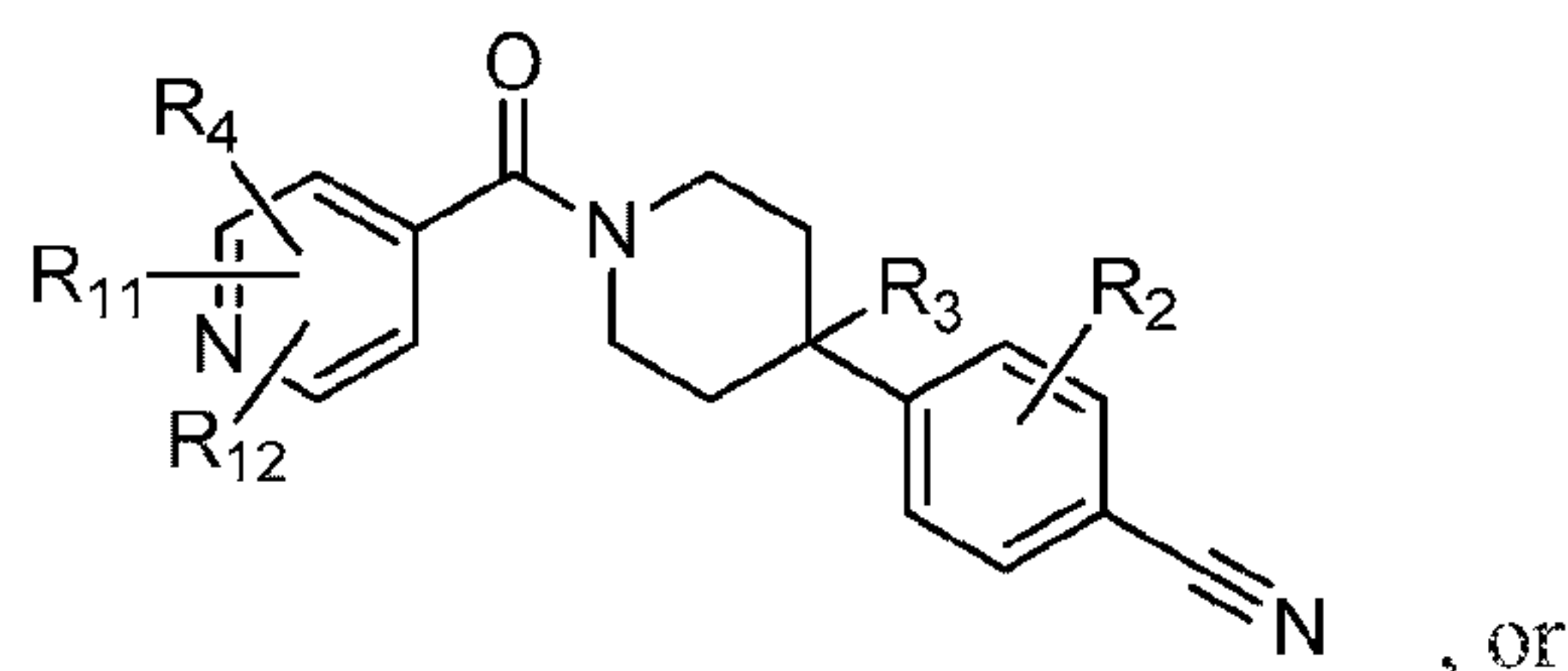
[0148] In certain aspects, the compounds of Structure (I) have one of the following Structures (I-E), (I-F), (I-G), (I-H):



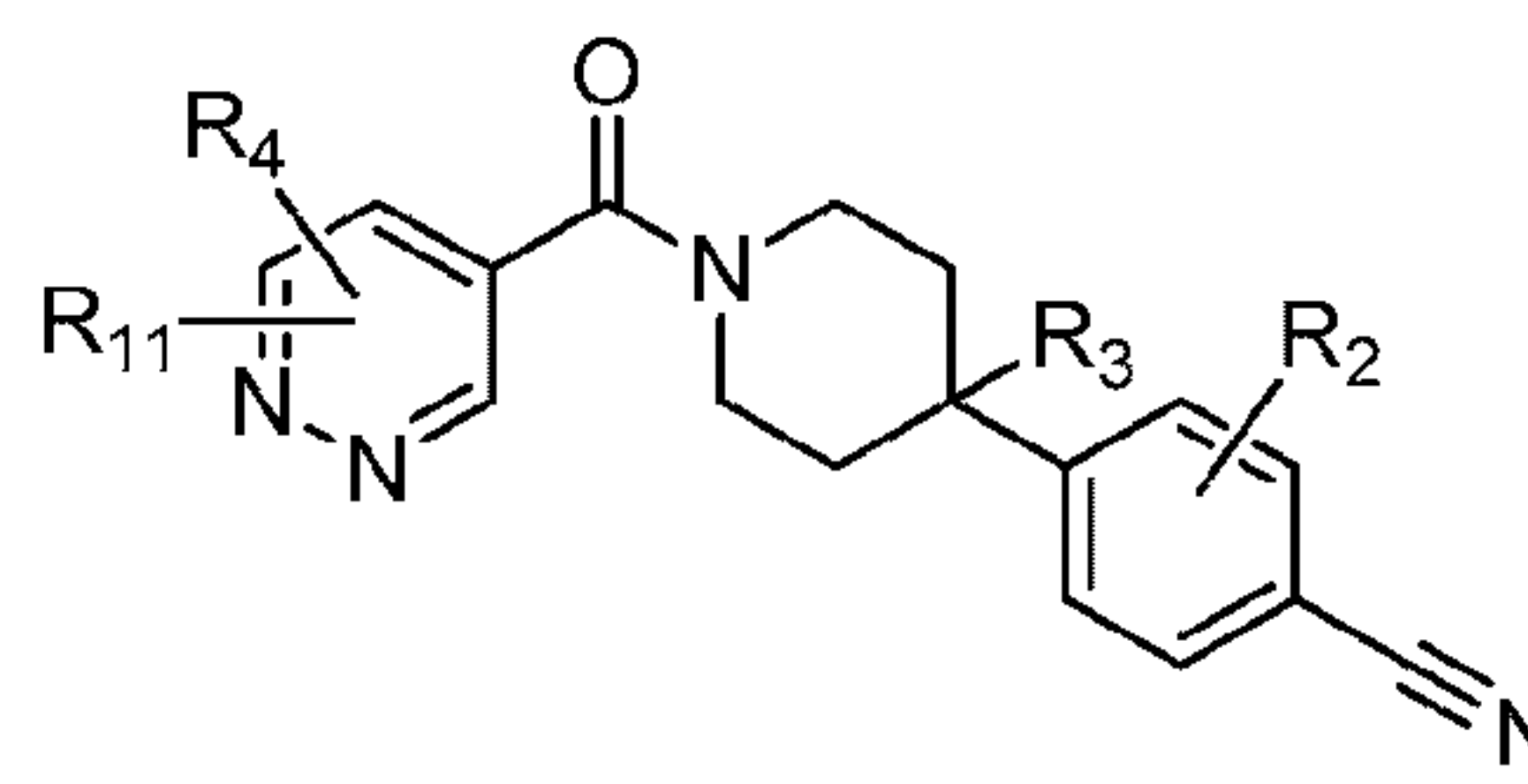
(I-E)



(I-F)



(I-G)



(I-H)

or a pharmaceutically acceptable salt thereof, wherein:

R_2 is hydrogen, halo, C_{1-6} alkoxy, C_{1-6} alkyl, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R_4 is hydrogen, heteroaryl, heterocyclyl, $-C(=O)N(R_5R_6)$, $-N(R_7)C(=O)R_8$, $-N(R_9R_{10})$, C_{1-6} alkyl, C_{1-6} alkoxy, $-S(=O)_2R_{20}$, or R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

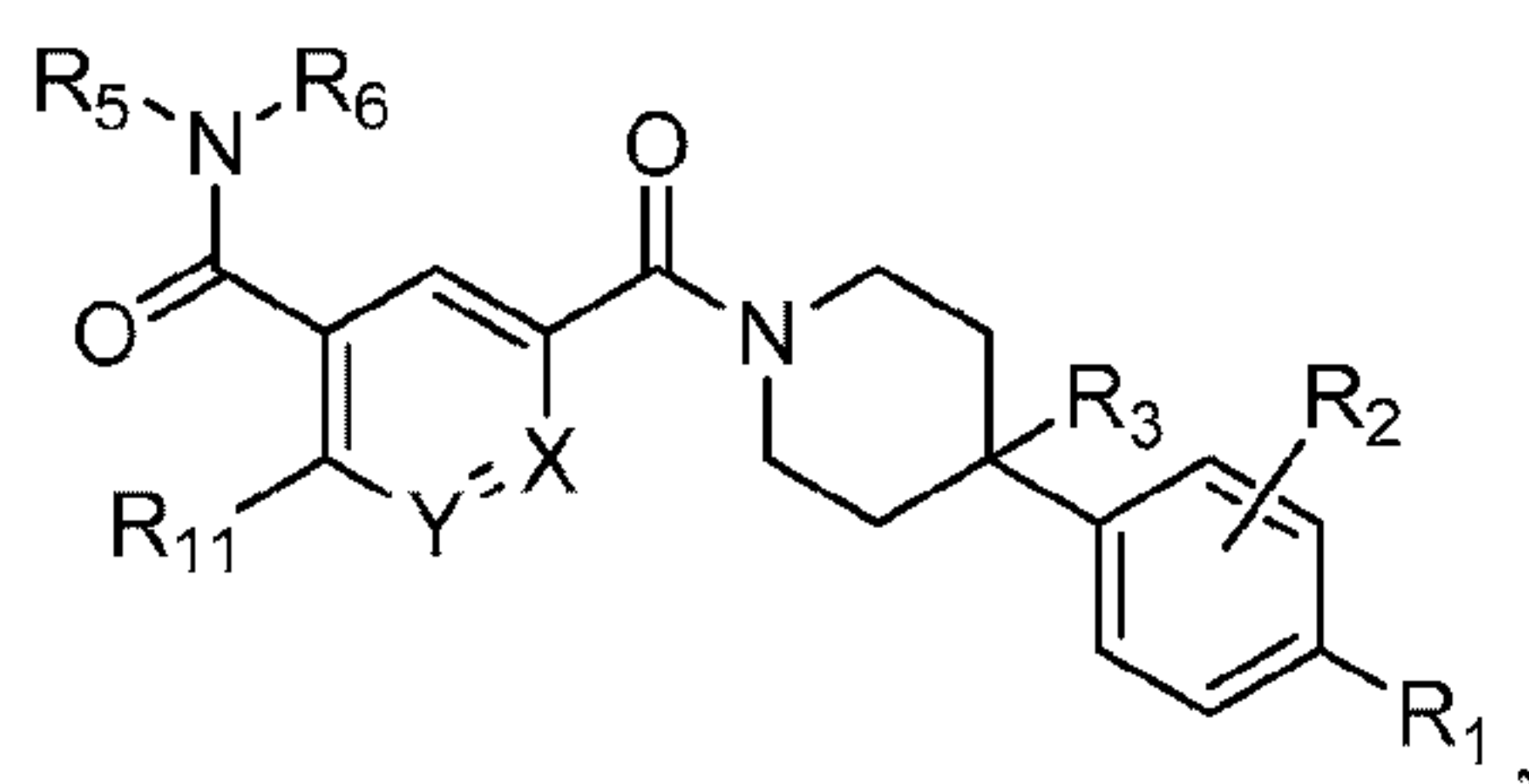
R_{11} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl, or R_{11} and R_{12} taken together with the atoms to which they are attached join together to form a heteroaryl;

R_{12} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, or R_{11} and R_{12} taken together with the atoms to which they are attached join together to form a heteroaryl;

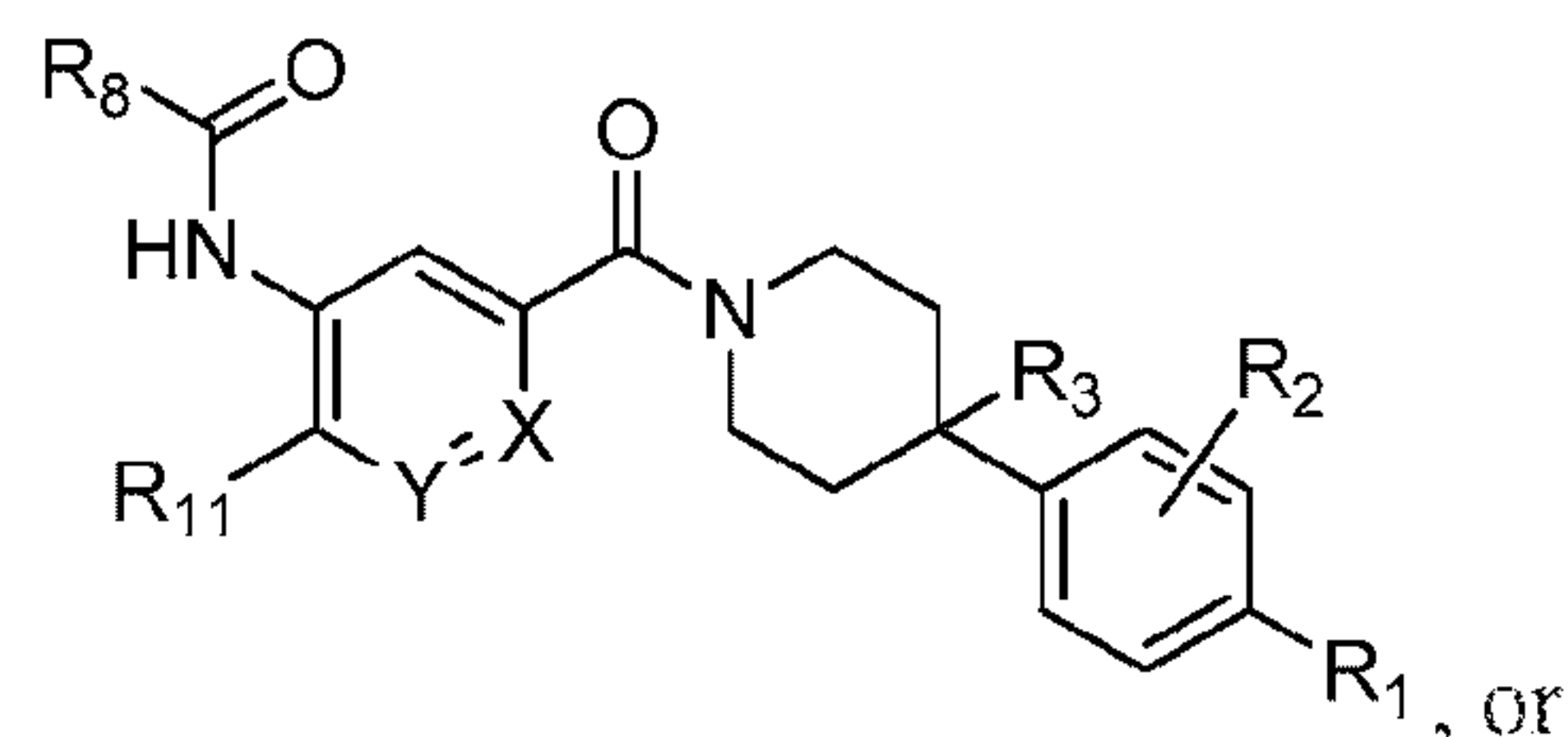
R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{13} , and R_{14} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylamino, or $-N(R_{15}R_{16})$; and

R_{15} and R_{16} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, or alkylamino.

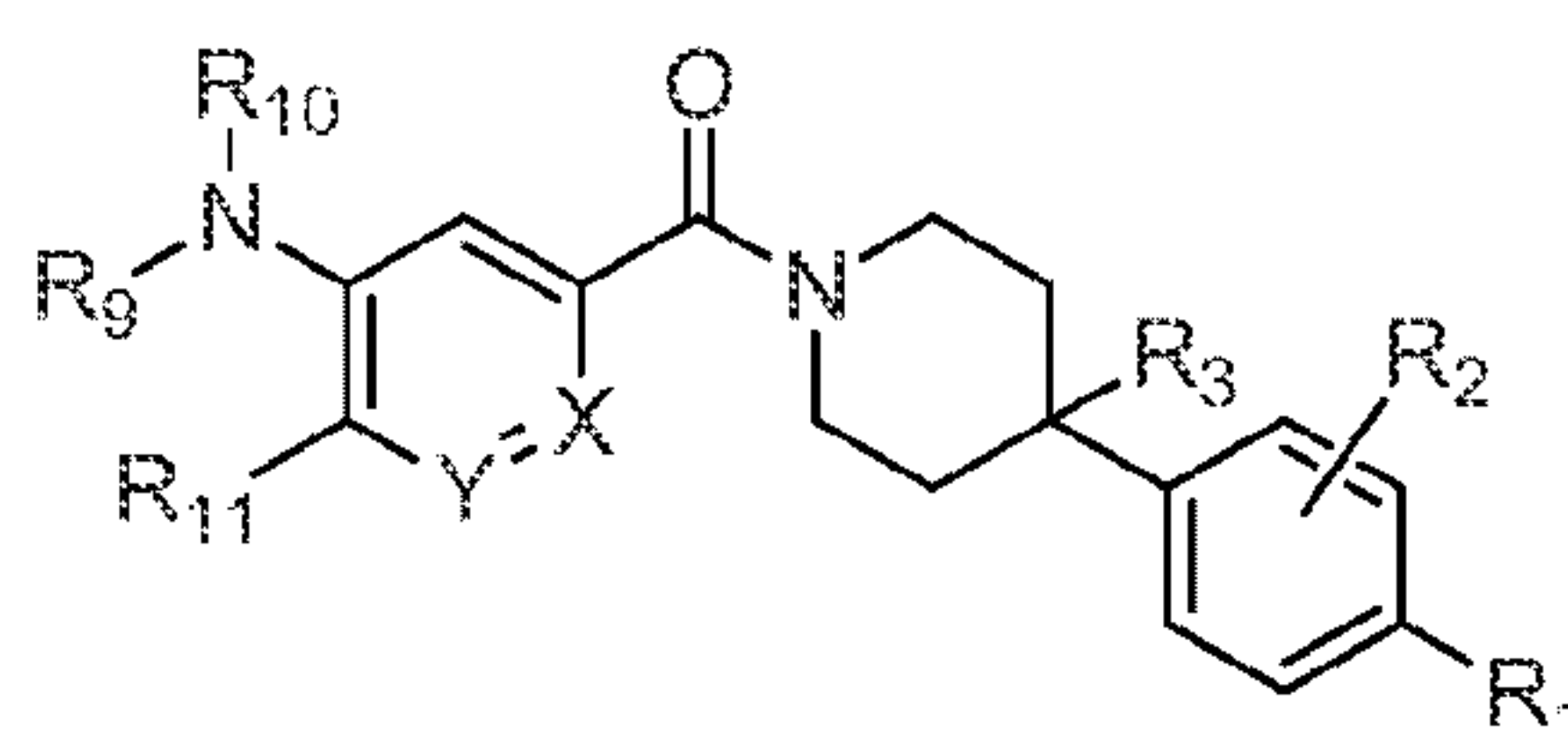
[0149] In certain aspects, the compounds of Structure (I) have one of the following Structures (I-I), (I-J), or (I-K):



(I-I)



(I-J)



(I-K)

or a pharmaceutically acceptable salt thereof, wherein:

X and Y are each independently CR or NR' , wherein R is H or C_{1-6} alkyl and R' is H, C_{1-6} alkyl, or absent;

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$,

$-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

q is 0, 1, 2, 3, or 4;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_2 is hydrogen, halo, C_{1-6} alkoxy, C_{1-6} alkyl, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

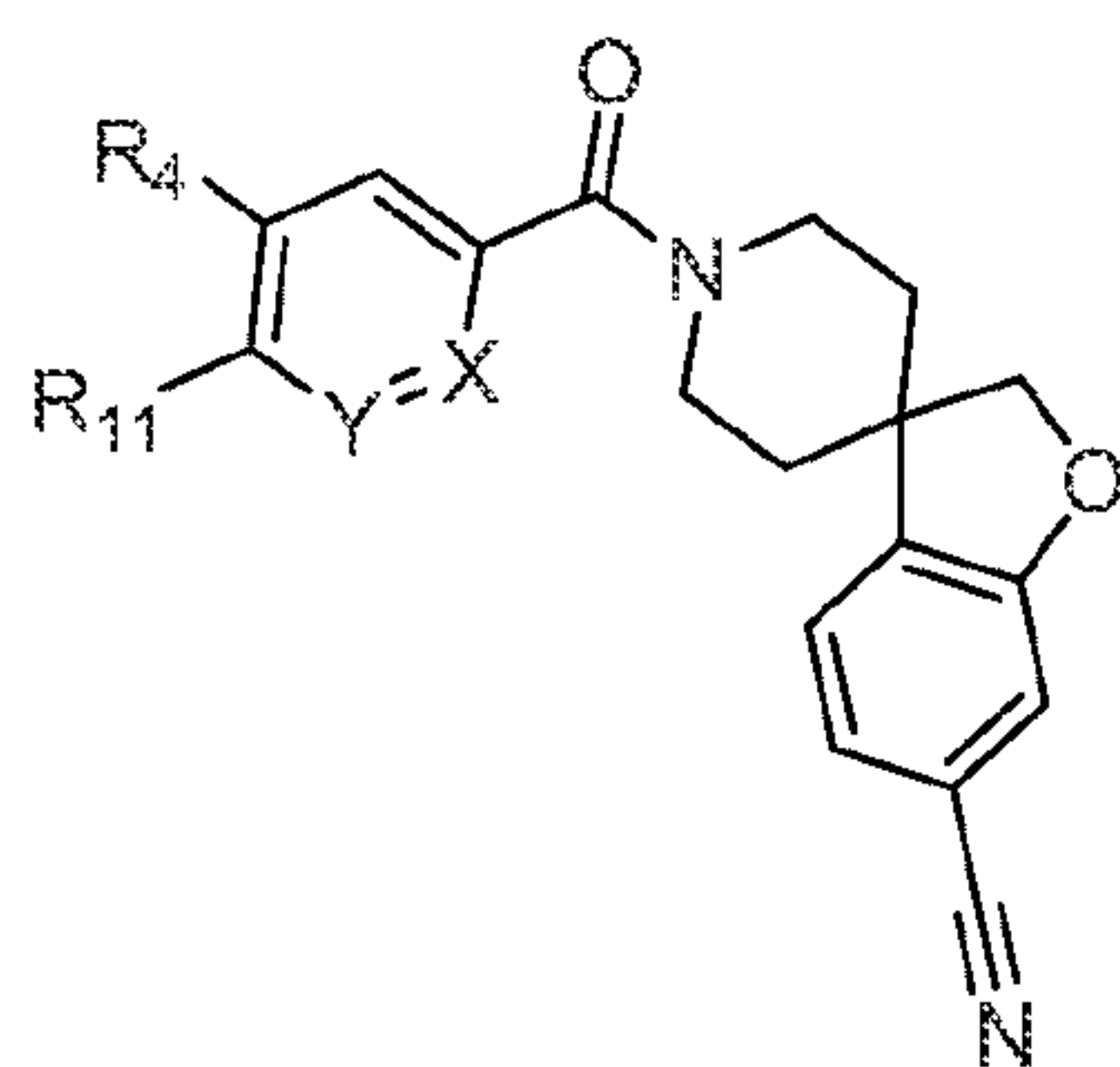
R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R_{11} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylamino, or $-N(R_{15}R_{16})$; and

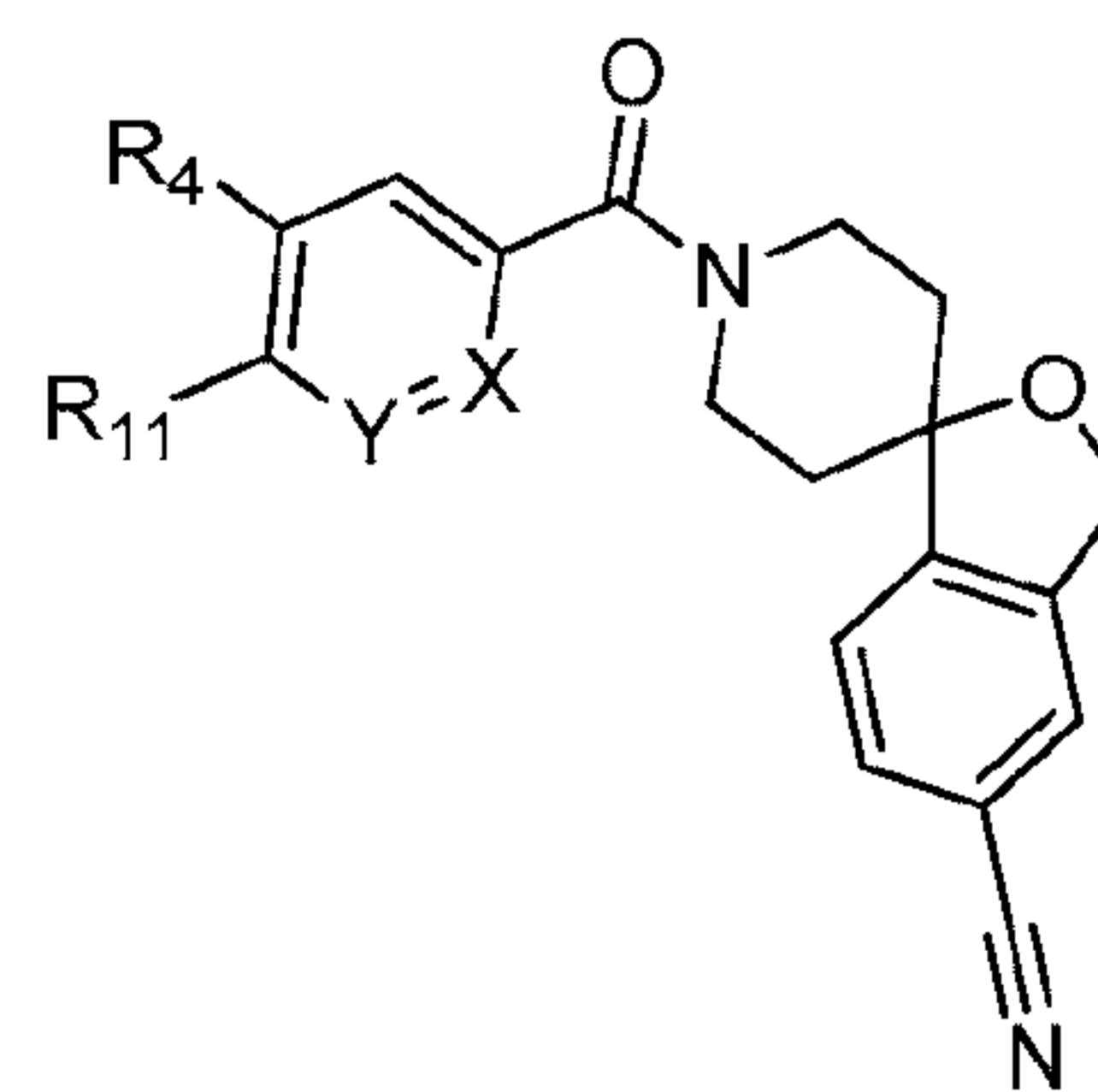
R_{15} and R_{16} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, or alkylamino.

[0150] In certain aspects, the compounds of Structure (I) have one of the following Structures (I-L) or (I-M):



(I-L)

or



(I-M)

or a pharmaceutically acceptable salt thereof, wherein:

X and Y are each independently CR or NR' , wherein R is H or C_{1-6} alkyl and R' is H, C_{1-6} alkyl, or absent;

R_4 is hydrogen, heteroaryl, heterocyclyl, $-C(=O)N(R_5R_6)$, $-N(R_7)C(=O)R_8$, $-N(R_9R_{10})$, C_{1-6} alkyl, C_{1-6} alkoxy, $-S(=O)_2R_{20}$, or R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

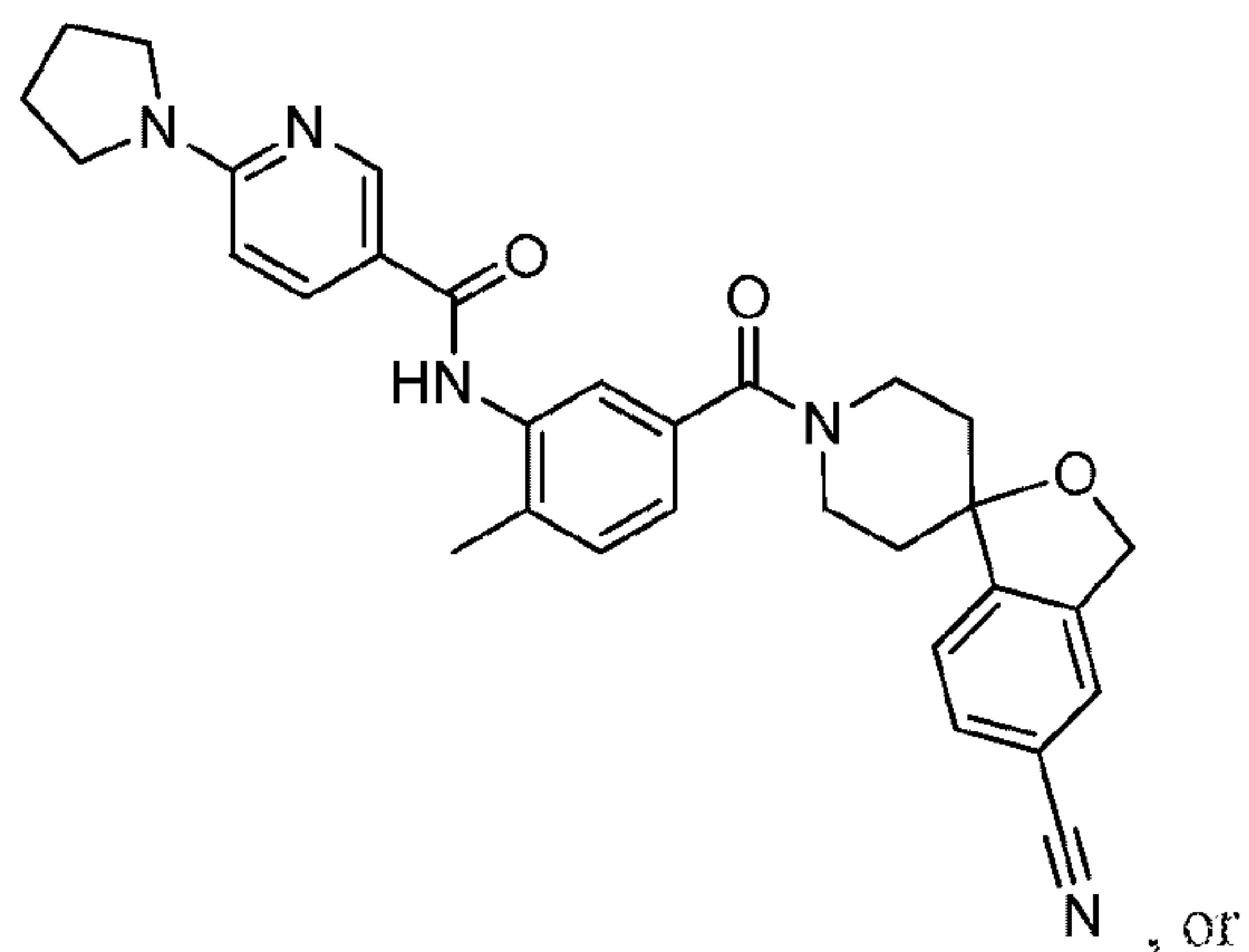
R_{11} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, or R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl;

R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylamino, or $-N(R_{15}R_{16})$; and

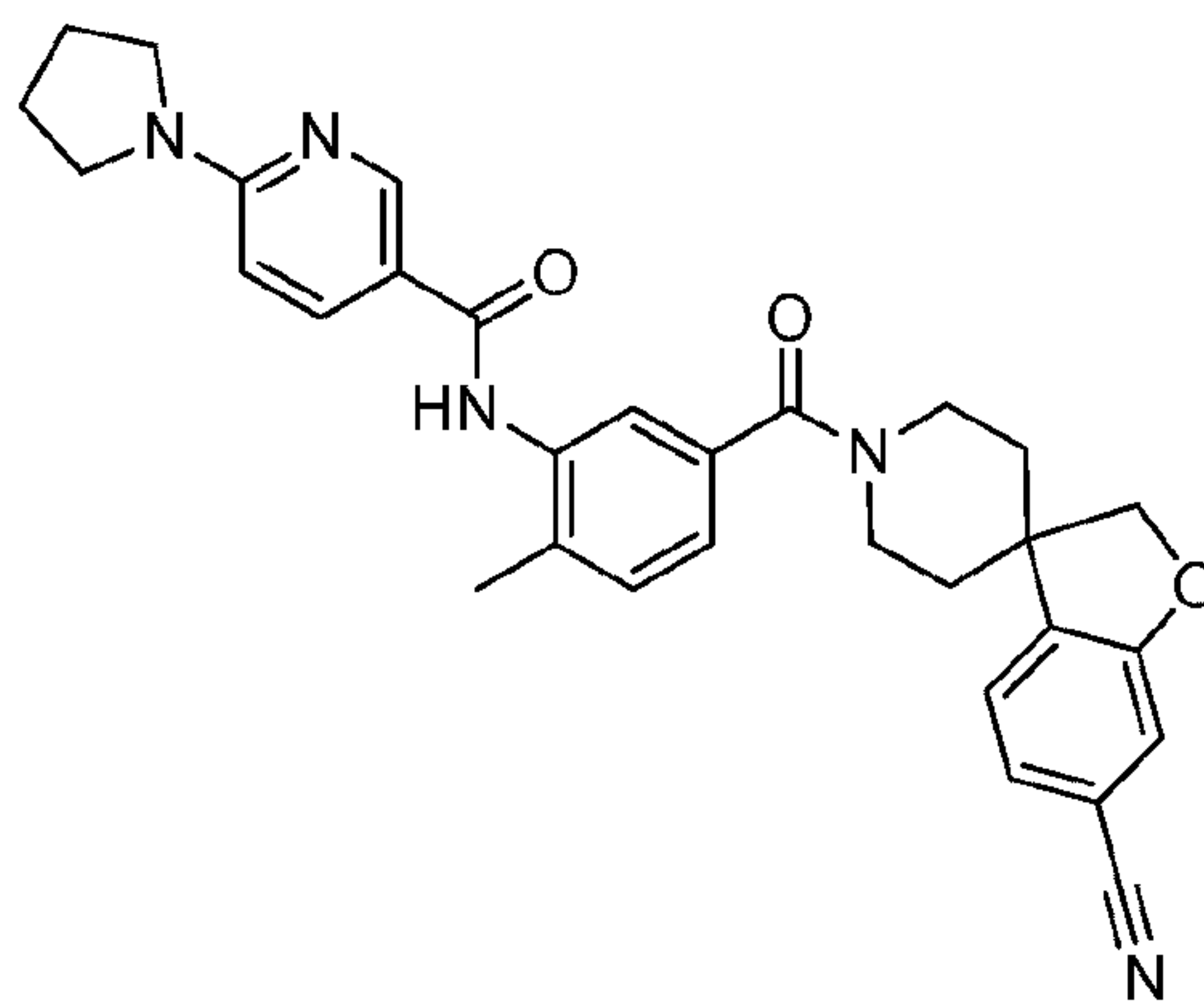
R_{15} and R_{16} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, or alkylamino.

[0151] In certain aspects, the compounds of Structure (I) have one of the following Structures (I-N) or (I-O):

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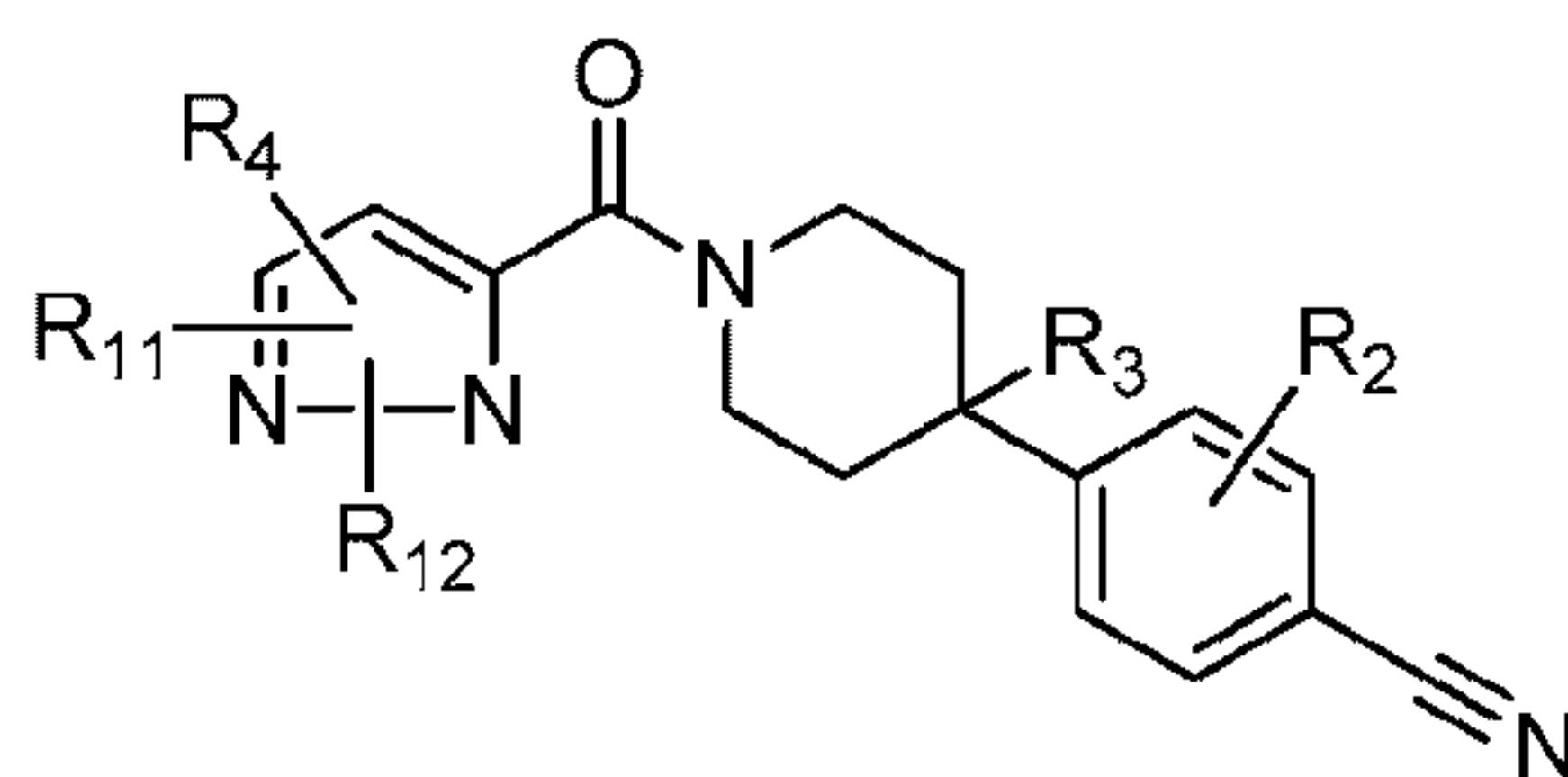
(I-N)



(I-O)

or a pharmaceutically acceptable salt thereof.

[0152] In certain aspects, the compounds of Structure (I) have the following Structure (I-P):



(I-P)

or a pharmaceutically acceptable salt thereof, wherein:

R_2 is hydrogen, halo, C_{1-6} alkoxy, C_{1-6} alkyl, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R_4 is hydrogen, heteroaryl, heterocyclyl, $-C(=O)N(R_5R_6)$, $-N(R_7)C(=O)R_8$, $-N(R_9R_{10})$, C_{1-6} alkyl, C_{1-6} alkoxy, $-S(=O)_2R_{20}$, or R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

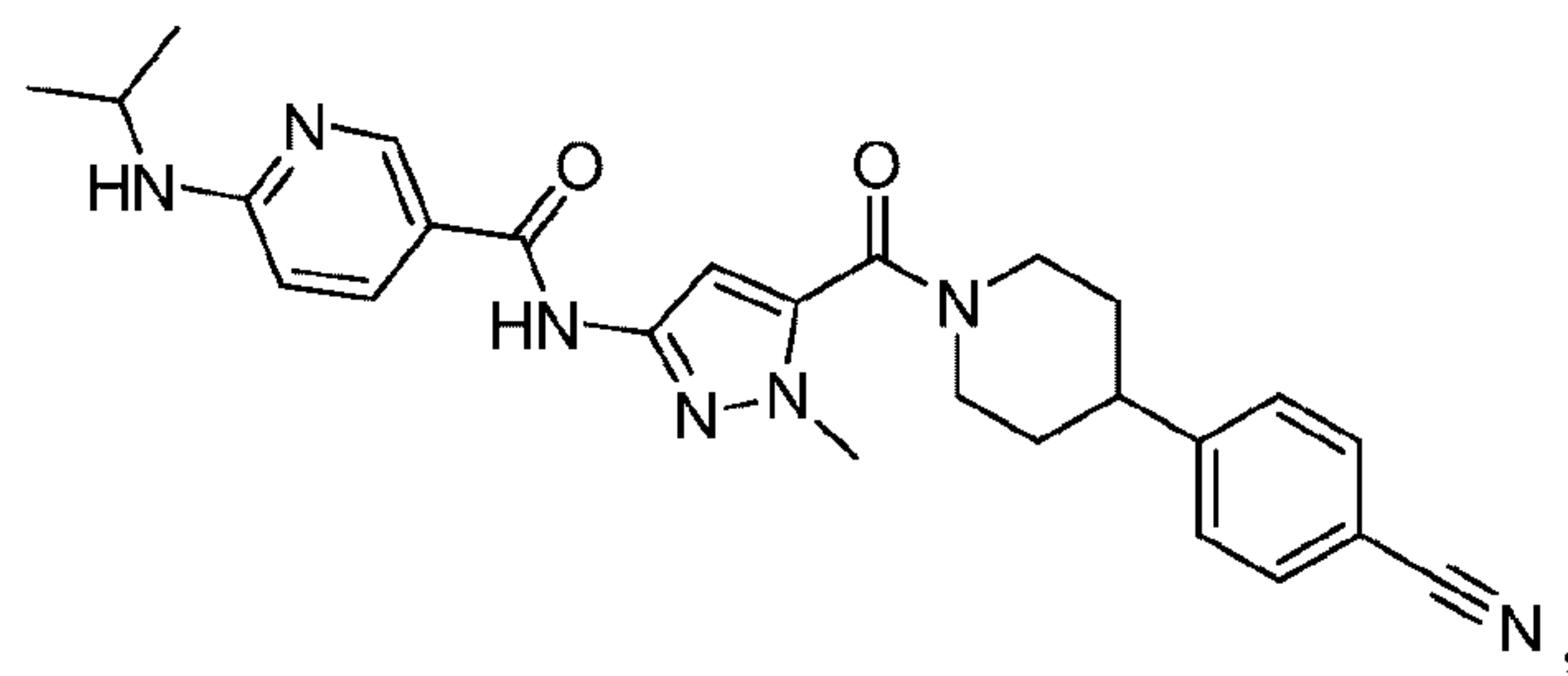
R_{11} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl, or R_{11} and R_{12} taken together with the atoms to which they are attached join together to form a heteroaryl;

R_{12} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, or R_{11} and R_{12} taken together with the atoms to which they are attached join together to form a heteroaryl;

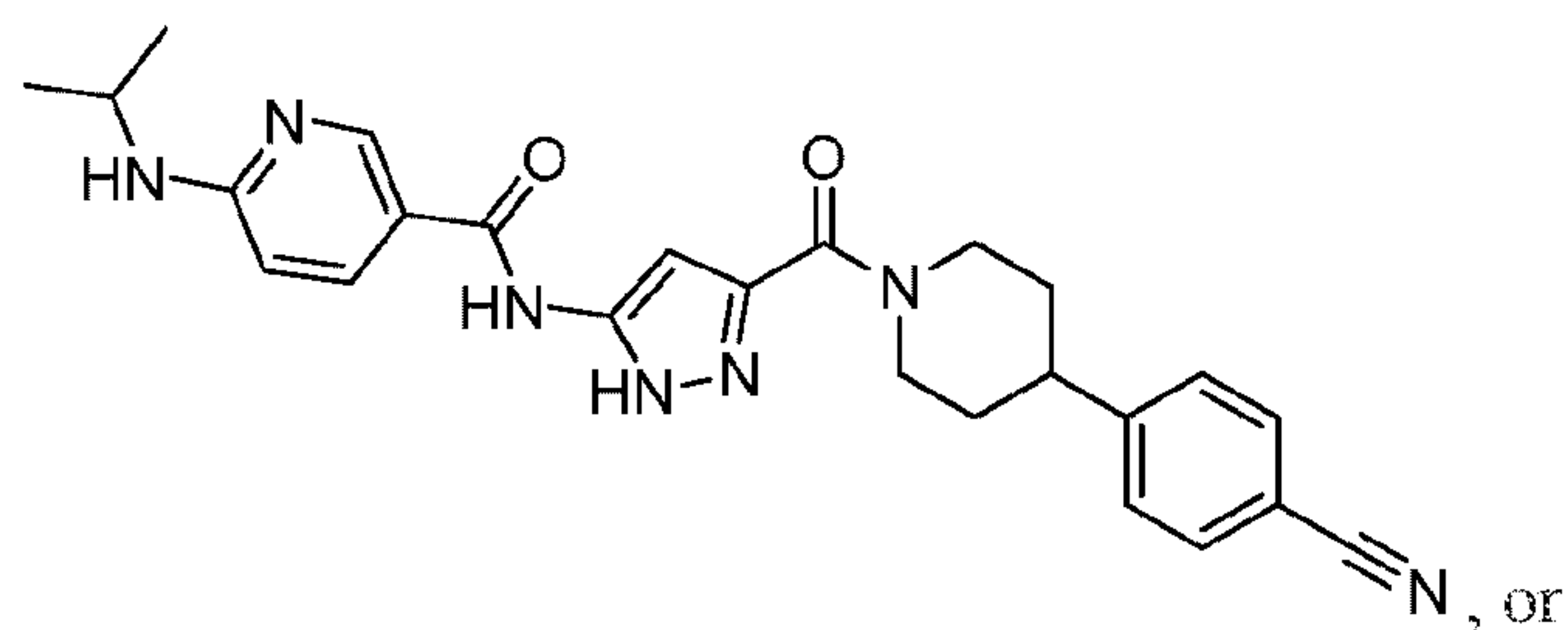
R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{13} , and R_{14} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylamino, or $-N(R_{15}R_{16})$; and

R_{15} and R_{16} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, or alkylamino.

[0153] In certain aspects, the compounds of Structure (I) have one of the following Structures (I-Q), (I-R), or (I-S):

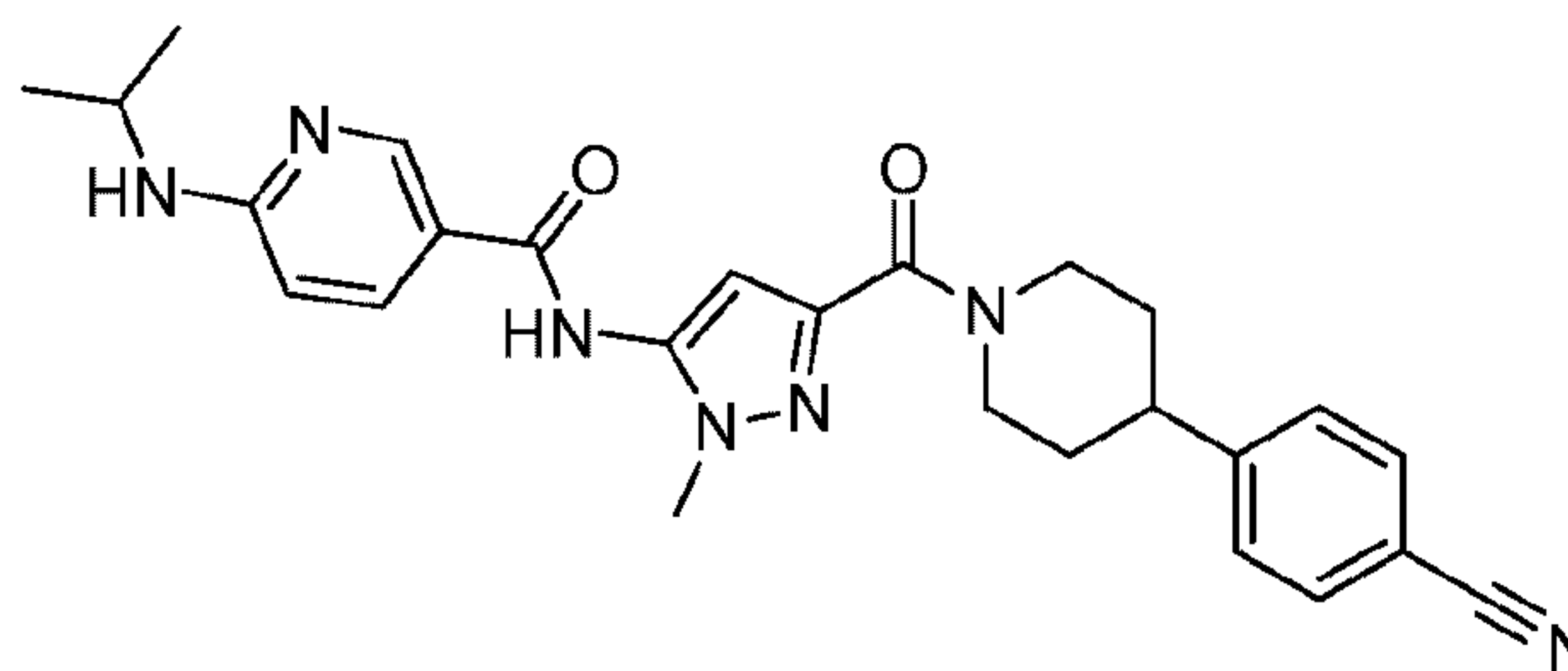


(I-Q)



(I-R)

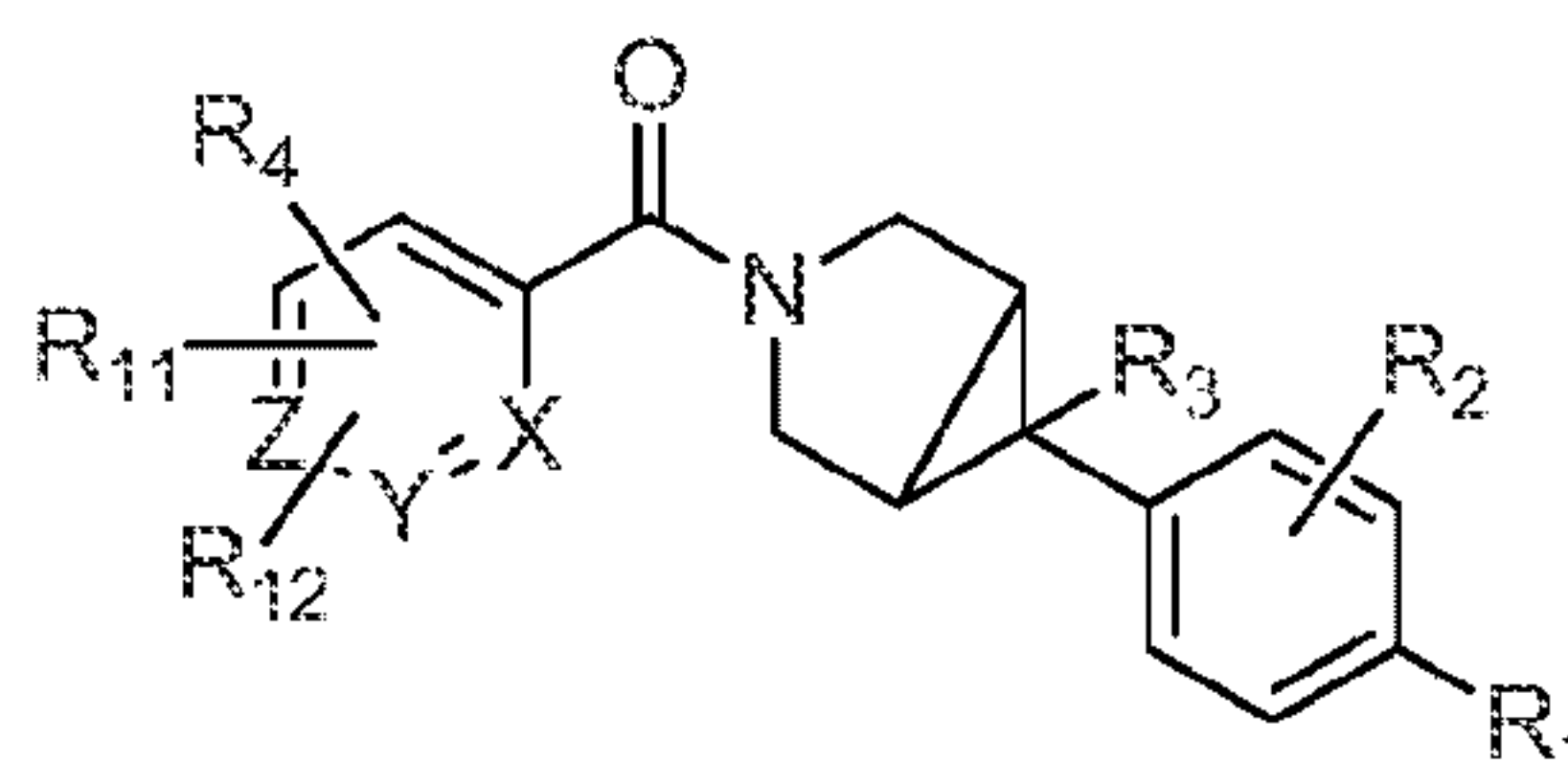
34



(I-S)

or a pharmaceutically acceptable salt thereof.

[0154] In certain aspects, the compounds of Structure (I) have the following Structure (I-T):



(I-T)

or a pharmaceutically acceptable salt thereof, wherein:

X, Y, and Z are each independently CR or NR', wherein R is H or C₁₋₆ alkyl and R' is H, C₁₋₆ alkyl, or absent;

R₁ is hydrogen, cyano, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, -C(=O)N(R₁₃)(R₁₄), -(CH₂)_qC(=O)N(R₁₃)(R₁₄), CF₃, -OCF₃, or -S(=O)₂R₂₀;

q is 0, 1, 2, 3, or 4;

R₂₀ is hydrogen or C₁₋₆ alkyl, C₁₋₆ alkoxy, or -N(R₁₃)(R₁₄);

R₂ is hydrogen, halo, C₁₋₆ alkoxy, C₁₋₆ alkyl, or R₂ and R₃ taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R₃ is hydrogen, hydroxyl, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, or R₂ and R₃ taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R₄ is hydrogen, heteroaryl, heterocyclyl, -C(=O)N(R₅R₆), -N(R₇)C(=O)R₈, -N(R₉R₁₀), C₁₋₆ alkyl, C₁₋₆ alkoxy, -S(=O)₂R₂₀, or R₄ and R₁₁ taken together with the atoms to which they are attached join together to form a heteroaryl;

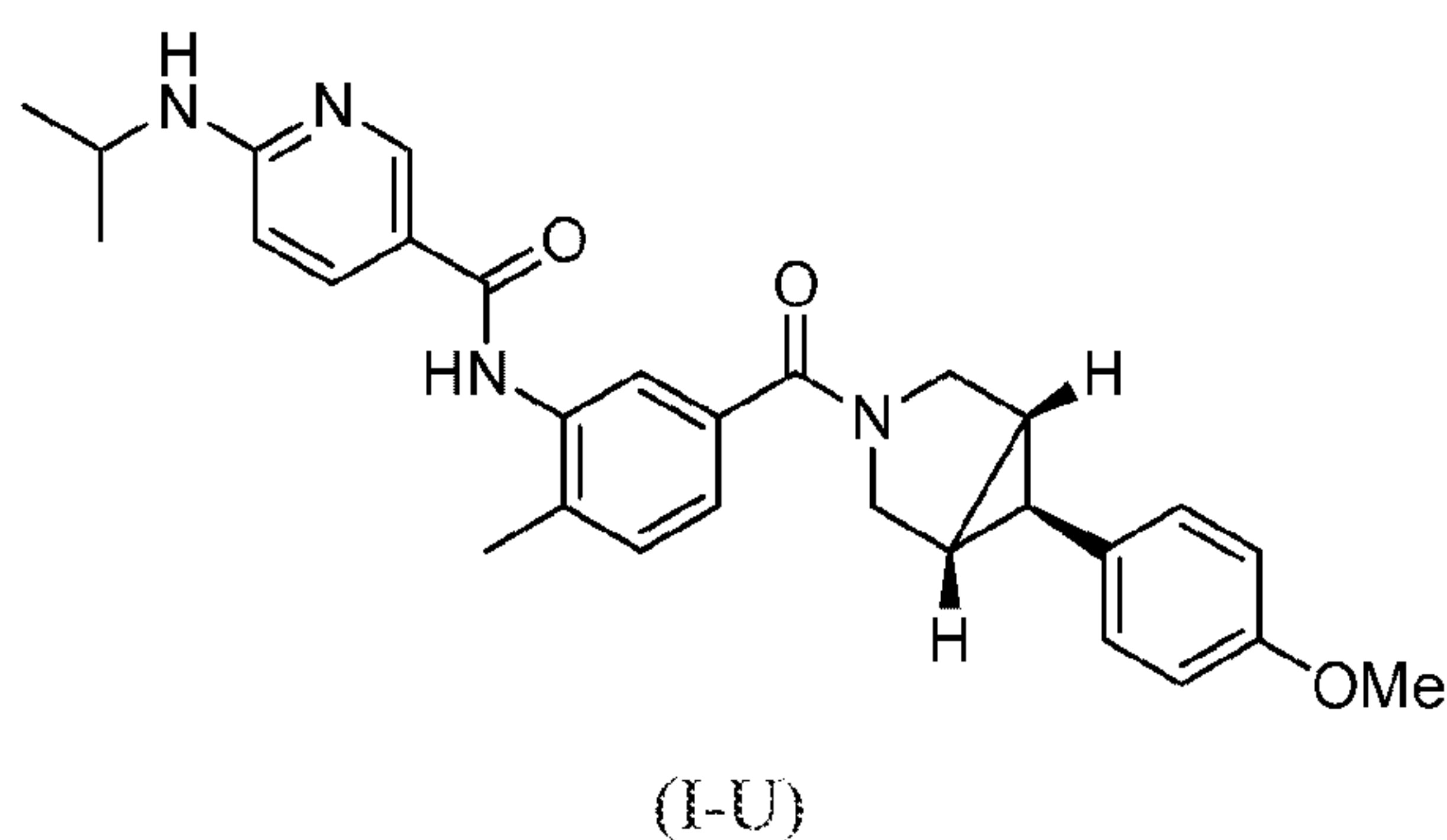
R₁₁ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy, -N(R₁₃R₁₄), CF₃, -OCF₃, -S(=O)₂R₂₀, R₄ and R₁₁ taken together with the atoms to which they are attached join together to form a heteroaryl, or R₁₁ and R₁₂ taken together with the atoms to which they are attached join together to form a heteroaryl;

R_{12} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, or R_{11} and R_{12} taken together with the atoms to which they are attached join together to form a heteroaryl;

R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{13} , and R_{14} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylamino, or $-N(R_{15}R_{16})$; and

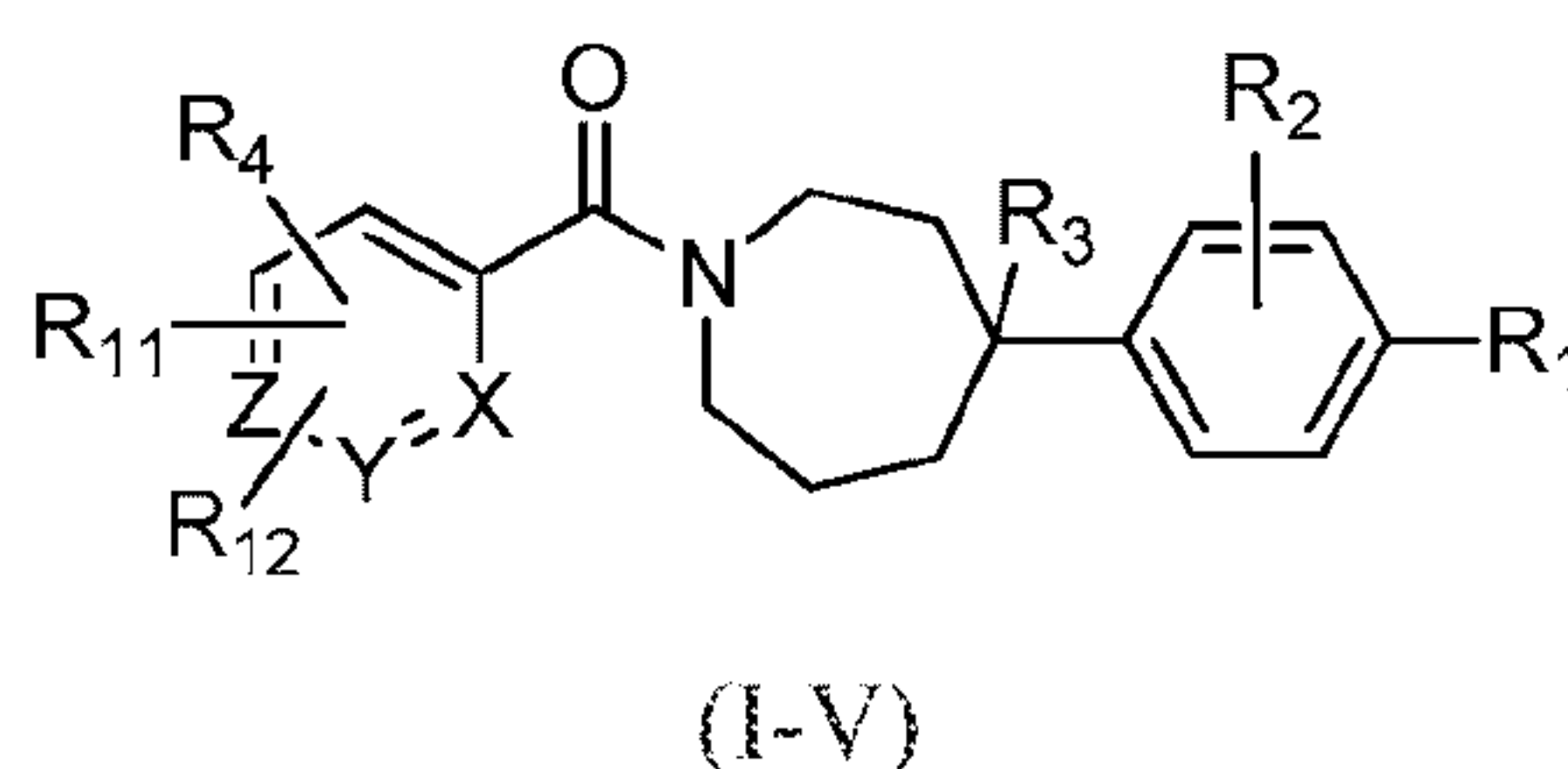
R_{15} and R_{16} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, or alkylamino.

[0155] In certain aspects, the compounds of Structure (I) have the following Structure (I-U):



or a pharmaceutically acceptable salt thereof.

[0156] In certain aspects, the compounds of Structure (I) have one of the following Structures (I-V):



or a pharmaceutically acceptable salt thereof, wherein:

X, Y, and Z are each independently CR or NR' , wherein R is H or C_{1-6} alkyl and R' is H, C_{1-6} alkyl, or absent;

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$, $-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

q is 0, 1, 2, 3, or 4;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_2 is hydrogen, halo, C_{1-6} alkoxy, C_{1-6} alkyl, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R_4 is hydrogen, heteroaryl, heterocyclyl, $-C(=O)N(R_5R_6)$, $-N(R_7)C(=O)R_8$, $-N(R_9R_{10})$, C_{1-6} alkyl, C_{1-6} alkoxy, $-S(=O)_2R_{20}$, or R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl;

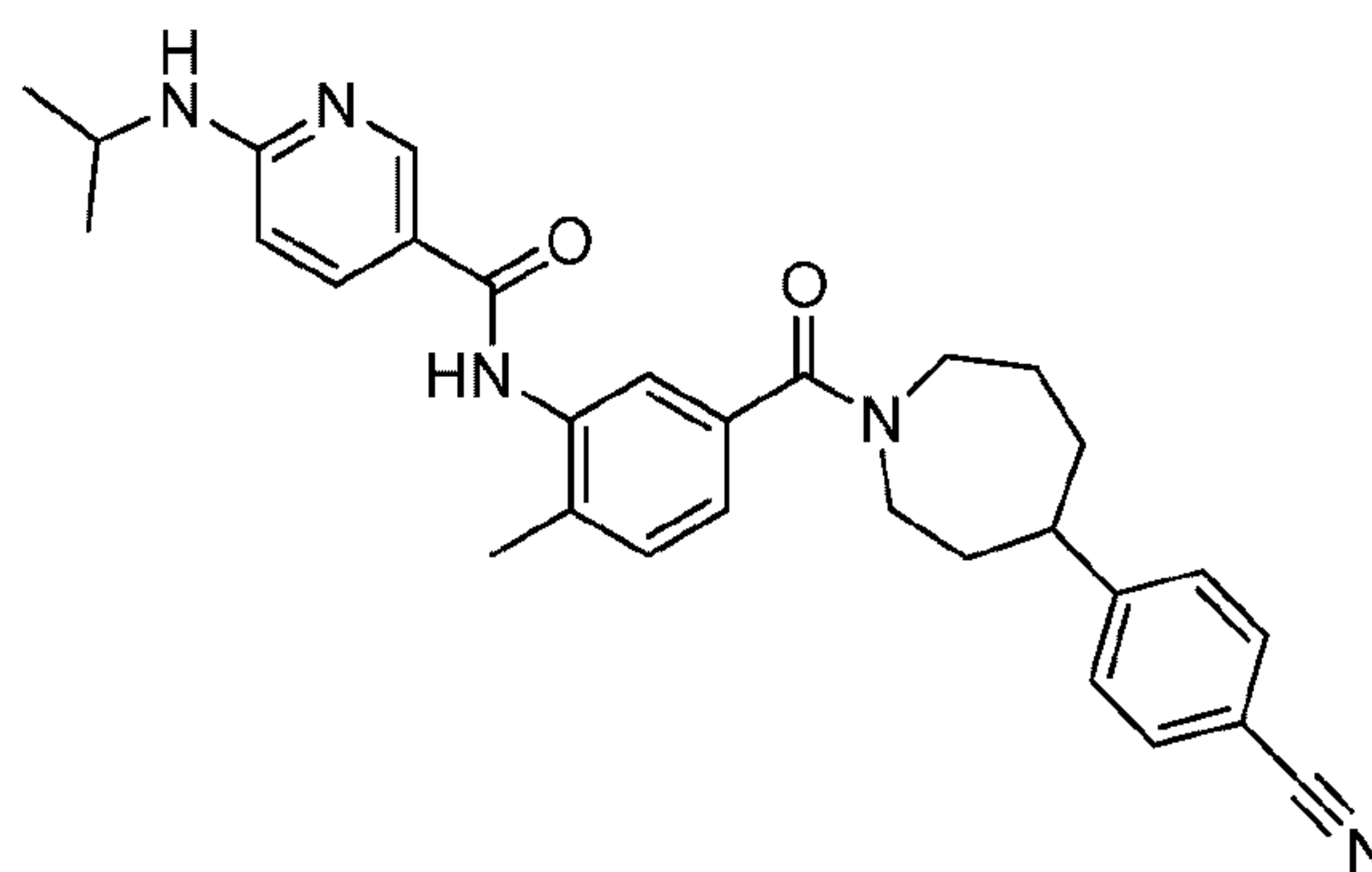
R_{11} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl, or R_{11} and R_{12} taken together with the atoms to which they are attached join together to form a heteroaryl;

R_{12} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, or R_{11} and R_{12} taken together with the atoms to which they are attached join together to form a heteroaryl;

R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{13} , and R_{14} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylamino, or $-N(R_{15}R_{16})$; and

R_{15} and R_{16} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, or alkylamino.

[0157] In certain aspects, the compound of Structure (I) has the following Structure (I-W):

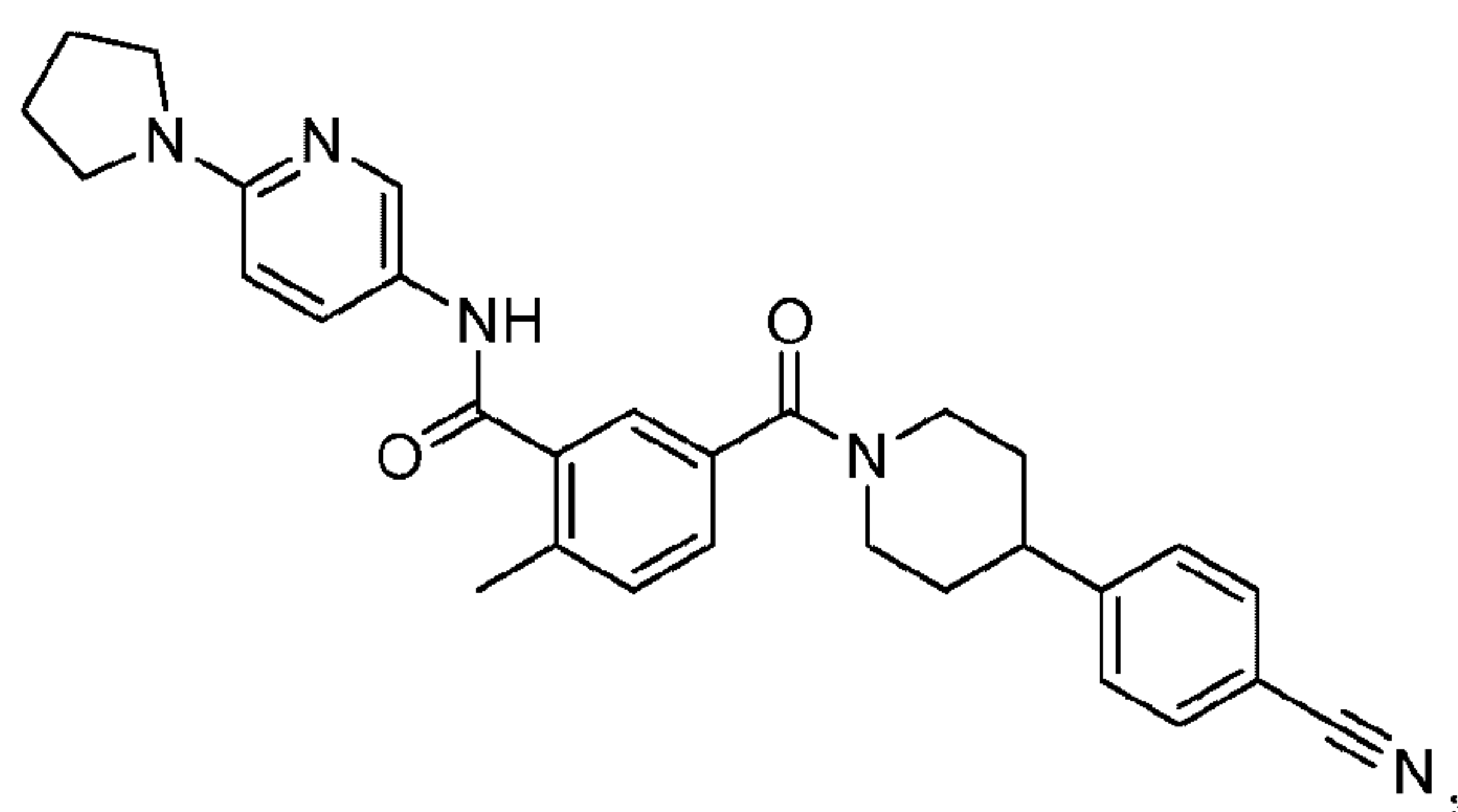


(I-W)

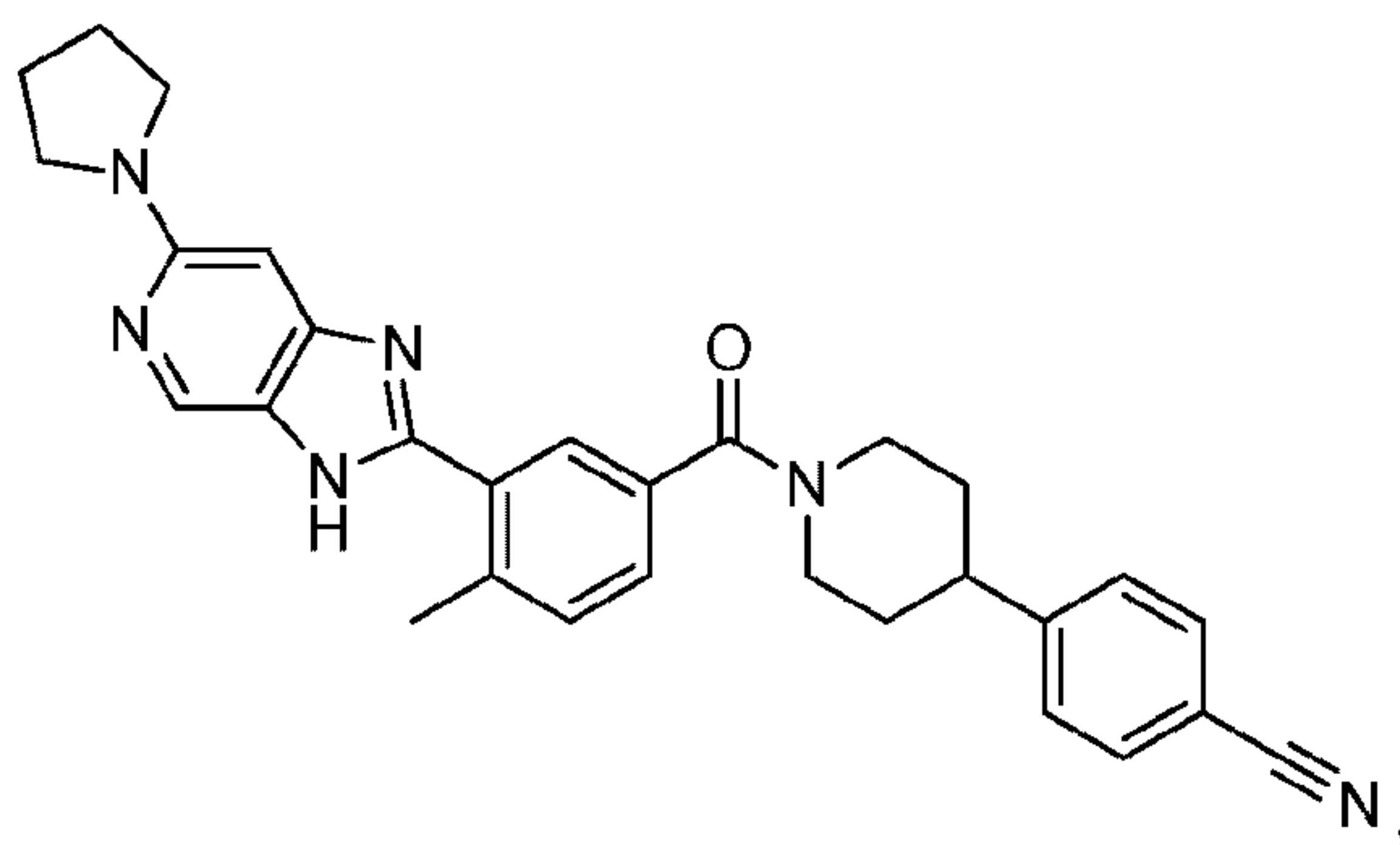
or a pharmaceutically acceptable salt thereof.

[0158] In certain aspects, the compounds of Structure (I) have one of the following Structures (I-X), (I-Y), (I-Z), (I-AA), (I-AB), (I-AC), (I-AD), (I-AF), (I-AG), or (I-AH):

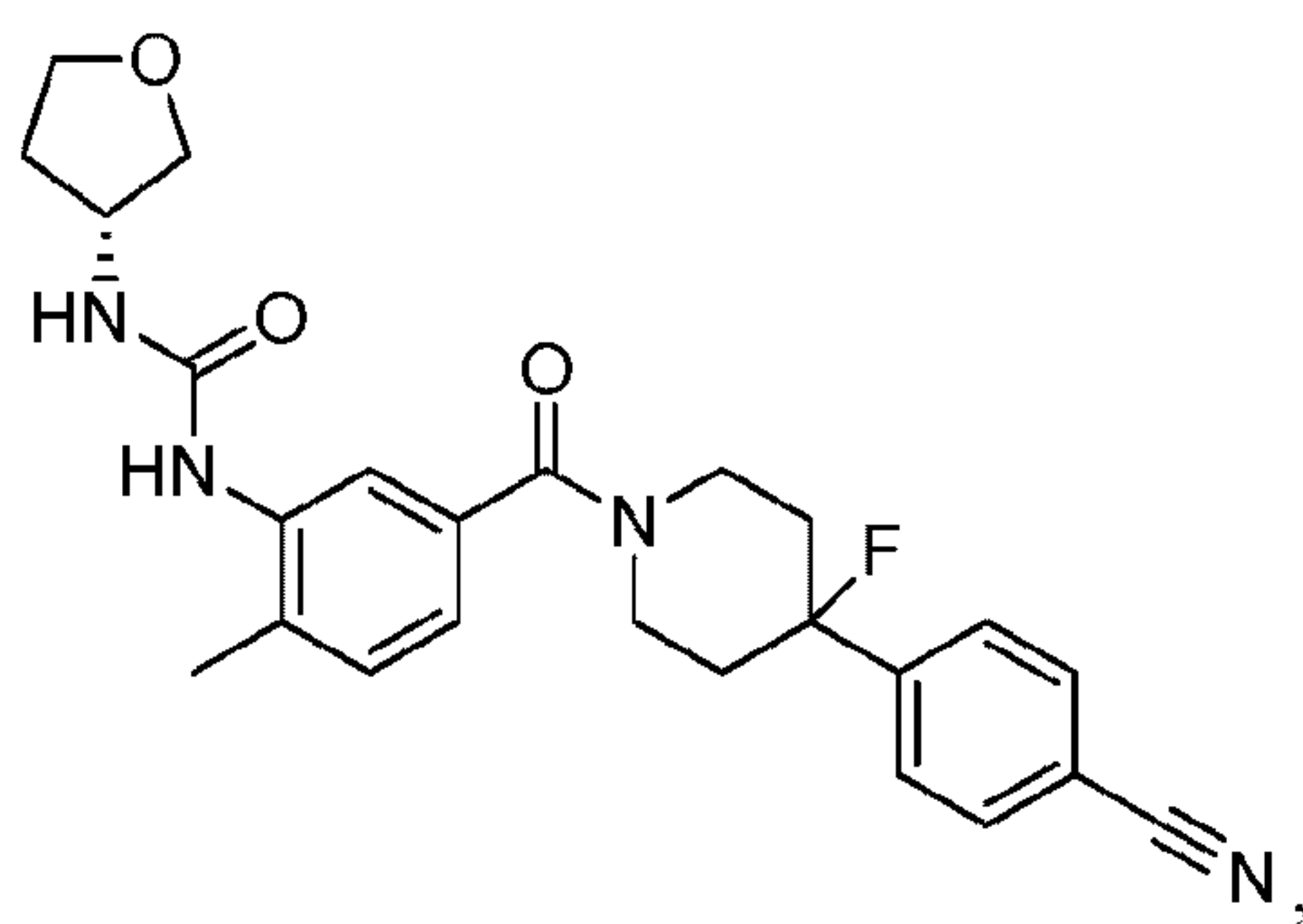
37



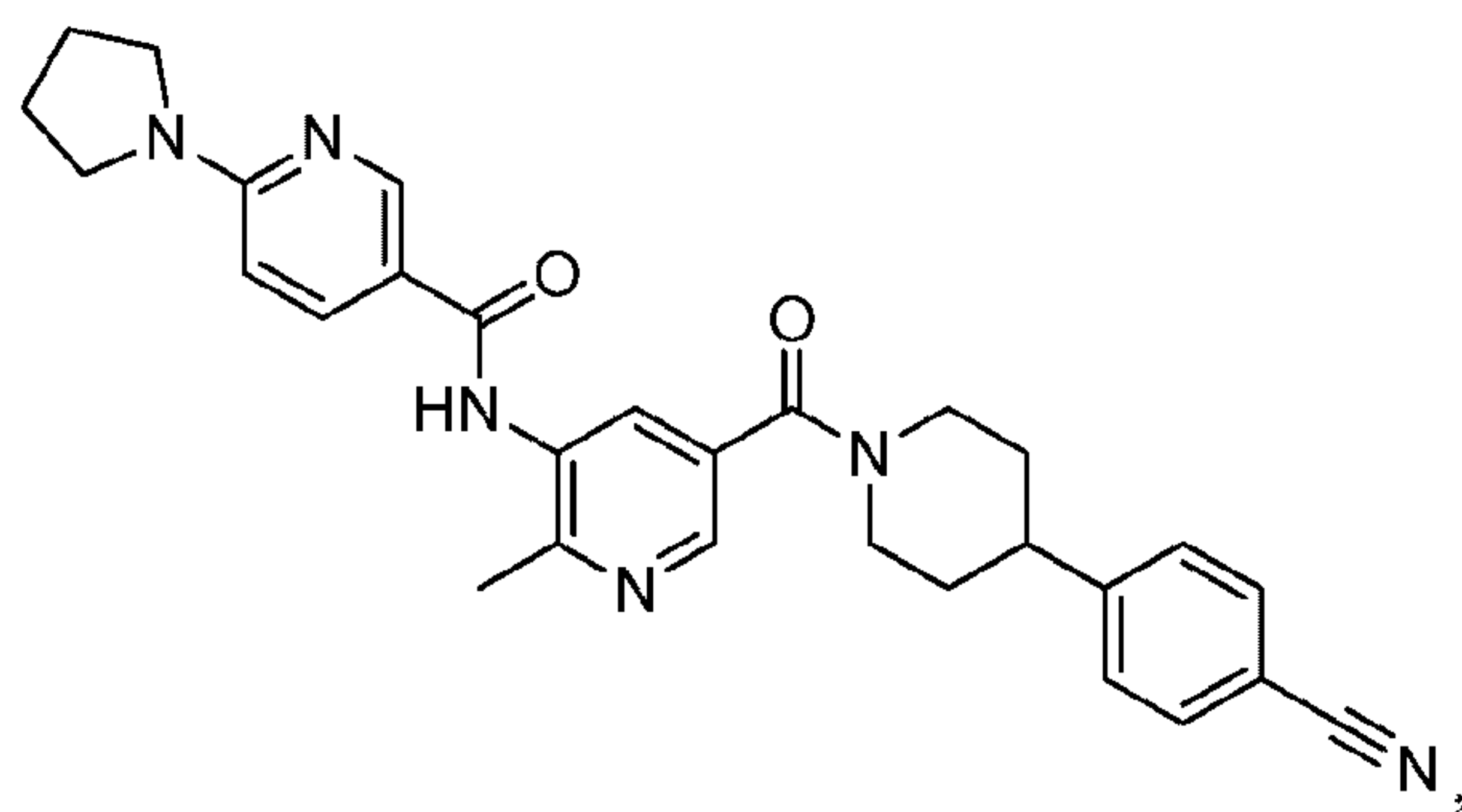
(I-X)



(I-Y)

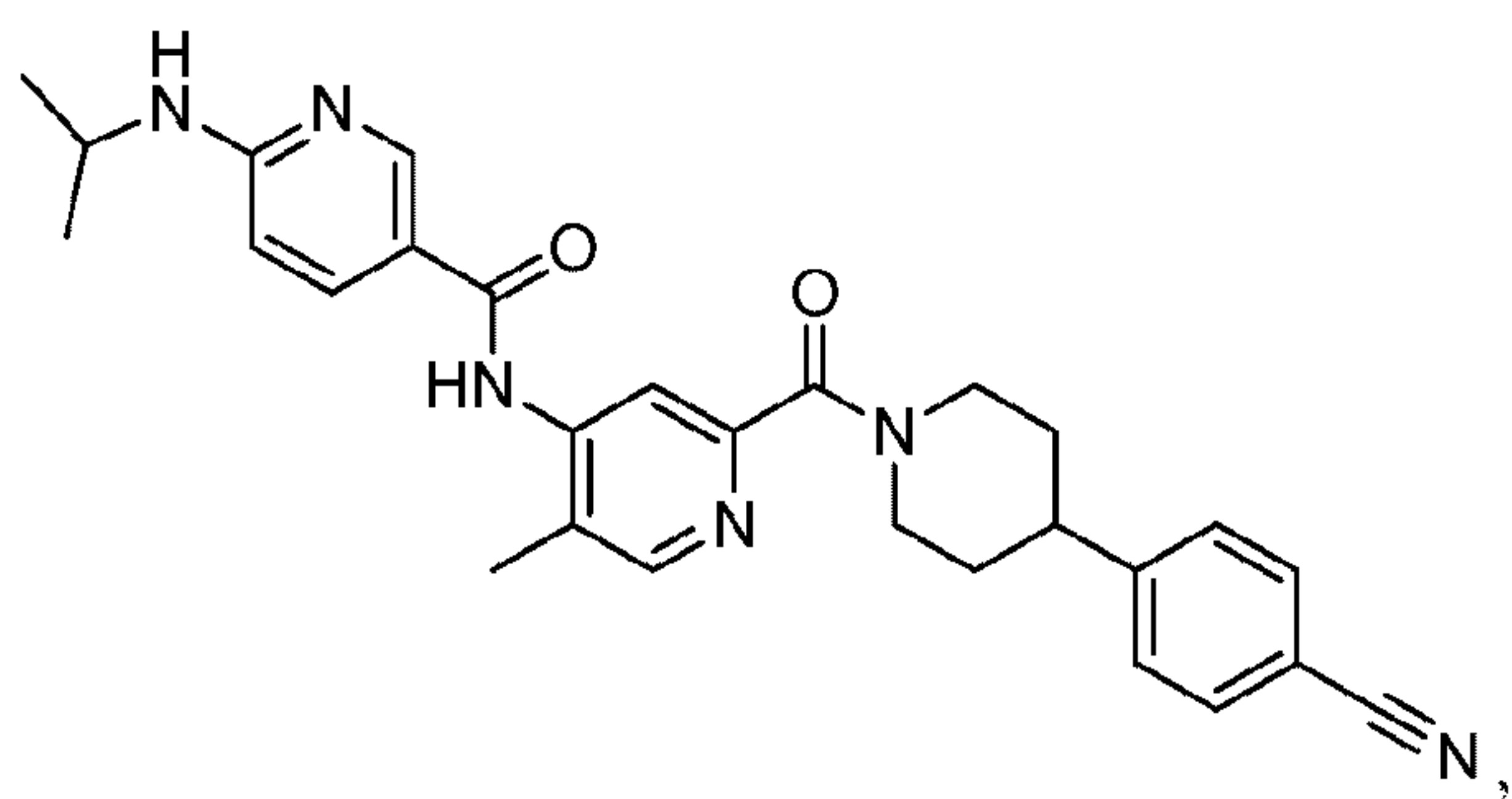


(I-Z)

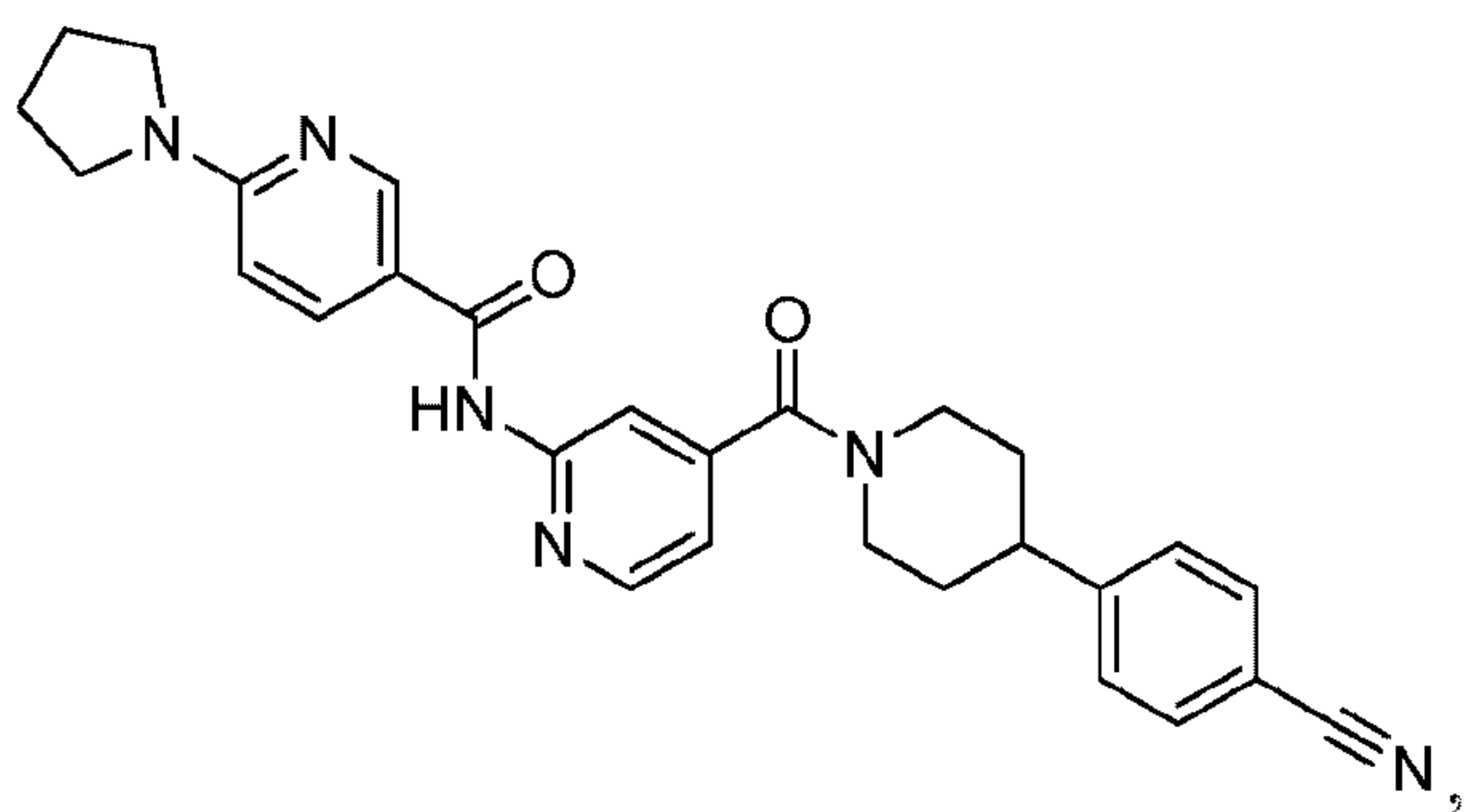


(I-AA)

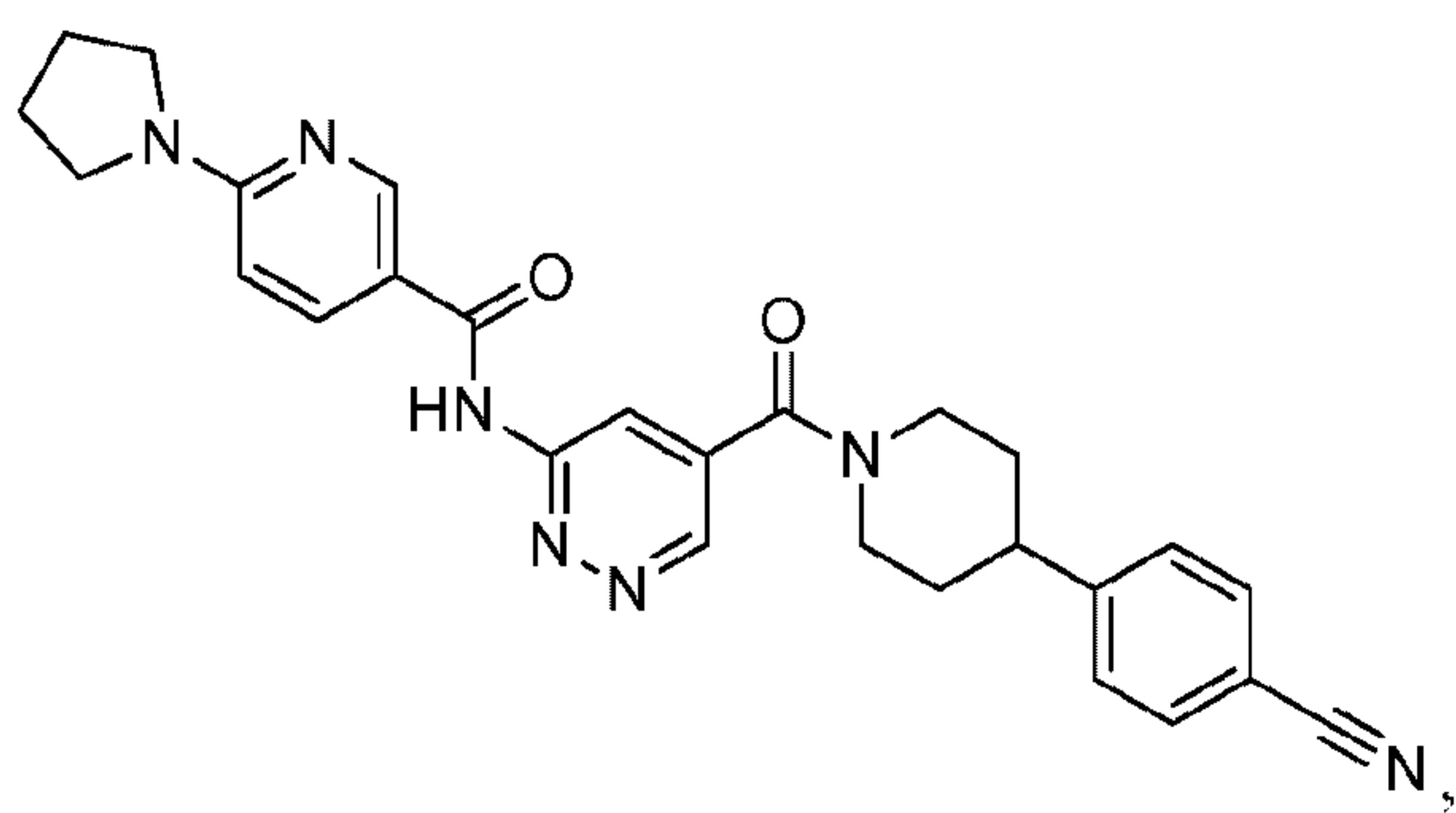
38



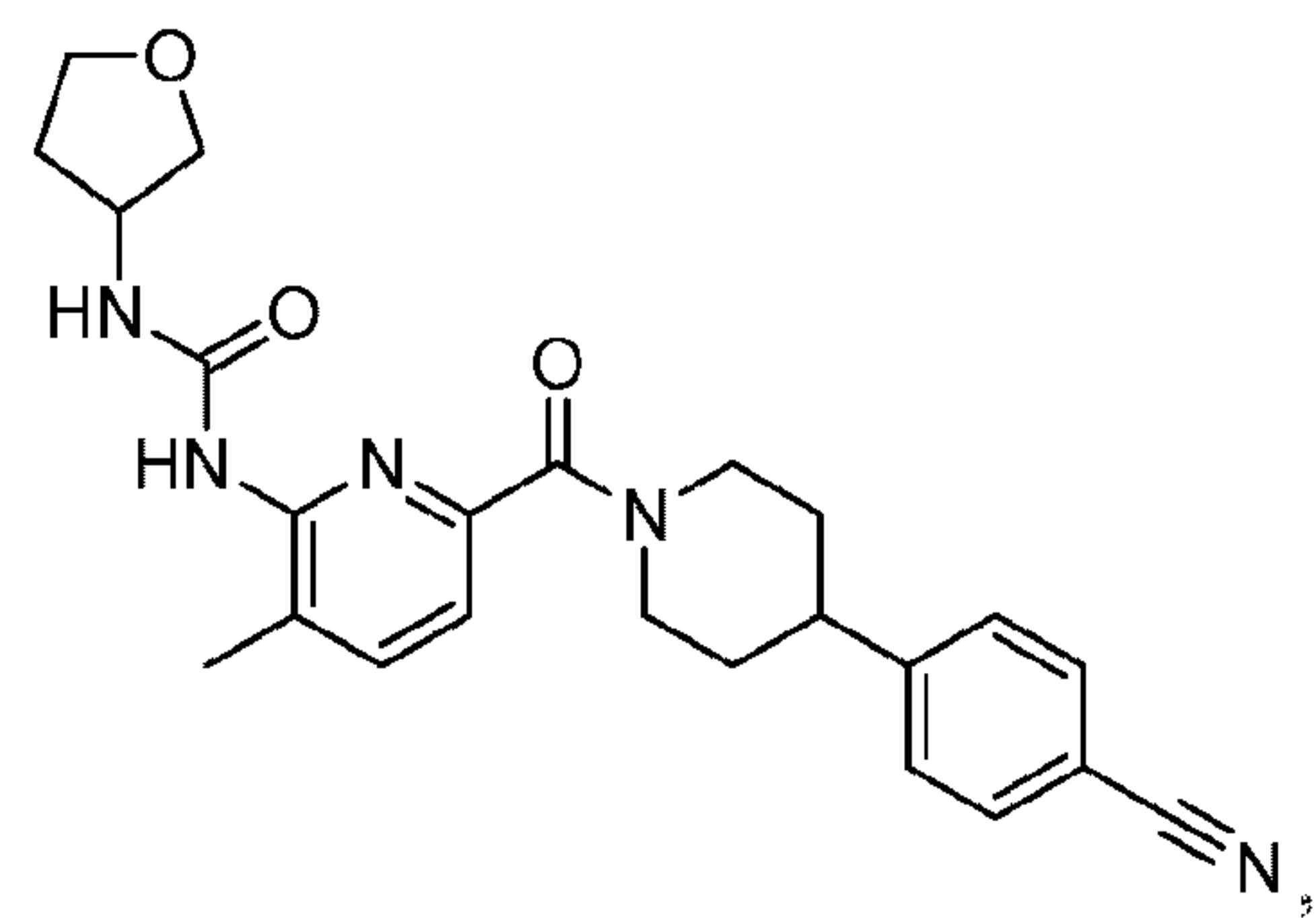
(I-AB)



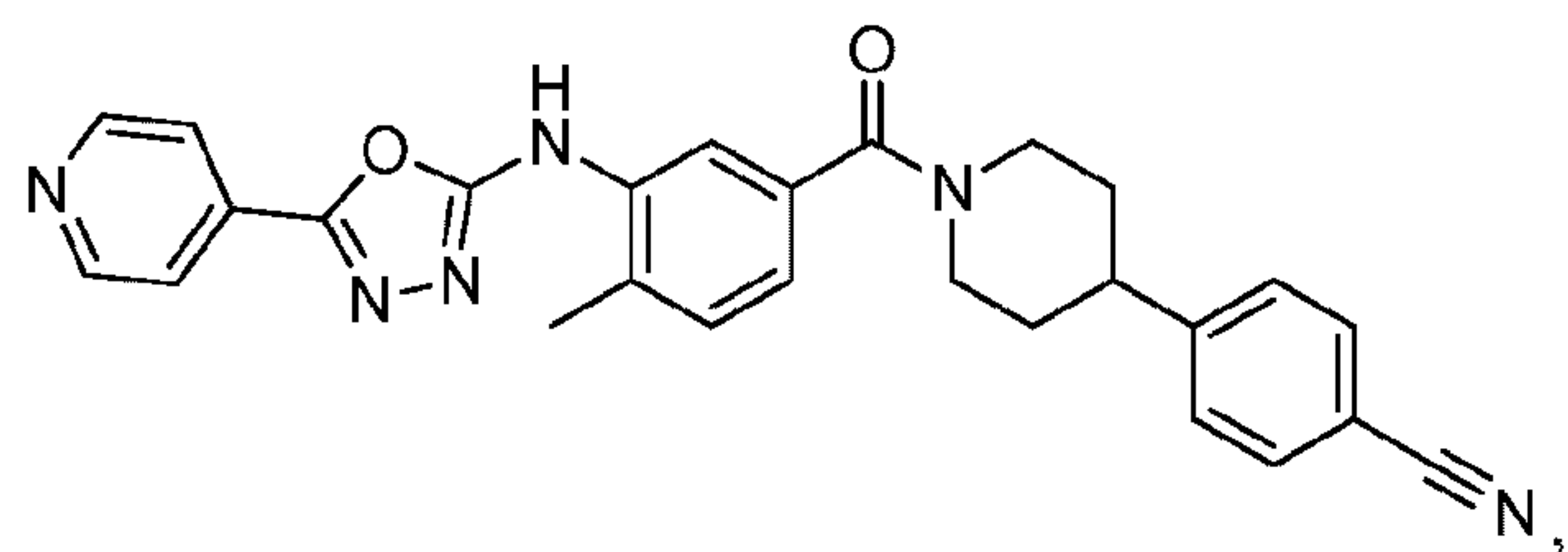
(I-AC)



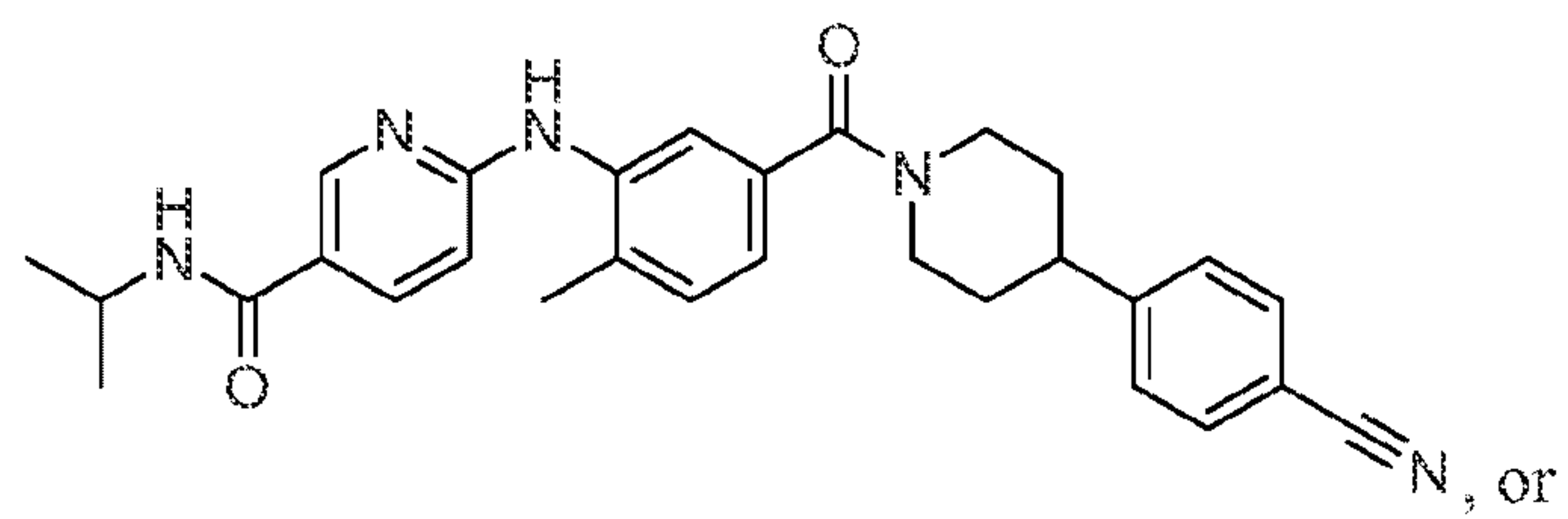
(I-AD)



(I-AE)

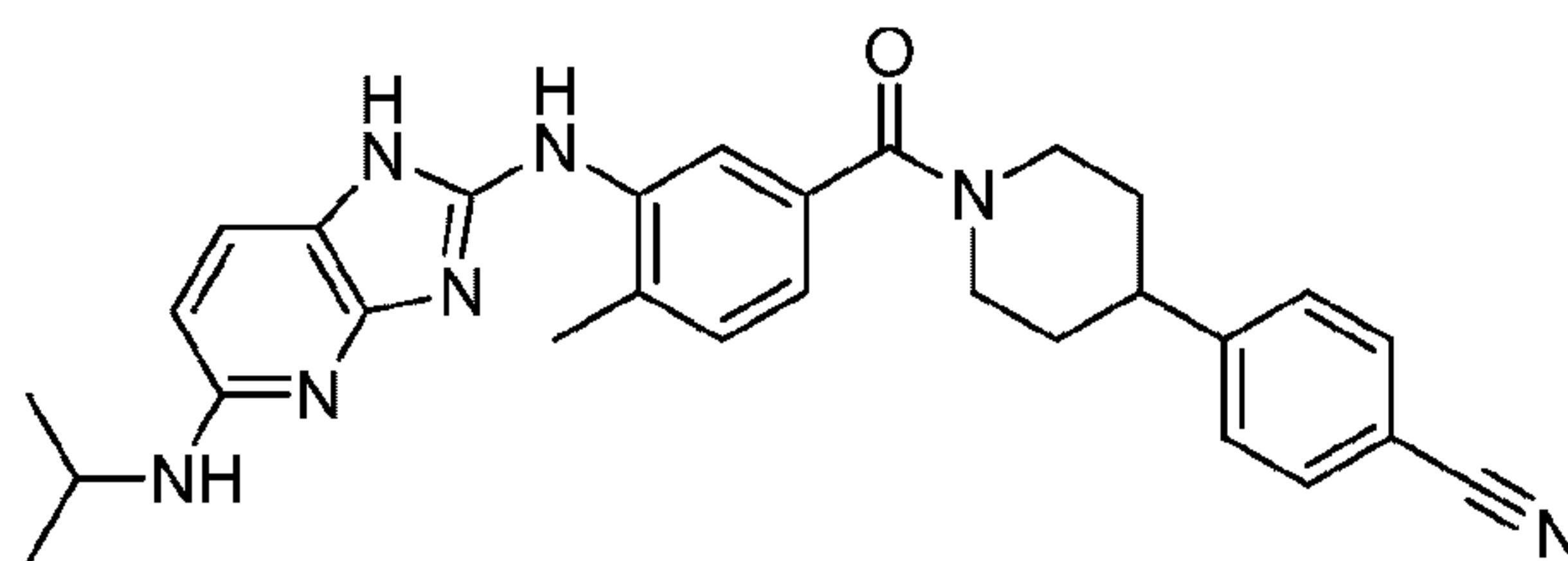


(I-AF)



(I-AG)

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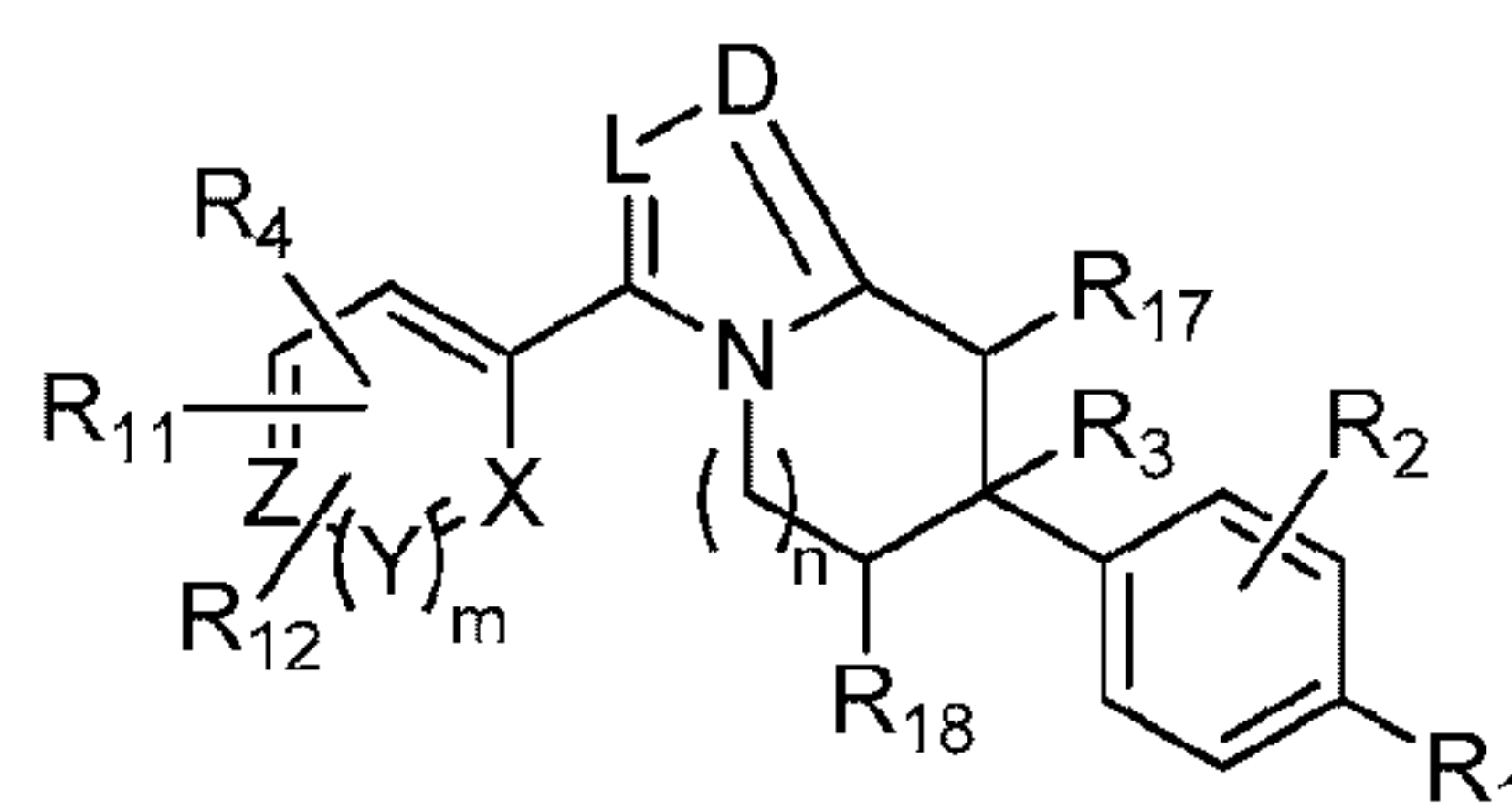


(I-AH)

or a pharmaceutically acceptable salt thereof.

Compounds of Structure (II)

[0159] In various aspects, the present disclosure provides for compounds of Structure (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein:

X, Y, and Z are each independently CR or NR', wherein R is H or C₁₋₆ alkyl and R' is H, C₁₋₆ alkyl, or absent;

L and D are each independently C or N;

R₁ is hydrogen, cyano, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, -C(=O)N(R₁₃)(R₁₄),

-(CH₂)_qC(=O)N(R₁₃)(R₁₄), CF₃, -OCF₃, or -S(=O)₂R₂₀;

q is 0, 1, 2, 3, or 4;

R₂₀ is hydrogen or C₁₋₆ alkyl, C₁₋₆ alkoxy, or -N(R₁₃)(R₁₄);

R₂ is hydrogen, halo, C₁₋₆ alkoxy, C₁₋₆ alkyl, or R₂ and R₃ taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R₃ is hydrogen, hydroxyl, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, or R₂ and R₃ taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R₄ is hydrogen, heteroaryl, heterocyclyl, -C(=O)N(R₅R₆), -N(R₇)C(=O)R₈, -N(R₉R₁₀), C₁₋₆ alkyl, C₁₋₆ alkoxy, -S(=O)₂R₂₀, or R₄ and R₁₁ taken together with the atoms to which they are attached join together to form a heteroaryl;

R₁₁ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy, -N(R₁₃R₁₄), CF₃, -OCF₃, -S(=O)₂R₂₀, R₄ and R₁₁ taken together with the atoms to which they are attached join together to form a heteroaryl, or R₁₁ and R₁₂ taken together with the atoms to which they are attached join together to form a heteroaryl;

R_{12} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, or R_{11} and R_{12} taken together with the atoms to which they are attached join together to form a heteroaryl;

R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{13} , and R_{14} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylamino, or $-N(R_{15}R_{16})$;

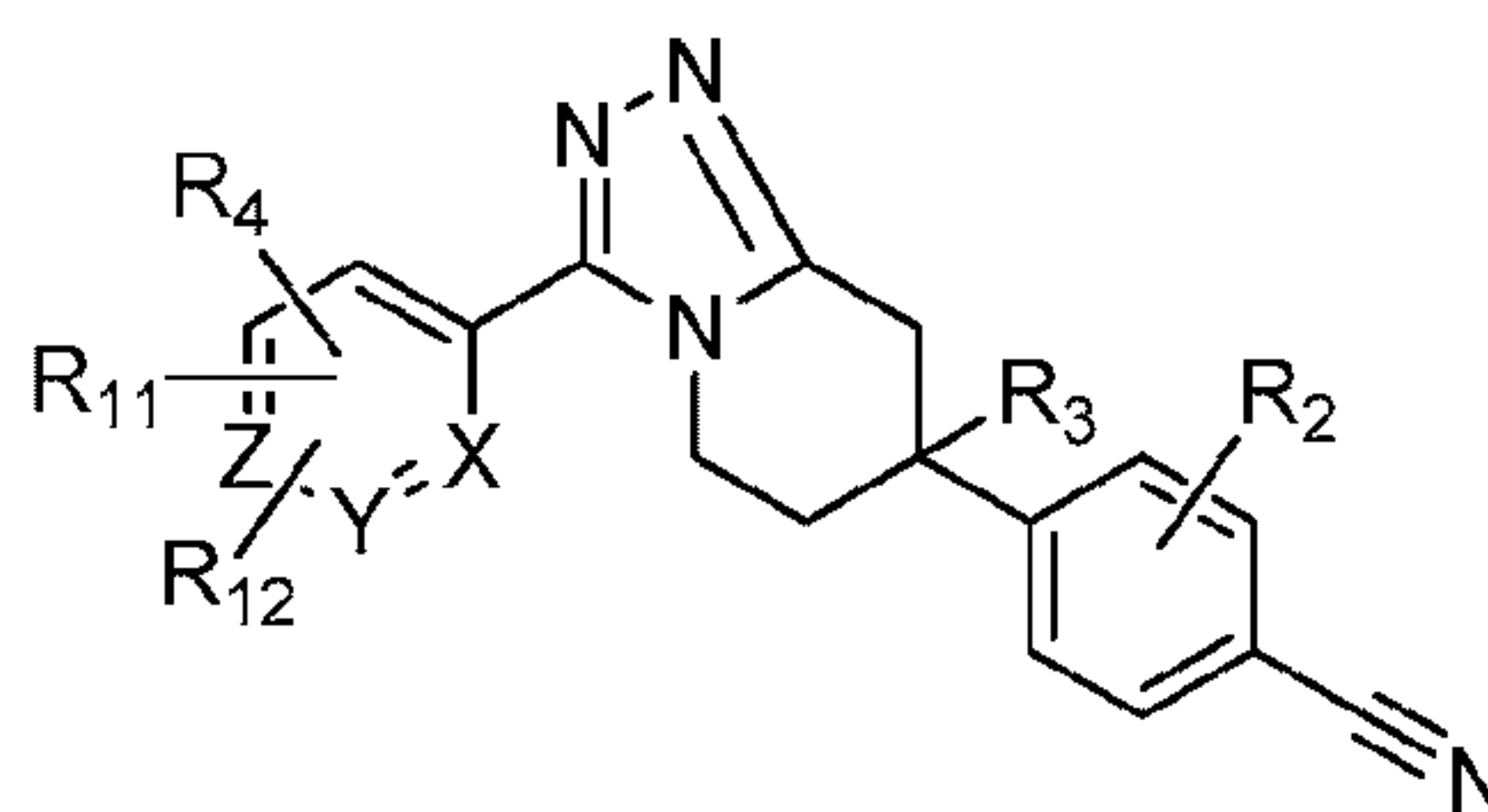
R_{15} and R_{16} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, or alkylamino;

R_{17} and R_{18} are each independently hydrogen or alkyl or can optionally join together to form a bond;

n is 1 or 2; and

m is 0 or 1.

[0160] In certain aspects, the compounds of Structure (II) have the following Structure (II-A):



(II-A)

or a pharmaceutically acceptable salt thereof, wherein:

X , Y , and Z are each independently CR or NR' , wherein R is H or C_{1-6} alkyl and R' is H, C_{1-6} alkyl, or absent;

R_2 is hydrogen, halo, C_{1-6} alkoxy, C_{1-6} alkyl, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R_4 is hydrogen, heteroaryl, heterocyclyl, $-C(=O)N(R_5R_6)$, $-N(R_7)C(=O)R_8$, $-N(R_9R_{10})$, C_{1-6} alkyl, C_{1-6} alkoxy, $-S(=O)_2R_{20}$, or R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

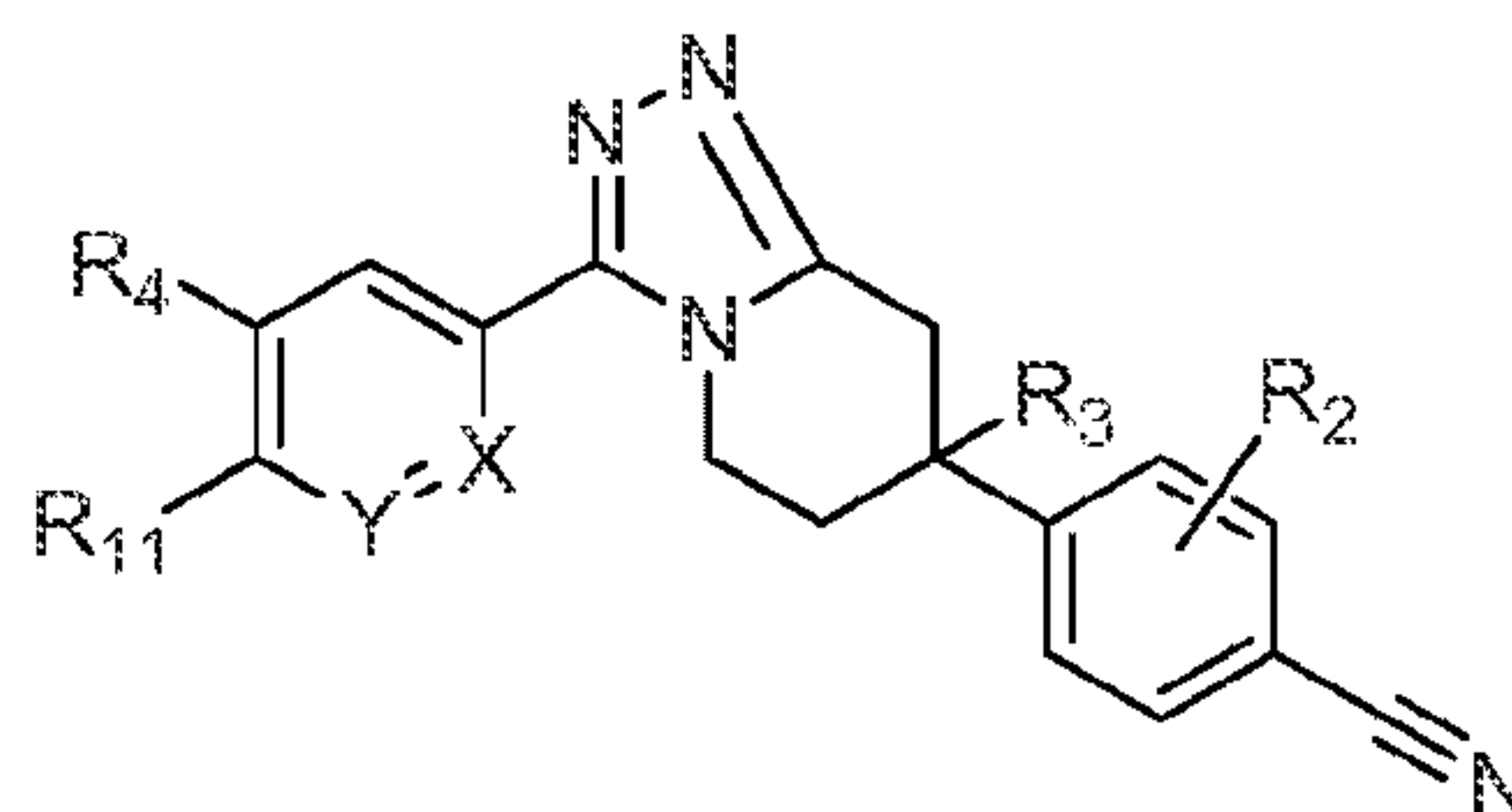
R_{11} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl, or R_{11} and R_{12} taken together with the atoms to which they are attached join together to form a heteroaryl;

R_{12} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, or R_{11} and R_{12} taken together with the atoms to which they are attached join together to form a heteroaryl;

R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{13} , and R_{14} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylamino, or $-N(R_{15}R_{16})$; and

R_{15} and R_{16} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, or alkylamino.

[0161] In certain aspects, the compounds of Structure (II) have the following Structure (II-B):



(II-B)

or a pharmaceutically acceptable salt thereof, wherein:

X and Y are each independently CR or NR', wherein R is H or C_{1-6} alkyl and R' is H, C_{1-6} alkyl, or absent;

R_2 is hydrogen, halo, C_{1-6} alkoxy, C_{1-6} alkyl, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or R_2 and R_3 taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R_4 is hydrogen, heteroaryl, heterocyclyl, $-C(=O)N(R_5R_6)$, $-N(R_7)C(=O)R_8$, $-N(R_9R_{10})$, C_{1-6} alkyl, C_{1-6} alkoxy, $-S(=O)_2R_{20}$, or R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl;

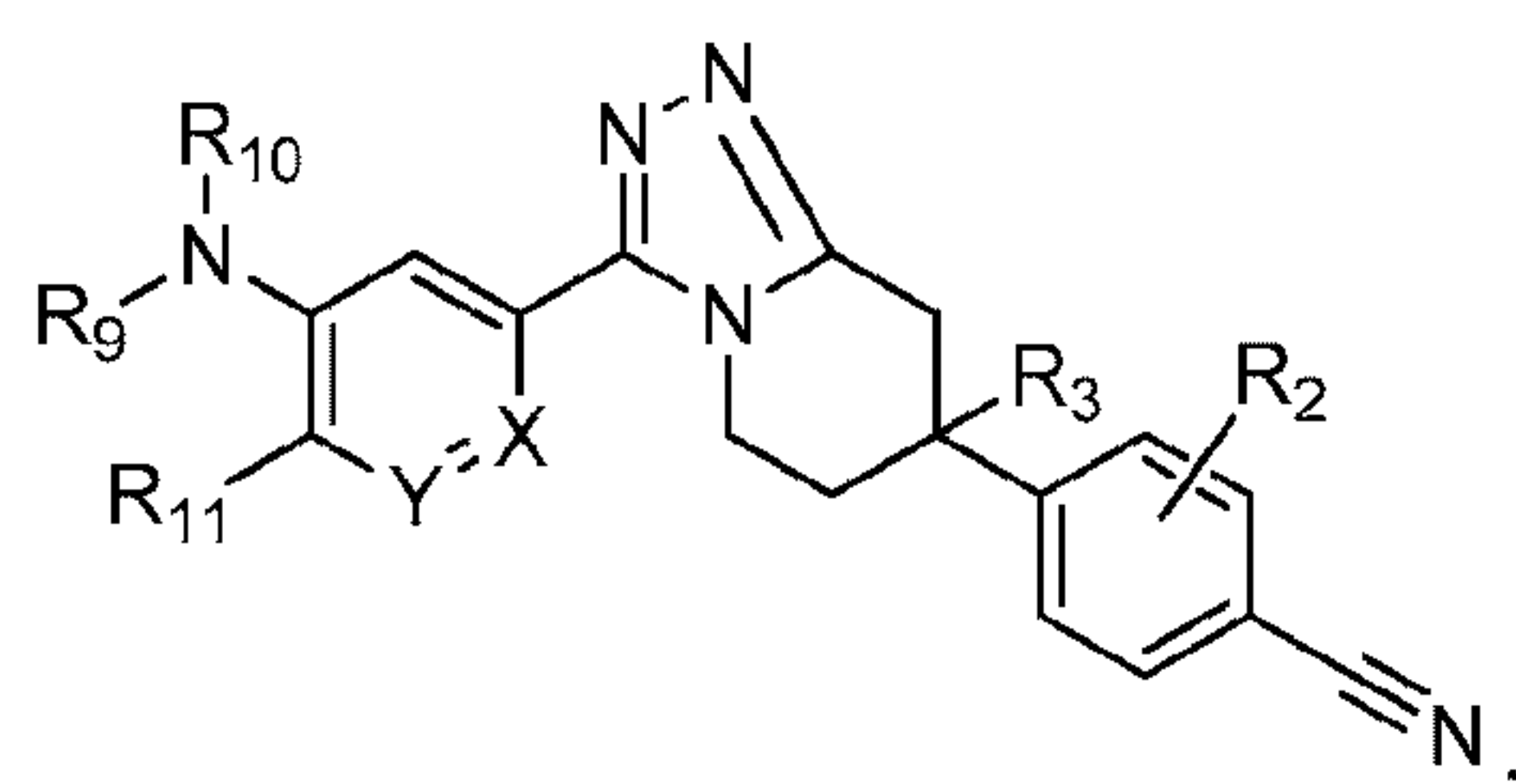
R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_{11} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, or R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl;

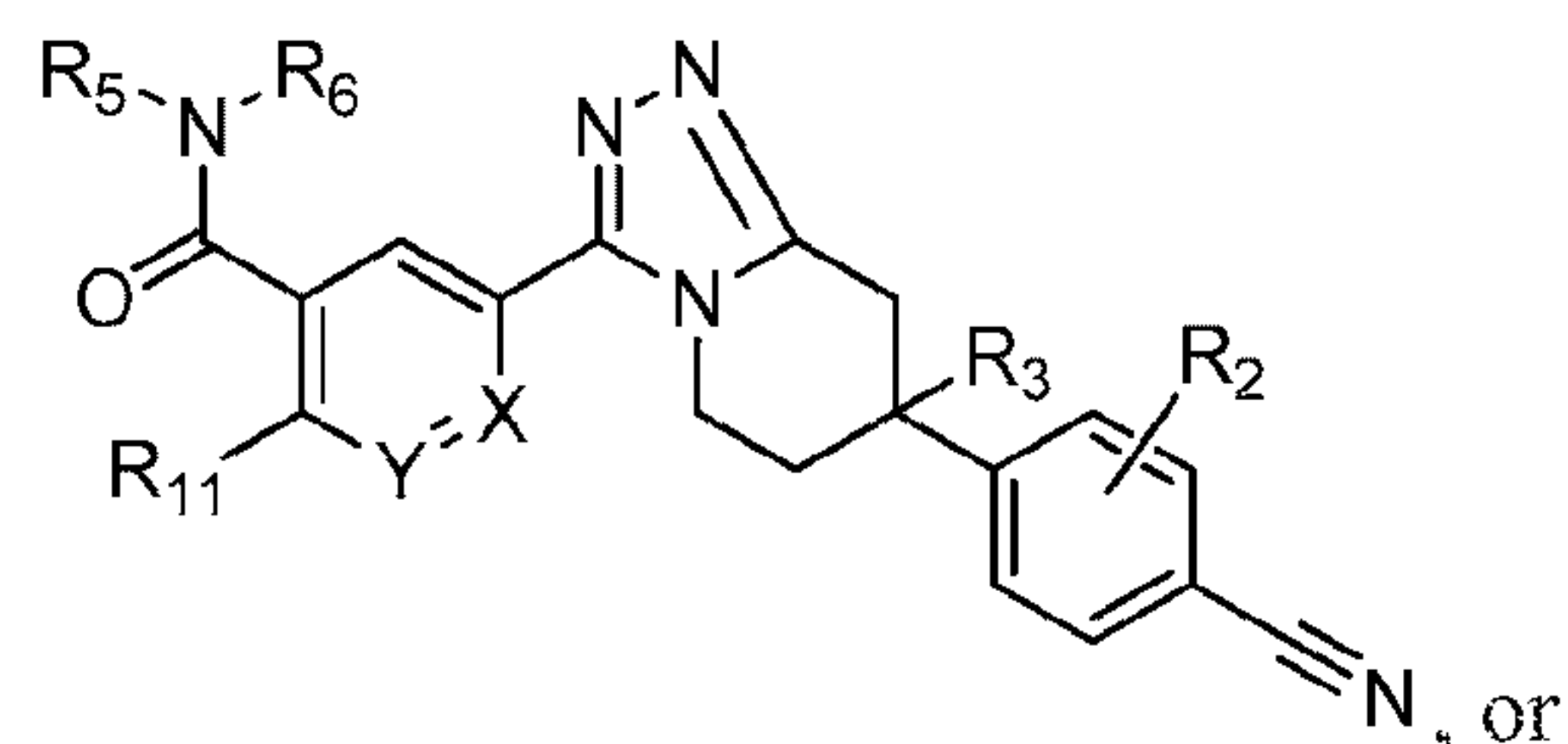
R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylamino, or $-N(R_{15}R_{16})$; and

R_{15} and R_{16} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, or alkylamino.

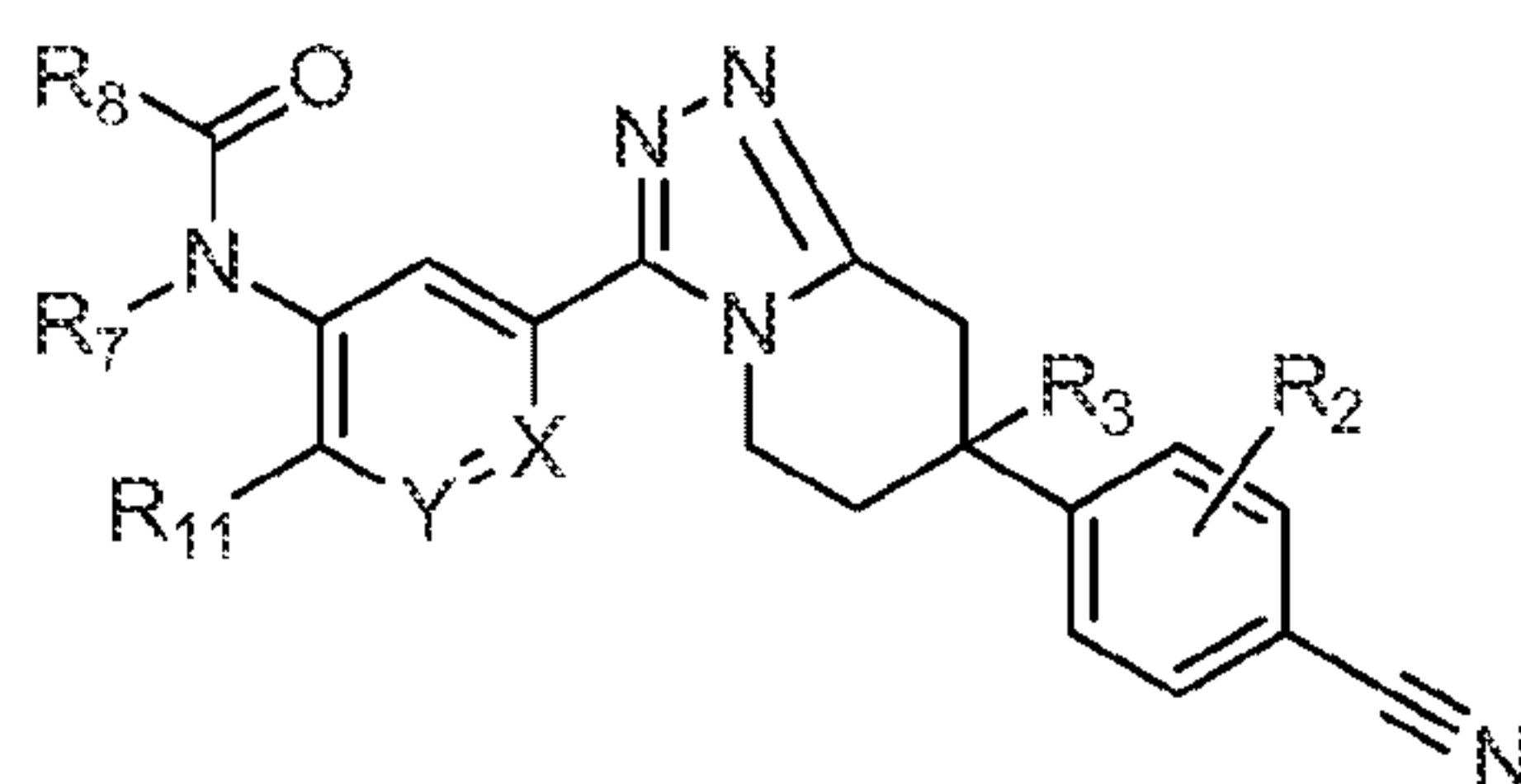
[0162] In certain aspects, the compounds of Structure (II) have one of the following Structures (II-C), (II-D), or (II-E):



(II-C)



(II-D)



(II-E)

or a pharmaceutically acceptable salt thereof, wherein:

X and Y are each independently CR or NR', wherein R is H or C₁₋₆ alkyl and R' is H, C₁₋₆ alkyl, or absent;

R₂ is hydrogen, halo, C₁₋₆ alkoxy, C₁₋₆ alkyl, or R₂ and R₃ taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R₃ is hydrogen, hydroxyl, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, or R₂ and R₃ taken together with the atoms to which they are attached form a 5-membered heterocyclyl;

R₁₁ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy, -N(R₁₃R₁₄), CF₃, -OCF₃, or -S(=O)₂R₂₀;

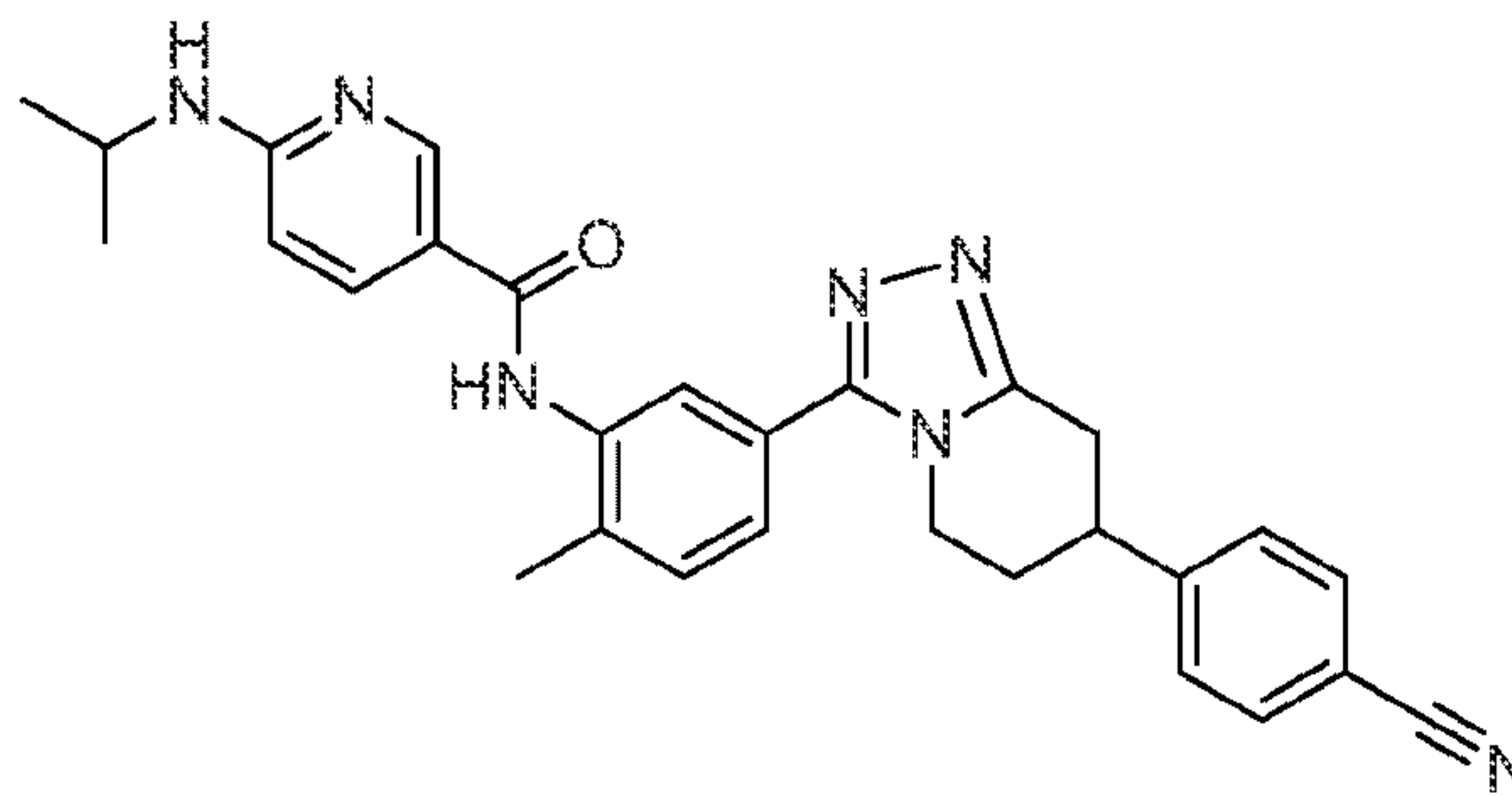
R₂₀ is hydrogen or C₁₋₆ alkyl, C₁₋₆ alkoxy, or -N(R₁₃)(R₁₄);

R₅, R₆, R₇, R₈, R₉, and R₁₀ are each independently H, C₁₋₆ alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylamino, or -N(R₁₅R₁₆); and

R₁₅ and R₁₆ are each independently H, C₁₋₆ alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, or alkylamino.

[0163] In certain aspects, the compound of Structure (II) has the following Structure (II-F):

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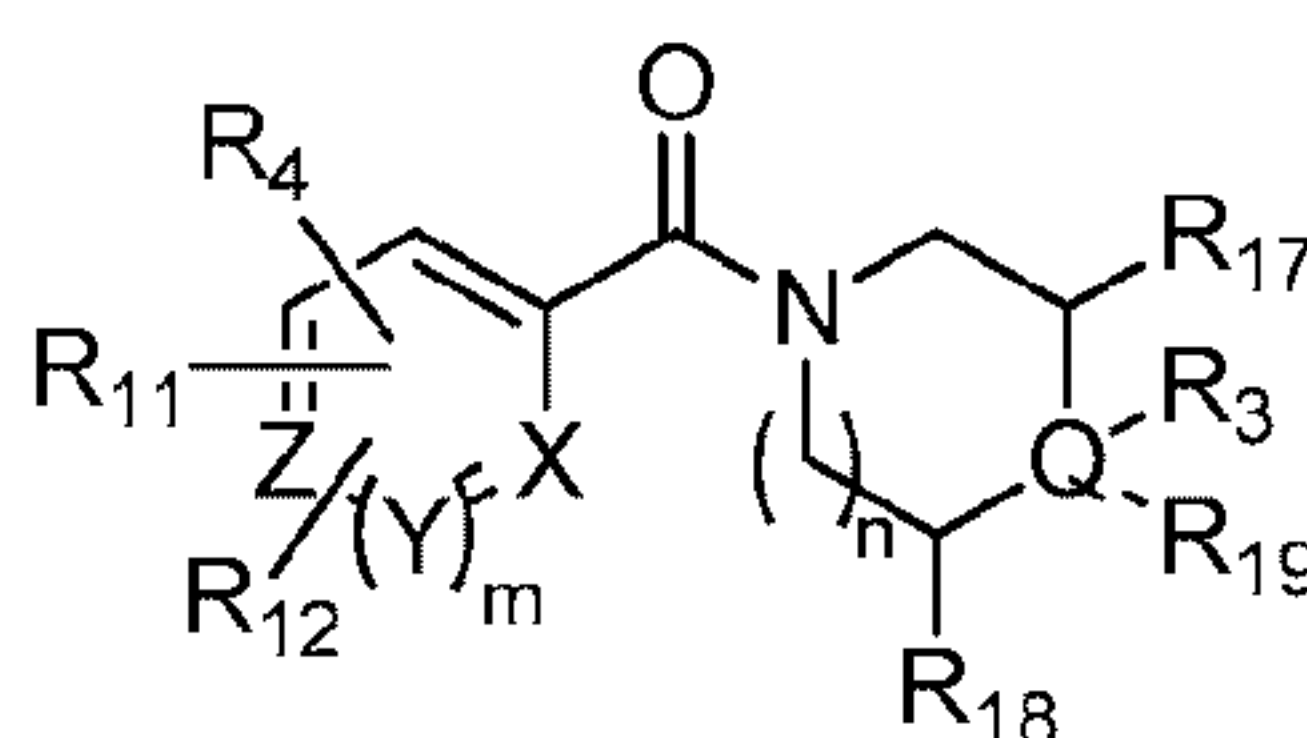


(II-F)

or a pharmaceutically acceptable salt thereof.

Compounds of Structure (III)

[0164] In various aspects, the present disclosure provides for compounds of Structure (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein:

X, Y, and Z are each independently CR or NR', wherein R is H or C₁₋₆ alkyl and R' is H, C₁₋₆ alkyl, or absent;

Q is C or N;

R₃ is hydrogen, hydroxyl, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, or if Q is N R₃ is absent;

R₄ is hydrogen, heteroaryl, heterocyclyl, -C(=O)N(R₅R₆), -N(R₇)C(=O)R₈, -N(R₉R₁₀), C₁₋₆ alkyl, C₁₋₆ alkoxy, -S(=O)₂R₂₀, or R₄ and R₁₁ taken together with the atoms to which they are attached join together to form a heteroaryl;

R₂₀ is hydrogen or C₁₋₆ alkyl, C₁₋₆ alkoxy, or -N(R₁₃)(R₁₄);

R₁₁ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy, -N(R₁₃R₁₄), CF₃, -OCF₃, -S(=O)₂R₂₀, R₄ and R₁₁ taken together with the atoms to which they are attached join together to form a heteroaryl, or R₁₁ and R₁₂ taken together with the atoms to which they are attached join together to form a heteroaryl;

R₁₂ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy, -N(R₁₃R₁₄), CF₃, -OCF₃, -S(=O)₂R₂₀, or R₁₁ and R₁₂ taken together with the atoms to which they are attached join together to form a heteroaryl;

R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₃, and R₁₄ are each independently H, C₁₋₆ alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylamino, or -N(R₁₅R₁₆);

R_{15} and R_{16} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, or alkylamino;

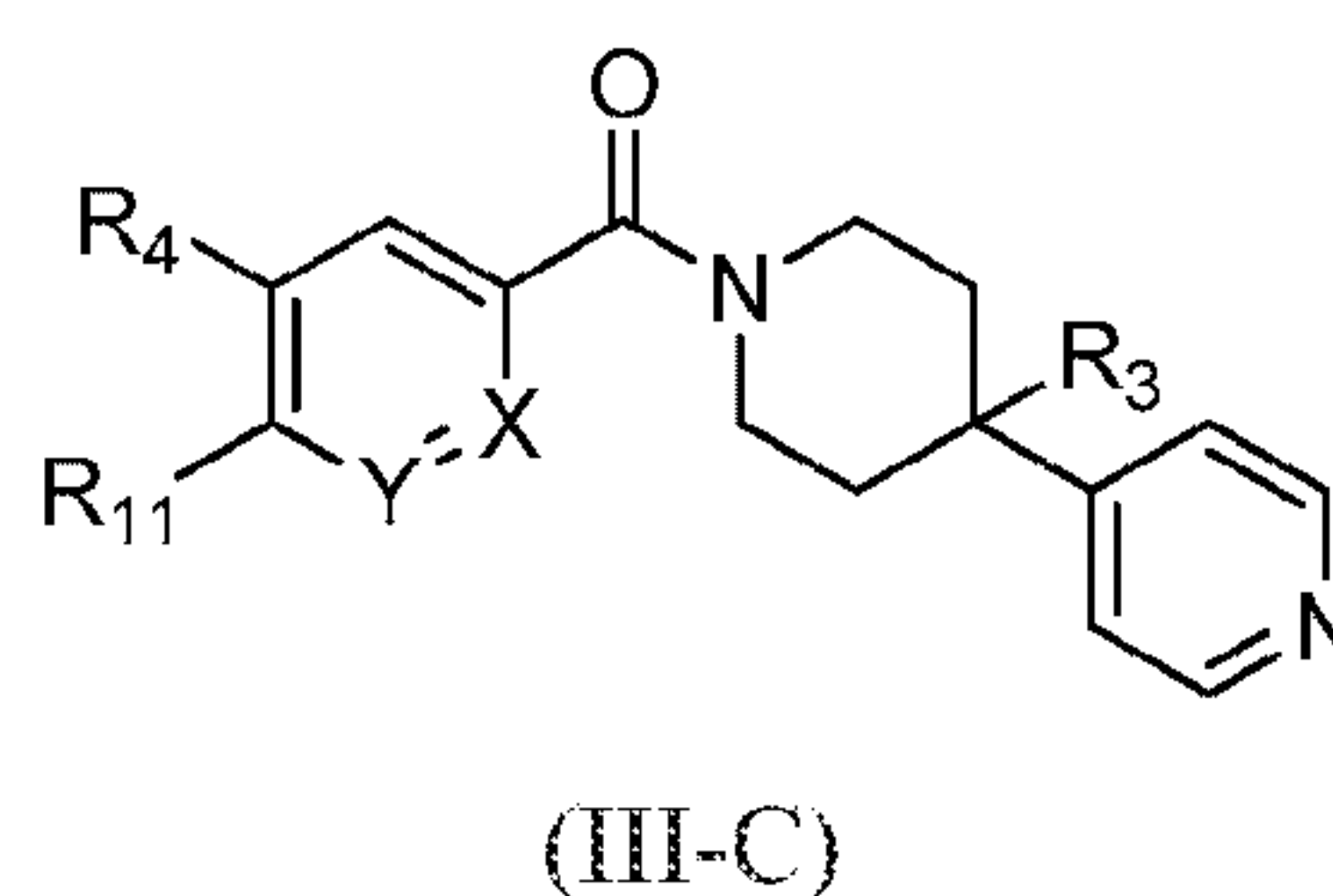
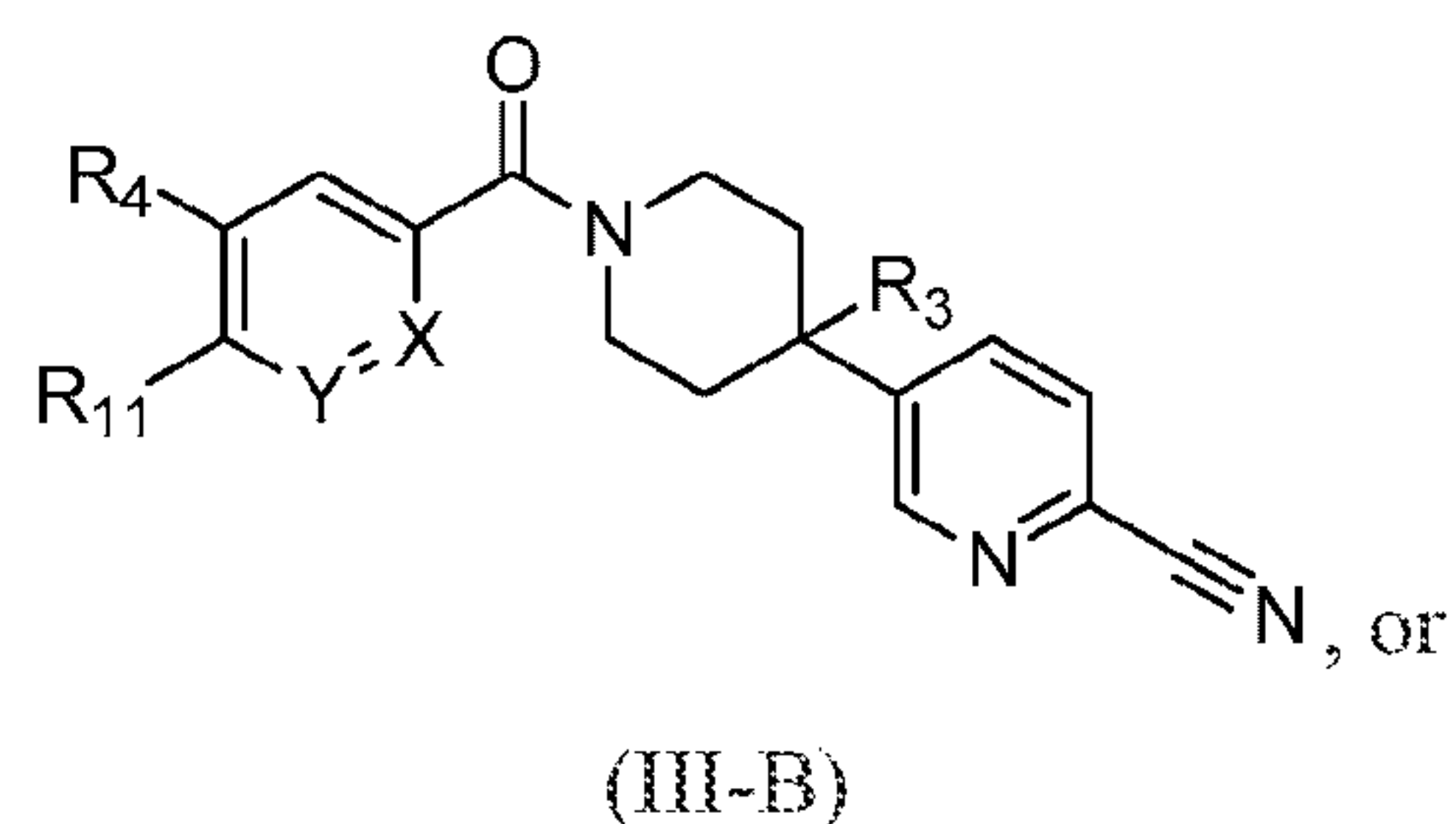
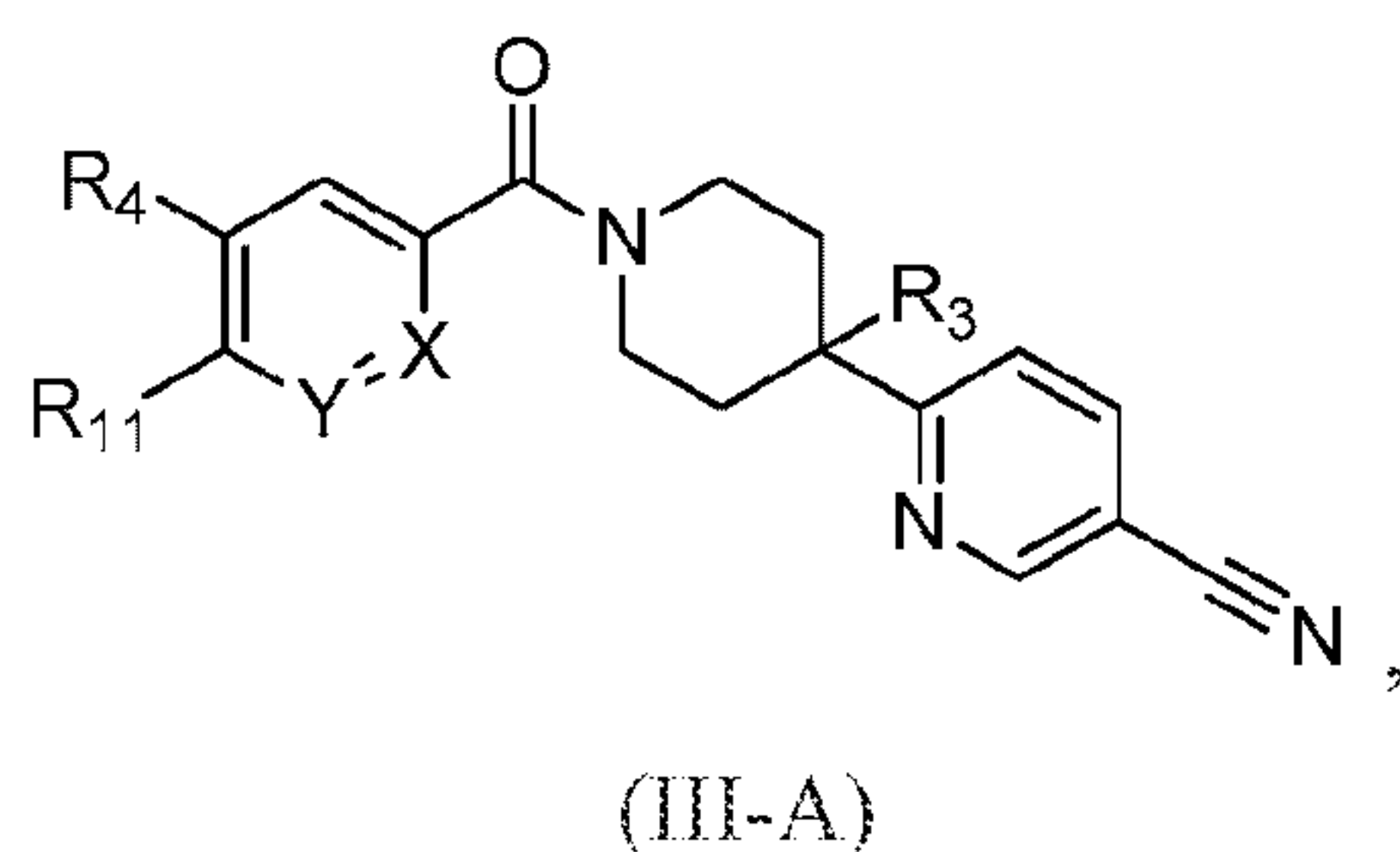
R_{17} and R_{18} are each independently hydrogen or alkyl or can optionally join together to form a bond;

R_{19} is aryl, heteroaryl, cycloalkyl, or heterocyclyl;

n is 0, 1, or 2; and

m is 0 or 1.

[0165] In certain aspects, the compounds of Structure (III) have one of the following Structures (III-A), (III-B), or (III-C):



or a pharmaceutically acceptable salt thereof, wherein:

X and Y are each independently CR or NR' , wherein R is H or C_{1-6} alkyl and R' is H, C_{1-6} alkyl, or absent;

R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, or C_{1-6} alkoxy;

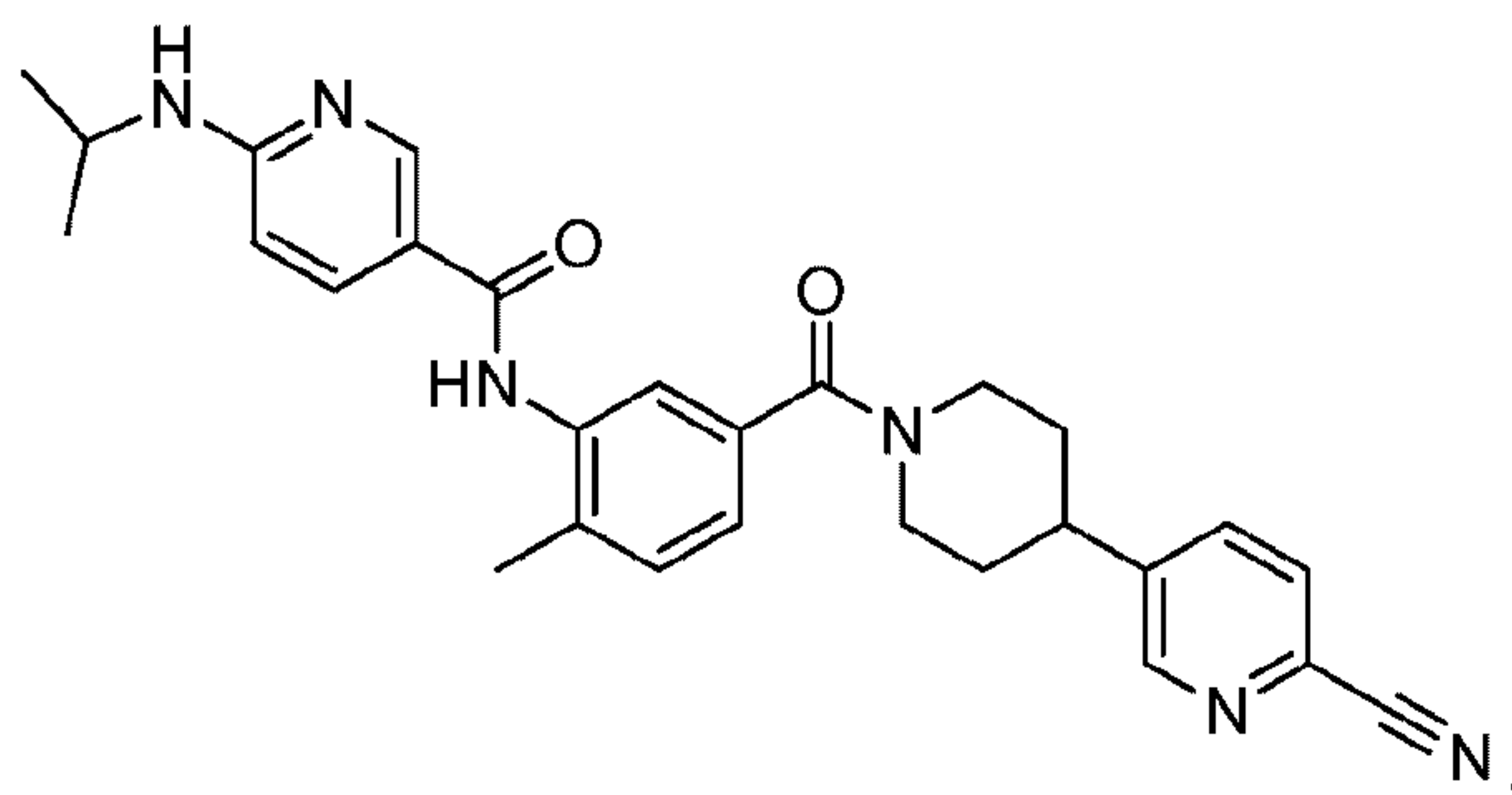
R_4 is hydrogen, heteroaryl, heterocyclyl, $-C(=O)N(R_5R_6)$, $-N(R_7)C(=O)R_8$, $-N(R_9R_{10})$, C_{1-6} alkyl, C_{1-6} alkoxy, $-S(=O)_2R_{20}$, or R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl;

R_{11} is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{13}R_{14})$, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, or R_4 and R_{11} taken together with the atoms to which they are attached join together to form a heteroaryl;

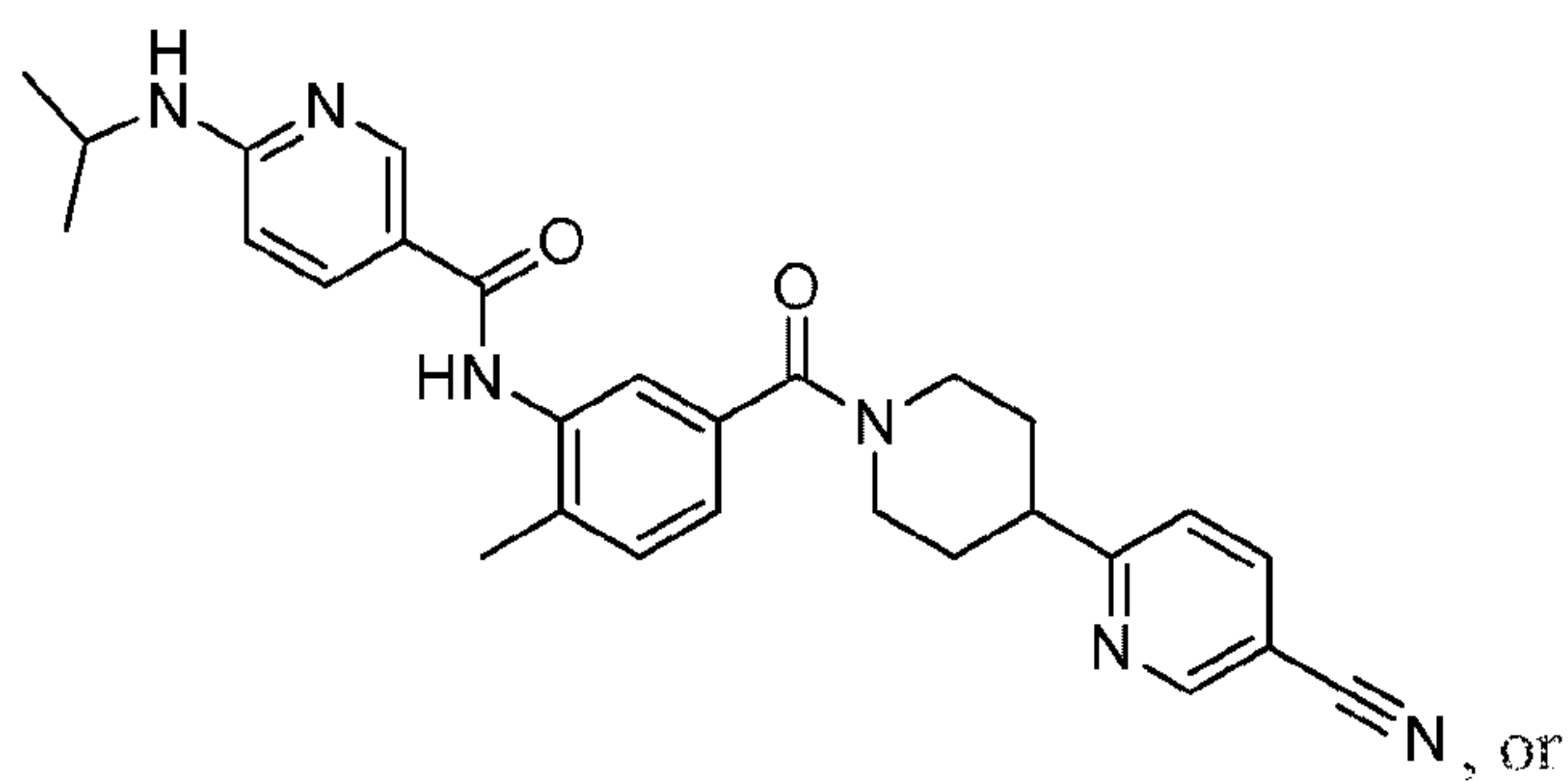
R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylamino, or $-N(R_{15}R_{16})$; and

R_{15} and R_{16} are each independently H, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, or alkylamino.

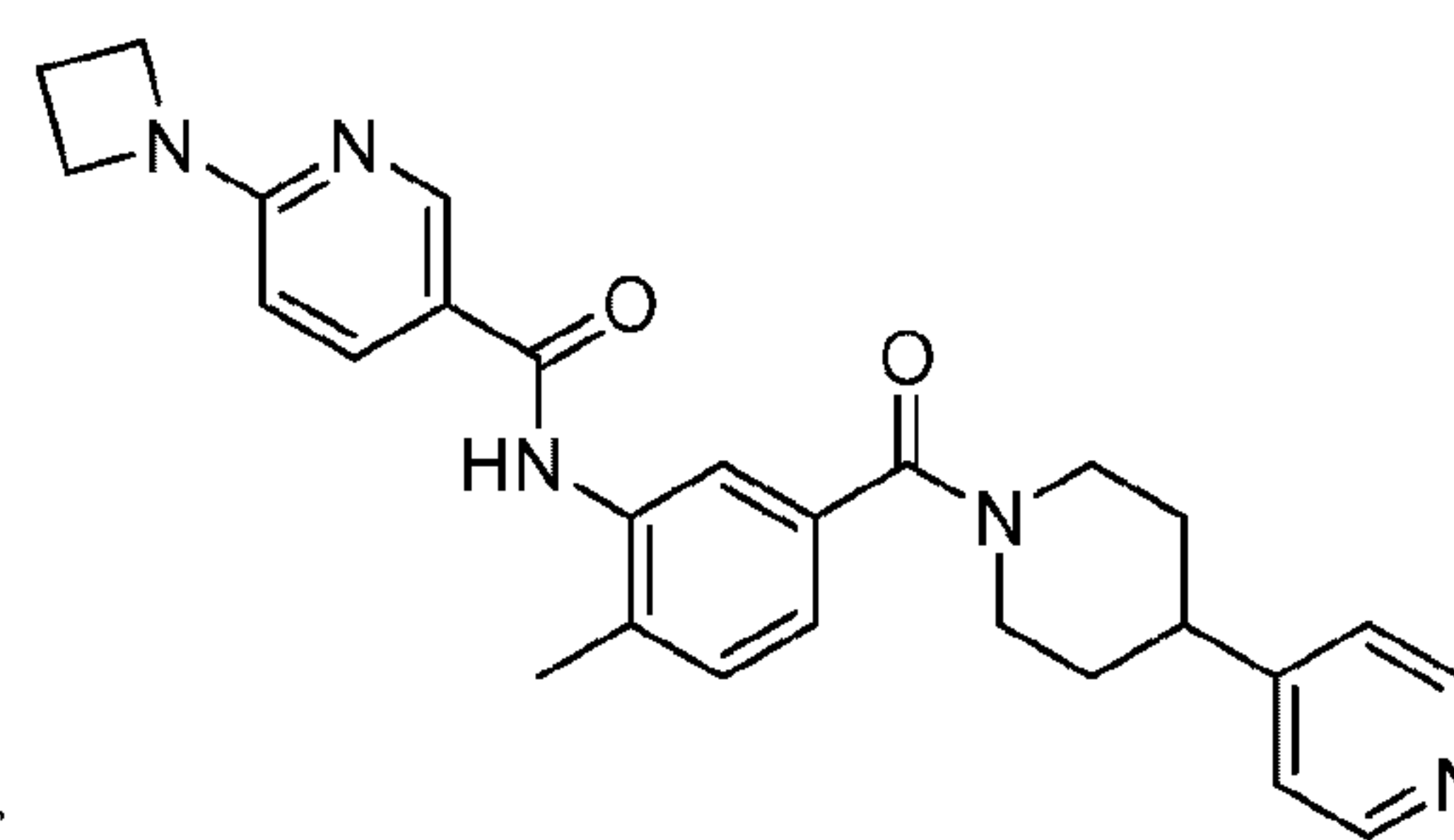
[0166] In certain aspects, the compounds of Structure (III) have one of the following Structures (III-D), (III-E), or (III-F):



(III-D)



(III-E)

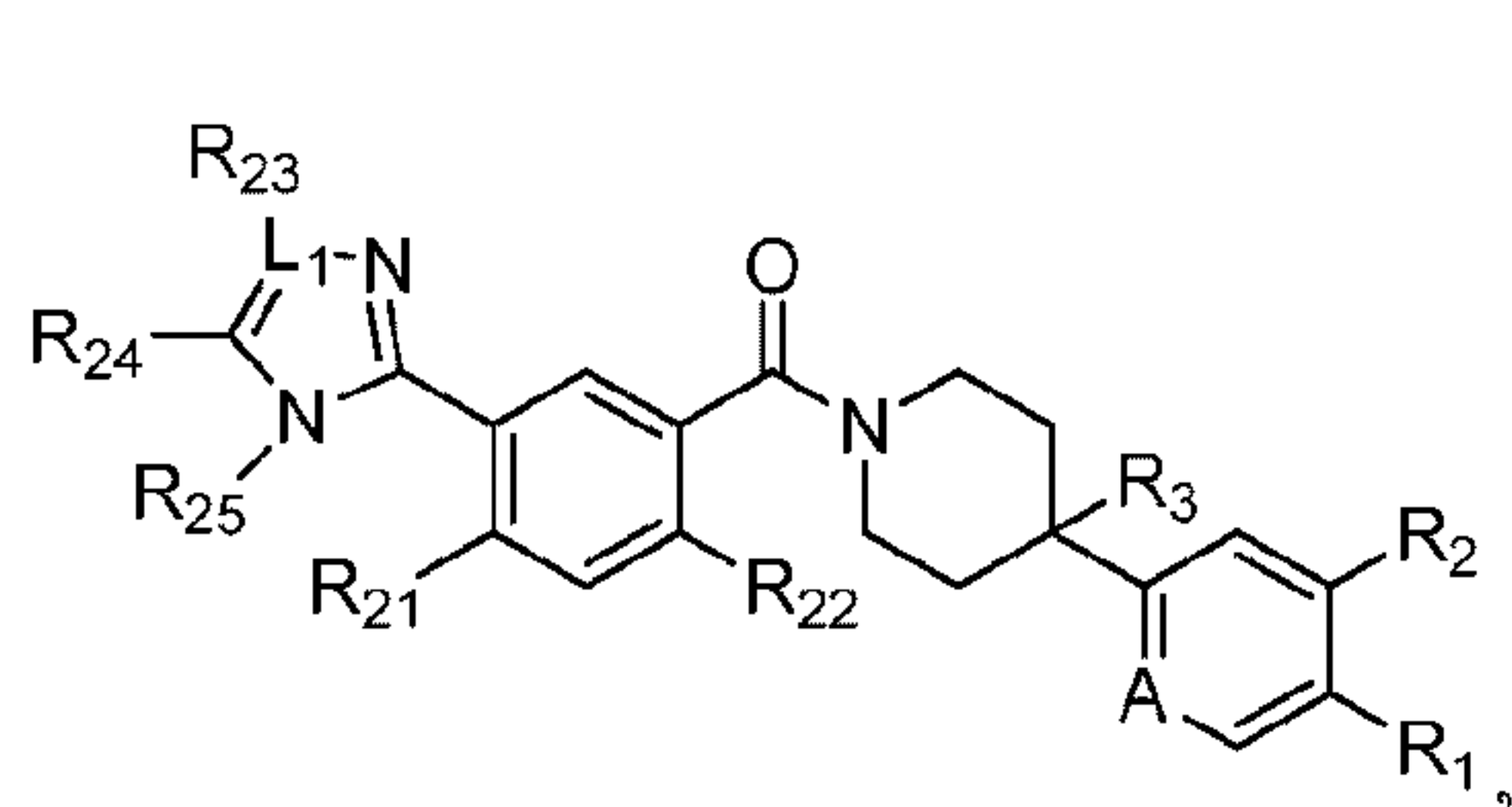


(III-F)

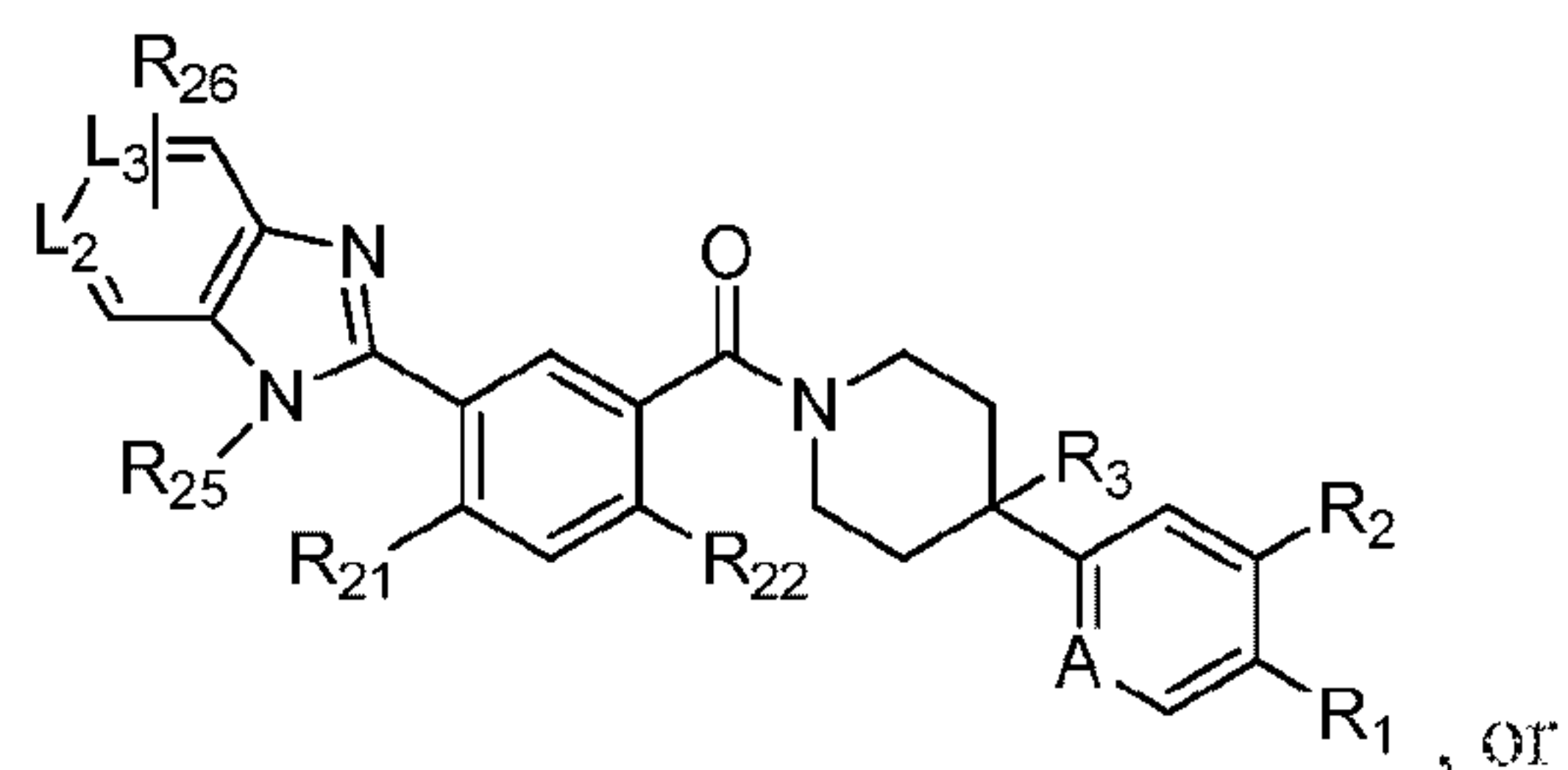
or a pharmaceutically acceptable salt thereof.

Compounds of Structure (IV)

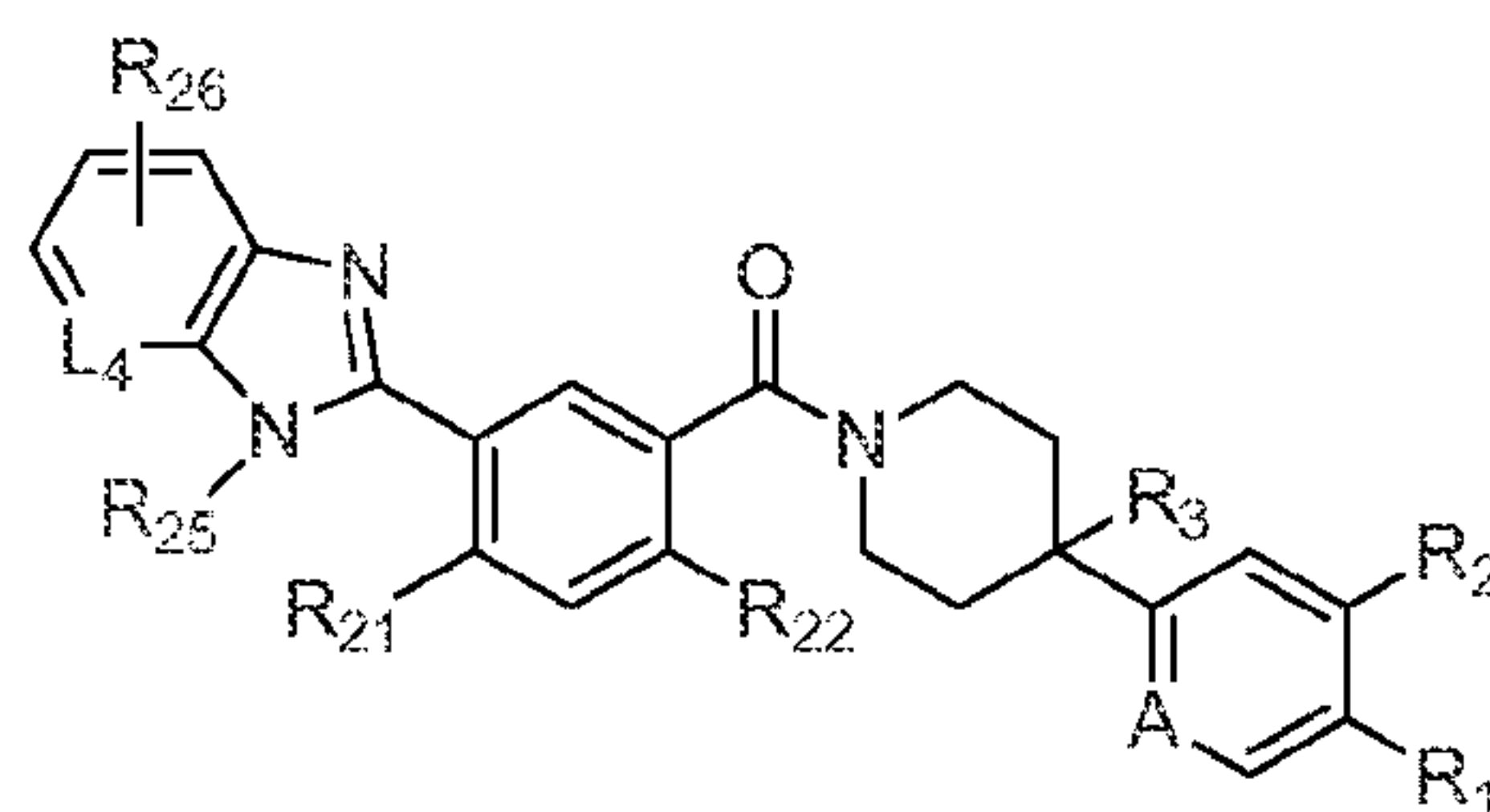
[0167] In certain aspects, the compounds of Structure (IV) have one of the following Structures (IV-A), (IV-B), or (IV-C):



(IV-A)



(IV-B)



(IV-C)

or a pharmaceutically acceptable salt thereof, wherein:

L_1, L_2, L_3, L_4 , and A are each independently CH or N;

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$,

$-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

q is 0, 1, 2, 3, or 4;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_2 is hydrogen, halo, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{21} and R_{22} are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy,

CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

R_{23} is hydrogen, $-N(R_{13})(R_{14})$, C_{1-6} alkyl, C_{1-6} alkoxy, is absent if L_1 is N, or R_{23} and

R_{24} taken together with the atoms to which they are attached join together to form a heterocyclyl, heteroaryl, or cycloalkyl;

R_{24} is hydrogen, $-N(R_{13})(R_{14})$, C_{1-6} alkyl, C_{1-6} alkoxy, $-(C_{1-6} \text{ alkoxy})(\text{heterocyclyl})$,

heterocyclyl, or R_{23} and R_{24} taken together with the atoms to which they are attached join together to form a heterocyclyl, heteroaryl, or cycloalkyl;

R_{26} is hydrogen, heteroaryl, heterocyclyl, $-N(R_{13})(R_{14})$, or $-S(=O)_2R_{20}$;

R_{13} and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl,

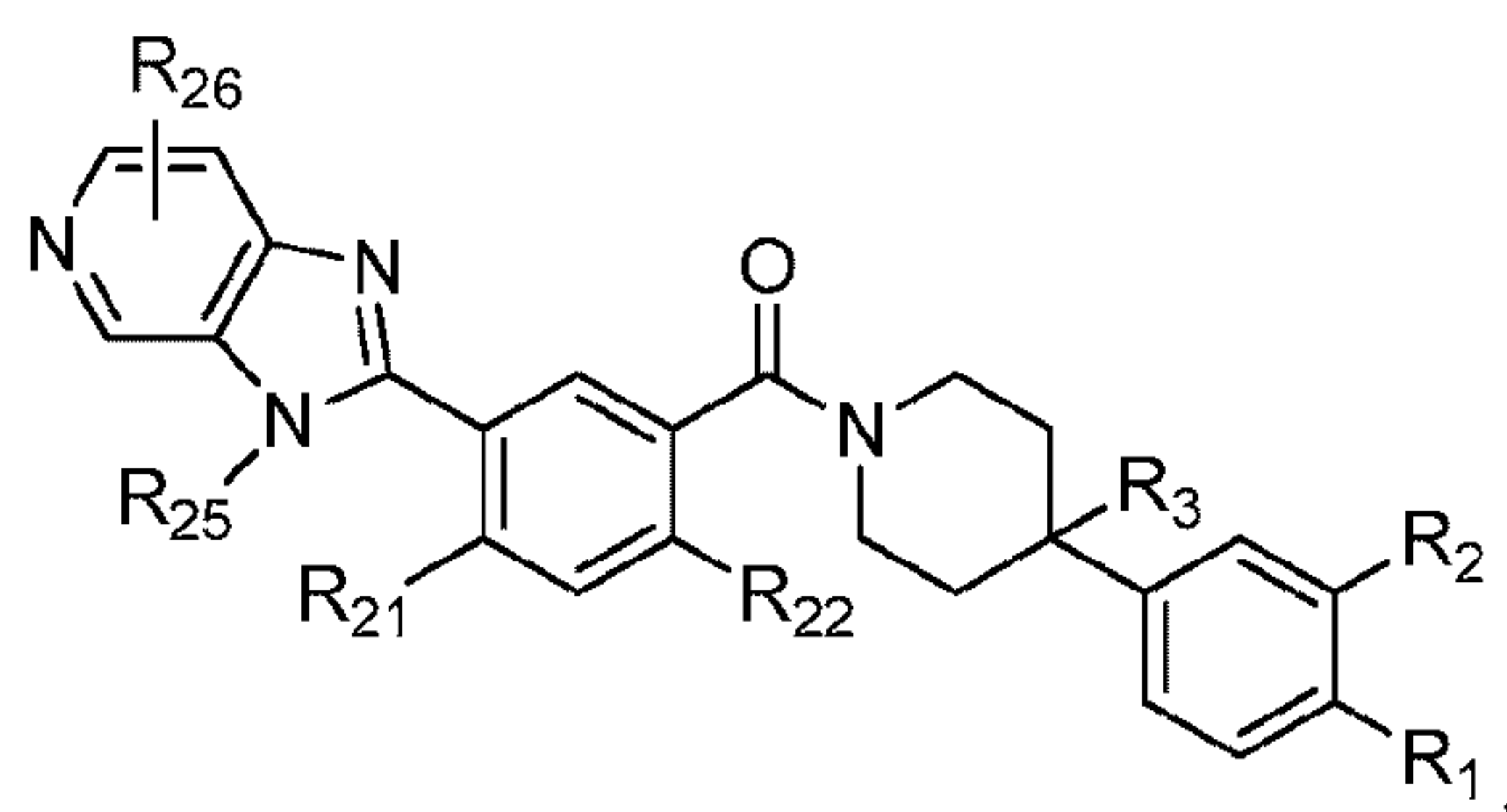
heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;

R_{25} is hydrogen, C_{1-6} alkyl, or C_{1-6} alkoxy; and

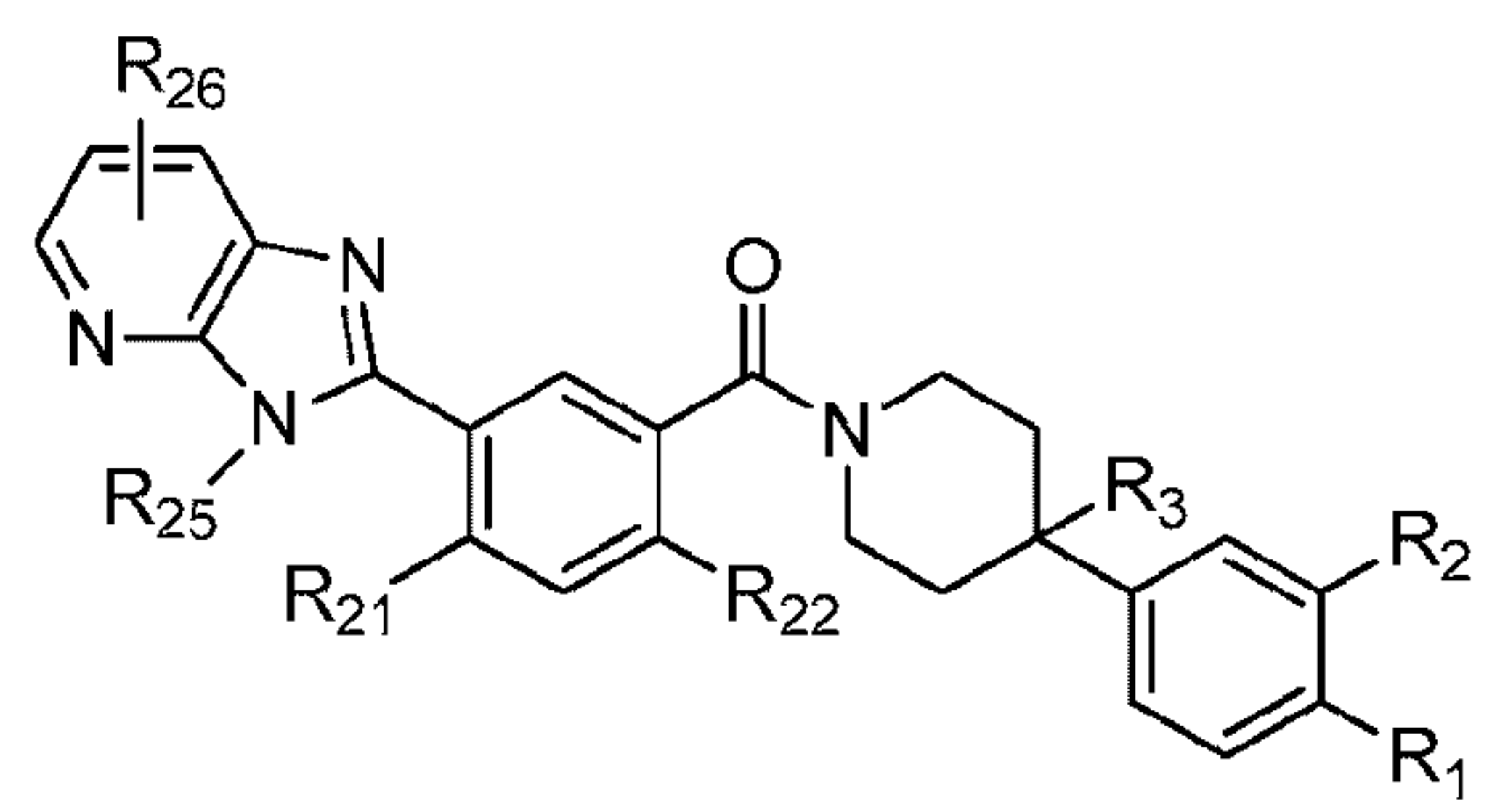
R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, cycloalkyl, aryl,

heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino.

[0168] In certain aspects, the compounds of Structure (IV) have one of the following Structures (IV-D) and (IV-E):



(IV-D)



(IV-E)

or a pharmaceutically acceptable salt thereof.

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$,

$-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

q is 0, 1, 2, 3, or 4;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_2 is hydrogen, halo, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{21} and R_{22} are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy,

CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

R_{26} is hydrogen, heteroaryl, heterocyclyl, $-N(R_{13})(R_{14})$, or $-S(=O)_2R_{20}$;

R_{13} and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl,

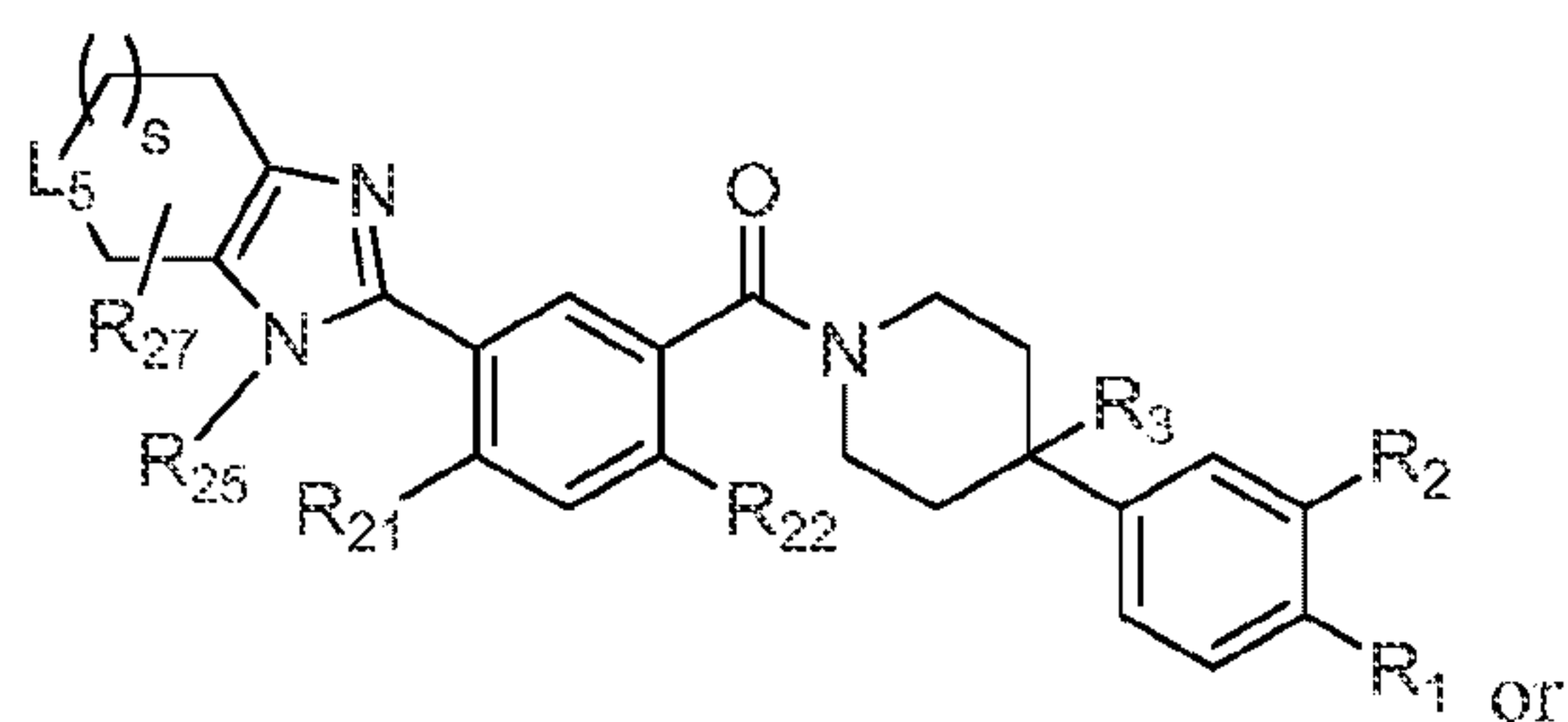
heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;

R_{25} is hydrogen, C_{1-6} alkyl, or C_{1-6} alkoxy; and

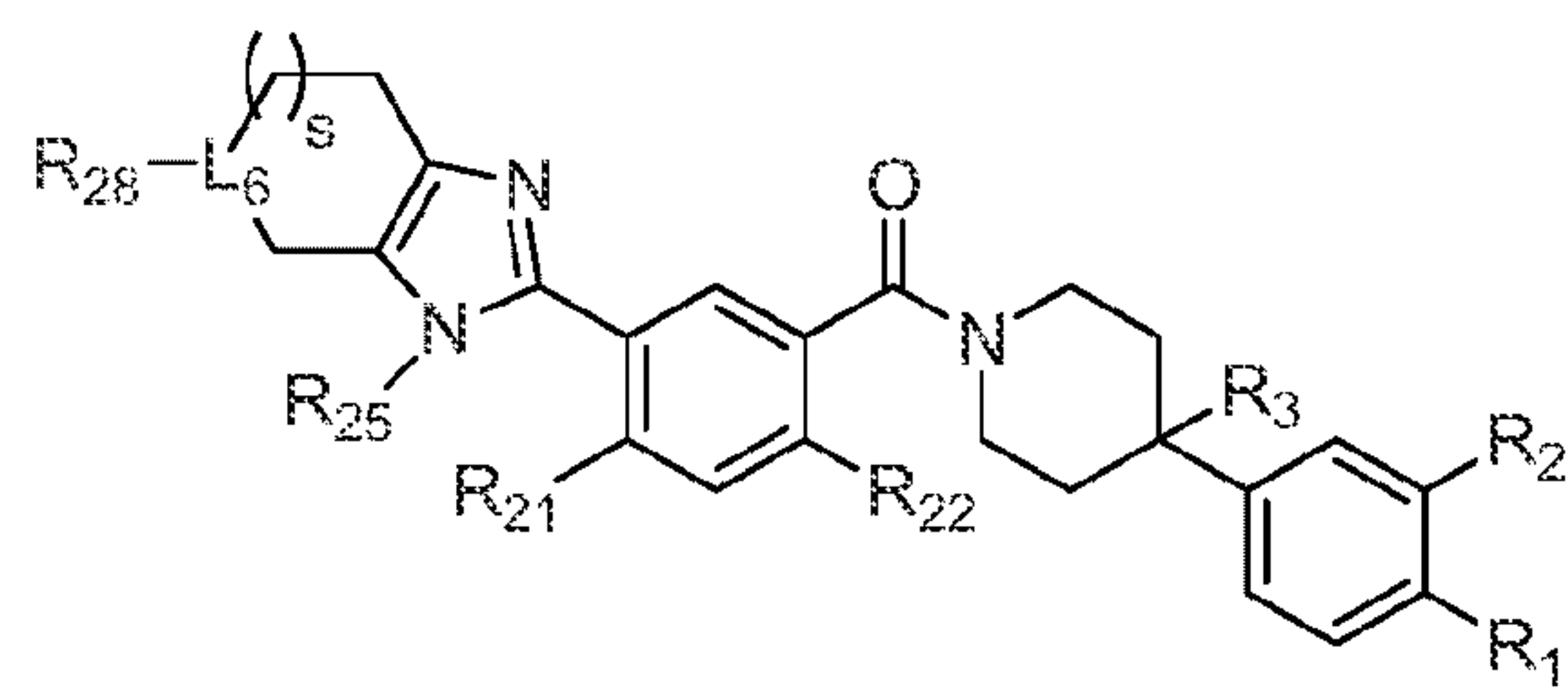
R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, cycloalkyl, aryl,

heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino.

[0169] In certain aspects, the compounds of Structure (IV) have one of the following Structures (IV-F) and (IV-G):



(IV-F)



(IV-G)

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$,

$-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

q is 0, 1, 2, 3, or 4;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_2 is hydrogen, halo, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{21} and R_{22} are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy,

CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

R_{13} and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl,

heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;

R_{25} is hydrogen, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino;

s is 0, 1, or 2;

L_5 is CH_2 , NH , S , or O ;

L_6 is CH or N ;

R_{27} is hydrogen, $-C(=O)R''$, $-S(=O)_2R_{20}$;

R_{28} is hydrogen, $-C(=O)R''$, $-S(=O)_2R_{20}$, or is absent if L_6 is O ; and

R'' is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$, or $-N(R_{13})(R_{14})$.

[0170] In certain aspects of Structure (IV), R_1 is hydrogen, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, or $-C(=O)N(R_{13})(R_{14})$.

[0171] In certain aspects of Structure (IV), R_1 is cyano.

[0172] In certain aspects of Structure (IV), R_2 is hydrogen or halo; R_2 is hydrogen.

[0173] In certain aspects of Structure (IV), R_3 is hydrogen.

[0174] In certain aspects of Structure (IV), R_{21} and R_{22} are each independently hydrogen or C_{1-6} alkyl.

[0175] In certain aspects of Structure (IV), R_{21} and R_{22} are each independently C_{1-6} alkyl.

[0176] In certain aspects of Structure (IV), R_{25} is hydrogen.

[0177] In certain aspects of Structure (IV), L_2 is N .

[0178] In certain aspects of Structure (IV), L_1 is CH .

[0179] In certain aspects of Structure (IV), L_3 is CH .

[0180] In certain aspects of Structure (IV), L_4 is CH .

[0181] In certain aspects of Structure (IV), A is N .

[0182] In certain aspects of Structure (IV), A is CH .

[0183] In certain aspects of Structure (IV), R_{26} is heterocyclyl.

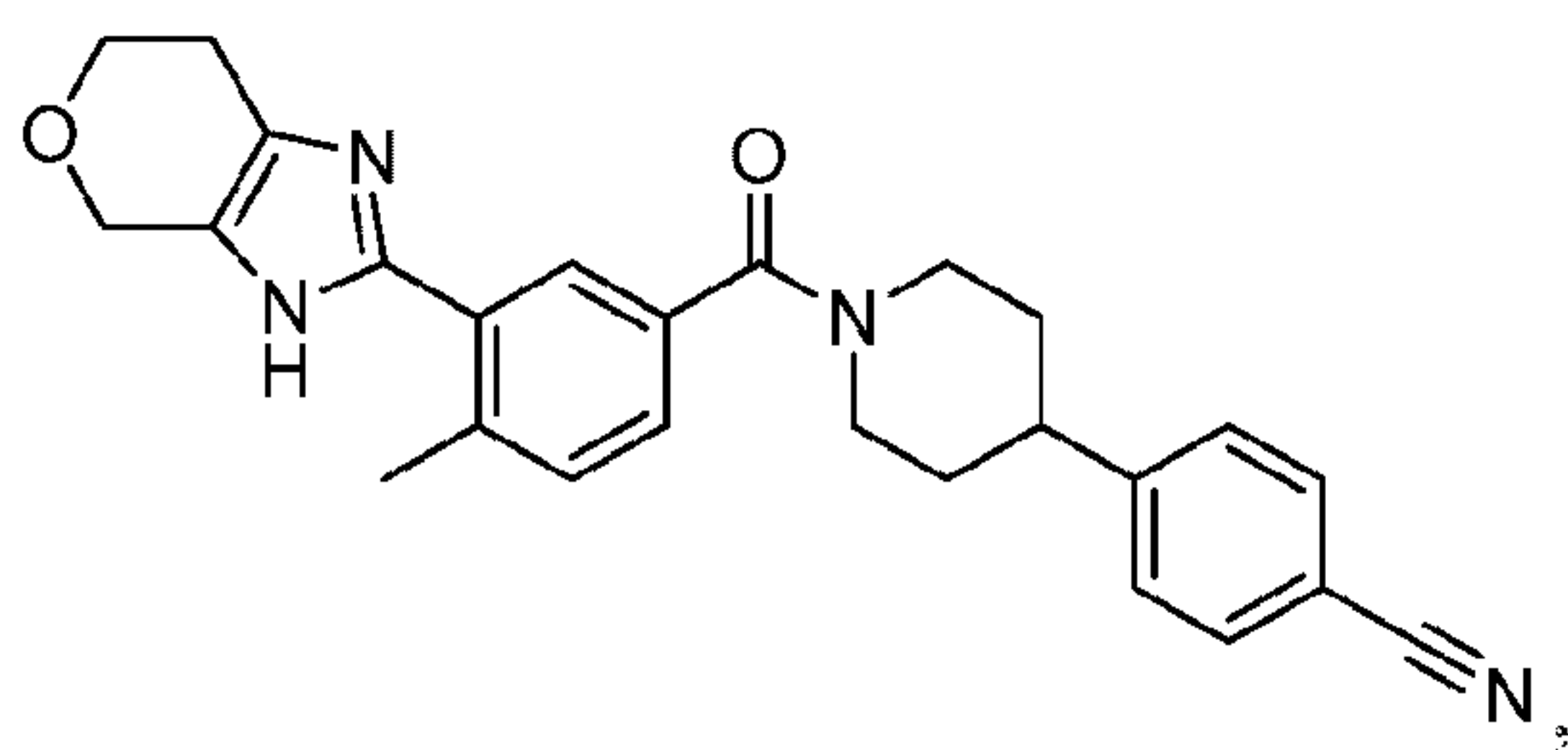
[0184] In certain aspects of Structure (IV), R_{24} is $-N(R_{13})(R_{14})$.

[0185] In certain aspects of Structure (IV), L_5 and L_6 are each independently N . In certain aspects of Structure (IV), s is 1.

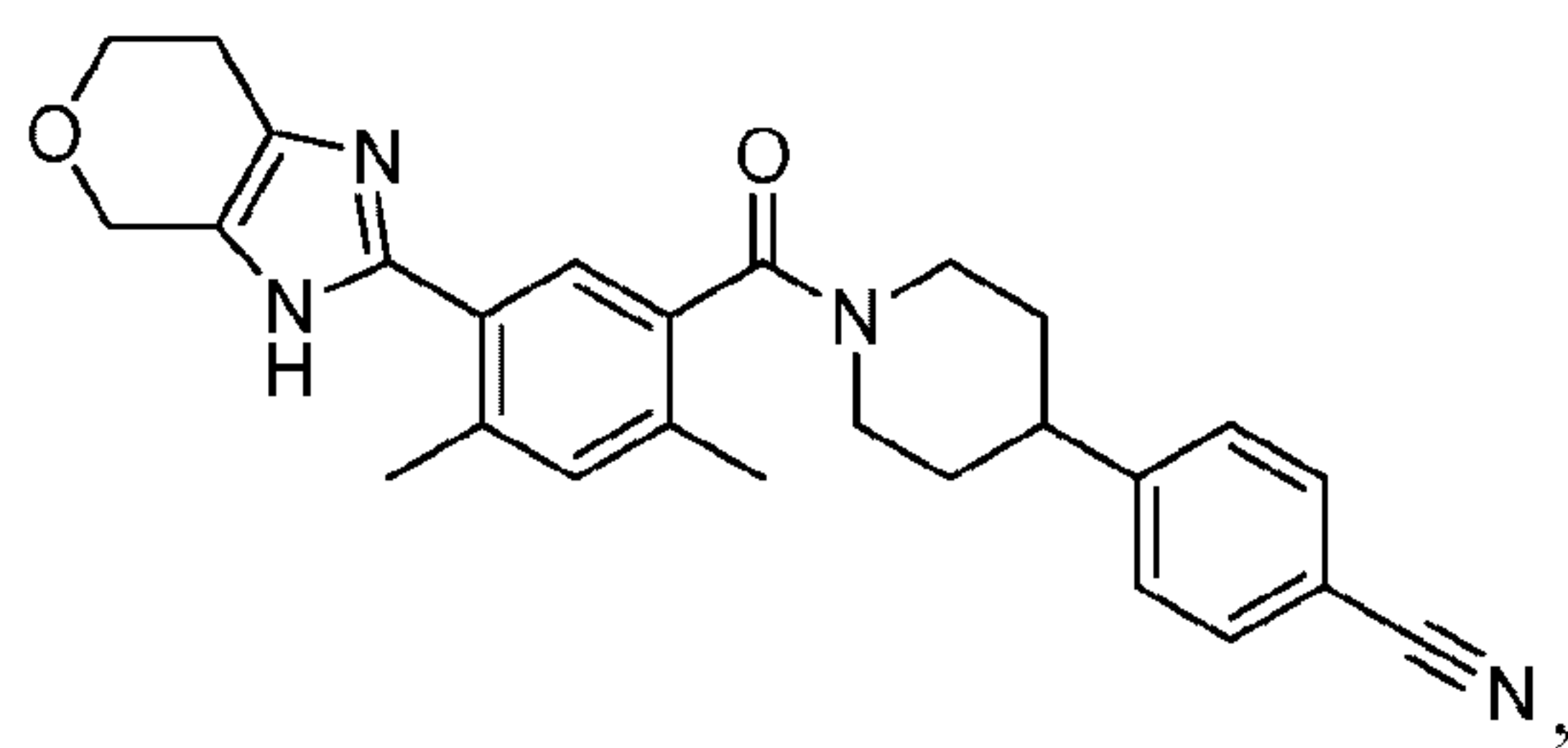
[0186] In certain aspects of Structure (IV), s is 0.

[0187] In certain aspects, the compounds of Structure (IV) have one of the following Structures (IV-H), (IV-I), (IV-J), (IV-K), (IV-L), (IV-M), (IV-N), or (IV-O):

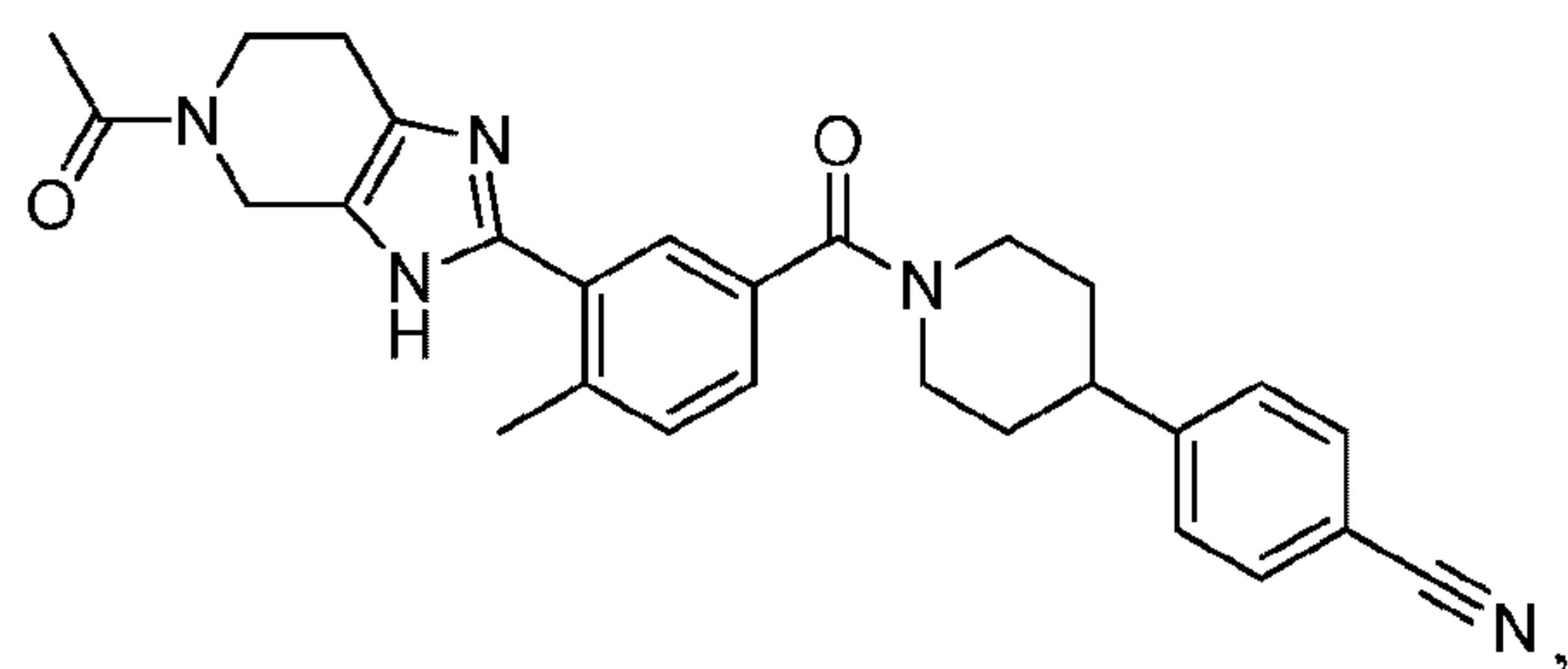
49



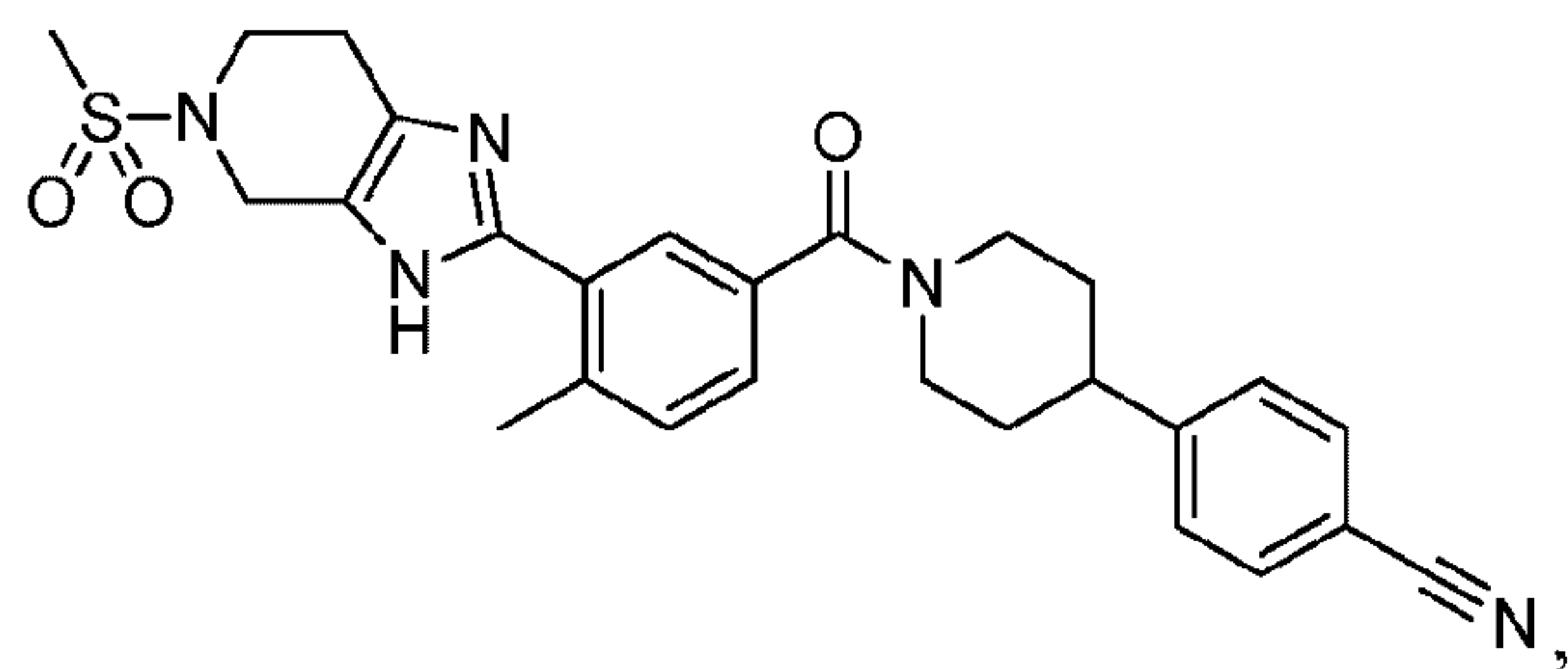
(IV-H)



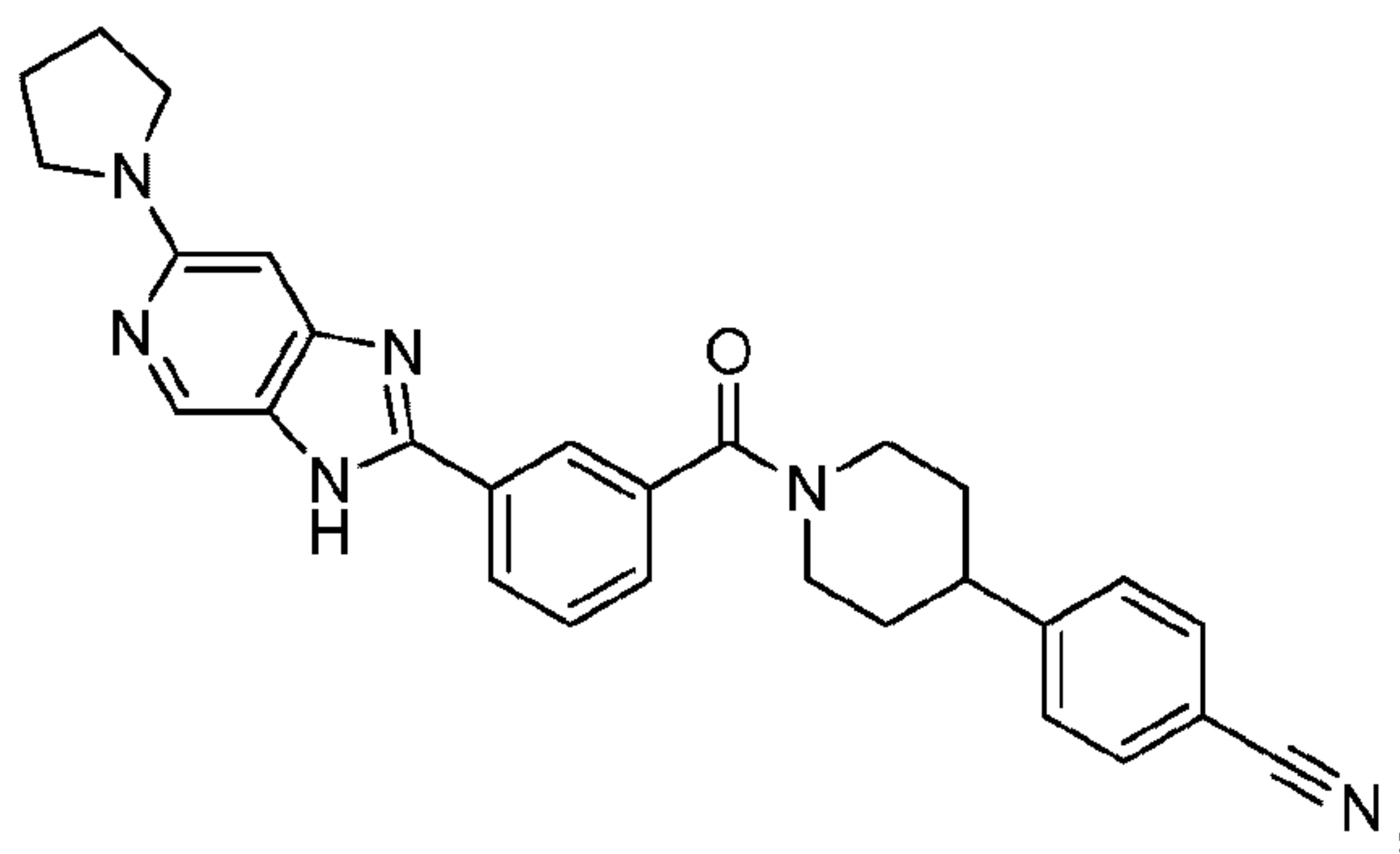
(IV-I)



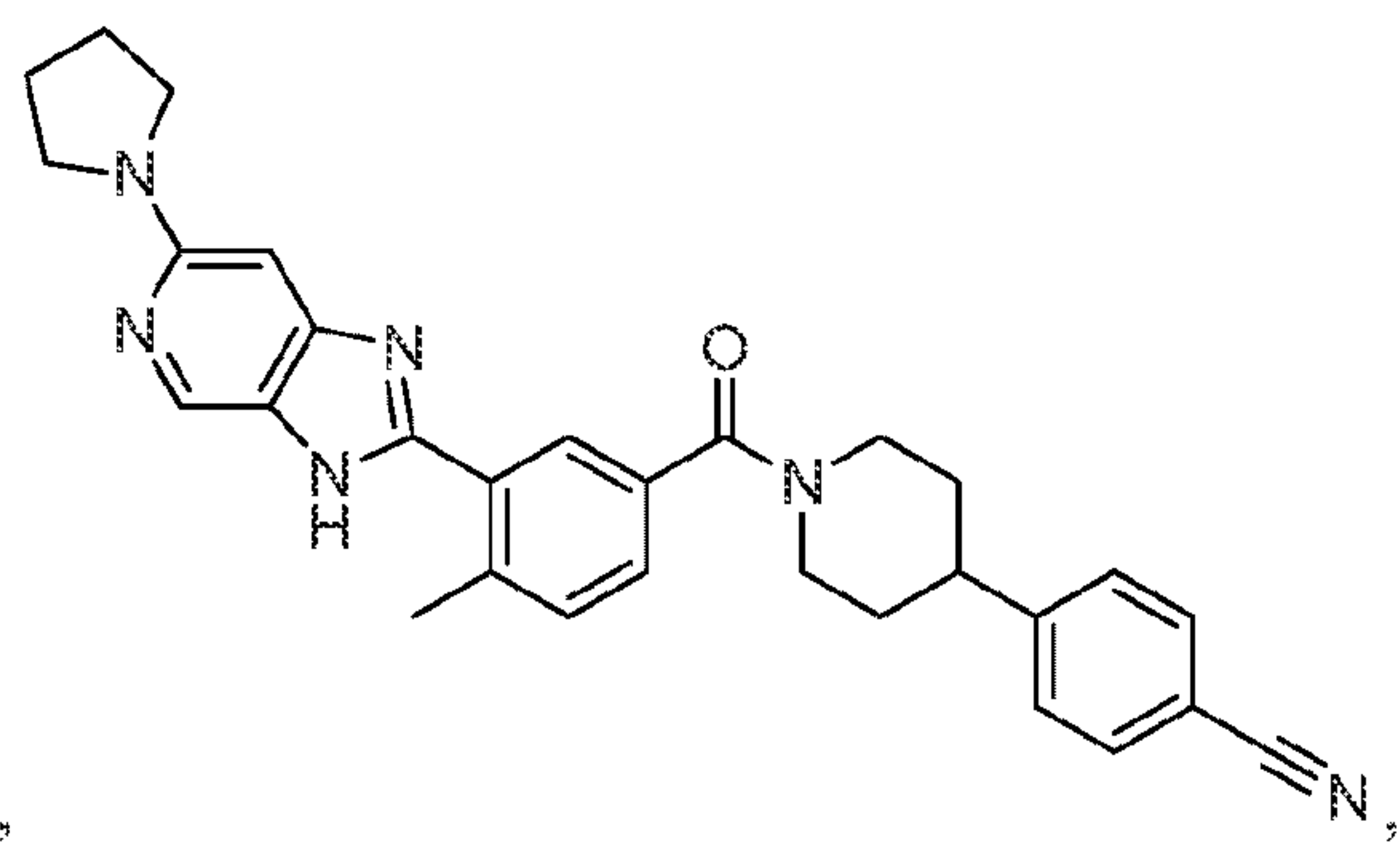
(IV-J)



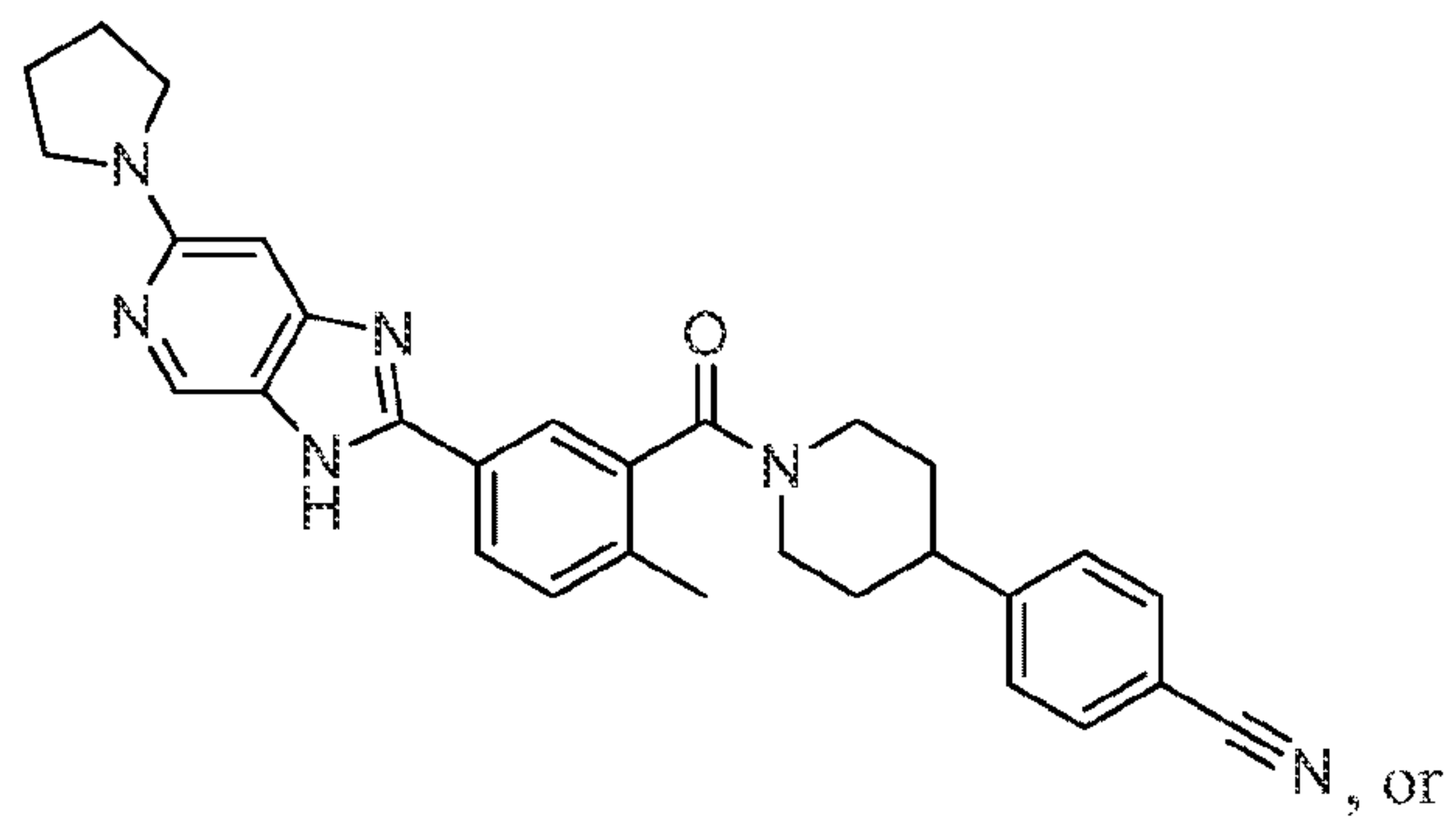
(IV-K)



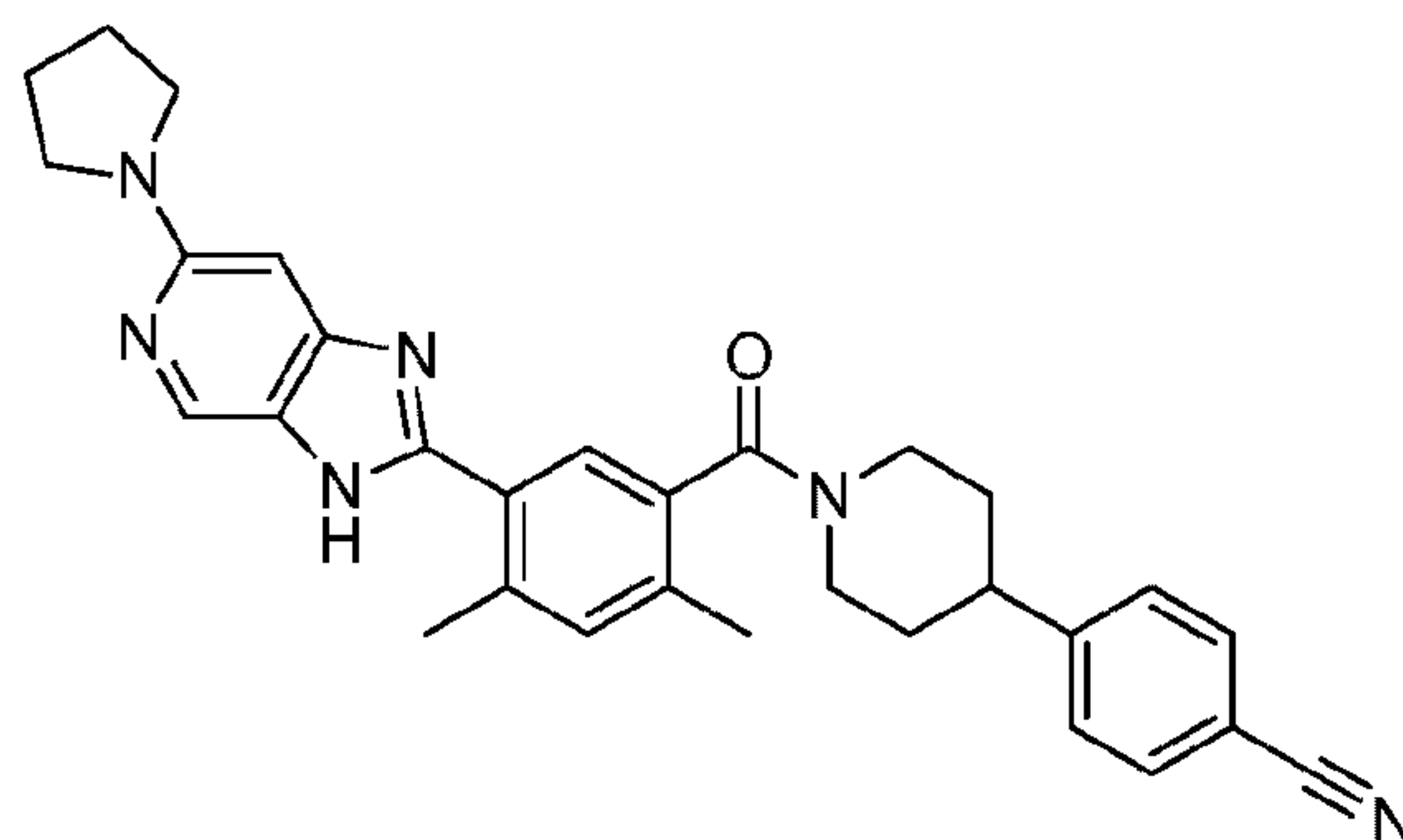
(IV-L)



(IV-M)



(IV-N)

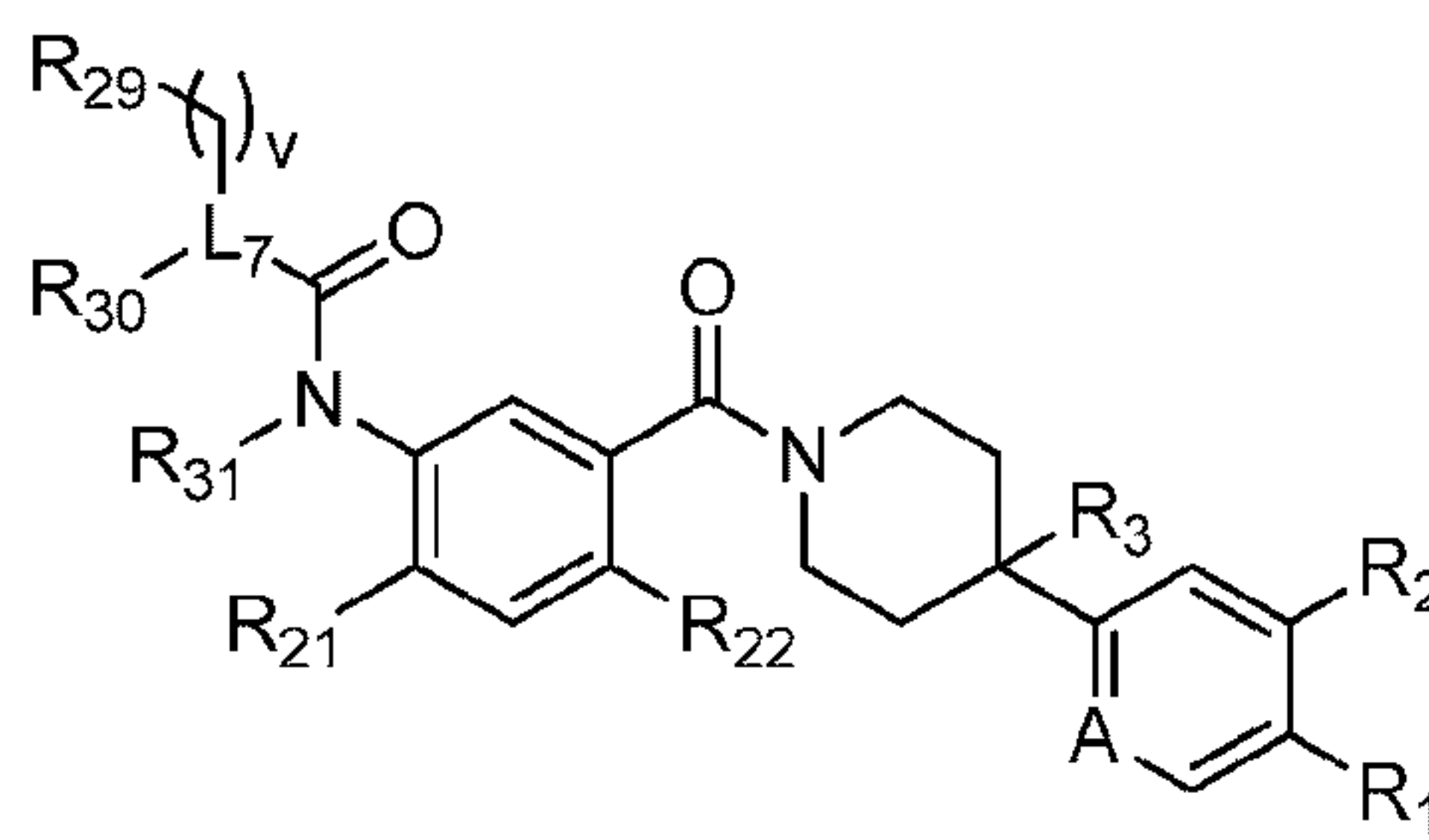


(IV-O)

or a pharmaceutically acceptable salt thereof.

Compounds of Structure (V)

[0188] In various aspects, the present disclosure provides for compounds of Structure (V):



(V)

or a pharmaceutically acceptable salt thereof, wherein:

L_7 is N or O, wherein R_{30} is absent if L_7 is O;

A is CH or N;

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$,

$-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

q is 0, 1, 2, 3, or 4;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_2 is hydrogen, halo, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_3 is halo, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{21} and R_{22} are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy,

CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

R_{29} and R_{30} are each independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxyalkyl,

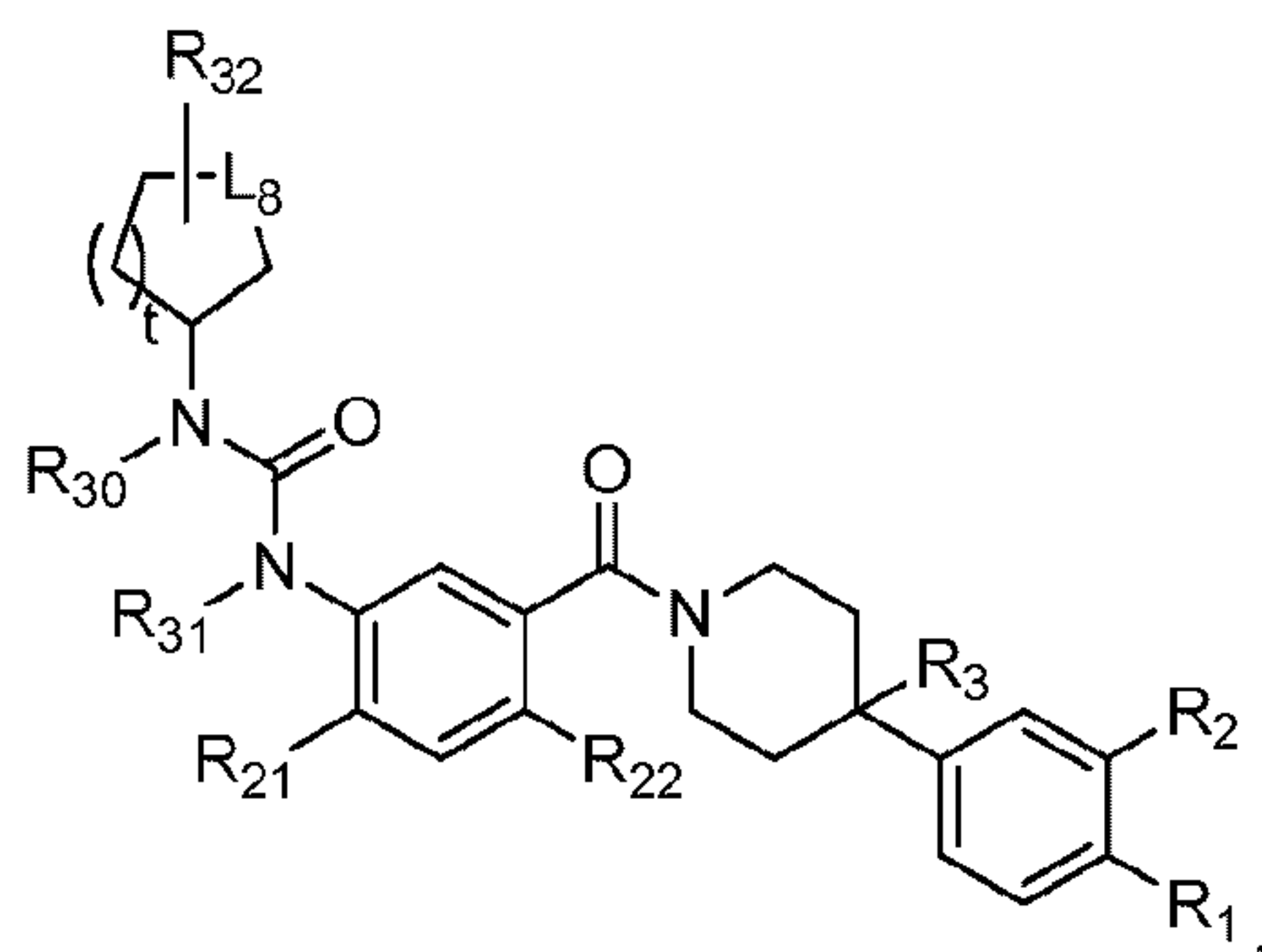
heteroaryl, heterocyclyl, $-N(R_{15}R_{16})$, $-C(=O)R_{46}$, $-R_{48}C(=O)R_{47}$, or R_{29} and R_{30}

taken together with the atoms to which they are attached join together to form a

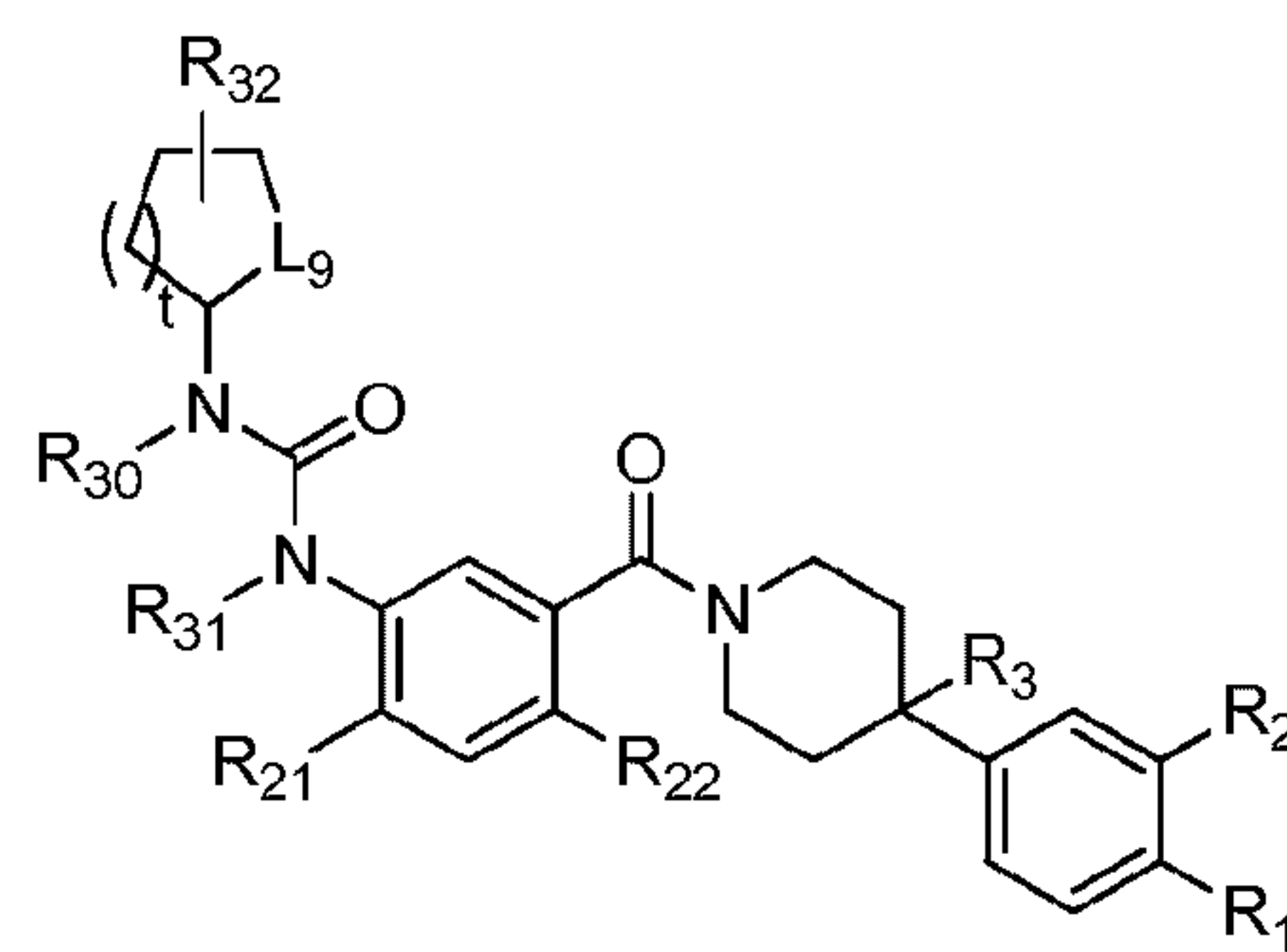
heteroaryl or heterocyclyl, wherein R_{30} is absent if L_7 is O;

R_{46} and R_{47} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;
 R_{48} is alkyl or is absent;
 R_{31} is hydrogen, C_{1-6} alkyl, or C_{1-6} alkoxy;
 R_{13} and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;
 R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino; and
 v is 0 or 1.

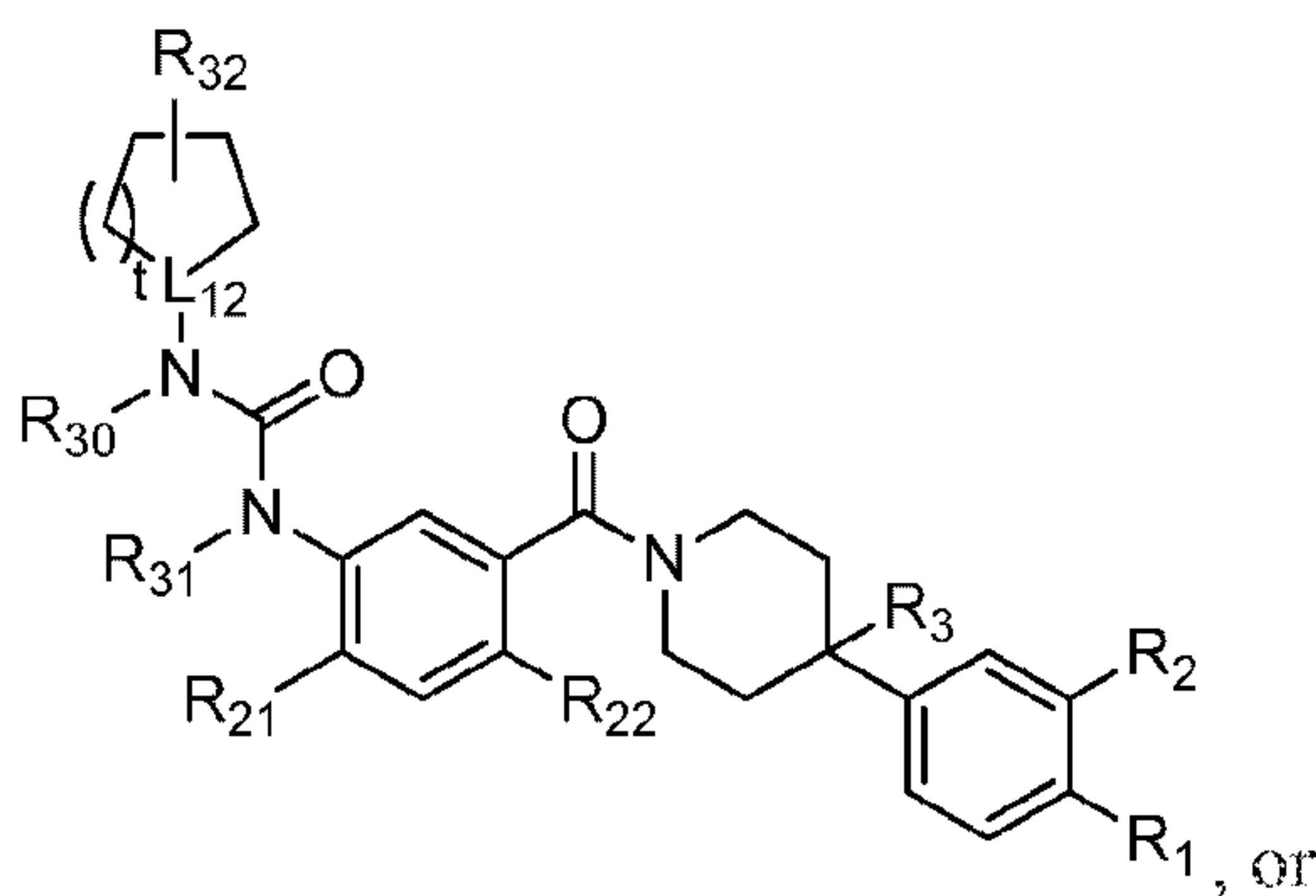
[0189] In certain aspects, the compounds of Structure (V) have one of the following Structures (V-A), (V-B), (V-C), or (V-D):



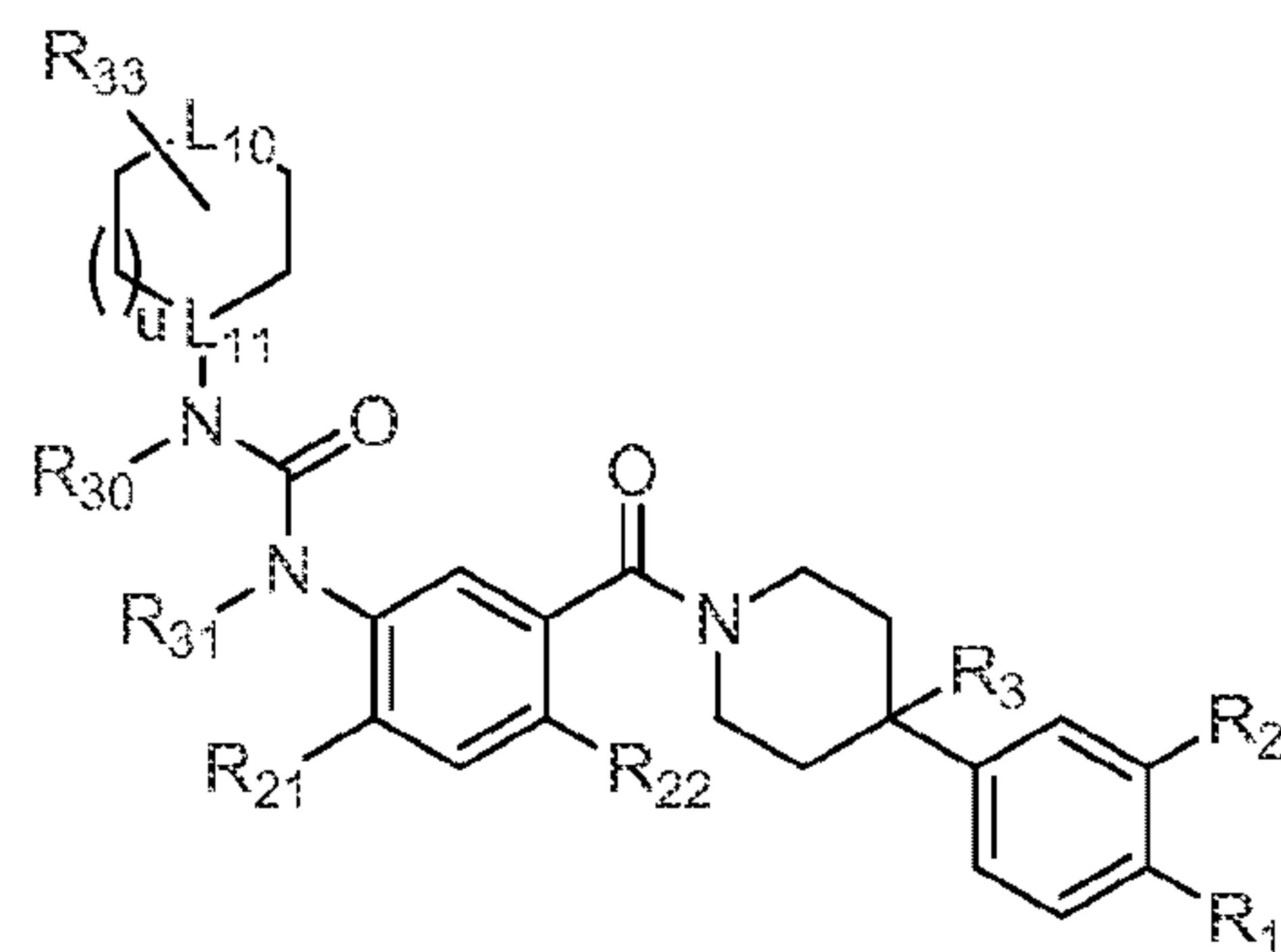
(V-A)



(V-B)



(V-C)



(V-D)

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$, $-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;
 q is 0, 1, 2, 3, or 4;
 R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;
 R_2 is hydrogen, halo, C_{1-6} alkoxy, or C_{1-6} alkyl;
 R_3 is halo, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{21} and R_{22} are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

R_{30} is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxyalkyl, heteroaryl, heterocyclyl, $-N(R_{15}R_{16})$, $-C(=O)R_{46}$, or $-R_{48}C(=O)R_{47}$, wherein R_{30} is absent if L_7 is O;

R_{46} and R_{47} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;

R_{48} is alkyl or is absent;

R_{31} is hydrogen, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{13} and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;

R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino;

L_8 , L_9 , and L_{10} are each independently CH_2 , NH , or O;

L_{11} and L_{12} are each independently CH or N;

R_{32} and R_{33} are each independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-S(=O)_2R_{20}$, $-C(=O)R_{46}$, hydroxyalkyl, hydroxyl, or are absent;

u is 0, 1, or 2; and

t is 0, 1, or 2.

[0190] In certain aspects of Structure (V), L_7 is N.

[0191] In certain aspects of Structure (V), L_7 is O.

[0192] In certain aspects of Structure (V), A is N.

[0193] In certain aspects of Structure (V), A is CH.

[0194] In certain aspects of Structure (V), R_1 is hydrogen, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, or $-C(=O)N(R_{13})(R_{14})$.

[0195] In certain aspects of Structure (V), R_1 is cyano.

[0196] In certain aspects of Structure (V), R_2 is hydrogen or halo.

[0197] In certain aspects of Structure (V), R_2 is hydrogen.

[0198] In certain aspects of Structure (V), R_3 is fluorine.

[0199] In certain aspects of Structure (V), R_{21} and R_{22} are each independently hydrogen or C_{1-6} alkyl.

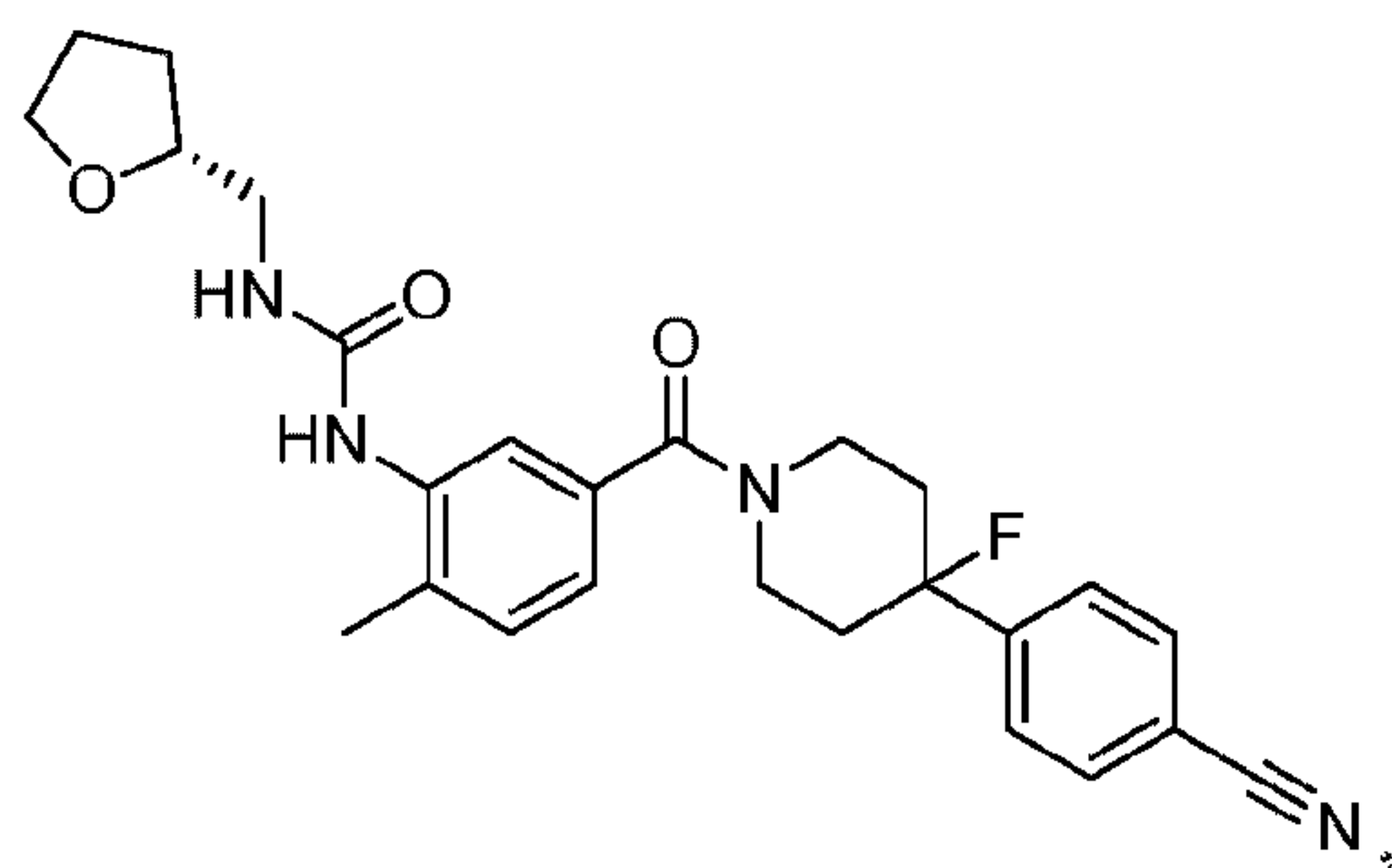
[0200] In certain aspects of Structure (V), R_{21} and R_{22} are each independently C_{1-6} alkyl.

[0201] In certain aspects of Structure (V), R_{31} is hydrogen.

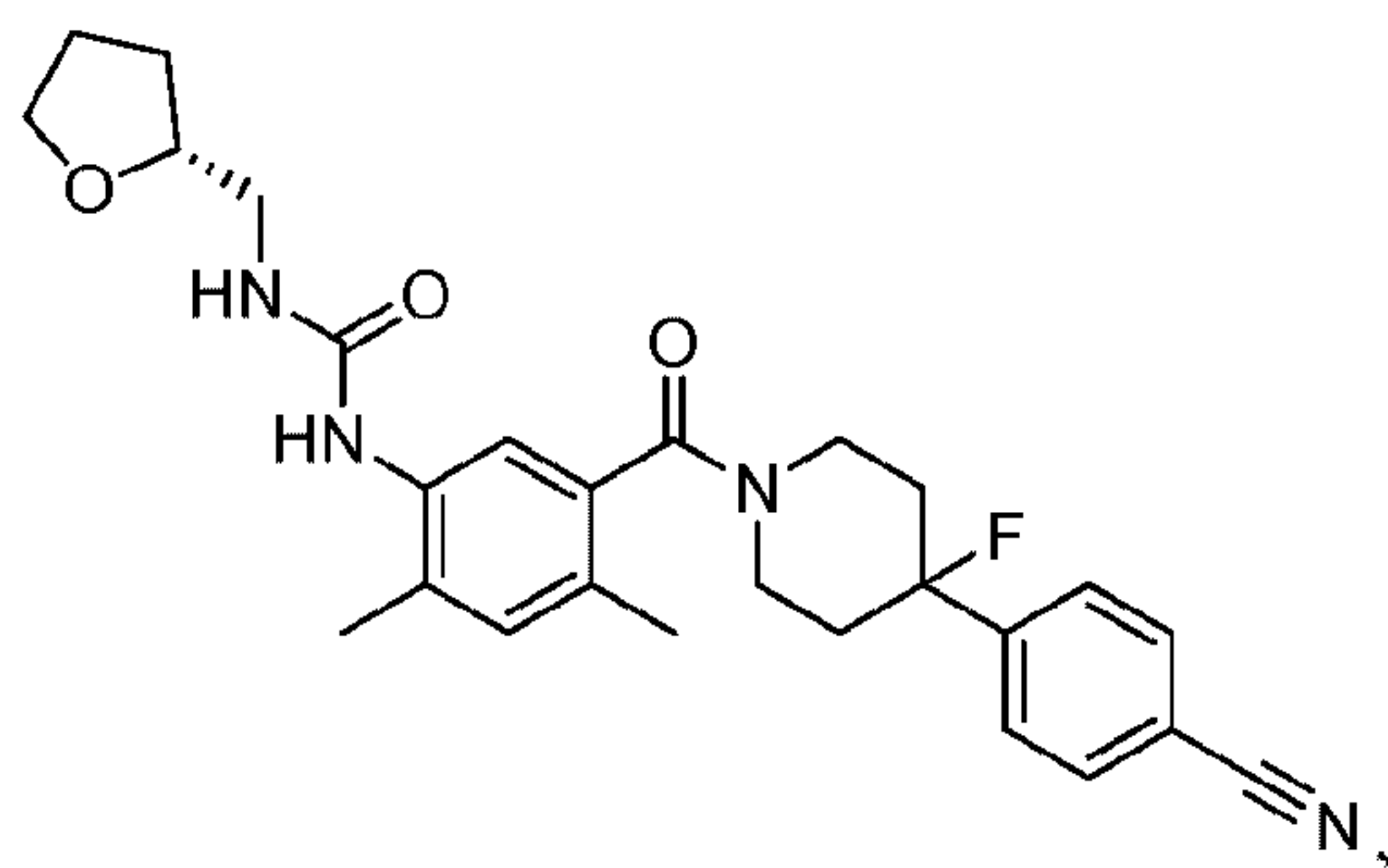
[0202] In certain aspects of Structure (V), R_{30} is hydrogen.

[0203] In certain aspects of Structure (V), L_8 is O.

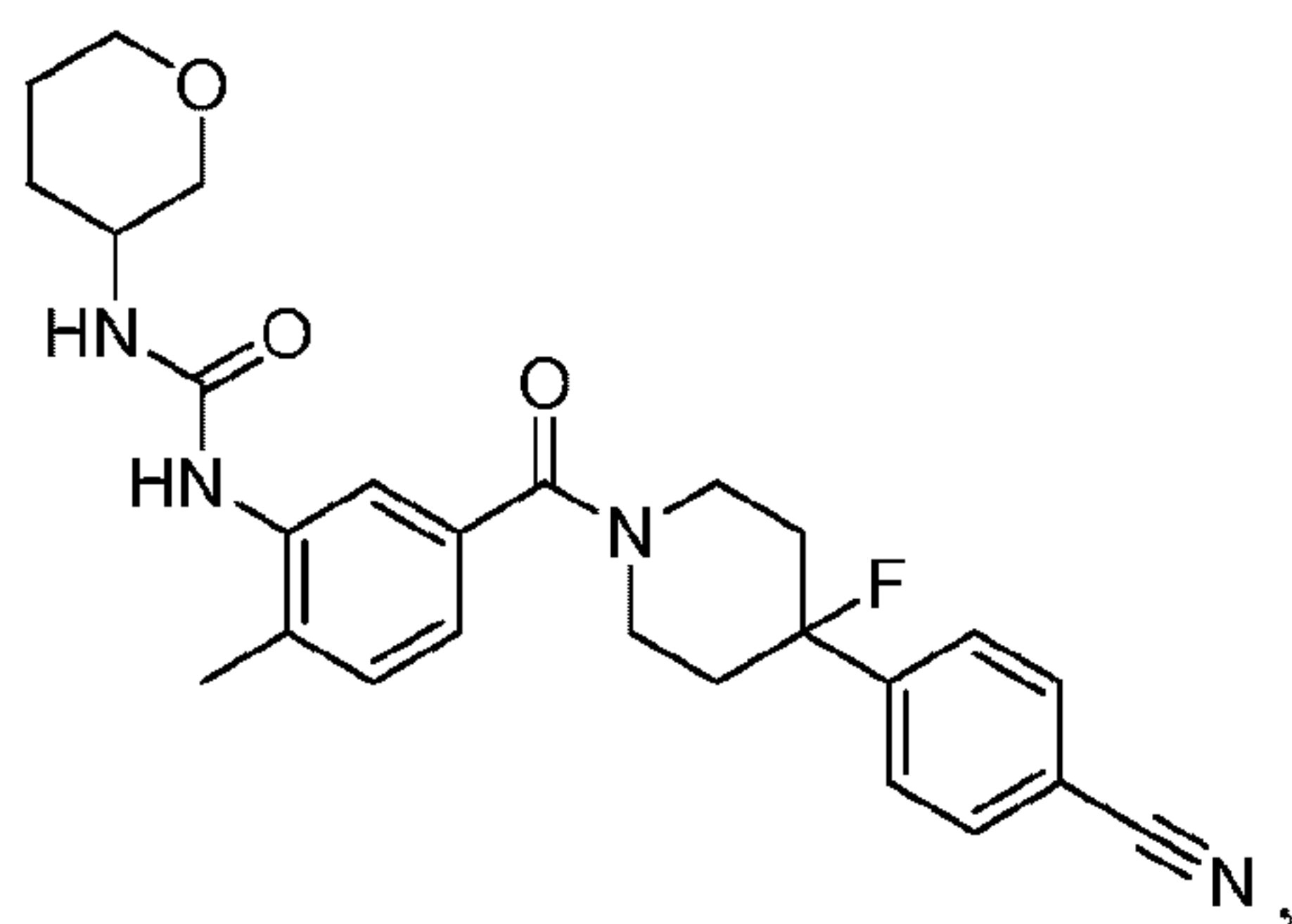
- [0204] In certain aspects of Structure (V), L_9 is O.
- [0205] In certain aspects of Structure (V), L_{10} is O and L_{11} is N.
- [0206] In certain aspects of Structure (V), L_{12} is N.
- [0207] In certain aspects of Structure (V), R_{32} and R_{33} are each independently hydrogen.
- [0208] In certain aspects, the compounds of Structure (V) have one of the following Structures (V-I), (V-J), (V-K), (V-L), (V-M), (V-N), or (V-O):



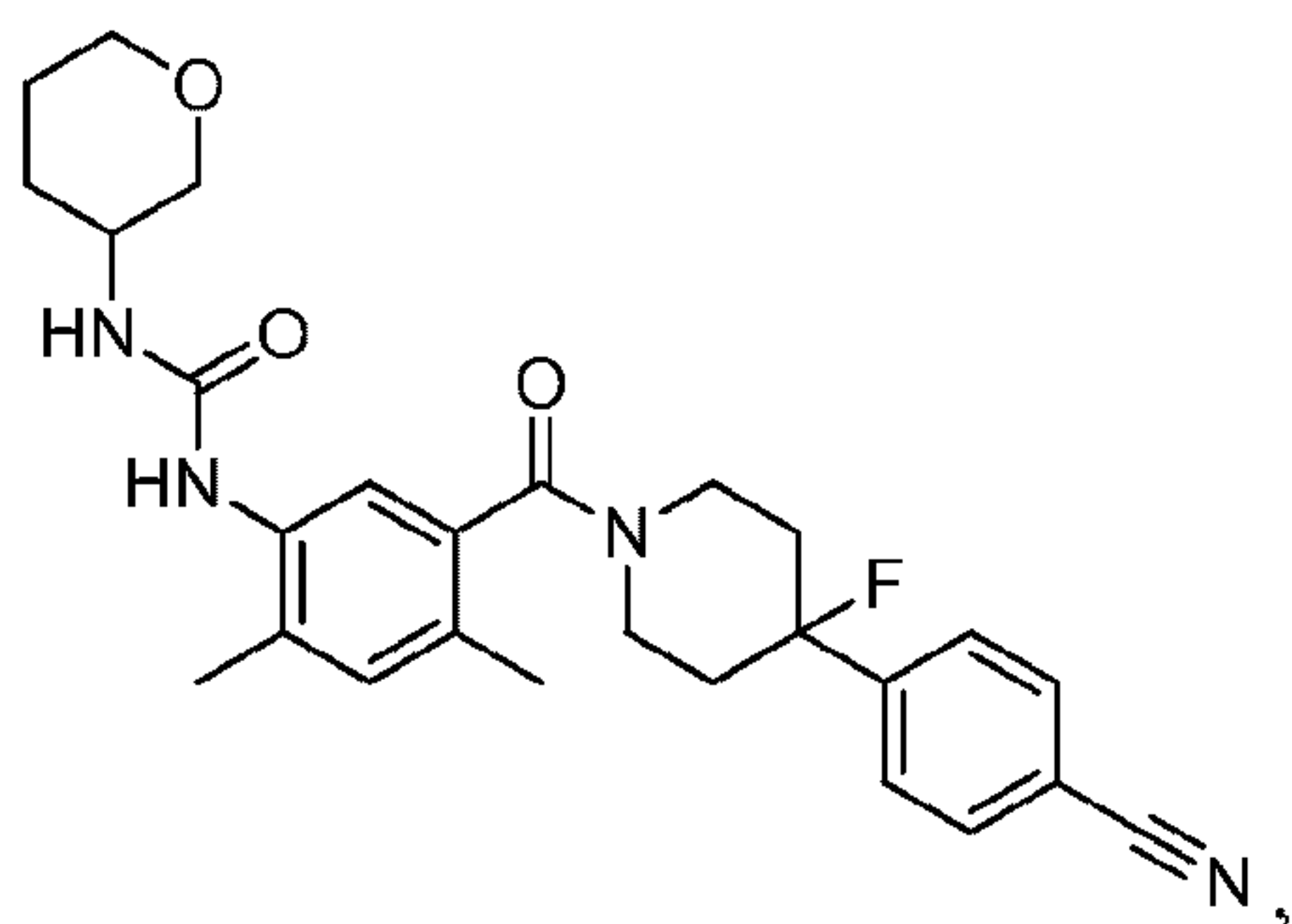
(V-I)



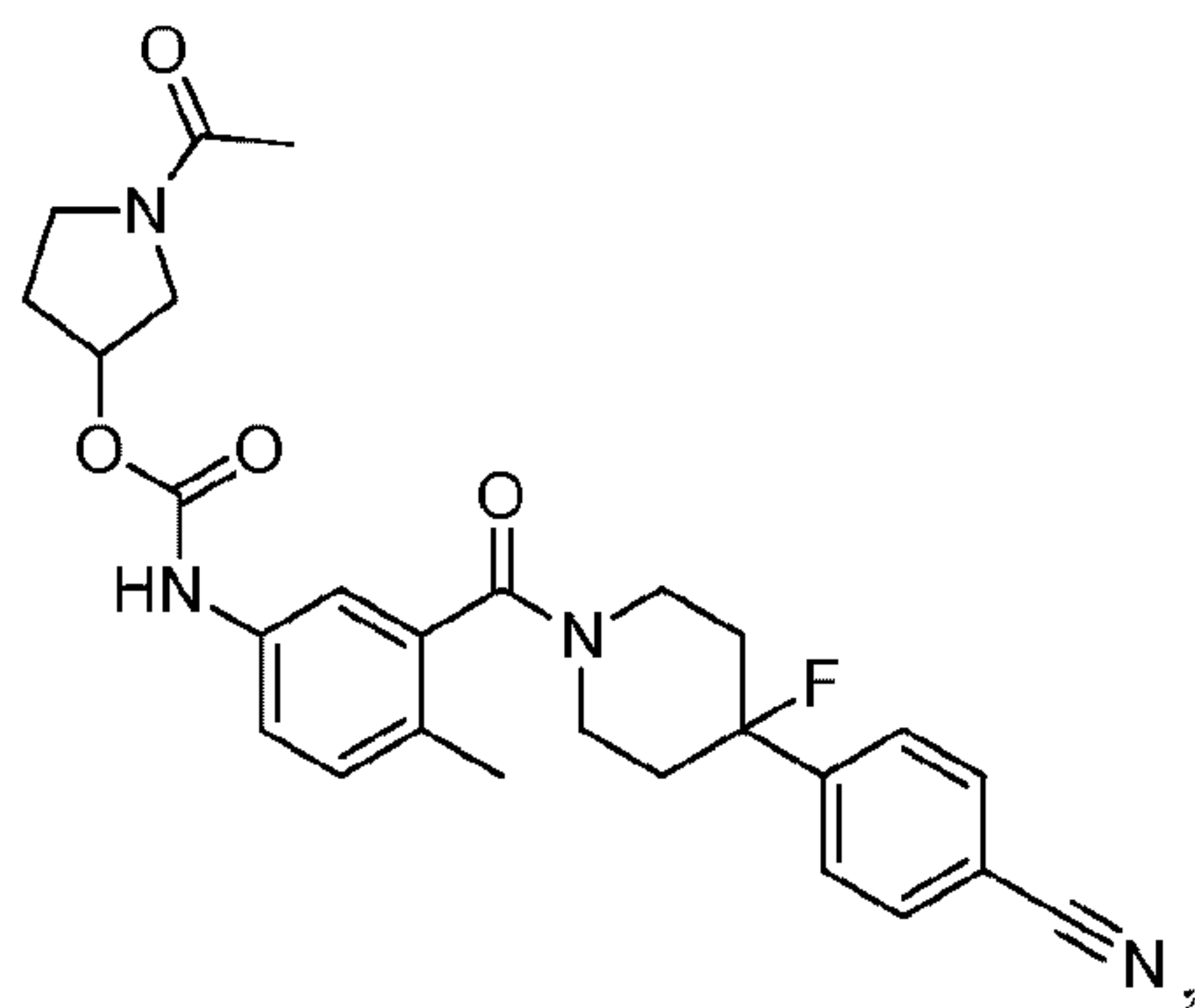
(V-J)



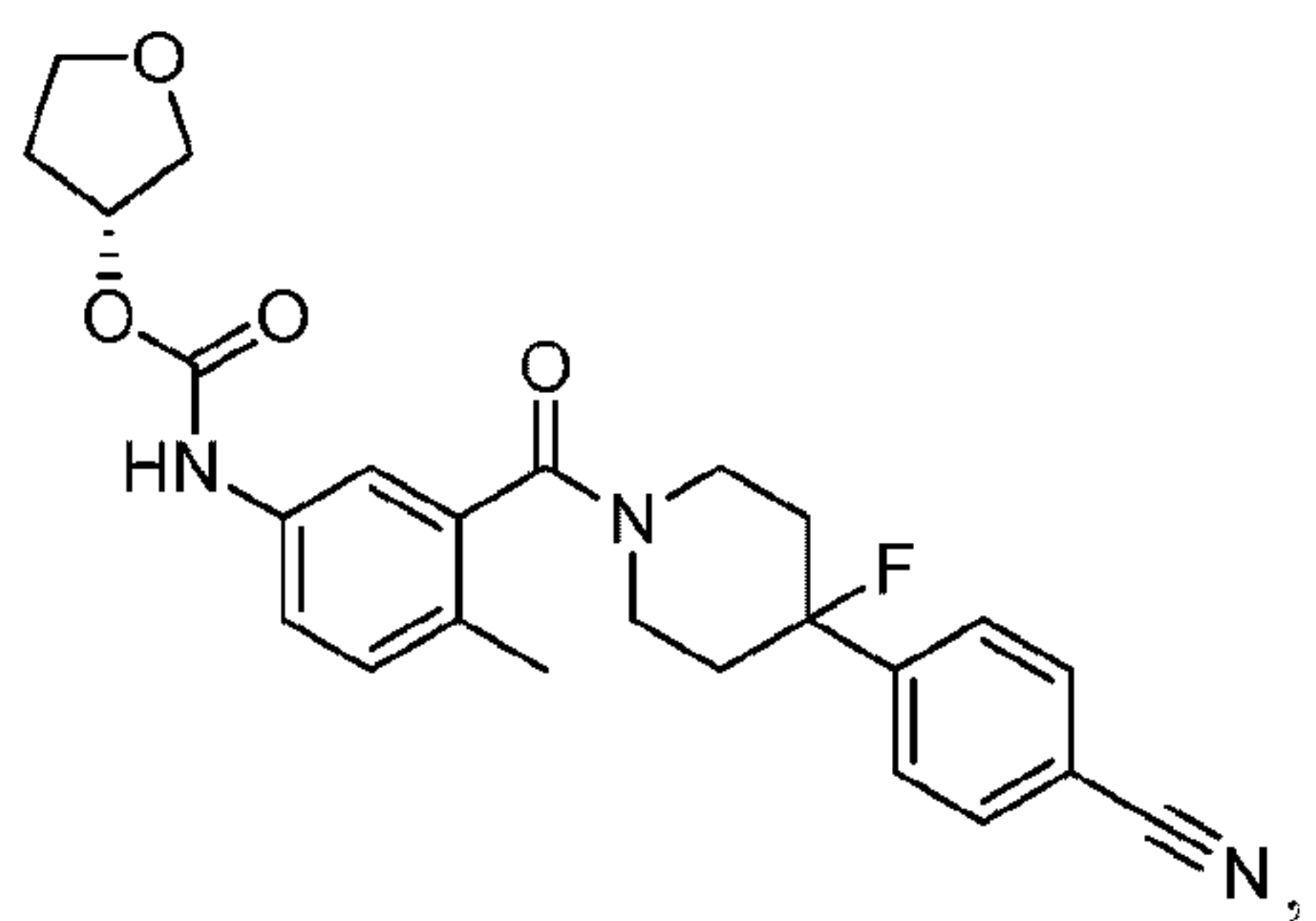
(V-K)



(V-L)

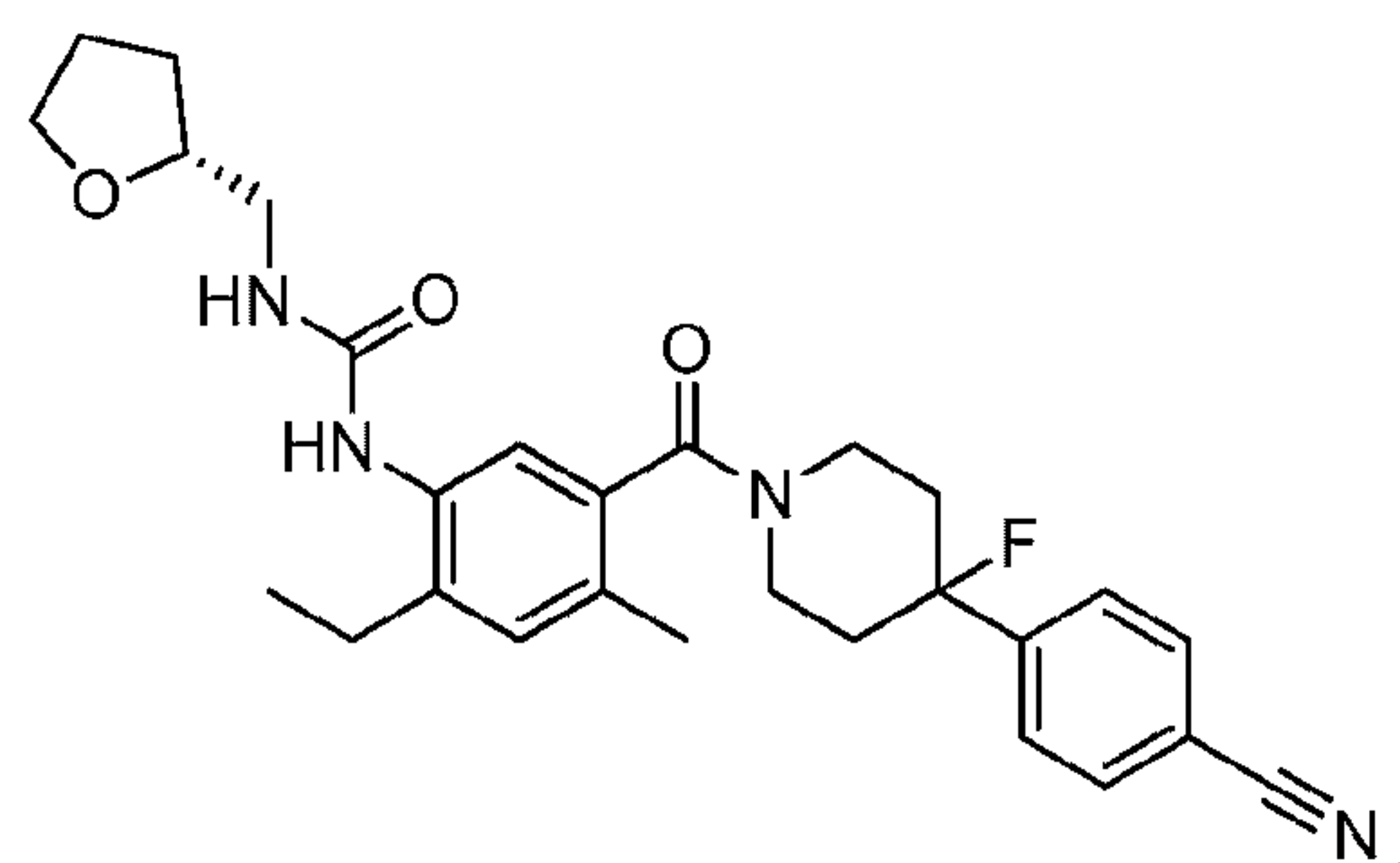


(V-M)



(V-N)

54

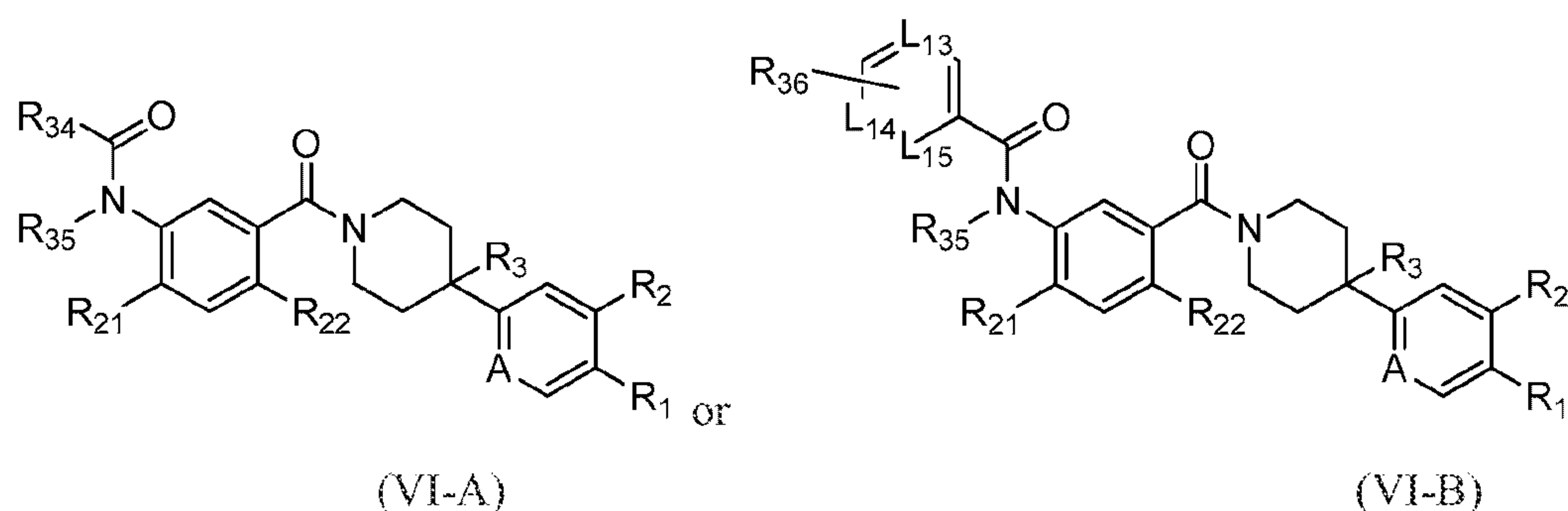


(V-O)

or a pharmaceutically acceptable salt thereof.

Compounds of Structure (VI)

[0209] In certain aspects, the compounds of Structure (VI) have one of the following Structures (VI-A) or (VI-B):



or a pharmaceutically acceptable salt thereof, wherein:

L_{13} , L_{14} , L_{15} , and A are each independently CH or N;

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$,

$-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

q is 0, 1, 2, 3, or 4;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_2 is hydrogen, halo, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_3 is halo, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{21} and R_{22} are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy,

CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

R_{34} is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, cycloalkyl, hydroxyl, hydroxyalkyl, aryl, heterocyclyl, heteroaryl, alkylamino, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, or $-N(R_{15}R_{16})$;

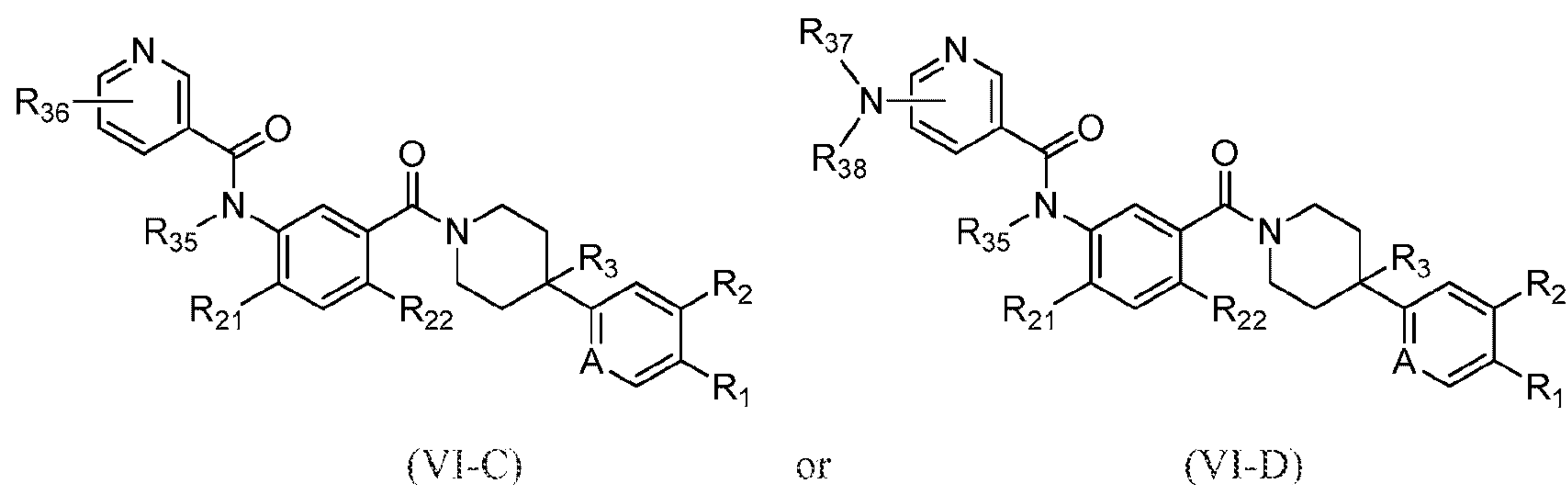
R_{35} is hydrogen, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{36} is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{15}R_{16})$, heterocyclyl, or heteroaryl;

R_{13} and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$; and

R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino.

[0210] In certain aspects, the compounds of Structure (VI) have one of the following Structures (VI-C) or (VI-D):



or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$,

$-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

q is 0, 1, 2, 3, or 4;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_2 is hydrogen, halo, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_3 is halo, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{21} and R_{22} are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy,

CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

R_{35} is hydrogen, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{36} is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R_{15}R_{16})$, heterocyclyl, or heteroaryl;

R_{13} and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl,

heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;

R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, cycloalkyl, aryl,

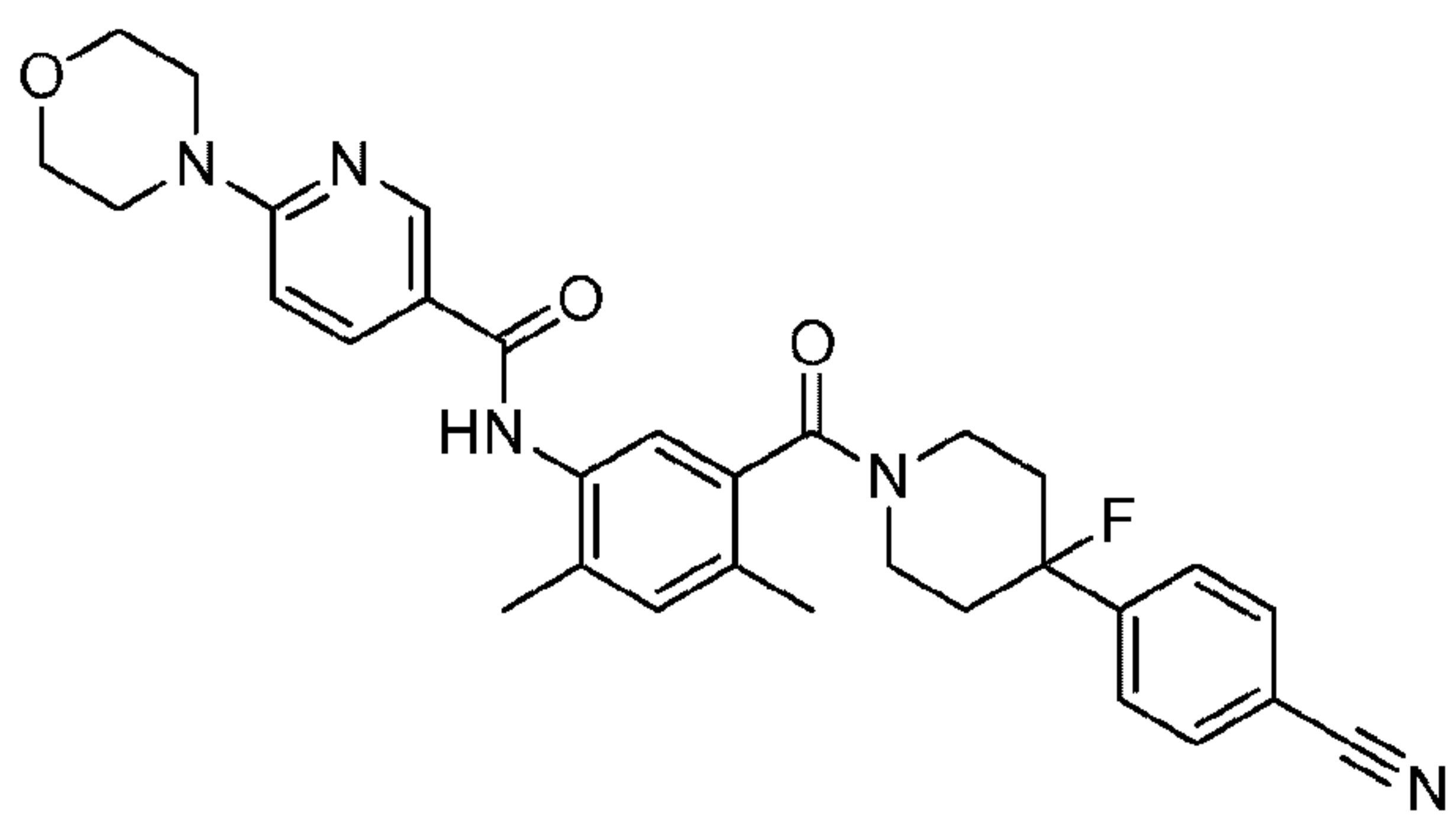
heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino; and

R_{37} and R_{38} are each independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxyalkyl,

heteroaryl, heterocyclyl, or R_{37} and R_{38} taken together with the atoms to which they are attached join together to form a heteroaryl or heterocyclyl.

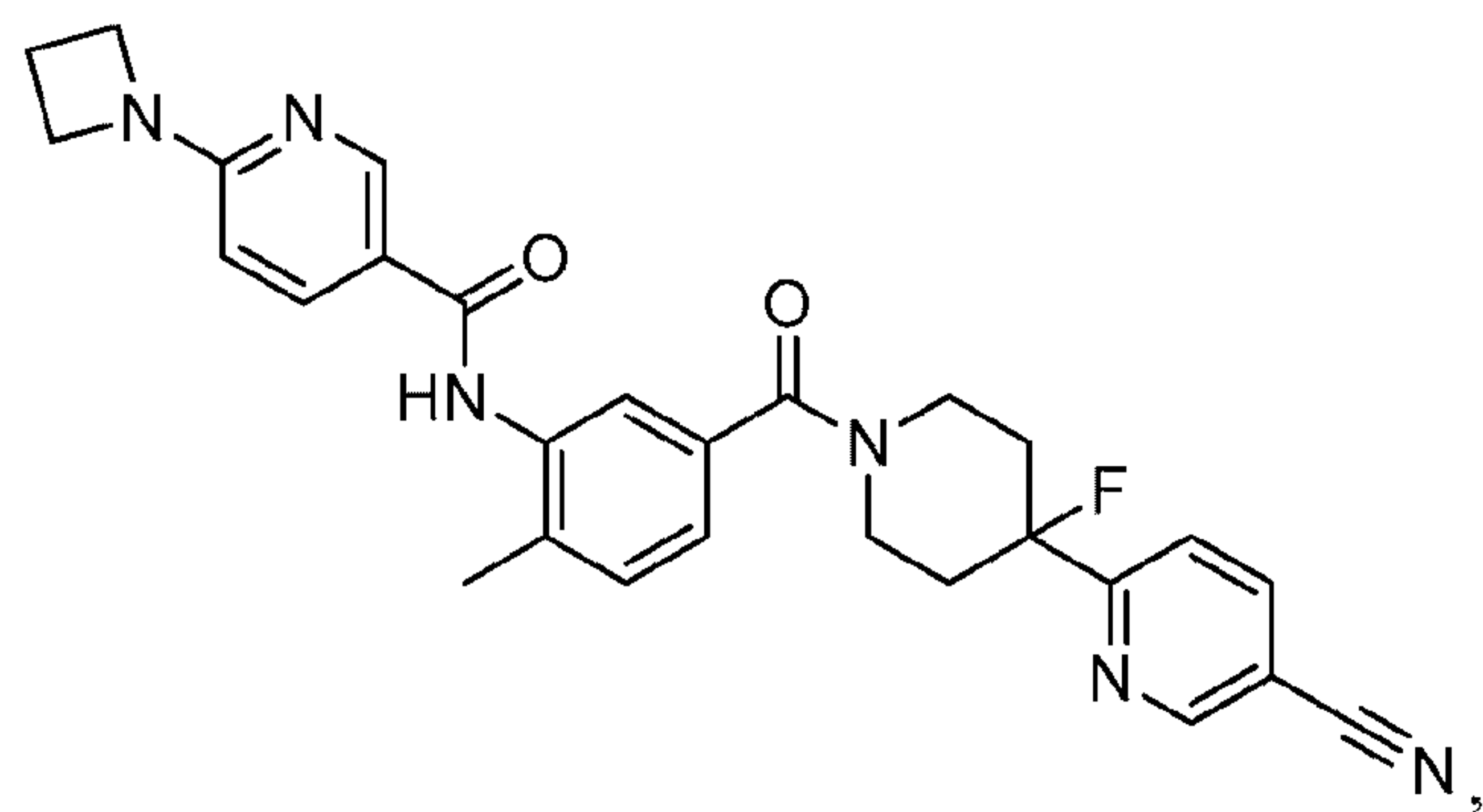
[0211] In certain aspects of Structure (VI), R_1 is hydrogen, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, or $-C(=O)N(R_{13})(R_{14})$.

- [0212] In certain aspects of Structure (VI), R_1 is cyano.
- [0213] In certain aspects of Structure (VI), R_2 is hydrogen or halo.
- [0214] In certain aspects of Structure (VI), R_2 is hydrogen.
- [0215] In certain aspects of Structure (VI), R_3 is fluorine.
- [0216] In certain aspects of Structure (VI), R_{21} and R_{22} are each independently hydrogen or C_{1-6} alkyl.
- [0217] In certain aspects of Structure (VI), R_{21} and R_{22} are each independently C_{1-6} alkyl.
- [0218] In certain aspects of Structure (VI), R_{35} is hydrogen.
- [0219] In certain aspects of Structure (VI), R_{34} is heteroaryl;
- [0220] In certain aspects of Structure (VI), R_{34} is thienyl, pyrrolyl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, pyranyl, tetrazolyl, pyrrolyl, pyrrolinyl, pyridazinyl, triazolyl, indolyl, isoindolyl, indoliziny, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl, oxadiazolyl, benzoxazolyl, benzoxadiazolyl, thiadiazolyl, benzothiazolyl, or benzothiadiazolyl.
- [0221] In certain aspects of Structure (VI), L_{13} is N.
- [0222] In certain aspects of Structure (VI), L_{14} and L_{15} are each independently CH.
- [0223] In certain aspects of Structure (VI), A is N.
- [0224] In certain aspects of Structure (VI), A is CH.
- [0225] In certain aspects, the compounds of Structure (VI) have one of the following Structures (VI-E), (VI-F), (VI-G), (VI-H), or (VI-I):

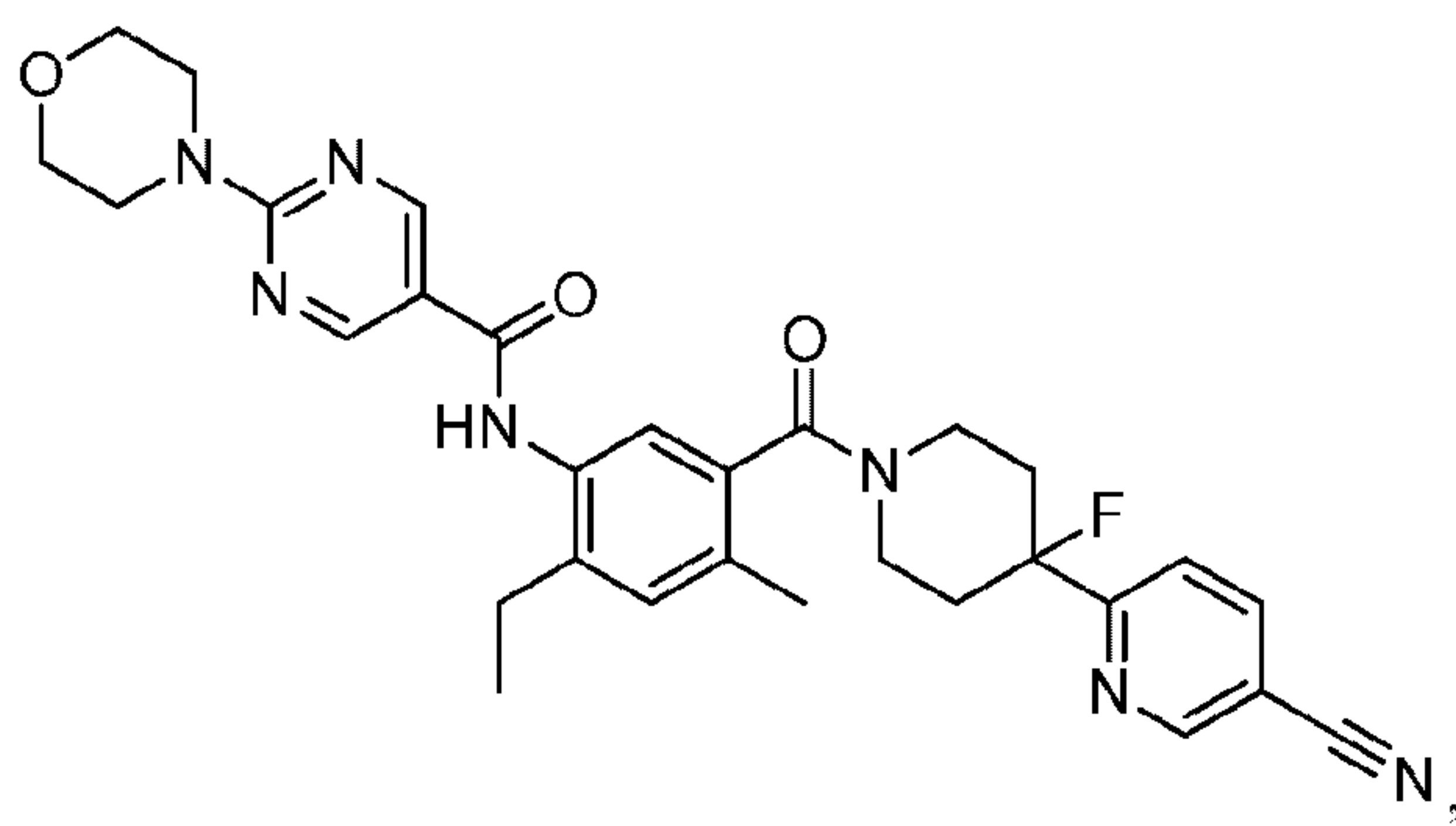


(VI-E)

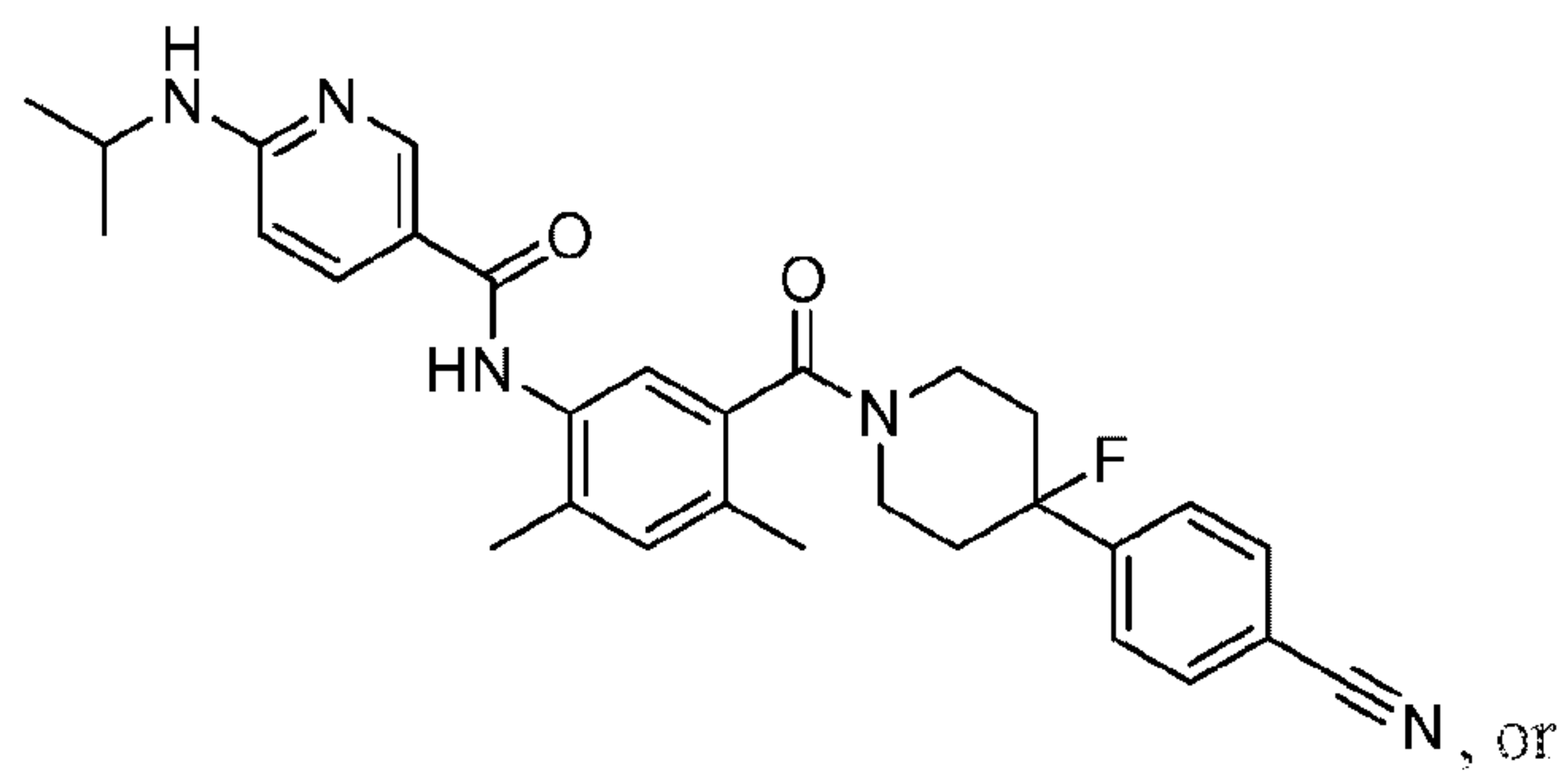
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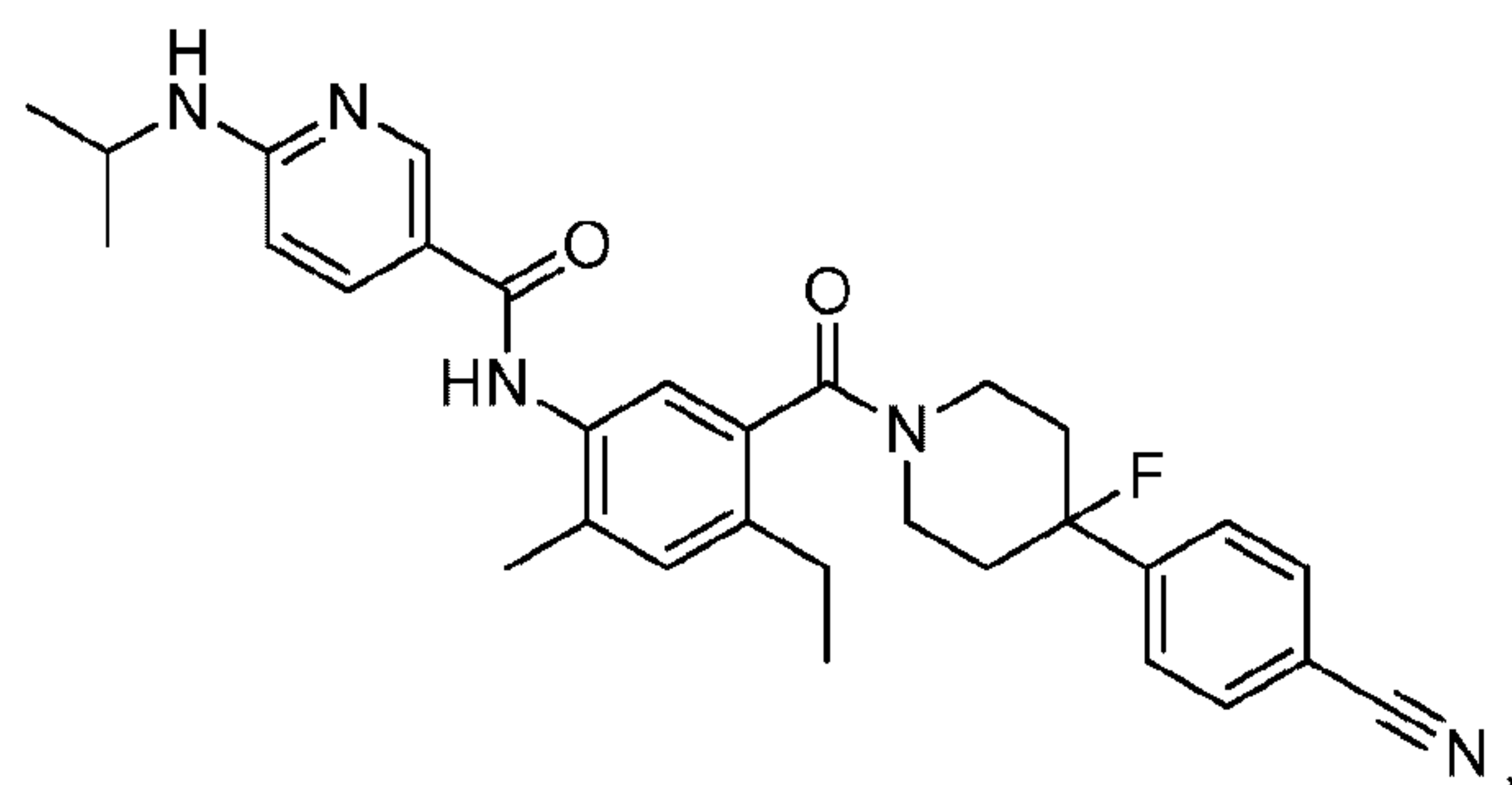
(VI-F)



(VI-G)



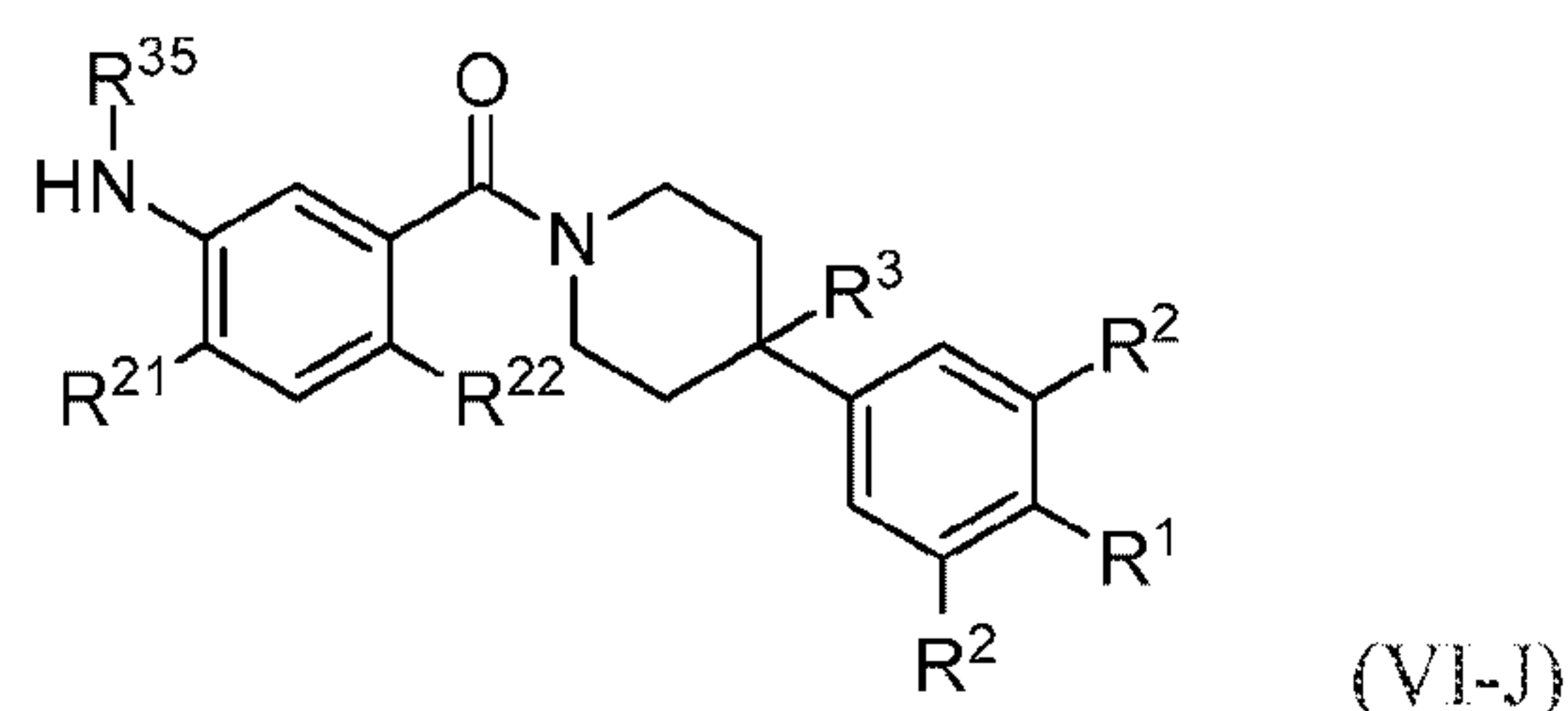
(VI-H)



(VI-I)

or a pharmaceutically acceptable salt thereof.

[0226] In various aspects, the present disclosure provides for compounds of Structure (VI-J):



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, -CN, halogen, C_1 - C_4 straight or branched alkyl, -O-(C_3 - C_5 cycloalkyl),

-O-(C_1 - C_4 straight or branched alkyl) wherein:

the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom; and

when R^1 is not H, -CN or halogen, it is optionally substituted with one or more halogens;

each R^2 is independently H, halogen or C_1 - C_4 straight or branched alkyl;

R^3 is H, -OH, or halogen;

R^{21} is cyclobutyl, azetidin-1-yl, or cyclopropyl;

R^{22} is H, halogen, or C_1 - C_2 alkyl;

R^{35} is -C(O)- R^{351} , -C(O)-NHR³⁵¹, -C(O)-O- R^{351} or S(O)₂ R^{351} ; and

R^{351} is C_1 - C_6 straight or branched alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, each of which is optionally substituted.

[0227] In some aspects of Structure (VI-J), R^3 is H or halogen.

[0228] In some aspects of Structure (VI-J), R^1 is halogen, -CN or C_1 - C_2 haloalkyl.

[0229] In some aspects of Structure (VI-J), R^{22} is C_1 - C_2 alkyl.

[0230] In some aspects of Structure (VI-J), R^{21} is cyclobutyl and R^{22} is C_1 - C_2 alkyl.

[0231] In some aspects of Structure (VI-J), R^{21} is cyclobutyl.

[0232] In some aspects of Structure (VI-J), R^3 is H or F.

[0233] In some aspects of Structure (VI-J), R^1 is -CN.

[0234] In some aspects of Structure (VI-J), R^1 is -CF₃.

[0235] In some aspects of Structure (VI-J), R^{22} is H, methyl or ethyl.

[0236] In some aspects of Structure (VI-J), R^{22} is H.

[0237] In some aspects of Structure (VI-J), R^{22} is methyl.

[0238] In some aspects of Structure (VI-J), R^{35} is -C(O)-NHR³⁵¹.

[0239] In some aspects of Structure (VI-J), R^{351} is isopropyl, isobutyl, (R)-3-tetrahydrofuranyl, (S)-3-tetrahydrofuranyl, (R)-(tetrahydrofuran-2-yl)methyl, (S)-(tetrahydrofuran-2-yl)methyl, (R)-tetrahydro-2H-pyran-3-yl or (S)-tetrahydro-2H-pyran-3-yl.

[0240] In some aspects of Structure (VI-J), R^{351} is (R)-(tetrahydrofuran-2-yl)methyl or (S)-(tetrahydrofuran-2-yl)methyl.

[0241] In some aspects of Structure (VI-J), R^1 is $-\text{CN}$, each R^2 is H, R^3 is H or F, R^{21} is C_3 - C_4 cycloalkyl, R^{22} is H, R^{35} is $-\text{C}(\text{O})-\text{NHR}^{351}$ where R^{351} is isopropyl, isobutyl, (R)-3-tetrahydrofuranyl, (S)-3-tetrahydrofuranyl, (R)-(tetrahydrofuran-2-yl)methyl, (S)-(tetrahydrofuran-2-yl)methyl, (R)-tetrahydro-2*H*-pyran-3-yl, or (S)-tetrahydro-2*H*-pyran-3-yl.

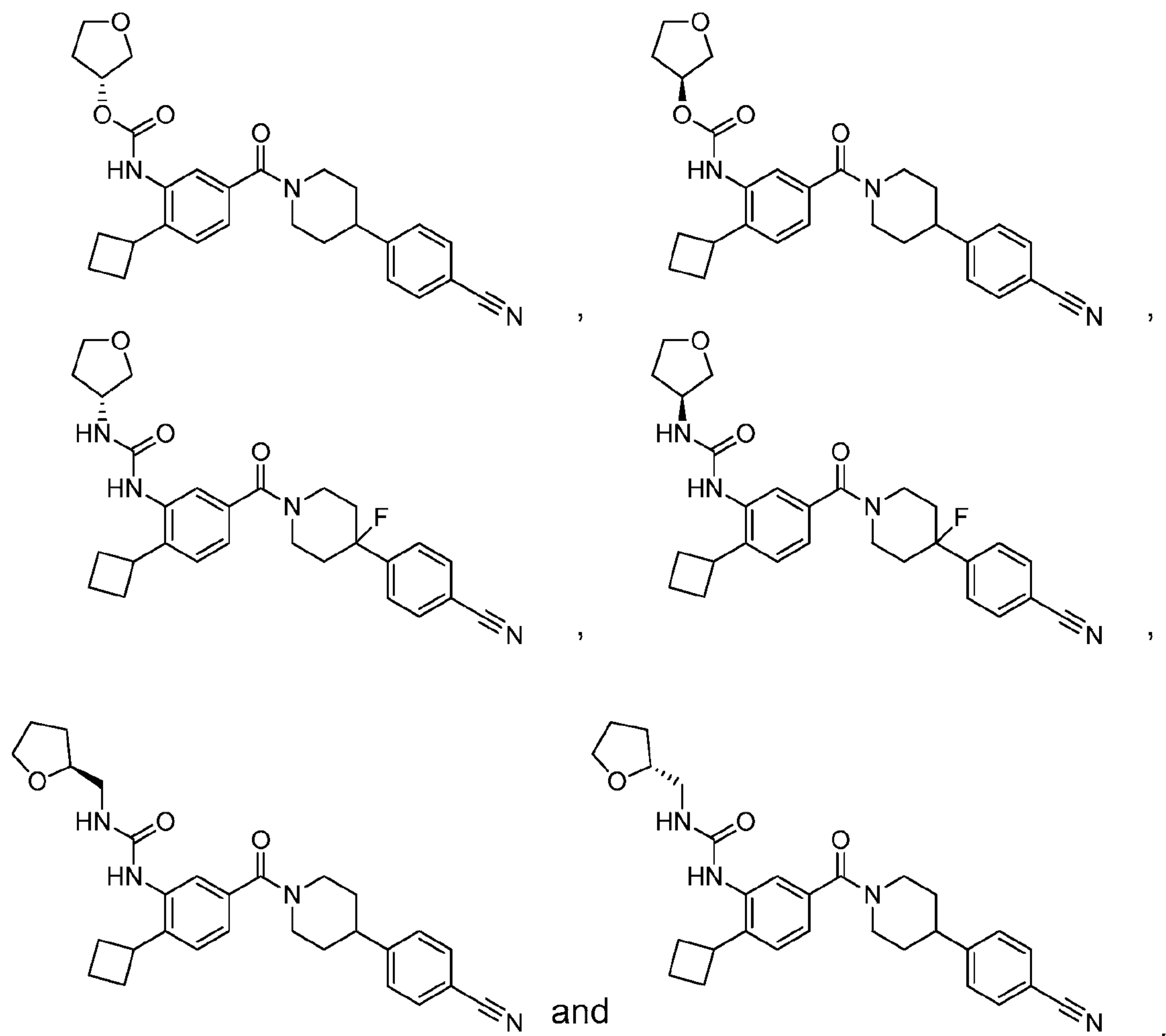
[0242] In some aspects of Structure (VI-J), R^{35} is $-\text{C}(\text{O})-\text{O}-R^{351}$.

[0243] In some aspects of Structure (VI-J), R^{351} is isopropyl, isobutyl, (R)-3-tetrahydrofuranyl, (S)-3-tetrahydrofuranyl, (R)-(tetrahydrofuran-2-yl)methyl, (S)-(tetrahydrofuran-2-yl)methyl, (R)-tetrahydro-2*H*-pyran-3-yl, or (S)-tetrahydro-2*H*-pyran-3-yl.

[0244] In some aspects of Structure (VI-J), R^1 is $-\text{CN}$, each R^2 is H, R^3 is H or F, R^{21} is C_3 - C_4 cycloalkyl, R^{22} is H, R^{35} is $-\text{C}(\text{O})-\text{O}-R^{351}$ where R^{351} is isopropyl, isobutyl, (R)-3-tetrahydrofuranyl, (S)-3-tetrahydrofuranyl, (R)-(tetrahydrofuran-2-yl)methyl, (S)-(tetrahydrofuran-2-yl)methyl, (R)-tetrahydro-2*H*-pyran-3-yl, or (S)-tetrahydro-2*H*-pyran-3-yl.

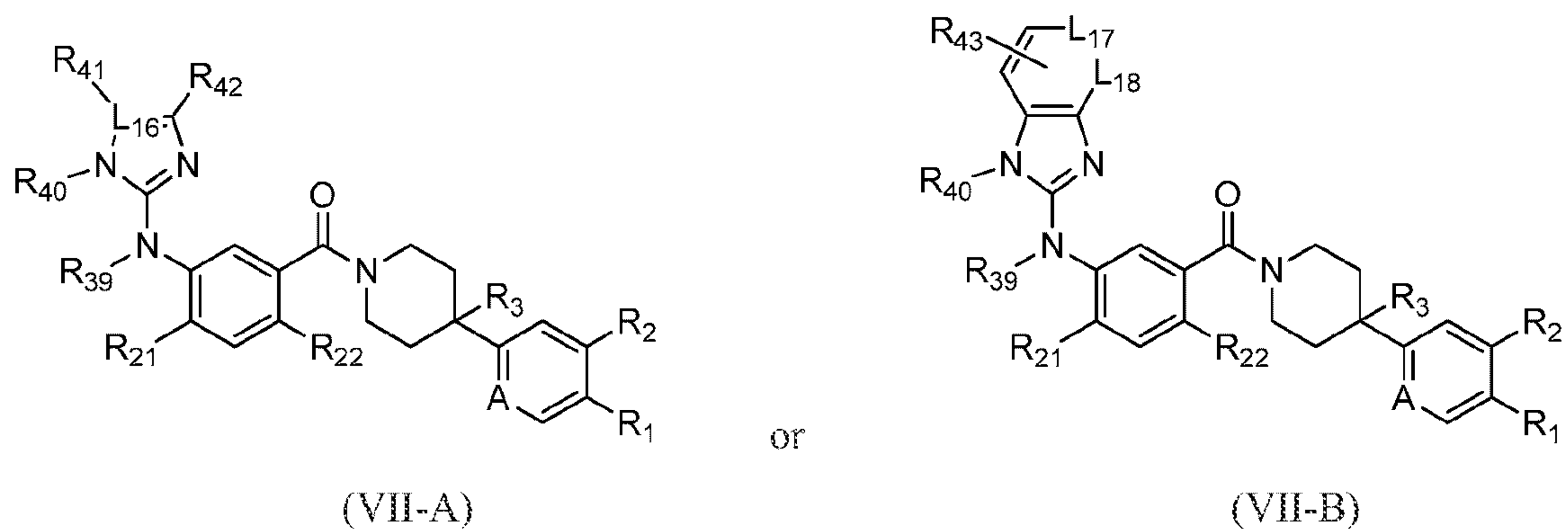
[0245] In some aspects of Structure (VI-J), R^{351} is (R)-3-tetrahydrofuranyl or (S)-3-tetrahydrofuranyl.

[0246] In some aspects of Structure (VI-J), compounds have a structure selected from the group consisting of:



Compounds of Structure (VII)

[0247] In certain aspects, the compounds of Structure (VII) have one of the following Structures (VII-A) or (VII-B):



or a pharmaceutically acceptable salt thereof, wherein:

L₁₆ is C or N, wherein R₄₁ is absent if L₁₆ is N;

L₁₇, L₁₈, and A are each independently CH or N;

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$,

$-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

q is 0, 1, 2, 3, or 4;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_2 is hydrogen, halo, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{21} and R_{22} are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

R_{40} , R_{42} , and R_{43} are each independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy,

$-S(=O)_2R_{20}$, $-C(=O)R$, hydroxyalkyl, hydroxyl, $-N(R_{13}R_{14})$, or R_{41} and R_{42} taken together with the atoms to which they are attached join together to form a heteroaryl or heterocyclyl;

R_{41} is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-S(=O)_2R_{20}$, $-C(=O)R$, hydroxyalkyl,

hydroxyl, $-N(R_{13}R_{14})$, R_{41} is absent if L_{16} is N, or R_{41} and R_{42} taken together with the atoms to which they are attached join together to form a heteroaryl or heterocyclyl;

R is hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;

R_{39} is hydrogen, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{13} and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl,

heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;
and

R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino.

[0248] In certain aspects of Structure (VII), R_1 is hydrogen, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, or $-C(=O)N(R_{13})(R_{14})$.

[0249] In certain aspects of Structure (VII), R_1 is cyano.

[0250] In certain aspects of Structure (VII), R_2 is hydrogen or halo.

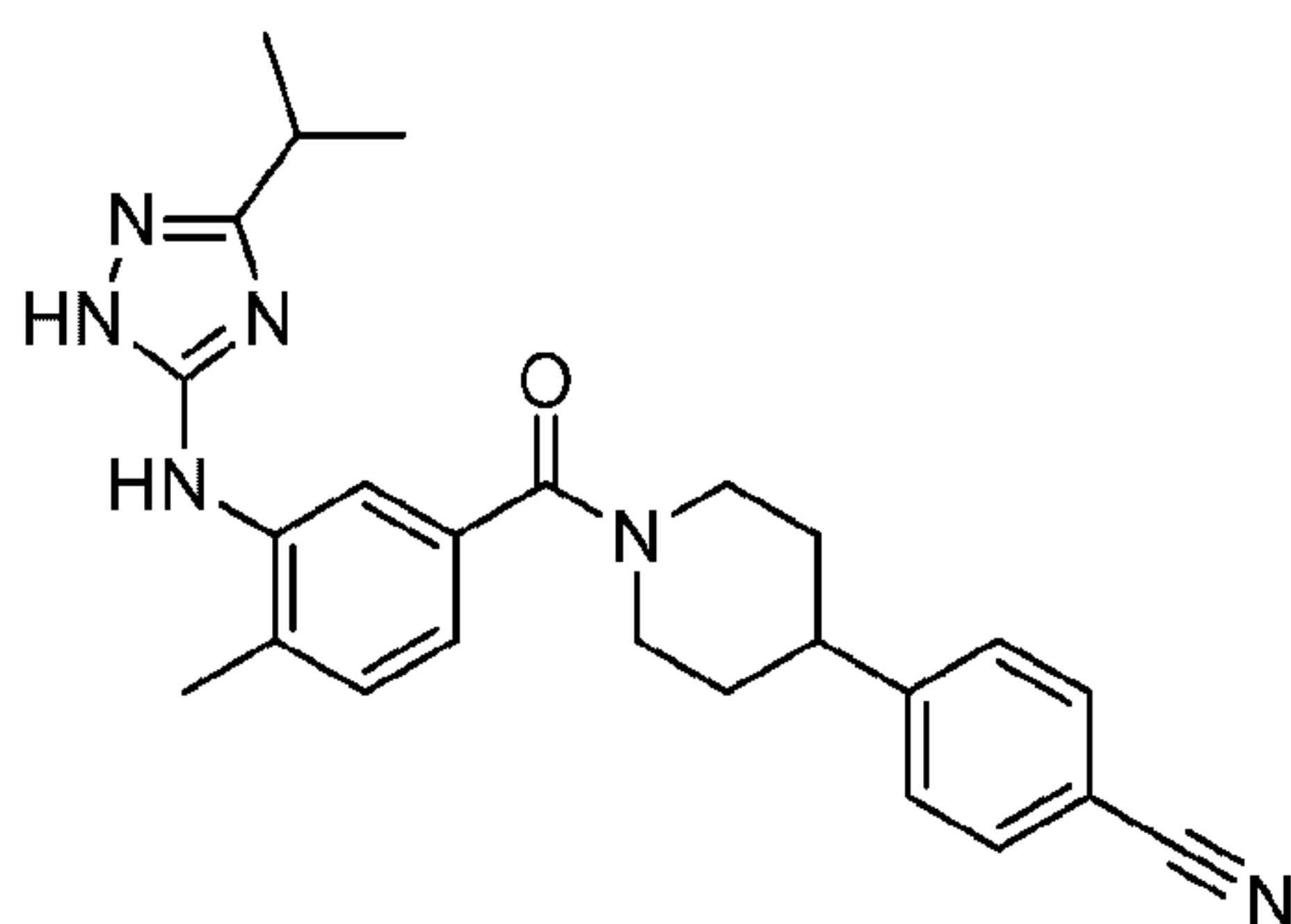
[0251] In certain aspects of Structure (VII), R_2 is hydrogen.

[0252] In certain aspects of Structure (VII), R_3 is hydrogen.

[0253] In certain aspects of Structure (VII), R_{21} and R_{22} are each independently hydrogen or C_{1-6} alkyl.

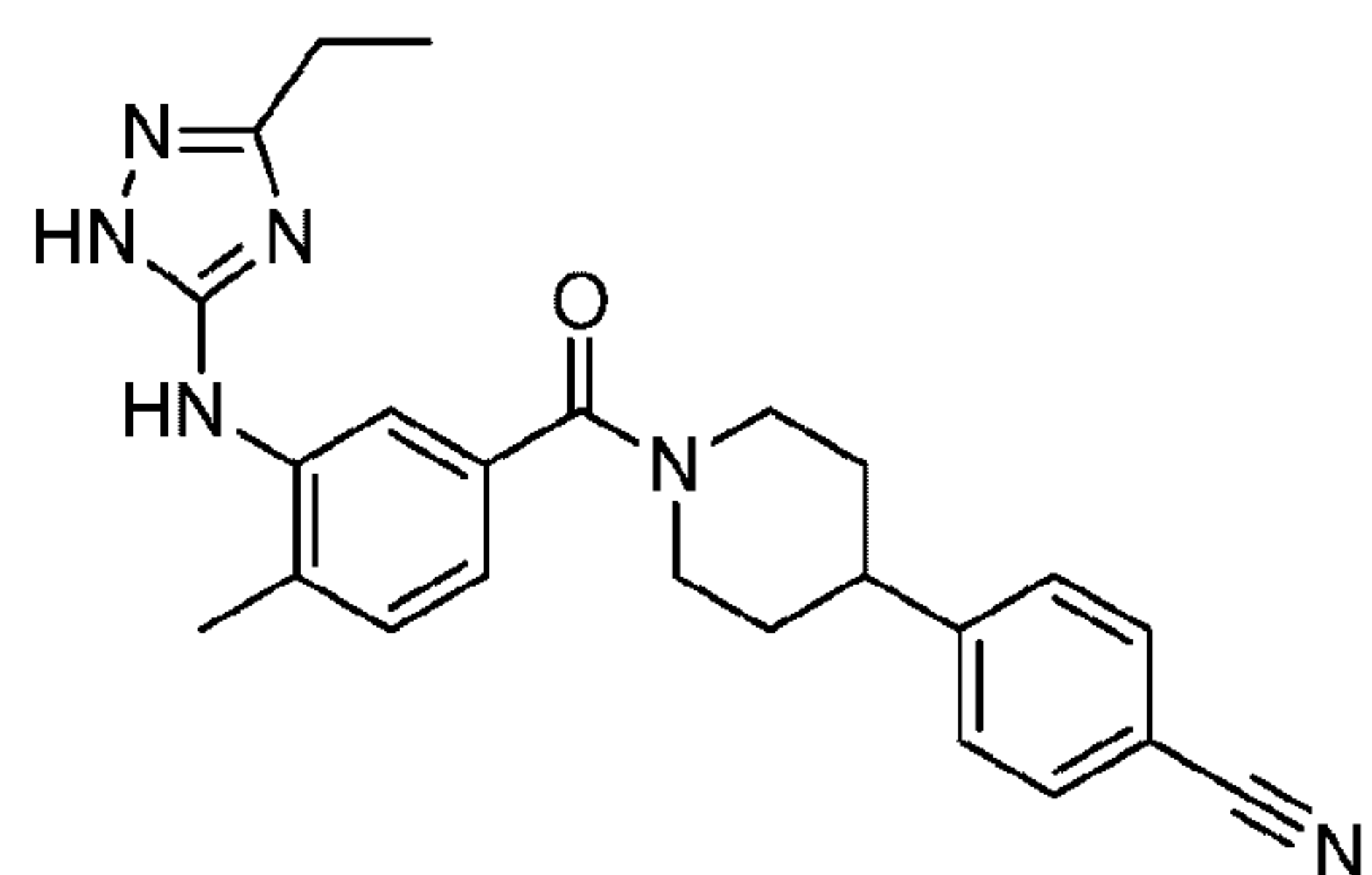
[0254] In certain aspects of Structure (VII), R_{21} and R_{22} are each independently C_{1-6} alkyl.

- [0255] In certain aspects of Structure (VII), R₃₉ is hydrogen.
- [0256] In certain aspects of Structure (VII), R₄₀ is hydrogen.
- [0257] In certain aspects of Structure (VII), L₁₆ is N.
- [0258] In certain aspects of Structure (VII), L₁₇ is N.
- [0259] In certain aspects of Structure (VII), L₁₈ is CH.
- [0260] In certain aspects of Structure (VII), L₁₈ is N.
- [0261] In certain aspects of Structure (VII), A is N.
- [0262] In certain aspects of Structure (VII), A is CH.
- [0263] In certain aspects of Structure (VII), R₄₂ is C₁₋₆ alkyl.
- [0264] In certain aspects of Structure (VII), R₄₁ is C₁₋₆ alkyl.
- [0265] In certain aspects, the compounds of Structure (VII) have one of the following Structures (VII-C) or (VII-D):



(VII-C)

or

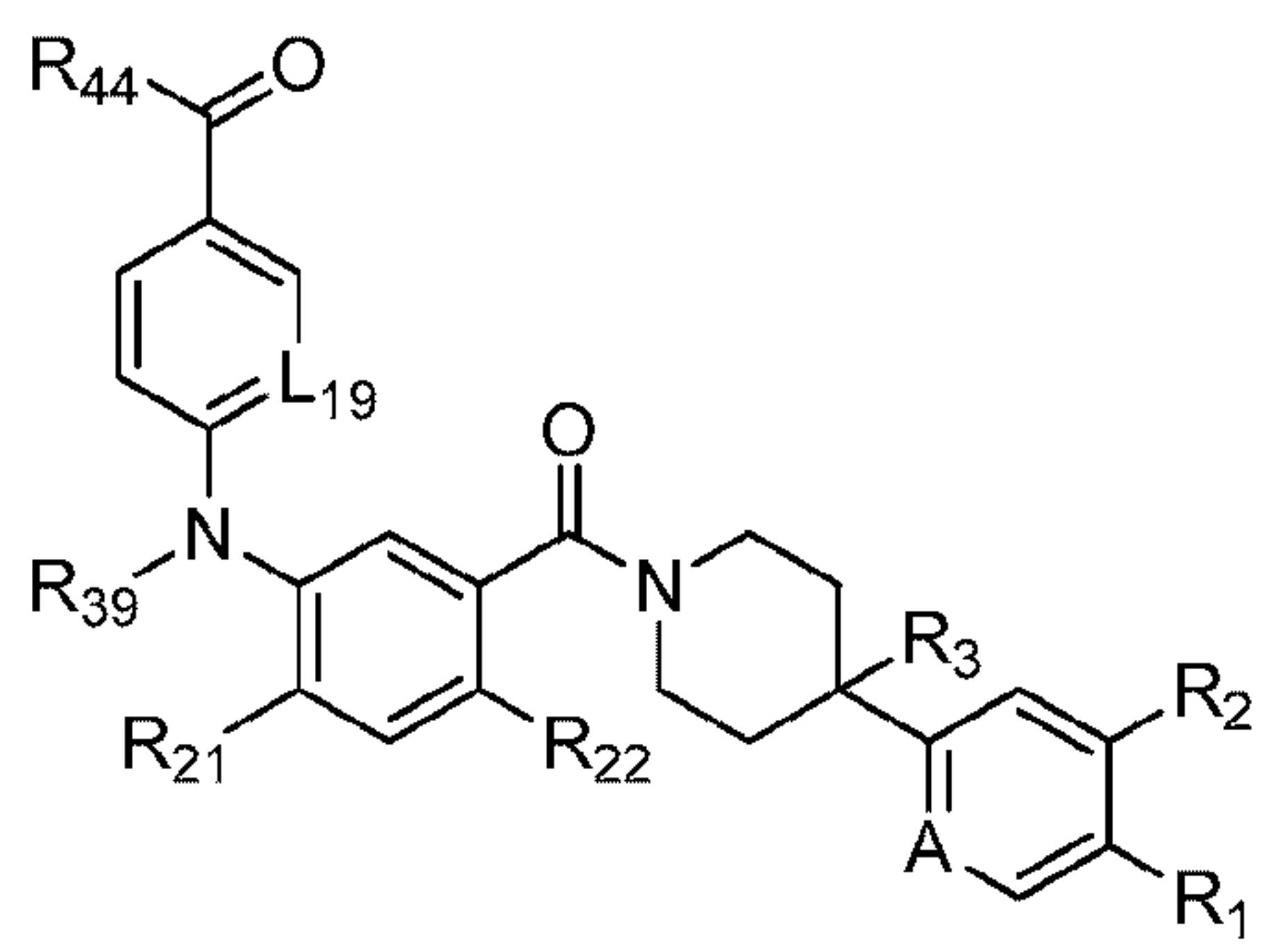


(VII-D)

or a pharmaceutically acceptable salt thereof.

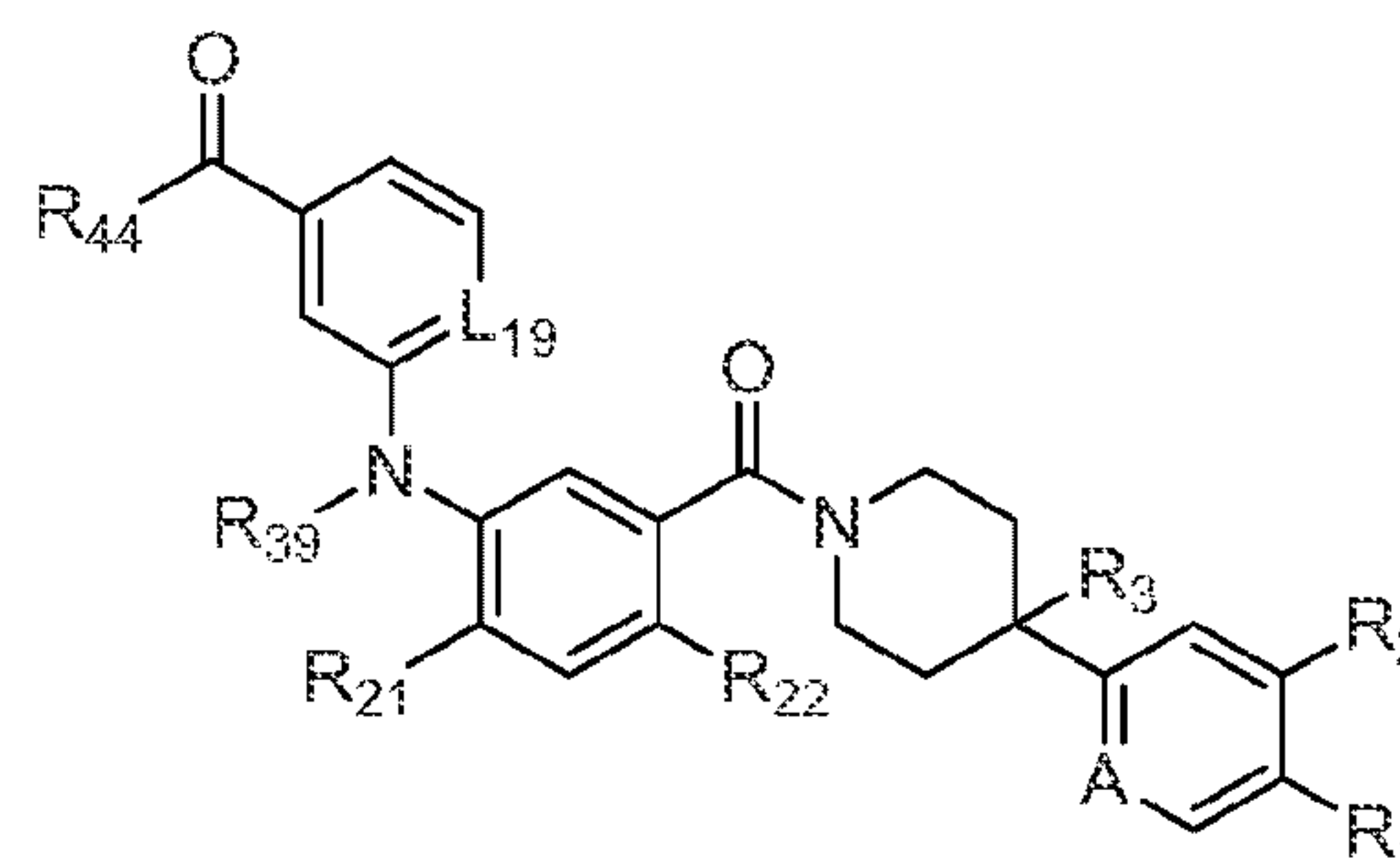
Compounds of Structure (VIII)

- [0266] In certain aspects, the compounds of Structure (VIII) have one of the following Structures (VIII-A), (VIII-B), or (VIII-C):



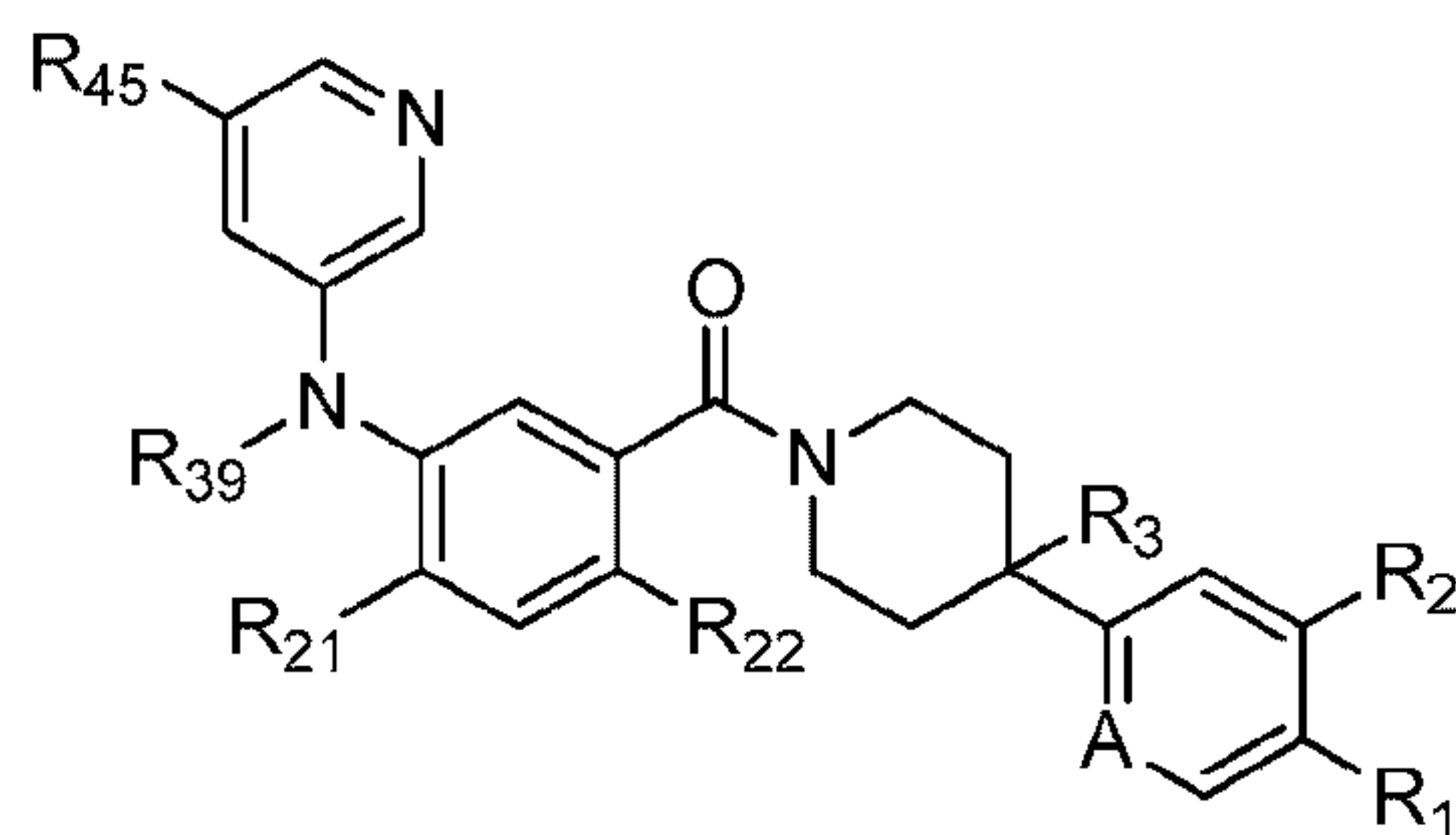
(VIII-A)

, or



(VIII-B)

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(VIII-C)

or a pharmaceutically acceptable salt thereof, wherein:

L_{19} and A are each independently CH or N;

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$, $-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

q is 0, 1, 2, 3, or 4;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_2 is hydrogen, halo, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{21} and R_{22} are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

R_{39} is hydrogen, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{44} and R_{45} are each independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, cycloalkyl, hydroxyalkyl, aryl, heterocyclyl, heteroaryl, alkylamino, $-S(=O)_2R_{20}$, $-C(=O)R$, or $-N(R_{13}R_{14})$; and

R_{13} and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$; and

R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino.

[0267] In certain aspects of Structure (VIII), R_1 is hydrogen, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, or $-C(=O)NN(R_{13})(R_{14})$.

[0268] In certain aspects of Structure (VIII), R_1 is cyano.

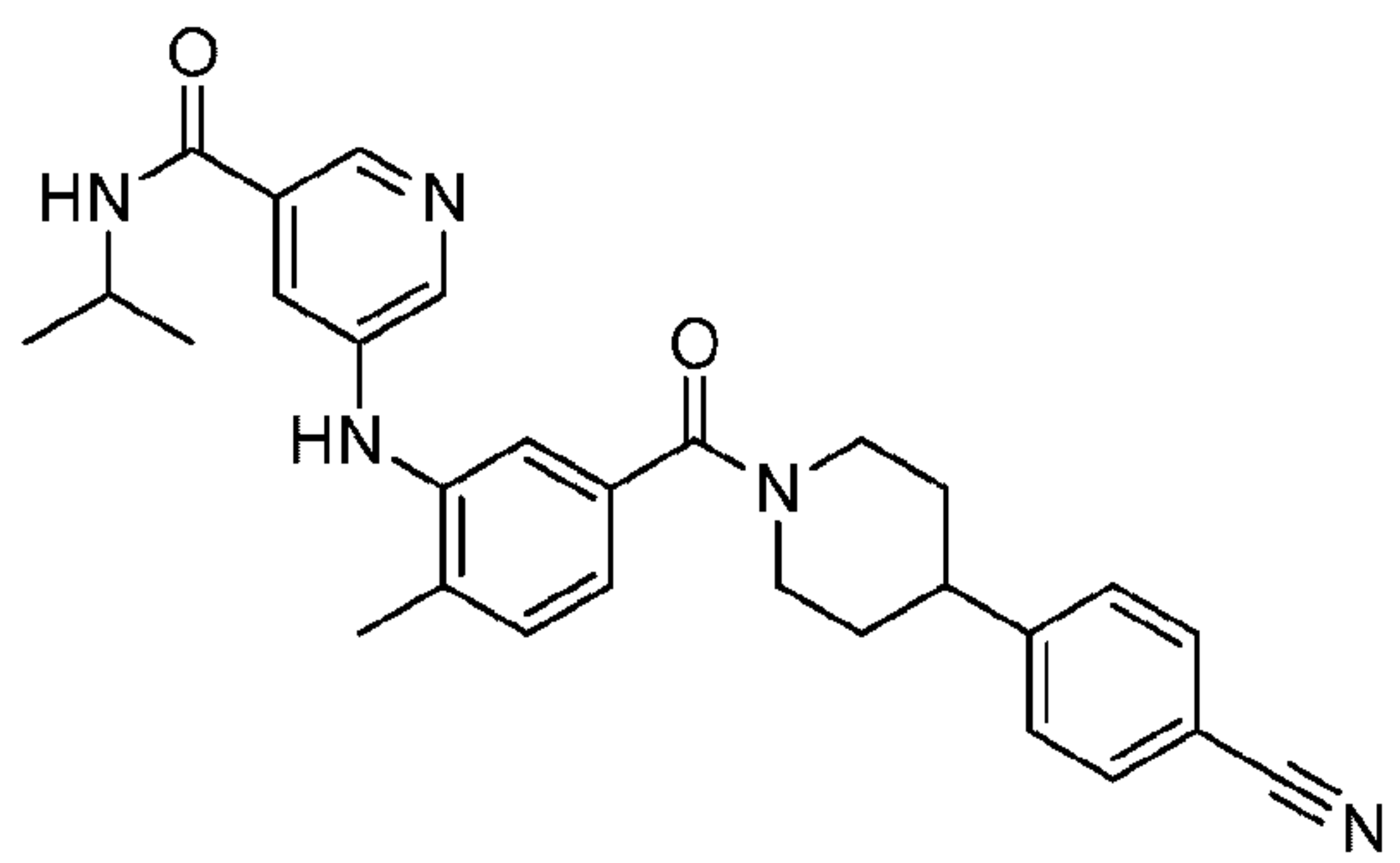
[0269] In certain aspects of Structure (VIII), R_2 is hydrogen or halo.

[0270] In certain aspects of Structure (VIII), R_2 is hydrogen.

[0271] In certain aspects of Structure (VIII), R_3 is hydrogen.

[0272] In certain aspects of Structure (VIII), R_{21} and R_{22} are each independently hydrogen or C_{1-6} alkyl.

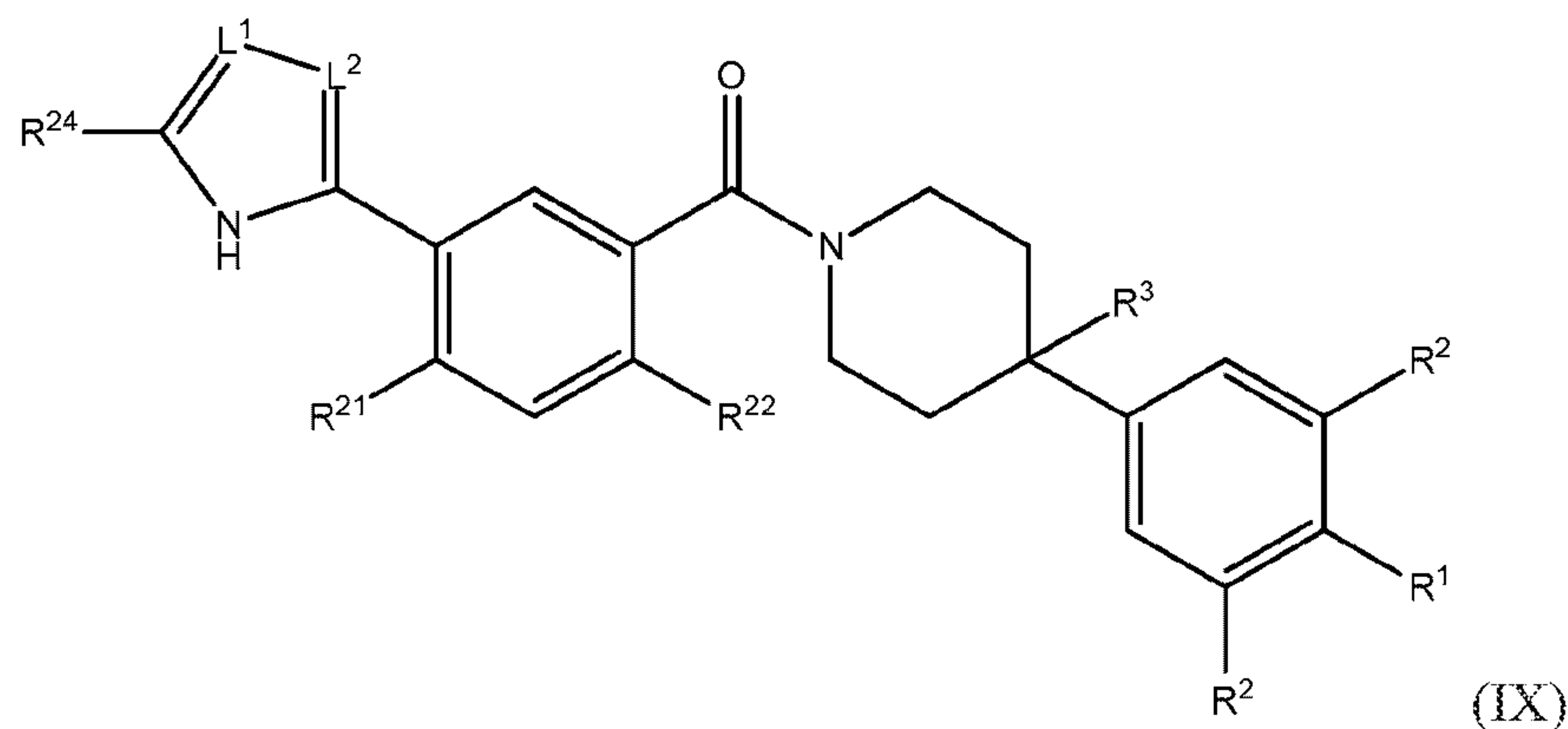
- [0273] In certain aspects of Structure (VIII), R_{21} and R_{22} are each independently C_{1-6} alkyl.
- [0274] In certain aspects of Structure (VIII), R_{39} is hydrogen.
- [0275] In certain aspects of Structure (VIII), L_{19} is N.
- [0276] In certain aspects of Structure (VIII), A is N.
- [0277] In certain aspects of Structure (VIII), A is CH.
- [0278] In certain aspects, the compounds of Structure (VIII) have the following Structure (VIII-D):



(VIII-D)

or a pharmaceutically acceptable salt thereof.

- [0279] In various aspects, compounds of formula IX are provided:



(IX)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, -CN, halogen, C_1 - C_4 straight or branched alkyl, -O-(C_3 - C_5 cycloalkyl) or -O-(C_1 - C_4 straight or branched alkyl) wherein:

C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom; and

when R^1 is not H, -CN or halogen, it is optionally substituted with one or more halogens;

each R^2 is independently hydrogen, halogen or C_1 - C_4 straight or branched alkyl;

R^3 is H, -OH, or halogen;

R^{21} is H, halogen, C_1 - C_4 straight or branched alkyl, C_3 - C_5 cycloalkyl wherein the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom;

R^{22} is H, halogen, or C_1 - C_2 alkyl;

R^{24} is H, C_1 - C_4 straight or branched alkyl, $-(C_1-C_4 \text{ alkyl})_t-OH$,
 $-(C_1-C_4 \text{ alkyl})_t-O-(C_3-C_5 \text{ cycloalkyl})$, or
 $-(C_1-C_4 \text{ alkyl})_t-O-(C_1-C_4 \text{ straight or branched alkyl})$ wherein:

t is 0 or 1;

the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom;

L^1 is CR^{23} or N;

L^2 is CH or N;

at least one of L^1 or L^2 is N; and

R^{23} is H or C_1 - C_4 straight or branched alkyl.

[0280] In some aspects of Structure (IX), R^{24} is C_1 - C_4 straight or branched alkyl, $-(C_1-C_4 \text{ alkyl})_t-O-(C_1-C_4 \text{ straight or branched alkyl})$ wherein t is 0 or 1.

[0281] In some aspects of Structure (IX), R^{21} is halogen, C_1 - C_4 straight or branched alkyl, C_3 - C_5 cycloalkyl wherein the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom, $-S(O)_u-(C_1-C_4 \text{ straight or branched alkyl})$ wherein u is 0 or 2, or $-S(O)_u-(C_3-C_5 \text{ cycloalkyl})$ wherein u is 0 or 2;

[0282] In some aspects of Structure (IX), R^3 is H or halogen.

[0283] In some aspects of Structure (IX), R^1 is halogen, $-CN$ or C_1 - C_2 haloalkyl.

[0284] In some aspects of Structure (IX), both L^1 and L^2 are N.

[0285] In some aspects of Structure (IX), R^{21} is C_1 - C_2 alkyl or C_3 - C_5 cycloalkyl and R^{22} is C_1 - C_2 alkyl.

[0286] In some aspects of Structure (IX), R^{21} is C_3 - C_5 cycloalkyl and R^{22} is C_1 - C_2 alkyl.

[0287] In some aspects of Structure (IX), R^{24} is $-(C_1-C_2 \text{ alkyl})_t-O-(C_1-C_2 \text{ alkyl})$ wherein t is 0 or 1.

[0288] In some aspects of Structure (IX), R^{21} is C_3 - C_5 cycloalkyl, R^{22} is C_1 - C_2 alkyl and R^{24} is C_1 - C_2 alkyl.

[0289] In some aspects of Structure (IX), R^{21} is cyclobutyl, R^{22} is C_1 - C_2 alkyl and R^{24} is C_1 - C_2 alkyl.

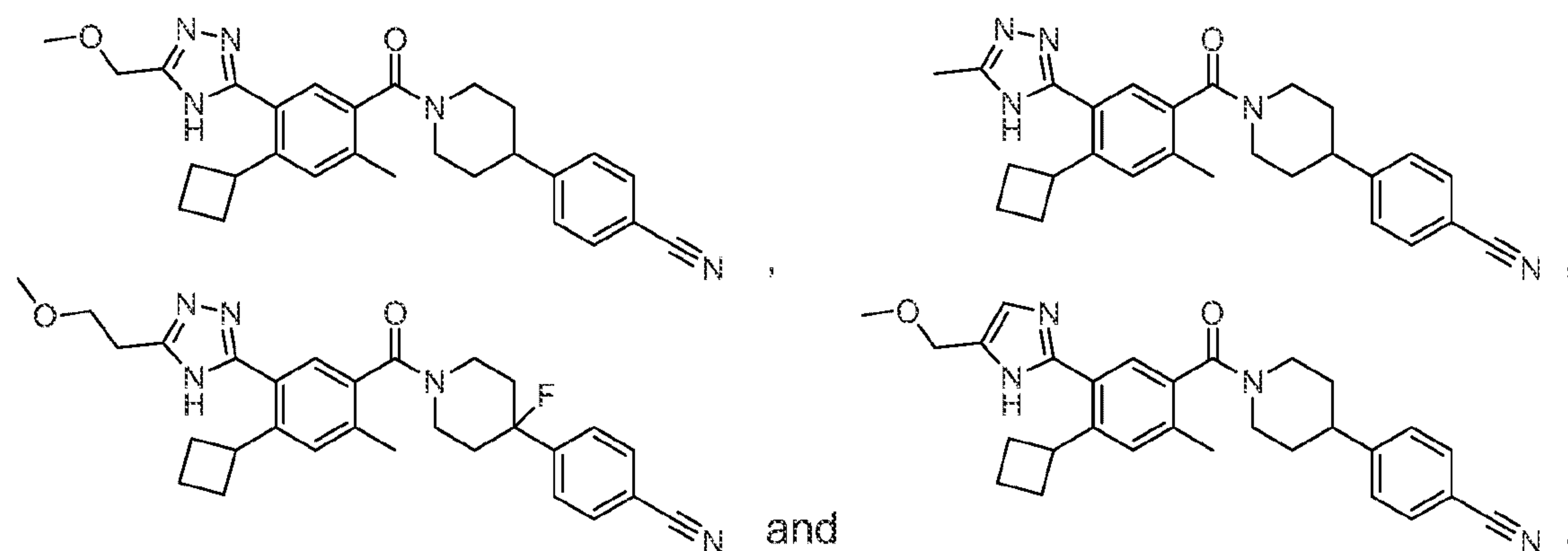
[0290] In some aspects of Structure (IX), R^{21} is cyclobutyl.

[0291] In some aspects of Structure (IX), R^3 is H or F.

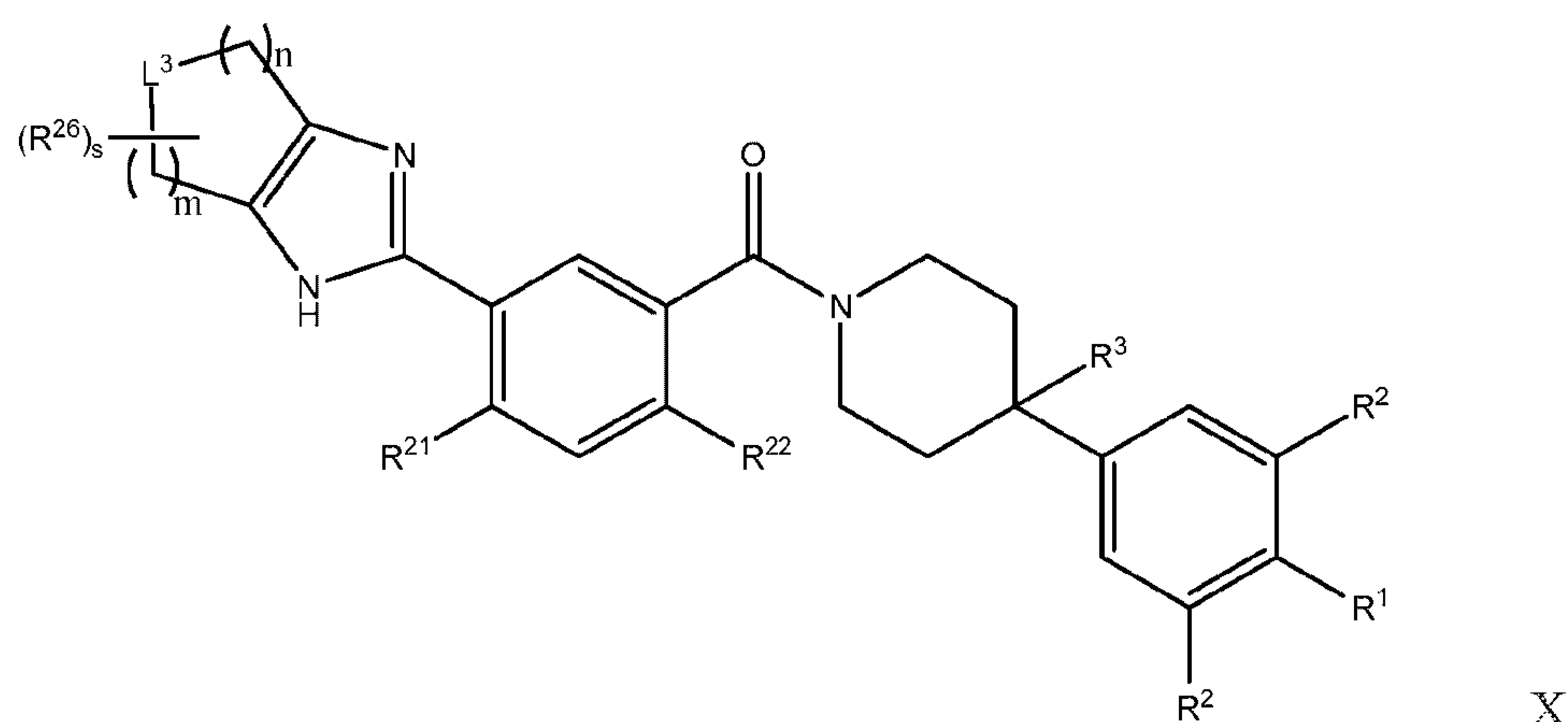
[0292] In some aspects of Structure (IX), R^1 is $-CN$.

[0293] In some aspects of Structure (IX), R^1 is $-CF_3$.

- [0294] In some aspects of Structure (IX), R^{22} is H, methyl or ethyl.
- [0295] In some aspects of Structure (IX), R^{22} is H.
- [0296] In some aspects of Structure (IX), R^{22} is methyl.
- [0297] In some aspects of Structure (IX), R^1 is $-\text{CN}$, each R^2 is hydrogen, R^3 is H or F, R^{21} is C_3 - C_4 cycloalkyl, R^{22} is methyl, L^1 and L^2 are N, and R^{24} is methyl, ethyl, hydroxymethyl, methoxymethyl, 2-methoxyethyl.
- [0298] In some aspects of Structure (IX), R^1 is $-\text{CN}$, each R^2 is H, R^3 is H or F, R^{21} is C_3 - C_4 cycloalkyl, R^{22} is methyl, L^1 and L^2 are N, and R^{24} is methoxy or ethoxy.
- [0299] In some aspects of Structure (IX), R^1 is $-\text{CN}$, each R^2 is H, R^3 is H or F, R^{21} is C_3 - C_4 cycloalkyl, R^{22} is methyl, L^1 is CH, L^2 is N, and R^{24} is methyl, ethyl, hydroxymethyl, methoxymethyl, or 2-methoxyethyl.
- [0300] In some aspects of Structure (IX), R^1 is $-\text{CN}$, each R^2 is H, R^3 is H or F, R^{21} is C_3 - C_4 cycloalkyl, R^{22} is methyl, L^1 is N, L^2 is CH, and R^{24} is methyl, ethyl, hydroxymethyl, methoxymethyl, or 2-methoxyethyl.
- [0301] In some aspects of Structure (IX), compounds have a structure selected from the group consisting of:



- [0302] In various aspects, compounds of Structure (X) are provided:



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, -CN, halogen, C_1 - C_4 straight or branched alkyl, -O-(C_3 - C_5 cycloalkyl),

-O-(C_1 - C_4 straight or branched alkyl) wherein:

the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom; and

when R^1 is not H, -CN or halogen, it is optionally substituted with one or more halogens;

each R^2 is independently hydrogen, halogen or C_1 - C_4 straight or branched alkyl;

R^3 is H, -OH or halogen;

L^3 is $C(R^{60})_2$, O or NR^{50} ;

each R^{60} is independently H, -OH, -CN, -O_t-(C_3 - C_5 cycloalkyl), -O-(C_1 - C_4 straight or branched alkyl), or -C(O)-N(R^{601})₂ wherein:

t is 0 or 1, and

the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom;

each R^{50} is independently H, -C(O)-O_t-(C_1 - C_4 straight or branched alkyl),

-C(O)-O_t-(C_3 - C_5 cyclic alkyl), - C_3 - C_5 cyclic alkyl optionally containing an oxygen or nitrogen heteroatom, -C(O)-N(R^{501})₂, C_1 - C_4 straight or branched alkyl wherein:

t is 0 or 1, and

the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom;

n is 1, 2 or 3;

m is 1 or 2;

R^{21} is H, halogen, C_1 - C_4 straight or branched alkyl, C_3 - C_5 cycloalkyl wherein the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom

R^{22} is H, halogen, C_1 - C_2 alkyl;

each R^{26} is independently -OH, -CN, halogen, C_1 - C_4 straight or branched alkyl,

-(C_1 - C_4 alkyl)_t-O_t-(C_3 - C_5 cycloalkyl), -(C_1 - C_4 alkyl)_t-O-(C_1 - C_4 straight or branched alkyl), -C(O)-O_t-(C_1 - C_4 alkyl), or -C(O)-N(R^{501})₂ wherein:

t is 0 or 1, and

the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom;

s is 0, 1 or 2;

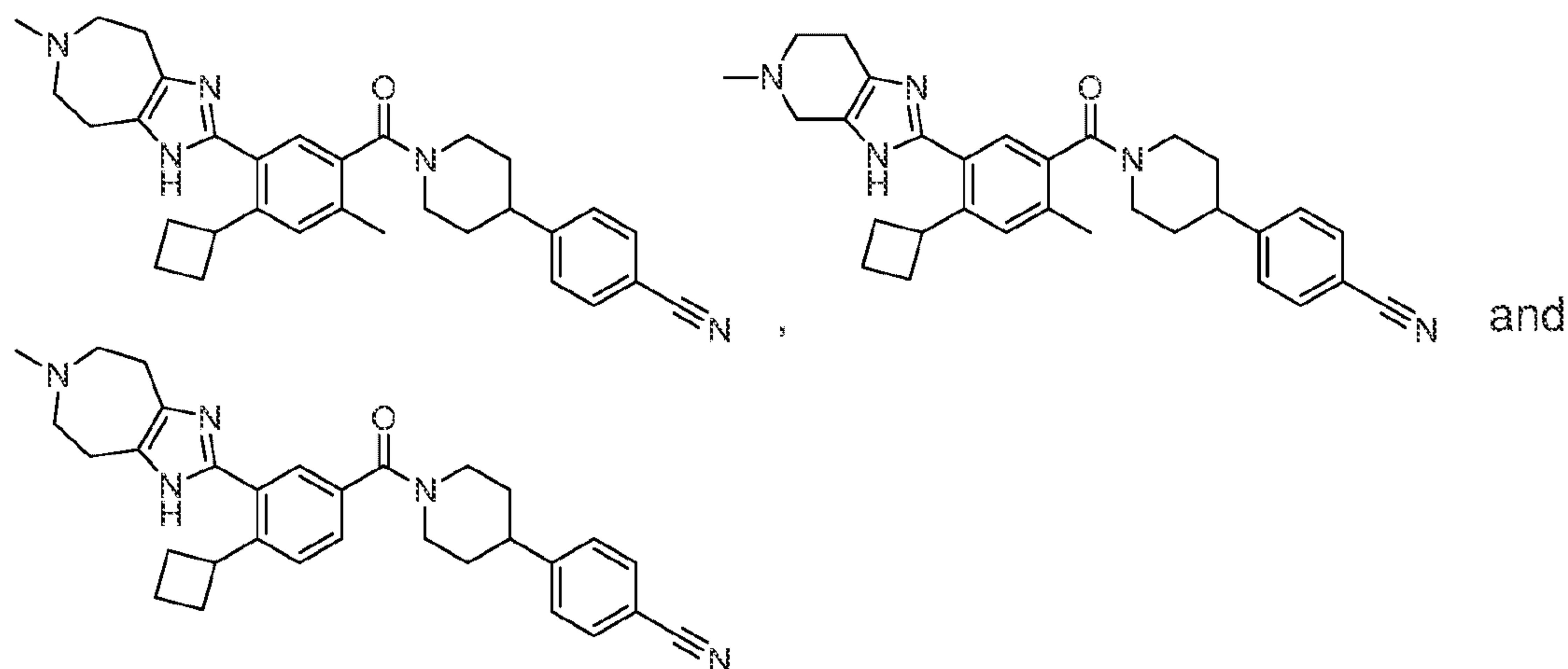
each R^{601} and R^{501} is independently H or C_1 - C_4 straight or branched alkyl; and

wherein two of R^{26} , R^{60} , R^{50} , R^{501} and R^{601} optionally join to form a ring wherein the two of R^{26} , R^{60} , R^{50} , R^{501} and R^{601} may be two R^{26} , two R^{60} , two R^{50} , two R^{501} or two R^{601} .

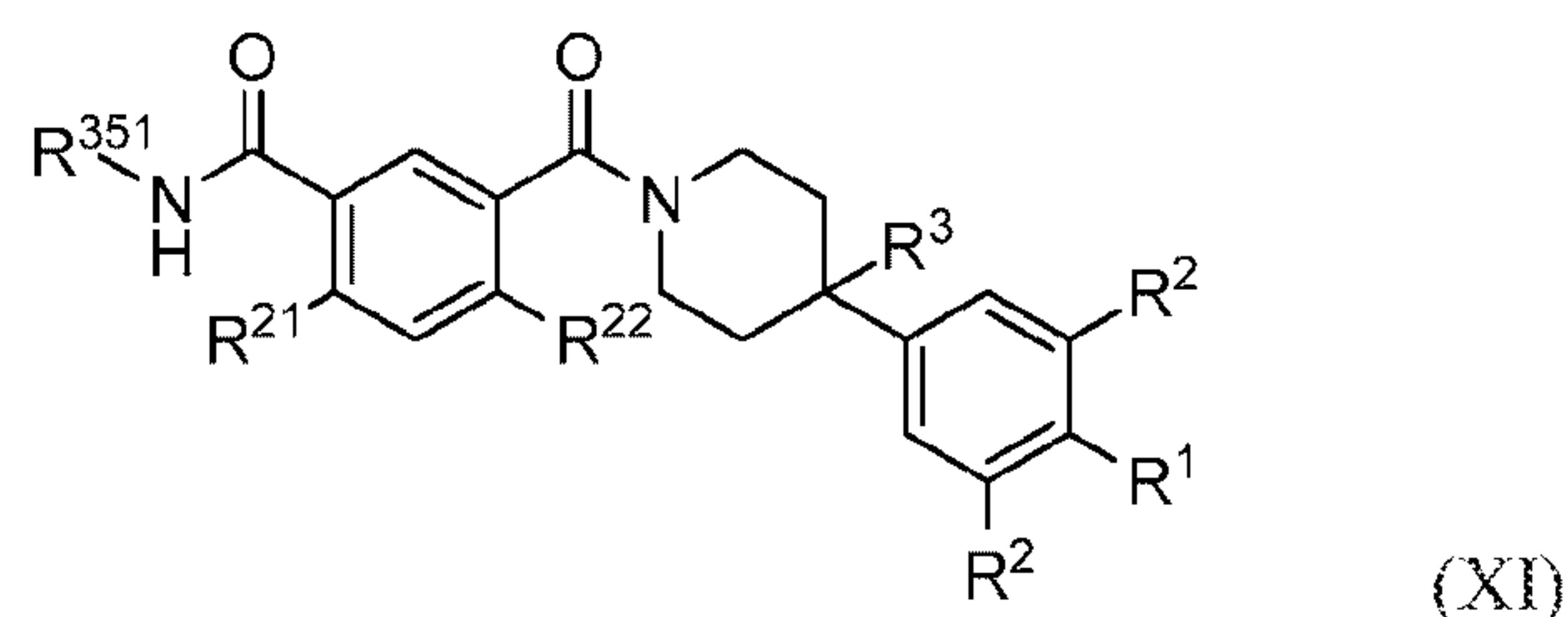
[0303] In some aspects of Structure (X), R^{21} is halogen, C_1 - C_4 straight or branched alkyl or C_3 - C_5 cycloalkyl.

- [0304] In some aspects of Structure (X), R^3 is H or halogen.
- [0305] In some aspects of Structure (X), R^1 is $-\text{CN}$ or $\text{C}_1\text{-C}_2$ haloalkyl.
- [0306] In some aspects of Structure (X), R^3 is H or F.
- [0307] In some aspects of Structure (X), R^1 is $-\text{CN}$.
- [0308] In some aspects of Structure (X), R^1 is $-\text{CF}_3$.
- [0309] In some aspects of Structure (X), n is 1.
- [0310] In some aspects of Structure (X), n is 2.
- [0311] In some aspects of Structure (X), m is 1.
- [0312] In some aspects of Structure (X), m is 2.
- [0313] In some aspects of Structure (X), R^{21} is $\text{C}_1\text{-C}_2$ alkyl or $\text{C}_3\text{-C}_5$ cycloalkyl and R^{22} is $\text{C}_1\text{-C}_2$ alkyl.
- [0314] In some aspects of Structure (X), R^{21} is $\text{C}_3\text{-C}_5$ cycloalkyl and R^{22} is $\text{C}_1\text{-C}_2$ alkyl.
- [0315] In some aspects of Structure (X), n is 2, m is 1, L^3 is $-\text{N}-\text{C}(\text{O})-\text{O}-(\text{C}_1\text{-C}_2 \text{ alkyl})$.
- [0316] In some aspects of Structure (X), L^3 is NR^{50} ; R^{50} is $\text{C}_1\text{-C}_2$ alkyl; R^{21} is cyclobutyl; R^{22} is H or methyl; R^3 is H; R^1 is $-\text{CN}$; m is 2 and n is 1 or 2.
- [0317] In some aspects of Structure (X), n is 2, m is 1, L^3 is O and s is 0.
- [0318] In some aspects of Structure (X), R^{22} is H, methyl or ethyl.
- [0319] In some aspects of Structure (X), R^{22} is methyl.
- [0320] In some aspects of Structure (X), R^{22} is H.
- [0321] In some aspects of Structure (X), R^1 is $-\text{CN}$, each R^2 is H, R^3 is H or F, R^{21} is $\text{C}_3\text{-C}_4$ cycloalkyl, R^{22} is methyl, n is 2 and L^3 is NR^{50} where R^{50} is methyl or ethyl.
- [0322] In some aspects of Structure (X), R^1 is $-\text{CN}$, each R^2 is H, R^3 is H or F, R^{21} is $\text{C}_3\text{-C}_4$ cycloalkyl, R^{22} is methyl, n is 2 and L^3 is O.
- [0323] In some aspects of Structure (X), the compound has a structure selected from the group consisting of:

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[0324] In various aspects, compounds of Structure (XI) are provided:



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, -CN, halogen, C_1 - C_4 straight or branched alkyl, -O-(C_3 - C_5 cycloalkyl),
-O-(C_1 - C_4 straight or branched alkyl) wherein:

the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom; and

when R^1 is not H, -CN or halogen, it is optionally substituted with one or more
halogens;

each R^2 is independently H, halogen or C_1 - C_4 straight or branched alkyl;

R^3 is H, -OH, or halogen;

R^{21} is cyclobutyl, azetidin-1-yl, or cyclopropyl;

R^{22} is H, halogen, C_1 - C_2 alkyl; and

R^{351} is C_1 - C_2 alkyl or C_2 -O-(C_1 or C_2 alkyl).

[0325] In some aspects of Structure (XI), R^3 is H or halogen.

[0326] In some aspects of Structure (XI), R^1 is halogen, -CN or C_1 - C_2 haloalkyl.

[0327] In some aspects of Structure (XI), R^{21} is C_3 - C_4 cycloalkyl and R^{22} is C_1 - C_2 alkyl.

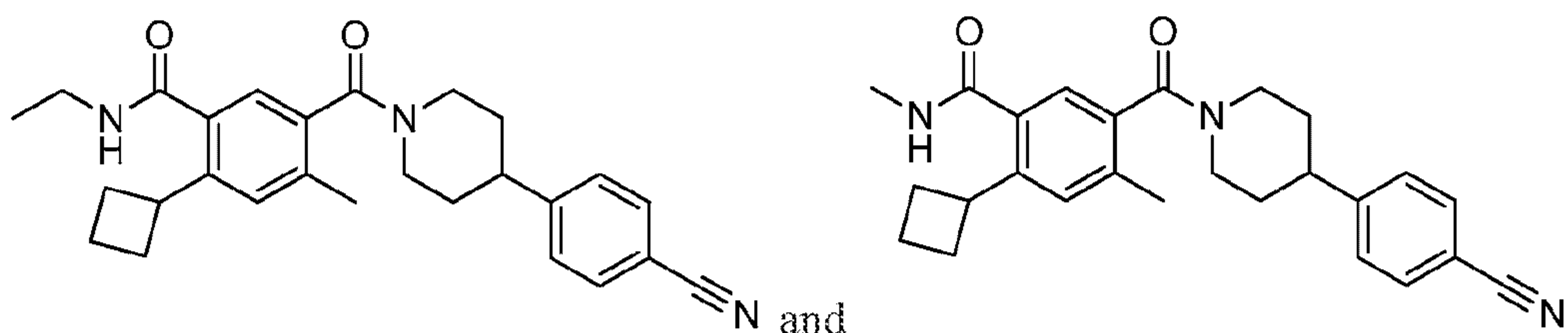
[0328] In some aspects of Structure (XI), R^{21} is cyclobutyl and R^{22} is C_1 - C_2 alkyl.

[0329] In some aspects of Structure (XI), R^{21} is cyclobutyl.

[0330] In some aspects of Structure (XI), R^3 is H or F.

[0331] In some aspects of Structure (XI), R^1 is -CN.

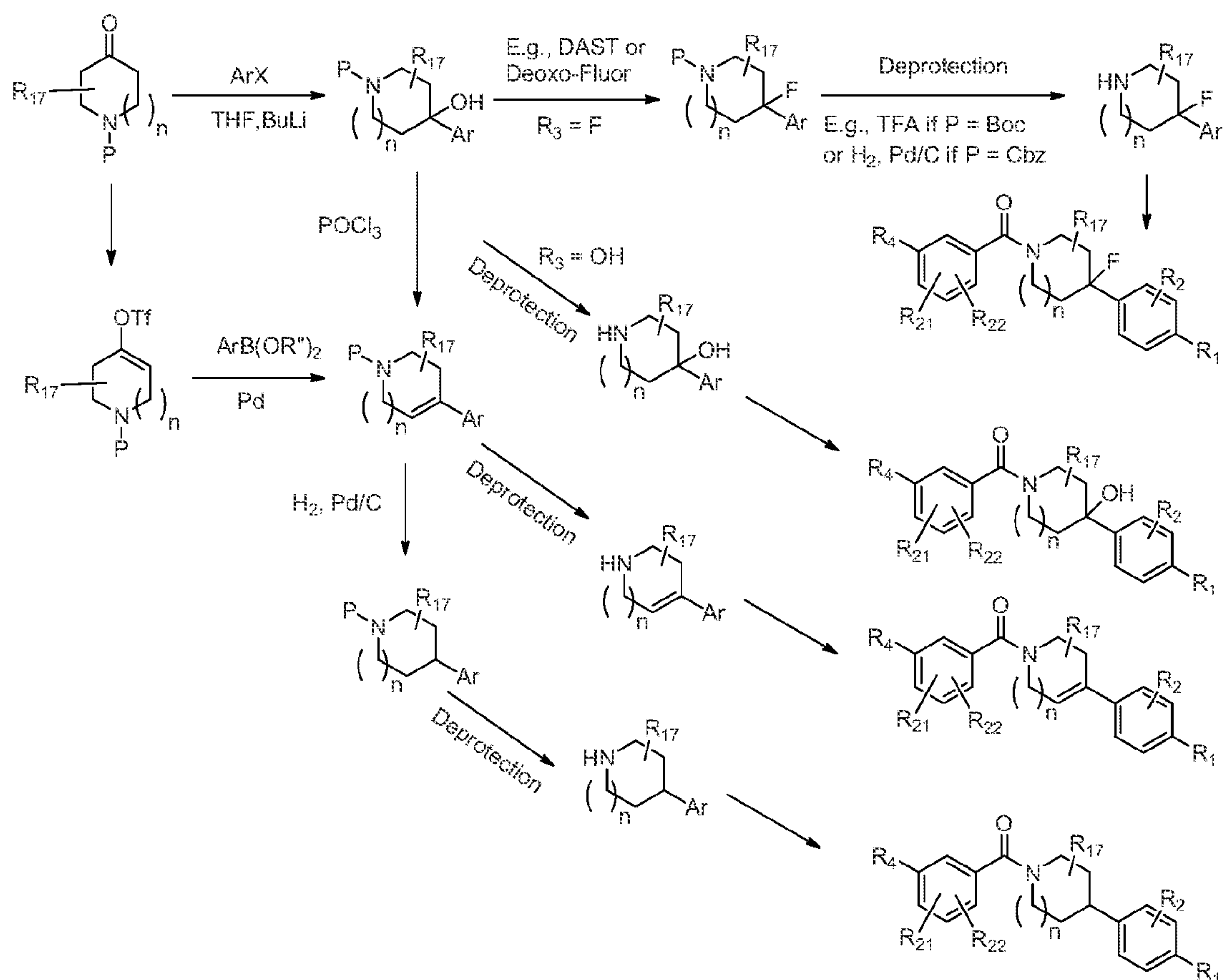
- [0332] In some aspects of Structure (XI), R^1 is $-\text{CF}_3$.
- [0333] In some aspects of Structure (XI), R^{22} is H, methyl or ethyl.
- [0334] In some aspects of Structure (XI), R^{22} is H.
- [0335] In some aspects of Structure (XI), R^{22} is methyl.
- [0336] In some aspects of Structure (XI), R^1 is $-\text{CN}$, each R^2 is H, R^3 is H or F, R^{21} is cyclobutyl, R^{22} is methyl and R^{351} is methyl or ethyl.
- [0337] In some aspects of Structure (XI), the compound has a structure selected from the group consisting of:



- [0338] In certain aspects, the present disclosure provides compounds having any one of the structures found in Table 1. According to the present disclosure, the compounds of Table 1 are inhibitors of fatty acid synthase.

Synthesis of Compounds

- [0339] Also described herein are methods of synthesizing the compounds of the present disclosure. Compounds of the present disclosure can be synthesized as indicated in **SYNTHETIC SCHEMES 1-13** below.

Scheme 1

wherein:

R'' is hydrogen or alkyl;

R₁ is hydrogen, cyano, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, -C(=O)N(R₁₃)(R₁₄), -
(CH₂)_qC(=O)N(R₁₃)(R₁₄), CF₃, -OCF₃, or -S(=O)₂R₂₀;

q is 0, 1, 2, 3, or 4;

R₂₀ is hydrogen or C₁₋₆ alkyl, C₁₋₆ alkoxy, or -N(R₁₃)(R₁₄);

R₂ is hydrogen, halo, C₁₋₆ alkoxy, or C₁₋₆ alkyl;

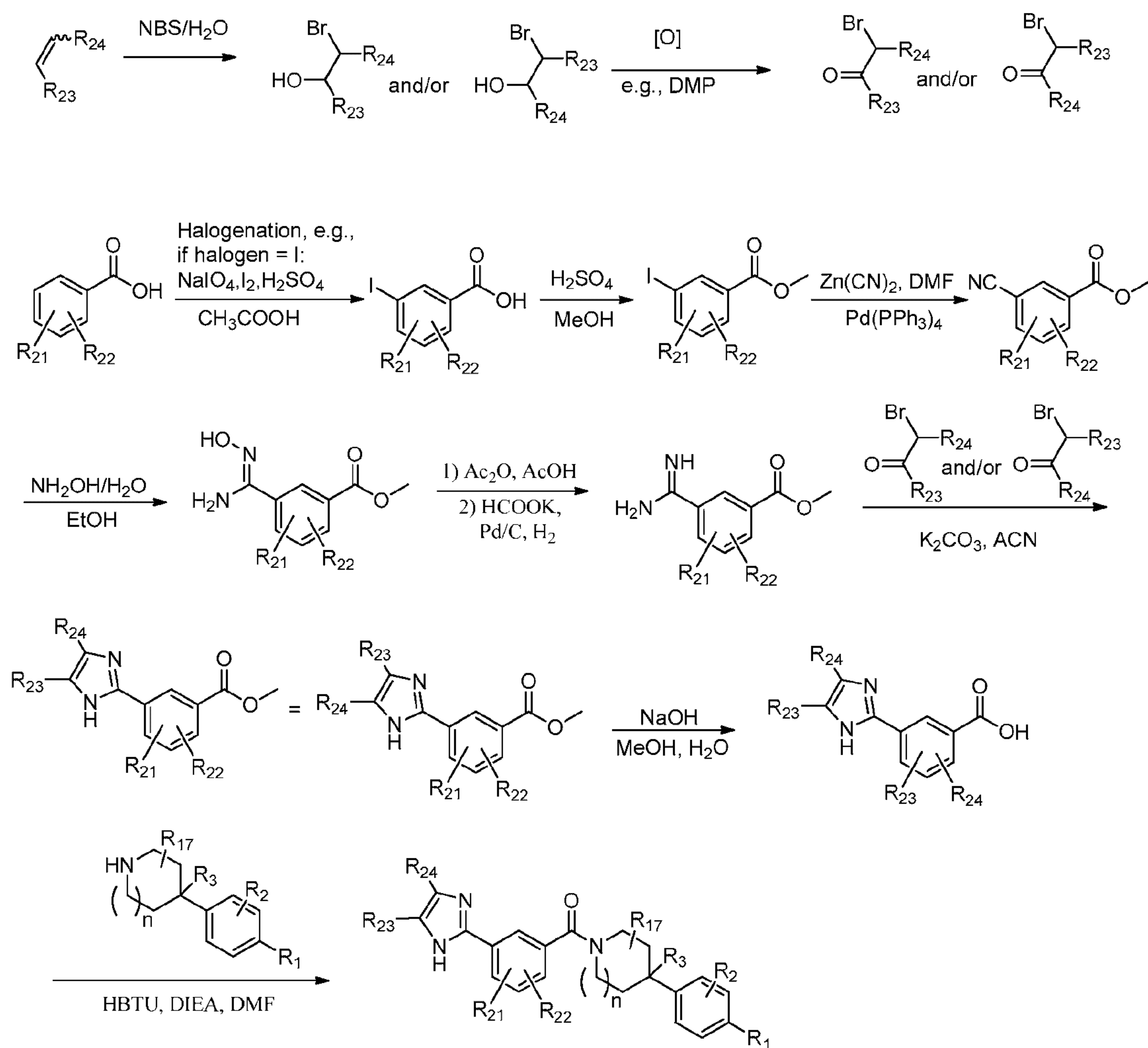
R₃ is hydrogen, hydroxyl, halo, C₁₋₆ alkyl, or C₁₋₆ alkoxy;

R₂₁ and R₂₂ are each independently hydrogen, halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy,
CF₃, -OCF₃, or -S(=O)₂R₂₀;

R₁₃ and R₁₄ are each independently hydrogen, C₁₋₆ alkyl, cycloalkyl, aryl,
heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, -N(R₁₅)(R₁₆), or -S(=O)₂R₂₀;

R₁₅ and R₁₆ are each independently hydrogen, C₁₋₆ alkyl, cycloalkyl, aryl,
heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino; and

R₁₇ is hydrogen or alkyl.

Scheme 2

wherein:

R₁ is hydrogen, cyano, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, -C(=O)N(R₁₃)(R₁₄), -
(CH₂)_qC(=O)N(R₁₃)(R₁₄), CF₃, -OCF₃, or -S(=O)₂R₂₀;

q is 0, 1, 2, 3, or 4;

R₂₀ is hydrogen or C₁₋₆ alkyl, C₁₋₆ alkoxy, or -N(R₁₃)(R₁₄);

R₂ is hydrogen, halo, C₁₋₆ alkoxy, or C₁₋₆ alkyl;

R₃ is hydrogen, hydroxyl, halo, C₁₋₆ alkyl, or C₁₋₆ alkoxy;

R₂₁ and R₂₂ are each independently hydrogen, halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy,
CF₃, -OCF₃, or -S(=O)₂R₂₀;

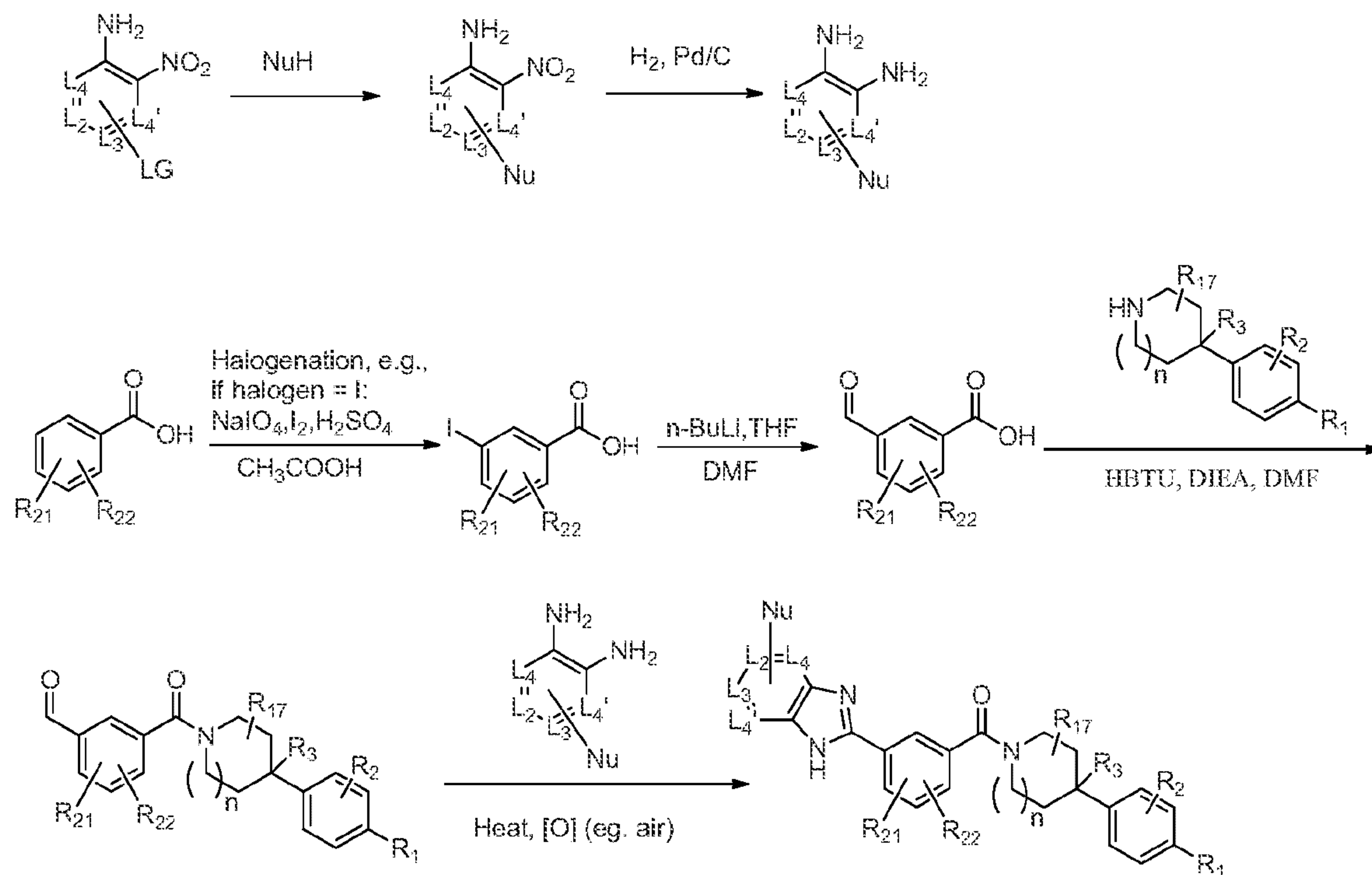
R₁₃ and R₁₄ are each independently hydrogen, C₁₋₆ alkyl, cycloalkyl, aryl,
heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, -N(R₁₅R₁₆), or -S(=O)₂R₂₀;

R₁₅ and R₁₆ are each independently hydrogen, C₁₋₆ alkyl, cycloalkyl, aryl,
heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino;

R_{23} is hydrogen, $-N(R_{13})(R_{14})$, C_{1-6} alkyl, C_{1-6} alkoxy, is absent if L_1 is N, or R_{23} and R_{24} taken together with the atoms to which they are attached join together to form a heterocyclyl, heteroaryl, or cycloalkyl; and

R_{24} is hydrogen, $-N(R_{13})(R_{14})$, C_{1-6} alkyl, C_{1-6} alkoxy, $-(C_{1-6} \text{ alkoxy})(\text{heterocyclyl})$, heterocyclyl, or R_{23} and R_{24} taken together with the atoms to which they are attached join together to form a heterocyclyl, heteroaryl, or cycloalkyl.

Scheme 3



wherein:

LG is a leaving group;

Nu is a nucleophile;

L_2 , L_3 , L_4 , and L_4' are each independently CH or N;

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$, $-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

q is 0, 1, 2, 3, or 4;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_2 is hydrogen, halo, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, or C_{1-6} alkoxy;

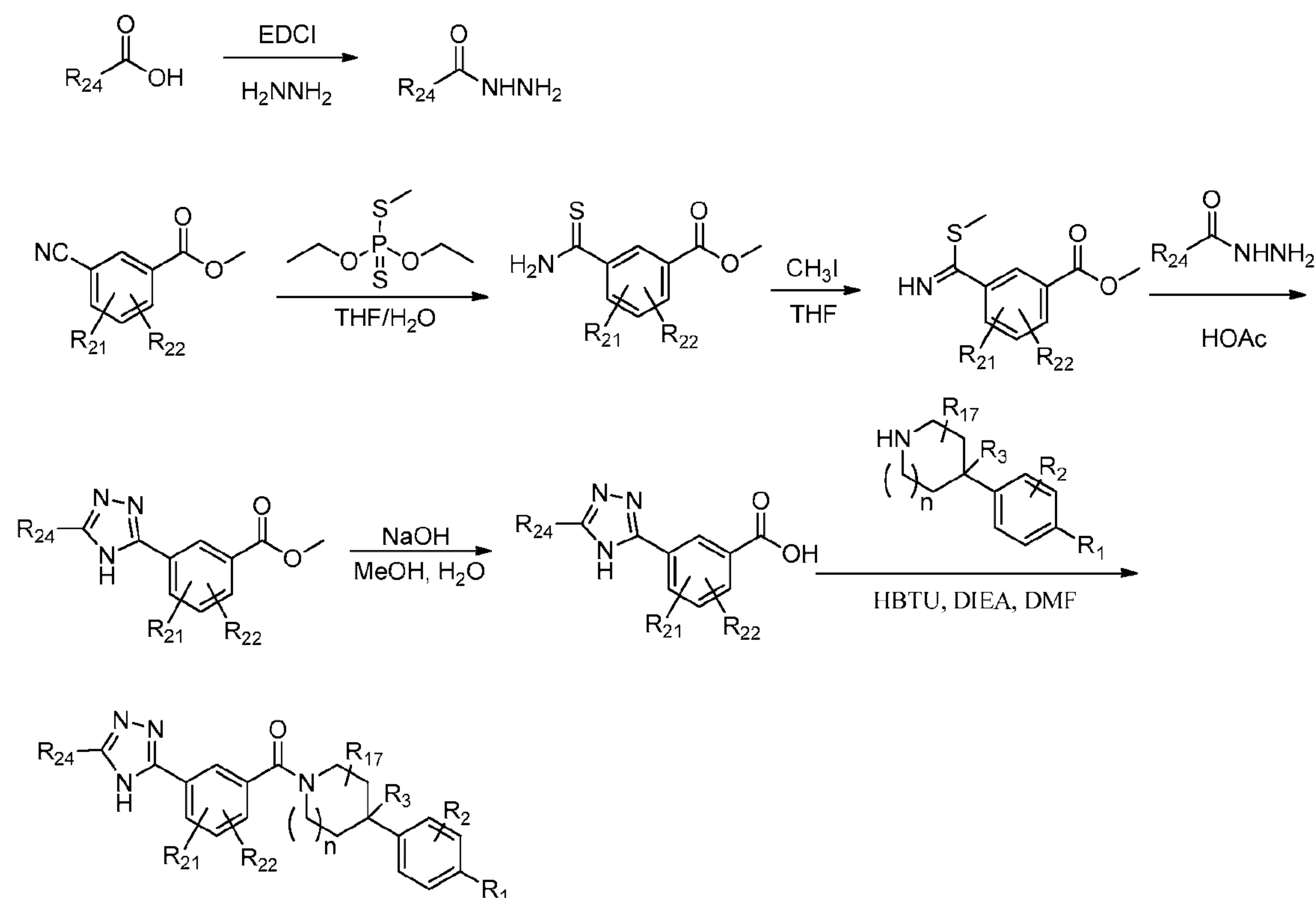
R_{21} and R_{22} are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

R_{13} and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;

R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino; and

R_{17} is hydrogen or alkyl.

Scheme 4



wherein:

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$, $-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

q is 0, 1, 2, 3, or 4;

R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;

R_2 is hydrogen, halo, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_{21} and R_{22} are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;

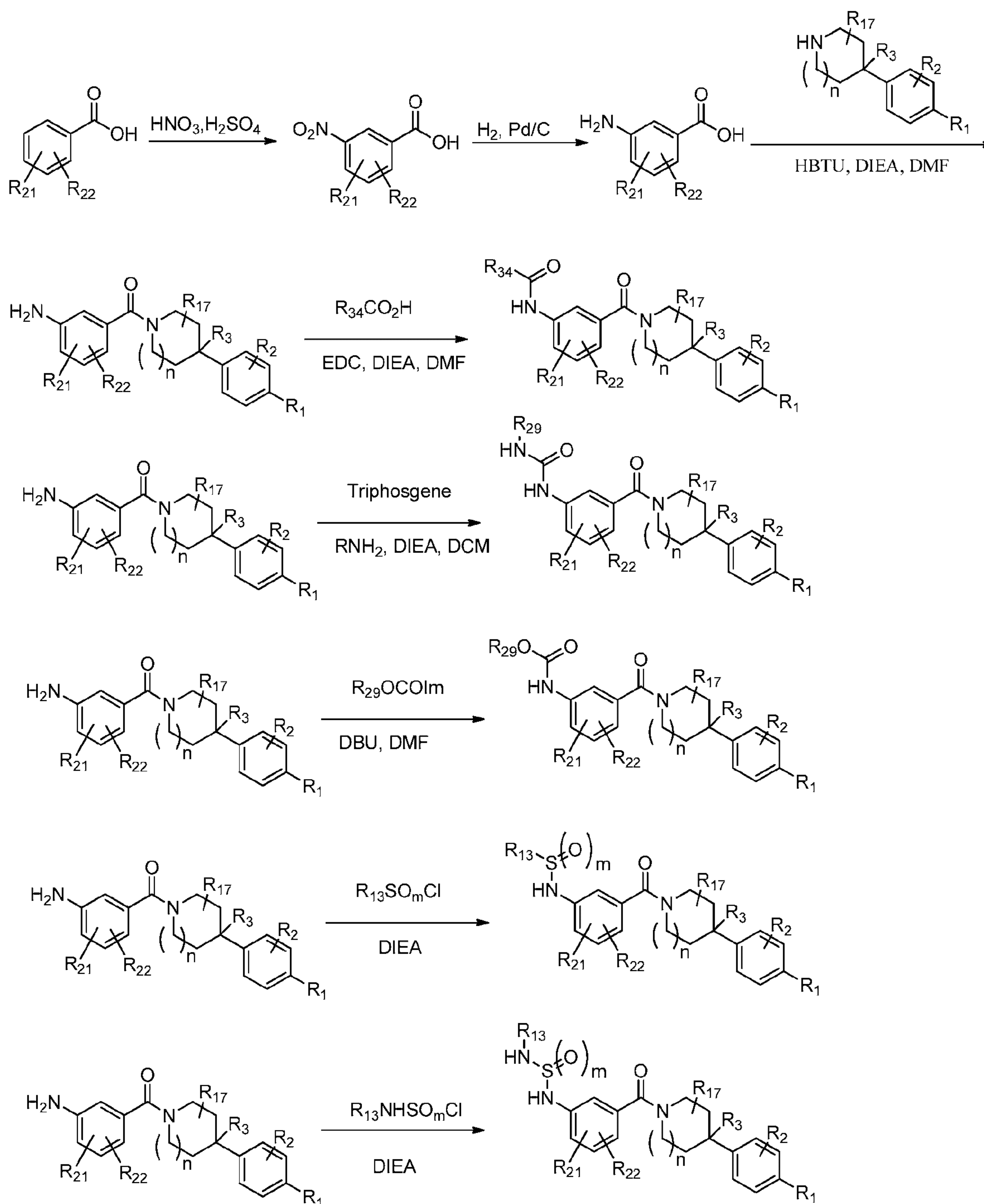
R_{13} and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;

R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino;

R_{17} is hydrogen or alkyl; and

R_{24} is hydrogen, $-N(R_{13})(R_{14})$, C_{1-6} alkyl, C_{1-6} alkoxy, $-(C_{1-6} \text{ alkoxy})(\text{heterocyclyl})$, or heterocyclyl.

Scheme 5



wherein:

R_1 is hydrogen, cyano, halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(=O)N(R_{13})(R_{14})$,
 $-(CH_2)_qC(=O)N(R_{13})(R_{14})$, CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;
 q is 0, 1, 2, 3, or 4;
 R_{20} is hydrogen or C_{1-6} alkyl, C_{1-6} alkoxy, or $-N(R_{13})(R_{14})$;
 R_2 is hydrogen, halo, C_{1-6} alkoxy, or C_{1-6} alkyl;
 R_3 is hydrogen, hydroxyl, halo, C_{1-6} alkyl, or C_{1-6} alkoxy;
 R_{21} and R_{22} are each independently hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy,
 CF_3 , $-OCF_3$, or $-S(=O)_2R_{20}$;
 R_{13} and R_{14} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl,
heterocyclyl, heteroaryl, hydroxyalkyl, alkylamino, $-N(R_{15}R_{16})$, or $-S(=O)_2R_{20}$;
 R_{15} and R_{16} are each independently hydrogen, C_{1-6} alkyl, cycloalkyl, aryl,
heterocyclyl, heteroaryl, hydroxyalkyl, or alkylamino;
 R_{17} is hydrogen or alkyl;
 R_{24} is hydrogen, $-N(R_{13})(R_{14})$, C_{1-6} alkyl, C_{1-6} alkoxy, $-(C_{1-6} \text{ alkoxy})(\text{heterocyclyl})$, or
heterocyclyl;
 R_{29} is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxyalkyl, heteroaryl, heterocyclyl,
 $-N(R_{15}R_{16})$, $-C(=O)R_{46}$, or $-R_{48}C(=O)R_{47}$;
 R_{34} is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, cycloalkyl, hydroxyl, hydroxyalkyl, aryl,
heterocyclyl, heteroaryl, alkylamino, CF_3 , $-OCF_3$, $-S(=O)_2R_{20}$, or $-N(R_{15}R_{16})$; and
 m 0, 1, or 2.

[0340] Schemes 6-13 provides a synthesis for exemplary compounds of formula IX
wherein:

R^1 is H, -CN, halogen, C_1 - C_4 straight or branched alkyl, $-O-(C_3$ - C_5 cycloalkyl),
 $-O-(C_1$ - C_4 straight or branched alkyl) wherein:
 C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom; and
when R^1 is not H, -CN or halogen, it is optionally substituted with one or more
halogens;

each R^2 is independently hydrogen, halogen or C_1 - C_4 straight or branched alkyl;

R^3 is H, -OH, or halogen;

R^{21} is H, halogen, C_1 - C_4 straight or branched alkyl, C_3 - C_5 cycloalkyl wherein the C_3 - C_5
cycloalkyl optionally includes an oxygen or nitrogen heteroatom;

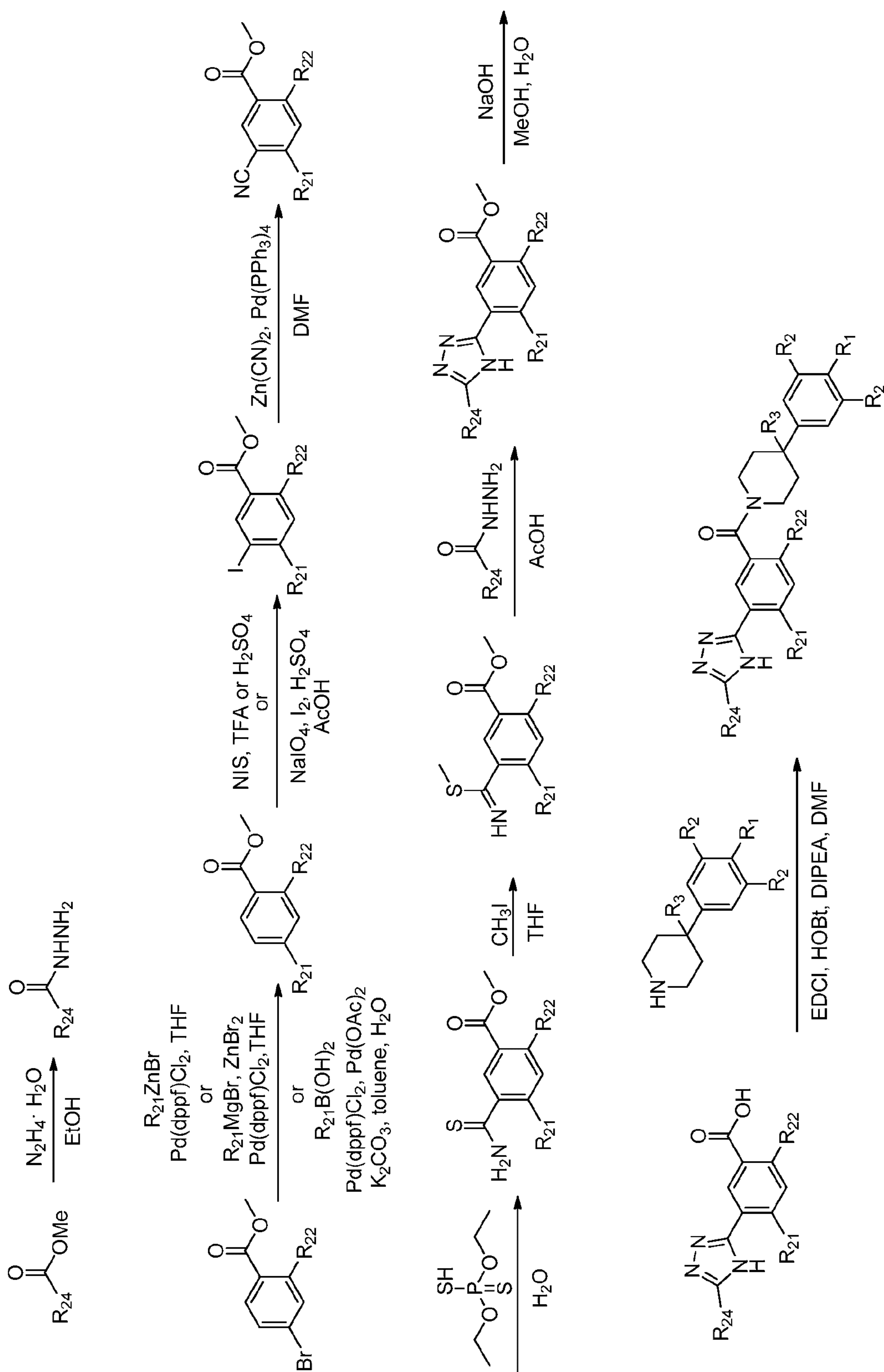
R^{22} is H, halogen, or C_1 - C_2 alkyl;

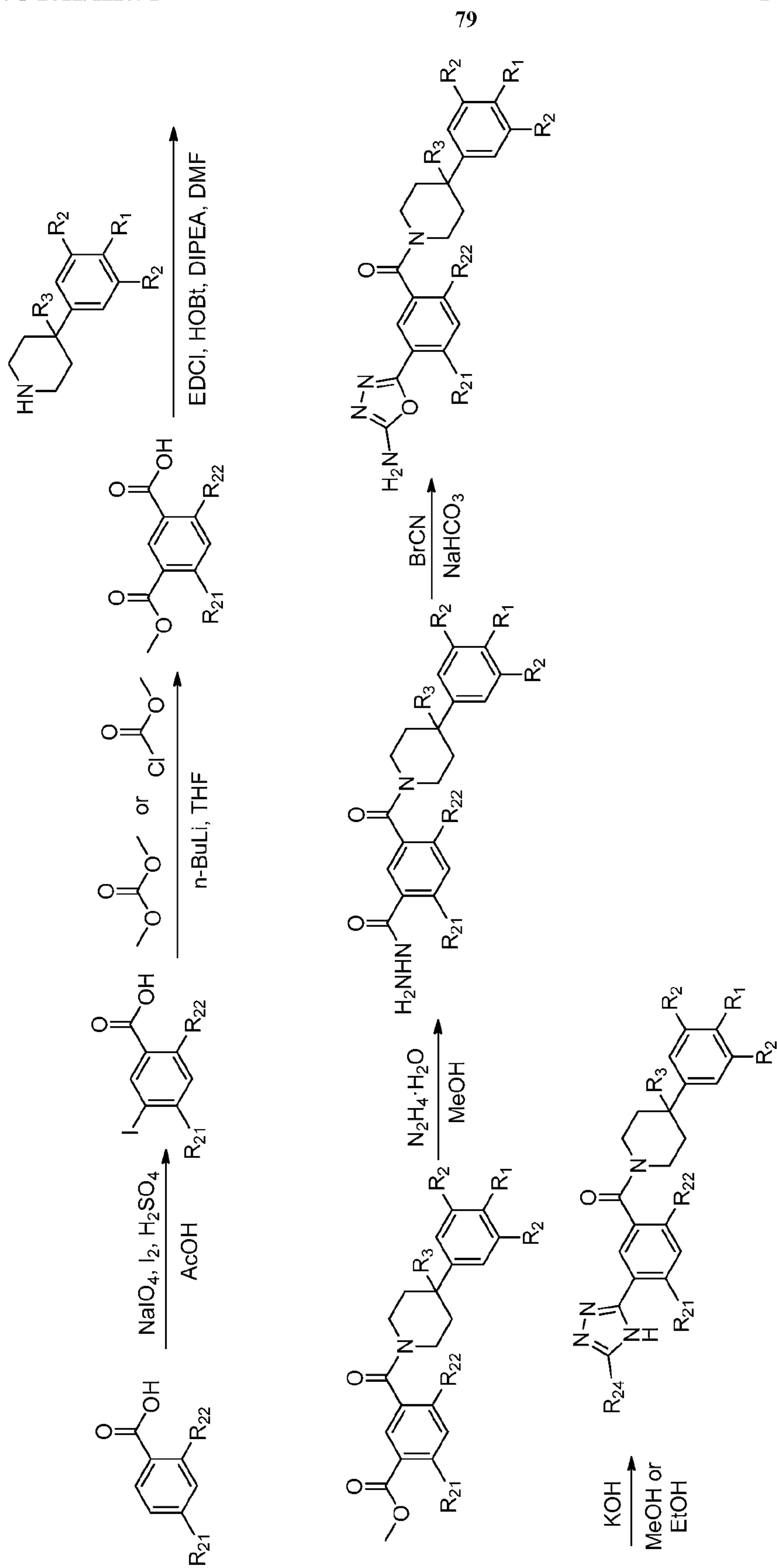
R^{23} is H or C_1 - C_4 straight or branched alkyl; and

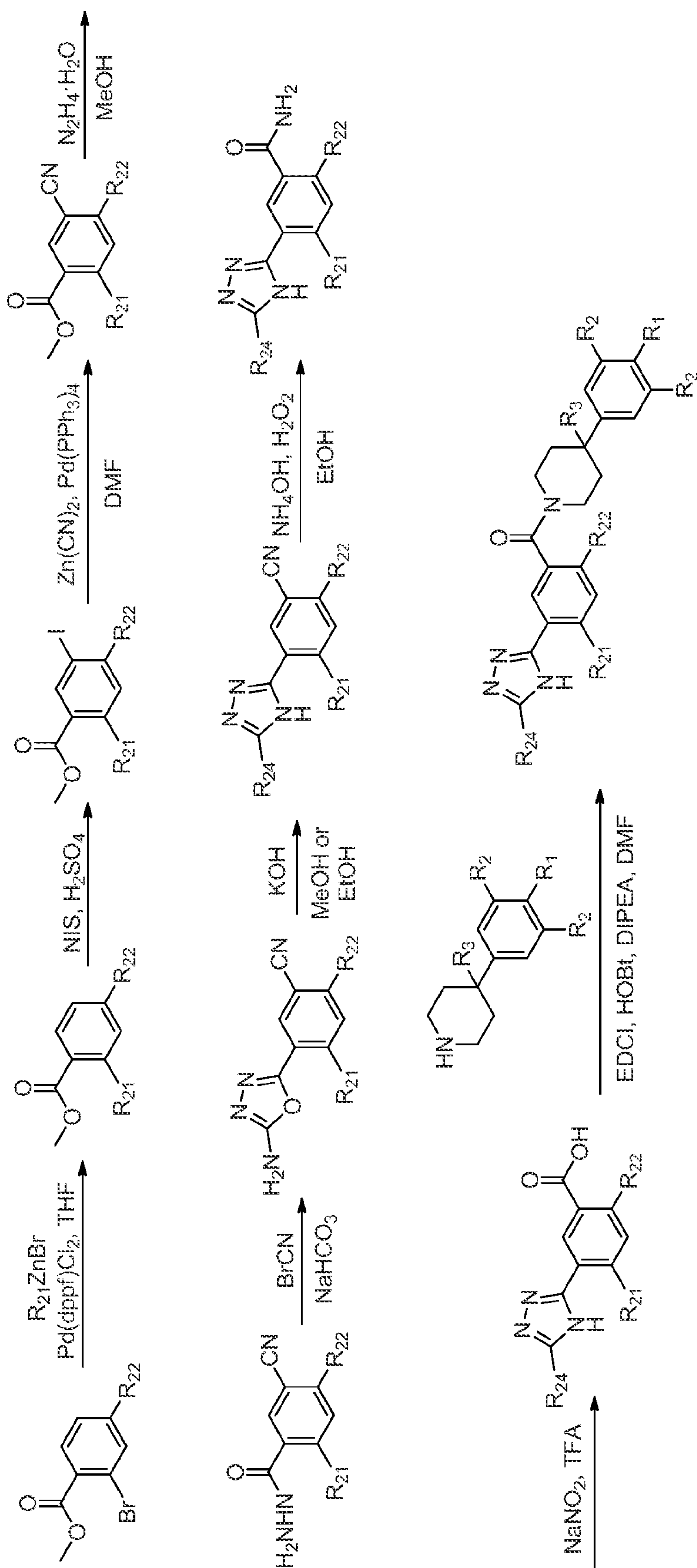
R^{24} is H, C_1 - C_4 straight or branched alkyl, $-(C_1-C_4 \text{ alkyl})_t-OH$,
 $-(C_1-C_4 \text{ alkyl})_t-O_t-(C_3-C_5 \text{ cycloalkyl})$, or $-(C_1-C_4 \text{ alkyl})_t-O-(C_1-C_4 \text{ straight or branched alkyl})$ wherein:

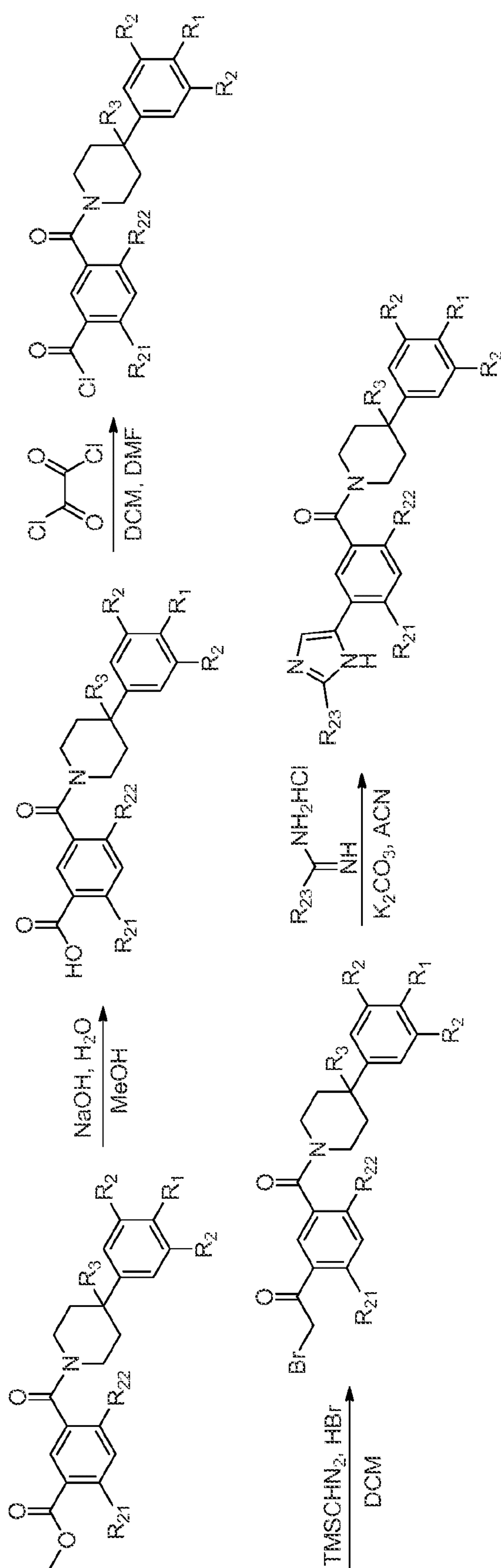
t is 0 or 1; and

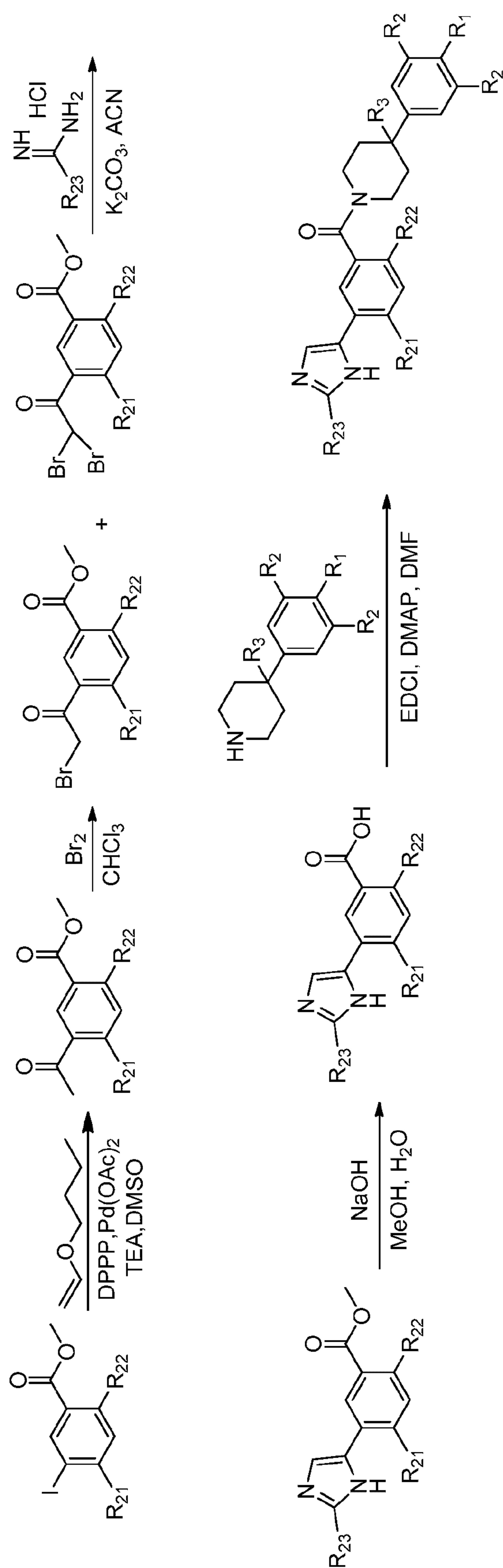
the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom.

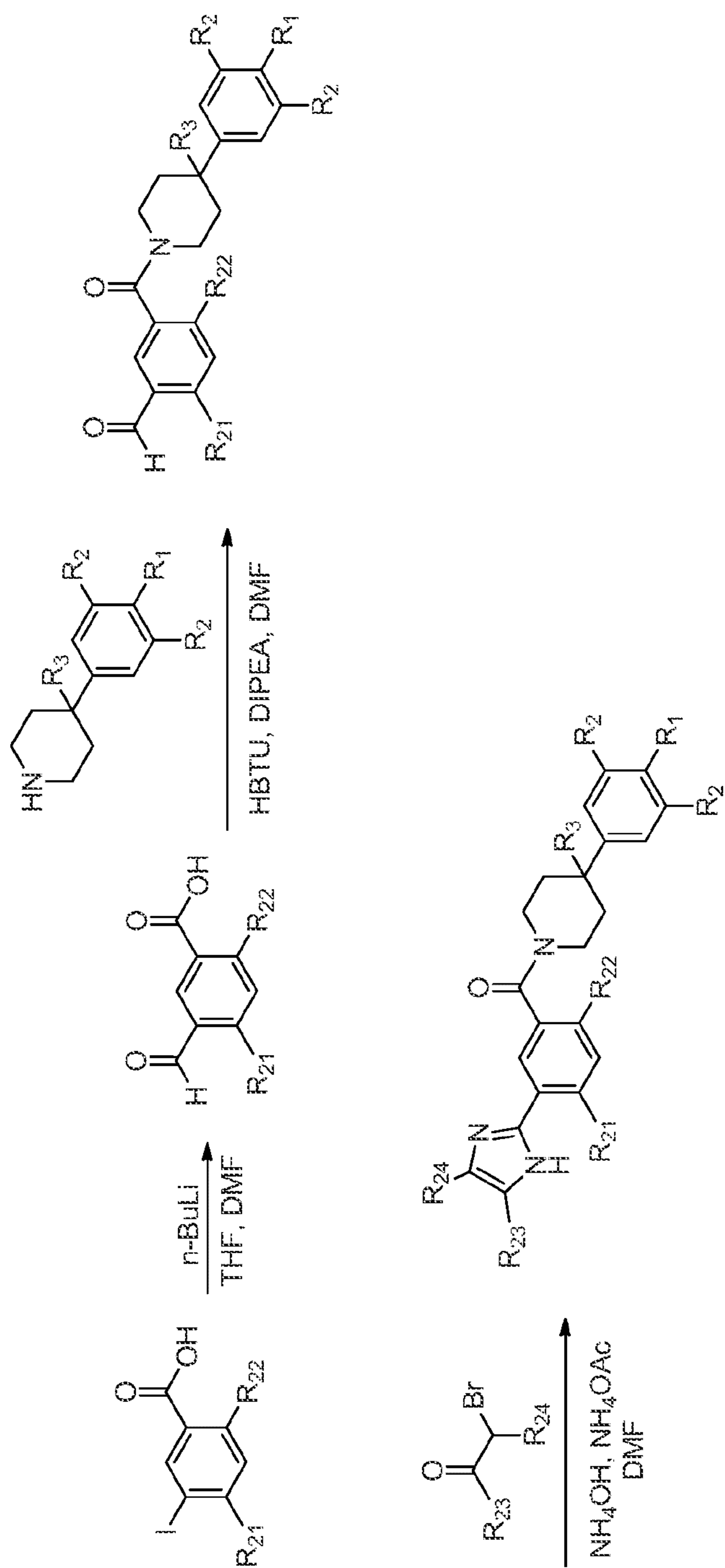


Scheme 7

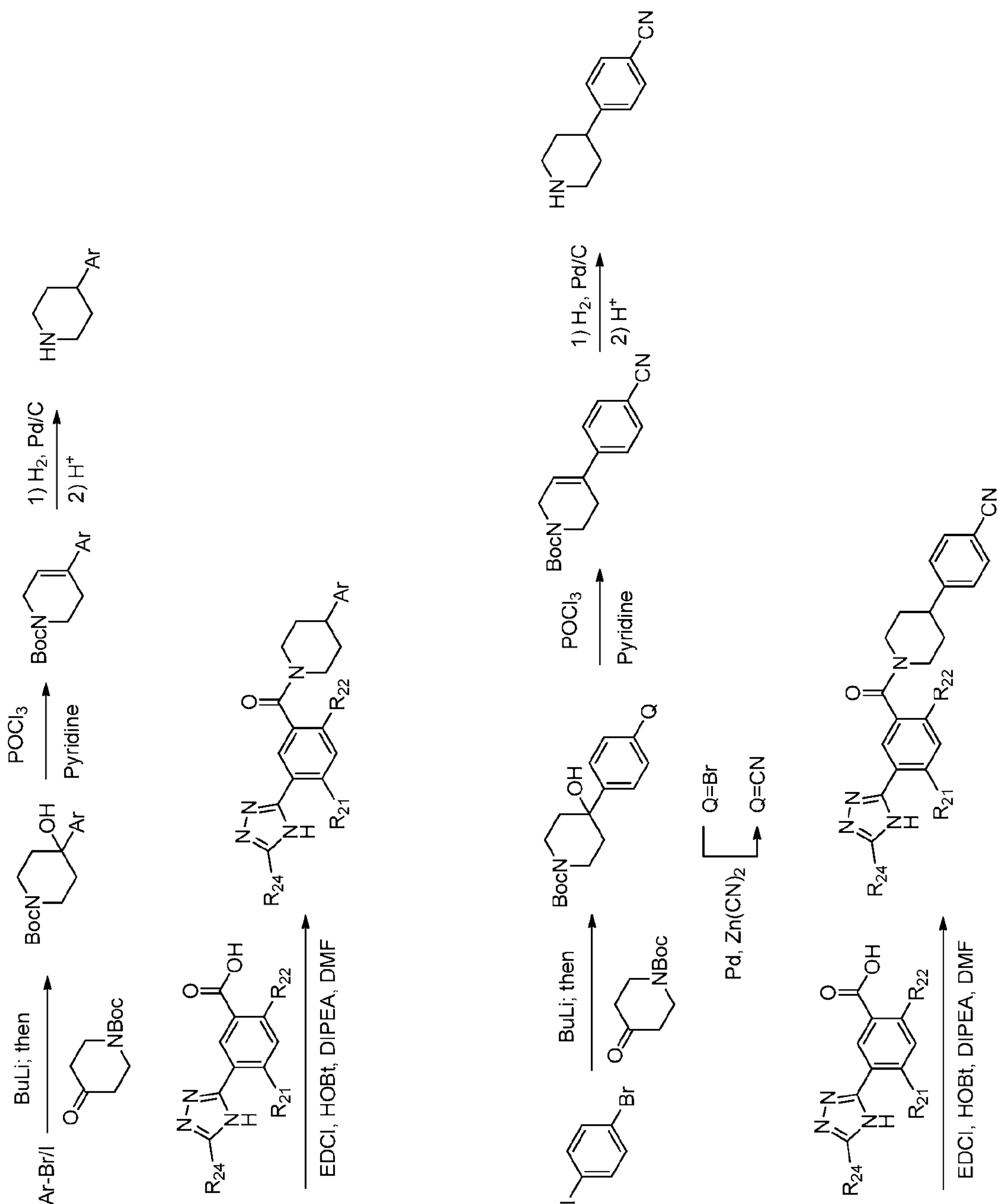


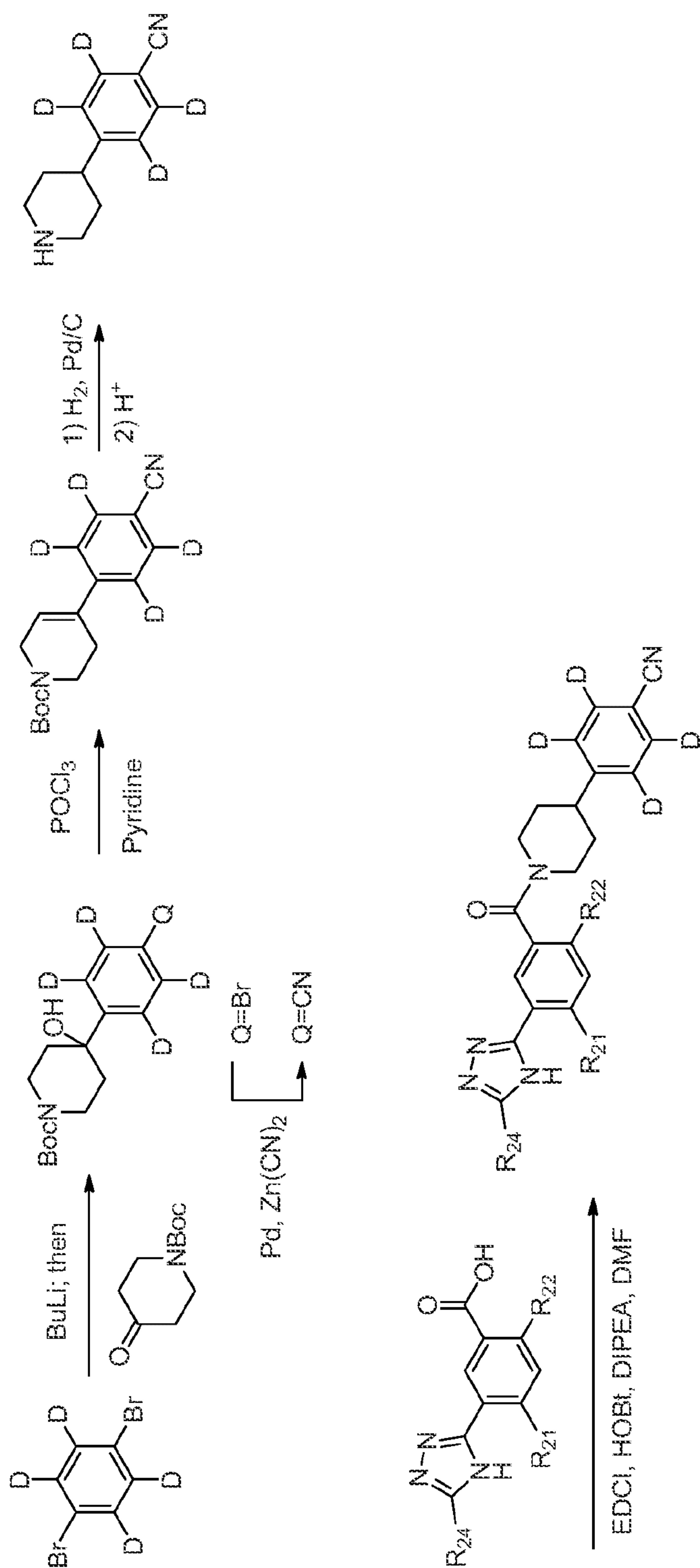
Scheme 9

Scheme 10

Scheme 11

Scheme 12



Scheme 13

[0341] Additional methods for producing particular compounds according to the present disclosure are provided in the **EXAMPLES**. One skilled in the art will recognize that other compounds of structures can be made by modifications to the specifically disclosed schemes employing methods known to those of skill in the art. Additional examples can be found in Table 1.

[0342] Many such techniques are well known in the art. However, many of the known techniques are elaborated in Compendium of Organic Synthetic Methods (Vol. 1, 1971; Vol. 2, 1974; Vol. 3, 1977; Vol. 4, 1980; Vol. 5, 1984; and Vol. 6 as well as March in Advanced Organic Chemistry (1985); Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes (1993); Advanced Organic Chemistry Part B: Reactions and Synthesis, Second Edition (1983); Advanced Organic Chemistry, Reactions, Mechanisms, and Structure, Second Edition (1977); Protecting Groups in Organic Synthesis, Second Edition; and Comprehensive Organic Transformations (1999).

Viral Infection Pathways

[0343] The host cell targets inhibited by the present compounds and methods play a role in the viral replication and/or infection pathways. Targeting of such host cell targets modulates the replication and/or infection pathways of the viruses. In preferred aspects the identified host cell targets are directly or indirectly modulated using the compositions of the present disclosure. The modulation of such host cell targets can also be performed by targeting entities in the upstream or downstream signaling pathways of the host cell targets.

[0344] According to the present disclosure, viral infection can be treated by targeting the fatty acid synthesis pathway, and in particular fatty acid synthase. HRV is representative of viruses that can be treated according to the present disclosure. Like other viruses, the replication of HRV involves six phases; transmission, entry, replication, biosynthesis, assembly, and exit. Entry occurs by endocytosis, replication and vRNP assembly takes place in the nucleus, and the virus buds from the plasma membrane. In the infected patient, the virus targets airway epithelial cells. The present compounds and methods target and modulate at least one host cell targets involved in such pathways.

[0345] For some viruses a great deal of progress has been made in the elucidation of the steps involved during infection of host cells. For example, experiments initiated in the early 1980s showed that influenza virus follows a stepwise, endocytic entry program with elements shared with other viruses such as alpha-and rhabdoviruses (Marsh and Helenius 1989; Whittaker 2006). The steps include: 1) Initial attachment to sialic acid containing glycoconjugates receptors on the cell surface; 2) signaling induced by the virus particle; 3)

endocytosis by clathrin-dependent and clathrin-independent cellular mechanism; 4) acid-induced, hemagglutinin (HA)-mediated penetration from late endosomes; 5) acid-activated, M2 and matrix protein (M1) dependent uncoating of the capsid; and, 6) intra-cytosolic transport and nuclear import of vRNPs. These steps depend on assistance from the host cell in the form of sorting receptors, vesicle formation machinery, kinase-mediated regulation, organelle acidification, and, most likely, activities of the cytoskeleton.

[0346] Influenza attachment to the cells surface occurs via binding of the HA1 subunit to cell surface glycoproteins and glycolipids that carry oligosaccharide moieties with terminal sialic acid residues (Skehel and Wiley 2000). The linkage by which the sialic acid is connected to the next saccharide contributes to species specificity. Avian strains including H5N1 prefer an α -(2,3)-link and human strains α -(2,6)-link (Matrosovich 2006). In epithelial cells, binding occurs preferentially to microvilli on the apical surface, and endocytosis occurs at base of these extensions (Matlin 1982). Whether receptor binding induces signals that prepare the cell for the invasion is not yet known, but it is likely because activation of protein kinase C and synthesis of phosphatidylinositol-3-phosphate (PI3P) are required for efficient entry (Sieczkarski et al. 2003; Whittaker 2006).

[0347] Endocytic internalization occurs within a few minutes after binding (Matlin 1982; Yoshimura and Ohnishi 1984). In tissue culture cells influenza virus makes use of three different types of cellular processes; 1) preexisting clathrin coated pits, 2) virus-induced clathrin coated pits, and 3) endocytosis in vesicles without visible coat (Matlin 1982; Sieczkarski and Whittaker 2002; Rust et al. 2004). Video microscopy using fluorescent viruses showed the virus particles undergoing actin-mediated rapid motion in the cell periphery followed by minus end-directed, microtubule-mediated transport to the perinuclear area of the cell. Live cell imaging indicated that the virus particles first entered a subpopulation of mobile, peripheral early endosomes that carry them deeper into the cytoplasm before penetration takes place (Lakadamyali et al. 2003; Rust et al. 2004). The endocytic process is regulated by protein and lipid kinases, the proteasome, as well as by Rabs and ubiquitin-dependent sorting factors (Khor et al. 2003; Whittaker 2006).

[0348] The membrane penetration step is mediated by low pH-mediated activation of the trimeric, metastable HA, and the conversion of this Type I viral fusion protein to a membrane fusion competent conformation (Maeda et al. 1981; White et al. 1982). This occurs about 16 min after internalization, and the pH threshold varies between strains in the 5.0-5.6 range. The target membrane is the limiting membrane of intermediate or late endosomes. The mechanism of fusion has been extensively studied (Kielian and Rey 2006). Further it was

observed that fusion itself does not seem to require any host cell components except a lipid bilayer membrane and a functional acidification system (Maeda et al. 1981; White et al. 1982). The penetration step is inhibited by agents such as lysosomotropic weak bases, carboxylic ionophores, and proton pump inhibitors (Matlin 1982; Whittaker 2006).

[0349] To allow nuclear import of the incoming vRNPs, the capsid has to be disassembled. This step involves acidification of the viral interior through the amantadine-sensitive M2-channels causes dissociation of M1 from the vRNPs (Bukrinskaya et al. 1982; Martin and Helenius 1991; Pinto et al. 1992). Transport of the individual vRNPs to the nuclear pore complexes and transfer into the nucleus depends on cellular nuclear transport receptors (O'Neill et al. 1995; Cros et al. 2005). Replication of the viral RNAs (synthesis of positive and negative strands), and transcription occurs in complexes tightly associated with the chromatin in the nucleus. It is evident that, although many of the steps are catalyzed by the viral polymerase, cellular factors are involved including RNA polymerase activating factors, a chaperone HSP90, hCLE, and a human splicing factor UAP56. Viral gene expression is subject to complex cellular control at the transcriptional level, a control system dependent on cellular kinases (Whittaker 2006).

[0350] The final assembly of an influenza particle occurs during a budding process at the plasma membrane. In epithelial cells, budding occurs at the apical membrane domain only (Rodriguez-Boulan 1983). First, the progeny vRNPs are transported within the nucleoplasm to the nuclear envelope, then from the nucleus to the cytoplasm, and finally they accumulate in the cell periphery. Exit from the nucleus is dependent on viral protein NEP and M1, and a variety of cellular proteins including CRM1 (a nuclear export receptor), caspases, and possibly some nuclear protein chaperones. Phosphorylation plays a role in nuclear export by regulating M1 and NEP synthesis, and also through the MAPK/ERK system (Bui et al. 1996; Ludwig 2006). G protein and protein kinase signaling is involved in influenza virus budding from infected host cells (Hui E. and Nayak D, 2002).

[0351] The three membrane proteins of the virus are synthesized, folded and assembled into oligomers in the ER (Doms et al. 1993). They pass through the Golgi complex; undergo maturation through modification of their carbohydrate moieties and proteolytic cleavage. After reaching the plasma membrane they associate with M1 and the vRNPs in a budding process that results in the inclusion of all eight vRNPs and exclusion of most host cell components except lipids.

[0352] Influenza infection is associated with activation of several signaling cascades including the MAPK pathway (ERK, JNK, p38 and BMK-1/ERK5), the I κ B/NF- κ B signaling

module, the Raf/MEK/ERK cascade, and programmed cell death (Ludwig 2006). These result in a variety of effects that limit the progress of infection such as transcriptional activation of IFN β , apoptotic cell death, and a block in virus escape of from late endosomes (Ludwig 2006).

[0353] Most previous studies on virus-cell interactions were performed in tissue culture using tissue culture- or egg-adapted virus strains. The viruses in these examples were adapted in such a manner that changes were induced that affected receptor binding and tropism (Matrosovich 2006). Infection with wild-type pathogenic strains provides a more natural picture of viral interaction with host proteins. It is known that in the human airways influenza A and B primarily infect non ciliated epithelial cells in the upper respiratory track carrying NeuSAc α -(2,6)-Gal, whereas avian strains infect ciliated epithelial cell with α -(2,3)-linked sialic acids deeper in the airways (Matrosovich et al. 2004a).

[0354] Additionally, progress has been made in the elucidation of the steps involved during infection by HRV of host cells. Selected events in rhinovirus infection of the normal human airway can be regarded as occurring sequentially. Initial steps in rhinovirus pathogenesis are believed to include viral entry through the nose, mucociliary transport of virus to the posterior pharynx, and initiation of infection in ciliated and non-ciliated epithelial cells of the upper airway. Viral replication peaks on average within 48 h of initiation of infection and persists for up to 3 wk. Infection is followed by activation of several inflammatory mechanisms, which can include release or generation of interleukins, bradykinins, prostaglandins, and possibly histamine and stimulation of parasympathetic reflexes. Pathophysiologic processes are initiated, which include vasodilatation of nasal blood vessels, transudation of plasma, glandular secretion, and stimulation of nerve fibers, causing pain and triggering sneeze and cough reflexes. The resultant clinical illness is a rhinosinusitis, pharyngitis, and bronchitis, which, on average, lasts one week.

[0355] Changes in gene expression profiles during *in vivo* rhinovirus infections have been identified (Proud D. et al. Am J Respir Crit Care Med Vol 178. pp 962–968, 2008). Nasal epithelial scrapings were obtained before and during experimental rhinovirus infection, and gene expression was evaluated by microarray. Viperin is identified as an antiviral protein induced by interferon (IFN), viral infections, and pathogen-associated molecules. Naturally acquired rhinovirus infections, cultured human epithelial cells, and short interfering RNA knockdown were used to further evaluate the role of viperin in rhinovirus infections. Symptom scores and viral titers were measured in subjects inoculated with rhinovirus or a sham control, and changes in gene expression were assessed 8 and 48 hours after inoculation.

Rhinovirus-induced changes in gene expression were not observed 8 hours after viral infection, but 11,887 gene transcripts were significantly altered in scrapings obtained 2 days post-inoculation. Major groups of up-regulated genes include chemokines, signaling molecules, interferon-responsive genes, and antivirals. Rhinovirus infection significantly alters the expression of many genes associated with the immune response, including chemokines and antivirals. Some of the genes markedly induced by HRV-16 infection include but are not limited to CCL2, CCL8, CXCL11, CXCL10, CXCL13, CXCL9, CCL20, IFIT2, GBP1, IFIT1, GIP2, IFIT4, IL28B, IRF7, CIG5, NOS2A, OAS3, OASL, OAS2, OAS1, MX2, MX1, PLSCR1, SOCS1, SOCS2, MDA5, RIGI, SOCS3, ICAM-1, HAPLN3, MMP12, EPSTI1, and TNC.

Fatty Acid Synthesis Pathway

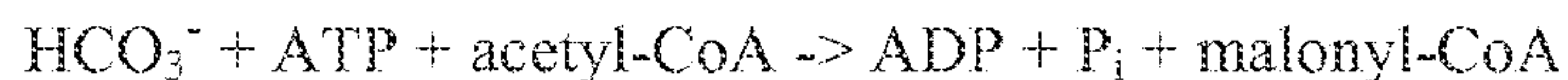
[0356] Various aspects of the present disclosure relate to compositions and methods that modulate the activity of the fatty acid synthesis pathway to treat a viral infection or treat cancer. The fatty acid synthesis pathway in humans can use four enzymes: 1) acetyl-CoA carboxylase (ACC), which can synthesize malonyl-CoA; 2) malic enzyme, which can produce NADPH; 3) citrate lyase, which can synthesize acetyl-CoA; and 4) fatty acid synthase, which can catalyze NADPH-dependent synthesis of fatty acids from acetyl-CoA and malonyl-CoA. In various aspects, the present disclosure relates to treatment of viral infections and cancer by modulating the activity of the fatty acid synthase protein.

[0357] The final products of fatty acid synthase are free fatty acids which can use separate enzymatic derivatization with coenzyme-A for incorporation into other products. In humans, fatty acid synthesis can occur in two sites: the liver, where palmitic acid can be made (Roncari, (1974) *Can. J. Biochem.*, 52:221-230) and lactating mammary gland, where C₁₀-C₁₄ fatty acids can be made (Thompson, et al., (1985) *Pediatr. Res.*, 19:139-143).

[0358] Fatty acids can be synthesized in the cytoplasm from acetyl-CoA. Acetyl-CoA can be generated from pyruvate by pyruvate dehydrogenase (PDH) and by β -oxidation of fatty acids in the mitochondria. A "citrate shuttle" can transport acetyl-CoA from the mitochondria to the cytoplasm. Acetyl-CoA can react with oxaloacetate to yield citrate, and a tricarboxylate translocase can transport citrate from the mitochondria to the cytosol. In the cytoplasm, citrate can be cleaved back to oxaloacetate and acetyl-CoA, a reaction that can be catalyzed by ATP-citrate lyase. Oxaloacetate can be converted back to pyruvate for re-entry into mitochondria.

[0359] Acetyl-CoA can be converted to malonyl-CoA. Acetyl-CoA carboxylase (ACC) is a complex multifunctional, biotin-containing, enzyme system that can catalyze carboxylation

of acetyl-CoA to malonyl-CoA. This conversion is an irreversible, rate-limiting step in fatty acid synthesis. ACC can carry out three functions: biotin carboxyl carrier protein, biotin carboxylase and carboxyltransferase. ATP-dependent carboxylation of biotin, a prosthetic group (cofactor) can be followed by transfer of the carboxyl group to acetyl-CoA.



[0360] There are two ACC forms, alpha and beta, encoded by two different genes *ACC-alpha* (also known as *ACC*, *ACAC*, *ACCI*, *ACCA*, and *ACACA*) can encode protein highly enriched in lipogenic tissues. Multiple alternatively spliced transcript variants divergent in the sequence and encoding distinct isoforms have been found for this gene. *ACC-beta* (also known as *ACC2*, *ACCB*, *HACC275*, and *ACACB*) can encode protein thought to control fatty acid oxidation by means of the ability of malonyl-CoA to inhibit carnitine-palmitoyl-CoA transferase I, the rate-limiting step in fatty acid uptake and oxidation by mitochondria. *ACC-beta* may be involved in the regulation of fatty acid oxidation, rather than fatty acid biosynthesis. There is evidence for the presence of two *ACC-beta* isoforms.

[0361] ACC can be regulated by the phosphorylation/dephosphorylation of targeted serine residues. For example, AMP-activated kinase (AMPK) can phosphorylate ACC, and this phosphorylation can inhibit the ability of ACC to produce malonyl-CoA. On *ACACA*, AMPK can phosphorylate Ser79, Ser1200, and Ser1215 (Park S.H. et al. (2002) *J. Appl. Physiol.* 92:2475-82). AMPK can phosphorylate Ser218 on *ACACB* (Hardie D.G. (1992) *Biochim. Biophys. Acta* 1123:231-8). Also, cAMP-dependent protein kinase (Protein Kinase A, or PKA) can phosphorylate ACC.

[0362] ACC can be regulated by allosteric transformation by citrate or palmitoyl-CoA. For example, citrate can be a positive effector (i.e. citrate can allosterically activate ACC). Citrate concentration can be high when there is adequate acetyl-CoA entering the Krebs Cycle. Excess acetyl-CoA can then be converted via malonyl-CoA to fatty acids. Palmitoyl-CoA can be a negative effector. Palmitoyl-CoA, which is the product of Fatty Acid Synthase (FASN), can promote the inactive conformation of ACC, which can reduce production of malonyl-CoA (a feedback inhibition process). AMP can regulate fatty acid synthesis by regulating the availability of malonyl-CoA. Insulin binding a receptor can activate a phosphatase to dephosphorylate ACC, which can remove the inhibitory effect.

[0363] The fatty acid synthase gene (also known as *FAS*, *OA-519*, *SDR27X1*; *MGC14367*; *MGC15706*; *FASN*) is involved in fatty acid synthesis. The enzyme encoded by this gene is a multifunctional protein of approximately 272 kDa with multiple domains, each with distinct enzyme activities that can play a role in fatty acid biosynthesis. FASN can

catalyze the synthesis of palmitate from acetyl-CoA and malonyl-CoA, in the presence of NADPH, into long-chain saturated fatty acids. In some cancer cell lines, FASN protein has been found to be fused with estrogen receptor-alpha (ER-alpha), in which the N-terminus of FASN is fused in-frame with the C-terminus of ER-alpha.

[0364] FASN protein can exist in the cytosol as a dimer of identical subunits. FASN consists of three catalytic domains in the N-terminal section (-ketoacyl synthase (KS), malonyl/acetyltransferase (MAT), and dehydrase (DH)). The N-terminal section is separated by a core region of about 600 amino acids from four C-terminal domains (enoyl reductase (ER), -ketoacyl reductase (KR), acyl carrier protein (ACP), and thioesterase (TE)). The crystal structure of a mammalian fatty acid synthase has been reported (Maier T. et al. (2008) *Science* 321: 1315-1322). Each of the catalytic domains of FASN can be targeted in the methods of treating viral infection of the provided invention.

[0365] The enzymatic steps of fatty acid synthesis can involve decarboxylative condensation, reduction, dehydration, and another reduction and can result in a saturated acyl moiety. NADPH can be an electron donor in reductive reactions.

Antiviral Activity

[0366] In various aspects, the present disclosure provides methods for treating viral infection in a subject, the method comprising administering to a subject in need of such treatment an effective amount of a compound of Structures (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) or as provided in Table 1.

[0367] In various aspects, the disclosure provides methods for treating a viral infection, the method comprising administering the compounds of the present disclosure to a subject in need thereof the agent.

[0368] The present disclosure contemplates the treatment of any viral infection that targets the fatty acid synthesis pathway in a host, and in particular by modulating the activity of fatty acid synthase. For example, the present methods can be used to treat influenza infection, adenovirus infection, respiratory syncytial virus infection, poxvirus infection, poliomyelitis infection, hepatitis C infection, yellow fever infection, dengue fever infection, rhinovirus infection, and the like.

[0369] In various aspects, the present disclosure provides methods for treating hepatitis C infection by administering to the subject one or more compounds disclosed herein. In modulating the FASN pathway in the subject, hepatitis C infection is treated. It has been shown that expression of FASN is upregulated in human hepatoma cell line Huh7 when these cells are infected with HCV. Inhibiting FASN production with a FASN inhibitor reduced the

production of HCV. Thus administration to a subject of the compounds of the present disclosure. (Yang, W. et al. (2008) *Hepatology* 48(5):1396-1403). It is demonstrated in the **EXAMPLES** that FASN inhibition correlates to inhibition of HCV.

[0370] In certain aspects, the methods of inhibiting viral infection can be performed *in vitro*. In further aspects, the methods of inhibiting viral infection can be performed *in vivo*.

[0371] In certain aspects the compounds of the present disclosure may be used in combination with other antiviral treatments in the treating of viral infection.

[0372] In various aspects, the viral infection is a human yellow fever infection. In further aspects, the viral infection is a human hepatitis C infection. In yet further aspects, the viral infection is a human rhinoviral infection.

[0373] In various aspects the compounds of the present disclosure can be used for the treatment of infection of an animal subject, such as a human, by any of a plethora of viruses.

[0374] In certain aspects, the compounds of the present disclosure can be used for the inhibition of a host by a respiratory virus. Respiratory viruses are most commonly transmitted by airborne droplets or nasal secretions and can lead to a wide spectrum of illness.

Respiratory viruses include the respiratory syncytial virus (RSV), influenza viruses, coronaviruses such as SARS, adenoviruses, parainfluenza viruses and rhinoviruses (HRV).

[0375] According to one aspect, the present disclosure can be used to treat infection by HRV. The genus of rhinoviruses is a member of the *Picornaviridae* family of viruses. Genera within the family include the Genus *Enterovirus*, *Rhinovirus*, *Cardiovirus*, *Aphthovirus*, *Hepatovirus*, *Parechovirus*, *Erbovirus*, *Kobuvirus*, *Teschovirus*. Human rhinoviruses (HRV) include the most common viruses that infect humans and can cause the common cold. HRV are lytic in nature. Rhinoviruses have single-stranded positive sense RNA genomes of between 7.2 and 8.5kb in length. At the 5' end of these genomes is a virus-encoded protein, and like mammalian mRNA, there is also a 3' poly-A tail. The 5'-terminal UMP of the viral RNA is covalently linked to the small viral protein VPg (Paul AV, et al. *Nature* 1998, 393(6682):280-284). The 5'UTR contains two structural elements. One is the 5'-cloverleaf structure involved in the plus-strand RNA synthesis and in the process of switching from translation to replication (Huang H, et al. *Biochemistry* 2001, 40(27):8055-8064). The other is the internal ribosomal entry site (IRES) which promotes translation of the polyprotein. In addition, species-specific internal *cis*-acting replication elements (*cre*) have been identified in human enteroviruses (HEV), HRV-A and HRV-B (Gerber K, Wimmer E, Paul AV, *J Virol* 2001, 75(22):10979-10990). The viral particles themselves are not enveloped and are

icosahedral in structure. Rhinoviruses also grow best in temperatures between 33-35°C. They are also sensitive to acidic environment.

[0376] HRV viral proteins are transcribed as a single long polypeptide, which is cleaved into the viral structural and nonstructural proteins. Rhinoviruses are composed of a capsid that contains four viral proteins VP1, VP2, VP3 and VP4 (Rossmann M, et al. 1985 *Nature* 317 (6033): 145–53; Smith T, et al. 1986, *Science* 233 (4770): 1286–93). The isometric nucleocapsids are 22-40nm in diameter. VP1, VP2, and VP3 form the major part of the protein capsid. The much smaller VP4 protein has a more extended structure and lies at interface between the capsid and the RNA genome. There are 60 copies of each of these proteins assembled as an icosahedron. Human antibodies that target epitopes lying on the exterior regions of VP1-VP3 play a role in the immune response to HRVs.

[0377] HRVs have two general modes of transmission: 1) via aerosols of respiratory droplets and 2) from contaminated surfaces, including direct person-to-person contact. The primary route of entry for rhinoviruses is the upper respiratory tract. Afterwards, an HRV binds to ICAM-1 (Inter-Cellular Adhesion Molecule 1) also known as CD54 (Cluster of Differentiation 54) receptors on respiratory epithelial cells. As the virus replicates and spreads, infected cells release chemokines and cytokines, which in turn activate inflammatory mediators. Infection occurs rapidly, with the rhinovirus adhering to surface receptors within 15 minutes of entering the respiratory tract. The incubation period is generally 8-10 hours before symptoms begin to occur. HRVs are the most frequent cause of infection across all age groups of the human population. Replication is often restricted to the upper respiratory tract leading to self-limited illnesses such as the common cold. However, HRV infections can also exacerbate pre-existing airway disorders, invade the lower respiratory tract and lead to serious complications.

[0378] In another aspect, the compounds of the present disclosure can be used for the treatment of infection by the influenza virus by targeting the pathways that the virus relies on for infection or replication. Influenza viruses belong to Orthomyxoviridae family of viruses. This family also includes Thogoto viruses and Dhoriviruses. There are several types and subtypes of influenza viruses known, which infect humans and other species. Influenza type A viruses infect people, birds, pigs, horses, seals and other animals, but wild birds are the natural hosts for these viruses. Influenza type A viruses are divided into subtypes and named on the basis of two proteins on the surface of the virus: hemagglutinin (HA) and neuraminidase (NA). For example, an “H7N2 virus” designates an influenza A subtype that has an HA 7 protein and an NA 2 protein. Similarly an “H5N1” virus has an HA 5 protein

and an NA 1 protein. There are 16 known HA subtypes and 9 known NA subtypes. Many different combinations of HA and NA proteins are possible. Only some influenza A subtypes (i.e., H1N1, H1N2, and H3N2) are currently in general circulation among people. Other subtypes are found most commonly in other animal species. For example, H7N7 and H3N8 viruses cause illness in horses, and H3N8 also has recently been shown to cause illness in dogs (see www.cdc.gov/flu/avian/gen-info/flu-viruses.htm).

[0379] Antiviral agents which target host cell proteins involved in influenza infection can be used to protect high-risk groups (hospital units, institutes caring for elderly, immuno-suppressed individuals), and on a case by case basis. A potential use for antiviral agents is to limit the spread and severity of the future pandemics whether caused by avian H5N1 or other strains of influenza virus. Avian influenza A viruses of the subtypes H5 and H7, including H5N1, H7N7, and H7N3 viruses, have been associated with high pathogenicity, and human infection with these viruses have ranged from mild (H7N3, H7N7) to severe and fatal disease (H7N7, H5N1). Human illness due to infection with low pathogenicity viruses has been documented, including very mild symptoms (e.g., conjunctivitis) to influenza-like illness. Examples of low pathogenicity viruses that have infected humans include H7N7, H9N2, and H7N2 (see www.cdc.gov/flu/avian/gen-info/flu-viruses.htm).

[0380] Influenza B viruses are usually found in humans but can also infect seals. Unlike influenza A viruses, these viruses are not classified according to subtype. Influenza B viruses can cause morbidity and mortality among humans, but in general are associated with less severe epidemics than influenza A viruses. Although influenza type B viruses can cause human epidemics, they have not caused pandemics. (see www.cdc.gov/flu/avian/gen-info/flu-viruses.htm).

[0381] Influenza type C viruses cause mild illness in humans and do not cause epidemics or pandemics. These viruses can also infect dogs and pigs. These viruses are not classified according to subtype. (see www.cdc.gov/flu/avian/gen-info/flu-viruses.htm).

[0382] Influenza viruses differ from each other in respect to cell surface receptor specificity and cell tropism, however they use common entry pathways. The compounds of the present disclosure advantageously target pathways that are common to multiple viruses giving rise to broader antiviral activity. Thus, the present compounds can also prove useful against unrelated viruses that use similar pathways. For example, the agents can protect airway epithelial cells against a number of different viruses in addition to influenza viruses.

[0383] In certain aspects, the compounds of the present disclosure can be used for the treatment of infection by adenoviruses. Most adenoviruses commonly cause respiratory

illness; symptoms of respiratory illness caused by adenovirus infection range from the common cold syndrome to pneumonia, croup, and bronchitis. Patients with compromised immune systems are especially susceptible to severe complications of adenovirus infection. Acute respiratory disease (ARD), first recognized among military recruits during World War II, can be caused by adenovirus infections during conditions of crowding and stress. Adenoviruses are medium-sized (90-100 nm), nonenveloped icosohedral viruses containing double-stranded DNA. There are 49 immunologically distinct types (6 subgenera: A through F) that can cause human infections. Adenoviruses are unusually stable to chemical or physical agents and adverse pH conditions, allowing for prolonged survival outside of the body. Some adenoviruses, such as AD2 and Ad5 (species C) use clathrin mediated endocytosis and macropinocytosis for infectious entry. Other adenoviruses, such as Ad3 (species B) use dynamin dependent endocytosis and macropinocytosis for infectious entry.

[0384] In certain aspects, the compounds of the present disclosure can be used for the treatment of infection by respiratory syncytial virus (RSV). RSV is the most common cause of bronchiolitis and pneumonia among infants and children under 1 year of age. Illness begins most frequently with fever, runny nose, cough, and sometimes wheezing. During their first RSV infection, between 25% and 40% of infants and young children have signs or symptoms of bronchiolitis or pneumonia, and 0.5% to 2% require hospitalization. Most children recover from illness in 8 to 15 days. The majority of children hospitalized for RSV infection are under 6 months of age. RSV also causes repeated infections throughout life, usually associated with moderate-to-severe cold-like symptoms; however, severe lower respiratory tract disease can occur at any age, especially among the elderly or among those with compromised cardiac, pulmonary, or immune systems. RSV is a negative-sense, enveloped RNA virus. The virion is variable in shape and size (average diameter of between 120 and 300 nm), is unstable in the environment (surviving only a few hours on environmental surfaces), and is readily inactivated with soap and water and disinfectants.

[0385] In certain aspects, the compounds of the present disclosure can be used for the treatment of infection by human parainfluenza virus (HPIV). HPIVs are second to respiratory syncytial virus (RSV) as a common cause of lower respiratory tract disease in young children. Similar to RSV, HPIVs can cause repeated infections throughout life, usually manifested by an upper respiratory tract illness (e.g., a cold and/or sore throat). HPIVs can also cause serious lower respiratory tract disease with repeat infection (e.g., pneumonia, bronchitis, and bronchiolitis), especially among the elderly, and among patients with compromised immune systems. Each of the four HPIVs has different clinical and

epidemiologic features. The most distinctive clinical feature of HPIV-1 and HPIV-2 is croup (i.e., laryngotracheobronchitis); HPIV-1 is the leading cause of croup in children, whereas HPIV-2 is less frequently detected. Both HPIV-1 and -2 can cause other upper and lower respiratory tract illnesses. HPIV-3 is more often associated with bronchiolitis and pneumonia. HPIV-4 is infrequently detected, possibly because it is less likely to cause severe disease. The incubation period for HPIVs is generally from 1 to 7 days. HPIVs are negative-sense, single-stranded RNA viruses that possess fusion and hemagglutinin-neuraminidase glycoprotein “spikes” on their surface. There are four serotypes types of HPIV (1 through 4) and two subtypes (4a and 4b). The virion varies in size (average diameter between 150 and 300 nm) and shape, is unstable in the environment (surviving a few hours on environmental surfaces), and is readily inactivated with soap and water.

[0386] In various aspects, the compounds of the present disclosure can be used for the treatment of infection by coronavirus. Coronavirus is a genus of animal virus belonging to the family Coronaviridae. Coronaviruses are enveloped viruses with a positive-sense single-stranded RNA genome and a helical symmetry. The genomic size of coronaviruses ranges from approximately 16 to 31 kilobases, extraordinarily large for an RNA virus. The name “coronavirus” is derived from the Latin corona, meaning crown, as the virus envelope appears under electron microscopy to be crowned by a characteristic ring of small bulbous structures. This morphology is actually formed by the viral spike peplomers, which are proteins that populate the surface of the virus and determine host tropism. Coronaviruses are grouped in the order Nidovirales, named for the Latin nidus, meaning nest, as all viruses in this order produce a 3' co-terminal nested set of subgenomic mRNA's during infection. Proteins that contribute to the overall structure of all coronaviruses are the spike, envelope, membrane and nucleocapsid. In the specific case of SARS a defined receptor-binding domain on S mediates the attachment of the virus to its cellular receptor, angiotensin-converting enzyme 2.

[0387] The present disclosure contemplates the treatment of any viral infection that targets the fatty acid synthesis pathway in a host, and in particular by modulating the activity of fatty acid synthase. For example, the present methods can be used to treat infections caused by Abelson leukemia virus, Abelson murine leukemia virus, Abelson's virus, Acute laryngotracheobronchitis virus, Adelaide River virus, Adeno associated virus group, Adenovirus, African horse sickness virus, African swine fever virus, AIDS virus, Aleutian mink disease parvovirus, Alpharetrovirus, Alphavirus, ALV related virus, Amapari virus, Aphthovirus, Aquareovirus, Arbovirus, Arbovirus C, arbovirus group A, arbovirus group B,

Arenavirus group, Argentine hemorrhagic fever virus, Argentine hemorrhagic fever virus,
 Arterivirus, Astrovirus, Ateline herpesvirus group, Aujeszky's disease virus, Aura virus,
 Ausduk disease virus, Australian bat lyssavirus, Aviadenovirus, avian erythroblastosis virus,
 avian infectious bronchitis virus, avian leukemia virus, avian leukosis virus, avian
 lymphomatosis virus, avian myeloblastosis virus, avian paramyxovirus, avian
 pneumoencephalitis virus, avian reticuloendotheliosis virus, avian sarcoma virus, avian type
 C retrovirus group, Avihepadnavirus, Avipoxvirus, B virus, B19 virus, Babanki virus, baboon
 herpesvirus, baculovirus, Barmah Forest virus, Bebaru virus, Berrimah virus, Betaretrovirus,
 Birnavirus, Bittner virus, BK virus, Black Creek Canal virus, bluetongue virus, Bolivian
 hemorrhagic fever virus, Boma disease virus, border disease of sheep virus, borna virus,
 bovine alphaherpesvirus 1, bovine alphaherpesvirus 2, bovine coronavirus, bovine ephemeral
 fever virus, bovine immunodeficiency virus, bovine leukemia virus, bovine leukosis virus,
 bovine mammillitis virus, bovine papillomavirus, bovine papular stomatitis virus, bovine
 parvovirus, bovine syncytial virus, bovine type C oncovirus, bovine viral diarrhea virus,
 Buggy Creek virus, bullet shaped virus group, Bunyamwera virus supergroup, Bunyavirus,
 Burkitt's lymphoma virus, Bwamba Fever, CA virus, Calicivirus, California encephalitis
 virus, camelpox virus, canarypox virus, canid herpesvirus, canine coronavirus, canine
 distemper virus, canine herpesvirus , canine minute virus, canine parvovirus, Cano Delgadito
 virus, caprine arthritis virus, caprine encephalitis virus, Caprine Herpes Virus, Capripox
 virus, Cardiovirus, caviid herpesvirus 1, Cercopithecine herpesvirus 1, cercopithecine
 herpesvirus 1, Cercopithecine herpesvirus 2, Chandipura virus, Changuinola virus, channel
 catfish virus, Charleville virus, chickenpox virus, Chikungunya virus, chimpanzee
 herpesvirus, chub reovirus, chum salmon virus, Cocal virus, Coho salmon reovirus, coital
 exanthema virus, Colorado tick fever virus, Coltivirus, Columbia SK virus, common cold
 virus, contagious ecthyma virus, contagious pustular dermatitis virus, Coronavirus, Corriparta
 virus, coryza virus, cowpox virus, coxsackie virus, CPV (cytoplasmic polyhedrosis virus),
 cricket paralysis virus, Crimean-Congo hemorrhagic fever virus, croup associated virus,
 Cryptovirus, Cypovirus, Cytomegalovirus, cytomegalovirus group, cytoplasmic polyhedrosis
 virus, deer papillomavirus, deltaretrovirus, dengue virus, Dengovirus, Dependovirus, Dhoru
 virus, diplorna virus, Drosophila C virus, duck hepatitis B virus, duck hepatitis virus 1, duck
 hepatitis virus 2, duovirus, Duvenhage virus, Deformed wing virus DWV, eastern equine
 encephalitis virus, eastern equine encephalomyelitis virus, EB virus, Ebola virus, Ebola-like
 virus, echo virus, echovirus, echovirus 10, echovirus 28, echovirus 9, ectromelia virus, EEE
 virus, EIA virus, EIA virus, encephalitis virus, encephalomyocarditis group virus,

encephalomyocarditis virus, Enterovirus, enzyme elevating virus, enzyme elevating virus (LDH), epidemic hemorrhagic fever virus, epizootic hemorrhagic disease virus, Epstein-Barr virus, equid alphaherpesvirus 1, equid alphaherpesvirus 4, equid herpesvirus 2, equine abortion virus, equine arteritis virus, equine encephalosis virus, equine infectious anemia virus, equine morbillivirus, equine rhinopneumonitis virus, equine rhinovirus, Eubenangu virus, European elk papillomavirus, European swine fever virus, Everglades virus, Eyach virus, felid herpesvirus 1, feline calicivirus, feline fibrosarcoma virus, feline herpesvirus, feline immunodeficiency virus, feline infectious peritonitis virus, feline leukemia /sarcoma virus, feline leukemia virus, feline panleukopenia virus, feline parvovirus, feline sarcoma virus, feline syncytial virus, Filovirus, Flanders virus, Flavivirus, foot and mouth disease virus, Fort Morgan virus, Four Corners hantavirus, fowl adenovirus 1, fowlpox virus, Friend virus, Gammaretrovirus, GB hepatitis virus, GB virus, German measles virus, Getah virus, gibbon ape leukemia virus, glandular fever virus, goatpox virus, golden shinner virus, Gonometa virus, goose parvovirus, granulosis virus, Gross' virus, ground squirrel hepatitis B virus, group A arbovirus, Guanarito virus, guinea pig cytomegalovirus, guinea pig type C virus, Hantaan virus, Hantavirus, hard clam reovirus, hare fibroma virus, HCMV (human cytomegalovirus), hemadsorption virus 2, hemagglutinating virus of Japan, hemorrhagic fever virus, hendra virus, Henipaviruses, Hepadnavirus, hepatitis A virus, hepatitis B virus group, hepatitis C virus, hepatitis D virus, hepatitis delta virus, hepatitis E virus, hepatitis F virus, hepatitis G virus, hepatitis nonA nonB virus, hepatitis virus, hepatitis virus (nonhuman), hepatoencephalomyelitis reovirus 3, Hepatovirus, heron hepatitis B virus, herpes B virus, herpes simplex virus, herpes simplex virus 1, herpes simplex virus 2, herpesvirus, herpesvirus 7, Herpesvirus ateles, Herpesvirus hominis, Herpesvirus infection, Herpesvirus saimiri, Herpesvirus suis, Herpesvirus varicellae, Highlands J virus, Hirame rhabdovirus, hog cholera virus, human adenovirus 2, human alphaherpesvirus 1, human alphaherpesvirus 2, human alphaherpesvirus 3, human B lymphotropic virus, human betaherpesvirus 5, human coronavirus, human cytomegalovirus group, human foamy virus, human gammaherpesvirus 4, human gammaherpesvirus 6, human hepatitis A virus, human herpesvirus 1 group, human herpesvirus 2 group, human herpesvirus 3 group, human herpesvirus 4 group, human herpesvirus 6, human herpesvirus 8, human immunodeficiency virus, human immunodeficiency virus 1, human immunodeficiency virus 2, human papillomavirus, human T cell leukemia virus, human T cell leukemia virus I, human T cell leukemia virus II, human T cell leukemia virus III, human T cell lymphoma virus I, human T cell lymphoma virus II, human T cell lymphotropic virus type 1, human T cell lymphotropic

virus type 2, human T lymphotropic virus I, human T lymphotropic virus II, human T lymphotropic virus III, Ichnovirus, infantile gastroenteritis virus, infectious bovine rhinotracheitis virus, infectious haematopoietic necrosis virus, infectious pancreatic necrosis virus, influenza virus A, influenza virus B, influenza virus C, influenza virus D, influenza virus pr8, insect iridescent virus, insect virus, iridovirus, Japanese B virus, Japanese encephalitis virus, JC virus, Junin virus, Kaposi's sarcoma-associated herpesvirus, Kemerovo virus, Kilham's rat virus, Klamath virus, Kolongo virus, Korean hemorrhagic fever virus, kumba virus, Kysanur forest disease virus, Kyzylagach virus, La Crosse virus, lactic dehydrogenase elevating virus, lactic dehydrogenase virus, Lagos bat virus, Langur virus, lapine parvovirus, Lassa fever virus, Lassa virus, latent rat virus, LCM virus, Leaky virus, Lentivirus, Leporipoxvirus, leukemia virus, leukovirus, lumpy skin disease virus, lymphadenopathy associated virus, Lymphocryptovirus, lymphocytic choriomeningitis virus, lymphoproliferative virus group, Machupo virus, mad itch virus, mammalian type B oncovirus group, mammalian type B retroviruses, mammalian type C retrovirus group, mammalian type D retroviruses, mammary tumor virus, Mapuera virus, Marburg virus, Marburg-like virus, Mason Pfizer monkey virus, Mastadenovirus, Mayaro virus, ME virus, measles virus, Menangle virus, Mengo virus, Mengovirus, Middelburg virus, milkers nodule virus, mink enteritis virus, minute virus of mice, MLV related virus, MM virus, Mokola virus, Molluscipoxvirus, Molluscum contagiosum virus, monkey B virus, monkeypox virus, Mononegavirales, Morbillivirus, Mount Elgon bat virus, mouse cytomegalovirus, mouse encephalomyelitis virus, mouse hepatitis virus, mouse K virus, mouse leukemia virus, mouse mammary tumor virus, mouse minute virus, mouse pneumonia virus, mouse poliomyelitis virus, mouse polyomavirus, mouse sarcoma virus, mousepox virus, Mozambique virus, Mucambo virus, mucosal disease virus, mumps virus, murid betaherpesvirus 1, murid cytomegalovirus 2, murine cytomegalovirus group, murine encephalomyelitis virus, murine hepatitis virus, murine leukemia virus, murine nodule inducing virus, murine polyomavirus, murine sarcoma virus, Muromegalovirus, Murray Valley encephalitis virus, myxoma virus, Myxovirus, Myxovirus multiforme, Myxovirus parotitidis, Nairobi sheep disease virus, Nairovirus, Nanirnavirus, Nariva virus, Ndumo virus, Neethling virus, Nelson Bay virus, neurotropic virus, New World Arenavirus, newborn pneumonitis virus, Newcastle disease virus, Nipah virus, noncytopathogenic virus, Norwalk virus, nuclear polyhedrosis virus (NPV), nipple neck virus, O'nyong'nyong virus, Ockelbo virus, oncogenic virus, oncogenic viruslike particle, oncornavirus, Orbivirus, Orf virus, Oropouche virus, Orthohepadnavirus, Orthomyxovirus, Orthopoxvirus, Orthoreovirus, Orungo, ovine papillomavirus, ovine

catarrhal fever virus, owl monkey herpesvirus, Palyam virus, Papillomavirus, Papillomavirus sylvilagi, Papovavirus, parainfluenza virus, parainfluenza virus type 1, parainfluenza virus type 2, parainfluenza virus type 3, parainfluenza virus type 4, Paramyxovirus, Parapoxvirus, paravaccinia virus, Parvovirus, Parvovirus B19, parvovirus group, Pestivirus, Phlebovirus, phocine distemper virus, Picodnavirus, Picornavirus, pig cytomegalovirus - pigeonpox virus, Piry virus, Pixuna virus, pneumonia virus of mice, Pneumovirus, poliomyelitis virus, poliovirus, Polydnavirus, polyhedral virus, polyoma virus, Polyomavirus, Polyomavirus bovis, Polyomavirus cercopithecii, Polyomavirus hominis 2, Polyomavirus maccacae 1, Polyomavirus muris 1, Polyomavirus muris 2, Polyomavirus papionis 1, Polyomavirus papionis 2, Polyomavirus sylvilagi, Pongine herpesvirus 1, porcine epidemic diarrhea virus, porcine hemagglutinating encephalomyelitis virus, porcine parvovirus, porcine transmissible gastroenteritis virus, porcine type C virus, pox virus, poxvirus, poxvirus variolae, Prospect Hill virus, Provirus, pseudocowpox virus, pseudorabies virus, psittacinepox virus, quailpox virus, rabbit fibroma virus, rabbit kidney vacuolating virus, rabbit papillomavirus, rabies virus, raccoon parvovirus, raccoonpox virus, Ranikhet virus, rat cytomegalovirus, rat parvovirus, rat virus, Rauscher's virus, recombinant vaccinia virus, recombinant virus, reovirus, reovirus 1, reovirus 2, reovirus 3, reptilian type C virus, respiratory infection virus, respiratory syncytial virus, respiratory virus, reticuloendotheliosis virus, Rhabdovirus, Rhabdovirus carpia, Rhadinovirus, Rhinovirus, Rhizidiovirus, Rift Valley fever virus, Riley's virus, rinderpest virus, RNA tumor virus, Ross River virus, Rotavirus, rougeole virus, Rous sarcoma virus, rubella virus, rubeola virus, Rubivirus, Russian autumn encephalitis virus, SA 11 simian virus, SA2 virus, Sabia virus, Sagiyama virus, Saimirine herpesvirus 1, salivary gland virus, sandfly fever virus group, Sandjimba virus, SARS virus, SDAV (sialodacryoadenitis virus), sealpox virus, Semliki Forest Virus, Seoul virus, sheeppox virus, Shope fibroma virus, Shope papilloma virus, simian foamy virus, simian hepatitis A virus, simian human immunodeficiency virus, simian immunodeficiency virus, simian parainfluenza virus, simian T cell lymphotropic virus, simian virus, simian virus 40, Simplexvirus, Sin Nombre virus, Sindbis virus, smallpox virus, South American hemorrhagic fever viruses, sparrowpox virus, Spumavirus, squirrel fibroma virus, squirrel monkey retrovirus, SSV 1 virus group, STLV (simian T lymphotropic virus) type I, STLV (simian T lymphotropic virus) type II, STLV (simian T lymphotropic virus) type III, stomatitis papulosa virus, submaxillary virus, suid alphaherpesvirus 1, suid herpesvirus 2, Suipoxvirus, swamp fever virus, swinepox virus, Swiss mouse leukemia virus, TAC virus, Tacaribe complex virus, Tacaribe virus, Tanapox virus, Taterapox virus, Tench reovirus, Theiler's

encephalomyelitis virus, Theiler's virus, Thogoto virus, Thottapalayam virus, Tick borne encephalitis virus, Tioman virus, Togavirus, Torovirus, tumor virus, Tupaia virus, turkey rhinotracheitis virus, turkeypox virus, type C retroviruses, type D oncovirus, type D retrovirus group, ulcerative disease rhabdovirus, Una virus, Uukuniemi virus group, vaccinia virus, vacuolating virus, varicella zoster virus, Varicellovirus, Varicola virus, variola major virus, variola virus, Vasin Gishu disease virus, VEE virus, Venezuelan equine encephalitis virus, Venezuelan equine encephalomyelitis virus, Venezuelan hemorrhagic fever virus, vesicular stomatitis virus, Vesiculovirus, Vilyuisk virus, viper retrovirus, viral haemorrhagic septicemia virus, Visna Maedi virus, Visna virus, volepox virus, VSV (vesicular stomatitis virus), Wallal virus, Warrego virus, wart virus, WEE virus, West Nile virus, western equine encephalitis virus, western equine encephalomyelitis virus, Whataroa virus, Winter Vomiting Virus, woodchuck hepatitis B virus, woolly monkey sarcoma virus, wound tumor virus, WRSV virus, Yaba monkey tumor virus, Yaba virus, Yatapoxvirus, yellow fever virus, and the Yug Bogdanovac virus.

Utility in Metabolic Disorders

[0388] In various aspects, the compounds of the present disclosure have utility in the treating of metabolic diseases. FASN has been demonstrated to be involved in regulation of glucose, lipids and cholesterol metabolism. Mice with a liver-specific inactivation of FASN have normal physiology unless fed a zero-fat diet, in which case they develop hypoglycemia and fatty liver, both of which are reversed with dietary fat. (Chakravarthy, M. V., *et al.* (2005) *Cell Metabolism* 1:309-322). *Db/+* mice fed a high fructose diet exhibit reduced liver triglyceride levels and improved insulin sensitivity when treated for 28 days with platensimycin, a covalent inhibitor of FASN. (Wu, M. *et al.* (2011) *PNAS* 108(13):5378-5383). Ambient glucose levels are also reduced in *db/db* mice following treatment with platensimycin. These results provide evidence that inhibiting FASN can yield therapeutically relevant benefits in animal models of diabetes and related metabolic disorders. Thus the disclosed FASN inhibitors are useful in the treatment of disorders characterized by dysregulation in these systems. Without limitation, examples include steatosis and diabetes.

Anticancer Activity

[0389] In various aspects, the present disclosure provides methods for treating cancer in subject, the method comprising administering to a subject in need of such treatment an effective amount of a compound of Structures (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) or as provided in Table 1. In further aspects, compounds having Structure (I),

(II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) or as provided in Table 1 can be used for the manufacture of a medicament for treating cancer.

[0390] In certain aspects, the present disclosure provides a method for inhibiting tumor cell growth in a subject, the method comprising administering to a subject in need of such treatment an effective amount of a compound of Structure (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) or as provided in Table 1. In further aspects, the tumor can be derived from ovary, breast, lung, thyroid, lymph node, kidney, ureter, bladder, ovary, teste, prostate, bone, skeletal muscle, bone marrow, stomach, esophagus, small bowel, colon, rectum, pancreas, liver, smooth muscle, brain, spinal cord, nerves, ear, eye, nasopharynx, oropharynx, salivary gland, or heart tissue. In certain aspects, the present compounds can be administered concurrently with one or more additional anti-cancer treatments.

[0391] Rapidly proliferating cancer cells activate the fatty acid synthesis pathway to supply the high levels of lipids needed for membrane assembly and oxidative metabolism. (Flavin, R. *et al.* (2010) *Future Oncology*. 6(4):551-562) Inhibitors of fatty acid synthesis have demonstrated *in vivo* activity in preclinical cancer models. (Orita, H. *et al.* (2007) *Clinical Cancer Research*. 13(23):7139-7145 and Puig, T. *et al.* (2011) *Breast Cancer Research*, 13(6):R131) Additionally, fatty acid synthesis supports new blood vessel formation and inhibitors of this pathway have activity in *in vitro* models of angiogenesis. (Browne, C.D., *et al.* (2006) *The FASEB Journal*, 20(12):2027-2035). The presently disclosed compounds demonstrated the ability to selectively induce cell-cycle arrest in HUVEC cells without causing general cell death by apoptosis. See **EXAMPLES**.

[0392] The cancer treatment of the present invention includes an anti-tumor effect that may be assessed by conventional means such as the response rate, the time to disease progression and/or the survival rate. Anti-tumor effects of the present invention include, but are not limited to, inhibition of tumor growth, tumor growth delay, regression of tumor, shrinkage of tumor, increased time to regrowth of tumor on cessation of treatment and slowing of disease progression. For example, it is expected that when the combination of the present invention is administered to a warm-blooded animal such as a human, in need of treatment for cancer involving a solid tumor, such a method of treatment will produce an effect, as measured by, for example, one or more of: the extent of the anti-tumor effect, the response rate, the time to disease progression and the survival rate.

Methods of Treatment

[0393] Also provided herein are pharmaceutical compositions comprising the compounds of the present disclosure. The present compositions and methods have antiviral and/or anticancer activity.

[0394] In various aspects, the present disclosure provides pharmaceutical compositions comprising any one of the compounds of Structures (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X) or (XI) and a pharmaceutically acceptable carrier, excipient, or diluent.

[0395] In certain aspects, the present disclosure provides pharmaceutical compositions comprising any one of the compounds of Table 1 and a pharmaceutically acceptable carrier, excipient, or diluent.

[0396] Certain aspects of the present disclosure relates to methods of using pharmaceutical compositions and kits comprising one or more agents that inhibit the fatty acid synthesis pathway to inhibit or decrease a viral infection or for the treatment of cancer. Certain aspects of the present disclosure relates to methods of using pharmaceutical compositions and kits comprising one or more agents that inhibit fatty acid synthase to inhibit or decrease a viral infection or for the treatment of cancer. Another aspect of the present invention provides methods, pharmaceutical compositions, and kits for the treatment of animal subjects having a viral infection or cancer or at risk of developing a viral infection or cancer. The term “subject” as used herein includes humans as well as other mammals. The term “treating” as used herein includes achieving a therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying viral infection. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying viral infection such that an improvement is observed in the animal subject, notwithstanding the fact that the subject can still be afflicted with the underlying virus.

[0397] For aspects where a prophylactic benefit is desired, a pharmaceutical composition of the invention can be administered to a patient at risk of developing viral infection such as HRV, or HIV, or to a patient reporting one or more of the physiological symptoms of a viral infection, even though a diagnosis of the condition may not have been made. Administration can prevent the viral infection from developing, or it can reduce, lessen, shorten and/or otherwise ameliorate the viral infection that develops. The pharmaceutical composition can modulate the fatty acid synthesis pathway, e.g., *FASN* gene expression or FASN protein activity. Wherein, the term modulate includes inhibition of the fatty acid synthesis pathway,

e.g., *FASN* gene expression or FASN protein activity or alternatively activation of the fatty acid synthesis pathway, e.g., *FASN* gene expression or FASN protein activity.

[0398] Reducing the activity of the fatty acid synthesis pathway, e.g., *FASN* gene expression or FASN protein activity, is also referred to as “inhibiting” the fatty acid synthesis pathway, e.g., *FASN* gene expression or FASN protein activity. The term “inhibits” and its grammatical conjugations, such as “inhibitory,” do not require complete inhibition, but refer to a reduction in fatty acid synthesis activity, e.g., *FASN* gene expression or FASN protein activity. In another aspect, such reduction is by at least 50%, at least 75%, at least 90%, and can be by at least 95% of the activity of the enzyme in the absence of the inhibitory effect, e.g., in the absence of an inhibitor. Conversely, the phrase “does not inhibit” and its grammatical conjugations refer to situations where there is less than 20%, less than 10%, and can be less than 5%, of reduction in enzyme activity in the presence of the agent. Further the phrase “does not substantially inhibit” and its grammatical conjugations refer to situations where there is less than 30%, less than 20%, and in some aspects less than 10% of reduction in enzyme activity in the presence of the agent.

[0399] Increasing the activity of the fatty acid synthesis pathway, e.g., *FASN* gene expression or FASN protein activity, is also referred to as “activating” the fatty acid synthesis pathway, e.g., *FASN* gene expression or FASN protein activity. The term “activated” and its grammatical conjugations, such as “activating,” do not require complete activation, but refer to an increase in fatty acid synthesis pathway activity, e.g., *FASN* gene expression or FASN protein activity. In another aspect such increase is by at least 50%, at least 75%, at least 90%, and can be by at least 95% of the activity of the enzyme in the absence of the activation effect, e.g., in the absence of an activator. Conversely, the phrase “does not activate” and its grammatical conjugations refer to situations where there is less than 20%, less than 10%, and can be less than 5%, of an increase in enzyme activity in the presence of the agent. Further the phrase “does not substantially activate” and its grammatical conjugations refer to situations where there is less than 30%, less than 20%, and in another aspect less than 10% of an increase in enzyme activity in the presence of the agent.

[0400] The ability to reduce enzyme activity is a measure of the potency or the activity of an agent, or combination of agents, towards or against the enzyme. Potency can be measured by cell free, whole cell and/or *in vivo* assays in terms of IC₅₀, K_i and/or ED₅₀ values. An IC₅₀ value represents the concentration of an agent required to inhibit enzyme activity by half (50%) under a given set of conditions. A K_i value represents the equilibrium affinity constant for the binding of an inhibiting agent to the enzyme. An ED₅₀ value represents the

dose of an agent required to effect a half-maximal response in a biological assay. Further details of these measures will be appreciated by those of ordinary skill in the art, and can be found in standard texts on biochemistry, enzymology, and the like.

[0401] The present invention also includes kits that can be used to treat viral infections or treat cancer. These kits comprise an agent or combination of agents that inhibit the fatty acid synthesis pathway, e.g., *FASN* gene expression or *FASN* protein activity, and optionally instructions teaching the use of the kit according to the various methods and approaches described herein. Such kits can also include information, such as scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the agent. Such information can be based on the results of various studies, for example, studies using experimental animals involving *in vivo* models and studies based on human clinical trials. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like.

Formulations, Routes of Administration, and Effective Doses

[0402] Yet another aspect of the present invention relates to formulations, routes of administration and effective doses for pharmaceutical compositions comprising an agent or combination of agents of the instant invention. Such pharmaceutical compositions can be used to treat viral infections as described above.

[0403] Compounds of the invention can be administered as pharmaceutical formulations including those suitable for oral (including buccal and sub-lingual), rectal, nasal, topical, transdermal patch, pulmonary, vaginal, suppository, or parenteral (including intramuscular, intraarterial, intrathecal, intradermal, intraperitoneal, subcutaneous and intravenous) administration or in a form suitable for administration by aerosolization, inhalation or insufflation. General information on drug delivery systems can be found in Ansel et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems* (Lippencott Williams & Wilkins, Baltimore Md. (1999)).

[0404] In various aspects, the pharmaceutical composition includes carriers and excipients (including but not limited to buffers, carbohydrates, mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents, suspending agents, thickening agents and/or preservatives), water, oils including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like, saline solutions, aqueous dextrose and glycerol solutions, flavoring agents, coloring agents, detackifiers and other acceptable additives, adjuvants, or binders,

other pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH buffering agents, tonicity adjusting agents, emulsifying agents, wetting agents and the like. Examples of excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. In another aspect, the pharmaceutical preparation is substantially free of preservatives. In another aspect, the pharmaceutical preparation can contain at least one preservative. General methodology on pharmaceutical dosage forms is found in Ansel et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems* (Lippencott Williams & Wilkins, Baltimore Md. (1999)). It will be recognized that, while any suitable carrier known to those of ordinary skill in the art can be employed to administer the compositions of this invention, the type of carrier will vary depending on the mode of administration.

[0405] Compounds can also be encapsulated within liposomes using well-known technology. Biodegradable microspheres can also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Pat. Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763; 5,814,344 and 5,942,252.

[0406] The compound can be administered in liposomes or microspheres (or microparticles). Methods for preparing liposomes and microspheres for administration to a patient are well known to those of skill in the art. U.S. Pat. No. 4,789,734, describes methods for encapsulating biological materials in liposomes. Essentially, the material is dissolved in an aqueous solution, the appropriate phospholipids and lipids added, along with surfactants if required, and the material dialyzed or sonicated, as necessary. A review of known methods is provided by G. Gregoriadis, Chapter 14, "Liposomes," *Drug Carriers in Biology and Medicine*, pp. 2.sup.87-341 (Academic Press, 1979).

[0407] Microspheres formed of polymers or proteins are well known to those skilled in the art, and can be tailored for passage through the gastrointestinal tract directly into the blood stream. Alternatively, the compound can be incorporated and the microspheres, or composite of microspheres, implanted for slow release over a period of time ranging from days to months. See, for example, U.S. Pat. Nos. 4,906,474, 4,925,673 and 3,625,214, and Jein, TIPS 19: 155-157 (1998).

[0408] The concentration of drug can be adjusted, the pH of the solution buffered and the isotonicity adjusted to be compatible with intravenous injection, as is well known in the art.

[0409] The compounds of the invention can be formulated as a sterile solution or suspension, in suitable vehicles, well known in the art. The pharmaceutical compositions can be sterilized by conventional, well-known sterilization techniques, or can be sterile filtered. The resulting aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile solution prior to administration. Suitable formulations and additional carriers are described in Remington “The Science and Practice of Pharmacy” (20th Ed., Lippincott Williams & Wilkins, Baltimore MD).

[0410] The agents or their pharmaceutically acceptable salts can be provided alone or in combination with one or more other agents or with one or more other forms. For example a formulation can comprise one or more agents in particular proportions, depending on the relative potencies of each agent and the intended indication. For example, in compositions for targeting two different host targets, and where potencies are similar, about a 1:1 ratio of agents can be used. The two forms can be formulated together, in the same dosage unit e.g., in one cream, suppository, tablet, capsule, aerosol spray, or packet of powder to be dissolved in a beverage; or each form can be formulated in a separate unit, e.g., two creams, two suppositories, two tablets, two capsules, a tablet and a liquid for dissolving the tablet, two aerosol sprays, or a packet of powder and a liquid for dissolving the powder, etc.

[0411] The term “pharmaceutically acceptable salt” means those salts which retain the biological effectiveness and properties of the agents used in the present invention, and which are not biologically or otherwise undesirable. For example, a pharmaceutically acceptable salt does not interfere with the beneficial effect of an agent of the invention in inhibiting the fatty acid synthesis pathway, e.g., inhibiting *FASN* gene expression or FASN protein activity.

[0412] Typical salts are those of the inorganic ions, such as, for example, sodium, potassium, calcium, magnesium ions, and the like. Such salts include salts with inorganic or organic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, methanesulfonic acid, p-toluenesulfonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, mandelic acid, malic acid, citric acid, tartaric acid or maleic acid. In addition, if the agent(s) contain a carboxy group or other acidic group, it can be converted into a pharmaceutically acceptable addition salt with inorganic or organic bases. Examples of suitable bases include sodium hydroxide, potassium hydroxide, ammonia, cyclohexylamine, dicyclohexyl-amine, ethanolamine, diethanolamine, triethanolamine, and the like.

[0413] A pharmaceutically acceptable ester or amide refers to those which retain biological effectiveness and properties of the agents used in the present invention, and which

are not biologically or otherwise undesirable. For example, the ester or amide does not interfere with the beneficial effect of an agent of the invention in inhibiting the fatty acid synthesis pathway, e.g., inhibiting *FASN* gene expression or FASN protein activity. Typical esters include ethyl, methyl, isobutyl, ethylene glycol, and the like. Typical amides include unsubstituted amides, alkyl amides, dialkyl amides, and the like.

[0414] In another aspect, an agent can be administered in combination with one or more other compounds, forms, and/or agents, e.g., as described above. Pharmaceutical compositions comprising combinations of a fatty acid synthesis pathway inhibitor e.g., an inhibitor of *FASN* gene expression or FASN protein activity with one or more other active agents can be formulated to comprise certain molar ratios. For example, molar ratios of about 99:1 to about 1:99 of a fatty acid synthesis pathway inhibitor e.g., an inhibitor of *FASN* gene expression or FASN protein activity, to the other active agent can be used. In some subset of the aspects, the range of molar ratios of fatty acid synthesis pathway inhibitor e.g., an inhibitor of *FASN* gene expression or FASN protein activity: other active agent is selected from about 80:20 to about 20:80; about 75:25 to about 25:75, about 70:30 to about 30:70, about 66:33 to about 33:66, about 60:40 to about 40:60; about 50:50; and about 90:10 to about 10:90. The molar ratio of a fatty acid synthesis pathway inhibitor e.g., an inhibitor of *FASN* gene expression or FASN protein activity: other active agent can be about 1:9, and in another aspect can be about 1:1. The two agents, forms and/or compounds can be formulated together, in the same dosage unit e.g., in one cream, suppository, tablet, capsule, or packet of powder to be dissolved in a beverage; or each agent, form, and/or compound can be formulated in separate units, e.g., two creams, suppositories, tablets, two capsules, a tablet and a liquid for dissolving the tablet, an aerosol spray a packet of powder and a liquid for dissolving the powder, etc.

[0415] If necessary or desirable, the agents and/or combinations of agents can be administered with still other agents. The choice of agents that can be co-administered with the agents and/or combinations of agents of the instant invention can depend, at least in part, on the condition being treated. Agents of particular use in the formulations of the present invention include, for example, any agent having a therapeutic effect for a viral infection, including, e.g., drugs used to treat inflammatory conditions. For example, in treatments for HRV, in some aspects formulations of the instant invention can additionally contain one or more conventional anti-inflammatory drugs, such as an NSAID, e.g., ibuprofen, naproxen, acetaminophen, ketoprofen, or aspirin. In some alternative aspects for the treatment of influenza formulations of the instant invention can additionally contain one or more

conventional influenza antiviral agents, such as amantadine, rimantadine, zanamivir, and oseltamivir. In treatments for retroviral infections, such as HIV, formulations of the instant invention can additionally contain one or more conventional antiviral drug, such as protease inhibitors (lopinavir/ritonavir (Kaletra), indinavir (Crixivan), ritonavir (Norvir), nelfinavir (Viracept), saquinavir hard gel capsules (Invirase), atazanavir (Reyataz), amprenavir (Agenerase), fosamprenavir (Telzir), tipranavir (Aptivus)), reverse transcriptase inhibitors, including non-Nucleoside and Nucleoside/nucleotide inhibitors (AZT (zidovudine, Retrovir), ddI (didanosine, Videx), 3TC (lamivudine, Epivir), d4T (stavudine, Zerit), abacavir (Ziagen), FTC (emtricitabine, Emtriva), tenofovir (Viread), efavirenz (Sustiva) and nevirapine (Viramune)), fusion inhibitors T20 (enfuvirtide, Fuzeon), integrase inhibitors (MK-0518 and GS-9137), and maturation inhibitors (PA-457 (Bevirimat)). As another example, formulations can additionally contain one or more supplements, such as vitamin C, E or other anti-oxidants.

[0416] In certain aspects, the compounds of the present disclosure can be administered in combination with a known cancer therapeutic. For example, the compounds can be administered in combination with paclitaxel (commercially available as Taxol, Bristol-Myers Squibb), doxorubicin (also known under the trade name Adriamycin), vincristine (known under the trade names Oncovin, Vincasar PES, and Vincrex), actinomycin D, altretamine, asparaginase, bleomycin, busulphan, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, cytarabine, dacarbazine, daunorubicin, epirubicin, etoposide, fludarabine, fluorouracil, gemcitabine, hydroxyurea, idarubicin, ifosfamide, irinotecan, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitozantrone, oxaliplatin, procarbazine, steroids, streptozocin, taxotere, tamoxifen, thioguanine, thiotepa, tomudex, topotecan, treosulfan, UFT (uracil-tegufur), vinblastine, and vindesine, or the like.

[0417] The agent(s) (or pharmaceutically acceptable salts, esters or amides thereof) can be administered per se or in the form of a pharmaceutical composition wherein the active agent(s) is in an admixture or mixture with one or more pharmaceutically acceptable carriers. A pharmaceutical composition, as used herein, can be any composition prepared for administration to a subject. Pharmaceutical compositions for use in accordance with the present invention can be formulated in conventional manner using one or more physiologically acceptable carriers, comprising excipients, diluents, and/or auxiliaries, e.g., which facilitate processing of the active agents into preparations that can be administered. Proper formulation can depend at least in part upon the route of administration chosen. The agent(s) useful in the present invention, or pharmaceutically acceptable salts, esters, or

amides thereof, can be delivered to a patient using a number of routes or modes of administration, including oral, buccal, topical, rectal, transdermal, transmucosal, subcutaneous, intravenous, and intramuscular applications, as well as by inhalation.

[0418] For oral administration, the agents can be formulated readily by combining the active agent(s) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the agents of the invention to be formulated as tablets, including chewable tablets, pills, dragees, capsules, lozenges, hard candy, liquids, gels, syrups, slurries, powders, suspensions, elixirs, wafers, and the like, for oral ingestion by a patient to be treated. Such formulations can comprise pharmaceutically acceptable carriers including solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents. A solid carrier can be one or more substances which can also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier generally is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about one (1) to about seventy (70) percent of the active compound. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. Generally, the agents of the invention will be included at concentration levels ranging from about 0.5%, about 5%, about 10%, about 20%, or about 30% to about 50%, about 60%, about 70%, about 80% or about 90% by weight of the total composition of oral dosage forms, in an amount sufficient to provide a desired unit of dosage.

[0419] Aqueous suspensions for oral use can contain agent(s) of this invention with pharmaceutically acceptable excipients, such as a suspending agent (e.g., methyl cellulose), a wetting agent (e.g., lecithin, lysolecithin and/or a long-chain fatty alcohol), as well as coloring agents, preservatives, flavoring agents, and the like.

[0420] In another aspect, oils or non-aqueous solvents can be required to bring the agents into solution, due to, for example, the presence of large lipophilic moieties. Alternatively, emulsions, suspensions, or other preparations, for example, liposomal preparations, can be used. With respect to liposomal preparations, any known methods for preparing liposomes for treatment of a condition can be used. See, for example, Bangham et al., J. Mol. Biol. 23: 238-252 (1965) and

Szoka et al., Proc. Natl Acad. Sci. USA 75: 4194-4198 (1978). Ligands can also be attached to the liposomes to direct these compositions to particular sites of action. Agents of this invention can also be integrated into foodstuffs, e.g., cream cheese, butter, salad dressing, or ice cream to facilitate solubilization, administration, and/or compliance in certain patient populations.

[0421] Pharmaceutical preparations for oral use can be obtained as a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; flavoring elements, cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone (PVP). If desired, disintegrating agents can be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. The agents can also be formulated as a sustained release preparation.

[0422] Dragee cores can be provided with suitable coatings. For this purpose, concentrated sugar solutions can be used, which can optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments can be added to the tablets or dragee coatings for identification or to characterize different combinations of active agents.

[0423] Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active agents can be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers can be added. All formulations for oral administration should be in dosages suitable for administration.

[0424] Other forms suitable for oral administration include liquid form preparations including emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions, or solid form preparations which are intended to be converted shortly before use to liquid form preparations. Emulsions can be prepared in solutions, for example, in aqueous propylene glycol solutions or can contain emulsifying agents, for example, such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active

component in water and adding suitable colorants, flavors, stabilizers, and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents. Suitable fillers or carriers with which the compositions can be administered include agar, alcohol, fats, lactose, starch, cellulose derivatives, polysaccharides, polyvinylpyrrolidone, silica, sterile saline and the like, or mixtures thereof used in suitable amounts. Solid form preparations include solutions, suspensions, and emulsions, and can contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0425] A syrup or suspension can be made by adding the active compound to a concentrated, aqueous solution of a sugar, e.g., sucrose, to which can also be added any accessory ingredients. Such accessory ingredients can include flavoring, an agent to retard crystallization of the sugar or an agent to increase the solubility of any other ingredient, e.g., as a polyhydric alcohol, for example, glycerol or sorbitol.

[0426] When formulating compounds of the invention for oral administration, it can be desirable to utilize gastroretentive formulations to enhance absorption from the gastrointestinal (GI) tract. A formulation which is retained in the stomach for several hours can release compounds of the invention slowly and provide a sustained release that can be used in methods of the invention. Disclosure of such gastro-retentive formulations are found in Klausner, E.A.; Lavy, E.; Barta, M.; Cserepes, E.; Friedman, M.; Hoffman, A. 2003 "Novel gastroretentive dosage forms: evaluation of gastroretentivity and its effect on levodopa in humans." Pharm. Res. 20, 1466-73, Hoffman, A.; Stepensky, D.; Lavy, E.; Eyal, S. Klausner, E.; Friedman, M. 2004 "Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms" Int. J. Pharm. 11, 141-53, Streubel, A.; Siepmann, J.; Bodmeier, R.; 2006 "Gastroretentive drug delivery systems" Expert Opin. Drug Deliver. 3, 217-3, and Chavanpatil, M.D.; Jain, P.; Chaudhari, S.; Shear, R.; Vavia, P.R. "Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin" Int. J. Pharm. 2006 epub March 24. Expandable, floating and bioadhesive techniques can be utilized to maximize absorption of the compounds of the invention.

[0427] The compounds of the invention can be formulated for parenteral administration (e.g., by injection, for example bolus injection or continuous infusion) and can be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions can take such forms as suspensions,

solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol.

[0428] For injectable formulations, the vehicle can be chosen from those known in art to be suitable, including aqueous solutions or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles. The formulation can also comprise polymer compositions which are biocompatible, biodegradable, such as poly(lactic-co-glycolic)acid. These materials can be made into micro or nanospheres, loaded with drug and further coated or derivatized to provide superior sustained release performance. Vehicles suitable for periocular or intraocular injection include, for example, suspensions of therapeutic agent in injection grade water, liposomes and vehicles suitable for lipophilic substances. Other vehicles for periocular or intraocular injection are well known in the art.

[0429] In a preferred aspect, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition can also include a solubilizing agent and a local anesthetic such as lidocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

[0430] When administration is by injection, the active compound can be formulated in aqueous solutions, specifically in physiologically compatible buffers such as Hanks solution, Ringer's solution, or physiological saline buffer. The solution can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active compound can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use. In another aspect, the pharmaceutical composition does not comprise an adjuvant or any other substance added to enhance the immune response stimulated by the peptide. In another aspect, the pharmaceutical composition comprises a substance that inhibits an immune response to the peptide. Methods of formulation are known in the art, for

example, as disclosed in Remington's Pharmaceutical Sciences, latest edition, Mack Publishing Co., Easton P.

[0431] In addition to the formulations described previously, the agents can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation or transcutaneous delivery (for example subcutaneously or intramuscularly), intramuscular injection or use of a transdermal patch. Thus, for example, the agents can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0432] In another aspect, pharmaceutical compositions comprising one or more agents of the present invention exert local and regional effects when administered topically or injected at or near particular sites of infection. Direct topical application, e.g., of a viscous liquid, solution, suspension, dimethylsulfoxide (DMSO)-based solutions, liposomal formulations, gel, jelly, cream, lotion, ointment, suppository, foam, or aerosol spray, can be used for local administration, to produce for example local and/or regional effects. Pharmaceutically appropriate vehicles for such formulation include, for example, lower aliphatic alcohols, polyglycols (e.g., glycerol or polyethylene glycol), esters of fatty acids, oils, fats, silicones, and the like. Such preparations can also include preservatives (e.g., p-hydroxybenzoic acid esters) and/or antioxidants (e.g., ascorbic acid and tocopherol). See also Dermatological Formulations: Percutaneous absorption, Barry (Ed.), Marcel Dekker Incl, 1983. In another aspect, local/topical formulations comprising a fatty acid synthesis pathway inhibitor e.g., an inhibitor of *FASN* gene expression or FASN protein activity, are used to treat epidermal or mucosal viral infections.

[0433] Pharmaceutical compositions of the present invention can contain a cosmetically or dermatologically acceptable carrier. Such carriers are compatible with skin, nails, mucous membranes, tissues and/or hair, and can include any conventionally used cosmetic or dermatological carrier meeting these requirements. Such carriers can be readily selected by one of ordinary skill in the art. In formulating skin ointments, an agent or combination of agents of the instant invention can be formulated in an oleaginous hydrocarbon base, an anhydrous absorption base, a water-in-oil absorption base, an oil-in-water water-removable base and/or a water-soluble base. Examples of such carriers and excipients include, but are not limited to, humectants (e.g., urea), glycols (e.g., propylene glycol), alcohols (e.g., ethanol), fatty acids (e.g., oleic acid), surfactants (e.g., isopropyl myristate and sodium lauryl sulfate), pyrrolidones, glycerol monolaurate, sulfoxides, terpenes (e.g., menthol), amines,

amides, alkanes, alkanols, water, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[0434] Ointments and creams can, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions can be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Pat. Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches can be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[0435] Lubricants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel, a coagulated aerosol of synthetic silica, or mixtures thereof. A lubricant can optionally be added, in an amount of less than about 1 weight percent of the pharmaceutical composition.

[0436] The compositions according to the present invention can be in any form suitable for topical application, including aqueous, aqueous-alcoholic or oily solutions, lotion or serum dispersions, aqueous, anhydrous or oily gels, emulsions obtained by dispersion of a fatty phase in an aqueous phase (O/W or oil in water) or, conversely, (W/O or water in oil), microemulsions or alternatively microcapsules, microparticles or lipid vesicle dispersions of ionic and/or nonionic type. These compositions can be prepared according to conventional methods. Other than the agents of the invention, the amounts of the various constituents of the compositions according to the invention are those conventionally used in the art. These compositions in particular constitute protection, treatment or care creams, milks, lotions, gels or foams for the face, for the hands, for the body and/or for the mucous membranes, or for cleansing the skin. The compositions can also consist of solid preparations constituting soaps or cleansing bars.

[0437] Compositions of the present invention can also contain adjuvants common to the cosmetic and dermatological fields, such as hydrophilic or lipophilic gelling agents, hydrophilic or lipophilic active agents, preserving agents, antioxidants, solvents, fragrances,

fillers, sunscreens, odor-absorbers and dyestuffs. The amounts of these various adjuvants are those conventionally used in the fields considered and, for example, are from about 0.01% to about 20% of the total weight of the composition. Depending on their nature, these adjuvants can be introduced into the fatty phase, into the aqueous phase and/or into the lipid vesicles.

[0438] In another aspect, ocular viral infections can be effectively treated with ophthalmic solutions, suspensions, ointments or inserts comprising an agent or combination of agents of the present invention. Eye drops can be prepared by dissolving the active ingredient in a sterile aqueous solution such as physiological saline, buffering solution, etc., or by combining powder compositions to be dissolved before use. Other vehicles can be chosen, as is known in the art, including but not limited to: balance salt solution, saline solution, water soluble polyethers such as polyethylene glycol, polyvinyls, such as polyvinyl alcohol and povidone, cellulose derivatives such as methylcellulose and hydroxypropyl methylcellulose, petroleum derivatives such as mineral oil and white petrolatum, animal fats such as lanolin, polymers of acrylic acid such as carboxypolymethylene gel, vegetable fats such as peanut oil and polysaccharides such as dextrans, and glycosaminoglycans such as sodium hyaluronate. If desired, additives ordinarily used in the eye drops can be added. Such additives include isotonizing agents (e.g., sodium chloride, etc.), buffer agent (e.g., boric acid, sodium monohydrogen phosphate, sodium dihydrogen phosphate, etc.), preservatives (e.g., benzalkonium chloride, benzethonium chloride, chlorobutanol, etc.), thickeners (e.g., saccharide such as lactose, mannitol, maltose, etc.; e.g., hyaluronic acid or its salt such as sodium hyaluronate, potassium hyaluronate, etc.; e.g., mucopolysaccharide such as chondroitin sulfate, etc.; e.g., sodium polyacrylate, carboxyvinyl polymer, crosslinked polyacrylate, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents known to those skilled in the art).

[0439] The solubility of the components of the present compositions can be enhanced by a surfactant or other appropriate co-solvent in the composition. Such cosolvents include polysorbate 20, 60, and 80, Pluronic F68, F-84 and P-103, cyclodextrin, or other agents known to those skilled in the art. Such co-solvents can be employed at a level of from about 0.01% to 2% by weight.

[0440] The compositions of the invention can be packaged in multidose form. Preservatives can be preferred to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, Onamer M, or other

agents known to those skilled in the art. In the prior art ophthalmic products, such preservatives can be employed at a level of from 0.004% to 0.02%. In the compositions of the present application the preservative, preferably benzalkonium chloride, can be employed at a level of from 0.001% to less than 0.01%, e.g. from 0.001% to 0.008%, preferably about 0.005% by weight. It has been found that a concentration of benzalkonium chloride of 0.005% can be sufficient to preserve the compositions of the present invention from microbial attack.

[0441] In another aspect, viral infections of the ear can be effectively treated with otic solutions, suspensions, ointments or inserts comprising an agent or combination of agents of the present invention.

[0442] In another aspect, the agents of the present invention are delivered in soluble rather than suspension form, which allows for more rapid and quantitative absorption to the sites of action. In general, formulations such as jellies, creams, lotions, suppositories and ointments can provide an area with more extended exposure to the agents of the present invention, while formulations in solution, e.g., sprays, provide more immediate, short-term exposure.

[0443] In another aspect relating to topical/local application, the pharmaceutical compositions can include one or more penetration enhancers. For example, the formulations can comprise suitable solid or gel phase carriers or excipients that increase penetration or help delivery of agents or combinations of agents of the invention across a permeability barrier, e.g., the skin. Many of these penetration-enhancing compounds are known in the art of topical formulation, and include, e.g., water, alcohols (e.g., terpenes like methanol, ethanol, 2-propanol), sulfoxides (e.g., dimethyl sulfoxide, decylmethyl sulfoxide, tetradecylmethyl sulfoxide), pyrrolidones (e.g., 2-pyrrolidone, N-methyl-2-pyrrolidone, N-(2-hydroxyethyl)pyrrolidone), laurocapram, acetone, dimethylacetamide, dimethylformamide, tetrahydrofurfuryl alcohol, L- α -amino acids, anionic, cationic, amphoteric or nonionic surfactants (e.g., isopropyl myristate and sodium lauryl sulfate), fatty acids, fatty alcohols (e.g., oleic acid), amines, amides, clofibric acid amides, hexamethylene lauramide, proteolytic enzymes, α -bisabolol, d-limonene, urea and N,N-diethyl-m-toluamide, and the like. Additional examples include humectants (e.g., urea), glycols (e.g., propylene glycol and polyethylene glycol), glycerol monolaurate, alkanes, alkanols, ORGELASE, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and/or other polymers. In another aspect, the pharmaceutical compositions will include one or more such penetration enhancers.

[0444] In another aspect, the pharmaceutical compositions for local/topical application can include one or more antimicrobial preservatives such as quaternary ammonium compounds, organic mercurials, p-hydroxy benzoates, aromatic alcohols, chlorobutanol, and the like.

[0445] Gastrointestinal viral infections can be effectively treated with orally- or rectally delivered solutions, suspensions, ointments, enemas and/or suppositories comprising an agent or combination of agents of the present invention.

[0446] Respiratory viral infections can be effectively treated with aerosol solutions, suspensions or dry powders comprising an agent or combination of agents of the present invention. Administration by inhalation is particularly useful in treating viral infections of the lung, such as an HRV infection. The aerosol can be administered through the respiratory system or nasal passages. For example, one skilled in the art will recognize that a composition of the present invention can be suspended or dissolved in an appropriate carrier, e.g., a pharmaceutically acceptable propellant, and administered directly into the lungs using a nasal spray or inhalant. For example, an aerosol formulation comprising a fatty acid synthesis pathway inhibitor e.g., an inhibitor of *FASN* gene expression or FASN protein activity, can be dissolved, suspended or emulsified in a propellant or a mixture of solvent and propellant, e.g., for administration as a nasal spray or inhalant. Aerosol formulations can contain any acceptable propellant under pressure, such as a cosmetically or dermatologically or pharmaceutically acceptable propellant, as conventionally used in the art.

[0447] An aerosol formulation for nasal administration is generally an aqueous solution designed to be administered to the nasal passages in drops or sprays. Nasal solutions can be similar to nasal secretions in that they are generally isotonic and slightly buffered to maintain a pH of about 5.5 to about 6.5, although pH values outside of this range can additionally be used. Antimicrobial agents or preservatives can also be included in the formulation.

[0448] An aerosol formulation for inhalations and inhalants can be designed so that the agent or combination of agents of the present invention is carried into the respiratory tree of the subject when administered by the nasal or oral respiratory route. Inhalation solutions can be administered, for example, by a nebulizer. Inhalations or insufflations, comprising finely powdered or liquid drugs, can be delivered to the respiratory system as a pharmaceutical aerosol of a solution or suspension of the agent or combination of agents in a propellant, e.g., to aid in disbursement. Propellants can be liquefied gases, including halocarbons, for example, fluorocarbons such as fluorinated chlorinated hydrocarbons,

hydrochlorofluorocarbons, and hydrochlorocarbons, as well as hydrocarbons and hydrocarbon ethers.

[0449] Halocarbon propellants useful in the present invention include fluorocarbon propellants in which all hydrogens are replaced with fluorine, chlorofluorocarbon propellants in which all hydrogens are replaced with chlorine and at least one fluorine, hydrogen-containing fluorocarbon propellants, and hydrogen-containing chlorofluorocarbon propellants. Halocarbon propellants are described in Johnson, U.S. Pat. No. 5,376,359, issued Dec. 27, 1994; Byron et al., U.S. Pat. No. 5,190,029, issued Mar. 2, 1993; and Purewal et al., U.S. Pat. No. 5,776,434, issued Jul. 7, 1998. Hydrocarbon propellants useful in the invention include, for example, propane, isobutane, n-butane, pentane, isopentane and neopentane. A blend of hydrocarbons can also be used as a propellant. Ether propellants include, for example, dimethyl ether as well as the ethers. An aerosol formulation of the invention can also comprise more than one propellant. For example, the aerosol formulation can comprise more than one propellant from the same class, such as two or more fluorocarbons; or more than one, more than two, more than three propellants from different classes, such as a fluorohydrocarbon and a hydrocarbon. Pharmaceutical compositions of the present invention can also be dispensed with a compressed gas, e.g., an inert gas such as carbon dioxide, nitrous oxide or nitrogen.

[0450] Aerosol formulations can also include other components, for example, ethanol, isopropanol, propylene glycol, as well as surfactants or other components such as oils and detergents. These components can serve to stabilize the formulation and/or lubricate valve components.

[0451] The aerosol formulation can be packaged under pressure and can be formulated as an aerosol using solutions, suspensions, emulsions, powders and semisolid preparations. For example, a solution aerosol formulation can comprise a solution of an agent of the invention such as a fatty acid synthesis pathway inhibitor e.g., an inhibitor of *FASN* gene expression or *FASN* protein activity, in (substantially) pure propellant or as a mixture of propellant and solvent. The solvent can be used to dissolve the agent and/or retard the evaporation of the propellant. Solvents useful in the invention include, for example, water, ethanol and glycols. Any combination of suitable solvents can be use, optionally combined with preservatives, antioxidants, and/or other aerosol components.

[0452] An aerosol formulation can also be a dispersion or suspension. A suspension aerosol formulation can comprise a suspension of an agent or combination of agents of the instant invention, e.g., a fatty acid synthesis pathway inhibitor, e.g., an inhibitor of *FASN*

gene expression or FASN protein activity, and a dispersing agent. Dispersing agents useful in the invention include, for example, sorbitan trioleate, oleyl alcohol, oleic acid, lecithin and corn oil. A suspension aerosol formulation can also include lubricants, preservatives, antioxidant, and/or other aerosol components.

[0453] An aerosol formulation can similarly be formulated as an emulsion. An emulsion aerosol formulation can include, for example, an alcohol such as ethanol, a surfactant, water and a propellant, as well as an agent or combination of agents of the invention, e.g., a fatty acid synthesis pathway, e.g., an inhibitor of *FASN* gene expression or FASN protein activity. The surfactant used can be nonionic, anionic or cationic. One example of an emulsion aerosol formulation comprises, for example, ethanol, surfactant, water and propellant. Another example of an emulsion aerosol formulation comprises, for example, vegetable oil, glyceryl monostearate and propane.

[0454] The compounds of the invention can be formulated for administration as suppositories. A low melting wax, such as a mixture of triglycerides, fatty acid glycerides, Witepsol S55 (trademark of Dynamite Nobel Chemical, Germany), or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

[0455] The compounds of the invention can be formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0456] It is envisioned additionally, that the compounds of the invention can be attached releasably to biocompatible polymers for use in sustained release formulations on, in or attached to inserts for topical, intraocular, periocular, or systemic administration. The controlled release from a biocompatible polymer can be utilized with a water soluble polymer to form a instillable formulation, as well. The controlled release from a biocompatible polymer, such as for example, PLGA microspheres or nanospheres, can be utilized in a formulation suitable for intra ocular implantation or injection for sustained release administration, as well. Any suitable biodegradable and biocompatible polymer can be used.

[0457] Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are present in an effective amount, i.e., in an amount effective to achieve therapeutic and/or prophylactic benefit in a host with at least one viral infection or in a subject having cancer. The actual amount effective for a particular application will depend on the condition or conditions being treated, the condition of the

subject, the formulation, and the route of administration, as well as other factors known to those of skill in the art. Determination of an effective amount of a fatty acid synthesis pathway inhibitor e.g., an inhibitor of *FASN* gene expression or FASN protein activity, is well within the capabilities of those skilled in the art, in light of the disclosure herein, and will be determined using routine optimization techniques.

[0458] The effective amount for use in humans can be determined from animal models. For example, a dose for humans can be formulated to achieve circulating, liver, topical and/or gastrointestinal concentrations that have been found to be effective in animals. One skilled in the art can determine the effective amount for human use, especially in light of the animal model experimental data described herein. Based on animal data, and other types of similar data, those skilled in the art can determine the effective amounts of compositions of the present invention appropriate for humans.

[0459] The effective amount when referring to an agent or combination of agents of the invention will generally mean the dose ranges, modes of administration, formulations, etc., that have been recommended or approved by any of the various regulatory or advisory organizations in the medical or pharmaceutical arts (e.g., FDA, AMA) or by the manufacturer or supplier.

[0460] Further, appropriate doses for a fatty acid synthesis pathway inhibitor e.g., an inhibitor of *FASN* gene expression or FASN protein activity, can be determined based on *in vitro* experimental results. For example, the *in vitro* potency of an agent in inhibiting a fatty acid synthesis pathway component, e.g., *FASN* gene expression or FASN protein activity, provides information useful in the development of effective *in vivo* dosages to achieve similar biological effects.

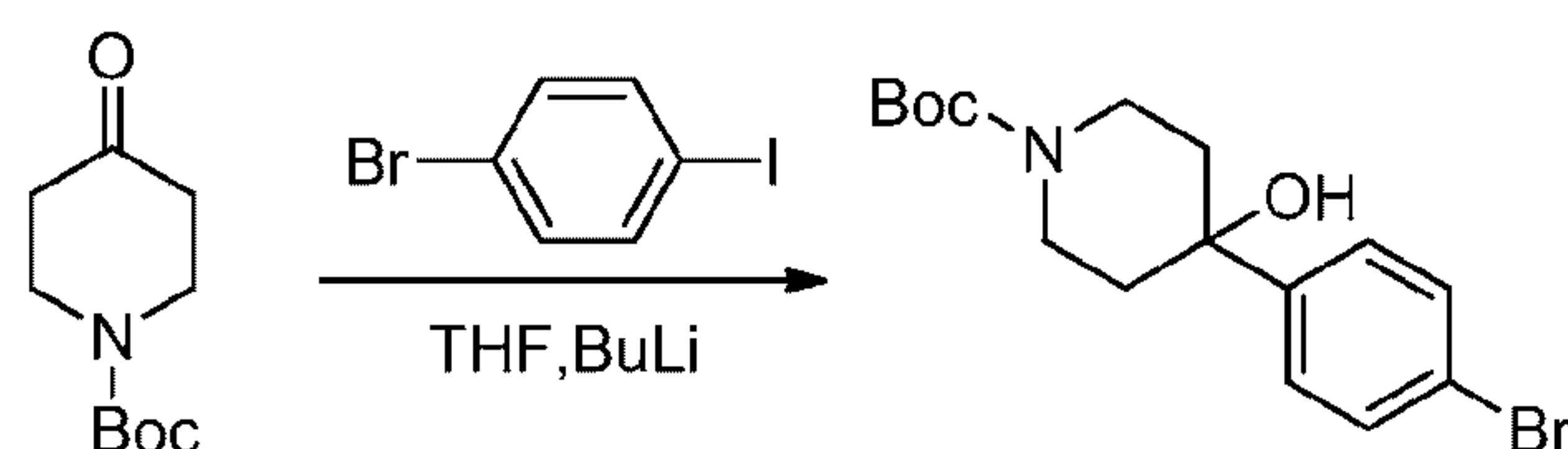
[0461] In another aspect, administration of agents of the present invention can be intermittent, for example administration once every two days, every three days, every five days, once a week, once or twice a month, and the like. In another aspect, the amount, forms, and/or amounts of the different forms can be varied at different times of administration.

[0462] A person of skill in the art would be able to monitor in a patient the effect of administration of a particular agent. For example, HIV viral load levels can be determined by techniques standard in the art, such as measuring CD4 cell counts, and/or viral levels as detected by PCR. Other techniques would be apparent to one of skill in the art.

[0463] Having now generally described various aspects and aspects of the invention, the same will be more readily understood through reference to the following examples which are provided by way of illustration, and are not intended to be limiting, unless specified.

EXAMPLESExample – Synthesis of Compounds of the Present Disclosure

[0464] **General:** All reactions and manipulations described were carried out in well ventilated fume-hoods. Operations and reactions carried out at elevated or reduced pressure were carried out behind blast shields. Abbreviations: ACN, acetonitrile; AcOH, acetic acid; AIBN, azobisisobutyronitrile; BuLi, butyl lithium; CDI, 1,1'-Carbonyldiimidazole; DBU, 1,8-Diazabicyclo[5.4.0]undec-7-ene; DCE, 1,2-dichloroethane; DCM, dichloromethane or methylene chloride; DIEA, N,N-Diisopropylethylamine; DMAP, 4-dimethylaminopyridine; DMF, N,N-dimethylformamide; DMSO, dimethylsulfoxide; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; EtOAc, ethyl acetate; EtOH, Ethanol; HATU, 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate; HBTU, O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate or 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate; HMPA, hexamethylphosphoramide; HOAc, acetic acid; HOBT, 1-Hydroxybenzotriazole; LDA, lithium diisopropylamine; MeOH, methanol; MsCl, methanesulfonyl chloride; MsOH, methanesulfonic acid; NBS, N-bromosuccinimide; NIS, N-iodosuccinimide; PE, petroleum ether; PTAT, phenyltrimethylammonium tribromide; PTSA, p-toluenesulfonic acid; Py, pyridine; Pyr, pyridine; TEA, triethylamine; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TMSCl, chlorotrimethylsilane; TsOH, p-toluenesulfonic acid.

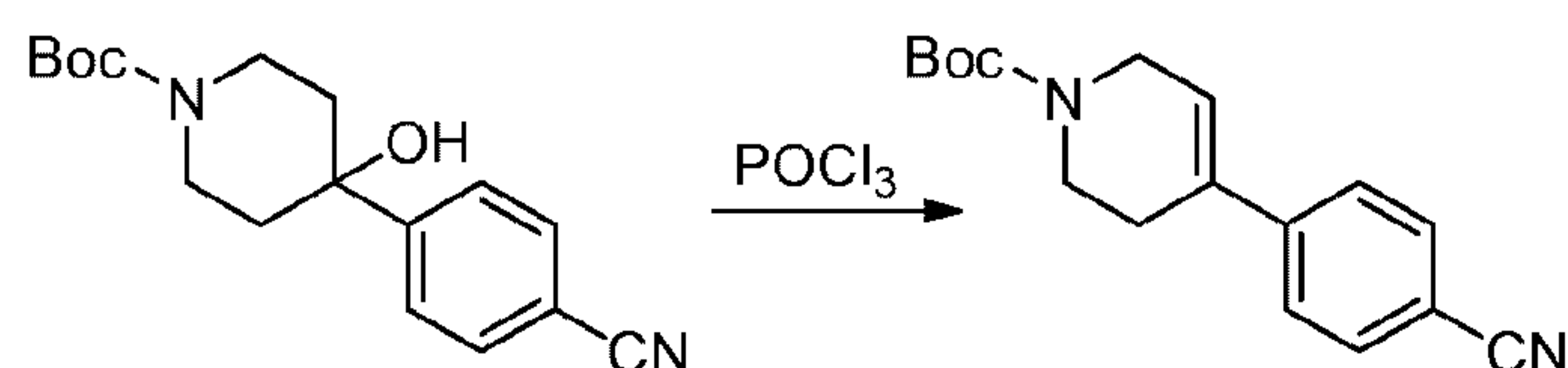


[0465] **Compound 1.1. tert-Butyl 4-(4-bromophenyl)-4-hydroxypiperidine-1-carboxylate.** To a stirred solution of 1-bromo-4-iodobenzene (93.7 g, 331.21 mmol, 1.10 equiv) in tetrahydrofuran (800 mL) under nitrogen at -78°C was added dropwise of a solution of butyllithium (150 mL, 2.43 M in THF, 1.05 equiv) during 30 min. The resulting solution was stirred for 2 h at -78°C. To this was then added a solution of tert-butyl 4-oxopiperidine-1-carboxylate (60 g, 301.13 mmol, 1.00 equiv) in tetrahydrofuran (800 mL) dropwise with stirring at -78°C during 30 min. After stirring for 1 h at -78°C, reaction was carefully quenched with 350 mL of H₂O. The resulting mixture was extracted with 2x400 mL of ethyl acetate and the combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified using silica gel column chromatography with ethyl

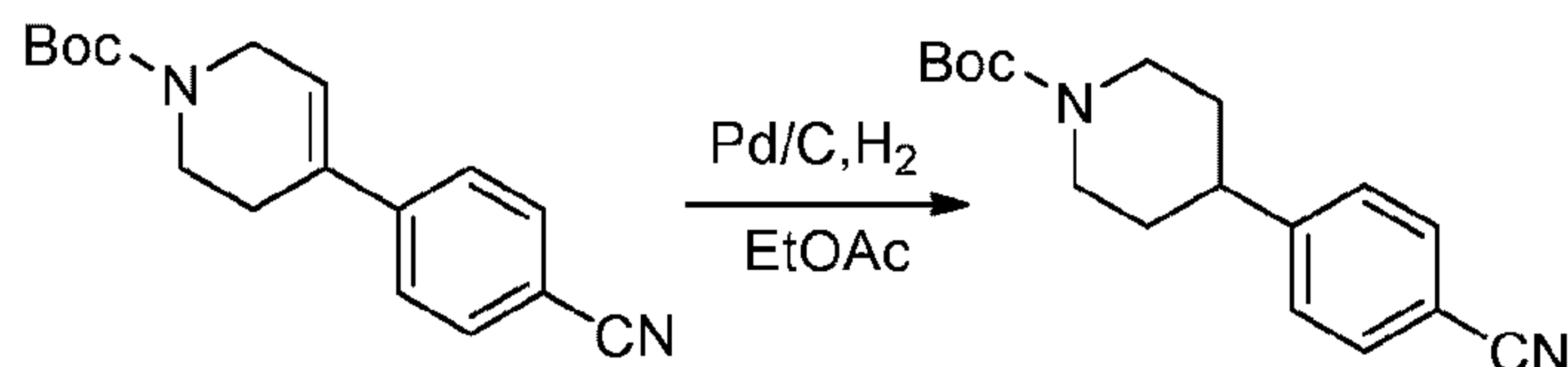
acetate/petroleum ether (1:200-1:10) as eluent to yield 91 g (85%) of the title compound as a yellow oil.



[0466] Compound 1.2. tert-Butyl 4-(4-cyanophenyl)-4-hydroxypiperidine-1-carboxylate. A solution of tert-butyl 4-(4-bromophenyl)-4-hydroxypiperidine-1-carboxylate (compound 1.1, 36 g, 101.05 mmol, 1.00 equiv), Pd(PPh₃)₄ (11.7 g, 10.12 mmol, 0.05 equiv), and Zn(CN)₂ (17.9 g, 152.44 mmol, 1.51 equiv) in DMF (400 mL) under nitrogen was stirred overnight at 80°C. After reaching ambient temperature, the reaction was then quenched by the addition of 600 mL of FeSO₄ (aq., sat.) and diluted with ethyl acetate. The resulting mixture was stirred vigorously then filtered through celite and washed with 1 M FeSO₄, water, and ethyl acetate. The layers were separated and the aqueous phase was extracted with 2 x 300 mL of ethyl acetate. The combined organic layers were washed with 1x200 mL of potassium carbonate (aq., sat.) followed by 1x200 mL of brine, dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:200-1:5) as eluent to yield 23 g (75%) of the title compound as a white solid.

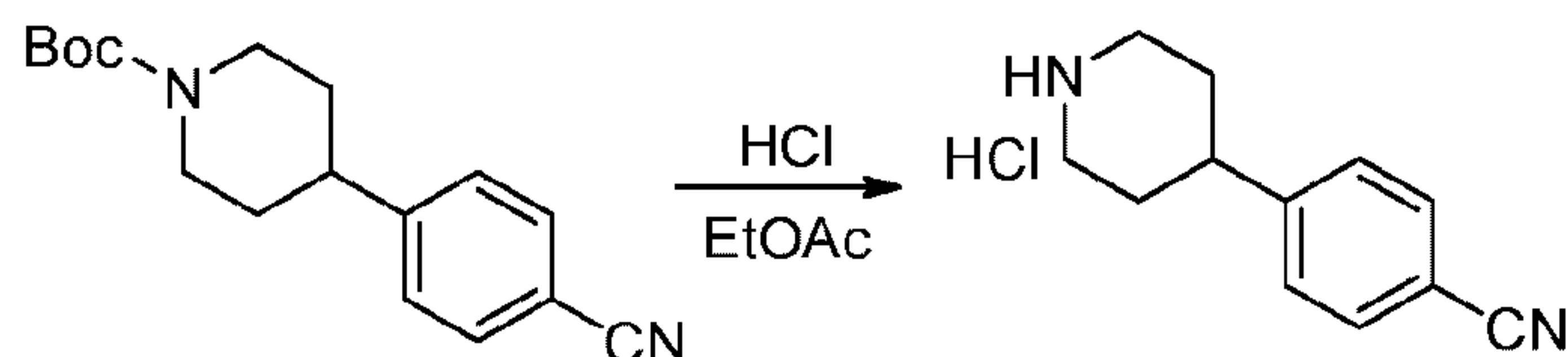


[0467] Compound 1.3. tert-Butyl 4-(4-cyanophenyl)-5,6-dihydropyridine-1(2H)-carboxylate. Into a round-bottom flask, was placed a solution of tert-butyl 4-(4-cyanophenyl)-4-hydroxypiperidine-1-carboxylate (compound 1.2, 2 g, 6.61 mmol, 1.00 equiv) in pyridine (40 mL). POCl₃ (10.16 g, 66.26 mmol, 10.02 equiv) was carefully added. The resulting mixture was stirred under nitrogen overnight at room temperature and then concentrated under vacuum. The residue was taken up in 20 mL of DCM, washed with 2x20 mL of sodium bicarbonate (aq), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified using silica gel column chromatography with PE/EtOAc (100:1-30:1) as eluent to yield 1.4 g (74%) of the title compound as a white solid.



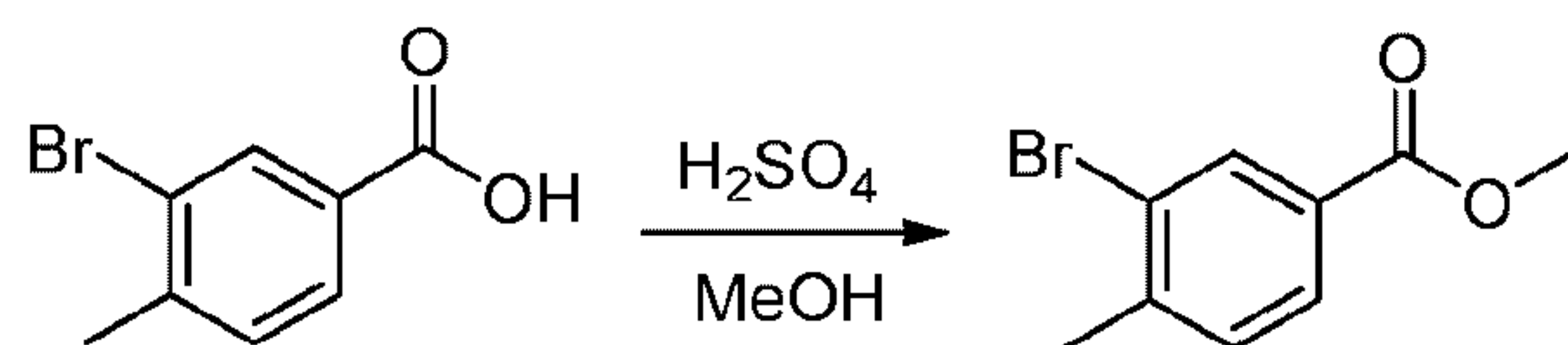
[0468] Compound 1.4. tert-Butyl 4-(4-cyanophenyl)piperidine-1-carboxylate.

Around-bottom flask, containing a solution of tert-butyl 4-(4-cyanophenyl)-5,6-dihydropyridine-1(2H)-carboxylate (compound **1.3**, 500 mg, 1.76 mmol, 1.00 equiv) in ethyl acetate (20 mL) was purged with nitrogen gas. To the solution was then added palladium on carbon (0.1 g, 10%, 60% water) and the flask was then further purged with nitrogen. The atmosphere was then changed to hydrogen and the mixture was stirred overnight at room temperature. After purging the system with nitrogen, the solids were removed by filtration and the filtrate was concentrated under reduced pressure to yield 0.2 g (40%) of the title compound as a yellow oil.



[0469] Compound 1.5. 4-(Piperidin-4-yl)benzonitrile hydrochloride.

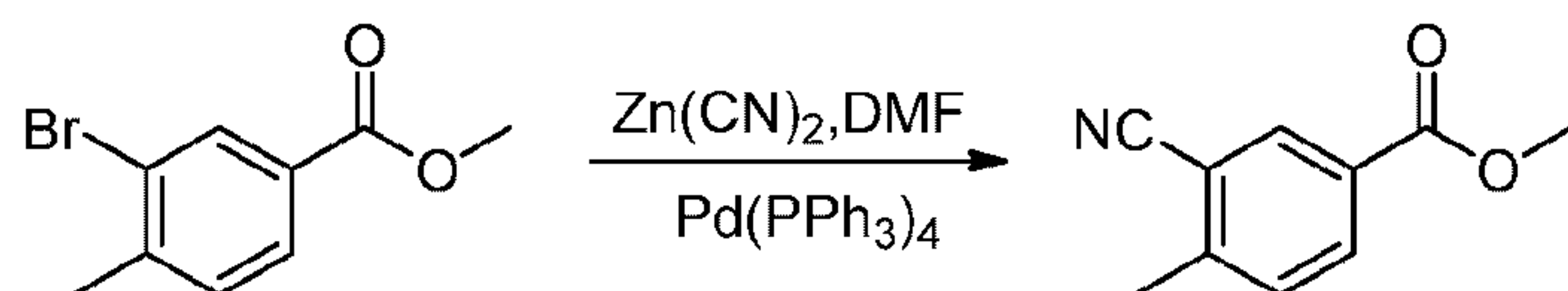
Into a 100-mL 3-necked round-bottom flask, was placed a solution of tert-butyl 4-(4-cyanophenyl)piperidine-1-carboxylate (compound **1.4**, 4 g, 13.99 mmol, 1.00 equiv) in ethyl acetate (60 mL). Hydrogen chloride (gas) was bubbled through the solution and the resulting mixture was stirred for 1 h at room temperature. The formed precipitate was collected by filtration and dried to yield 2.2 g (71%) of the title compound as a white solid. m/z (ES⁺) 187 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.72 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 3.54 (d with fine structure, J = 12.6 Hz, 2H), 3.18 (t with fine structure, J = 12.2 Hz, 2H), 3.12-1.97 (m, 1H), 2.11 (d with fine structure, J = 14.1 Hz, 2H), 2.04-1.84 (m, 2H).



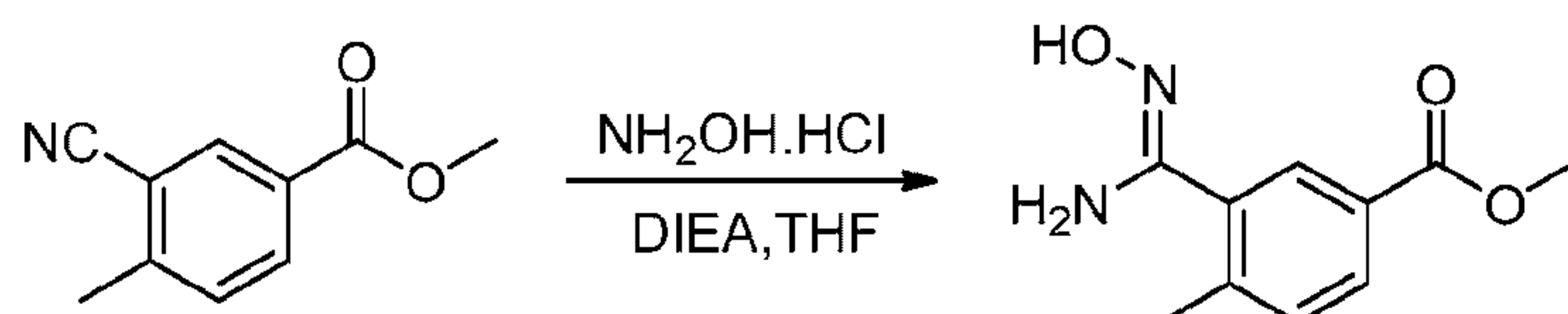
[0470] Compound 1.6. Methyl 3-bromo-4-methylbenzoate.

A solution of 3-bromo-4-methylbenzoic acid (20 g, 93.00 mmol, 1.00 equiv) and sulfuric acid (20 mL) in methanol (100 mL) was stirred overnight at 80°C. The mixture was then concentrated under reduced pressure and the residue was diluted with 500 mL of ethyl acetate. The resulting mixture was washed with 3x200 mL of water, 1x200 mL of sodium bicarbonate (aq), followed by 1x200

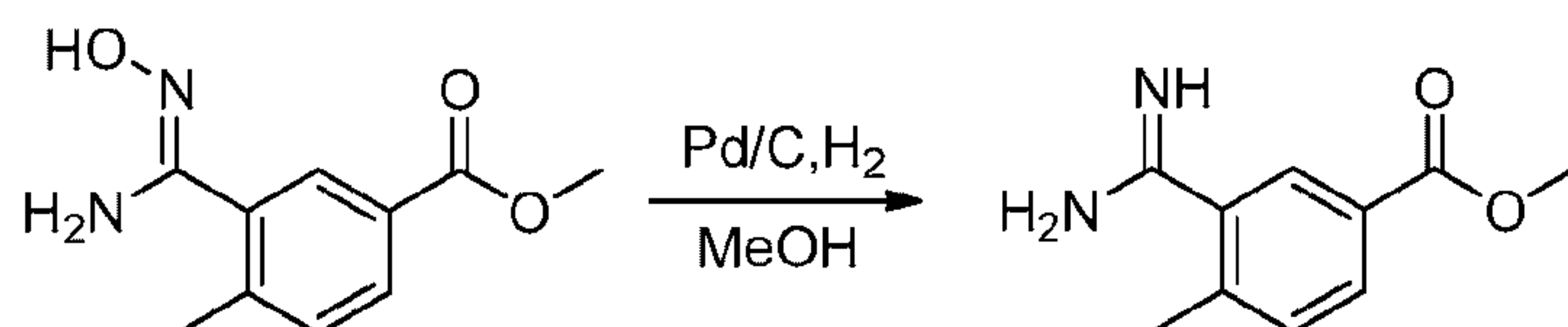
mL of brine. The organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and dried to yield 20 g (94%) of the title compound as a dark red oil.



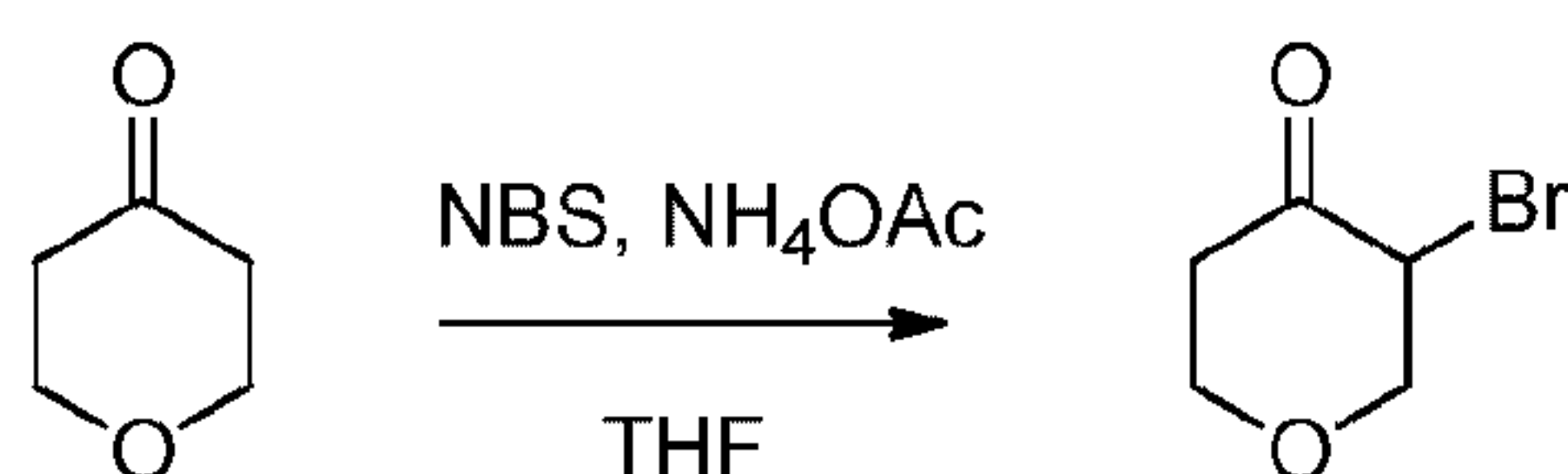
[0471] Compound 1.7. Methyl 3-cyano-4-methylbenzoate. A mixture of methyl 3-bromo-4-methylbenzoate (compound 1.6, 18 g, 78.58 mmol, 1.00 equiv), Zn(CN)_2 (11.1 g, 94.87 mmol, 1.20 equiv), and $\text{Pd(PPh}_3)_4$ (7.3 g, 6.32 mmol, 0.08 equiv) in N,N-dimethylformamide (250 mL) was stirred under a nitrogen atmosphere at 100°C overnight. After cooling to room temperature, the reaction was then quenched by careful addition of 200 mL of FeSO_4 (aq., sat.) and diluted with ethyl acetate. The resulting mixture was stirred vigorously then filtered through celite and washed with 1 M FeSO_4 , water, and ethyl acetate. The layers were separated and the aqueous phase was extracted with 2 x 500 mL of ethyl acetate. The combined organic layers were washed with 3x200 mL of brine, dried over (Na_2SO_4), and concentrated under reduced pressure. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:50) as eluent to yield 11 g (76%) of the title compound as an off-white solid.



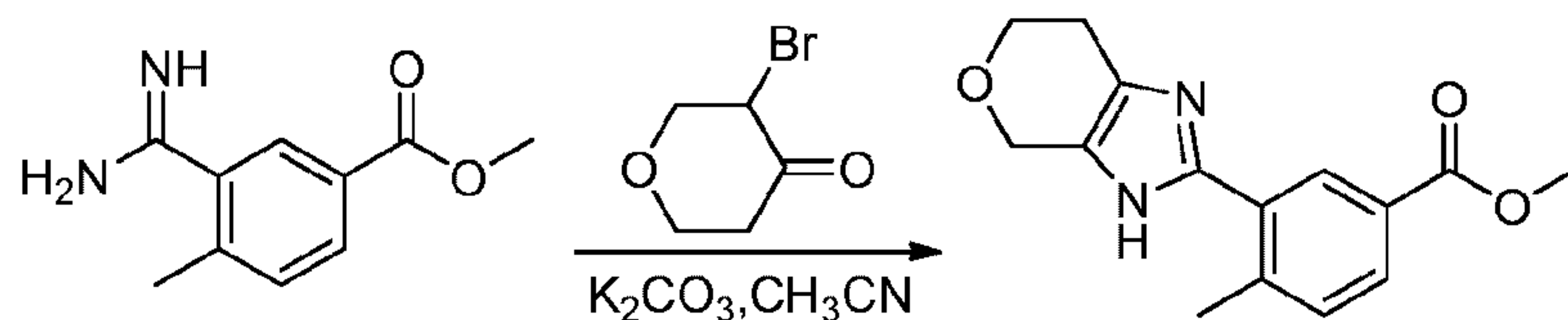
[0472] Compound 1.8. Methyl 3-(N'-hydroxycarbamimidoyl)-4-methylbenzoate. A mixture of methyl 3-cyano-4-methylbenzoate (compound 1.7, 8 g, 43.38 mmol, 1.00 equiv, 95%), $\text{NH}_2\text{OH.HCl}$ (3.785 g, 54.86 mmol, 1.20 equiv), and N,N-Diisopropylethylamine (DIEA, 17.7 g, 136.95 mmol, 3.00 equiv) in tetrahydrofuran (100 mL) was stirred overnight at 70°C. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was taken up in water and the pH was adjusted to 2-3 with hydrogen chloride (aqueous, 1 M). After washing the mixture with 3x40 mL of ethyl acetate, the pH of the aqueous layer was adjusted to 8-9 with NaOH (aqueous, 2 M) followed by extraction with 3x30 mL of ethyl acetate. The combined organic layers were dried over (Na_2SO_4) and concentrated under reduced pressure to yield 2.76 g (29%) of the title compound as a white solid.



[0473] Compound 1.9. Methyl 3-carbamimidoyl-4-methylbenzoate. A round-bottom flask, containing a solution of methyl 3-(N'-hydroxycarbamimidoyl)-4-methylbenzoate (compound 1.8, 8 g, 36.50 mmol, 1.00 equiv, 95%) in methanol (150 mL) was purged with nitrogen gas. To the solution was added palladium on carbon (9 g, 10%, 60% water) and the flask was then further purged with nitrogen gas. The atmosphere was then changed to hydrogen and the mixture was stirred overnight at 25°C under a balloon. After purging the system with nitrogen, the solids were removed by filtration and the filtrate was concentrated under reduced pressure to yield 4 g (54%) of the title compound as a brown solid.

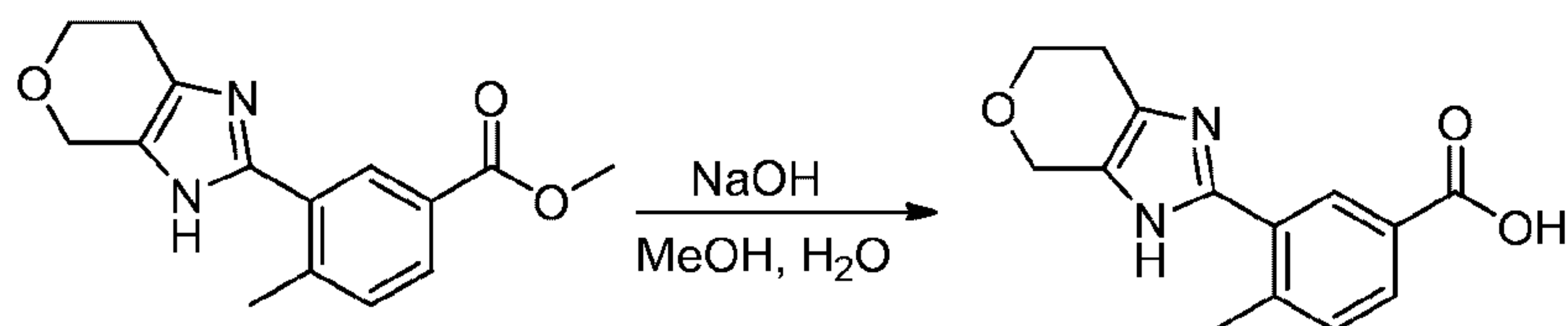


[0474] Compound 1.10.1 3-Bromodihydro-2H-pyran-4(3H)-one. To a mixture of dihydro-2H-pyran-4(3H)-one (10 g, 99.88 mmol, 1.00 equiv) and NH₄OAc (3.56 g, 46.23 mmol) in tetrahydrofuran (100 mL) at 0°C under nitrogen was added in several batches N-bromosuccinimide (17.8 g, 100.00 mmol, 1.00 equiv). The resulting mixture was stirred overnight at 30°C under nitrogen. The reaction mixture was then filtered and the filtrate was concentrated. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1/10-1/5) as eluent to yield 15 g (50%) of the title compound as a brown oil.

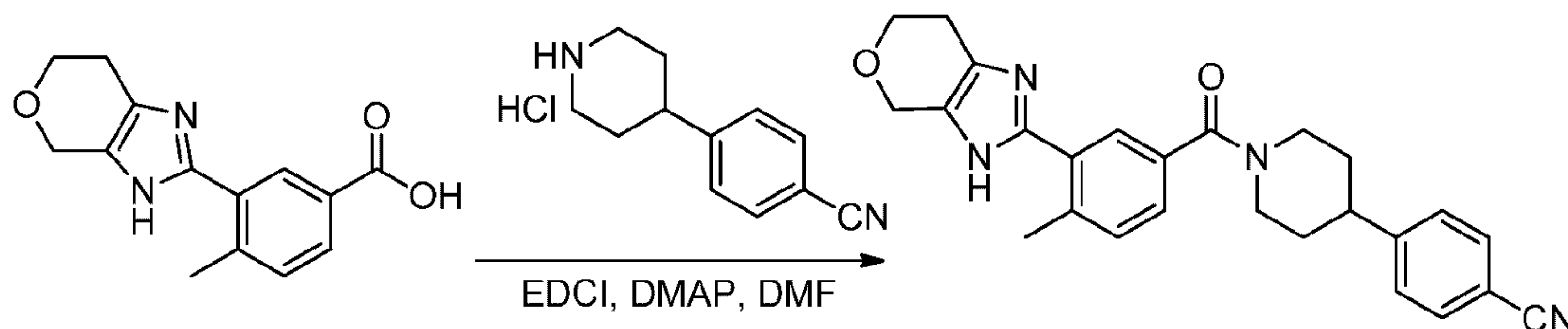


[0475] Compound 1.10. Methyl 4-methyl-3-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)benzoate. A mixture of methyl 3-carbamimidoyl-4-methylbenzoate (compound 1.9, 400 mg, 1.98 mmol, 1.00 equiv, 95%), 3-bromodihydro-2H-pyran-4(3H)-one (compound 1.10.1, 750 mg, 2.09 mmol, 1.00 equiv), and potassium carbonate (580 mg, 4.20 mmol, 2.00 equiv) in CH₃CN (15 mL) was stirred overnight at 80°C under nitrogen. After cooling to ambient temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in 50 mL of ethyl acetate and washed with 2x10 mL of

H₂O. The organic phase was dried over (Na₂SO₄) and concentrated under reduced pressure. The residue was purified using silica gel column chromatography and purified using ethyl acetate/petroleum ether (1/3) to yield 0.21 g (37%) of the title compound as a white solid.

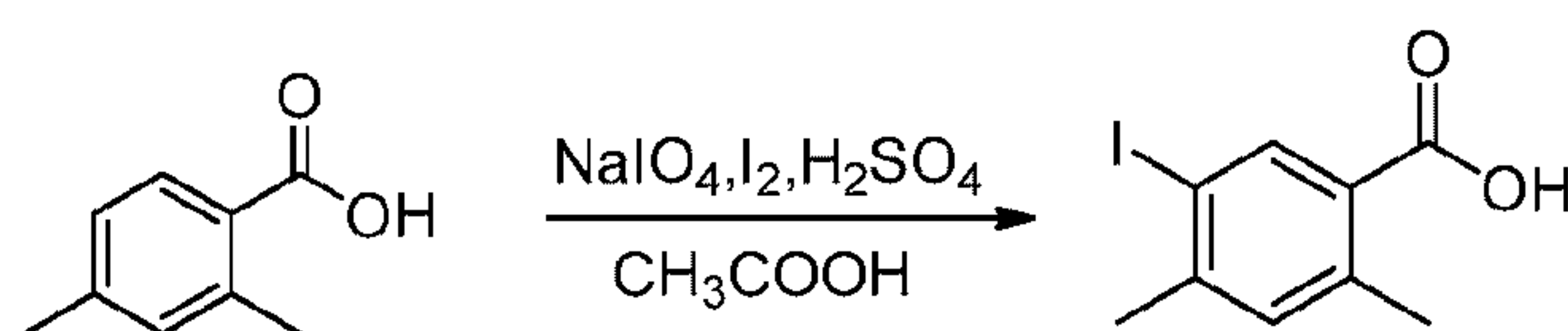


[0476] Compound 1.11. 4-Methyl-3-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)benzoic acid. A mixture of methyl 4-methyl-3-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)benzoate (compound **1.10**, 210 mg, 0.73 mmol, 1.00 equiv, 95%) and sodium hydroxide (92.65 mg, 2.32 mmol, 3.00 equiv) in 12 mL methanol/H₂O (2:1) was stirred for at 60°C in an oil bath. After 2 h, the reaction mixture was concentrated under reduced pressure and the residue was taken up in 5 mL of H₂O. The resulting mixture was washed with 3x10 mL of ethyl acetate and the pH of the aqueous layer was then adjusted to 2-3 using hydrogen chloride (aq., 2 M). The resulting mixture was extracted with 3x30 mL of ethyl acetate. The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to yield 0.21 g (89%) of the title compound as a white solid.

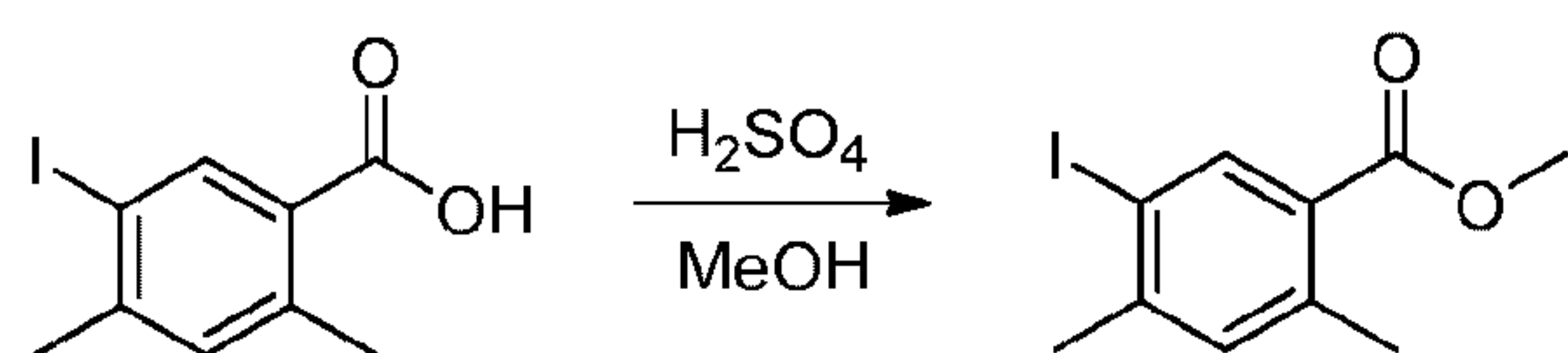


[0477] Compound 1. Methyl 4-(1-(4-methyl-3-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)benzoyl)piperidin-4-yl)benzonitrile. A mixture of 4-methyl-3-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)benzoic acid (compound **1.11**, 60 mg, 0.22 mmol, 1.00 equiv, 95%), EDCI (88.4 mg, 0.46 mmol, 2.00 equiv), DMAP (85.12 mg, 0.70 mmol, 3.00 equiv), and 4-(piperidin-4-yl)benzonitrile hydrochloride (compound **1.5**, 52 mg, 0.23 mmol, 1.00 equiv) in DMF was stirred at room temperature. After 3h, the reaction mixture was diluted with 40 mL of DCM and washed with 2x10 mL of NH₄Cl (aq.sat.) followed by 2x10 mL of brine. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The crude product (~100 mg) was purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-006(Waters)): Column, SunFire Prep C18, 19*150mm 5um; mobile phase, WATER WITH 0.05%TFA and CH₃CN (15.0% CH₃CN up to 42.0% in 12 min, up to 100.0% in 1 min); Detector, uv 254/220nm. The fractions containing pure compound were

combined and lyophilized to yield 32.9 mg (34%) of the title compound as a white solid. m/z (ES+) 427 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.73-7.65 (m, 4H), 7.61 (d, J = 5.7 Hz, 1H), 7.50 (d, J = 6.0 Hz, 2H), 4.89-4.78 (1H partially obscured by water peak), 4.81 (s, 2H), 4.10 (t, J = 4.1 Hz, 2H), 3.94-3.81 (m, 1H), ~3.35 (1H partially obscured by methanol solvent peak), 3.08-1.95 (m, 2H), 2.92 (t, J = 4.1 Hz, 2H), 2.52 (s, 3H), 2.08-1.92 (m, 1H), 1.92-1.65 (m, 3H). ¹H NMR (400 MHz, CDCl₃): δ 7.63 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 7.30 (s, 1H), 7.50 (m, 2H), 4.89 (d, J = 13.0 Hz, 1H), 4.81 (s, 2H), 4.05 (t, J = 5.2 Hz, 2H), 3.77 (d, J = 13.2 Hz, 1H), 3.30 (t, J = 13.0 Hz, 1H), 3.01-2.84 (m, 4H), 2.34 (s, 3H), 2.06 (d, J = 13.7 Hz, 1H), 1.86 (d, J = 12.9 Hz, 1H), 1.76 (q, J = 12.8 Hz, 1H), 1.57 (q, J = 11.7 Hz, 1H).

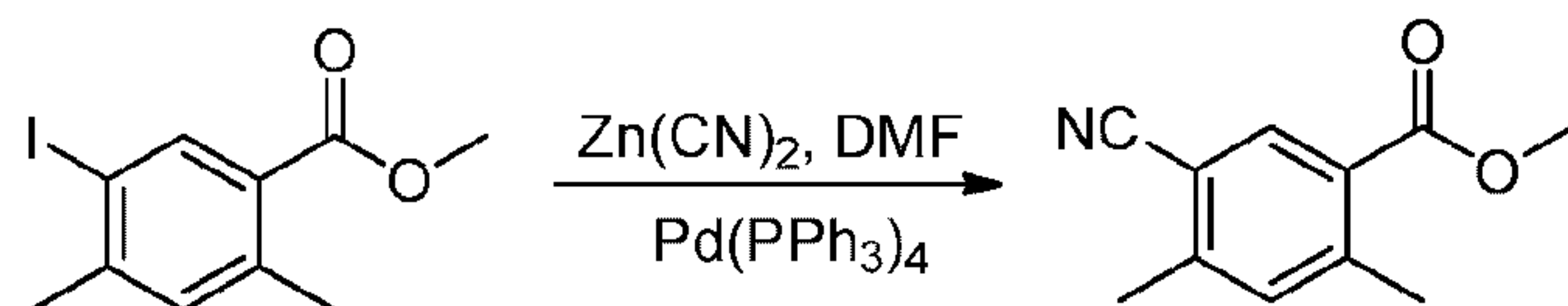


[0478] Compound 2.1. 5-Iodo-2,4-dimethylbenzoic acid. A solution of 2,4-dimethylbenzoic acid (20 g, 133.18 mmol, 1.00 equiv), sodium periodate (14.27 g, 66.72 mmol, 0.50 equiv), iodine (37.25 g, 146.76 mmol, 1.10 equiv), and sulfuric acid (1.96 g, 19.98 mmol, 0.15 equiv) in acetic acid (150 mL) was stirred at 110°C in an oil bath. After 6 h, the reaction mixture was allowed to reach ambient temperature and was then diluted with 1.2 L of water. To this was carefully added 800 mL of aq Na₂S₂O₃ (aq., sat.). The resulting solids were collected by filtration, dissolved in 1.2 L of ethyl acetate, and washed with 1x300 mL of Na₂S₂O₃ (aq., sat.) followed by 1x400 mL of brine. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The crude residue was re-crystallized from ethanol:H₂O (2:1) to yield 30 g (82%) of the title compound as a white solid.

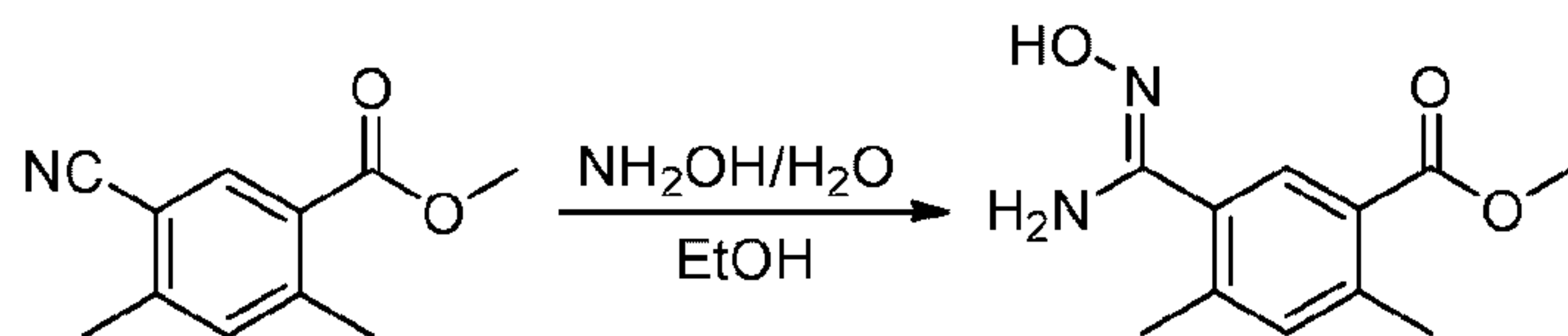


[0479] Compound 2.2. Methyl 5-iodo-2,4-dimethylbenzoate. A solution of 5-iodo-2,4-dimethylbenzoic acid (compound 2.1, 10 g, 32.60 mmol, 1.00 equiv, 90%) and sulfuric acid (10 mL) in methanol (100 mL) was stirred overnight at 80°C. After cooling to room temperature, the mixture was concentrated under reduced pressure and the residue was diluted with 200 mL of ethyl acetate. The resulting mixture was washed with 3x50 mL of water, 2x50 mL of sodium bicarbonate (aq. sat.), followed by 2x50 mL of brine. The organic

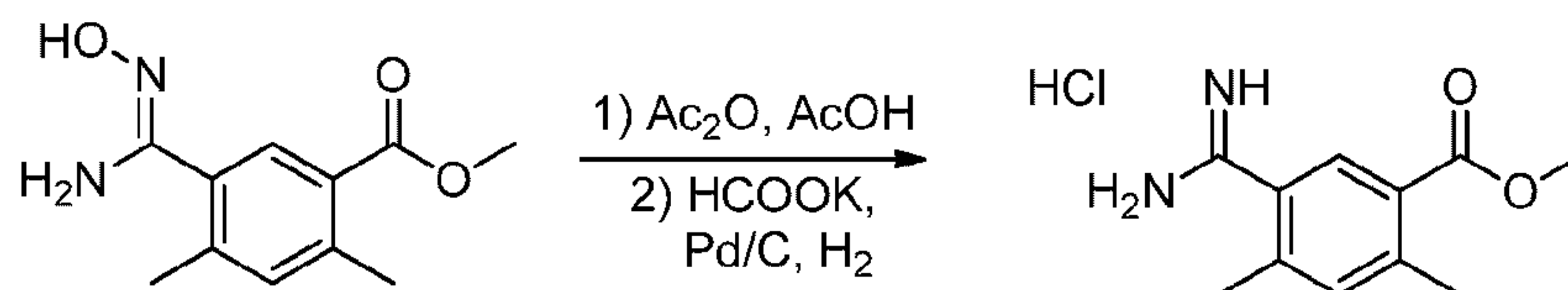
phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield 9.2 g (88%) of the title compound as a yellow oil.



[0480] Compound 2.3. Methyl 5-cyano-2,4-dimethylbenzoate. A solution of methyl 5-iodo-2,4-dimethylbenzoate (compound 2.2, 9.2 g, 31.71 mmol, 1.00 equiv), Zn(CN)_2 (4.46 g, 38.12 mmol, 1.20 equiv), and $\text{Pd(PPh}_3)_4$ (2.93 g, 2.54 mmol, 0.08 equiv) in N,N-dimethylformamide (120 mL) was stirred under a nitrogen atmosphere at 100°C overnight. After cooling to room temperature, the reaction was then quenched by careful addition of 100 mL of FeSO_4 (aq., sat.) and diluted with ethyl acetate. The resulting mixture was stirred vigorously then filtered through celite and washed with 1 M FeSO_4 , water, and ethyl acetate. The layers were separated and the aqueous phase was extracted with 2 x 100 mL of ethyl acetate. The combined organic layers were washed with 2x20 mL of brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:5) as eluent to yield 6.2 g (93%) of the title compound as a white solid.

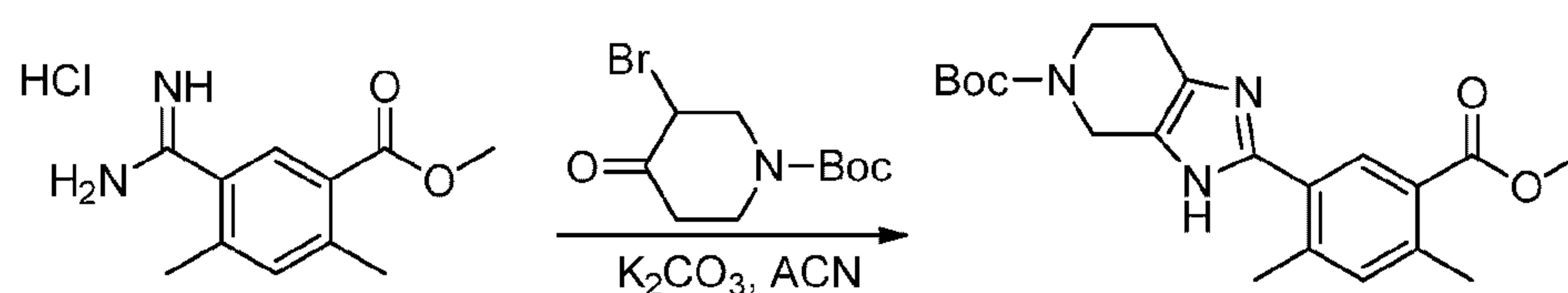


[0481] Compound 2.4. Methyl 5-(N'-hydroxycarbamimidoyl)-2,4-dimethylbenzoate. A solution of methyl 5-cyano-2,4-dimethylbenzoate (compound 2.3, 6 g, 28.54 mmol, 1.00 equiv, 90%) and NH_2OH (10 mL, 5.00 equiv, 50% in water) in EtOH (20 mL) was stirred at 100°C in an oil bath. After 2h, the mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with 100 mL of ethyl acetate, washed with 2x20 mL of brine, dried (Na_2SO_4), and concentrated under reduced pressure to yield 4.66 g (66%) of the title compound as a white solid.

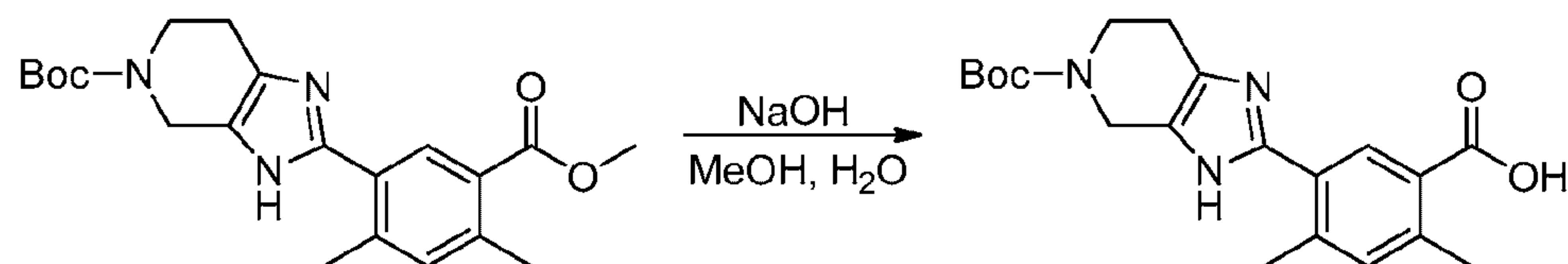


[0482] Compound 2.5. Methyl 5-carbamimidoyl-2,4-dimethylbenzoate hydrochloride. A solution of methyl 5-(N'-hydroxycarbamimidoyl)-2,4-dimethylbenzoate

(compound **2.4**, 4.66 g, 18.87 mmol, 1.00 equiv, 90%) and Ac₂O (2.36 g, 23.09 mmol, 1.10 equiv) in AcOH (21 mL) was stirred at room temperature. After 5 minutes, the flask was purged with nitrogen and HCOOK (8.8 g, 104.76 mmol, 5.00 equiv) and palladium on carbon (10%, 2.33 g) were added. The flask was purged with nitrogen followed by hydrogen. The mixture was stirred under a hydrogen atmosphere (balloon) at room temperature for 4 h. After purging the system with nitrogen, the solids were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 50 mL of ethanol and the pH was adjusted to 5-6 with hydrogen chloride (aq., 5 M). The resulting solids were removed by filtration and the filtrate was concentrated under reduced pressure to yield 4 g of the title compound as a white solid.

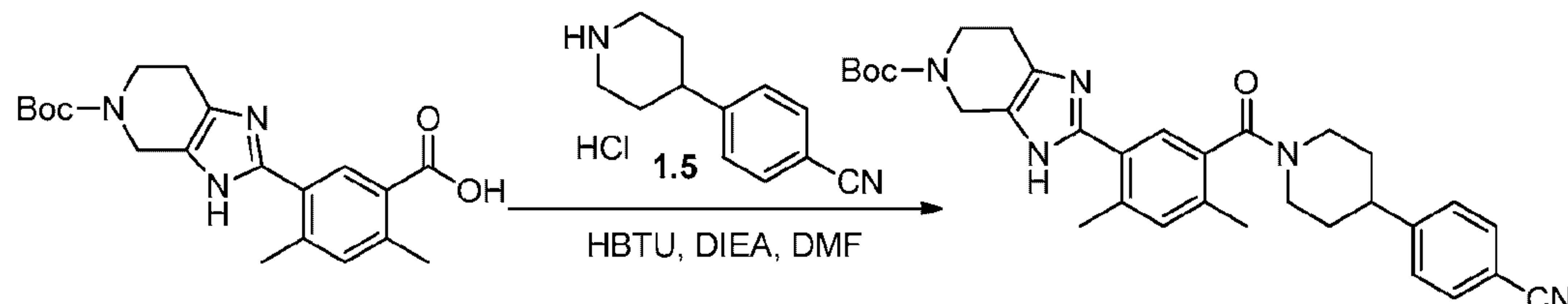


[0483] Compound 2.6. tert-Butyl 2-(5-(methoxycarbonyl)-2,4-dimethylphenyl)-6,7-dihydro-3H-imidazo[4,5-c]pyridine-5(4H)-carboxylate. A mixture of methyl methyl 5-carbamimidoyl-2,4-dimethylbenzoate hydrochloride (compound **2.5**, 500 mg, 90%), tert-butyl 3-bromo-4-oxopiperidine-1-carboxylate (860 mg, 2.78 mmol), and potassium carbonate (570 mg, 4.12 mmol) in CH₃CN (15 mL) was stirred overnight under nitrogen at 80°C. After cooling to ambient temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in 25 mL of ethyl acetate and washed with 2x10 mL of H₂O. The organic phase was dried (Na₂SO₄) and concentrated under reduced pressure. The crude product thus obtained was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:3) as eluent to yield 0.3 g of the title compound as a white solid.

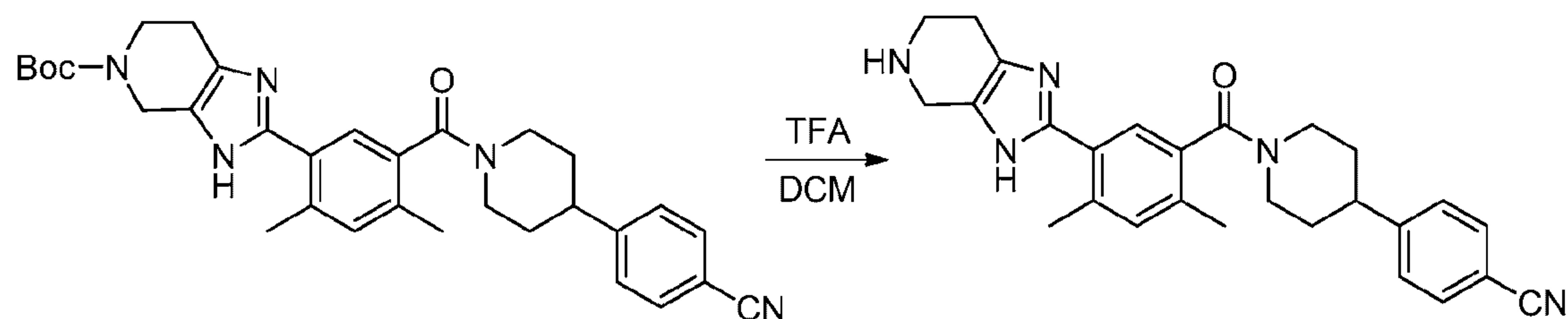


[0484] Compound 2.7. 5-(5-(tert-Butoxycarbonyl)-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-yl)-2,4-dimethylbenzoic acid. A mixture of tert-butyl 2-(5-(methoxycarbonyl)-2,4-dimethylphenyl)-6,7-dihydro-3H-imidazo[4,5-c]pyridine-5(4H)-carboxylate (compound **2.6**, 300 mg, 0.70 mmol, 1.00 equiv, 90%) and sodium hydroxide (62 mg, 1.55 mmol, 2.00 equiv) in 15 mL methanol/H₂O (2:1) was stirred for at 40°C in an oil

bath. After 2 h, the reaction mixture was concentrated to about 1/3 of the volume under reduced pressure. The pH value of the remaining mixture was adjusted to 3-4 with hydrogen chloride (aq., 1 M). The resulting solids were collected by filtration and dried in an oven under reduced pressure to yield 0.2 g (69%) of the title compound as a yellow solid.

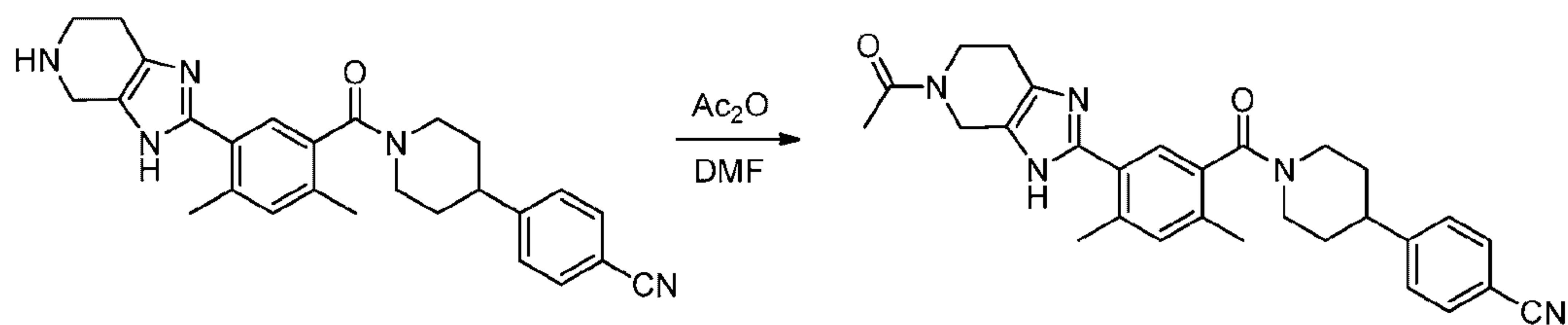


[0485] **Compound 2.8. tert-Butyl 2-(5-(4-(4-cyanophenyl)piperidine-1-carboxyl)-2,4-dimethylphenyl)-6,7-dihydro-3H-imidazo[4,5-c]pyridine-5(4H)-carboxylate.** A solution of compound 2.7 (125 mg, 0.30 mmol, 1.00 equiv, 90%), DIEA (130.5 mg, 1.01 mmol, 3.00 equiv), HBTU (256.2 mg, 0.68 mmol, 2.00 equiv), and 4-(piperidin-4-yl)benzonitrile hydrochloride (compound 1.5, 75 mg, 0.30 mmol, 1.00 equiv) in DMF (5 mL) was stirred overnight at room temperature. The reaction mixture was then diluted with 50 mL of ethyl acetate, washed with 2x20 mL of brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified using silica gel column chromatography and purified using ethyl acetate/petroleum ether (1:1) to yield 0.1 g (55%) of the title compound as a yellow solid.

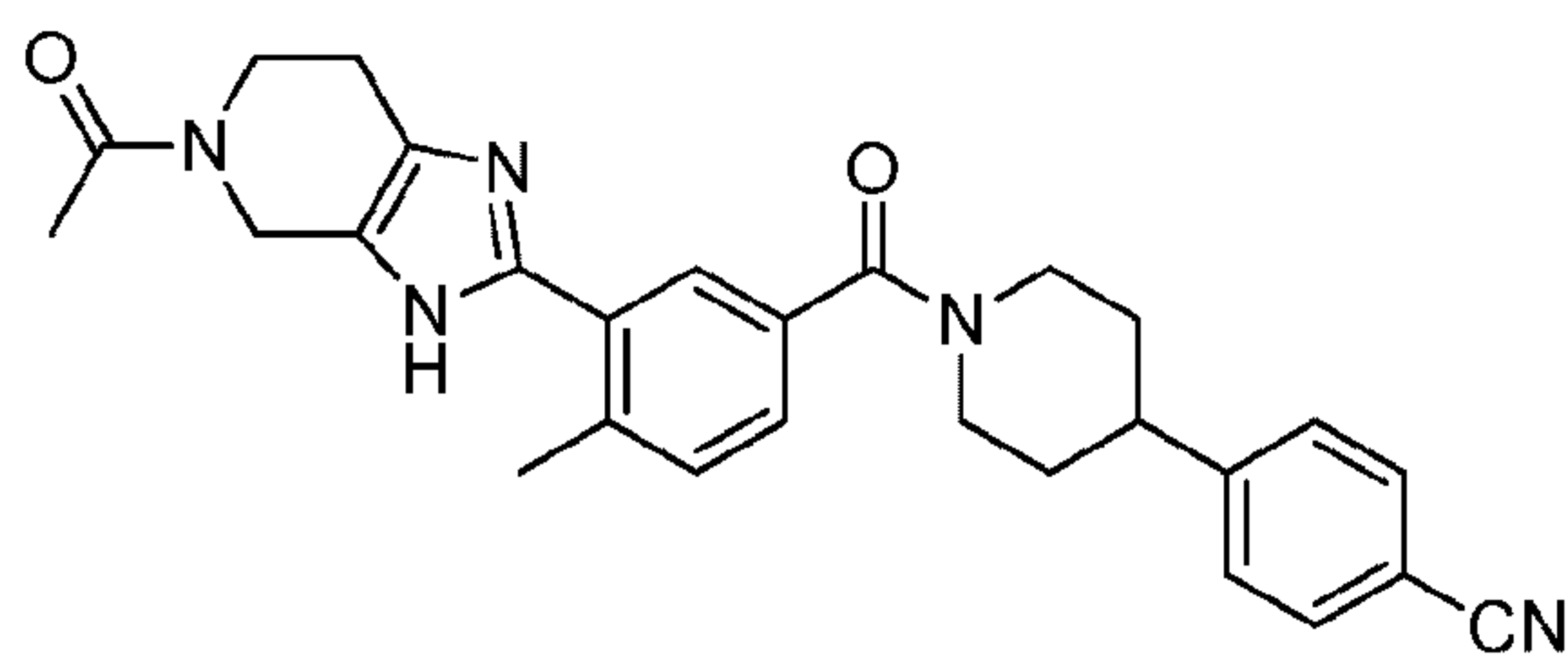


[0486] **Compound 2.9. 4-(1-(2,4-Dimethyl-5-(4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile.** To a solution of tert-butyl 2-(5-(4-(4-cyanophenyl)piperidine-1-carboxyl)-2,4-dimethylphenyl)-6,7-dihydro-3H-imidazo[4,5-c]pyridine-5(4H)-carboxylate (compound 2.8, 100 mg, 0.17 mmol, 1.00 equiv, 90%) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL). The resulting mixture was stirred at room temperature. After 2 h, the reaction mixture was concentrated under reduced pressure. The residue was taken up in dichloromethane and washed with sodium bicarbonate (aq., sat.). The organic phase was dried (Na₂SO₄) and concentrated under reduced pressure to yield 0.1 g (68%) of the title compound as a yellow solid.

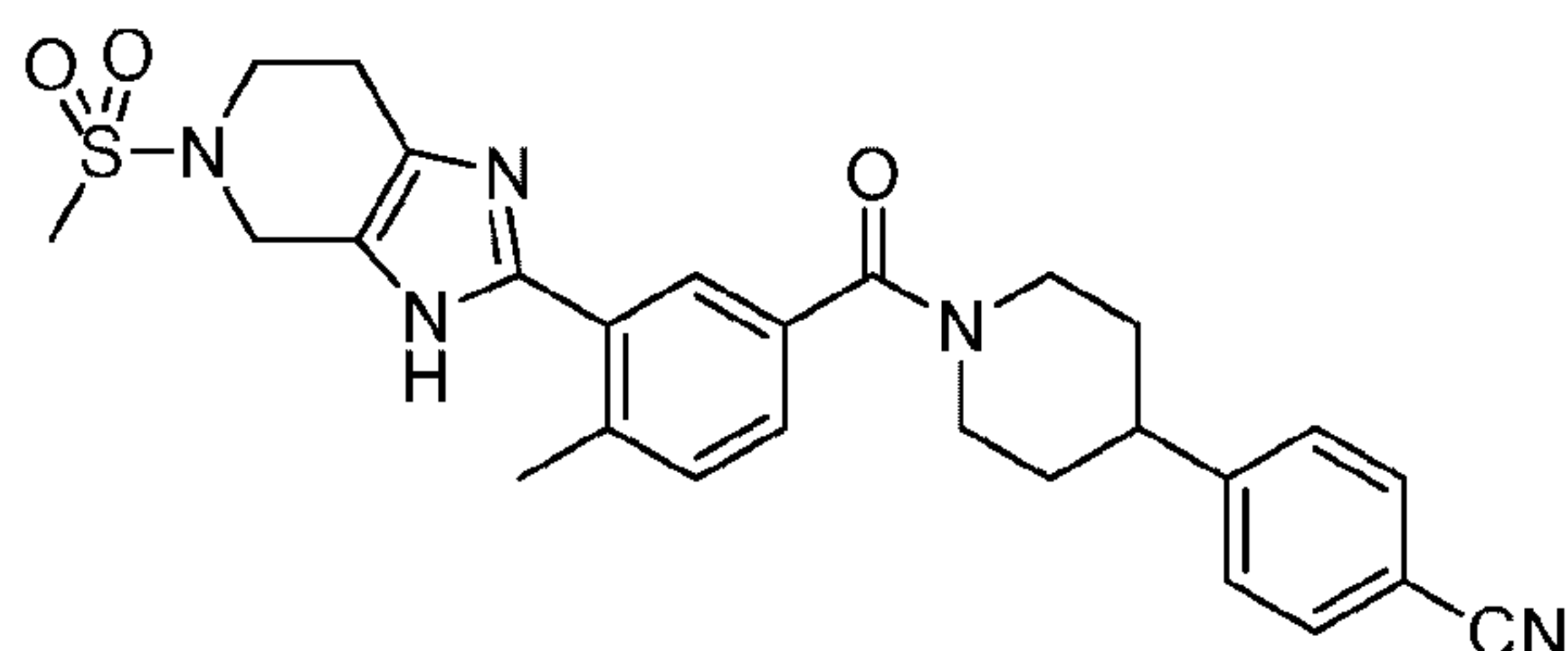
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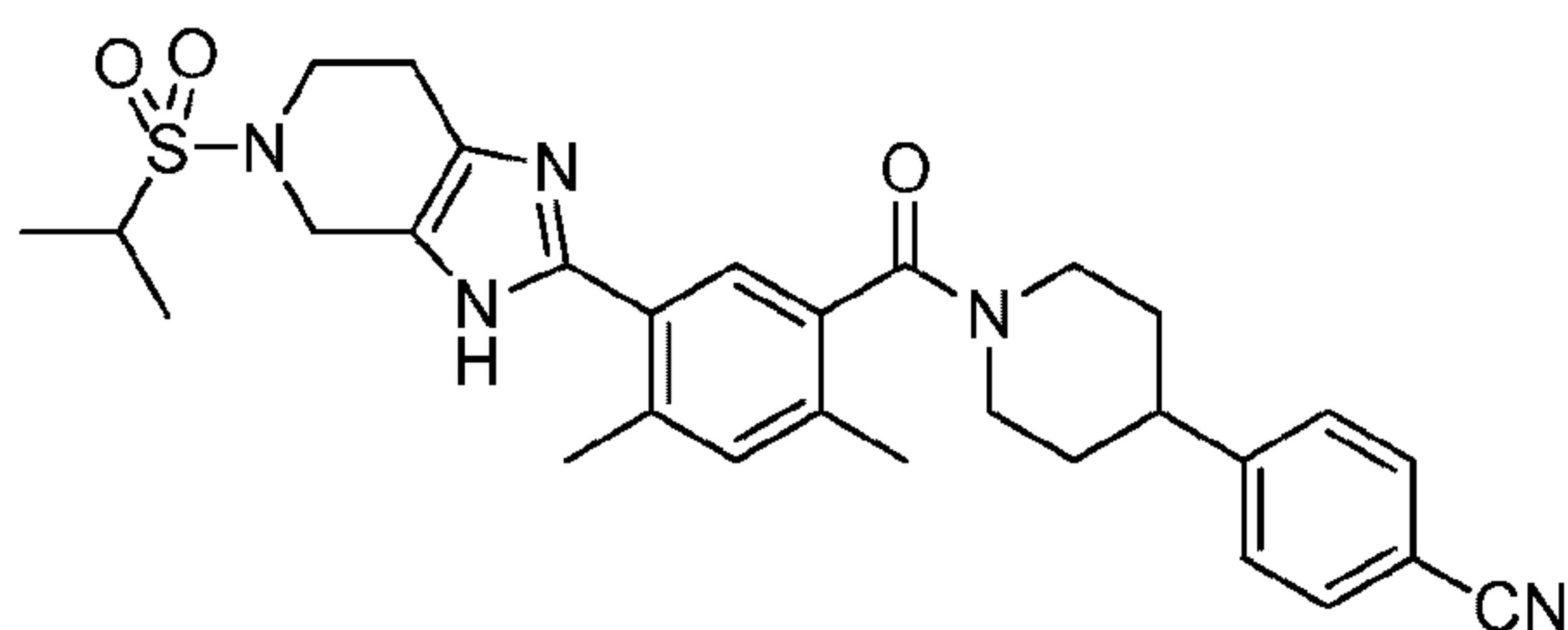
[0487] **Compound 2.** 4-(1-(5-(5-Acetyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-yl)-2,4-dimethylbenzoyl)piperidin-4-yl)benzonitrile. To a stirred mixture of 4-(1-(2,4-dimethyl-5-(4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **2.9**, 20 mg, 0.02 mmol, 1.00 equiv, 50%) in DMF (2 mL) under nitrogen was added a solution of Ac₂O (2.4 mg, 0.02 mmol, 1.00 equiv) in DMF (0.2 mL) dropwise at 0°C. The resulting solution was stirred for 1 h at 0~3°C in a water/ice bath. The reaction mixture was then diluted with 50 mL of ethyl acetate and washed with 2x20 mL of brine. The organic phase was dried (Na₂SO₄) and concentrated under reduced pressure. The crude residue (50 mg) was purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-006(Waters)): Column, xbridge C18; mobile phase, WATER WITH 0.05%NH₃.H₂O and CH₃CN (hold 5% CH₃CN in 2 min, up to 20%-46%in 10 min, up to 100% in 12 min, down to 20% in 14 min); Detector, UV 254/220nm. The fractions containing pure compound were combined and lyophilized to yield 5.5 mg of the title compound as a white solid. *m/z* (ES+) 482 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.69 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 8.1 Hz, 2H), 7.39 - 7.28 (m, 2H), 4.90 (m, 1H, partially obscured by the solvent peak), 4.67 and 4.62 (2 singlets, acetamide rotamers, MeCONCH₂-imidazole, 2H), 3.92 (m, 2H), 3.66 (m, 1H), 3.23 (m, 1H), 3.00 (m, 2H), 2.85-2.76 (m, 2H), 2.48 (s, 3H), 2.41 and 2.31 (2 singlets, aryl amide rotamers, ArCH₃, 3H), 2.25 and 2.22 (2 singlets, acetamide rotamers, CH₃CON, 3H), 2.04 (m, 1H), 1.92-1.20 (m, 3H).



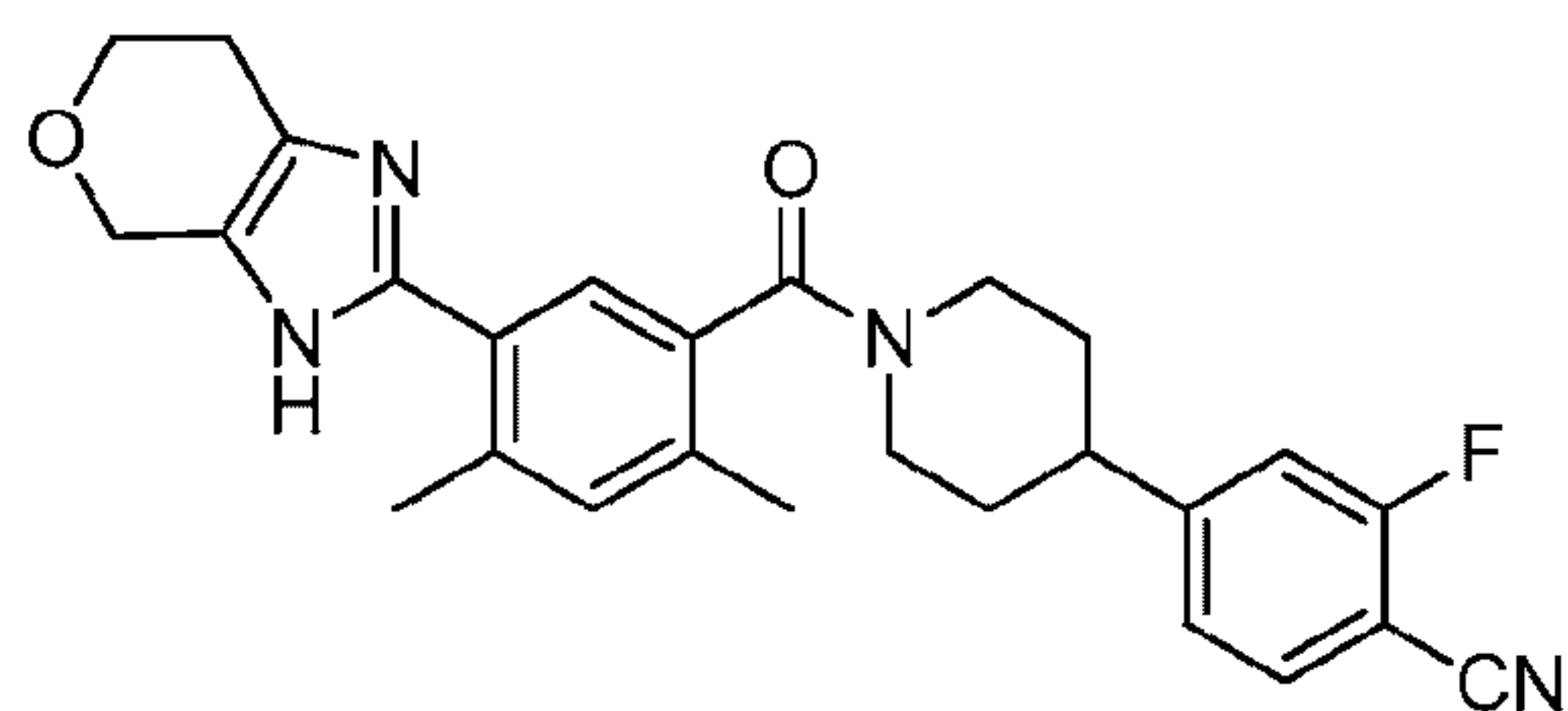
[0488] **Compound 3.** 4-(1-(3-(5-Acetyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-yl)-4-methylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds **1** and **2**. *m/z* (ES+) 468 (M+H)⁺.



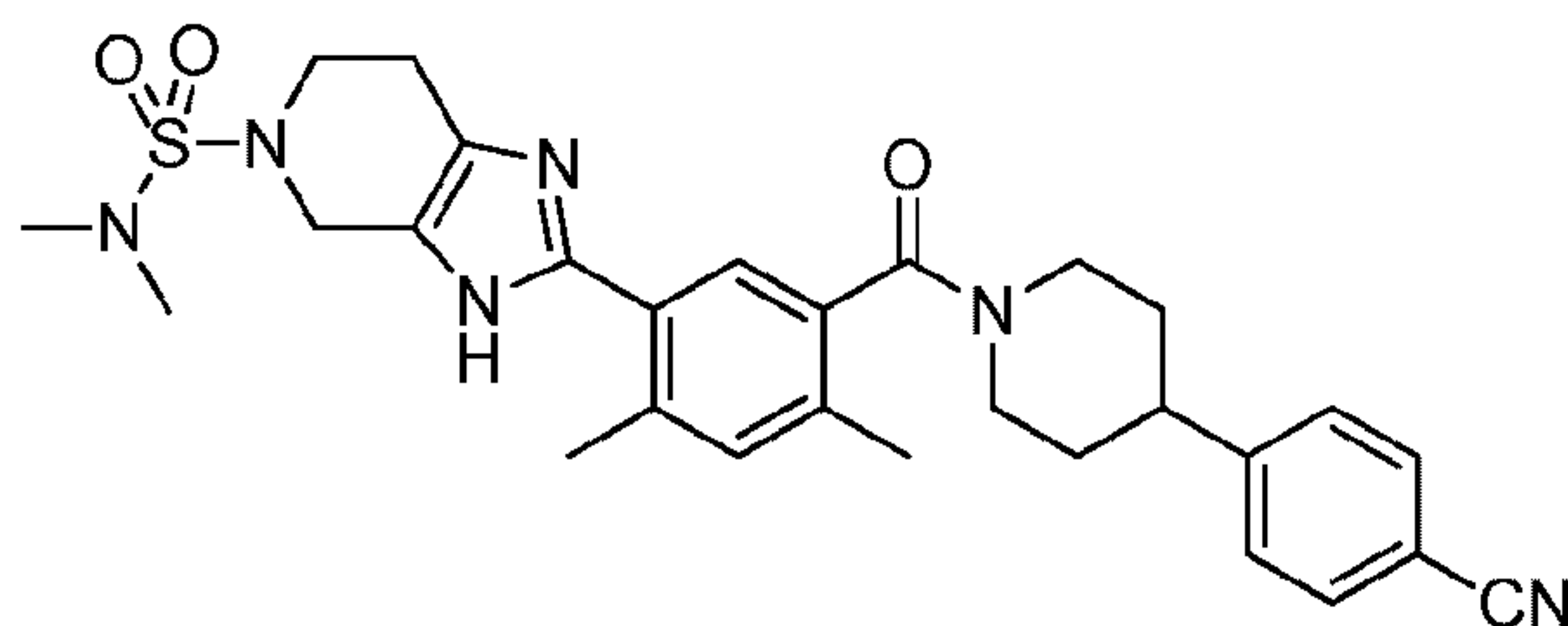
[0489] Compound 4. 4-(1-(4-Methyl-3-(5-(methylsulfonyl)-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds 1 and 2. m/z (ES+) 504 (M+H)⁺.



[0490] Compound 5. 4-(1-(5-(5-(Isopropylsulfonyl)-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-yl)-2,4-dimethylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds 1 and 2. m/z (ES+) 546 (M+H)⁺.

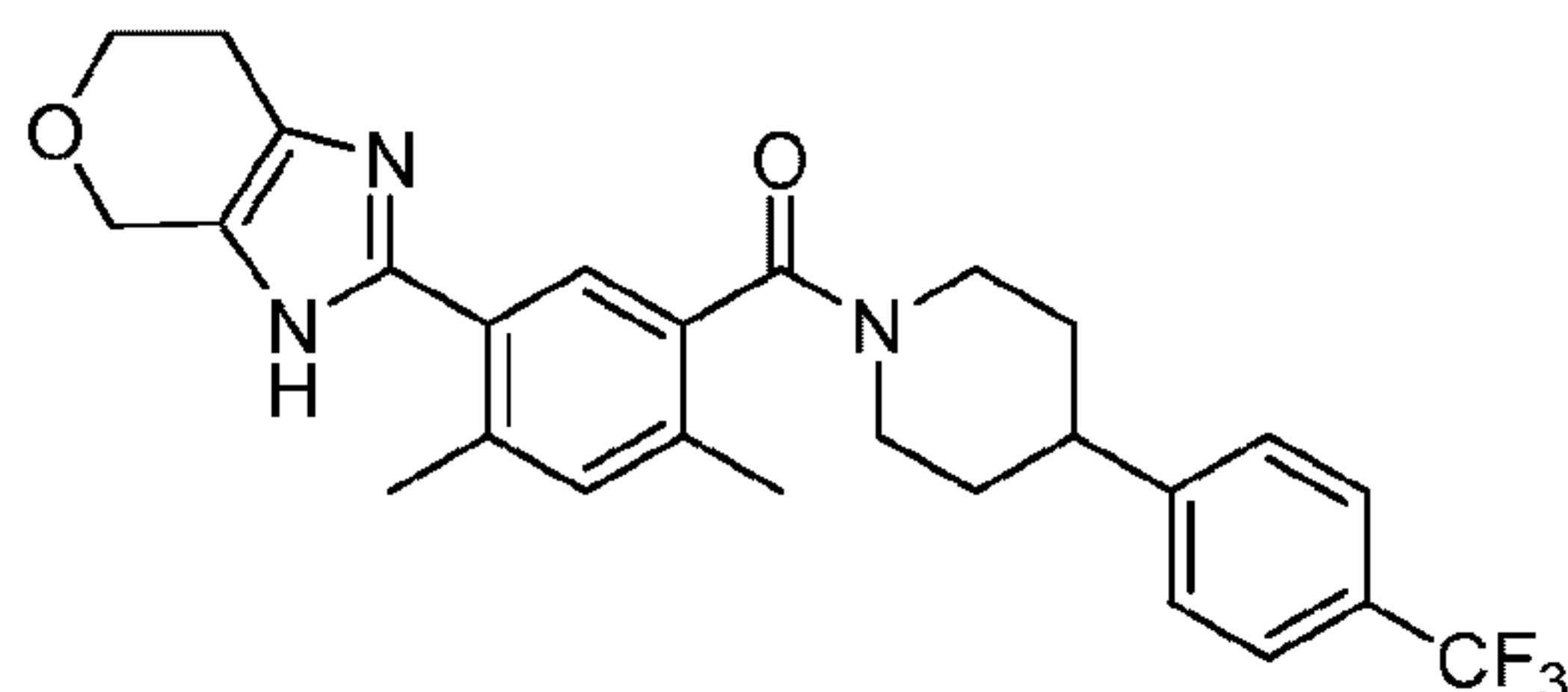


[0491] Compound 6. 4-(1-(2,4-Dimethyl-5-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)benzoyl)piperidin-4-yl)-2-fluorobenzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds 1 and 2. m/z (ES+) 459 (M+H)⁺.

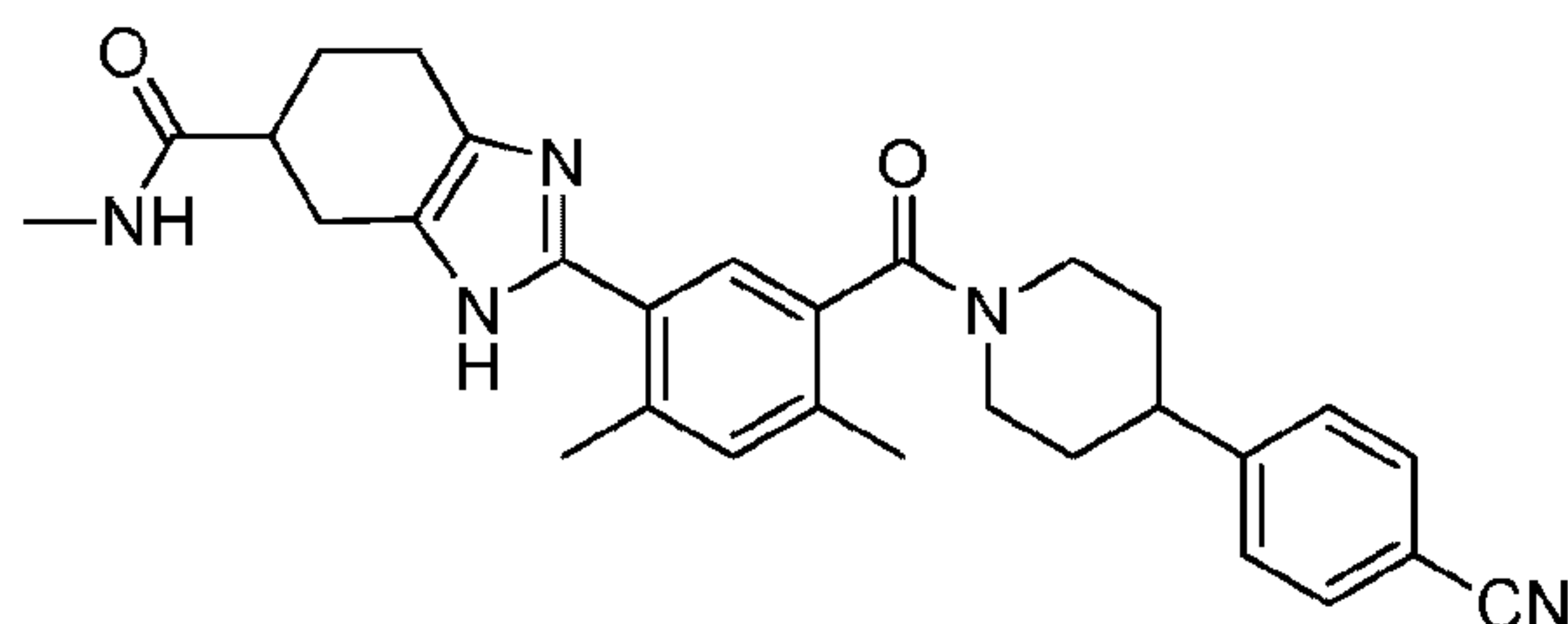


[0492] Compound 7. 2-(5-(4-(4-Cyanophenyl)piperidine-1-carbonyl)-2,4-dimethylphenyl)-N,N-dimethyl-6,7-dihydro-3H-imidazo[4,5-c]pyridine-5(4H)-sulfonamide. The title compound was prepared using standard chemical manipulations and

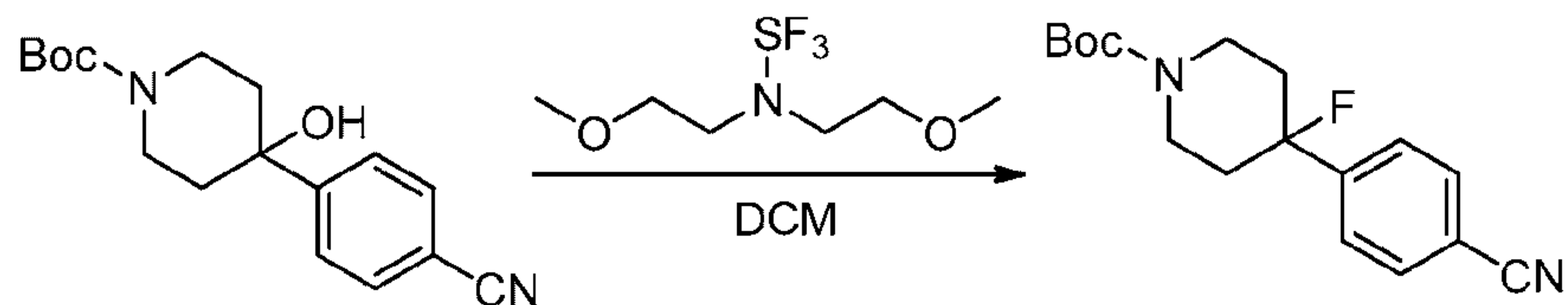
procedures similar to those used for the preparation of compounds **1** and **2**. m/z (ES+) 547 (M+H)⁺.



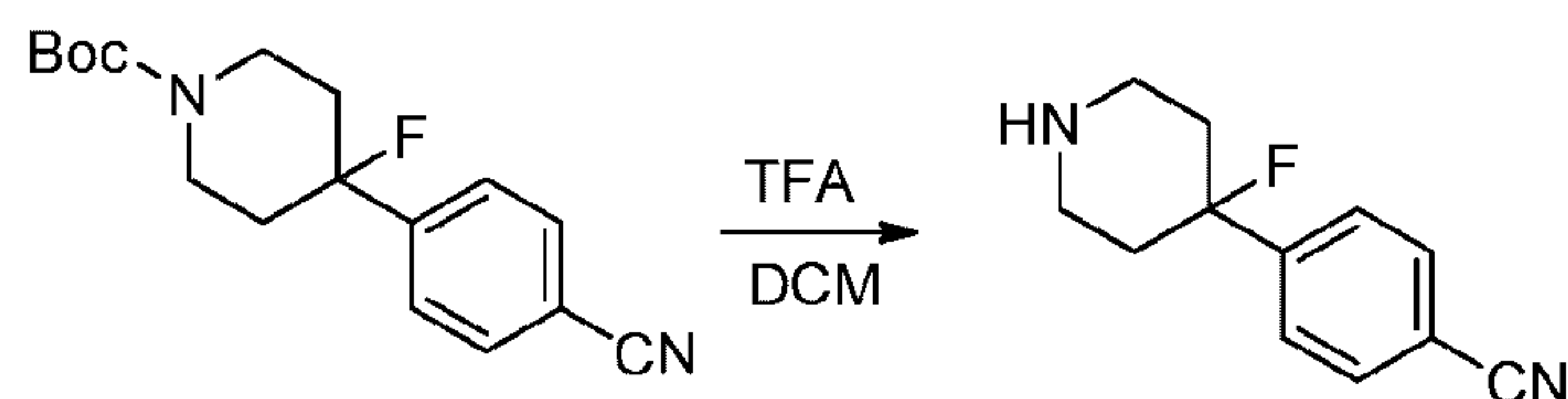
[0493] Compound 8. (2,4-Dimethyl-5-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)phenyl)(4-(4-(trifluoromethyl)phenyl)piperidin-1-yl)methanone. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds **1** and **2**. m/z (ES+) 484 (M+H)⁺.



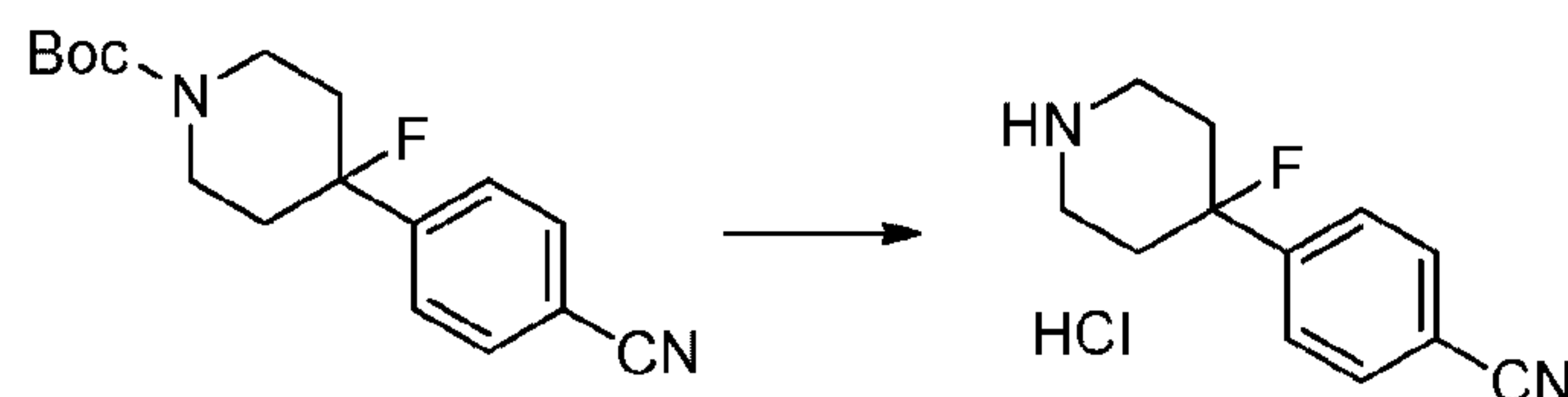
[0494] Compound 9. 2-(5-(4-(4-Cyanophenyl)piperidine-1-carbonyl)-2,4-dimethylphenyl)-N-methyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carboxamide. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds **1** and **2**. m/z (ES+) 496 (M+H)⁺.



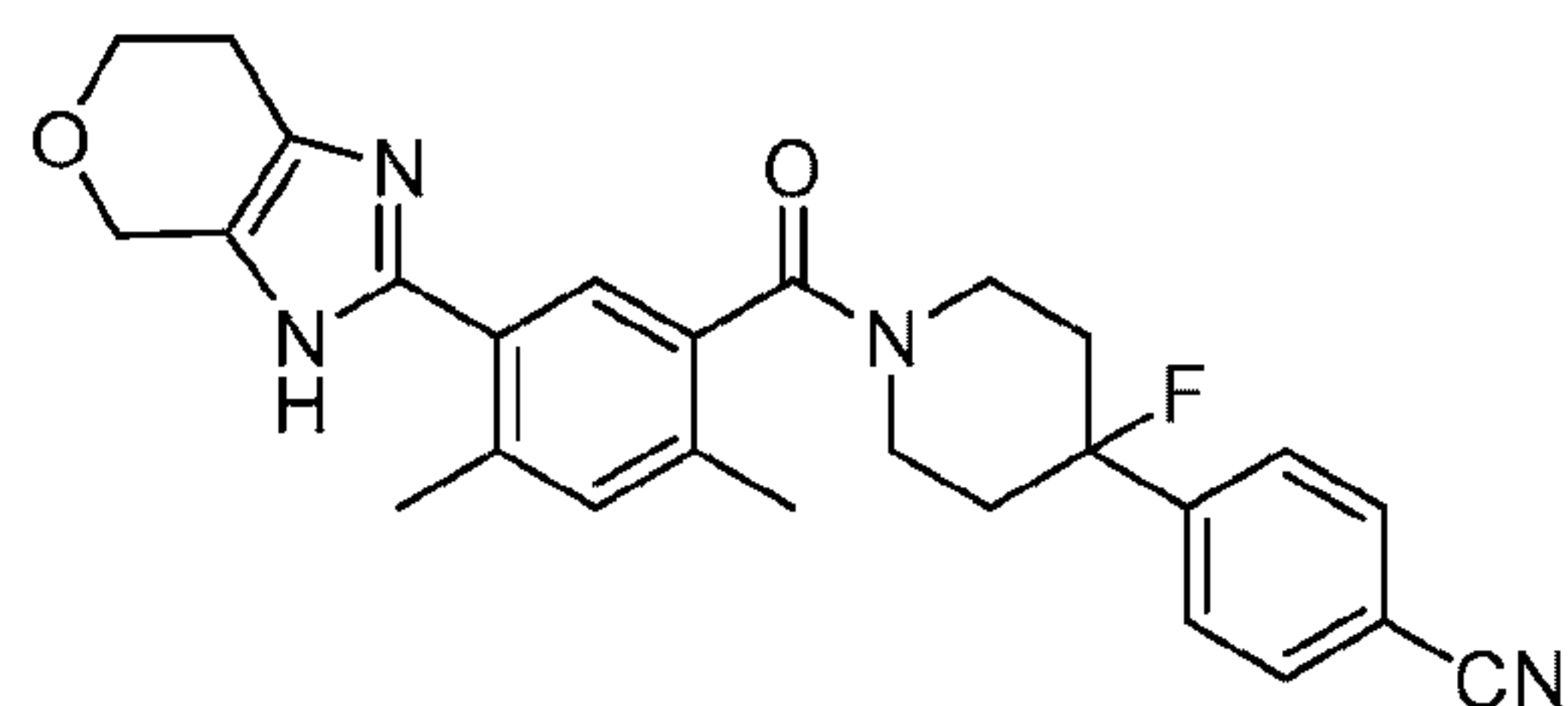
[0495] Compound 11.1. *tert*-Butyl 4-(4-cyanophenyl)-4-fluoropiperidine-1-carboxylate. To a stirred solution of compound **1.2** (5 g, 16.54 mmol, 1.00 equiv) in dichloromethane (250 mL) under nitrogen at -78°C was added dropwise Deoxo-Fluor® (4.4 g, 19.89 mmol, 1.20 equiv). The resulting mixture was stirred for 1 h at -78°C. The reaction mixture was then *carefully* quenched by the addition of 50 mL of sodium bicarbonate (aq.sat.) and extracted with 3x100 mL of dichloromethane. The combined organic layers were washed with 150 mL of brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:30) as eluent to yield 2.5 g (35%) of the title compound as a white solid.



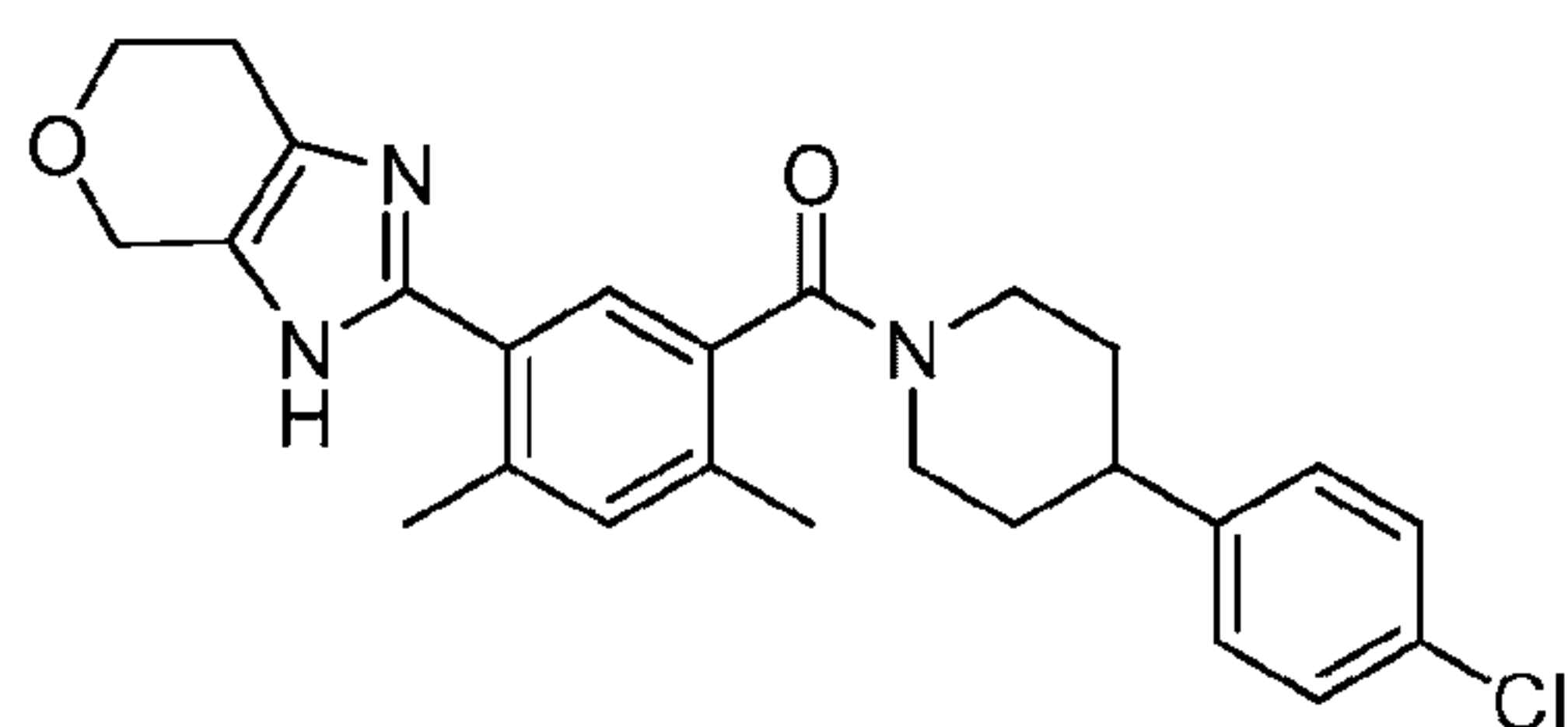
[0496] Compound 11.2. 4-(4-Fluoropiperidin-4-yl)benzonitrile. To a stirred solution of compound 11.1 (620 mg, 1.02 mmol, 1.00 equiv, 50%) in DCM (40 mL) was added dropwise trifluoroacetic acid (6 g, 52.62 mmol, 51.66 equiv). After stirring at ambient temperature for 2h, the mixture was concentrated under reduced pressure. The residue was taken up in DCM and treated with aqueous sodium bicarbonate. The phases were separated and the aqueous layer was extracted with 2x50 mL DCM. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure to yield 0.4 g of the title compound as a light yellow solid. m/z (ES+) 205 (M+H)⁺.



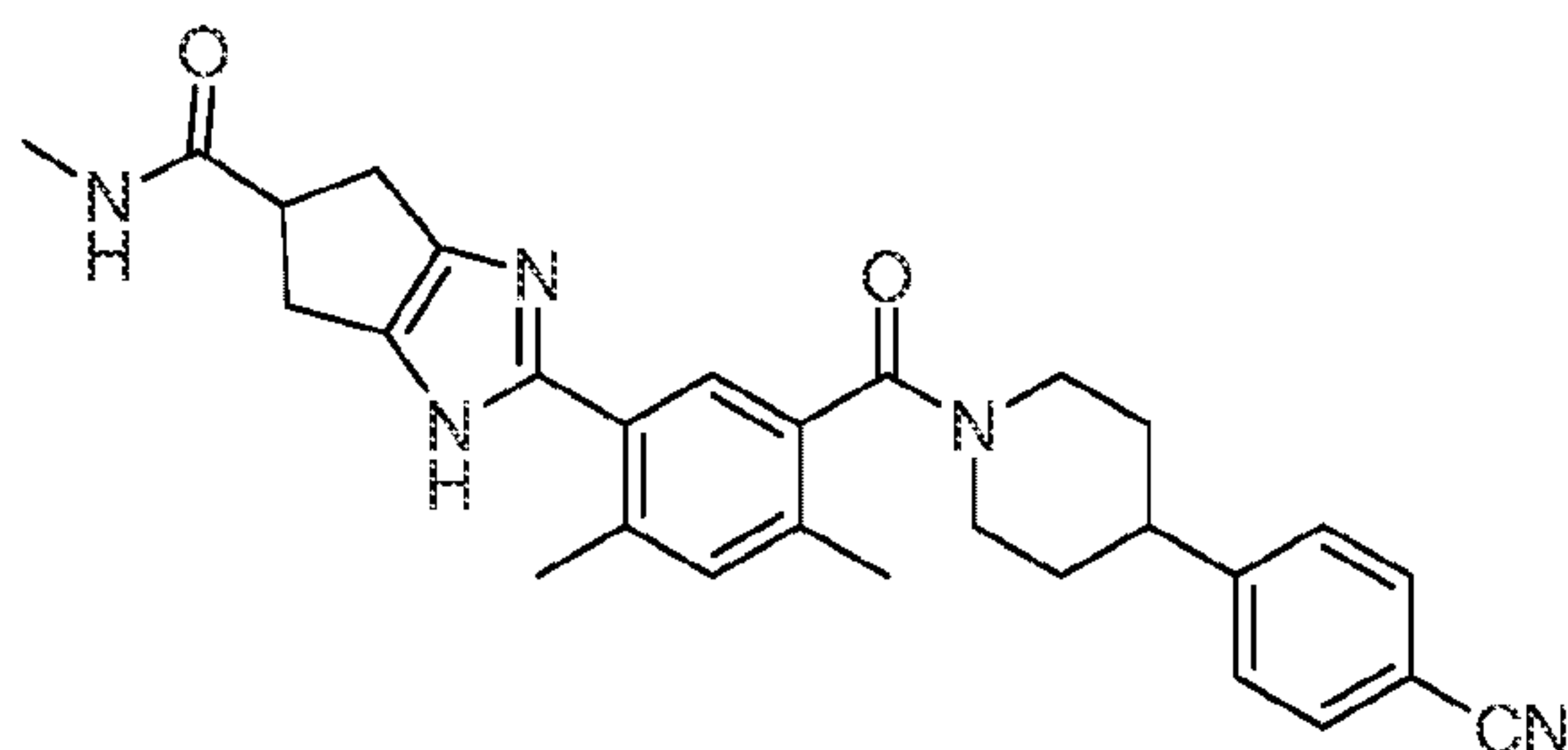
[0497] Compound 11.2 HCl salt. 4-(4-Fluoropiperidin-4-yl)benzonitrile hydrochloride. The title compound was prepared using standard chemical manipulations and a procedure similar to that used for the preparation of compound 1.5 and using compound 11.1 in place of compound 1.4. m/z (ES+) 205 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.83 (d, J = 6.3 Hz, 2H), 7.68 (d, J = 6.3 Hz, 2H), 3.55-3.32 (m, 4H), 2.58-2.40 (m, 2H), 2.28-2.22 (m, 2H).



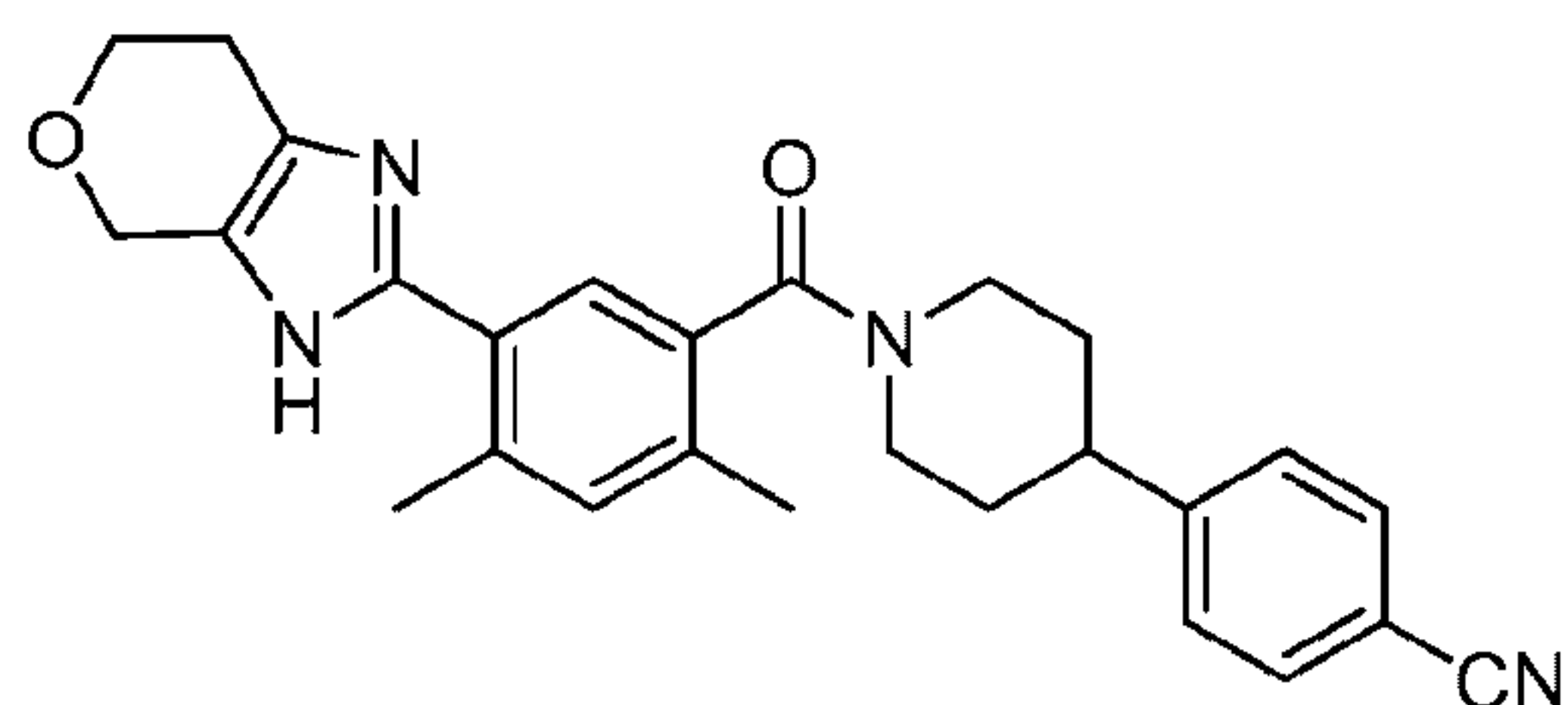
[0498] Compound 11. 4-(1-(2,4-Dimethyl-5-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)benzoyl)-4-fluoropiperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds 1 and 2 and using compound 11.2 in place of compound 1.5. m/z (ES+) 459 (M+H)⁺.



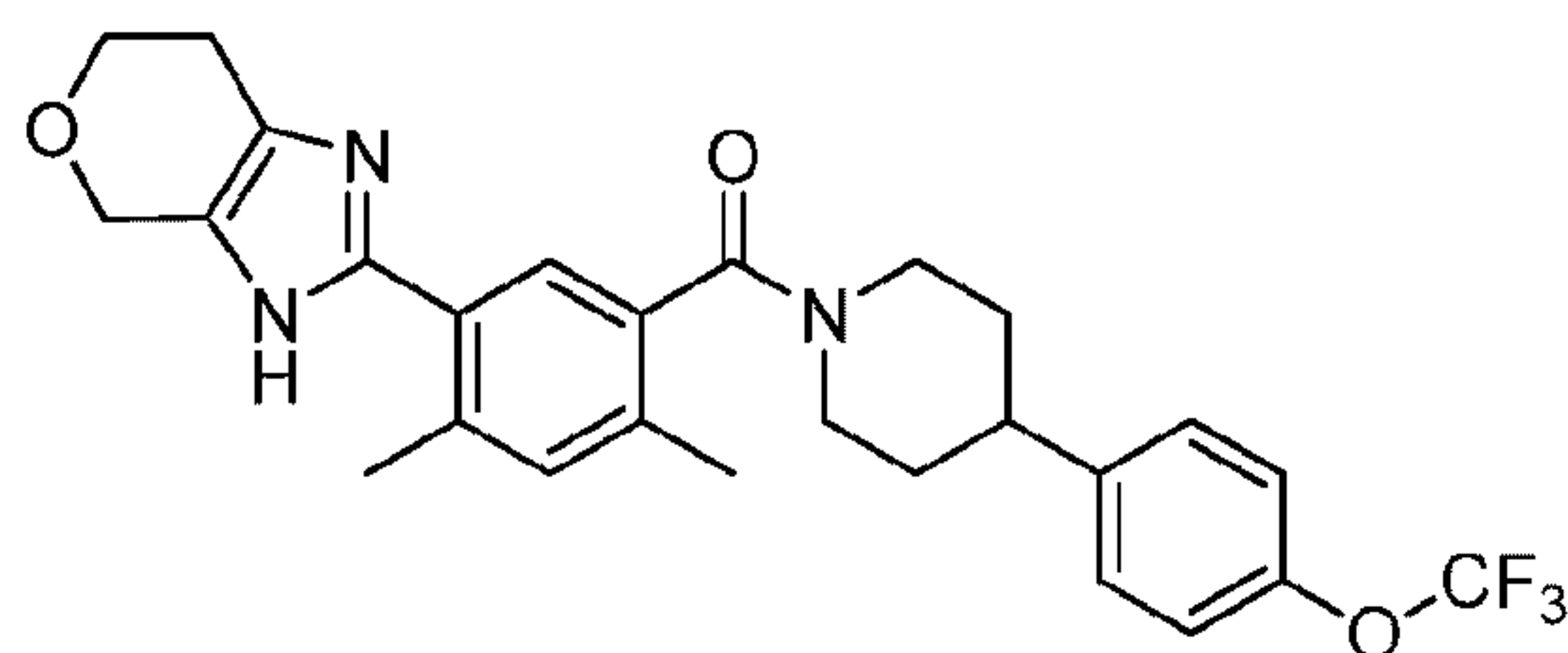
[0499] Compound 12. (4-(4-Chlorophenyl)piperidin-1-yl)(2,4-dimethyl-5-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)phenyl)methanone. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds 1 and 2. m/z (ES+) 450 (M+H)⁺.



[0500] Compound 13. 2-(5-(4-(4-Cyanophenyl)piperidine-1-carbonyl)-2,4-dimethylphenyl)-N-methyl-1,4,5,6-tetrahydrocyclopenta[d]imidazole-5-carboxamide. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds 1 and 2. m/z (ES+) 482 (M+H)⁺.

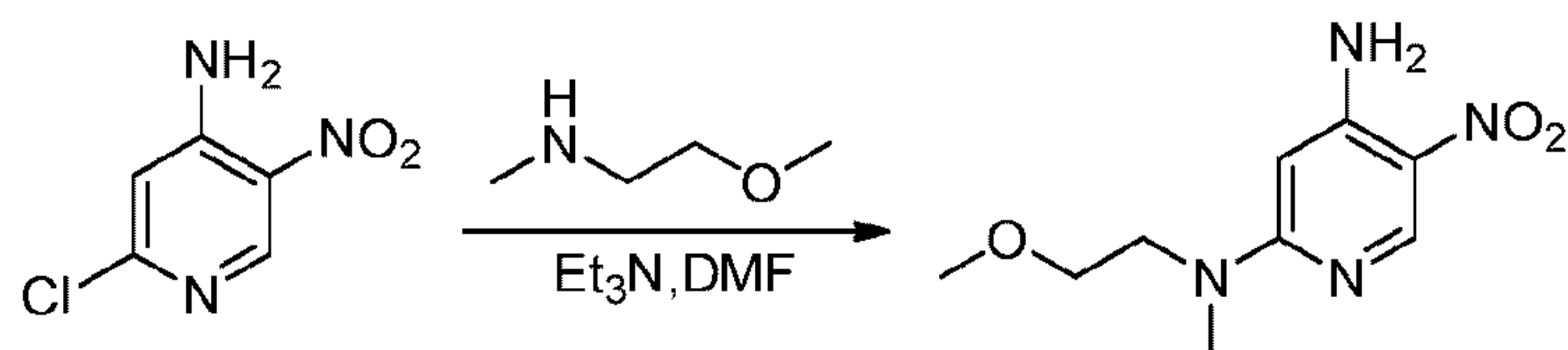


[0501] Compound 14. 4-(1-(2,4-Dimethyl-5-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds 1 and 2. m/z (ES+) 441 (M+H)⁺.

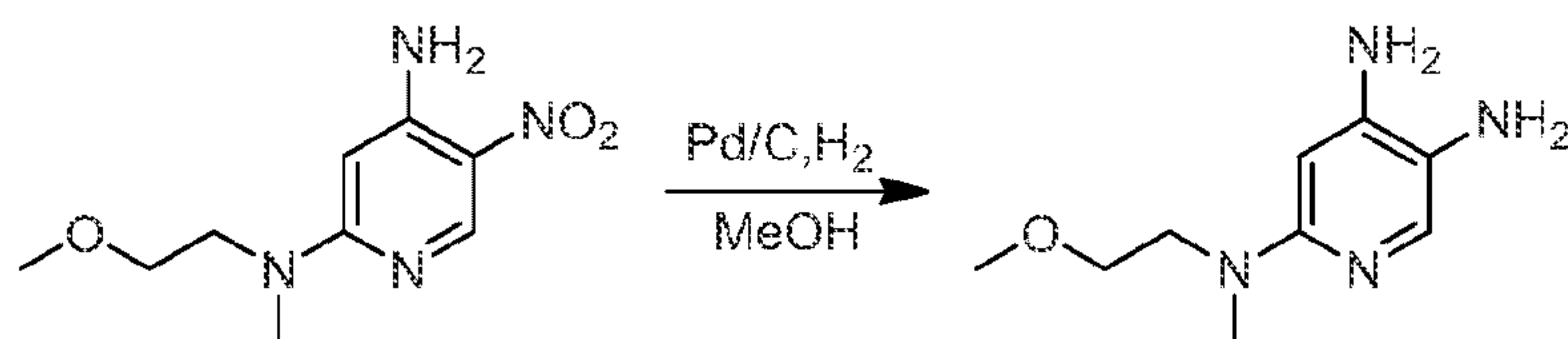


[0502] Compound 15. (2,4-Dimethyl-5-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)phenyl)(4-(4-(trifluoromethoxy)phenyl)piperidin-1-yl)methanone. The title compound

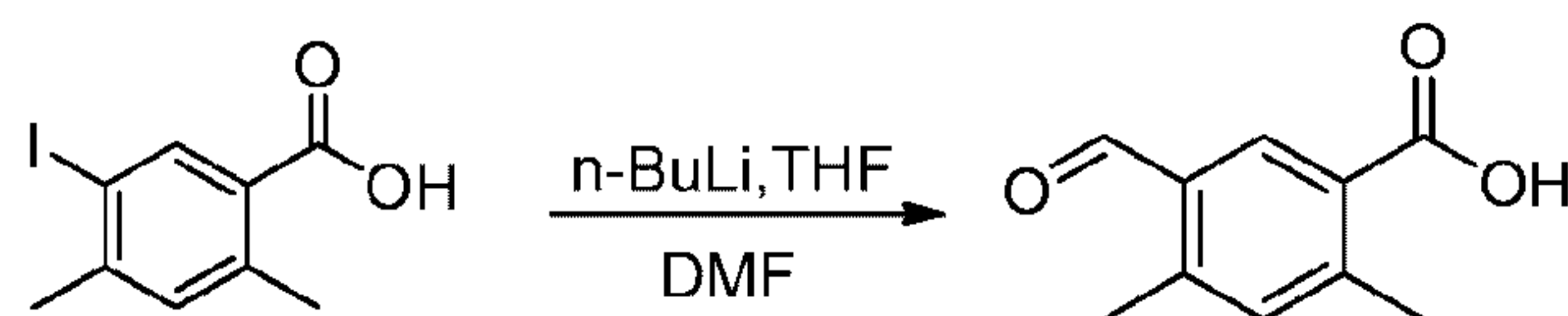
was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds 1 and 2. m/z (ES⁺) 500 (M+H)⁺.



[0503] Compound 16.1. N²-(2-Methoxyethyl)-N²-methyl-5-nitropyridine-2,4-diamine. A solution of 2-chloro-5-nitropyridin-4-amine (500 mg, 2.88 mmol, 1.00 equiv), triethylamine (1.167 g, 11.53 mmol, 4.00 equiv), and (2-methoxyethyl)(methyl)amine (514 mg, 5.77 mmol, 2.00 equiv) in DMF (20 mL) was stirred in a sealed tube at 55°C behind a blast shield overnight. After cooling to room temperature, the mixture was diluted with 100 mL of water and extracted with 3x150 mL of ethyl acetate. The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to yield 723 mg (crude) of the title compound as a dark red oil.

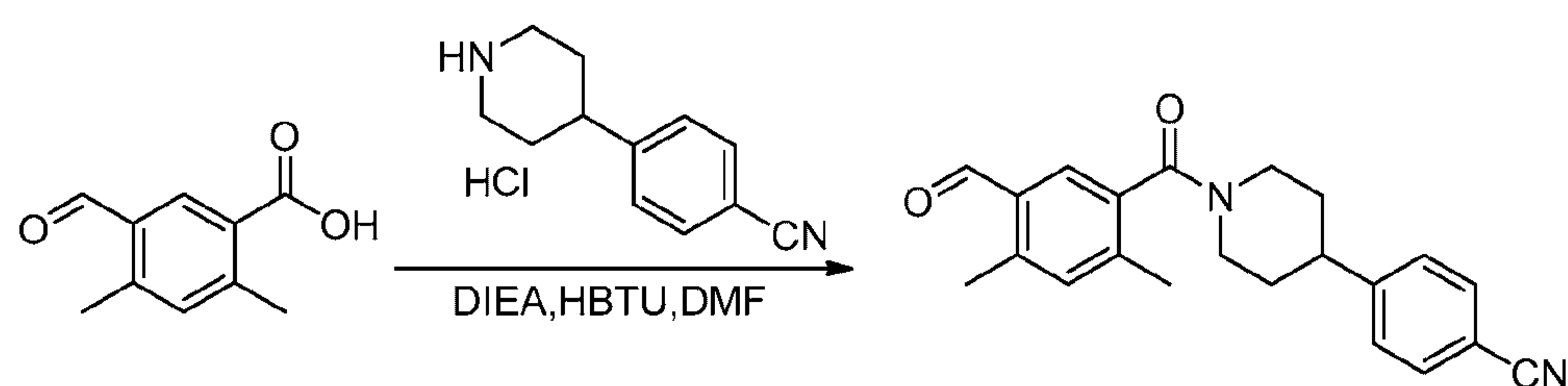


[0504] Compound 16.2. N²-(2-Methoxyethyl)-N²-methylpyridine-2,4,5-triamine. Around-bottom flask, containing a solution of compound 16.1 (400 mg, 1.77 mmol, 1.00 equiv) in methanol (30 mL) was purged with nitrogen gas. To the solution was then added palladium on carbon (40 mg, 10%, 60% water). The flask was purged further with nitrogen and the atmosphere was then changed to hydrogen. The mixture was stirred at room temperature under a balloon with hydrogen for 4 h. After purging the system with nitrogen, the solids were removed by filtration and the filtrate was concentrated under reduced pressure to yield 300 mg (86%) of the title compound as a light brown solid. The crude product was found to be unstable and used immediately.

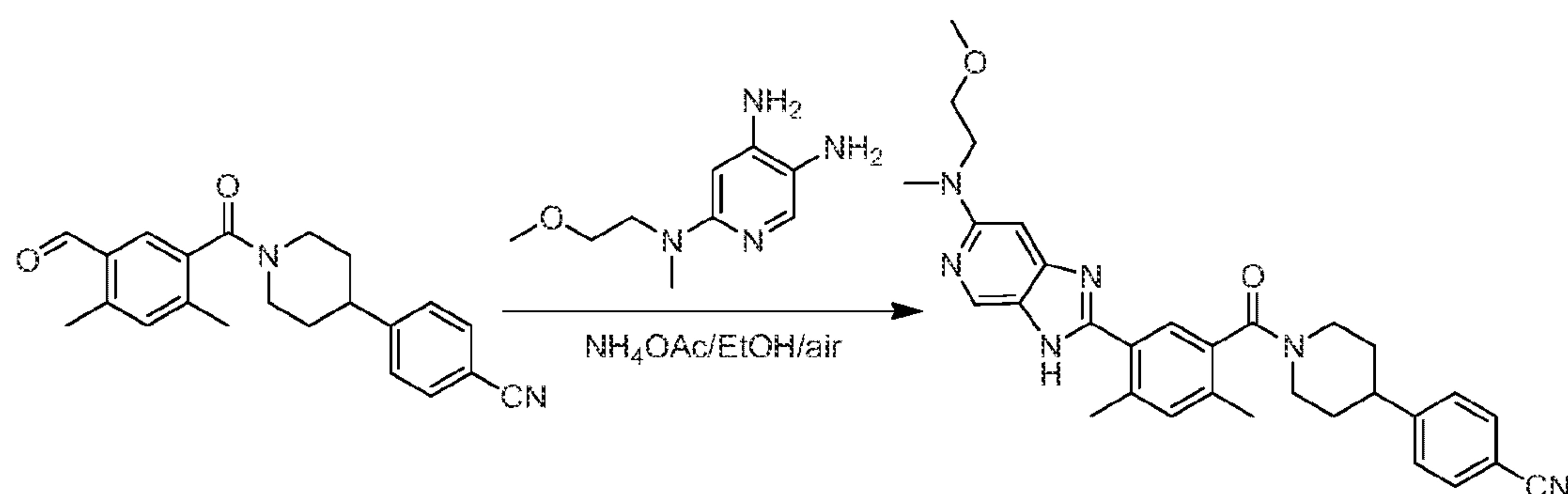


[0505] Compound 16.3. 5-Formyl-2,4-dimethylbenzoic acid. To a stirred solution of 5-iodo-2,4-dimethylbenzoic acid (compound 2.1, 5 g, 18.11 mmol, 1.00 equiv) in tetrahydrofuran (150 mL) under nitrogen at -78°C was added n-BuLi (2.5 M in THF, 18 mL, 2.50 equiv) dropwise. After stirring at -78°C for 1 h, DMF (5 g, 68.4 mmol, 3.80 equiv) was added dropwise. The resulting mixture was stirred at -78°C for an additional 0.5 h and then

carefully quenched by slow addition of 50 mL of water. The pH was then adjusted to ~3-4 using aqueous HCl (aq., 6 M). The mixture was extracted with 3x200 mL of ethyl acetate. The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue thus obtained was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:10-1:5) as gradient to yield 2.4 g (74%) of the title compound as a white solid.

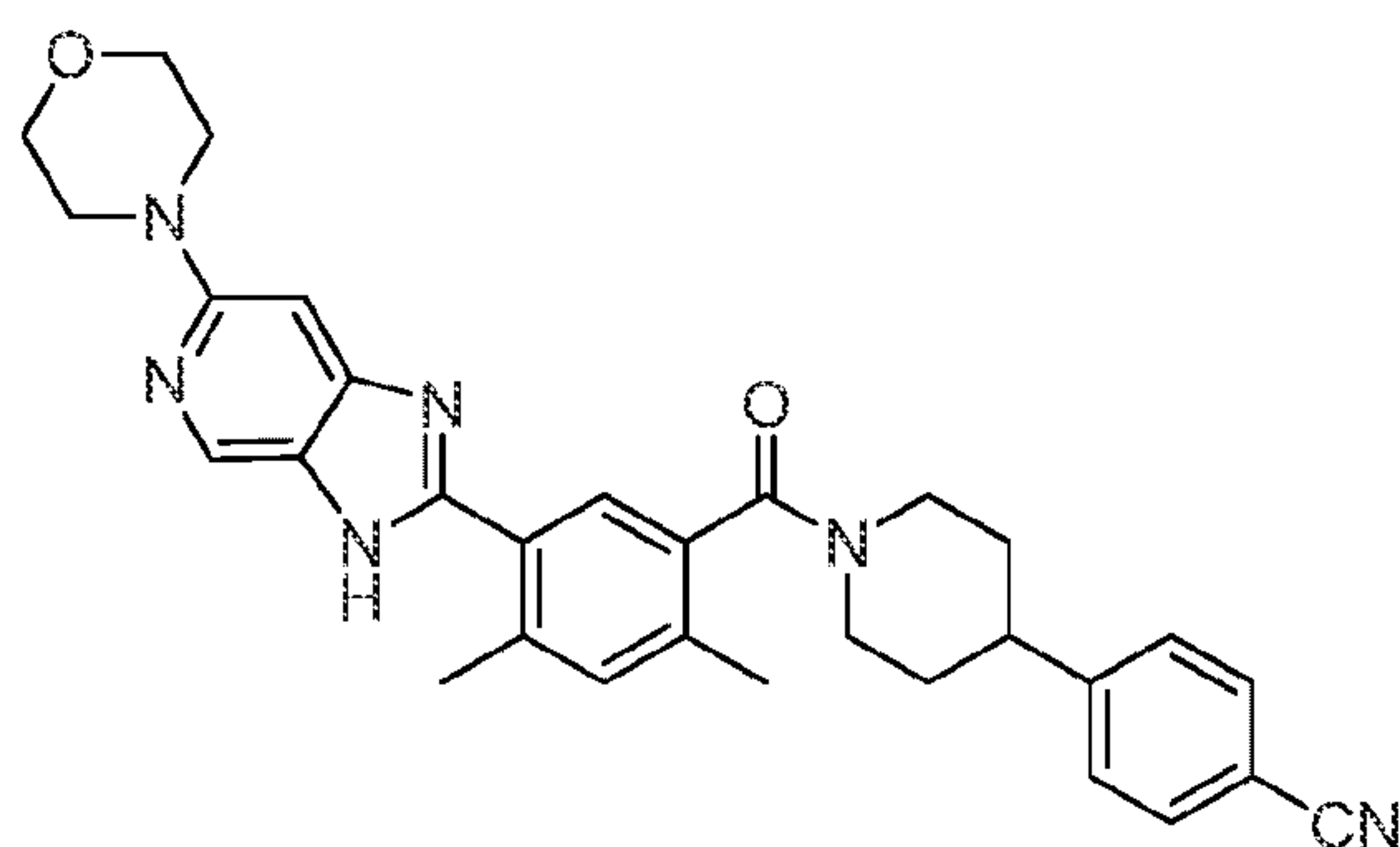


[0506] Compound 16.4. 4-(1-(5-Formyl-2,4-dimethylbenzoyl)piperidin-4-yl)benzonitrile. To a stirred solution of 5-formyl-2,4-dimethylbenzoic acid (compound 16.3, 950 mg, 5.33 mmol, 1.10 equiv) in DMF (15 mL) was added DIEA (2.48 g, 19.19 mmol, 4.00 equiv) followed by HBTU (3.67 g, 9.68 mmol, 2.00 equiv), and 4-(piperidin-4-yl)benzonitrile hydrochloride (compound 1.5, 1.07 g, 4.80 mmol, 1.00 equiv). After stirring overnight at ambient temperature, the reaction was quenched by the addition of 60 mL of water. The resulting mixture was extracted with 3x150 mL of ethyl acetate and the organic layers were combined, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:10-1:3) as eluent to yield 1.4 g (84%) of the title compound as a brown oil.

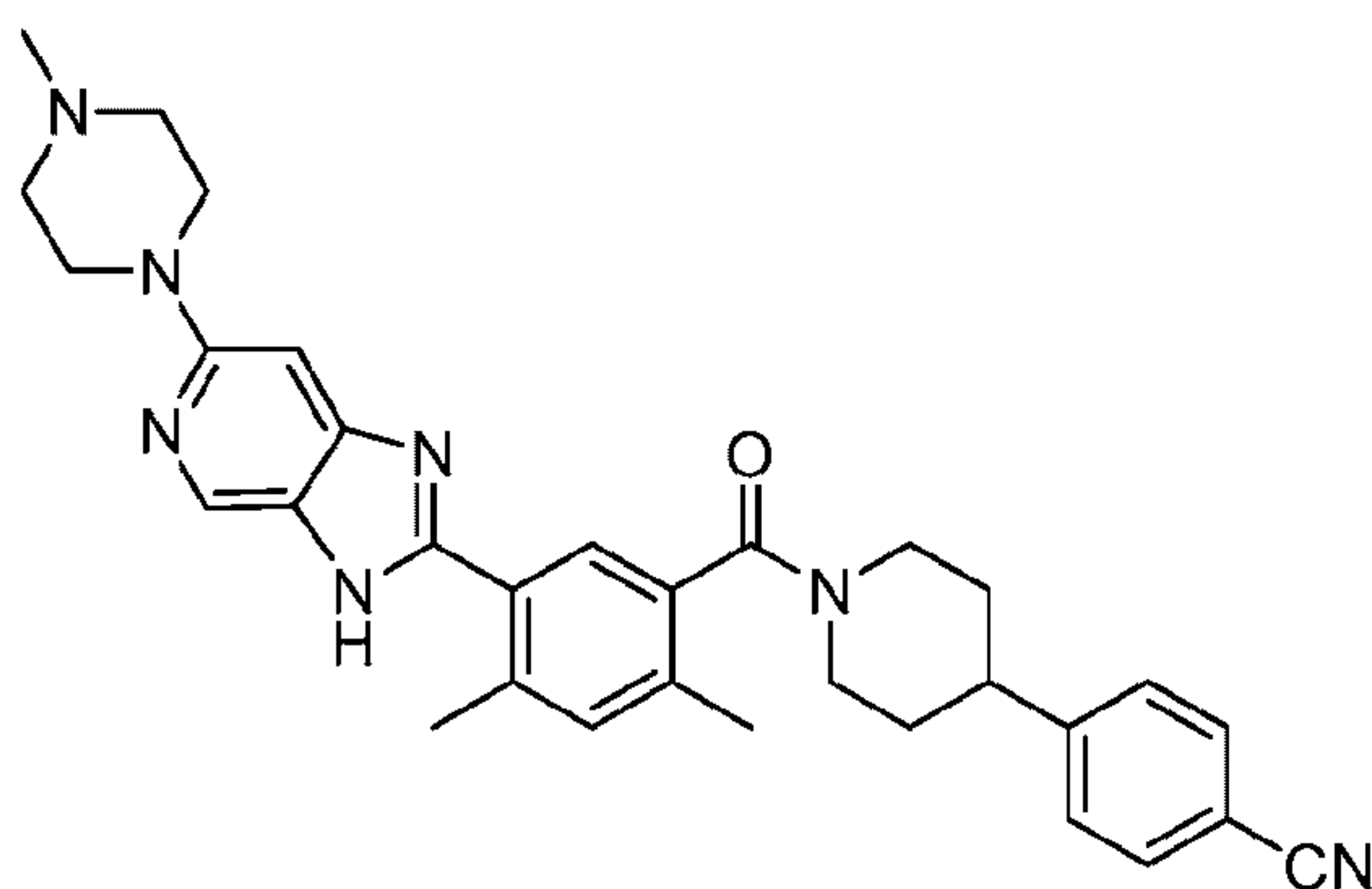


[0507] Compound 16. 4-(1-(5-(6-((2-Methoxyethyl)(methyl)amino)-3H-imidazo[4,5-c]pyridin-2-yl)-2,4-dimethylbenzoyl)piperidin-4-yl)benzonitrile. A solution of compound 16.2 (300 mg, 1.53 mmol, 1.30 equiv), compound 16.4 (407 mg, 1.17 mmol, 1.00 equiv), and ammonium acetate (362 mg, 4.70 mmol, 4.00 equiv) in ethanol (20 mL) was stirred overnight at 70°C in an oil bath. The resulting mixture was then concentrated under vacuum and the

residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:10-2:1) as eluent to yield ~200 mg of product which was further purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-006(Waters)): Column, SunFire Prep C18, 19*150mm 5um; mobile phase, WATER WITH 0.05%TFA and CH₃CN (hold 5.0% CH₃CN in 2 min, up to 25.0% in 1 min, up to 55.0% in 12 min, up to 100.0% in 1 min); Detector, UV 254/220nm. The fractions containing pure compound were combined and lyophilized to yield 150 mg (24%) of the title compound as a white solid. *m/z* (ES+) 523 (M+H)⁺. ¹H NMR (300 MHz, CDCl₃): δ 8.57-8.38 (m, 1H), 7.78-7.53 (m, 4H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.28-7.12 (m, 2H), 5.06-4.88 (m, 1H), 3.71 (app s, 5H), 3.50 (s, 3H), 3.41-3.05 (m, 4H), 3.01-2.75 (m, 2H), 2.68 (s, 3H), 2.42 & 2.31 (2 singlets, amide rotamers, ArCH₃, 3H), 2.12-1.93 (m, 1H), 1.93-1.39 (m, 3H).

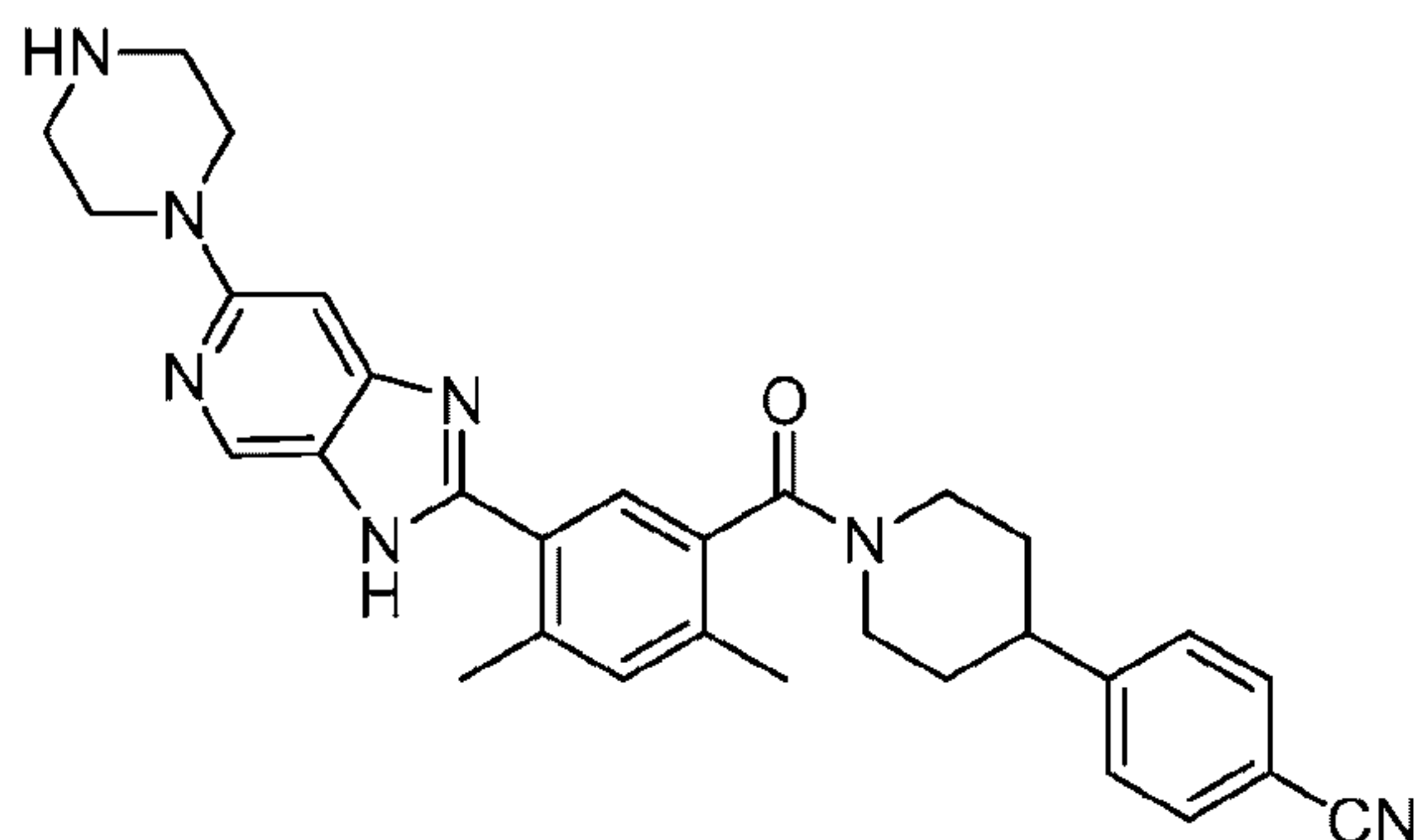


[0508] **Compound 17. 4-(1-(2,4-Dimethyl-5-(6-morpholino-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile.** The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of compound 16. *m/z* (ES+) 521 (M+H)⁺.

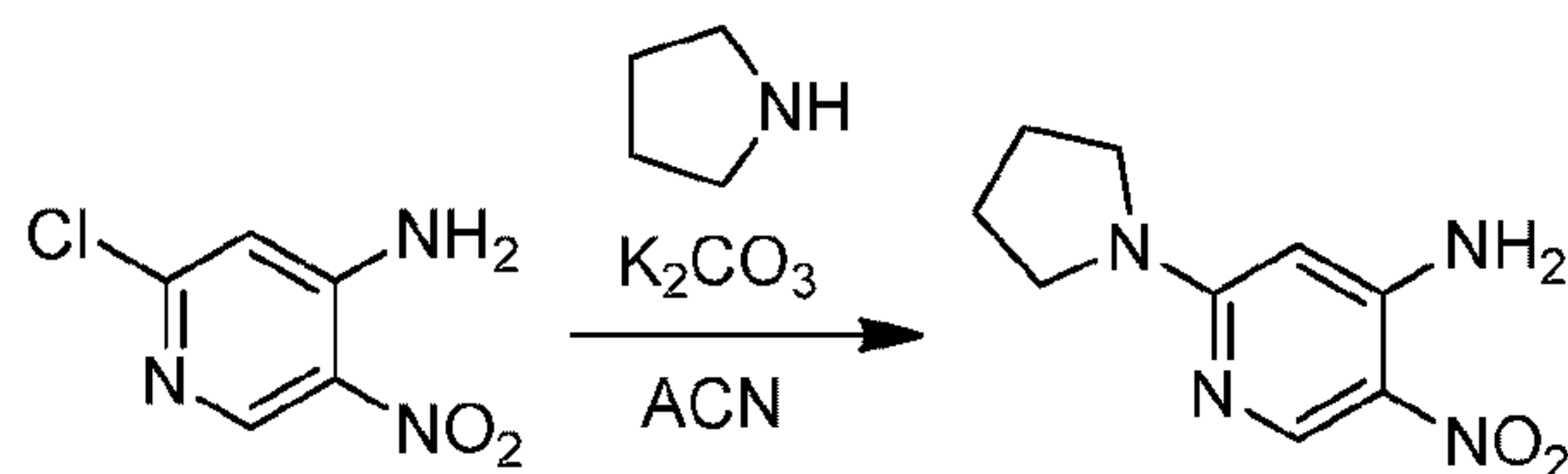


[0509] **Compound 18. 4-(1-(2,4-Dimethyl-5-(6-(4-methylpiperazin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile.** The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of compound 16. *m/z* (ES+) 534 (M+H)⁺. ¹H NMR (300 MHz, DMSO-d₆): 8.73 (s, 1H), 7.76 (d, *J* = 7.5 Hz, 2H), 7.66 & 7.56 (2 singlets, amide rotamers, Ar-H, 1H), 7.49 (d,

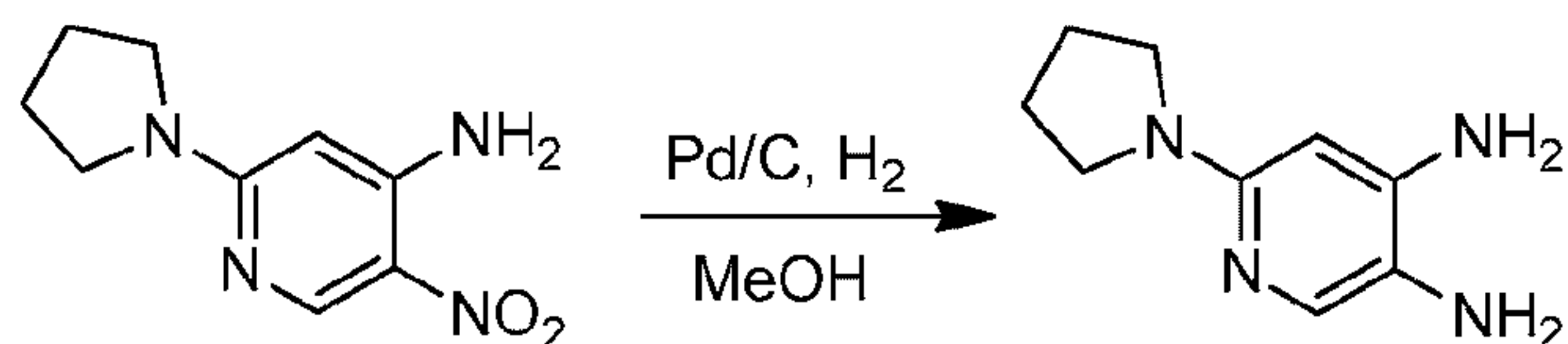
$J = 8.1$ Hz, 2H), 7.37 (s, 1H), 7.12 (s, 1H), 4.81-4.67 (m, 1H), 4.30 (br s, 2H), 3.70-3.37 (m, 3H), 3.37-3.05 (m, 5H), 3.05-1.80 (m, 5H), 2.60 (s, 3H), 2.37 & 2.27 (2 singlets, amide rotamers, Ar-CH₃, 3H), 2.02-1.87 (m, 1H), 1.87-2.40 (m, 3H).



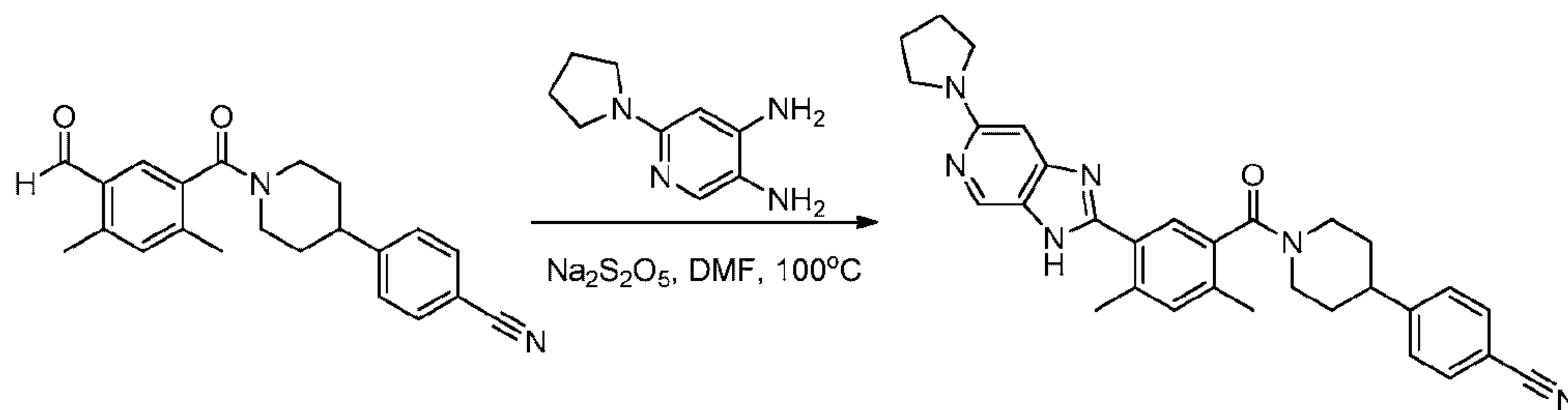
[0510] Compound 19. 4-(1-(2,4-Dimethyl-5-(6-(piperazin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of compound 16. m/z (ES+) 519 (M+H)⁺.



[0511] Compound 20.1. 5-Nitro-2-(pyrrolidin-1-yl)pyridin-4-amine. A 500 mL round bottom flask equipped with a reflux condenser was charged with 2-chloro-5-nitropyridin-4-amine (2.00 g, 11.5 mmol, 1.0 equiv), pyrrolidine (2.86 mL, 34.6 mmol, 3.0 equiv), potassium carbonate (4.78 g, 34.6 mmol, 3.0 equiv) and acetonitrile (50 mL). The mixture was heated at 70 °C overnight under nitrogen then cooled to room temperature. The yellow solids were collected by filtration and washed with acetonitrile, water and hexanes. The solids were dried to obtain the title compound as a bright yellow solid (1.43 g, 1st crop). The solvents from the filtrate were removed and the aqueous was extracted with ethyl acetate. The organic extracts was dried (Na₂SO₄), filtered and removed *in vacuo* to obtain additional product as an orange/yellow solid (820 mg, 2nd crop). The 2nd crop of product was triturated with ethyl acetate (3 mL) and then filtered and washed with ethyl acetate (2 x 1 mL) and diethyl ether (3 mL) to obtain a bright yellow solid (751 mg). The total yield of 5-nitro-2-(pyrrolidin-1-yl)pyridin-4-amine obtained was 2.18 g (91%). m/z (ES+) 209.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 8.79 (s, 1H), 7.39 (br s, 2H), 5.63 (s, 1H), 3.40 (br s, 4H), 1.93 (br s, 4H).

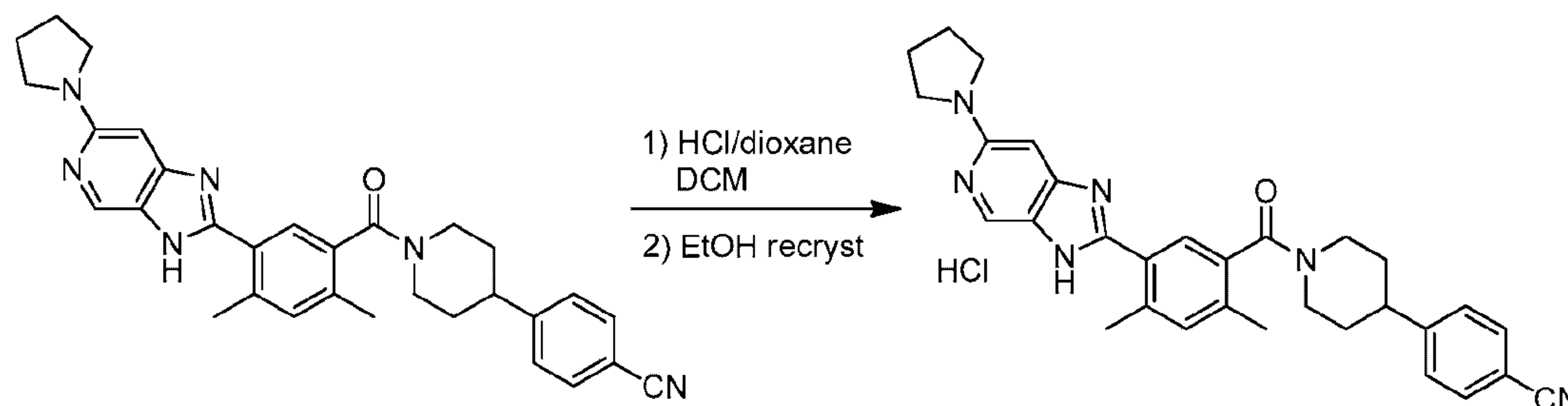


[0512] Compound 20.2. 6-(Pyrrolidin-1-yl)pyridine-3,4-diamine. To a 100 mL round bottom flask was added 5-nitro-2-(pyrrolidin-1-yl)pyridin-4-amine (compound **20.1**, 800 mg, 3.84 mmol, 1.0 equiv) and Pd on carbon (10 wt % Pd, 400 mg, 0.38 mmol, 0.1 equiv). The system was purged with nitrogen and charged with methanol (19 mL) followed by hydrogen. The mixture was stirred at room temperature under hydrogen for 4 hours then purged with nitrogen. The mixture was filtered through celite and washed extensively with MeOH. The solvents were removed *in vacuo* to obtain the title compound as a purple solid (641 mg, 94%). *m/z* (ES⁺) 179.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.27 (s, 1H), 5.62 (s, 1H), 5.14 (br s, 2H), 3.67 (br s, 2H), 3.23-3.13 (m, 4H), 1.91-1.79 (m, 4H).



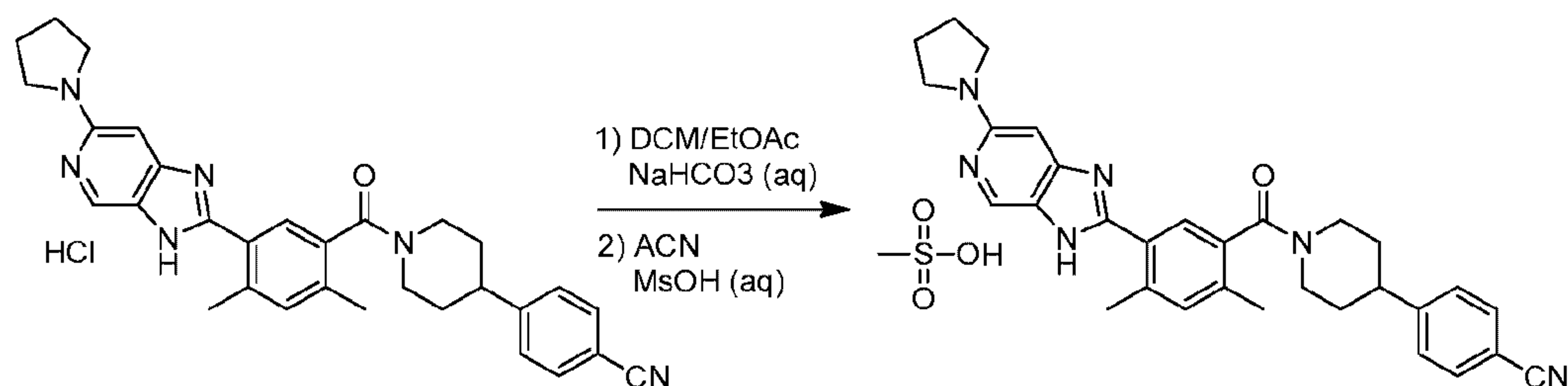
[0513] Compound 20. 4-(1-(2,4-Dimethyl-5-(6-(pyrrolidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile. To a 100 mL round bottom flask was added 6-(pyrrolidin-1-yl)pyridine-3,4-diamine (compound **20.2**, 641 mg, 3.60 mmol, 1.0 equiv), 4-(1-(5-formyl-2,4-dimethylbenzoyl)piperidin-4-yl)benzonitrile (compound **16.4**, 1.25 g, 3.60 mmol, 1.0 equiv), sodium metabisulfite (890 mg, 4.68 mmol, 1.3 equiv) and DMF (36 mL). The mixture was heated at 100 °C under air for 22 hours then allowed to cool to room temperature. Water (80 mL) was added slowly to the stirred solution until no further product precipitated. The solids were filtered and washed with water (2 x 15 mL) and dried to a brown solid (1.42 g). Additional product precipitated from the filtrate upon standing which was filtered and washed with water (2 x 10 mL) to obtain an off white solid (241 mg). The above reaction was repeated a second time in the exact manner and quantities as described to yield additional product (1.26 g of brown solid upon initial precipitation, plus 288 mg of off white solid from additional precipitation). The aqueous filtrates from the two reactions were combined and aqueous NaHCO₃ was added to adjust the pH to 7. The aqueous was extracted with DCM/2% MeOH (300 mL), dried (Na₂SO₄), filtered and evaporated to obtain a brown solid (547 mg). All products obtained were combined and purified by silica gel

chromatography (DCM/MeOH) to obtain the title compound as a yellow solid (2.37 g, 65% based on the theoretical yield for the two reactions). m/z (ES⁺) 505.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 12.41 (br s, 1H), 8.52 (s, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.66 & 7.56 (2 br singlets, amide rotamers, ArH, 1H), 7.49 (s, J = 8.2 Hz, 2H), 7.29 (s, 1H), 6.31 (br s, 1H), 4.79-4.67 (m, 1H), 3.54-3.34 (m, 5H), 3.17 (app t, J = 11.8, 1H), 2.99-2.82 (m, 2H), 2.63 (s, 3H), 2.33 & 2.24 (2 singlets, amide rotamers, ArCH₃, 3H), 2.03-1.87 (m, 5H), 1.82-1.38 (m, 3H). Elemental analysis (C₃₁H₃₂N₆O•1.3 H₂O, 528.04), found (calcd), C: 70.66 (70.51); H: 6.54 (6.60); N: 15.78 (15.92).

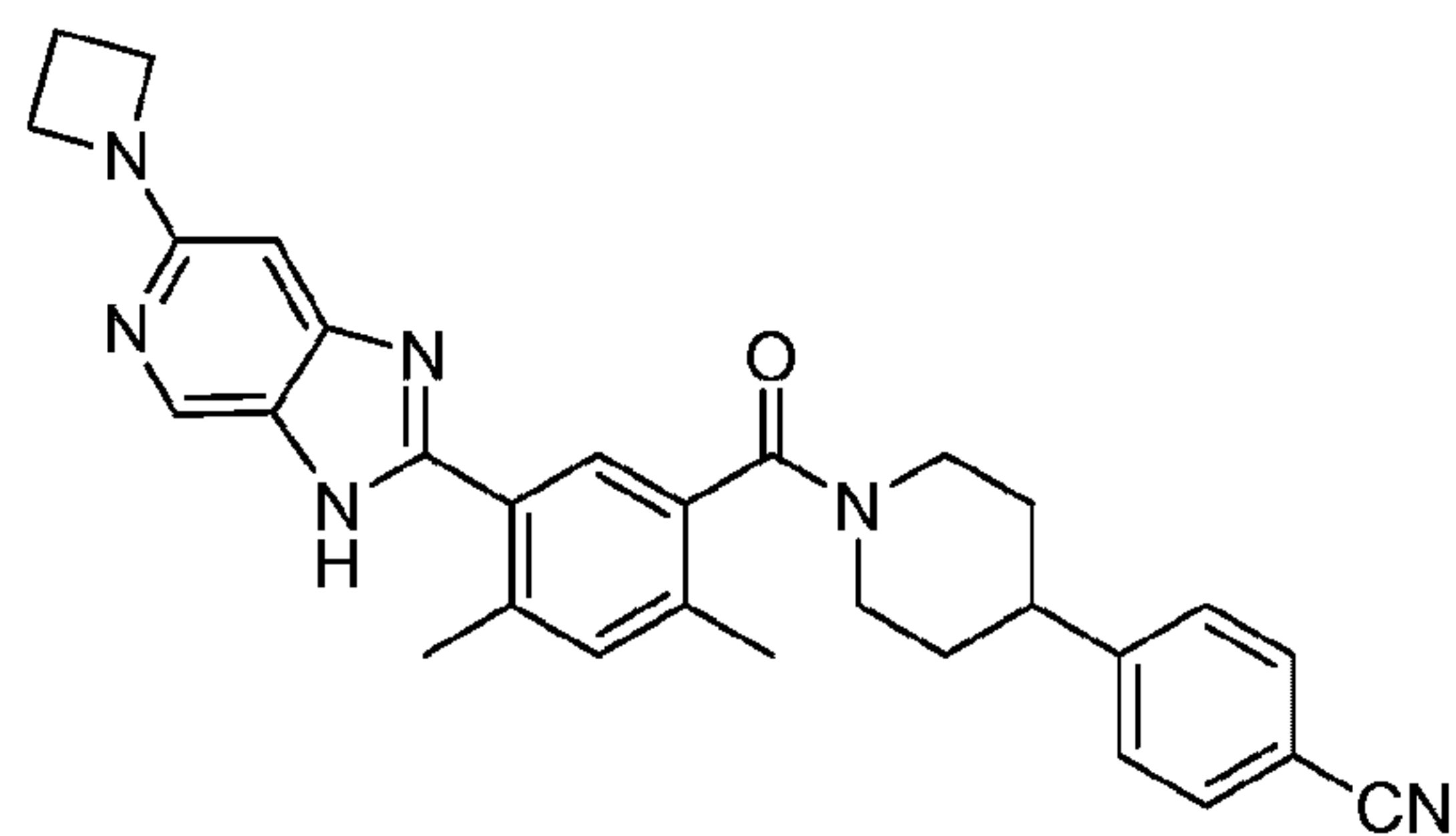


[0514] Compound 20 HCl salt. 4-(1-(2,4-Dimethyl-5-(6-(pyrrolidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile hydrochloride.

Dichloromethane (~50 mL) was added to 4-(1-(2,4-dimethyl-5-(6-(pyrrolidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile (compound 20 free base, 2.31 g, 4.58 mmol) until it completely dissolved and then 4M HCl in dioxane (5 mL, 20 mmol, 4.3 equiv) was added. The solvents were removed and the residue was dissolved in DCM and removed *in vacuo*. The resulting hydrochloride salt was recrystallized from boiling ethanol (180 mL) and allowed to cool to room temperature slowly. The mixture sat at room temperature overnight and then placed in the freezer for 4 hours. The resulting solids were filtered and washed with cold ethanol (25 mL) followed by diethyl ether (25 mL). The solids were dried to obtain an off white to light grey solid (1.82 g, 73%). ¹H NMR (400 MHz, DMSO-d₆): δ 13.59 & 13.46 (2 br singlets, imidazole NH tautomers, 1H), 13.29 (br s, 1H), 8.62 (br s, 1H), 7.83 & 7.67 (2 singlets, amide rotamers, ArH, 1H), 7.78 (d, J = 7.8 Hz, 2H), 7.58-7.45 (m, 2H), 7.37 (s, 1H), 6.71 (br s, 1H), 4.80-4.68 (m, 1H), 3.65-3.38 (m, 5H), 3.25-3.12 (m, 1H), 3.00-2.82 (m, 2H), 2.66 (s, 3H), 2.37 & 2.27 (2 singlets, amide rotamers, ArCH₃, 3H), 2.13-2.01 (m, 4H), 1.98-1.87 (m, 1H), 1.82-1.40 (m, 3H). Elemental analysis (C₃₁H₃₂N₆O•1.0 HCl•2.4 H₂O, 584.32), found (calcd), C: 63.80 (63.72); H: 6.32 (6.52); N: 14.25 (14.38).

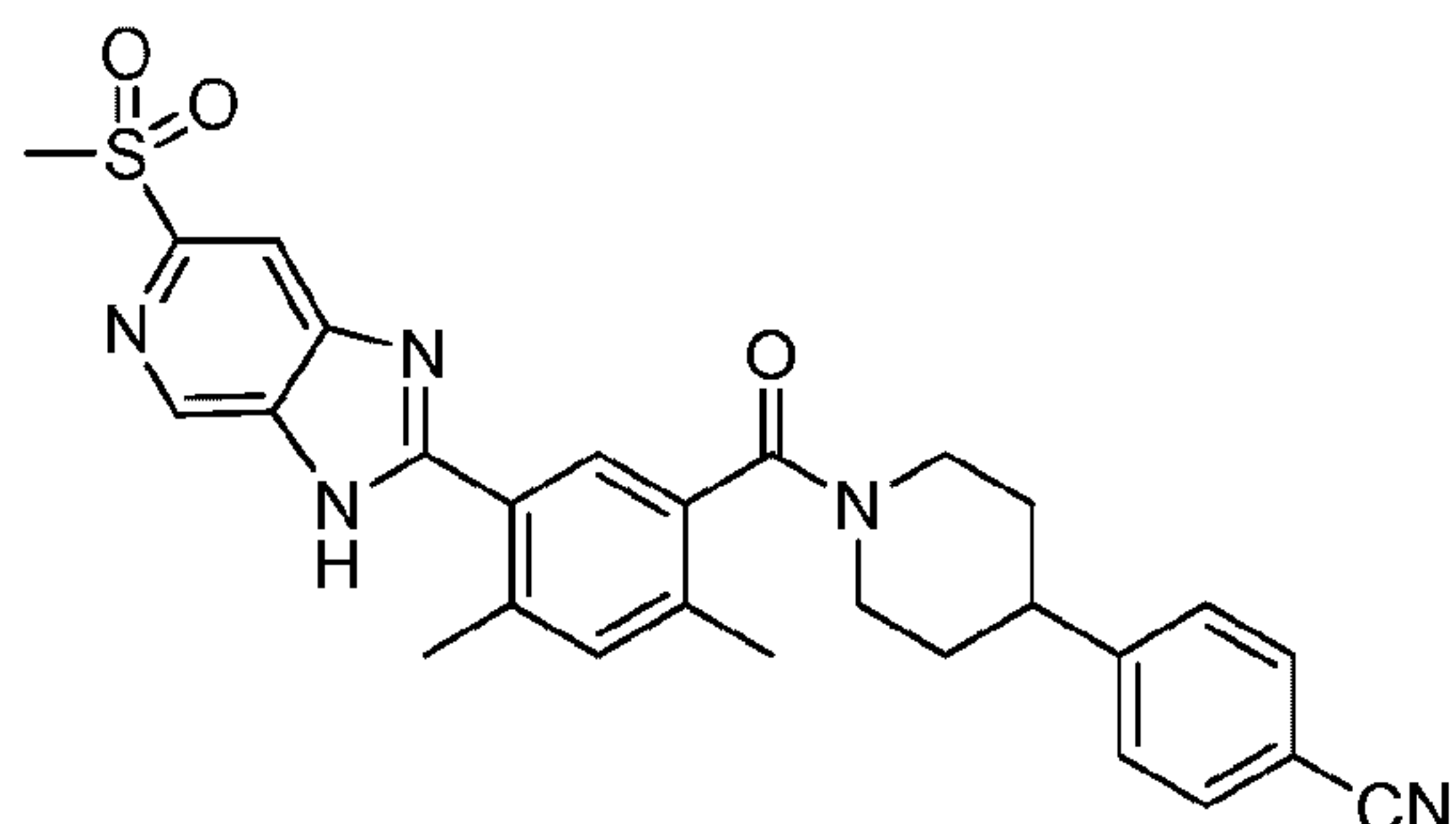


[0515] Compound 20 MsOH salt. 4-(1-(2,4-Dimethyl-5-(6-(pyrrolidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile methanesulfonate. 4-(1-(2,4-Dimethyl-5-(6-(pyrrolidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile hydrochloride (compound 20 HCl salt, 1.82 g, 3.36 mmol) was added to water (100 mL) plus saturated NaHCO₃ (50 mL) and extracted with 1:1 DCM/EtOAc (500 mL) plus MeOH (25 mL). Once the entire product completely dissolved, the layers were separated and the aqueous was extracted with additional 1:1 DCM/EtOAc (100 mL). The combined organics was dried (Na₂SO₄), filtered and evaporated to a light yellow powder (1.68 g, 3.33 mmol). The free base material was dissolved in hot acetonitrile (10 mL), then a 1.0 M aqueous methanesulfonic acid solution (3.33 mL, 3.33 mmol, 1.0 equiv) was added and mixed well. Additional water (6 mL) was added and the mixture was frozen and dried on the lyophilizer to obtain a yellow powder (1.99 g, 99%). *m/z* (ES+) 505.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 13.29 (br s, 1H), 13.10 (br s, 1H), 8.65 (br s, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.74 & 7.64 (2 singlets, amide rotamers, ArH, 1H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.37 (s, 1H), 6.74 (br s, 1H), 4.80-4.68 (m, 1H), 3.65-3.38 (m, 5H), 3.26-3.12 (m, 1H), 3.01-2.83 (m, 2H), 2.64 (s, 3H), 2.37 & 2.27 (2 singlets, amide rotamers, ArCH₃, 3H), 2.32 (s, 3H) 2.12-2.00 (m, 4H), 1.98-1.88 (m, 1H), 1.82-1.39 (m, 3H). Elemental analysis (C₃₁H₃₂N₆O•1.0 MsOH•1.7 H₂O, 631.36), found (calcd), C: 60.96 (60.88); H: 6.14 (6.29); N: 13.21 (13.31); S: 5.08 (5.08).

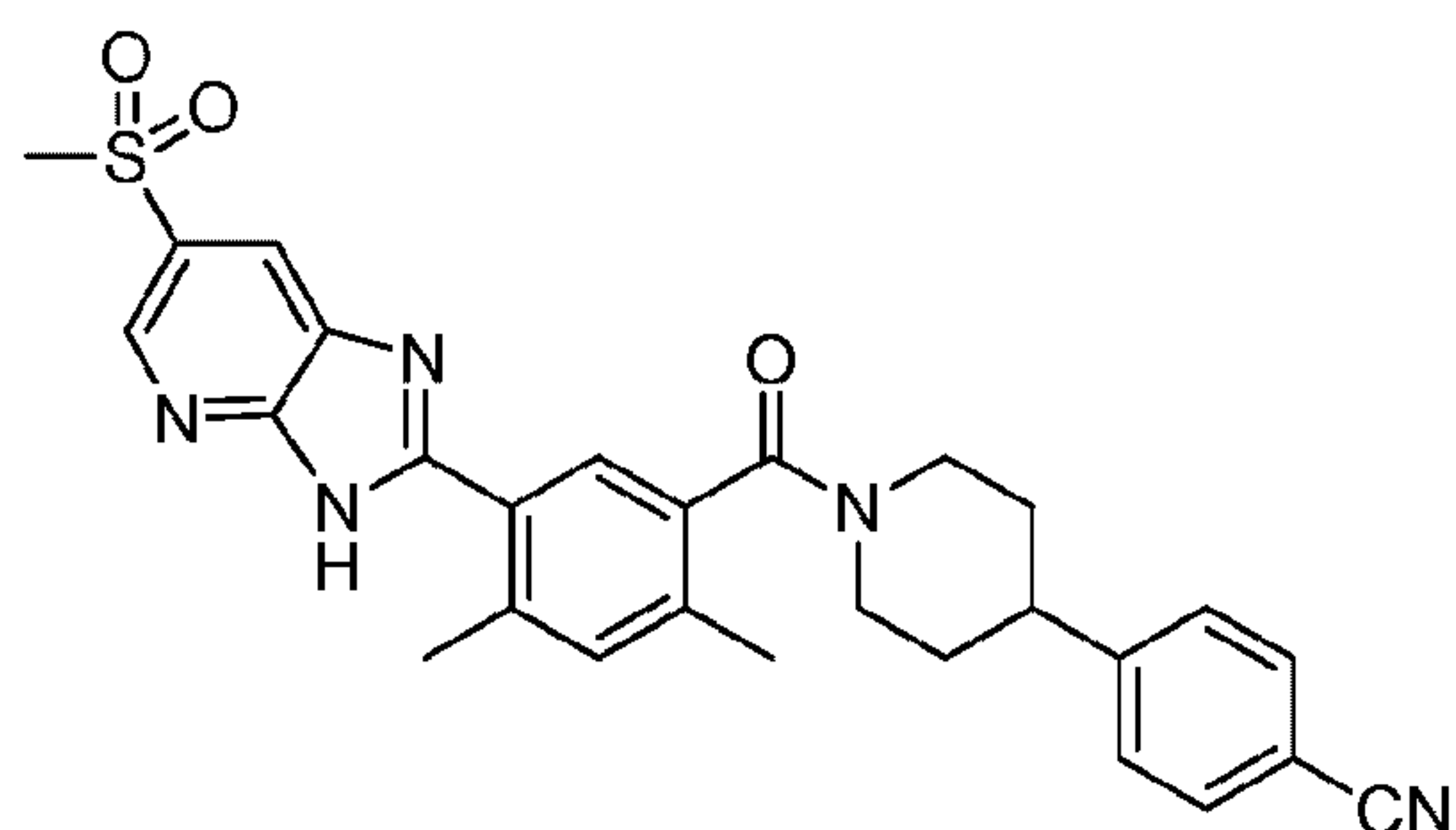


[0516] Compound 21. 4-(1-(5-(6-(Azetidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)-2,4-dimethylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using

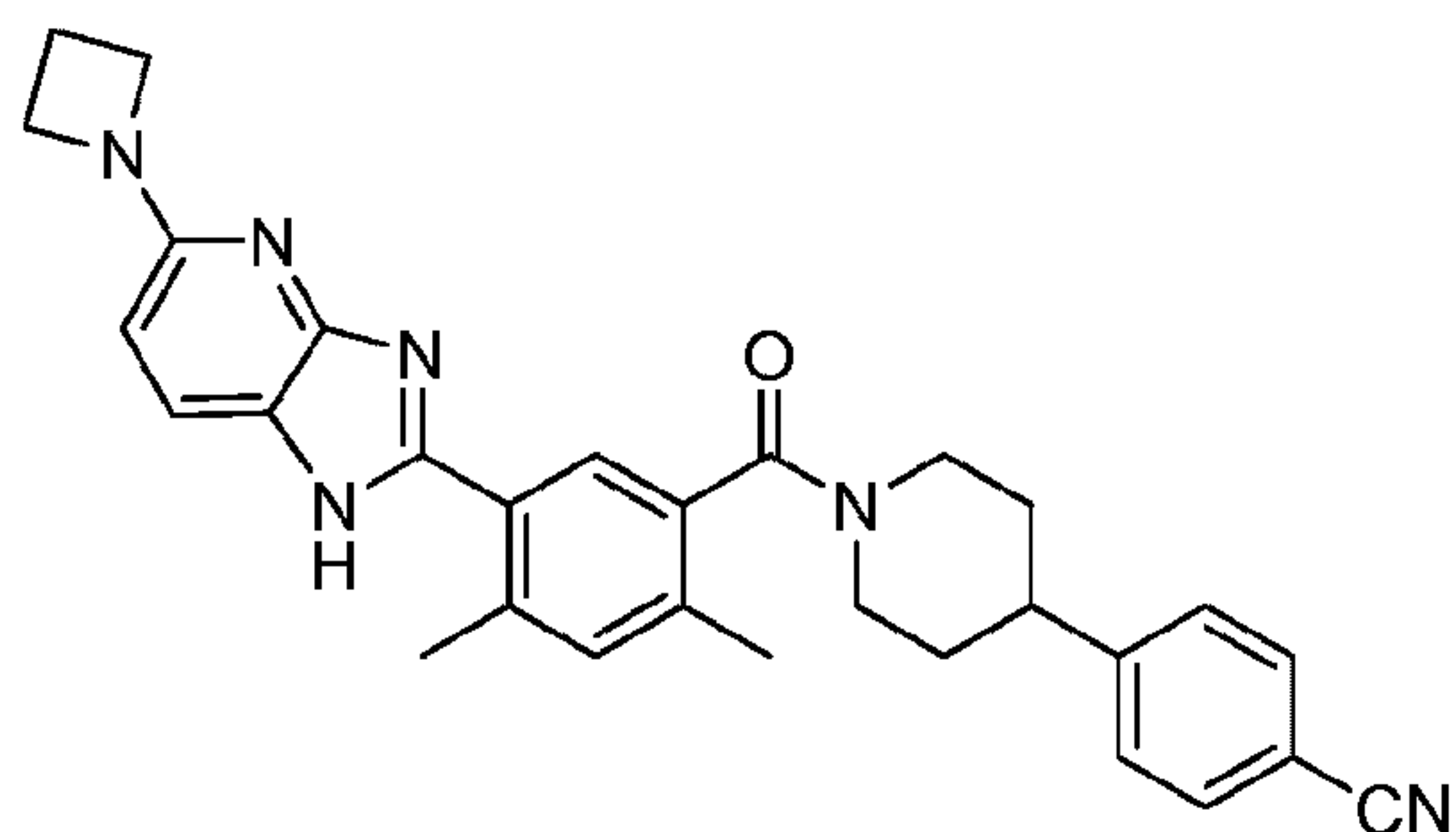
standard chemical manipulations and procedures similar to those used for preparation of compound **16**. m/z (ES⁺) 491 (M+H)⁺.



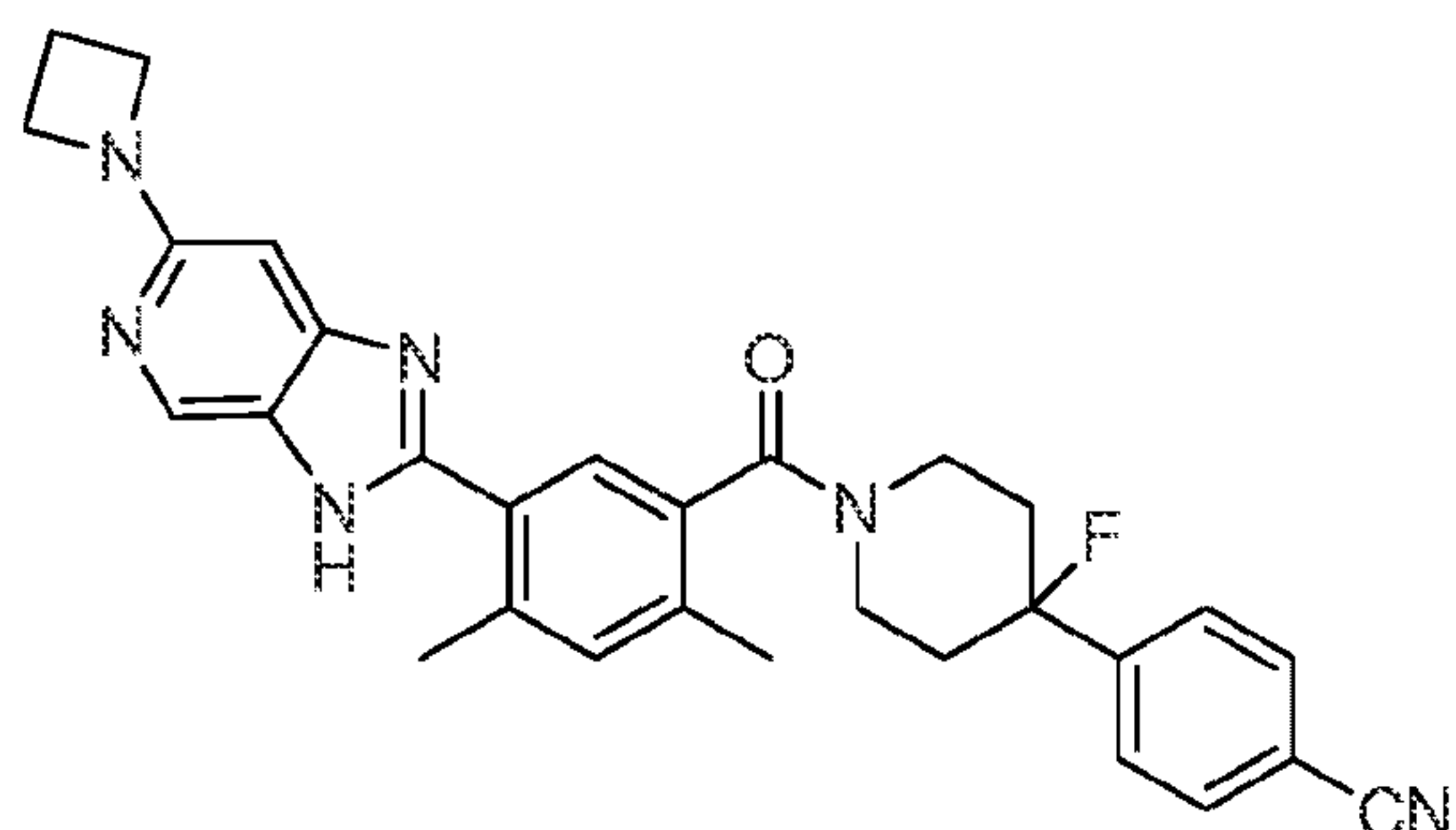
[0517] **Compound 22. 4-(1-(2,4-Dimethyl-5-(6-(methylsulfonyl)-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile.** The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of compound **16**. m/z (ES⁺) 514 (M+H)⁺.



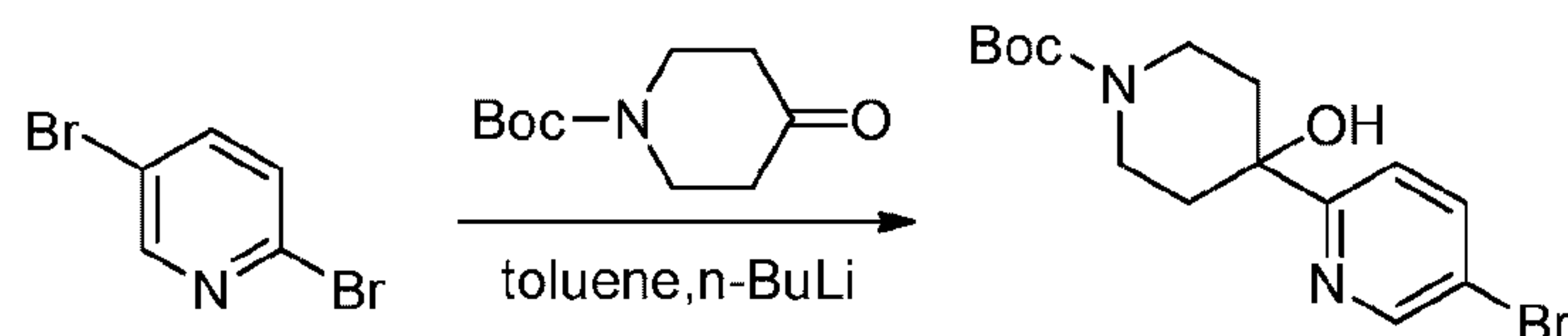
[0518] **Compound 23. 4-(1-(2,4-Dimethyl-5-(6-(methylsulfonyl)-3H-imidazo[4,5-b]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile.** The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of compound **16**. m/z (ES⁺) 514 (M+H)⁺. ¹H NMR (300 MHz, DMSO-d₆ + D₂O): δ 8.87 (d, J = 1.8 Hz, 1H), 8.52 (d, J = 2.1 Hz, 1H), 7.74 (d, J = 7.5 Hz, 2H), 7.66 & 7.56 (2 singlets, amide rotamers, Ar-H, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.38 (br s, 1H), 4.76-4.63 (m, 1H), 3.57-3.38 (m, 1H), 3.31 (s, 3H), 3.28-3.13 (m, 1H), 3.03-2.85 (m, 2H), 2.60 (s, 3H), 2.35 & 2.27 (2 singlets, amide rotamers, Ar-CH₃, 3H), 2.00-1.85 (m, 1H), 1.85-1.32 (m, 3H).



[0519] **Compound 24.** 4-(1-(5-(5-(Azetidin-1-yl)-1H-imidazo[4,5-b]pyridin-2-yl)-2,4-dimethylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of compound **16** but using 6-chloro-3-nitropyridin-2-amine and azetidine hydrochloride in place of 2-chloro-5-nitropyridin-4-amine and (2-methoxyethyl)(methyl)amine respectively. m/z (ES+) 491 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD): δ 8.06 (d, J = 9.0 Hz, 1H), 7.70-7.42 (m, 6H), 6.60 (d, J = 9.0 Hz, 1H), 4.90 (m, 1H, partially obscured by the solvent peak), 4.32 (m, 4H), 3.65 (m, 1H), 3.03 (m, 1H), 2.62 (s, 3H), 2.57 (m, 3H), 2.48 and 2.38 (2 singlets, amide rotamers, ArCH₃, 3H), 2.04 (m, 1H), 1.96-1.68 (m, 4H).

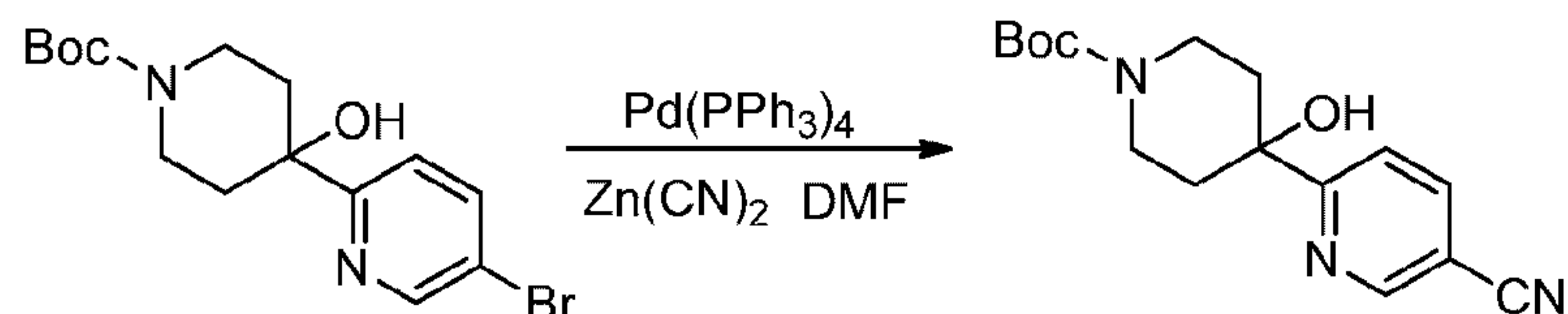


[0520] **Compound 25.** 4-(1-(5-(6-(Azetidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)-2,4-dimethylbenzoyl)-4-fluoropiperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of compound **16** and using compound **11.2** in place of compound **1.5**. m/z (ES+) 509 (M+H)⁺.

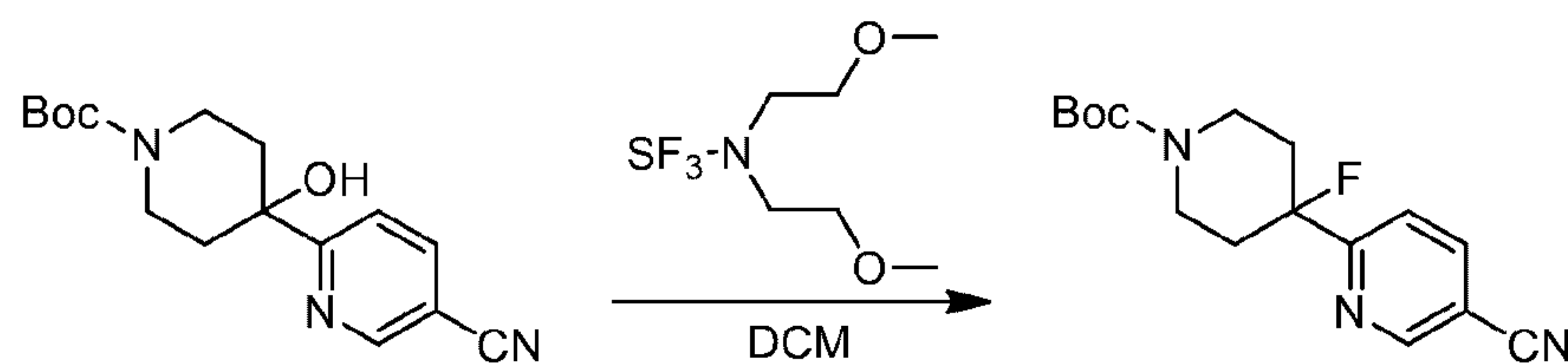


[0521] **Compound 26.1.** tert-Butyl 4-(5-bromopyridin-2-yl)-4-hydroxypiperidine-1-carboxylate. To a stirred solution of 2,5-dibromopyridine (10 g, 42.19 mmol, 1.00 equiv) in toluene (1000 mL) under nitrogen at -78°C was added dropwise n-BuLi (18 mL, 2.5 M in toluene). After 1 h at -78°C, a solution of tert-butyl 4-oxopiperidine-1-carboxylate (10 g,

50.25 mmol, 1.19 equiv) in toluene (200 mL) was added dropwise while stirring. After an additional 2 h of stirring at -78°C , the reaction was then carefully quenched by the addition of 300 mL of water. The resulting mixture was extracted with 3x500 mL of ethyl acetate. The combined organic layers were washed with 1x300 mL of brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:100-1:5) to yield 6.5 g (42%) of the title compound as a yellow oil.

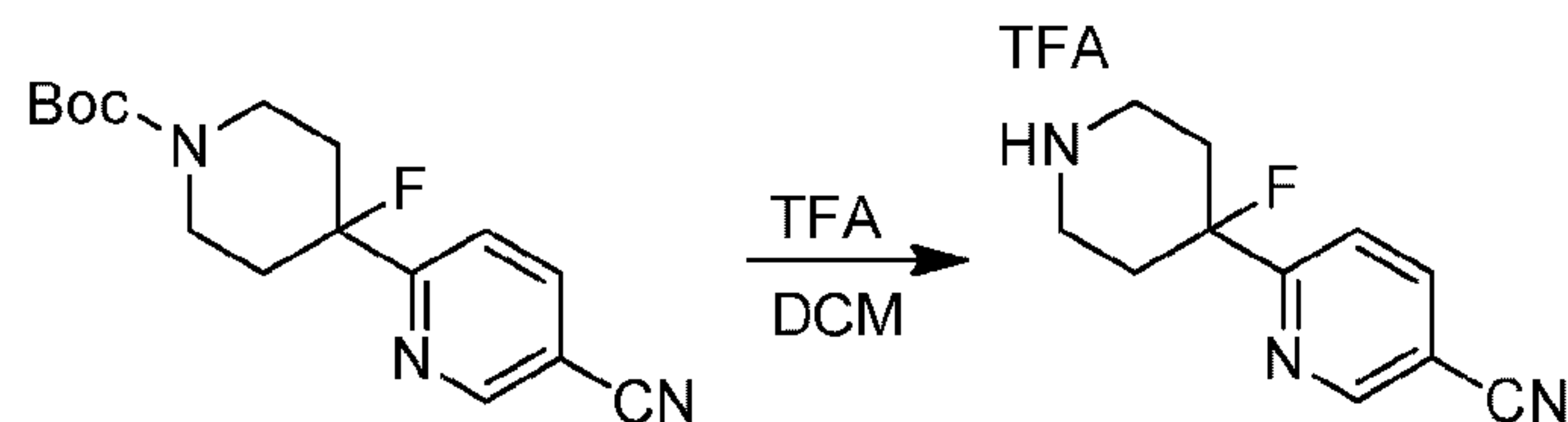


[0522] Compound 26.2. tert-Butyl 4-(5-cyanopyridin-2-yl)-4-hydroxypiperidine-1-carboxylate. A mixture of tert-butyl 4-(5-bromopyridin-2-yl)-4-hydroxypiperidine-1-carboxylate (compound **26.1**, 1 g, 2.80 mmol, 1.00 equiv), zinc cyanide (400 mg, 3.42 mmol, 1.22 equiv), $\text{Pd(PPh}_3)_4$ (200 mg, 0.17 mmol, 0.06 equiv) in DMF (50 mL) was stirred under nitrogen for 2 h at 100°C . After cooling to room temperature, the reaction was then quenched by careful addition of 300 mL of FeSO_4 (aq., sat.) and diluted with ethyl acetate. The resulting mixture was stirred vigorously then filtered through celite and washed with 1 M FeSO_4 , water, and ethyl acetate. The layers were separated and the aqueous phase was extracted with 2 x 100 mL of ethyl acetate. The combined organic layers were washed with 1x100 mL of brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:100-1:4) yield 0.5 g (58%) of the title compound as a yellow oil.

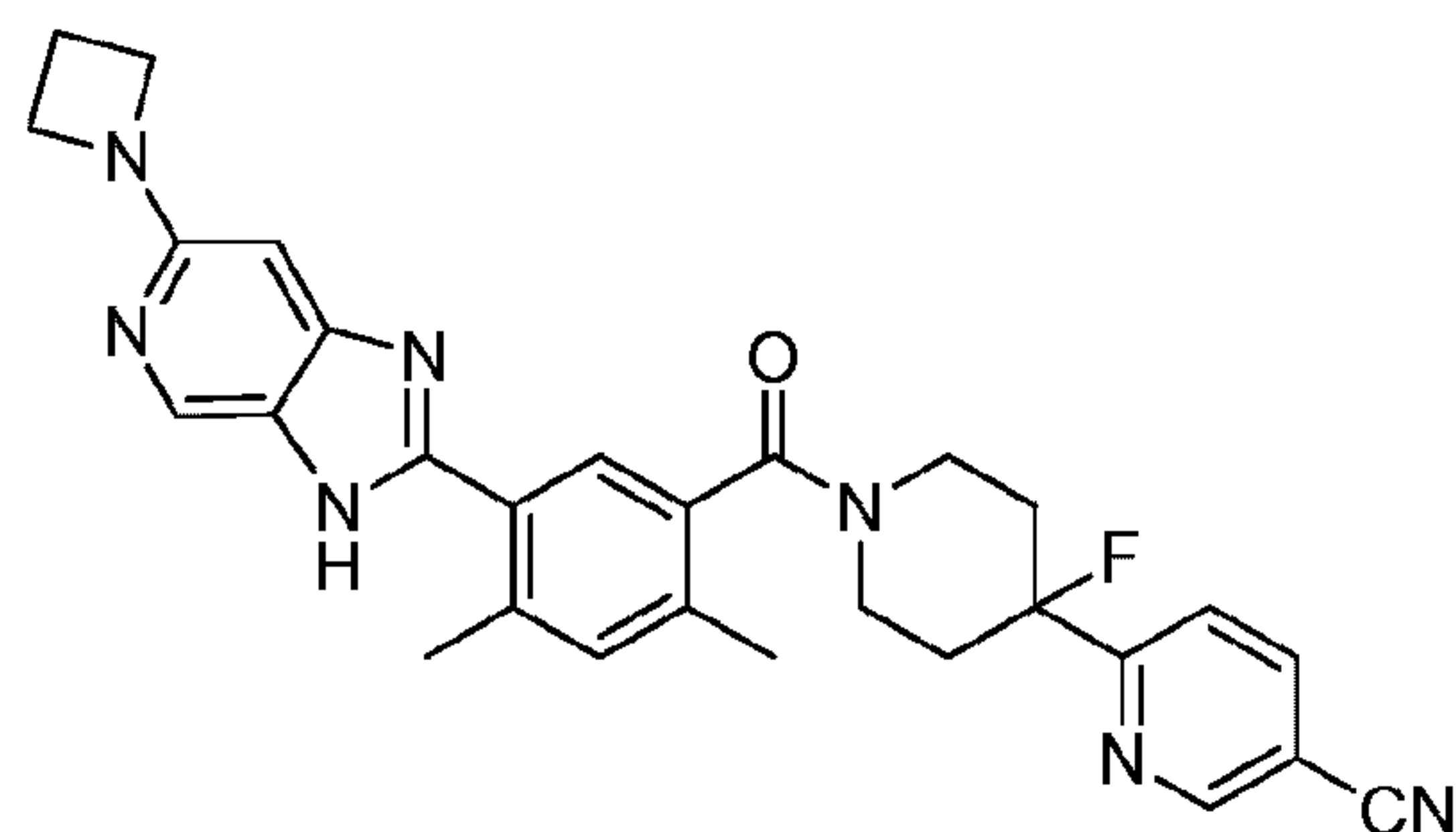


[0523] Compound 26.3. tert-Butyl 4-(5-cyanopyridin-2-yl)-4-fluoropiperidine-1-carboxylate. To a solution of tert-butyl 4-(5-cyanopyridin-2-yl)-4-hydroxypiperidine-1-carboxylate (compound **26.2**, 1 g, 3.13 mmol, 1.00 equiv, 95%) in dichloromethane (50 mL) under nitrogen at -78°C was added dropwise a solution of bis(2-methoxyethyl)aminosulfur trifluoride (830 mg, 3.75 mmol, 1.20 equiv) in dichloromethane (10 mL) during the course of 1 min. The resulting mixture was stirred for 1 h at -78°C . The reaction was then carefully quenched by dropwise addition of water and washed with 2x20 mL of sodium

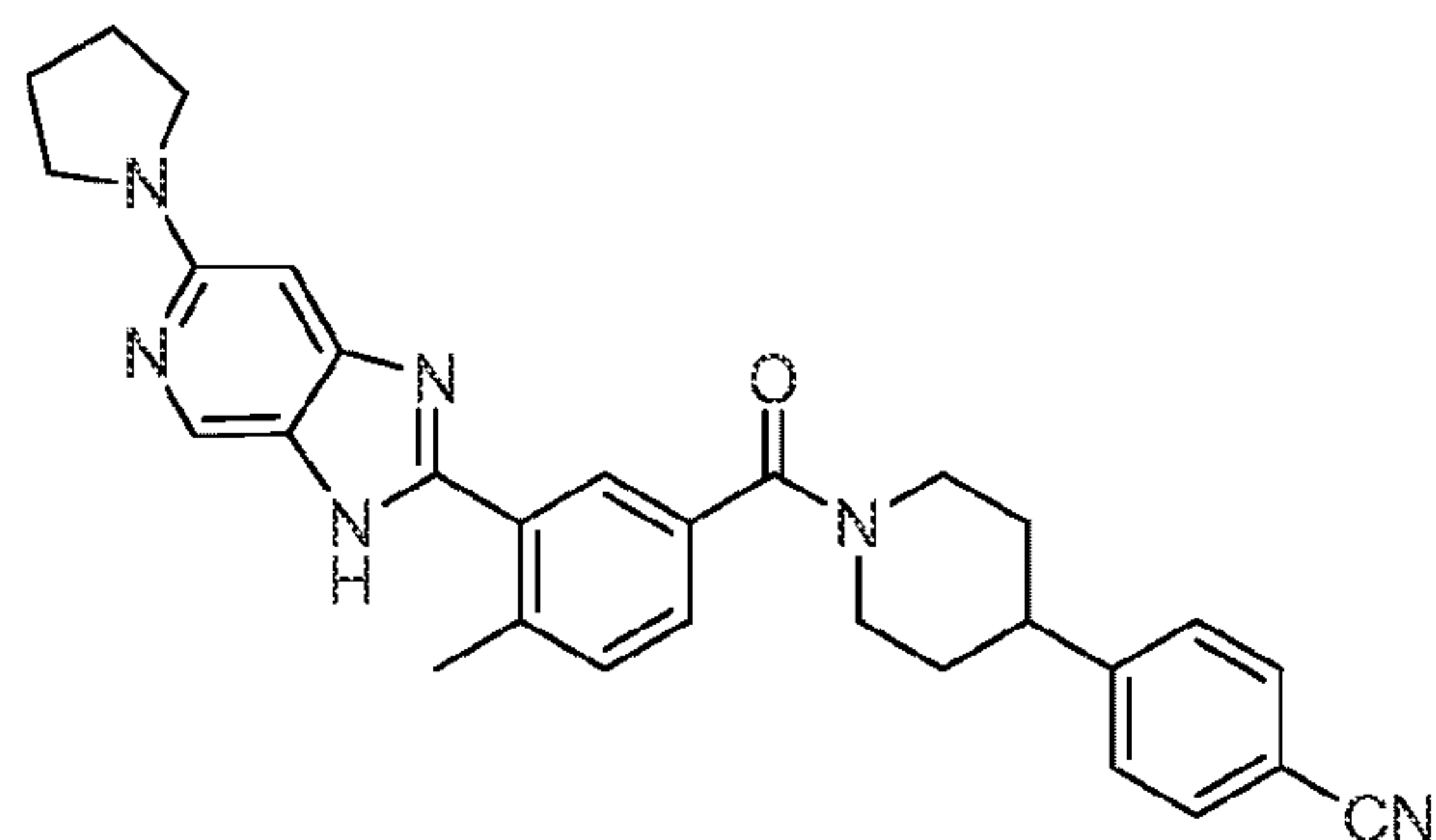
bicarbonate(aq) followed by 3x20 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:10) to yield 0.38 g (38%) of the title compound as a white solid.



[0524] Compound 26.4. 6-(4-Fluoropiperidin-4-yl)nicotinonitrile trifluoroacetate. To a stirred solution of tert-butyl 4-(5-cyanopyridin-2-yl)-4-fluoropiperidine-1-carboxylate (compound 26.3, 1 g, 3.11 mmol, 1.00 equiv, 95%) in dichloromethane (20 mL) was added dropwise TFA (3.75 g, 32.89 mmol, 10.57 equiv). After stirring for 1 h at 25°C, the mixture was concentrated under reduced pressure to yield 0.5 g of the title compound as a brown oil.

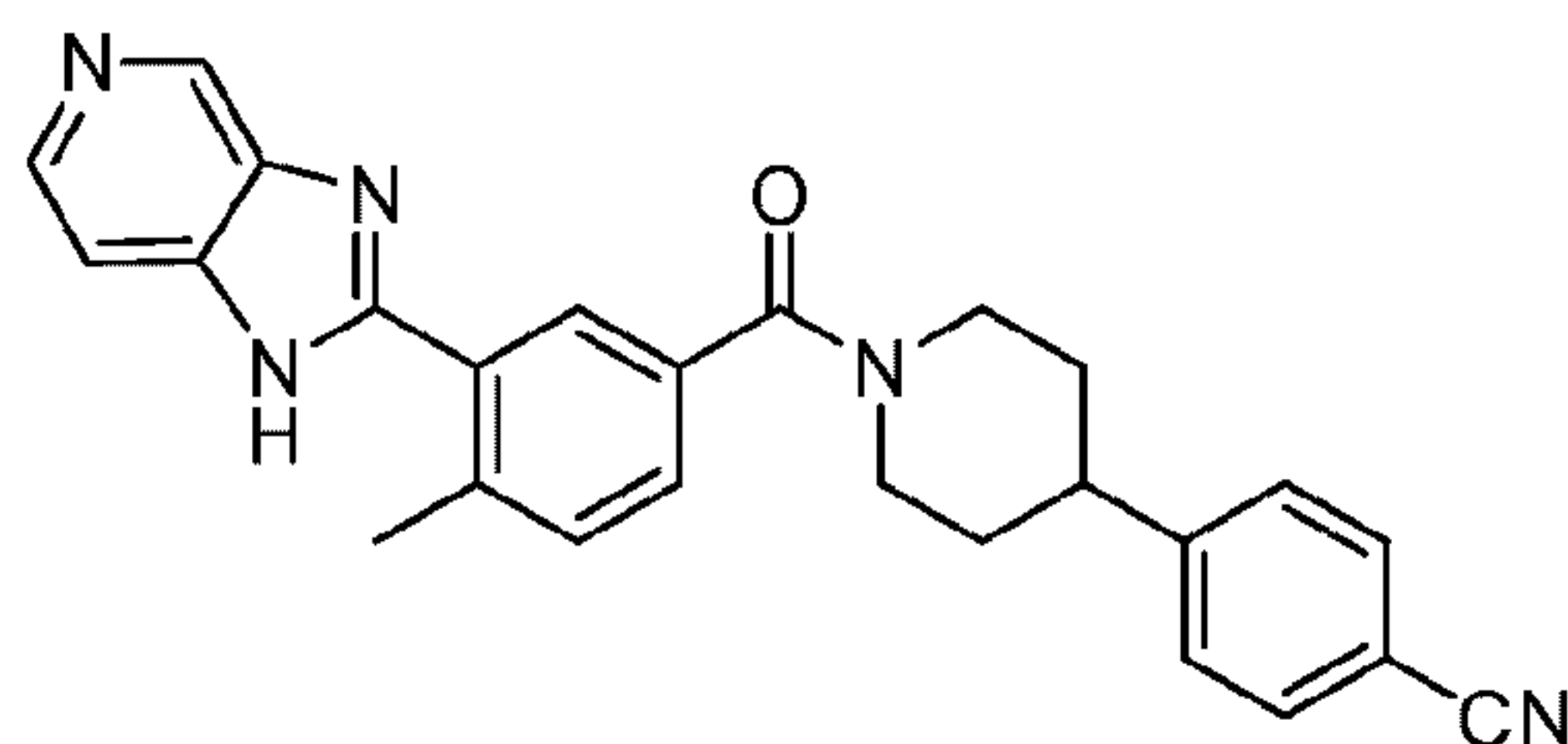


[0525] Compound 26. 6-(1-(5-(6-(Azetidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)-2,4-dimethylbenzoyl)-4-fluoropiperidin-4-yl)nicotinonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of compound 16 but using compound 26.4 in place of compound 1.5. m/z (ES⁺) 509 (M+H)⁺.

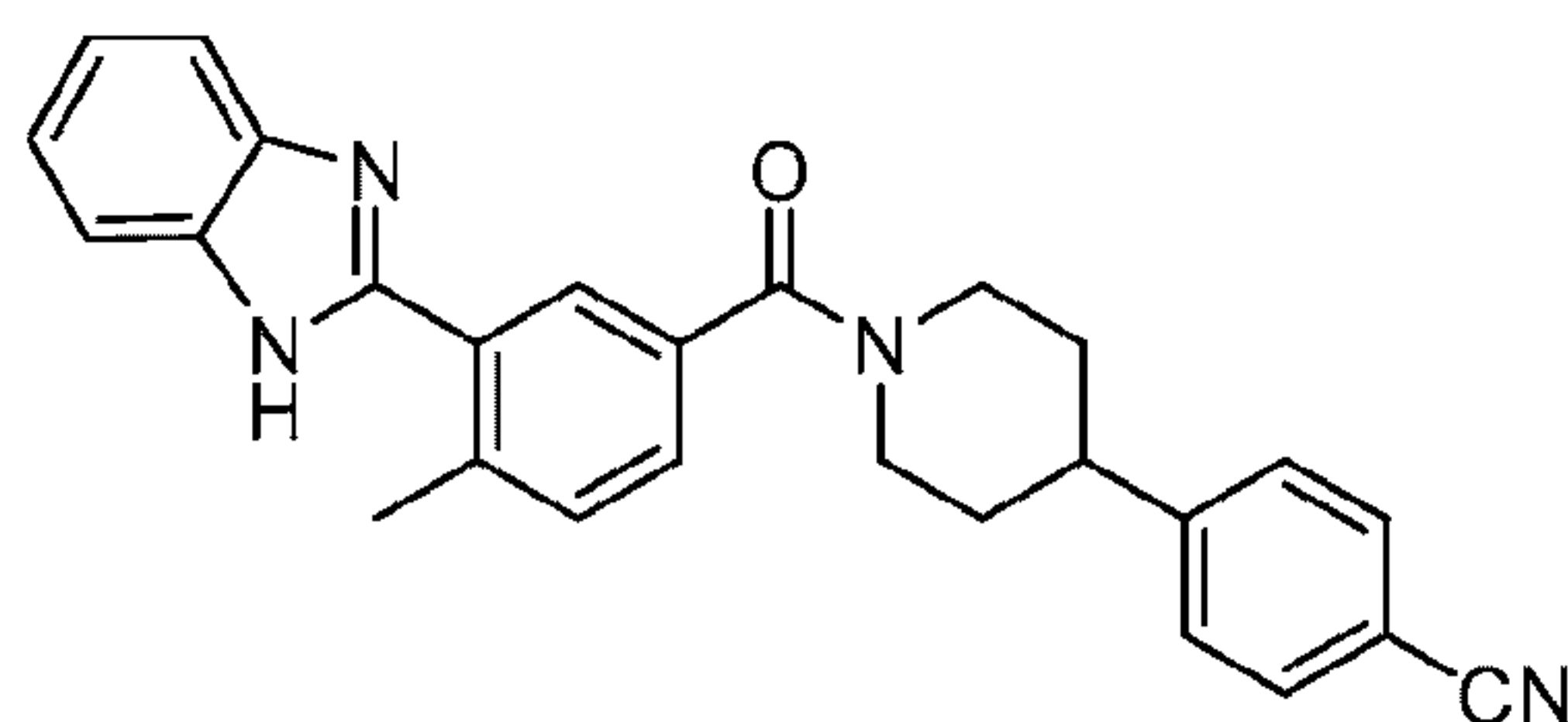


[0526] Compound 27. 4-(1-(4-Methyl-3-(6-(pyrrolidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of

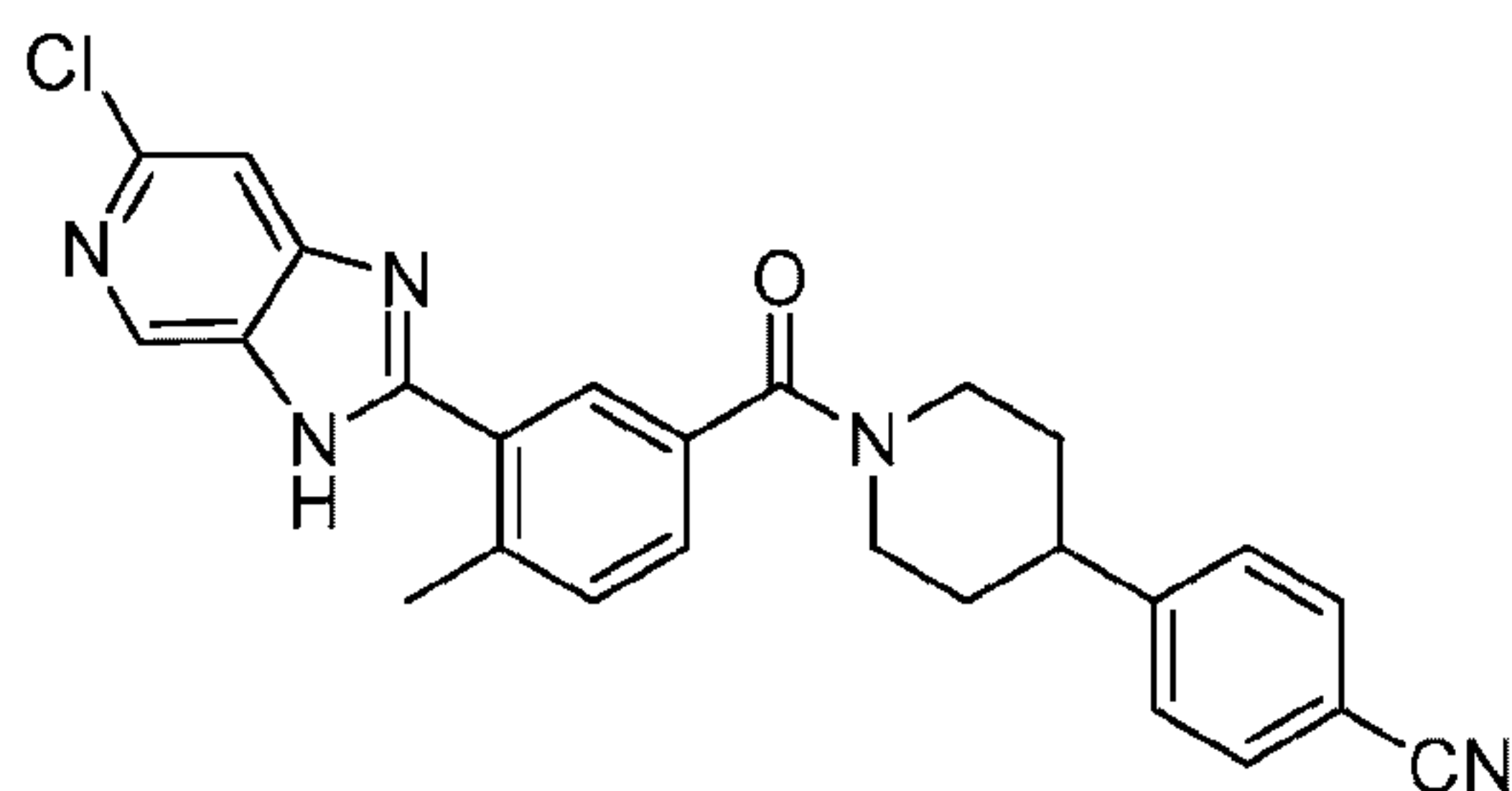
compound **16** but using 3-bromo-4-methylbenzoic acid in place of 5-iodo-2,4-dimethylbenzoic acid. m/z (ES⁺) 491 (M+H)⁺.



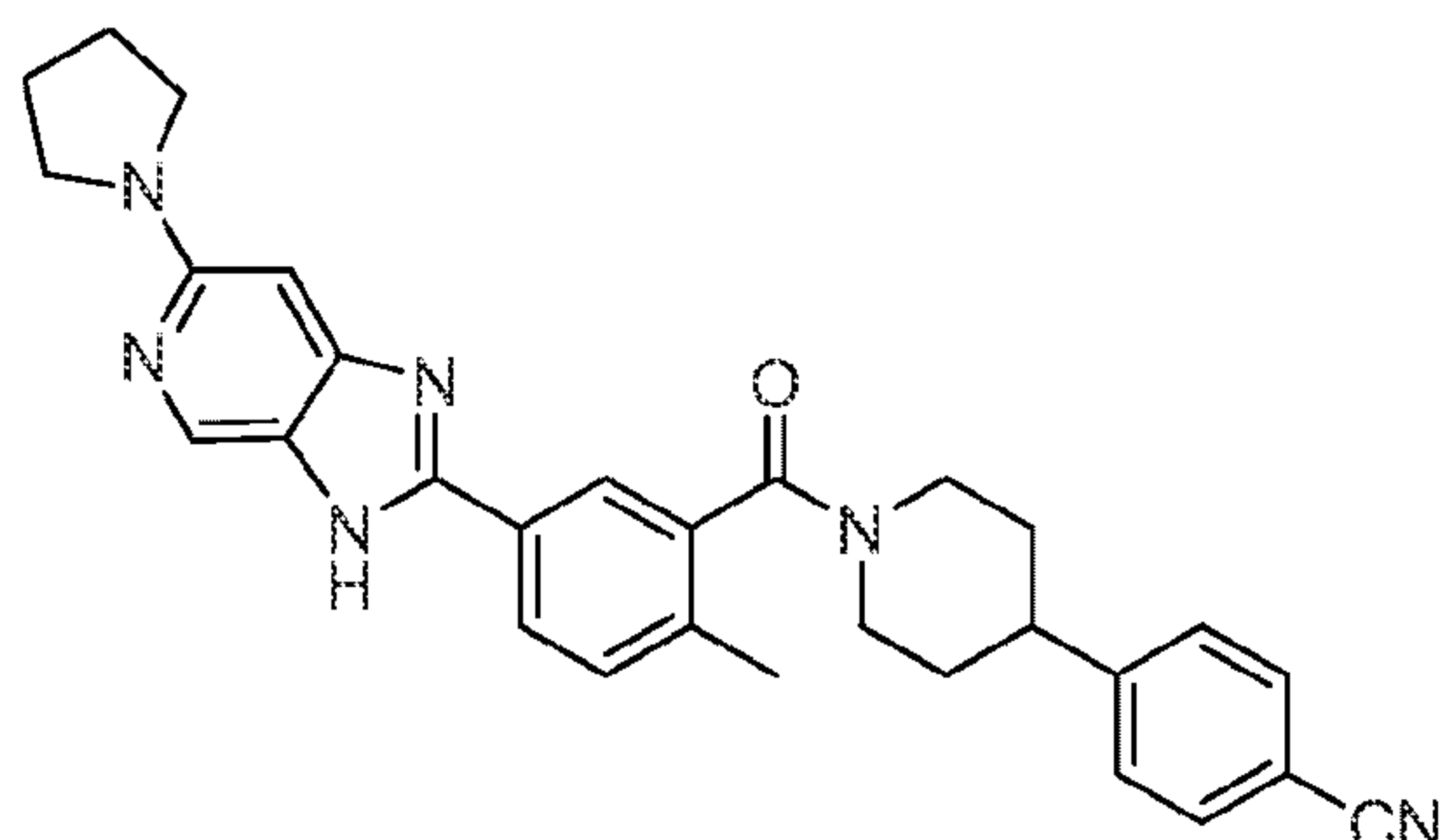
[0527] Compound 28. 4-(1-(3-(1H-Imidazo[4,5-c]pyridin-2-yl)-4-methylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of compounds **16** and **27**. m/z (ES⁺) 422 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD): δ 9.35 (s, 1H), 8.60 (d, J = 6.6 Hz, 1H), 8.19 (d, J = 6.6 Hz, 1H), 7.92 (s, 1H), 7.73-7.58 (m, 4H), 7.50 (d, J = 8.1 Hz, 1H), ~4.9 (1H, partially obscured by water peak), 4.06-3.87 (m, 1H), 3.13-2.95 (m, 3H), 2.73 (s, 3H), 2.11-1.63 (m, 4H).



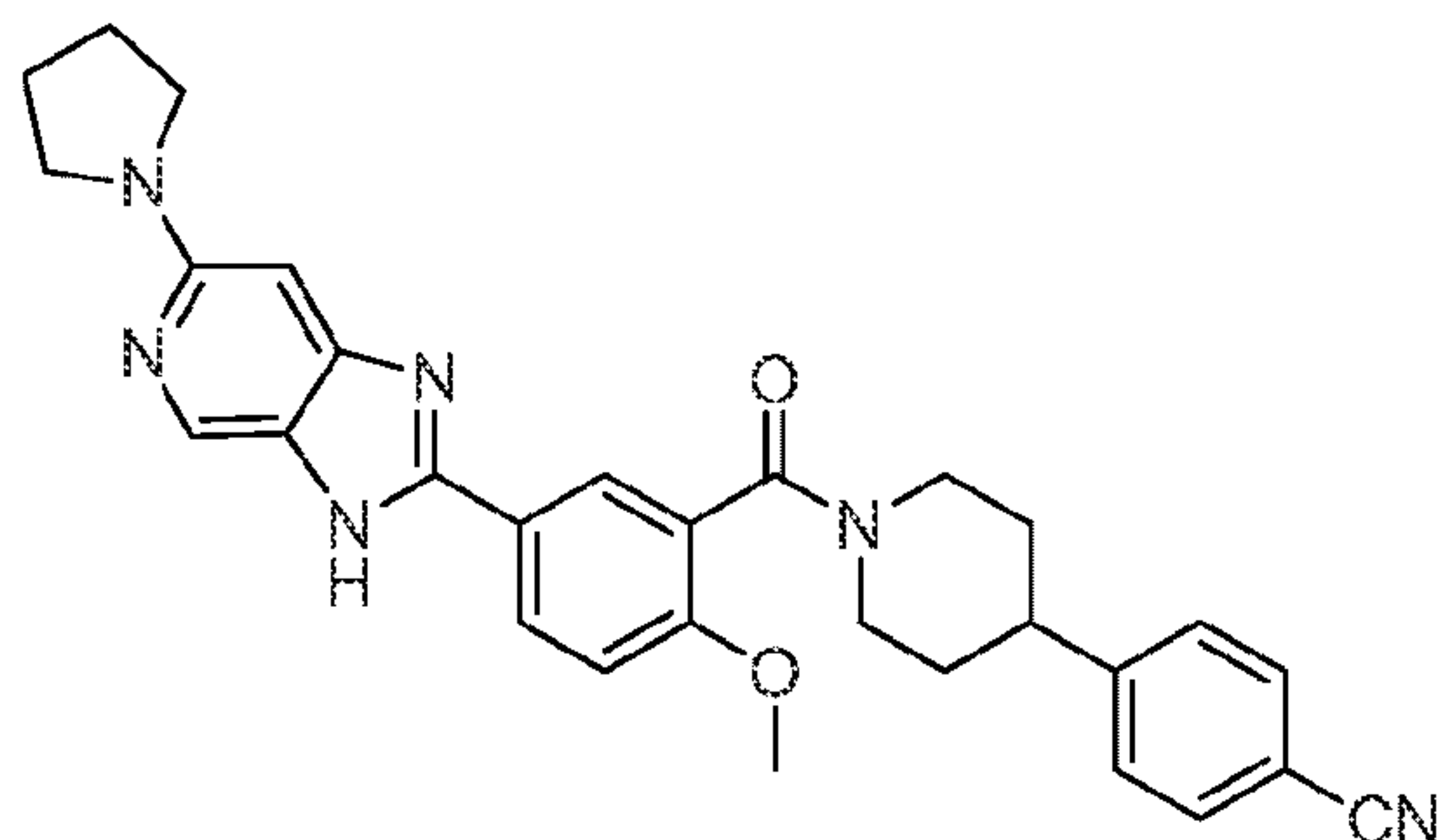
[0528] Compound 29. 4-(1-(3-(1H-Benzo[d]imidazol-2-yl)-4-methylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of compounds **16** and **27**. m/z (ES⁺) 421 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.87-7.77 (m, 3H), 7.75-7.60 (m, 4H), 7.60-7.47 (m, 4H), ~4.85 (1H, partially obscured by water peak), 4.04-3.89 (m, 1H), 3.13-2.95 (m, 3H), 2.61 (s, 3H), 2.11-1.69 (m, 4H).



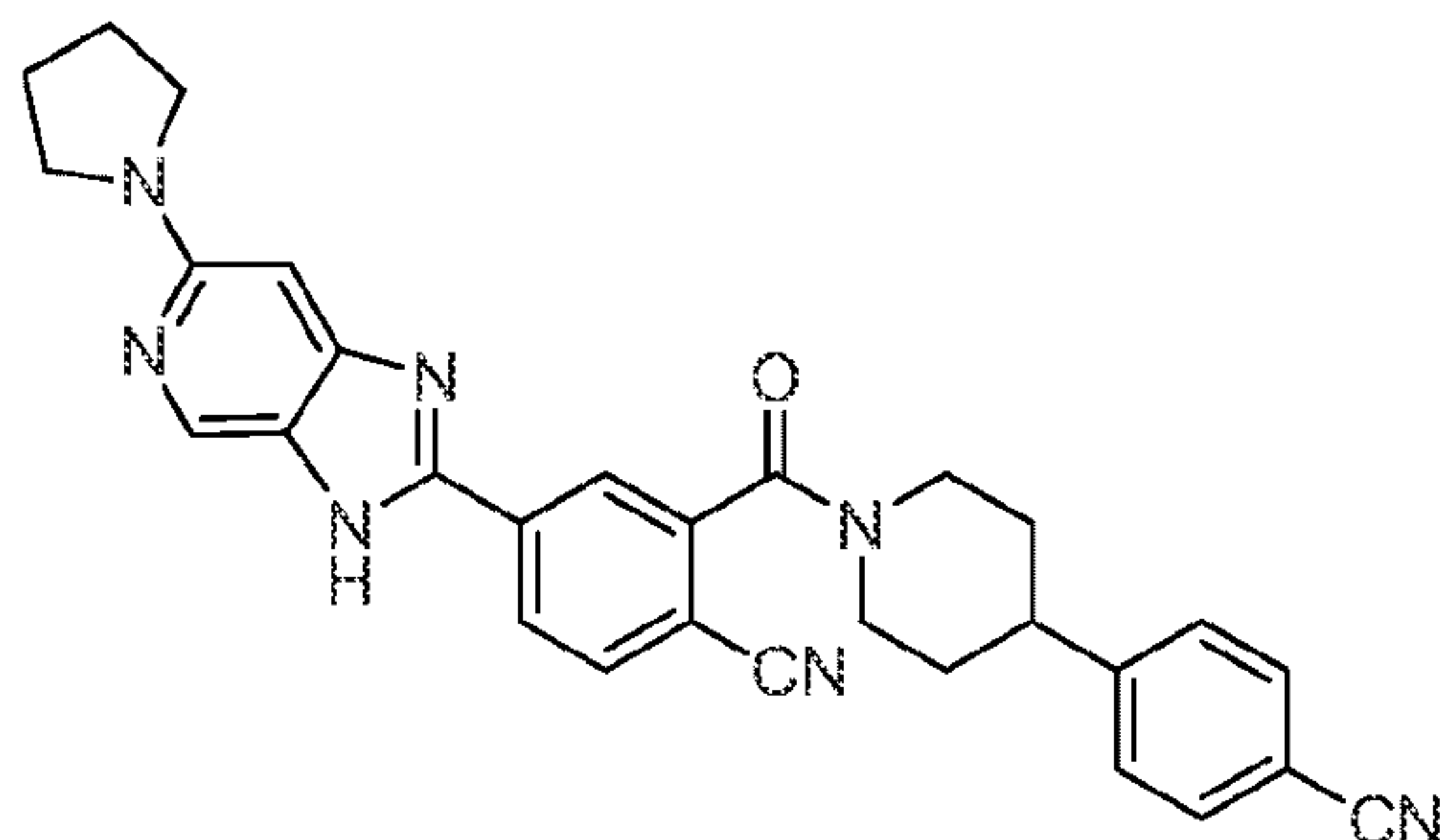
[0529] Compound 30. 4-(1-(3-(6-Chloro-3H-imidazo[4,5-c]pyridin-2-yl)-4-methylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of compounds **16** and **27**. m/z (ES⁺) 456 (M+H)⁺.



[0530] Compound 31. 4-(1-(2-Methyl-5-(6-(pyrrolidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of compound 16 but using 5-bromo-2-methylbenzoic acid in place of 5-iodo-2,4-dimethylbenzoic acid (compound 2.1). m/z (ES+) 491 (M+H)⁺. ¹H NMR (300 MHz, DMSO-d₆): δ 12.63 (br s, 1H), 8.06 (d, J = 7.8 Hz, 1H), 8.01 & 7.91 (2 singlets, amide rotamers, Ar-H, 1H), 7.81 (d, J = 6.6 Hz, 2H), 7.58-7.42 (m, 3H), 6.31 (s, 1H), 4.85 (m, 1H), 3.57-3.35 (m, 5H), 3.30-3.13 (m, 1H), 3.07-1.85 (m, 2H), 2.39 & 2.29 (2 singlets, amide rotamers, Ar-CH₃, 3H), 2.10-1.89 (m, 5H), 1.87-1.40 (m, 3H).

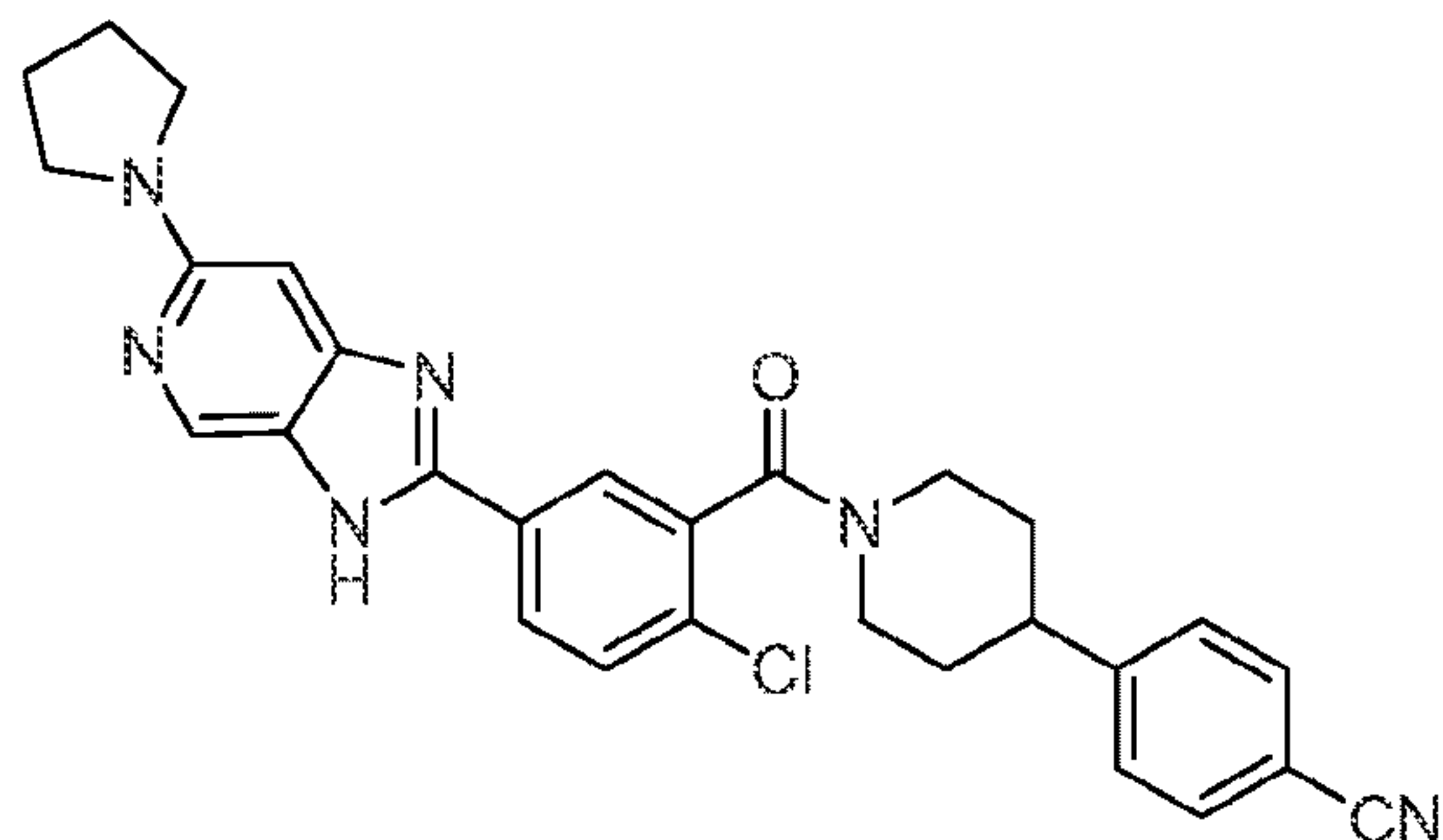


[0531] Compound 32. 4-(1-(2-Methoxy-5-(6-(pyrrolidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of compound 16. m/z (ES+) 507 (M+H)⁺.

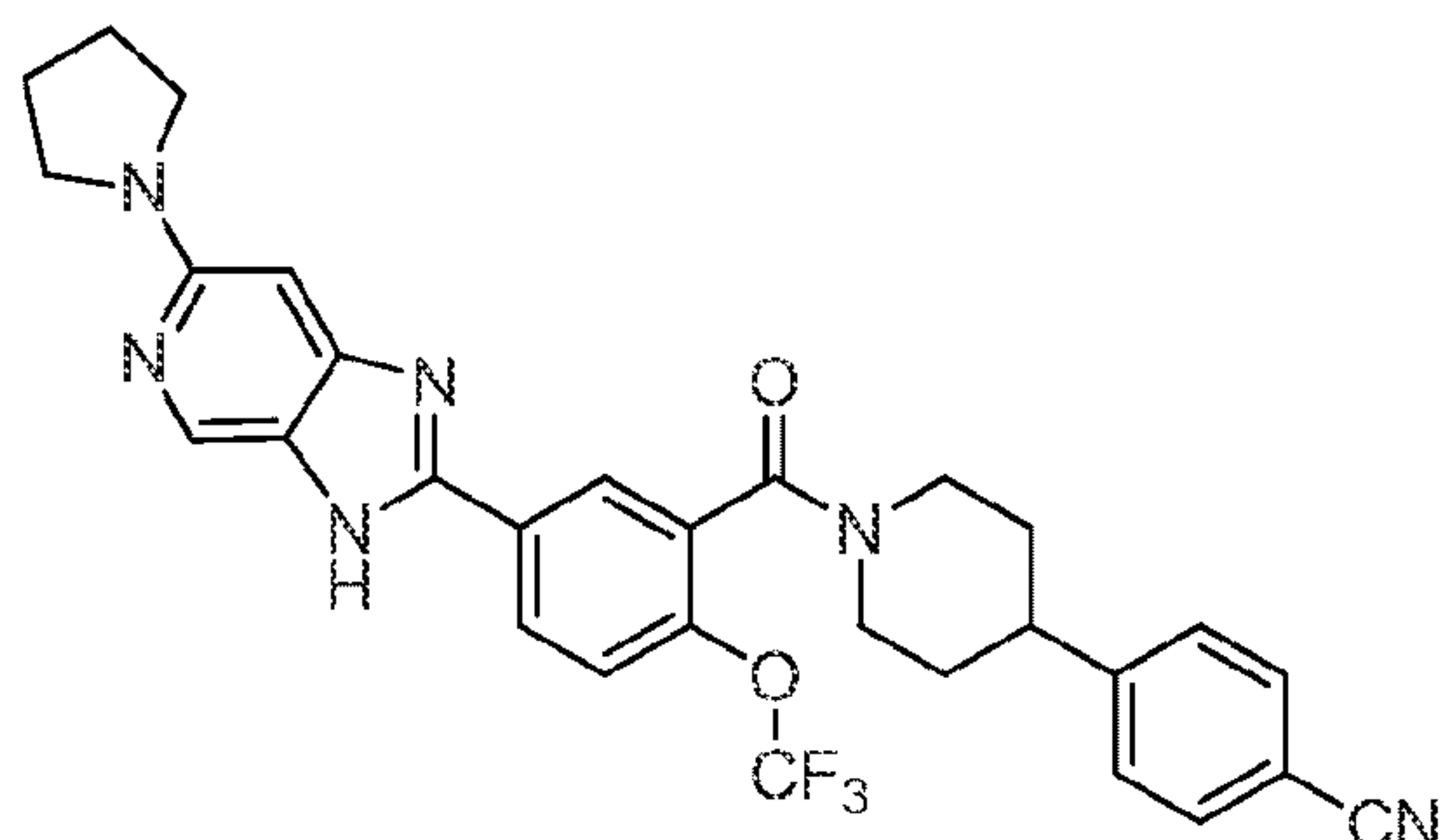


[0532] Compound 33. 2-(4-(4-Cyanophenyl)piperidine-1-carbonyl)-4-(6-(pyrrolidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)benzonitrile. The title compound was prepared using

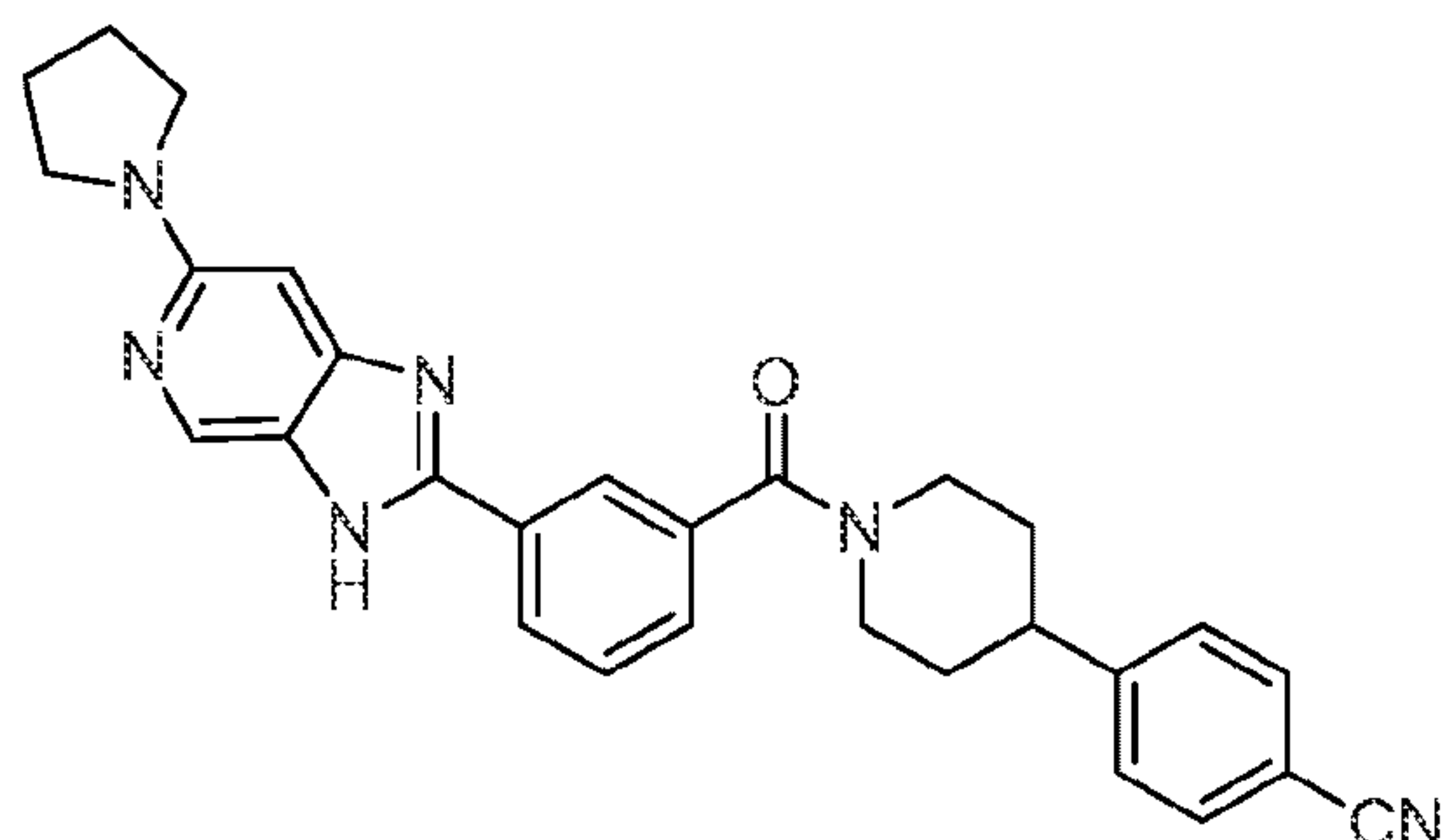
standard chemical manipulations and procedures similar to those used for preparation of compound **16**. m/z (ES⁺) 502 (M+H)⁺.



[0533] Compound **34**. 4-(1-(2-Chloro-5-(6-(pyrrolidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of compound **16**. m/z (ES⁺) 511 (M+H)⁺.

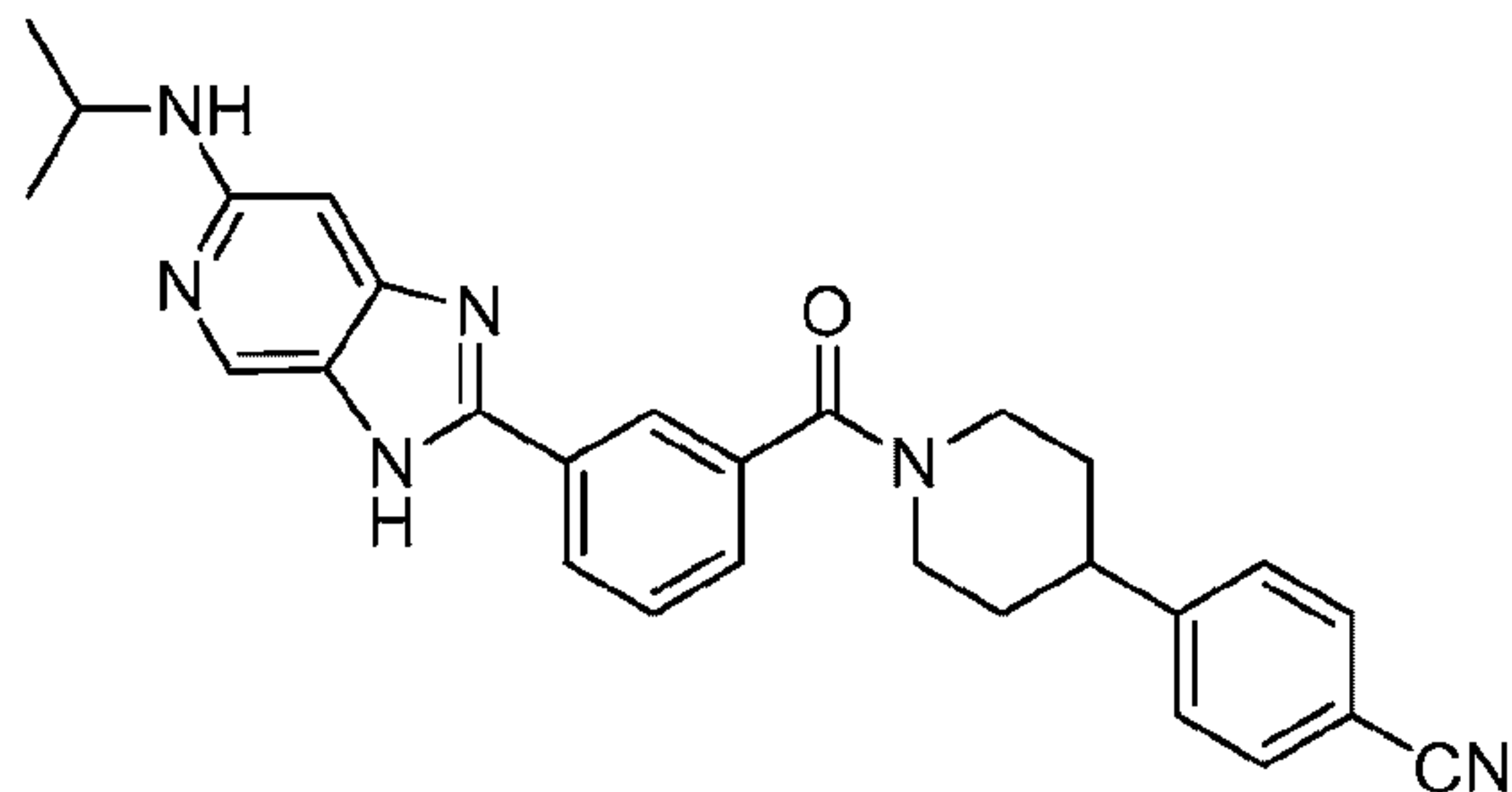


[0534] Compound **35**. 4-(1-(5-(6-(Pyrrolidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)-2-(trifluoromethoxy)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of compound **16**. m/z (ES⁺) 561 (M+H)⁺.

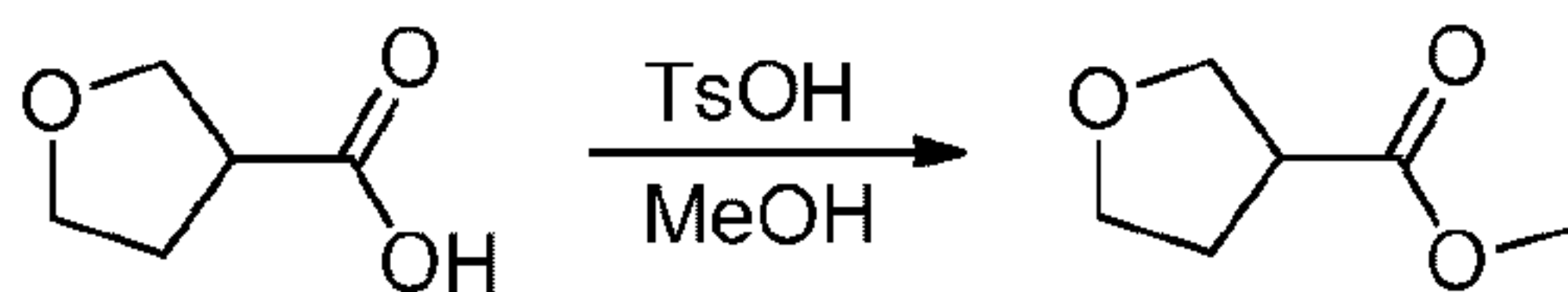


[0535] Compound **36**. 4-(1-(3-(6-(Pyrrolidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of compound **16**. m/z (ES⁺) 477 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD): δ 8.44 (s, 1H), 8.25-8.17 (m, 2H), 7.77-7.63 (m, 4H), 7.51 (d, J = 8.1 Hz, 2H), 6.59 (s, 1H), ~4.85 (1H, partially obscured by

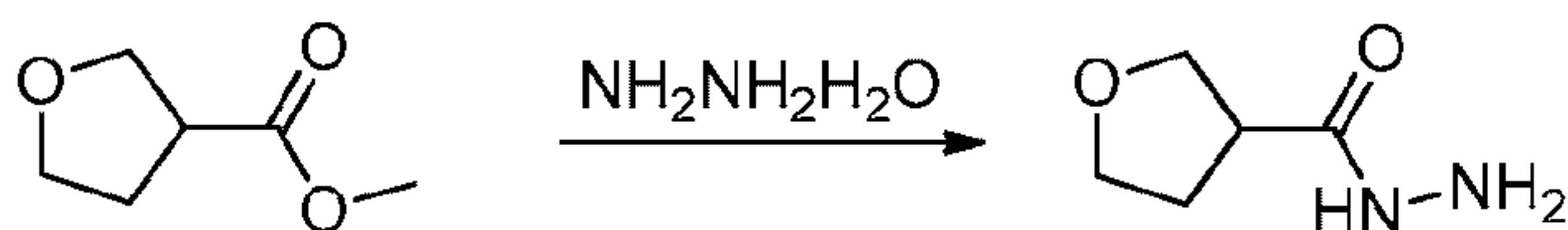
water peak), 3.98-3.83 (m, 1H), 3.61-3.48 (m, 4H), ~3.4 (1H, partially obscured by methanol solvent peak), 3.12-2.96 (m, 2H), 2.22-2.09 (m, 4H), 2.09-1.95 (m, 1H), 1.95 (m, 3H).



[0536] Compound 37. 4-(1-(3-(6-(isopropylamino)-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of compound 16. m/z (ES+) 465 (M+H)⁺.

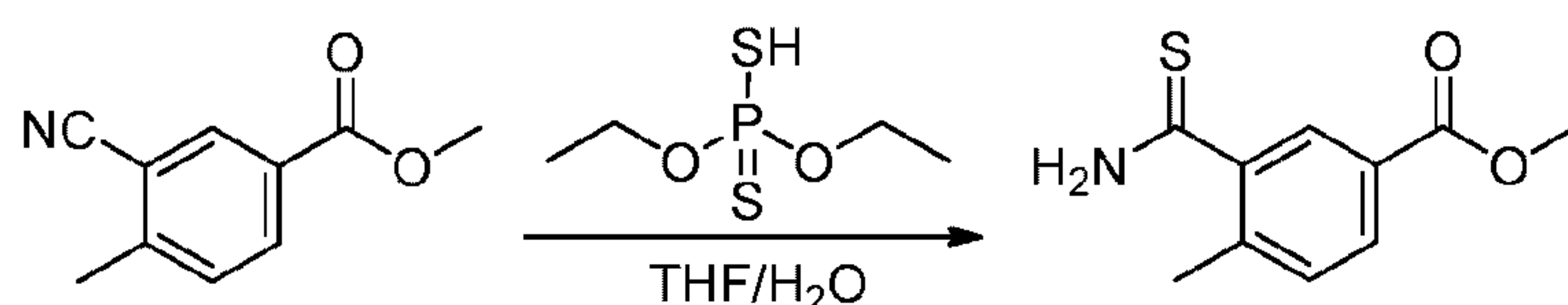


[0537] Compound 38.1. Methyl tetrahydrofuran-3-carboxylate. A solution of tetrahydrofuran-3-carboxylic acid (540 mg, 4.65 mmol, 1.00 equiv) and TsOH (10 mg, 0.06 mmol, 0.01 equiv) in methanol (40 mL) was stirred at 66°C in an oil bath. After 16 h, the resulting mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in 10 mL of ether, washed with 1x20 mL of NaHCO₃ (aq., sat.) followed by 3x20 mL of brine, and concentrated under reduced pressure to yield 0.40 g (66%) of the title compound as a colorless oil.

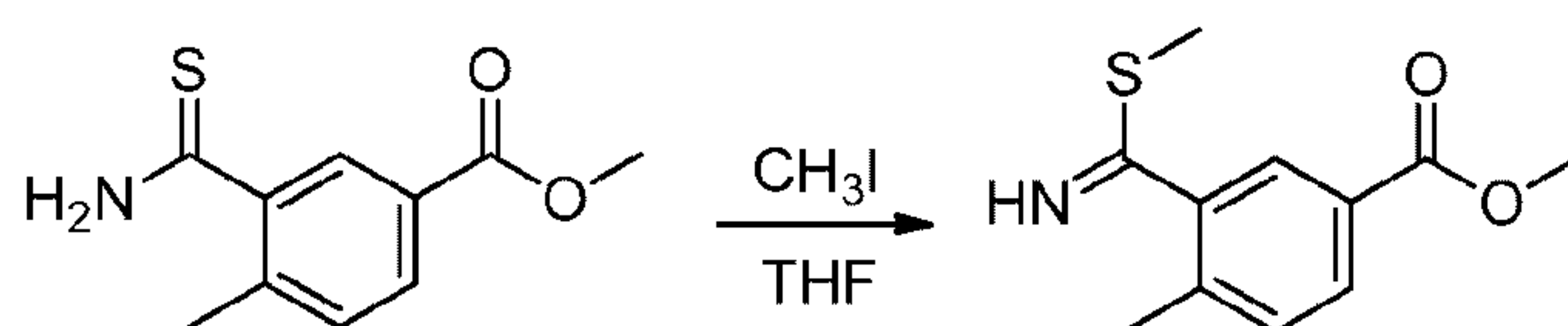


[0538] Compound 38.2. Tetrahydrofuran-3-carbohydrazide. Into a round-bottom flask, was placed hydrazine hydrate (20 mL). To this was added methyl tetrahydrofuran-3-carboxylate (compound 38.1, 390 mg, 3.00 mmol, 1.00 equiv) dropwise with stirring. The resulting mixture was stirred at 50°C in an oil bath. After 3 h, the reaction mixture was concentrated and dried under reduced pressure to yield 0.29 g (74%) of the title compound as a colorless oil.

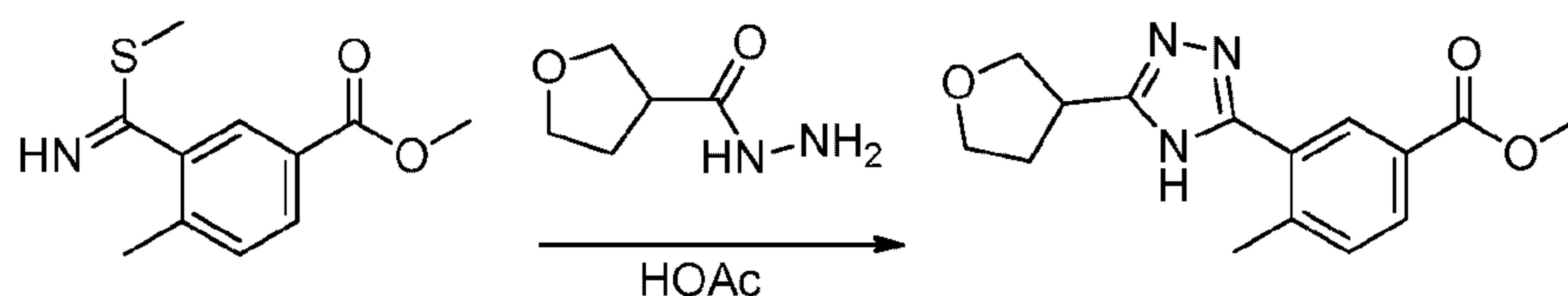
153



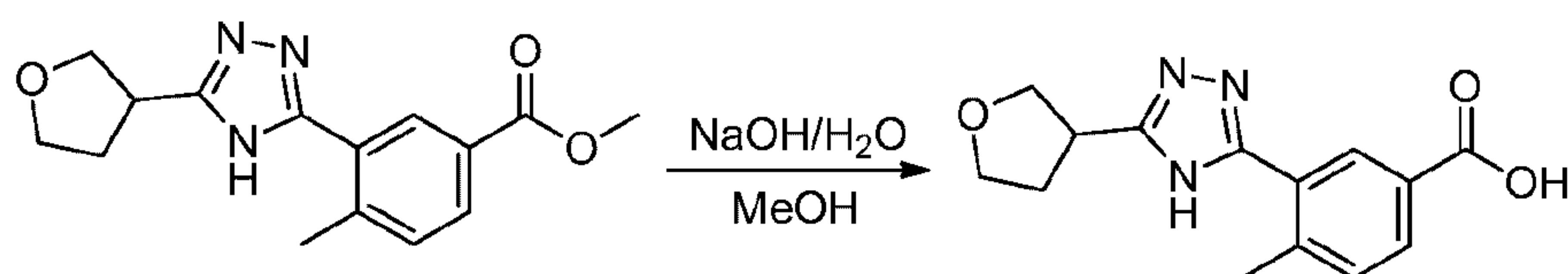
[0539] Compound 38.3. Methyl 3-carbamothioyl-4-methylbenzoate. A solution of methyl 3-cyano-4-methylbenzoate (compound 1.7, 880 mg, 5.02 mmol, 1.00 equiv) and O,O'-diethyl dithiophosphate (1.41 g, 8.29 mmol, 1.50 equiv) in THF/H₂O (40 mL) was stirred at 80°C (**CAUTION:** significant gas evolution occurs - this and all other reactions described herein should be carried out in well ventilated fume hoods). After 3 h, the organic solvent was removed under reduced pressure and the residual aqueous phase was extracted with 3x20 mL of ethyl acetate. The combined organic layers were concentrated under reduced pressure to yield 0.85 g (79%) of the title compound as a light yellow solid.



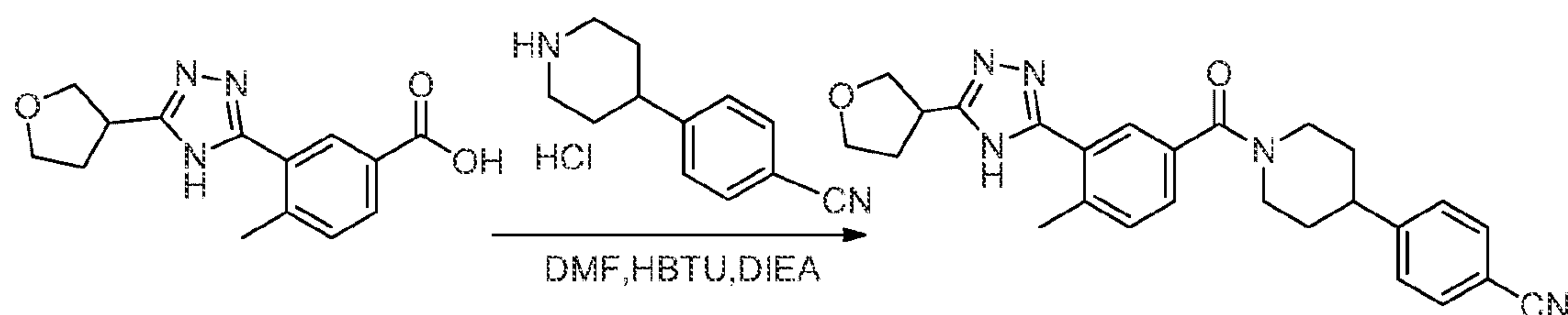
[0540] Compound 38.4. Methyl 3-(imino(methylthio)methyl)-4-methylbenzoate. To a stirred solution of methyl 3-carbamothioyl-4-methylbenzoate (compound 38.3, 2.10 g, 9.85 mmol, 1.00 equiv) in tetrahydrofuran (30 mL) was added iodomethane (2.8 g, 19.73 mmol, 2.00 equiv) dropwise. The resulting mixture was stirred at room temperature. After 3 h, the reaction mixture was concentrated under reduced pressure and the residue was dried under vacuum to yield 1.6 g (73%) of the title compound as a light yellow solid.



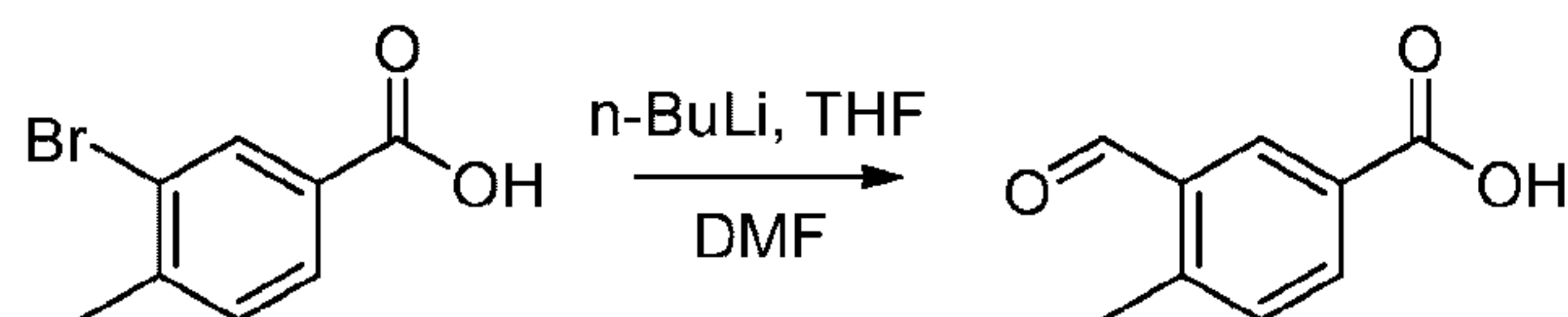
[0541] Compound 38.5. Methyl 4-methyl-3-(5-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)benzoate. A solution of tetrahydrofuran-3-carbohydrazide (compound 38.2, 195 mg, 1.50 mmol, 1.50 equiv) and compound 38.4 (223 mg, 1.00 mmol, 1.00 equiv) in AcOH (30 mL) was stirred at 80°C. After 4 h, the reaction mixture was concentrated under reduced pressure and the residue was dried under high-vacuum to yield 153 mg (53%) of the title compound as yellow oil.



[0542] Compound 38.6. 4-Methyl-3-(5-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)benzoic acid. To a stirred solution of compound 38.5 (57 mg, 0.20 mmol, 1.00 equiv) in methanol (20 mL) was added sodium hydroxide (aqueous, 1 M, 0.2 mL) dropwise. The resulting mixture was stirred at room temperature. After 4 h, the organic solvent was removed under reduced pressure. The residual aqueous layer was washed with 2x20 mL of ethyl acetate. The pH of the aqueous phase was then adjusted to 4 with hydrogen chloride (aq., 1 M) and the resulting solids were collected by filtration and dried to yield 23 mg (42%) of the title compound as a light yellow solid.

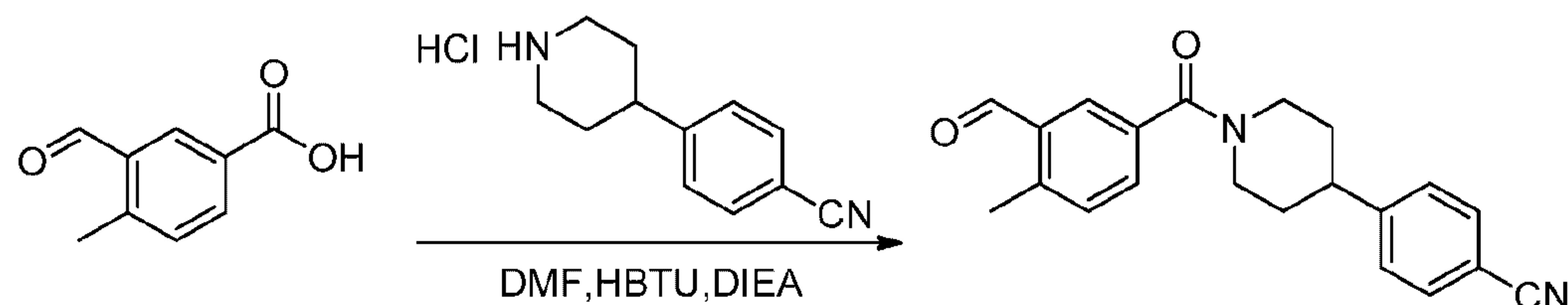


[0543] Compound 38. 4-(1-(4-Methyl-3-(5-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile. A mixture of compound 38.6 (137 mg, 0.50 mmol, 1.00 equiv), HBTU (228 mg, 0.60 mmol, 1.20 equiv), DIEA (162 mg, 1.25 mmol, 2.50 equiv), and 4-(piperidin-4-yl)benzonitrile hydrochloride (1.5, 111 mg, 0.50 mmol, 1.00 equiv) in DMF (20 mL) was stirred at room temperature. After 1 h, the reaction was quenched by the addition of 20 mL of water and resulting mixture was extracted with 3x20 mL of ethyl acetate. The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:100-1:3) to yield 35 mg (16%) of the title compound as a brown solid. m/z (ES⁺) 442 (M+H)⁺.



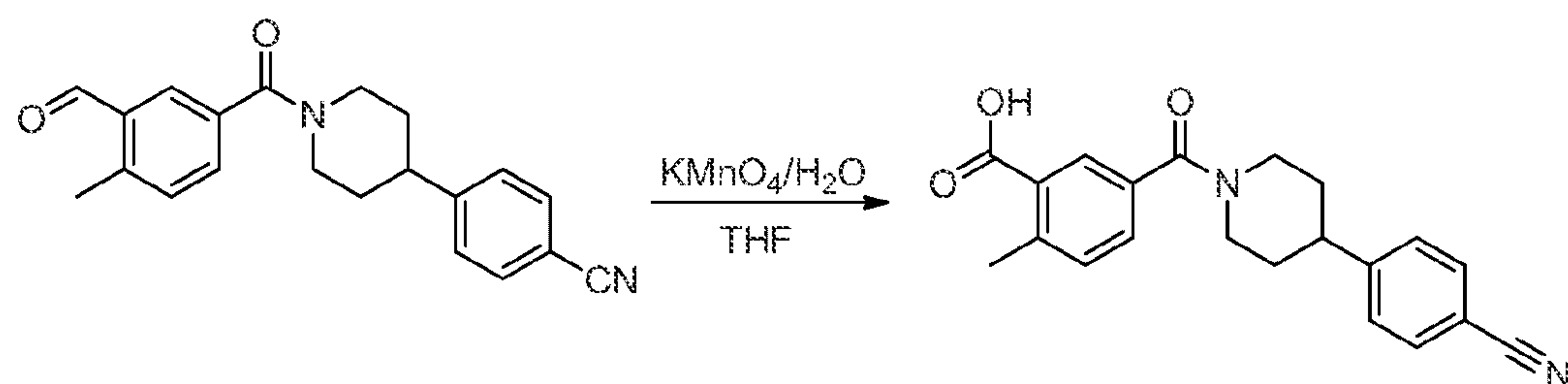
[0544] Compound 39.1. 3-Formyl-4-methylbenzoic acid. To a stirred solution of 3-bromo-4-methylbenzoic acid (2.14 g, 10.00 mmol, 1.00 equiv) in tetrahydrofuran (30 mL) under nitrogen at -78°C was added n-BuLi (10 mL, 2.5 M in THF, 2.50 equiv) dropwise. After stirring for 1 h below -70°C , DMF (5 mL) was slowly added. The resulting solution was warmed slowly to room temperature and stirred for 1 h. After carefully quenching the

reaction by slowly adding 50 mL of water, the pH was adjusted to ~3-4 using aqueous HCl (6 M). The resulting mixture was extracted with 2x50 mL of ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield 1.6 g (98%) of the title compound as a yellow solid.



[0545] Compound 39.2. 4-(1-(3-Formyl-4-methylbenzoyl)piperidin-4-yl)benzonitrile.

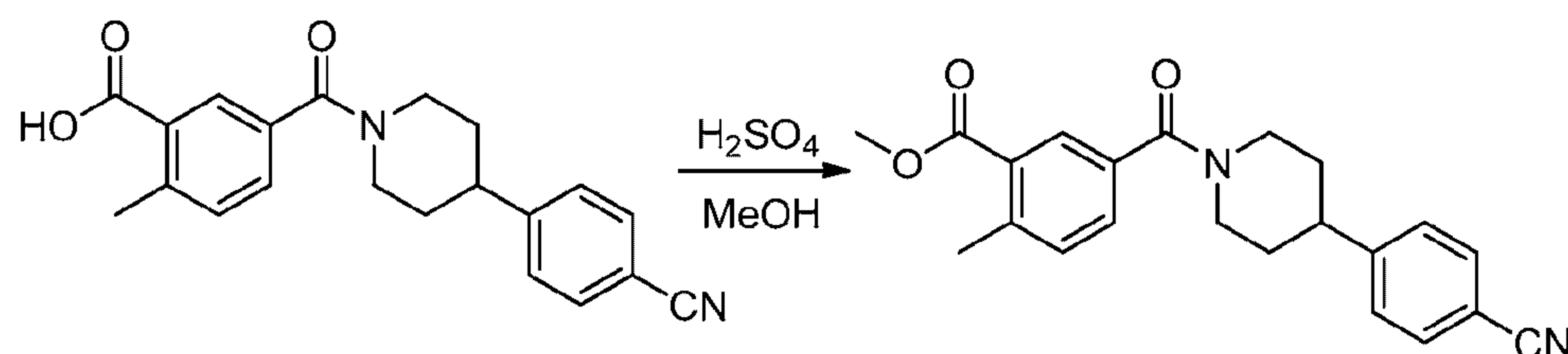
A mixture of 3-formyl-4-methylbenzoic acid (compound 39.1, 660 mg, 4.02 mmol, 1.00 equiv), HBTU (2 g, 5.28 mmol, 1.30 equiv) in N,N-dimethylformamide (20 mL) was stirred at room temperature. After 1 h, 4-(piperidin-4-yl)benzonitrile hydrochloride (1.5, 890 mg, 4.01 mmol, 1.00 equiv) and DIEA (1.03 g, 7.98 mmol, 2.00 equiv) were added. The resulting mixture was stirred for 5 h at room temperature and then overnight at 60°C in. After cooling to ambient temperature, the reaction mixture was diluted with 100 mL of EtOAc and washed with 2x50 mL of NH₄Cl (aq., sat.) followed by 2x50 mL of sodium bicarbonate (aq., sat.). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield 1 g (75%) of the title compound as a brown oil.



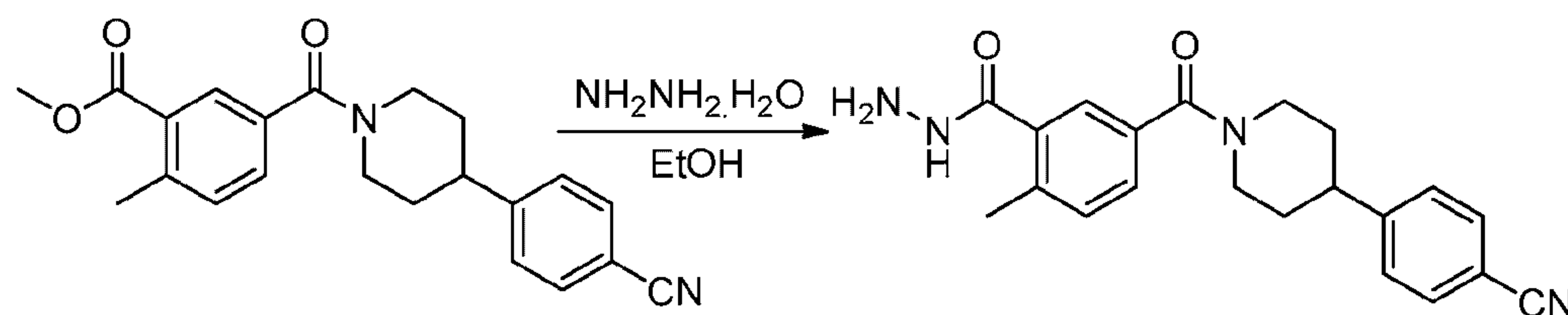
[0546] Compound 39.3. 5-(4-(4-Cyanophenyl)piperidine-1-carbonyl)-2-methylbenzoic acid.

To a stirred mixture of 4-(1-(3-formyl-4-methylbenzoyl)piperidin-4-yl)benzonitrile (compound 39.2, 600 mg, 1.81 mmol, 1.00 equiv) in THF (5 mL) was added dropwise a solution of KMnO₄ (1 g) in water (10 mL). The resulting mixture was stirred overnight at 60°C in an oil bath. After cooling to ambient temperature, the solids were removed by filtration and the pH of the filtrate was adjusted to ≥ 10 with sodium hydroxide (aqueous, 1 M). The resulting mixture was washed with 20 mL of ethyl acetate. Aqueous 1 M HCl was then employed to adjust the pH of the aqueous layer to ~4. The resulting aqueous phase was extracted with 2x100 mL of ethyl acetate and the combined organic layers were

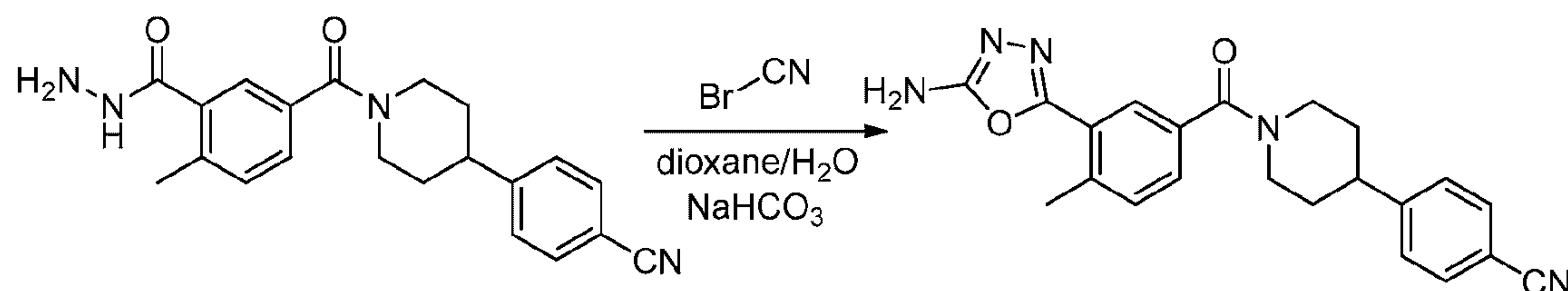
dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield 500 mg (80%) of the title compound as light yellow oil.



[0547] Compound 39.4. Methyl 5-(4-(4-cyanophenyl)piperidine-1-carbonyl)-2-methylbenzoate. To a stirred mixture of 5-(4-(4-cyanophenyl)piperidine-1-carbonyl)-2-methylbenzoic acid (compound 39.3, 1.392 g, 4.00 mmol, 1.00 equiv) in methanol (50 mL) was added sulfuric acid (784 mg, 7.99 mmol, 2.00 equiv), dropwise. The resulting mixture was heated to reflux overnight in an oil bath. After cooling to ambient temperature, the organic solvent was removed under reduced pressure. The residue was diluted with 20 mL of EtOAc and was washed with 1x100 mL of saturated sodium bicarbonate(aq) followed by 1x100 mL of brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to yield 1.303 g (90%) of the title compound as a white solid.

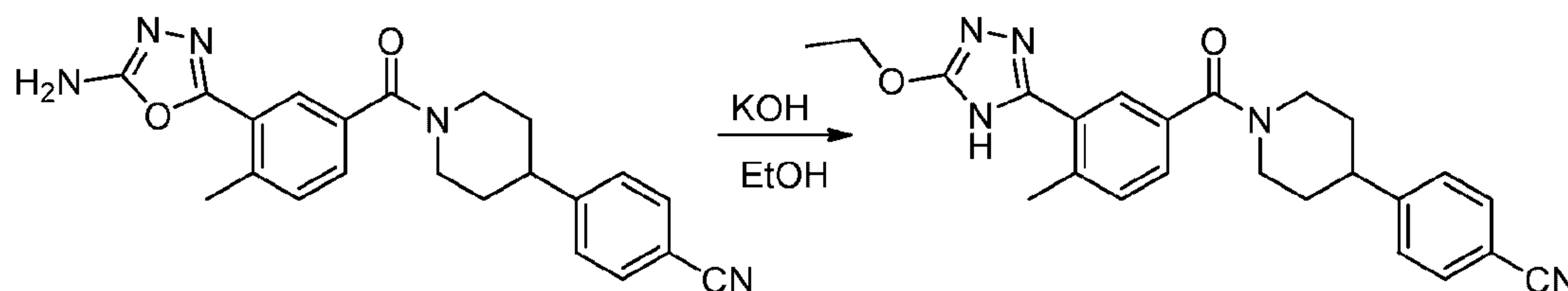


[0548] Compound 39.5. 5-(4-(4-Cyanophenyl)piperidine-1-carbonyl)-2-methylbenzohydrazide. A solution of compound 39.4 (1.503 g, 4.15 mmol, 1.00 equiv) and hydrazine hydrate (10 mL) in ethanol (50 mL) was heated at reflux in an oil bath. After 2 h, the mixture was concentrated under reduced pressure and the residue was dissolved in 20 mL of EtOAc. The resulting mixture was washed with 1x50 mL of H_2O and 1x50 mL of brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to yield 1.353 g (90%) of the title compound as a white solid.

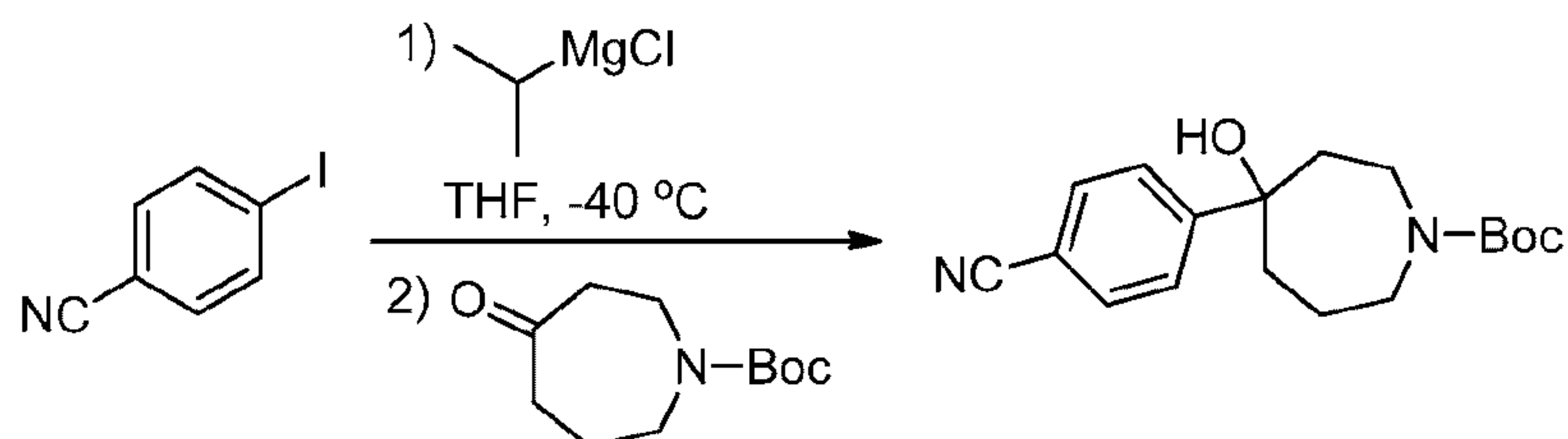


[0549] Compound 39.6. 4-(1-(3-(5-Amino-1,3,4-oxadiazol-2-yl)-4-methylbenzoyl)piperidin-4-yl)benzonitrile. A mixture of compound 39.5 (380 mg, 1.05 mmol, 1.00 equiv) and sodium bicarbonate (105.8 mg, 1.26 mmol, 1.20 equiv) in

dioxane/H₂O (1:1) (50 mL) was stirred at room temperature. After 5 minutes, cyanogen bromide (212 mg, 2.00 mmol, 2.00 equiv) was added. The resulting mixture was stirred for 3 h at room temperature. The resulting solution was stirred for 3 h at room temperature, then quenched with 30 mL of FeSO₄ (aq., sat.) and diluted with ethyl acetate. The resulting mixture was stirred vigorously then filtered through celite and washed with 1 M FeSO₄, water, and ethyl acetate. The layers were separated and the aqueous phase was extracted with 2 x 50 mL of ethyl acetate. The combined organic layers were washed with 2 x 50 mL of brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. This resulted in 397 mg (98%) of an off-white solid.

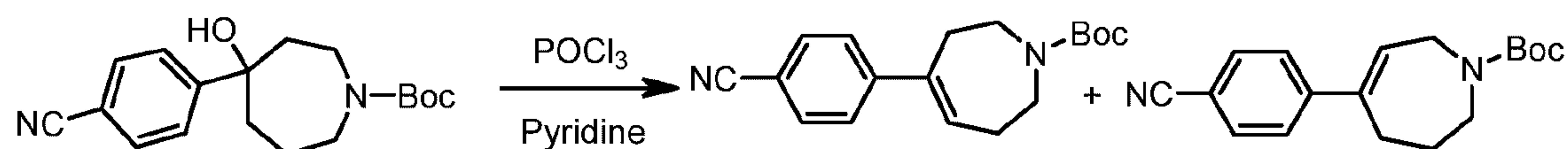


[0550] Compound 39. 4-(1-(3-(5-Ethoxy-4H-1,2,4-triazol-3-yl)-4-methylbenzoyl)piperidin-4-yl)benzonitrile. A mixture of compound 39.6 (397 mg, 1.02 mmol, 1.00 equiv) and potassium hydroxide (287 mg, 5.12 mmol, 5.00 equiv) in ethanol (25 mL) was heated at reflux overnight. After cooling the reaction mixture to room temperature with a water bath, the pH was adjusted to ~7 with acetic acid. The resulting mixture was concentrated under reduced pressure. The residue was taken up in ethyl acetate and washed with water. The organic layer was dried (Na₂SO₄) and concentrated. The crude residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:5-1:0). The product was further purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-006(Waters)): Column, SunFire Prep C18, 5μm, 19*150mm; mobile phase, WATER WITH 0.05%TFA and CH₃CN (hold 5.0% CH₃CN in 2 min, up to 30.0% in 1 min, up to 59.0% in 12 min, up to 100.0% in 2 min); Detector,UV 254/220nm. The fractions containing pure compound were combined and lyophilized to yield 51.9 mg (12%) of the title compound as a white solid. *m/z* (ES⁺) 416 (M+H)⁺.

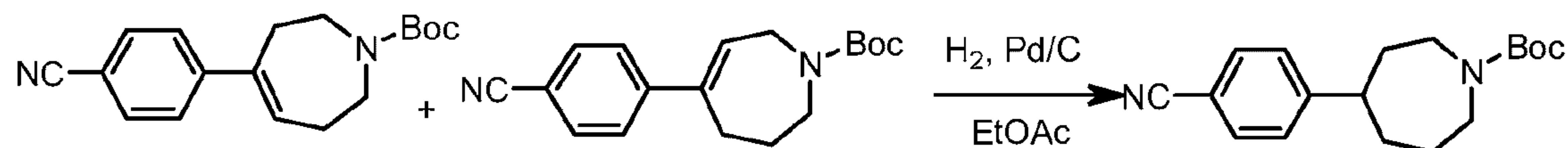


[0551] Compound 40.1. tert-Butyl 4-(4-cyanophenyl)-4-hydroxyazepane-1-carboxylate. A solution of 4-iodobenzonitrile (510 mg, 2.22 mmol, 1.1 equiv) in THF (3mL)

was added to a 10 mL round-bottom flask and the system purged with nitrogen. The mixture was cooled to -40°C then isopropylmagnesium chloride (1.16 mL of a 2.0 M soln in THF, 2.32 mmol, 1.15 equiv) was added dropwise over 20 minutes. The resulting mixture was stirred at -40°C for 2 hours then tert-butyl 4-oxoazepane-1-carboxylate (431 mg, 2.02 mmol, 1.0 equiv) in THF (0.5 mL) was added dropwise over 15 minutes. The resulting mixture was stirred at -40°C for 1 hour then diluted into ethyl acetate (15 mL) and washed with 0.2 M HCl (10 mL), 0.1 M HCl (5 mL), saturated sodium bicarbonate (5 mL) then brine (5 mL). The organics were dried (Na_2SO_4), filtered and evaporated. To remove remaining ketone and aldol by-product, the residue was dissolved in acetonitrile (3 mL) then hydrazine (0.2 mL) was added and heated at 60°C for 4 hours. The mixture was diluted with EtOAc (20 mL) and washed with water (20 mL), followed by 0.5 M phosphoric acid (3 x 20 mL), saturated sodium bicarbonate (10 mL) and brine (10 mL). The organics were dried (Na_2SO_4), filtered and evaporated. The residue was purified by silica column chromatography (hexanes/ethyl acetate) to obtain the title compound as a pink oil which solidified upon standing (303 mg, 47%). m/z (ES+) 317 ($\text{M}+\text{H}$)⁺.

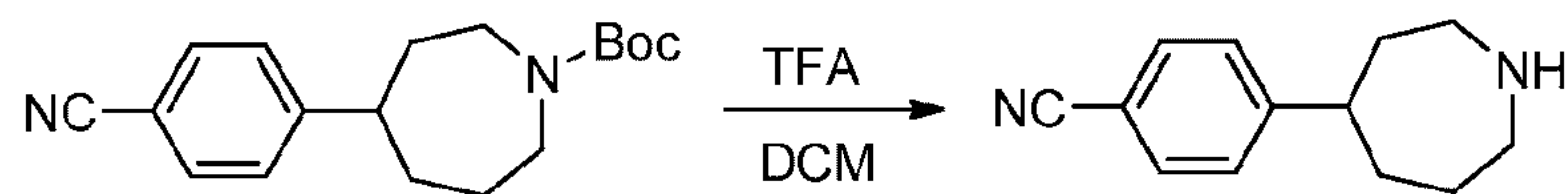


[0552] Compound 40.2. tert-Butyl 4-(4-cyanophenyl)-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate and tert-butyl 5-(4-cyanophenyl)-2,3,4,7-tetrahydro-1H-azepine-1-carboxylate. In a vial containing tert-butyl 4-(4-cyanophenyl)-4-hydroxyazepane-1-carboxylate (compound **40.1**, 200 mg, 0.63 mmol, 1.0 equiv) was added pyridine (3 mL) and phosphorus oxychloride (438 μL , 4.7 mmol, 7.5 equiv) and the mixture was stirred at room temperature for 45 hours. The solvents were removed *in vacuo* and the residue was dissolved in DCM (5 mL) and washed with water (10 mL). The aqueous layer was extracted with DCM (5 mL) and the combined organics were washed with saturated sodium bicarbonate (2 x 10 mL), dried (Na_2SO_4), filtered and concentrated to obtain a mixture of the title compounds as a pale yellow oil (167 mg, 89%). m/z (ES+) 299 ($\text{M}+\text{H}$)⁺.

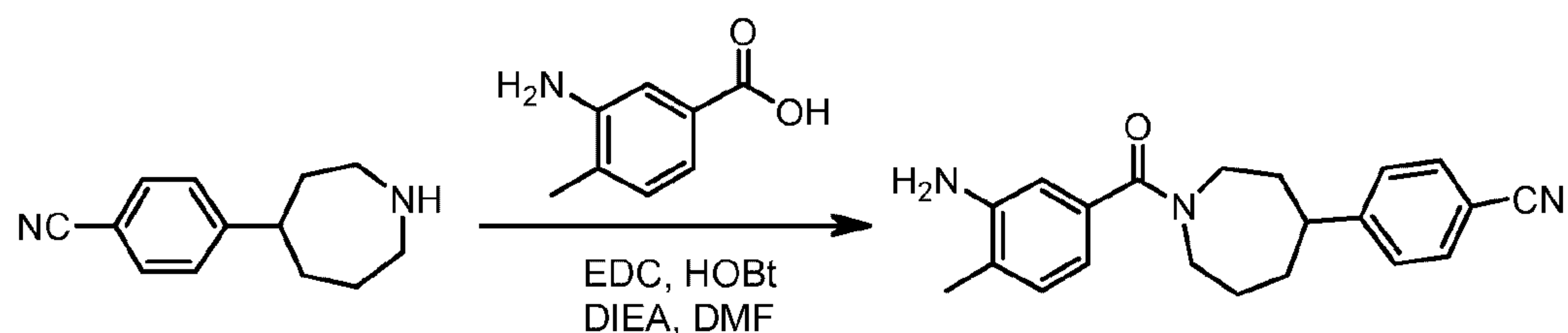


[0553] Compound 40.3. tert-Butyl 4-(4-cyanophenyl)azepane-1-carboxylate. To a 25 mL round bottom flask containing a mixture of tert-butyl 4-(4-cyanophenyl)-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate and tert-butyl 5-(4-cyanophenyl)-2,3,4,7-tetrahydro-1H-azepine-1-carboxylate (compound **40.2**, 167 mg, 0.56 mmol) was added 10% palladium

on carbon (40 mg) and ethyl acetate (6 mL). The system was purged with nitrogen then charged with hydrogen and stirred at room temperature. After purging the system with nitrogen, the mixture was filtered through celite and the filtrate was concentrated. The residue was purified by preparative TLC to obtain a colorless wax (77 mg, 45%). m/z (ES+) 245 (M minus t-butyl+H)⁺.

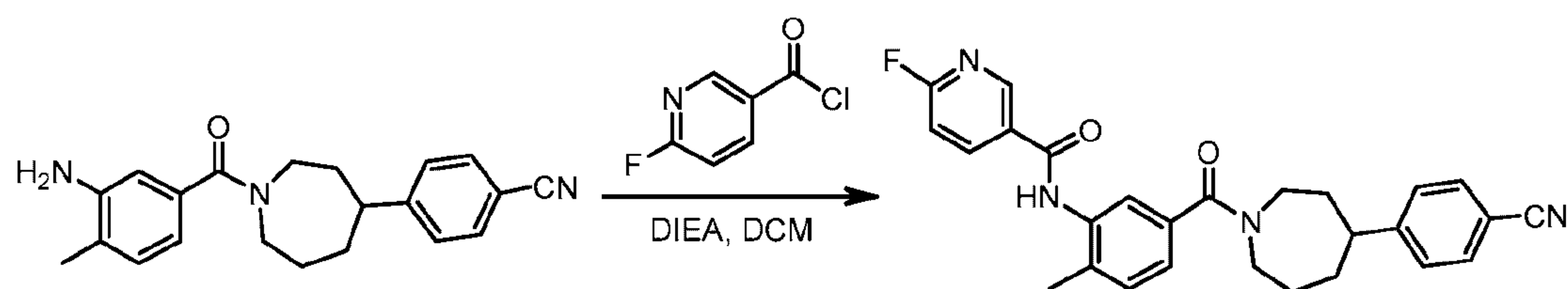


[0554] Compound 40.4. 4-(Azepan-4-yl)benzonitrile. To a vial containing tert-butyl 4-(4-cyanophenyl)azepane-1-carboxylate (compound 40.3, 77 mg, 0.257 mmol, 1.0 equiv) was added DCM (500 μ L) and trifluoroacetic acid (198 μ L, 2.57 mmol, 10 equiv) and the mixture was stirred vented for 90 min. The mixture was diluted into ethyl acetate (5 mL) and washed with saturated sodium bicarbonate (5 mL). The aqueous was adjusted to pH 10-11 and extracted with addition ethyl acetate until no product remained. The combined organics were dried (Na₂SO₄), filtered and concentrated to obtain the title compound as a yellow oil (51 mg, theoretical). m/z (ES+) 201 (M+H)⁺.

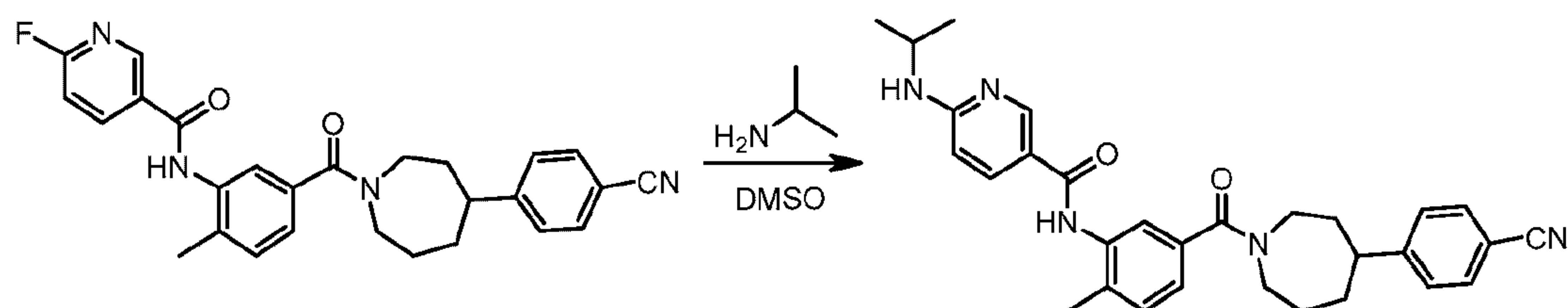


[0555] Compound 40.5. 4-(1-(3-Amino-4-methylbenzoyl)azepan-4-yl)benzonitrile. To a 4-mL vial was added 3-amino-4-methylbenzoic acid (27 mg, 0.18 mmol, 1.0 equiv), 4-(azepan-4-yl)benzonitrile (compound 40.4, 40 mg, 0.2 mmol, 1.1 equiv), hydroxybenzotriazole (39 mg of 20 wt % H₂O, 0.23 mmol, 1.3 equiv), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (44 mg, 0.23 mmol, 1.3 equiv), DMF (1 mL) and *N,N*-diisopropylethylamine (93 μ L, 0.54 mmol, 3.0 equiv). The mixture was stirred at room temperature for 4 hours then diluted into ethyl acetate (10 mL) and washed with brine (10 mL). The aqueous was extracted with ethyl acetate (3 mL) and the combined organics were washed with brine (10 mL), 1 M NaH₂PO₄ (5 mL) and brine (10 mL). The organics were dried (Na₂SO₄), filtered and concentrated to obtain the title compound as a brown solid (45 mg, 74%). m/z (ES+) 334 (M+H)⁺.

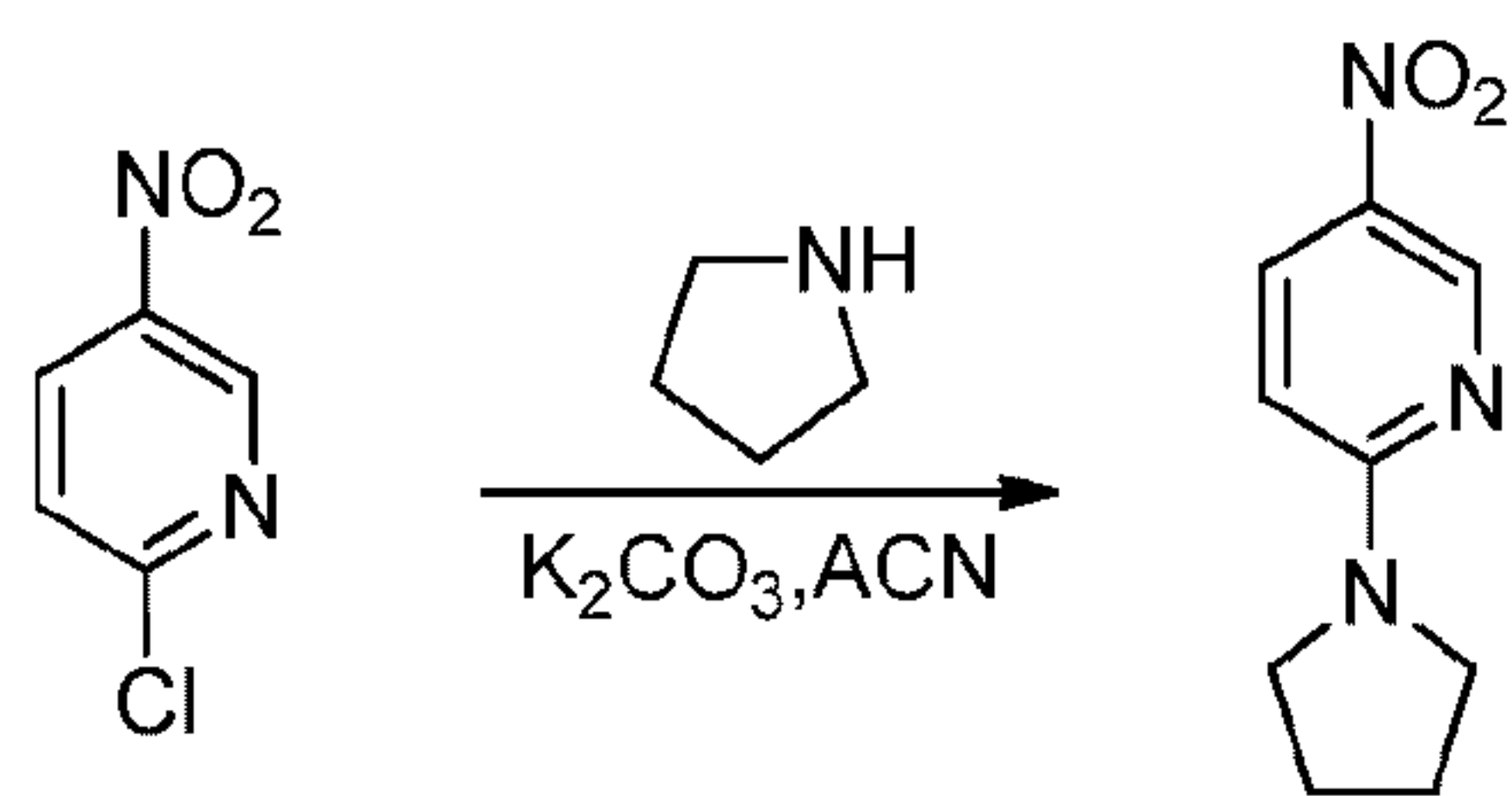
160



[0556] Compound 40.6. N-(5-(4-(4-Cyanophenyl)azepane-1-carbonyl)-2-methylphenyl)-6-fluoronicotinamide. To a 4-mL vial containing 4-(1-(3-amino-4-methylbenzoyl)azepan-4-yl)benzonitrile (compound **40.5**, 44 mg, 0.13 mmol, 1.0 equiv) was added dichloromethane (1 mL) and *N,N*-diisopropylethylamine (35 μ L, 0.20 mmol, 1.5 equiv). A solution of 6-fluoronicotinoyl chloride (22 mg, 0.14 mmol, 1.05 equiv) in dichloromethane (1 mL) was added dropwise over about 2 minutes. The resulting mixture was stirred at room temperature for 19 hours then diluted with dichloromethane (5 mL) and washed with 1 M NaH_2PO_4 (3 mL), saturated sodium bicarbonate (3 mL) and brine (3 mL). The organics were dried (Na_2SO_4), filtered and concentrated to obtain the title compound as a brown wax (64 mg, theoretical). m/z (ES+) 457 ($\text{M}+\text{H}$)⁺.

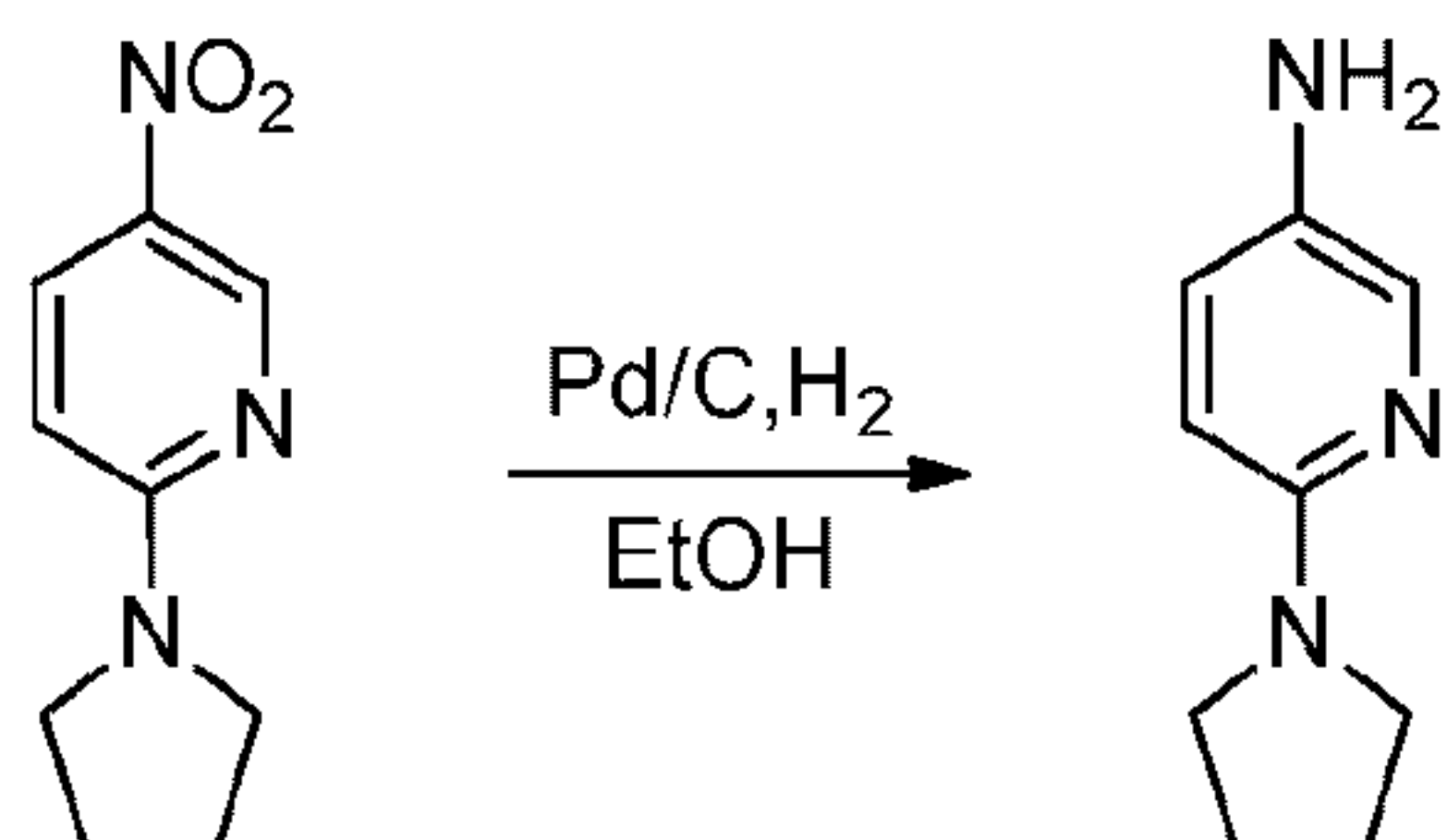


[0557] Compound 40. N-(5-(4-(4-Cyanophenyl)azepane-1-carbonyl)-2-methylphenyl)-6-(isopropylamino)nicotinamide. To a vial containing N-(5-(4-(4-cyanophenyl)azepane-1-carbonyl)-2-methylphenyl)-6-fluoronicotinamide (compound **40.6**, 61 mg, 0.13 mmol) was added dimethylsulfoxide (1 mL) and isopropylamine (1 mL). The mixture was stirred at 35 $^{\circ}\text{C}$ for 2 hours then at room temperature for 16 hours followed by 35 $^{\circ}\text{C}$ for an additional 4 hours. The excess isopropyl amine was removed *in vacuo* and the remaining solution was purified by preparative HPLC to yield the product as an off white powder (TFA salt, 39 mg, 49%). m/z (ES+) 496 ($\text{M}+\text{H}$)⁺.

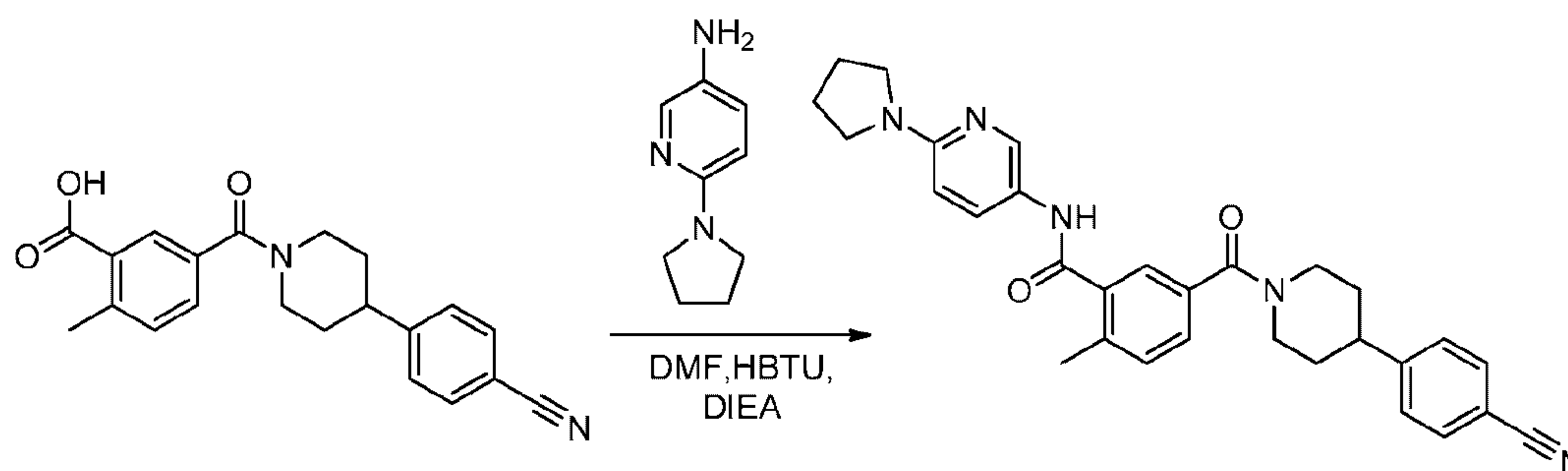


[0558] Compound 41.1. 5-Nitro-2-(pyrrolidin-1-yl)pyridine. A mixture of 2-chloro-5-nitropyridine (1.58 g, 10.00 mmol, 1.00 equiv), pyrrolidine (710 mg, 10.00 mmol, 1.00 equiv) and potassium carbonate (2.76 g, 20.00 mmol, 2.00 equiv) in CH_3CN (20 mL) was

stirred at 60°C in an oil bath. After 2 h, the reaction mixture was allowed to reach ambient temperature. The solids were filtered off and the filtrate was concentrated under reduced pressure. The residue was triturated with 1x20 mL of petroleum ether to yield 1.8 g (93%) of the title compound as a yellow solid.

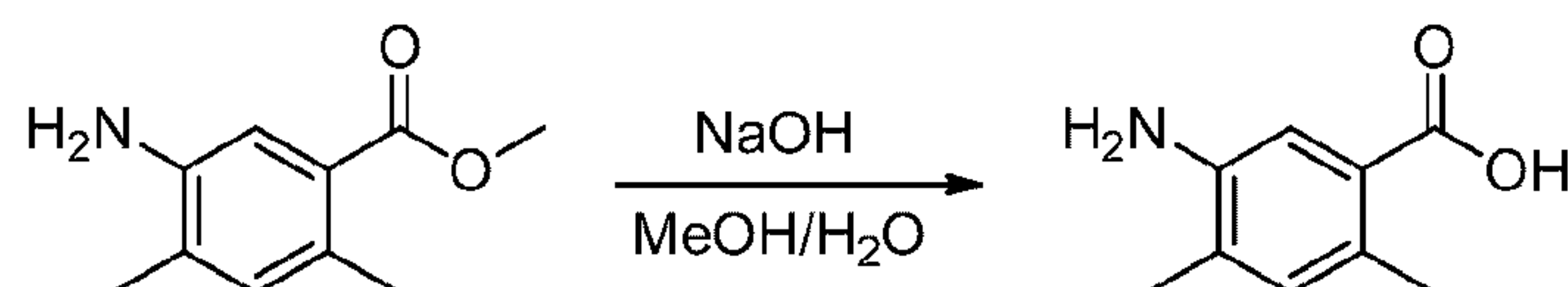


[0559] Compound 41.2. 6-(Pyrrolidin-1-yl)pyridin-3-amine. Around-bottom flask, containing a solution of 5-nitro-2-(pyrrolidin-1-yl)pyridine (compound **40.1**, 1.93 g, 10.00 mmol, 1.00 equiv) in ethanol (30 mL) was purged with nitrogen. Palladium on carbon (0.4 g, 10%, 60% water) was added. After further purging the system with nitrogen, the atmosphere was changed to hydrogen and the resulting mixture was stirred overnight at room temperature. After purging the system with nitrogen, the solids were filtered off and the filtrate was concentrated under reduced pressure and dried to yield 1.6 g (98%) of the title compound as a brown solid.

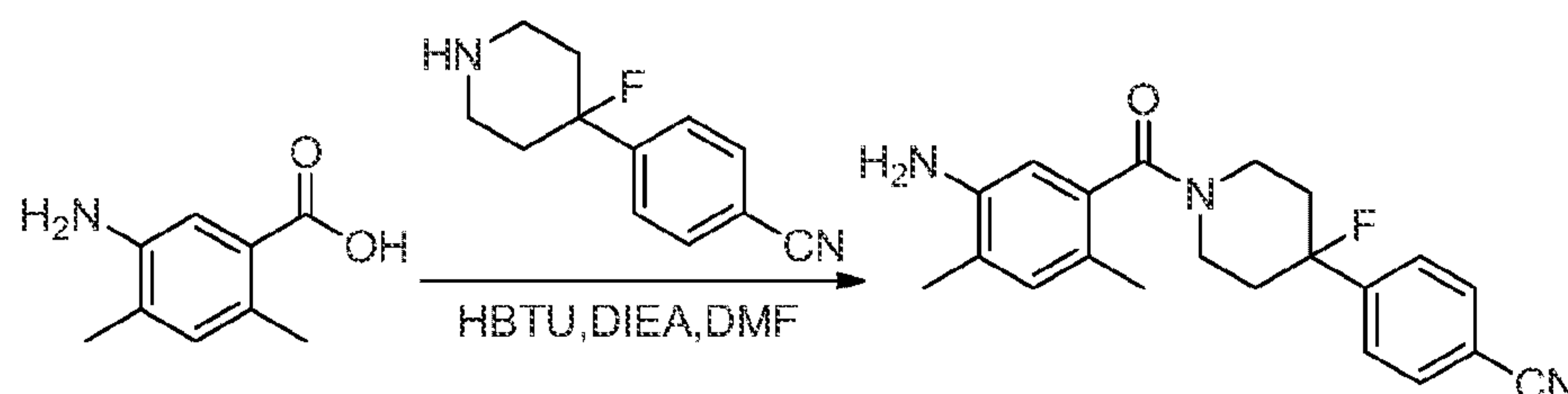


[0560] Compound 41. 5-(4-(4-Cyanophenyl)piperidine-1-carbonyl)-2-methyl-N-(6-(pyrrolidin-1-yl)pyridin-3-yl)benzamide. A mixture of compound **39.3** (528 mg, 1.52 mmol, 1.00 equiv) and HBTU (635 mg, 2.28 mmol, 1.50 equiv) in DMF (30 mL) was stirred for 30 min at room temperature. To this was added 6-(pyrrolidin-1-yl)pyridin-3-amine (compound **41.2**, 299 mg, 1.82 mmol, 1.20 equiv) and DIEA (50 mg). The resulting mixture was stirred overnight at 60°C in an oil bath. After cooling to room temperature, the reaction mixture was diluted with 50 mL of EtOAc and washed with 2x30 mL of NH₄Cl (aq., sat.) followed by 2x30 mL of sodium bicarbonate (aq., sat.). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-016(Waters)): Column, SunFire Prep C18, 19*150mm 5um; mobile phase, Water with 50mmolNH₄HCO₃ and

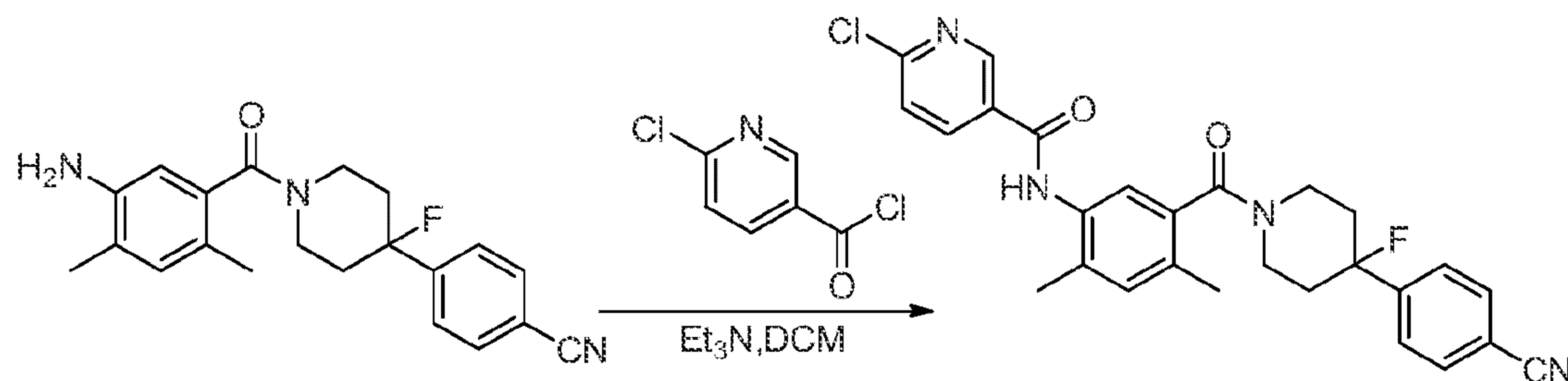
CH₃CN (10% CH₃CN up to 32% in 3 min, up to 51% in 20 min, up to 100% in 1 min, down to 10% in 1 min); Detector, UV 220NMnm. The fractions containing pure compound were combined and lyophilized to yield 50 mg (7%) of the title compound as a solid. *m/z* (ES⁺) 494 (M+H)⁺.



[0561] Compound 42.1. 5-Amino-2,4-dimethylbenzoic acid. A mixture of methyl 5-amino-2,4-dimethylbenzoate (1.2 g, 6.70 mmol, 1.00 equiv) and sodium hydroxide (1.5 g, 37.50 mmol, 5.60 equiv) in methanol/H₂O (20/20 mL) was stirred overnight at 50°C. After cooling to ambient temperature, the organic phase was removed under reduced pressure. The pH of the remaining aqueous layer was adjusted to ~4-5 with hydrogen chloride (aq., 2 M). The resulting solids were collected by filtration and dried to yield 1.0 g of a yellow solid.

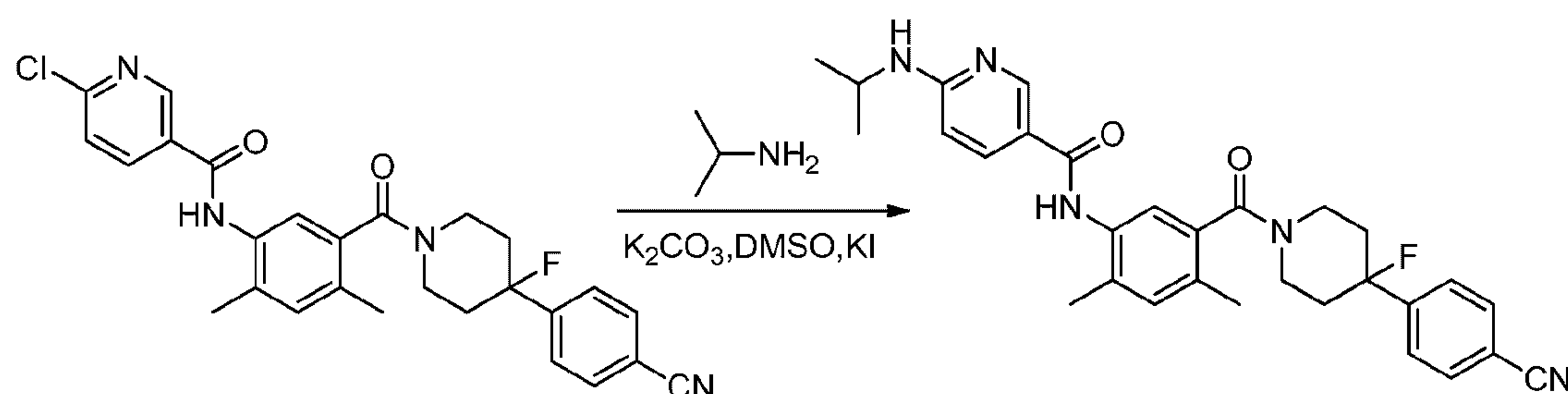


[0562] Compound 42.2. 4-(1-(5-Amino-2,4-dimethylbenzoyl)-4-fluoropiperidin-4-yl)benzonitrile. A mixture of 5-amino-2,4-dimethylbenzoic acid (compound 42.1, 2.264 g, 13.71 mmol, 1.00 equiv), HBTU (7.803 g, 20.59 mmol, 1.50 equiv), 4-(4-fluoropiperidin-4-yl)benzonitrile (compound 11.2, 2.8 g, 13.71 mmol, 1.00 equiv), and DIEA (3.541 g, 27.45 mmol, 2.00 equiv) in DMF (50 mL) was stirred at room temperature. After 1 h, the mixture was diluted with 100 mL of EtOAc and washed with 1x100 mL of water followed by 1x100 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield 3.51 g (73%) of the title compound as a white solid.



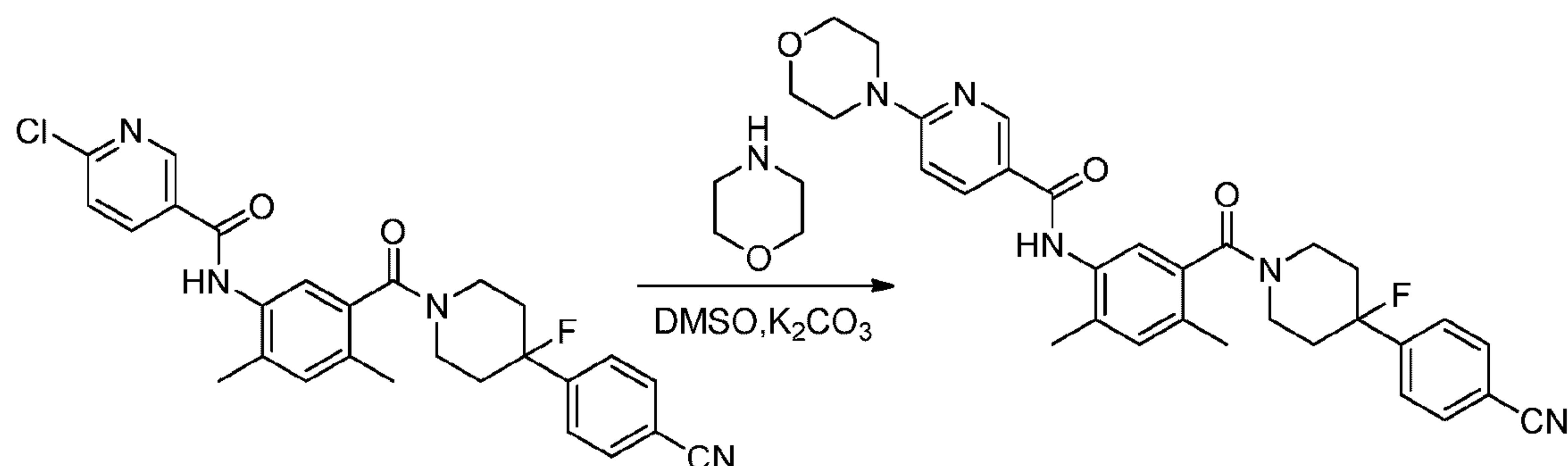
[0563] Compound 42.3. 6-Chloro-N-(5-(4-(4-cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2,4-dimethylphenyl)nicotinamide. To a mixture of compound 42.2 (3.51 g, 9.99 mmol, 1.00 equiv) and triethylamine (2.02 g, 19.96 mmol, 2.00 equiv) in DCM (50 mL)

under nitrogen at 0°C was added dropwise a solution of 6-chloropyridine-3-carbonyl chloride (1.936 g, 11.00 mmol, 1.10 equiv) in DCM (50 mL). After stirring for 1 h at 0°C, the reaction mixture was quenched by careful addition of 50 mL of water and extracted with 2x50 mL of dichloromethane. The combined organic layers were washed with 2x50 mL of brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield 4.41 g (90%) of the title compound as a yellow solid.

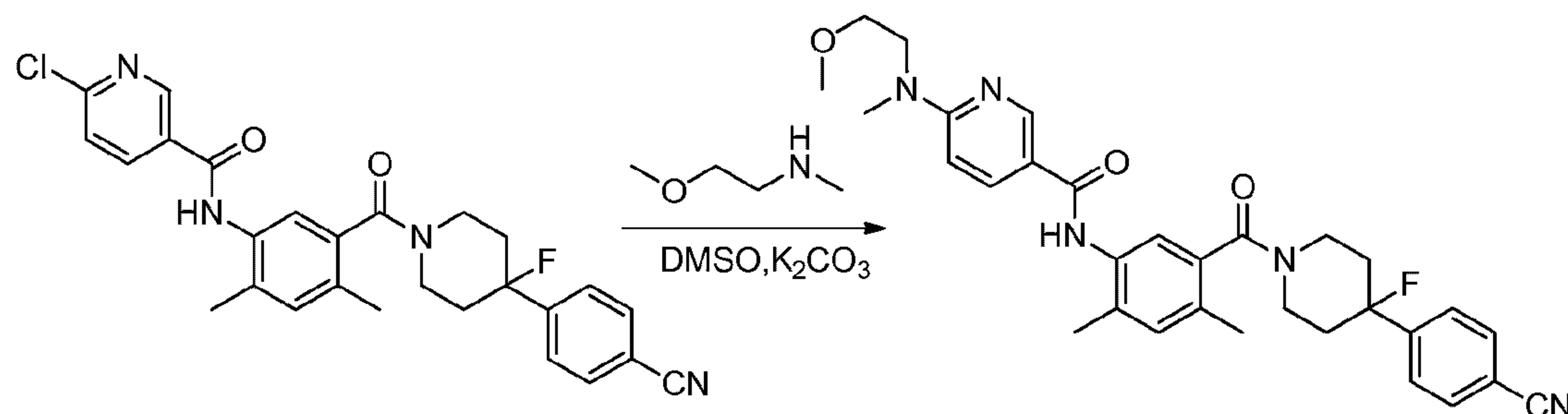


[0564] Compound 42. N-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2,4-dimethylphenyl)-6-(isopropylamino)nicotinamide. A mixture of compound **42.3** (392 mg, 0.80 mmol, 1.00 equiv), propan-2-amine (472 mg, 7.99 mmol, 10.00 equiv), potassium carbonate (221 mg, 1.60 mmol, 2.01 equiv), KI (66.4 mg, 0.40 mmol, 0.50 equiv) in DMSO (10 mL) was heated at 100°C in a sealed tube behind a blast shield. After 48, the mixture was allowed to reach ambient temperature and was then diluted with 20 mL of EtOAc. The mixture was washed with 1x20 mL of water followed by 1x20 mL of brine. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product (~300 mg) was purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-002(Agilent)): Column, SunFire Prep C18, 19*150mm 5um; mobile phase, WATER WITH 0.05%TFA and CH3CN (15.0% CH3CN up to 40.0% in 6 min, up to 100.0% in 2 min, down to 15.0% in 2 min); Detector, uv 220&254nm. The fractions containing pure compound were combined and lyophilized to yield 158 mg (39%) of the title compound as an off-white solid. *m/z* (ES+) 514 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD, *ppm*): δ 8.49 (s, 1H), 8.32 (d, *J* = 9.9Hz, 1H), 7.79 (d, *J* = 8.1Hz, 2H), 7.67 (d, *J* = 7.5Hz, 2H), 7.40-7.22 (m, 2H), 7.07 (d, *J* = 9.6Hz, 1H), 4.85 (m, 1H), 4.03 (m, 1H), 3.80-3.42 (m, 2H), 3.29 (m, 1H), 2.48-2.03 (m, 9H), 1.95 (m, 1H), 1.39 (d, *J* = 6.3Hz, 6H).

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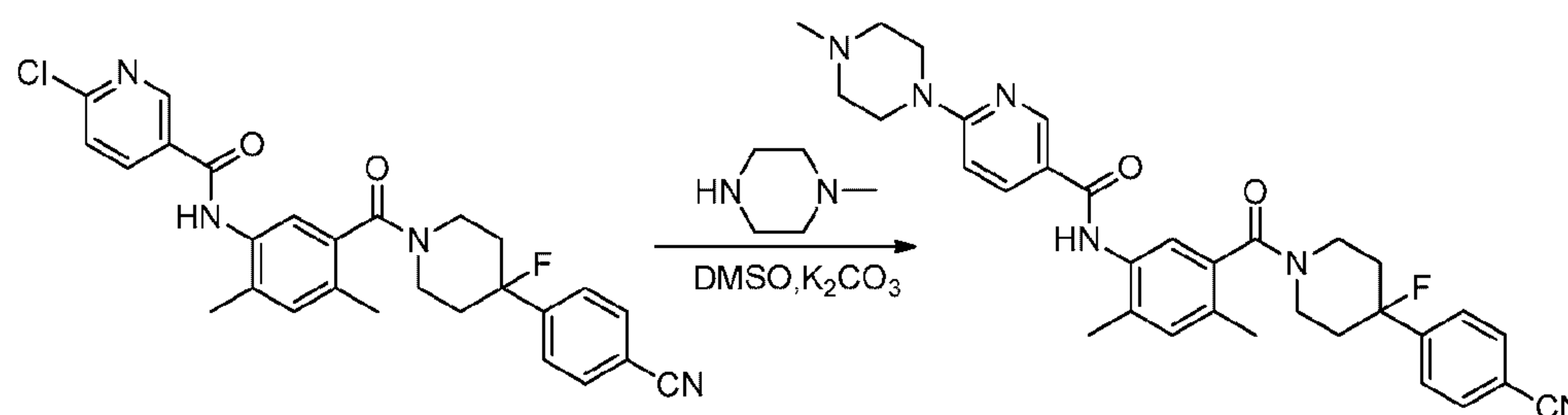


[0565] Compound 43. N-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2,4-dimethylphenyl)-6-morpholinonicotinamide. A mixture of compound **42.3** (392 mg, 0.80 mmol, 1.00 equiv), morpholine (348 mg, 3.99 mmol, 5.00 equiv), and potassium carbonate (221 mg, 1.60 mmol, 2.01 equiv) in DMSO (10 mL) was stirred overnight at 100°C in a sealed tube behind a blast shield. After cooling to ambient temperature, the reaction mixture was diluted with 20 mL of EtOAc and was washed with 1x20 mL of water followed by 1x20 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product (300 mg) was purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-002(Agilent)): Column, 1#-PrepC-005(XBridge C18 19*150 186002979 170130047113 03), n; mobile phase, WATER WITH 0.05%TFA and CH₃CN (15.0% CH₃CN up to 50.0% in 10 min, up to 100.0% in 1 min, hold 100.0% in 1 min, down to 15.0% in 2 min); Detector, uv 220&254nm. The fractions containing pure compound were combined and lyophilized to yield 106 mg (25%) of the title compound as a white solid. *m/z* (ES⁺) 542 (M+H)⁺.

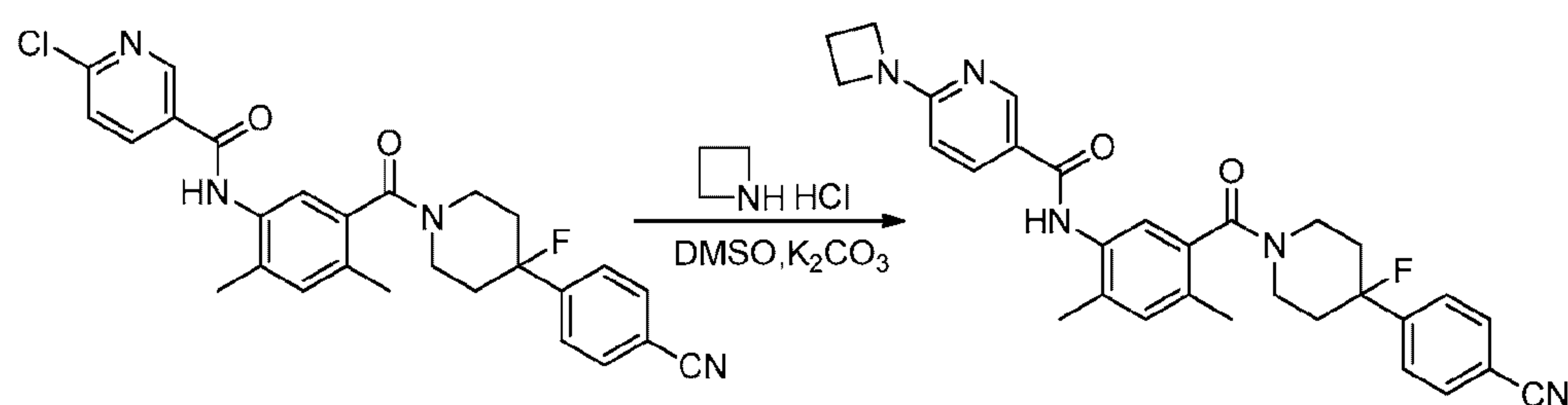


[0566] Compound 44. N-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2,4-dimethylphenyl)-6-((2-methoxyethyl)(methyl)amino)nicotinamide. The title compound was synthesized in a similar manner to that described for compound **43** to yield a white solid (219 mg, 50%). *m/z* (ES⁺) 544 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD): δ 8.56 (s with fine structure, 1H), 8.41 (d with fine structure, *J* = 9.9 Hz, 1H), 7.79 (br d, *J* = 8.1 Hz, 2H), 7.67 (br d, *J* = 6.9 Hz, 2H), 7.44-7.19 (m, 3H), 4.88-4.73 (m, 1H), 3.94 (t, *J* = 5.0 Hz, 2H), 3.73 (t,

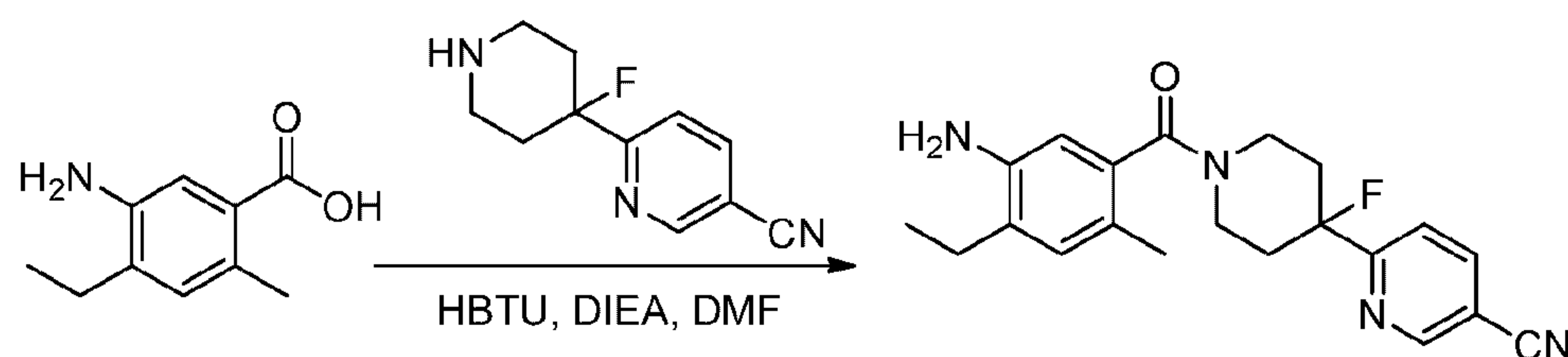
$J = 5.0$ Hz, 2H), 3.70-3.47 (m, 2H), 3.39 (s, 3H), 3.36 (s, 3H), 3.36-3.21 (m, 1H), 2.46-2.22 (m, 6H), 2.22-1.85 (m, 4H).



[0567] Compound 45. N-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2,4-dimethylphenyl)-6-(4-methylpiperazin-1-yl)nicotinamide. The title compound was synthesized in a similar manner to that described for compound 43 to yield a white solid (180 mg, 44%). m/z (ES+) 555 (M+H)⁺.

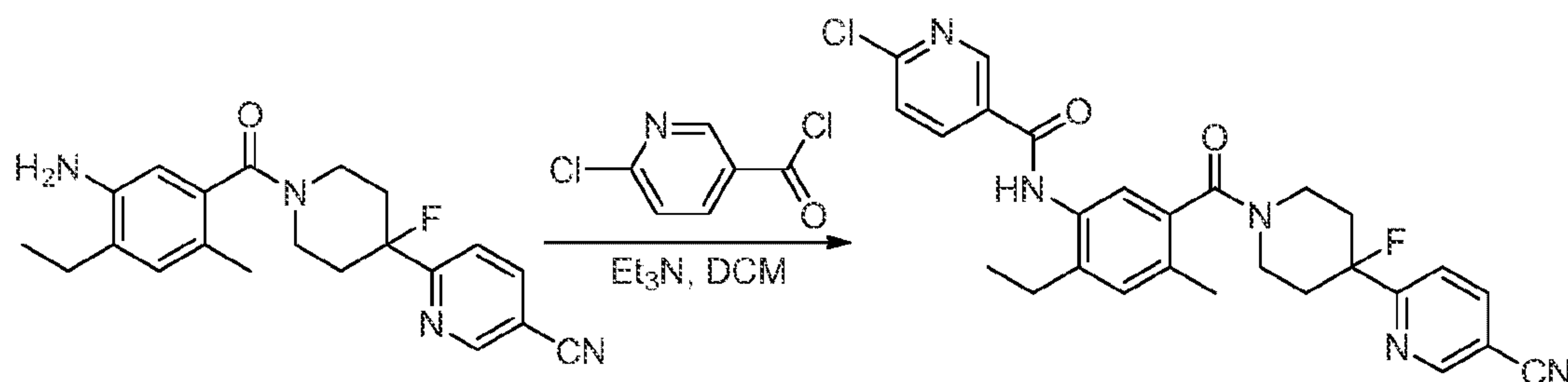


[0568] Compound 46. 6-(Azetidin-1-yl)-N-(5-(4-(4-cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2,4-dimethylphenyl)nicotinamide. The title compound was synthesized in a similar manner to that described for compound 43 to yield a white solid (180 mg, 44%). m/z (ES+) 512 (M+H)⁺.

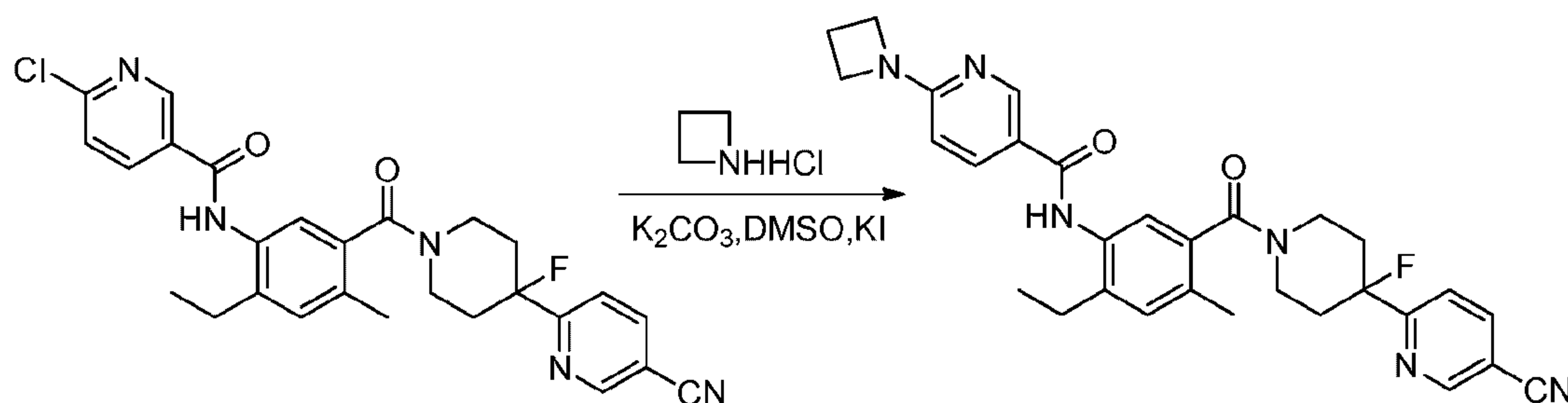


[0569] Compound 47.1. 6-(1-(5-Amino-4-ethyl-2-methylbenzoyl)-4-fluoropiperidin-4-yl)nicotinonitrile. The title compound was synthesized in a similar manner to that described for 42.2 and using compound 26.4 in place of compound 1.5 to yield a brown oil (280 mg, 89%).

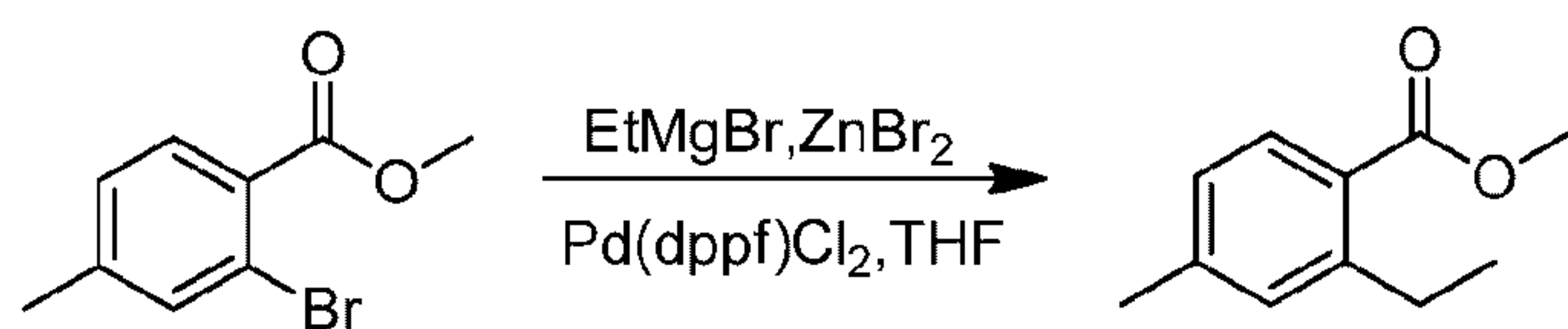
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[0570] **Compound 47.2. 6-Chloro-N-(5-(4-(5-cyanopyridin-2-yl)-4-fluoropiperidine-1-carbonyl)-2-ethyl-4-methylphenyl)nicotinamide.** The title compound was synthesized in a similar manner to that described for compound 42.3 to yield a brown oil (350 mg, 91%).

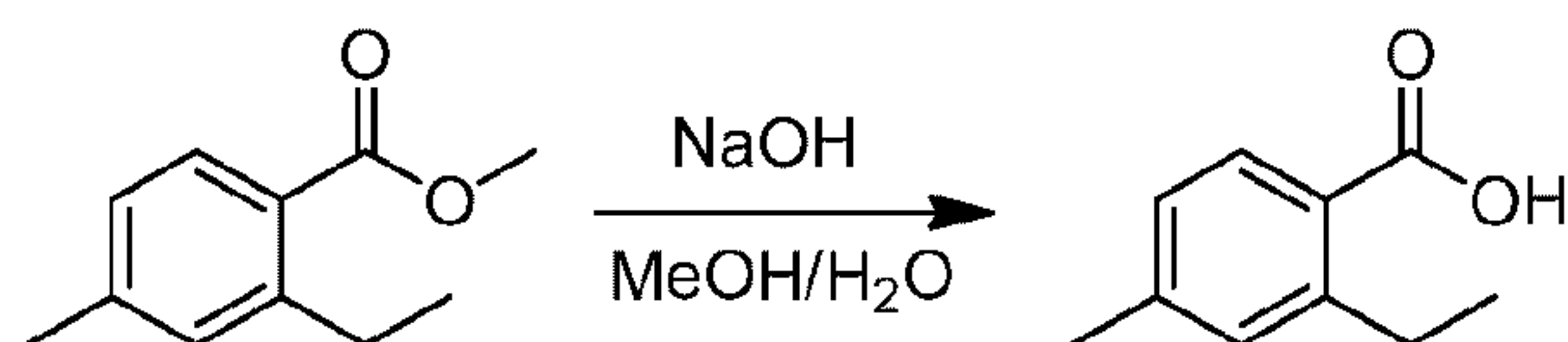


[0571] **Compound 47. 6-(Azetidin-1-yl)-N-(5-(4-(5-cyanopyridin-2-yl)-4-fluoropiperidine-1-carbonyl)-2-ethyl-4-methylphenyl)nicotinamide.** The title compound was synthesized in a similar manner to that described for compound 43 to yield a white solid (187 mg, 54%). m/z (ES+) 527 ($M+H$)⁺. ¹H NMR (300 MHz, DMSO- d_6): δ 9.88 (s, 1H), 9.06 (s, 1H), 8.59 (d, $J = 1.8$ Hz, 1H), 8.43 (dd, $J = 8.4$ Hz, $J = 2.1$ Hz, 1H), 8.23 (d, $J = 9.3$ Hz, 1H), 7.81 (d, $J = 8.1$ Hz, 1H), 7.22 (s, 1H), 7.17 (br s, 1H), 6.74 (d, $J = 9.0$ Hz, 1H), 4.68-4.53 (m, 1H), 4.23 (t, $J = 7.7$ Hz, 4H), 3.54-3.32 (m, 2H), 3.22-3.05 (m, 1H), 2.59 (q, $J = 7.5$ Hz, 2H), 2.50-2.38 (m, 2H), 2.35-1.80 (m, 7H), 1.14 (t, 3H).

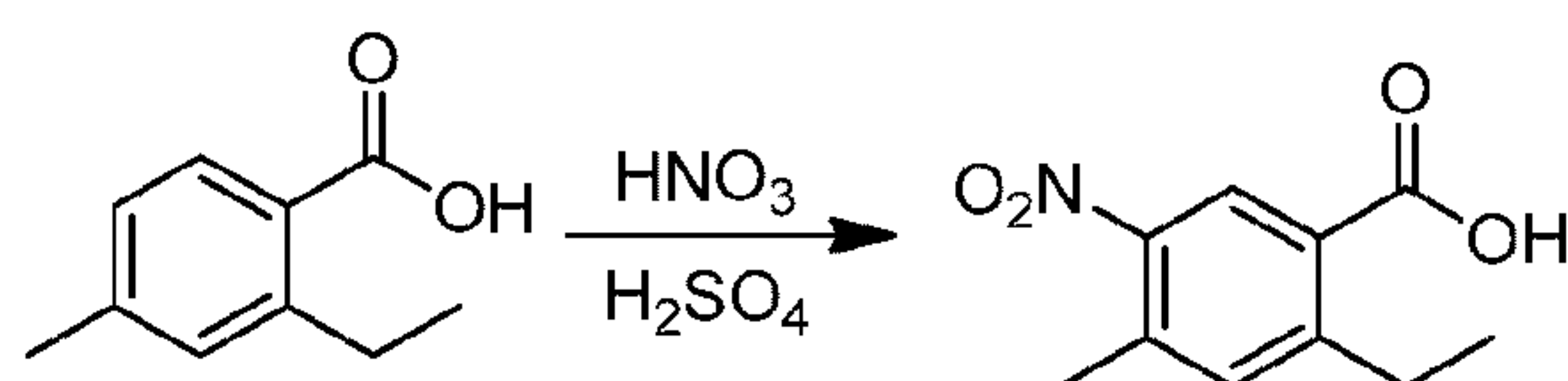


[0572] **Compound 48.1. Methyl 2-ethyl-4-methylbenzoate.** To a stirred mixture of ZnBr₂ (13 g, 57.72 mmol, 2.00 equiv) in THF (230 mL) under nitrogen at 0°C was added dropwise EtMgBr (19.5 mL, 3 M in THF). After 30 minutes at 0°C, the temperature was lowered to -78°C and Pd(dppf)Cl₂ (2 g, 2.73 mmol, 0.09 equiv) was added followed by dropwise addition of a solution of methyl 2-bromo-4-methylbenzoate (6.6 g, 28.81 mmol, 1.00 equiv) in tetrahydrofuran (200 mL). The resulting mixture was allowed to slowly reach ambient temperature and stirred under nitrogen overnight. The reaction mixture was quenched by the careful addition of 20 mL NH₄Cl (aq., sat.) and extracted with 3x100 mL of ethyl acetate. The combined organic layers were washed with 1x200 mL of brine, dried over

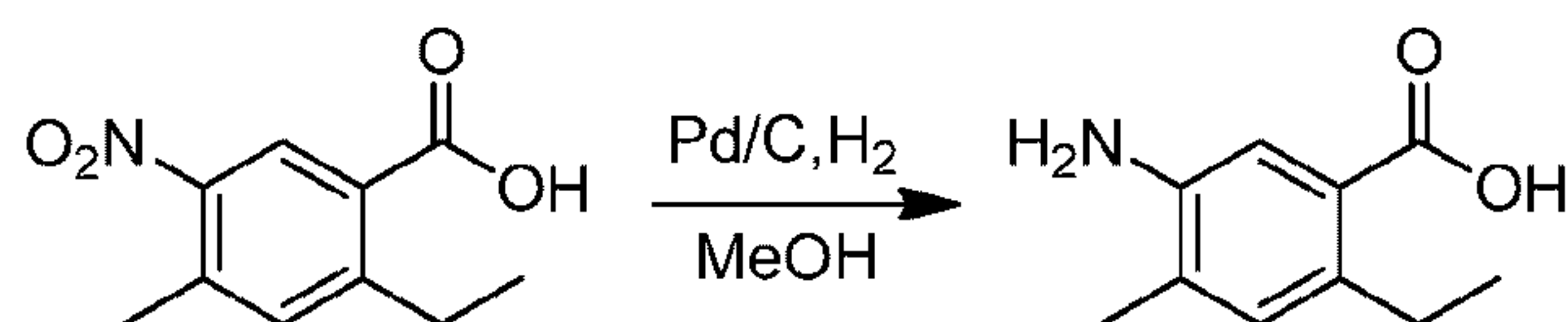
anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:30) as eluent to yield 3.7 g (72%) of the title compound as a colorless oil.



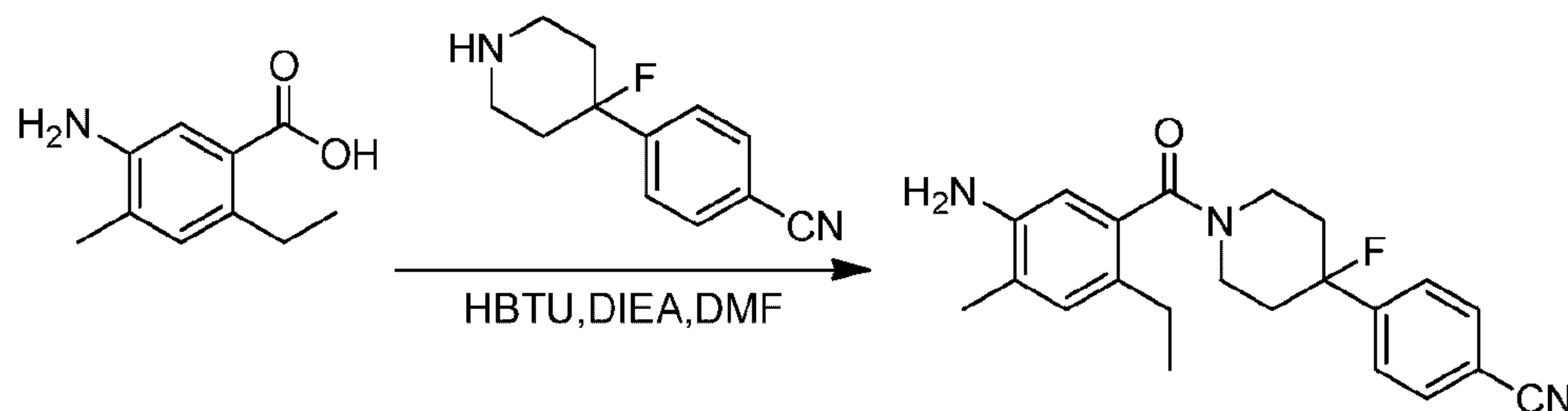
[0573] Compound 48.2. 2-Ethyl-4-methylbenzoic acid. A mixture of compound 48.1, 3.7 g, 20.76 mmol, 1.00 equiv) and sodium hydroxide (4 g, 100.01 mmol, 4.82 equiv) in methanol/H₂O (30/20 mL) was stirred overnight at 50°C. After cooling to ambient temperature, the organic solvent was removed under reduced pressure. The pH of the residual aqueous layer was adjusted to 3-4 with hydrogen chloride (aq., 1 M). The resulting precipitate was collected by filtration and dried to yield in 3.0 g (83%) of the title compound as a white solid.



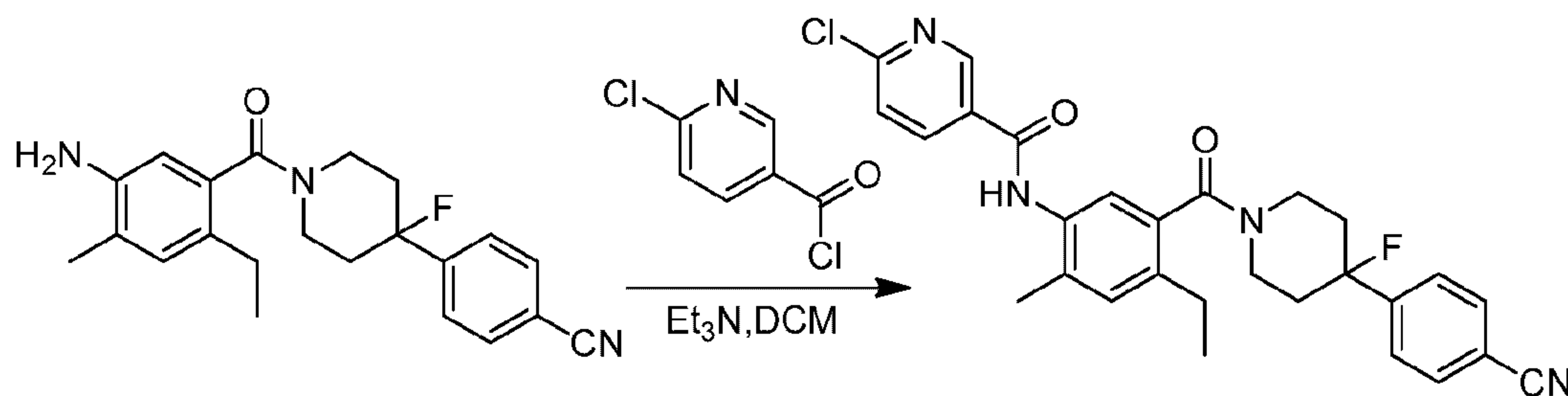
[0574] Compound 48.3. 2-Ethyl-4-methyl-5-nitrobenzoic acid. To a stirred mixture of 2-ethyl-4-methylbenzoic acid (compound 48.2, 2 g, 12.18 mmol, 1.00 equiv) in sulfuric acid (30 mL) at -10°C was added dropwise a solution of nitric acid (1.6 g, 16.50 mmol, 2.08 equiv) in sulfuric acid (10 mL). After stirring for 30 min at -10°C, 200 mL of H₂O/ice was carefully added and the resulting mixture was extracted with 50 mL of ethyl acetate. The organic phase was washed with 2x50 mL of brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by re-crystallization from ethyl acetate/petroleum ether in the ratio 1:10 to yield 1.0 g (37%) of 2-ethyl-4-methyl-5-nitrobenzoic acid as a light-yellow solid.



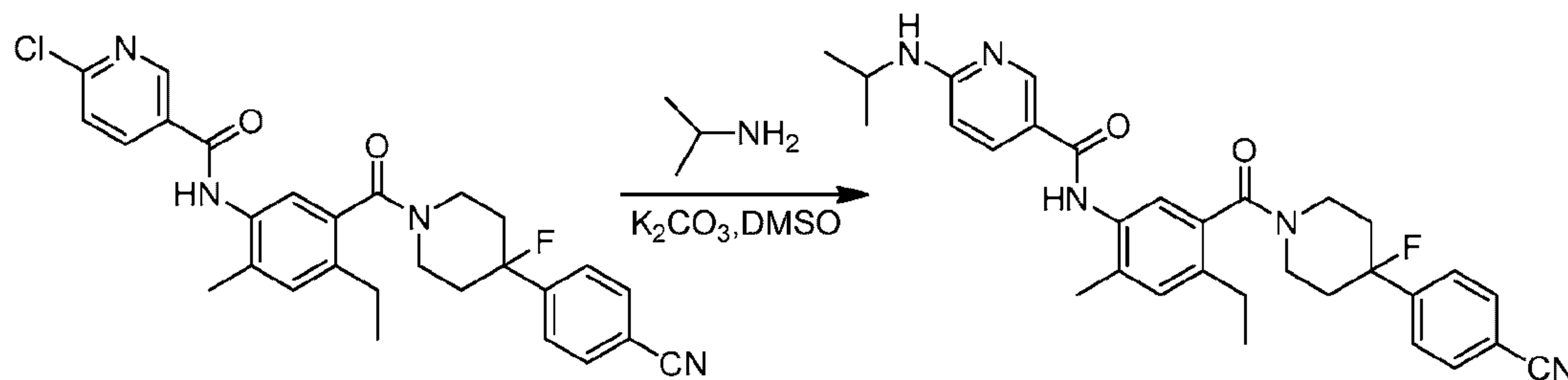
[0575] Compound 48.4. 5-Amino-2-ethyl-4-methylbenzoic acid. The title compound was synthesized from 48.3 (1 g, 4.78 mmol) using a procedure similar to that described for the preparation of 1.9 to yield the title compound as a light pink solid (900 mg, 97%).



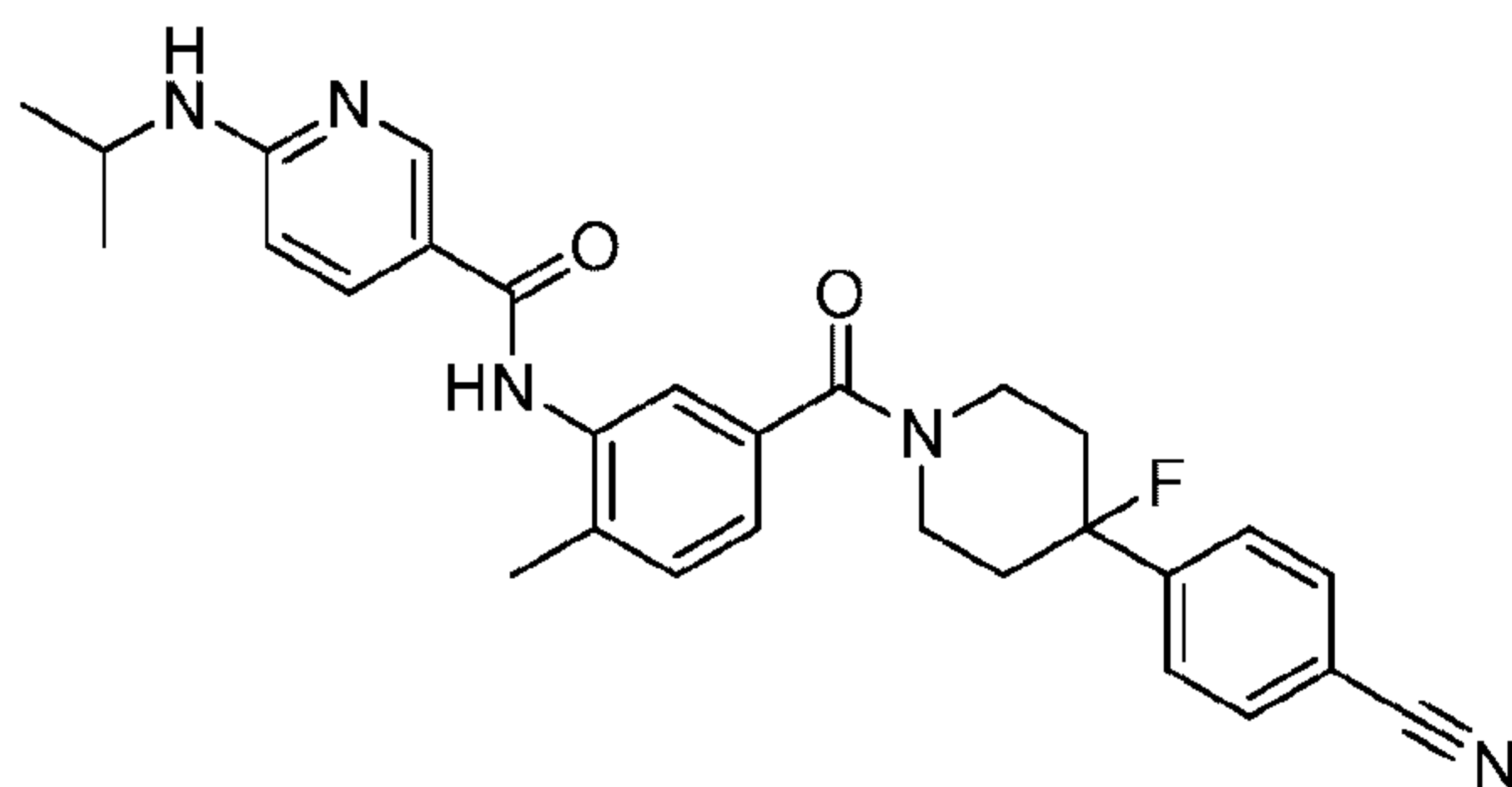
[0576] Compound 48.5. 4-(1-(5-Amino-2-ethyl-4-methylbenzoyl)-4-fluoropiperidin-4-yl)benzonitrile. A mixture of 5-amino-2-ethyl-4-methylbenzoic acid (compound 48.4, 100 mg, 0.56 mmol, 1.00 equiv), 4-(4-fluoropiperidin-4-yl) benzonitrile (compound 11.2, 140 mg, 0.69 mmol, 1.23 equiv), HBTU (320 mg, 0.84 mmol, 1.51 equiv), and DIEA (150 mg, 1.16 mmol, 2.08 equiv) in DMF (20 mL) was stirred for 48 h at room temperature. Water (30 mL) was added and the resulting mixture was extracted with 3x20 mL of ethyl acetate. The combined organic layers were washed with 1x50 mL of brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified using silica gel column chromatography with PE:EtOAc (1:1) to yield 130 mg (38%) of the title compound as a light yellow solid.



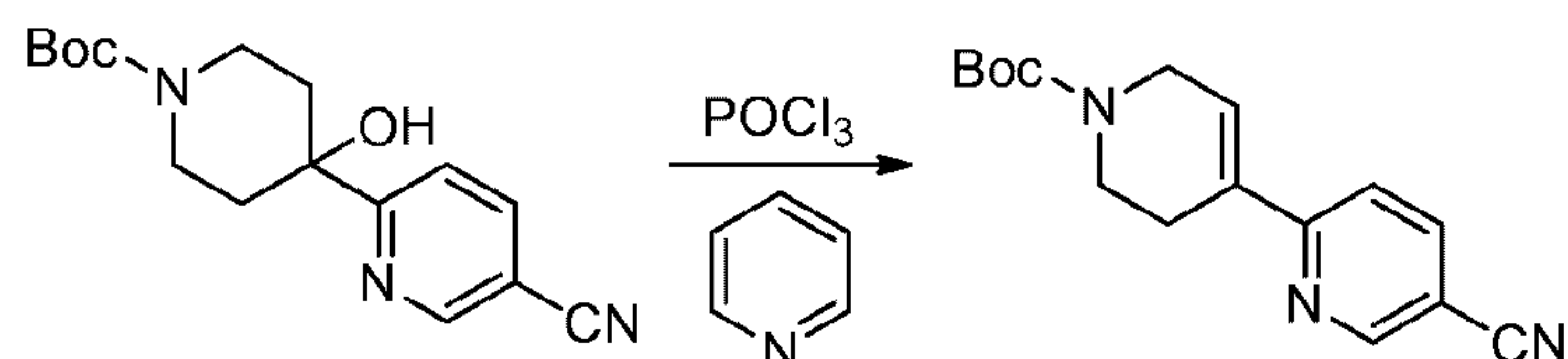
[0577] Compound 48.6. 6-Chloro-N-(5-(4-(4-cyanophenyl)-4-fluoropiperidine-1-carbonyl)-4-ethyl-2-methylphenyl)nicotinamide. The title compound was synthesized in a similar manner to that described for compound 42.3 and using compound 48.5 in place of compound 42.2 to yield a light yellow solid (200 mg, 87%).



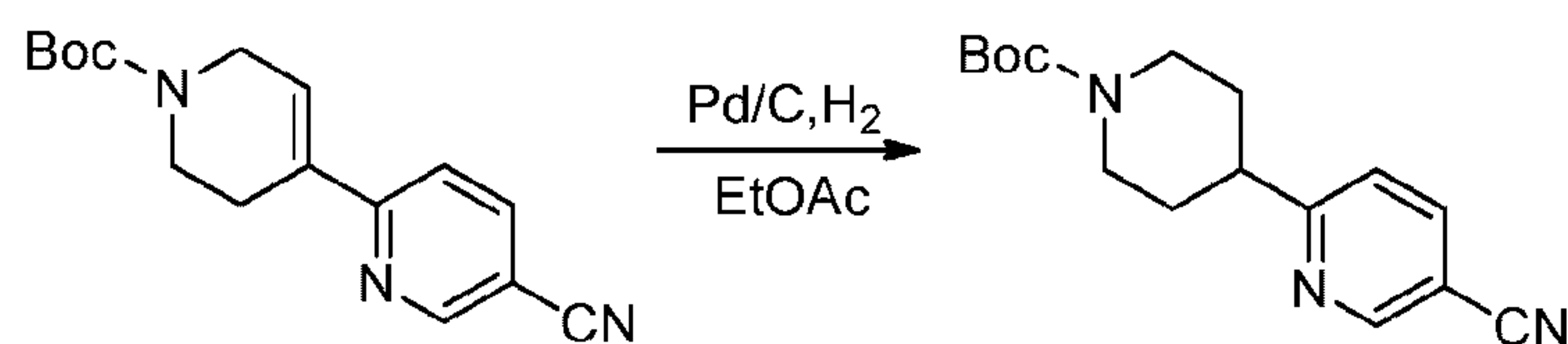
[0578] Compound 48. N-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-4-ethyl-2-methylphenyl)-6-(isopropylamino)nicotinamide. The title compound was synthesized in a similar manner to that described for compound 43 and using compound 48.6 in place of compound 42.3 to yield an off-white solid (32 mg, 30%). *m/z* (ES⁺) 528 (M+H)⁺.



[0579] **Compound 49. N-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2-methylphenyl)-6-(isopropylamino)nicotinamide.** The title compound was synthesized using readily available reagents and procedures similar to those described for compound 43. m/z (ES⁺) 500 (M+H)⁺.

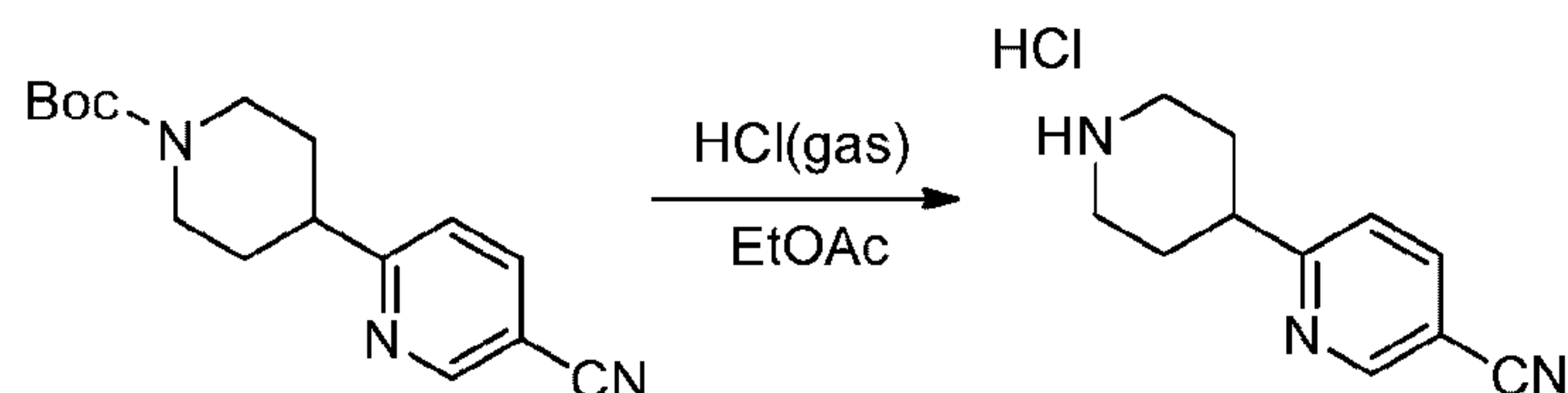


[0580] **Compound 50.1. tert-Butyl 5-cyano-5',6'-dihydro-[2,4'-bipyridine]-1'(2'H)-carboxylate.** To a stirred mixture of tert-butyl 4-(5-cyanopyridin-2-yl)-4-hydroxypiperidine-1-carboxylate (compound 26.2, 500 mg, 1.65 mmol, 1.00 equiv) in pyridine (20 mL) was added dropwise phosphoryl trichloride (2.5 g, 16.34 mmol, 9.90 equiv) at 10-15°C. The resulting solution was stirred for 18 h at 15~20°C. The reaction was then carefully quenched by the addition of 20 mL of water and extracted with 3x100 mL of ethyl acetate. The combined organic phases were washed with 2x50 mL of aqueous HCl (1 M) followed by 1x100 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:100 to 1:7) as eluent to yield 0.3 g (64%) of the title compound as a yellow solid.

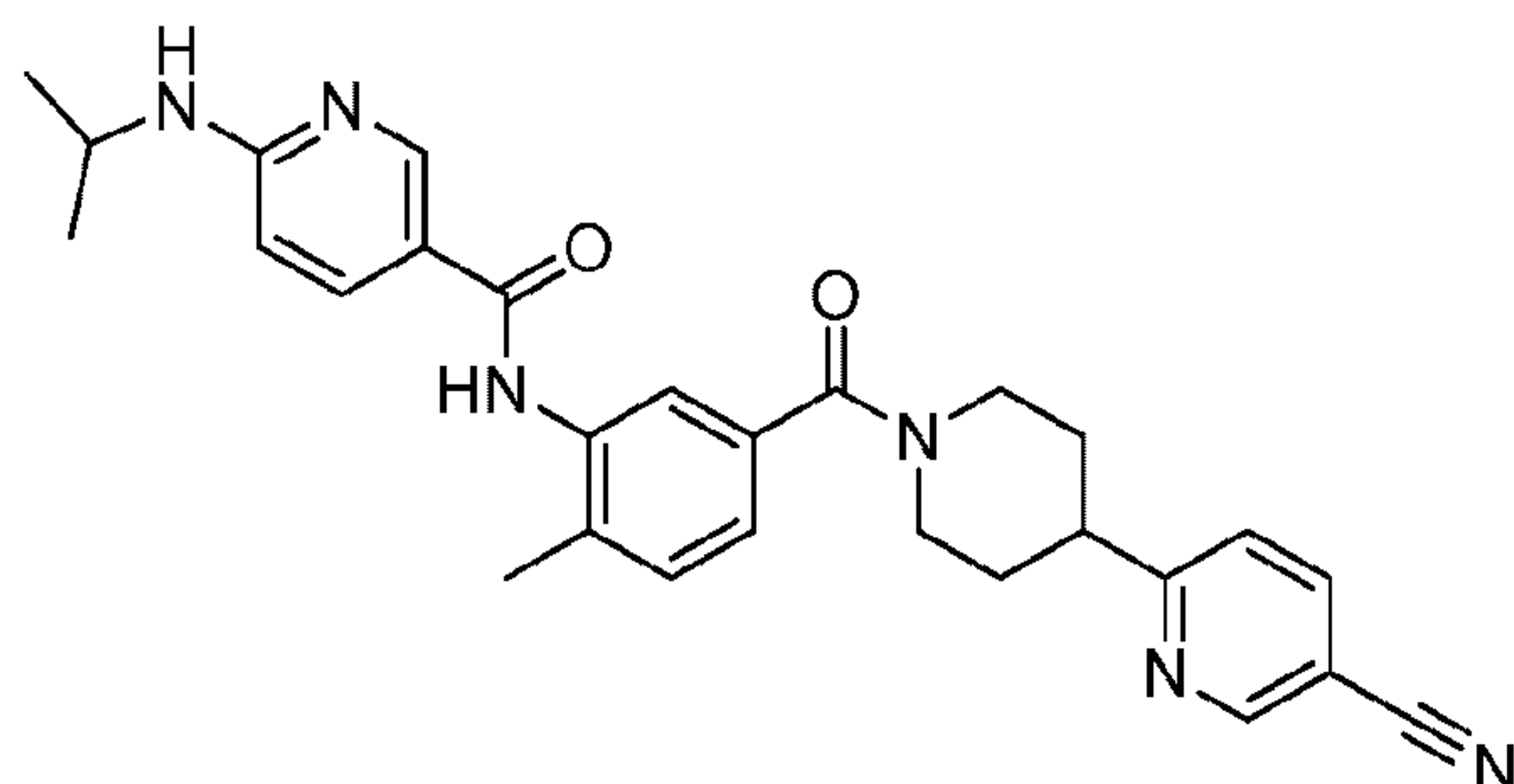


[0581] **Compound 50.2. tert-butyl 4-(5-cyanopyridin-2-yl)piperidine-1-carboxylate.** Around-bottom flask, containing a solution of compound 50.1 (300 mg, 1.05 mmol, 1.00 equiv) in ethyl acetate (20 mL), was purged with nitrogen gas. To the solution was then added palladium on carbon (40 mg, 10%) and the flask was purged further with nitrogen gas. The atmosphere was then changed to hydrogen and the mixture was stirred for 16 h at 15~20°C. After purging the system with nitrogen, the solids were removed by filtration and

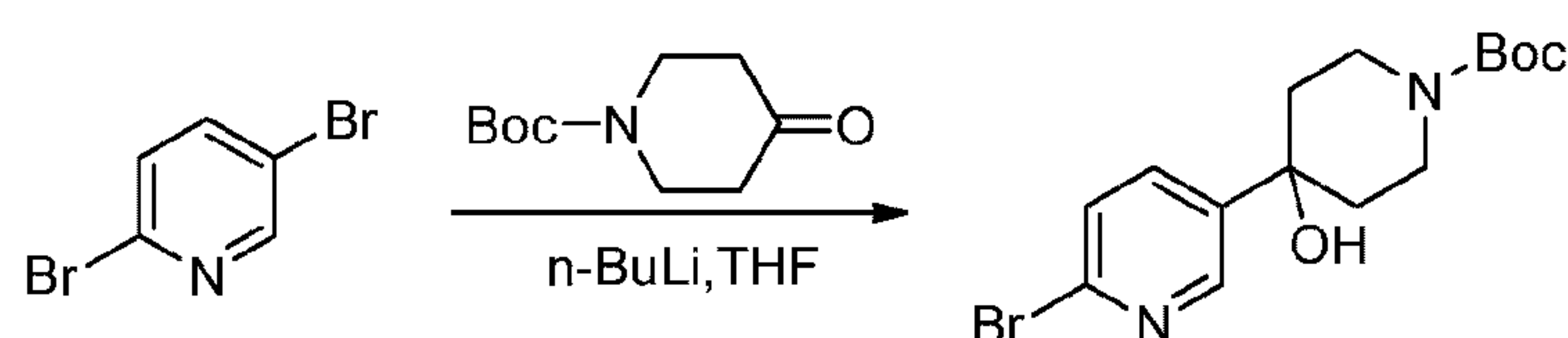
the filtrate was concentrated under reduced pressure to yield 0.2 g (66%) of the title compound as a yellow oil.



[0582] Compound 50.3. 6-(Piperidin-4-yl)nicotinonitrile hydrochloride. Through a solution of tert-butyl 4-(5-cyanopyridin-2-yl)piperidine-1-carboxylate (compound 50.2, 200 mg, 0.70 mmol, 1.00 equiv) in ethyl acetate (20 mL) was bubbled HCl gas. The resulting mixture was stirred for 40 min at 5-10°C. The resulting precipitate was collected by filtration and dried to yield 150 mg (97%) of the title compound as a white solid.

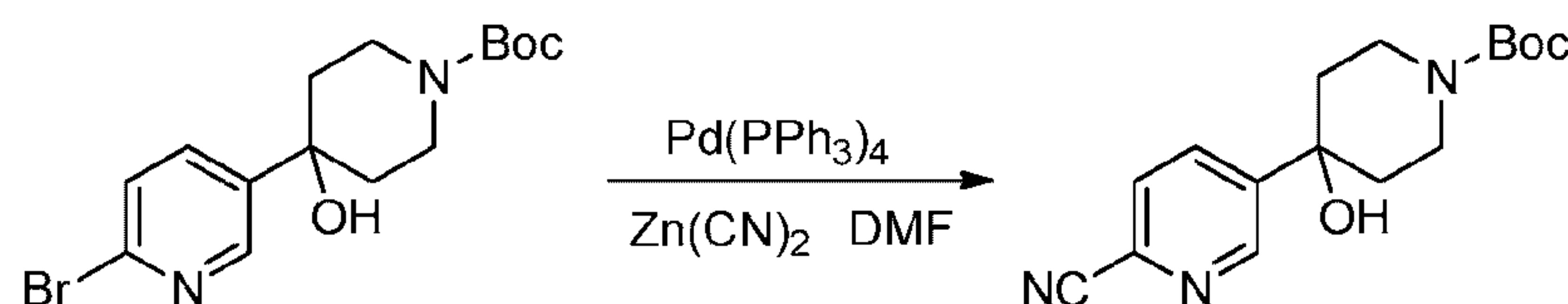


[0583] Compound 50. N-(5-(4-(5-Cyanopyridin-2-yl)piperidine-1-carbonyl)-2-methylphenyl)-6-(isopropylamino)nicotinamide. The title compound was synthesized using readily available reagents and procedures similar to those described for compound 43 but using compound 50.3 in place of compound 11.2. m/z (ES⁺) 483 (M+H)⁺.

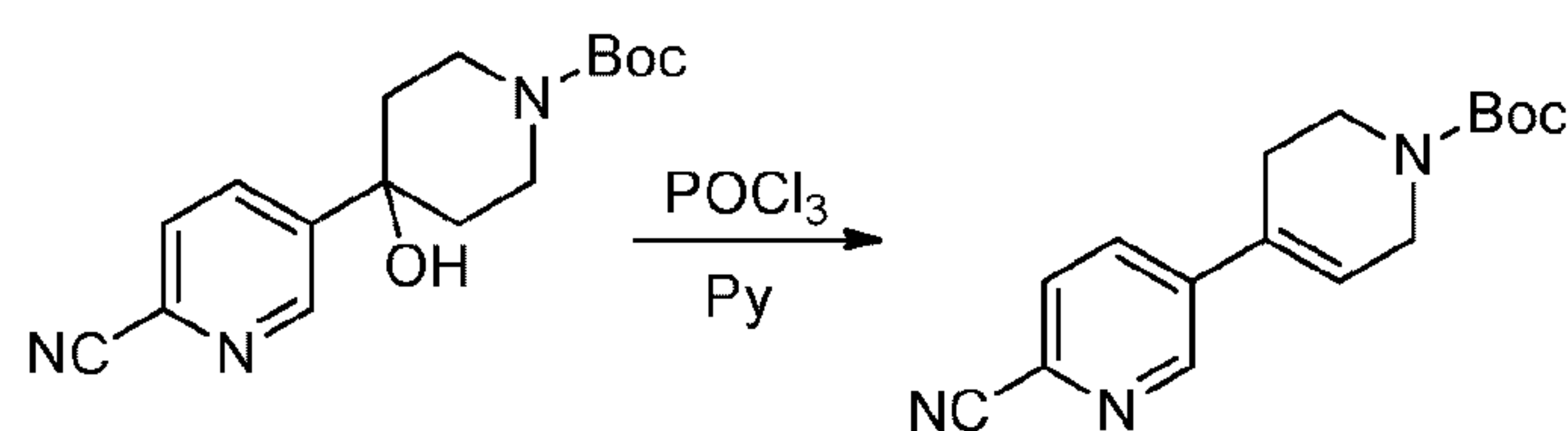


[0584] Compound 51.1. tert-Butyl 4-(6-bromopyridin-3-yl)-4-hydroxypiperidine-1-carboxylate. To a solution of 2,5-dibromopyridine (10 g, 42.55 mmol, 1.00 equiv) in tetrahydrofuran (400 mL) under nitrogen at -78°C was added dropwise n-BuLi (19 mL, 2.4 M in THF). After 1 h at -78°C, a solution of tert-butyl 4-oxopiperidine-1-carboxylate (9.5 g, 47.74 mmol, 1.12 equiv) in tetrahydrofuran (100 mL) was added dropwise. The resulting mixture was stirred for an additional hour at -78°C. The reaction was then warmed to -30°C and carefully quenched by the addition of 300 mL of water. The resulting mixture was extracted with 3x200 mL of ethyl acetate and the combined organic layers were washed with

1x200 mL of brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:3) as eluent to yield 5 g (33%) of the title compound as a yellow solid.

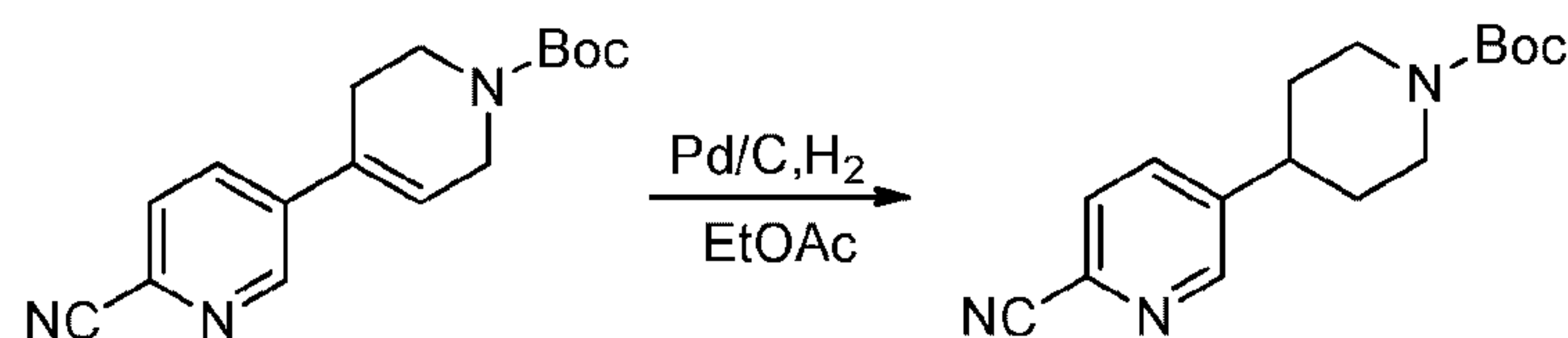


[0585] Compound 51.2. tert-Butyl 4-(6-cyanopyridin-3-yl)-4-hydroxypiperidine-1-carboxylate. To a mixture of tert-butyl 4-(6-bromopyridin-3-yl)-4-hydroxypiperidine-1-carboxylate (compound **51.1**, 1 g, 2.81 mmol, 1.00 equiv) in DMF (50 mL) under nitrogen at 50°C was added Zn(CN)₂ (400 mg, 3.42 mmol, 1.22 equiv) at 50°C followed by Pd(PPh₃)₄ (200 mg, 0.17 mmol, 0.06 equiv) at 80°C. The resulting mixture was then stirred for 1 h at 120°C. After cooling to ambient temperature, the reaction was quenched by the addition of 200 mL of FeSO₄ (aq., sat.) and diluted with ethyl acetate. The resulting mixture was stirred vigorously then filtered through celite and washed with 1 M FeSO₄, water, and ethyl acetate. The layers were separated and the aqueous phase was extracted with 2 x 100 mL of ethyl acetate. The combined organic layers were washed with 1x200 mL of brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:5-1:3) as eluent to yield 0.6 g (70%) of the title compound as a light yellow oil.



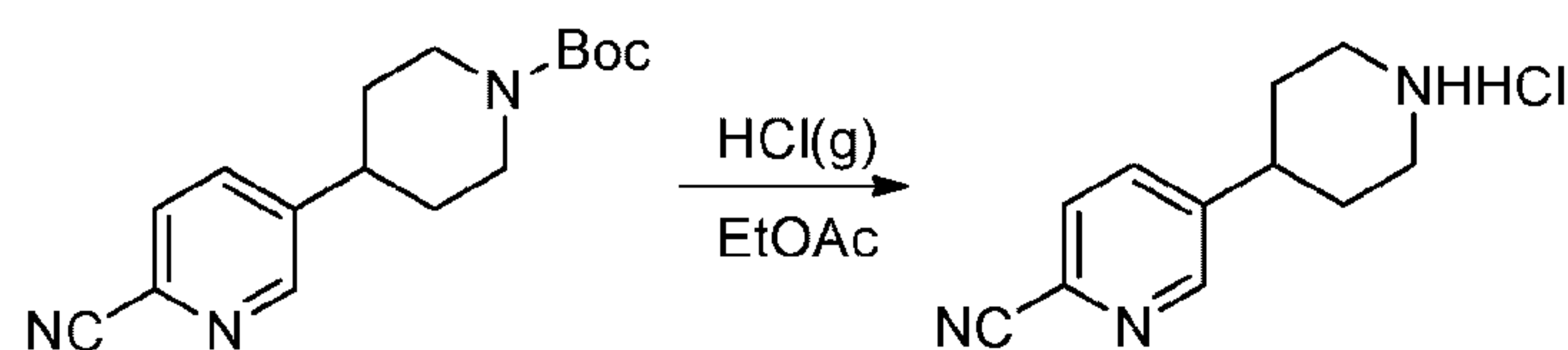
[0586] Compound 51.3. tert-Butyl 6-cyano-5',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate. To solution of tert-butyl 4-(6-cyanopyridin-3-yl)-4-hydroxypiperidine-1-carboxylate (compound **51.2**, 600 mg, 1.98 mmol, 1.00 equiv) in pyridine (15 mL) under nitrogen at 10-15°C was carefully added POCl₃ (3 g, 19.74 mmol, 9.97 equiv). After stirring overnight under nitrogen in a water/ice bath, the mixture was concentrated and the residue was dissolved in 50 mL of ethyl acetate. The organic phase was washed with 1x50 mL of hydrogen chloride (aq. 1M) followed by 1x50 mL of sodium bicarbonate (aq.sat.). The organic layer was then dried over anhydrous sodium sulfate and concentrated under reduced

pressure. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:10) as the eluent to yield 0.26 g (46%) of the title compound as a white solid.

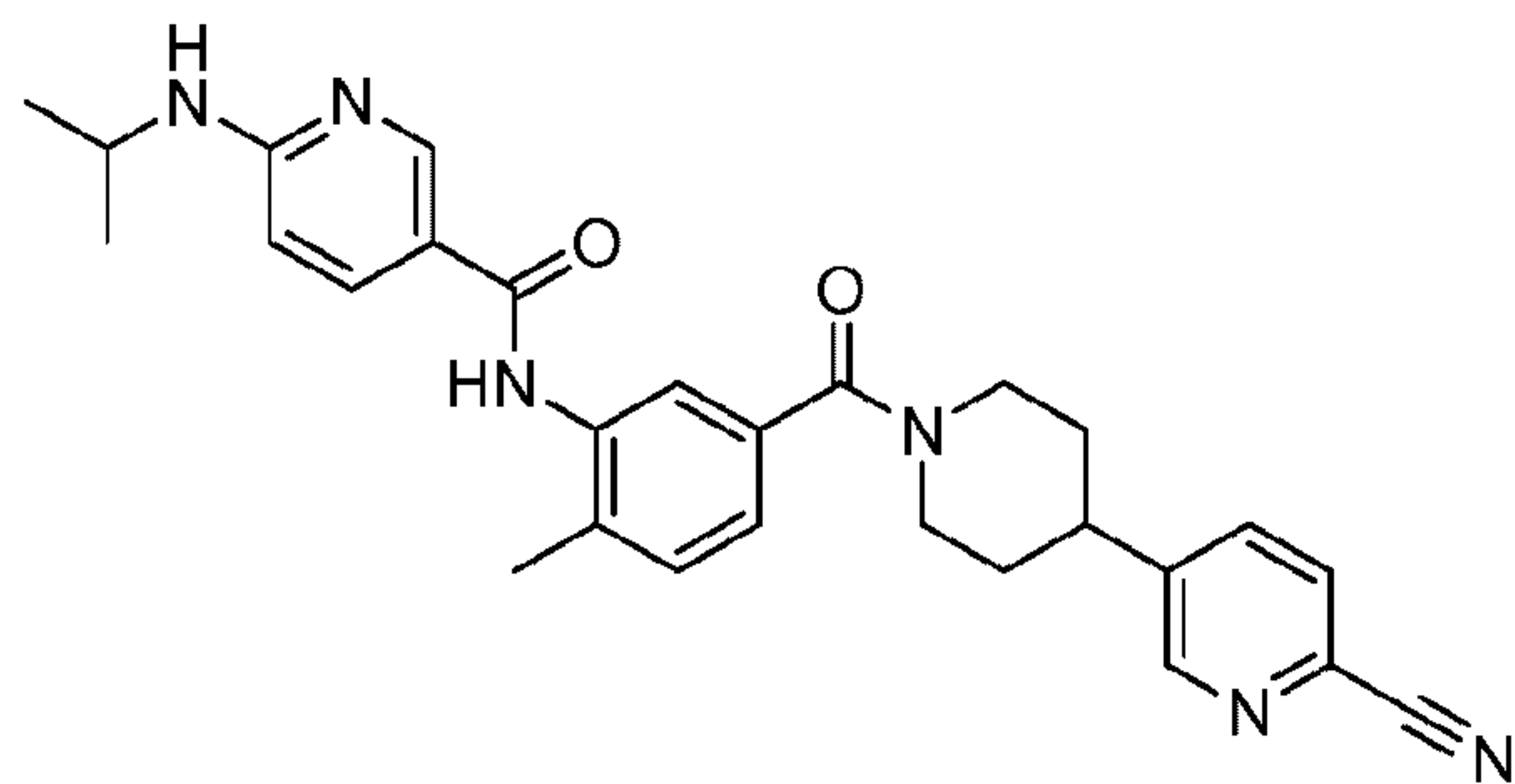


[0587] Compound 51.4. tert-Butyl 4-(6-cyanopyridin-3-yl)piperidine-1-carboxylate.

A round-bottom flask, containing a solution of compound **51.3** (260 mg, 0.91 mmol, 1.00 equiv) in ethyl acetate (40 mL) was purged with nitrogen gas. To the solution was then added palladium on carbon (0.1 g, 10%, 60% water) and the flask was purged further with nitrogen gas. The atmosphere was then changed to hydrogen and the mixture was stirred for 16 h at 15~20°C. After purging the system with nitrogen, the solids were removed by filtration and the filtrate was concentrated under reduced pressure. The crude residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:5). This resulted in 0.18 g (69%) of the title compound as a colorless oil.

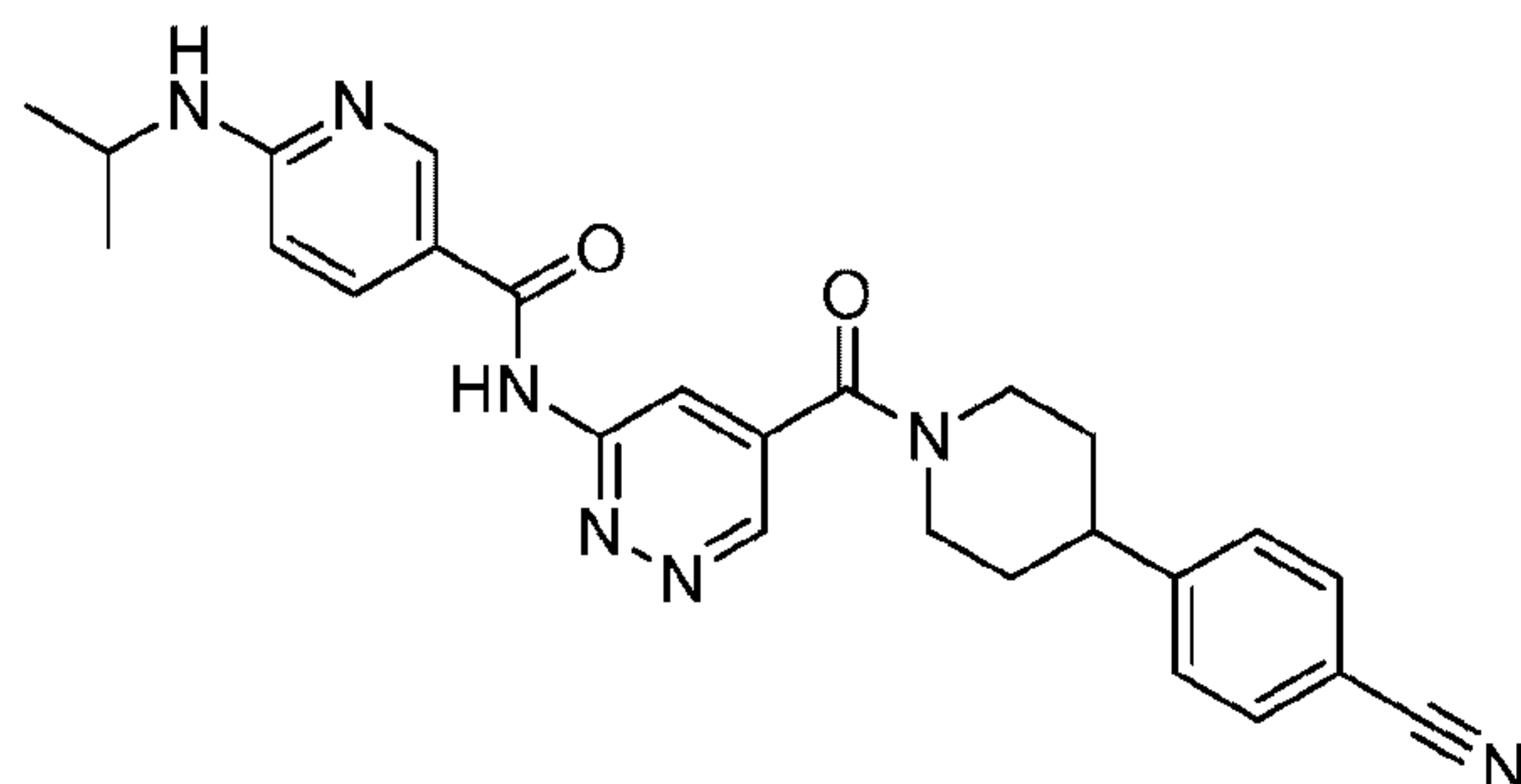


[0588] Compound 51.5. 5-(Piperidin-4-yl)picolinonitrile hydrochloride. Into a cooled (5-10°C) solution of tert-butyl 4-(6-cyanopyridin-3-yl)piperidine-1-carboxylate (**51.4**, 180 mg, 0.63 mmol, 1.00 equiv) in ethyl acetate (30 mL) was bubbled hydrogen chloride gas. The mixture was stirred for 30 min at 5-10°C and the resulting solids were collected by filtration and dried to yield 0.11 g (78%) of 5-(piperidin-4-yl)picolinonitrile hydrochloride as a white solid.

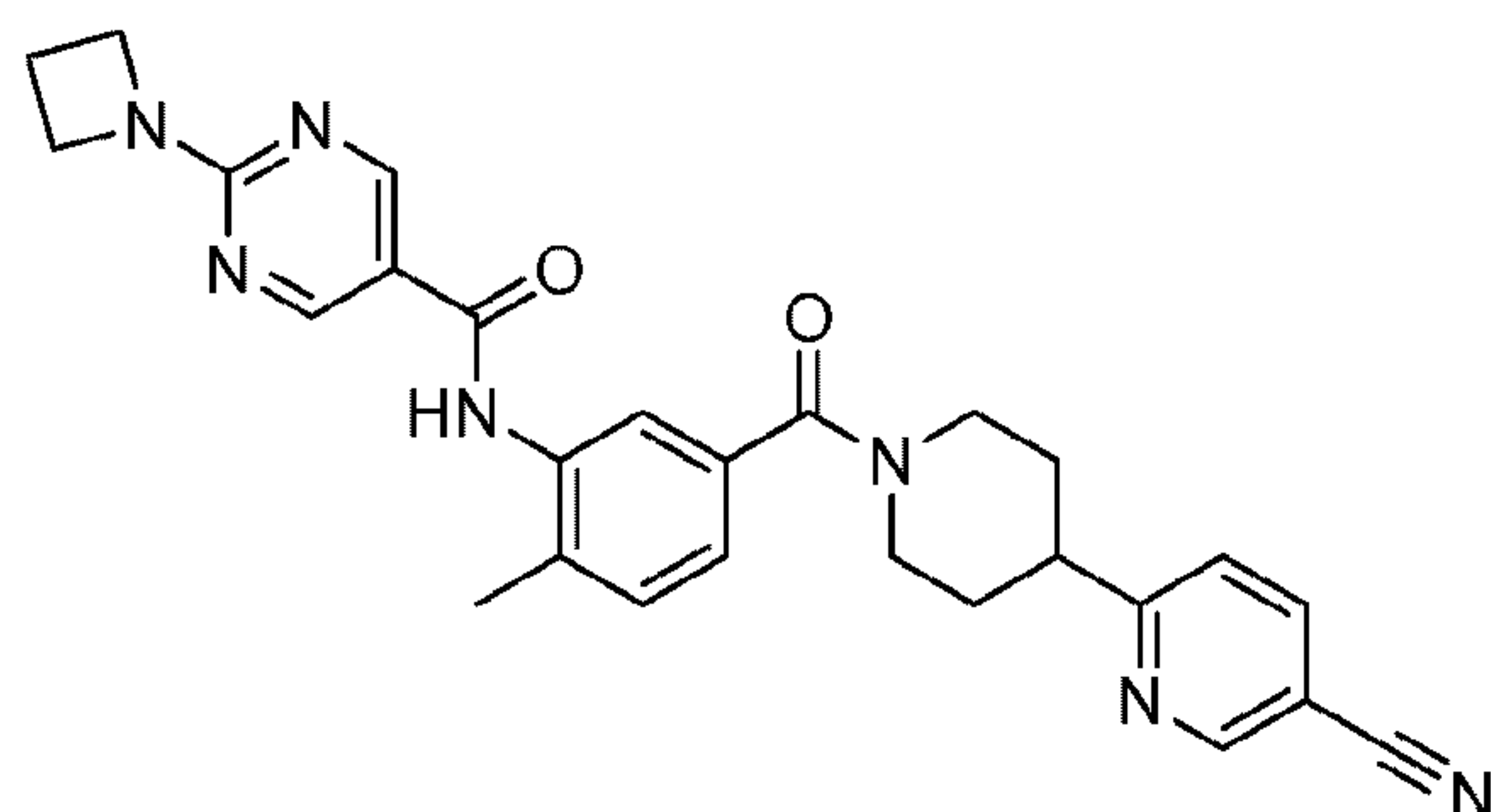


[0589] Compound 51. N-(5-(4-(6-Cyanopyridin-3-yl)piperidine-1-carbonyl)-2-methylphenyl)-6-(isopropylamino)nicotinamide. The title compound was synthesized

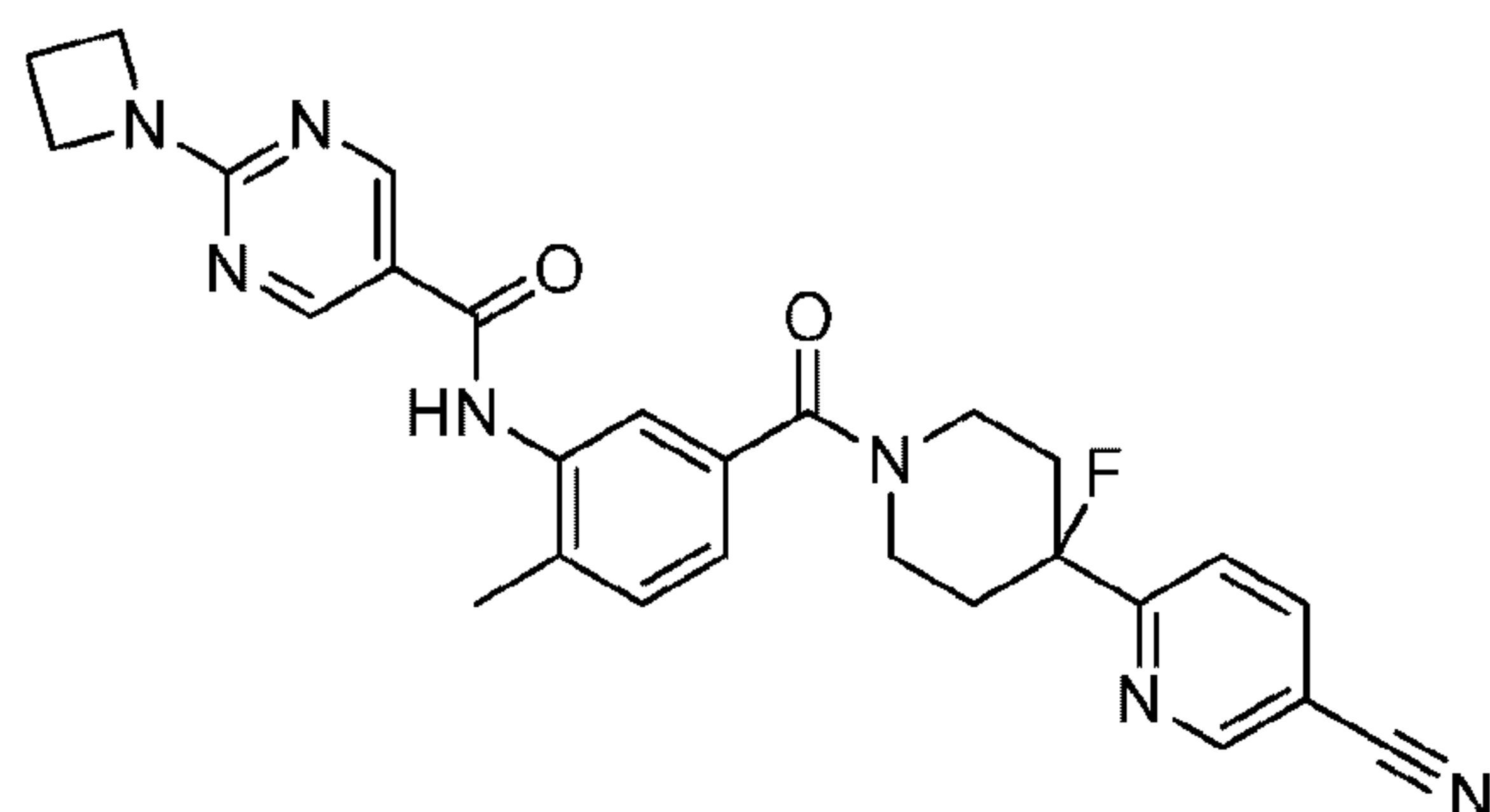
using readily available reagents and procedures similar to those described for compound **43** but using compound **51.5** in place of compound **11.2**. m/z (ES⁺) 483 (M+H)⁺.



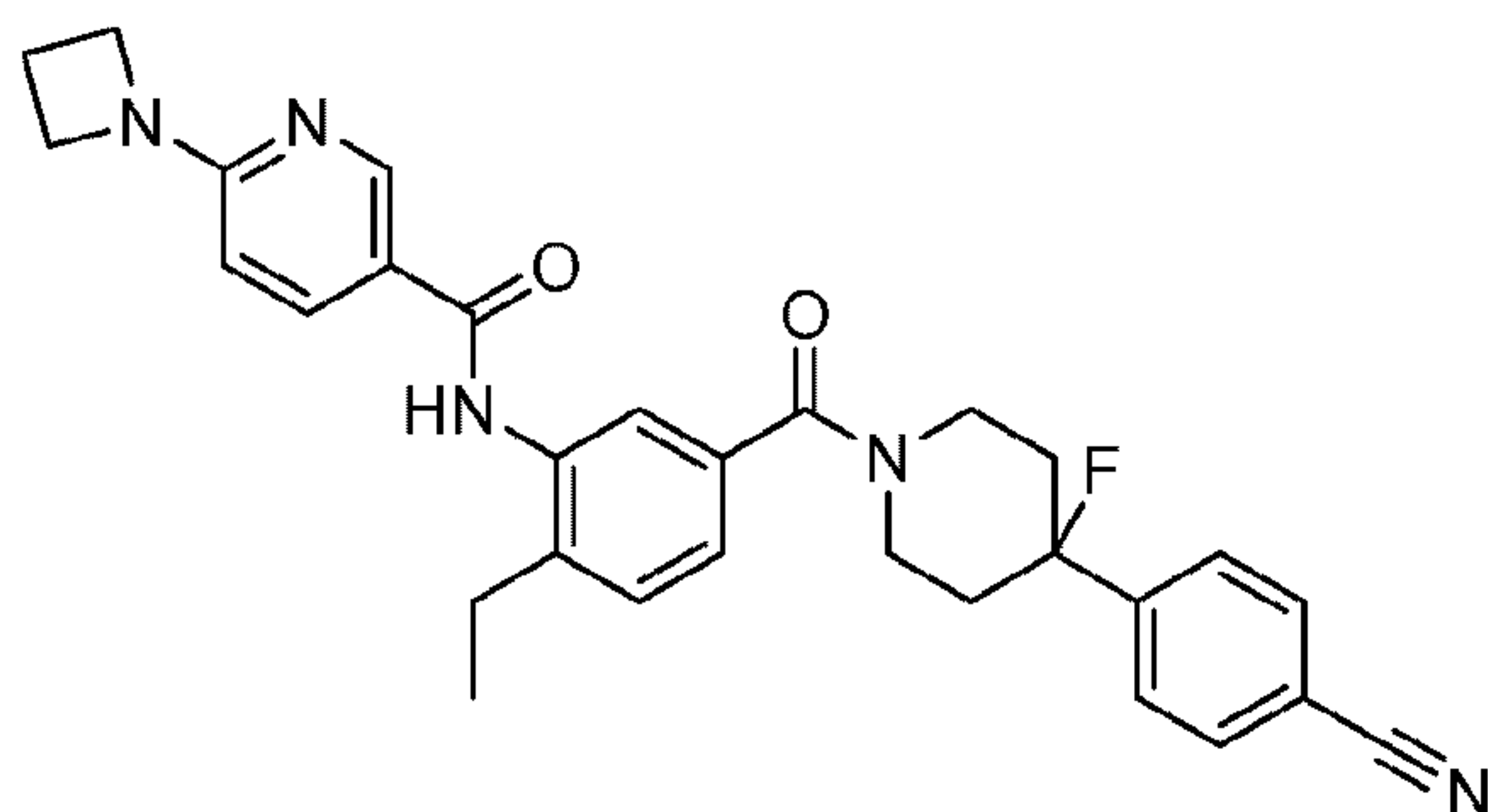
[0590] Compound **52**. N-(5-(4-(4-Cyanophenyl)piperidine-1-carbonyl)pyridazin-3-yl)-6-(isopropylamino)nicotinamide. The title compound was synthesized using readily available reagents and procedures similar to those described for compound **43**. m/z (ES⁺) 470 (M+H)⁺.



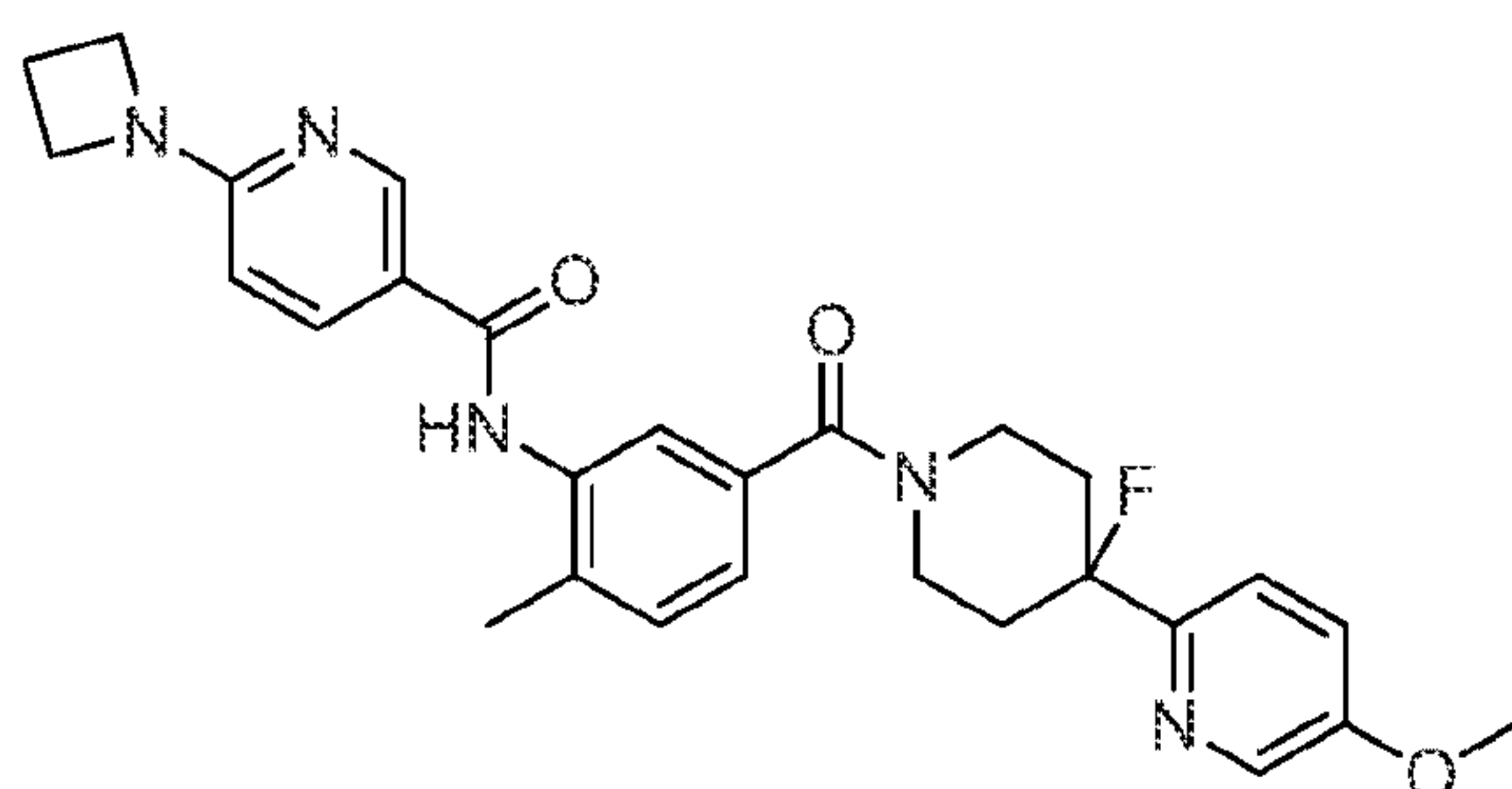
[0591] Compound **53**. 2-(Azetidin-1-yl)-N-(5-(4-(5-cyanopyridin-2-yl)piperidine-1-carbonyl)-2-methylphenyl)pyrimidine-5-carboxamide. The title compound was synthesized using readily available reagents and procedures similar to those described for compound **50**. m/z (ES⁺) 482 (M+H)⁺.



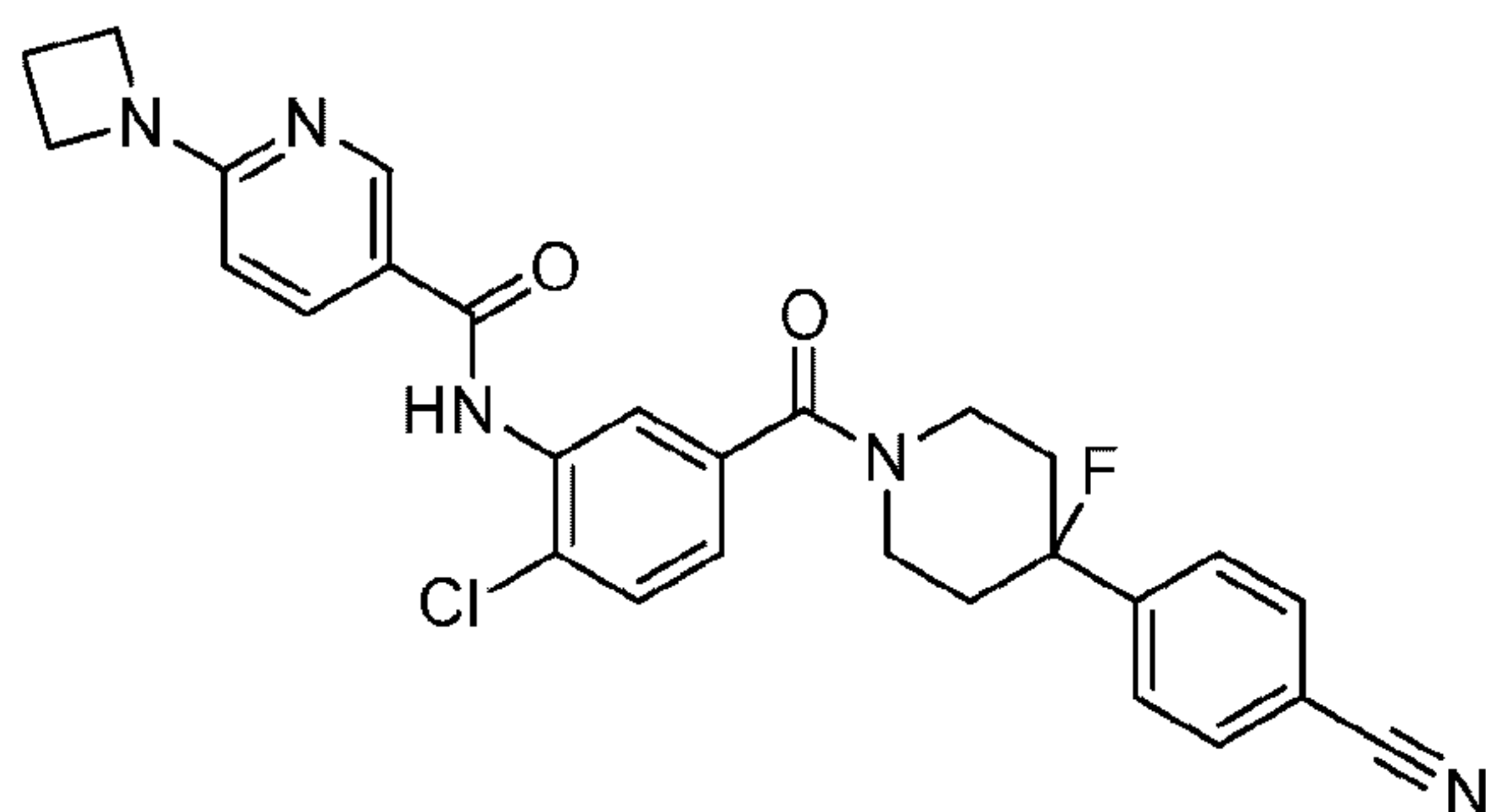
[0592] Compound **54**. 2-(Azetidin-1-yl)-N-(5-(4-(5-cyanopyridin-2-yl)-4-fluoropiperidine-1-carbonyl)-2-methylphenyl)pyrimidine-5-carboxamide. The title compound was synthesized using readily available reagents and procedures similar to those described for compound **47**. m/z (ES⁺) 500 (M+H)⁺.



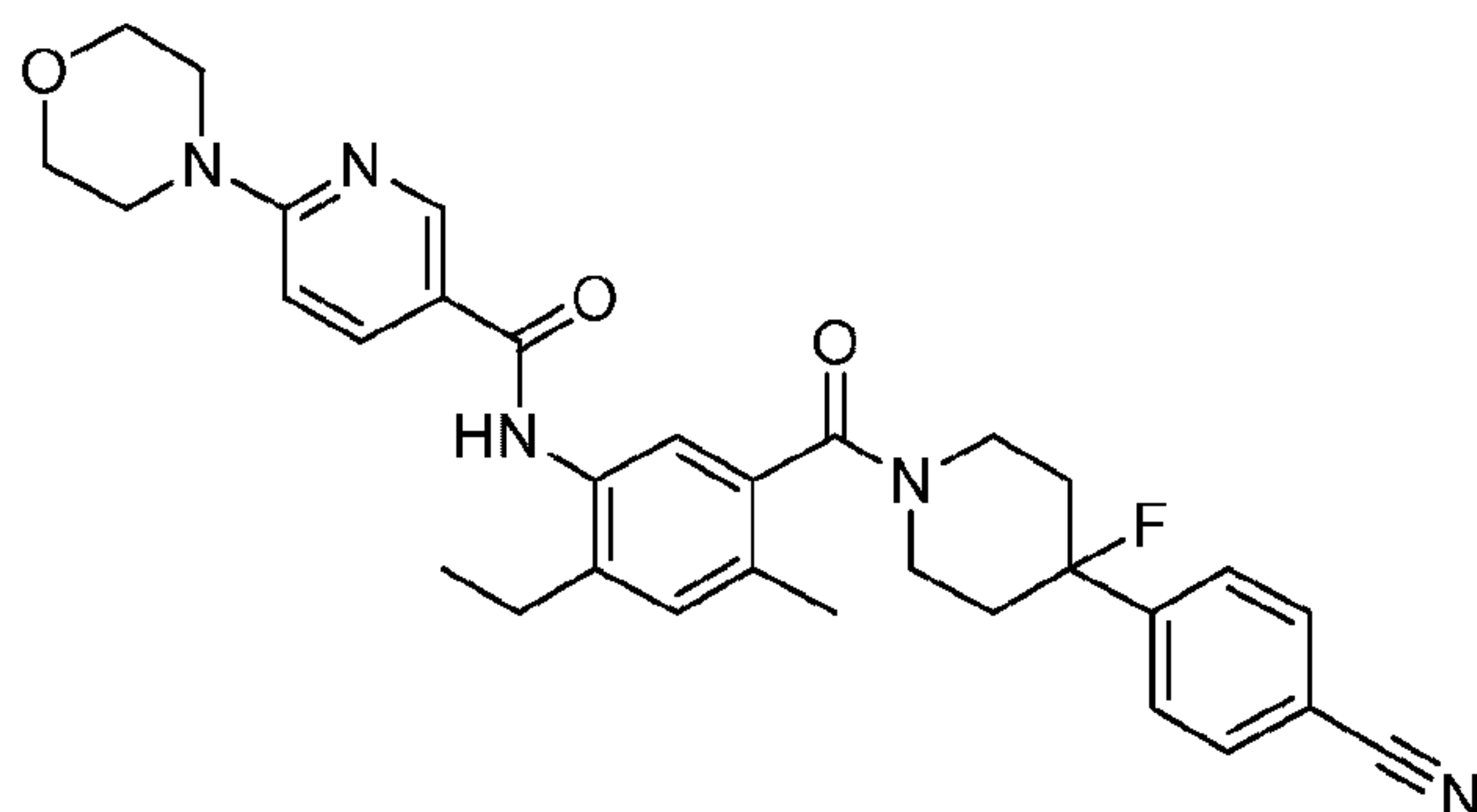
[0593] Compound 55. 6-(Azetidin-1-yl)-N-(5-(4-(4-cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2-ethylphenyl)nicotinamide. The title compound was synthesized using readily available reagents and procedures similar to those described for compound **43**, m/z (ES+) 512 (M+H)⁺.



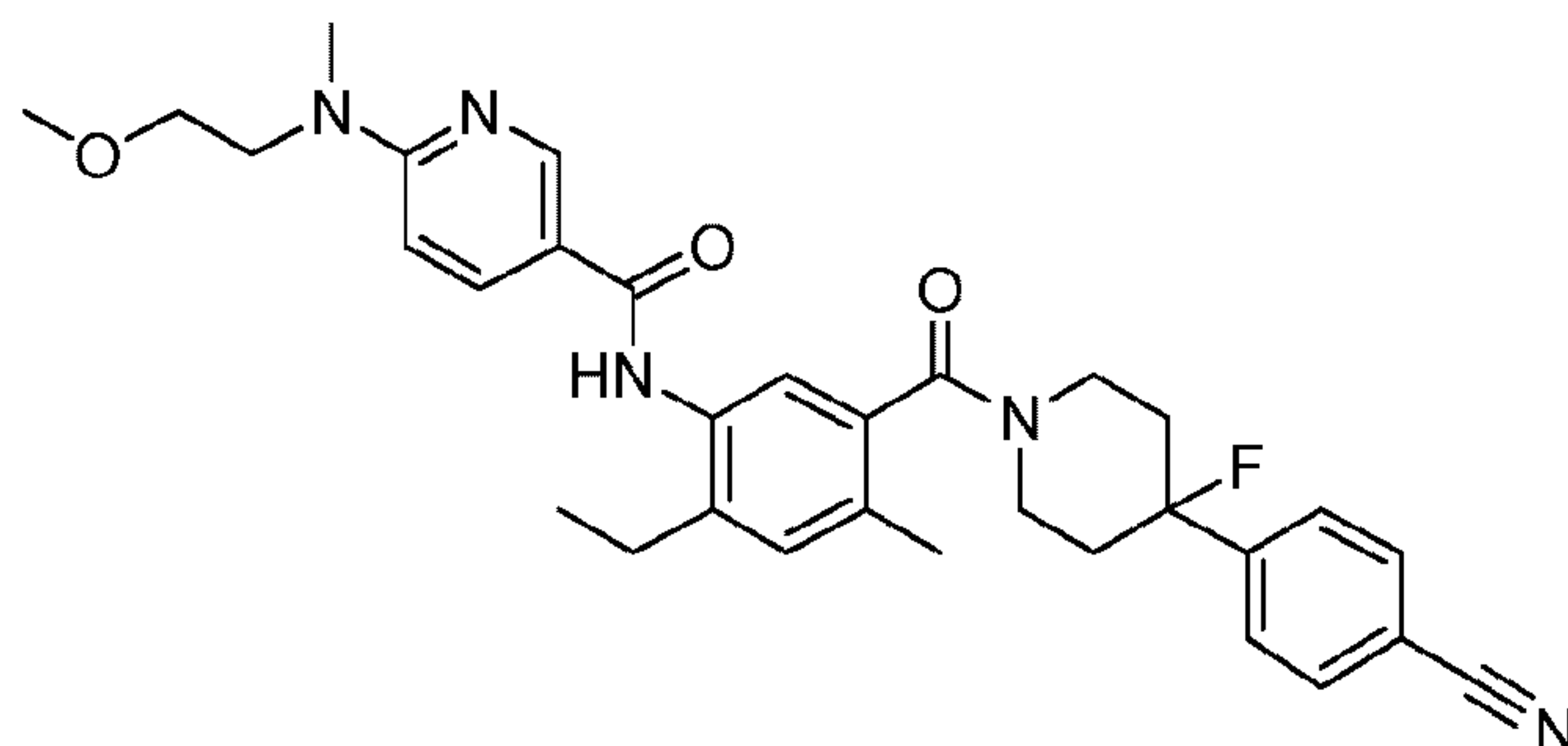
[0594] Compound 56. 6-(Azetidin-1-yl)-N-(5-(4-fluoro-4-(5-methoxypyridin-2-yl)piperidine-1-carbonyl)-2-methylphenyl)nicotinamide. The title compound was synthesized using readily available reagents and procedures similar to those described for compound **43**, m/z (ES+) 504 (M+H)⁺.



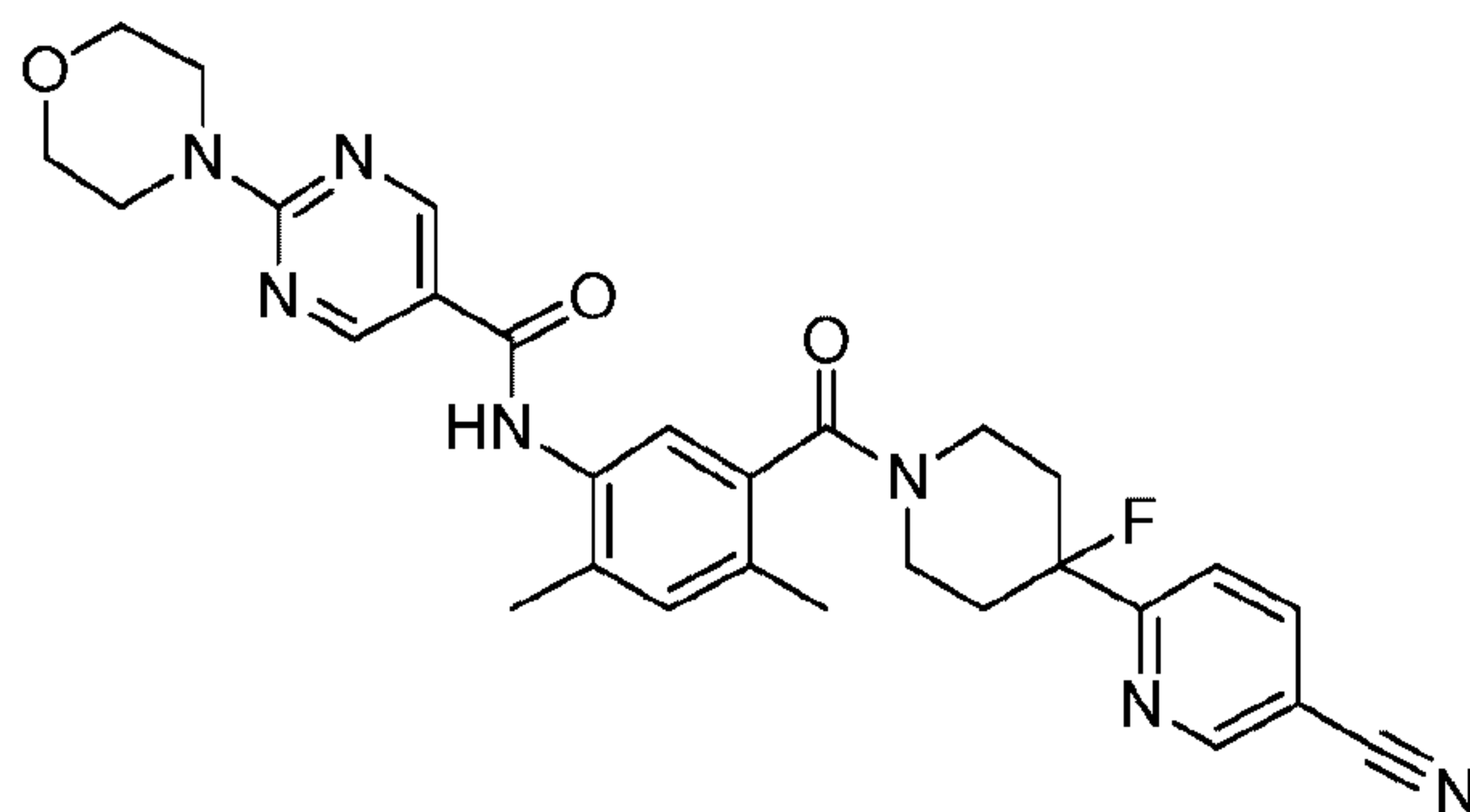
[0595] Compound 57. 6-(Azetidin-1-yl)-N-(2-chloro-5-(4-(4-cyanophenyl)-4-fluoropiperidine-1-carbonyl)phenyl)nicotinamide. The title compound was synthesized using readily available reagents and procedures similar to those described for compound **43**, m/z (ES+) 518 (M+H)⁺.



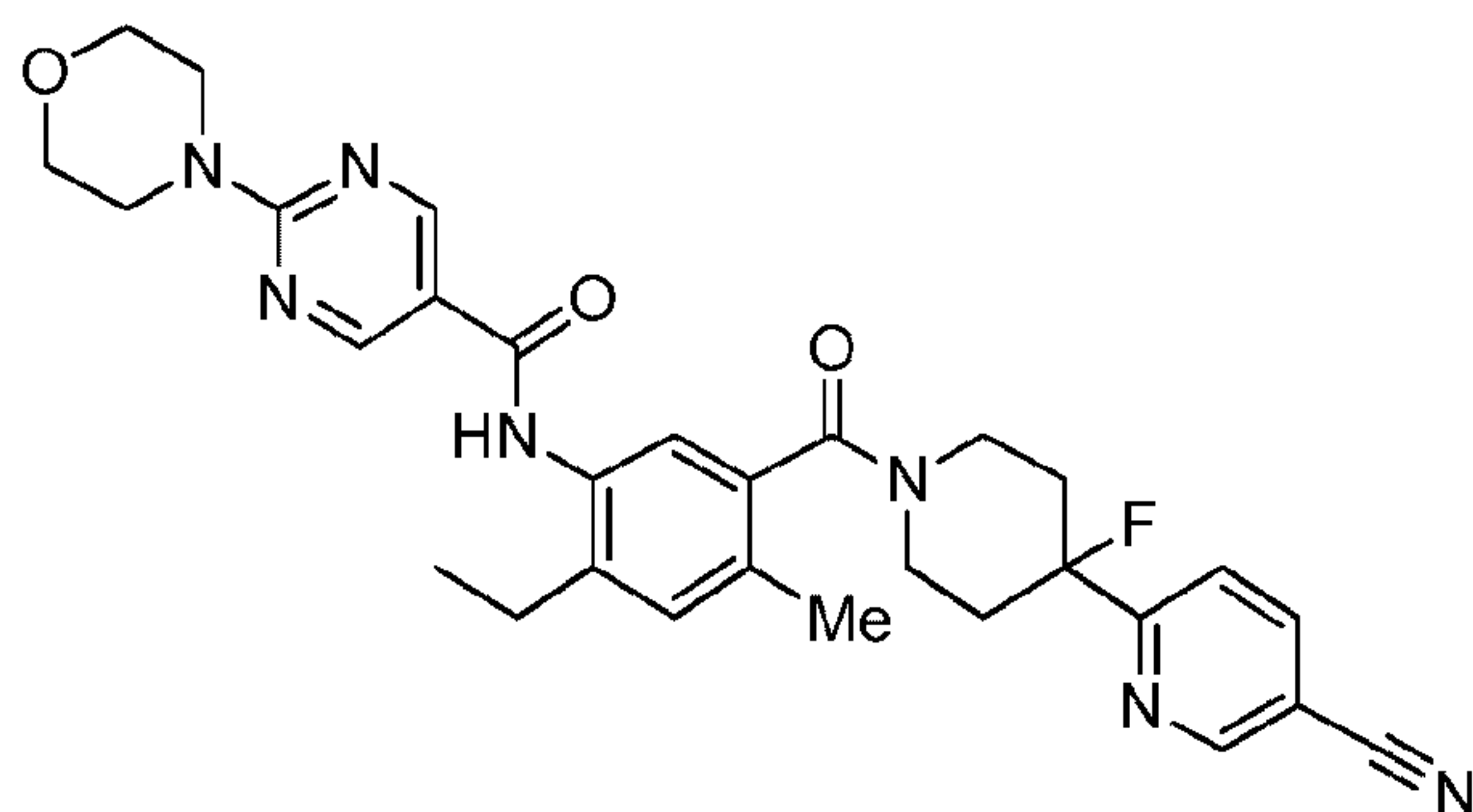
[0596] Compound 58. N-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2-ethyl-4-methylphenyl)-6-morpholinonicotinamide. The title compound was synthesized using readily available reagents and procedures similar to those described for compound 43. m/z (ES+) 556 (M+H)⁺.



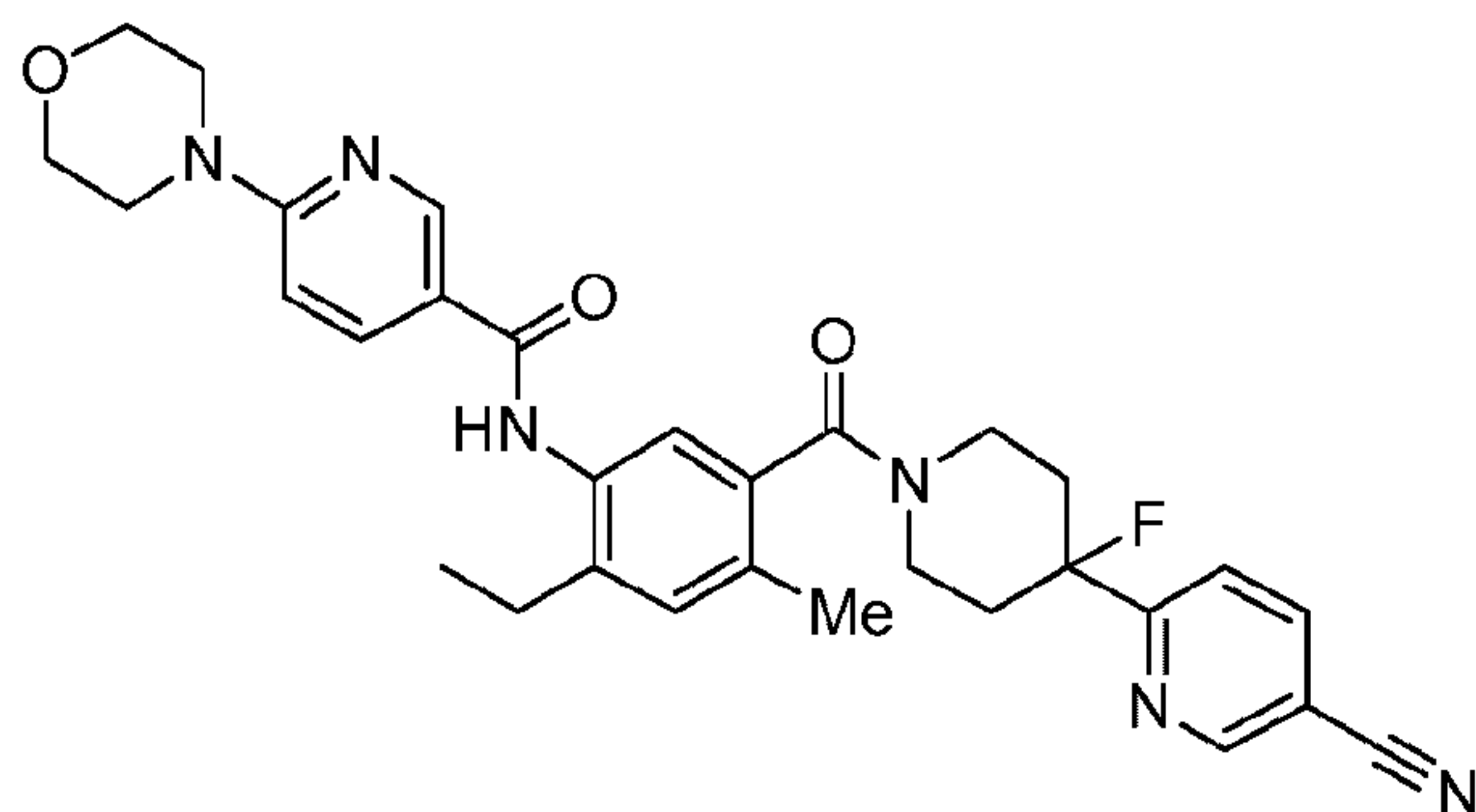
[0597] Compound 60. N-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2-ethyl-4-methylphenyl)-6-((2-methoxyethyl)(methyl)amino)nicotinamide. The title compound was synthesized using readily available reagents and procedures similar to those described for compound 43. m/z (ES+) 558 (M+H)⁺.



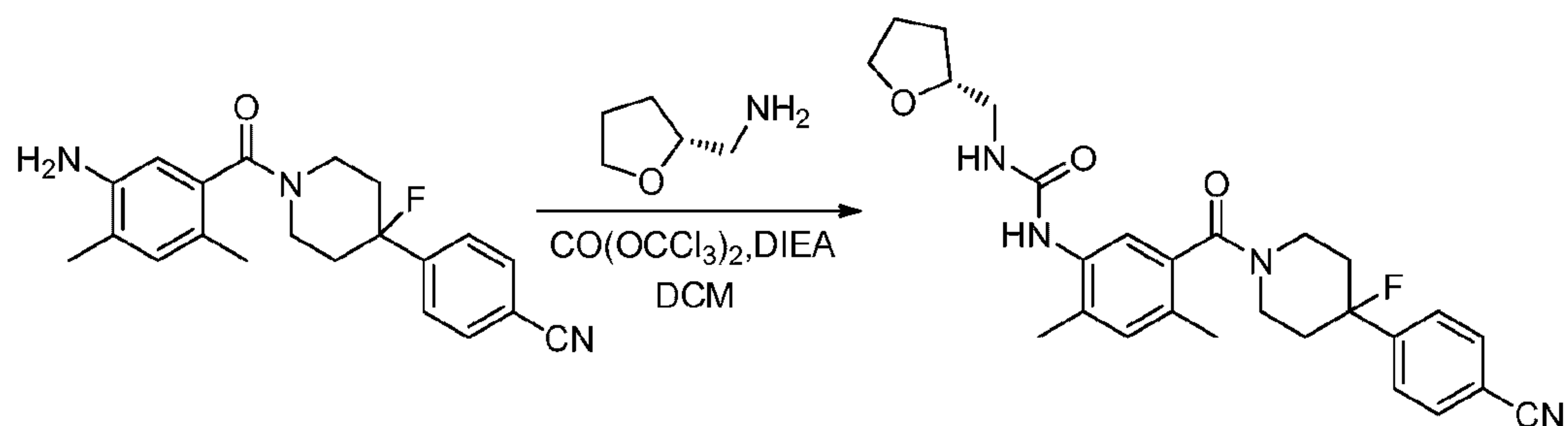
[0598] Compound 61. N-(5-(4-(5-Cyanopyridin-2-yl)-4-fluoropiperidine-1-carbonyl)-2,4-dimethylphenyl)-2-morpholinopyrimidine-5-carboxamide. The title compound was synthesized using readily available reagents and procedures similar to those described for compound 47. m/z (ES+) 544 (M+H)⁺.



[0599] Compound 62. N-(5-(4-(5-Cyanopyridin-2-yl)-4-fluoropiperidine-1-carbonyl)-2-ethyl-4-methylphenyl)-2-morpholinopyrimidine-5-carboxamide. The title compound was synthesized using readily available reagents and procedures similar to those described for compound 47. m/z (ES⁺) 558 (M+H)⁺.

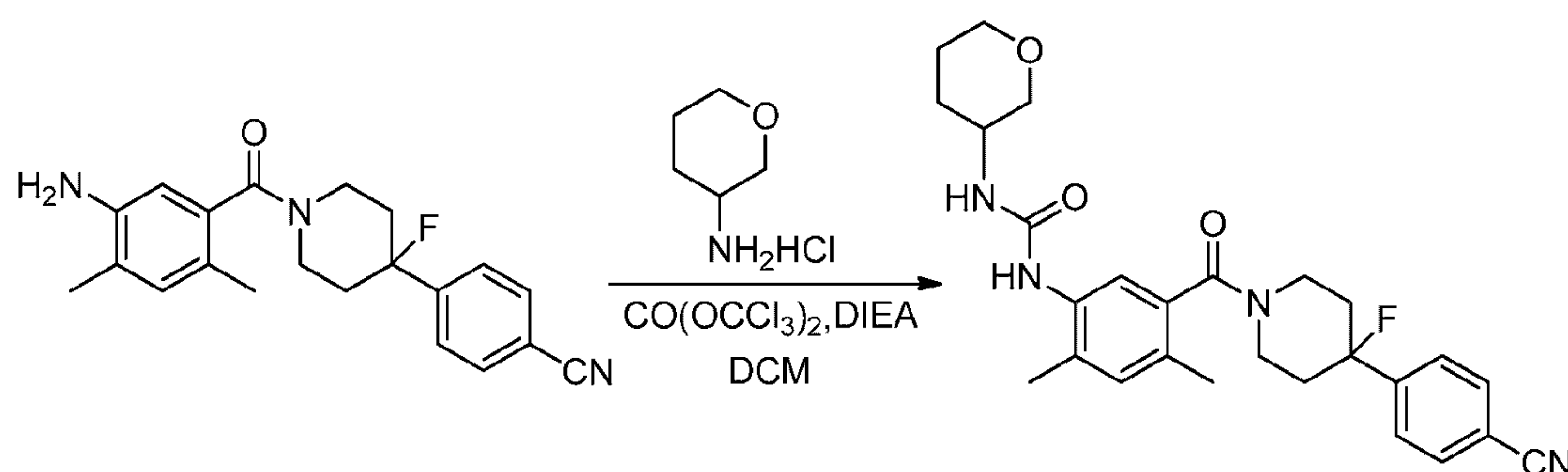


[0600] Compound 63. N-(5-(4-(5-Cyanopyridin-2-yl)-4-fluoropiperidine-1-carbonyl)-2-ethyl-4-methylphenyl)-6-morpholinonicotinamide. The title compound was synthesized using readily available reagents and procedures similar to those described for compound 47. m/z (ES⁺) 557 (M+H)⁺.

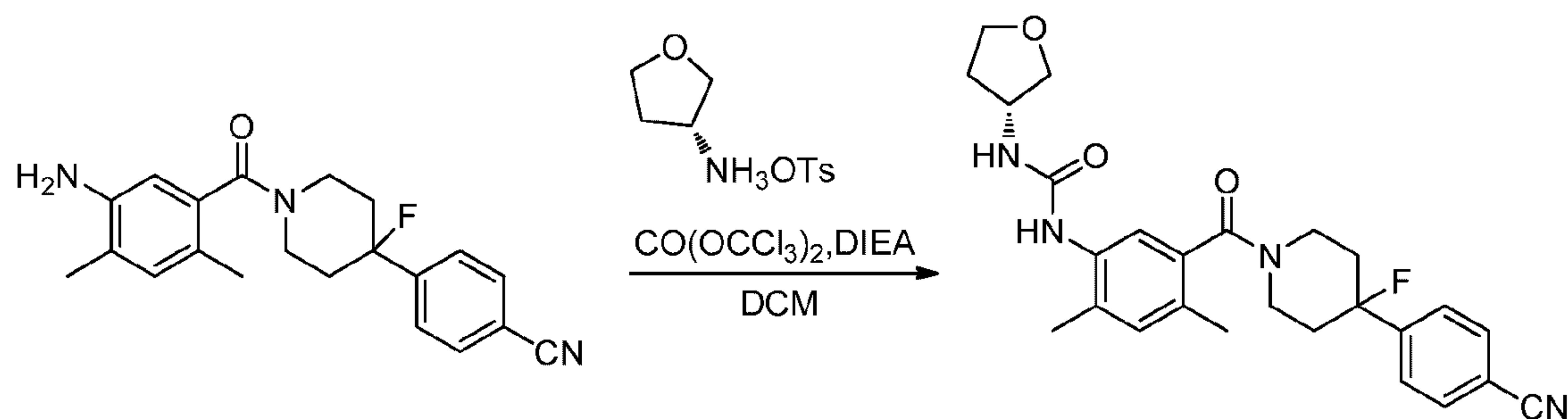


[0601] Compound 64. (R)-1-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2,4-dimethylphenyl)-3-((tetrahydrofuran-2-yl)methyl)urea. A mixture of 4-(1-(5-amino-2,4-dimethylbenzoyl)-4-fluoropiperidin-4-yl)benzonitrile (compound 42.2, 150 mg, 0.43 mmol, 1.00 equiv), DIEA (560 mg, 4.33 mmol, 10.15 equiv), and CO(OCCl₃)₂ (160 mg, 0.54 mmol, 1.26 equiv) in DCM (50 mL) was stirred under nitrogen at room temperature. After 0.5 h, (R)-(tetrahydrofuran-2-yl)methanamine (52 mg, 0.51 mmol, 1.20 equiv) was added. After stirring for 2 h at room temperature, the mixture was washed with 2x50 mL of

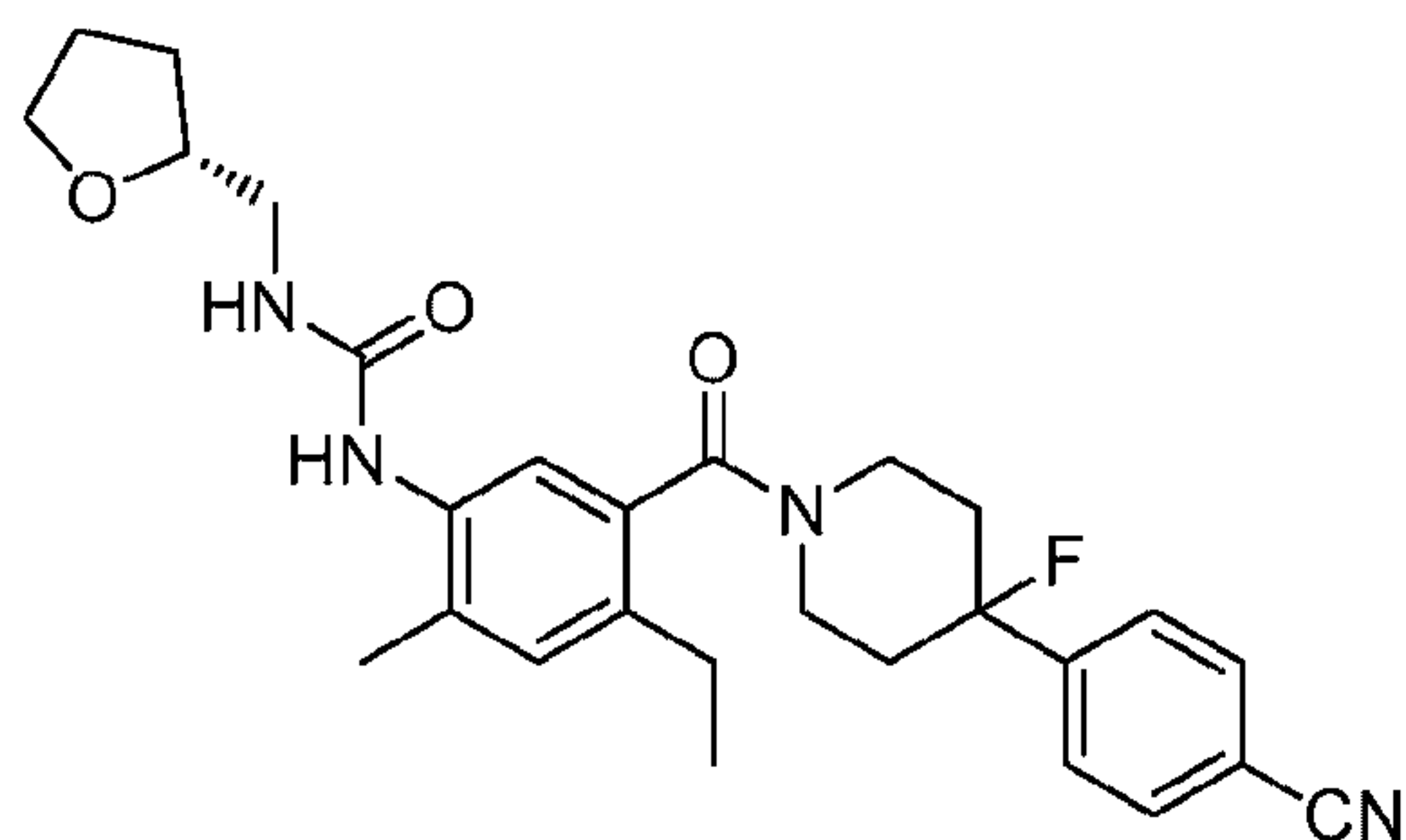
water and 1x50 mL of brine. The organic phase was concentrated under reduced pressure and the residue (~200 mg) was purified by prep-HPLC with the following conditions (1#-Pre-HPLC-006(Waters)): Column, SunFire Prep C18, 19*150mm 5um; mobile phase, WATER WITH 0.05%TFA and CH₃CN (hold 5.0% CH₃CN in 2 min, up to 35.0% in 1 min, up to 65.0% in 12 min, up to 100.0% in 1 min); Detector, UV 254/220nm. The fractions containing pure compound were combined and lyophilized to yield 110 mg (54%) of the title compound as a light yellow solid. *m/z* (ES⁺) 479 (M+H)⁺. ¹H NMR (300 MHz, DMSO, ppm): δ 7.91 (d, *J* = 8.1 Hz, 2H), 7.77-7.69 (m, 4H), 7.04 (s, 1H), 6.68 (s, 1H), 4.64 (m, 1H), 3.89-3.82 (m, 2H), 3.71 (m, 1H), 3.33-3.23 (m, 3H), 3.11-3.09 (m, 2H), 2.18-2.03 (m, 8H), 1.97-1.84 (m, 4H), 1.57 (m, 1H).



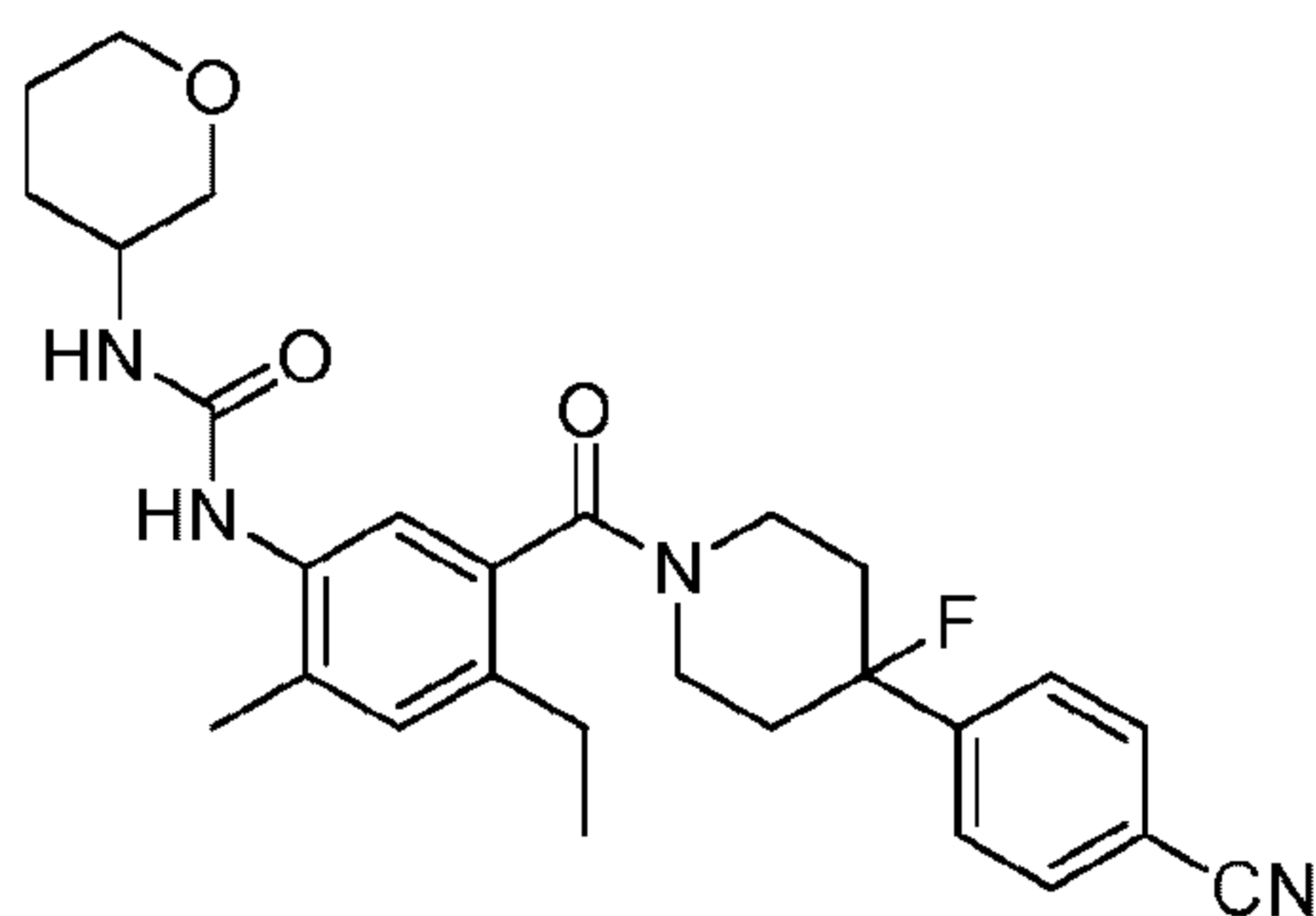
[0602] Compound 65. 1-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2,4-dimethylphenyl)-3-(tetrahydro-2H-pyran-3-yl)urea. The title compound was synthesized in a similar manner to that described for compound 64 to yield a yellow solid (111 mg, 53%). *m/z* (ES⁺) 479 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.78-7.50 (m, 3H), 7.13 (s, 1H), 4.88-4.72 (m, 1H), 3.94-3.82 (m, 1H), 3.82-3.68 (m, 2H), 3.68-3.33 (m, 3H), 3.33-3.19 (m, 2H), 2.42-2.08 (m, 8H), 2.08-1.74 (m, 4H), 1.74-1.54 (m, 2H).



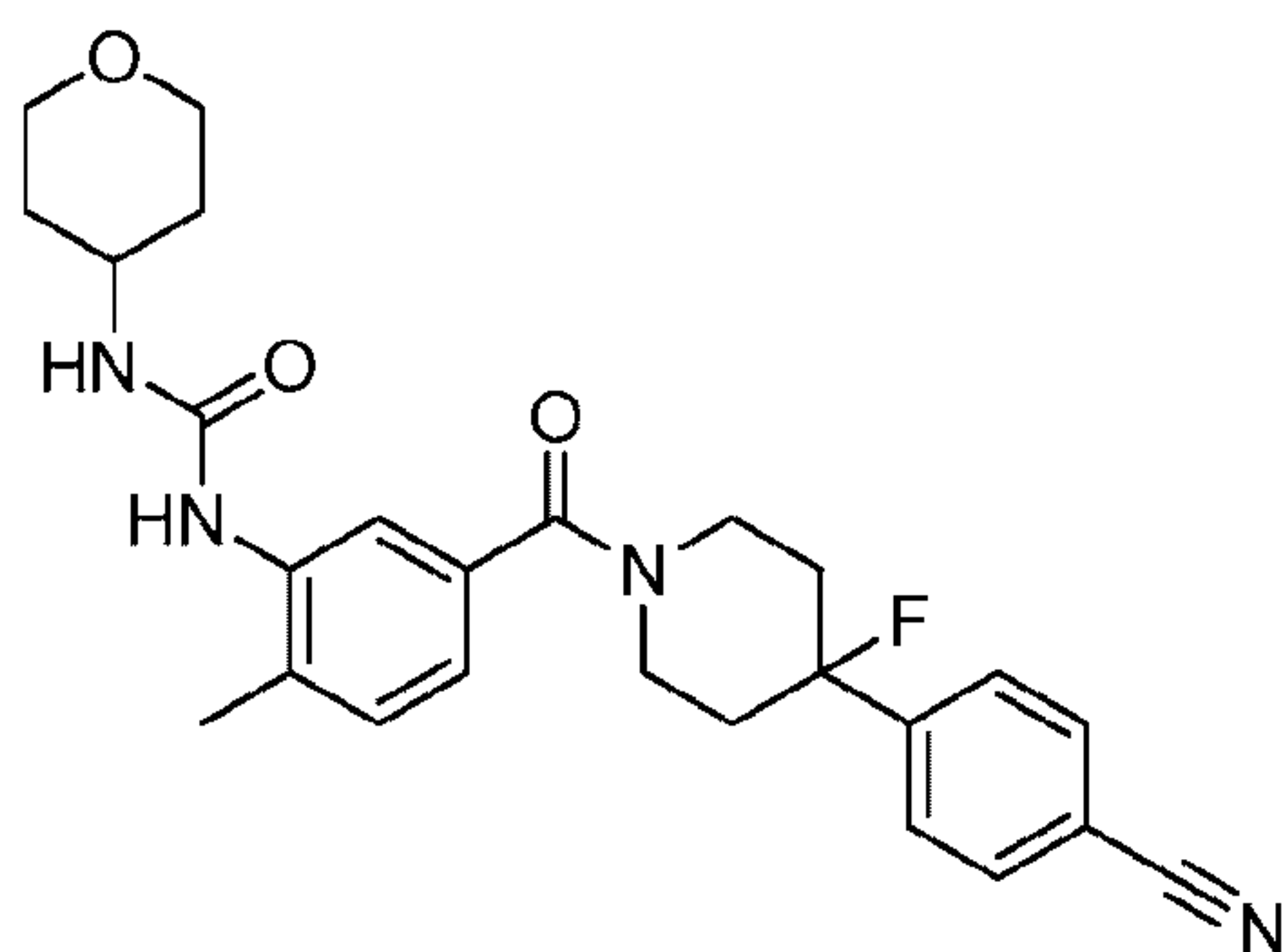
[0603] Compound 66. (R)-1-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2,4-dimethylphenyl)-3-(tetrahydrofuran-3-yl)urea. The title compound was synthesized in a similar manner to that described for compound 64 to yield a light yellow solid (105 mg, 53%). *m/z* (ES⁺) 465 (M+H)⁺.



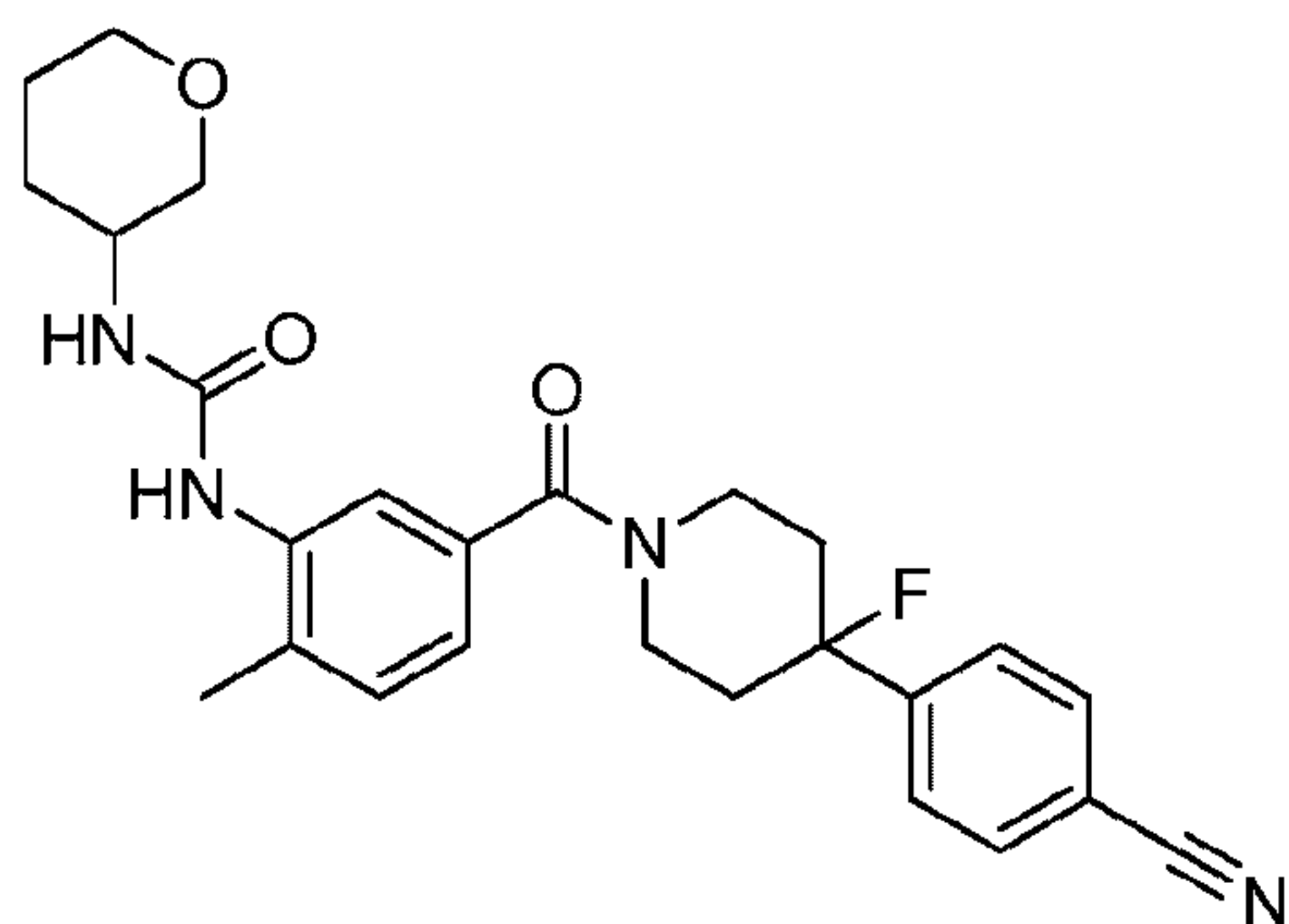
[0604] Compound 67. (R)-1-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-4-ethyl-2-methylphenyl)-3-((tetrahydrofuran-2-yl)methyl)urea. The title compound was synthesized in a similar manner to that described for compound 64 but using compound 48.5 in place of compound 42.2. m/z (ES+) 493 (M+H)⁺.



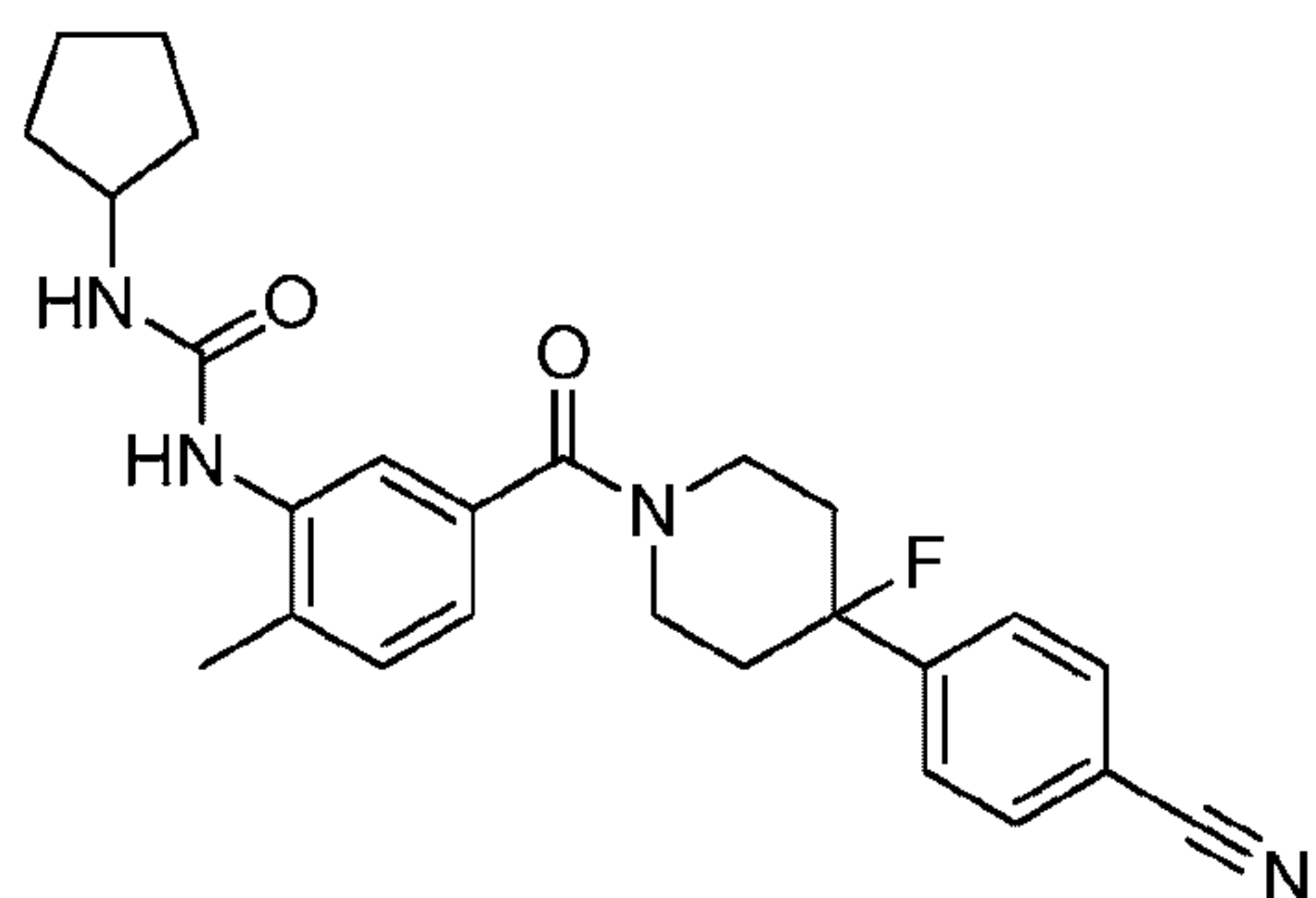
[0605] Compound 68. 1-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-4-ethyl-2-methylphenyl)-3-(tetrahydro-2H-pyran-3-yl)urea. The title compound was synthesized in a similar manner to that described for compound 64 but using compound 48.5 in place of compound 42.2. m/z (ES+) 493 (M+H)⁺.



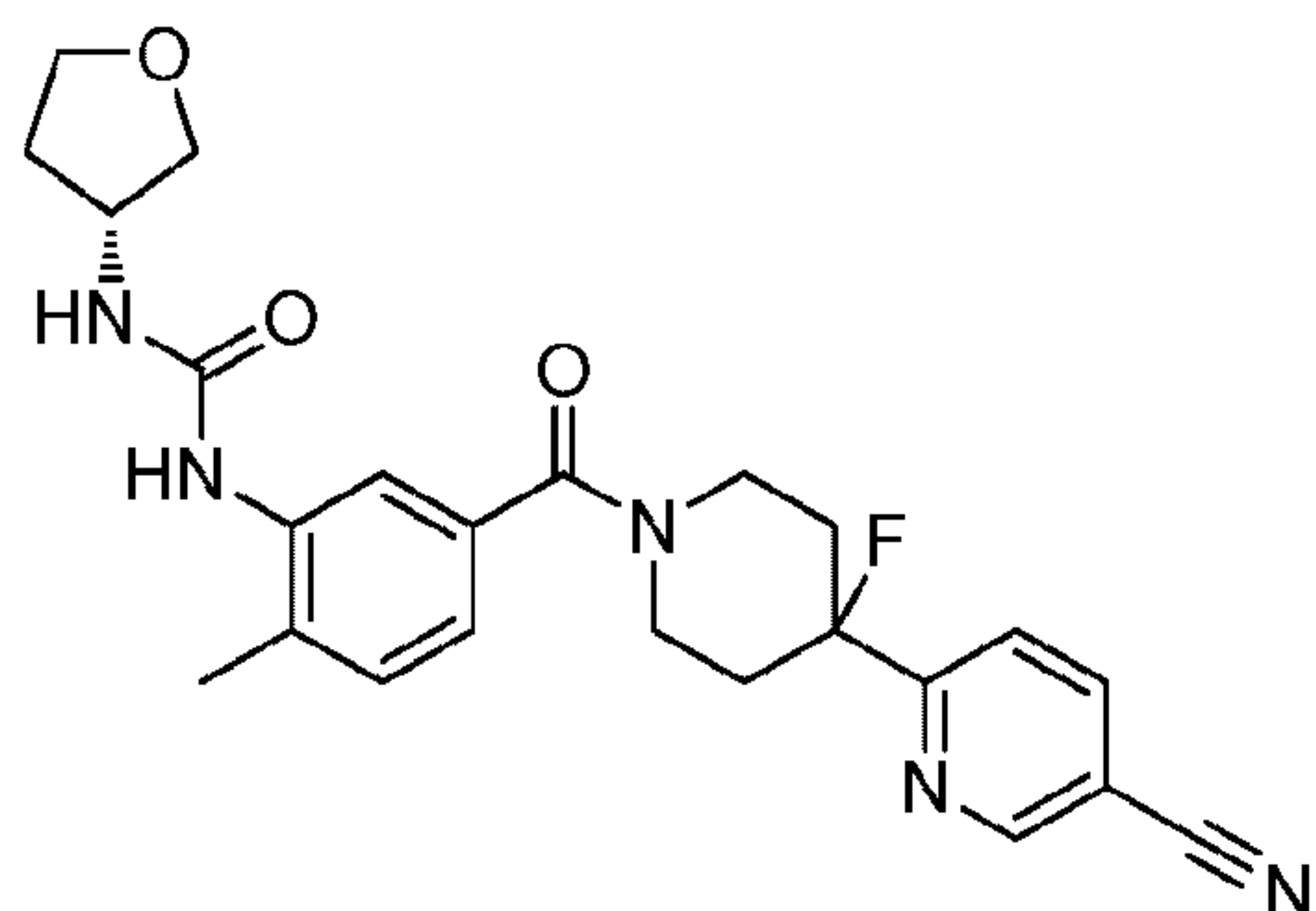
[0606] Compound 69. 1-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2-methylphenyl)-3-(tetrahydro-2H-pyran-4-yl)urea. The title compound was synthesized using readily available reagents and procedures similar to those described for compound 64. m/z (ES+) 465 (M+H)⁺.



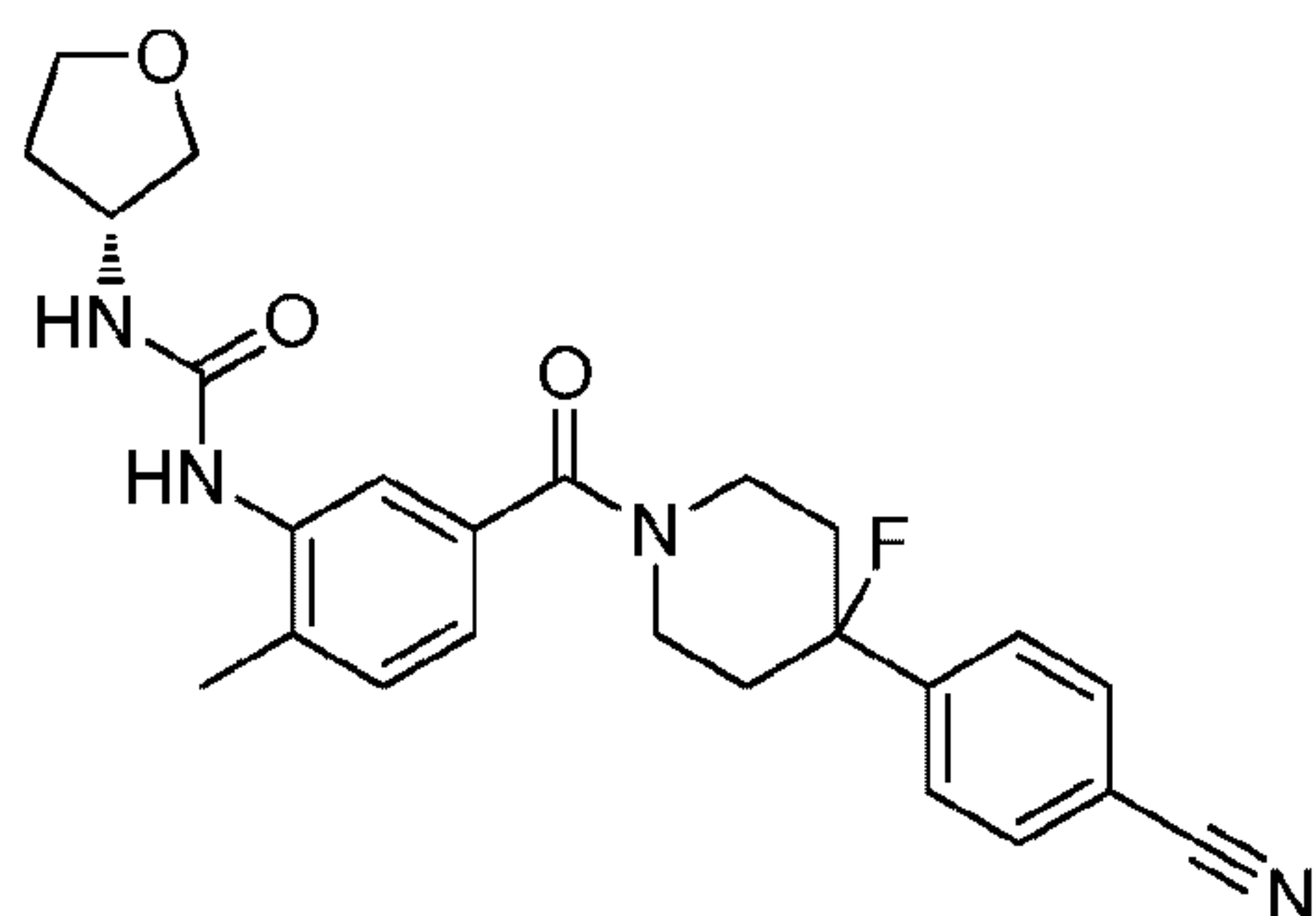
[0607] Compound 70. 1-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2-methylphenyl)-3-(tetrahydro-2H-pyran-3-yl)urea. The title compound was synthesized using readily available reagents and procedures similar to those described for compound 64. m/z (ES⁺) 465 (M+H)⁺.



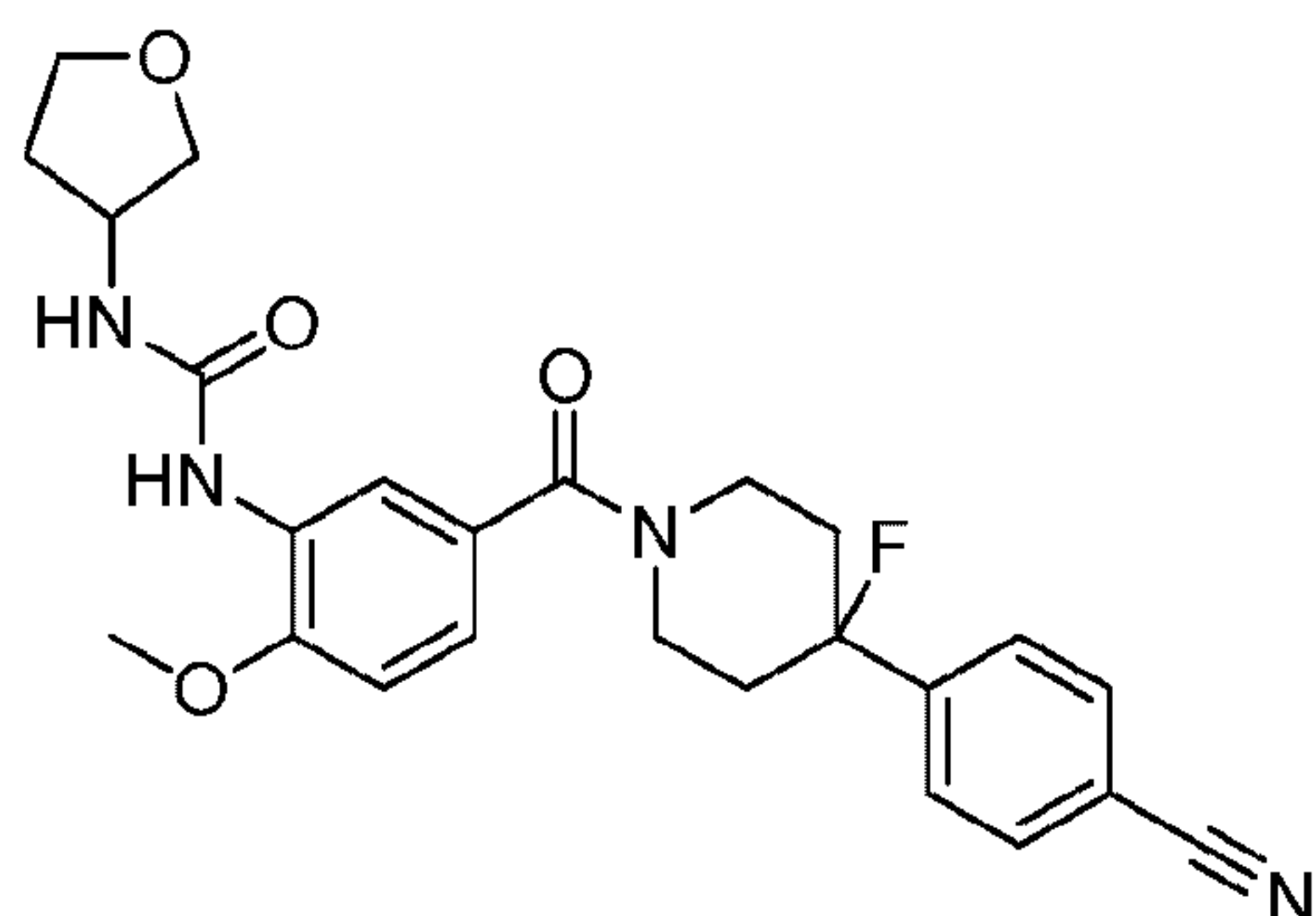
[0608] Compound 71. 1-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2-methylphenyl)-3-cyclopentylurea. The title compound was synthesized using readily available reagents and procedures similar to those described for compound 64. m/z (ES⁺) 449 (M+H)⁺.



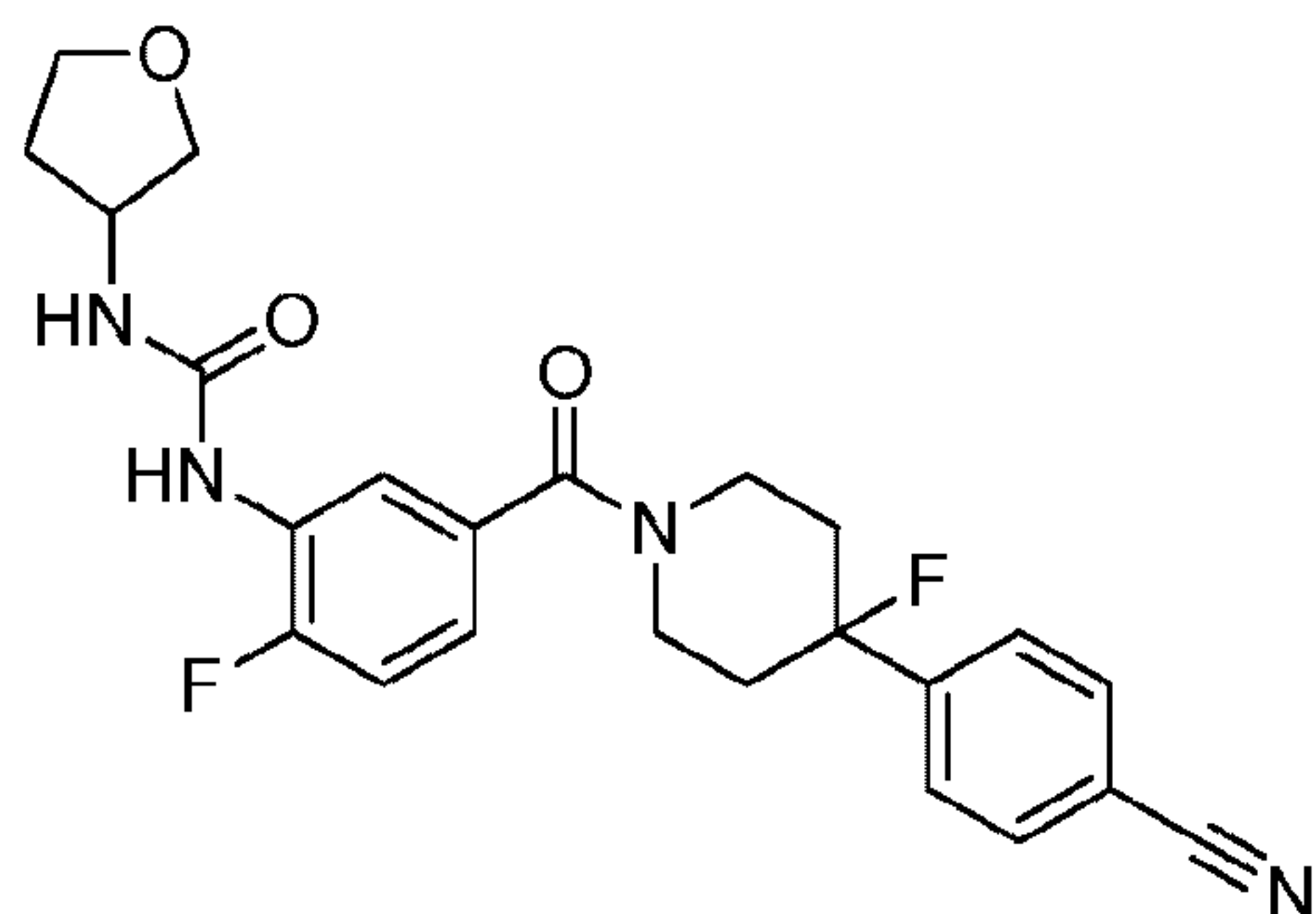
[0609] Compound 72. (R)-1-(5-(4-(5-Cyanopyridin-2-yl)-4-fluoropiperidine-1-carbonyl)-2-methylphenyl)-3-(tetrahydrofuran-3-yl)urea. The title compound was synthesized using readily available reagents and procedures similar to those described for compound 64. m/z (ES⁺) 452 (M+H)⁺.



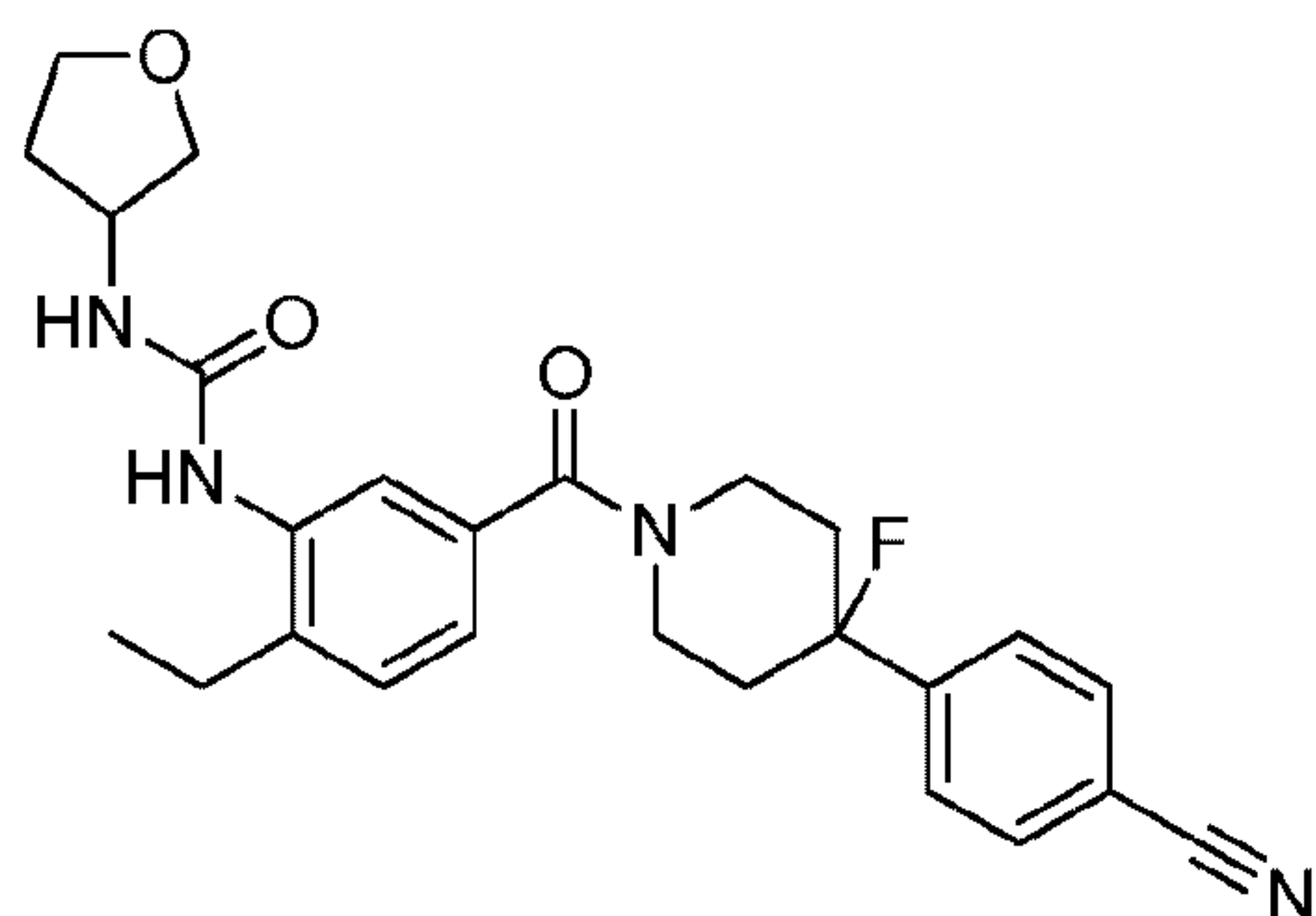
[0610] **Compound 73. (R)-1-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2-methylphenyl)-3-(tetrahydrofuran-3-yl)urea.** The title compound was synthesized using readily available reagents and procedures similar to those described for compound 64. m/z (ES+) 451 (M+H)⁺.



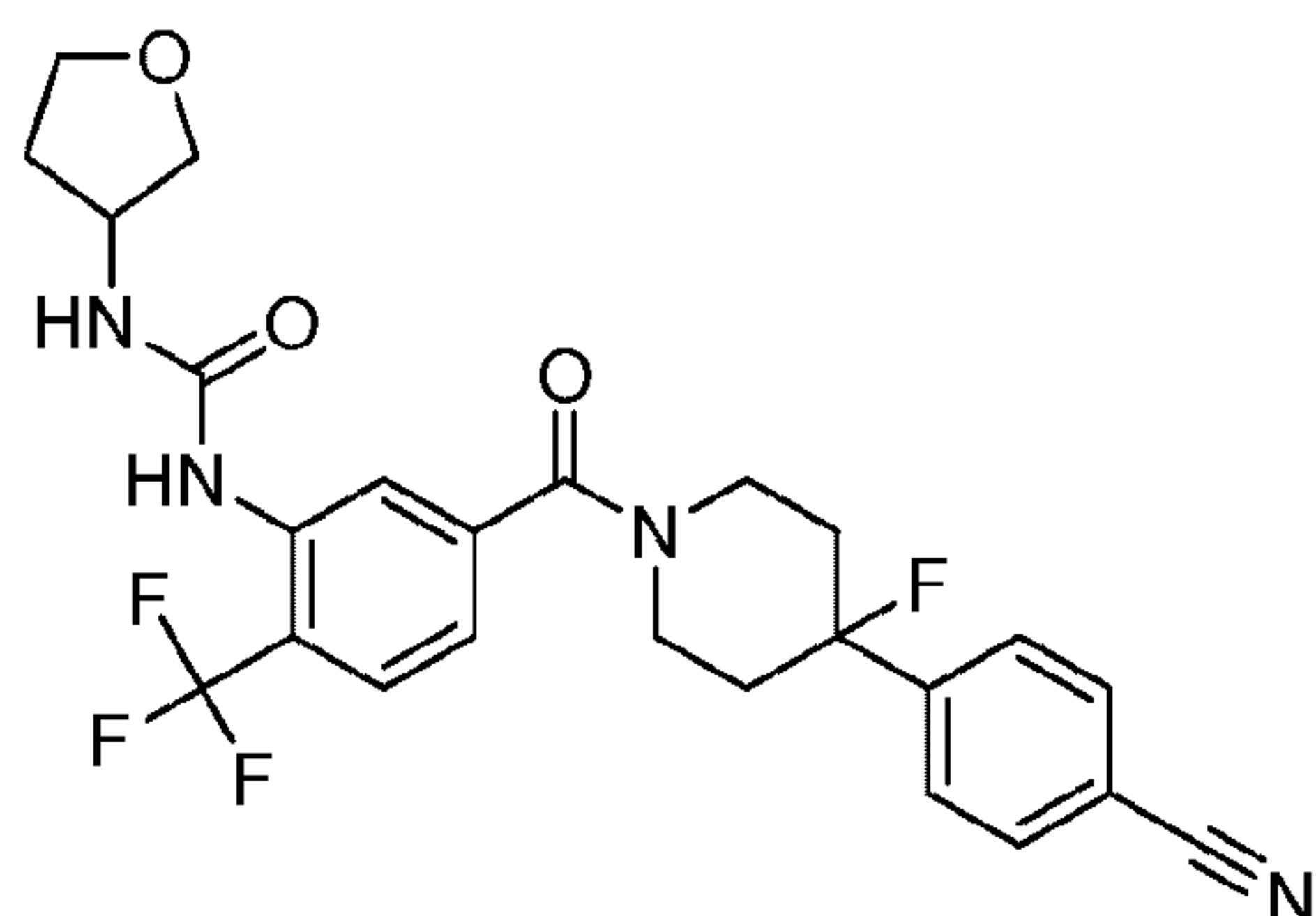
[0611] **Compound 74. 1-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2-methoxyphenyl)-3-(tetrahydrofuran-3-yl)urea.** The title compound was synthesized using readily available reagents and procedures similar to those described for compound 64. m/z (ES+) 467 (M+H)⁺.



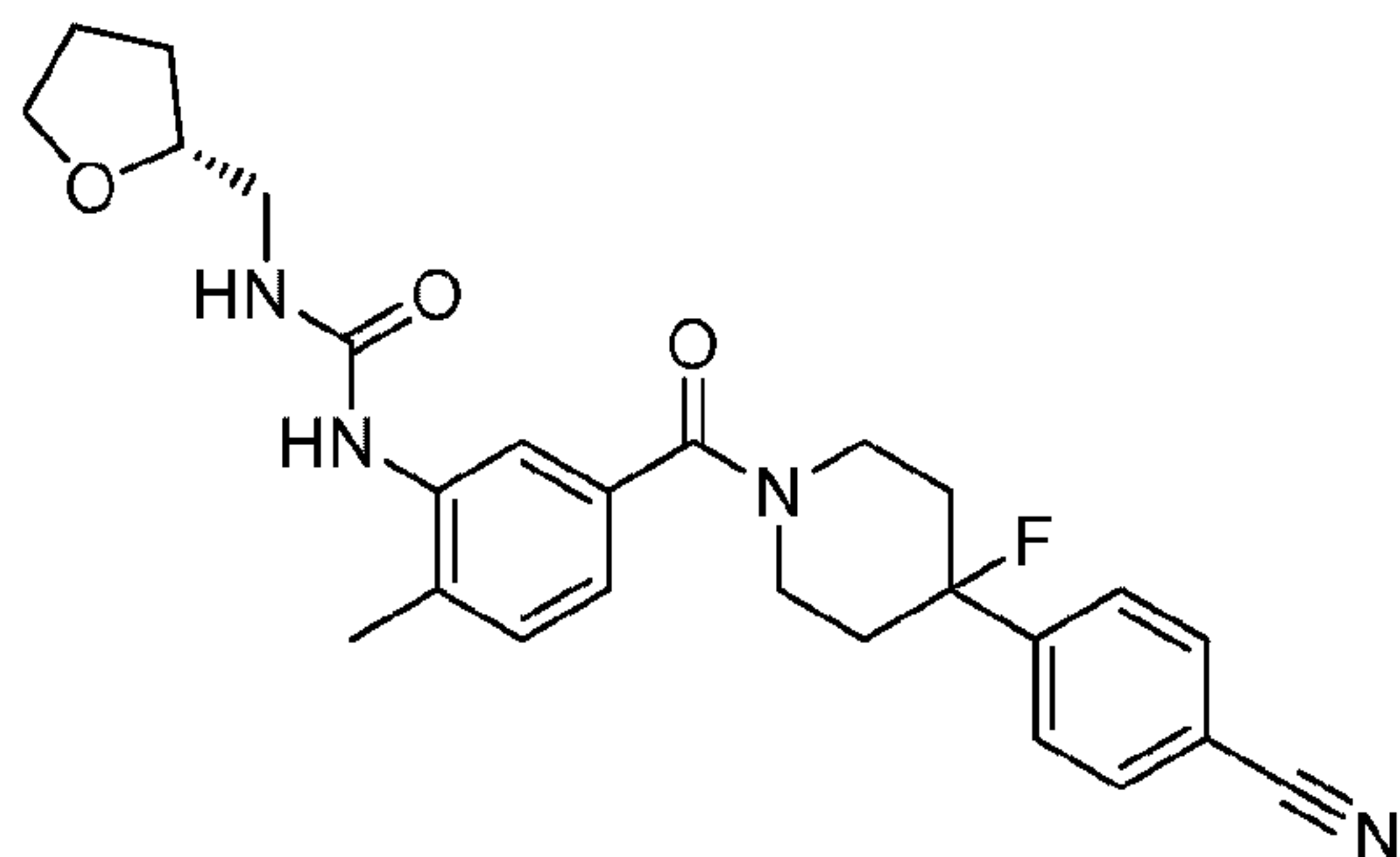
[0612] **Compound 75. 1-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2-fluorophenyl)-3-(tetrahydrofuran-3-yl)urea.** The title compound was synthesized using readily available reagents and procedures similar to those described for compound 64. m/z (ES+) 455 (M+H)⁺.



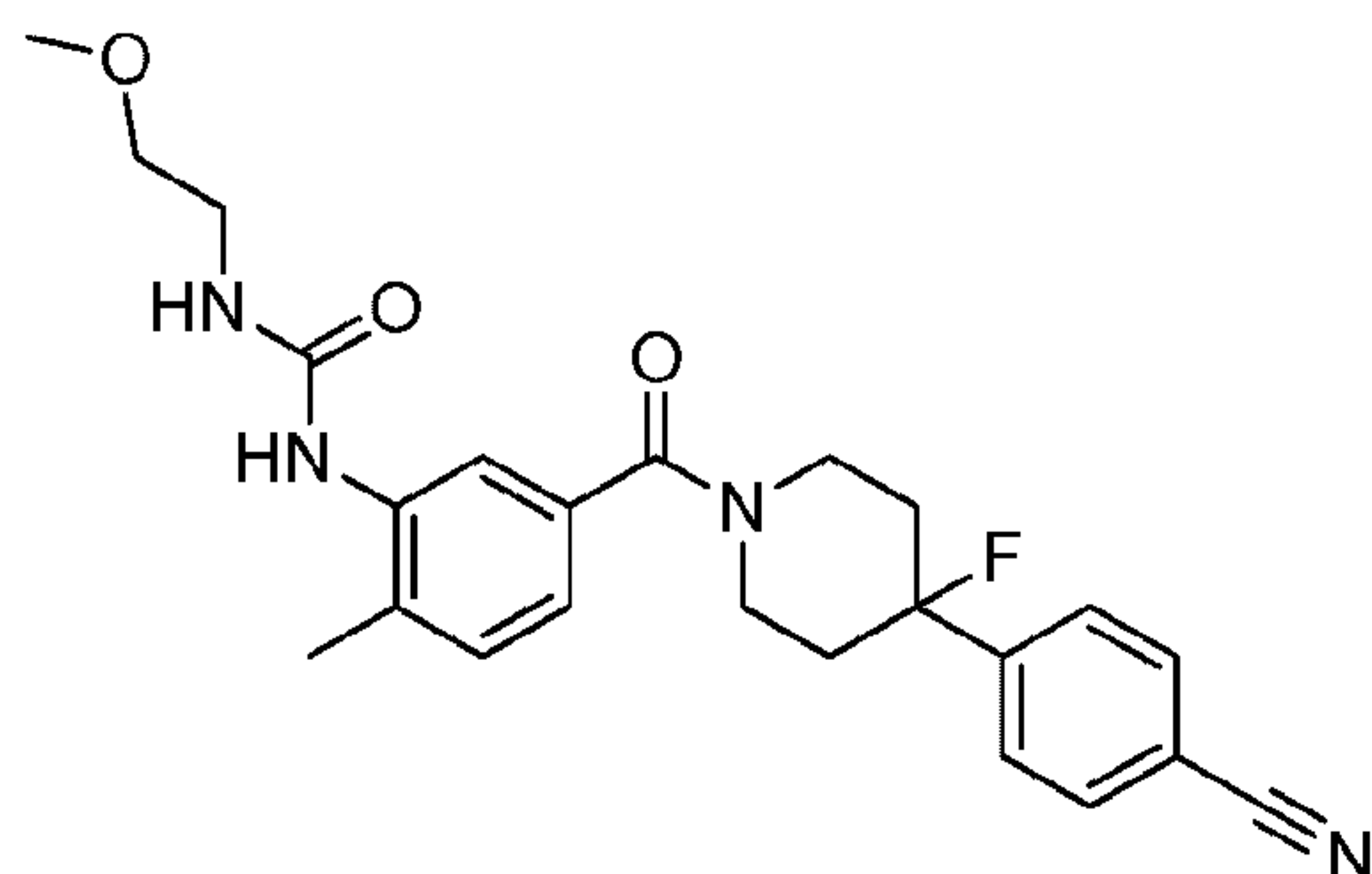
[0613] Compound 76. 1-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2-ethylphenyl)-3-(tetrahydrofuran-3-yl)urea. The title compound was synthesized using readily available reagents and procedures similar to those described for compound 64. m/z (ES+) 465 (M+H)⁺.



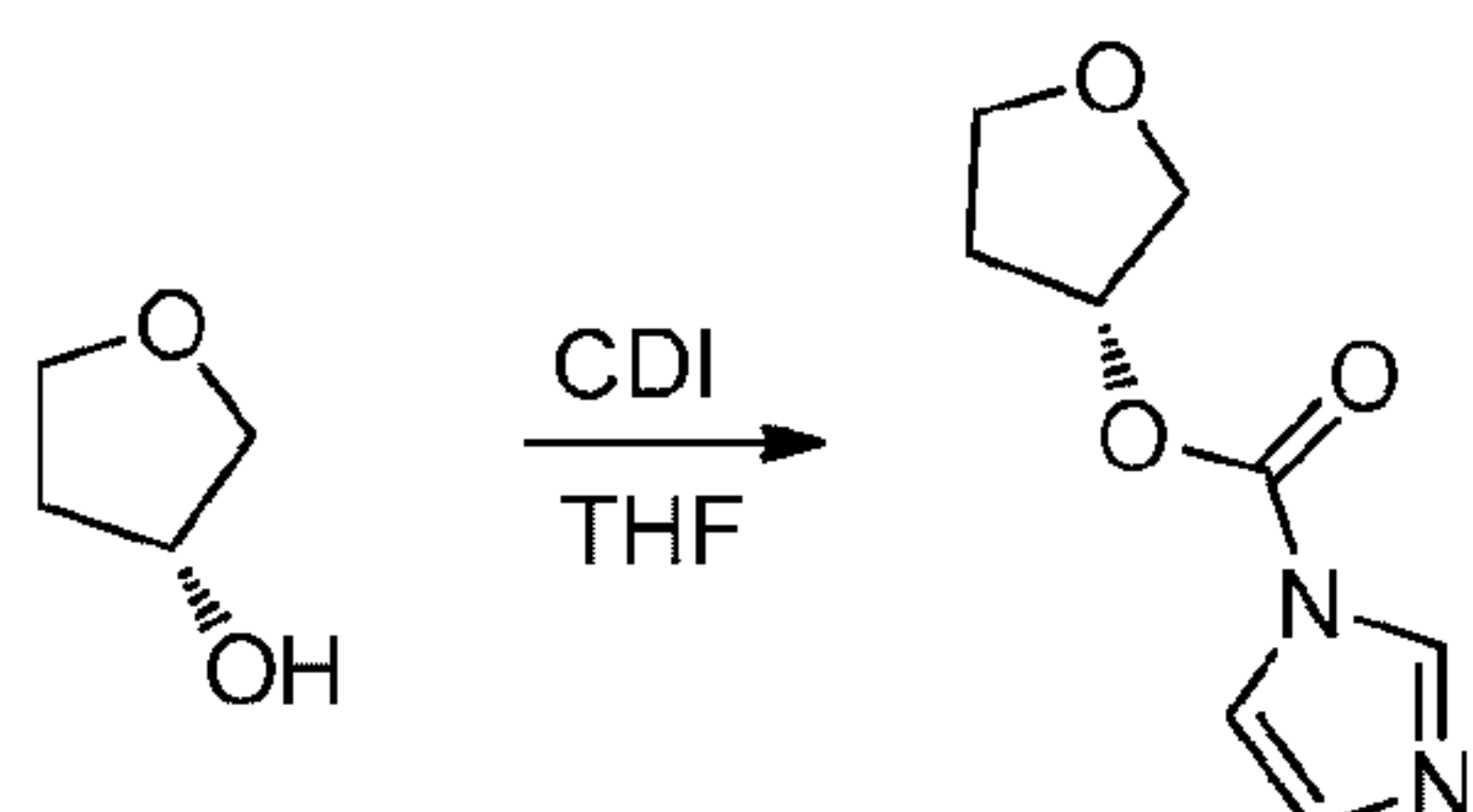
[0614] Compound 77. 1-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2-(trifluoromethyl)phenyl)-3-(tetrahydrofuran-3-yl)urea. The title compound was synthesized using readily available reagents and procedures similar to those described for compound 64. m/z (ES+) 505 (M+H)⁺.



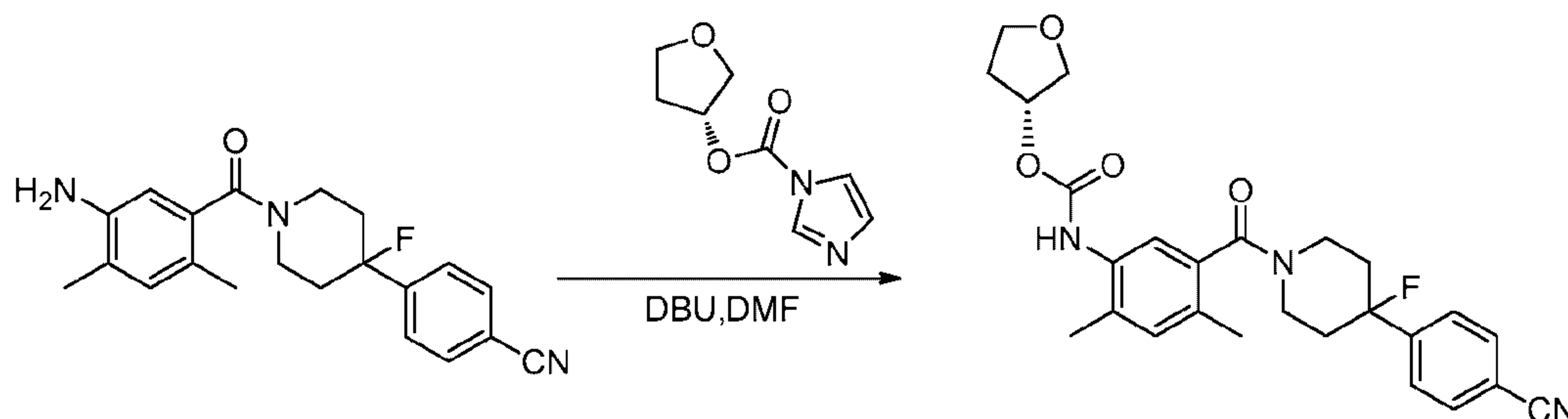
[0615] Compound 78. (R)-1-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2-methylphenyl)-3-((tetrahydrofuran-2-yl)methyl)urea. The title compound was synthesized using readily available reagents and procedures similar to those described for compound 64. m/z (ES+) 465 (M+H)⁺.



[0616] **Compound 79. 1-(5-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2-methylphenyl)-3-(2-methoxyethyl)urea.** The title compound was synthesized using readily available reagents and procedures similar to those described for compound **64**. m/z (ES⁺) 439 (M+H)⁺.

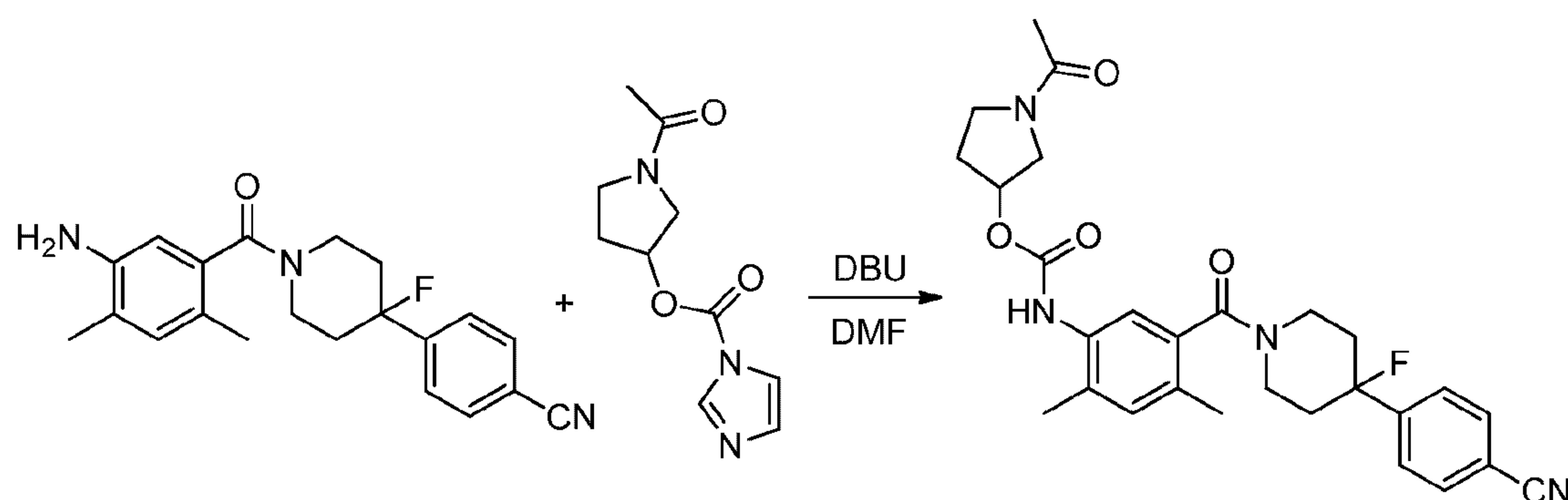


[0617] **Compound 80.1. (R)-Tetrahydrofuran-3-yl 1H-imidazole-1-carboxylate.** A solution of (R)-tetrahydrofuran-3-ol (500 mg, 5.68 mmol, 1.00 equiv) and CDI (2 g, 12.33 mmol, 2.17 equiv) in tetrahydrofuran (50 mL) was stirred overnight under nitrogen at 60°C. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was dissolved in 30 mL of DCM and washed with 1x50 mL of H₂O. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The crude residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:1) to yield 0.95 g (92%) of the title compound as a white solid.

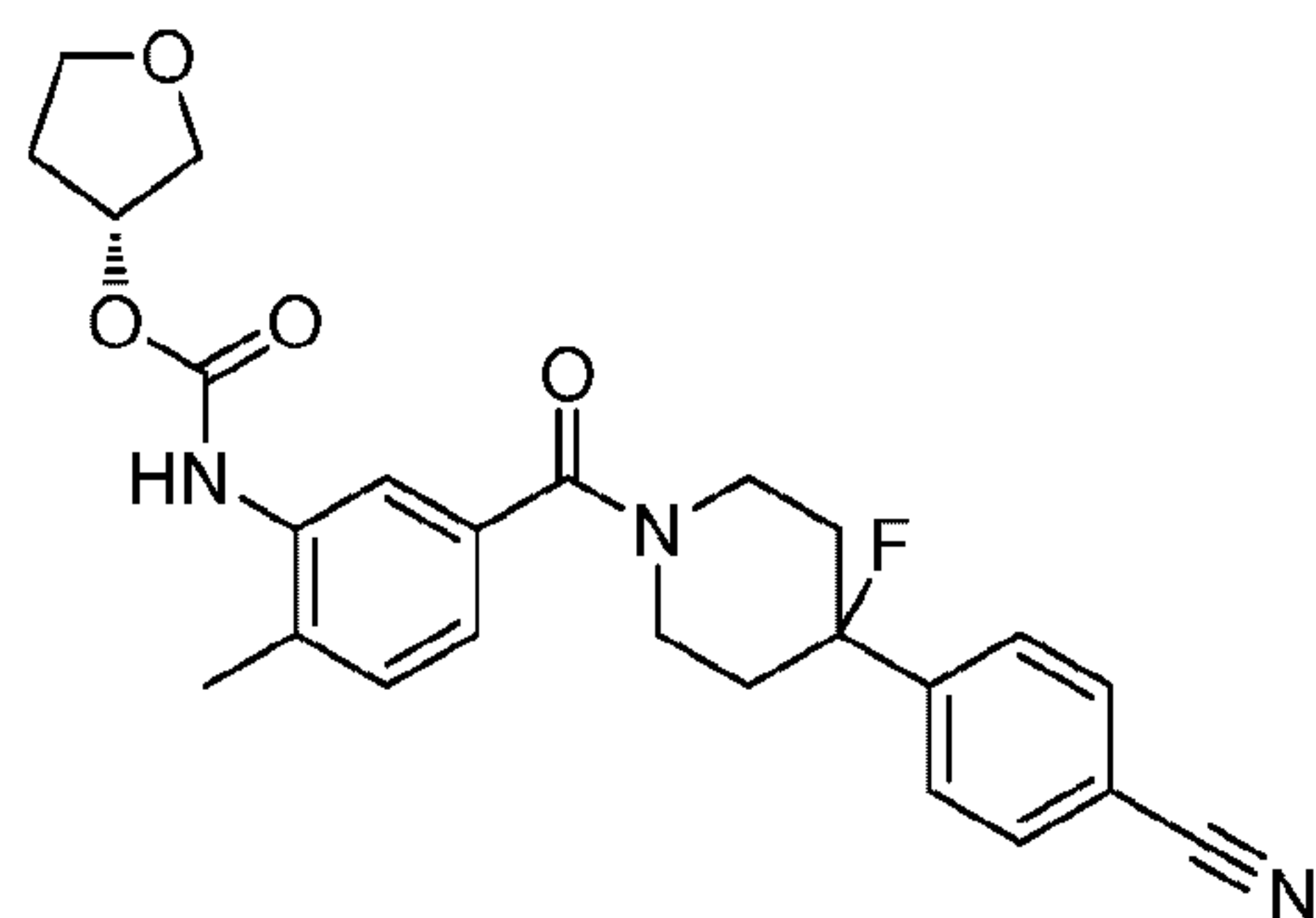


[0618] **Compound 80. (R)-Tetrahydrofuran-3-yl (5-(4-(4-cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2,4-dimethylphenyl)carbamate.** A mixture of compound **42.2** (200 mg, 0.57 mmol, 1.00 equiv), (R)-tetrahydrofuran-3-yl 1H-imidazole-1-carboxylate (**80.1**, 124 mg, 0.68 mmol, 1.20 equiv), and DBU (2.6 mg, 0.02 mmol, 0.03 equiv) in DMF (50 mL) was stirred for 16 h under nitrogen at 120°C. After cooling to ambient temperature,

the reaction was quenched by the addition of 200 mL of water. The resulting mixture was extracted with 3x100 mL of ethyl acetate. The combined organic layers were washed with 1x100 mL of brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue (200 mg) was purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-002(Agilent)): Column, SunFire Prep C18, 19*150mm 5um; mobile phase, WATER WITH 0.05%TFA and CH₃CN (40.0% CH₃CN up to 45.0% in 8 min, hold 45.0% in 2 min, up to 100.0% in 1 min, down to 40.0% in 2 min); Detector, uv 220 254nm. 47.4 mg product was obtained. The fractions containing pure compound were combined and lyophilized to yield 47.4 mg (18%) of the title compound as a white solid. *m/z* (ES⁺) 466 (M+H)⁺.

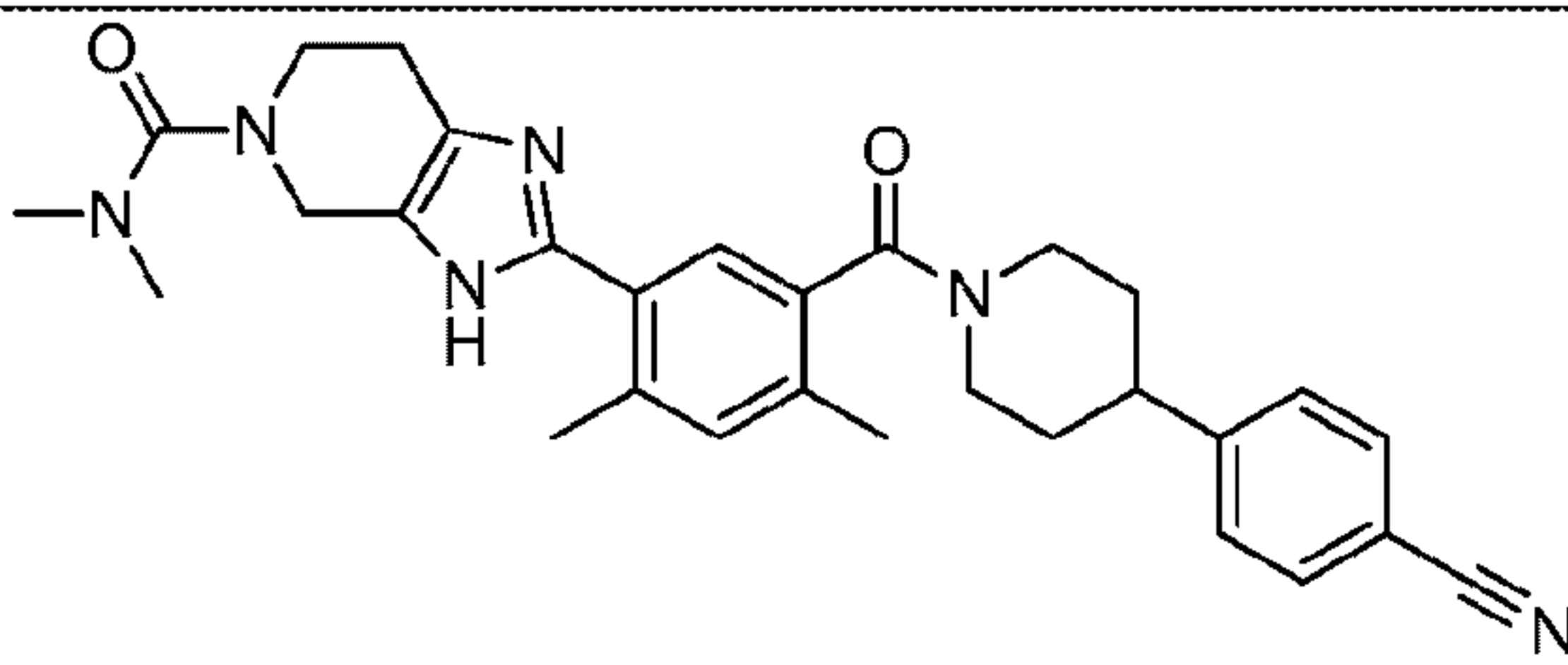
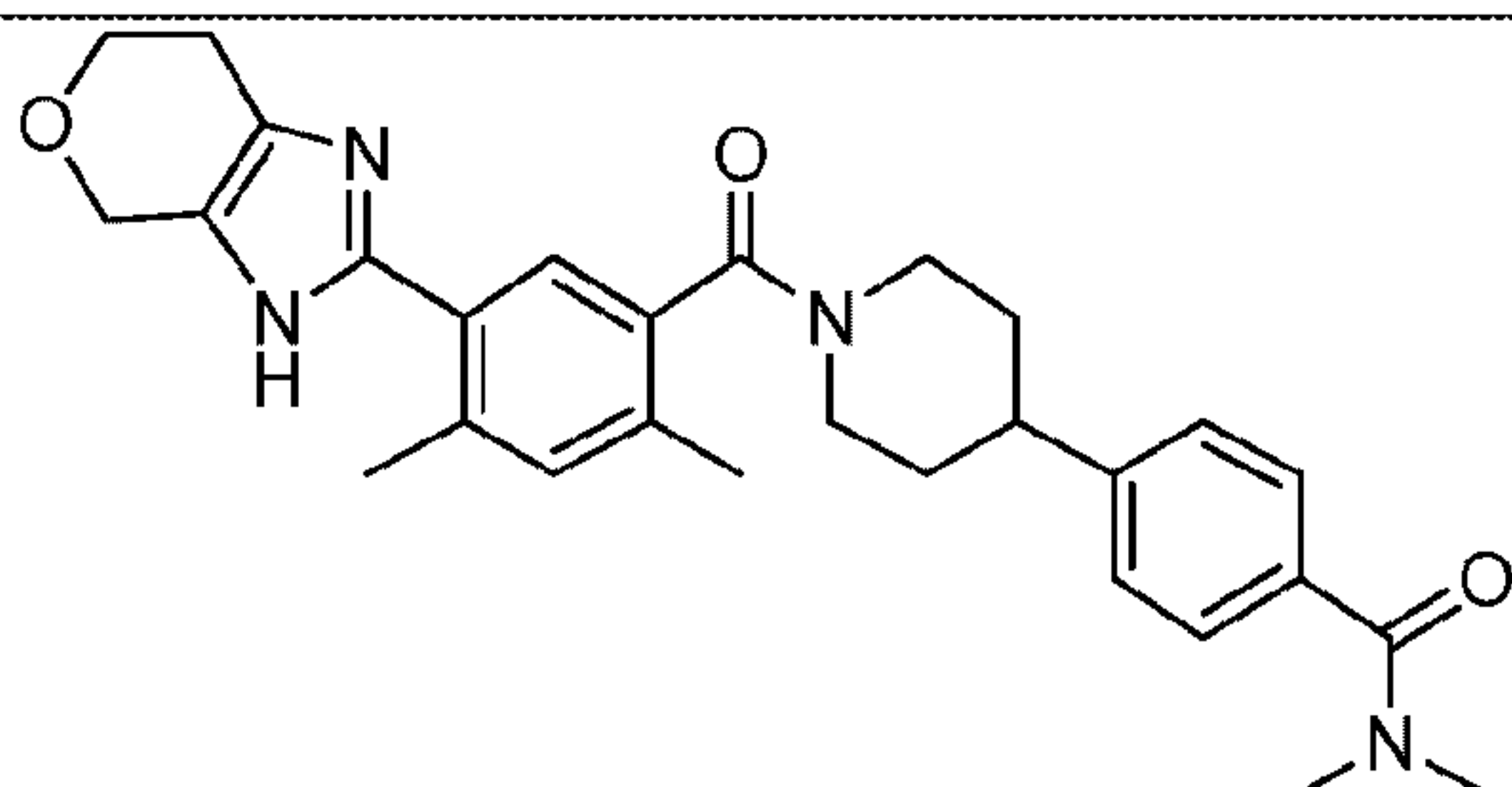
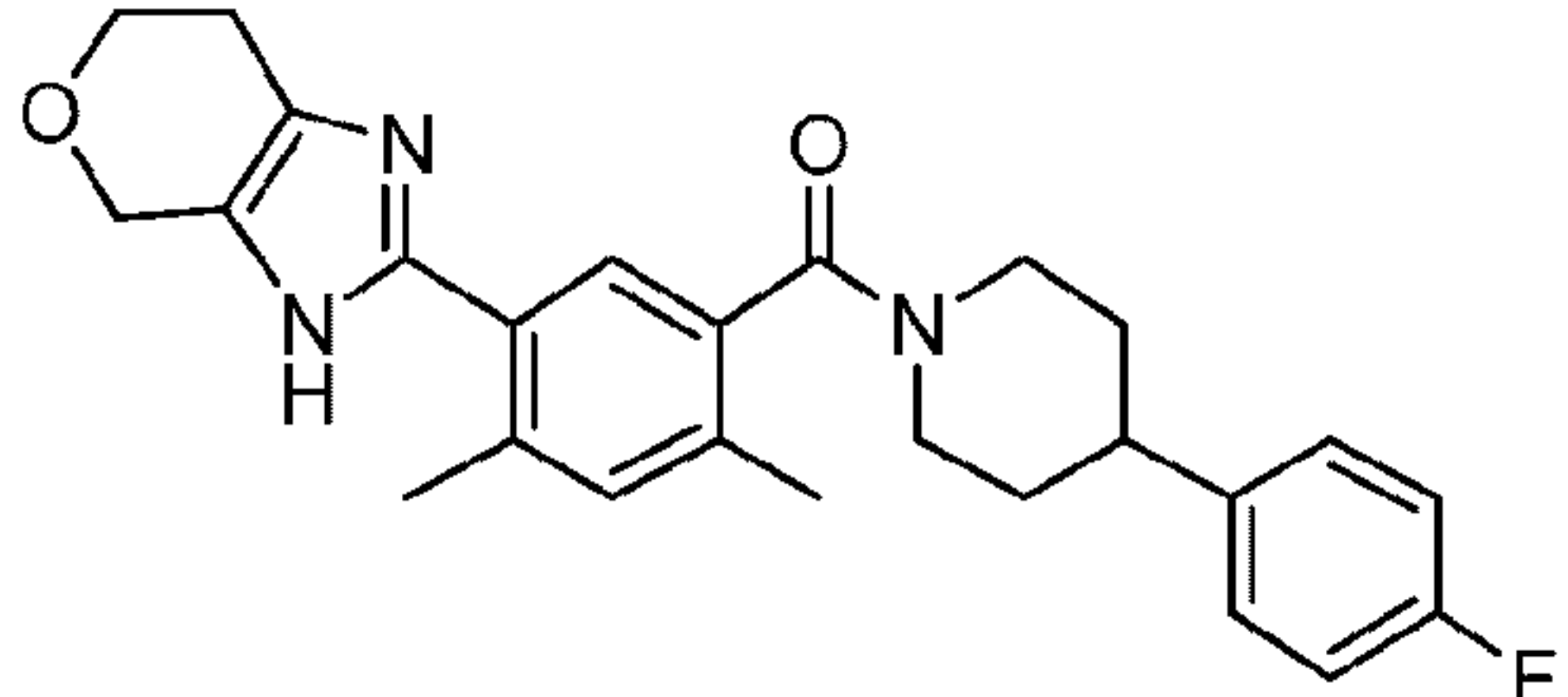
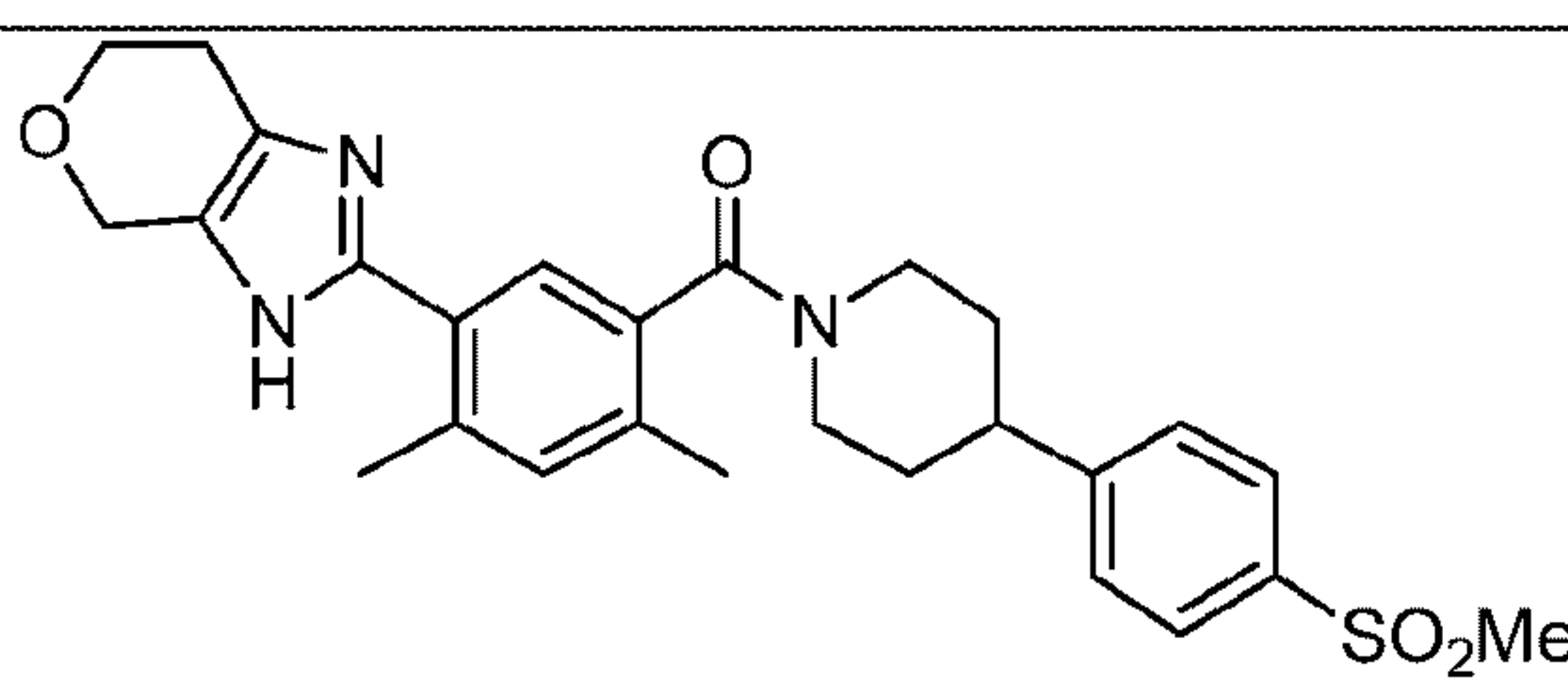
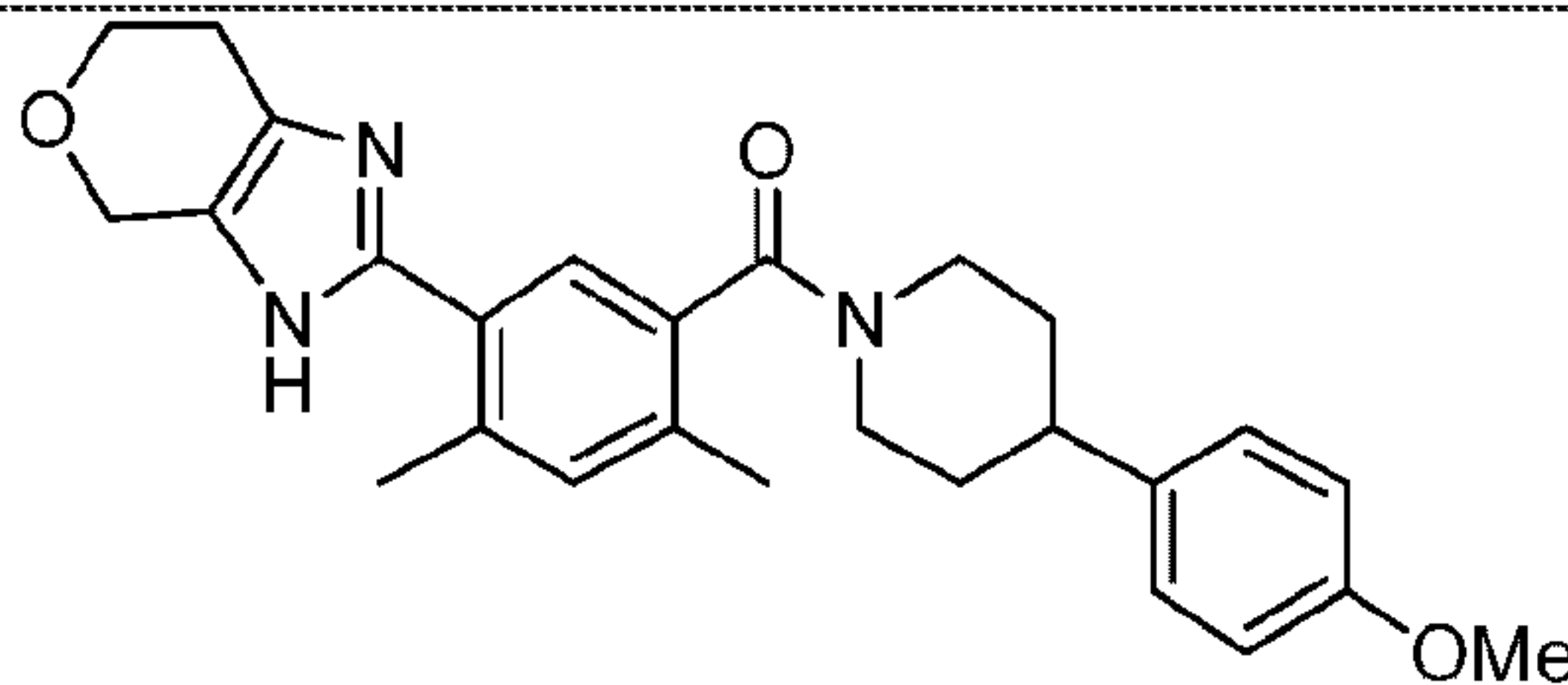


[0619] **Compound 81. 1-Acetylpyrrolidin-3-yl (5-(4-(4-cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2,4-dimethylphenyl)carbamate.** The title compound was synthesized in a similar manner to that described for compound 80 to yield a white solid (113 mg, 39%). *m/z* (ES⁺) 507 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.77-7.61 (m, 2H), 7.52 & 7.33 (2 br singlets, amide rotamers, Ar-H, 1H), 7.17 (s, 1H), 5.41-5.28 (m, 1H), 4.87-4.72 (m, 1H), 3.88-3.42 (m, 6H), 3.33-3.19 (m, 1H), 2.42-1.82 (m, 15H).

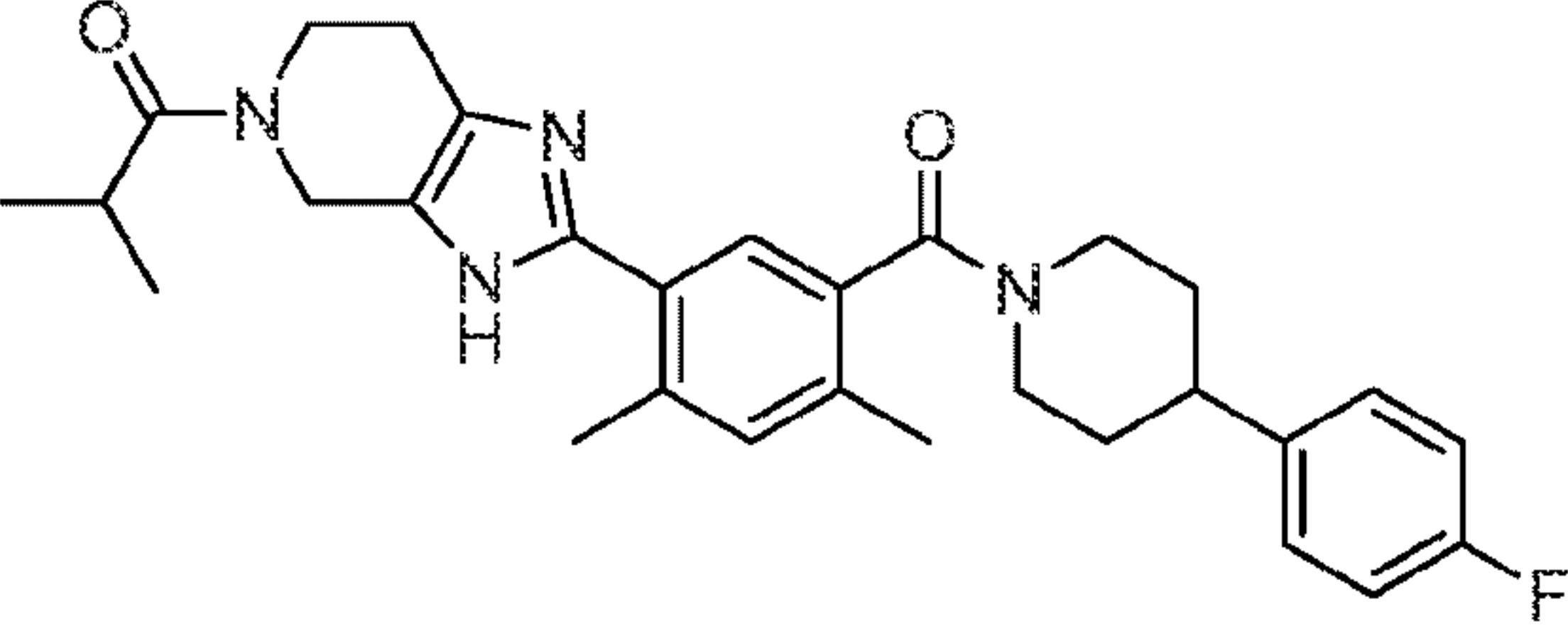
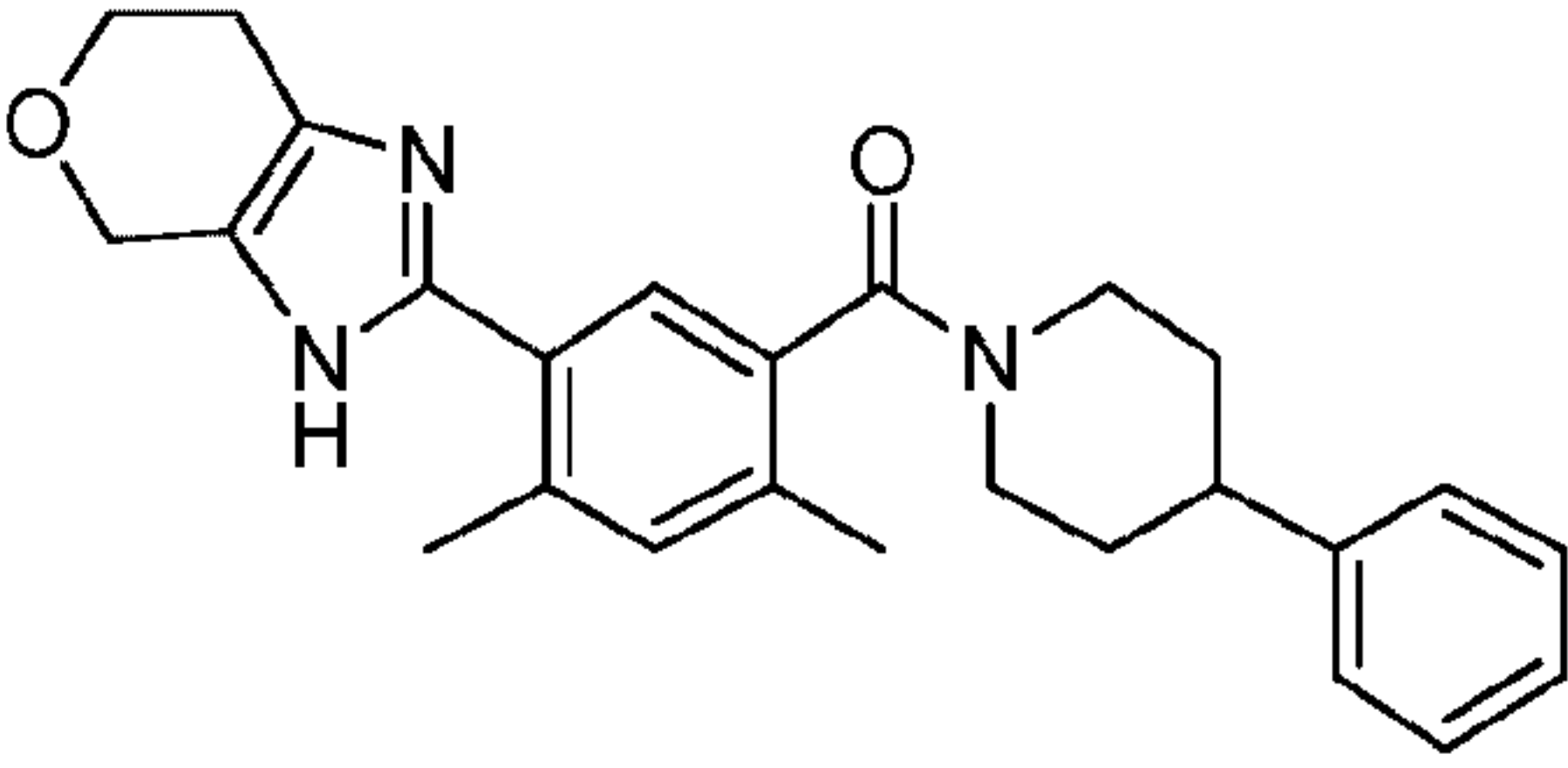
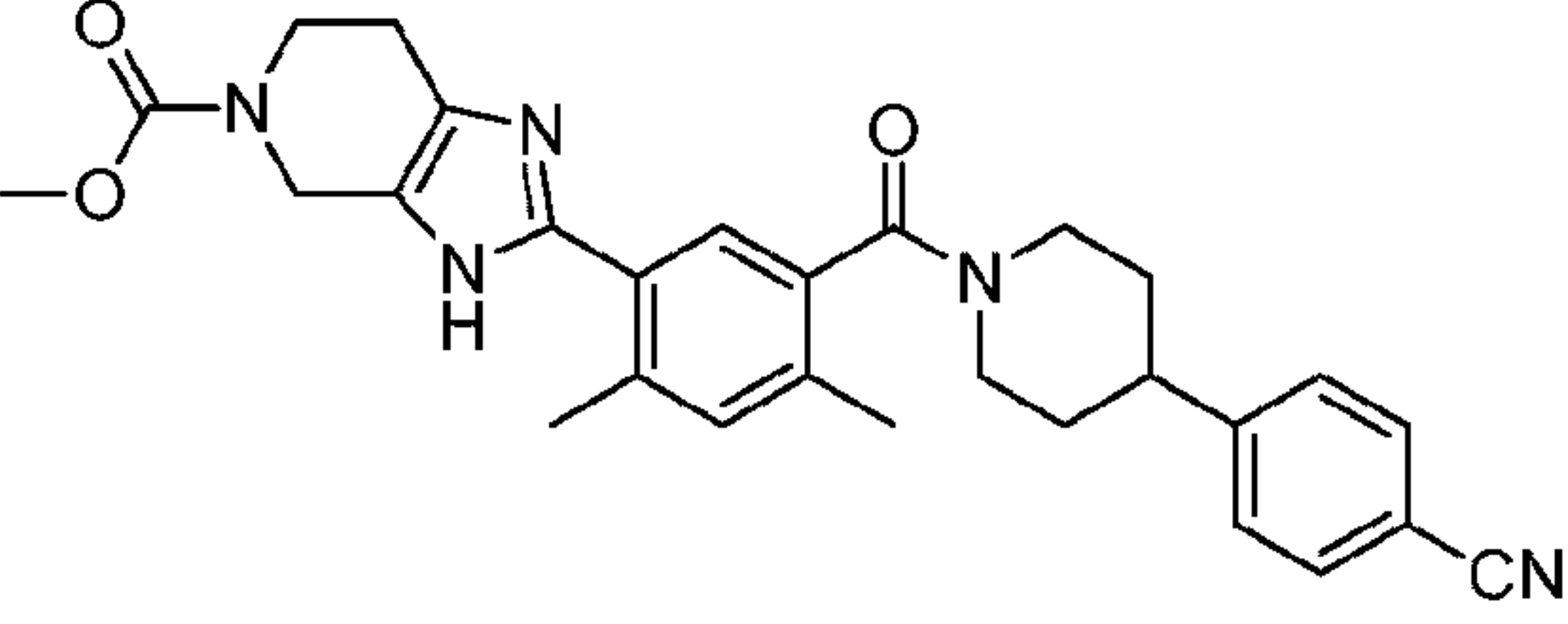
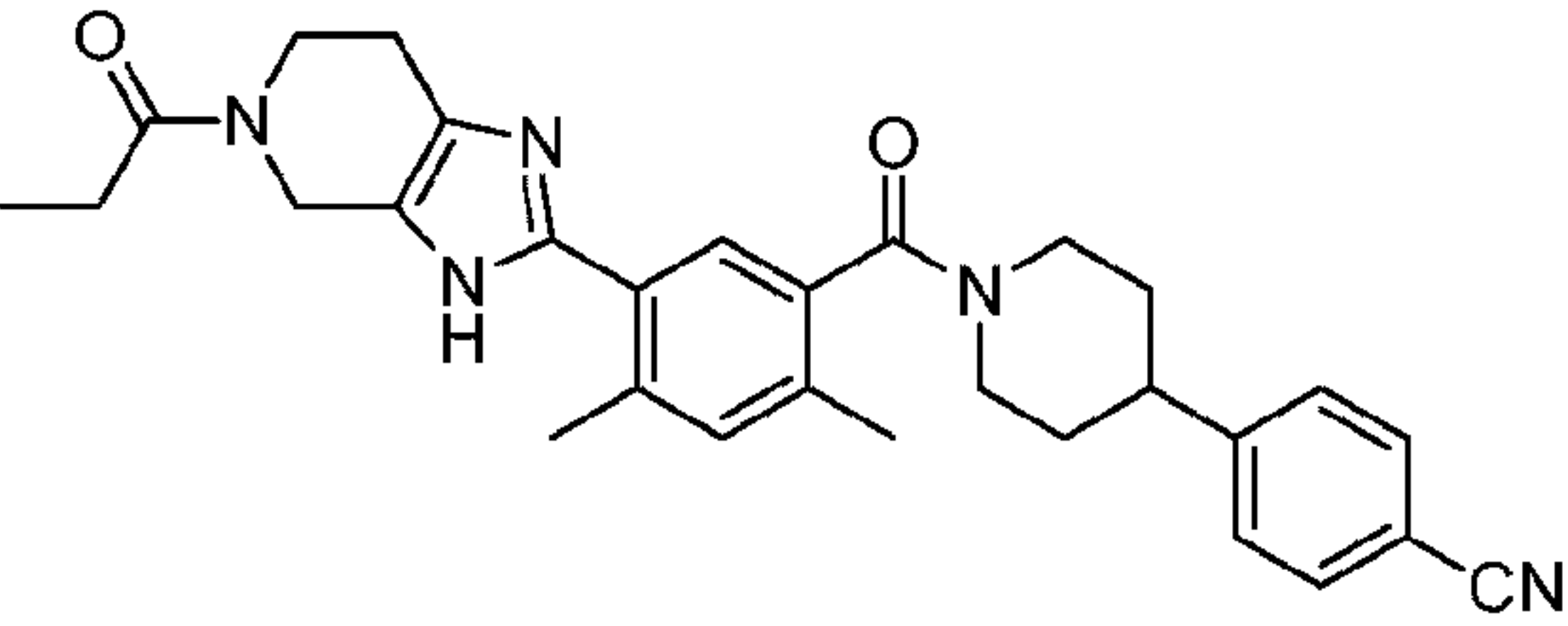
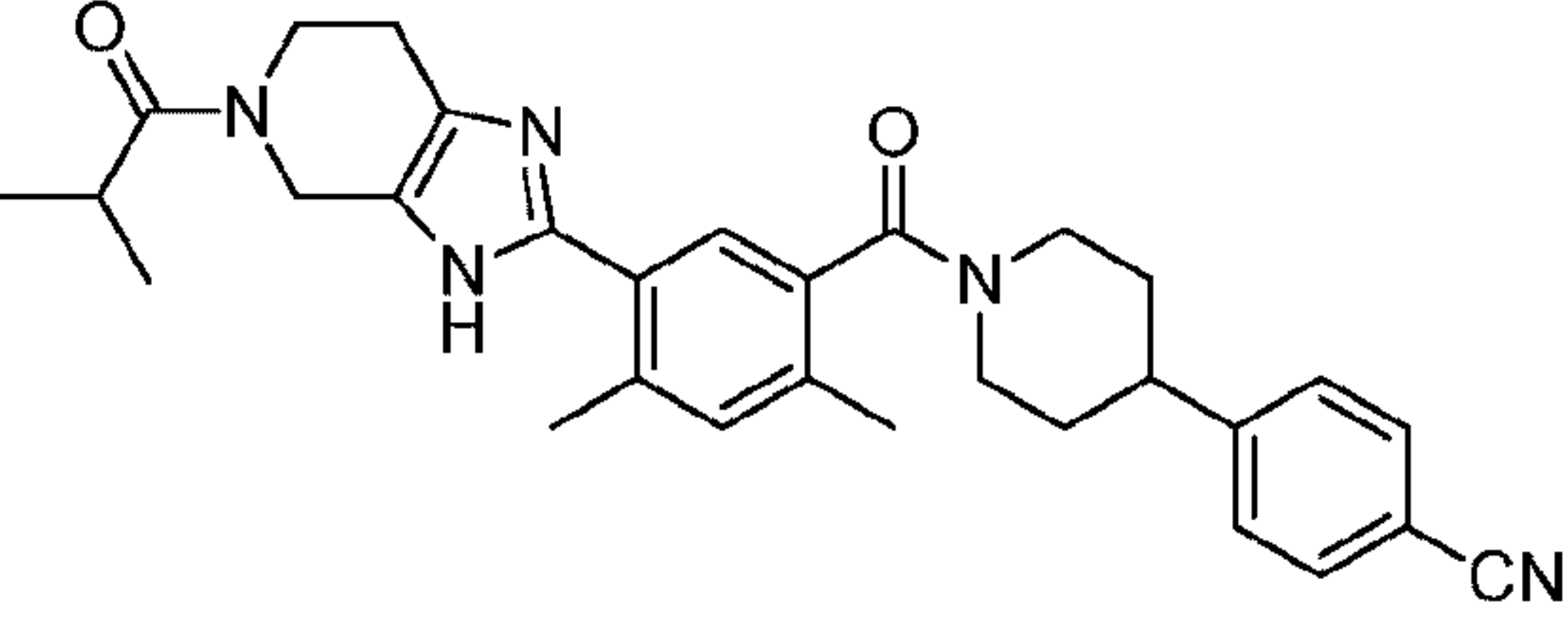
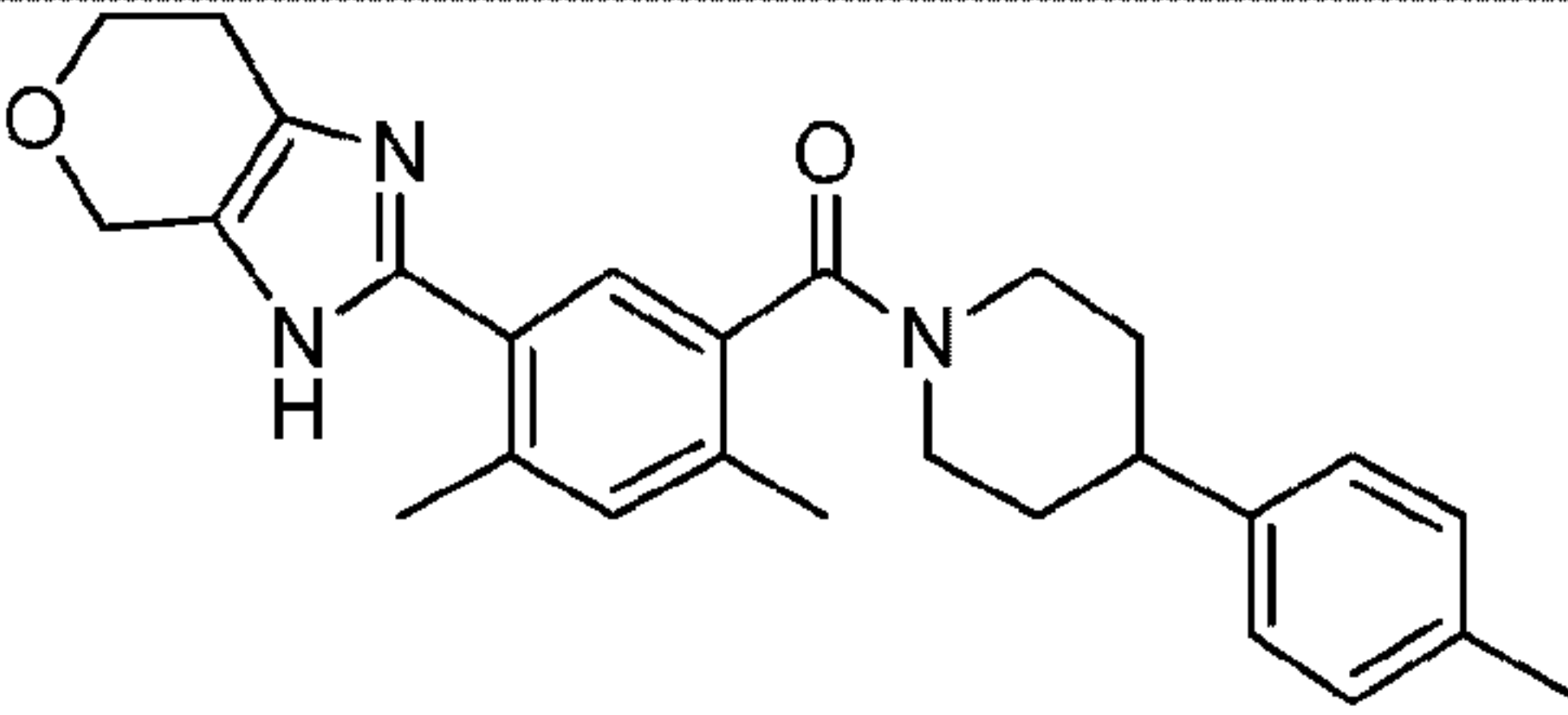


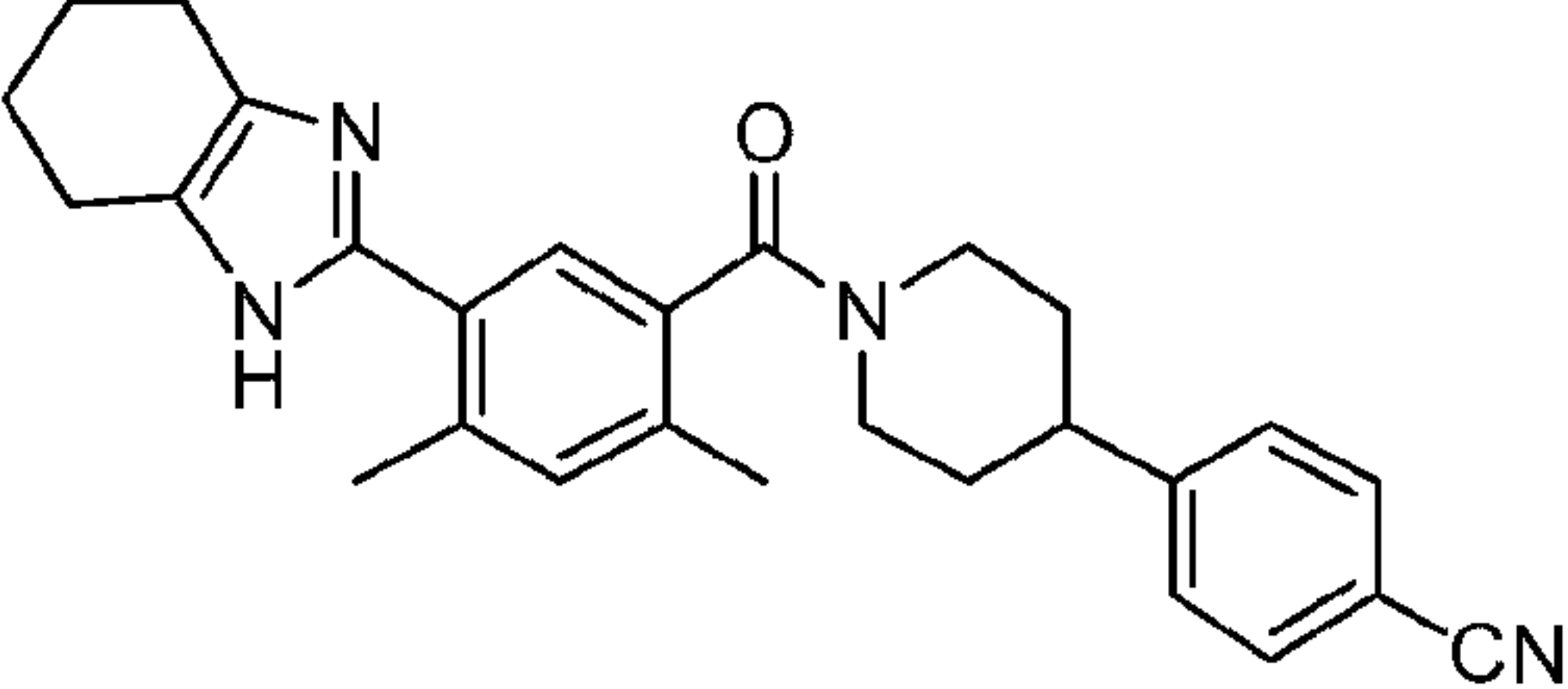
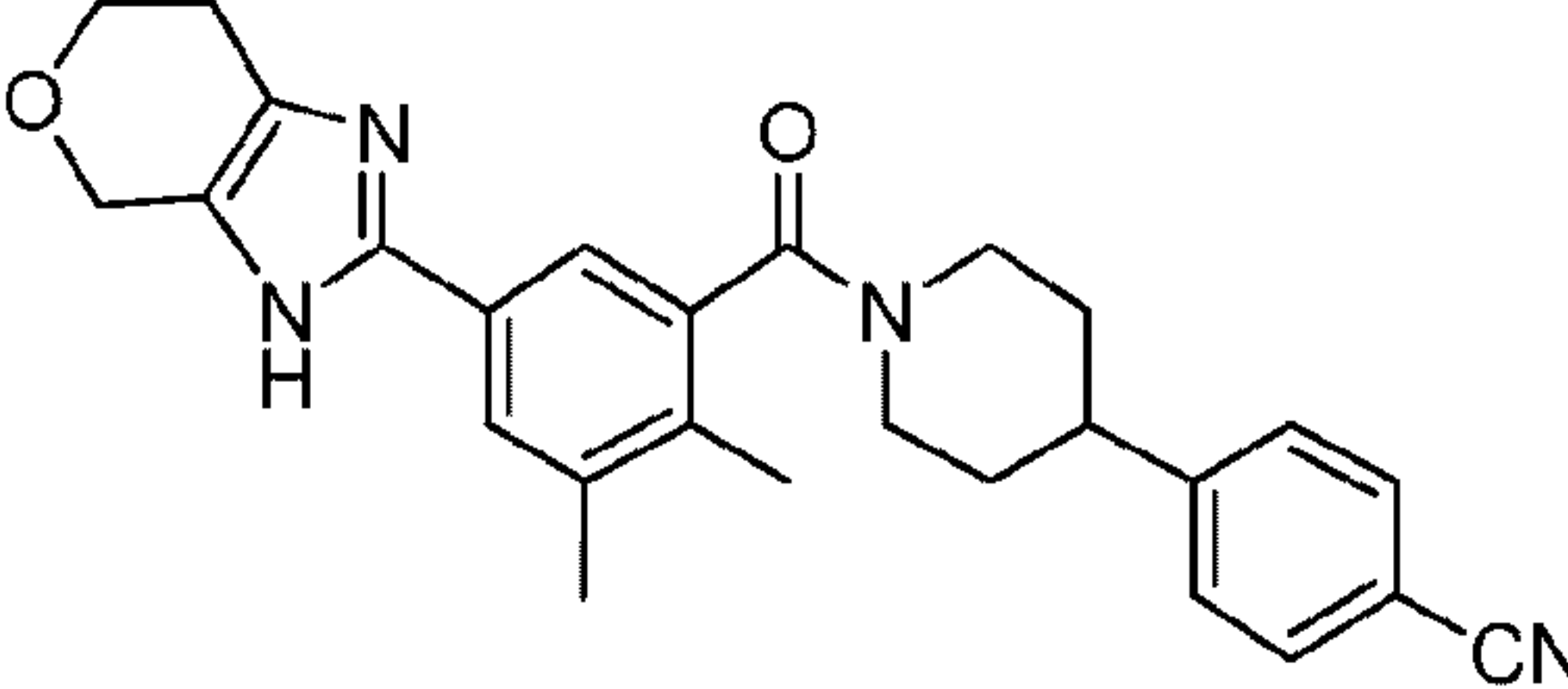
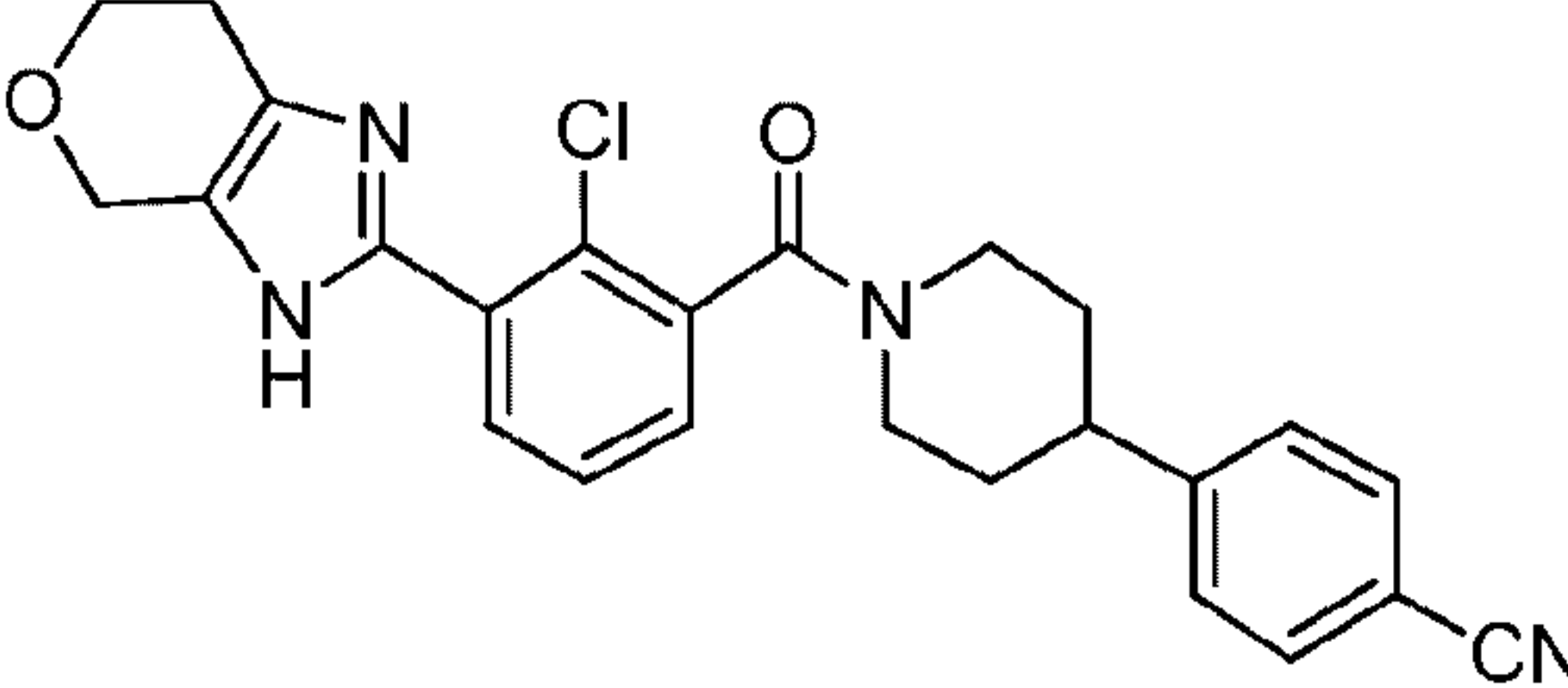
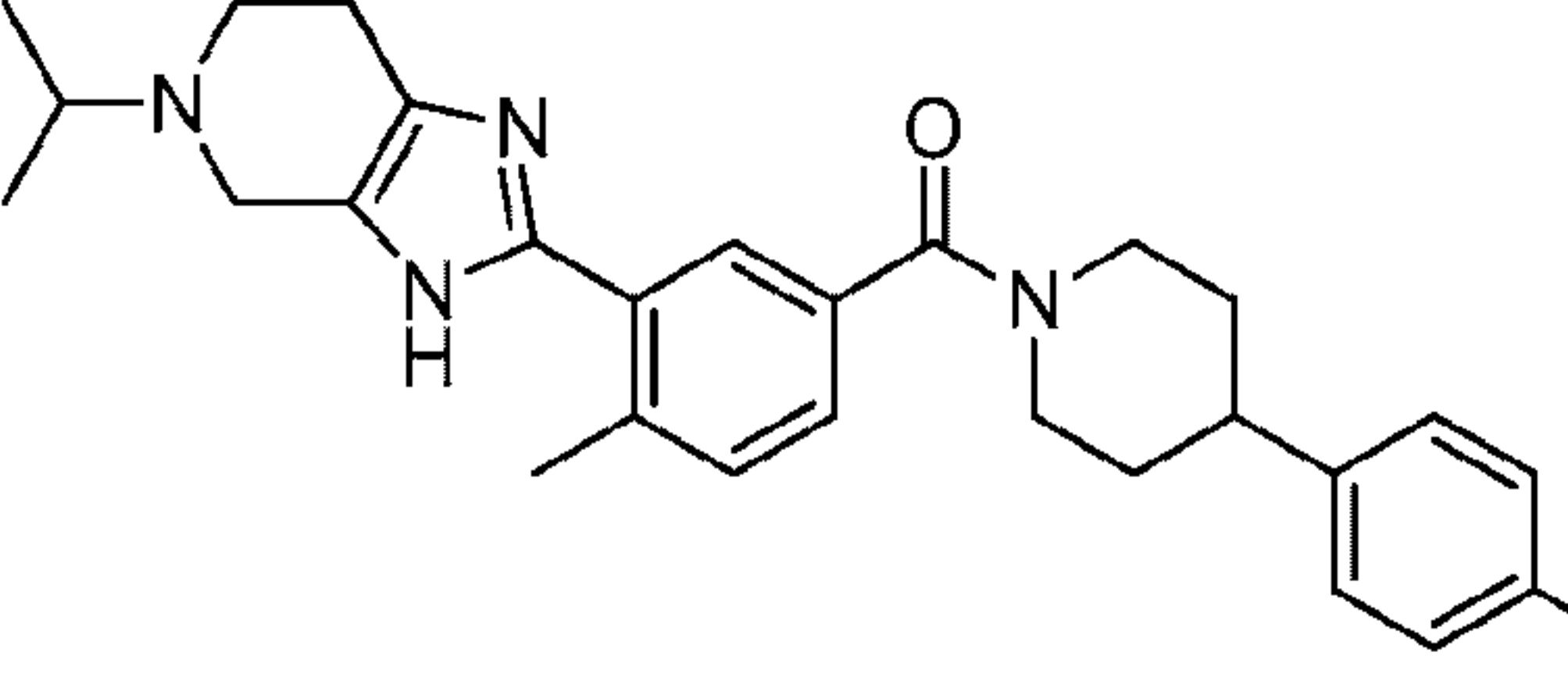
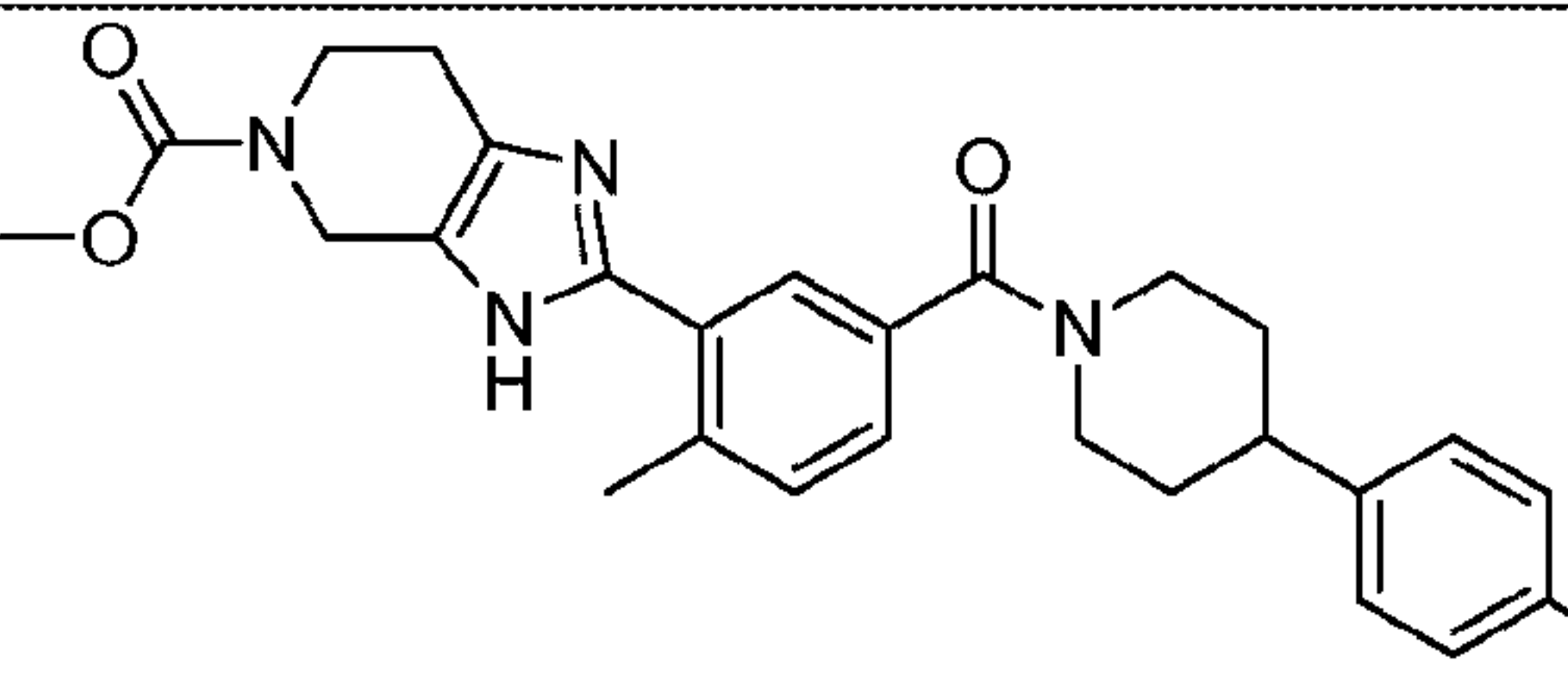
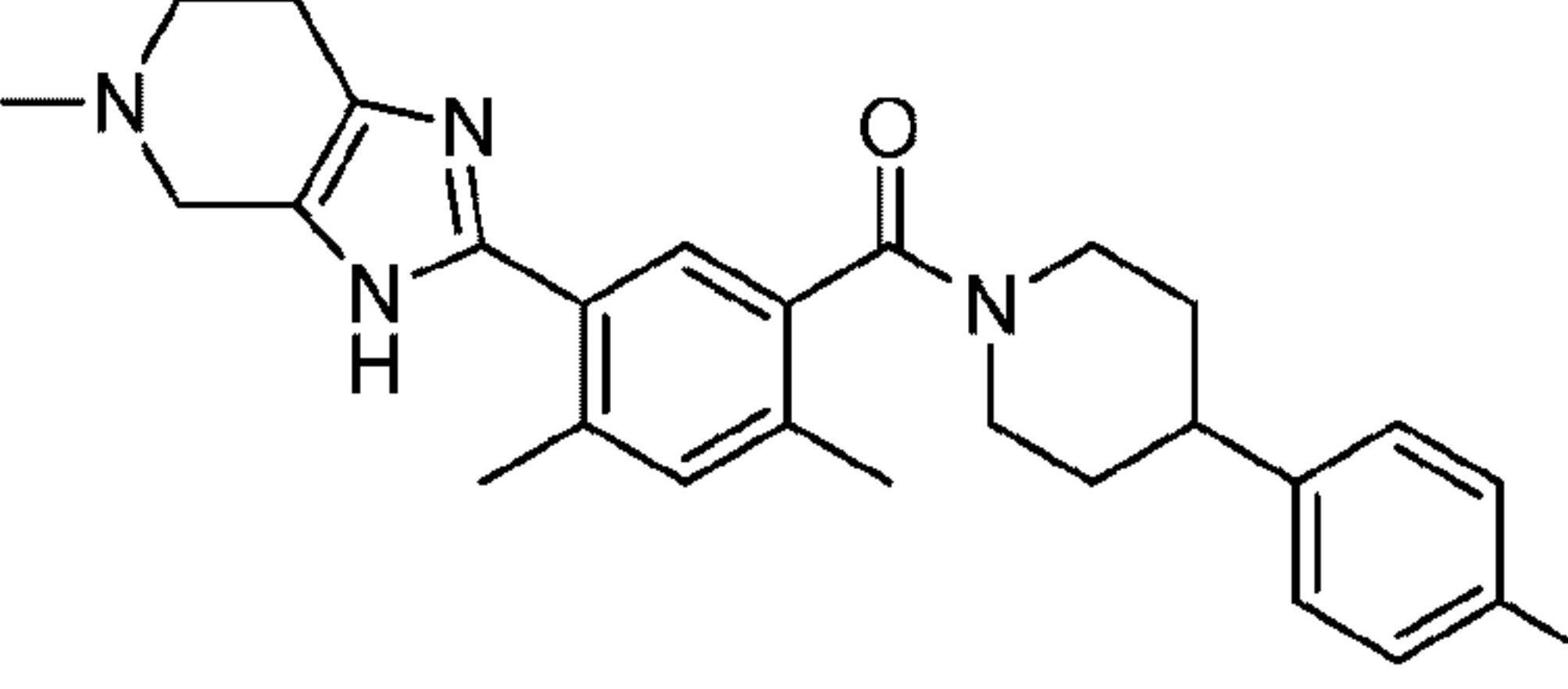
[0620] **Compound 82. (R)-Tetrahydrofuran-3-yl (5-(4-(4-cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2-methylphenyl)carbamate.** The title compound was synthesized using readily available reagents and procedures similar to those described for compound 80. *m/z* (ES⁺) 452 (M+H)⁺.

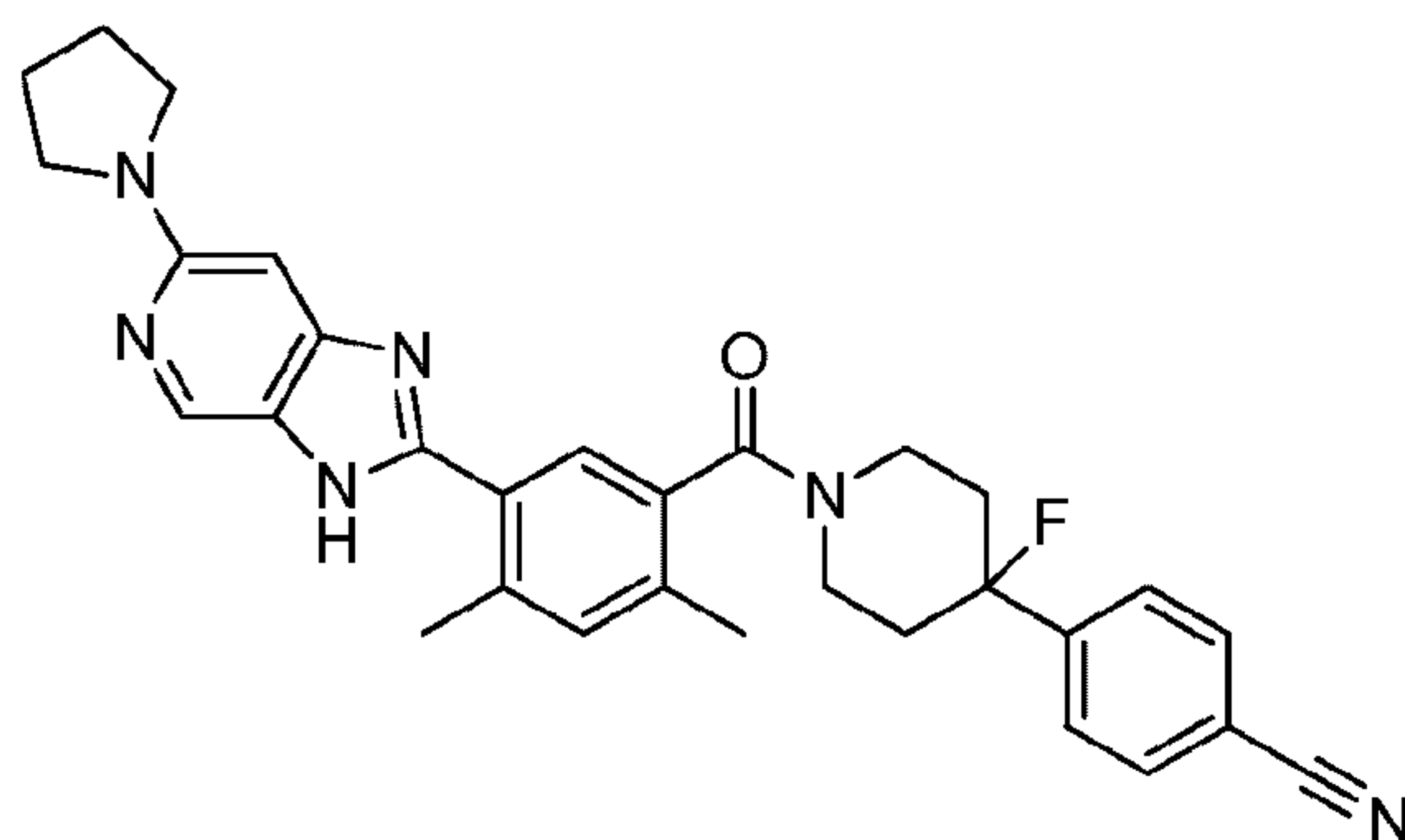
[0621] The compounds in the following table were prepared using standard chemical manipulations, readily available starting materials, and procedures similar to those used for the preparation of compounds 1 and 2:

Cmpnd #	Compound Name	Compound Structure	<i>m/z</i> (ES ⁺)
83	2-(5-(4-(4-cyanophenyl)piperidine-1-carbonyl)-2,4-dimethylphenyl)-N,N-dimethyl-6,7-dihydro-3H-imidazo[4,5-c]pyridine-5(4H)-carboxamide		511 (M+H) ⁺
84	4-(1-(2,4-dimethyl-5-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)benzoyl)piperidin-4-yl)-N,N-dimethylbenzamide		487 (M+H) ⁺
85	(2,4-dimethyl-5-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)phenyl)(4-(4-fluorophenyl)piperidin-1-yl)methanone		434 (M+H) ⁺
86	(2,4-dimethyl-5-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)phenyl)(4-(4-(methylsulfonyl)phenyl)piperidin-1-yl)methanone		494 (M+H) ⁺
87	(2,4-dimethyl-5-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)phenyl)(4-(4-methoxyphenyl)piperidin-1-yl)methanone		446 (M+H) ⁺

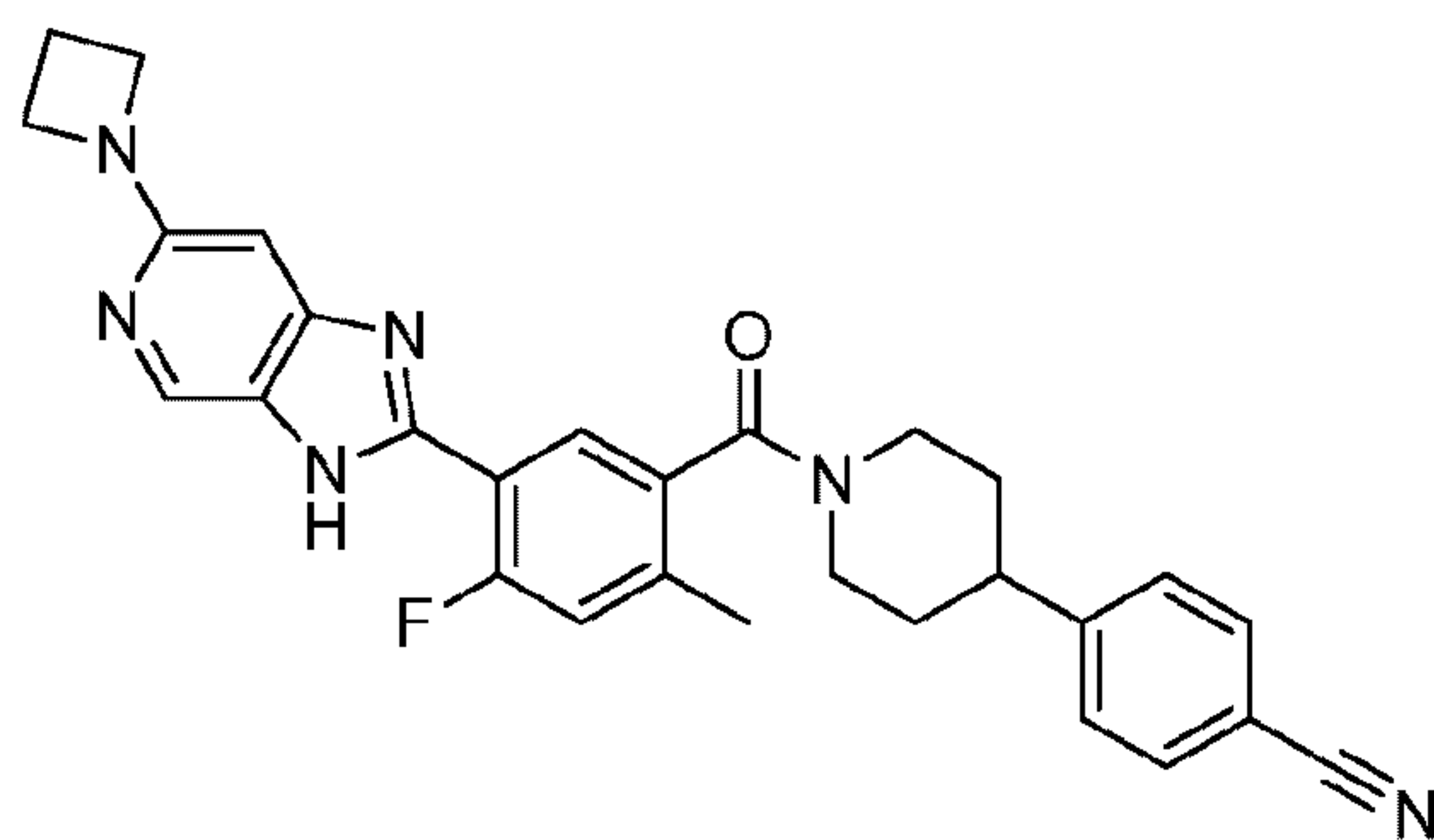
Cmpnd #	Compound Name	Compound Structure	<i>m/z</i> (ES+)
88	1-(2-(2,4-dimethyl-5-(4-(4-(trifluoromethyl)phenyl)piperidine-1-carbonyl)phenyl)-6,7-dihydro-3H-imidazo[4,5-c]pyridin-5(4H)-yl)ethanone		525 (M+H) ⁺
89	4-(1-(5-(5-(cyclopropanecarbonyl)-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-yl)-2,4-dimethylbenzoyl)piperidin-4-yl)benzonitrile		508 (M+H) ⁺
90	1-(2-(5-(4-(4-fluorophenyl)piperidine-1-carbonyl)-2,4-dimethylphenyl)-6,7-dihydro-3H-imidazo[4,5-c]pyridin-5(4H)-yl)ethanone		475 (M+H) ⁺
91	4-(1-(4-methoxy-2-methyl-5-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)benzoyl)piperidin-4-yl)benzonitrile		457 (M+H) ⁺
92	(4-(4-fluorophenyl)piperidin-1-yl)(5-(5-(isopropylsulfonyl)-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-yl)-2,4-dimethylphenyl)methanone		539 (M+H) ⁺

Cmpnd #	Compound Name	Compound Structure	<i>m/z</i> (ES ⁺)
93	1-(2-(5-(4-(4-fluorophenyl)piperidine-1-carbonyl)-2,4-dimethylphenyl)-6,7-dihydro-3H-imidazo[4,5-c]pyridin-5(4H)-yl)-2-methylpropan-1-one		503 (M+H) ⁺
94	(2,4-dimethyl-5-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)phenyl)(4-phenylpiperidin-1-yl)methanone		416 (M+H) ⁺
95	methyl 2-(5-(4-(4-cyanophenyl)piperidine-1-carbonyl)-2,4-dimethylphenyl)-6,7-dihydro-3H-imidazo[4,5-c]pyridine-5(4H)-carboxylate		498 (M+H) ⁺
96	4-(1-(2,4-dimethyl-5-(5-propionyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile		496 (M+H) ⁺
97	4-(1-(5-(5-isobutyryl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-yl)-2,4-dimethylbenzoyl)piperidin-4-yl)benzonitrile		510 (M+H) ⁺
98	(2,4-dimethyl-5-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)phenyl)(4-(p-tolyl)piperidin-1-yl)methanone		430 (M+H) ⁺

Cmpnd #	Compound Name	Compound Structure	<i>m/z</i> (ES ⁺)
99	4-(1-(2,4-dimethyl-5-(4,5,6,7-tetrahydro-1H-benzo[d]imidazol-2-yl)benzoyl)piperidin-4-yl)benzonitrile		439 (M+H) ⁺
100	4-(1-(2,3-dimethyl-5-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)benzoyl)piperidin-4-yl)benzonitrile		441 (M+H) ⁺
101	4-(1-(2-chloro-3-(3,4,6,7-tetrahydropyrano[3,4-d]imidazol-2-yl)benzoyl)piperidin-4-yl)benzonitrile		447 (M+H) ⁺
102	4-(1-(3-(5-isopropyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-yl)-4-methylbenzoyl)piperidin-4-yl)benzonitrile		468 (M+H) ⁺
103	methyl 2-(5-(4-(4-cyanophenyl)piperidine-1-carbonyl)-2-methylphenyl)-6,7-dihydro-3H-imidazo[4,5-c]pyridine-5(4H)-carboxylate		484 (M+H) ⁺
104	(2,4-dimethyl-5-(5-methyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-2-yl)phenyl)(4-(4-(trifluoromethyl)phenyl)piperidin-1-yl)methanone		497 (M+H) ⁺

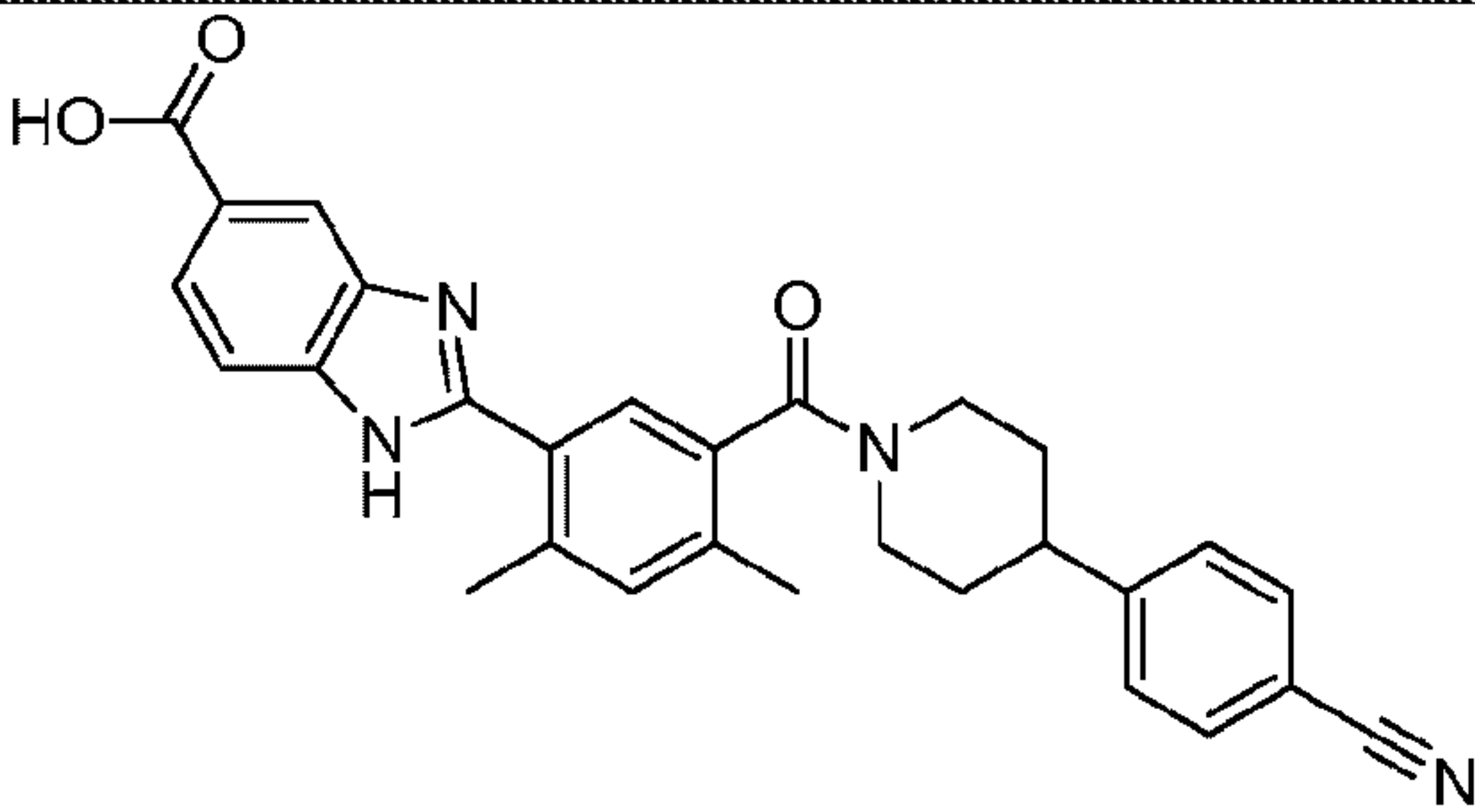
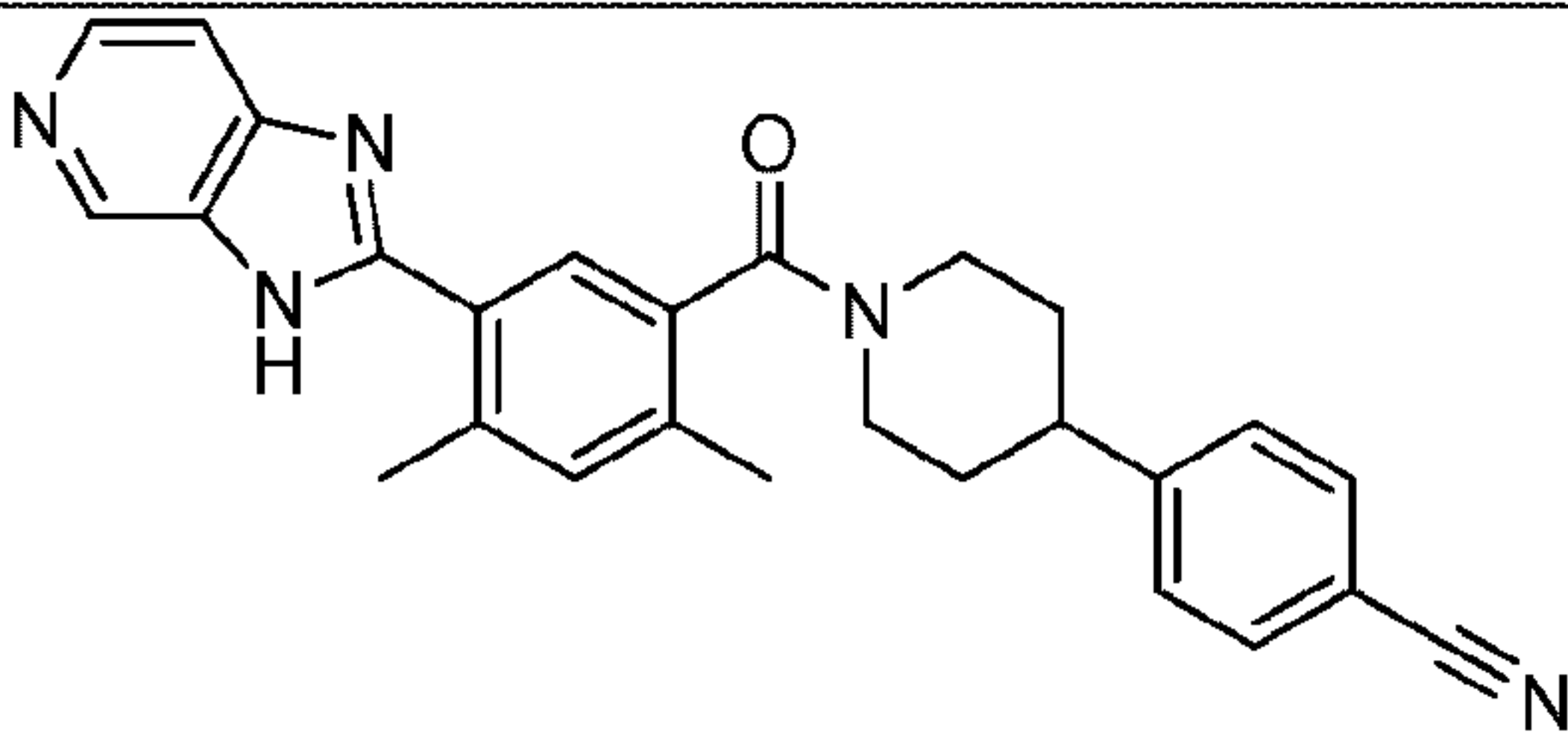
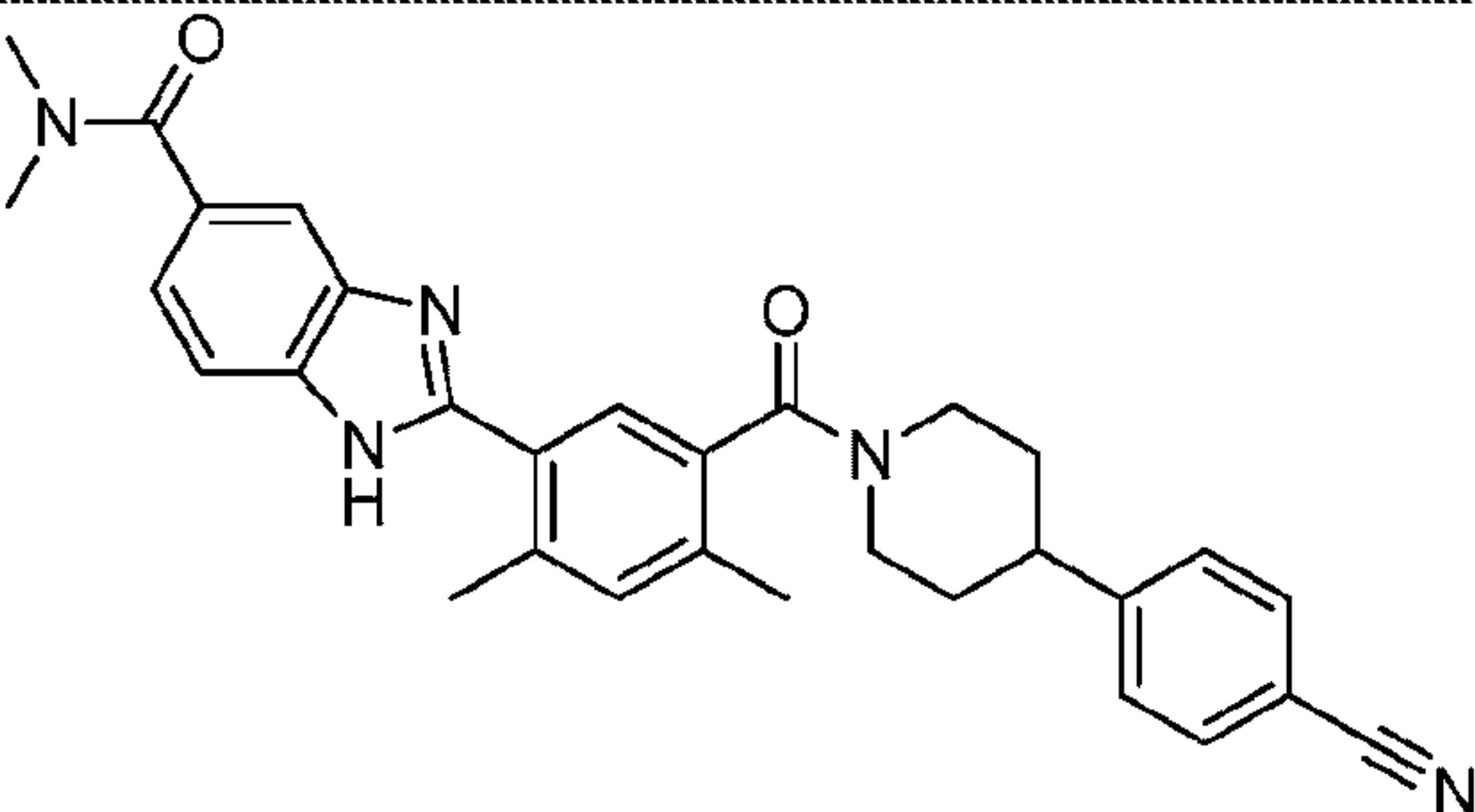
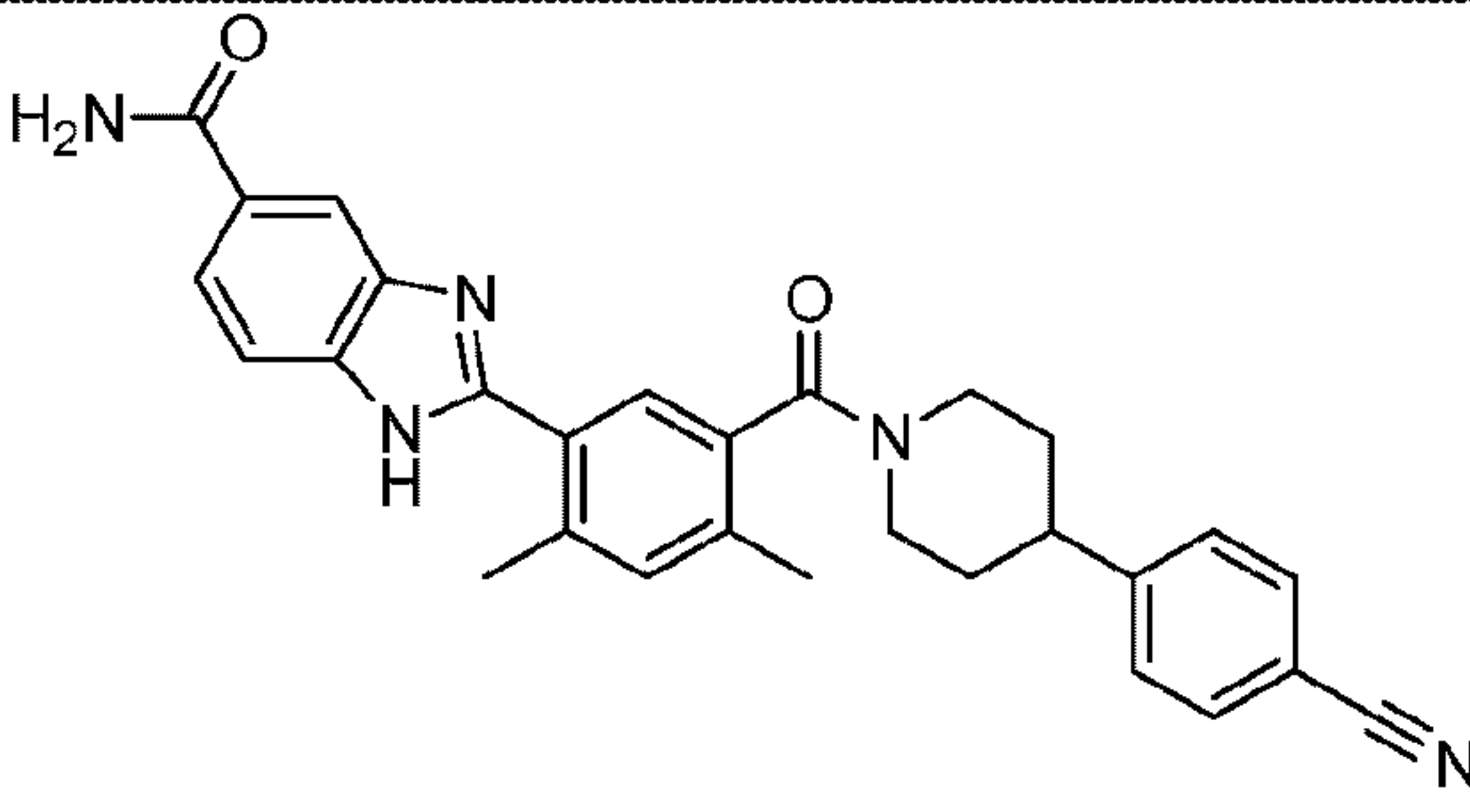
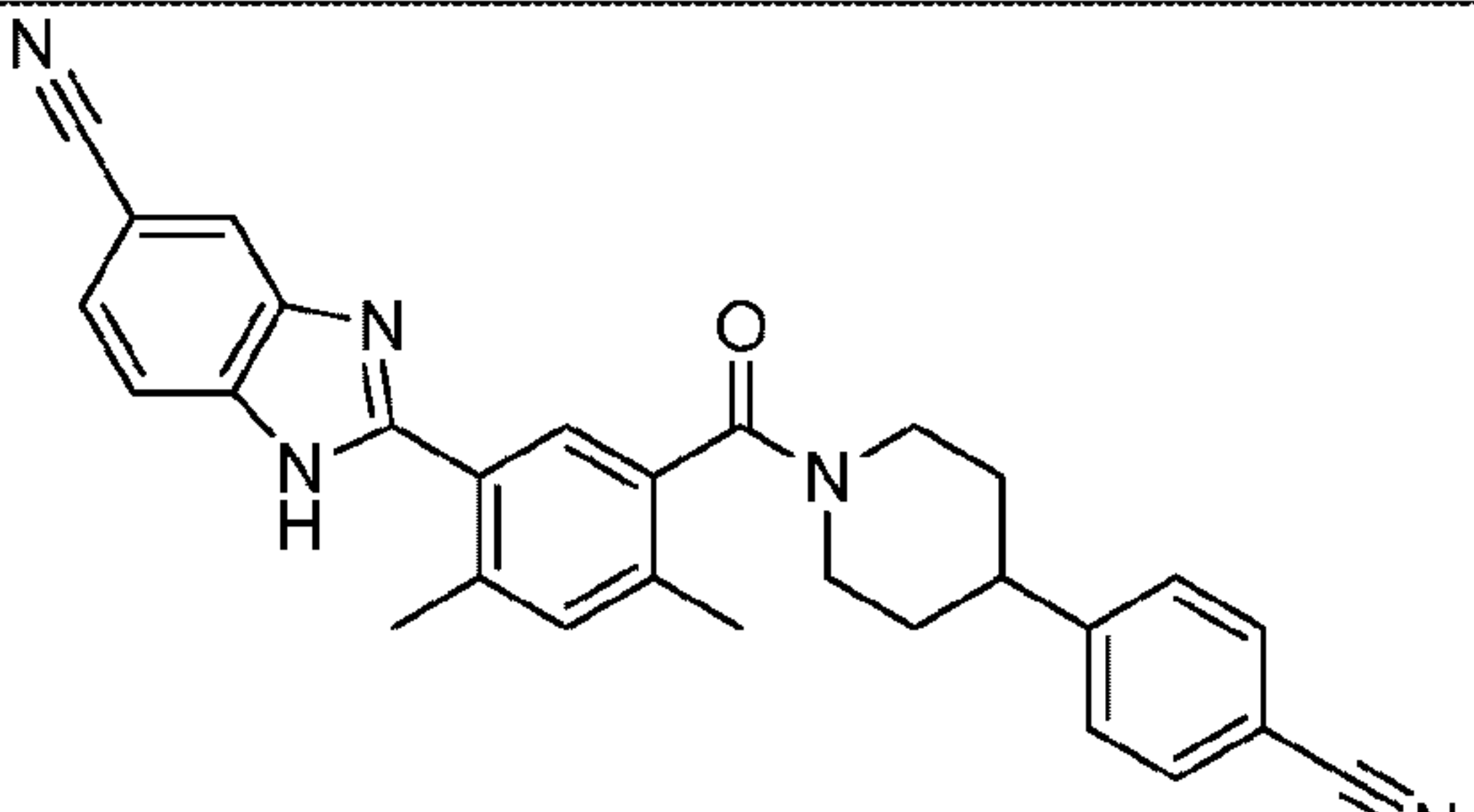


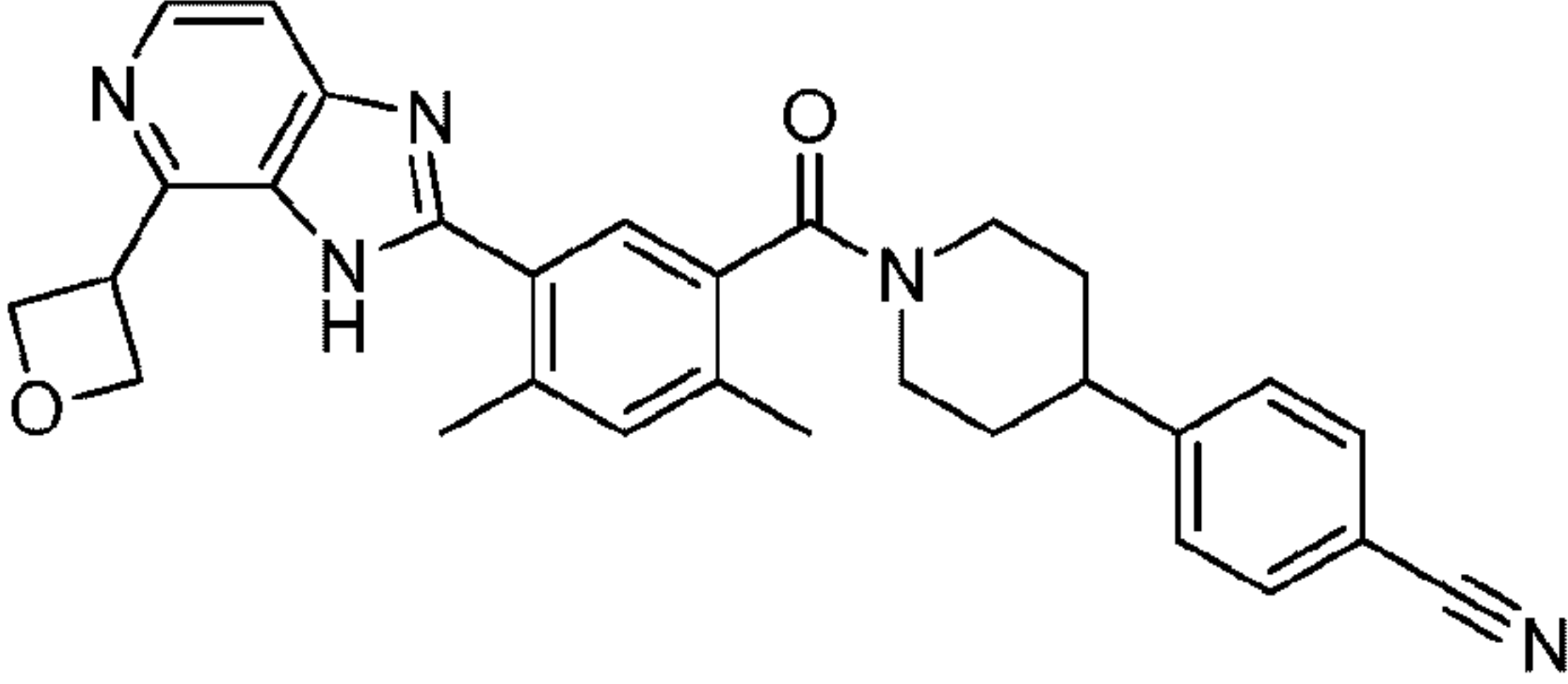
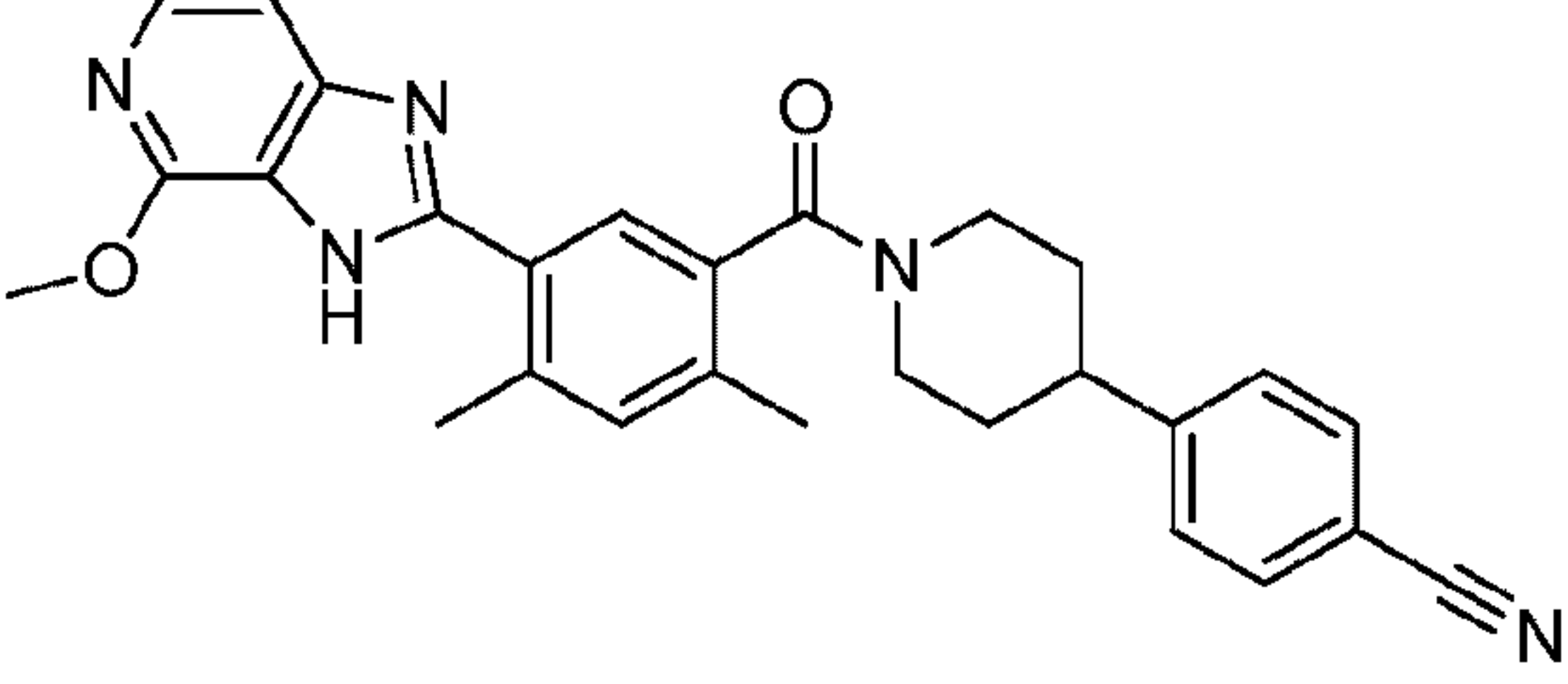
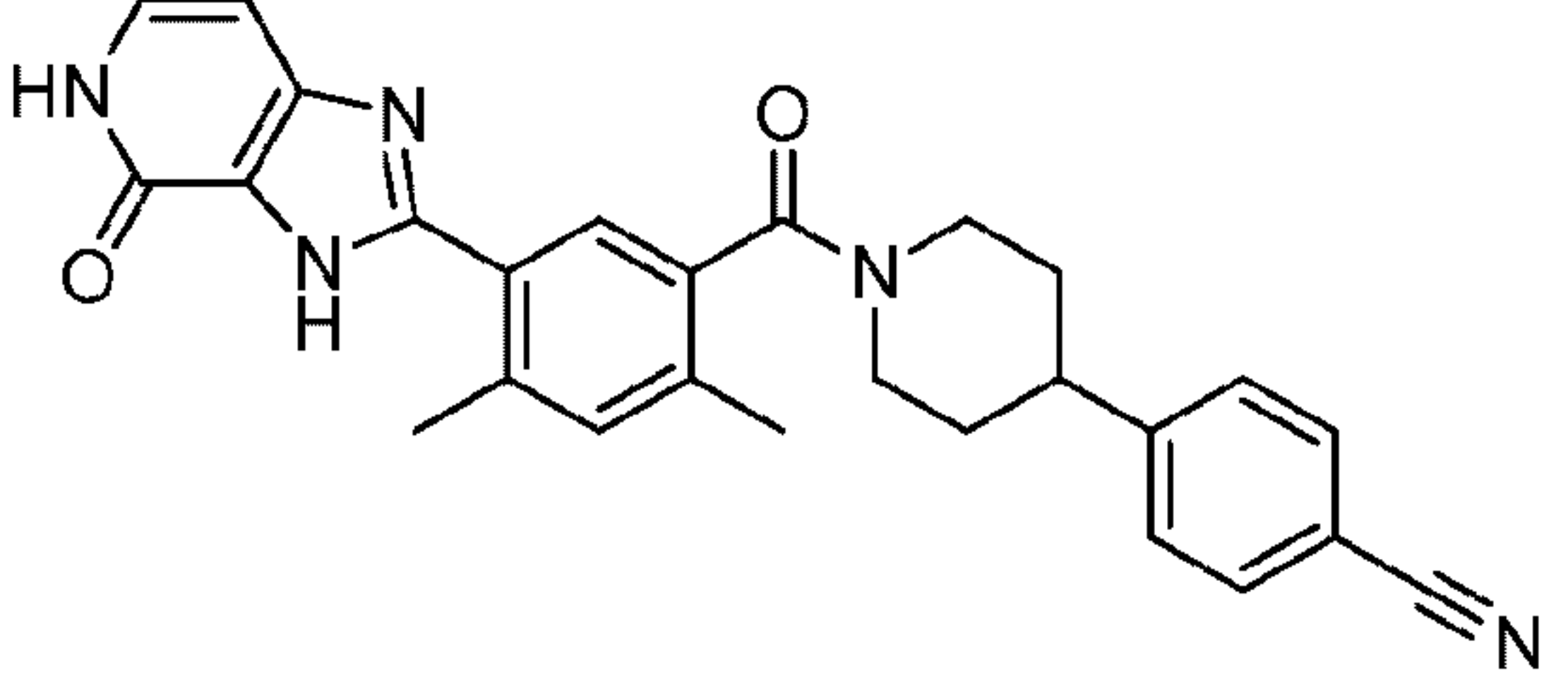
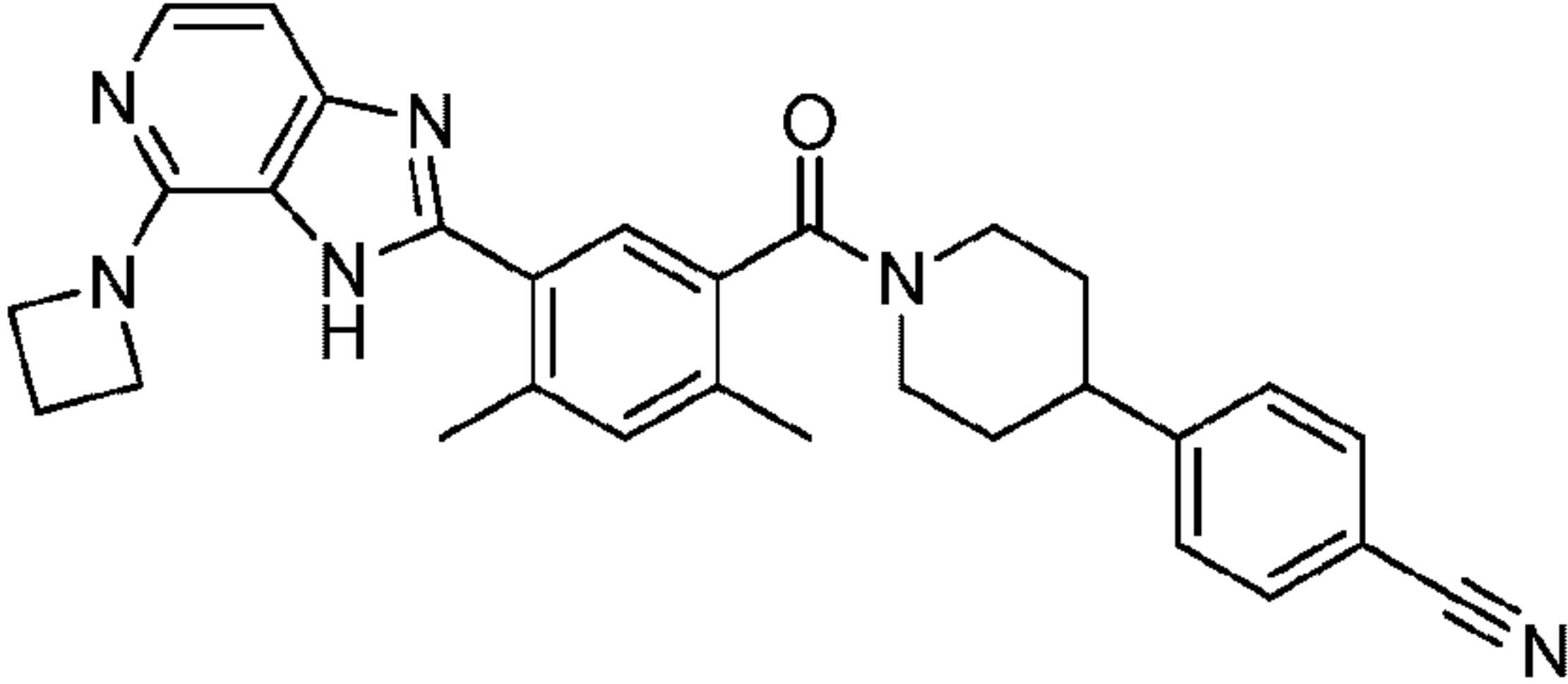
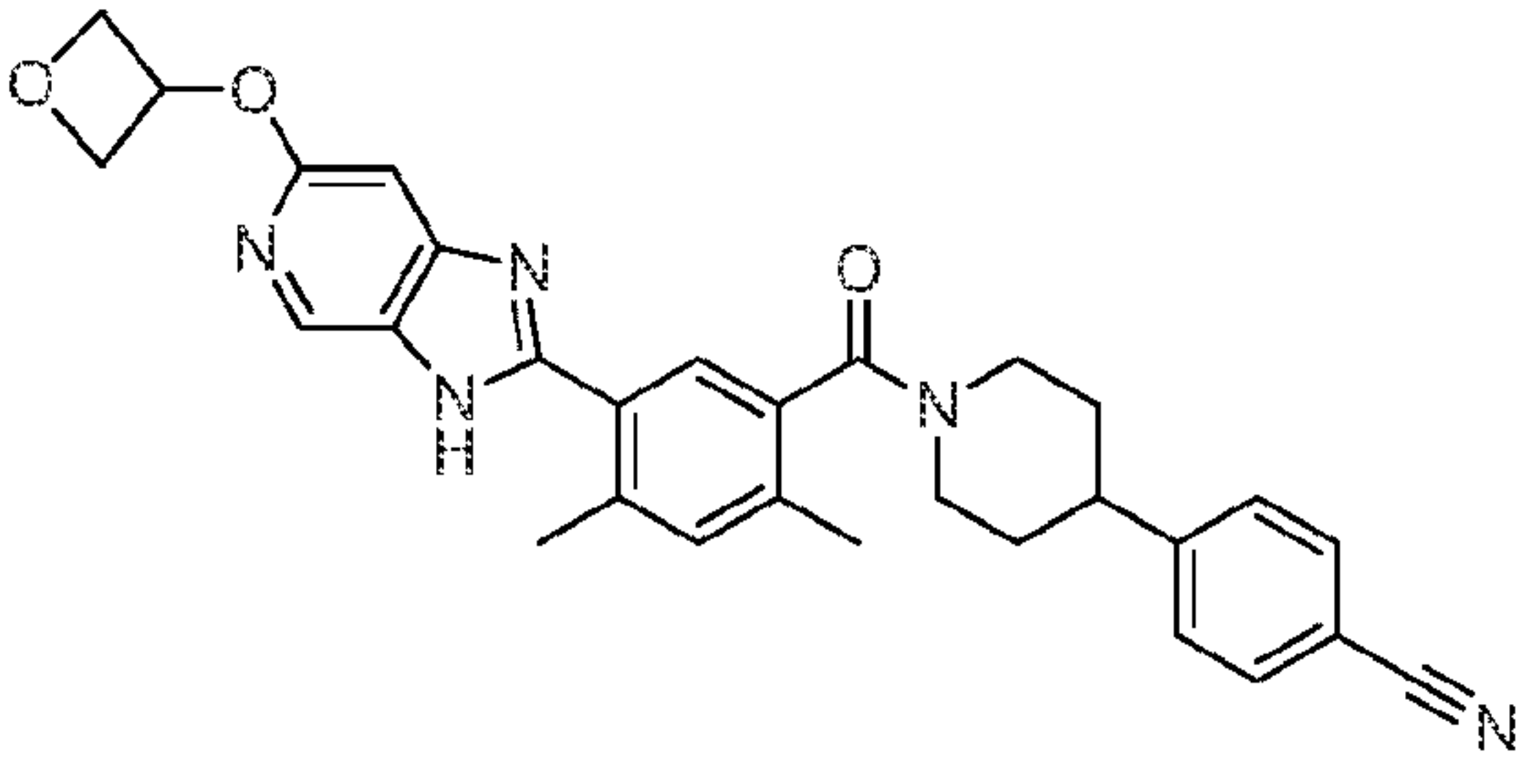
[0622] **Compound 105.** 4-(1-(2,4-Dimethyl-5-(6-(pyrrolidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)-4-fluoropiperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound **20**, except compound **11.2 HCl salt** was used in place of compound **1.5**. m/z (ES⁺) 523 (M+H)⁺.

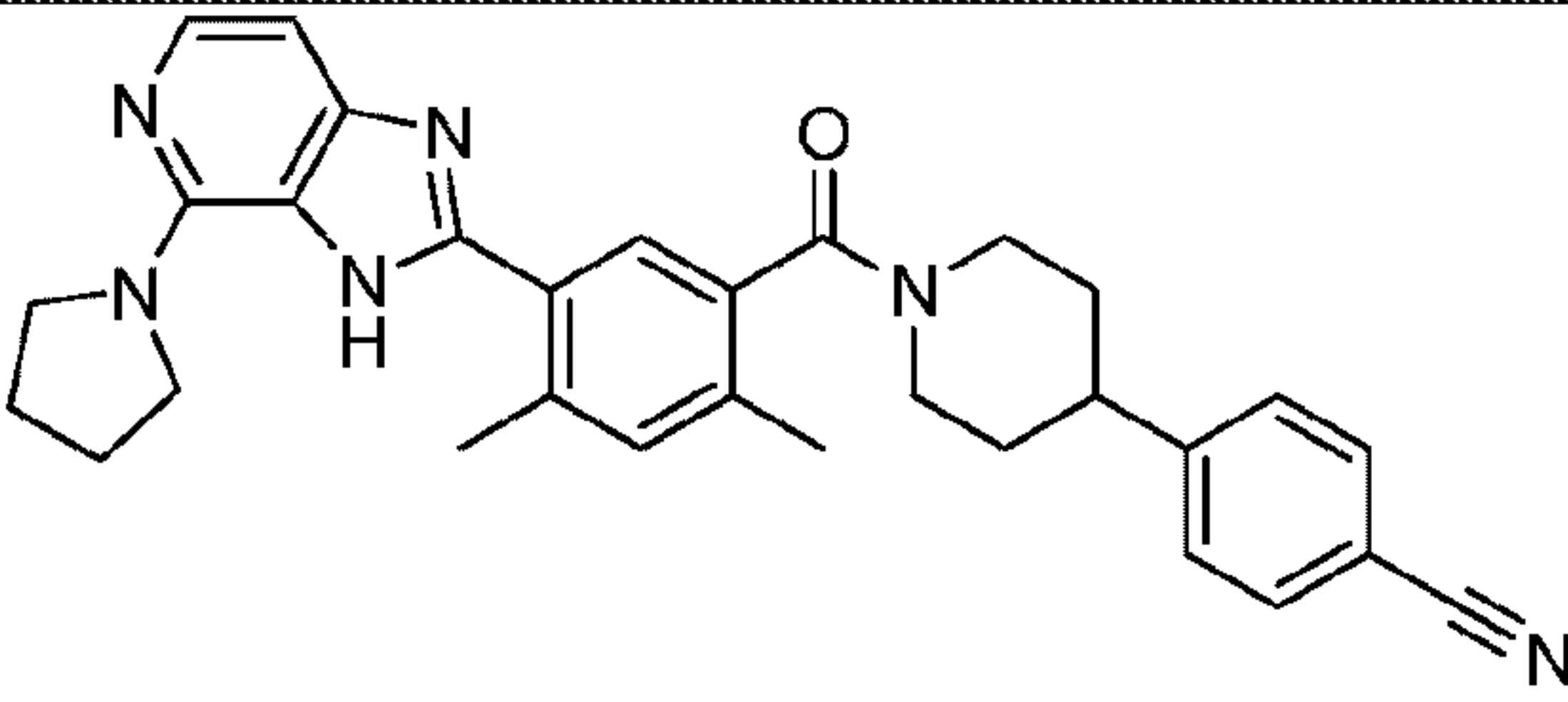


[0623] **Compound 106.** 4-(1-(5-(6-(Azetidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)-4-fluoro-2-methylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound **20**, except 4-fluoro-2-methylbenzoic acid and azetidine were used in place of 2,4-dimethylbenzoic acid and pyrrolidine respectively. m/z (ES⁺) 495 (M+H)⁺.

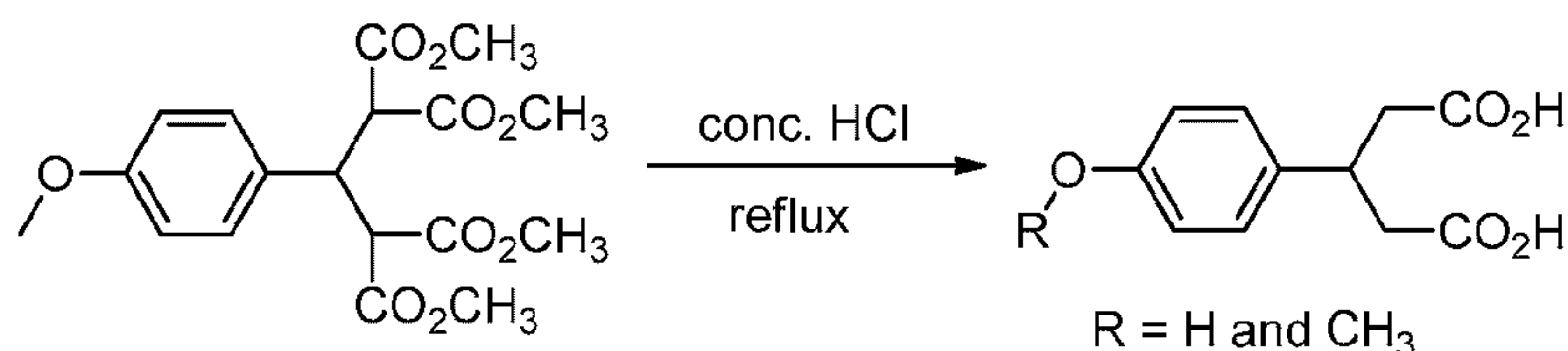
[0624] The compounds in the following table were prepared using standard chemical manipulations, readily available starting materials, and procedures similar to those used for the preparation of compound **20**:

Cmpnd #	Compound Name	Compound Structure	<i>m/z</i> (ES ⁺)
107	2-(5-(4-(4-cyanophenyl)piperidine-1-carbonyl)-2,4-dimethylphenyl)-1H-benzo[d]imidazole-5-carboxylic acid		479 (M+H) ⁺
108	4-(1-(5-(3H-imidazo[4,5-c]pyridin-2-yl)-2,4-dimethylbenzoyl)piperidin-4-yl)benzonitrile		436 (M+H) ⁺
109	2-(5-(4-(4-cyanophenyl)piperidine-1-carbonyl)-2,4-dimethylphenyl)-N,N-dimethyl-1H-benzo[d]imidazole-5-carboxamide		506 (M+H) ⁺
110	2-(5-(4-(4-cyanophenyl)piperidine-1-carbonyl)-2,4-dimethylphenyl)-1H-benzo[d]imidazole-5-carboxamide		478 (M+H) ⁺
111	2-(5-(4-(4-cyanophenyl)piperidine-1-carbonyl)-2,4-dimethylphenyl)-1H-benzo[d]imidazole-5-carbonitrile		460 (M+H) ⁺

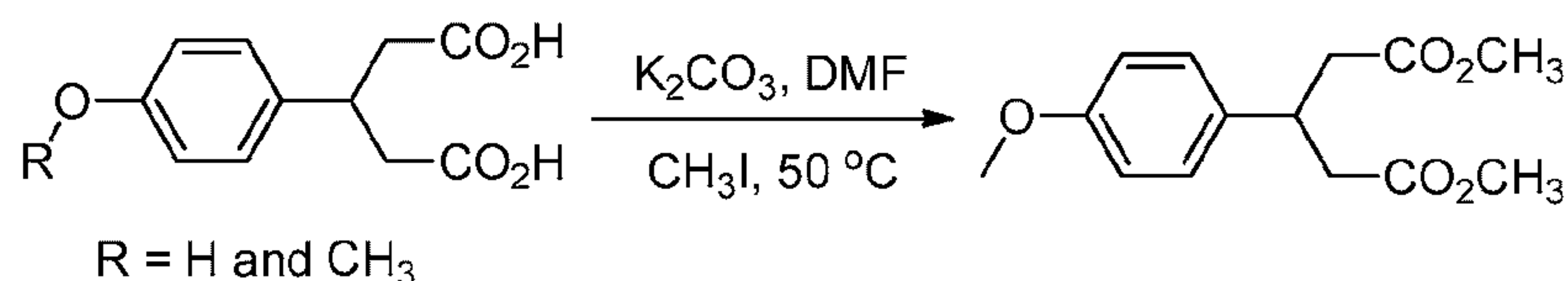
Cmpnd #	Compound Name	Compound Structure	<i>m/z</i> (ES ⁺)
112	4-(1-(2,4-dimethyl-5-(4-(oxetan-3-yl)-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile		492 (M+H) ⁺
113	4-(1-(5-(4-methoxy-3H-imidazo[4,5-c]pyridin-2-yl)-2,4-dimethylbenzoyl)piperidin-4-yl)benzonitrile		466 (M+H) ⁺
114	4-(1-(2,4-dimethyl-5-(4-oxo-4,5-dihydro-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile		452 (M+H) ⁺
115	4-(1-(5-(4-(azetidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)-2,4-dimethylbenzoyl)piperidin-4-yl)benzonitrile		491 (M+H) ⁺
116	4-(1-(2,4-dimethyl-5-(6-(oxetan-3-yloxy)-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile		508 (M+H) ⁺

Cmpnd #	Compound Name	Compound Structure	<i>m/z</i> (ES ⁺)
117	4-(1-(2,4-dimethyl-5-(4-(pyrrolidin-1-yl)-3H-imidazo[4,5-c]pyridin-2-yl)benzoyl)piperidin-4-yl)benzonitrile		505 (M+H) ⁺

[0625] Compound 118.1. Tetramethyl 2-(4-methoxyphenyl)propane-1,1,3,3-tetracarboxylate. A mixture of (*E*)-*N*-(4-methoxybenzylidene)-4-methylbenzenesulfonamide (2.89 g, 10 mmol), dimethyl malonate (3.43 mL, 30 mmol), *t*-BuOK (2.24 g, 20 mmol) in anhydrous *t*-BuOH (20 mL) was heated at 50 °C for 4 h. After cooling to room temperature, the reaction mixture was poured into saturated aqueous NH₄Cl and extracted with CH₂Cl₂ (3x). The combined organic layer was dried over MgSO₄, filtered, and then concentrated. The residue was purified by flash column chromatography with EtOAc in hexane (10%, 20%, 30%, then 40%) to give the title compound as a clear oil (3.255 g, 85% yield).

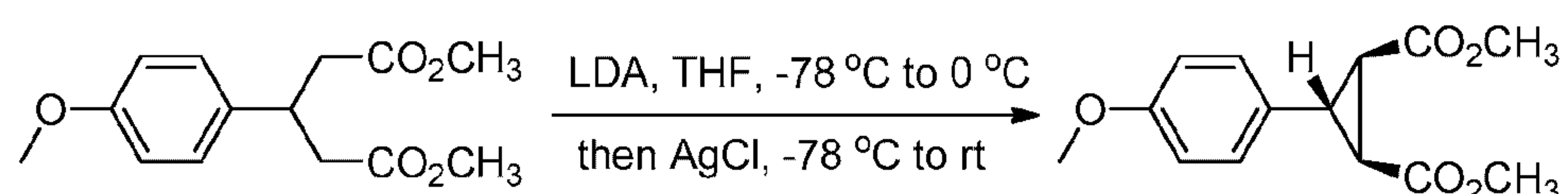


[0626] Compound 118.2. 3-(4-Methoxyphenyl)pentanedioic acid and 3-(4-hydroxyphenyl)pentanedioic acid. A mixture of tetramethyl 2-(4-methoxyphenyl)propane-1,1,3,3-tetracarboxylate (compound 118.1, 6.0 g, 15.7 mmol) in concentrated HCl (37%, 80 mL) was heated under reflux overnight. After cooling to room temperature, the suspension was filtered. The filtrate was washed with water and dried under vacuum to give 2.66 g product as a mixture of 3-(4-methoxyphenyl)pentanedioic acid (major, LCMS observed [M-H]⁻ 237) and 3-(4-hydroxyphenyl)pentanedioic acid (minor, LCMS observed [M-H]⁻ 223).



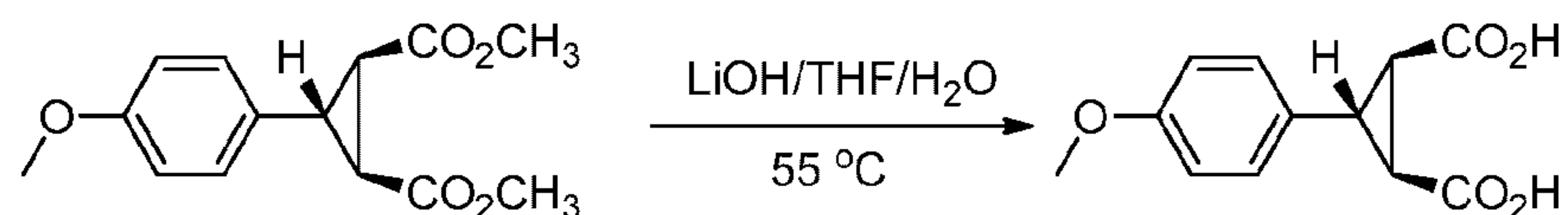
[0627] Compound 118.3. Dimethyl 3-(4-methoxyphenyl)pentanedioate. A mixture of the product (compound 118.2) obtained from the previous step (2.66 g), K₂CO₃ (6.56 g, 47.5

mmol) and CH_3I (3 mL, 47.5 mmol) in DMF (10 mL) was heated at 50 °C in a pressure tube overnight. After cooling to room temperature, the reaction mixture was poured into saturated aqueous NaHCO_3 and extracted with EtOAc (3x). The combined organic extract was dried over MgSO_4 , filtered and concentrated. The residue was purified by flash column chromatography with EtOAc in hexane (20%, 30%, 40%, then 50%) to give the title compound as a clear oil (2.0 g, 48% yield over two steps).

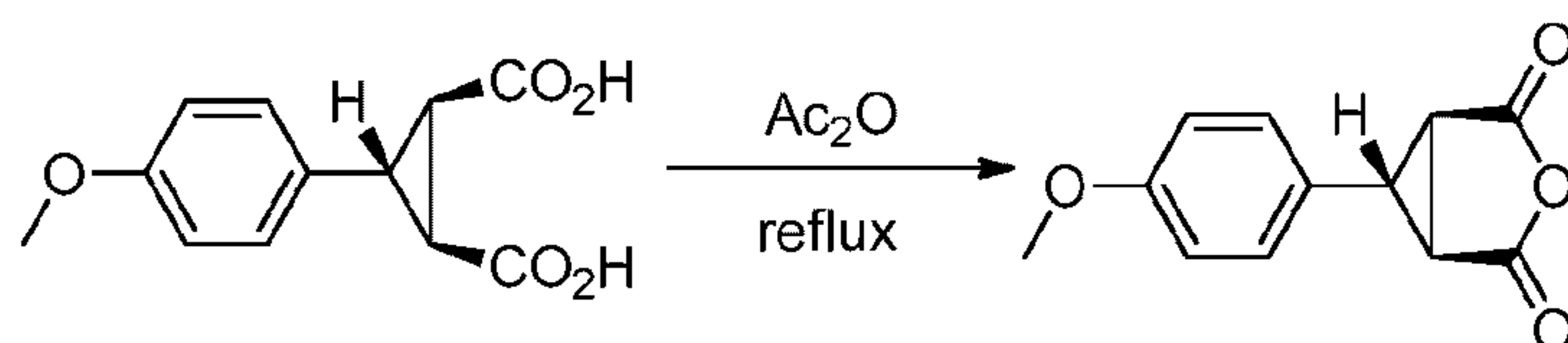


[0628] Compound 118.4. Dimethyl 3-(4-methoxyphenyl)cyclopropane-1,2-dicarboxylate. To a solution of LDA (18.8 mmol) in THF (60 mL) at -78 °C was added a solution of dimethyl 3-(4-methoxyphenyl)pentanedioate (2.0 g, 7.52 mmol) in THF (10 mL) dropwise. After stirring at -78 °C for 1 h, the dry ice-acetone bath was removed. The reaction mixture was stirred for 30 min before being cooled to -78 °C. Solid AgCl (2.2 g, 15.4 mmol) was added all at once. The reaction mixture was stirred at -78 °C for 1 h and then room temperature overnight. Saturated aqueous NH_4Cl was added. The mixture was vigorously stirred for 10 min. The suspension was filtered through celite. The filtrate was extracted with EtOAc (3x). The combined organic extract was dried over MgSO_4 , filtered, and concentrated. The residue was purified by flash column chromatography with EtOAc in hexane (10%, 15%, 20%, then 30%) to give the title compound as a pale yellow solid (0.87 g, 44% yield).

^1H NMR (CDCl_3 , 400 Hz) δ 7.09 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H), 3.77 (s, 6H), 3.17 (t, J = 7.6 Hz, 1H), 2.36 (d, J = 7.6 Hz, 2H).

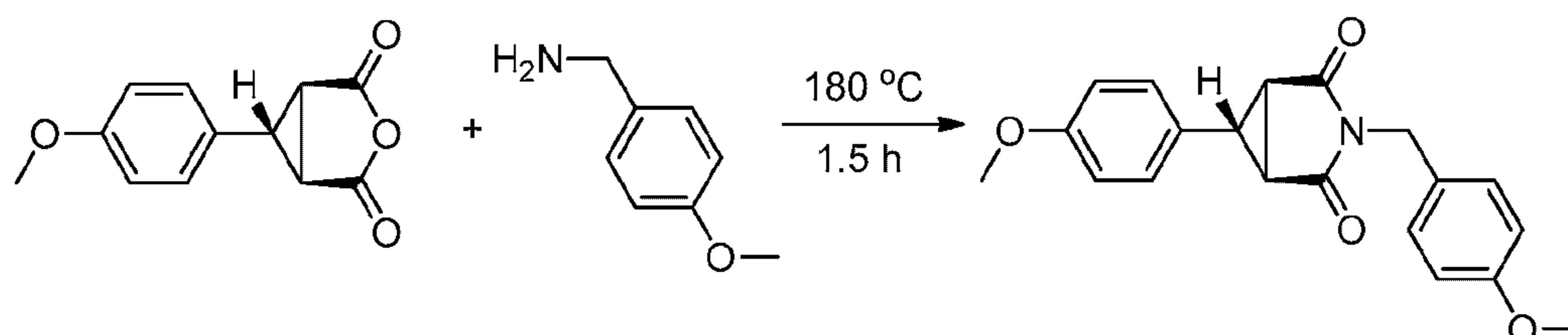


[0629] Compound 118.5. 3-(4-Methoxyphenyl)cyclopropane-1,2-dicarboxylic acid. A mixture of dimethyl 3-(4-methoxyphenyl)cyclopropane-1,2-dicarboxylate (0.88 g, 3.33 mmol) and LiOH (2M in H_2O , 10 mL) in THF (30 mL) was stirred at 55 °C overnight. After cooling to room temperature, the reaction mixture was poured into 1N HCl and extracted with EtOAc (3x). The combined organic extract was dried over MgSO_4 , filtered, and concentrated to give the title compound as a light yellow solid.



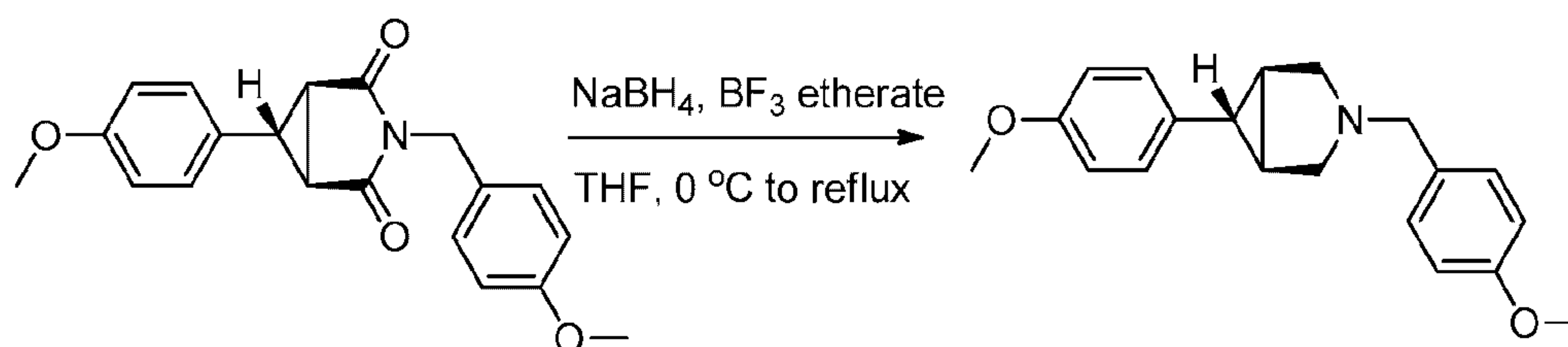
[0630] Compound 118.6. 6-(4-Methoxyphenyl)-3-oxabicyclo[3.1.0]hexane-2,4-dione.

A mixture of 3-(4-methoxyphenyl)cyclopropane-1,2-dicarboxylic acid (crude product from the previous step) in Ac_2O (20 mL) was heated under reflux for 1 h. Excess Ac_2O was removed under reduced pressure. The crude product was used in the next step without further purification.



[0631] Compound 118.7. 3-(4-Methoxybenzyl)-6-(4-methoxyphenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione.

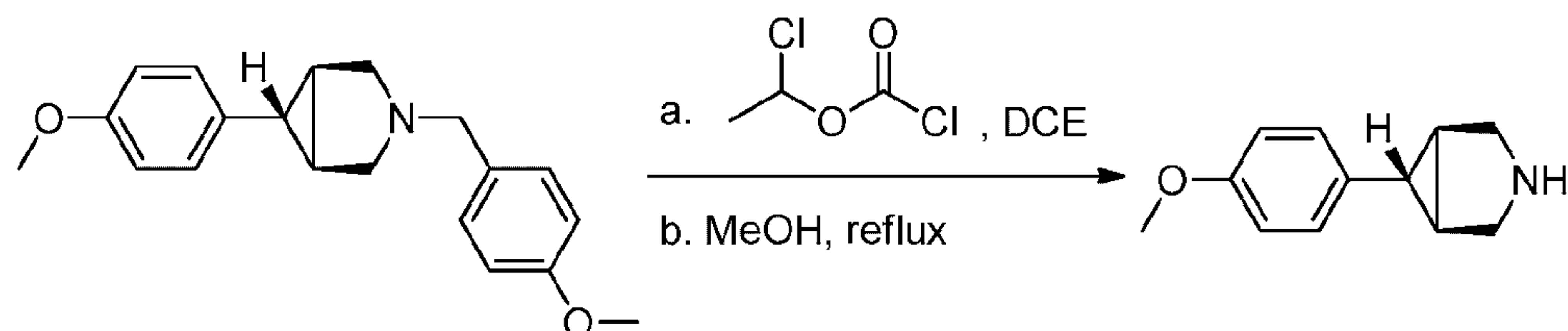
A mixture of 6-(4-methoxyphenyl)-3-oxabicyclo[3.1.0]hexane-2,4-dione (crude product from the previous step) and (4-methoxyphenyl)methanamine was heated at 180 °C for 1.5 h. After cooling to room temperature, the reaction mixture was dissolved in CH_2Cl_2 and purified by flash column chromatography with EtOAc in hexane (20%, 30%, then 40%) to give the title compound as a yellow solid (0.71 g, 63% yield over three steps). MS $[\text{M}+\text{H}]^+$: 338.



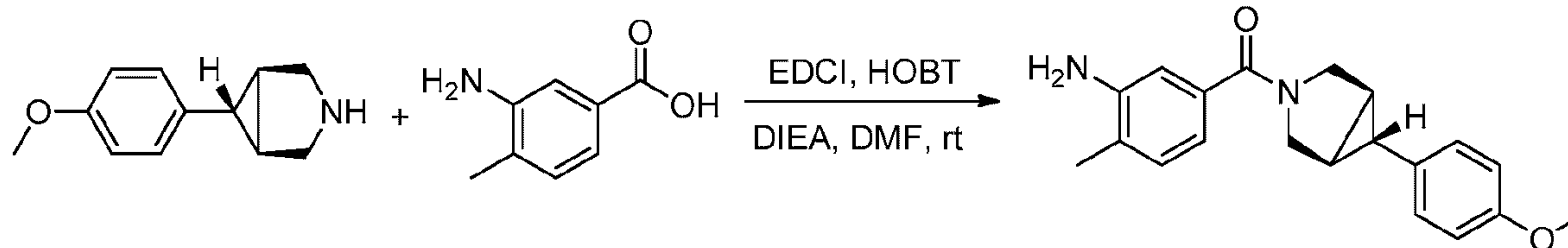
[0632] Compound 118.8. 3-(4-Methoxybenzyl)-6-(4-methoxyphenyl)-3-azabicyclo[3.1.0]hexane.

A mixture of 3-(4-methoxybenzyl)-6-(4-methoxyphenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (0.86 g, 2.6 mmol), NaBH_4 (0.296 g, 7.8 mmol) and BF_3 etherate (1.0 mL, 7.8 mmol) in THF was heated under reflux overnight. After cooling to 0 °C, a solution of piperazine (2 g) in H_2O (20 mL) was added. The mixture was stirred at room temperature for 2 h, poured into H_2O and extracted with EtOAc (3x). The combined organic extract was dried over MgSO_4 , filtered and then concentrated. The residue was purified by flash column chromatography with EtOAc in hexane (10%, 20%, then 30%) to give a white

solid. To a suspension of the solid in THF (20 mL) and H₂O (10 mL) was added piperazine (3 g). After heating the mixture under reflux overnight, it was poured into brine and extracted with EtOAc (3x). The combined organic extract was dried over MgSO₄, filtered and concentrated to give the title compound as white solid (0.51 g, 65% yield). MS [M+H]⁺: 310.

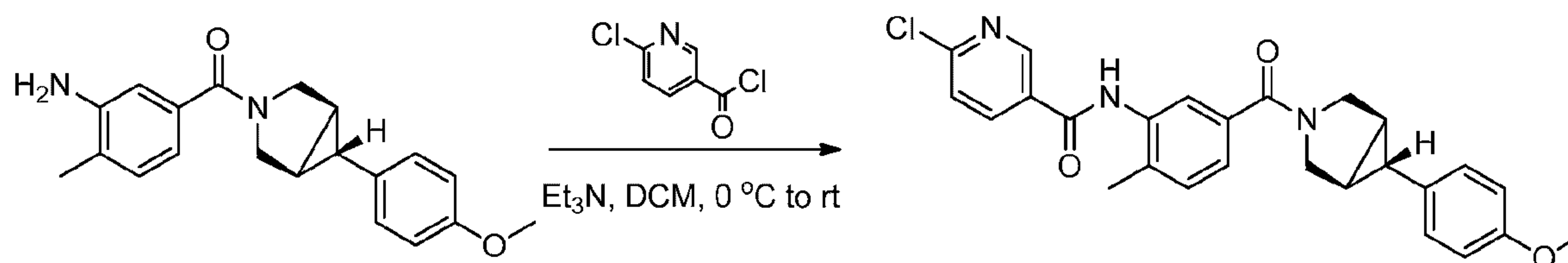


[0633] Compound 118.9. 6-(4-Methoxyphenyl)-3-azabicyclo[3.1.0]hexane. To a solution of (1R,5S,6S)-3-(4-Methoxybenzyl)-6-(4-methoxyphenyl)-3-azabicyclo[3.1.0]hexane (0.5 g, 1.6 mmol) in DCE (30 mL) at 0 °C was added 1-chloroethyl chloroformate (0.21 mL, 1.9 mmol, 1.2 equiv). The reaction mixture was stirred at 0 °C for 30 min, heated under reflux for 1 h and then concentrated under reduced pressure. MeOH (20 mL) was added. The resulting mixture was heated under reflux for 40 min and then concentrated. The residue was purified by preparative TLC to give the title compound as a white crystalline solid (155 mg, 51% yield). MS [M+H]⁺: 190.

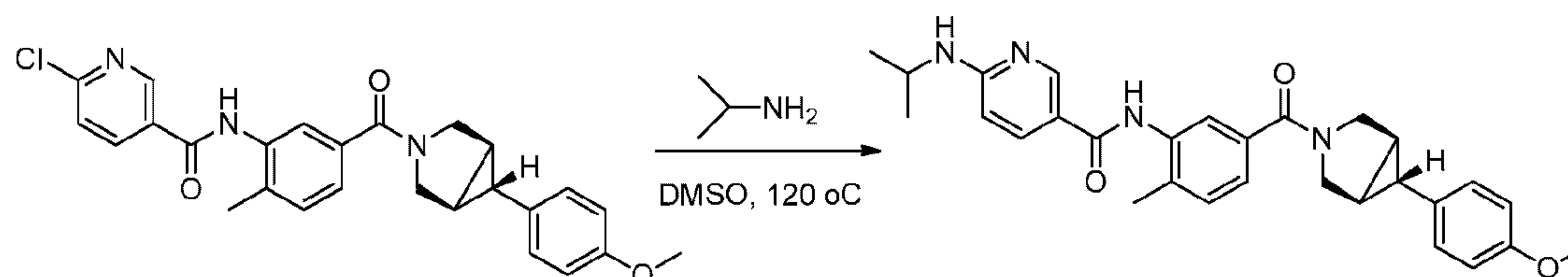


[0634] Compound 118.10. (3-Amino-4-methylphenyl)(6-(4-methoxyphenyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone. A mixture of 6-(4-Methoxyphenyl)-3-azabicyclo[3.1.0]hexane (0.124 g, 0.82 mmol), 3-amino-4-methylbenzoic acid (0.155 g, 0.82 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI, 0.172 g, 0.90 mmol), 1-hydroxybenzotriazole (~20% H₂O, 0.122 g, 0.90 mmol) and diisopropylethylamine (0.71 mL, 4.1 mmol) in DMF (3 mL) was stirred at room temperature overnight. The reaction mixture was poured into saturated aqueous NaHCO₃ and extracted with EtOAc (3x). The combined organic extract was dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography with EtOAc in hexane (60%, then 100%) to give the title compound as a white foam (0.15 g, 57% yield).

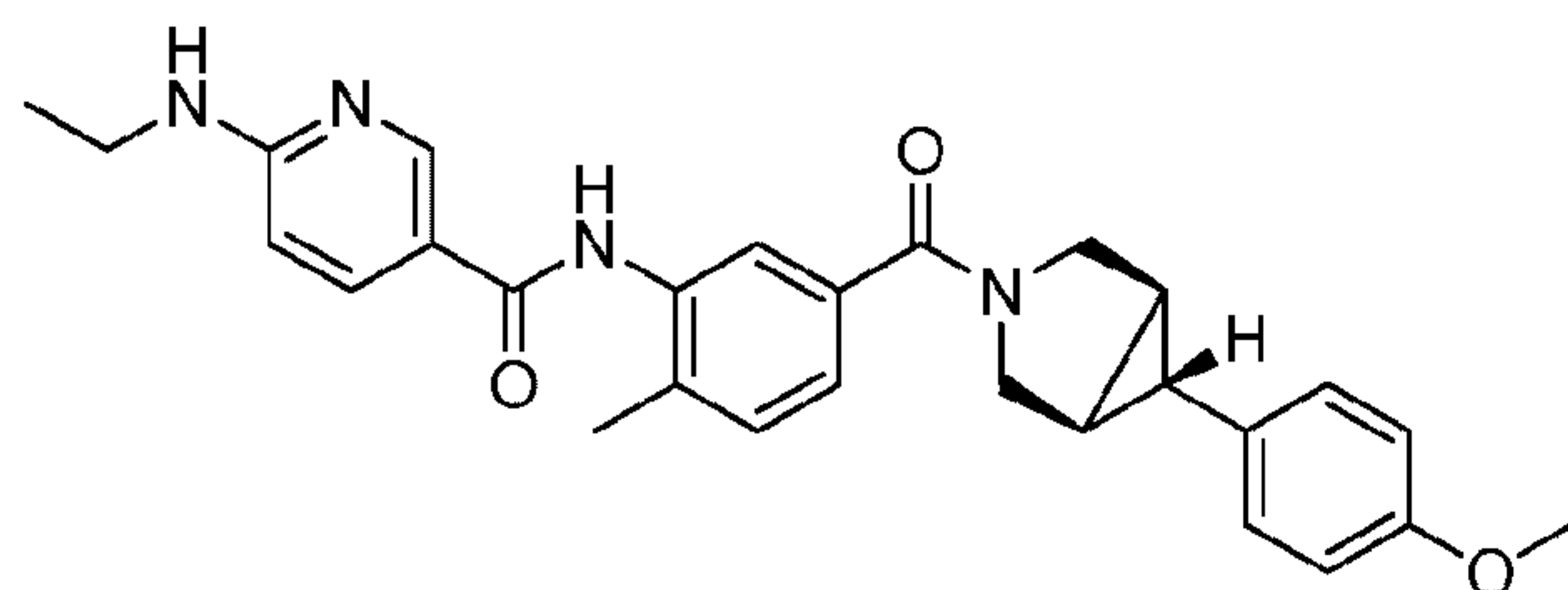
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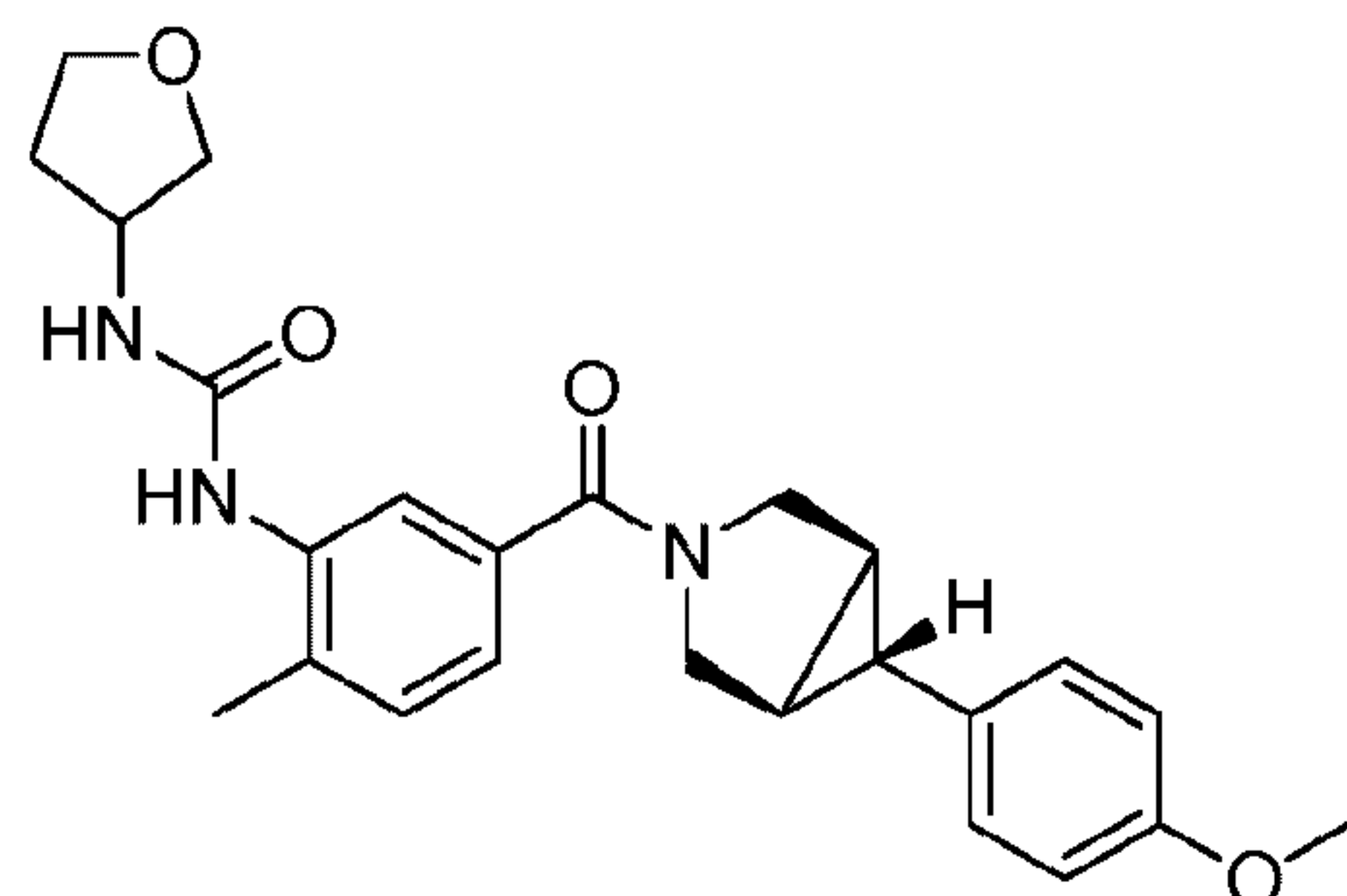
[0635] Compound 118.11. 6-Chloro-N-(5-(6-(4-methoxyphenyl)-3-azabicyclo[3.1.0]hexane-3-carbonyl)-2-methylphenyl)nicotinamide. To a solution of (3-Amino-4-methylphenyl)(6-(4-methoxyphenyl)-3-azabicyclo[3.1.0]hexan-3-yl)methanone (150 mg, 0.47 mmol) and Et₃N (0.25 mL, 1.8 mmol) in CH₂Cl₂ (4 mL) at 0 °C was added 6-chloronicotinoyl chloride (106 mg, 0.6 mmol). The ice bath was removed after the addition. The reaction mixture was stirred at room temperature for 1.5 h and then purified by flash column chromatography with EtOAc in hexane (60%, then 100%) to give the title compound as a white foam (0.172 g, 80% yield). MS [M+H]⁺: 462, 464.



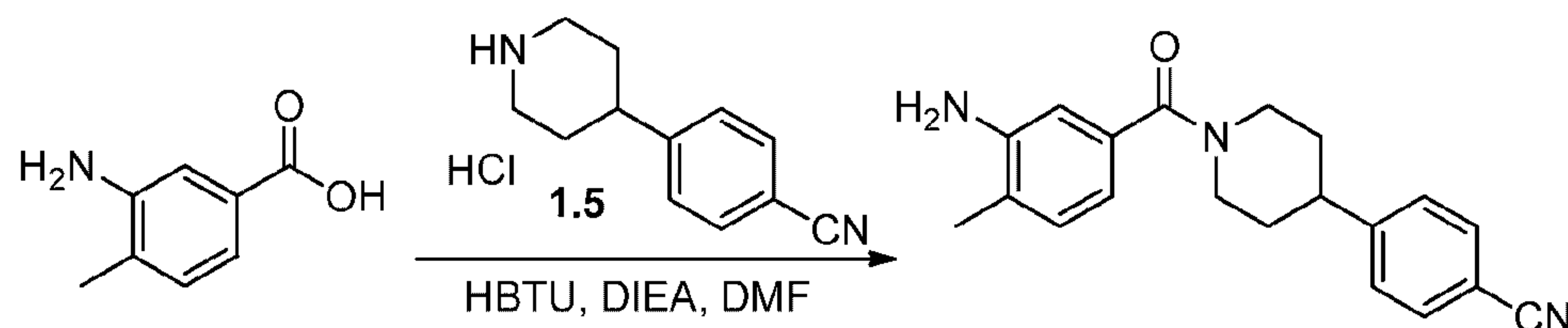
[0636] Compound 118. 6-(Isopropylamino)-N-(5-(6-(4-methoxyphenyl)-3-azabicyclo[3.1.0]hexane-3-carbonyl)-2-methylphenyl)nicotinamide. A mixture of 6-chloro-N-(5-(6-(4-methoxyphenyl)-3-azabicyclo[3.1.0]hexane-3-carbonyl)-2-methylphenyl)nicotinamide (compound 118.11, 0.107 g, 0.23 mmol) and isopropylamine (1.5 mL) in DMSO (1.5 mL) was heated at 120 °C in a sealed pressure tube overnight. After cooling to room temperature, the reaction mixture was poured into saturated aqueous NaHCO₃ and extracted with EtOAc (3x). The combined organic extract was dried over MgSO₄, filtered and concentrated. The residue was triturated with hexane to give the title compound as a white powder (40 mg, 36% yield). MS [M+H]⁺: 485. ¹H-NMR (DMSO-d₆, 400 Hz) δ 9.63 (s, 1H), 8.69 (d, J = 3 Hz, 1H), 7.95-7.90 (m, 1H), 7.55-7.51 (m, 1H), 7.39-7.30 (m, 2H), 7.10-7.03 (m, 3H), 6.84 (d, J = 9.2 Hz, 2H), 6.52 (d, J = 9.2 Hz, 1H), 4.17-4.07 (m, 2H), 3.85-3.77 (m, 1H), 3.74 (s, 3H), 3.65-3.51 (m, 2H), 2.30 (s, 3H), 1.87 (s, 2H), 1.69 (t, J = 3.7 Hz, 1H), 1.20 (d, J = 7.2 Hz, 6H).



[0637] Compound 119. 6-(Ethylamino)-N-(5-(6-(4-methoxyphenyl)-3-azabicyclo[3.1.0]hexane-3-carbonyl)-2-methylphenyl)nicotinamide. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound **118**. MS $[M+H]^+$: 471. ^1H NMR (DMSO- d_6 , 400 Hz) δ 9.62 (s, 1H), 8.66 (d, $J = 2.4$ Hz, 1H), 7.91 (dd, $J = 2.4, 9.0$ Hz, 1H), 7.50 (s, 1H), 7.34-7.24 (m, 2H), 7.18 (t, $J = 6.0$ Hz, 1H), 7.02 (d, $J = 8.8$ Hz, 2H), 6.81 (d, $J = 8.8$ Hz, 2H), 6.50 (d, $J = 9.2$ Hz, 1H), 4.08 (d, $J = 12.4$ Hz, 1H), 3.81-3.75 (m, 1H), 3.70 (s, 3H), 3.59 (d, $J = 11.2$ Hz, 1H), 3.52 (d, $J = 13.2$ Hz, 1H), 3.37-3.30 (m, 2H), 2.26 (s, 3H), 1.84 (s, 2H), 1.66 (t, $J = 3.2$ Hz, 1H), 1.16 (t, $J = 8.4$ Hz, 3H).

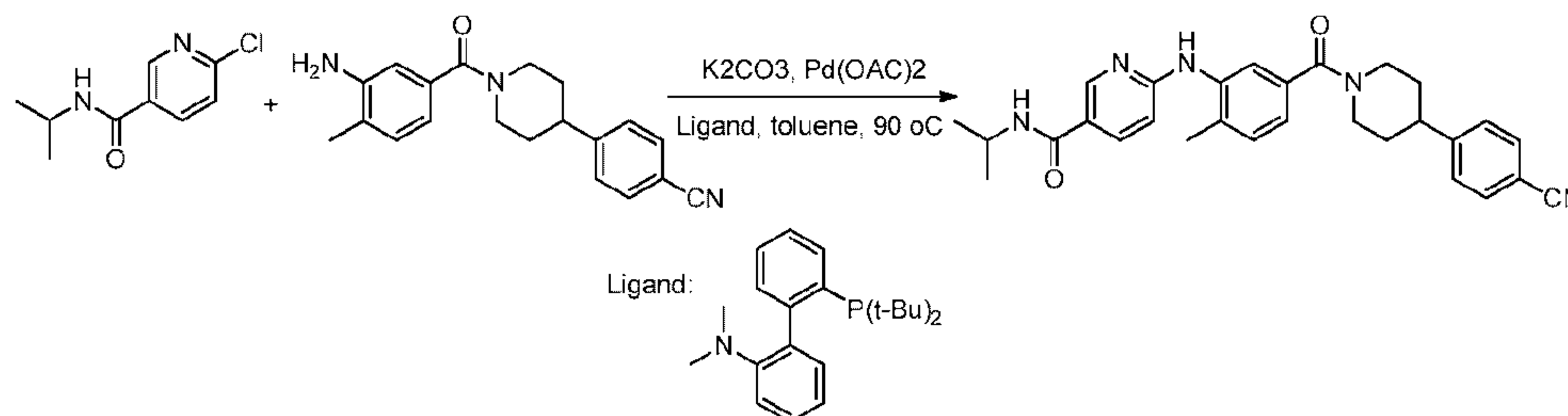


[0638] Compound 120. 1-(5-(6-(4-Methoxyphenyl)-3-azabicyclo[3.1.0]hexane-3-carbonyl)-2-methylphenyl)-3-(tetrahydrofuran-3-yl)urea. The title compound was prepared using readily available reagents and procedures similar to those used for the preparation of compounds **64** and **118**. m/z (ES $^+$) 436 (M+H) $^+$.

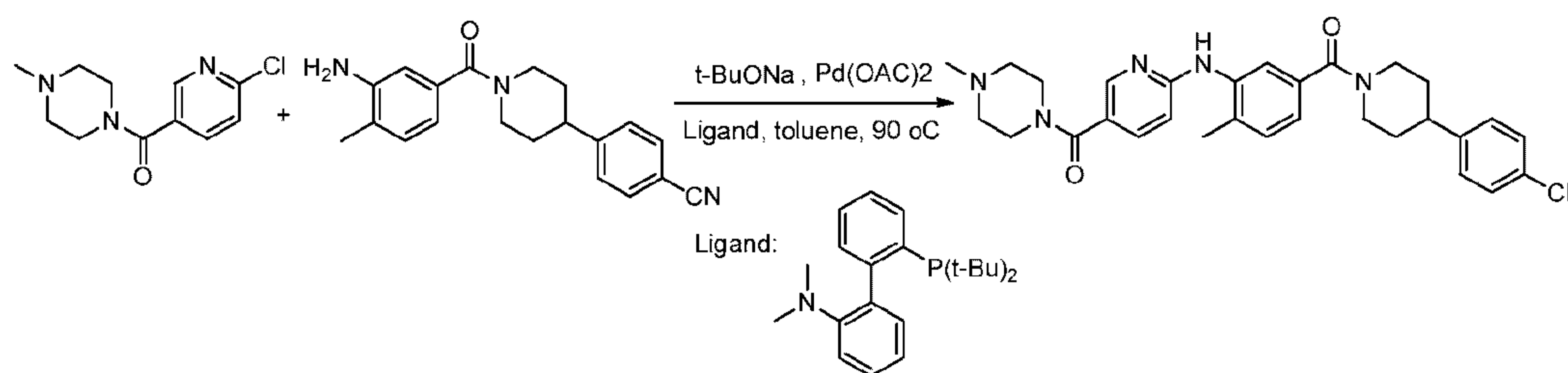


[0639] Compound 121.1. 4-(1-(3-Amino-4-methylbenzoyl)piperidin-4-yl)benzonitrile. A solution of 3-amino-4-methylbenzoic acid (1.36g, 9.0mmol), (4-(piperidin-4-yl)benzonitrile HCl salt (compound **1.5**, 2.0 g, 9.0 mmol), EDCI (1.89 g, 9.9 mmol), HOBT (1.66 g, 9.9 mmol, with 20% H_2O) and DIEA (3.13ml, 18.0mmol) in DMF (50ml) was stirred

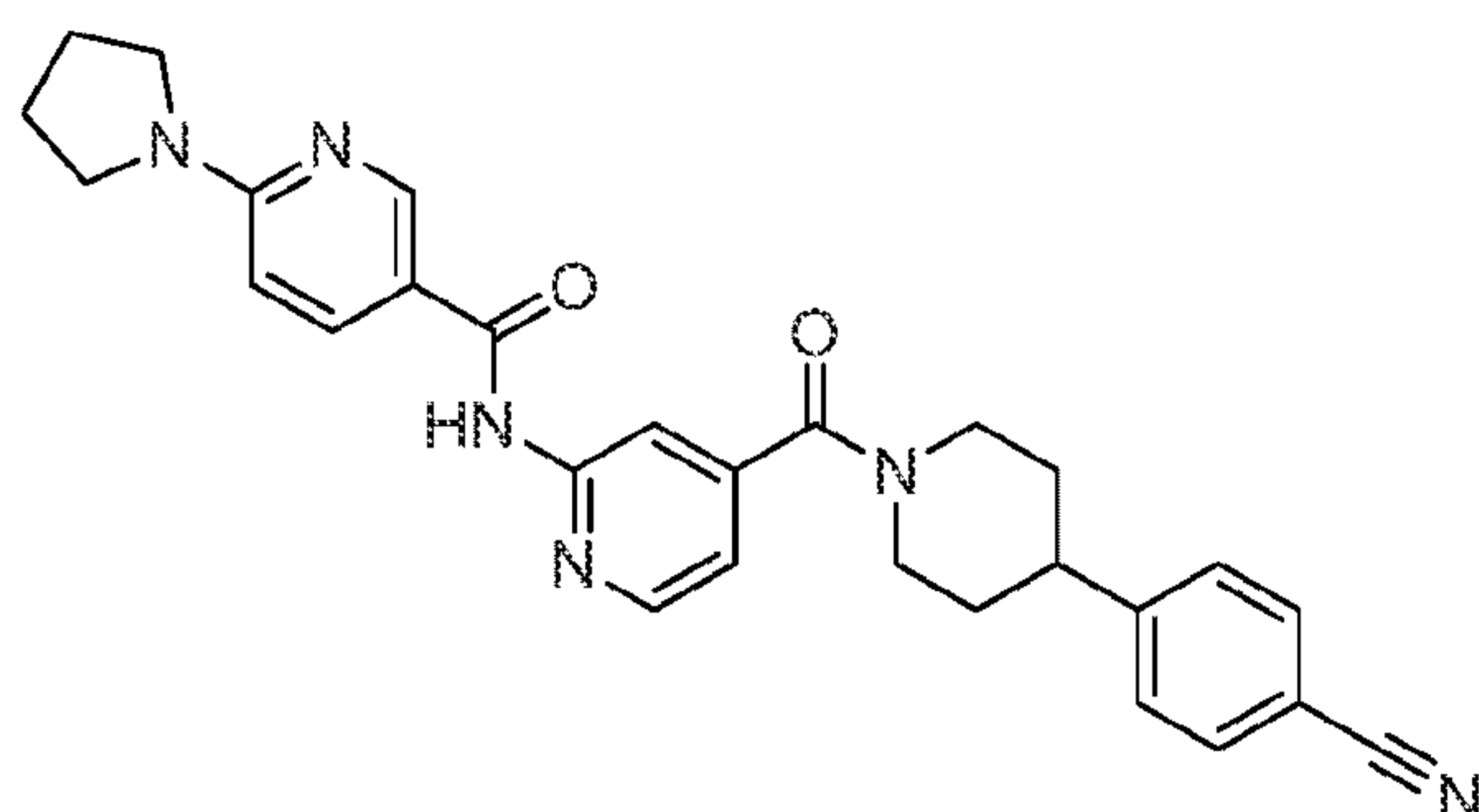
at room temperature overnight. The reaction mixture was poured into cold water (300ml) and off white solids precipitated. The precipitate was filtered, washed with water and dried under reduced pressure in an oven to yield 2.88g (100%) of the title compound. m/z (ES⁺) 320 (M+H)⁺.



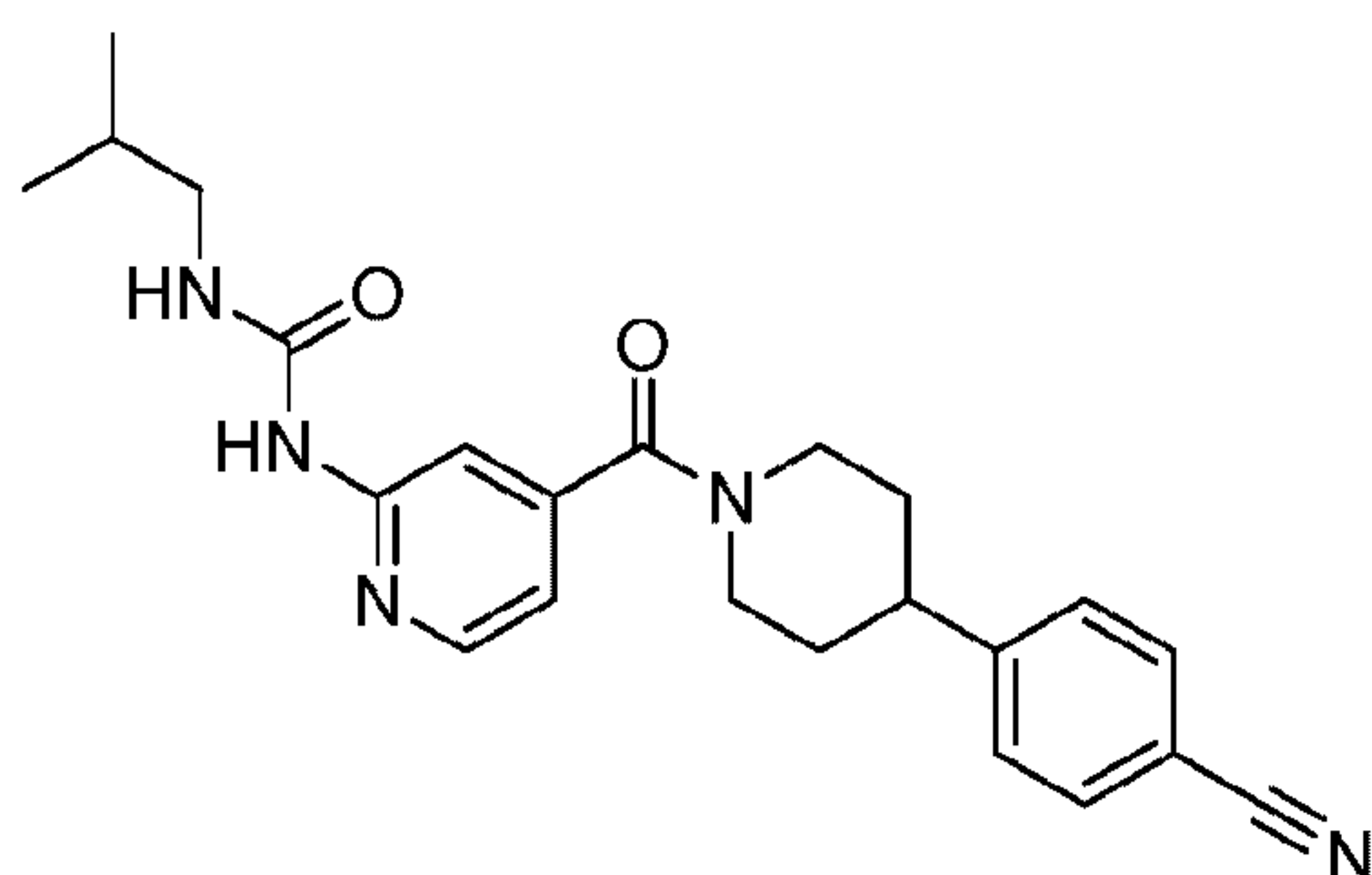
[0640] Compound 121. 6-((5-(4-(4-Cyanophenyl)piperidine-1-carbonyl)-2-methylphenyl)amino)-N-isopropylpyridin-2-ylamine. A mixture of 6-chloro-N-isopropylpyridin-2-ylamine (0.055 g, 0.26 mmol), 4-(1-(3-amino-4-methylbenzoyl)piperidin-4-yl)benzonitrile (**121.1**, 0.1 g, 0.31 mmol), K_2CO_3 (0.171 g, 1.24 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) and the ligand (10.2 mg, 0.03 mmol) in toluene (5 mL) was heated at 90 °C under argon for 3 h. After cooling to room temperature, the reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic extract was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography with EtOAc in hexane (60%, 80%, then 100%) to give the title compound as an off-white powder after lyophilization from CH_3CN/H_2O (11.2 mg, 9% yield). m/z (ES⁺) 482 (M+H)⁺.



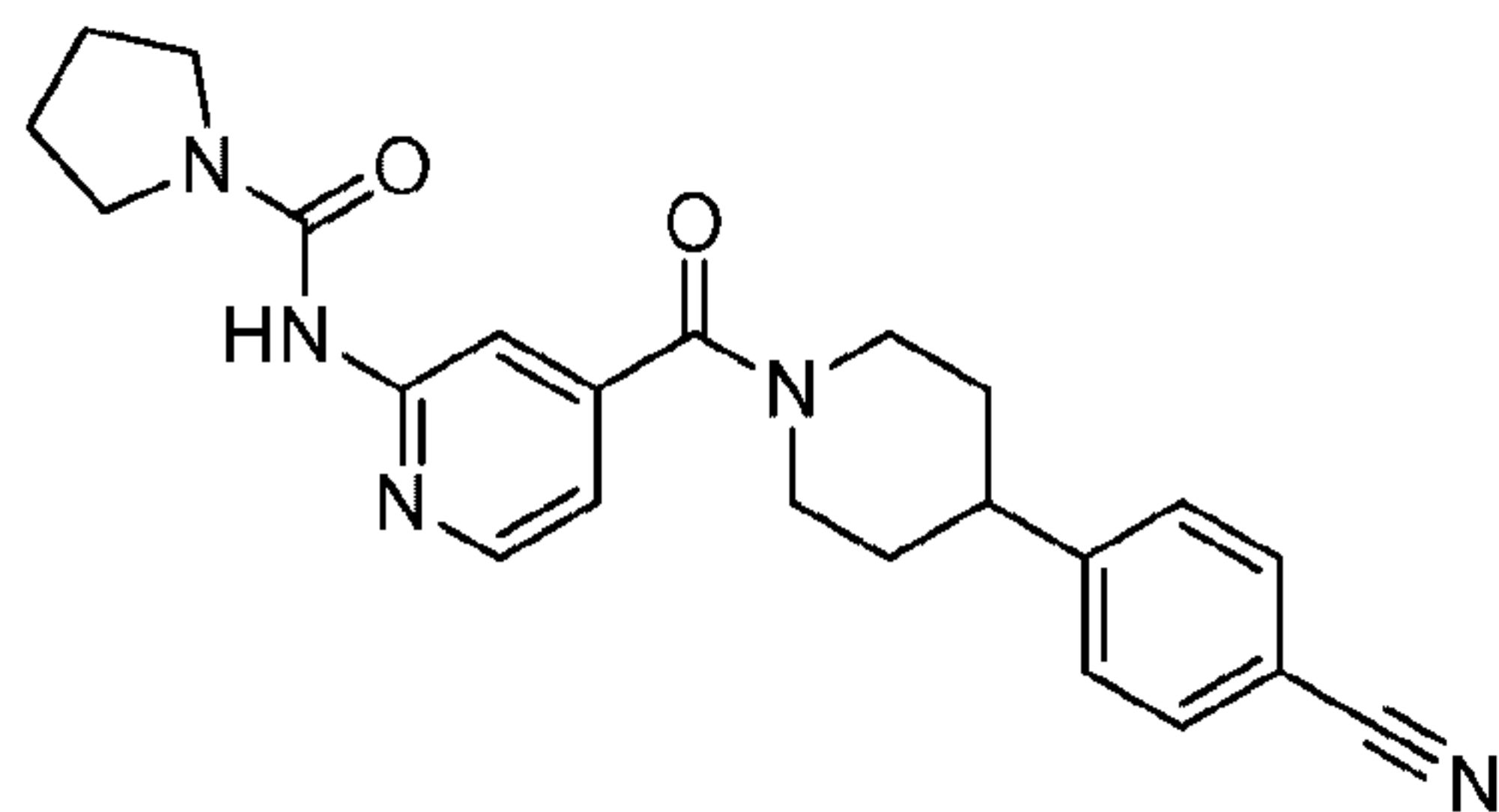
[0641] Compound 122. 4-(1-(4-Methyl-3-((5-(4-methylpiperazine-1-carbonyl)pyridin-2-yl)amino)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound **121** replacing K_2CO_3 with $t-BuONa$. m/z (ES⁺) 524 (M+H)⁺.



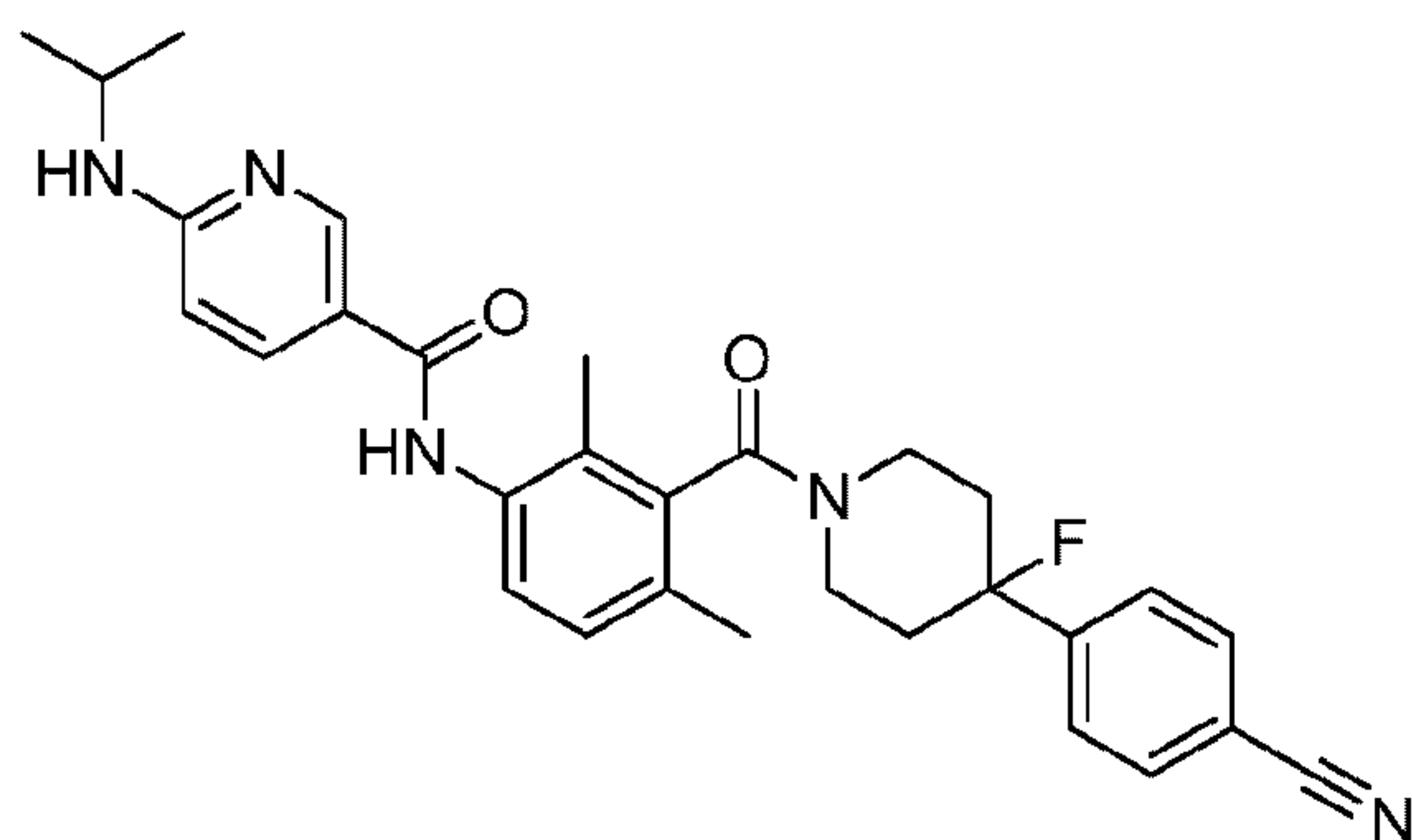
[0642] **Compound 123. N-(4-(4-(4-Cyanophenyl)piperidine-1-carbonyl)pyridin-2-yl)-6-(pyrrolidin-1-yl)nicotinamide.** The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound **43** and using 2-aminoisonicotinic acid in place of 3-amino-4-methylbenzoic acid. m/z (ES⁺) 481 (M+H)⁺.



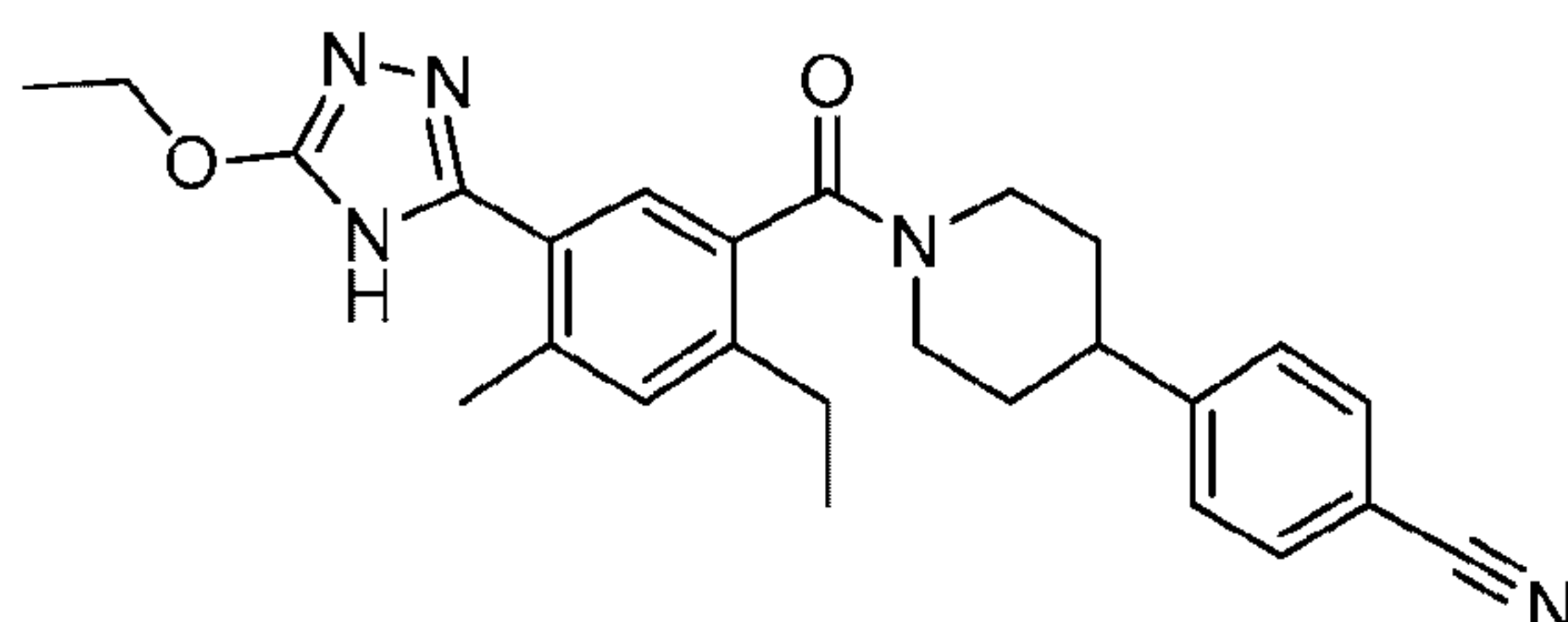
[0643] **Compound 124. 1-(4-(4-(4-Cyanophenyl)piperidine-1-carbonyl)pyridin-2-yl)-3-isobutylurea.** The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound **64** and using 2-aminoisonicotinic acid in place of 3-amino-4-methylbenzoic acid. m/z (ES⁺) 406 (M+H)⁺.



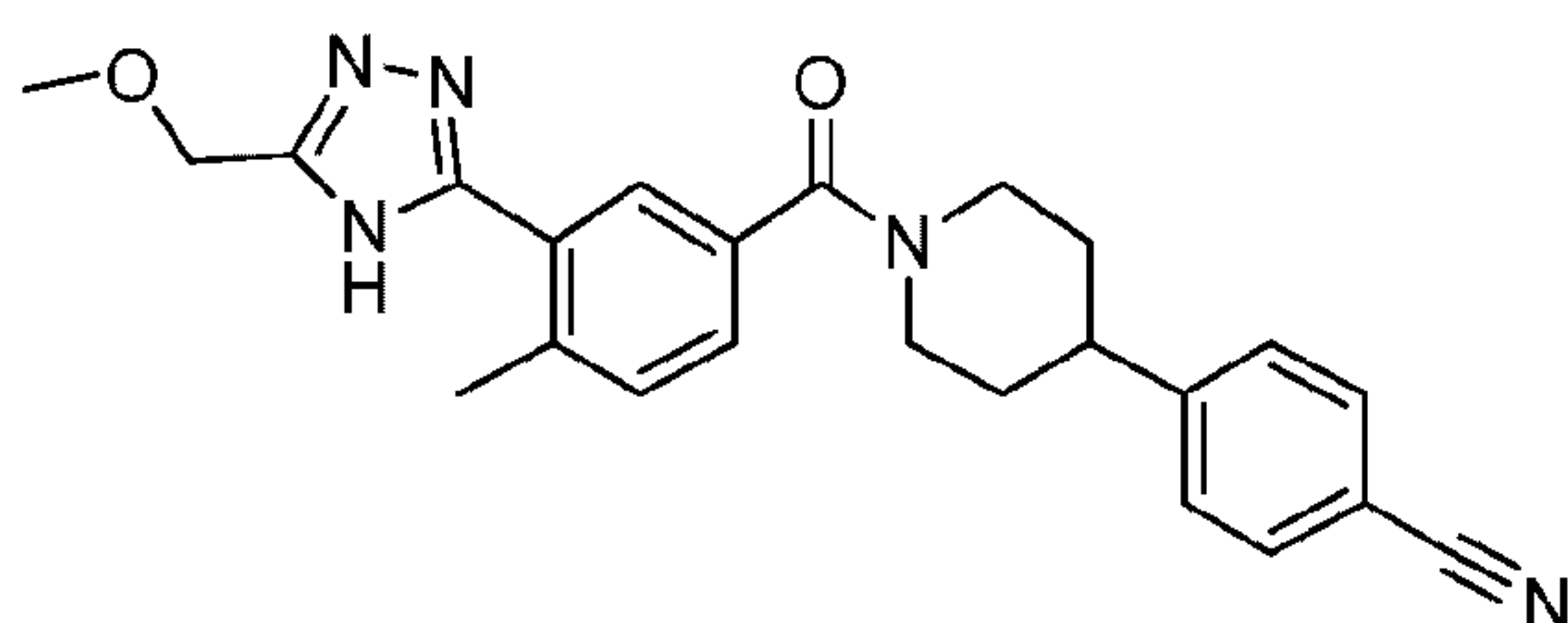
[0644] **Compound 125. N-(4-(4-(4-Cyanophenyl)piperidine-1-carbonyl)pyridin-2-yl)pyrrolidine-1-carboxamide.** The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound **64** and using 2-aminoisonicotinic acid in place of 3-amino-4-methylbenzoic acid. m/z (ES⁺) 404 (M+H)⁺.



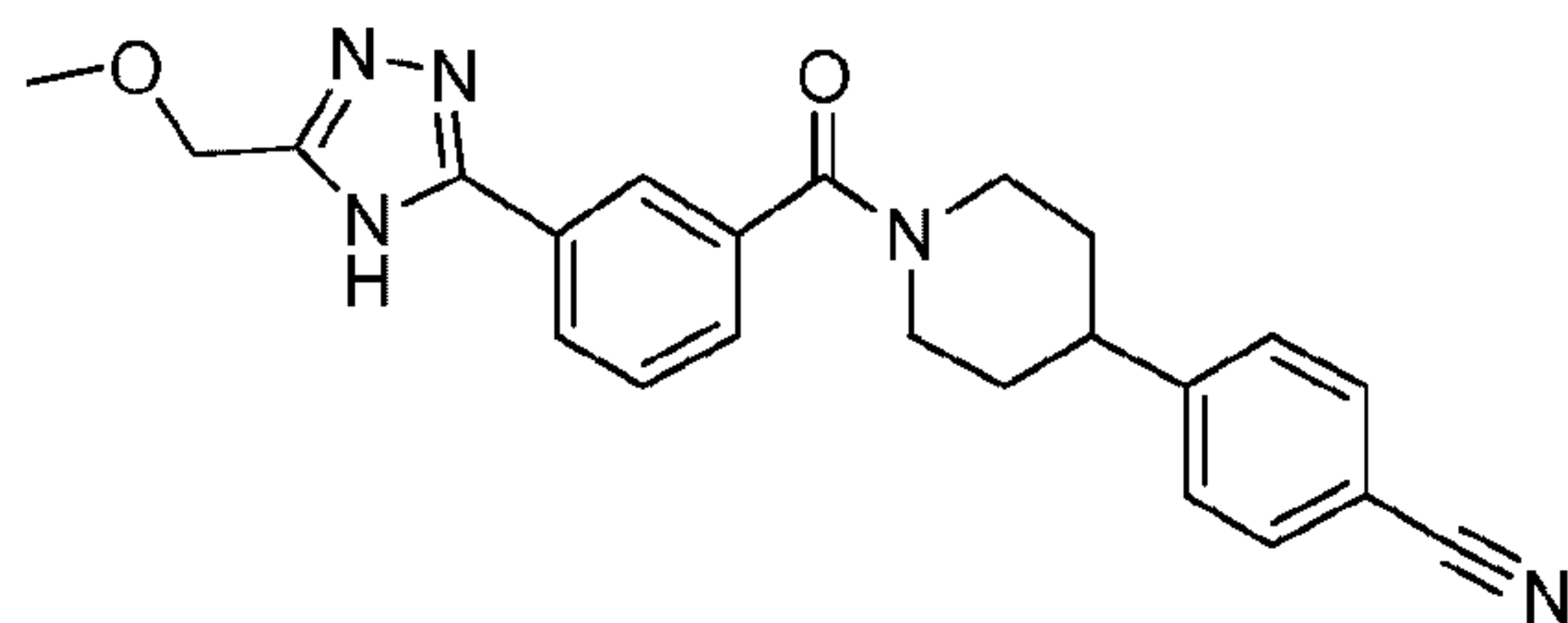
[0645] **Compound 126. N-(3-(4-(4-Cyanophenyl)-4-fluoropiperidine-1-carbonyl)-2,4-dimethylphenyl)-6-(isopropylamino)nicotinamide.** The title compound was prepared using readily available reagents and procedures similar to those used for the preparation of compound **43** and using 3-amino-2,6-dimethylbenzoic acid in place of 3-amino-4-methylbenzoic acid. m/z (ES⁺) 514 (M+H)⁺.



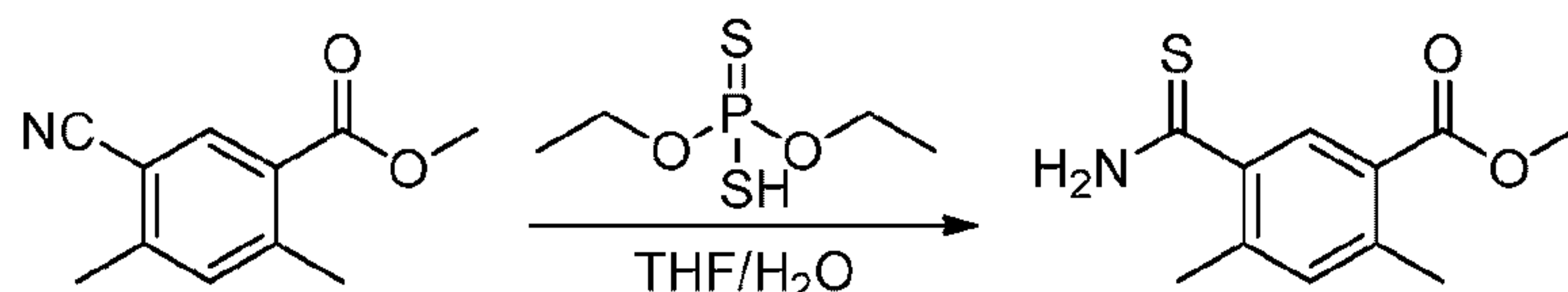
[0646] **Compound 127. 4-(1-(5-(5-Ethoxy-4H-1,2,4-triazol-3-yl)-2-ethyl-4-methylbenzoyl)piperidin-4-yl)benzonitrile.** The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound **39**. m/z (ES⁺) 445 (M+H)⁺.



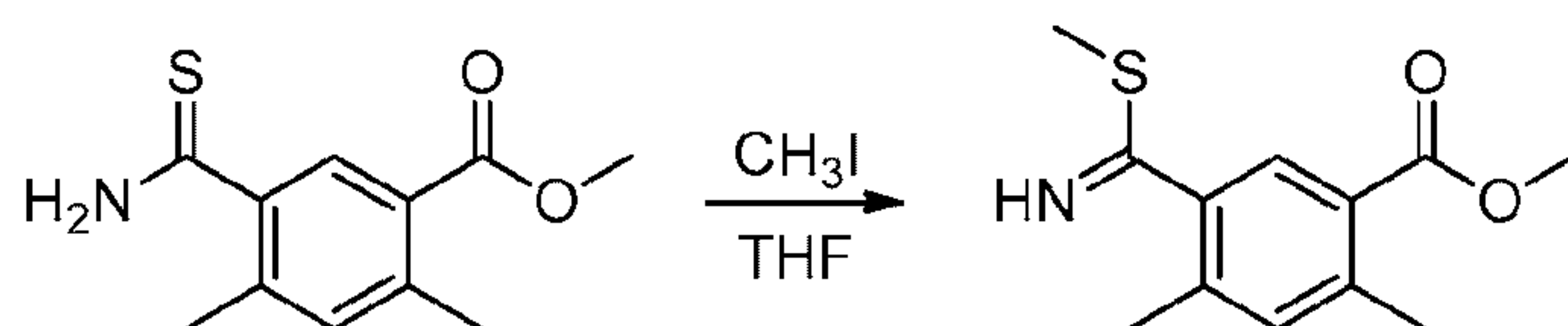
[0647] **Compound 128. 4-(1-(3-(5-(Methoxymethyl)-4H-1,2,4-triazol-3-yl)-4-methylbenzoyl)piperidin-4-yl)benzonitrile.** The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(4-methyl-3-(5-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **38**). m/z (ES⁺) 416 (M+H)⁺.



[0648] Compound 129. 4-(1-(3-(5-(Methoxymethyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound 38. m/z (ES⁺) 402 (M+H)⁺.

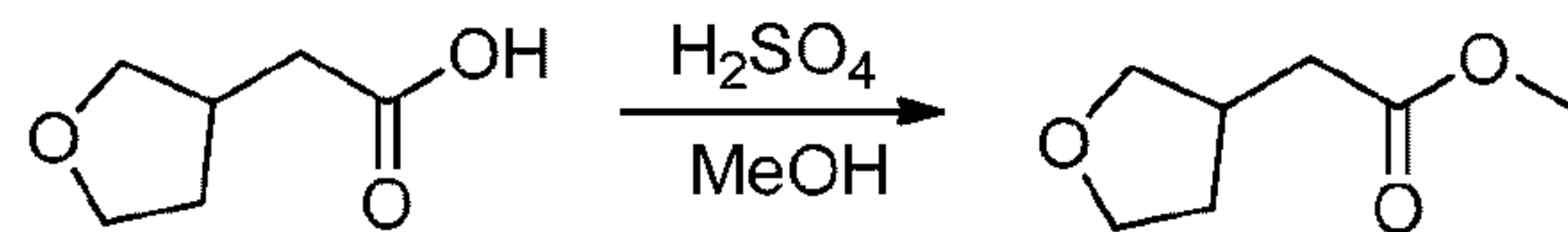


[0649] Compound 130.1. Methyl 5-carbamothioyl-2,4-dimethylbenzoate. To a round-bottom flask was added a solution of methyl 5-cyano-2,4-dimethylbenzoate (compound 2.3, 1.78 g, 9.41 mmol, 1.00 equiv) in tetrahydrofuran/H₂O (30/3 mL). O,O'-diethyl dithiophosphate (3.30 g, 17.7 mmol, 2.00 equiv) was added and the resulting mixture was stirred for 2 days at 85 °C (**CAUTION:** significant gas evolution occurs - this and all other reactions described herein should be carried out in well ventilated fume hoods). After cooling to ambient temperature, the mixture was extracted with 2 x 50 mL of ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:10) as eluent to furnish 1.20 g (57%) of the title compound as a yellow solid.

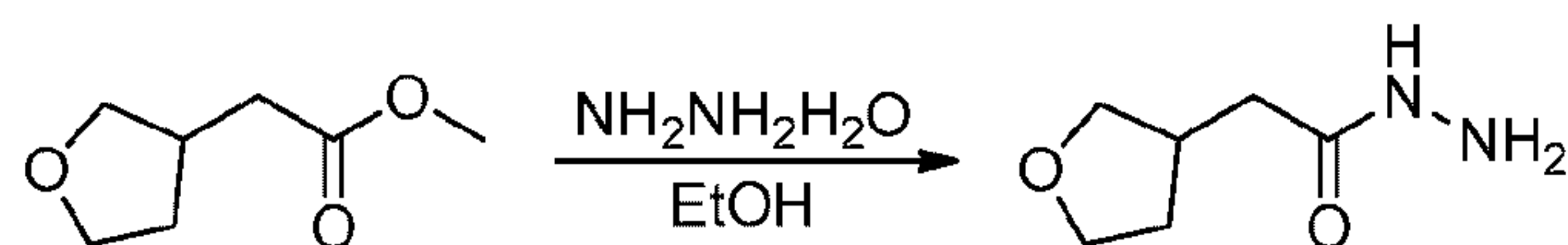


[0650] Compound 130.2. Methyl 5-(imino(methylthio)methyl)-2,4-dimethylbenzoate. To a solution of methyl 5-carbamothioyl-2,4-dimethylbenzoate (compound 130.1, 3.10 g, 12.5 mmol, 1.00 equiv, 90%) in tetrahydrofuran (30 mL) was added CH₃I (3.95 g, 27.8 mmol, 2.00 equiv) and the resulting mixture was stirred overnight at 25 °C. The organic layer was washed with 2 x 30 mL of Na₂S₂O₄ (aq.) and 1 x 30 mL of brine, dried over

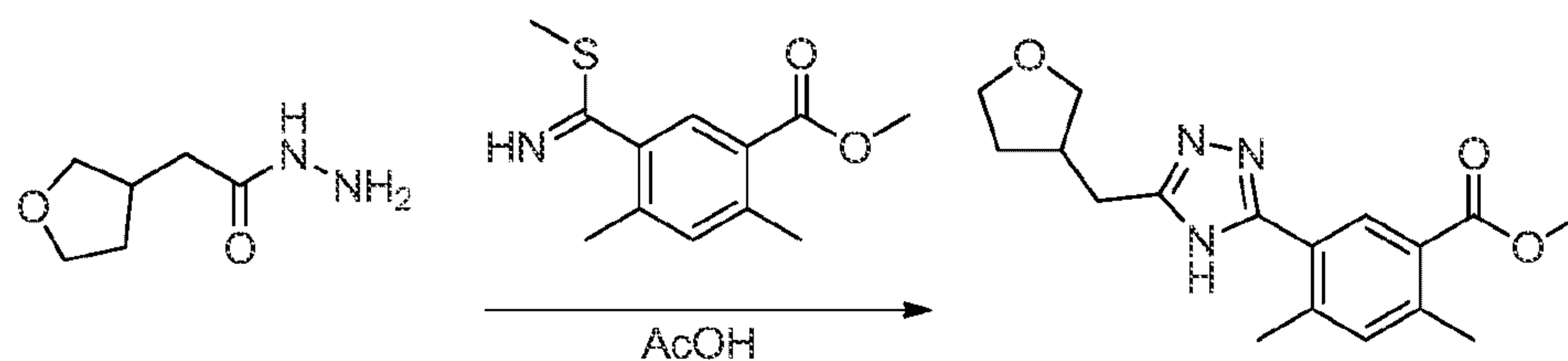
anhydrous sodium sulfate, and concentrated *in vacuo*. This resulted in 2.10 g (64%) of methyl 5-(imino(methylthio)methyl)-2,4-dimethylbenzoate as a yellow oil.



[0651] Compound 130.3. Methyl 2-(tetrahydrofuran-3-yl)acetate. A mixture of 2-(tetrahydrofuran-3-yl)acetic acid (2.00 g, 15.4 mmol, 1.00 equiv) and sulfuric acid (2 mL) in methanol (20 mL) was stirred for 3h at 80 °C in an oil bath. After cooling to ambient temperature, the mixture was diluted with 50 mL of ether and washed with 2 x 20 mL of water, 2 x 20 mL of sodium bicarbonate (aq., sat. Note: gas evolution), and 2 x 20 mL of brine. The organic phase was then dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield 1.50 g (68%) of the title compound as a yellow oil.

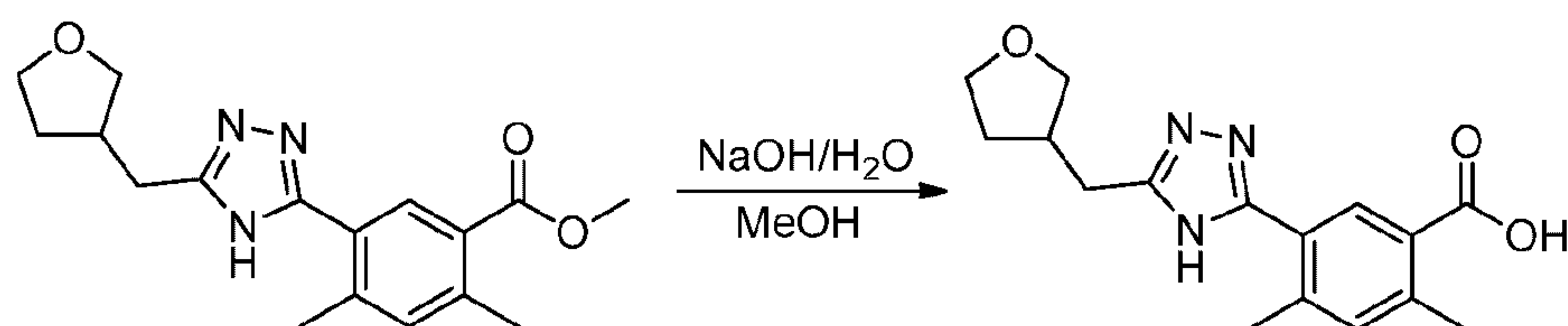


[0652] Compound 130.4. 2-(Tetrahydrofuran-3-yl)acetohydrazide. To a round-bottom flask was added a solution of methyl 2-(tetrahydrofuran-3-yl)acetate (compound 130.3, 1.50 g, 10.4 mmol, 1.00 equiv) and NH₂NH₂·H₂O (1.04 g, 20.8 mmol, 2.00 equiv) in methanol (15 mL). The resulting mixture was stirred overnight at 80 °C in an oil bath. After cooling to ambient temperature, the mixture was concentrated *in vacuo* to yield 1.20 g (80%) of the title compound as a yellow oil.

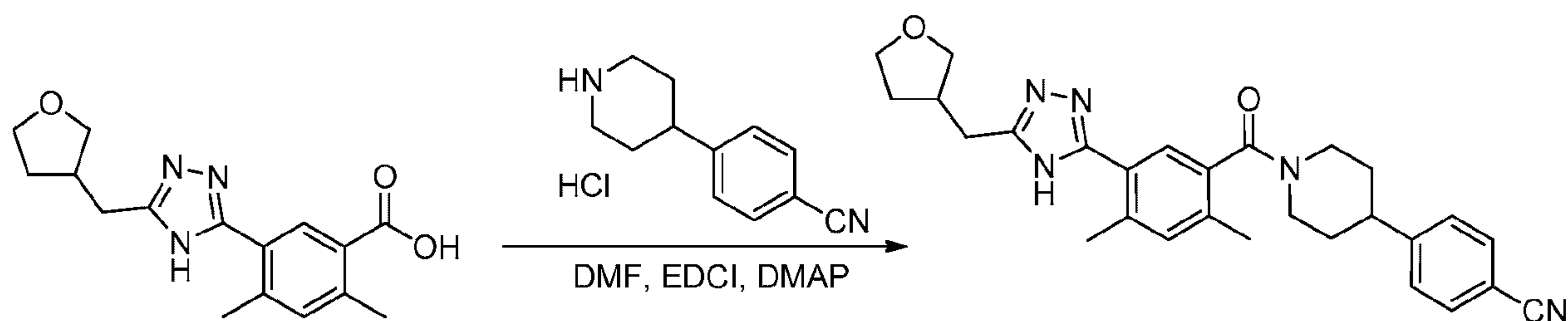


[0653] Compound 130.5. Methyl 2,4-dimethyl-5-(5-((tetrahydrofuran-3-yl)methyl)-4H-1,2,4-triazol-3-yl)benzoate. To a round-bottom flask was added a solution of 2-(tetrahydrofuran-3-yl)acetohydrazide (compound 130.4, 1.20 g, 8.32 mmol, 1.50 equiv) in acetic acid (4 mL). Methyl 2,4-dimethyl-5-(methylsulfanylmethyl) carboximidoylbenzoate (compound 130.2, 1.30 g, 5.48 mmol, 1.00 equiv) was added and the resulting mixture was stirred overnight at 100 °C in an oil bath. After cooling to ambient temperature, the mixture was concentrated *in vacuo*. The residue was diluted with 50 mL of ethyl acetate, then washed with 2 x 20 mL of water and 2 x 20 mL of brine. The organic phase was dried over

anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (0:1-1:10-1:1) as eluent to furnish 0.600 g (35%) of the title compound as a yellow solid.

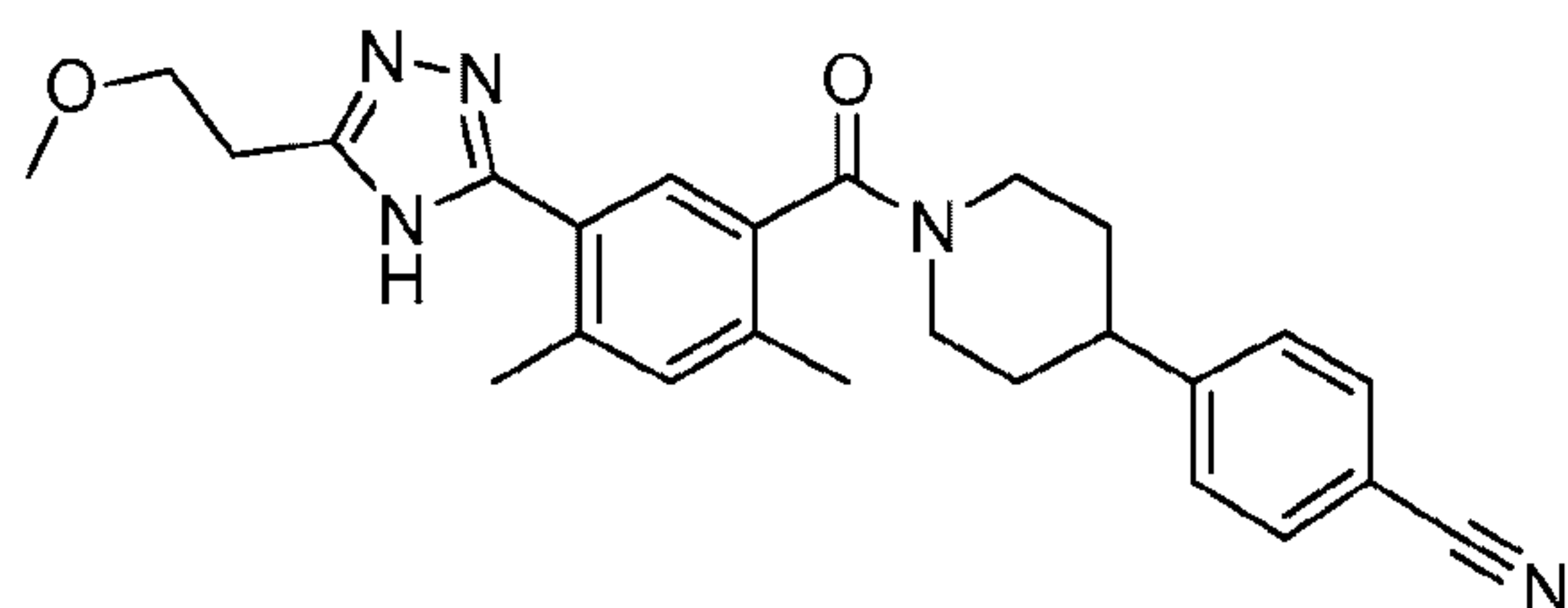


[0654] Compound 130.6. 2,4-Dimethyl-5-(5-((tetrahydrofuran-3-yl)methyl)-4H-1,2,4-triazol-3-yl)benzoic acid. To a round-bottom flask was added a solution of methyl 2,4-dimethyl-5-(5-((tetrahydrofuran-3-yl)methyl)-4H-1,2,4-triazol-3-yl)benzoate (compound **130.5**, 600 mg, 1.90 mmol, 1.00 equiv) in methanol (10 mL). A solution of sodium hydroxide (381 mg, 9.53 mmol, 5.00 equiv) in water (5 mL) was added and the resulting mixture was stirred for 3h at 70 °C in an oil bath. After cooling to room temperature, the organic solvent was then removed under reduced pressure and the pH of the remaining aqueous phase was adjusted to 3-4 with hydrogen chloride (aq., 1 M). The resulting solids were collected via filtration and dried in an oven under reduced pressure to yield 0.500 g (87%) of the title compound as a yellow solid.

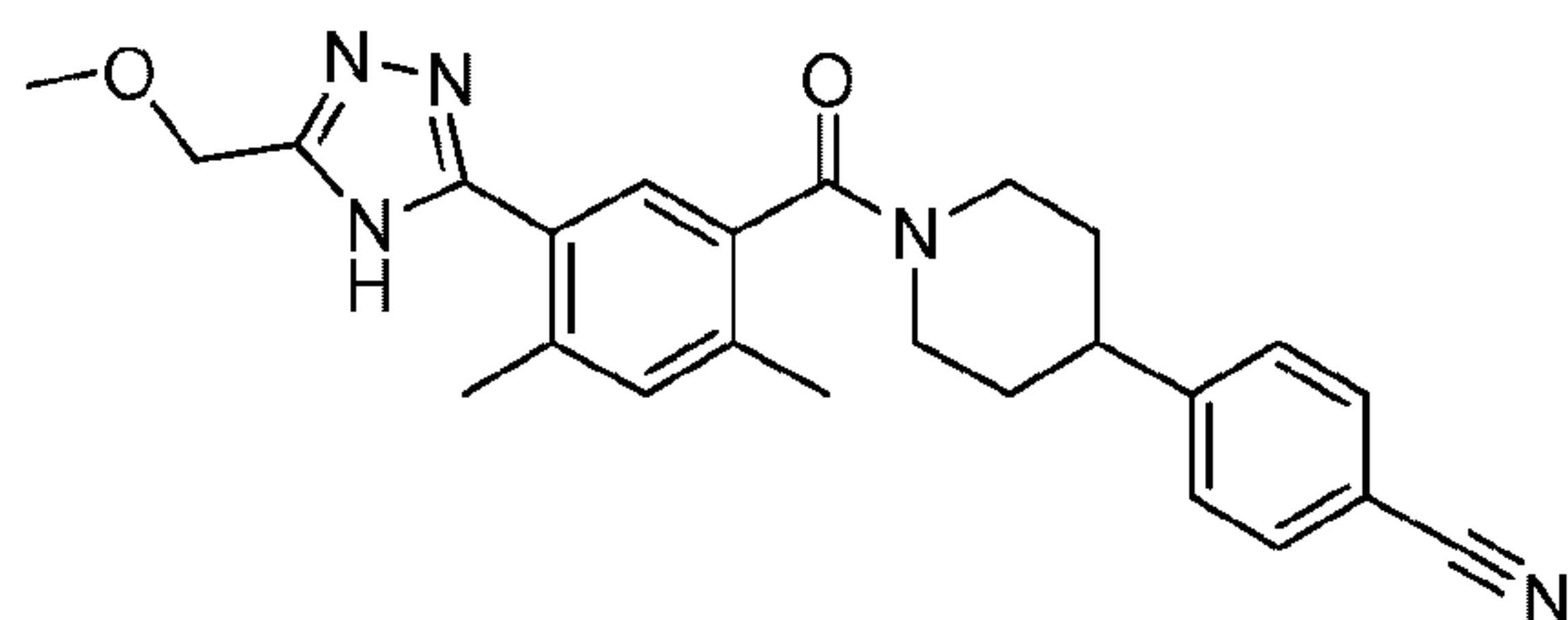


Compound 130. 4-(1-(2,4-Dimethyl-5-(5-((tetrahydrofuran-3-yl)methyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile. A mixture of compound **130.6** (200 mg, 0.660 mmol, 1.00 equiv), EDCI (253 mg, 1.32 mmol, 2.00 equiv), DMAP (243 mg, 1.99 mmol, 3.00 equiv), and 4-(piperidin-4-yl)benzonitrile hydrochloride (compound **1.5**, 148 mg, 0.660 mmol, 1.00 equiv) in DMF (5 mL) was stirred for 3h at 25 °C, then diluted with 50 mL of ethyl acetate. The organic layer was washed with 2 x 10 mL of water, 2 x 10 mL of brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product (~300 mg) was purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-001(SHIMADZU)): Column, SunFire Prep C18, 19*150mm 5um; mobile phase, water with 0.05%TFA and CH₃CN (28% CH₃CN up to 52% in 8 min, up to 100% in 1 min, down to 28% in 1 min); Detector, Waters 2489 254&220nm. The fractions containing pure

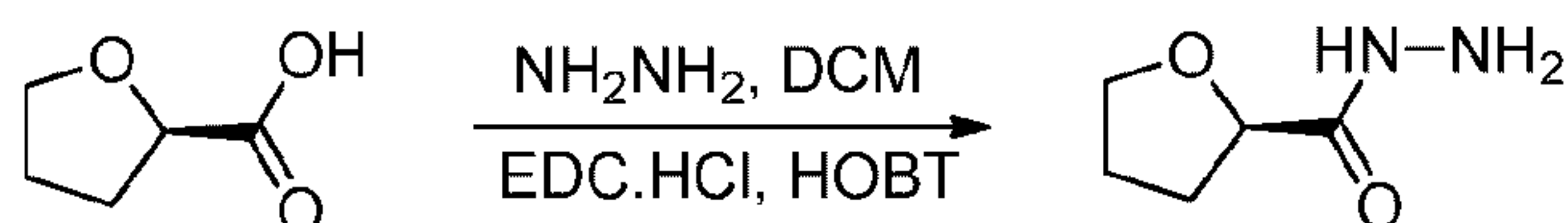
compound were combined and lyophilized to yield 168 mg (52%) of the title compound as a white solid. m/z (ES+) 470 (M+H)⁺. ¹H-NMR (400Hz, CD₃OD): δ 7.68 (d, J = 8.0Hz, 2H), 7.61 (s, 1H), 7.50-7.49 (m, 2H), 7.33-7.31 (m, 1H), 4.90-4.88 (m, 1H), 3.95-3.92 (m, 2H), 3.90-3.81 (m, 1H), 3.79-3.77 (m, 1H), 3.69-3.55 (m, 1H), 3.28-3.25 (m, 1H), 3.03-2.94 (m, 4H), 2.81-2.73 (m, 1H), 2.53 (s, 3H), 2.43 and 2.33 (2s, amide rotamers, ArCH₃, 3H), 2.19-2.15 (m, 1H), 2.13-2.05 (m, 1H), 1.94-1.68 (m, 4H).



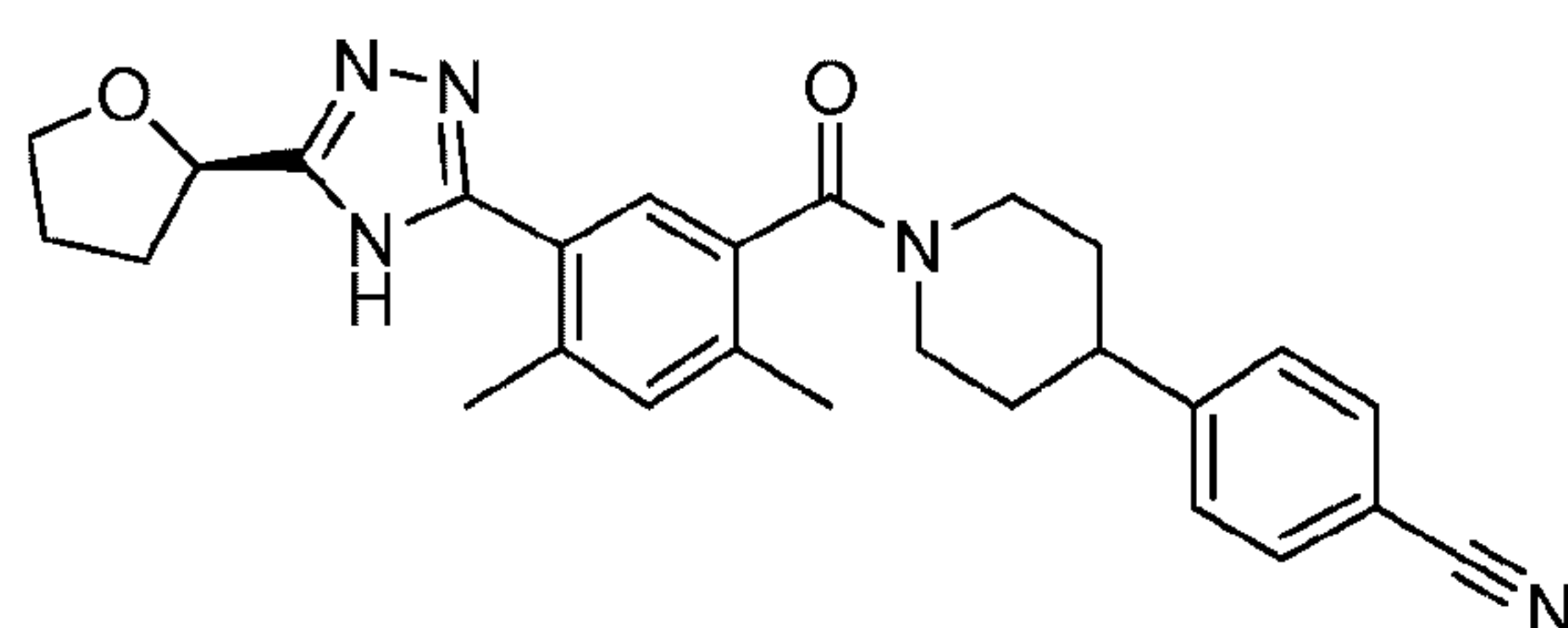
[0655] Compound 131. 4-(1-(5-(5-(2-Methoxyethyl)-4H-1,2,4-triazol-3-yl)-2,4-dimethylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(2,4-dimethyl-5-(5-((tetrahydrofuran-3-yl)methyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **130**), using 3-methoxypropanehydrazide (compound **143.1**) instead of 2-(tetrahydrofuran-3-yl)acetohydrazide (compound **130.4**). m/z (ES+) 444 (M+H)⁺.



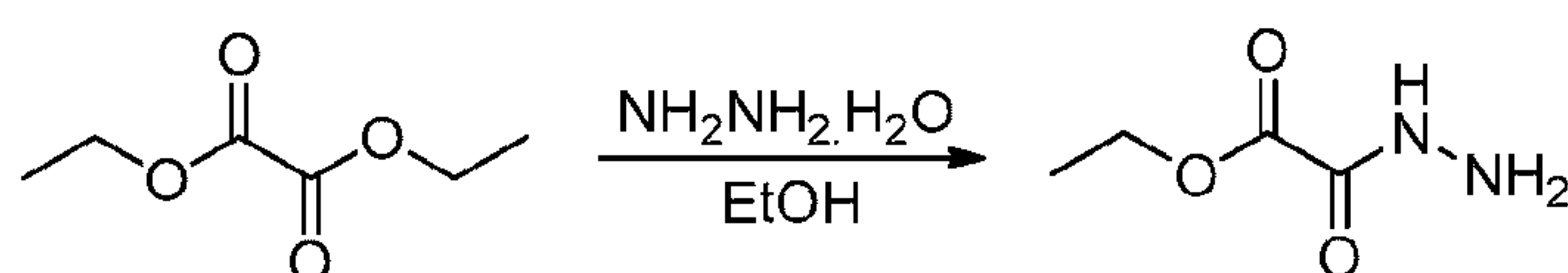
[0656] Compound 132. 4-(1-(5-(5-(Methoxymethyl)-4H-1,2,4-triazol-3-yl)-2,4-dimethylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(2,4-dimethyl-5-(5-((tetrahydrofuran-3-yl)methyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **130**), using 2-methoxyacetohydrazide (compound **190.6**) instead of 2-(tetrahydrofuran-3-yl)acetohydrazide (compound **130.4**). m/z (ES+) 430 (M+H)⁺.



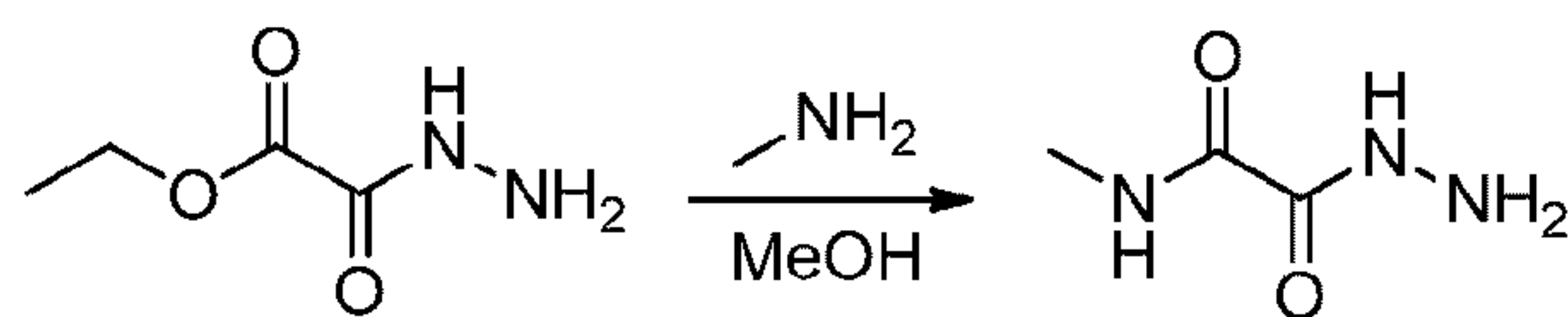
[0657] **Compound 133.1. (R)-Tetrahydrofuran-2-carbohydrazide.** A mixture of (R)-tetrahydrofuran-2-carboxylic acid (5.00 g, 43.1 mmol, 1.00 equiv), EDCI (12.4 g, 64.6 mmol, 1.50 equiv) and HOBT (8.70 g, 64.4 mmol, 1.50 equiv) in dichloromethane (100 mL) was stirred for 30 min at 25 °C. To the mixture was then added hydrazine (2.00 g, 62.4 mmol, 1.50 equiv) dropwise. The resulting mixture was stirred overnight at 25 °C. The solids were removed by filtration, and the filtrate was concentrated *in vacuo* to furnish 25.0 g (crude) of (R)-tetrahydrofuran-2-carbohydrazide as a yellow oil.



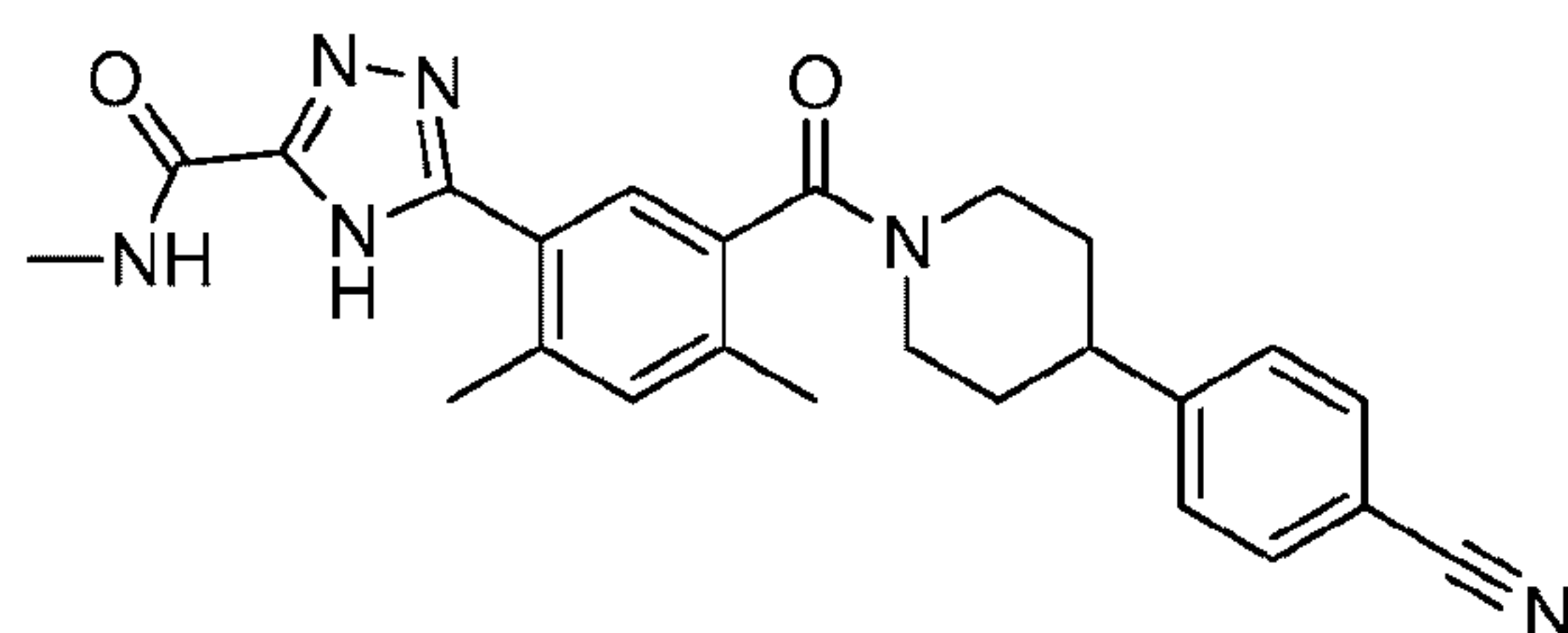
[0658] **Compound 133. (R)-4-(1-(2,4-Dimethyl-5-(5-(tetrahydrofuran-2-yl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile.** The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(2,4-dimethyl-5-(5-((tetrahydrofuran-3-yl)methyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound 130), using (R)-tetrahydrofuran-2-carbohydrazide (compound 133.1) instead of 2-(tetrahydrofuran-3-yl)acetohydrazide (compound 130.4). m/z (ES⁺) 446 (M+H)⁺.



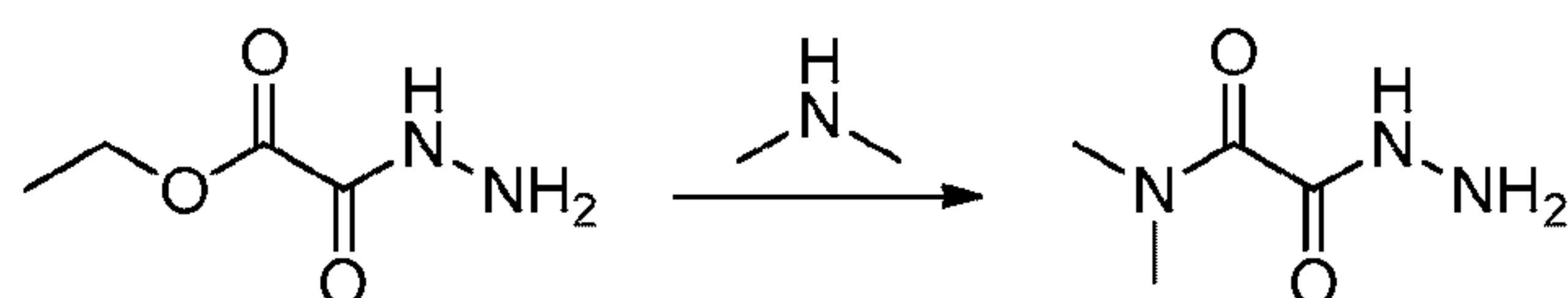
[0659] **Compound 134.1. Ethyl 2-hydrazinyl-2-oxoacetate.** To a round-bottom flask was added a solution of diethyl oxalate (10.0 g, 68.4 mmol, 1.00 equiv) in ethanol (100 mL). Hydrazine hydrate (2.75 g, 85.8 mmol, 1.00 equiv) was added and the resulting mixture was stirred for 3 h at 80 °C. After cooling to ambient temperature, the solids were removed *via* filtration and the filtrate was concentrated *in vacuo* to yield 8.00 g (80%) of the title compound as a colorless oil.



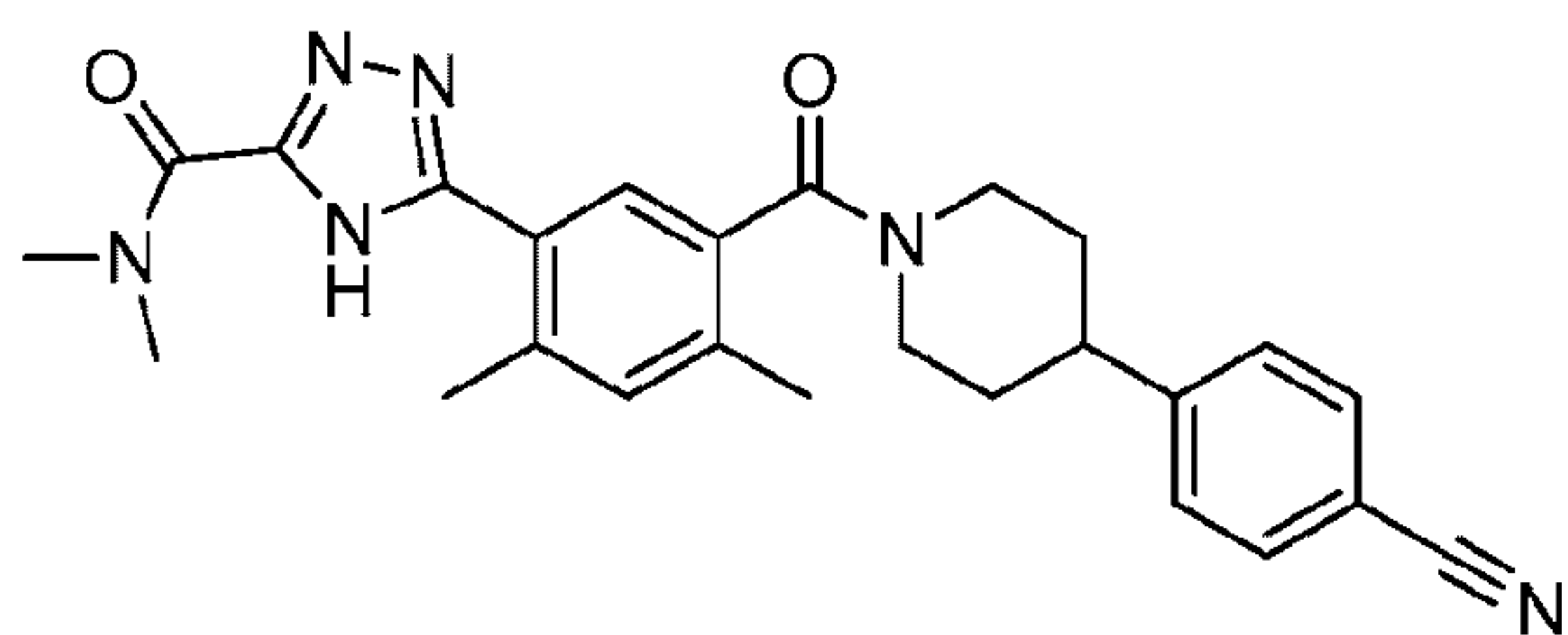
[0660] Compound 134.2. 2-Hydrazinyl-N-methyl-2-oxoacetamide. To a round-bottom flask was added a solution of ethyl 2-hydrazinyl-2-oxoacetate (compound 134.1, 300 mg, 2.04 mmol, 1.00 equiv, 90%) in methanol (10 mL). Methyl amine (10 mL, 40% in water) was added and the resulting mixture was stirred overnight at 70 °C. After cooling to ambient temperature, the solids were collected by filtration and dried to yield 250 mg (94%) of the title compound as a white solid.



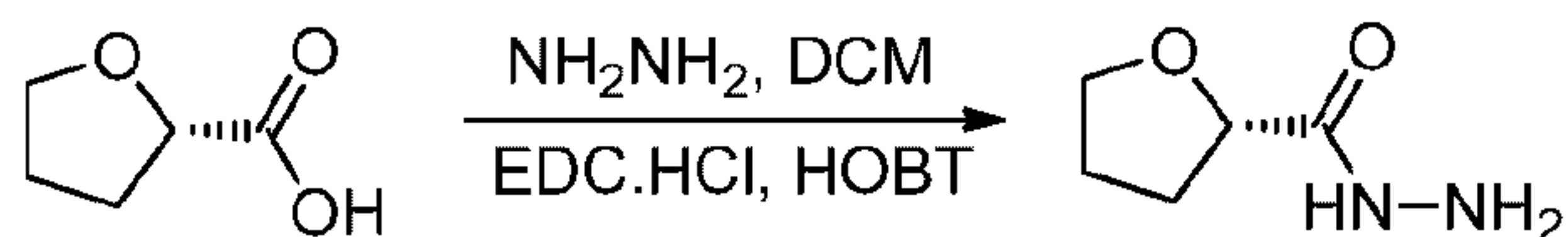
[0661] Compound 134. 5-(5-(4-(4-Cyanophenyl)piperidine-1-carbonyl)-2,4-dimethylphenyl)-N-methyl-4H-1,2,4-triazole-3-carboxamide. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound 130, using compound 134.2 instead of compound 130.4. m/z (ES+) 443 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.69 (d, J = 8.1 Hz, 2H), 7.62-7.43 (m, 3H), 7.32 (s, 1H), ~4.9 (1H partially obscured by water peak), 3.73-3.58 (m, 1H), 3.32-3.18 (m, 1H partially obscured by methanol solvent peak), 3.07-1.91 (m, 5H), 2.58 (s, 3H), 2.43 & 2.33 (2 singlets, amide rotamers, Ar-CH₃, 3H), 2.10-1.93 (m, 1H), 1.93-1.52 (m, 3H).



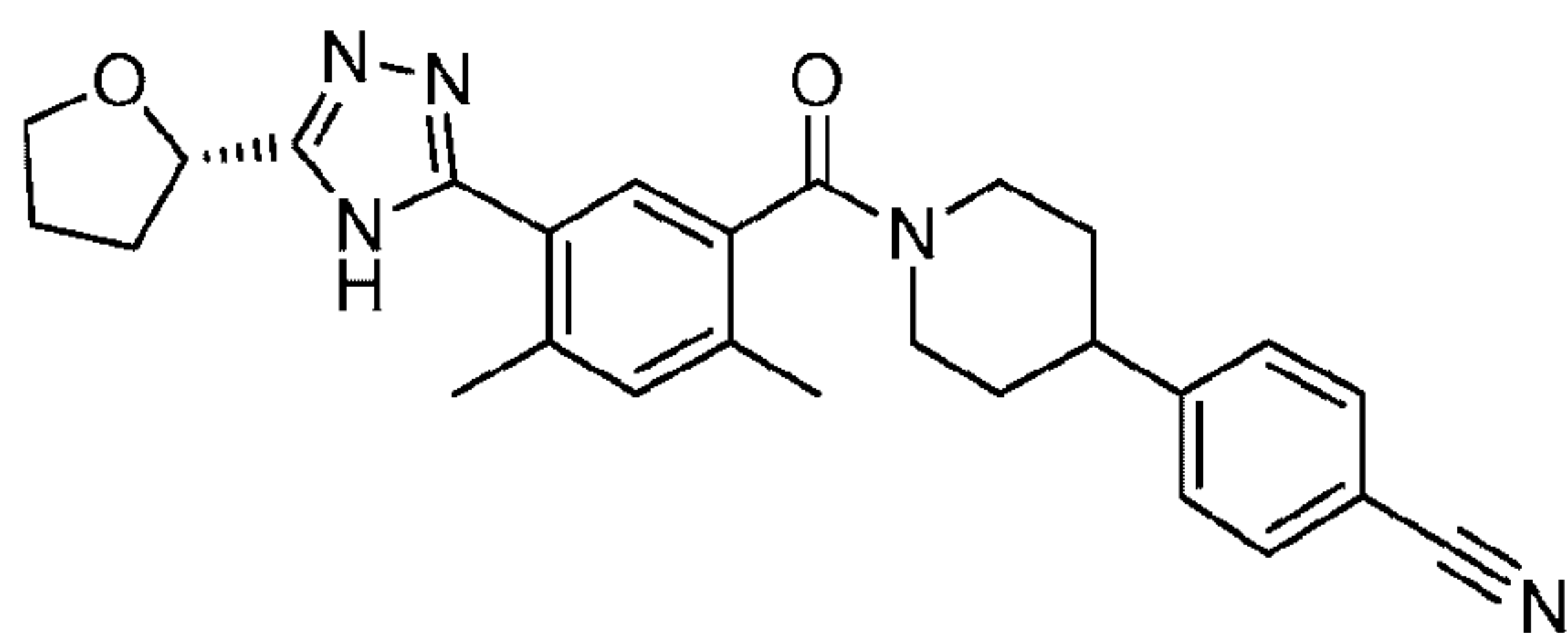
[0662] Compound 135.1. 2-Hydrazinyl-N,N-dimethyl-2-oxoacetamide. To a round-bottom flask was added ethyl 2-hydrazinyl-2-oxoacetate (compound 134.1, 2.00 g, 13.6 mmol, 1.00 equiv, 90%). Dimethylamine (10 mL) was added to the reaction, and then the reaction was stirred overnight at 70 °C in an oil bath. The mixture was cooled to room temperature and concentrated *in vacuo* to yield 1.50 g (76%) of the title compound as a colorless oil.



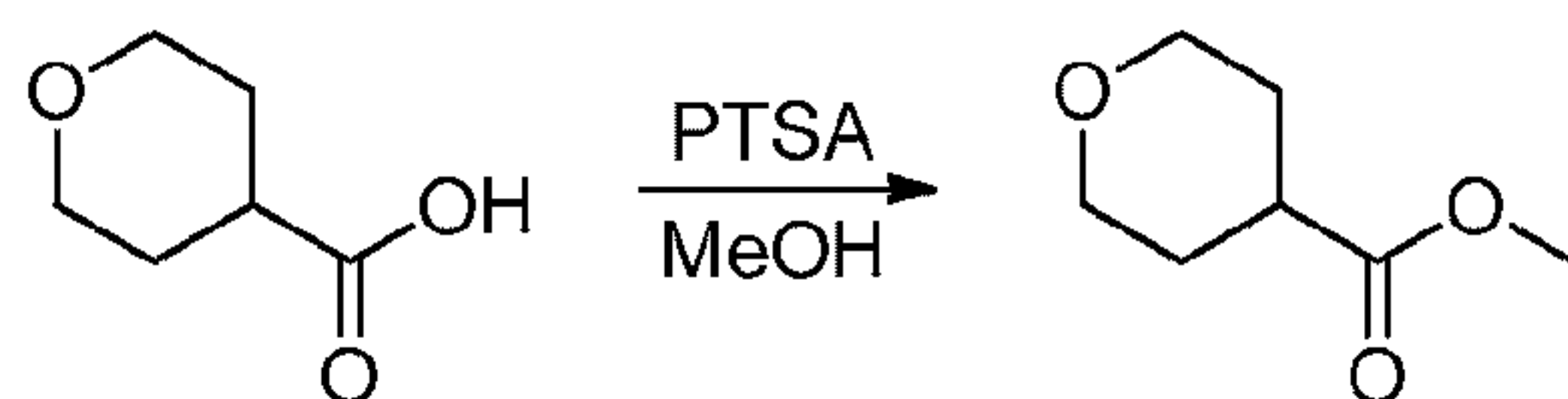
[0663] Compound 135. 5-(5-(4-(4-Cyanophenyl)piperidine-1-carbonyl)-2,4-dimethylphenyl)-*N,N*-dimethyl-4H-1,2,4-triazole-3-carboxamide. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(2,4-dimethyl-5-(5-((tetrahydrofuran-3-yl)methyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **130**), using 2-hydrazinyl-*N,N*-dimethyl-2-oxoacetamide (compound **135.1**) instead of 2-(tetrahydrofuran-3-yl)acetohydrazide (compound **130.4**). m/z (ES⁺) 457 (M+H)⁺.



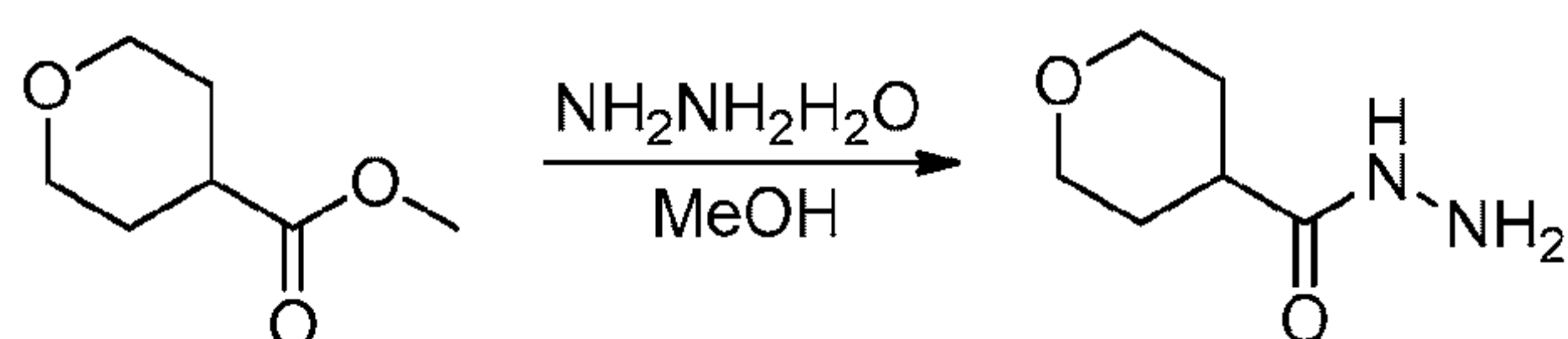
[0664] Compound 136.1. (*S*)-Tetrahydrofuran-2-carbohydrazide. To a round-bottom flask was added a solution of (*S*)-tetrahydrofuran-2-carboxylic acid (3.00 g, 23.3 mmol, 1.00 equiv, 90%) in dichloromethane (40 mL). NH₂NH₂ (2 mL, 2.00 equiv), HOBT (5.20 g, 38.5 mmol, 1.50 equiv), and EDCI (7.50 g, 39.1 mmol, 1.50 equiv) were added and the resulting mixture was stirred overnight at 25 °C. The solids were removed by filtration, and the filtrate was concentrated *in vacuo* to furnish 2.50 g (74%) of (*S*)-tetrahydrofuran-2-carbohydrazide as a yellow oil.



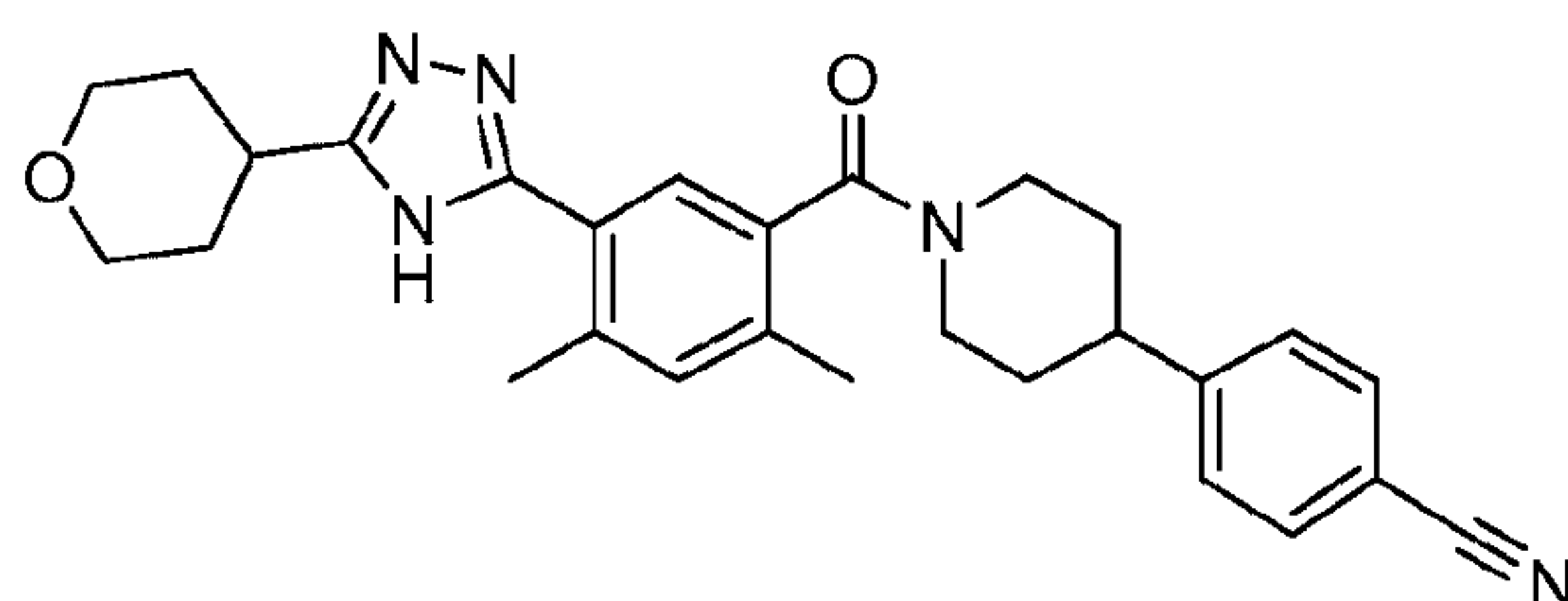
[0665] Compound 136. (*S*)-4-(1-(2,4-Dimethyl-5-(5-(tetrahydrofuran-2-yl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(2,4-dimethyl-5-(5-((tetrahydrofuran-3-yl)methyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **130**), using (*S*)-tetrahydrofuran-2-carbohydrazide (compound **136.1**) instead of 2-(tetrahydrofuran-3-yl)acetohydrazide (compound **130.4**). m/z (ES⁺) 456 (M+H)⁺.



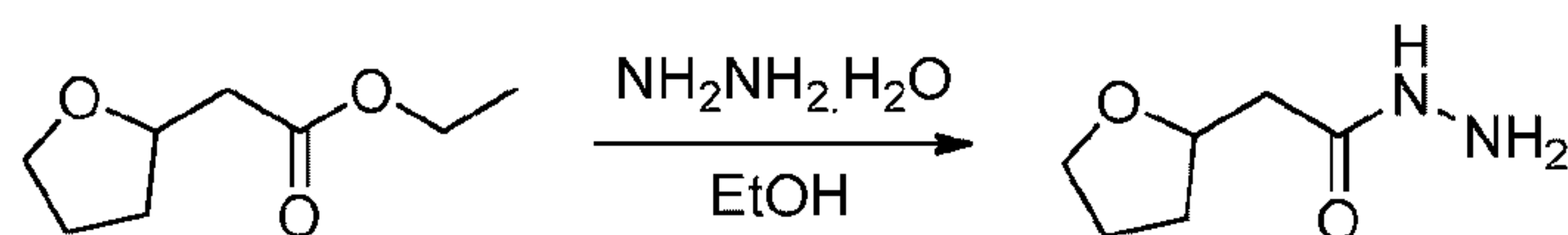
[0666] Compound 137.1. Methyl tetrahydro-2H-pyran-4-carboxylate. To a solution of tetrahydro-2H-pyran-4-carboxylic acid (520 mg, 4.00 mmol, 1.00 equiv) in methanol (50 mL) was added PTSA (35.0 mg, 0.200 mmol). The resulting mixture was stirred overnight at 80 °C in an oil bath, then cooled to ambient temperature and concentrated *in vacuo*. The residue was diluted with 30 mL of water and extracted with 3 x 30 mL of DCM. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. This resulted in 500 mg (87%) of methyl tetrahydro-2H-pyran-4-carboxylate as a colorless oil.



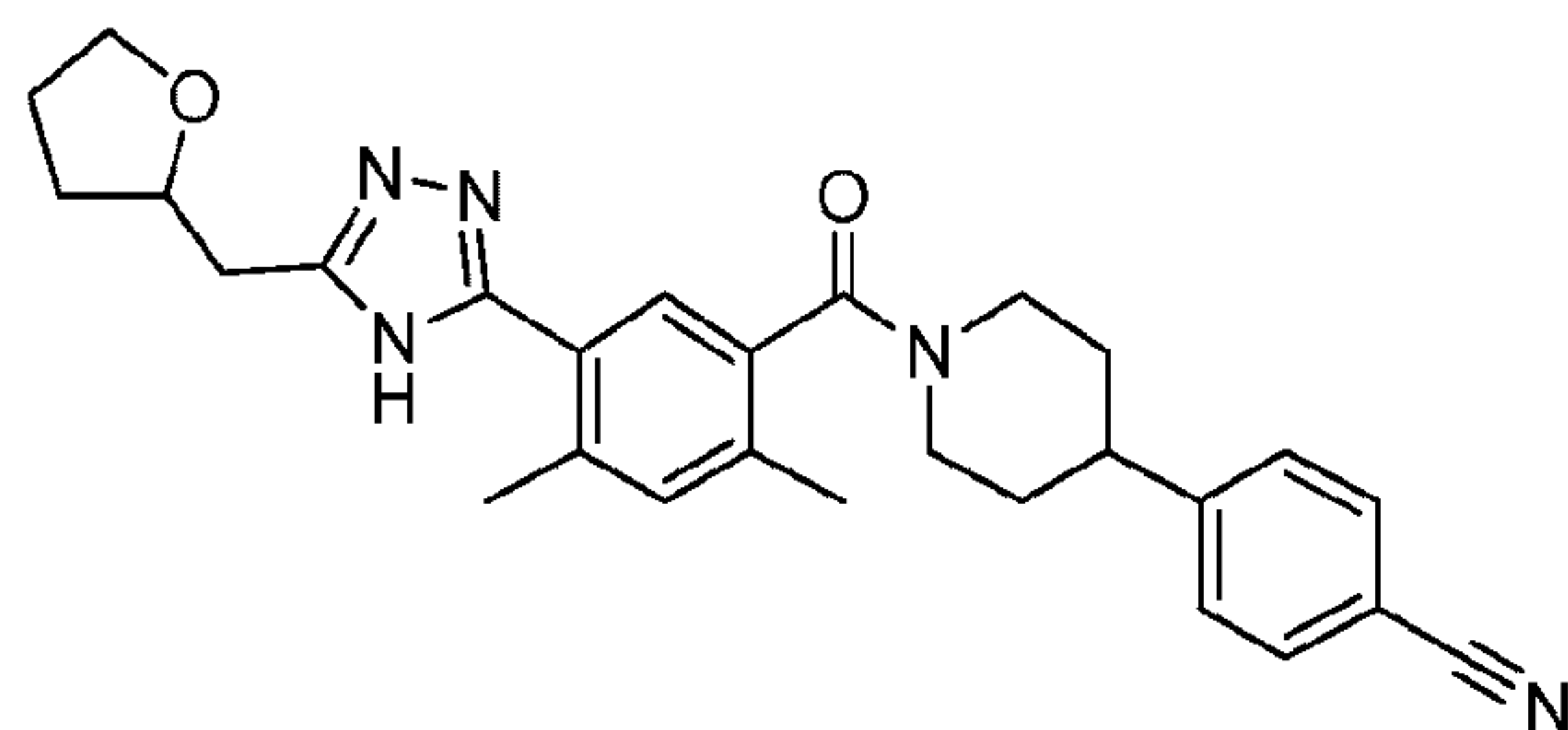
[0667] Compound 137.2. Tetrahydro-2H-pyran-4-carbohydrazide. To a round-bottom flask was added a solution of methyl tetrahydro-2H-pyran-4-carboxylate (compound 137.1, 5.00 g, 31.2 mmol, 1.00 equiv, 90%) in methanol (50 mL). Hydrazine hydrate (5.20 g, 83.2 mmol, 3.00 equiv) was added and the resulting mixture was stirred overnight at 40 °C in an oil bath. After cooling to ambient temperature, the mixture was concentrated *in vacuo* to yield 4.00 g (80%) of tetrahydro-2H-pyran-4-carbohydrazide as a white solid.



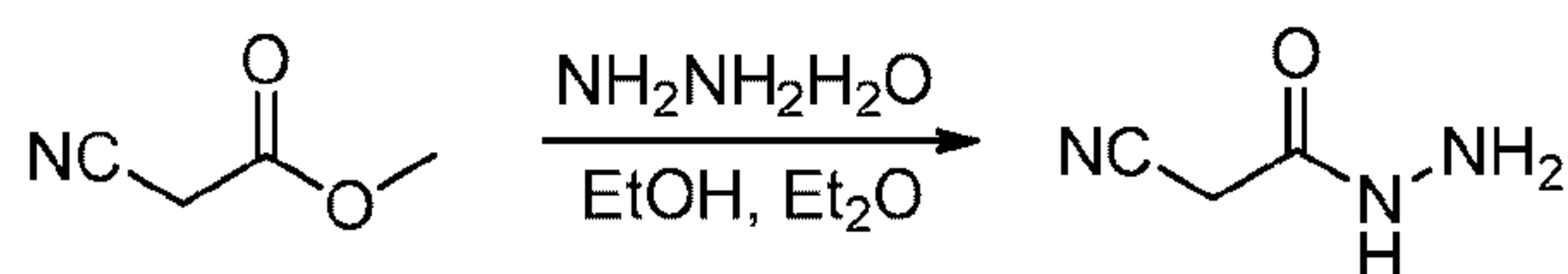
[0668] Compound 137. 4-(1-(2,4-Dimethyl-5-(5-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(2,4-dimethyl-5-(5-((tetrahydrofuran-3-yl)methyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound 130), using tetrahydro-2H-pyran-4-carbohydrazide (compound 137.2) instead of 2-(tetrahydrofuran-3-yl)acetohydrazide (compound 130.4). m/z (ES⁺) 470 (M+H)⁺.



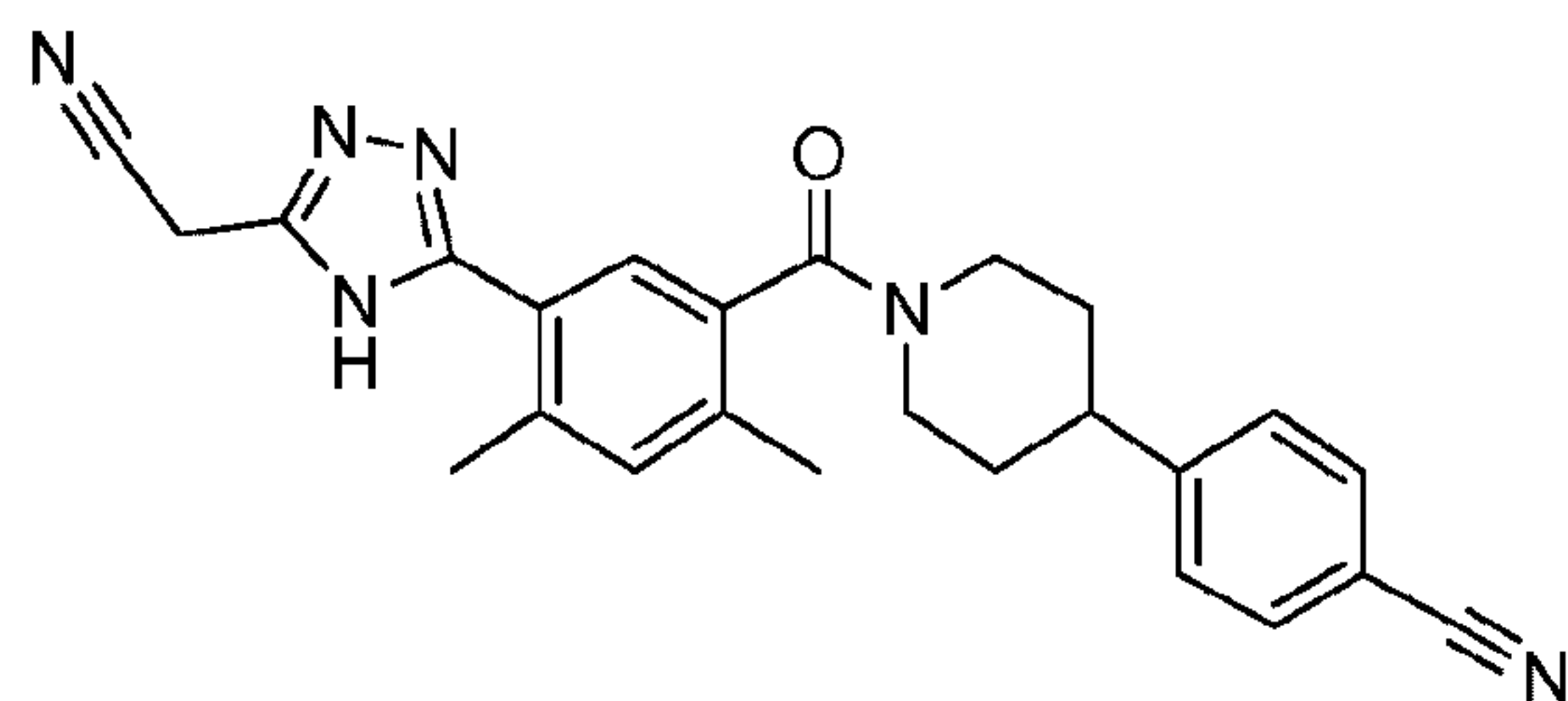
[0669] **Compound 138.1. 2-(Tetrahydrofuran-2-yl)acetohydrazide.** To a round-bottom flask was added a solution of ethyl 2-(tetrahydrofuran-2-yl)acetate (2.00 g, 12.6 mmol, 1.00 equiv) in ethanol (20 mL). $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (1.27 g, 25.4 mmol, 2.00 equiv) was added to the reaction. The resulting solution was stirred overnight at 80°C in an oil bath, then cooled to room temperature and concentrated *in vacuo*. This resulted in 2.10 g (92%) of 2-(tetrahydrofuran-2-yl)acetohydrazide as a yellow oil.



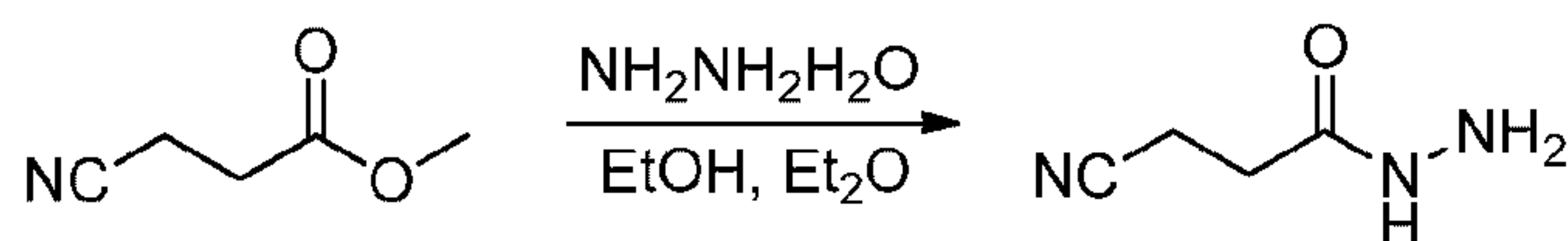
[0670] **Compound 138. 4-(1-(2,4-Dimethyl-5-(5-((tetrahydrofuran-2-yl)methyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile.** The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(2,4-dimethyl-5-(5-((tetrahydrofuran-3-yl)methyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound 130), using 2-(tetrahydrofuran-2-yl)acetohydrazide (compound 138.1) instead of 2-(tetrahydrofuran-3-yl)acetohydrazide (compound 130.4). m/z (ES+) 470 ($\text{M}+\text{H}$)⁺.



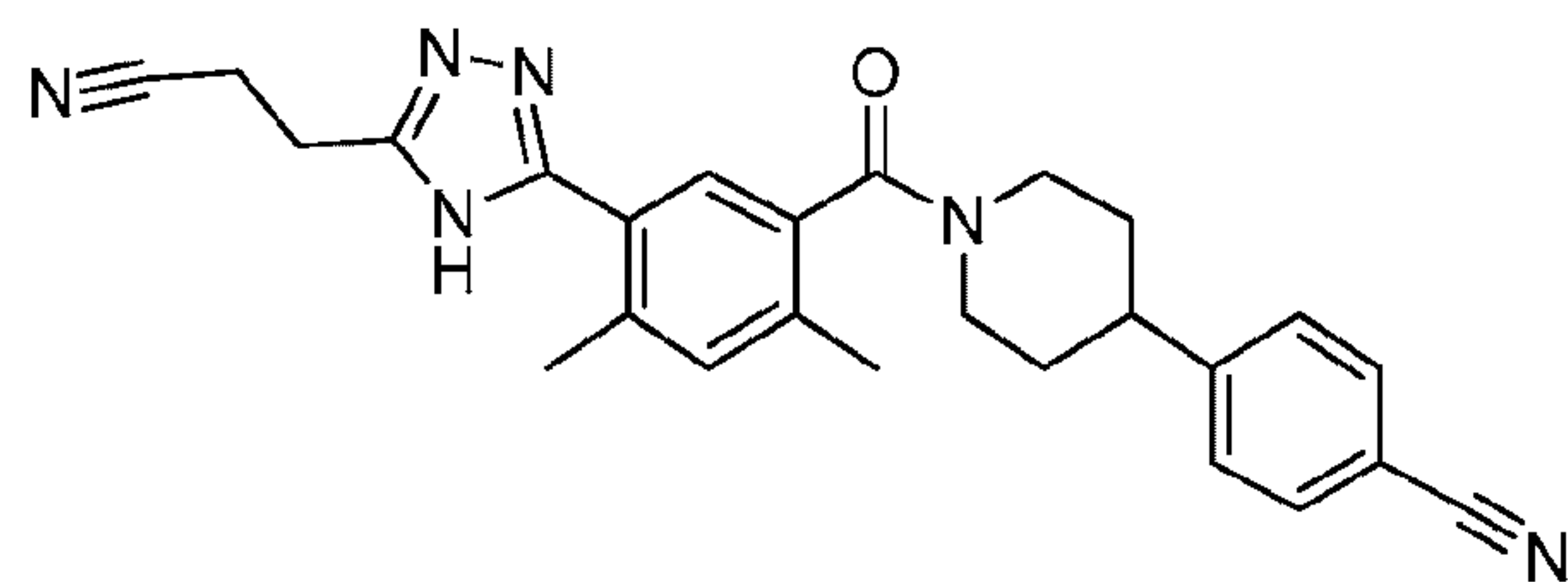
[0671] **Compound 139.1. 2-Cyanoacetohydrazide.** To a a solution of $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (3.50 g, 70.0 mmol, 1.00 equiv) in a solvent mixture of ethanol and Et_2O (35/35 mL) at 0 °C was added dropwise a solution of methyl 2-cyanoacetate (7.00 g, 70.6 mmol, 1.00 equiv) in ethanol (5 mL). The resulting mixture was stirred for 3h at room temperature, then washed with 2 x 30 mL of ether. The solids were collected by filtration to yield 5.00 g (68%) of 2-cyanoacetohydrazide as a white solid.



[0672] Compound 139. 4-(1-(5-(5-(cyanomethyl)-4H-1,2,4-triazol-3-yl)-2,4-dimethylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(2,4-dimethyl-5-(5-((tetrahydrofuran-3-yl)methyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **130**), using 2-cyanoacetohydrazide (compound **139.1**) instead of 2-(tetrahydrofuran-3-yl)acetohydrazide (compound **130.4**). m/z (ES+) 425 ($M+H$)⁺. ¹H-NMR (300Hz, CD₃OD): δ 7.70 (d, J = 8.4Hz, 2H), 7.54-7.42 (m, 3H), 7.35 (s, 1H), 4.87-4.80 (m, 1H), 4.12 (s, 2H), 3.77-3.65 (m, 1H), 3.27-3.23 (m, 1H), 3.09-2.99 (m, 2H), 2.55 (s, 3H), 2.43 and 2.33 (2 singlets, amide rotamers, ArCH₃, 3H), 2.05-2.00 (m, 1H), 1.83-1.76 (m, 3H).

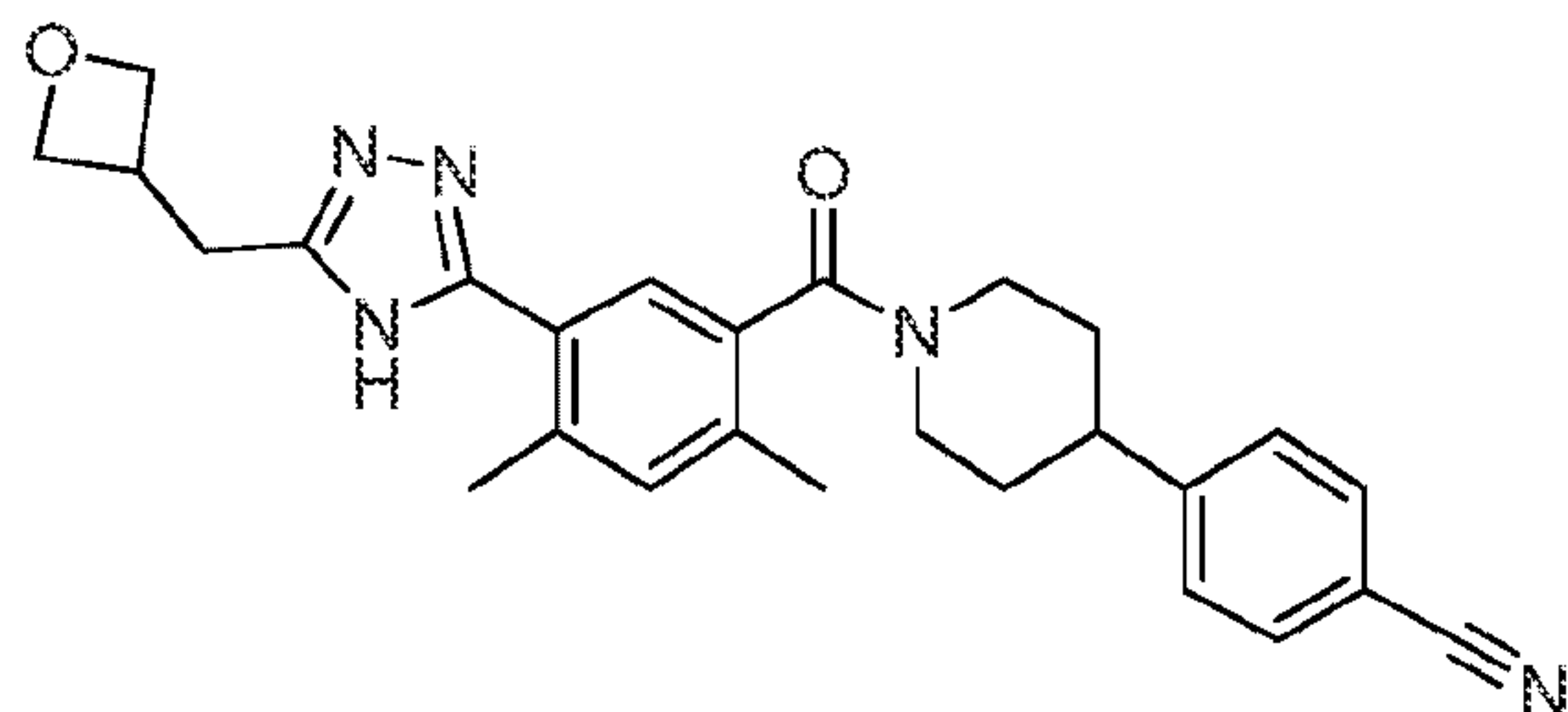


[0673] Compound 140.1. 3-cyanopropanehydrazide. To a round-bottom flask was added a solution of NH₂NH₂·H₂O (1.25 g, 25.1 mmol, 1.00 equiv) in ether/EtOH (8/8 mL). To this was added methyl 3-cyanopropanoate (2.84 g, 25.1 mmol, 1.00 equiv) dropwise. The resulting solution was stirred for 2h at room temperature, then concentrated *in vacuo*. This resulted in 1.40 g (49%) of 3-cyanopropanehydrazide as a colorless oil.

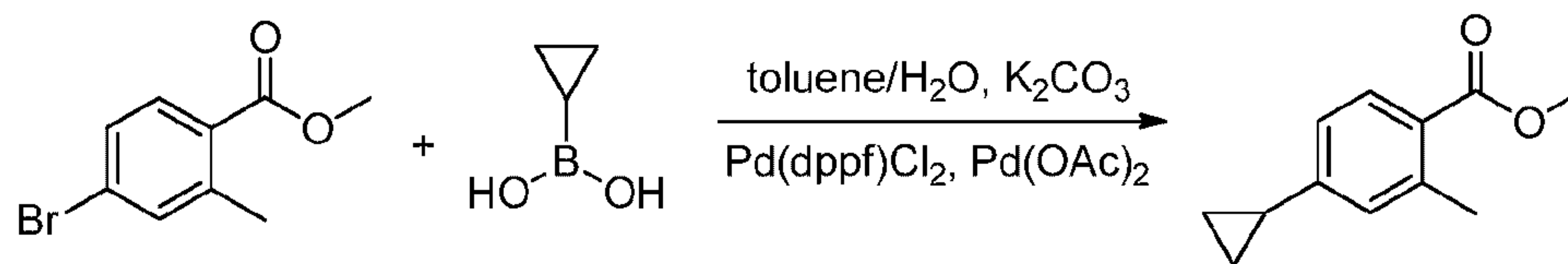


[0674] Compound 140. 4-(1-(5-(5-(2-cyanoethyl)-4H-1,2,4-triazol-3-yl)-2,4-dimethylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(2,4-dimethyl-5-(5-((tetrahydrofuran-3-yl)methyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **130**), using 3-cyanopropanehydrazide

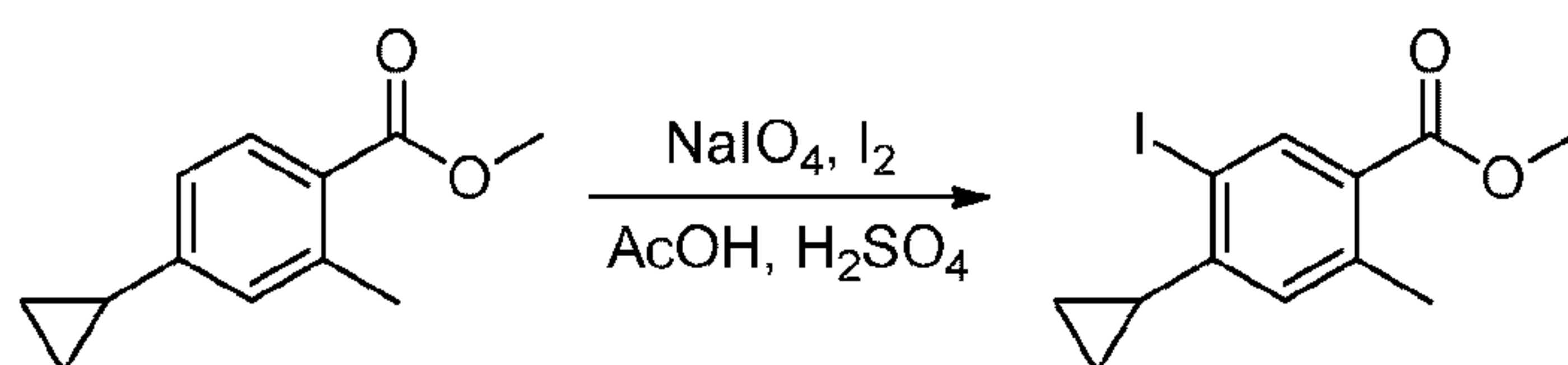
(compound **140.1**) instead of 2-(tetrahydrofuran-3-yl)acetohydrazide (compound **130.4**). m/z (ES+) 439 (M+H)⁺. ¹H-NMR (300Hz, CD₃OD): δ 7.68 (d, 2H), 7.58-4.47 (m, 3H), 7.30 (s, 1H), 4.89-4.80 (m, 1H), 3.65-3.62 (m, 1H), 3.32-3.30 (m, 1H), 3.15 (t, 2H), 3.03-2.95 (m, 4H), 2.50 (s, 3H), 2.42 and 2.32 (2 singlets, amide rotamers, ArCH₃, 3H), 2.03-2.00 (m, 1H), 1.83-1.78 (m, 3H).



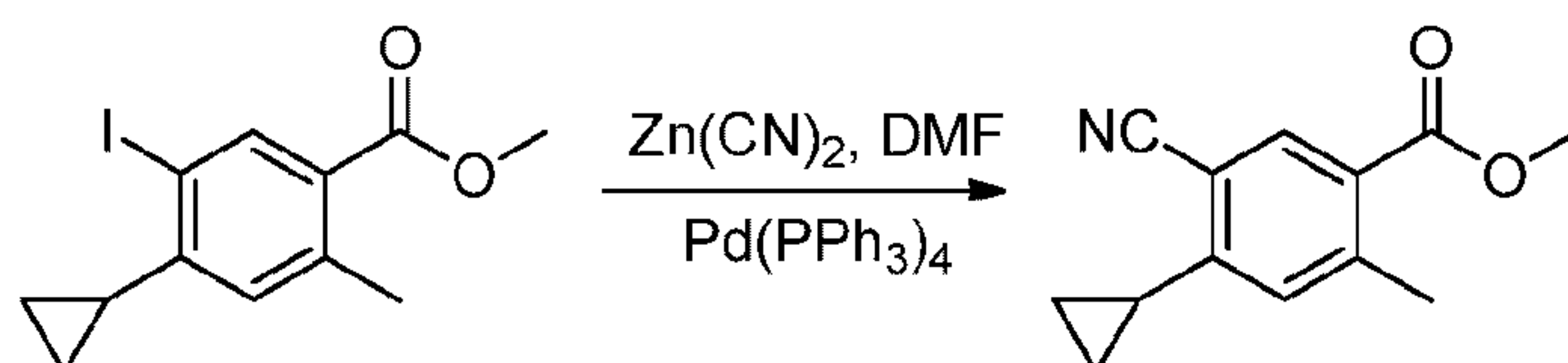
[0675] **Compound 141. 4-(1-(2,4-Dimethyl-5-(5-(oxetan-3-ylmethyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile.** The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(2,4-dimethyl-5-(5-((tetrahydrofuran-3-yl)methyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **130**). m/z (ES+) 456 (M+H)⁺.



[0676] **Compound 142.1. Methyl 4-cyclopropyl-2-methylbenzoate.** To a solution of methyl 4-bromo-2-methylbenzoate (5.00 g, 20.7 mmol, 1.00 equiv, 95%) in a mixture of toluene and H₂O (20 mL/1 mL) were added potassium carbonate (6.10 g, 44.1 mmol, 2.00 equiv), cyclopropylboronic acid (2.30 g, 26.8 mmol, 1.20 equiv), Pd(dppf)Cl₂ (900 mg, 1.23 mmol, 0.05 equiv), and Pd(OAc)₂ (250 mg, 1.12 mmol, 0.05 equiv). The reaction mixture was purged with nitrogen and stirred at 80 °C overnight. After cooling to room temperature, the mixture was then concentrated *in vacuo*. The resulting residue was purified via silica gel column chromatography with ethyl acetate/petroleum ether (1:50) as eluent to yield 2.68 g (61%) of methyl 4-cyclopropyl-2-methylbenzoate as a colorless oil.

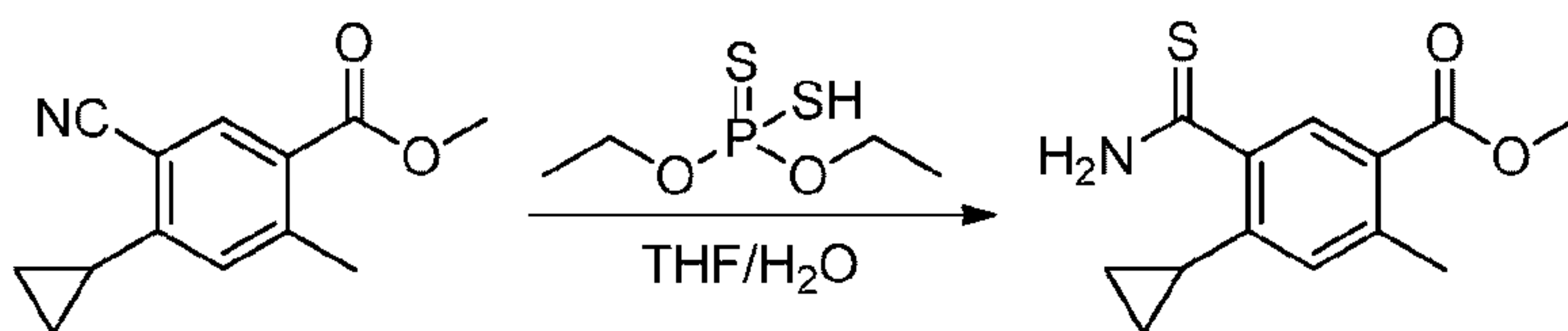


[0677] **Compound 142.2. Methyl 4-cyclopropyl-5-iodo-2-methylbenzoate.** To a solution of methyl 4-cyclopropyl-2-methylbenzoate (compound 142.1, 2.68 g, 13.4 mmol, 1.00 equiv, 95%) in AcOH (50 mL) were added NaIO_4 (1.51 g, 7.08 mmol, 0.50 equiv), I_2 (3.58 g, 14.1 mmol, 1.00 equiv), and sulfuric acid (201 mg, 2.01 mmol, 0.15 equiv, 98%). The reaction mixture was stirred at 110 °C overnight. After cooling to ambient temperature, 100 mL of water was added. The resulting mixture was diluted with 100 mL of ethyl acetate, then washed with 3 x 30 mL of $\text{Na}_2\text{S}_2\text{O}_3$ (aq., sat.) and 1 x 30 mL of brine. The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified via silica gel column chromatography with ethyl acetate/petroleum ether (1/50) as eluent to yield 2.00 g (45%) of methyl 4-cyclopropyl-5-iodo-2-methylbenzoate as a colorless oil.



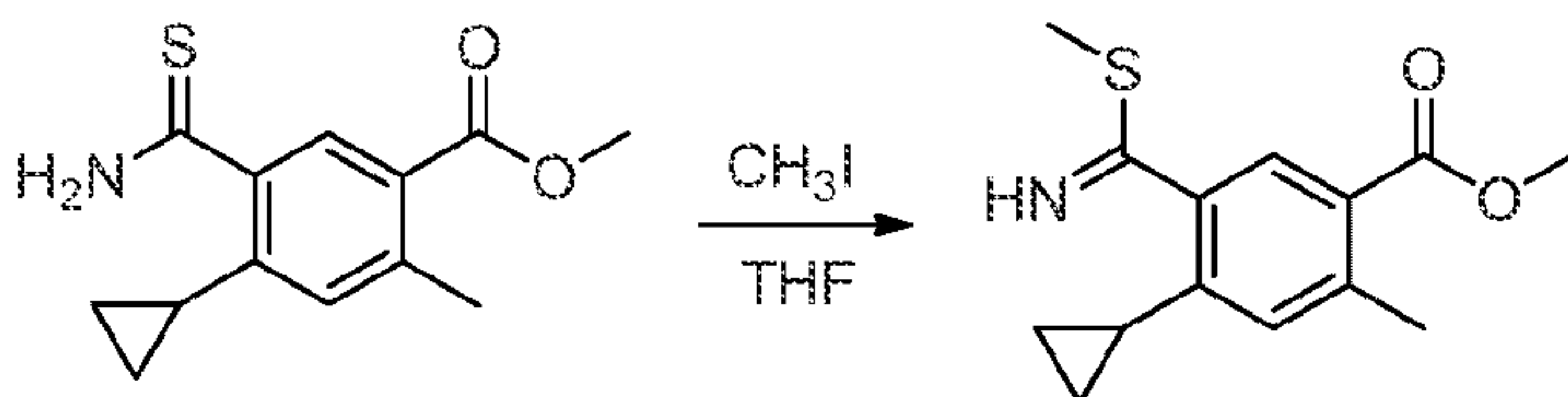
[0678] **Compound 142.3. Methyl 5-cyano-4-cyclopropyl-2-methylbenzoate.** To a solution of methyl 4-cyclopropyl-5-iodo-2-methylbenzoate (compound 142.2, 2.00 g, 6.01 mmol, 1.00 equiv, 95%) in DMF (16 mL) was added $\text{Zn}(\text{CN})_2$ (890 mg, 7.58 mmol, 1.27 equiv) and $\text{Pd}(\text{PPh}_3)_4$ (731 mg, 0.630 mmol, 0.11 equiv). The resulting solution was stirred at 100 °C under nitrogen overnight. After cooling to ambient temperature, the reaction was then quenched by the addition of 100 mL of FeSO_4 (aq., sat.) and diluted with ethyl acetate. The resulting mixture was stirred vigorously then filtered through celite and washed with 1 M FeSO_4 , water, and ethyl acetate. The layers were separated and the aqueous phase was extracted with 2 x 100 mL of ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified via silica gel column chromatography with ethyl acetate/petroleum ether (1/50) as eluent to yield 1.10 g (81%) of methyl 5-cyano-4-cyclopropyl-2-methylbenzoate as a light yellow oil.

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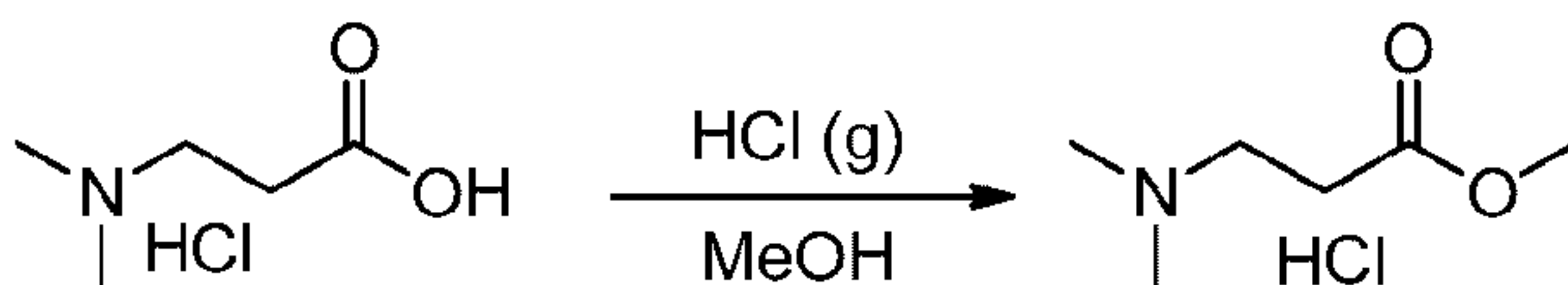
[0679] Compound 142.4. Methyl 5-carbamothioyl-4-cyclopropyl-2-methylbenzoate.

To a solution of methyl 5-cyano-4-cyclopropyl-2-methylbenzoate (compound **142.3**, 1.65 g, 7.28 mmol, 1.00 equiv, 95%) in a mixture of tetrahydrofuran and H₂O (20 mL/5 mL) was added *O,O'*-diethylphosphorodithioate (3.79 g, 22.3 mmol, 2.00 equiv). The resulting mixture was stirred at 80 °C overnight (**CAUTION**: significant gas evolution occurs - this and all other reactions described herein should be carried out in well ventilated fume hoods). After cooling to ambient temperature, the reaction was quenched with 100 mL of water. The resulting solution was extracted with 100 mL of ethyl acetate. The combined organic layers were washed with 3 x 30 mL of brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified via silica gel column chromatography with ethyl acetate/petroleum ether (1/5) as eluent to furnish 0.880 g (46%) of methyl 5-carbamothioyl-4-cyclopropyl-2-methylbenzoate as a white solid.



[0680] Compound 142.5. Methyl 4-cyclopropyl-2-methyl-5-(methylsulfany)carboximidoylbenzoate.

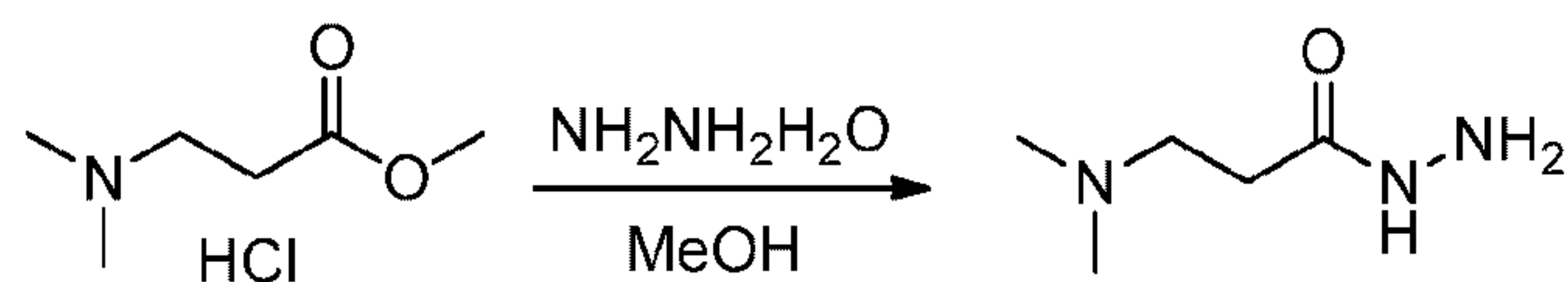
To a round-bottom flask was added a solution of methyl 5-carbamothioyl-4-cyclopropyl-2-methylbenzoate (compound **142.4**, 880 mg, 3.35 mmol, 1.00 equiv, 95%) in tetrahydrofuran (10 mL). Iodomethane (1.00 g, 7.05 mmol, 2.00 equiv) was added and the resulting mixture and stirred at room temperature overnight. The mixture was then concentrated *in vacuo* to yield 0.800 g (86%) of methyl 4-cyclopropyl-2-methyl-5-(methylsulfany)carboximidoylbenzoate as a colorless liquid.



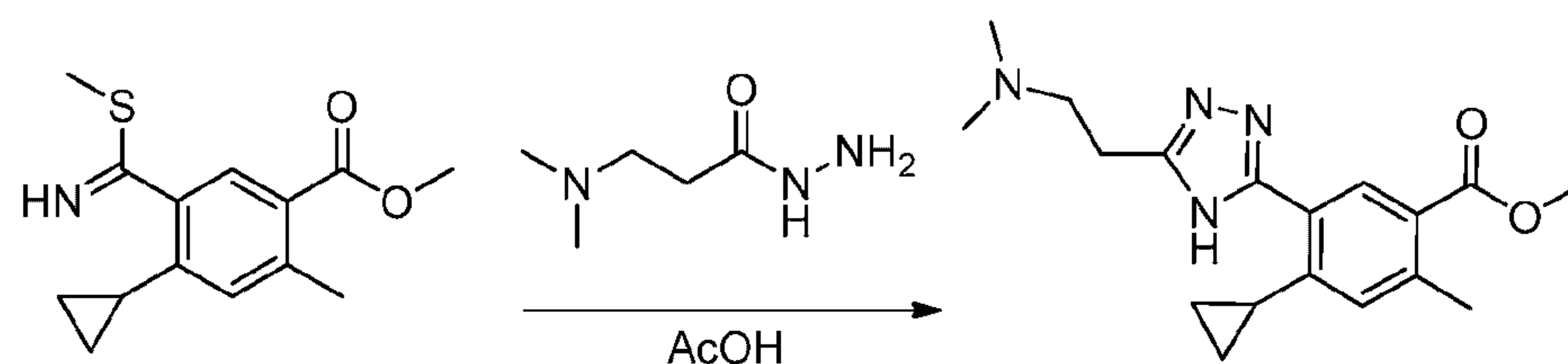
[0681] Compound 142.6. Methyl 3-(dimethylamino)propanoate hydrochloride.

To a round-bottom flask was added a solution of 3-(dimethylamino)propanoic acid (2.00 g, 17.1 mmol, 1.00 equiv) in methanol (60 mL). Hydrogen chloride (g) was bubbled into the

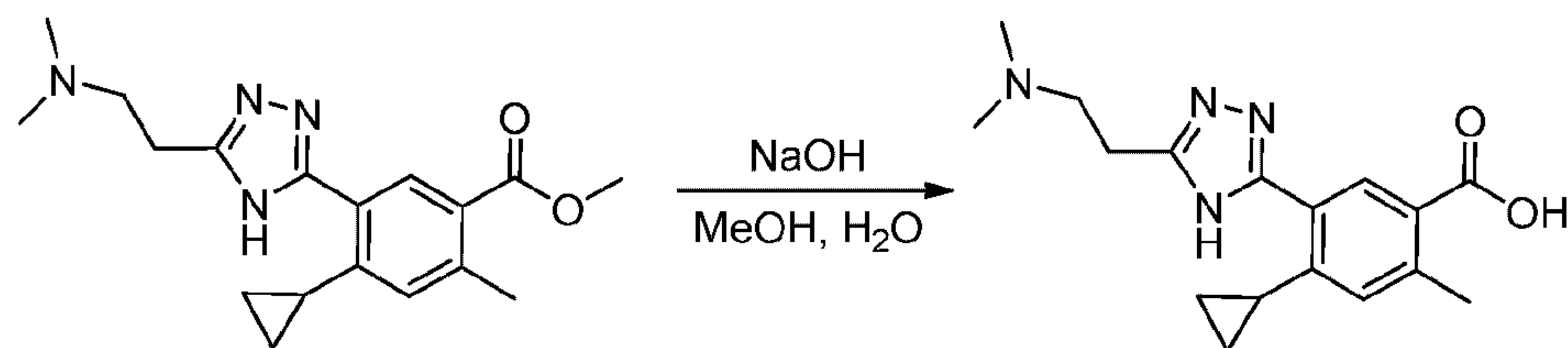
reaction mixture and the resulting solution was stirred for 4 h at 25 °C. Concentration of the reaction mixture *in vacuo* afforded 2.00 g of title compound as a colorless oil.



[0682] Compound 142.7. 3-(Dimethylamino)propanehydrazide. To a solution of methyl 3-(dimethylamino)propanoate hydrochloride (compound 142.6, 2.00 g, 15.3 mmol, 1.00 equiv) in methanol (40 mL) was added hydrazine hydrate (6 mL, 6.00 equiv). The reaction mixture was stirred at 70 °C for 3 h. The mixture was concentrated *in vacuo* and then dissolved in 50 mL of H₂O and washed with 2 x 10 mL of ethyl acetate. The aqueous layers were combined and concentrated *in vacuo* to afford 1.30 g (65%) of 3-(dimethylamino)propanehydrazide as a colorless oil.

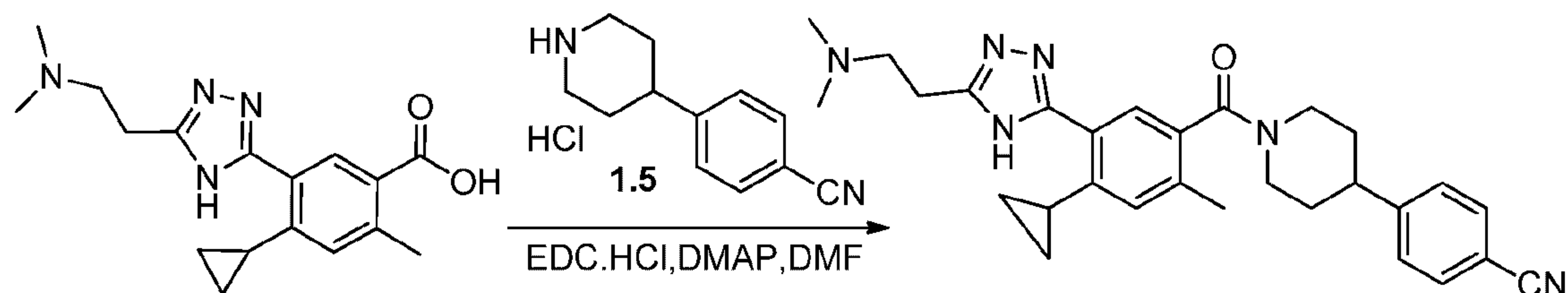


[0683] Compound 142.8. Methyl 4-cyclopropyl-5-(5-(2-(dimethylamino)ethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoate. A solution of 3-(dimethylamino)propanehydrazide (compound 142.7, 1.20 g, 9.15 mmol, 5.00 equiv) and methyl 4-cyclopropyl-2-methyl-5-(methylsulfanyl)carboximidoylbenzoate (compound 142.5, 600 mg, 2.28 mmol, 1.00 equiv) in AcOH (30 mL) was stirred at 80 °C overnight. After cooling to ambient temperature, the pH was adjusted to 8-9 with sodium hydroxide (aq., 1 M). The resulting mixture was extracted with 2 x 100 mL of ethyl acetate and the combined organic layers were concentrated *in vacuo*. The residue was purified via silica column chromatography with dichloromethane/methanol (10/1) as eluent to give 504 mg (67%) of the title compound as a white solid.

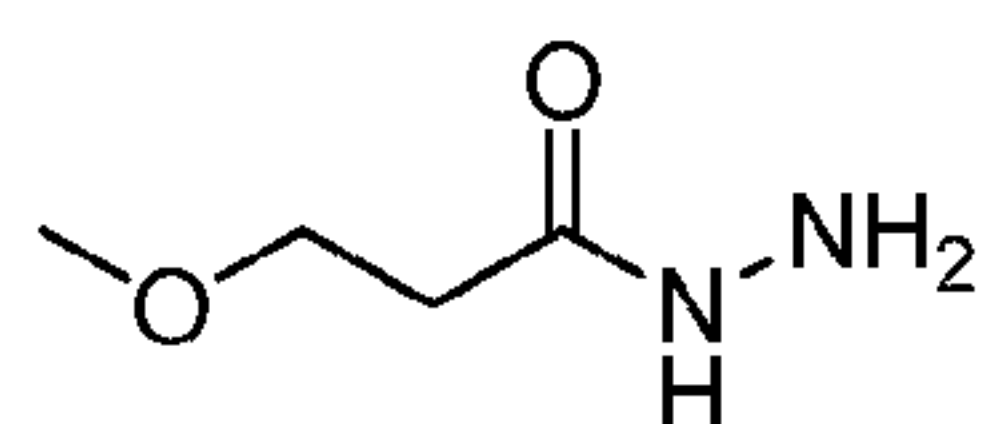


[0684] Compound 142.9. 4-Cyclopropyl-5-(5-(2-(dimethylamino)ethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoic acid. To a solution of compound 142.8 (200 mg, 0.610

mmol, 1.00 equiv) in a mixture of methanol and H₂O (6 mL/3 mL) was added sodium hydroxide (97.6 mg, 2.44 mmol, 4.00 equiv) in water (1 mL). After stirring at 60 °C overnight, the organic solvent was removed under reduced pressure. The residual aqueous layer was washed with 20 mL of ethyl acetate. The pH was then adjusted to 4-5 with HCl (aq., 3 M), and the resulting mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo* to afford 280 mg (73%) of the title compound as a brown solid.

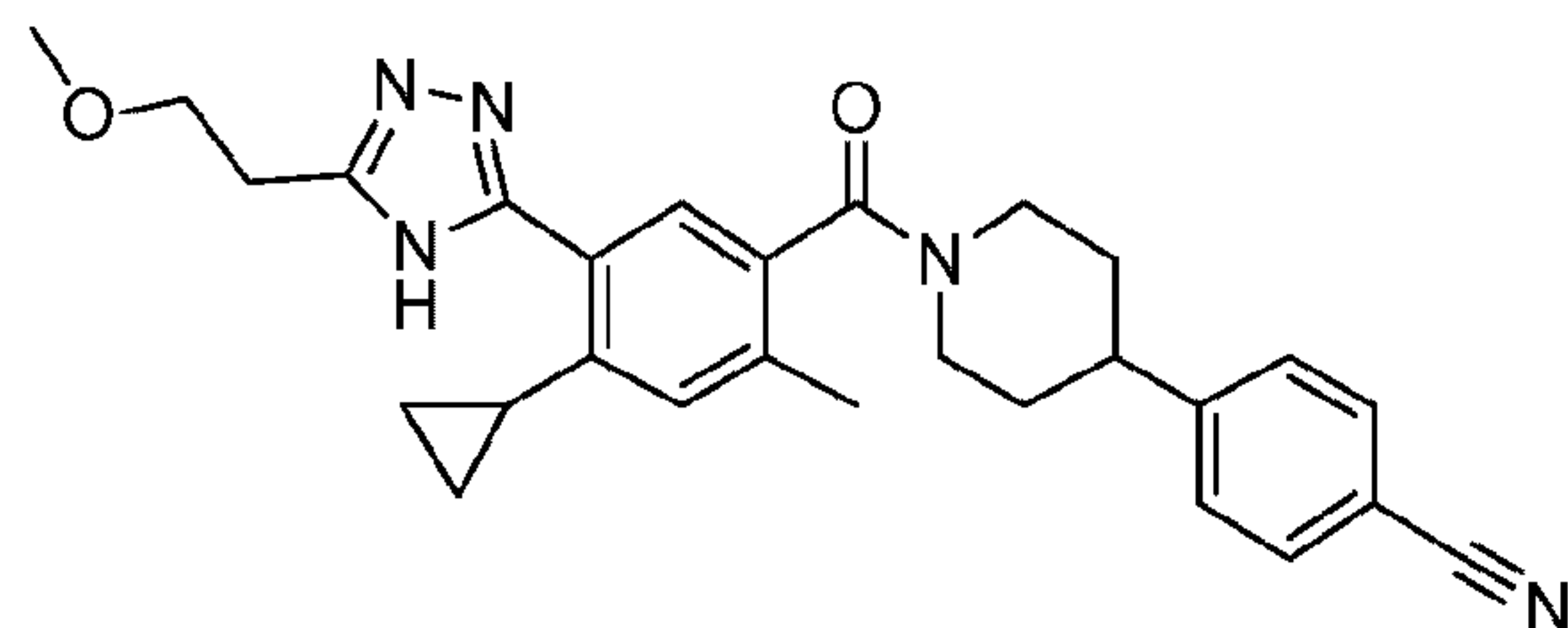


[0685] Compound 142. 4-(1-(4-Cyclopropyl-5-(5-(2-(dimethylamino)ethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)piperidin-4-yl)benzonitrile To a solution of compound 2661.9 (250 mg, 0.800 mmol, 1.00 equiv) in *N,N*-dimethylformamide (3 mL) were added 4-(piperidin-4-yl)benzonitrile hydrochloride (compound 1.5, 175 mg, 0.790 mmol, 1.00 equiv), EDCI (302 mg, 1.58 mmol, 2.00 equiv), and DMAP (194 mg, 1.59 mmol, 2.00 equiv). The resulting mixture was stirred at 25 °C overnight and then diluted with water. The mixture was extracted with 3 x 50 mL of ethyl acetate. The combined organic layers were washed with 2 x 20 mL of NH₄Cl (aq) and 2 x 20 mL of brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified via silica gel column chromatography with dichloromethane/methanol (10/1) as eluent. The product (~150 mg) was further purified by Prep-HPLC with the following conditions [(1#-Pre-HPLC-001(SHIMADZU)): Column, Xbridge Prep C18, 5um, 19*150mm; mobile phase, water with 0.03% NH₃ H₂O and CH₃CN (32.0% CH₃CN up to 47.0% in 7 min, up to 100.0% in 1 min, down to 32.0% in 1 min); Detector, Waters 2489 254&220nm]. The fractions containing pure compound were combined and lyophilized to yield 70.3 mg (18%) of the title compound as a white solid. *m/z* (ES+) 483 (M+H)⁺.

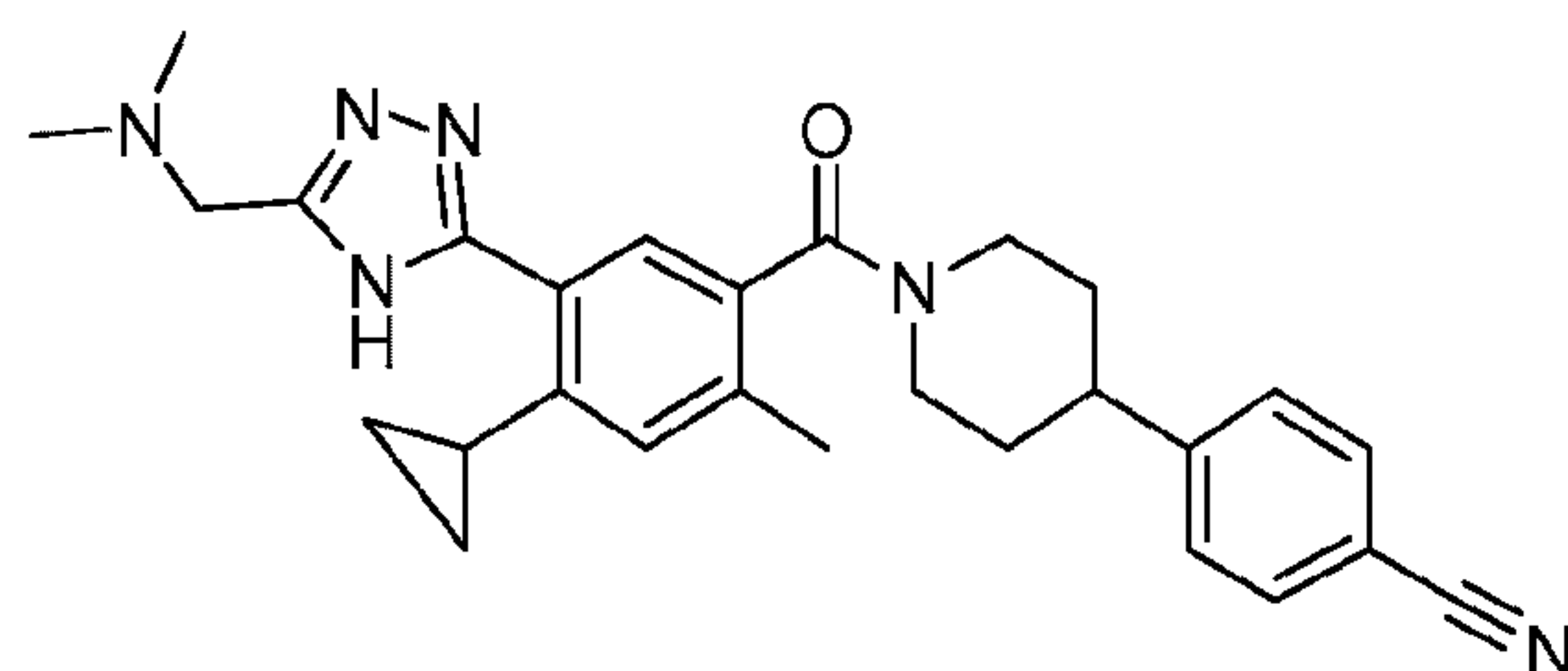


[0686] Compound 143.1. 3-Methoxypropanehydrazide. A mixture of methyl 3-methoxypropanoate (5.0 g, 42.33 mmol) and hydrazine (1.36 g, 42.33 mmol) was heated at 50 °C for two hours. The mixture was concentrated and dried under reduced pressure to give

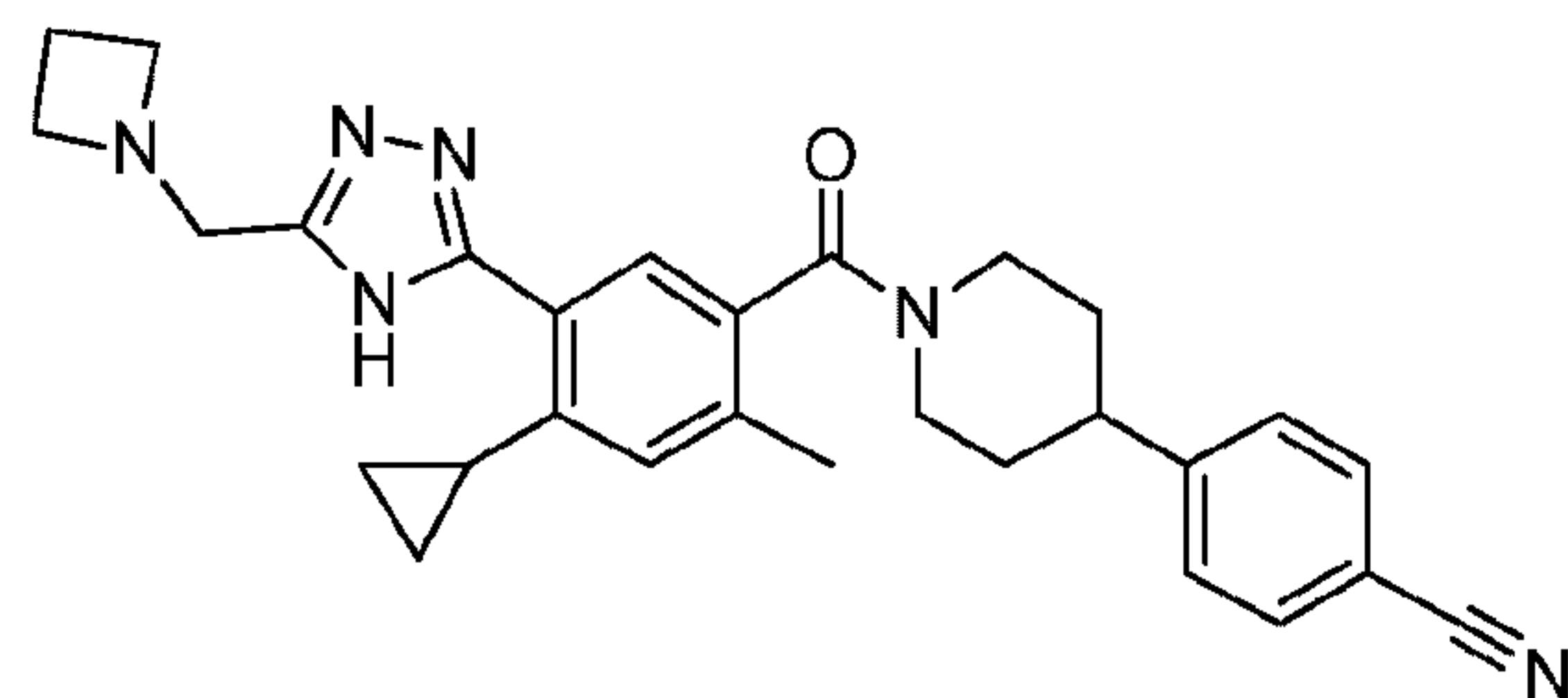
the product as a clear oil. Yield: 5.0 g, 100%. m/z (ES+) 119 (M+H)⁺. ¹H NMR (400 MHz, Chloroform-d) δ 7.86 (br, 1H), 4.05 – 3.71 (m, 2H), 3.63 (t, 2H), 3.34 (s, 3H), 2.42 (t, 2H).



[0687] **Compound 143.** 4-(1-(4-Cyclopropyl-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound 142 and using compound 143.1 in place of 142.7. m/z (ES+) 471 (M+H)⁺.

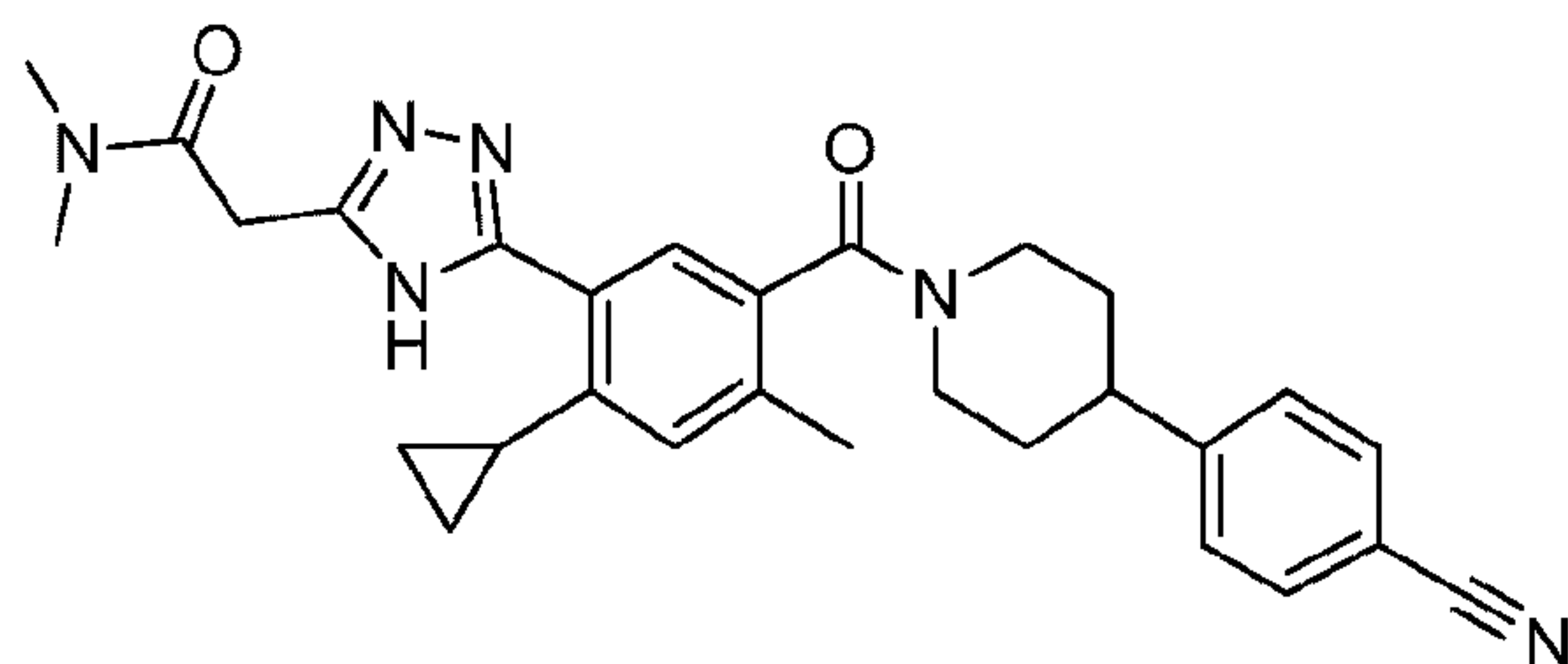


[0688] **Compound 144.** 4-(1-(4-Cyclopropyl-5-(5-((dimethylamino)methyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound 142. m/z (ES+) 469 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.69 (d, J = 6.3 Hz, 2H), 7.49 (d, J = 6.0 Hz, 2H), 7.47 & 7.39 (2 singlets, amide rotamers, Ar-H, 1H), 7.03 (s, 1H), ~4.9 (1H partially obscured by water peak), 3.74 (s, 2H), 3.72-3.57 (m, 1H), 3.32-3.22 (m, 1H partially obscured by methanol solvent peak), 3.00 (t with fine structure, J = 8.9 Hz, 2H), 2.49-2.27 (m, 2H), 2.10-1.98 (m, 2H), 1.93-1.51 (m, 3H), 1.05-0.90 (m, 2H), 0.79-0.64 (m, 2H).

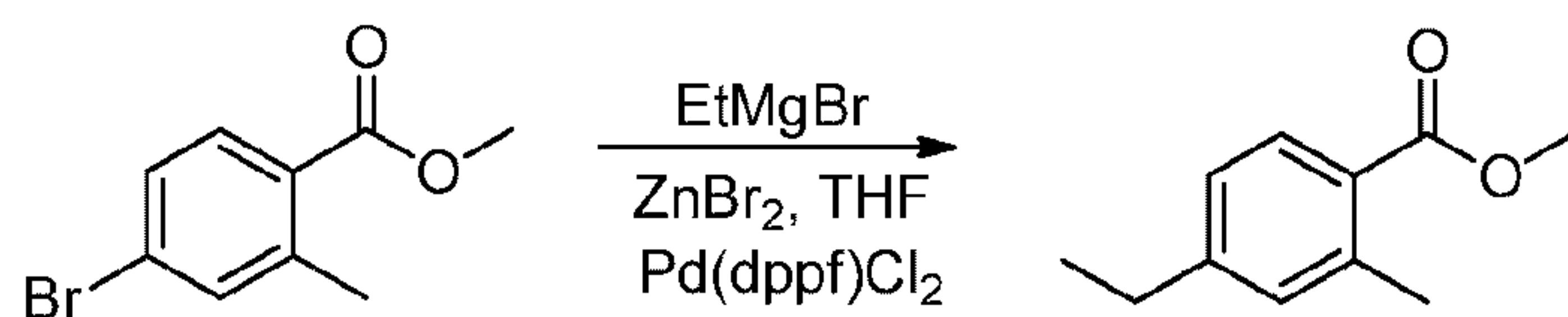


[0689] **Compound 145.** 4-(1-(5-(5-(Azetidin-1-ylmethyl)-4H-1,2,4-triazol-3-yl)-4-cyclopropyl-2-methylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was

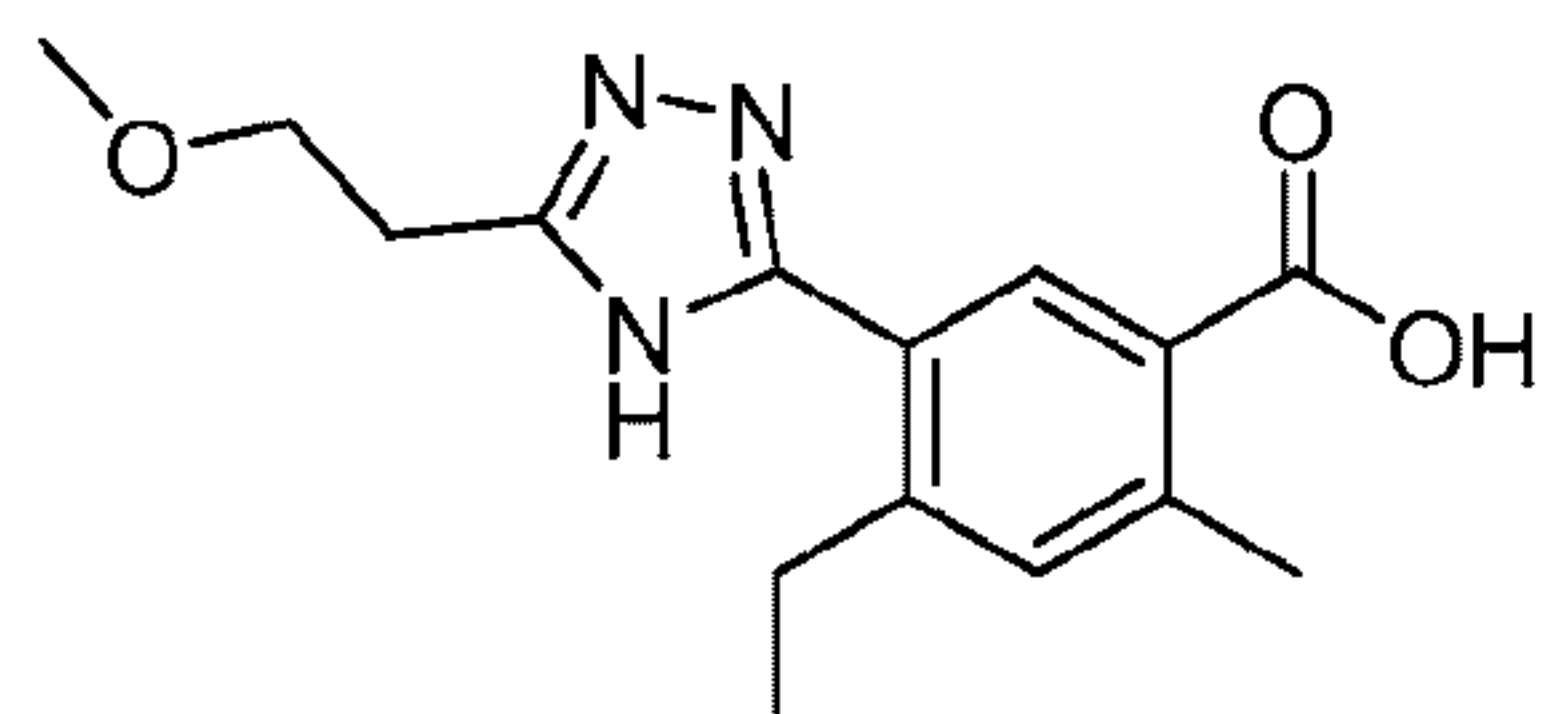
prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound **142**. m/z (ES+) 481 (M+H)⁺.



[0690] **Compound 146. 2-(5-(5-(4-(4-Cyanophenyl)piperidine-1-carbonyl)-2-cyclopropyl-4-methylphenyl)-4H-1,2,4-triazol-3-yl)-N,N-dimethylacetamide.** The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound **142**. m/z (ES+) 497 (M+H)⁺.

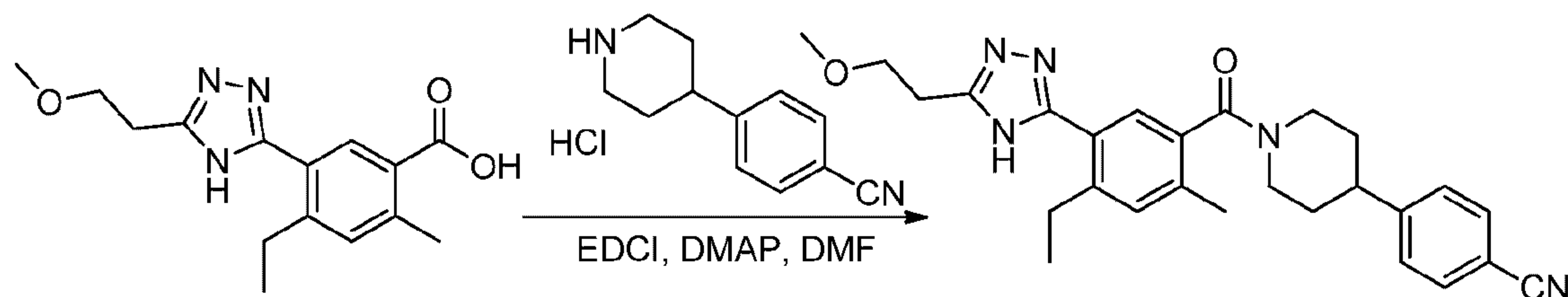


[0691] **Compound 147.1. Methyl 4-ethyl-2-methylbenzoate.** To a stirred mixture of ZnBr₂ (4.50 g, 20.0 mmol, 2.00 equiv) in tetrahydrofuran (50 mL) under nitrogen at 0 °C was added EtMgBr (6.6 mL, 2.00 equiv, 3M in THF) dropwise. After stirring for 30 min at 0 °C, the temperature was lowered to -78 °C and Pd(dppf)Cl₂ (1.08 g, 1.48 mmol, 0.30 equiv) was added followed by a solution of methyl 4-bromo-2-methylbenzoate (compound **152.1**, 2.30 g, 10.0 mmol, 1.00 equiv) in tetrahydrofuran (20 mL). The resulting mixture was stirred for 30 min at -78 °C, warmed to room temperature, and stirred overnight. The reaction mixture was carefully quenched with 60 mL of NH₄Cl (aq.) and extracted with 3 x 50 mL of ethyl acetate. The combined organic phases were dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:100-1:5) as eluent to furnish 1.50 g (84%) of methyl 4-ethyl-2-methylbenzoate as a brown oil.

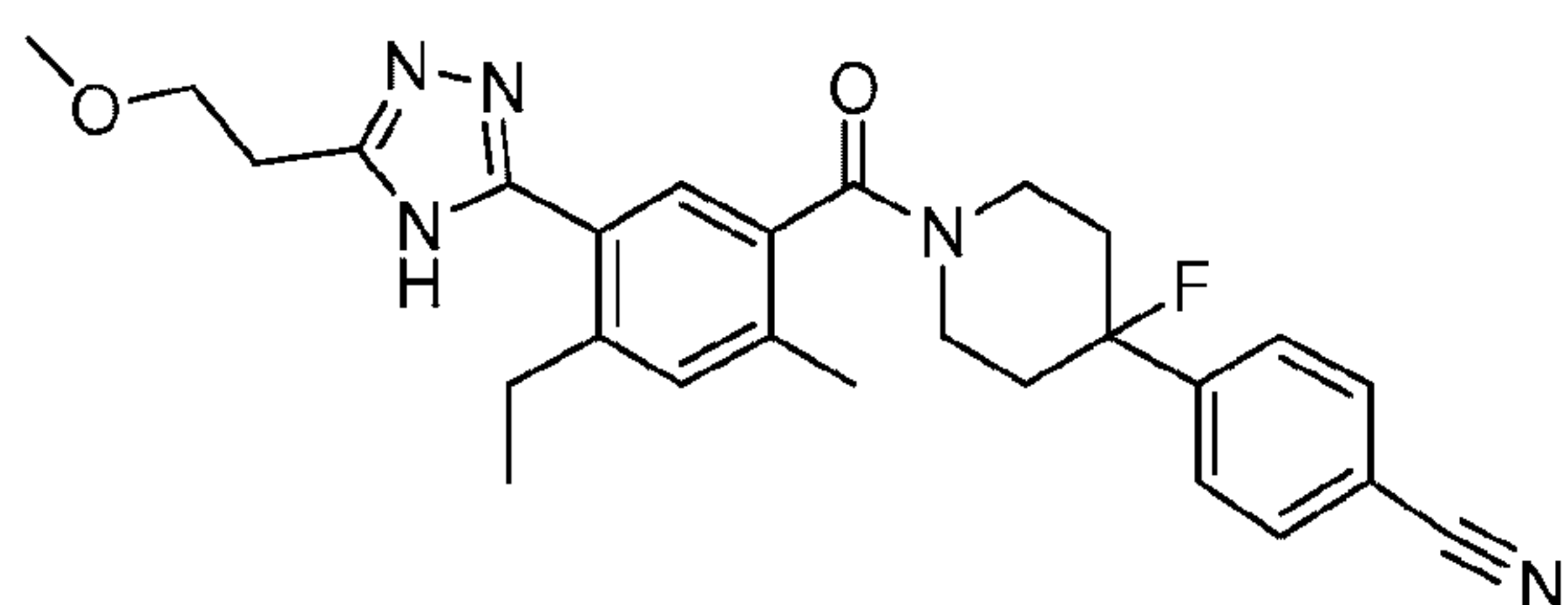


[0692] **Compound 147.2. 4-Ethyl-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoic acid.** The title compound was prepared using standard chemical

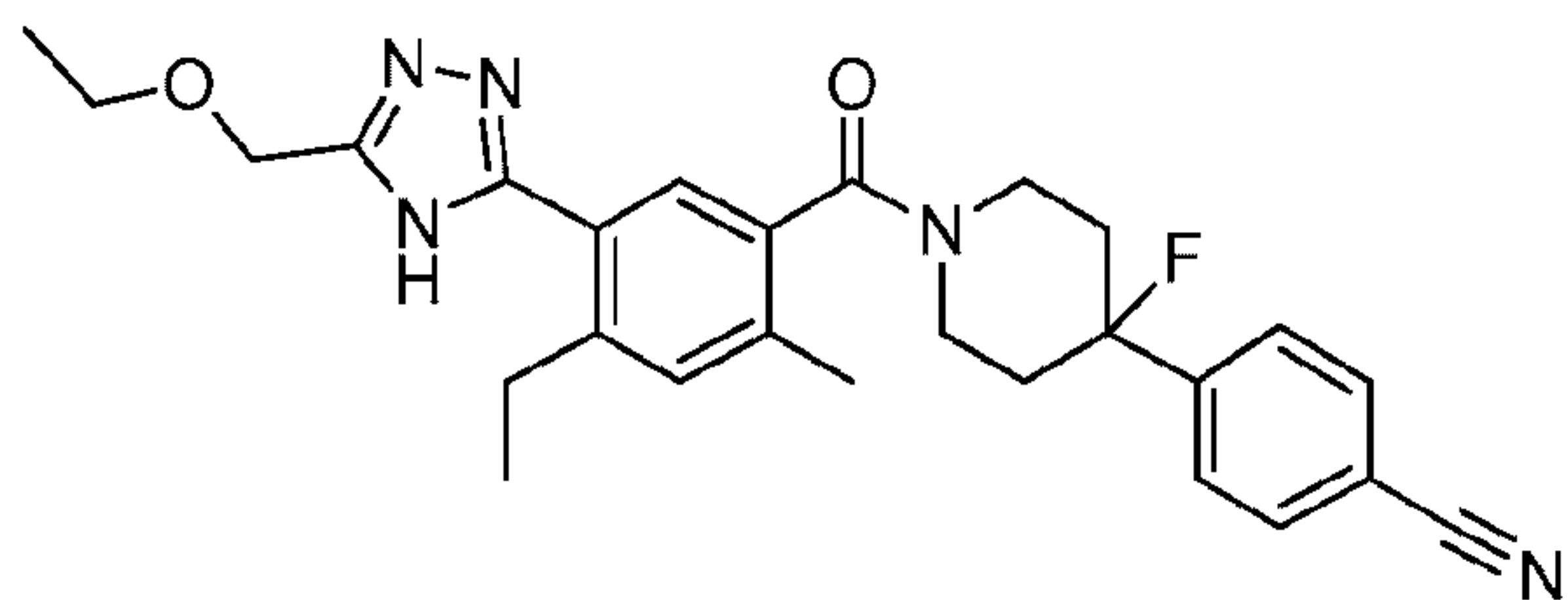
manipulations and procedures similar to those used for the preparation of compound **142.9** and using compounds **147.1** and **143.1** instead of compounds **142.1** and **142.7**.



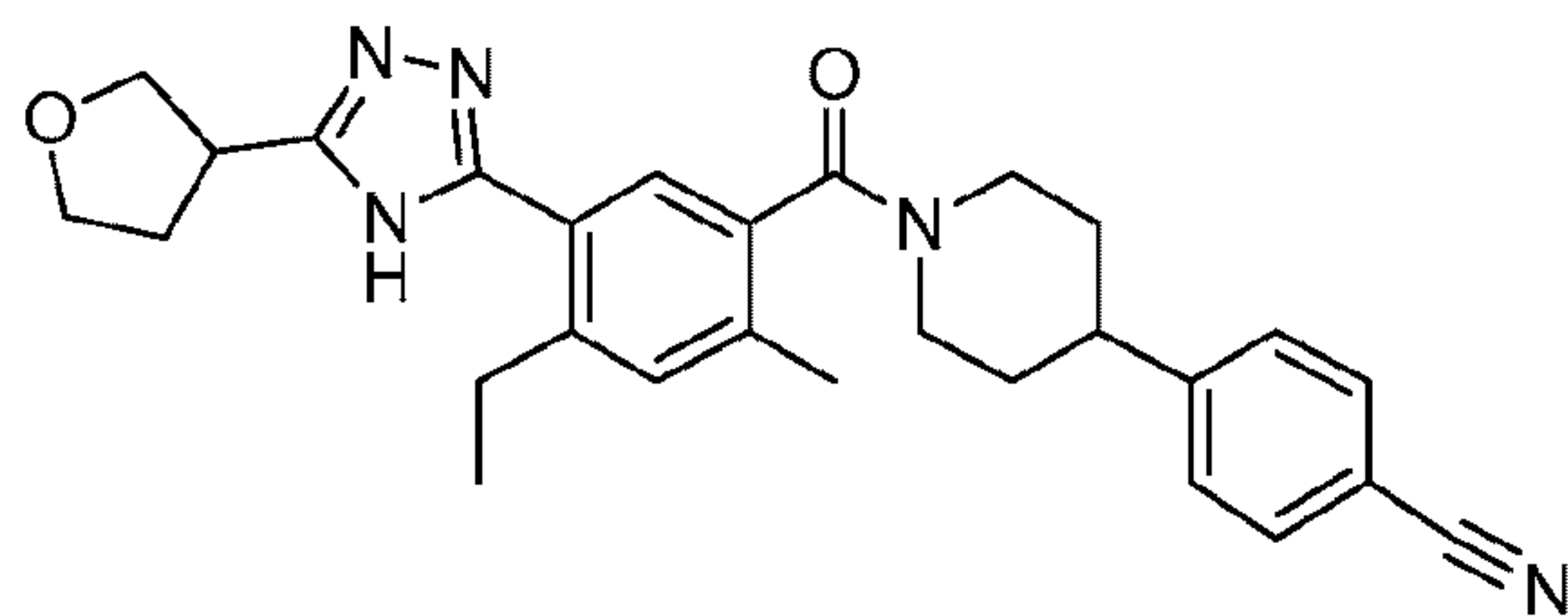
[0693] Compound **147**. 4-(1-(4-Ethyl-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)piperidin-4-yl)benzonitrile. To a solution of compound (**147.2**, 100 mg, 0.350 mmol, 1.00 equiv) in DMF (10 mL) under nitrogen were added EDCI (132 mg, 0.690 mmol, 2.00 equiv) and DMAP (85.0 mg, 0.700 mmol, 2.00 equiv). The resulting mixture was stirred 30 min at 25 °C followed by the addition of 4-(piperidin-4-yl)benzonitrile (compound **1.5**, 129 mg, 2.77 mmol, 2.00 equiv). The reaction mixture was stirred for 25 h at 25 °C, then quenched with 40 mL of ice water, and extracted with 3 x 50 mL of ethyl acetate. The combined organic layers were washed with 1 x 50 mL of brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:100-1:1) as eluent. The crude product (50 mg) was purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-001(SHIMADZU)): Column, Xbridge Prep C18, 5µm, 19*150mm; mobile phase, water with 0.03%NH₃H₂O and CH₃CN (33% CH₃CN up to 52% in 10 min, up to 100% in 1 min, down to 33% in 1 min); Detector, Waters 2489 254&220nm. The fractions containing pure compound were combined and lyophilized to yield 20.2 mg (12%) of the title compound as a white solid. *m/z* (ES⁺) 458 (M+H)⁺.



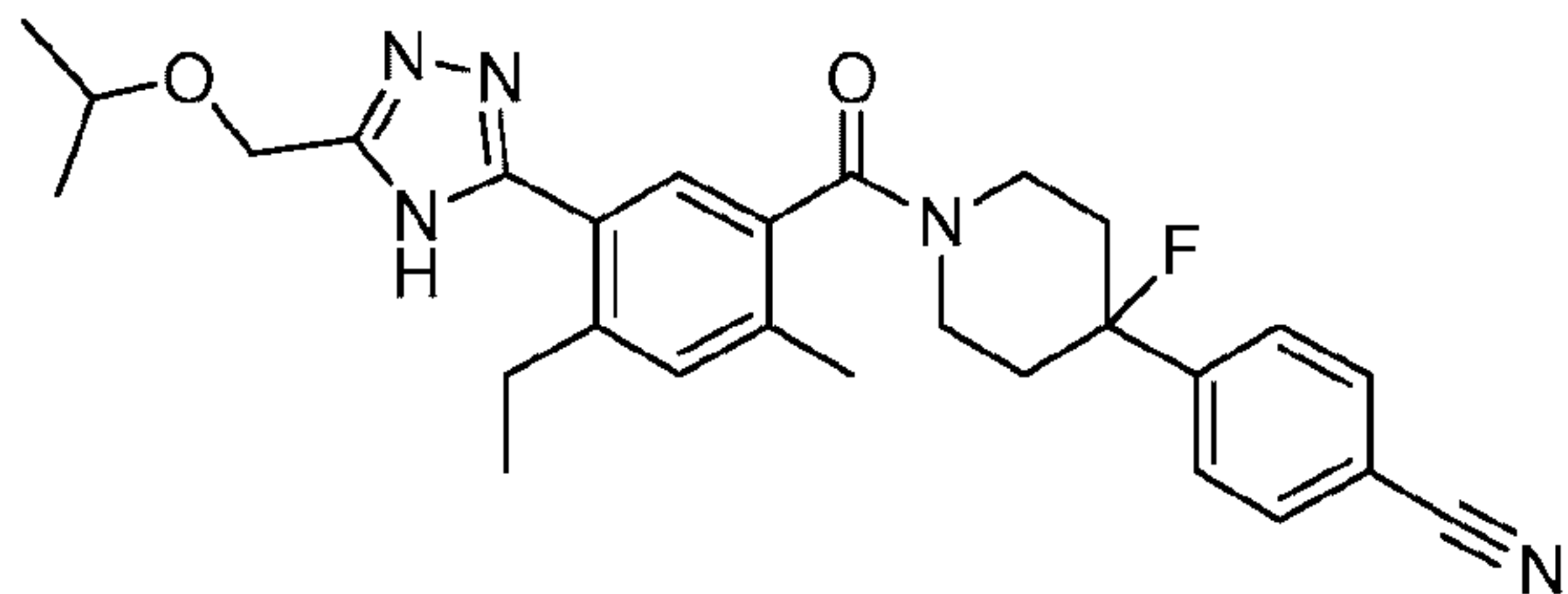
[0694] Compound **148**. 4-(1-(4-ethyl-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation compound **147** and using compound **11.2 HCl salt** instead compound **1.5**. *m/z* (ES⁺) 476 (M+H)⁺.



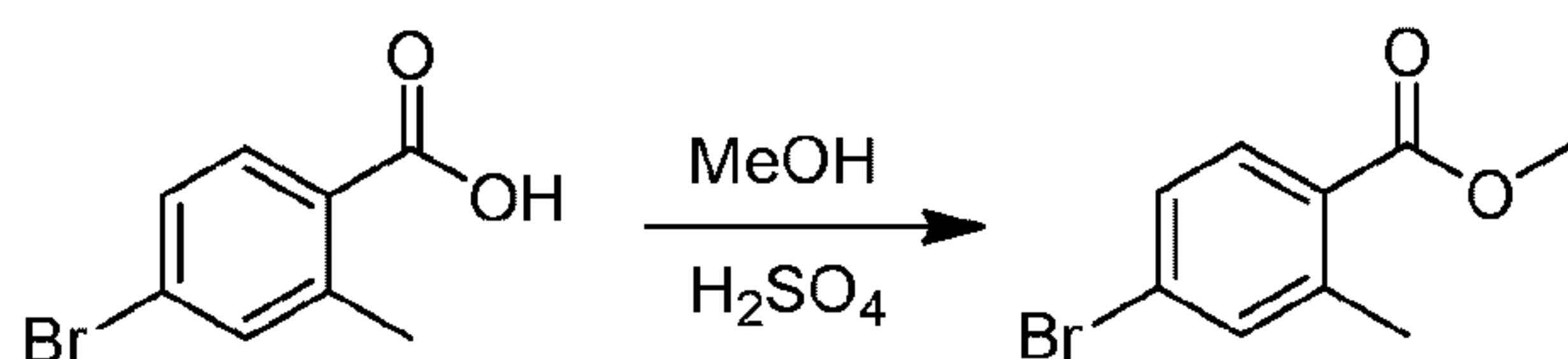
[0695] Compound 149. 4-(1-(5-(5-(Ethoxymethyl)-4H-1,2,4-triazol-3-yl)-4-ethyl-2-methylbenzoyl)-4-fluoropiperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds 147 and 148. m/z (ES⁺) 476 (M+H)⁺.



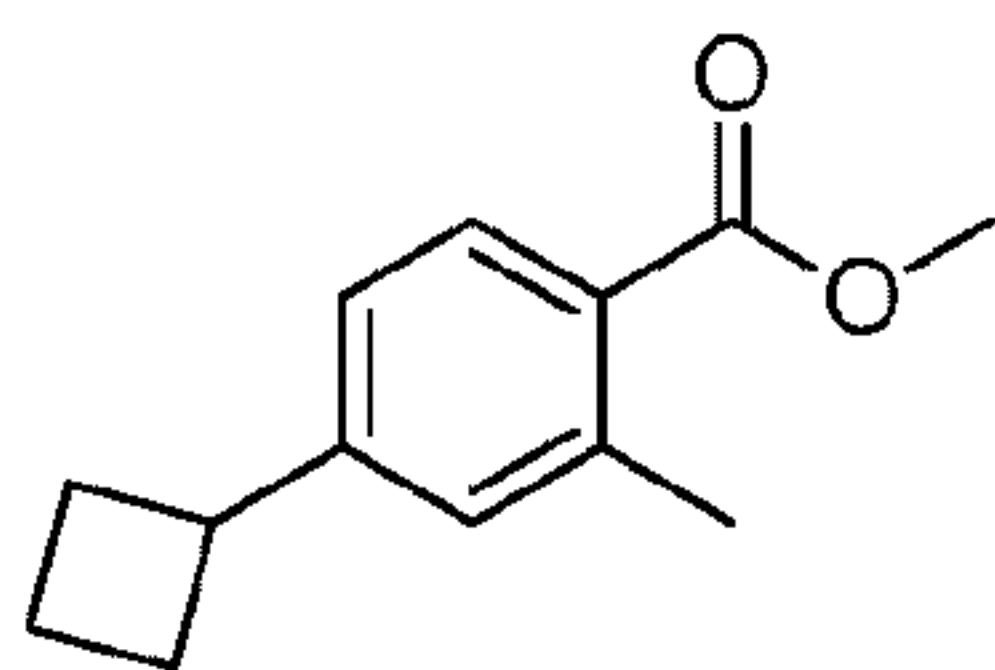
[0696] Compound 150. 4-(1-(4-Ethyl-2-methyl-5-(5-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(4-ethyl-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)piperidin-4-yl)benzonitrile (compound 147). m/z (ES⁺) 470 (M+H)⁺.



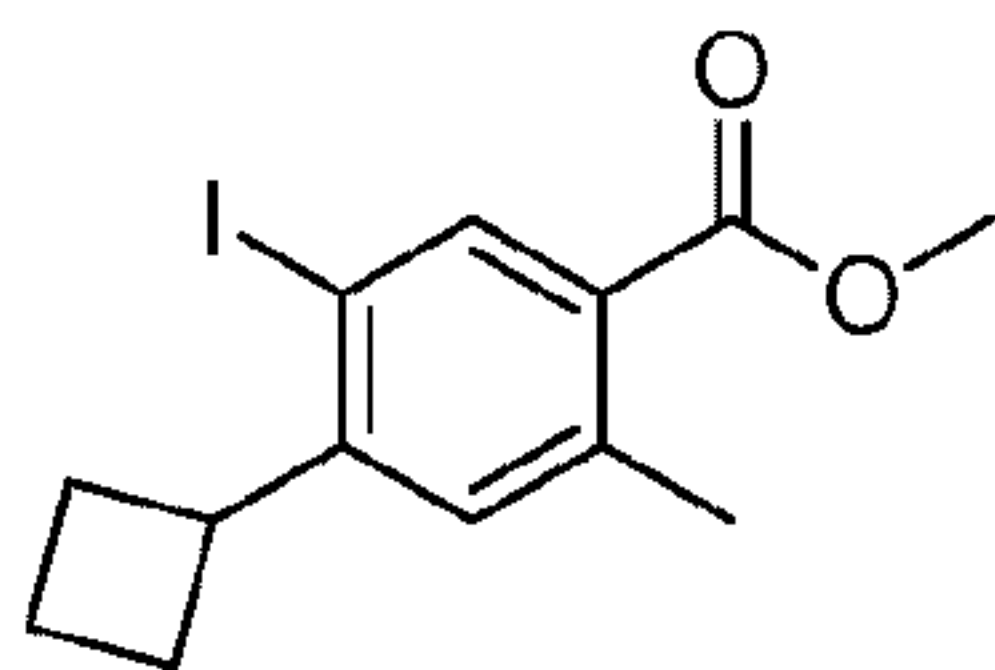
[0697] Compound 151. 4-(1-(4-Ethyl-5-(5-(isopropoxymethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds 147 and 148. m/z (ES⁺) 490 (M+H)⁺. ¹H-NMR (300 MHz, CD₃OD): δ 7.78 (d, 2H), 7.69-7.34 (m, 4H), 4.82-4.78 (m, 1H), 4.72 (s, 2H), 3.80 (quintet, 1H), 3.57-3.55 (m, 2H), 3.30-3.25 (m, 1H), 2.94 (q, 2H), 2.46 and 2.35 (2 singlets, amide rotamers, ArCH₃, 3H), 2.35-2.1 (m, 3H), 2.0-1.95 (m, 1H), 1.30 (d, 6H), 1.14 (t, 3H).



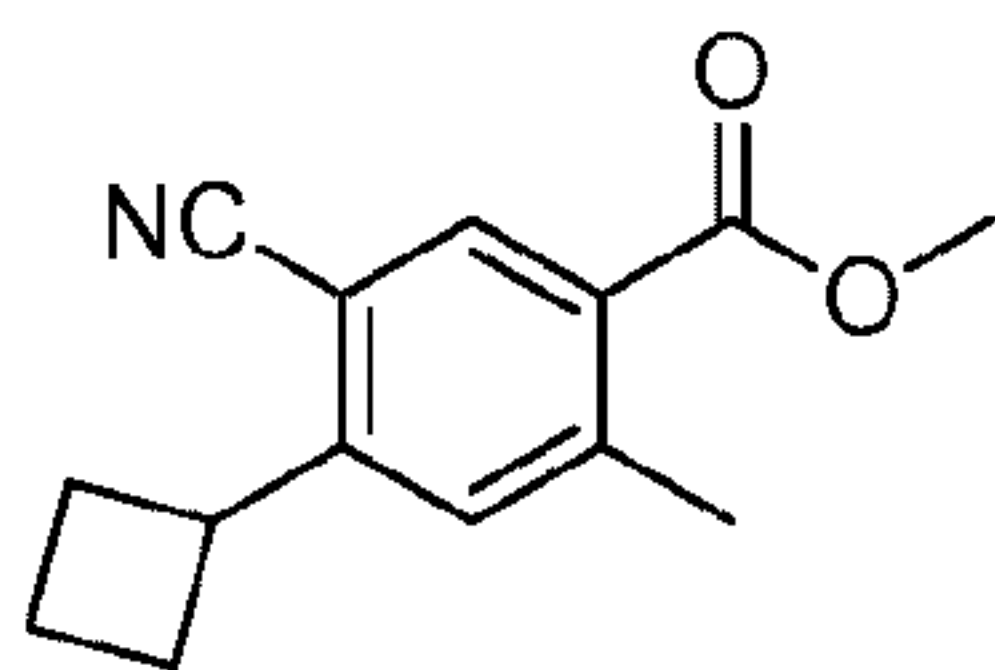
[0698] Compound 152.1. Methyl 4-bromo-2-methylbenzoate. To a solution of 4-bromo-2-methylbenzoic acid (5.11 g, 23.8 mmol, 1.0 equiv) in methanol (25 mL) was added dropwise sulfuric acid (2.0 mL) over about 3 minutes (mildly exothermic). The resulting mixture was refluxed for 4 hours. After cooling to room temperature, the reaction mixture was carefully quenched into saturated aqueous NaHCO_3 (100 mL) (note – significant gas evolution) and extracted with dichloromethane (200 mL x 1 then 50 mL x 1). The combined organic phases were washed with a mixture of brine/saturated NaHCO_3 (9:1)(50 mL), dried (Na_2SO_4), and concentrated under reduced pressure to obtain the title compound as a colorless oil (5.28 g, 97%). ^1H NMR (400 MHz, CDCl_3): δ 7.78 (d, $J = 8.0$ Hz, 1 H), 7.42 (d, $J = 1.6$ Hz, 1H), 7.38 (dd, $J = 1.6$ Hz, 1H), 3.89 (s, 3H), 2.58 (s, 3H).



[0699] Compound 152.2. Methyl 4-cyclobutyl-2-methylbenzoate. Cyclobutylzinc(II) bromide (50 mL, 0.5 M in THF, 25.0 mmol) was added to a mixture of methyl 4-bromo-2-methylbenzoate (compound **152.1**, 5.2g, 22.7mmol) and $\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$ (1.85g, 2.27 mmol). The mixture was degassed and the flask was filled with argon through a balloon. The mixture was heated at 65°C under argon for 24 hours. The mixture was cooled to 0°C and quenched with water (10 mL). The mixture was diluted with EtOAc (200 mL), washed with water then with brine. The EtOAc layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified using column (silica gel) chromatography (hexanes : EtOAc 30:1 to 20:1). Yield: 4.1 g, clear oil, 89.1%. ^1H NMR (400 MHz, Chloroform- d) δ 7.86 (d, 1H), 7.12 – 7.02 (m, 2H), 3.88 (s, 3H), 3.59 – 3.48 (m, 1H), 2.59 (s, 3H), 2.35 (m, 2H), 2.22 – 1.96 (m, 3H), 1.86-1.84 (m, 1H).

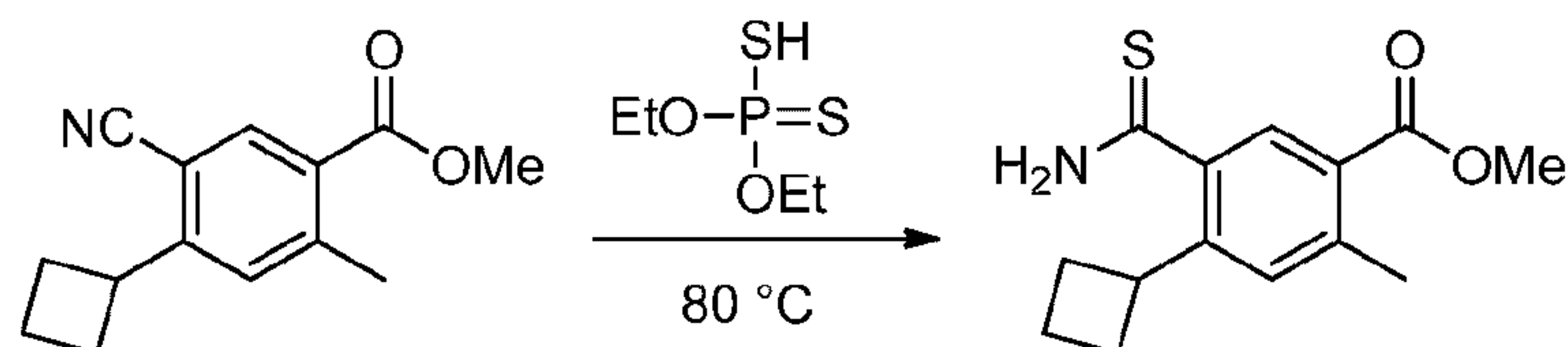


[0700] Compound 152.3. Methyl 4-cyclobutyl-5-iodo-2-methylbenzoate. N-Iodosuccinimide (3.52 g, 15.6 mmol) was added portionwise to a solution of methyl 4-cyclobutyl-2-methylbenzoate (compound **152.2**, 3.2 g, 15.6 mmol) in concentrated sulfuric acid (25 ml) at 0 °C. The mixture was stirred at 0 °C for 30 min and at RT for 2 hours. The mixture turned very thick. The mixture was cooled to 0 °C again and MeOH (30 ml) was added. The mixture was heated at 60 °C for 2 hours. The methanol was removed under reduced pressure and the residue was poured into ice water (100 ml). The mixture was extracted with EtOAc (2x). The combined organic layers were washed with brine, then aq. 1N NaHCO₃ (note-significant gas evolution), dried (Na₂SO₄) and concentrated. The residue was purified using column (silica gel) chromatography (hexanes : EtOAc 30:1 to 20:1). Yield: 4.17 g, light yellow oil, 81%. ¹H NMR (400 MHz, Chloroform-d) δ 8.33 (s, 1H), 7.14 (s, 1H), 3.87 (s, 3H), 3.67 – 3.54 (m, 1H), 2.57 (s, 3H), 2.51 – 2.40 (m, 2H), 2.14 – 1.97 (m, 3H), 1.82-1.79 (m, 1H).



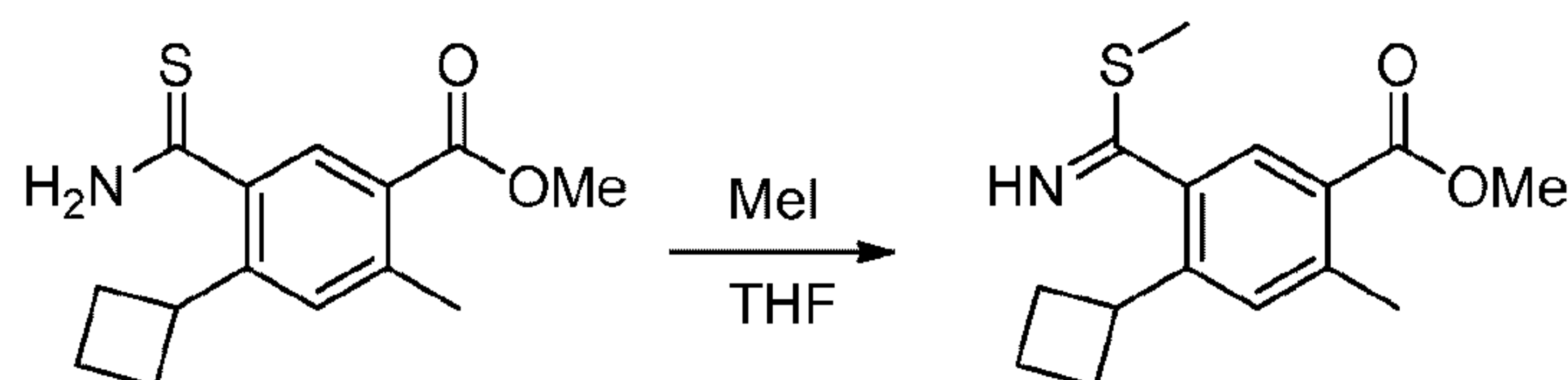
[0701] Compound 152.4. Methyl 5-cyano-4-cyclobutyl-2-methylbenzoate. A mixture of methyl 4-cyclobutyl-5-iodo-2-methylbenzoate (compound **152.3**, 4.17 g, 12.64 mmol), Zn(CN)₂ (2.96 g, 25.21 mmol) and Pd(PPh₃)₄ (0.73 g, 0.63 mmol) in DMF (30ml) was degassed and the flask was filled with argon through a balloon. The mixture was heated at 100 °C under argon overnight. After cooling to ambient temperature, the mixture was quenched with saturated aq. FeSO₄ (20 ml) and diluted with EtOAc (200 ml). The greenish solid was removed by filtration through celite. The filtrate was partitioned between water and EtOAc. The EtOAc layer was washed with brine, dried (Na₂SO₄), and concentrated. The residue was purified using column (silica gel) chromatography (hexanes : EtOAc 30 : 1 to 20 : 1). Yield: 2.55 g, white solid, 88%. ¹H NMR (400 MHz, Chloroform-d) δ 8.16 (s, 1H), 7.28 (s, 1H), 3.90 (s, 3H), 3.86-3.82 (m, 1H), 2.68 (s, 3H), 2.55 – 2.45 (m, 2H), 2.27 – 2.04 (m, 3H), 1.89-1.87 (m, 1H).

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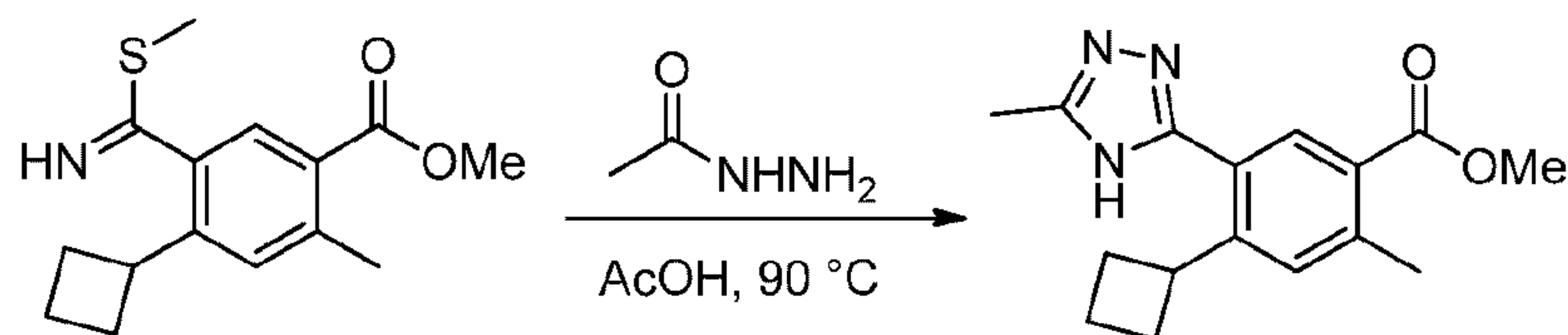
[0702] Compound 152.5. Methyl 5-carbamothioyl-4-cyclobutyl-2-methylbenzoate.

To a round-bottom flask were added methyl 5-cyano-4-cyclobutyl-2-methylbenzoate (compound **152.4**, 3.63 g, 0.015 mol), O,O'-diethyl dithiophosphate (10 mL) and water (1 mL). The reaction mixture was heated to 80 °C for 3 hours (**CAUTION**: significant gas evolution occurs - this and all other reactions described herein should be carried out in well ventilated fume hoods). After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The combined organic layers were washed successively with saturated aqueous NaHCO₃ (50 mL) and brine (50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. Purification by SiO₂ flash chromatography (hexanes/ethyl acetate = 80/20 to 50/50) afforded methyl 5-carbamothioyl-4-cyclobutyl-2-methylbenzoate as a yellow solid (3.06 g, 78% yield). *m/z* (ES⁺) 264 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.93 (s, 1H), 7.82 (s, 1H), 7.26 (s, 1H), 6.92 (s, 1H), 4.19 (m, 1H), 3.89 (s, 3H), 2.64 (s, 3H), 2.40 (m, 2H), 2.29 – 2.15 (m, 2H), 2.12 – 2.00 (m, 1H), 1.95 – 1.84 (m, 1H).

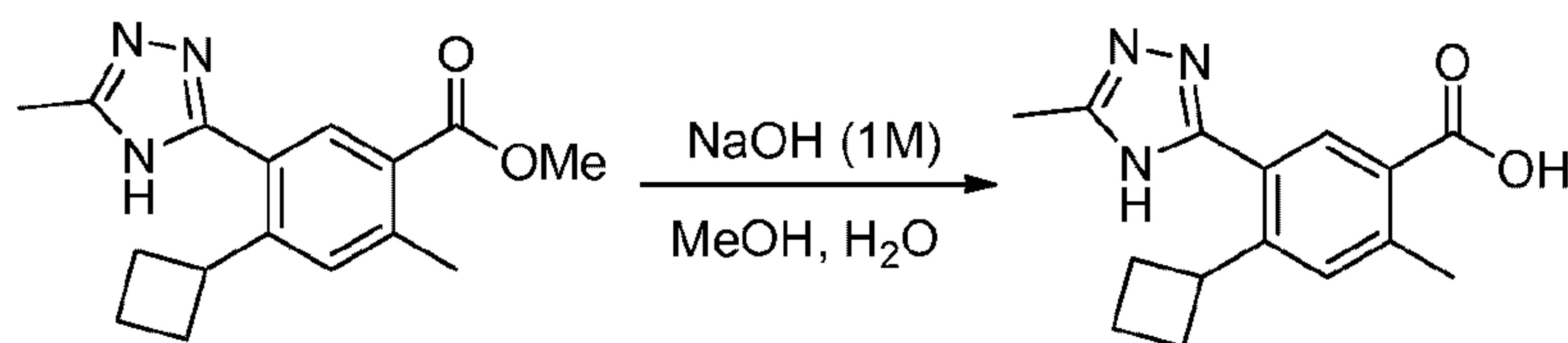


[0703] Compound 152.6. Methyl 4-cyclobutyl-5-(imino(methylthio)methyl)-2-methylbenzoate. To a round-bottom flask was added methyl 5-carbamothioyl-4-cyclobutyl-2-methylbenzoate (compound **152.5**, 861 mg, 3.27 mmol) in THF (10 mL). Iodomethane (912 mg, 6.42 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 7 hours. The reaction mixture was concentrated *in vacuo* and purified by SiO₂ flash chromatography (ethyl acetate to ethyl acetate/methanol = 95/5) to afford methyl 4-cyclobutyl-5-(imino(methylthio)methyl)-2-methylbenzoate as a yellowish oil (807 mg, 89% yield). *m/z* (ES⁺) 278 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 7.67 (s, 1H), 7.40 (s, 1H), 3.88 – 3.71 (m, 4H), 2.57 (s, 3H), 2.44 (s, 3H), 2.22-2.19 (m, 2H), 2.12 (m, 2H), 1.98 – 1.86 (m, 1H), 1.82 – 1.70 (m, 1H).

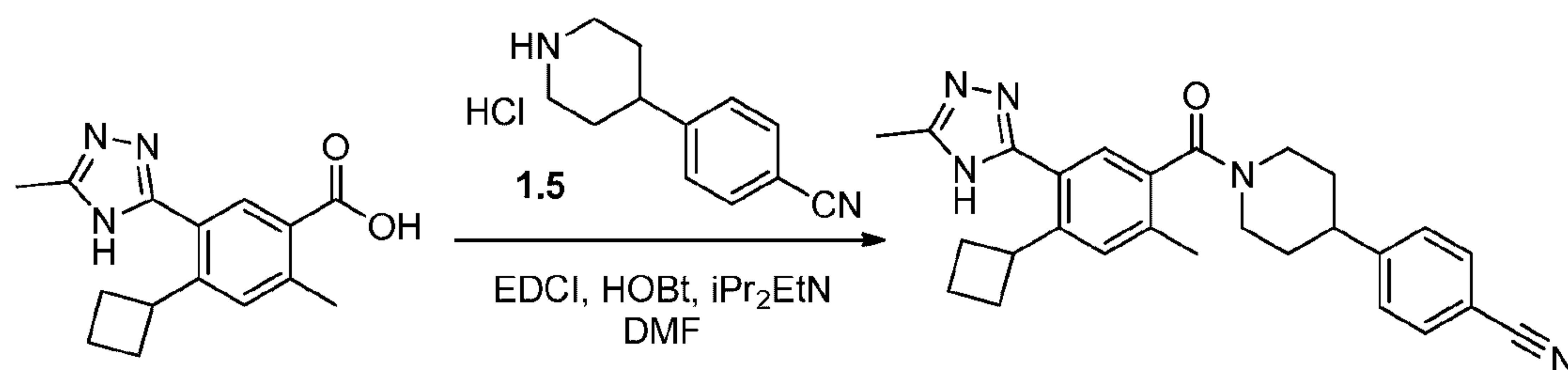
222



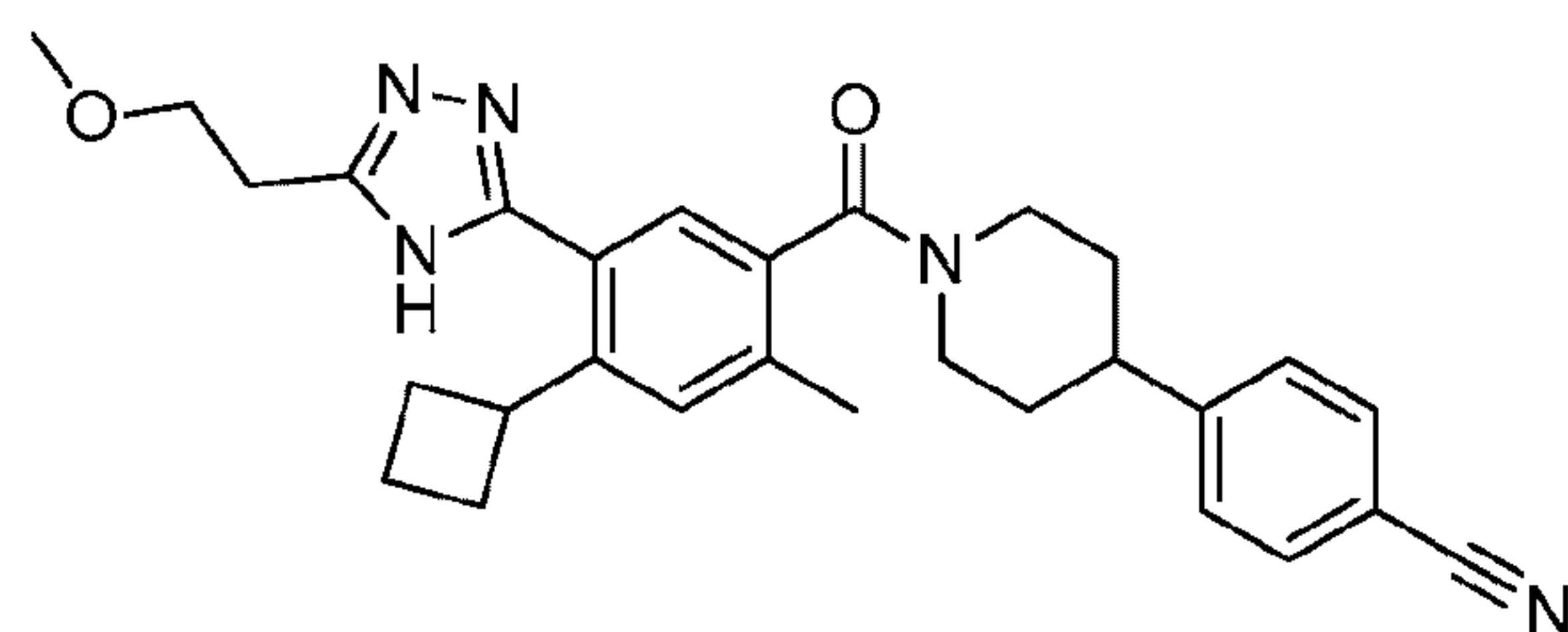
[0704] **Compound 152.7. Methyl 4-cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoate.** To a round-bottom flask were added methyl 4-cyclobutyl-5-(imino(methylthio)methyl)-2-methylbenzoate (compound **152.6**, 556 mg, 0.002 mol) and acetohydrazide (223 mg, 0.003 mol) in 6 mL acetic acid. The reaction mixture was heated to 90 °C for 3 hours. After cooling to room temperature, the reaction mixture was partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was washed with brine (2 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. Purification via SiO₂ flash chromatography (hexanes/ethyl acetate = 50/50 to 30/70) afforded the title compound as a white solid (243 mg, 43% yield). *m/z* (ES⁺) 286 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.23 (s, 1H), 7.32 (s, 1H), 4.24 – 4.05 (m, 1H), 3.89 (s, 3H), 2.69 (s, 3H), 2.54 (s, 3H), 2.23–2.20 (m, 2H), 2.16 – 2.05 (m, 2H), 2.05 – 1.88 (m, 1H), 1.88 – 1.71 (m, 1H).



[0705] **Compound 152.8. 4-Cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoic acid.** To a solution of methyl 4-cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoate (compound **152.7**, 240 mg, 0.842 mmol) in methanol (5 mL) was added aqueous NaOH (6 mL, 1M). The resulting mixture was heated to 50 °C for 6 hours. After cooling to ambient temperature, the reaction mixture was acidified with 1N HCl to pH 2 and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, and concentrated *in vacuo* to afford 4-cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoic acid (260 mg, quantitative) as a white solid. *m/z* (ES⁺) 272 (M+H)⁺.

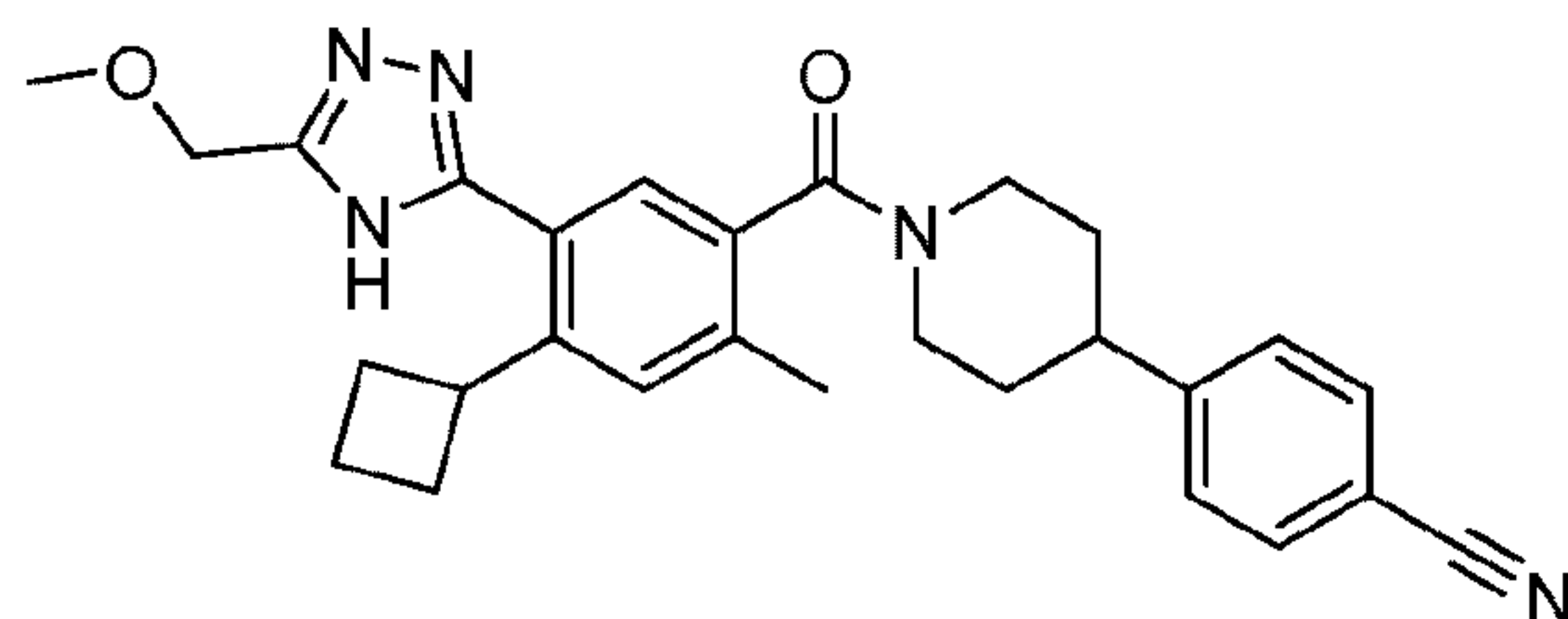


[0706] Compound 152. 4-(1-(4-Cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile. To a solution of 4-cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoic acid (compound **152.8**, 260 mg, 0.95 mmol) in DMF (4 mL) were added 4-(piperidin-4-yl)benzonitrile hydrochloride salt (compound **1.5**, 232 mg, 1.045 mmol), EDC (272 mg, 1.425 mmol), HOBT (39 mg, 0.285 mmol), and DIEA (367.7 mg, 2.85 mmol). The resulting mixture was stirred at room temperature for 16 hours. The mixture was quenched with saturated aqueous NaHCO₃ (20 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification via SiO₂ column chromatography (dichloromethane/methanol = 95/5) afforded 4-(1-(4-cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile as a white solid (193 mg, 44% yield). *m/z* (ES⁺) 440 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD): δ 7.69 (d, J = 5.4 Hz, 2H), 7.56-7.30 (m, 4H), 1 proton obscured by methanol solvent peak, 4.10-3.98 (m, 1H), 3.64 (t, J = 10.7 Hz, 1H), 3.33-3.21 (m, 1H), 3.00 (t, J = 8.9 Hz, 2H), 2.58 (s, 3H), 2.48 and 2.38 (2 singlets, amide rotamers, ArCH₃, 3H), 2.28-1.92 (m, 6H), 1.92-1.55 (m, 4H). ¹H NMR (400 MHz, DMSO-d₆): δ 13.66 (s, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.62-7.34 (m, 4H), 4.78-4.63 (m, 1H), 4.31 (br s, 1H), 3.45 (br s, 1H), 3.15 (app t, J = 12.3 Hz, 1H), 2.99-2.78 (m, 2H), 2.44-1.80 (m, 12H), 1.80-1.37 (m, 4H).

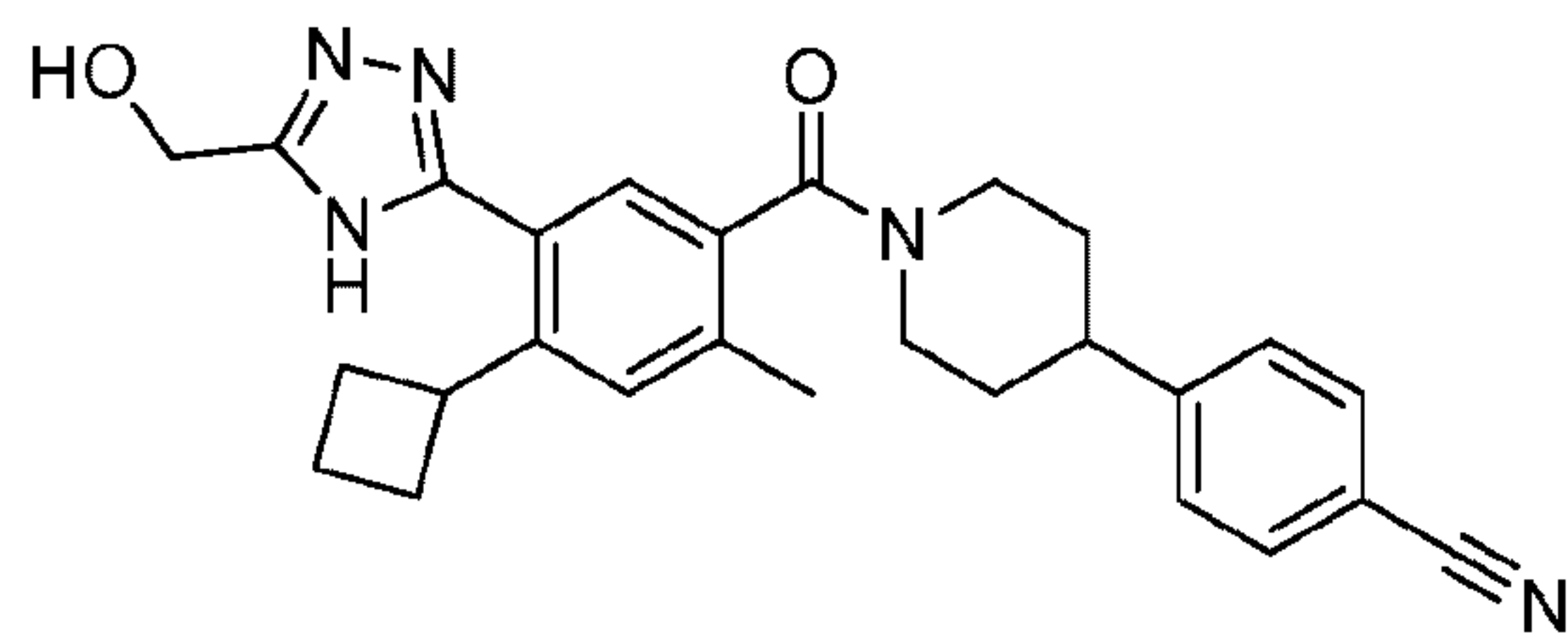


[0707] Compound 153. 4-(1-(4-Cyclobutyl-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(4-cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **152**), but using 3-methoxypropanehydrazide (compound **143.1**) in

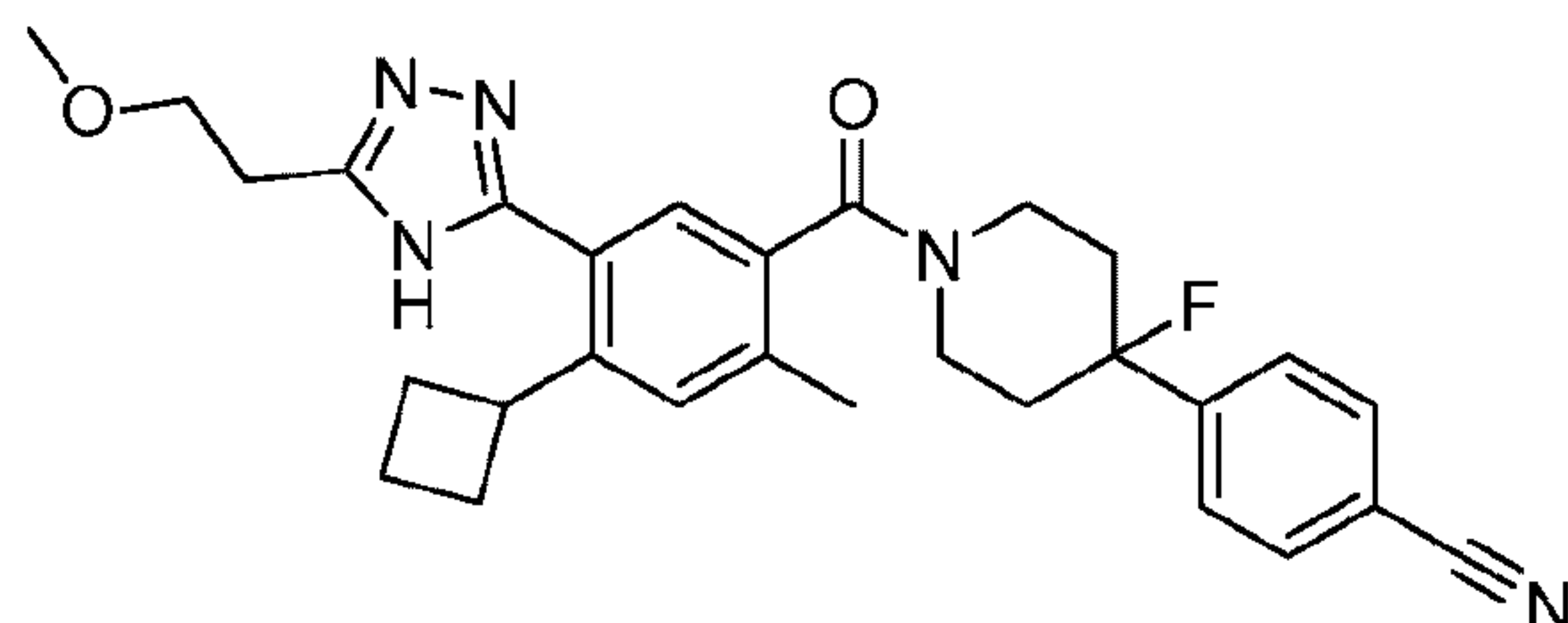
place of acetohydrazide. m/z (ES+) 484 (M+H)⁺, 967 (2M+H)⁺. ¹H NMR (400 MHz, Chloroform-d) δ 11.50 - 11.33 (br s, 1H), 7.66 - 7.44 (m, 3H), 7.33 - 7.27 (m, 3H), 4.98 (d, 1H), 4.24 - 4.12 (m, 1H), 3.78 (t, 2H), 3.70 (d, 1H), 3.44 (s, 3H), 3.14 - 3.03 (m, 3H), 2.90 - 2.75 (m, 2H), 2.42 and 2.34 (2 singlets, amide rotamers, ArCH₃, 3H), 2.17 (d, 2H), 2.08 - 1.88 (m, 3H), 1.84 - 1.51 (m, 5H).



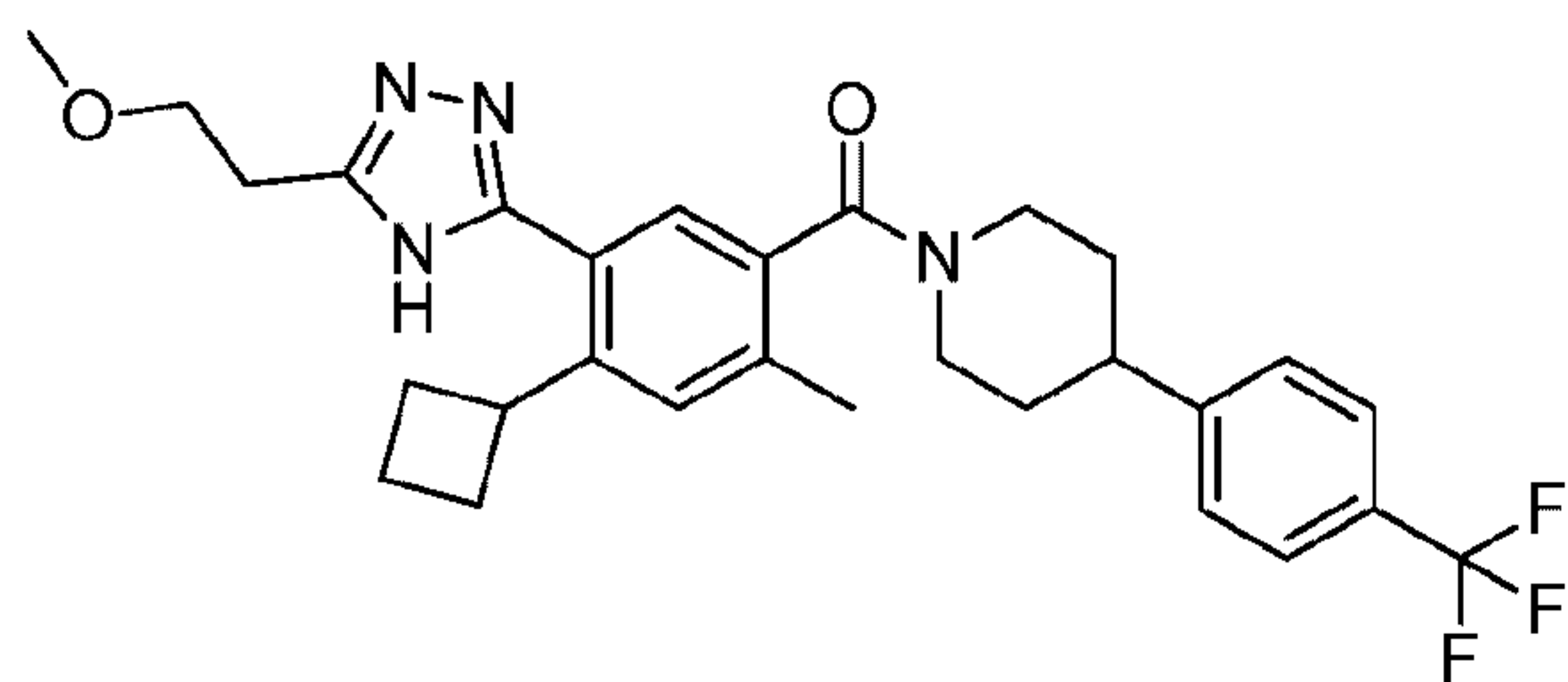
[0708] Compound 154. 4-(1-(4-Cyclobutyl-5-(5-(methoxymethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(4-cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **152**) but using 2-methoxyacetohydrazide (compound **190.6**) in place of acetohydrazide. m/z (ES+) 470 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃): δ 12.15 (br s, 1H), 7.64-7.57 (m, 2H), 7.43 & 7.33 (2 singlets, amide rotamers, Ar-H, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.20 (s, 1H), 5.04-4.92 (m, 1H), 4.65 (s, 2H), 4.18-4.03 (m, 1H), 3.63 (br d, J = 13.2 Hz, 1H), 3.51 (s, 3H), 3.08 (t with fine structure, J = 12.8 Hz, 1H), 2.93-2.77 (m, 2H), 2.38 & 2.30 (2 singlets, amide rotamers, ArCH₃, 3H), 2.25-1.84 (m, 6H), 1.84-1.43 (m, 4H).



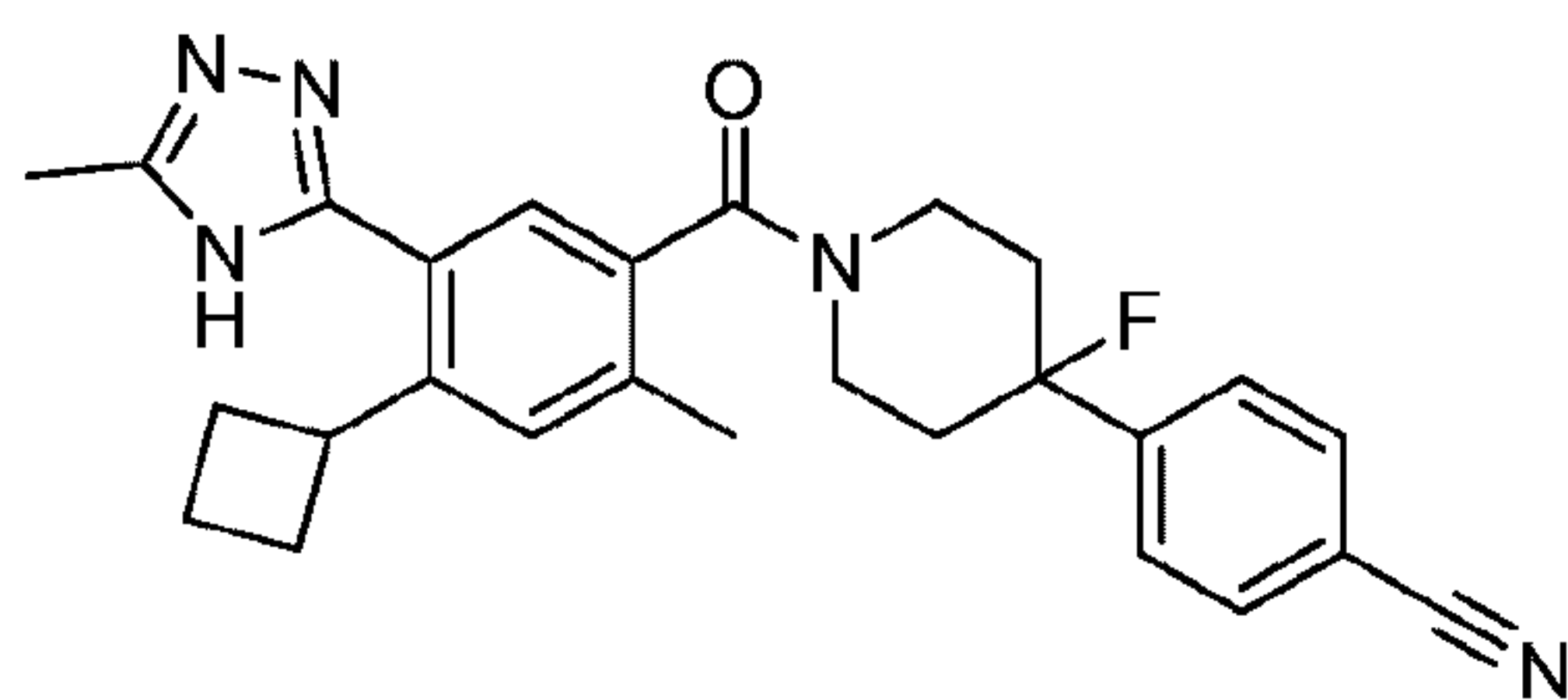
[0709] Compound 155. 4-(1-(4-Cyclobutyl-5-(5-(hydroxymethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound **152** but using 2-hydroxyacetohydrazide in place of acetohydrazide. m/z (ES+) 456 (M+H)⁺.



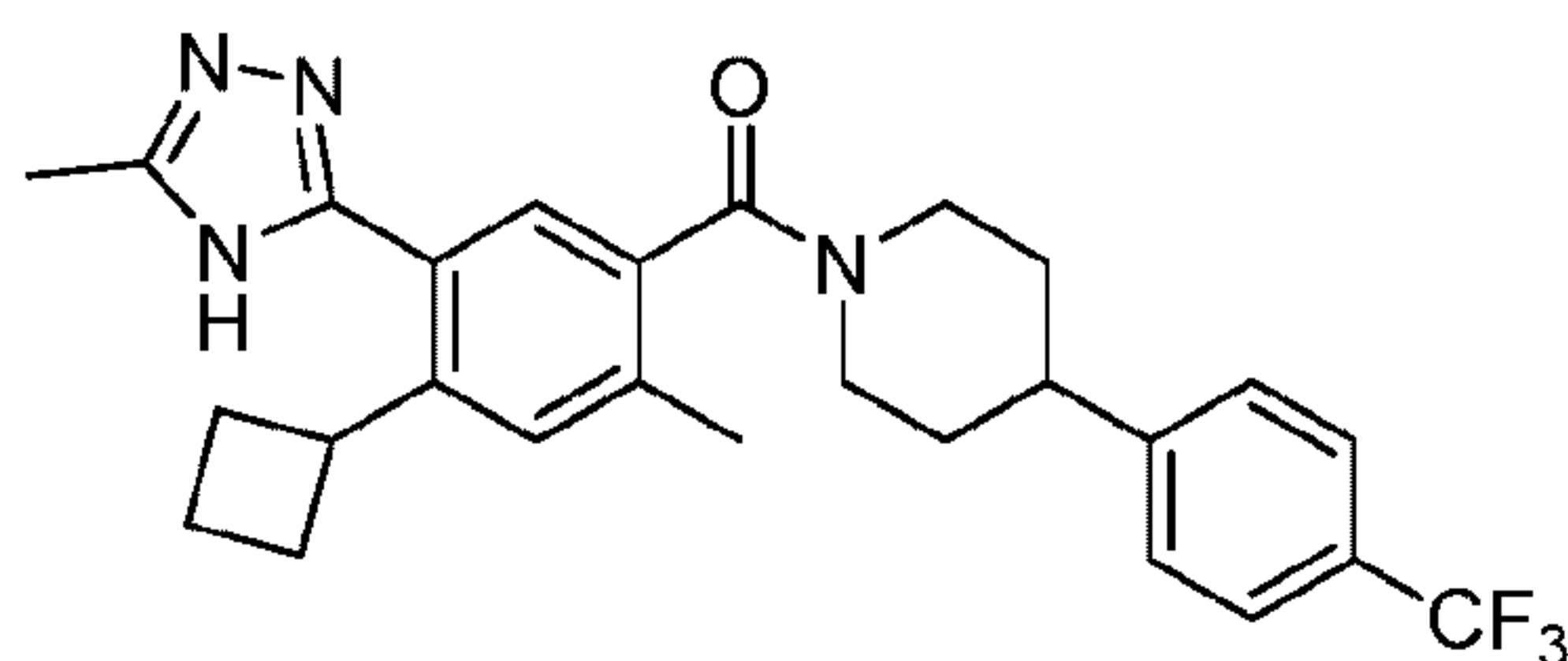
[0710] Compound 156. 4-(1-(4-Cyclobutyl-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(4-cyclobutyl-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)piperidin-4-yl)benzonitrile (compound **153**), using 4-(4-fluoropiperidin-4-yl)benzonitrile hydrochloride salt (compound **11.2 HCl salt**) instead of 4-(piperidin-4-yl)benzonitrile hydrochloride salt (compound **1.5**). m/z (ES+) 501.8 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃): δ 11.46 (br s, 1H), 7.75-7.45 (m, 3H), 7.49 (d, J = 8.4 Hz, 2H), 7.32 (s, 1H), 4.89 (br d, J = 13.2 Hz, 1H), 4.28-4.15 (m, 1H), 3.79 (t, J = 6.0 Hz, 2H), 3.70-3.45 (m, 2H), 3.46 (s, 3H), 3.31-3.17 (m, 1H), 3.13 (t, J = 6.0 Hz, 2H), 2.45 & 2.38 (2 br singlets, amide rotamers, Ar-CH₃, 3H), 2.30-1.68 (m, 10H).



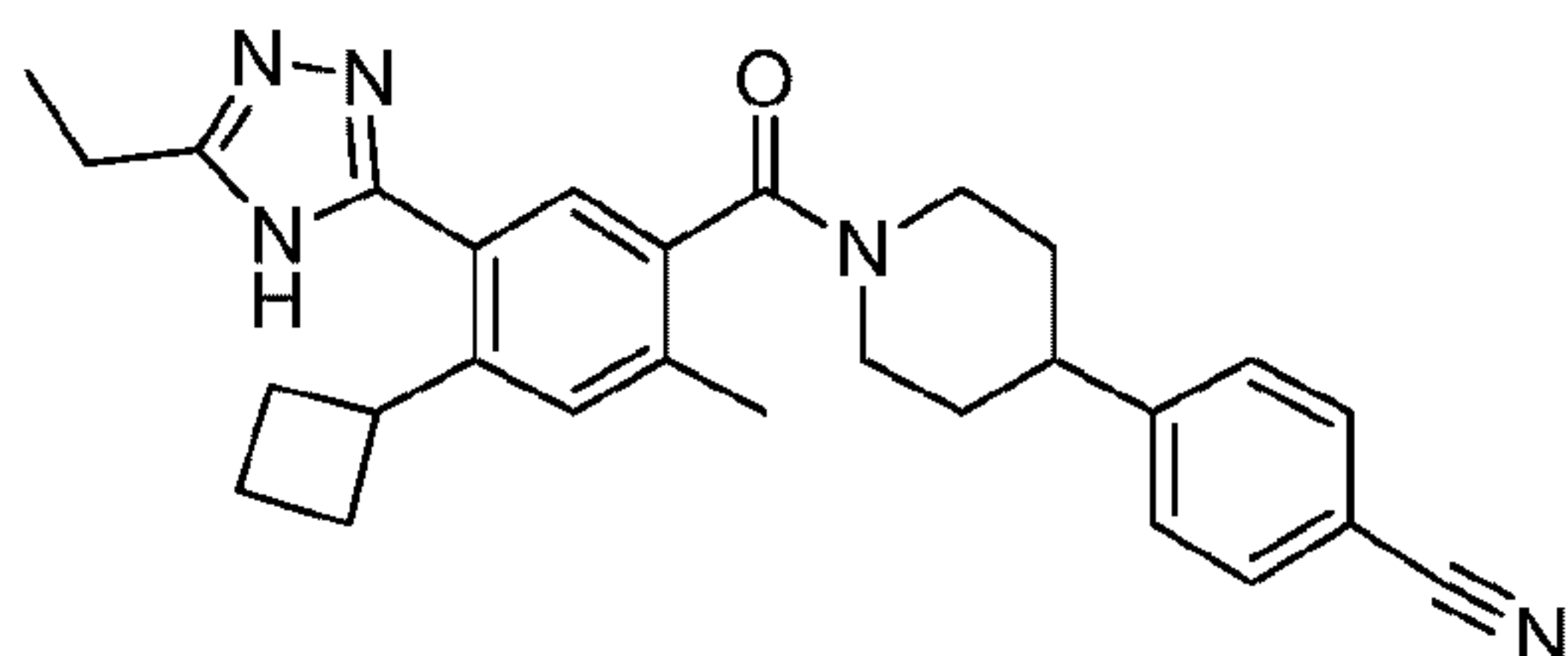
[0711] Compound 157. (4-Cyclobutyl-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)-2-methylphenyl)(4-(4-(trifluoromethyl)phenyl)piperidin-1-yl)methanone. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(4-cyclobutyl-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)piperidin-4-yl)benzonitrile (compound **153**), using 4-(4-(trifluoromethyl)phenyl)piperidine hydrochloride salt instead of 4-(piperidin-4-yl)benzonitrile hydrochloride salt (compound **1.5**). m/z (ES+) 527 (M+H)⁺. ¹H NMR (400 MHz, Chloroform-d) δ 11.30 – 11.10 (br, 1H), 7.60-7.47 (m, 3H), 7.35-7.28 (m, 3H), 5.10-4.93 (m, 1H), 4.24-4.13 (m, 1H), 3.78 (t, 2H), 3.70 (d, 1H), 3.45 (s, 3H), 3.12 t, 2H), 3.15-3.05 (m, 1H), 2.90-2.75 (m, 2H), 2.44 and 2.35 (2 singlets, amide rotamers, ArCH₃, 3H), 2.25-2.13 (m, 2H), 2.13-1.85 (m, 4H), 1.87-1.66 (m, 4H).



[0712] **Compound 158.** 4-(1-(4-Cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl)-4-fluoropiperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(4-cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **152**), using compound **11.2 HCl salt** instead of compound **1.5**. m/z (ES⁺) 458 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 13.66 (s, 1H), 7.66 (d, 2H), 7.51 (d, 3H), 7.38 (s, 1H), 4.72 (d, 1H), 4.30 (br s, 1H), 3.46 (br s, 1H), 3.16 (dd, 1H), 3.04 – 2.78 (m, 2H), 2.38 and 2.36 (2 singlets, amide rotamers, ArCH₃, 3H), 2.35-2.27 (m, 3H), 2.22 – 1.82 (m, 6H), 1.81-1.56 (m, 3H).

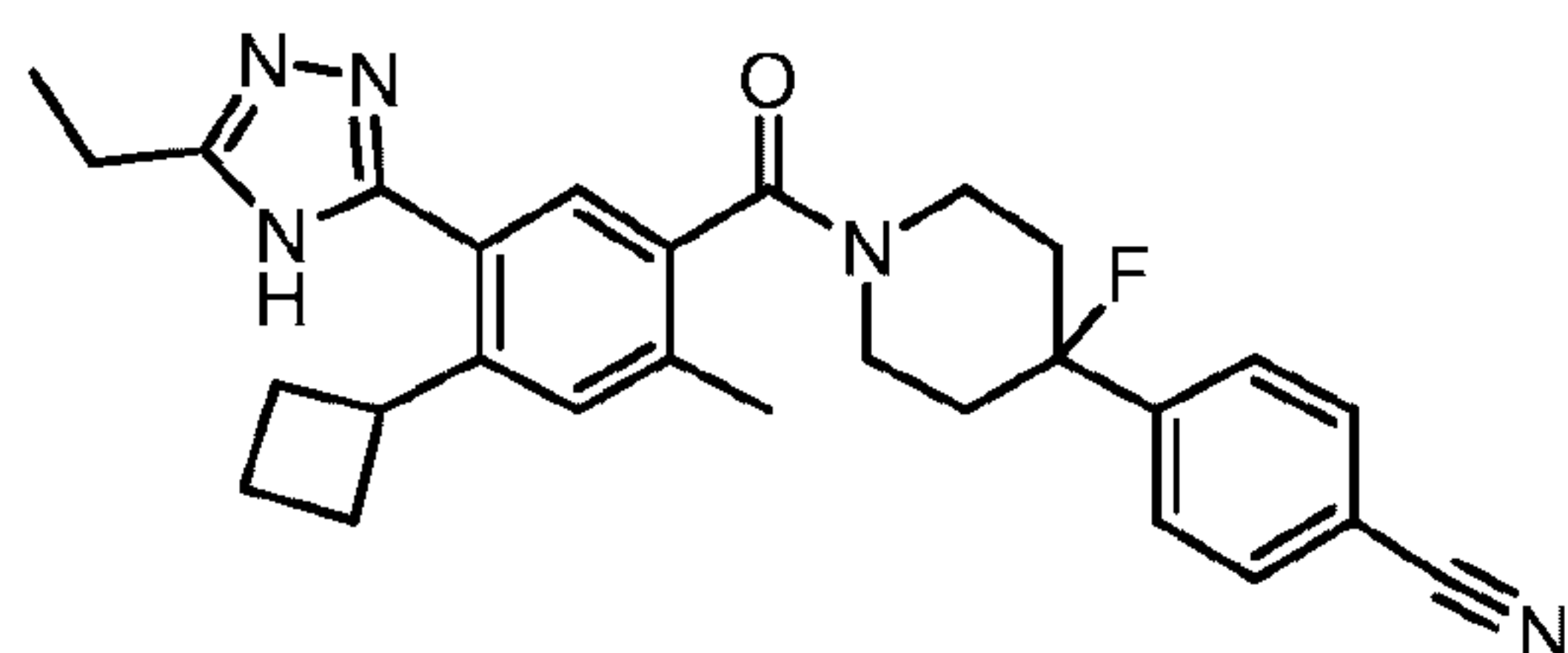


[0713] **Compound 159.** (4-Cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)phenyl)(4-(4-(trifluoromethyl)phenyl)piperidin-1-yl)methanone. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(4-cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **152**). m/z (ES⁺) 483 (M+H)⁺.

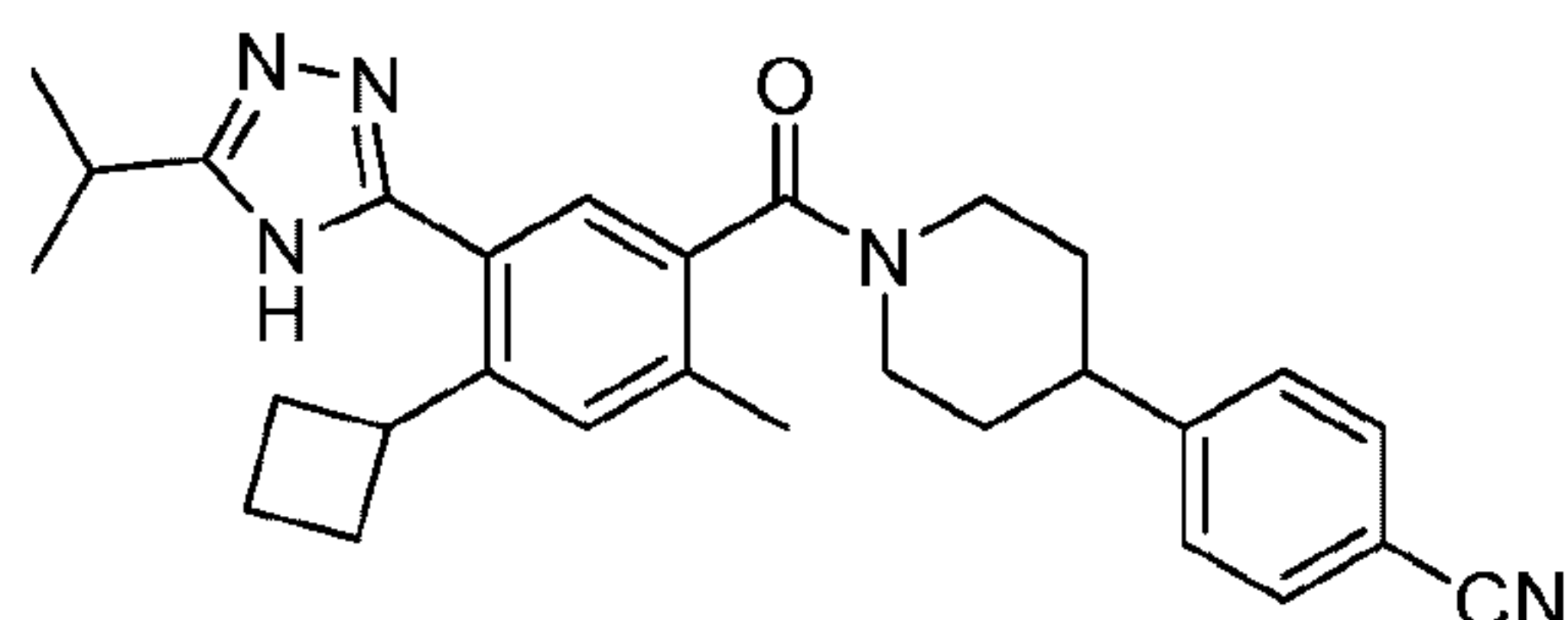


[0714] **Compound 160.** 4-(1-(4-Cyclobutyl-5-(5-ethyl-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound **152** and using propionohydrazide instead of acetohydrazide. m/z (ES⁺) 454 (M+H)⁺. ¹H NMR (400 MHz, Chloroform-d) δ 7.75 – 7.43 (m, 3H), 7.40 – 7.17 (m, 3H),

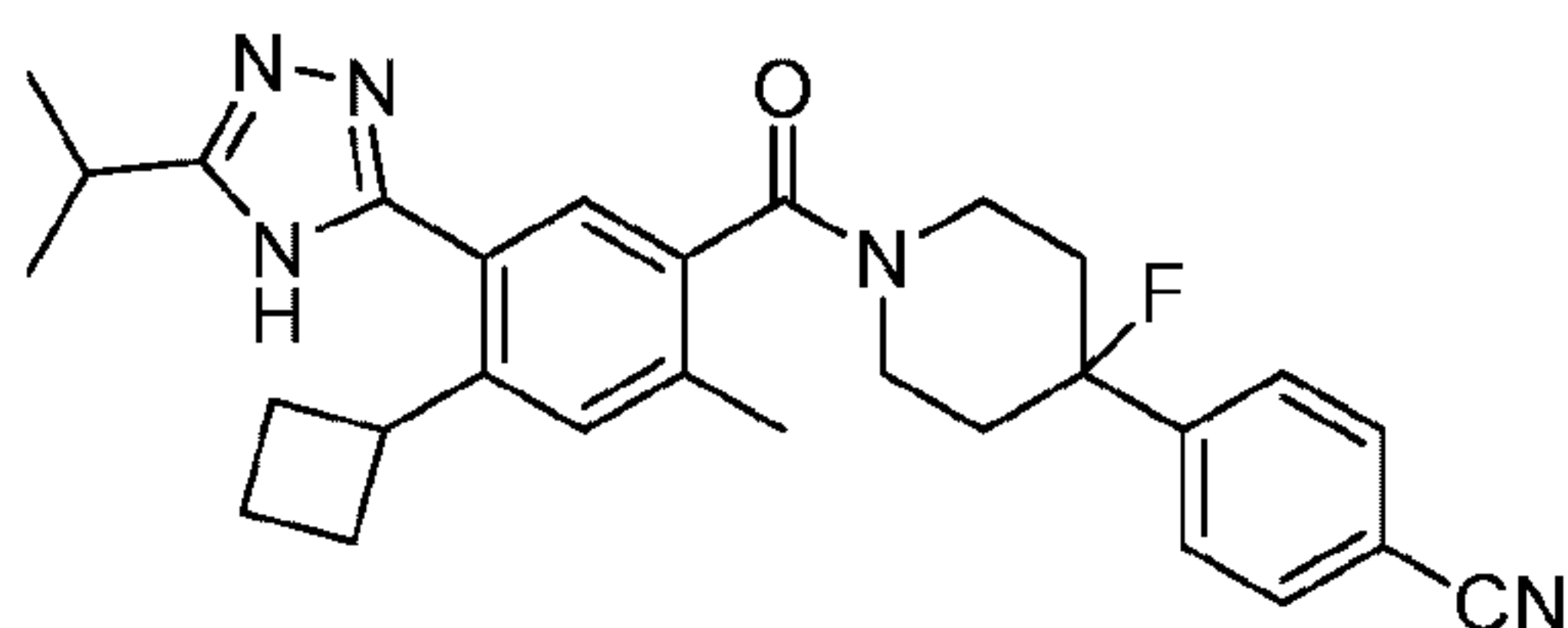
5.18 – 4.81 (m, 1H), 4.30 – 3.91 (m, 1H), 3.84 – 3.55 (m, 1H), 3.21 – 2.99 (m, 1H), 2.92 – 2.69 (m, 4H), 2.40 and 2.32 (2 singlets, amide rotamers, ArCH_3 , 3H), 2.25 – 1.84 (m, 7H), 1.83 – 1.42 (m, 3H), 1.32 (t, 3H).



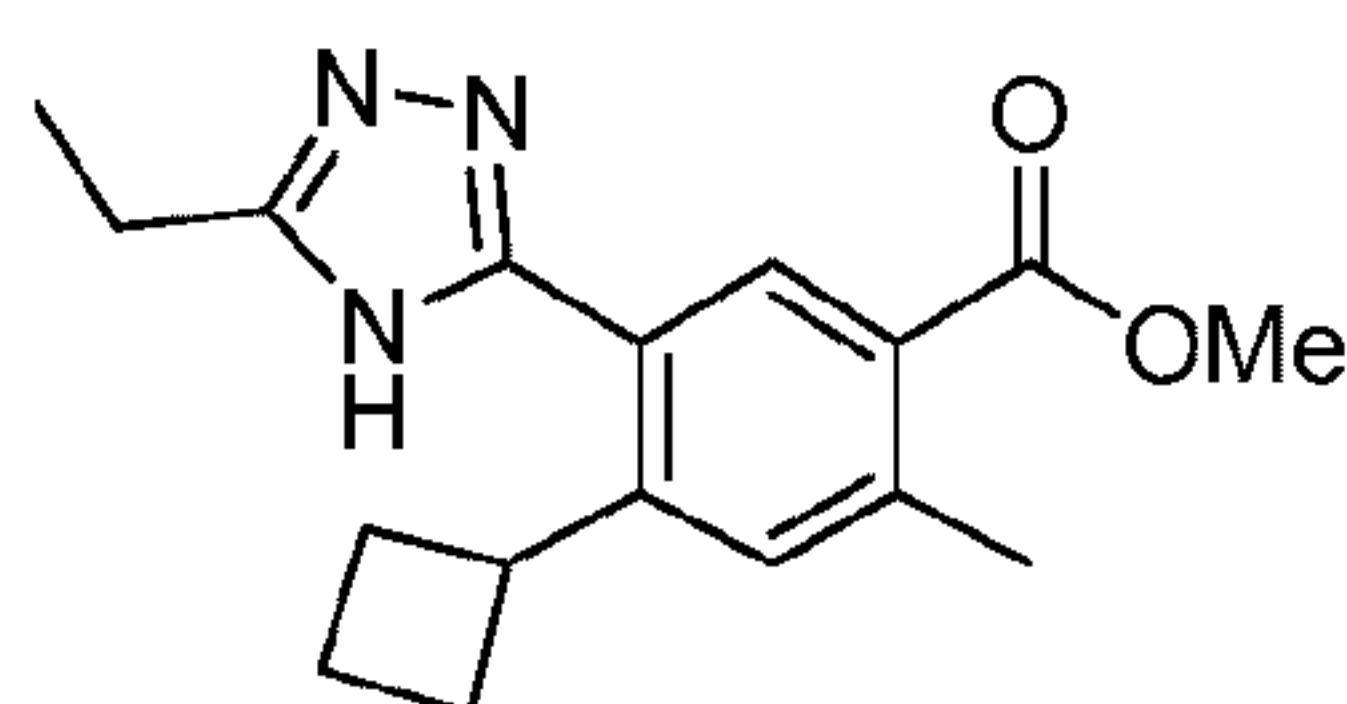
[0715] Compound 161. 4-(1-(4-Cyclobutyl-5-(5-ethyl-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl) benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(4-cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **152**). m/z (ES+) 472 ($\text{M}+\text{H}$)⁺. ¹H NMR (400 MHz, Chloroform- d) δ 7.79 – 7.57 (m, 2H), 7.57 – 7.18 (m, 4H), 4.86 (dd, 1H), 4.14 (s, 1H), 3.62-3.40 (m, 4H), 3.22 (t, 1H), 2.77 (q, 2H), 2.31 & 2.41 (2 singlets, amide rotamers, 3H), 2.29 – 1.47 (m, 8H), 1.30 (t, 3H).



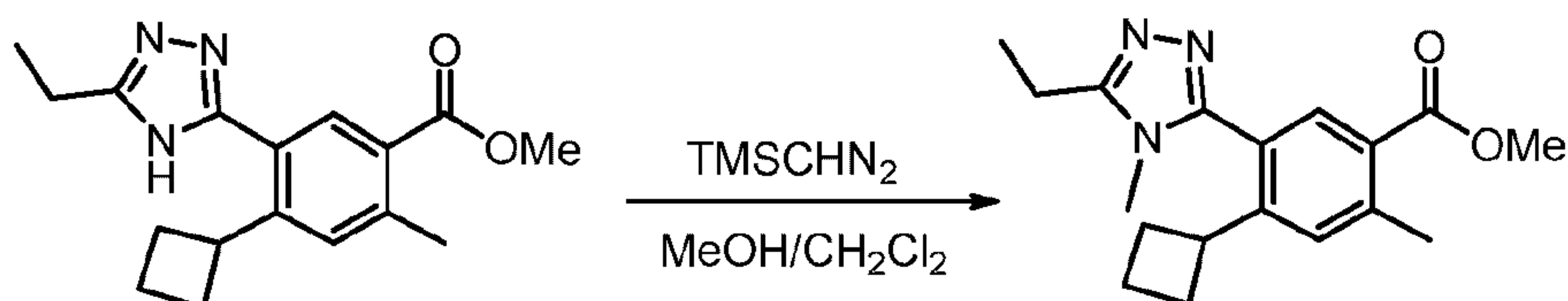
[0716] Compound 162. 4-(1-(4-Cyclobutyl-5-(5-isopropyl-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(4-cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **152**). m/z (ES+) 468 ($\text{M}+\text{H}$)⁺. ¹H NMR (400 MHz, DMSO- d_6) δ 13.67 (s, 1H), 7.77 (d, 2H), 7.49-7.47 (m, 3H), 7.36 (s, 1H), 4.72 (d, 1H), 4.29 (s, 1H), 3.46 (d, 1H), 3.12 (m, 2H), 2.98 – 2.75 (m, 2H), 2.31 (d, 3H), 2.23 – 1.81 (m, 6H), 1.83 – 1.36 (m, 4H), 1.31 (d, 6H).



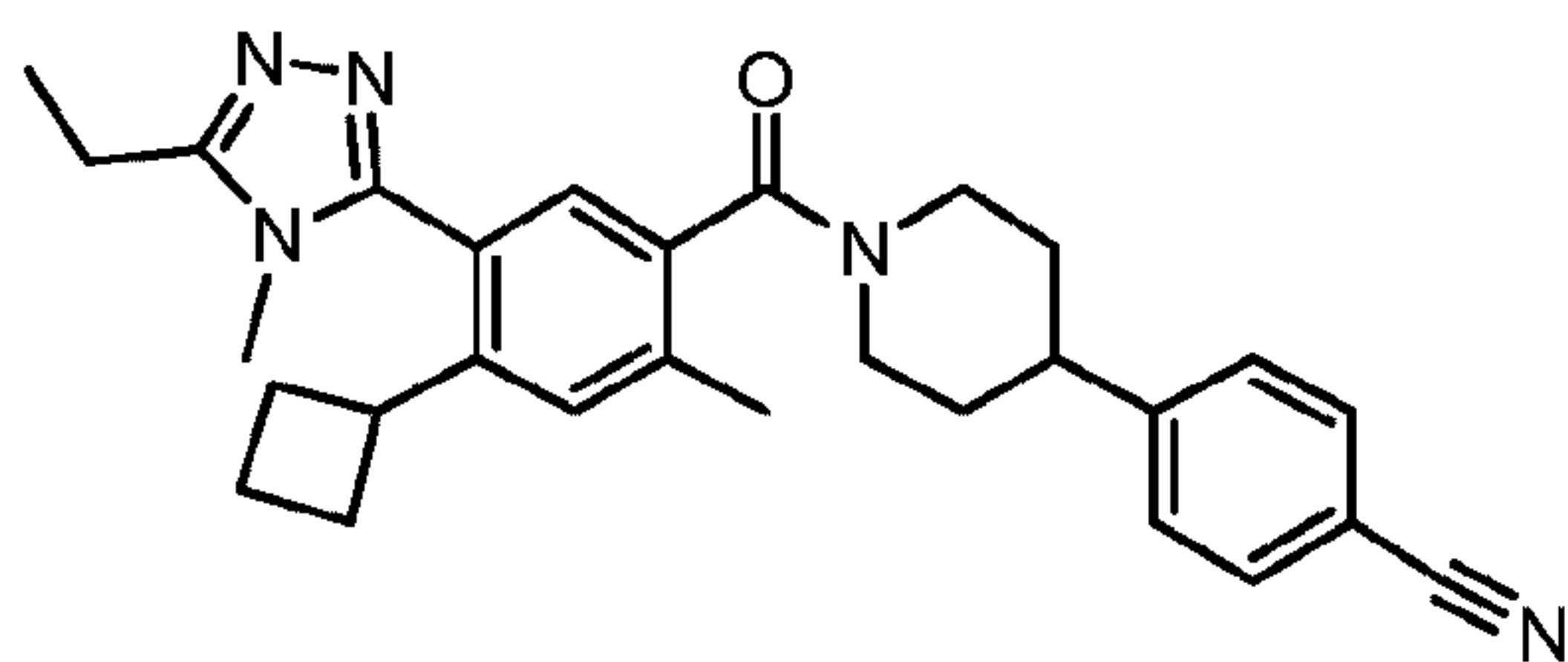
[0717] **Compound 163.** 4-(1-(4-Cyclobutyl-5-(5-isopropyl-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(4-cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **152**). m/z (ES⁺) 486 (M+H)⁺.



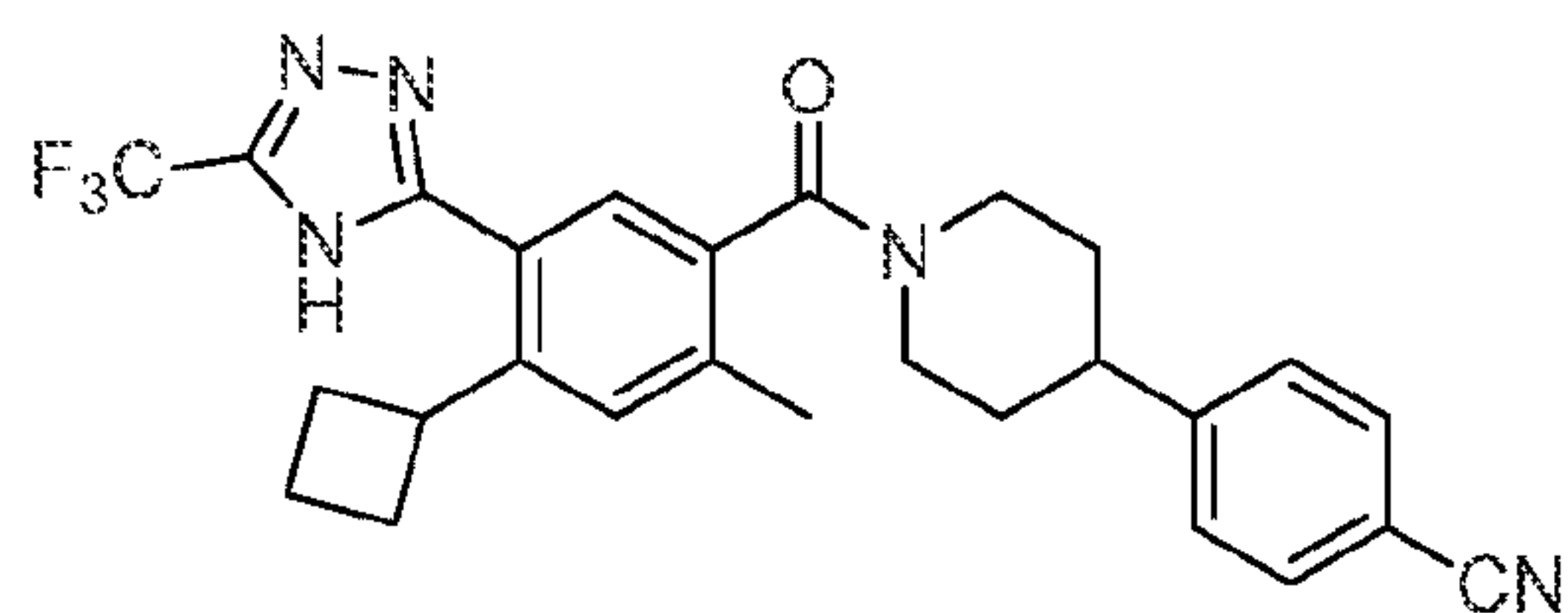
[0718] **Compound 164.1.** 4-(1-(4-Cyclobutyl-5-(5-isopropyl-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound **152.7** and using propionohydrazide instead of acetohydrazide.



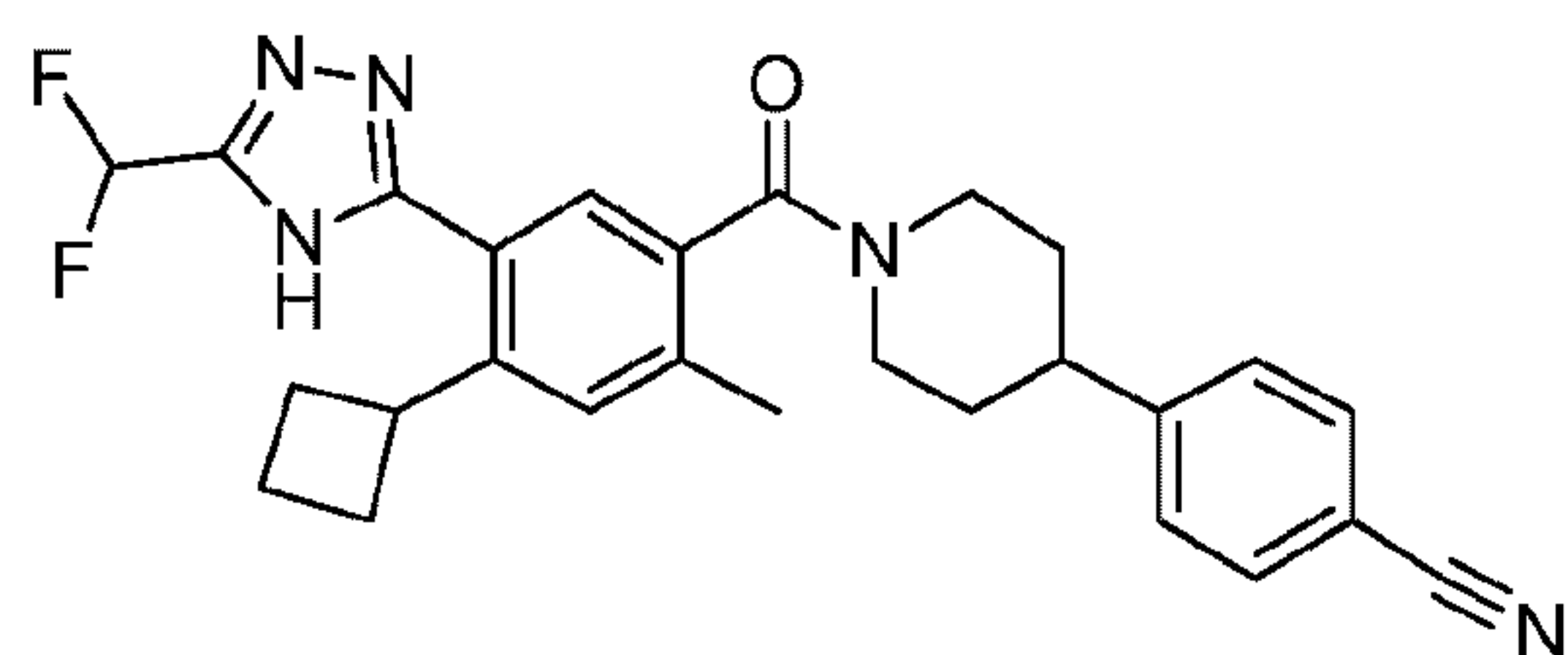
[0719] **Compound 164.2.** Methyl 4-cyclobutyl-5-(5-ethyl-N-methyl-4H-1,2,4-triazol-3-yl)-2-methylbenzoate. Methyl 4-cyclobutyl-5-(5-ethyl-4H-1,2,4-triazol-3-yl)-2-methylbenzoate (compound **164.1**, 87 mg, 0.29 mmol) was dissolved in methanol and dichloromethane (1:1 v/v) (6 ml). ((Trimethylsilyl) methyl) diazomethane (2.0 M in ether) (220 μ l, 0.44 mmol) was added. The mixture was stirred for 16 hours and quenched with HOAc (300 μ l). The volatiles were removed *in vacuo* to afford an oil (85 mg). The residue was carried as crude onto the next step without further purification. m/z (ES⁺) 314 (M+H)⁺.



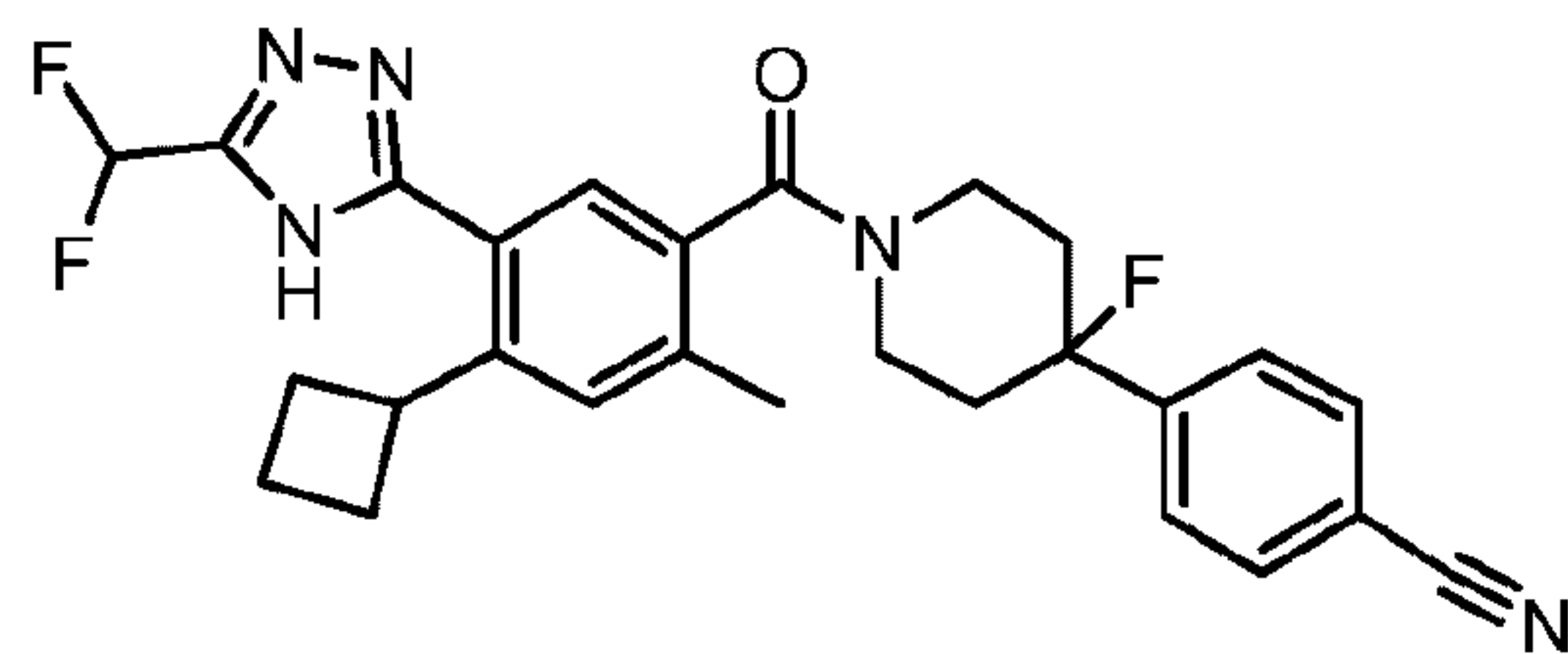
[0720] **Compound 164.** 4-(1-(4-Cyclobutyl-5-(5-ethyl-N-methyl-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)piperidin-4-yl)benzonitrile. The title compound (mixture of N-methyl isomers) was prepared using standard chemical manipulations and procedures similar to those used for preparation of compound **152** and using compound **164.2** instead of compound **152.7**. m/z (ES+) 468 (M+H)⁺.



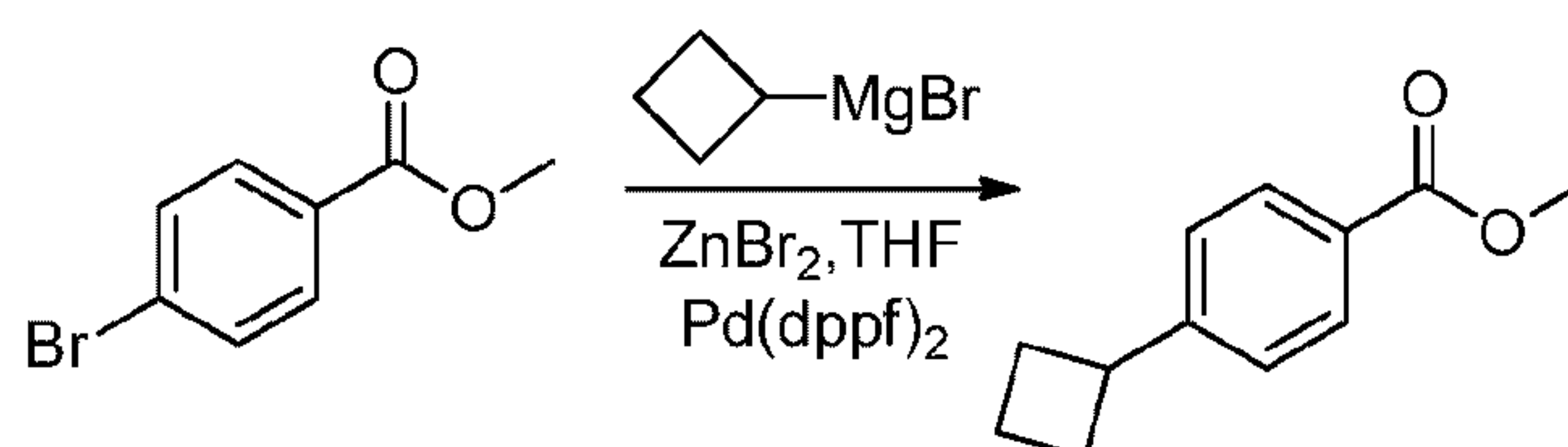
[0721] **Compound 165.** 4-(1-(4-Cyclobutyl-2-methyl-5-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of 4-(1-(4-cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **152**). m/z (ES+) 494.0 (M+H)⁺.



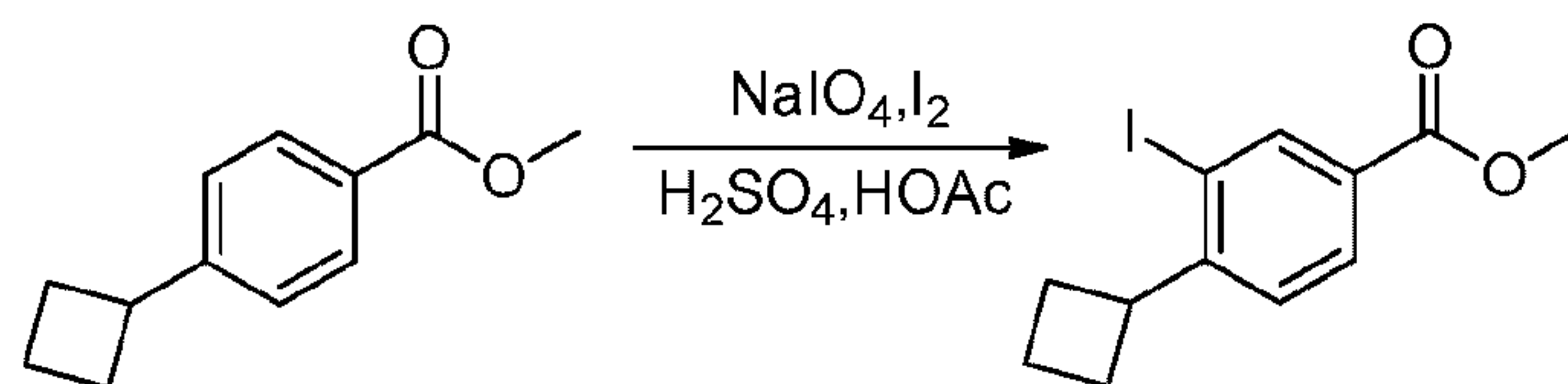
[0722] **Compound 166.** 4-(1-(4-Cyclobutyl-5-(5-(difluoromethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of 4-(1-(4-cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **152**). m/z (ES+) 476 (M+H)⁺.



[0723] Compound 167. 4-(1-(4-Cyclobutyl-5-(5-(difluoromethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)-4-fluoropiperidin-4-yl) benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for preparation of 4-[1-[4-cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl]-4-piperidyl]benzonitrile (compound **152**). m/z (ES⁺) 494 (M+H)⁺.

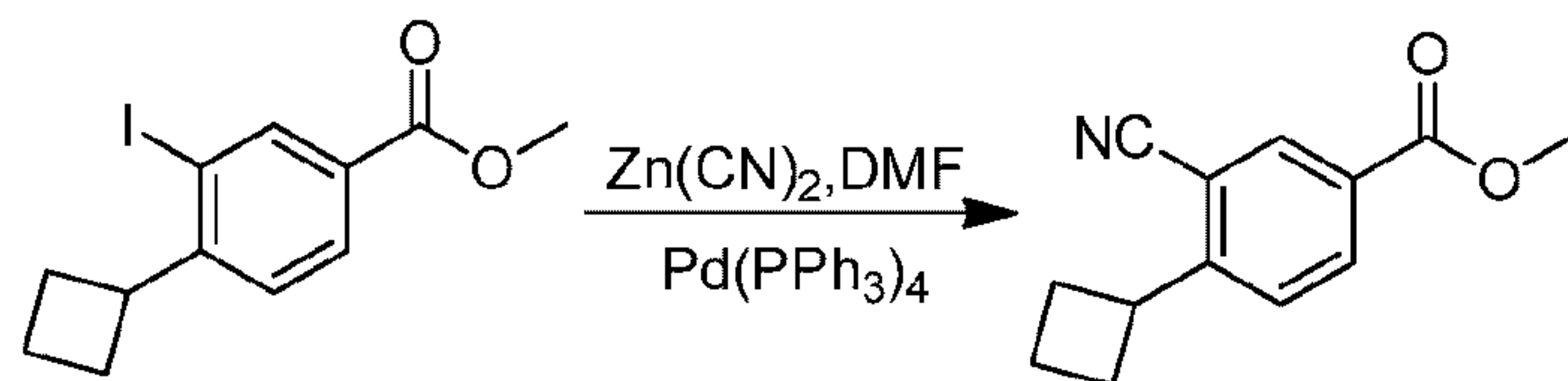


[0724] Compound 168.1. Methyl 4-cyclobutylbenzoate. To a stirred mixture of ZnBr₂ (83.0 g, 368.53 mmol, 4.00 equiv) in THF (500 mL) under nitrogen at 0 °C was added a solution of bromo(cyclobutyl)magnesium (242 mL, 364 mmol, 1.5 M in THF) dropwise during 20 min. To the resulting mixture were added Pd(dppf)Cl₂ (2.00 g, 0.10 equiv) and methyl 4-bromobenzoate (20 g, 93.00 mmol, 1.00 equiv) at -40 °C. The resulting mixture was stirred at -40 °C for 1h under nitrogen, and then carefully quenched with 500 mL of NH₄Cl (aq., sat.). The mixture was extracted with 3 x 500 mL of ethyl acetate. The combined organic layers were washed with 3 x 500 mL of brine, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield 18.0 g (crude) of the title compound as a light yellow oil.

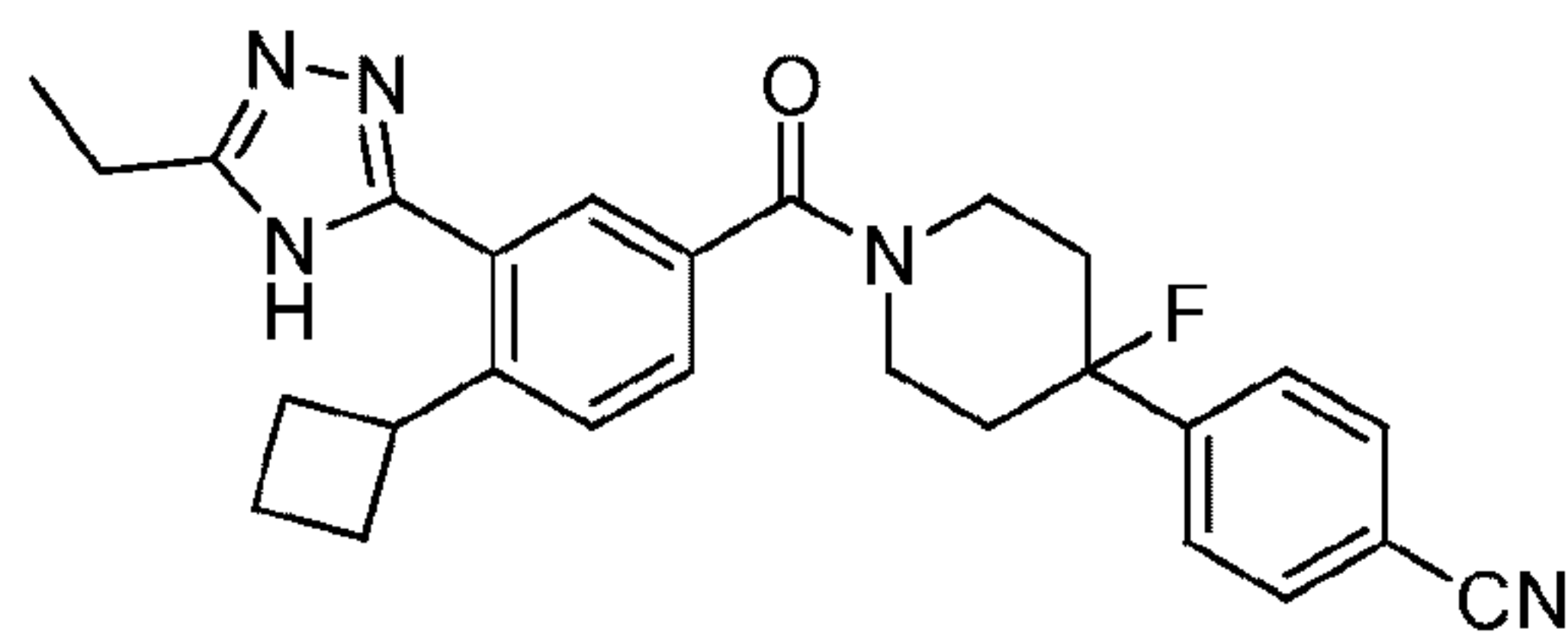


[0725] Compound 168.2. Methyl 4-cyclobutyl-3-iodobenzoate. To a solution of methyl 4-cyclobutylbenzoate (**168.1**, 2.00 g, 10.5 mmol, 1.00 equiv) in acetic acid (30 mL) were carefully added sodium periodate (1.00 g, 4.68 mmol, 0.50 equiv), iodine (3.00 g, 11.8 mmol, 1.10 equiv) and sulfuric acid (0.15 g, 0.15 equiv). The resulting mixture was stirred overnight at 100 °C. After cooling to room temperature, the reaction was then quenched by carefully

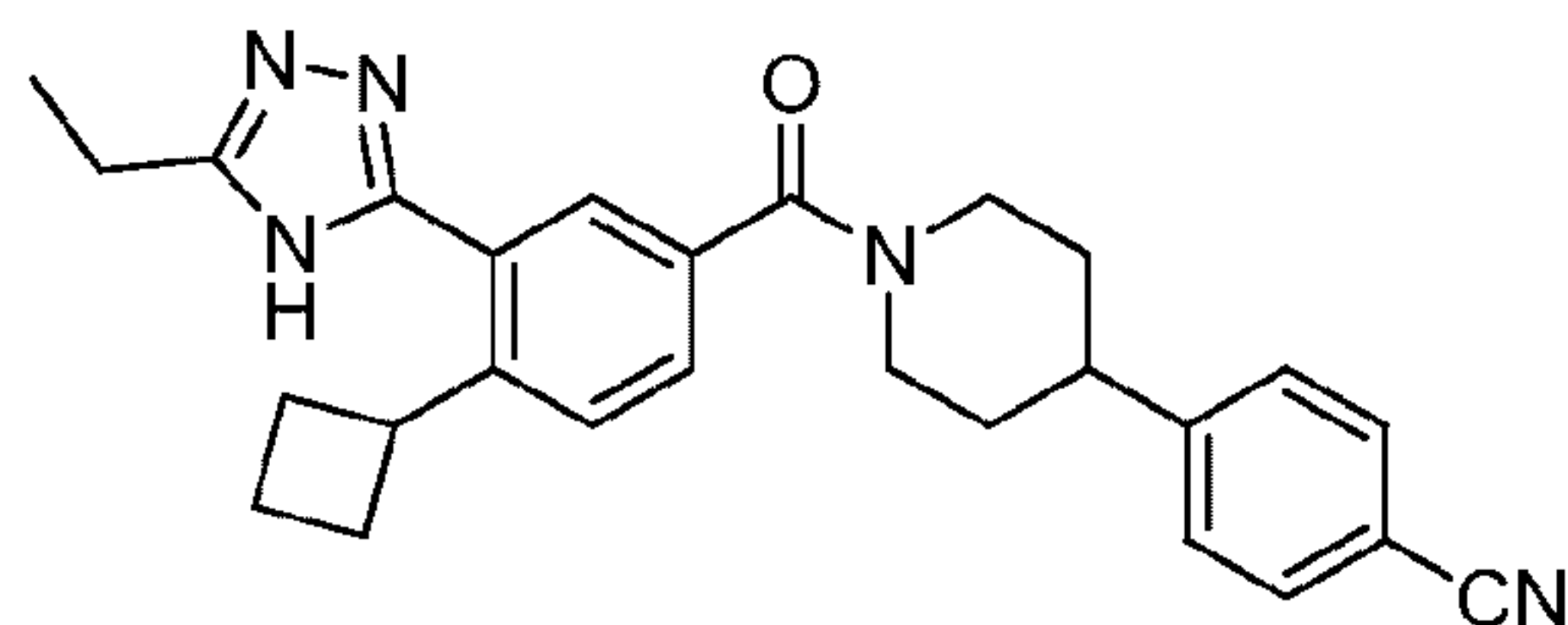
adding 30 mL of $\text{Na}_2\text{S}_2\text{O}_3$ (aq., sat.) and the resulting mixture was extracted with 3 x 20 mL of ethyl acetate. The combined organic layers were washed with 3 x 20 mL of brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield 1.50 g (45%) of the title compound as a yellow oil.



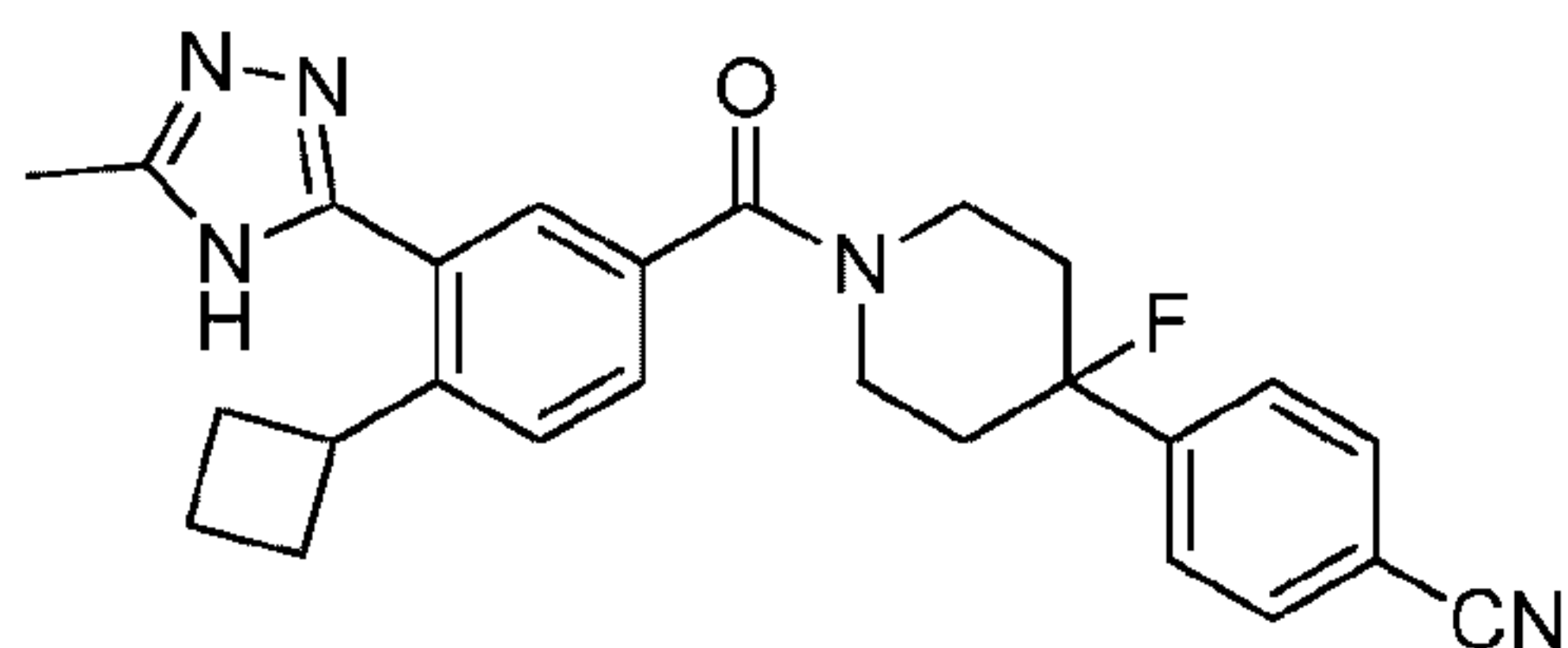
[0726] Compound 168.3. Methyl 3-cyano-4-cyclobutylbenzoate. The title compound (2.60 g (95%), white solid) was prepared using standard chemical manipulations and a procedure similar to that used for the preparation of compound **152.4** and using compound **168.2** (4.00 g, 12.7 mmol) in place of compound **152.3**.



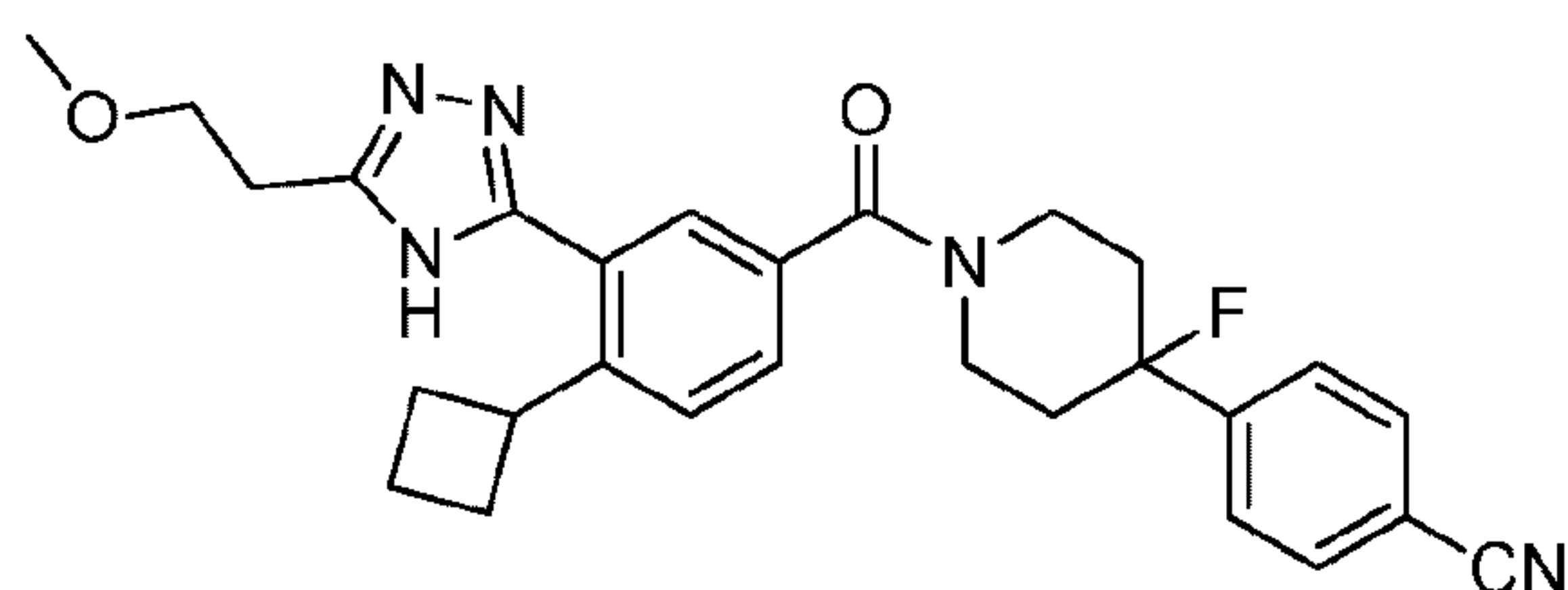
[0727] Compound 168. 4-(1-(4-Cyclobutyl-3-(5-ethyl-4H-1,2,4-triazol-3-yl)benzoyl)-4-fluoropiperidin-4-yl)benzonitrile. The title compound was prepared using procedures similar to those used for preparation of compound **152** and using **168.3** in place of **152.4**. m/z (ES⁺) 458 (M+H)⁺.



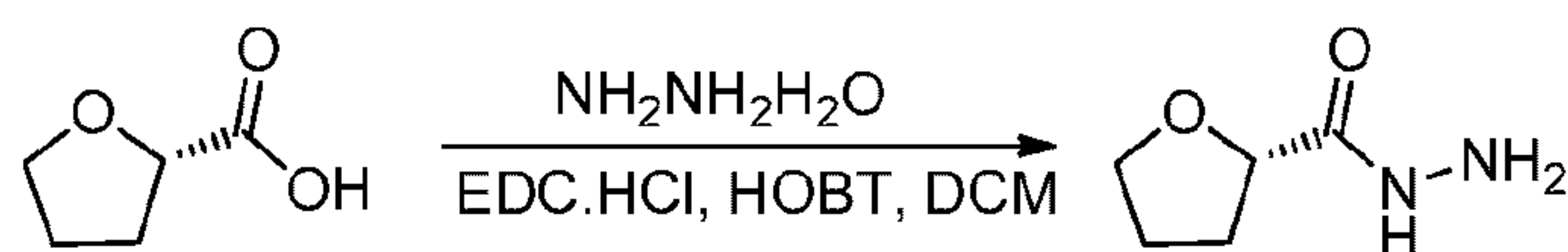
[0728] Compound 169. 4-(1-(4-Cyclobutyl-3-(5-ethyl-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using procedures similar to those used for preparation of compound **152** and using **168.3** in place of **152.4**. m/z (ES⁺) 440 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD) δ 7.88 (d, 2H), 7.67-7.50 (m, 3H), 7.47 (d, 2H), 4.89-4.75 (m, 1H), 4.25-3.73 (m, 2H), 3.35-3.25 (m, 1H), 3.16-2.75 (m, 4H), 2.30-1.94 (m, 6H), 1.93-1.56 (m, 4H), 1.51-1.32 (m, 3H).



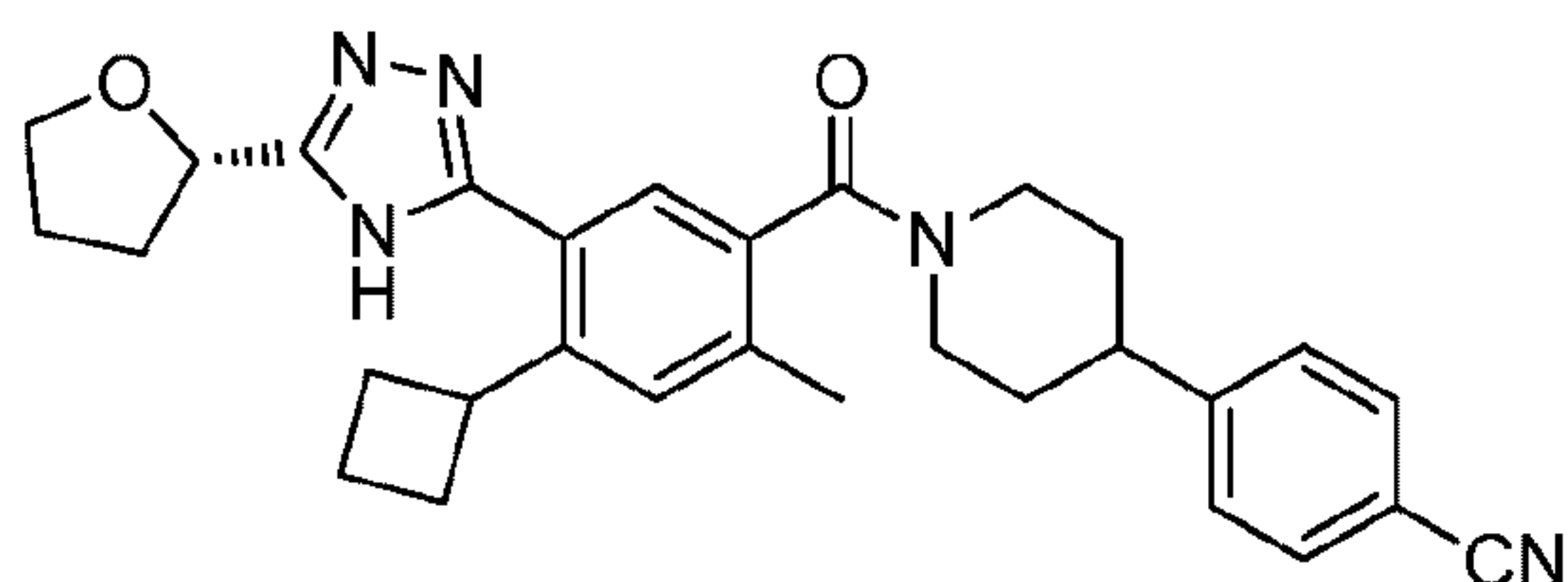
[0729] **Compound 170.** 4-(1-(4-Cyclobutyl-3-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl)-4-fluoropiperidin-4-yl)benzonitrile. The title compound was prepared using procedures similar to those used for preparation of compound **152** and using compounds **168.3** and **11.2 HCl salt** in place of compounds **152.4** and **1.5** respectively. m/z (ES+) 444 (M+H)⁺.



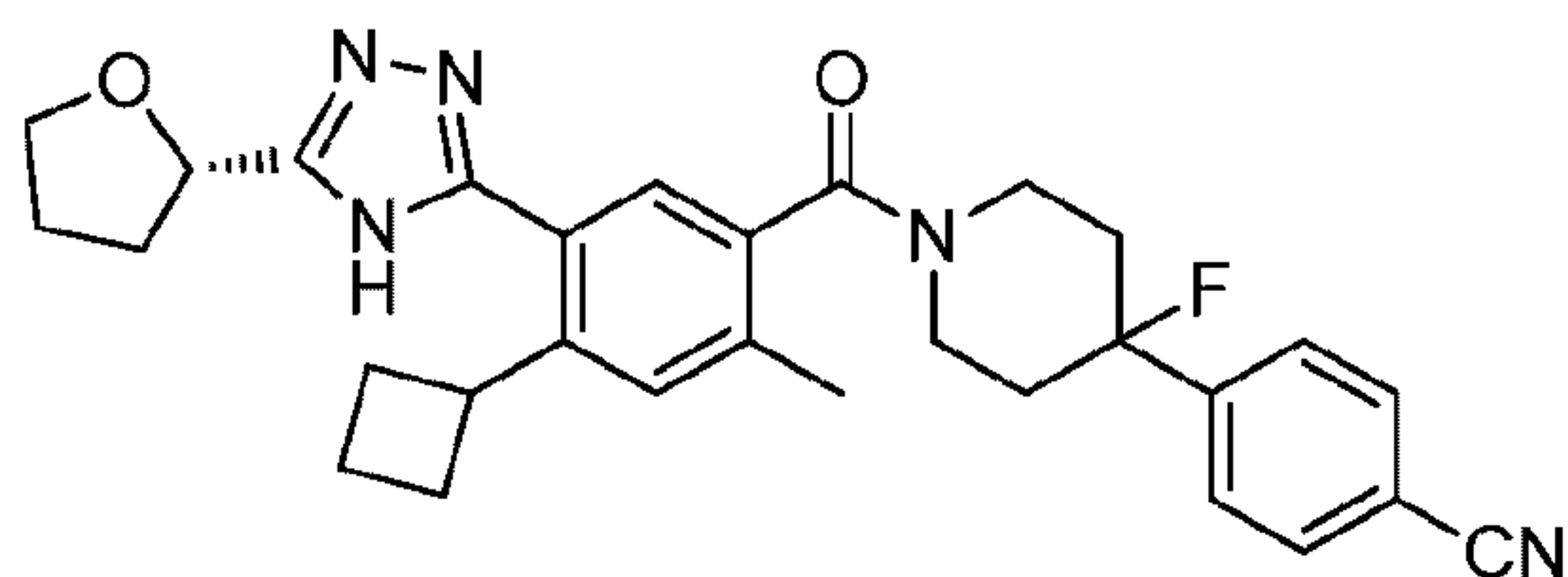
[0730] **Compound 171.** 4-(1-(4-Cyclobutyl-3-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)benzoyl)-4-fluoropiperidin-4-yl)benzonitrile. The title compound was prepared using procedures similar to those used for preparation of compounds **152** and **156** and using **168.3** in place of **152.4**. m/z (ES+) 488 (M+H)⁺.



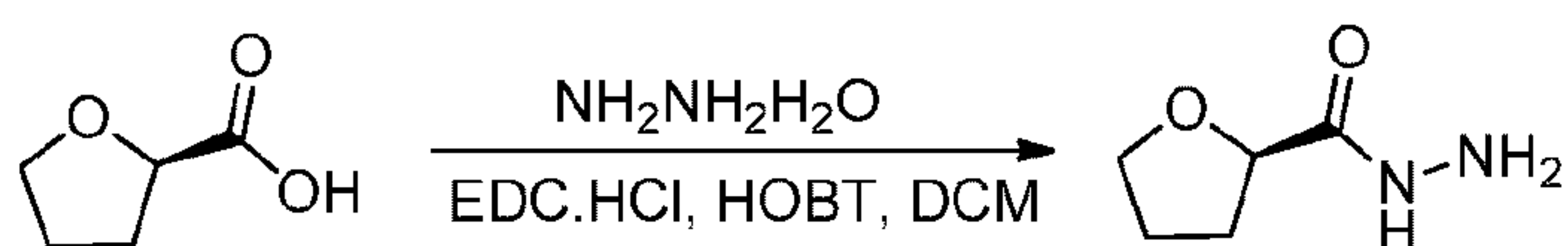
[0731] **Compound 172.1. (S)-Tetrahydrofuran-2-carbohydrazide.** To a round-bottom flask was added a solution of (S)-tetrahydrofuran-2-carboxylic acid (3.00 g, 25.8 mmol, 1.00 equiv) in dichloromethane (40 mL). EDC·HCl (7.50 g, 39.1 mmol, 1.50 equiv), HOBT (5.20 g, 38.5 mmol, 1.50 equiv), and hydrazine hydrate (2 mL, 2.00 equiv, 99%) were added to the reaction. The resulting solution was stirred overnight at room temperature. The solids were removed by filtration and the filtrate was concentrated *in vacuo* to furnish 5.38 g (80%) of the title compound as a yellow oil.



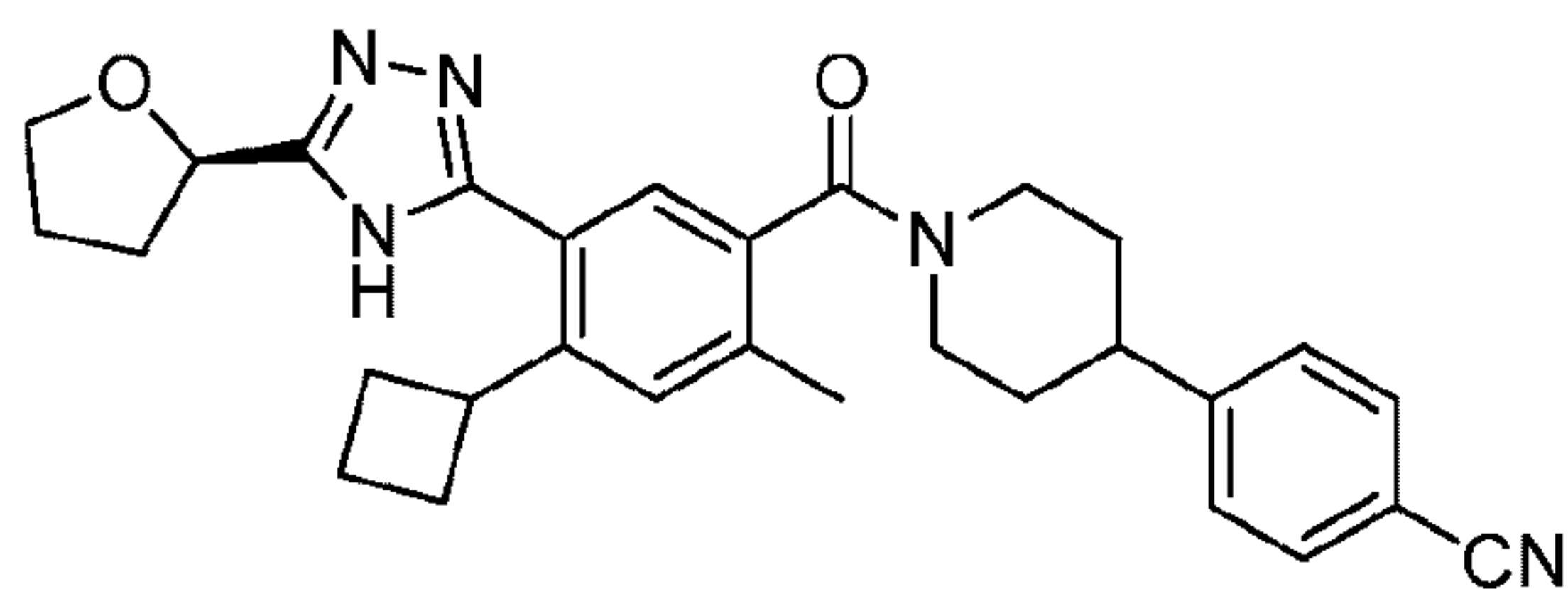
[0732] Compound 172. (S)-4-(1-(4-Cyclobutyl-2-methyl-5-(5-(tetrahydrofuran-2-yl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(4-cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **152**), using (S)-tetrahydrofuran-2-carbohydrazide (compound **172.1**) in place of acetohydrazide. m/z (ES⁺) 496 (M+H)⁺.



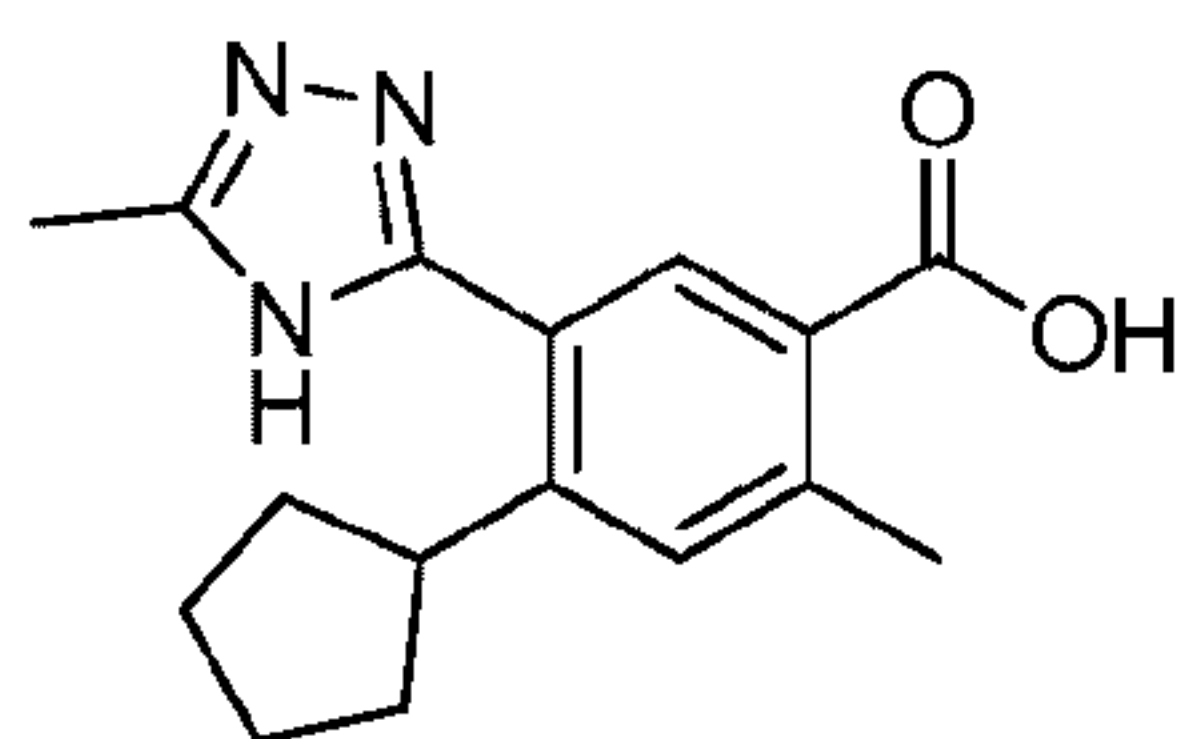
[0733] Compound 173. (S)-4-(1-(4-Cyclobutyl-2-methyl-5-(5-(tetrahydrofuran-2-yl)-4H-1,2,4-triazol-3-yl)benzoyl)-4-fluoropiperidin-4-yl)benzonitrile. The title compound was prepared using procedures similar to those used for the preparation of compound **172** and using compound **11.2 HCl salt** in place of compound **1.5**. m/z (ES⁺) 514 (M+H)⁺.



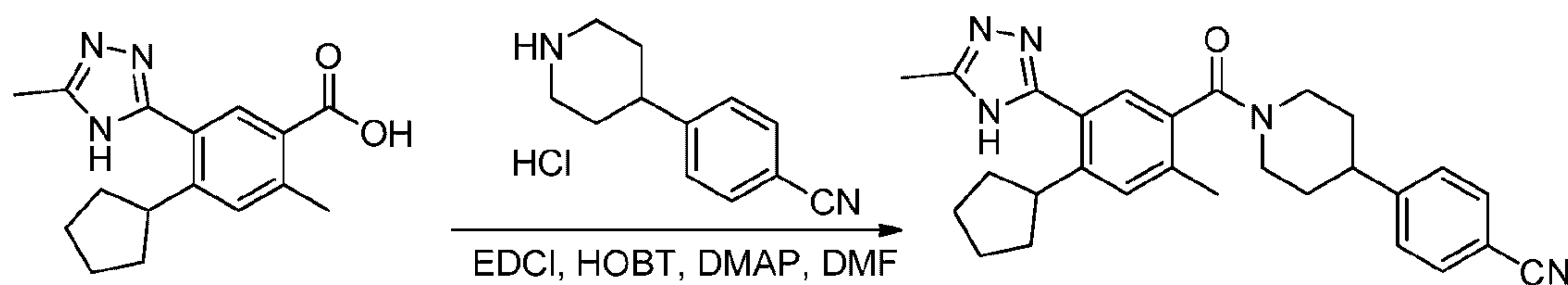
[0734] Compound 174.1. (R)-Tetrahydrofuran-2-carbohydrazide. To a round-bottom flask was added a solution of (R)-tetrahydrofuran-2-carboxylic acid (3.00 g, 25.8 mmol, 1.00 equiv) in dichloromethane (60 mL). EDC·HCl (7.37 g, 38.5 mmol, 1.50 equiv), HOBT (5.24 g, 38.8 mmol, 1.50 equiv), and hydrazine hydrate (2.60 g, 51.9 mmol, 2.00 equiv) were added to the reaction. The resulting solution was stirred overnight at 25 °C. The solids were removed with filtration. The filtrate was concentrated *in vacuo* to yield 2.00 g (59%) of (R)-tetrahydrofuran-2-carbohydrazide as a yellow oil.



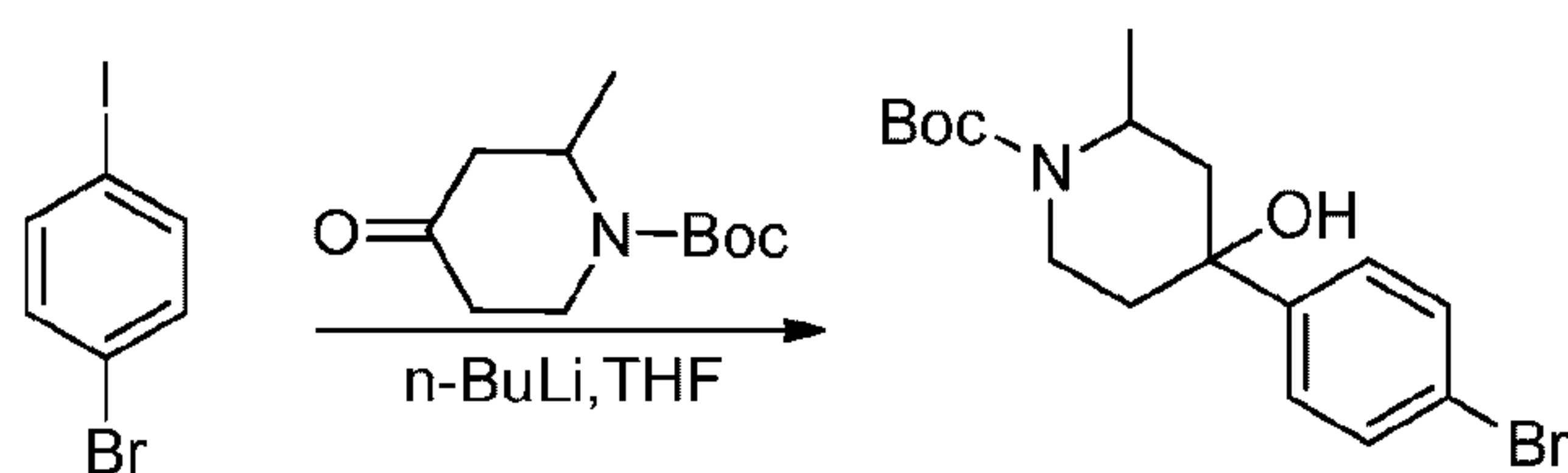
[0735] **Compound 174.1. (R)-4-(1-(4-Cyclobutyl-2-methyl-5-(5-(tetrahydrofuran-2-yl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile.** The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of 4-(1-(4-cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile (compound **152**), using (*R*)-tetrahydrofuran-2-carbohydrazide (compound **174.1**) in place of acetohydrazide. m/z (ES+) 496 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD) δ 7.70 (d, 2H), 7.49-7.41 (m, 4H), 5.15 (t, 1H), 4.89-4.80 (m, 1H), 4.14-3.92 (m, 3H), 3.65-3.51 (m, 1H), 3.33-3.27 (m, 1H), 3.03-2.95 (m, 2H), 2.47-2.37 (m, 4H), 2.24-1.91 (m, 9H), 1.83-1.71 (m, 4H).



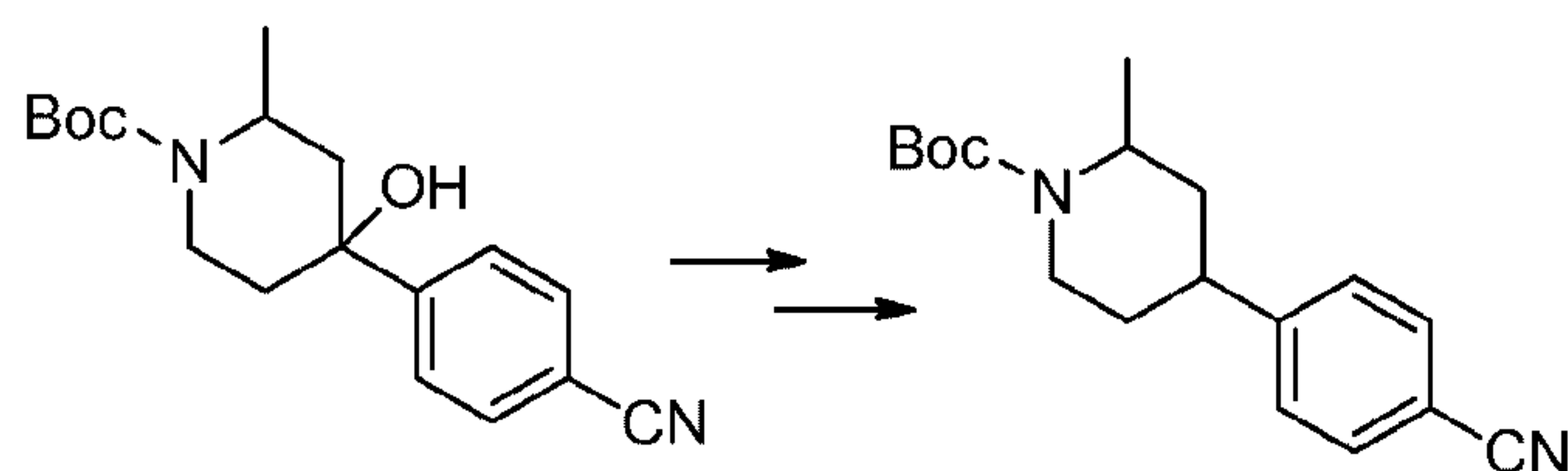
[0736] **Compound 175.1. 4-Cyclopentyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoic acid.** The title compound was synthesized using standard chemical manipulations and procedures similar to those used for the preparation of compound **152.8** and using bromo(cyclopentyl)magnesium in place of bromo(cyclobutyl)magnesium.



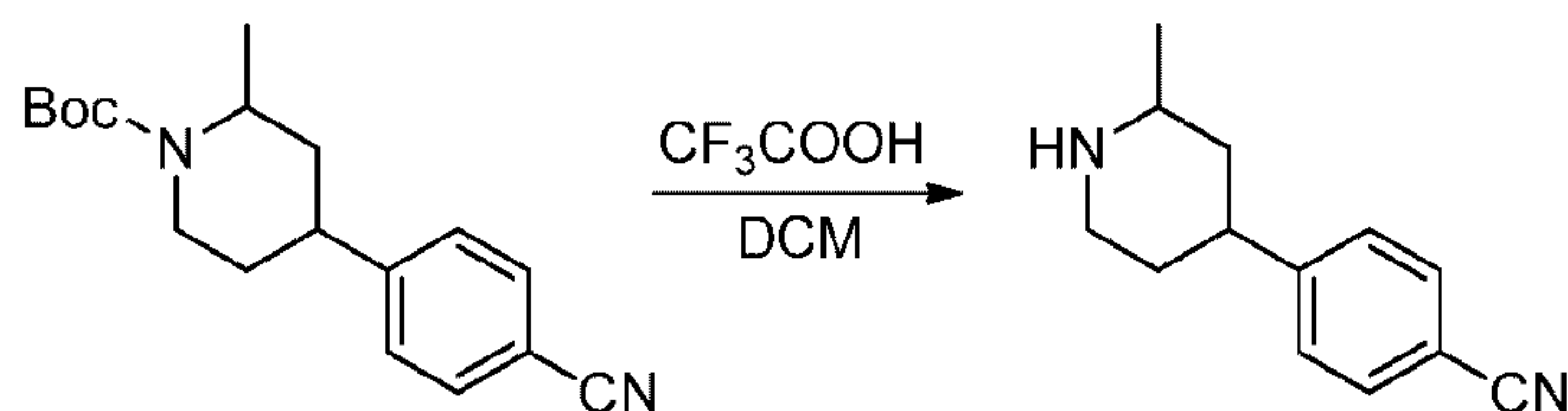
[0737] **Compound 175. 4-(1-(4-Cyclopentyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile.** The title compound was synthesized using a procedure similar to that used for the preparation of compound **152** and using compound **175.1** in place of compound **152.8**. m/z (ES+) 495 (M+H)⁺.



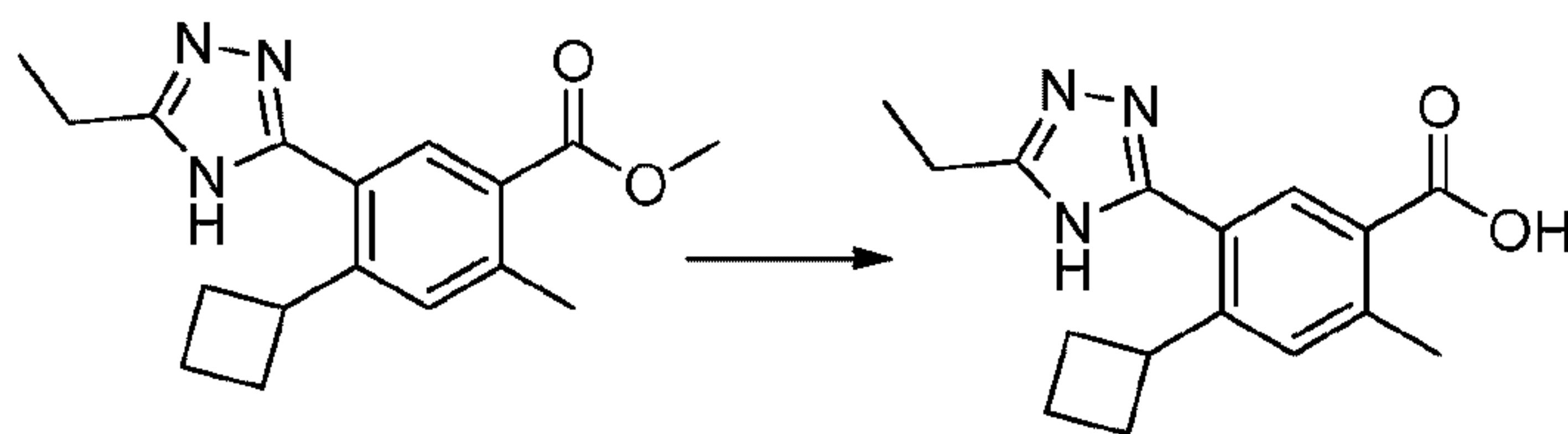
[0738] **Compound 176.1. *tert*-Butyl 4-(4-bromophenyl)-4-hydroxy-2-methylpiperidine-1-carboxylate.** The title compound was synthesized using a procedure similar to that used for the preparation of compound 1.1 and using *tert*-butyl 2-methyl-4-oxopiperidine-1-carboxylate in place of *tert*-butyl 4-oxopiperidine-1-carboxylate.



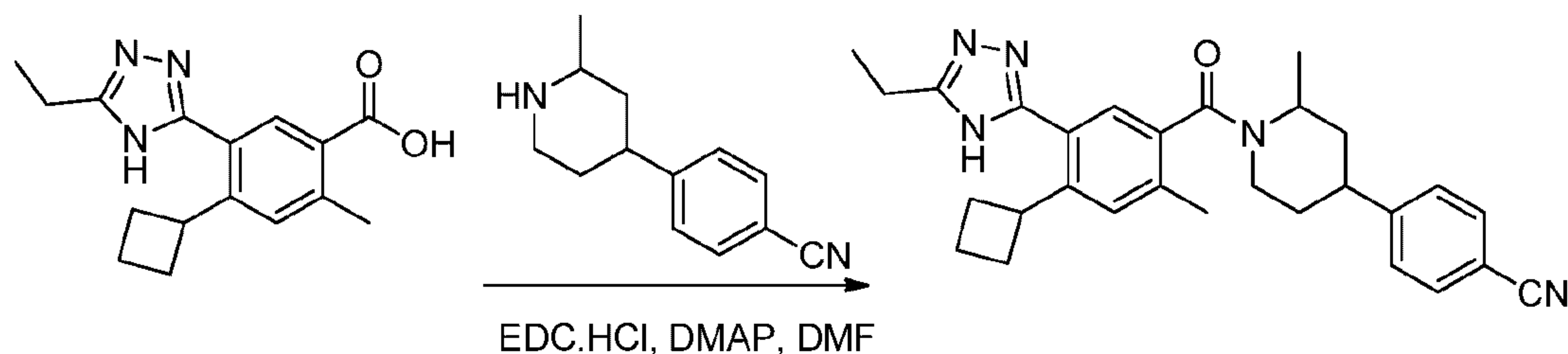
[0739] **Compound 176.2. *tert*-Butyl 4-(4-cyanophenyl)-2-methylpiperidine-1-carboxylate.** The title compound was synthesized using procedures similar to those used for the preparation of compound 1.4 and using compound 176.1 in place of compound 1.1.



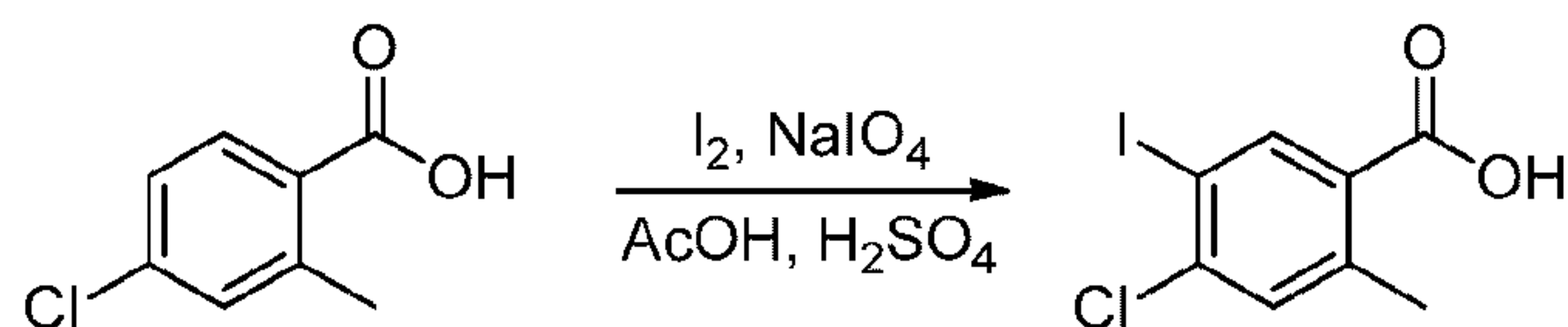
[0740] **Compound 176.3. 4-(2-Methylpiperidin-4-yl)benzonitrile.** To a solution of *tert*-butyl 4-(4-cyanophenyl)-2-methylpiperidine-1-carboxylate (compound 176.2, 500 mg, 1.50 mmol, 1.00 equiv, 90%) in dichloromethane (3 mL) was added TFA dropwise (1 mL). The resulting mixture was stirred for 1.5 h at room temperature, then diluted with 30 mL of dichloromethane. The resulting mixture was washed with sodium bicarbonate (aq., 1 M. Note: significant gas evolution). The aqueous phase was extracted with 2 x 50 mL of dichloromethane and the combined organic layers were dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified using silica gel column chromatography with methanol/dichloromethane (1:50-1:20) as eluent to yield 280 mg (93%) of 4-(2-methylpiperidin-4-yl)benzonitrile as a colorless oil.



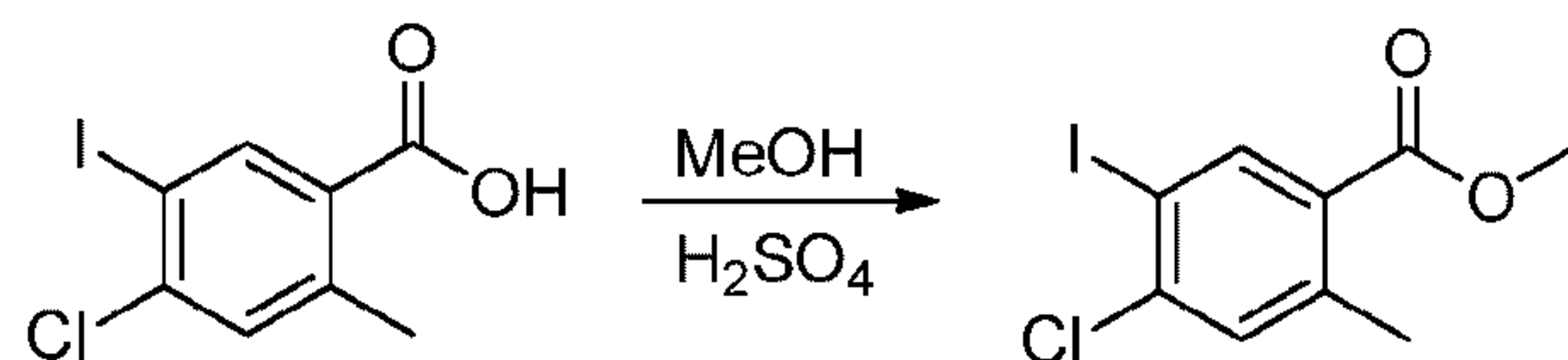
[0741] **Compound 176.4. *tert*-Butyl 4-(4-cyanophenyl)-2-methylpiperidine-1-carboxylate.** The title compound was synthesized using a procedure similar to that used for the preparation of compound **152.8** and using compound **164.1** in place of compound **152.7**.



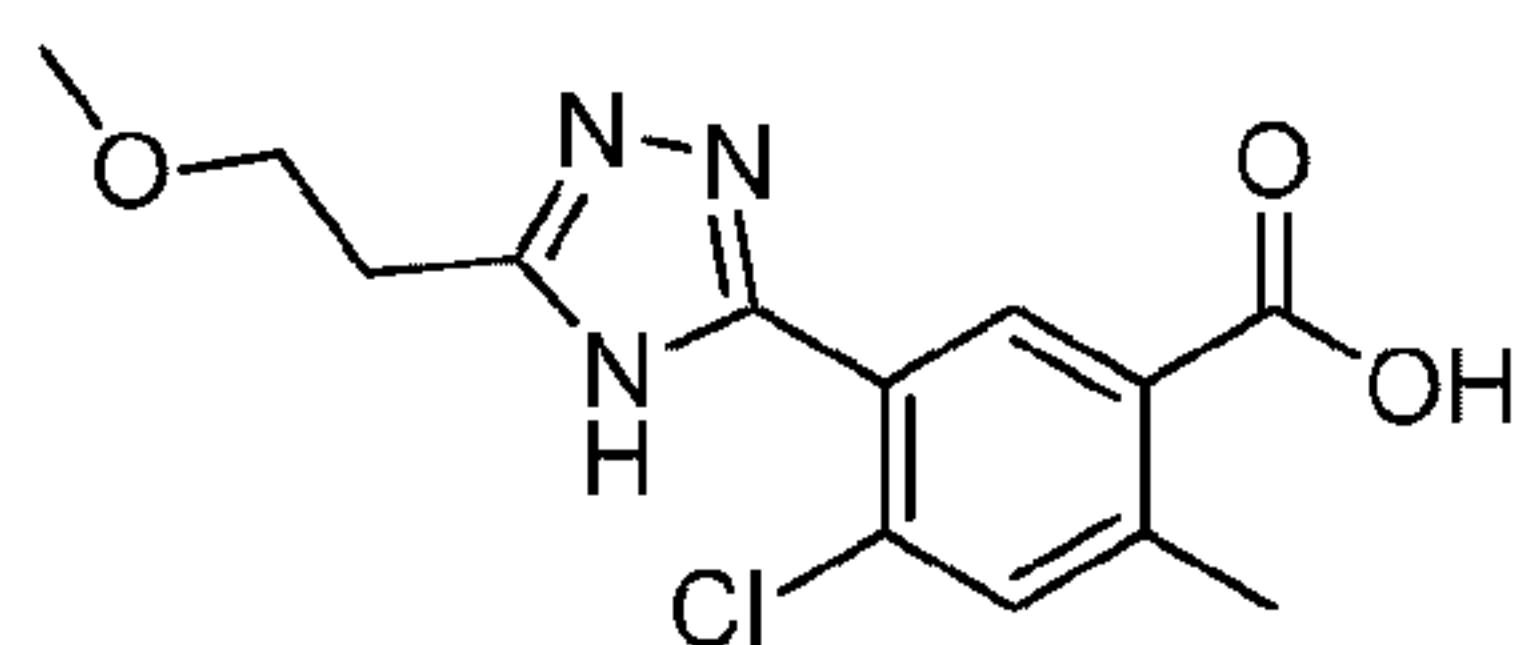
[0742] **Compound 176. 4-(1-(4-Cyclobutyl-5-(5-ethyl-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)-2-methylpiperidin-4-yl)benzonitrile.** To a round-bottom flask was added a solution of 4-(2-methylpiperidin-4-yl)benzonitrile (compound **176.3**, 210 mg, 0.940 mmol, 1.00 equiv, 90%) in *N,N*-dimethylformamide (2 mL). EDC·HCl (404 mg, 2.11 mmol, 2.00 equiv), 4-dimethylaminopyridine (257 mg, 2.10 mmol, 2.00 equiv), and 4-cyclobutyl-5-(5-ethyl-4H-1,2,4-triazol-3-yl)-2-methylbenzoic acid (compound **176.4**, 300 mg, 1.05 mmol, 1.00 equiv) were added to the reaction mixture. The resulting solution was stirred for 4h at 25 °C, then diluted with 50 mL of ethyl acetate. The resulting mixture was washed with 2 x 30 mL of NH₄Cl (aq., sat.) and 2 x 30 mL of brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified using silica gel column chromatography with dichloromethane/methanol (20:1) as eluent. The crude product (~20 mg) was further purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-001(SHIMADZU)): Column, SunFire Prep C18, 19*150mm 5um; mobile phase, water with 0.05%TFA and CH₃CN (48% CH₃CN up to 49% in 8 min, up to 100% in 3 min, down to 48% in 2 min); Detector, Waters 2489 254&220nm. The fractions containing pure compound were combined and lyophilized to yield 3.8 mg (1%) of the title compound as a white solid. *m/z* (ES⁺) 468 (M+H)⁺.



[0743] Compound 177.1. 4-Chloro-5-iodo-2-methylbenzoic acid. To a round-bottom flask was added a solution of 4-chloro-2-methylbenzoic acid (30.0 g, 176 mmol, 1.00 equiv) in acetic acid (300 mL). NaIO₄ (19.0 g, 88.8 mmol, 0.50 equiv), I₂ (49.0 g, 193 mmol, 1.10 equiv), and sulfuric acid (3 mL) were added to the reaction. The resulting mixture was stirred overnight at 110 °C. After cooling to ambient temperature, the reaction was carefully quenched with 500 mL of Na₂S₂O₃ (aq., sat.). The resulting solids were collected by filtration and then dissolved in 500 mL of ethyl acetate. The organic phase was washed with 2 x 200 mL of brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. This resulted in 20.0 g (38%) of 4-chloro-5-iodo-2-methylbenzoic acid as a white solid.

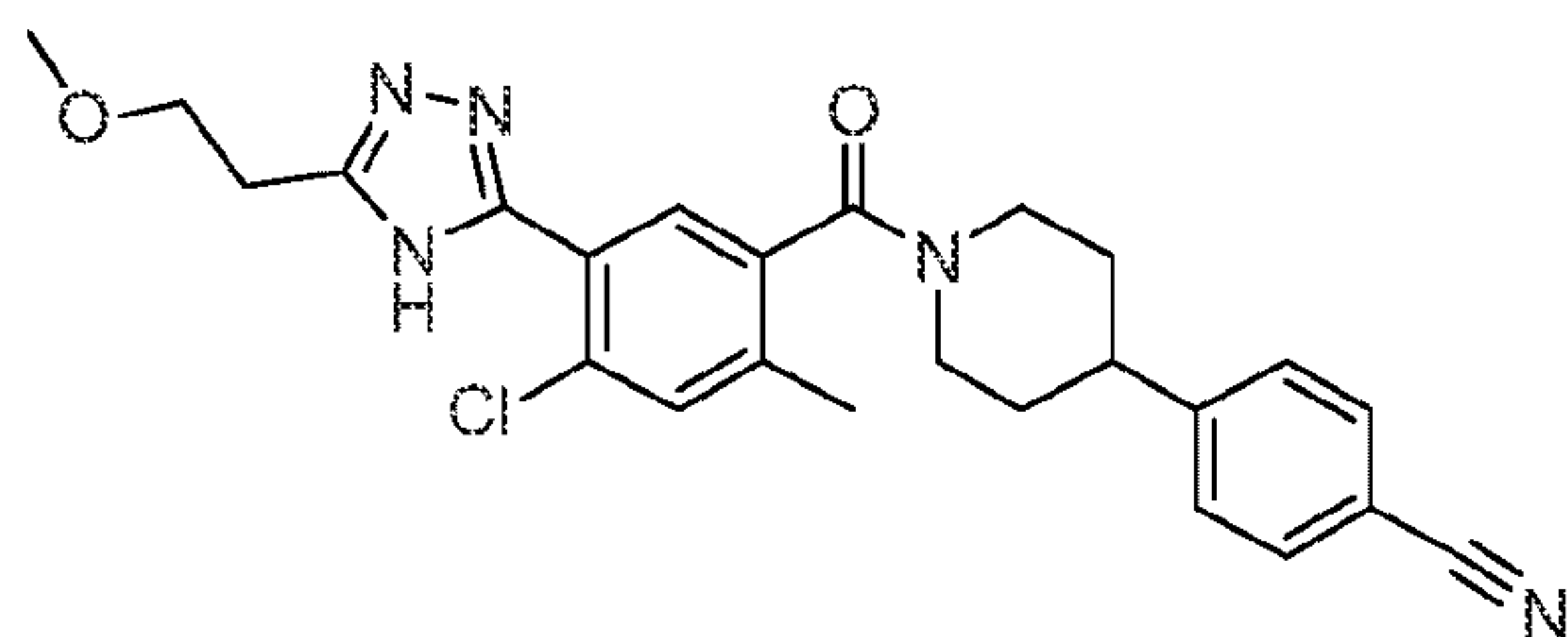


[0744] Compound 177.2. Methyl 4-chloro-5-iodo-2-methylbenzoate. To a solution of 4-chloro-5-iodo-2-methylbenzoic acid (compound 177.1, 20.0 g, 67.5 mmol, 1.00 equiv) in methanol (100 mL) was added sulfuric acid (5 mL) dropwise. The resulting mixture was stirred overnight at 75 °C. After cooling to ambient temperature, the methanol was removed under reduced pressure. The pH value of the remaining aqueous layer was carefully adjusted to 7 with sodium bicarbonate (aq., 1 M. Note: significant gas evolution). The aqueous phase was extracted with 2 x 200 mL of ethyl acetate and the combined organic layers were washed with 2 x 100 mL of brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:50) as eluent to furnish 20.0 g (95%) of methyl 4-chloro-5-iodo-2-methylbenzoate as a light yellow liquid.

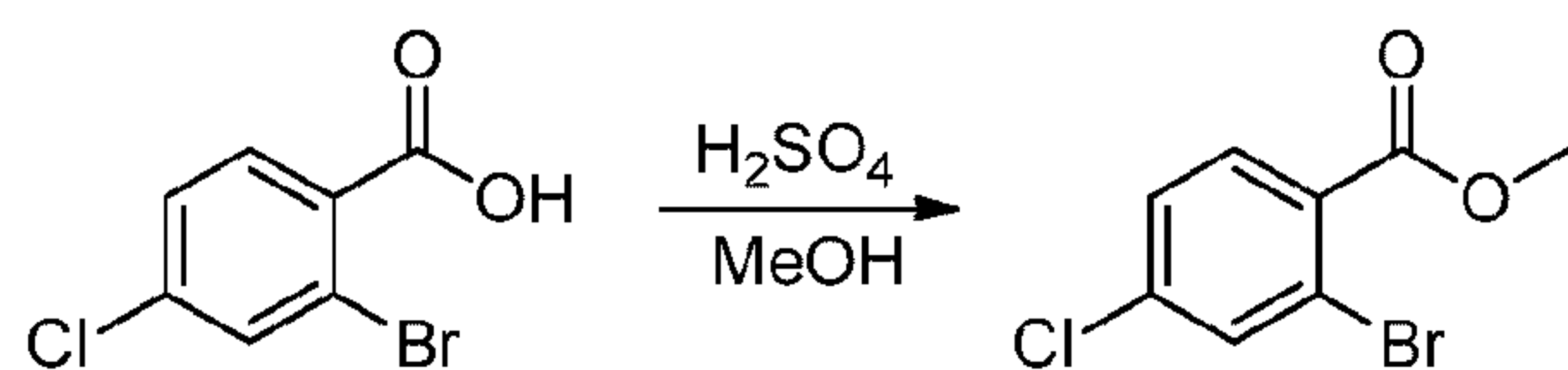


[0745] Compound 177.3. 4-Chloro-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoic acid. The title compound was prepared using standard chemical

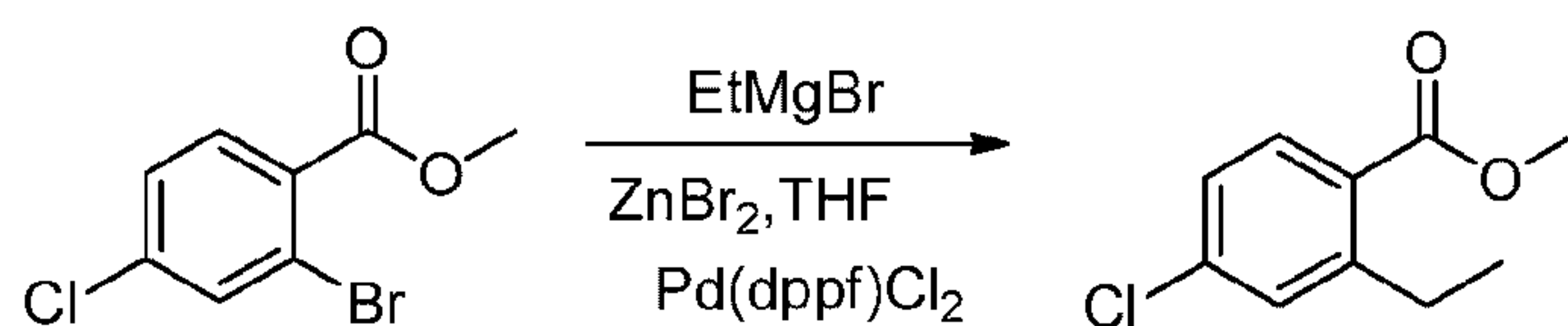
manipulations and procedures similar to those used for the preparation of compound **152.8** but using compounds **177.2** and **143.1** instead of compound **152.3** and acetoxydrazide respectively.



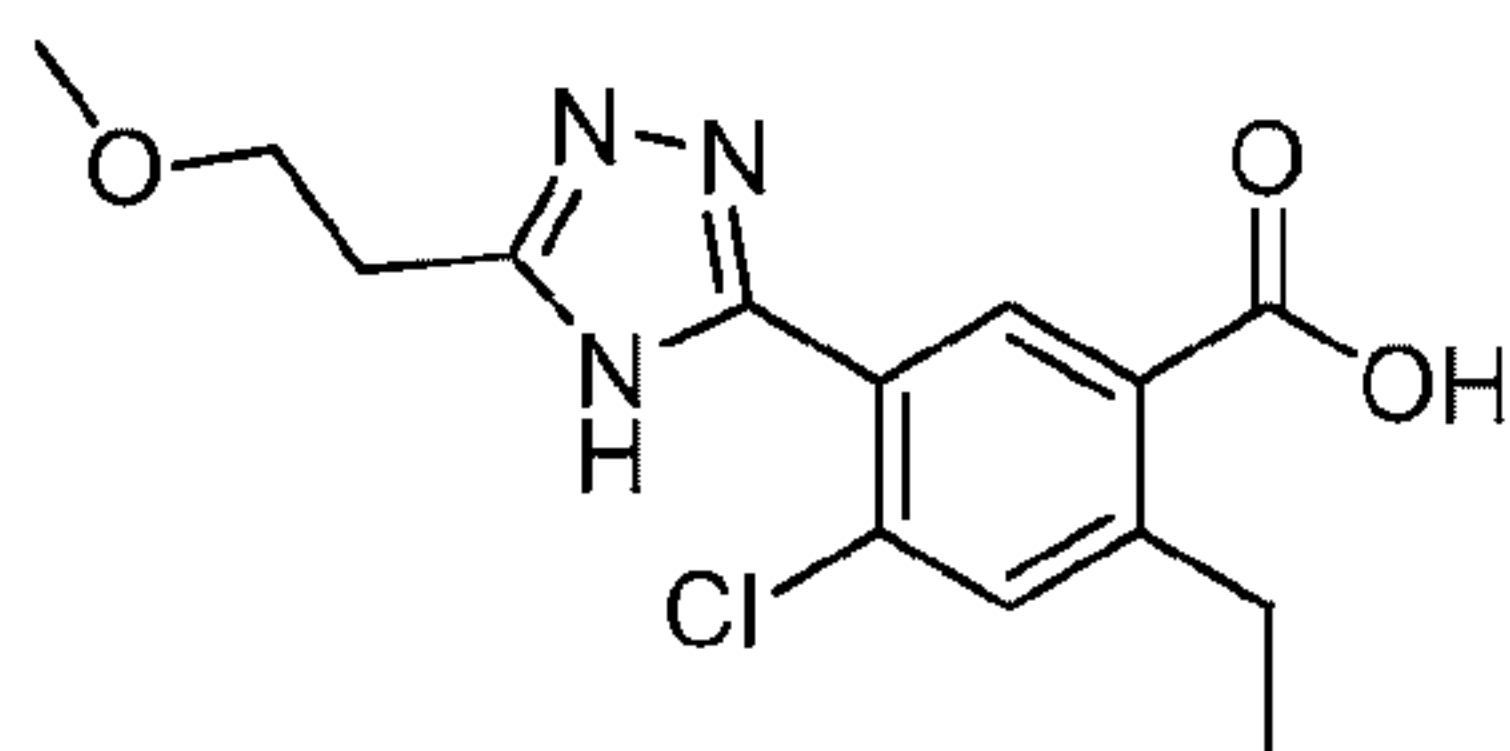
[0746] Compound **177. 4-(1-(4-Chloro-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)-2-methylbenzoyl)piperidin-4-yl)benzonitrile**. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound **152** but using compound **177.3** instead of compound **152.8**. m/z (ES⁺) 464 (M+H)⁺.



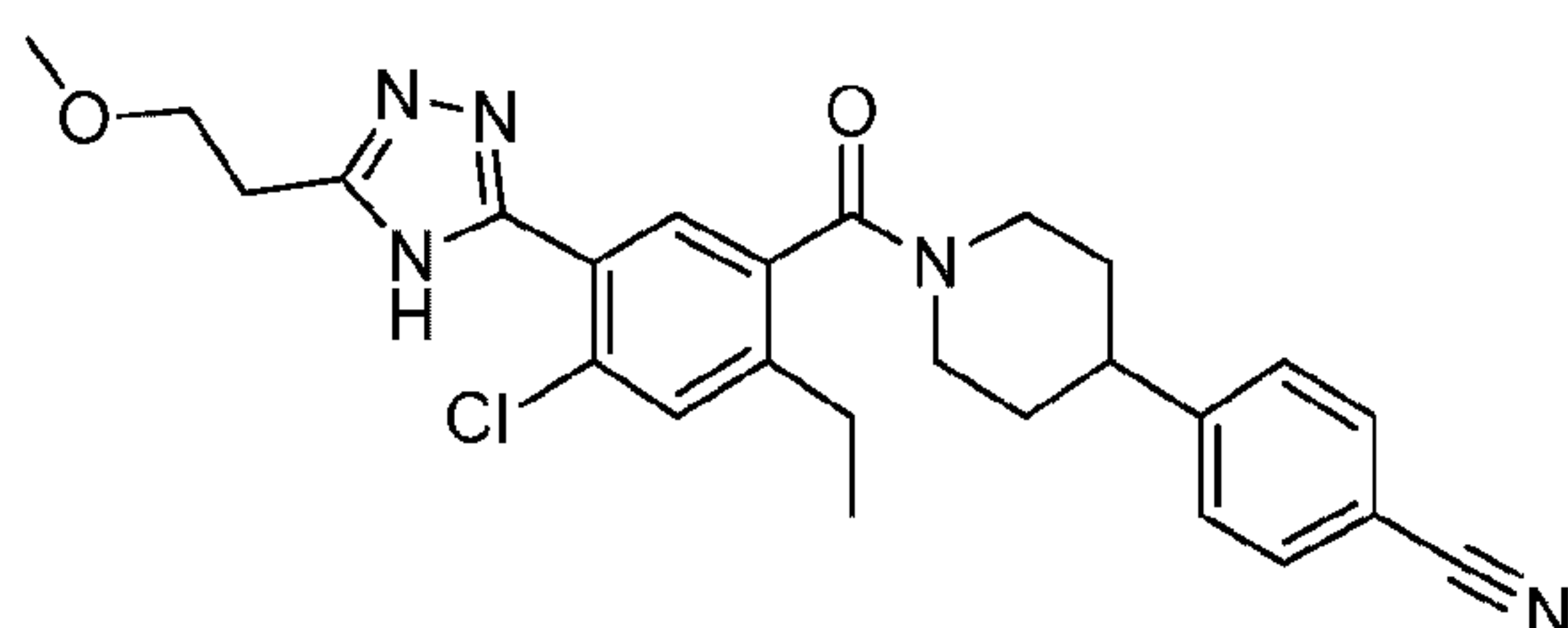
[0747] Compound **178.1. 2-Bromo-4-chlorobenzoate**. The title compound (17.0 g light yellow solid, 80%) was prepared using a procedure similar to that used for the preparation of compound **177.2** but using 2-bromo-4-chlorobenzoic acid (20.0 g) in place of compound **177.1**.



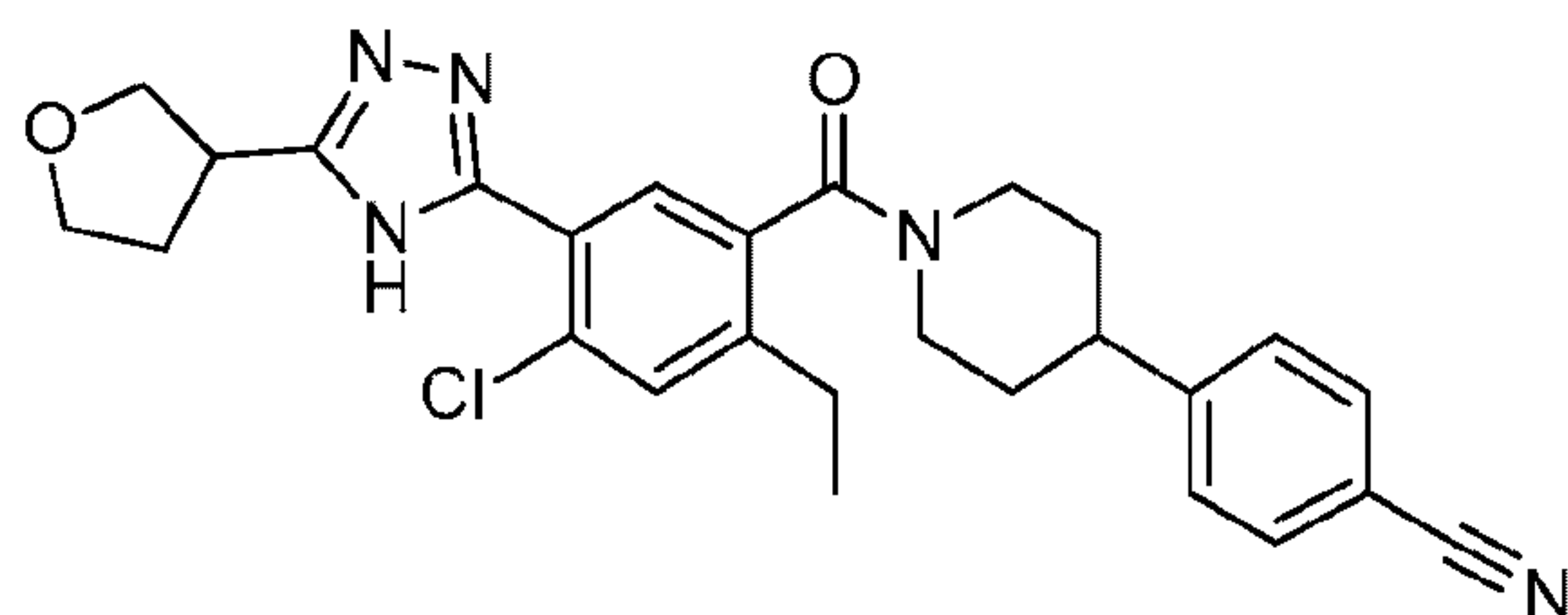
[0748] Compound **178.2. Methyl 4-chloro-2-ethylbenzoate**. The title compound (2.20 g light colorless liquid, 55%) was prepared using a procedure similar to that used for the preparation of compound **48.1** but using compound **178.1** (5.00 g) in place of methyl 2-bromo-4-methylbenzoate.



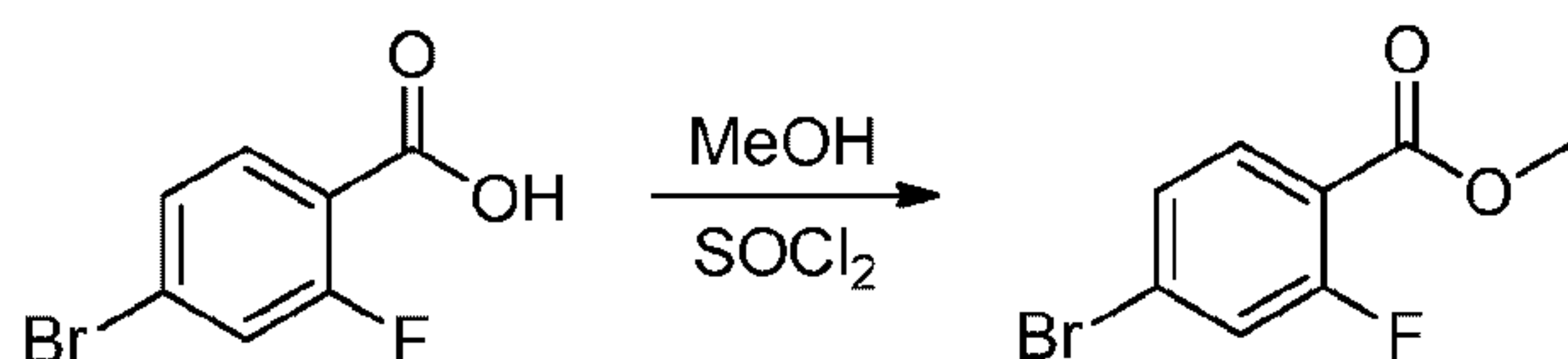
[0749] **Compound 178.3. 4-Chloro-2-ethyl-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)benzoic acid.** The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound **152.8** using compound **178.2** and 3-methoxypropanehydrazide (compound **143.1**) instead of compound **152.2** and acetoydrazide respectively.



[0750] **Compound 178. 4-(1-(4-Chloro-2-ethyl-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile.** The title compound was prepared using a procedure similar to that used for the preparation of compound **152** but using compound **178.3** in place of compound **152.8**. m/z (ES⁺) 478 (M+H)⁺.

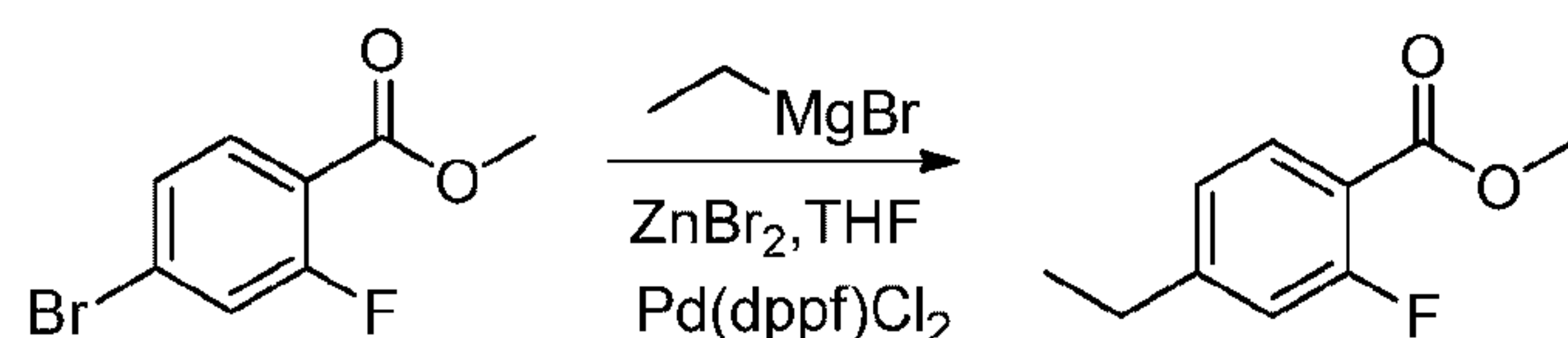


[0751] **Compound 179. 4-(1-(4-Chloro-2-ethyl-5-(5-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile.** The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds **38** and **178**. m/z (ES⁺) 490 (M+H)⁺.

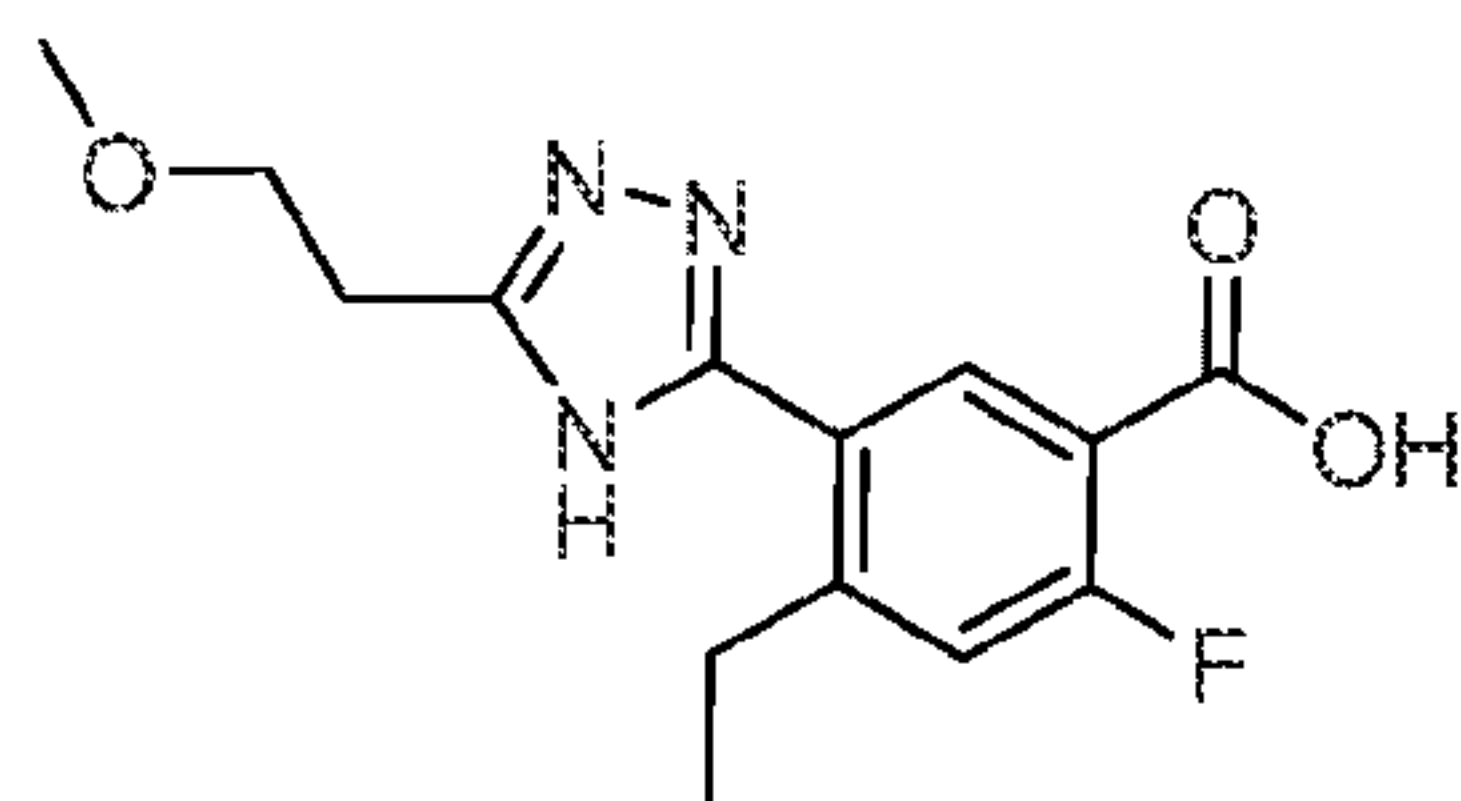


[0752] **Compound 180.1. Methyl 4-bromo-2-fluorobenzoate.** To a 500-mL three neck round-bottom flask was added a solution of 4-bromo-2-fluorobenzoic acid (30.0 g, 137

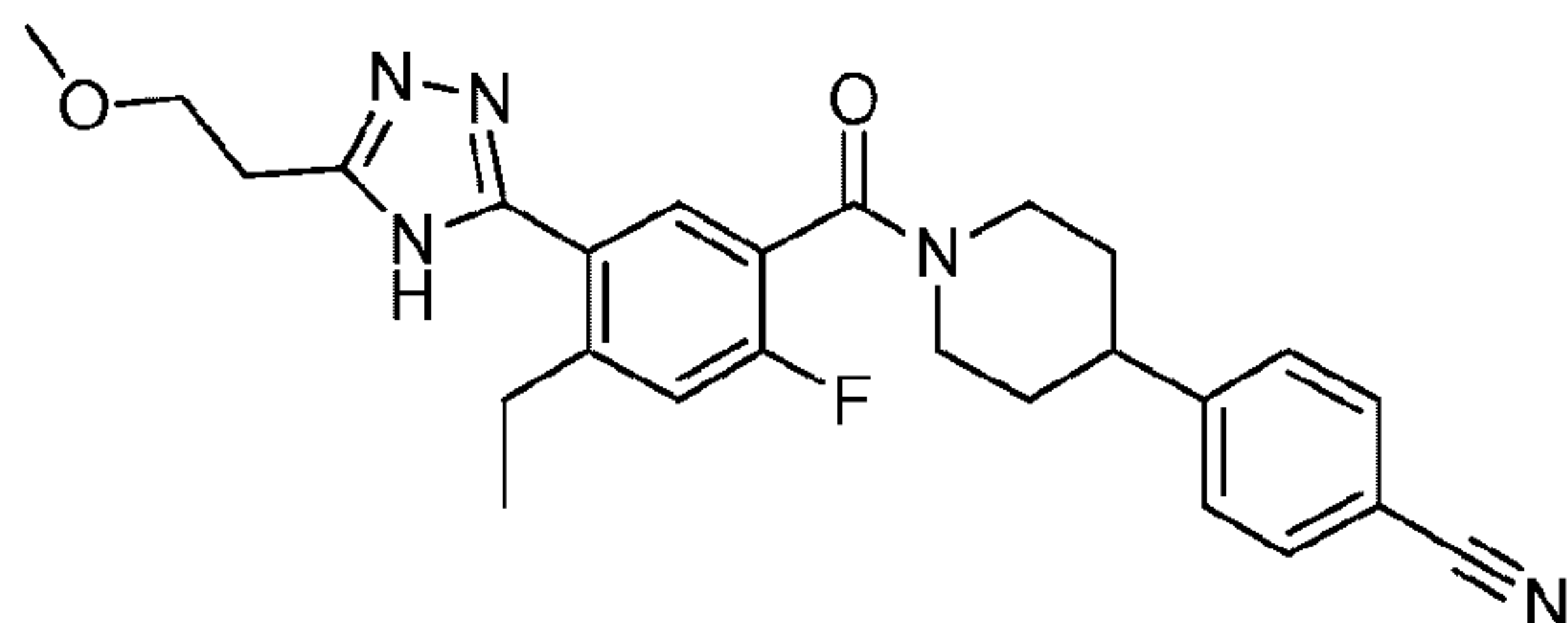
mmol, 1.00 equiv) in methanol (200 mL). SOCl_2 (24.0 g, 202 mmol, 1.50 equiv) was added dropwise at 0 °C. The resulting solution was stirred for 10 min at 0 °C, for 30 min at 25 °C, and then for 3 h at 50 °C. After cooling to room temperature, the resulting mixture was concentrated under reduced pressure. The residue was partitioned between water (100 mL) and ethyl acetate (100 mL). The aqueous phase was extracted with 100 mL of ethyl acetate. The combined organic layers were washed with 1 x 100 mL of water, 1 x 100 mL of sodium bicarbonate (aq. sat.) and 1 x 100 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield 30.0 g (94%) of the title compound as a light yellow solid.



[0753] Compound 180.2. Methyl 4-ethyl-2-fluorobenzoate. The title compound (3.80 g light colorless oil, 97%) was prepared using a procedure similar to that used for the preparation of compound **48.1** but using compound **180.1** (5.00 g) in place of methyl 2-bromo-4-methylbenzoate.

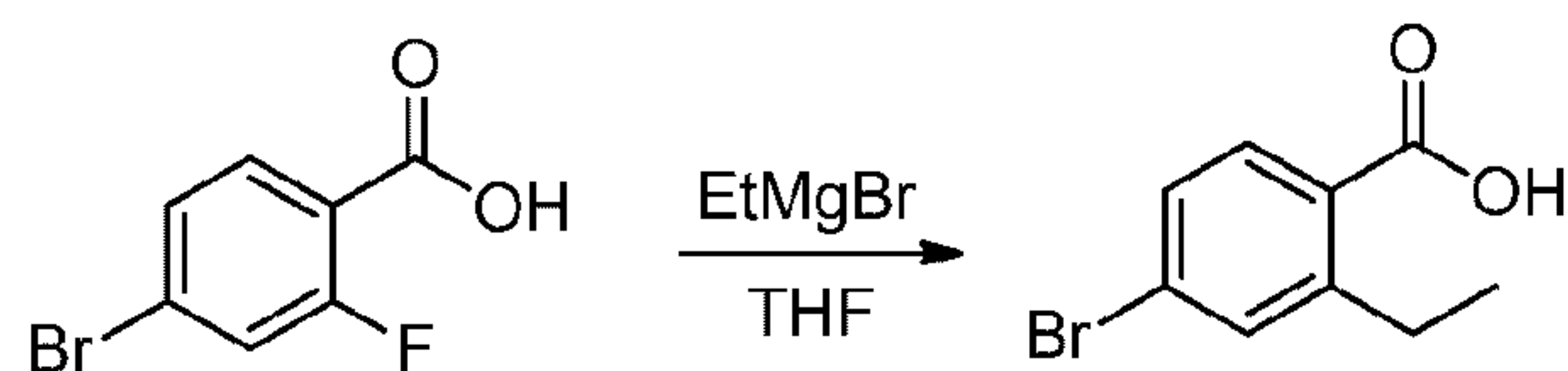


[0754] Compound 180.3. 4-Ethyl-2-fluoro-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)benzoic acid. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound **152.8** using compounds **180.2** and **143.1** instead of compound **152.2** and acetoxydrazide respectively.

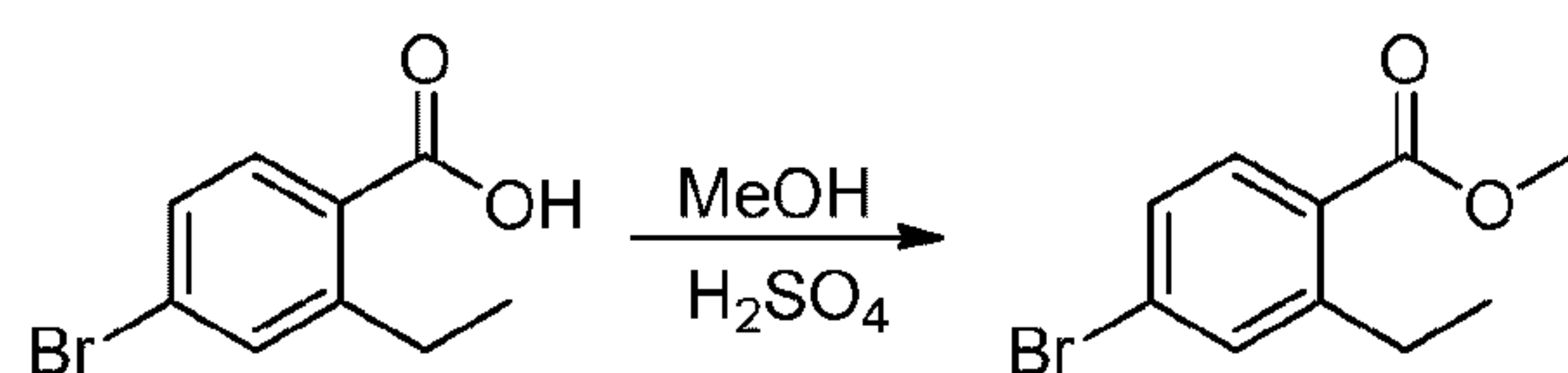


[0755] Compound 180. 4-(1-(4-Ethyl-2-fluoro-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of

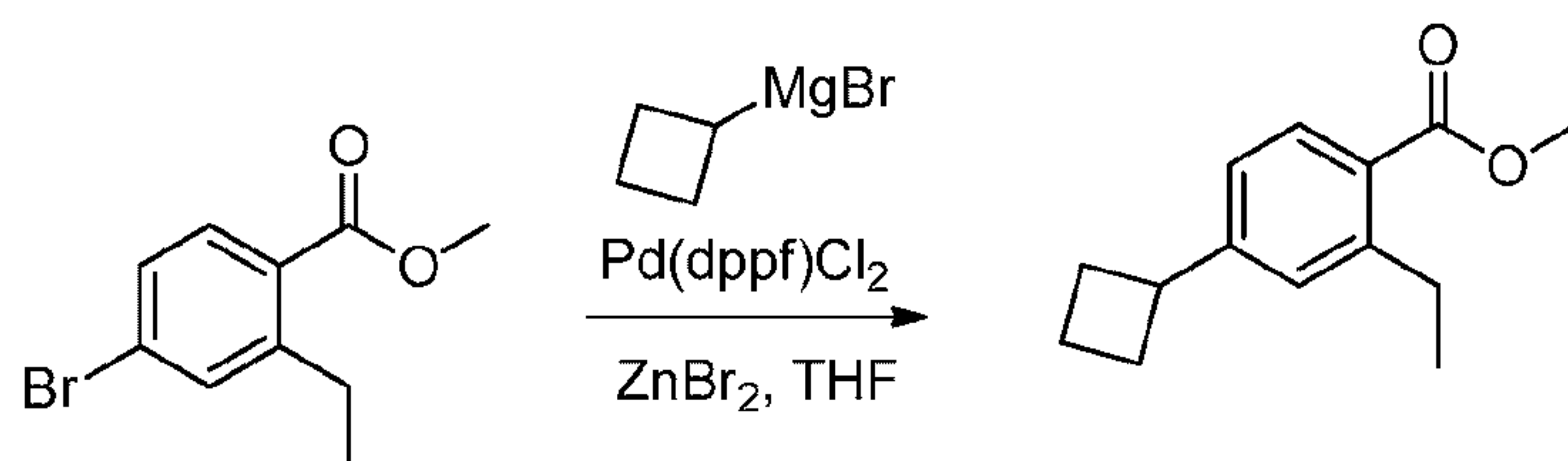
compound **152** but using compound **180.3** in place of compound **152.8**. m/z (ES+) 462 (M+H)⁺.



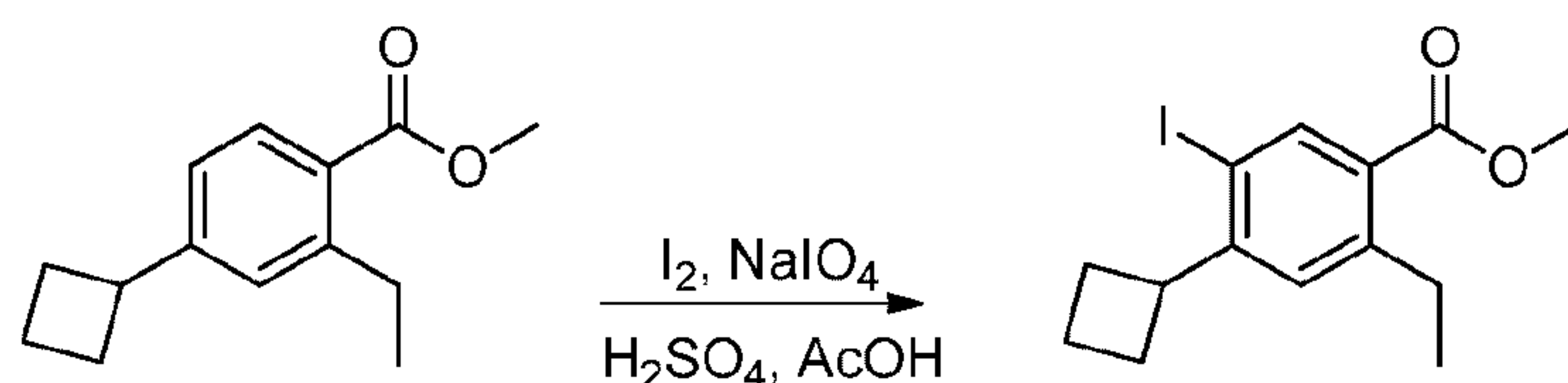
[0756] Compound 181.1. 4-Bromo-2-ethylbenzoic acid. To a 1 L three neck round-bottom flask, which was purged and maintained with a nitrogen atmosphere, was added 4-bromo-2-fluorobenzoic acid (50.0 g, 228 mmol, 1.00 equiv) in tetrahydrofuran (500 mL). A solution of ethylmagnesium bromide (250 mL, 3 M in THF) was added dropwise at 0 °C. The resulting solution was stirred for 3-4 h at 0 °C. The mixture was then carefully quenched by dropwise addition of water at 0 °C. After complete quench of the reaction, additional water was added and the pH was adjusted to 2-3 with hydrogen chloride (aqueous, 2 M). The mixture was extracted with 2 x 200 mL of ethyl acetate and the organic layers were combined. Sodium hydroxide (2N, aq.) was employed to adjust the pH to 7-8. The resulting mixture was washed with 2 x 200 mL of ethyl acetate. The pH value of the aqueous solution was adjusted to 2-3 with 2N hydrogen chloride, then extracted with 2 x 200 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. This resulted in 30.0 g (57%) of 4-bromo-2-ethylbenzoic acid as a yellow solid.



[0757] Compound 181.2. Methyl 4-bromo-2-ethylbenzoate. The title compound (25.0 g light yellow liquid, 79%) was prepared using a procedure similar to that used for the preparation of compound **177.2** but using compound **181.1** (30.0 g) in place of compound **177.1**.

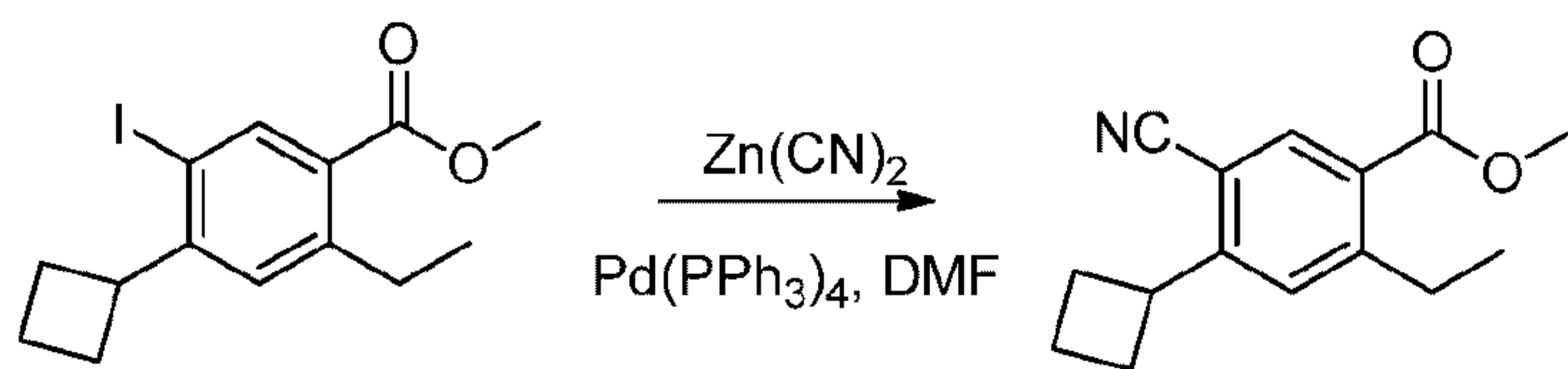


[0758] Compound 181.3. Methyl 4-cyclobutyl-2-ethylbenzoate. To a stirred mixture of ZnBr_2 (33.5 g, 149 mmol, 4.00 equiv) in THF (350 mL) under nitrogen at 0 °C was added dropwise a solution of cyclobutylmagnesium bromide (148 mmol in 50 mL THF). After stirring at 0 °C for 0.5 h, the temperature was lowered to -78 °C and Pd(dppf)Cl_2 (2.00 g, 2.73 mmol, 0.07 equiv) was added followed by the addition of a solution of methyl 4-bromo-2-ethylbenzoate (compound **181.2**, 9.00 g, 37.0 mmol, 1.00 equiv) in tetrahydrofuran (10 mL) dropwise at the same temperature. The reaction mixture was slowly allowed to reach ambient temperature and then stirred overnight. The reaction was carefully quenched with a saturated NH_4Cl aqueous solution (100 mL). The resulting mixture was extracted with 500 mL of ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography with ethyl acetate/petroleum ether (1:50) to furnish 8.00 g (99%) of the desired product as a light yellow oil.

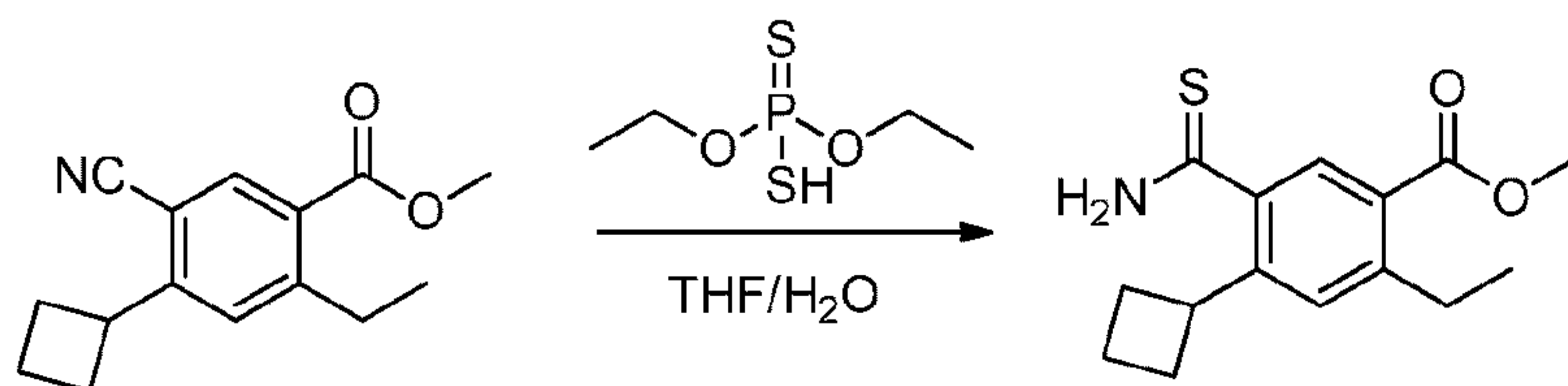


[0759] Compound 181.4. Methyl 4-cyclobutyl-2-ethyl-5-iodobenzoate. To a solution of methyl 4-cyclobutyl-2-ethylbenzoate (compound **181.3**, 7.70 g, 35.3 mmol, 1.00 equiv) in acetic acid (80 mL) was added iodine (8.98 g, 35.4 mmol, 1.00 equiv), NaIO_4 (3.78 g, 17.7 mmol, 0.50 equiv), and sulfuric acid (0.870 g, 8.87 mmol, 0.25 equiv). The reaction mixture was stirred at 60 °C overnight. After cooling to room temperature, the reaction was slowly quenched with $\text{Na}_2\text{S}_2\text{O}_3$ (aq., sat.). The mixture was extracted with 200 mL of ethyl acetate and the organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography with ethyl acetate/petroleum ether (1:50) to furnish 10.5 g (86%) of the desired product as a colorless solid.

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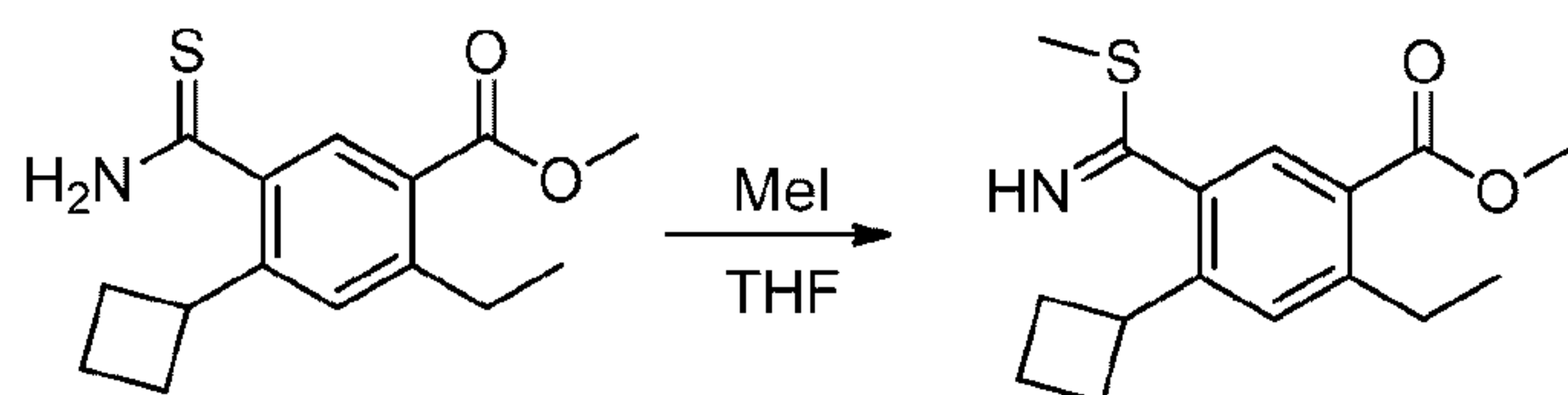


[0760] Compound 181.5. Methyl 5-cyano-4-cyclobutyl-2-ethylbenzoate. To a round-bottom flask, which was purged and maintained with a nitrogen atmosphere, was added a solution of methyl 4-cyclobutyl-2-ethyl-5-iodobenzoate (compound **181.4**, 5.50 g, 16.0 mmol, 1.00 equiv) in *N,N*-dimethylformamide (150 mL). Zinc cyanide (2.78 g, 23.7 mmol, 1.50 equiv) and Pd(PPh₃)₄ (1.83 g, 1.59 mmol, 0.10 equiv) were added to the reaction mixture. The resulting solution was stirred at 100 °C for 15 h under nitrogen. After cooling to ambient temperature, the reaction was carefully quenched with 300 mL of FeSO₄ (aq., sat.) and diluted with ethyl acetate. The resulting mixture was stirred vigorously then filtered through celite and washed with 1 M FeSO₄, water, and ethyl acetate. The layers were separated and the aqueous phase was extracted with 2 x 300 mL of ethyl acetate. The combined organic layers were washed with 2 x 300 mL of brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:100-1:50) as eluent to furnish 3.20 g (82%) of methyl 5-cyano-4-cyclobutyl-2-ethylbenzoate as a light yellow oil.

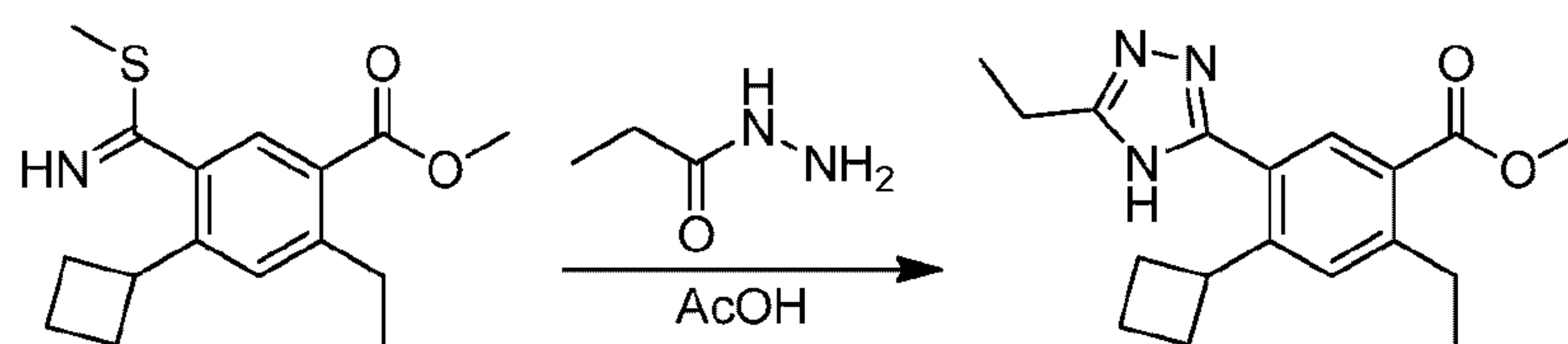


[0761] Compound 181.6. Methyl 5-carbamothioyl-4-cyclobutyl-2-ethylbenzoate. To a round-bottom flask was added a solution of methyl 5-cyano-4-cyclobutyl-2-ethylbenzoate (compound **181.5**, 3.00 g, 12.3 mmol, 1.00 equiv) in a solvent mixture of tetrahydrofuran and H₂O (80 mL/40 mL). To this was added O,O'-diethyl dithiophosphate (6.69 g, 35.9 mmol, 3.00 equiv) dropwise with stirring. The resulting solution was stirred at 85 °C for 48 h (**CAUTION:** significant gas evolution occurs - this and all other reactions described herein should be carried out in well ventilated fume hoods). After cooling to ambient temperature, the mixture was then concentrated *in vacuo*. The crude product was purified by re-crystallization from petroleum ether to furnish 1.30 g (38%) of methyl 5-carbamothioyl-4-cyclobutyl-2-ethylbenzoate as a light yellow solid.

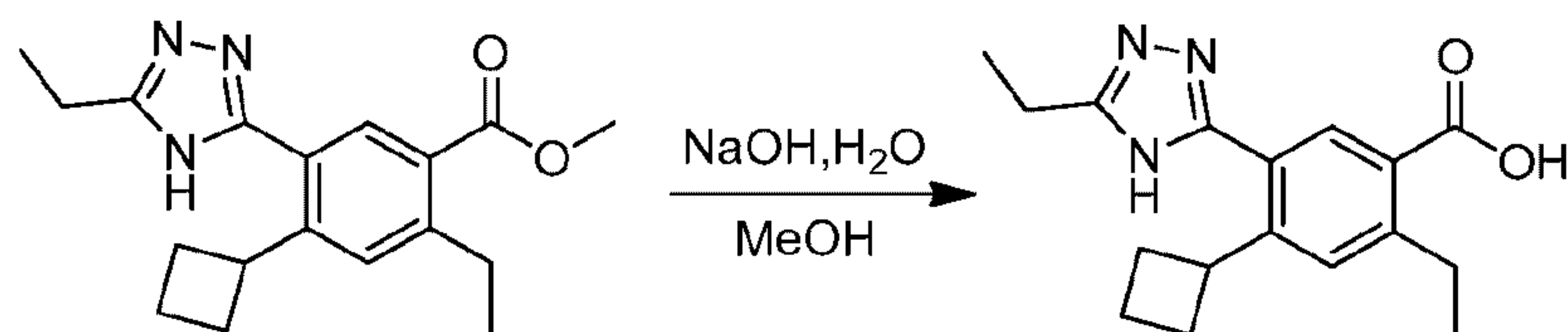
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[0762] Compound 181.7. Methyl 4-cyclobutyl-2-ethyl-5-(imino(methylthio)methyl)benzoate. To a round-bottom flask was added a solution of methyl 5-carbamothioyl-4-cyclobutyl-2-ethylbenzoate (compound **181.6**, 1.50 g, 5.41 mmol, 1.00 equiv) in tetrahydrofuran (30 mL). This was followed by the addition of iodomethane (3.80 g, 26.8 mmol, 5.00 equiv) dropwise with stirring. The resulting solution was stirred at 25 °C for 15 h, then concentrated *in vacuo*. This resulted in 1.80 g (97%) of the title compound as a yellow oil.

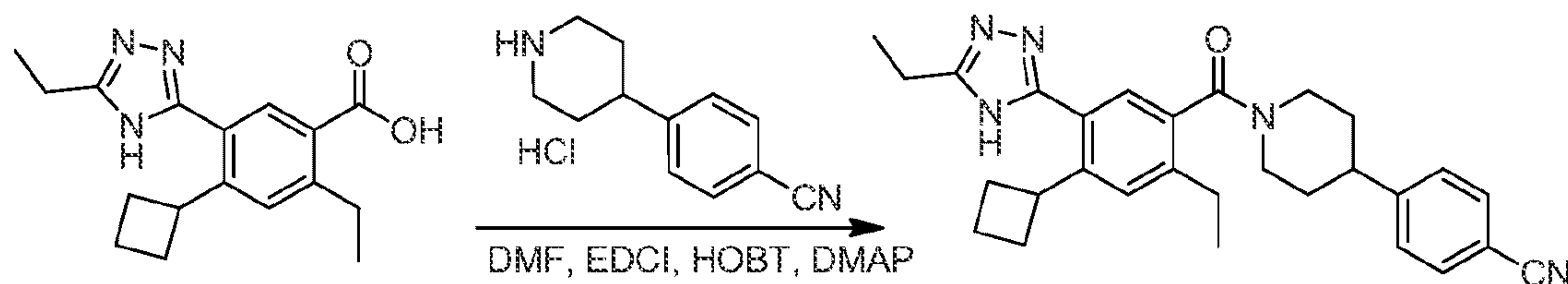


[0763] Compound 181.8. Methyl 4-cyclobutyl-2-ethyl-5-(5-ethyl-4H-1,2,4-triazol-3-yl)benzoate. To a round-bottom flask was added a solution of methyl 4-cyclobutyl-2-ethyl-5-(methylsulfanylmethyl)benzoate (compound **181.7**, 900 mg, 3.09 mmol, 1.00 equiv) in AcOH (20 mL). Propionohydrazide (880 mg, 9.99 mmol, 3.00 equiv) was added and the resulting mixture was stirred at 90 °C for 2h. After cooling to ambient temperature, the mixture was then concentrated *in vacuo*. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (1:50-1:3) as eluent to give 0.360 g (37%) of the title compound as a clear oil.

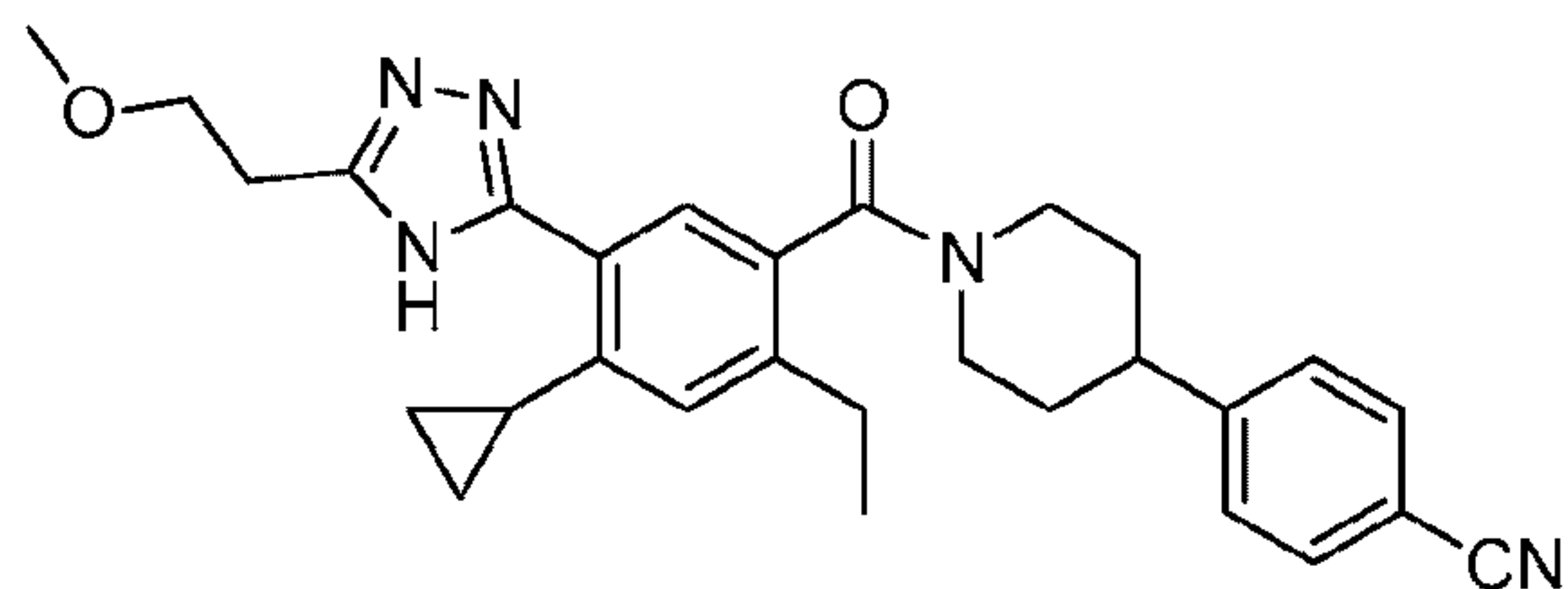


[0764] Compound 181.9. 4-Cyclobutyl-2-ethyl-5-(5-ethyl-4H-1,2,4-triazol-3-yl)benzoic acid. To a round-bottom flask was added a solution of methyl 4-cyclobutyl-2-ethyl-5-(5-ethyl-4H-1,2,4-triazol-3-yl)benzoate (compound **181.8**, 360 mg, 1.15 mmol, 1.00 equiv) in methanol (20 mL). A solution of sodium hydroxide (460 mg, 11.5 mmol, 10.0 equiv) in water (10 mL) was added to the reaction mixture. The resulting solution was stirred at 25 °C for 15 h. The organic solvent was then removed under reduced pressure. The pH

value of the remaining aqueous phase was adjusted to 2-3 with hydrogen chloride (aq., 2 M). The resulting precipitate was collected by filtration and dried under high-vacuum to yield 320 mg (93%) of the title compound as a white solid.

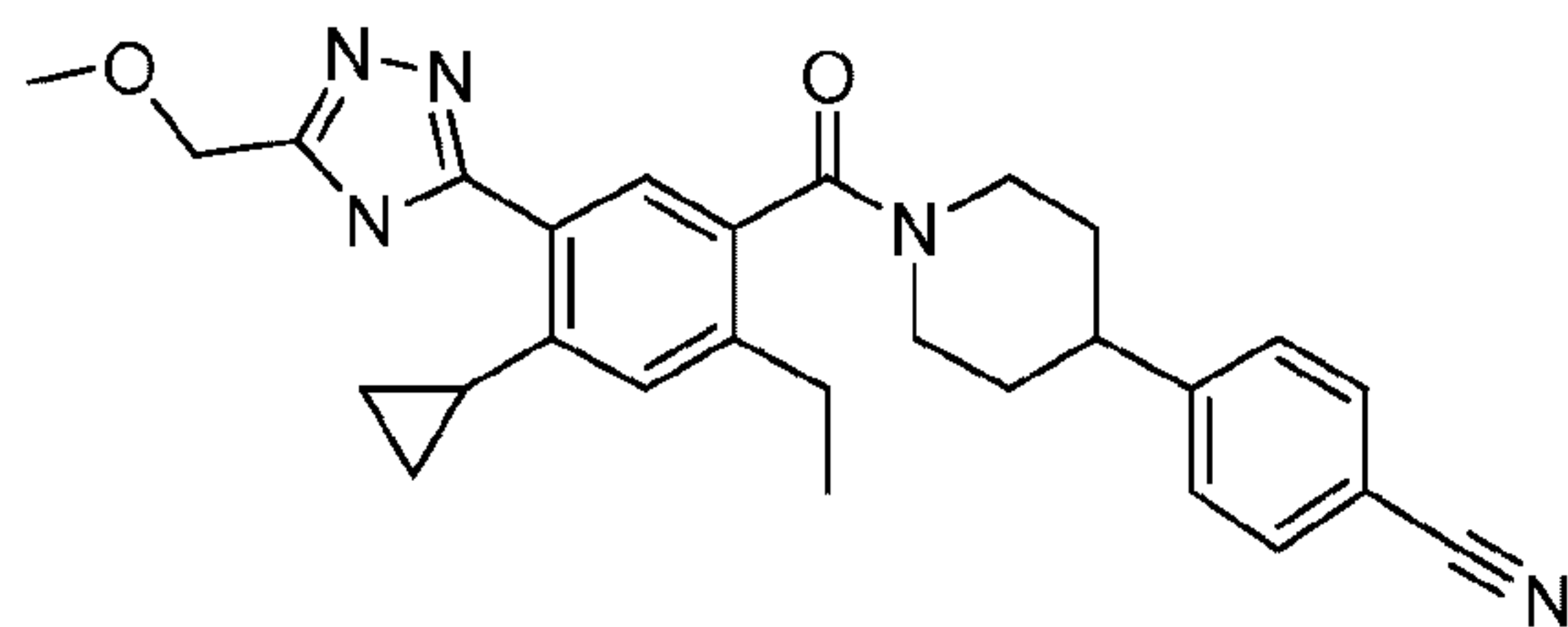


[0765] Compound 181. 4-(1-(4-Cyclobutyl-2-ethyl-5-(5-ethyl-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile. To a solution of 4-cyclobutyl-2-ethyl-5-(5-ethyl-4H-1,2,4-triazol-3-yl)benzoic acid (compound **181.9**, 160 mg, 0.530 mmol, 1.00 equiv) in *N,N*-dimethylformamide (20 mL) were added EDCI (113 mg, 0.590 mmol, 1.11 equiv), DMAP (197 mg, 1.62 mmol, 3.03 equiv), and HOBT (87.5 mg, 0.650 mmol, 1.21 equiv). After 5 min, 4-(piperidin-4-yl)benzonitrile hydrochloride (compound **1.5**, 110 mg, 0.590 mmol, 1.10 equiv) was added. The resulting mixture was stirred at 25 °C for 15 h, then quenched with 100 mL of ice water. The mixture was extracted with 2x150 mL of ethyl acetate. The combined organic layers were washed with 3x150 mL of brine, dried over anhydrous sodium sulfate, and concentrated. The crude product (~150 mg) was purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-001(SHIMADZU)): Column, SunFire Prep C18, 19*150mm 5um; mobile phase, water with 0.05%TFA and CH₃CN (47% CH₃CN up to 61% in 6 min, up to 100% in 1.5 min, down to 47% in 1.5 min); Detector, Waters 2489 254&220nm. The fractions containing pure compound were combined and lyophilized to yield 99.5 mg (40%) of the title compound as a white solid *m/z* (ES+) 468 (M+H)⁺. ¹H-NMR (300 MHz, CD₃OD): δ 7.71-7.69 (m, 2H), 7.50-7.32 (m, 4H), 4.03-3.99 (m, 1H), 3.65-3.5 (m, 1H), 3.32-3.20 (m, 1H), 2.90-2.95 (m, 4H), 2.70-2.74 (m, 2H), 2.20-1.98 (m, 6H), 1.98-1.79 (m, 4H), 1.41 (t, 3H), 1.39-1.28 (m, 3H).

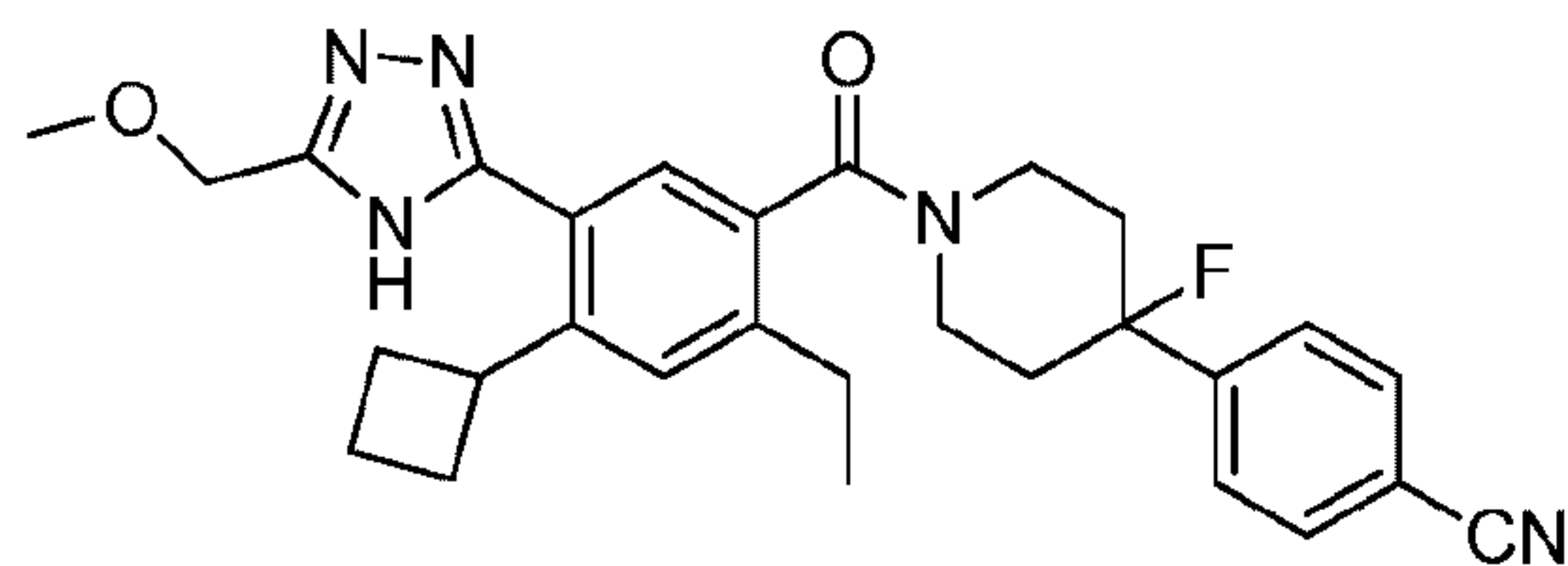


[0766] Compound 182. 4-(1-(4-Cyclopropyl-2-ethyl-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of

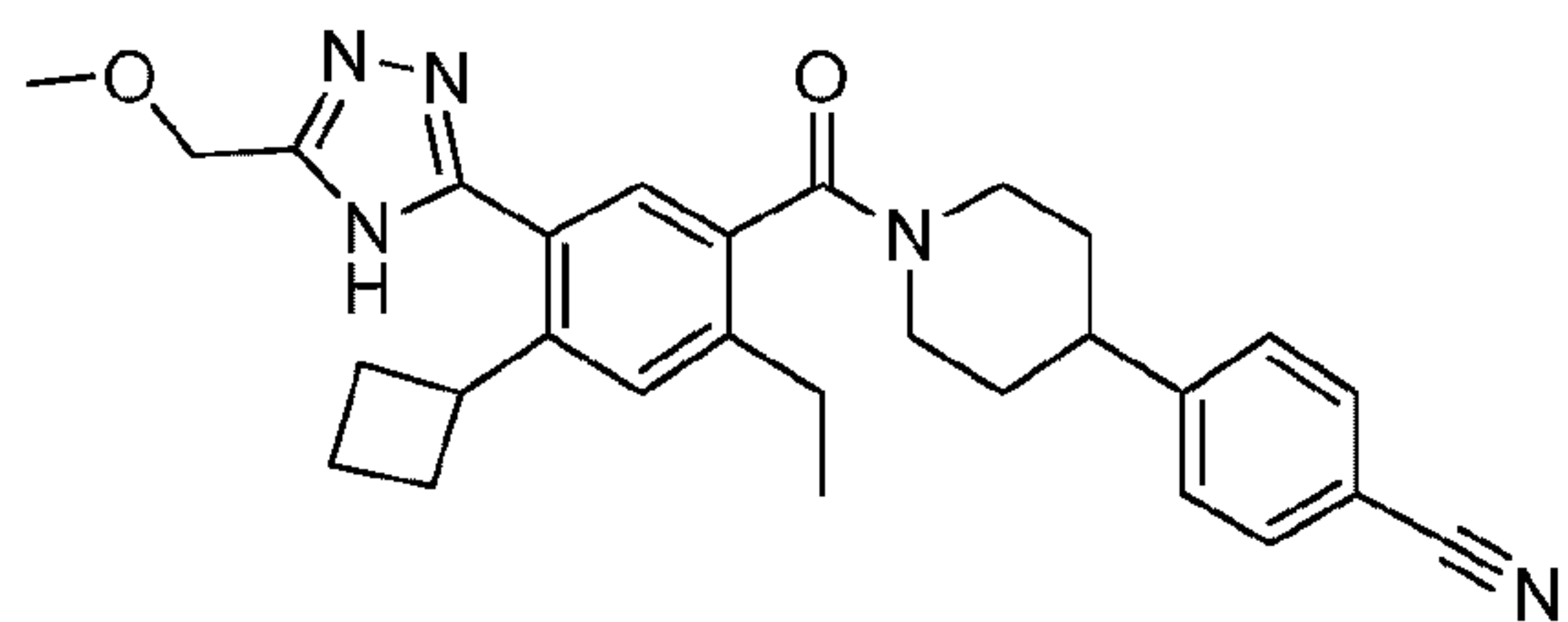
compounds **143** and **181**. m/z (ES+) 484 (M+H)⁺. ¹H-NMR (300 MHz, CD₃OD): δ 7.67 (d, 2H), 7.49-7.37 (m, 3H), 7.11-7.05 (m, 1H), 4.89-4.80 (m, 1H), 3.81 (t, 2H), 3.77-3.60 (m, 1H), 3.4 (s, 3H), 3.37-3.32 (m, 1H), 3.14 (t, 2H), 3.15-2.9 (m, 2H), 2.92-2.5 (m, 2H), 2.39-2.36 (m, 1H), 2.02-1.85 (m, 1H), 1.85-1.69 (m, 3H), 1.32-1.21 (m, 3H), 1.0-0.95 (m, 2H), 0.77-0.69 (m, 2H).



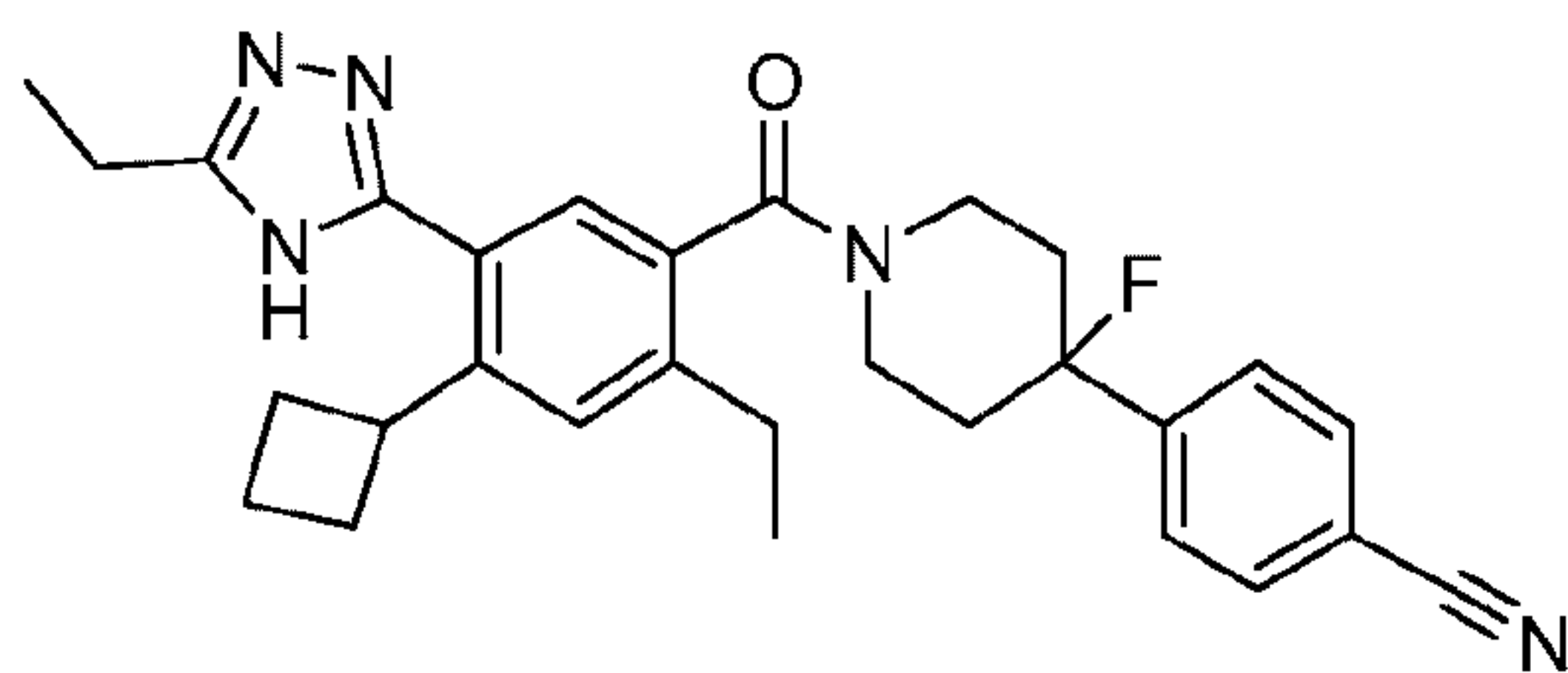
[0767] **Compound 183.** 4-(1-(4-Cyclopropyl-2-ethyl-5-(5-(methoxymethyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds **143** and **181**. m/z (ES+) 470 (M+H)⁺.



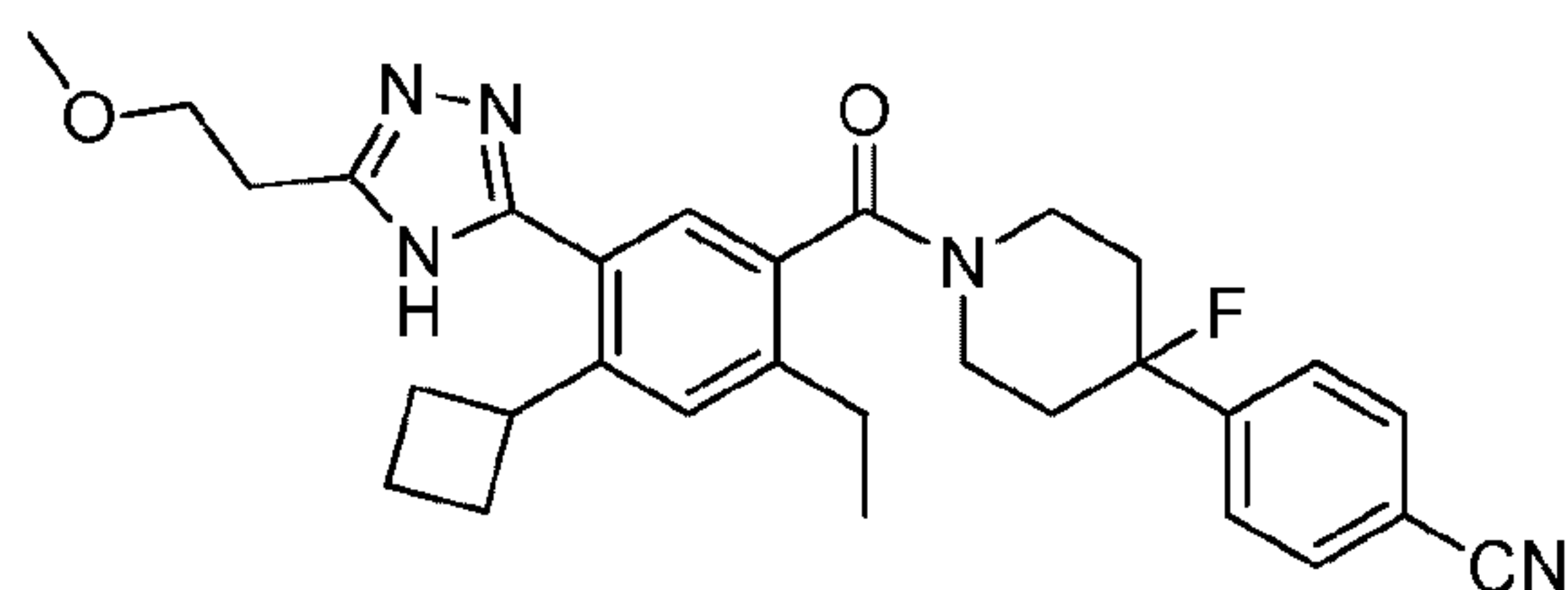
[0768] **Compound 184.** 4-(1-(4-Cyclobutyl-2-ethyl-5-(5-(methoxymethyl)-4H-1,2,4-triazol-3-yl)benzoyl)-4-fluoropiperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds **143** and **181** and using compound **11.2 HCl** salt in place of compound **1.5**. m/z (ES+) 502 (M+H)⁺.



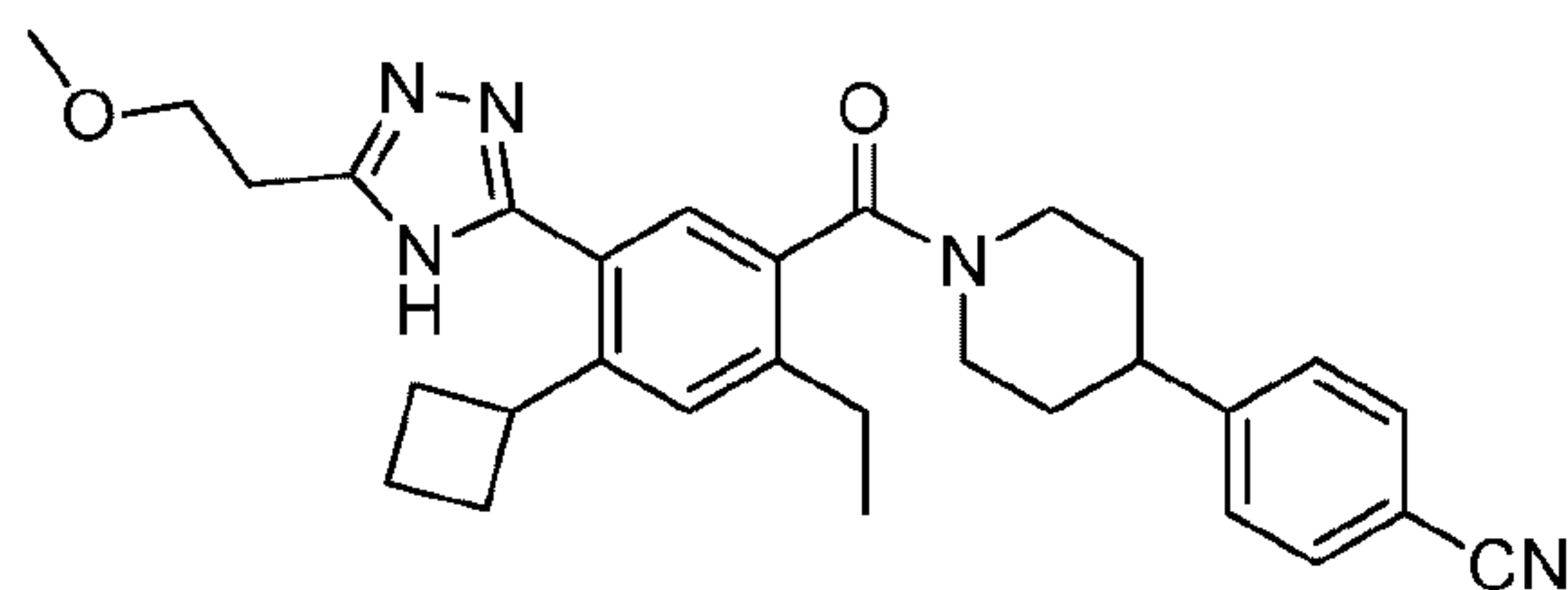
[0769] **Compound 185.** 4-(1-(4-Cyclobutyl-2-ethyl-5-(5-(methoxymethyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds **143** and **181**. m/z (ES+) 484 (M+H)⁺.



[0770] **Compound 186.** 4-(1-(4-Cyclobutyl-2-ethyl-5-(5-ethyl-4H-1,2,4-triazol-3-yl)benzoyl)-4-fluoropiperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compound **181** and using compound **11.2 HCl salt** in place of compound **1.5**. m/z (ES+) 486 (M+H)⁺.

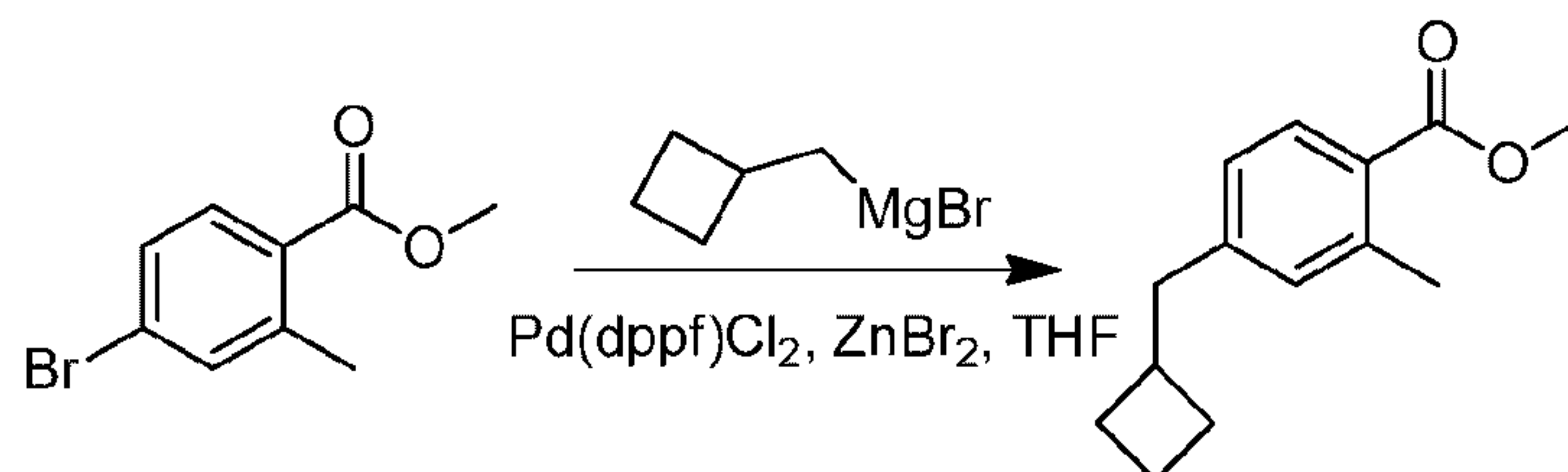


[0771] **Compound 187.** 4-(1-(4-Cyclobutyl-2-ethyl-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)benzoyl)-4-fluoropiperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds **143** and **181** and using compound **11.2 HCl salt** in place of compound **1.5**. m/z (ES+) 516 (M+H)⁺. ¹H-NMR (300 MHz, CD₃OD): δ 7.77 (d, 2H), 7.66-7.47 (m, 2H), 7.47-7.35 (m, 2H), 4.89-4.83 (m, 1H), 4.08-4.03 (t, 1H), 3.79 (t, 2H), 3.55 (t, 2H), 3.33 (s, 3H), 3.28-3.20 (m, 1H), 3.12 (t, 2H), 2.80-2.68 (m, 2H), 2.27-1.68 (m, 10H), 1.27 (t, 3H).

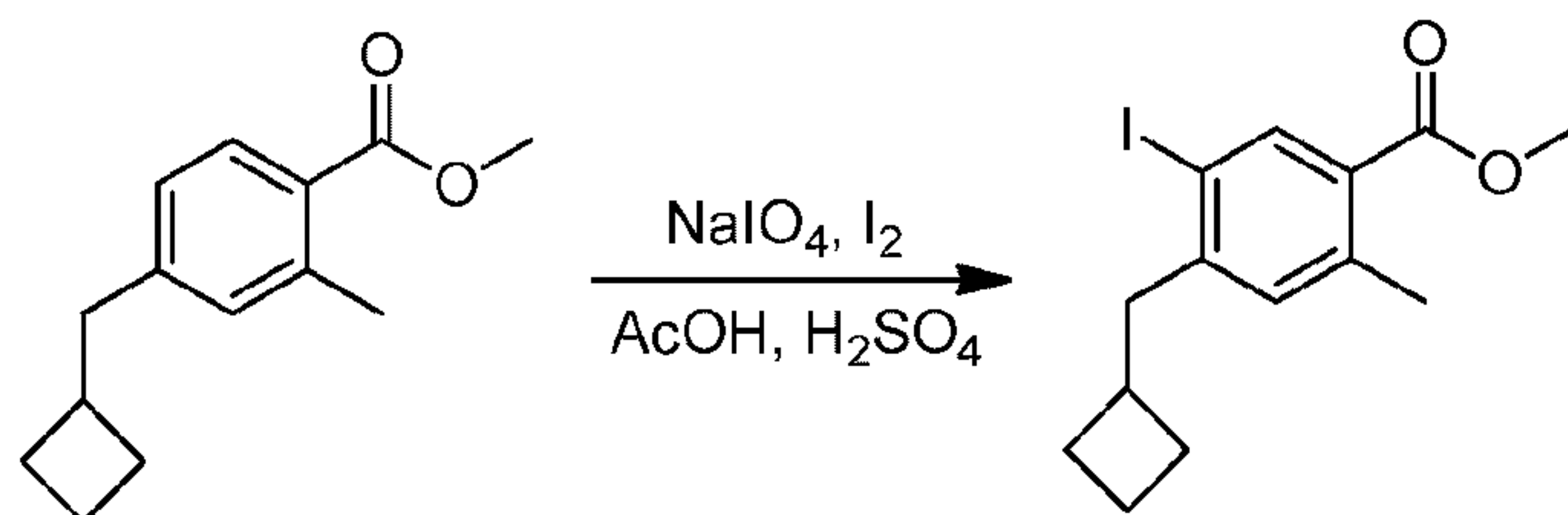


[0772] **Compound 188.** 4-(1-(4-Cyclobutyl-2-ethyl-5-(5-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile. The title compound was prepared using standard chemical manipulations and procedures similar to those used for the preparation of compounds **143** and **181**. m/z (ES+) 498 (M+H)⁺. ¹H-NMR (300 MHz, CD₃OD): δ 7.67 (d, 2H), 7.44-7.31 (m, 4H), 4.89 (s, 1H), 4.04-3.98 (m, 1H), 3.79 (t, 2H), 3.66-3.60 (m, 1H), 3.33

(s, 3H), 3.23-3.12 (m, 1H), 3.10 (t, 2H), 3.02 (t, 2H), 2.77-2.66 (m, 2H), 2.19-2.04 (m, 6H), 1.80-1.68 (m, 4H), 1.31-1.26 (m, 3H).



[0773] Compound 189.1. Methyl 4-(cyclobutylmethyl)-2-methylbenzoate. The title compound (4.00 g, yellow oil, 84%) was prepared using a procedure similar to that used for the preparation of compound **181.3** using compound **152.1** (5.00 g) and cyclobutylmethylmagnesium bromide in place of compound **181.2** and cyclobutylmagnesium bromide respectively.



[0774] Compound 189.2. Methyl 4-(cyclobutylmethyl)-5-iodo-2-methylbenzoate. To a round-bottom flask was added a solution of methyl 4-(cyclobutylmethyl)-2-methylbenzoate (compound **189.1**, 8.40 g, 38.5 mmol, 1.00 equiv) in AcOH (150 mL). NaIO₄ (5.00 g, 23.4 mmol, 0.50 equiv), iodine (10.0 g, 39.4 mmol, 1.00 equiv), and sulfuric acid (0.3 mL) were added to the reaction mixture. The resulting solution was stirred at 60 °C for 12 h. After cooling to room temperature, the reaction was quenched with 200 mL of NaHSO₃ (aq). The mixture was extracted with 2 x 200 mL of ethyl acetate, and the combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography with ethyl acetate/petroleum ether (20:1) as eluent to furnish 8.00 g (60%) of methyl 4-(cyclobutylmethyl)-5-iodo-2-methylbenzoate as a white solid.

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

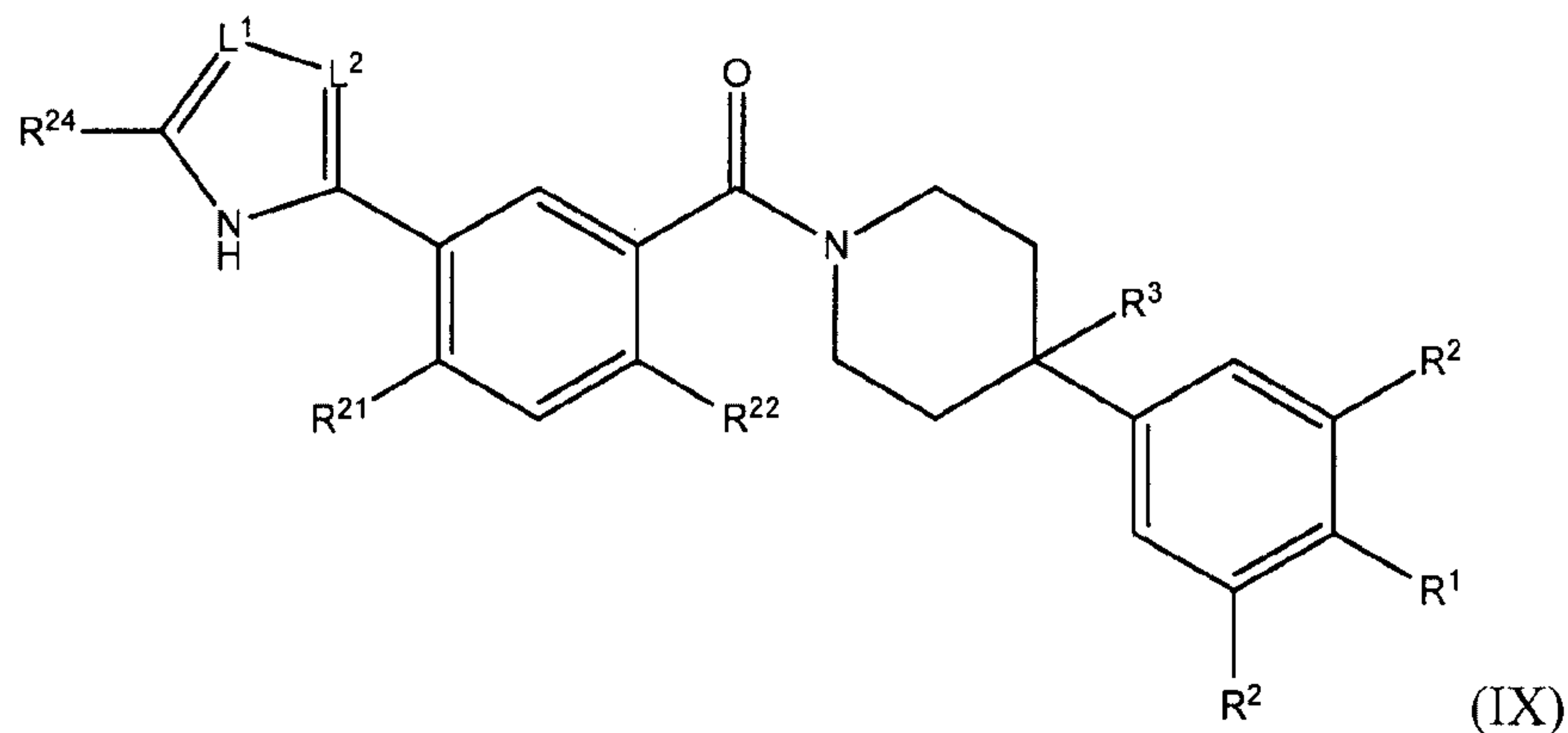
**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

CLAIMS:

1. A compound of Structure (IX):



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, -CN, halogen, C_1 - C_4 straight or branched alkyl, -O-(C_3 - C_5 cycloalkyl), or -O-(C_1 - C_4 straight or branched alkyl) wherein:

C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom; and

when R^1 is not H, -CN or halogen, it is optionally substituted with one or more halogens;

each R^2 is independently hydrogen, halogen or C_1 - C_4 straight or branched alkyl;

R^3 is H, -OH, or halogen;

R^{21} is H, halogen, C_1 - C_4 straight or branched alkyl, or C_3 - C_5 cycloalkyl wherein the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom;

R^{22} is H, halogen, or C_1 - C_2 alkyl;

R^{24} is H, C_1 - C_4 straight or branched alkyl, -(C_1 - C_4 alkyl)_t-OH, -(C_1 - C_4 alkyl)_t-O-(C_3 - C_5 cycloalkyl), or -(C_1 - C_4 alkyl)_t-O-(C_1 - C_4 straight or branched alkyl) wherein:

t is 0 or 1;

the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom;

L^1 is CR^{23} or N;

L^2 is CH or N;

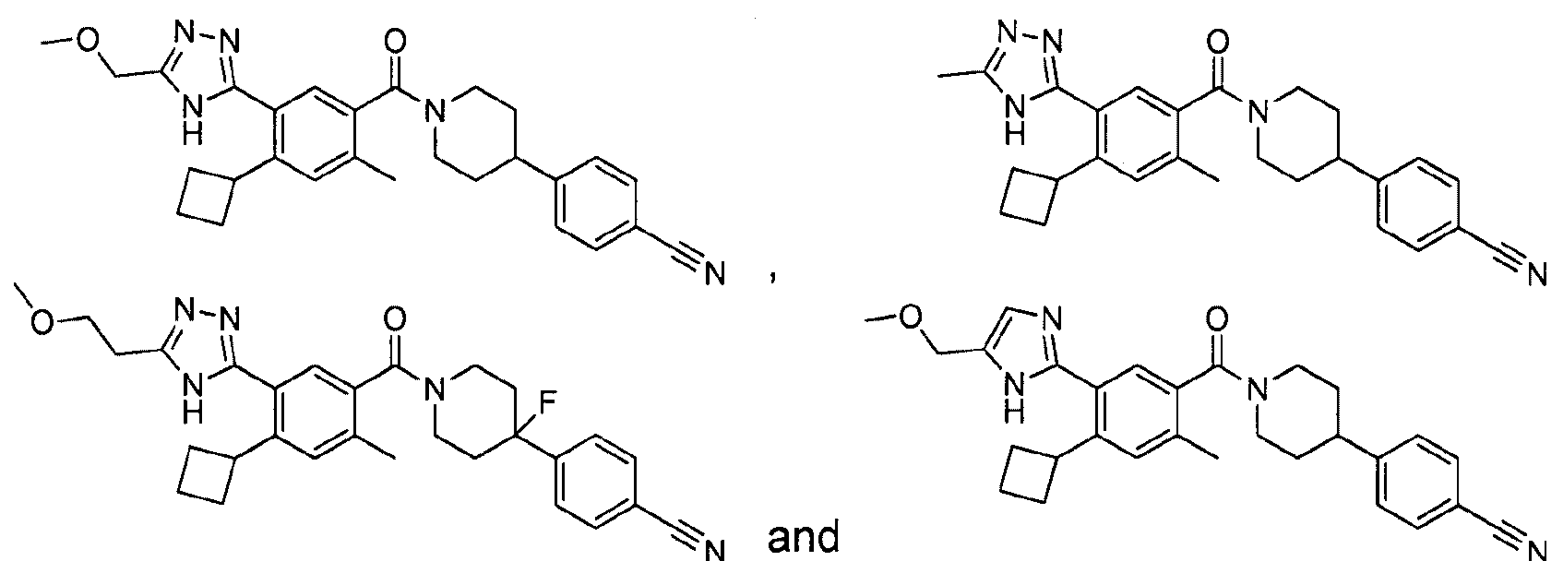
at least one of L^1 or L^2 is N; and

R^{23} is H or C_1 - C_4 straight or branched alkyl.

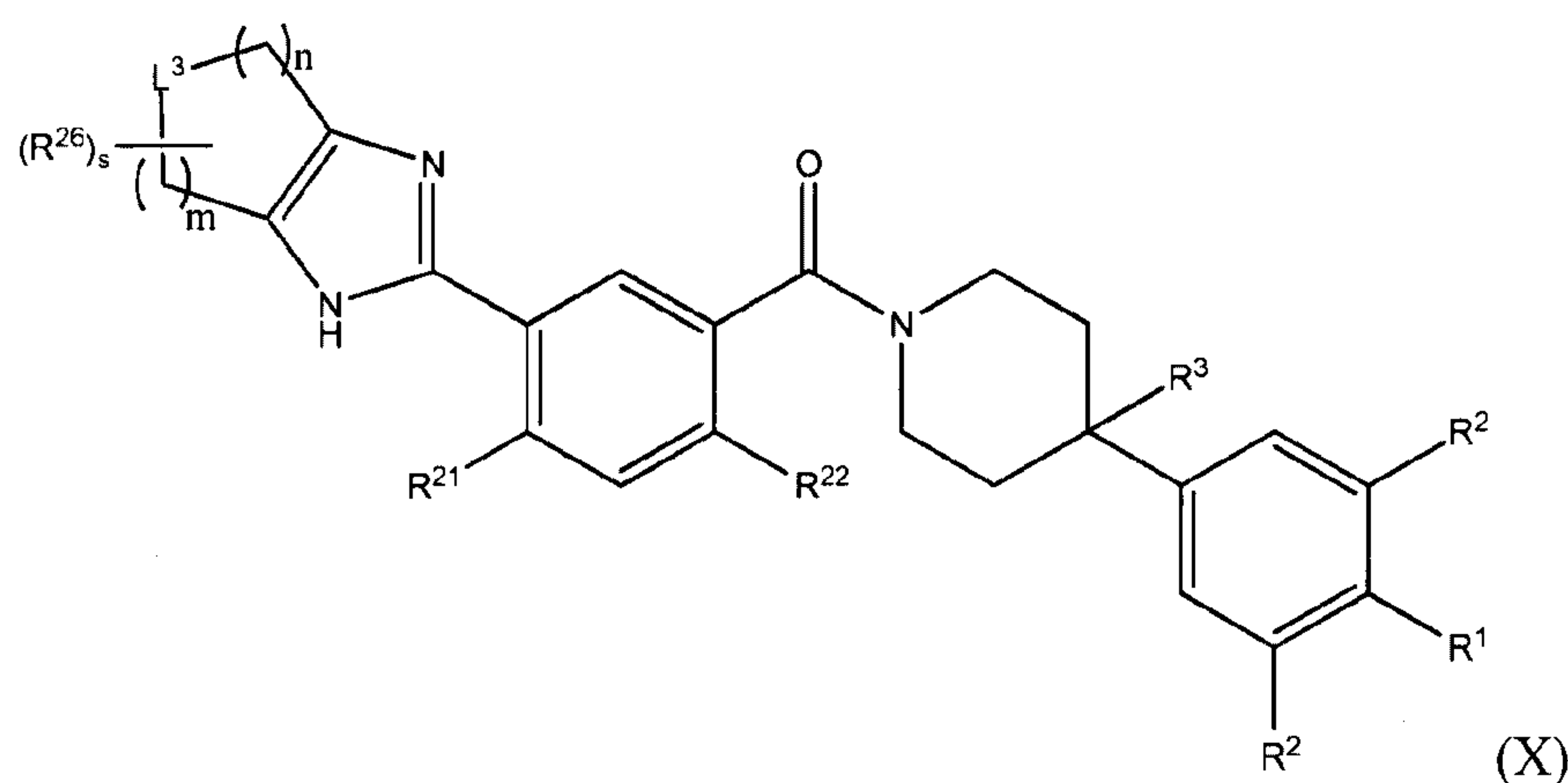
2. The compound of claim 1, wherein R^{24} is C_1 - C_4 straight or branched alkyl or $-(C_1$ - C_4 alkyl) $_t$ -O- $(C_1$ - C_4 straight or branched alkyl) wherein t is 0 or 1.
3. The compound of claim 1 or 2, wherein R^{21} is halogen, C_1 - C_4 straight or branched alkyl or C_3 - C_5 cycloalkyl wherein the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom.
4. The compound of any one of claims 1 to 3, wherein R^3 is H or halogen.
5. The compound of any one of claims 1 to 4, wherein R^1 is halogen, $-CN$ or C_1 - C_2 haloalkyl.
6. The compound of any one of claims 1 to 5, wherein both L^1 and L^2 are N.
7. The compound of any one of claims 1 to 6, wherein R^{21} is C_1 - C_2 alkyl or C_3 - C_5 cycloalkyl and R^{22} is C_1 - C_2 alkyl.
8. The compound of any one of claims 1 to 7, wherein R^{21} is C_3 - C_5 cycloalkyl and R^{22} is C_1 - C_2 alkyl.
9. The compound of any one of claims 1 to 8, wherein R^{24} is $-(C_1$ - C_2 alkyl) $_t$ -O- $(C_1$ - C_2 alkyl) wherein t is 0 or 1.
10. The compound of any one of claims 1 to 8, wherein R^{21} is C_3 - C_5 cycloalkyl, R^{22} is C_1 - C_2 alkyl and R^{24} is C_1 - C_2 alkyl.
11. The compound of claim 10, wherein R^{21} is cyclobutyl, R^{22} is C_1 - C_2 alkyl and R^{24} is C_1 - C_2 alkyl.
12. The compound of any one of claims 1 to 9, wherein R^{21} is cyclobutyl.

13. The compound of any one of claims 1 to 12, wherein R^3 is H or F.
14. The compound of any one of claims 1 to 13, wherein R^1 is $-\text{CN}$.
15. The compound of any one of claims 1 to 13, wherein R^1 is $-\text{CF}_3$.
16. The compound of any one of claims 1 to 6, wherein R^{22} is H, methyl or ethyl.
17. The compound of claim 16, wherein R^{22} is H.
18. The compound of any one of claims 1 to 16, wherein R^{22} is methyl.
19. The compound of claim 1, wherein R^1 is $-\text{CN}$, each R^2 is H, R^3 is H or F, R^{21} is $\text{C}_3\text{-C}_4$ cycloalkyl, R^{22} is methyl, L^1 and L^2 are N, and R^{24} is methyl, ethyl, hydroxymethyl, methoxymethyl, or 2-methoxyethyl.
20. The compound of claim 1, wherein R^1 is $-\text{CN}$, each R^2 is H, R^3 is H or F, R^{21} is $\text{C}_3\text{-C}_4$ cycloalkyl, R^{22} is methyl, L^1 and L^2 are N, and R^{24} is methyl or ethyl.
21. The compound of claim 1, wherein R^1 is $-\text{CN}$, each R^2 is H, R^3 is H or F, R^{21} is $\text{C}_3\text{-C}_4$ cycloalkyl, R^{22} is methyl, L^1 is CH, L^2 is N, and R^{24} is methyl, ethyl, hydroxymethyl, methoxymethyl, or 2-methoxyethyl.
22. The compound of claim 1, wherein R^1 is $-\text{CN}$, each R^2 is H, R^3 is H or F, R^{21} is $\text{C}_3\text{-C}_4$ cycloalkyl, R^{22} is methyl, L^1 is N, L^2 is CH, and R^{24} is methyl, ethyl, hydroxymethyl, methoxymethyl, or 2-methoxyethyl.

23. The compound of claim 1, having a formula selected from the group consisting of:



24. A compound of Structure (X):



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, -CN, halogen, C_1 - C_4 straight or branched alkyl, -O-(C_3 - C_5 cycloalkyl), or -O-(C_1 - C_4 straight or branched alkyl) wherein:

the C_3 - C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom; and

when R^1 is not H, -CN or halogen, it is optionally substituted with one or more halogens;

each R^2 is independently hydrogen, halogen or C_1 - C_4 straight or branched alkyl;

R^3 is H, -OH or halogen;

L^3 is $C(R^{60})_2$, O or NR^{50} ;

each R^{60} is independently H, -OH, -CN, $-O_t-(C_3-C_5 \text{ cycloalkyl})$, $-O-(C_1-C_4 \text{ straight or branched alkyl})$, or $-C(O)-N(R^{601})_2$ wherein:

t is 0 or 1, and

the C_3-C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom;

each R^{50} is independently H, $-C(O)-O_t-(C_1-C_4 \text{ straight or branched alkyl})$, $-C(O)-O_t-(C_3-C_5 \text{ cycloalkyl})$, $-C_3-C_5$ cyclic alkyl optionally containing an oxygen or nitrogen heteroatom, $-C(O)-N(R^{501})_2$, or C_1-C_4 straight or branched alkyl wherein:

t is 0 or 1, and

the C_3-C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom;

n is 1, 2 or 3;

m is 1 or 2;

R^{21} is H, halogen, C_1-C_4 straight or branched alkyl, or C_3-C_5 cycloalkyl wherein the C_3-C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom;

R^{22} is H, halogen, or C_1-C_2 alkyl;

each R^{26} is independently -OH, -CN, halogen, C_1-C_4 straight or branched alkyl, $-(C_1-C_4 \text{ alkyl})_t-O_t-(C_3-C_5 \text{ cycloalkyl})$, $-(C_1-C_4 \text{ alkyl})_t-O-(C_1-C_4 \text{ straight or branched alkyl})$, $-C(O)-O_t-(C_1-C_4 \text{ alkyl})$, or $-C(O)-N(R^{501})_2$ wherein:

t is 0 or 1, and

the C_3-C_5 cycloalkyl optionally includes an oxygen or nitrogen heteroatom;

s is 0, 1 or 2;

each R^{601} and R^{501} is independently H or C_1-C_4 straight or branched alkyl; and

wherein two of R^{26} , R^{60} , R^{50} , R^{501} and R^{601} optionally join to form a ring wherein the two of R^{26} , R^{60} , R^{50} , R^{501} and R^{601} may be two R^{26} , two R^{60} , two R^{50} , two R^{501} or two R^{601} .

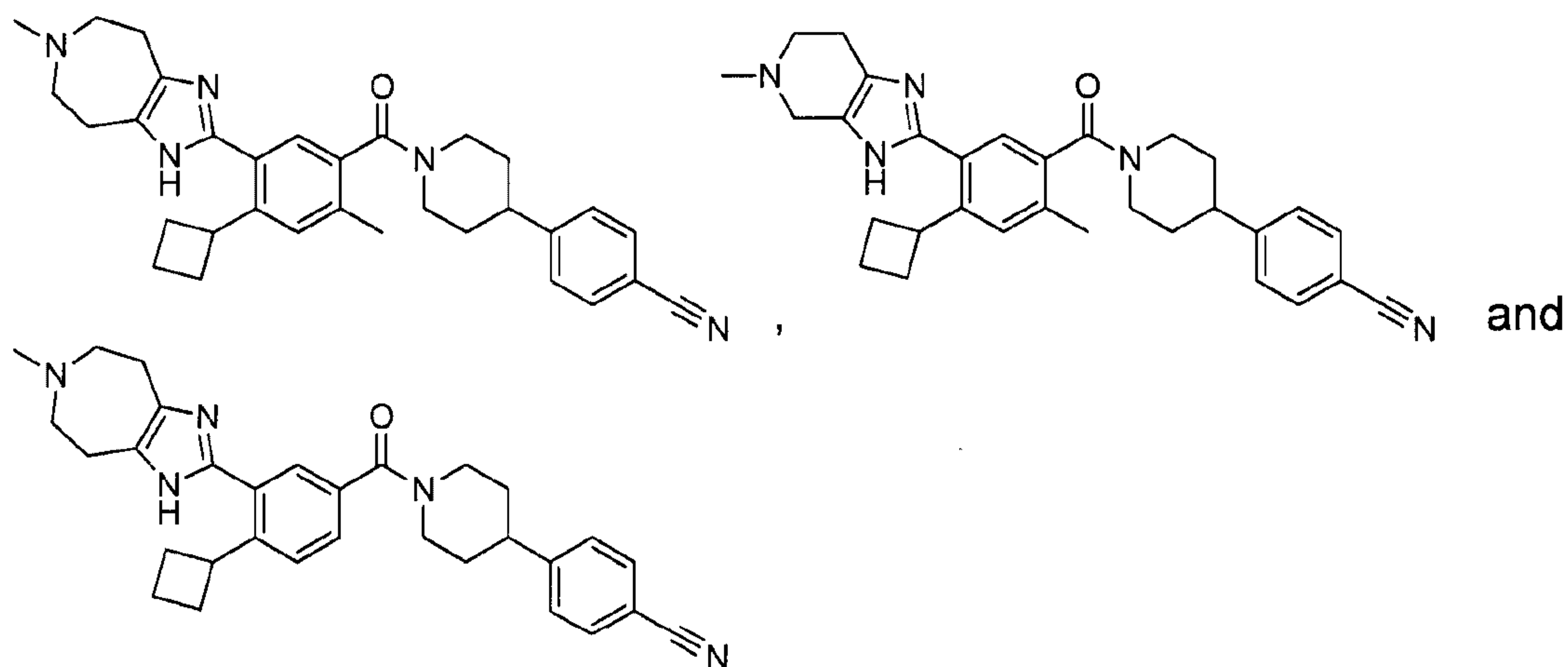
25. The compound of claim 24, wherein R^{21} is halogen, C_1-C_4 straight or branched alkyl or C_3-C_5 cycloalkyl.

26. The compound of claim 24 or 25, wherein R^3 is H or halogen.

27. The compound of any one of claims 24 to 26, wherein R^1 is -CN or C_1-C_2 haloalkyl.

28. The compound of any one of claims 24 to 27, wherein R^3 is H or F.
29. The compound of any one of claims 24 to 28, wherein R^1 is $-\text{CN}$.
30. The compound of any one of claims 24 to 28, wherein R^1 is $-\text{CF}_3$.
31. The compound of any one of claims 24 to 30, wherein n is 1.
32. The compound of any one of claims 24 to 30, wherein n is 2.
33. The compound of any one of claims 24 to 32, wherein m is 1.
34. The compound of any one of claims 24 to 32, wherein m is 2.
35. The compound of any one of claims 24 to 34, wherein R^{21} is $\text{C}_1\text{-C}_2$ alkyl or $\text{C}_3\text{-C}_5$ cycloalkyl and R^{22} is $\text{C}_1\text{-C}_2$ alkyl.
36. The compound of any one of claims 24 to 35, wherein R^{21} is $\text{C}_3\text{-C}_5$ cycloalkyl and R^{22} is $\text{C}_1\text{-C}_2$ alkyl.
37. The compound of any one of claims 24 to 30, wherein n is 2, m is 1, L^3 is $-\text{N}-\text{C}(\text{O})-\text{O}-(\text{C}_1\text{-C}_2 \text{ alkyl})$.
38. The compound of any one of claims 24 to 29, wherein L^3 is NR^{50} ; R^{50} is $\text{C}_1\text{-C}_2$ alkyl; R^{21} is cyclobutyl; R^{22} is H or methyl; R^3 is H; R^1 is $-\text{CN}$; m is 2 and n is 1 or 2.
39. The compound of any one of claims 24 to 30, wherein n is 2, m is 1, L^3 is O and s is 0.
40. The compound of any one of claims 24 to 34, wherein R^{22} is H, methyl or ethyl.

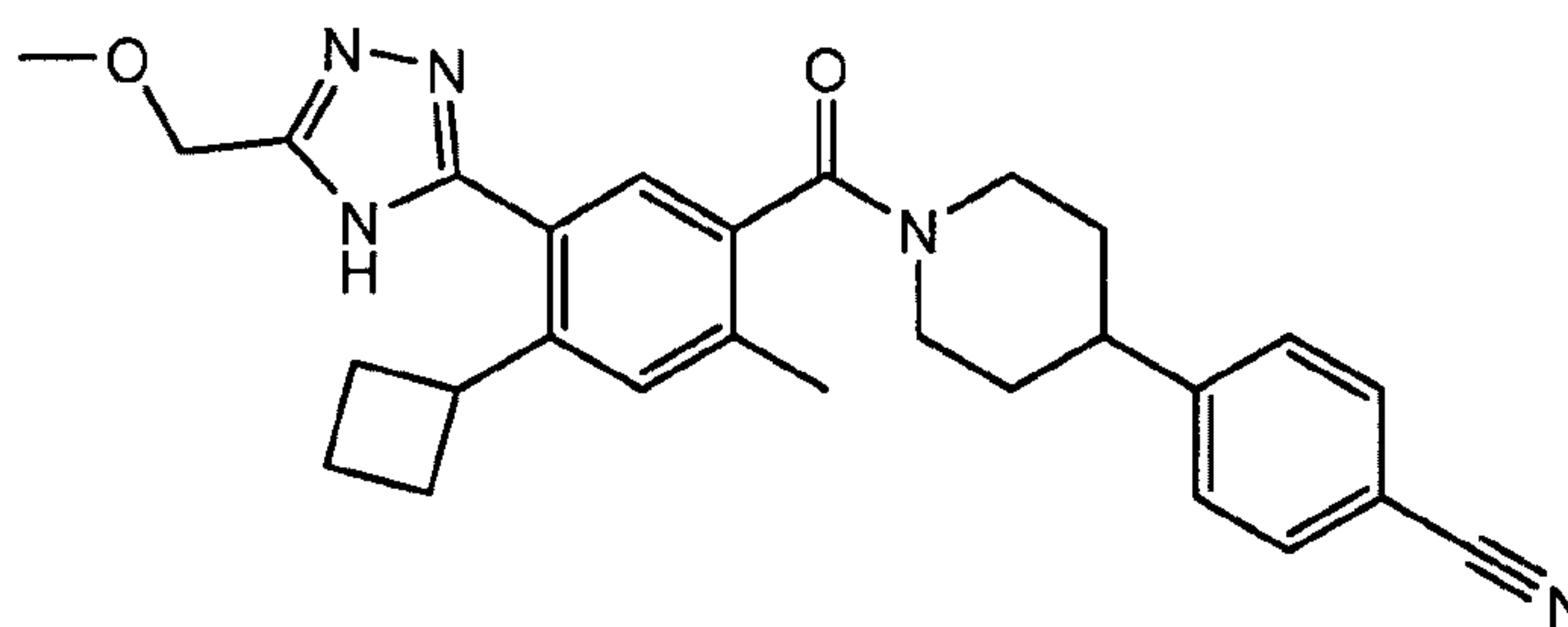
41. The compound of any one of claims 24 to 38, wherein R^{22} is methyl.
42. The compound of any one of claims 24 to 34, wherein R^{22} is H.
43. The compound of claim 24, wherein R^1 is $-\text{CN}$, each R^2 is H, R^3 is H or F, R^{21} is $\text{C}_3\text{-C}_4$ cycloalkyl, R^{22} is methyl, n is 2 and L^3 is NR^{50} wherein R^{50} is methyl or ethyl.
44. The compound of claim 24, wherein R^1 is $-\text{CN}$, each R^2 is H, R^3 is H or F, R^{21} is $\text{C}_3\text{-C}_4$ cycloalkyl, R^{22} is methyl, n is 2 and L^3 is O.
45. The compound of claim 24, having a formula selected from the group consisting of:



46. A pharmaceutical composition comprising any one of the compounds of any one of claims 1 to 45, and a pharmaceutically acceptable carrier, excipient, or diluent.
47. Use of a compound of any one of claims 1 to 45, for the treatment of a viral infection in a subject.
48. The use of claim 47, wherein the viral infection comprises hepatitis C infection.

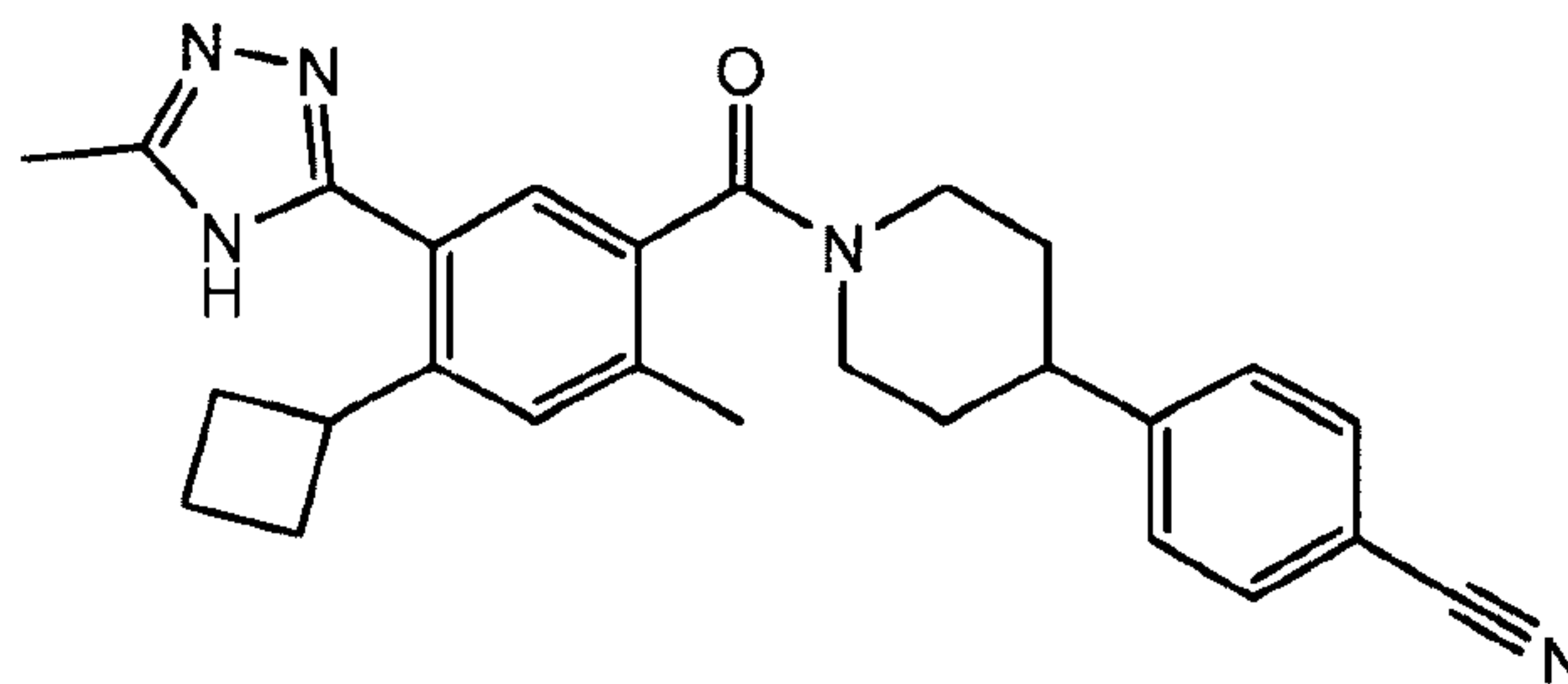
49. Use of a compound of any one of claims 1 to 45, for the treatment of a condition characterized by dysregulation of a fatty acid synthase function in a subject.
50. Use of a compound of any one of claims 1 to 45, for the treatment of cancer in a subject.
51. The use of claim 50, wherein the cancer is breast cancer.
52. Use of a compound of any one of claims 1 to 45, in the manufacture of a medicament for the treatment of a viral infection in a subject.
53. The use of claim 52, wherein the viral infection comprises hepatitis C infection.
54. Use of a compound of any one of claims 1 to 45, in the manufacture of a medicament for the treatment of a condition characterized by dysregulation of a fatty acid synthase function in a subject.
55. Use of a compound of any one of claims 1 to 45, in the manufacture of a medicament for the treatment of cancer in a subject.
56. The use of claim 55, wherein the cancer is breast cancer.
57. A compound of any one of claims 1 to 45, for the treatment of a viral infection in a subject.
58. The compound of claim 57, wherein the viral infection comprises hepatitis C infection.

59. A compound of any one of claims 1 to 45, for the treatment of a condition characterized by dysregulation of a fatty acid synthase function in a subject.
60. A compound of any one of claims 1 to 45, for the treatment of cancer in a subject.
61. The compound of claim 60, wherein the cancer is breast cancer.
62. The compound of claim 1, having the formula:



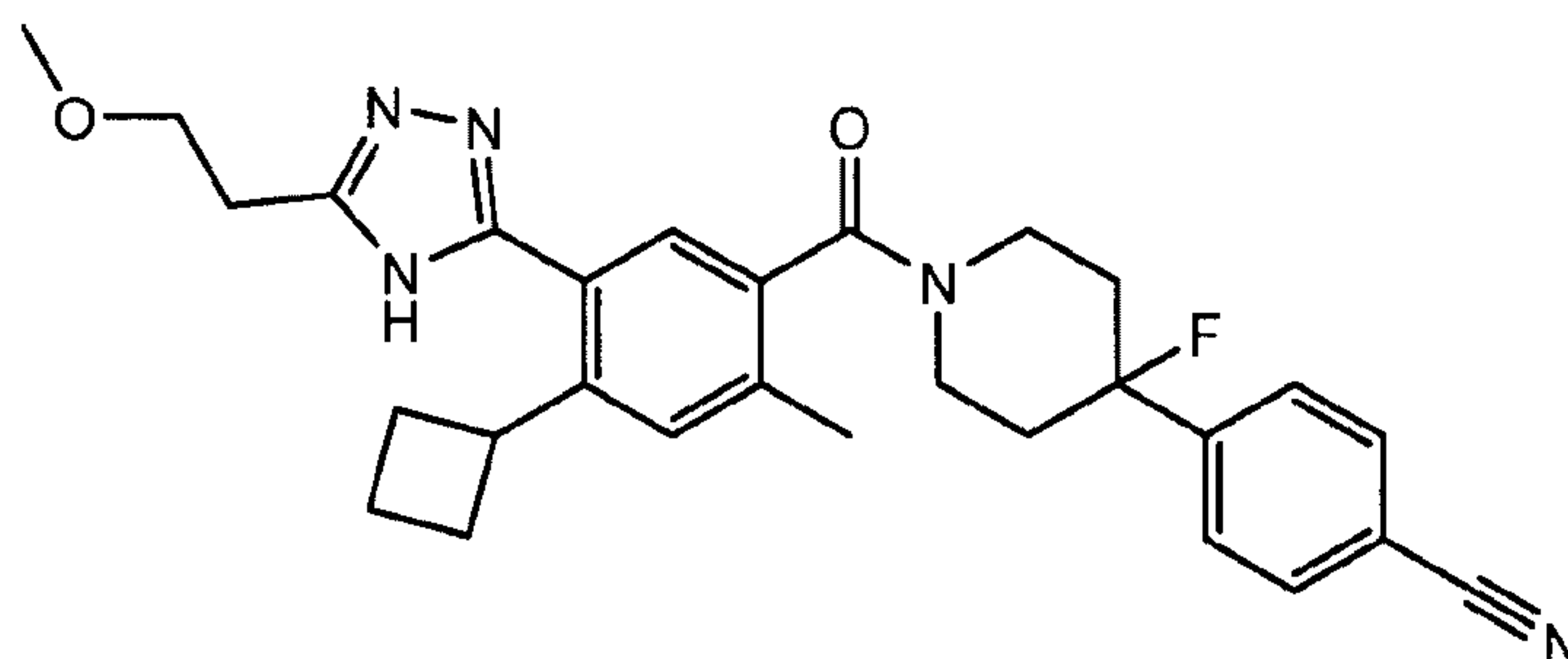
or a pharmaceutically acceptable salt thereof.

63. The compound of claim 1, having the formula:



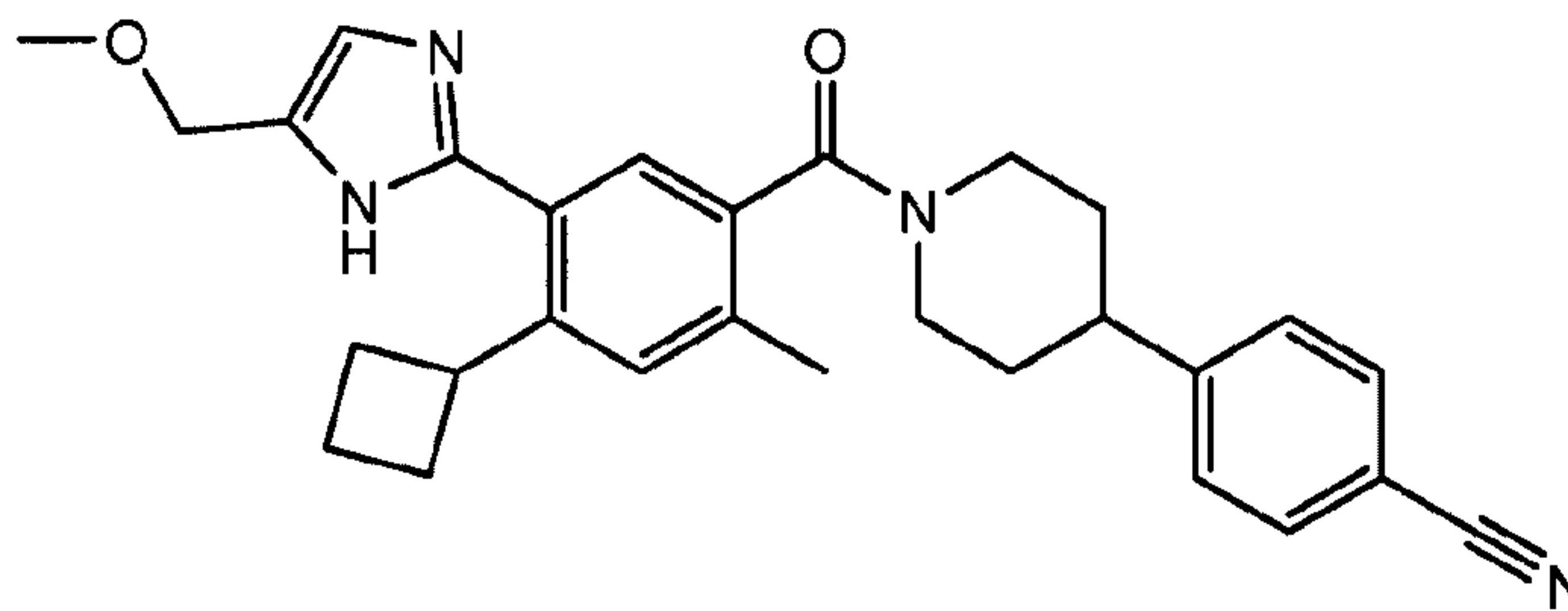
or a pharmaceutically acceptable salt thereof.

64. The compound of claim 1, having the formula:



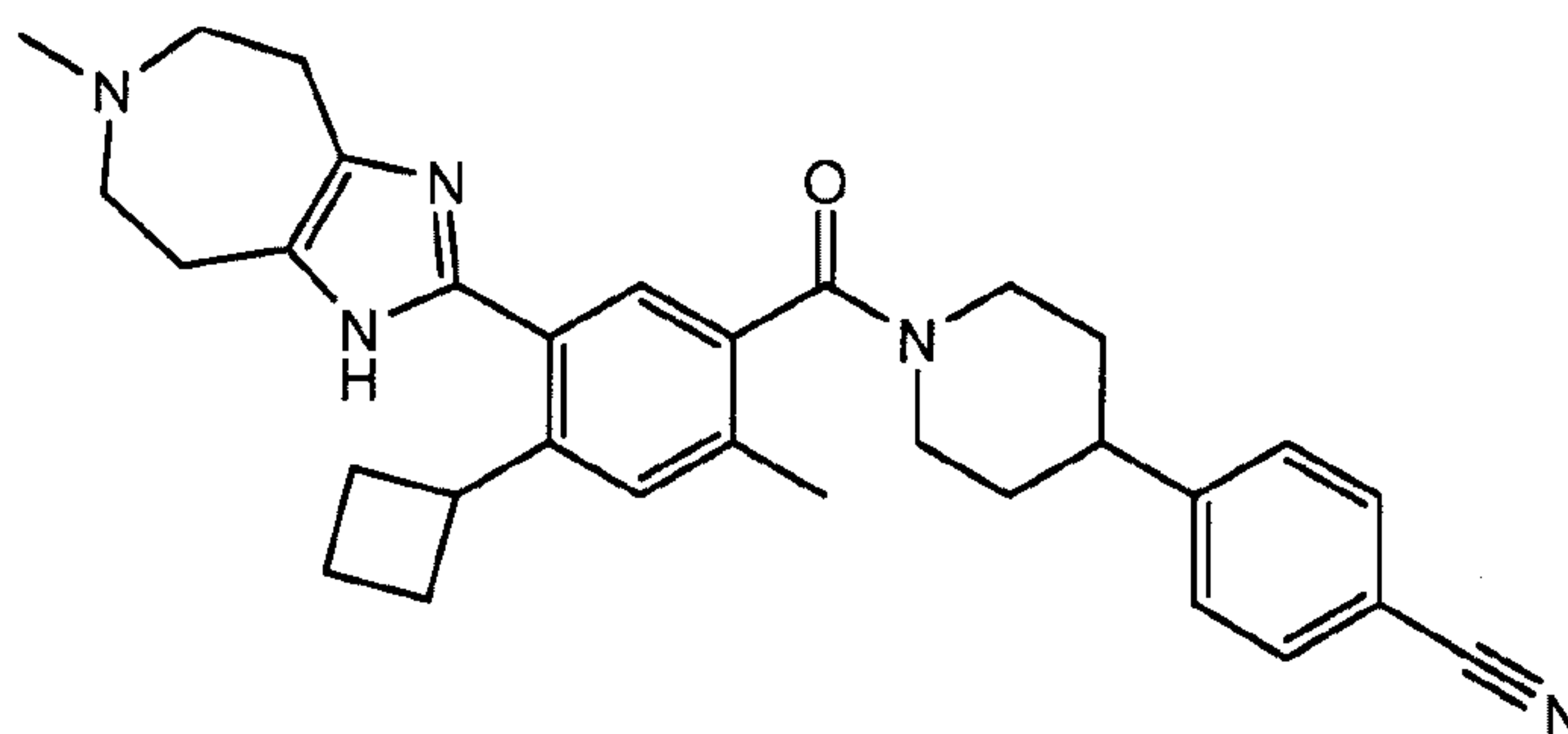
or a pharmaceutically acceptable salt thereof.

65. The compound of claim 1, having the formula:



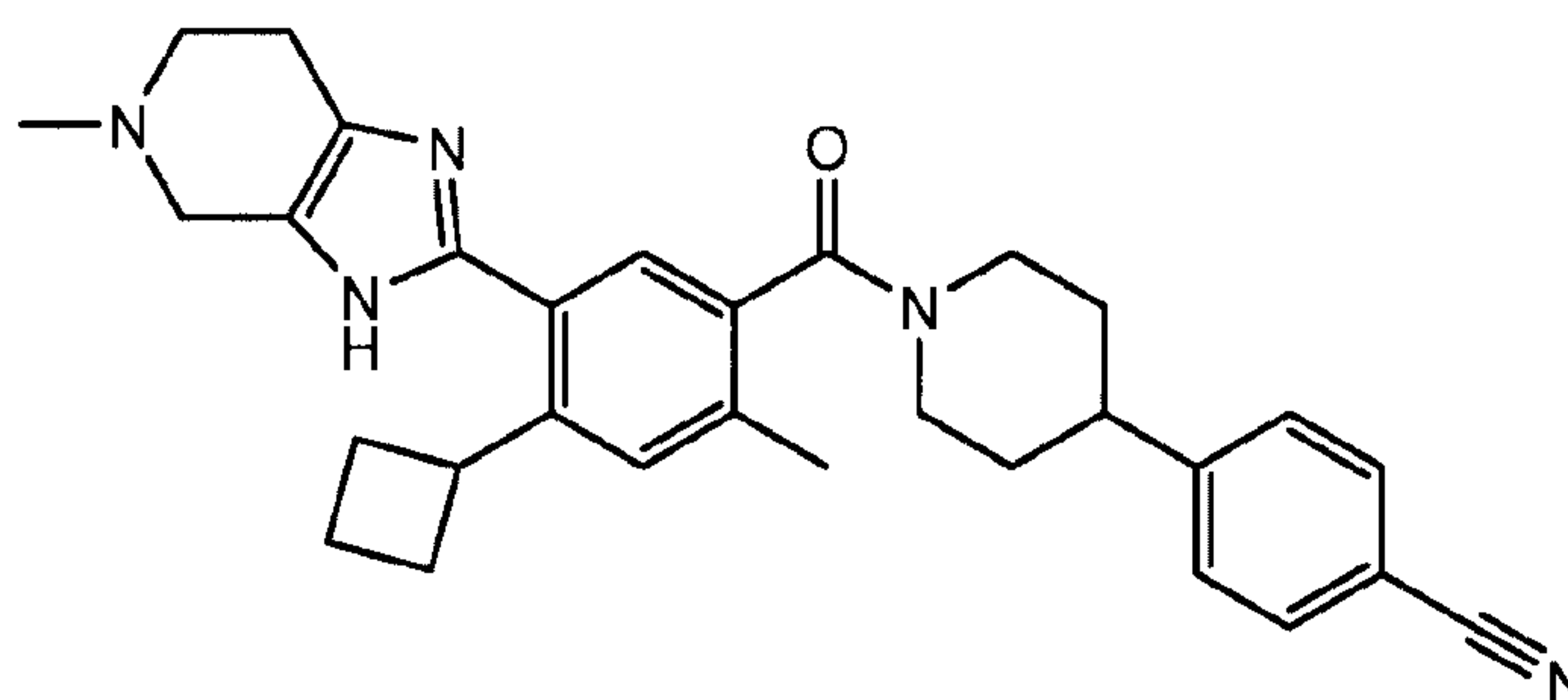
or a pharmaceutically acceptable salt thereof.

66. The compound of claim 1, having the formula:



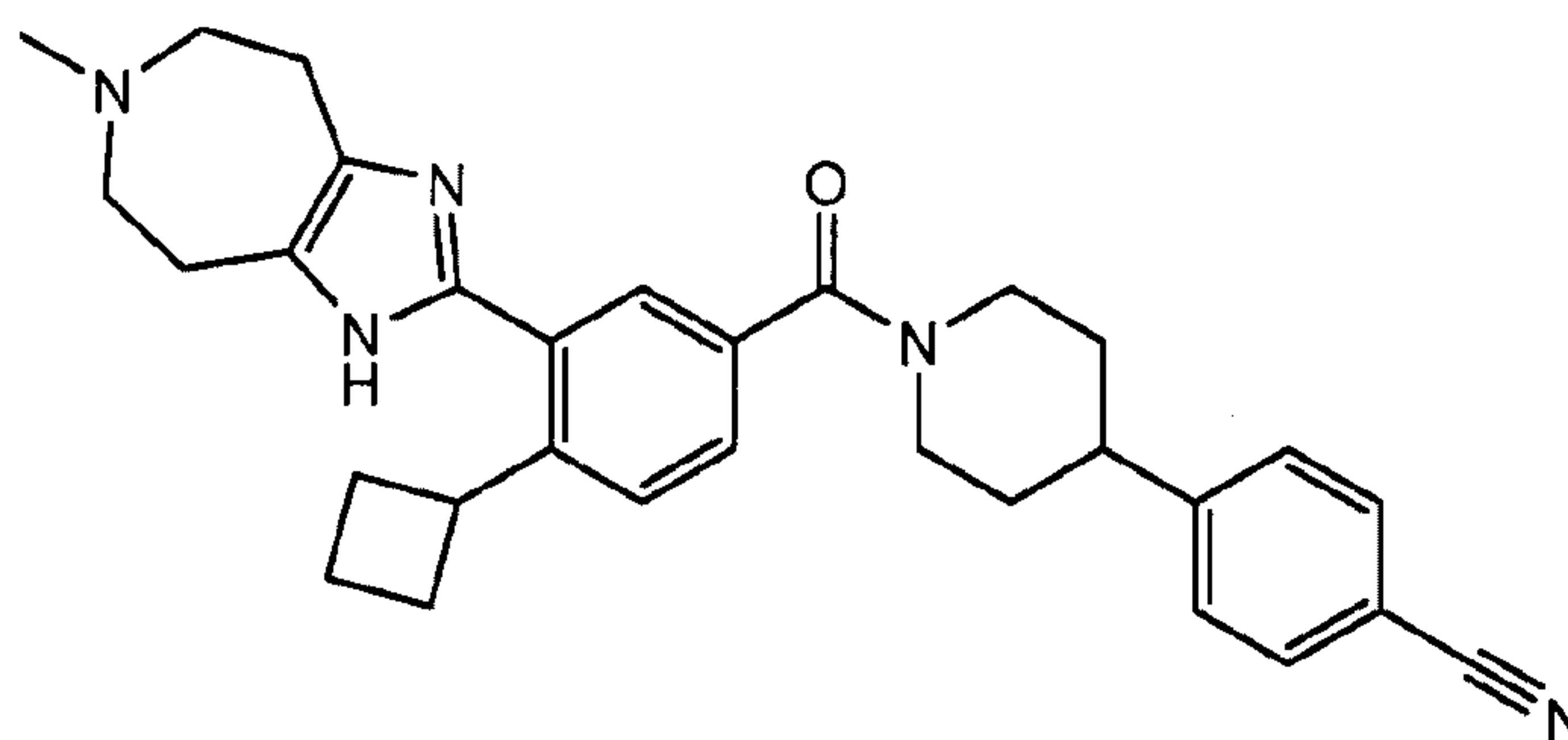
or a pharmaceutically acceptable salt thereof.

67. The compound of claim 1, having the formula:



or a pharmaceutically acceptable salt thereof.

68. The compound of claim 1, having the formula:



or a pharmaceutically acceptable salt thereof.

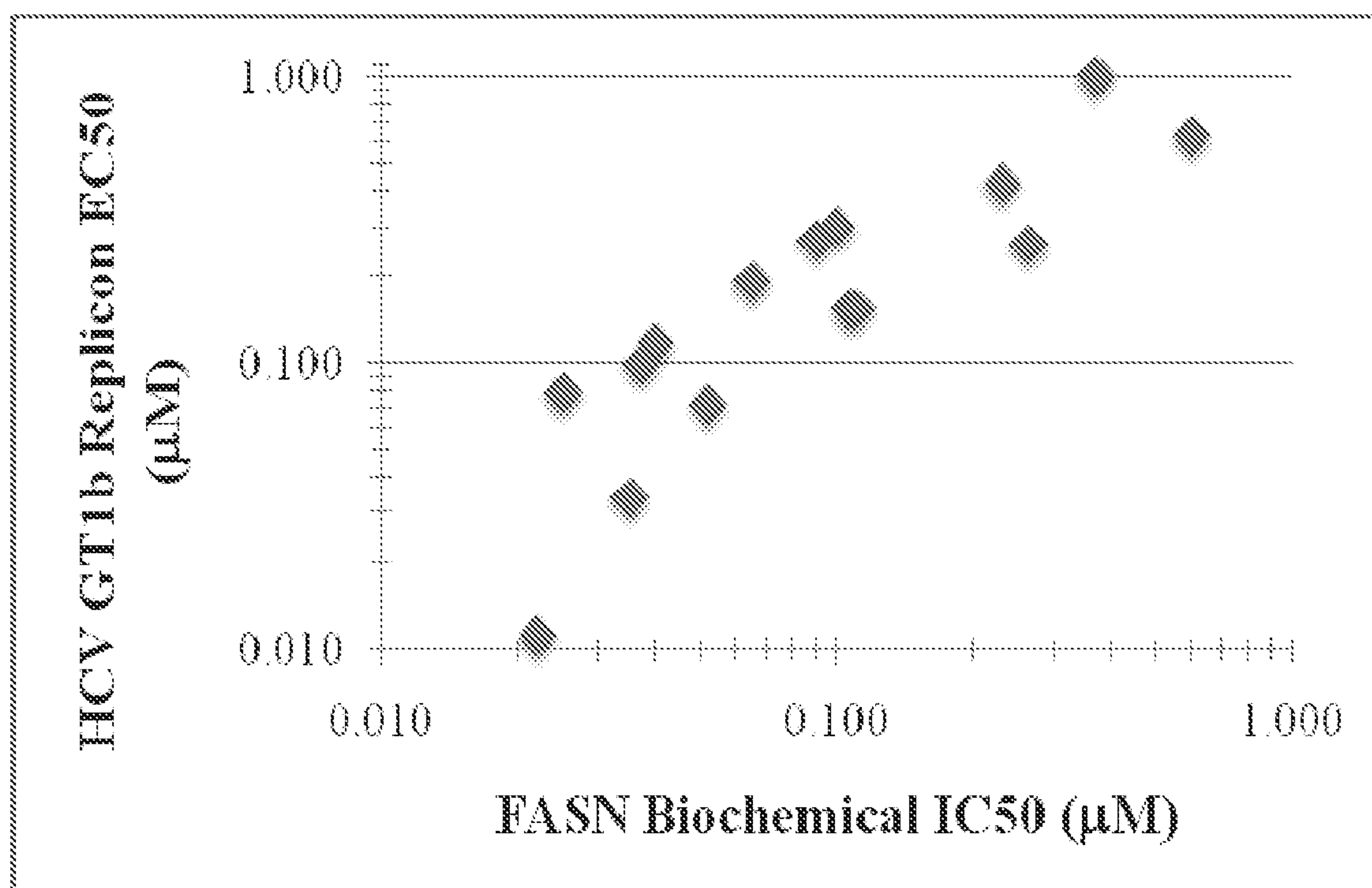


FIG. 1

