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- (54) **BENZOIMIDAZOL-1,2-YL AMIDES AS KV7 CHANNEL ACTIVATORS**
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6,855,714	B2	2/2005	Blume et al.
7,501,447	B2	3/2009	Liu et al.
8,466,201	B2	6/2013	Edwards et al.
9,481,653	B2	11/2016	Resnick et al.
9,650,376	B2	5/2017	Resnick et al.
9,914,708	B2*	3/2018	Harried C07D 235/30
10,106,536	B2	10/2018	Resnick et al.
2003/0109549	A1	6/2003	Ito et al.
2003/0181480	A1	9/2003	McMahon et al.
2006/0069117	A1	3/2006	Rault et al.
2008/0039442	A1	2/2008	Blom et al.
2009/0062290	A1	3/2009	Christos et al.
2011/0124858	A1	5/2011	Iwata et al.
2016/0031875	A1	2/2016	Resnick et al.
2016/0075663	A1	3/2016	Resnick et al.
2017/0114022	A1	4/2017	Harried et al.
2017/0240547	A1	8/2017	Resnick et al.

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This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

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- (60) Provisional application No. 62/050,023, filed on Sep. 12, 2014.

- (51) **Int. Cl.**
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- (52) **U.S. Cl.**
CPC **C07D 235/30** (2013.01); **C07D 401/04** (2013.01); **C07D 401/12** (2013.01); **C07D 403/04** (2013.01); **C07D 405/12** (2013.01); **C07D 413/04** (2013.01)

- (58) **Field of Classification Search**
CPC C07D 235/30
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(56) **References Cited**

U.S. PATENT DOCUMENTS

3,920,669	A	11/1975	Kristinsson et al.
4,002,623	A	1/1977	Kadin
4,247,556	A	1/1981	von Bebenburg et al.
4,391,811	A	7/1983	Leshner et al.

FOREIGN PATENT DOCUMENTS

EP	2218718	A1	8/2010
JP	2001199968	A	7/2001
JP	07072181		8/2015
WO	9601833	A1	1/1996
WO	2001089499	A2	11/2001
WO	2004108712	A1	12/2004
WO	2005021547	A2	3/2005
WO	2007022305	A2	2/2007
WO	2007039297	A1	4/2007
WO	2009085230	A1	7/2009
WO	2010051819	A1	5/2010
WO	20100080503	A1	7/2010
WO	2010094645	A1	8/2010
WO	2011051452	A1	5/2011
WO	2012003576	A1	1/2012
WO	2012004698	A1	1/2012
WO	2012018668	A1	2/2012
WO	2014145852	A2	9/2014

(Continued)

OTHER PUBLICATIONS

Chemical Abstracts Registry No. 1390407-52-9, indexed in the Registry file on STN CAS Online Aug. 13, 2012. (Year: 2012).*

Chemical Abstracts Registry No. 1387901-08-7, indexed in the Registry file on STN CAS Online Aug. 8, 2012. (Year: 2012).*

The Handbook of Pharmaceutical Excipients, Fourth Edition, Raymond C. Rowe, Ed., Pharmaceutical Press and American Pharmaceutical Association, 2003, pp. 219-221. (Year: 2003).*

Internet Archive WayBack Machine, {<https://web.archive.org/web/20111204050304/http://www.uorsy.com:80/screening.php>}, (accessed Dec. 13, 2018), web pages dated Dec. 4, 2011 (Year: 2011).*

(Continued)

Primary Examiner — Laura L Stockton

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(57) **ABSTRACT**

Optionally substituted benzoimidazol-1,2-yl amides, such as compounds of Formula 1 or Formula 2, can be used to treat disorders associated with a Kv7 potassium channel activator. Compositions, medicaments, and dosage forms related to the treatment are also disclosed herein.

16 Claims, No Drawings

(56)

References Cited

FOREIGN PATENT DOCUMENTS

WO	2016040952	A3	5/2016
WO	2018081825	A1	5/2018

OTHER PUBLICATIONS

Langguth, et al. "Potassium channels as promising new targets for pharmacologic treatment of tinnitus: Can Internet-based 'crowd sensing' initiated by patients speed up the transition from bench to bedside?" (2016): 251-254.

Orhan; Expert Opin. Pharmacother. 2012, 13, 1807-1816.

Chemical Abstracts Registry No. 689297-99-2, indexed in the Registry file on STN CAS Online Jun. 4, 2004.

Chemical Abstracts Registry No. 1298059-85-4, indexed in the Registry file on STN CAS Online May 20, 2011.

Dadiboyena et al., Synthesis, 2012, 44(2), pp. 215-218.

Chemical Abstracts Registry No. 1370729-32-0, indexed in the Registry file on STN CAS Online Apr. 27, 2012.

An English translation of JP 07/072181 B (Goto et al.), 1995.

Chemical Abstracts Registry No. 1445709-80-7, indexed in the Registry file on STN CAS Online Jul. 19, 2013.

PubChem CID 21428920, National Center for Biotechnology Information. PubChem Compound Database; CID=21428920, <https://pubchem.ncbi.nlm.nih.gov/compound/21428920> (accessed Apr. 27, 2016), create date Dec. 5, 2007.

PubChem CID 60339539, National Center for Biotechnology Information. PubChem Compound Database; CID=60339539, <https://pubchem.ncbi.nlm.nih.gov/compound/60339539> (accessed Apr. 27, 2016), create date Oct. 18, 2012.

PubChem CID 60339611, National Center for Biotechnology Information. PubChem Compound Database; CID=60339611, <https://pubchem.ncbi.nlm.nih.gov/compound/60339611> (accessed Apr. 27, 2016), create date Oct. 18, 2012.

PubChem CID 47251124, National Center for Biotechnology Information. PubChem Compound Database; CID=47251124, <https://pubchem.ncbi.nlm.nih.gov/compound/47251124> (accessed Apr. 27, 2016), create date Nov. 26, 2010.

PubChem CID 52655712, National Center for Biotechnology Information. PubChem Compound Database; CID=52655712, <https://pubchem.ncbi.nlm.nih.gov/compound/52655712> (accessed Apr. 27, 2016), create date May 20, 2011.

PubChem CID 53531705, National Center for Biotechnology Information. PubChem Compound Database; CID=53531705, <https://pubchem.ncbi.nlm.nih.gov/compound/53531705> (accessed Apr. 27, 2016), create date Dec. 3, 2011.

International Search Report and Written Opinion dated Mar. 2, 2016 for International Application No. PCT/US2015/050027 filed on Sep. 14, 2015.

Pubchem. Substance Record for SID 128950369. Deposit Date: Dec. 4, 2011. [retrieved on Oct. 15, 2015]. Retrieved from the Internet. <URL: <https://pubchem.ncbi.nlm.nih.gov/substance/128950369/version/1>>. entire document.

Pubchem. Substance Record for SID 131669753. Deposit Date: Jan. 24, 2012. [retrieved on Nov. 30, 2015]. Retrieved from the Internet. <URL: <https://pubchem.ncbi.nlm.nih.gov/substance/131669753/version/1#section=To-p>>. entire document.

Pubchem. Substance Record for SID 131669753. Deposit Date: Jan. 24, 2012. [retrieved on Nov. 30, 2015]. Retrieved from the Internet. <URL: <https://pubchem.ncbi.nlm.nih.gov/substance/131669753/version/1#section=To-p>>. entire document.

SciFinder Search. , No Date Available.

SciFinder Search 2. , No Date Available.

SciFinder Search 3. , No Date Available.

Dadiboyena, et al. "Parallel synthesis of aminobenzimidazole-tethered thiazoles." Synthesis 44, No. 02 (2012): 215-218.

Ding et al. "Aryl-substituted aminobenzimidazoles targeting the hepatitis C virus internal ribosome entry site." Bioorganic & medicinal chemistry letters 24, No. 14 (2014): 3113-3117.

Ding et al: "Aryl-substituted aminobenzimidazoles targeting the hepatitis C virus internal ribosome entry site", Bioorganic & Medicinal Chemistry Letters, vol. 24, No. 14, May 14, 2014 (May 14, 2014), pp. 3113-3117, XP029033865, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2014.05.009; * compounds 4ba, 4ca *.

Supplementary European Search Report for European Patent Application No. 15840730.4 dated Jan. 8, 2018.

Descours et al. "New Tricyclic Compounds: Pyrido[2',3':4,5]-andPyrido[3',4,5]-Imidazo[1,2-a]Pyrimidines" 1990, Heterocycles 31(2)259-265.

Hasegawa et al. "Discovery of Novel Benzimidazoles as Potent Inhibitors of TIE-2 and VEGFR-2 Tyrosine Kinase Receptors" Aug. 4, 2007, J. Med. Chem. 50(18):4453-4470.

International Search Report and Written Opinion dated Jul. 31, 2018 for PCT/US2018/032050 filed on May 10, 2018.

International Search Report and Written Opinion dated Sep. 18, 2014 for PCT/US2014/030686 filed on Mar. 17, 2014.

Xiong et al. "Activation of Kv7 (KCNQ) Voltage-gated Potassium Channels by Synthetic Compounds" Feb. 2008, Trends in Pharmacol. Sci. 29(2):99-107.

Weller et al. "The Idiopathic Hypereosinophilic Syndrome" 1994, Blood 83(10):2759-2779.

Supplementary European Search Report dated Aug. 8, 2016 for EP 14765415.6.

STN Chemical Abstracts for Registry Nos. 1145687-44-0, 1145686-94-7, 1145686-93-6, 1145686-91-4, 1145686-90-3, 1145686-79-8, 1145686-4104, 1145686-39-0 and 1145686-29-8 all entered on May 12, 2009.

Sorensen et al. "Synthesis and Structure-Activity Relationship Studies of 2-(N-Substituted)-aminobenzimidazoles as Potent Negative Gating Modulators of Small Conductance Ca²⁺-Activated K⁺ Channels" Dec. 11, 2008, 51(23):7625-7634.

Munro et al. "Kv7 (KCNQ) Channel Modulators and Neuropathic Pain" May 31, 2007, J. Med. Chem. 50(11):2576-2582.

International Search Report and Written Opinion for PCT/US2017/059393 dated Feb. 28, 2018.

Watanabe et al. "Disruption of the Epilepsy KCNQ2 Gene Results in Neural Hyperexcitability" 2000, J. Neurochem. 75:28-33.

International Search Report and Written Opinion for PCT/US2018/058425 dated Mar. 18, 2019.

* cited by examiner

**BENZOIMIDAZOL-1,2-YL AMIDES AS KV7
CHANNEL ACTIVATORS**

CROSS-REFERENCE TO RELATED CASES

The present application is a continuation of U.S. patent application Ser. No. 15/339,590, (U.S. Publication No. 2017-0114022 A1) filed Oct. 31, 2016, which is a continuation of U.S. patent application Ser. No. 14/853,815, (U.S. Publication No. 2016-0075663 A1) filed Sep. 14, 2015, now U.S. Pat. No. 9,481,653, issued Nov. 1, 2016, which claims the benefit of U.S. Provisional application No. 62/050,023, filed Sep. 12, 2014, the entire disclosures of which are incorporated herein by reference.

BACKGROUND

Potassium (K^+) channels, present on the plasma membranes of most cell types, are the most diverse class of all ion channels and are associated with a wide range of physiological functions including the regulation of the electrical properties of excitable cells. The primary pore-forming (α) subunits of these highly selective cation channels are divided into three primary structural classes based on the number of transmembrane (TM)-spanning regions and pore (P) regions: currently there are known to be 6TM/1P, 2TM/1P and 4TM/2P K^+ channels. The Kv7 genes (originally termed KCNQ, a name assigned by the HUGO Gene Nomenclature Committee (HGNC)) were assigned to a subfamily of voltage-gated K^+ channels by the International Union of Pharmacology (IUPHAR). The Kv7 subfamily consists of five homologous pore-forming subunits, Kv7.1-7.5, that have a structure typical of voltage-gated K^+ channels with 6TM-spanning regions (S1-S6) flanked by intracellular N-terminal and C-terminal domains, a typical voltage-sensor domain located in S4 comprised of alternating positively-charged residues and a single P region between S5 and S6 of each subunit. The channels are formed as tetramers of the primary subunits, either as homotetramers or heterotetramers. Neurons are known to express Kv7 channels comprised of Kv7.2-7.5 α subunits. Some of these gene products may be exclusively neuronal while others, such as Kv7.4 and Kv7.5, can be found in other tissues such as smooth and skeletal muscle.

Native M-channels, and the corresponding macroscopic M-current, were first characterized in amphibian sympathetic neurons. M-channels were notable because they were slowly activating and non-inactivating, active at membrane potentials at or near the resting membrane potential of neurons and muscarinic cholinergic agonists produced a reduction in the M-current, demonstrating a direct and inhibitory link between G-protein coupled receptors (GPCRs) and a physiological K^+ current. It was not until the cloning of this subfamily of genes that the pharmacological and biophysical identity was established between Kv7.2/7.3 (and likely Kv7.5/7.3) heteromultimers and the elusive 'M'-channel, providing significant new evidence for their importance in neuronal regulation.

The distributions of these channels, both regionally and developmentally, as well as their biophysical characteristics, support their role in providing enduring resistance to depolarizing excitatory influences. Under physiological conditions, as was demonstrated with native M-channels, they can be very effective at regulating the sub-threshold excitability of certain neuronal populations with significant roles in regulating the frequency and ultimately the pattern of action potential discharge in many types of neurons. Their impor-

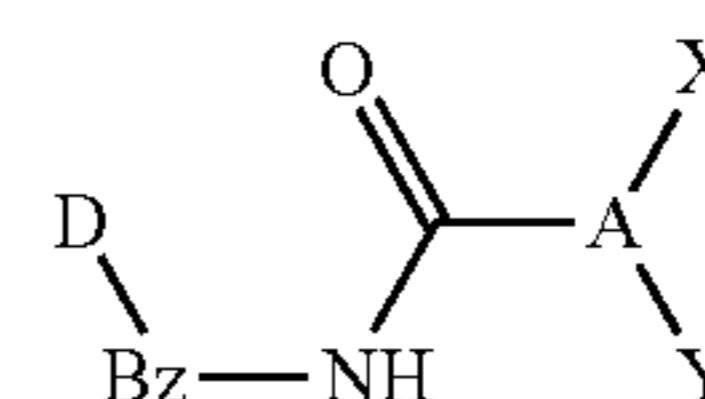
tance in neuronal regulation was punctuated by the discovery that neuronal Kv7 mutations lead to benign familial neonatal convulsions (BFNC) indicating that reduction or removal of the influence of Kv7.2 and Kv7.3 channels can dramatically alter neuronal excitability. Mutation analyses demonstrated their involvement in BFNC and suggested their utility as targets for anti-epileptic drugs (AEDs).

Unlike established pharmacological terminology for GPCRs, the mode of action of K^+ channel modulators, in particular compounds that activate the channel, is still being refined. The application of voltage-clamp techniques to the study of ion channel pharmacology enabled detailed biophysical studies on either whole-cell currents or single channels, allowing some characterization of the nature of compound-channel interactions but not preventing ongoing confusion around the terminology. The term opener or activator is commonly used throughout the literature but does not adequately describe the mode of action of all these 'positive modulator' compounds. In general, openers or activators are expected to increase the open probability of the channel or increase macroscopic current amplitude, but this nomenclature is really too simplistic. For example, retigabine, the first publicly disclosed Kv7 opener, has a complex and interesting profile in that it has inhibitory activity at higher membrane potentials. Neuronal Kv7 channel openers may work in concert with the activity of a channel over the 'normal' activation-voltage range and enhance currents without significantly affecting the activation threshold while others can significantly alter the activation threshold. In addition, some openers appear to remove the voltage-dependence of activation entirely. Whether these effects represent some continuum is currently unclear since the effects are often concentration-dependent. Clearly, the modes of interaction of compounds that can increase channel current are complex and in most cases not well understood and the implications of these profiles on neuronal responsiveness and systems physiology are also unclear. Retigabine is modestly potent, not highly specific, but it is a very effective opener of Kv7.2, Kv7.5 and heteromultimeric Kv7 channels. Its effects are characterized by a significant increase in channel current over a narrow voltage range. As mentioned above, at more positive voltages the opener is less effective and under some conditions channel current significantly decreases at more positive voltages relative to control currents (this 'crossover' voltage-dependence of opener action is a characteristic of many neuronal Kv7 channel openers). This effect is also concentration-dependent and is more pronounced at higher concentrations.

SUMMARY

Described herein are compounds that can be potent and/or at least biased for the Kv7.2/7.3 heteromultimer over the Kv7.4 homomultimer. These compounds may have reduced untoward side effects as compared to retigabine.

Some embodiments include a compound represented by Formula 1:



Formula 1

3

wherein D is optionally substituted C₃₋₆ carbocyclyl, C₂₋₅ heterocyclyl, or C₁₋₄ alkyl; Bz is optionally substituted benzoimidazol-1,2-diyl or optionally substituted benzoimidazol-1,2,6-triyl; A is C₁₋₈ alkyl; X is H, F, CF₃, optionally substituted phenyl, or optionally substituted pyridinyl; and Y is H, F, Cl, Br, I, or a moiety having a molecular weight of 15 Da to 300 Da and consisting of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br.

Some embodiments include a composition comprising a compound described herein, such as a compound of Formula 1 or Formula 2, wherein the composition is pharmaceutically acceptable.

Some embodiments include a pharmaceutical dosage form comprising a compound described herein, such as a compound of Formula 1 or Formula 2.

Some embodiments include a method of treating a disorder associated with a Kv7 potassium channel activator comprising administering an effective amount of a compound described herein, such as a compound of Formula 1 or Formula 2, to a mammal in need thereof.

Some embodiments include use of a compound of Formula 1 or Formula 2, in the manufacture of a medicament for the treatment of a disorder associated with a Kv7 potassium channel activator.

DETAILED DESCRIPTION

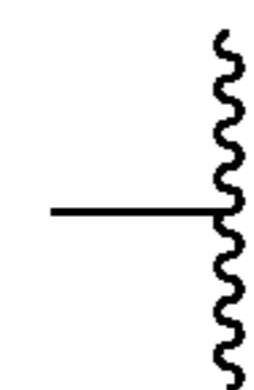
Unless otherwise indicated, when a compound or chemical structural feature such as benzoimidazol-1,2-yl is referred to as being “optionally substituted,” it includes a feature that has no substituents (i.e. unsubstituted), or a feature that is “substituted,” meaning that the feature has one or more substituents. The term “substituent” has the broadest meaning known to one of ordinary skill in the art and includes a moiety that replaces one or more hydrogen atoms attached to a parent compound or structural feature. In some embodiments, a substituent may be an ordinary organic moiety known in the art, which may have a molecular weight (e.g. the sum of the atomic masses of the atoms of the substituent) of 15 Da to 50 Da, 15 Da to 100 Da, 15 Da to 150 Da, 15 Da to 200 Da, 15 Da to 300 Da, or 15 Da to 500 Da. In some embodiments, a substituent comprises, or consists of: 0-30, 0-20, 0-10, or 0-5 carbon atoms; and 0-30, 0-20, 0-10, or 0-5 heteroatoms, wherein each heteroatom may independently be: N, O, S, Si, F, Cl, Br, or I; provided that the substituent includes one C, N, O, S, Si, F, Cl, Br, or I atom. Examples of substituents include, but are not limited to, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, acyl, acyloxy, alkylcarboxylate, thiol, alkylthio, cyano, halo, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxyl, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, etc.

For convenience, the term “molecular weight” is used with respect to a moiety or part of a molecule to indicate the sum of the atomic masses of the atoms in the moiety or part of a molecule, even though it may not be a complete molecule.

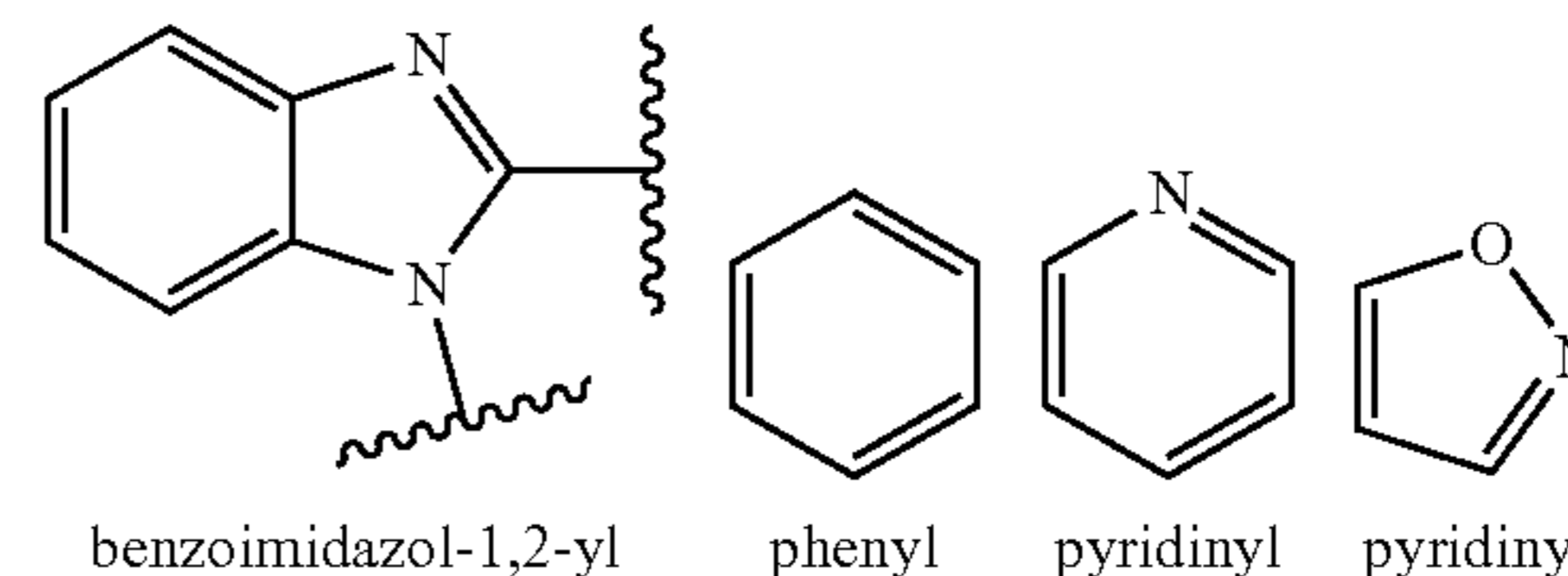
The structures associated with some of the chemical names referred to herein are depicted below. These structures may be unsubstituted, as shown below, or a substituent may independently be in any position normally occupied by

4

a hydrogen atom when the structure is unsubstituted. Unless a point of attachment is indicated by



attachment may occur at any position normally occupied by a hydrogen atom.



As used herein, the term “alkyl” has the broadest meaning generally understood in the art and may include a moiety composed of carbon and hydrogen containing no double or triple bonds. Alkyl may be linear alkyl, branched alkyl, cycloalkyl, or a combination thereof and in some embodiments, may contain from one to thirty-five carbon atoms. In some embodiments, alkyl may include C₁₋₁₀ linear alkyl, such as methyl (—CH₃), methylene (—CH₂—), ethyl (—CH₂CH₃), ethylene (—C₂H₄—), propylene (—C₃H₆—), n-butyl (—CH₂CH₂CH₂CH₃), n-pentyl (—CH₂CH₂CH₂CH₂CH₃), n-hexyl (—CH₂CH₂CH₂CH₂CH₂CH₃), etc.; C₃₋₁₀ branched alkyl, such as C₃H₇ (e.g. isopropyl), C₄H₉ (e.g. branched butyl isomers), C₅H₁₁ (e.g. branched pentyl isomers), C₆H₁₃ (e.g. branched hexyl isomers), C₇H₁₅ (e.g. heptyl isomers), etc.; C₃₋₁₀ cycloalkyl, such as C₃H₅ (e.g. cyclopropyl), C₄H₇ (e.g. cyclobutyl isomers such as cyclobutyl, methylcyclopropyl, etc.), C₅H₉ (e.g. cyclopentyl isomers such as cyclopentyl, methylcyclobutyl, dimethylcyclopropyl, etc.) C₆H₁₁ (e.g. cyclohexyl isomers), C₇H₁₃ (e.g. cycloheptyl isomers), etc.; and the like.

As used herein, the term “carbocyclyl” has the broadest meaning generally understood in the art and includes rings free of heteroatoms, such as cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.; cycloalkenyl, e.g. cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl; cycloalkynyl, e.g. cyclopropynyl, cyclobutylnyl, cyclopentynyl, cyclohexynyl; as well as aryl rings free of heteroatoms.

As used herein the term “aryl” has the broadest meaning generally understood in the art and may include an aromatic ring or aromatic ring system such as phenyl, naphthyl, etc.

The term “heterocyclyl” includes any ring or ring system containing a heteroatom such as N, O, S, P, etc. Heterocyclyl includes heteroaryl rings or ring systems (such as those listed below) and non-aromatic rings or ring systems. Examples of non-aromatic heterocyclyl include azetidiny, oxatany, thietany, pyrrolidinyl, tetrahydrofuranyl, thiolanyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, dioxalanyl, dithiolanyl, tetrahydropyranly, piperidinyl, piperazinyl, morpholino, etc.

The term “heteroaryl” also has the meaning understood by a person of ordinary skill in the art and includes an “aryl” which has one or more heteroatoms in the ring or ring system, such as pyridinyl, furyl, thienyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, oxadiazolyl, isoxazolyl, indolyl, qui-

5

nolinyl, benzofuranyl, benzothienyl, benzooxazolyl, benzothiazolyl, benzoimidazolyl, etc.

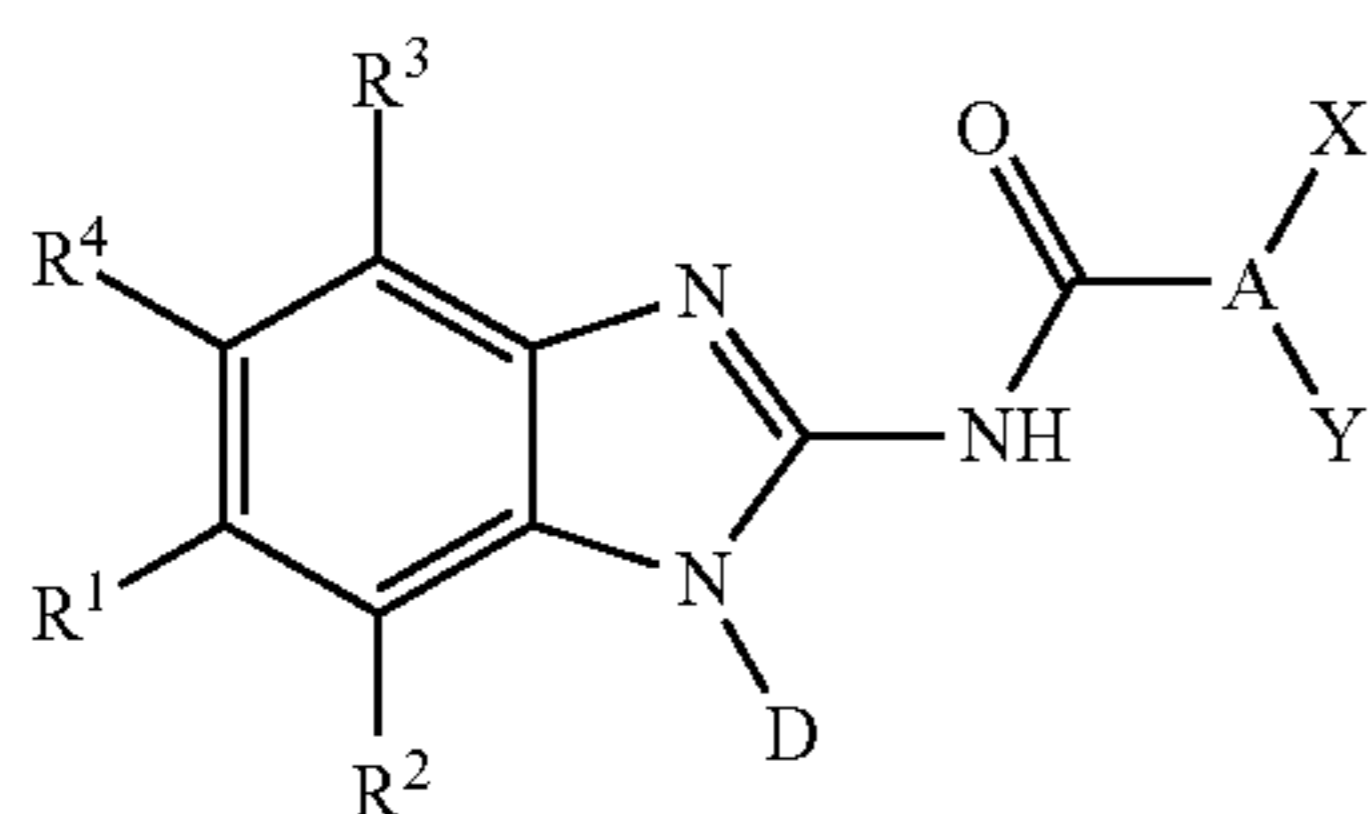
Unless otherwise indicated, any reference to a compound herein by structure, name, or any other means includes pharmaceutically acceptable salts, such as HCl, HBr, HI, H₂SO₄, acetate, citrate, sodium, potassium, and ammonium salts; prodrugs, such as ester prodrugs; alternate solid forms, such as polymorphs, solvates, hydrates, etc.; tautomers; or any other chemical species that may rapidly convert to a compound described herein under conditions in which the compounds are used as described.

If stereochemistry is not indicated, a name or structural representation includes any stereoisomer or any mixture of stereoisomers.

With respect to Formula 1, Bz can be optionally substituted benzoimidazol-1,2-yl. If the benzoimidazol-1,2-yl is substituted, it may have 1, 2, 3, or 4 substituents. Any substituent may be included on the benzoimidazol-1,2-yl. In some embodiments, some or all of the substituents on the benzoimidazol-1,2-yl may have: from 0 to 10 carbon atoms and from 0 to 10 heteroatoms, wherein each heteroatom is independently: O, N, S, F, Cl, Br, or I (provided that there is at least 1 non-hydrogen atom); and/or a molecular weight of 15 g/mol to 500 g/mol. In some embodiments, some or all of the substituents may each have a molecular weight of 15 Da to 200 Da, 15 Da to 100 Da, or 15 Da to 50 Da, and consist of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br. In some embodiments, Bz can be optionally substituted benzoimidazol-1,2-diyl. In some embodiments, Bz can be optionally substituted benzoimidazol-1, 2, 6-triyl.

For example, with respect to Formula 1, the substituents of Bz may be C₁₋₁₀ optionally substituted alkyl, such as CH₃, C₂H₅, C₃H₇, cyclic C₃H₅, C₄H₉, cyclic C₄H₇, C₅H₁₁, cyclic C₅H₉, C₆H₁₃, cyclic C₆H₁₁, etc., which may be optionally substituted; C₁₋₁₀ optionally substituted alkoxy such as OCH₃, OC₂H₅, OC₃H₇, cyclic OC₃H₅, OC₄H₉, cyclic OC₄H₇, OC₅H₁₁, cyclic OC₅H₉, OC₆H₁₃, cyclic OC₆H₁₁, etc.; halo, such as F, Cl, Br, I; OH; CN; NO₂; C₁₋₆ fluoroalkyl, such as CF₃, CF₂H, C₂F₅, etc.; C₁₋₆ fluoroalkoxy, such as OCF₃, OCF₂H, OC₂F₅, etc.; a C₁₋₁₀ ester such as —O₂CCH₃, —CO₂CH₃, —O₂CC₂H₅, —CO₂C₂H₅, —O₂C-phenyl, —CO₂-phenyl, etc.; a C₁₋₁₀ ketone such as —COCH₃, —COC₂H₅, —COC₃H₇, —CO-phenyl, etc.; or a C₁₋₁₀ amine such as NH₂, NH(CH₃), N(CH₃)₂, N(CH₃)C₂H₅, etc. In some embodiments, a substituent of Bz may be F, Cl, Br, I, CN, NO₂, C₁₋₄ alkyl, C₁₋₄ alkyl-OH, C₁₋₃ O-alkyl, CF₃, COH, C₁₋₄ CO-alkyl, CO₂H, C₁₋₄ CO₂-alkyl, NH₂, or C₁₋₄ alkylamino.

Some embodiments include a compound represented by Formula 2:



Formula 2

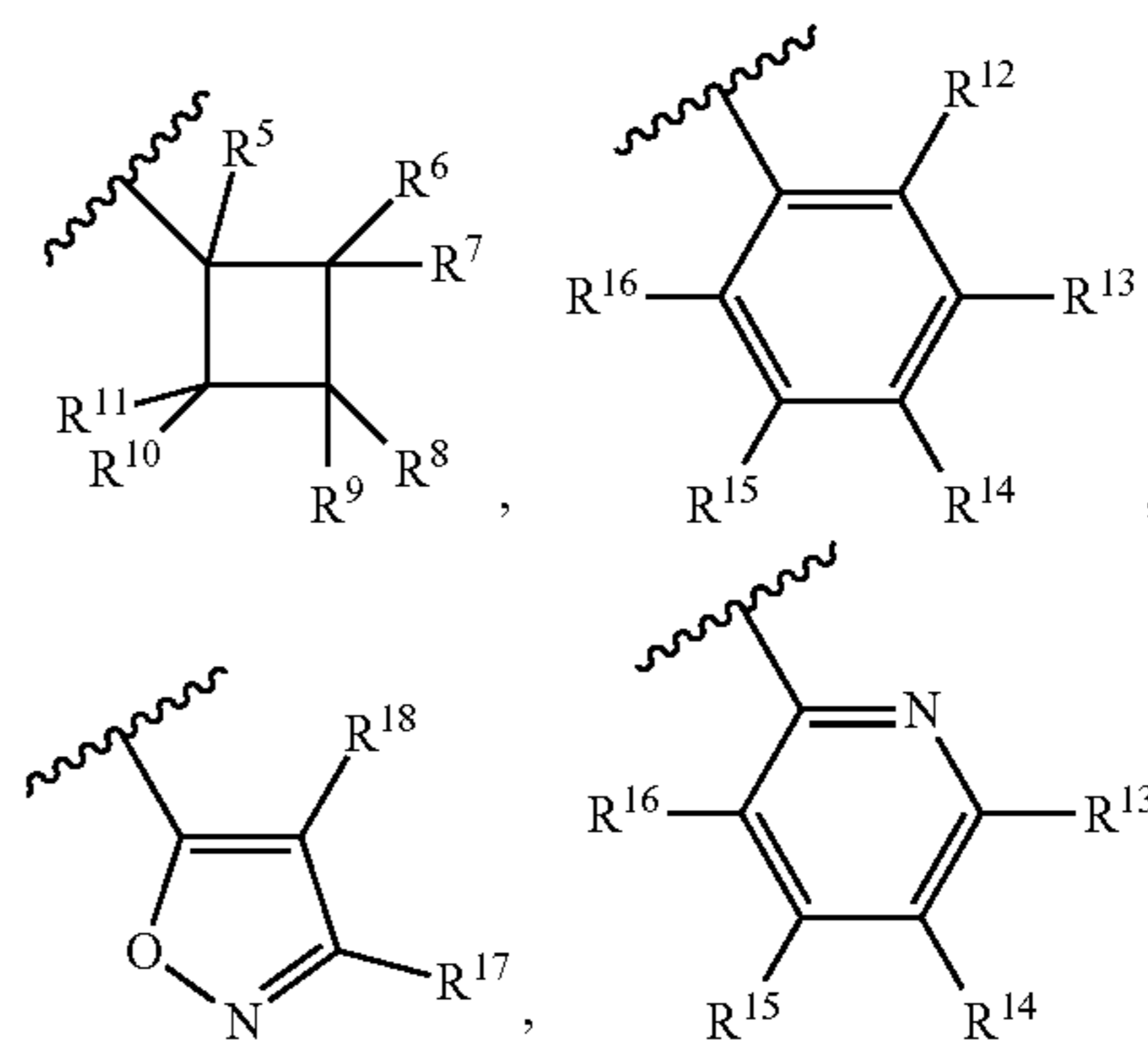
With respect to any relevant structural representation, such as Formula 1 or 2, D is optionally substituted C₃₋₆ carbocyclyl or C₂₋₅ heterocyclyl. If D is substituted cyclobutyl, it may have 1, 2, 3, 4, 5, 6, or 7 substituents. If D is

6

substituted phenyl, it may have 1, 2, 3, 4, or 5 substituents. If D is substituted isoxazolyl, it may have 1 or 2. D may include any substituent. In some embodiments, some or all of the substituents of D may have: from 0 to 10 carbon atoms and from 0 to 10 heteroatoms, wherein each heteroatom is independently: O, N, S, F, Cl, Br, or I (provided that there is at least 1 non-hydrogen atom); and/or a molecular weight of 15 g/mol to 500 g/mol. In some embodiments, some or all of the substituents may each have a molecular weight of 15 Da to 200 Da, 15 Da to 100 Da, or 15 Da to 50 Da, and consist of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br.

For example, with respect to any relevant structural representation, such as Formula 1 or 2, the substituents of D may be C₁₋₁₀ optionally substituted alkyl, such as CH₃, C₂H₅, C₃H₇, cyclic C₃H₅, C₄H₉, cyclic C₄H₇, C₅H₁₁, cyclic C₅H₉, C₆H₁₃, cyclic C₆H₁₁, etc., which may be optionally substituted; C₁₋₁₀ optionally substituted alkoxy such as OCH₃, OC₂H₅, OC₃H₇, cyclic OC₃H₅, OC₄H₉, cyclic OC₄H₇, OC₅H₁₁, cyclic OC₅H₉, OC₆H₁₃, cyclic OC₆H₁₁, etc.; halo, such as F, Cl, Br, I; OH; CN; NO₂; C₁₋₆ fluoroalkyl, such as CF₃, CF₂H, C₂F₅, etc.; C₁₋₆ fluoroalkoxy, such as OCF₃, OCF₂H, OC₂F₅, etc.; a C₁₋₁₀ ester such as —O₂CCH₃, —CO₂CH₃, —O₂CC₂H₅, —CO₂C₂H₅, —O₂C-phenyl, —CO₂-phenyl, etc.; a C₁₋₁₀ ketone such as —COCH₃, —COC₂H₅, —COC₃H₇, —CO-phenyl, etc.; or a C₁₋₁₀ amine such as NH₂, NH(CH₃), N(CH₃)₂, N(CH₃)C₂H₅, etc. In some embodiments, a substituent of D may be F, Cl, Br, I, CN, NO₂, C₁₋₄ alkyl, C₁₋₄ alkyl-OH, C₁₋₃ O-alkyl, CF₃, COH, C₁₋₄ CO-alkyl, CO₂H, C₁₋₄ CO₂-alkyl, NH₂, or C₁₋₄ alkylamino.

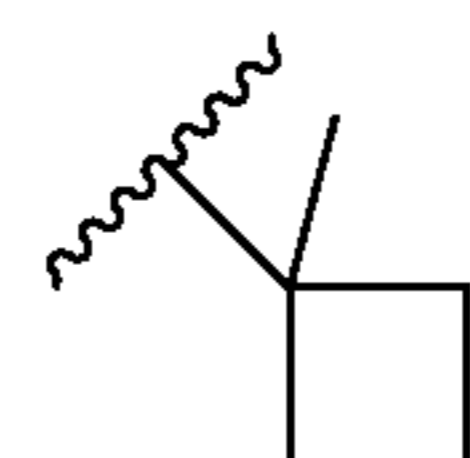
With respect to any relevant structural representation, such as Formula 1 or 2, in some embodiments, D is:



or optionally substituted C₂₋₄ alkyl.

With respect to any relevant structural representation, such as Formula 1 or 2, in some embodiments, D is optionally substituted cyclobutyl, optionally substituted phenyl, optionally substituted isoxazolyl, or isopropyl.

With respect to any relevant structural representation, such as Formula 1 or 2, in some embodiments, D is optionally substituted cyclobutyl. In some embodiments, D is cyclobutyl. In some embodiments, D is

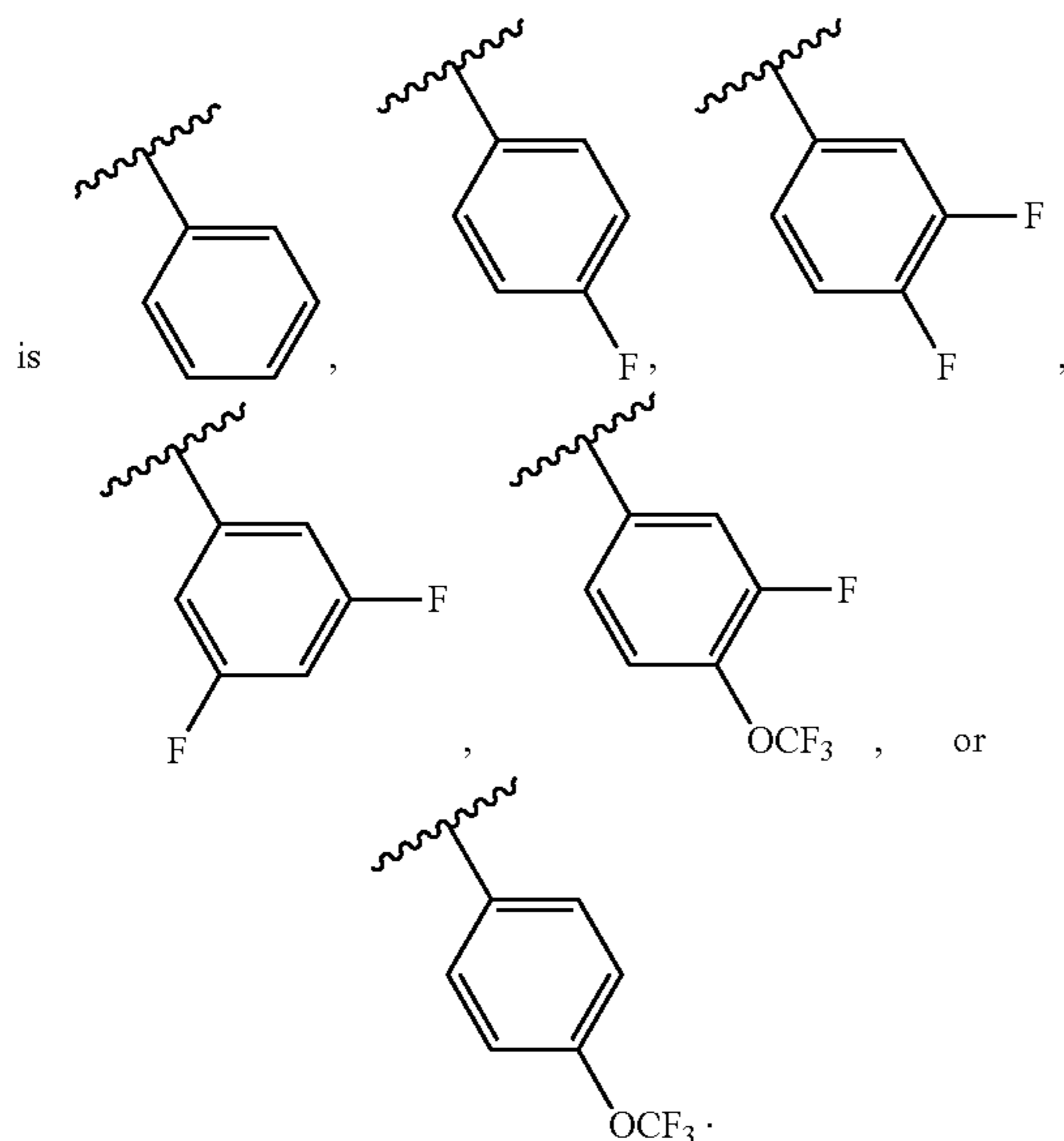


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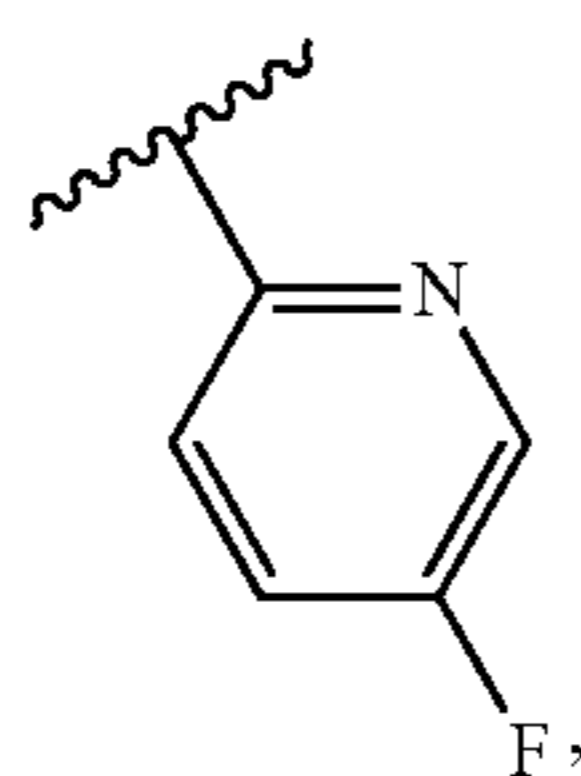
With respect to any relevant structural representation, such as Formula 1 or 2, in some embodiments, D is isopropyl.

With respect to any relevant structural representation, such as Formula 1 or 2, in some embodiments, D is t-butyl, or tert-butyl.

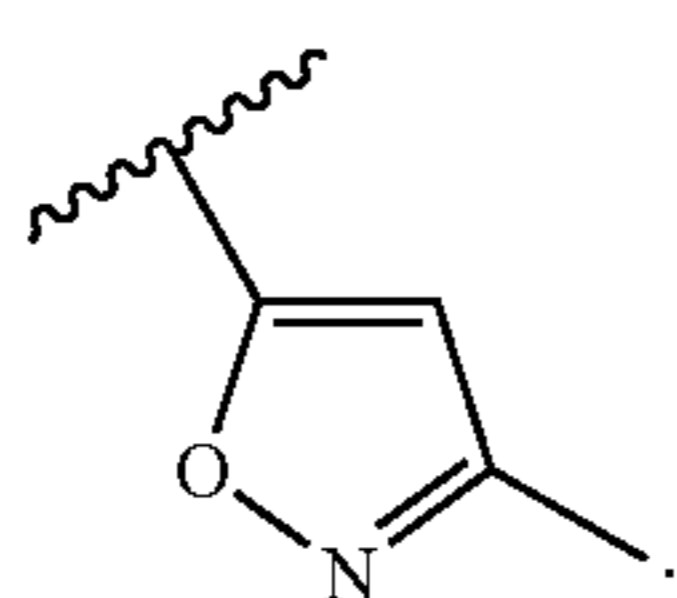
With respect to any relevant structural representation, such as Formula 1 or 2, in some embodiments, D is optionally substituted phenyl. In some embodiments D



With respect to any relevant structural representation, such as Formula 1 or 2, in some embodiments, D is optionally substituted pyridinyl, such as optionally substituted pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl. In some embodiments, D is

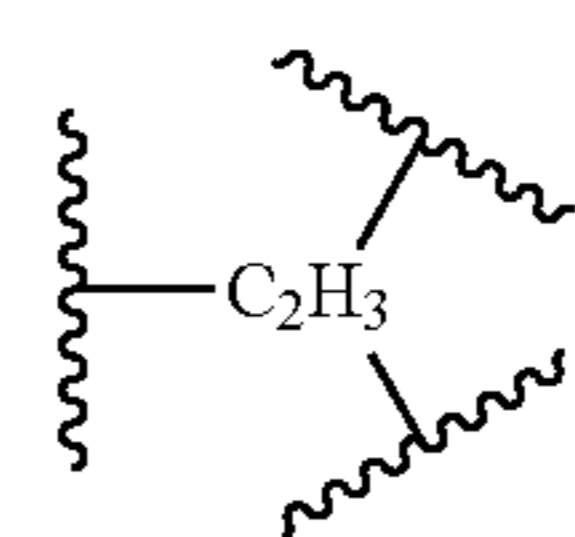


With respect to any relevant structural representation, such as Formula 1 or 2, in some embodiments, D is optionally substituted isoxazolyl. In some embodiments, D is

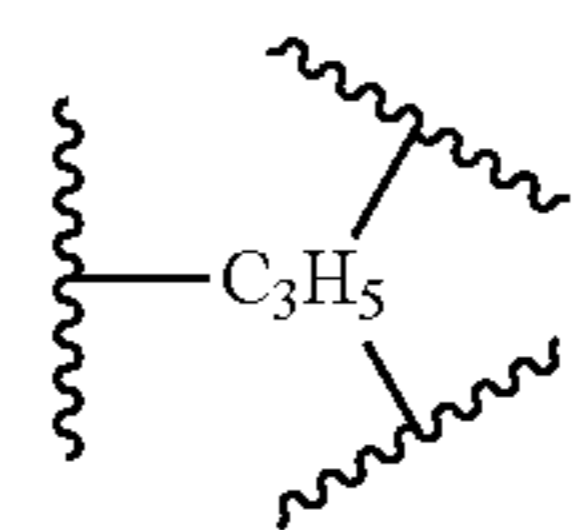


With respect to any relevant structural representation, such as Formula 1 or 2, A is C₂₋₈ alkyl, such as linear or branched

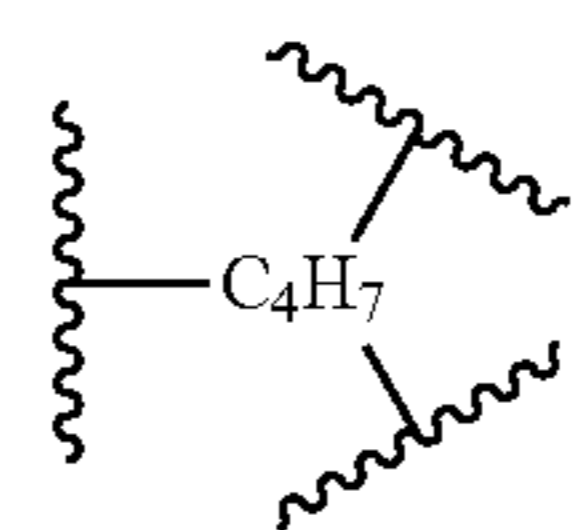
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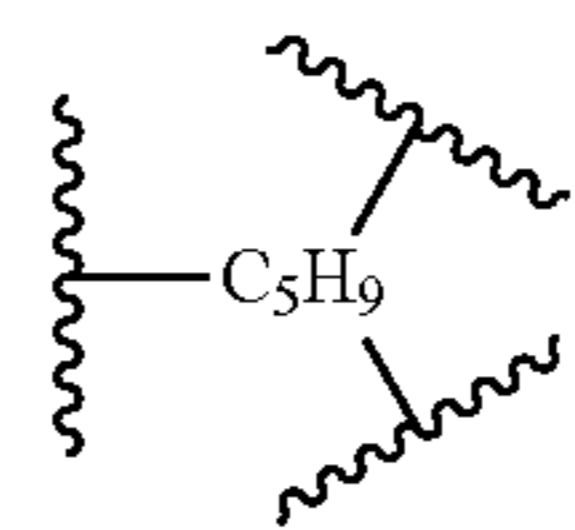
linear or branched



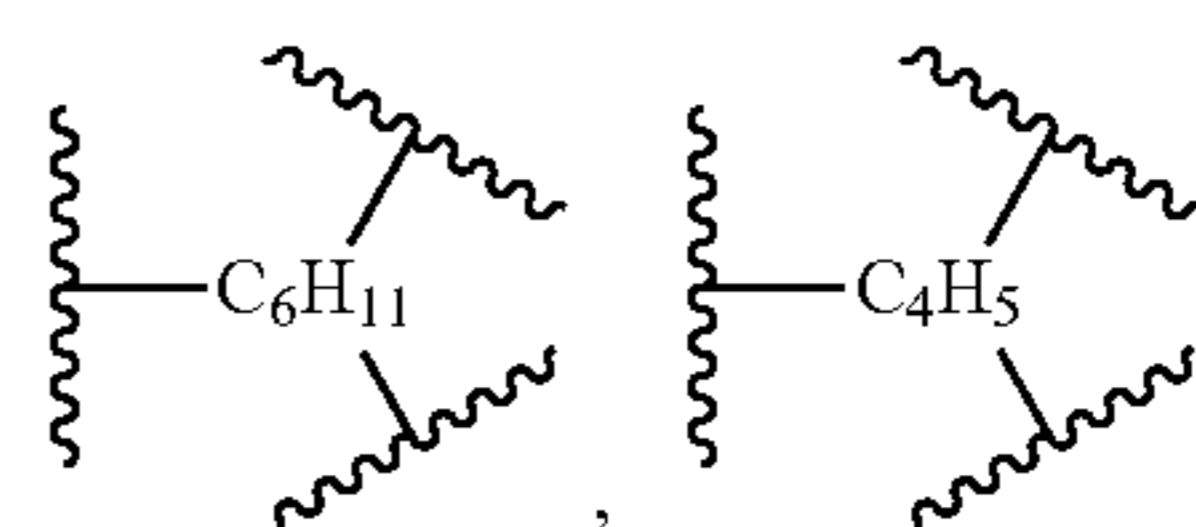
linear or branched



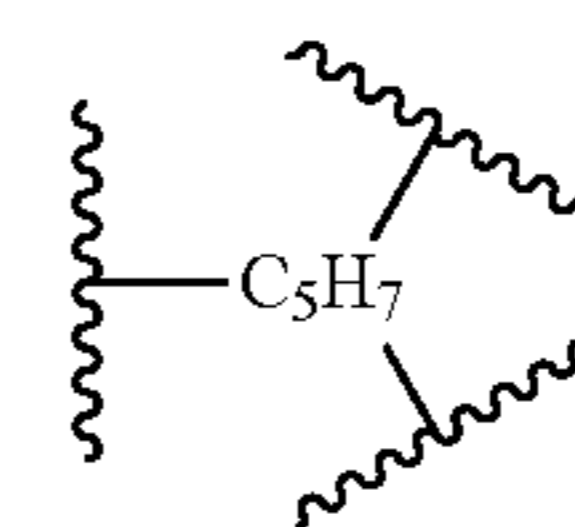
linear or branched



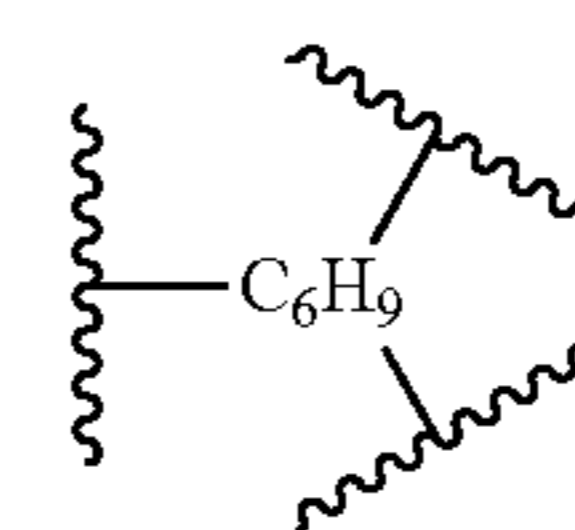
linear or branched



containing one ring,

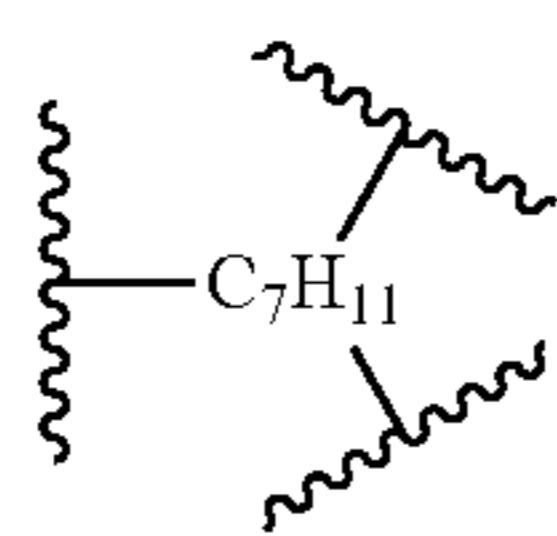


containing one ring,

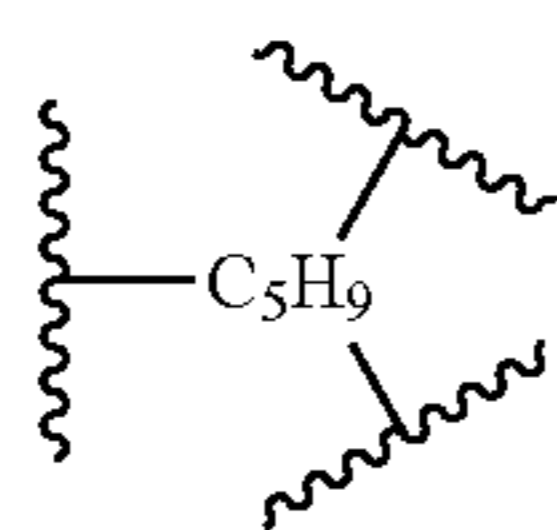


containing one ring,

9



containing one ring, or



containing a bicyclic ring system.

With respect to any relevant structural representation, such as Formula 1 or 2, X is H, F, CF₃, optionally substituted phenyl, or optionally substituted pyridinyl. In some embodiments, X is H. In some embodiments, X is F. In some embodiments, X is CF₃.

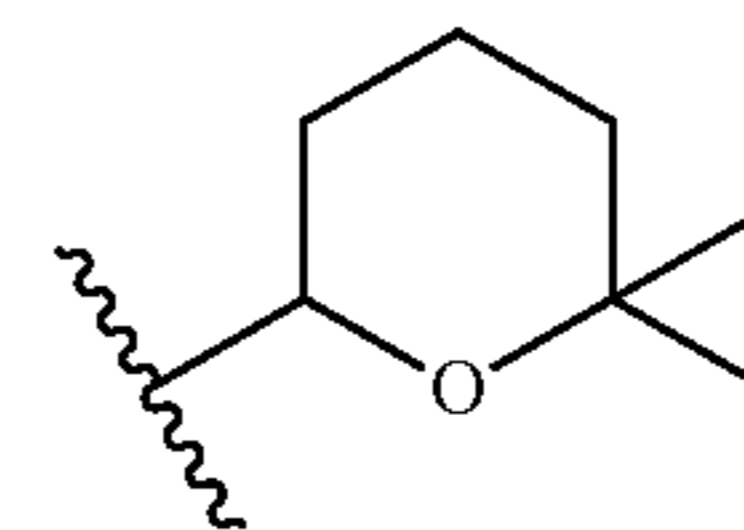
With respect to any relevant structural representation, such as Formula 1 or 2, if X is substituted phenyl, it may have 1, 2, 3, 4, or 5, substituents. If X is substituted pyridinyl, it may have 1, 2, 3, or 4 substituents. In some embodiments, some or all of the substituents of X may have: from 0 to 10 carbon atoms and from 0 to 10 heteroatoms, wherein each heteroatom is independently: O, N, S, F, Cl, Br, or I (provided that there is at least 1 non-hydrogen atom); and/or a molecular weight of 15 g/mol to 500 g/mol. In some embodiments, some or all of the substituents may each have a molecular weight of 15 Da to 200 Da, 15 Da to 100 Da, or 15 Da to 50 Da, and consist of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br.

For example, with respect to any relevant structural representation, such as Formula 1 or 2, the substituents of X may be C₁₋₁₀ optionally substituted alkyl, such as CH₃, C₂H₅, C₃H₇, cyclic C₃H₅, C₄H₉, cyclic C₄H₇, C₅H₁₁, cyclic C₅H₉, C₆H₁₃, cyclic C₆H₁₁, etc., which may be optionally substituted; C₁₋₁₀ optionally substituted alkoxy such as OCH₃, OC₂H₅, OC₃H₇, cyclic OC₃H₅, OC₄H₉, cyclic OC₄H₇, OC₅H₁₁, cyclic OC₅H₉, OC₆H₁₃, cyclic OC₆H₁₁, etc.; halo, such as F, Cl, Br, I; OH; CN; NO₂; C₁₋₆ fluoroalkyl, such as CF₃, CF₂H, C₂F₅, etc.; C₁₋₆ fluoroalkoxy, such as OCF₃, OCF₂H, OC₂F₅, etc.; a C₁₋₁₀ ester such as —O₂CCH₃, —CO₂CH₃, —O₂CC₂H₅, —CO₂C₂H₅, —O₂C-phenyl, —CO₂-phenyl, etc.; a C₁₋₁₀ ketone such as —COCH₃, —COC₂H₅, —COC₃H₇, —CO-phenyl, etc.; or a C₁₋₁₀ amine such as NH₂, NH(CH₃), N(CH₃)₂, N(CH₃)C₂H₅, etc. In some embodiments, a substituent of X may be F, Cl, Br, I, CN, NO₂, C₁₋₄ alkyl, C₁₋₄ alkyl-OH, C₁₋₃ O-alkyl, CF₃, COH, C₁₋₄ CO-alkyl, CO₂H, C₁₋₄ CO₂-alkyl, NH₂, or C₁₋₄ alkylamino.

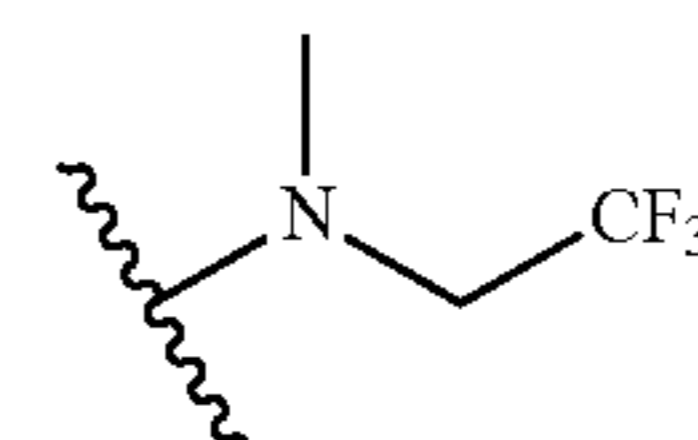
With respect to any relevant structural representation, such as Formula 1 or 2, Y is H, F, Cl, Br, I, or a moiety having a molecular weight of 15 Da to 300 Da and consisting of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br. In some embodiments, Y is H, F, Cl, Br, I, CN, —COH, C₁₋₆ —CO-alkyl, CF₃, OH, C₁₋₅ O-alkyl, C₀₋₆ amino, or C₀₋₆ fluoroamino. In some embodiments, Y is H, F, CF₃, OH, C₁₋₅ O-alkyl, C₀₋₆ amino, or C₀₋₆ fluoroamino. In some embodiments, Y is H. In some embodiments, Y is OH. In some embodiments, Y is F. In some embodiments, Y is CF₃. In

10

some embodiments, Y is C₁₋₃ O-alkyl, such as —OCH₃, OC₂H₅, OC₃H₇, etc. In some embodiments, Y is C₀₋₆ fluoroamino. In some embodiments, Y is optionally substituted tetrahydropyranyl, such as

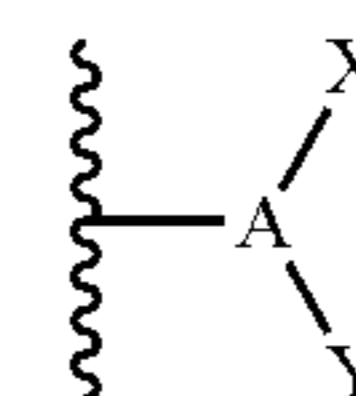


In some embodiments Y may include a C₁₋₈ alkyl that may include one or two C₃₋₆ carbocyclyl rings. In some embodiments, wherein Y includes at least one carbocyclyl rings, the rings may be connected to each other. In some embodiments, Y is —C(CF₃)₂OH (or 1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl). In some embodiments Y is

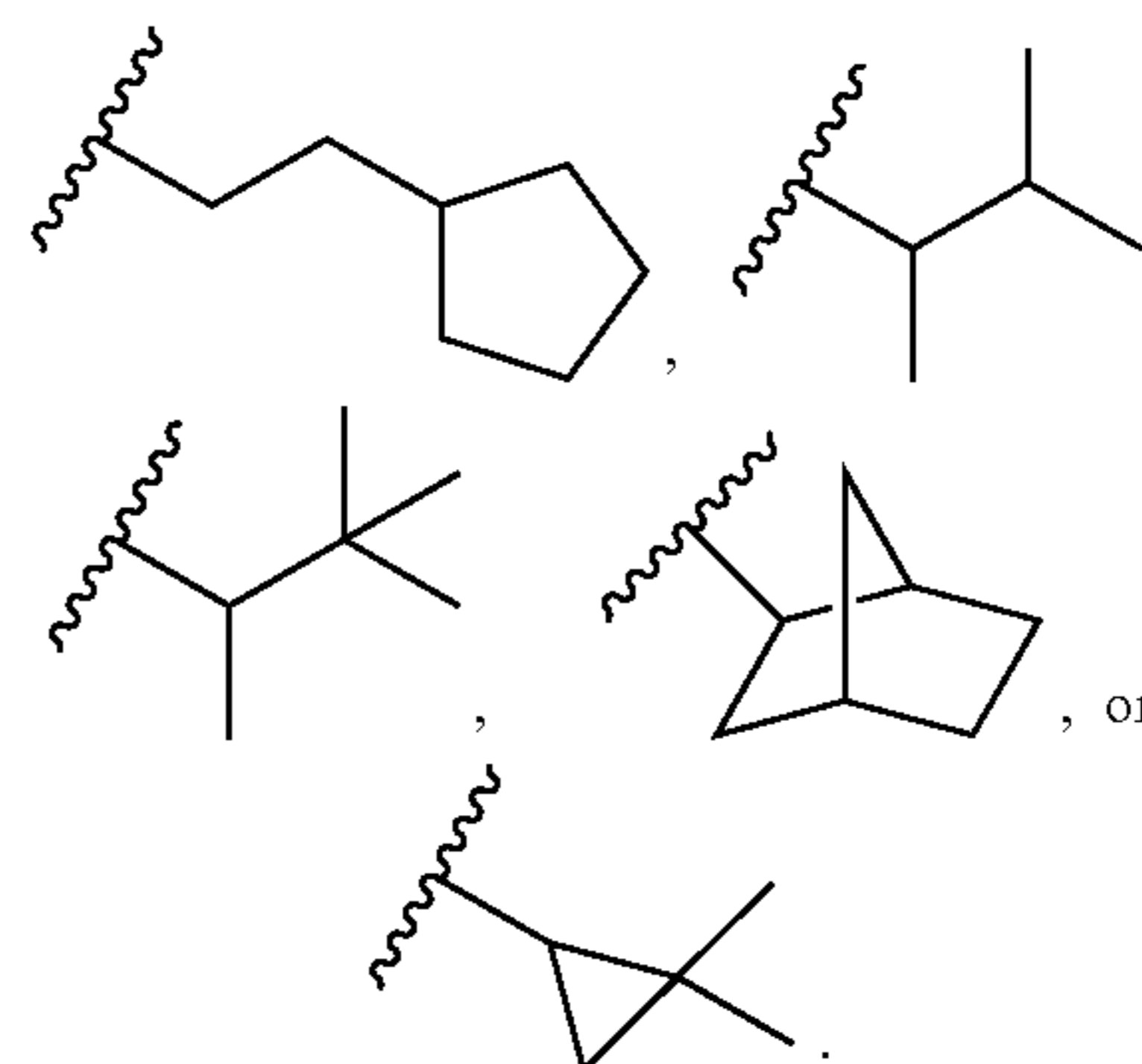


(or methyl(2,2,2-trifluoroethyl)amino). In some embodiments, Y is dimethylamino.

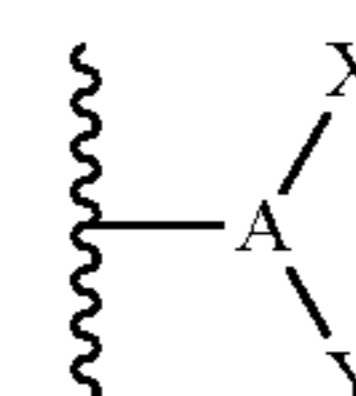
With respect to any relevant structural representation, such as Formula 1 or 2, in some embodiments



is C₂₋₈ alkyl, such as

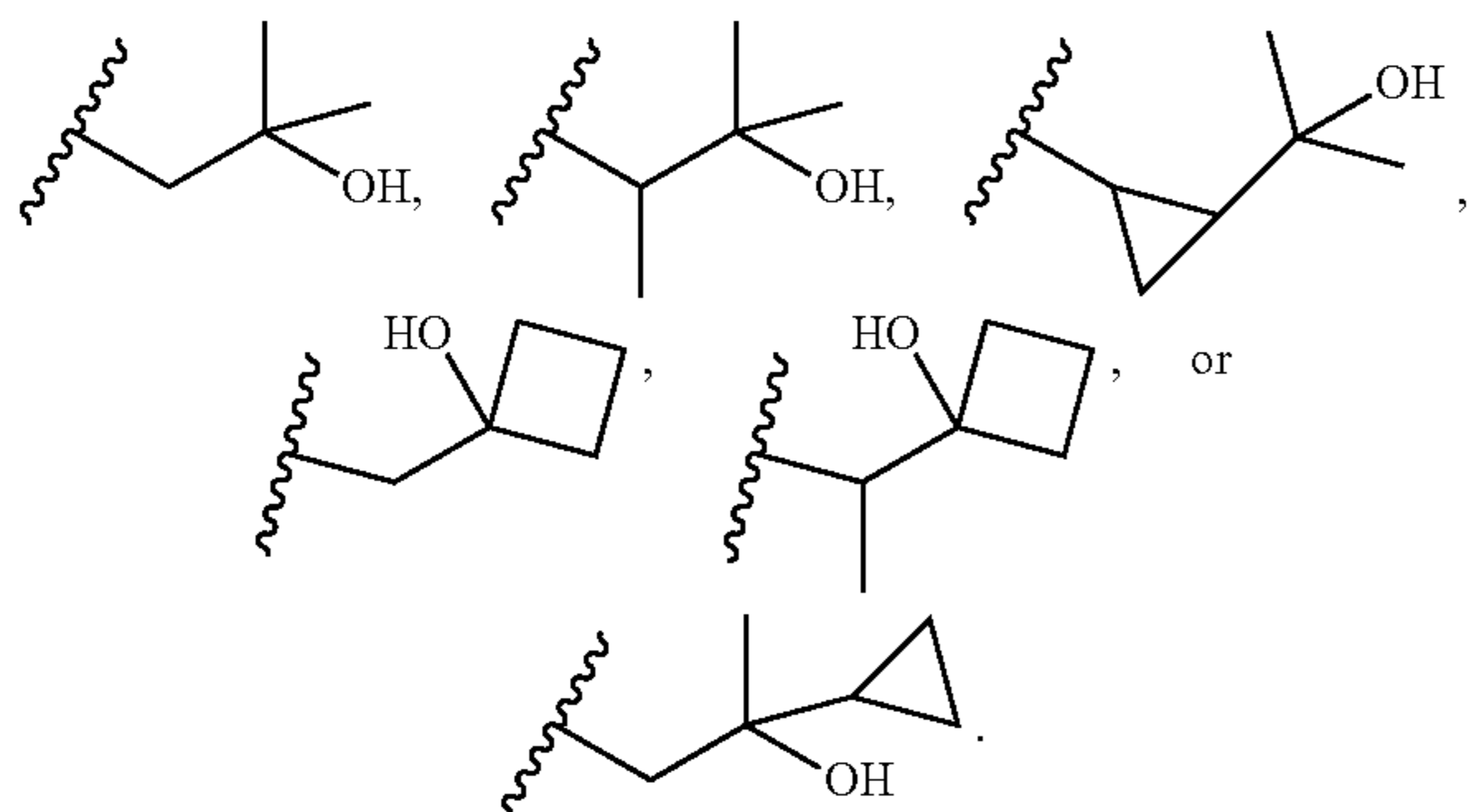


With respect to any relevant structural representation, such as Formula 1 or 2, in some embodiments

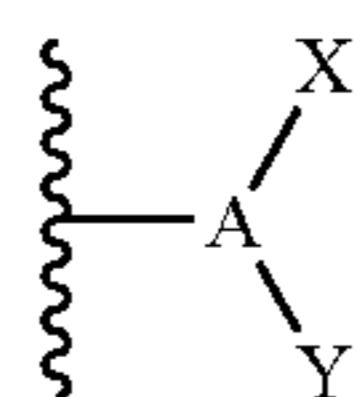


11

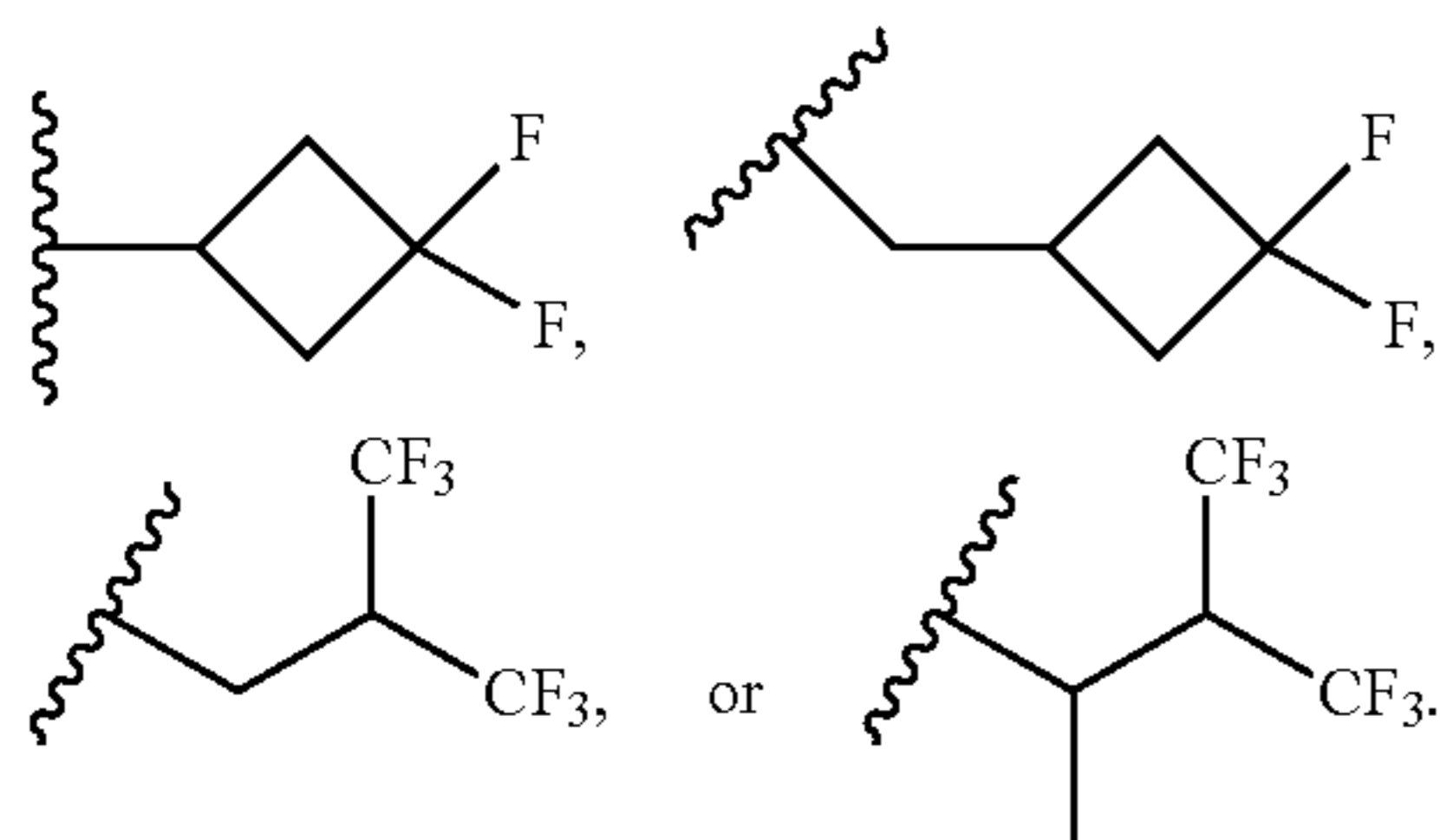
is C₂₋₈ hydroxyalkyl, such as



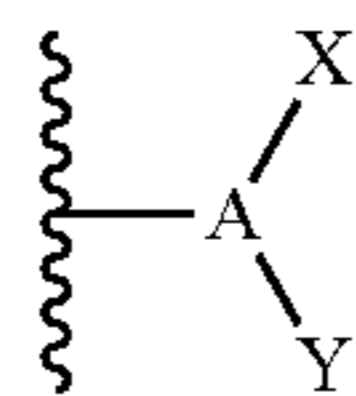
With respect to any relevant structural representation, such as Formula 1 or 2, in some embodiments



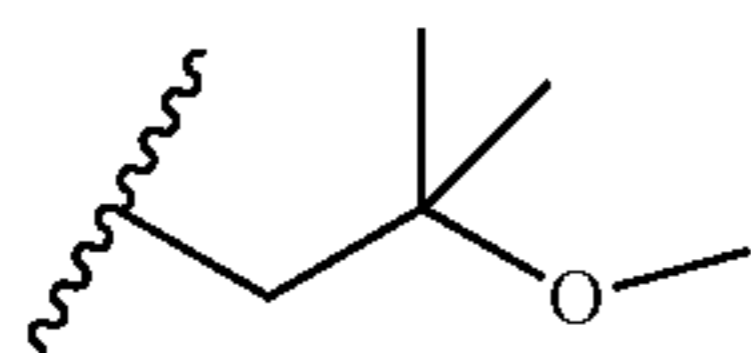
is C₂₋₈ fluoroalkyl such as



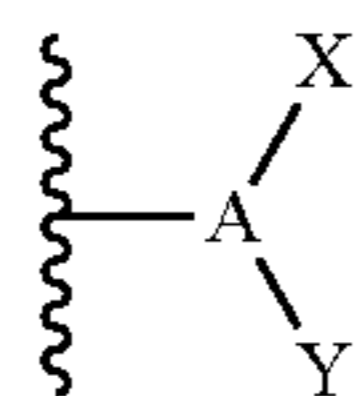
With respect to any relevant structural representation, such as Formula 1 or 2, in some embodiments



is C₂₋₈ alkoxyalkyl, such as

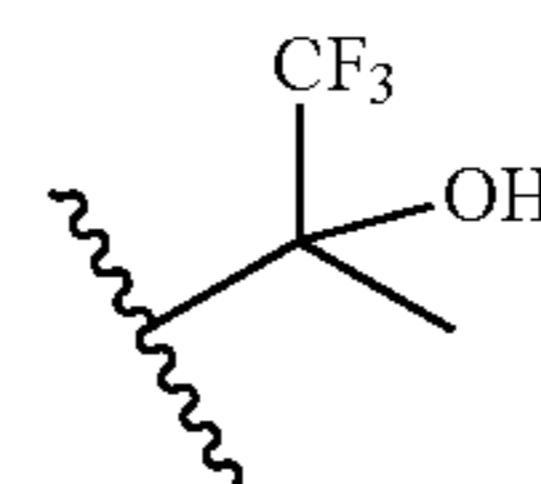


With respect to any relevant structural representation, such as Formula 1 or 2, in some embodiments

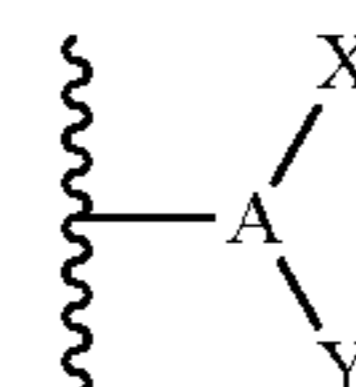


12

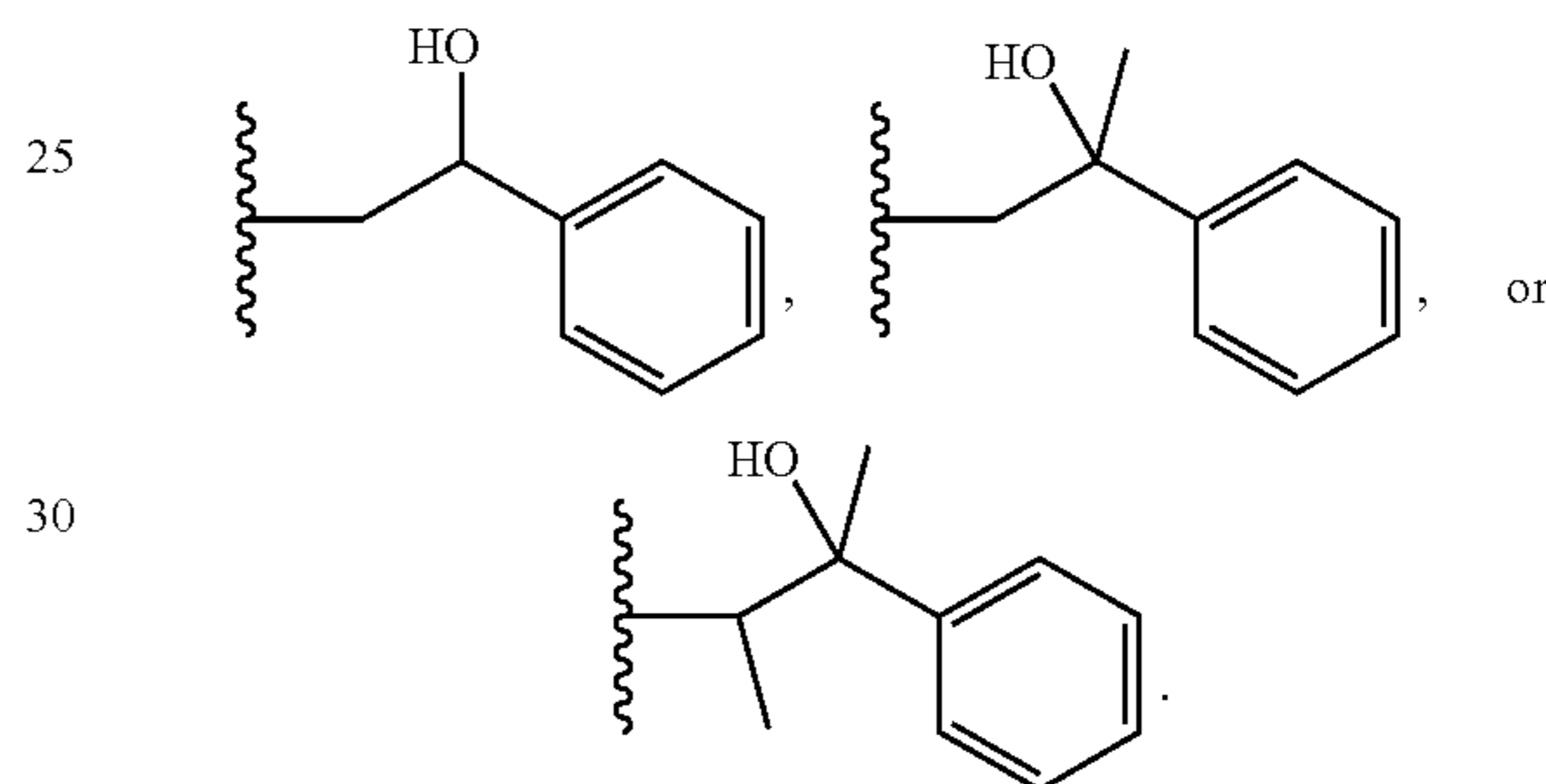
is C₂₋₈ hydroxyfluoroalkyl, such as



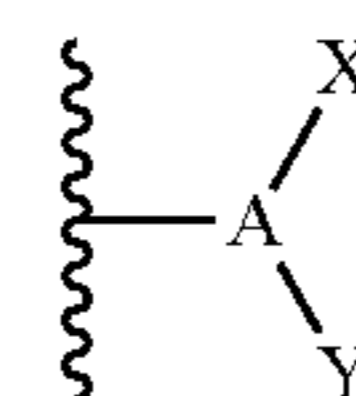
With respect to any relevant structural representation, such as Formula 1 or 2, in some embodiments



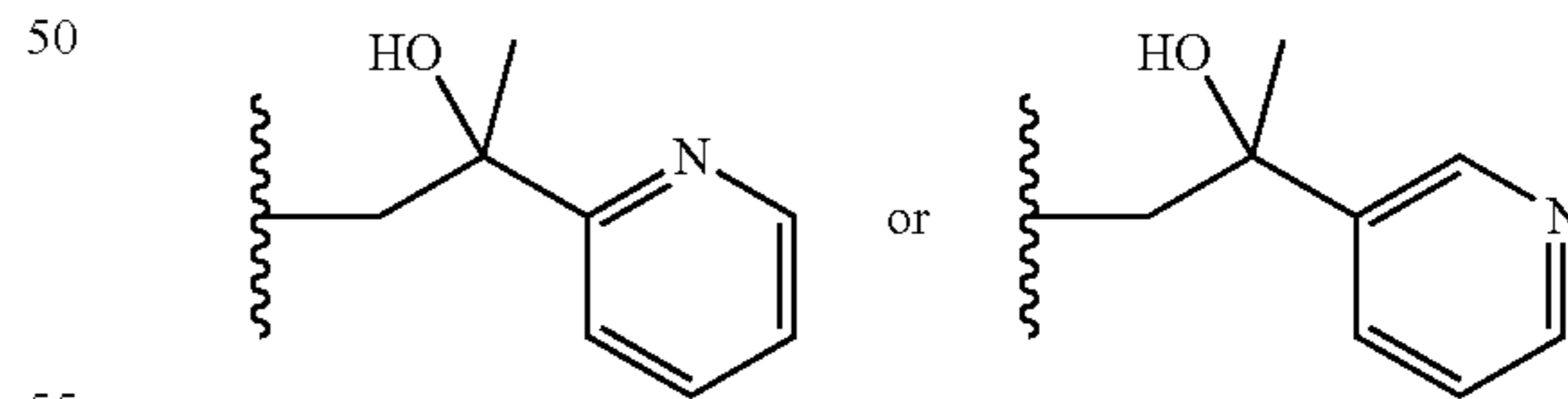
is optionally substituted 2-hydroxy-2-phenylethyl, such as



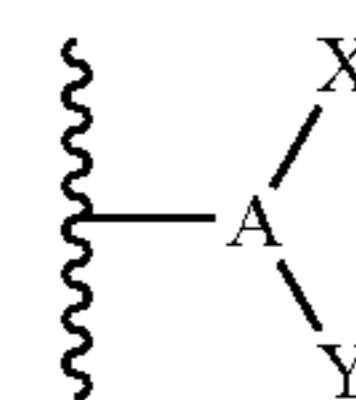
With respect to any relevant structural representation, such as Formula 1 or 2, in some embodiments



is optionally substituted 2-hydroxy-2-phenylpyridinyl, such as

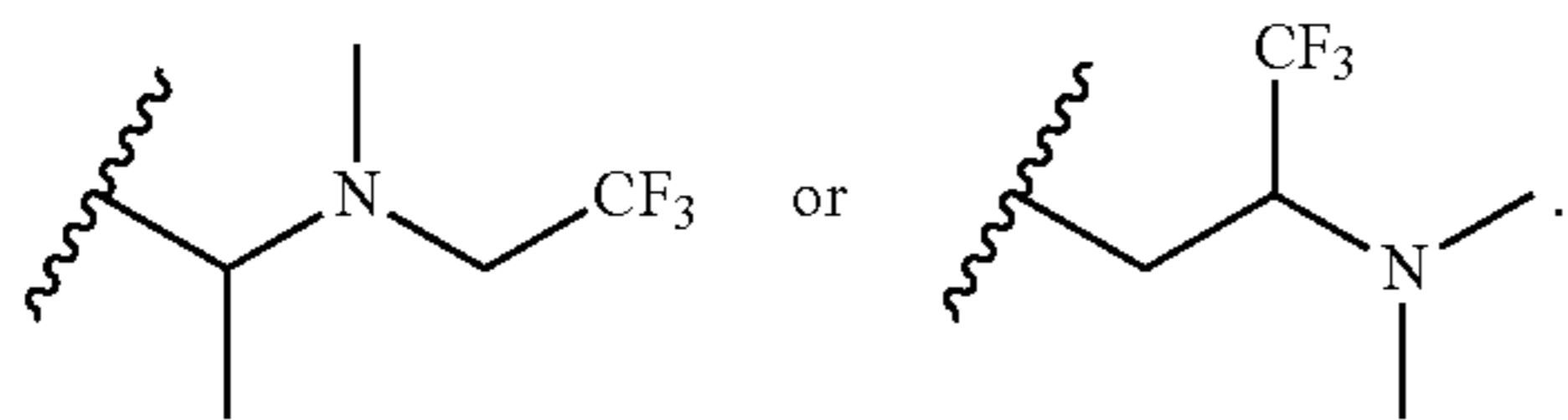


With respect to any relevant structural representation, such as Formula 1 or 2, in some embodiments



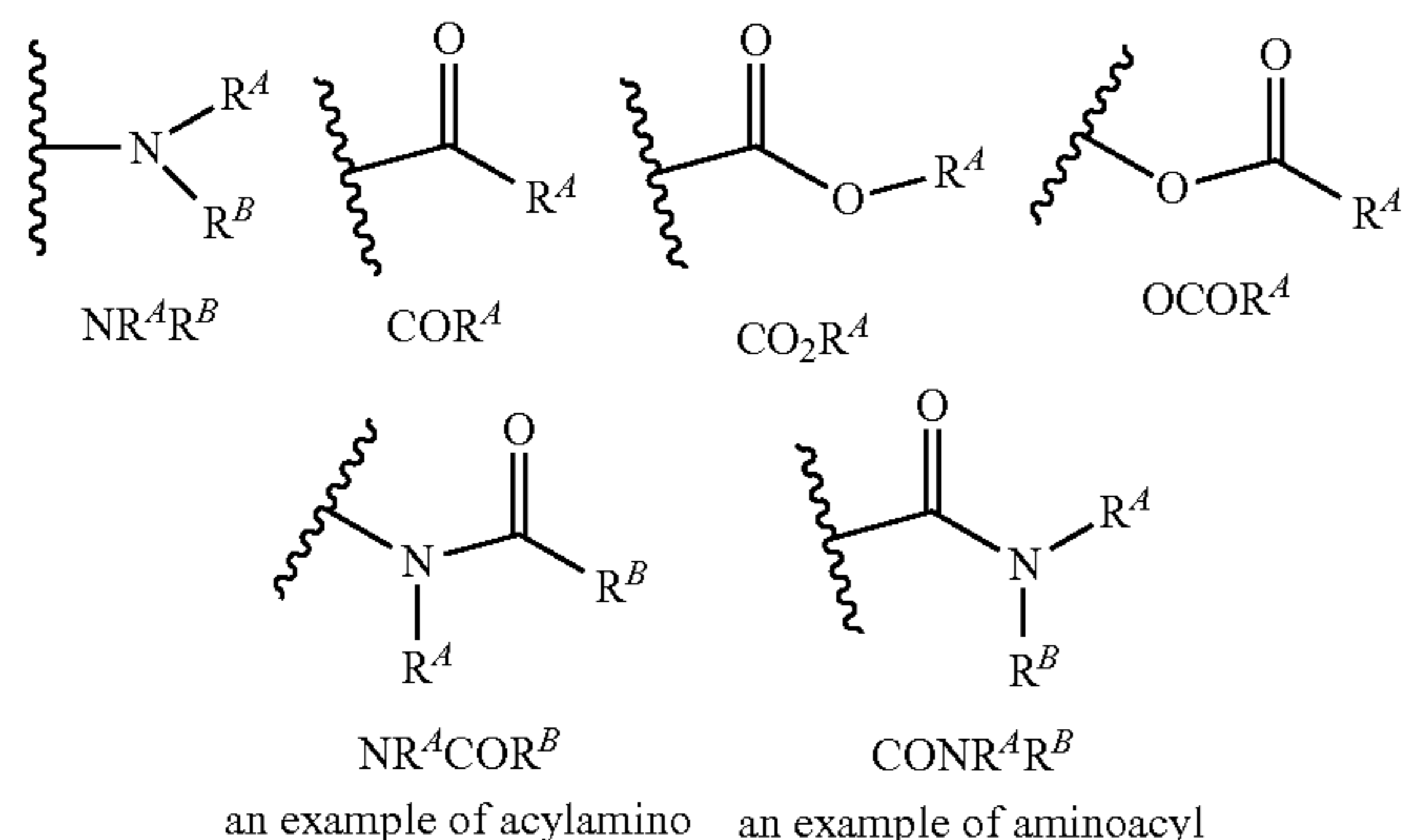
13

is optionally substituted C_{2-8} fluoroaminoalkyl, such as



Generally R^{1-18} , may be H or any substituent, such as a substituent having 0 to 12 atoms or 0 to 6 carbon atoms and 0 to 5 heteroatoms, wherein each heteroatom is independently: O, N, S, F, Cl, Br, or I, and/or having a molecular weight of 15 g/mol to 300 g/mol. Any of R^{1-18} may comprise: a) 1 or more alkyl moieties optionally substituted with, or optionally connected by or to, b) 1 or more functional groups, such as $C=C$, $C\equiv C$, CO , CO_2 , CON , NCO_2 , OH , SH , O , S , N , $N=C$, F , Cl , Br , I , CN , NO_2 , CO_2H , NH_2 , etc.; or may be a substituent having no alkyl portion, such as F , Cl , Br , I , NO_2 , CN , NH_2 , OH , COH , CO_2H , etc. In some embodiments, each of R^{1-18} is independently H, F, Cl, Br, I, or a substituent having a molecular weight of 15 Da to 300 Da, 15 Da to 200 Da, 15 Da to 100 Da, or 15 Da to 60 Da, and consisting of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br.

With respect to any relevant structural representation, such as Formula 2, some non-limiting examples of R^{1-18} may include R^A , F, Cl, Br, CN, OR^A , C_{1-3} fluoroalkyl, C_{1-4} hydroxyalkyl, NO_2 , $NR^A R^B$, COR^A , $CO_2 R^A$, $OCOR^A$, $NR^A COR^B$, $CONR^A R^B$, etc. In some embodiments, R^{1-18} may be H; F; Br; CN; C_{1-3} fluoroalkyl, such as CHF_2 , CF_3 , etc; OH; NH_2 ; C_{1-6} alkyl, such as methyl, ethyl, propyl isomers (e.g. n-propyl and isopropyl), cyclopropyl, butyl isomers, cyclobutyl isomers (e.g. cyclobutyl and methylcyclopropyl), pentyl isomers, cyclopentyl isomers, hexyl isomers, cyclohexyl isomers, etc.; C_{1-6} alkoxy, such as —O-methyl, —O-ethyl, isomers of —O-propyl, —O-cyclopropyl, isomers of —O-butyl, isomers of —O-cyclobutyl, isomers of —O-pentyl, isomers of —O-cyclopentyl, isomers of —O-hexyl, isomers of —O-cyclohexyl, etc.; C_{1-4} hydroxyalkyl, such as $-CH_2OH$, $-C_2H_4-OH$, $-C_3H_6-OH$, C_4H_8-OH , etc.; C_{2-5} — CO_2 -alkyl, such as $-CO_2-CH_3$, $-CO_2-C_2H_5$, $-CO_2-C_3H_7$, $-CO_2-$



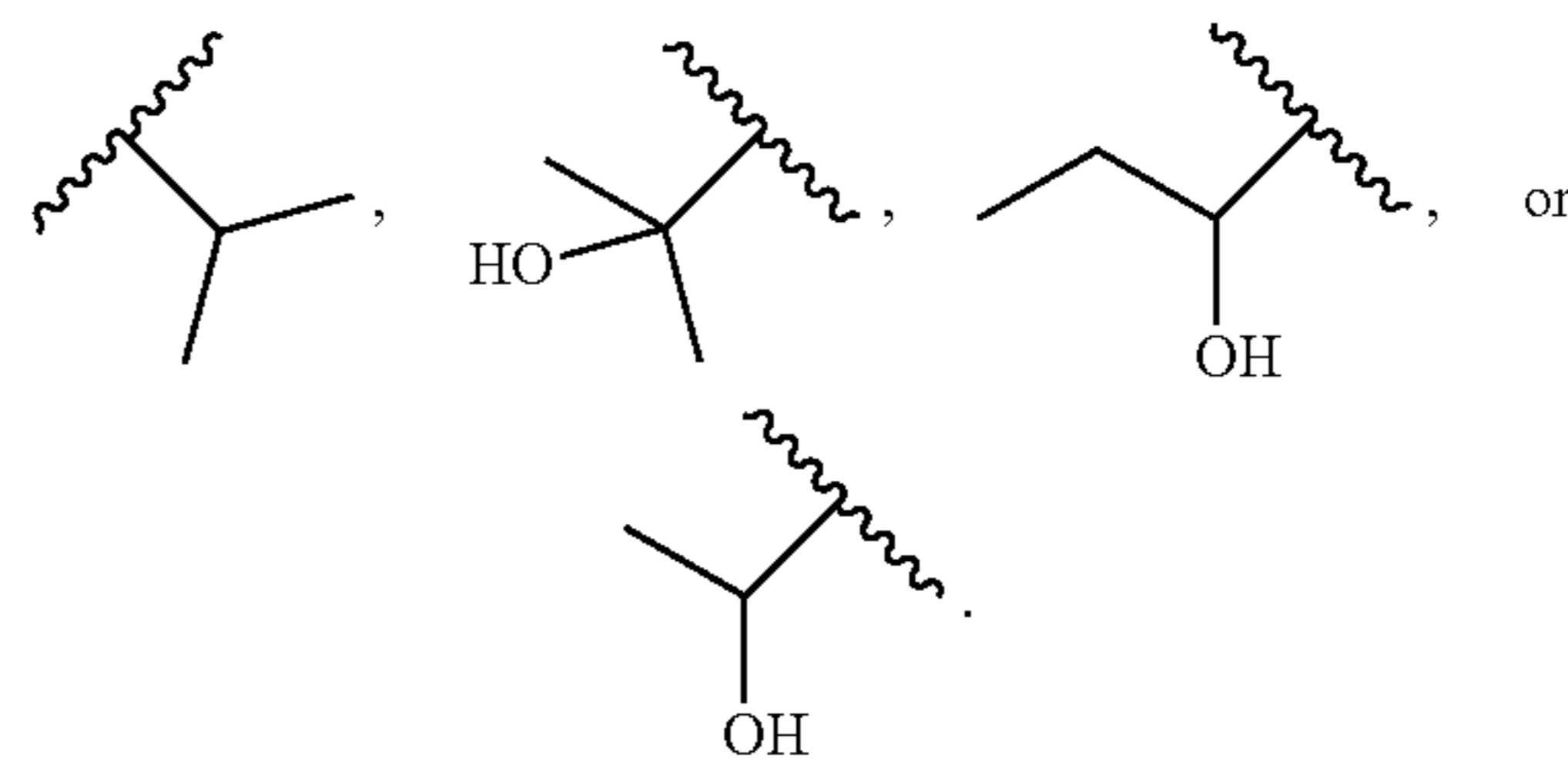
With respect to any relevant structural representation, each R^A may independently be H, or C_{1-12} alkyl, including: linear or branched alkyl having a formula $C_a H_{a+1}$, or cycloalkyl having a formula $C_a H_{a-1}$, wherein a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, such as linear or branched alkyl

14

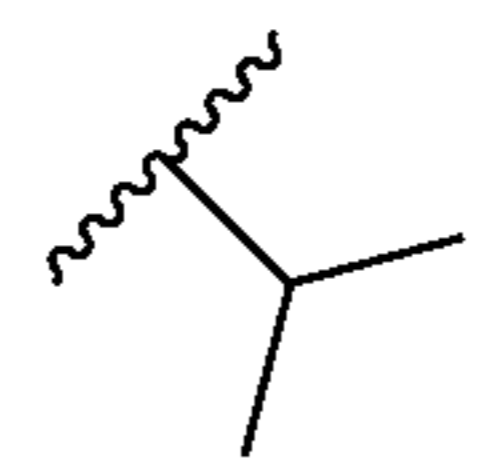
of a formula: CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , C_5H_{11} , C_6H_{13} , C_7H_{15} , C_8H_{17} , C_9H_{19} , $C_{10}H_{21}$, etc., or cycloalkyl of a formula: C_3H_5 , C_4H_7 , C_5H_9 , C_6H_{11} , C_7H_{13} , C_8H_{15} , C_9H_{17} , $C_{10}H_{19}$, etc. In some embodiments, R^A may be H or C_{1-6} alkyl. In some embodiments, R^A may be H or C_{1-3} alkyl. In some embodiments, R^A may be H or CH_3 . In some embodiments, R^A may be H.

With respect to any relevant structural representation, each R^B may independently be H, or C_{1-12} alkyl, including: linear or branched alkyl having a formula $C_a H_{a+1}$, or cycloalkyl having a formula $C_a H_{a-1}$, wherein a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, such as linear or branched alkyl of a formula: CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , C_5H_{11} , C_6H_{13} , C_7H_{15} , C_8H_{17} , C_9H_{19} , $C_{10}H_{21}$, etc., or cycloalkyl of a formula: C_3H_5 , C_4H_7 , C_5H_9 , C_6H_{11} , C_7H_{13} , C_8H_{15} , C_9H_{17} , $C_{10}H_{19}$, etc. In some embodiments, R^B may be H or C_{1-3} alkyl. In some embodiments, R^B may be H or CH_3 . In some embodiments, R^B may be H.

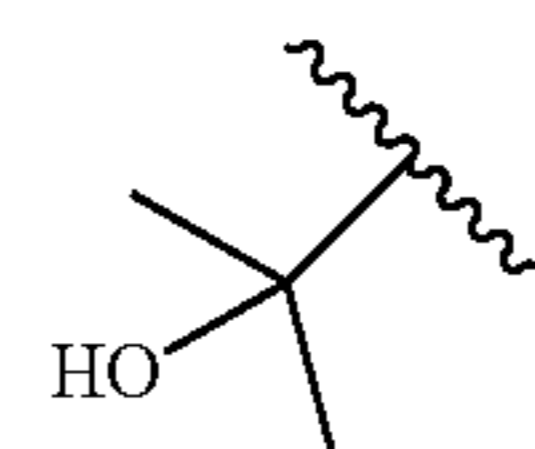
With respect to any relevant structural representation, such as Formula 2, in some embodiments R^1 is H, F, Cl, Br, CN, OCH_3 , CHF_2 , CF_3 , C_{1-4} — CO_2 -alkyl, C_{1-4} alkyl, or C_{1-4} hydroxyalkyl. In some embodiments, R^1 is H, Cl, Br, CN, OCH_3 , CHF_2 , CF_3 , — $CO_2CH_2CH_3$, — CH_2OH ,



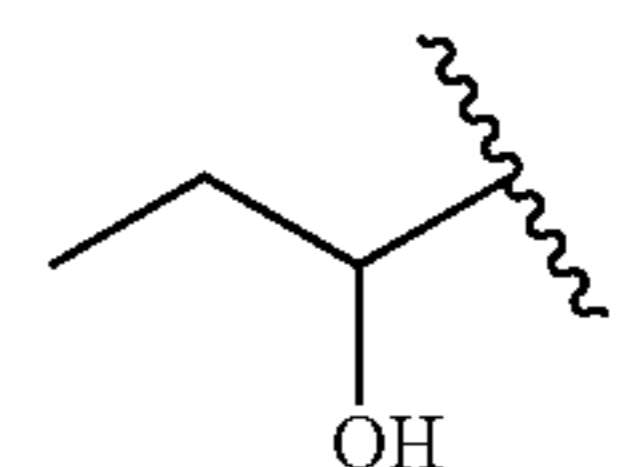
In some embodiments, R^1 is H. In some embodiments, R^1 is Cl. In some embodiments, R^1 is Br. In some embodiments, R^1 is CN. In some embodiments, R^1 is OCH_3 . In some embodiments, R^1 is CHF_2 . In some embodiments, R^1 is CF_3 . In some embodiments, R^1 is — $CO_2CH_2CH_3$. In some embodiments, R^1 is — CH_2OH . In some embodiments, R^1 is



In some embodiments, R^1 is



In some embodiments, R^1 is



17

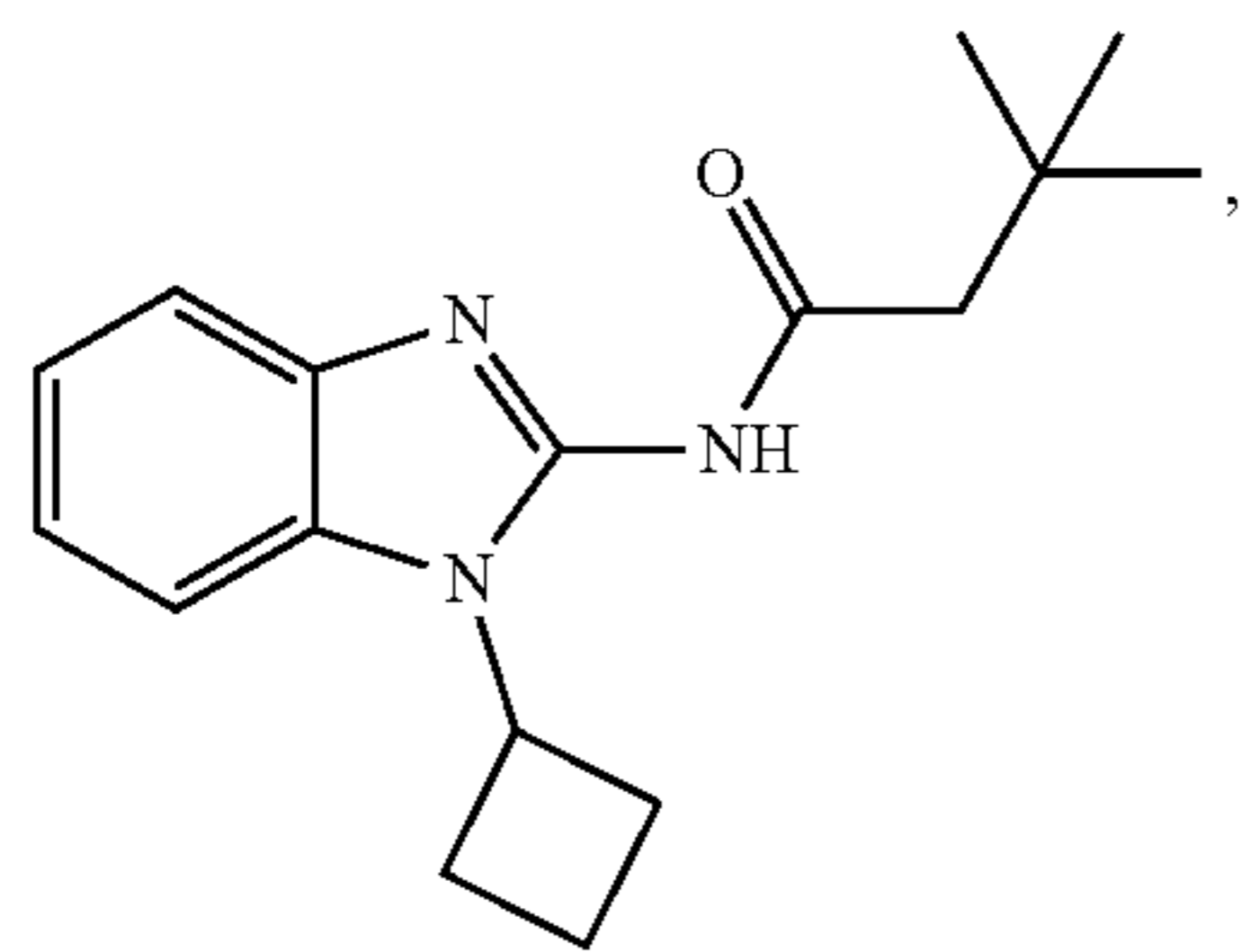
With respect to any relevant structural representation, such as Formula 2, in some embodiments R^{11} is H, F, Cl, Br, CN, OCH_3 , CHF_2 , CF_3 , C_{1-4} $-CO_2$ -alkyl, C_{1-4} alkyl, or C_{1-4} hydroxyalkyl. In some embodiments, R^{11} is H. With respect to the embodiments recited in this paragraph, in some embodiments, the remaining groups of R^{1-18} may independently be R^A , F, Cl, Br, CN, OR^A , C_{1-3} fluoroalkyl, C_{1-4} hydroxyalkyl, NO_2 , $NR^A R^B$, COR^A , $CO_2 R^A$, $OCORA$, $NR^A COR^B$, $CONR^A R^B$, etc. In some embodiments, the remaining groups of R^{1-18} may be H, F, Cl, Br, CN, C_{1-3} fluoroalkyl, OH, NH_2 , C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-4} $-CO_2$ -alkyl, or C_{1-4} hydroxyalkyl.

With respect to any relevant structural representation, such as Formula 2, in some embodiments R^{12} is H, F, Cl, Br, CN, OCH_3 , CHF_2 , CF_3 , C_{1-4} $-CO_2$ -alkyl, C_{1-4} alkyl, or C_{1-4} hydroxyalkyl. In some embodiments, R^{12} is H. With respect to the embodiments recited in this paragraph, in some embodiments, the remaining groups of R^{1-18} may independently be R^A , F, Cl, Br, CN, OR^A , C_{1-3} fluoroalkyl, C_{1-4} hydroxyalkyl, NO_2 , $NR^A R^B$, COR^A , $CO_2 R^A$, $OCORA$, $NR^A COR^B$, $CONR^A R^B$, etc. In some embodiments, the remaining groups of R^{1-18} may be H, F, Cl, Br, CN, C_{1-3} fluoroalkyl, OH, NH_2 , C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-4} $-CO_2$ -alkyl, or C_{1-4} hydroxyalkyl.

With respect to any relevant structural representation, such as Formula 2, in some embodiments R^{13} is H, F, Cl, Br, CN, OCH_3 , CHF_2 , CF_3 , C_{1-4} $-CO_2$ -alkyl, C_{1-4} alkyl, or C_{1-4} hydroxyalkyl. In some embodiments, R^{13} is H. With respect to the embodiments recited in this paragraph, in some embodiments, the remaining groups of R^{1-18} may independently be R^A , F, Cl, Br, CN, OR^A , C_{1-3} fluoroalkyl, C_{1-4} hydroxyalkyl, NO_2 , $NR^A R^B$, COR^A , $CO_2 R^A$, $OCORA$, $NR^A COR^B$, $CONR^A R^B$, etc. In some embodiments, the remaining groups of R^{1-18} may be H, F, Cl, Br, CN, C_{1-3} fluoroalkyl, OH, NH_2 , C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-4} $-CO_2$ -alkyl, or C_{1-4} hydroxyalkyl.

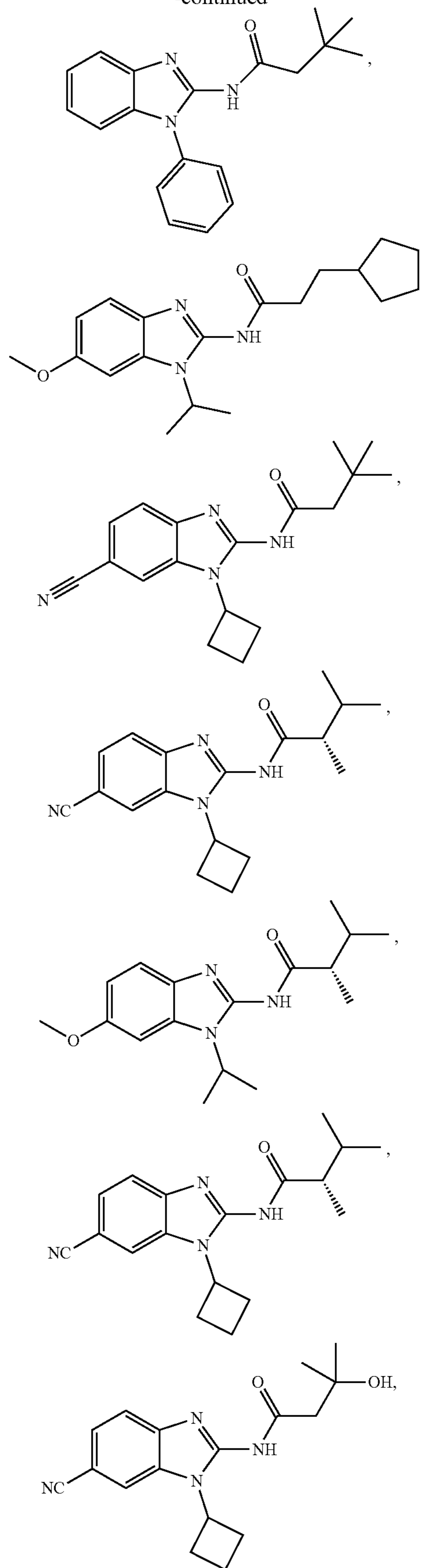
With respect to any relevant structural representation, such as Formula 2, in some embodiments R^{14} is H, F, Cl, Br, CN, OCH_3 , CHF_2 , CF_3 , C_{1-4} $-CO_2$ -alkyl, C_{1-4} alkyl, or C_{1-4} hydroxyalkyl. In some embodiments, R^{14} is H. In some embodiments, R^{14} is F. With respect to the embodiments recited in this paragraph, in some embodiments, the remaining groups of R^{1-18} may independently be R^A , F, Cl, Br, CN, OR^A , C_{1-3} fluoroalkyl, C_{1-4} hydroxyalkyl, NO_2 , $NR^A R^B$, COR^A , $CO_2 R^A$, $OCORA$, $NR^A COR^B$, $CONR^A R^B$, etc. In some embodiments, the remaining groups of R^{1-18} may be H, F, Cl, Br, CN, C_{1-3} fluoroalkyl, OH, NH_2 , C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-4} $-CO_2$ -alkyl, or C_{1-4} hydroxyalkyl.

Some embodiments include:



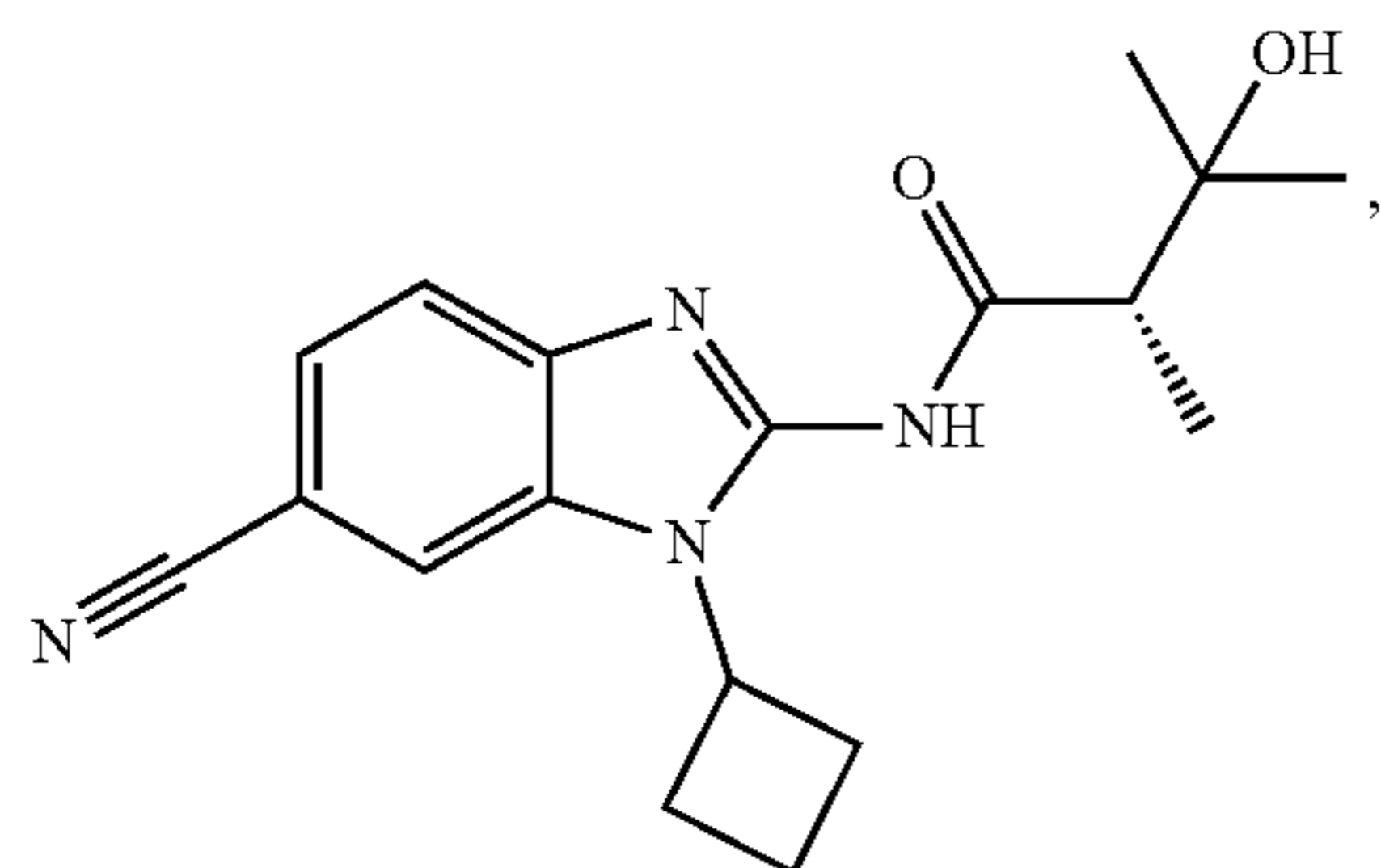
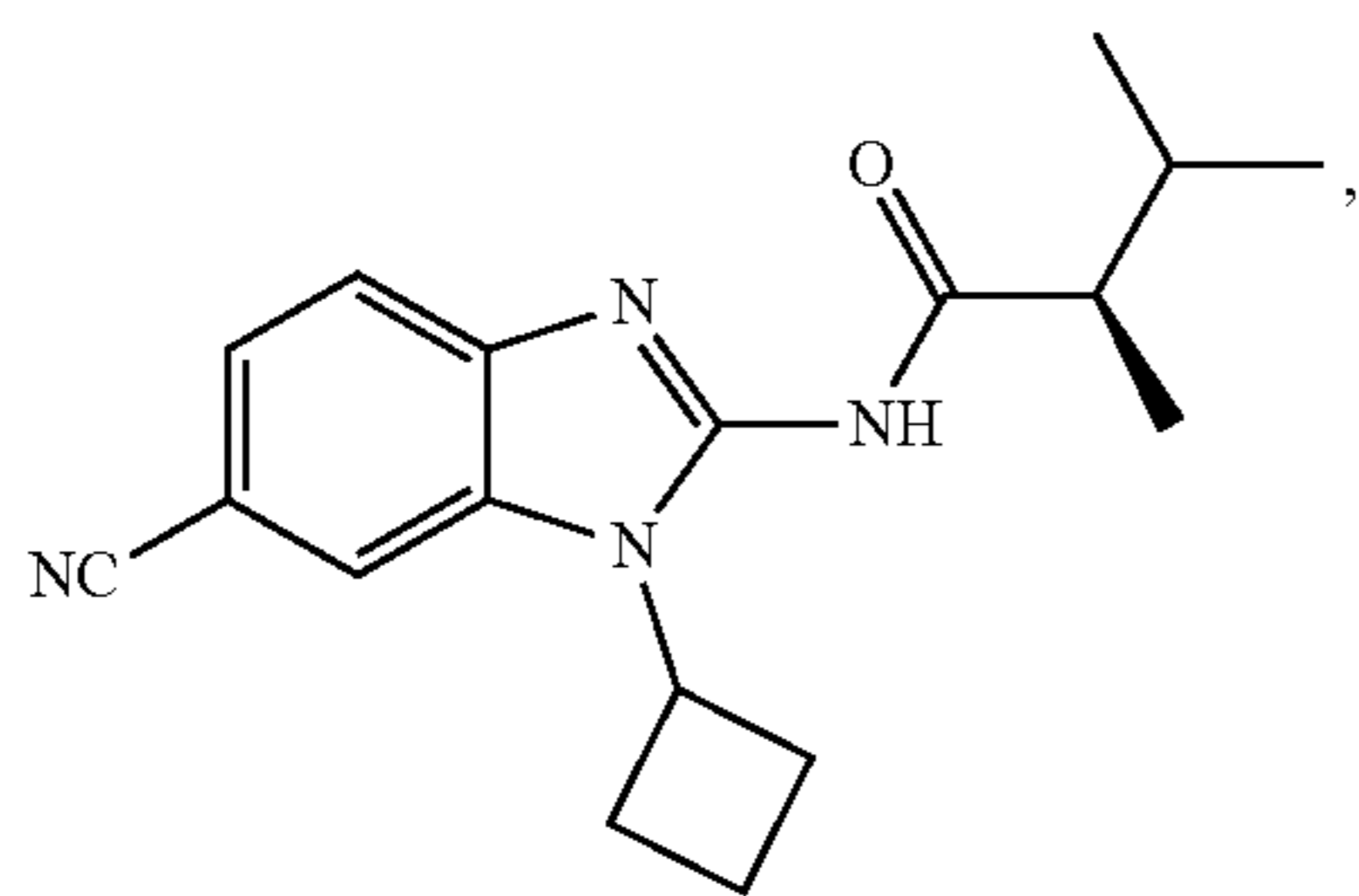
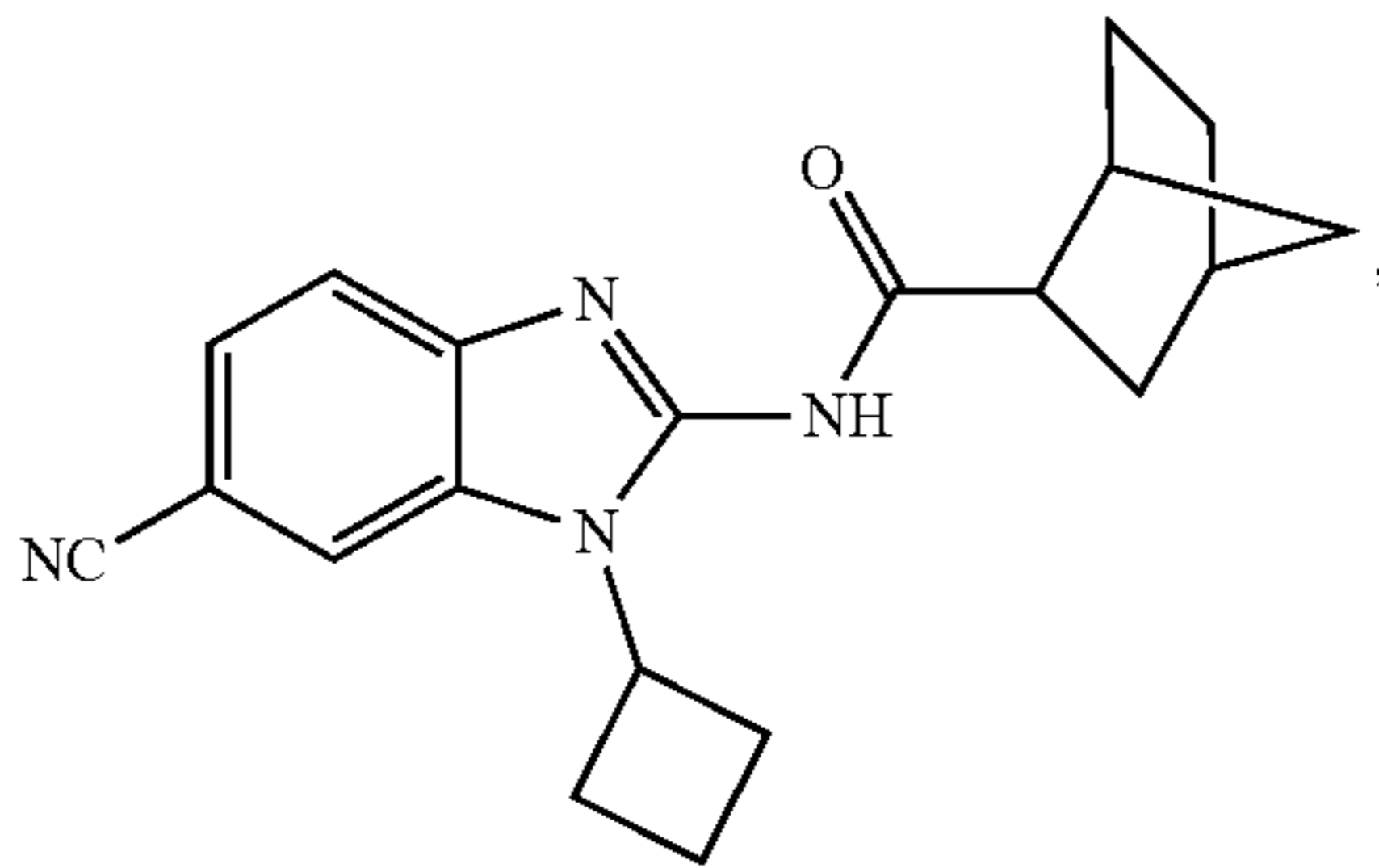
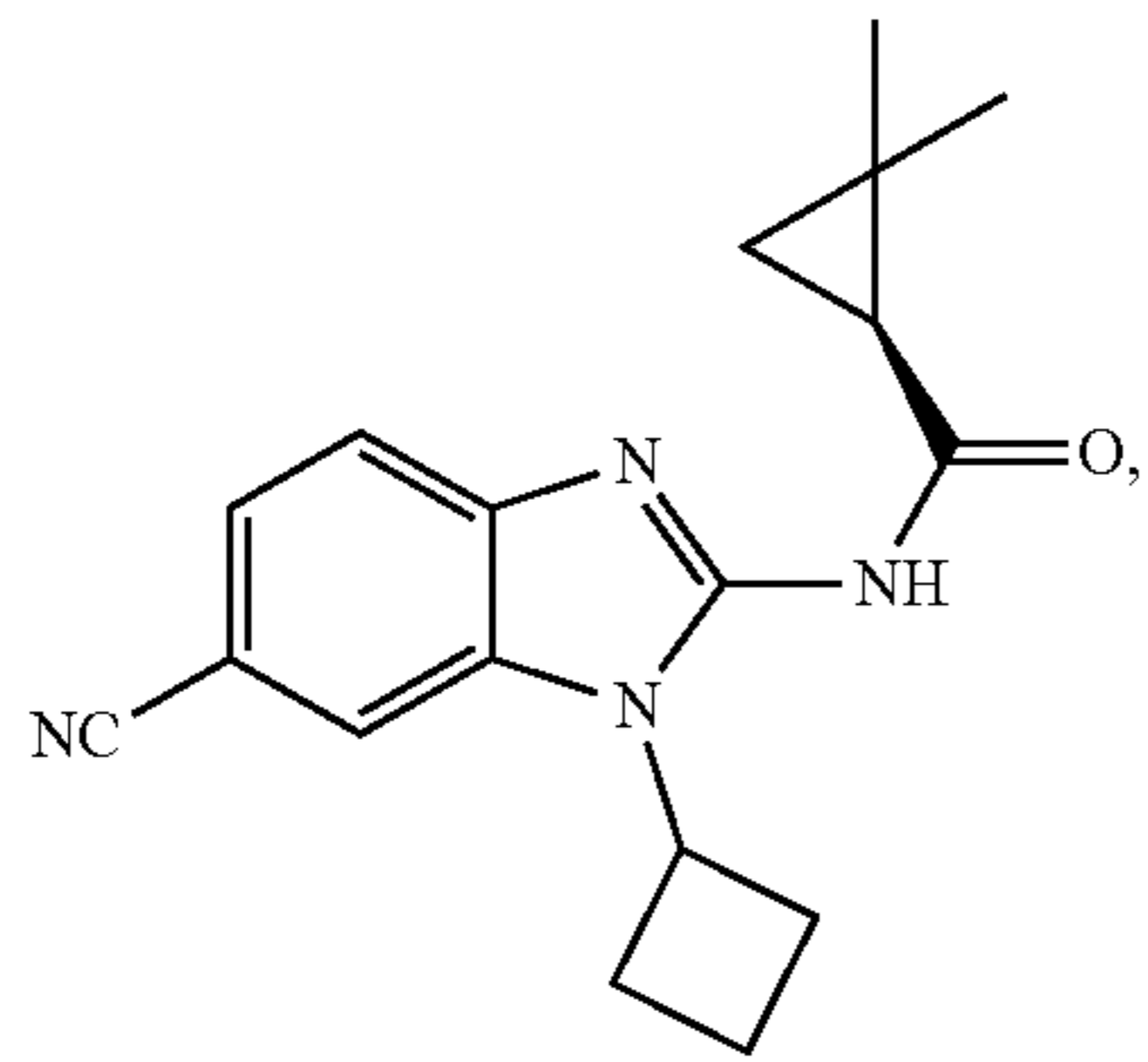
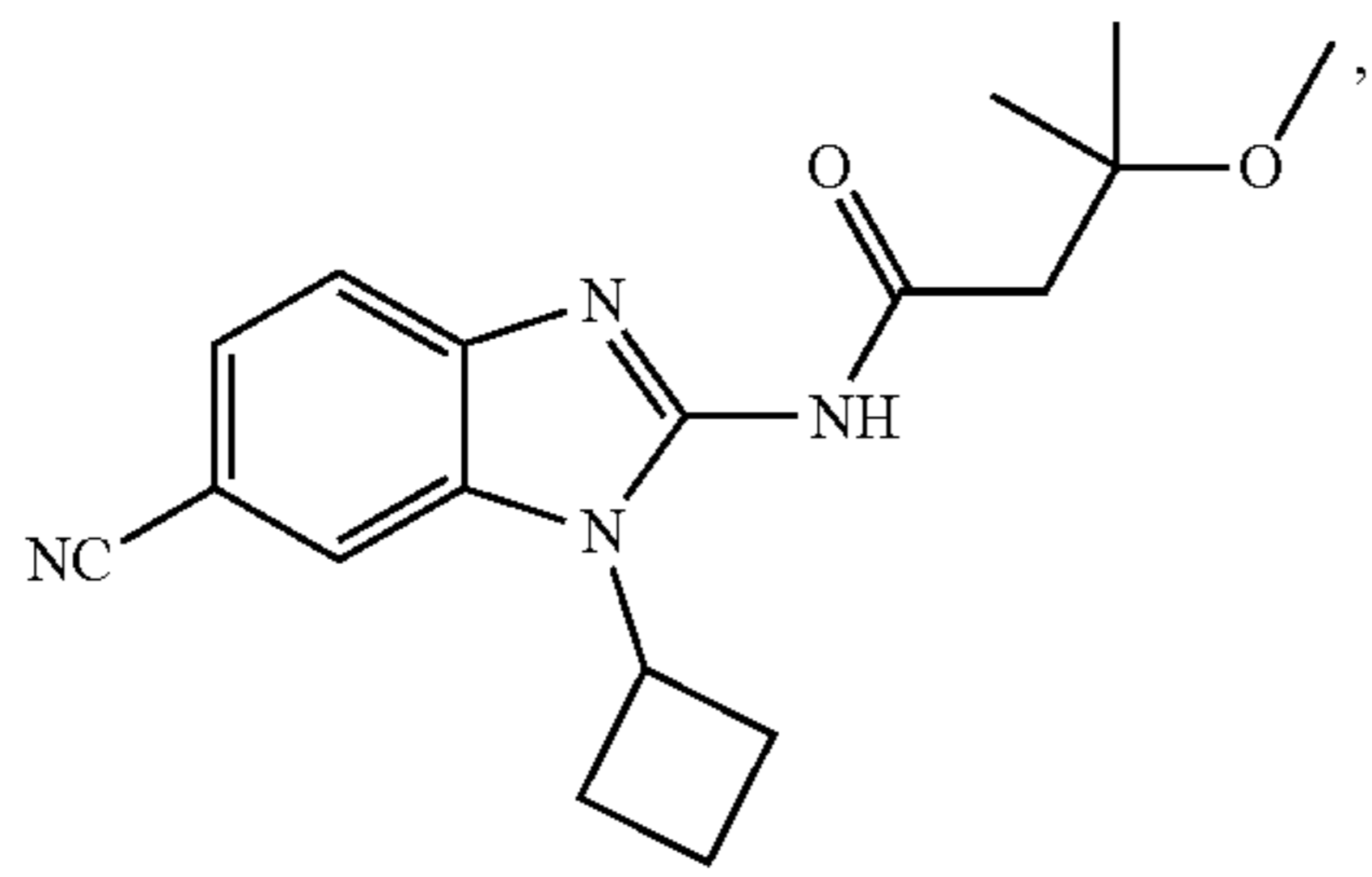
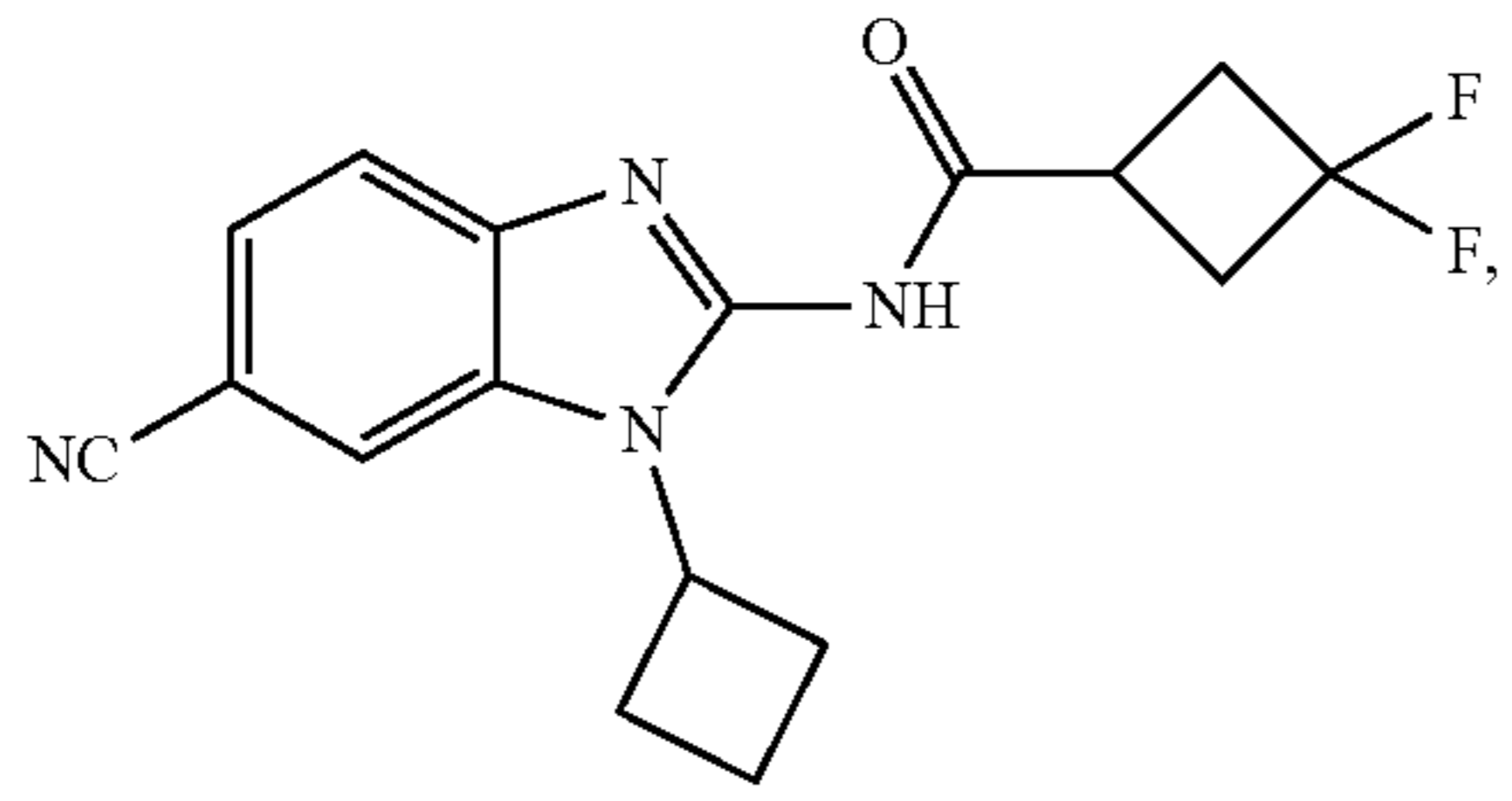
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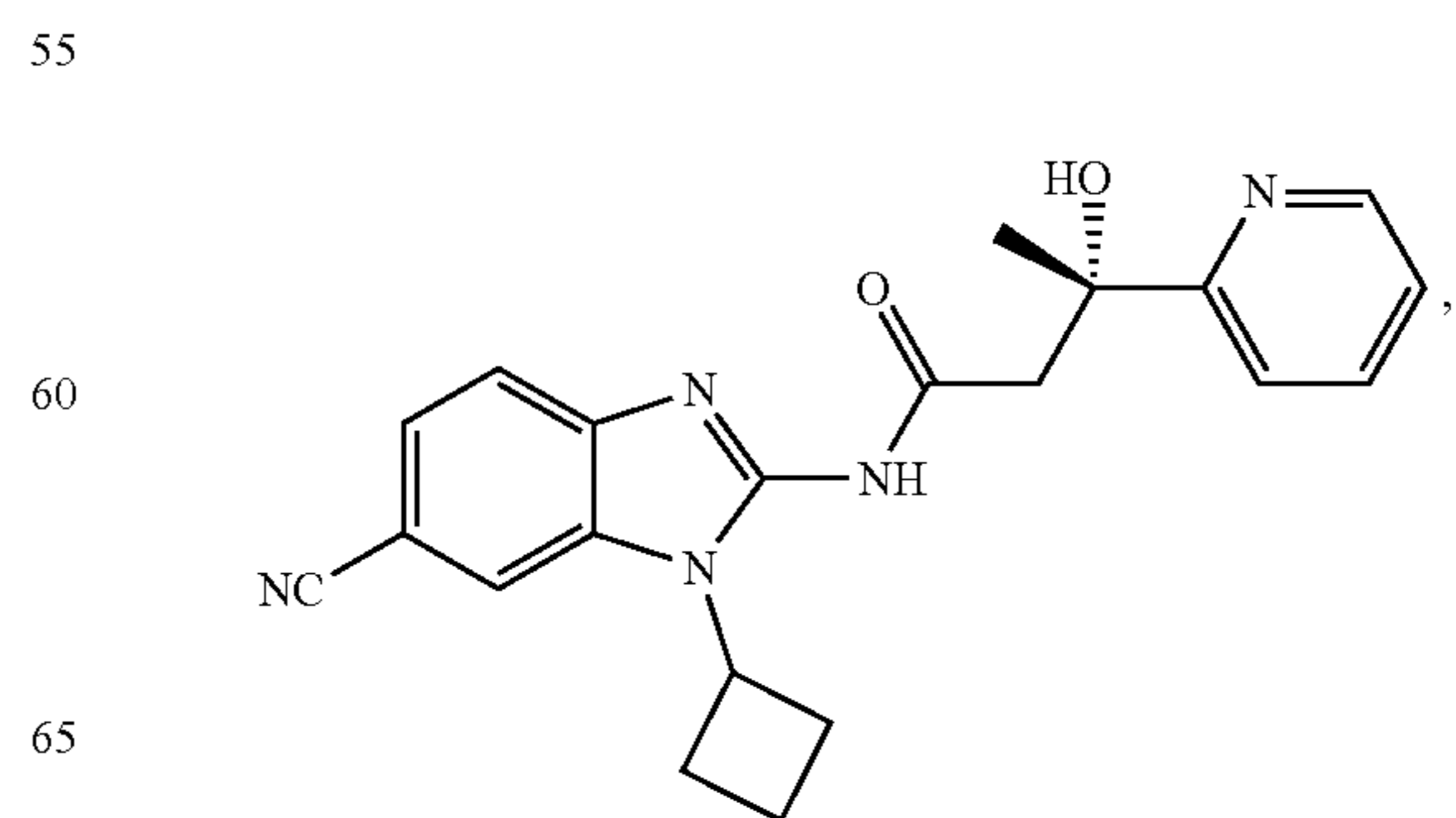
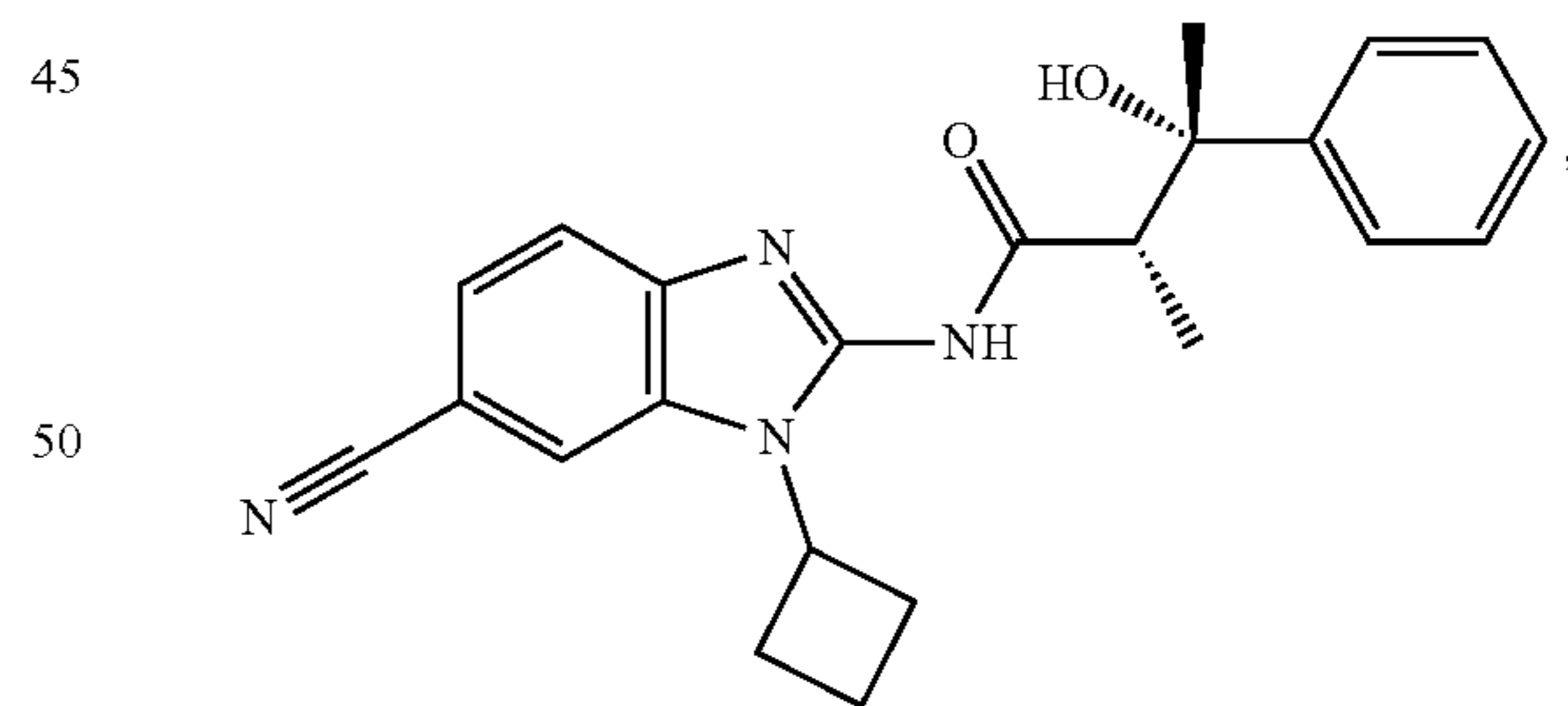
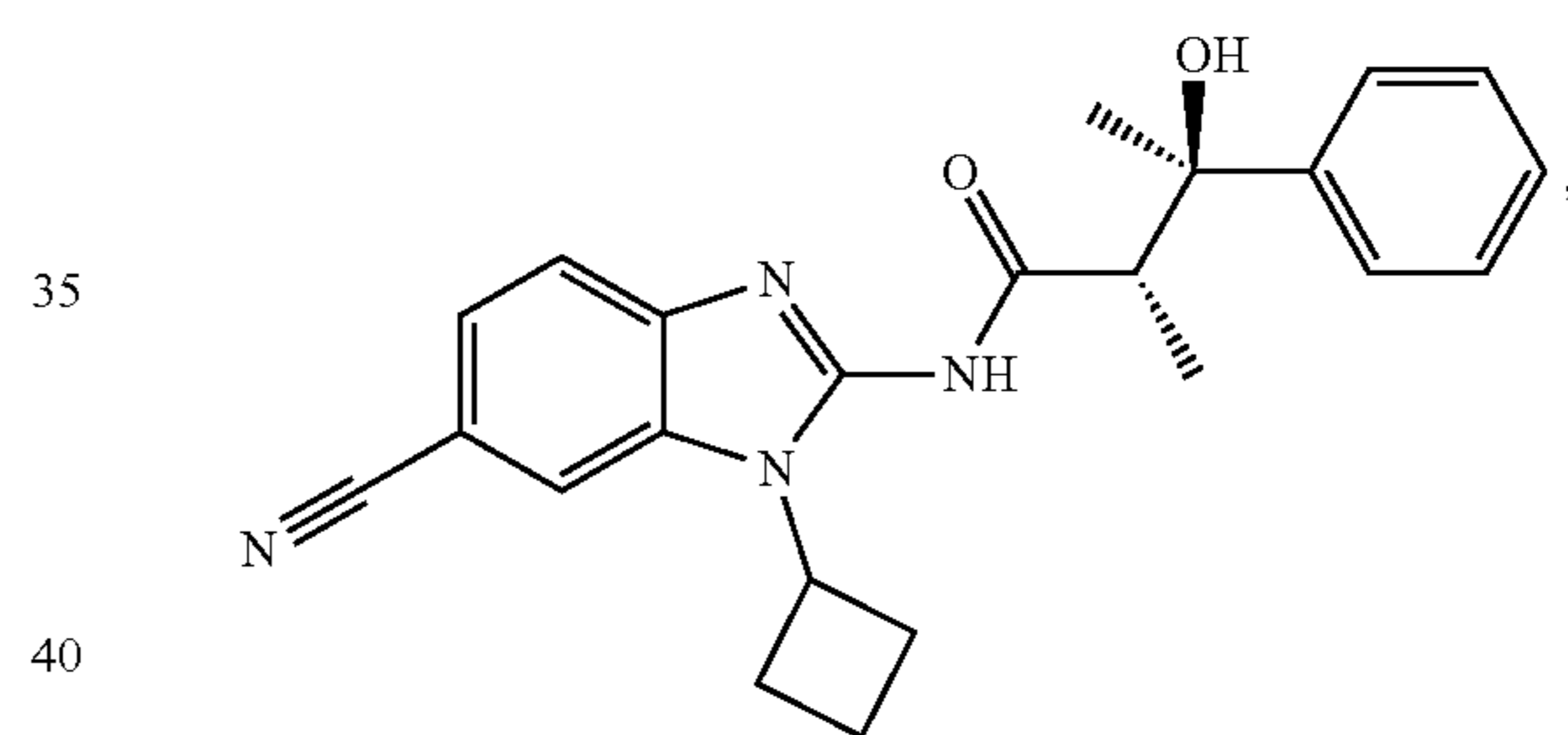
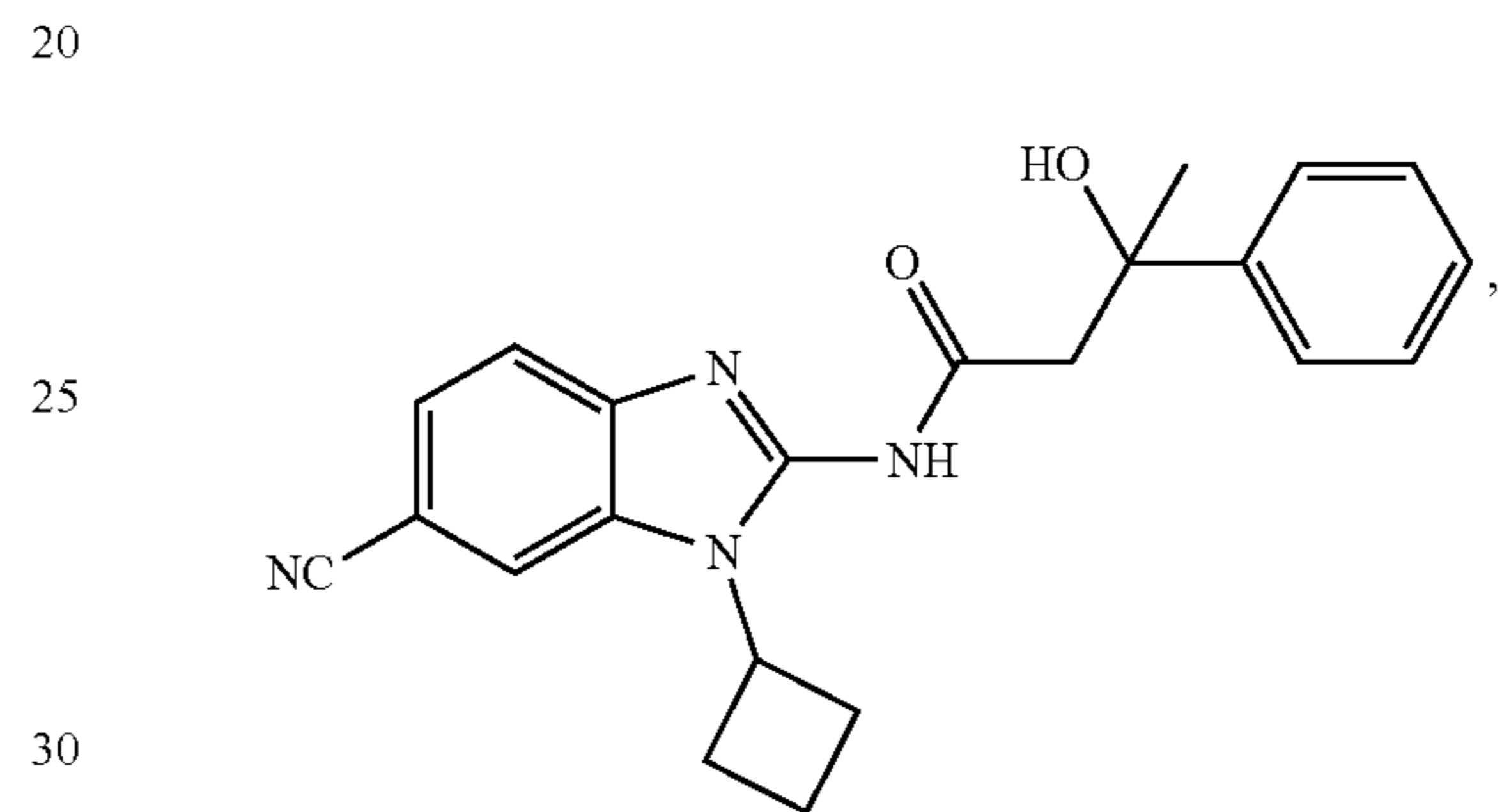
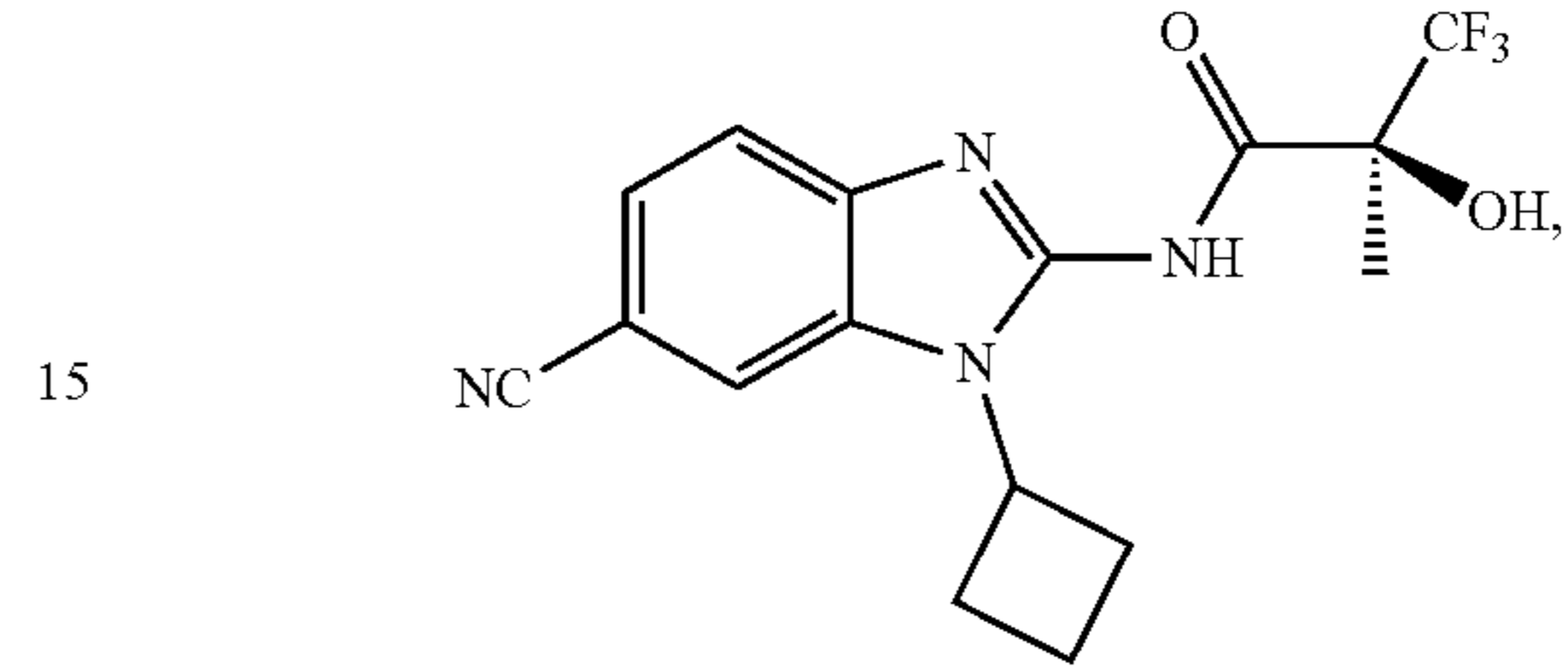
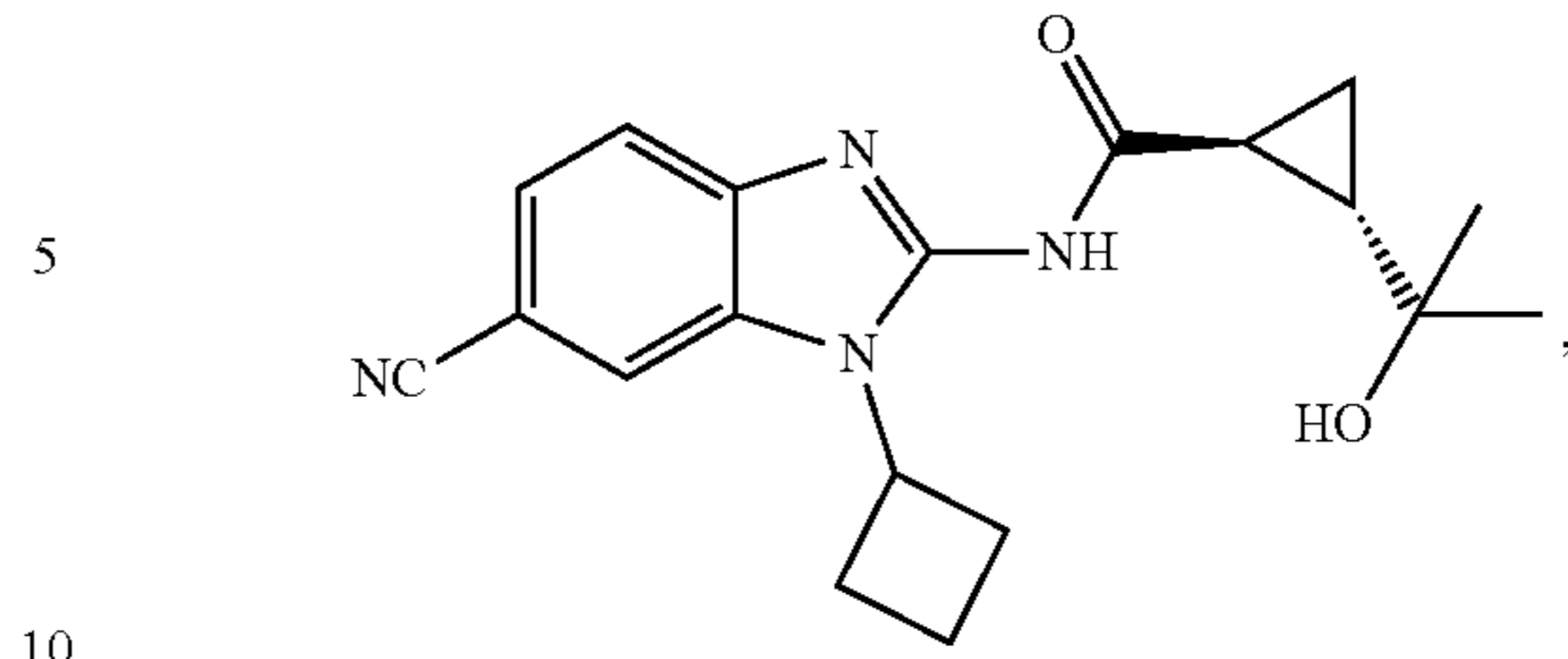
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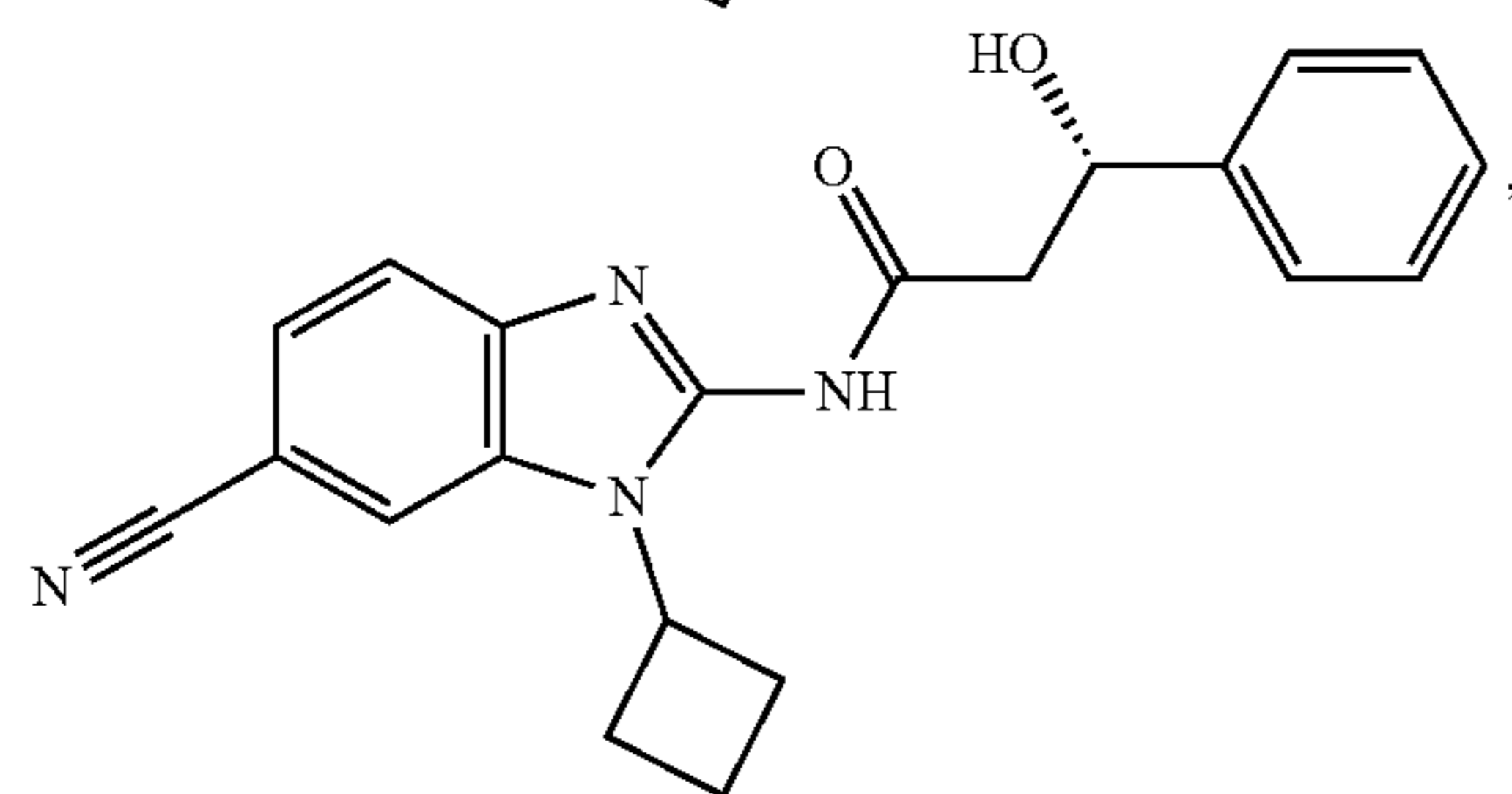
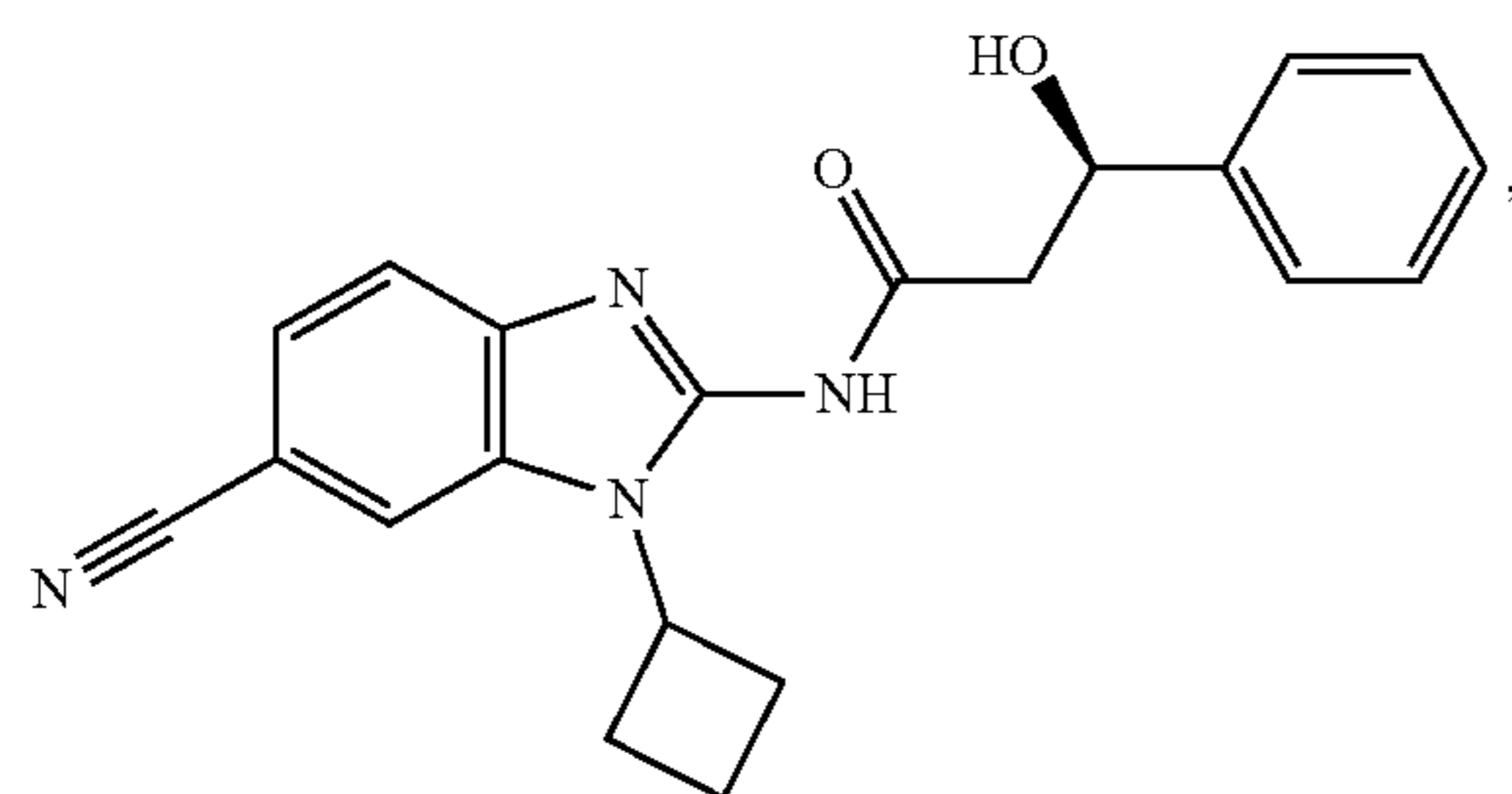
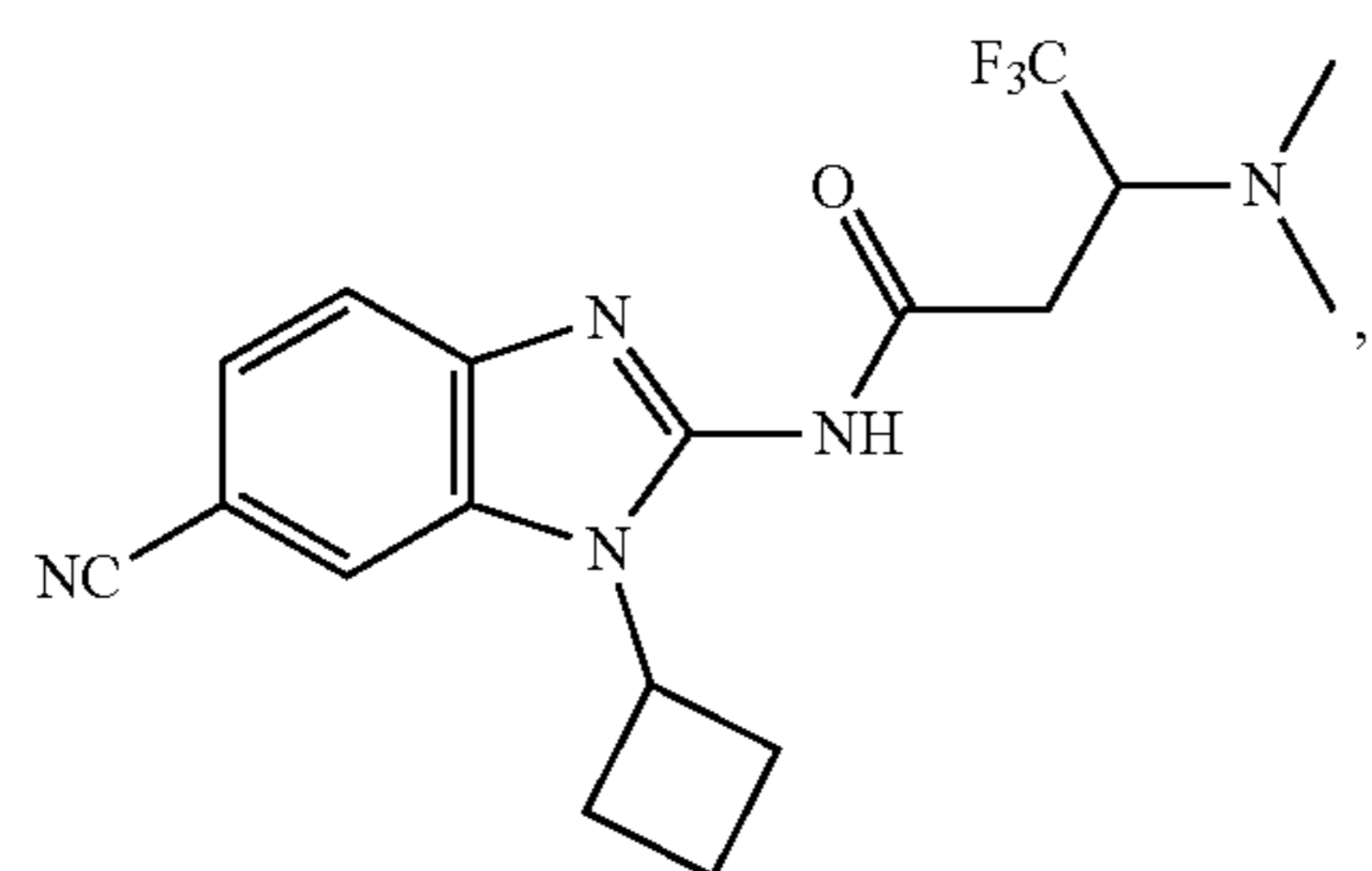
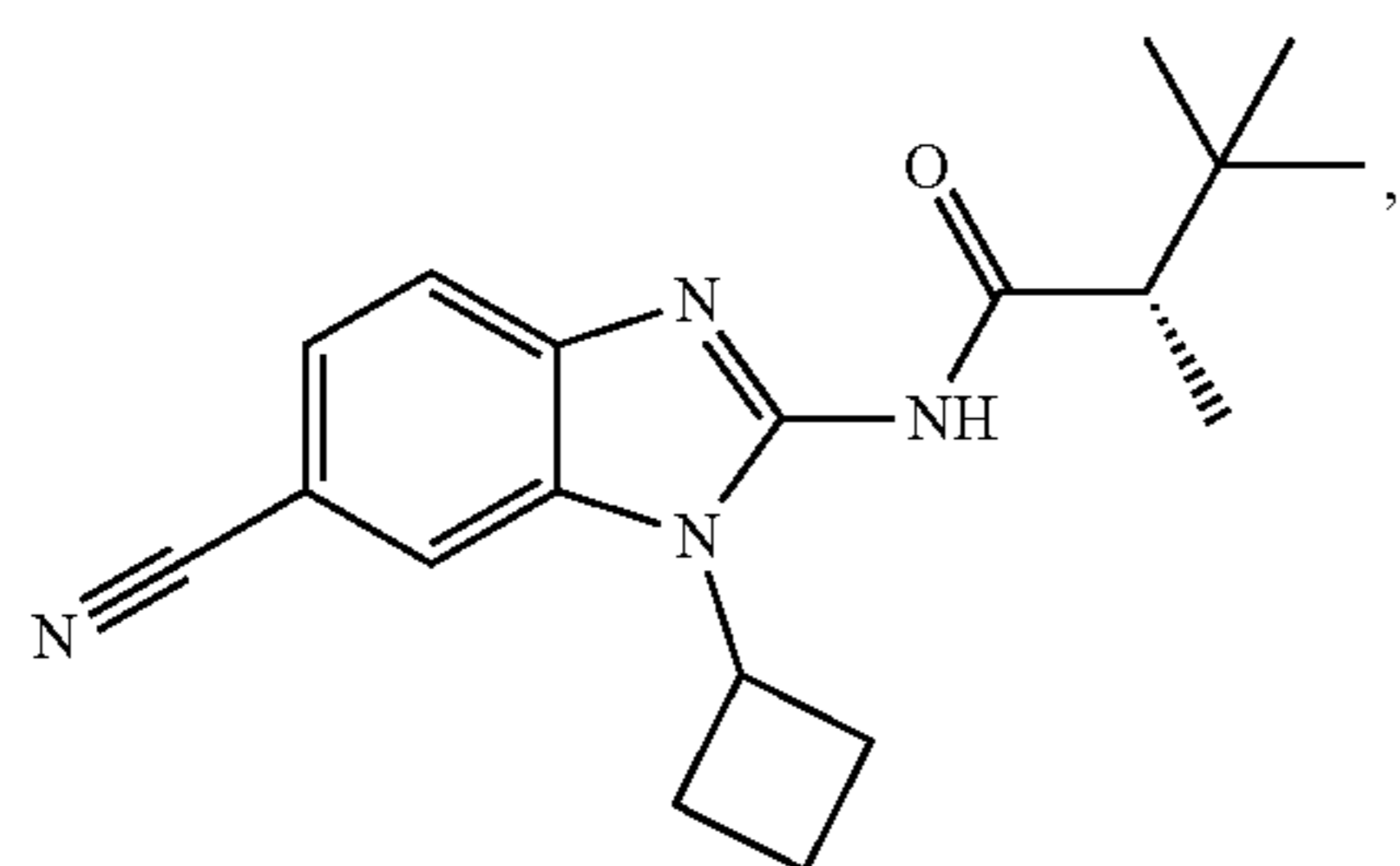
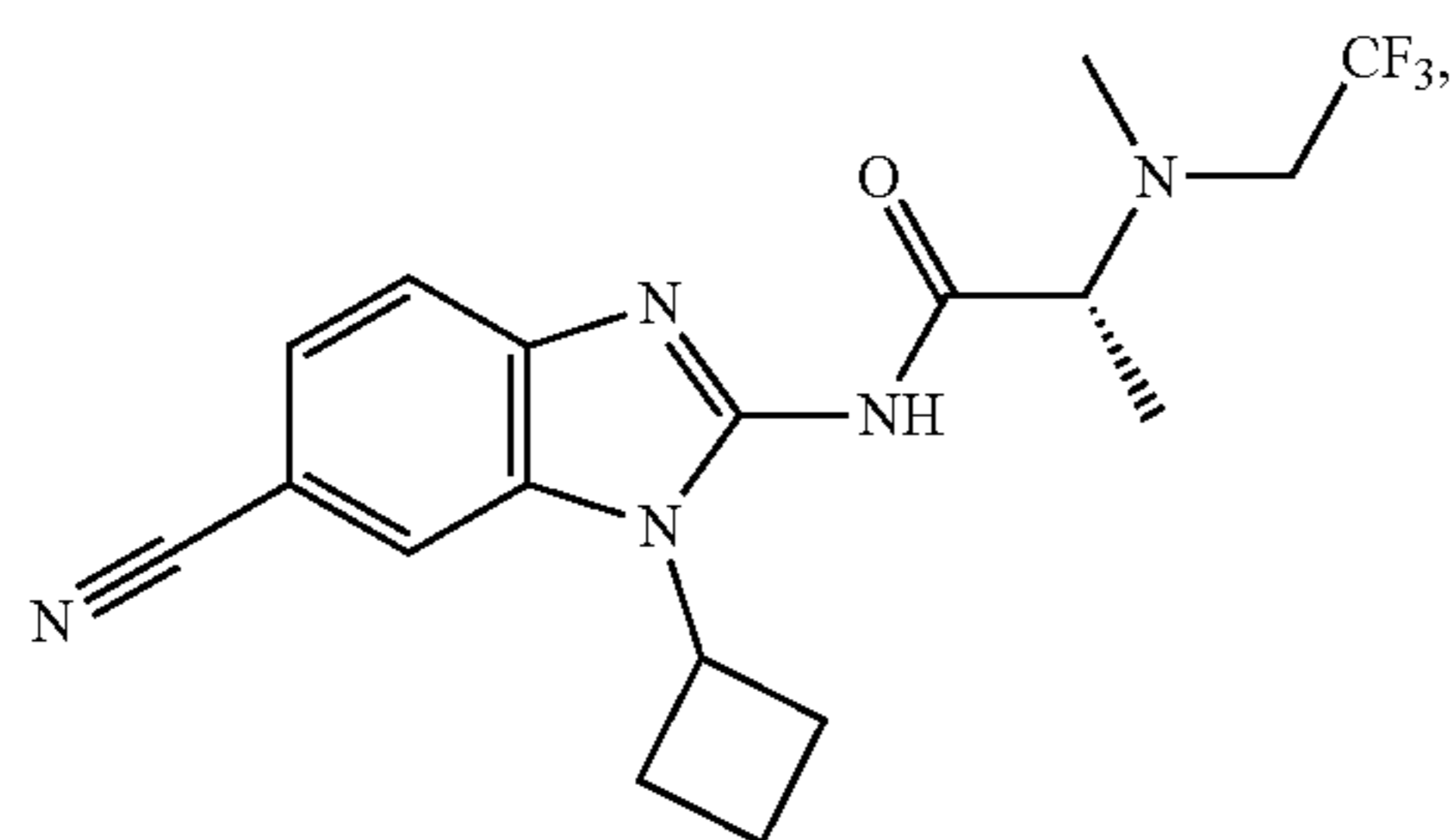
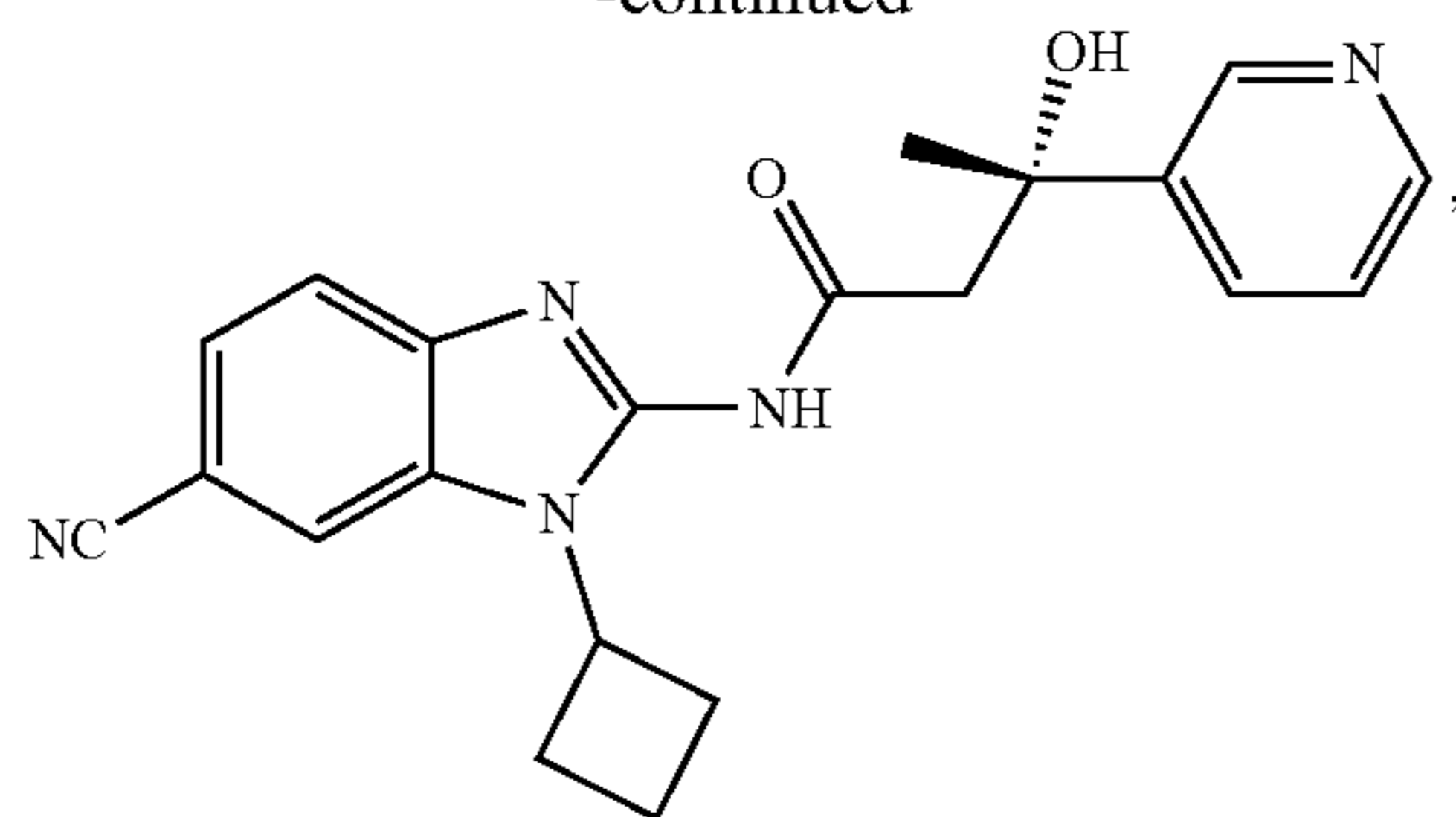
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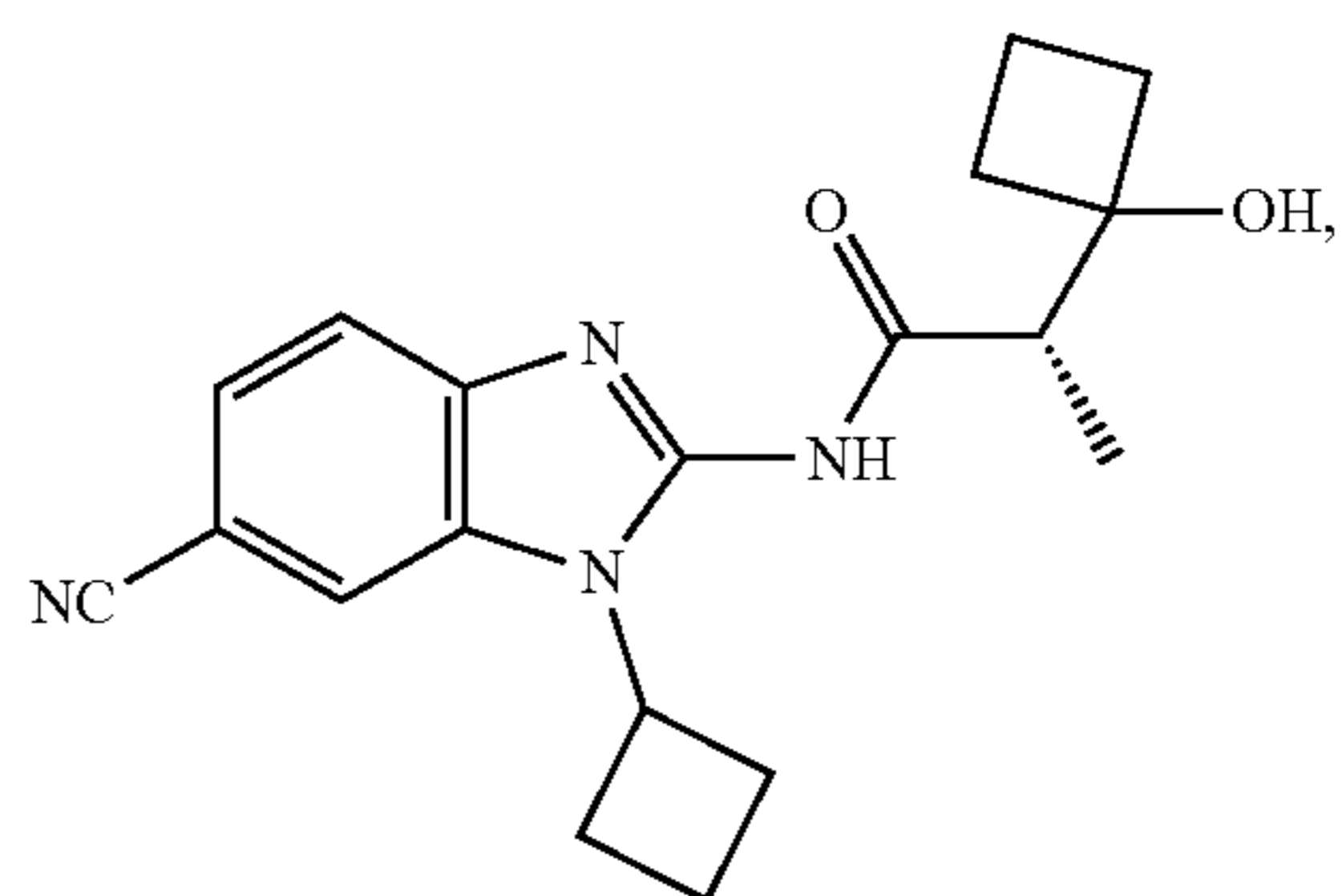
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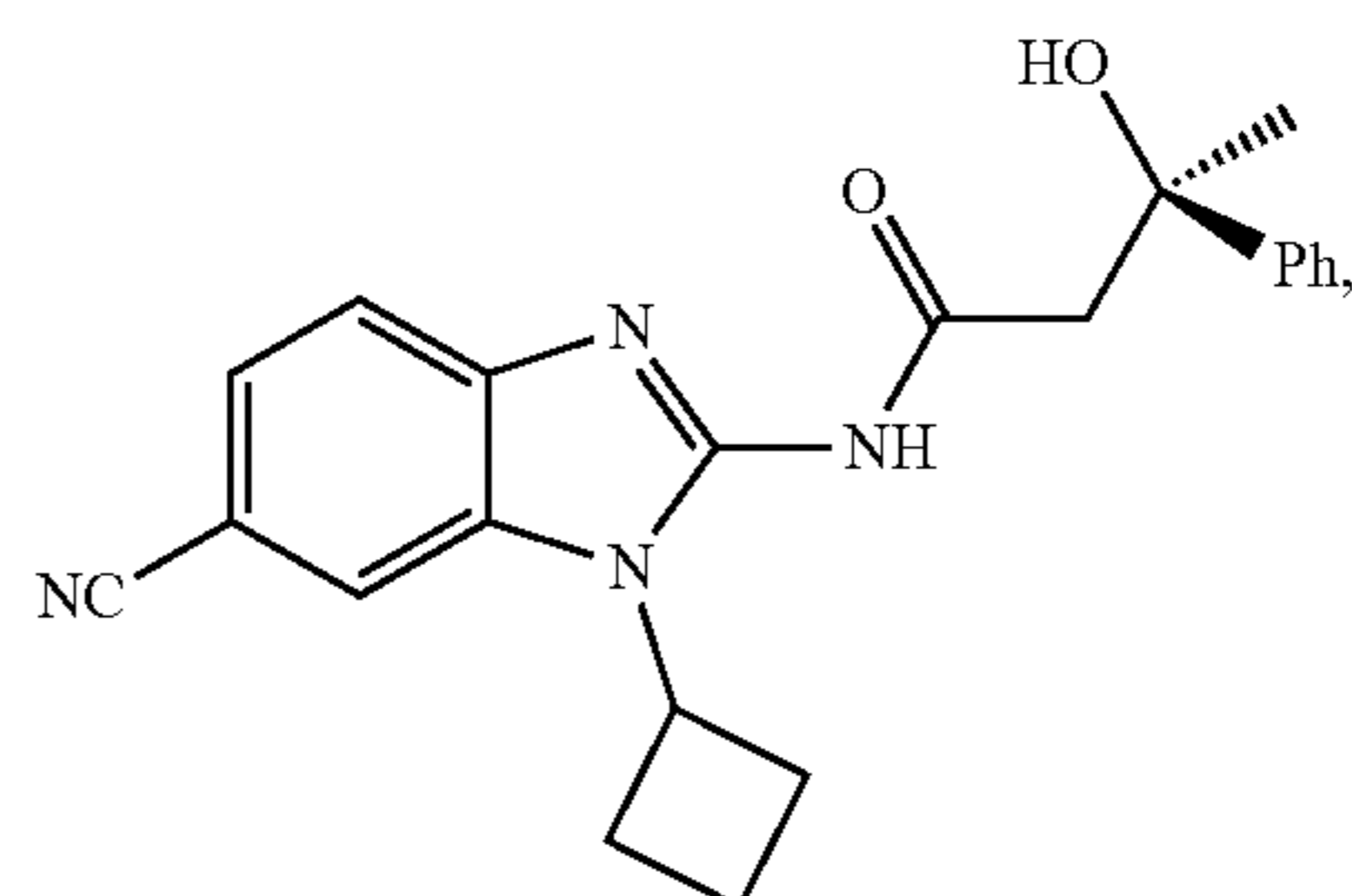
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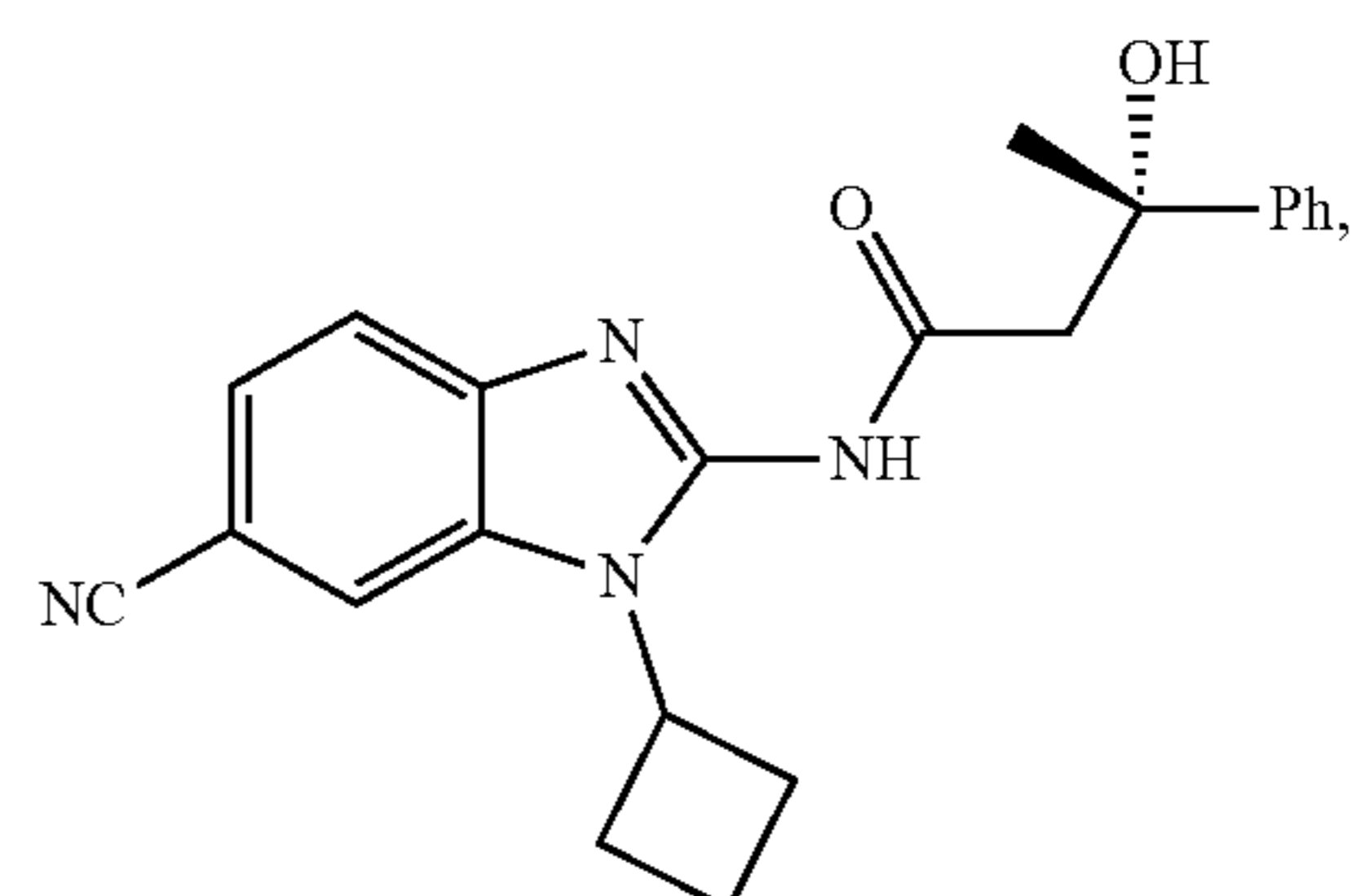
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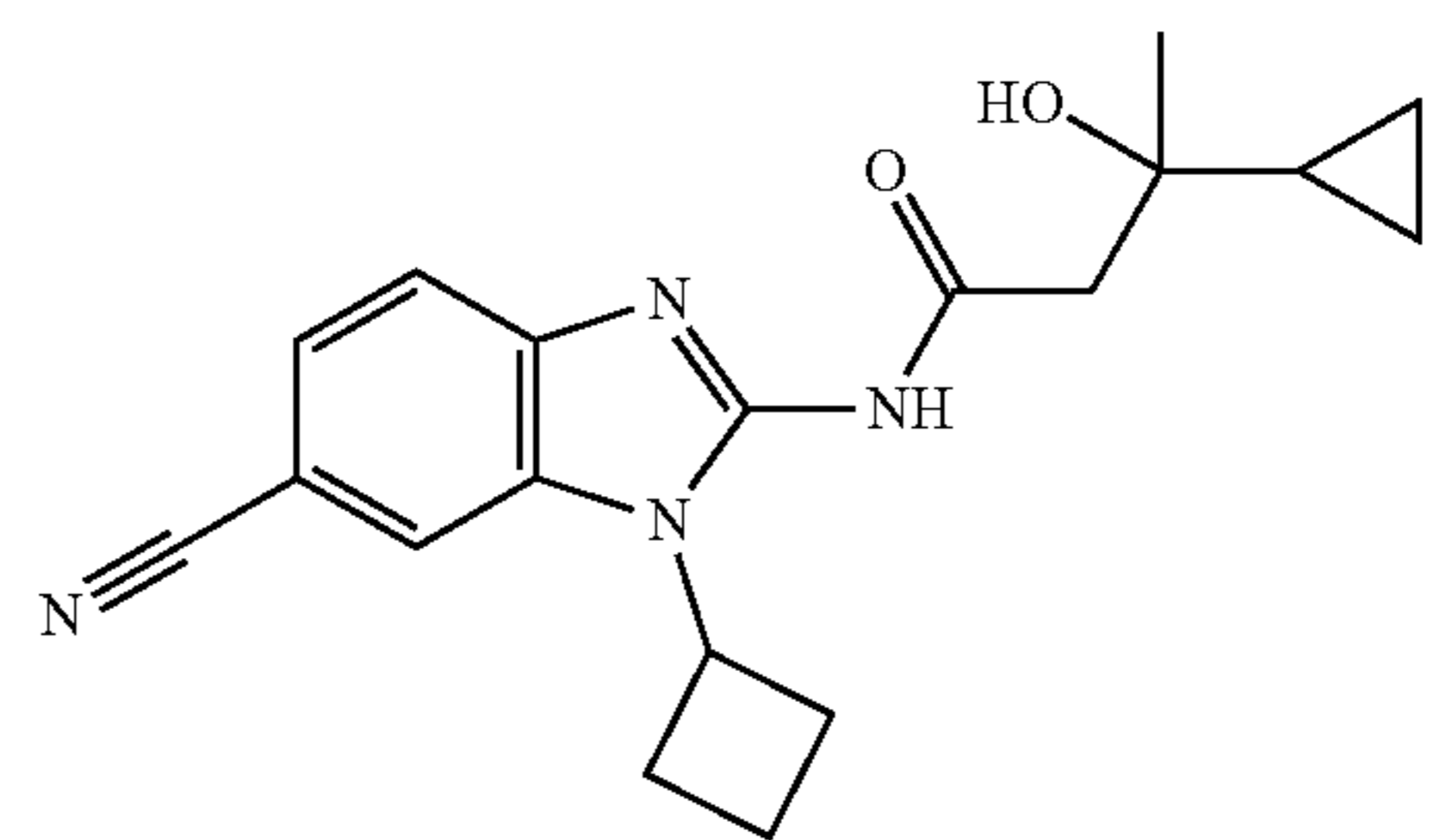
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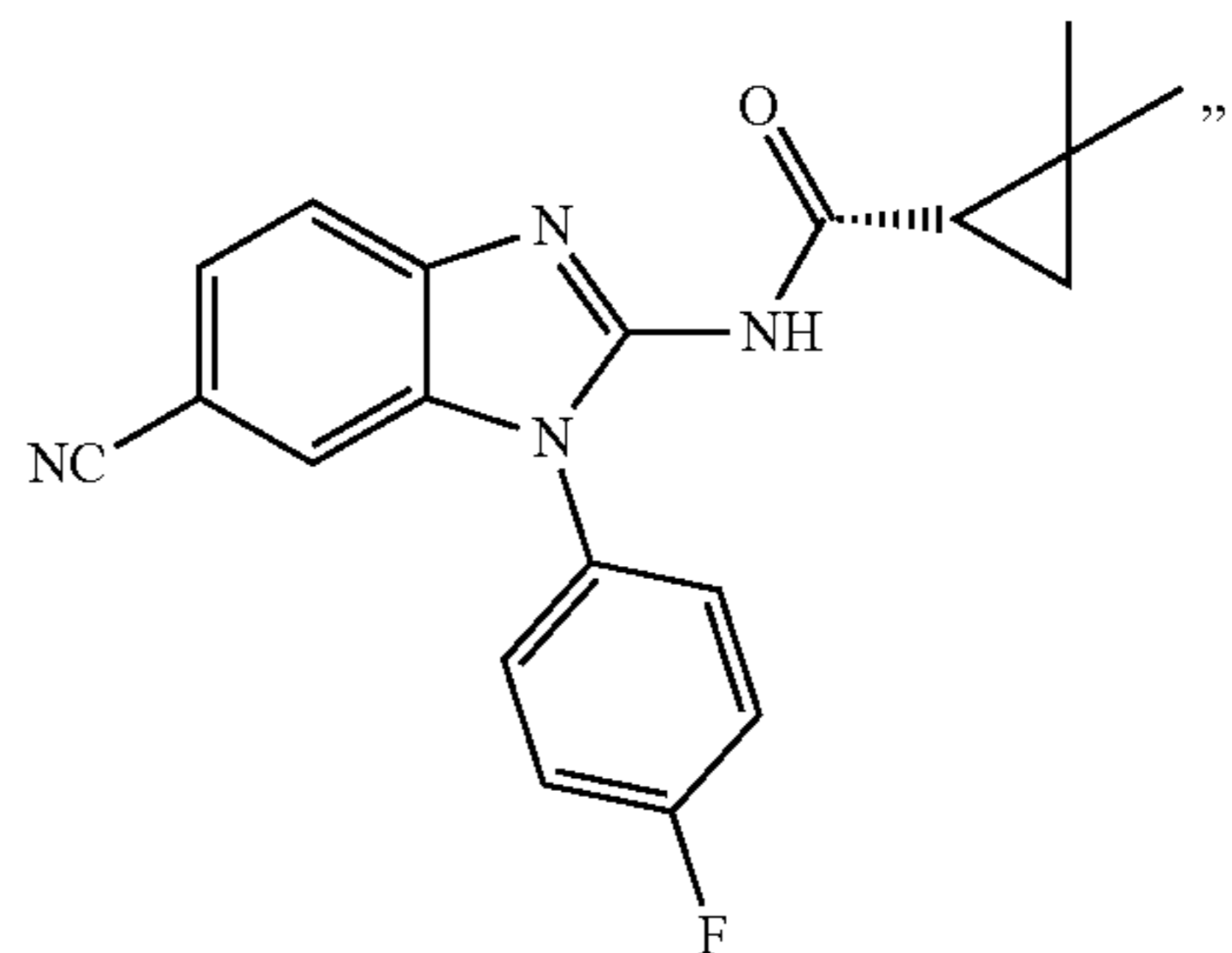
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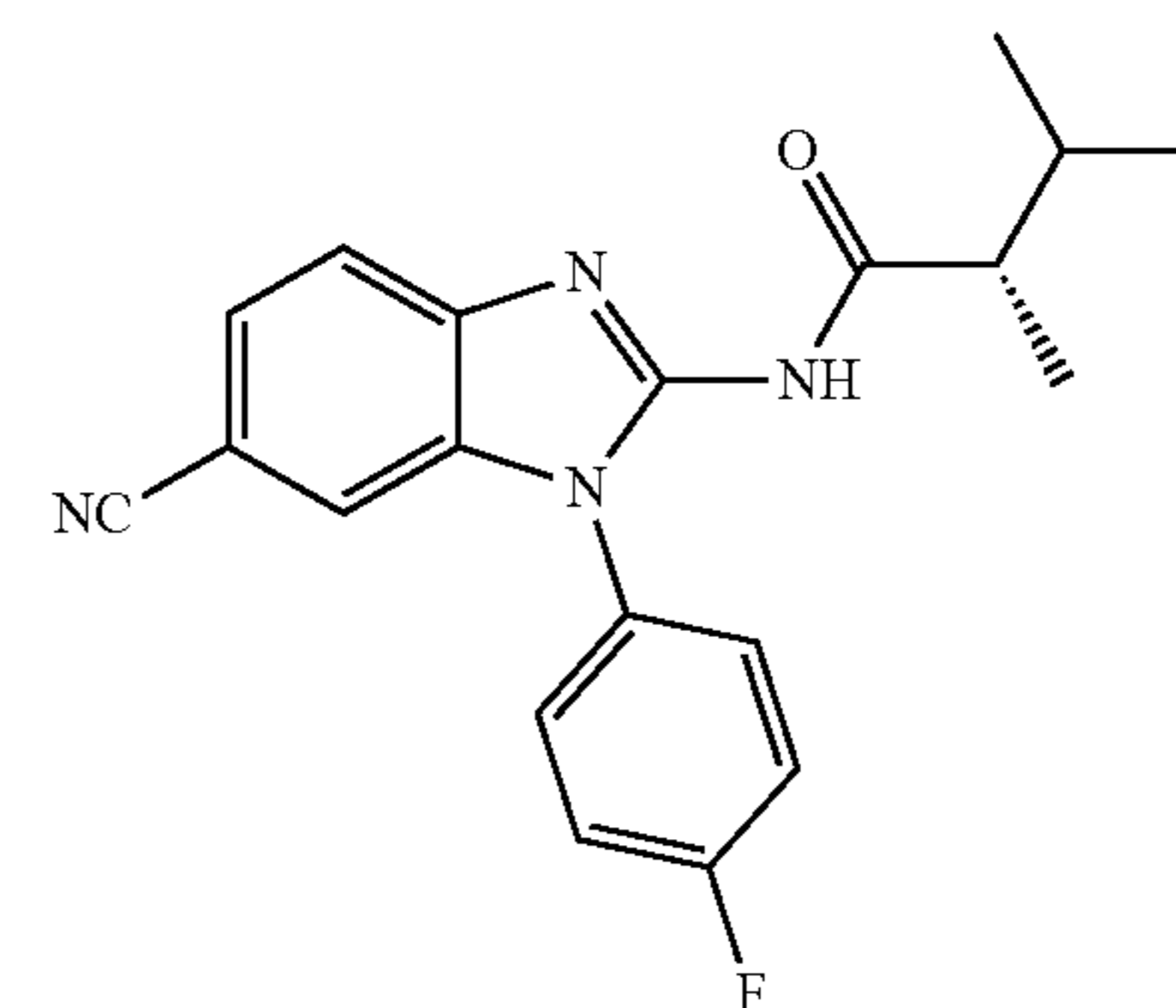
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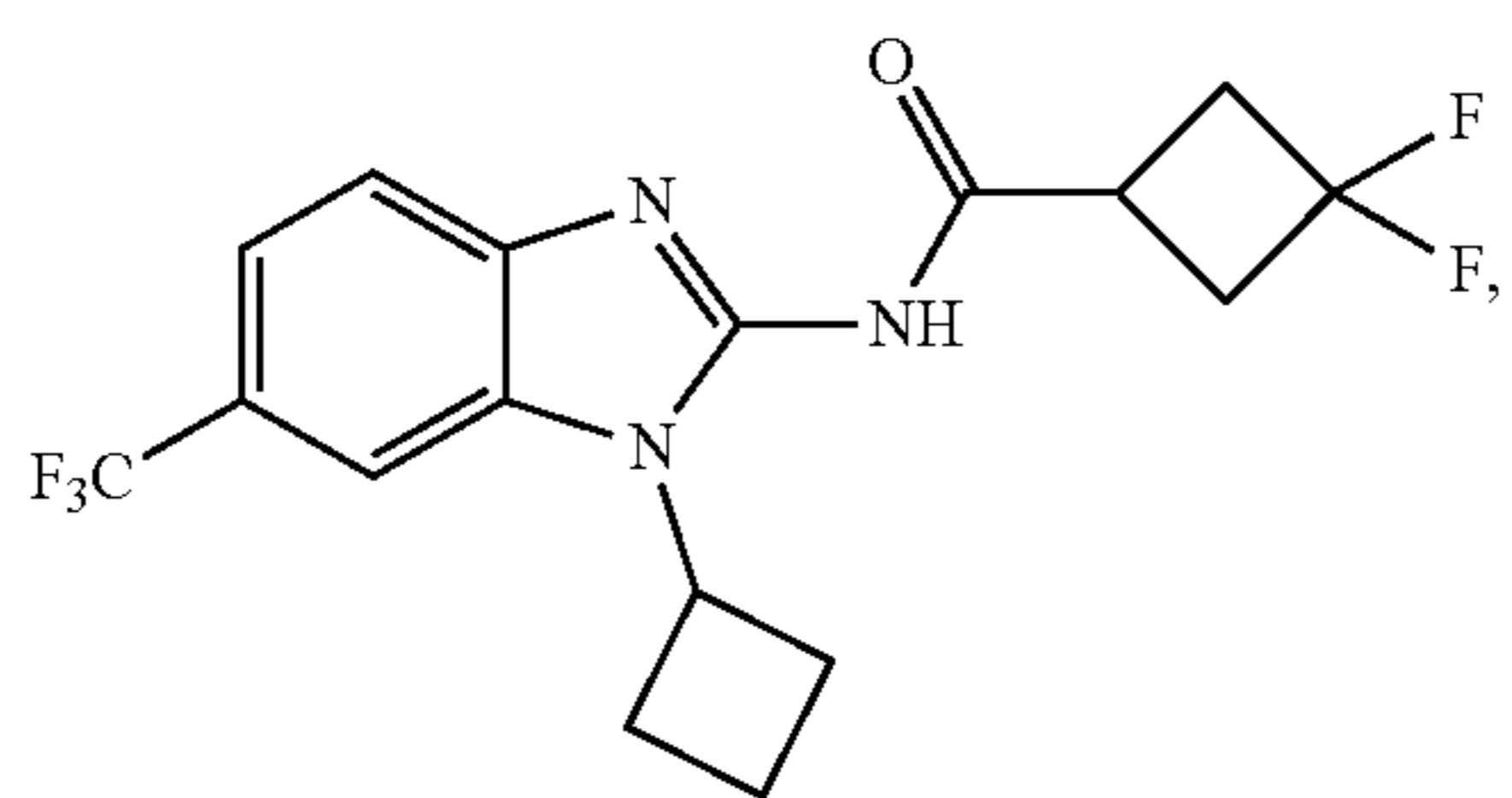
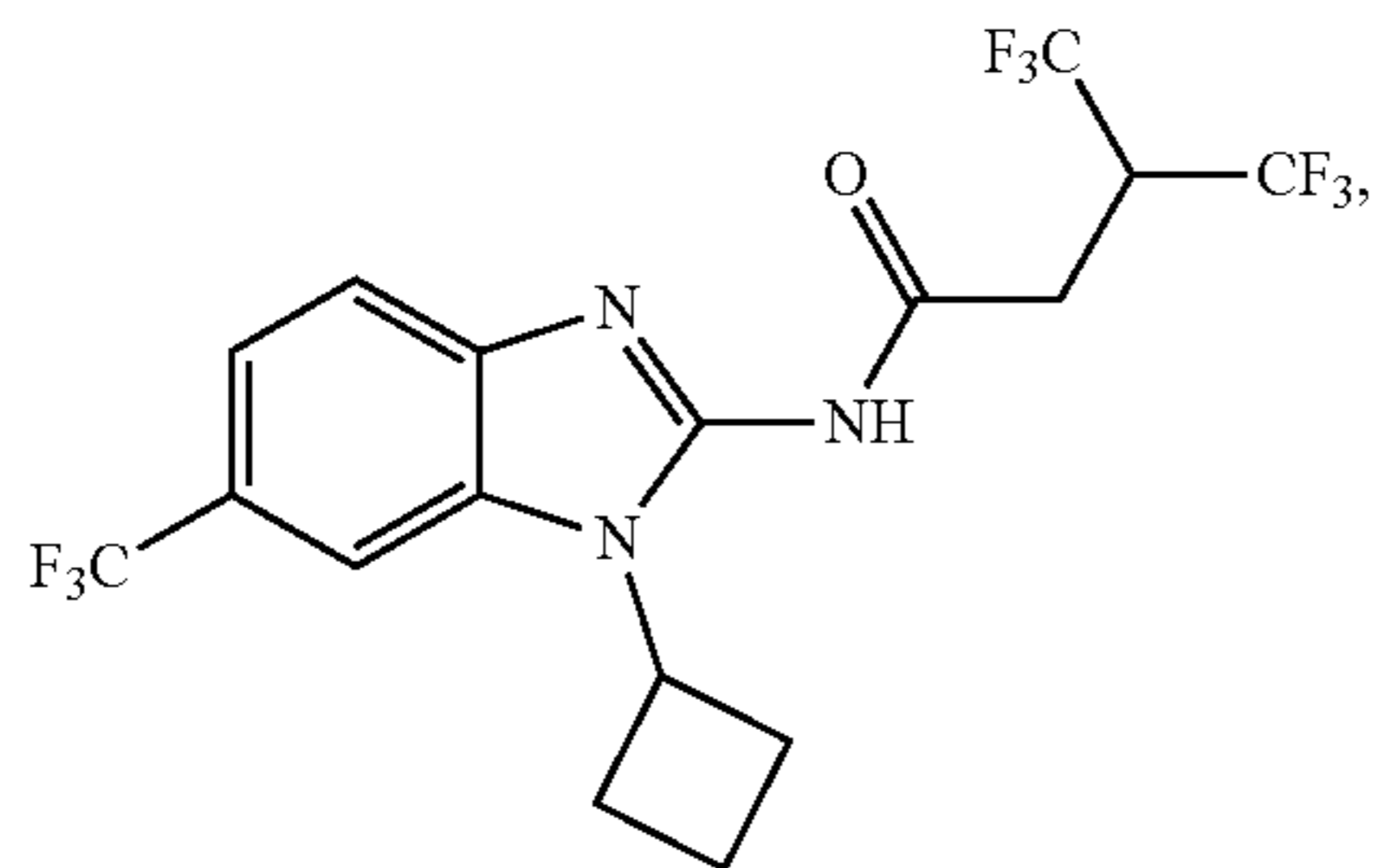
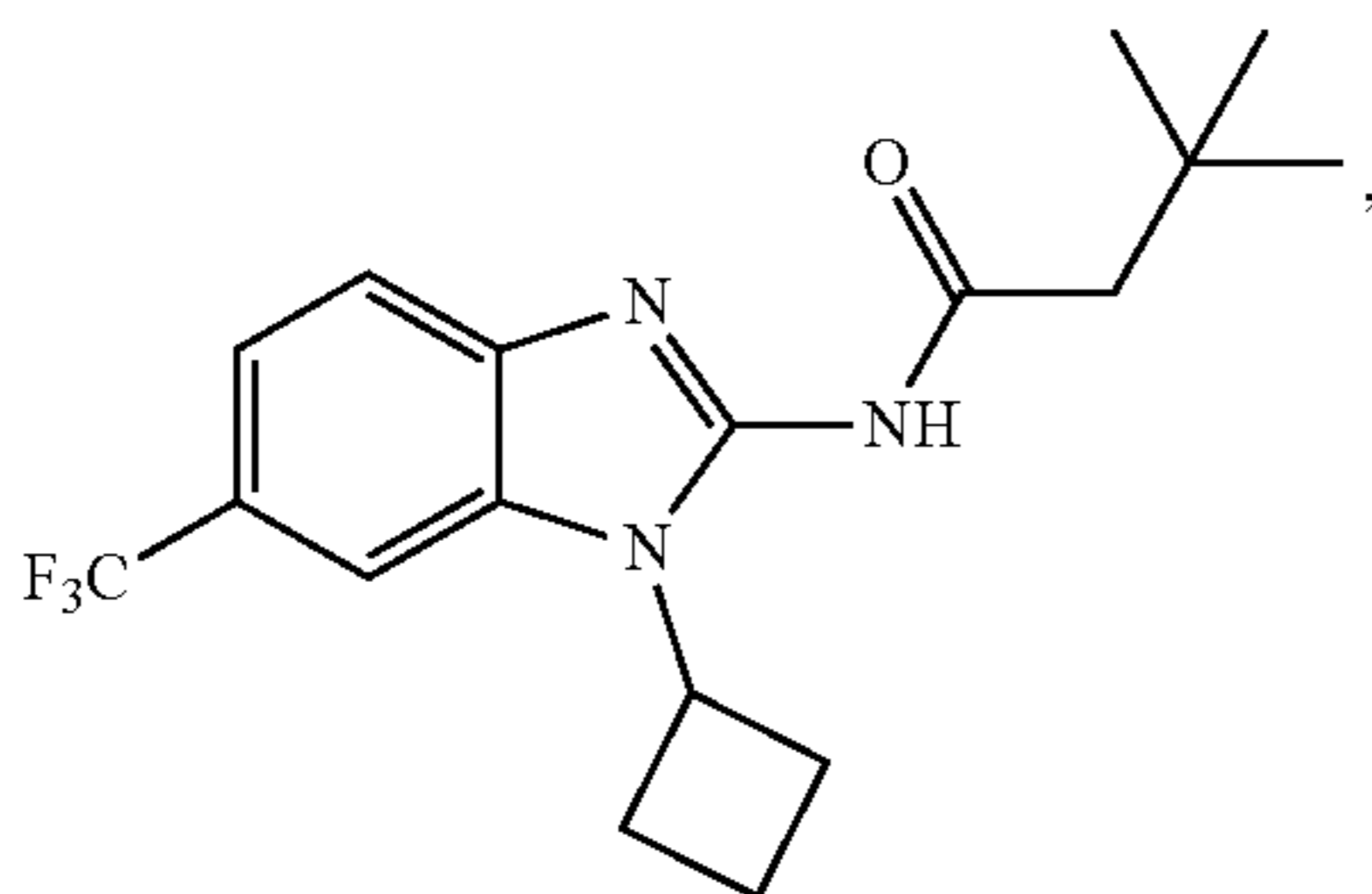
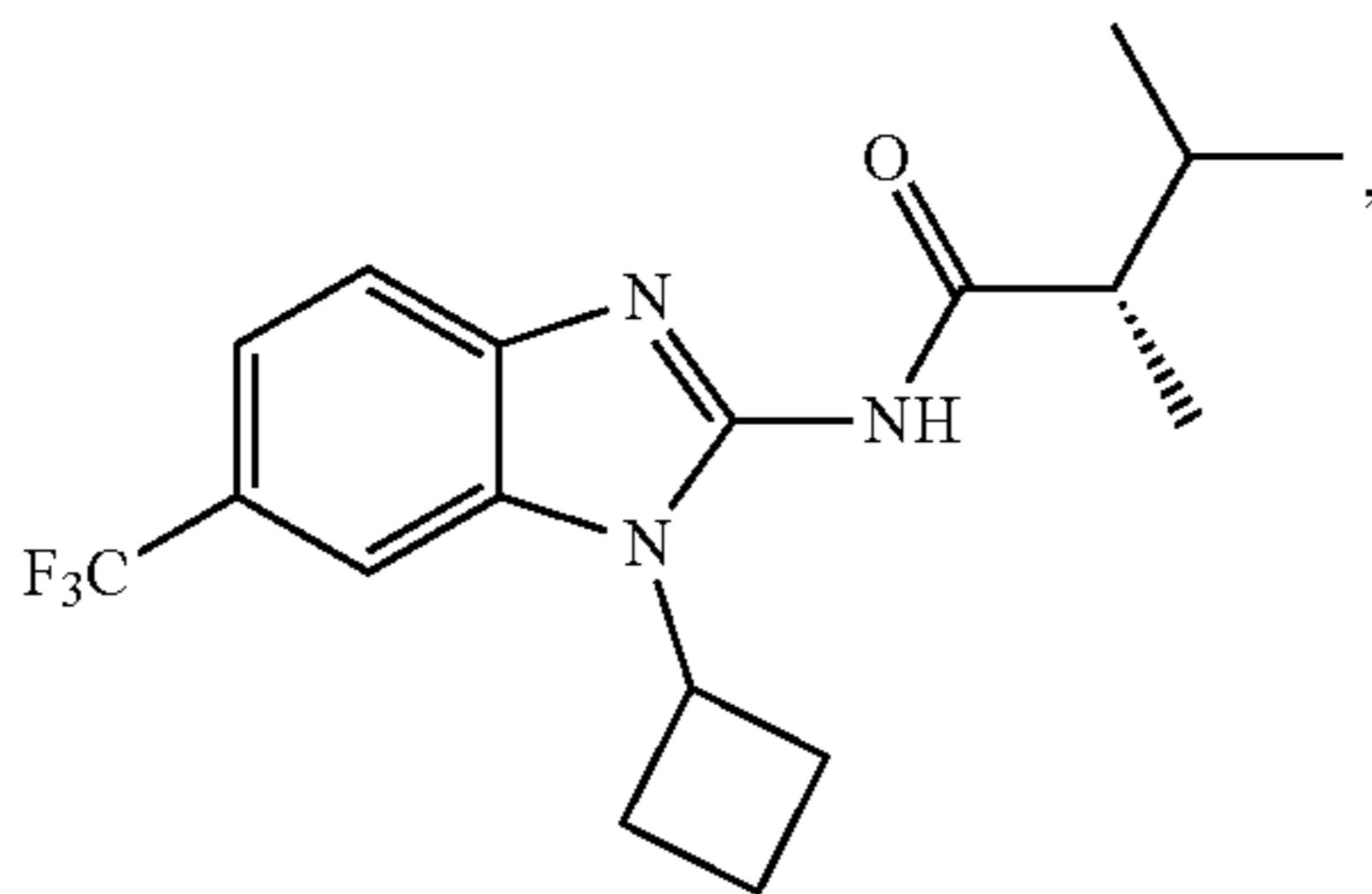
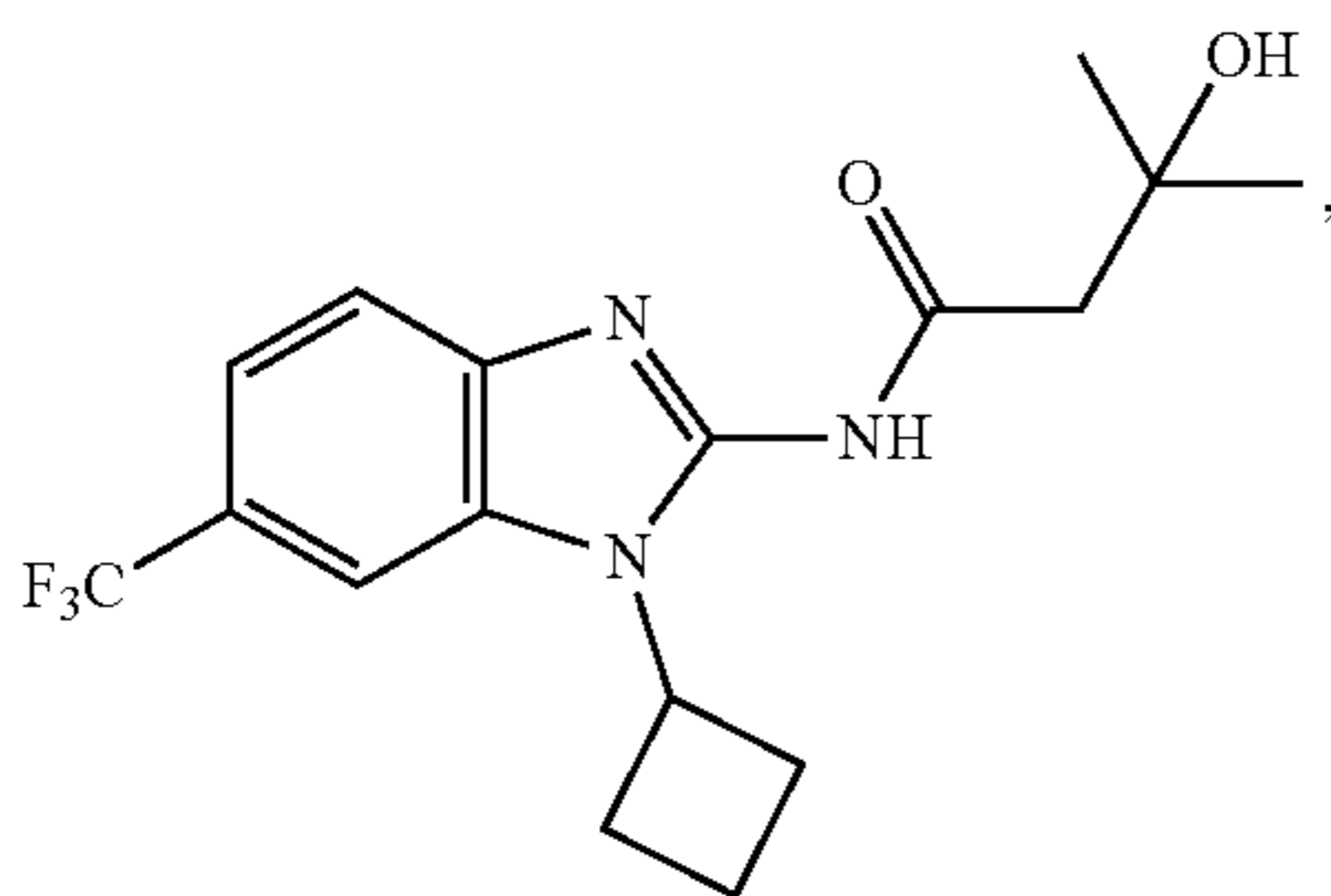
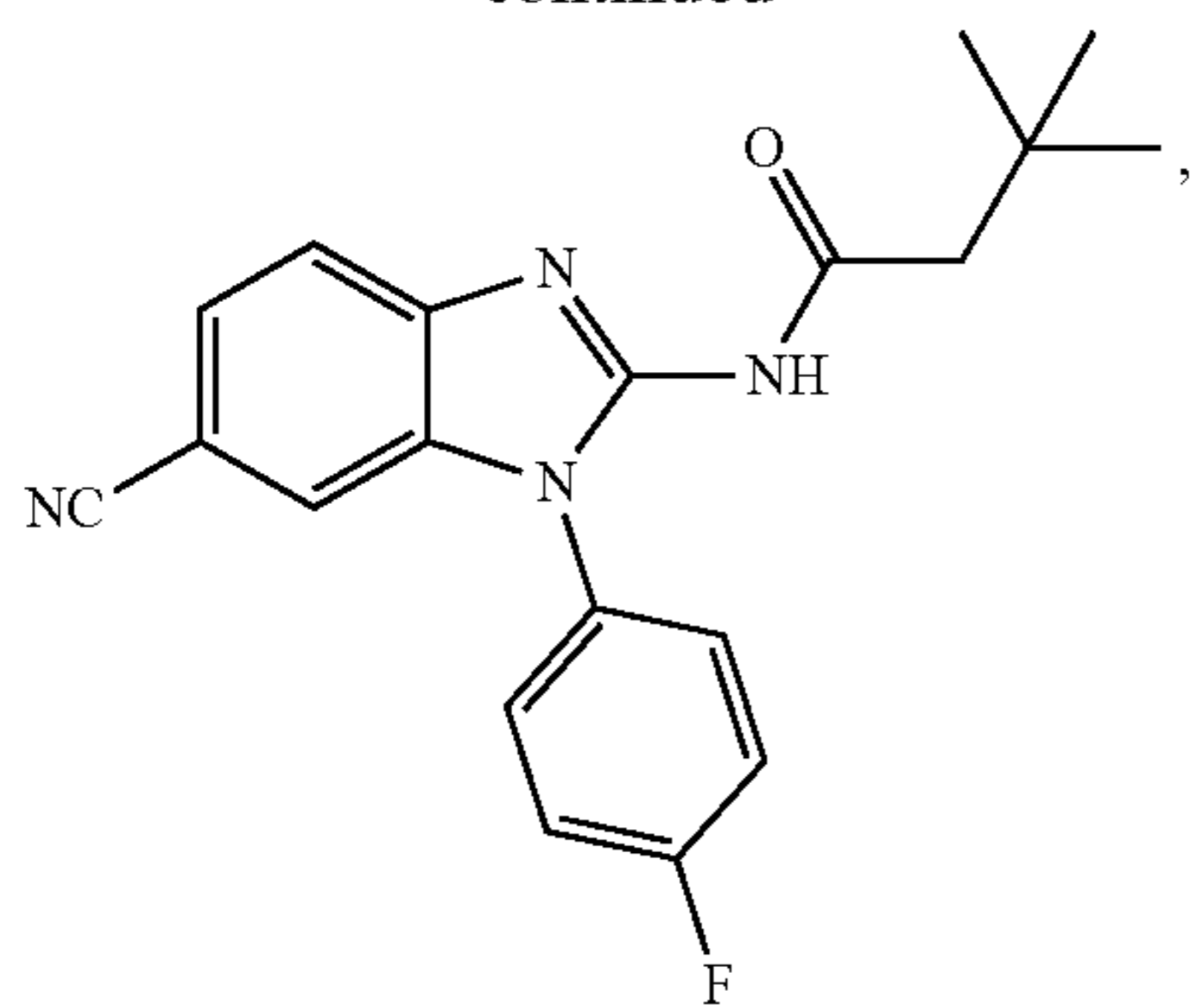


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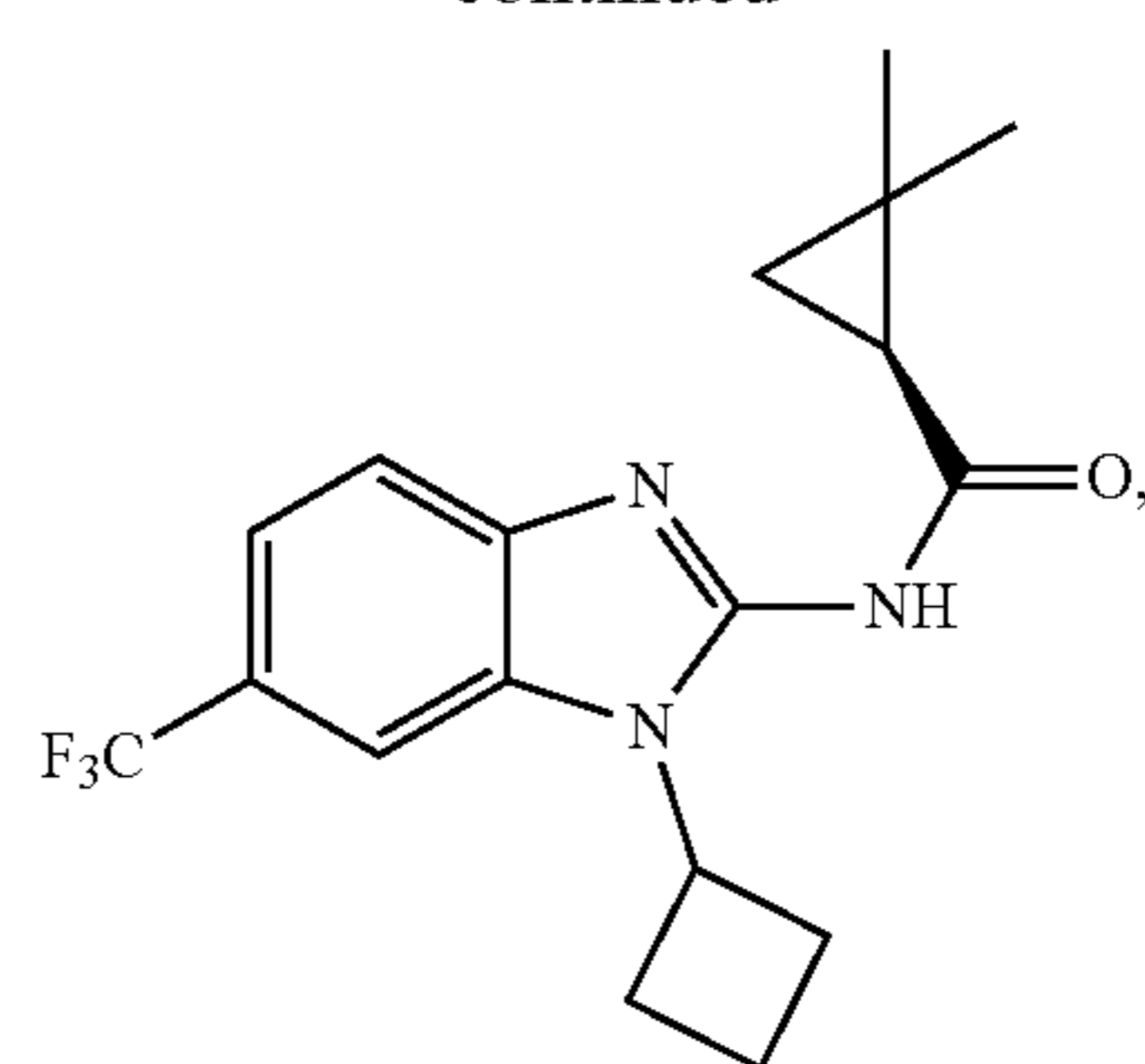
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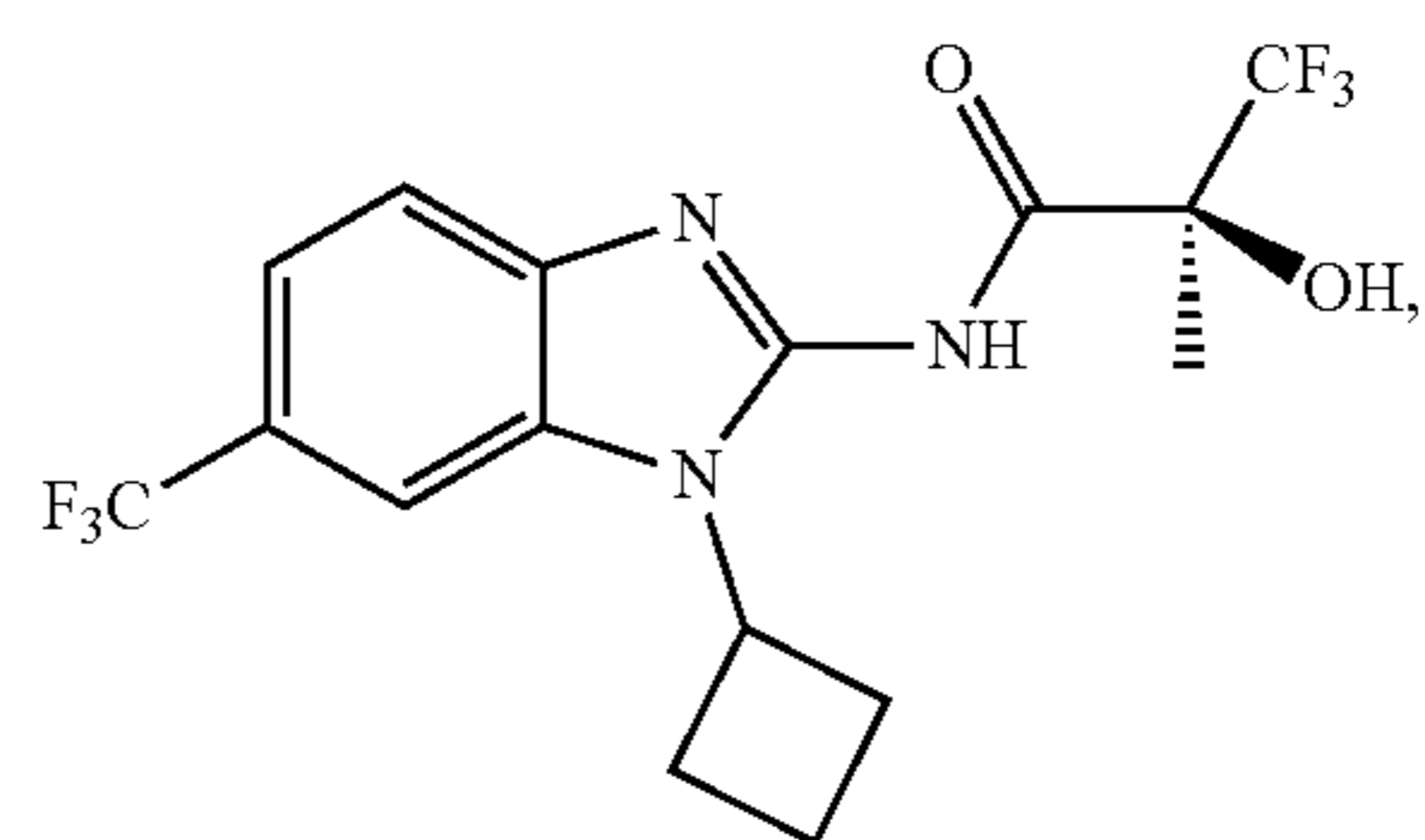
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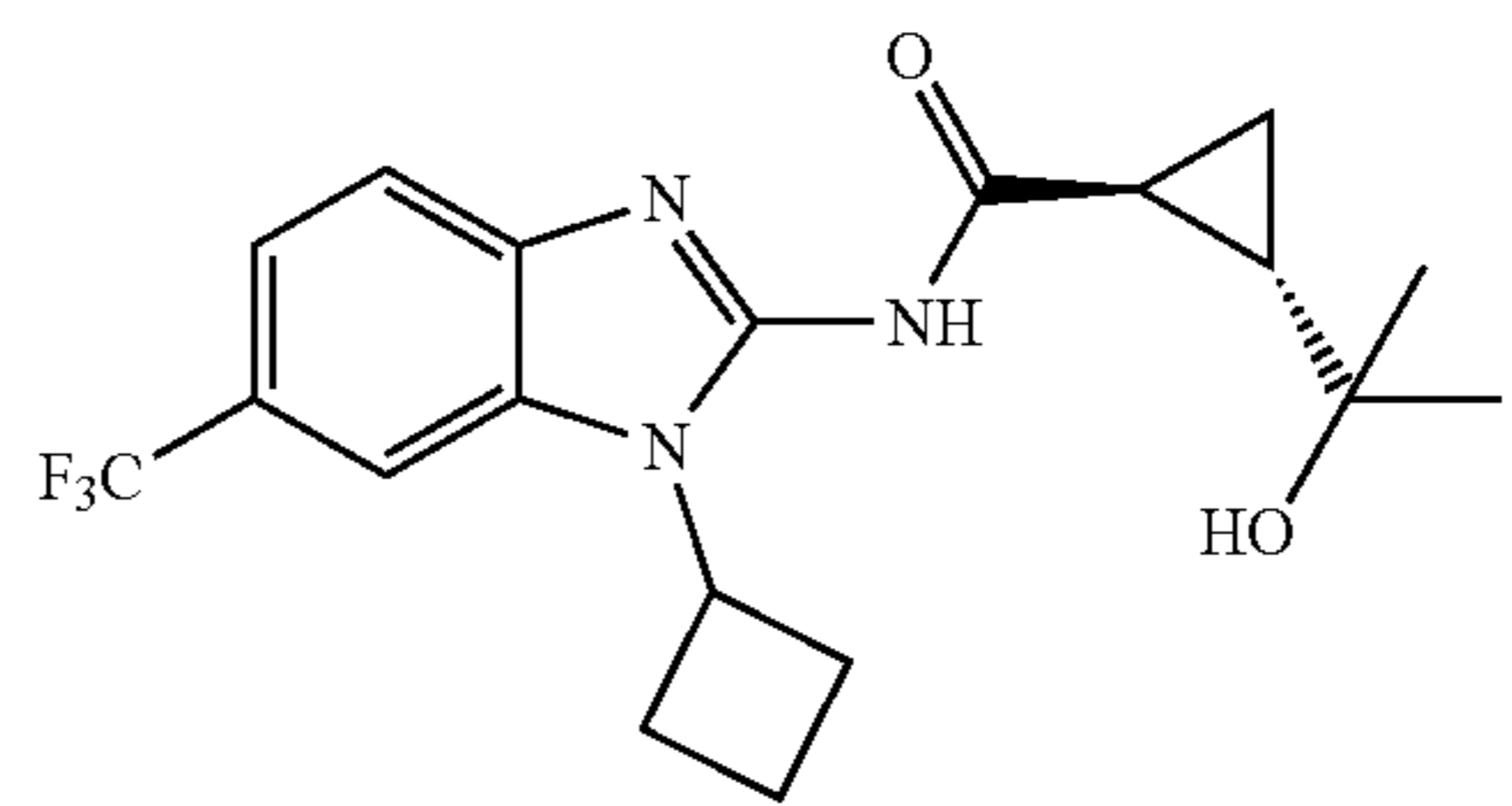


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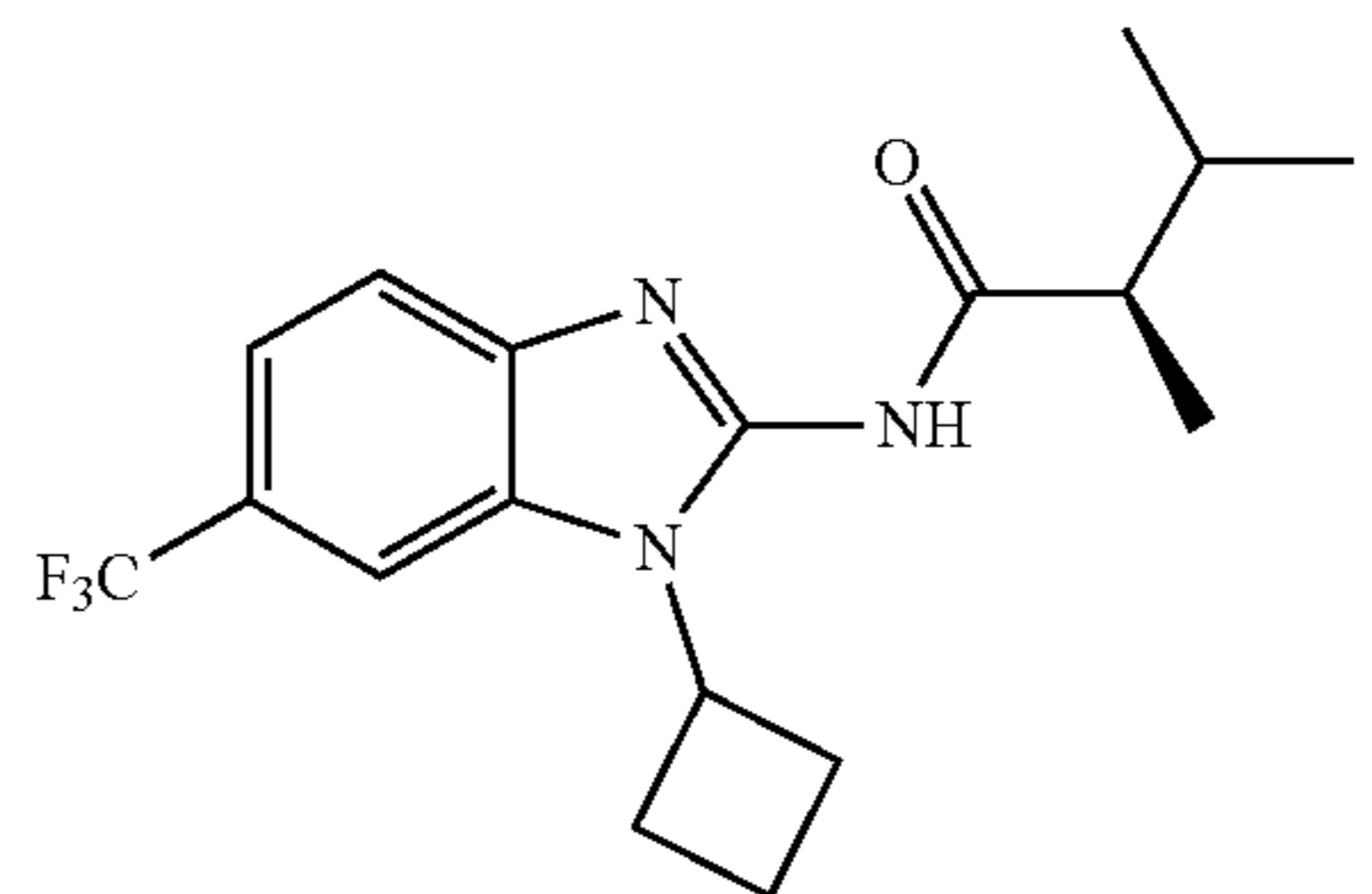
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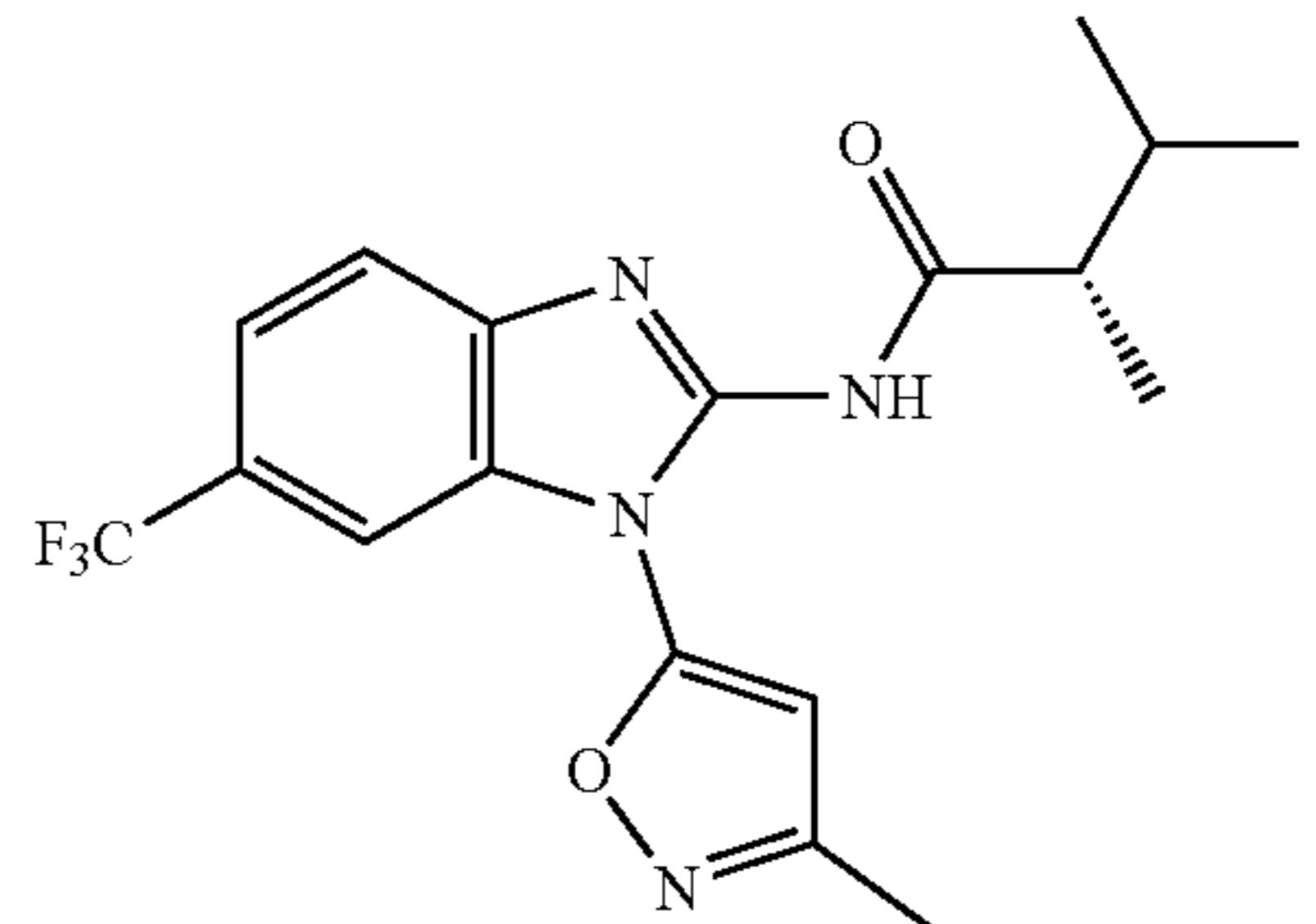
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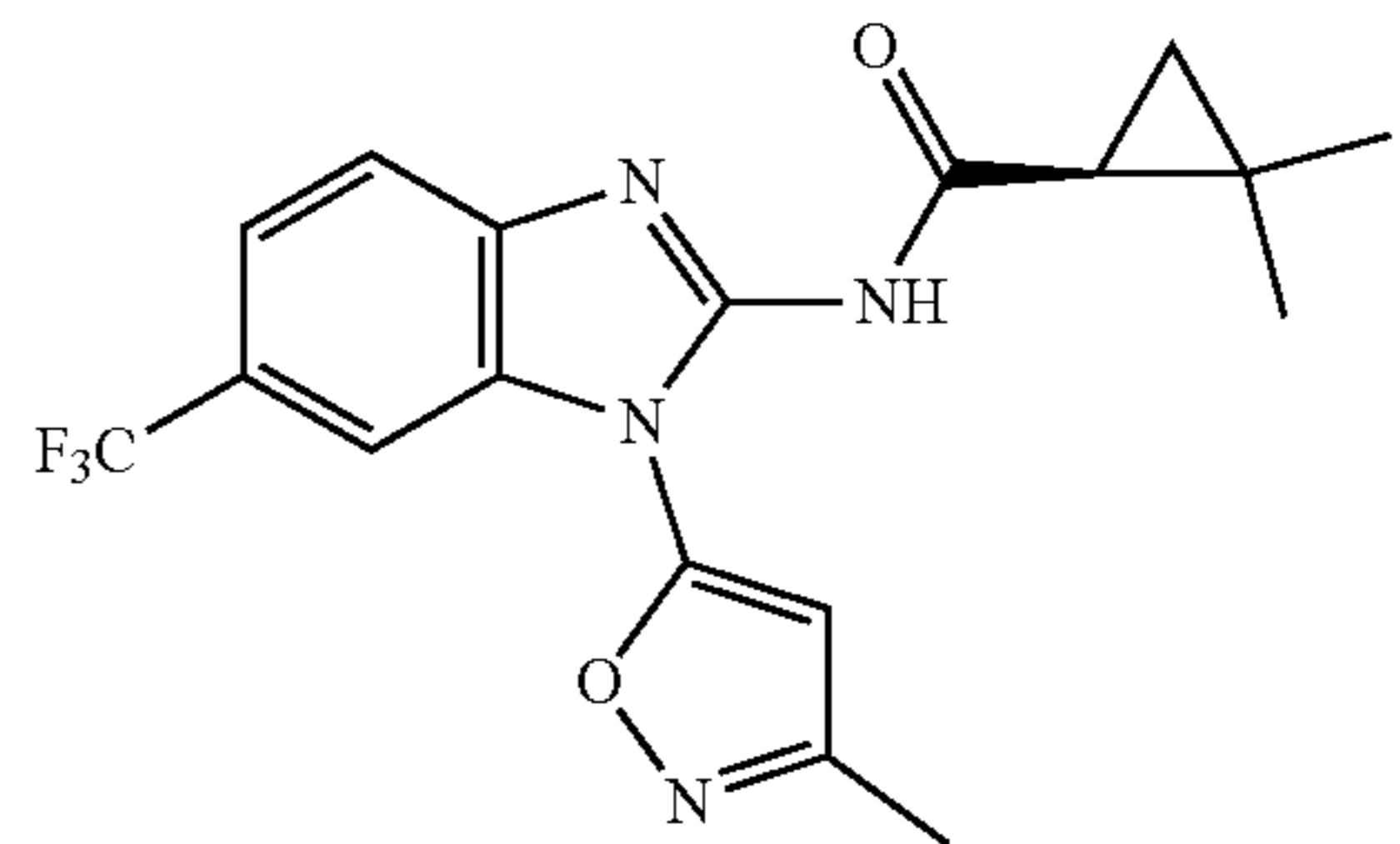
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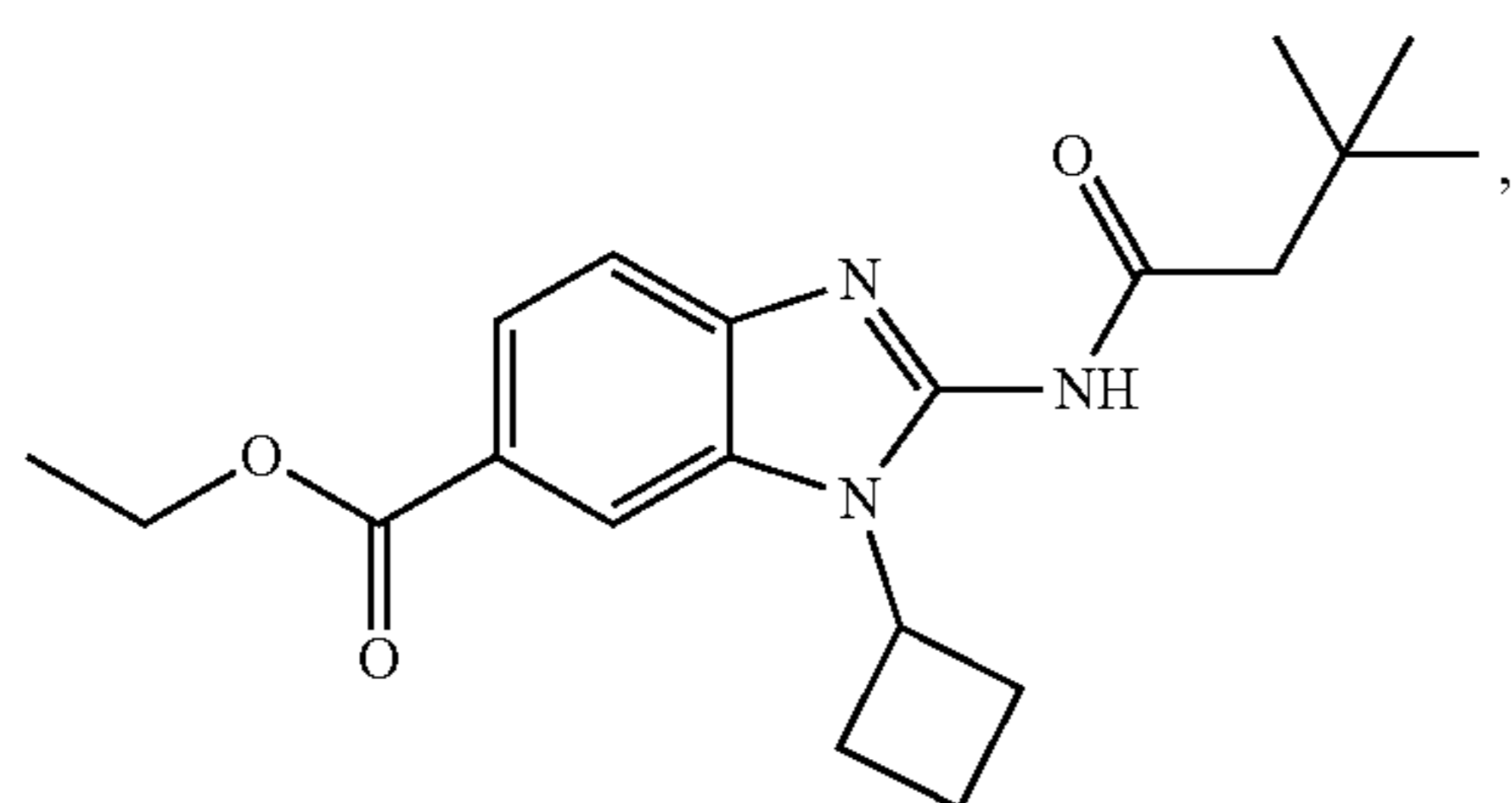
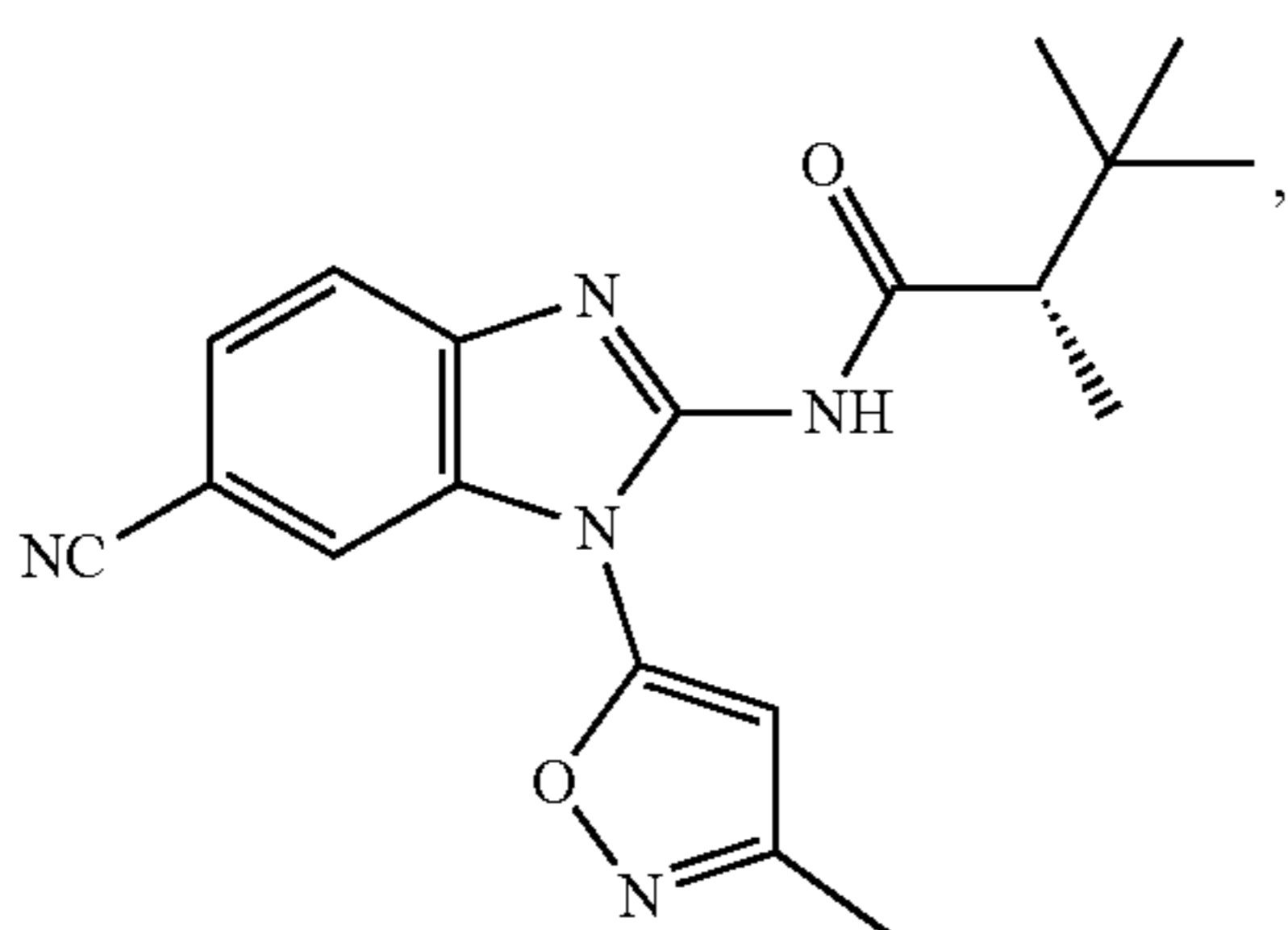
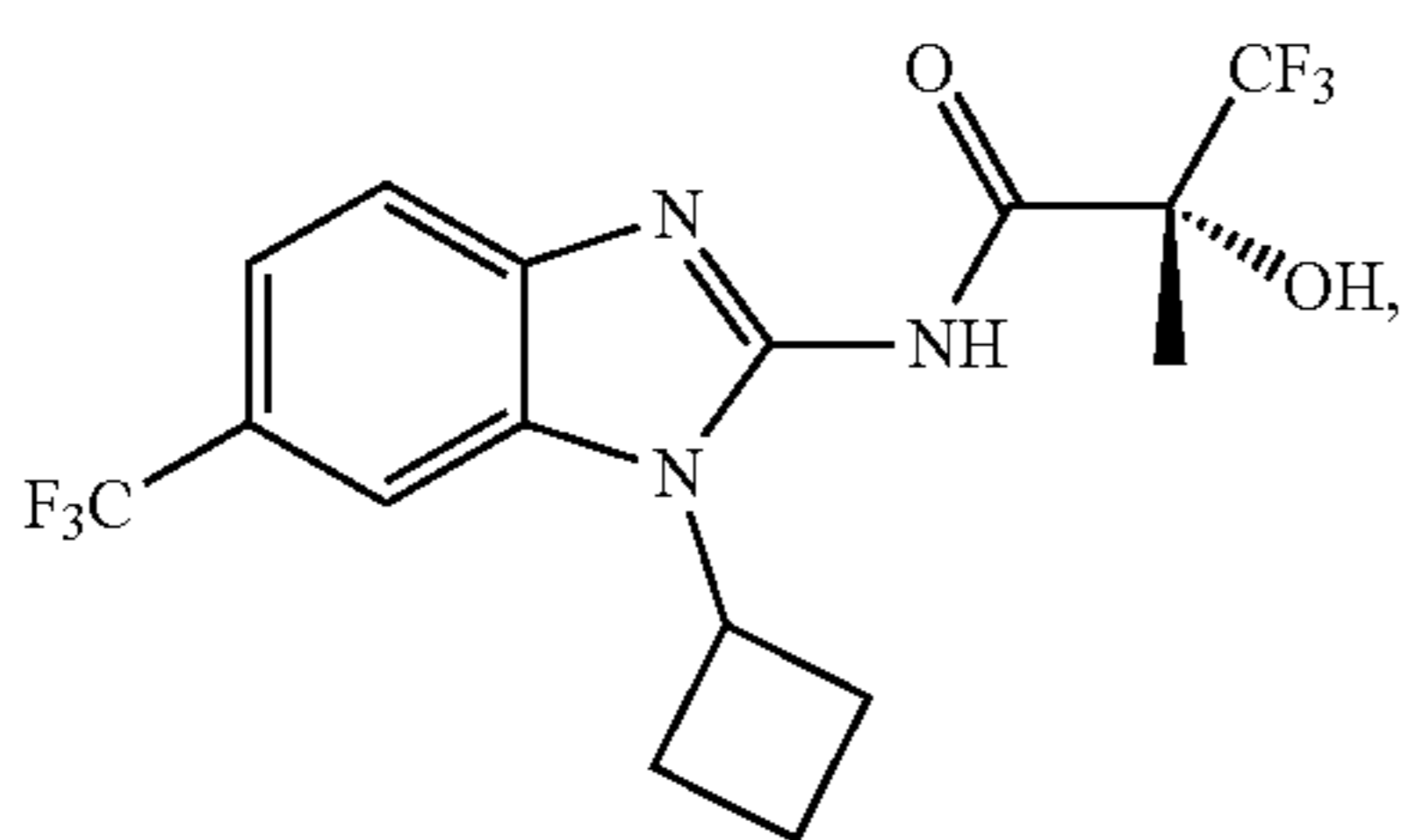
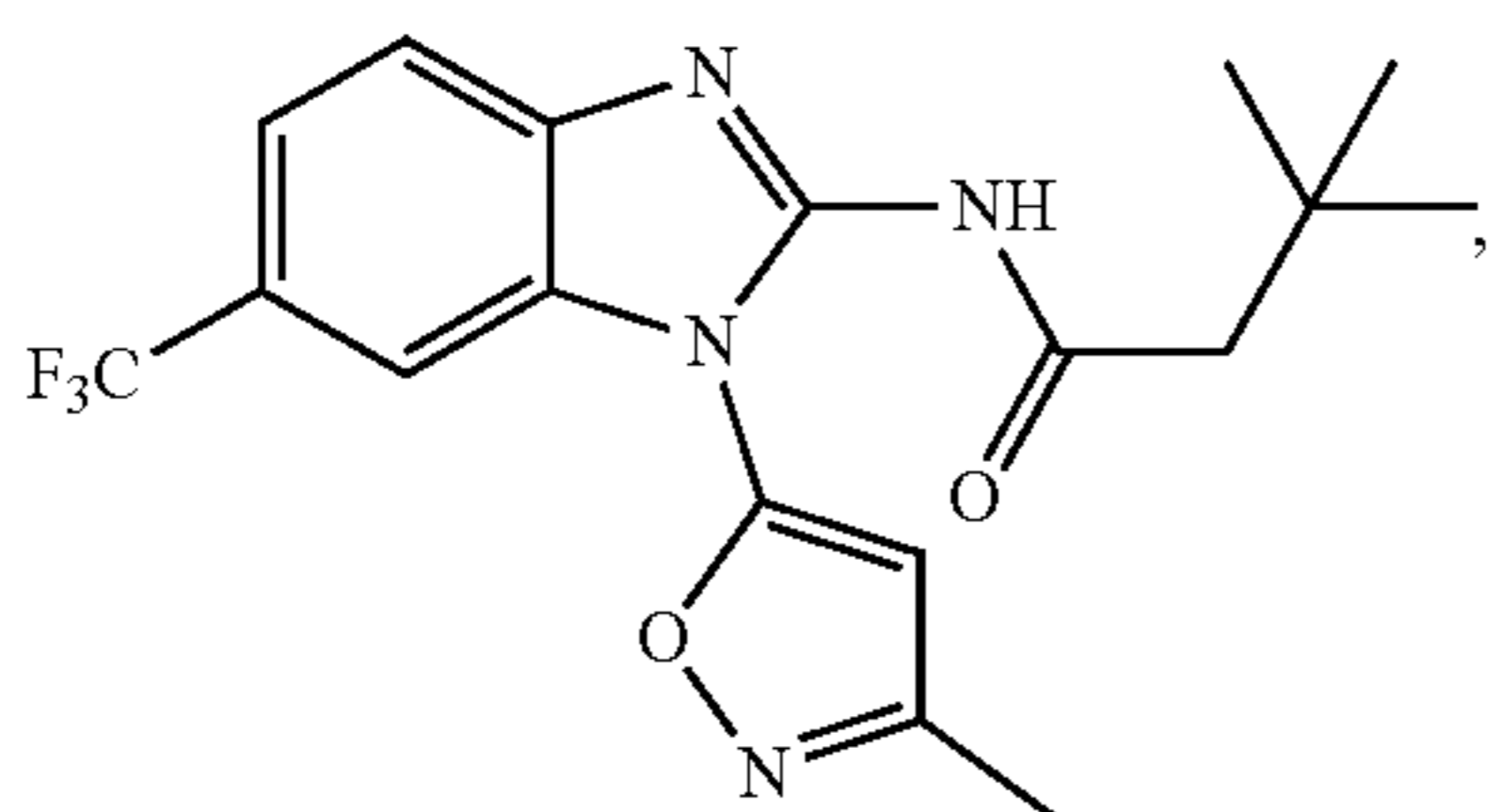
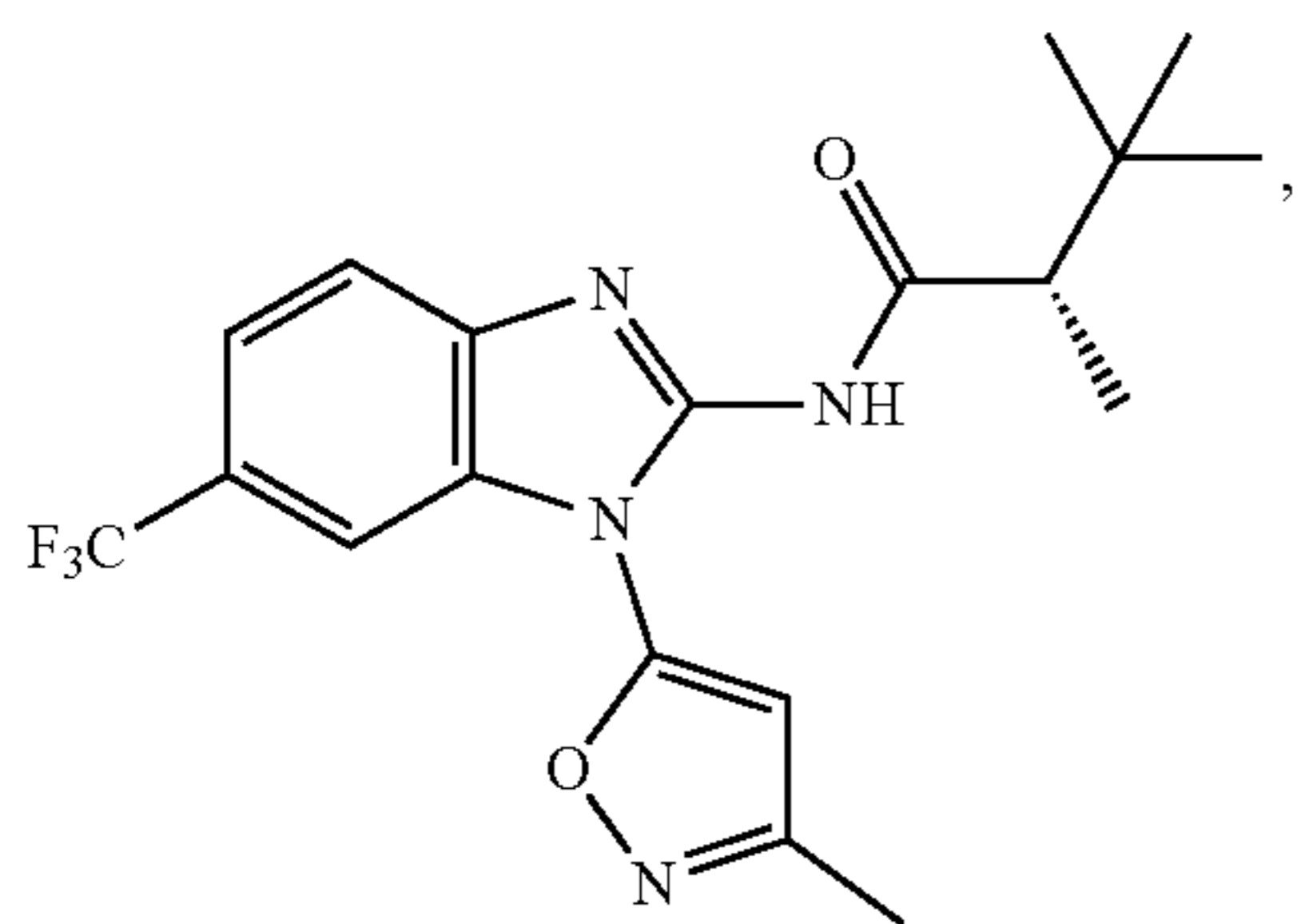
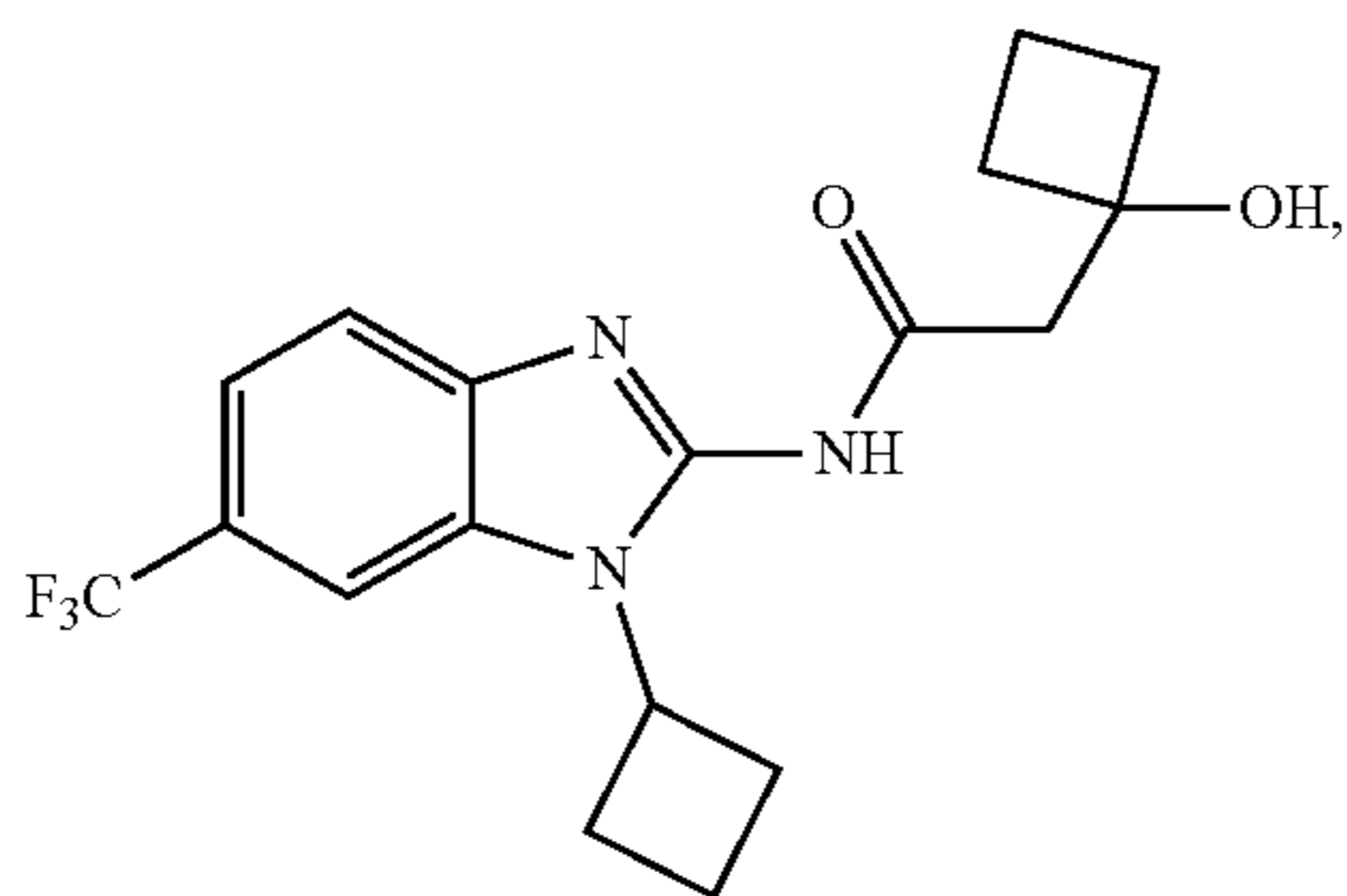
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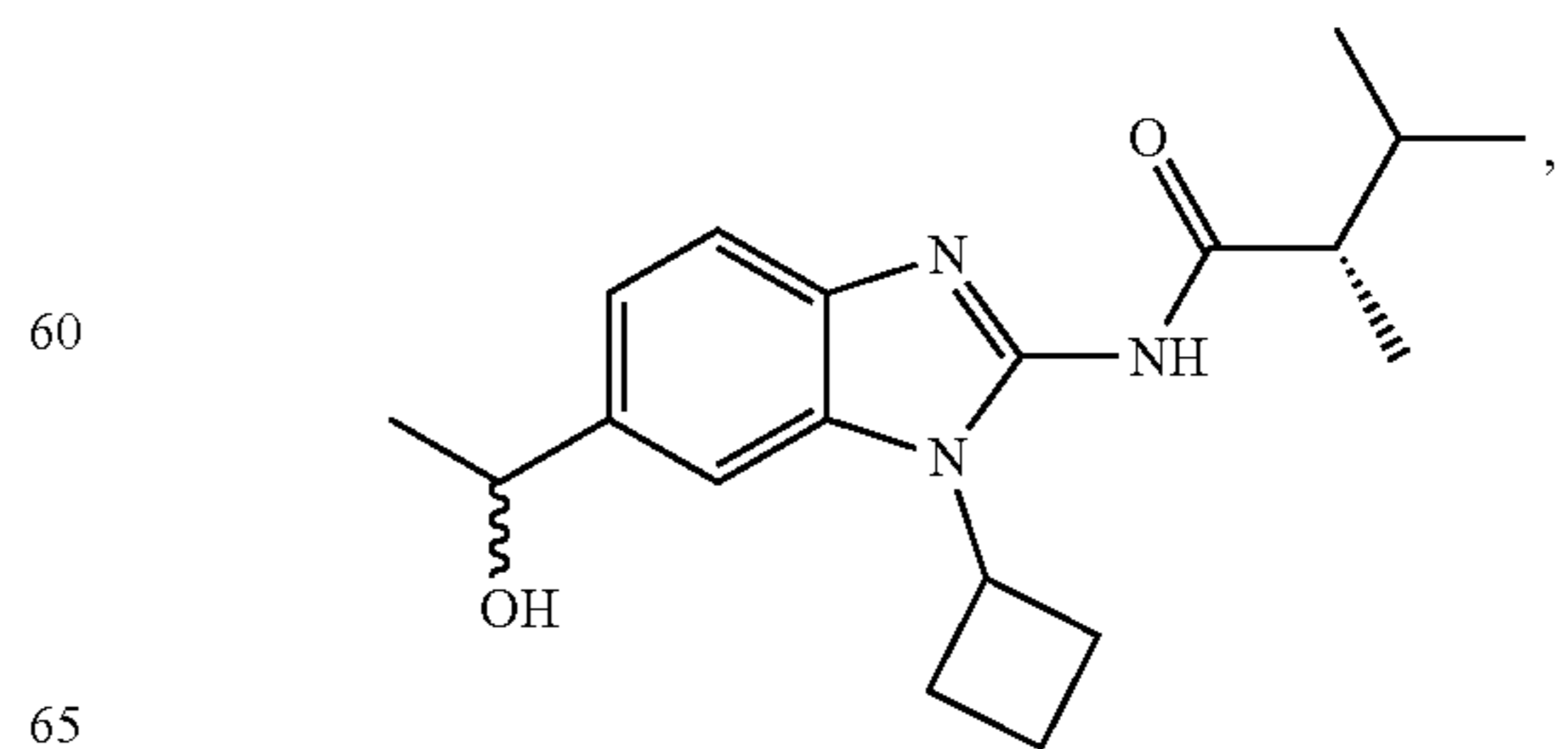
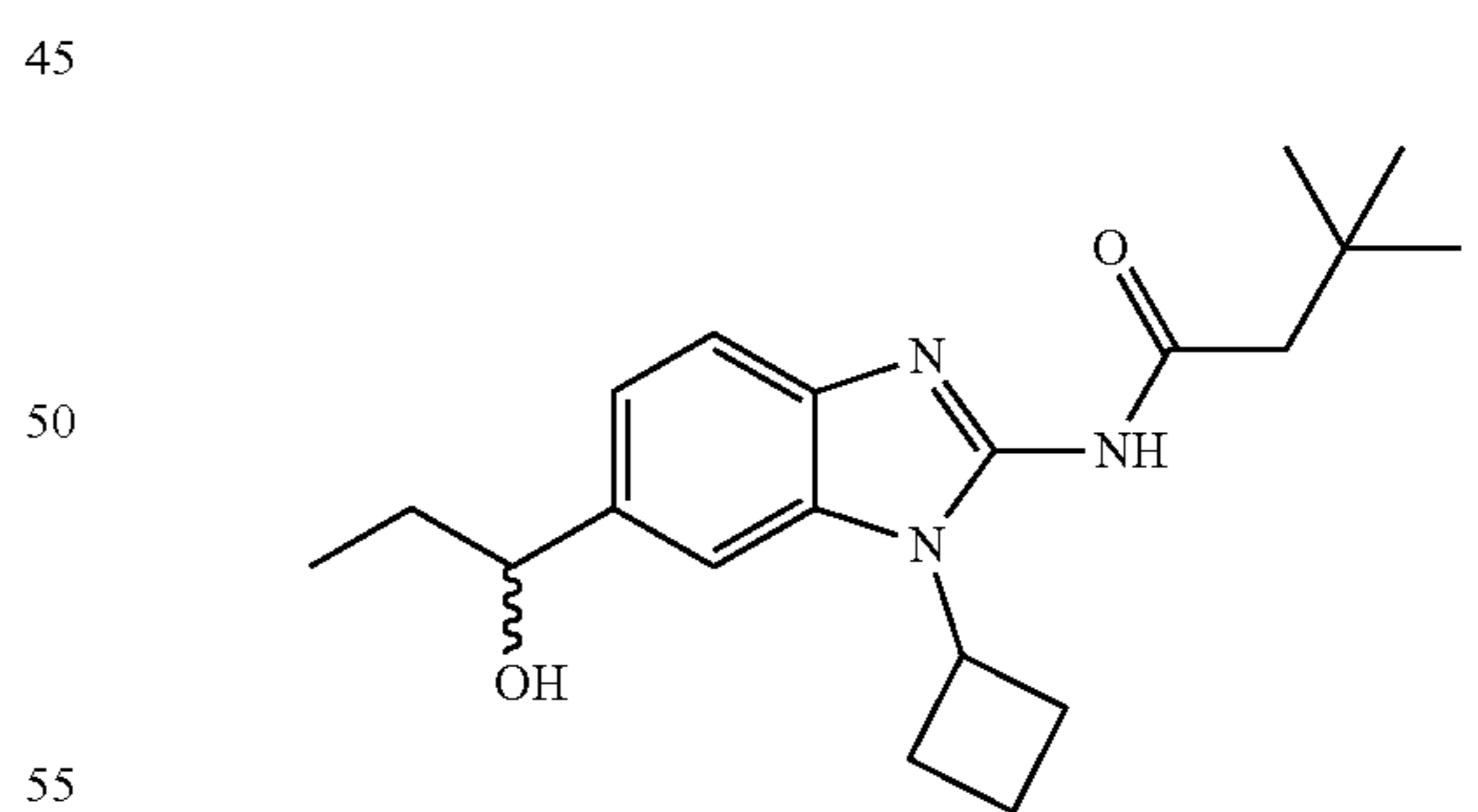
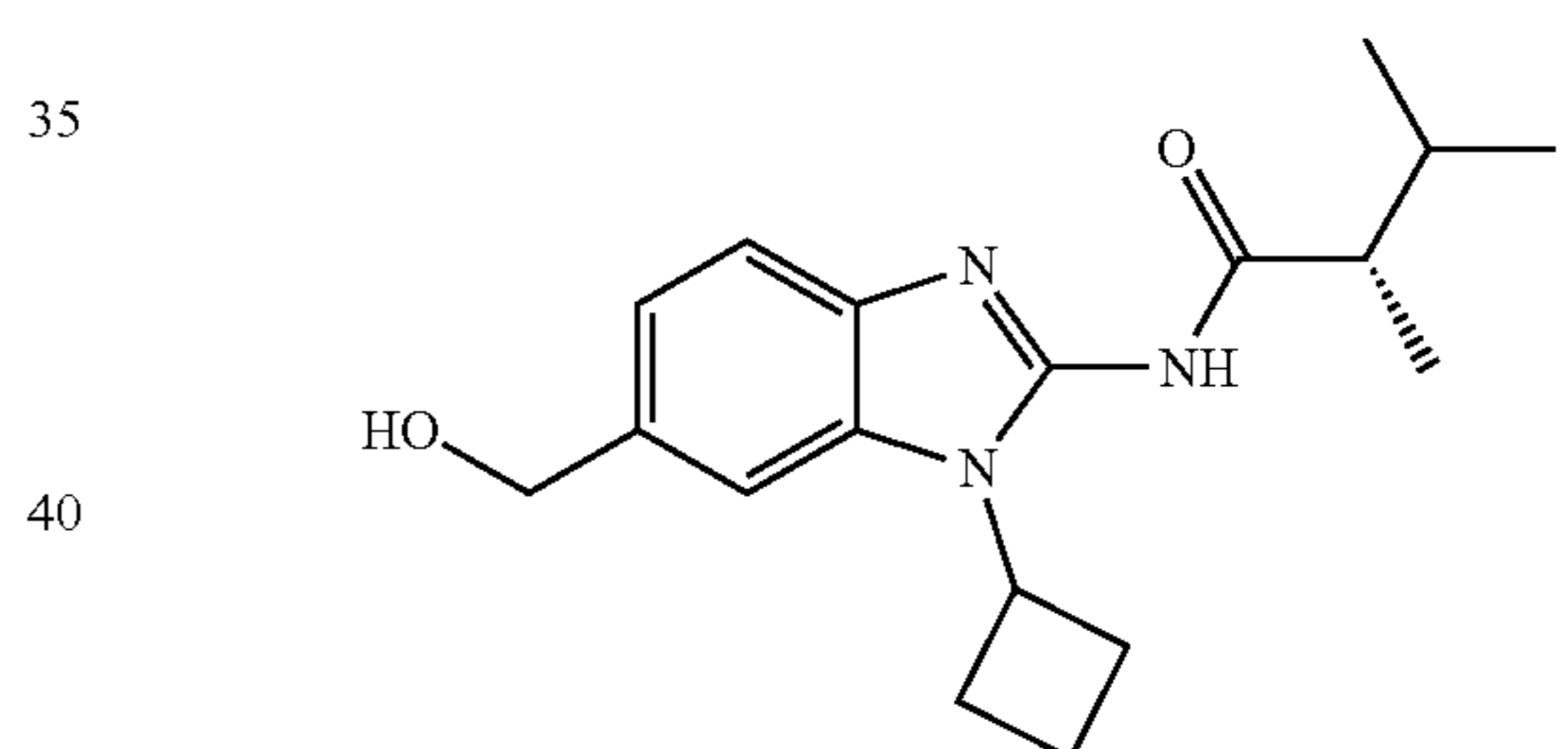
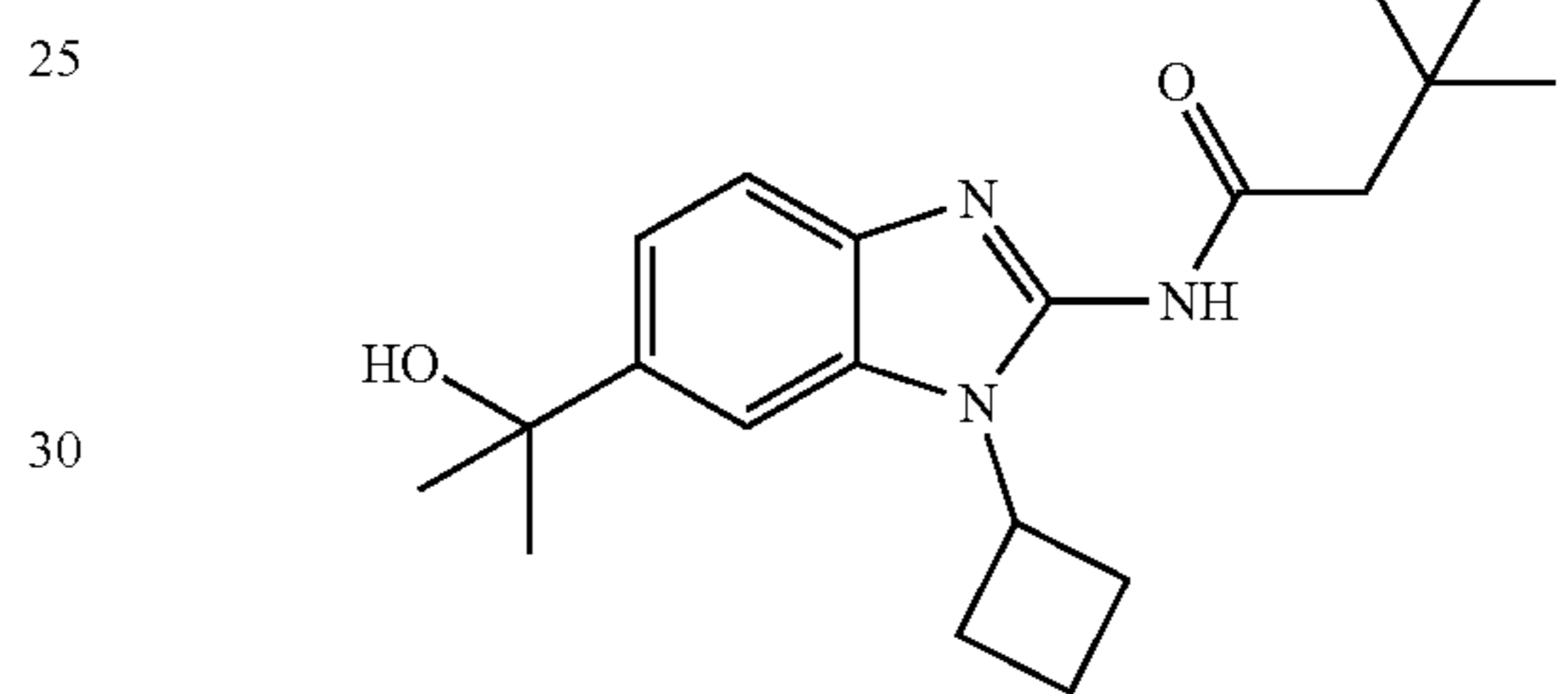
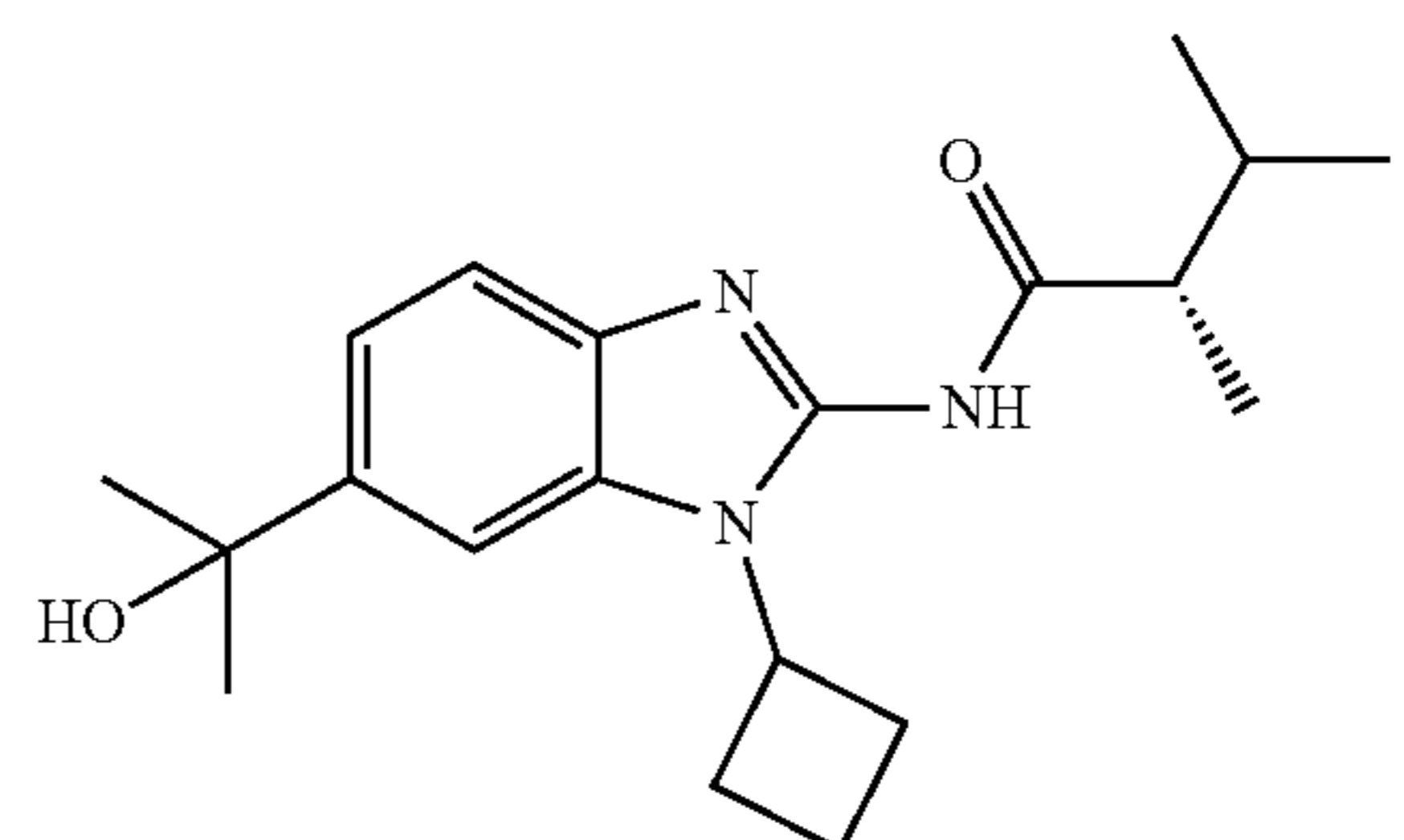
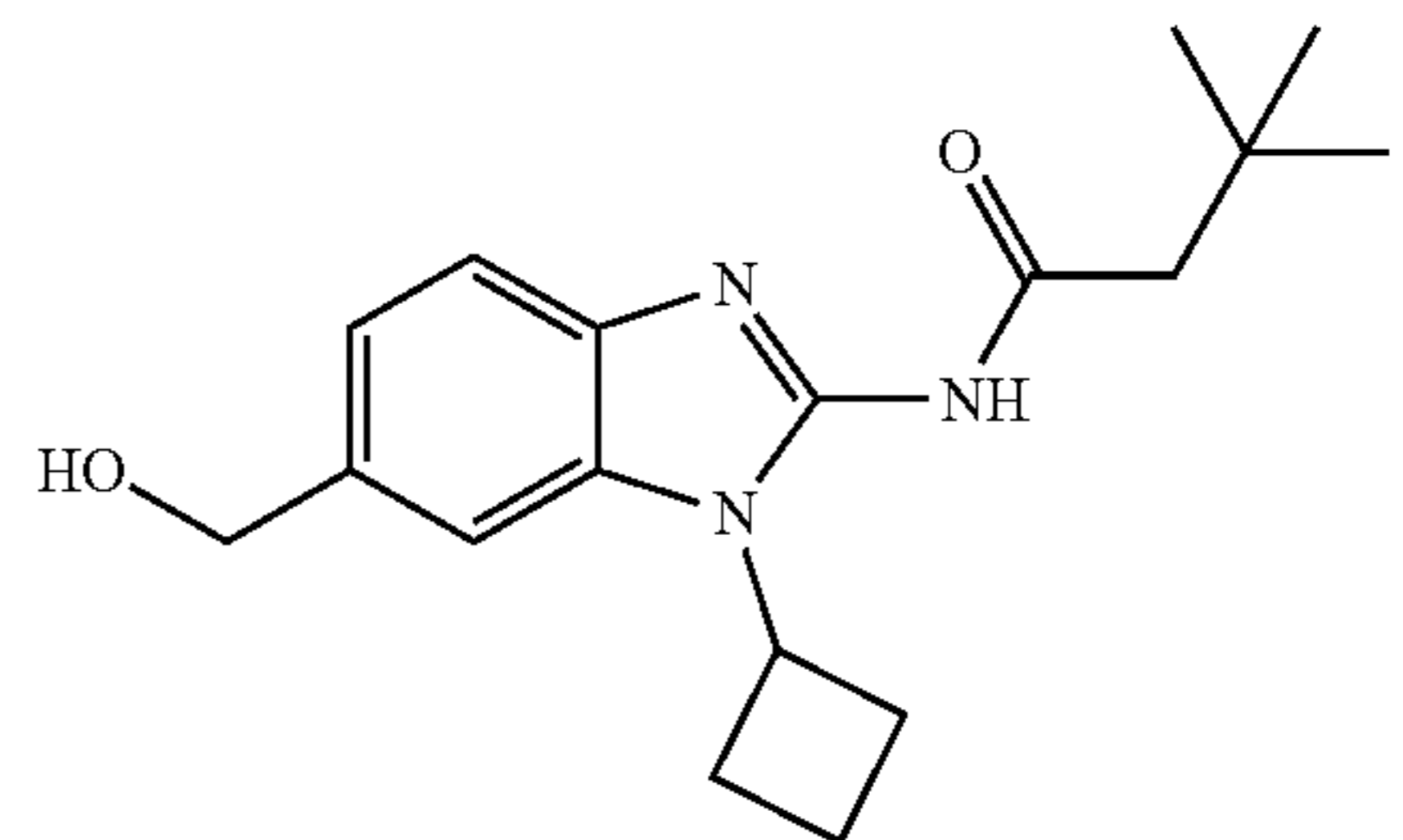
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26

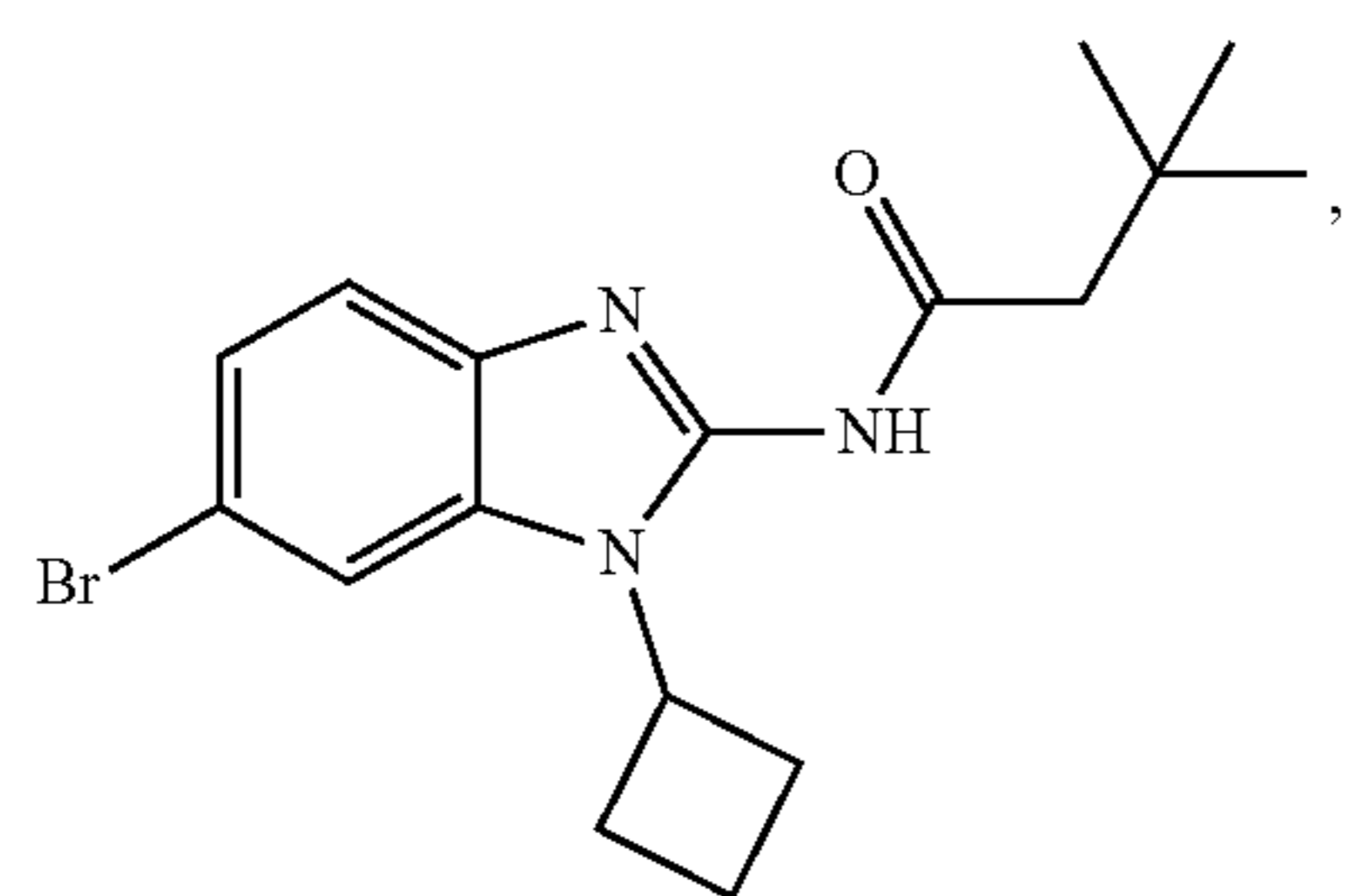
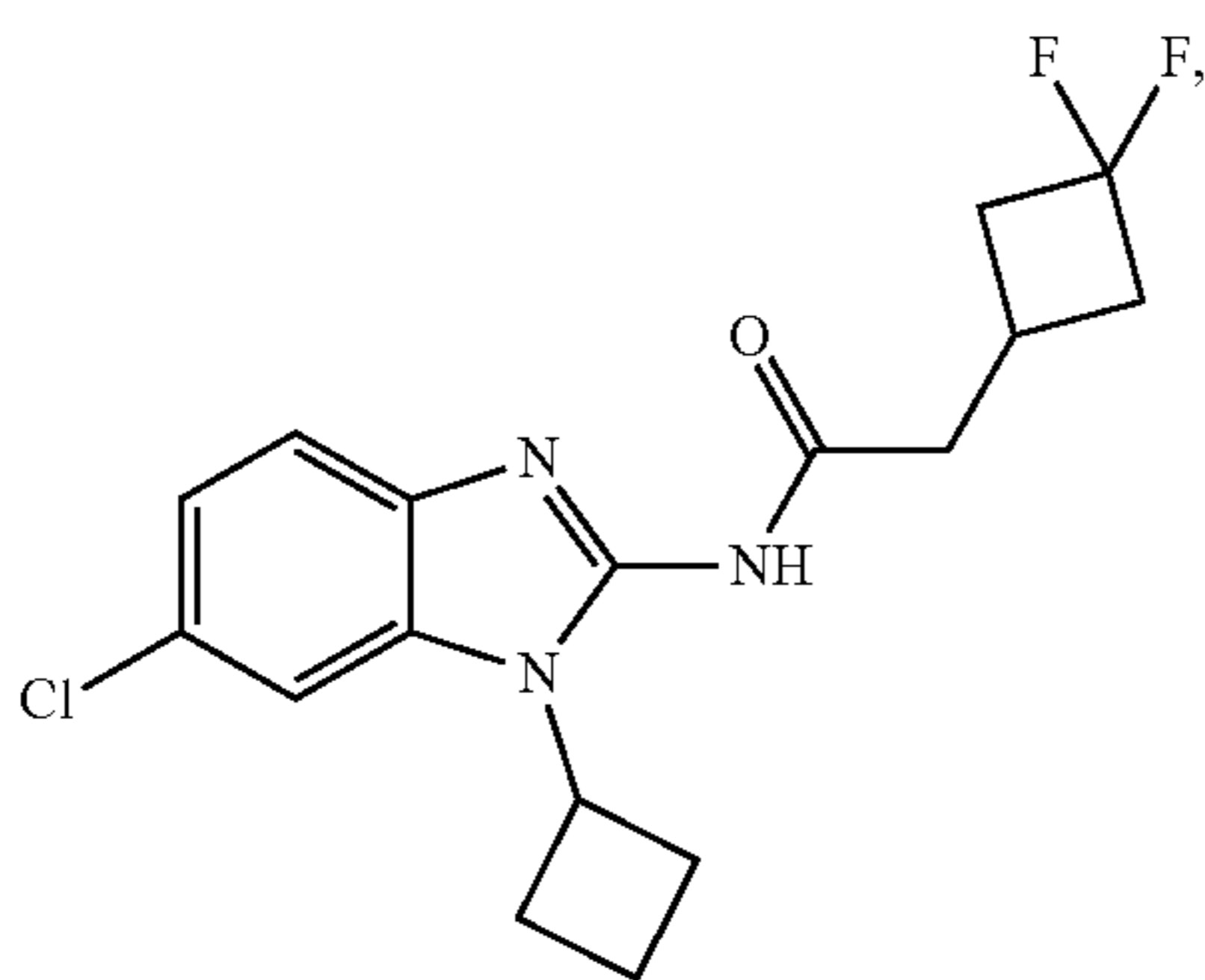
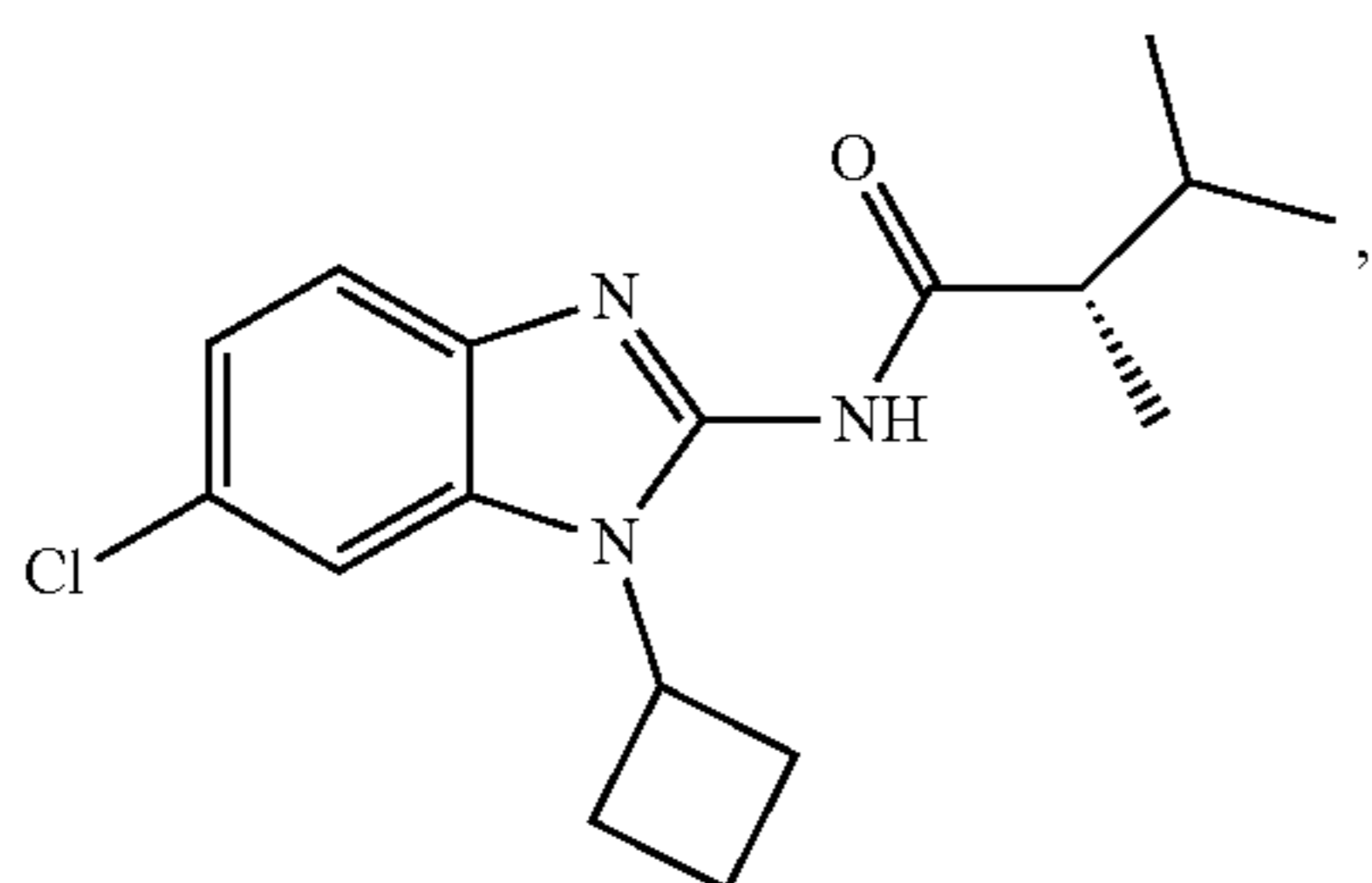
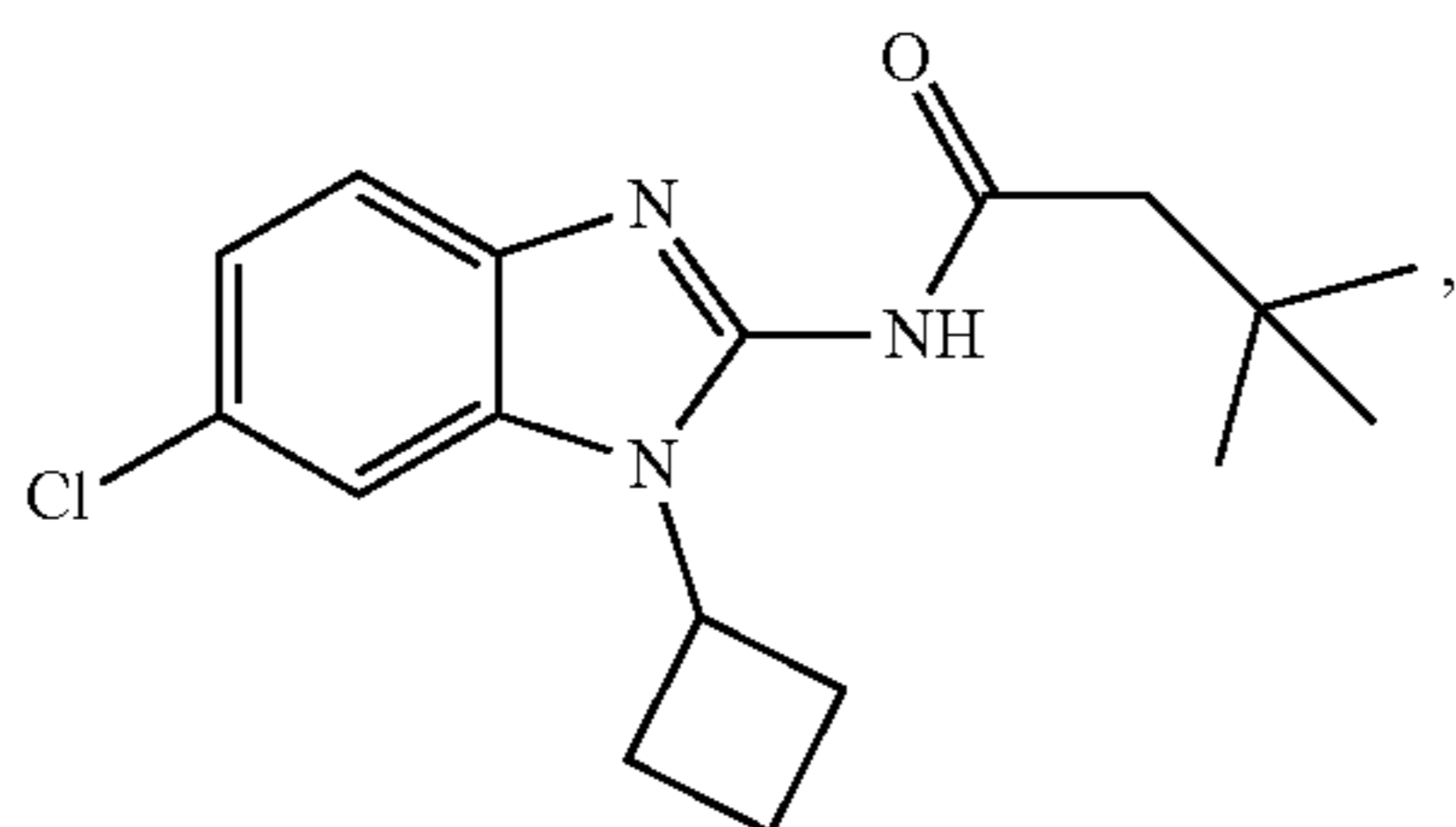
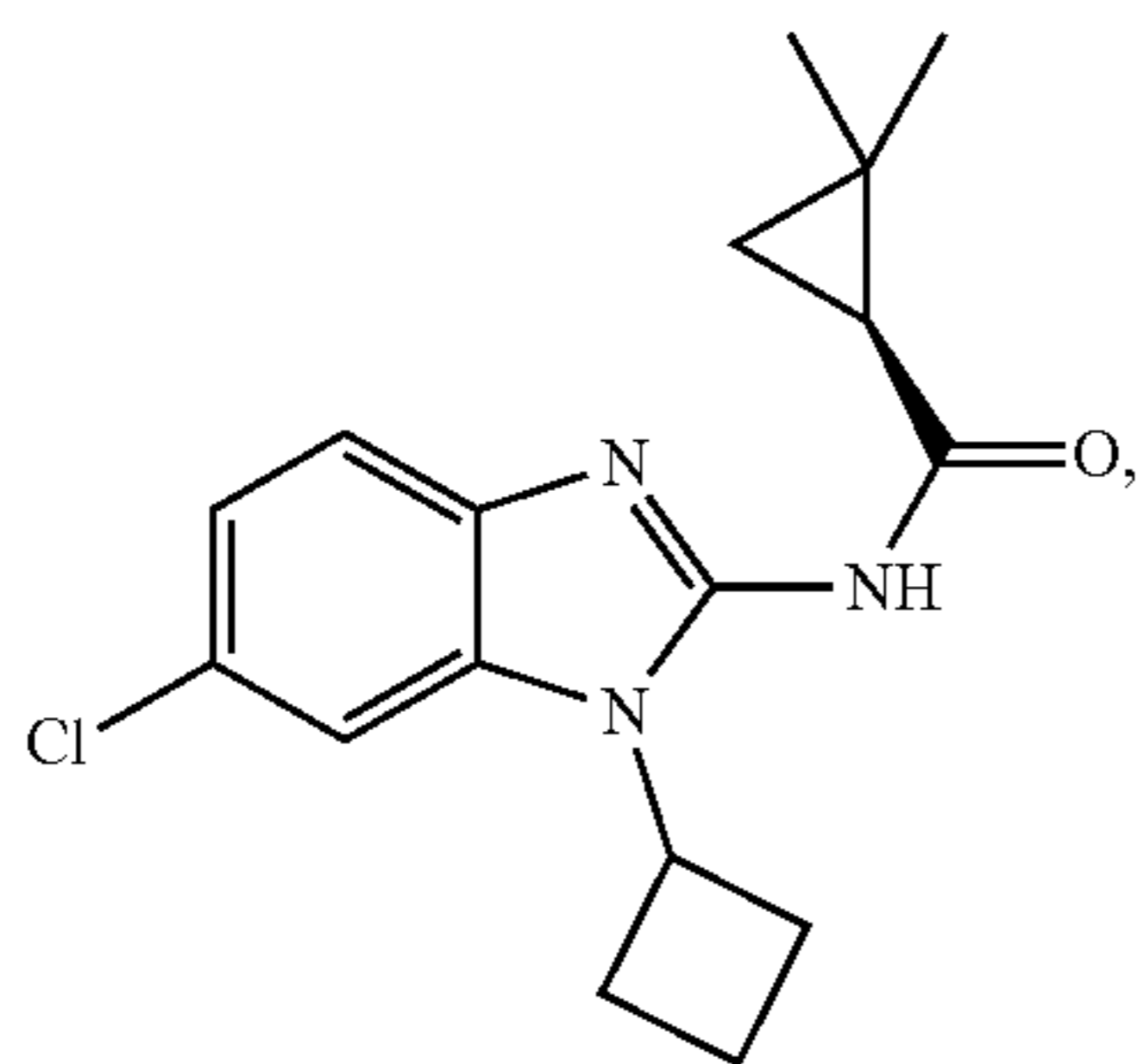
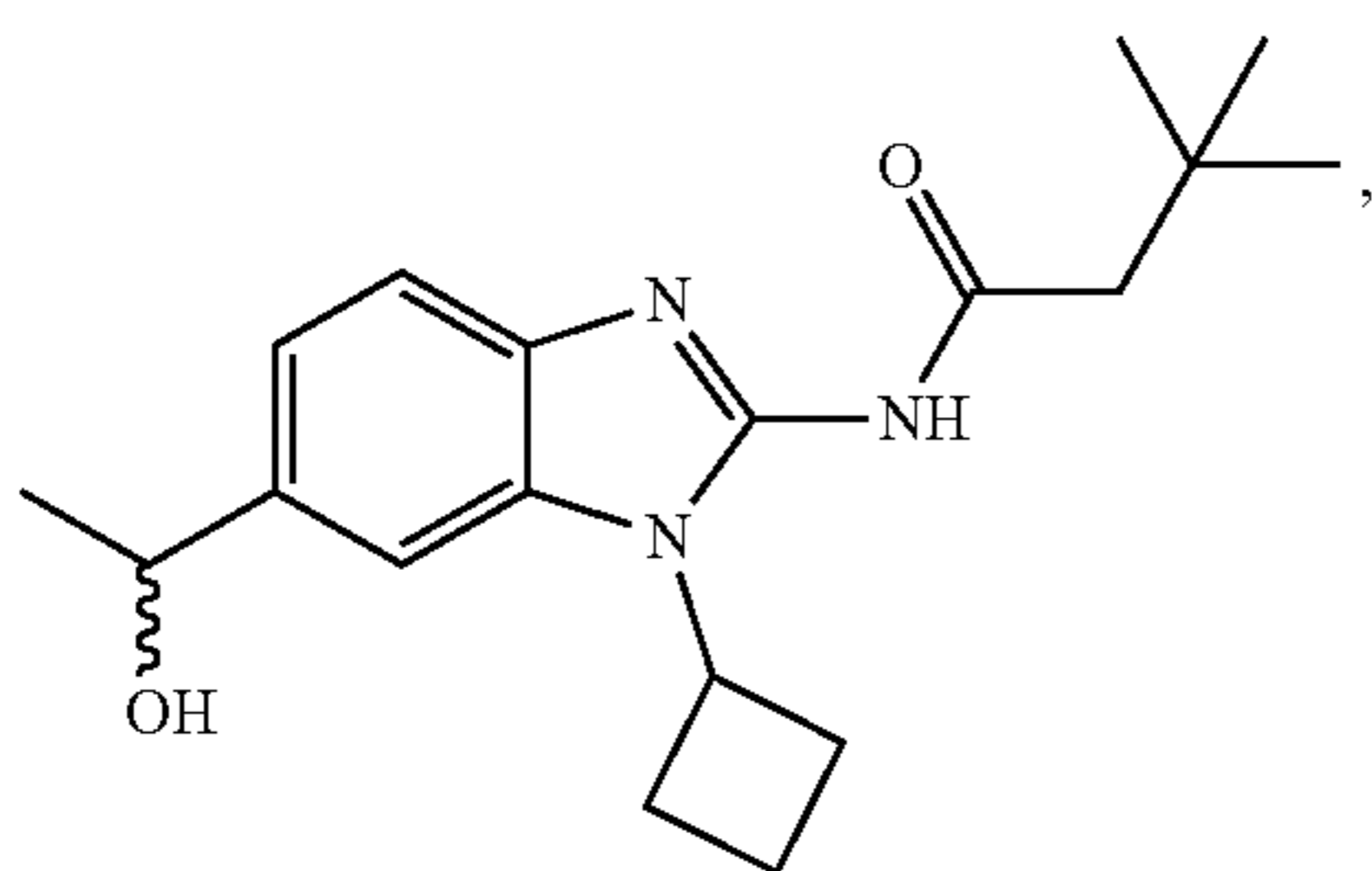
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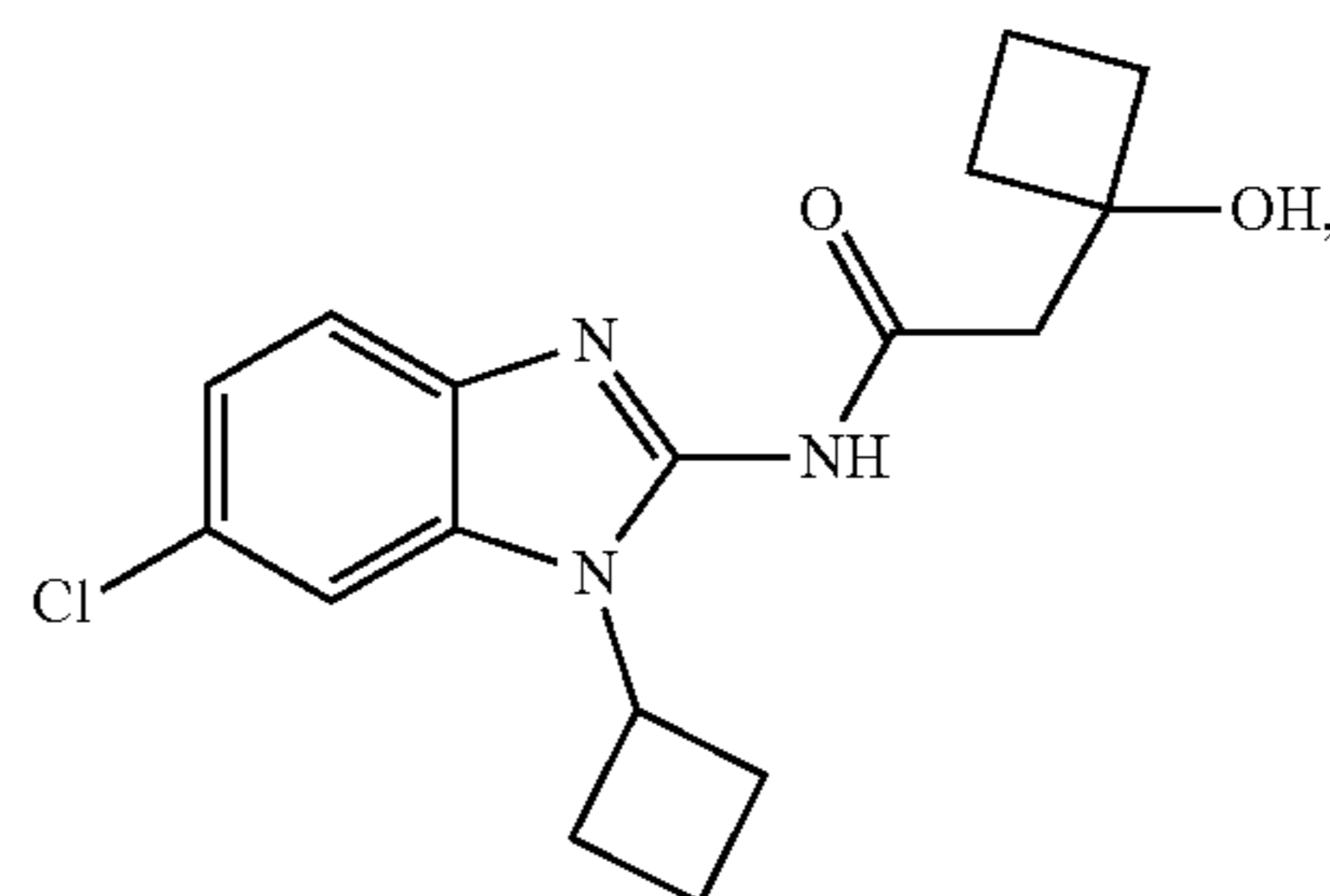
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28

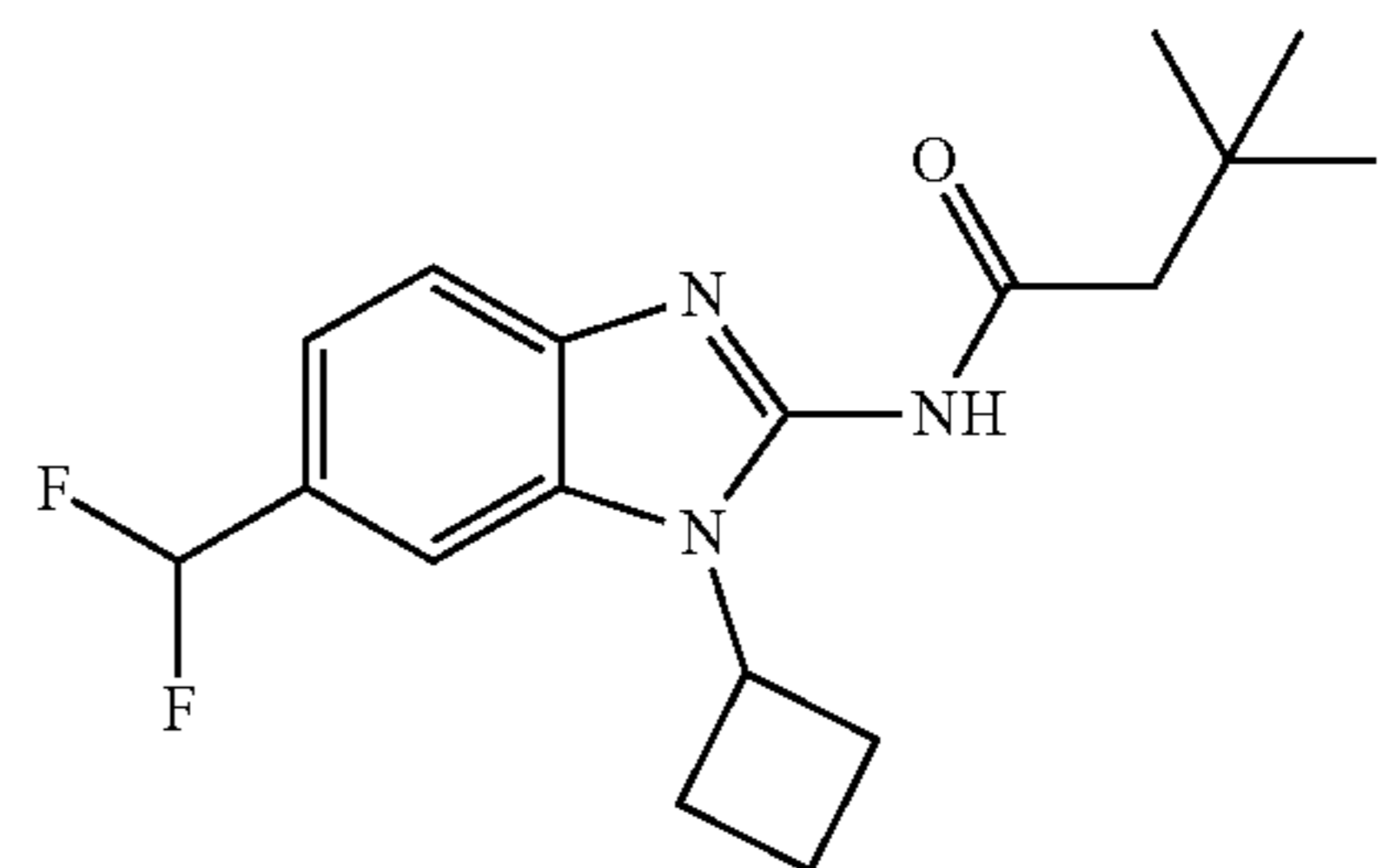
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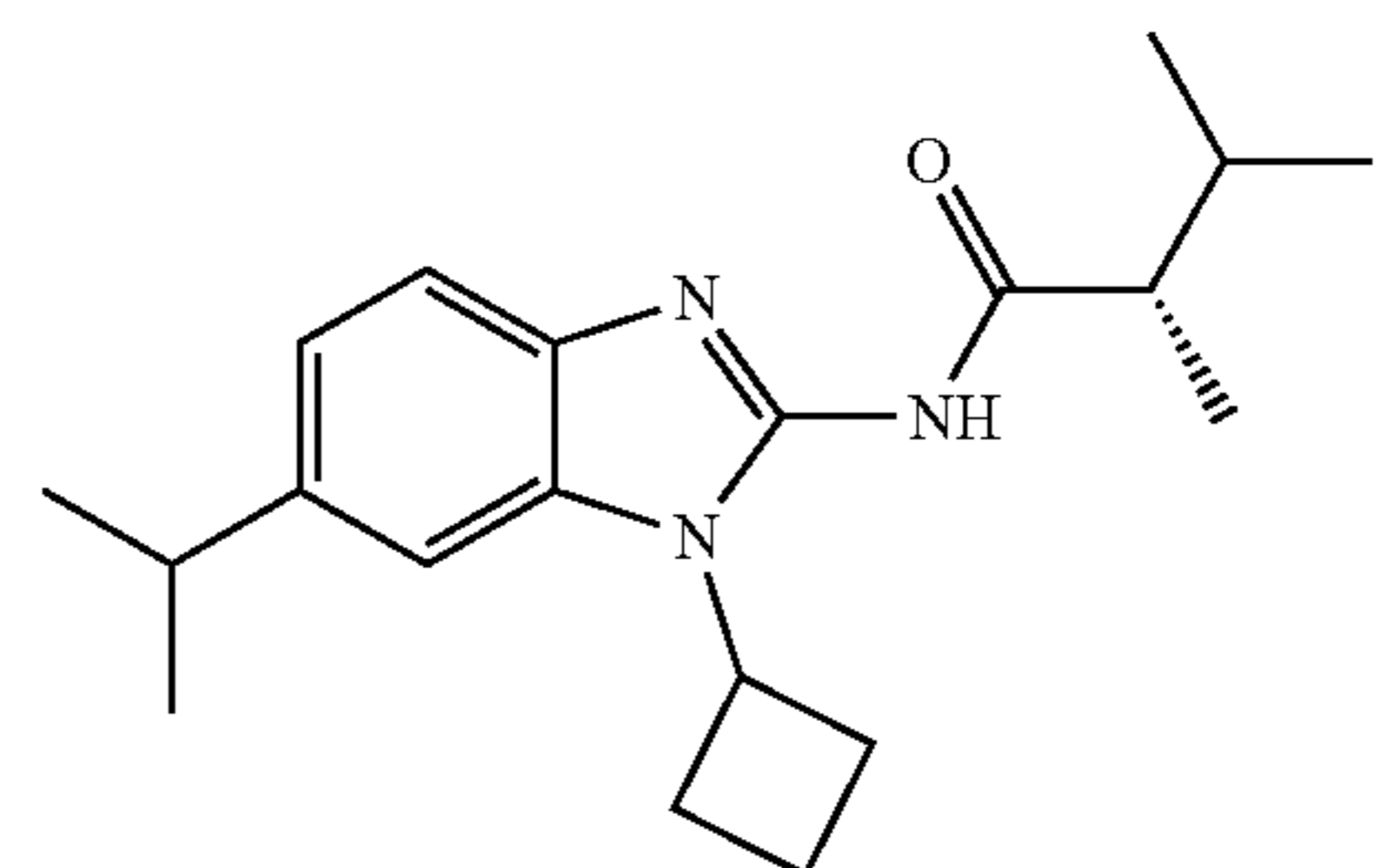
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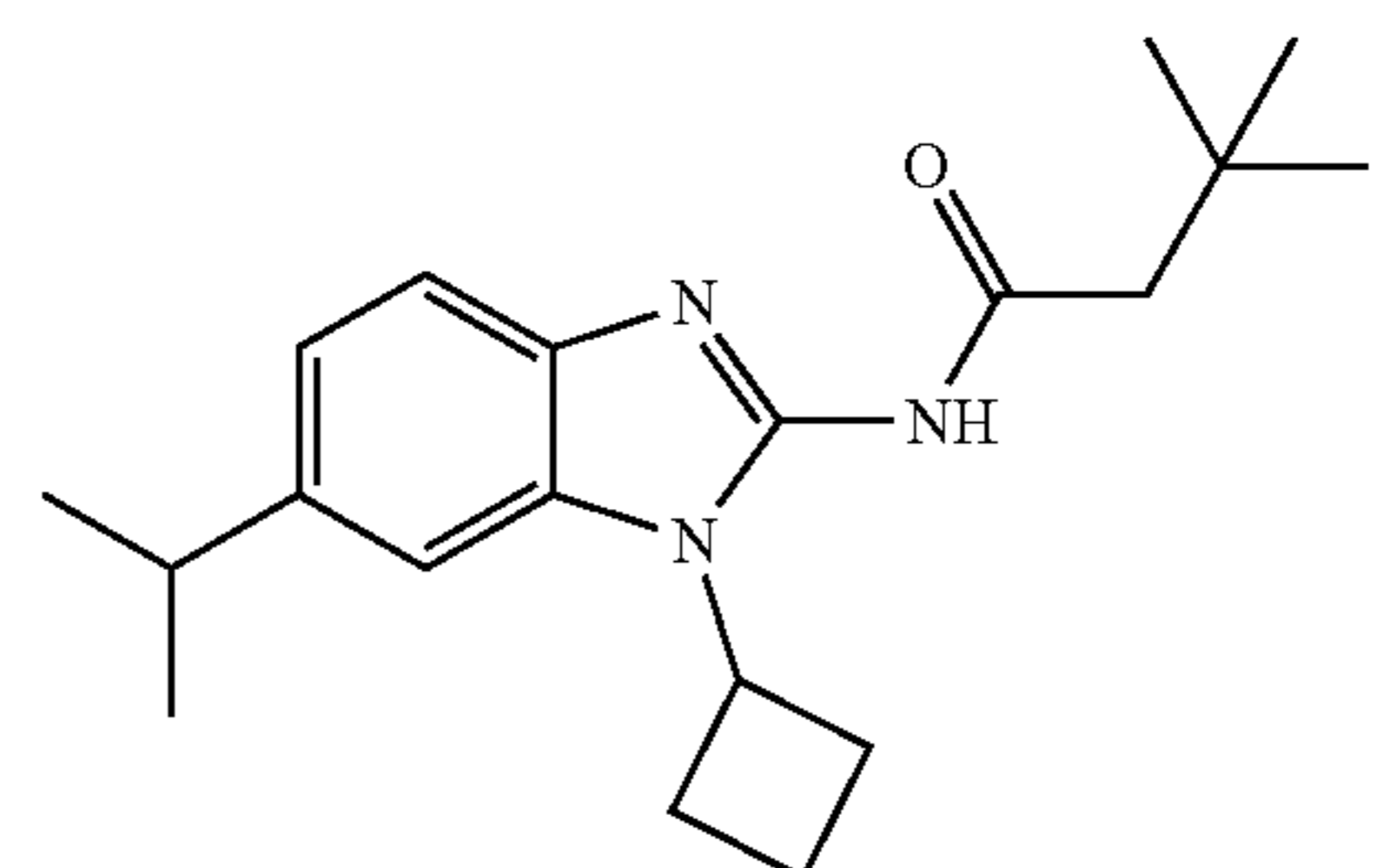
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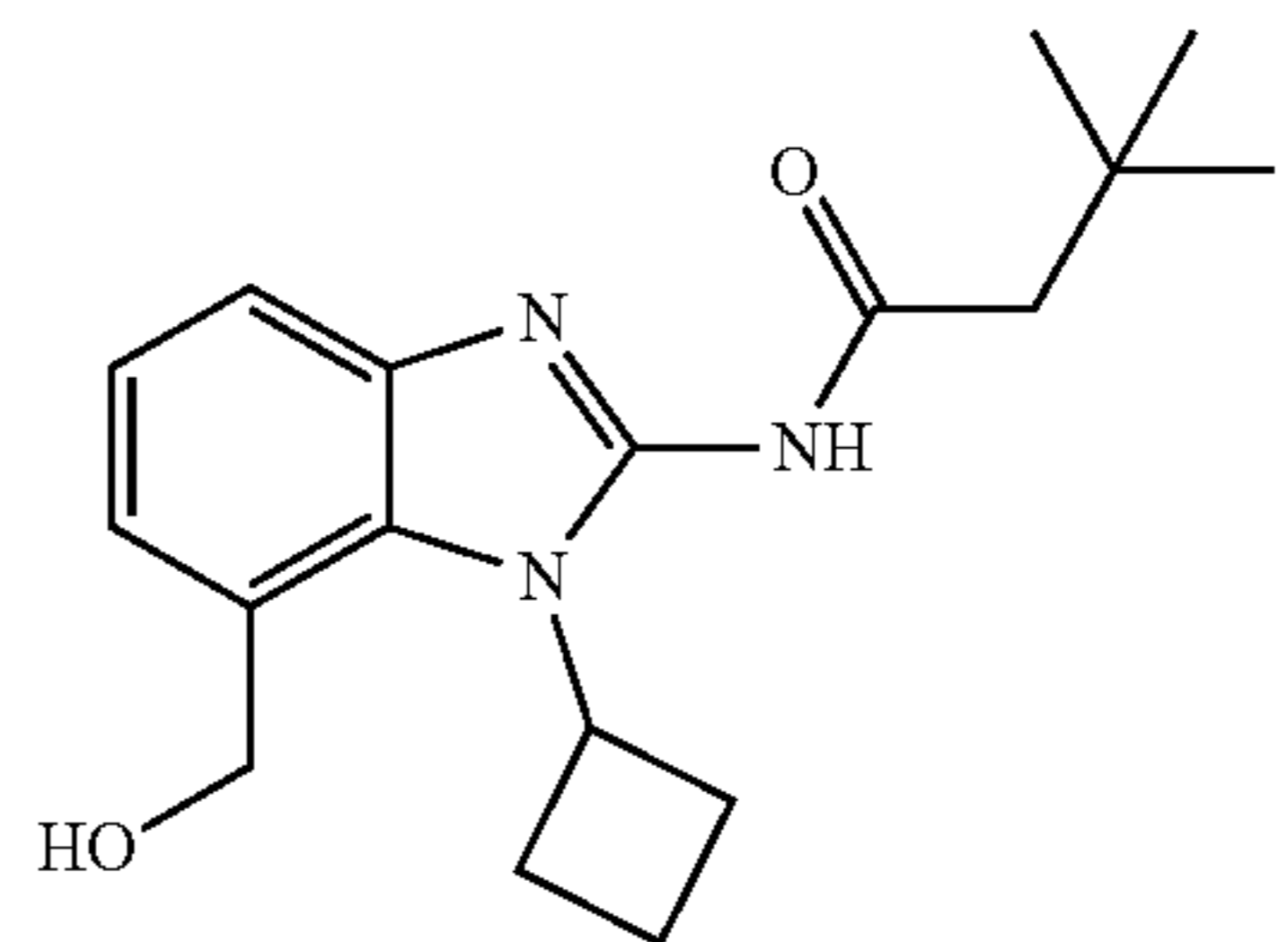
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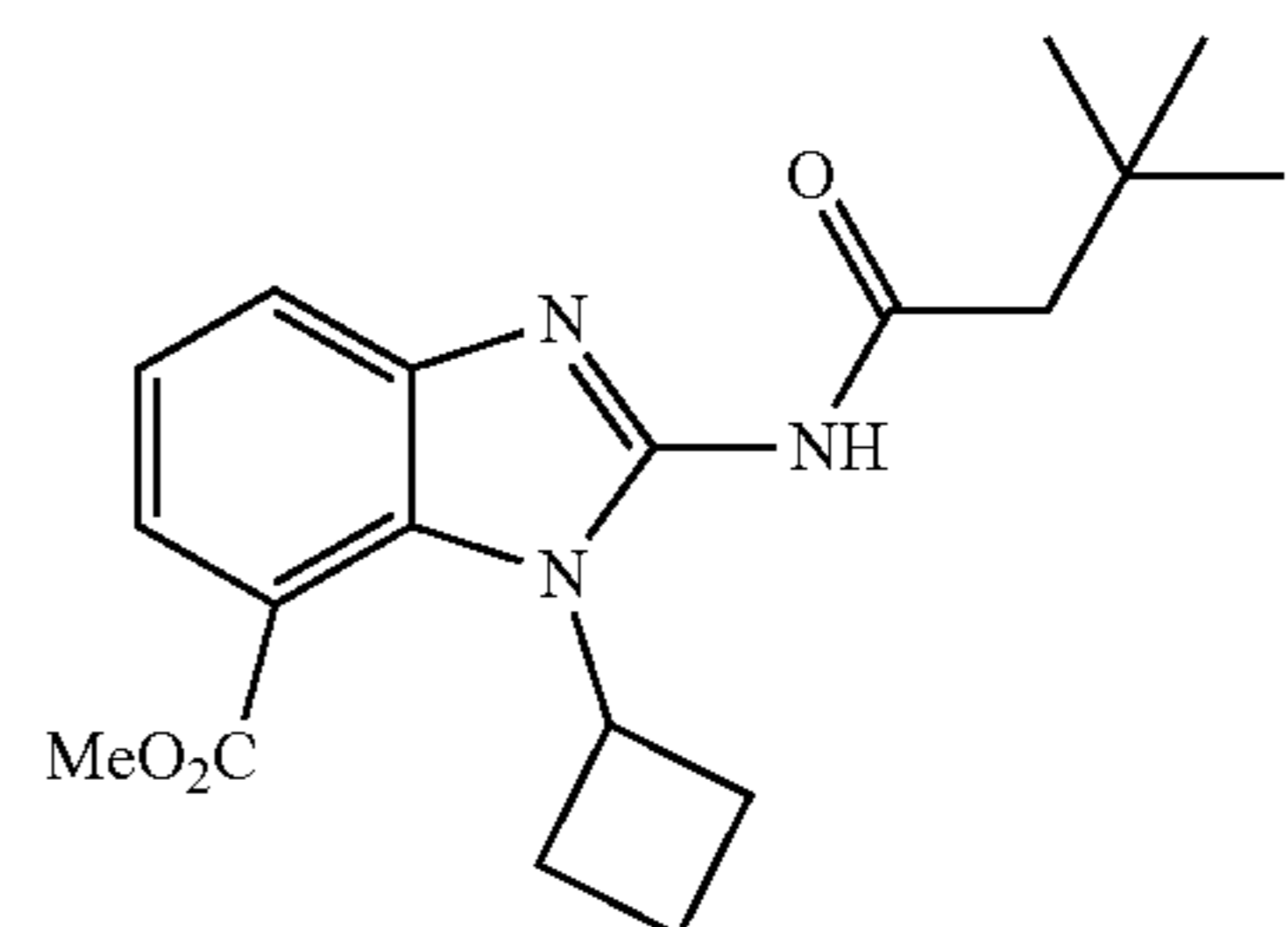
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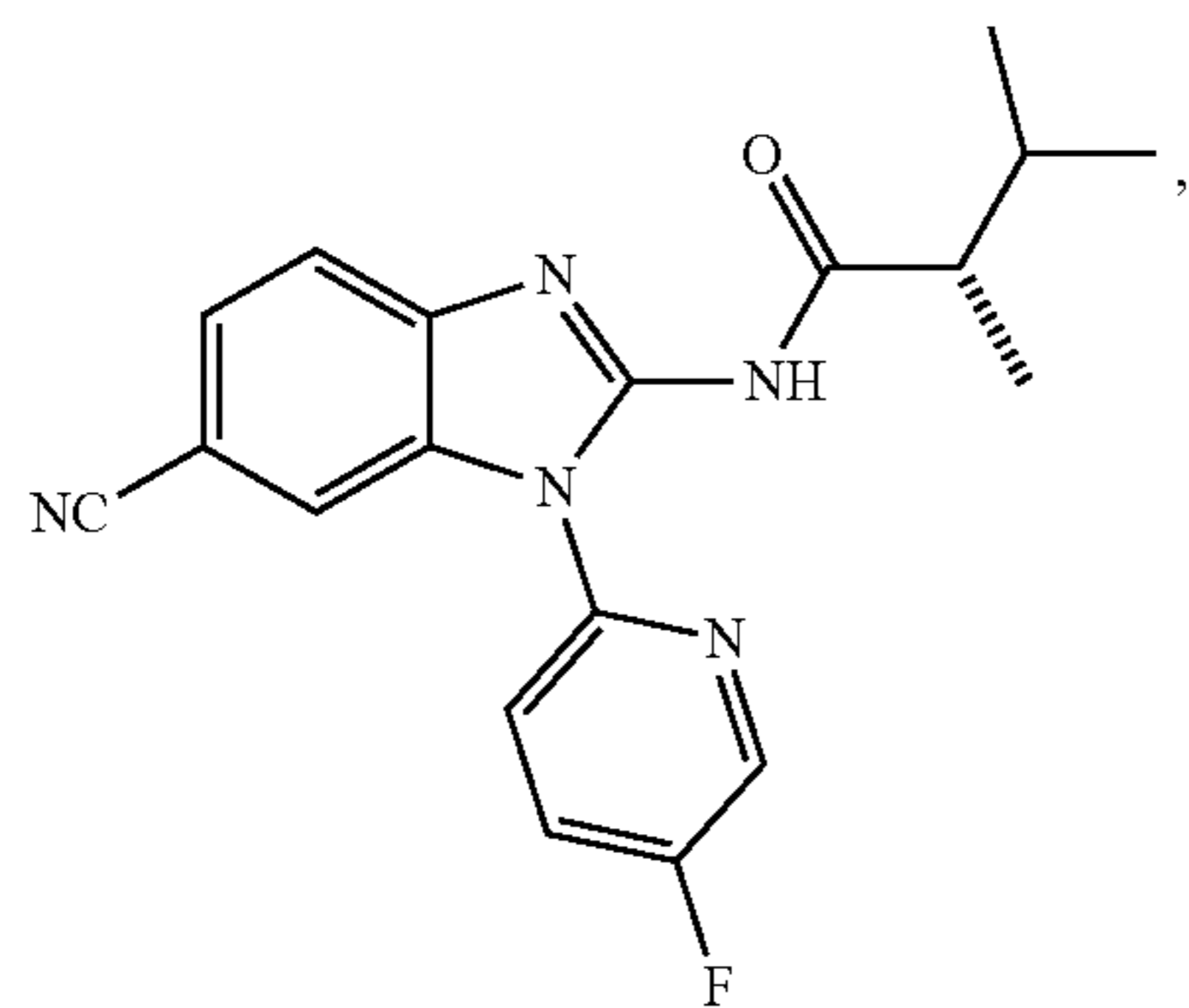
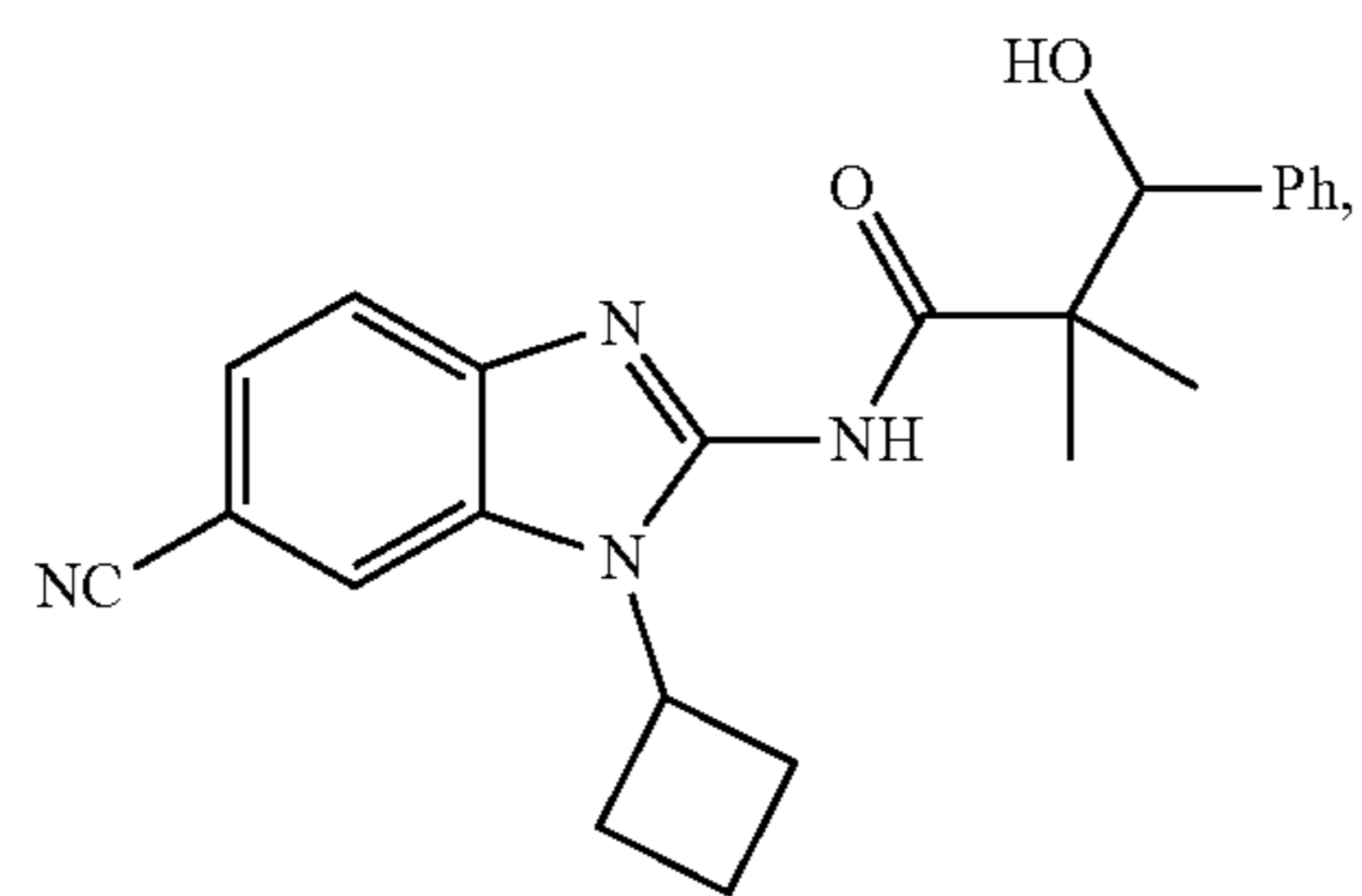
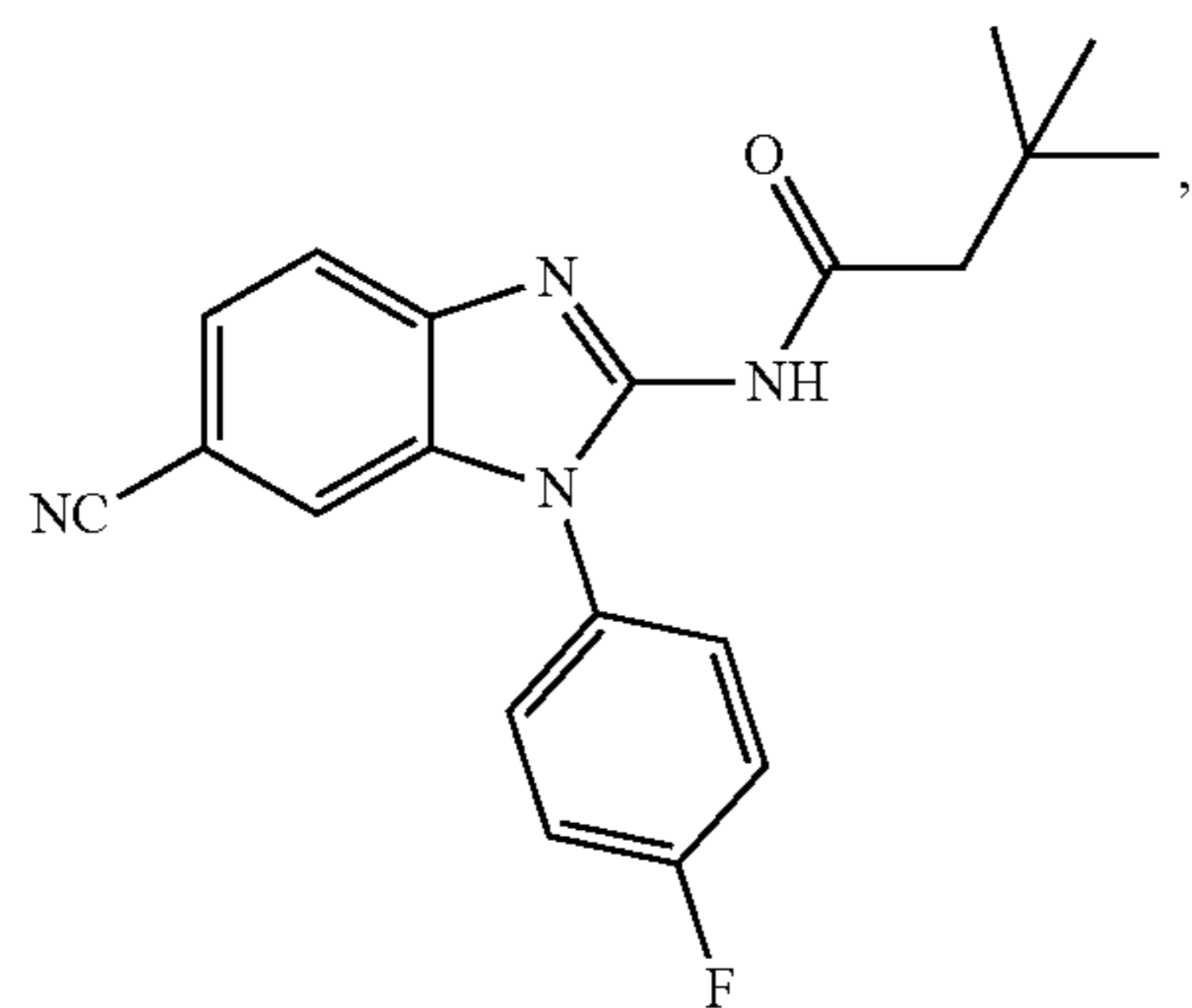
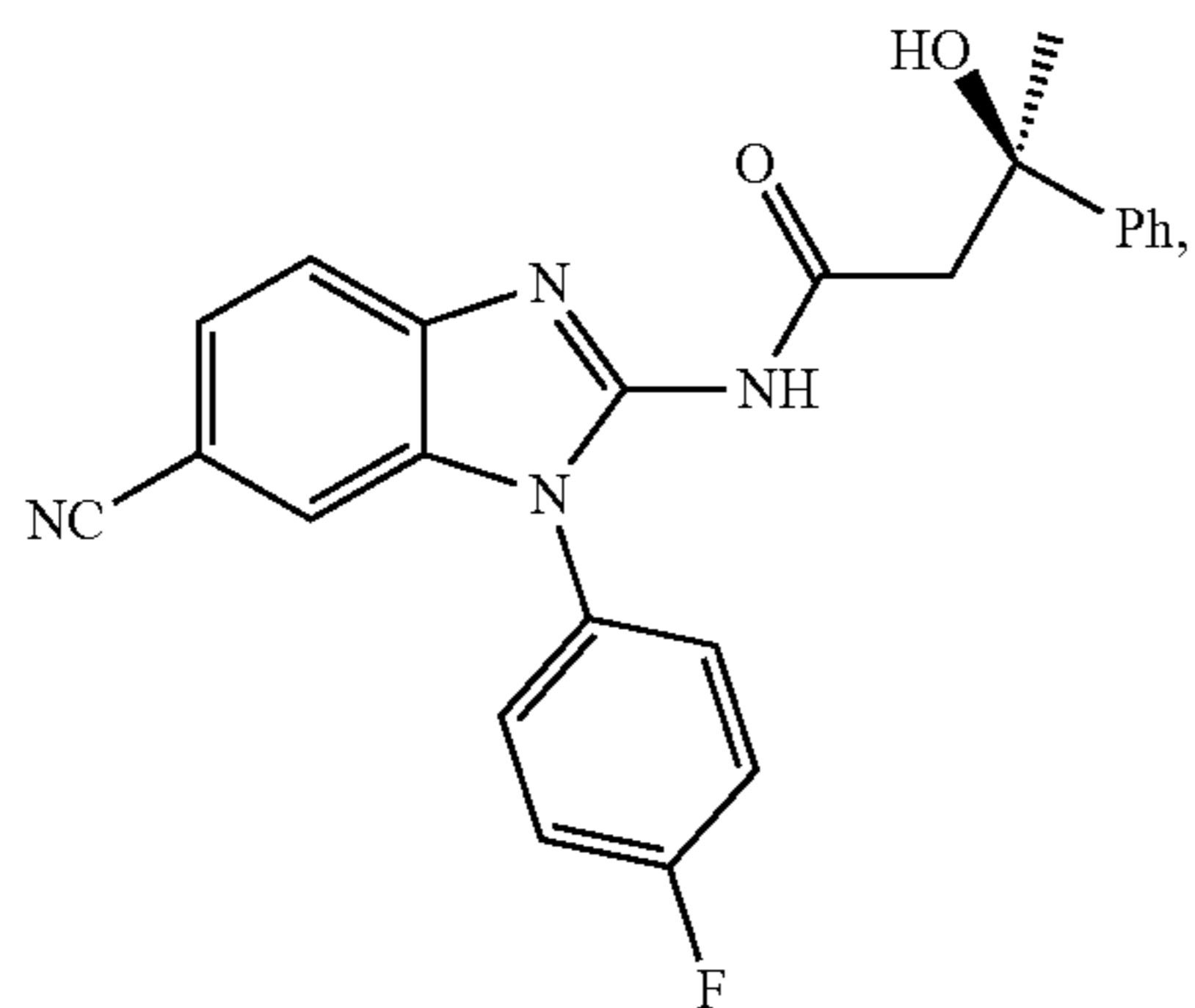
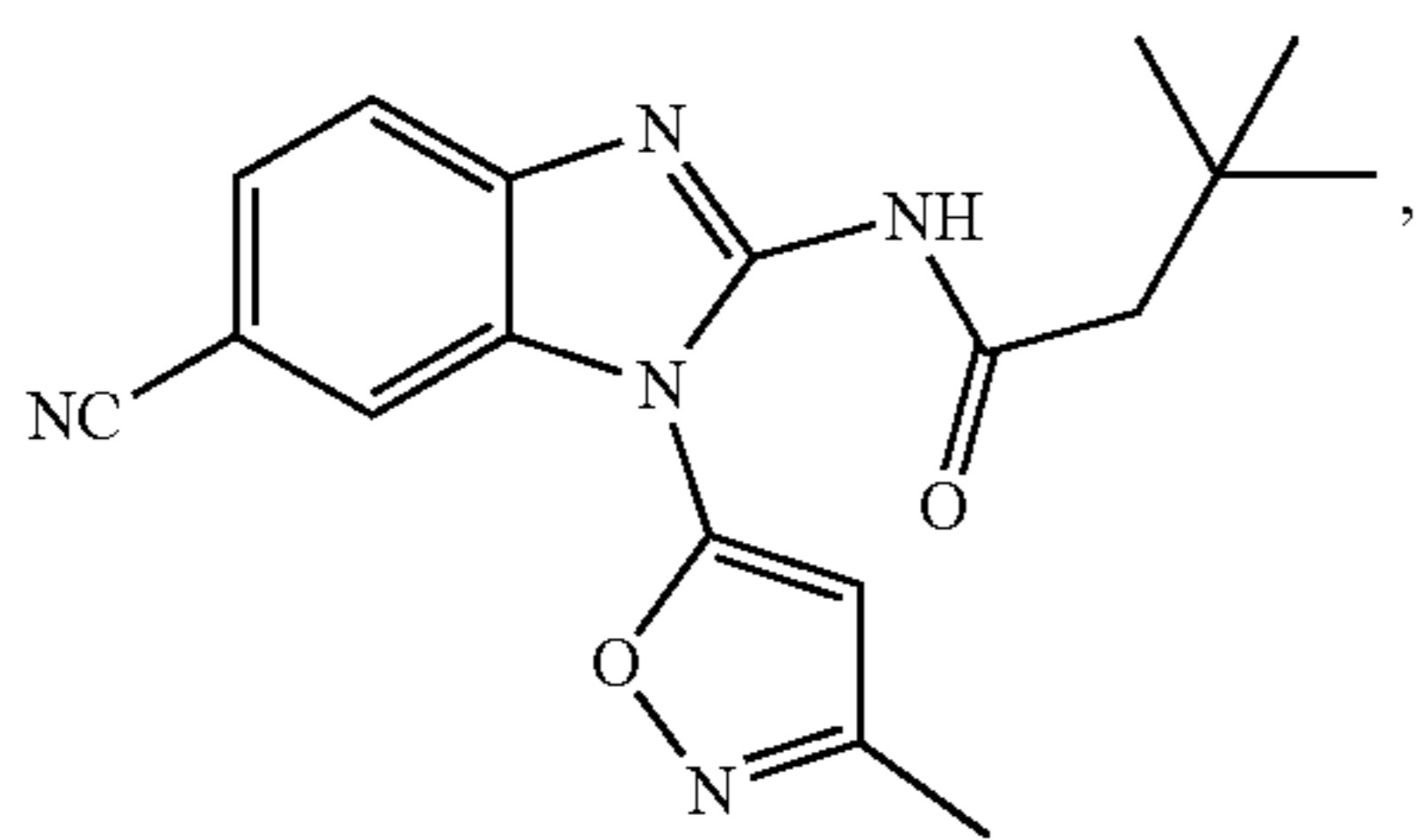
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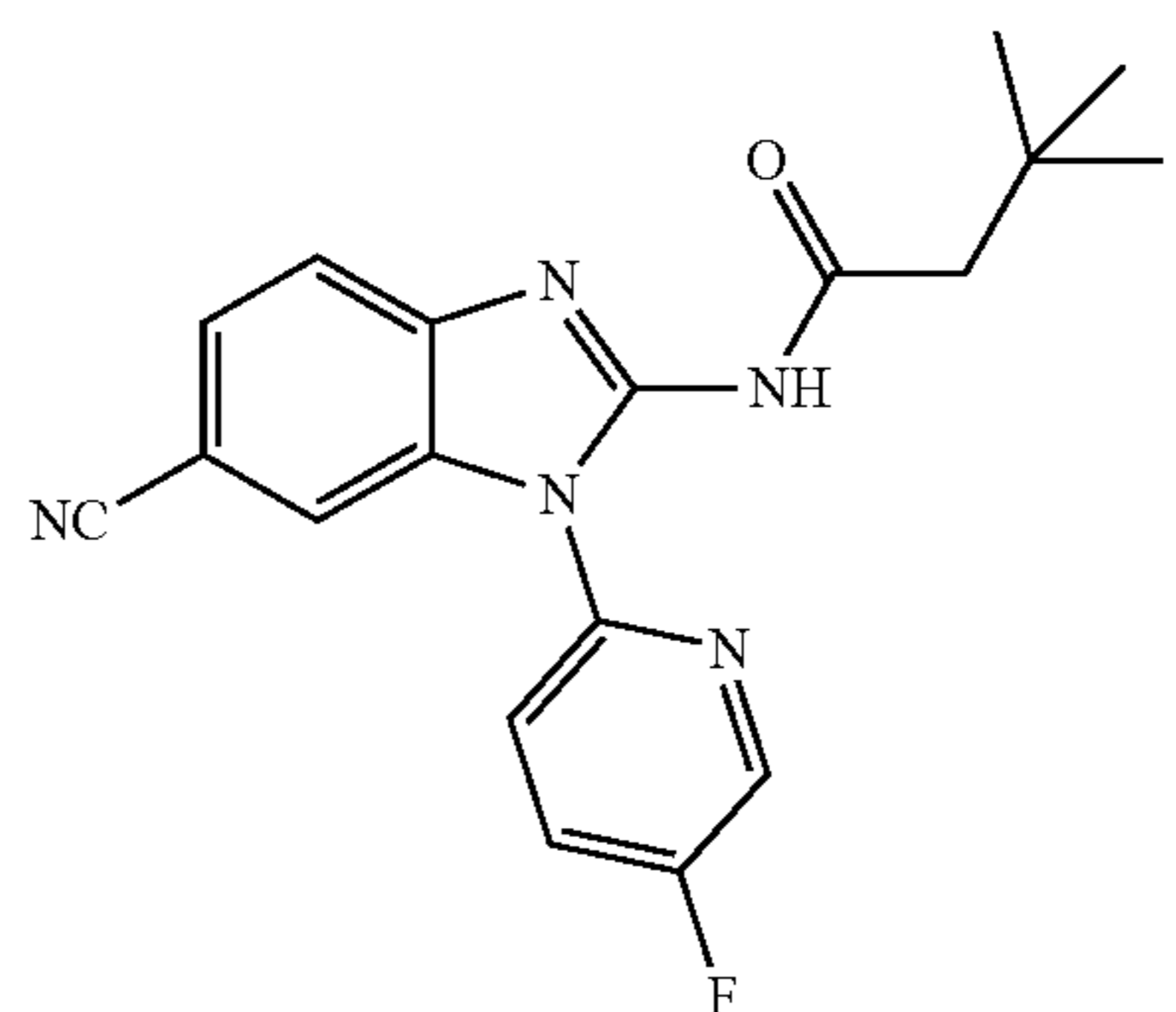
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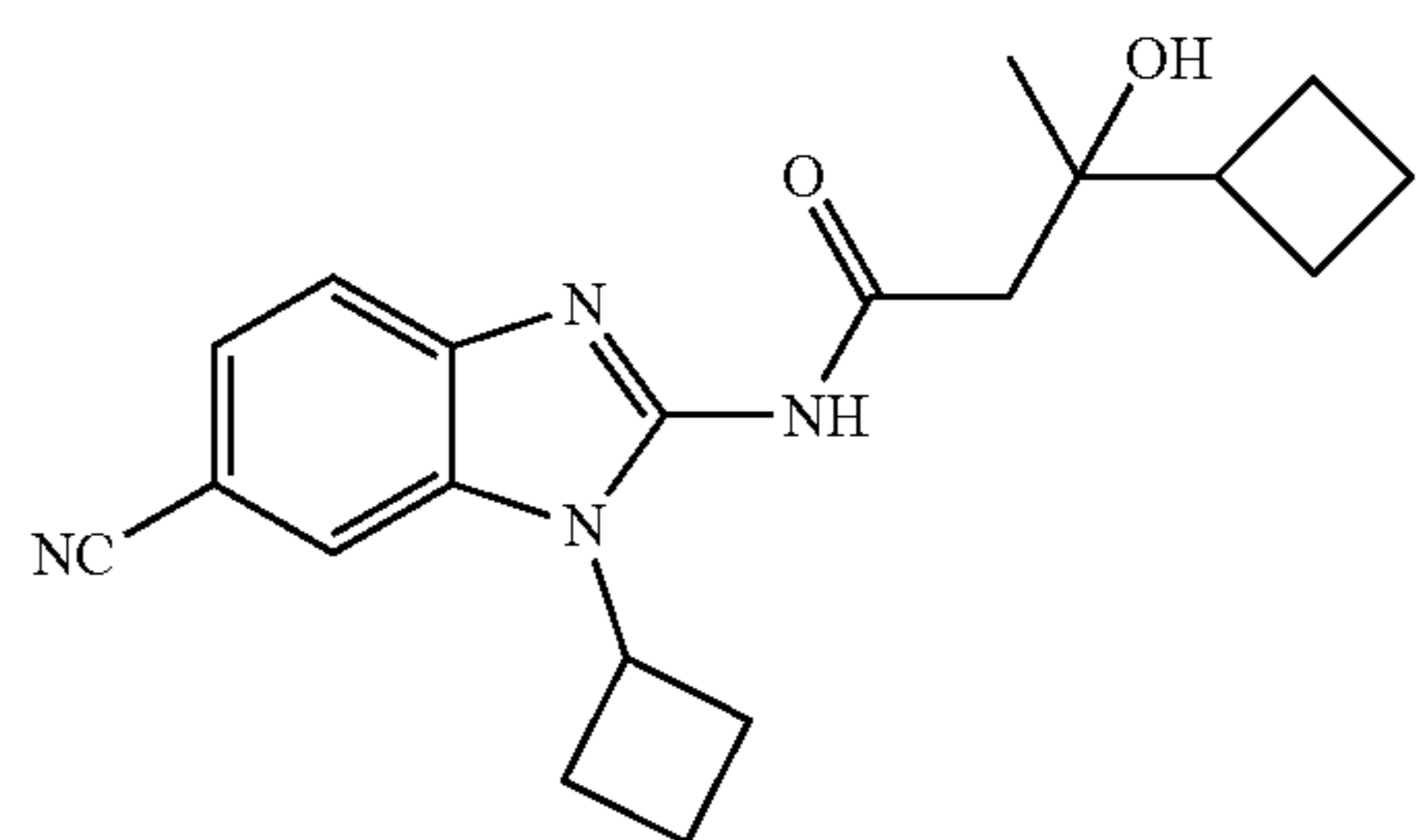
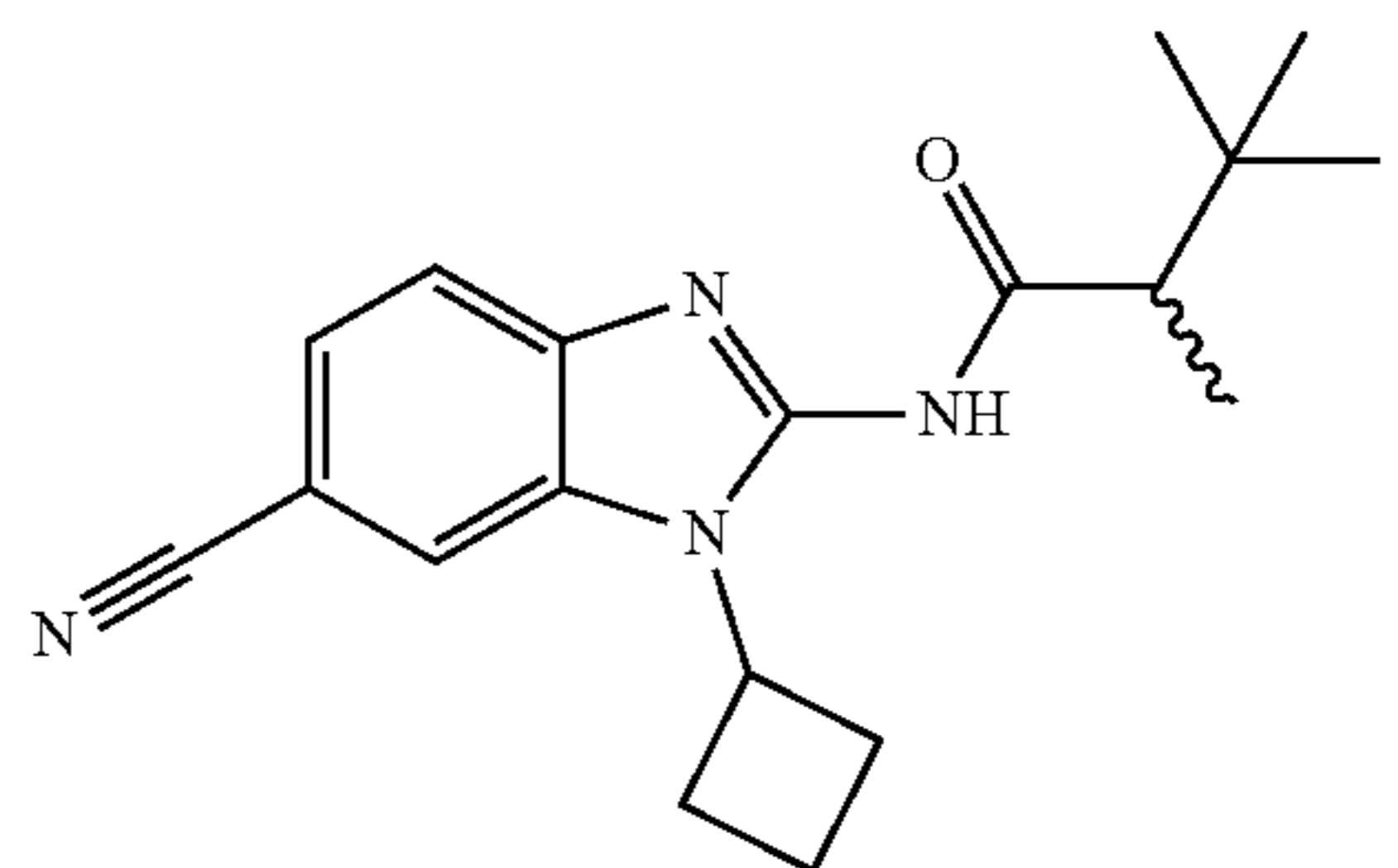
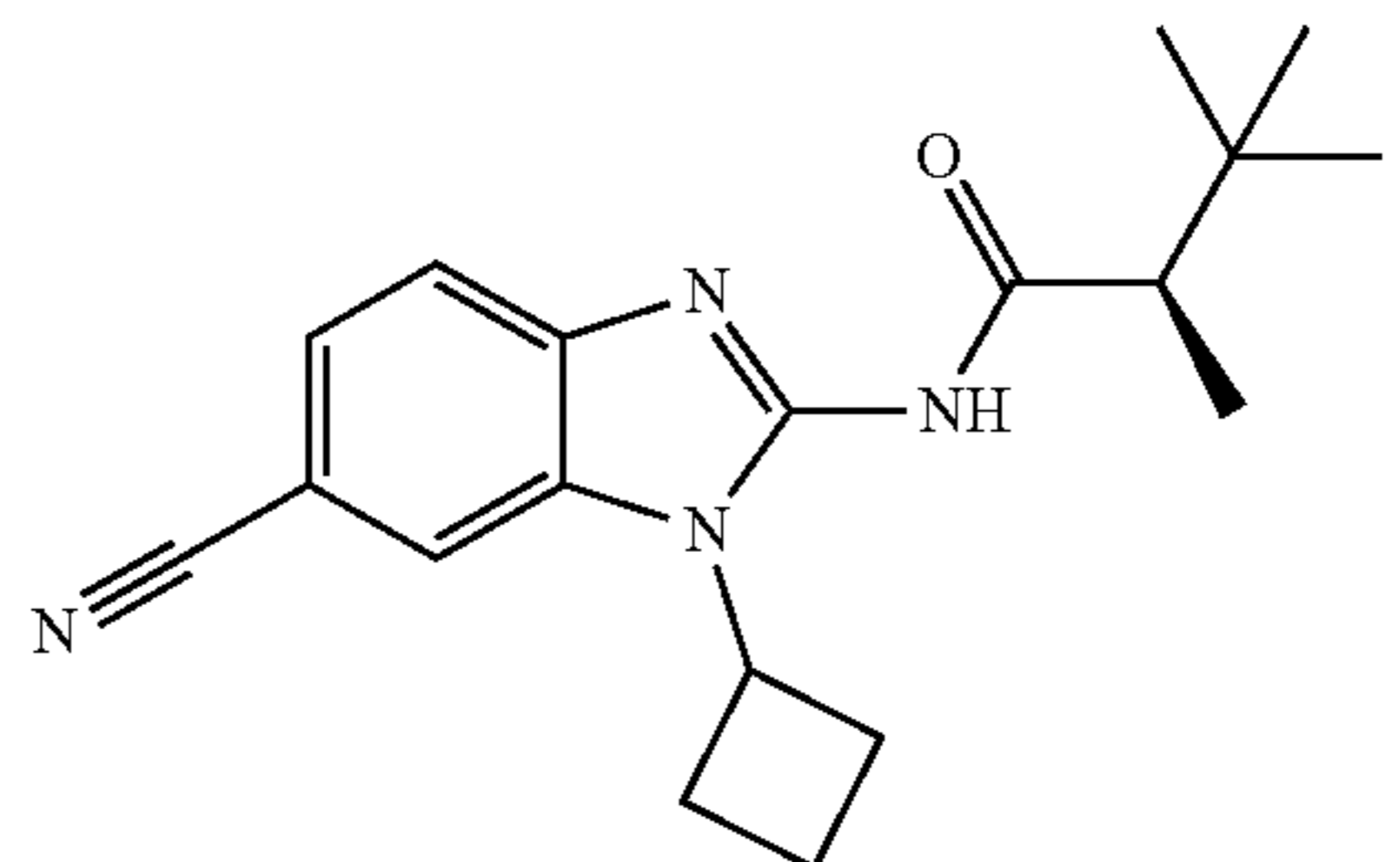
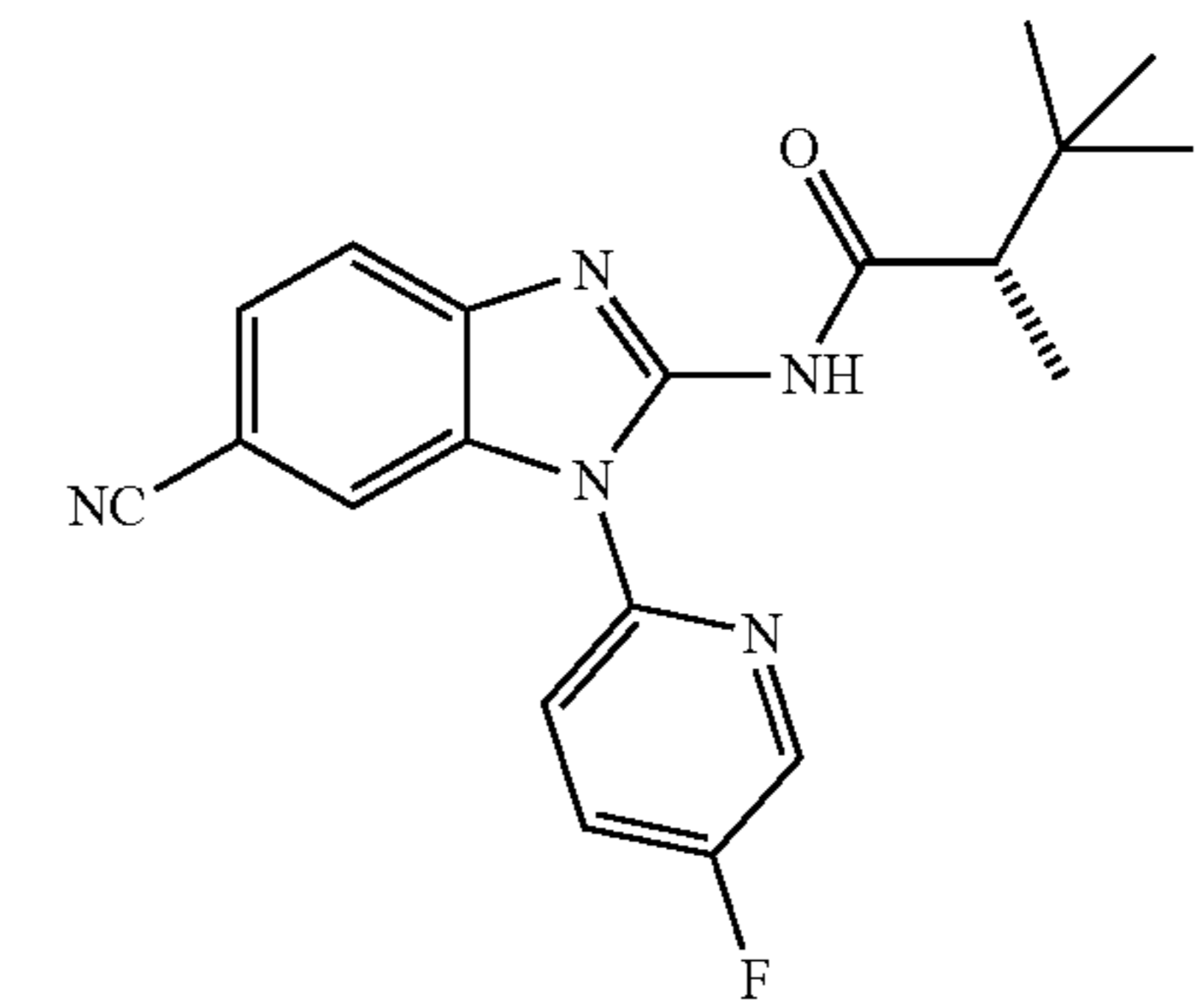
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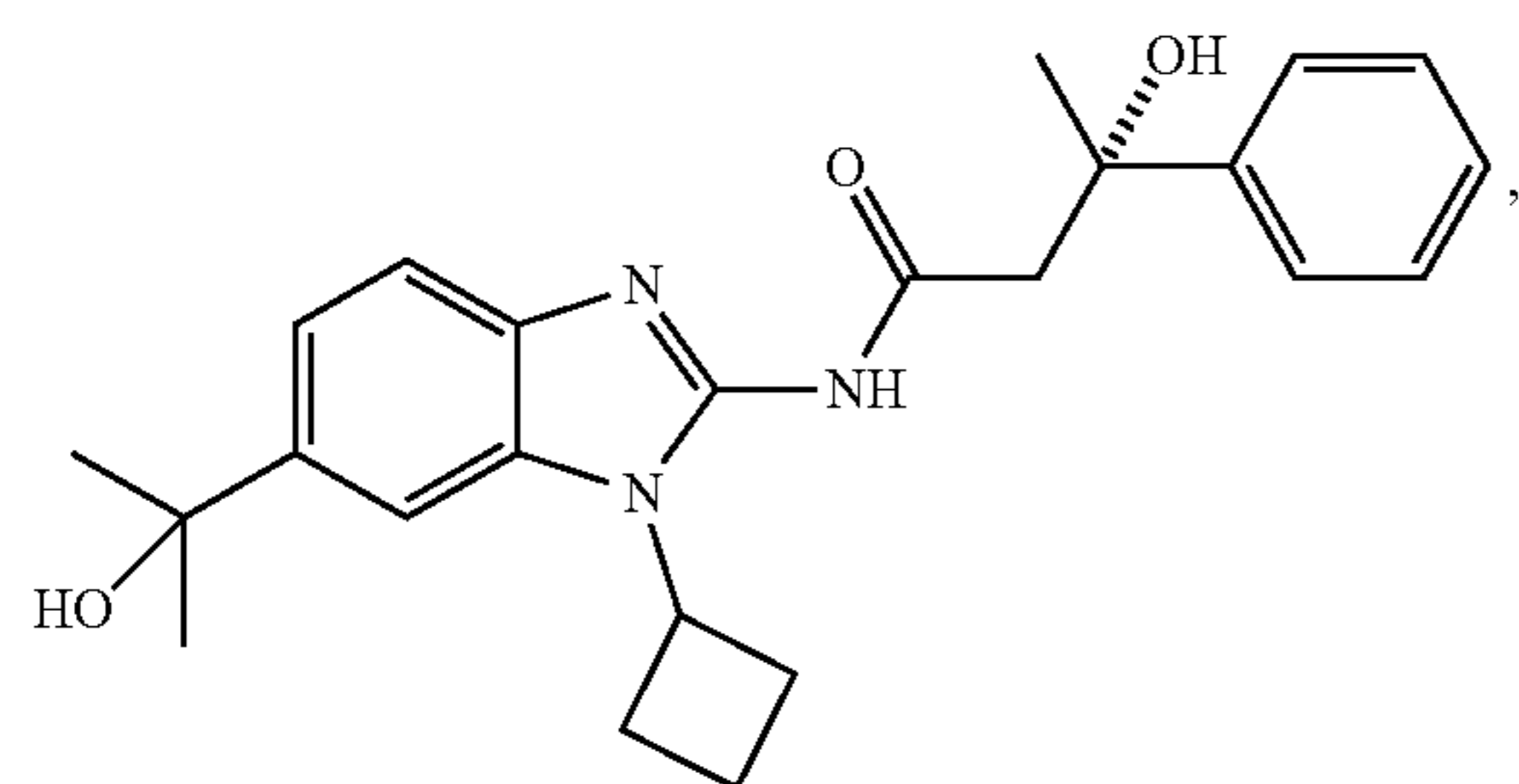
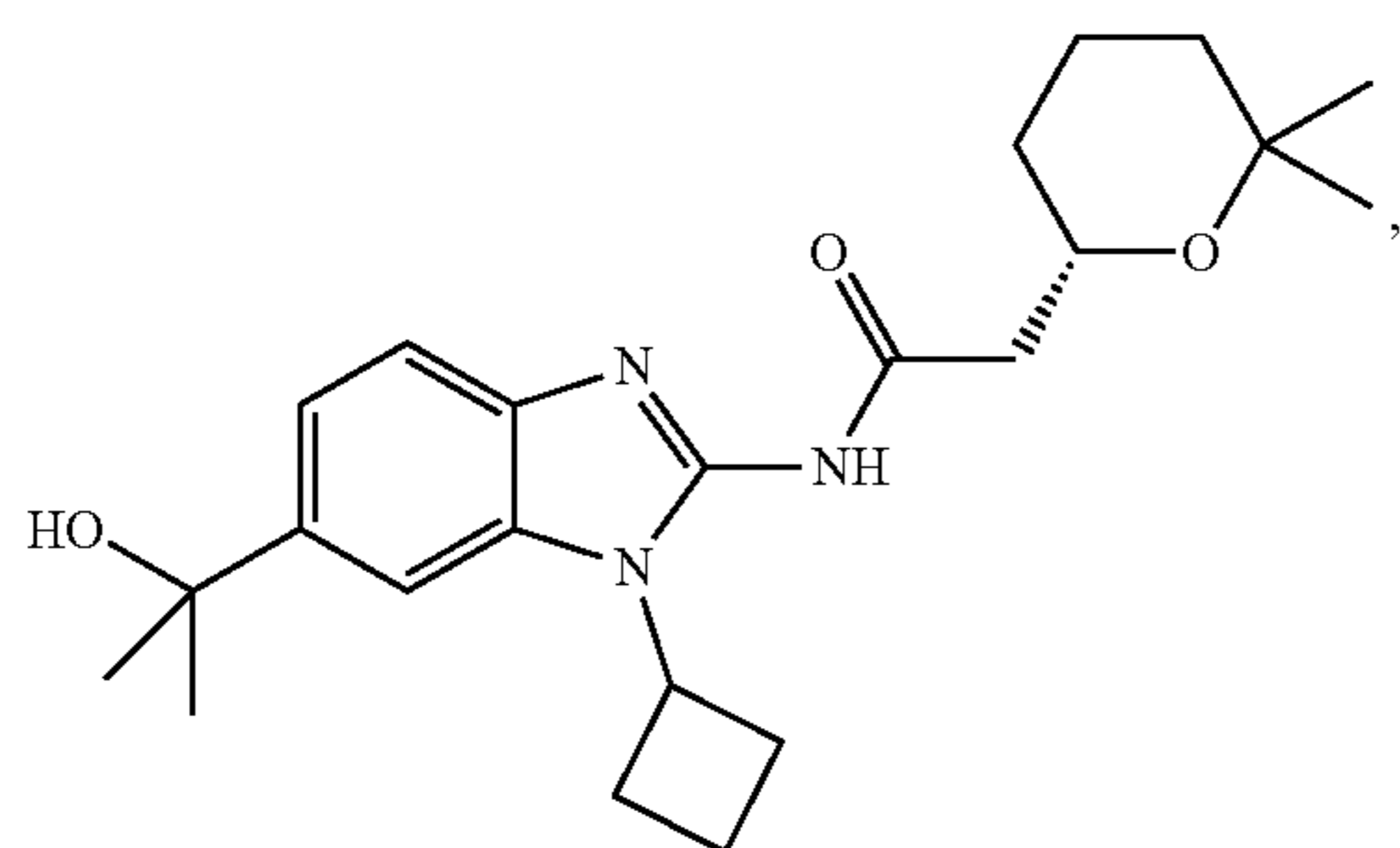
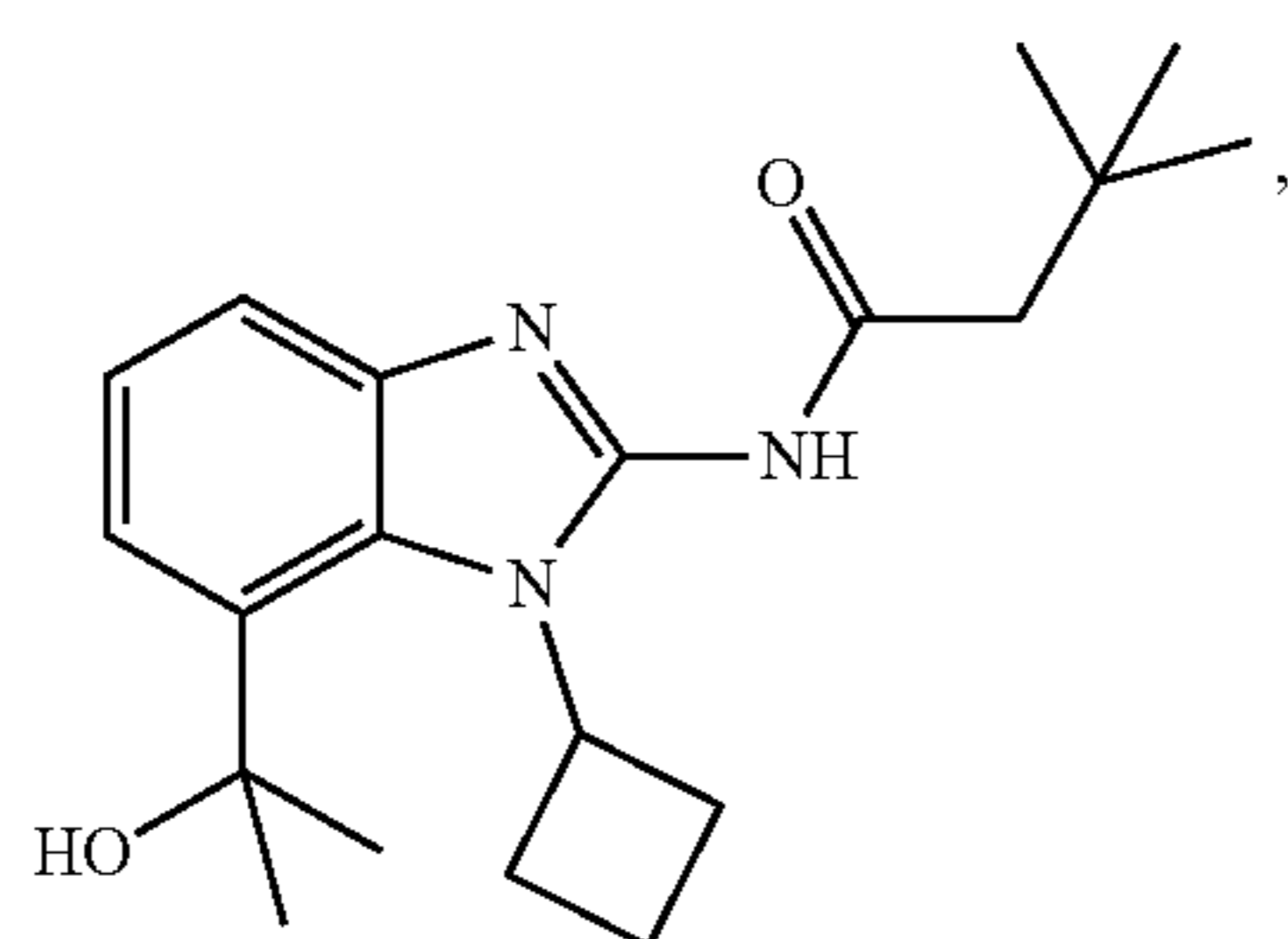
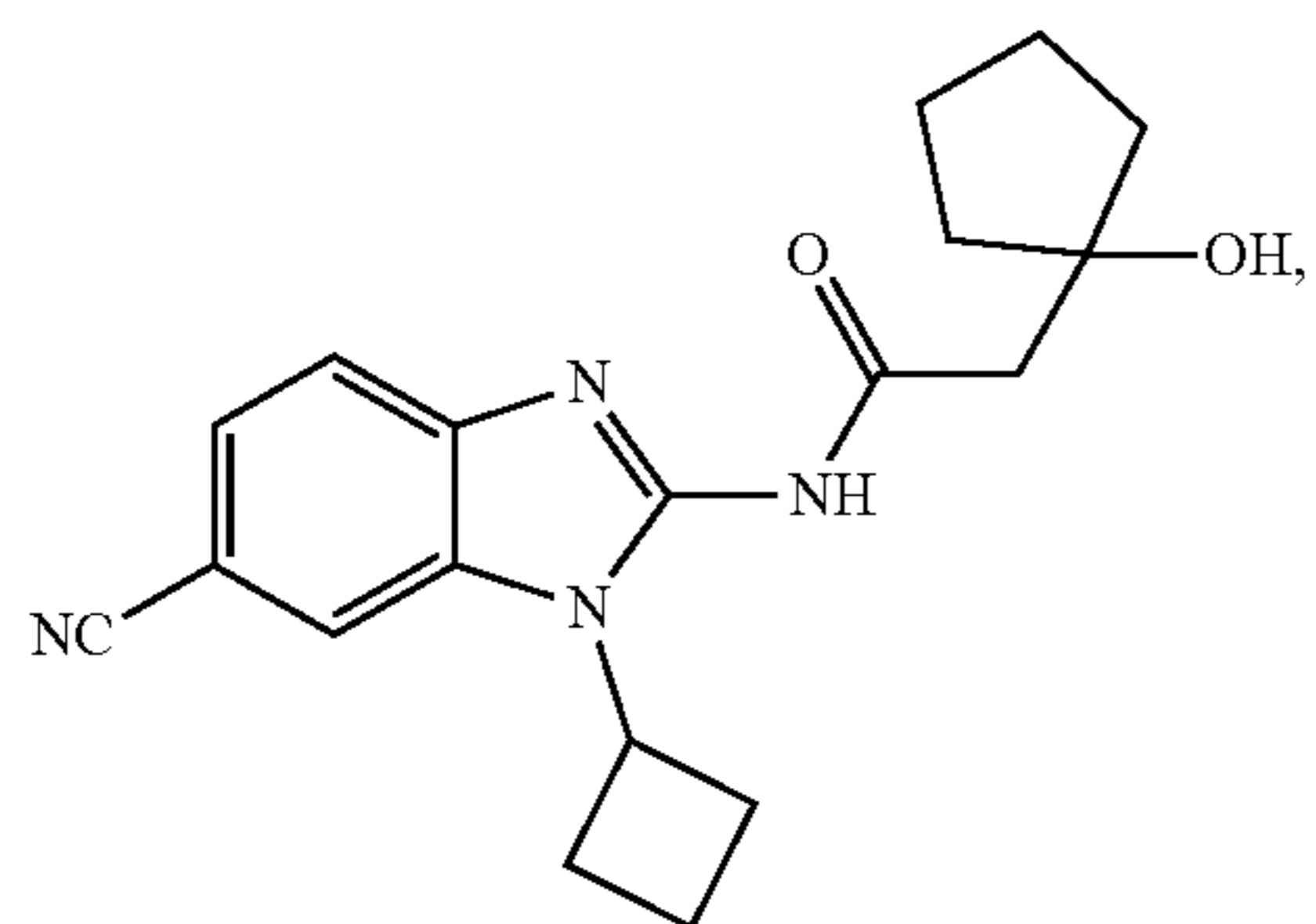
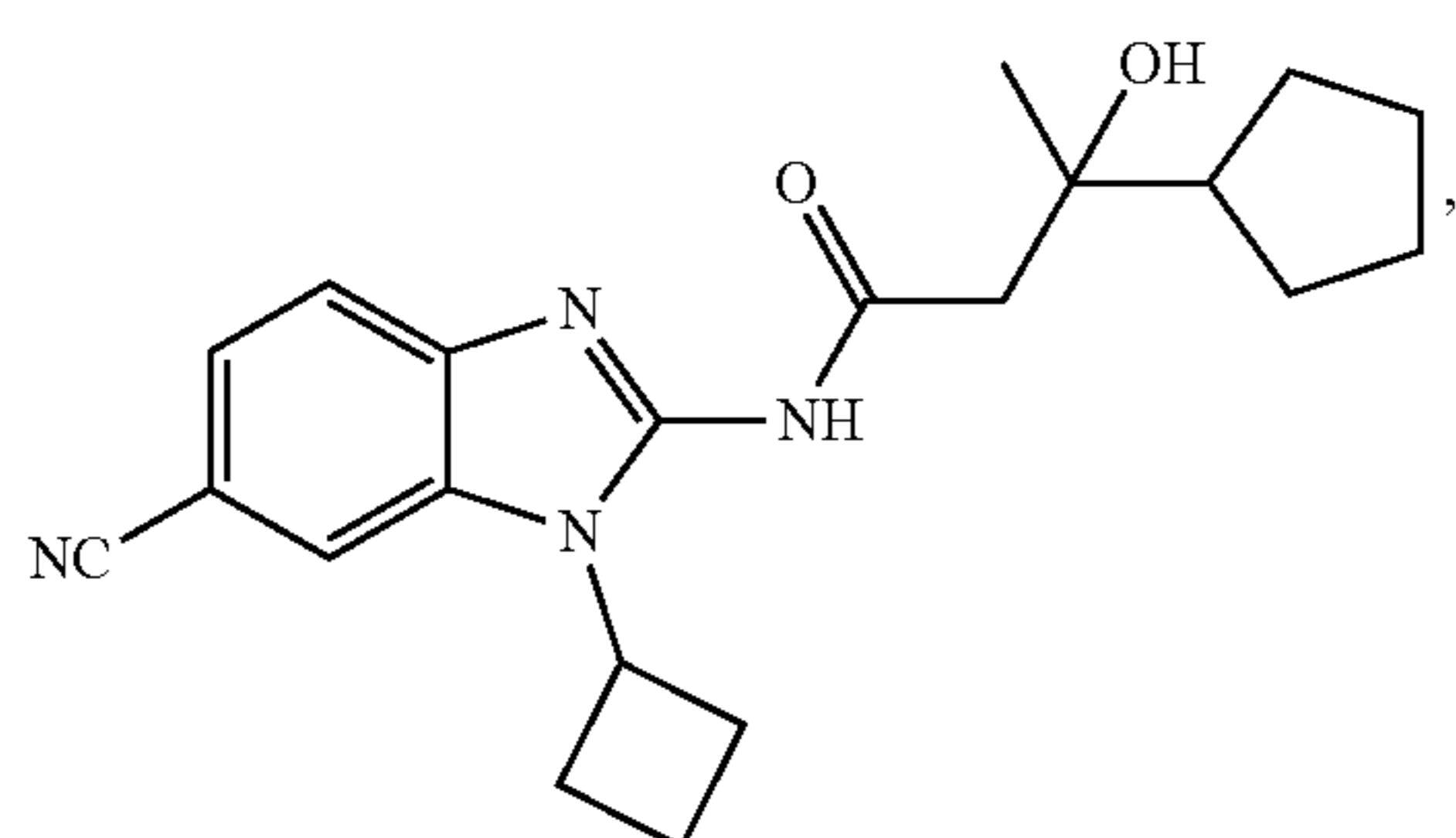
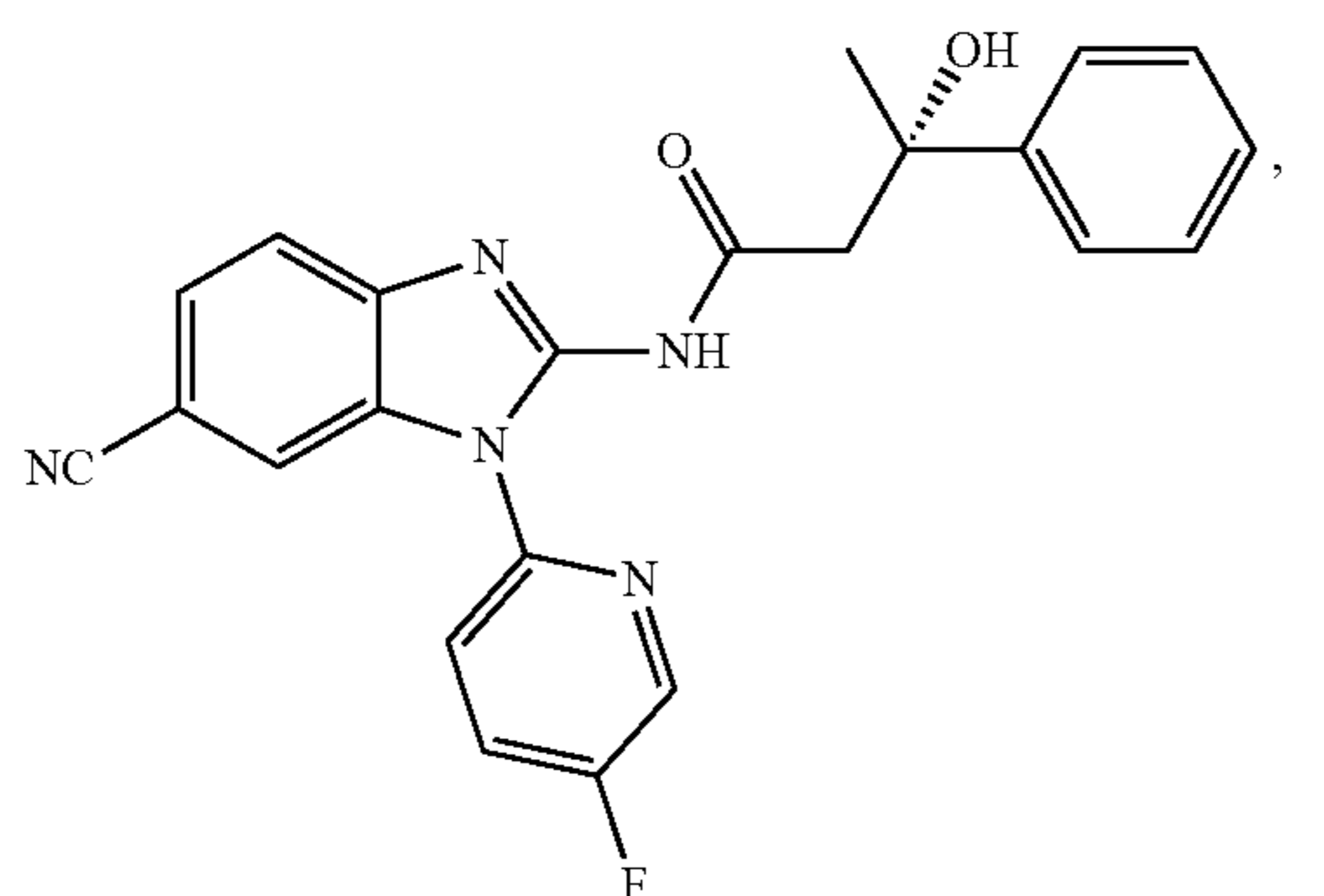
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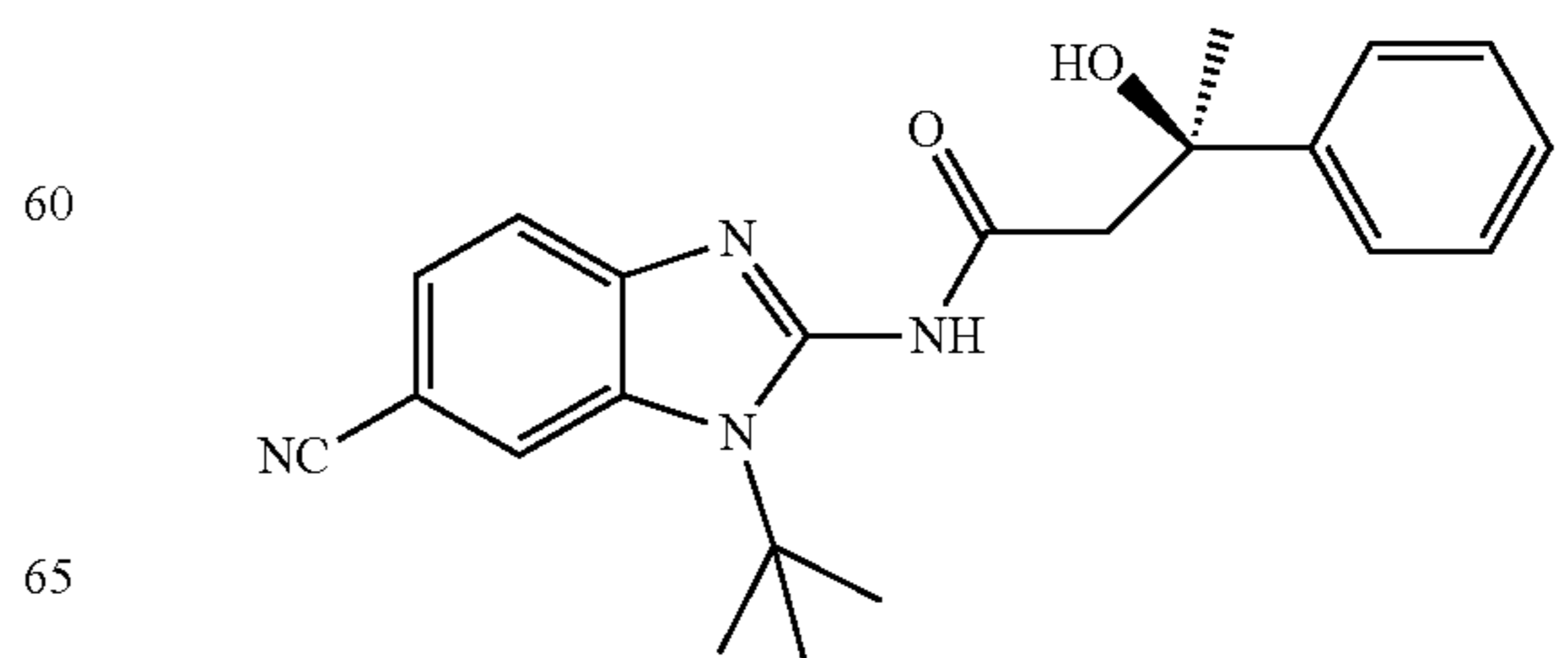
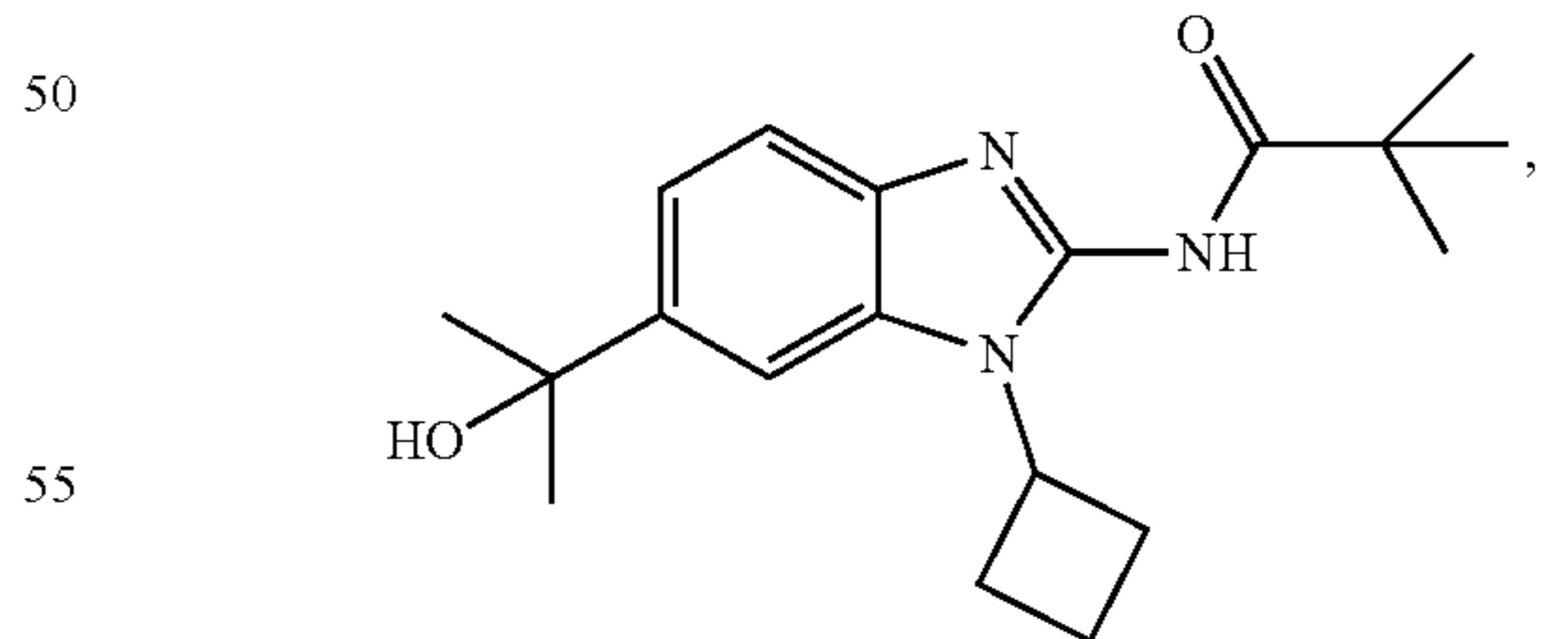
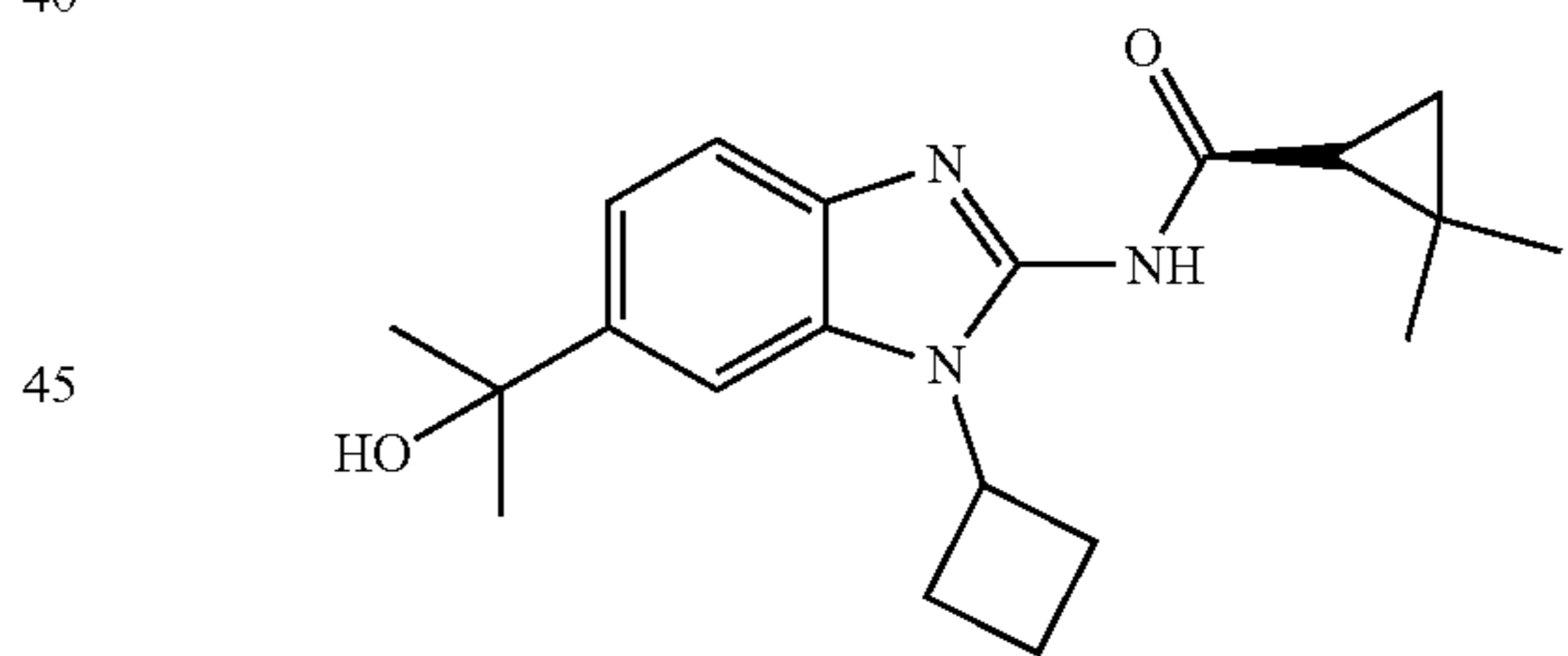
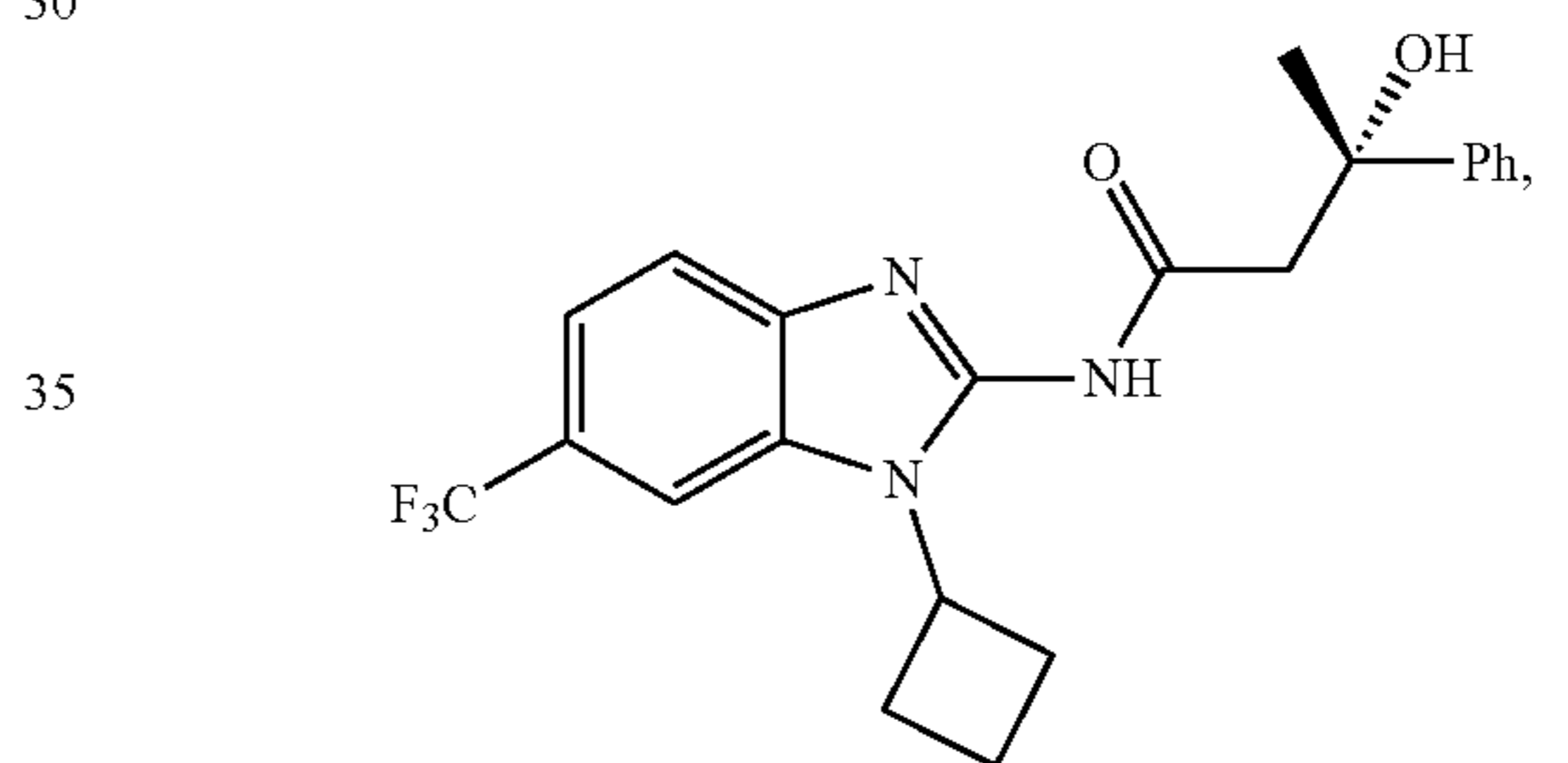
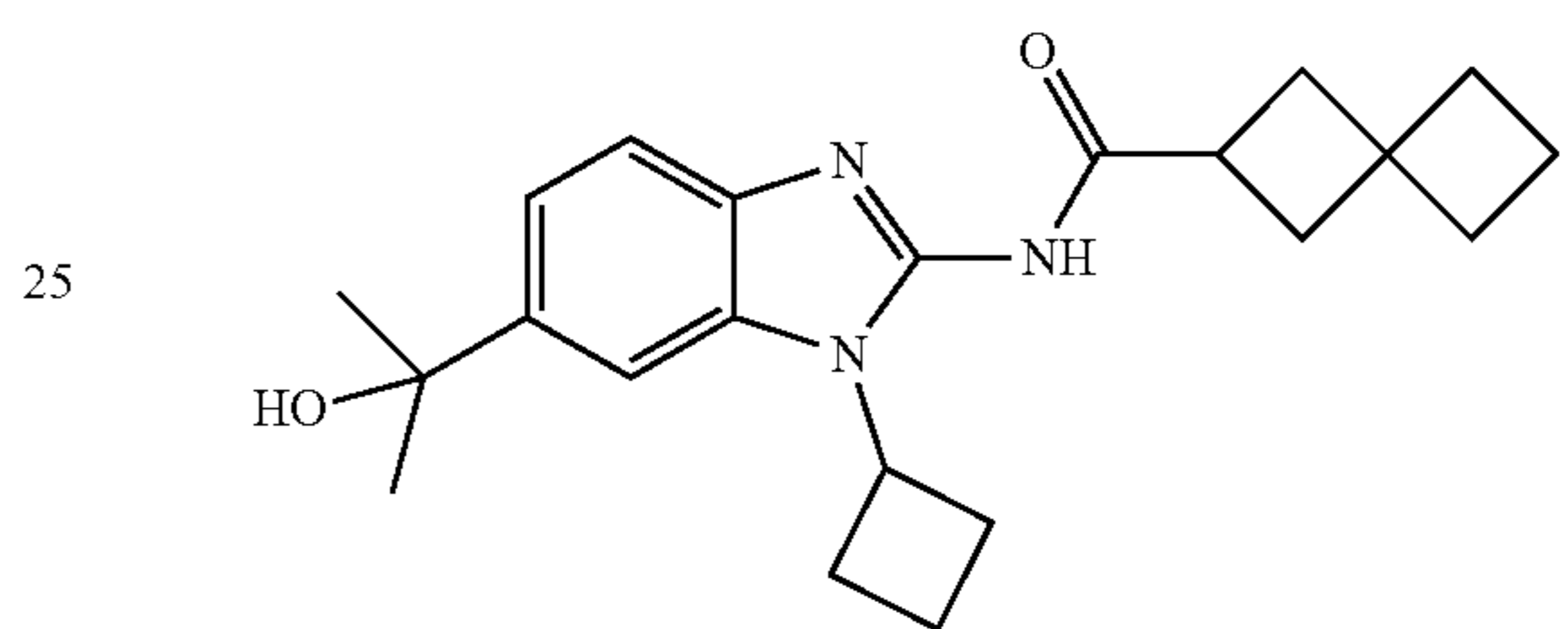
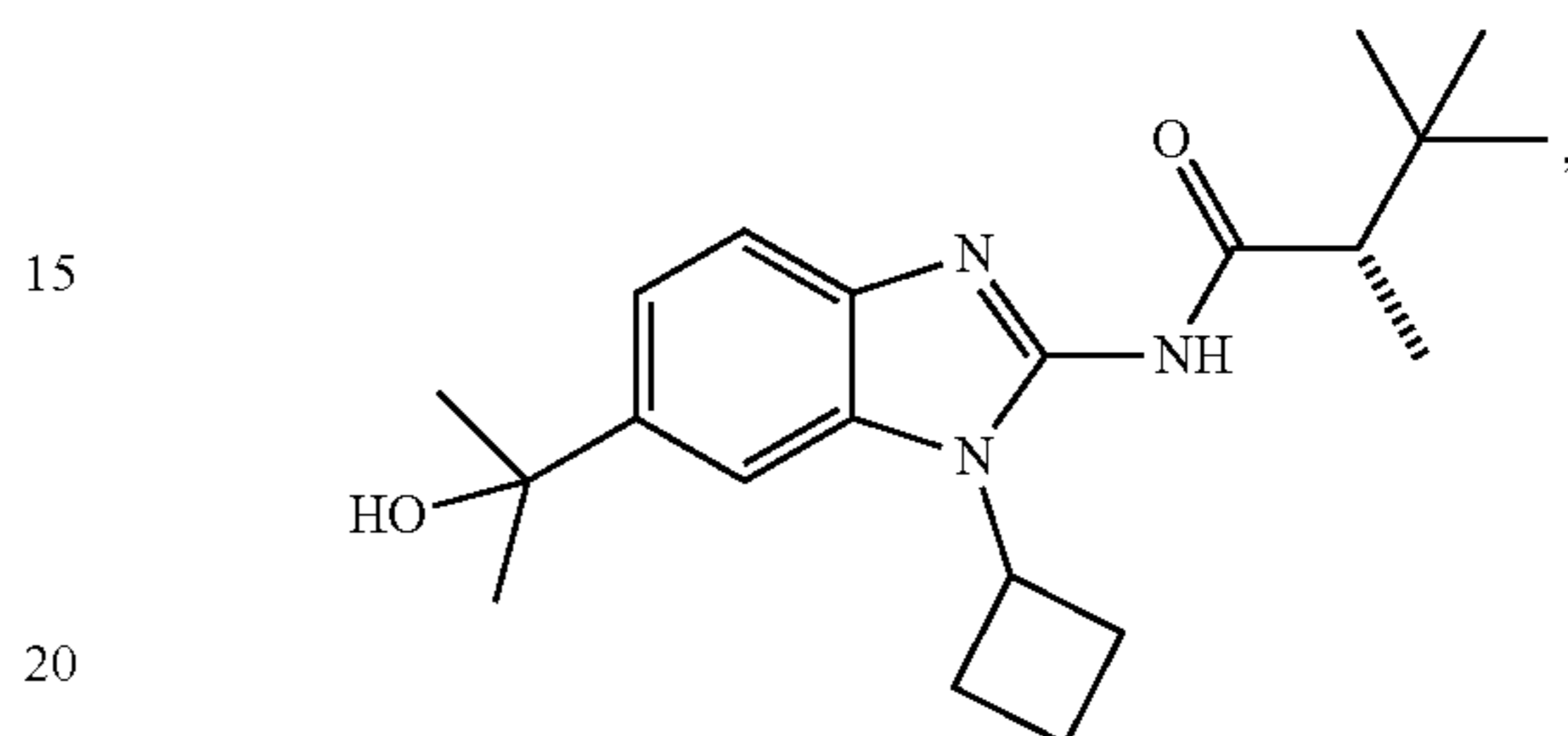
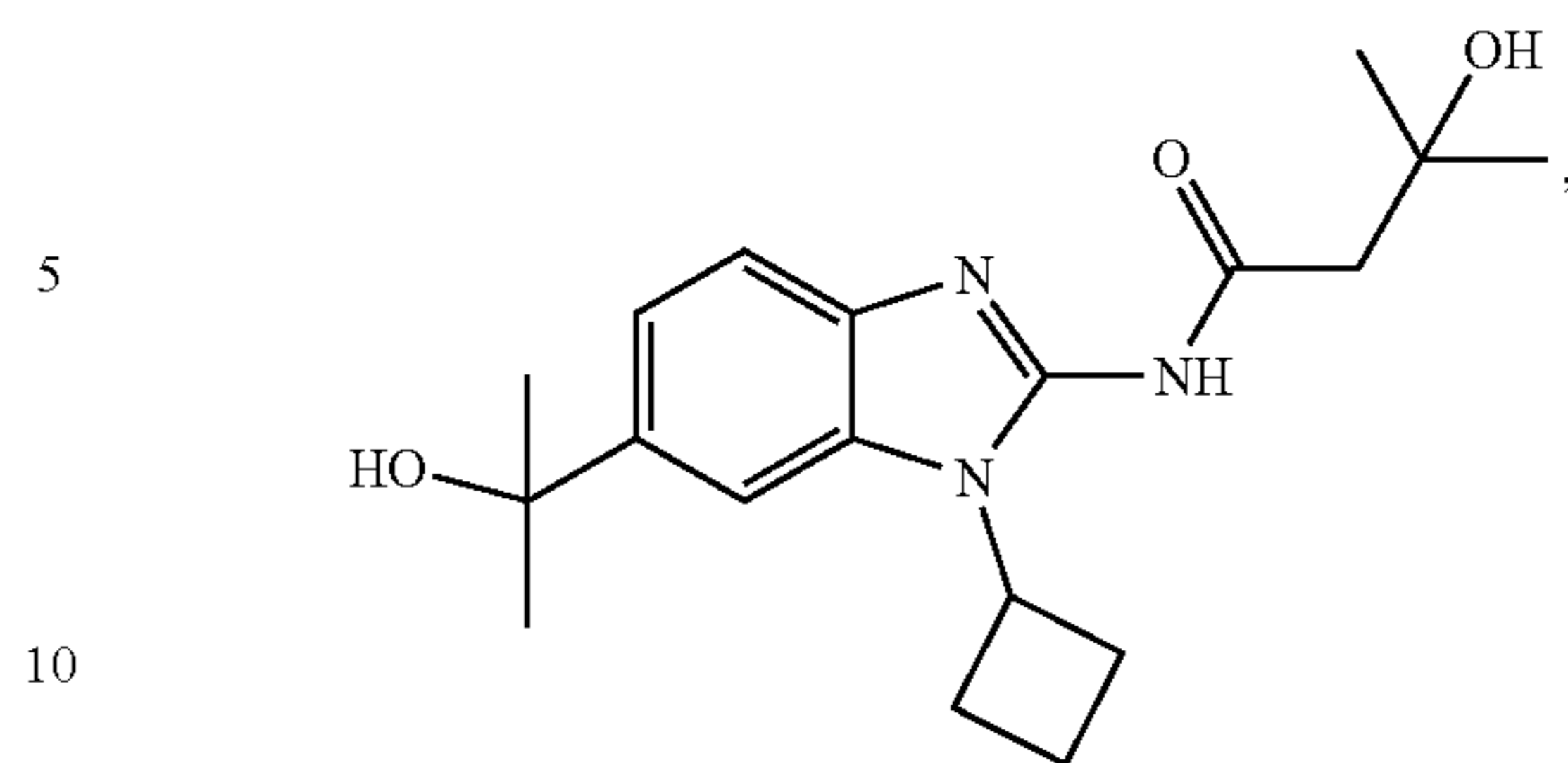
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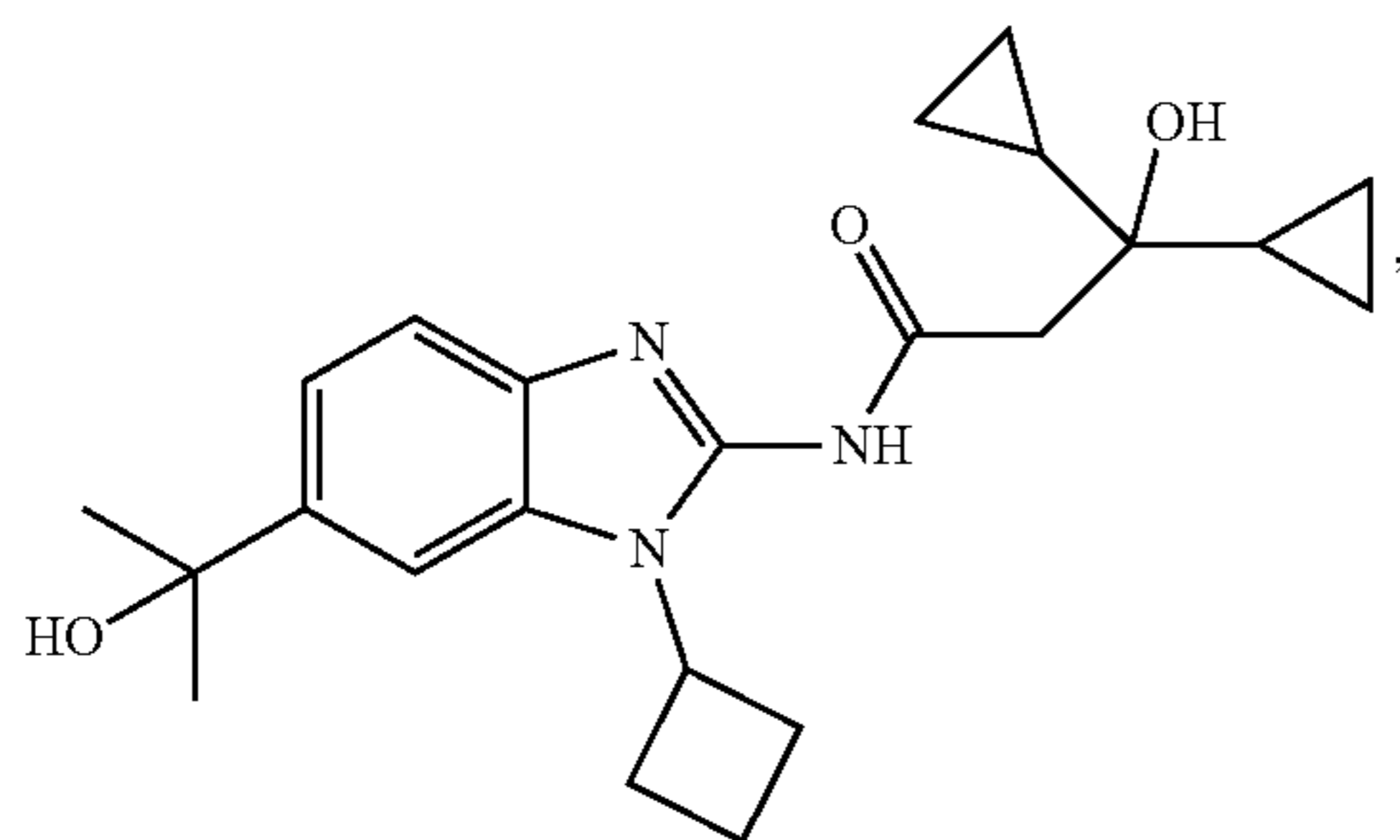
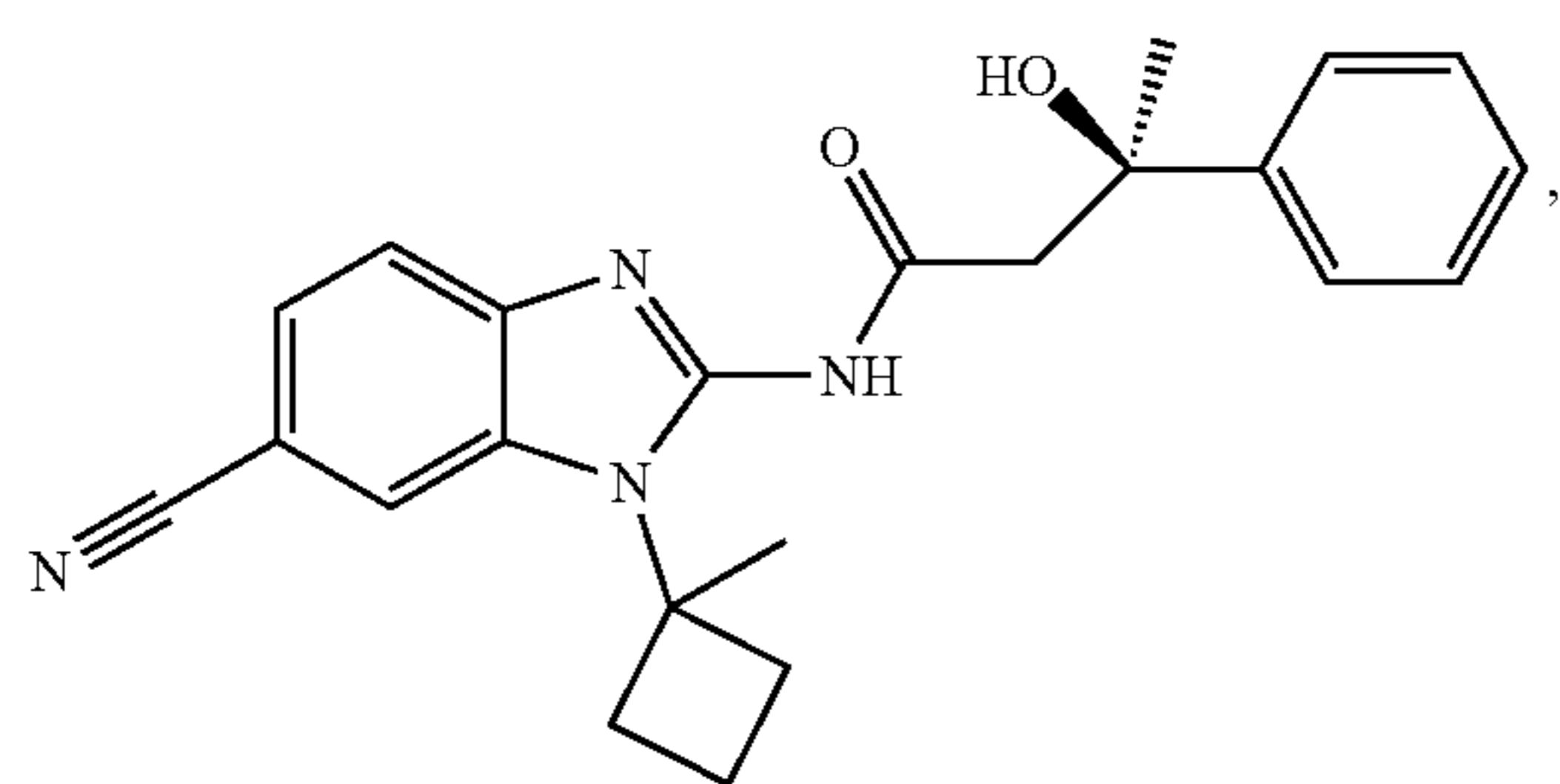
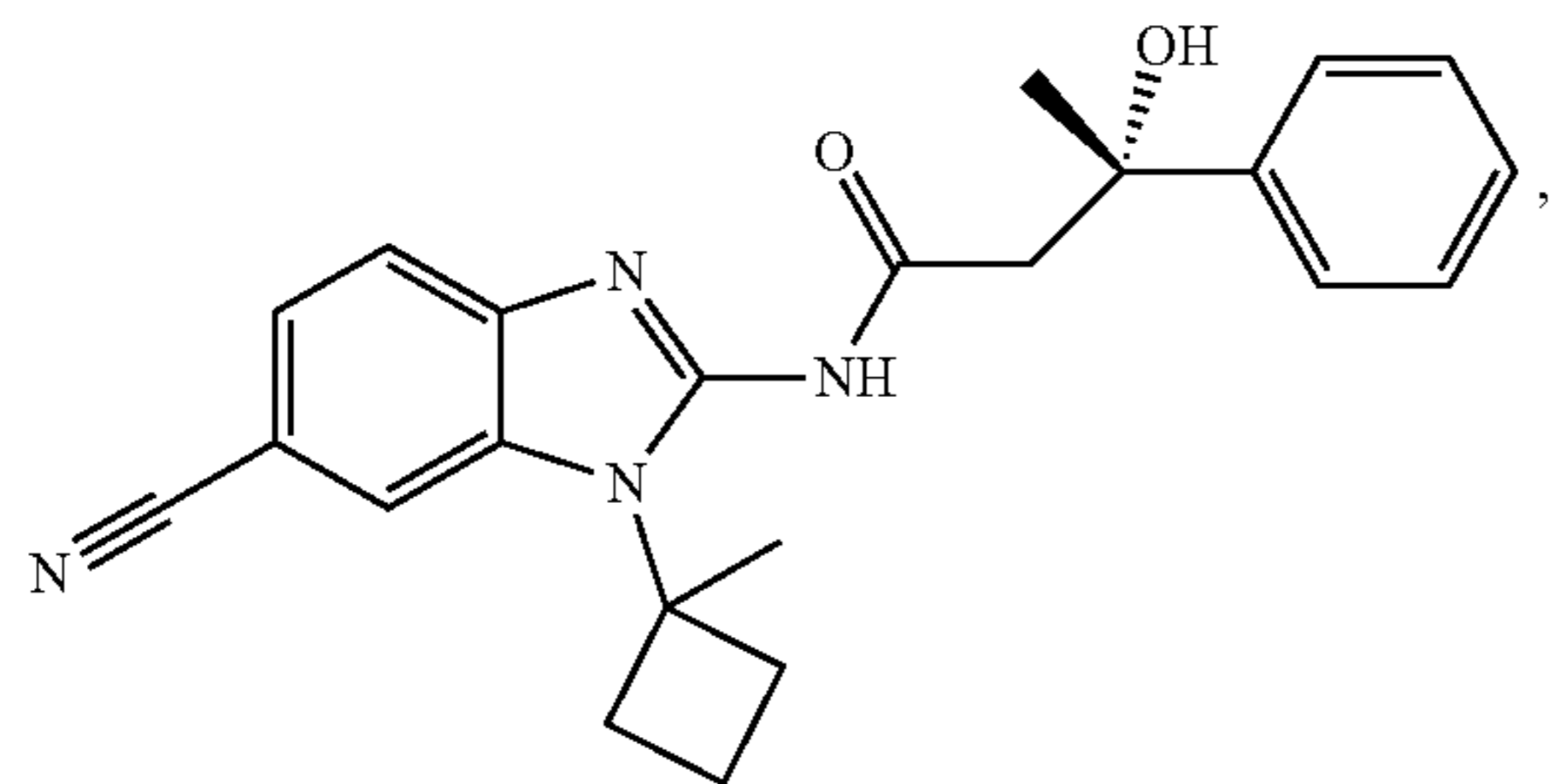
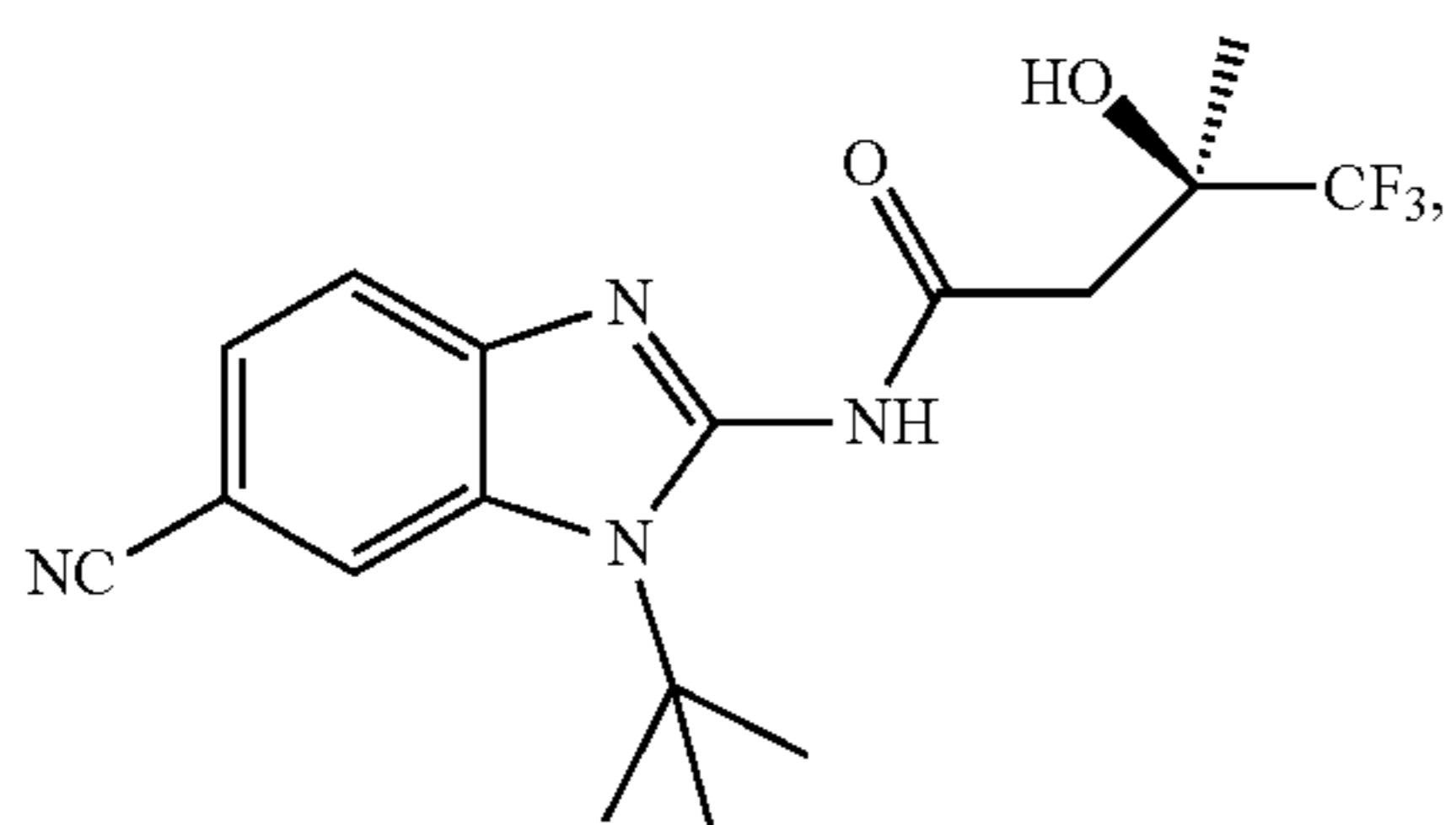
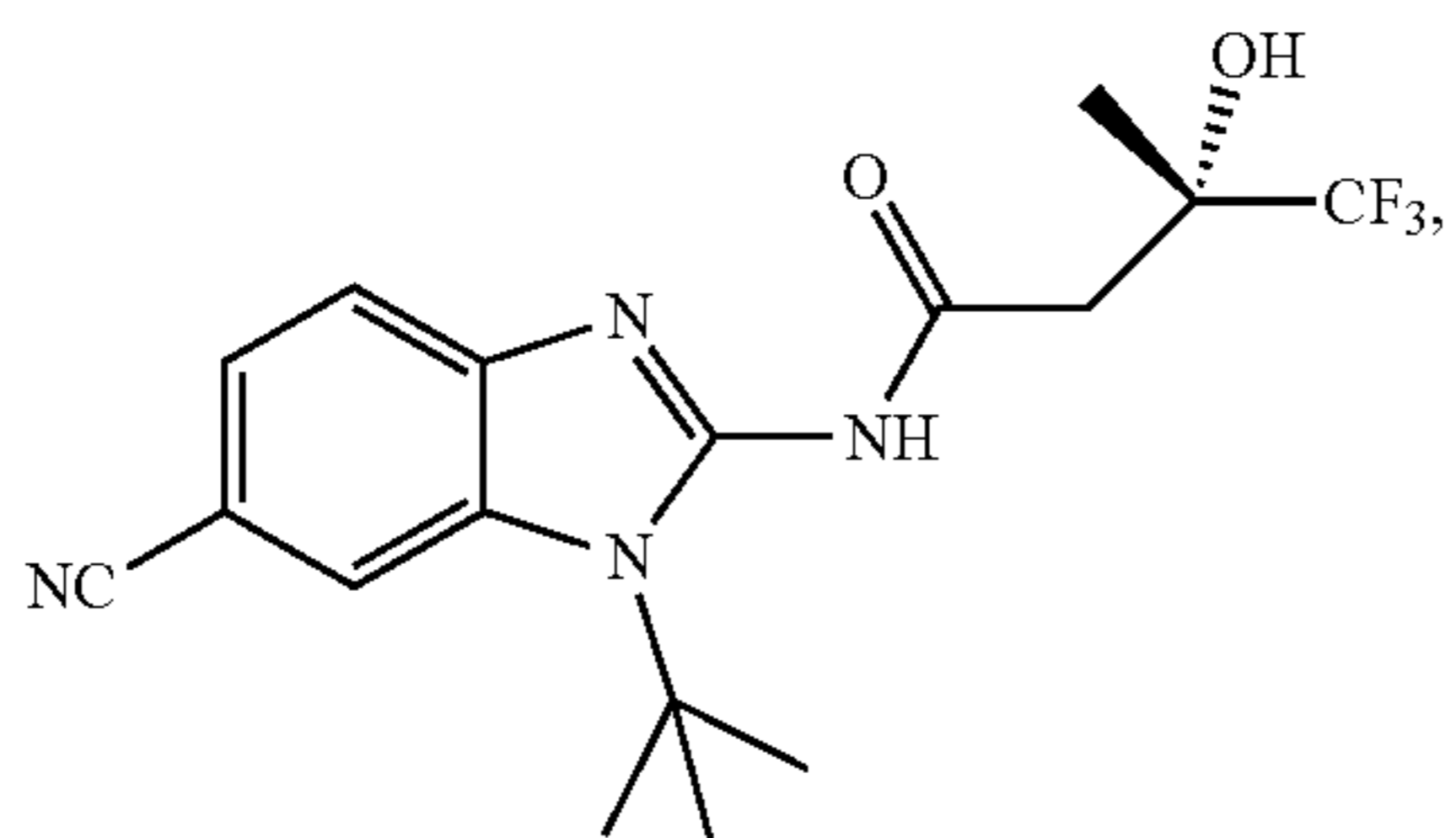
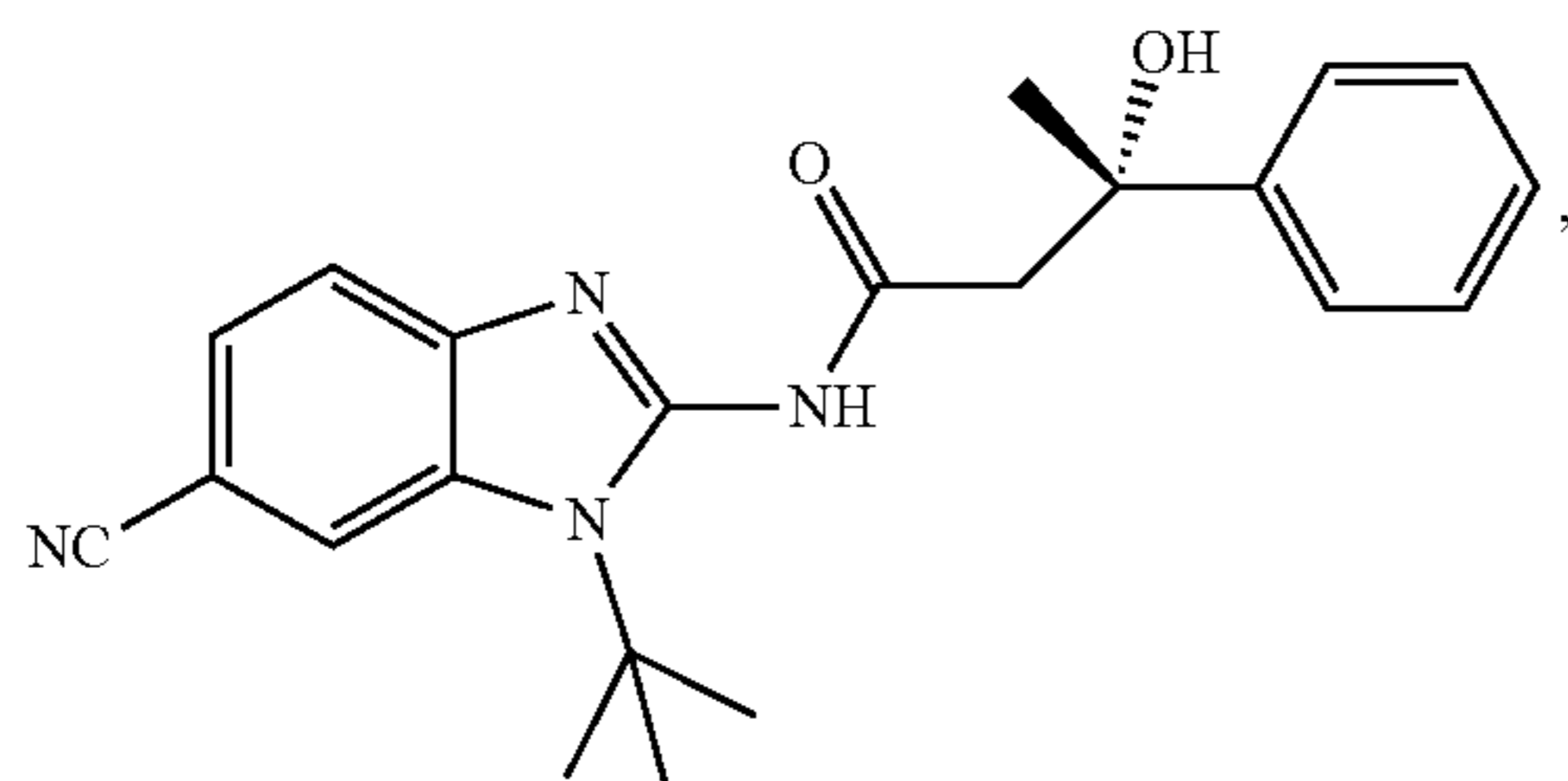
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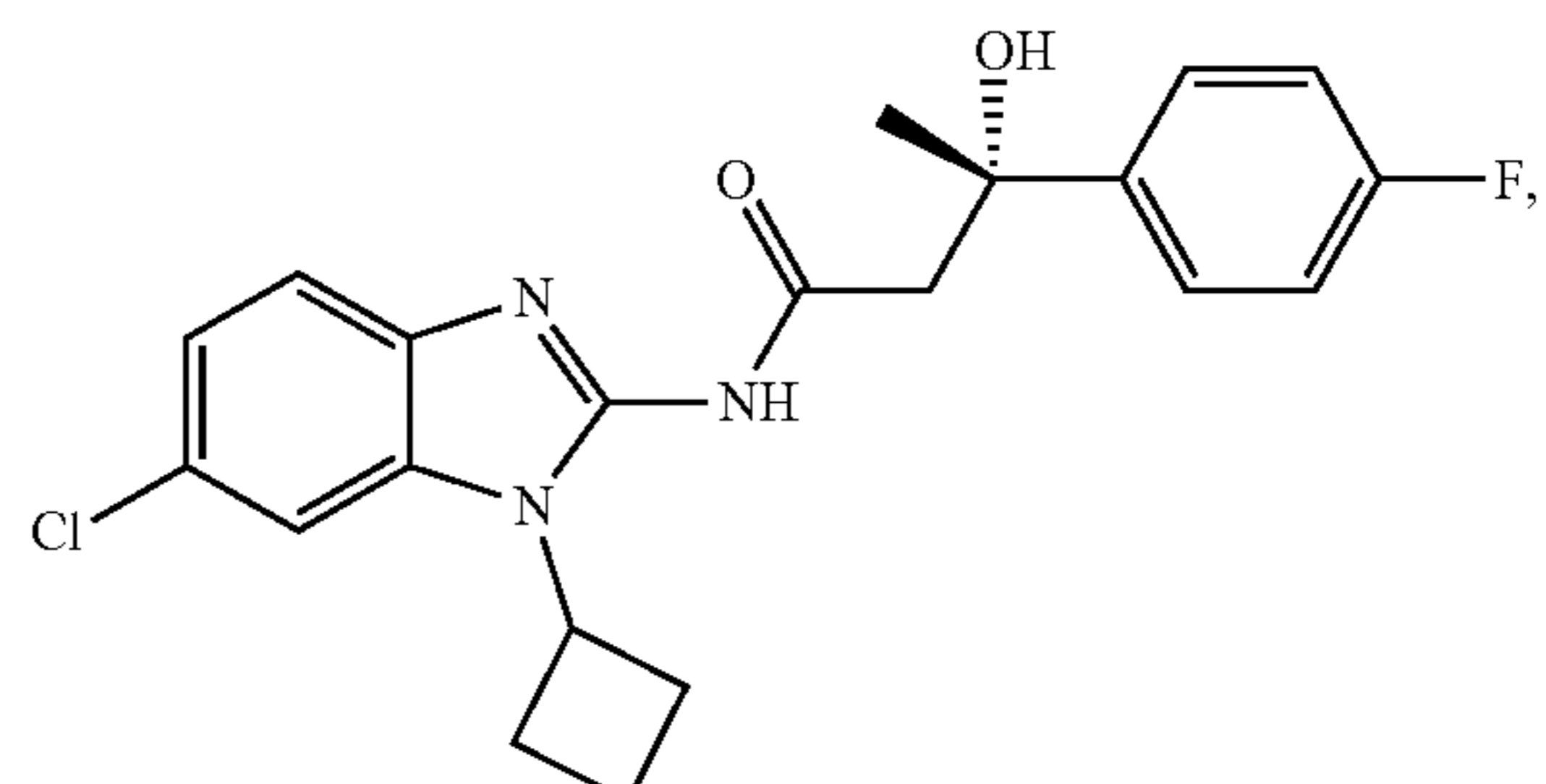
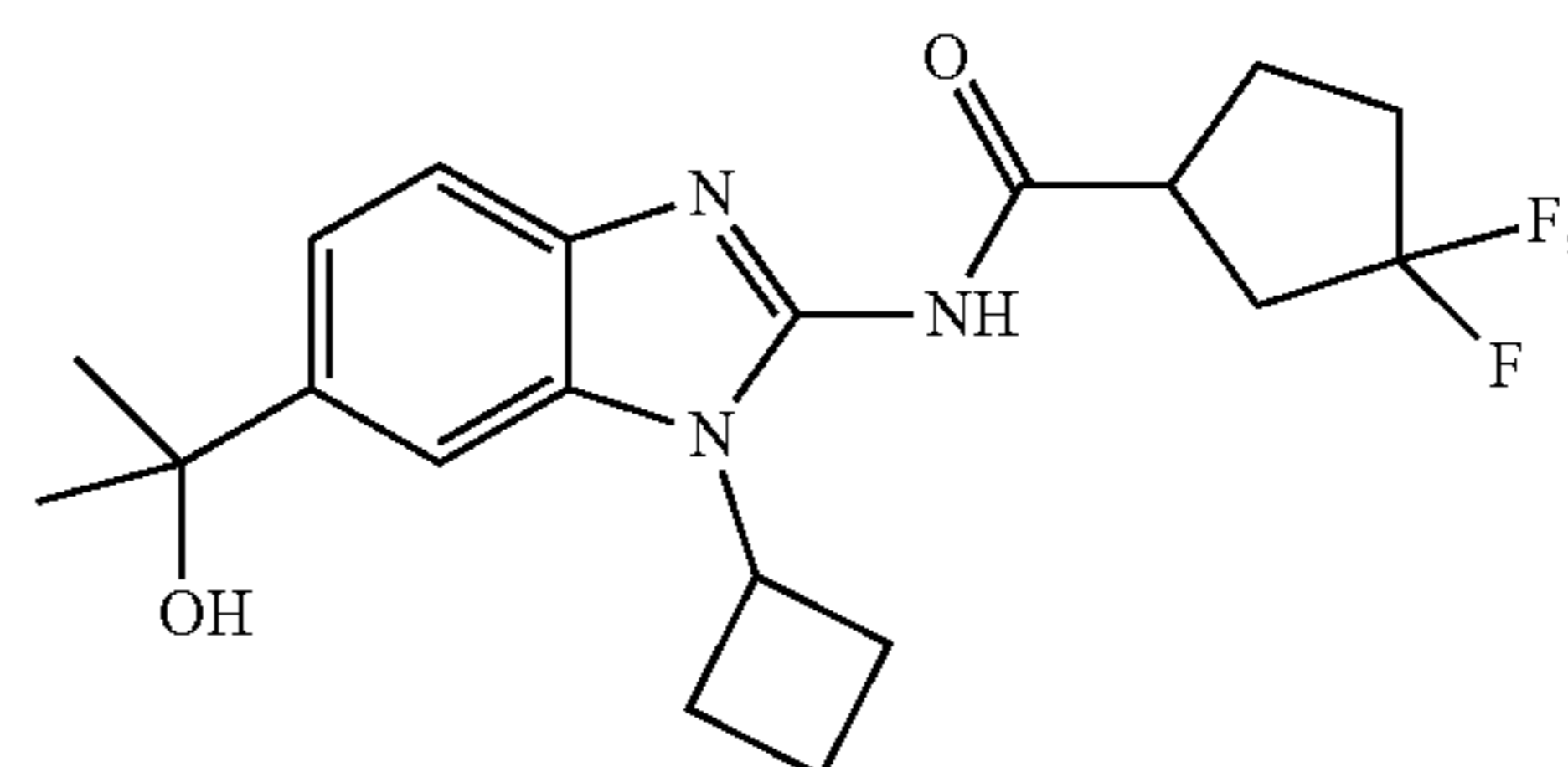
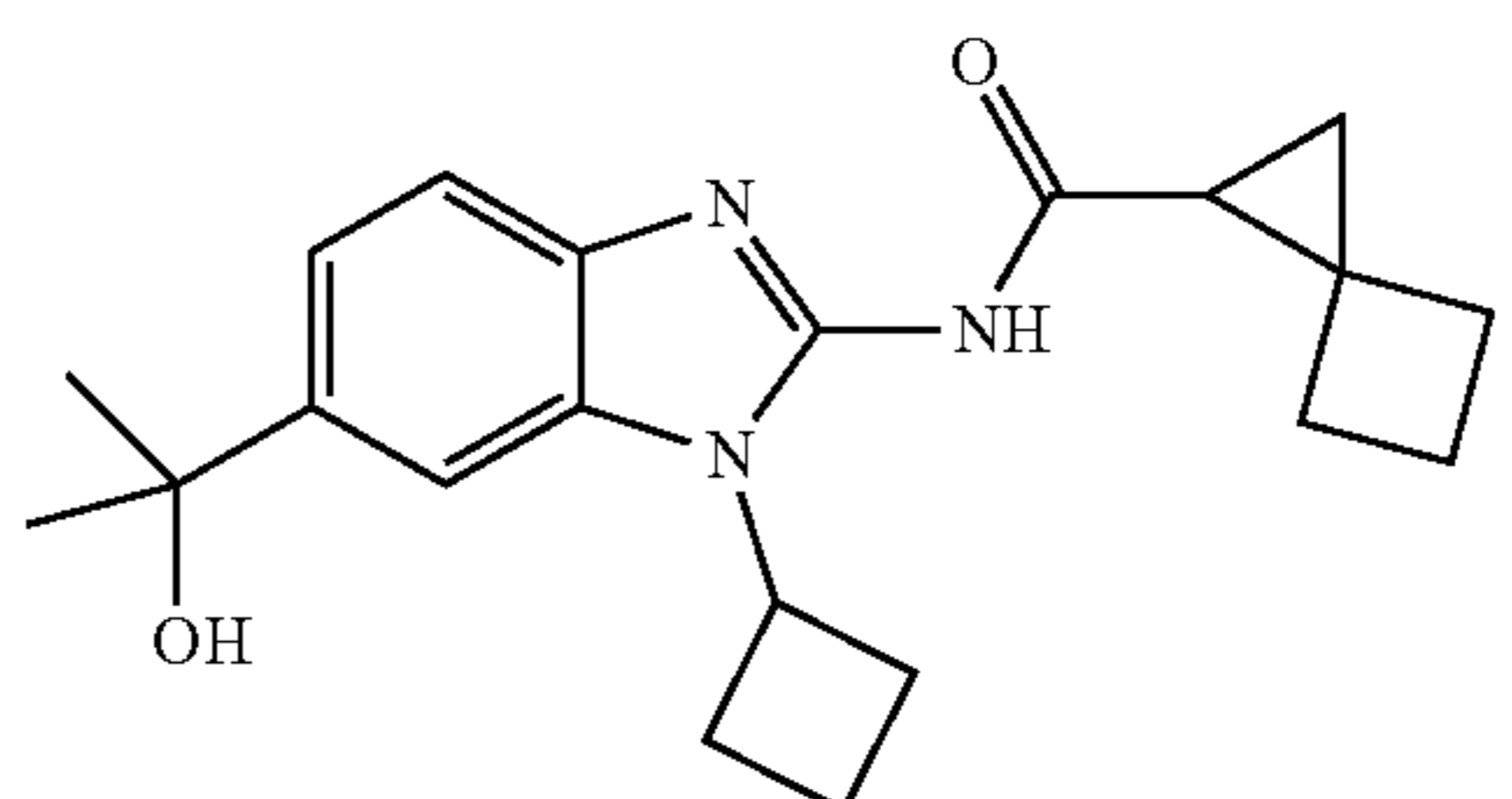
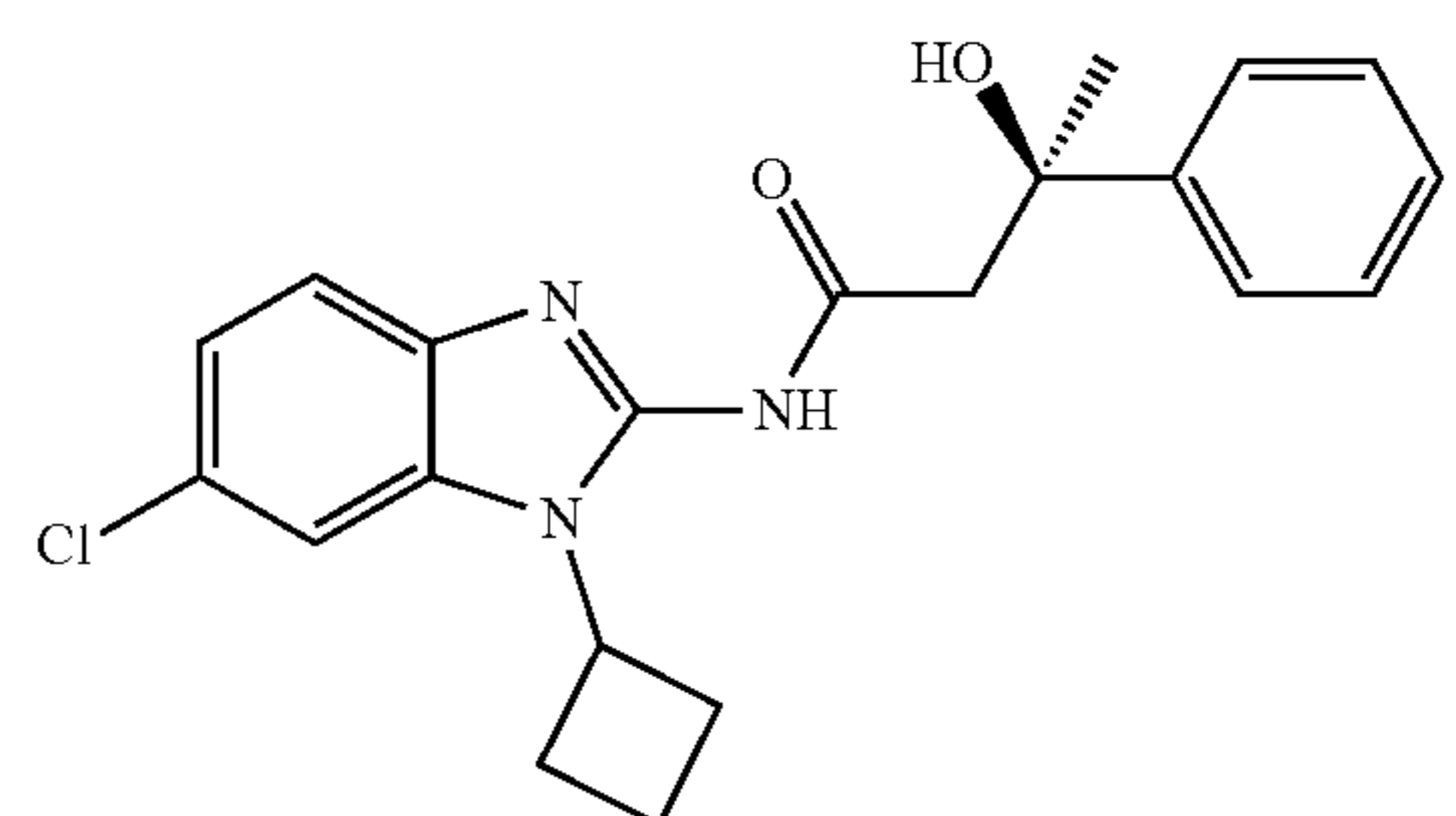
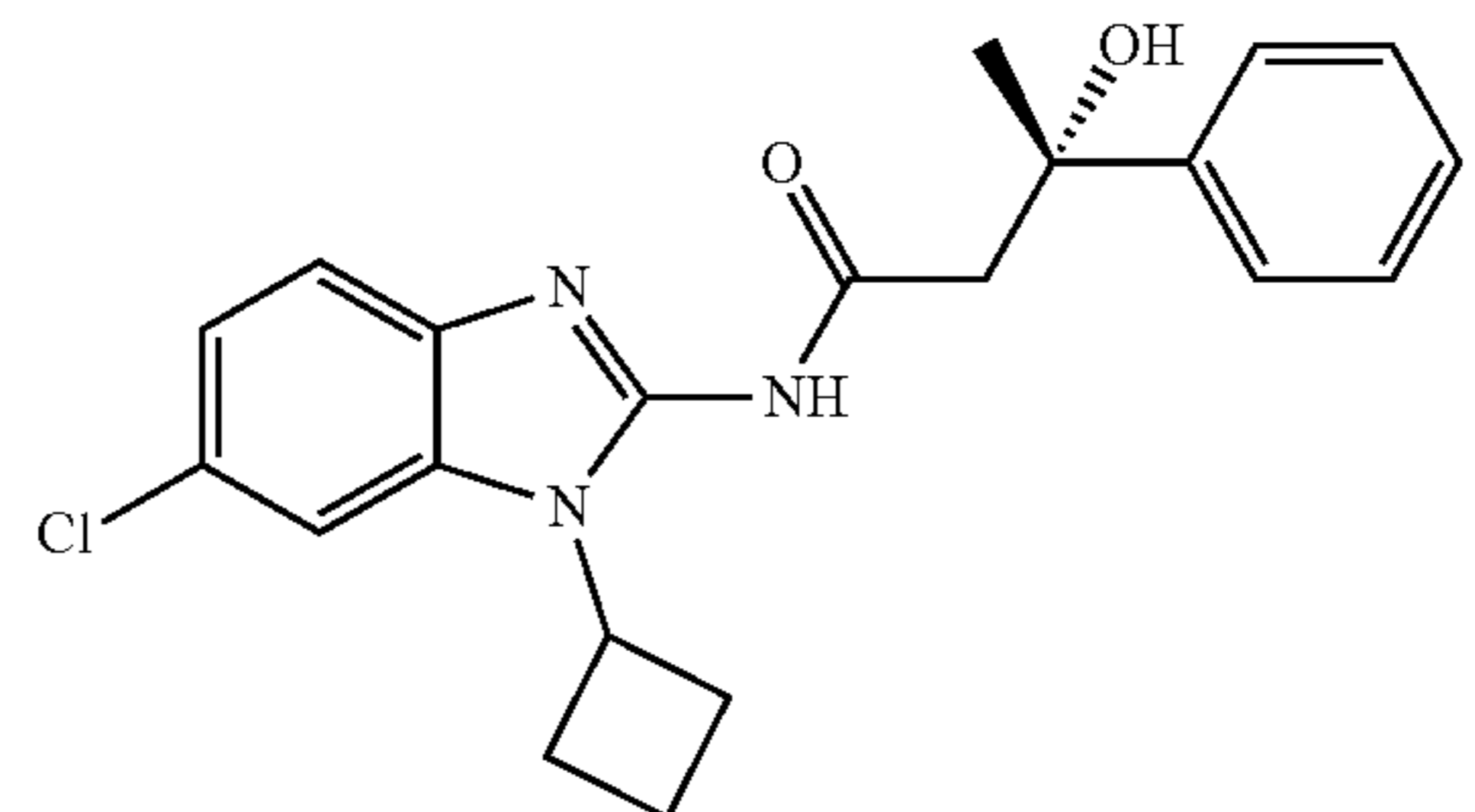
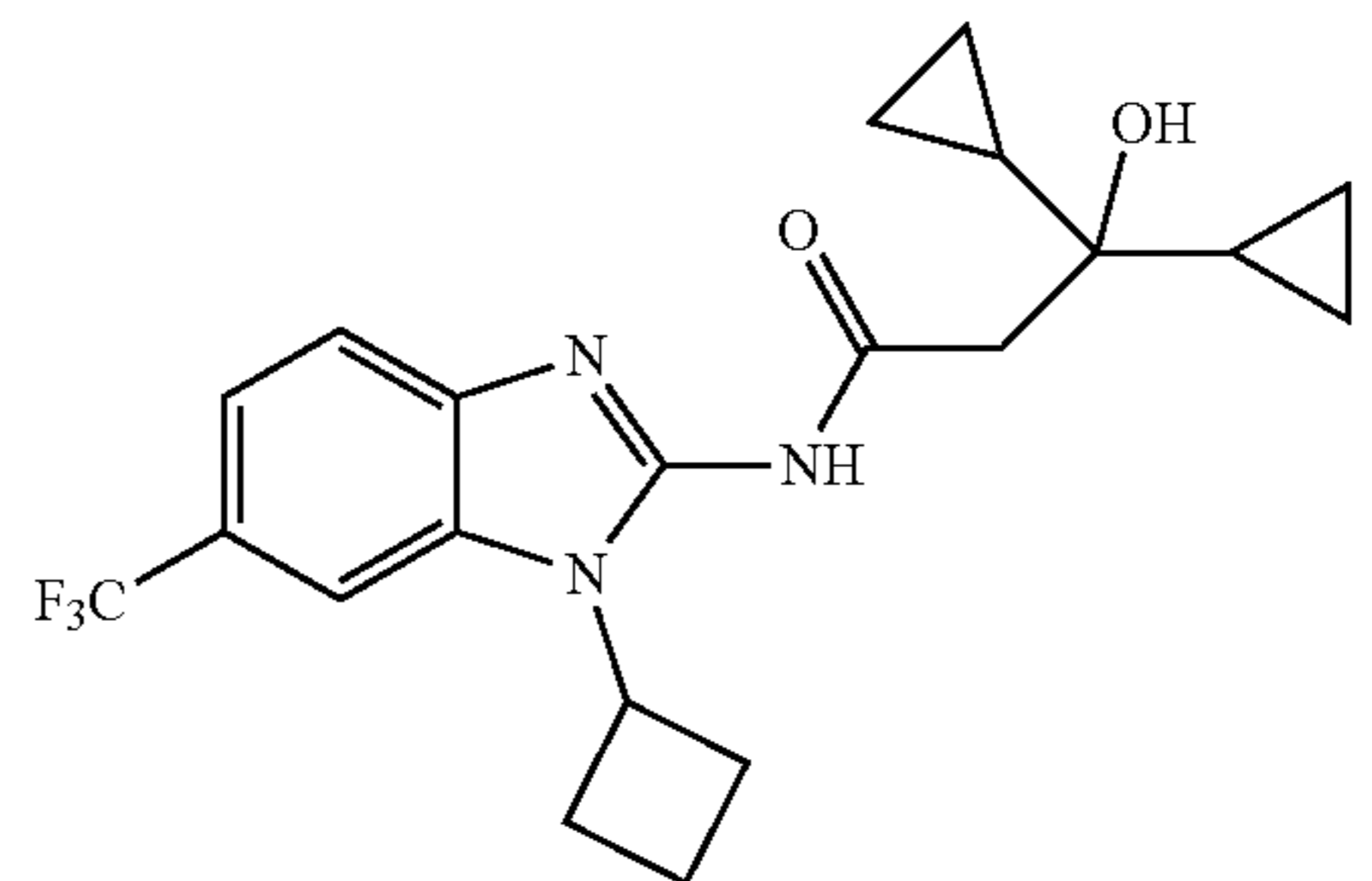
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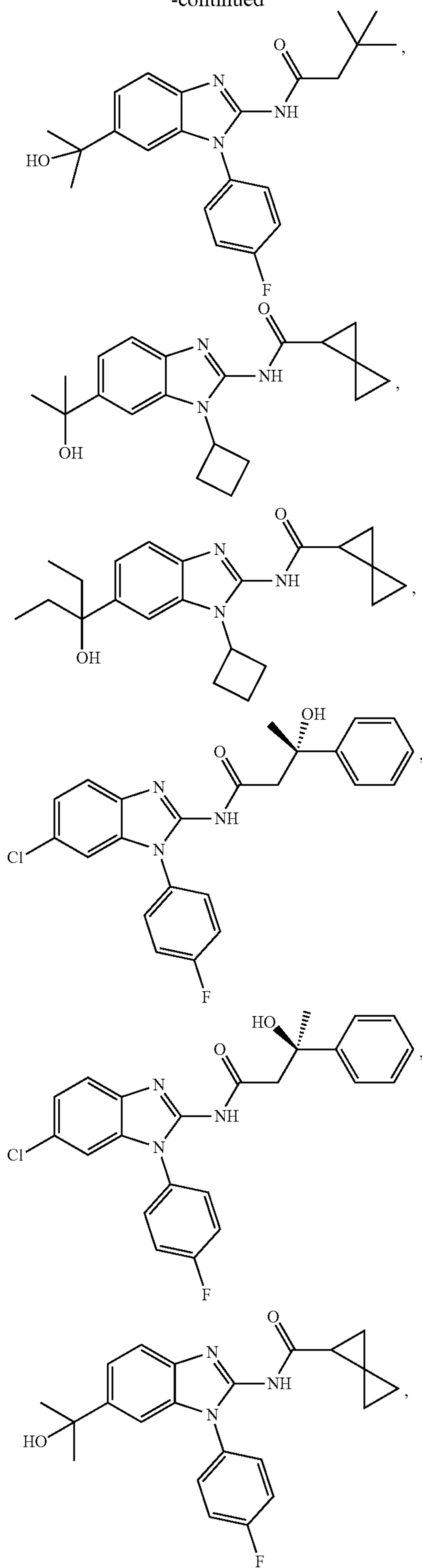
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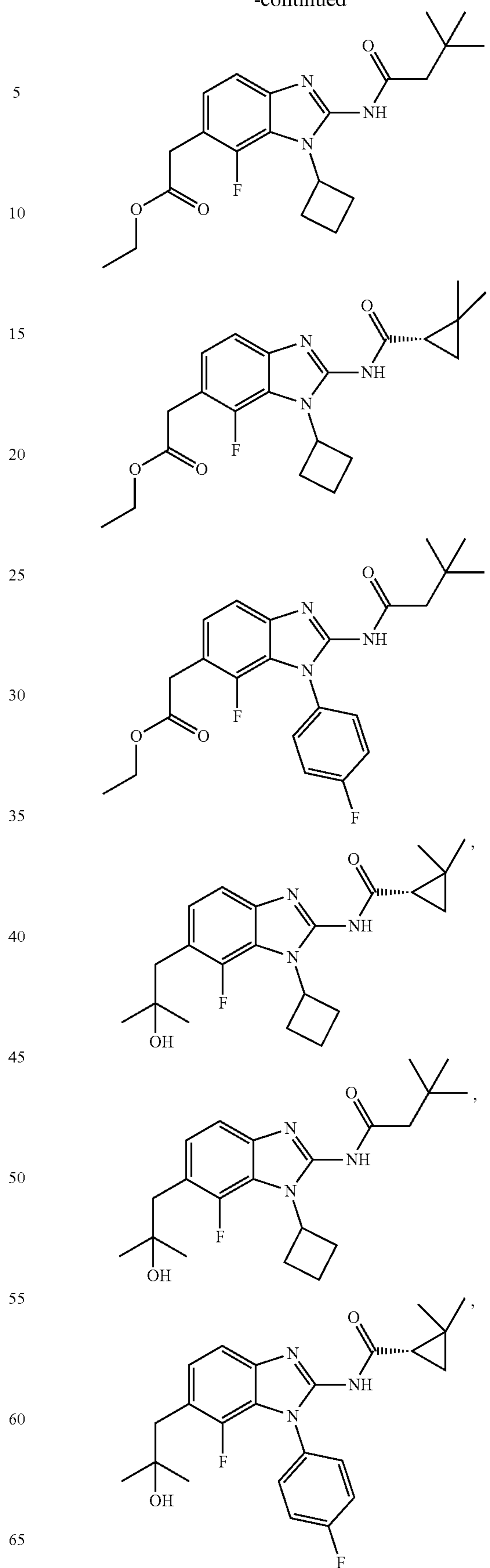
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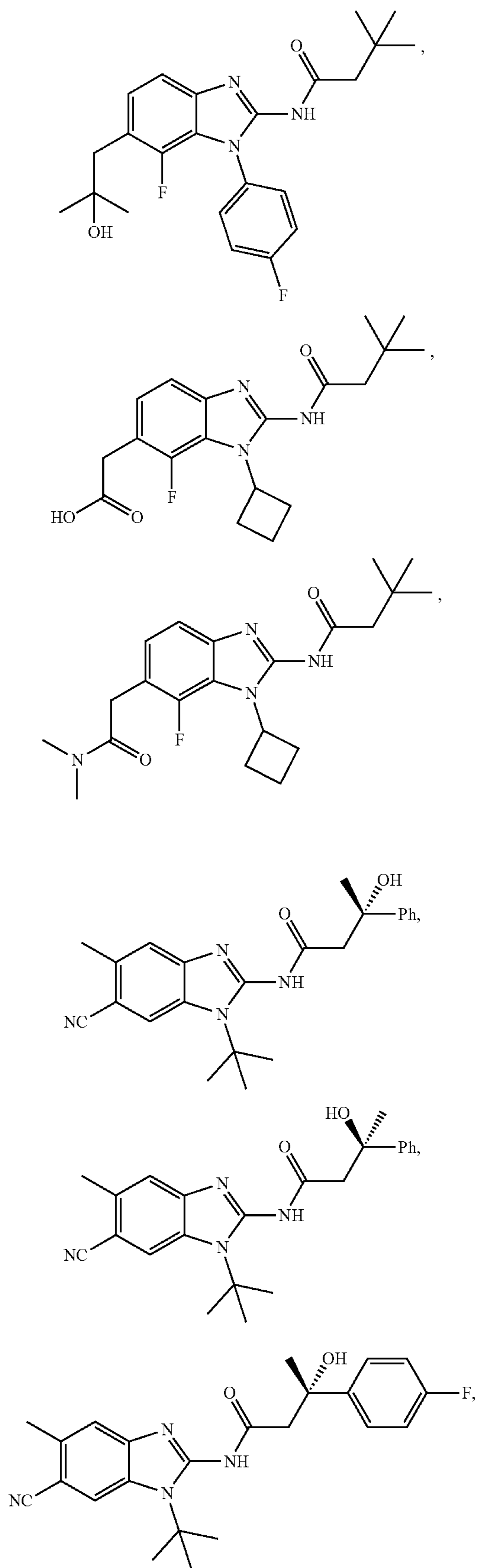
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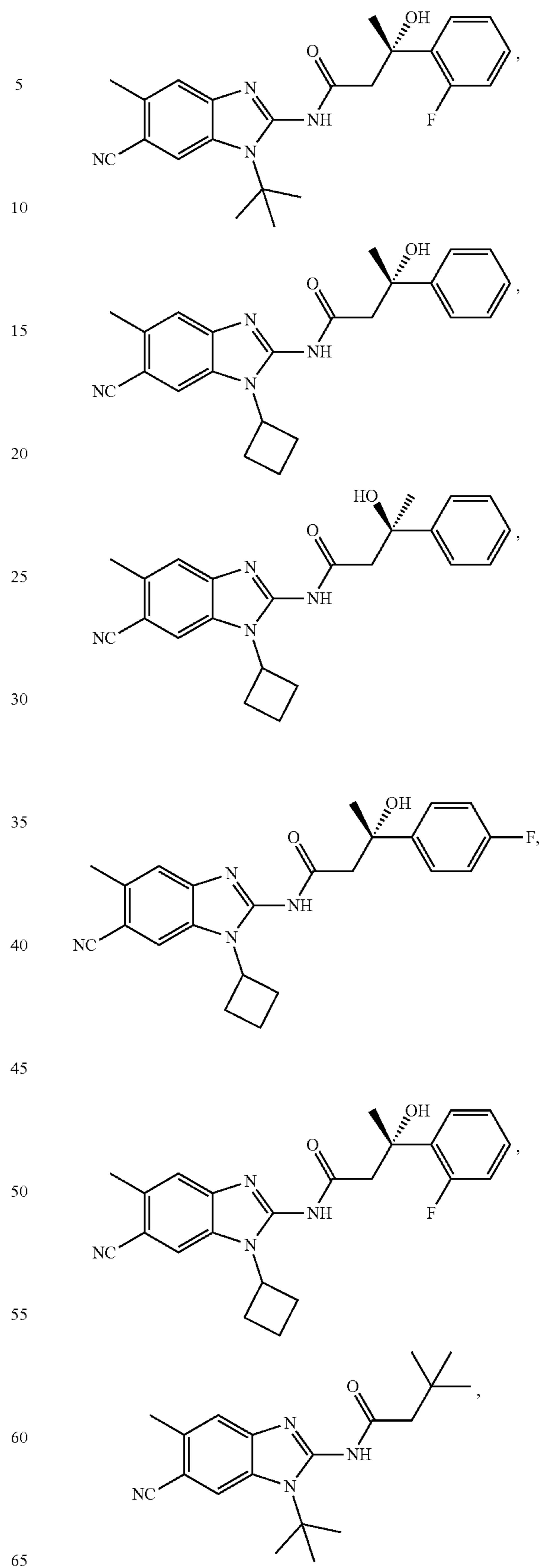
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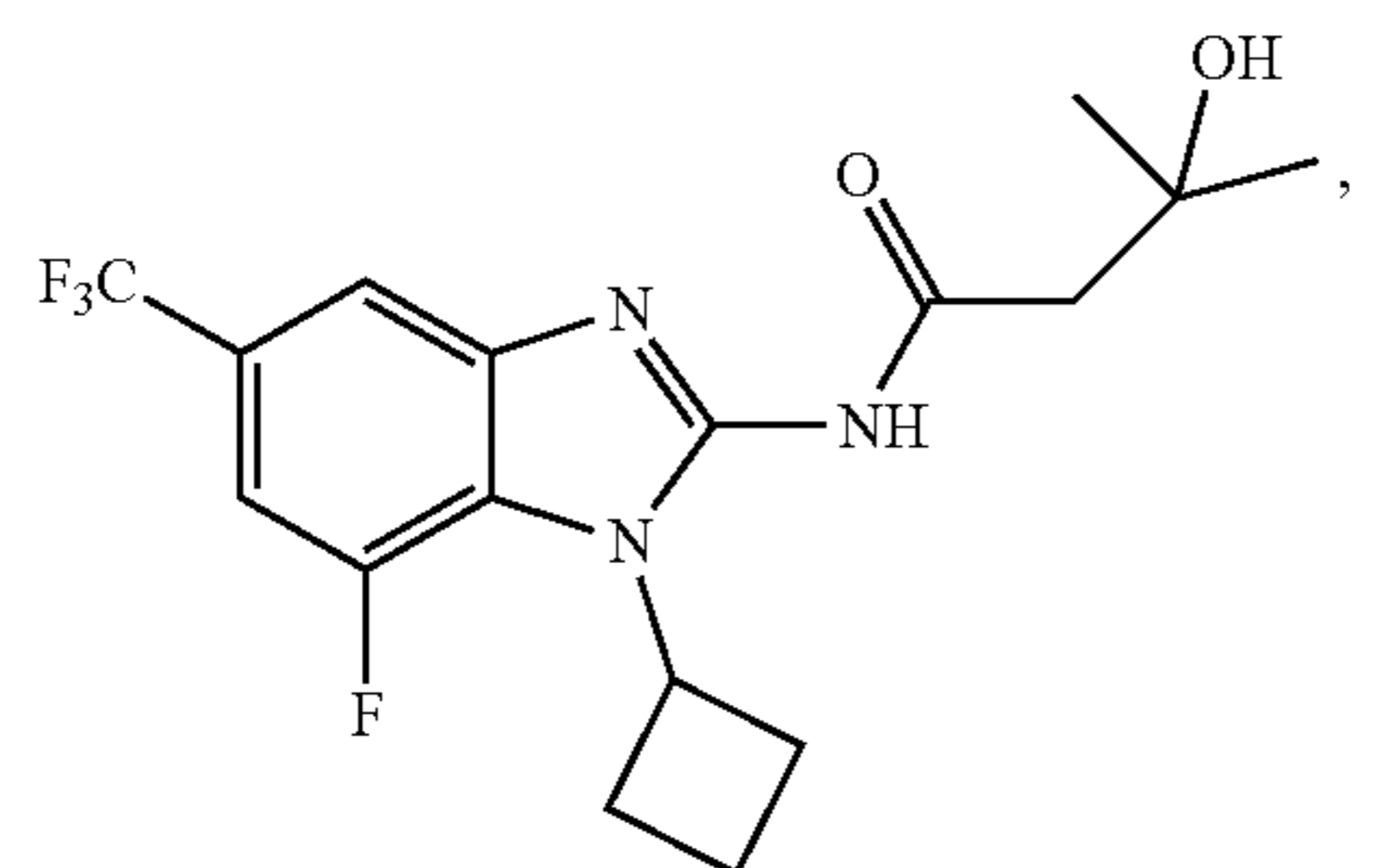
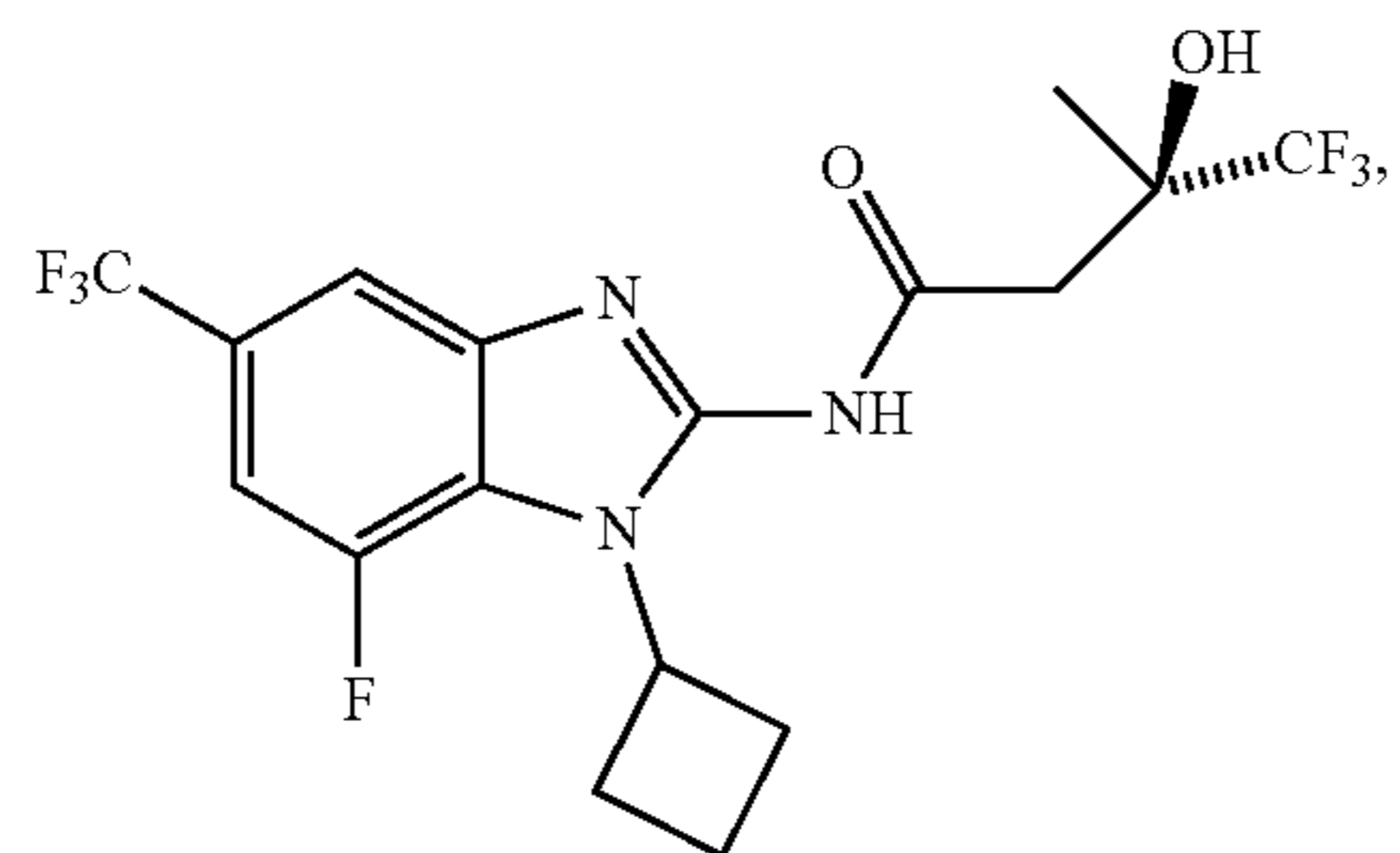
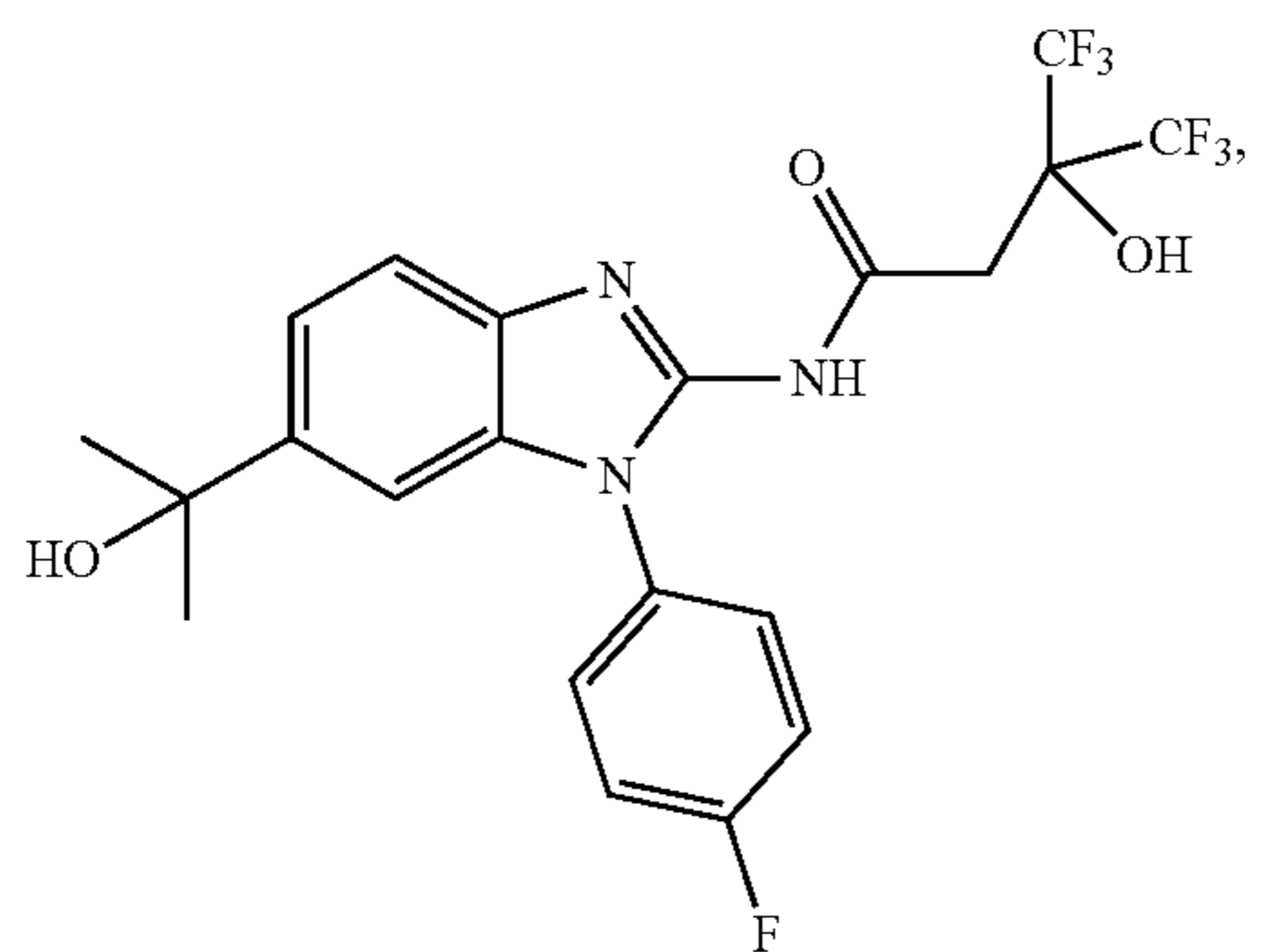
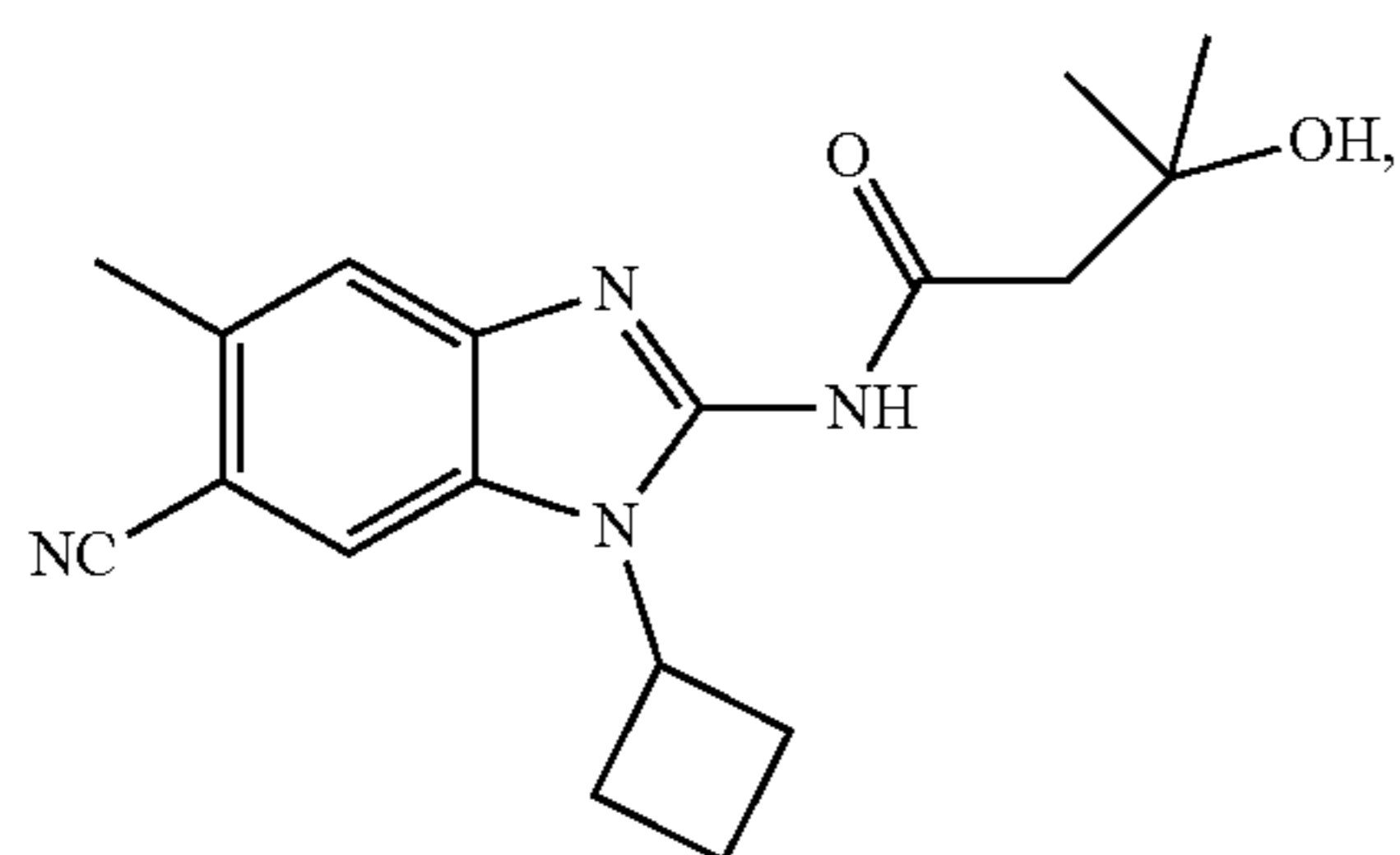
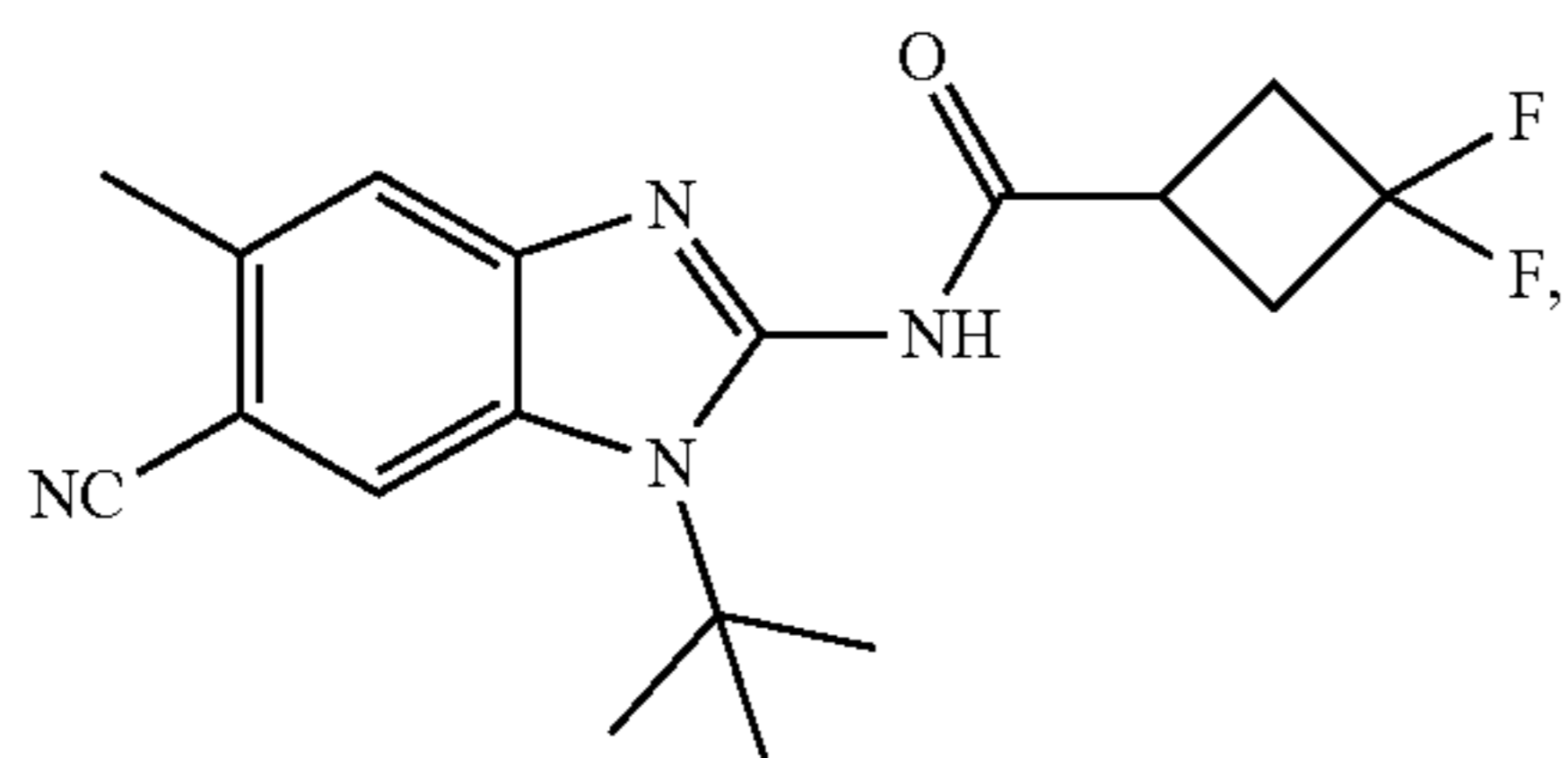
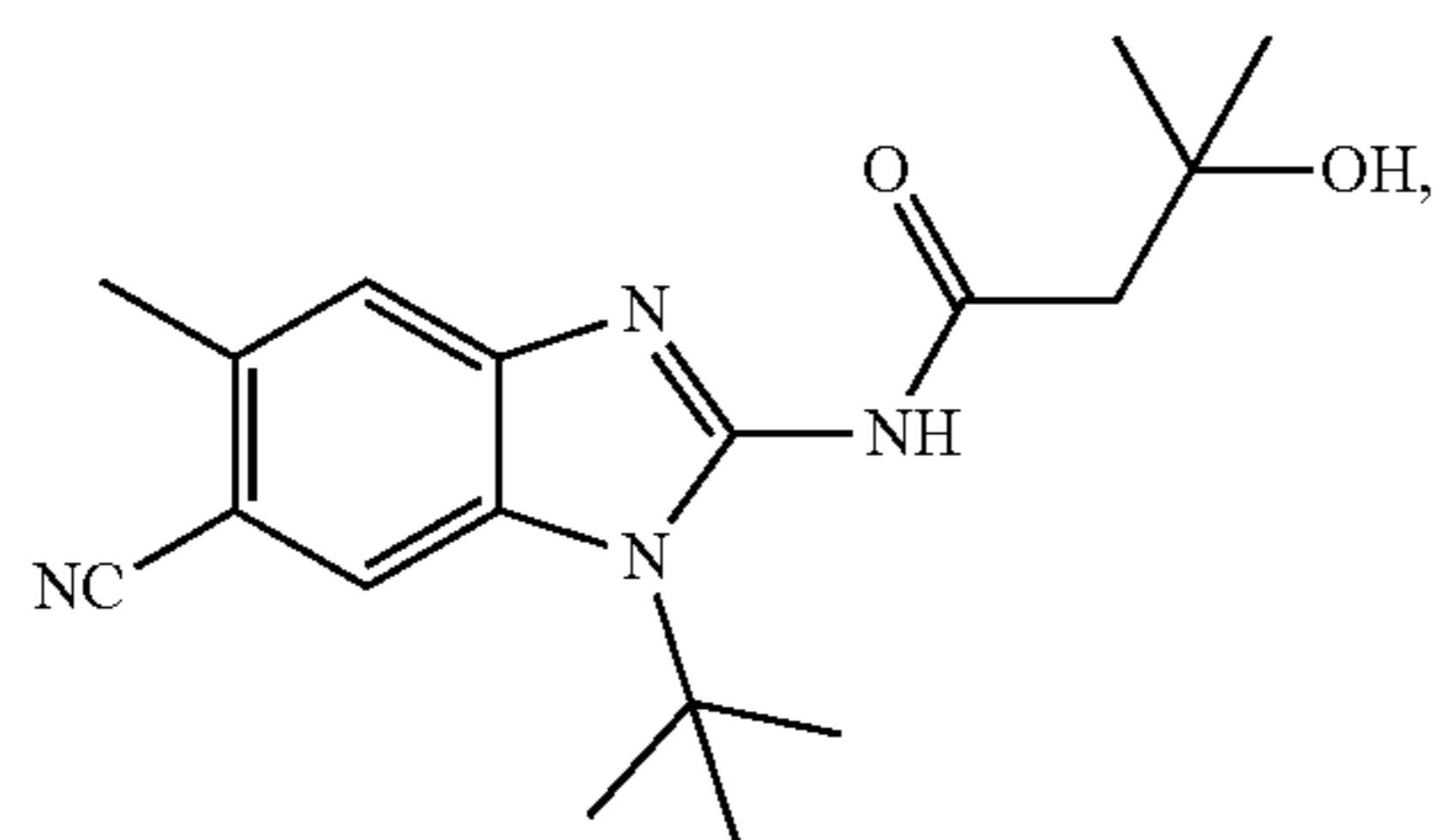
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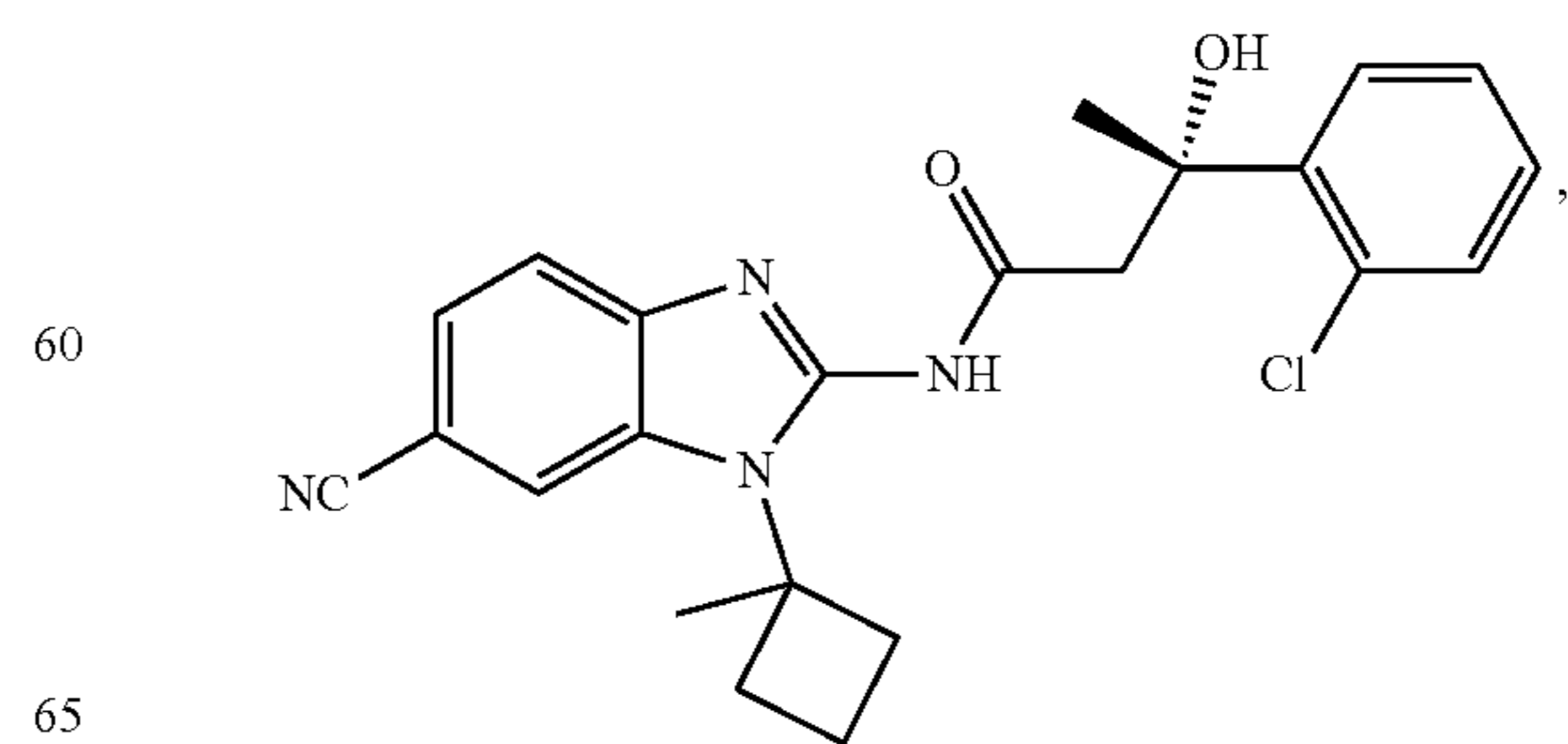
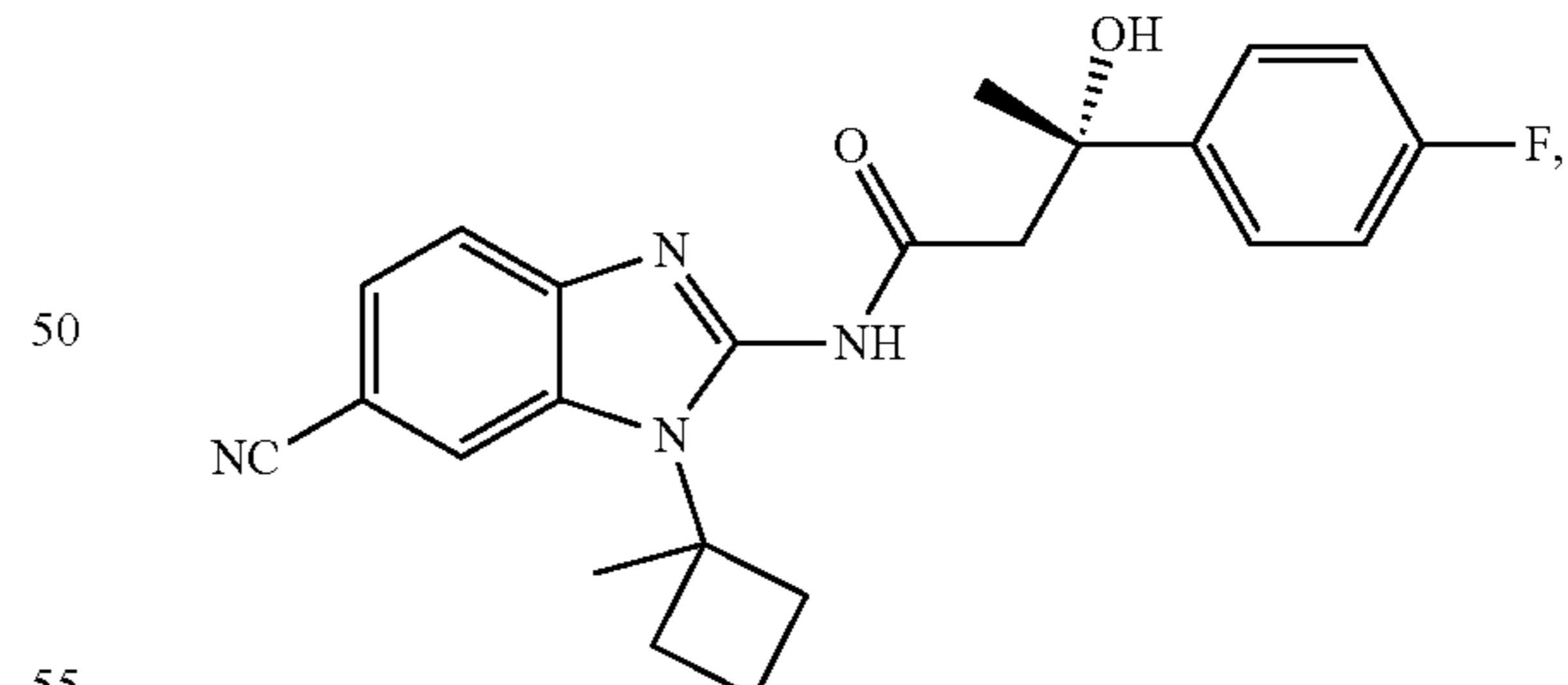
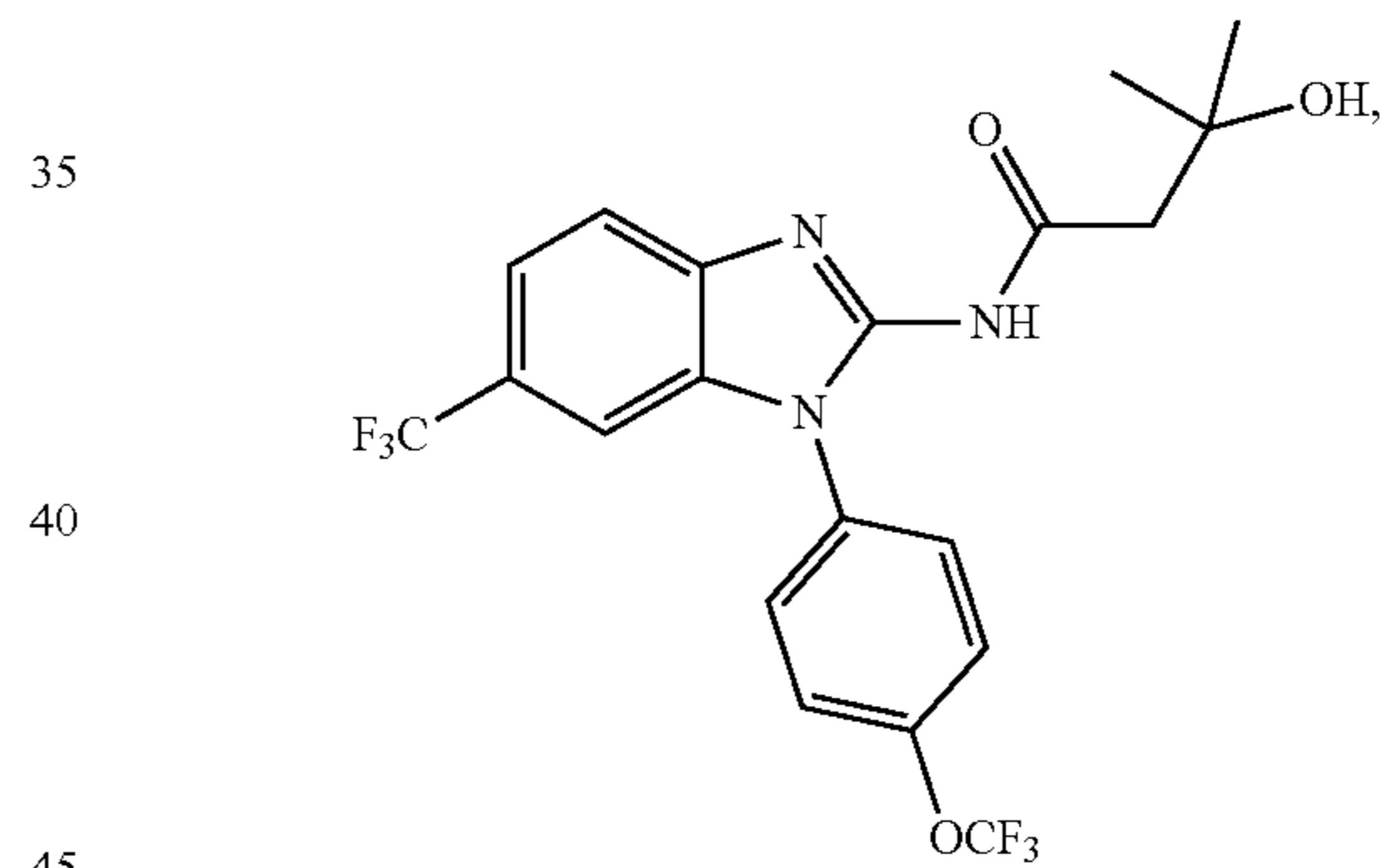
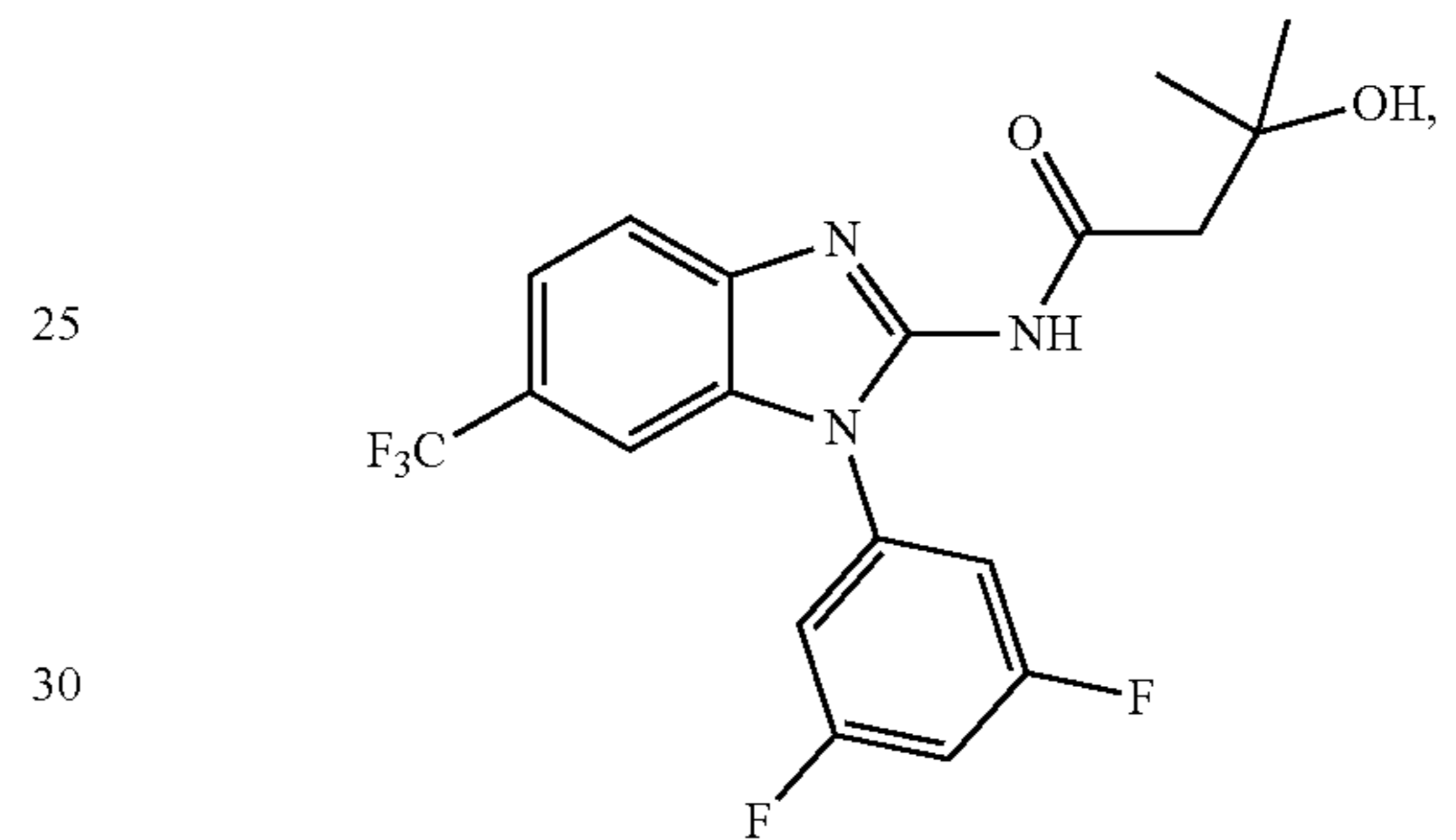
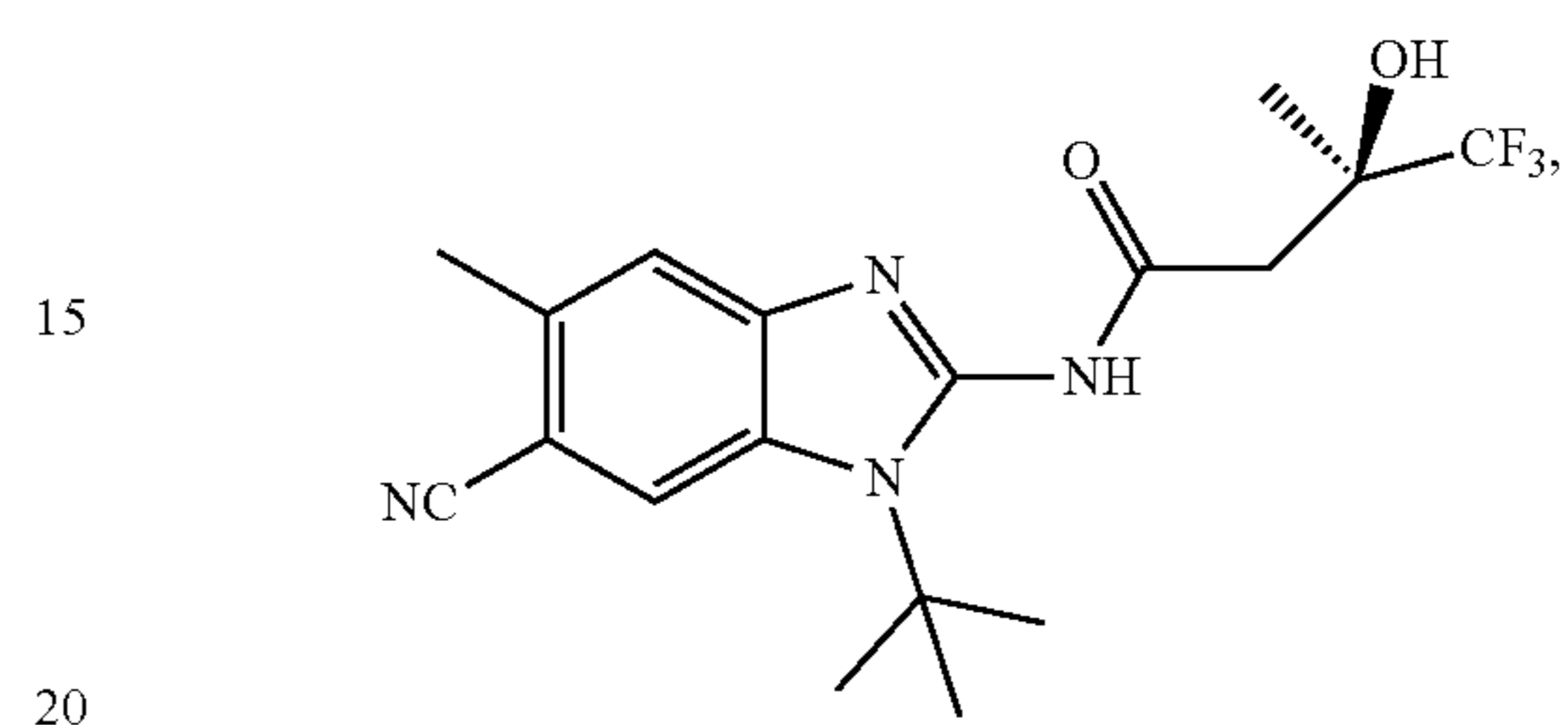
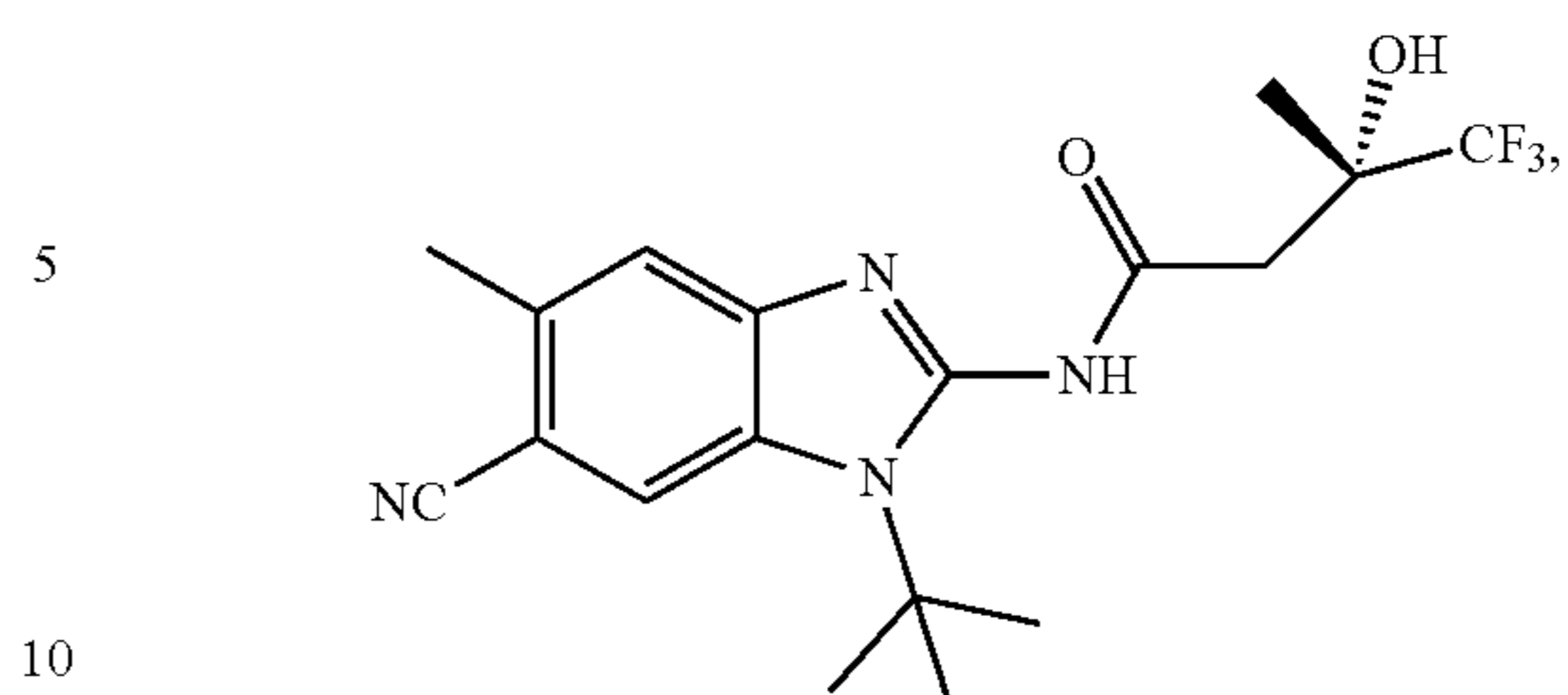
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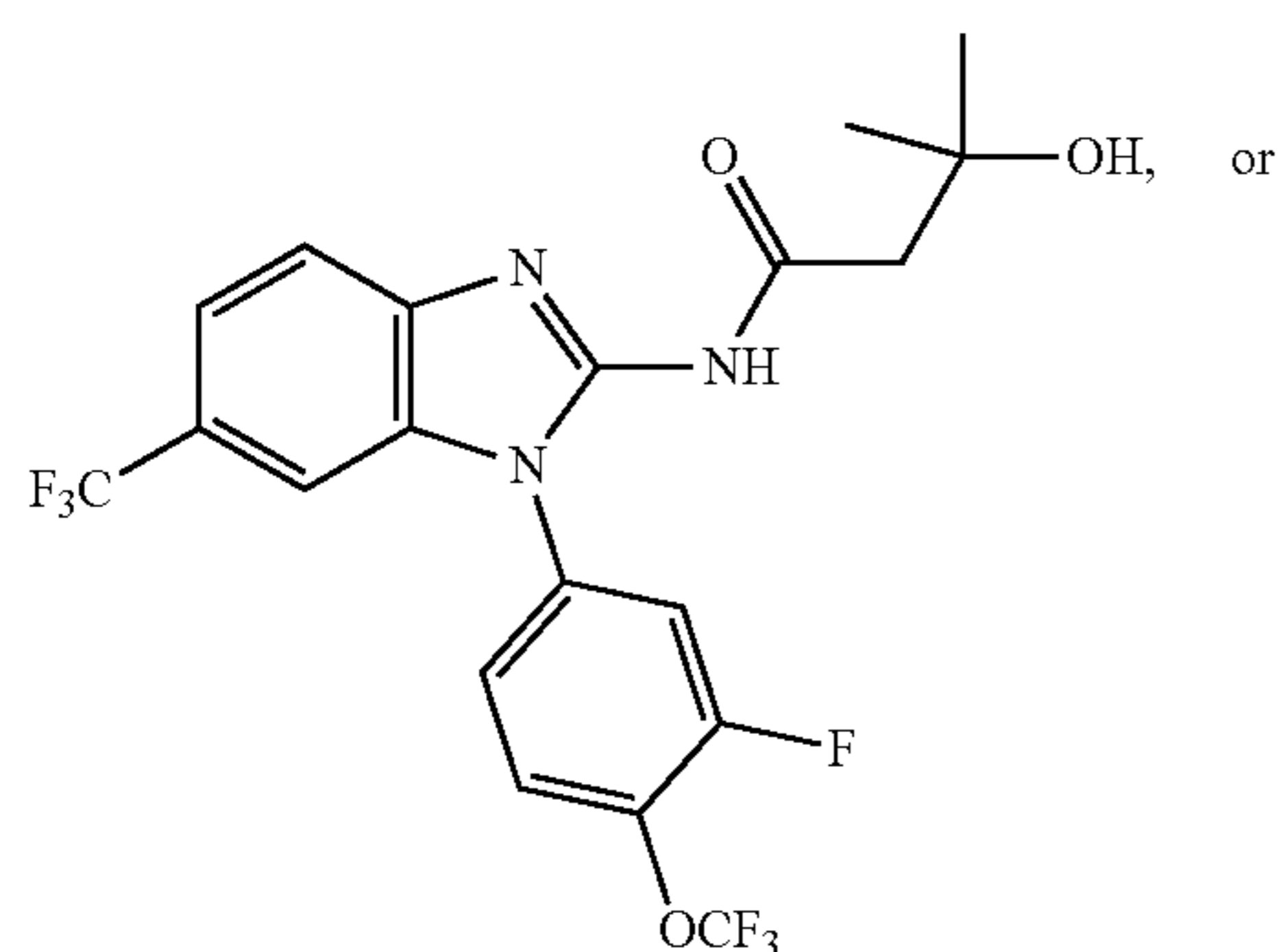
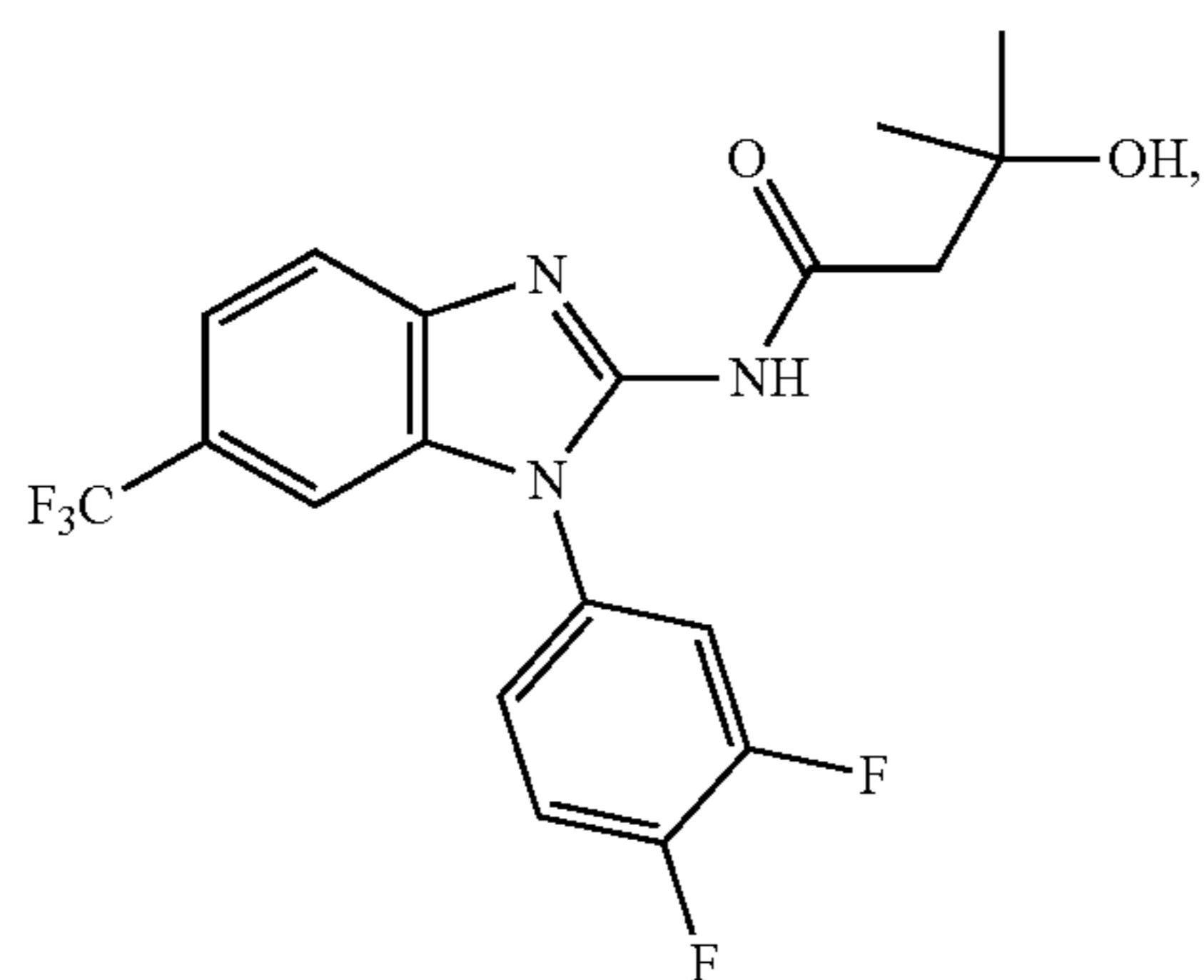
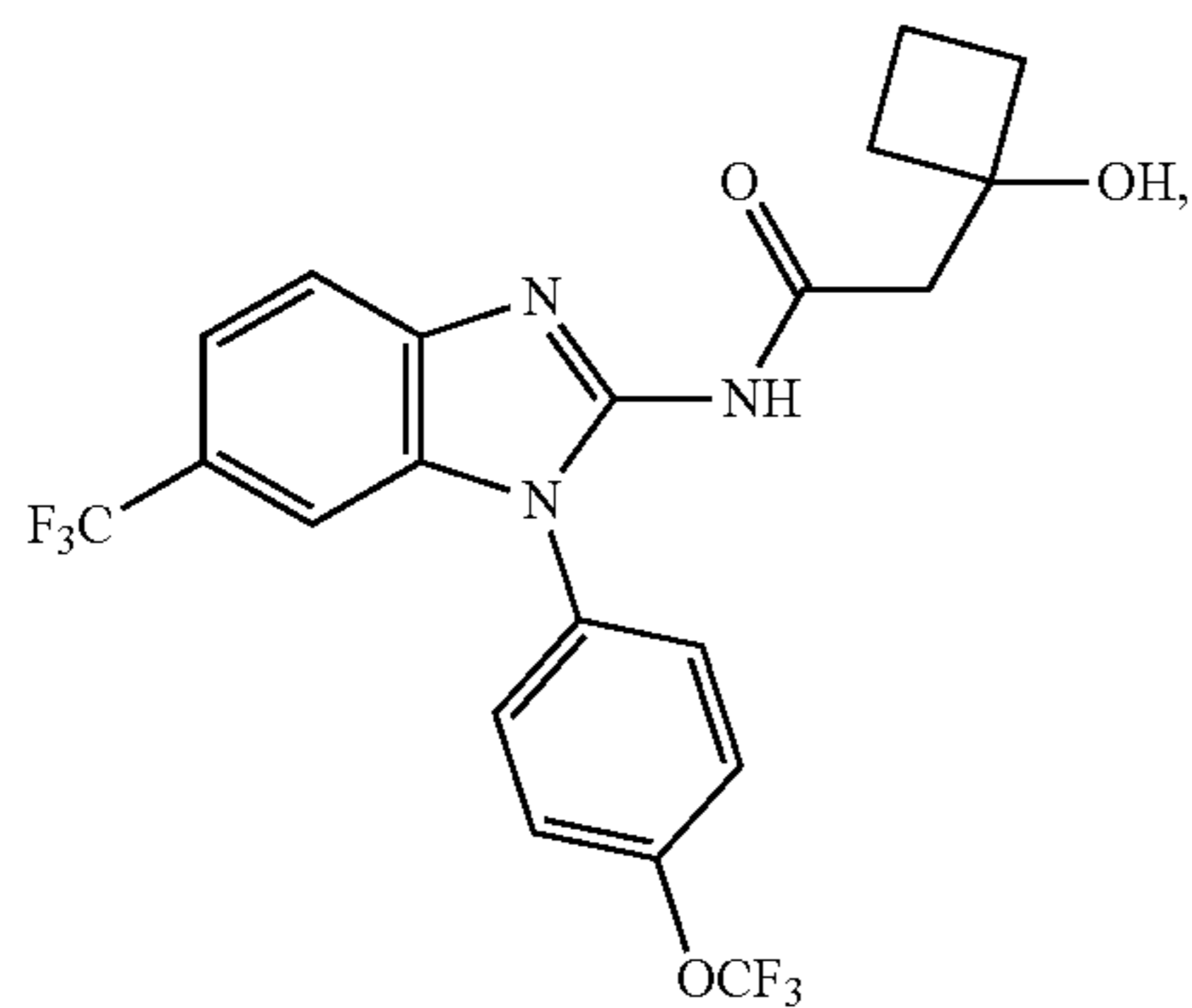
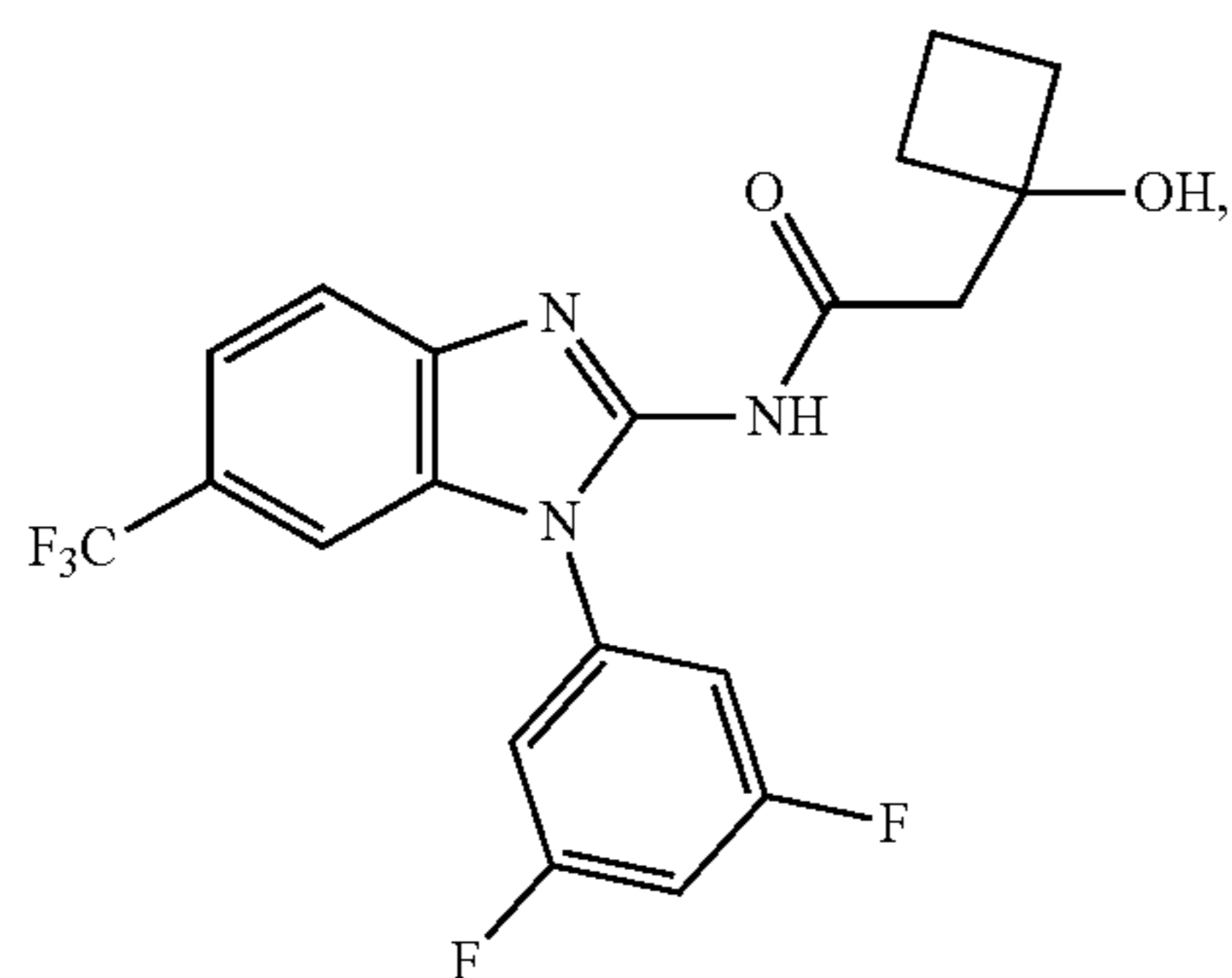
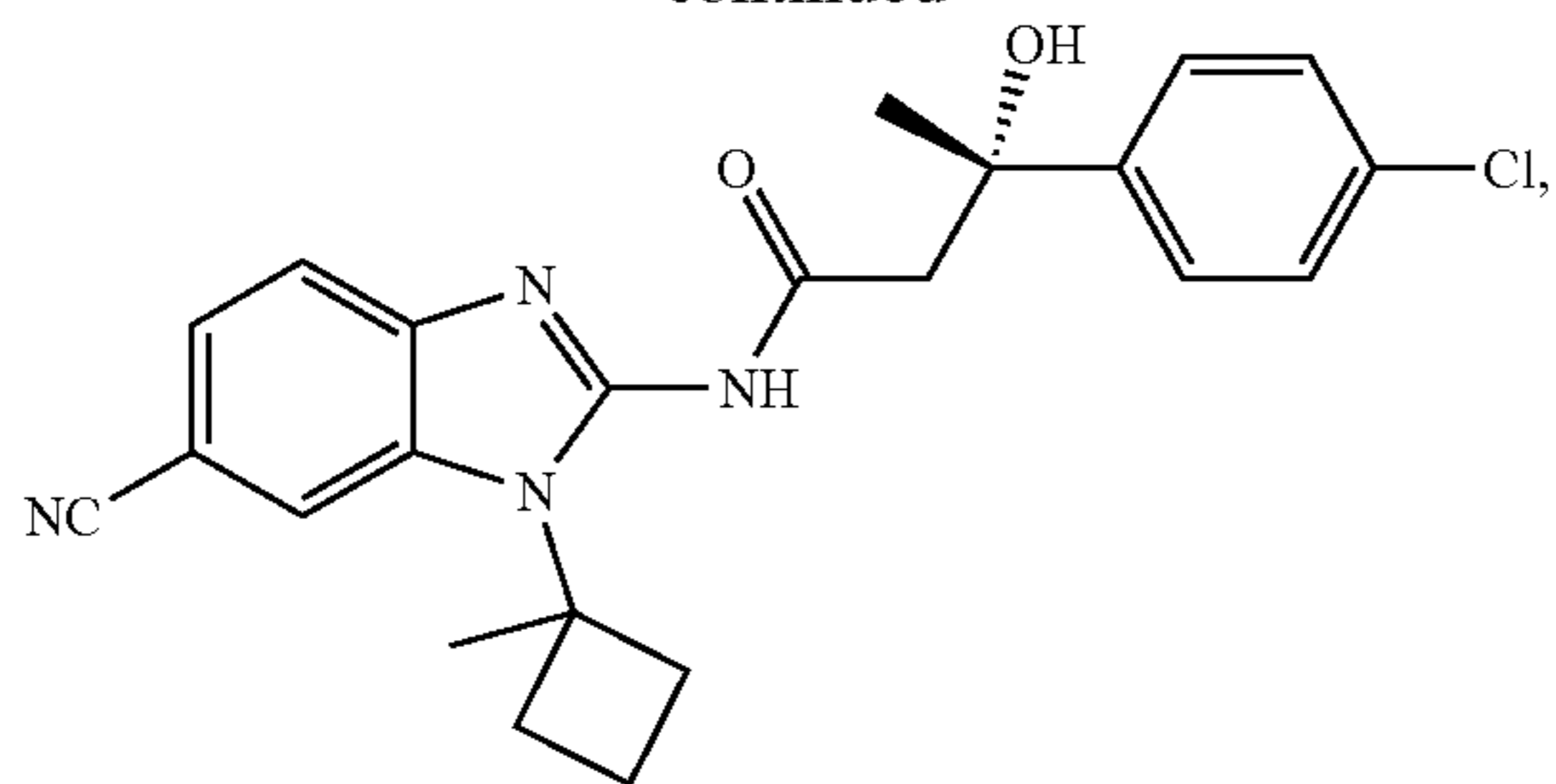
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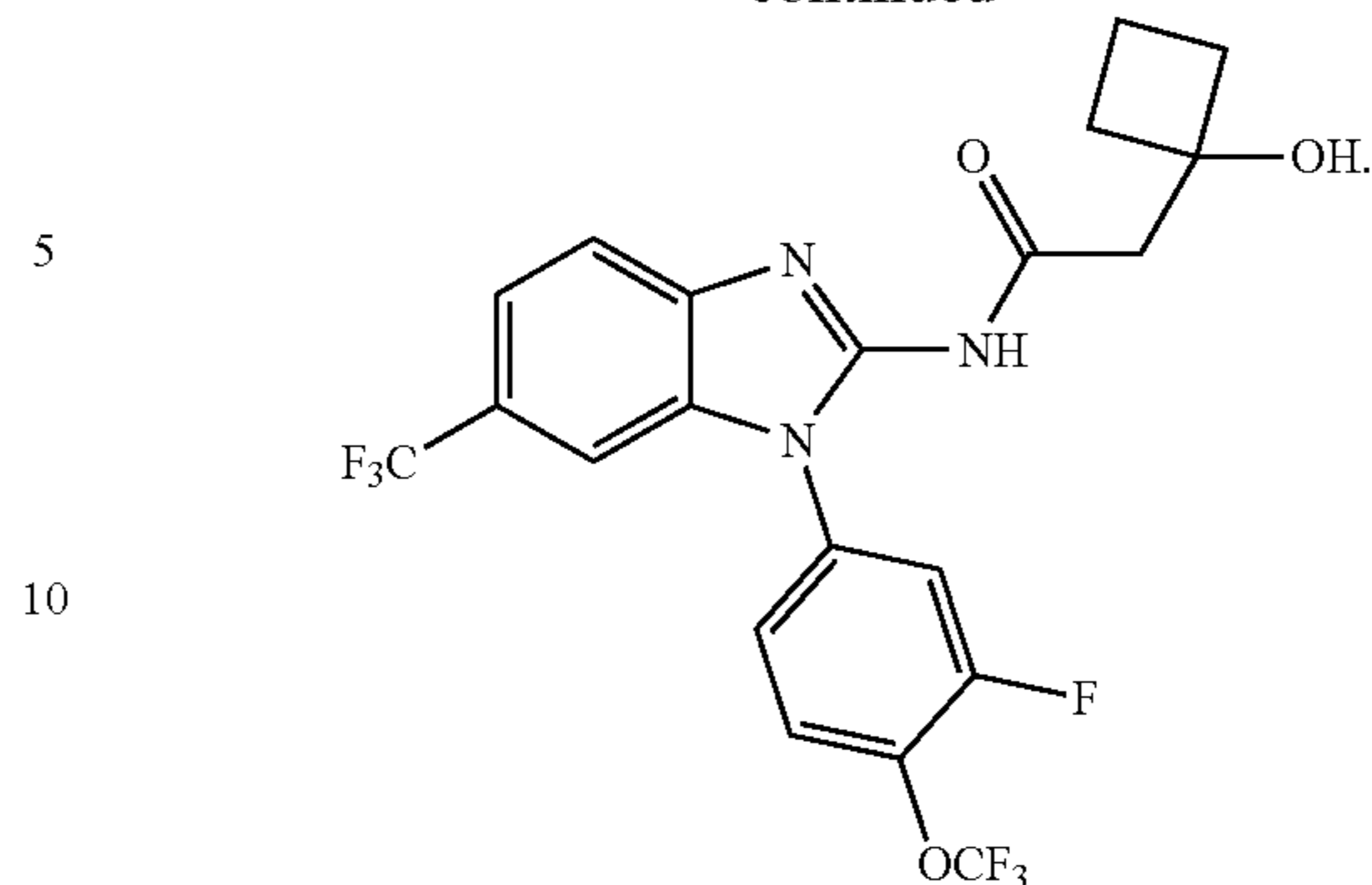
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The compounds described herein, such as a compound of Formula 1 or Formula 2, (referred to hereafter as a “subject compound” or “subject compounds”) can be used to treat a disorder associated with a Kv7 potassium channel activator. Treatment of a disorder includes diagnosis, cure, mitigation, treatment, or prevention of the disorder in man or other animals. In some embodiments, the disorder is epilepsy, pain, migraine, a disorder of neurotransmitter release, a smooth muscle contractility disorder, a dyskinesia, dystonia, mania, or a hearing disorder. In some embodiments, the disorder is epilepsy, neuropathic pain, inflammatory pain, persistent pain, cancer pain, postoperative pain, migraine, anxiety, substance abuse, schizophrenia, a bladder disorder, a vasculature disorder, a dyskinesia, dystonia, mania, a hearing disorder, or tinnitus.

Appropriate excipients for use in a pharmaceutical composition comprising a subject compound (referred to hereafter as “subject compositions” or a “subject composition”) may include, for example, one or more carriers, binders, fillers, vehicles, disintegrants, surfactants, dispersion or suspension aids, thickening or emulsifying agents, isotonic agents, preservatives, lubricants, and the like or combinations thereof, as suited to a particular dosage from desired. Remington’s Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof.

A subject composition may be formulated for any desirable route of delivery including, but not limited to, parenteral, intravenous, intradermal, subcutaneous, oral, inhalative, transdermal, topical, transmucosal, rectal, interacisternal, intravaginal, intraperitoneal, buccal, and intraocular.

Parenteral, intradermal or subcutaneous formulations may be sterile injectable aqueous or oleaginous suspensions or solutions. Acceptable vehicles, solutions, suspensions and solvents may include, but are not limited to, water or other sterile diluent; saline; Ringer’s solution; sodium chloride; fixed oils such as mono- or diglycerides; fatty acids such as oleic acid; polyethylene glycols; glycerine; propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfate; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. A parenteral preparation may be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use may include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include, but are not limited to, saline, bacteriostatic water, CREMOPHOR EL® (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). The solvent or dispersion medium may contain, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Preventing growth of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. The composition may also include isotonic agents such as, for example, sugars; polyalcohols such as mannitol; sorbitol; or sodium chloride. Prolonged absorption of injectable compositions can be enhanced by addition of an agent that delays absorption, such as, for example, aluminum monostearate or gelatin.

Oral compositions may include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. Tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose; a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

In addition to oral or injected administration, systemic administration may be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants may be used. Such penetrants are generally known in the art and include, for example, detergents, bile salts, and fusidic acid derivatives. Transdermal administration may include a bioactive agent and may be formulated into ointments, salves, gels, or creams as generally known in the art. Transmucosal administration may be accomplished through the use of nasal sprays or suppositories.

A subject compound may be administered in a therapeutically effective amount, according to an appropriate dosing regimen. As understood by a skilled artisan, an exact amount required may vary from subject to subject, depending on a subject's species, age and general condition, the severity of the infection, the particular agent(s) and the mode of administration. In some embodiments, about 0.001 mg/kg to about 50 mg/kg, of the pharmaceutical composition based on the subject's body weight is administered, one or more times a day, to obtain the desired therapeutic effect. In other embodiments, about 0.01 mg/kg to about 25 mg/kg, of the pharmaceutical composition based on the subject's body weight is administered, one or more times a day, to obtain the desired therapeutic effect.

A total daily dosage of a subject compound can be determined by the attending physician within the scope of sound medical judgment. A specific therapeutically effective dose level for any particular patient or subject will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the

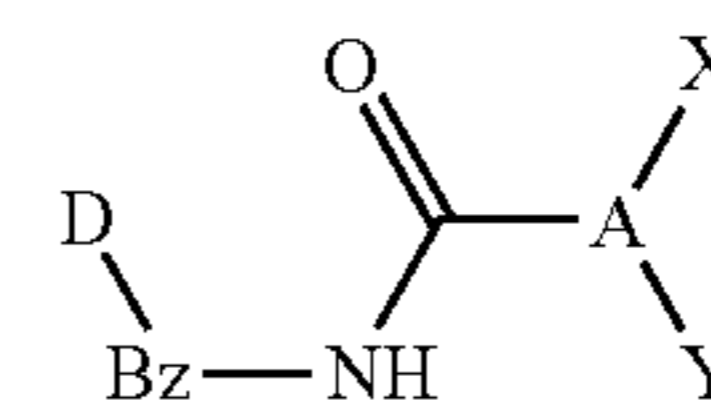
patient or subject; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and other factors well known in the medical arts.

EMBODIMENTS SECTION

The following example embodiments are contemplated.

Embodiment 1

A compound represented by a formula:



wherein D is optionally substituted C₃₋₆ carbocyclyl, optionally substituted C₂₋₅ heterocyclyl, isopropyl, or t-butyl;

Bz is optionally substituted benzoimidazol-1,2-diyl;

A is C₁₋₈ alkyl;

X is H, F, CF₃, optionally substituted phenyl, or optionally substituted pyridinyl;

and

Y is H, F, Cl, Br, I, or a moiety having a molecular weight of 15 Da to 300 Da and consisting of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br.

Embodiment 2

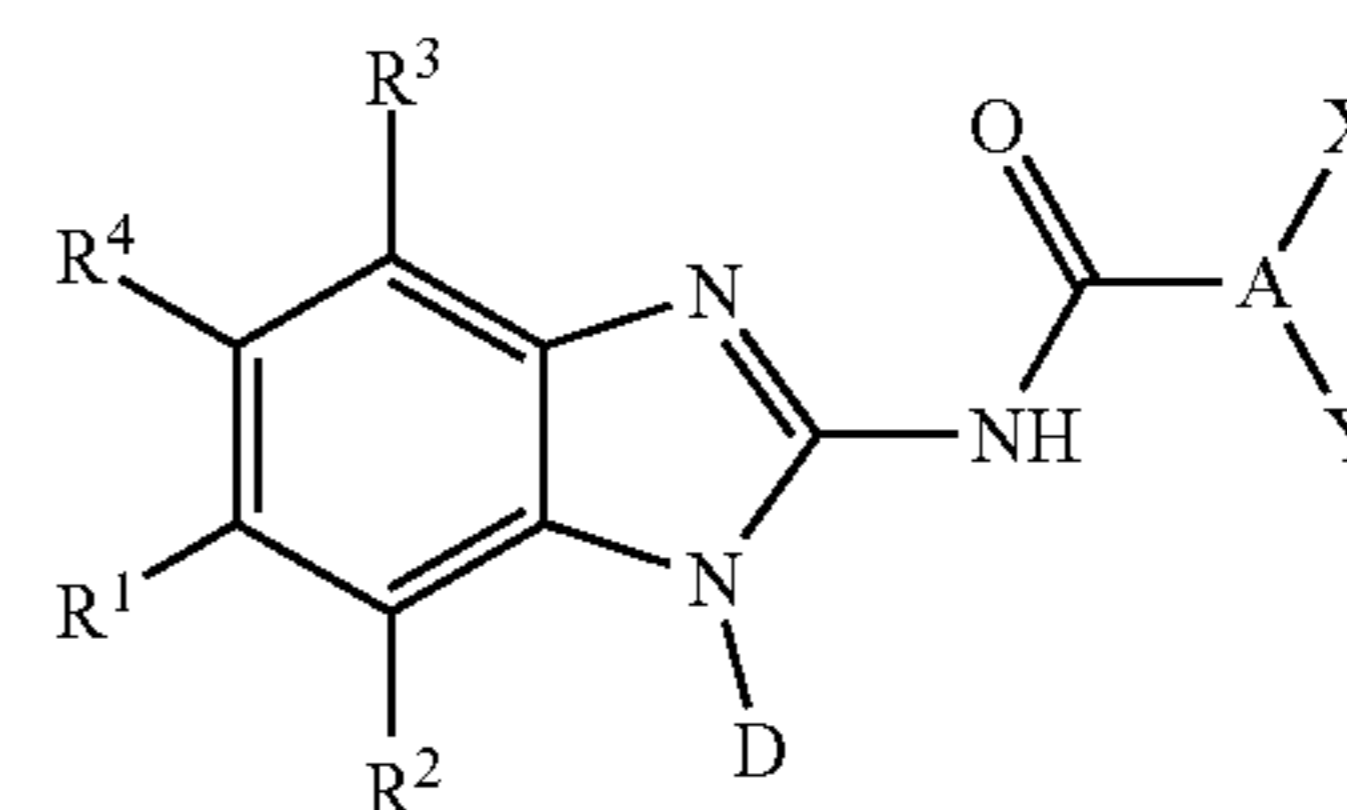
The compound of embodiment 1, wherein each substituent of D, Bz, or X, if present, independently has a molecular weight of 15 Da to 200 Da and consists of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br.

Embodiment 3

The compound of embodiment 1 or 2, wherein Y is H, F, Cl, Br, I, CN, —COH, C₁₋₆ —CO-alkyl, CF₃, OH, C₁₋₅ O-alkyl, C₀₋₆ amino, or C₀₋₆ fluoroamino.

Embodiment 4

The compound of embodiment 1, 2, or 3, further represented by a formula:



wherein R¹, R², R³, and R⁴ are independently H, F, Cl, Br, I, or a substituent having a molecular weight of 15 Da to 200 Da and consisting of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br.

45

Embodiment 5

The compound of embodiment 1, 2, 3, or 4, wherein Y is H, F, CF₃, OH, C₁₋₅ O-alkyl, C₀₋₆ alkylamino, optionally substituted tetrahydropyranyl, or C₀₋₆ fluoroalkylamino.

Embodiment 6

The compound of embodiment 4 or 5, wherein R¹ is H, Cl, Br, —OCH₃, —CN, —CF₃, —CH₂OH, —COOCH₂CH₃, —C(CH₃)₂OH, —CHOHCH₂CH₃, —CHOHC H₃, —CHF₂, —CH(CH₃)₂, —C(CH₂CH₃)OH, —CH₂COOCH₂CH₃, —CH₂C(CH₃)₂OH, —CH₂COO H, or —CH₂CON(CH₃)₂.

Embodiment 7

The compound of embodiment 4, 5, or 6, wherein R² is H, F, —CH₂OH, —CO₂Me, or —C(CH₃)₂OH.

Embodiment 8

The compound of embodiment 4, 5, 6, or 7, wherein R³ is H.

Embodiment 9

The compound of embodiment 4, 5, 6, 7, or 8, wherein R⁴ is H, —CH₃, or —CF₃.

Embodiment 10

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, or 9, wherein D is optionally substituted cyclobutyl, optionally substituted phenyl, optionally substituted isoxazolyl, optionally substituted pyridinyl, isopropyl, or t-butyl.

Embodiment 11

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein each substituent of D, X, and Y, if present, independently has a molecular weight of 15 Da to 200 Da and consists of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br.

Embodiment 12

The compound of embodiment 4, 5, 6, 7, 8, 9, 10, or 11, wherein R¹ is H, Cl, Br, CN, OCH₃, CF₃, —CO₂CH₂CH₃, C₁₋₄ alkyl, or C₁₋₄ hydroxyalkyl.

Embodiment 13

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, wherein D is optionally substituted cyclobutyl.

Embodiment 14

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, wherein D is cyclobutyl.

Embodiment 15

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, wherein D is optionally substituted phenyl.

46

Embodiment 16

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, wherein D is optionally substituted isoxazolyl.

Embodiment 17

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, wherein D is isopropyl.

Embodiment 18

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, wherein D is t-butyl.

Embodiment 19

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, wherein D is optionally substituted pyridinyl.

Embodiment 20

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19, wherein X is optionally substituted phenyl.

Embodiment 21

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19, wherein X is CF₃.

Embodiment 22

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19, wherein X is F.

Embodiment 23

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19, wherein X is optionally substituted pyridinyl.

Embodiment 24

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19, wherein X is H.

Embodiment 25

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24, wherein Y is H.

Embodiment 26

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24, wherein Y is OH.

Embodiment 27

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24, wherein Y is F.

47

Embodiment 28

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24, wherein Y is CF₃.

Embodiment 29

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24, wherein Y is C₁₋₃ O-alkyl.

Embodiment 30

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24, wherein Y is C₀₋₆ fluoroamino.

Embodiment 31

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24, wherein Y is dimethylamino.

Embodiment 32

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24, wherein Y is methyl(2,2,2-trifluoroethyl)amino.

Embodiment 33

The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24, wherein Y is optionally substituted tetrahydropyranyl.

Embodiment 34

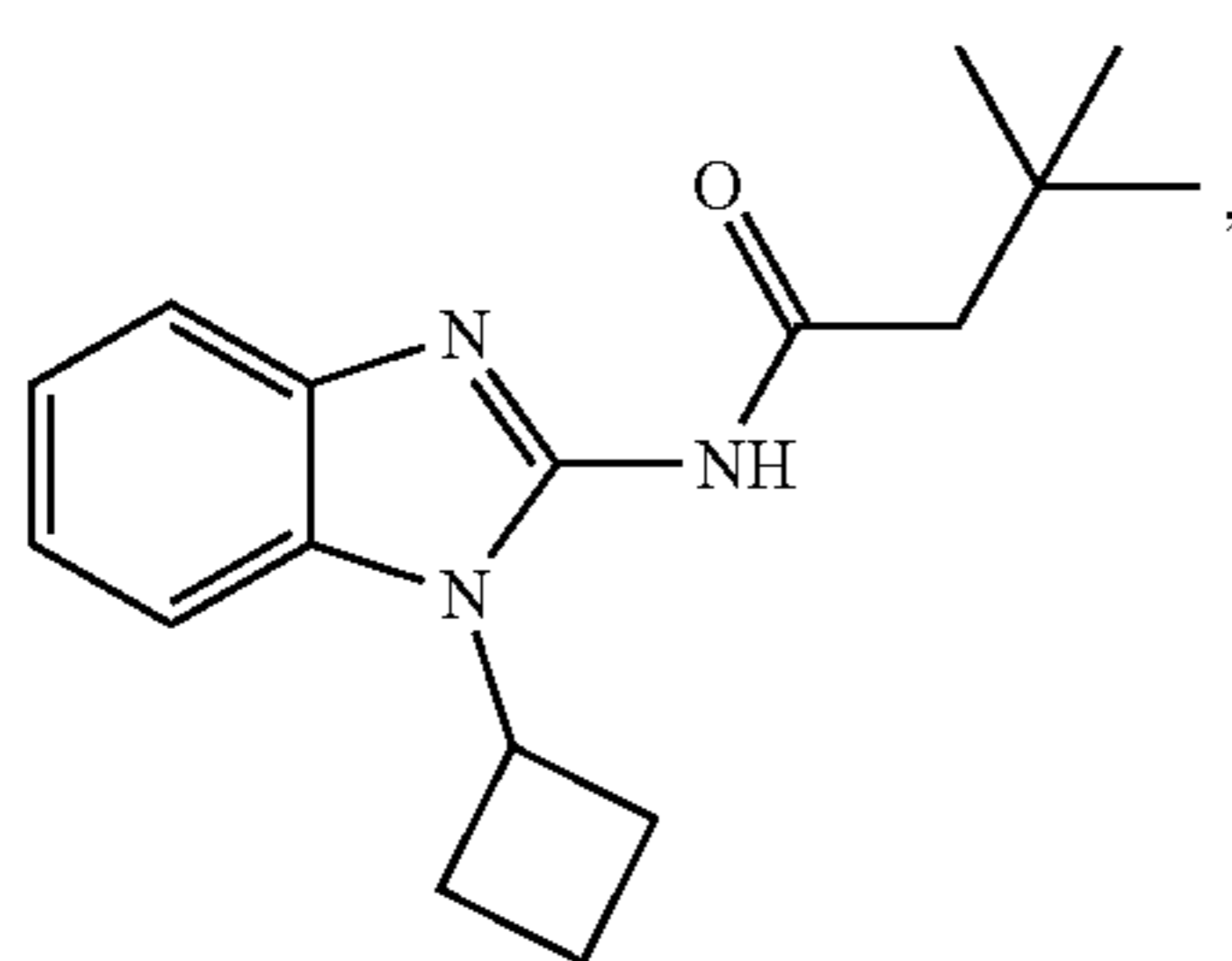
The compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24, wherein Y is 1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl.

Embodiment 35

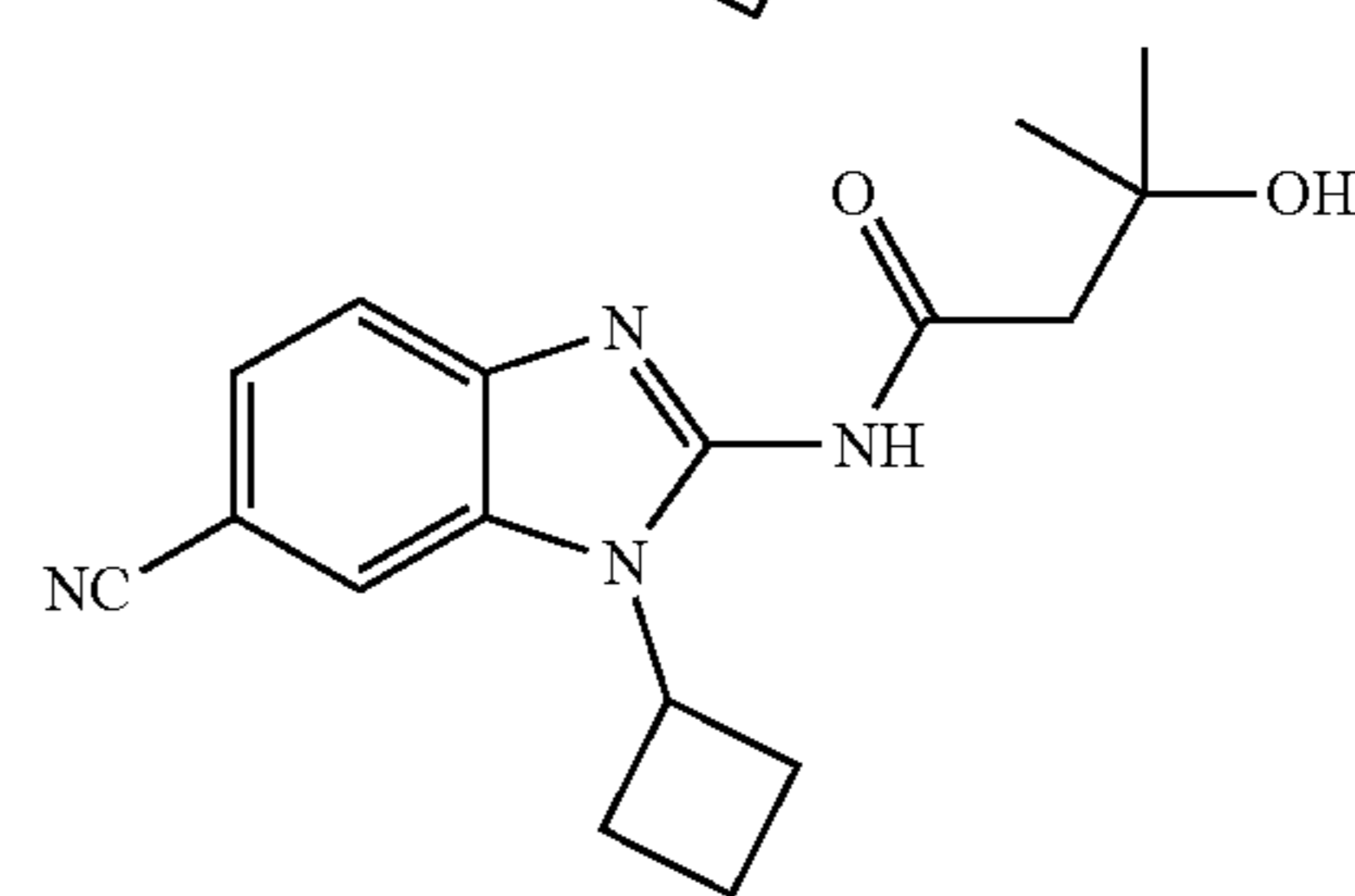
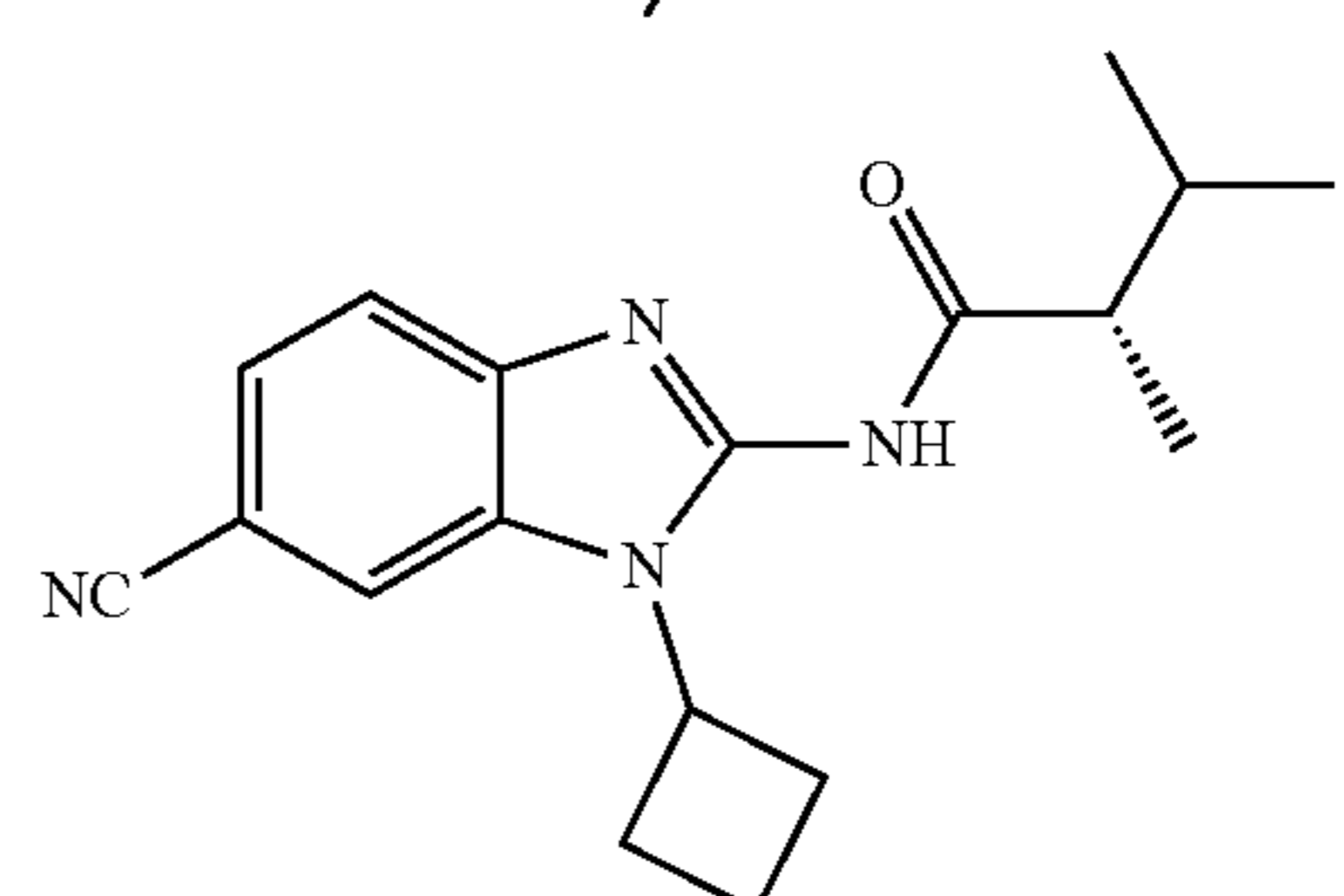
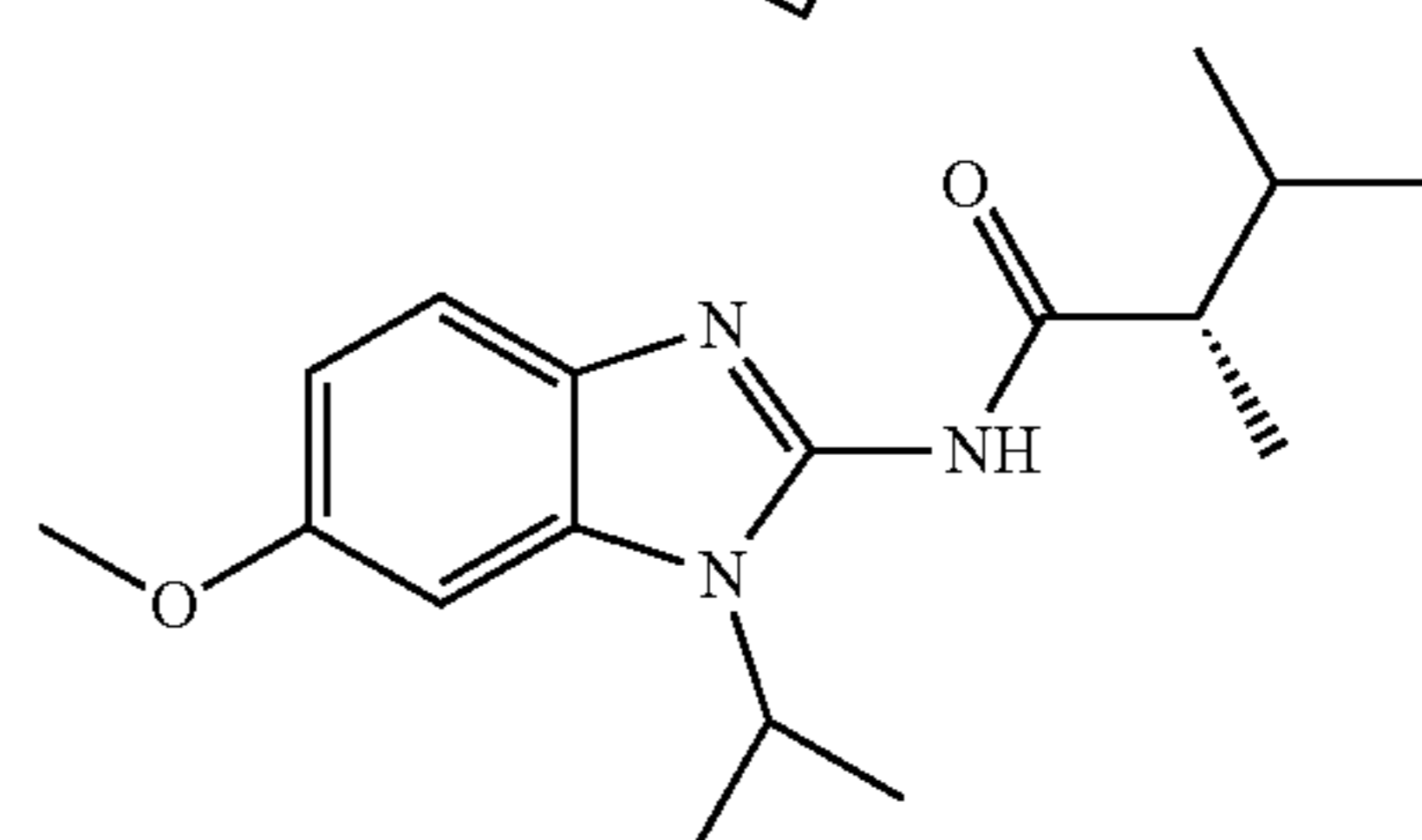
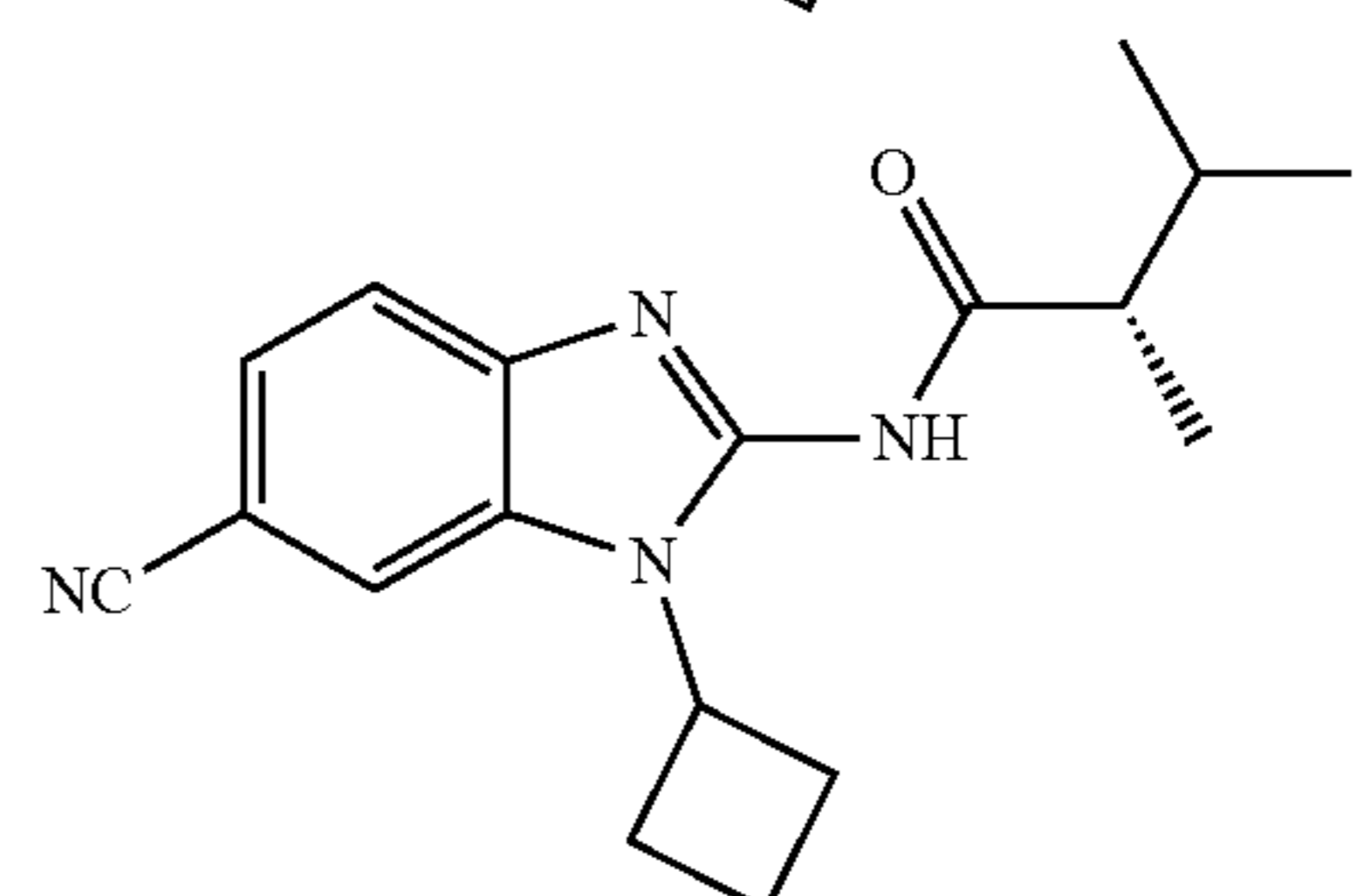
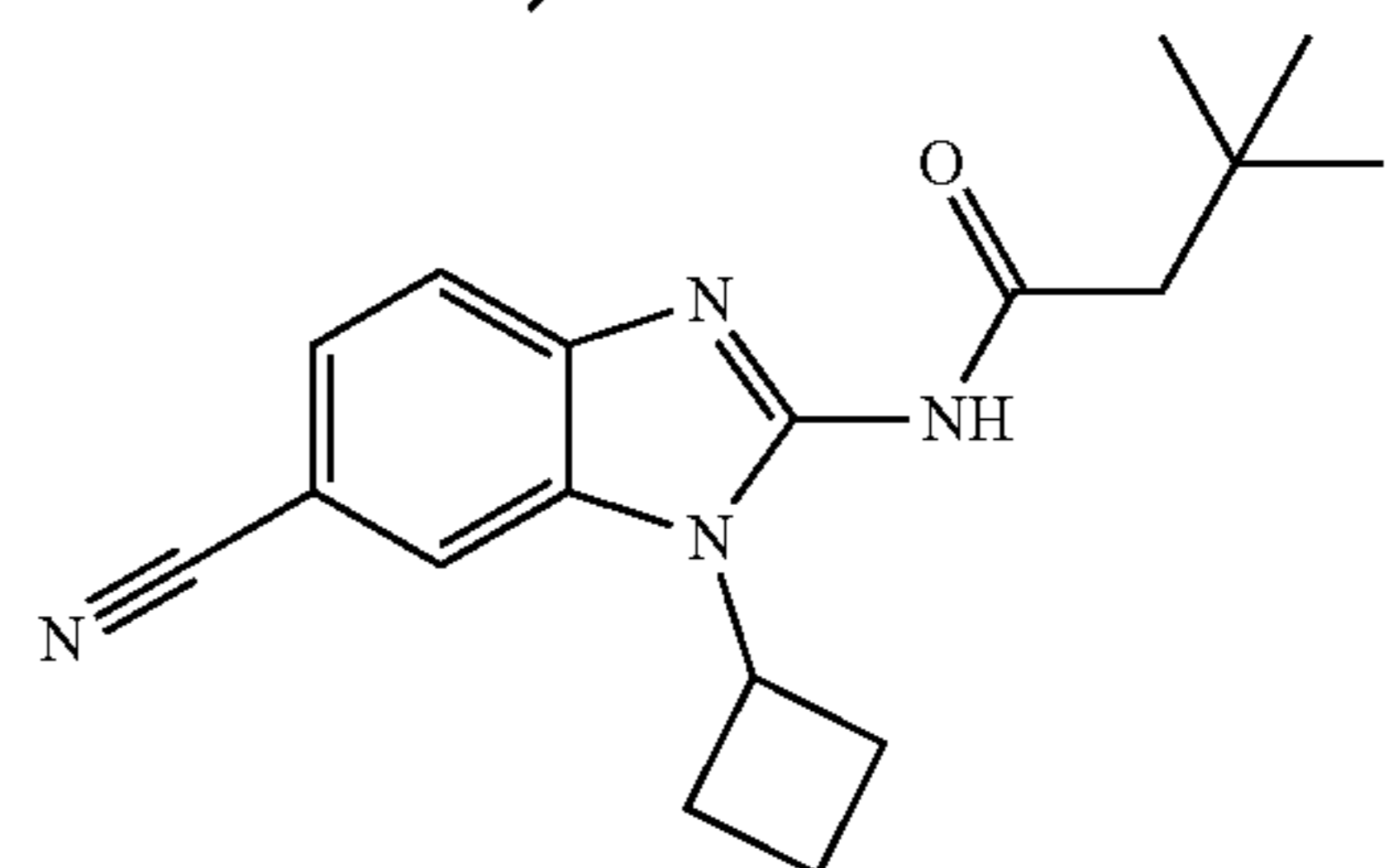
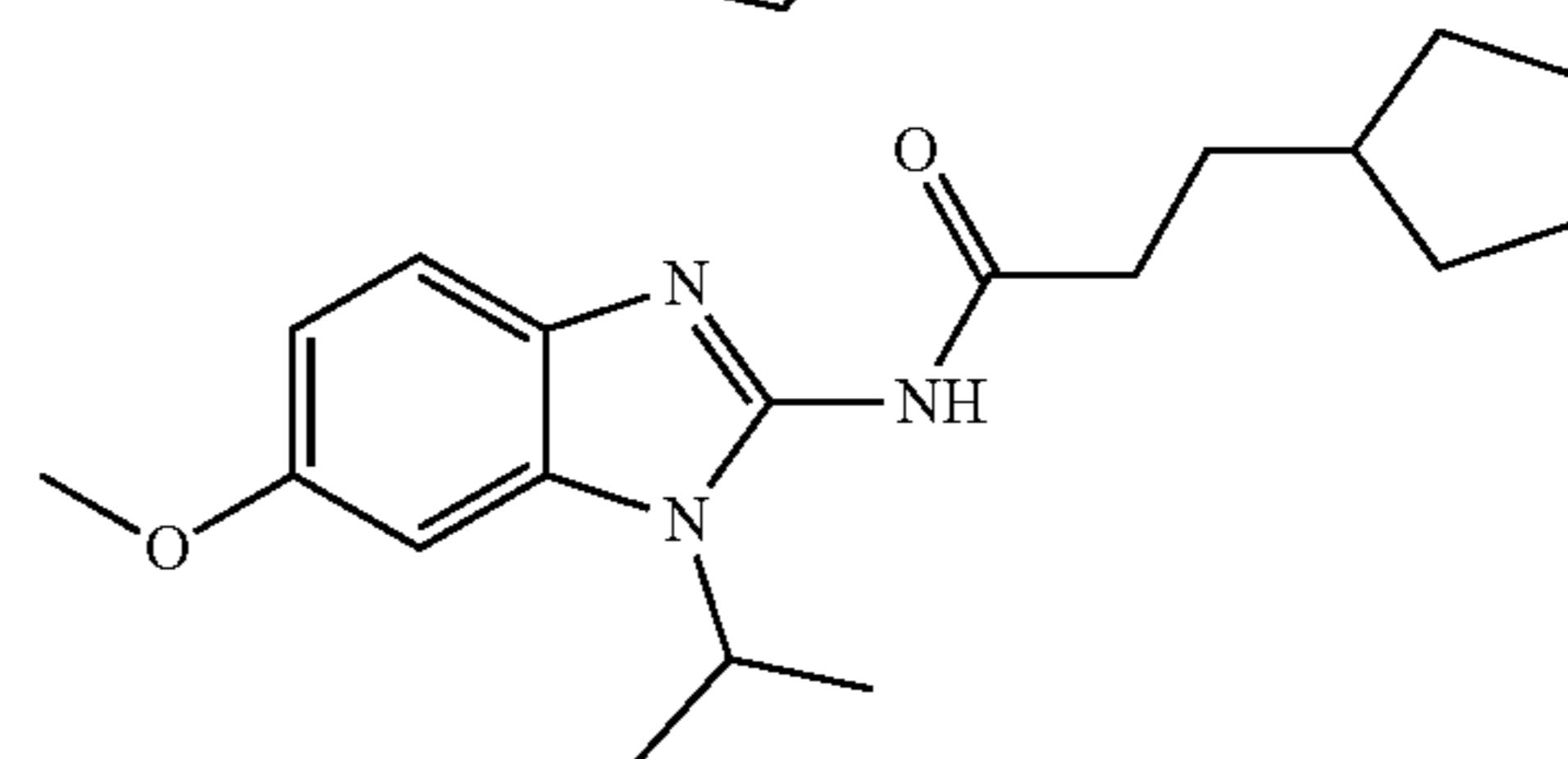
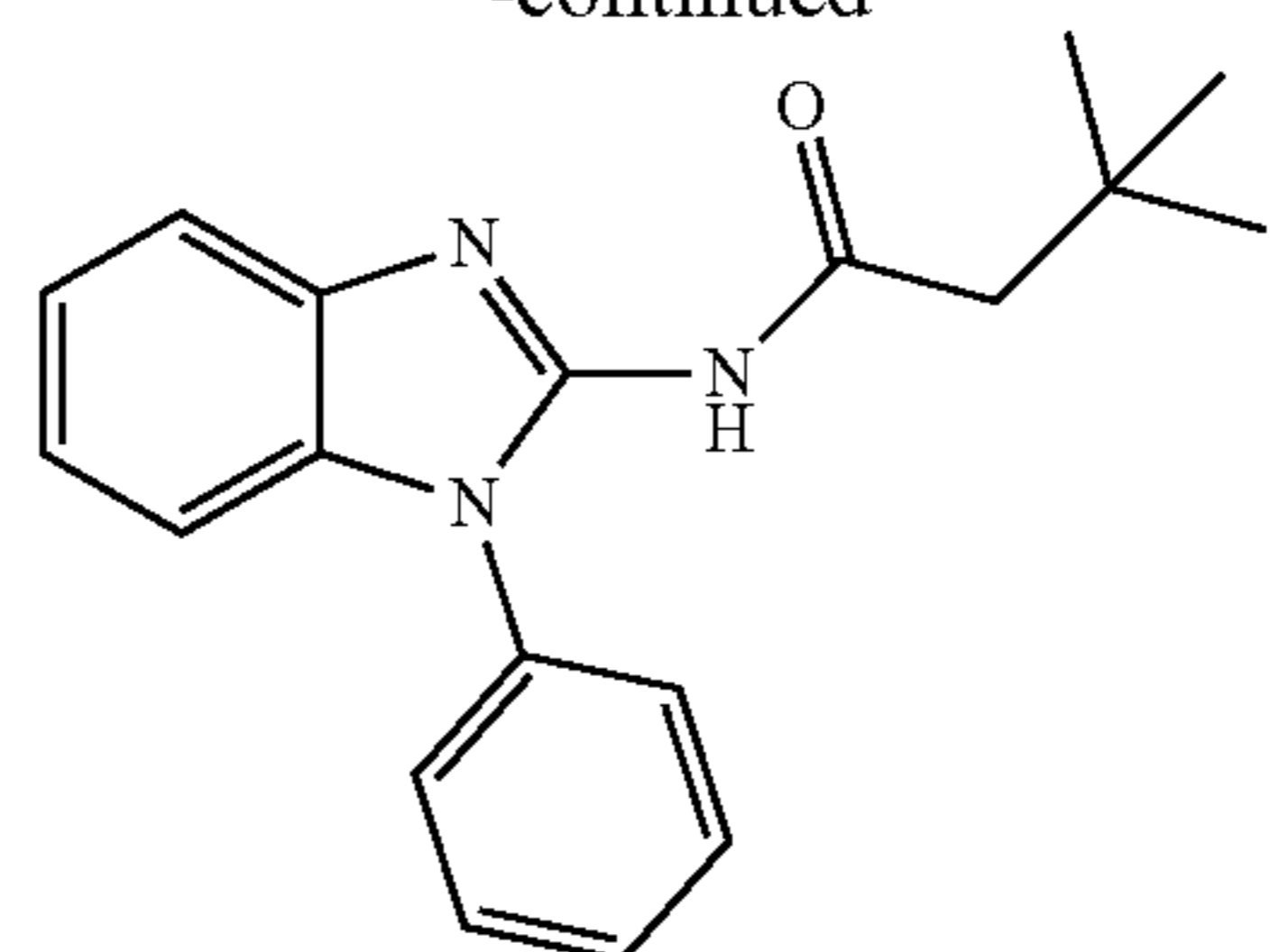
The compound of embodiment 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, or 34, wherein A is C₂₋₈ alkyl; and wherein at least one of R¹, R², R³, and R⁴ are independently F, Cl, Br, I, or a substituent having a molecular weight of 15 Da to 200 Da and consisting of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br.

Embodiment 36

A compound represented by a formula:

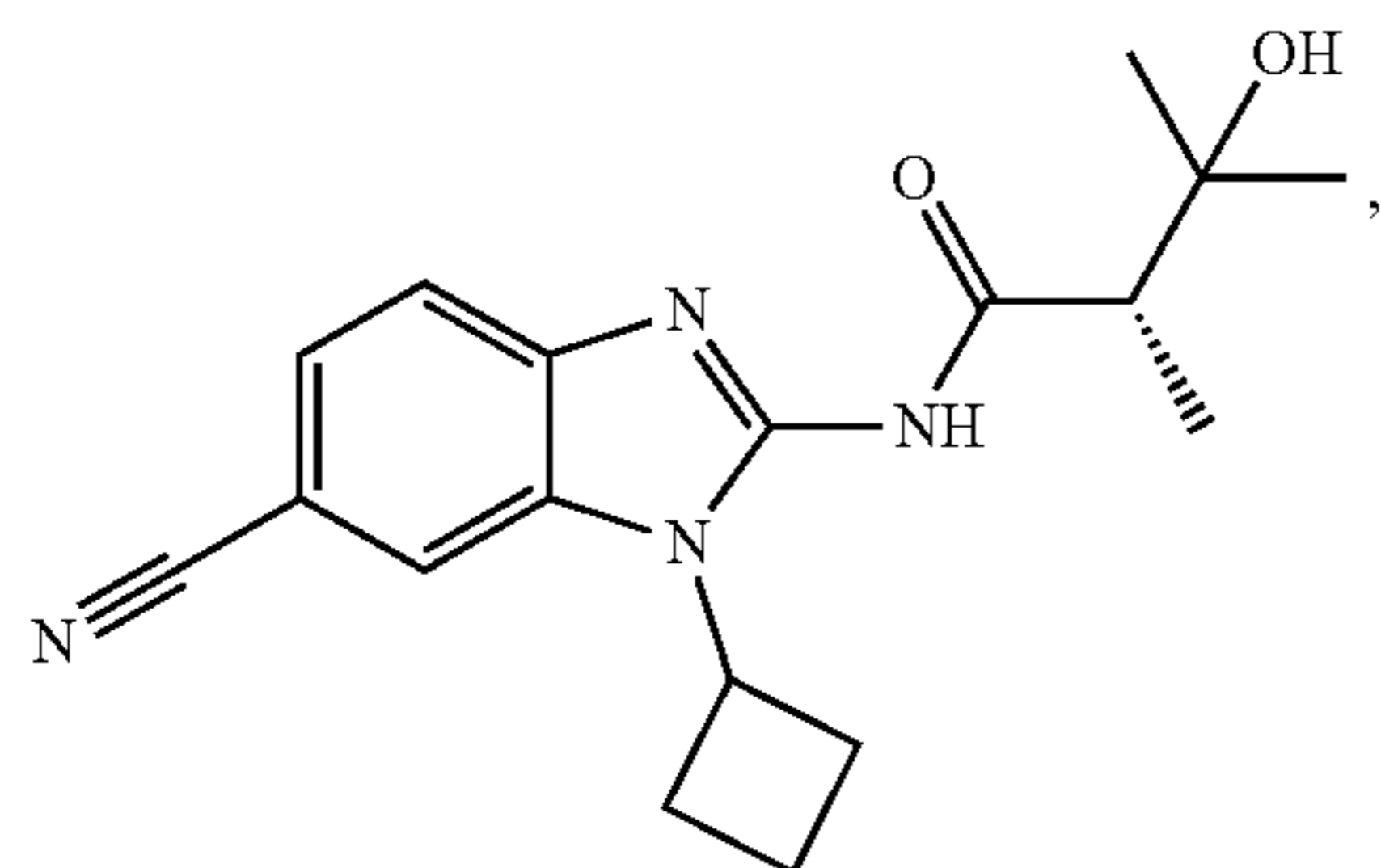
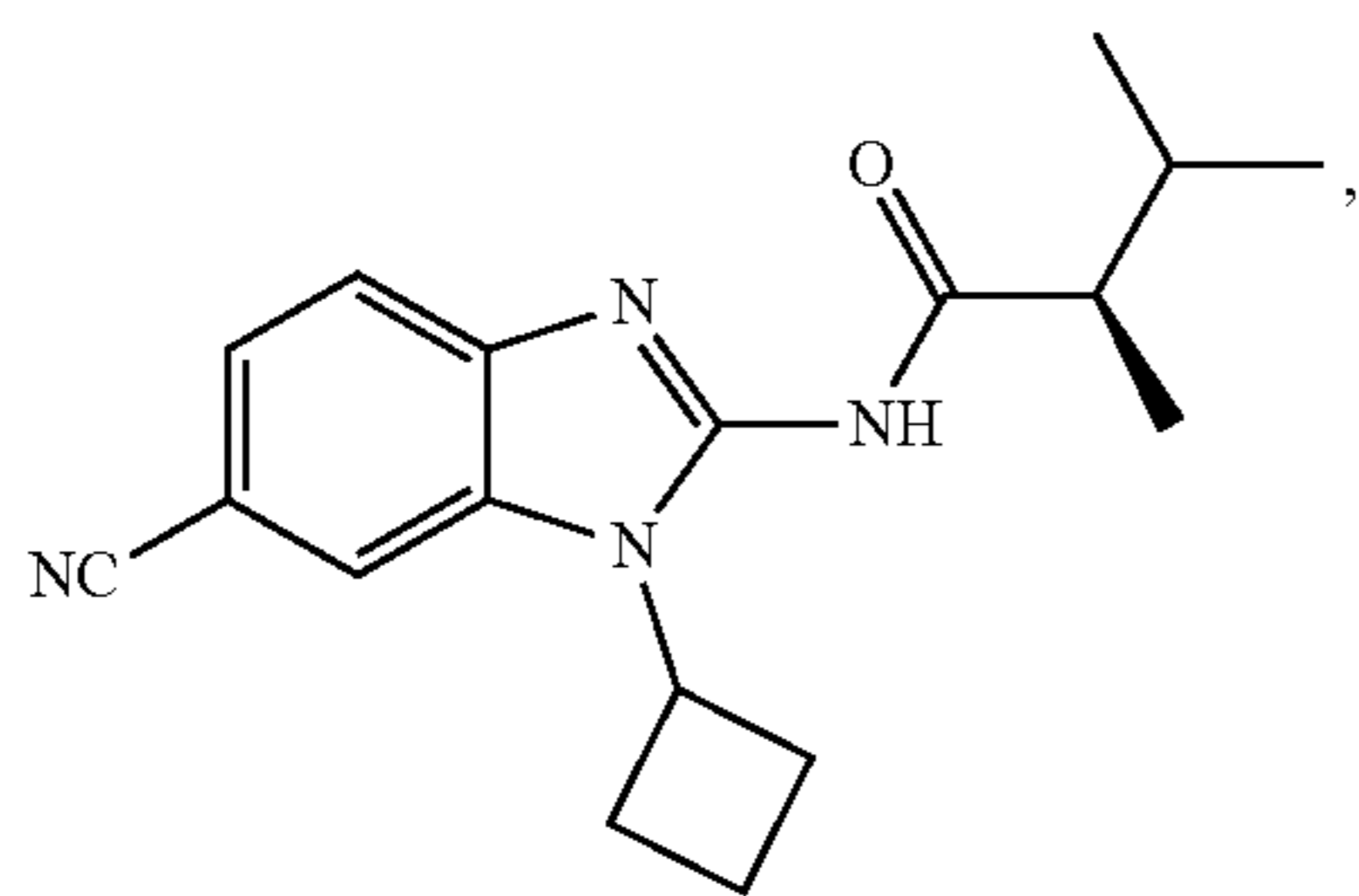
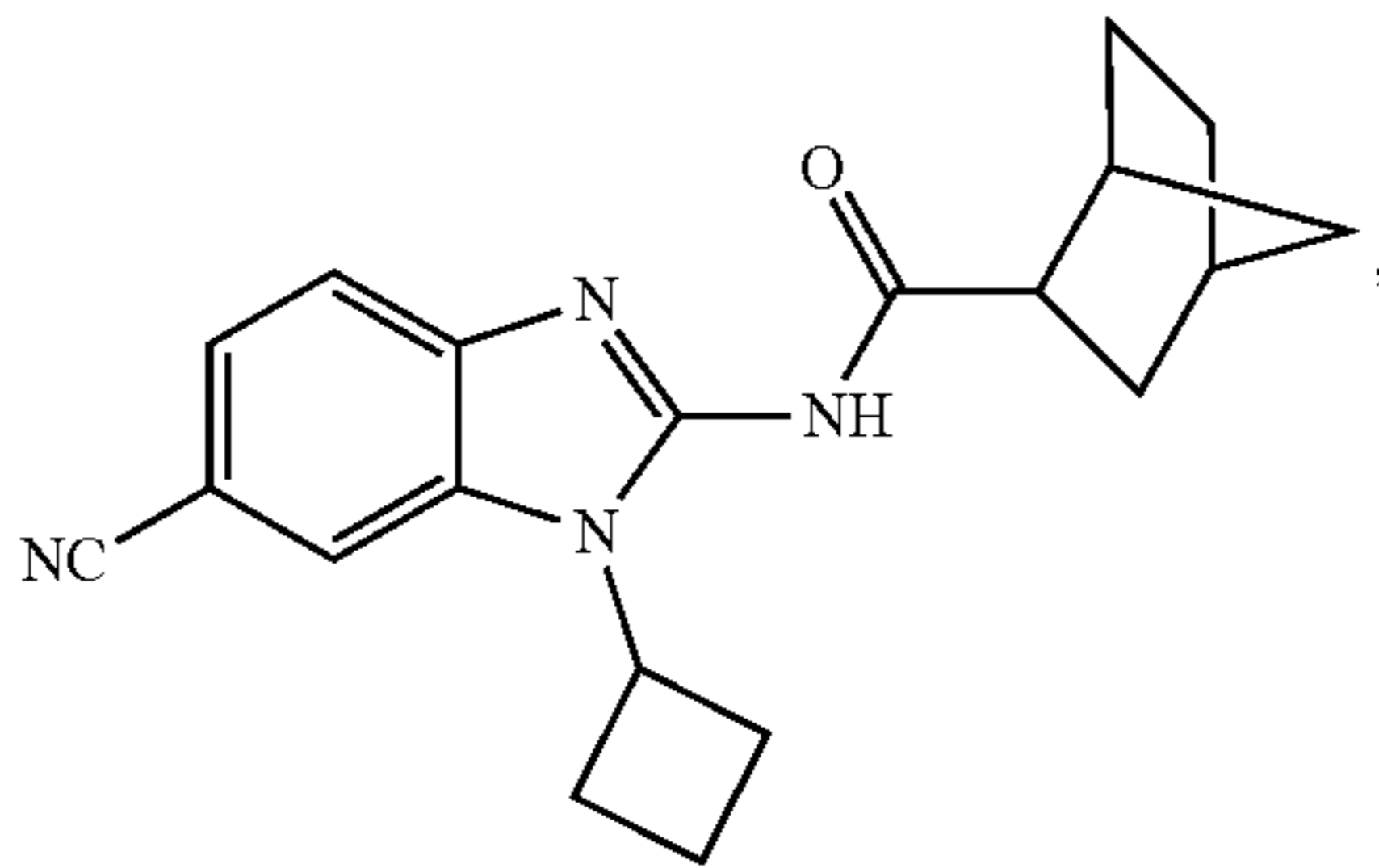
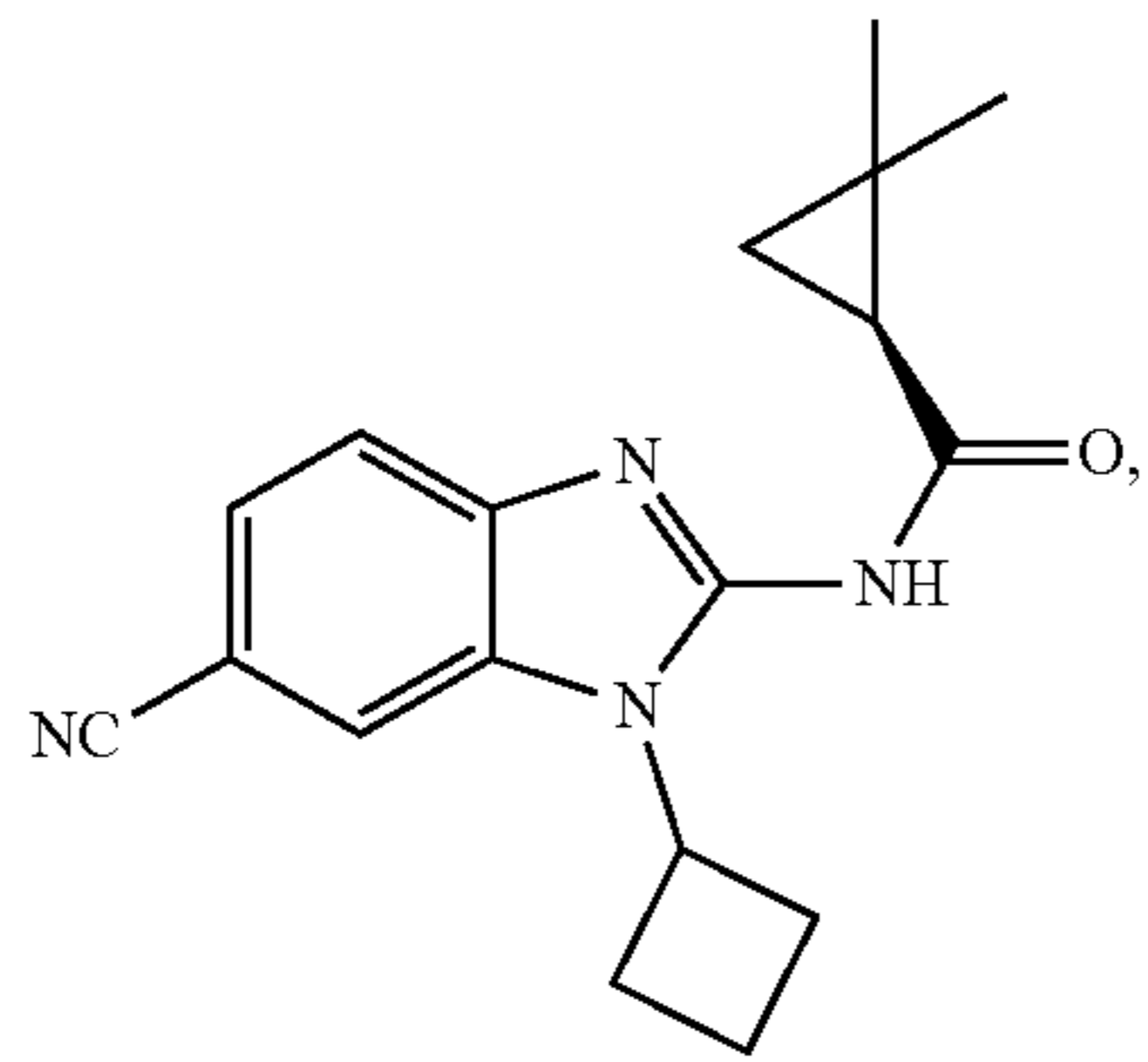
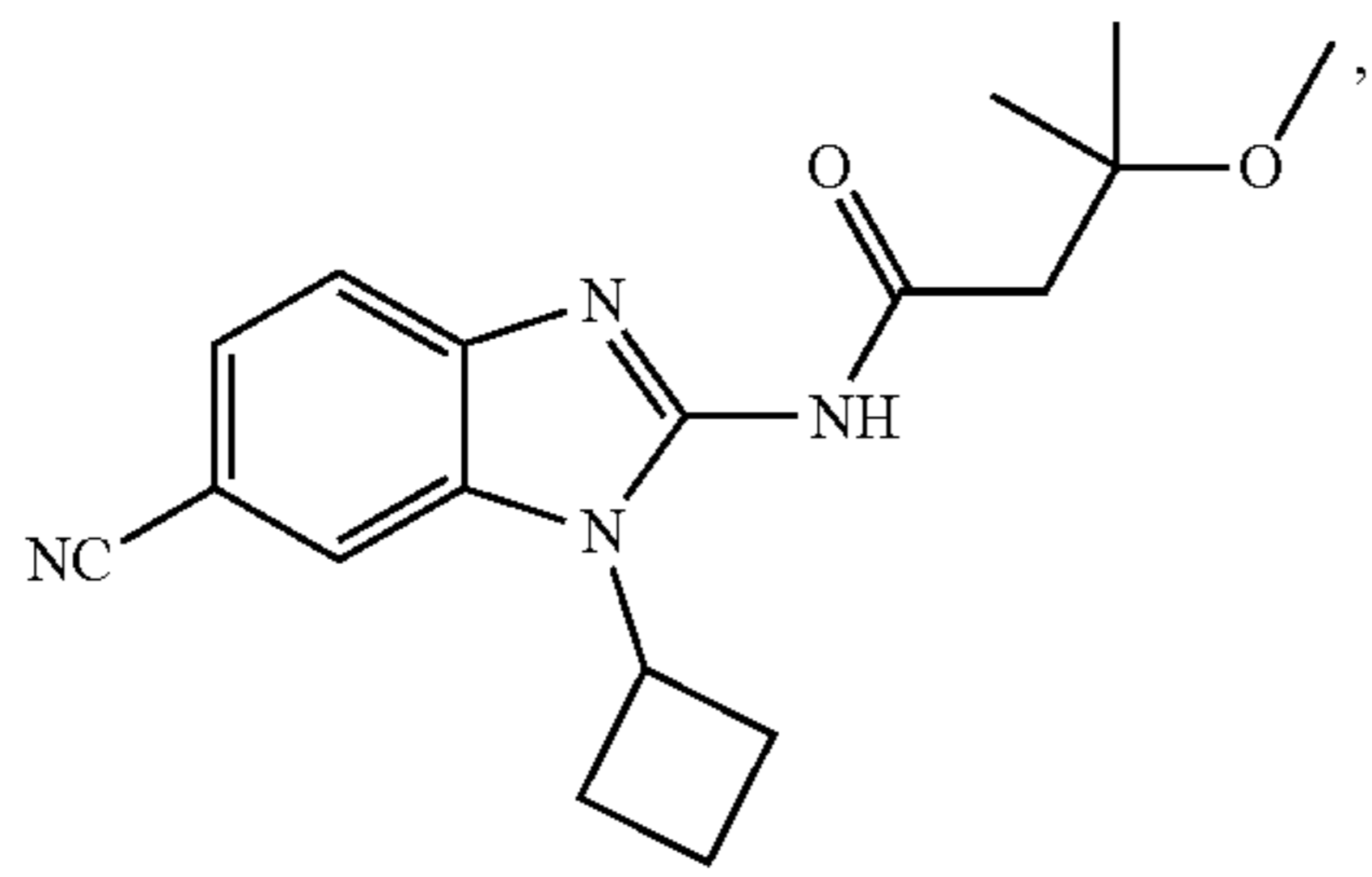
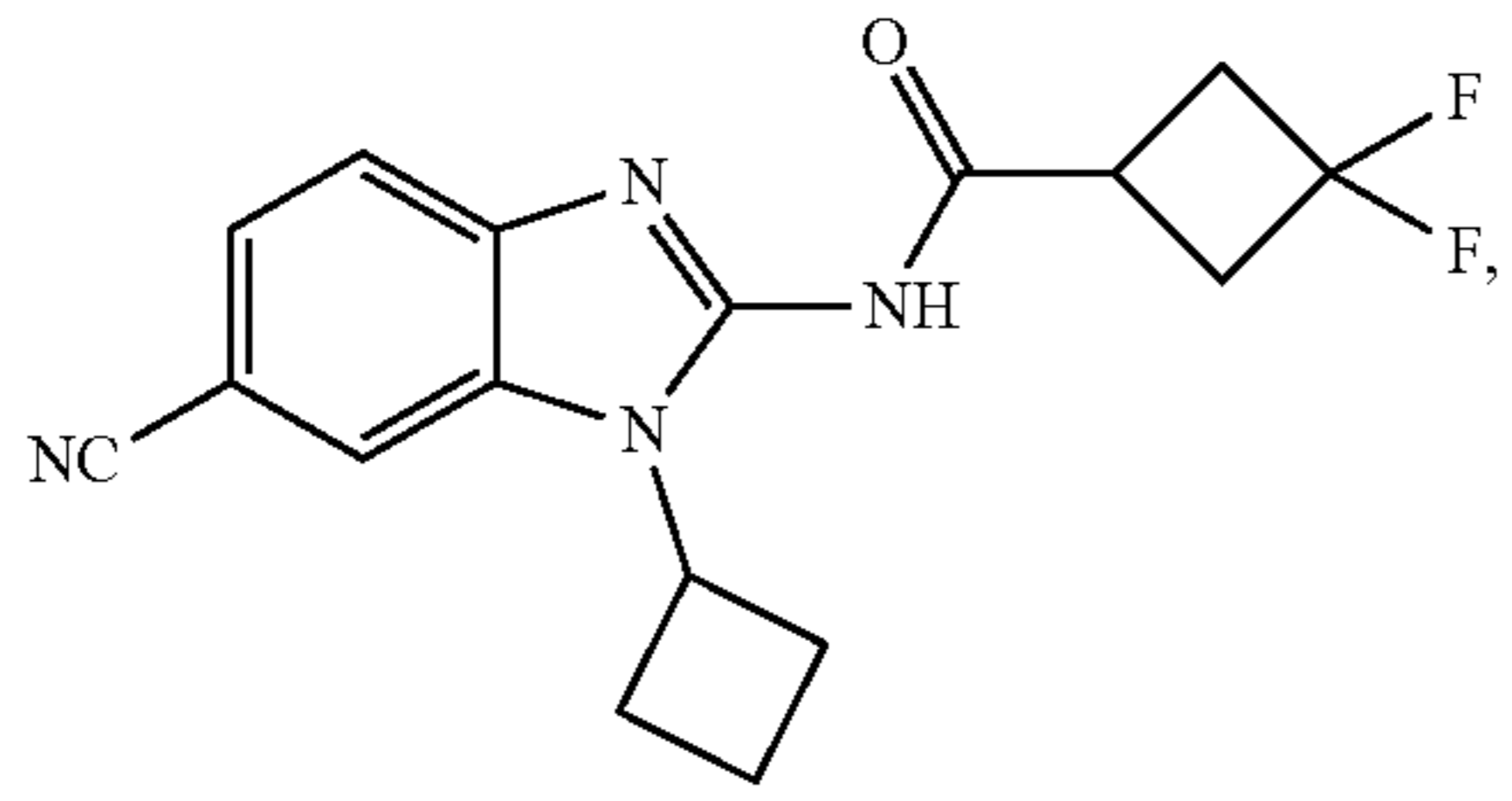
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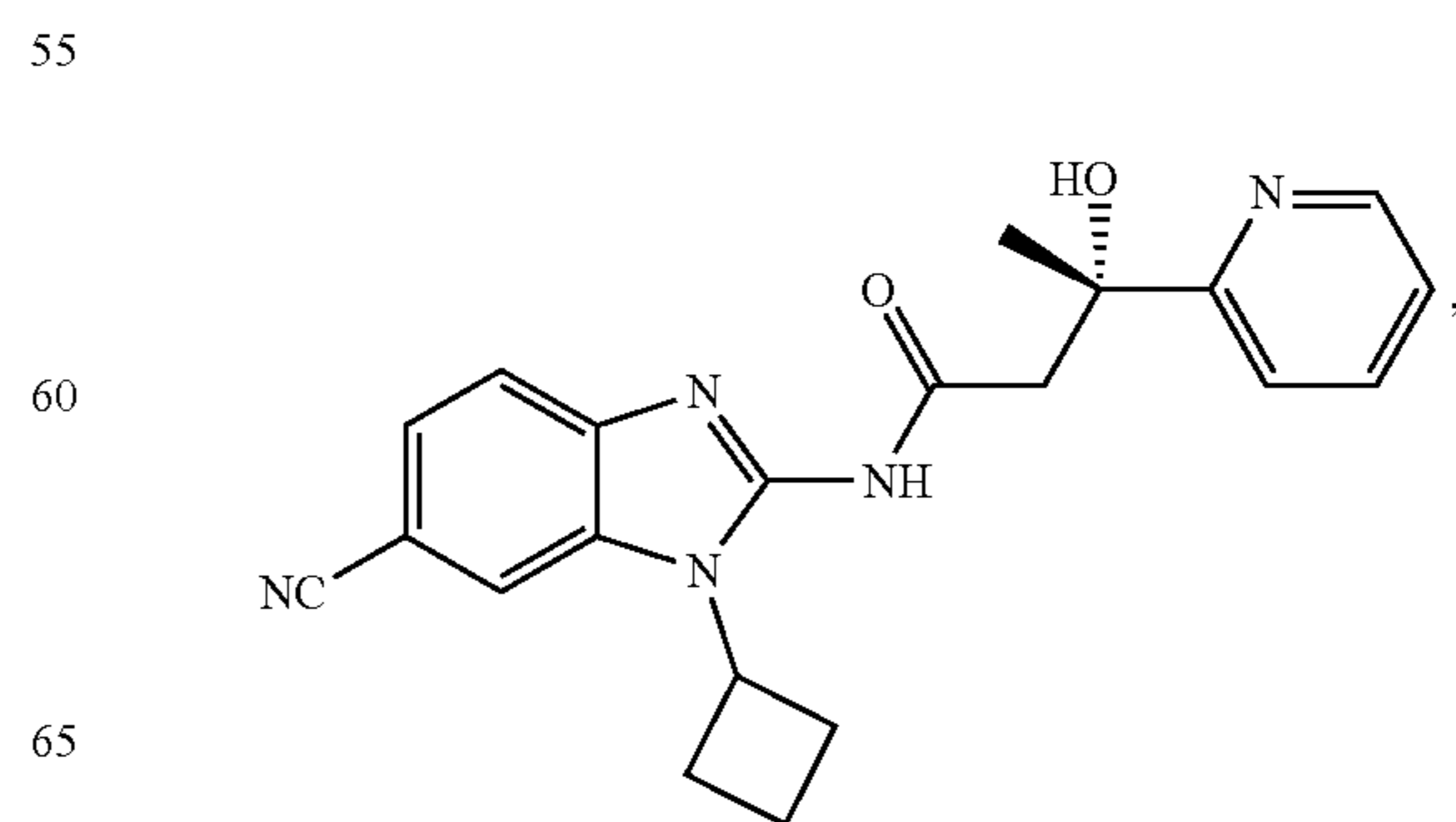
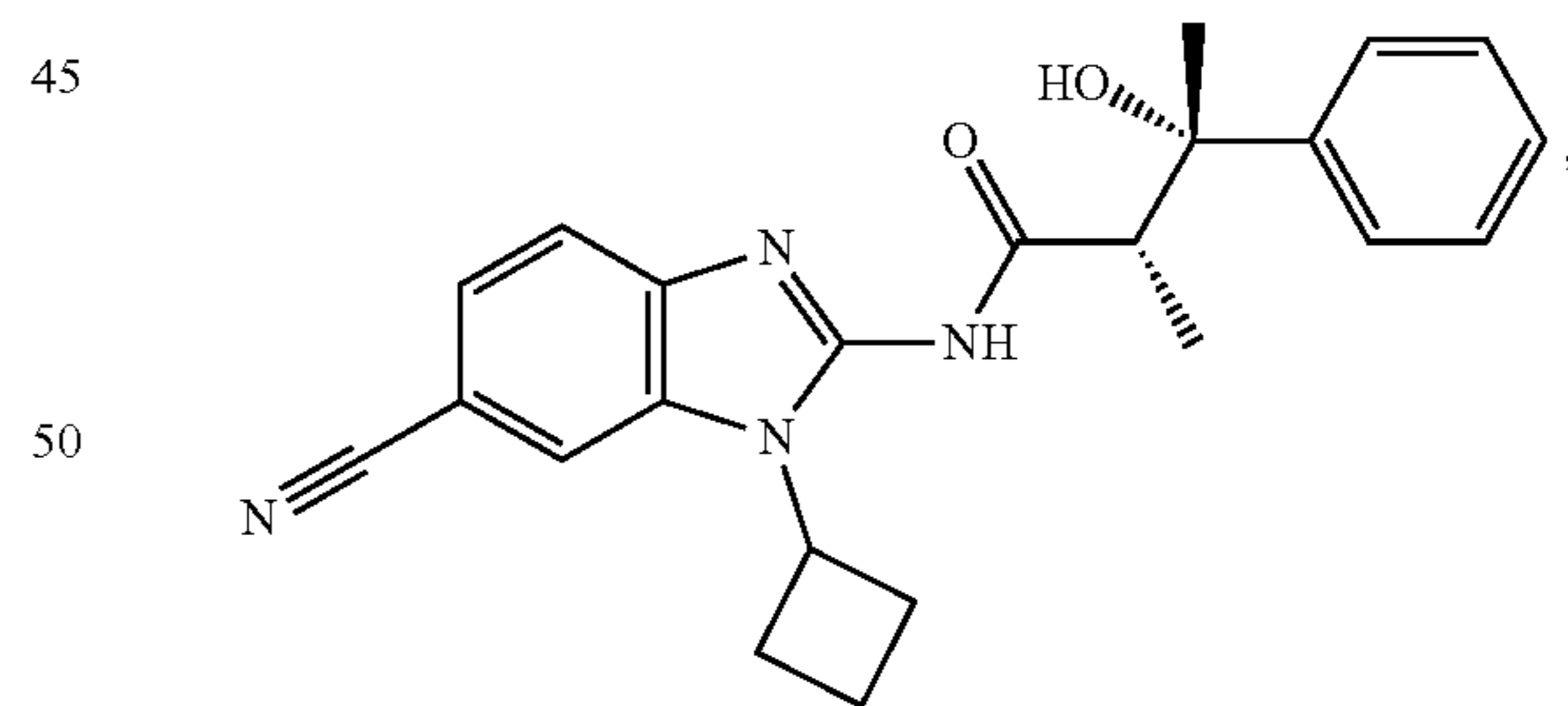
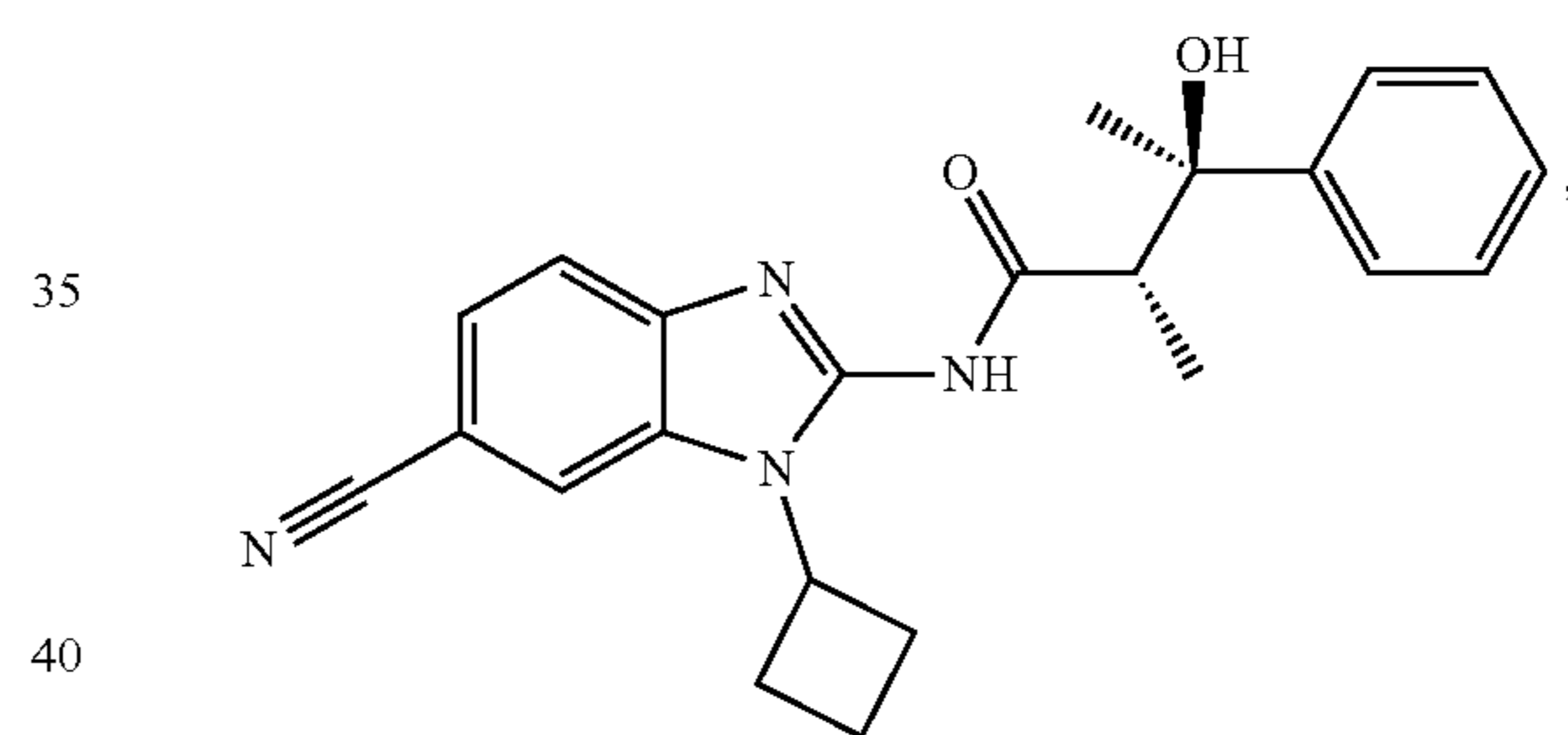
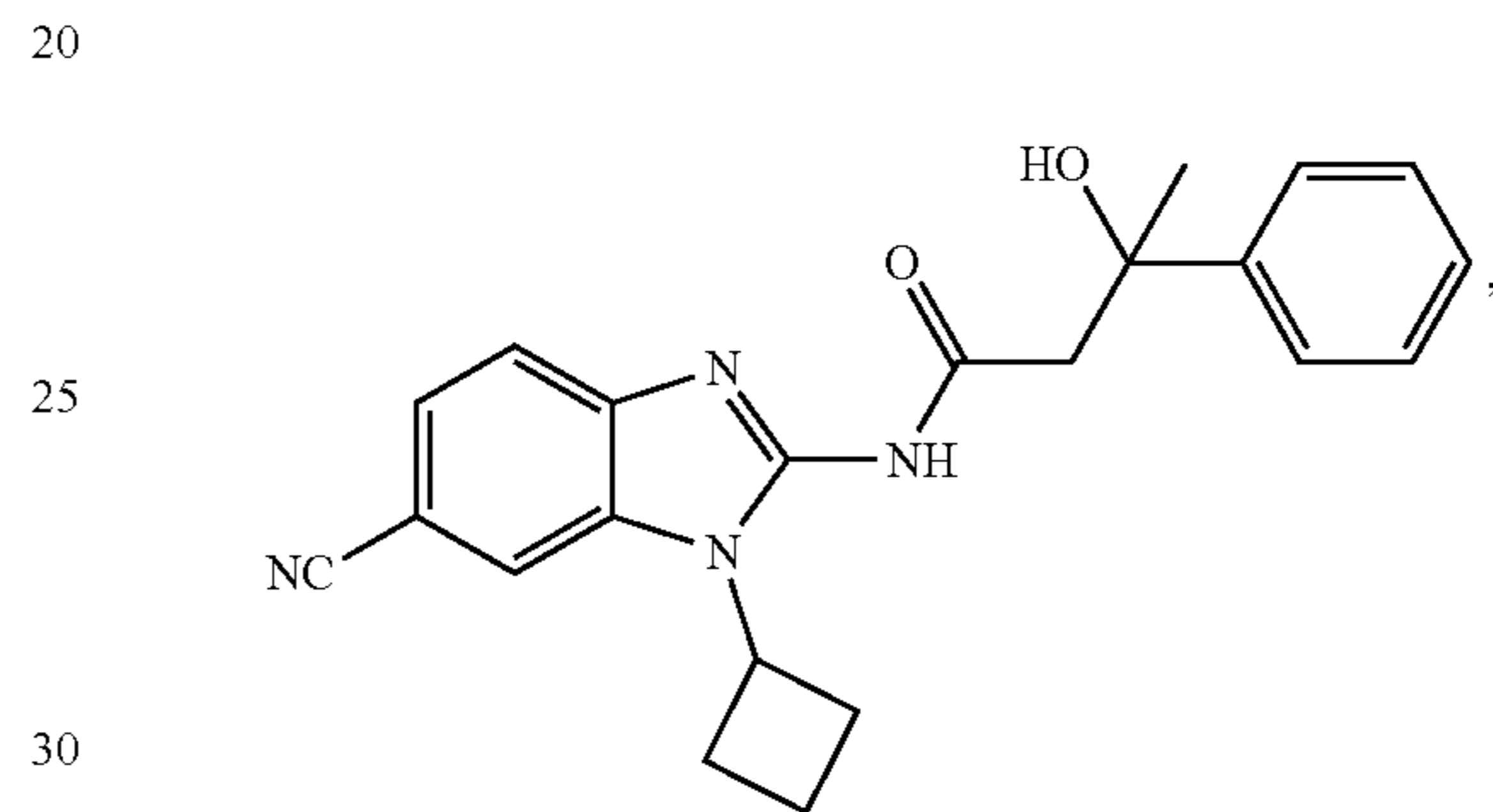
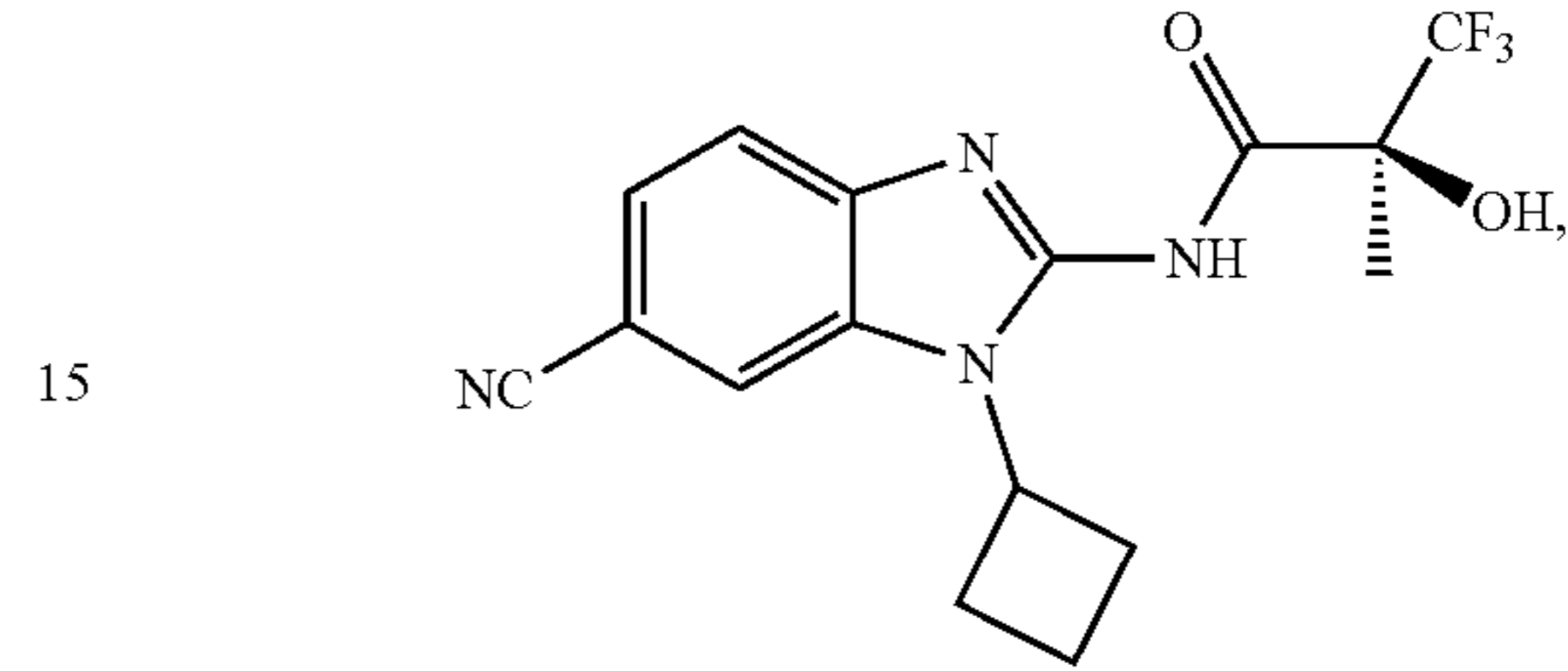
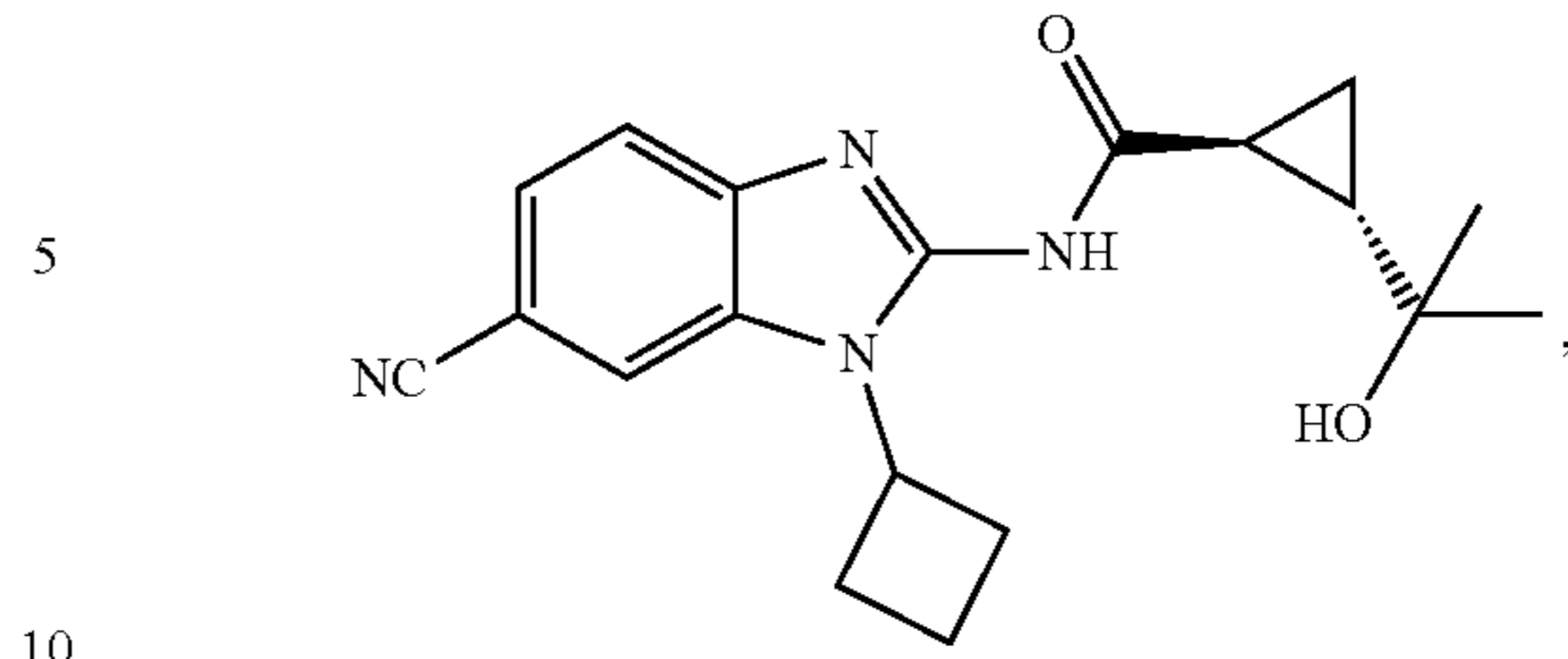
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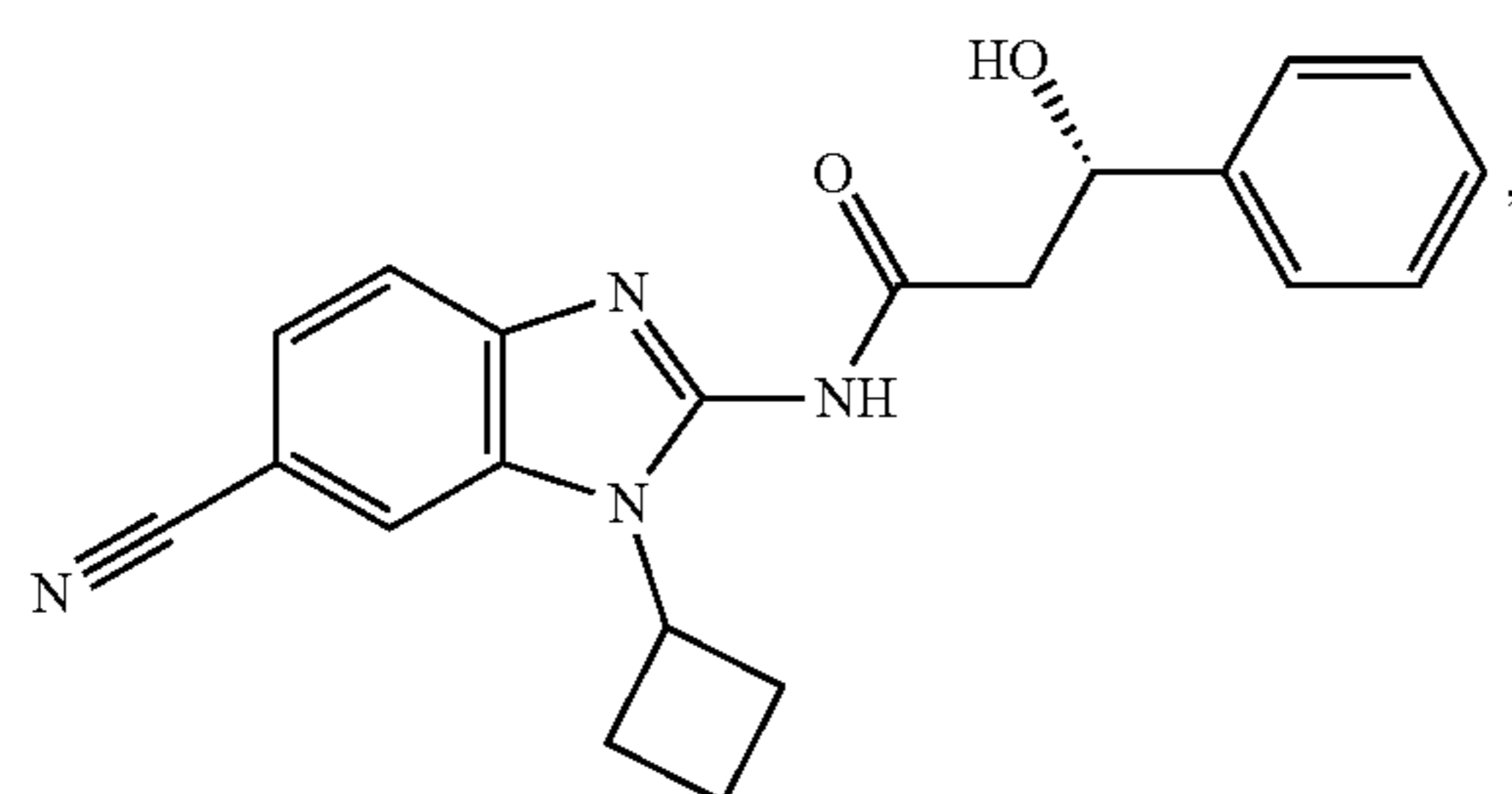
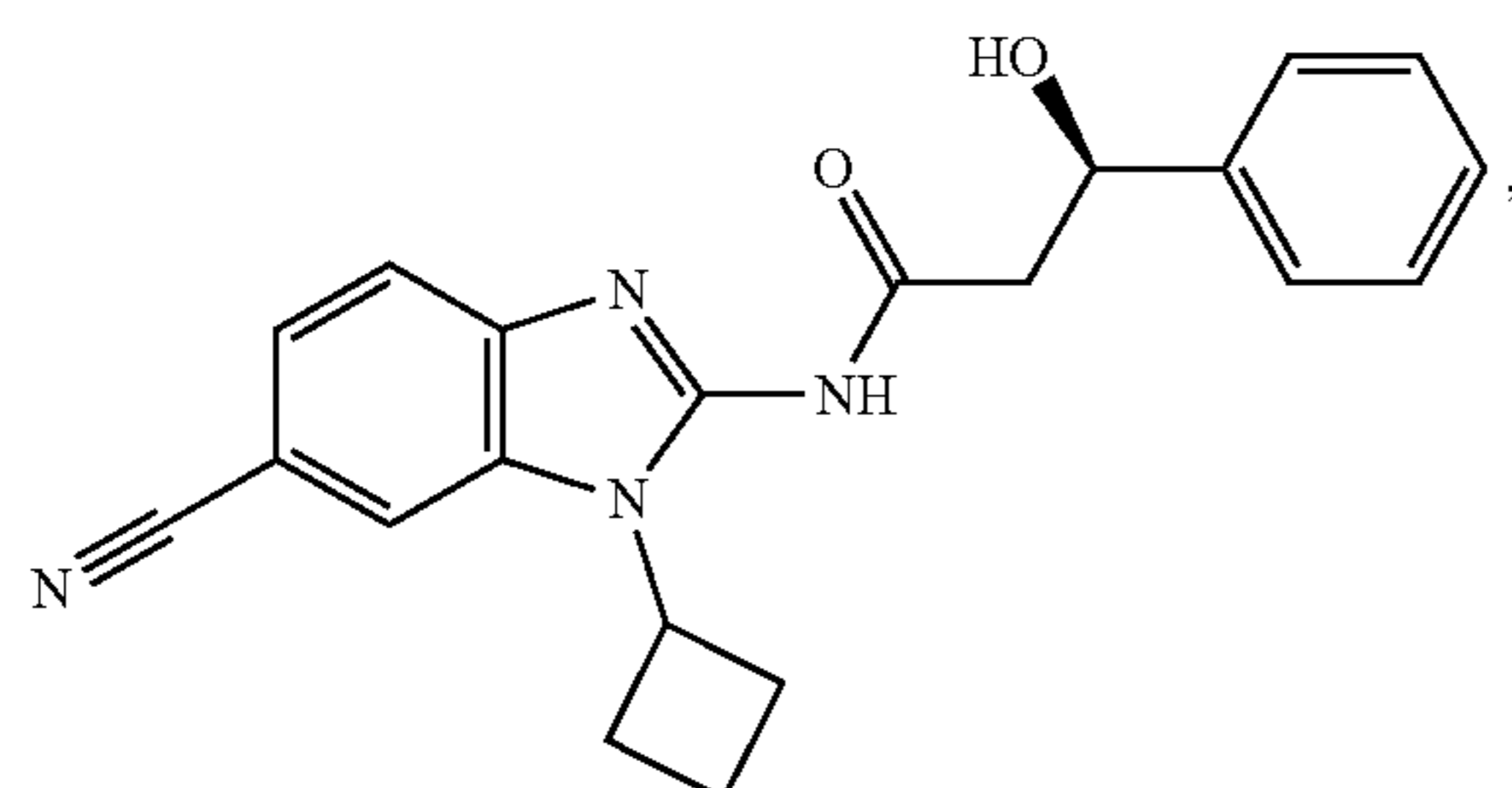
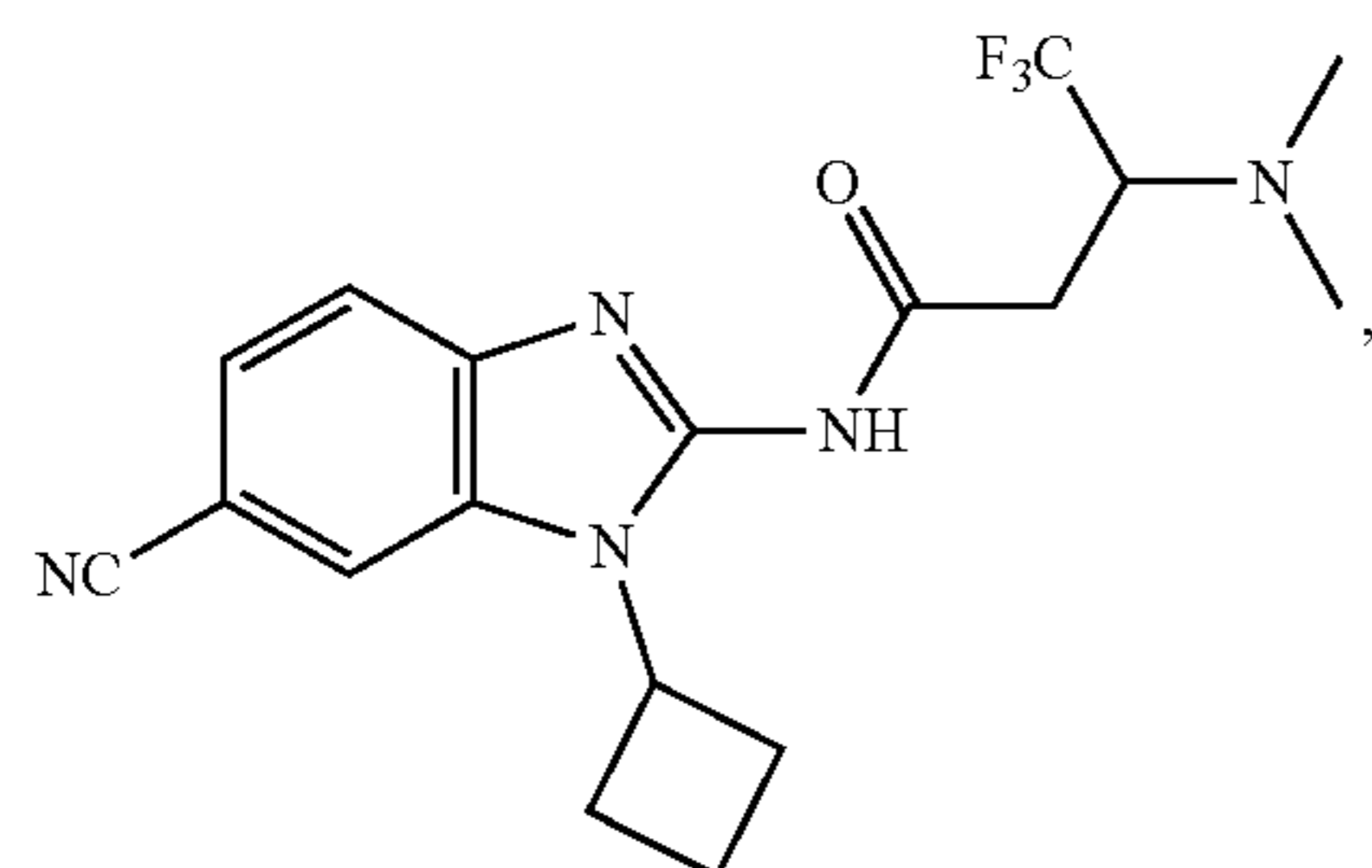
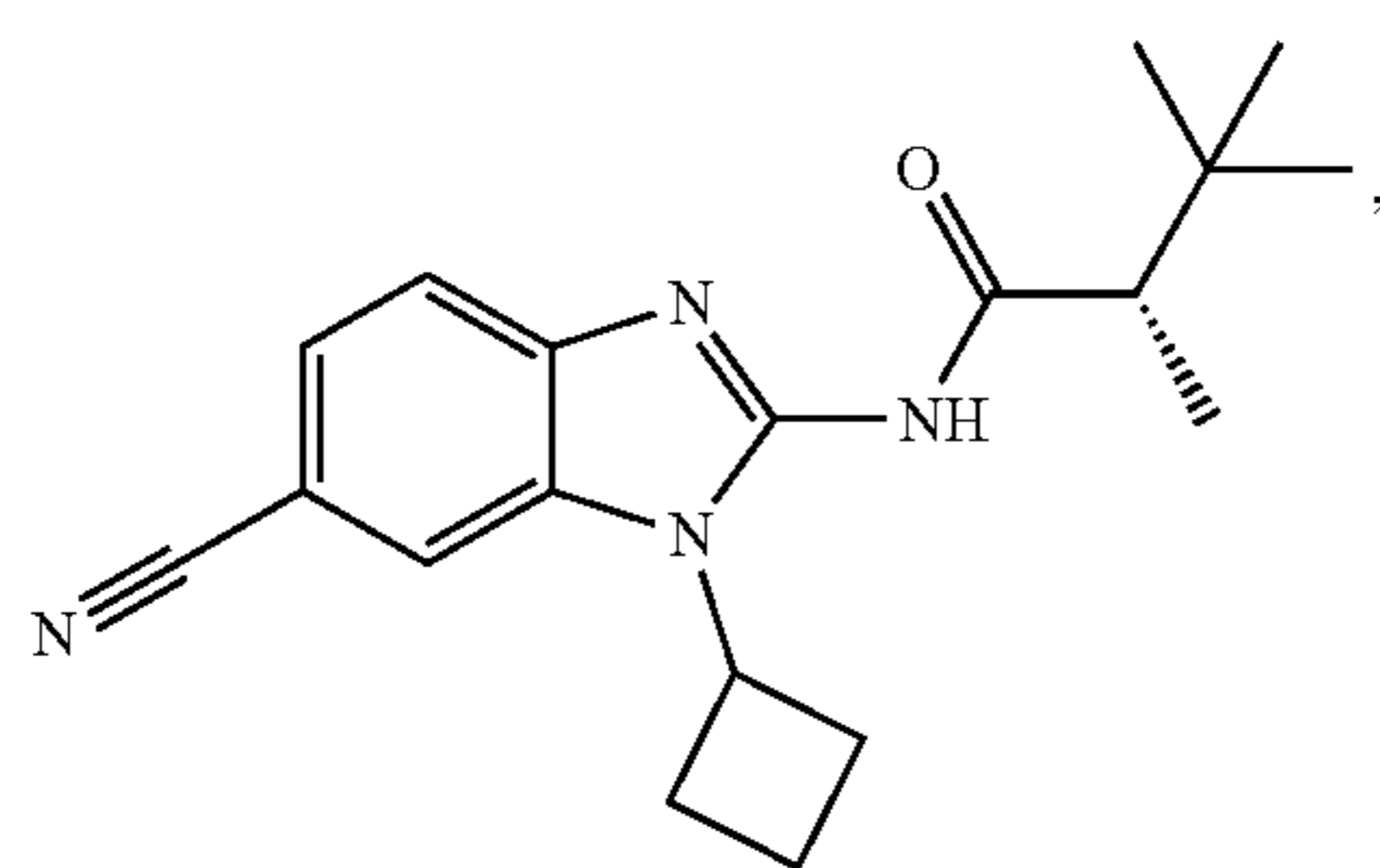
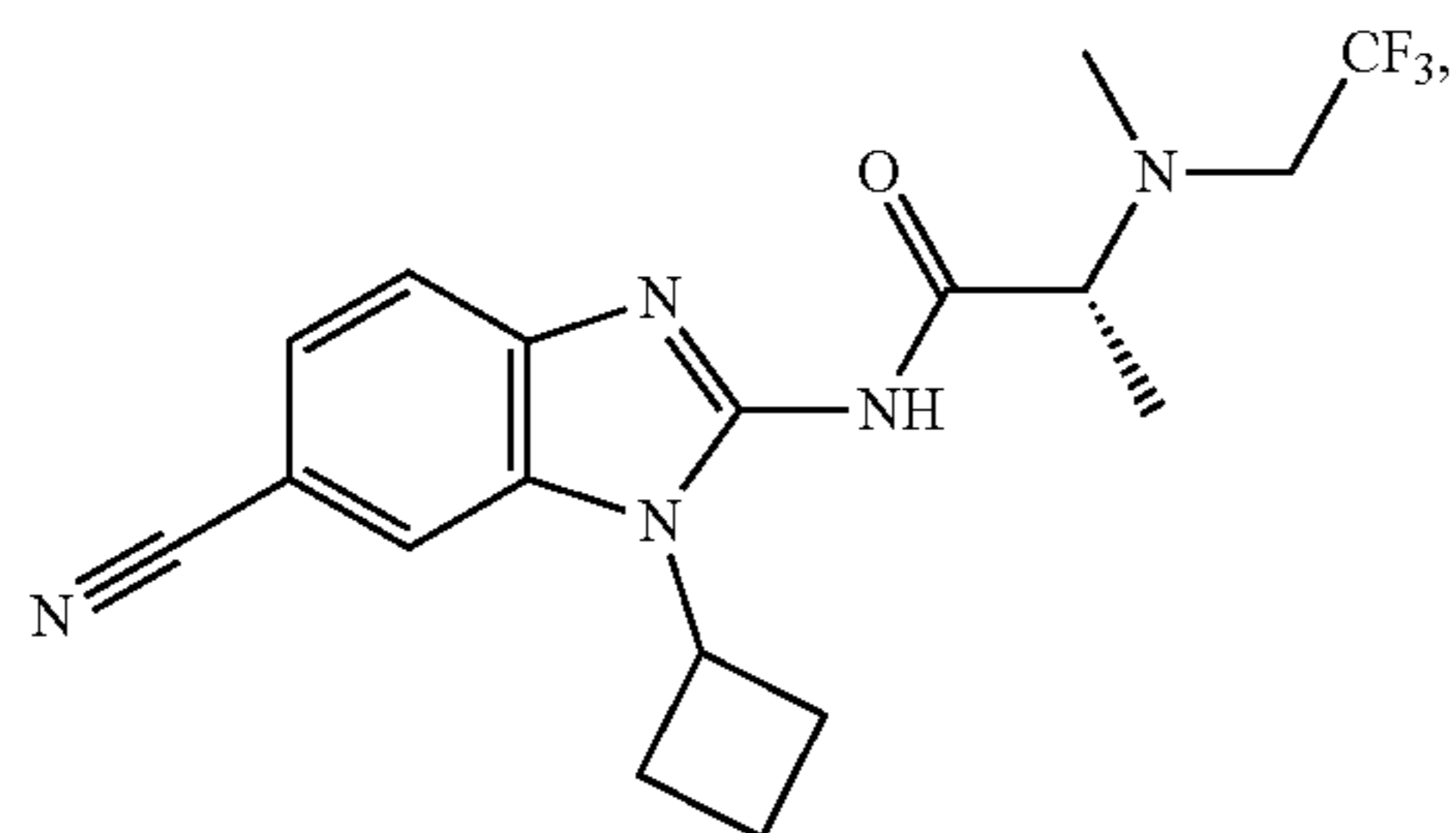
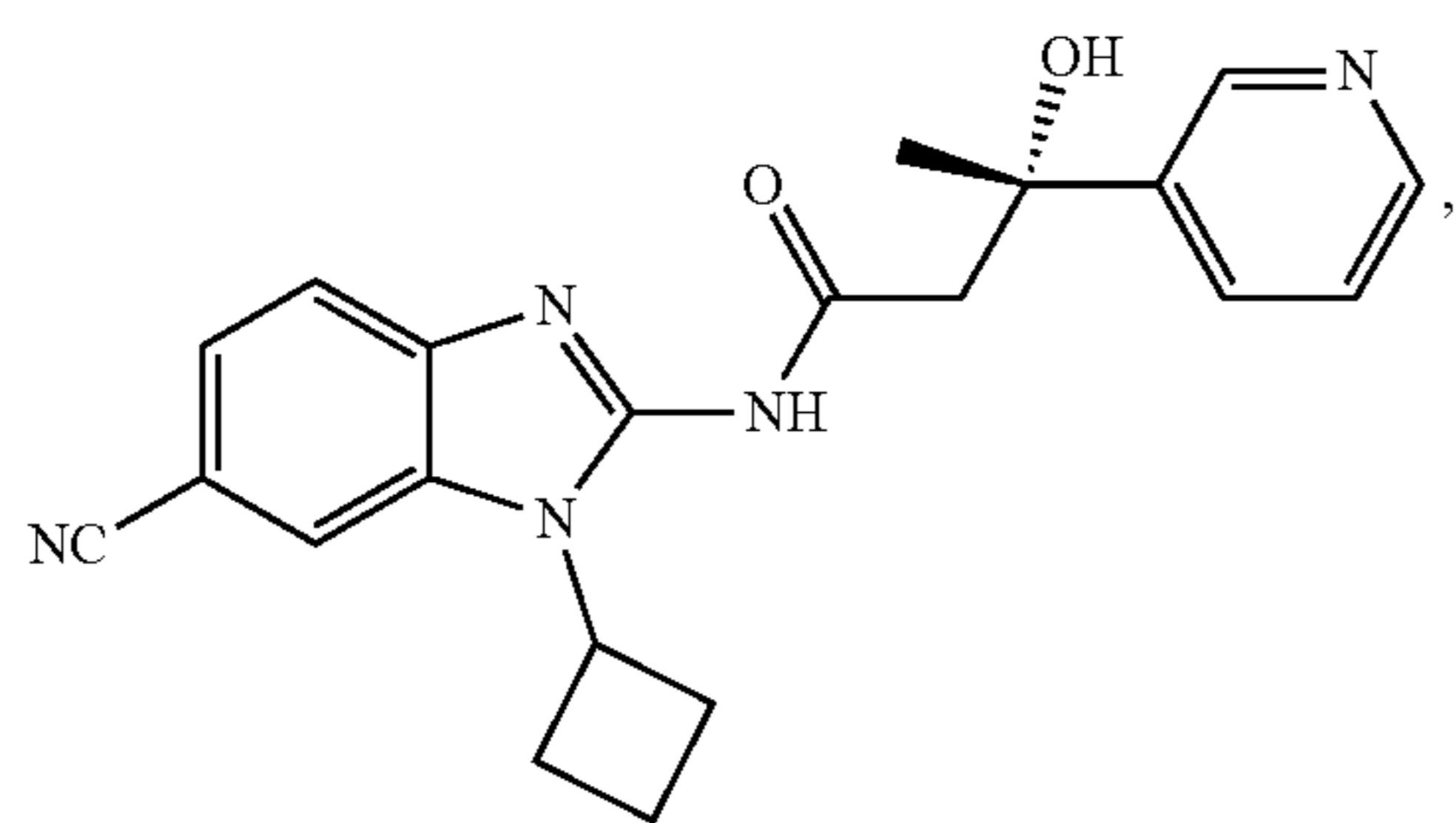
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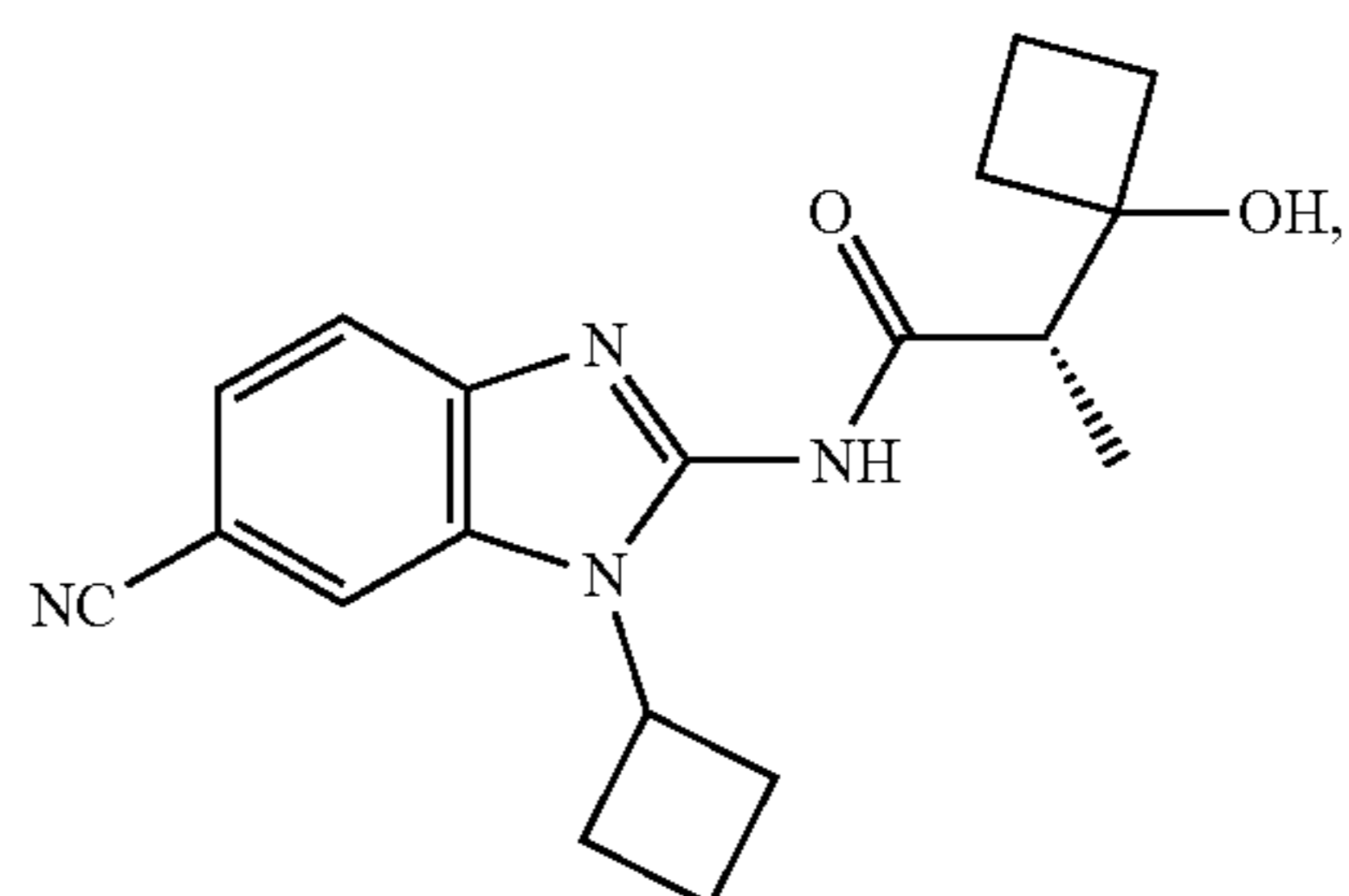
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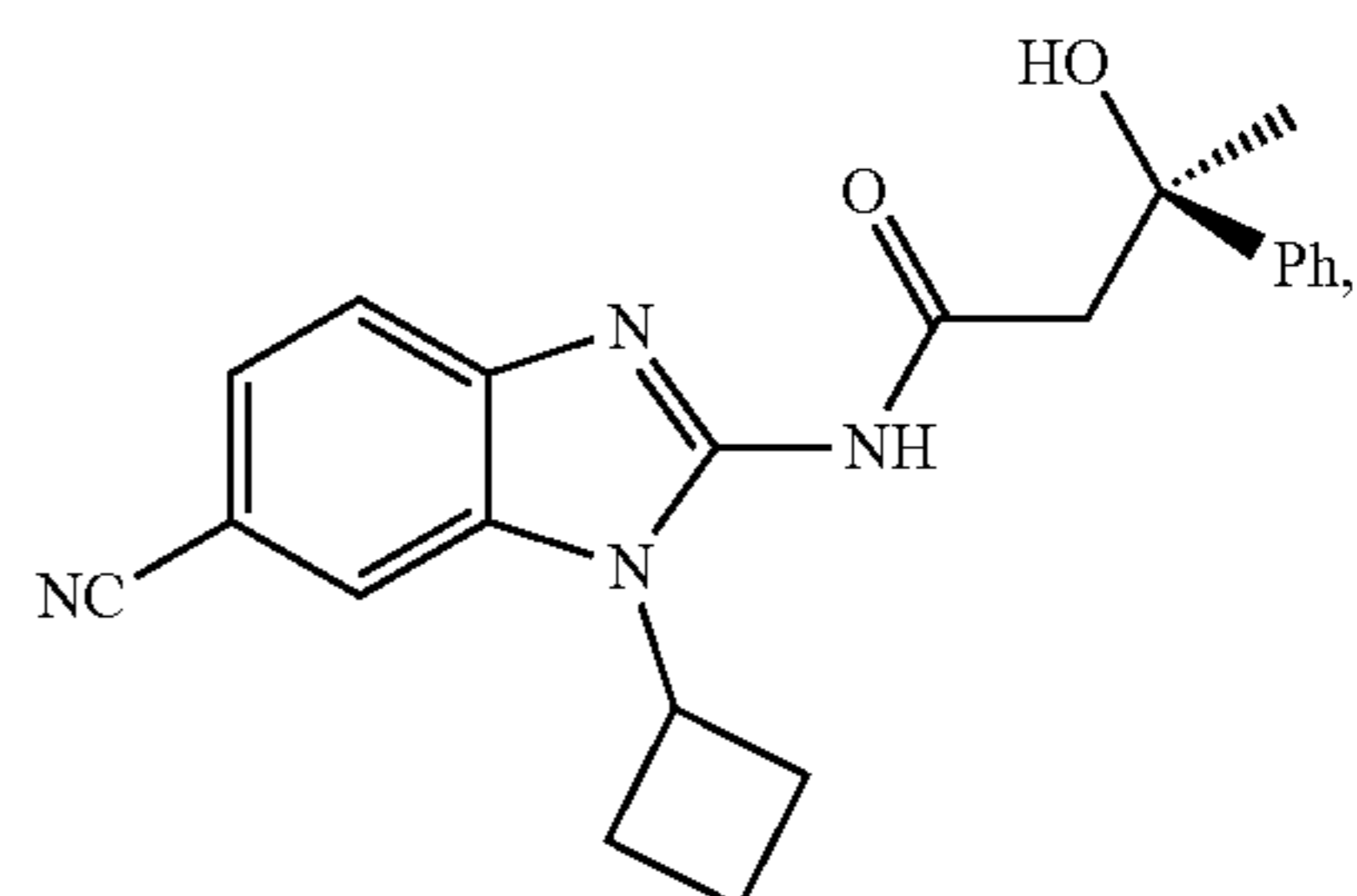
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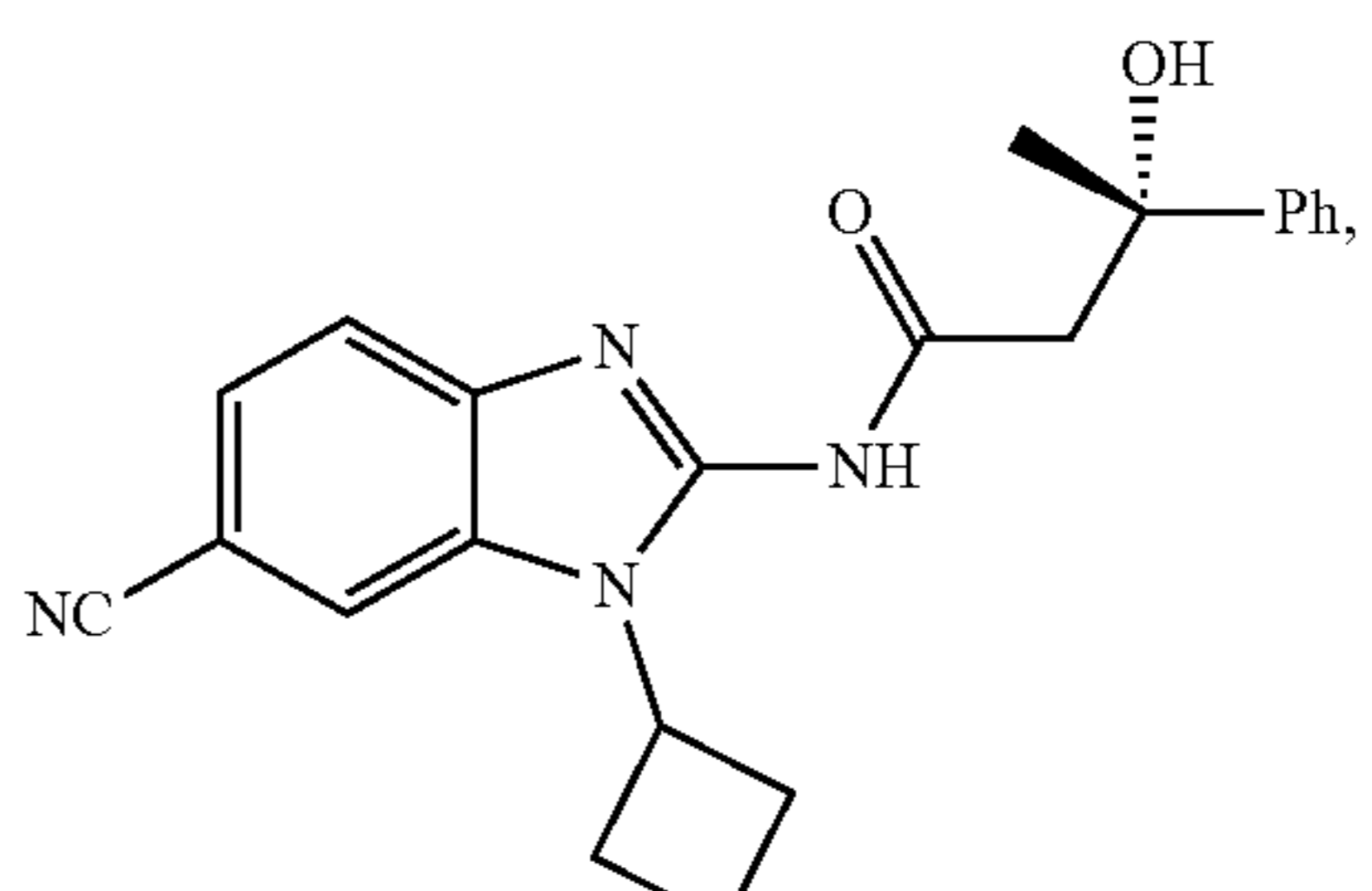
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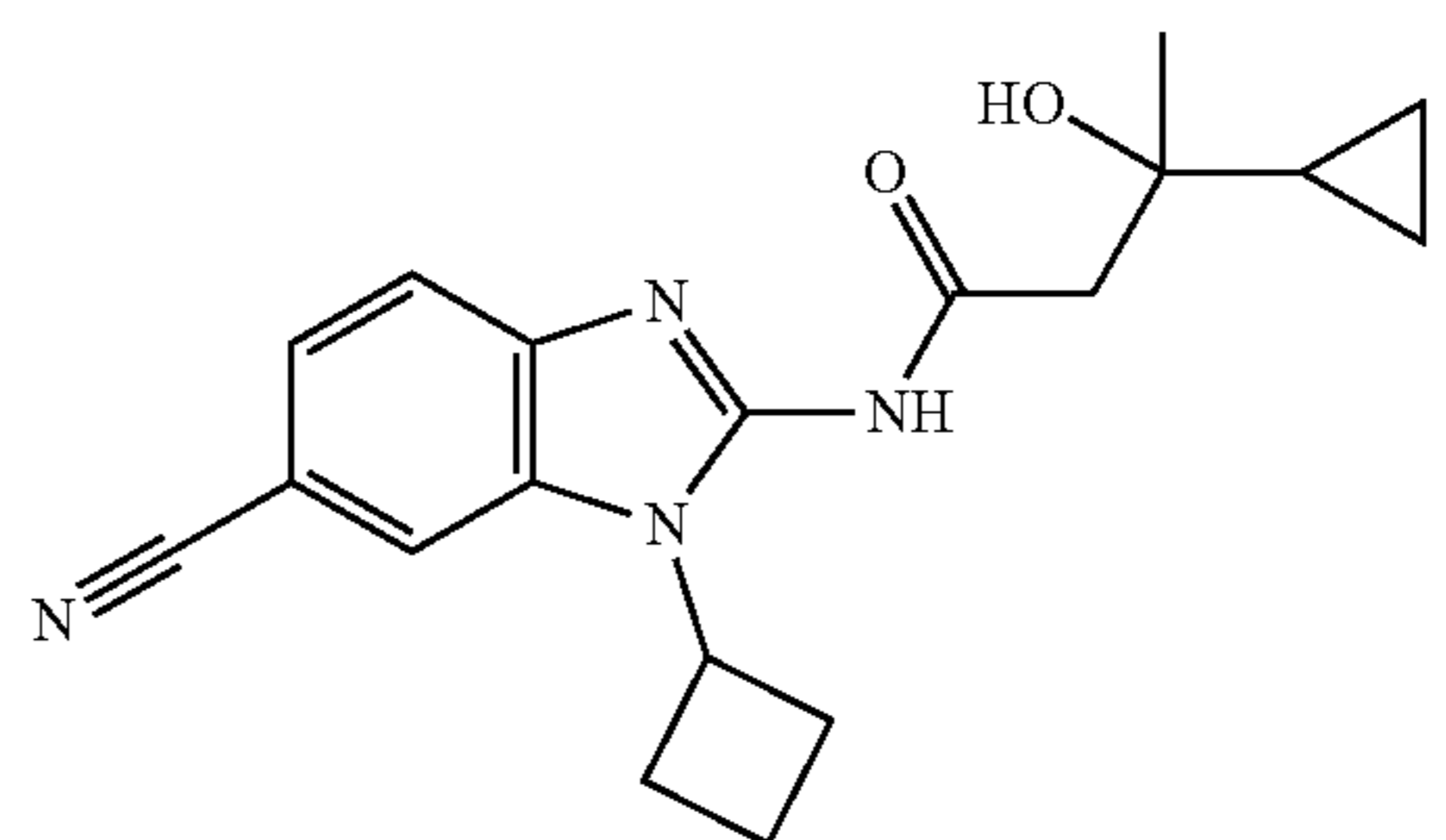
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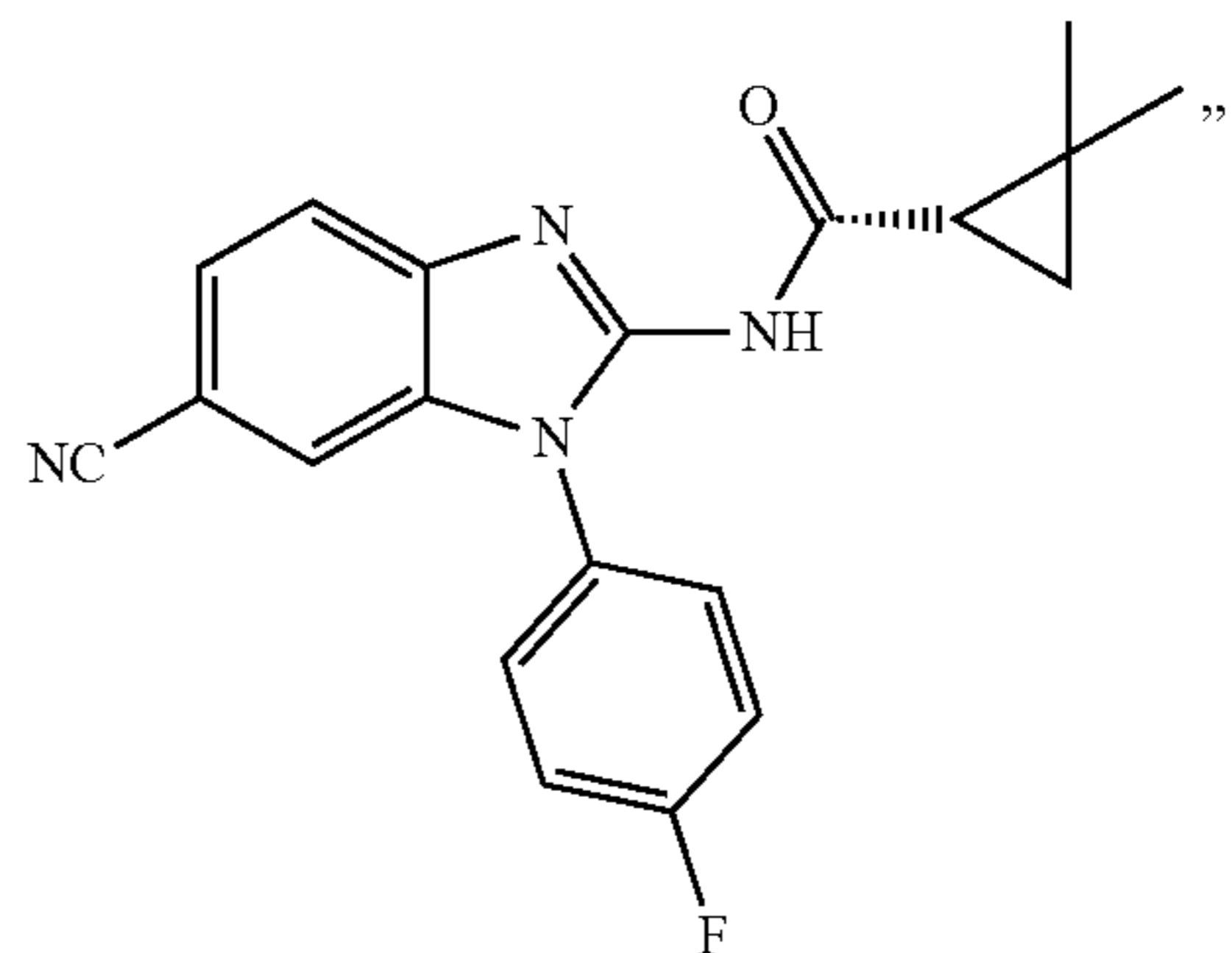
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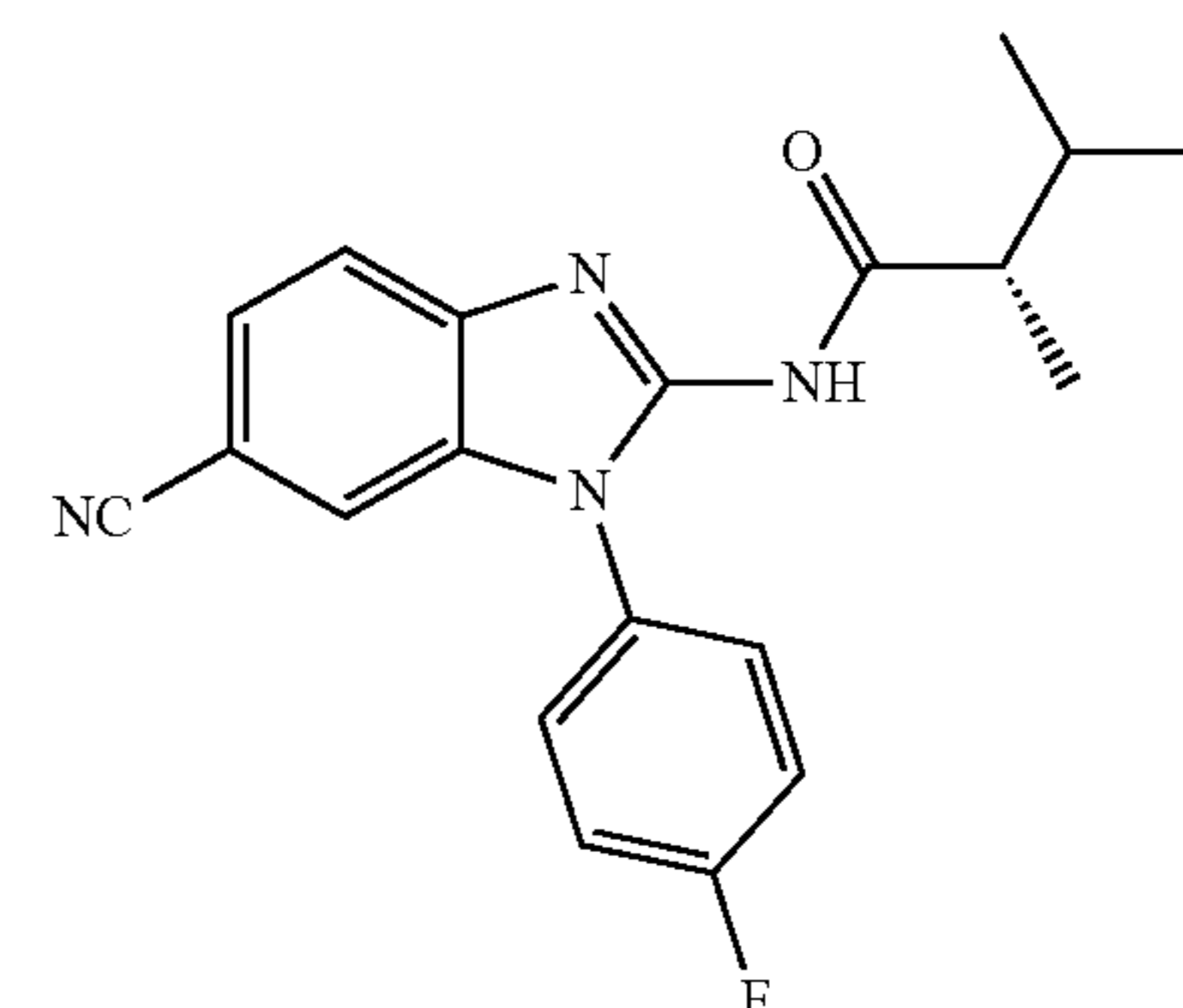
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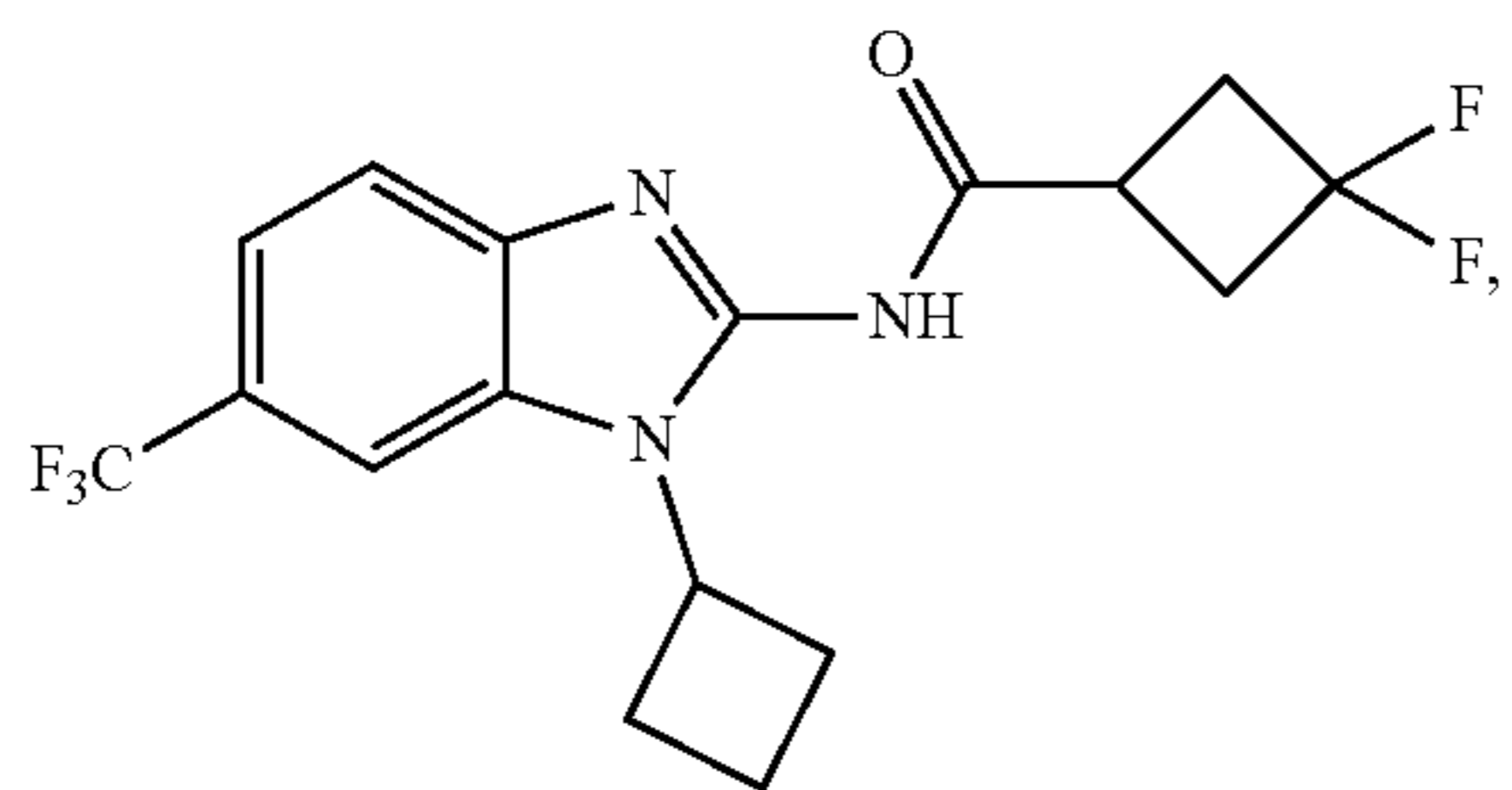
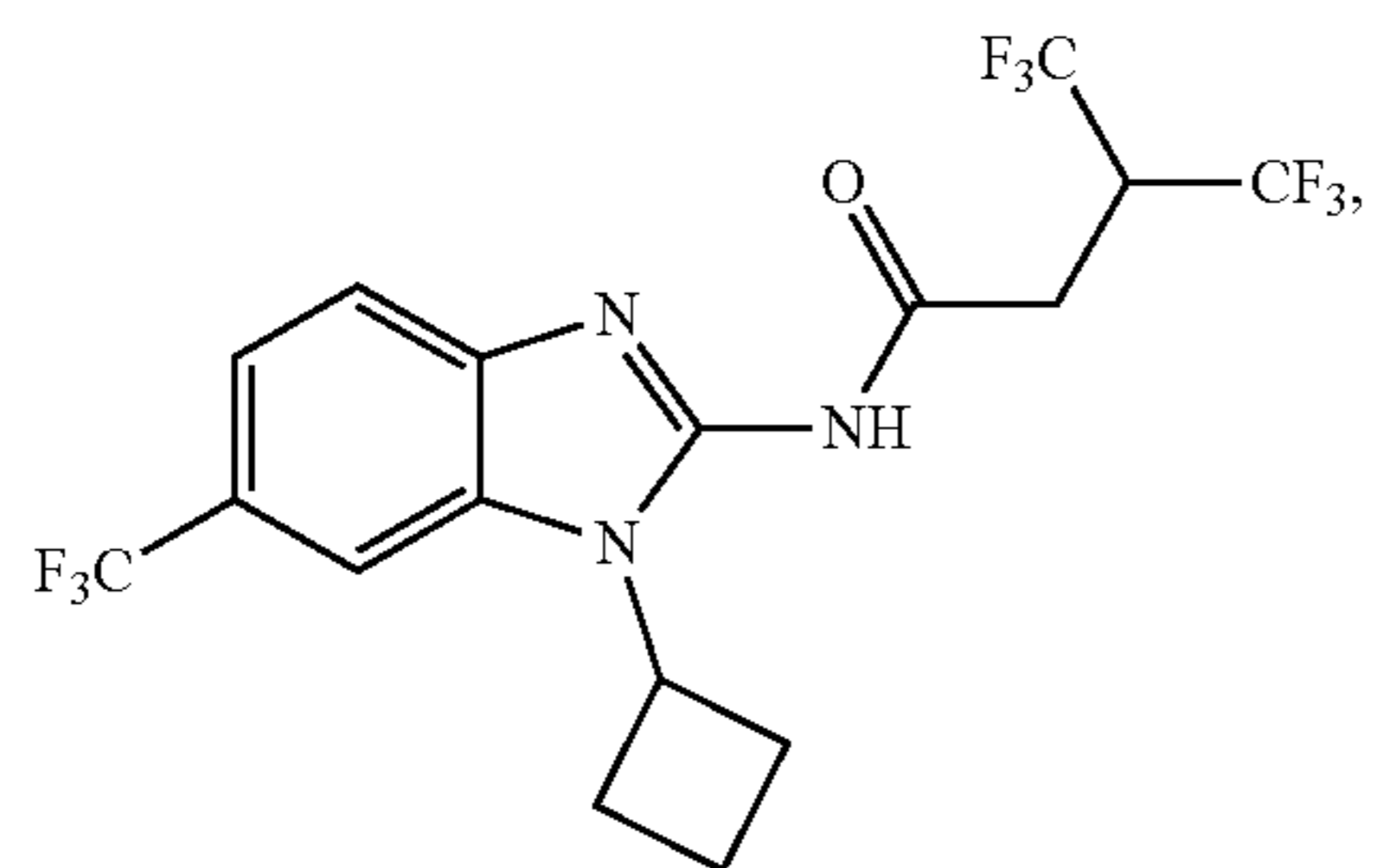
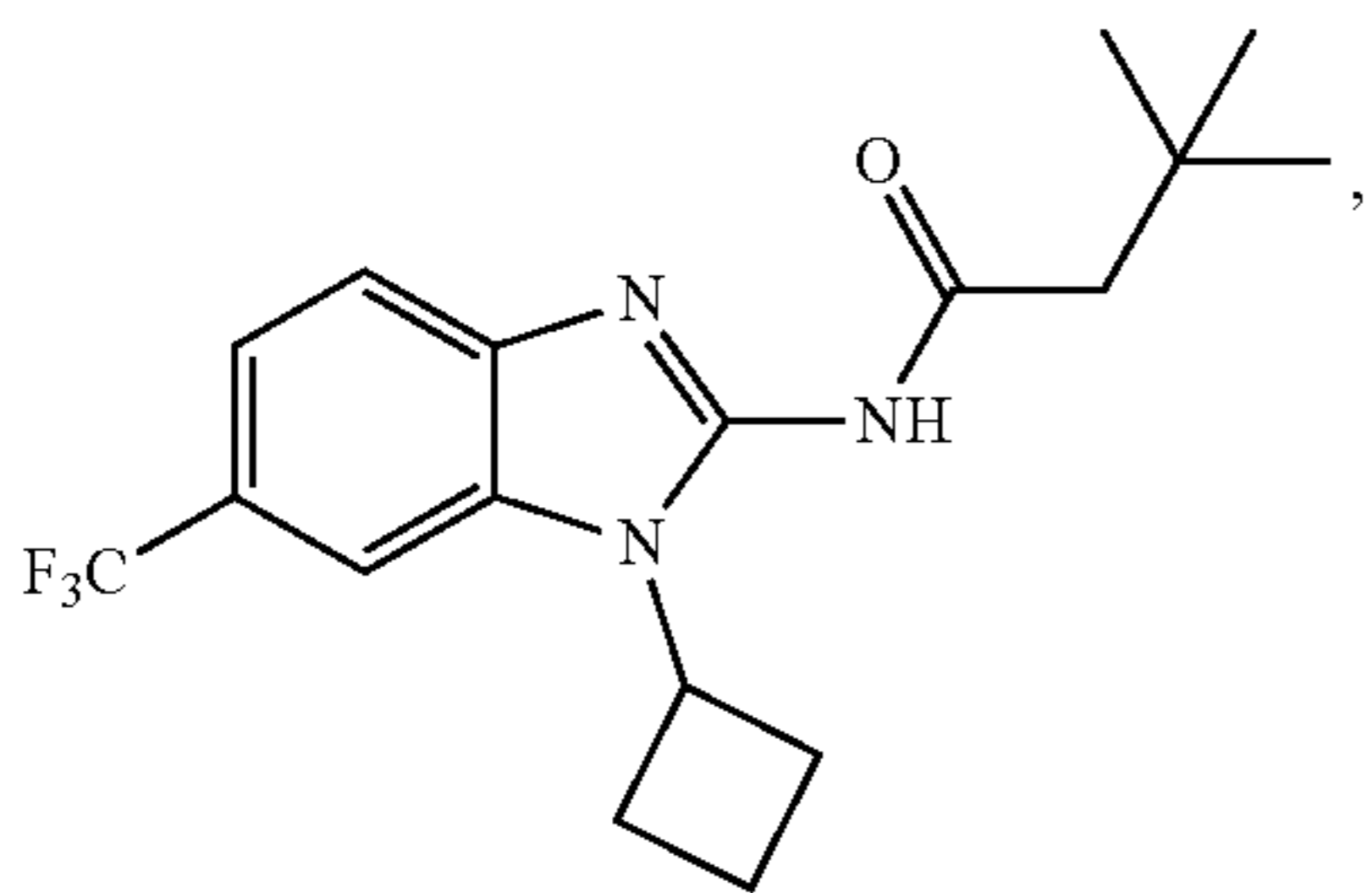
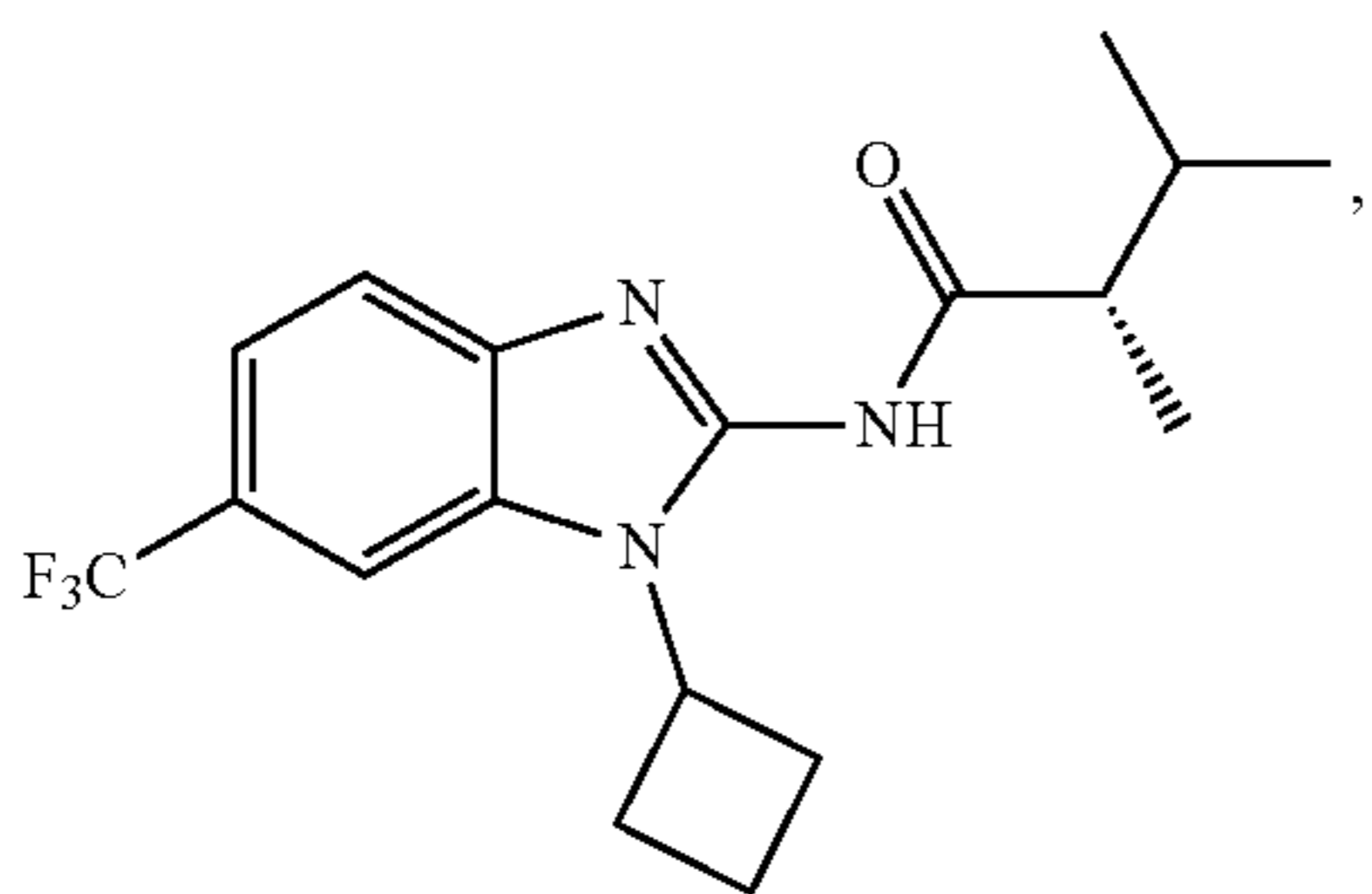
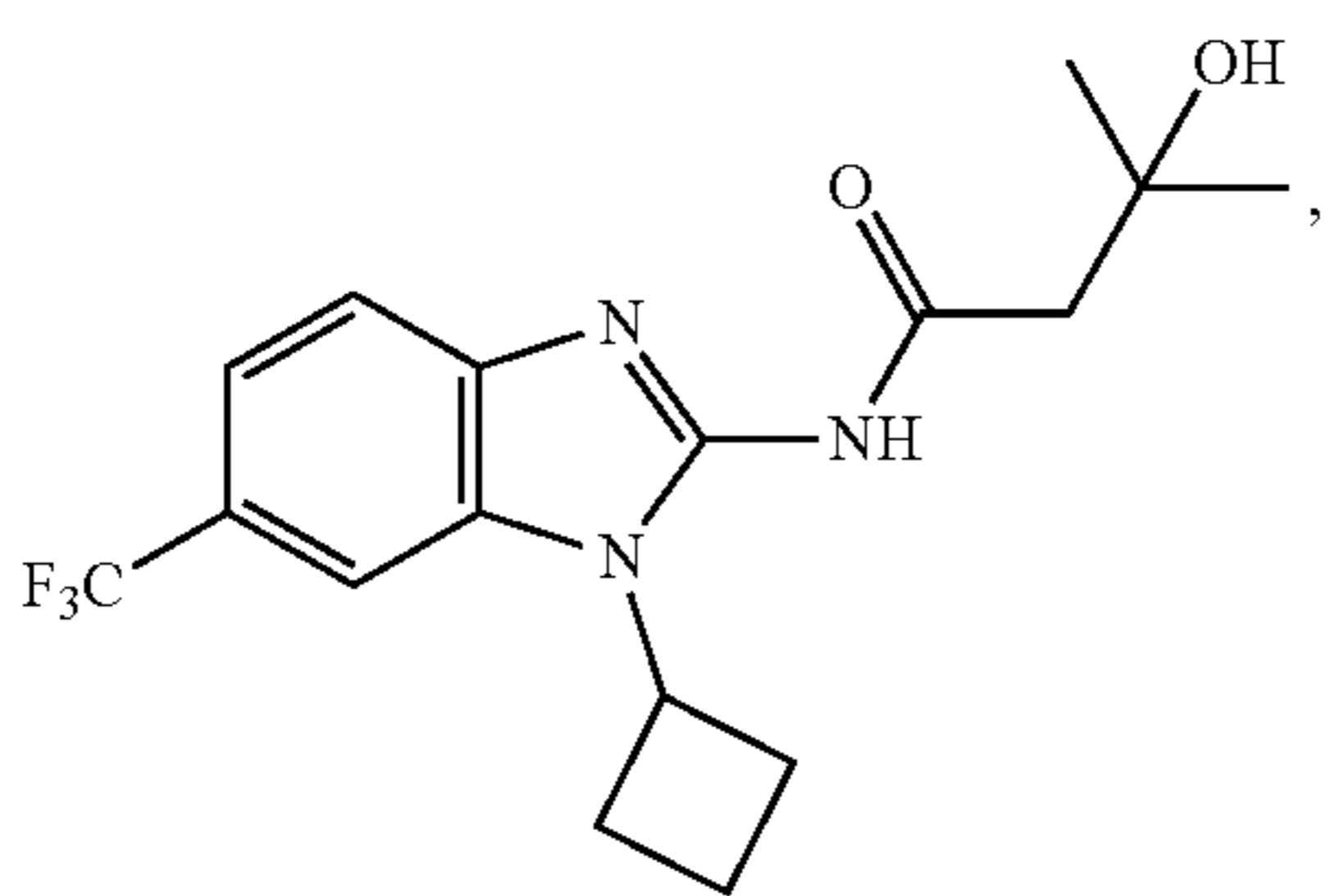
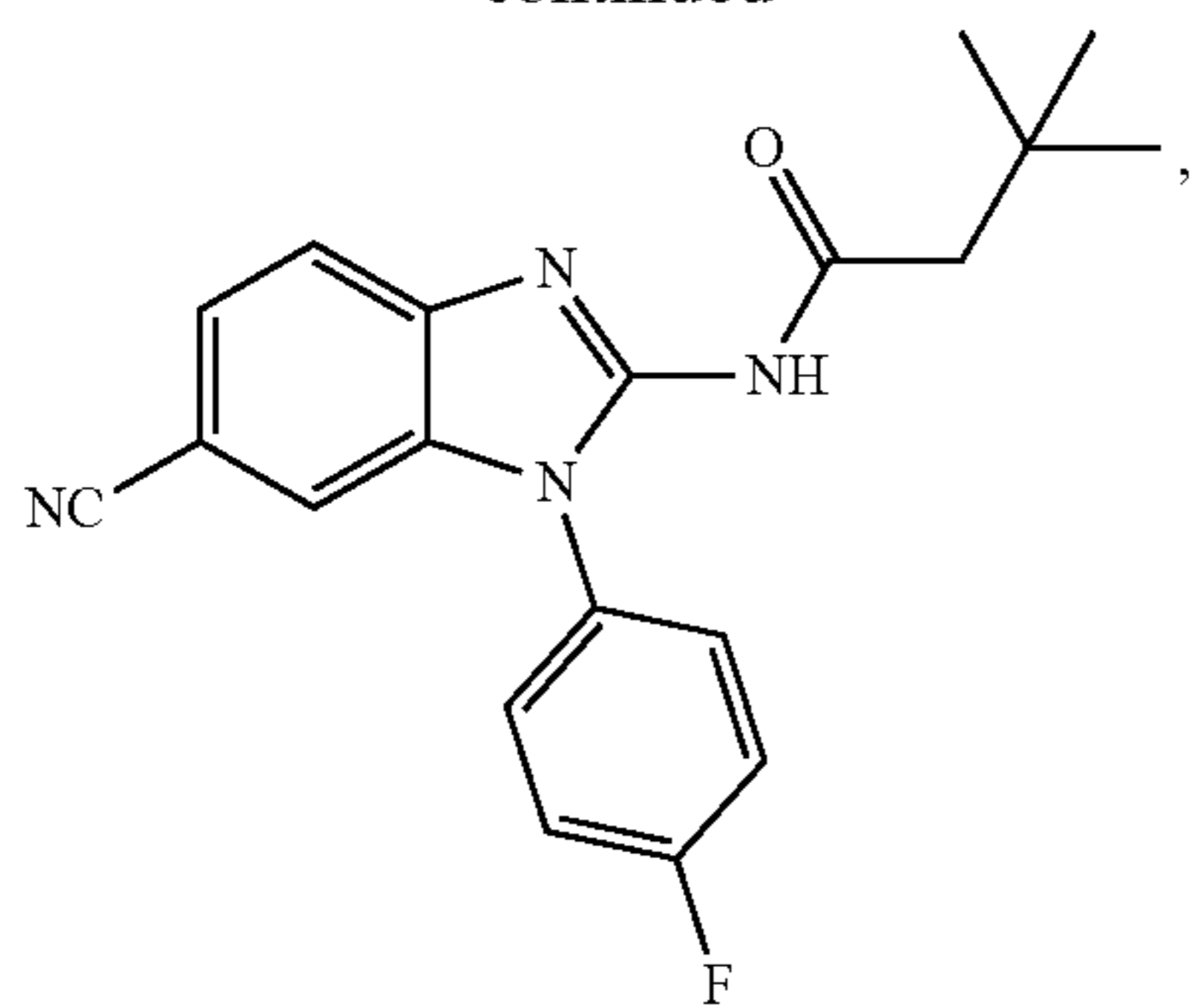


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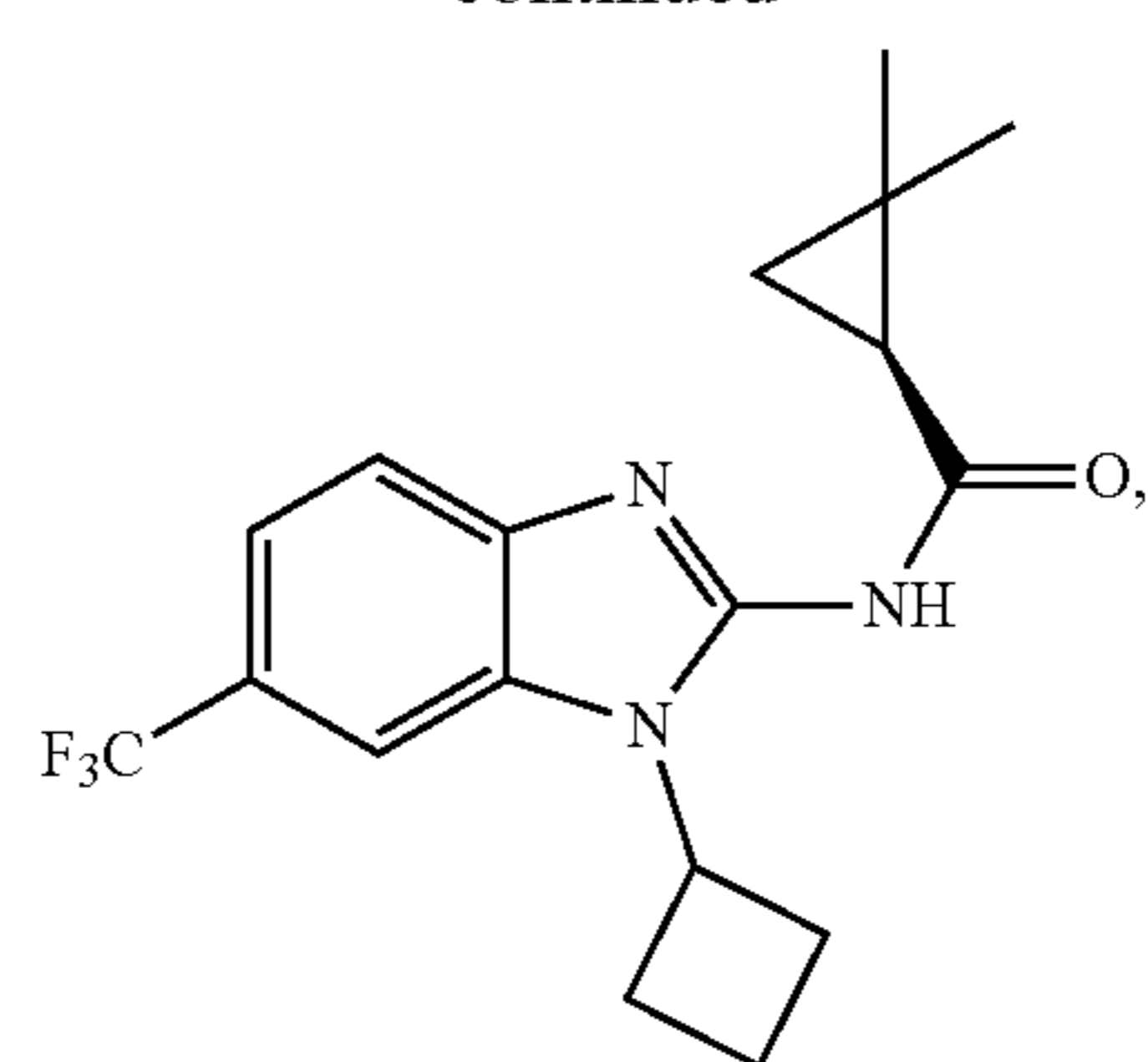
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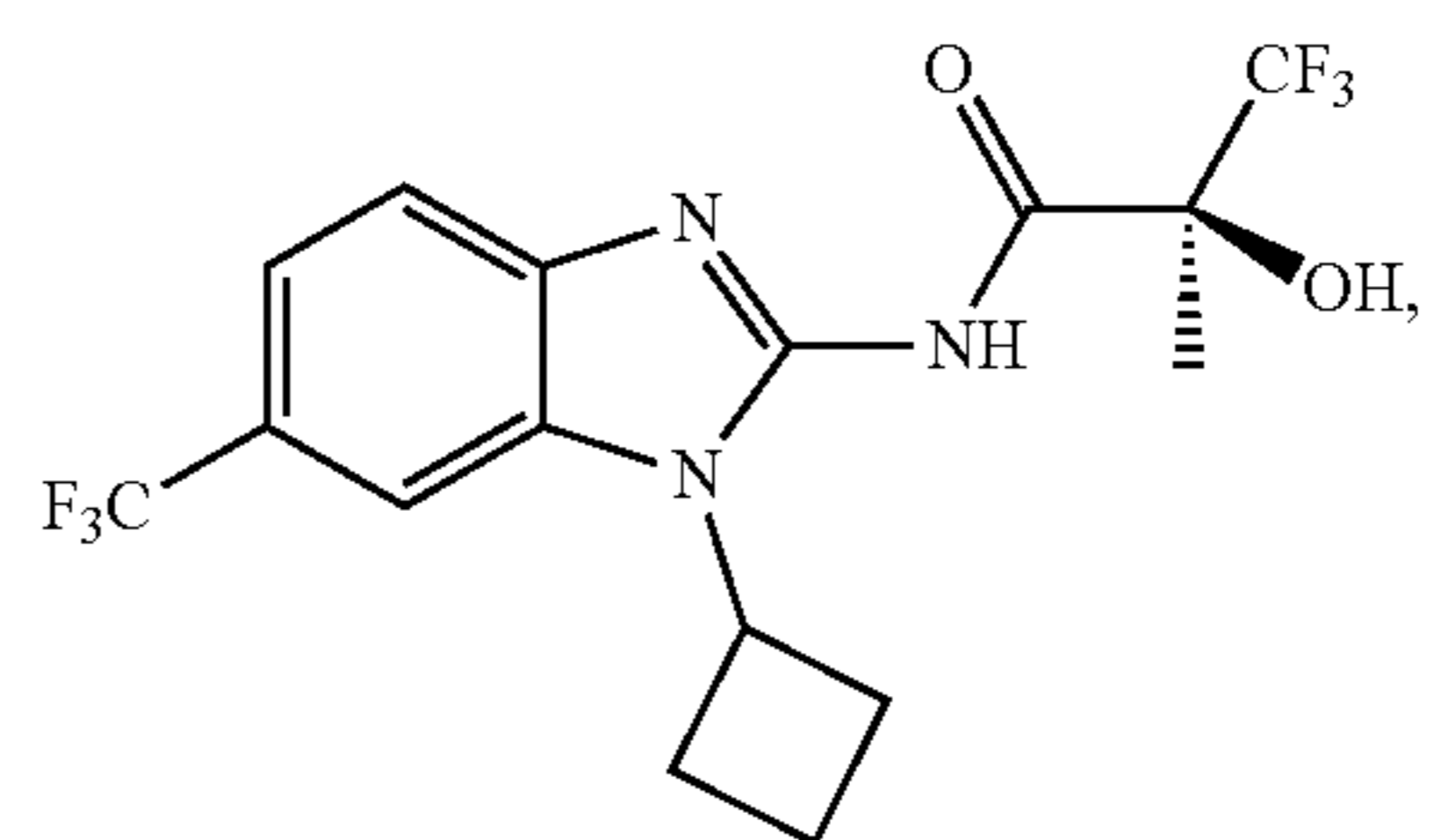
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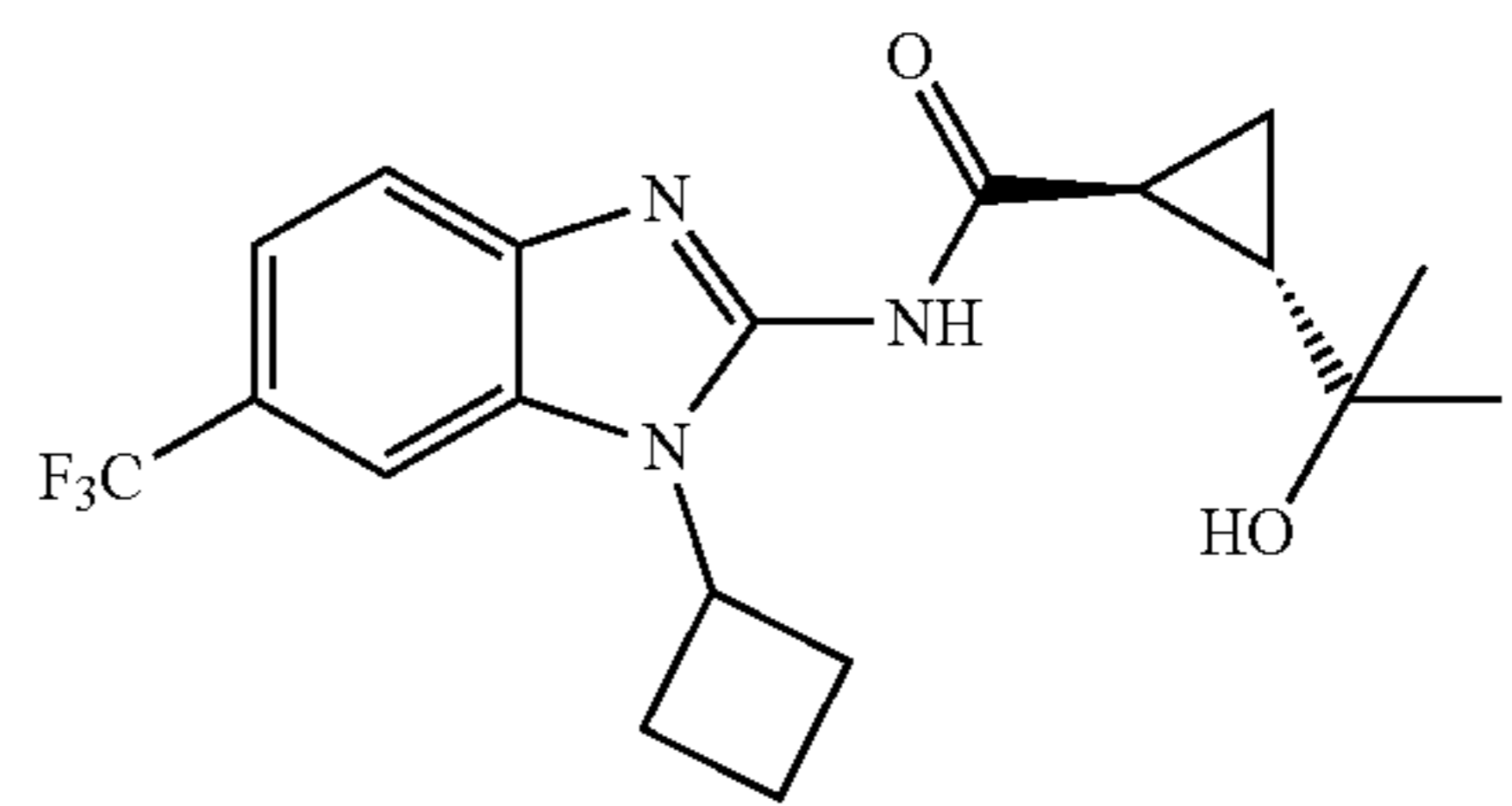
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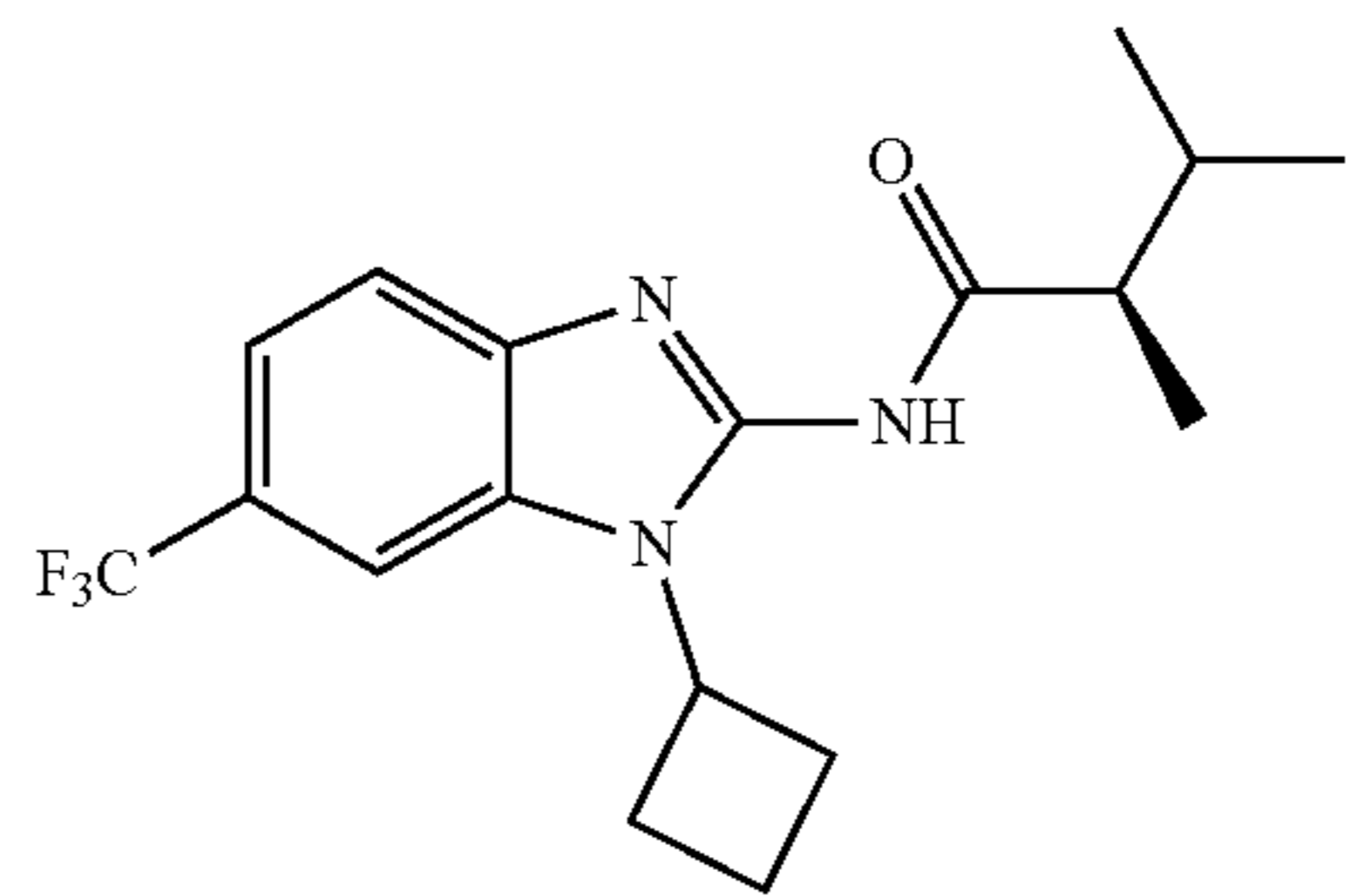
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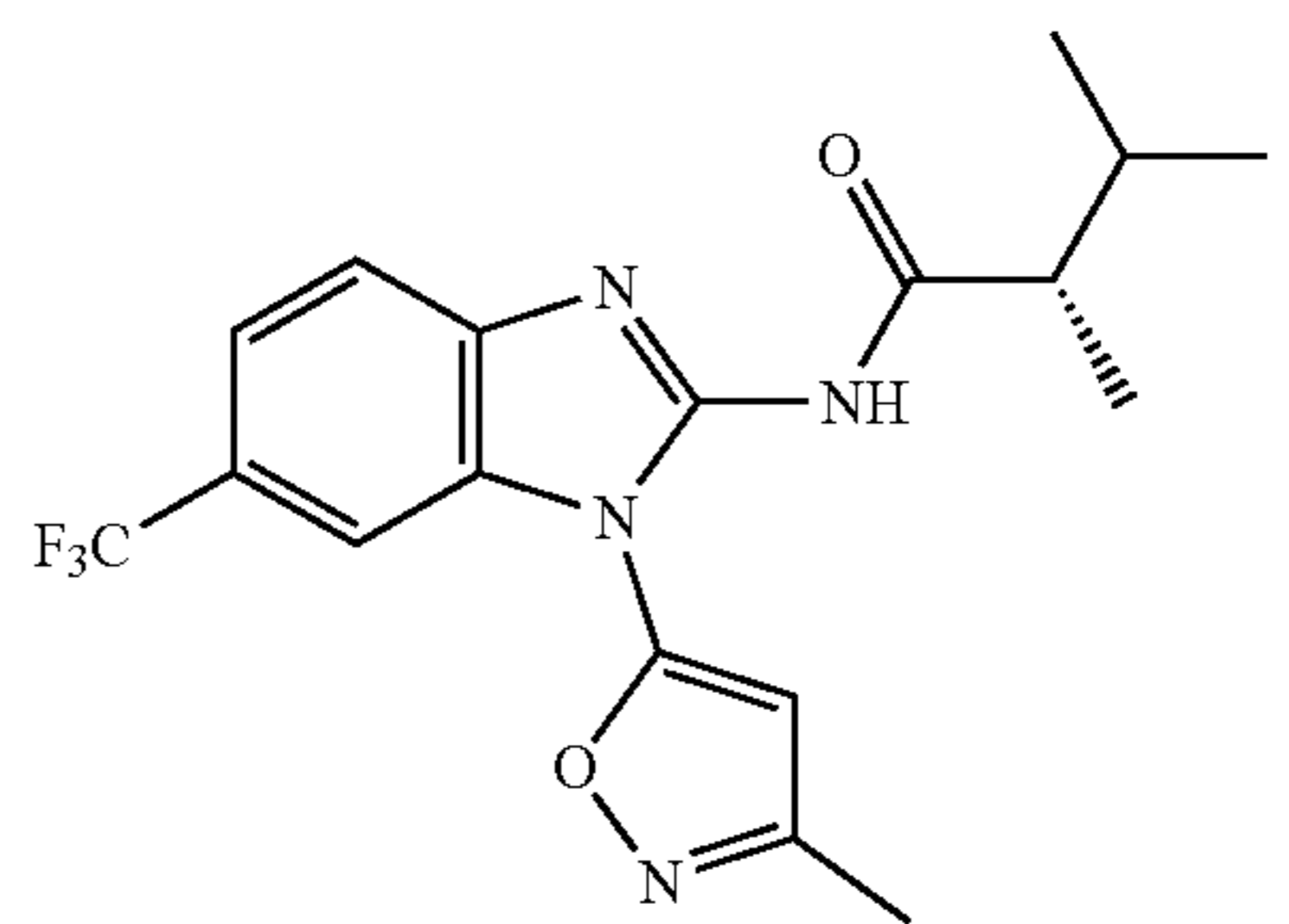
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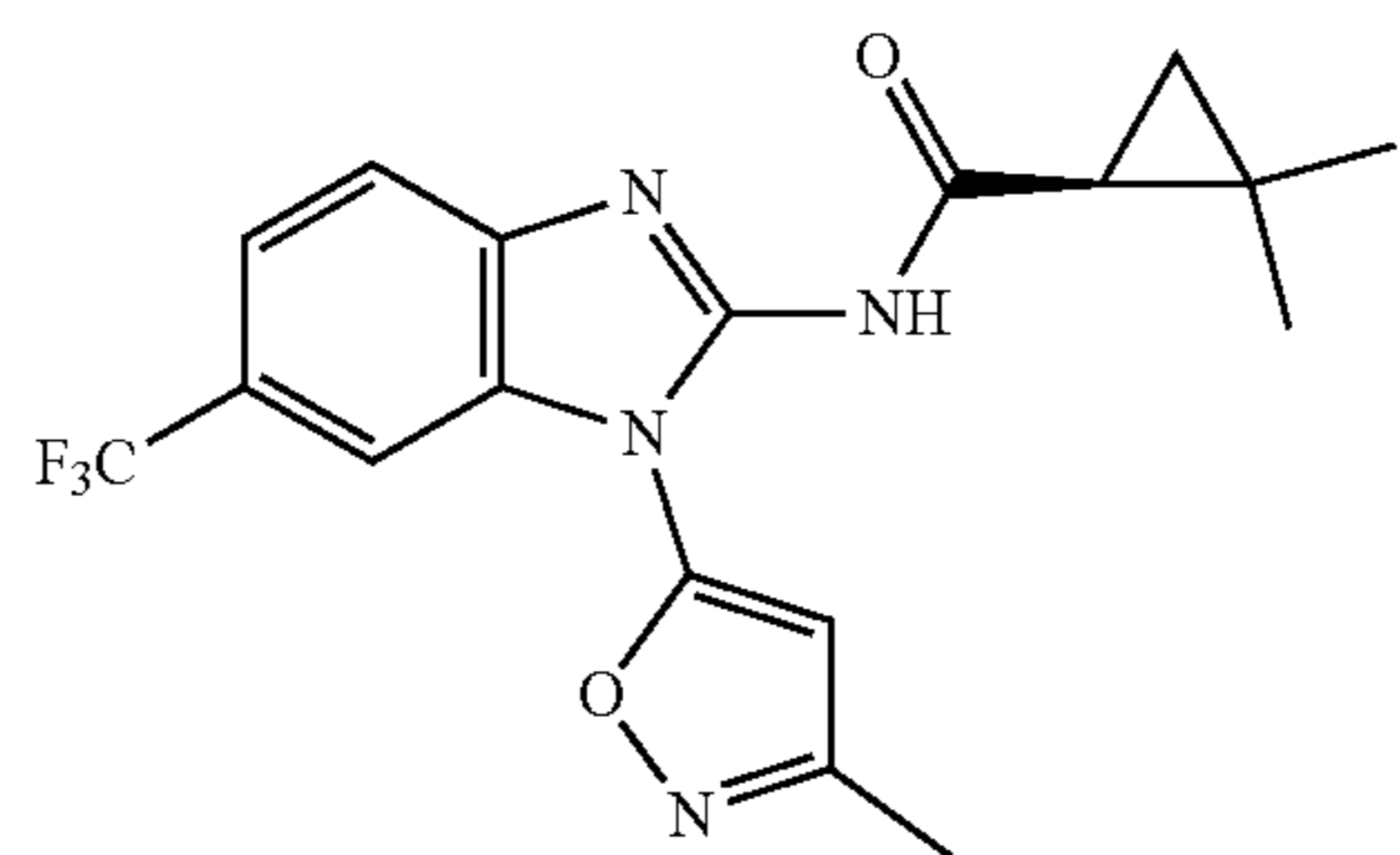
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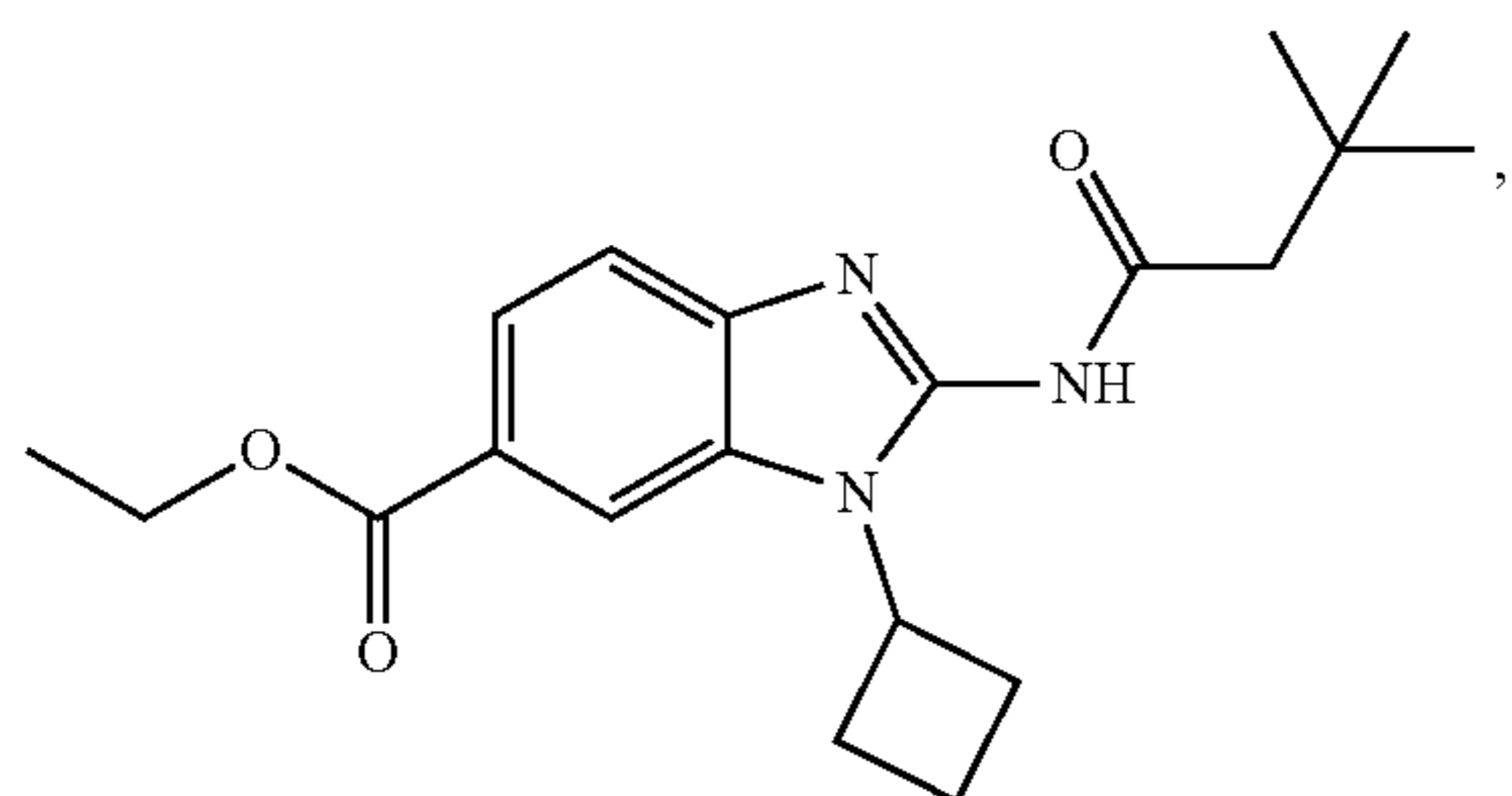
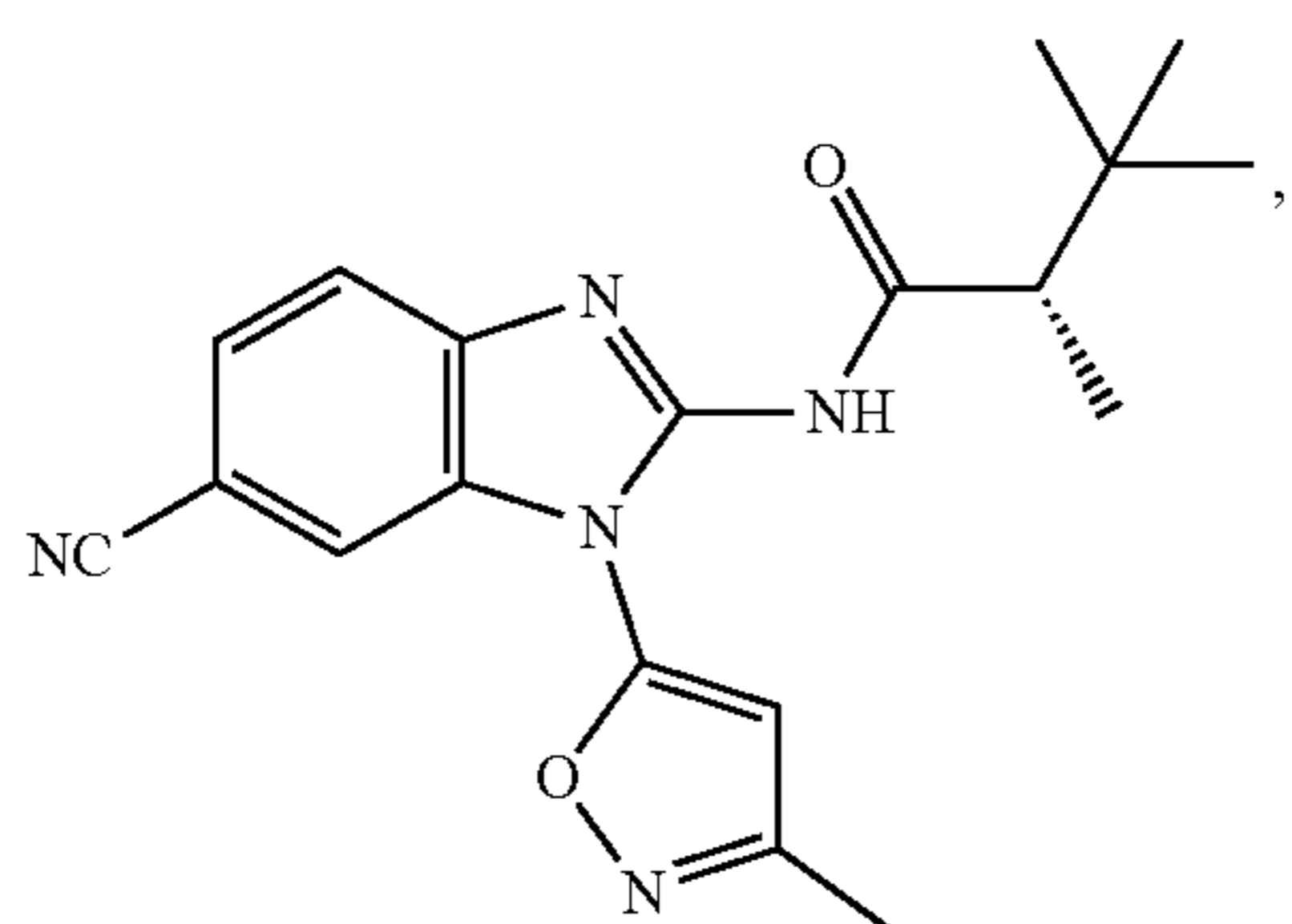
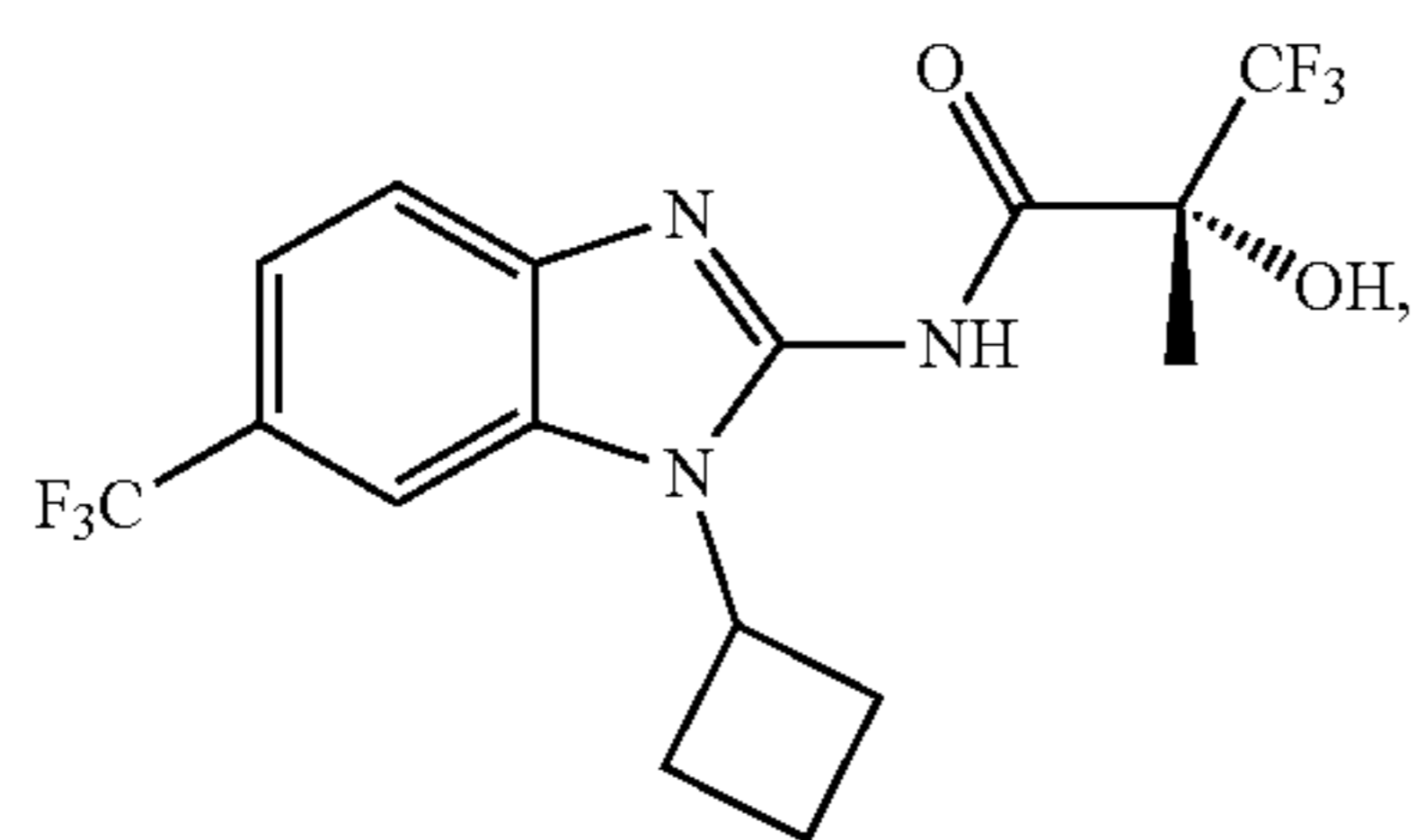
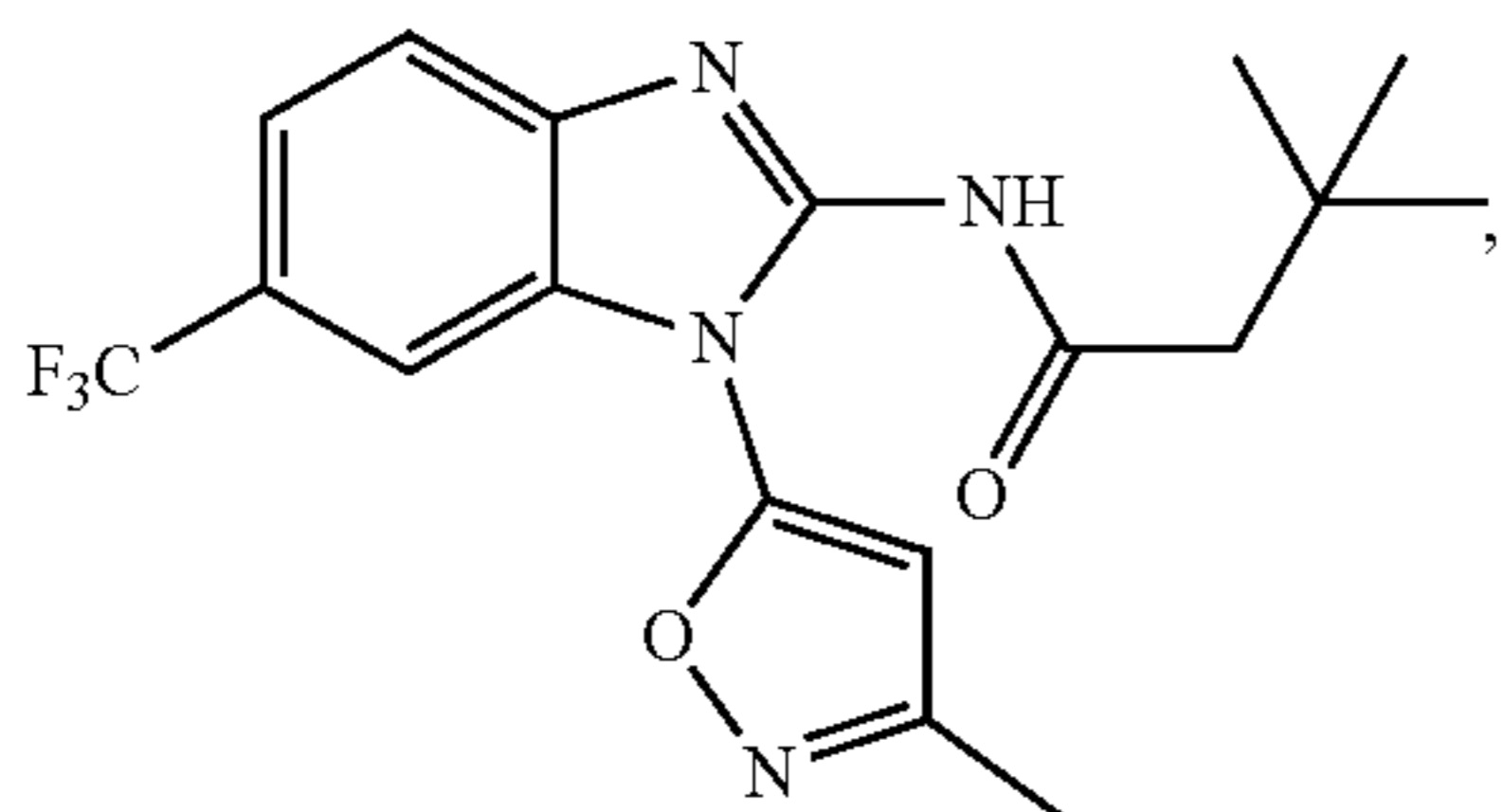
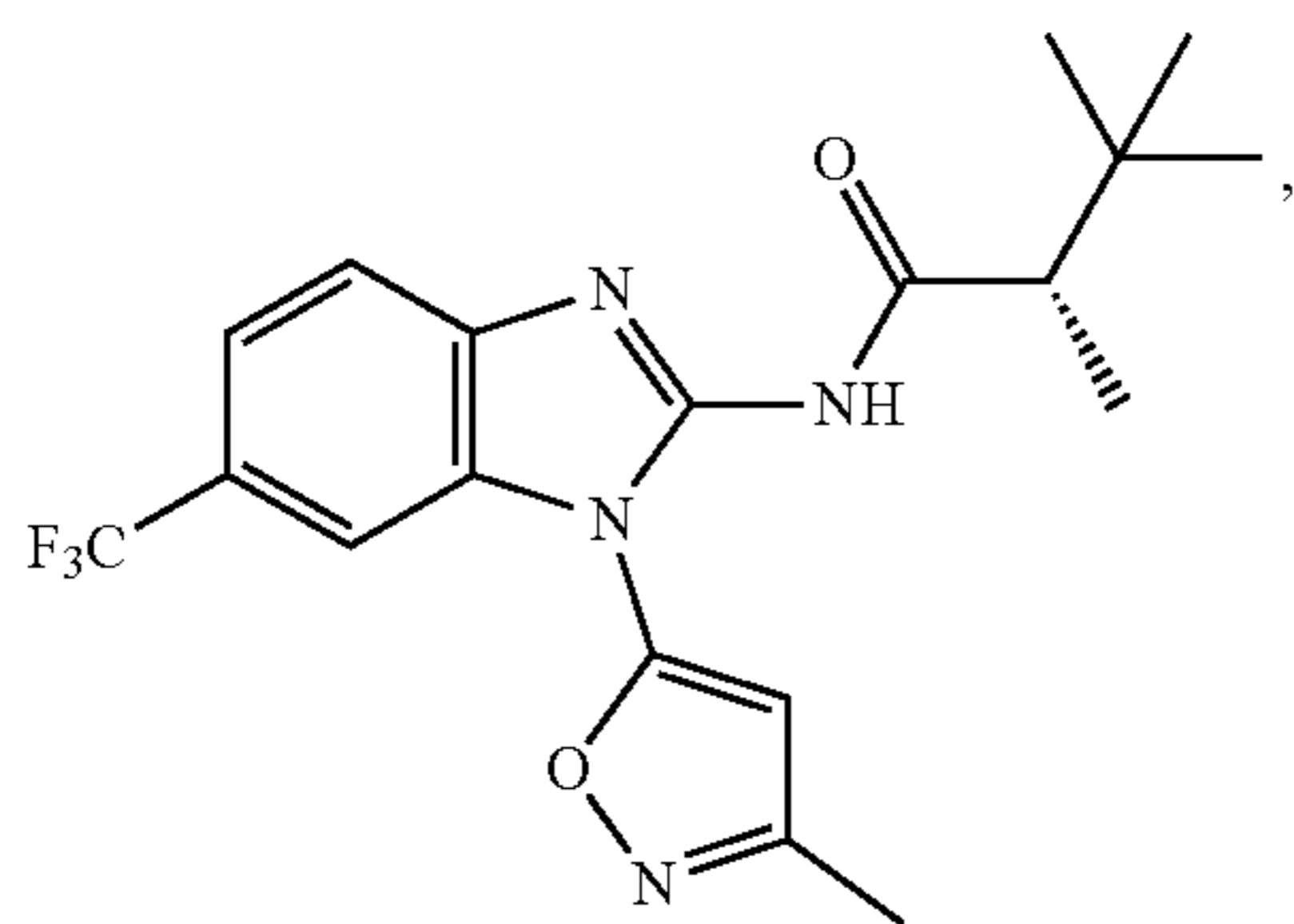
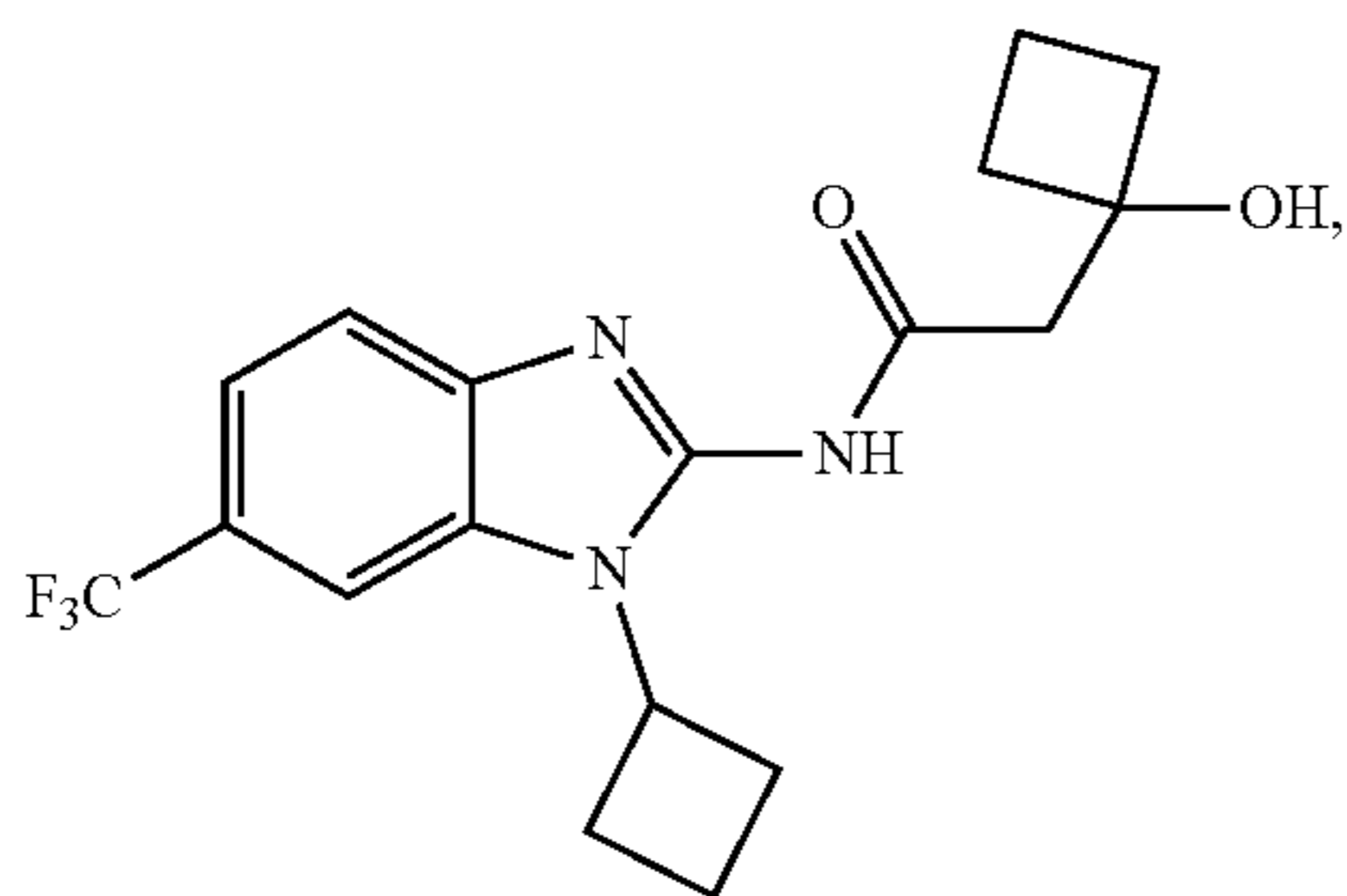
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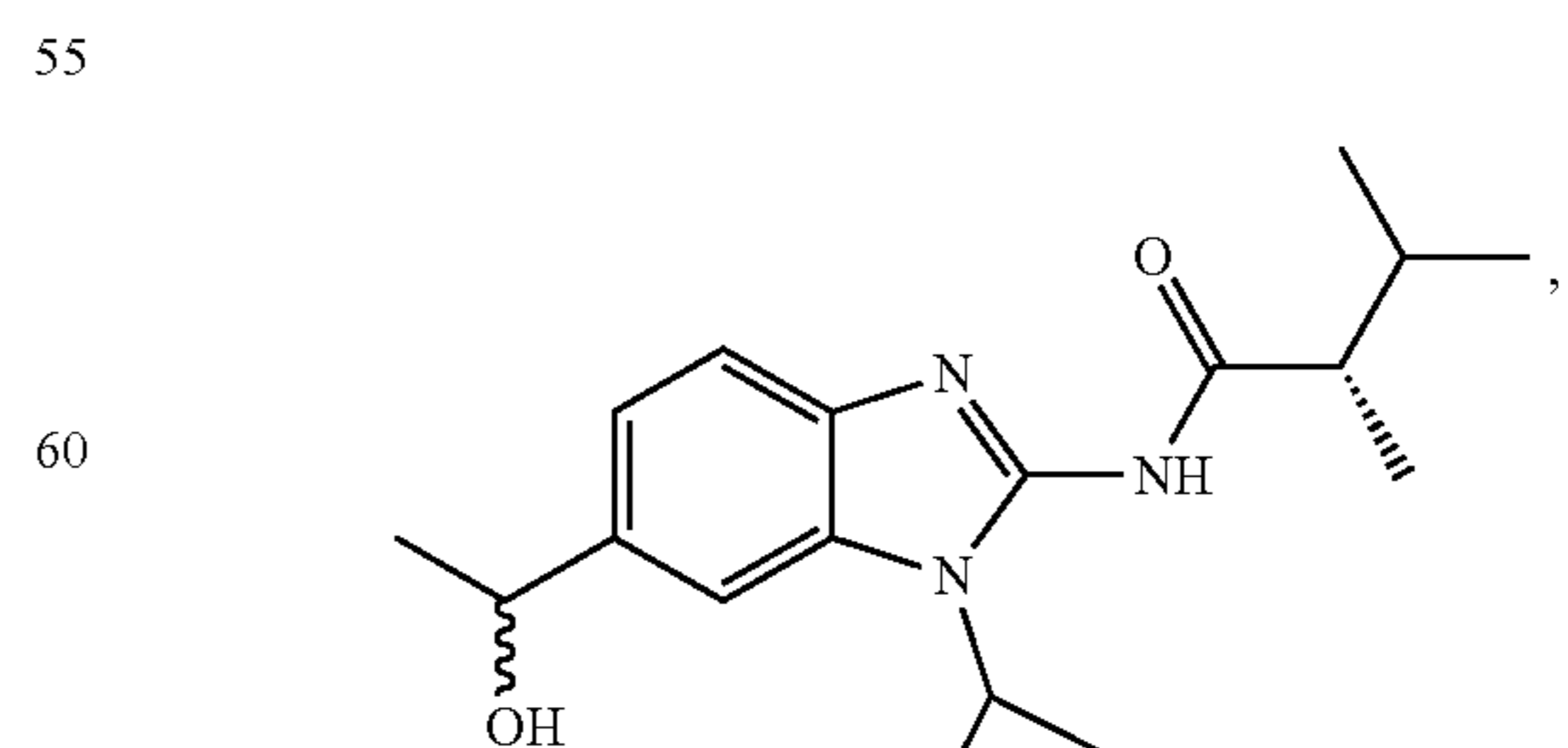
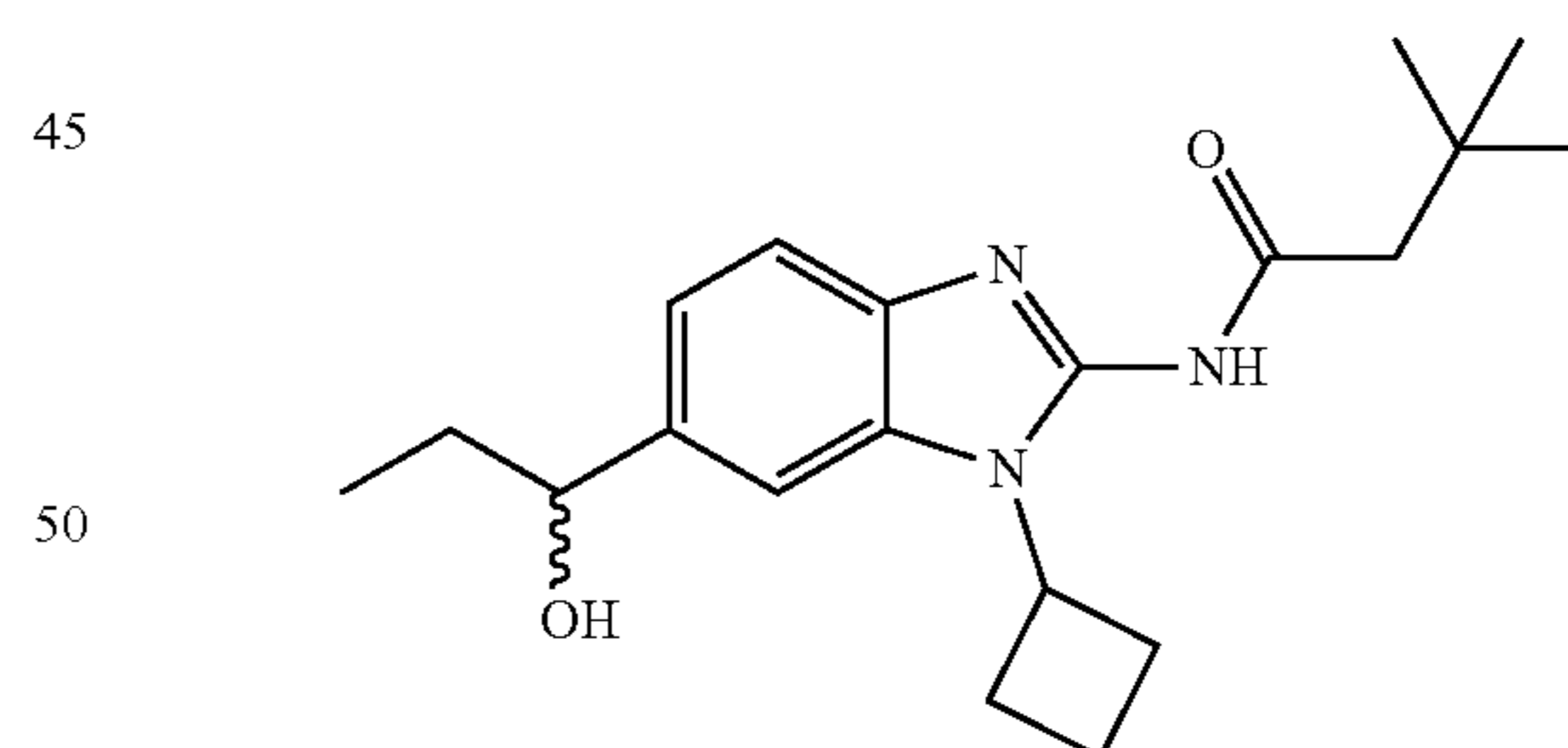
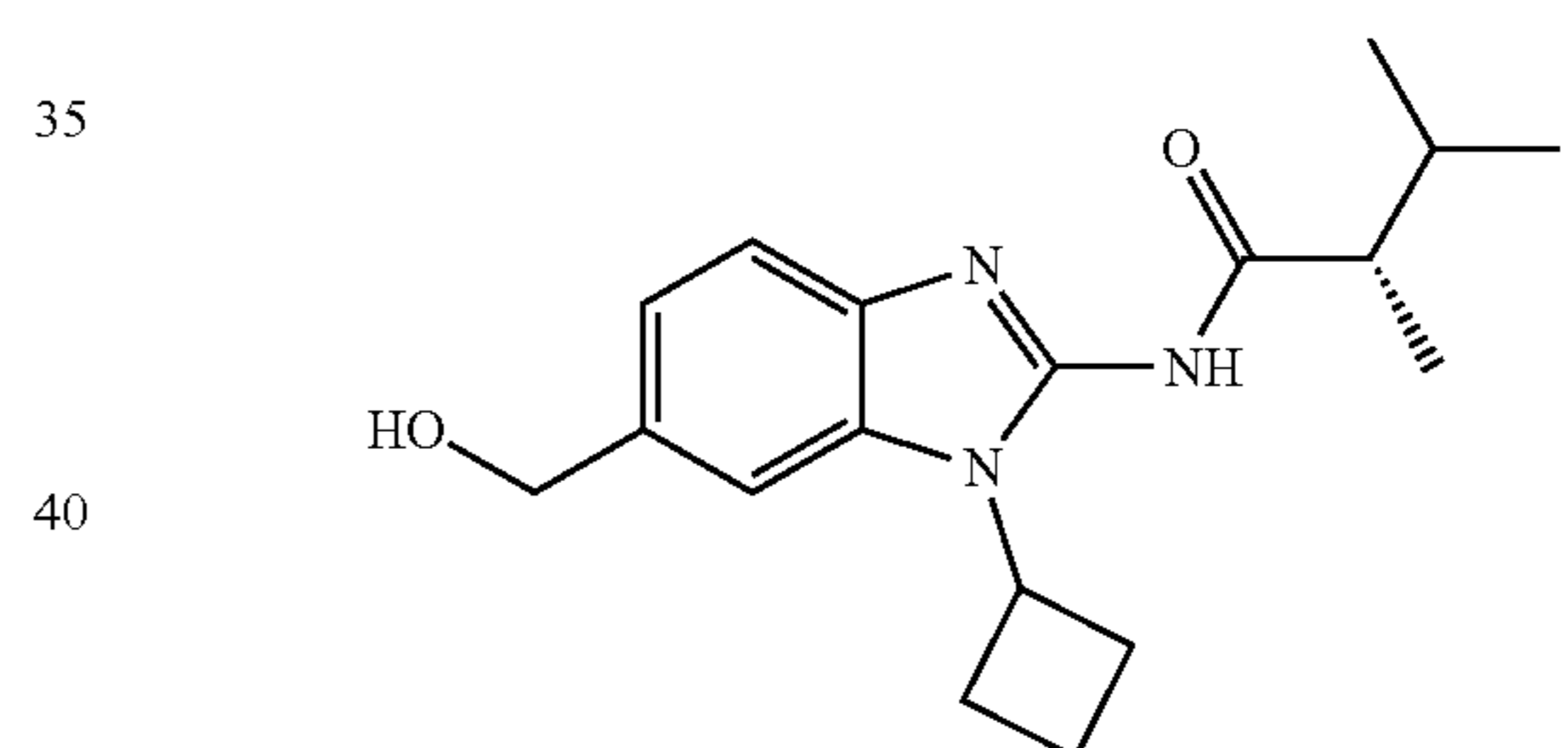
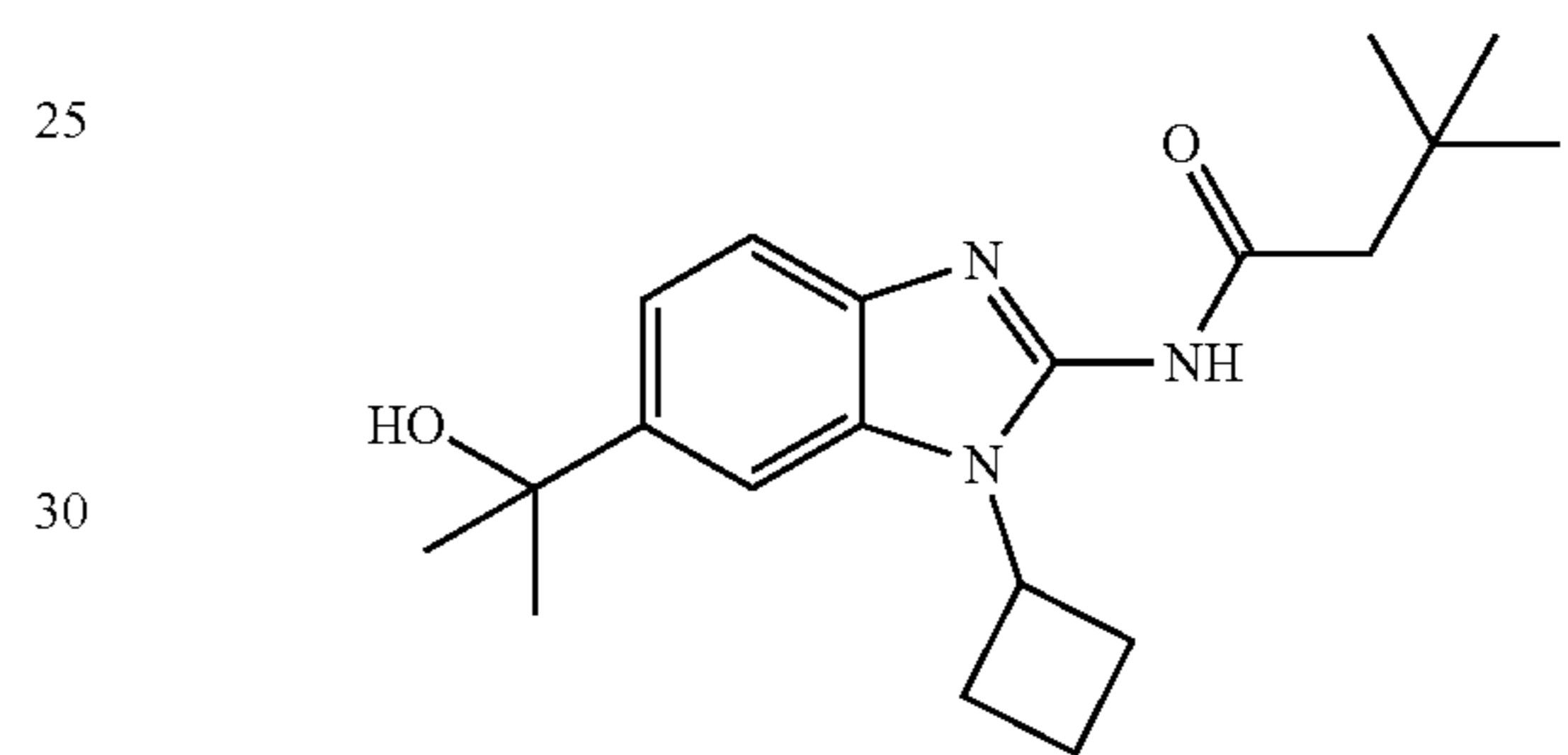
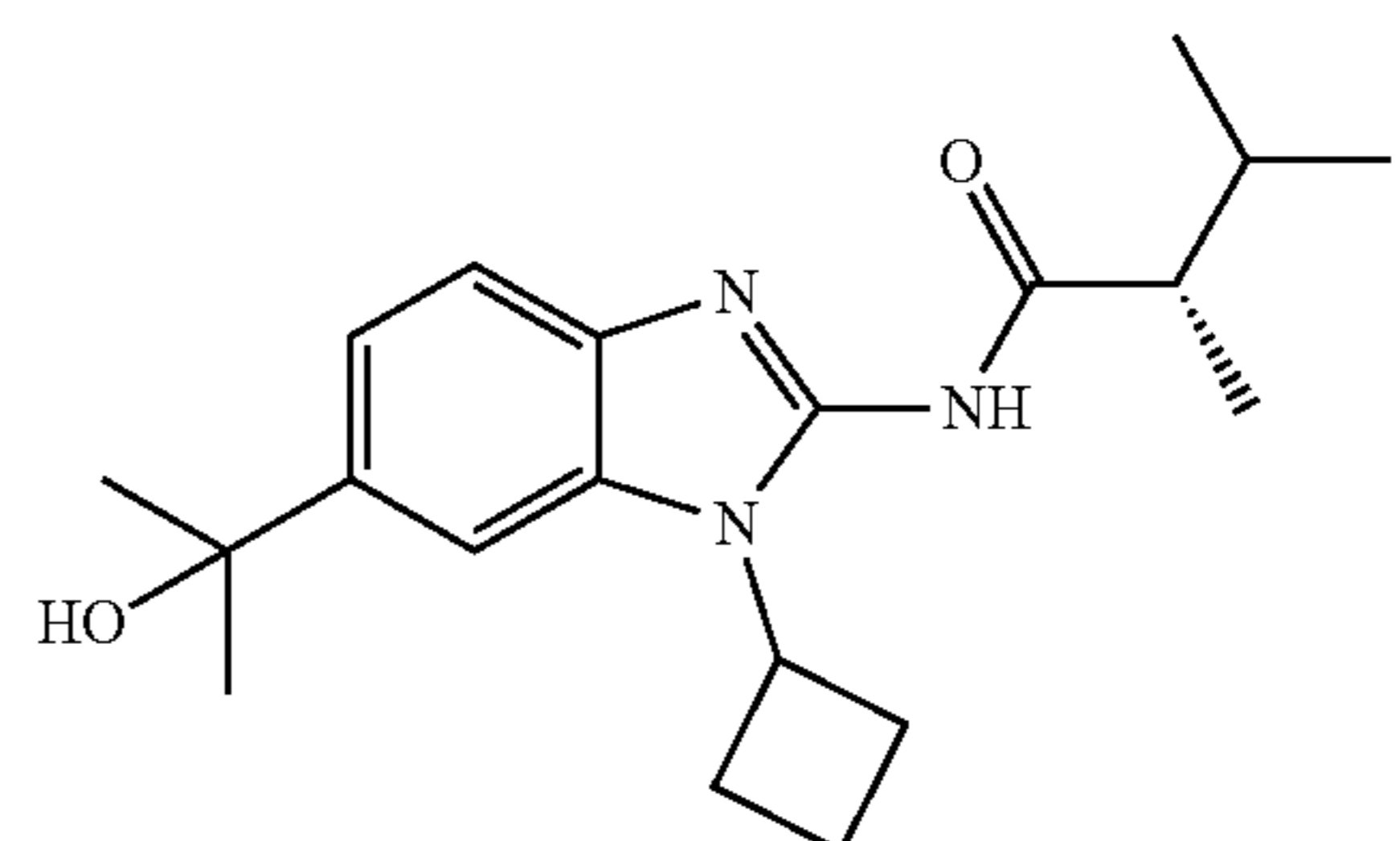
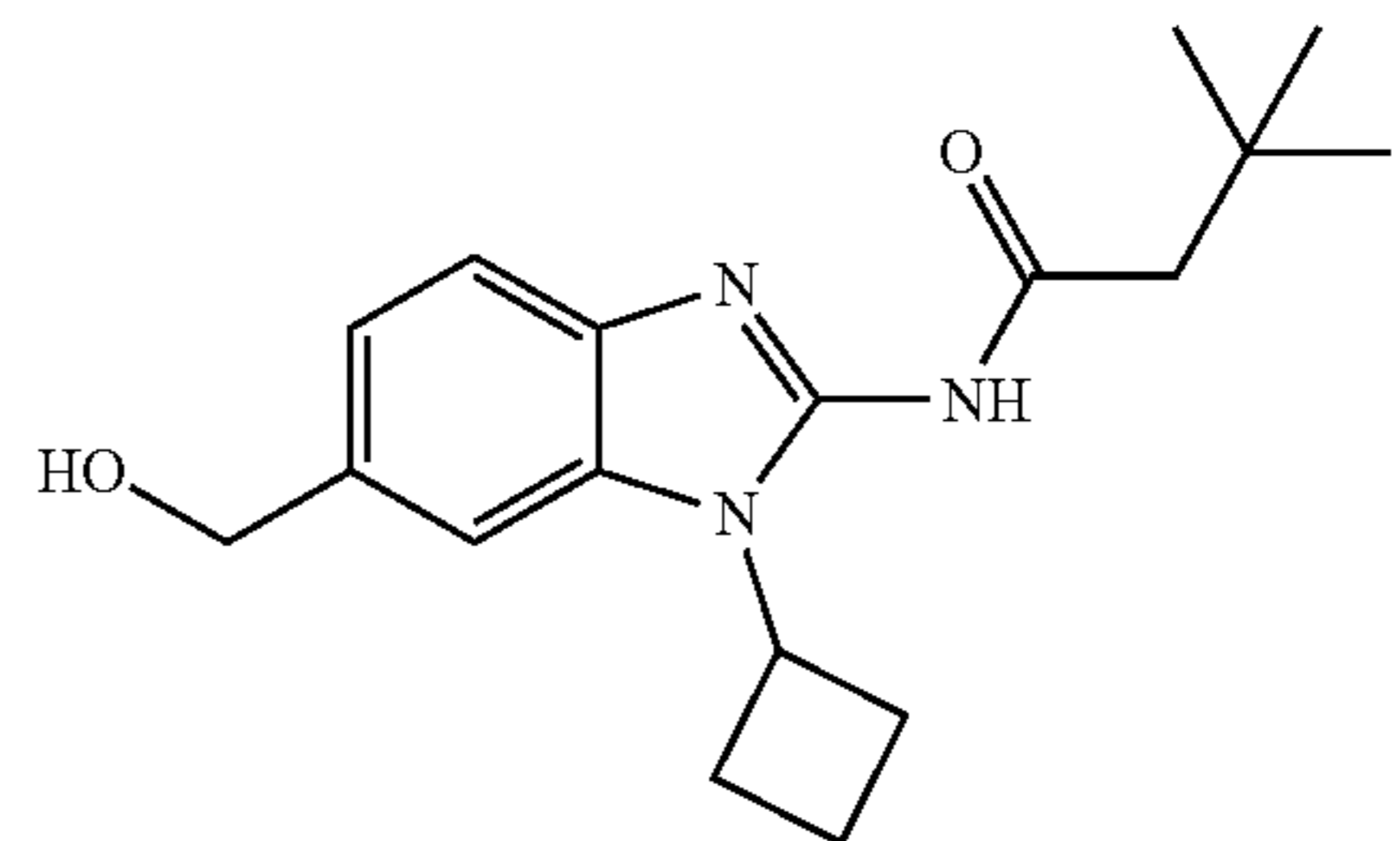
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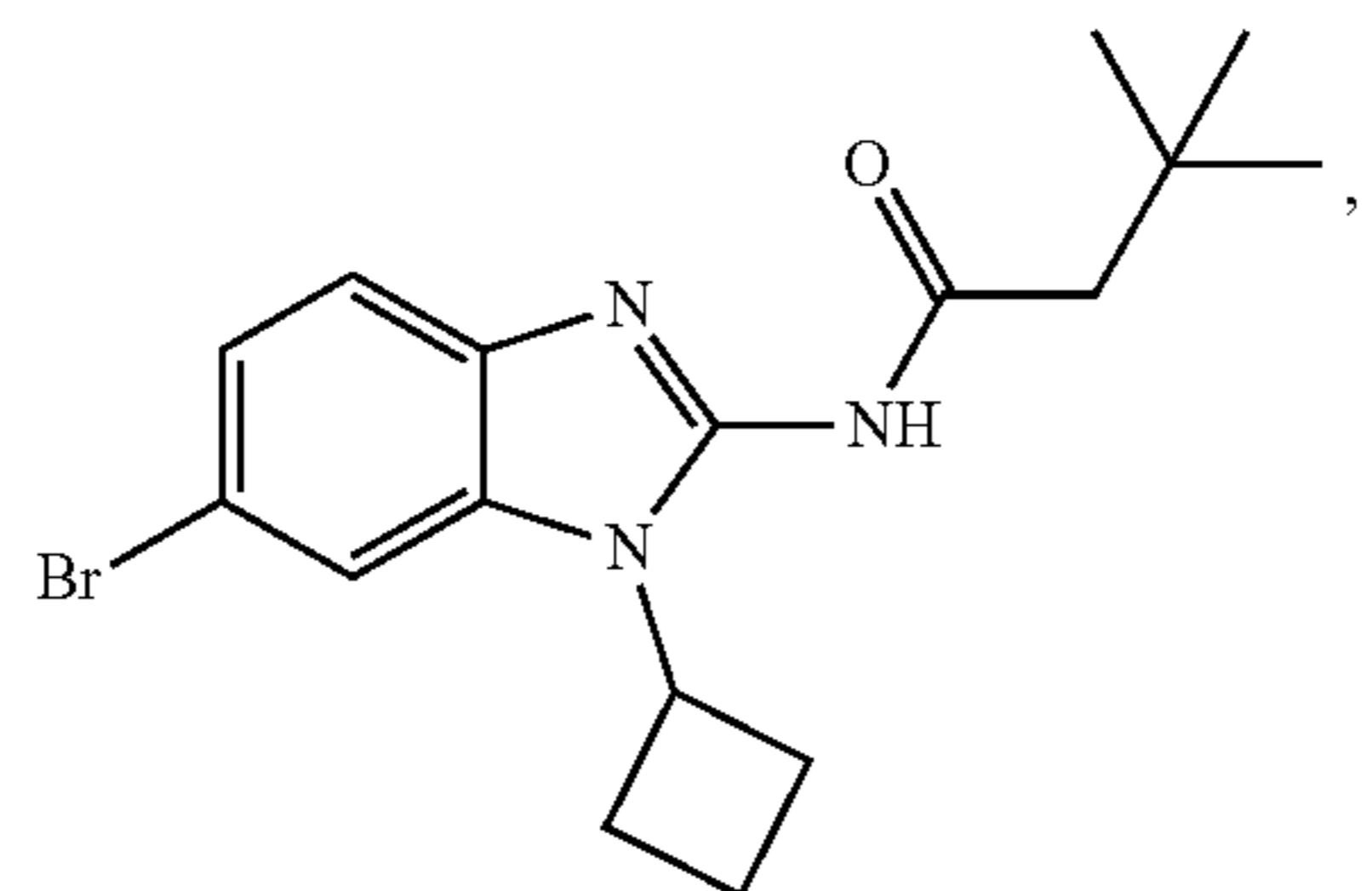
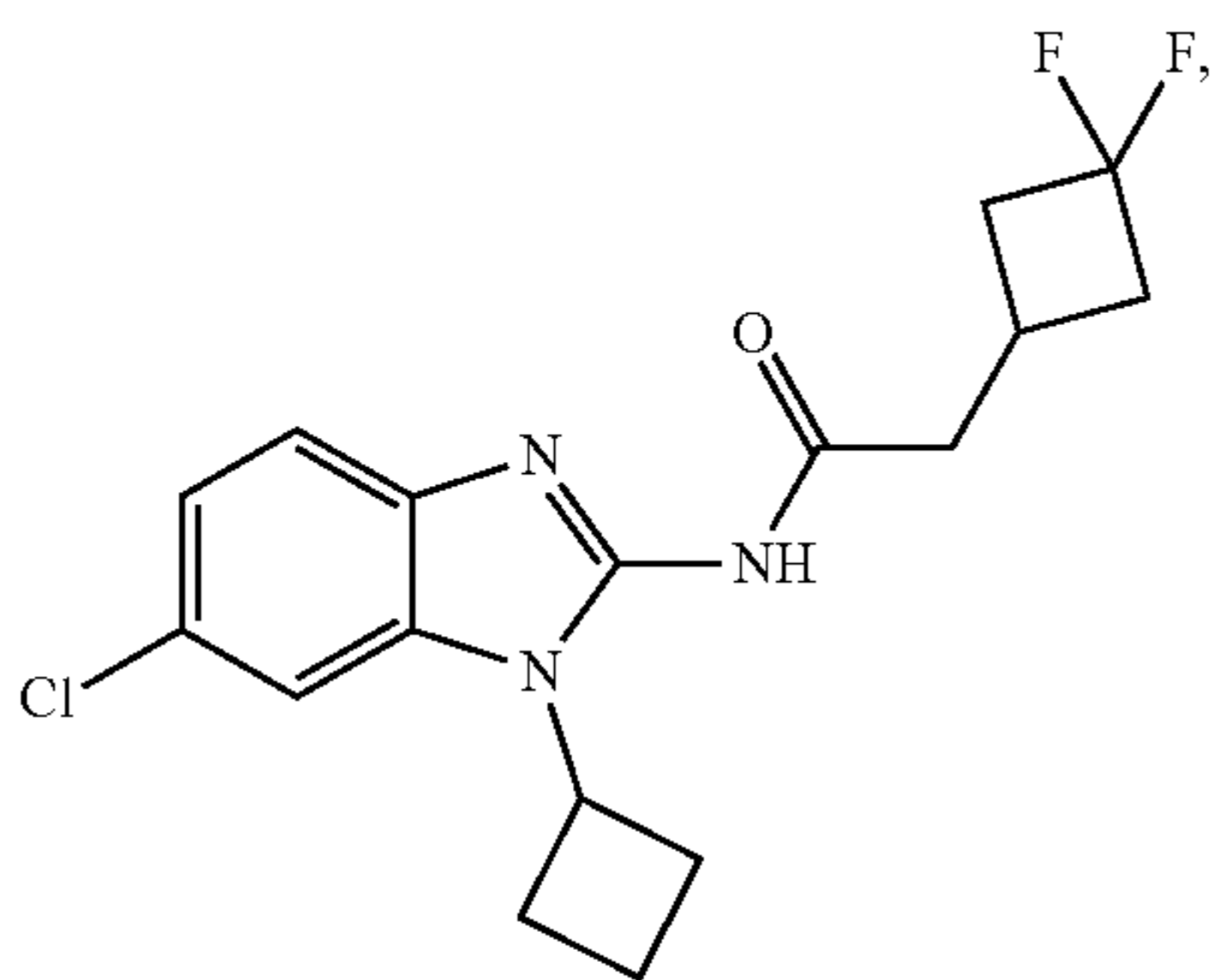
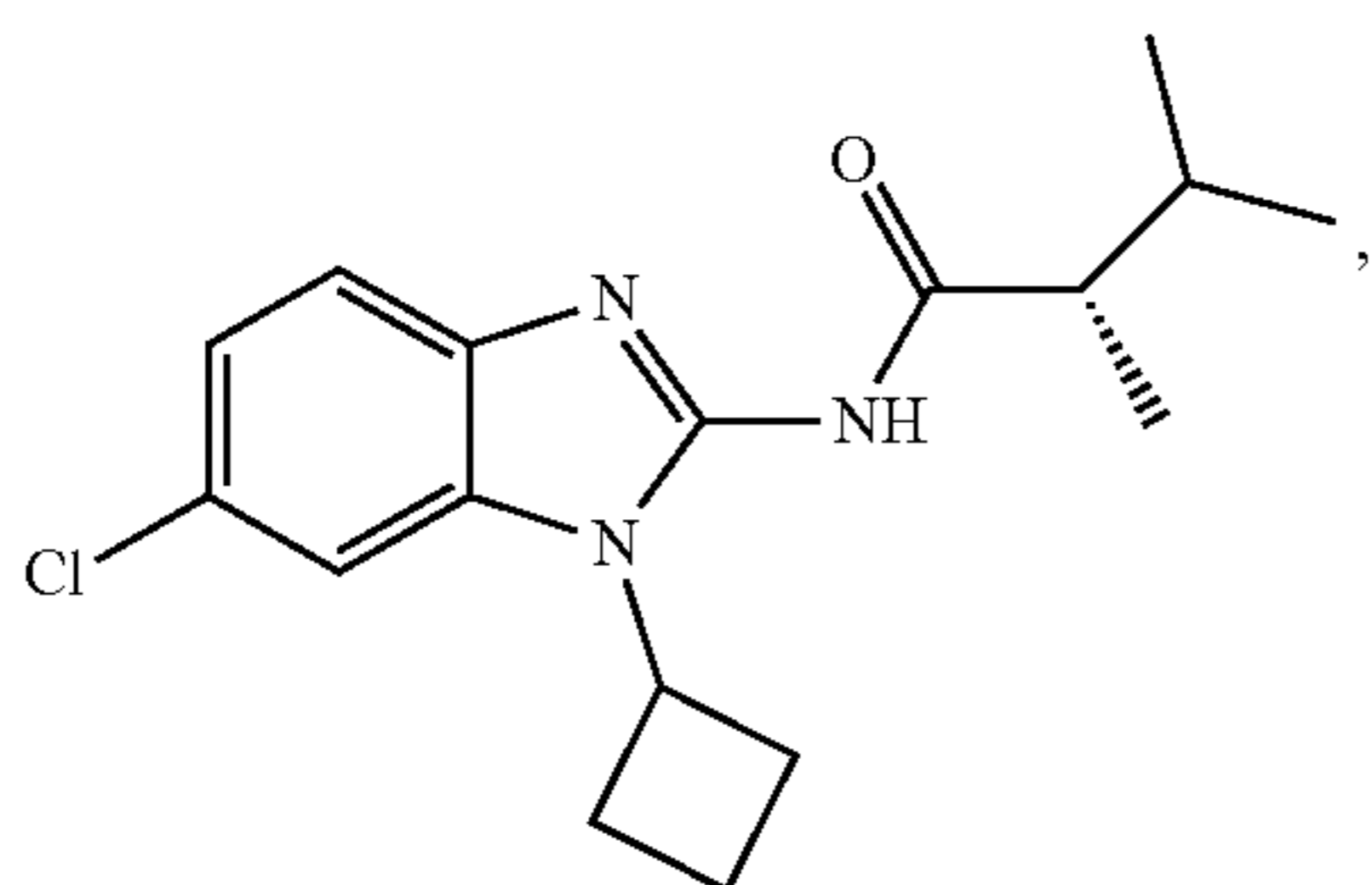
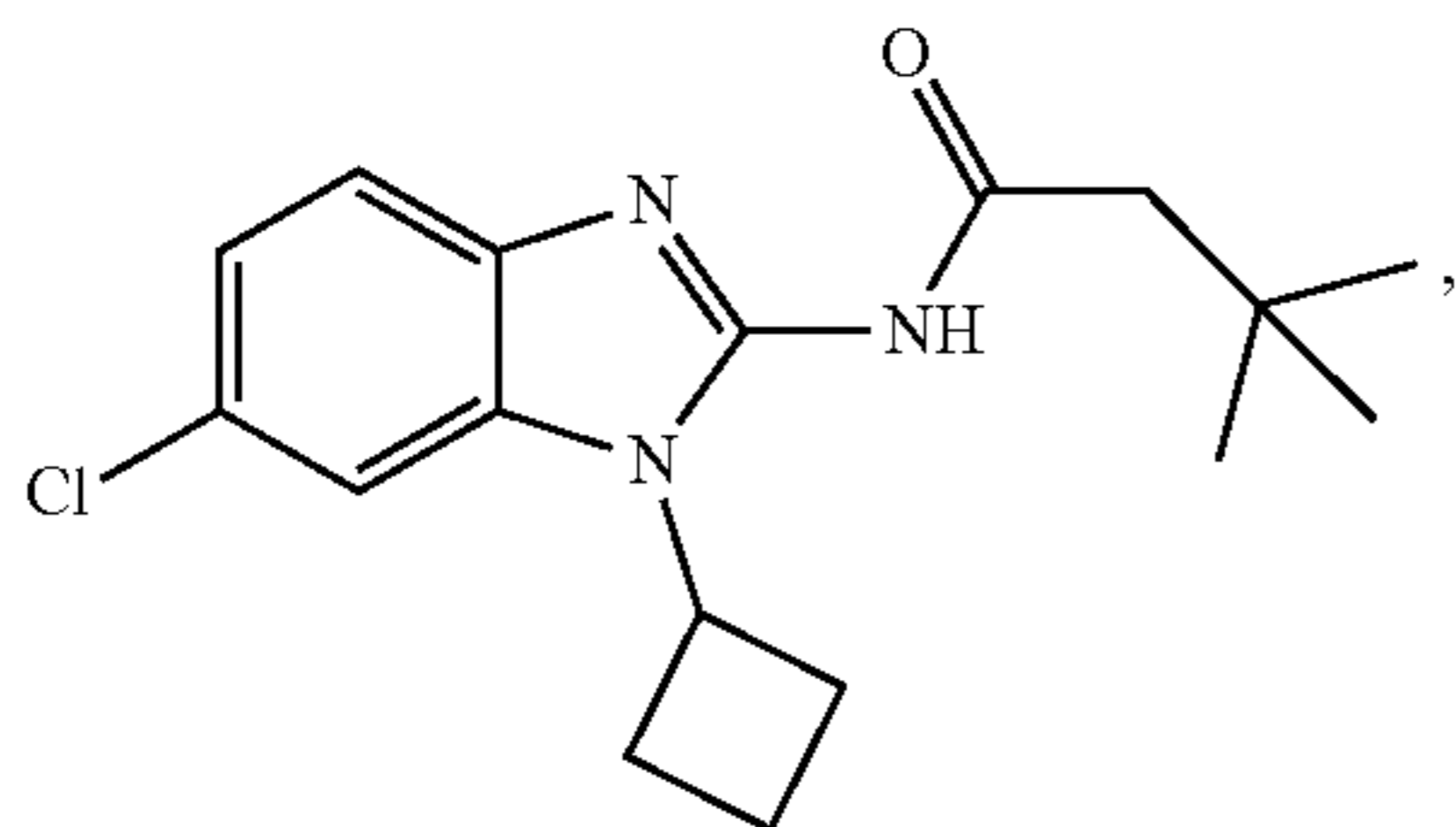
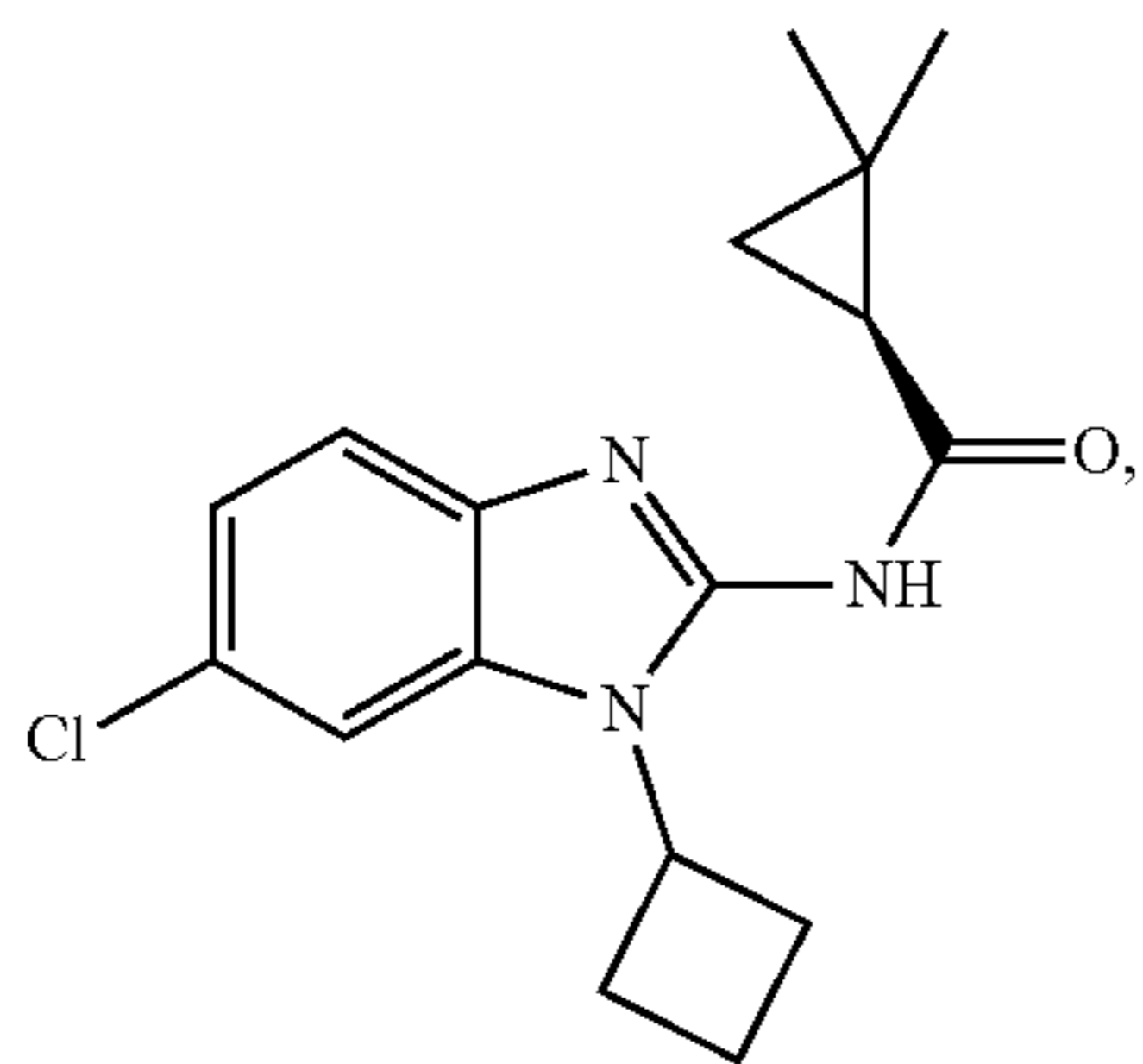
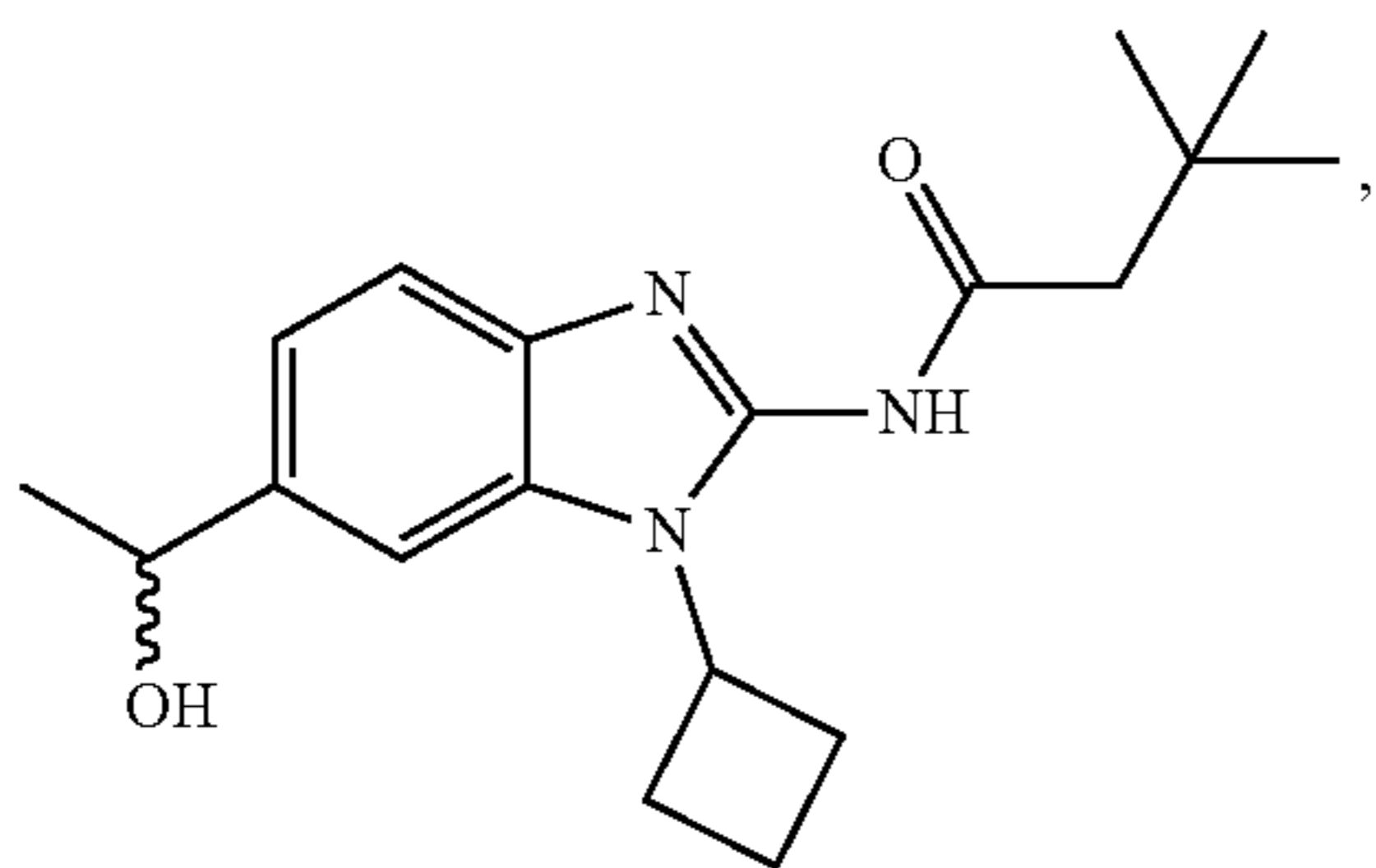
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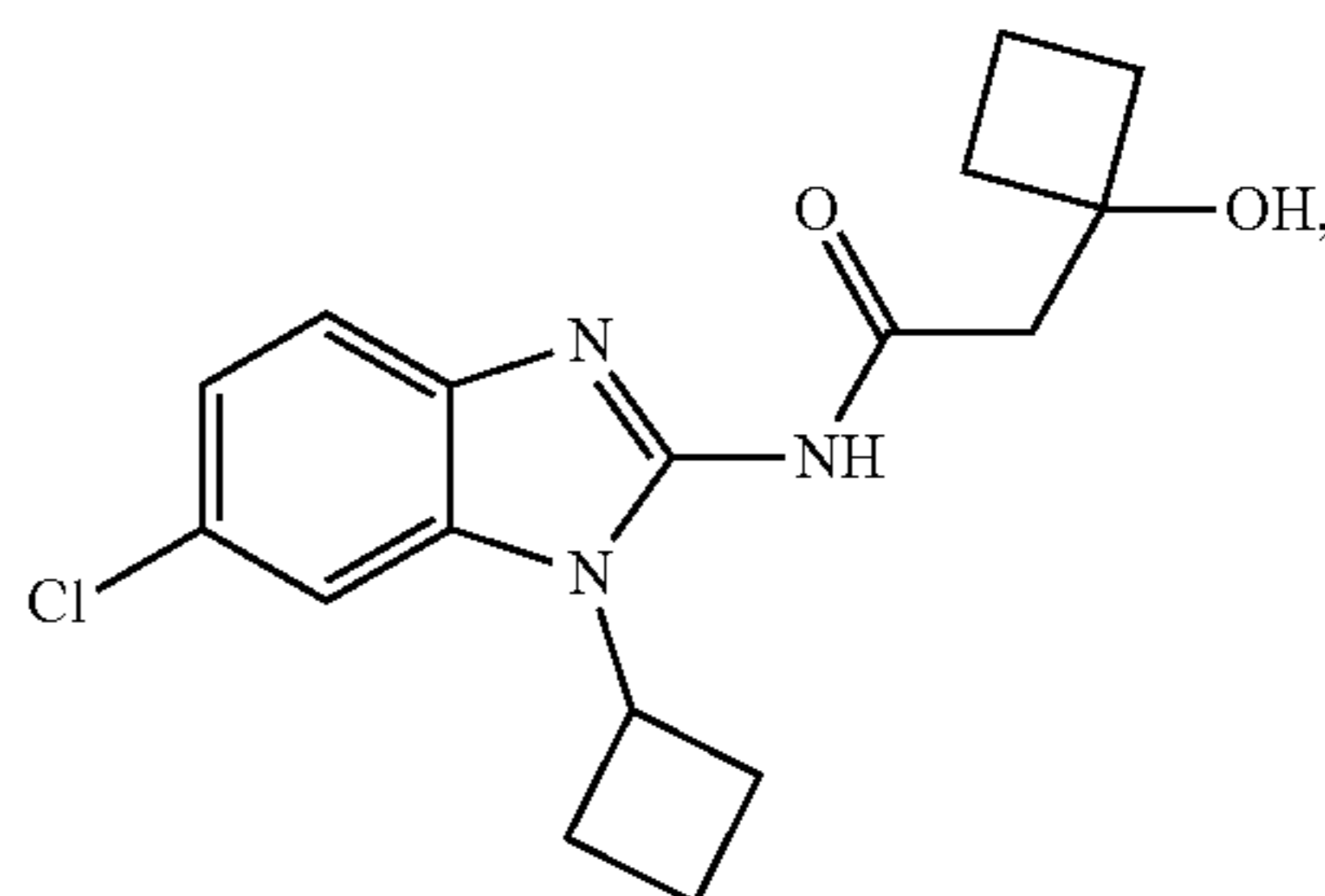
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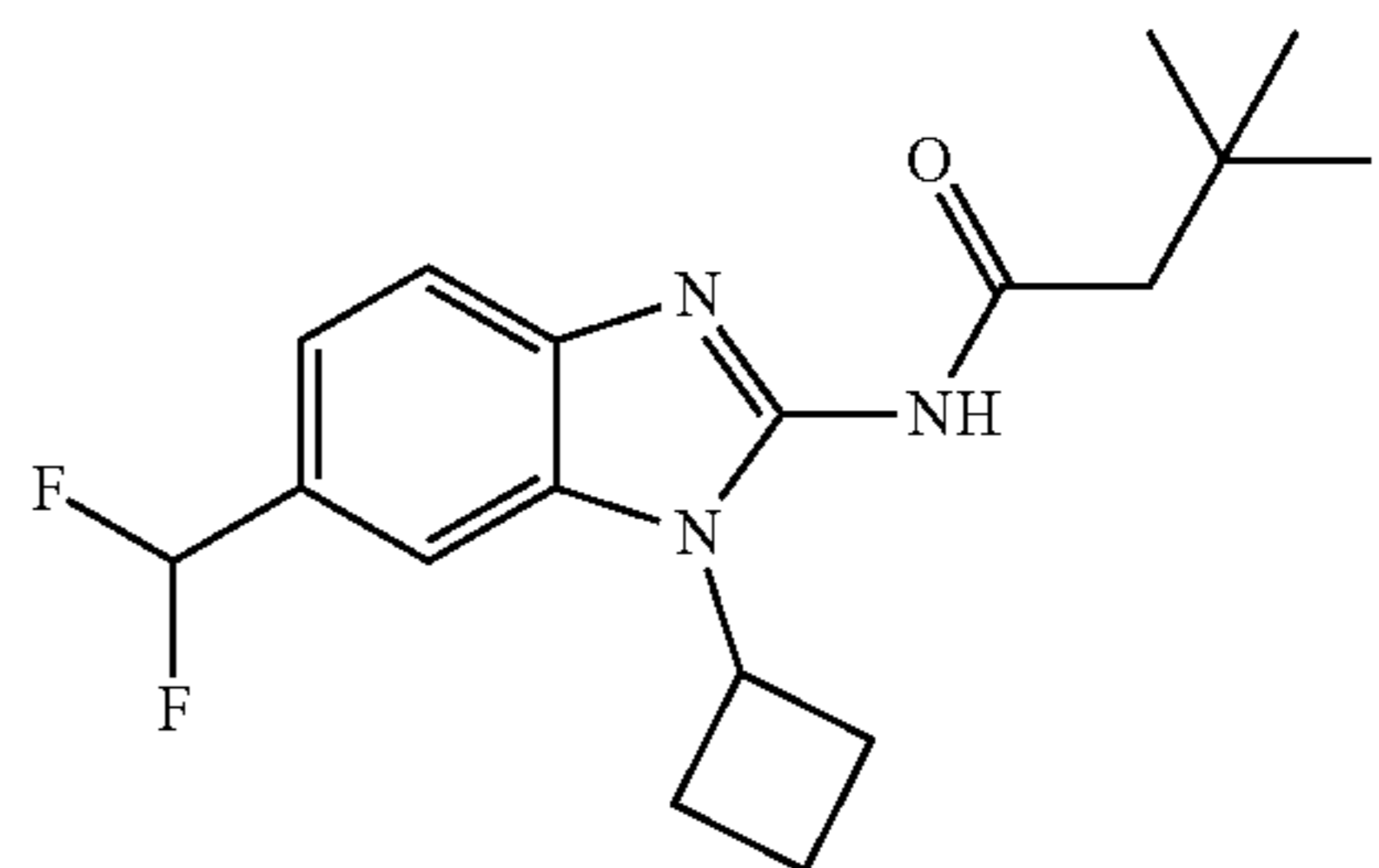
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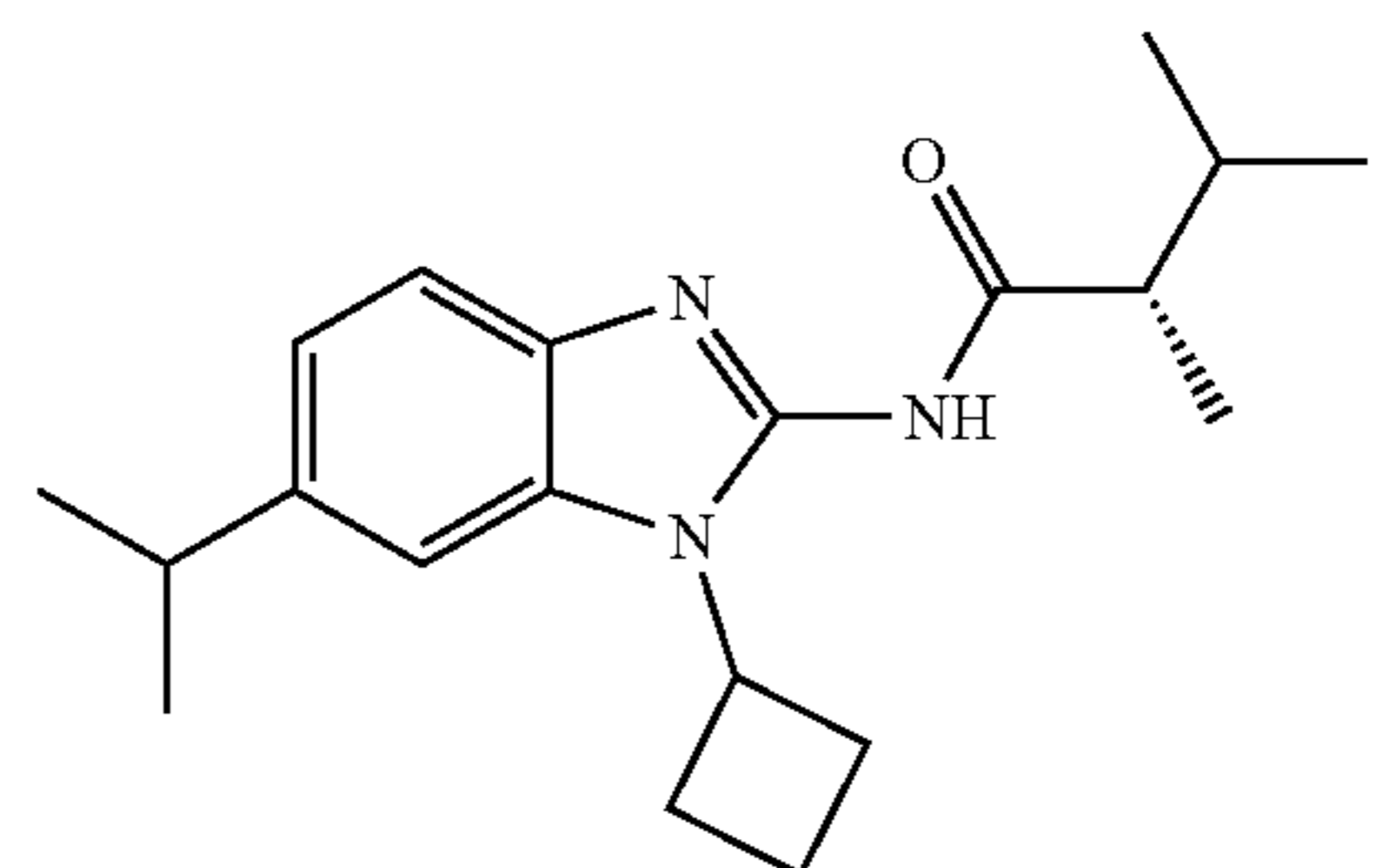
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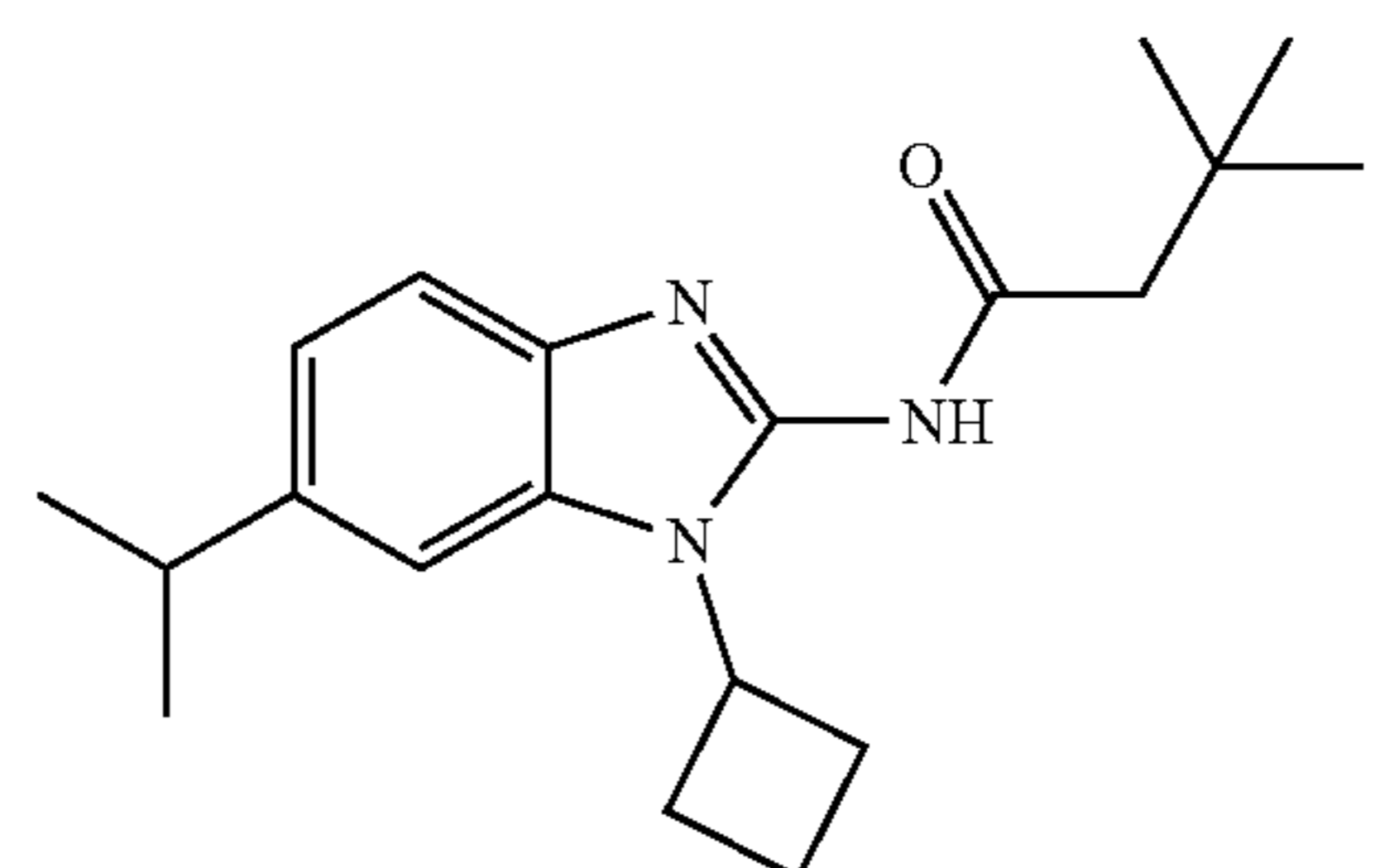
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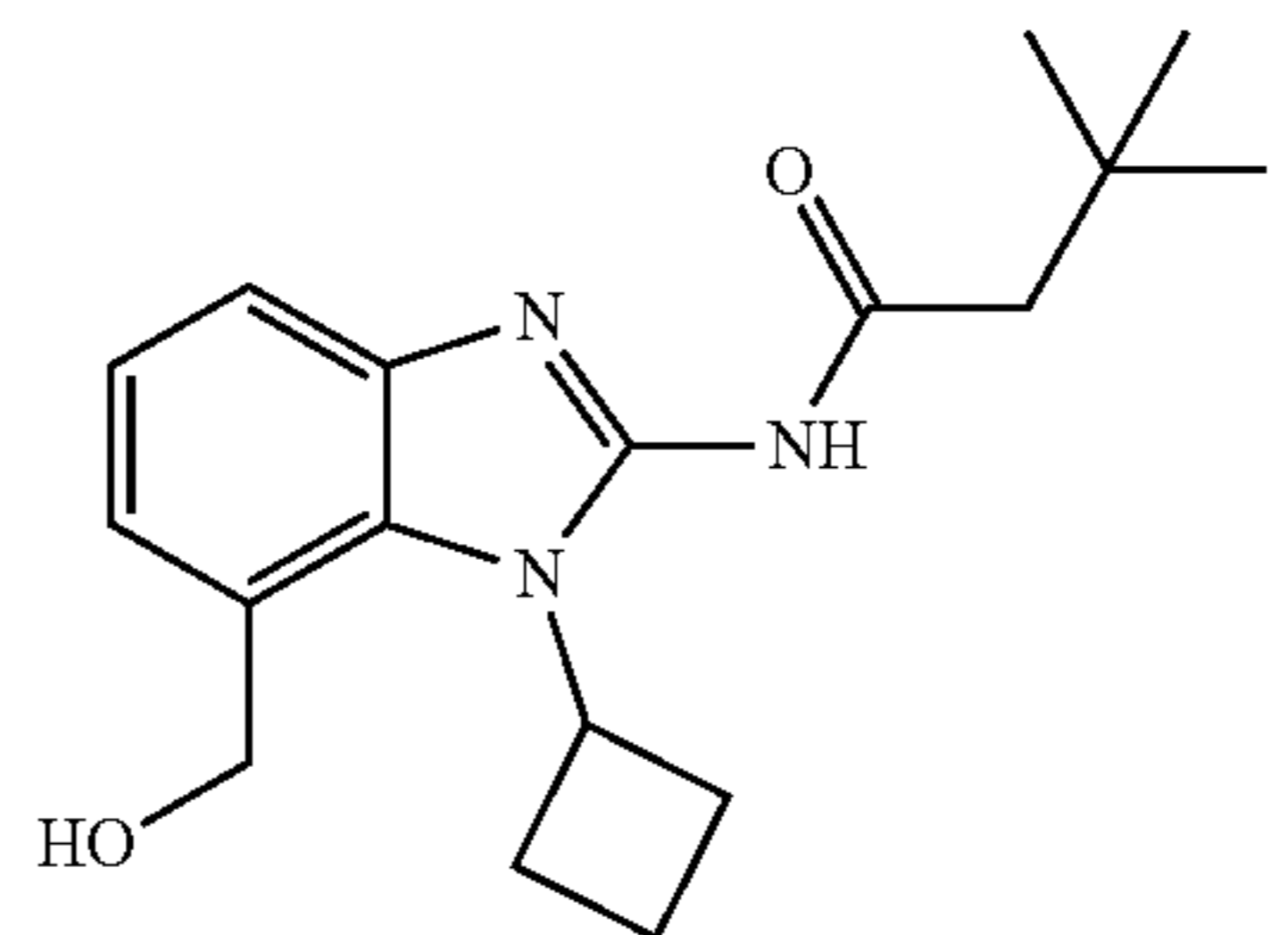
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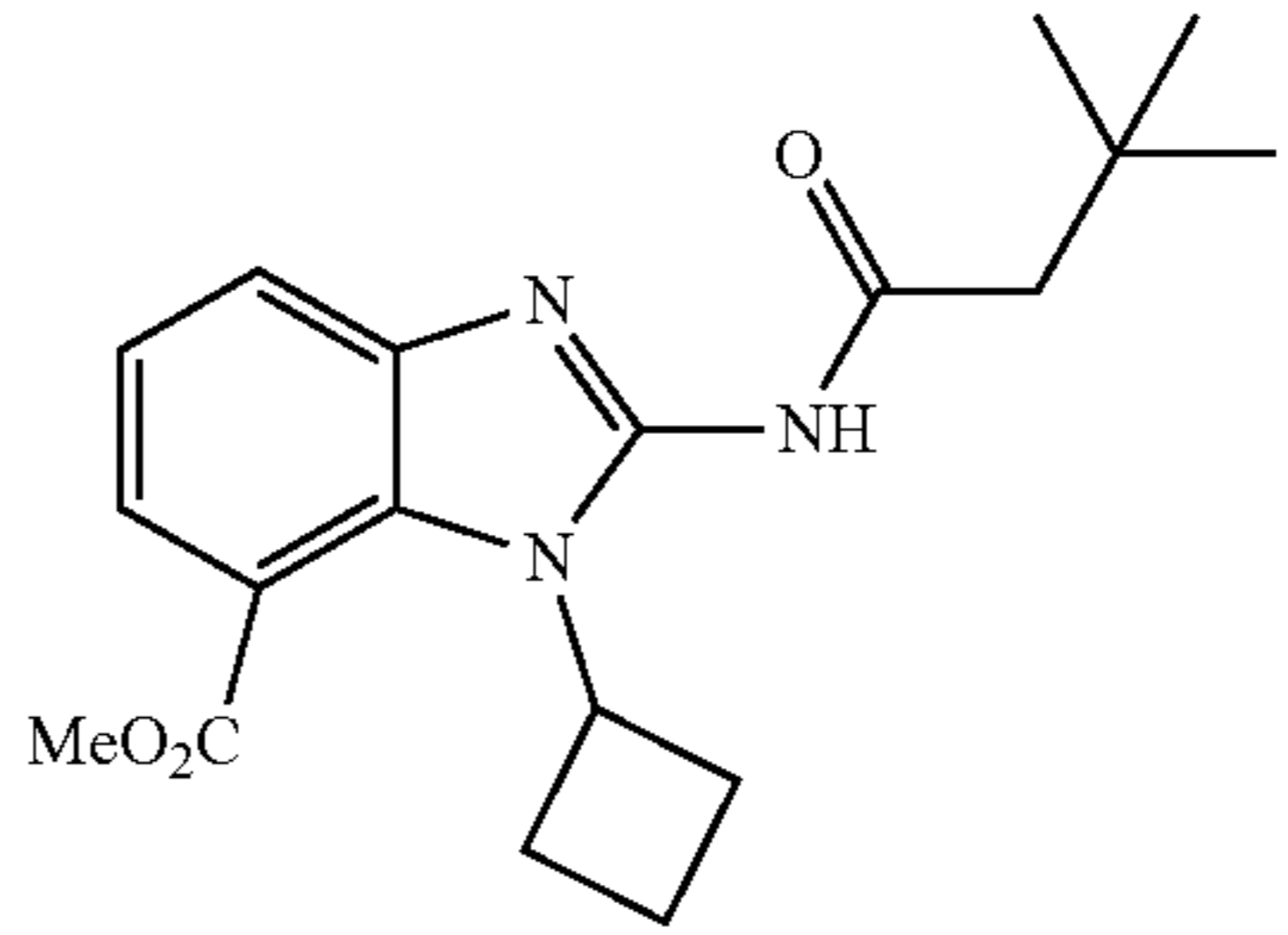
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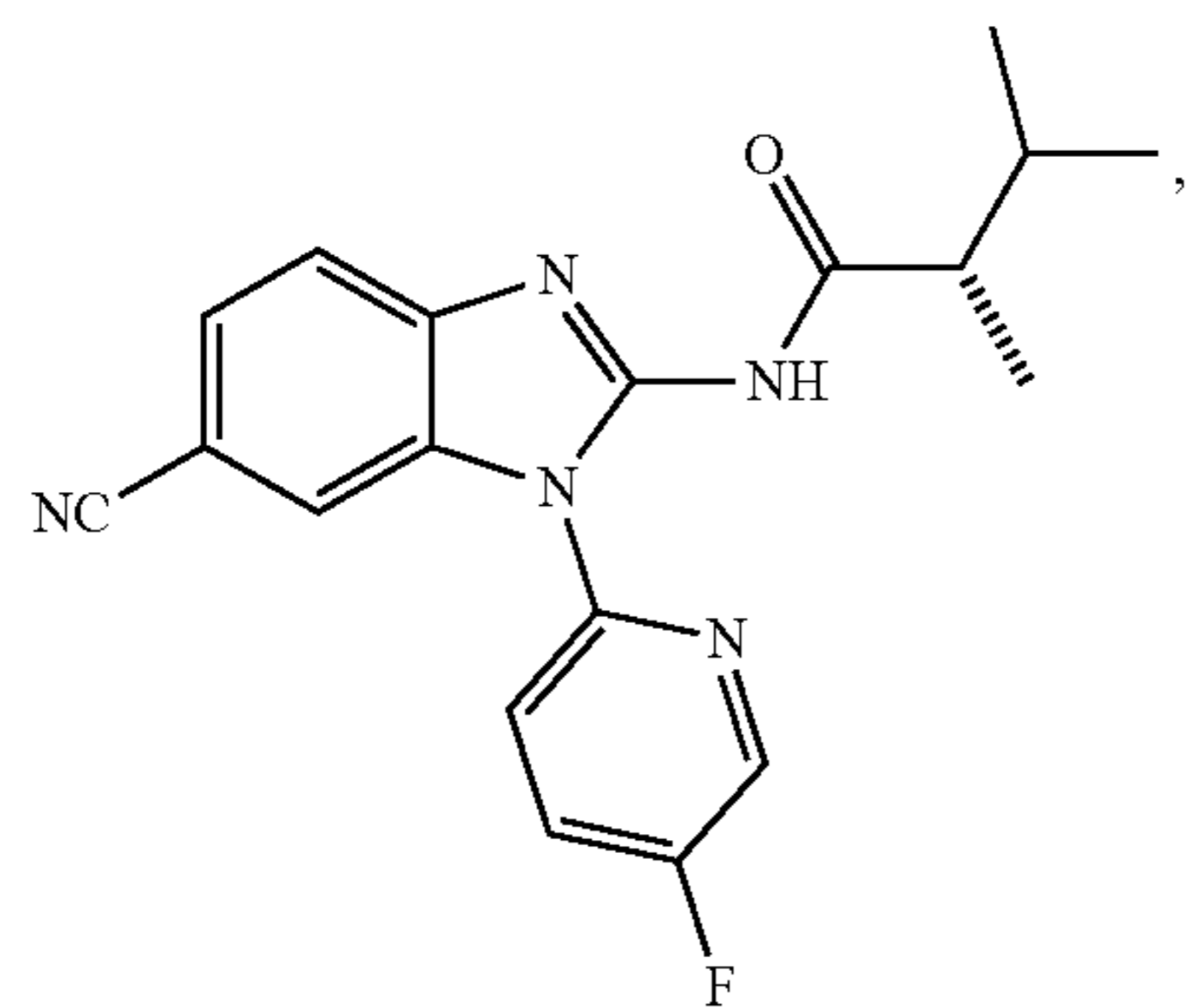
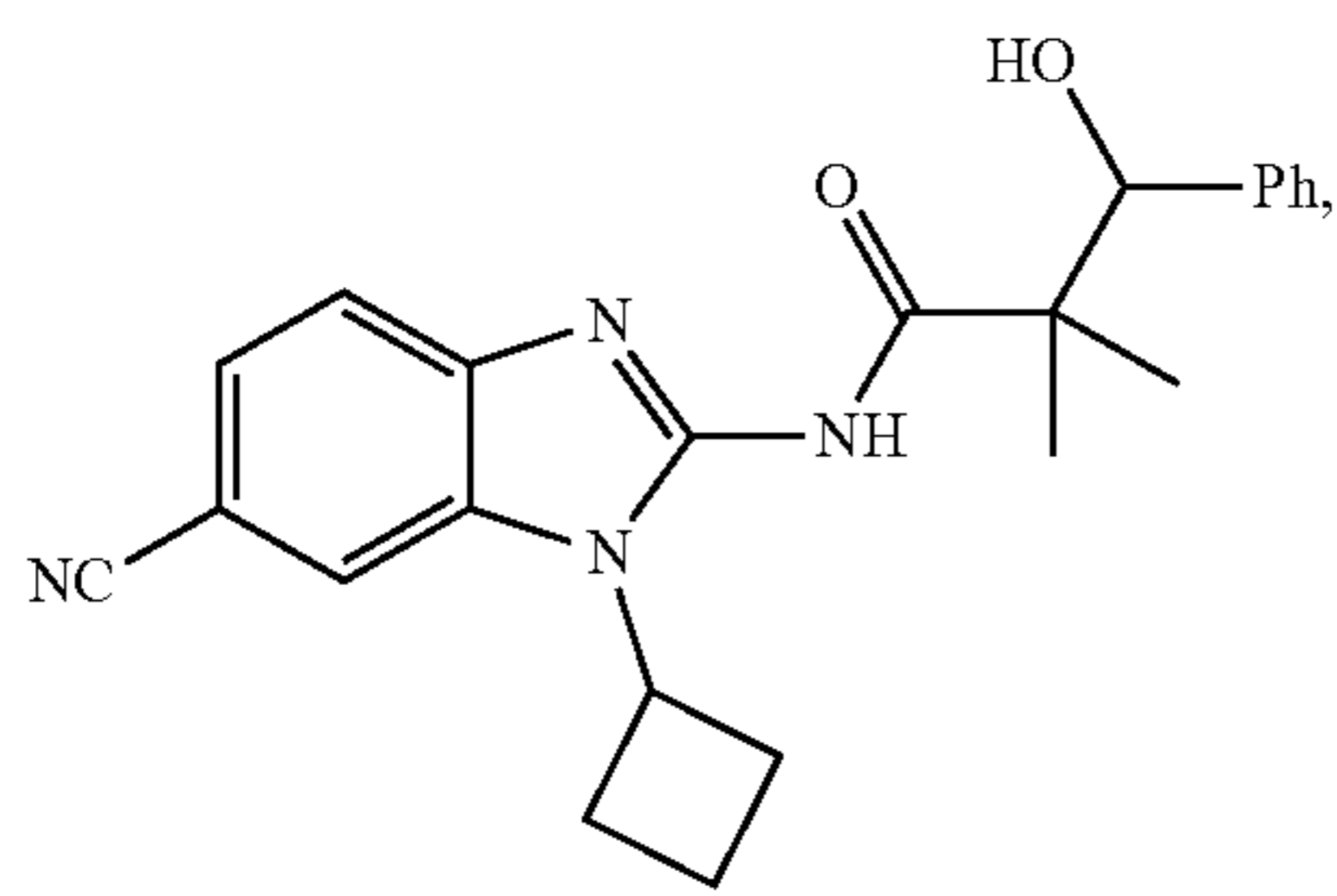
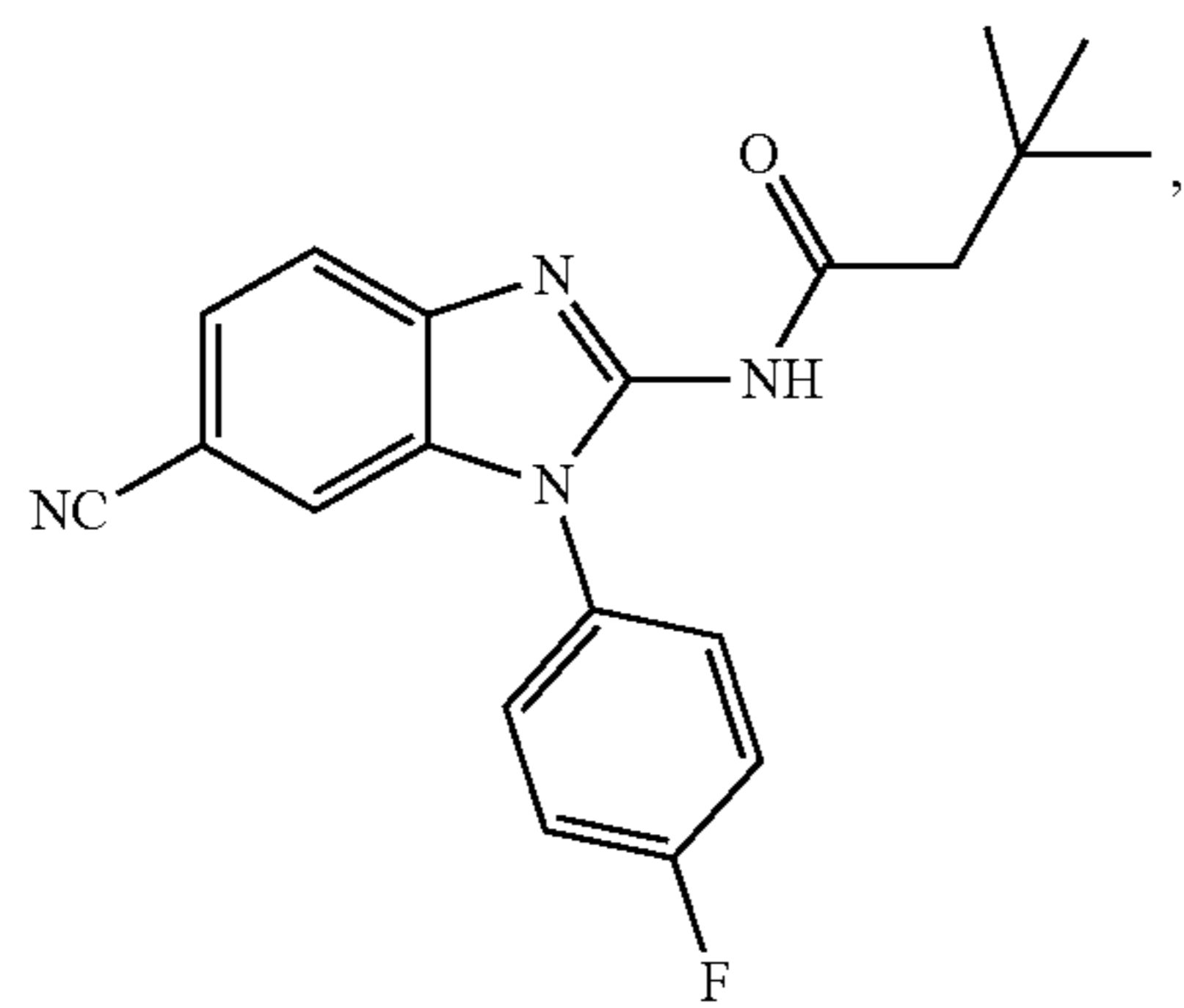
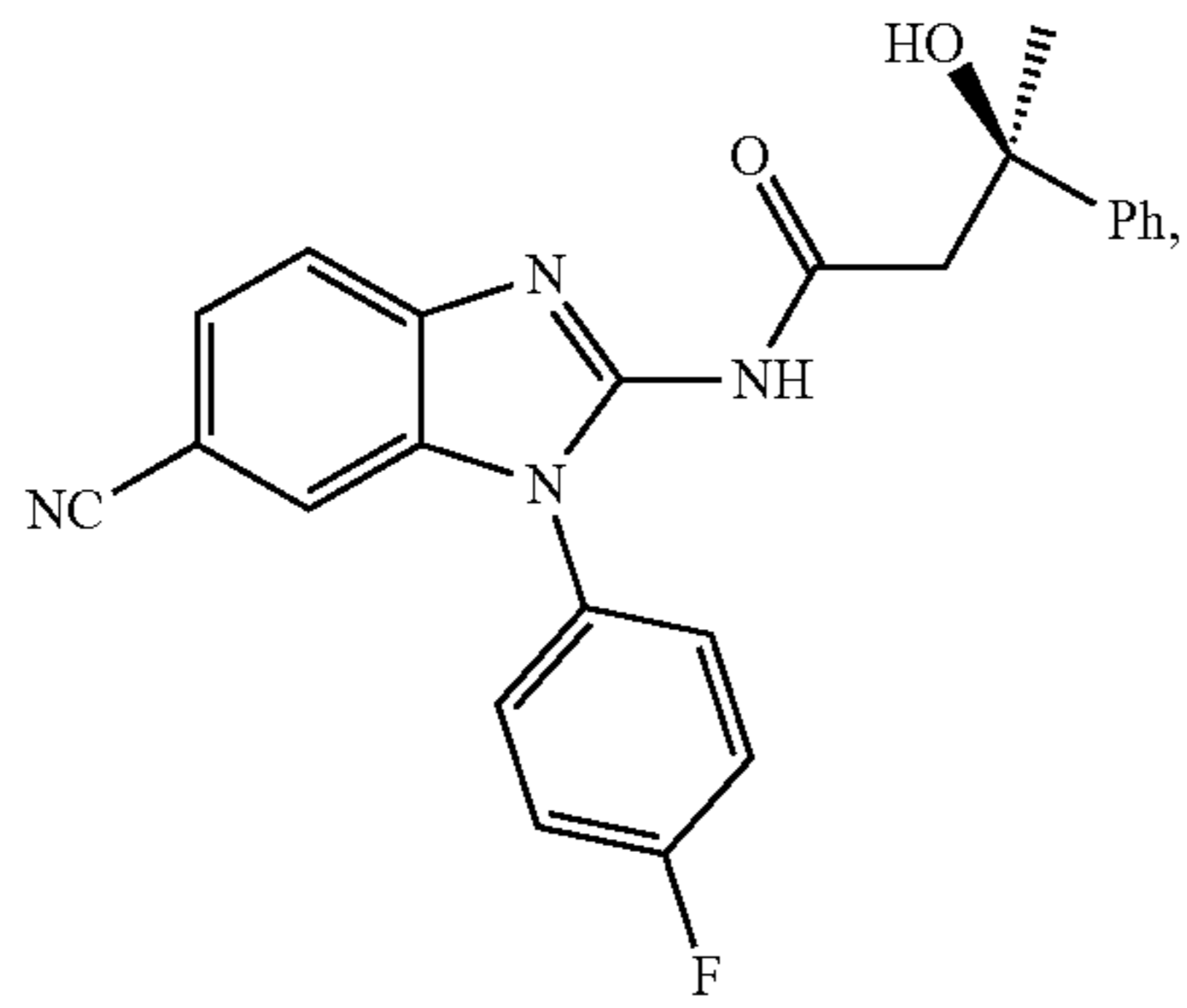
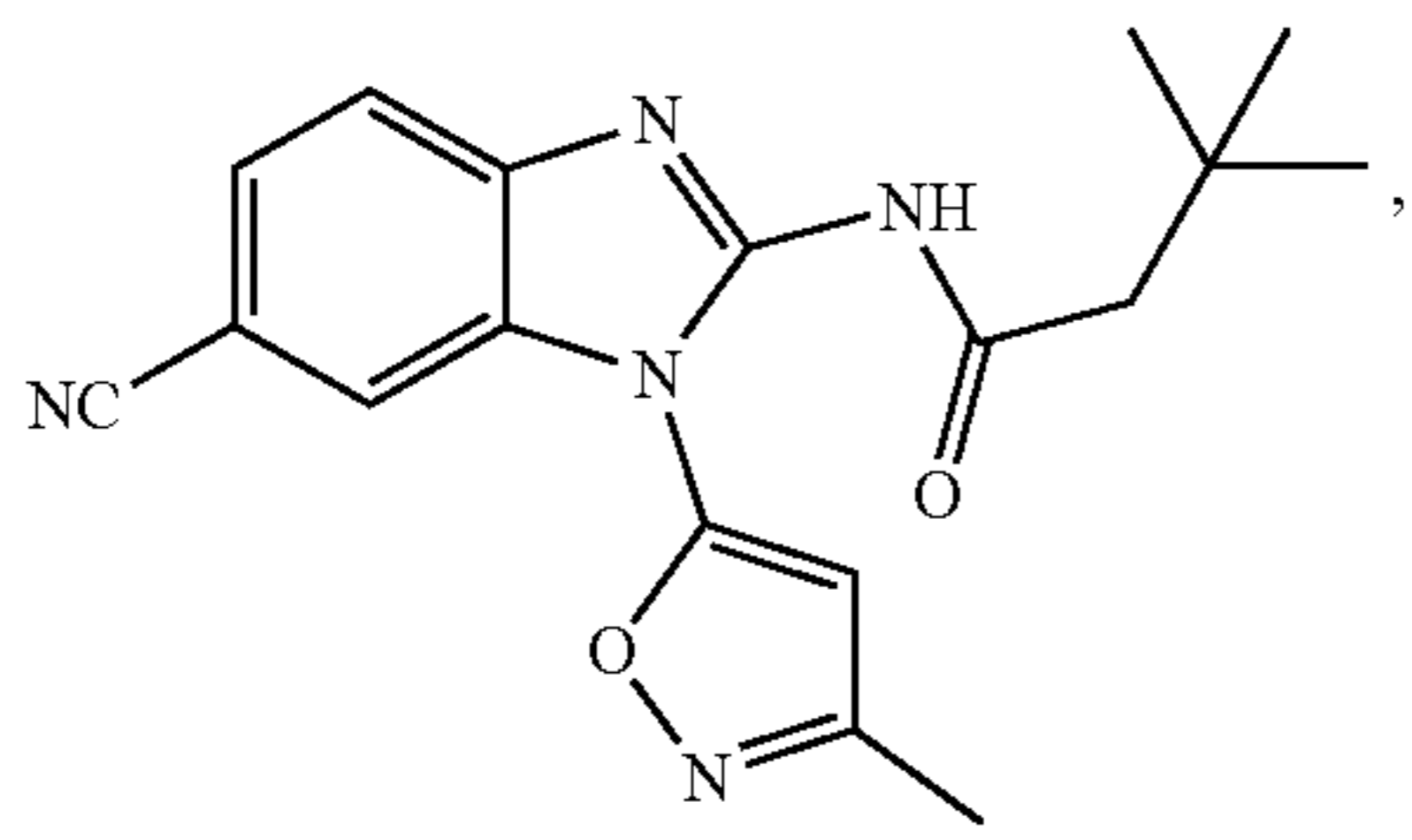
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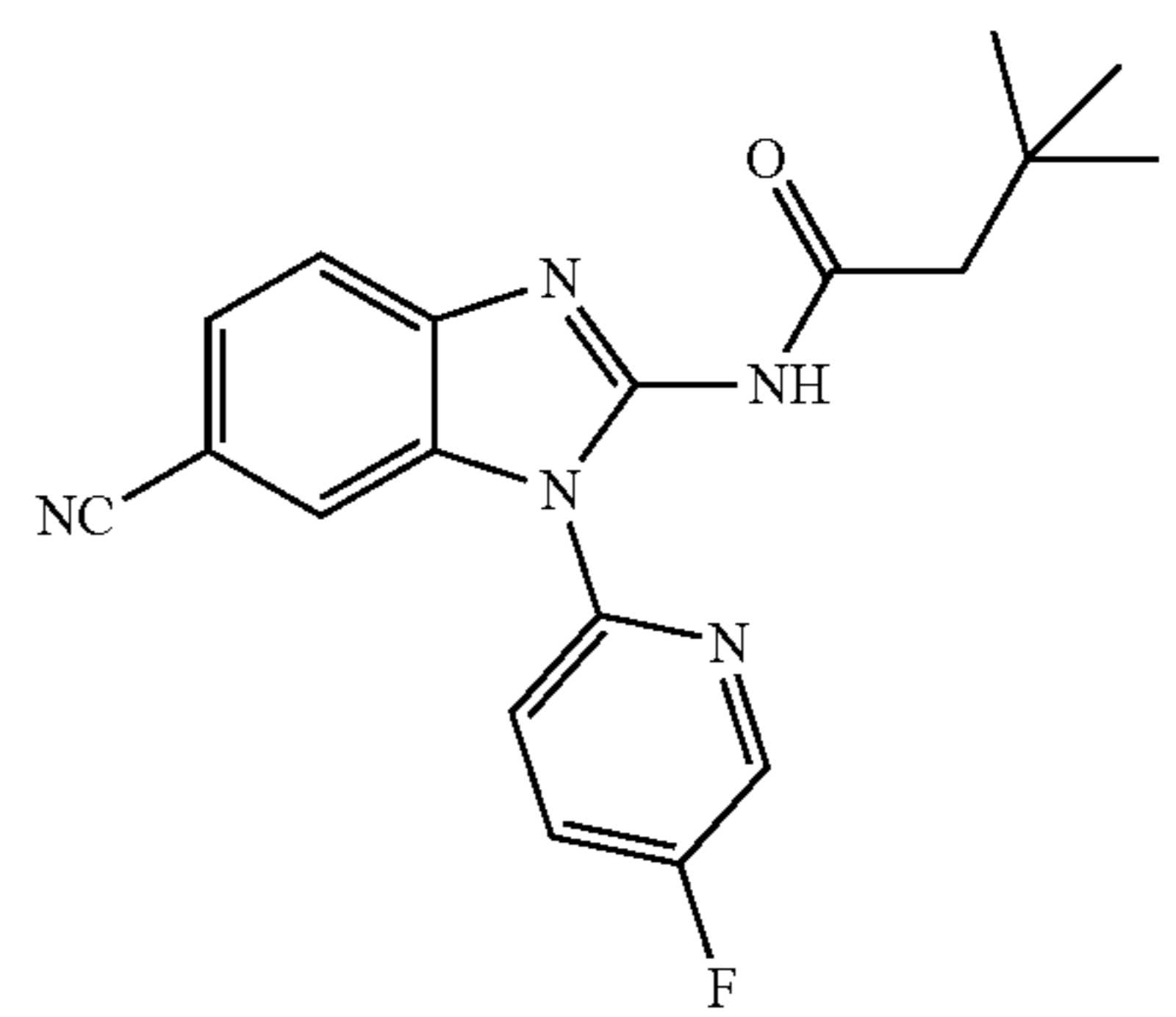
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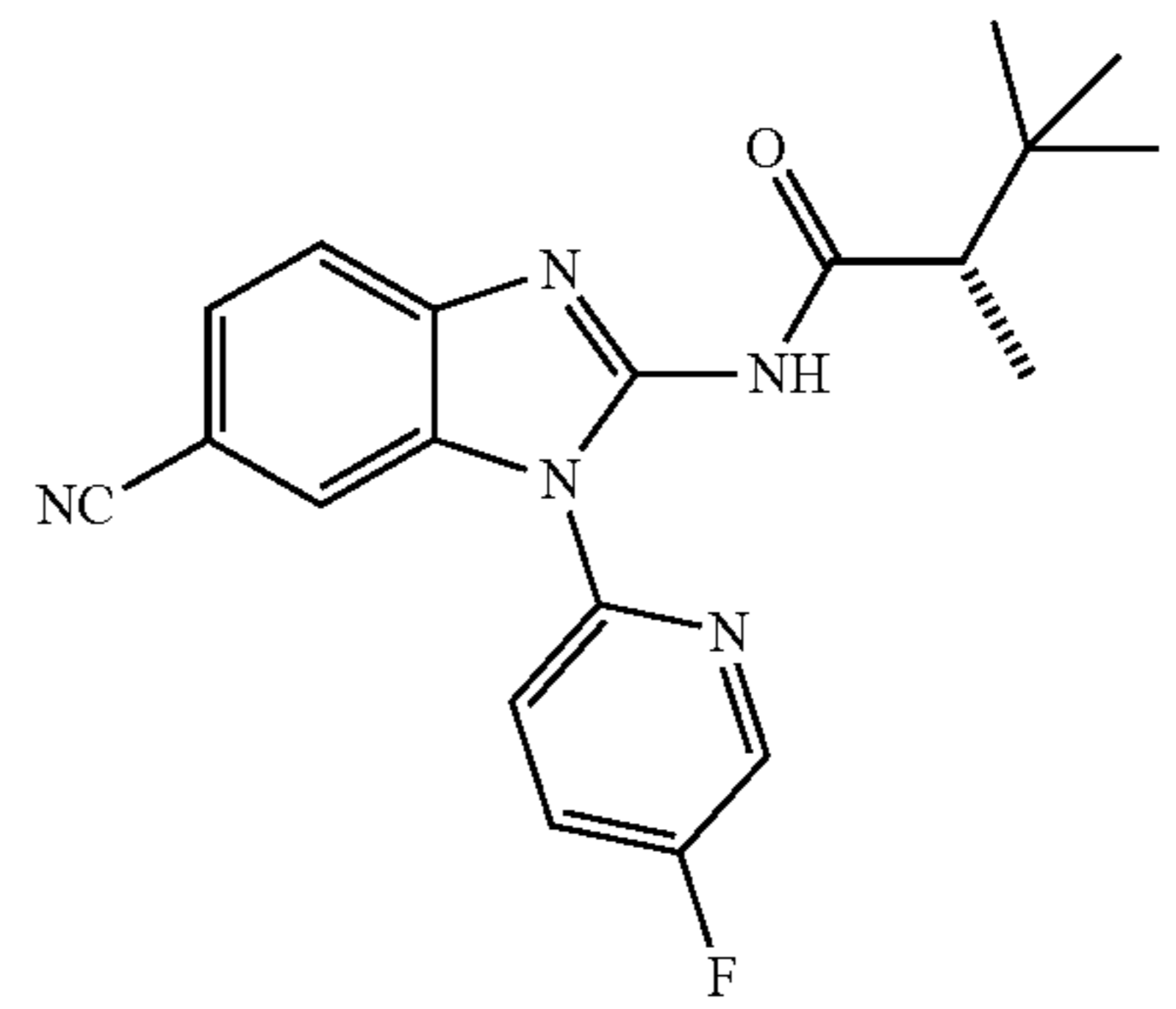
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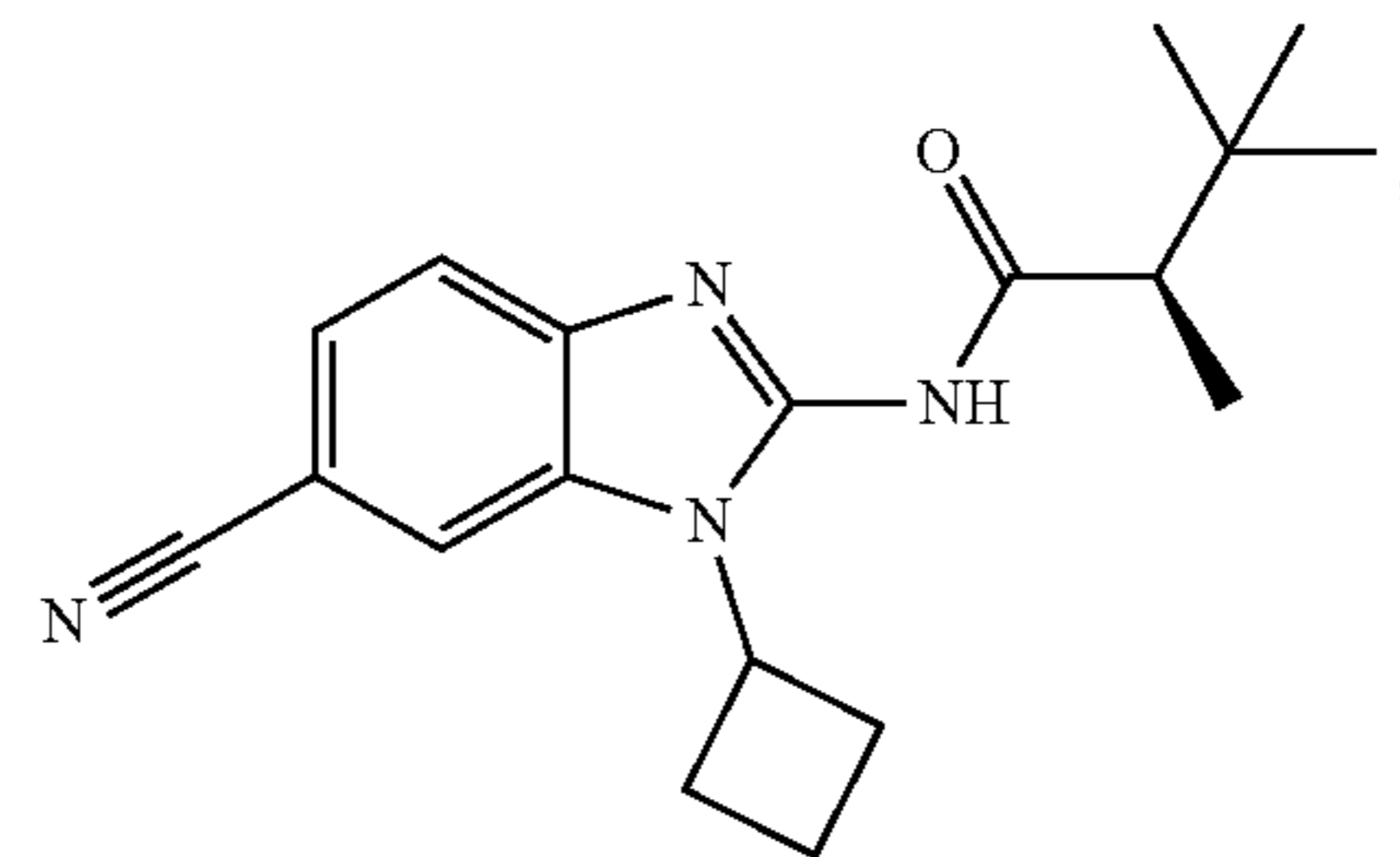
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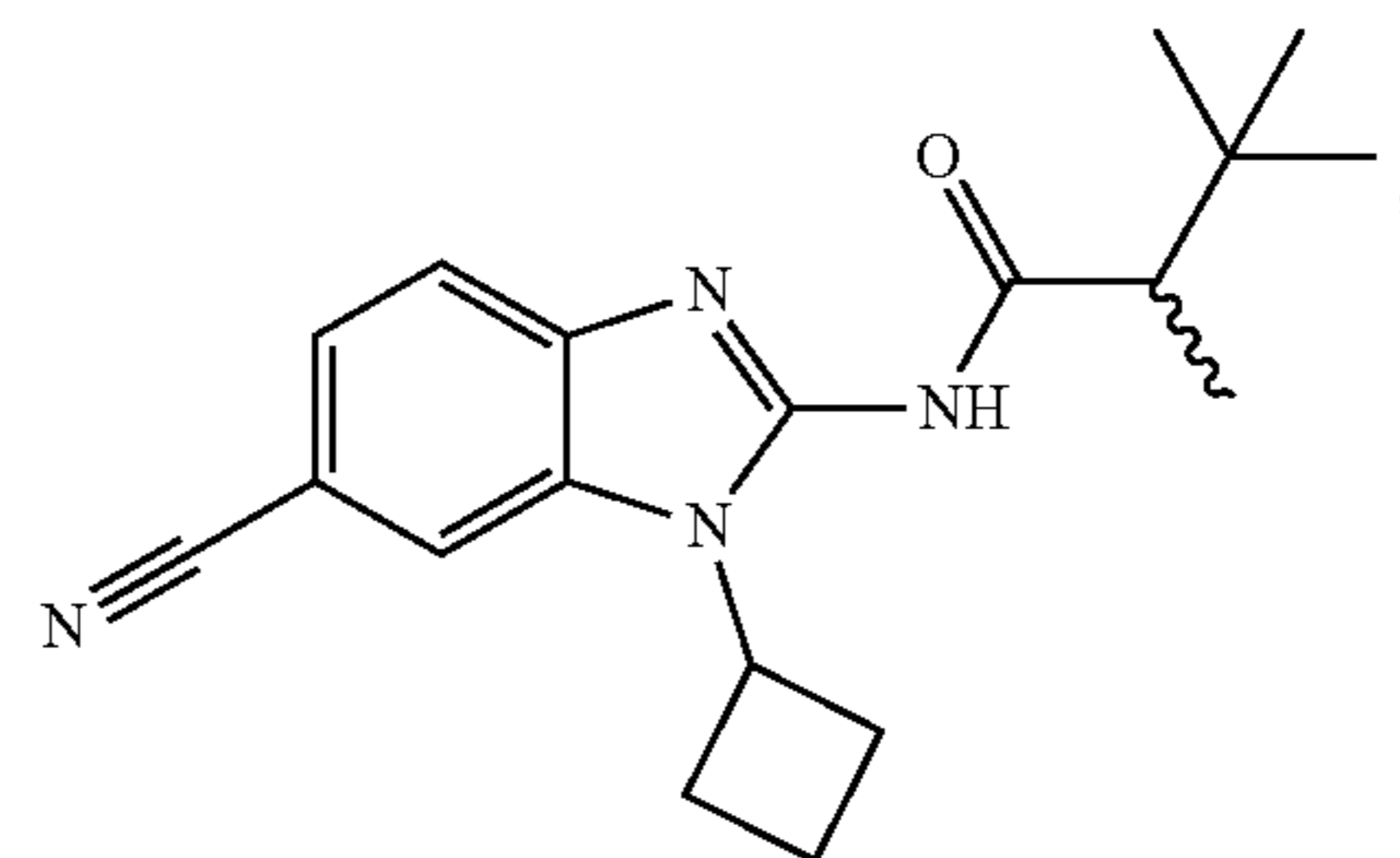
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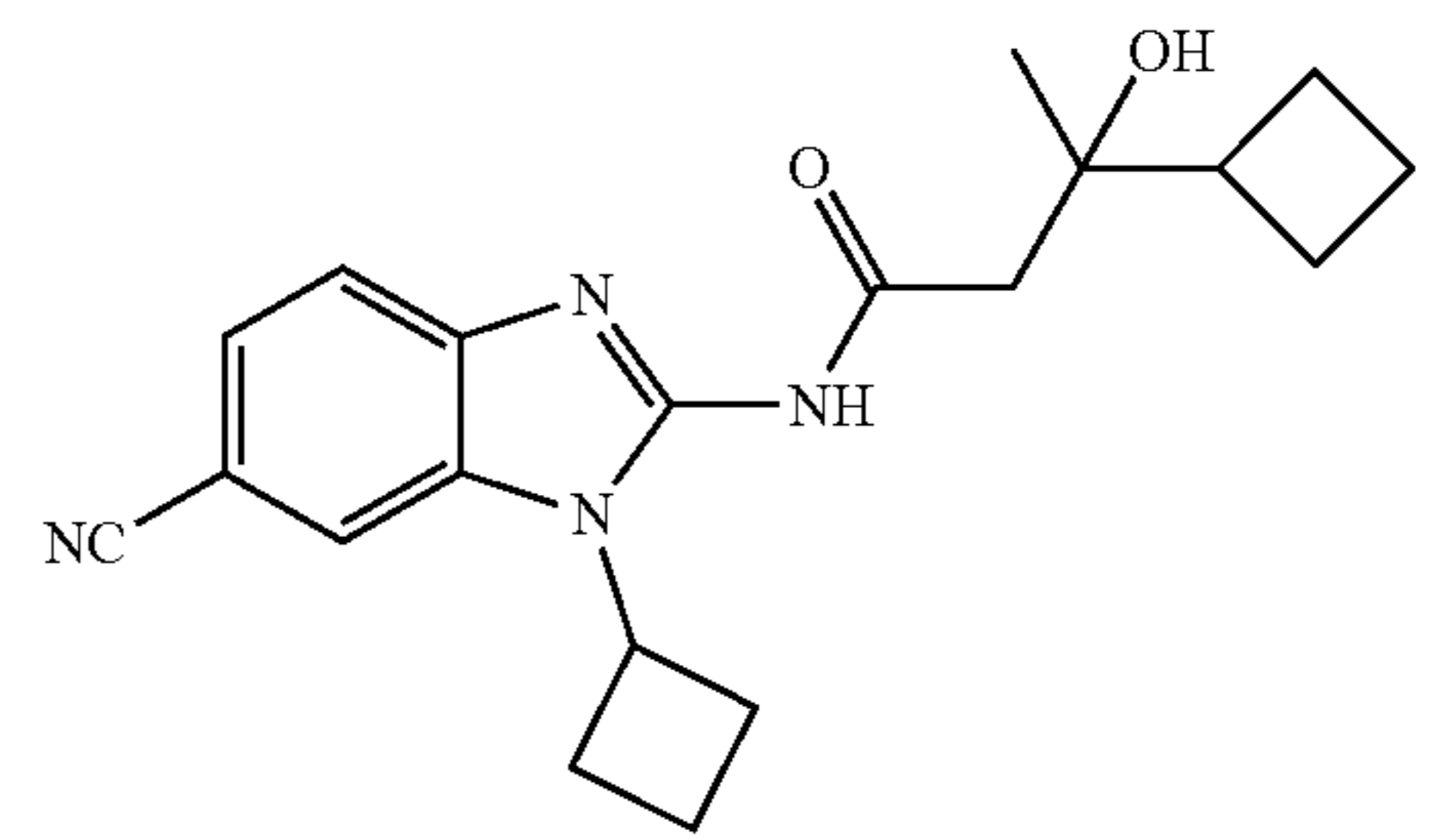
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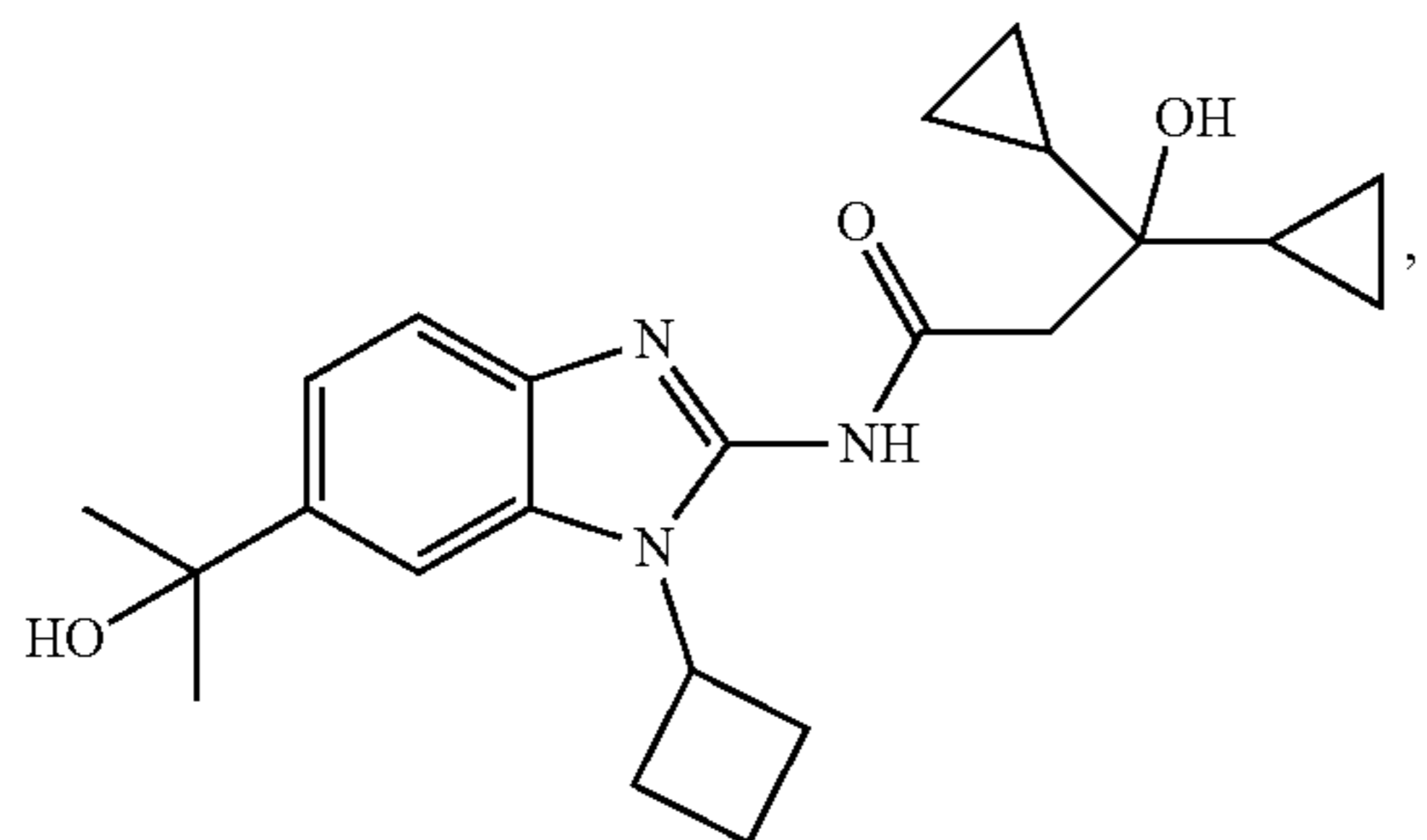
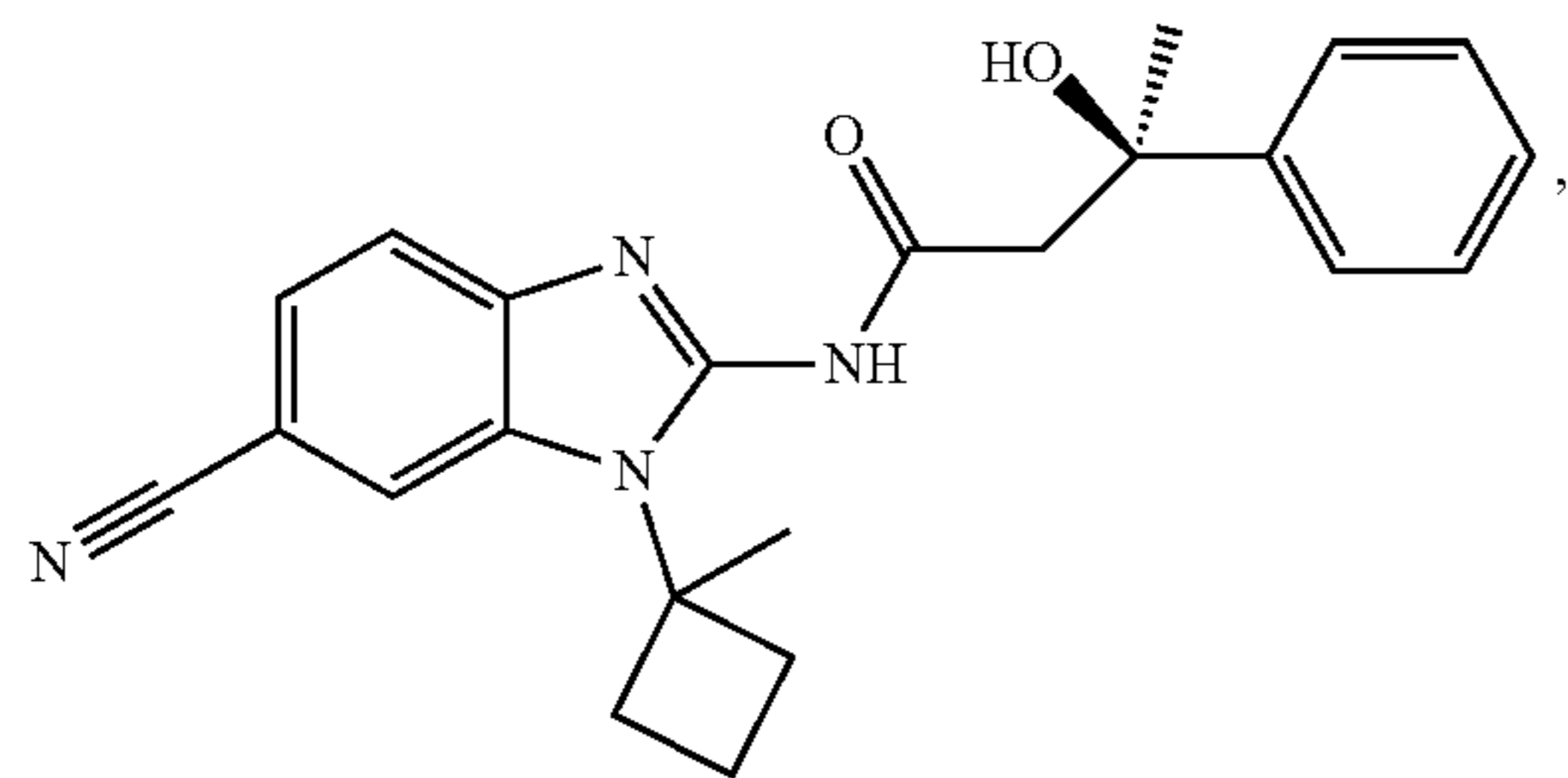
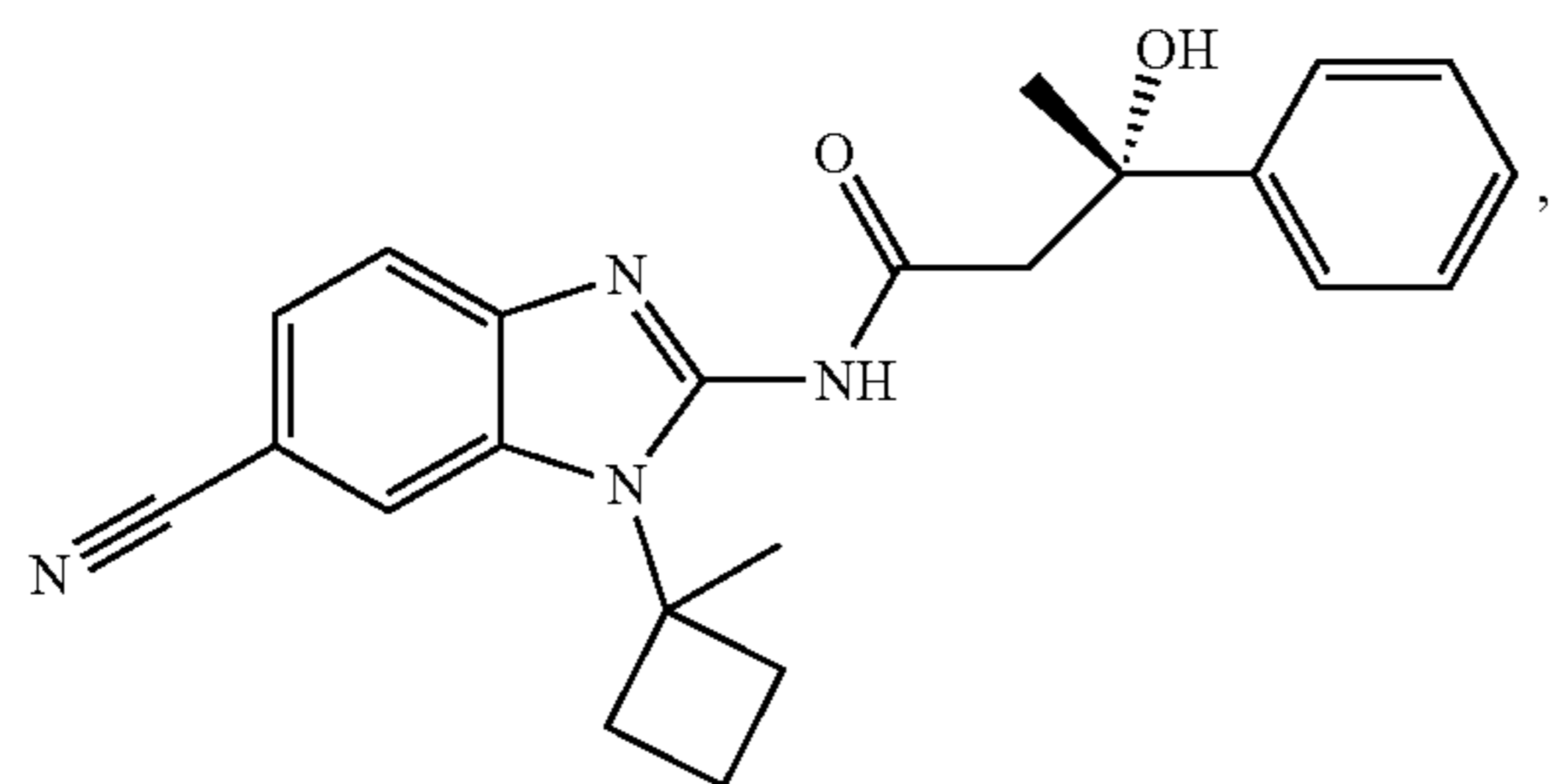
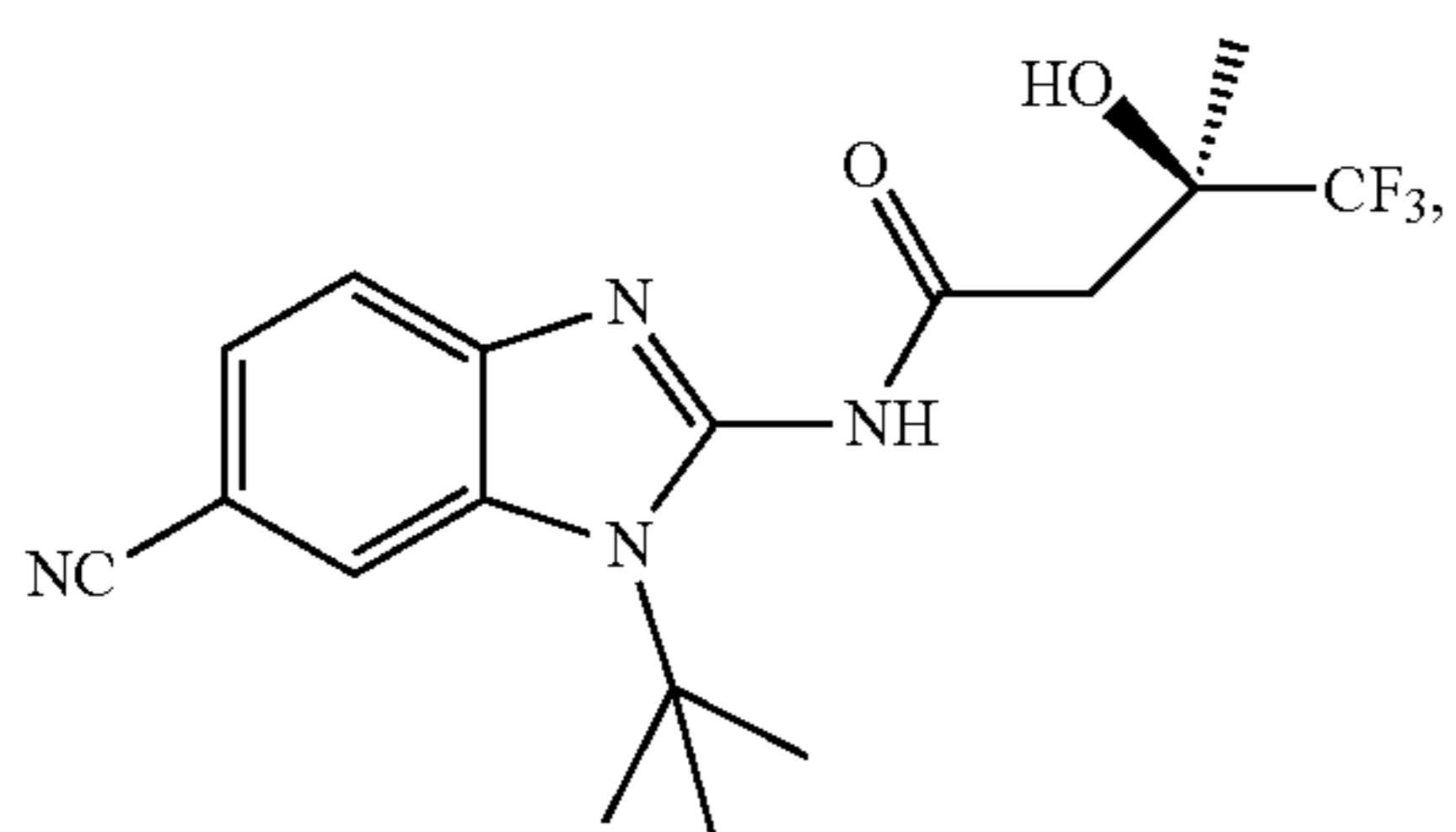
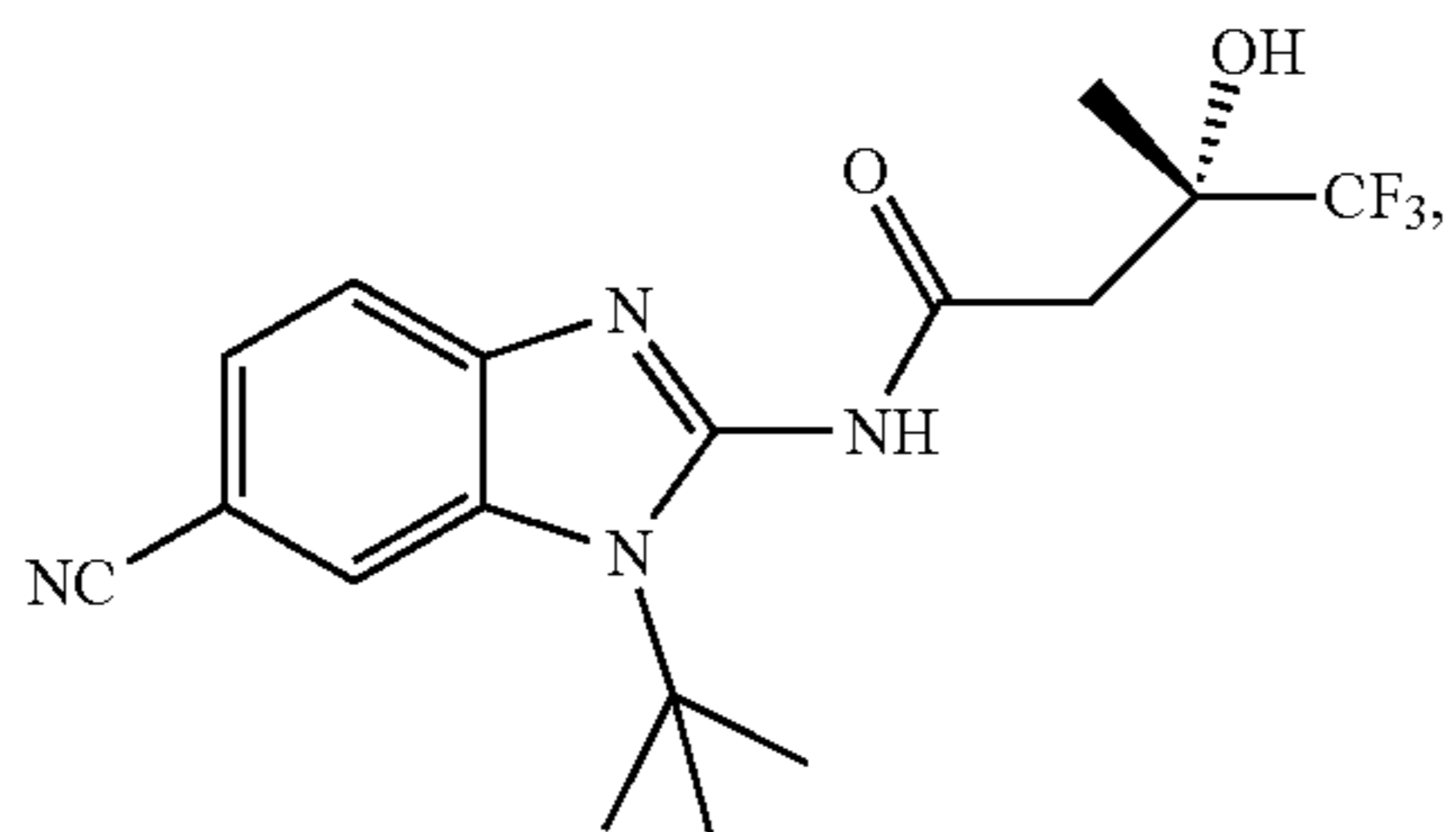
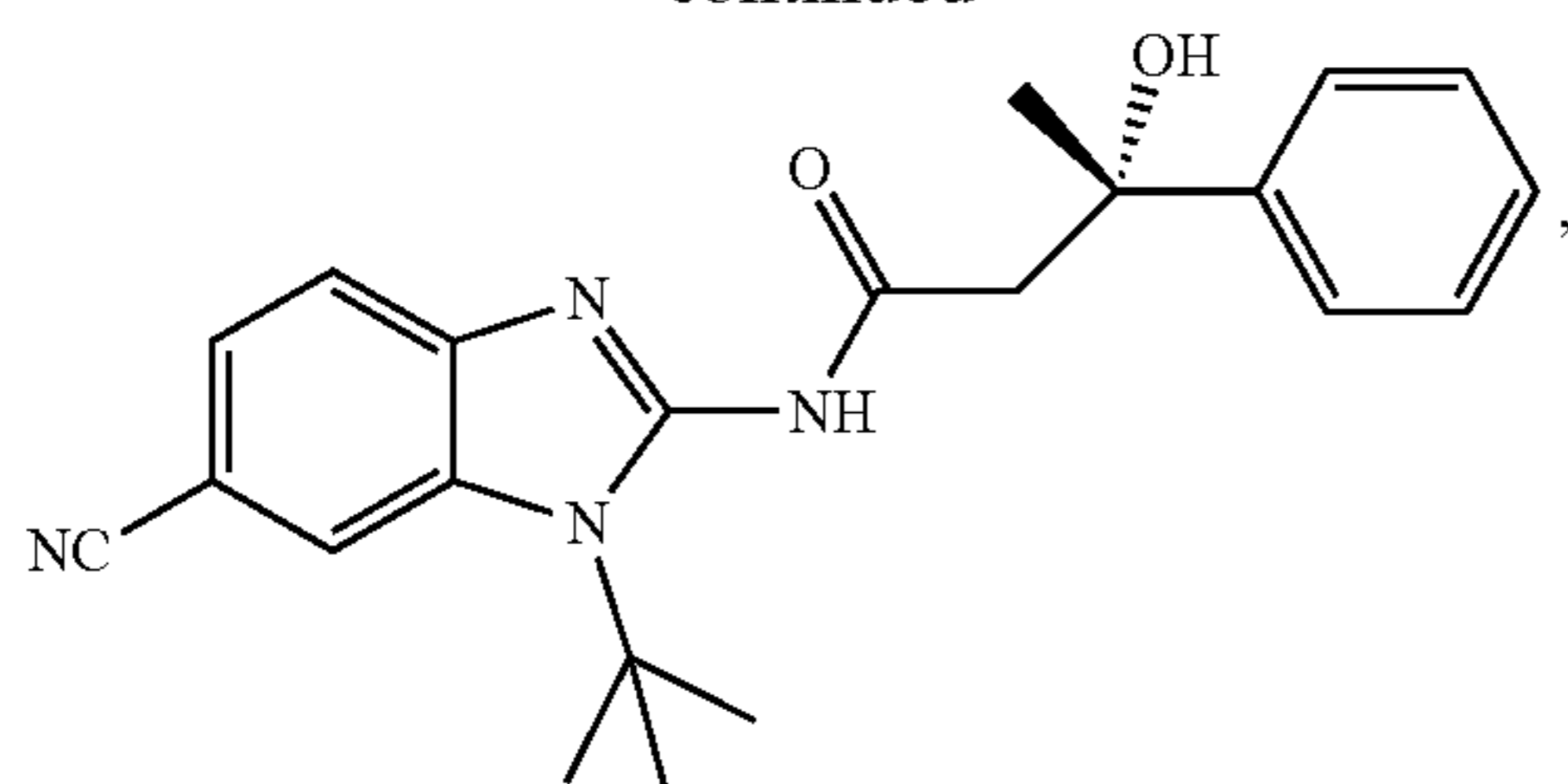
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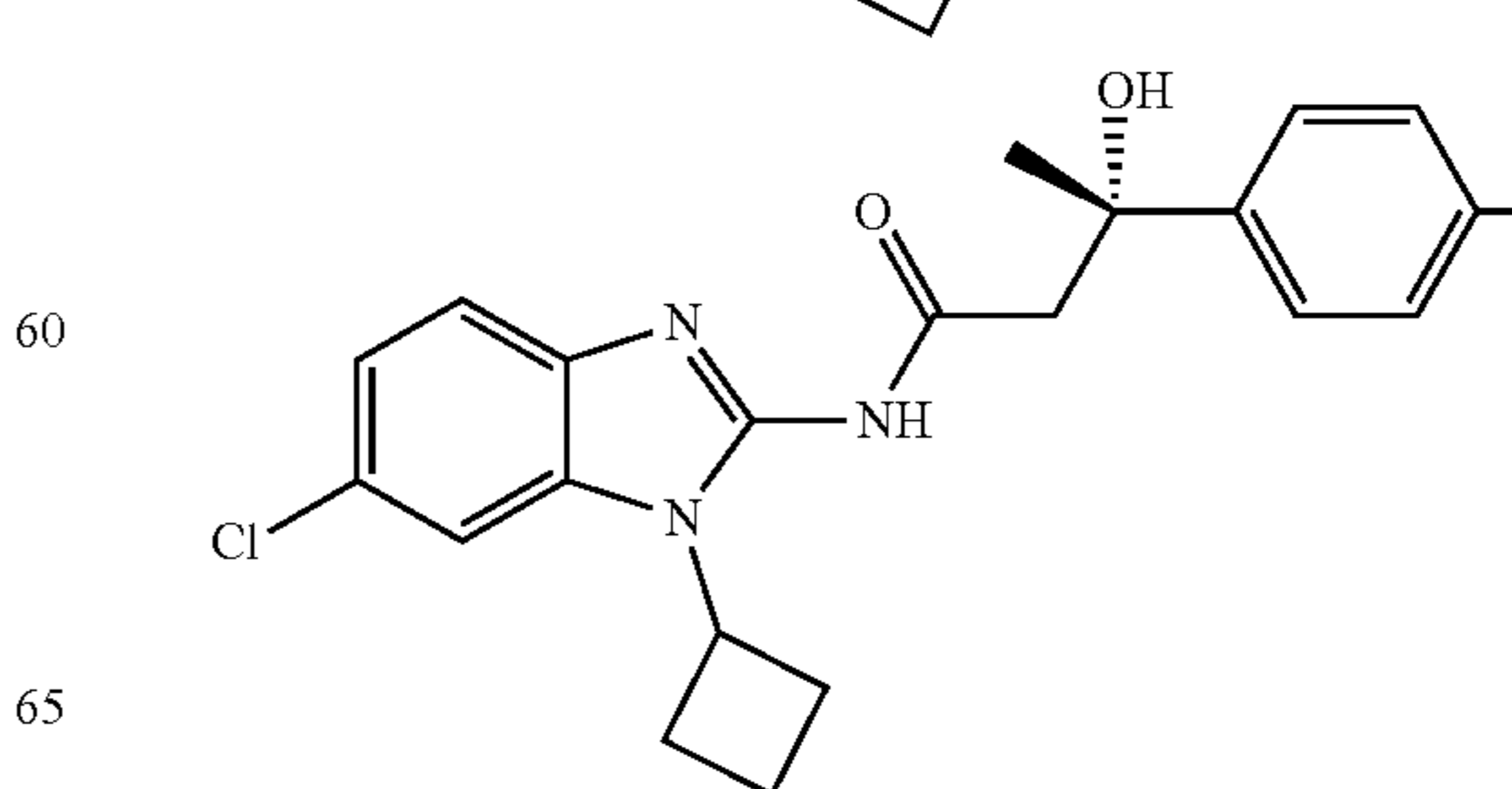
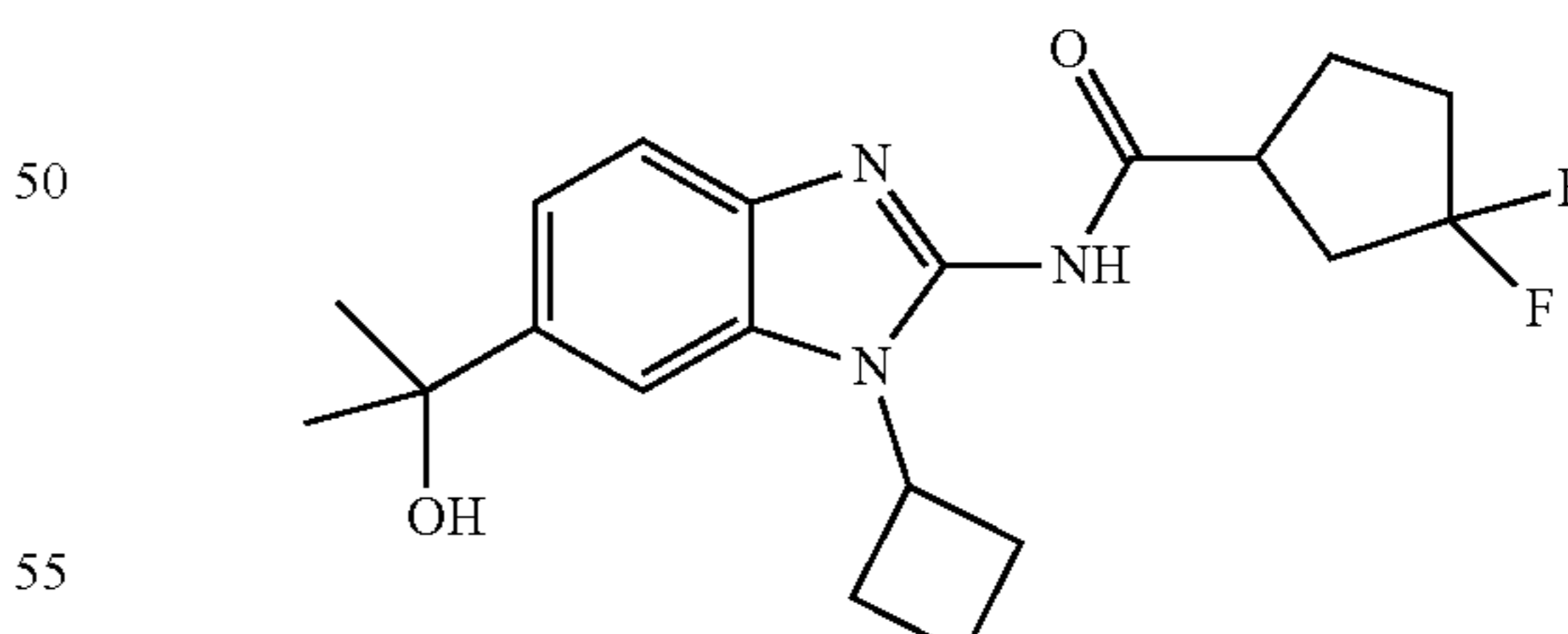
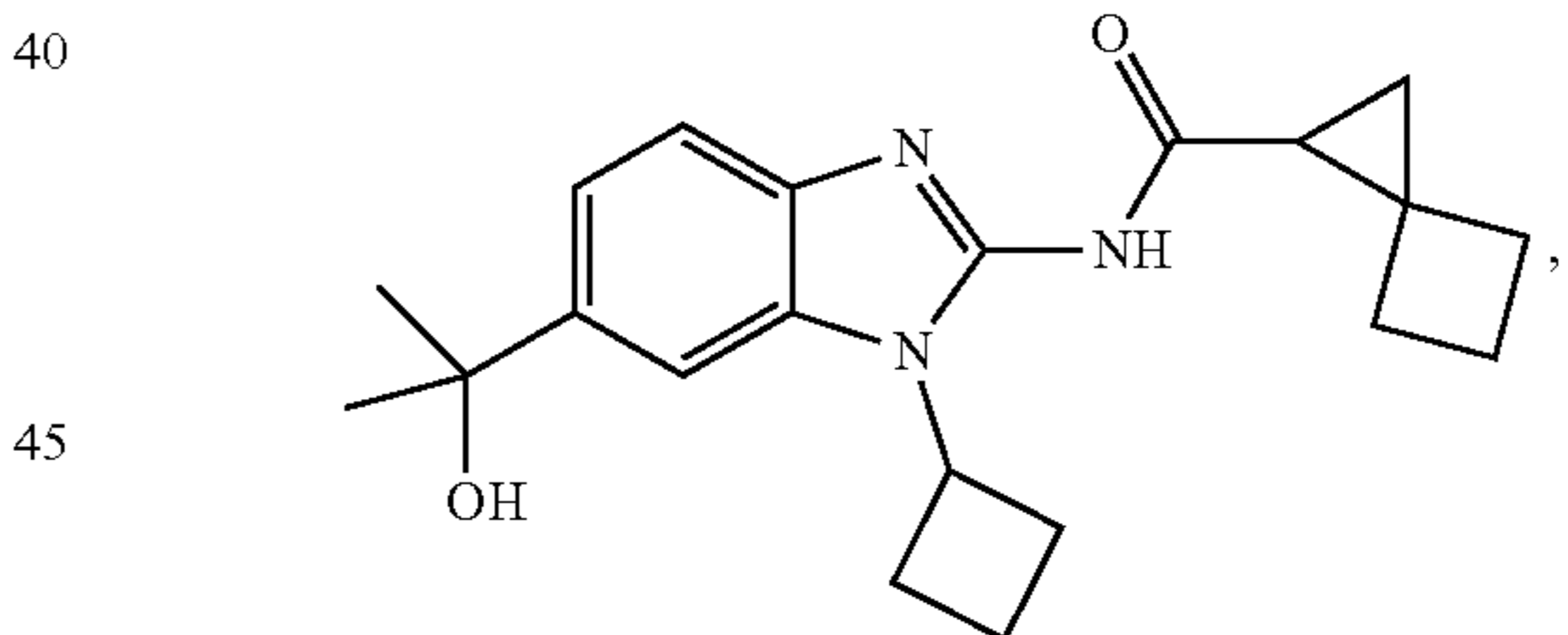
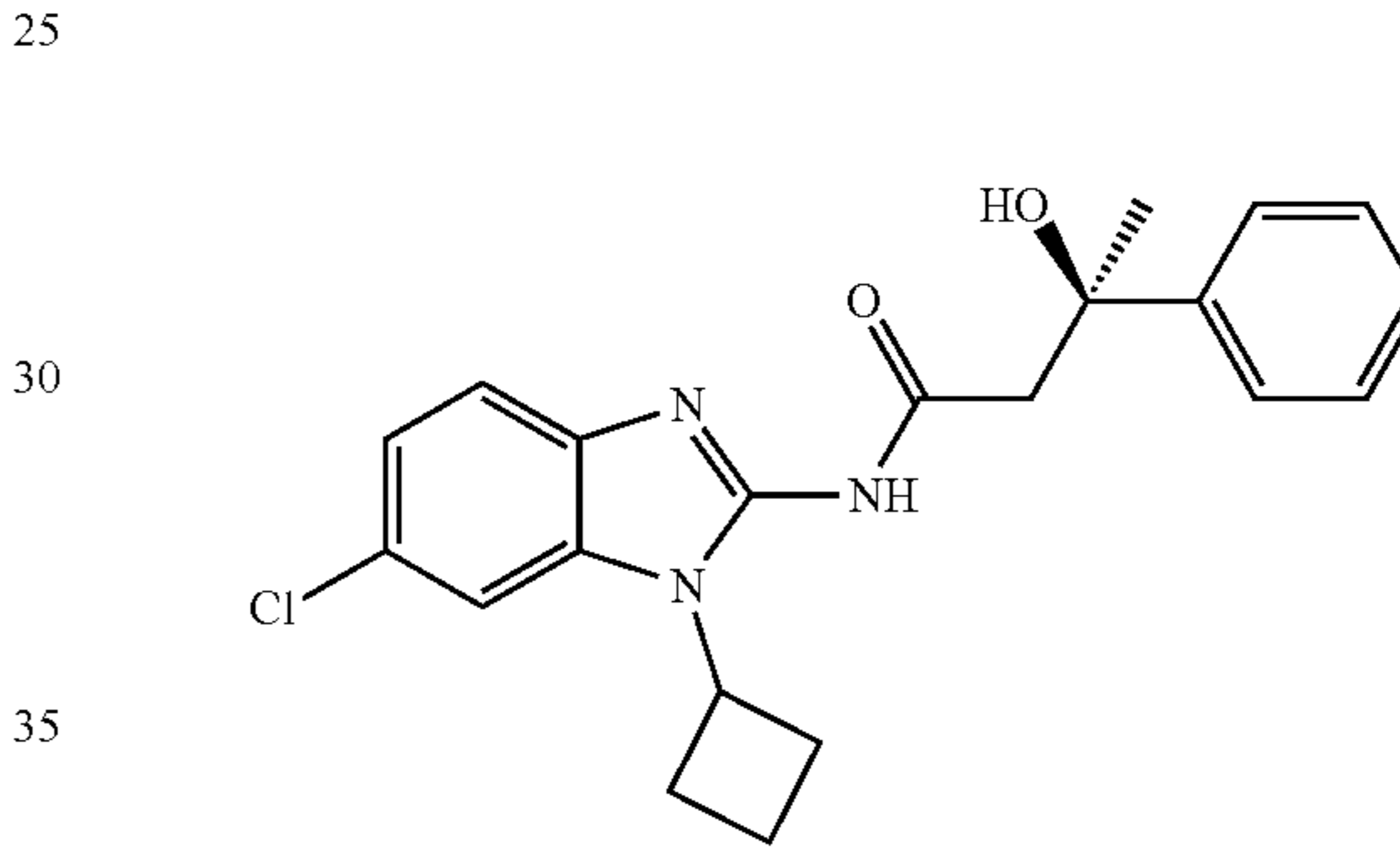
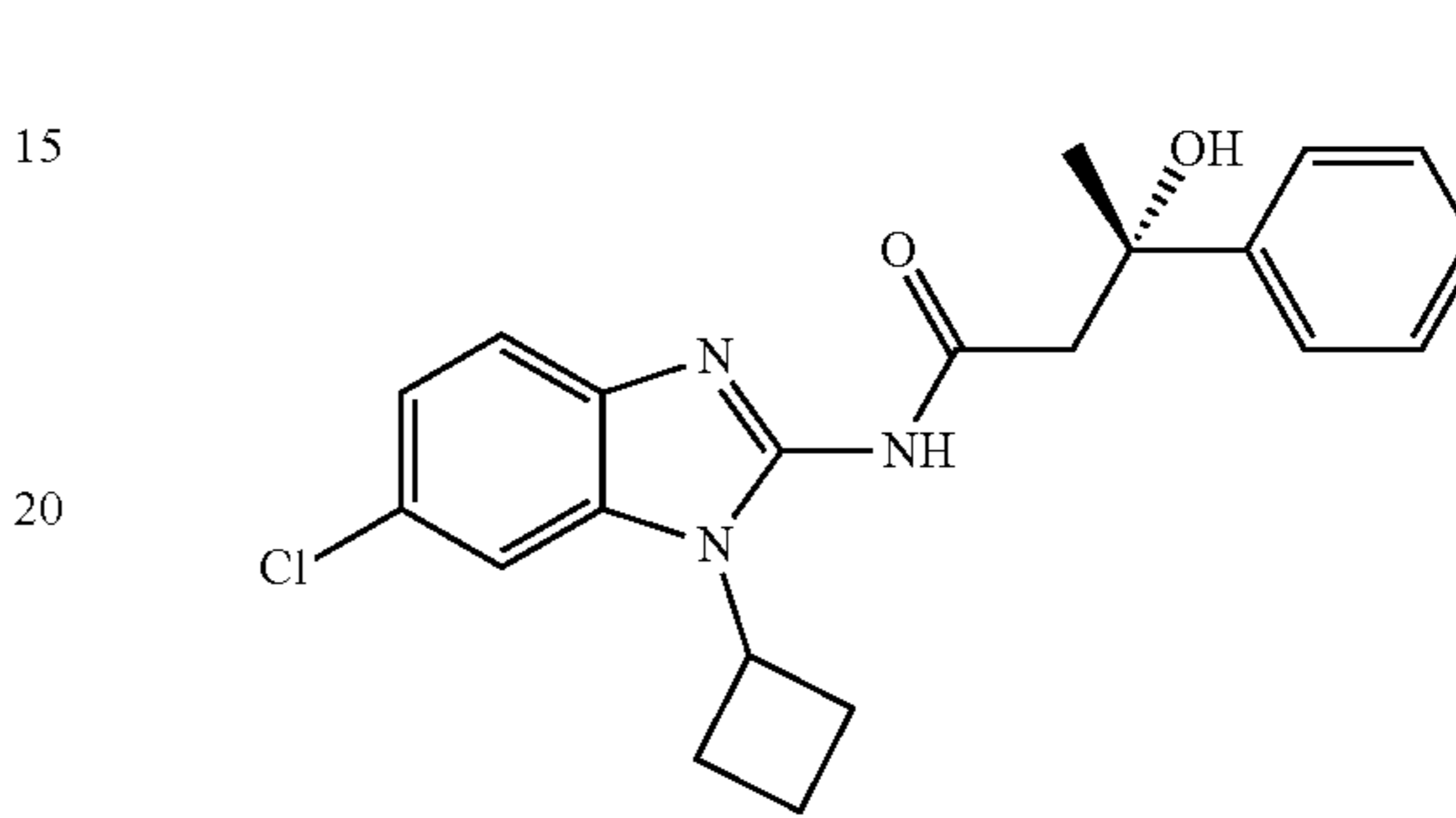
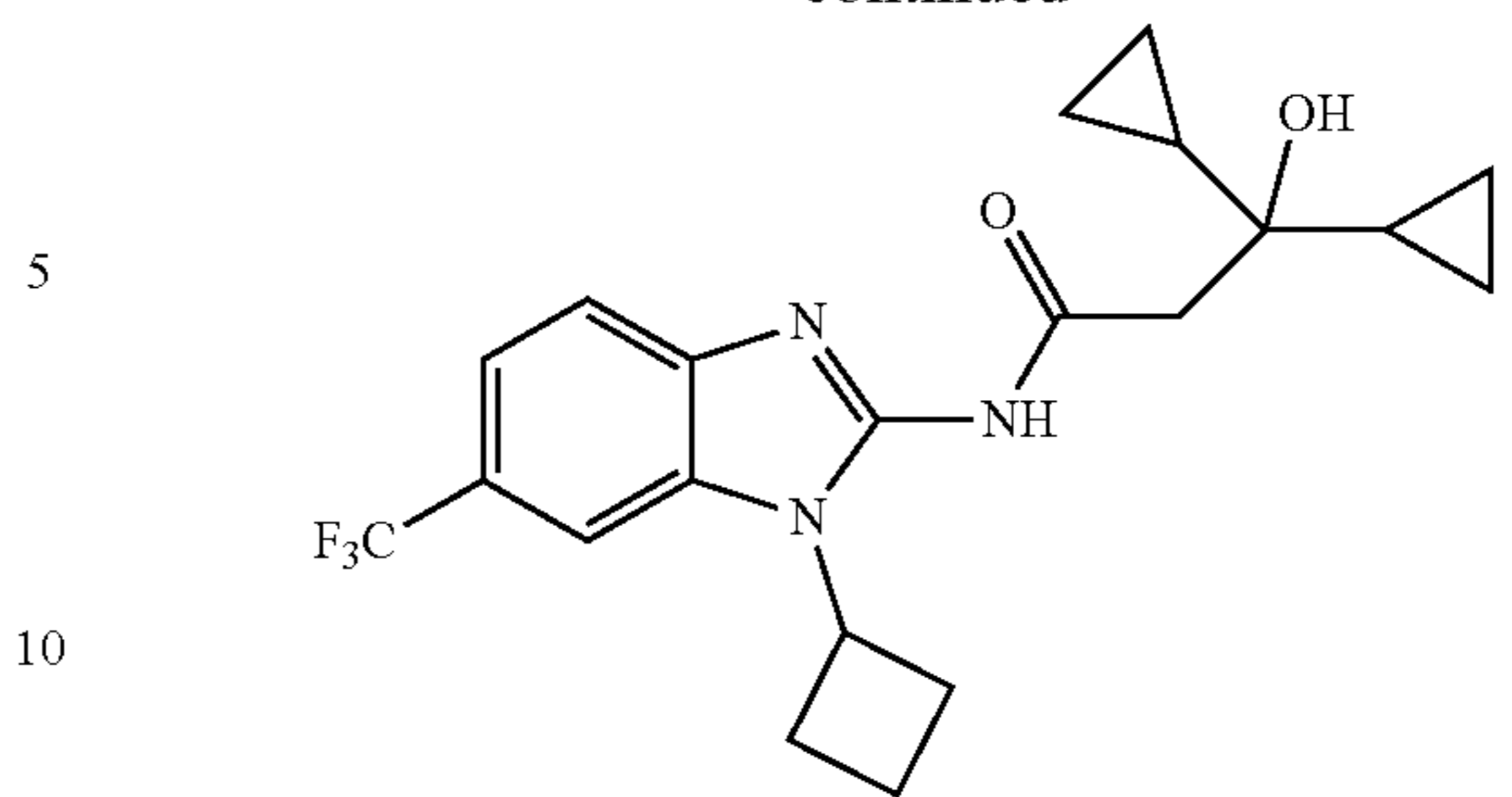
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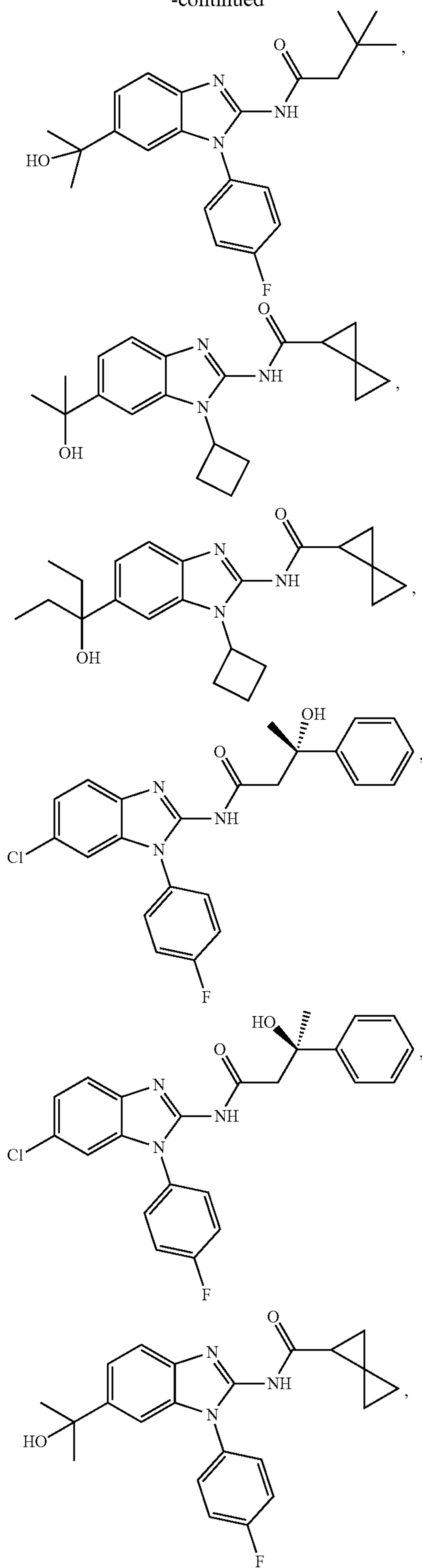
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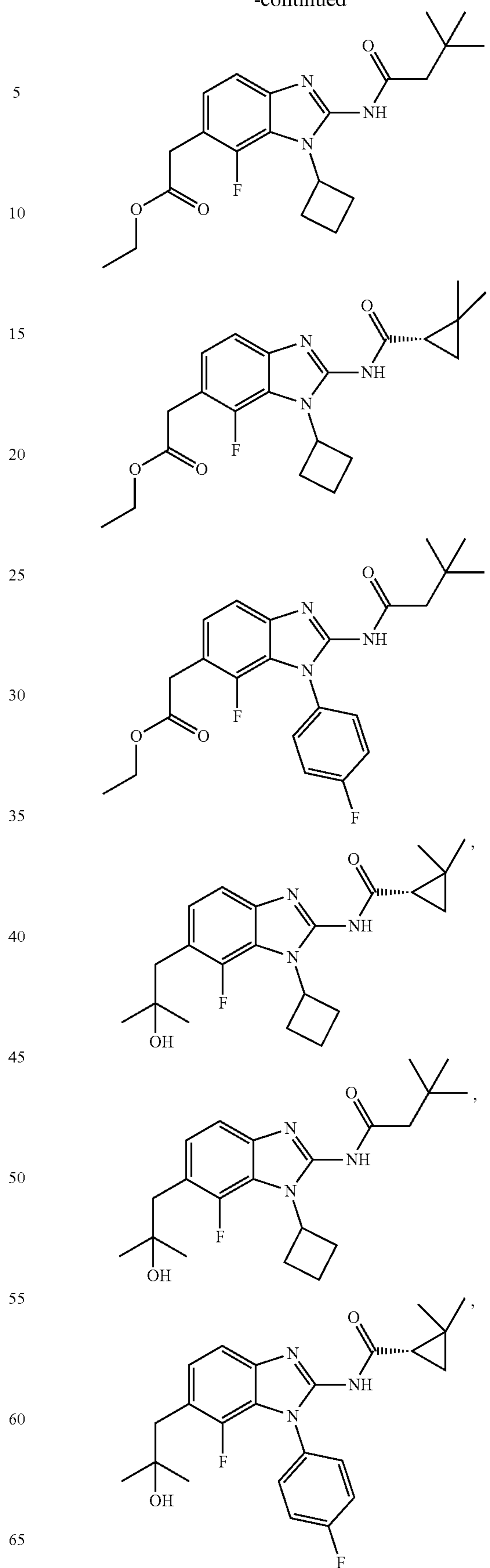
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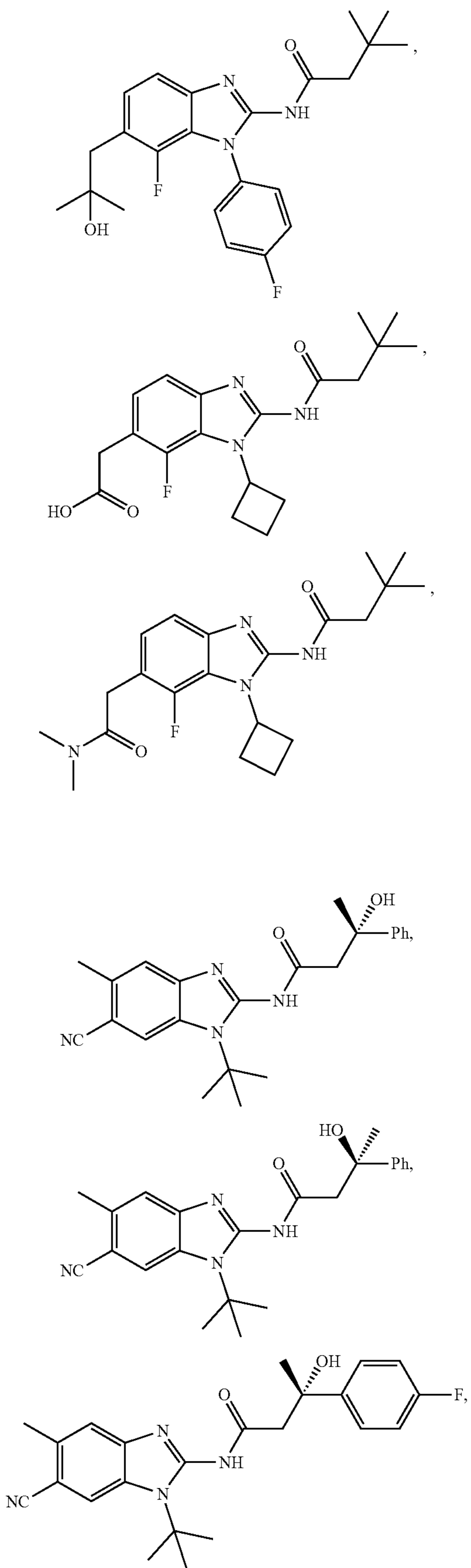
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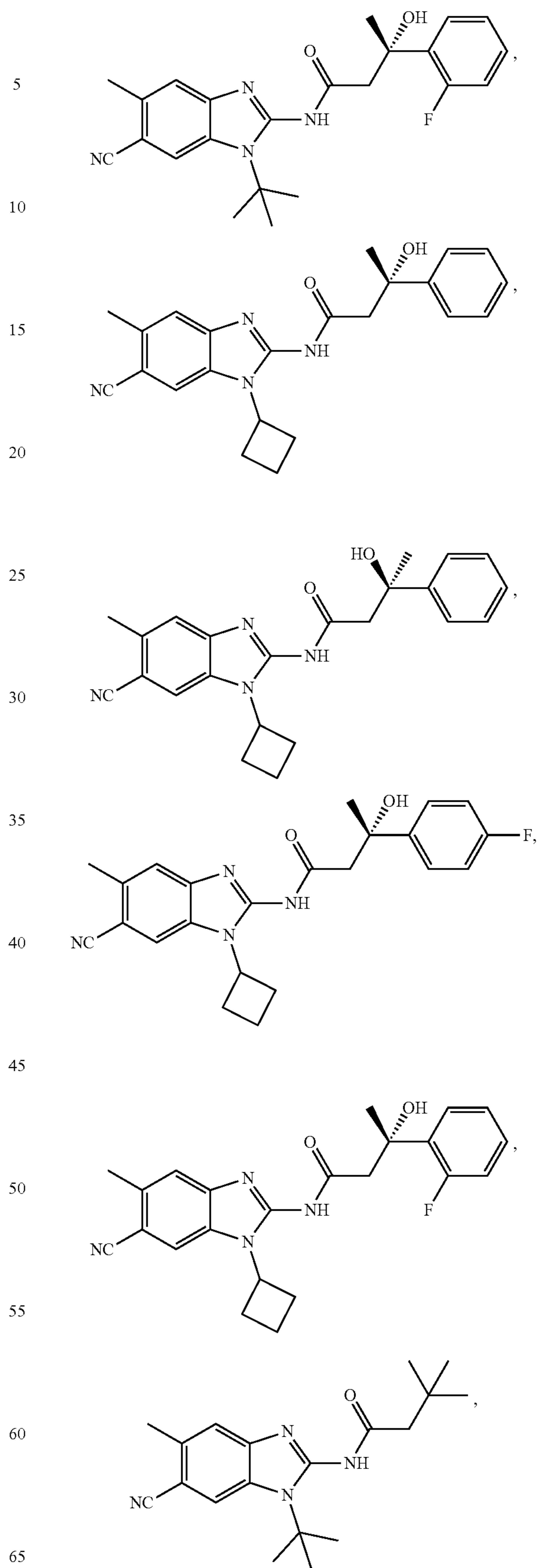
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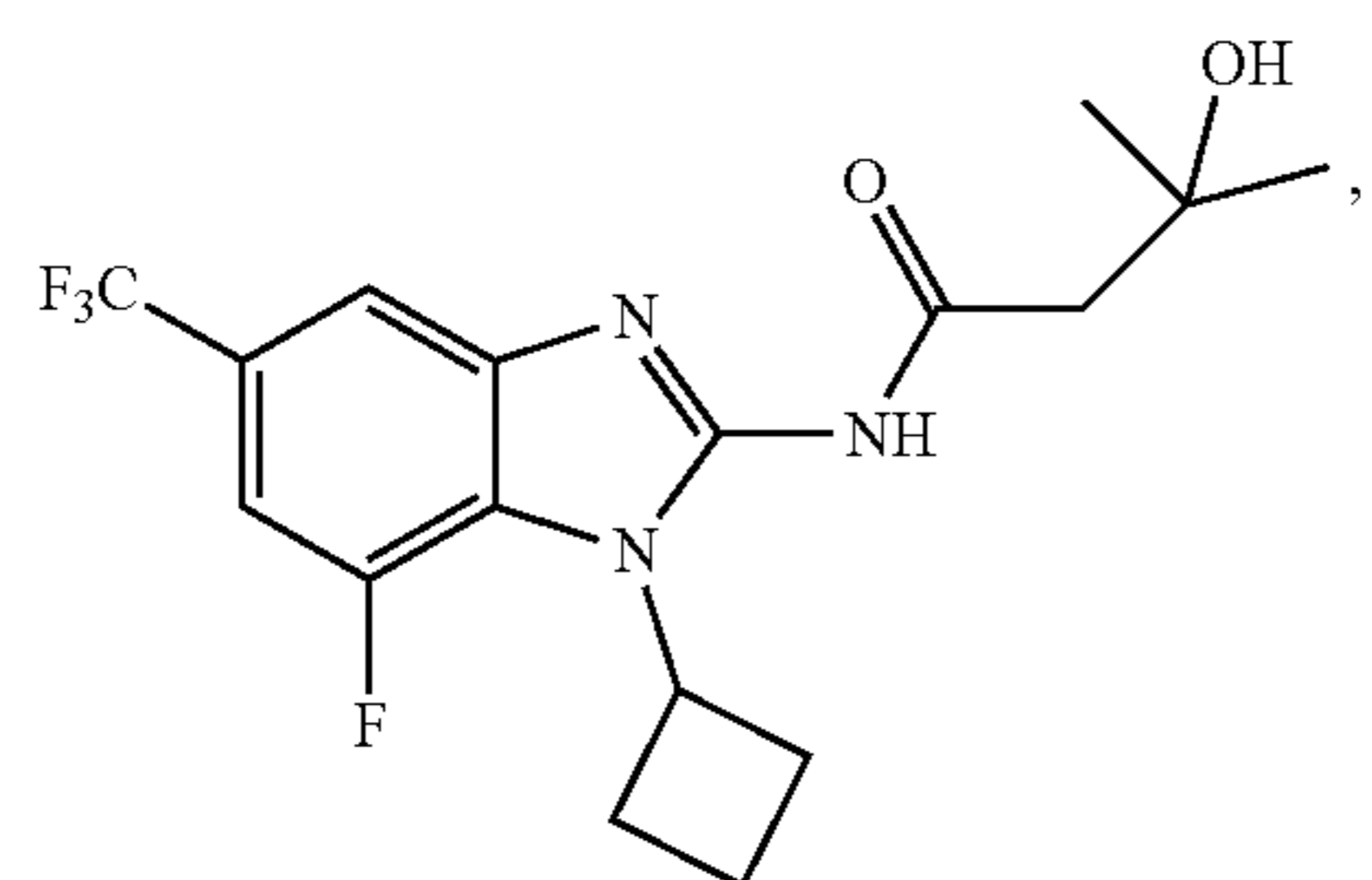
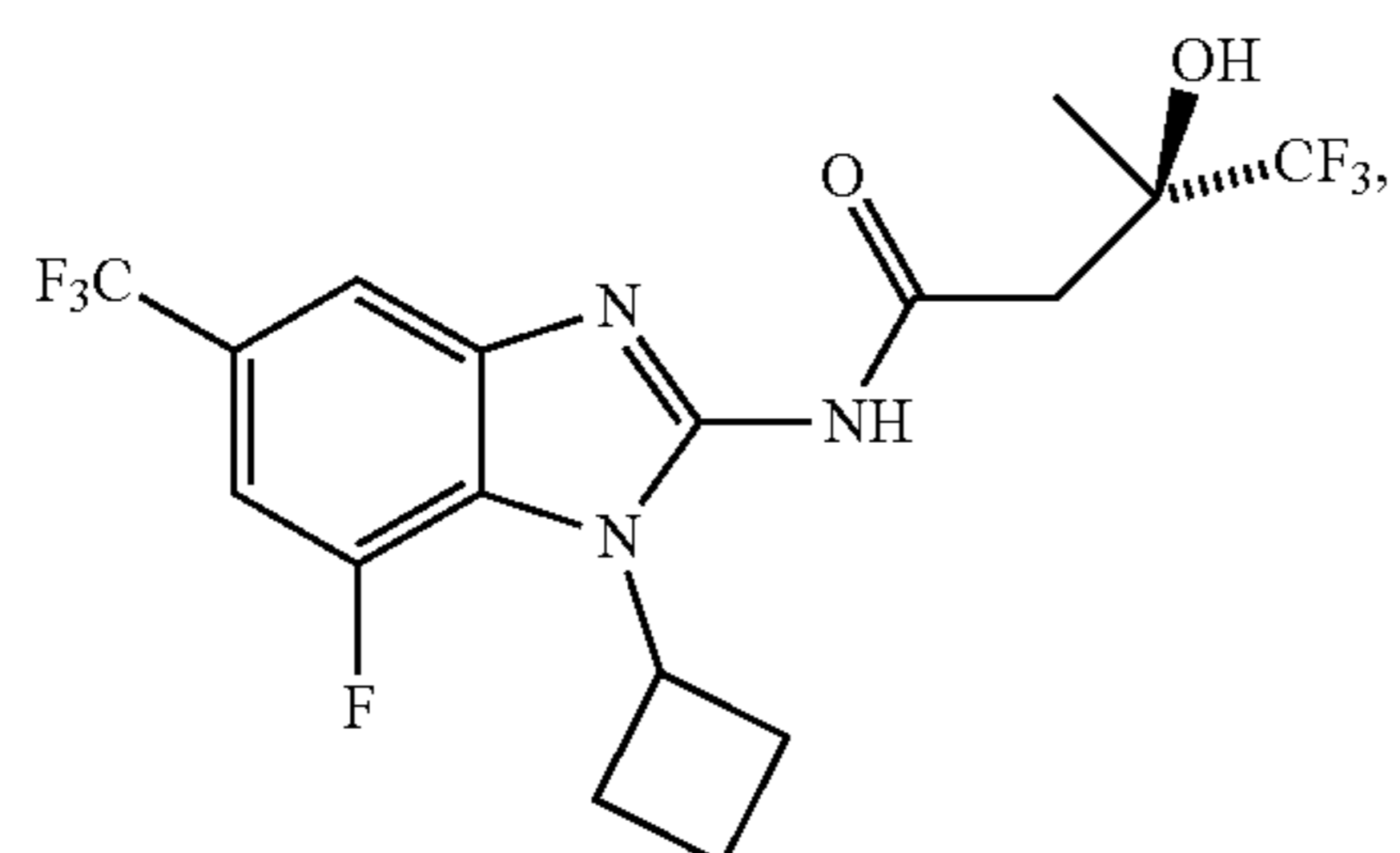
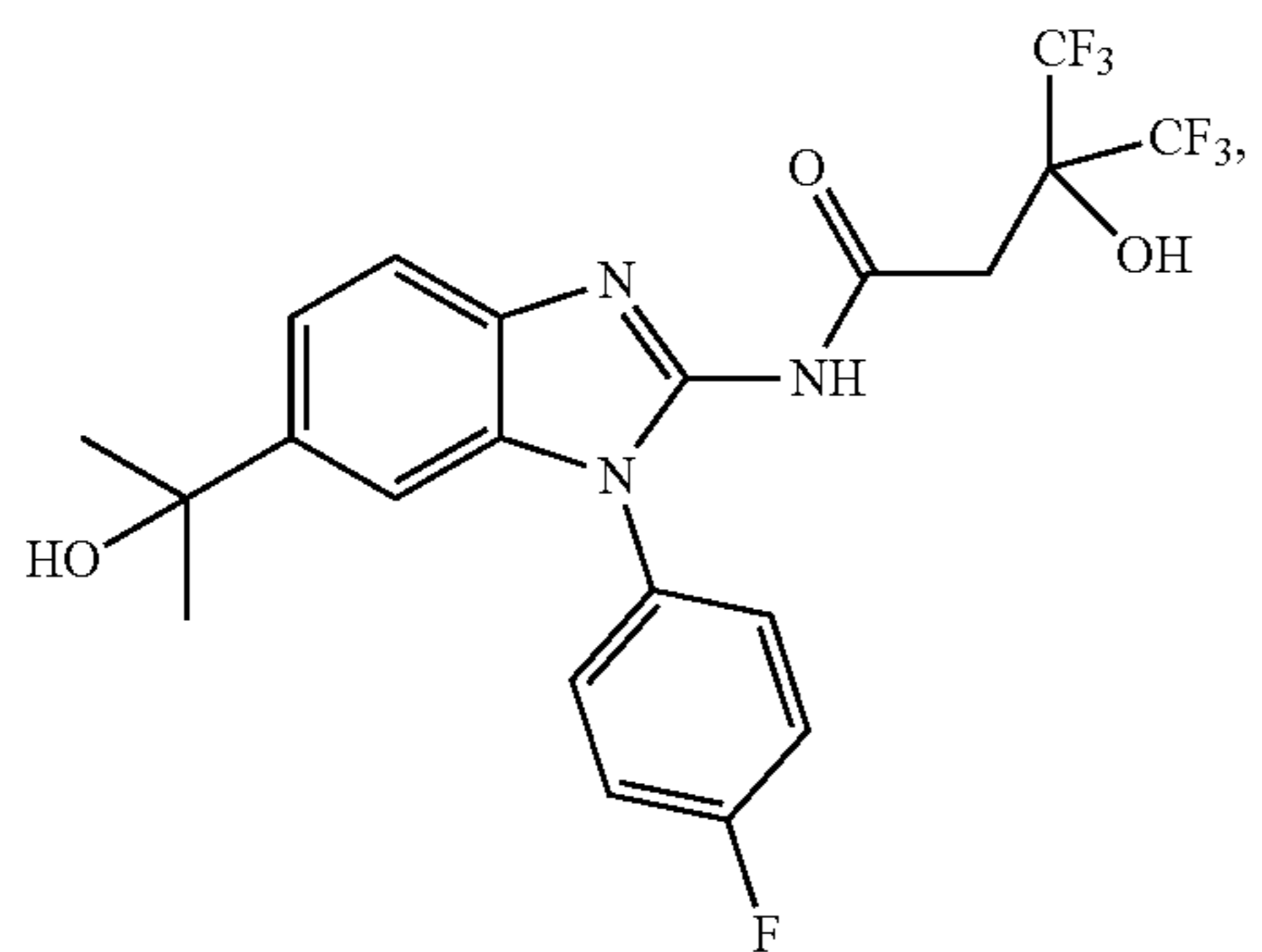
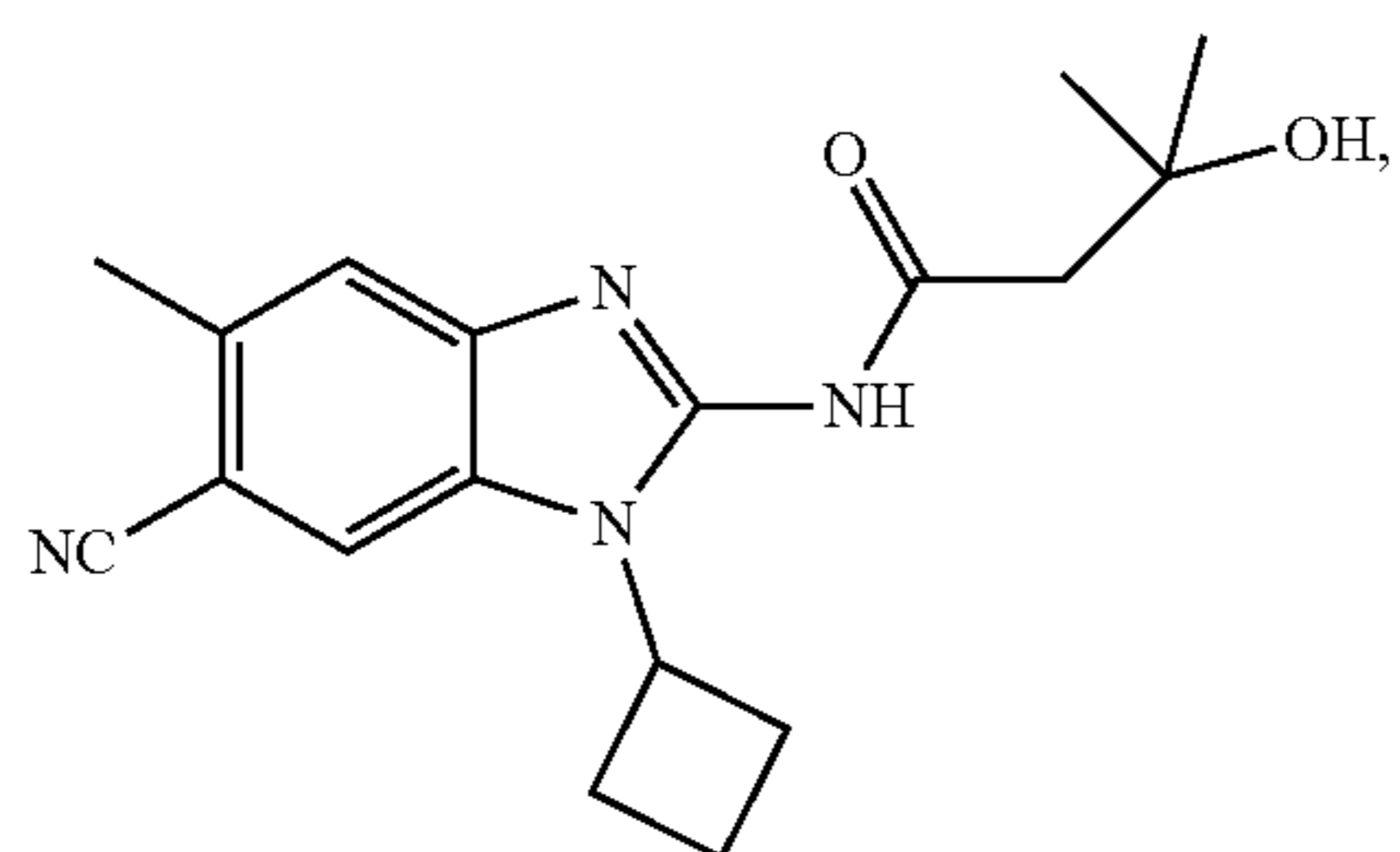
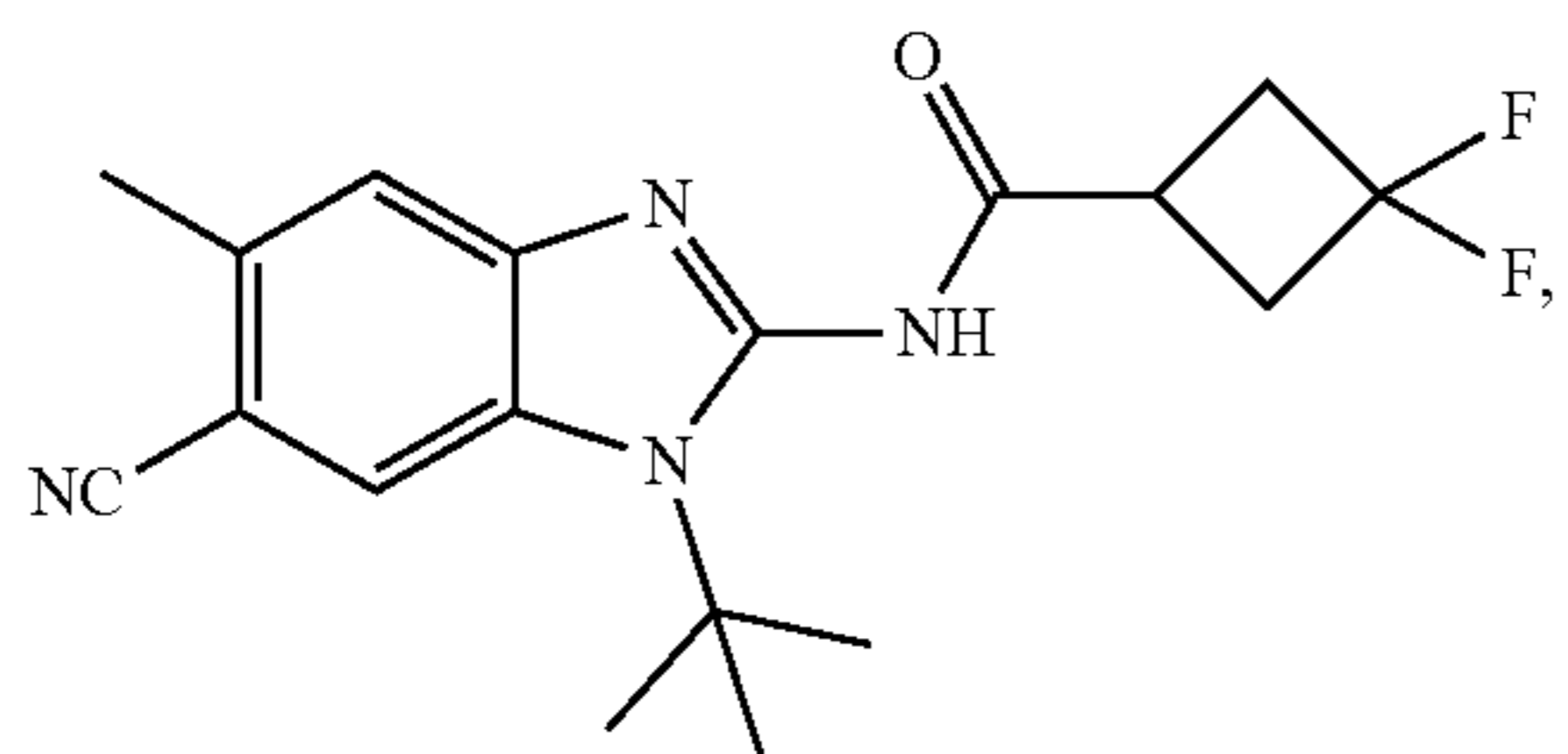
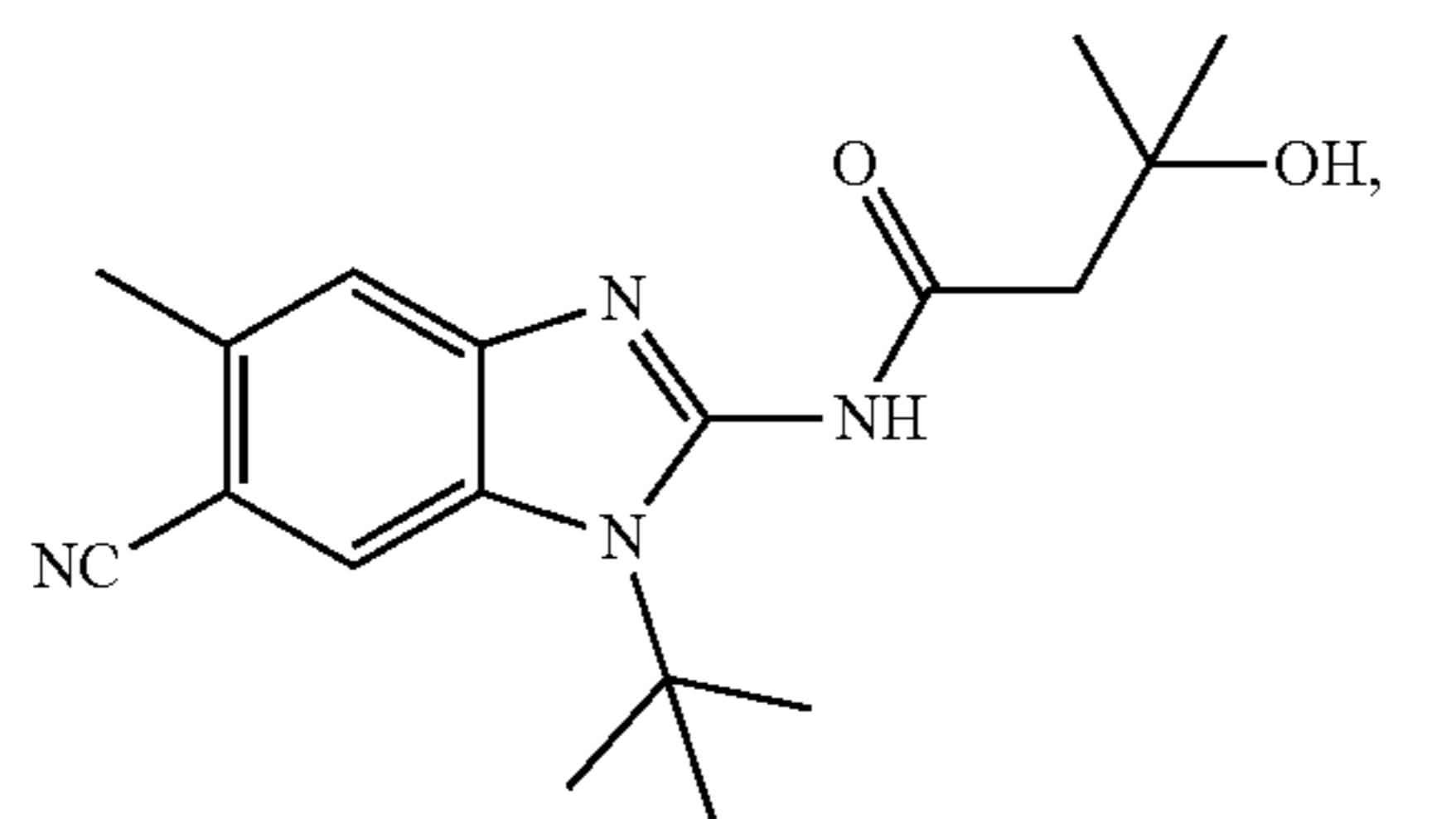
68

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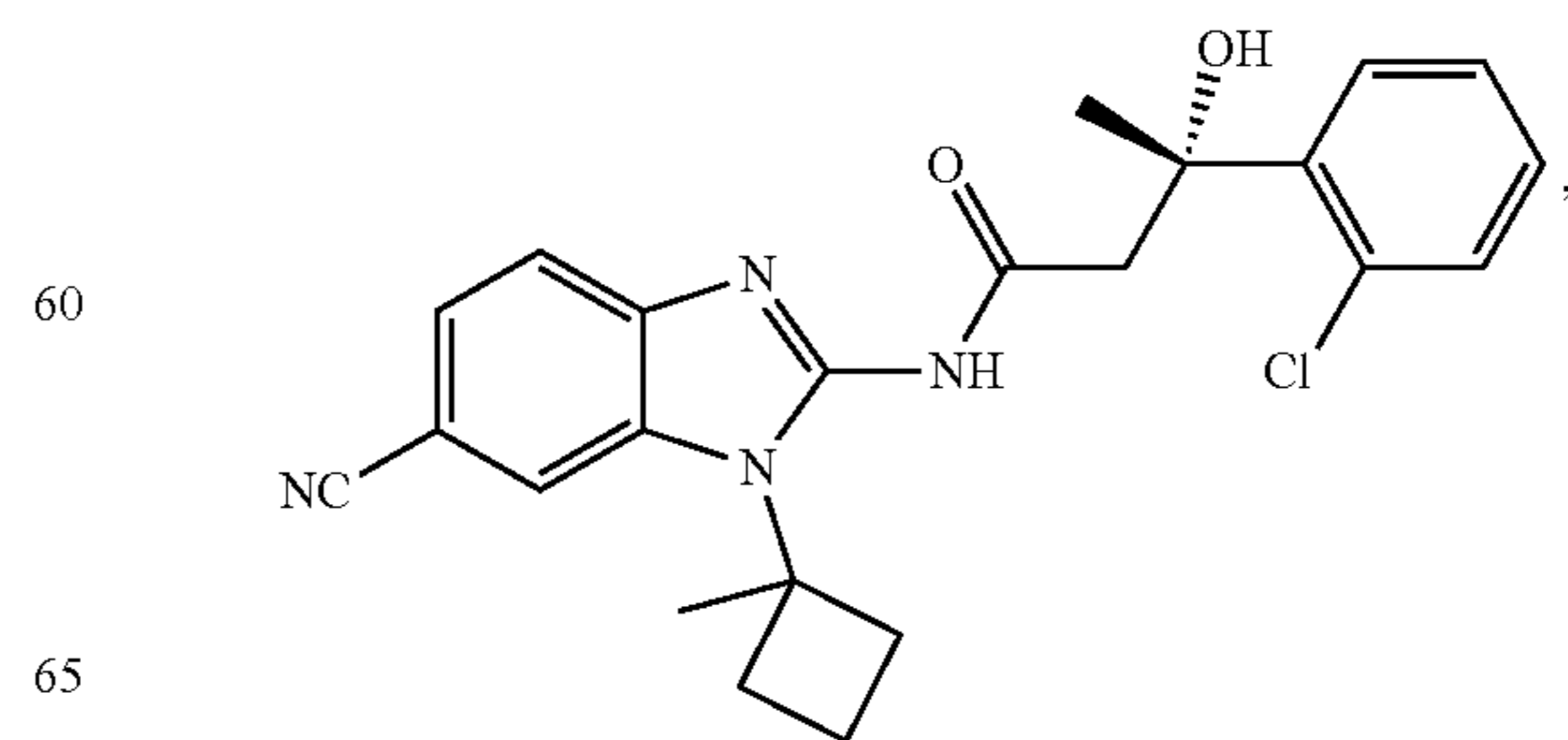
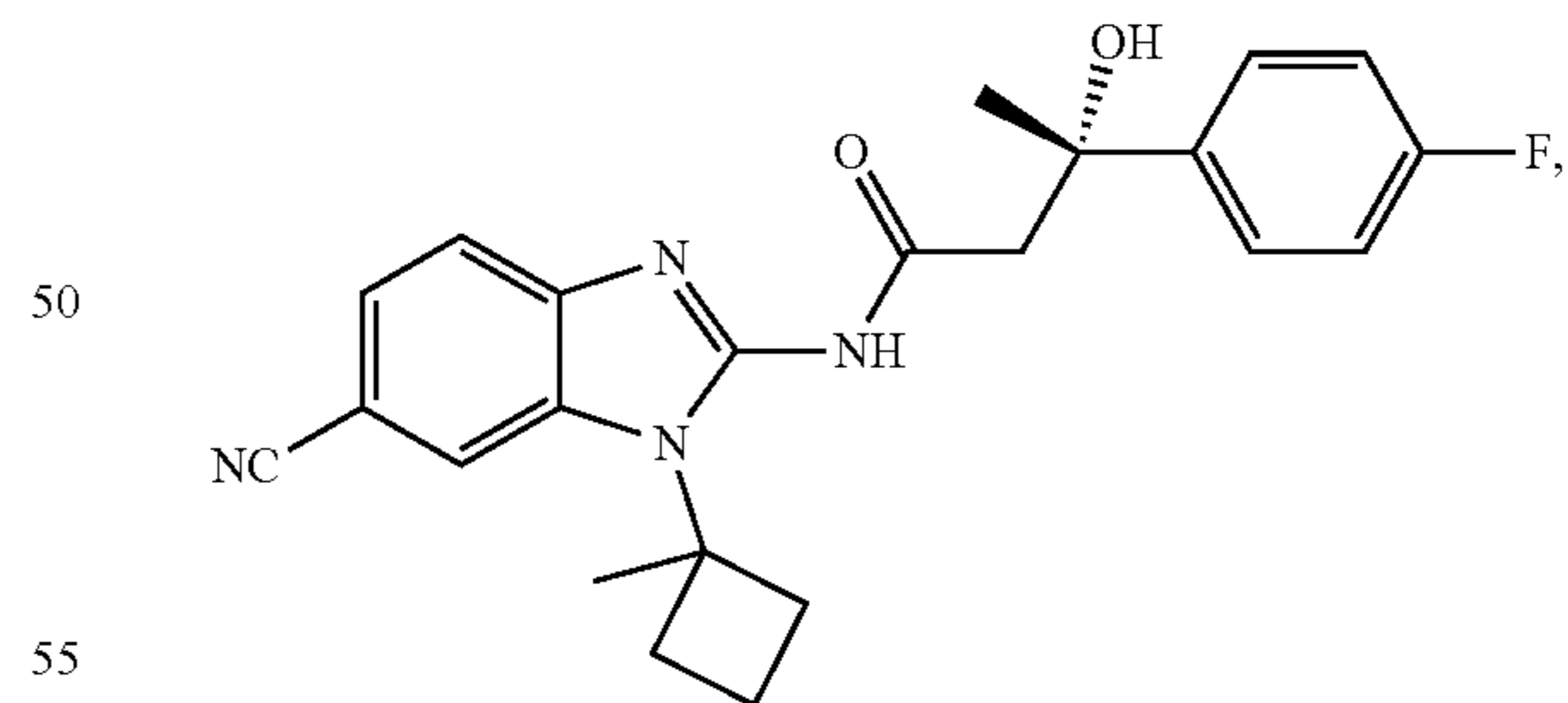
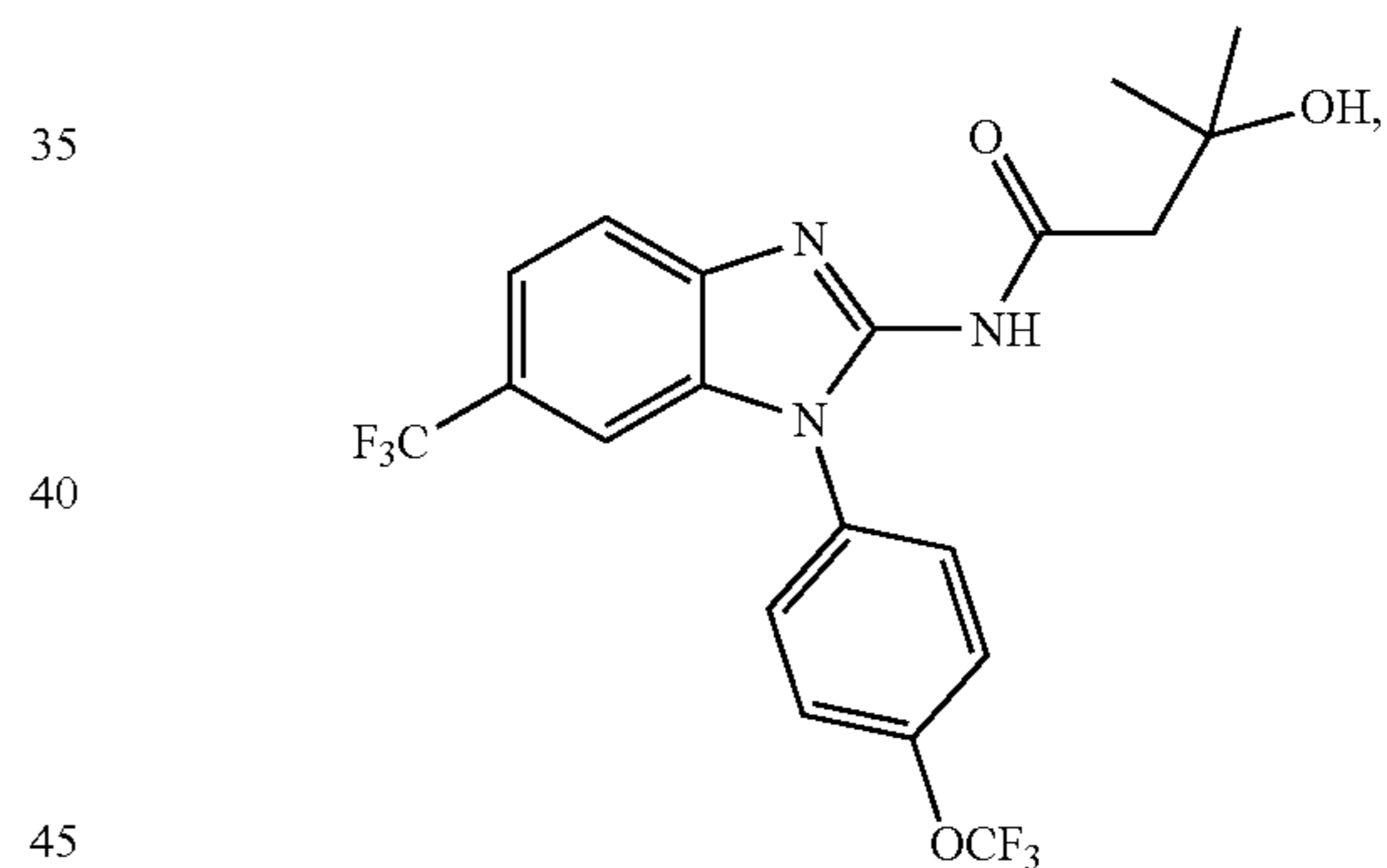
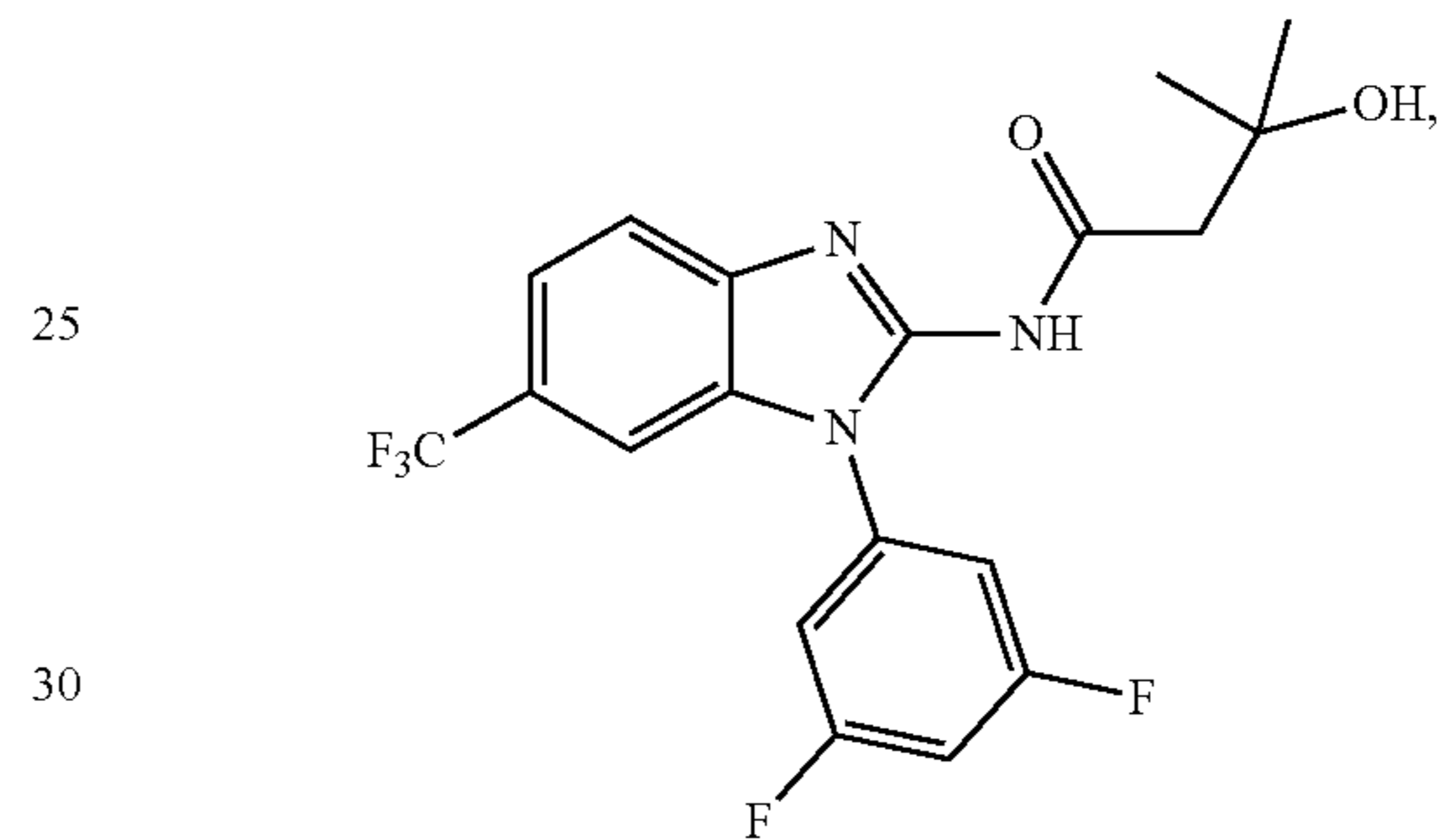
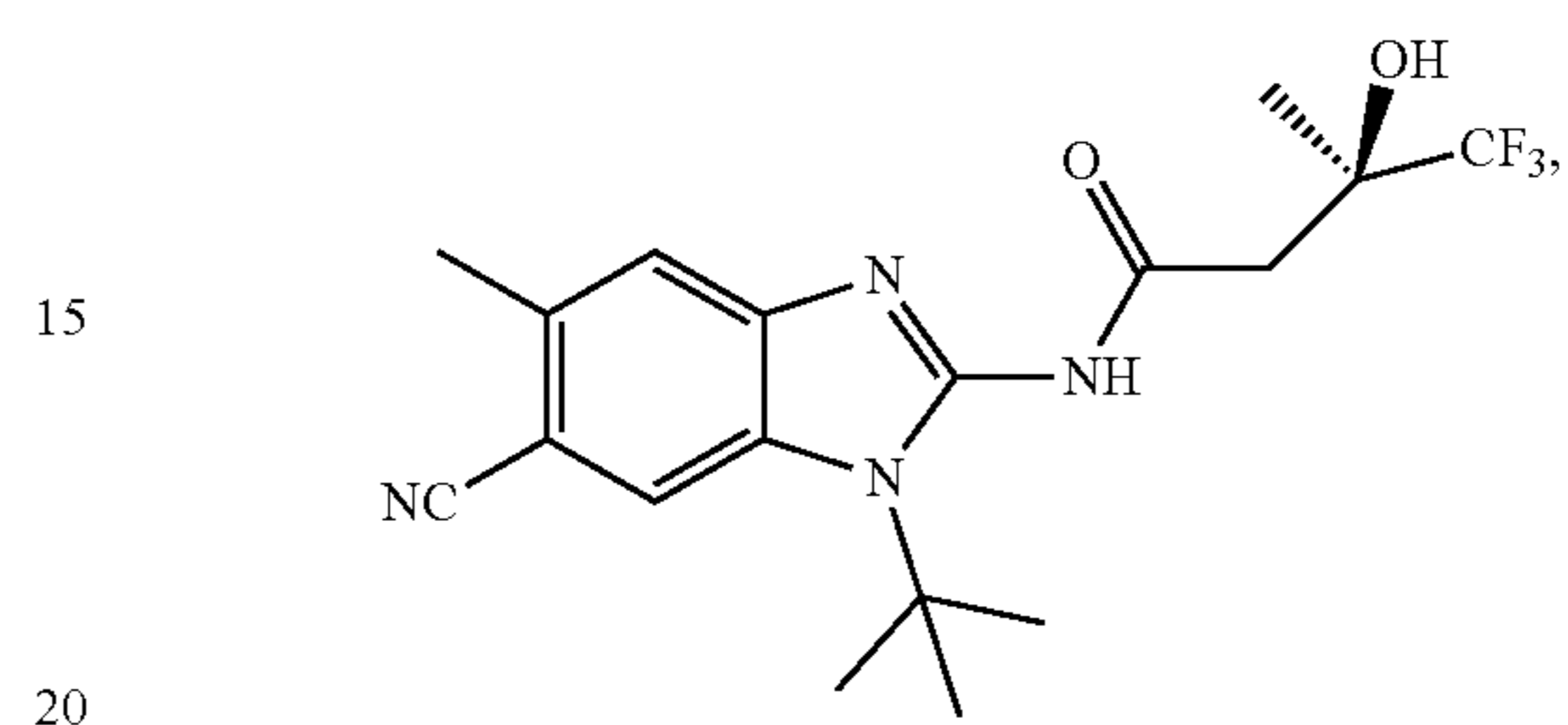
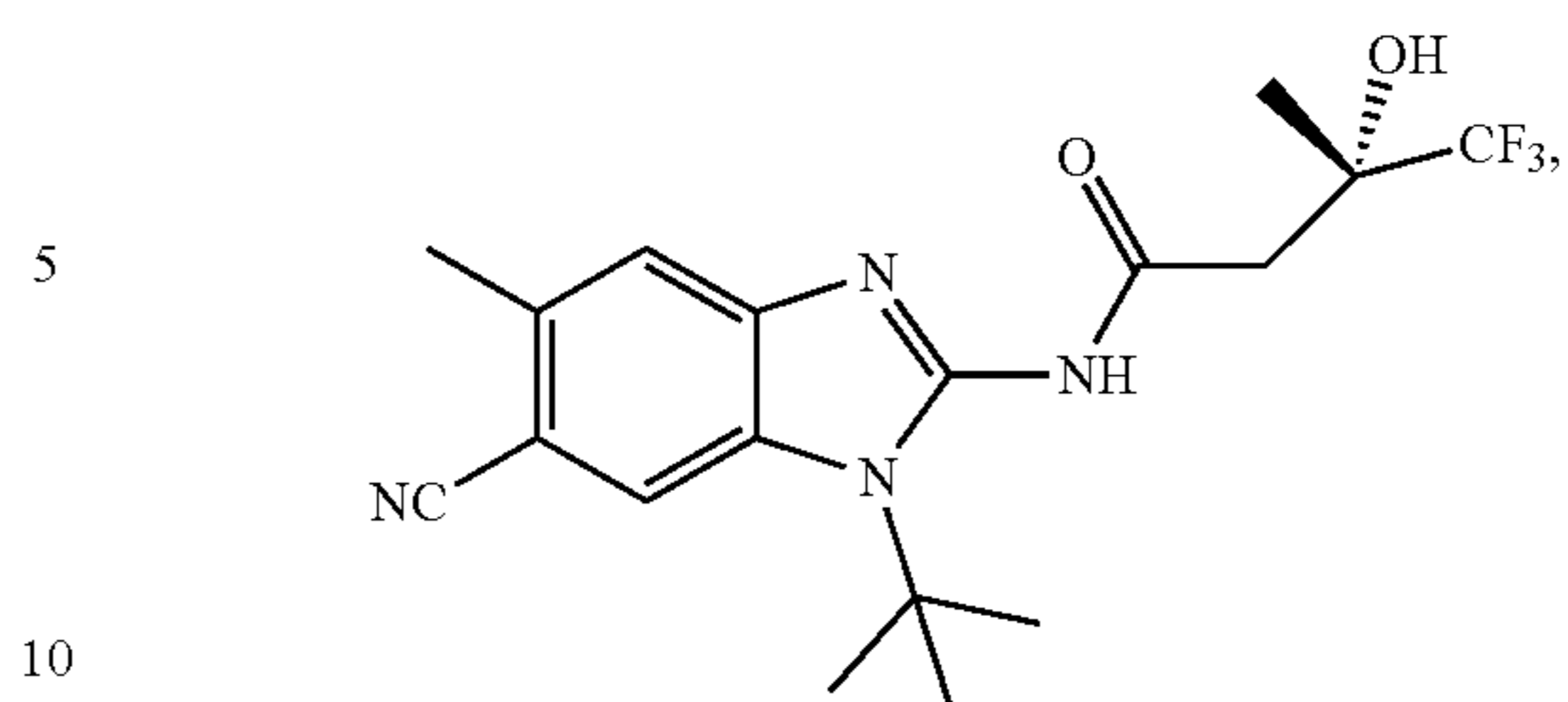
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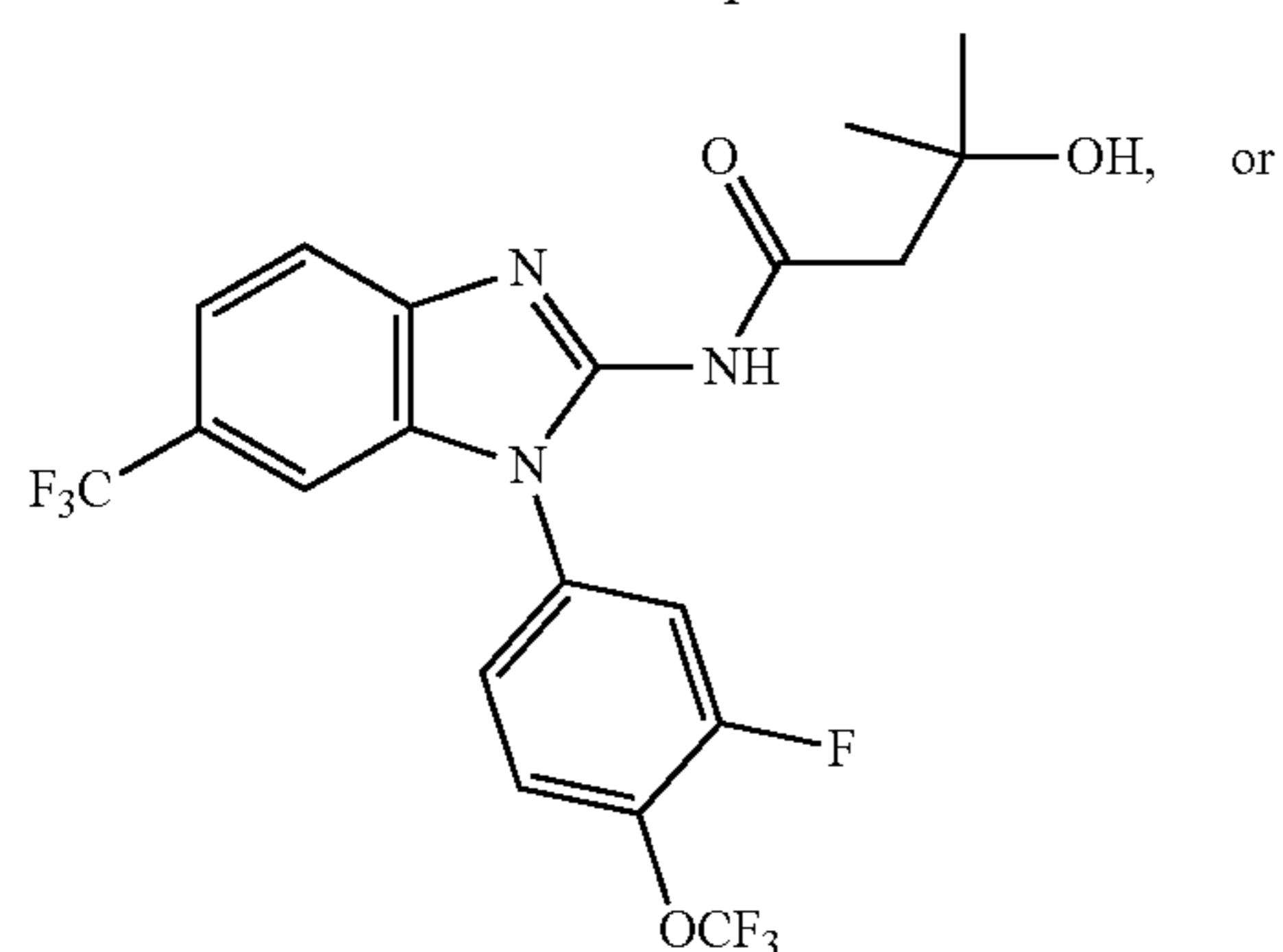
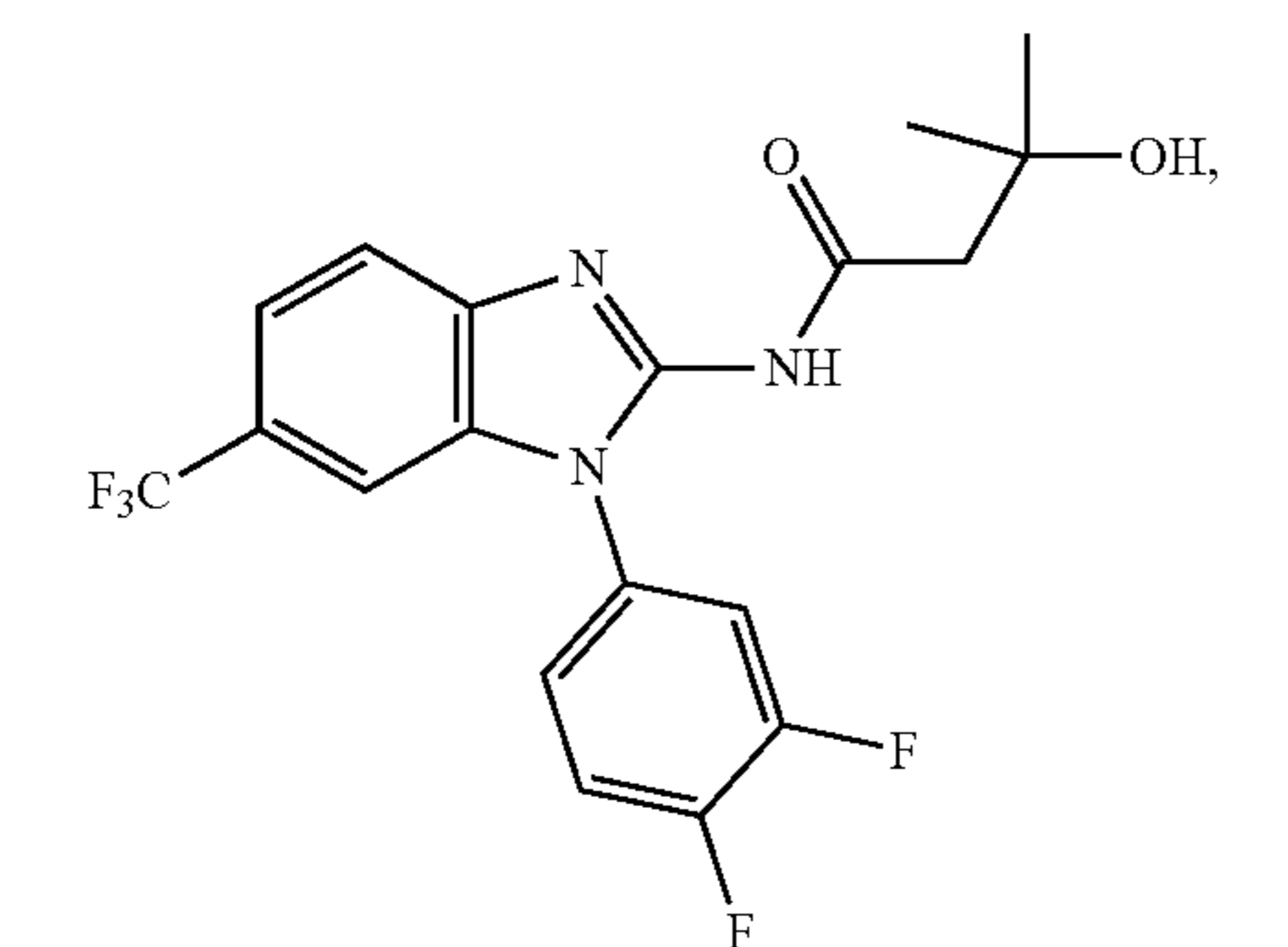
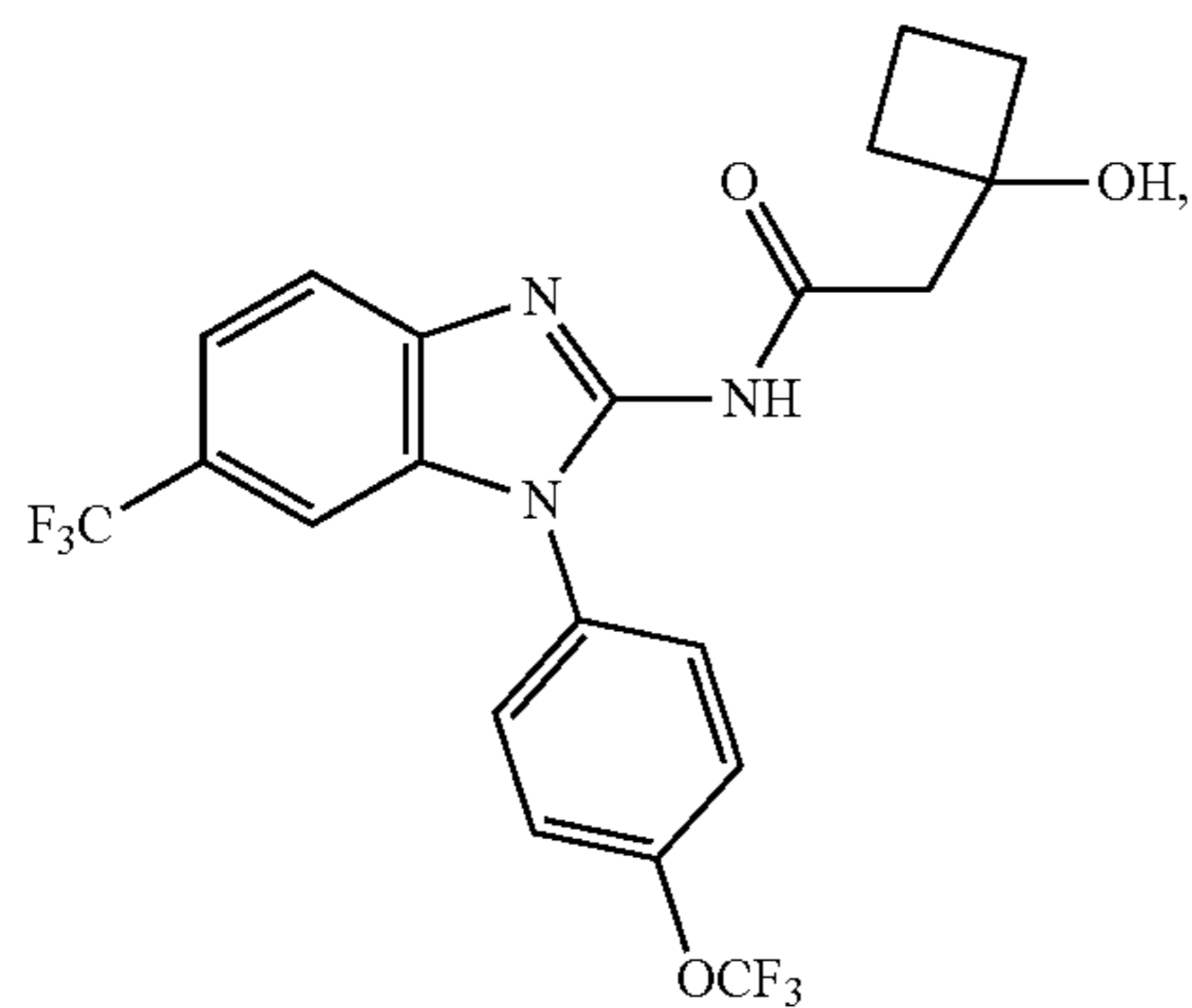
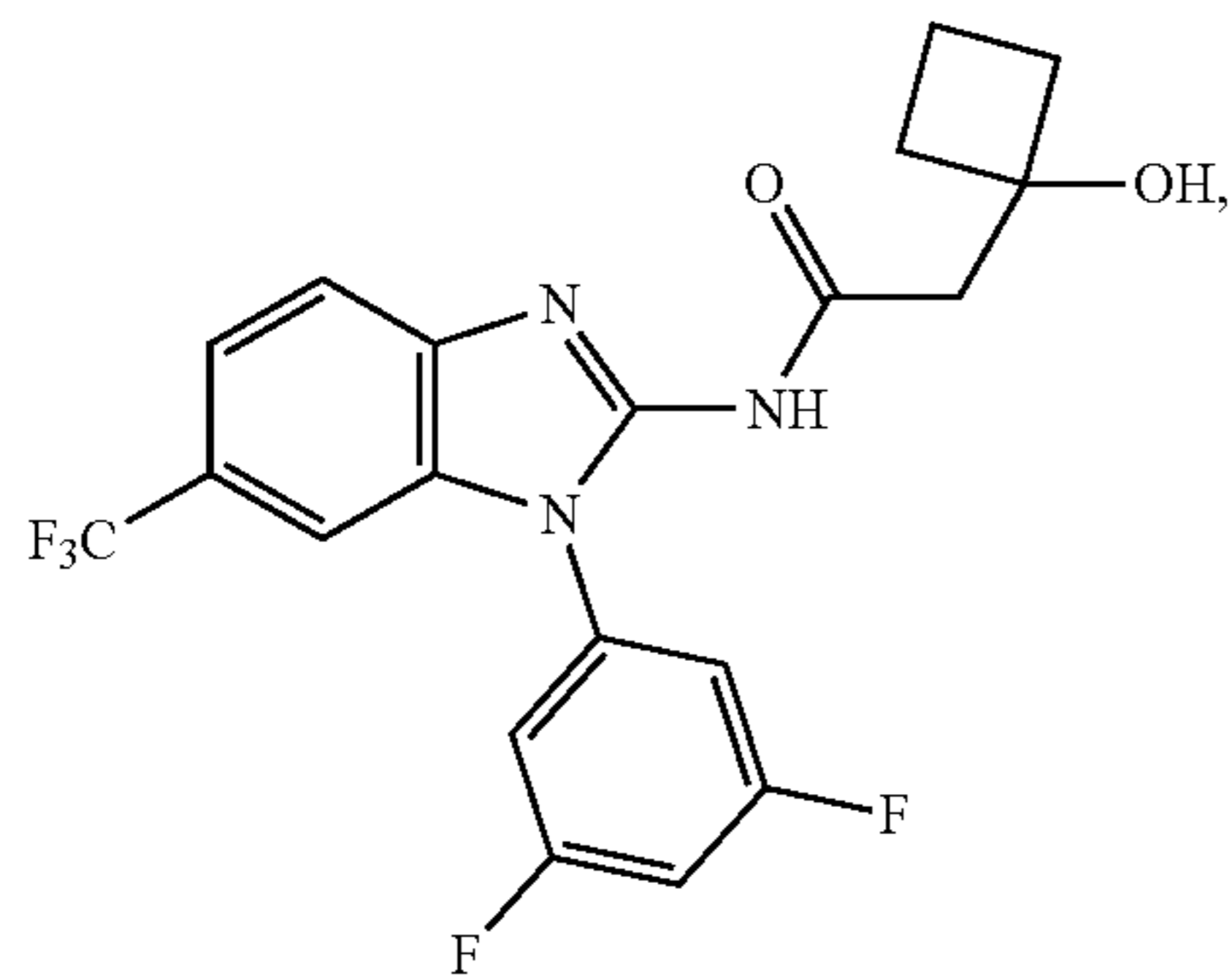
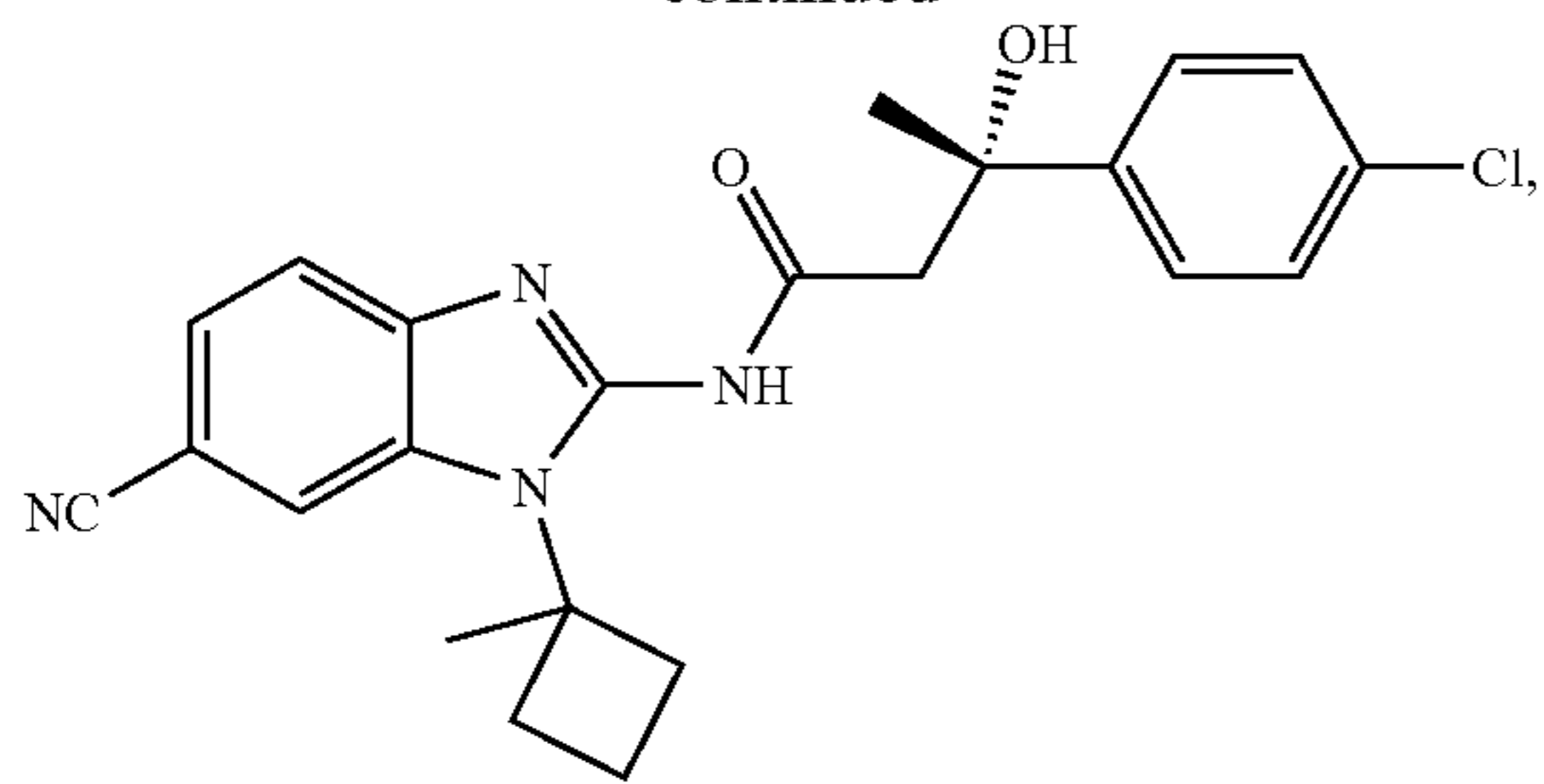
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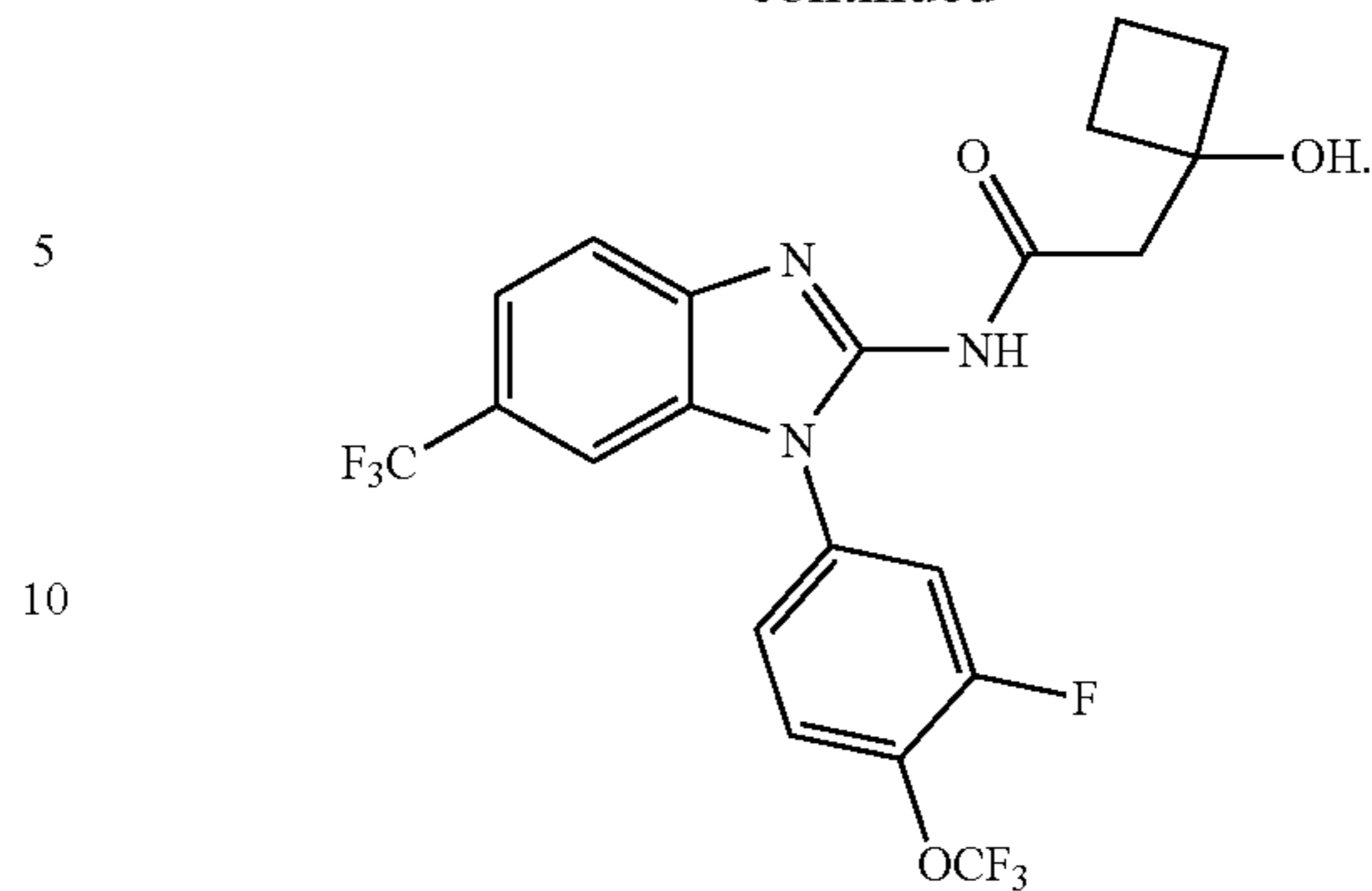
71

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72

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Embodiment 37

A composition comprising a compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36, wherein the composition is pharmaceutically acceptable.

Embodiment 38

A pharmaceutical dosage form comprising a compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36.

Embodiment 39

A method of treating a disorder associated with a Kv7 potassium channel activator comprising administering an effective amount of a compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36, to a mammal in need thereof.

Embodiment 40

The method of embodiment 39, wherein the disorder is epilepsy, pain, migraine, a disorder of neurotransmitter release, a smooth muscle contractility disorder, a dyskinesia, dystonia, mania, or a hearing disorder.

Embodiment 41

The method of embodiment 39, wherein the disorder is epilepsy, neuropathic pain, inflammatory pain, persistent pain, cancer pain, postoperative pain, migraine, anxiety, substance abuse, schizophrenia, a bladder disorder, a vasculature disorder, a dyskinesia, dystonia, mania, a hearing disorder, or tinnitus.

Embodiment 42

Use of a compound of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36, in the manufacture of a medicament for the treatment of a disorder associated with a Kv7 potassium channel activator.

Embodiment 43

The use of embodiment 42, wherein the disorder is epilepsy, pain, migraine, a disorder of neurotransmitter

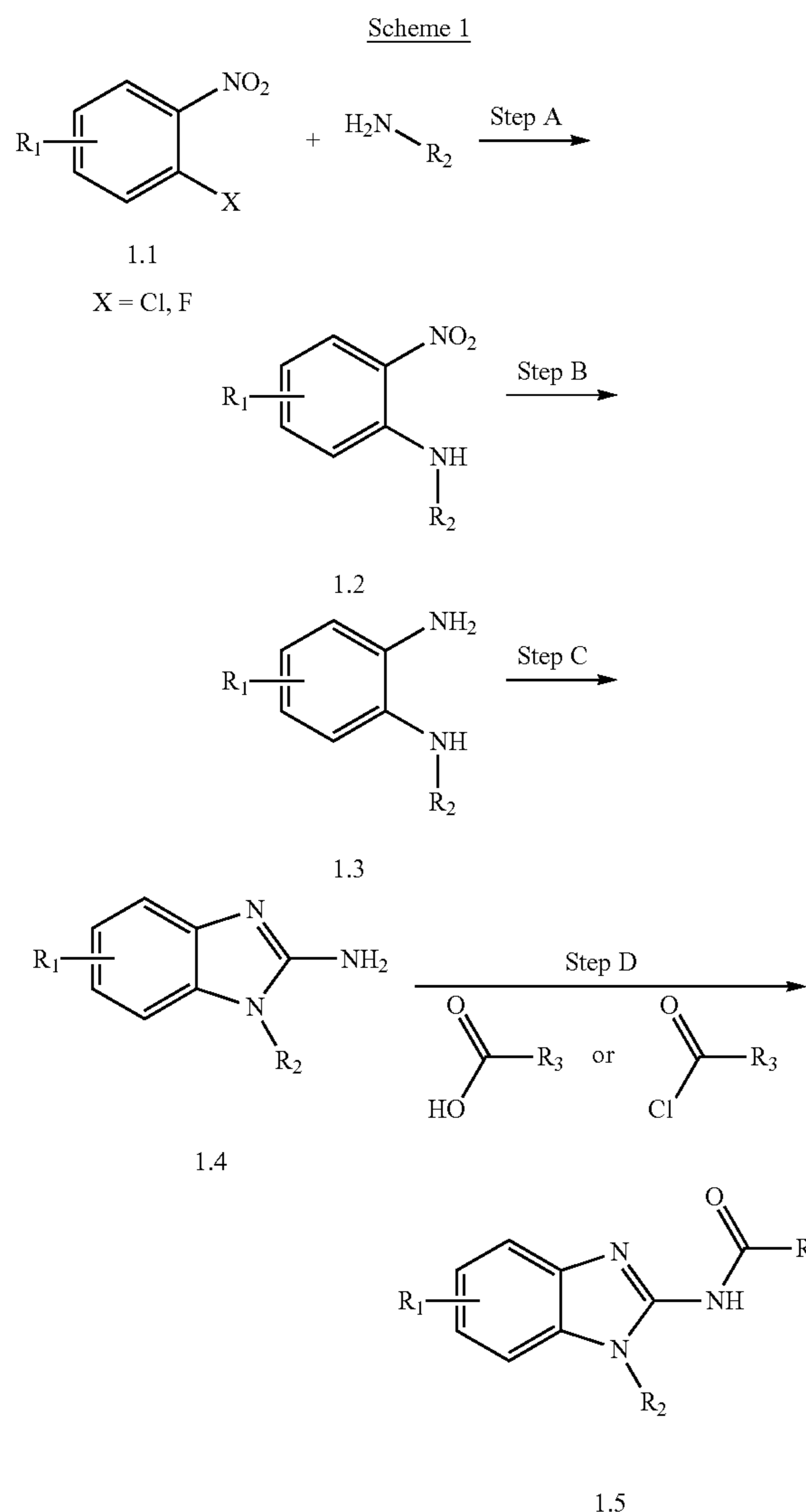
73

release, a smooth muscle contractility disorder, a dyskinesia, dystonia, mania, or a hearing disorder.

Embodiment 44

The use of embodiment 42, wherein the disorder is epilepsy, neuropathic pain, inflammatory pain, persistent pain, cancer pain, postoperative pain, migraine, anxiety, substance abuse, schizophrenia, a bladder disorder, a vasculature disorder, a dyskinesia, dystonia, mania, a hearing disorder, or tinnitus.

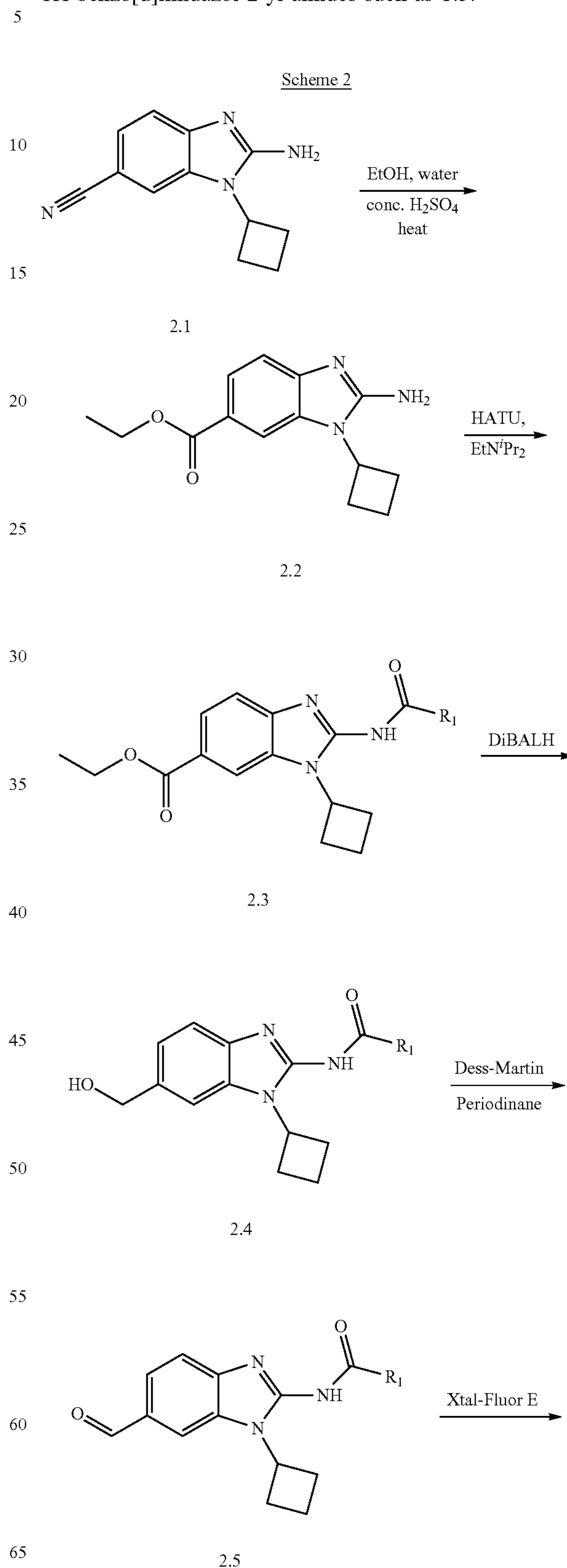
EXPERIMENTAL SECTION



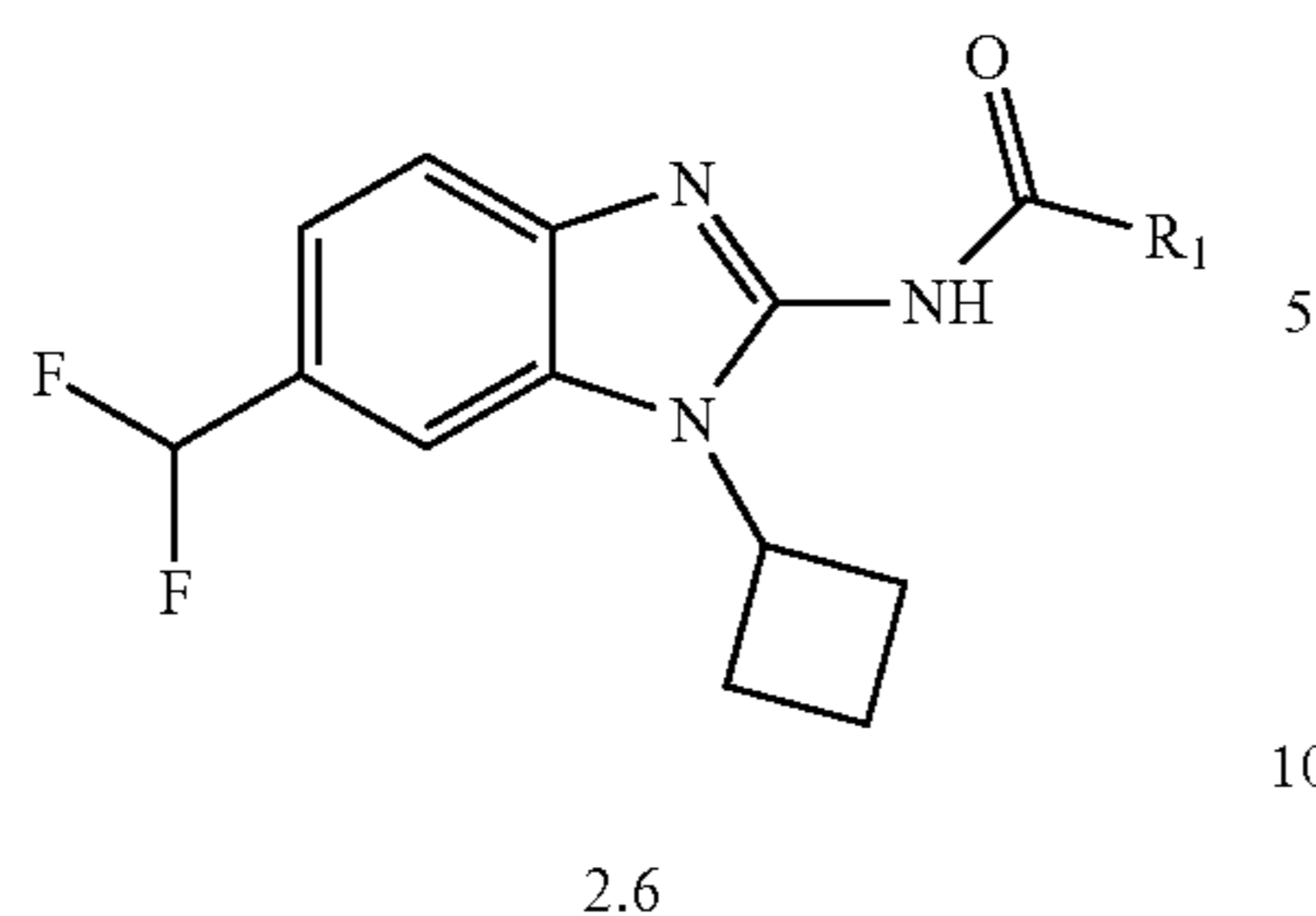
Scheme 1 shows a general methodology for the synthesis of 1H-benzo[d]imidazol-2-yl amides 1.5. An appropriately substituted 1-fluoro-2-nitrobenzene 1.1 is reacted with a primary amine to afford 1-amino-2-nitrobenzene 1.2. Alternatively, a 1-chloro-2-nitrobenzene is reacted with a primary amine under palladium catalysis to provide the desired 1-amino-2-nitrobenzene 1.2. The nitro group may be reduced to the corresponding amine by a variety of well-established methods to provide 1,2-diaminobenzenes 1.3.

74

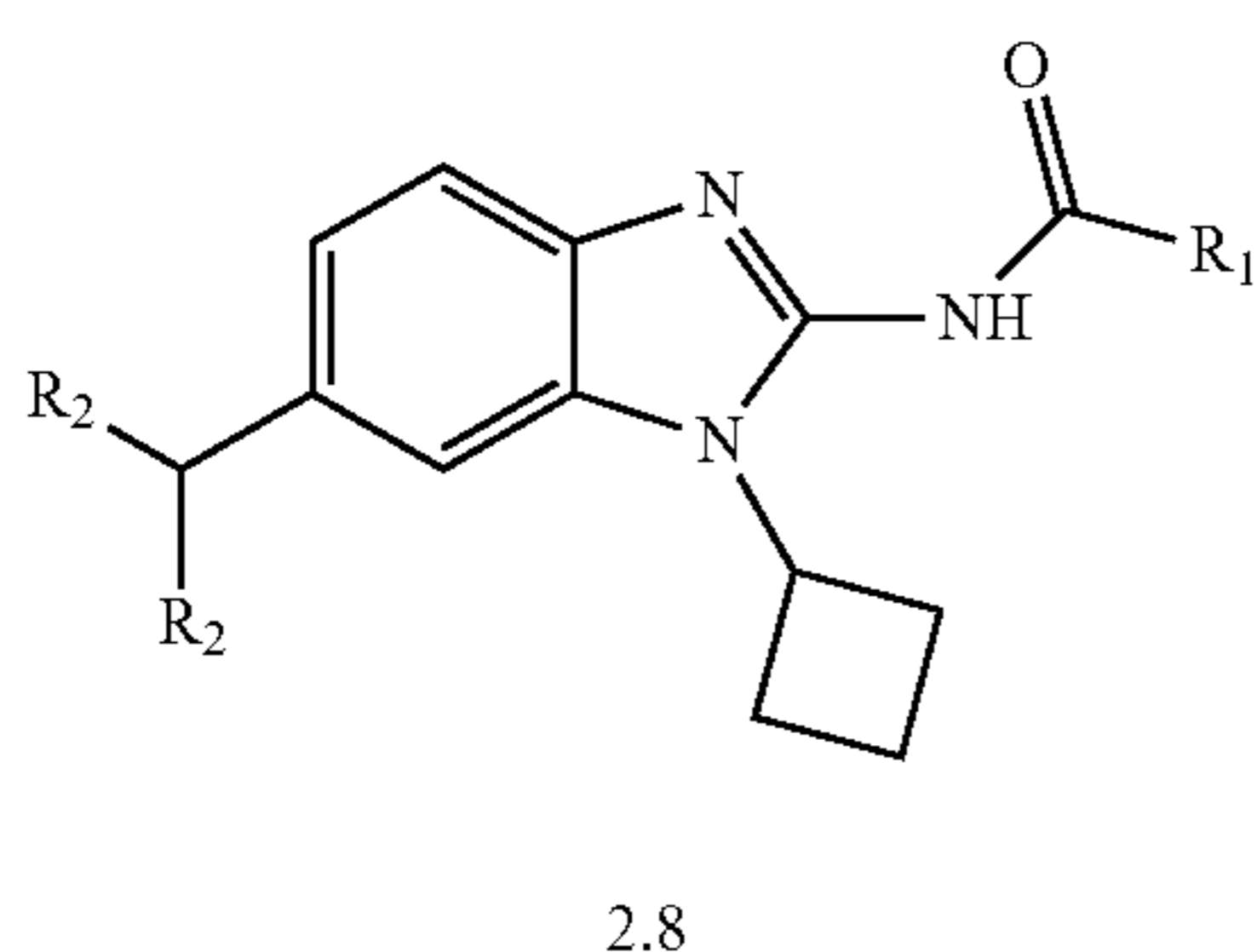
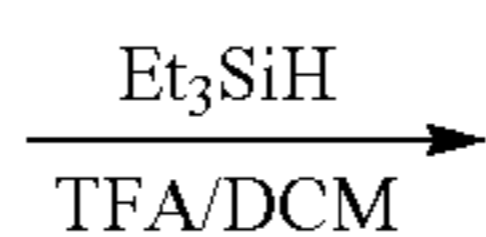
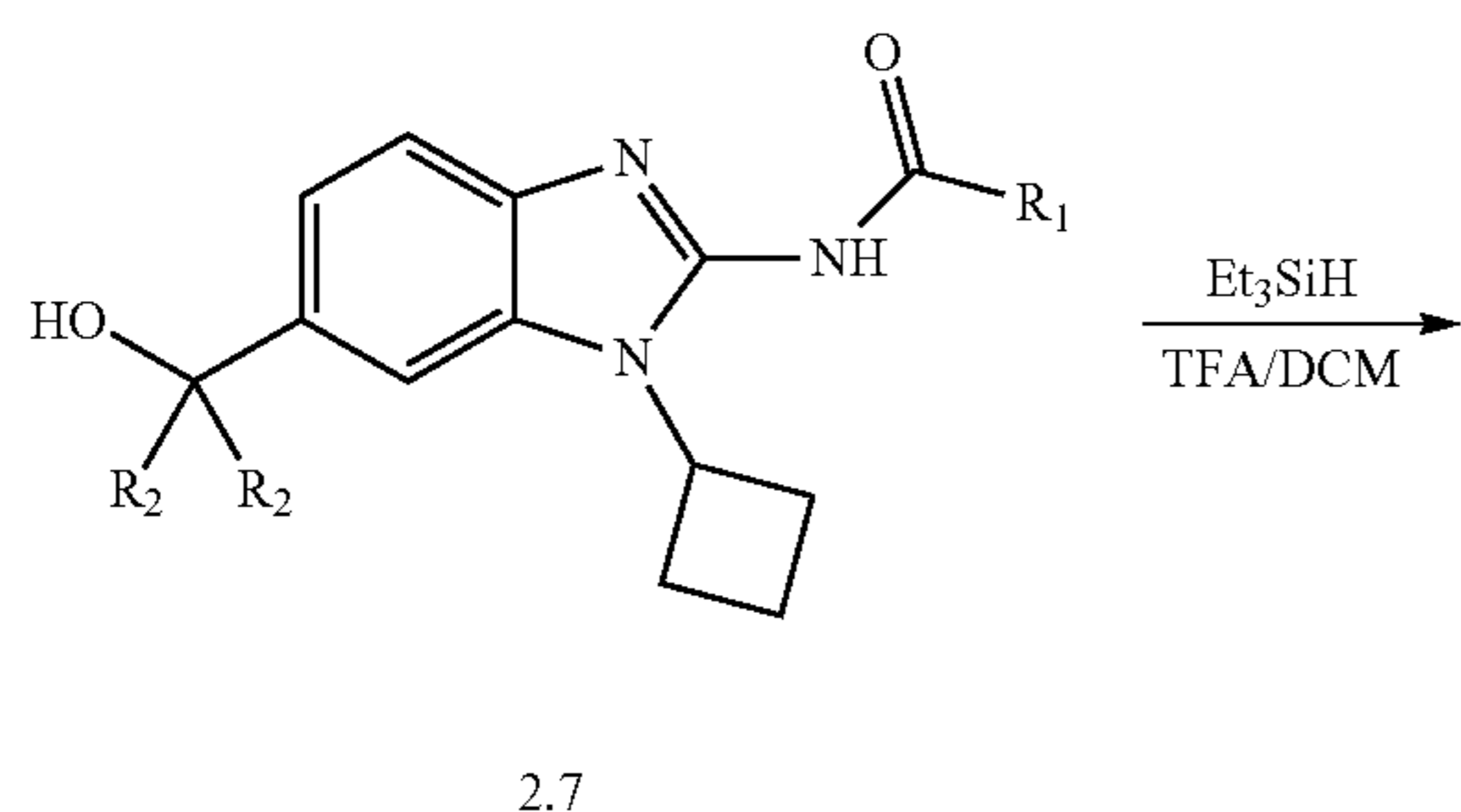
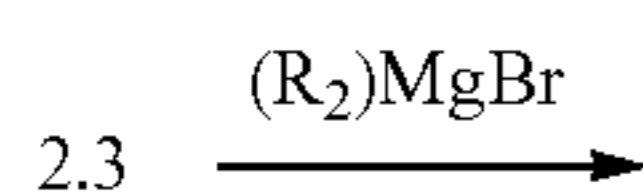
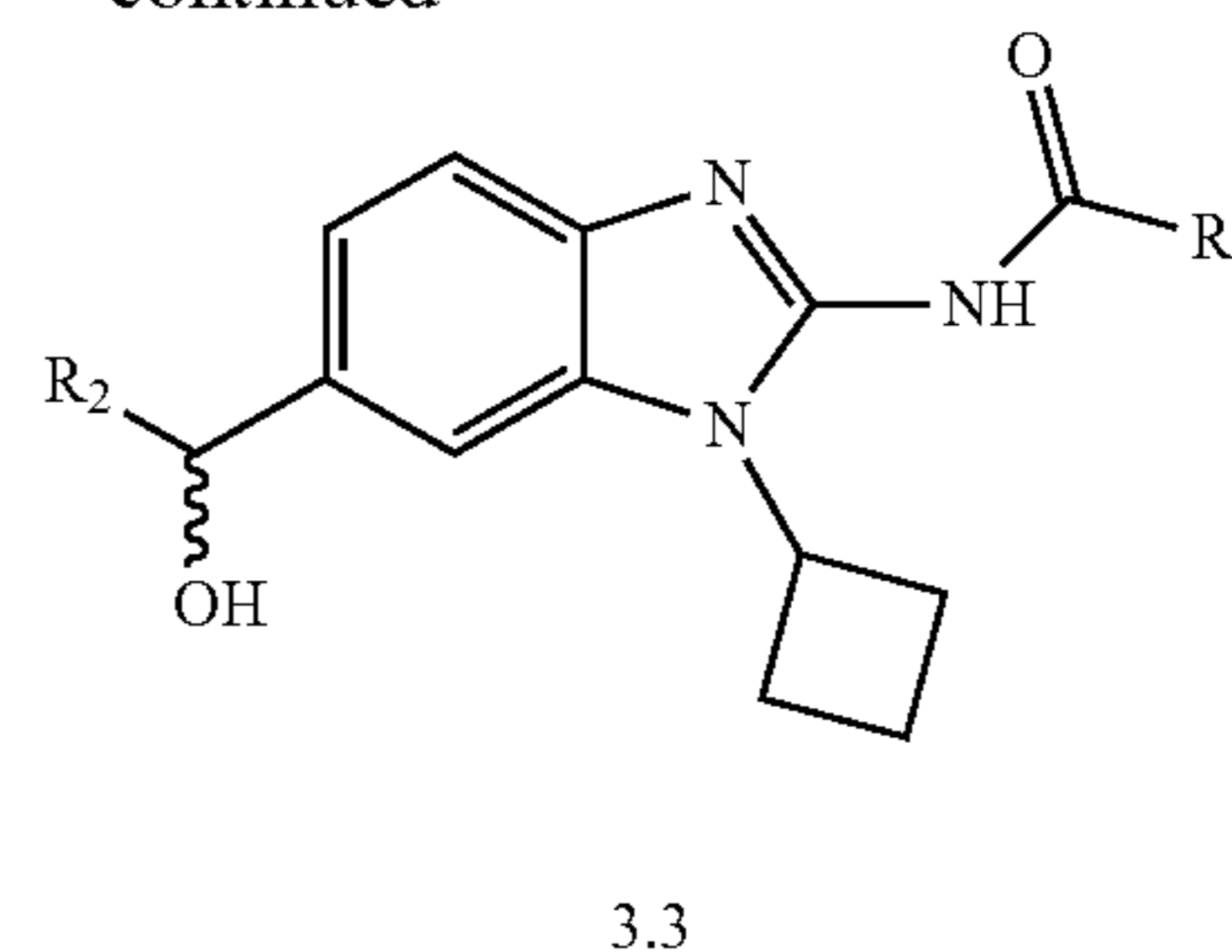
Reaction of 1.3 with cyanogen bromide affords 1H-benzo[d]imidazol-2-amine 1.4. Amide coupling with either an appropriate carboxylic acid or acyl chloride can afford 1H-benzo[d]imidazol-2-yl amides such as 1.5.



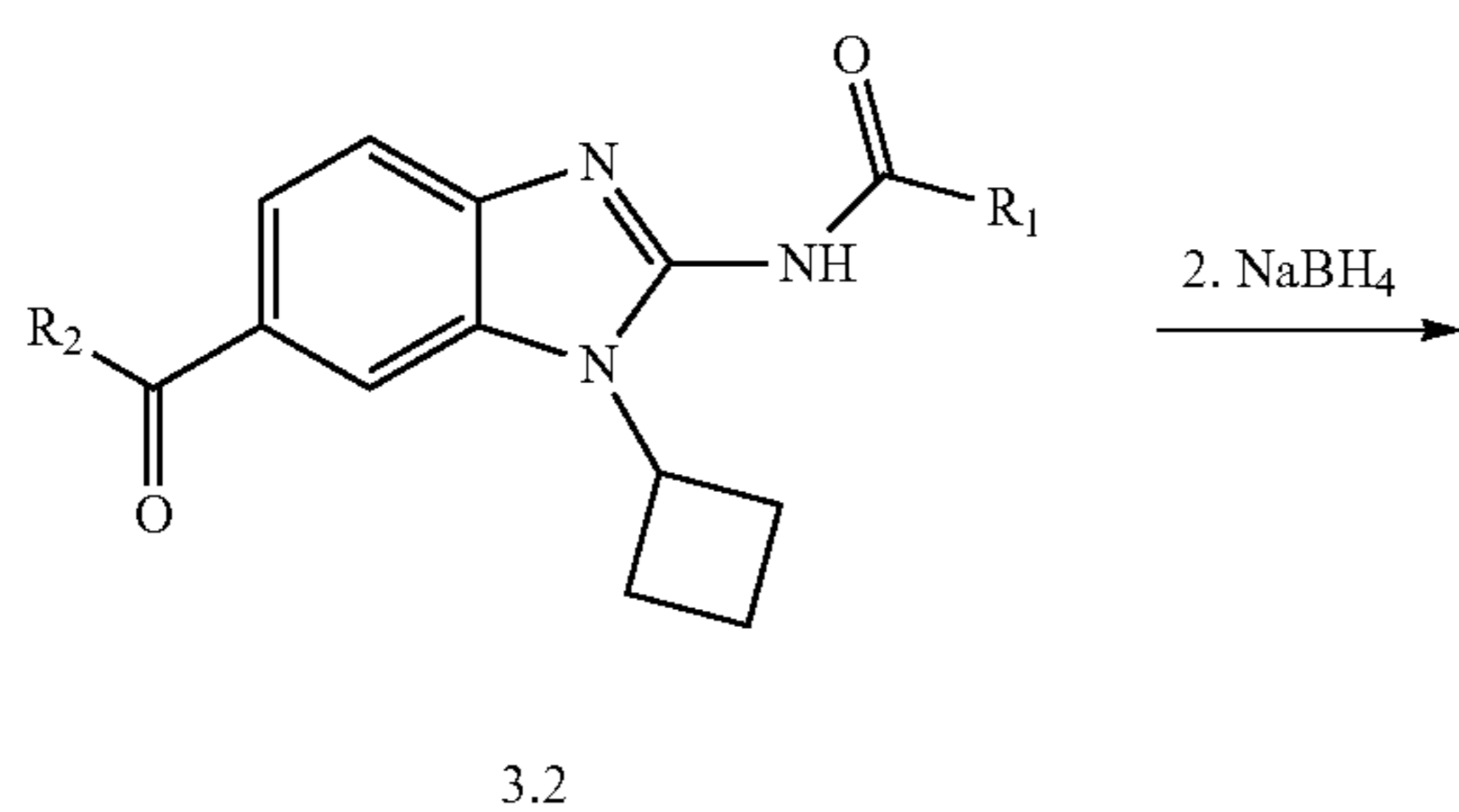
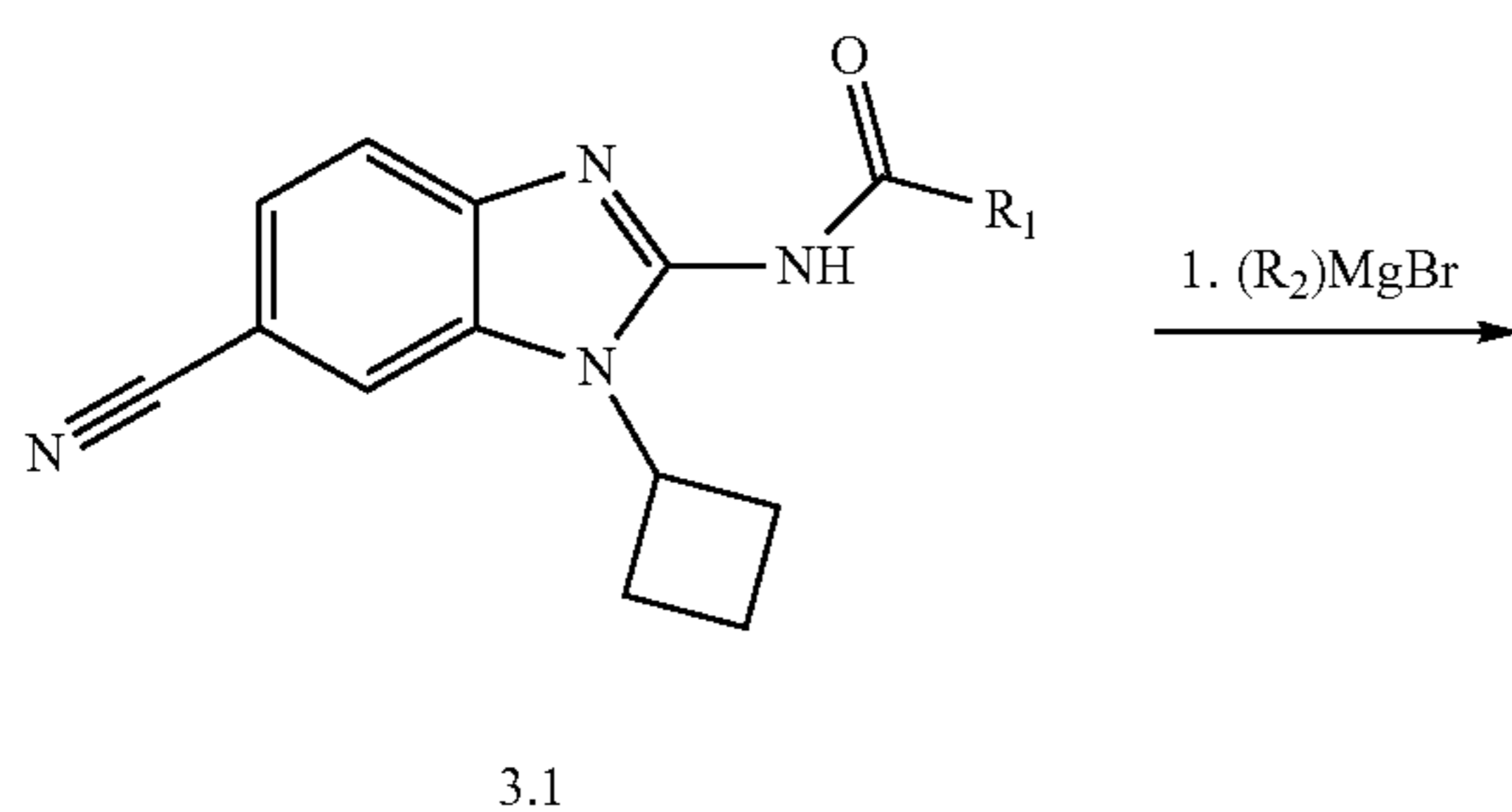
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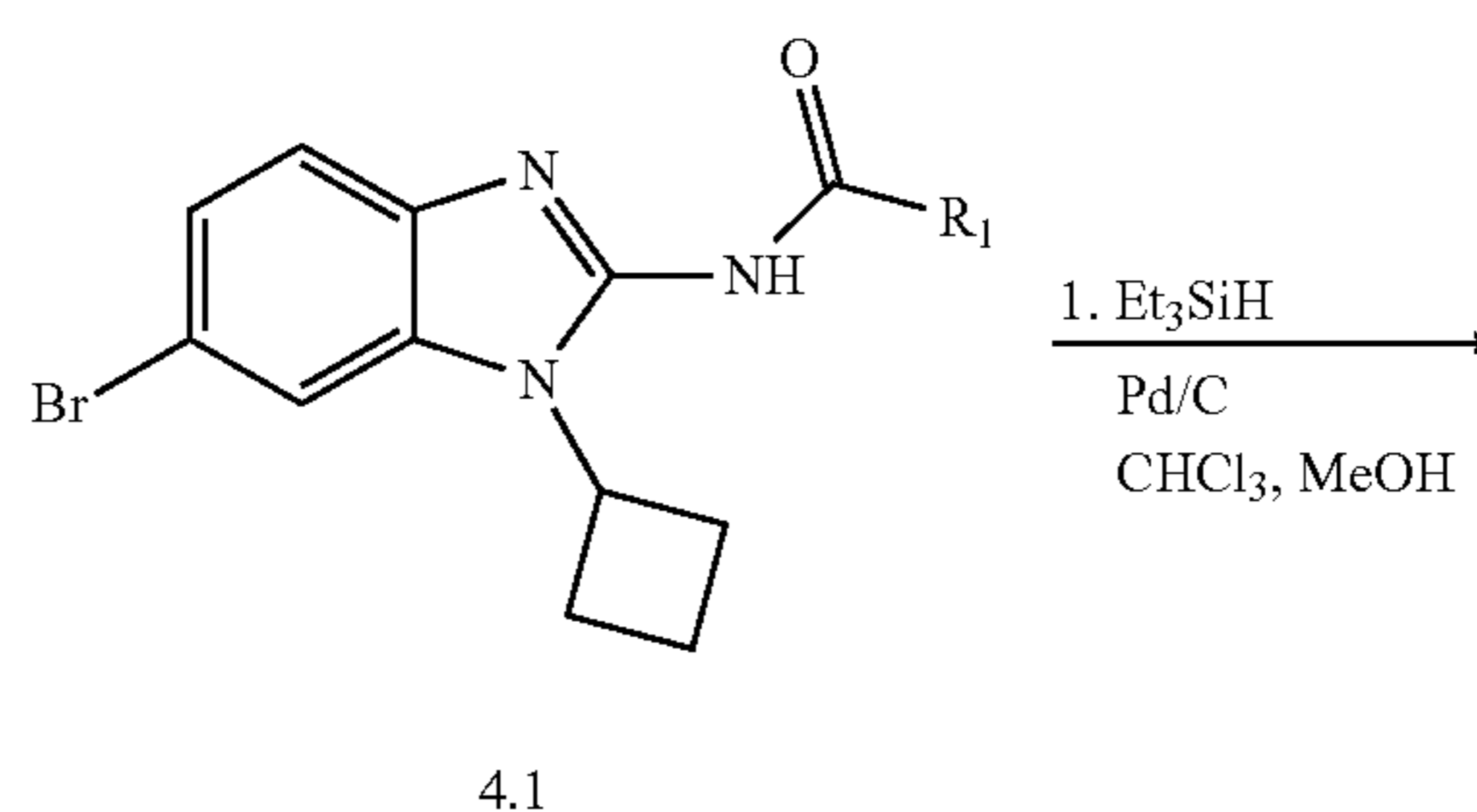
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Scheme 3



Scheme 4

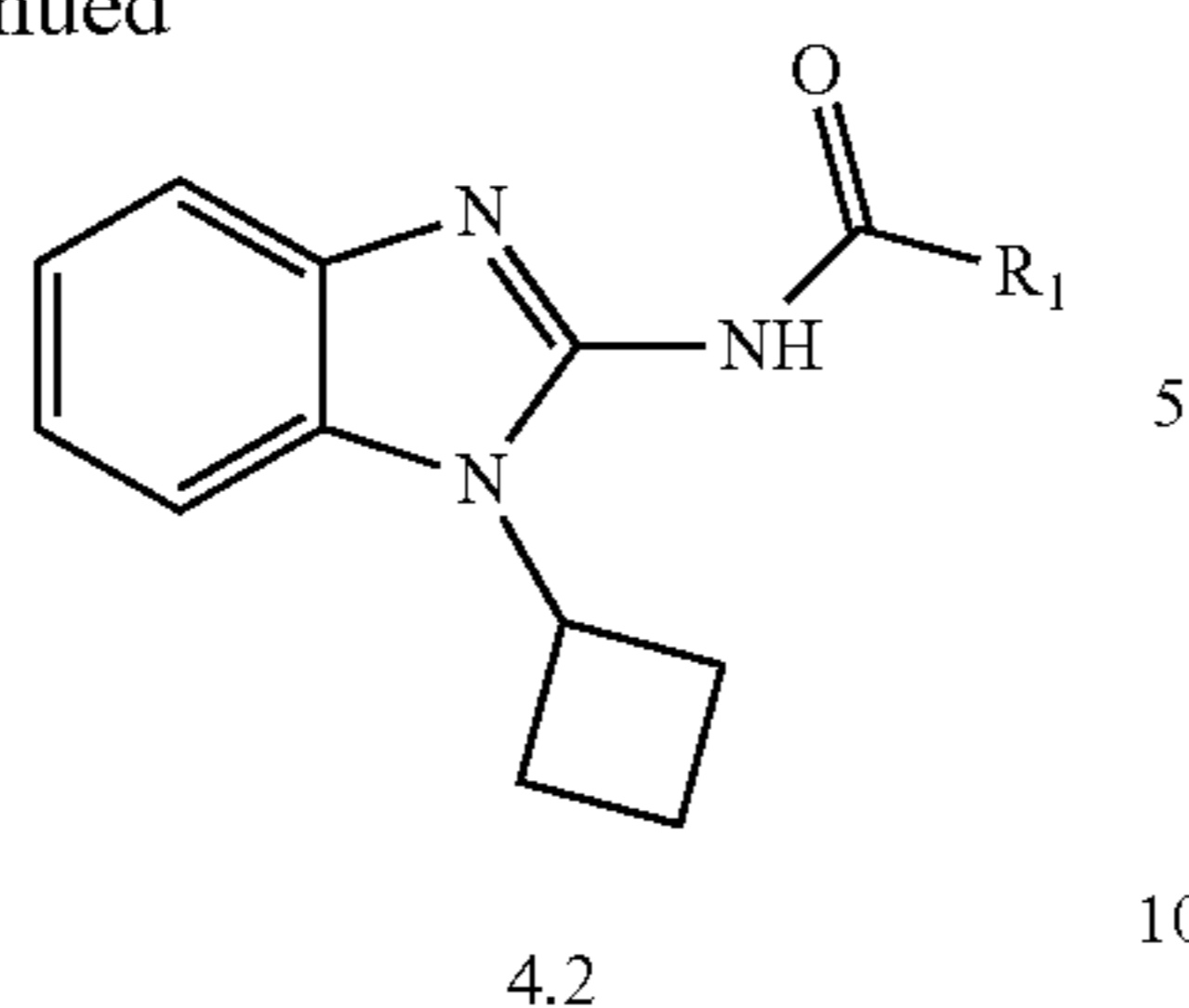


Scheme 2 and Scheme 3 describe general methodologies that may be used to create novel Kv7 modulators after the initial amide bond forming reaction has been used to synthesize 1H-benzo[d]imidazol-2-yl amides such as 2.3. Sulfuric acid-promoted ethanolysis of the nitrile in 2-amino-1-cyclobutyl-1H-benzo[d]imidazole-6-carbonitrile (2.1) gives the ethyl ester 2.2. This amino-heterocycle may be used as the amine in a standard amide bond forming reaction to give the ester amide 2.3. The ethyl ester may serve as a synthetic handle to access various other functional groups. The ester may be reduced with DiBAL-H to the primary alcohol 2.4. Alternatively, excess Grignard reagent may be used to generate a tertiary alcohol 2.7. The primary alcohol 2.4 may be readily oxidized with the Dess-Martin periodinane or a similar oxidant to generate an intermediate aldehyde 2.5. The aldehyde 2.5 may serve as the input for a difluorination reaction, for example using Xtal-FluorE reagent, to provide the difluoromethyl-substituted amides 2.6 (see Couturier, M, et al, *J. Org. Chem.* 2010, 75, 3401-3411). The tertiary alcohols 2.7 may be reduced under the action of triethylsilane and trifluoroacetic acid in dichloromethane to give the branched benzylic alkyl groups present in amides 2.8. It is noteworthy that the new molecules 2.4-2.8 are convenient as intermediates for further conversion into additional benzoring substituents, such as amides, ethers, and heterocycles, using known methodologies.

A range of functional groups may be orthogonally transformed in the presence of the amide functionality of 1H-benzo[d]imidazol-2-yl amides. Scheme 3 shows how the nitrile 3.1 may be selectively reacted with a Grignard reagent to produce an aryl ketone 3.2. This ketone may be reduced with common hydride reagents, such as sodium borohydride, to give the secondary alcohol 3.3. Such ketone reductions may be conducted in a stereochemically-defined manner, using a variety of chiral reducing reagents known in the literature (e.g. via CBS reagent, see Corey, E J, Shibata, S, Bakshi, R K, *J. Org. Chem.* 1988, 53, 2861-2863).

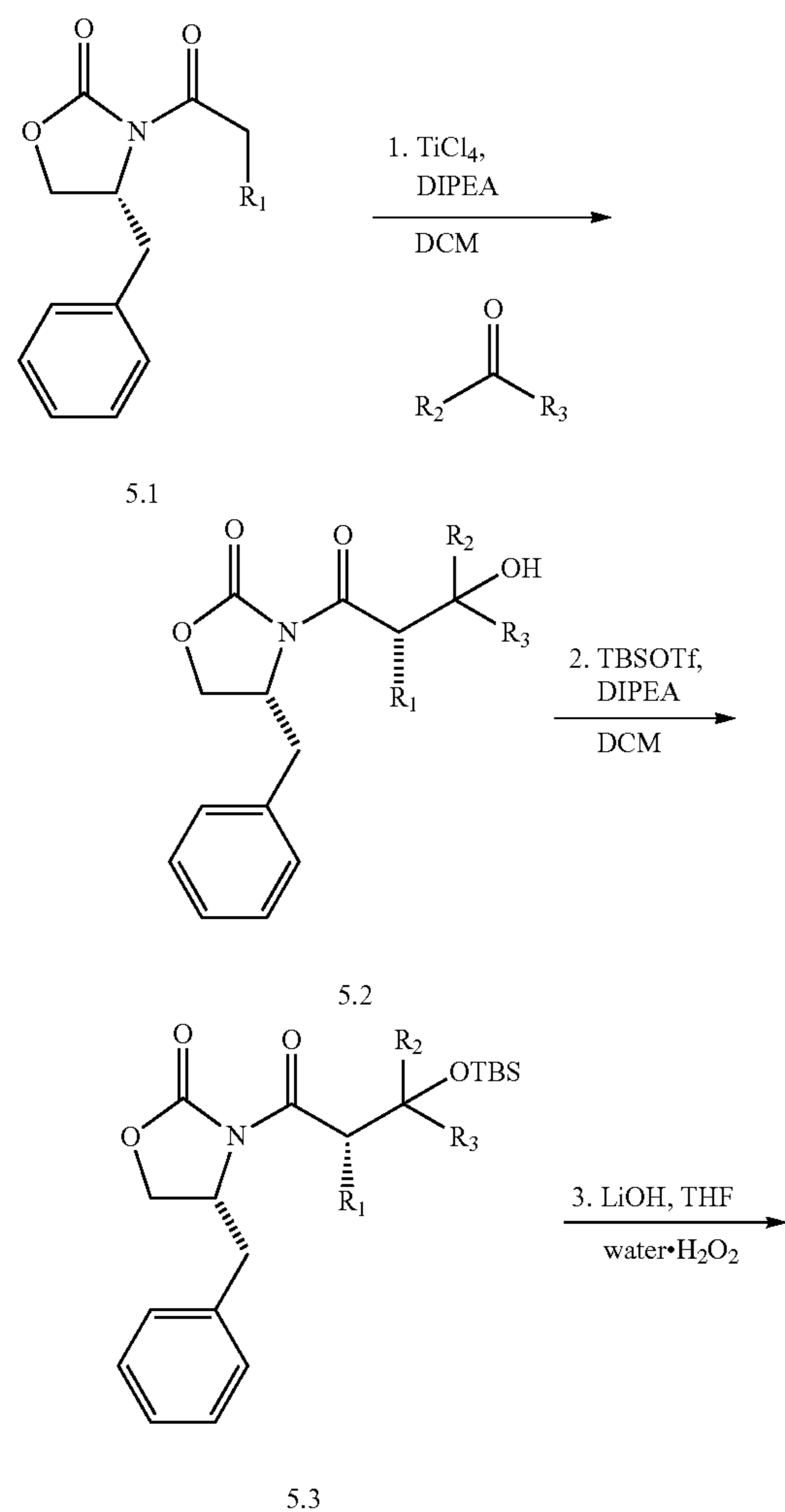
77

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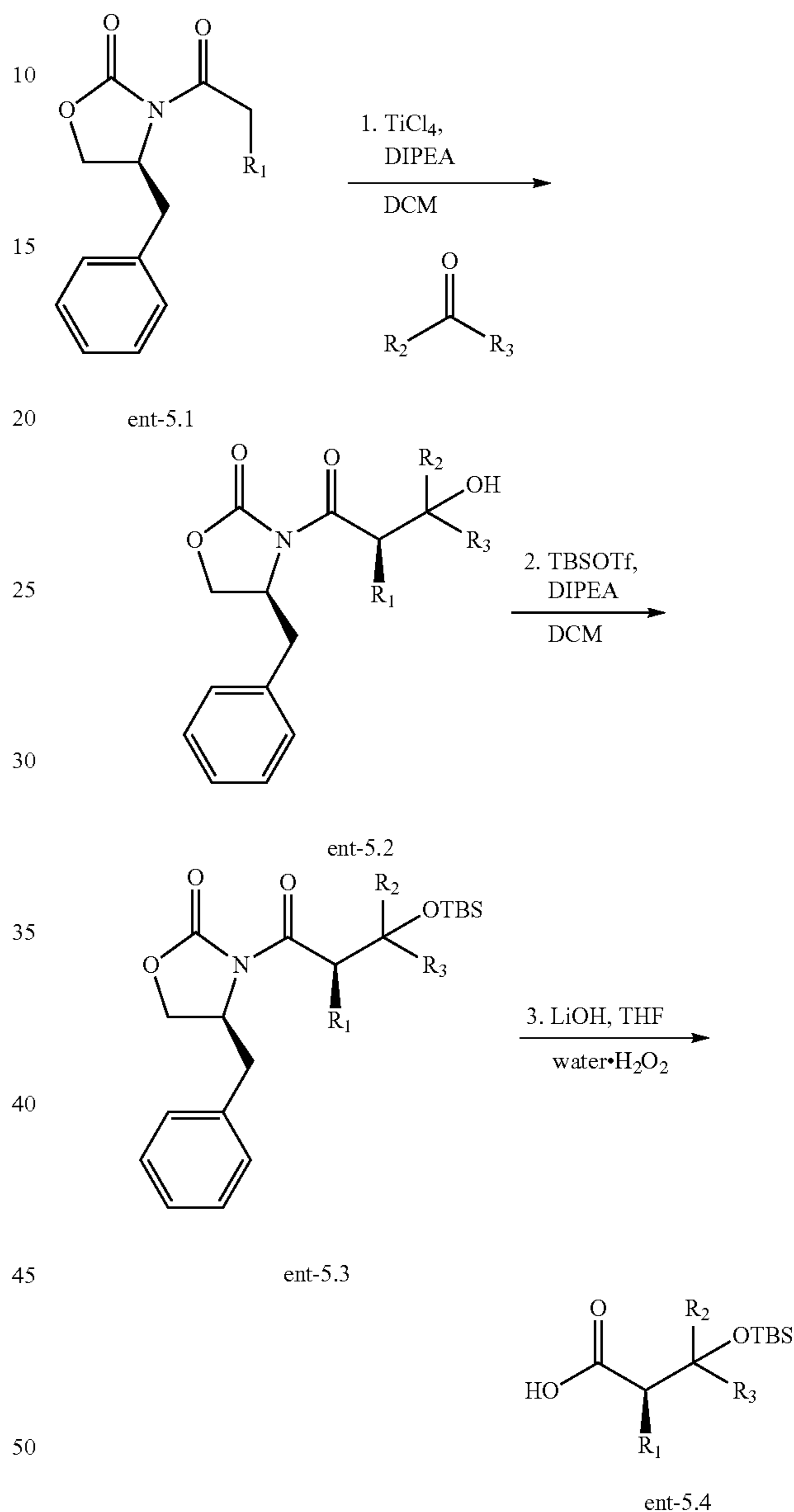
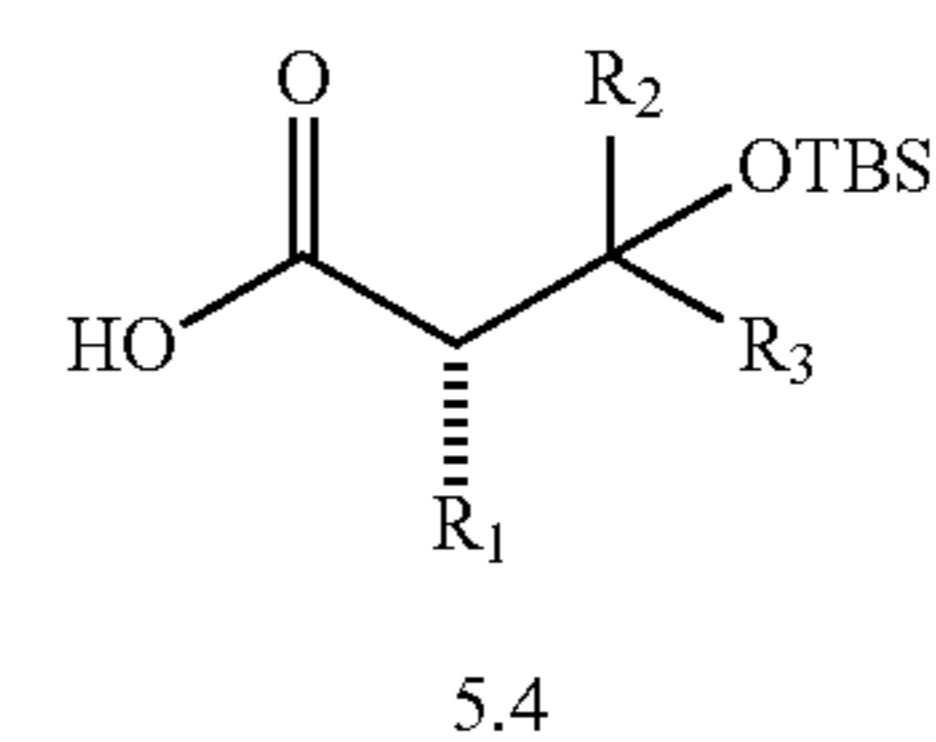
The general methodology of Scheme 1 may be used to synthesize a wide range of functionalized 1H-benzo[d]imidazol-2-yl amides. Bromide 4.1 in Scheme 4 is an example of a halogenated-1H-benzo[d]imidazol-2-yl amide that also provides an orthogonally reactive functional group. The bromide may be reduced with the action of triethylsilane in chloroform and methanol with a catalytic amount of palladium on charcoal to give the debrominated product 4.2 (see Mandal, P K, McMurray, J S, *J. Org. Chem.* 2007, 72, 6599-6601). The aromatic bromide in 4.1 may also be used to perform palladium cross coupling reactions such as Sonogashira, Suzuki, or Stille reactions to provide alkynes, biaryl or other cross coupled products.

Scheme 5



78

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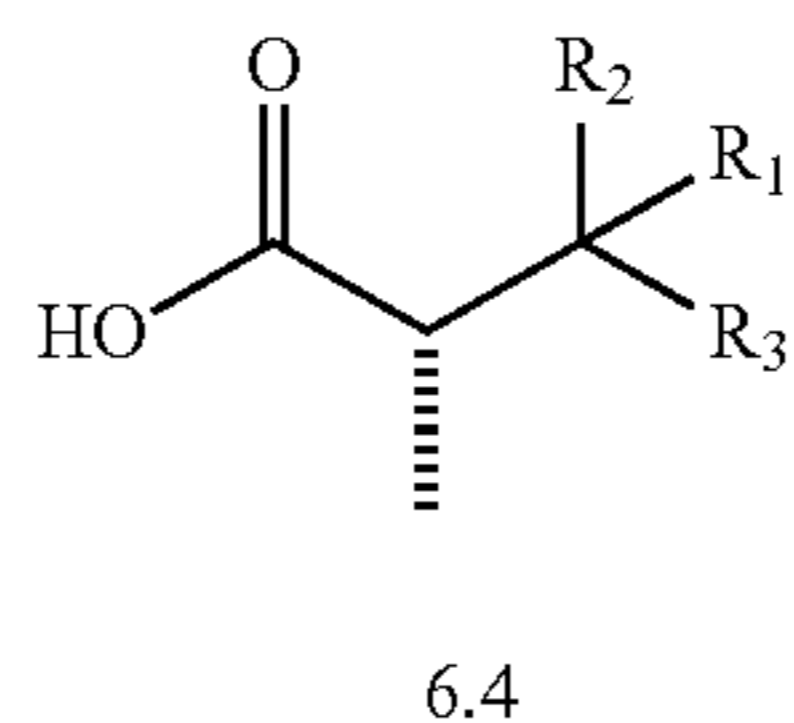
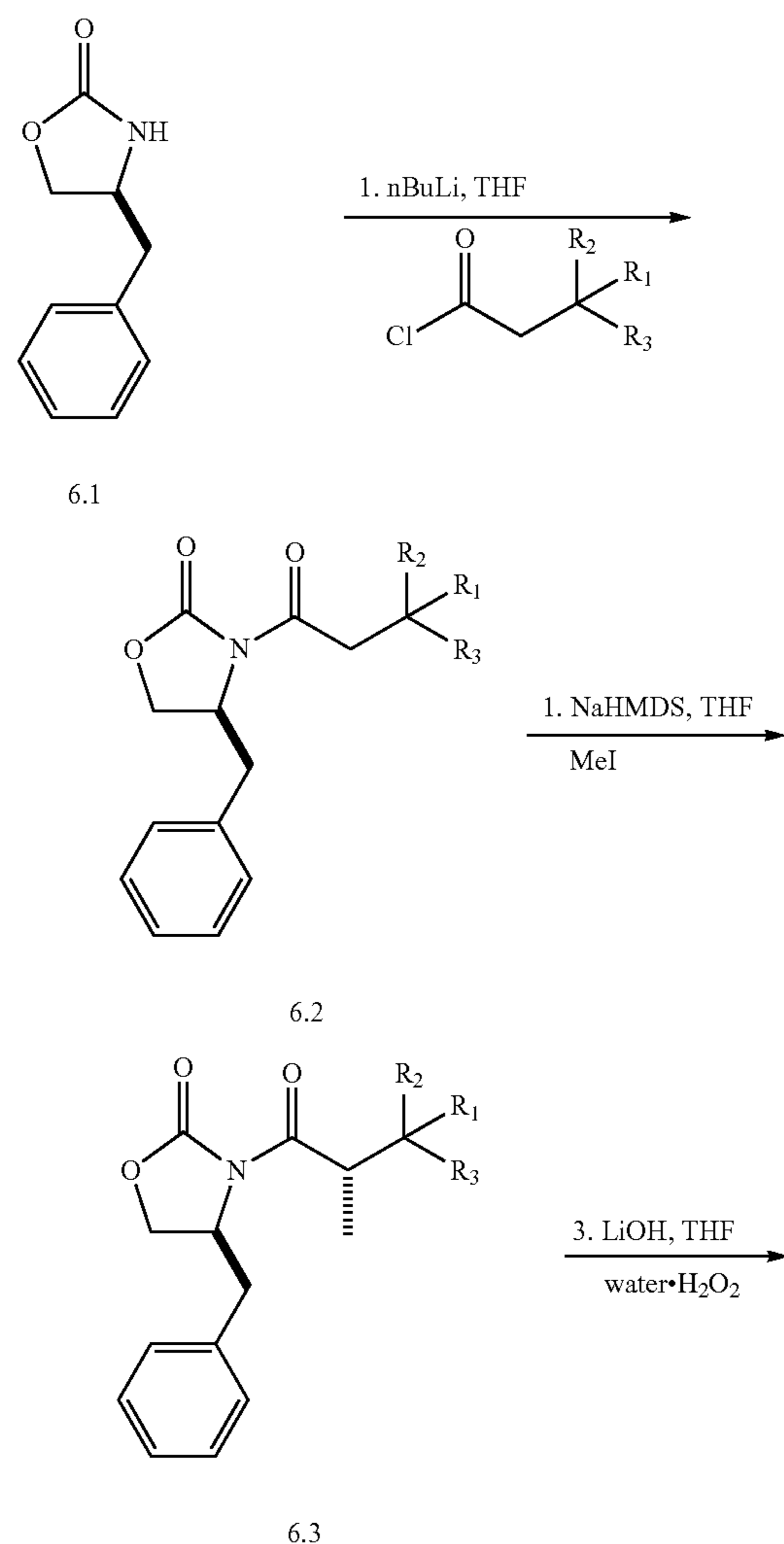


Scheme 5 describes a general synthetic method for the synthesis of chiral α -alkyl carboxylic acids that contain β -silyloxy ether protected acids 5.4 or ent-5.4. These optically active acids are used as the acid component in amide forming reaction (Step D of Scheme 1) to give β -tertiary alcohol amides. The diastereoselective bond construction via titanium enolate chemistry described by Evans was used to condense chiral imide 5.1 or ent-5.1 with a ketone or other electrophile to give diastereomerically pure aldol adducts 5.2 or ent-5.2, respectively (see Evans, D A, Urpi, F, Somers, T C, Clark, J S, Bilodeau, M T, *J. Am. Chem. Soc.* 1990, 112, 8215-8216). The proper choice of chiral imide 5.1 will give rise to the desired absolute stereochemistry of the α -stereocenter in the carboxylic acids 5.4 or ent-5.4. Silyl ether

79

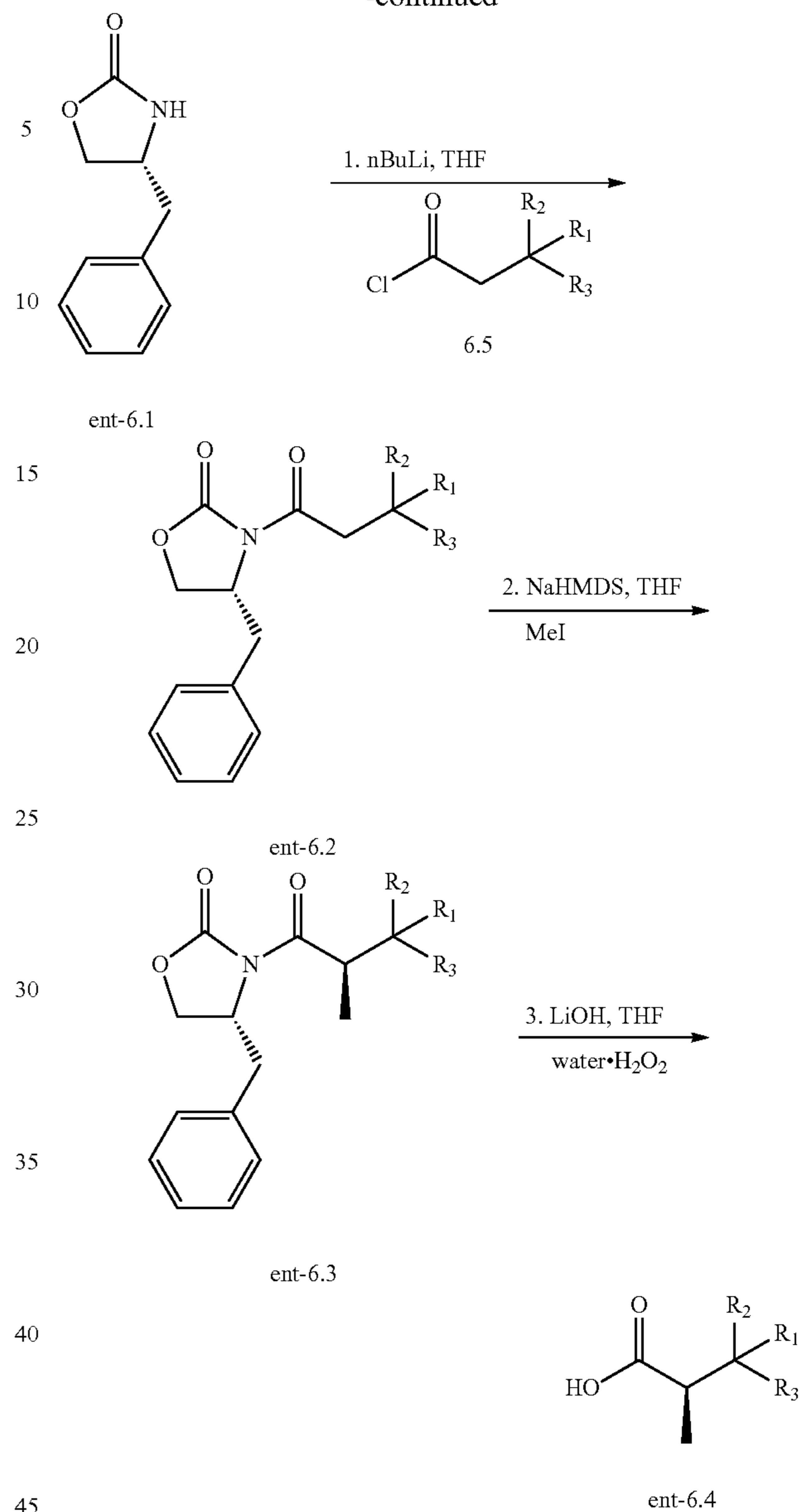
protection of the aldol adducts 5.2 and ent-5.2 with tert-butyltrimethylsilyltriflate and diisopropylethylamine gives the tert-butyltrimethylsilyl ethers 5.3 and ent-5.3. Standard acyl oxazolidinone hydrolysis conditions using lithium hydroxide and hydrogen peroxide in tetrahydrofuran and water provides the desired acids 5.4 or ent-5.4 (see Evans, D A, Britton, T C, Ellman, J A, *Tetrahedron Lett.* 1987, 28(49), 6141-6144). Proper selection of ketones or other electrophiles in the titanium enolate chemistry will give rise to appropriately substituted aldol adducts that vary in the nature of the R₂ and R₃ groups. Changing the R₁ group of the starting imides 5.1 and ent-5.1 may be used to vary the size and nature of the R₁ group in the acids 5.4 or ent-5.4. This methodology allows one to synthesize a wide range of optically active acids with absolute stereocontrol of the α-chiral center to the carbonyl of the carboxylic acid.

Scheme 6



80

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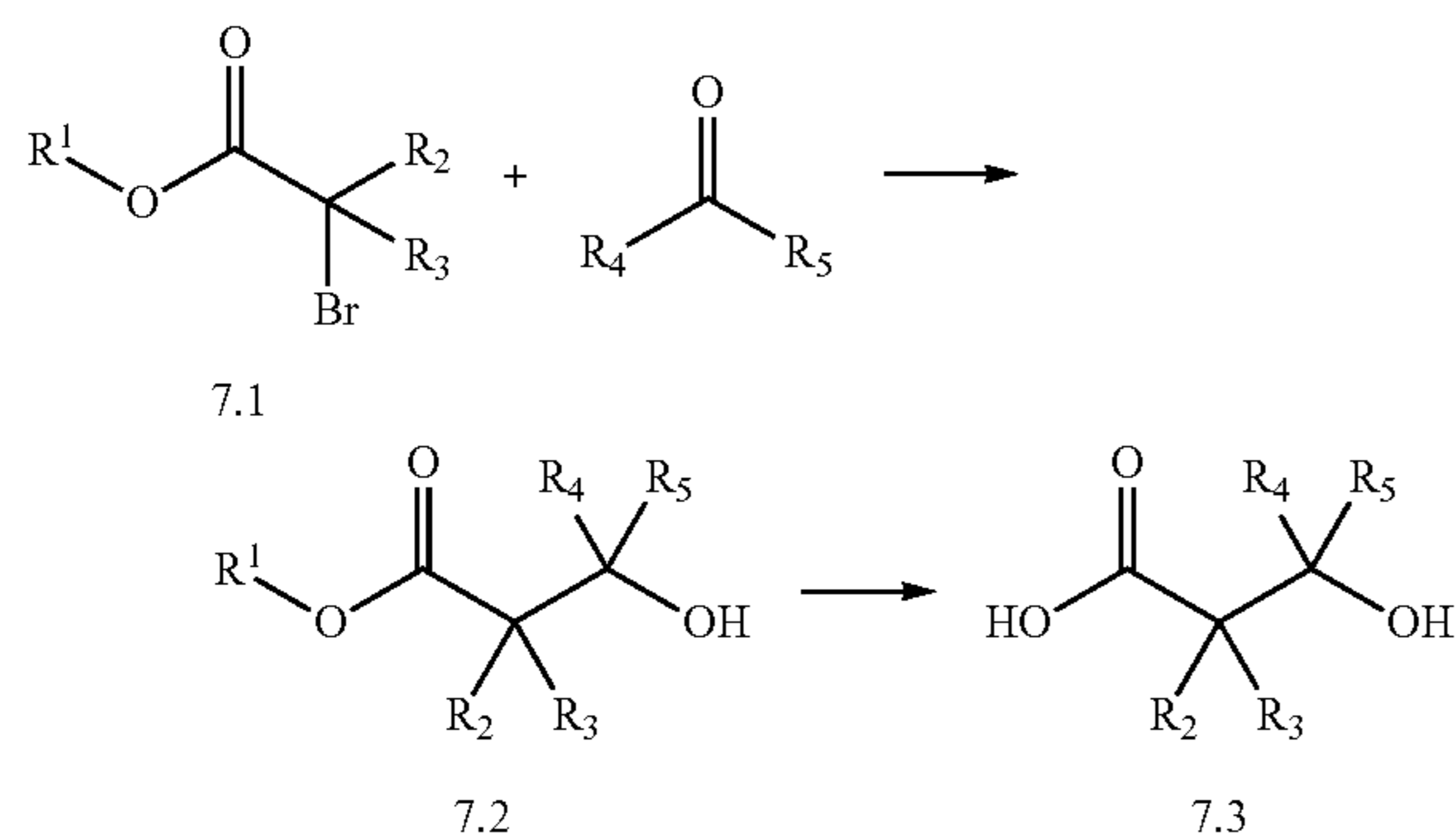


A general synthetic method for the synthesis of enantiomerically pure α-methyl-β-branched chiral carboxylic acids 6.4 or ent-6.4 is described in Scheme 6. Both of the enantiomerically pure oxazolidinones (S)-4-benzyloxazolidin-2-one 6.1 and (R)-4-benzyloxazolidin-2-one ent-6.1 are commercially available. These oxazolidinones may be readily acylated by deprotonation with n-butyl lithium followed by reaction with acid chlorides 6.5 to give the chiral imides 6.2 and ent-6.2, respectively. There are a large number of commercially available acid chlorides 6.5 with wide variation about the R₁, R₂ and R₃ groups of this input. This allows for the rapid synthesis of chiral imides 6.2 and ent-6.2 that have differing substitution at the β-position to the exocyclic carbonyl group. The asymmetric alkylation reaction of chiral imide sodium enolates as developed by Evans may then be used to introduce a methyl group in a stereoselective fashion (see Evans, D A, Ennis, M D, Mathre, D J, *J. Am. Chem. Soc.* 1982, 104, 1737-1739). The sodium enolate of imide 6.2 may be produced by treatment of 6.2 with sodium hexamethyldisilazide in tetrahydrofuran.

81

The resultant sodium enolate may then be stereoselectively methylated by the addition of methyl iodide. The pure and single diastereomers 6.3 and ent-6.3 may be isolated by silica gel column chromatography. Alternatively, the single diastereomers may be obtained by recrystallization of crystalline products 6.3 and ent-6.3. The well-known chiral auxiliary hydrolysis conditions as described above for Scheme 5 give the optically active α -methyl β -branched chiral carboxylic acids 6.4 or ent-6.4, respectively.

Scheme 7

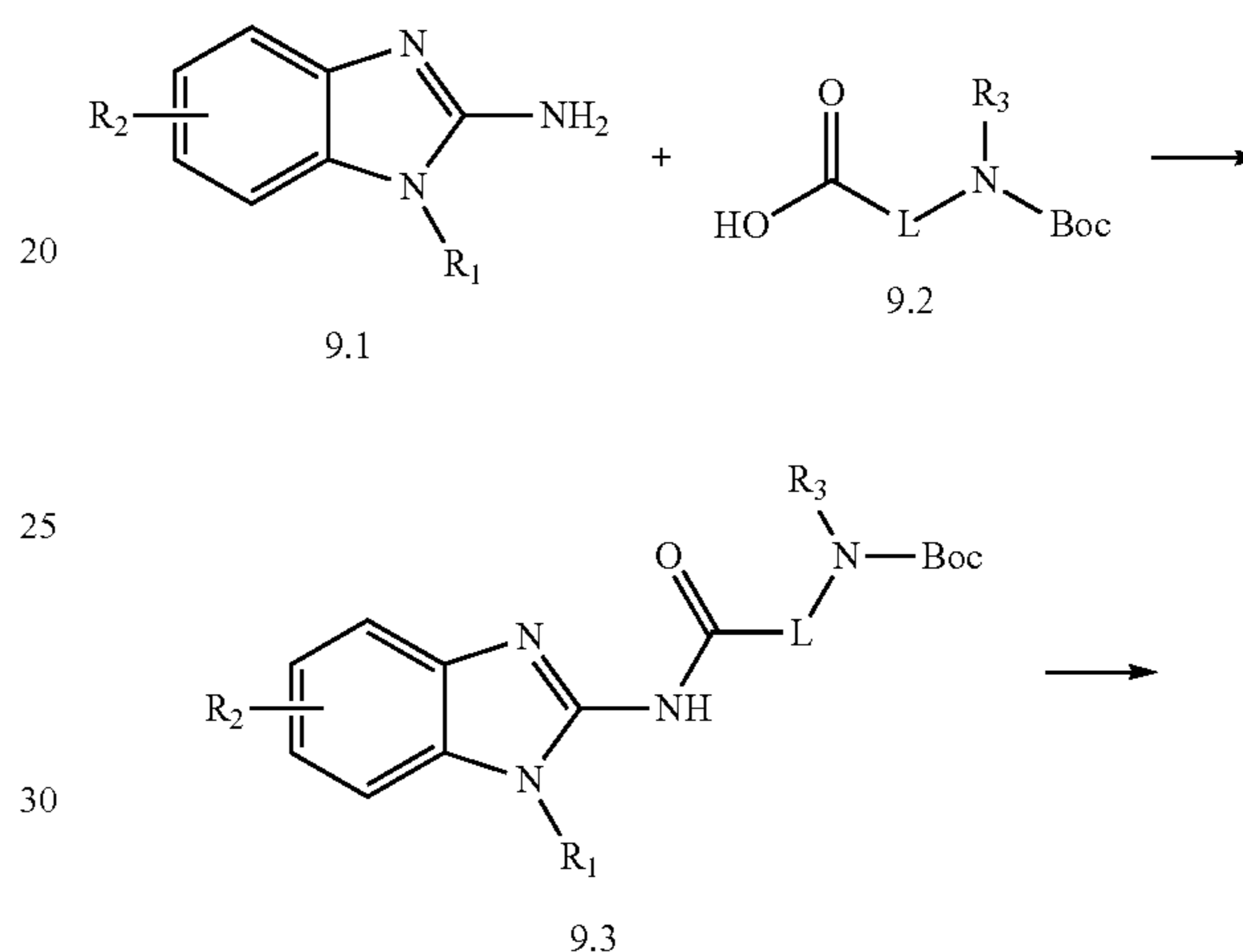


Scheme 7 shows a general methodology for the synthesis of 3-hydroxypropanoic acids such as 7.3. An appropriately substituted 2-bromoethanoic ester 7.1 is reacted with a ketone or aldehyde to afford 3-hydroxypropanoic esters 7.2. The ester group may be hydrolyzed to the corresponding acid by saponification to provide 3-hydroxypropanoic acids such as 7.3.

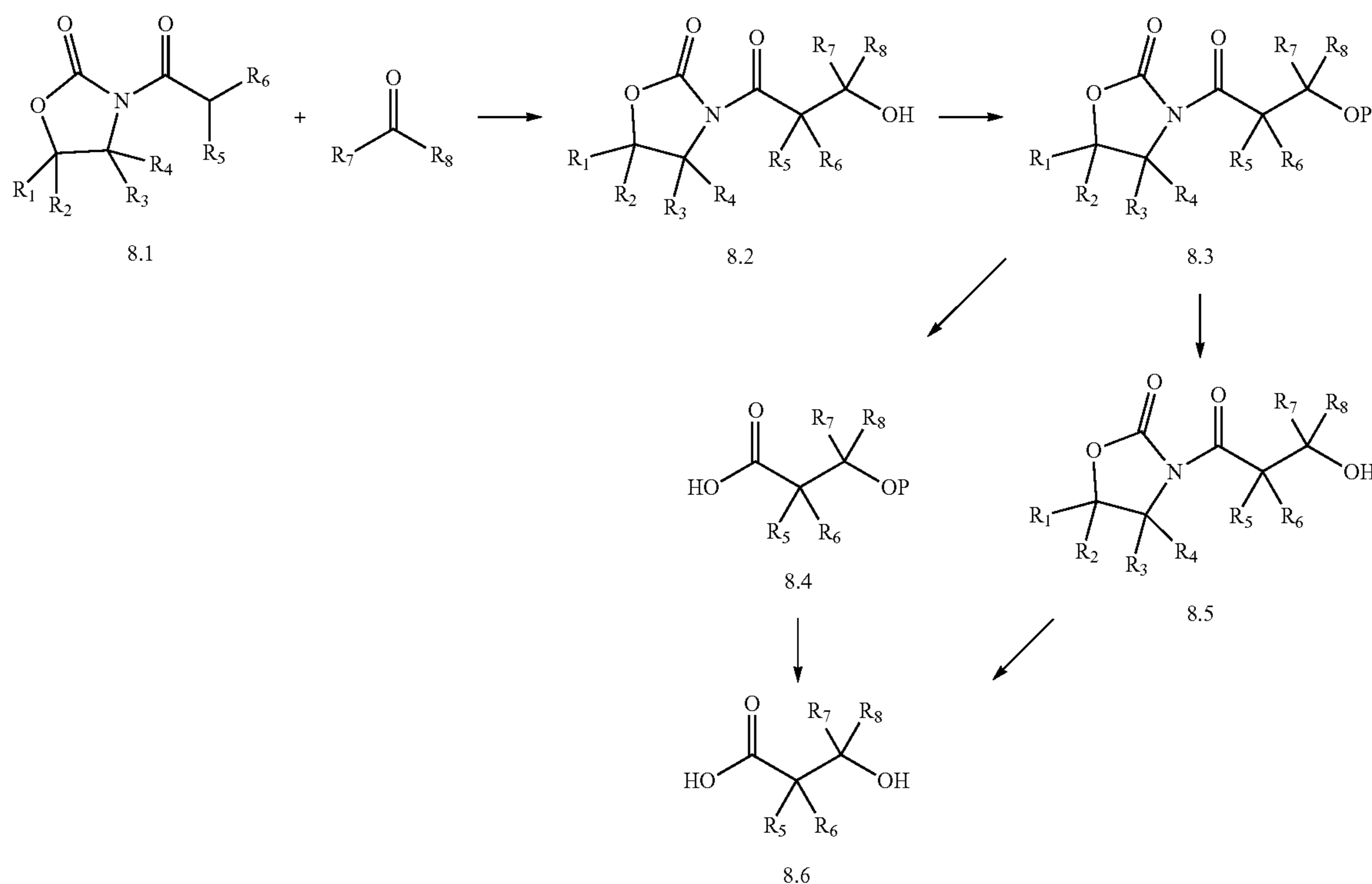
82

Scheme 8 depicts additional methods for the preparation of optionally substituted 3-hydroxypropanoic acids. An appropriately substituted 3-acetyloxazolidin-2-one 8.1 is reacted with a ketone or aldehyde to afford 3-(3-hydroxypropanoyl)oxazolidin-2-ones 8.2. The hydroxyl group is functionalized with a protecting group to provide diastereomers 8.3 that are separable by silica gel chromatography. Each diastereomer 8.3 is then reacted in a two-step sequence, in either order, of hydroxyl group deprotection and oxazolidinone cleavage to provide 3-hydroxypropanoic acids such as 8.6.

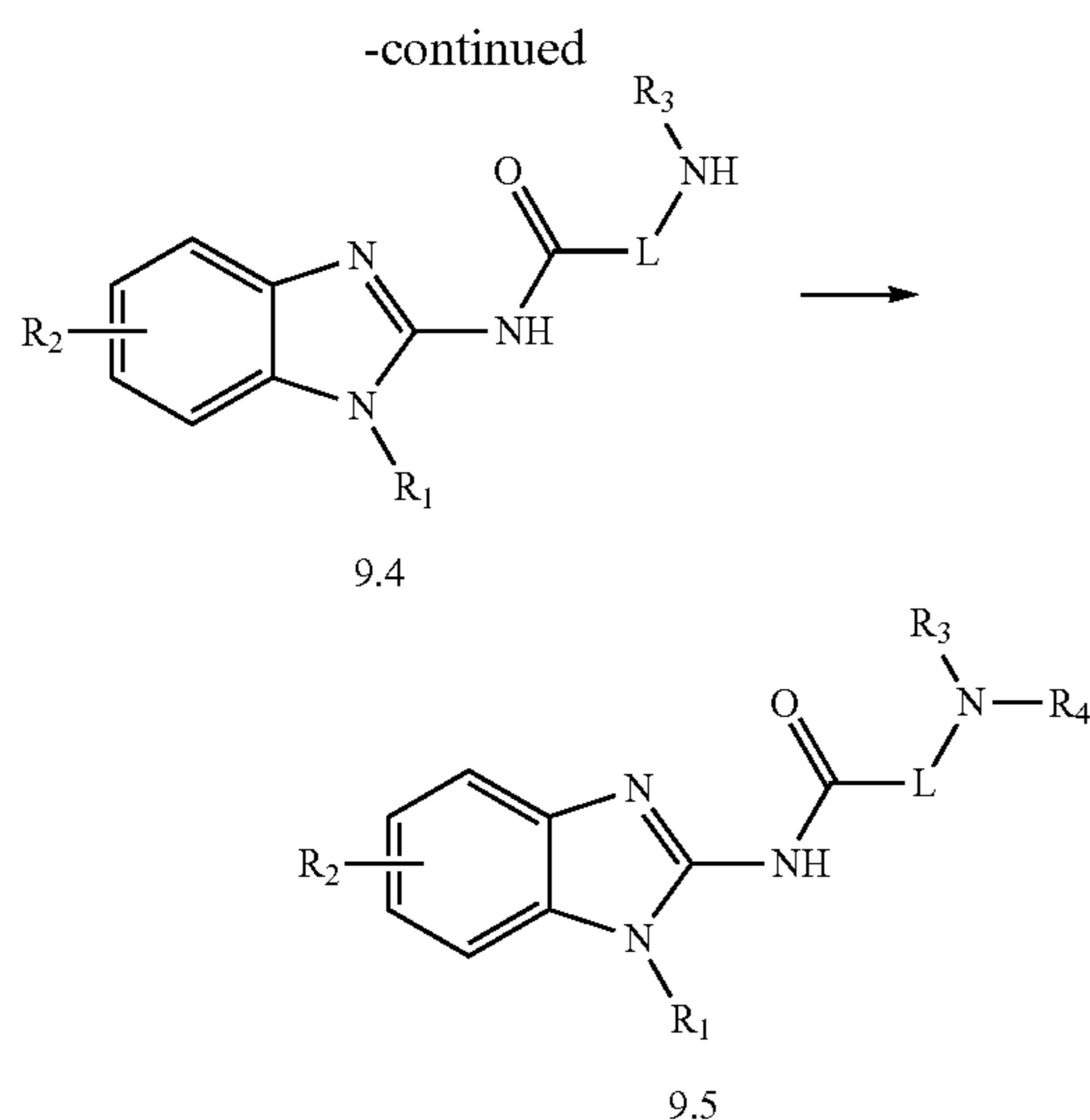
Scheme 9



Scheme 8

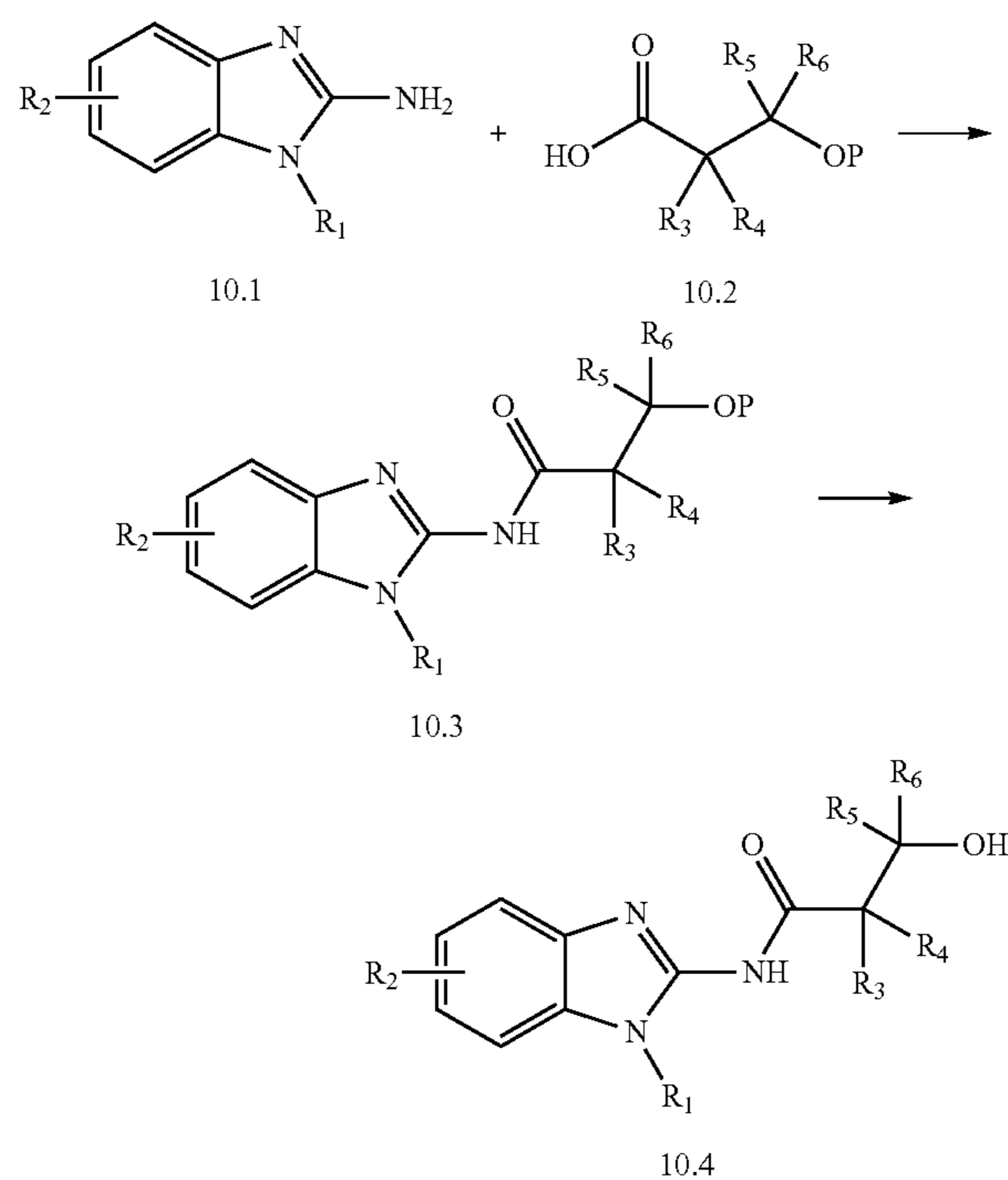


83



Scheme 9 describes methods that can be applied to the syntheses of amino acid substituted 1H-benzo[d]imidazol-2-yl) amides such as 9.4. Appropriately substituted 1H-benzo[d]imidazol-2-yl) amines 9.1 may be coupled with carbamate-protected amino acid derivatives such as 9.2 to afford the corresponding amides 9.3. The carbamate protecting group can be removed from the amine via one of a number of strongly acidic reagents to afford amines like 9.4. Such secondary amines can then be further functionalized under standard amine alkylation conditions to provide tertiary amine-containing 1H-benzo[d]imidazol-2-yl) amides such as 9.5.

Scheme 10



Scheme 10 describes methods that can be employed to prepare 1H-benzo[d]imidazol-2-yl) amides substituted with hydroxyl-containing amides such as 10.4. Appropriately

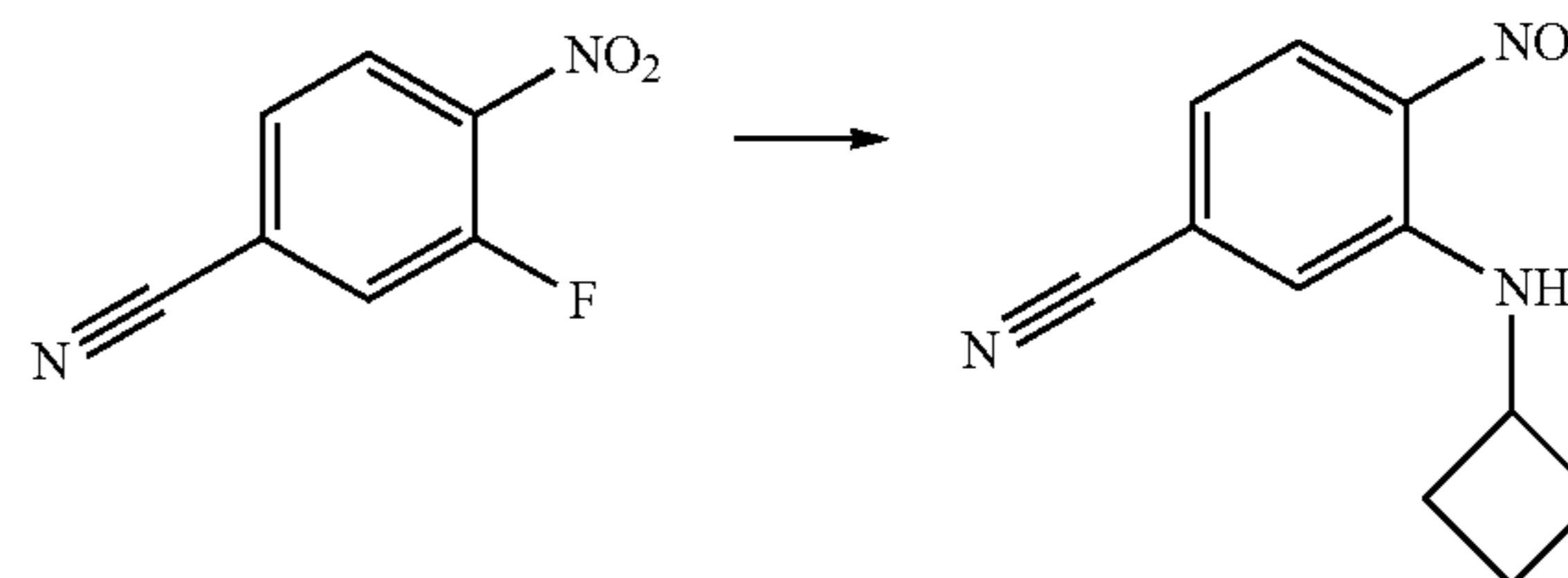
84

substituted 1H-benzo[d]imidazol-2-yl) amines 10.1 may be coupled with protected alcohol derivatives such as 10.2 to afford the corresponding amides 10.3. The alcohol protecting group can be removed via several methods including tetrabutylammonium fluoride to provide alcohol-containing 1H-benzo[d]imidazol-2-yl) amides such as 10.4.

Synthetic Methods

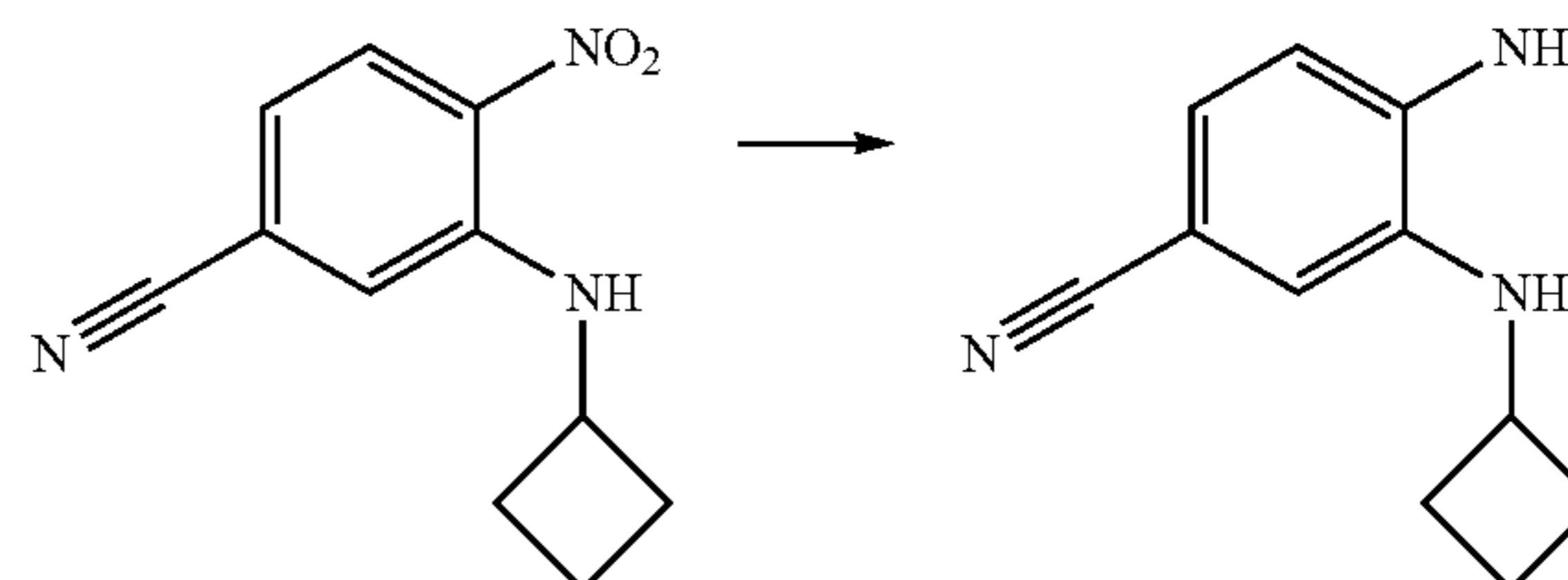
Section 1. Representative Procedures for the Preparation of 1H-benzo[d]imidazol-2-yl) Intermediates (Compounds 1.4, Scheme 1)

Method 1



Step A. Preparation of 3-(cyclobutylamino)-4-nitrobenzonitrile

A 500 mL round-bottom flask was charged with 3-fluoro-4-nitrobenzonitrile (5.00 g, 30.1 mmol) and tetrahydrofuran (100 mL) and placed in a 0° C. bath. After 5 minutes, cyclobutylamine hydrochloric acid (3.60 g, 33.0 mmol) was added in one portion with stirring before the dropwise addition of diisopropylethylamine (15 mL, 82 mmol). The mixture was allowed to stir at 0° C. for 1 hour. The ice bath was removed and the flask was allowed to warm to room temperature and allowed to stir overnight. The bulk of the tetrahydrofuran was removed on a rotary evaporator before the mixture was diluted with EtOAc (200 mL). The organic layer was washed with saturated aqueous ammonium chloride twice, saturated aqueous sodium bicarbonate, and brine and then dried over anhydrous sodium sulfate. The dried solution was filtered and concentrated to give the desired product as a crude orange solid (6.25 g). TLC $R_f=0.70-0.45$ streak in 20% EtOAc in hexanes. MS (ESI) m/z 218.0 (MH^+). 1H NMR ($CDCl_3$): δ 8.24 (d, $J=8.68$ Hz, 1H), 8.11 (bs, 1H), 7.01 (d, $J=1.48$ Hz, 1H), 6.86 (dd, $J=8.72, 1.64$, 1H), 4.09-4.00 (m, 1H), 2.60-2.51 (m, 2H), 2.11-1.88 (m, 4H).

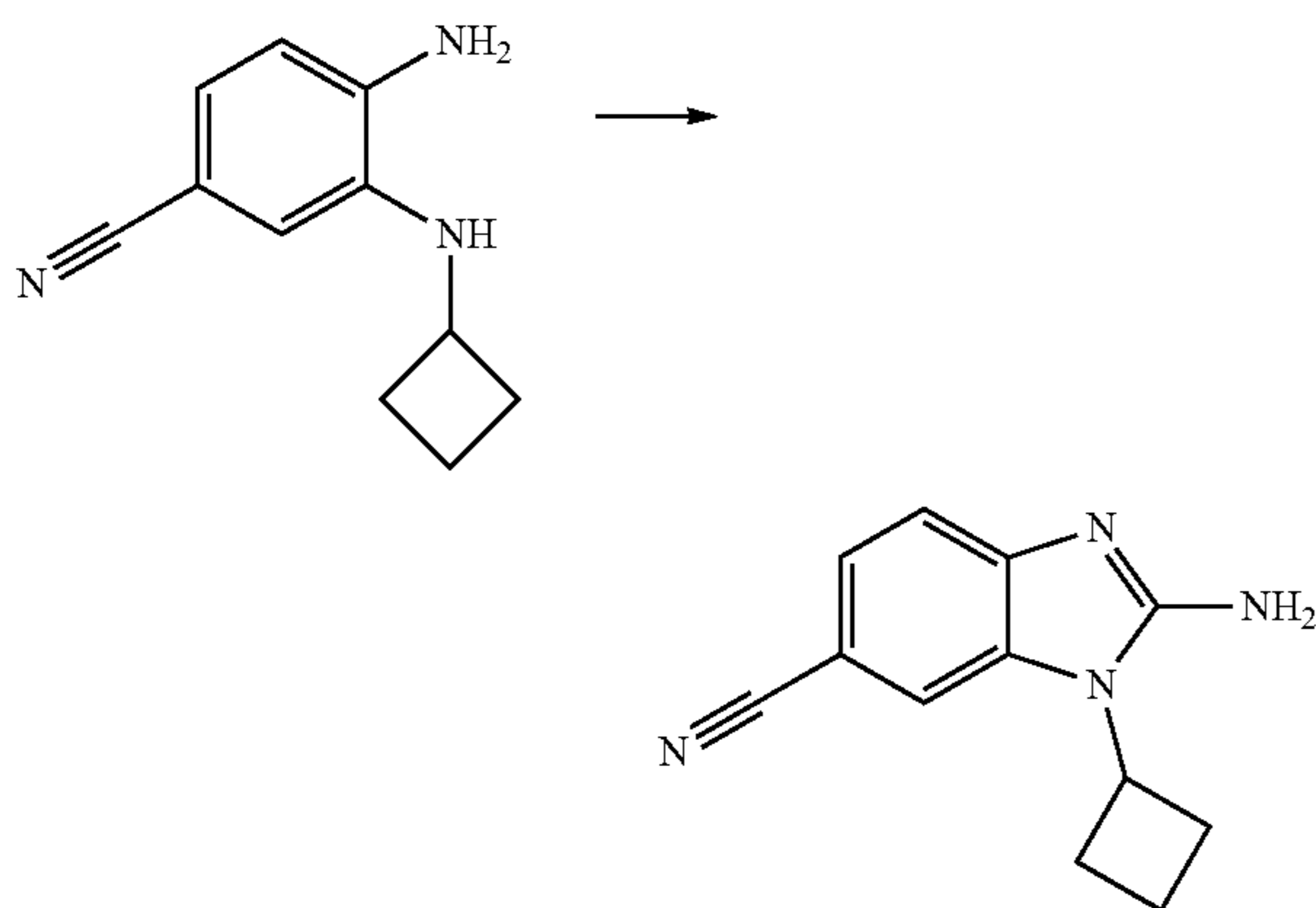


Step B. Preparation of 4-amino-3-(cyclobutylamino) benzonitrile

To a solution of 3-(cyclobutylamino)-4-nitrobenzonitrile (6.50 g, 30.1 mmol) in EtOH (160 mL) was added iron

85

powder (8.8 g, 150 mmol) and a solution of ammonium chloride (8.1 g, 150 mmol) in water (30 mL). The mixture was heated in a sand bath at 90° C. for 16 hours while being exposed to air. The mixture was allowed to cool, diluted with EtOAc (200 mL) and the resulting mixture was filtered through Celite. The Celite was rinsed with saturated aqueous sodium bicarbonate and EtOAc. The combined filtrates were separated and the aqueous layer was extracted with EtOAc. The combined organics were washed with brine, dried with anhydrous sodium sulfate and concentrated to provide the crude title compound (6.2 g). The material was subjected to a 120 g Isco silica gel column (10 to 40% EtOAc in hexanes) to provide the desired product (4.17 g) in a 74% yield for two steps as a pink colored solid. MS (ESI) m/z 188.0 (MH^+). 1H NMR ($CDCl_3$): δ 7.01 (dd, $J=8.00, 1.76$ Hz, 1H), 6.73 (d, $J=1.72$ Hz, 1H), 6.68 (d, $J=8.0$ Hz, 1H), 3.92-3.85 (m, 1H), 3.65-3.45 (br m, 2H), 2.53-2.44 (m, 2H), 1.88-1.83 (m, 4H).



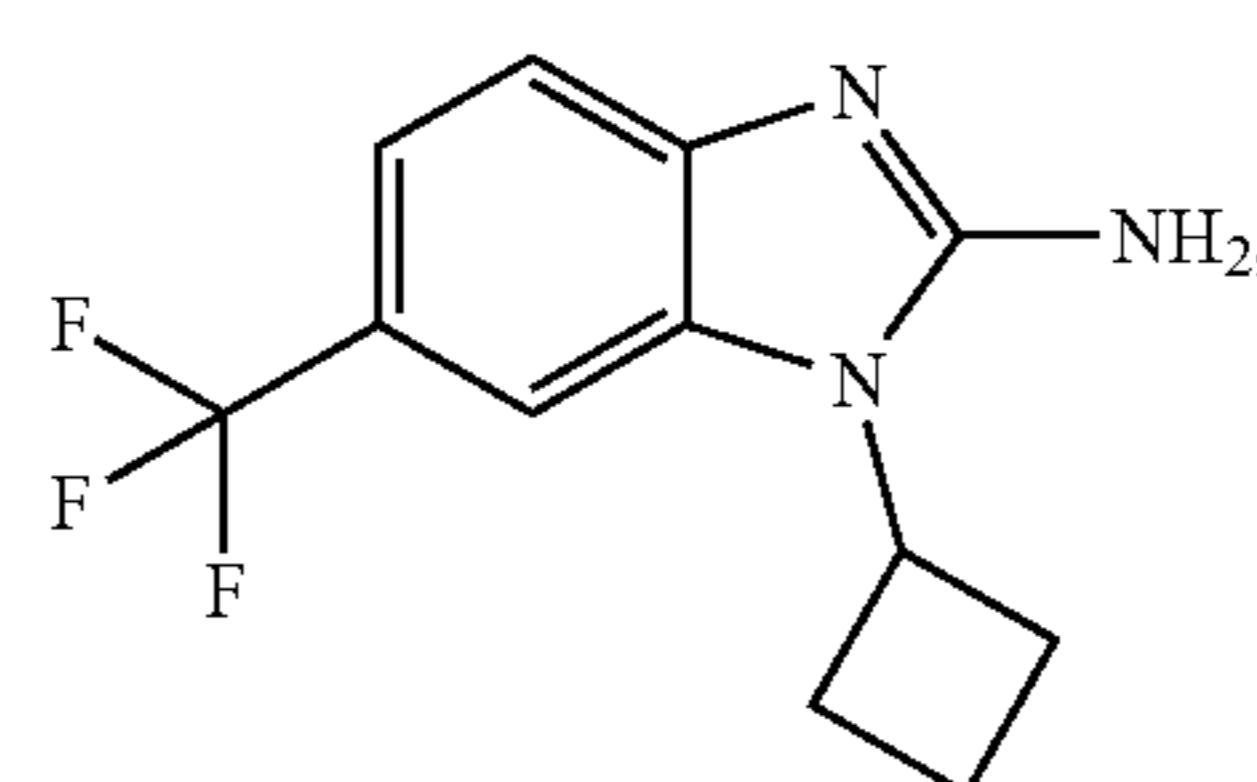
Step C. Preparation of 2-amino-1-cyclobutyl-1H-benzo[d]imidazole-6-carbonitrile

To a solution of 4-amino-3-(cyclobutylamino) benzotrile (4.0 g, 21.3 mmol) in EtOH (100 mL) was added a solution of cyanogen bromide (3 M in CH_2Cl_2 , 14 mL, 42 mmol). The mixture was stirred at room temperature for 18 hours and then concentrated in vacuo. The residue was partitioned between EtOAc (150 mL) and aqueous Na_2CO_3 (10%, 100 mL). The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a pink solid (4.5 g). The solid was subjected to a hexanes and EtOAc trituration to provide the title compound as a pale pink solid (3.1 g, 69%). $R_f=0.1$ streak in 100% EtOAc. MS (ESI) m/z 213.2 (MH^+). 1H NMR ($MeOH-d_4$): δ 7.78 (s, 1H), 7.38 (d, $J=8.28$, 1H), 7.28 (d, $J=8.20$, 1H), 4.92-4.81 (m, 1H), 2.88-2.78 (m, 2H), 2.54-2.45 (m, 2H), 2.08-1.78 (m, 2H). An additional portion of the desired product (1.0 g) was recovered from the trituration solvent and showed to be desired product with >90% purity by 1H NMR.

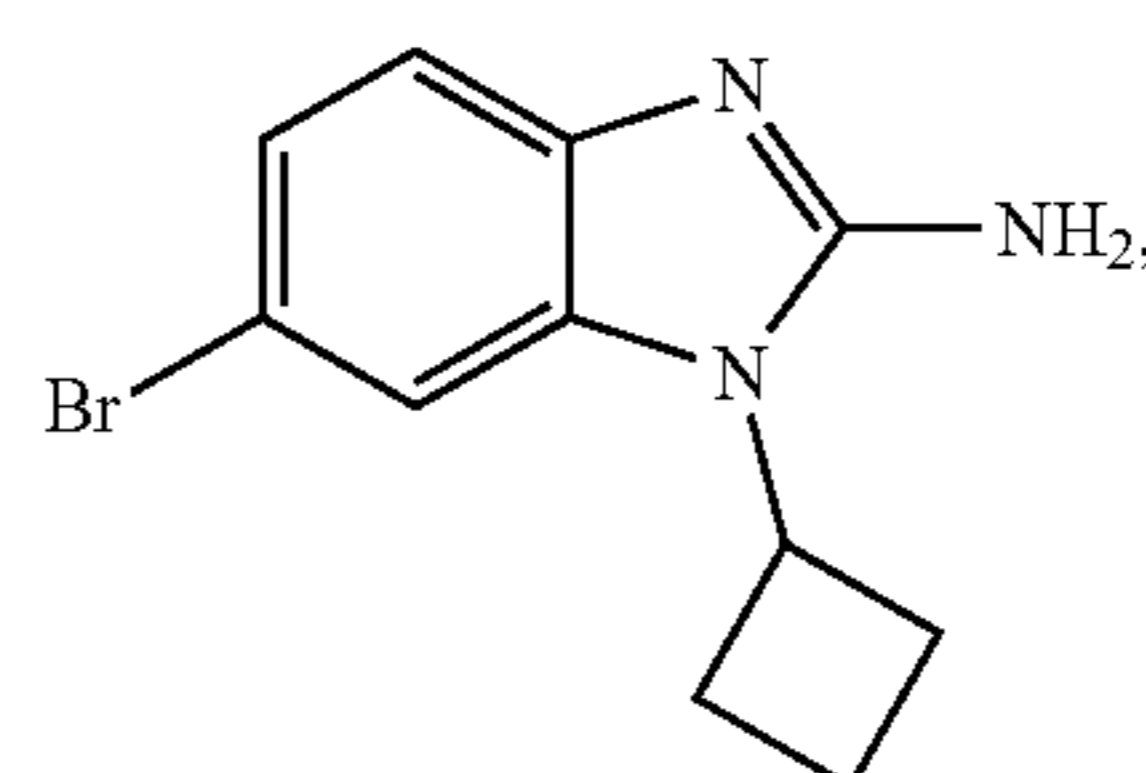
The following 1H-benzo[d]imidazol-2-amines were prepared using the general procedures described in Section 1, Method 1, with appropriate starting materials. Alternative procedures for certain starting materials are described in the Methods 2-5.

86

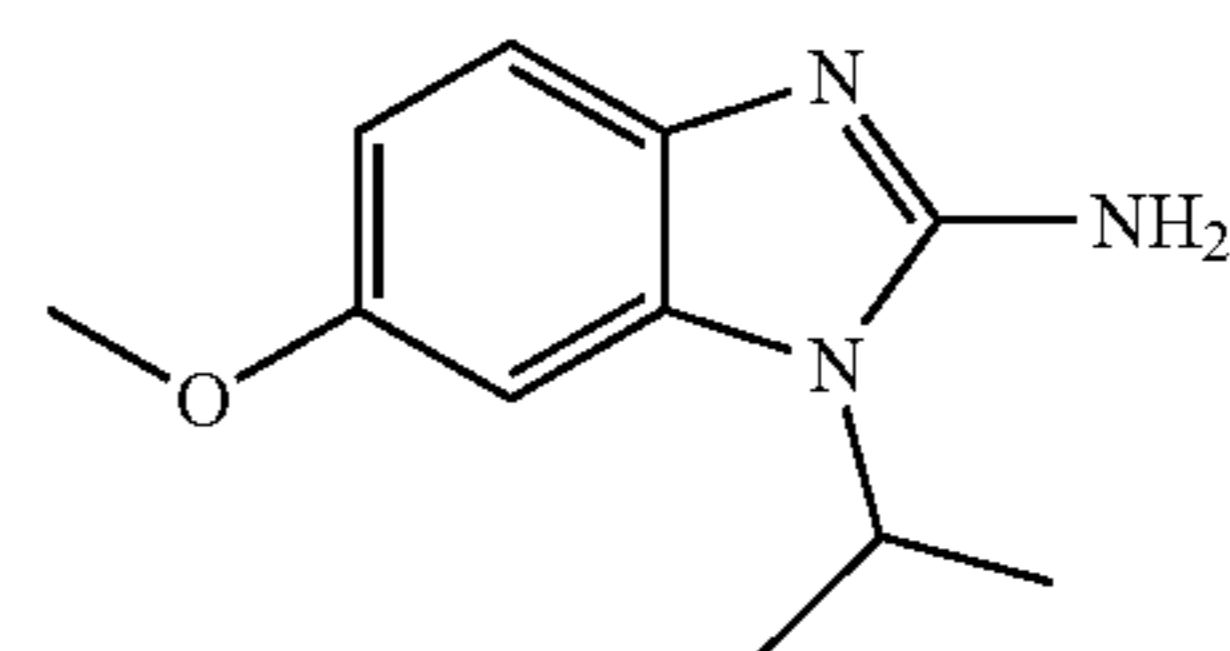
1-cyclobutyl-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-amine



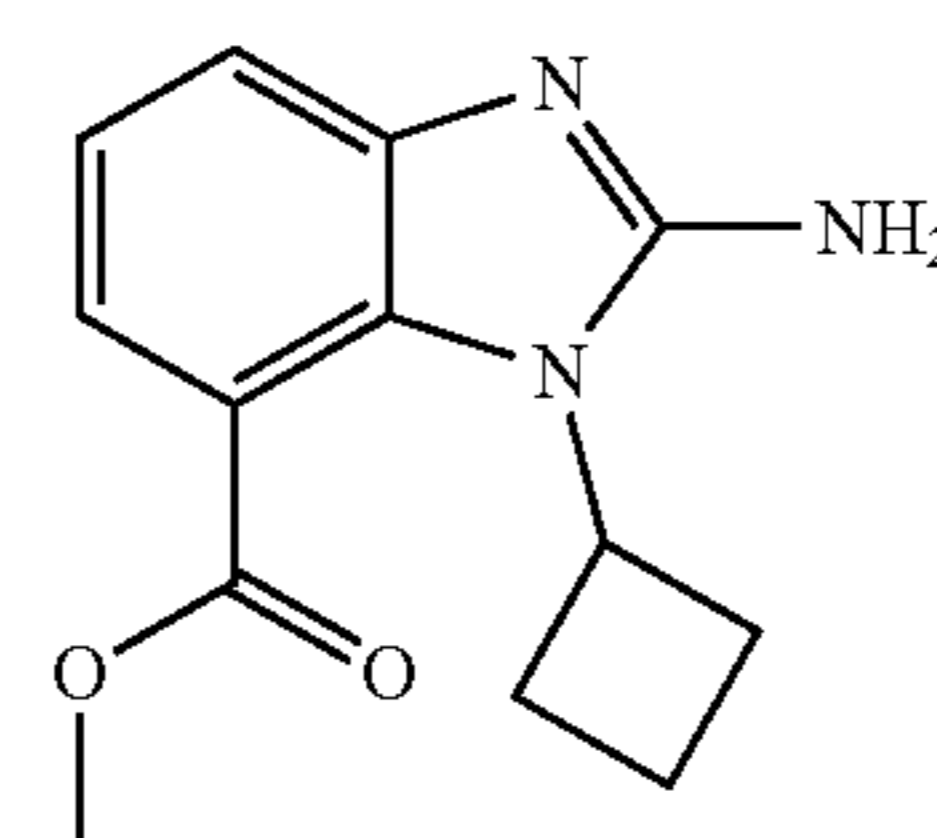
6-bromo-1-cyclobutyl-1H-benzo[d]imidazol-2-amine



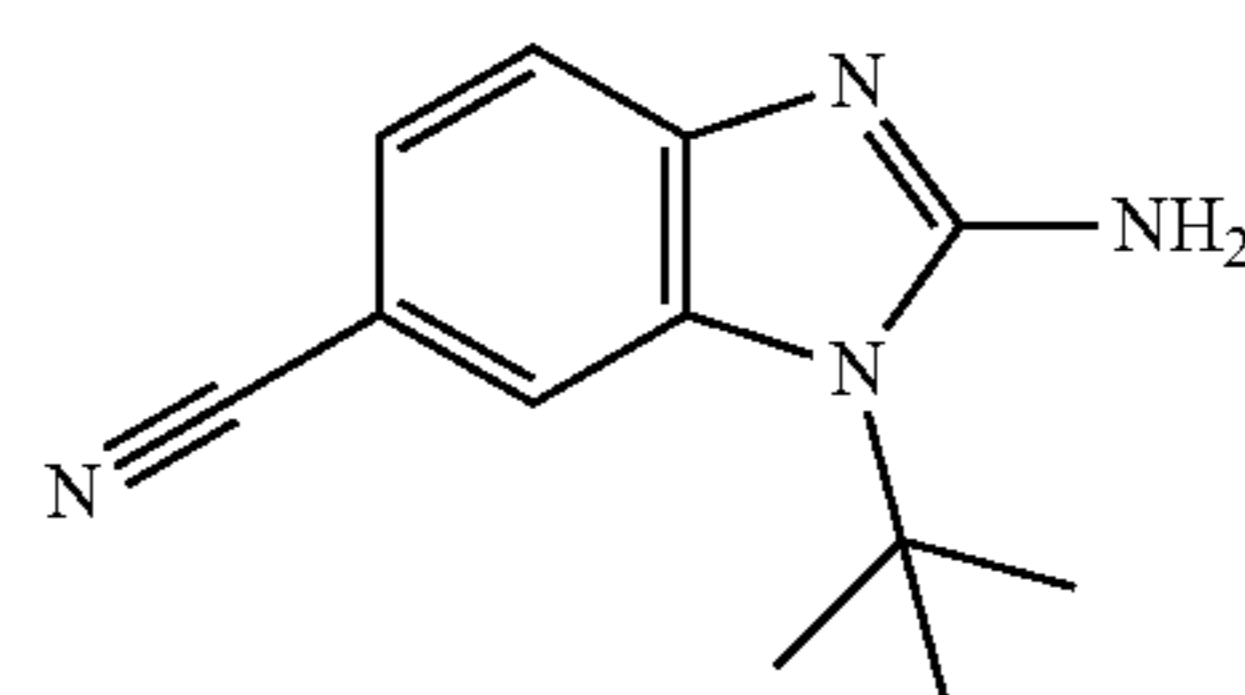
1-isopropyl-6-methoxy-1H-benzo[d]imidazol-2-amine



methyl 2-amino-1-cyclobutyl-1H-benzo[d]imidazole-7-carboxylate

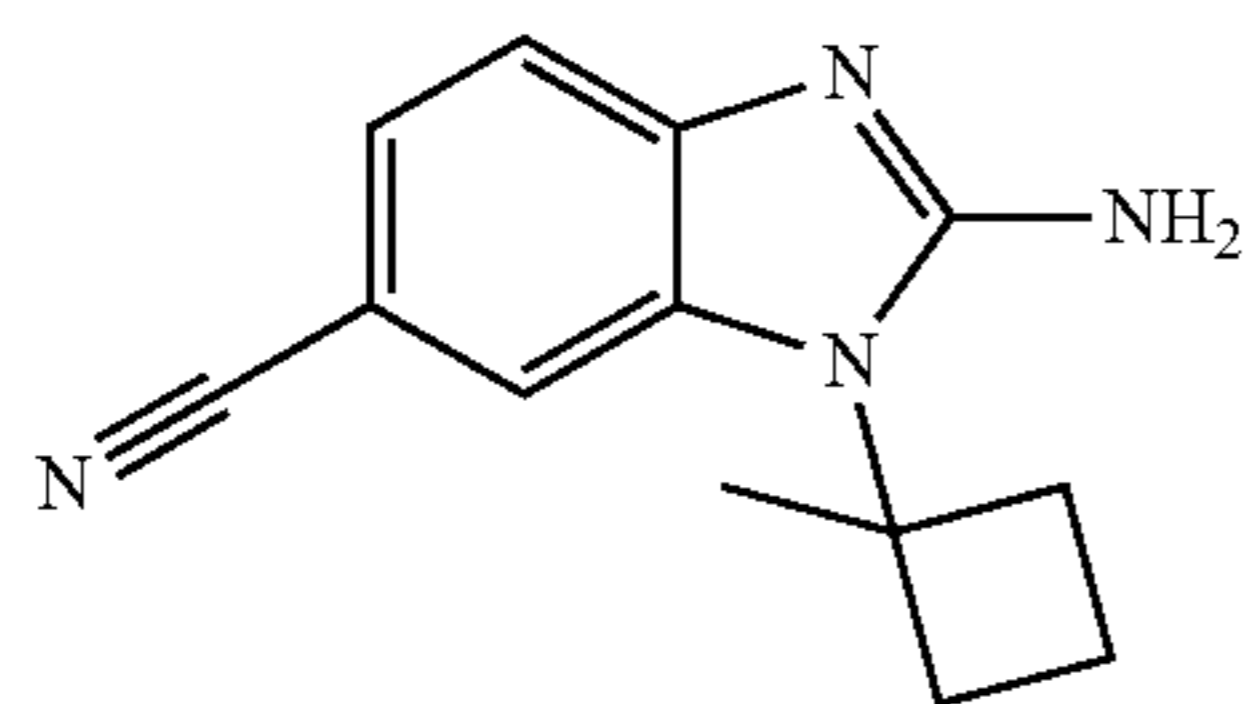


2-amino-1-(tert-butyl)-1H-benzo[d]imidazole-6-carbonitrile

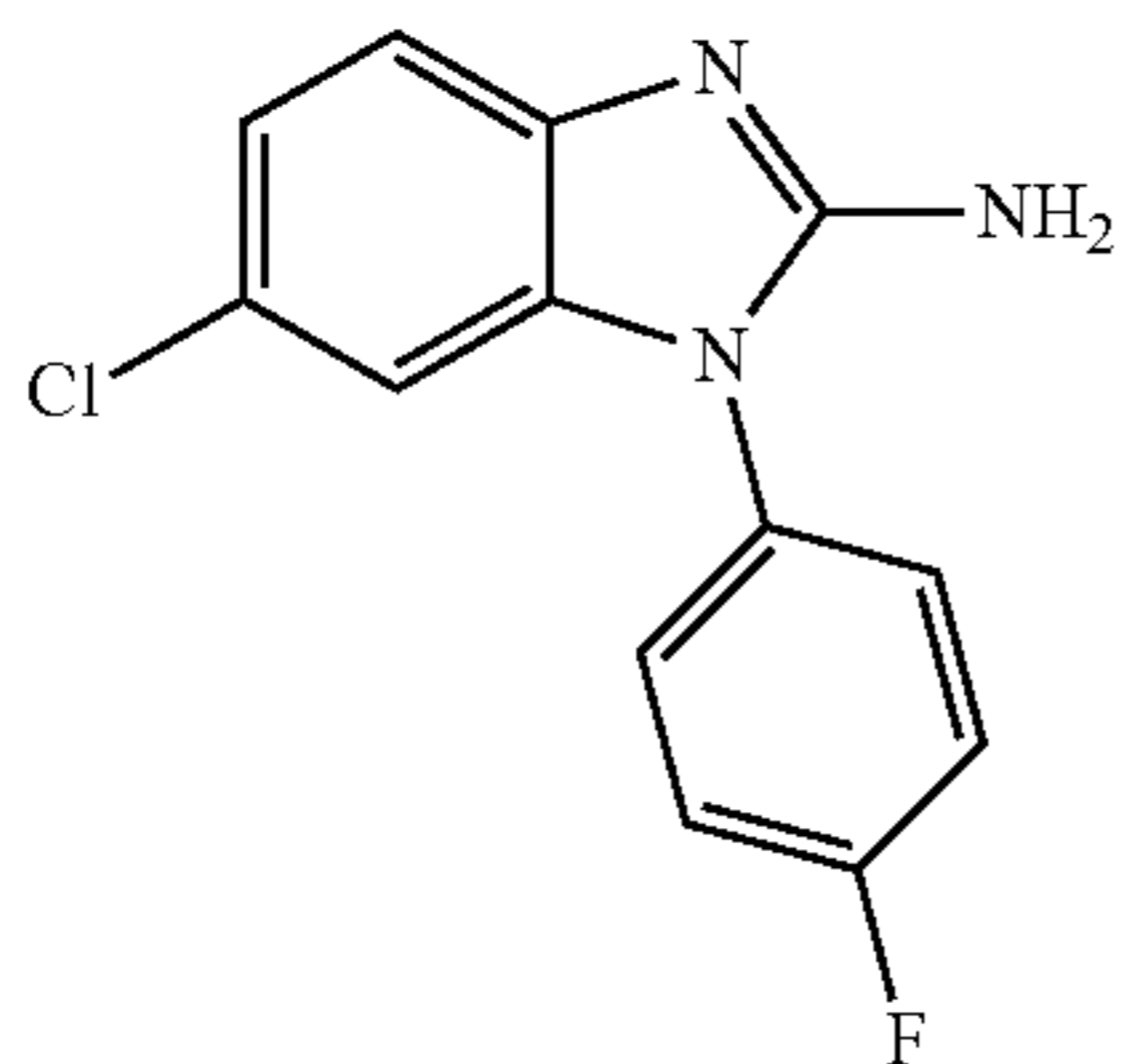


2-amino-1-(1-methylcyclobutyl)-1H-benzo[d]imidazole-6-carbonitrile

87

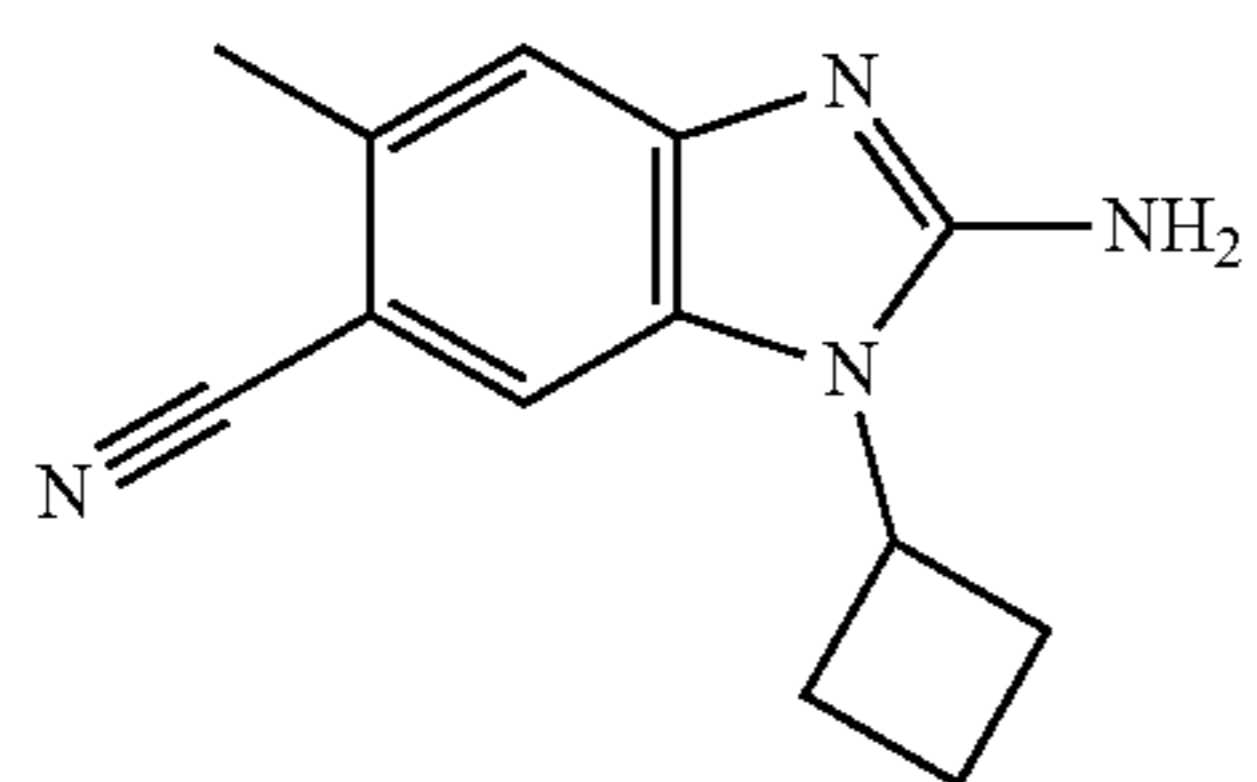


6-chloro-1-(4-fluorophenyl)-1H-benzo[d]imidazol-2-amine

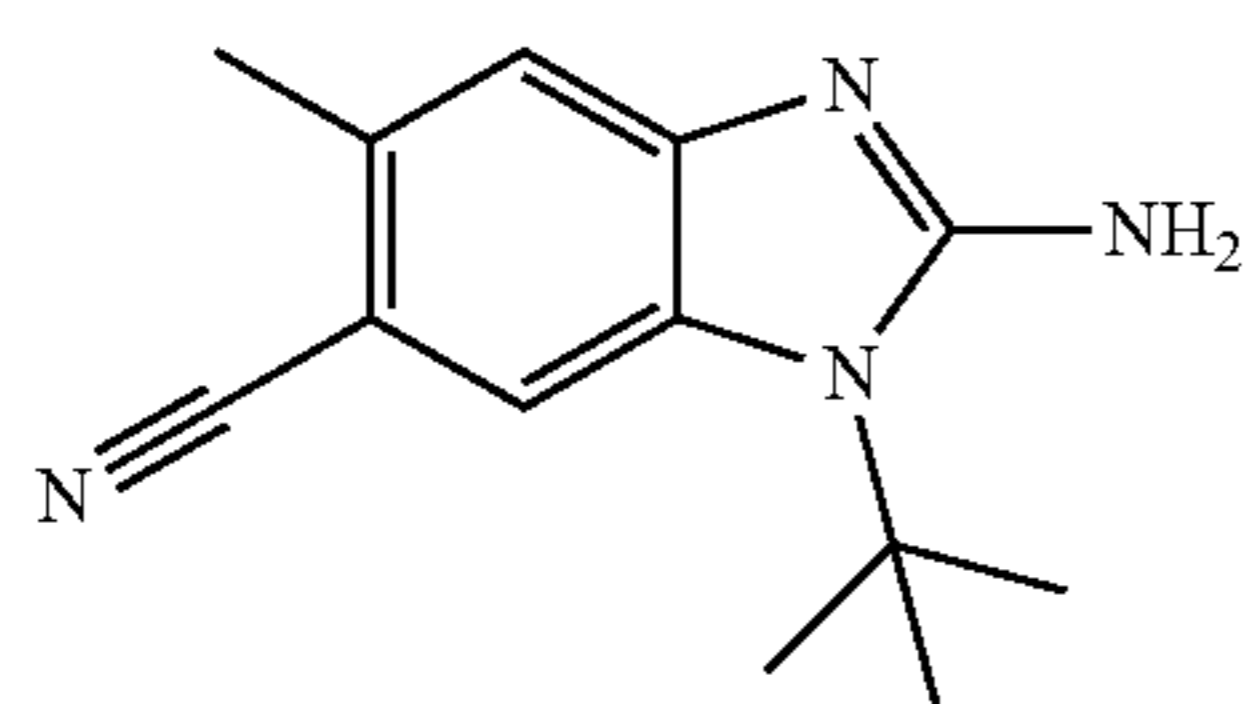


1-(3,5-difluorophenyl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-amine

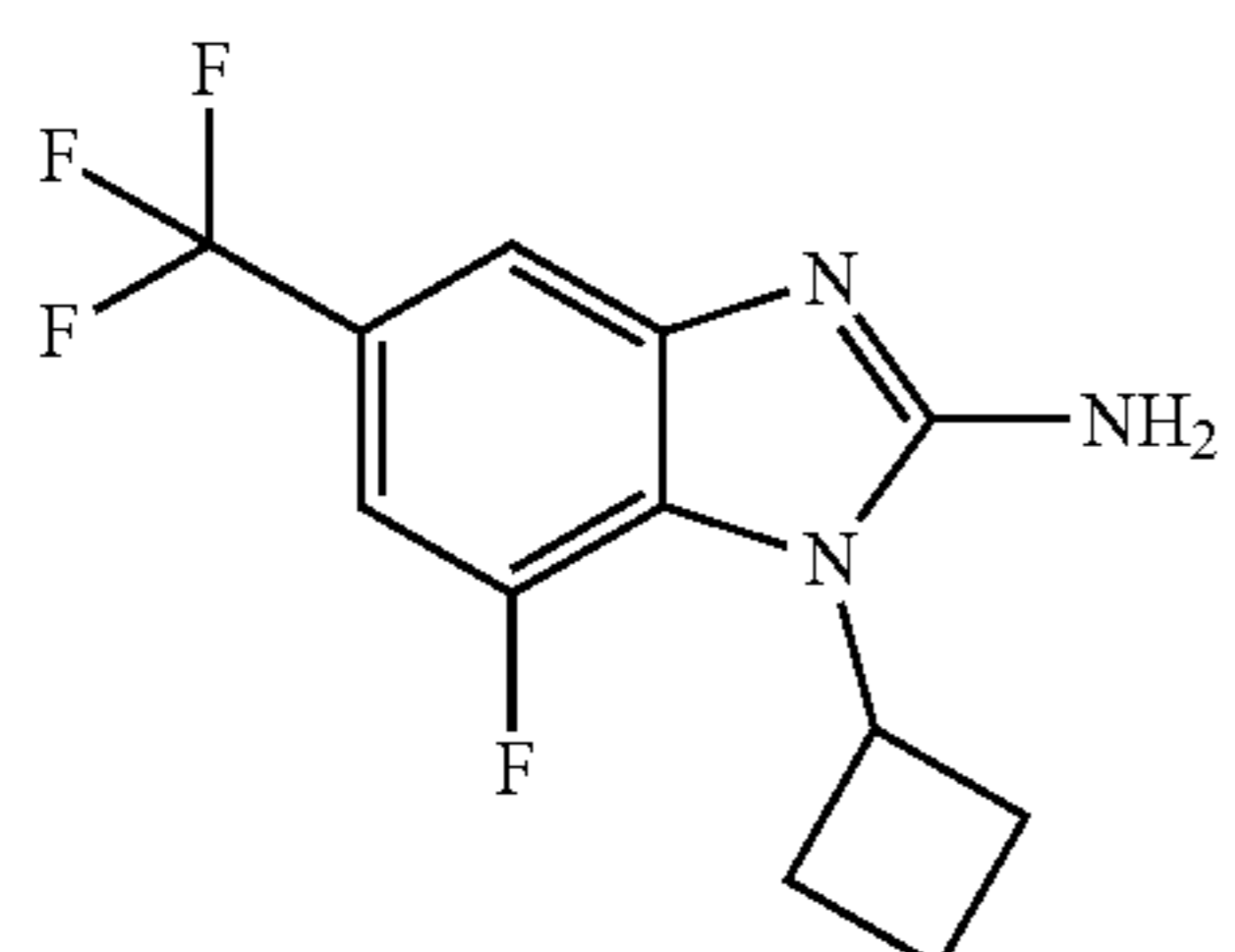
2-amino-1-cyclobutyl-5-methyl-1H-benzo[d]imidazole-6-carbonitrile



2-amino-1-(tert-butyl)-5-methyl-1H-benzo[d]imidazole-6-carbonitrile

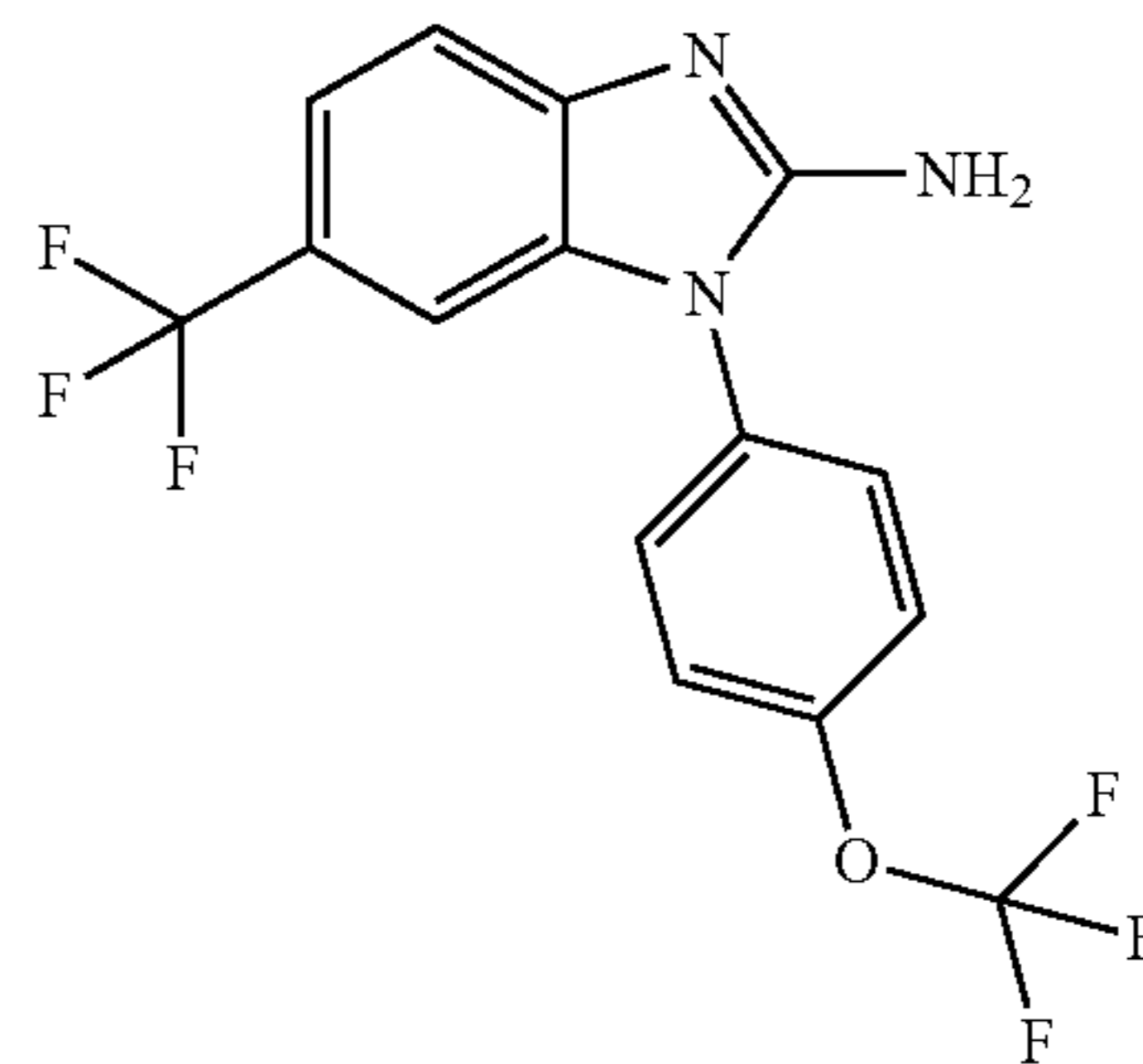


1-cyclobutyl-7-fluoro-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-amine

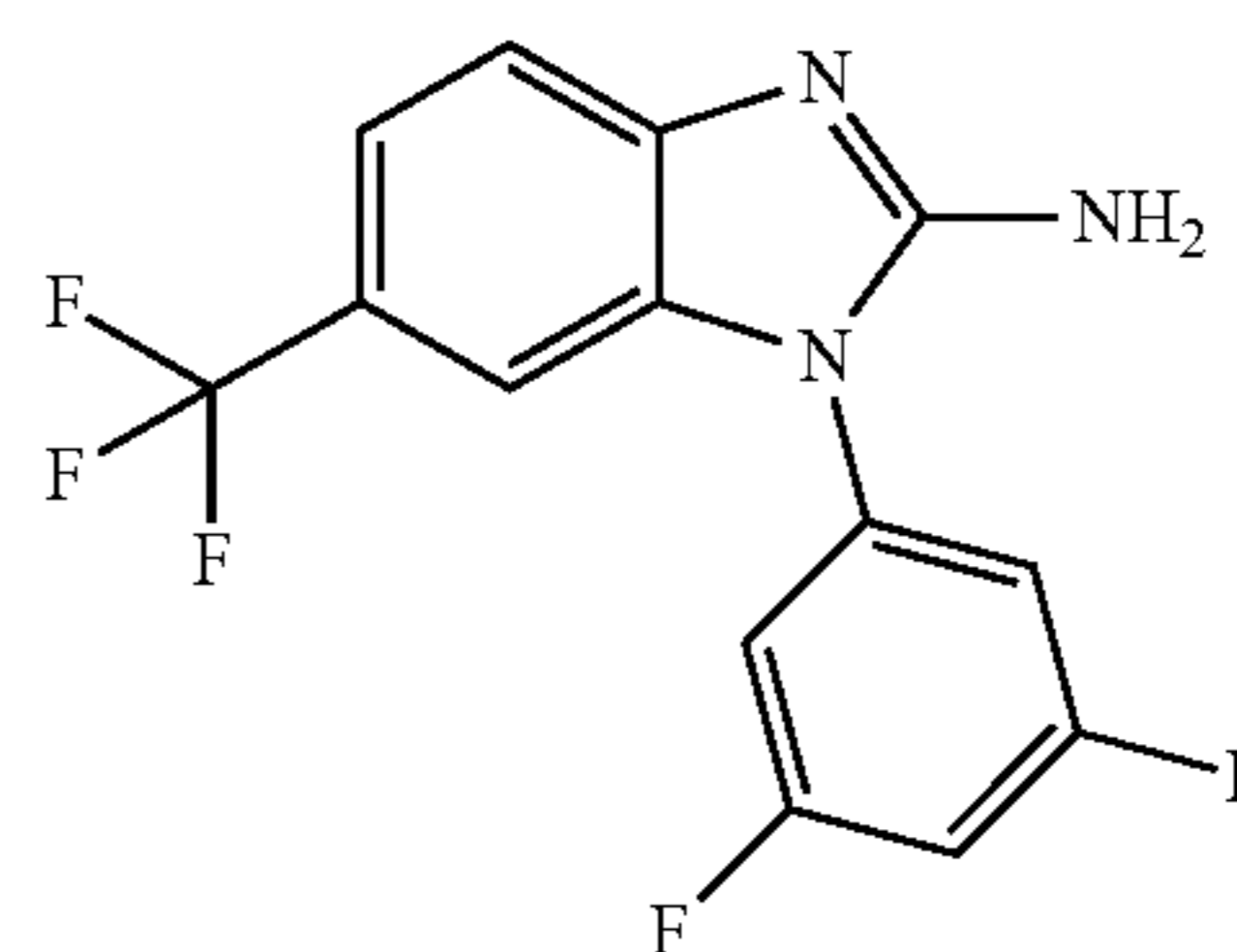


1-(4-(trifluoromethoxy)phenyl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-amine

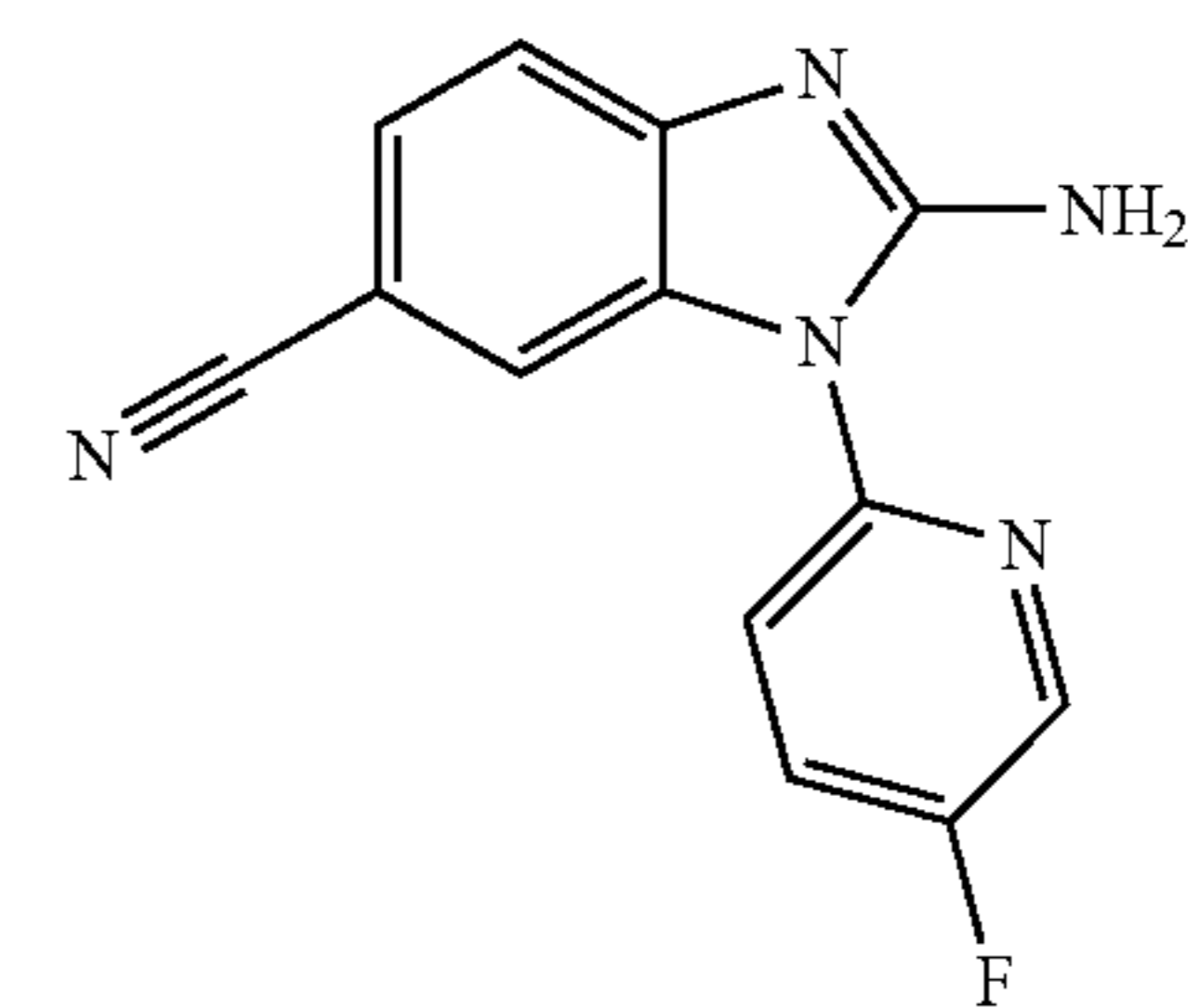
88



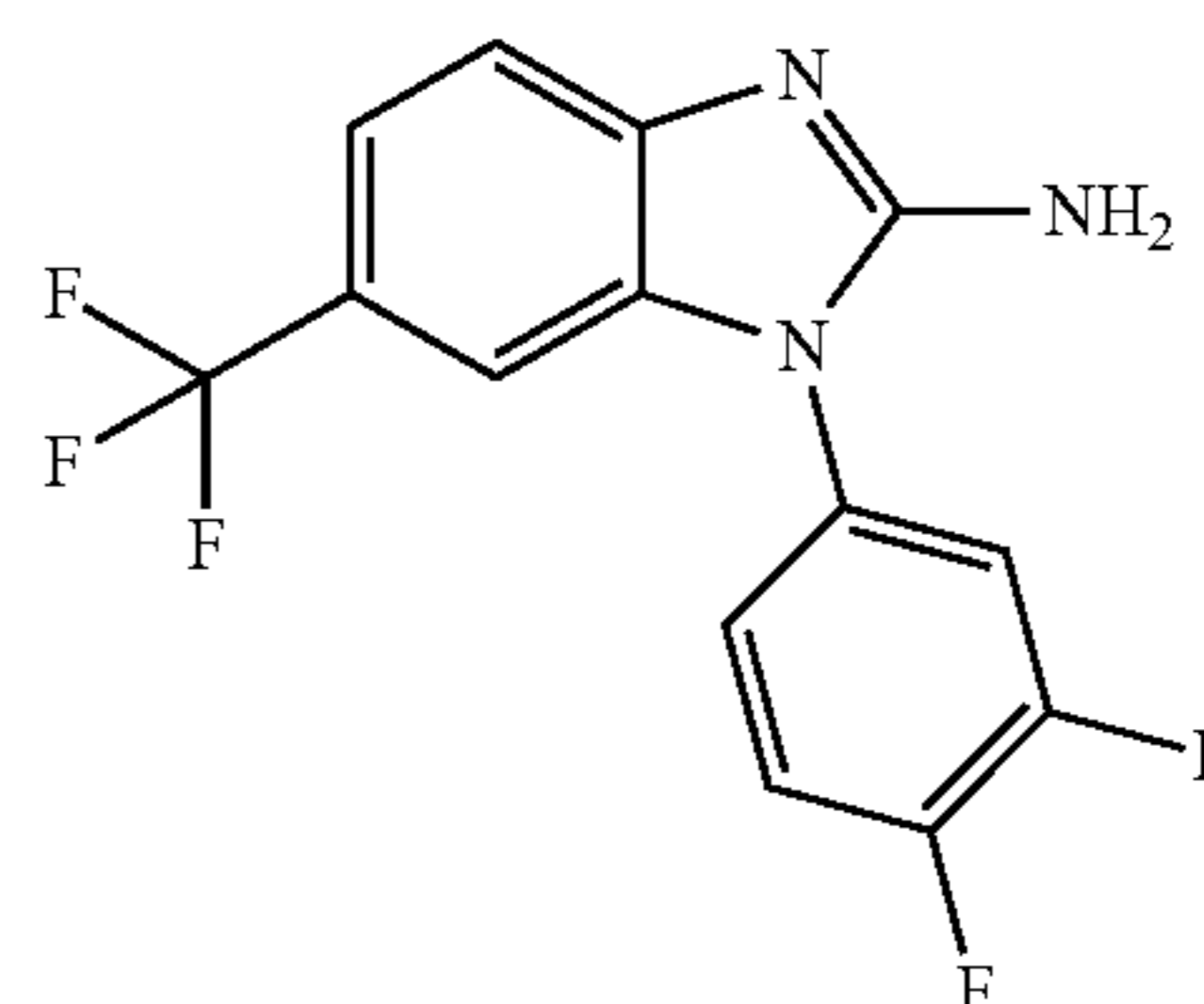
1-(3,4-difluorophenyl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-amine



1-(3,5-difluorophenyl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-amine

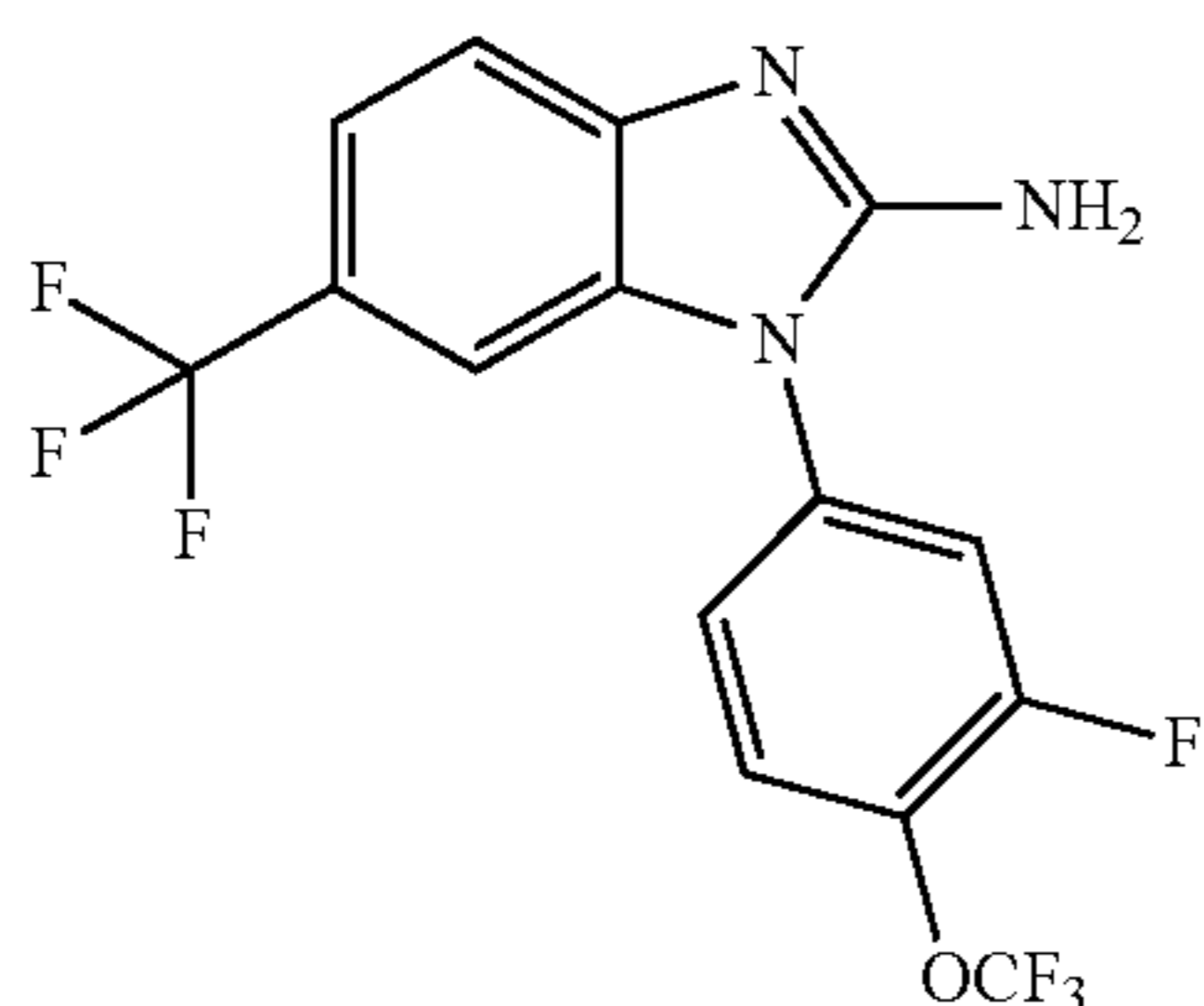


2-amino-1-(5-fluoropyridin-2-yl)-1H-benzo[d]imidazole-6-carbonitrile

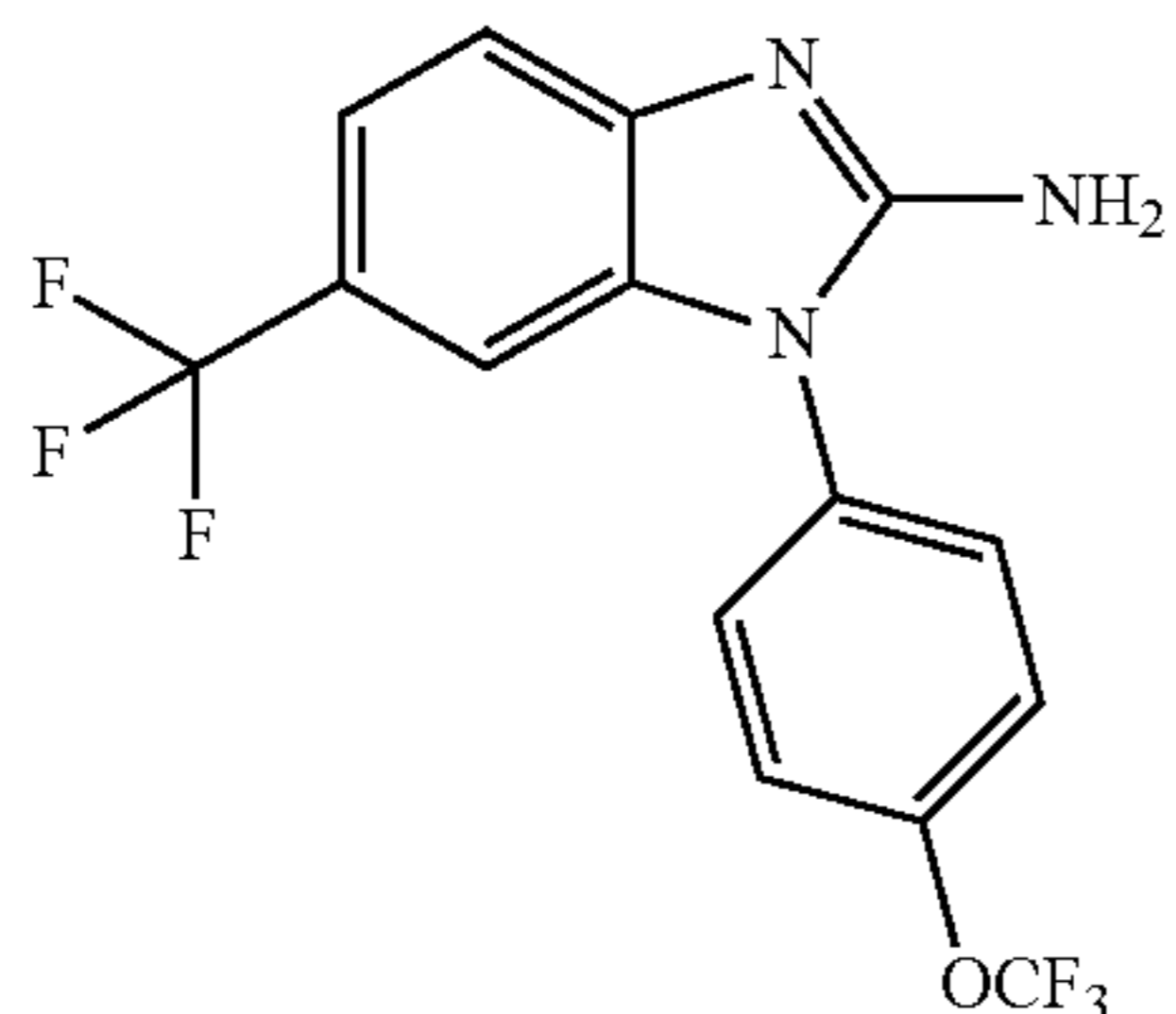


1-(3,4-difluorophenyl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-amine

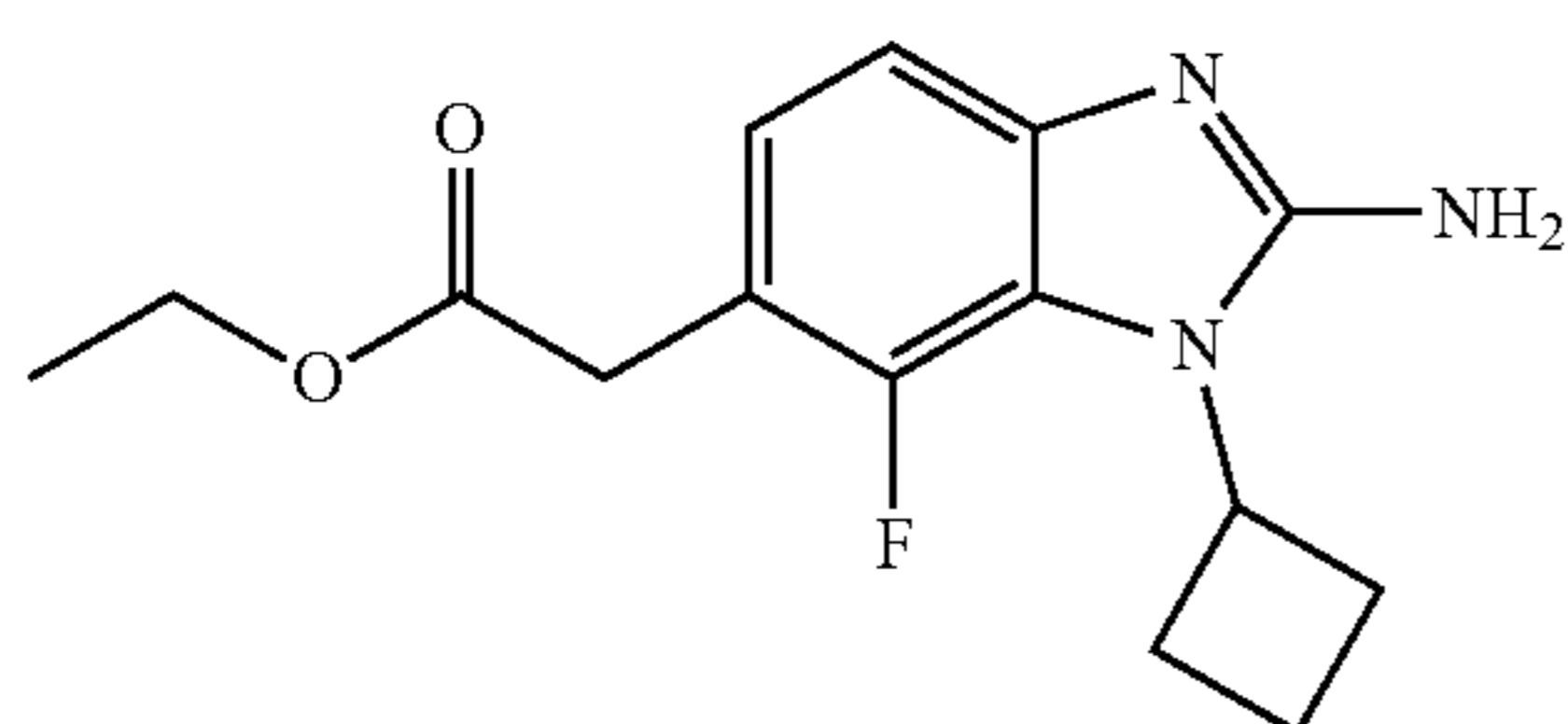
89



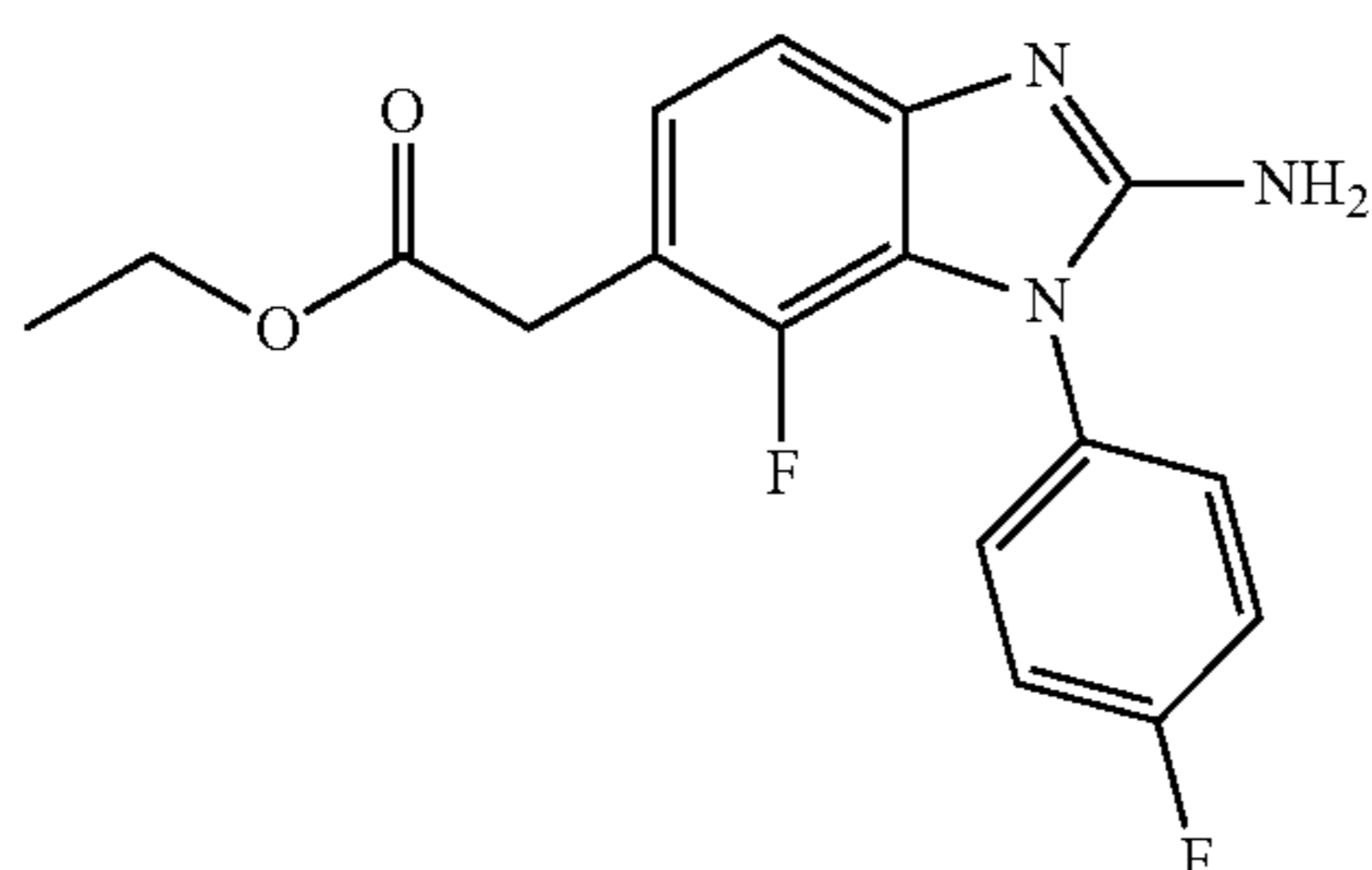
1-(4-(trifluoromethoxy)phenyl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-amine



ethyl 2-(2-amino-1-cyclobutyl-7-fluoro-1H-benzo[d]imidazol-6-yl)acetate

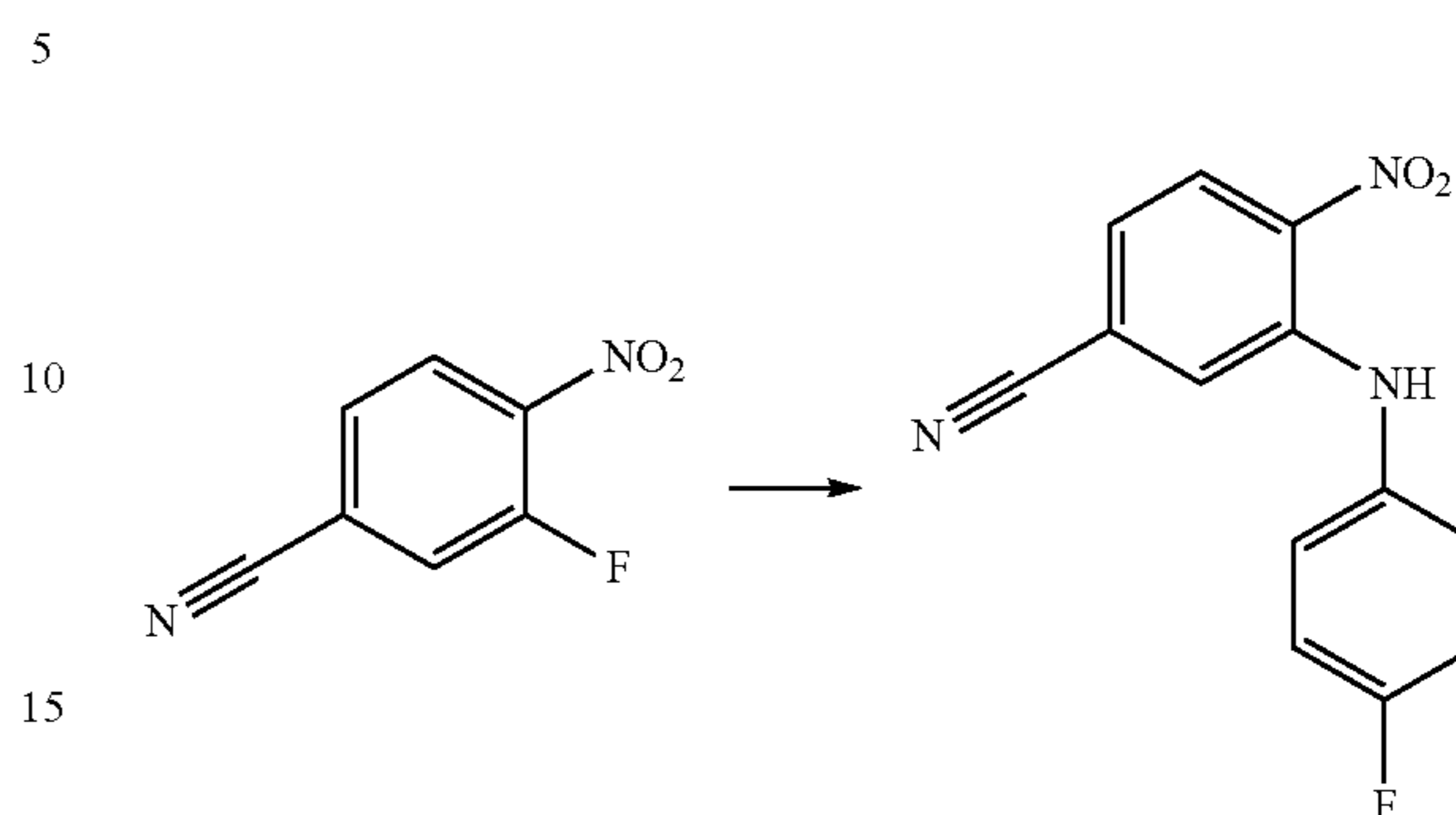


ethyl 2-(2-amino-7-fluoro-1-(4-fluorophenyl)-1H-benzo[d]imidazol-6-yl)acetate



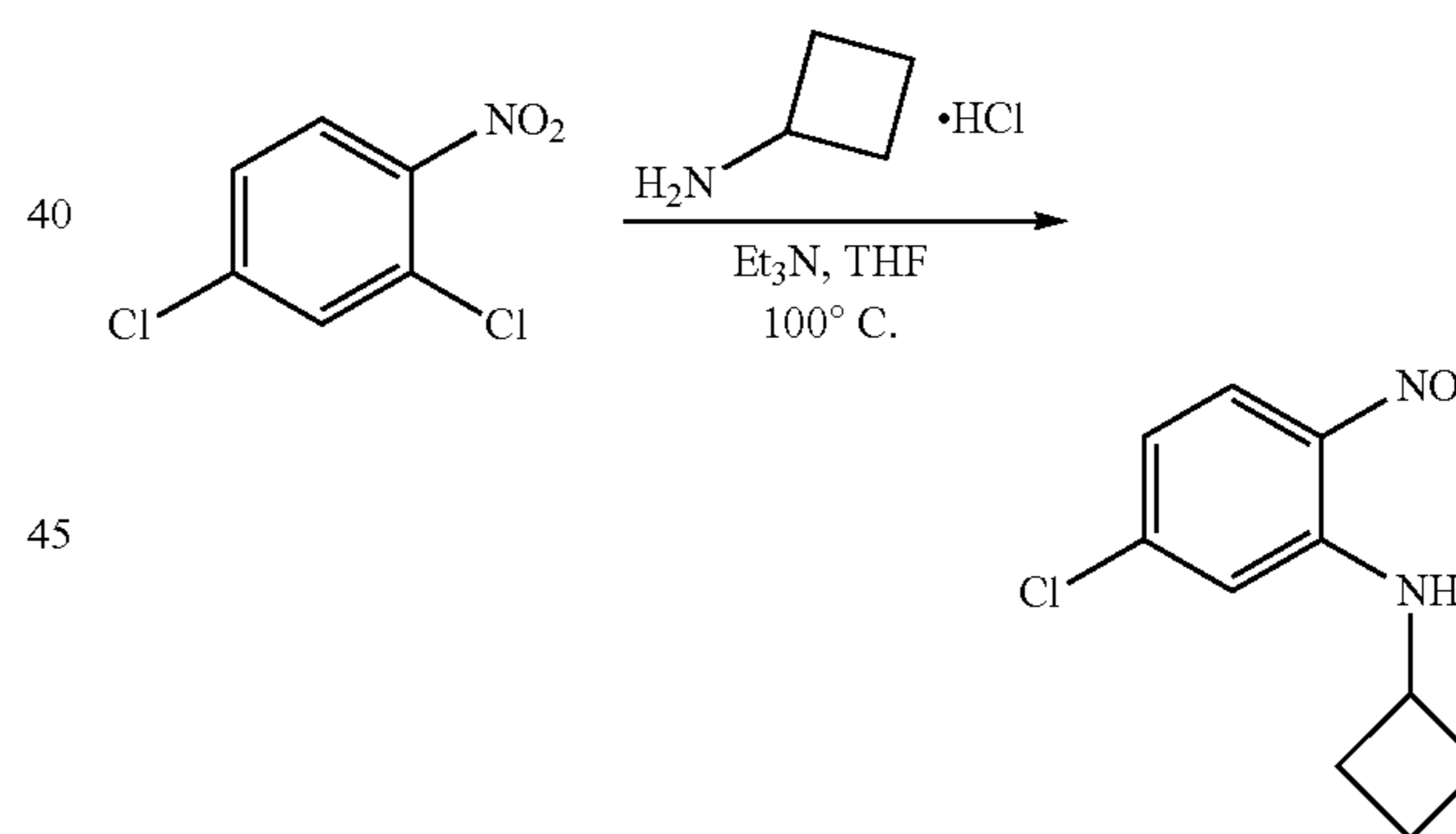
90

Method 2: Preparation of 3-((4-fluorophenyl)amino)-4-nitrobenzonitrile for Use in Method 1, Step B



A mixture of 3-fluoro-4-nitrobenzonitrile (2 g, 12 mmol), triethylamine (1.7 mL, 1.5 equivalents) and 4-fluoroaniline (1.7 mL, 1.5 equivalents) was heated at 60° C. under a nitrogen atmosphere for 60 hours. The resulting solid red-brown mass was cooled to ambient temperature and suspended in 50 mL of 1 N aqueous hydrochloric acid. The mixture was extracted extensively with dichloromethane and the organic extracts dried over anhydrous magnesium sulfate. Concentration of the organic extracts under reduced pressure afforded 2.9 g of a red solid, practically pure by LC/MS. MS (ESI) m/z 256 ($M-H^-$).

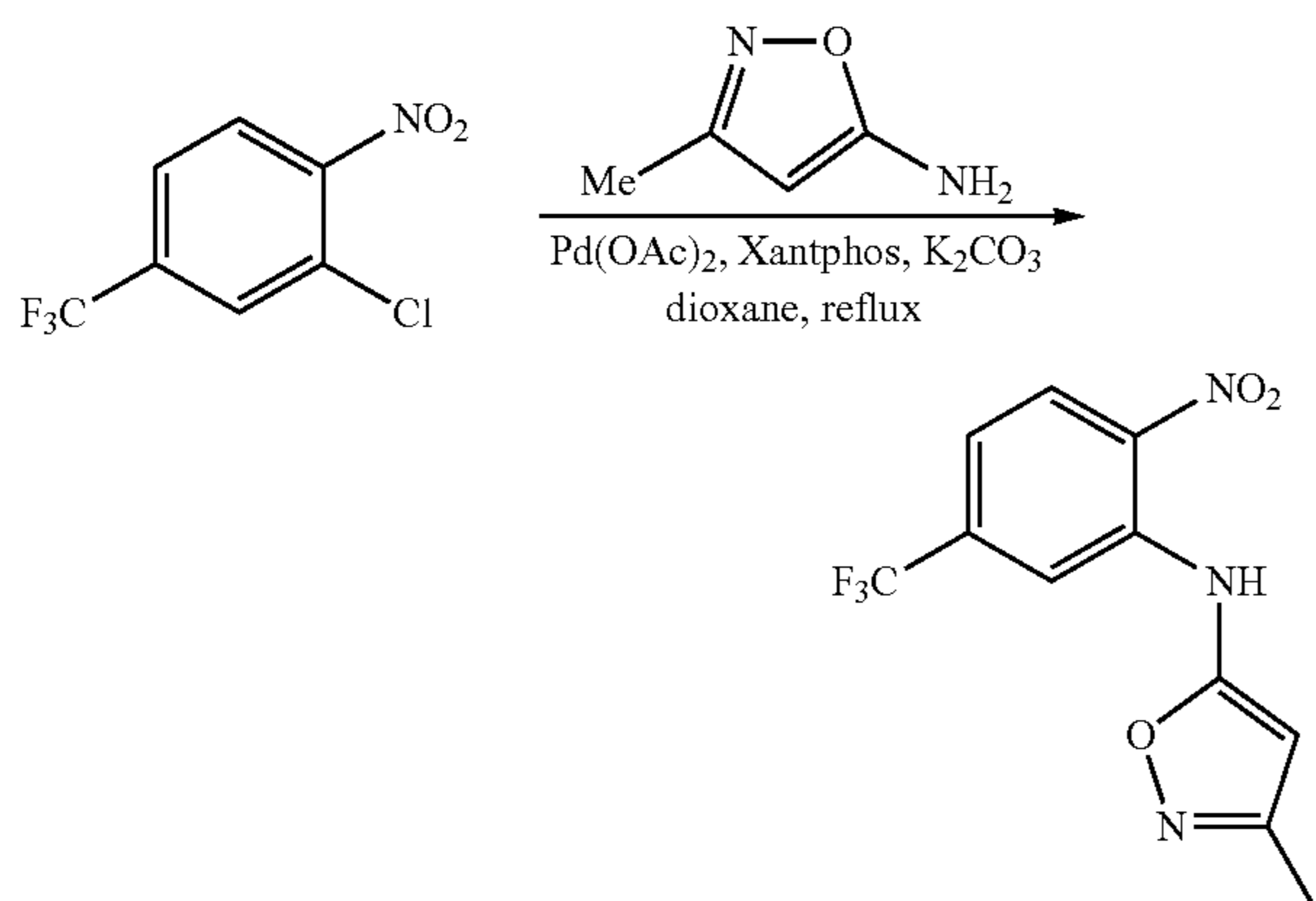
Method 3: Preparation of 5-chloro-N-cyclobutyl-2-nitroaniline for Use in Method 1, Step B



A mixture of cyclobutylamine hydrochloride (2.15 g), triethylamine (2.8 mL), 2,4-dichloro-1-nitrobenzene (3.84 g, 20 mmol, limiting reagent) and tetrahydrofuran (40 mL) was heated in a sealed vial at 100° C. for 16 hours. The reaction mixture was cooled to room temperature, and 0.2 equivalents of both cyclobutylamine hydrochloride and triethylamine added, and the resulting mixture was heated at 100° C. for an additional 17 hours. The cooled reaction mixture was diluted with water, extracted thoroughly with dichloromethane and ethyl acetate, the organic extracts dried over anhydrous magnesium sulfate and concentrated. Purification of the crude product by chromatography on silica with 20% dichloromethane in hexanes as eluent afforded the desired product (1.65 g) as an orange solid. 1H NMR ($CDCl_3$): δ 8.16 (NH, bs), 8.12 (1H, d), 6.70 (1H, s), 6.60 (1H, d), 4.02 (1H, m), 2.53 (2H, m), 2.03 (2H, m), 1.92 (2H, m).

91

Method 4: Preparation of 3-Methyl-N-(2-nitro-5-(trifluoromethyl)phenyl)isoxazol-5-amine for Use in Method 5



Palladium(II) acetate (1.00 g, 0.443 mmol) was added to Xantphos (0.513 g, 0.887 mmol) in degassed dioxane (10 mL) and the suspension was stirred for 15 minutes under N₂. The resulting solution was added to a mixture of 2-chloro-3-nitro-6-(trifluoromethyl)benzene (1.00 g, 4.43 mmol), 3-methylisoxazol-5-amine (0.522 g, 5.32 mmol) and K₂CO₃ (0.919 g, 6.65 mmol) in degassed dioxane (40 mL) and the reaction mixture was refluxed overnight. Conversion was confirmed by TLC and the solution was filtered through a plug of celite. The volatiles were removed and the crude residue was purified by chromatography on silica (0-100% EtOAc/hexanes) to give 0.811 g (63%) of the title compound. MS (ESI) m/z 288 (MH⁺).

The following intermediates were prepared for use in Method 1, Step B using the general procedure described in Section 1, Method 4, with appropriate starting materials.

3-((5-fluoropyridin-2-yl)amino)-4-nitrobenzotrile

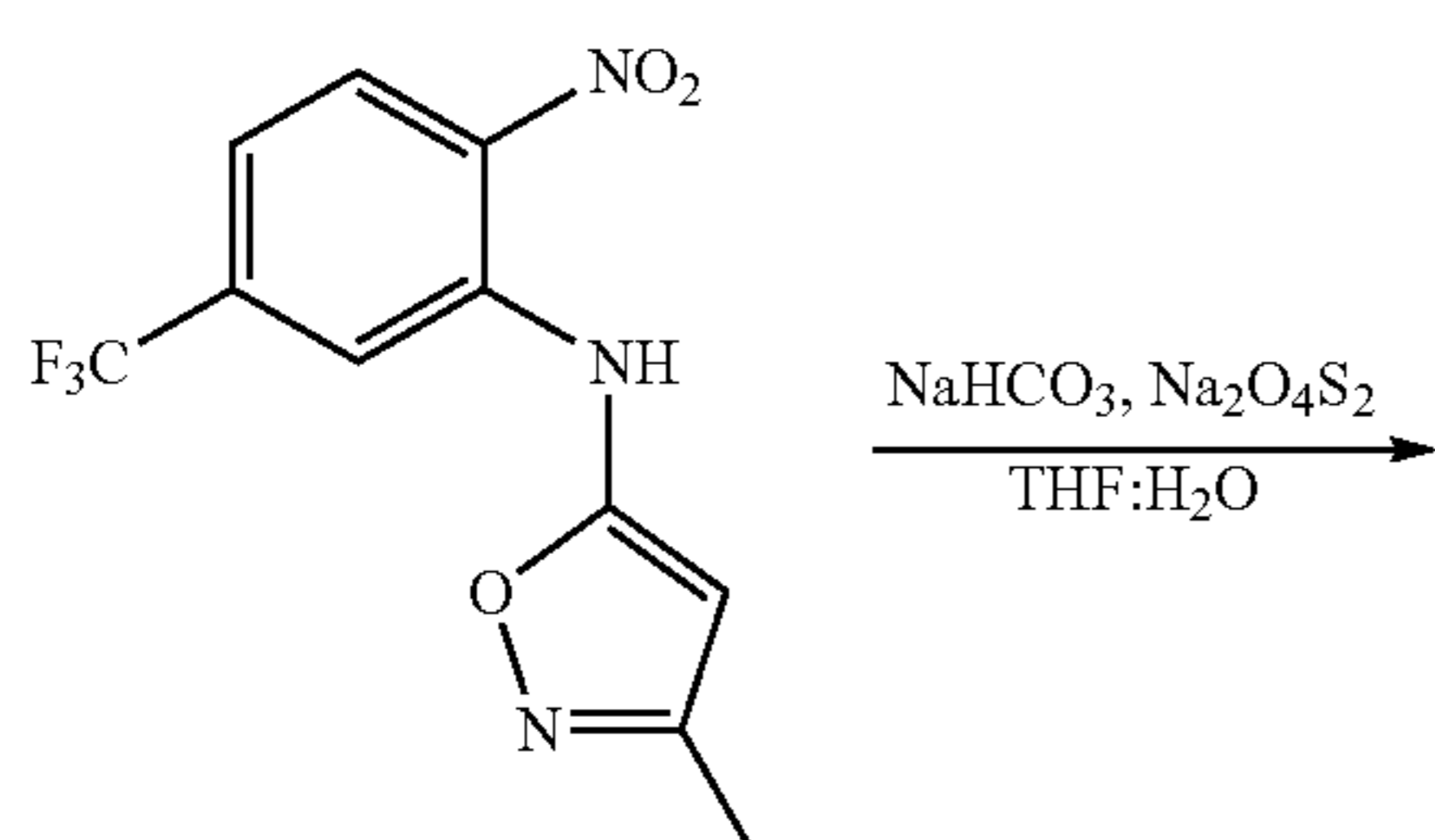
N-(3,5-difluorophenyl)-2-nitro-5-(trifluoromethyl)aniline

N-(3-fluoro-4-(trifluoromethoxy)phenyl)-2-nitro-5-(trifluoromethyl)aniline

2-nitro-N-(4-(trifluoromethoxy)phenyl)-5-(trifluoromethyl)aniline

N-(3,4-difluorophenyl)-2-nitro-5-(trifluoromethyl)aniline

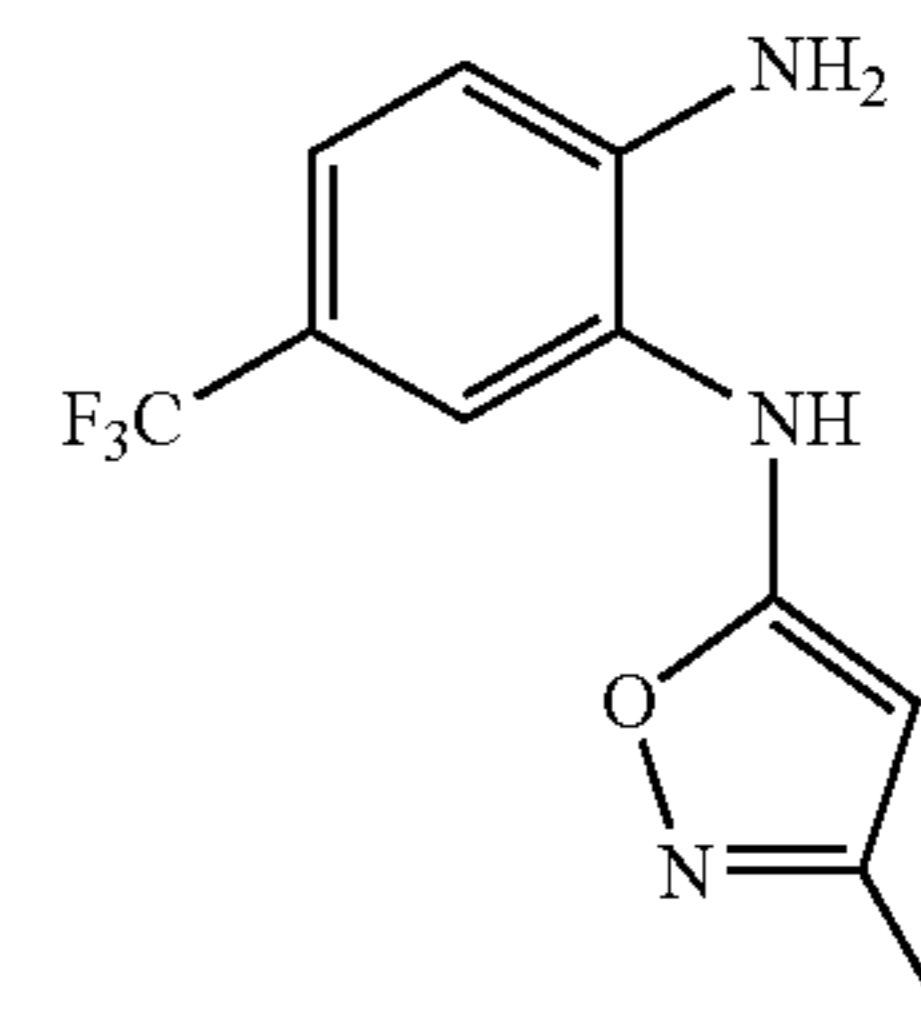
Method 5: Preparation of N¹-(3-methylisoxazol-5-yl)-5-(trifluoromethyl)benzene-1,2-diamine for Use in Method 1, Step C



92

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Sodium bicarbonate (0.410 g, 4.88 mmol) then sodium hydrosulfite (1.27 g, 7.31 mmol) were added to a solution of the nitro aromatic core (0.700 g, 2.44 mmol) in tetrahydrofuran:H₂O (2:1; 24 mL). The resulting reaction mixture was allowed to stir for 4 hours, diluted with H₂O and then extracted with EtOAc. The combined organics were dried (MgSO₄) and the volatiles removed to leave a crude residue that was purified by chromatography on silica (0-5% MeOH/dichloromethane) to give 380 mg (61%) of the title compound. MS (ESI) m/z 258 (MH⁺).

The following benzene-1,2-diamine was prepared using the general procedures described in Section 1, Methods 4 and 5, with appropriate starting materials, for use in Method 1, Step C:

4-amino-3-((3-methylisoxazol-5-yl)amino)benzotrile

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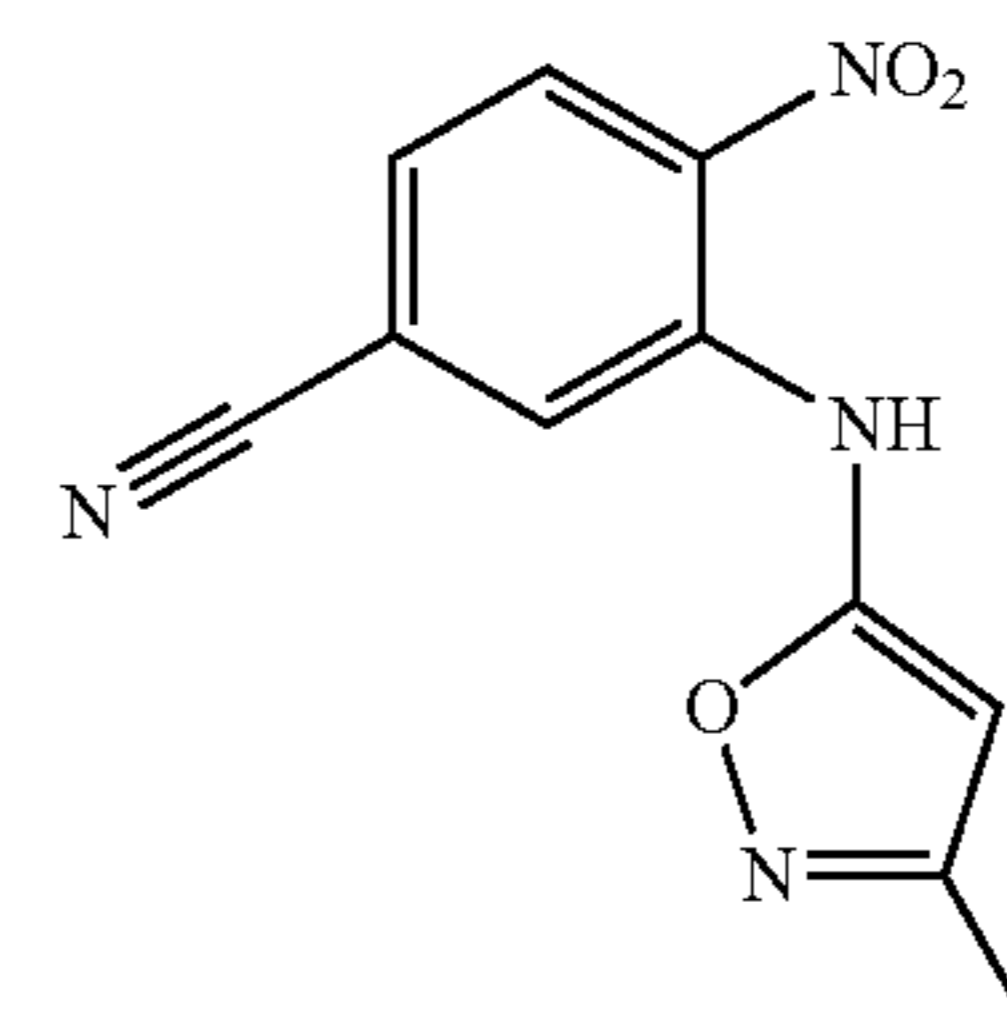
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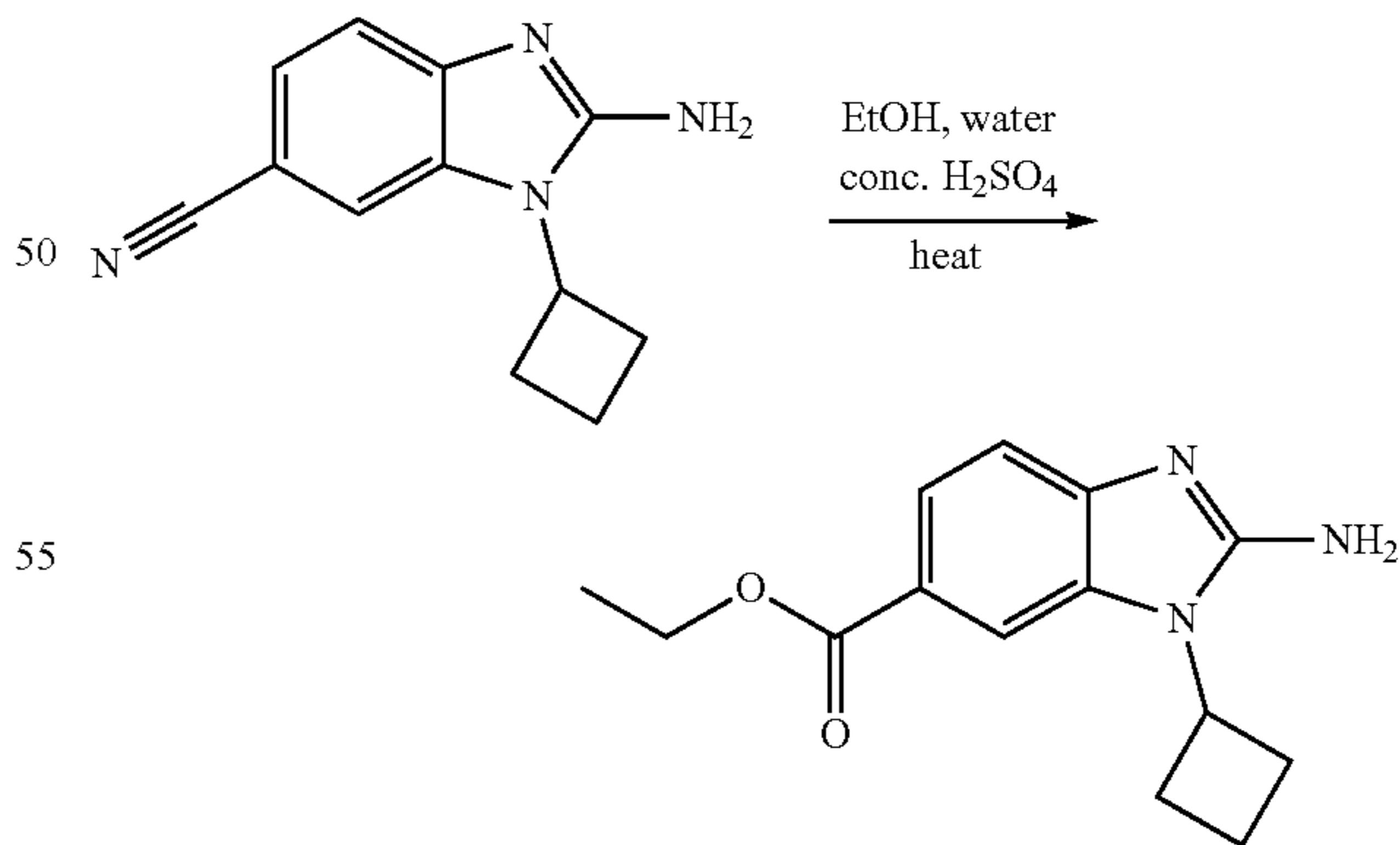
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Method 6: Preparation of ethyl 2-amino-1-cyclobutyl-1H-benzo[d]imidazole-6-carboxylate



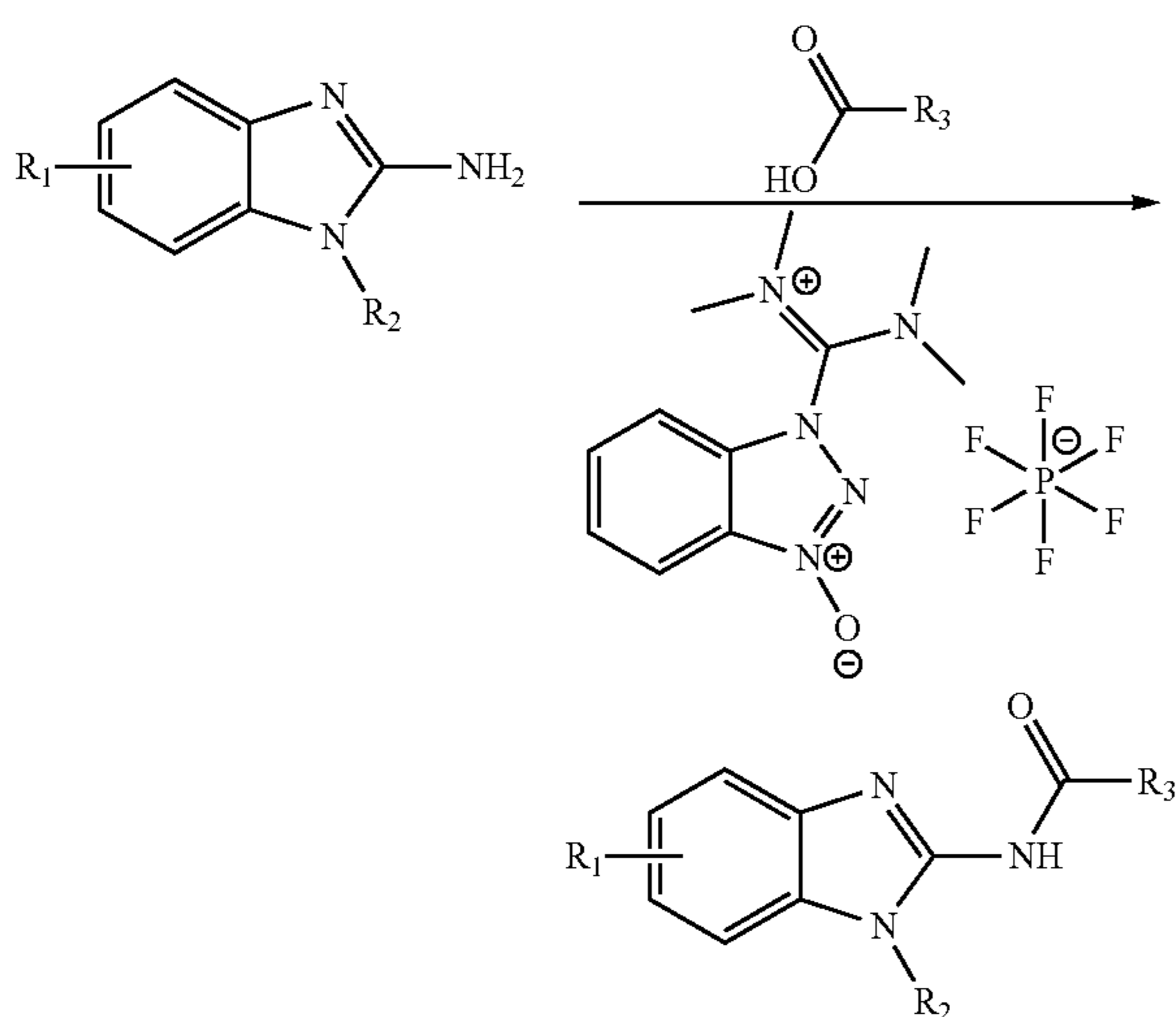
To a solution of 4-amino-3-(cyclobutylamino) benzotrile (1.5 g, 7.0 mmol) in EtOH (30 mL) was added water (3 mL) and concentrated sulfuric acid (3 mL). The solution was placed in a 150° C. sand bath with stirring for 4 days. The reaction was allowed to cool to ambient temperature and carefully quenched by pouring slowly into saturated aqueous

93

sodium bicarbonate. The mixture was diluted with EtOAc and the layers were separated. The aqueous layer was back extracted with dichloromethane and the combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated to give the title compound as a tan solid (790 mg, 43% yield). MS (ESI) m/z 260.0 (MH^+), retention time=2.21 min (Method B).

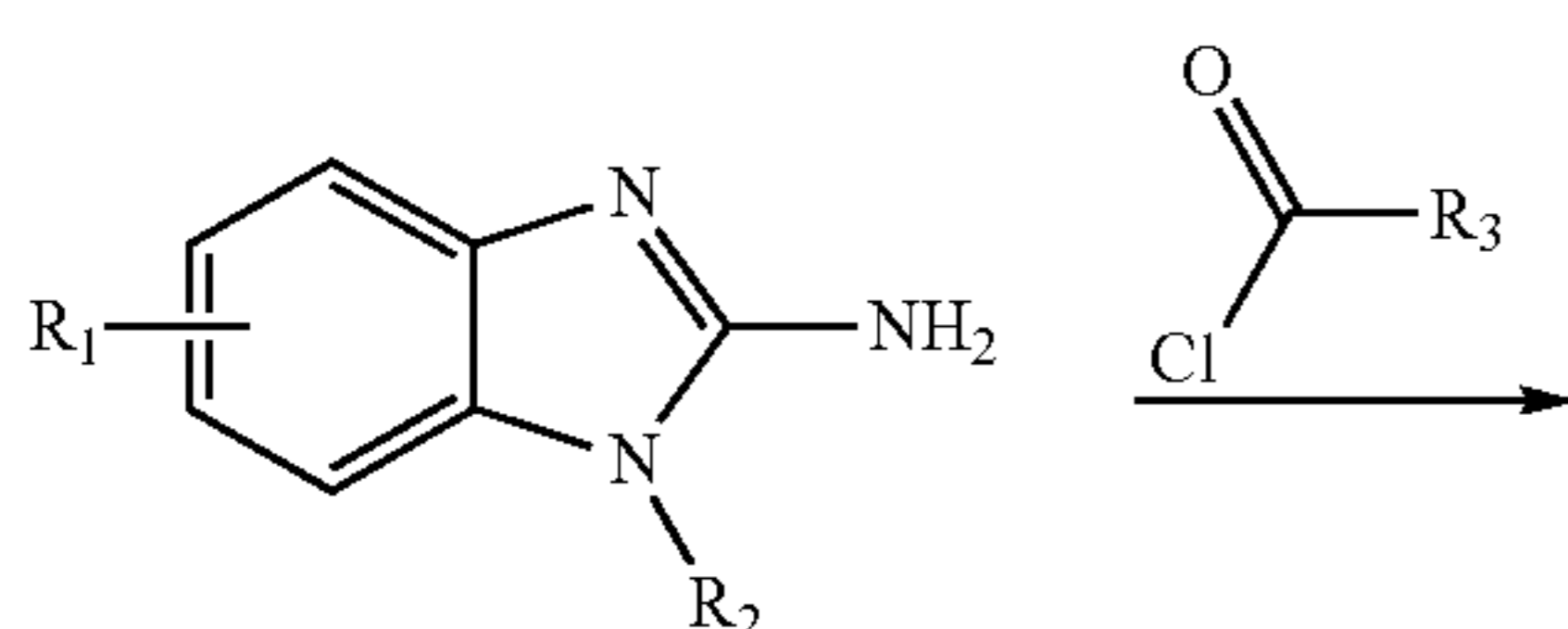
Section 2. Representative Procedures for the Preparation of 1H-benzo[d]imidazol-2-yl Amides (1.5, Scheme 1)

Method 7: General Procedure for Amide Formation Using HATU (1-((dimethylamino)(dimethyliminio)methyl)-1H-benzo[d][1,2,3]triazole 3-oxide hexafluorophosphate(V)) as Coupling Reagent



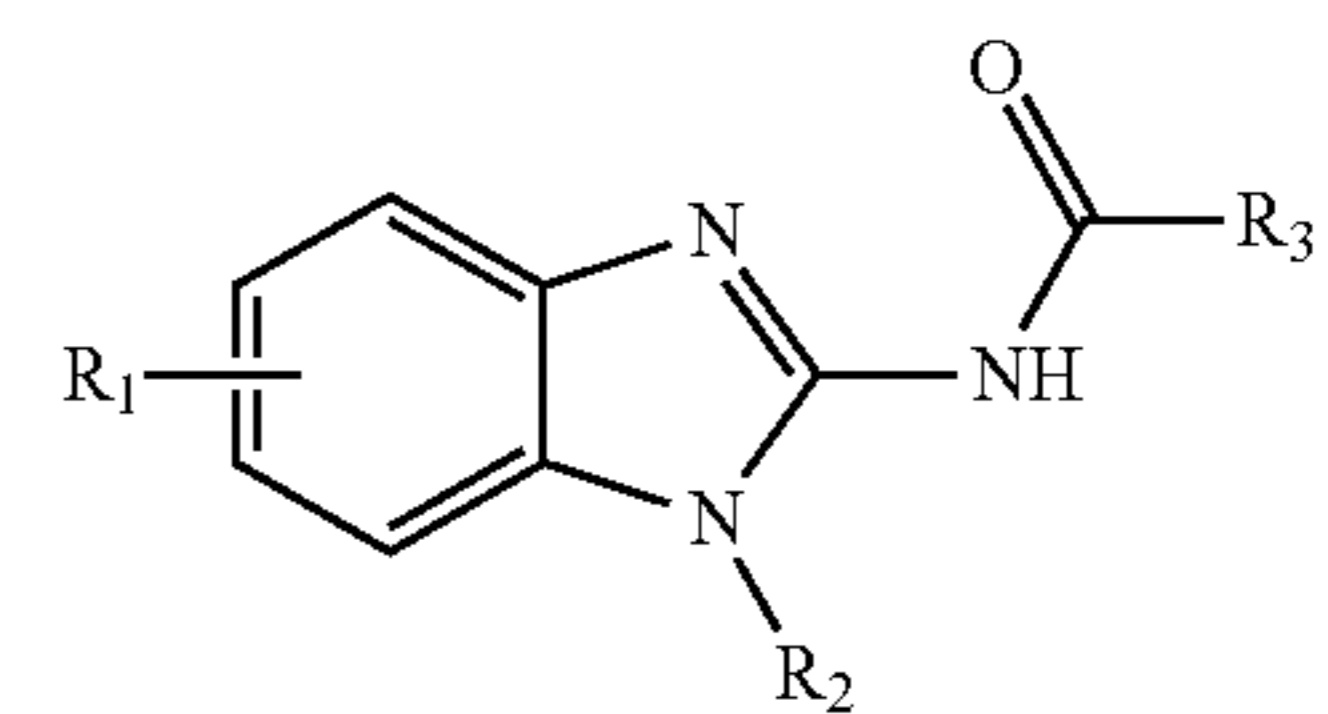
The appropriate carboxylic acid was dissolved in dimethylformamide or THF (0.20-0.7 M) and diisopropylethylamine or pyridine (2 equivalents) was added prior to the addition of 1-((dimethylamino)(dimethyliminio)methyl)-1H-benzo[d][1,2,3]triazole 3-oxide hexafluorophosphate(V) (HATU, 1.2 equivalents) in one portion. The reaction was allowed to stir at room temperature for 0 to 15 minutes prior to the addition of the required substituted 2-aminobenzimidazole (1 equivalent) and the flask was placed in a heated sand bath (40-65° C.) for 8 to 48 hours. The mixture was diluted with EtOAc and washed sequentially with saturated aqueous NH_4Cl (2 \times), saturated aqueous $NaHCO_3$ (2 \times), 10% aqueous Na_2CO_3 (2 \times), and brine. The organic layer was dried over Na_2SO_4 and concentrated. Purification by chromatography on silica (0-100% EtOAc/hexanes or 0-10% MeOH/dichloromethane) provided the title corresponding 1H-benzo[d]imidazol-2-yl amides.

Method 8: General Procedure for Amide Formation Using Acyl Chlorides



94

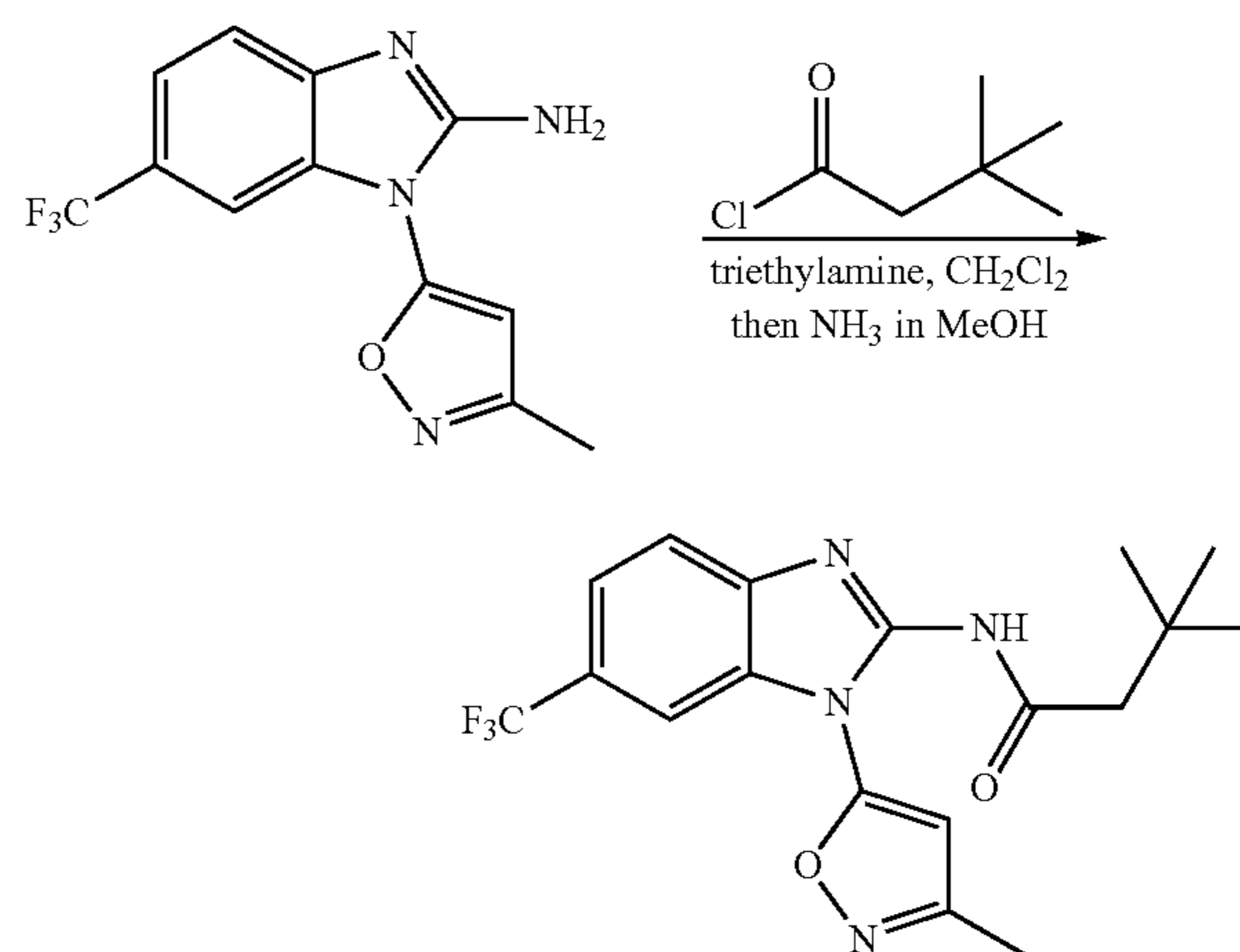
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To a solution appropriate 1H-benzo[d]imidazol-2-amine intermediate (0.22 mmol) in tetrahydrofuran (1 mL) was added pyridine (1.5 equivalents) and acyl chloride (1.2 equivalents). The reaction mixture was stirred for 18 hours. The mixture was partitioned between EtOAc and water. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica (0-100% EtOAc/hexanes) to provide title compounds.

Method 9: General Procedure for Amide Coupling Using Excess Acid Chloride Followed by Treatment with Ammonia

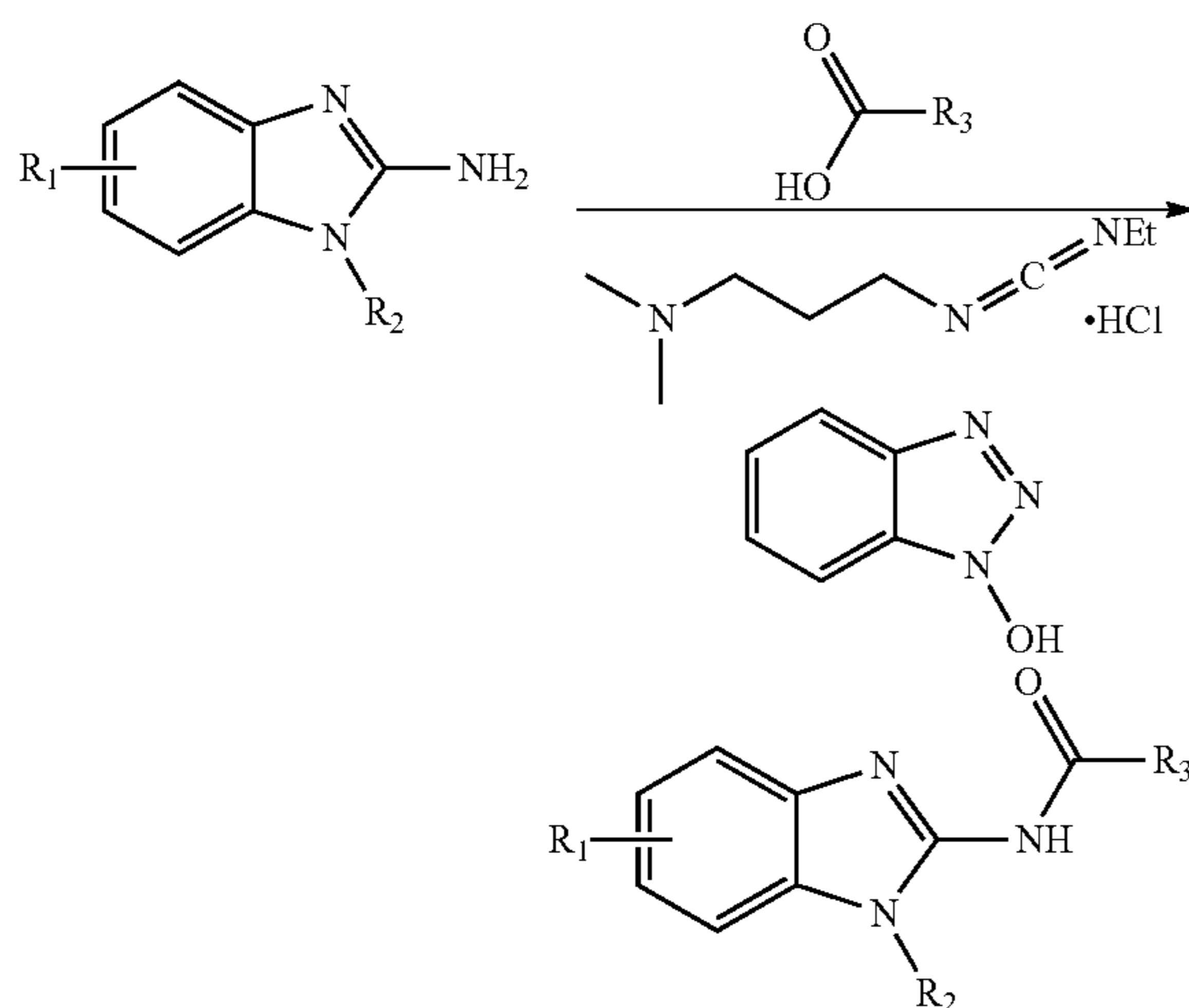
Example 46. Preparation of 3,3-dimethyl-N-(1-(3-methylisoxazol-5-yl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)butanamide



3,3-Dimethylbutanoyl chloride (0.187 mL, 1.04 mmol) was added dropwise to a 0° C. solution of 1-(3-methylisoxazol-5-yl)-6-(trifluoromethyl)-1H-benzimidazol-2-amine (0.030 g, 0.104 mmol) and triethylamine (0.180 mL, 1.56 mmol) in CH_2Cl_2 (1 mL) and the reaction mixture was allowed to warm to ambient temperature and stir for 30 minutes. Ammonia (2.0 M in MeOH, 1 mL) was added and the mixture was stirred at 50° C. for two hours before quenching with saturated aqueous NH_4Cl . The aqueous portion was extracted with EtOAc, the combined organics were dried ($MgSO_4$) and the volatiles removed to give a crude residue that was purified by chromatography on silica (0-5% MeOH/DCM) to yield 0.017 g (43%) of the title compound. MS (ESI) m/z 381 (MH^+).

95

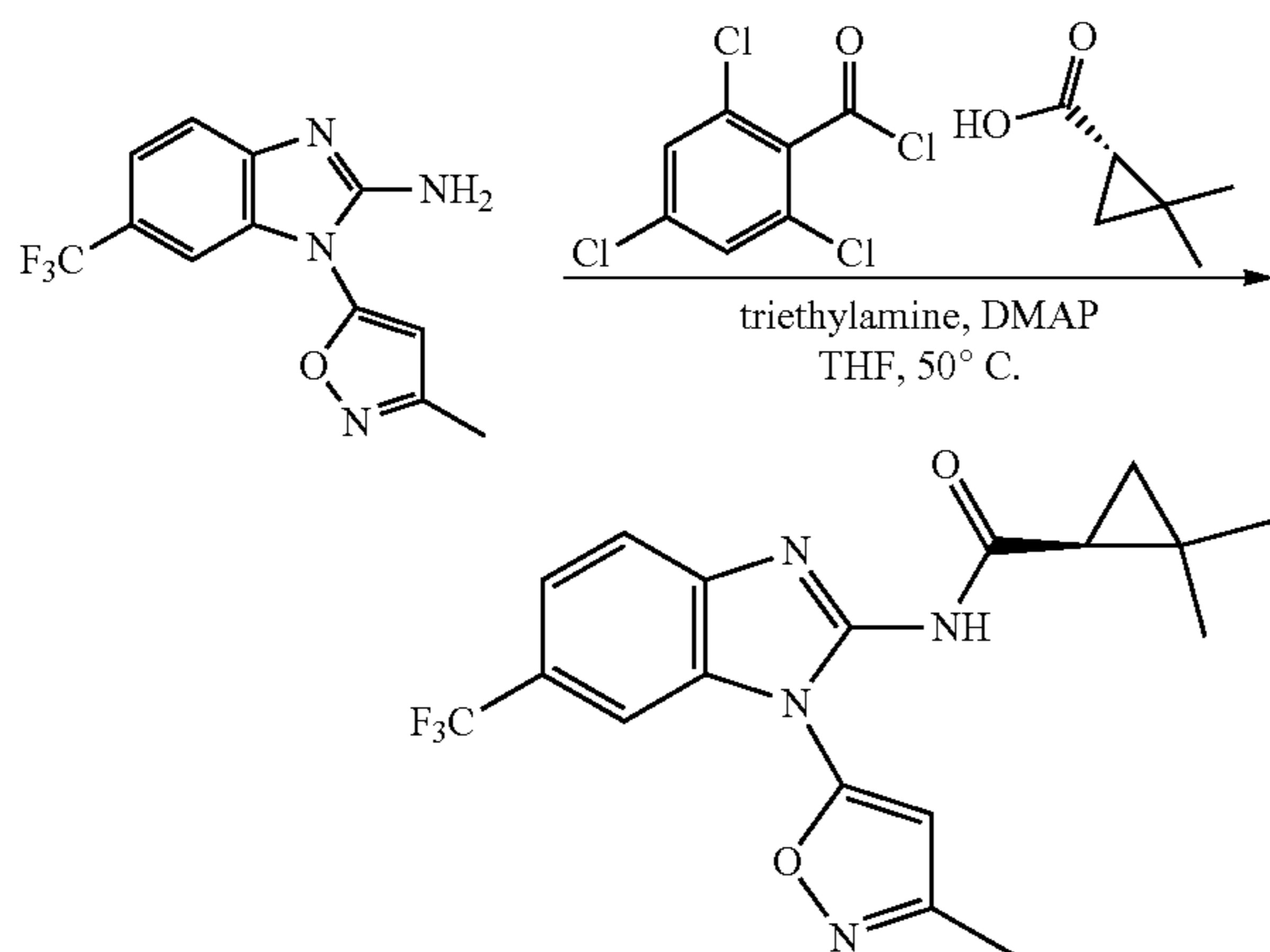
Method 10: General Procedure for Amide Formation Using EDC (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) and HOBt (1-hydroxybenzotriazole) as Coupling Reagents



A solution of the appropriate 1H-benzo[d]imidazol-2-amine (0.13 mmol), carboxylic acid (0.16 mmol), EDC (0.19 mmol), HOBt (0.19 mmol) and diisopropylethylamine (0.66 mmol) in tetrahydrofuran (1 mL) was heated at 50° C. under nitrogen for 2-4 hours. The reaction was cooled to room temperature, diluted with EtOAc and washed with water. The organic solution was concentrated in vacuo and purified by flash column chromatography (silica gel, 0-10% MeOH/DCM) to afford the title compounds.

Method 11: Representative Procedure for Amide Formation Using Yamaguchi Conditions

Example 45. Preparation of (S)-2,2-Dimethyl-N-(1-(3-methylisoxazol-5-yl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)cyclopropanecarboxamide

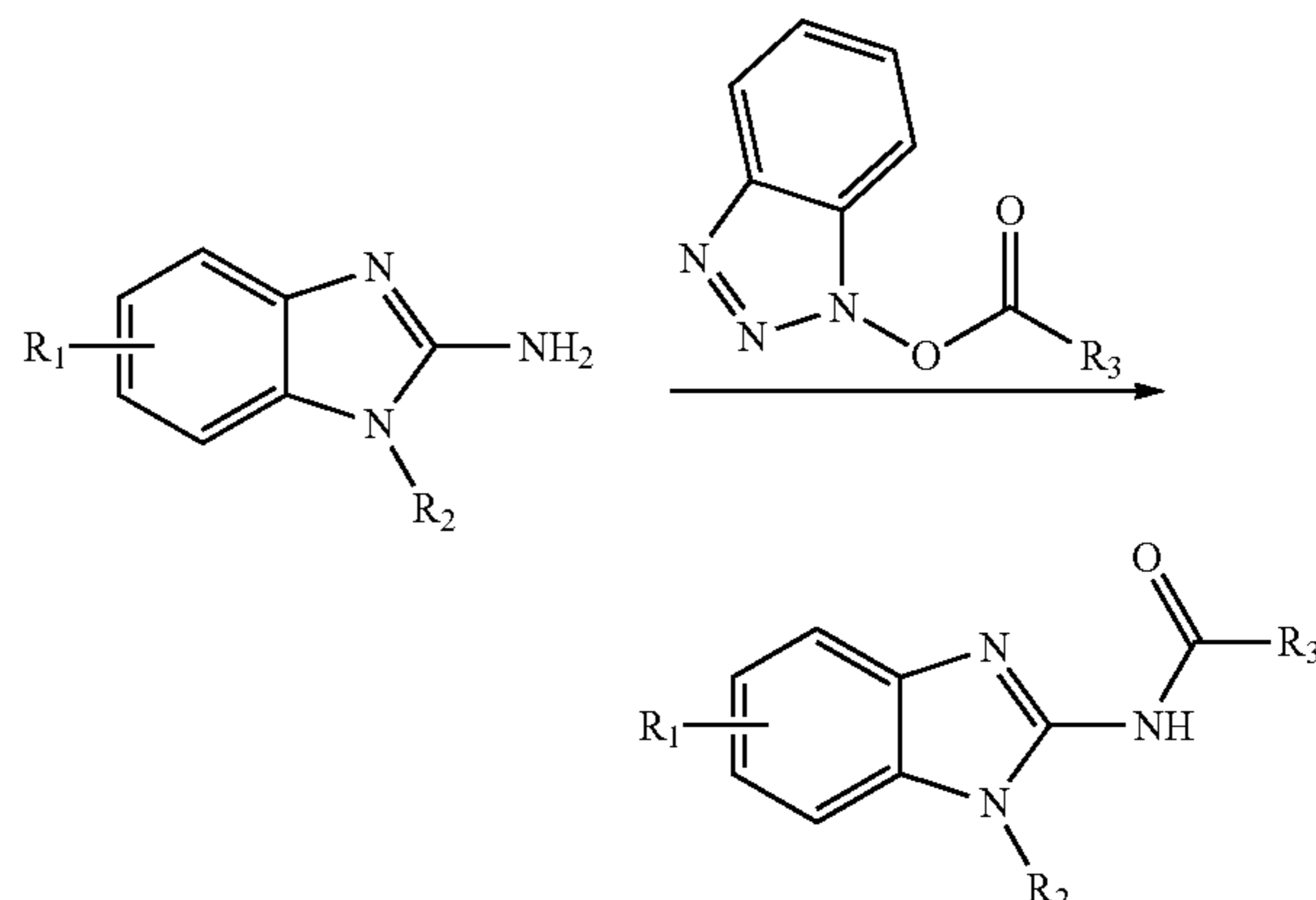


(S)-2,2-Dimethylcyclopropyl carboxylic acid (0.018 g, 0.159 mmol), triethylamine (0.042 mL, 0.318 mmol) and 2,4,6-trichlorobenzoyl chloride (0.025 mL, 0.159 mmol) was stirred in 1 mL tetrahydrofuran for 30 minutes. 1-(3-

96

Methylisoxazol-5-yl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-amine (0.030 g, 0.106 mmol) and 4-(dimethylamino)pyridine (0.003 g, 0.026 mmol) were added to the reaction mixture and the resulting solution was heated to 50° C. and stirred overnight. The reaction was quenched with H₂O, extracted (EtOAc 3×) and the combined organics were dried (MgSO₄) and the volatiles removed to give a crude product that was purified by chromatography on silica (0-100% EtOAc/hexanes) followed by HPLC (0-100% MeCN/H₂O) to yield 21 mg (71%) of the desired product. MS (ESI) m/z 379 (MH⁺).

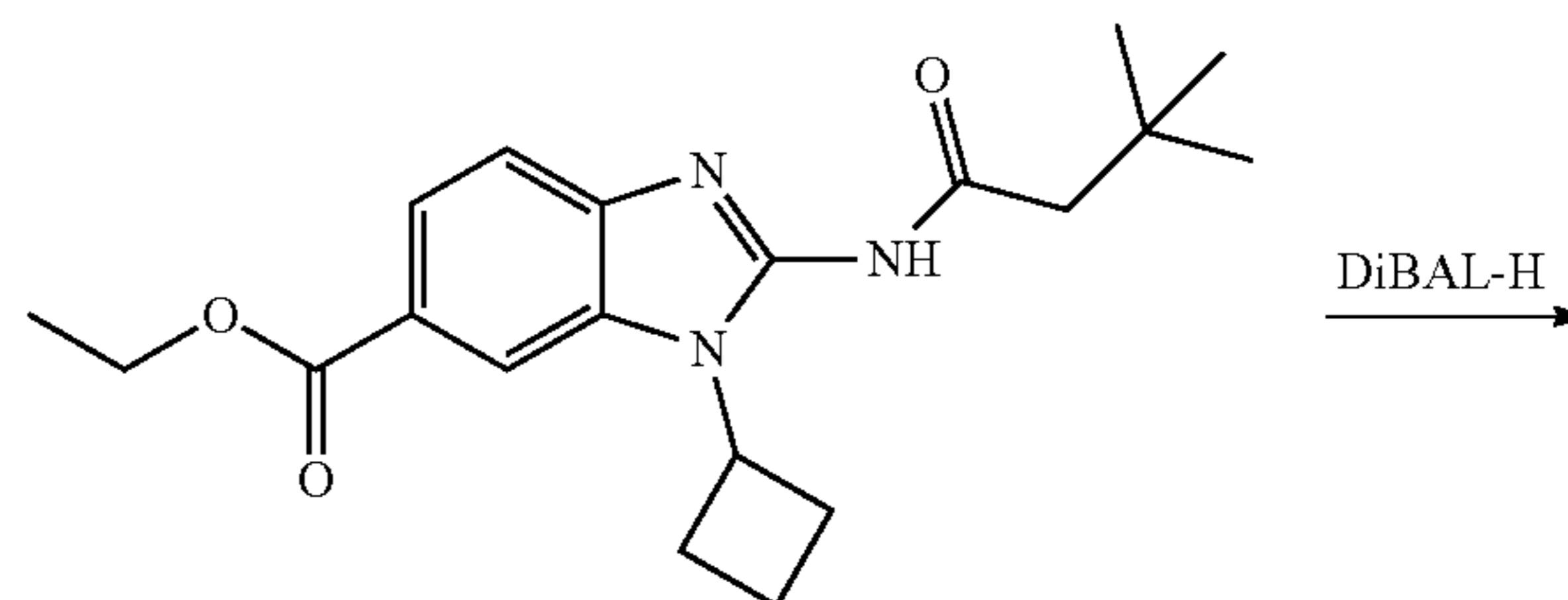
Method 12: General Procedure for Amide Formation Using Acylbenzotriazoles



A solution of appropriate 1H-benzo[d]imidazol-2-amine intermediate (0.66 mmol) and triethylamine (0.5 mL, 3.3 mmol, 5 equivalents) in tetrahydrofuran (3 mL) was stirred for 5 min at room temperature. To this solution was added a solution of an appropriate acylbenzotriazole (0.7 M in dichloromethane, 3.0 mL, 2.0 mmol, 3 equivalents; see Katritzky, A R, et al, *Synlett*, 2005, 11, 1656) and the mixture was placed in a 50° C. sand bath for 12 hours. The mixture was allowed to cool to room temperature and diluted with EtOAc (50 mL) and washed sequentially with saturated aqueous Na₂CO₃ (three times) and brine. The organic layer was dried over Na₂SO₄ and concentrated. Purification by chromatography on silica (0-100% EtOAc/hexane or 0-10% MeOH/dichloromethane) provided the title compounds.

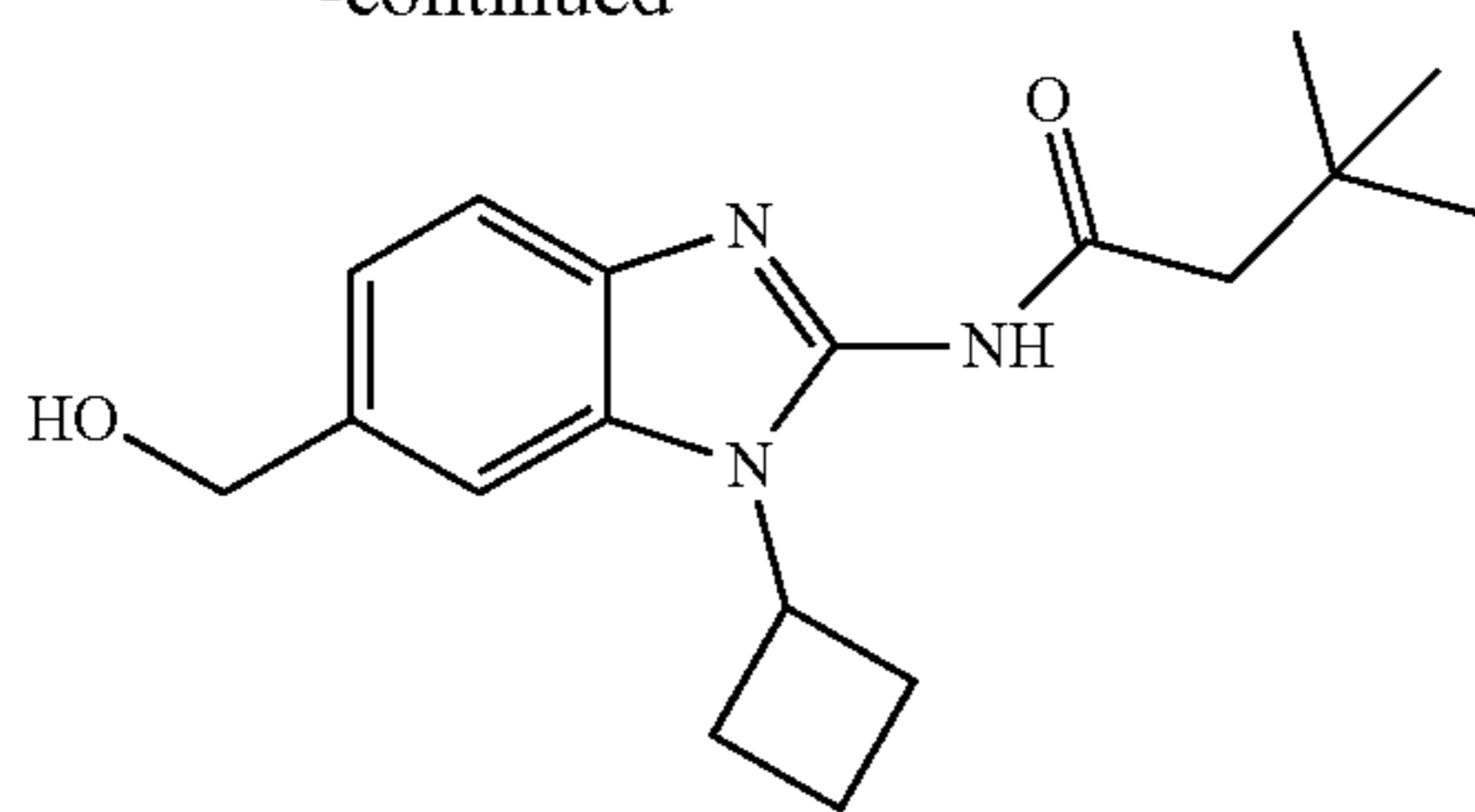
Section 3. Exemplary Syntheses for Examples in Table 1 Involving Further Transformation of 1H-benzo[d]imidazol-2-yl amides

Example 51. Preparation of N-(1-cyclobutyl-6-(hydroxymethyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide



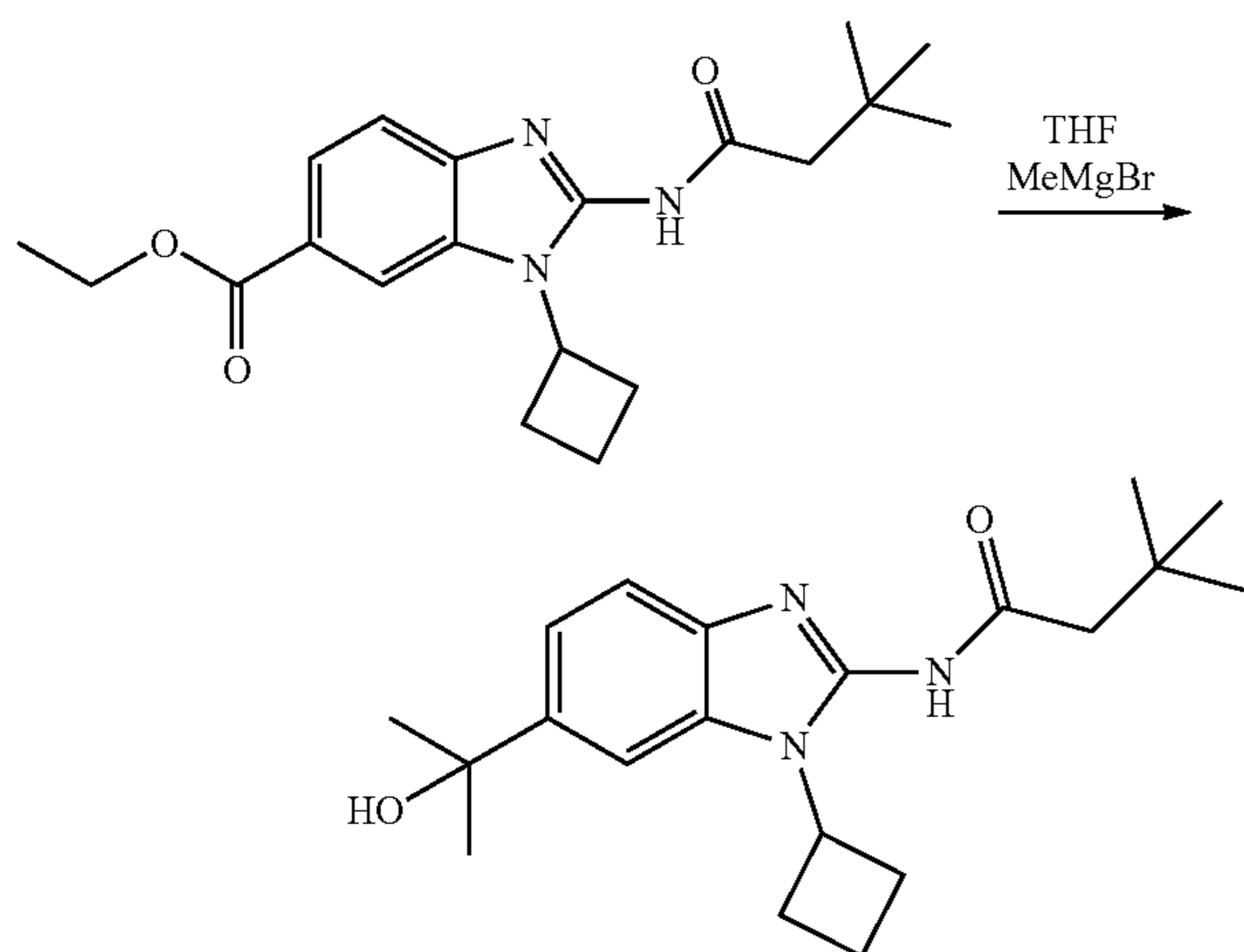
97

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A CH_2Cl_2 (15 mL) solution of ethyl 1-cyclobutyl-2-(3,3-dimethylbutanamido)-1H-benzo[d]imidazole-6-carboxylate (112 mg) was placed in a -78°C . bath for 10 minutes prior to the dropwise addition of diisobutylaluminum hydride (1.0 M in CH_2Cl_2 , 2 mL). The reaction was allowed to stir at -78°C . for 1 h before being quenched by the dropwise addition of MeOH (2 mL). The quenched reaction was diluted with CH_2Cl_2 (50 mL) and sodium/potassium tartrate (1 M, 50 mL) was added and the mixture was allowed to vigorously stir overnight. In this time frame, two clear layers developed and the aqueous portion was extracted with CH_2Cl_2 (2 \times), the combined organics were washed with brine, dried (Na_2SO_4) and the volatiles removed to give a crude residue that was purified via chromatography (Isco 12 g silica gel column, 0-10% MeOH/ CH_2Cl_2) to yield 56 mg (57%) of the title compound. MS (ESI) m/z 316.4 (MH^+), retention time=2.35 min. The material was further purified by subjecting to another Isco 12 g silica gel column (40 to 100% EtOAc in hexanes) to give 10 mg of the title compound.

Example 53. Preparation of N-(1-cyclobutyl-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide

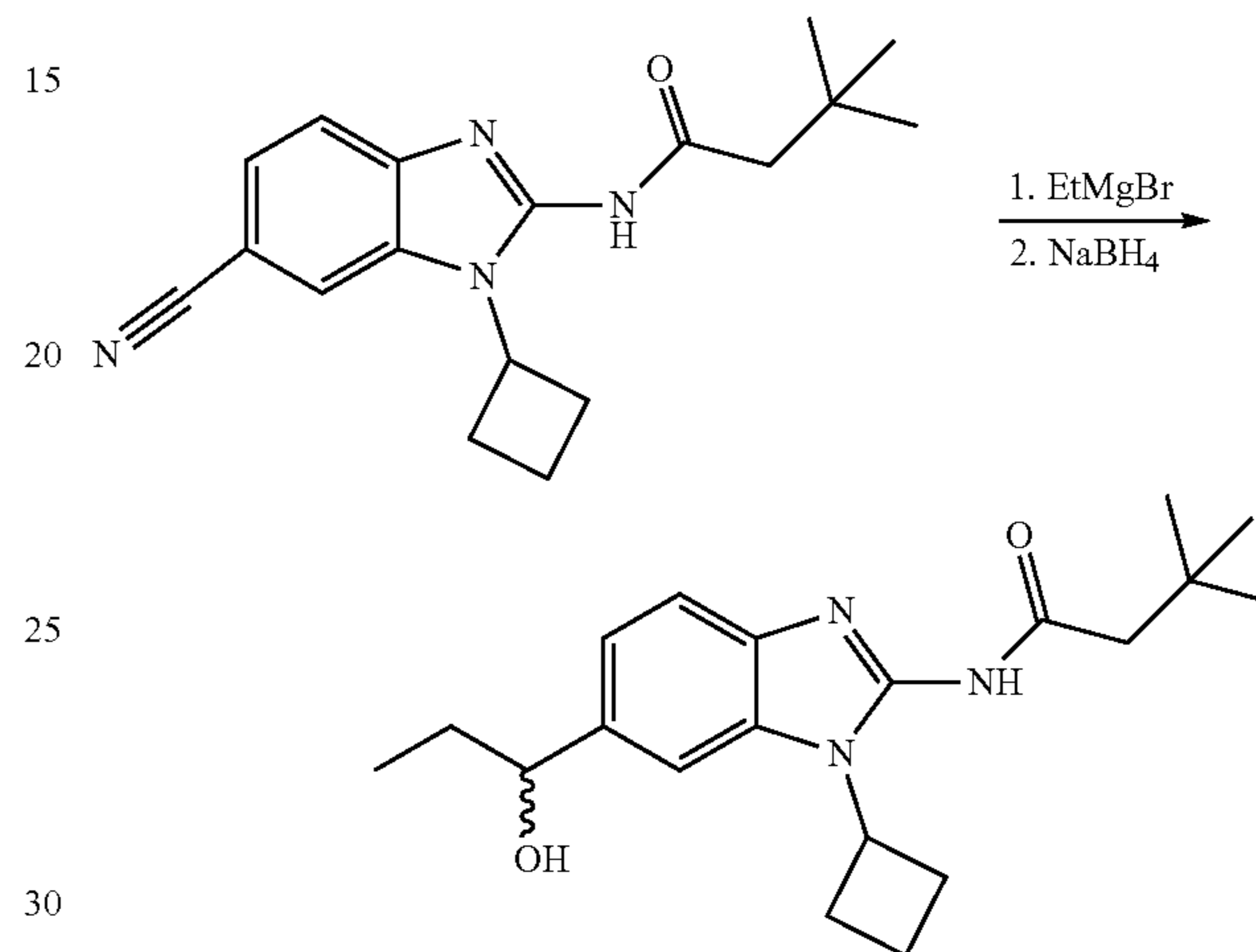


A tetrahydrofuran (2 mL) solution of ethyl 1-cyclobutyl-2-(3,3-dimethylbutanamido)-1H-benzo[d]imidazole-6-carboxylate (50 mg, 0.14 mmol) was allowed to chill at 0°C . for 10 minutes under nitrogen prior to the dropwise addition of methylmagnesium bromide (2 M in ether, 0.3 mL). The reaction was allowed to stir at 0°C . for 1.5 hours and then quenched by the addition of saturated sodium bicarbonate (25 mL) and EtOAc (25 mL). The aqueous layer was extracted twice with EtOAc and the combined organics were washed with brine, dried with sodium sulfate, filtered and

98

concentrated to give a crude residue. The crude material was subjected to column chromatography (two 4 g silica gel Isco columns in series, 5 to 50% EtOAc in hexanes) to give the title compound as a white solid (16 mg, 33% yield). MS (ESI) m/z 344.4 (MH^+), retention time=2.44 minutes (Method B).

Example 57. Preparation of N-(1-cyclobutyl-6-(1-hydroxyethyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide



Step A

A tetrahydrofuran (2 mL) solution of N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide (112 mg) was placed in a 0°C . bath for 10 minutes prior to the dropwise addition of ethylmagnesium bromide (3 M in diethyl ether, 0.45 mL). The reaction was allowed to stir at 0°C . for 1 h and then allowed to warm up to room temperature. The reaction was allowed to stir at room temperature overnight and then placed back in a 0°C . bath for 10 minutes before it was quenched with MeOH (0.5 mL). After 5 minutes, the quenched reaction was partitioned between saturated aqueous ammonium chloride (25 mL) and ethyl acetate (25 mL). The aqueous layer was extracted twice with ethyl acetate. The combined organics were washed with brine and dried with sodium sulfate. The dried reaction was filtered, concentrated and subjected to a 12 g silica gel Isco column (15 to 100% EtOAc in hexanes) to give the ethyl ketone compound N-(1-cyclobutyl-6-propionyl-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide (75 mg, 70%) as a white solid. MS (ESI) m/z 342.4 (MH^+), retention time=3.51 minutes (Method B).

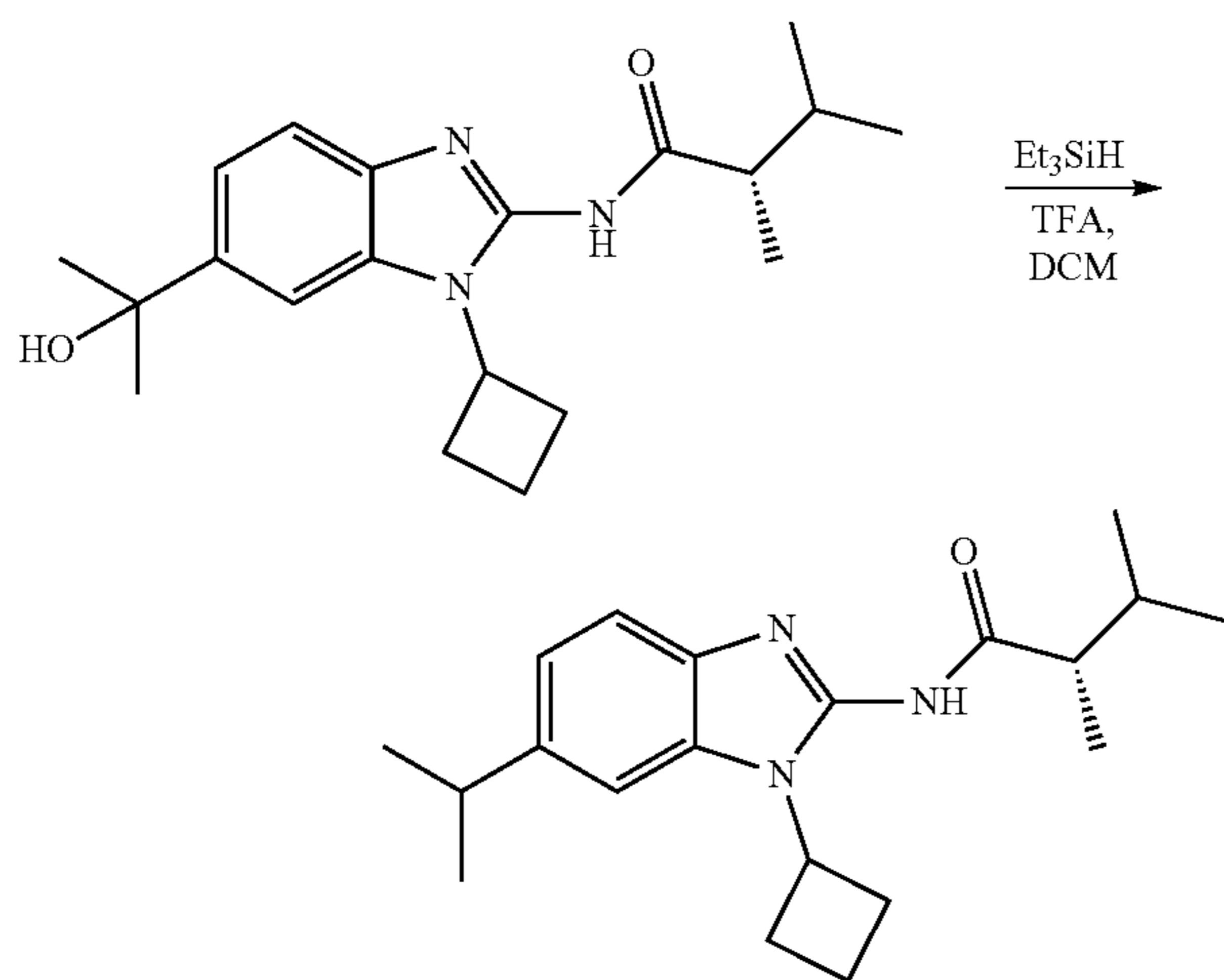
Step B

N-(1-Cyclobutyl-6-propionyl-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide (41 mg) was placed in a round-bottom flask with ethanol (6 mL) and the flask was allowed to chill in a 0°C . bath for 10 minutes before the portionwise addition of sodium borohydride (60 mg). The reaction was allowed to stir for 30 minutes and then quenched by the slow addition of HCl (1.0 M, 10 mL). The quenched reaction was diluted with EtOAc (30 mL) and allowed to stir for 1 hour. The aqueous layer was extracted with EtOAc (2 \times). The

99

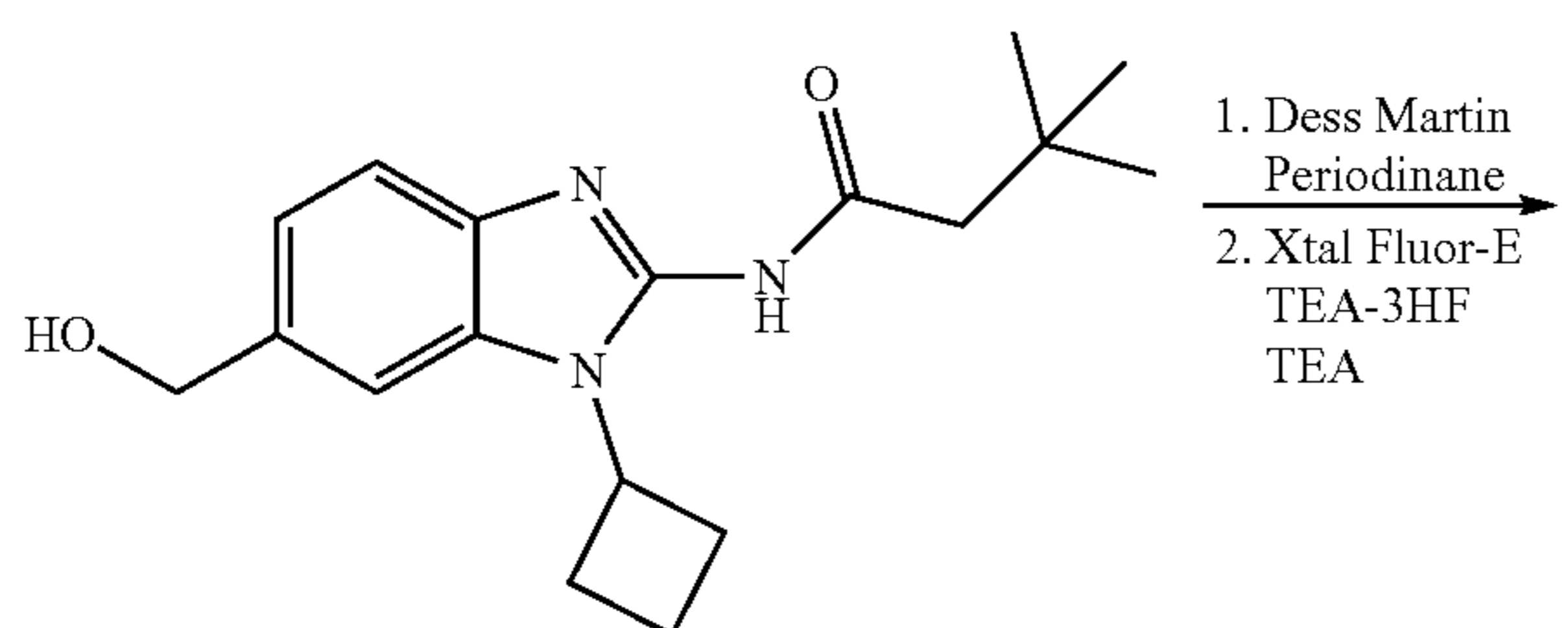
combined organics were washed with saturated aqueous sodium bicarbonate (40 mL), brine and dried with sodium sulfate. The dried solution was filtered and concentrated to give a crude material that was subjected to a 12 gram silica gel Isco column (20-50% EtOAc in hexanes) to give the title compound (25 mg, 60%) as a white solid. MS (ESI) m/z 344.4 (MH^+), retention time=2.57 minutes (Method B).

Example 65. Preparation of (S)—N-(1-cyclobutyl-6-isopropyl-1H-benzo[d]imidazol-2-yl)-2,3-dimethylbutanamide



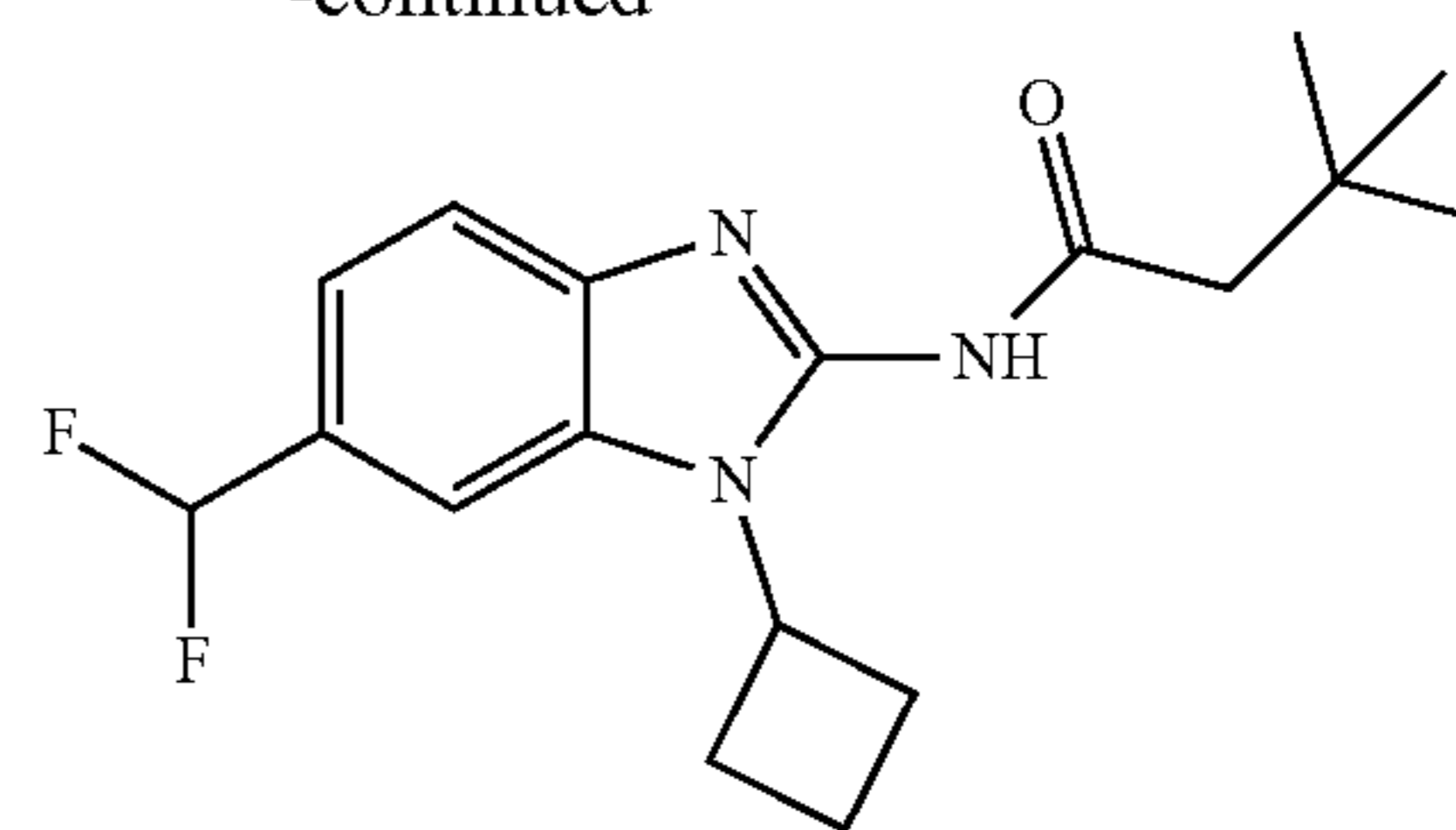
Solid (S)—N-(1-cyclobutyl-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)-2,3-dimethylbutanamide (15 mL) was dissolved in dichloromethane (2 mL). TFA (1.5 mL) was added before the dropwise addition of neat triethylsilane (1 mL). The reaction was allowed to stir overnight and then diluted with dichloromethane (15 mL) and washed with saturated sodium bicarbonate (20 mL). The aqueous layer was extracted twice with dichloromethane. The combined organics were washed with brine and dried with sodium sulfate. The dried solution was filtered and concentrated to give a crude product. The crude material was subjected to a high vacuum for 48 h prior to being subjected to column chromatography (4 gram Isco silica gel, 0-5% MeOH in dichloromethane) to give the title compound as a colorless oil (9 mg, 63% yield). MS (ESI) m/z 328.4 (MH^+), retention time=3.36 min (Method B).

Example 66. Preparation of N-(1-cyclobutyl-6-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide



100

-continued



Step A

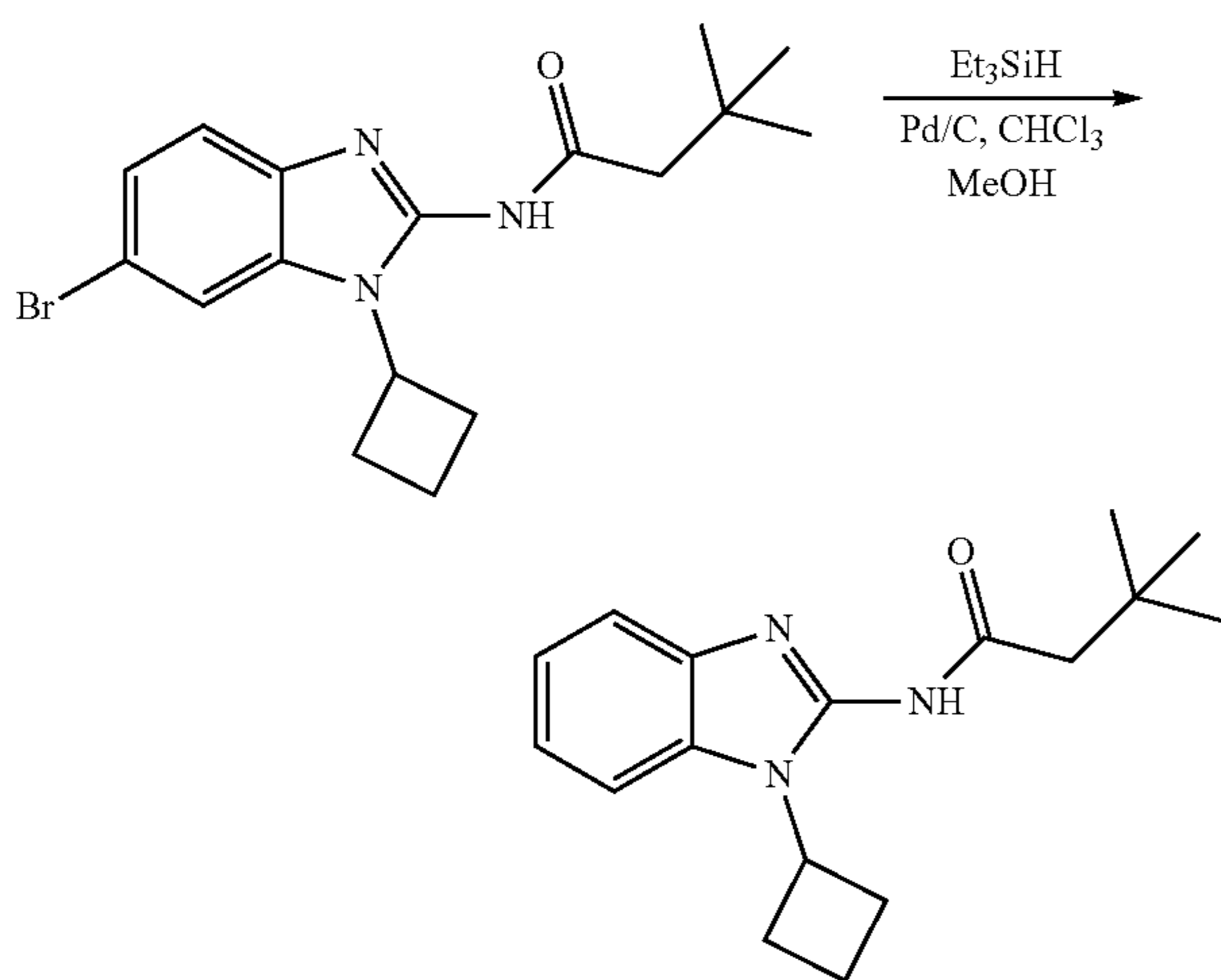
Solid N-(1-cyclobutyl-6-(hydroxymethyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide (100 mg) was dissolved in dichloromethane (5 mL) and solid sodium bicarbonate (106 mg, 4 equivalents) was added in one portion before the addition of Dess-Martin periodinane (270 mg, 2 equivalents) in one portion. The reaction turned from colorless to a red colored solution upon the addition of the Dess Martin reagent. The reaction was allowed to stir at room temperature for 1 hour before sodium thiosulfate (10%, 25 mL) and EtOAc (25 mL) were added to quench the reaction. The quenched reaction was allowed to stir for 1 hour and in this time the red colored solution faded to a colorless solution. The aqueous layer was extracted twice with EtOAc. The combined organic phases were washed with sodium bicarbonate, brine, and dried with sodium sulfate. The dried solution was filtered and concentrated to give a crude product which was subjected to column chromatography (12 gram Isco, 5 to 75% EtOAc in hexanes) to yield 83 mg (84%) of N-(1-cyclobutyl-6-formyl-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide that was used directly in the next reaction.

Step B

The freshly prepared aldehyde (N-(1-cyclobutyl-6-formyl-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide, 37 mg, 0.118 mmol) from the above experimental was dissolved in dichloromethane (2 mL) and TEA-3HF (58 mg, 3 equivalents) was added before the portionwise addition of XtalFluor-E (81 mg, 3 equivalents) at room temperature. LC/MS analysis at 3 hours of reaction time showed slow progression of the reaction. Therefore, two more equivalents of each reagent were added to the reaction. LC/MS analysis 4 hours later showed slow and clean conversion to the desired product. The reaction was allowed to stir overnight and then quenched by the addition of saturated sodium bicarbonate (20 mL) and diluted with dichloromethane (20 mL). The quenched reaction was allowed to stir for 15 minutes and then extracted with dichloromethane (3 \times) and the combined organics were washed with brine, dried with sodium sulfate, filtered and concentrated to give a crude material. The crude material was subjected to silica gel chromatography (12 gram Isco, 0-25% EtOAc in hexanes, product is higher in R_f than the corresponding aldehyde) to give the titled compound (7.5 mg, 19% yield) as a white solid. MS (ESI) m/z 336.4 (MH^+), retention time=3.37 min (Method B). The intermediate aldehyde was also recovered from the chromatography (16 mg, 43%). (See: Couturier, M. et al, *J. Org. Chem.* 2010, 75, 3401-3411).

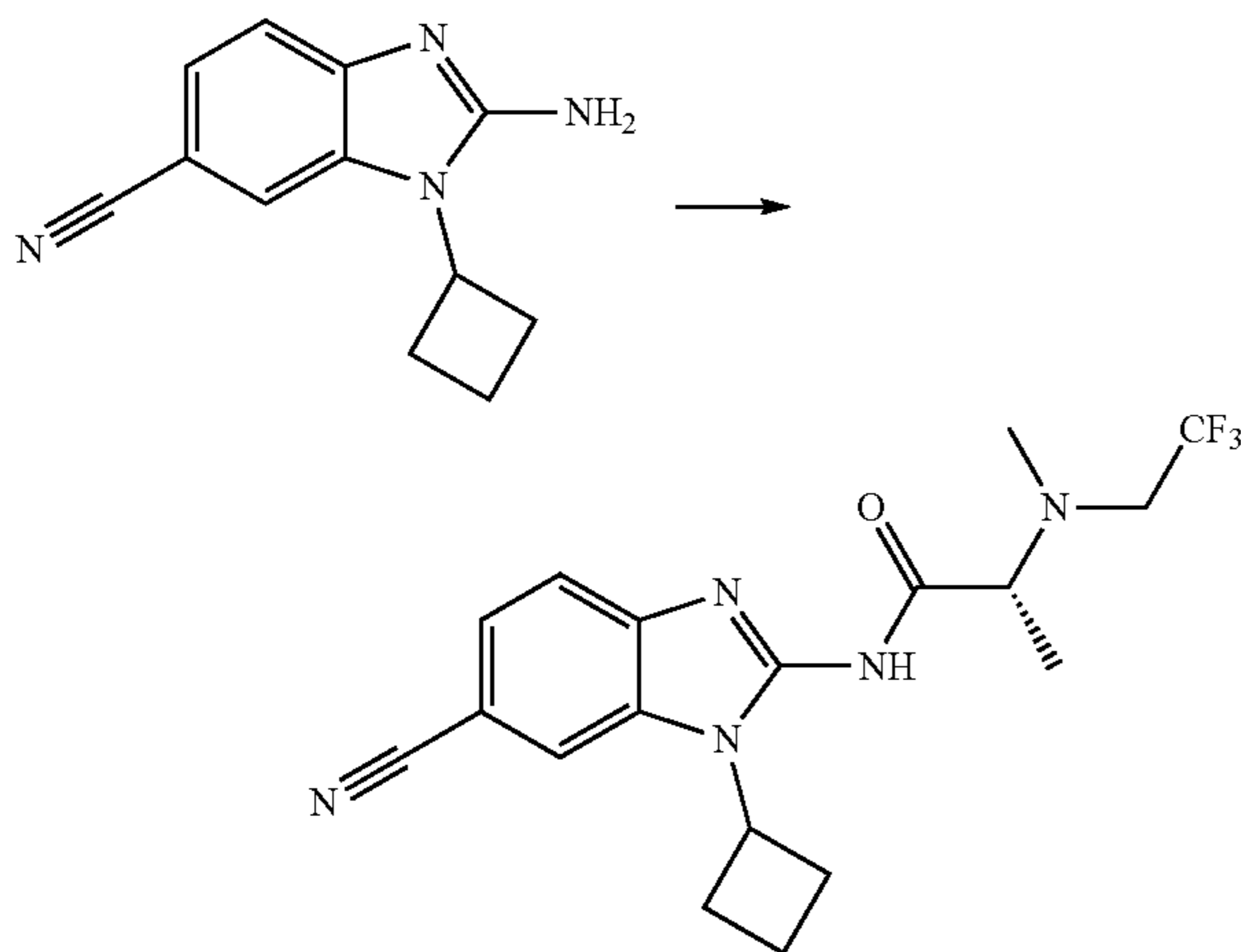
101

Example 1. Preparation of N-(1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide



Solid N-(6-bromo-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide (75 mg) was dissolved in chloroform (9 mL) and methanol (3 mL) before the addition of palladium on carbon (10%, 30 mg). The mixture was allowed to stir for 2 minutes before the dropwise addition of triethylsilane (0.9 mL). The reaction was allowed to stir for 30 minutes and then passed through filter paper. The filtrate was concentrated and subjected to silica gel chromatography (12 gram Isco column, 0 to 70% EtOAc in hexanes) to give the desired product that contained an impurity. The material was further purified by subjecting it to another silica gel column (4 gram silica gel Isco, 0-10% MeOH in dichloromethane) to give a pure sample of the titled compound (22 mg, 31% yield) as a foamy white solid. MS (ESI) m/z 286.4 (MH^+), retention time=2.71 min (Method B). (see Mandal, P K, McMurray, J S, *J. Org. Chem.* 2007, 72, 6599-6601).

Example 22. Preparation of (R)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2-(methyl(2,2,2-trifluoroethyl)amino)propanamide



102

Step A: Preparation of (R)-tert-butyl (1-((6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)amino)-1-oxopropan-2-yl)(methyl)carbamate

2-Amino-3-cyclobutyl-3H-imidazo[4,5-b]pyridine-5-carbonitrile (100 mg, 0.47 mmol) and (R)-2-((tert-butoxycarbonyl)(methyl)amino)propanoic acid (115 mg, 0.57 mmol) were used following Method 7 to provide the desired product (112 mg, 59%).

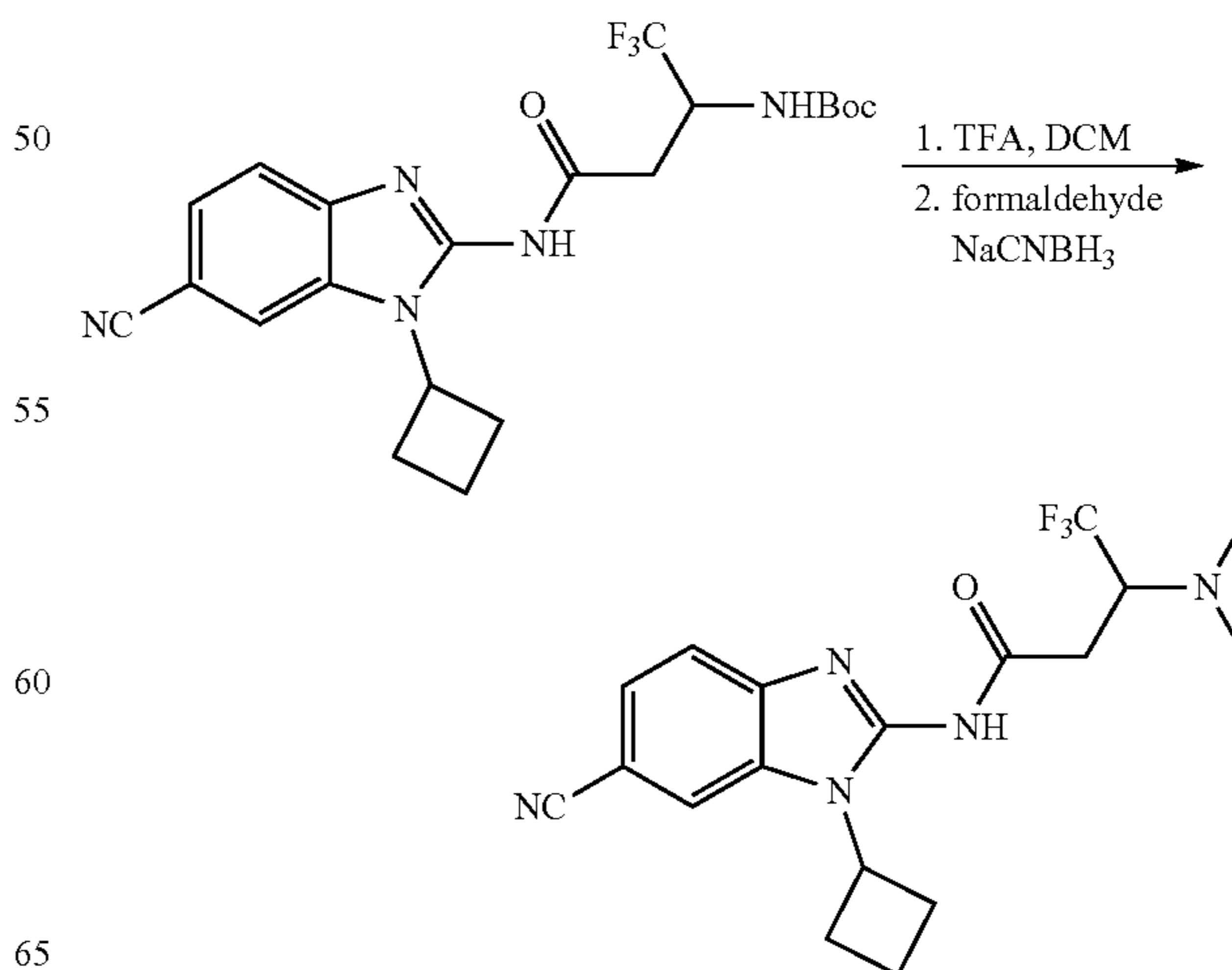
Step B: Preparation of (R)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2-(methylamino)propanamide Hydrochloride

To a solution of (R)-tert-butyl (1-((6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)amino)-1-oxopropan-2-yl)(methyl)carbamate (112 mg, 0.30 mmol) from Step A in MeOH (4 mL) was added concentrated aqueous hydrochloric acid (3 mL) at room temperature. The mixture was stirred for one hour and then concentrated in vacuo. The residue was concentrated twice from methanol to provide the desired product (98 mg, 99%).

Step C: Preparation of (R)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2-(methyl(2,2,2-trifluoroethyl)amino)propanamide

DIEA (130 μ L, 0.76 mmol) was added to a room temperature solution of (R)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2-(methylamino)propanamide hydrochloride from Step B in dimethylformamide (2 mL). The mixture was stirred for several minutes and then was treated with 2,2,2-trifluoroethyl trifluoromethanesulfonate (55 μ L, 0.38 mmol). The mixture was stirred for eight hours with additional DIEA (130 μ L, 0.76 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (55 μ L, 0.38 mmol) being added at two hour intervals over the duration of the reaction. The mixture was concentrated in vacuo and purified by silica gel chromatography (10-50% EtOAc/hexanes) to provide the title compound (24 mg, 21%). MS (ESI) m/z 380.4 (MH^+).

Example 24. Preparation of N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-(dimethylamino)-4,4-trifluorobutanamide

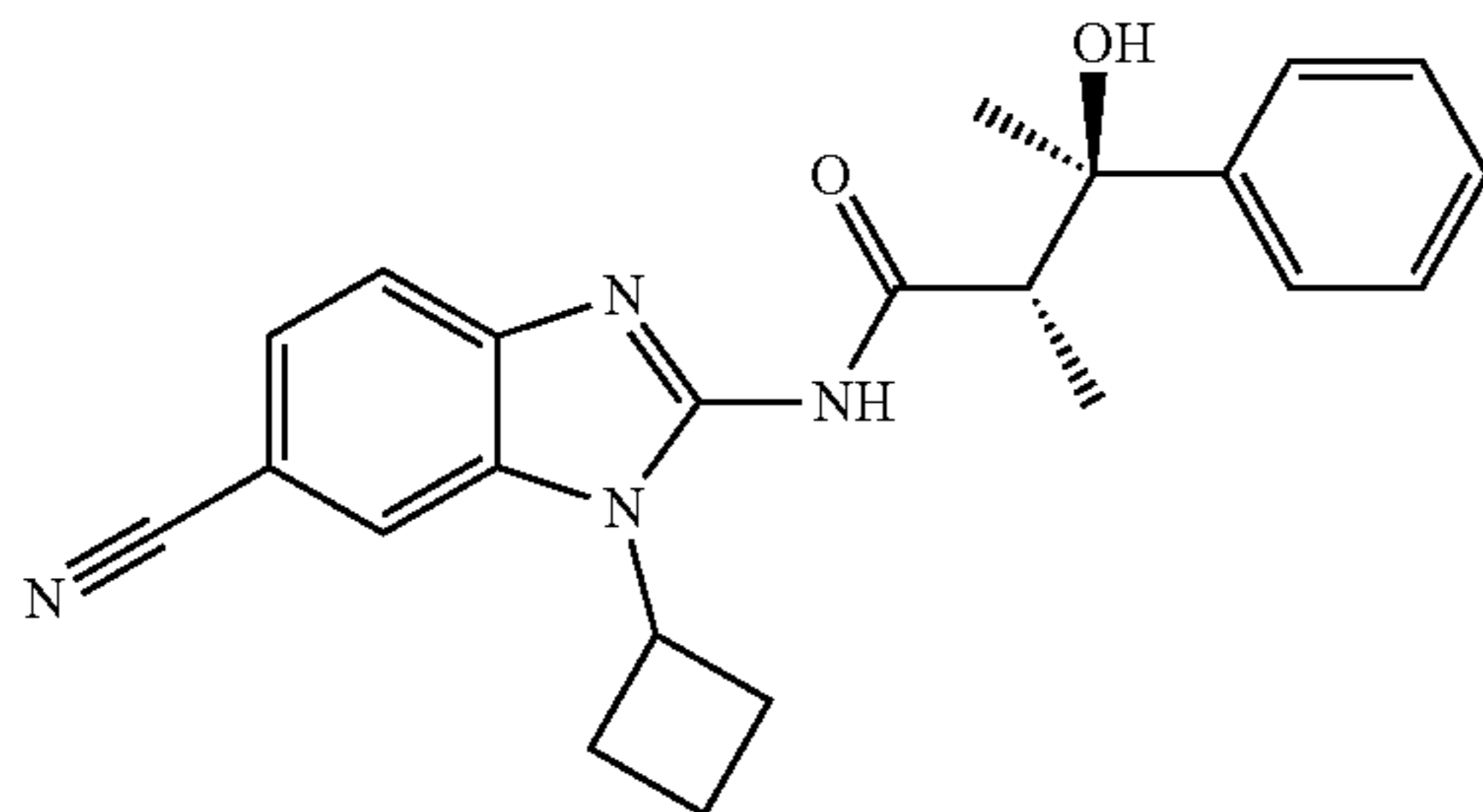


103

To tert-butyl (4-((6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)amino)-1,1,1-trifluoro-4-oxobutan-2-yl)carbamate (23 mg, 0.051 mmol, prepared according to the procedure of Method 7 using 3-((tert-butoxycarbonyl)amino)-4,4,4-trifluorobutanoic acid) in CH₂Cl₂ (1 mL) was added 5 CF₃CO₂H (1 mL) and the mixture was stirred at room temperature for 1 hour. Solvents were removed by rotary evaporation, the residue was dissolved in EtOAc, washed sequentially with saturated NaHCO₃, brine, then dried (Na₂SO₄), filtered and concentrated to give 3-amino-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-4,4,4-trifluorobutanamide (18 mg, 0.051 mmol) as a colorless oil. This material was dissolved in 20:1 CH₃OH/HOAc (0.5 mL) followed by Et₃N (9 μL, 0.10 mmol) and formaldehyde solution (37% in H₂O, 12 μL, 0.23 mmol). NaCNBH₃ (18 mg, 0.51 mmol) was added and the mixture was stirred at room temperature for 4 hours. Solvent was concentrated by rotary evaporation, the residue was distributed between saturated aqueous NaHCO₃ and EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc, the extracts were combined, dried (Na₂SO₄), filtered and concentrated. Purification was run on a 4 g silica gel column eluting with 0-50% EtOAc/hexanes to give the title compound (11.8 mg, 61%). MS (ESI) m/z 380.4 (MH⁺).

Section 4. Exemplary Syntheses for Examples in Table 1 Involving Preparation of Branched Chiral 1H-benzo[d]imidazol-2-yl Amides

Example 18. Preparation of (2S,3R)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-2-methyl-3-phenylbutanamide



Step A: Preparation of (2S,3R)-3-hydroxy-2-methyl-3-phenylbutanoic Acid

A solution of (R)-4-benzyl-3-propionyloxazolidin-2-one (1.0 g, 4.3 mmol) in tetrahydrofuran (10 mL) was added dropwise to a -78° C. solution of LiN(TMS)₂ (1.0 M in tetrahydrofuran, 4.5 mL, 4.5 mmol) in tetrahydrofuran (14 mL). The mixture was stirred for 30 minutes at -78° C. and then acetophenone (0.53 mL, 4.5 mmol) was added over 10 minutes. The -78° C. mixture was stirred for two hours and then quenched via the addition of saturated aqueous NH₄Cl. The mixture was warmed to room temperature and extracted twice with EtOAc. The combined organics were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (0-20% EtOAc/hexanes) to provide partially separated mixtures of the oxazolidinone starting material and four possible diastereomers (R_f=0.57 in 1:4 EtOAc/hexanes, 0.56 g, 37%, (2S,3S) containing fraction; R_f=0.50 in 1:4 EtOAc/hexanes, 0.26 g, 17%, (2S,3R)

104

containing fraction). Stereochemical assignment for the observed two major diastereomers were made via extrapolation from data reported in Bartoli, et al; *J. Org. Chem.*, 1995, 60, 3000.

Step B: Preparation of (R)-4-benzyl-3-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-methyl-3-phenylbutanoyl)oxazolidin-2-one

tert-Butyldimethylsilyl trifluoromethanesulfonate (200 μL, 0.88 mmol) was added dropwise to a solution of the diastereomeric mixture containing (2S,3R)-3-hydroxy-2-methyl-3-phenylbutanoic acid isolated from Step A (0.26 g, 0.74 mmol) and Et₃N (200 μL, 1.5 mmol) in CH₂Cl₂ (5 mL). The solution was stirred at room temperature for one hour and then partitioned between EtOAc and saturated aqueous NaHCO₃. The phases were separated and the organics were washed with saturated aqueous NaCl. The organics were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified twice by silica gel chromatography (0-20% EtOAc/hexanes and then 0-50% CH₂Cl₂/hexanes) to provide the expected product (0.11 g, 32%).

Step C: Preparation of (2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-methyl-3-phenylbutanoic acid

Lithium hydroxide (29 mg, 1.2 mmol) and 30% aqueous hydrogen peroxide (0.12 mL, 1.2 mmol) were added to a 0° C. mixture of (R)-4-benzyl-3-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-methyl-3-phenylbutanoyl)oxazolidin-2-one from Step B (110 mg, 0.24 mmol) in 1:1 tetrahydrofuran/H₂O (3 mL). The mixture was stirred at 0° C. to room temperature overnight. The mixture was adjusted to pH 2 via the addition of 1 M aqueous HCl and then treated with solid NaCl until the solids failed to dissolve. The mixture was then partitioned between saturated aqueous NaCl and EtOAc. The phases were separated and the aqueous layer was extracted again with EtOAc. The organics were combined, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (0-50% CH₂Cl₂/hexanes) to provide the expected product (10 mg, 24%).

Step D: Preparation of (2S,3R)-3-((tert-butyldimethylsilyl)oxy)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2-methyl-3-phenylbutanamide

A mixture of 2-amino-3-cyclobutyl-3H-imidazo[4,5-b]pyridine-5-carbonitrile (7.0 mg, 0.032 mmol), (2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-methyl-3-phenylbutanoic acid from Step C (10 mg, 0.032 mmol), HOBt (7.0 mg, 0.049 mmol), EDC (8.0 mg, 0.049 mmol) and diisopropylethylamine (17 μL, 0.097 mmol) in dimethylformamide (2 mL) were stirred at 50° C. for 3 days. The mixture was cooled to room temperature and partitioned between water and EtOAc. The aqueous phase was extracted twice more with EtOAc. The combined organics were washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated. This crude material was used as is in the next step.

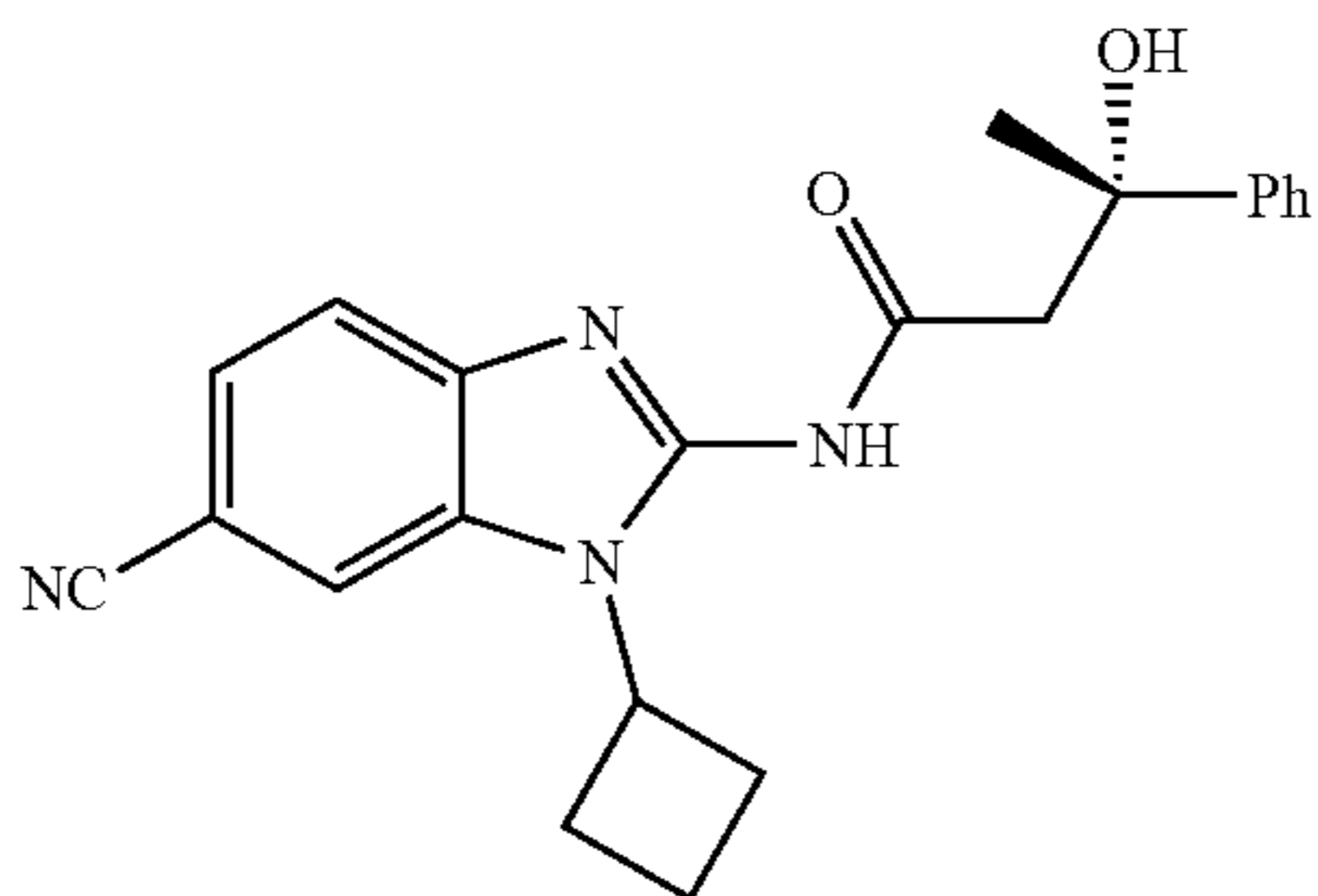
Step E: Preparation of (2S,3R)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-2-methyl-3-phenylbutanamide

TBAF (1.0 M tetrahydrofuran, 160 μL, 0.16 mmol) was added to a solution of the crude product from Step D above in tetrahydrofuran (0.32 mL). The mixture was stirred at 50°

105

C. overnight, cooled to room temperature and concentrated. The residue was purified by reverse phase chromatography (10% CH₃CN/H₂O to CH₃CN) to afford the title compound (1.7 mg, 14% over two steps). MS (ESI) m/z 389.2 (MH⁺).

Example 29. Preparation of (S)—N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide



Step A: Preparation of (S)-4-benzyl-3-((S)-3-hydroxy-3-phenylbutanoyl)oxazolidin-2-one

Lithium bis(trimethylsilyl)amide (1.0 M tetrahydrofuran, 9.2 mL, 9.2 mmol) was added over 15 minutes to a -78° C. suspension of (S)-3-acetyl-4-benzylloxazolidin-2-one (2.0 g, 9.2 mmol) in tetrahydrofuran (9 mL). The mixture was stirred at -78° C. for two hours. A solution of acetophenone (485 μL, 4.2 mmol) in tetrahydrofuran (3 mL) was added over 35 minutes. The mixture was stirred at -78° C. for one hour and then quenched via the addition of aqueous 0.5 M HCl. The mixture was warmed to room temperature and then extracted with CH₂Cl₂. The layers were separated and the aqueous phase was extracted twice more with CH₂Cl₂. The combined organics were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (0-30% EtOAc/hexanes) to provide the desired compound in a partially purified fashion (1.6 g) that was used as is. The stereochemistry was assigned as reported in Theurer, et al; *Tetrahedron*, 2010, 66, 3814.

Step B: Preparation of (S)-4-benzyl-3-((S)-3-((tert-butyl dimethylsilyl)oxy)-3-phenylbutanoyl)oxazolidin-2-one

tert-Butyldimethylsilyl trifluoromethanesulfonate (1.3 mL, 5.7 mmol) was added dropwise to a room temperature solution of the residue prepared as described in Step A and Et₃N (1.1 mL, 7.5 mmol) in CH₂Cl₂ (24 mL). The mixture was stirred at room temperature overnight and then partitioned between EtOAc and saturated aqueous NaHCO₃. The phases were separated and the organics were washed with saturated aqueous NaCl. The two aqueous phases were then sequentially extracted twice with EtOAc. The combined organics were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified twice by silica gel chromatography (0-30% EtOAc/hexanes and then 0-50% CH₂Cl₂/hexanes) to provide the expected product (0.57 g, 30% over two steps).

Step C: Preparation of (S)-3-((tert-butyl dimethylsilyl)oxy)-3-phenylbutanoic acid

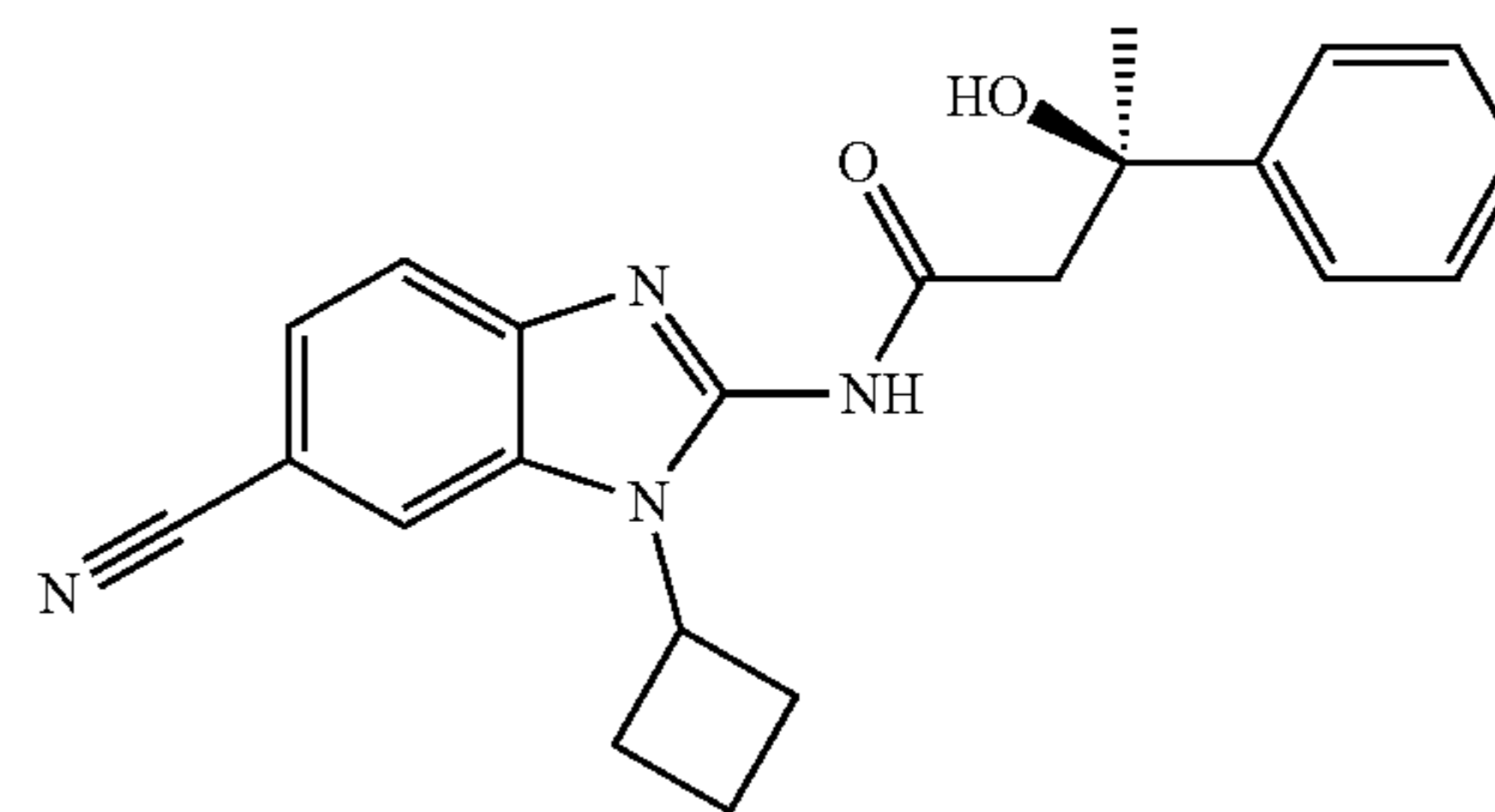
Lithium hydroxide (150 mg, 6.3 mmol) and 30% aqueous hydrogen peroxide (0.64 mL, 6.3 mmol) were added to a 0°

106

C. mixture of (S)-4-benzyl-3-((S)-3-((tert-butyl dimethylsilyl)oxy)-3-phenylbutanoyl)oxazolidin-2-one from Step B (570 mg, 1.3 mmol) in 1:1 tetrahydrofuran/H₂O (13 mL). The mixture was stirred at 0° C. to room temperature over 80 minutes. The mixture was adjusted to pH 2 via the addition of 1 M aqueous HCl and then treated with solid NaCl until the solids failed to dissolve. The mixture was then partitioned between saturated aqueous NaCl and EtOAc. The phases were separated and the aqueous layer was extracted again with EtOAc. The organics were combined, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (0-60% EtOAc/hexanes) to provide the expected product (0.21 g, 57%).

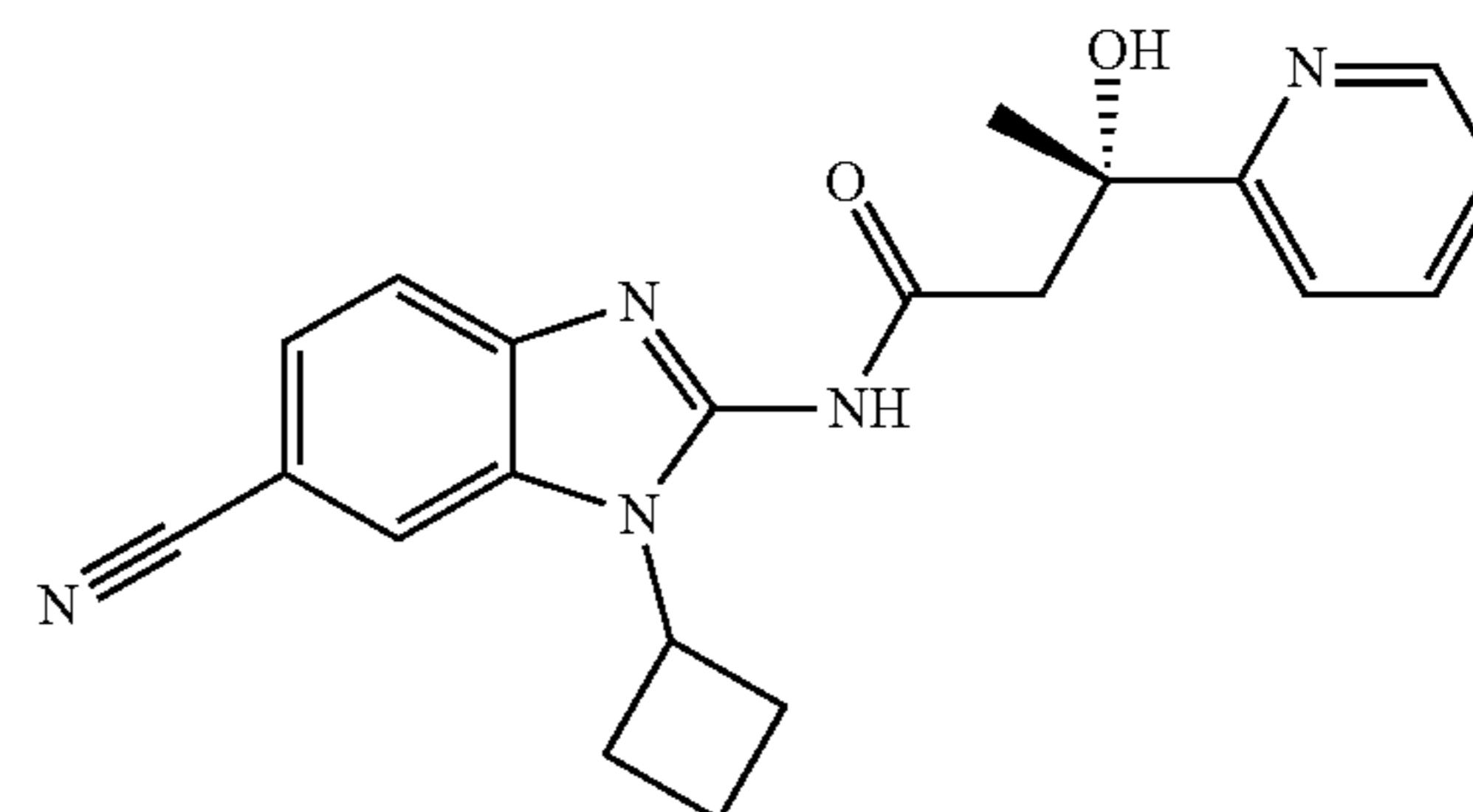
The title compound was then prepared using the procedures described in Step D and Step E of Example 18. MS (ESI) m/z 375 (MH⁺).

Example 30. Preparation of (R)—N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide



The same procedure was used to prepare the title compound as was used for Example 29 with the exception of starting with (R)-3-acetyl-4-benzylloxazolidin-2-one instead of the (S)-enantiomer. MS (ESI) m/z 375 (MH⁺).

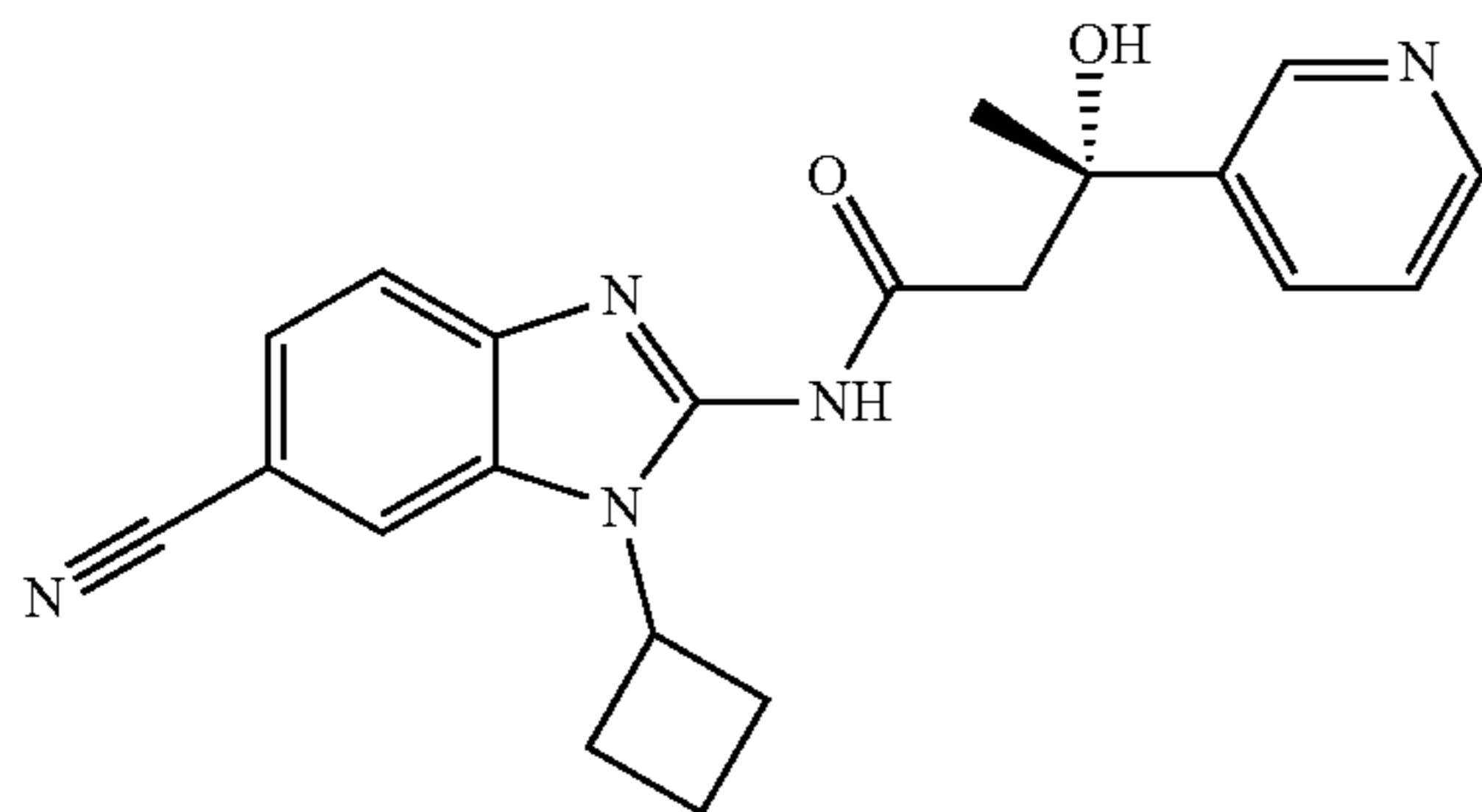
Example 20. Preparation of (S)—N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-(pyridin-2-yl)butanamide



The same procedure was used to prepare the title compound as was used for Example 29 with the exception of starting with (R)-3-acetyl-4-benzylloxazolidin-2-one instead of the (S)-enantiomer, and using 2-acetopyridine in place of acetophenone. MS (ESI) m/z 376 (MH⁺). Stereochemical assignment based on Peters R, et al., *J. Org. Chem.* 2006, 71, 7583-7595.

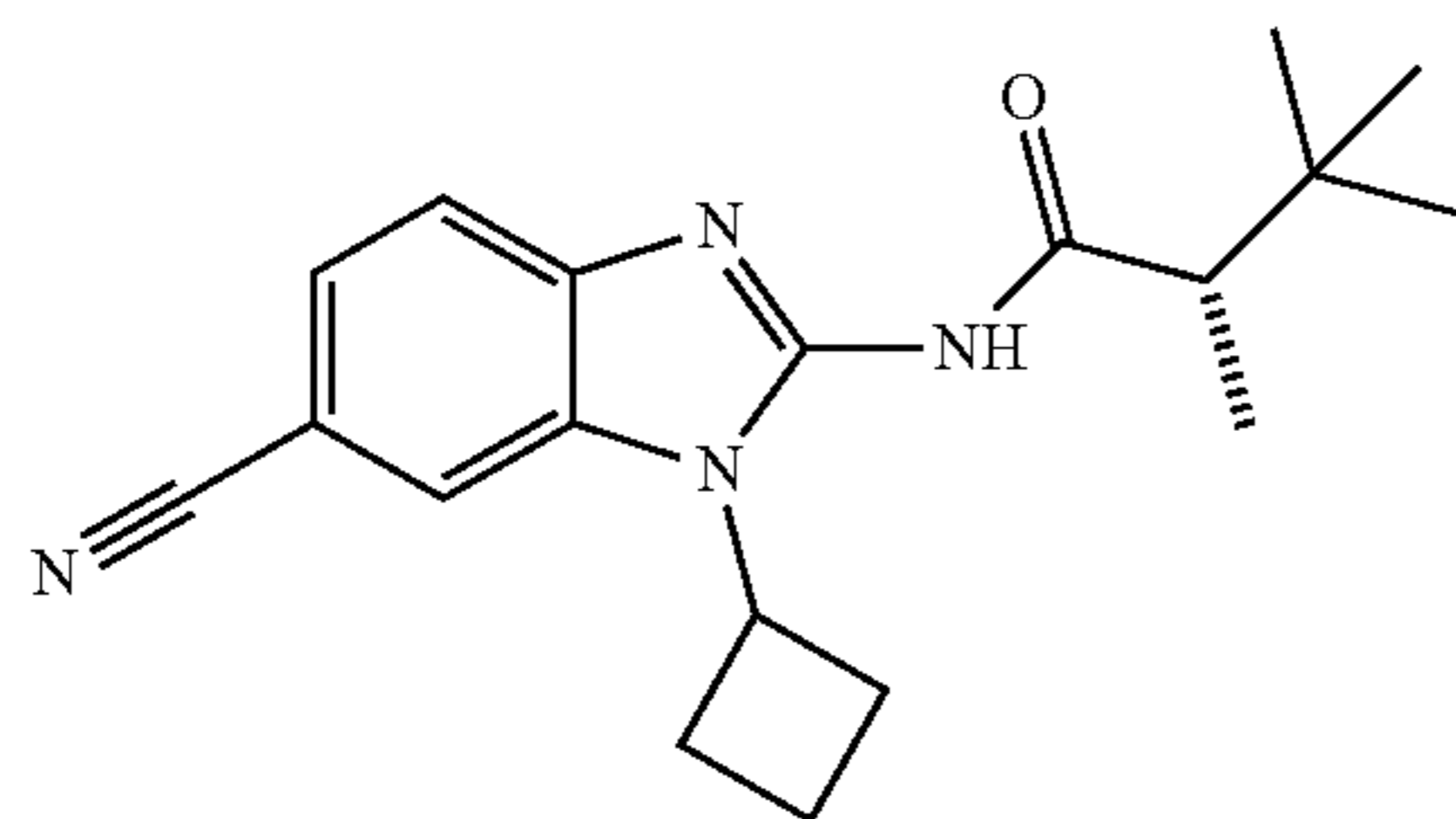
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Example 21. Preparation of (S)—N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-(pyridine-3-yl)butanamide

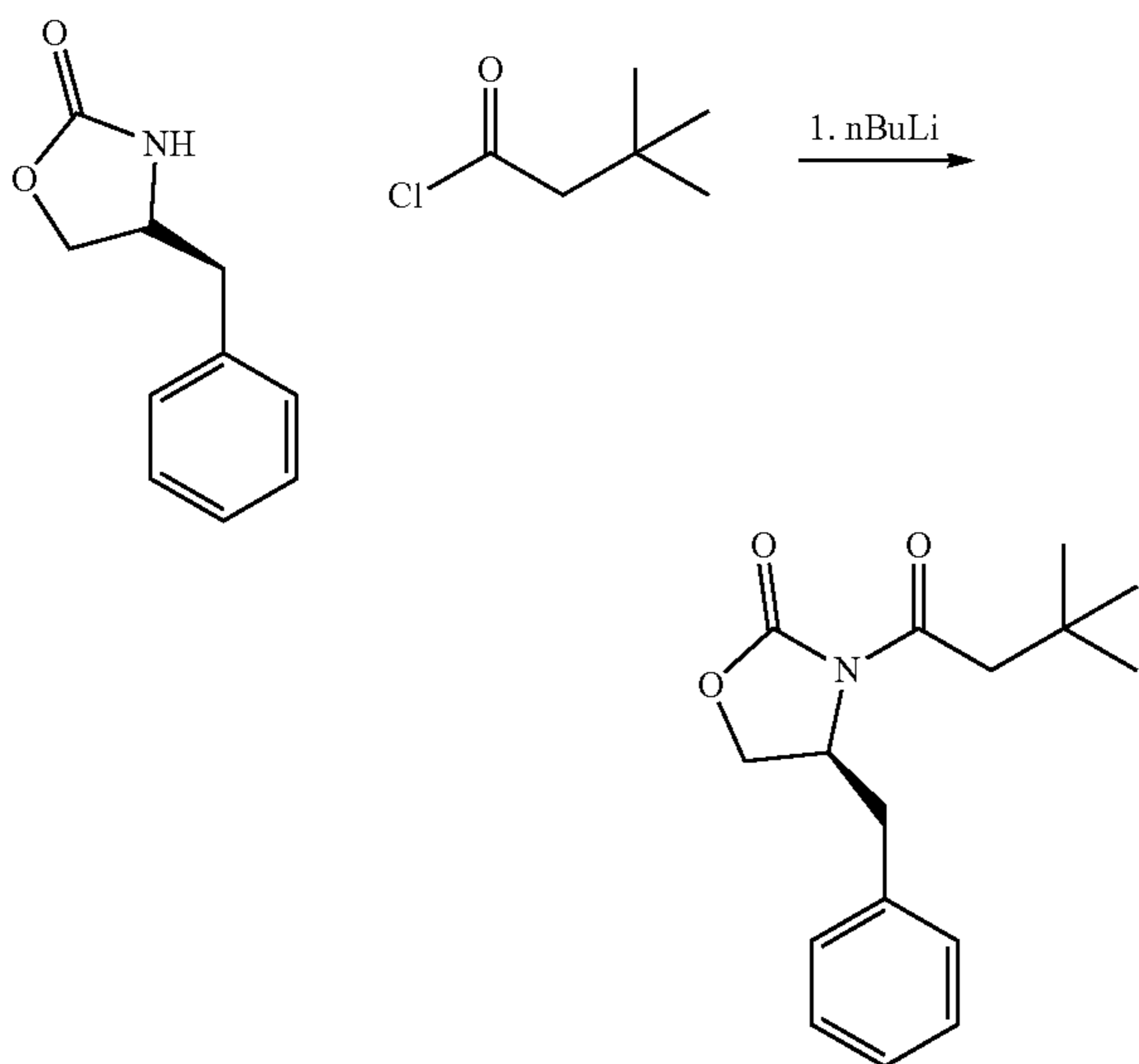


The same procedure was used to prepare the title compound as was used for Example 29 with the exception of starting with (R)-3-acetyl-4-benzyloxazolidin-2-one instead of the (S)-enantiomer and using 3-acetopyridine in place of acetophenone.

Example 23. Preparation of (S)—N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2,3,3-trimethylbutanamide



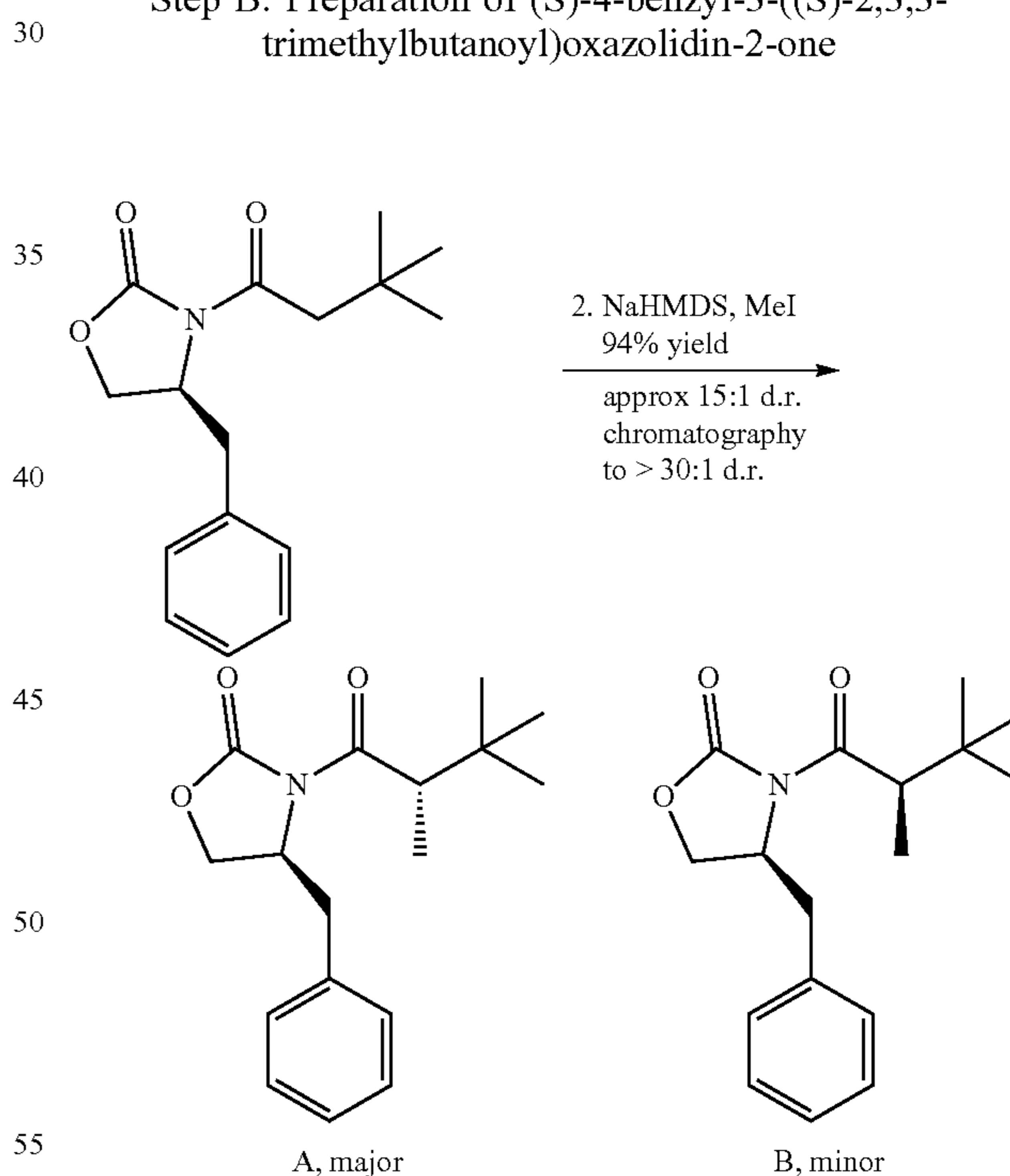
Step A: Preparation of (S)-4-benzyl-3-(3,3-dimethylbutanoyl)oxazolidin-2-one



108

A 1.0 L round bottom flask was charged with a stir bar, tetrahydrofuran (200 mL, anhydrous) and (S)-4-benzyloxazolidin-2-one (10.0 g, 56.4 mmol). The flask was placed in a -78°C . bath for 15 minutes prior to the addition of n-BuLi (2.5 M in hexanes, 25.0 mL, 1.1 equivalents) dropwise under a nitrogen atmosphere. The reaction was allowed to stir for 1 hour prior to the addition of 3,3-dimethylbutanoyl chloride (11.7 mL, 1.5 equivalents). The reaction was allowed to stir at -78°C . and then the cooling bath was removed and the flask was allowed to slowly warm to room temperature and stir overnight. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate (200 mL) and the bulk of the tetrahydrofuran was removed by rotary evaporation. The remaining residue was dissolved in ethyl acetate (300 mL) and washed sequentially with saturated aqueous sodium bicarbonate (twice), saturated aqueous sodium carbonate (twice), and brine and then dried over sodium sulfate. The dried solution was filtered and concentrated to give 20 g of crude product. The material was recrystallized from warm ethyl acetate (approximately 30 mL) and warm hexanes (approximately 70 mL) to give the first crop of the desired product (9.0 g, 58% yield) as white crystals. An additional second crop (3.8 g, 25% yield) was obtained from the mother liquor. ^1H NMR (CDCl_3): δ 7.36-7.22 (m, 5H), 4.73-4.67 (m, 1H), 4.18-4.12 (m, 2H), 3.34 (dd, $J=13.28$, 3.32 Hz, 1H), 2.99 (d, $J=14.9$ Hz, 1H), 2.86 (d, $J=14.9$ Hz, 1H), 2.71 (dd, $J=13.24$, 10.00 Hz, 1H), 1.09 (br s, 9H).

Step B: Preparation of (S)-4-benzyl-3-((S)-2,3,3-trimethylbutanoyl)oxazolidin-2-one

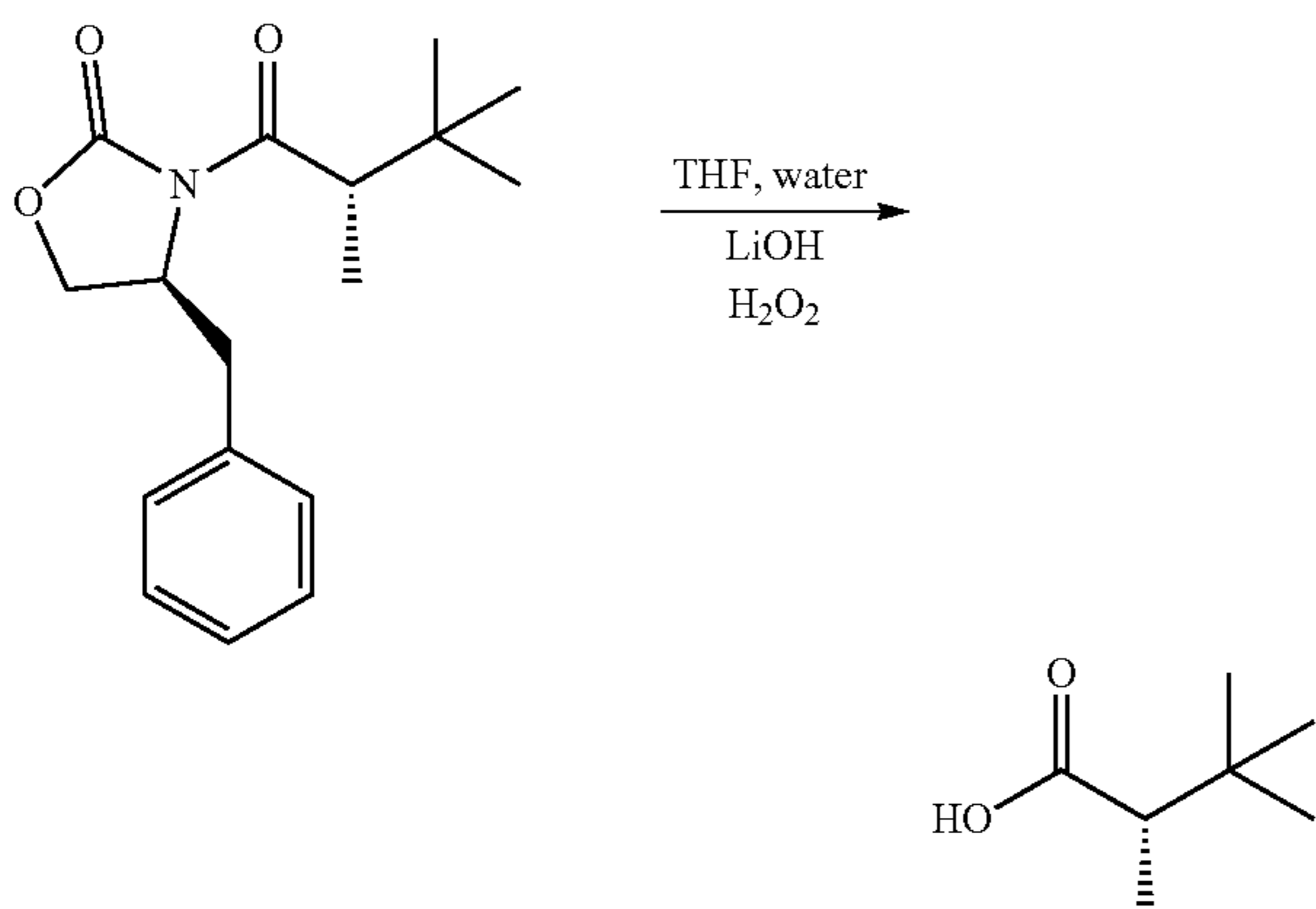


Freshly recrystallized (S)-4-benzyl-3-(3,3-dimethylbutanoyl)oxazolidin-2-one (8.75 g, 31.77 mmol) was azeotroped with dichloromethane (2 \times , 30 mL) and then placed under high vacuum for 10 minutes prior to being dissolved in tetrahydrofuran (40 mL). In a 1.0 L round bottom flask fitted with a balloon of nitrogen and a stir bar was placed NaHMDS (1.0 M in tetrahydrofuran, 35 mL, 1.1 equivalents) and the flask was placed in a -78°C . bath. After being chilled for 15 minutes, the 40 mL tetrahydrofuran solution of (S)-4-benzyl-3-(3,3-dimethylbutanoyl)oxazolidin-2-one

109

was added dropwise to the NaHMDS at -78°C . The formation of the sodium enolate was allowed to form over 1 hour at -78°C and then methyl iodide (6 mL, 3 equivalents) was added via syringe. The reaction was allowed to stir and slowly warm to room temperature overnight. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate (150 mL) and the bulk of the tetrahydrofuran was removed by rotary evaporation. The residue was transferred to a separatory funnel using ethyl acetate and saturated aqueous sodium bicarbonate. The layers were separated and the organic layer was washed with 10% aqueous sodium thiosulfate (150 mL) to remove the pale yellow color. The combined organic layers were back extracted with ethyl acetate (2 \times). The combined organics were washed with brine, dried with sodium sulfate, filtered and concentrated to give a white solid (8.61 g, 94% yield). ^1H NMR analysis indicated complete conversion of starting material to the methylated products and an approximately 15:1 diastereomeric ratio of products in favor of the desired (S)-4-benzyl-3-((S)-2,3,3-trimethylbutanoyl)oxazolidin-2-one diastereomer A. An attempt to enrich the diastereomeric ratio by recrystallization from warm hexanes failed to improve the diastereomeric ratio. Therefore, the initial solid product was divided into three portions and each one was subjected to column chromatography (Isco, 120 g silica gel, 0-10% EtOAc in hexanes). The higher running R_f fractions of the UV peak were cut off from the later running fractions to give a product of improved diastereomeric ratio (1.83 g, approximately 70:1 d.r.) as a white solid. The chromatography was repeated on the original product to give two samples of improved diastereomeric ratio (2.28 g, >20:1 d.r. and 4.59 g, 30:1 d.r.) in favor of (S)-4-benzyl-3-((S)-2,3,3-trimethylbutanoyl)oxazolidin-2-one diastereomer. Major diastereomer A ^1H NMR (CDCl_3): δ 7.33-7.23 (m, 5H), 4.73-4.67 (m, 1H), 4.17-4.13 (m, 2H), 3.90 (q, $J=7.00$ Hz, 1H), 3.28 (dd, $J=13.32, 3.20$ Hz, 1H), 2.77 (dd, $J=13.32, 9.72$ Hz, 1H), 1.20 (d, $J=7.00$ Hz, 3H), 1.02 (bs, 9H). The latter running R_f fraction were combined to give the desired product in a diminished diastereomeric ratio (360 mg, 3:1 d.r.) contaminated with the undesired (S)-4-benzyl-3-((R)-2,3,3-trimethylbutanoyl)oxazolidin-2-one minor diastereomer B (Reference: Evans, D A; Ennis, M D; Mathre, D J *J. Am. Chem. Soc.* 1982, 104, 1737-1739).

Step C: Preparation of (S)-2,3,3-trimethylbutanoic Acid



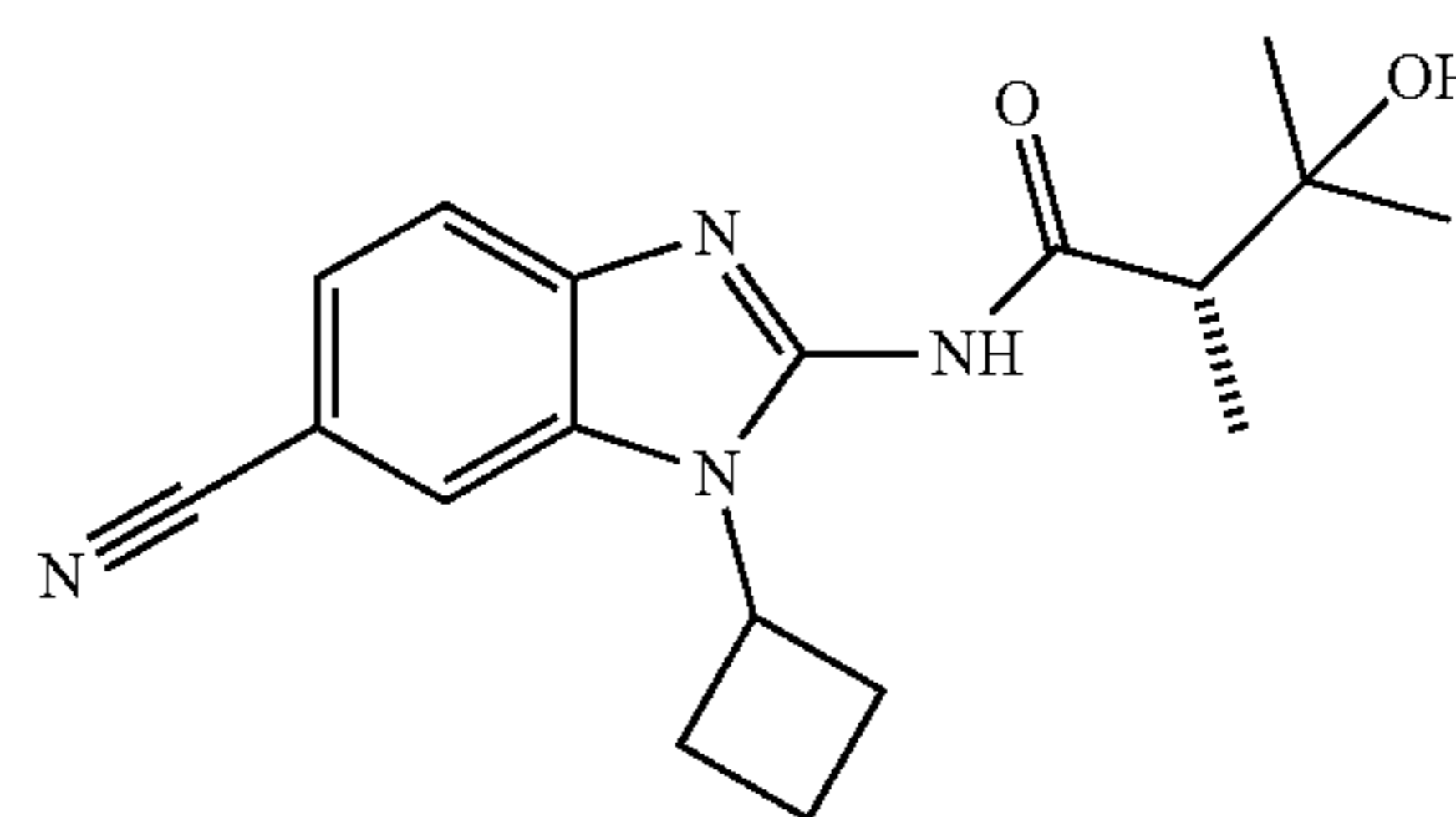
110

Solid (S)-4-benzyl-3-((S)-2,3,3-trimethylbutanoyl)oxazolidin-2-one (2.24 g, 7.73 mmol, diastereomer A from Step B above, approx. 30:1 d.r.) was dissolved in tetrahydrofuran (50 mL) and water (10 mL) and the flask was allowed to chill in a 0°C for 10 minutes prior to the addition of lithium hydroxide (326 mg, 13.6 mmol, 2 equivalents) in one portion. After a few minutes, hydrogen peroxide (30%, 6 mL) was added via syringe. After approximately 30 min, an additional portion of tetrahydrofuran (60 mL) and water (10 mL) were added to the flask. The reaction was allowed to stir at 0°C for 1 hour and then allowed to warm to room temperature and stirred for 24 hours. The flask was rechilled to 0°C and then quenched by the addition of sodium sulfite (19 g in 125 mL of water) and saturated aqueous sodium bicarbonate (75 mL). The quenched reaction was allowed to stir for 1.5 hours and then the bulk of the tetrahydrofuran was removed by rotary evaporation. The mixture was transferred to a separatory funnel using dichloromethane and saturated aqueous sodium bicarbonate. The aqueous layer was extracted with dichloromethane (3 \times 50 mL) to remove the bulk of the chiral auxiliary. The aqueous layer was carefully acidified with HCl (1 M, until pH=2) and then extracted with dichloromethane (4 \times 50 mL). The combined organics were washed with brine and dried with sodium sulfate. The dried solution was filtered and carefully evaporated to give the desired carboxylic acid as an oil (925 mg, >100% yield, dichloromethane impurity). The (S)-2,3,3-trimethylbutanoic acid was diluted up to a volume of 9 mL with dichloromethane to make a stock solution that was used directly in the amide coupling reaction. ^1H NMR (CDCl_3): δ 12.02 (br s, 1H), 2.29 (q, $J=7.08$ Hz, 1H), 1.13 (d, $J=7.08$ Hz, 3H), 0.99 (br s, 9H). (Reference: Evans, D A, Britton, T C, Ellman, J A, *Tetrahedron Lett.* 1987, 28(49), 6141-6144).

Step D: Preparation of (S)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2,3,3-trimethylbutanamide

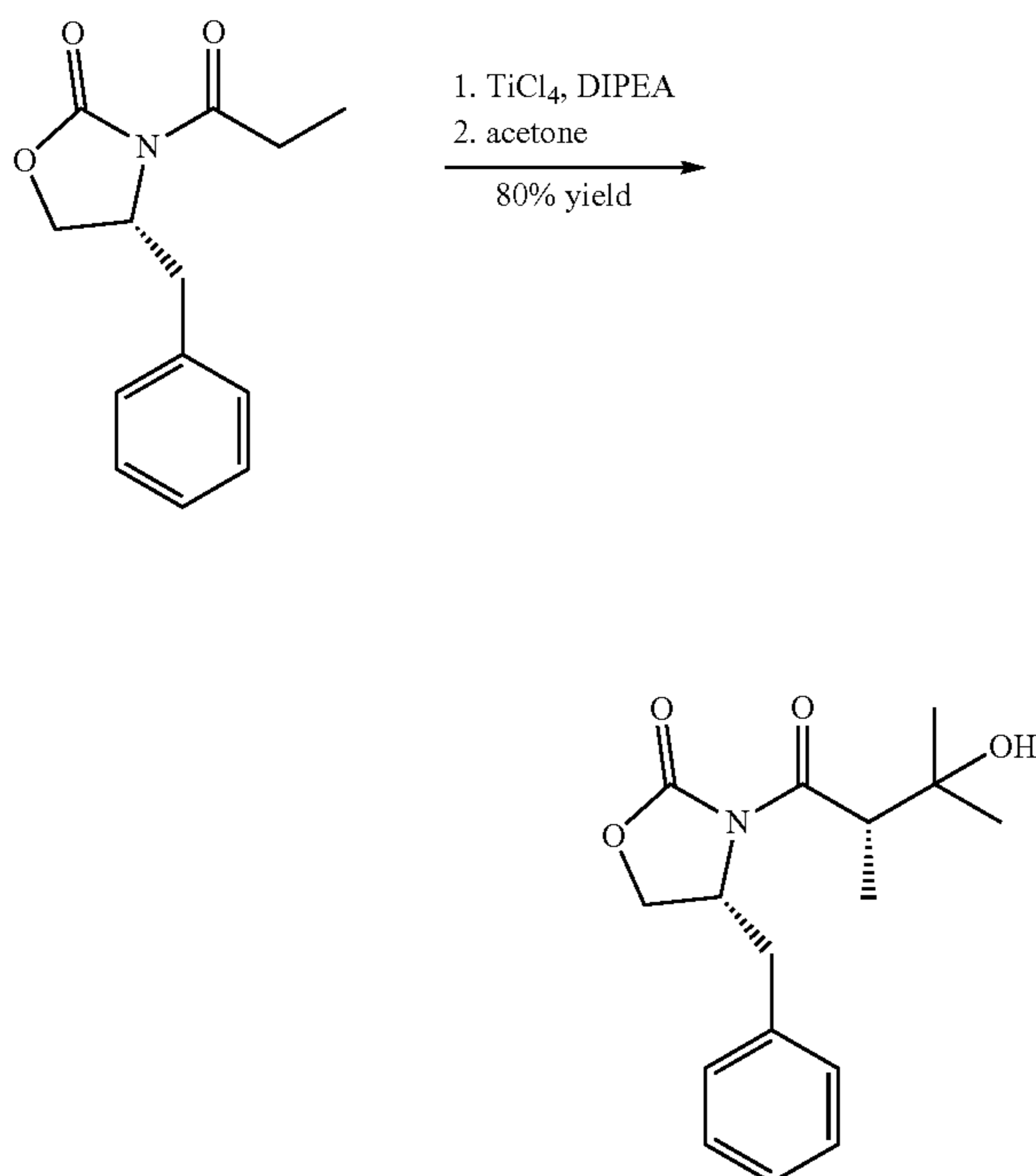
The dichloromethane stock solution of (S)-2,3,3-trimethylbutanoic acid from Step C above was transferred to a tared flask and carefully evaporated. This acid was dissolved in dimethylformamide and the standard amide coupling Method 7 was followed to give the desired product.

Example 13. Preparation of (S)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-2,3-dimethylbutanamide



111

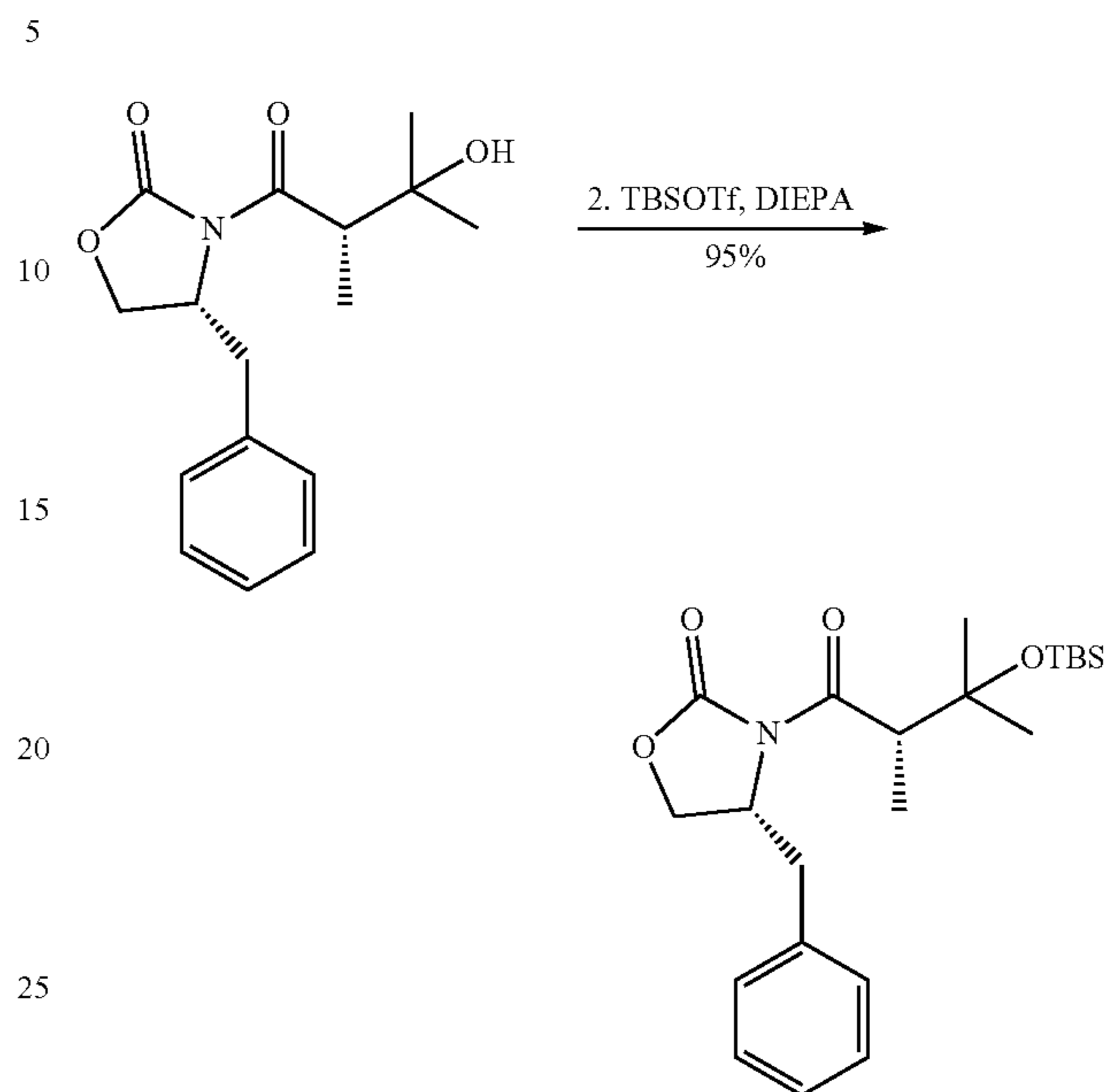
Step A. Preparation of (R)-4-benzyl-3-((S)-3-hydroxy-2,3-dimethylbutanoyl)oxazolidin-2-one



Commercially available (R)-4-benzyl-3-propionyloxazolidin-2-one (3.0 g, 12.85 mmol, 1.0 equivalents) was dissolved in dichloromethane (40 mL) and chilled to 0° C. for 10 minutes prior to the addition of TiCl_4 (1.0 M in dichloromethane, 14.15 mL, 1.1 equivalents) via syringe under an atmosphere of nitrogen. After 5 minutes, diisopropylethylamine (2.5 mL, 1.1 equivalents) was added dropwise via syringe. The reaction was allowed to stir at 0° C. for 1 hour and a dark-red titanium enolate formed. At this time, acetone (1.4 mL, 1.5 equivalents, dried over anhydrous potassium carbonate for 24 hours) was added via syringe. The reaction was allowed to stir at 0° C. for 15 minutes and then slowly allowed to warm to room temperature overnight. The reaction was quenched by the addition of aqueous ammonium chloride (1 M, 100 mL) and extracted with dichloromethane (three times). The combined organics were washed with brine, dried with sodium sulfate, filtered and concentrated to give 4.0 g of a crude oil. The crude oil was subjected to column chromatography (Isco, 120 g silica gel, 0-25% EtOAc in hexanes) to give the desired product (3.0 g, 80% yield) as a white solid. NMR analysis indicated a single diastereomer of the purified product. $R_f=0.75$ in 20% EtOAc in hexanes. $^1\text{H NMR}$ (CDCl_3): δ 7.32-7.23 (m, 5H), 4.72-4.66 (m, 1H), 4.20-4.13 (m, 2H), 3.95 (q, $J=7.00$ Hz, 1H), 3.38-3.34 (m, 2H), 2.75 (dd, $J=13.36, 9.88$ Hz, 1H), 1.35 (s, 3H), 1.24-1.23 (m, 6H). (Reference: Evans, D A, Urpi, F, Somers, T C, Clark, J S, Bilodeau, M T, *J. Am. Chem. Soc.* 1990, 112, 8215-8216).

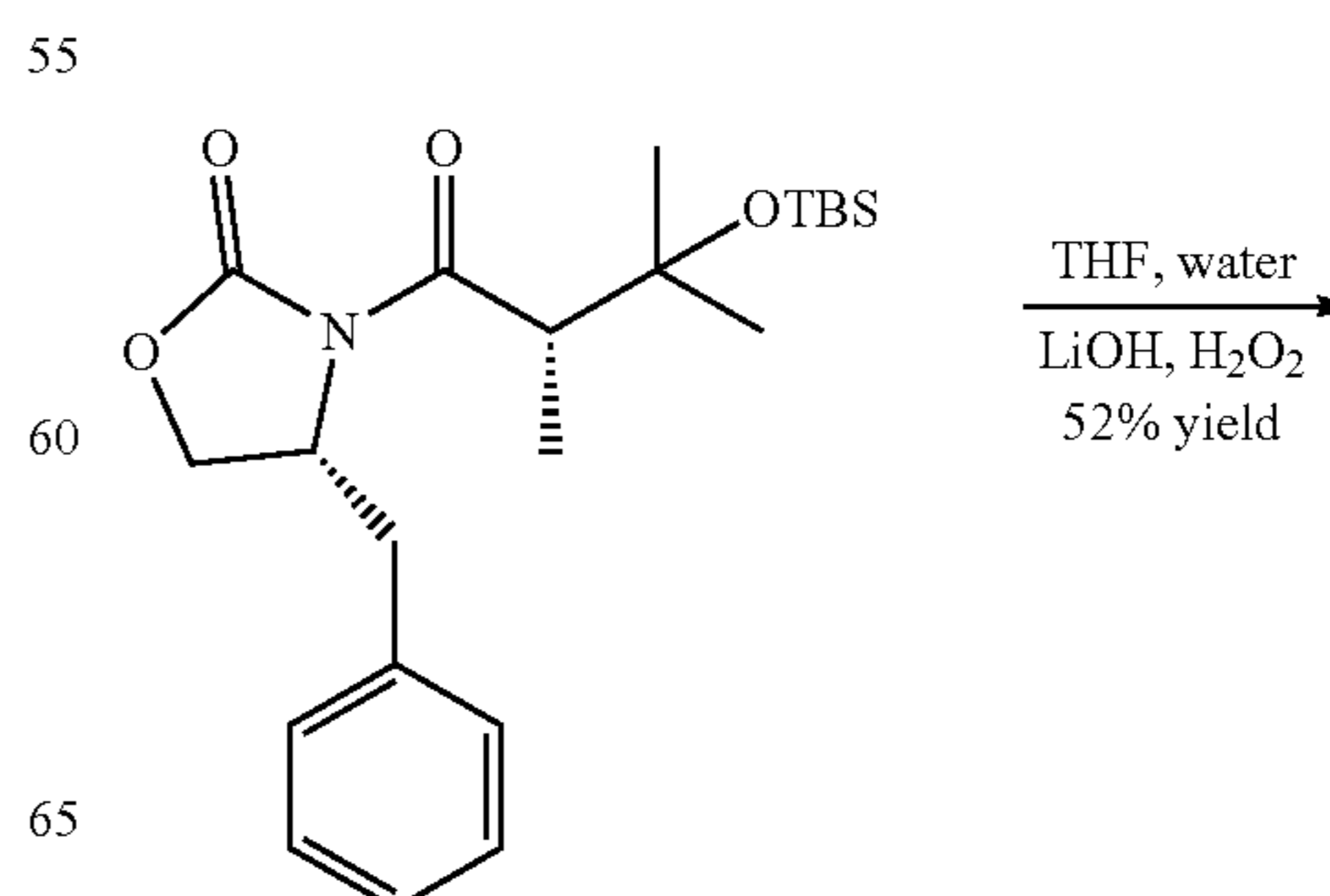
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Step B: Preparation of (R)-4-benzyl-3-((S)-3-((tert-butyl)dimethylsilyloxy)-2,3-dimethylbutanoyl)oxazolidin-2-one



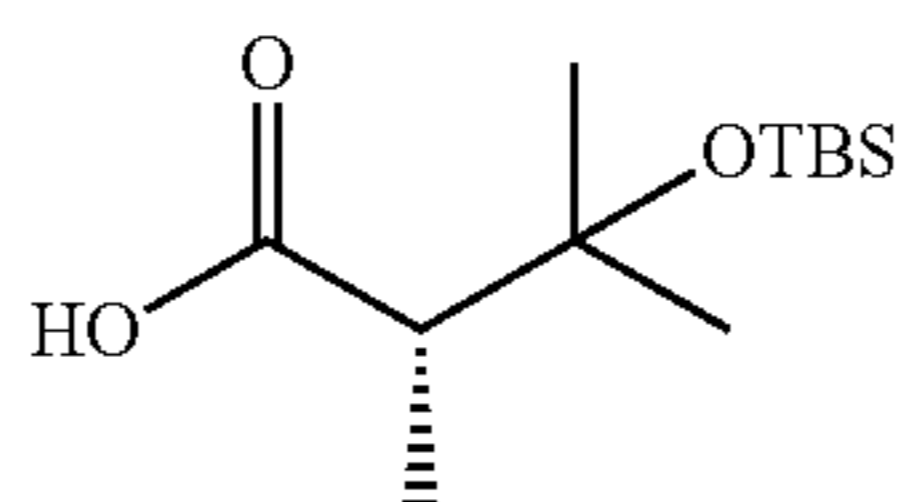
The solid tertiary alcohol (1000 mg, 3.43 mmol, 1.0 equivalents) from the above procedure, (R)-4-benzyl-3-((S)-3-hydroxy-2,3-dimethylbutanoyl)oxazolidin-2-one, was dissolved in dichloromethane (10 mL) and diisopropylethylamine (0.9 mL, 1.5 equivalents) was added via syringe. The flask was chilled for 10 minutes in a 0° C. bath prior to the drop wise addition of tert-butyl dimethylsilyl triflate (0.9 mL, 1.1 equivalents) via syringe. The reaction was allowed to stir overnight and then quenched by the addition of saturated aqueous sodium bicarbonate (50 mL). The aqueous layer was extracted twice with dichloromethane. The combined organics were washed with brine, dried with sodium sulfate, filtered and concentrated to give a crude oil. The crude material was subjected to silica gel column chromatography (Isco, 24 g silica gel, 0-20% EtOAc in hexanes) to give the desired TBS ether (1.23 g, 95%) as a white solid. $R_f=0.75$ in 20% EtOAc in hexanes. $^1\text{H NMR}$ (CDCl_3): δ 7.24-7.12 (m, 5H), 4.57-4.51 (m, 1H), 4.10-3.93 (m, 3H), 3.33 (dd, $J=13.08, 3.16$ Hz, 1H), 2.47 (dd, $J=13.00, 10.88$ Hz, 1H), 1.25 (s, 3H), 1.24 (s, 3H), 1.07 (d, $J=7.00$ Hz, 3H), 0.76 (bs, 9H), 0.00 (d, $J=5.72$ Hz, 6H).

Step C: Preparation of (S)-3-((tert-butyl)dimethylsilyloxy)-2,3-dimethylbutanoic Acid



113

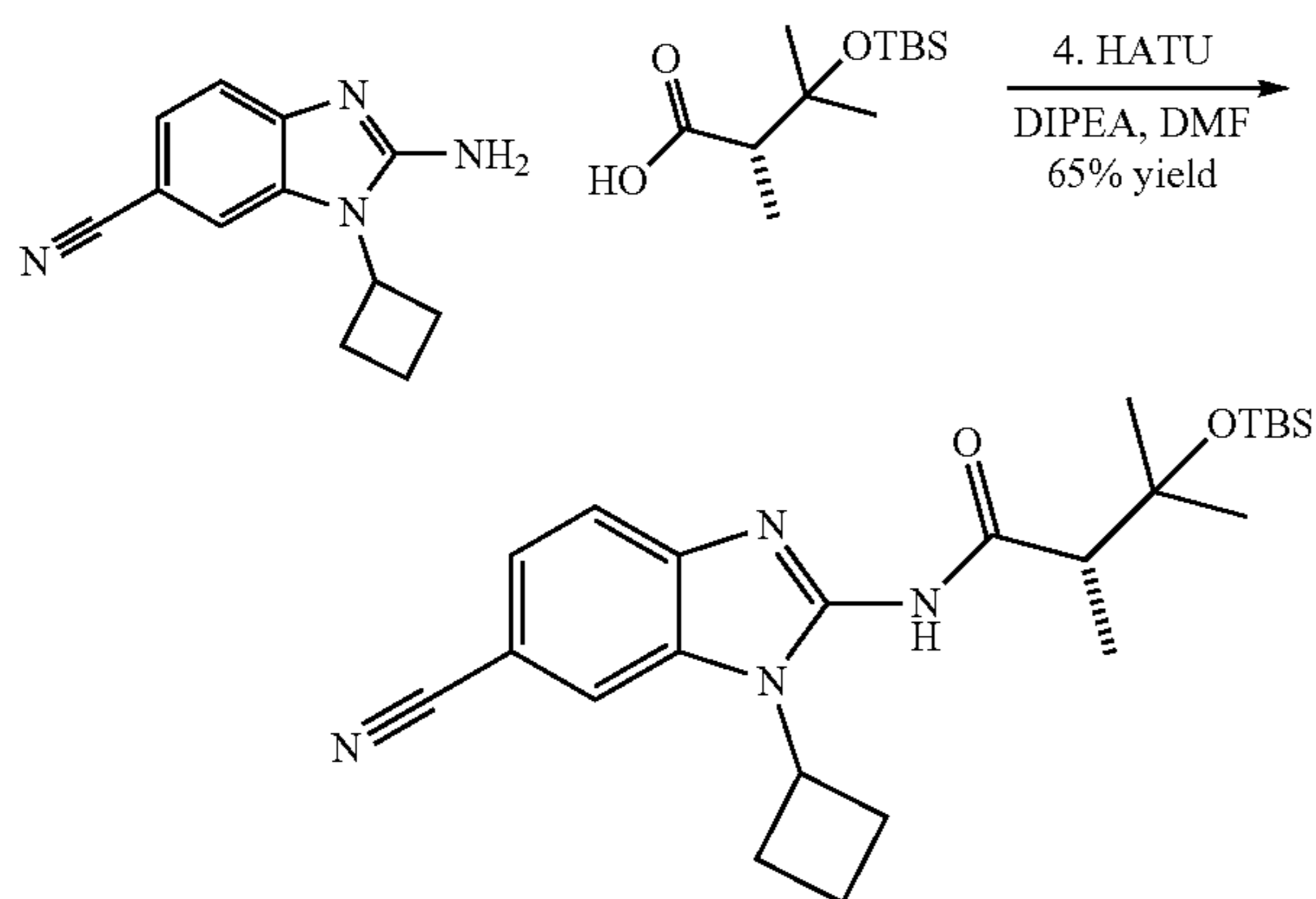
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Solid (R)-4-benzyl-3-((S)-3-((tert-butyl(dimethyl)silyloxy)-2,3-dimethylbutanoyl)oxazolidin-2-one (3.8 g, 9.7 mmol, >30:1 d.r) was dissolved in tetrahydrofuran (50 mL) and water (10 mL) and the flask was allowed to chill in a 0° C. for 5 minutes prior to the addition of lithium hydroxide (450 mg, 18.7 mmol, 2 equivalents) in one portion. After a few minutes, hydrogen peroxide (30%, 12 mL) was added via syringe. The reaction was allowed to stir at 0° C. for 1 hour and then allowed to warm to room temperature and stirred for 24 hours. The flask was rechilled to 0° C. and then quenched by the addition of sodium sulfite (12 g in 100 mL of water). The quenched reaction was allowed to stir for 1.5 hours and then the bulk of the tetrahydrofuran was removed by rotary evaporation. The mixture was transferred to a separatory funnel using dichloromethane and saturated aqueous sodium bicarbonate. The aqueous layer was extracted with dichloromethane (2x50 mL). This initial dichloromethane extract was found to contain both the chiral auxiliary and the desired TBS ether acid. The combined organics were washed with brine and dried with sodium sulfate, filtered and concentrated to give the crude product as oil (3.1 g). The crude material was subjected to silica gel column chromatography (Isco, 40 g, 0-25% EtOAc in hexanes, ELSD detection) to give the desired product as oil (1.2 g, 52% yield). $R_f=0.50$ in 20% EtOAc in hexanes, purple to anisaldehyde stain and is not UV active. $^1\text{H NMR}$ (CDCl_3): δ 10.4-9.80 (br s, 1H), 2.32 (q, $J=7.16$ Hz, 1H), 1.19 (s, 3H), 1.14 (s, 3H), 1.03 (d, $J=7.16$ Hz, 3H), 0.72 (s, 9H), 0.00 (s, 6H).

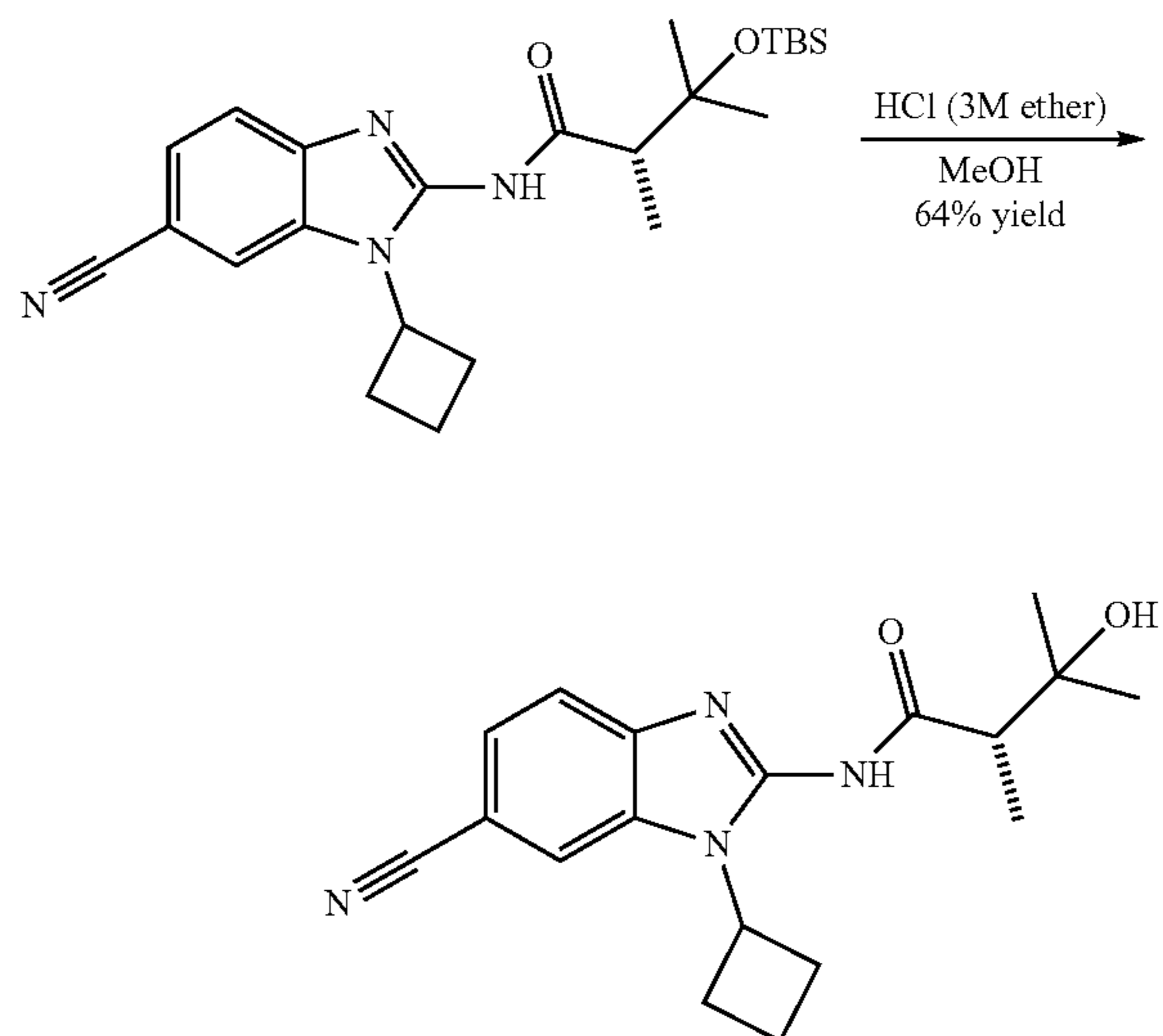
Step D: Preparation (S)-3-((tert-butyl(dimethyl)silyloxy)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2,3-dimethylbutanamide



Method 7 was used to provide the desired amide product (38 mg, 65% yield), isolated via column chromatography. The isolated material was contaminated with the activated ester of the corresponding carboxylic acid coupling partner. The material was taken forward to the next step without any further purification.

114

Step E: Preparation of (S)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-2,3-dimethylbutanamide Via Deprotection of TBDMS Ether



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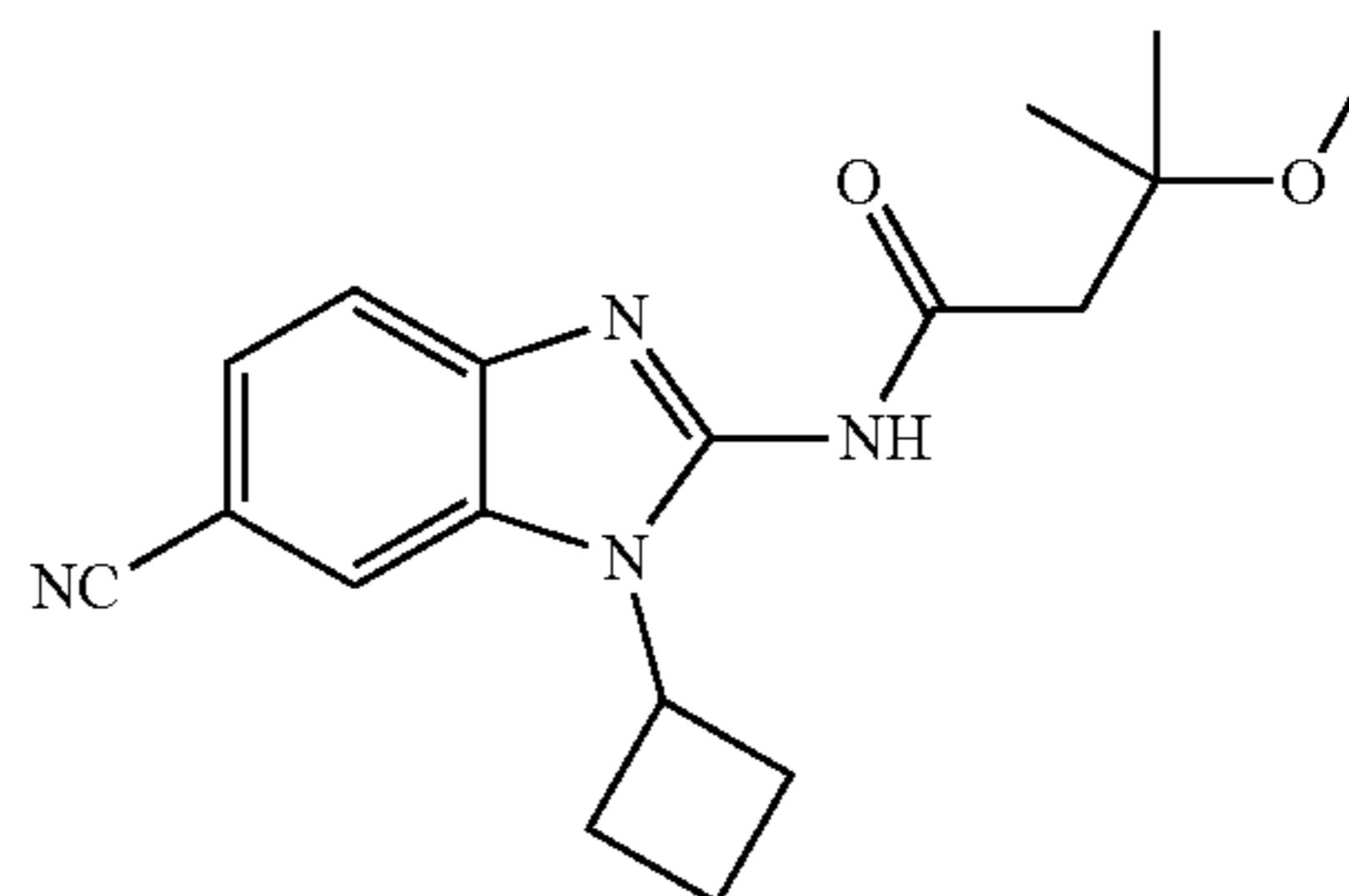
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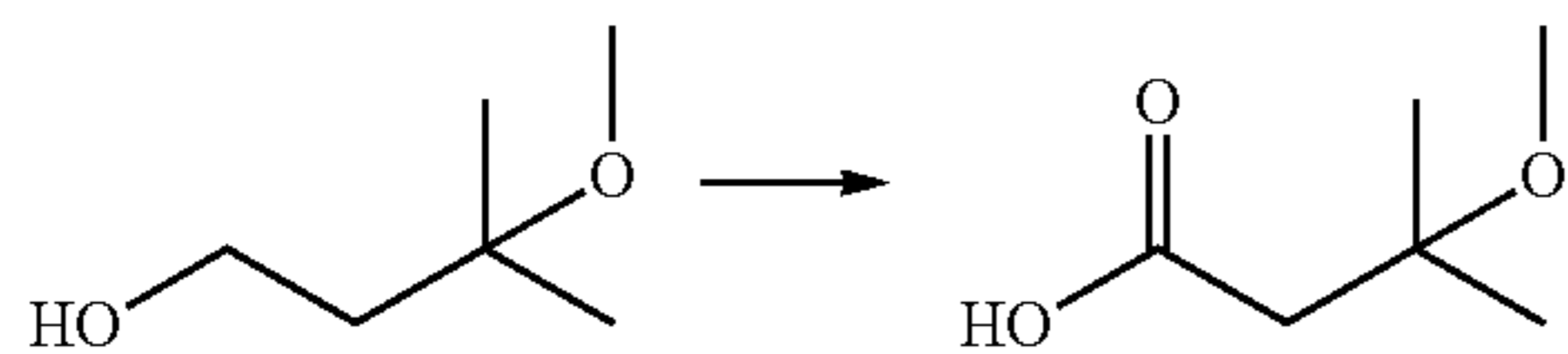
Crude (S)-3-((tert-butyl(dimethyl)silyloxy)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2,3-dimethylbutanamide from Step D above (38 mg) was dissolved in MeOH (4 mL) and HCl (3 M in diethyl ether, 2 mL) was added to the reaction via syringe. The reaction was allowed to stir at room temperature for 30 minutes when LC/MS analysis indicated a slow and clean deprotection of the TBS ether. The flask was placed in a 50° C. sand bath and allowed to stir capped for 20 hours. The flask was allowed to cool and then quenched by the careful addition of saturated aqueous sodium bicarbonate (30 mL) and ethyl acetate (30 mL). The aqueous layer was extracted twice with ethyl acetate. The combined organics were washed with brine, dried with sodium sulfate, filtered and concentrated to give a crude oil. The crude material was subjected to column chromatography (Isco, 12 g silica gel, 5-75% EtOAc in hexanes) to give the desired product (18 mg, 64% yield). MS (ESI) m/z 327.2 (MH^+).

Example 12. Preparation of N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-methoxy-3-methylbutanamide



115

Step A. Preparation of 3-methoxy-3-methylbutanoic acid

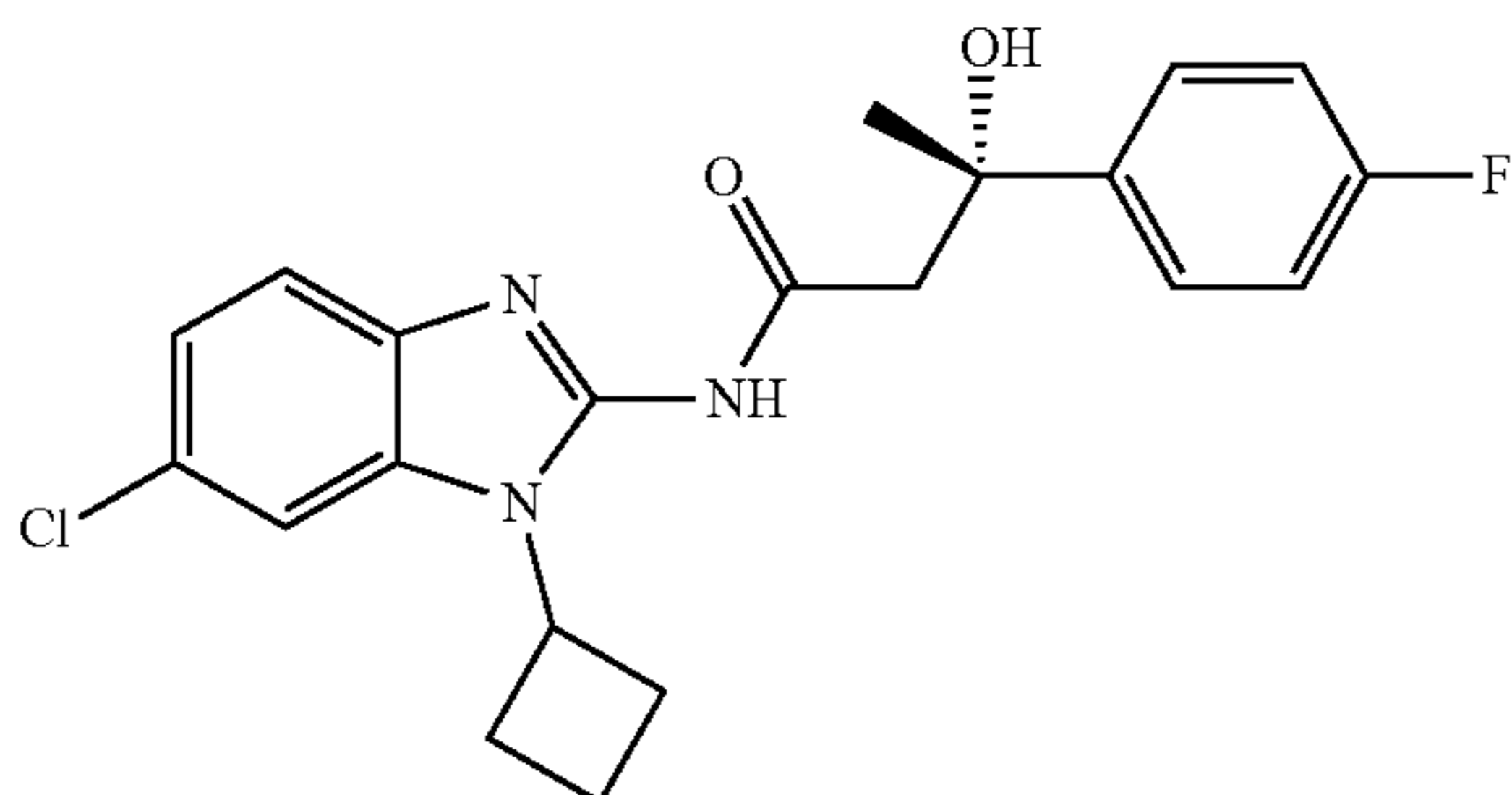


To a solution of 3-methoxy-3-methylbutan-1-ol (0.6 g, 5 mmol) in acetonitrile (20 mL) was added N-methyl morpholine N-oxide monohydrate (6.8 g, 50 mmol, 10 equivalents) and the mixture was allowed to stir at room temperature. After 5 min, tetrapropylammonium perruthenate (175 mg, 0.5 mmol, 0.1 equivalents) was added in one portion and the reaction was allowed to stir for 3 h before the bulk of the solvent was carefully removed on a rotary evaporator (caution, the product is volatile). The residue was purified by column chromatography (50-100% EtOAc/hexanes). The hexanes and EtOAc were removed by both rotary evaporator and a short period of time to high vacuum. The product is volatile and must not be left under vacuum for more than 30 sec. The resulting purified acid was diluted with dimethylformamide (7 mL) to make an approximately 0.2 M solution that was used for amide coupling reaction as is. $R_f=0.4$ to 0.8 streak in 100% EtOAc, not UV active, stains purple to anisaldehyde. $M-1=131.2$. $^1\text{H NMR}$ (CDCl_3): δ 12.0-9.0 (bs, 1H), 3.30 (s, 3H), 2.57 (s, 2H), 1.32 (s, 6H). (Reference: Schmidt, A-K C, Stark, B W, *Org. Lett.* 2011, 13, 4164-4167).

Step B. Preparation of N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-methoxy-3-methylbutanamide

The title compound was prepared from 3-methoxy-3-methylbutanoic acid and 4-amino-3-(cyclobutylamino) benzonitrile according to Method 7. MS (ESI) m/z 327 (MH^+).

Example 103. Preparation of (S)-N-(6-chloro-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-(4-fluorophenyl)-3-hydroxybutanamide



Step A: Preparation of (S)-4-benzyl-3-((S)-3-(4-fluorophenyl)-3-hydroxybutanoyl)oxazolidin-2-one

Lithium bis(trimethylsilyl)amide (1.0 M tetrahydrofuran, 6.6 mL, 6.6 mmol) was added over 15 minutes to a -78°C . suspension of (S)-3-acetyl-4-benzyl-oxazolidin-2-one (1.5 g, 6.6 mmol) in tetrahydrofuran (18 mL). The mixture was stirred at -78°C . for two hours. Acetophenone (330 μL , 3.2

116

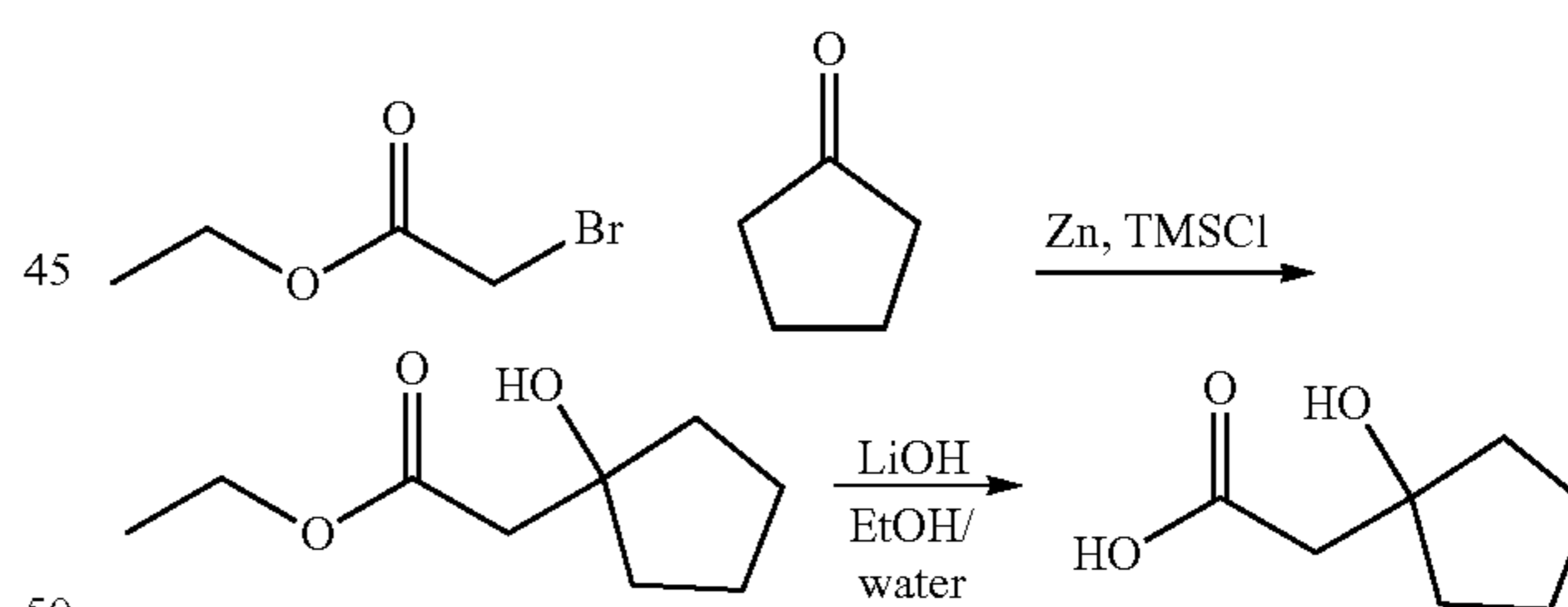
mmol) was added dropwise over 5 minutes. The mixture was stirred at -78°C . for one hour and then quenched via the addition of aqueous 0.5 M HCl. The mixture was warmed to room temperature and then extracted with CH_2Cl_2 . The layers were separated and the aqueous phase was extracted twice more with CH_2Cl_2 . The combined organics were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (0-30% EtOAc/hexanes) to provide the desired (0.80 g).

Step B: Preparation of (S)-3-(4-fluorophenyl)-3-hydroxybutanoic Acid

Lithium hydroxide (210 mg, 9.0 mmol) was added to a 0°C . mixture of (S)-4-benzyl-3-((S)-3-(4-fluorophenyl)-3-hydroxybutanoyl)oxazolidin-2-one (0.80 g, 2.2 mmol) and 50% aqueous hydrogen peroxide (0.51 mL, 9.0 mmol) in 1:1 tetrahydrofuran/ H_2O (9 mL). The mixture was stirred at 0°C . for 15 minutes, then at room temperature for three hours. The mixture was adjusted to pH 7 via the addition of 1 M aqueous HCl and then was diluted with EtOAc. The layers were separated, the aqueous phase was adjusted to pH 2 via the addition of 1 M aqueous HCl and then treated with solid NaCl until the solids failed to dissolve. The mixture was then partitioned between saturated aqueous NaCl and EtOAc. The phases were separated and the aqueous layer was extracted again with EtOAc. The organics were combined, dried over anhydrous Na_2SO_4 and concentrated to provide the expected product (0.35 g, 79%).

The title compound was then prepared using the procedures described in Step D of Example 18, substituting (S)-3-(4-fluorophenyl)-3-hydroxybutanoic acid for (2S,3R)-3-((tert-butyl dimethylsilyl)oxy)-2-methyl-3-phenylbutanoic acid and 6-chloro-1-cyclobutyl-1H-benzo[d]imidazol-2-amine for 2-amino-1-cyclobutyl-1H-benzo[d]imidazole-6-carbonitrile. MS (ESI) m/z 402 (MH^+).

Preparation of 2-(1-hydroxycyclopentyl)acetic Acid



Step A. Preparation of ethyl 2-(1-hydroxycyclopentyl)acetate

Chlorotrimethylsilane (181 μL , 1.4 mmol) was added to a suspension of zinc powder (1.2 g, 19 mmol) in Et_2O (30 mL). The mixture was stirred at room temperature for 15 minutes and then refluxed for 15 minutes. The heat source was removed and ethyl bromoacetate (1.8 mL, 14 mmol) was added dropwise to the warm mixture. The mixture was then refluxed for one hour and then stirred at room temperature for one hour. Cyclopentanone (1.0 g, 12 mmol) was then added dropwise. The resulting mixture was stirred for one hour and then poured into ice cold concentrated aqueous ammonia (80 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3×40 mL). The

combined organics were dried (K_2CO_3) and concentrated to yield 1.7 g of a colorless oil. This material was used as is in the next step.

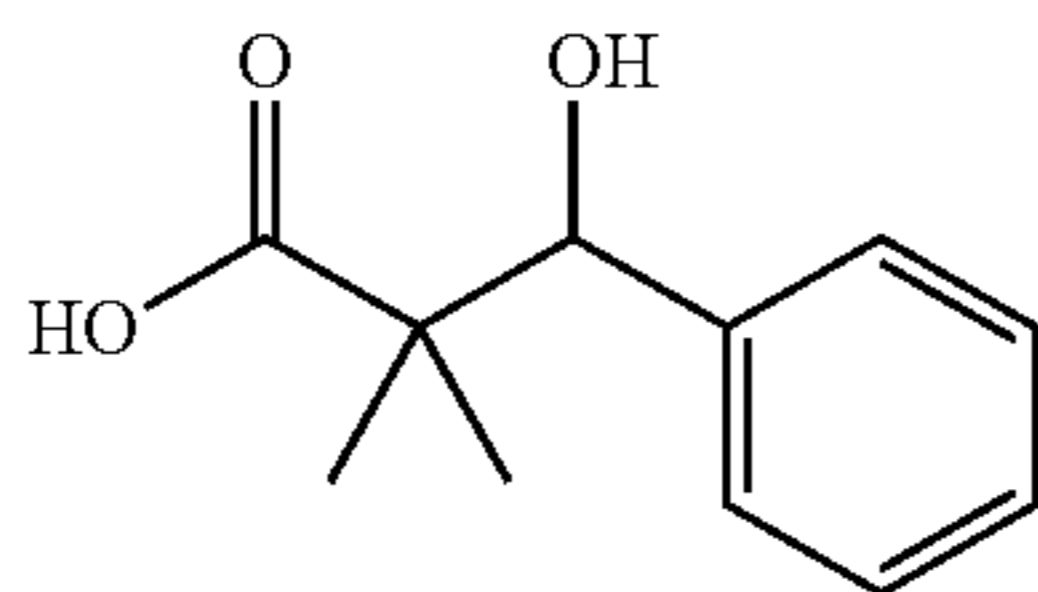
Step B. Preparation of
2-(1-hydroxycyclopentyl)acetic acid

Lithium hydroxide (1.4 g, 58 mmol) was added to a room temperature solution of the crude ester prepared as described in the previous step (1.0 g, 5.8 mmol) in 1:1 EtOH:water (29 mL). After 2 hours, the reaction was partitioned between water (100 mL) and MTBE (100 mL). The aqueous layer was isolated and the pH was adjusted to pH=2 with 1.0 N aqueous HCl. The aqueous mixture was extracted three times with EtOAc. The combined organics were dried (Na_2SO_4) and concentrated to afford the desired product (500 mg, 60%). (ESI) m/z 143.2 (M-H).

The following carboxylic acids were prepared using an analogous procedure to that described for preparation of 2-(1-hydroxycyclopentyl)acetic acid with appropriate starting materials.

3,3-dicyclopropyl-3-hydroxypropanoic acid
3-cyclopentyl-3-hydroxybutanoic acid
3-cyclobutyl-3-hydroxybutanoic acid

Preparation of
3-hydroxy-2,2-dimethyl-3-phenylpropanoic Acid



The preparation of 3-hydroxy-2,2-dimethyl-3-phenylpropanoic acid is detailed in *J. Org. Chem.*, 2012, 77 (11), 4885-4901.

Section 5. General Analytical Methods

LCMS was conducted on an Agilent 1100 MSD instrument equipped with an Ascentis Express C18, 10 cm×4.6 mm×2.7 mm column, using the following methods:

HPLC Method A

Solvent A: 0.1% formic acid in water

Solvent B: Acetonitrile

Flow rate: 1.4 mL/min

Method:

0-6.0 min gradient from B=10% to B=95%

6.0-8.0 min, hold B=95%

8.0-8.2 min, gradient from B=95% to B=10%

8.2-10.0 min, hold B=10%

HPLC Method B:

Solvent A: 0.1% formic acid in water

Solvent B: Acetonitrile

Flow rate: 1.4 mL/min

Method:

0-3.0 min gradient from B=10% to B=95%

3.0-4.0 min, hold B=95%

4.0-4.2 min, gradient from B=95% to B=10%

4.2-6.0 min, hold B=10%

Table 1 shows the structures of the various Examples prepared by these general methods, and indicates the general coupling method used, together with a summary of the LCMS analytical data.

TABLE 1

List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Re-tension time (min)	LCMS m/z
1	 C ₁₇ H ₂₃ N ₃ O	N-(1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7	B	2.7	286
2	C ₁₉ H ₂₁ N ₃ O	3,3-dimethyl-N-(1-phenyl-1H-benzo[d]imidazol-2-yl)butanamide	9	B	2.8	308

TABLE 1-continued

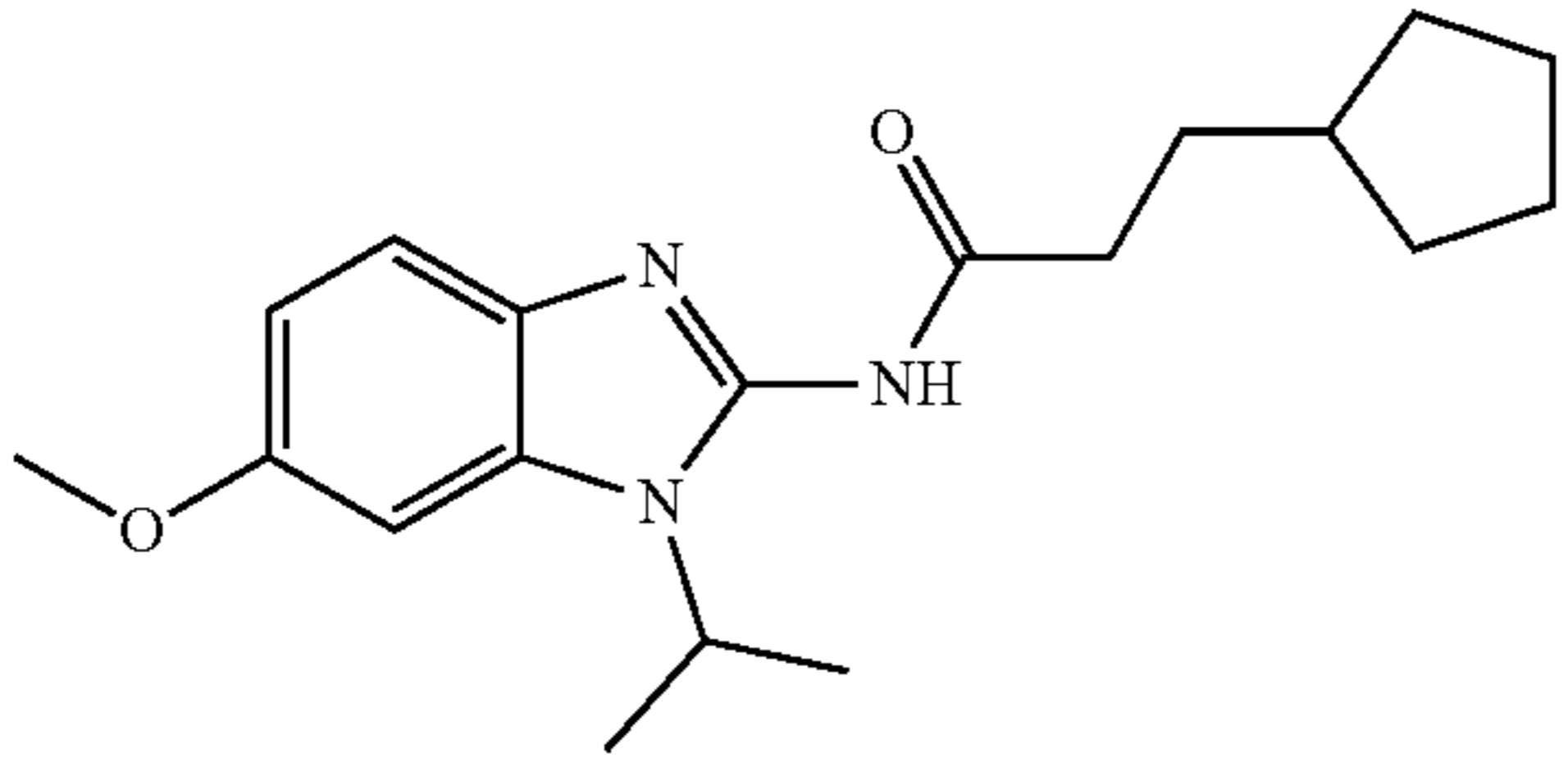
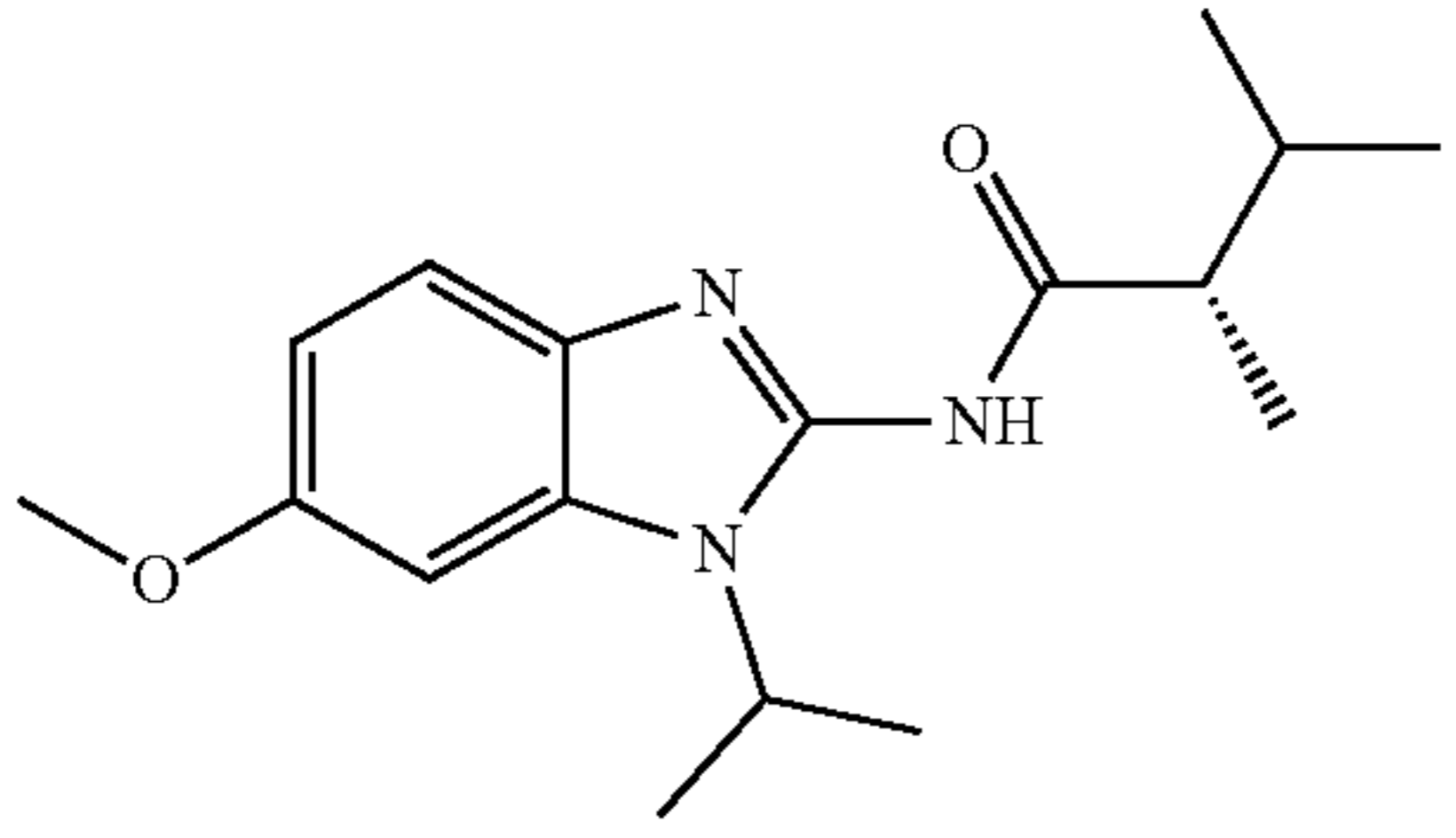
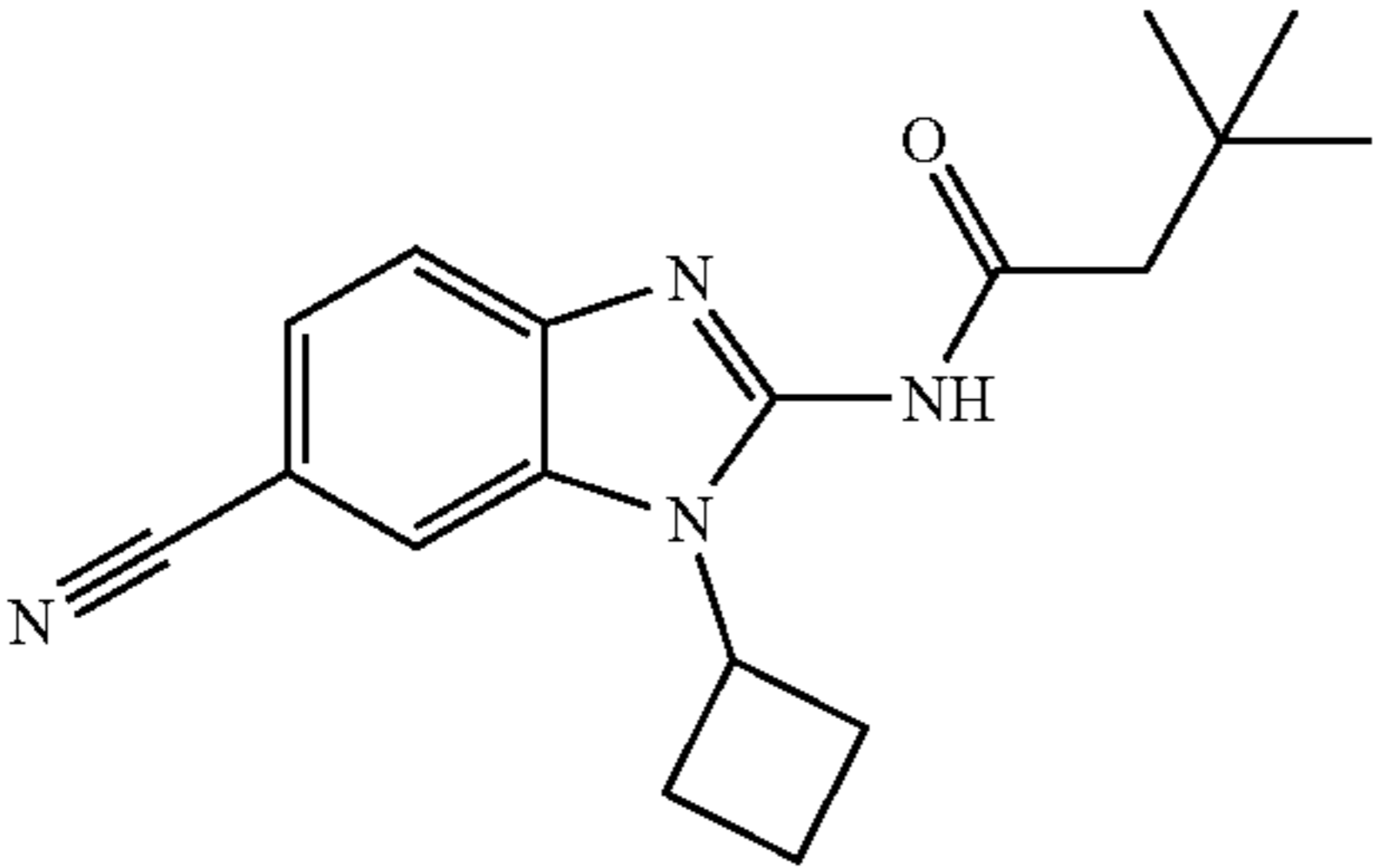
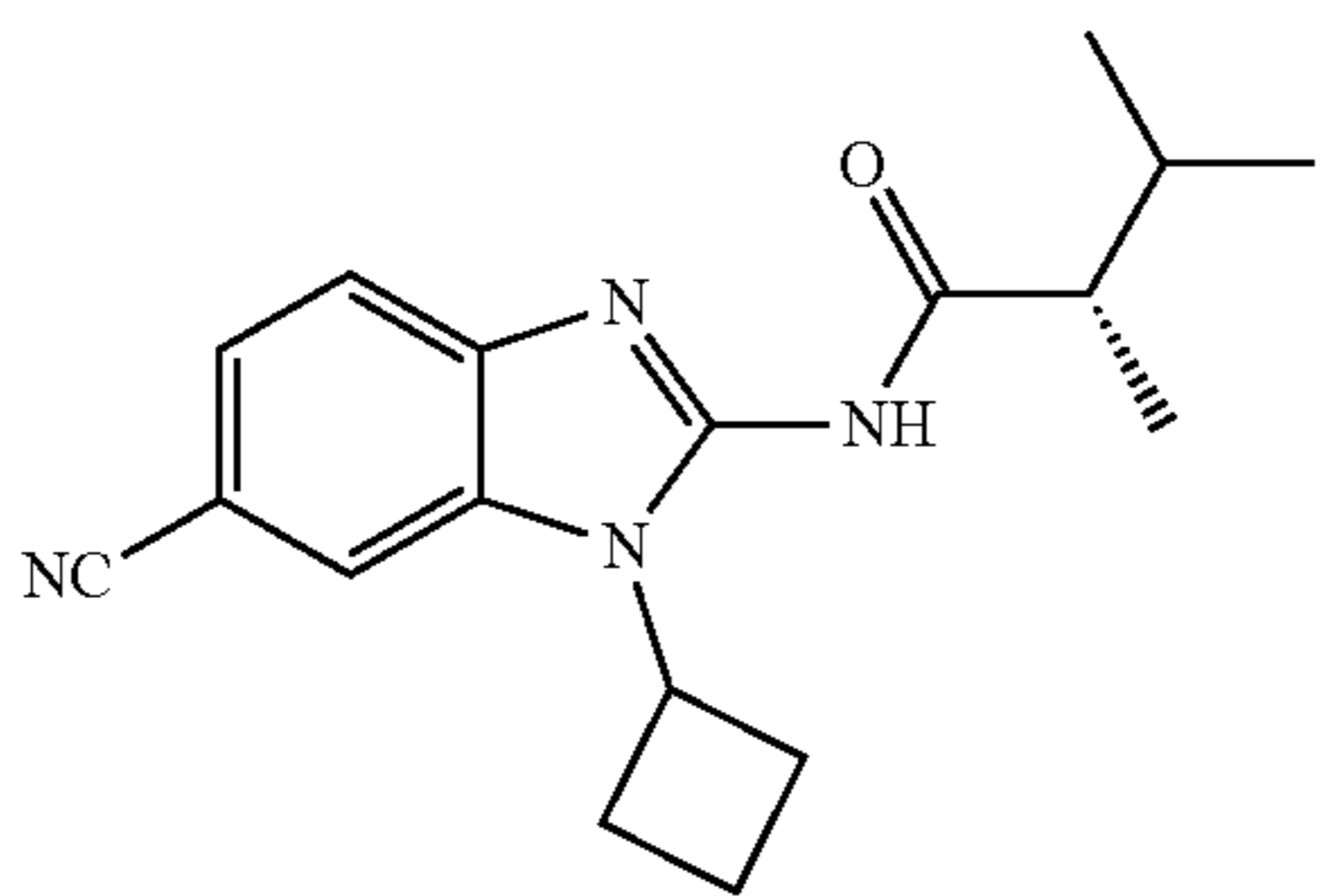
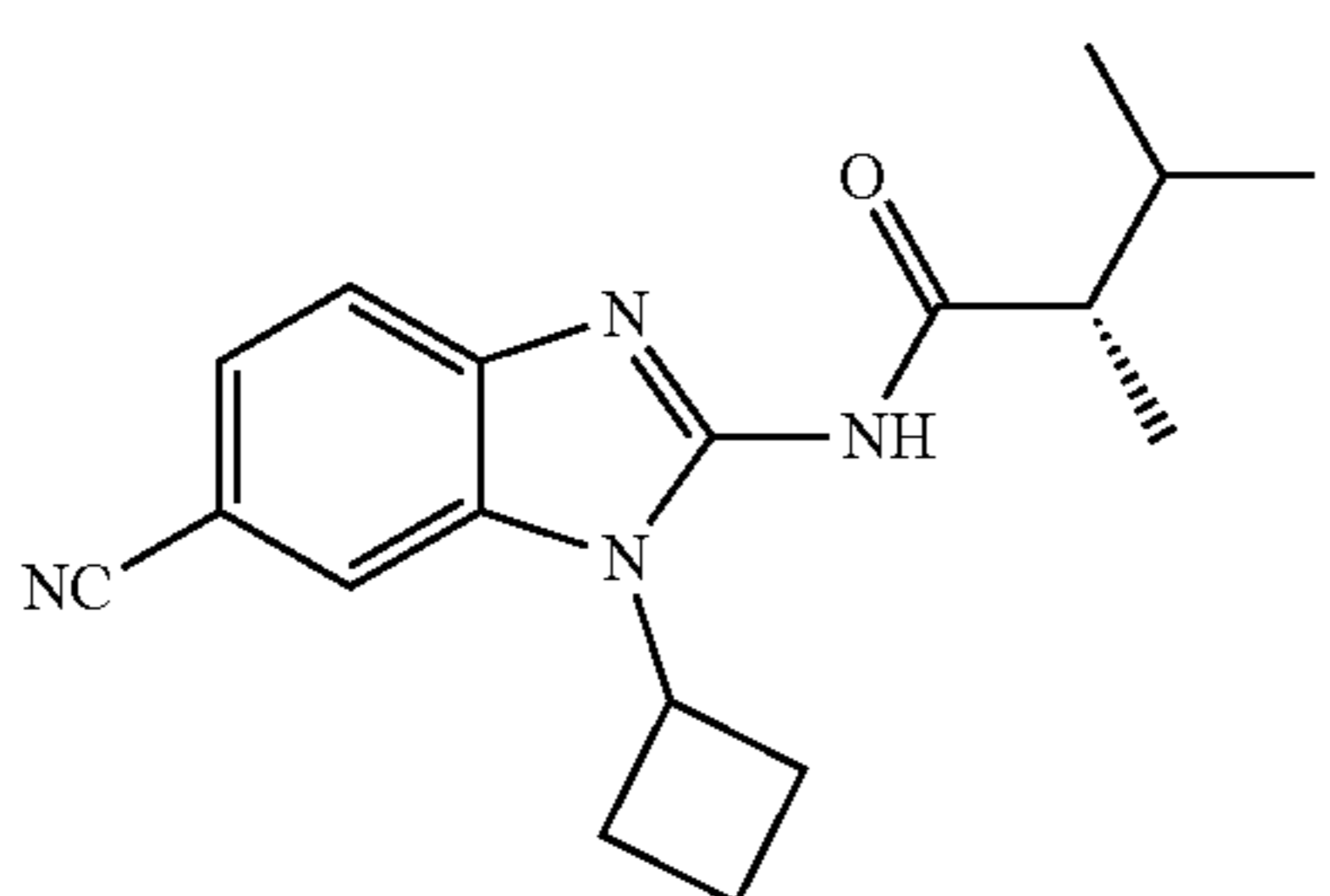
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
3	 C ₁₉ H ₂₇ N ₃ O ₂	3-cyclopentyl-N-(1-isopropyl-6-methoxy-1H-benzo[d]imidazol-2-yl)propanamide	12	A	5.5	330
4	 C ₁₇ H ₂₅ N ₃ O ₂	(S)-N-(1-isopropyl-6-methoxy-1H-benzo[d]imidazol-2-yl)-2,3-dimethylbutanamide	7	B	2.7	304
5	 C ₁₈ H ₂₂ N ₄ O	N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7	B	3.5	311
6	 C ₁₈ H ₂₂ N ₄ O	(S)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2,3-dimethylbutanamide	7	B	3.5	311
7	 C ₁₈ H ₂₂ N ₄ O	(S)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2,3-dimethylbutanamide	7	A	4.9	311

TABLE 1-continued

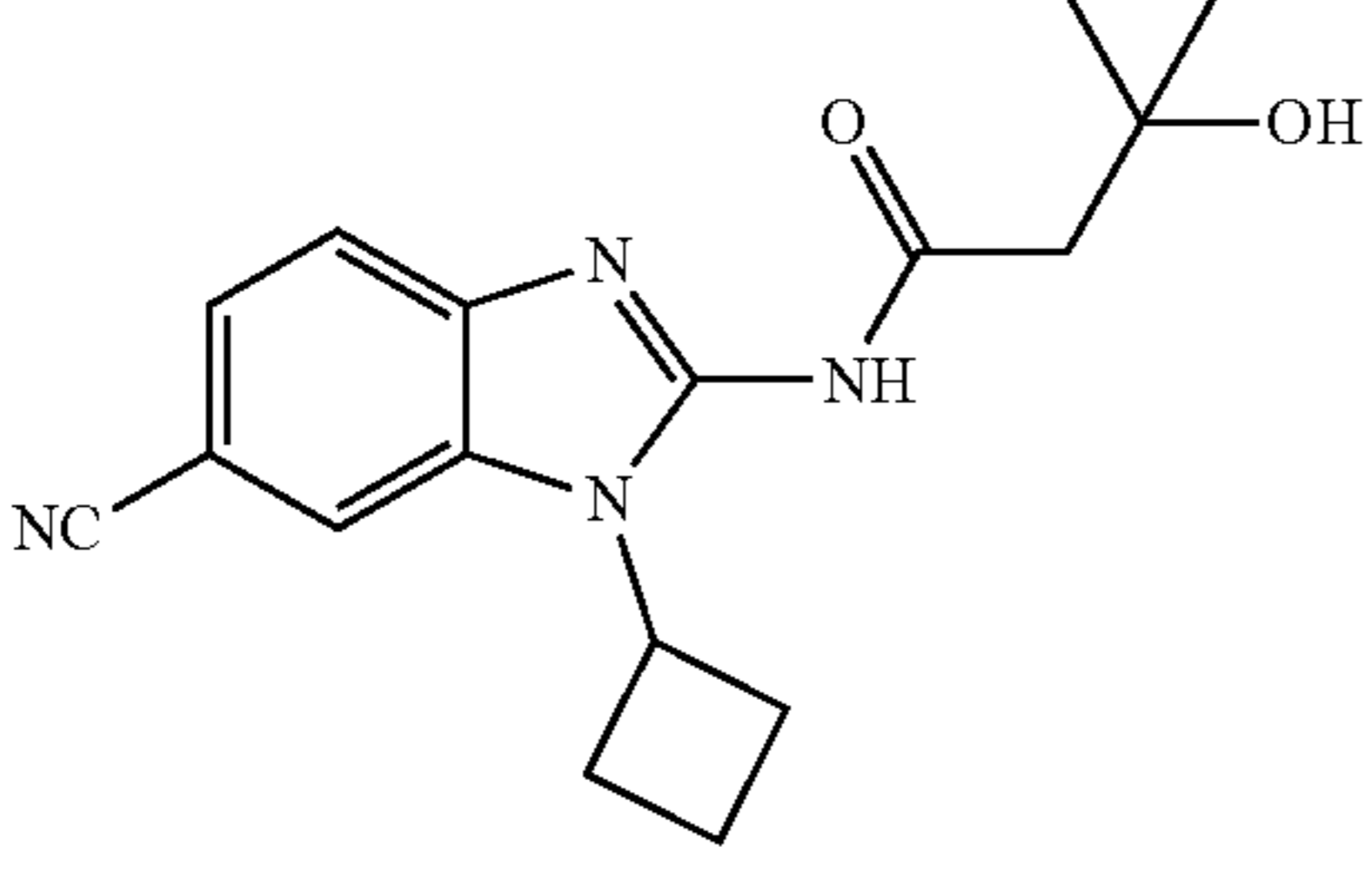
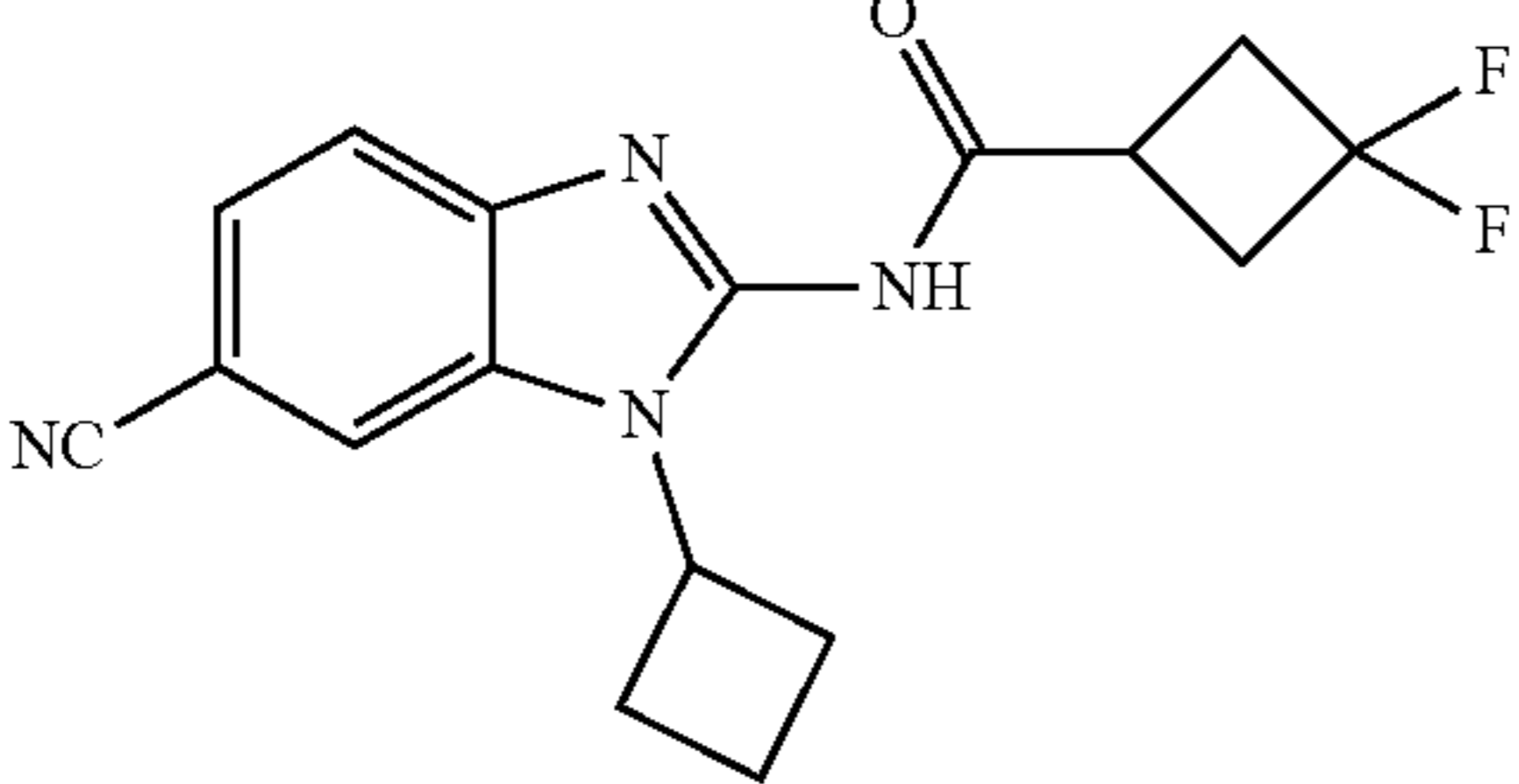
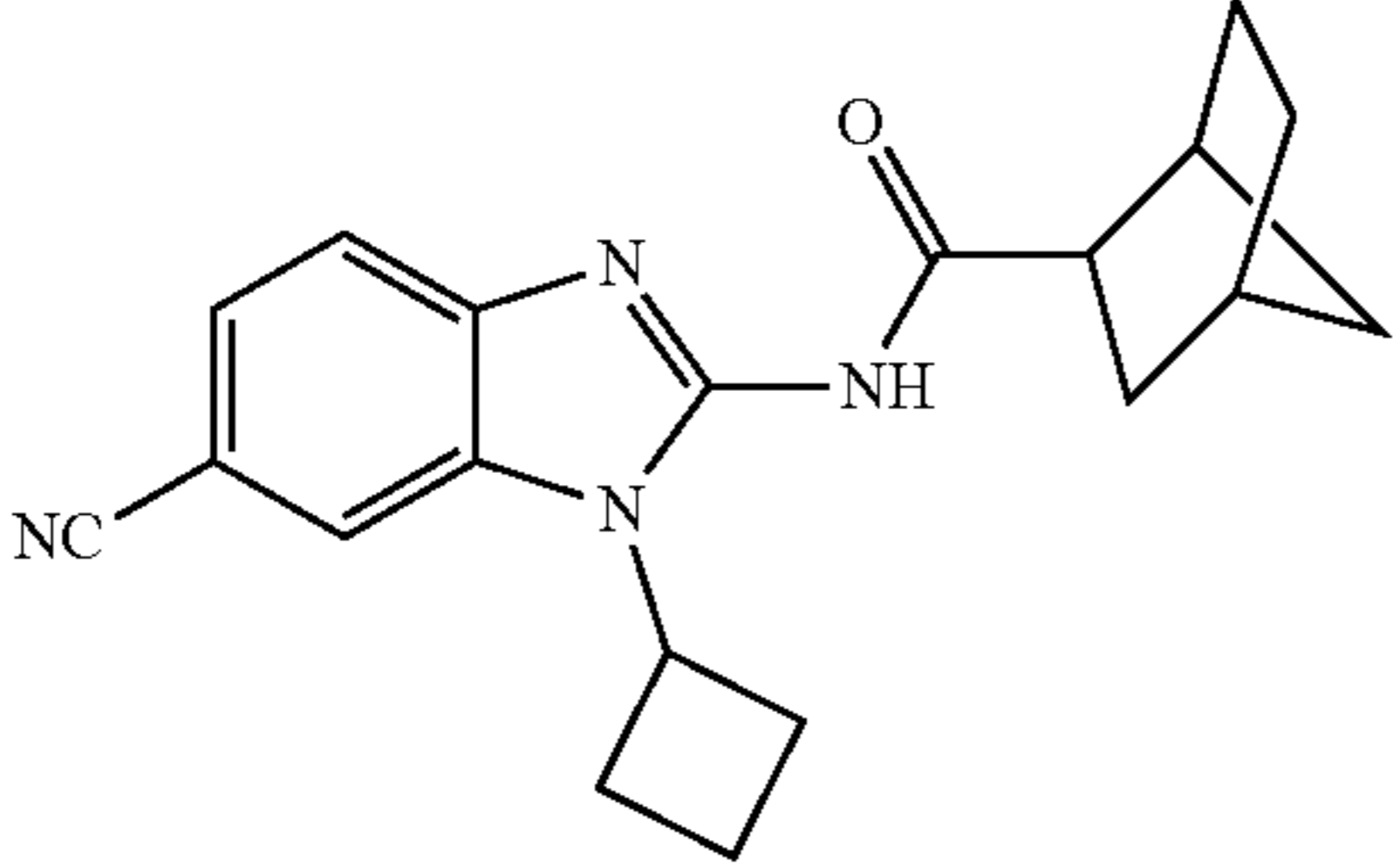
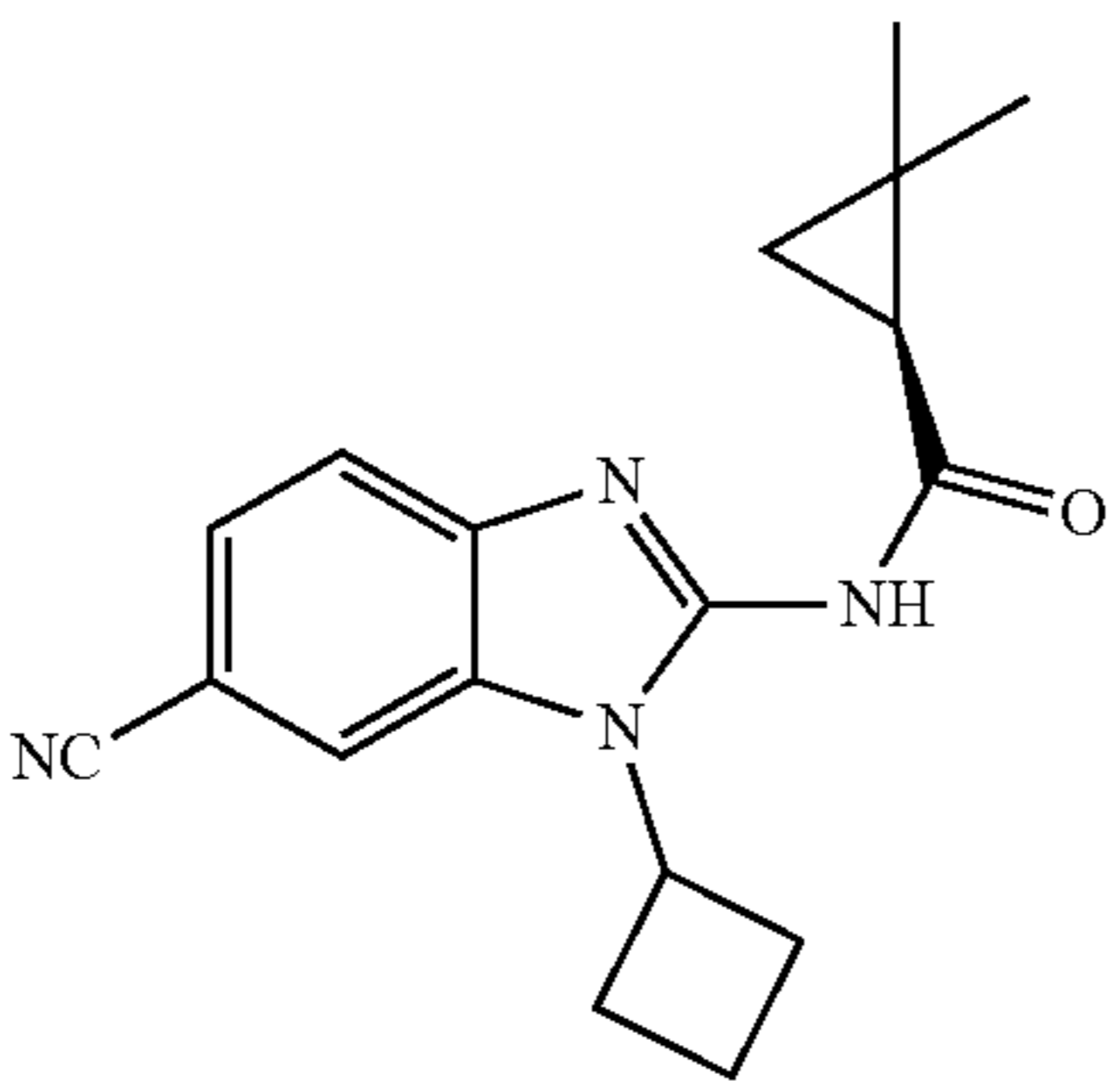
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Re-tension time (min)	LCMS m/z
8	 $C_{17}H_{20}N_4O_2$	N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-methylbutanamide	7	B	2.7	313
9	 $C_{17}H_{16}F_2N_4O$	N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3,3-difluorocyclobutane-1-carboxamide	7	B	3.5	331
10	 $C_{20}H_{22}N_4O$	(1S,2R,4R)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)bicyclo[2.2.1]heptane-2-carboxamide	7	B	3.6	335
11	 $C_{18}H_{20}N_4O$	(S)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2,2-dimethylcyclopropane-1-carboxamide	7	B	3.3	309

TABLE 1-continued

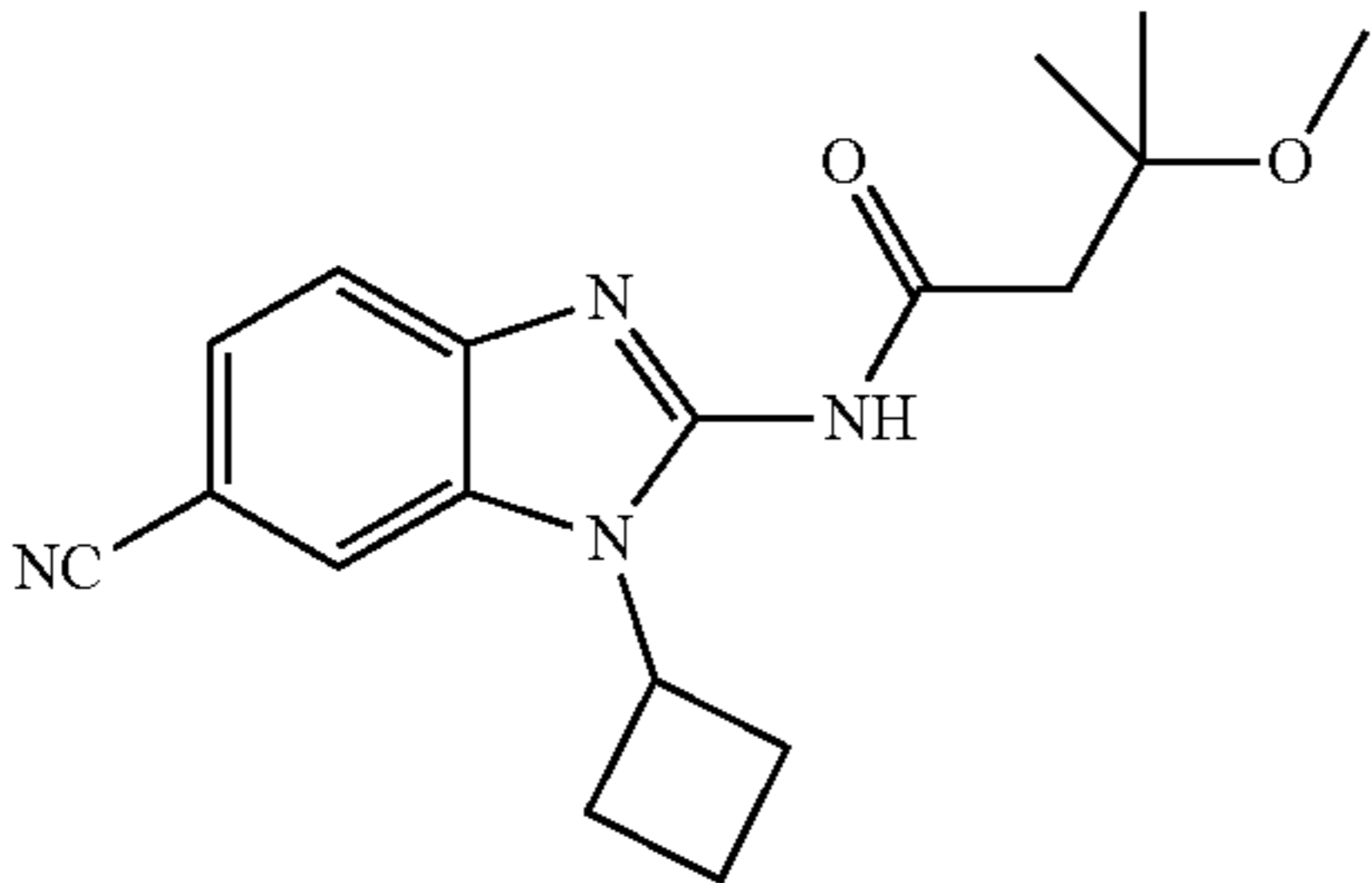
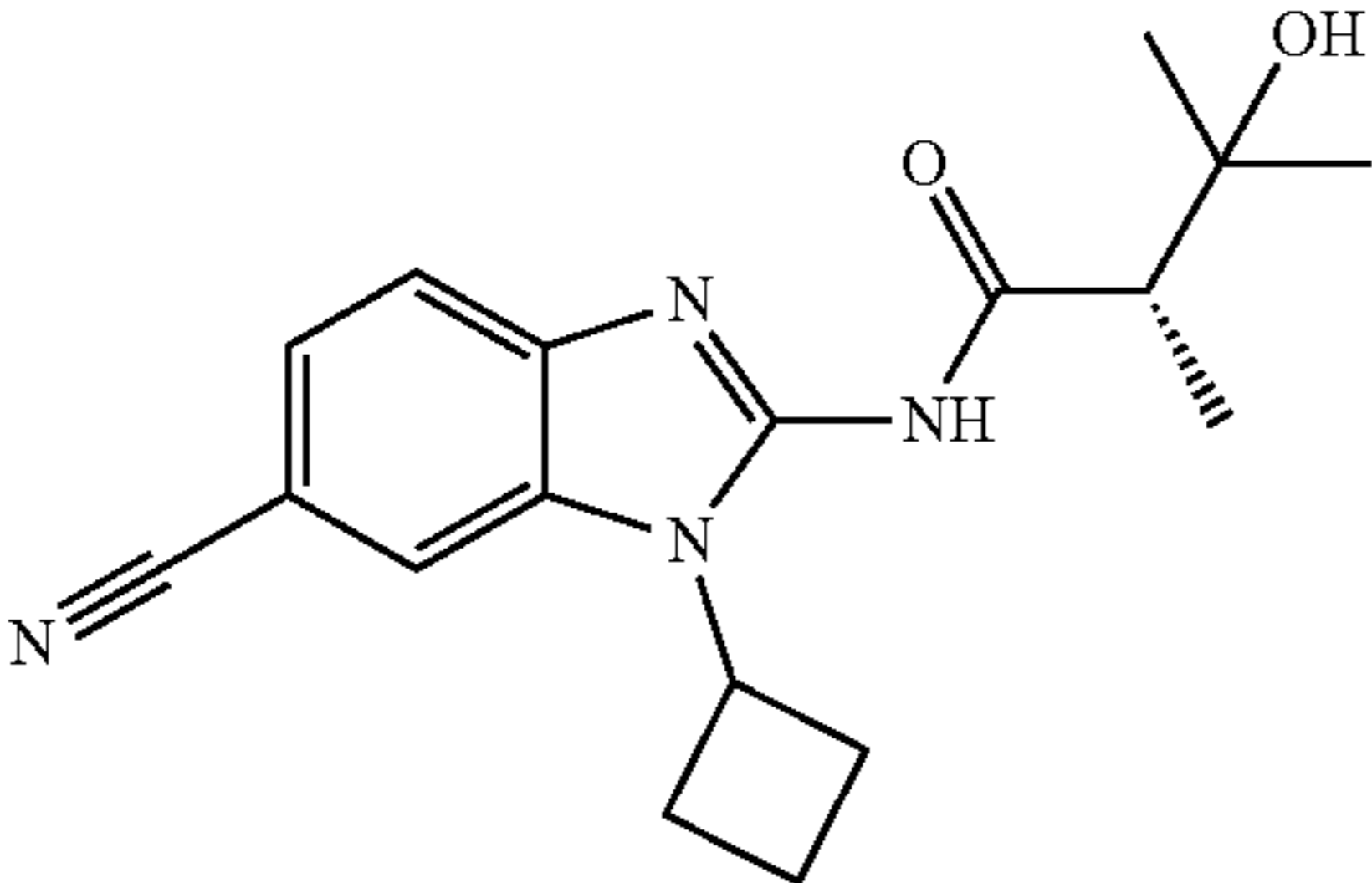
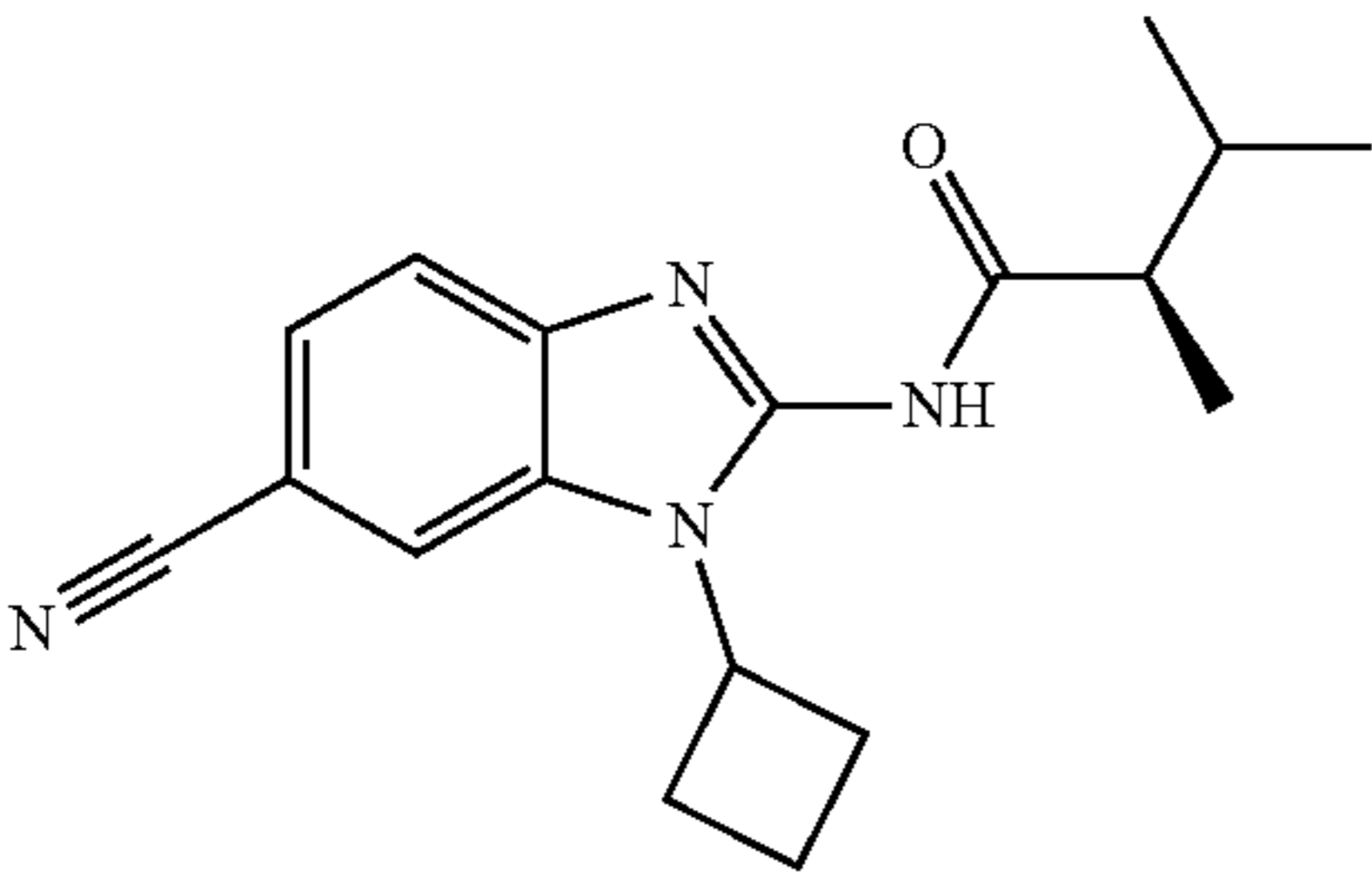
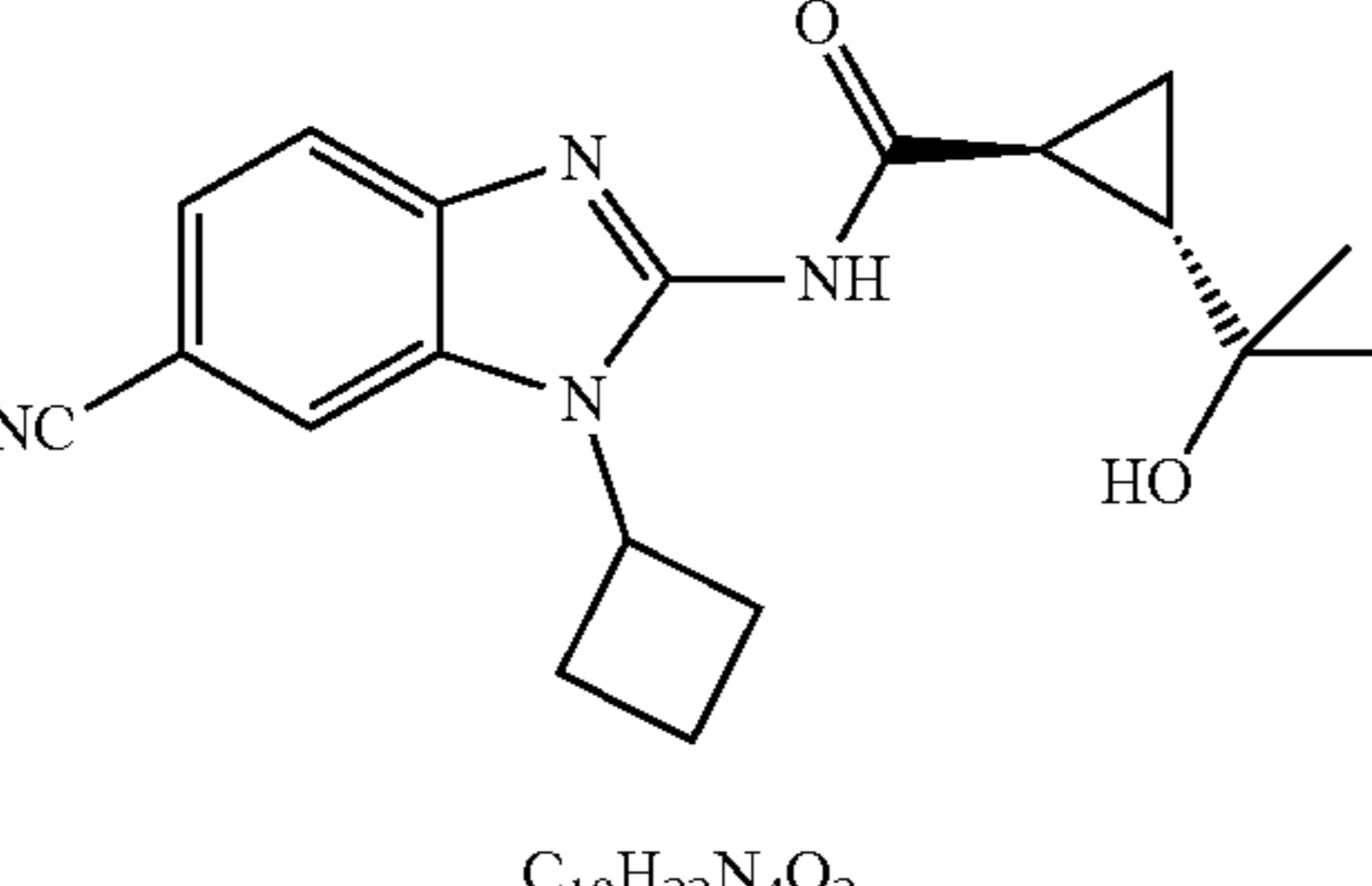
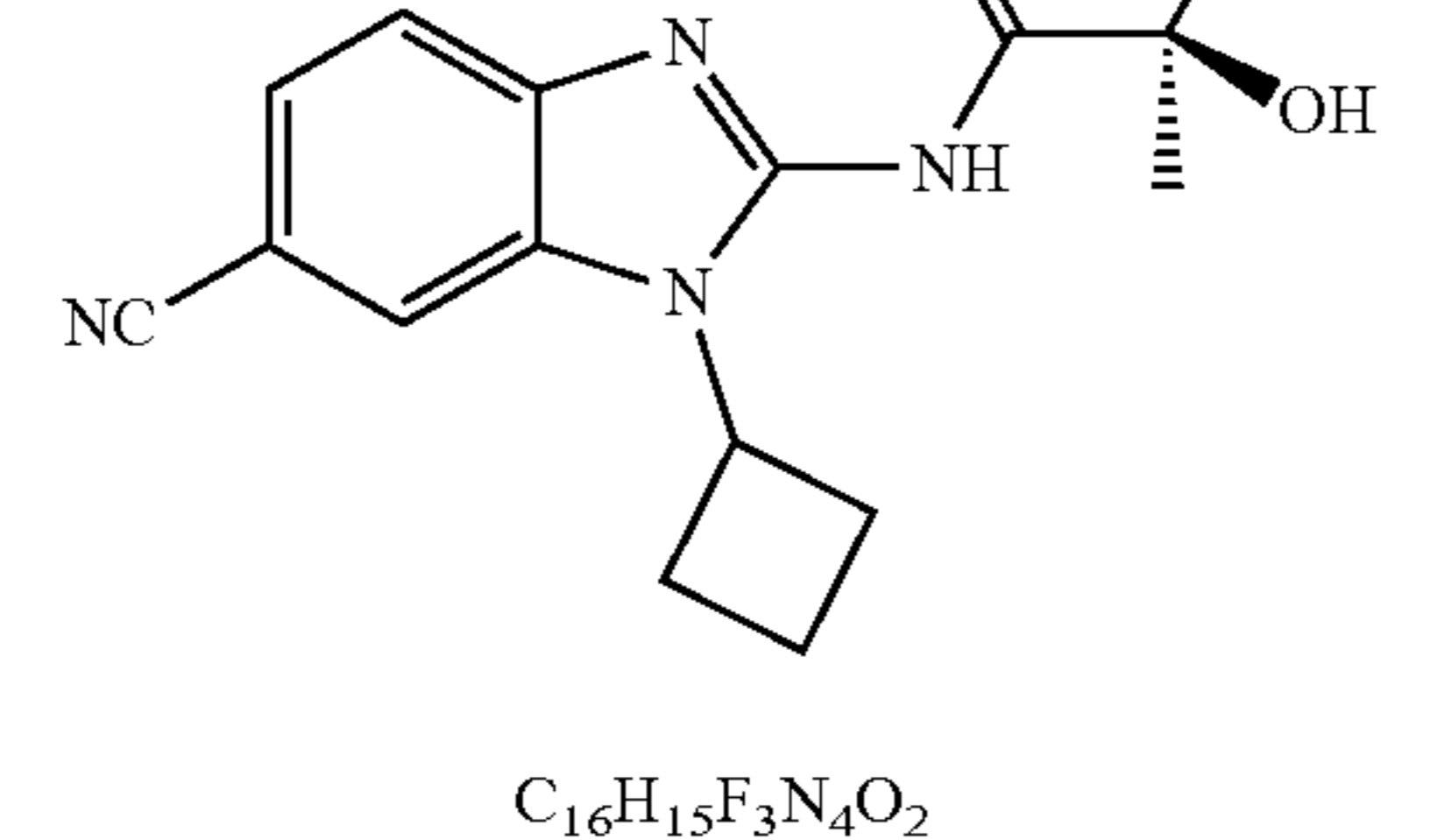
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
12	 $C_{18}H_{22}N_4O_2$	N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-methoxy-3-methylbutanamide	7	B	3.0	327
13	 $C_{18}H_{22}N_4O_2$	(S)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-2,3-dimethylbutanamide	7	B	2.9	327
14	 $C_{18}H_{22}N_4O$	(R)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2,3-dimethylbutanamide	7	B	3.5	311
15	 $C_{19}H_{22}N_4O_2$	(1S,2S)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2-(2-hydroxypropan-2-yl)cyclopropane-1-carboxamide	7	B	2.8	339
16	 $C_{16}H_{15}F_3N_4O_2$	(S)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide	7	B	3.8	353

TABLE 1-continued

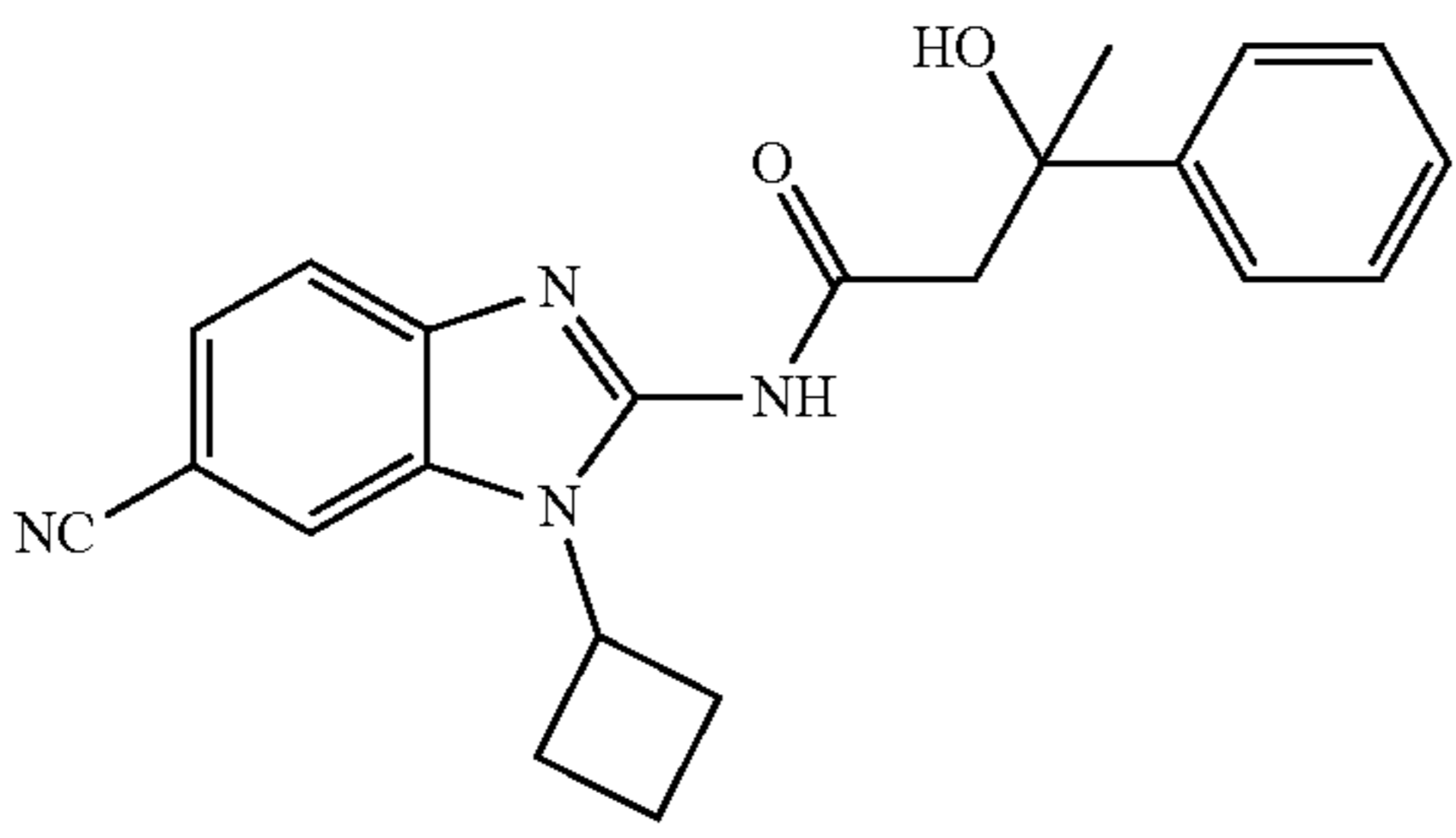
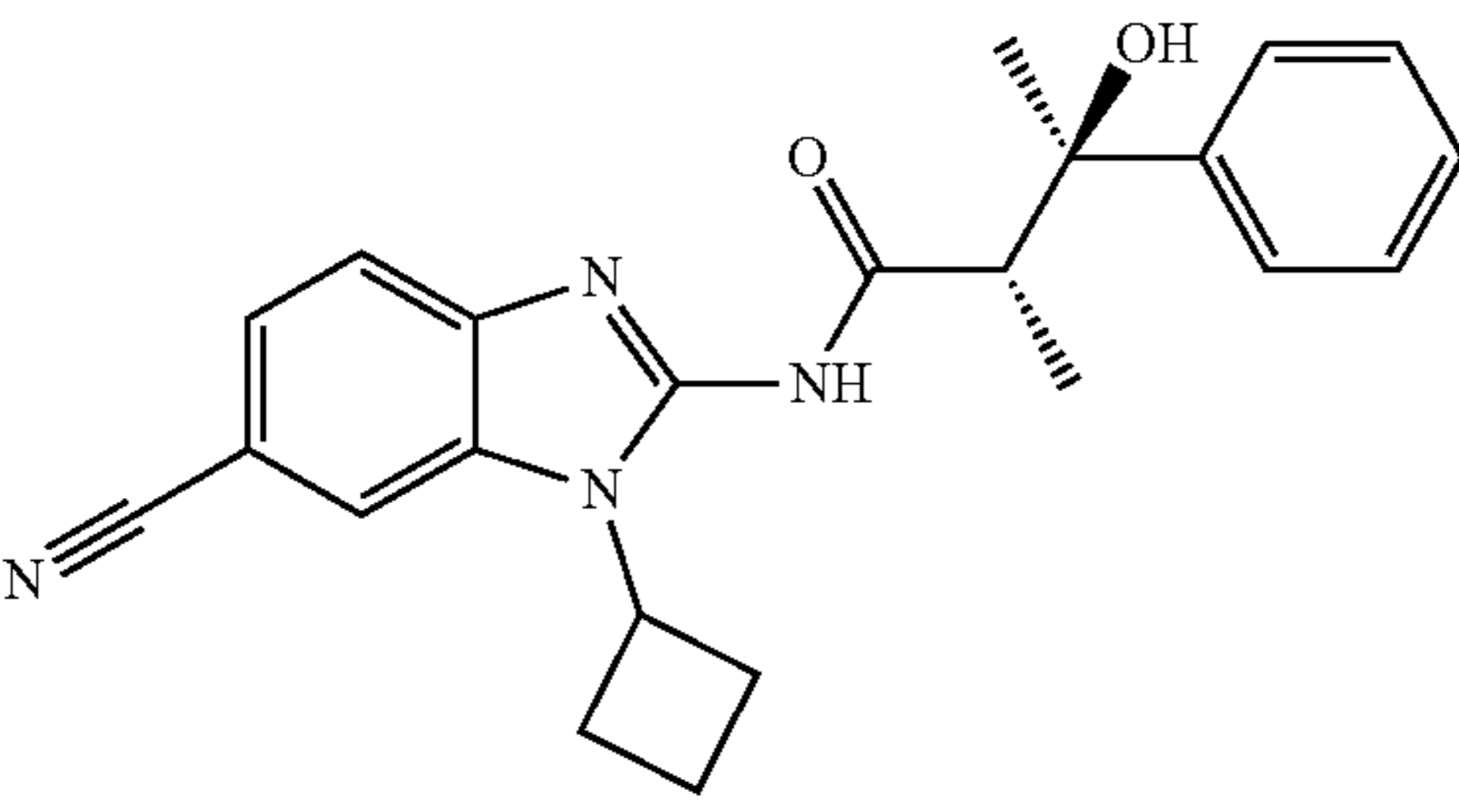
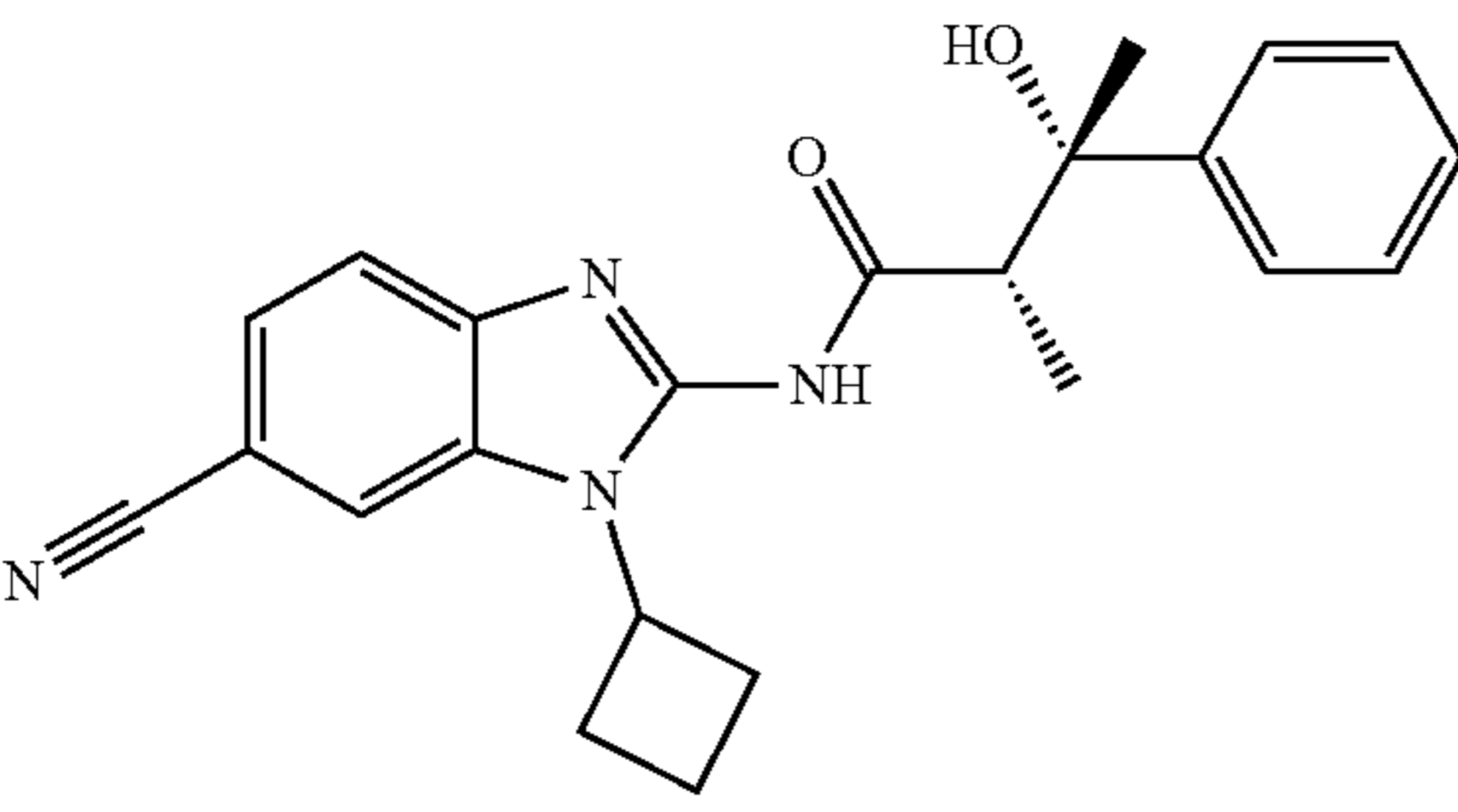
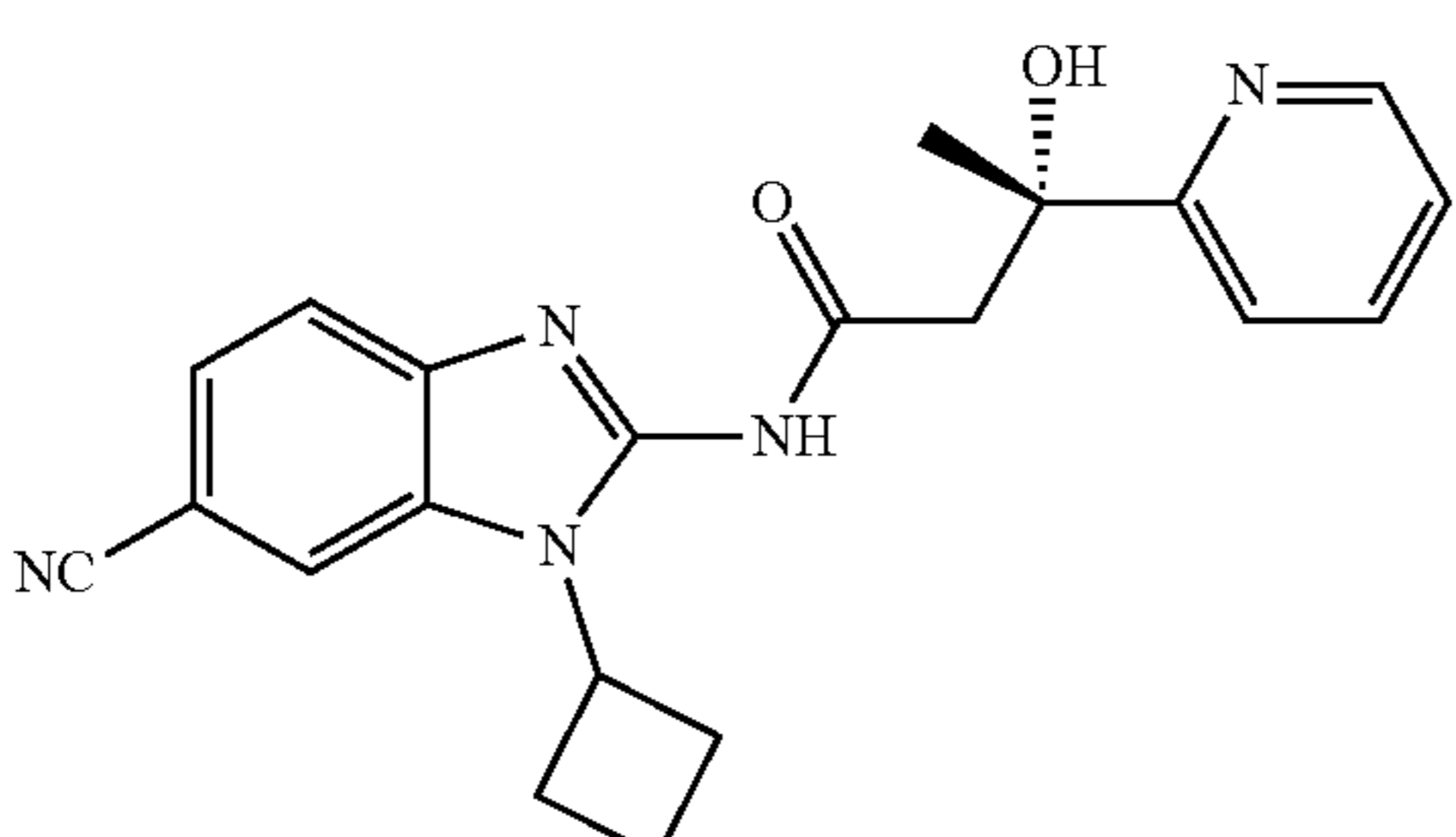
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Re-tension time (min)	LCMS m/z
17	 <chem>C22H22N4O2</chem>	N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	7	B	3.4	375
18	 <chem>C23H24N4O2</chem>	(2S,3R)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-2-methyl-3-phenylbutanamide	Ex 18	B	3.5	389
19	 <chem>C23H24N4O2</chem>	(2S,3S)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-2-methyl-3-phenylbutanamide	Ex 19	B	3.8	389
20	 <chem>C21H21N5O2</chem>	(S)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-(pyridin-2-yl)butanamide	7 (no base)	A	2.9	376

TABLE 1-continued

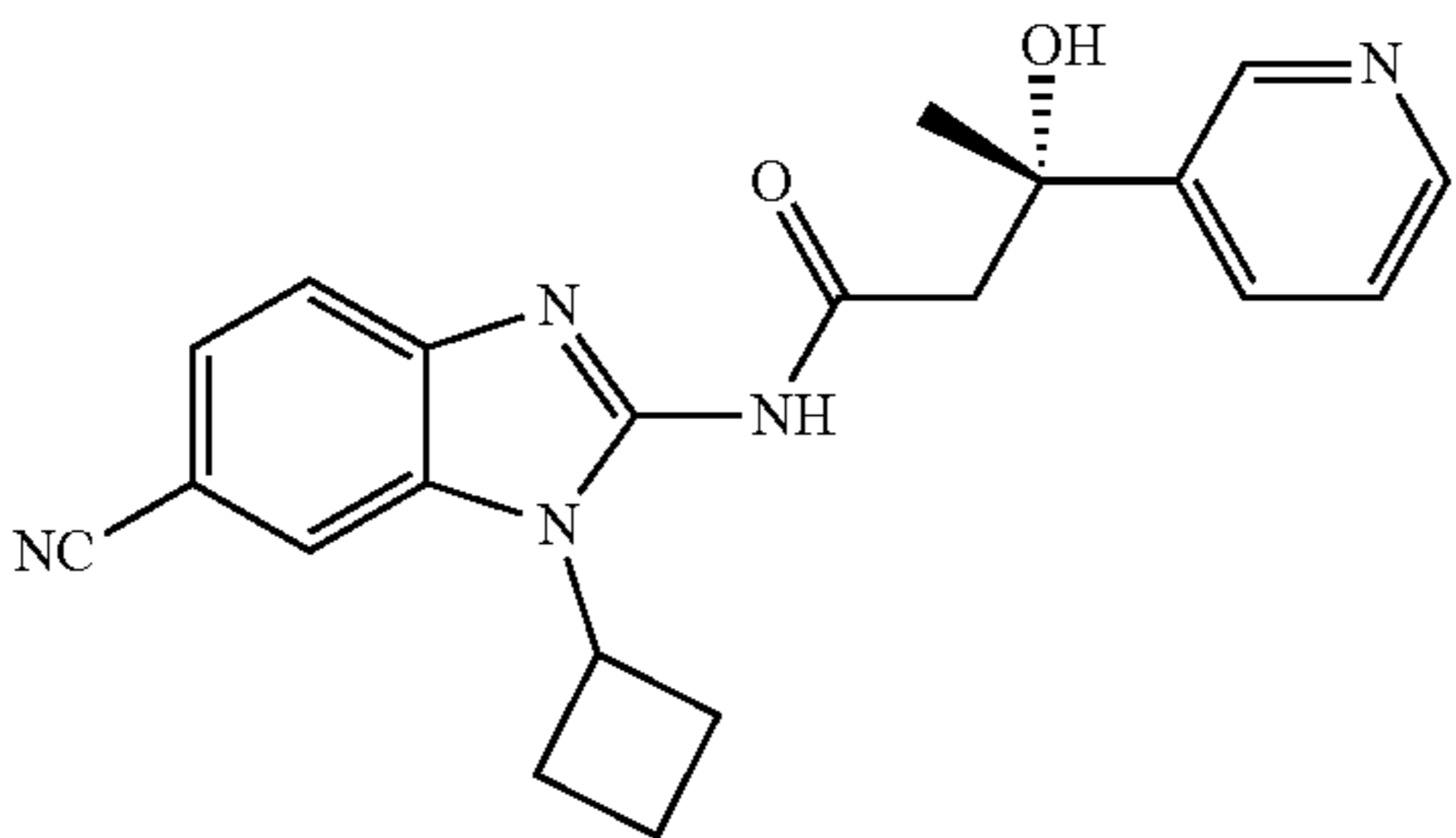
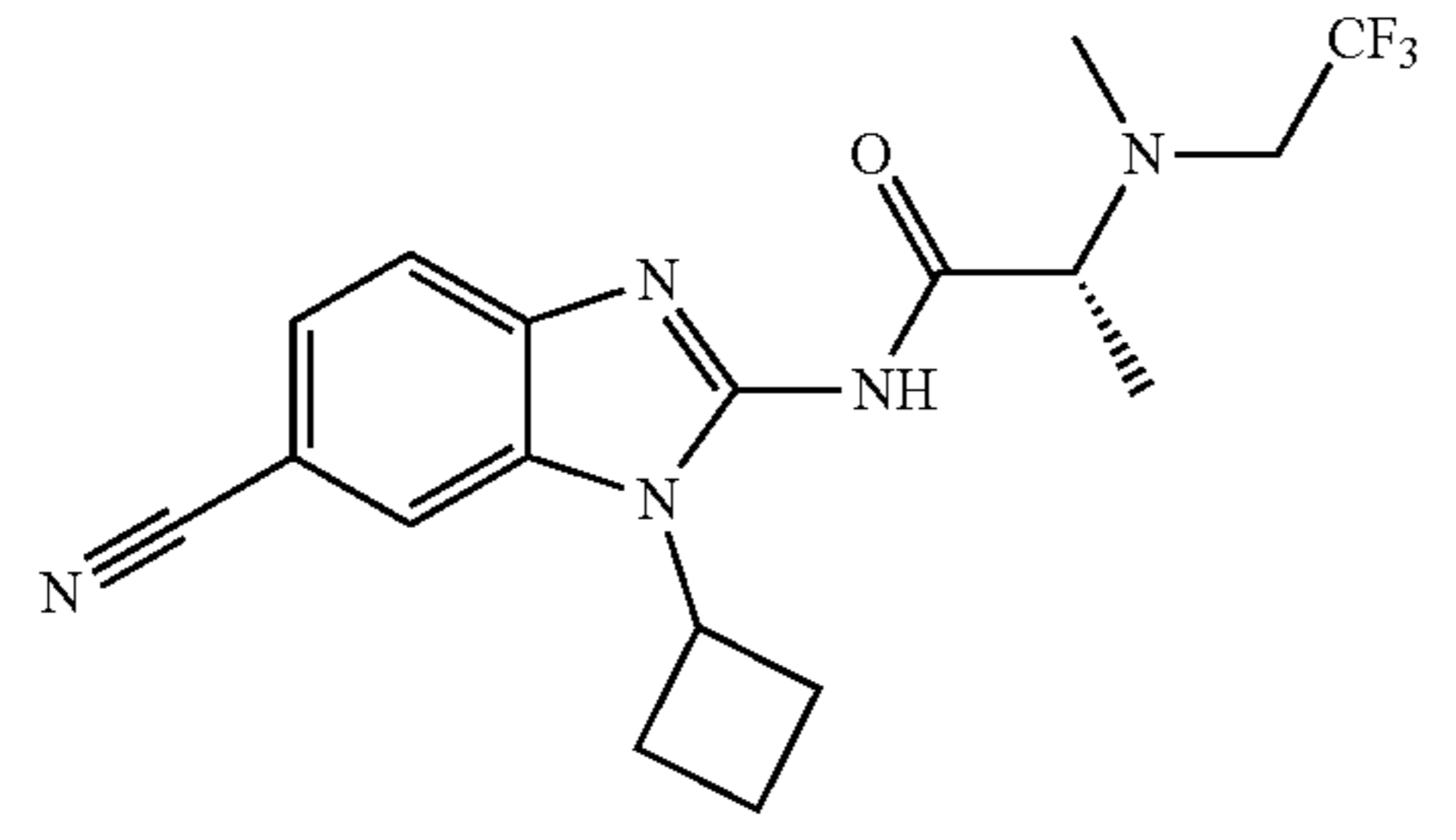
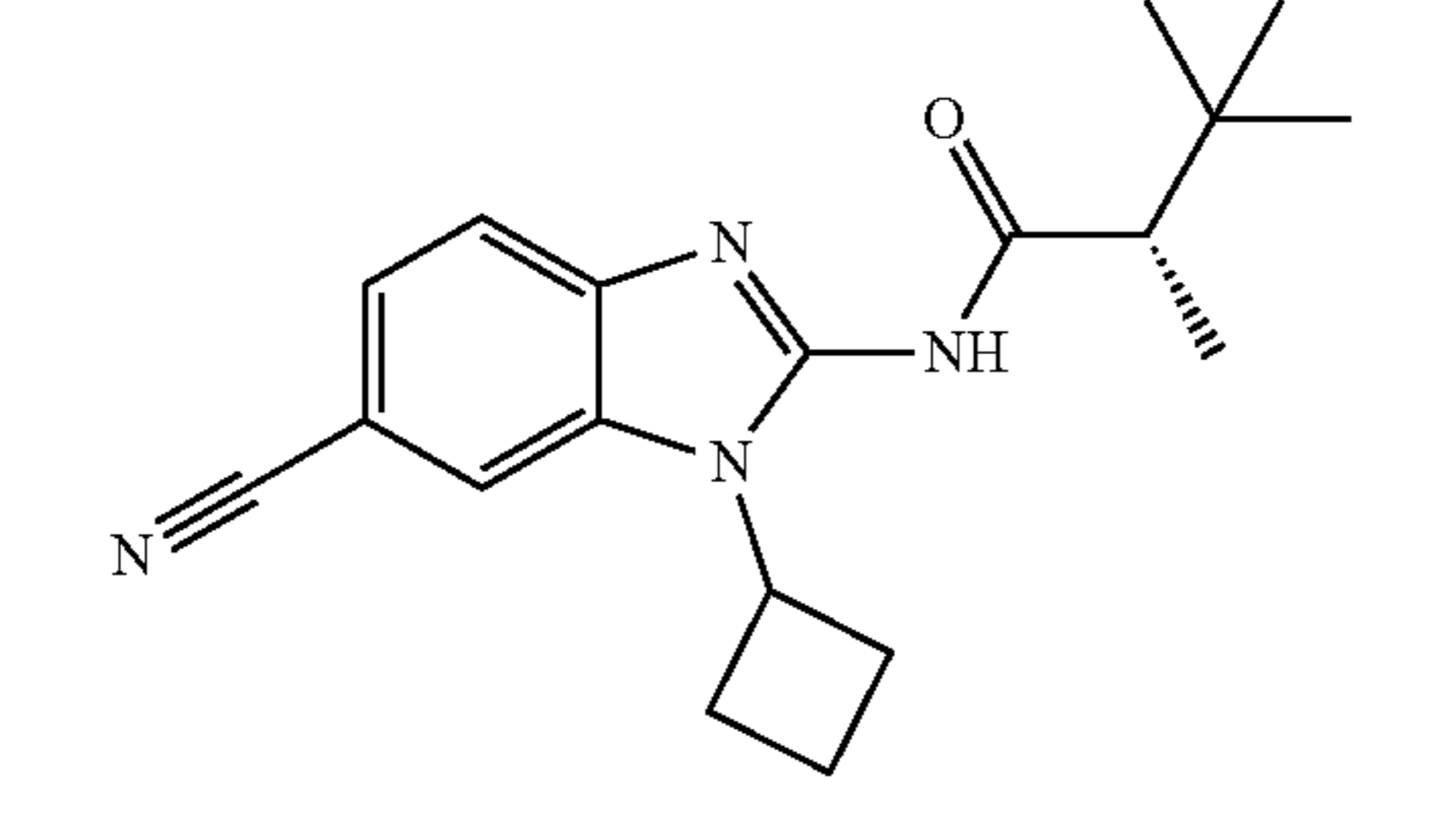
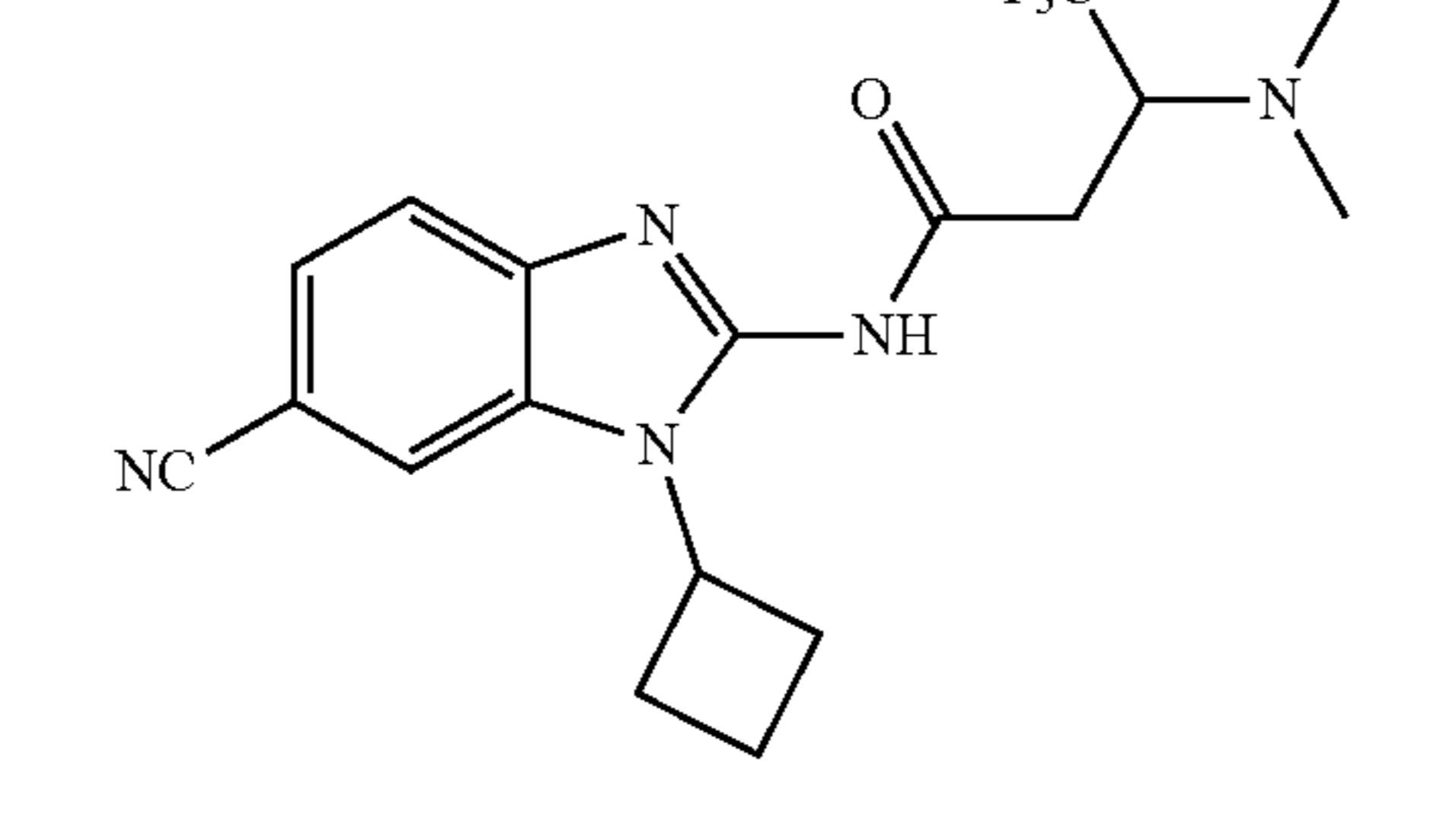
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Re-tension time (min)	LCMS m/z
21	 $C_{21}H_{21}N_5O_2$	(S)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-(pyridin-3-yl)butanamide	7	B	2.3	376
22	 $C_{18}H_{20}F_3N_5O$	(R)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2-(methyl(2,2,2-trifluoroethyl)amino)propanamide	7	B	3.6	380
23	 $C_{19}H_{24}N_4O$	(S)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2,3,3-trimethylbutanamide	7	A	5.3	325
24	 $C_{18}H_{20}F_3N_5O$	N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-(dimethylamino)-4,4,4-trifluorobutanamide	7	B	3.4	380

TABLE 1-continued

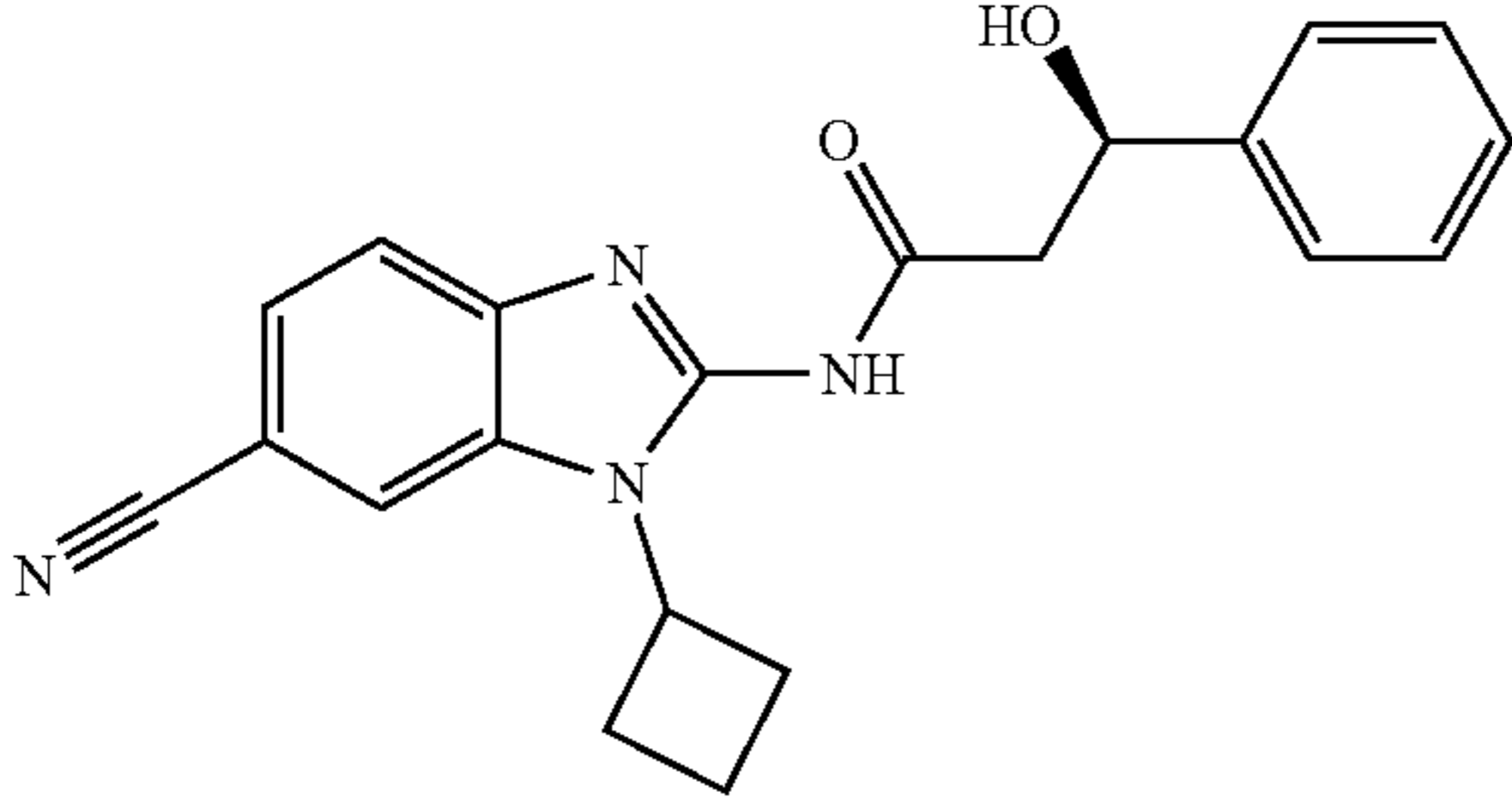
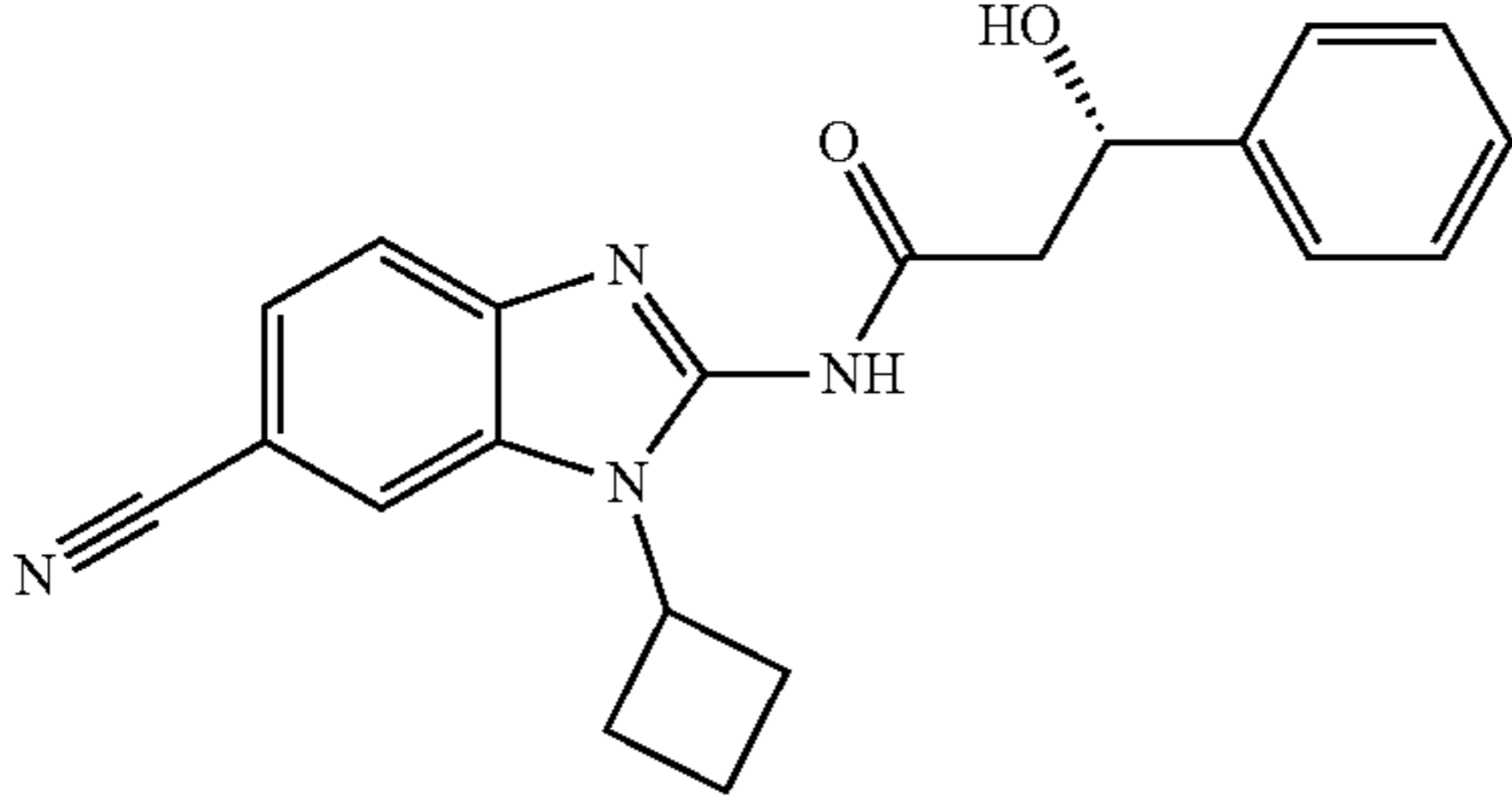
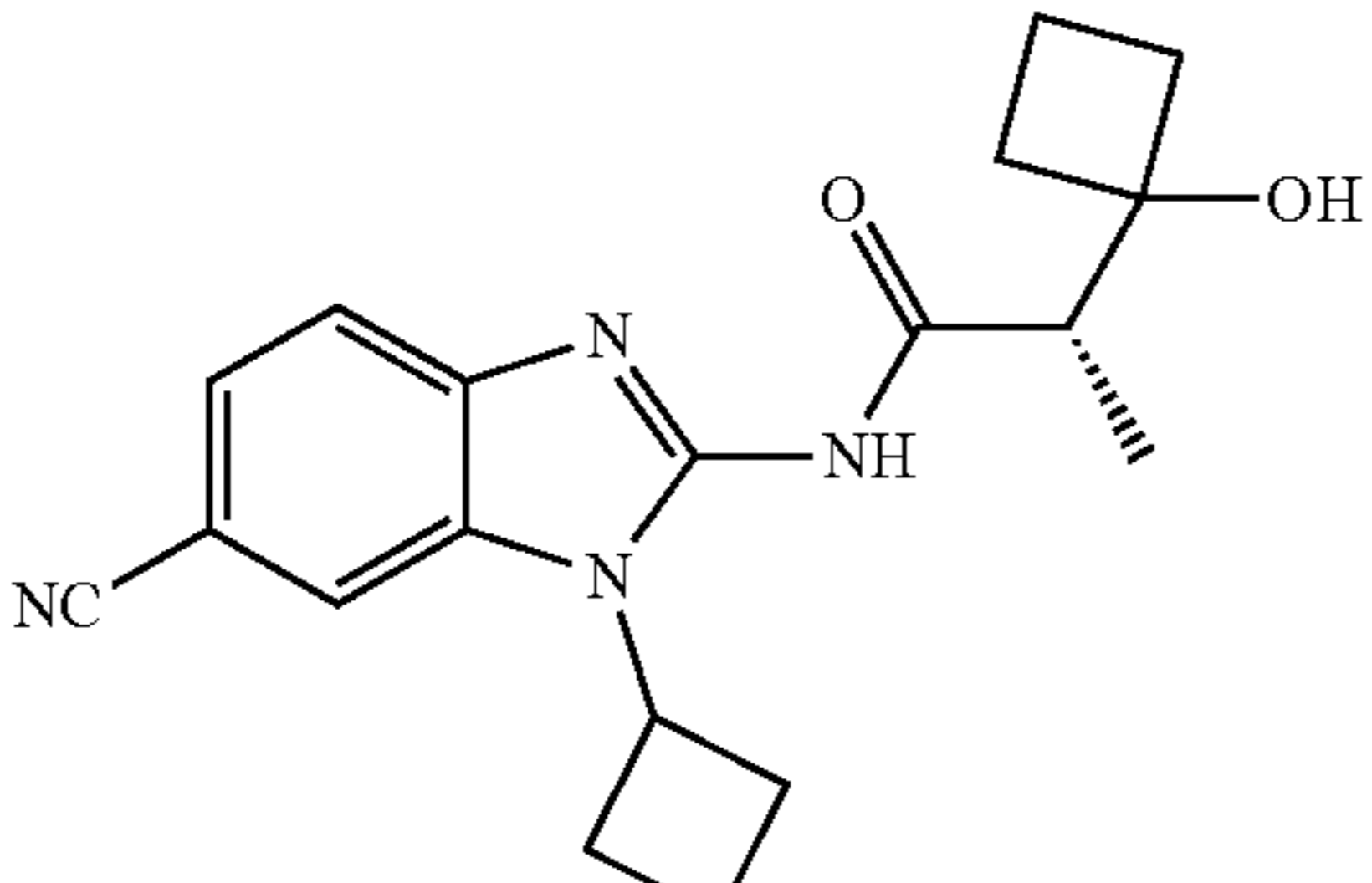
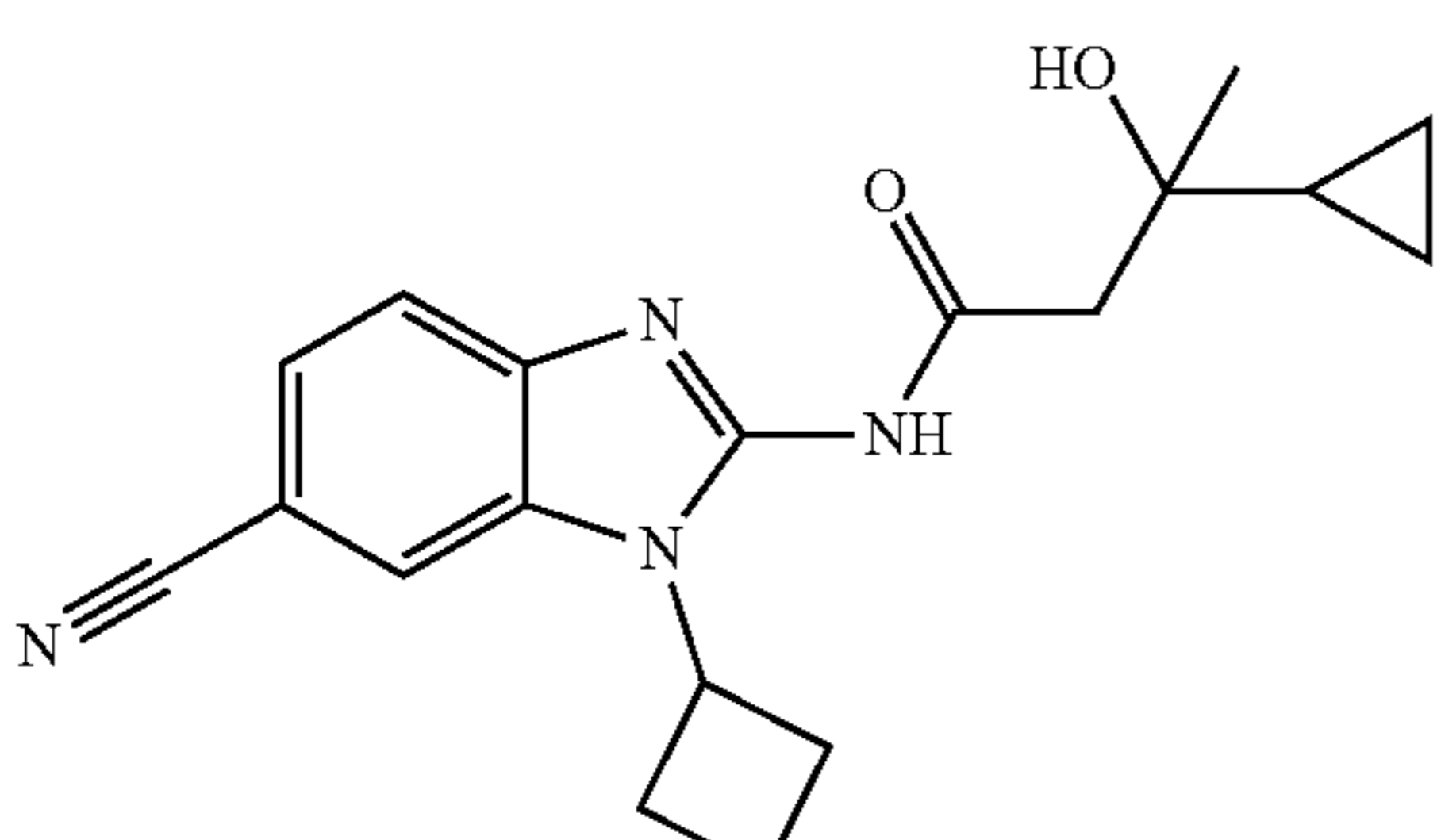
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Re-tension time (min)	LCMS m/z
25	 $C_{21}H_{20}N_4O_2$	(R)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylpropanamide	7	B	3.1	361
26	 $C_{21}H_{20}N_4O_2$	(S)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylpropanamide	7	B	3.1	361
27	 $C_{19}H_{22}N_4O_2$	(S)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2-(1-hydroxycyclobutyl)propanamide	7	B	3.1	339
28	 $C_{19}H_{22}N_4O_2$	N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-cyclopropyl-3-hydroxybutanamide	7	B	3.1	339

TABLE 1-continued

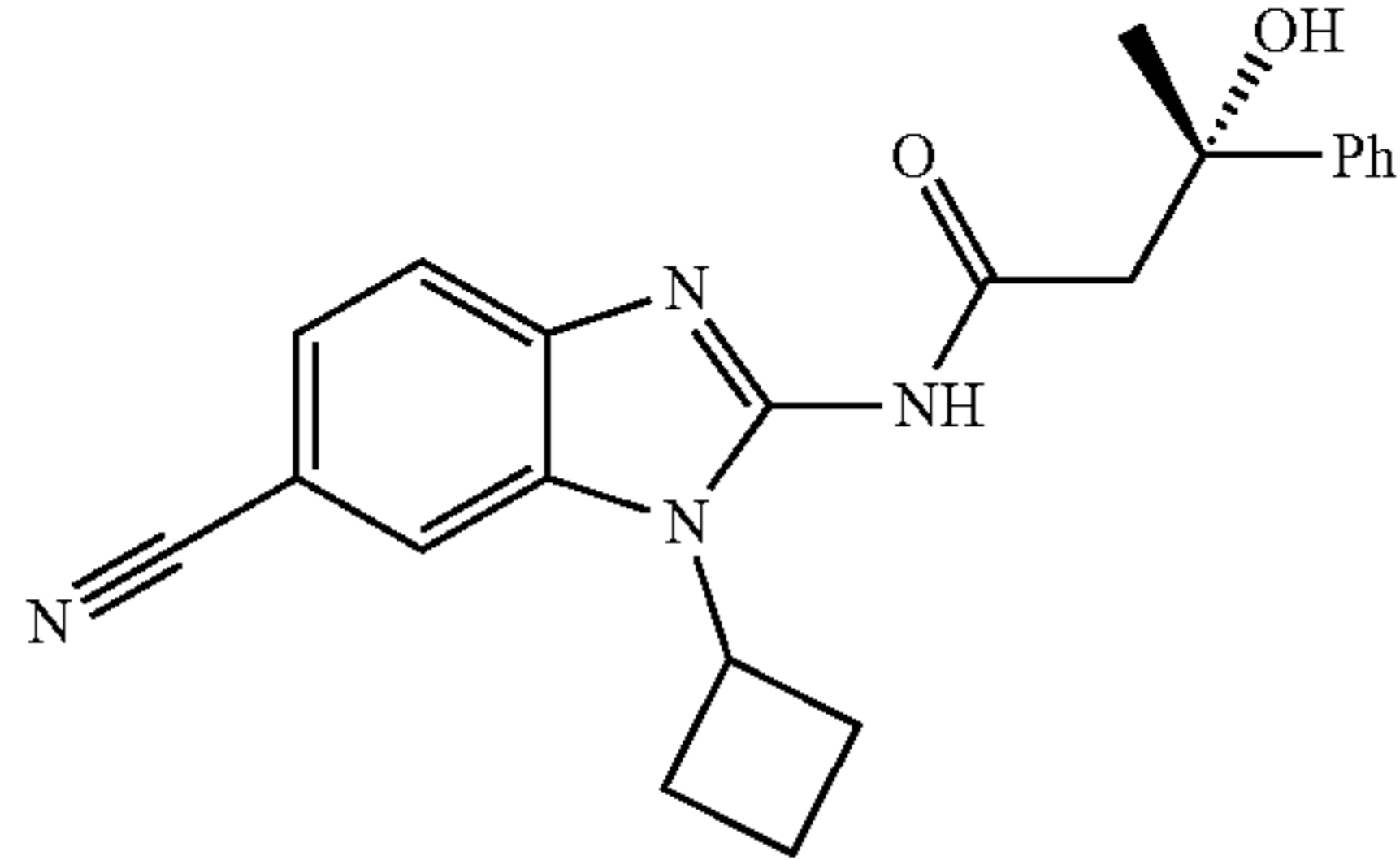
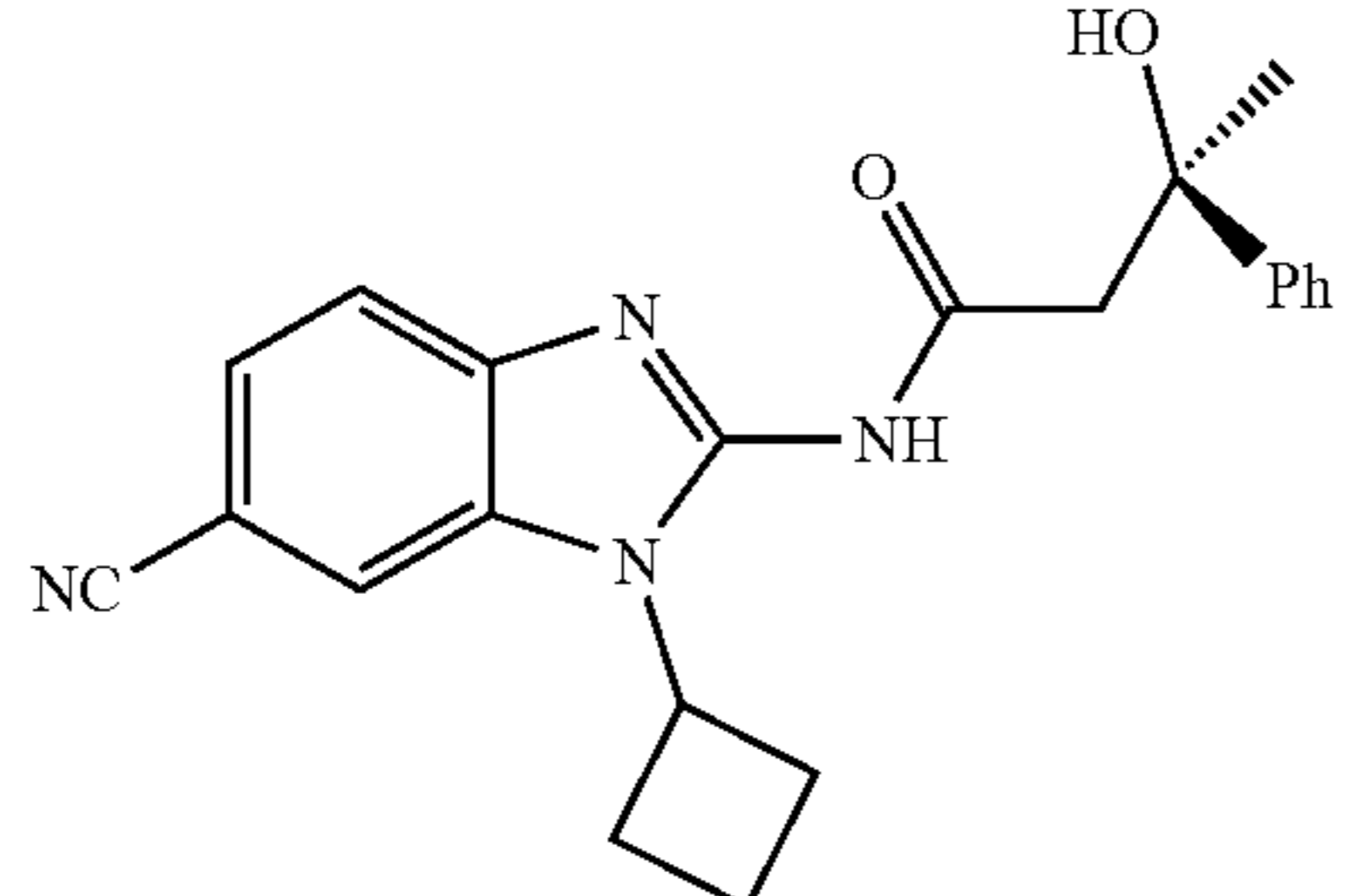
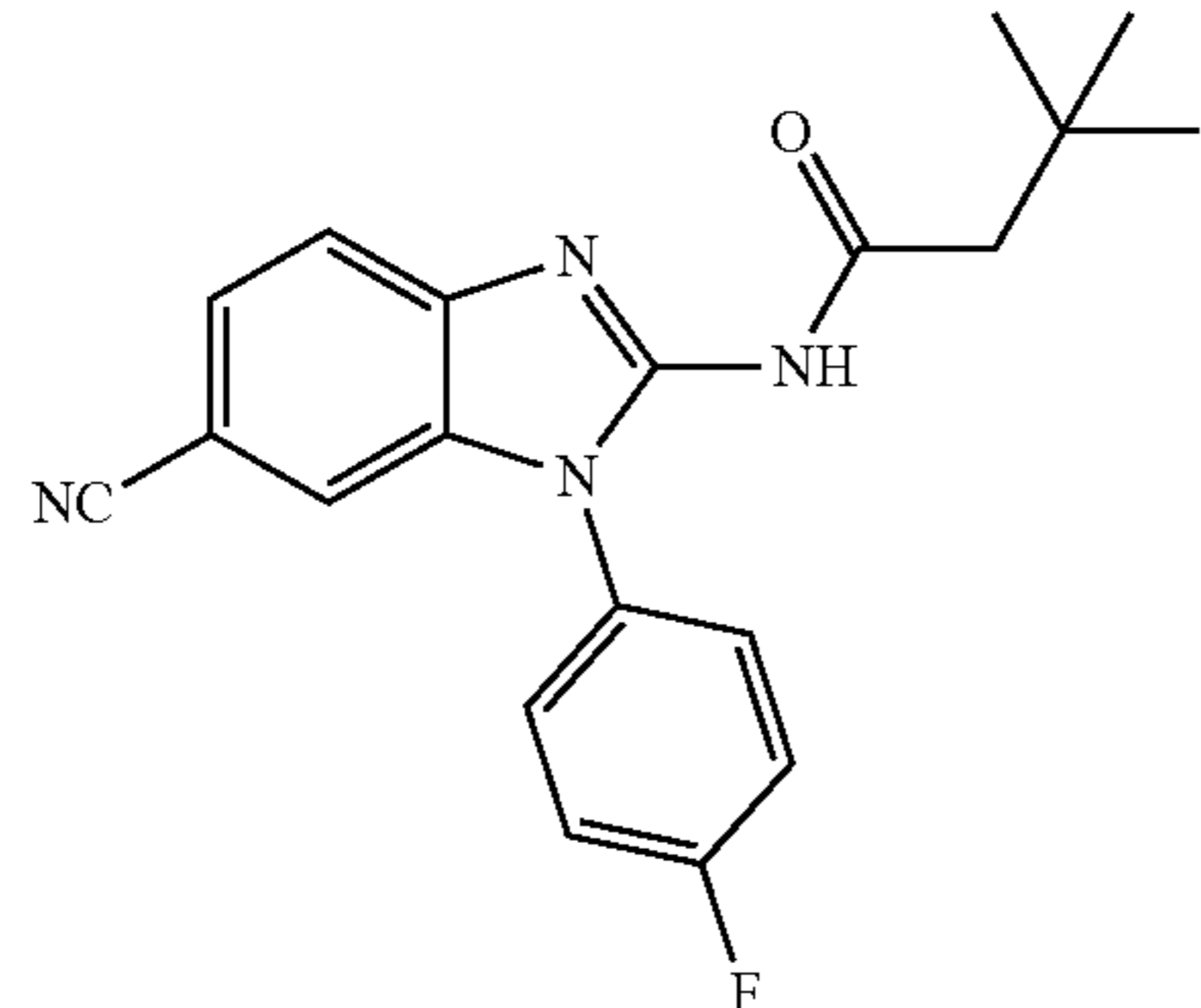
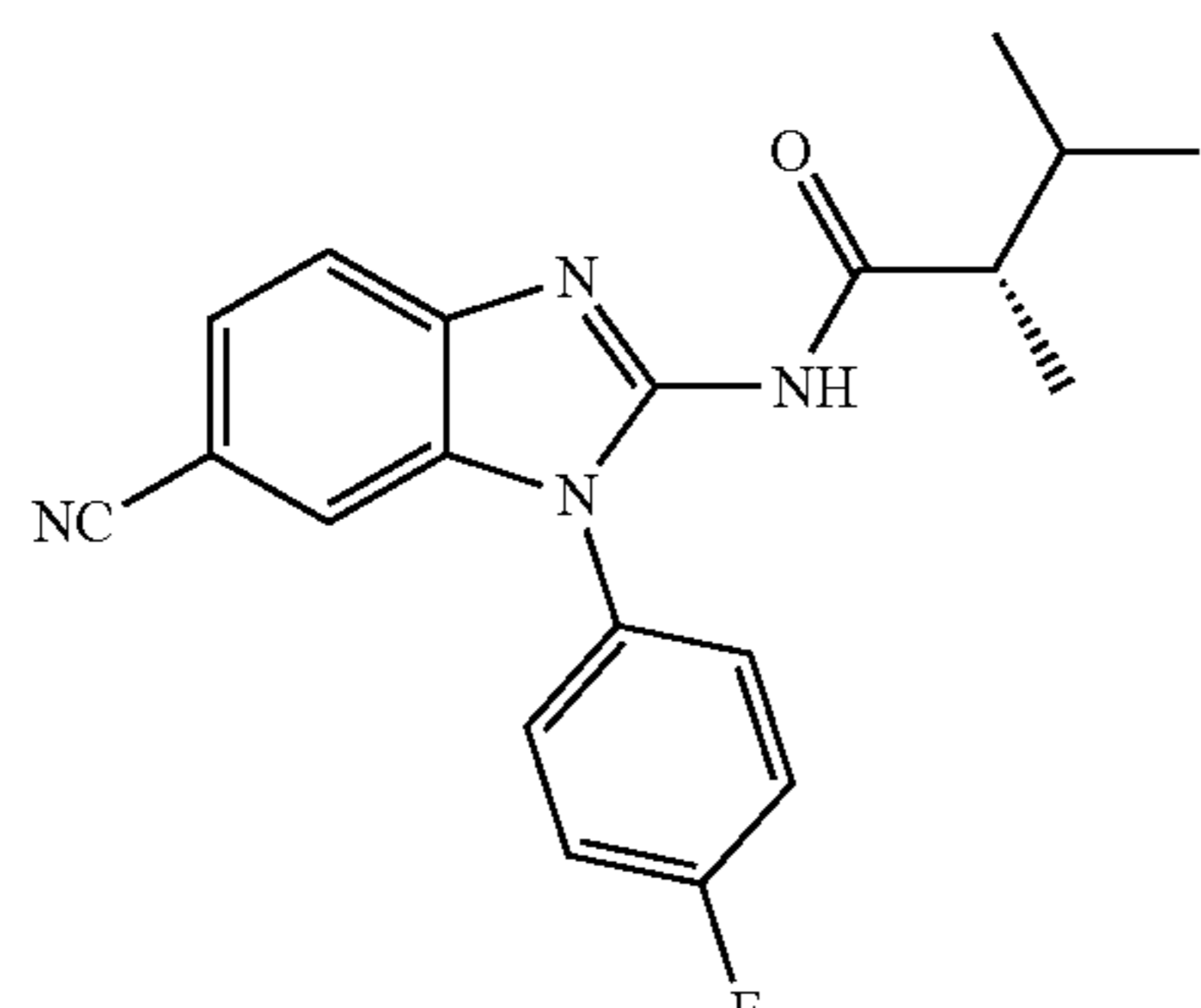
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
29	 <chem>C22H22N4O2</chem>	(S)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	10	B	3.4	375
30	 <chem>C22H22N4O2</chem>	(R)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	10	B	3.4	375
31	 <chem>C20H19FN4O</chem>	N-(6-cyano-1-(4-fluorophenyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7	B	3.5	351
32	 <chem>C20H19FN4O</chem>	(S)-N-(6-cyano-1-(4-fluorophenyl)-1H-benzo[d]imidazol-2-yl)-2,3-dimethylbutanamide	7	B	3.5	351

TABLE 1-continued

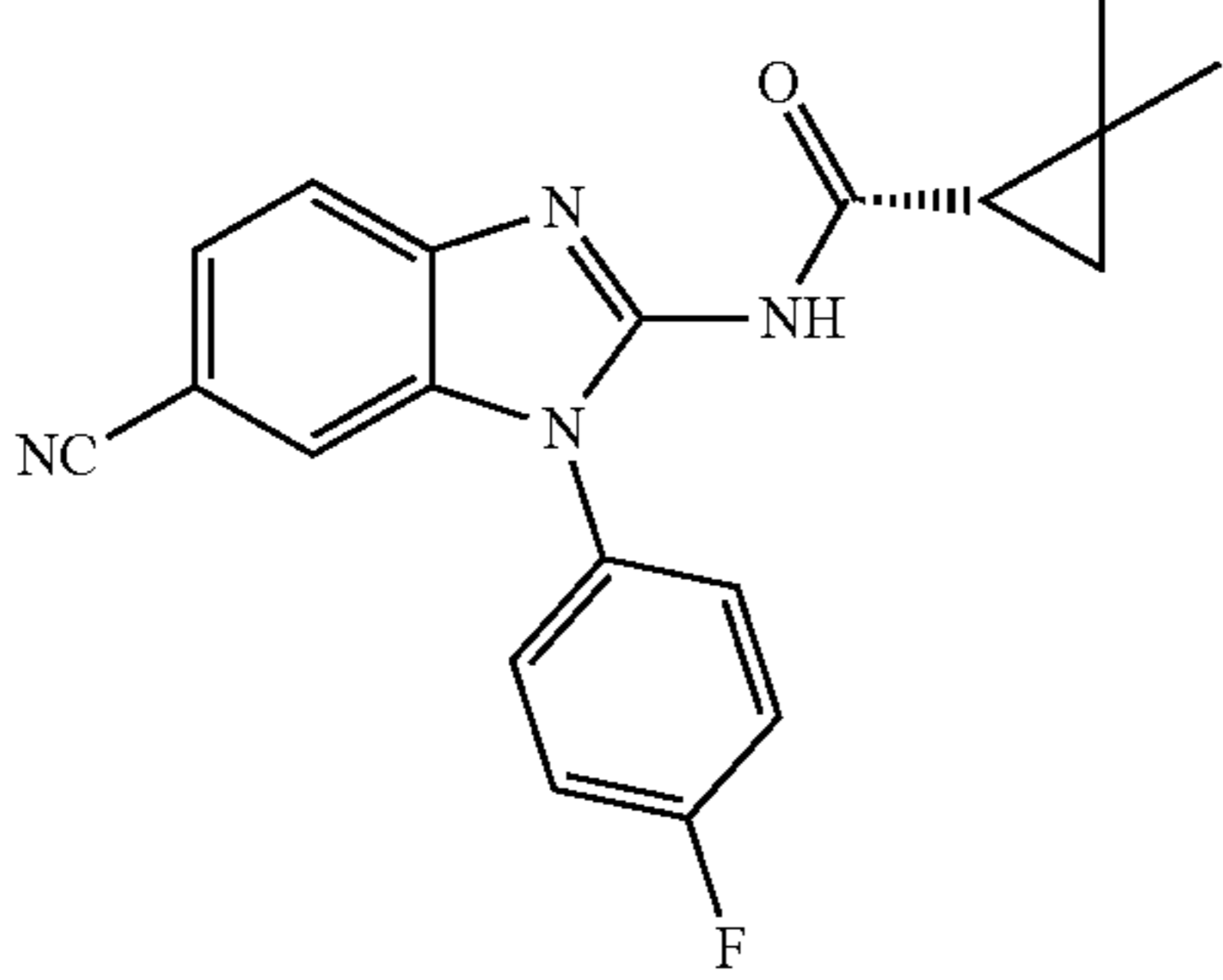
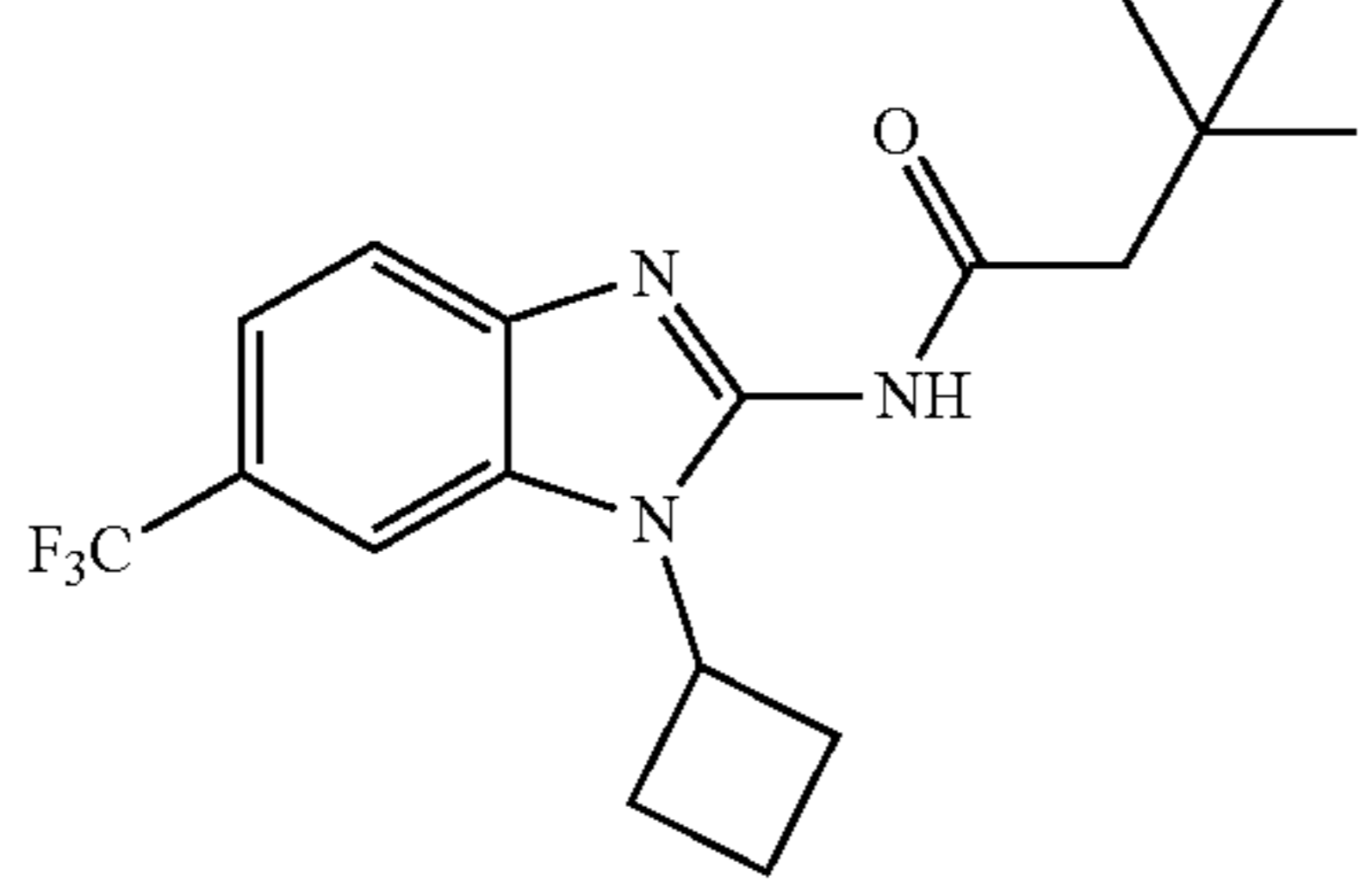
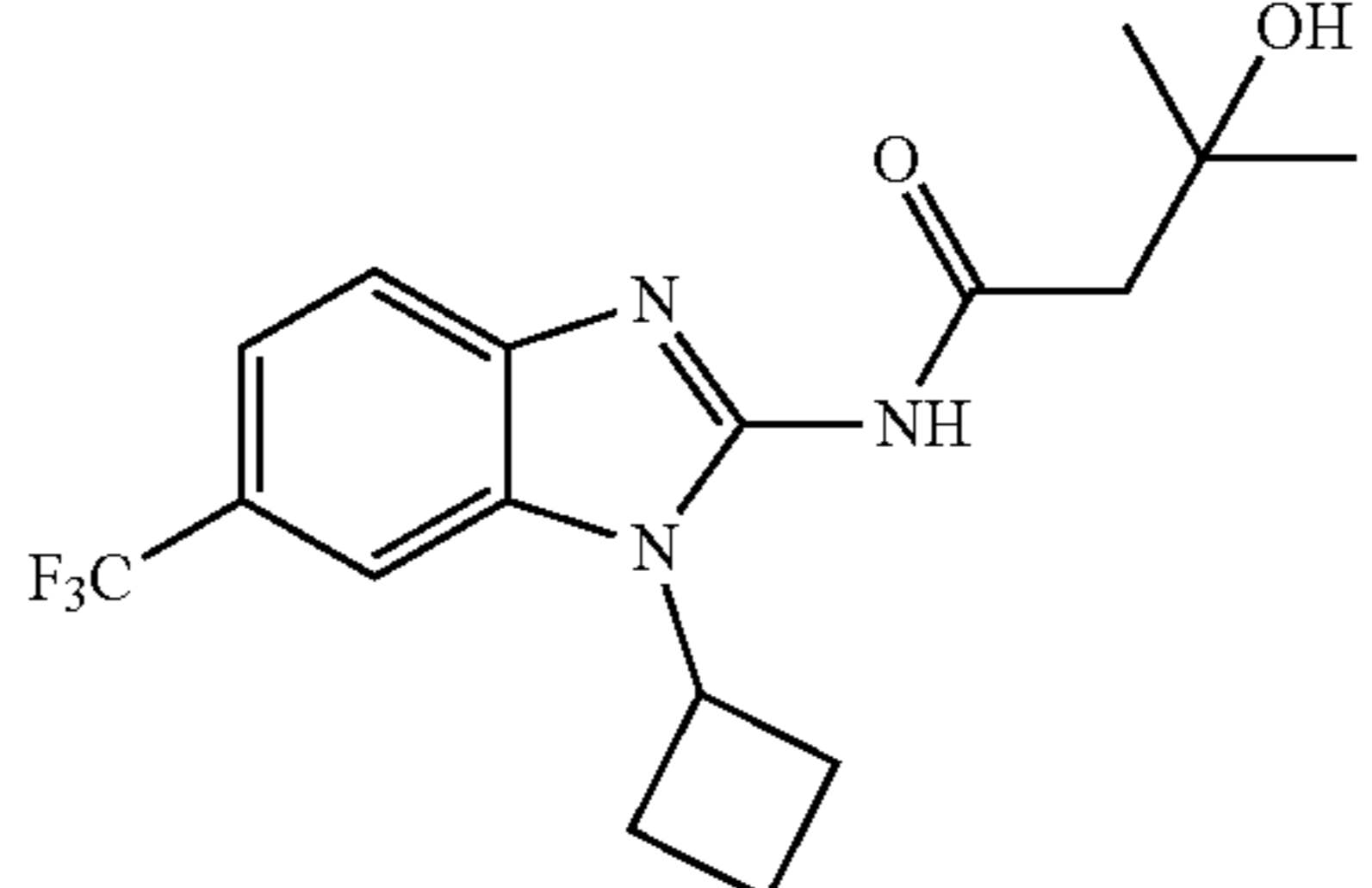
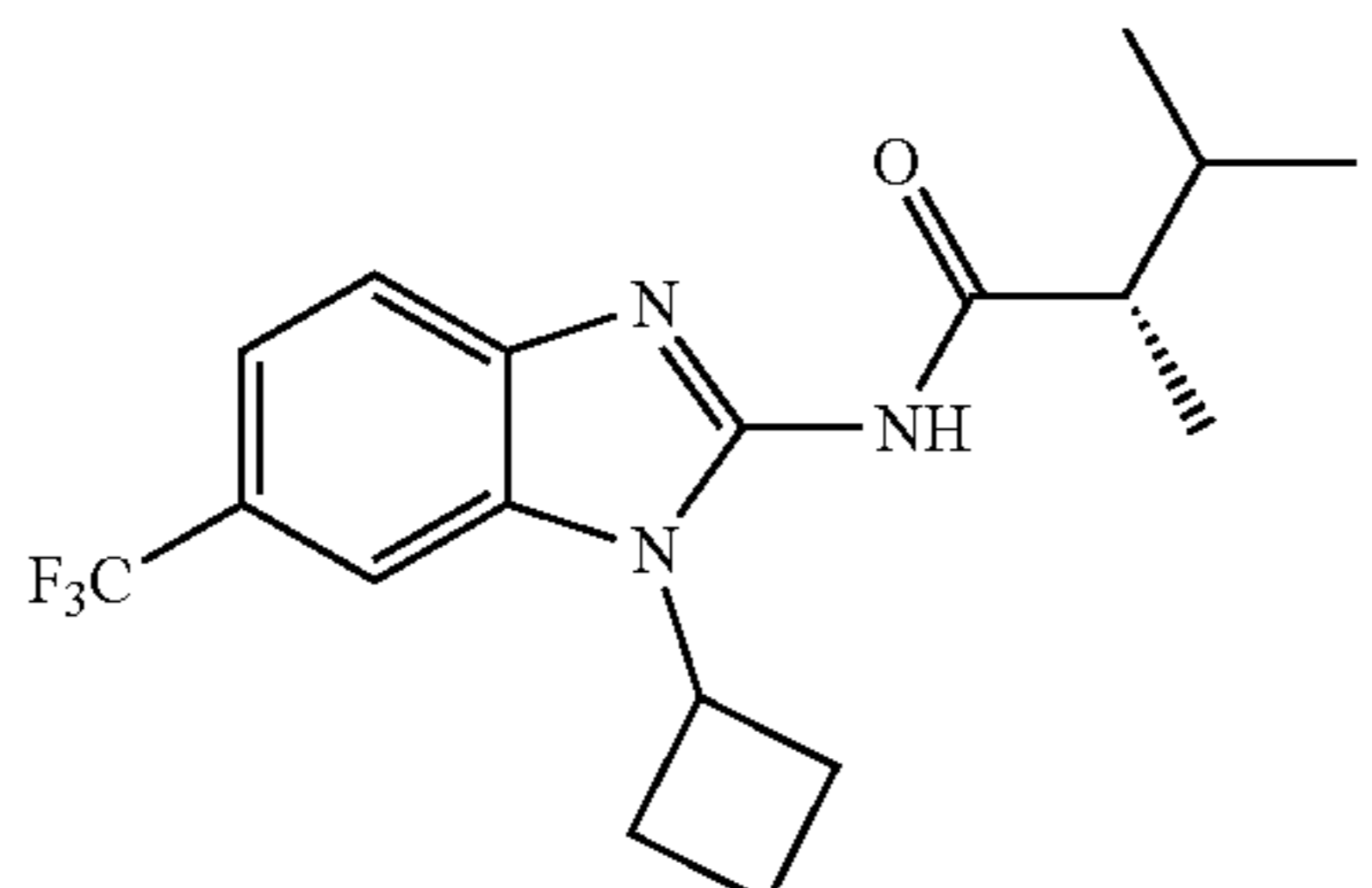
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
33	 <p style="text-align: center;">$C_{20}H_{17}FN_4O$</p>	(S)-N-(6-cyano-1-(4-fluorophenyl)-1H-benzo[d]imidazol-2-yl)-2,2-dimethylcyclopropane-1-carboxamide	7	B	3.4	349
34	 <p style="text-align: center;">$C_{18}H_{22}F_3N_3O$</p>	N-(1-cyclobutyl-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7	B	3.9	354
35	 <p style="text-align: center;">$C_{17}H_{20}F_3N_3O_2$</p>	N-(1-cyclobutyl-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-methylbutanamide	7	B	3.2	356
36	 <p style="text-align: center;">$C_{18}H_{22}F_3N_3O$</p>	(S)-N-(1-cyclobutyl-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-2,3-dimethylbutanamide	7	B	4.0	354

TABLE 1-continued

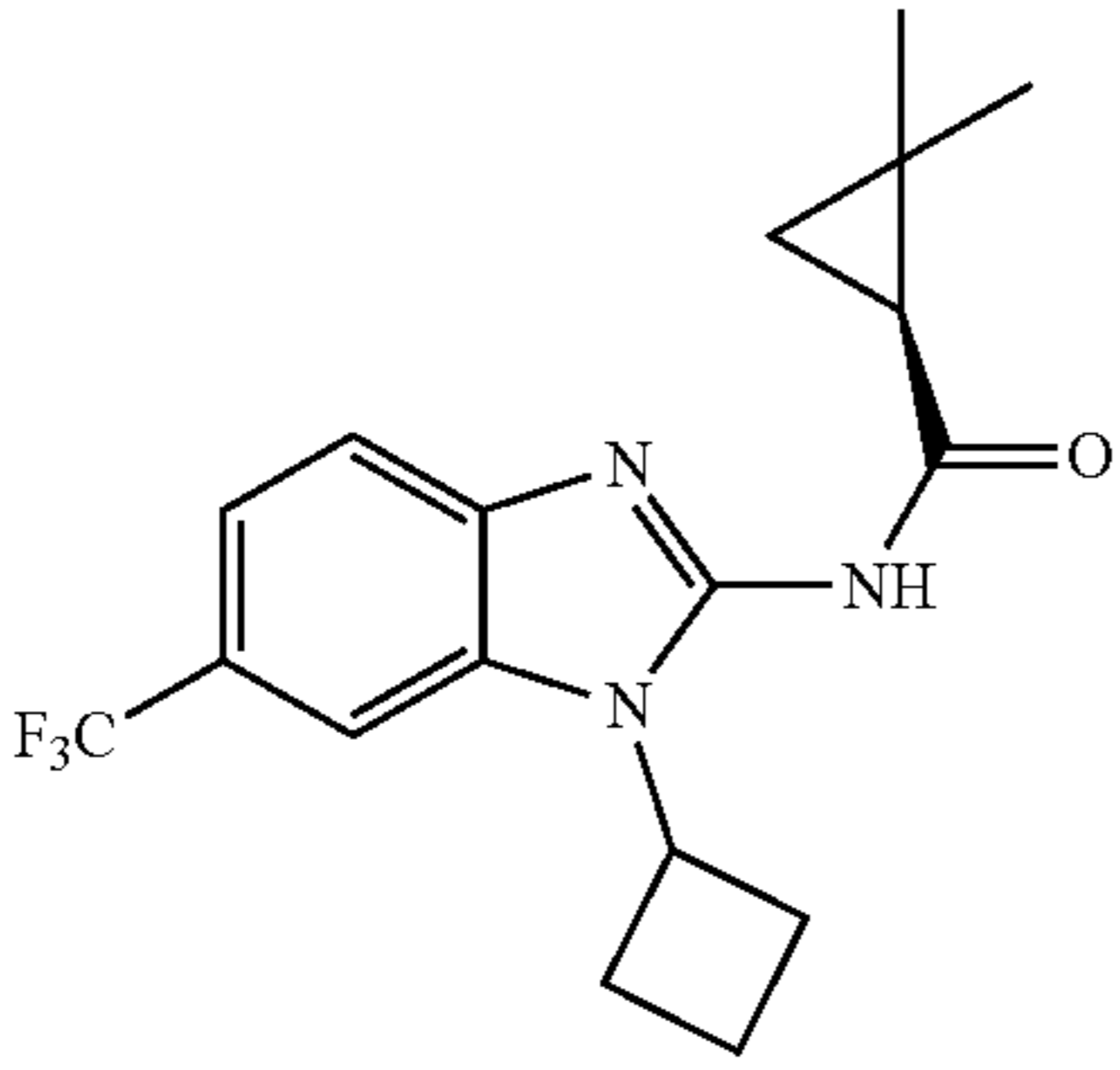
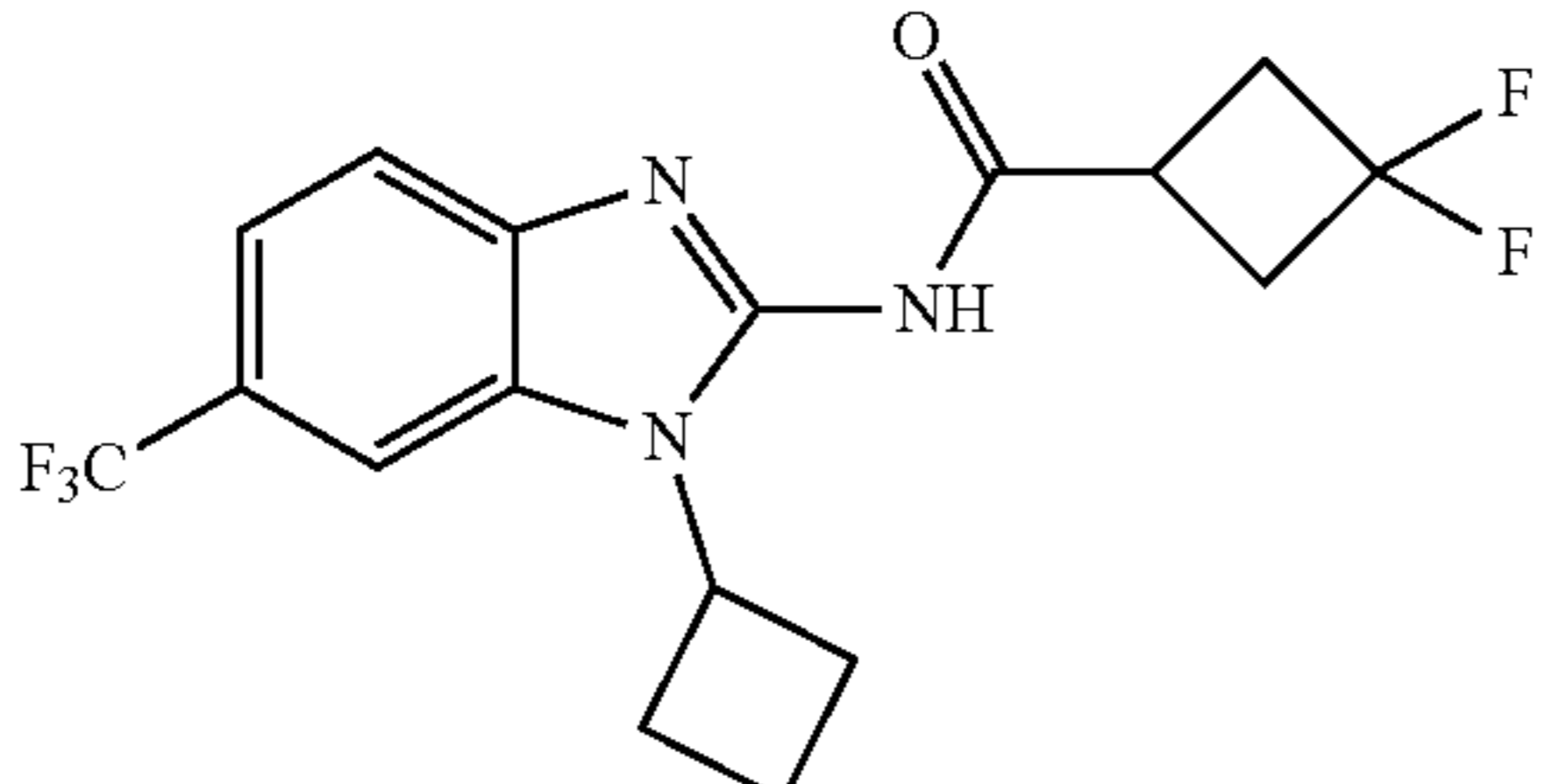
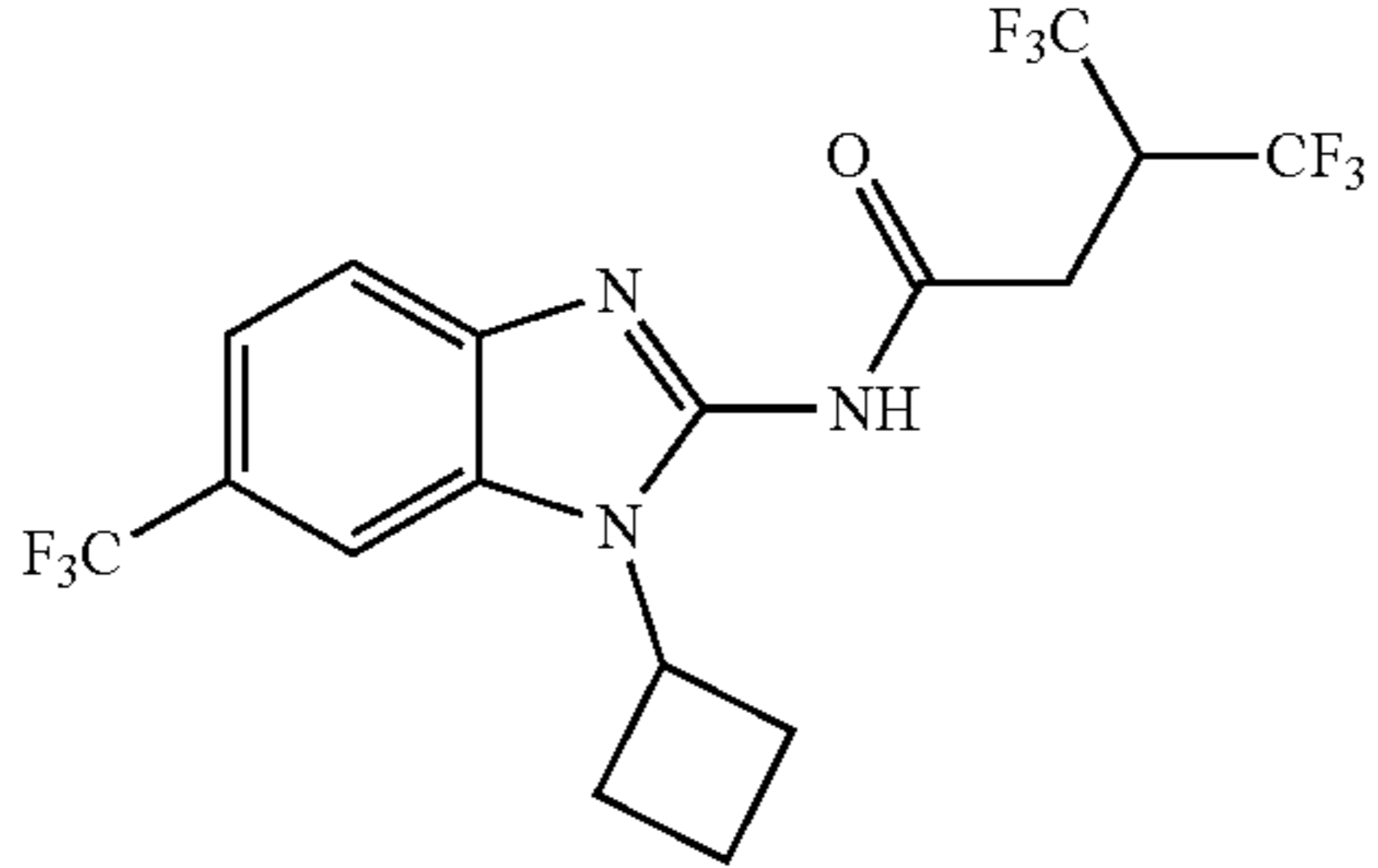
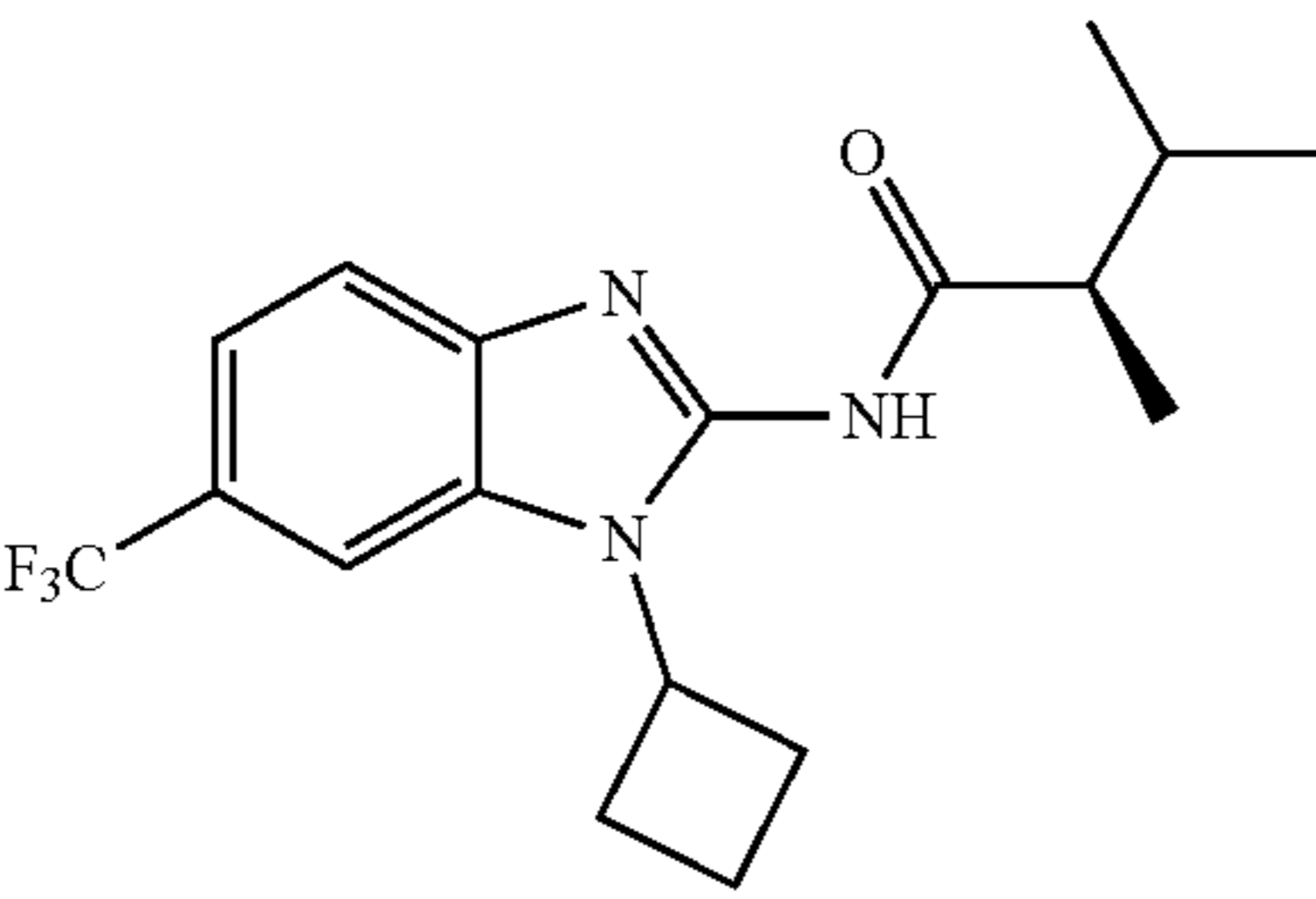
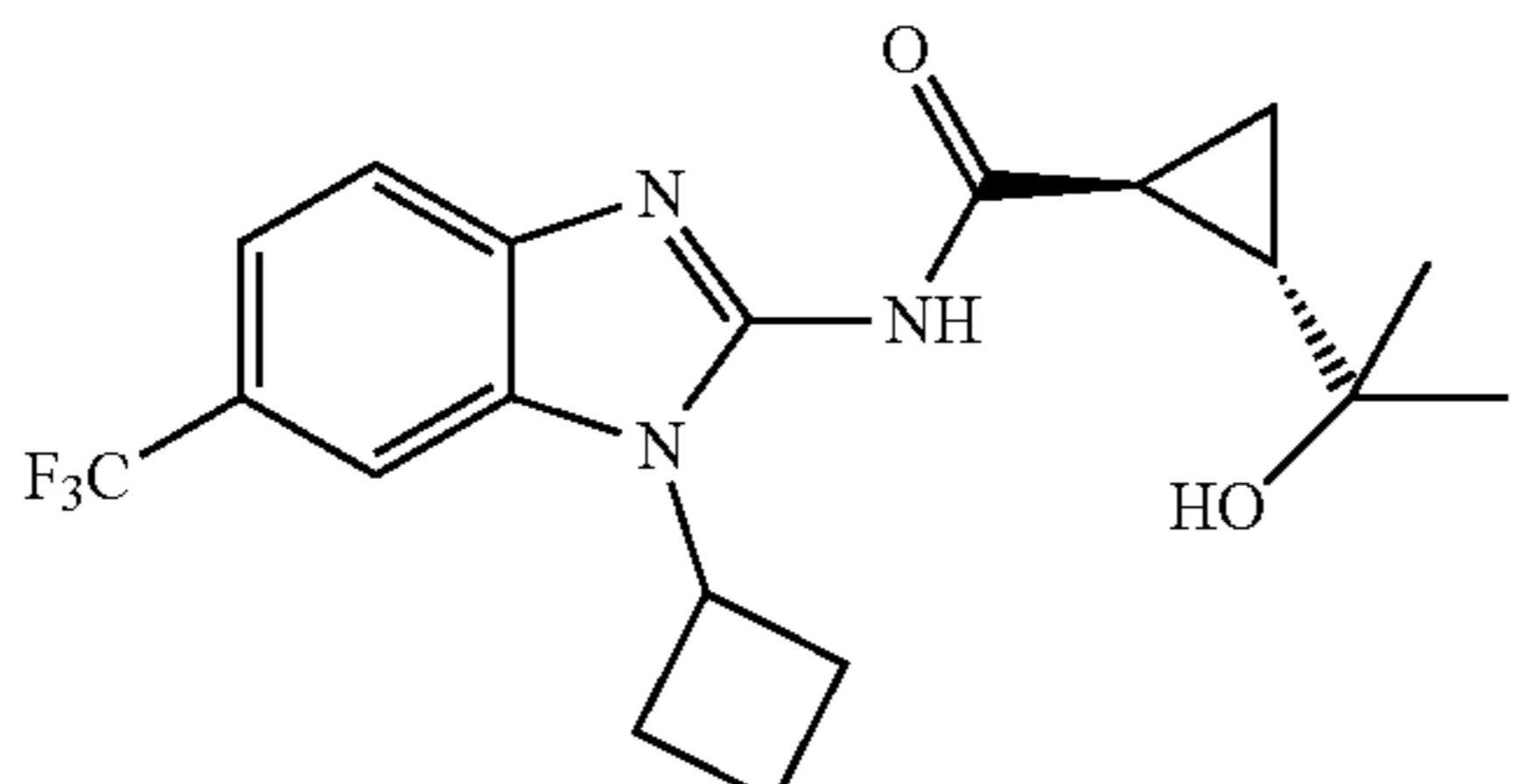
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
37	 <p>$C_{18}H_{20}F_3N_3O$</p>	(S)-N-(1-cyclobutyl-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-2,2-dimethylcyclopropane-1-carboxamide	7	B	3.8	352
38	 <p>$C_{17}H_{16}F_5N_3O$</p>	N-(1-cyclobutyl-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-3,3-difluorocyclobutane-1-carboxamide	7	B	4.1	374
39	 <p>$C_{17}H_{14}F_9N_3O$</p>	N-(1-cyclobutyl-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-4,4,4-trifluoro-3-(trifluoromethyl)butanamide	7	B	4.6	448
40	 <p>$C_{18}H_{22}F_3N_3O$</p>	(R)-N-(1-cyclobutyl-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-2,3-dimethylbutanamide	7	B	4.0	354
41		(1S,2S)-N-(1-cyclobutyl-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-2-(2-hydroxypropan-2-yl)cyclopropane-1-carboxamide	7	B	3.2	382

TABLE 1-continued

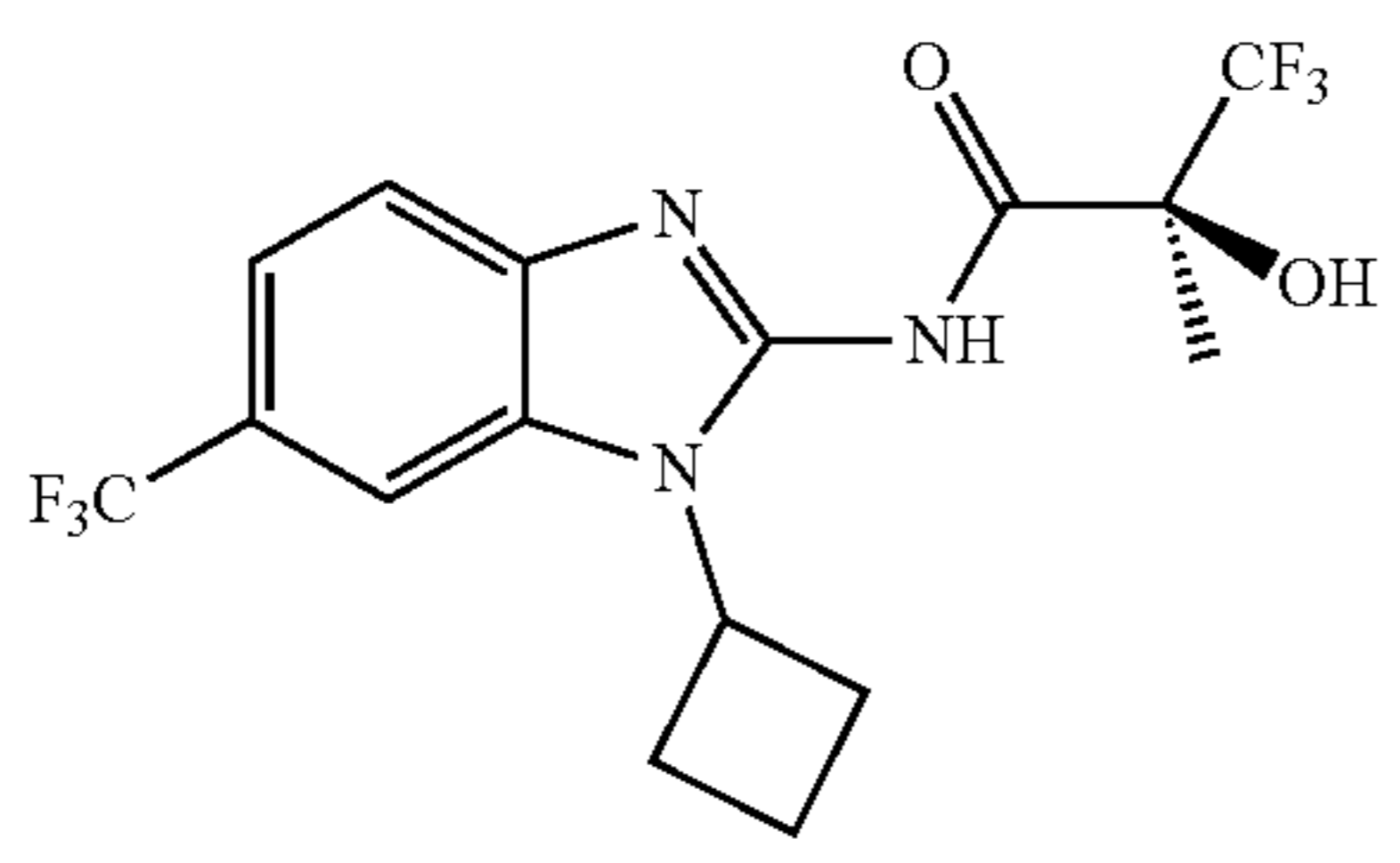
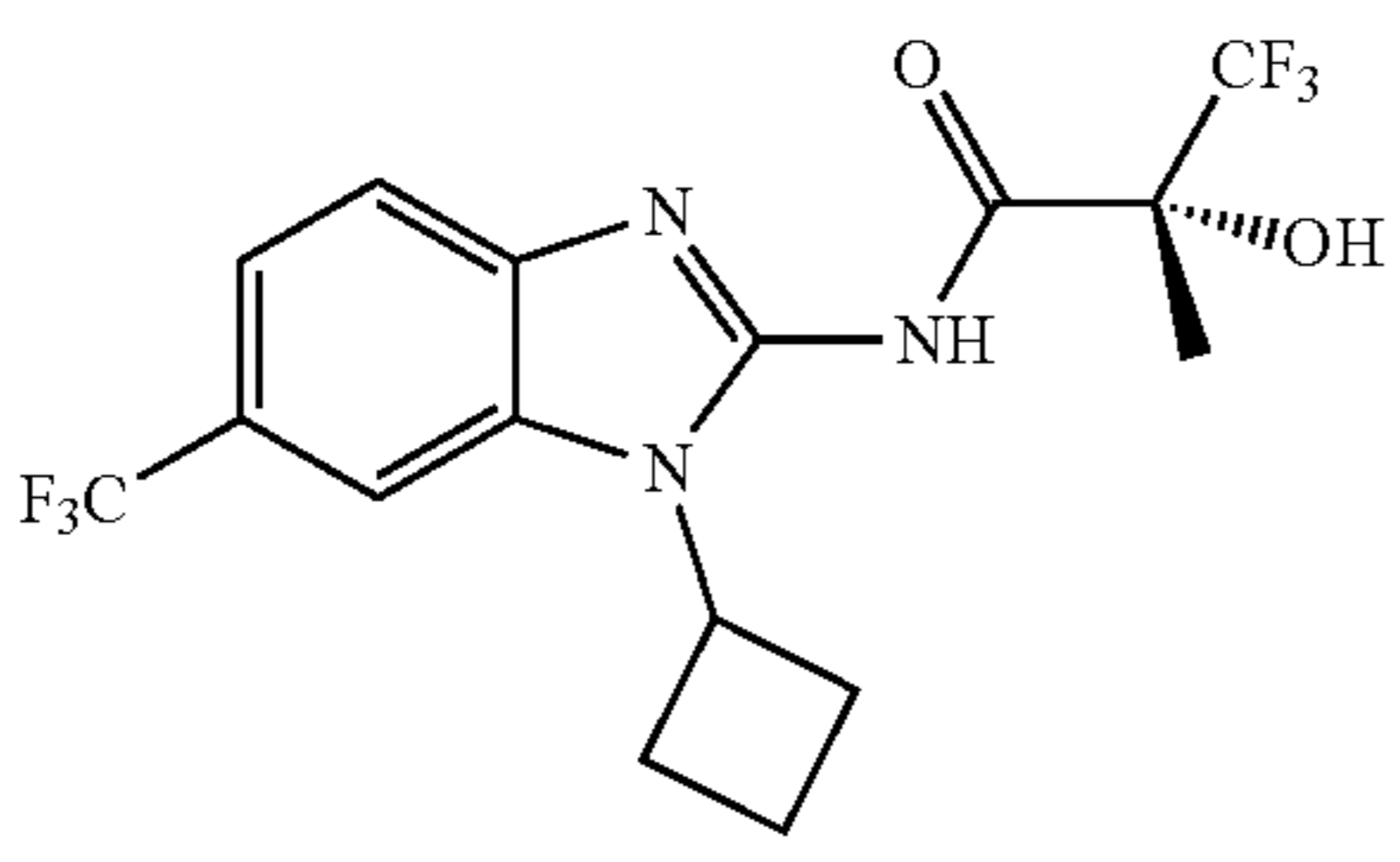
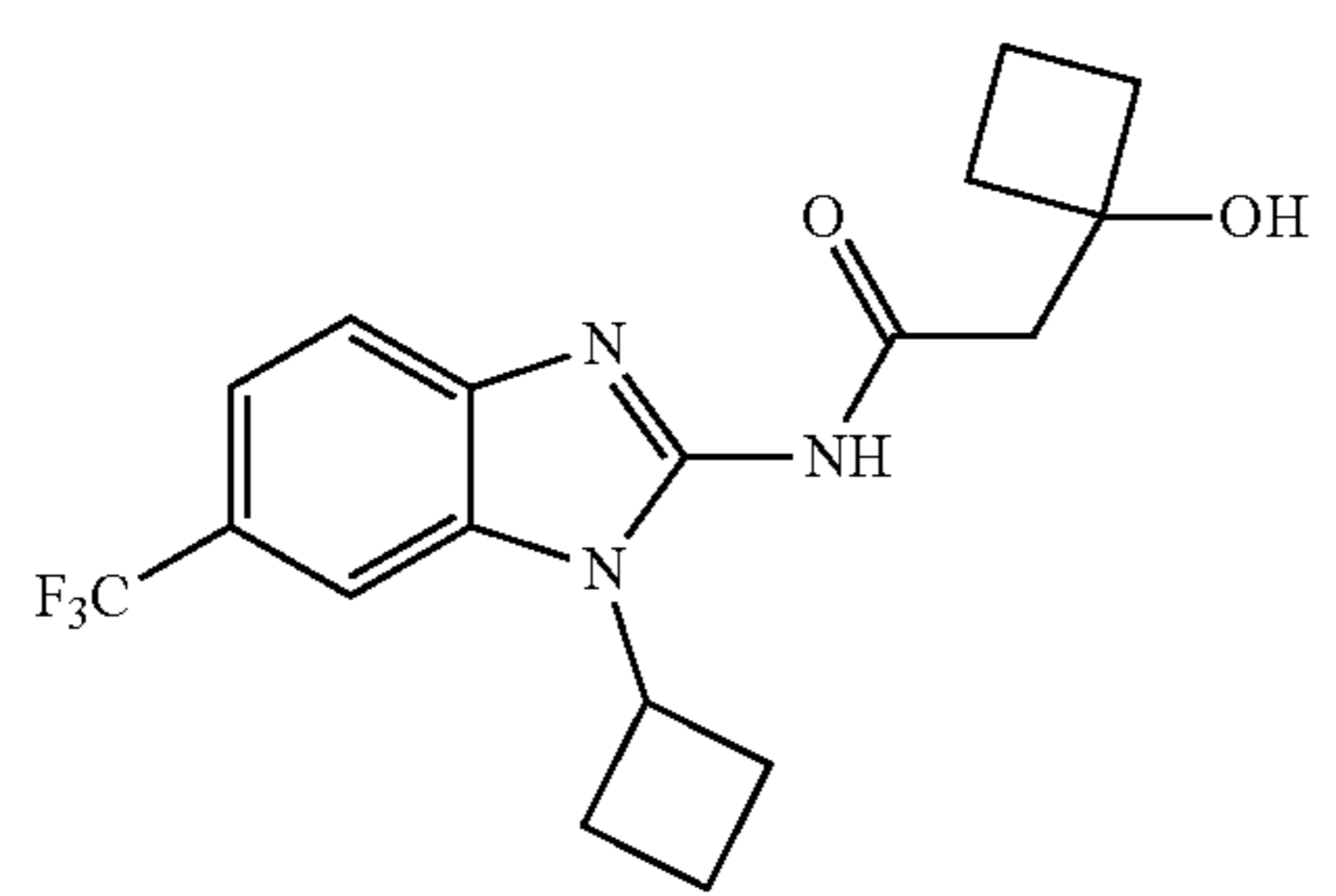
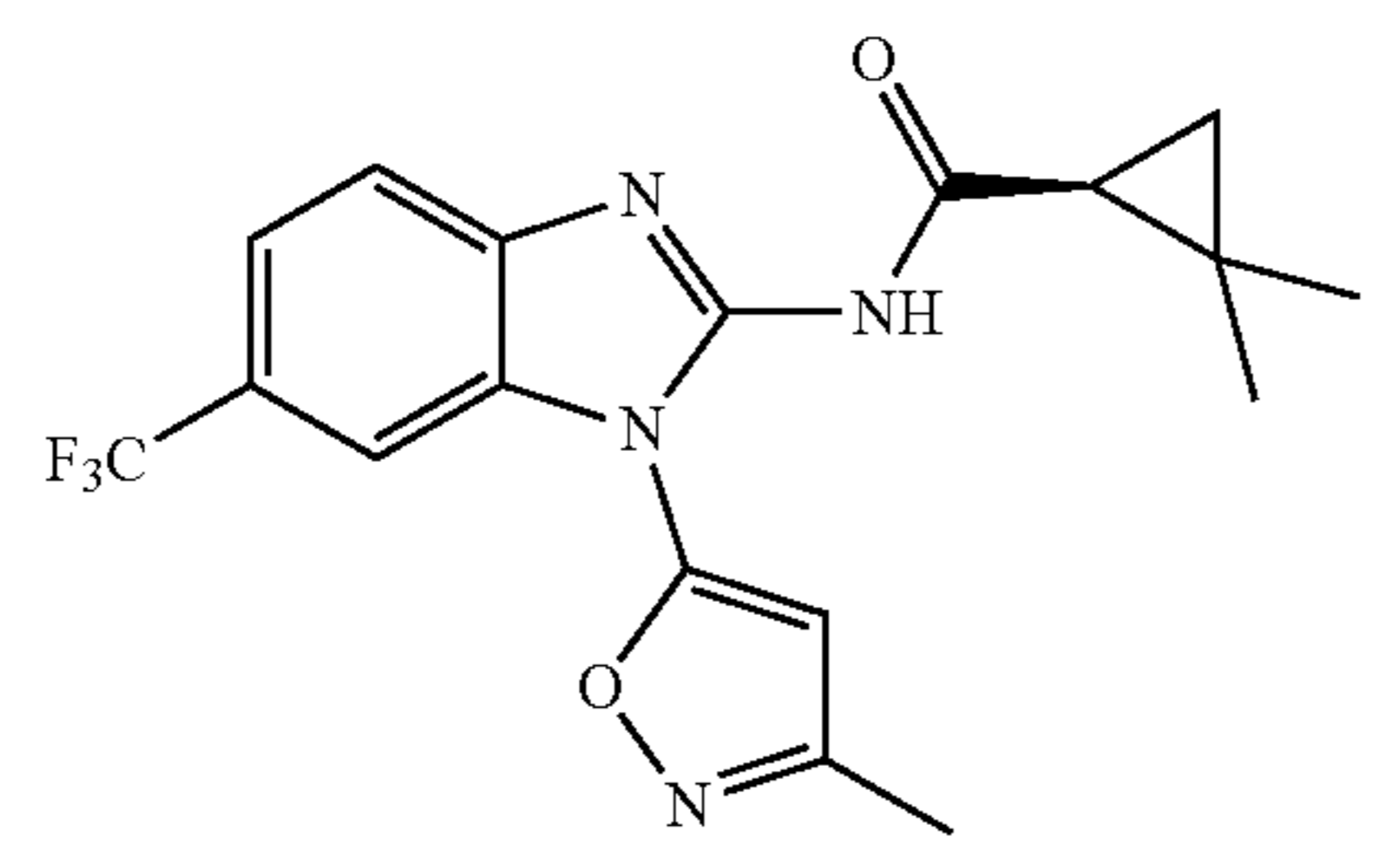
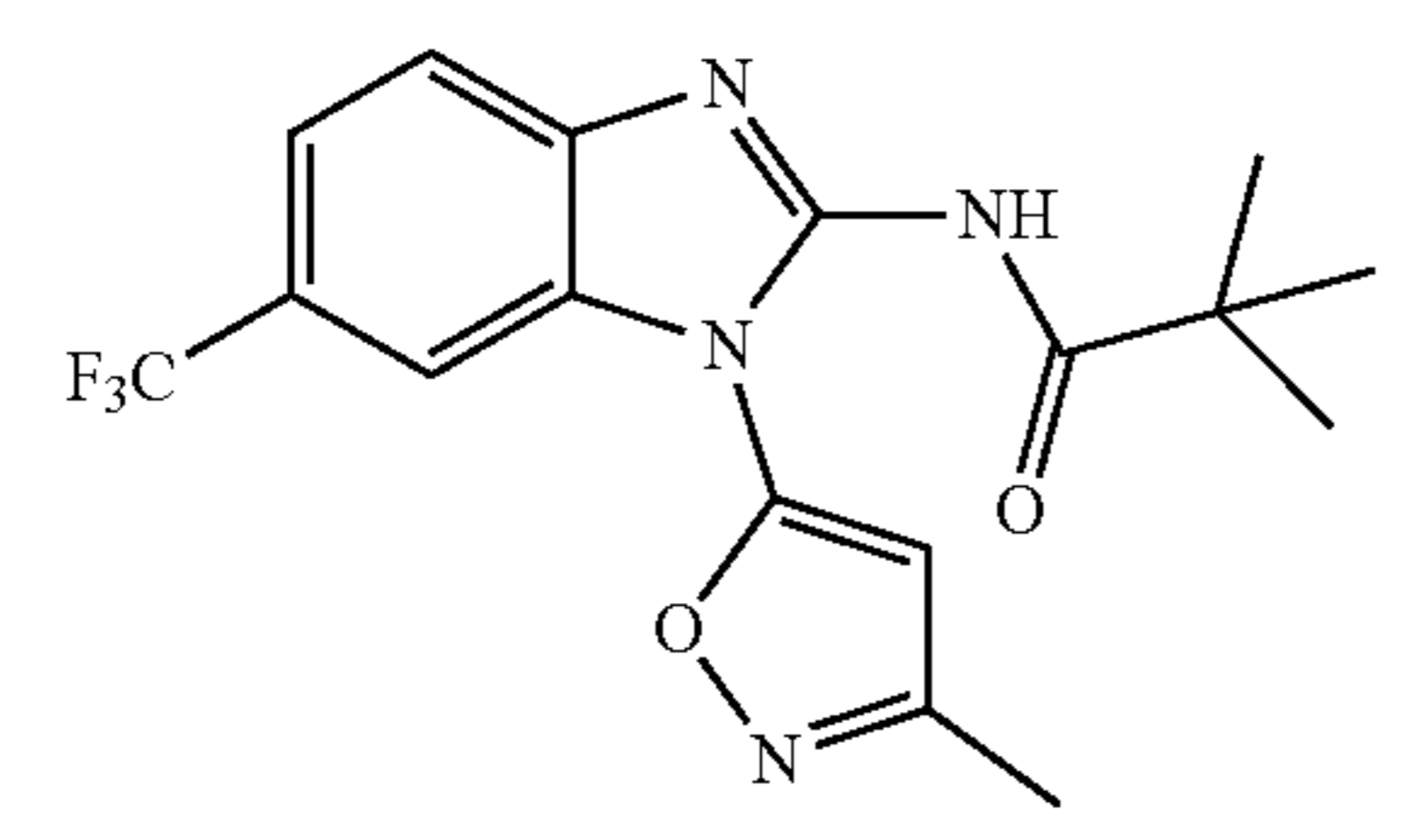
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
42	$C_{19}H_{22}F_3N_3O_2$ 	(S)-N-(1-cyclobutyl-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide	7	B	4.3	396
43	$C_{16}H_{15}F_6N_3O_2$ 	(R)-N-(1-cyclobutyl-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide	7	B	4.3	369
44	$C_{16}H_{15}F_6N_3O_2$ 	N-(1-cyclobutyl-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-2-(1-hydroxycyclobutyl)acetamide	7	B	3.4	368
45	$C_{18}H_{20}F_3N_3O_2$ 	(S)-2,2-dimethyl-N-(1-(3-methylisoxazol-5-yl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)cyclopropane-1-carboxamide	11	B	3.9	379
46	$C_{18}H_{17}F_3N_4O_2$ 	3,3-dimethyl-N-(1-(3-methylisoxazol-5-yl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)butanamide	9	B	3.9	381
	$C_{18}H_{19}F_3N_4O_2$					

TABLE 1-continued

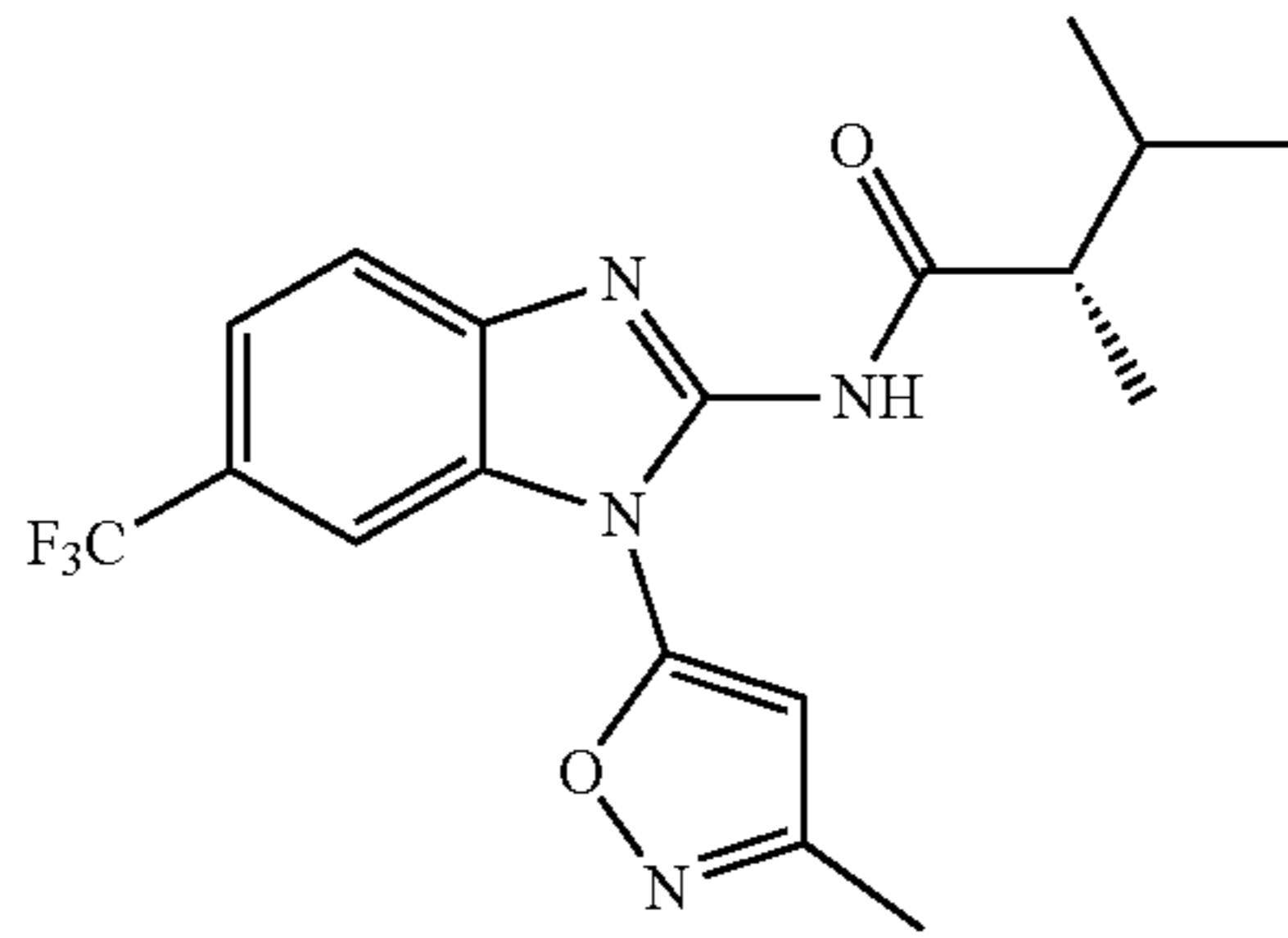
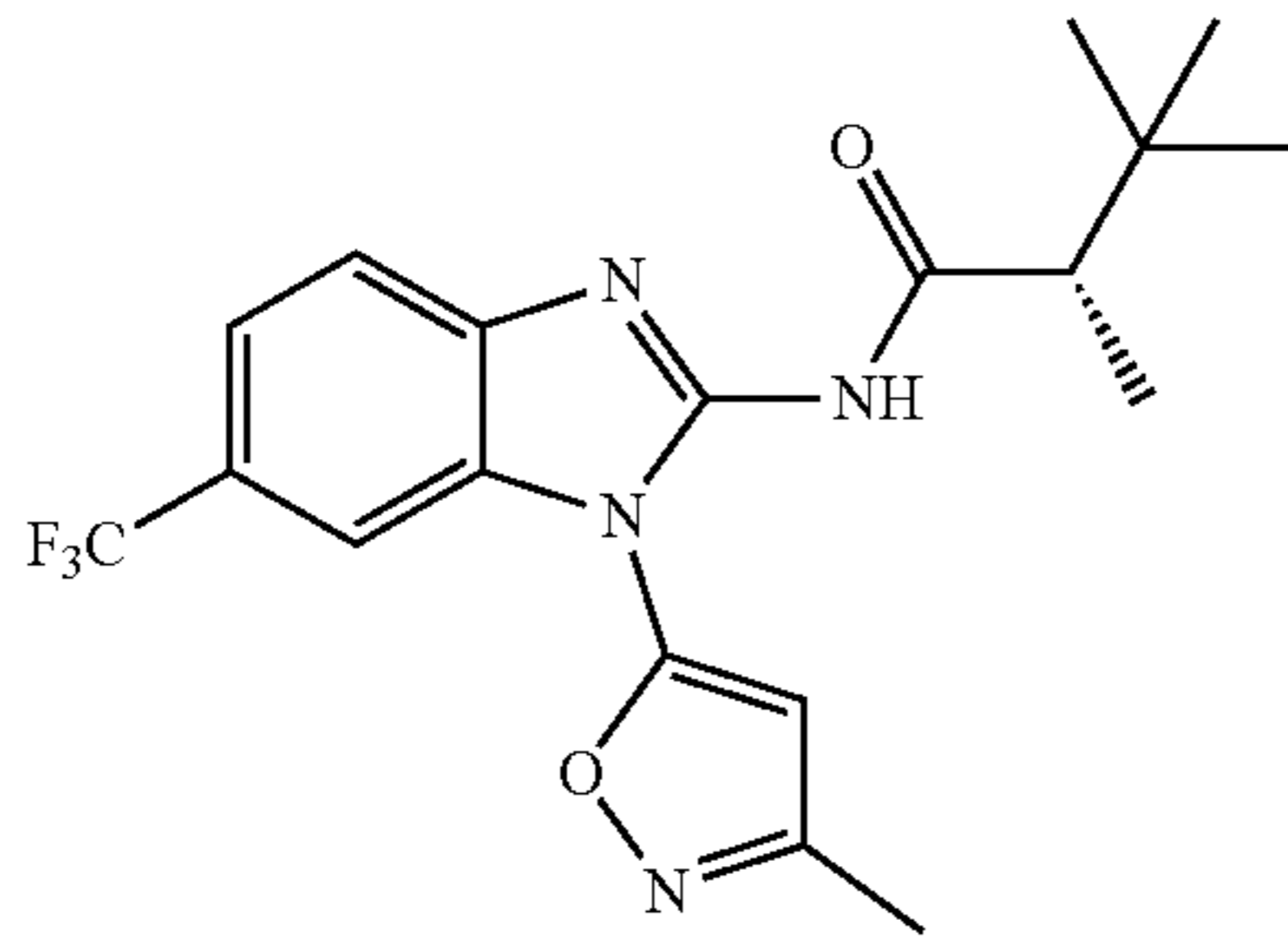
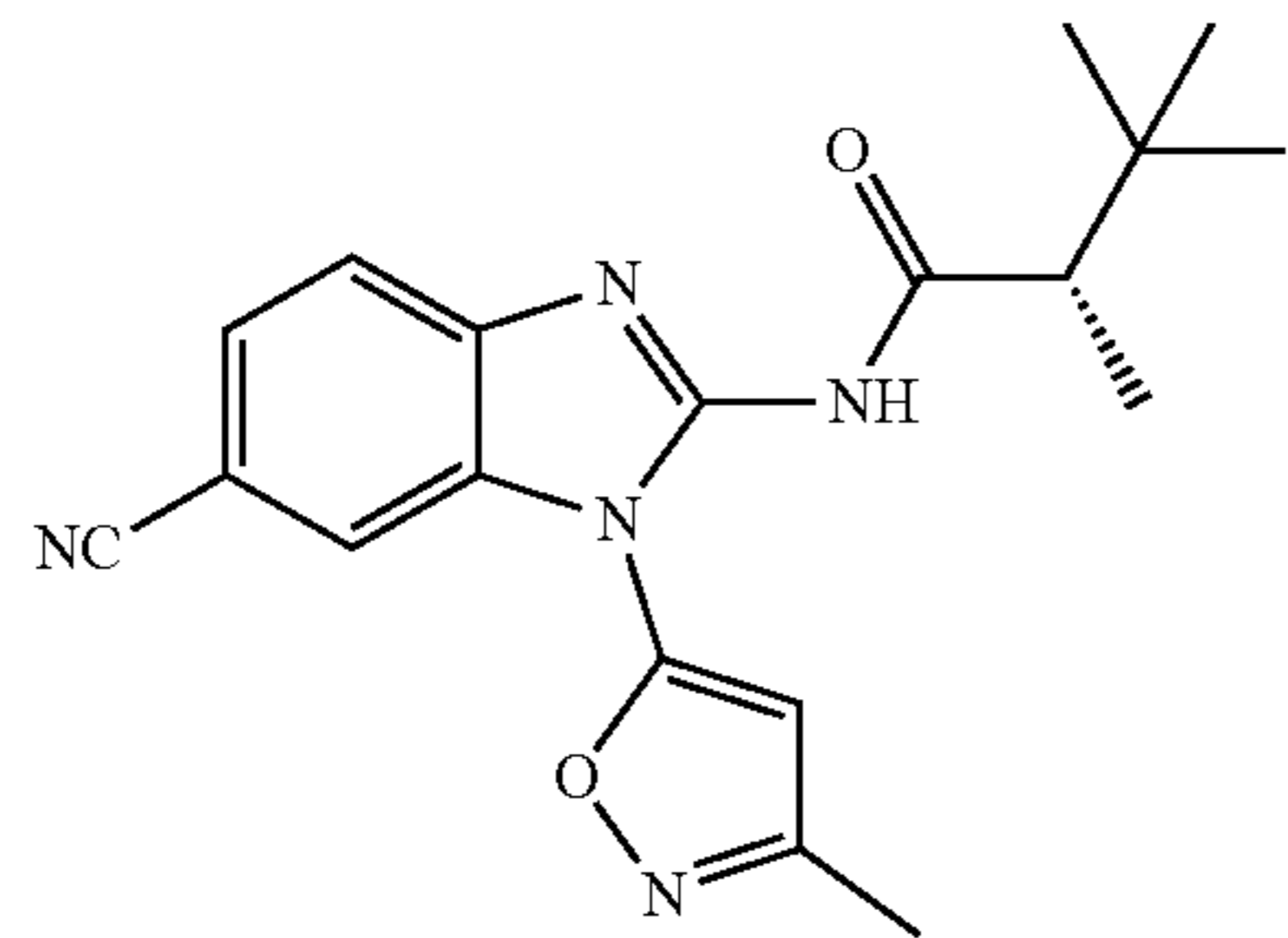
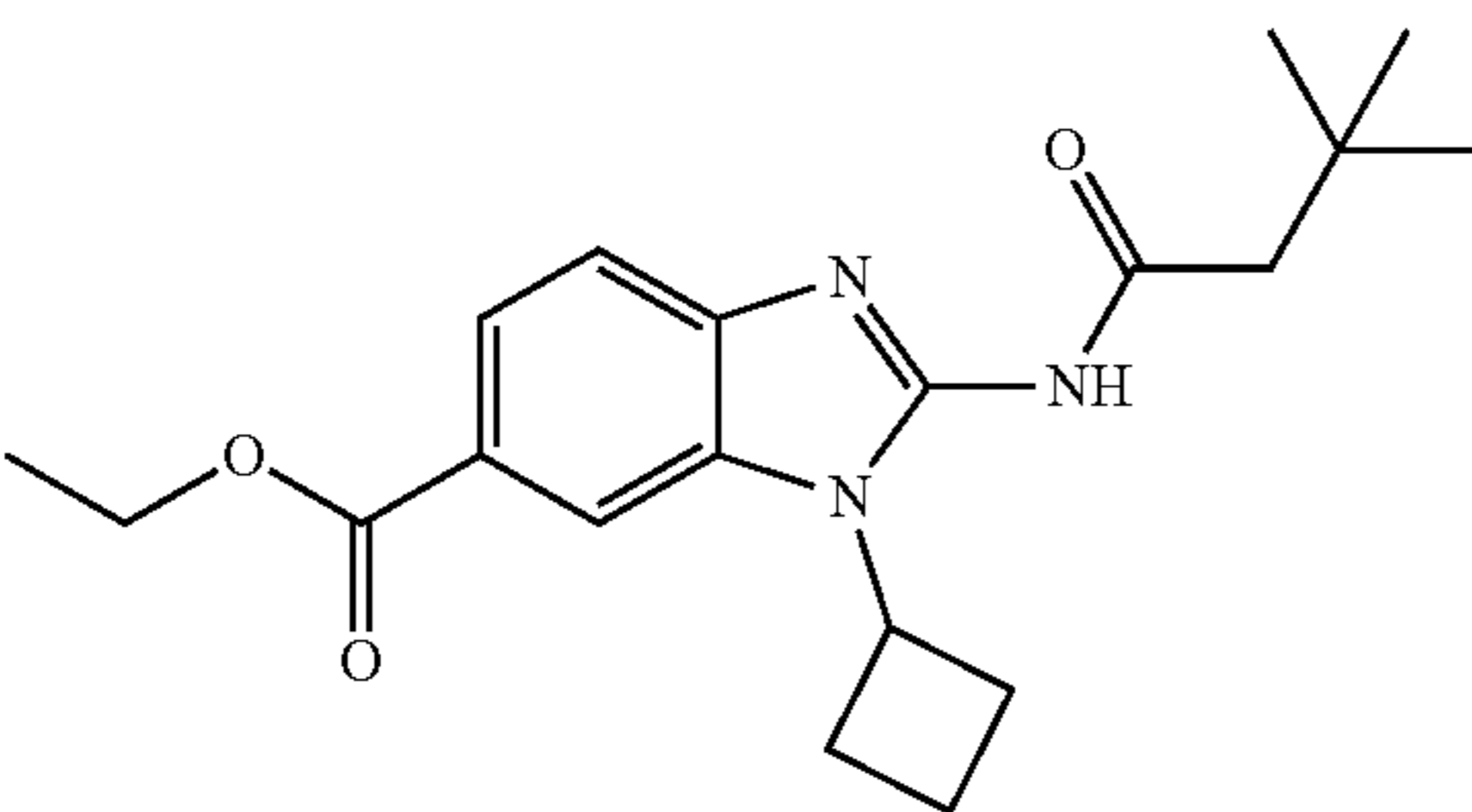
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
47	 $C_{18}H_{19}F_3N_4O_2$	(S)-2,3-dimethyl-N-(1-(3-methylisoxazol-5-yl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)butanamide	11	B	3.9	381
48	 $C_{19}H_{21}F_3N_4O_2$	(S)-2,3,3-trimethyl-N-(1-(3-methylisoxazol-5-yl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)butanamide	11	B	4.0	395
49	 $C_{19}H_{21}N_5O_2$	(S)-N-(6-cyano-1-(3-methylisoxazol-5-yl)-1H-benzo[d]imidazol-2-yl)-2,3,3-trimethylbutanamide	11	B	3.6	352
50	 $C_{20}H_{27}N_3O_3$	ethyl 1-cyclobutyl-2-(3,3-dimethylbutanamido)-1H-benzo[d]imidazole-6-carboxylate	7	B	3.7	358

TABLE 1-continued

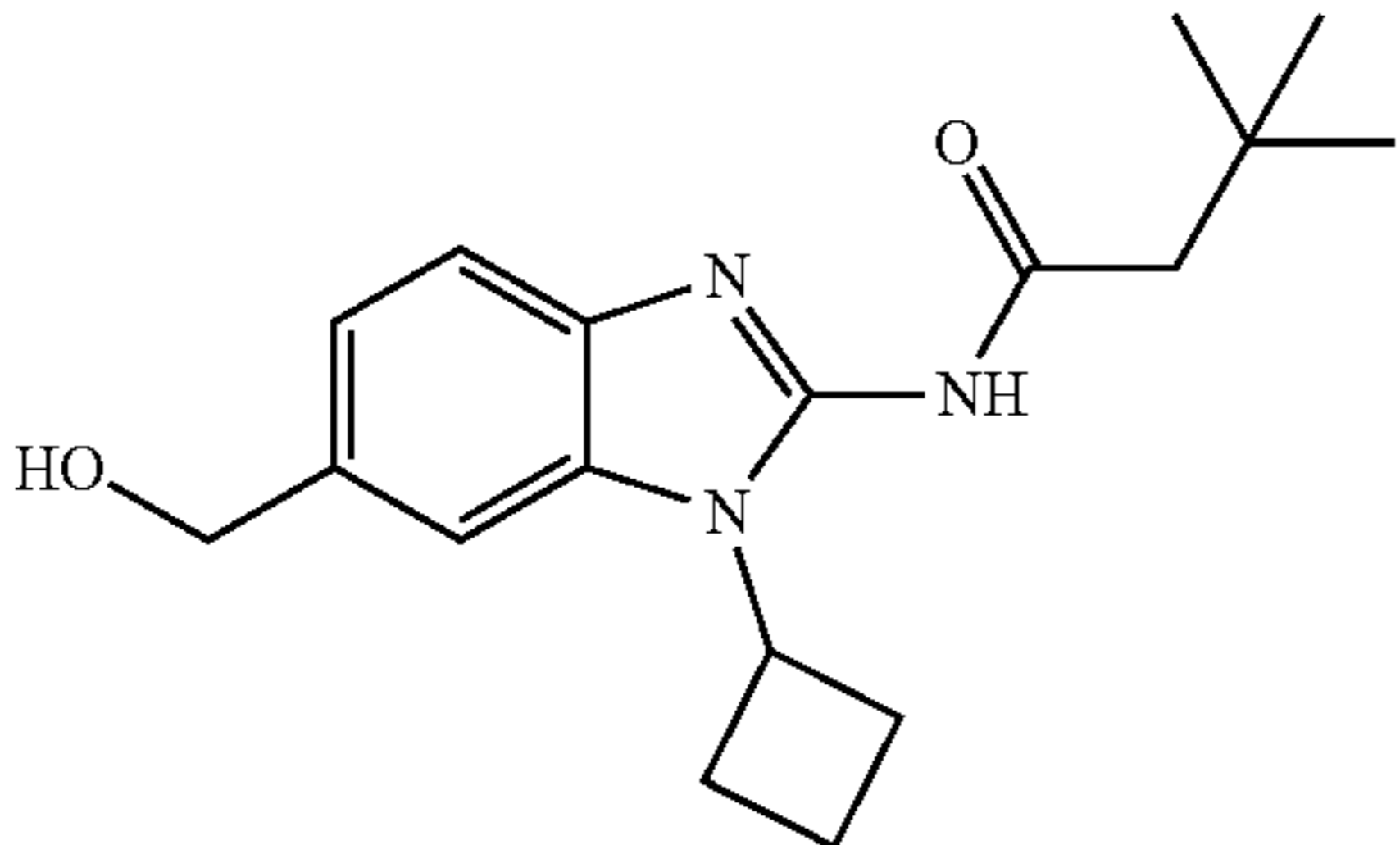
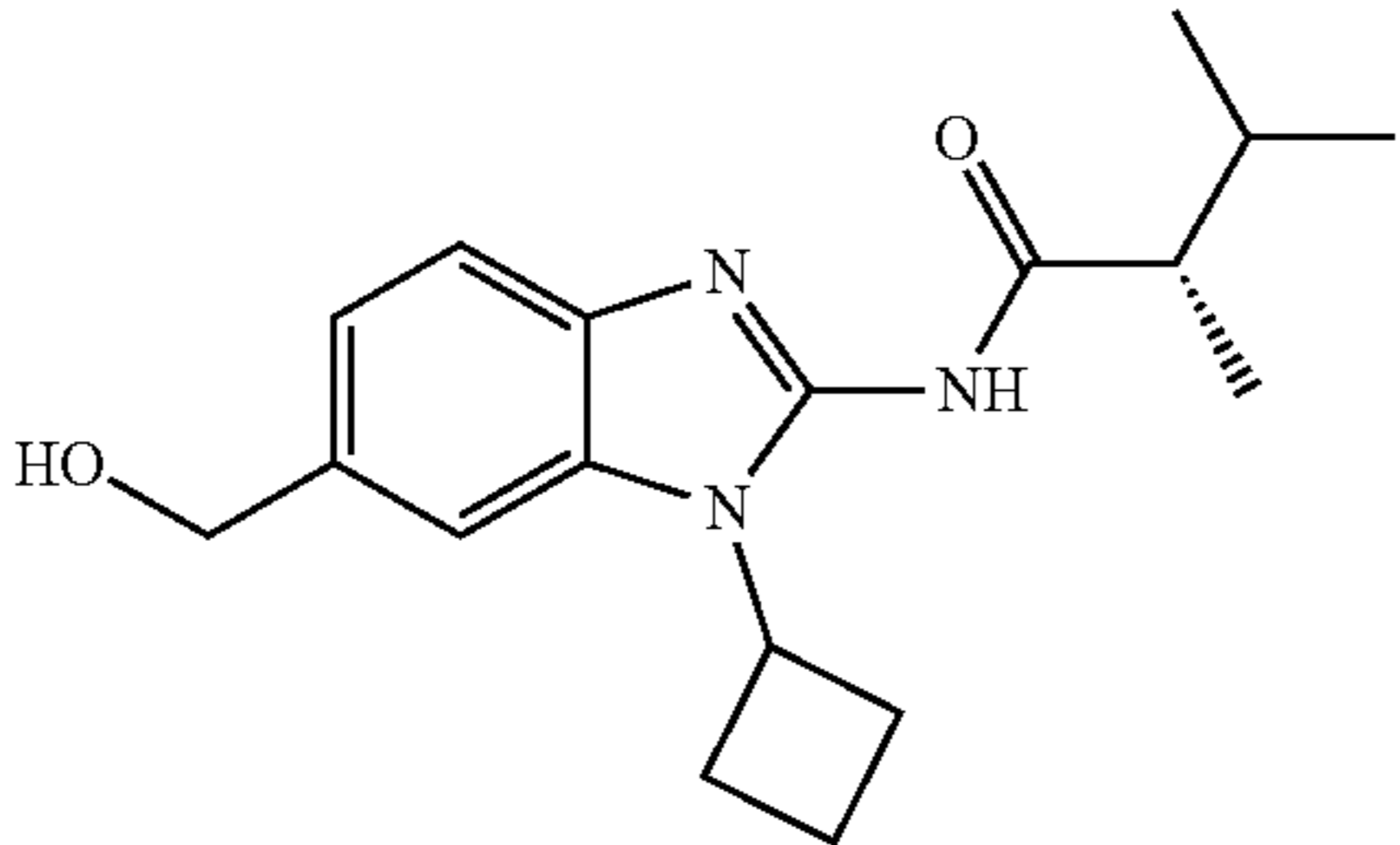
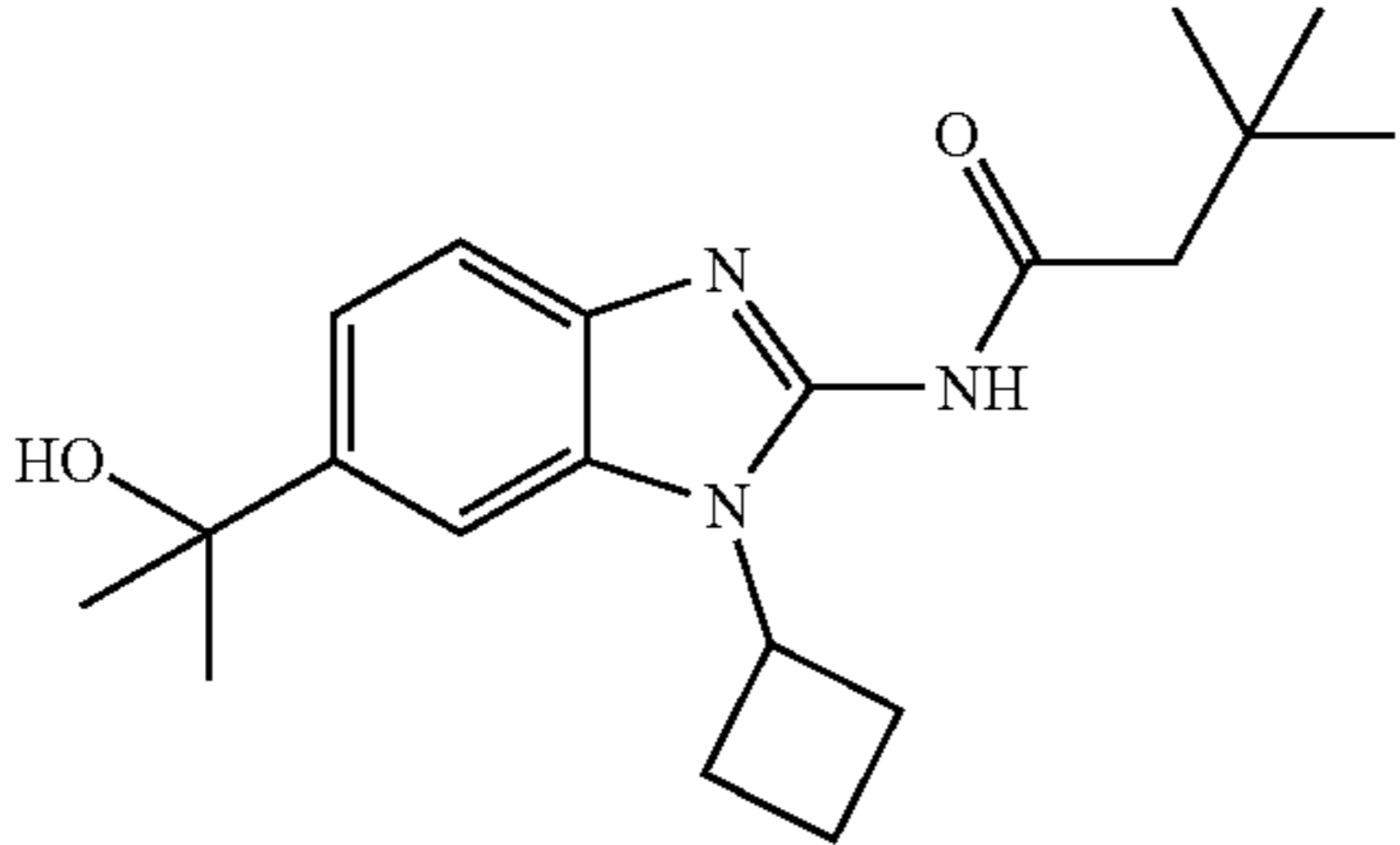
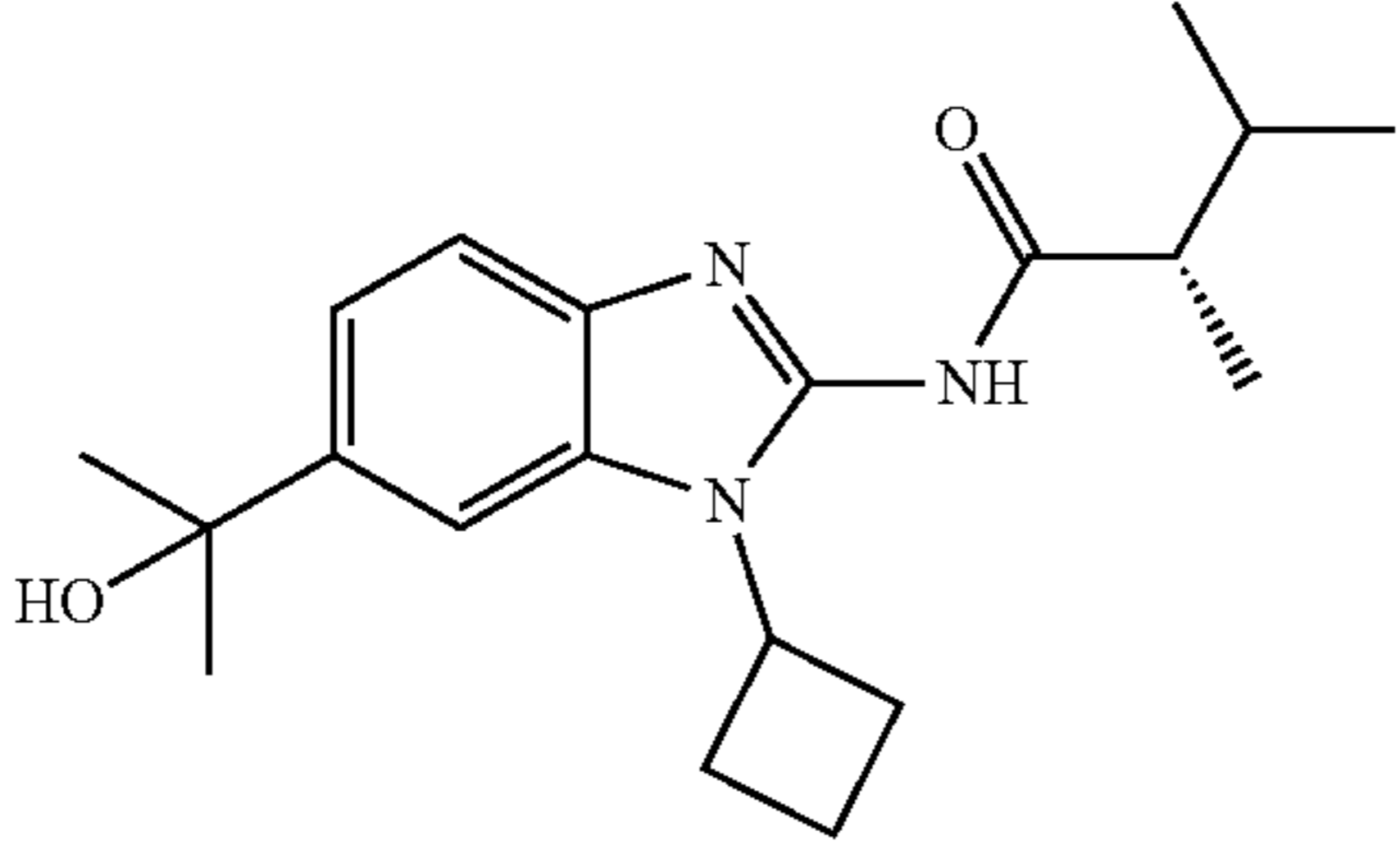
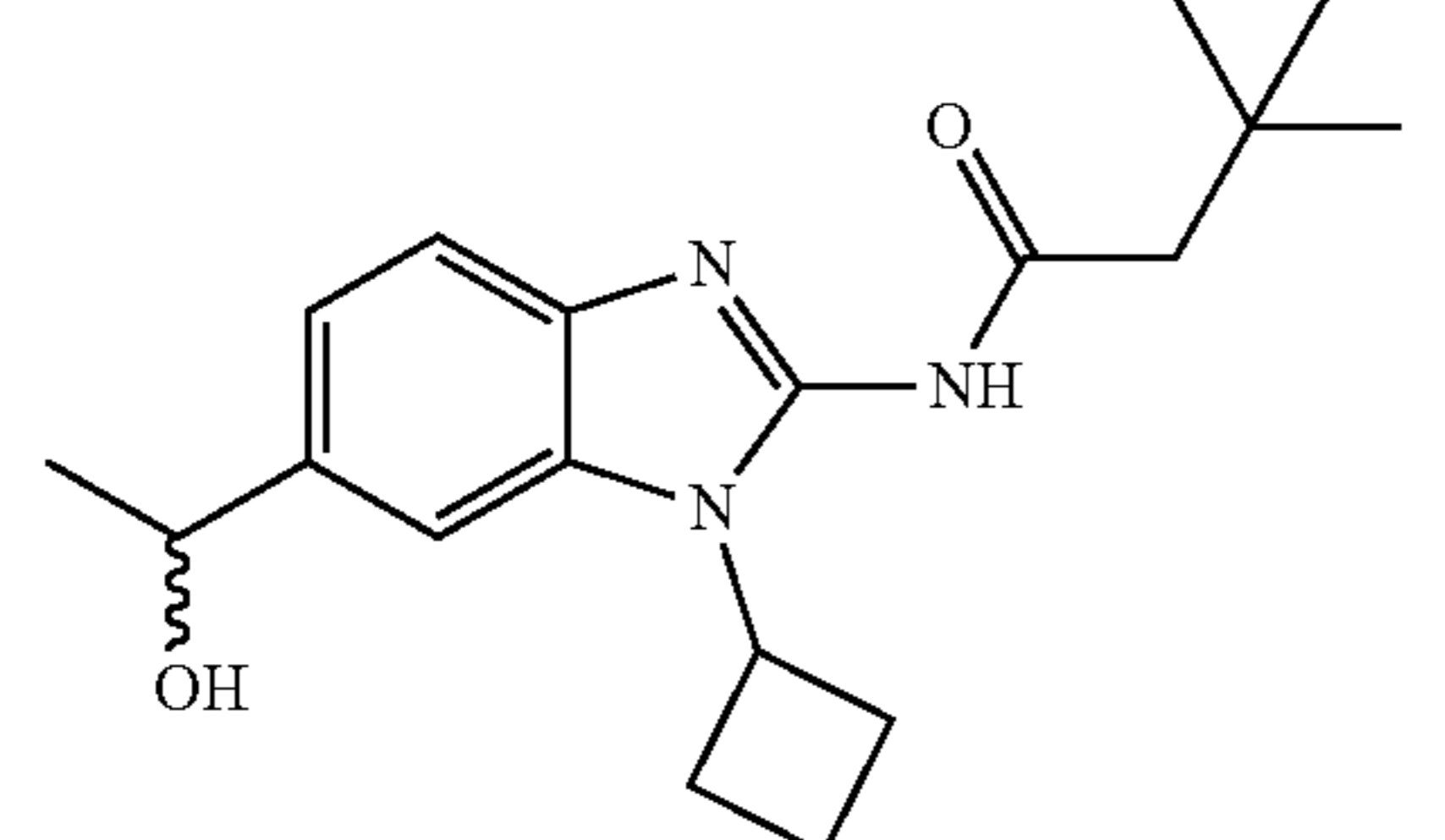
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
51	 $C_{18}H_{25}N_3O_2$	N-(1-cyclobutyl-6-(hydroxymethyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7	A	2.4	316
52	 $C_{18}H_{25}N_3O_2$	(S)-N-(1-cyclobutyl-6-(hydroxymethyl)-1H-benzo[d]imidazol-2-yl)-2,3-dimethylbutanamide	7	B	2.4	316
53	 $C_{20}H_{29}N_3O_2$	N-(1-cyclobutyl-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7	B	2.5	344
54	 $C_{20}H_{29}N_3O_2$	(S)-N-(1-cyclobutyl-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)-2,3-dimethylbutanamide	7	B	2.5	344
55		N-(1-cyclobutyl-6-(1-hydroxyethyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7	B	2.4	330

TABLE 1-continued

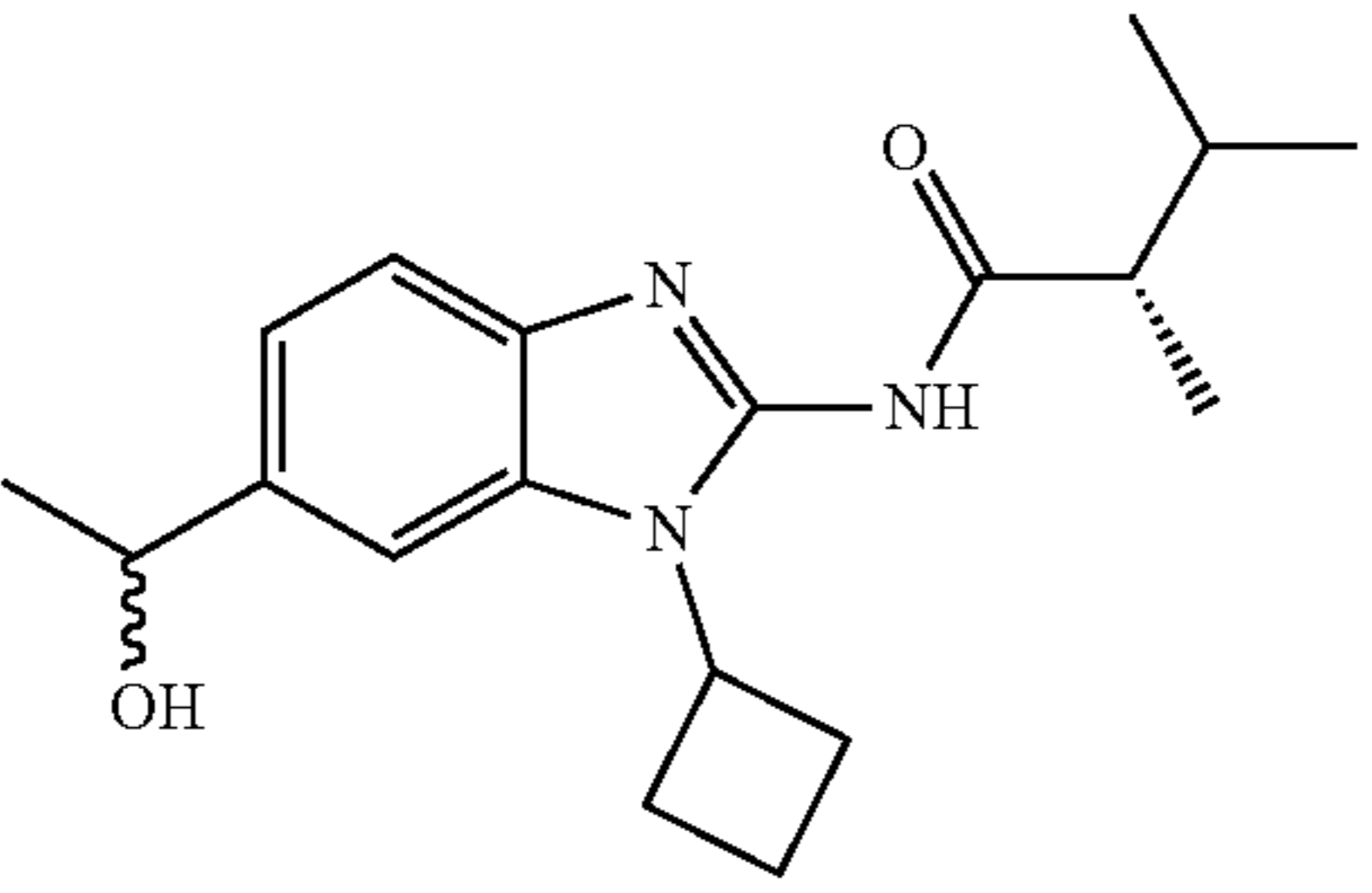
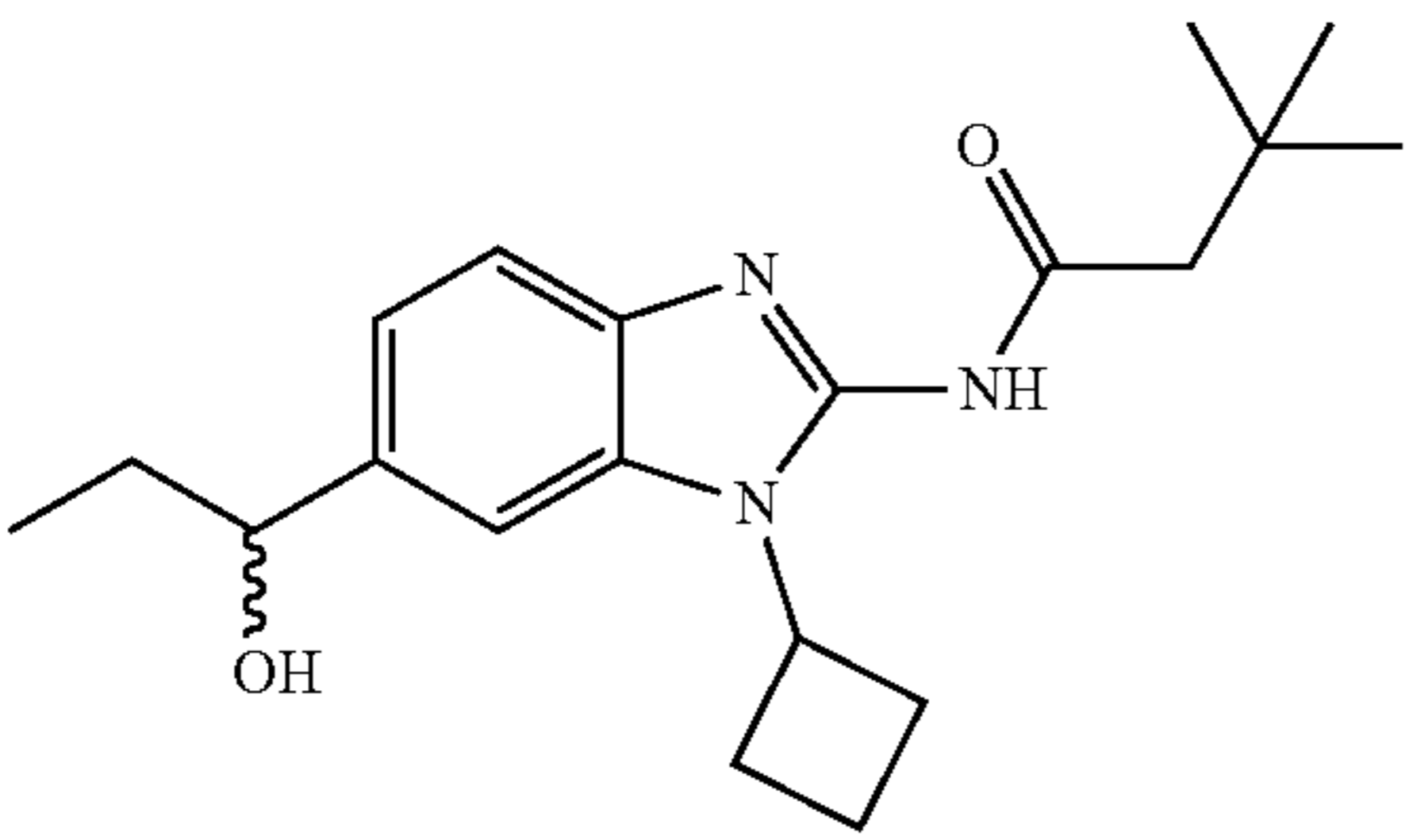
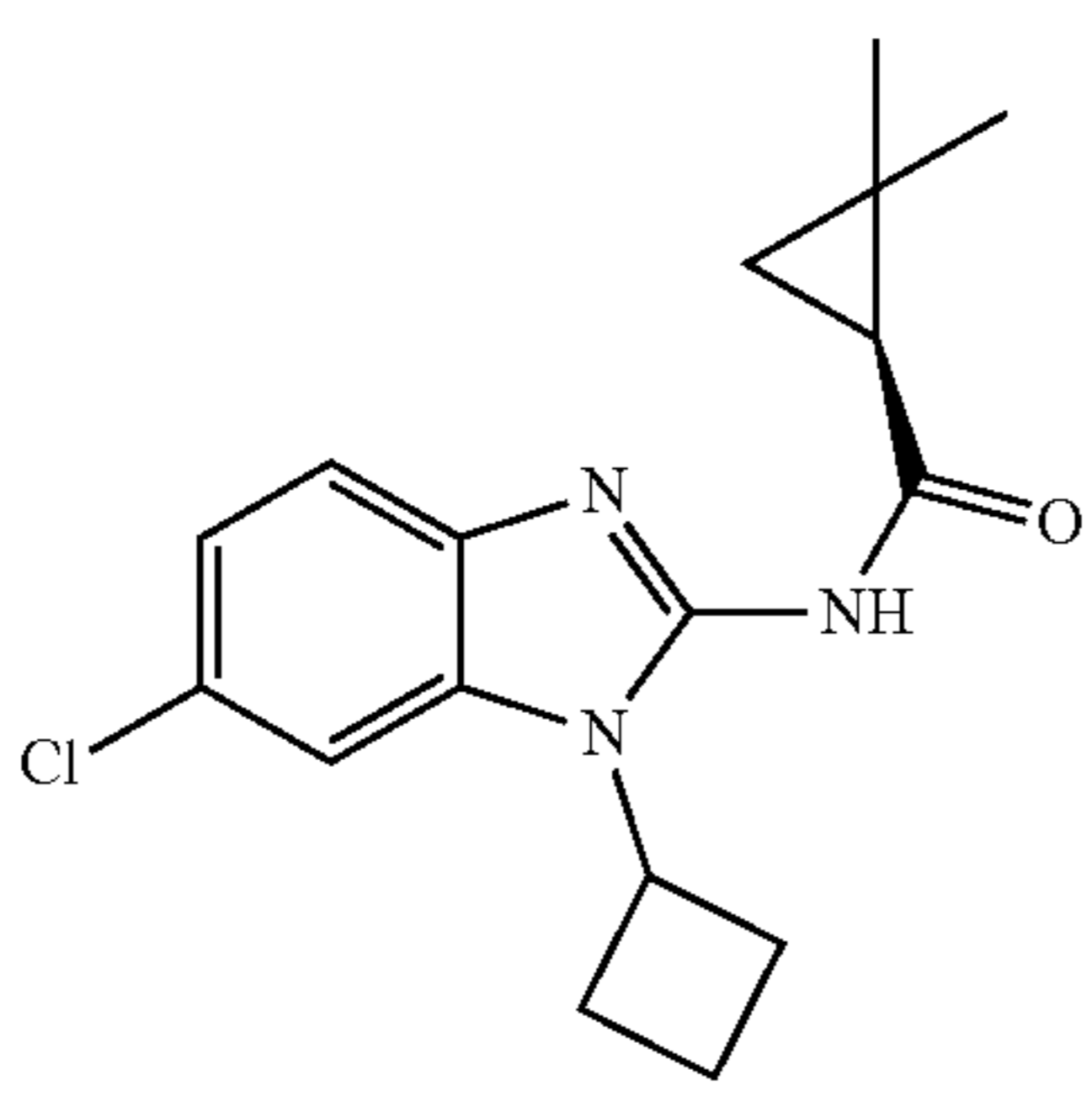
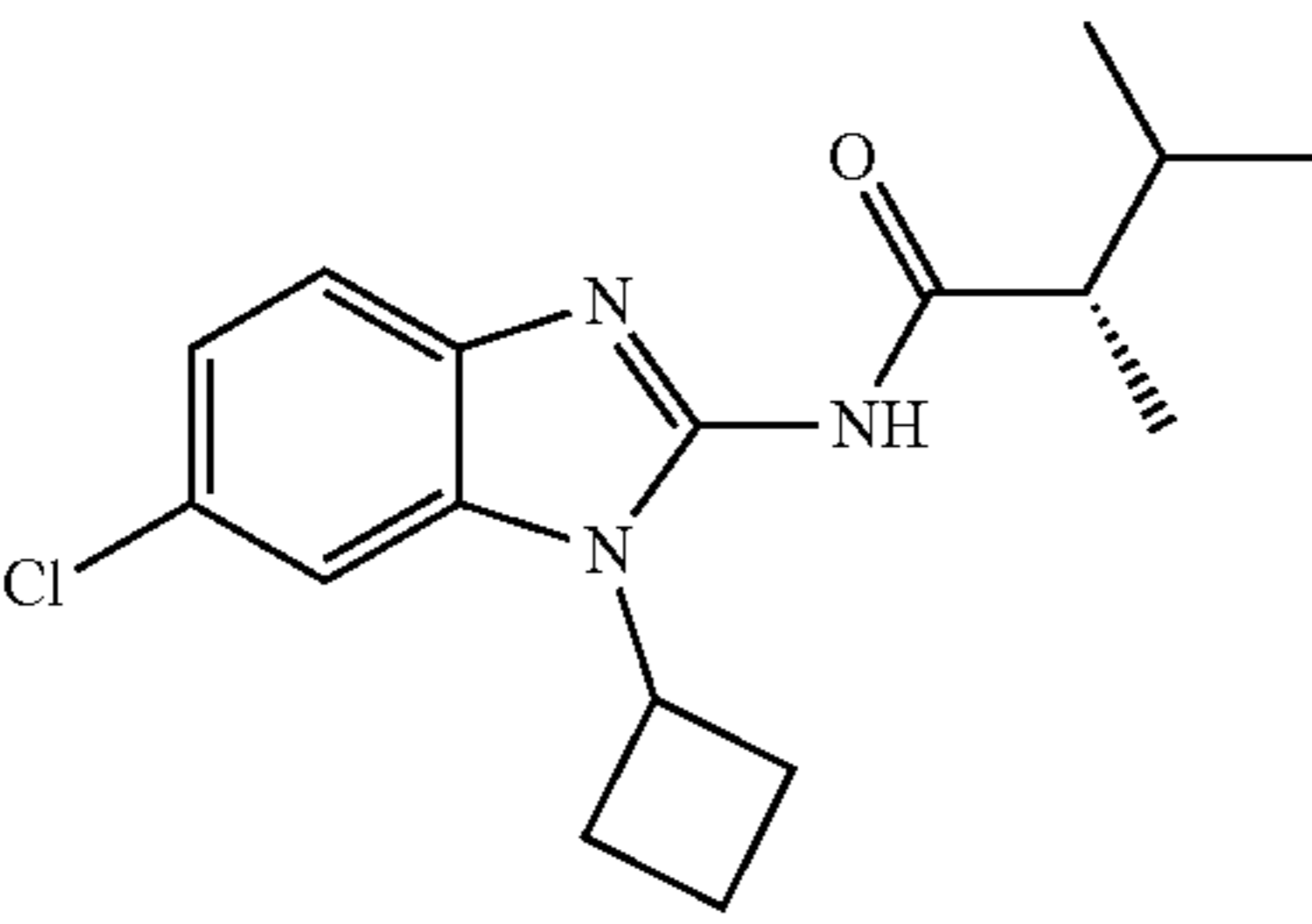
List of Examples, Synthetic Routes and Analytical Data							
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z	
	$C_{19}H_{27}N_3O_2$						
56		(2S)-N-(1-cyclobutyl-6-(1-hydroxyethyl)-1H-benzo[d]imidazol-2-yl)-2,3-dimethylbutanamide	7	B	2.4	330	
	$C_{19}H_{27}N_3O_2$						
57		N-(1-cyclobutyl-6-(1-hydroxypropyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7	B	2.6	344	
	$C_{20}H_{29}N_3O_2$						
58		(S)-N-(6-chloro-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2,2-dimethylcyclopropane-1-carboxamide	7	B	3.4	318	
	$C_{17}H_{20}ClN_3O$						
59		(S)-N-(6-chloro-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2,3-dimethylbutanamide	7	B	3.7	320	
	$C_{17}H_{22}ClN_3O$						

TABLE 1-continued

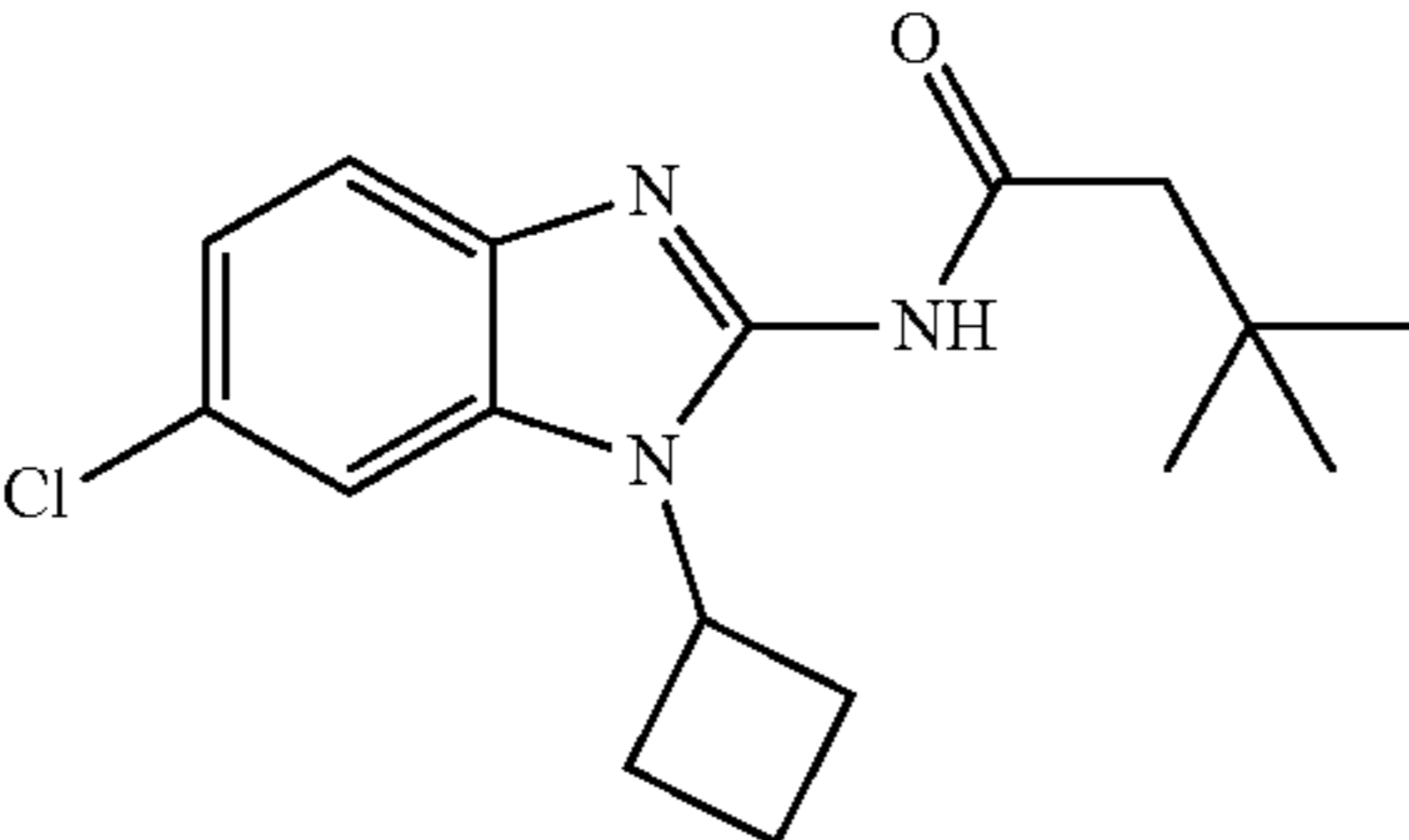
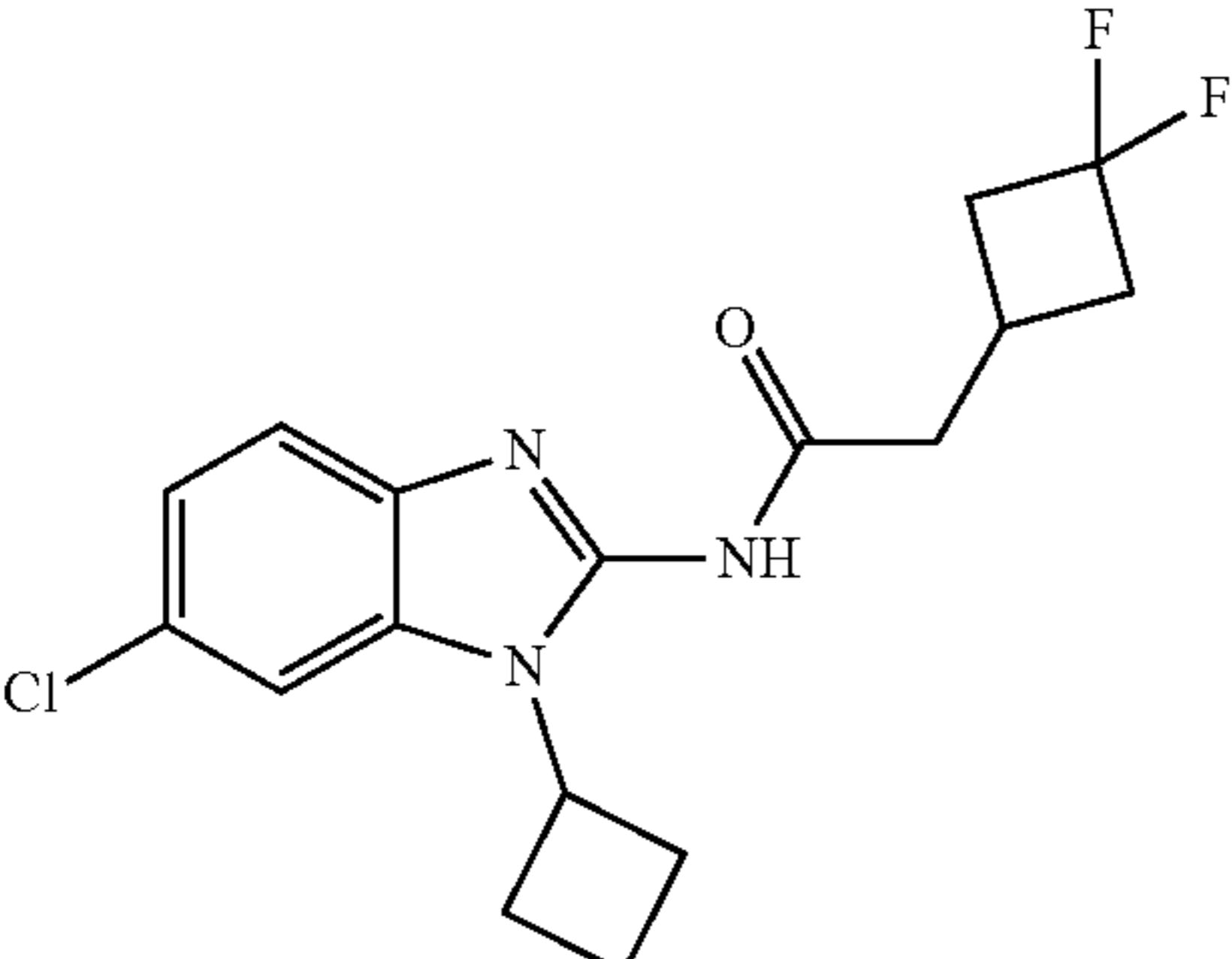
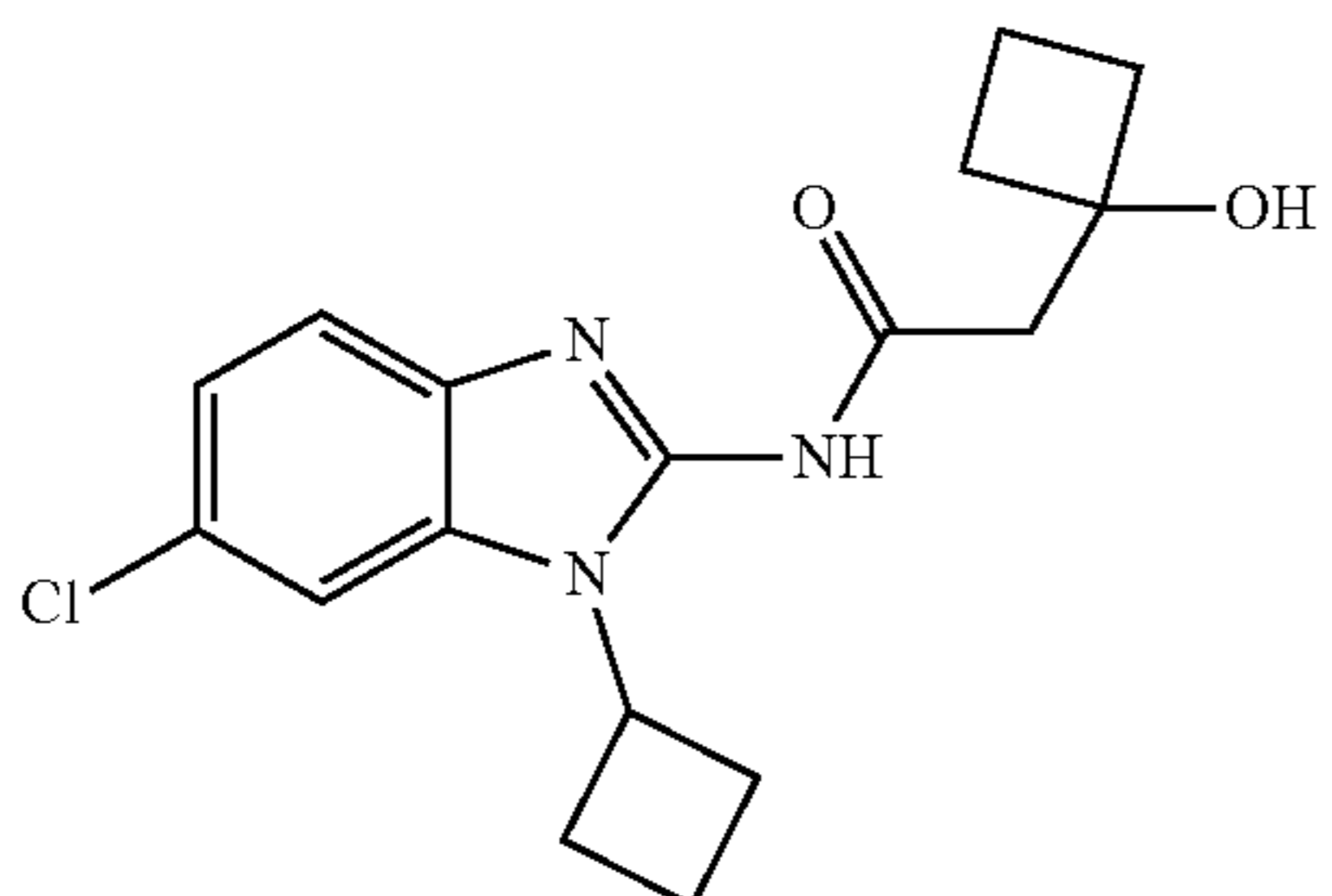
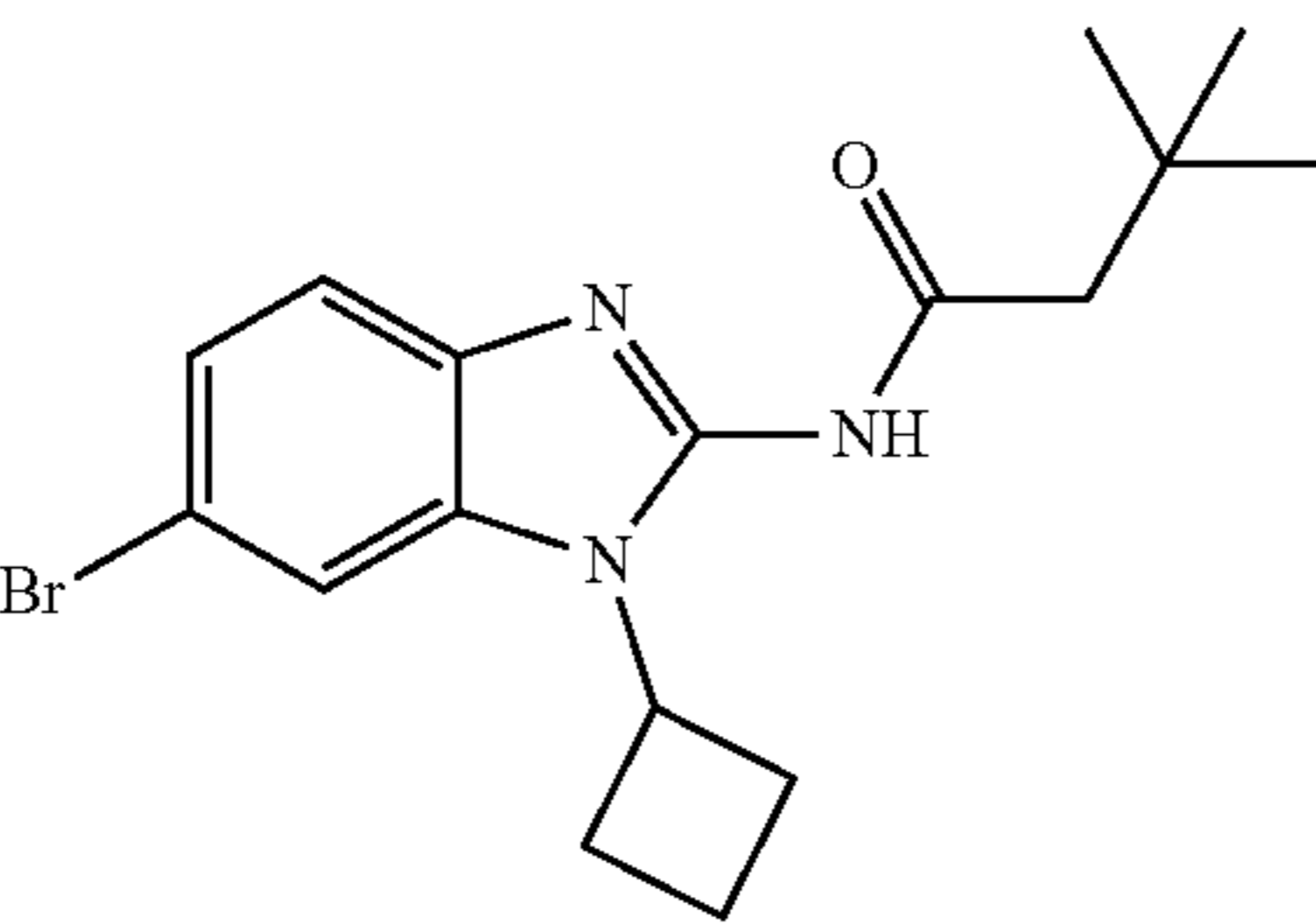
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
60	 <chem>CC(C)(C)CC(=O)Nc1nc2ccc(Cl)cc2n1C3CCC3</chem> $C_{17}H_{22}ClN_3O$	N-(6-chloro-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7	B	3.6	320
61	 <chem>CC(=O)Nc1nc2ccc(Cl)cc2n1C3CCC3C4C(F)FCC4</chem> $C_{17}H_{18}ClF_2N_3O$	N-(6-chloro-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2-(3,3-difluorocyclobutyl)acetamide	7	B	3.8	355
62	 <chem>CC(=O)Nc1nc2ccc(Cl)cc2n1C3CCC3C4C(O)CC4</chem> $C_{17}H_{20}ClN_3O_2$	N-(6-chloro-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2-(1-hydroxycyclobutyl)acetamide	7	B	3.0	334
63	 <chem>CC(C)(C)CC(=O)Nc1nc2ccc(Br)cc2n1C3CCC3</chem> $C_{17}H_{22}BrN_3O$	N-(6-bromo-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7	B	3.8	366

TABLE 1-continued

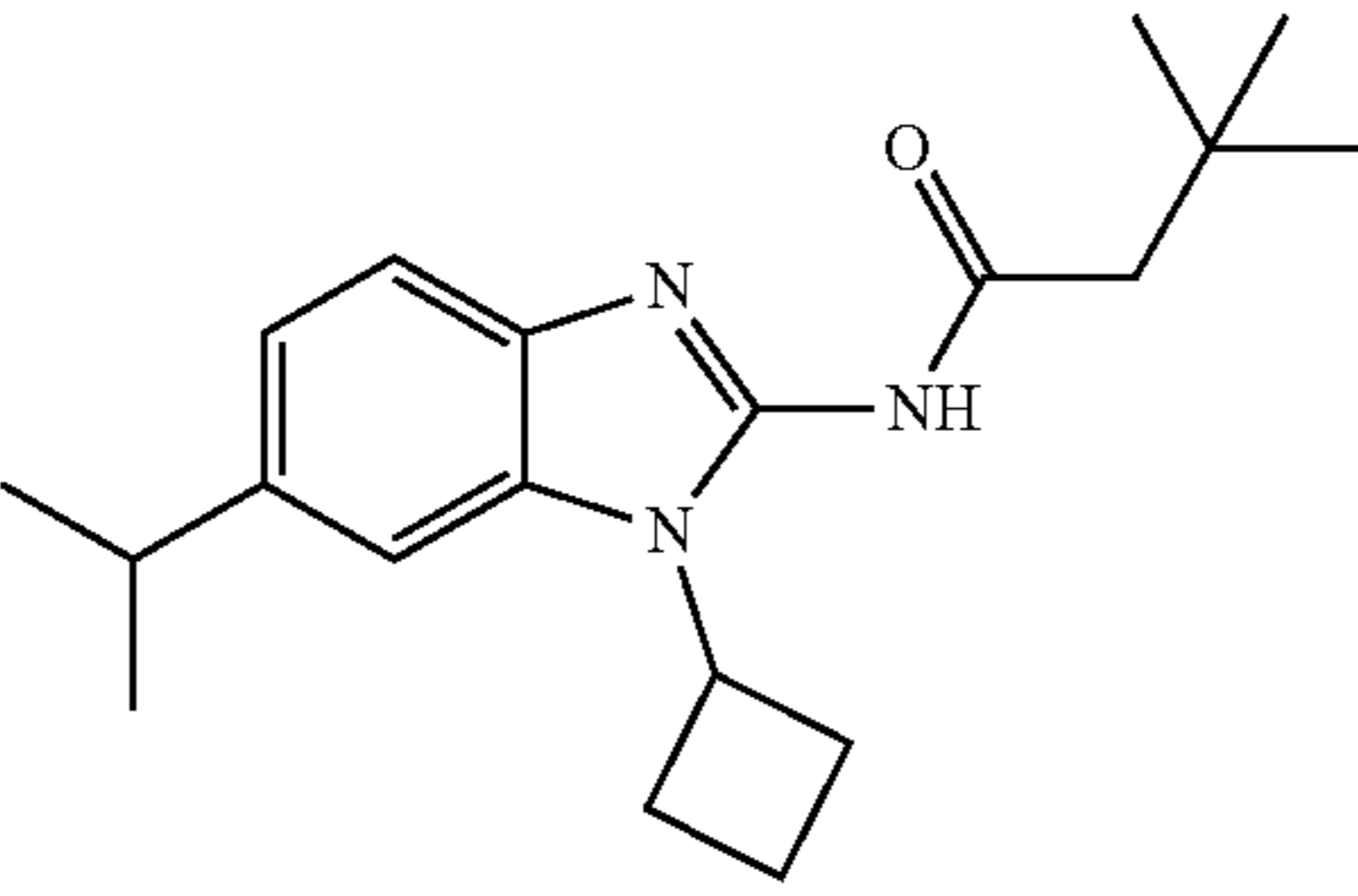
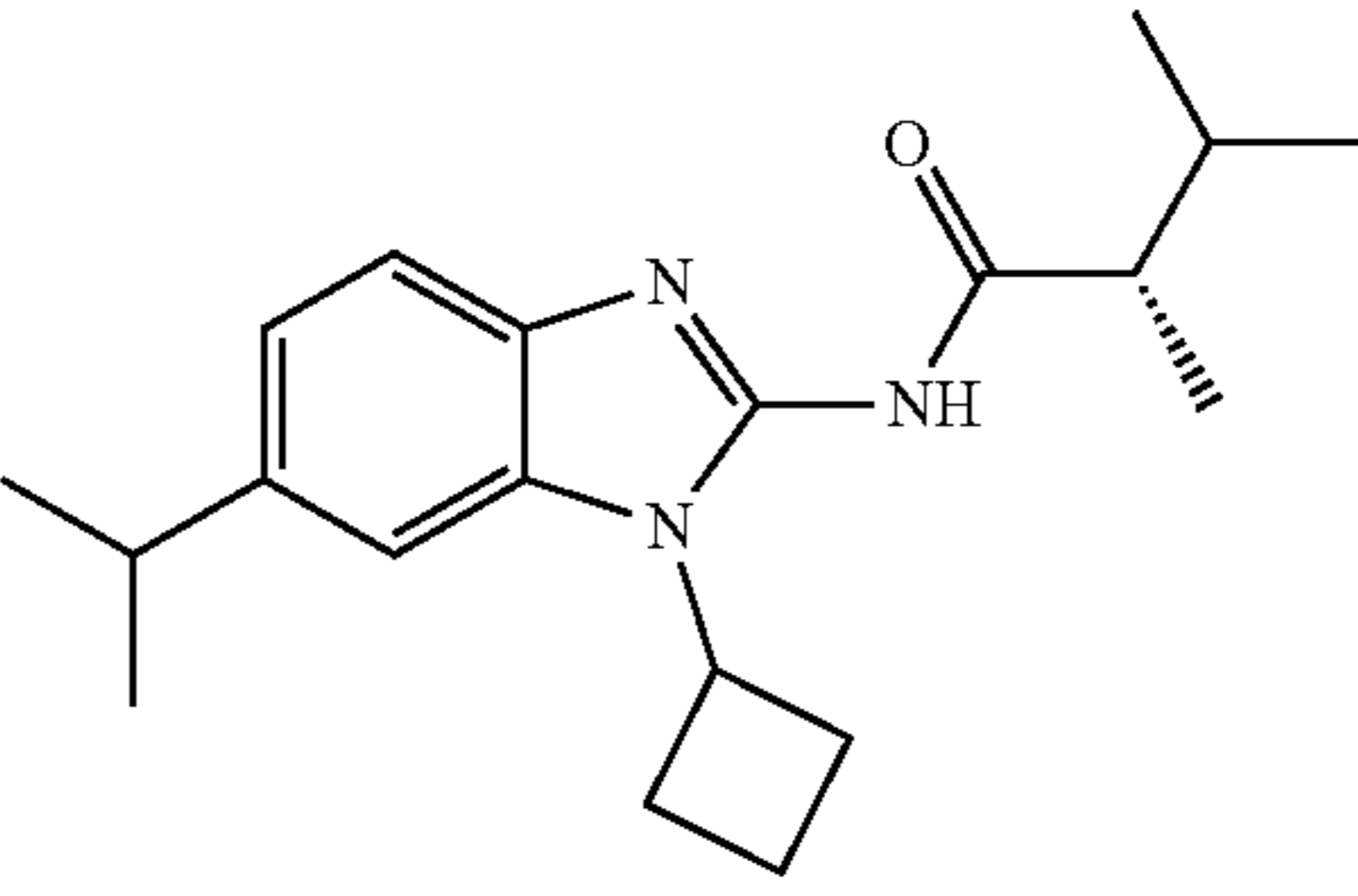
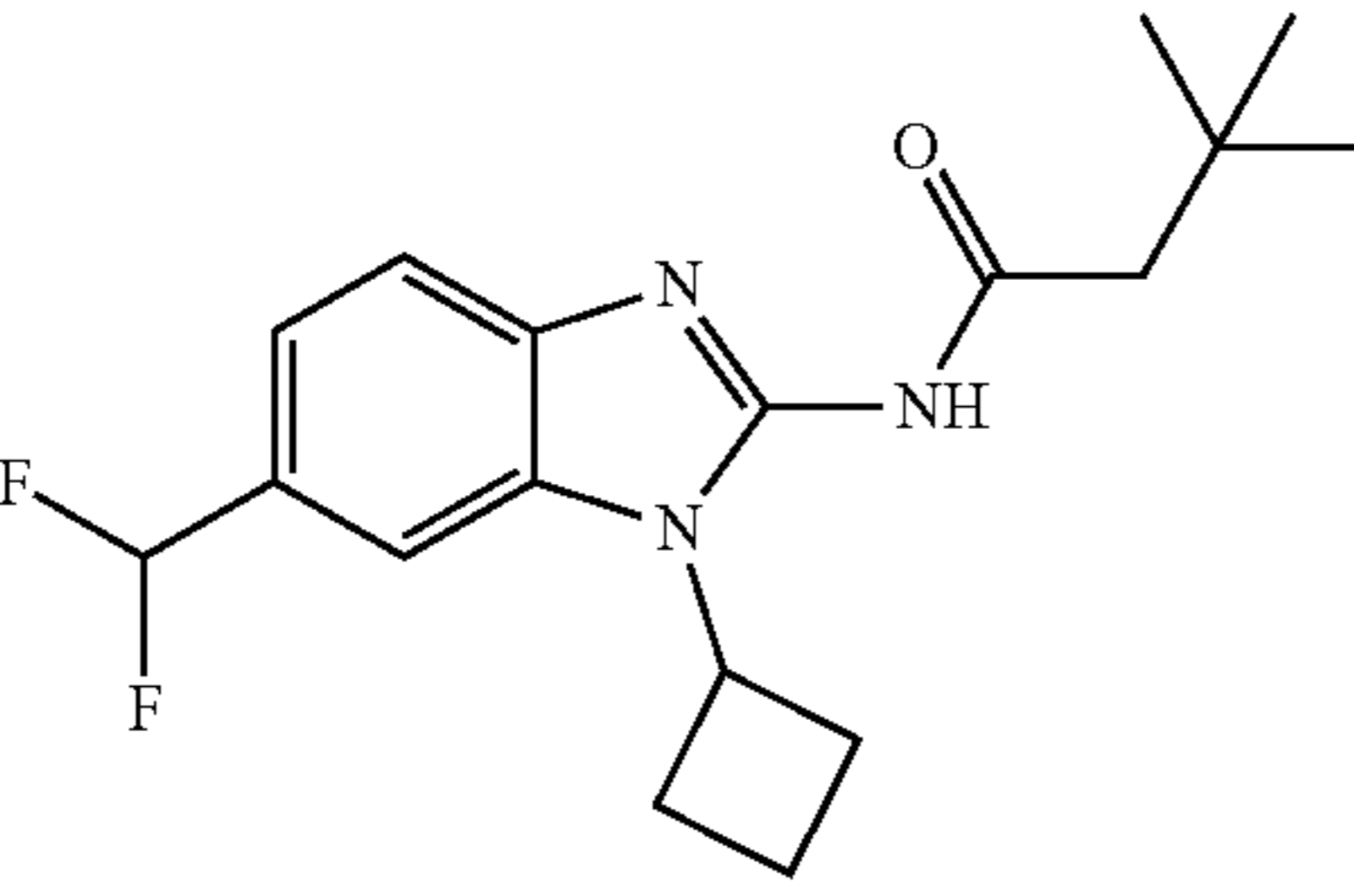
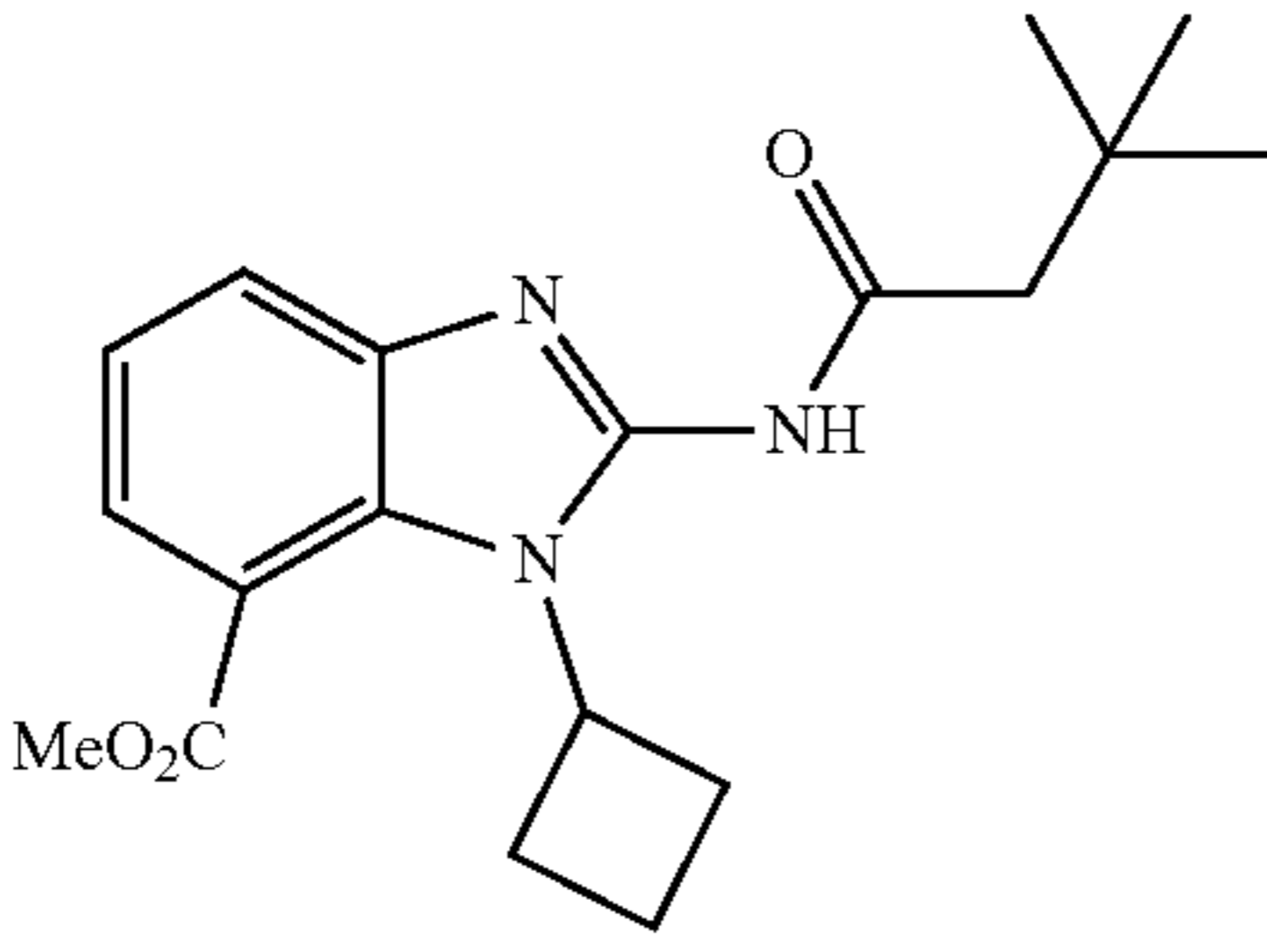
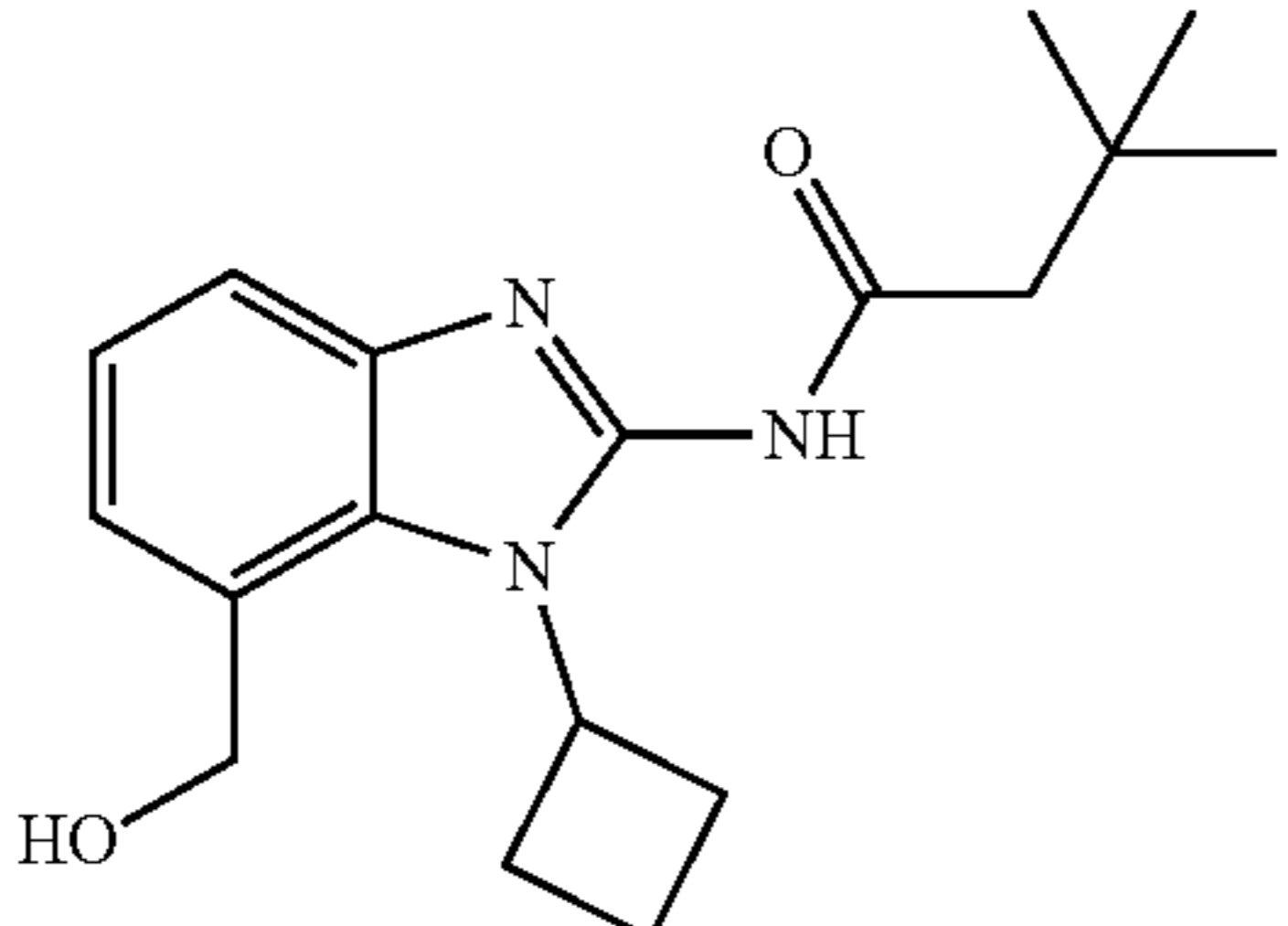
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
64		N-(1-cyclobutyl-6-isopropyl-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7	B	3.2	328
	$C_{20}H_{29}N_3O$					
65		(S)-N-(1-cyclobutyl-6-isopropyl-1H-benzo[d]imidazol-2-yl)-2,3-dimethylbutanamide	7	B	3.4	328
	$C_{20}H_{29}N_3O$					
66		N-(1-cyclobutyl-6-(difluoromethyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7	B	3.4	336
	$C_{18}H_{23}F_2N_3O$					
67		methyl 1-cyclobutyl-2-(3,3-dimethylbutanamido)-1H-benzo[d]imidazole-7-carboxylate	7	B	3.2	344
	$C_{19}H_{25}N_3O_3$					
68		N-(1-cyclobutyl-7-(hydroxymethyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7	B	2.7	316

TABLE 1-continued

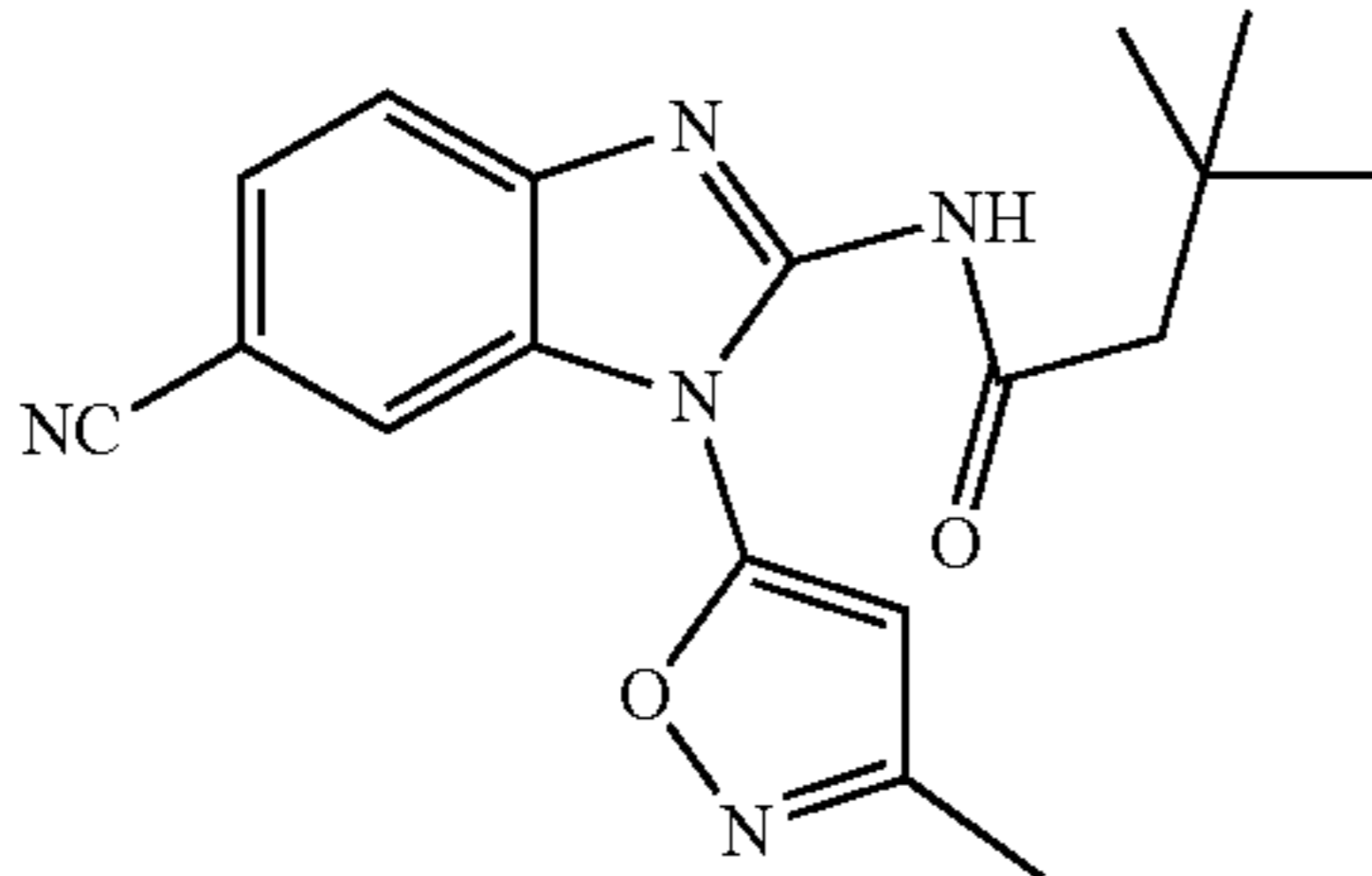
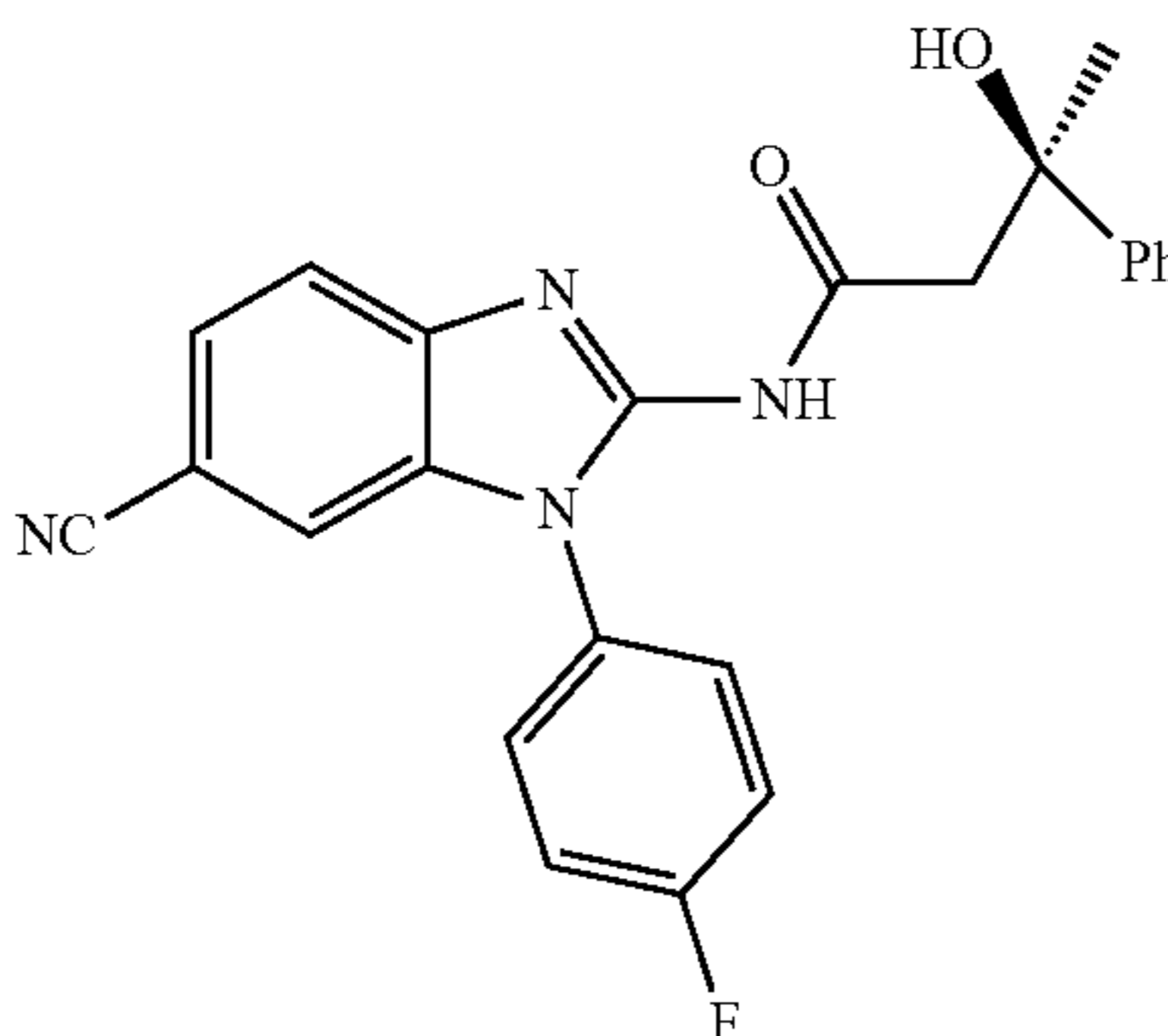
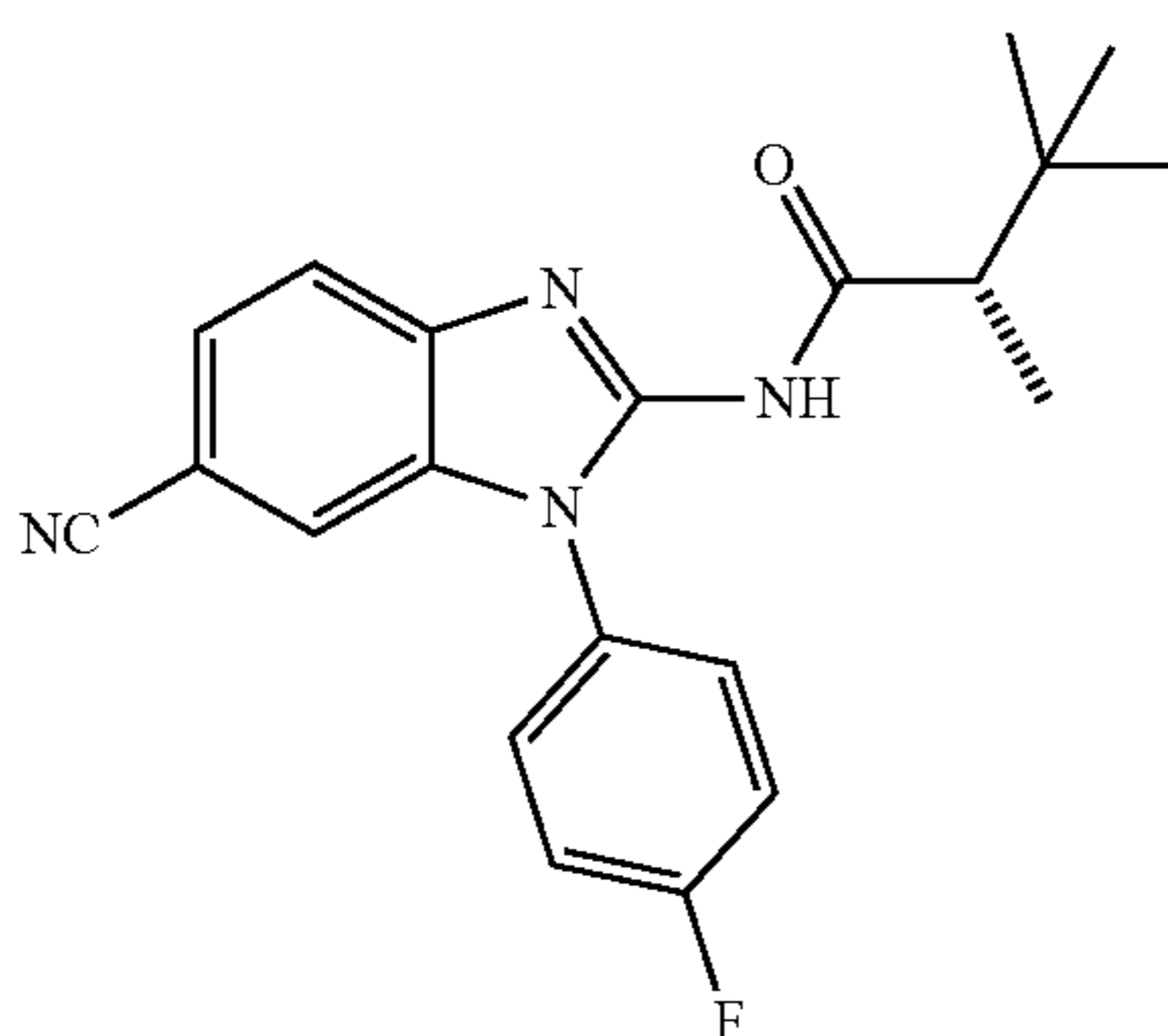
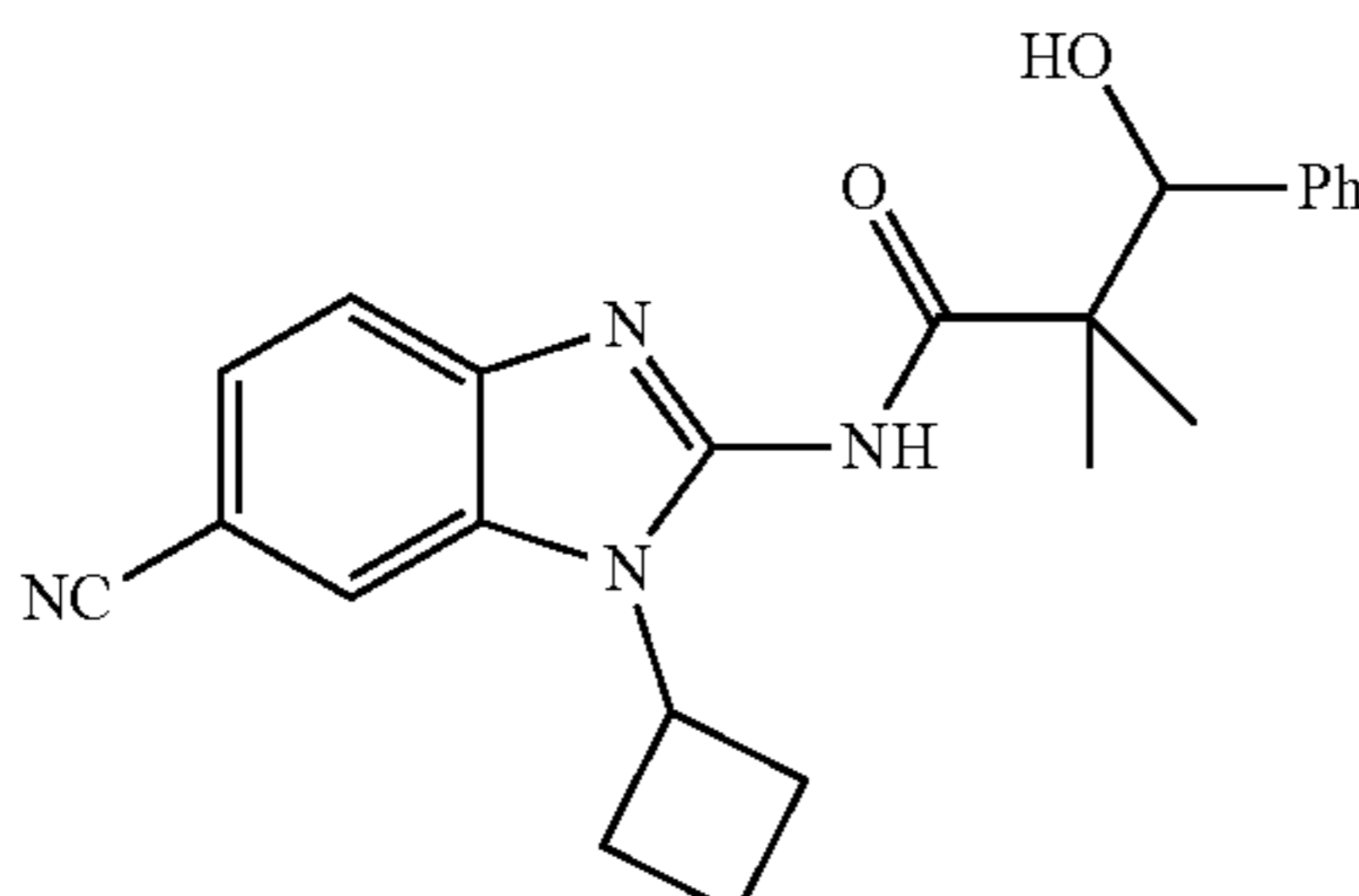
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
69	$C_{18}H_{25}N_3O_2$ 	N-(6-cyano-1-(3-methylisoxazol-5-yl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	9	B	3.4	338
70	$C_{18}H_{19}N_5O_2$ 	(R)-N-(6-cyano-1-(4-fluorophenyl)-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	7 with (R)-3-((tert-butyl-dimethylsilyl)oxy)-3-phenylbutanoic acid as acid, then procedure analagous to ex. 18, step E	B	3.4	415
71	$C_{24}H_{19}FN_4O_2$ 	(S)-N-(6-cyano-1-(4-fluorophenyl)-1H-benzo[d]imidazol-2-yl)-2,3,3-trimethylbutanamide	7	B	3.6	365
72	$C_{21}H_{21}FN_4O$ 	N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-2,2-dimethyl-3-phenylpropanamide	7	B	3.8	389
	$C_{23}H_{24}N_4O_2$					

TABLE 1-continued

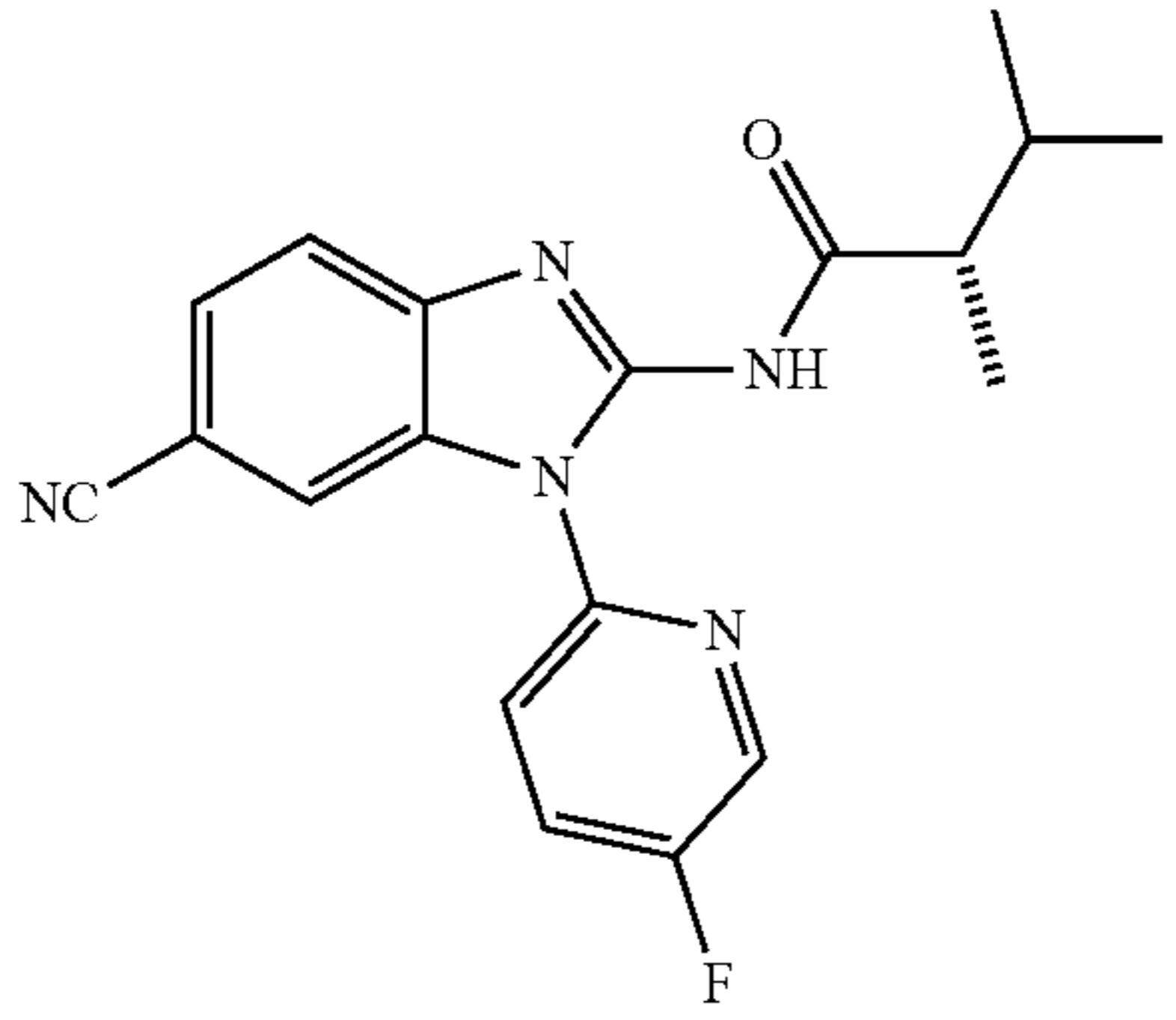
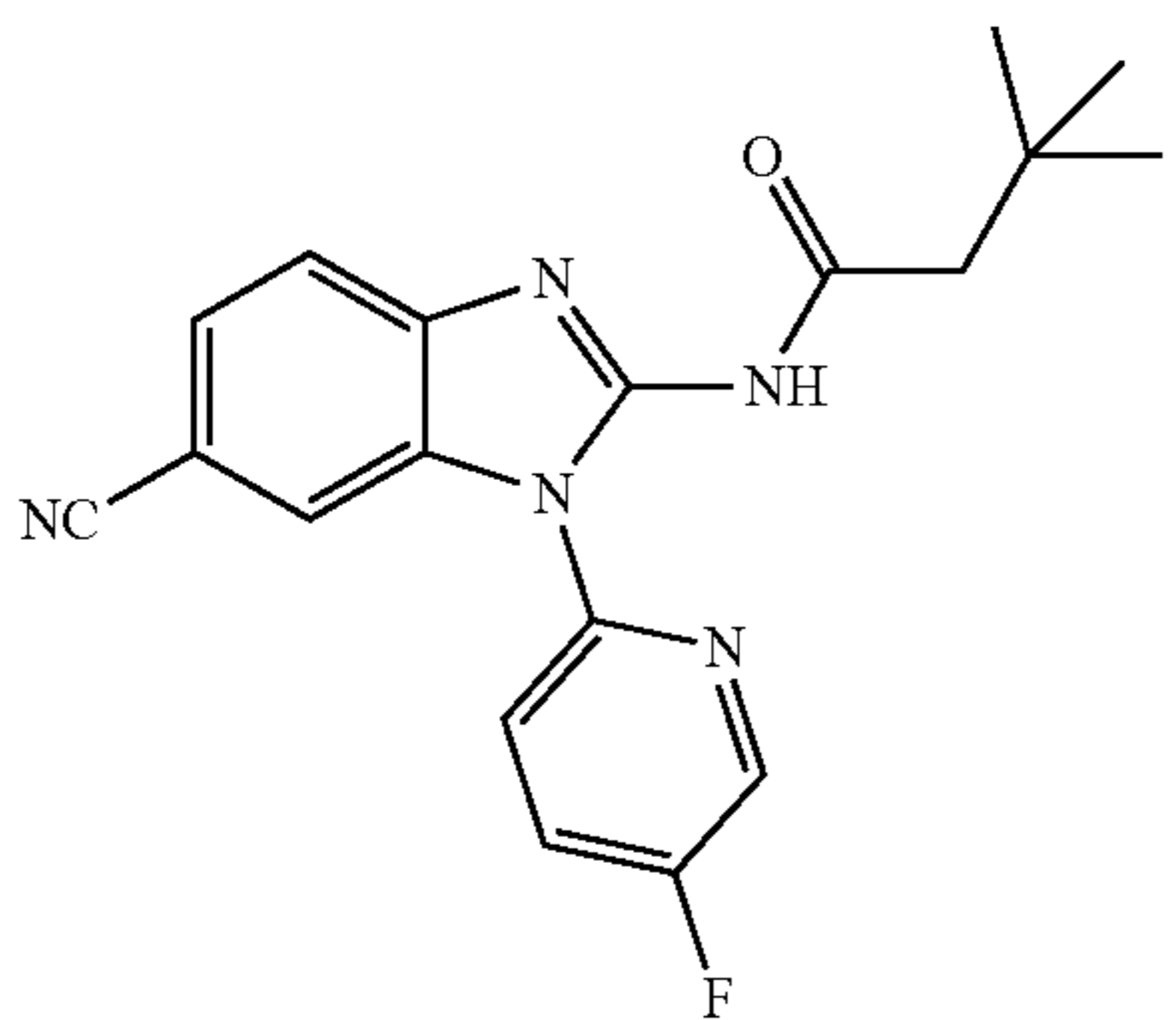
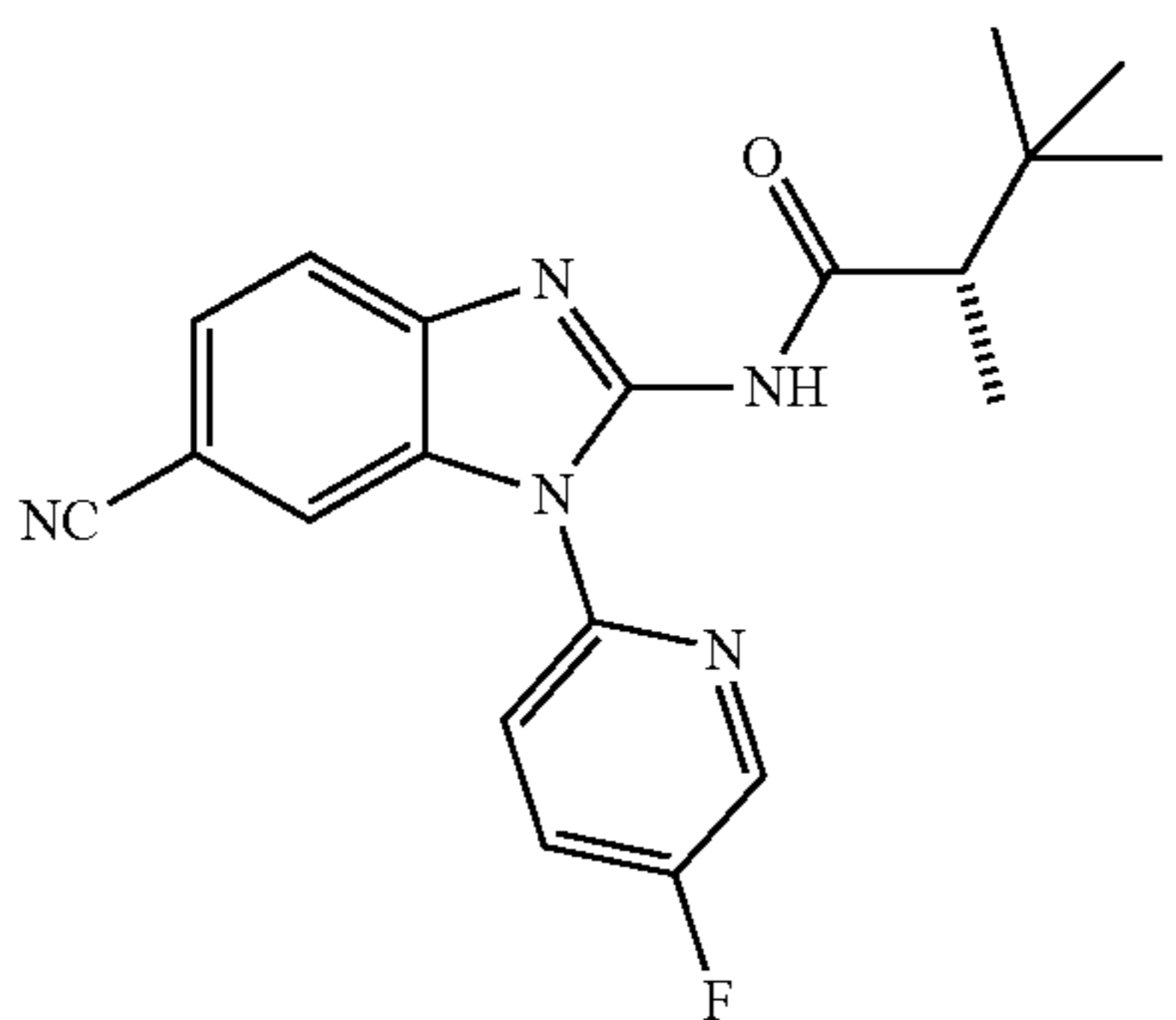
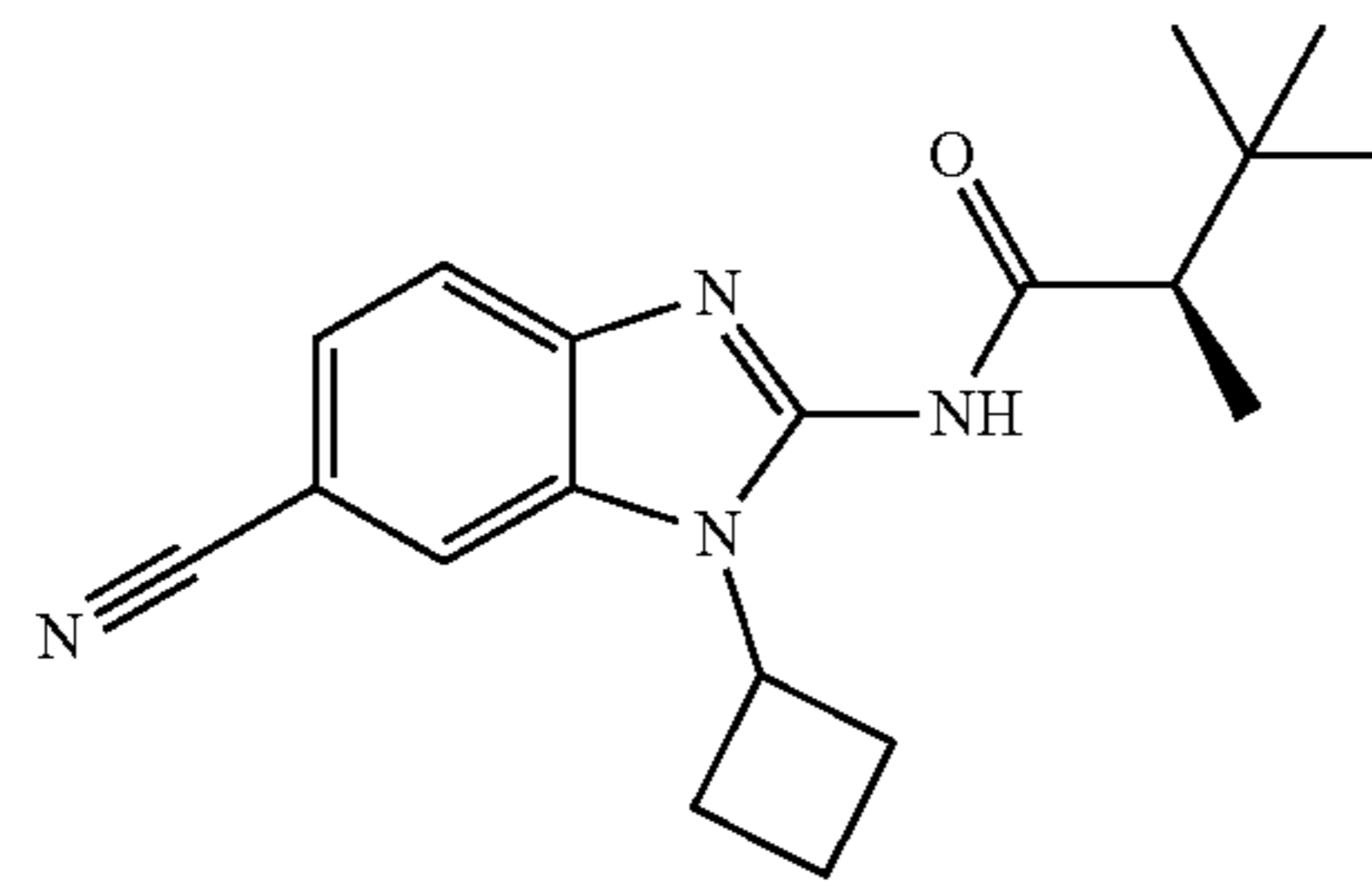
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
73	 <p style="text-align: center;">$C_{19}H_{18}FN_5O$</p>	(S)-N-(6-cyano-1-(5-fluoropyridin-2-yl)-1H-benzo[d]imidazol-2-yl)-2,3-dimethylbutanamide	7	B	3.4	352
74	 <p style="text-align: center;">$C_{19}H_{18}FN_5O$</p>	N-(6-cyano-1-(5-fluoropyridin-2-yl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	9	B	3.4	352
75	 <p style="text-align: center;">$C_{20}H_{20}FN_5O$</p>	(S)-N-(6-cyano-1-(5-fluoropyridin-2-yl)-1H-benzo[d]imidazol-2-yl)-2,3,3-trimethylbutanamide	7	B	3.6	366
76	 <p style="text-align: center;">$C_{19}H_{24}N_4O$</p>	(R)-N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2,3,3-trimethylbutanamide	7	A	5.3	325

TABLE 1-continued

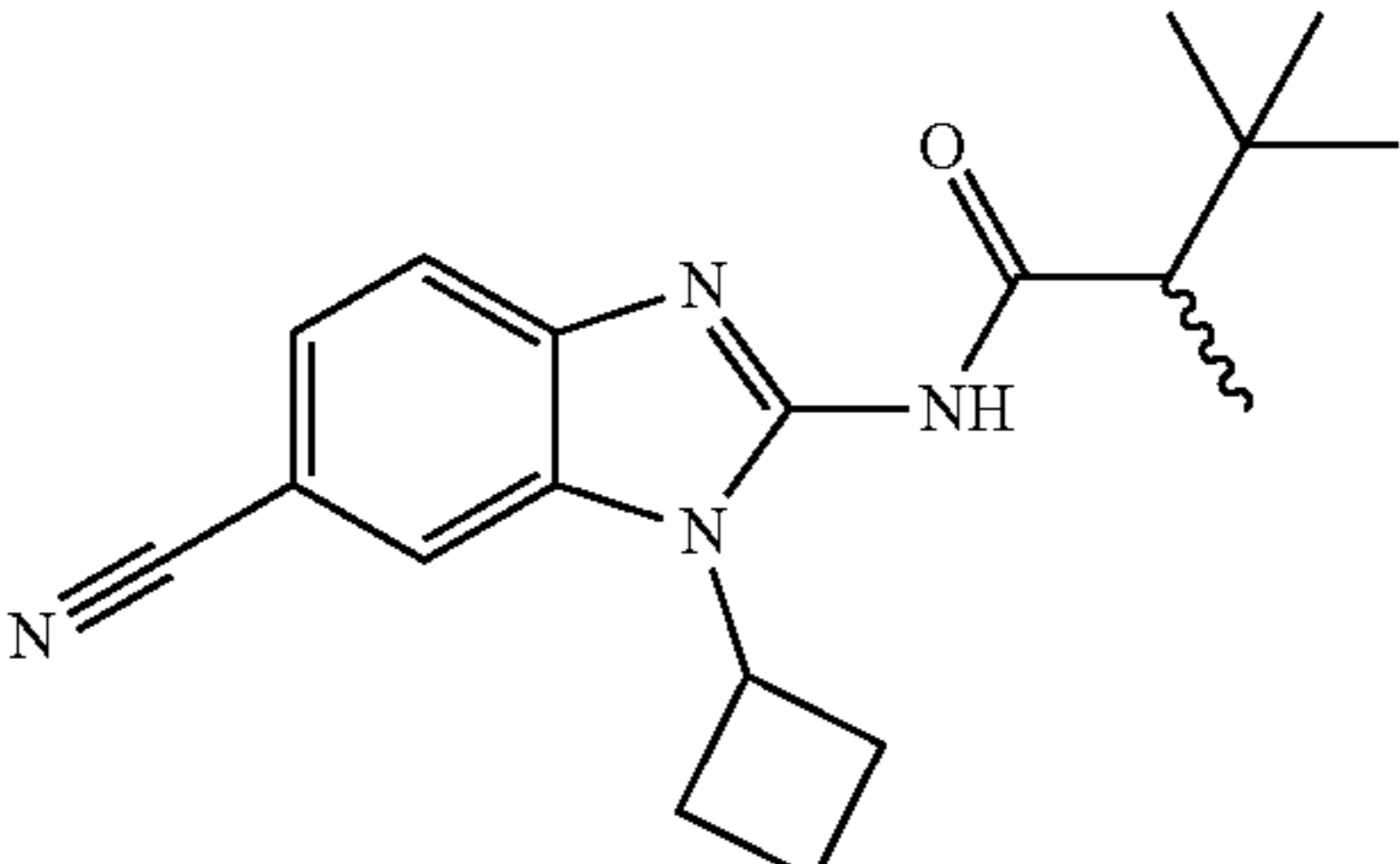
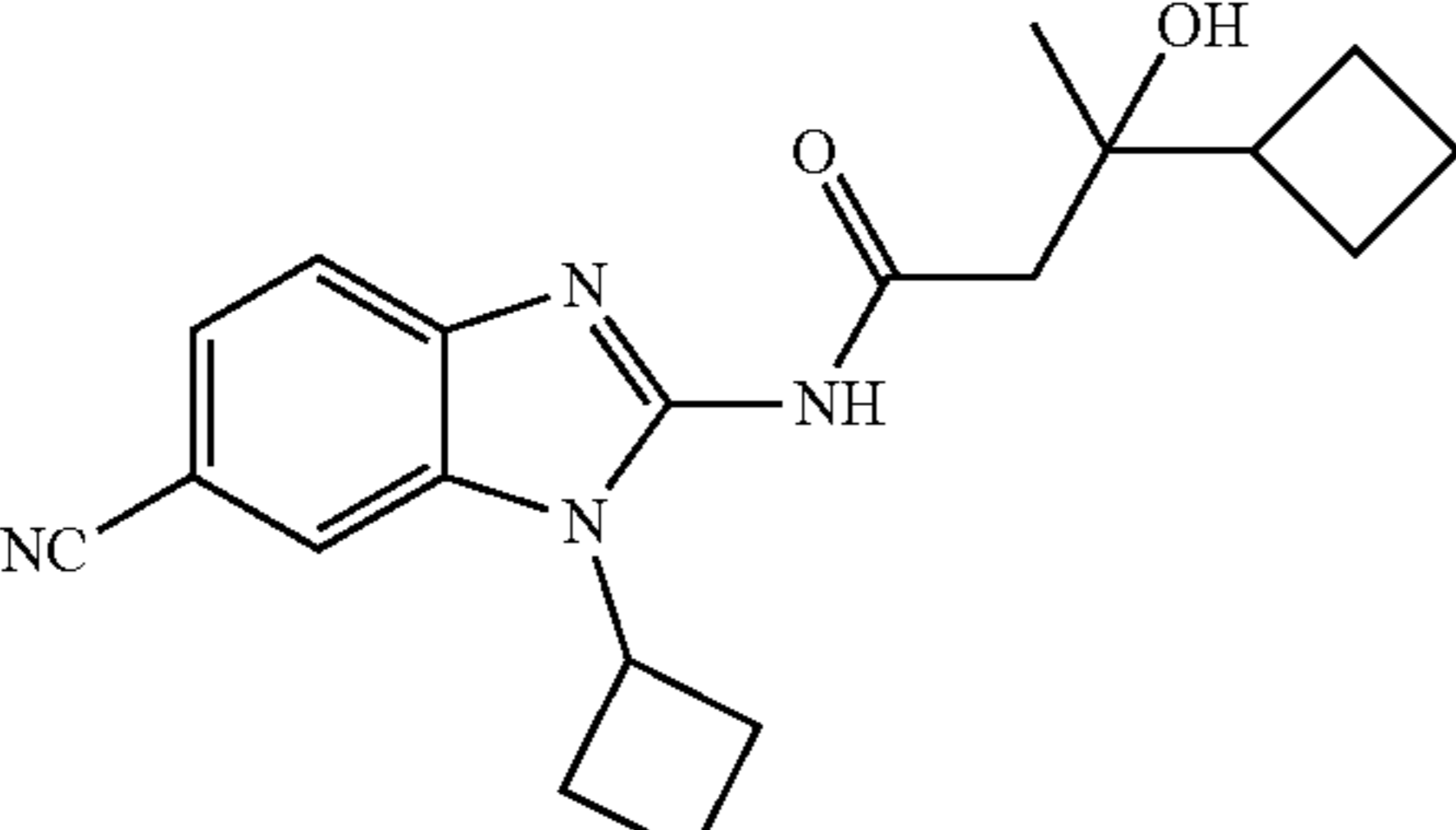
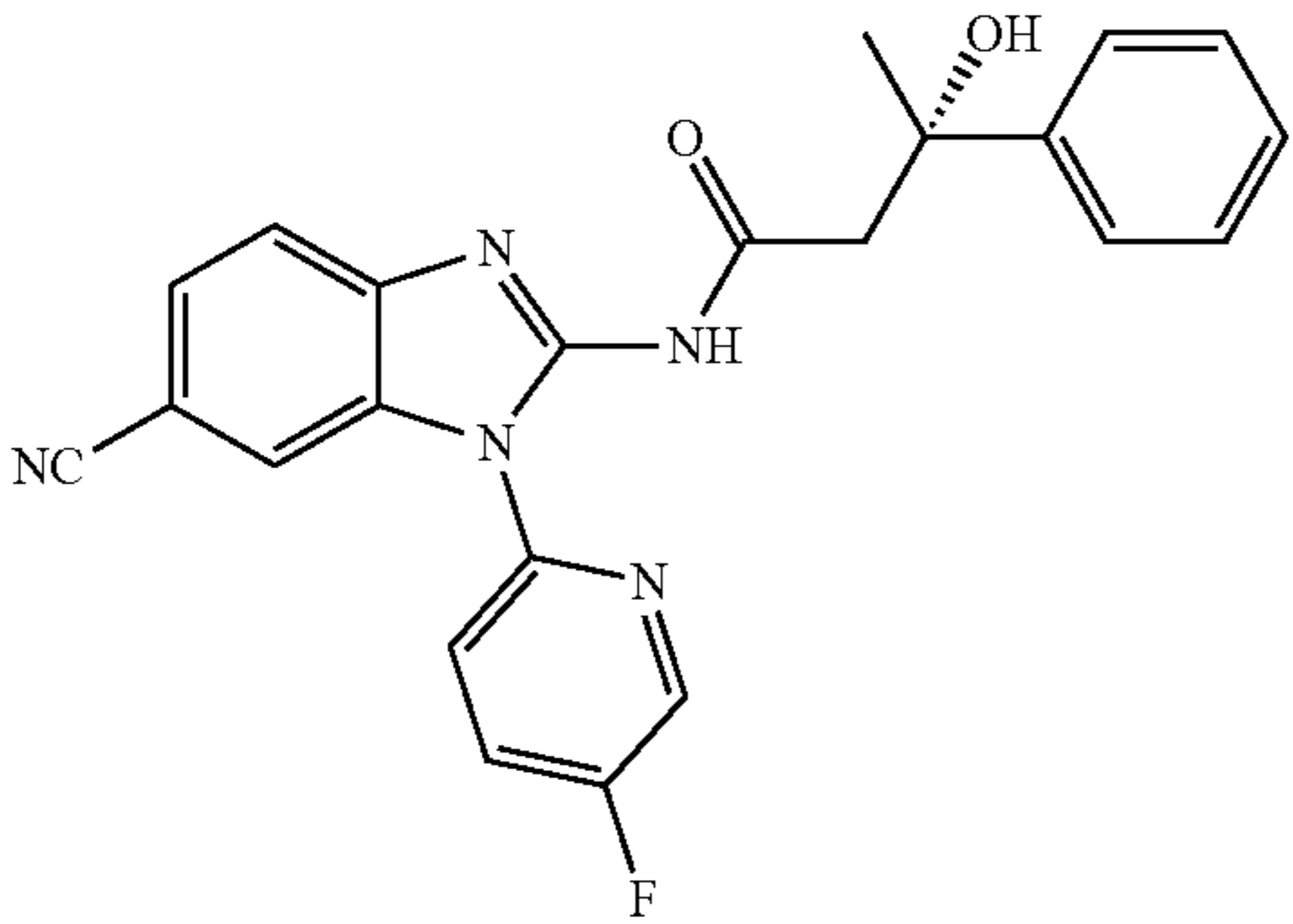
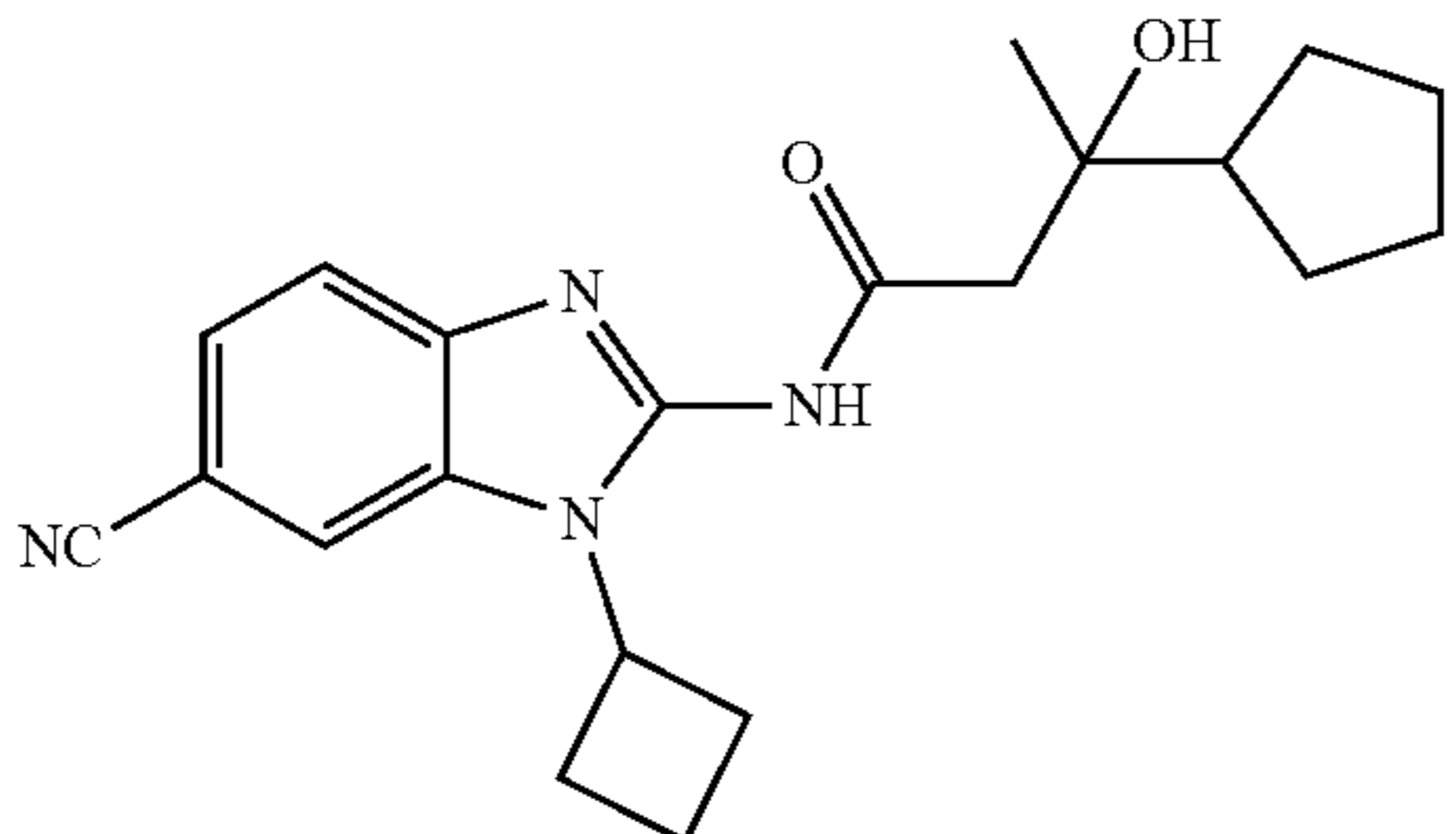
List of Examples, Synthetic Routes and Analytical Data							
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Re-tension time (min)	LCMS m/z	
77	 $C_{19}H_{24}N_4O$	N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2,3,3-trimethylbutanamide	7	A	5.3	325	
78	 $C_{20}H_{24}N_4O_2$	N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-cyclobut-3-hydroxybutanamide	7	B	3.3	353	
79	 $C_{23}H_{18}FN_5O_2$	(S)-N-(6-cyano-1-(5-fluoropyridin-2-yl)-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	7	B	3.3	416	
80	 $C_{21}H_{26}N_4O_2$	N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-cyclopentyl-3-hydroxybutanamide	7	B	3.5	367	

TABLE 1-continued

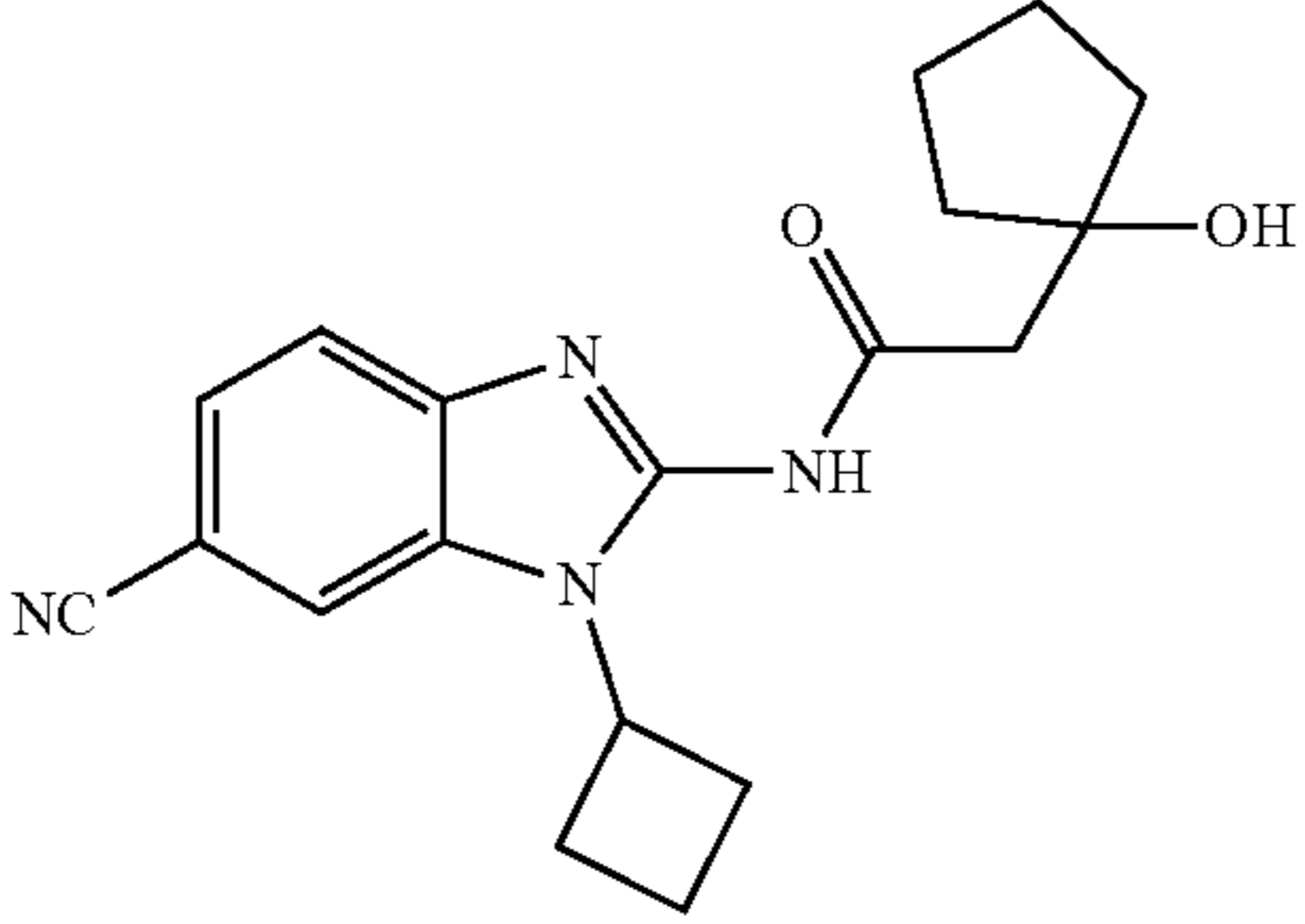
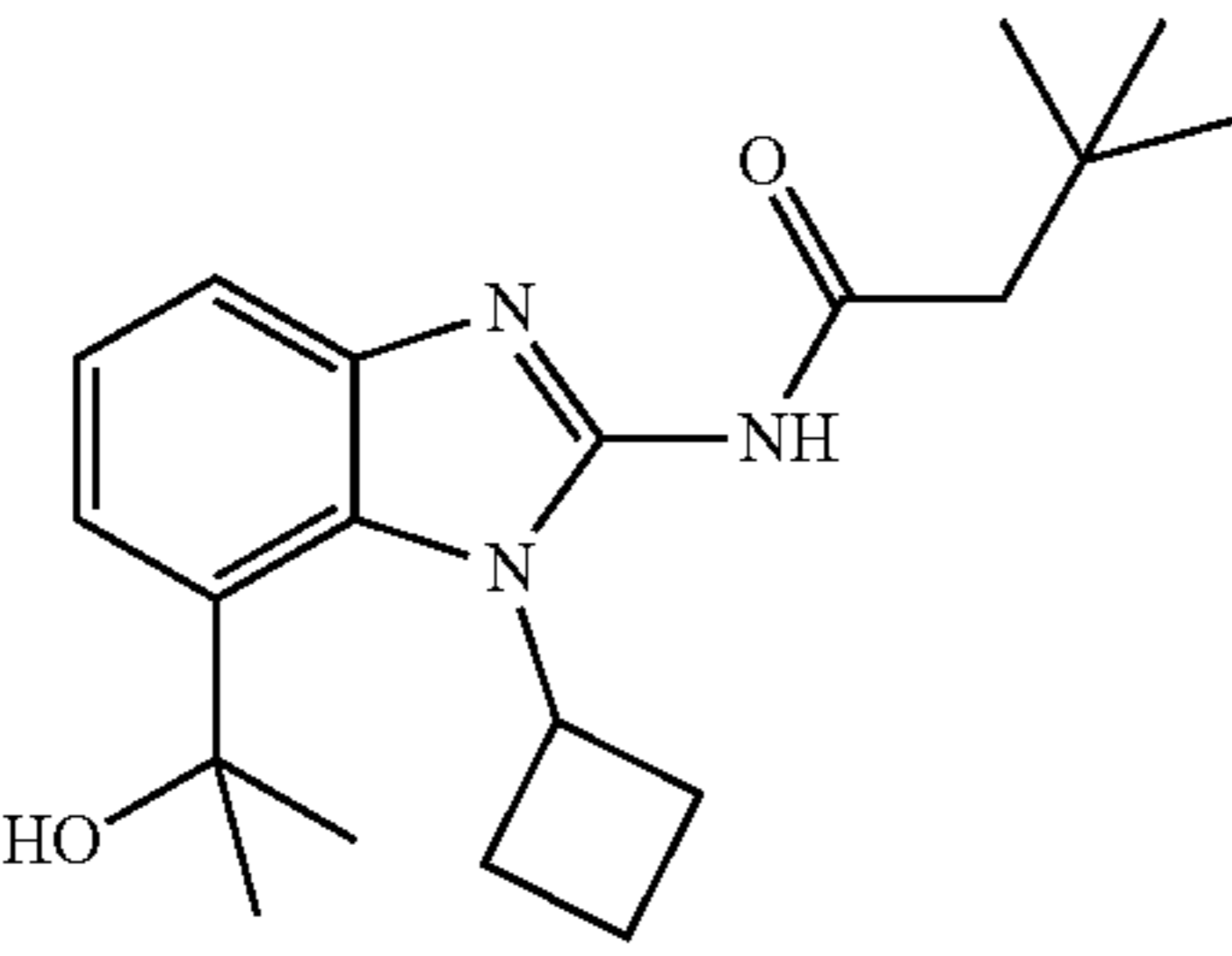
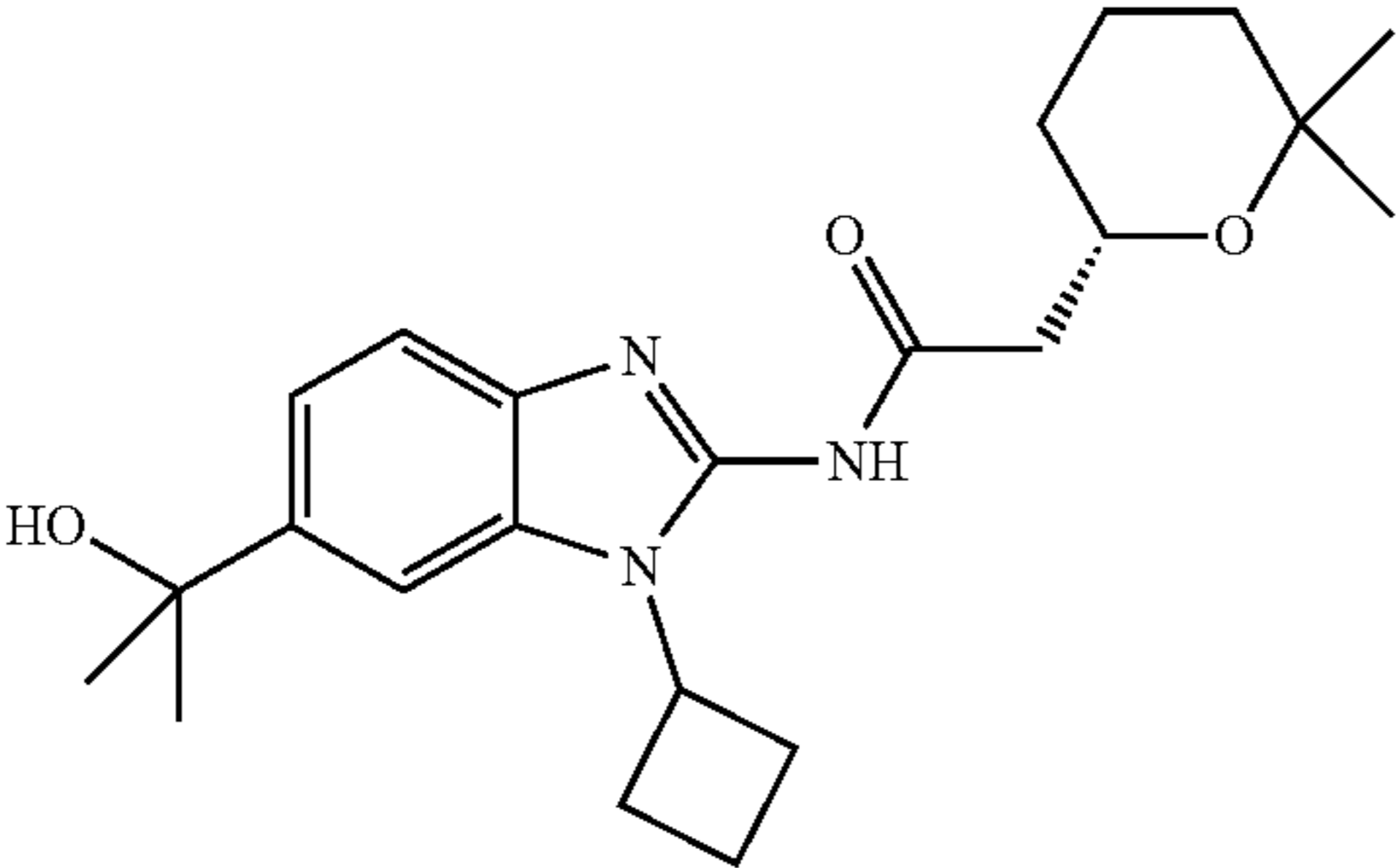
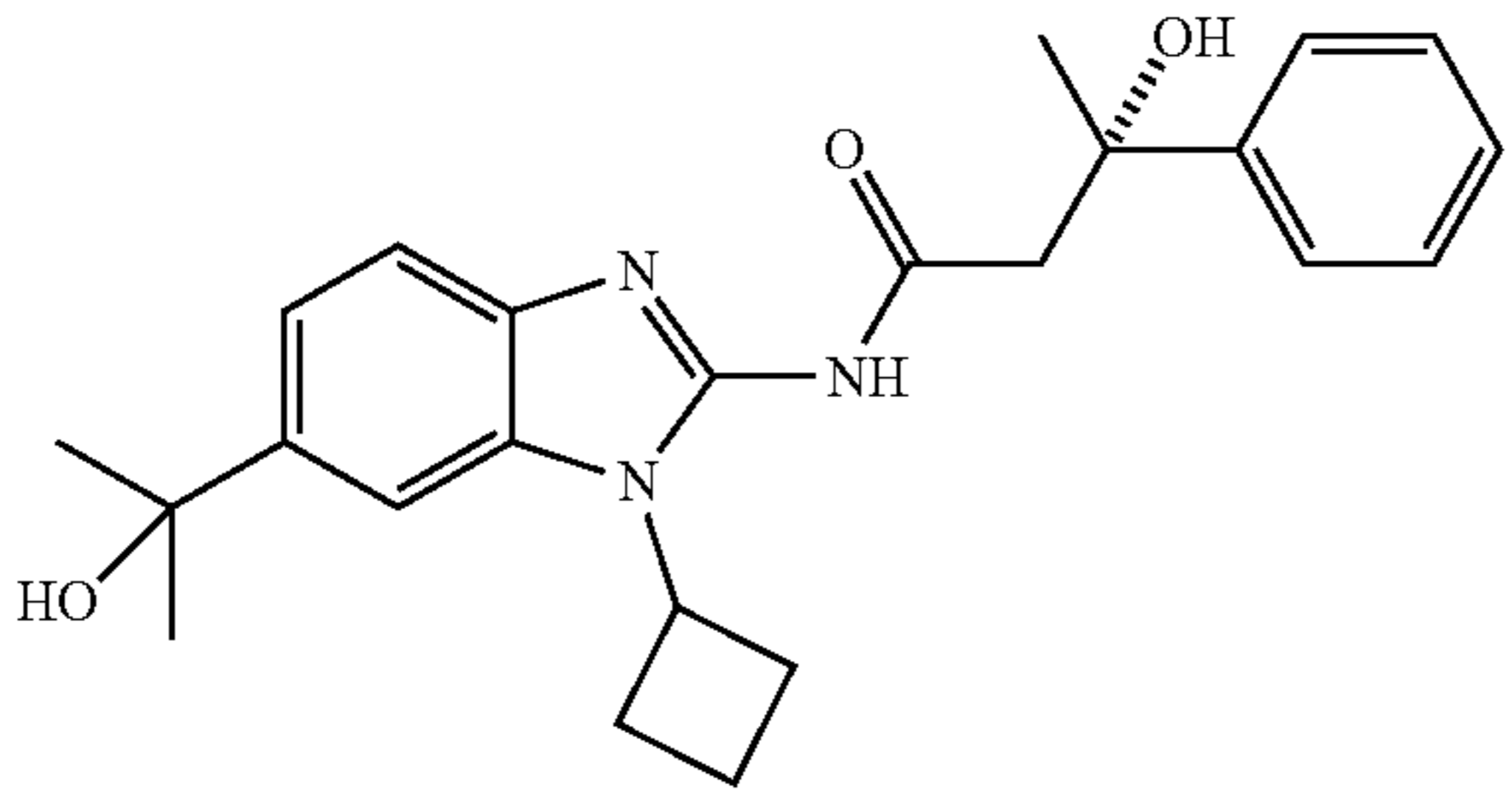
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
81	 <p>$C_{19}H_{22}N_4O_2$</p>	N-(6-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-2-(1-hydroxycyclopentyl)acetamide	7	B	3.0	339
82	 <p>$C_{20}H_{29}N_3O_2$</p>	N-(1-cyclobutyl-7-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7, followed by method described for Ex. 53 with Ex. 67 as starting material	B	3.5	344
83	 <p>$C_{23}H_{33}N_3O_3$</p>	(S)-N-(1-cyclobutyl-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-(6,6-dimethyltetrahydro-2H-pyran-2-yl)acetamide	7, followed by method described for Ex. 53	B	2.6	400
84	 <p>$C_{24}H_{29}N_3O_3$</p>	(S)-N-(1-cyclobutyl-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	7, followed by method described for Ex. 53	B	2.7	408

TABLE 1-continued

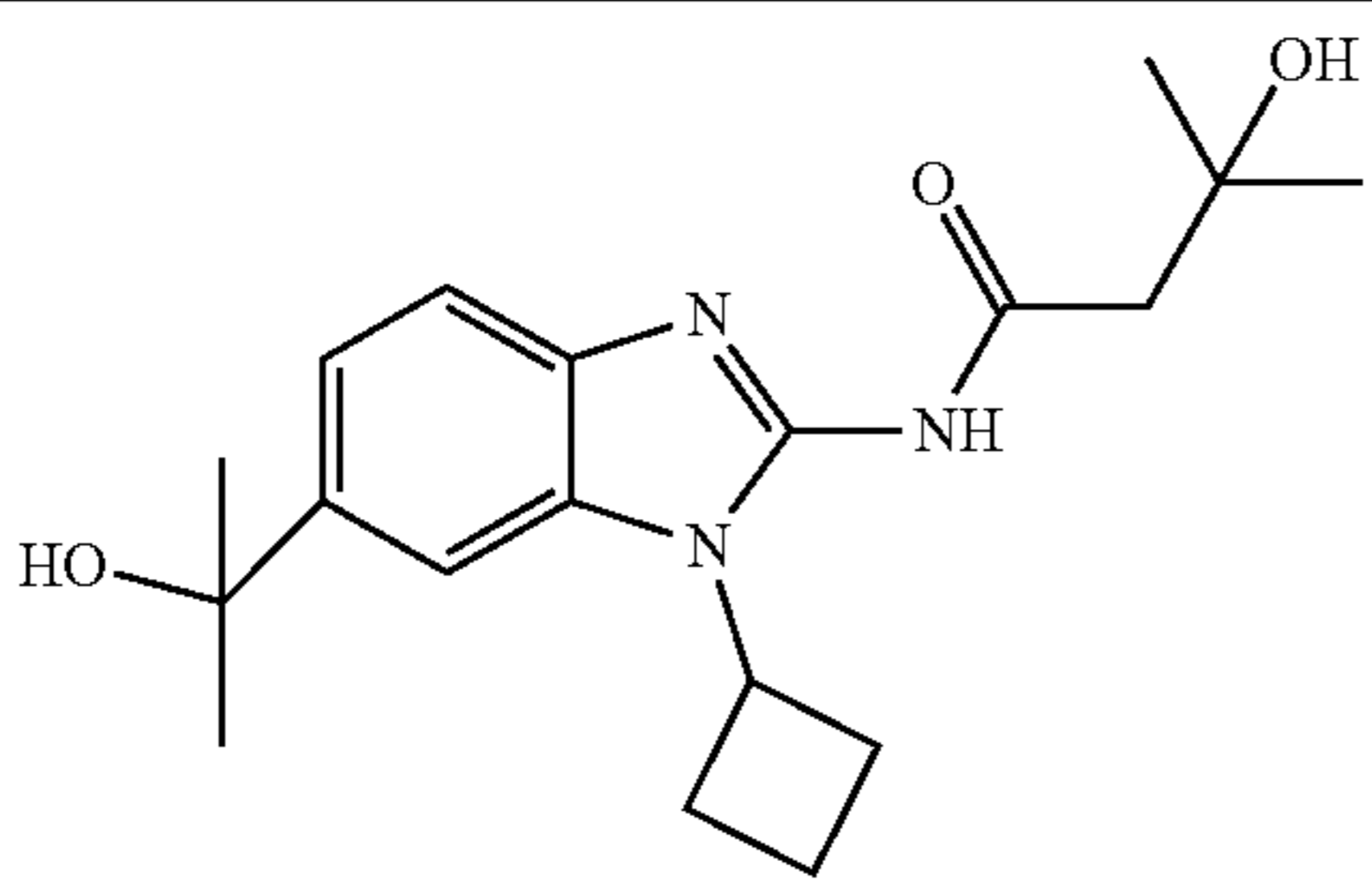
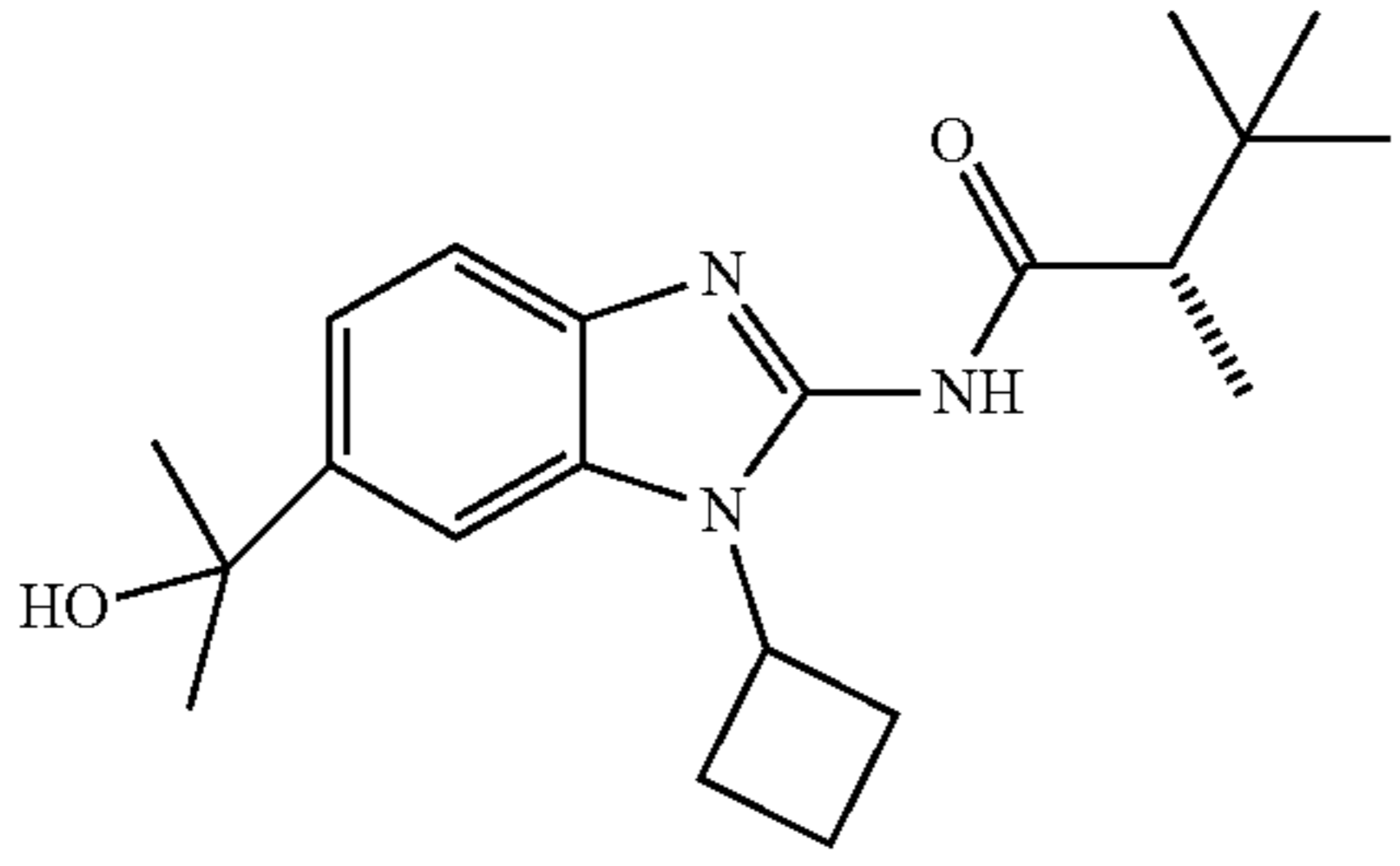
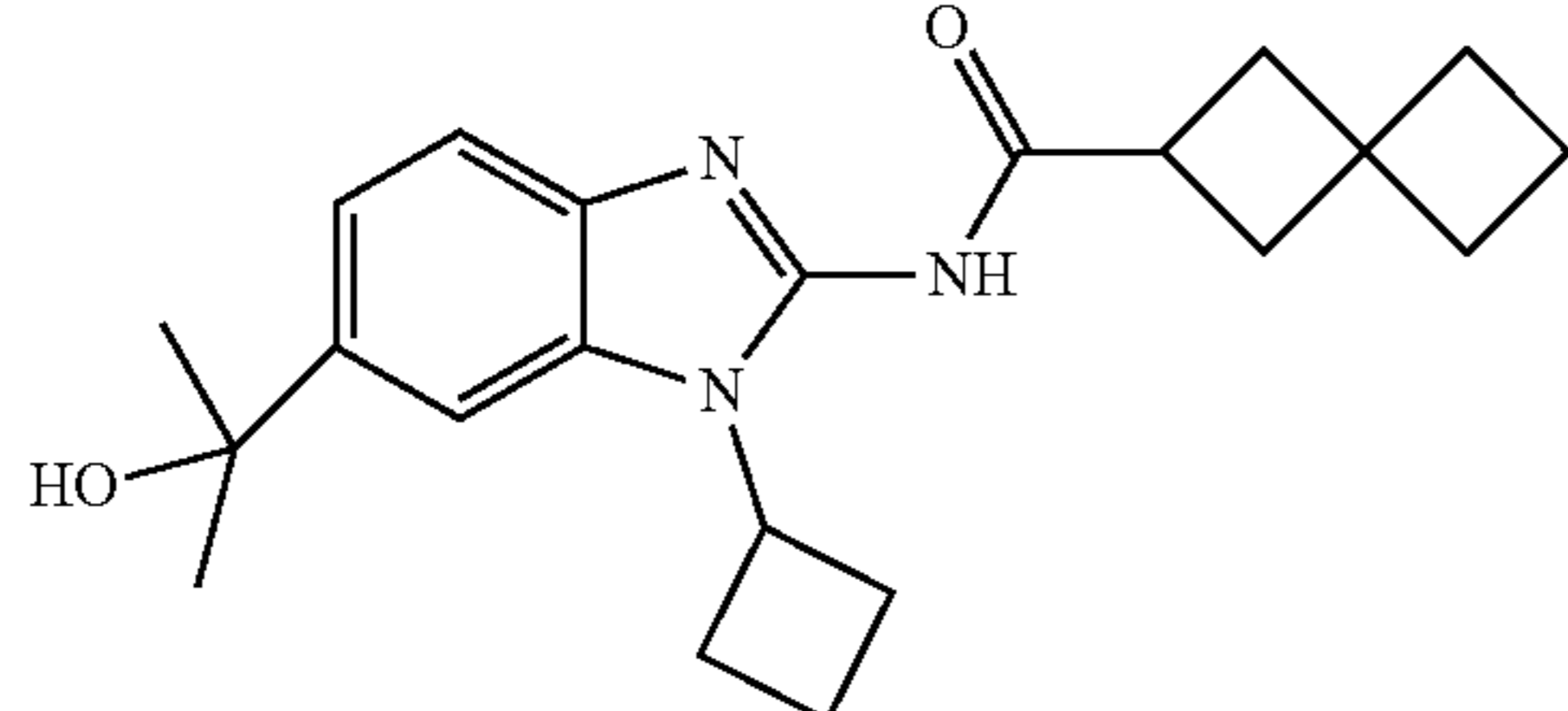
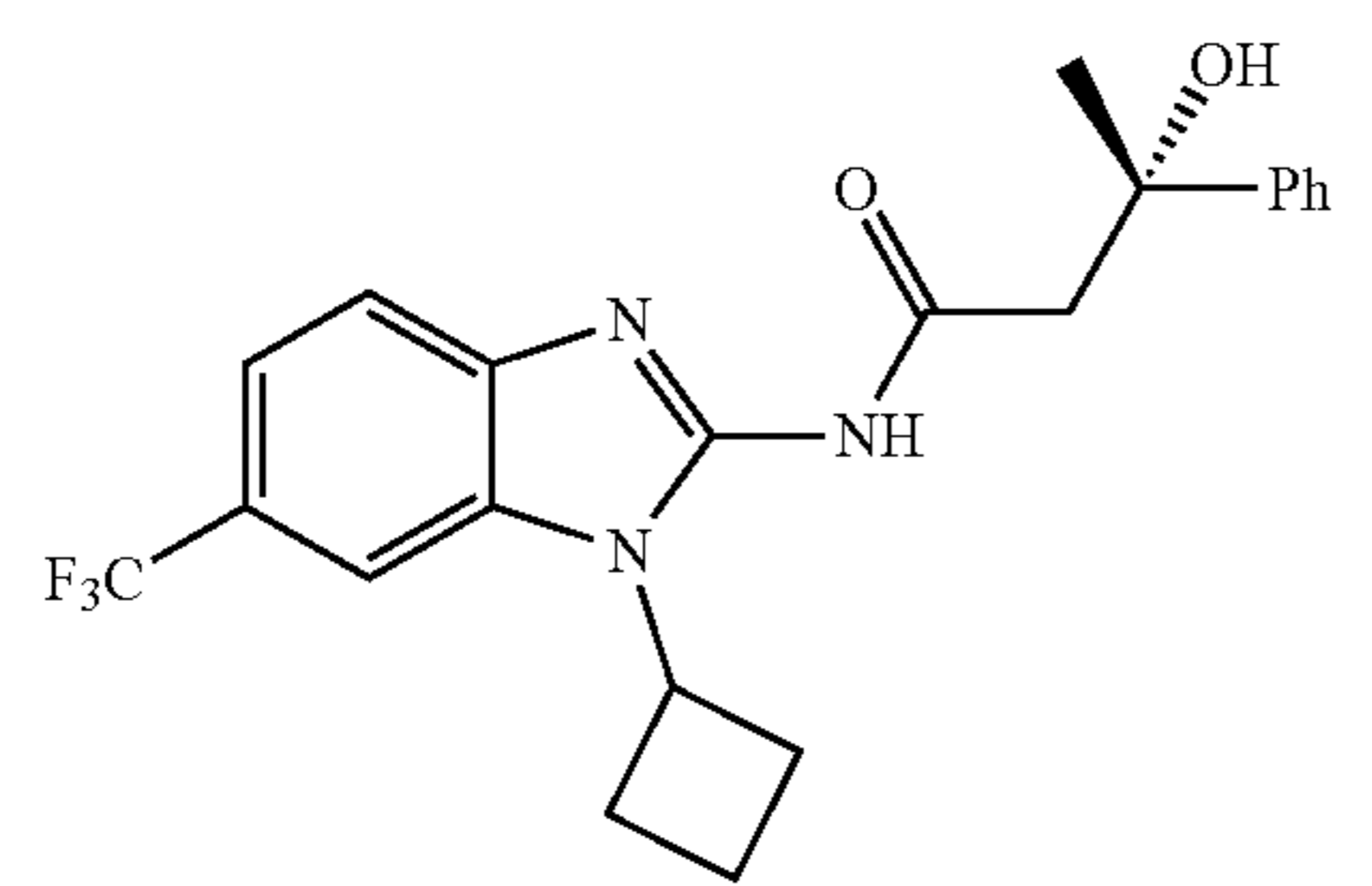
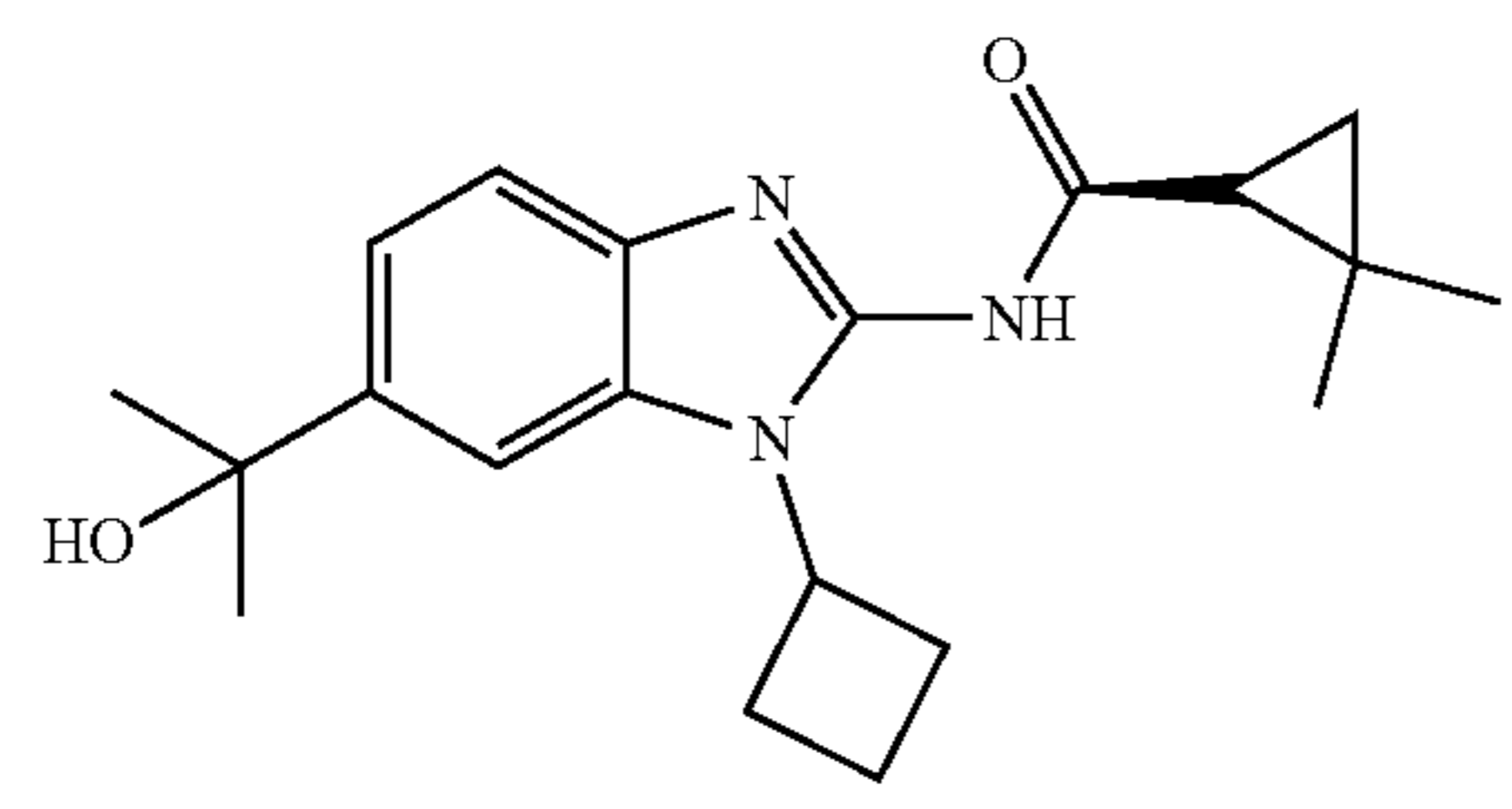
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
85	 $C_{19}H_{27}N_3O_3$	N-(1-cyclobutyl-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-methylbutanamide	7, followed by method described for Ex. 53	B	2.1	346
86	 $C_{21}H_{31}N_3O_2$	(S)-N-(1-cyclobutyl-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)-2,3,3-trimethylbutanamide	7, followed by method described for Ex. 53	B	2.6	358
87	 $C_{22}H_{29}N_3O_2$	N-(1-cyclobutyl-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)spiro[3.3]heptane-2-carboxamide	7, followed by method described for Ex. 53	B	2.7	368
88	 $C_{22}H_{22}F_3N_3O_2$	(S)-N-(1-cyclobutyl-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	7	B	3.9	418
89	 $C_{20}H_{27}N_3O_2$	(R)-N-(1-cyclobutyl-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)-2,2-dimethylcyclopropane-1-carboxamide	7, followed by method described for Ex. 53	B	2.4	342

TABLE 1-continued

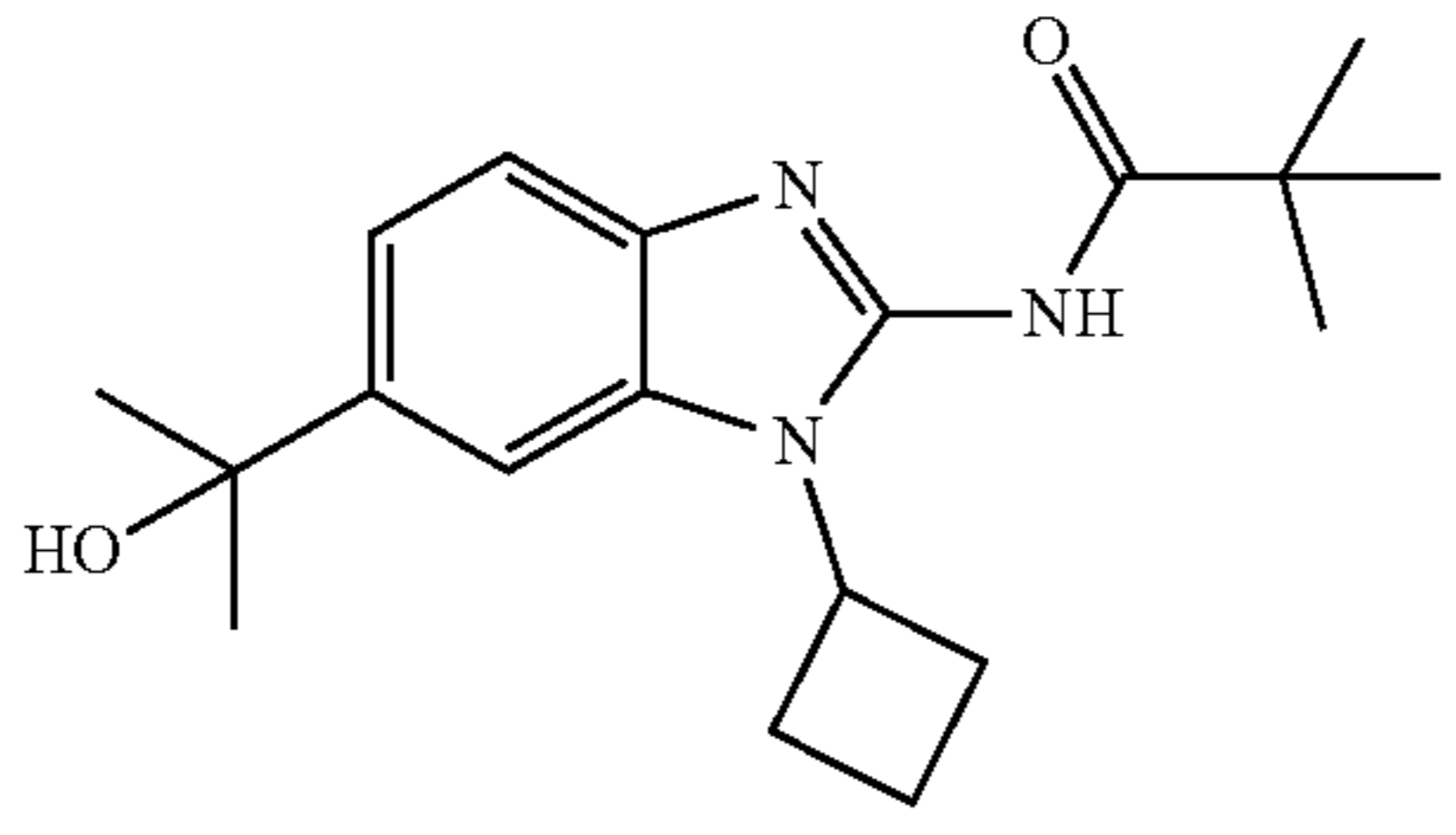
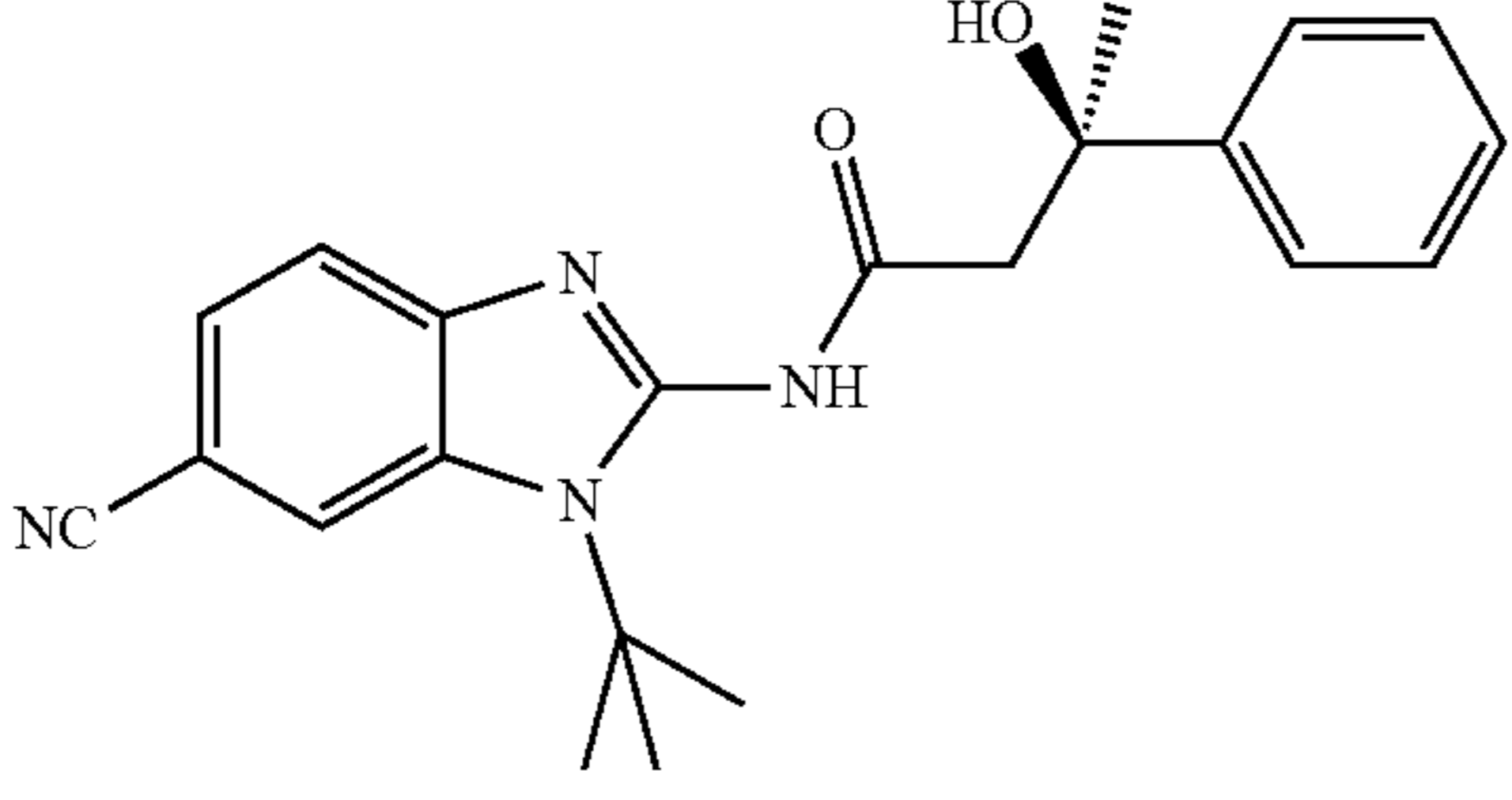
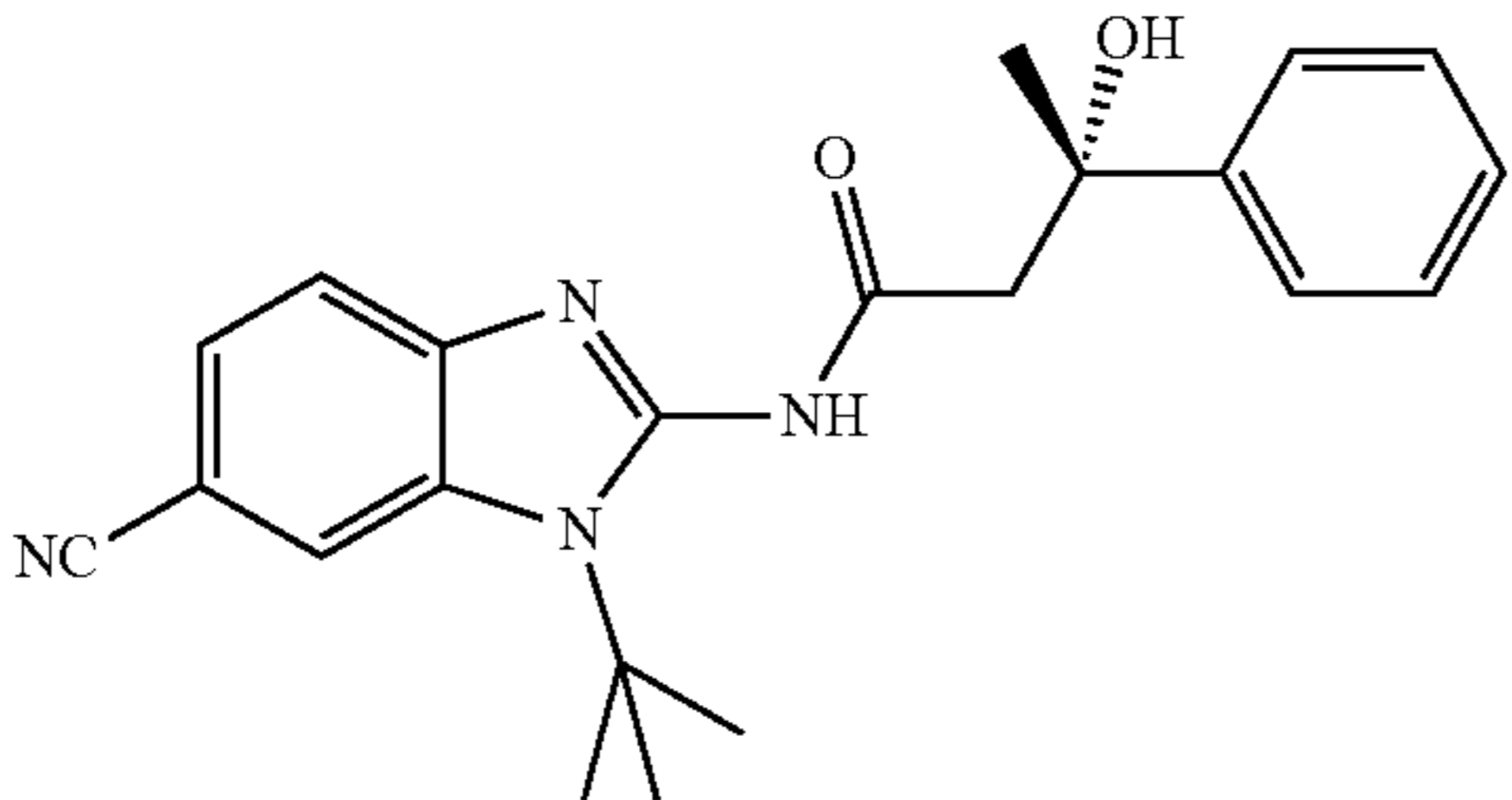
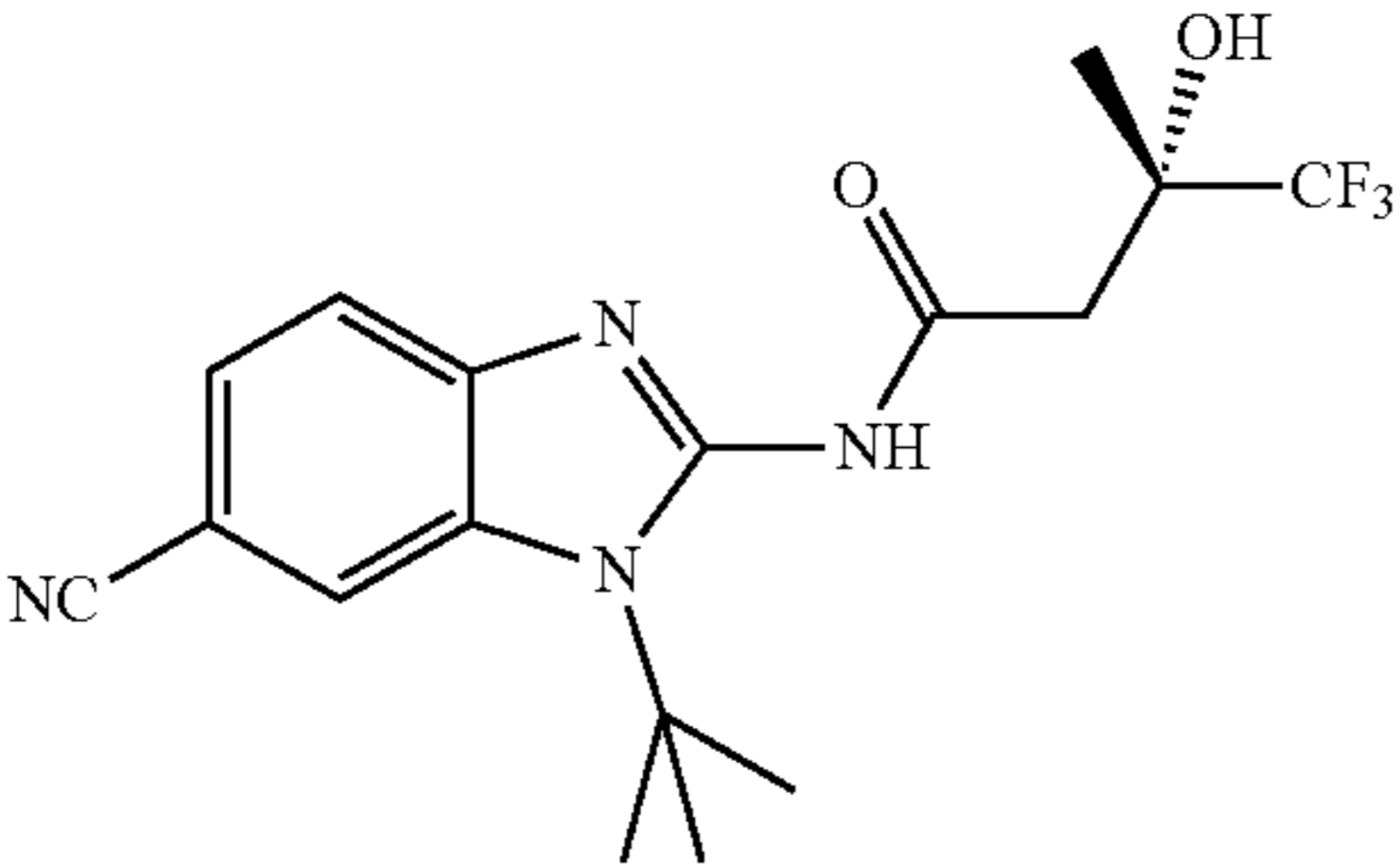
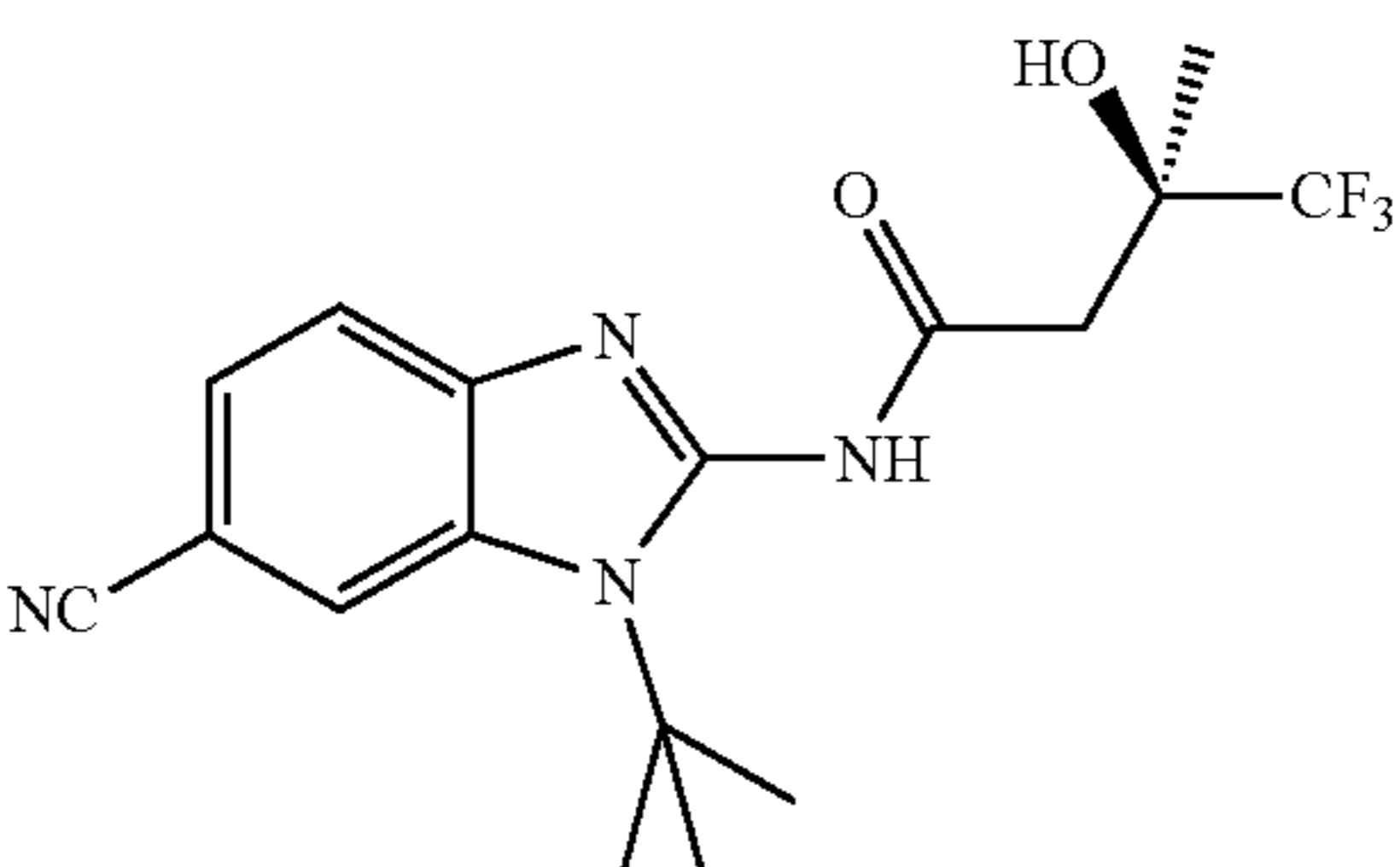
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
90	 $C_{19}H_{27}N_3O_2$	N-(1-cyclobutyl-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)pivalamide	7, followed by method described for Ex. 53	B	2.9	330
91	 $C_{22}H_{24}N_4O_2$	(R)-N-(1-(tert-butyl)-6-cyano-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	7	B	3.6	369
92	 $C_{22}H_{24}N_4O_2$	(S)-N-(1-(tert-butyl)-6-cyano-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	7	B	3.6	369
93	 $C_{17}H_{19}F_3N_4O_2$	(S)-N-(1-(tert-butyl)-6-cyano-1H-benzo[d]imidazol-2-yl)-4,4,4-trifluoro-3-hydroxy-3-methylbutanamide	7	B	3.5	377
94	 $C_{17}H_{19}F_3N_4O_2$	(R)-N-(1-(tert-butyl)-6-cyano-1H-benzo[d]imidazol-2-yl)-4,4,4-trifluoro-3-hydroxy-3-methylbutanamide	7	B	3.5	377

TABLE 1-continued

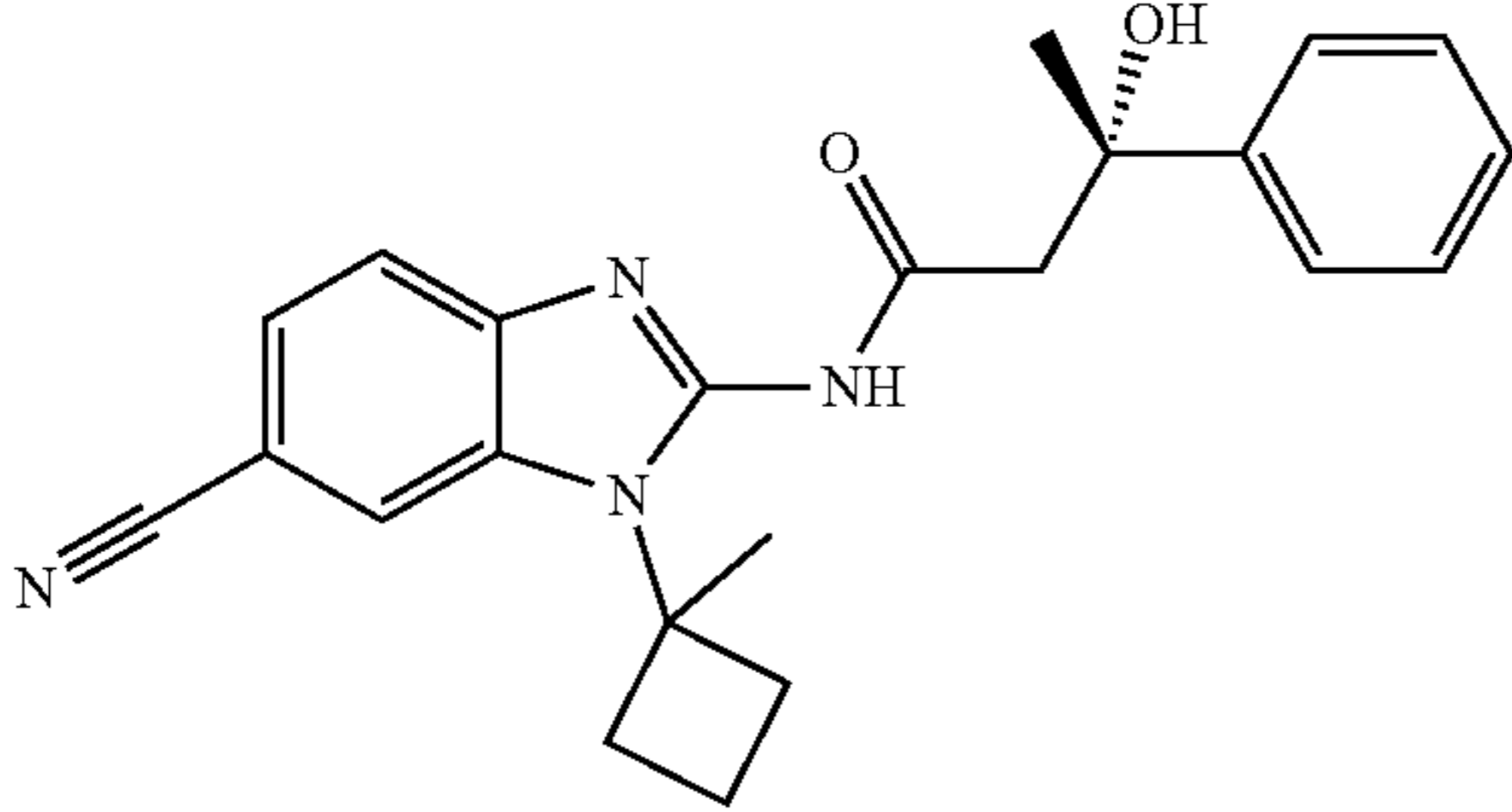
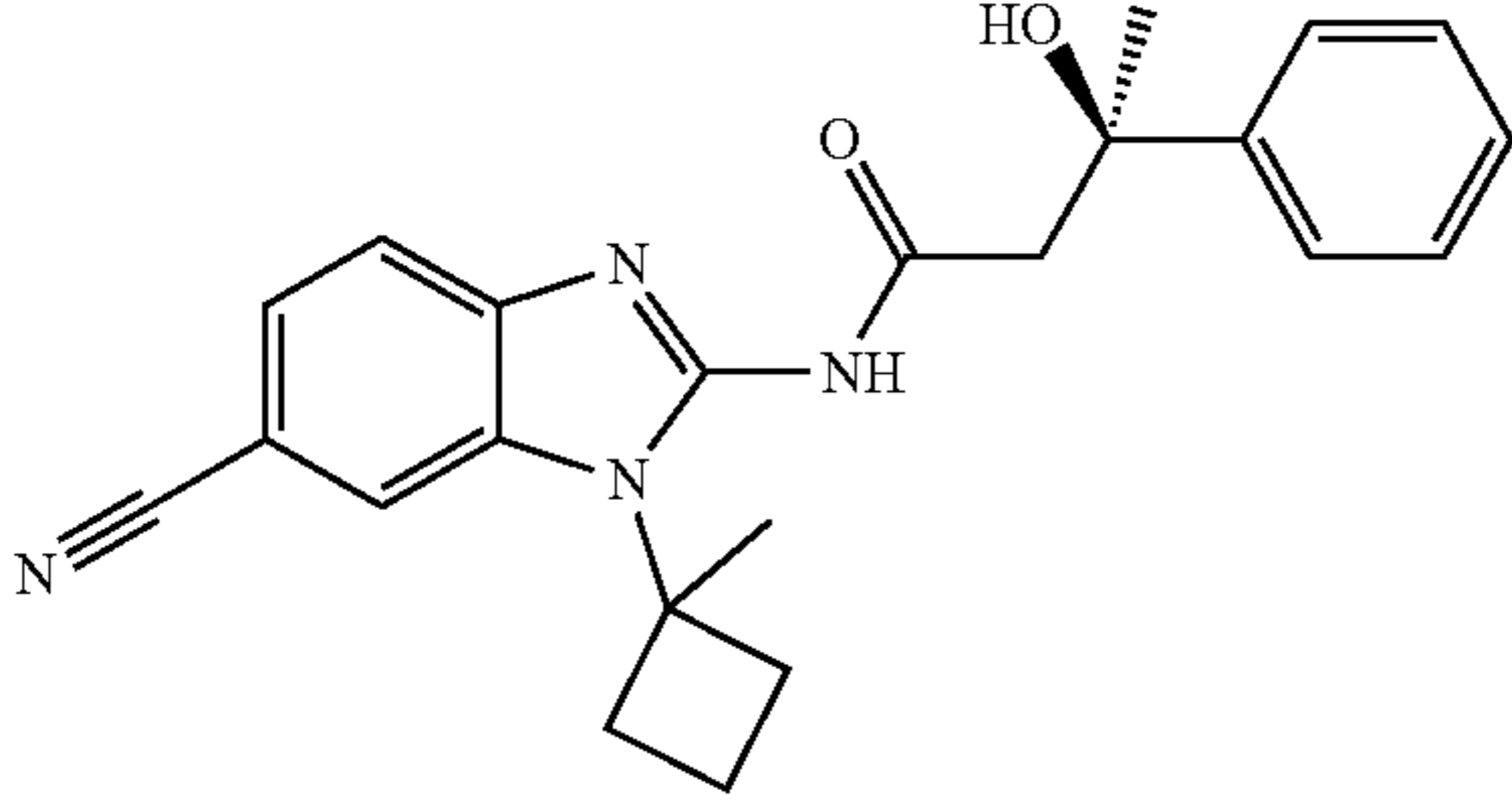
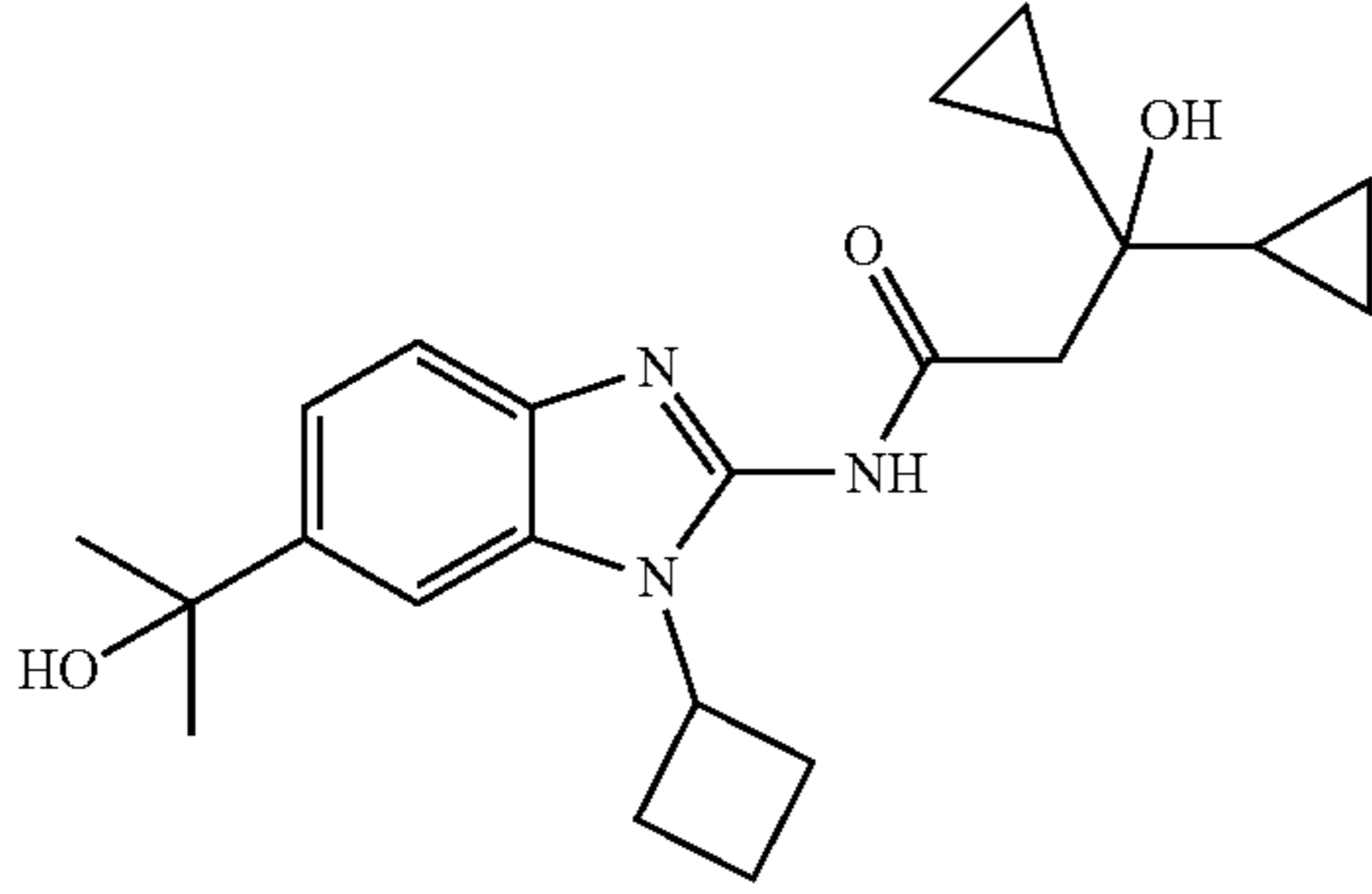
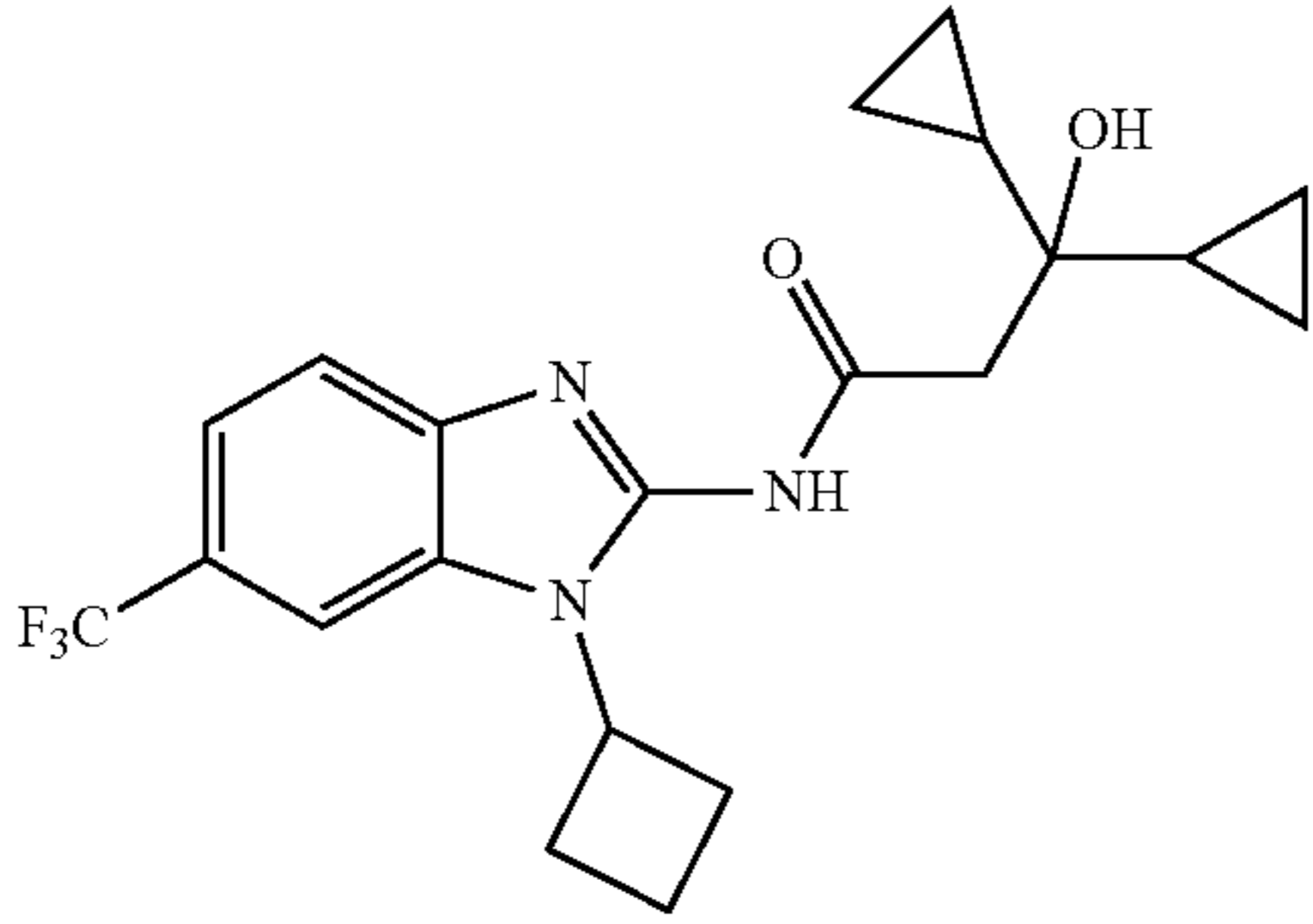
List of Examples, Synthetic Routes and Analytical Data							
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z	
95	 $C_{23}H_{24}N_4O_2$	(S)-N-(6-cyano-1-(1-methylcyclobutyl)-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	7	B	3.6	389	
96	 $C_{23}H_{24}N_4O_2$	(R)-N-(6-cyano-1-(1-methylcyclobutyl)-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	7	B	3.6	389	
97	 $C_{23}H_{31}N_3O_3$	N-(1-cyclobutyl-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)-3,3-dicyclopropyl-3-hydroxypropanamide	7, followed by method described for Ex. 53	B	2.6	398	
98	 $C_{21}H_{24}F_3N_3O_2$	N-(1-cyclobutyl-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-3,3-dicyclopropyl-3-hydroxypropanamide	7	B	4.0	408	

TABLE 1-continued

List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
99	 $C_{21}H_{22}ClN_3O_2$	(S)-N-(6-chloro-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	7	B	3.8	384
100	 $C_{21}H_{22}ClN_3O_2$	(R)-N-(6-chloro-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	7	B	3.7	384
101	 $C_{21}H_{27}N_3O_2$	N-(1-cyclobutyl-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)spiro[2.3]hexane-1-carboxamide	7, followed by method described for Ex. 53	B	2.5	354
102	 $C_{20}H_{25}F_2N_3O_2$	N-(1-cyclobutyl-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)-3,3-difluorocyclopentane-1-carboxamide	7, followed by method described for Ex. 53	B	2.7	378
103	 $C_{21}H_{21}ClFN_3O_2$	(S)-N-(6-chloro-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3-(4-fluorophenyl)-3-hydroxybutanamide	7	B	3.9	402

TABLE 1-continued

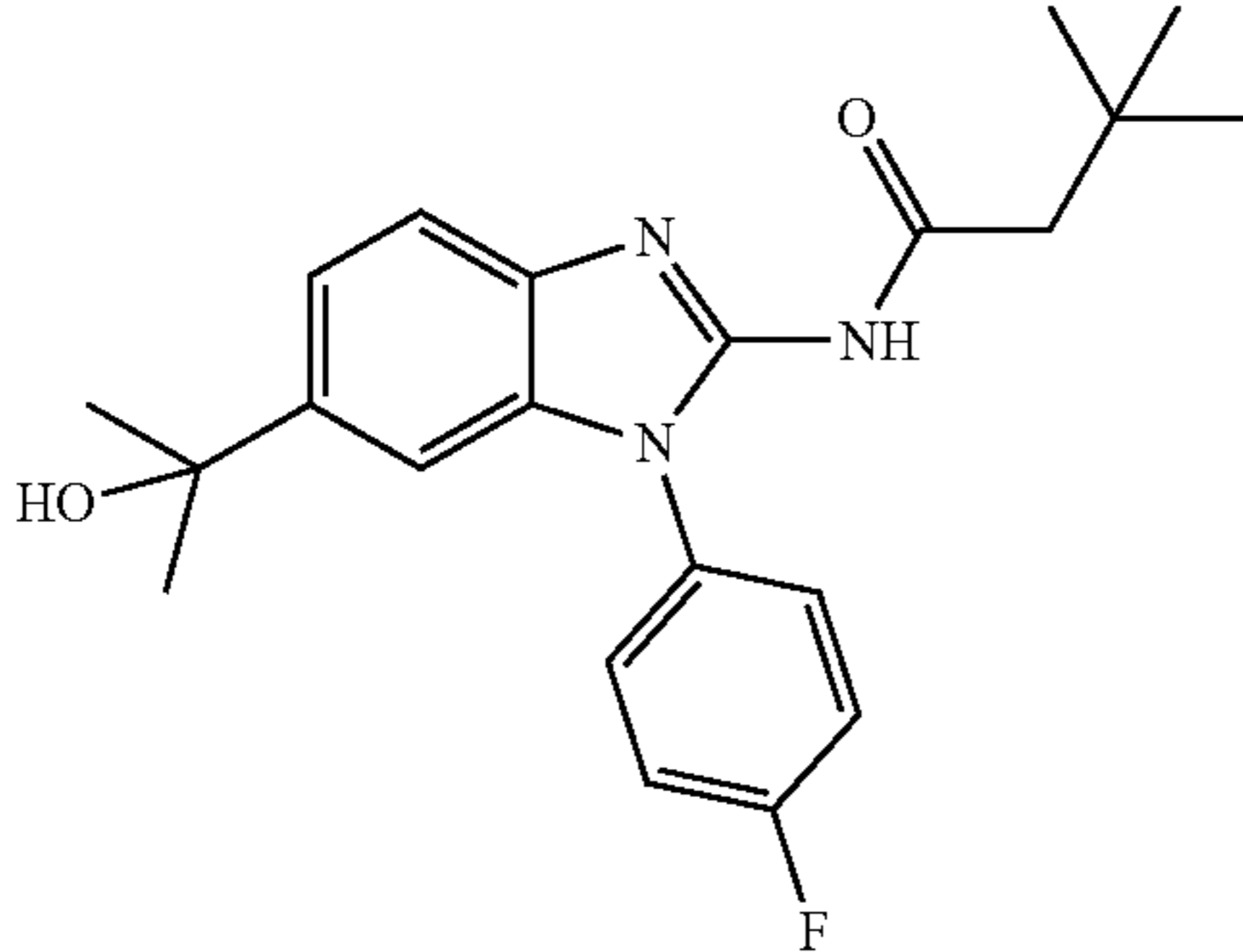
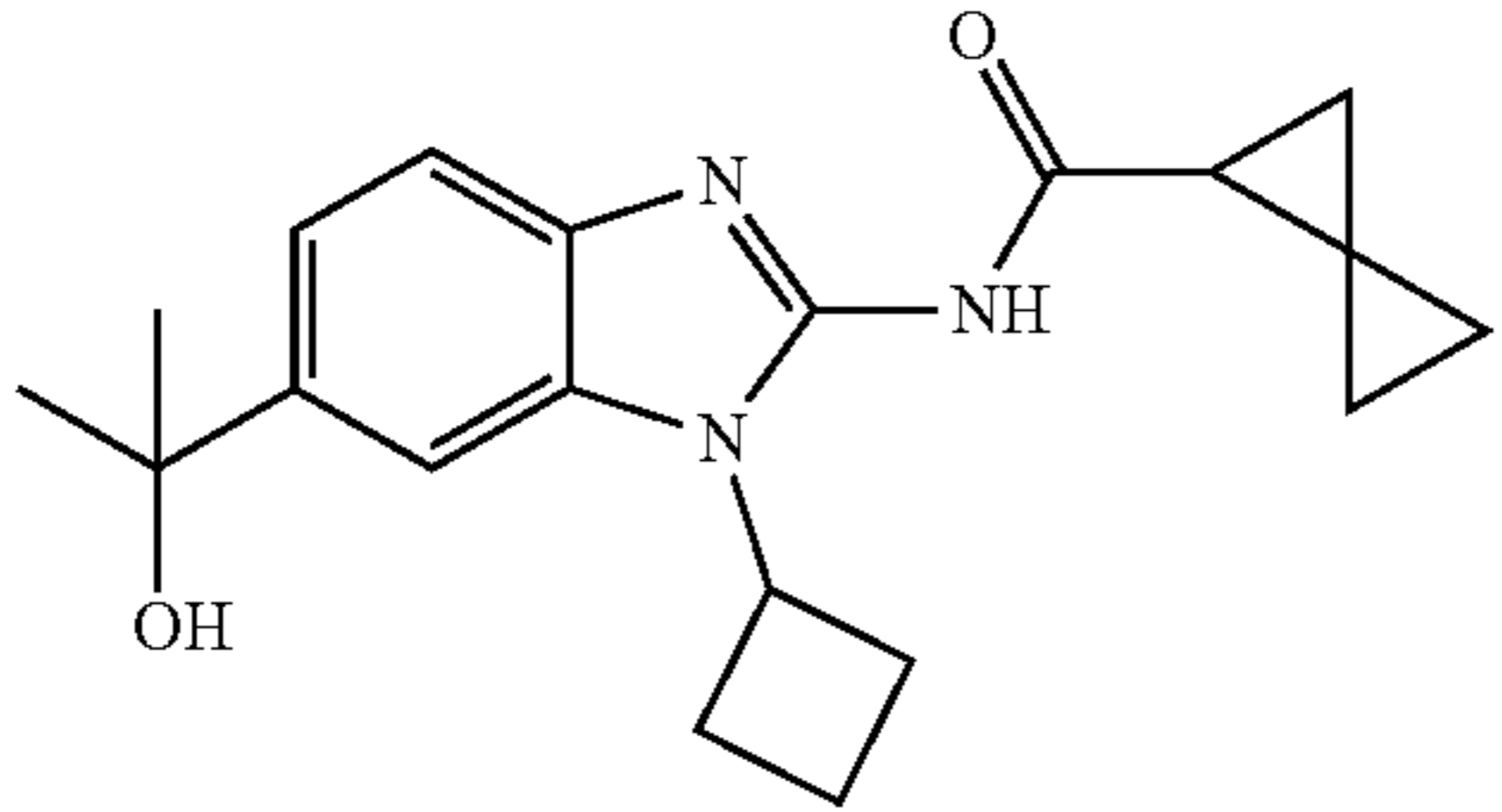
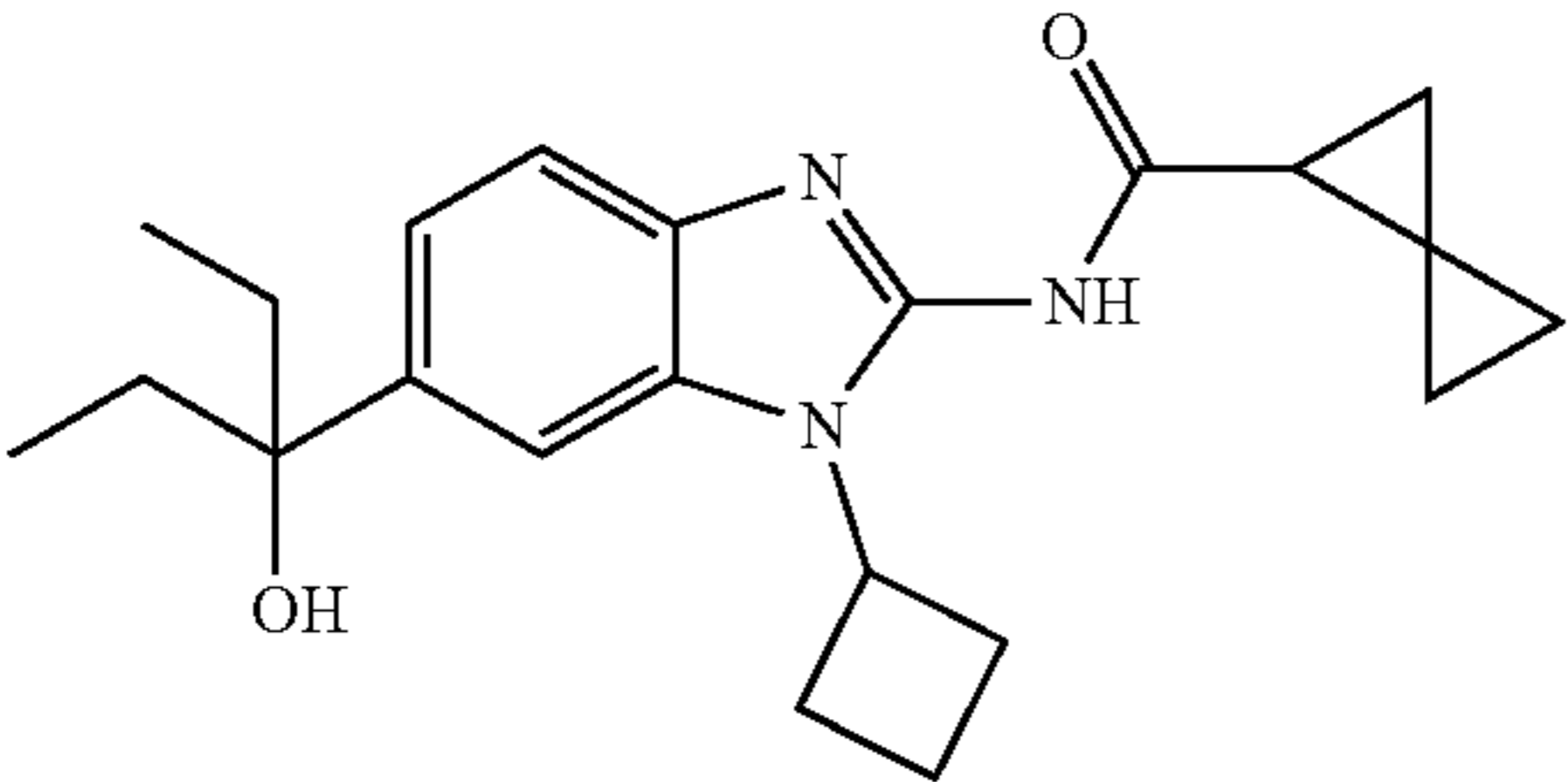
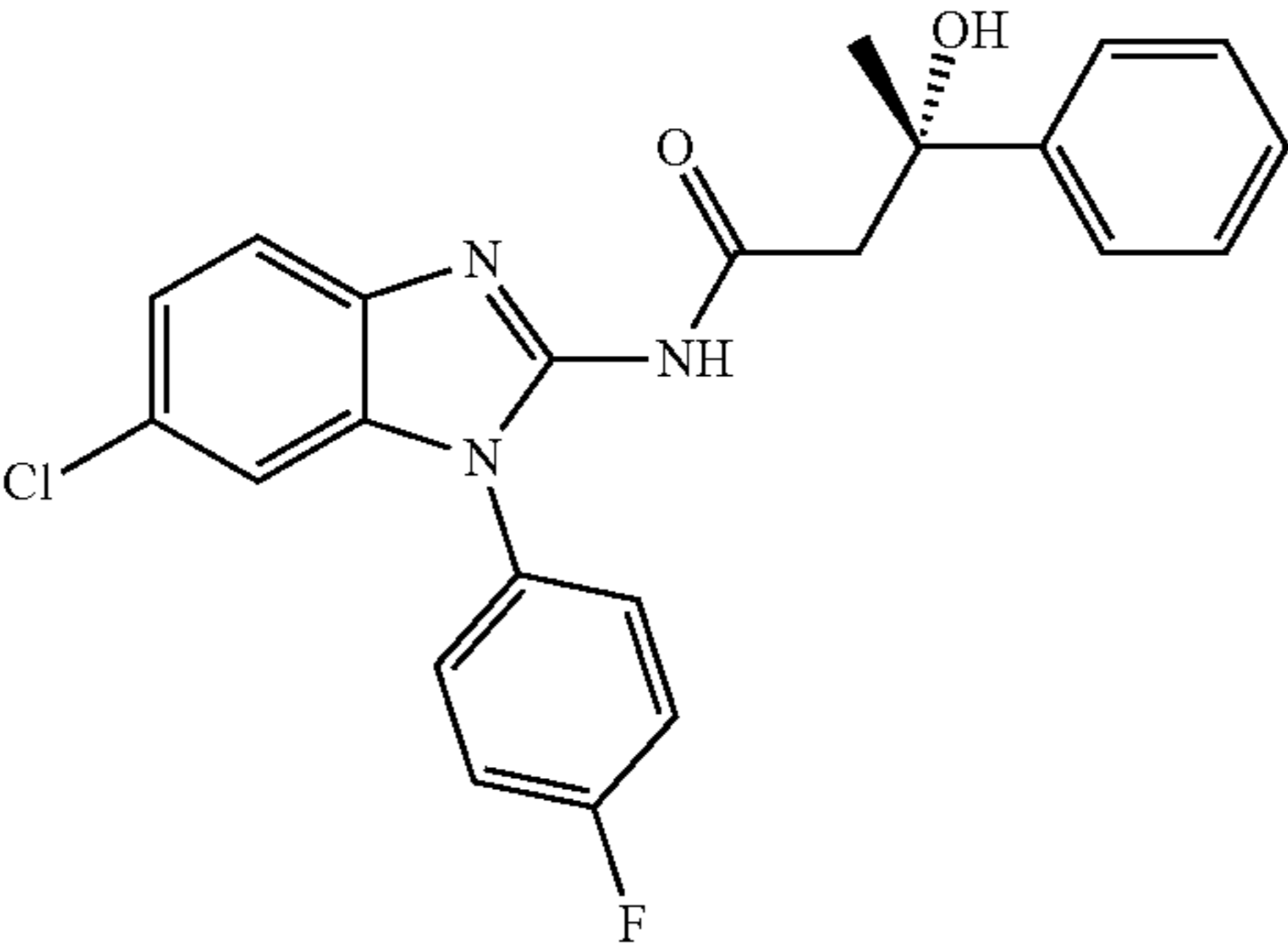
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
104	 <p style="text-align: center;">$C_{22}H_{26}FN_3O_2$</p>	N-(1-(4-fluorophenyl)-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7, followed by method described for Ex. 53	B	2.7	384
105	 <p style="text-align: center;">$C_{20}H_{25}N_3O_2$</p>	N-(1-cyclobutyl-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)spiro[2.2]pentane-1-carboxamide	7, followed by method described for Ex. 53	B	2.4	340
106	 <p style="text-align: center;">$C_{22}H_{29}N_3O_2$</p>	N-(1-cyclobutyl-5-(3-hydroxypentan-3-yl)-1H-benzo[d]imidazol-2-yl)spiro[2.2]pentane-1-carboxamide	7, followed by method described for Ex. 53 with EtMgBr	B	2.6	368
107	 <p style="text-align: center;">$C_{23}H_{19}ClFN_3O_2$</p>	(S)-N-(6-chloro-1-(4-fluorophenyl)-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	7	B	3.7	424

TABLE 1-continued

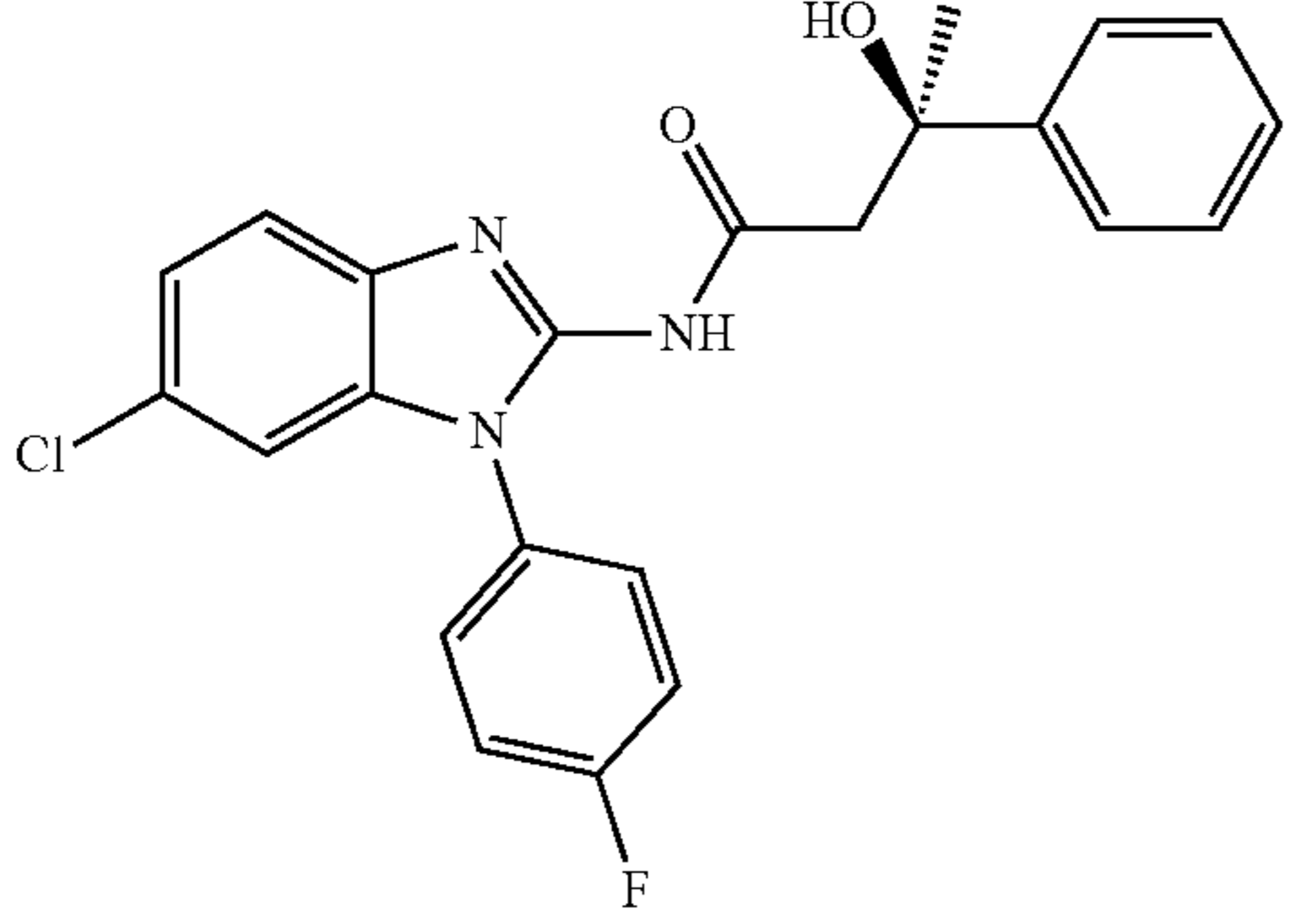
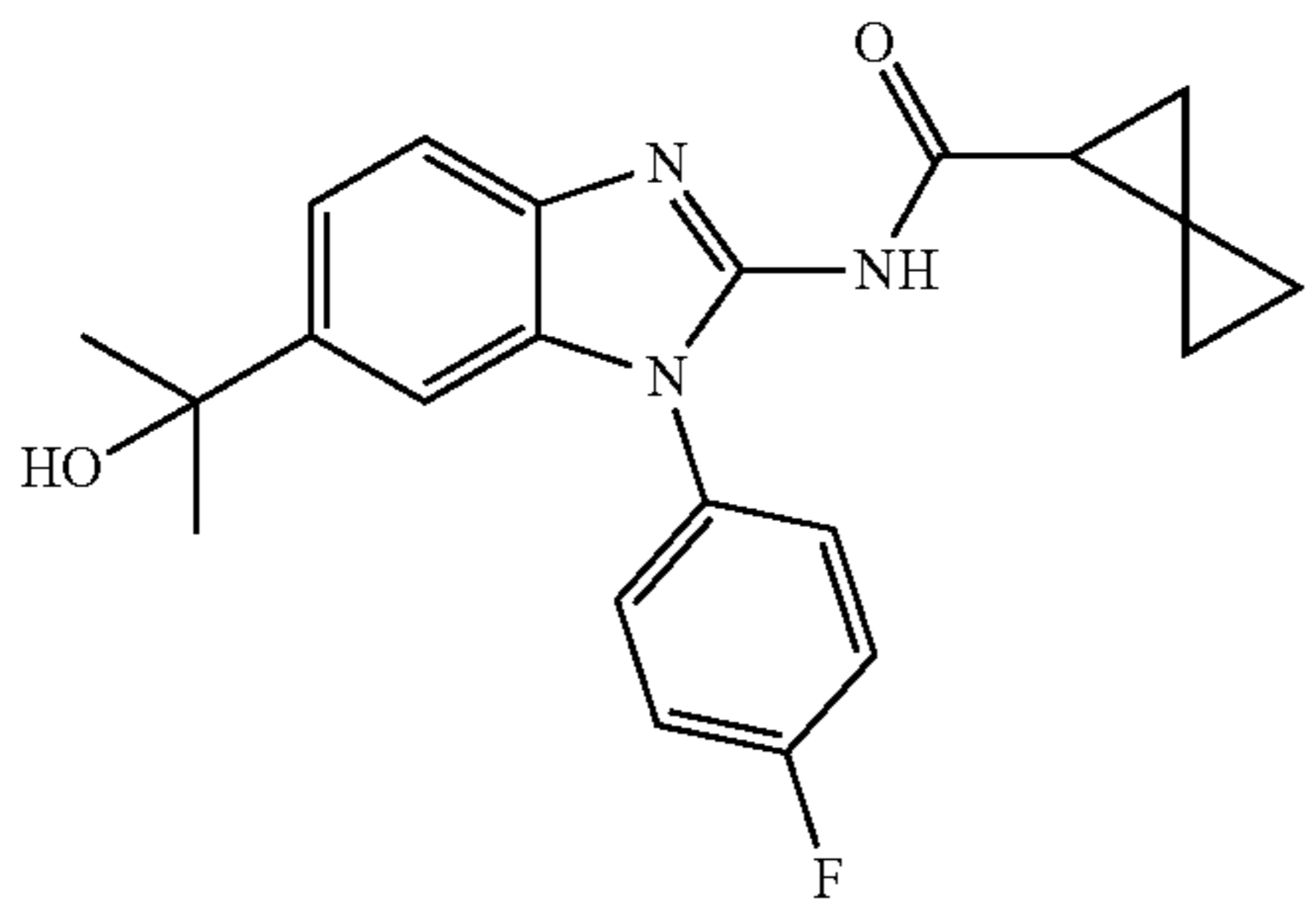
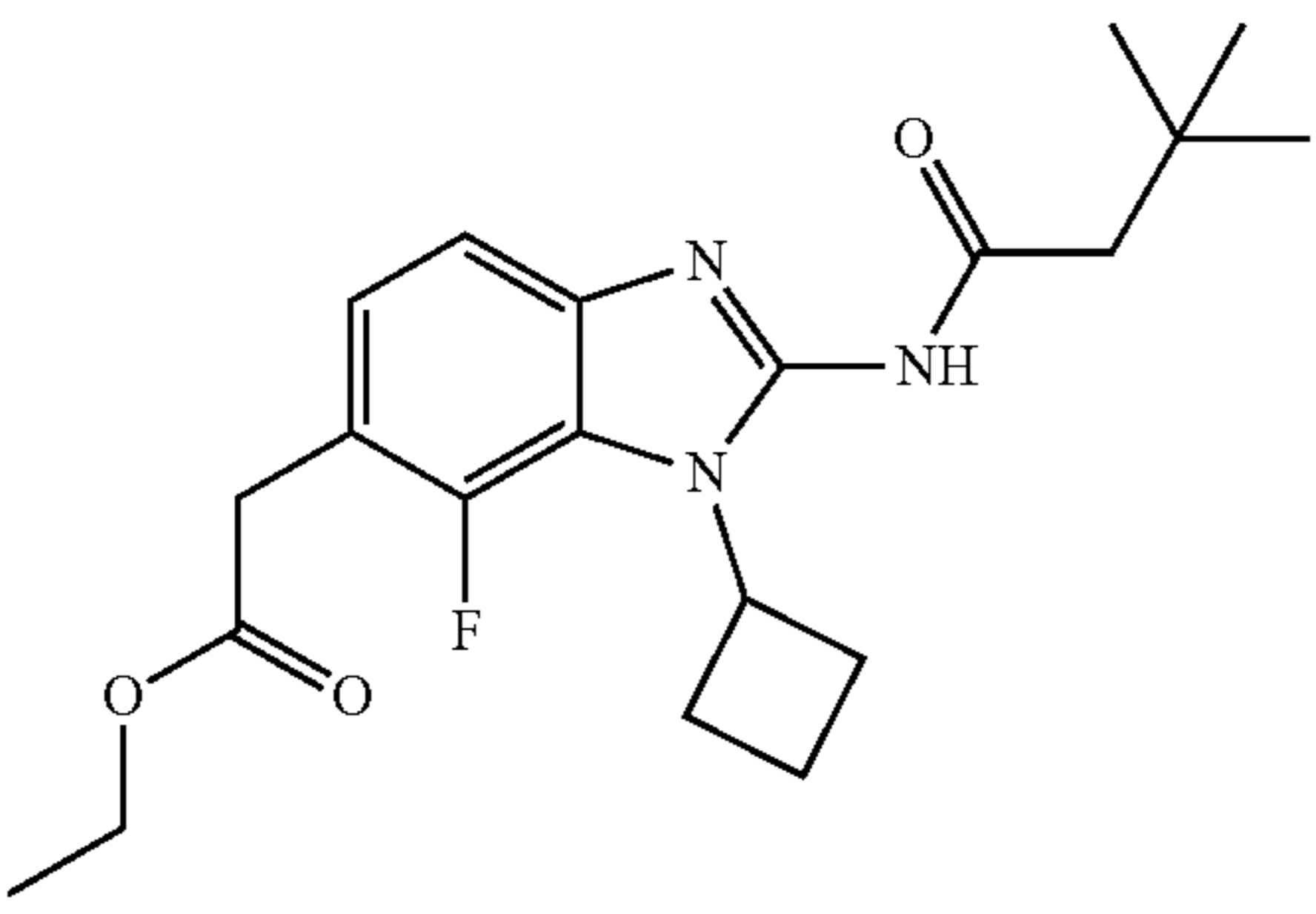
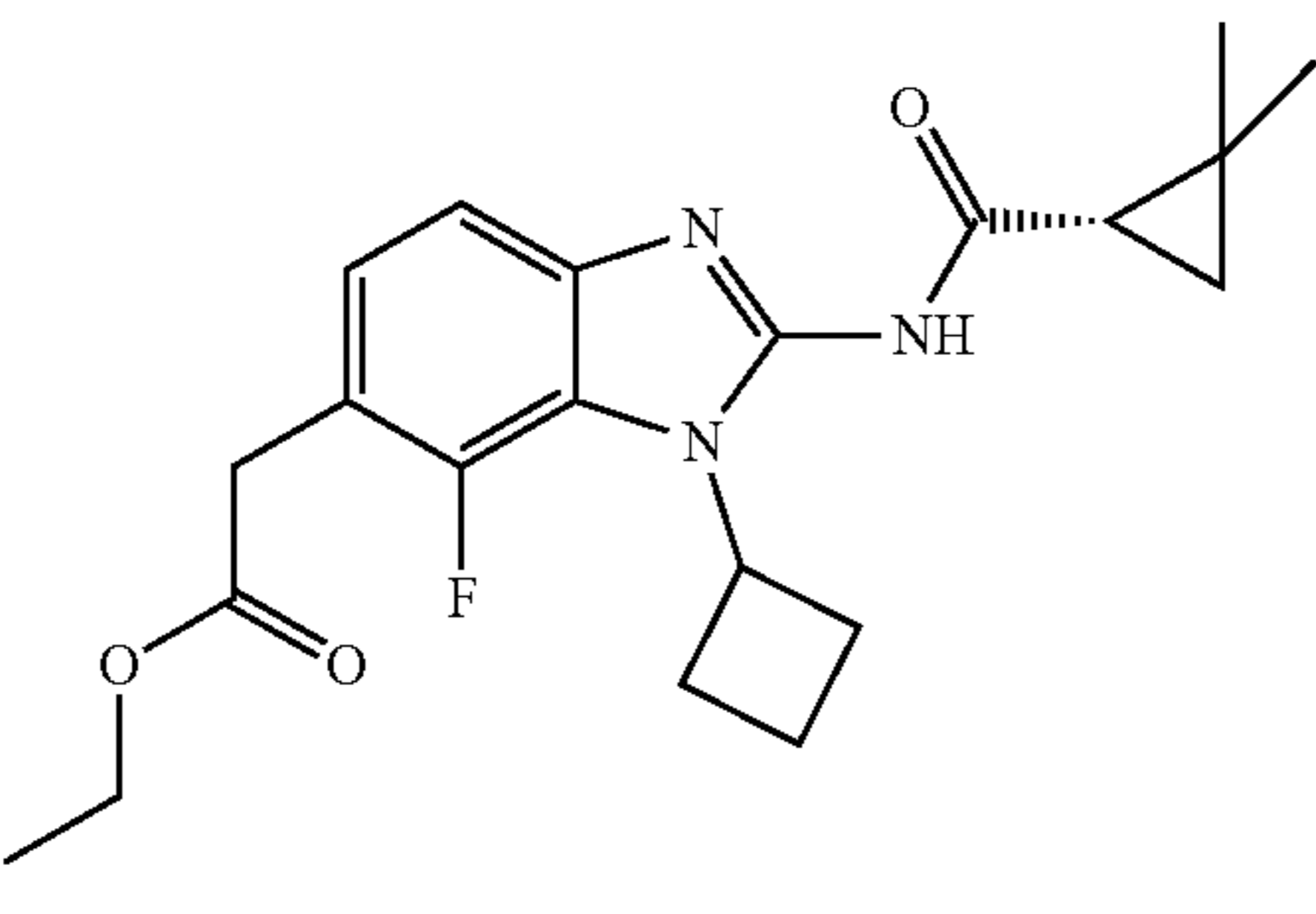
List of Examples, Synthetic Routes and Analytical Data							
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z	
108	 <p style="text-align: center;">$C_{23}H_{19}ClFN_3O_2$</p>	(R)-N-(6-chloro-1-(4-fluorophenyl)-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	7	B	3.7	424	
109	 <p style="text-align: center;">$C_{22}H_{22}FN_3O_2$</p>	N-(1-(4-fluorophenyl)-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)spiro[2.2]pentane-1-carboxamide	7, followed by method described for Ex. 53	B	2.5	380	
110	 <p style="text-align: center;">$C_{21}H_{28}FN_3O_3$</p>	ethyl 2-(1-cyclobutyl-2-(3,3-dimethylbutanamido)-7-fluoro-1H-benzo[d]imidazol-6-yl)acetate	7	A	5.4	390	
111	 <p style="text-align: center;">$C_{21}H_{26}FN_3O_3$</p>	ethyl (S)-2-(1-cyclobutyl-2-(2,2-dimethylcyclopropane-1-carboxamido)-7-fluoro-1H-benzo[d]imidazol-6-yl)acetate	7	B	3.6	388	

TABLE 1-continued

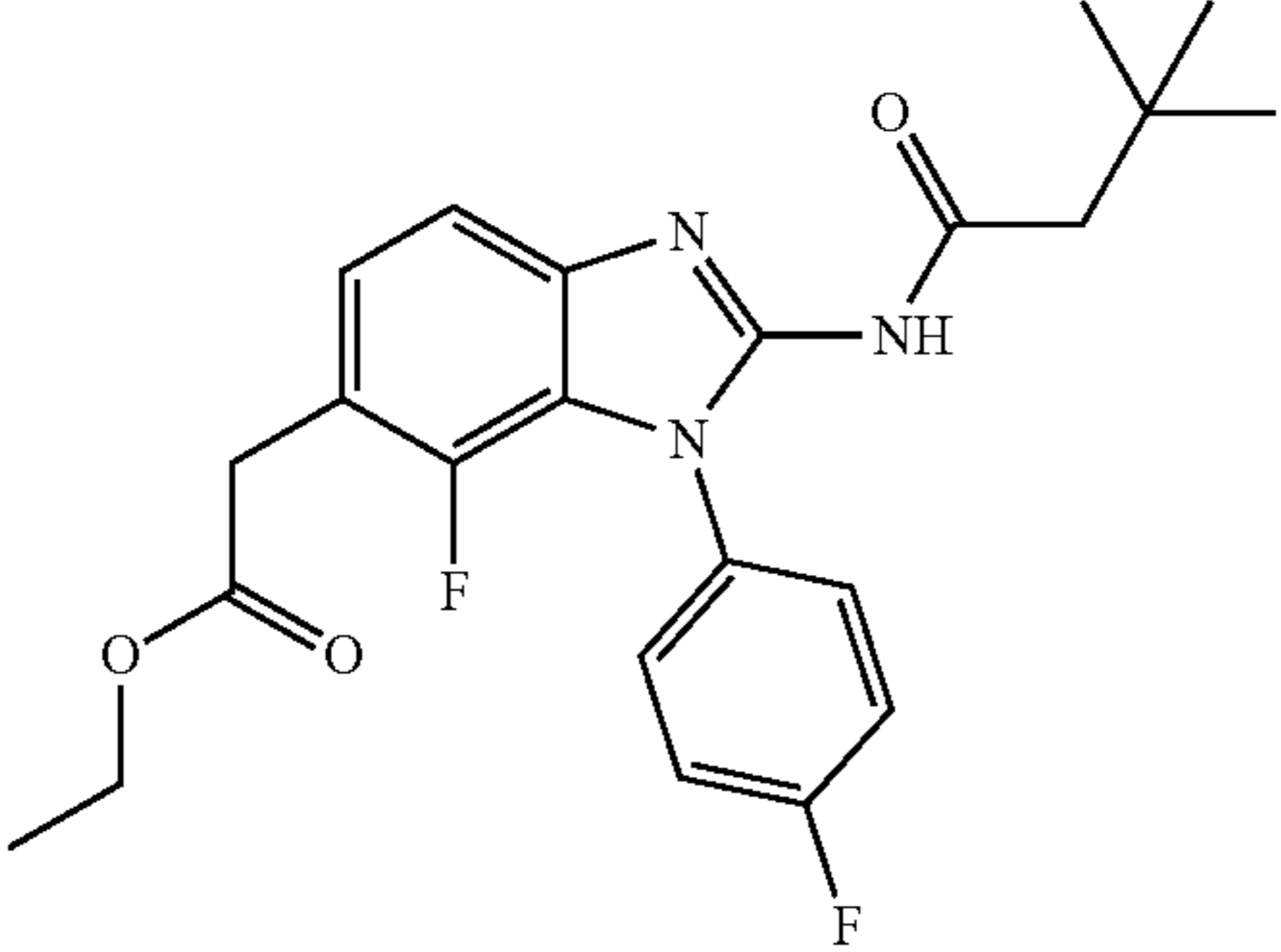
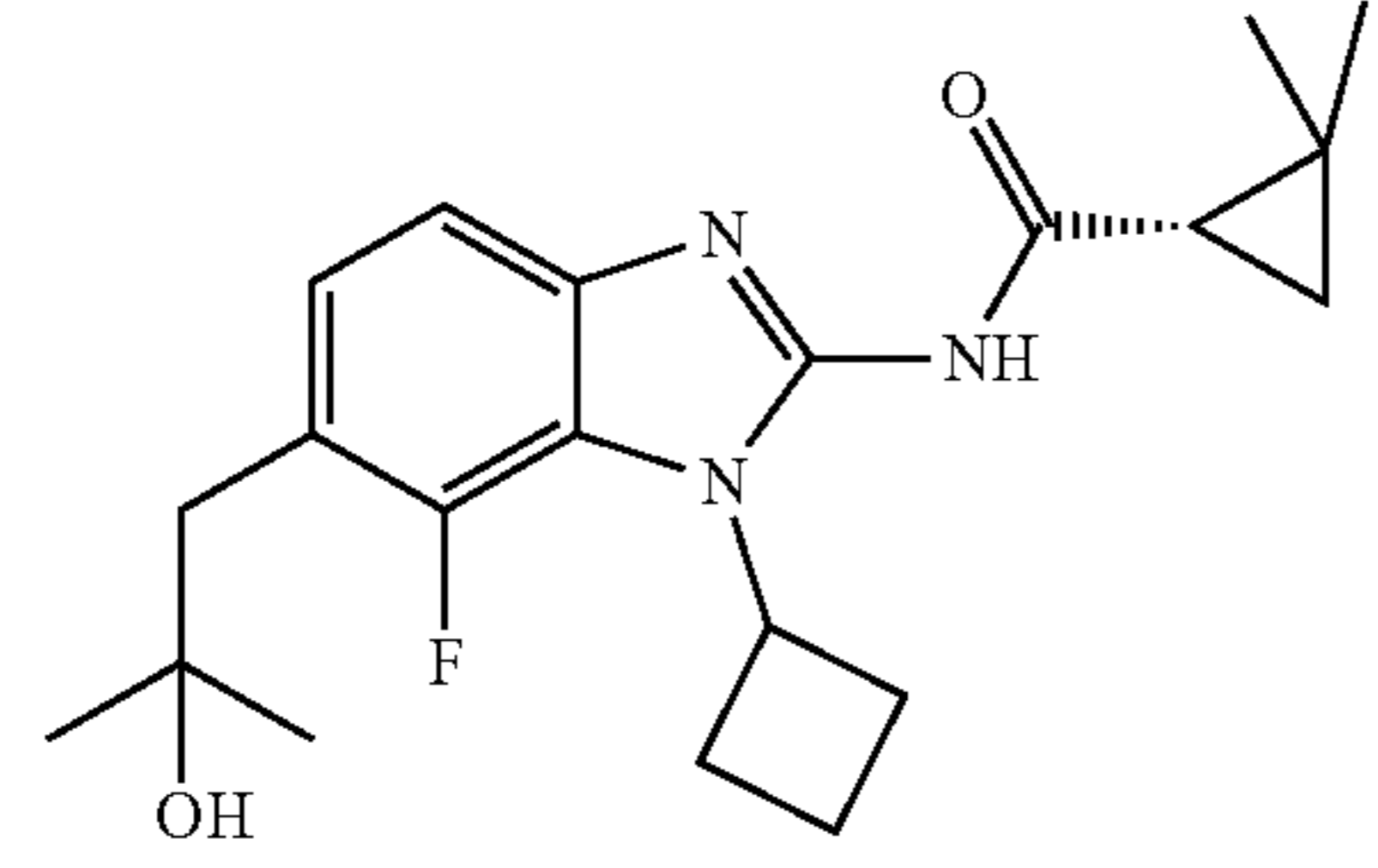
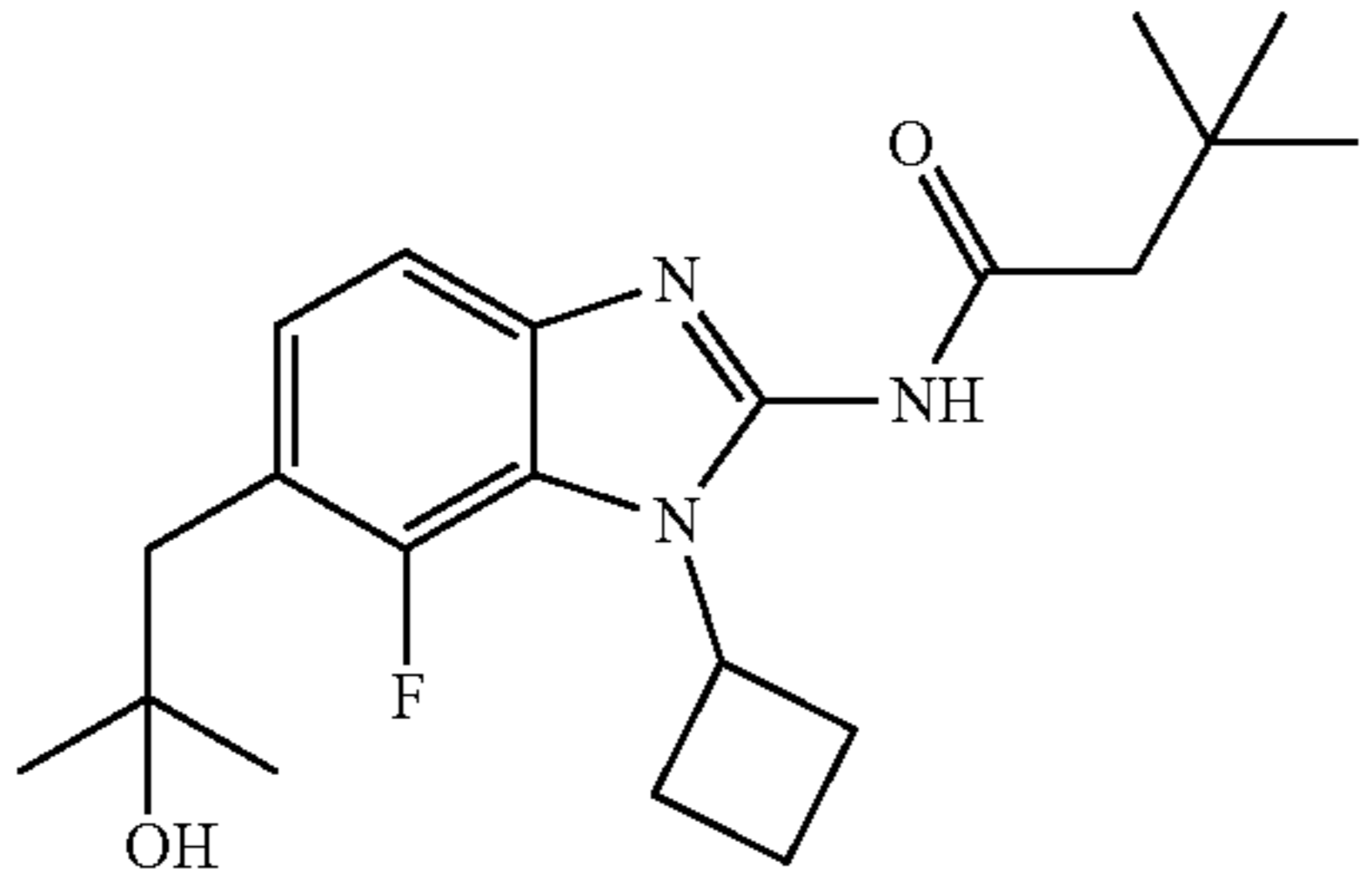
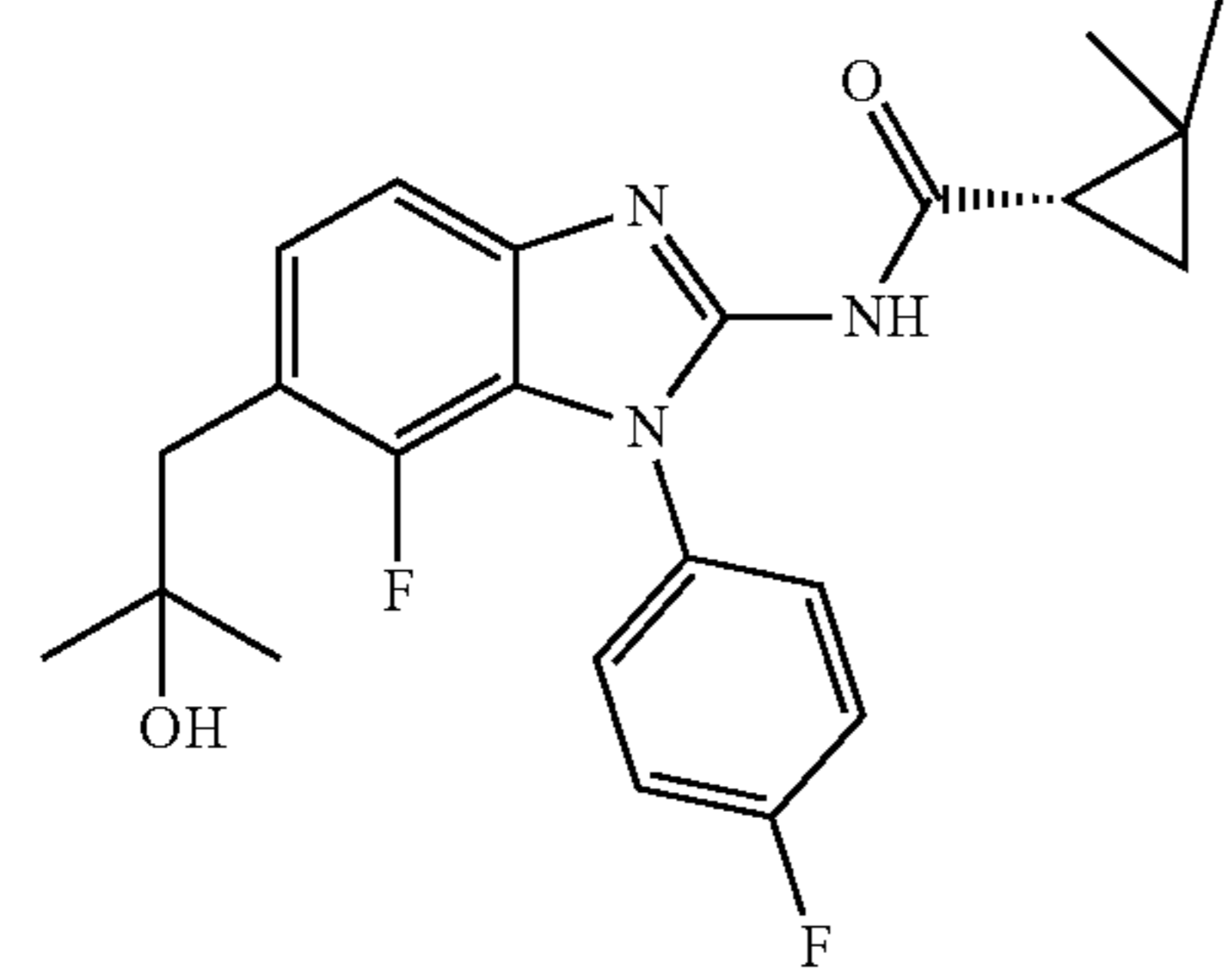
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
112	 <p style="text-align: center;">$C_{23}H_{25}F_2N_3O_3$</p>	ethyl 2-(2-(3,3-dimethylbutanamido)-7-fluoro-1-(4-fluorophenyl)-1H-benzo[d]imidazol-6-yl)acetate	7	B	3.7	430
113	 <p style="text-align: center;">$C_{21}H_{28}FN_3O_2$</p>	(S)-N-(1-cyclobutyl-7-fluoro-6-(2-hydroxy-2-methylpropyl)-1H-benzo[d]imidazol-2-yl)-2,2-dimethylcyclopropane-1-carboxamide	7	B	3.1	374
114	 <p style="text-align: center;">$C_{21}H_{30}FN_3O_2$</p>	N-(1-cyclobutyl-7-fluoro-6-(2-hydroxy-2-methylpropyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7, followed by method described for Ex. 53	B	3.2	376
115	 <p style="text-align: center;">$C_{23}H_{25}F_2N_3O_2$</p>	(S)-N-(7-fluoro-1-(4-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-1H-benzo[d]imidazol-2-yl)-2,2-dimethylcyclopropane-1-carboxamide	7, followed by method described for Ex. 53	B	3.1	414

TABLE 1-continued

List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
116	<p><chem>CC(C)(C)CC(=O)Nc1nc2cc(F)cc(CCC(O)C(C)C)c2n1</chem></p> <p>$C_{23}H_{27}F_2N_3O_2$</p>	N-(7-fluoro-1-(4-(2-hydroxy-2-methylpropyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7, followed by method described for Ex. 53	B	3.2	416
117	<p><chem>CC(C)(C)CC(=O)Nc1nc2cc(F)cc(CCC(=O)O)c2n1C3CCC3</chem></p> <p>$C_{19}H_{24}FN_3O_3$</p>	2-(1-cyclobutyl-2-(3,3-dimethylbutanamido)-7-fluoro-1H-benzo[d]imidazol-6-yl)acetic acid	7	B	2.9	362
118	<p><chem>CC(C)(C)CC(=O)Nc1nc2cc(F)cc(CCC(=O)N(C)C)c2n1C3CCC3</chem></p> <p>$C_{21}H_{29}FN_4O_2$</p>	N-(1-cyclobutyl-6-(2-(dimethylamino)-2-oxoethyl)-7-fluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7	B	2.9	389
119	<p><chem>CC(C)(C)CC(=O)Nc1nc2cc(C)c(C#N)c2n1C(C)C[C@@H](O)C3=CC=CC=C3</chem></p> <p>$C_{23}H_{26}N_4O_2$</p>	(S)-N-(1-(tert-butyl)-6-cyano-5-methyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	7	B	3.7	391

TABLE 1-continued

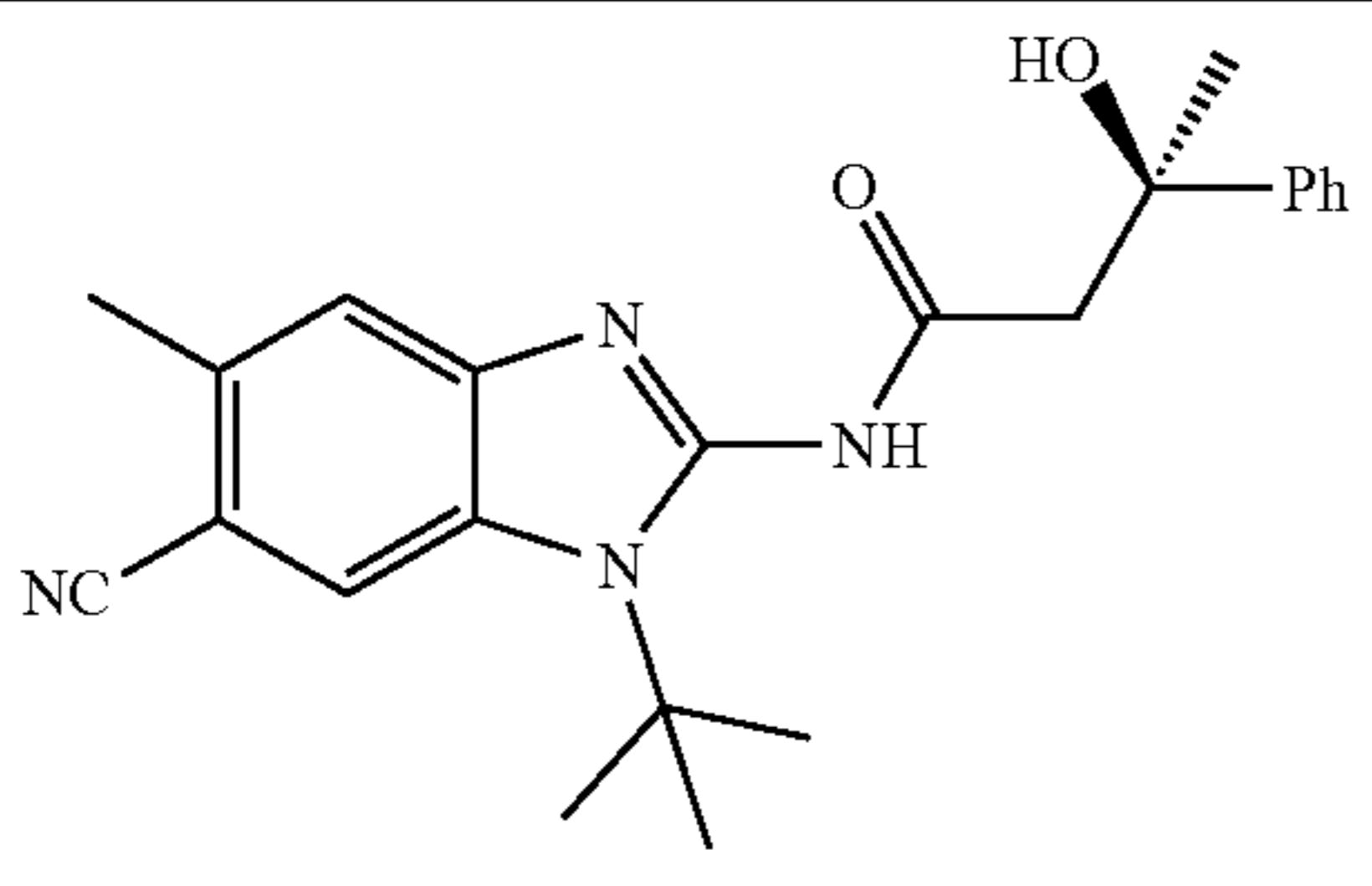
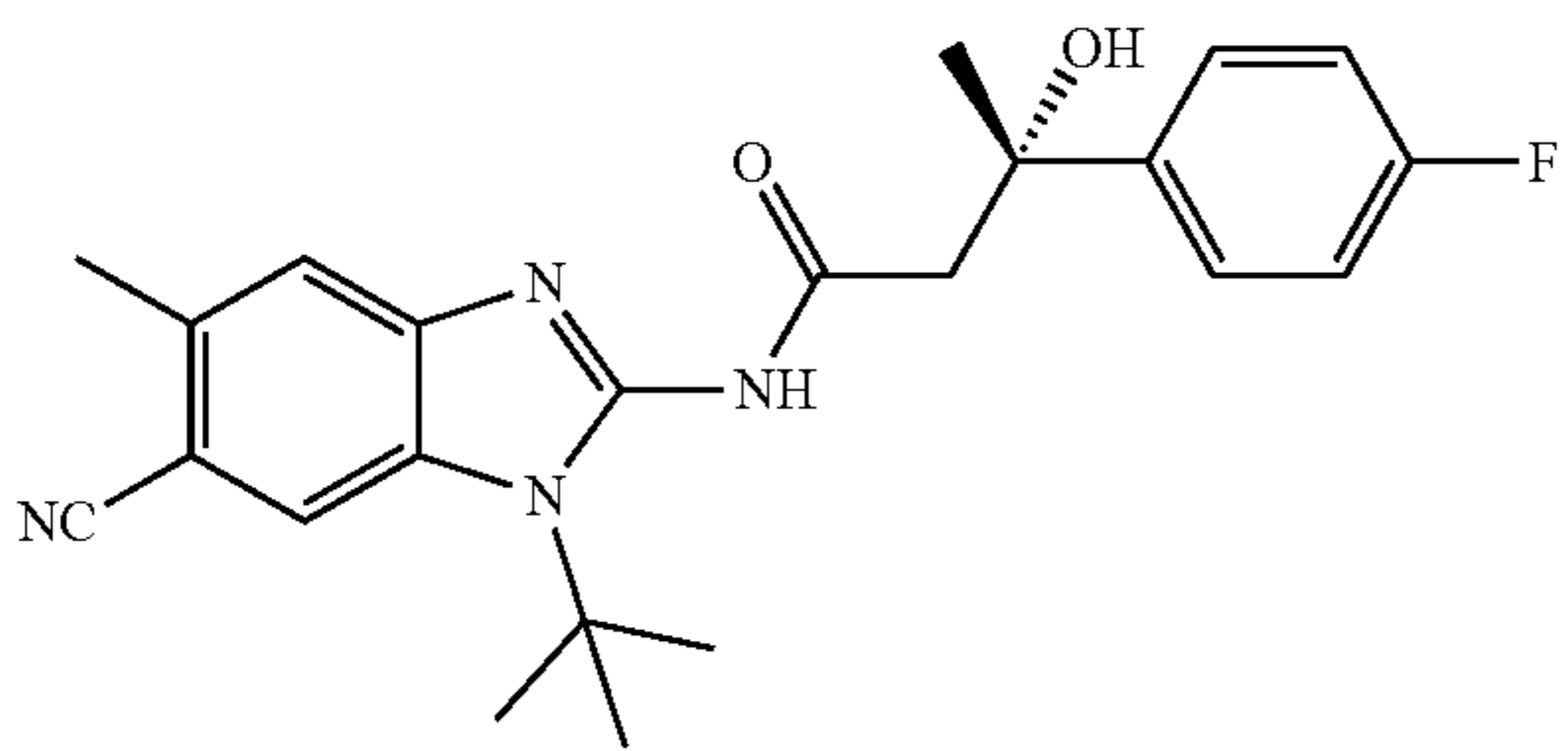
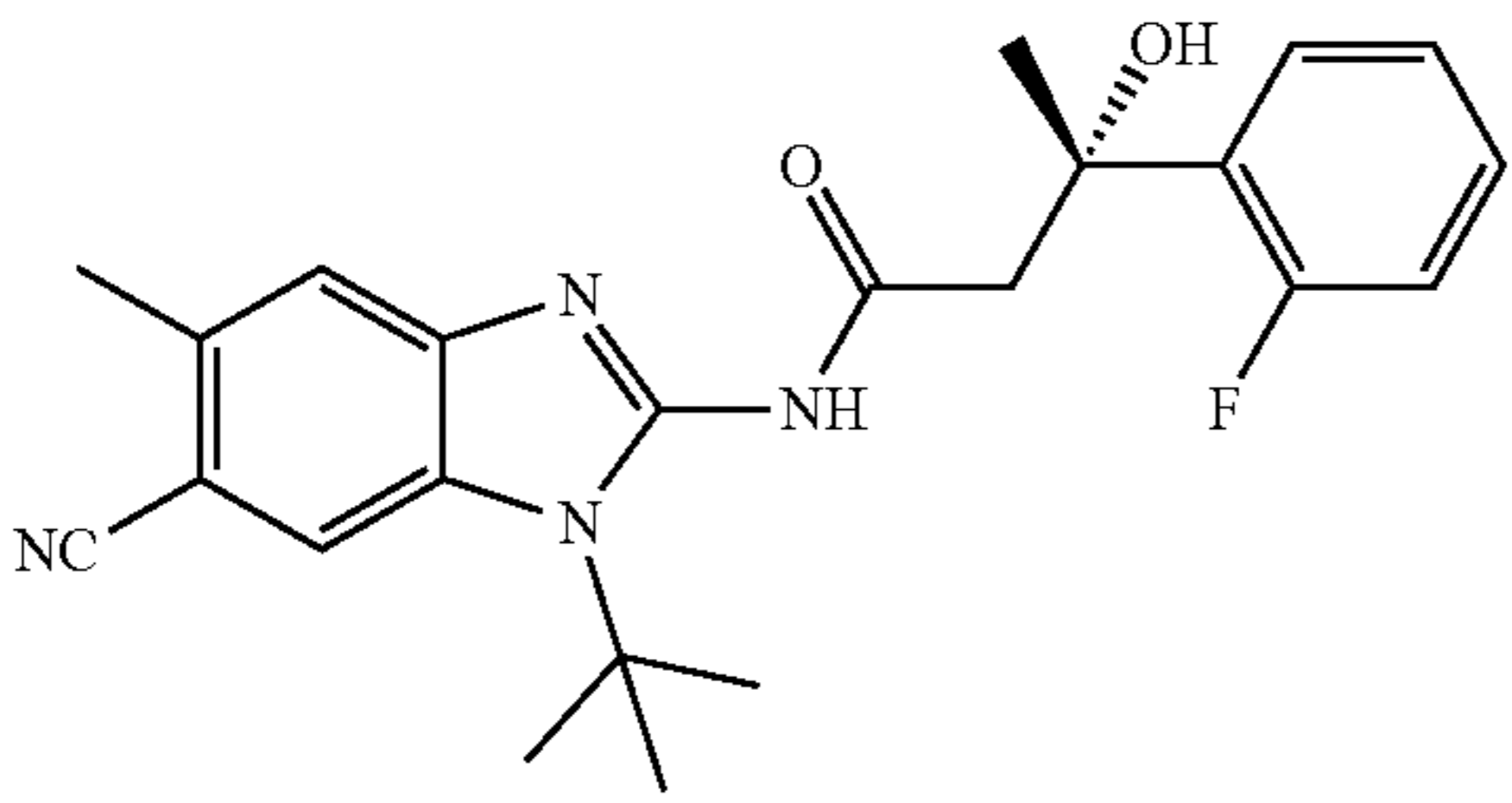
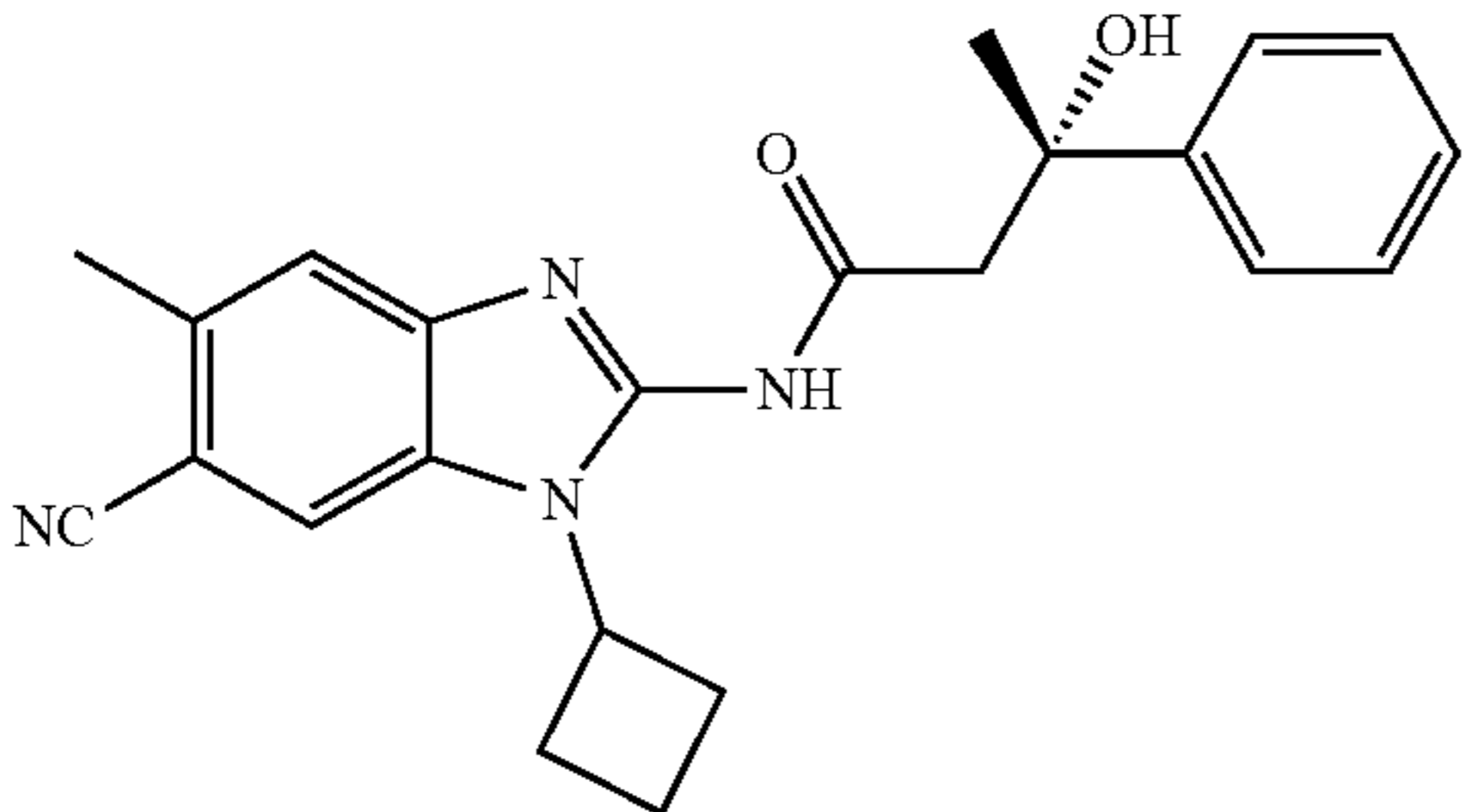
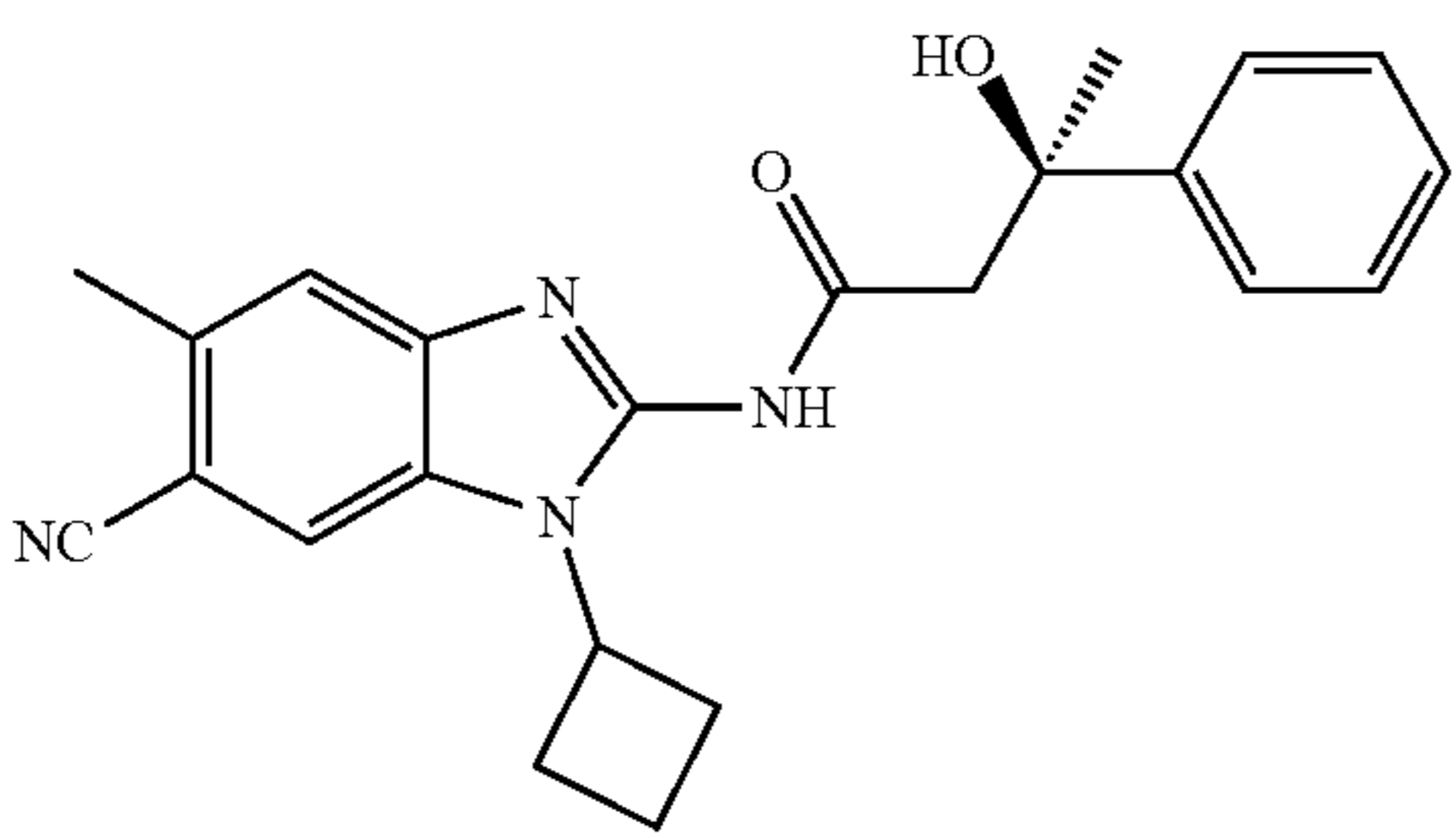
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
120	 $C_{23}H_{26}N_4O_2$	(R)-N-(1-(tert-butyl)-6-cyano-5-methyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	7	B	3.7	391
121	 $C_{23}H_{25}FN_4O_2$	(S)-N-(1-(tert-butyl)-6-cyano-5-methyl-1H-benzo[d]imidazol-2-yl)-3-(4-fluorophenyl)-3-hydroxybutanamide	7	B	3.8	409
122	 $C_{23}H_{25}FN_4O_2$	(S)-N-(1-(tert-butyl)-6-cyano-5-methyl-1H-benzo[d]imidazol-2-yl)-3-(2-fluorophenyl)-3-hydroxybutanamide	7	B	3.9	409
123	 $C_{23}H_{24}N_4O_2$	(S)-N-(6-cyano-1-cyclobutyl-5-methyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	7	B	3.5	389
124	 $C_{23}H_{24}N_4O_2$	(R)-N-(6-cyano-1-cyclobutyl-5-methyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-phenylbutanamide	7	B	3.5	389

TABLE 1-continued

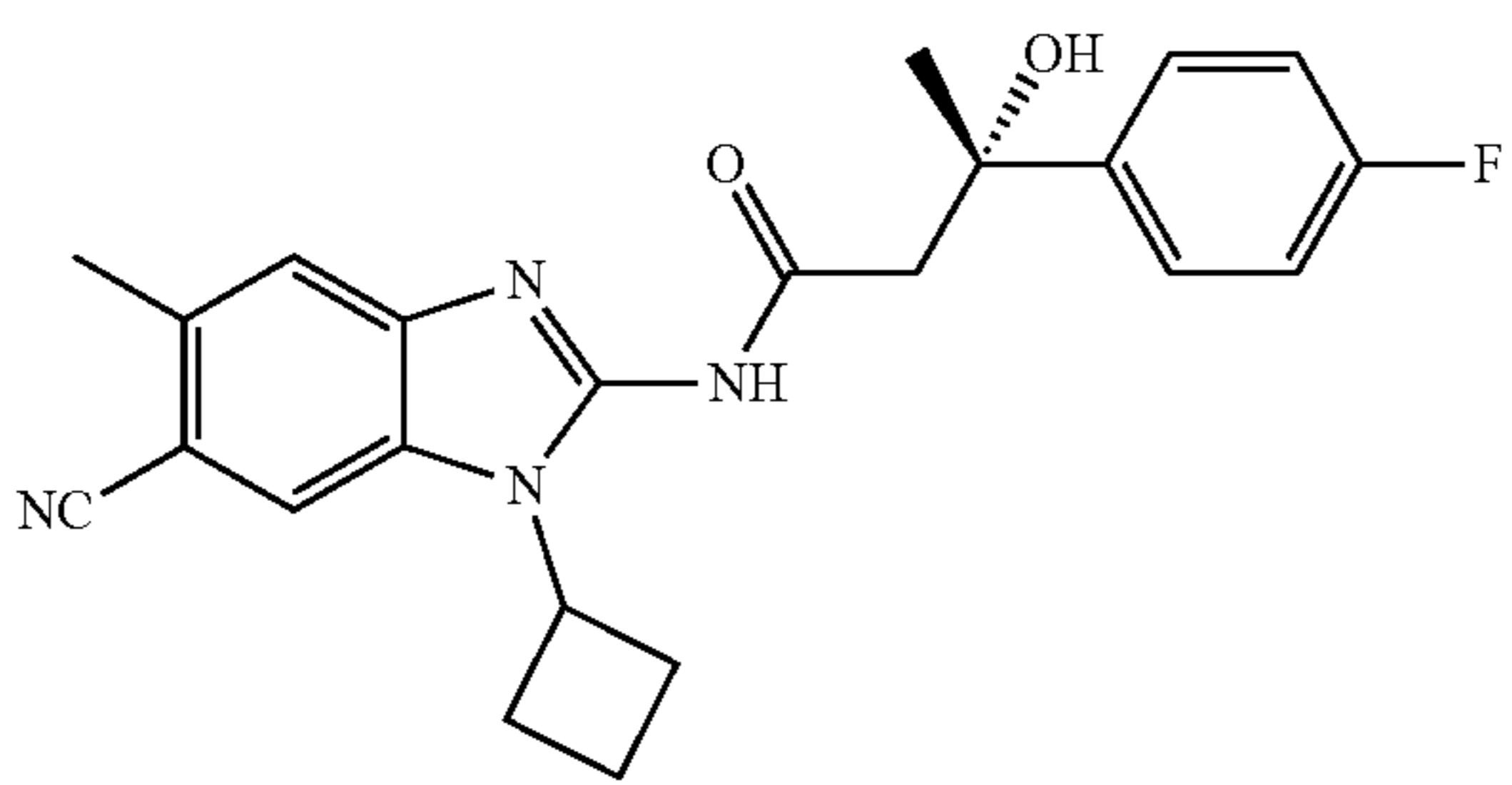
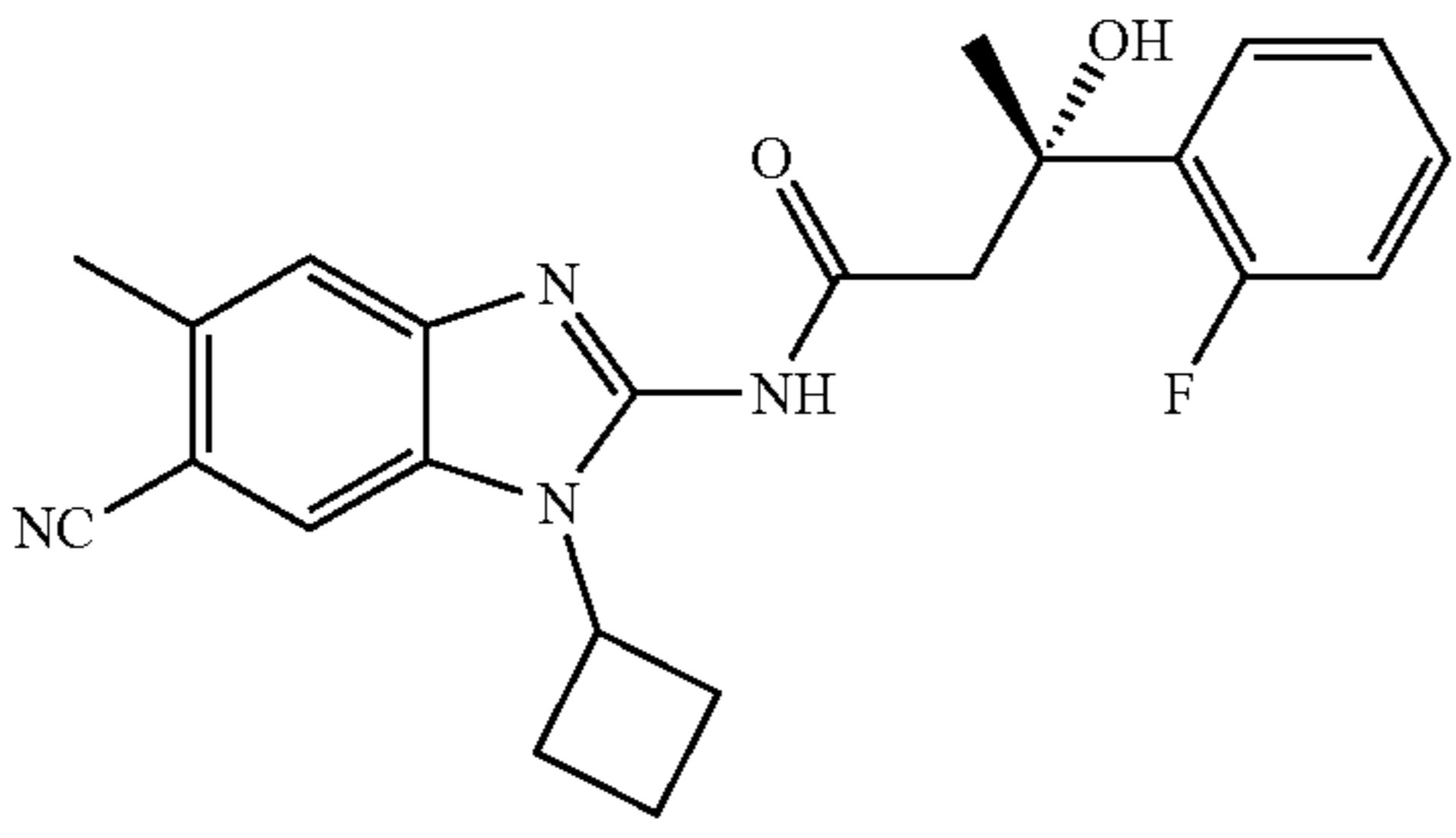
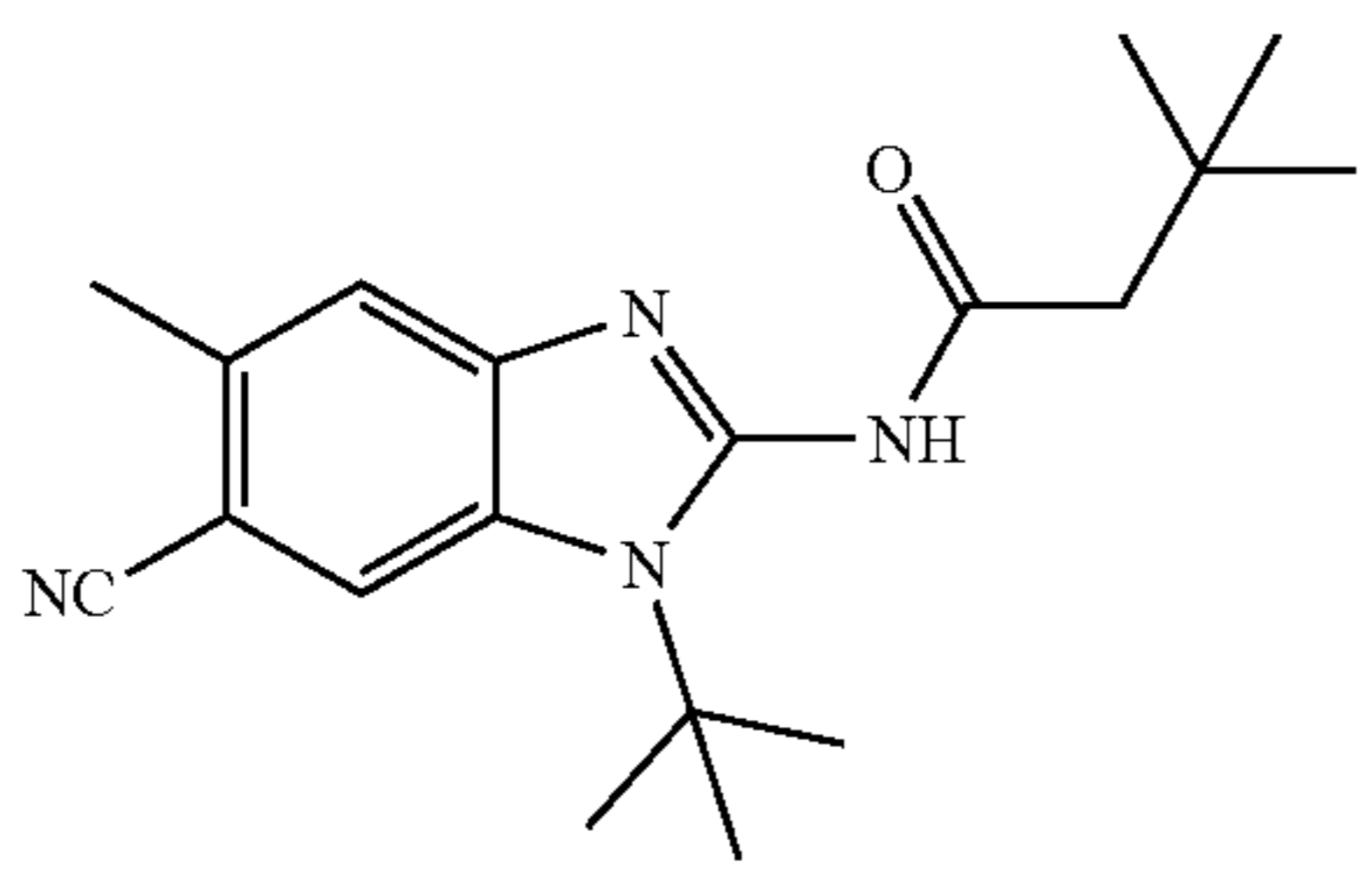
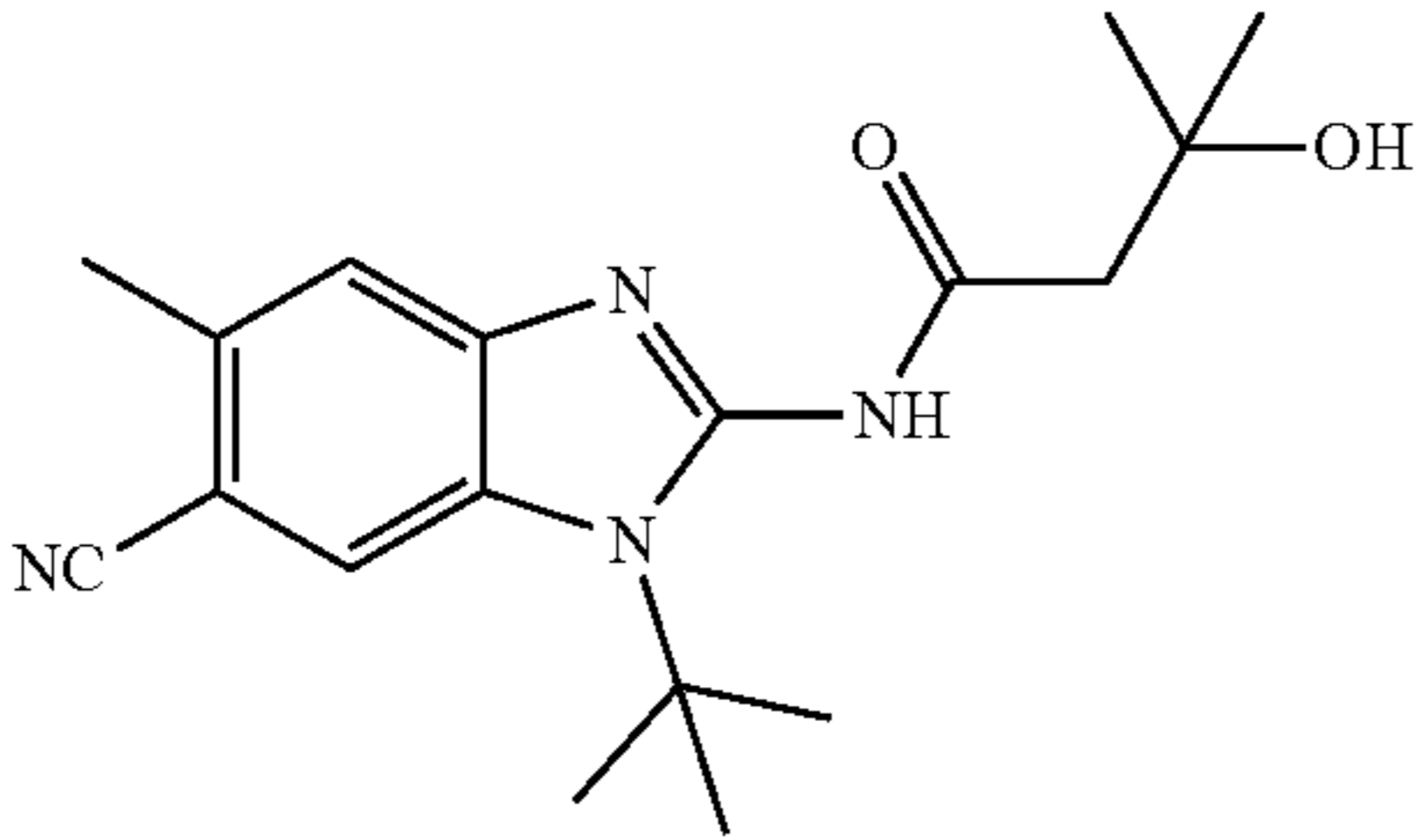
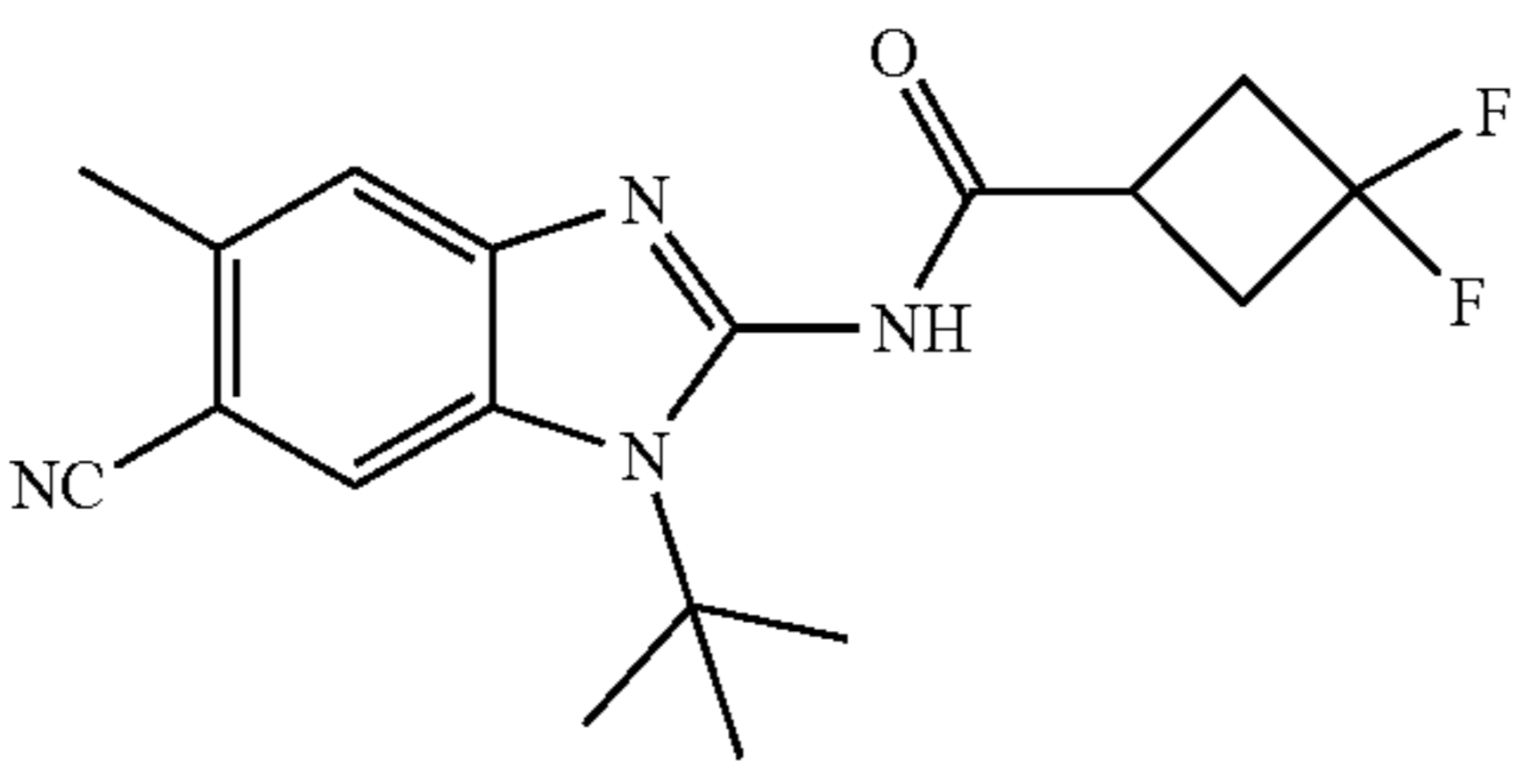
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
125	 <chem>Cc1c(C#N)c2c(c1)nc3c2C4CC4C(=O)N[C@@H](C)C(O)c5ccc(F)cc5</chem> $C_{23}H_{23}FN_4O_2$	(S)-N-(6-cyano-1-cyclobutyl-5-methyl-1H-benzo[d]imidazol-2-yl)-3-(4-fluorophenyl)-3-hydroxybutanamide	7	B	3.6	407
126	 <chem>Cc1c(C#N)c2c(c1)nc3c2C4CC4C(=O)N[C@@H](C)C(O)c5ccccc5F</chem> $C_{23}H_{23}FN_4O_2$	(S)-N-(6-cyano-1-cyclobutyl-5-methyl-1H-benzo[d]imidazol-2-yl)-3-(2-fluorophenyl)-3-hydroxybutanamide	7	B	3.7	407
127	 <chem>Cc1c(C#N)c2c(c1)nc3c2C(C)(C)C(C)(C)C(=O)N</chem> $C_{19}H_{26}N_4O$	N-(1-(tert-butyl)-6-cyano-5-methyl-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide	7	B	3.9	327
128	 <chem>Cc1c(C#N)c2c(c1)nc3c2C(C)(C)C(C)(C)C(=O)N[C@@H](C)O</chem> $C_{18}H_{24}N_4O_2$	N-(1-(tert-butyl)-6-cyano-5-methyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-methylbutanamide	7	B	2.8	329
129	 <chem>Cc1c(C#N)c2c(c1)nc3c2C(C)(C)C(C)(C)C(=O)N4C(F)CC(F)C4</chem> $C_{18}H_{20}F_2N_4O$	N-(1-(tert-butyl)-6-cyano-5-methyl-1H-benzo[d]imidazol-2-yl)-3,3-difluorocyclobutane-1-carboxamide	7	B	3.9	347

TABLE 1-continued

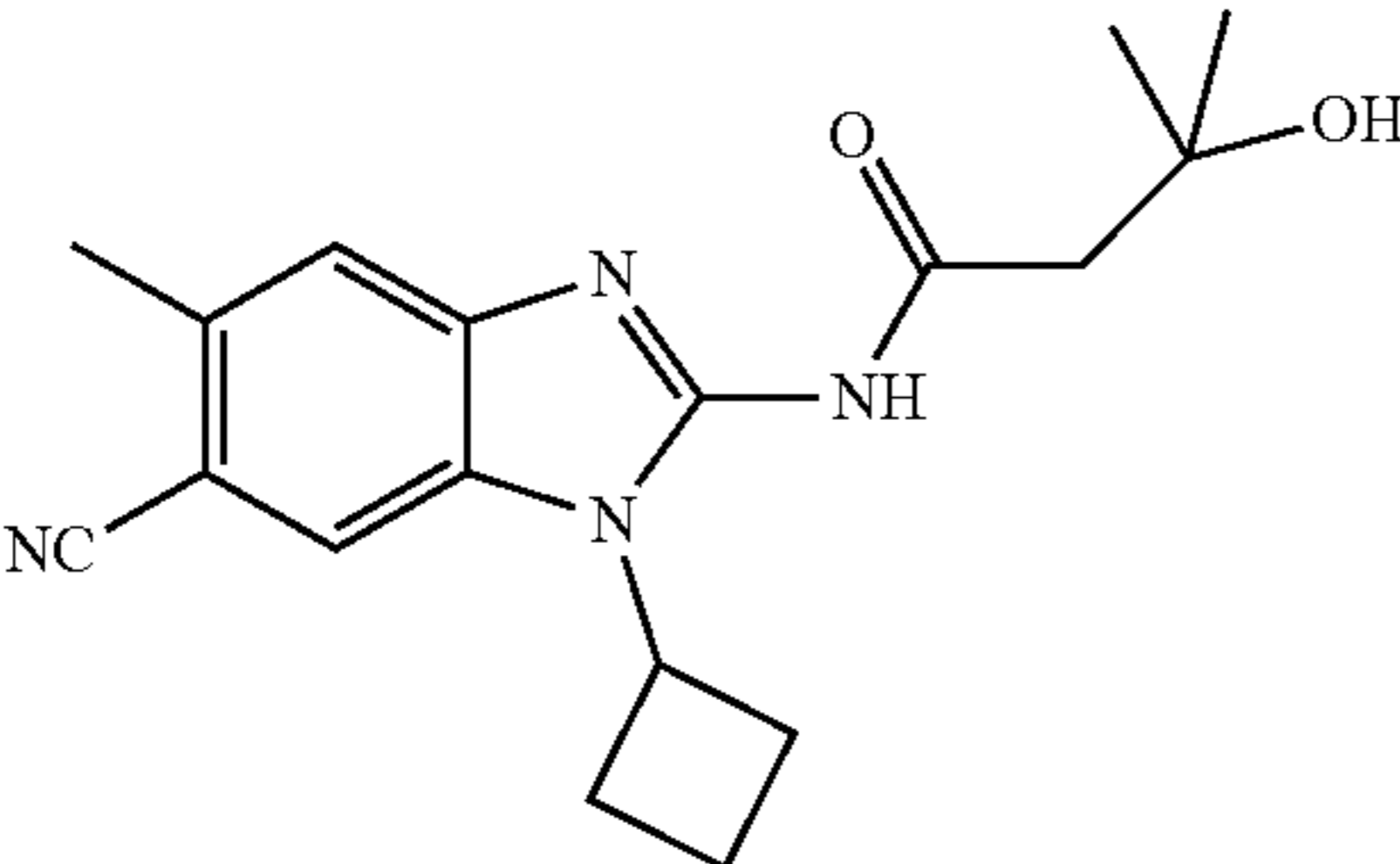
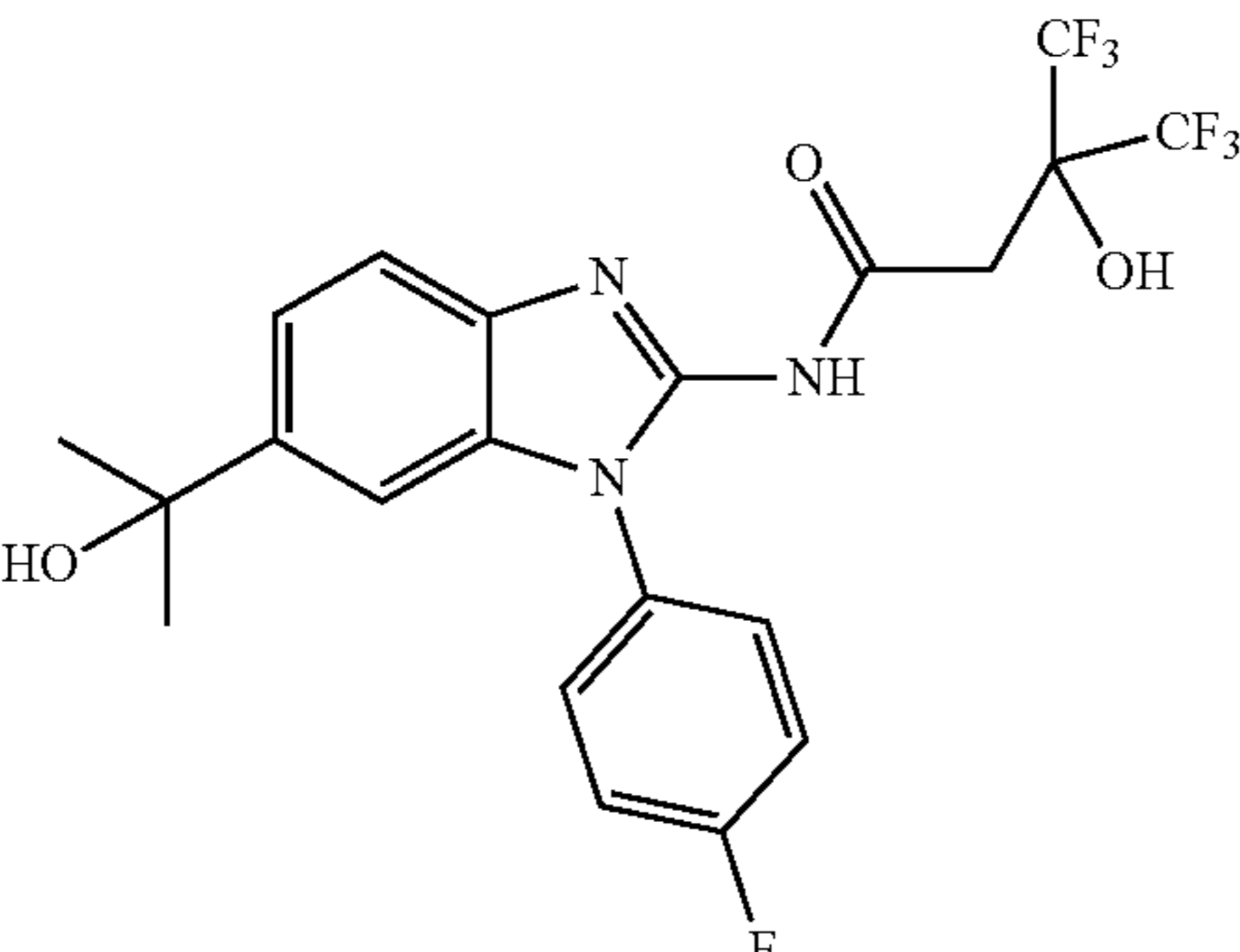
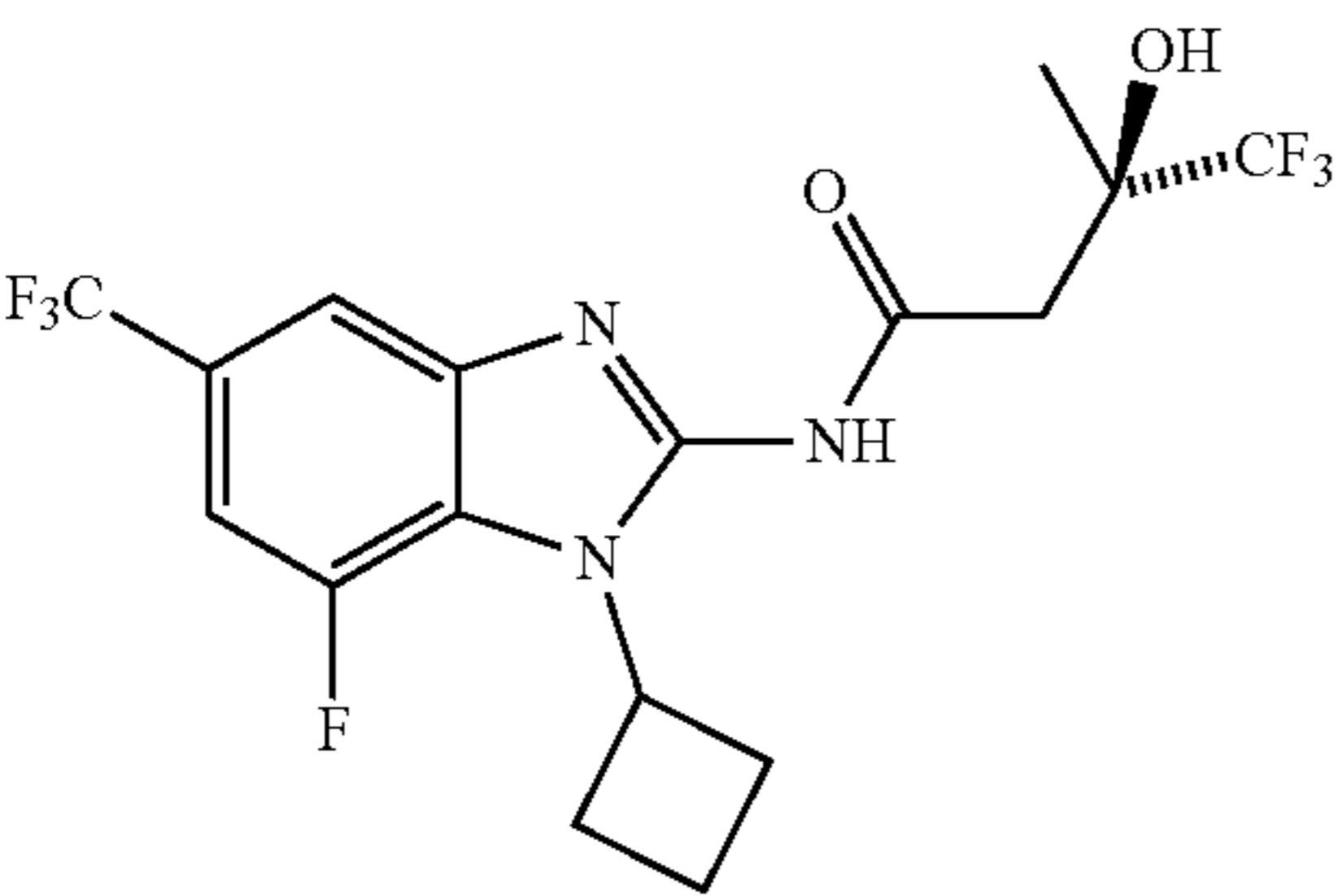
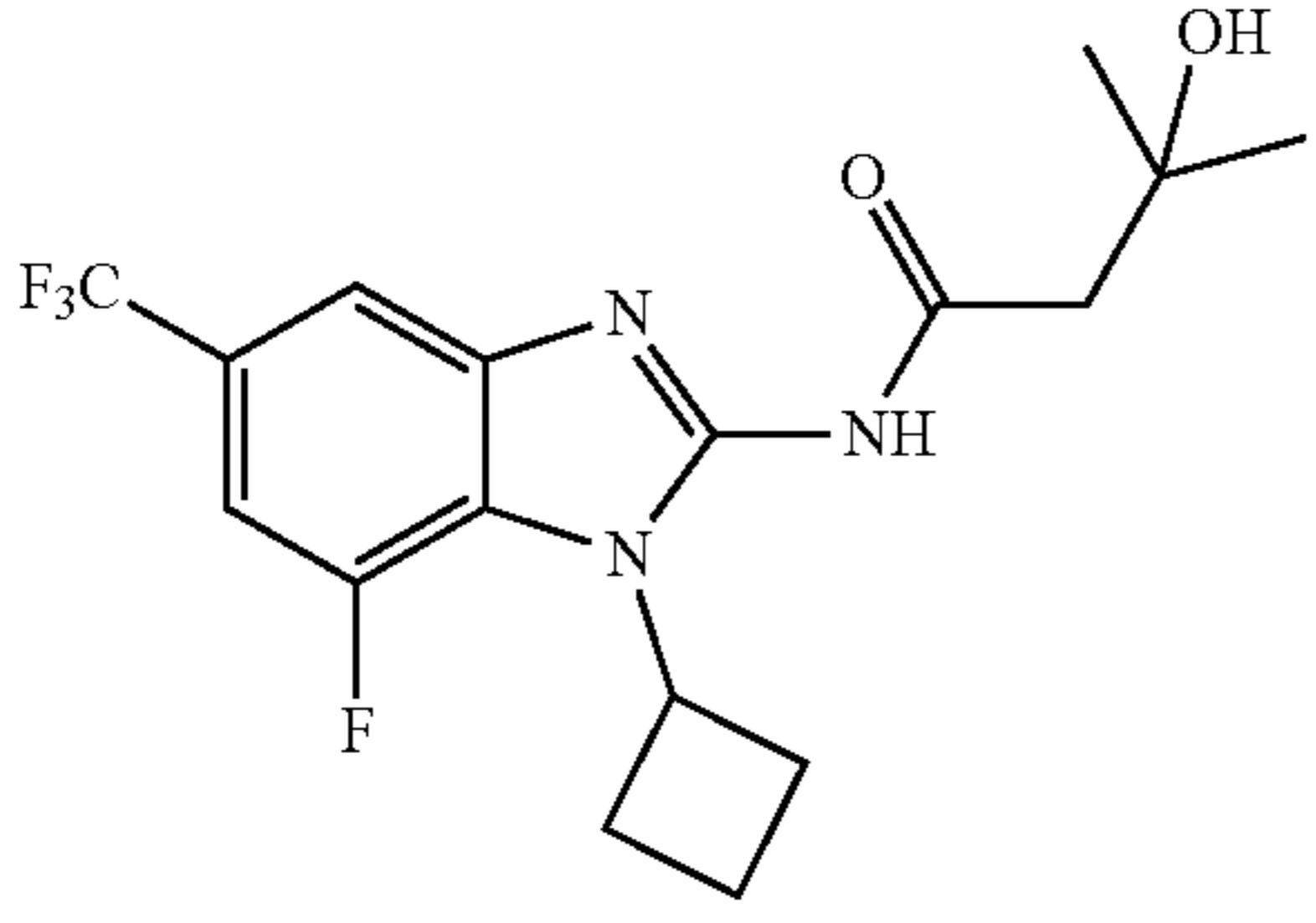
List of Examples, Synthetic Routes and Analytical Data							
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z	
130	 $C_{18}H_{22}N_4O_2$	N-(6-cyano-1-cyclobutyl-5-methyl-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-methylbutanamide	7	B	2.8	327	
131	 $C_{21}H_{18}F_7N_3O_3$	4,4,4-trifluoro-N-(1-(4-fluorophenyl)-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-(trifluoromethyl)butanamide	7, followed by method described for Ex. 53	B	3.8	494	
132	 $C_{17}H_{16}F_7N_3O_2$	(R)-N-(1-cyclobutyl-7-fluoro-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-4,4,4-trifluoro-3-hydroxy-3-methylbutanamide	7	B	4.1	428	
133	 $C_{17}H_{19}F_4N_3O_2$	N-(1-cyclobutyl-7-fluoro-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-methylbutanamide	7	B	3.5	374	

TABLE 1-continued

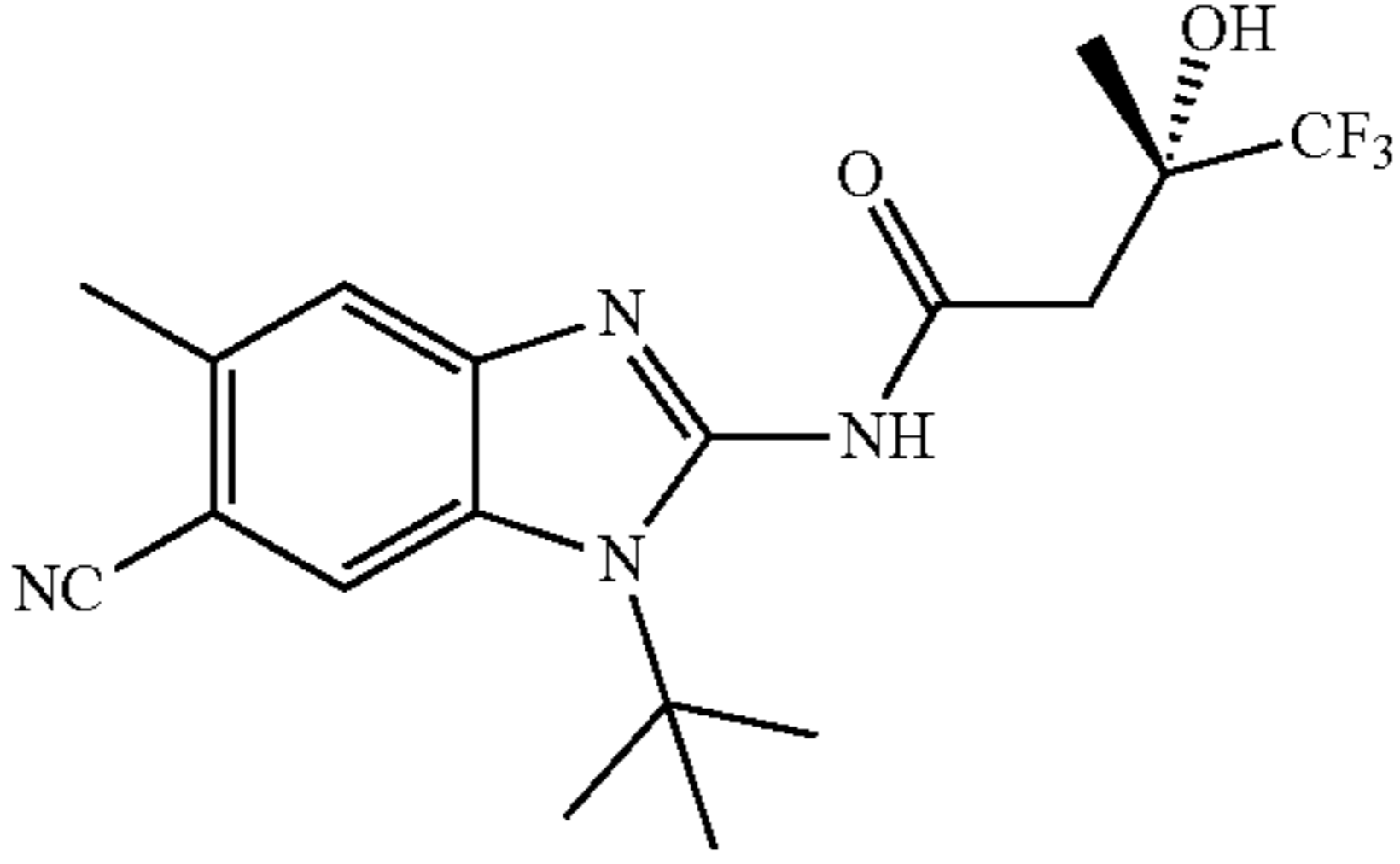
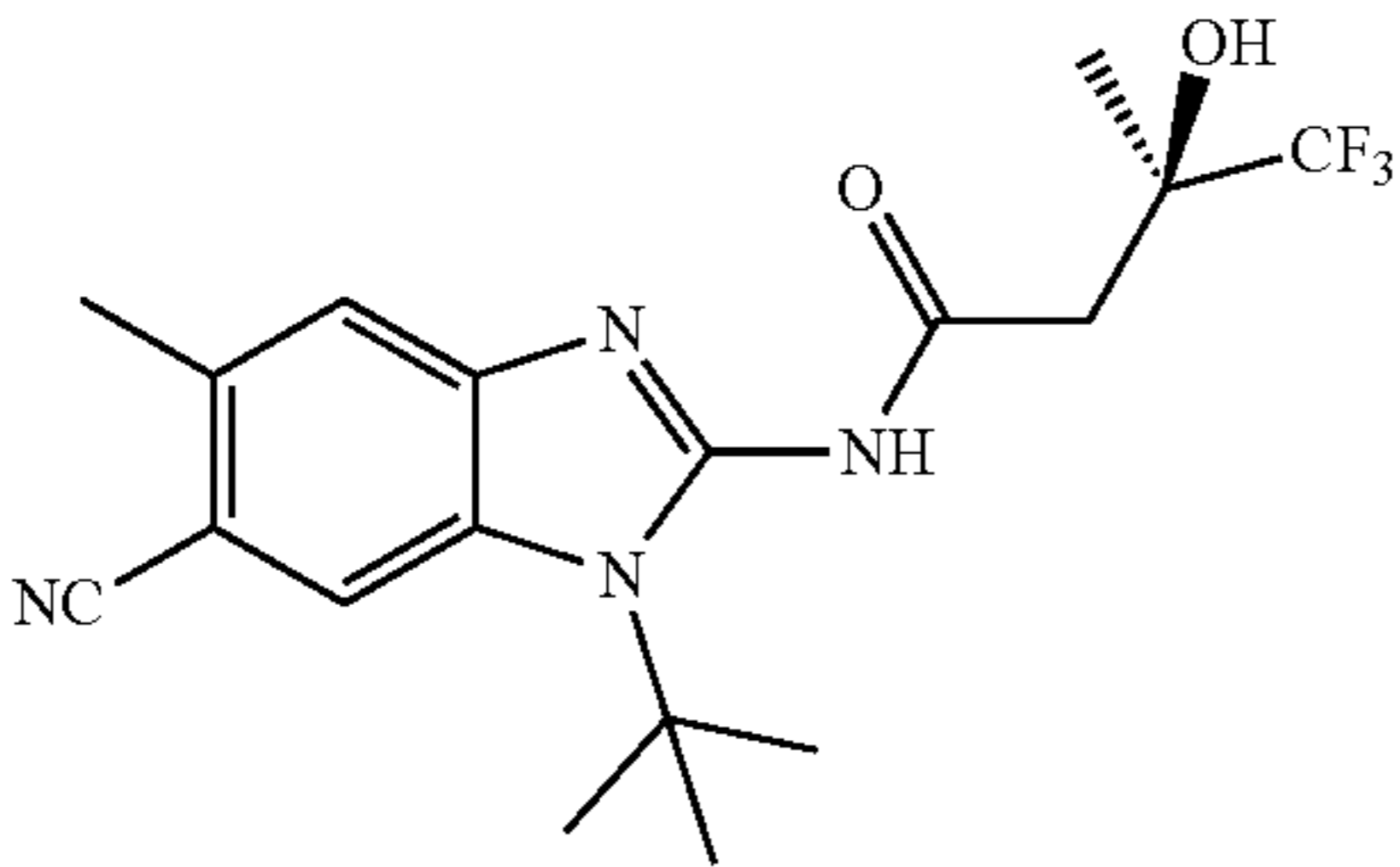
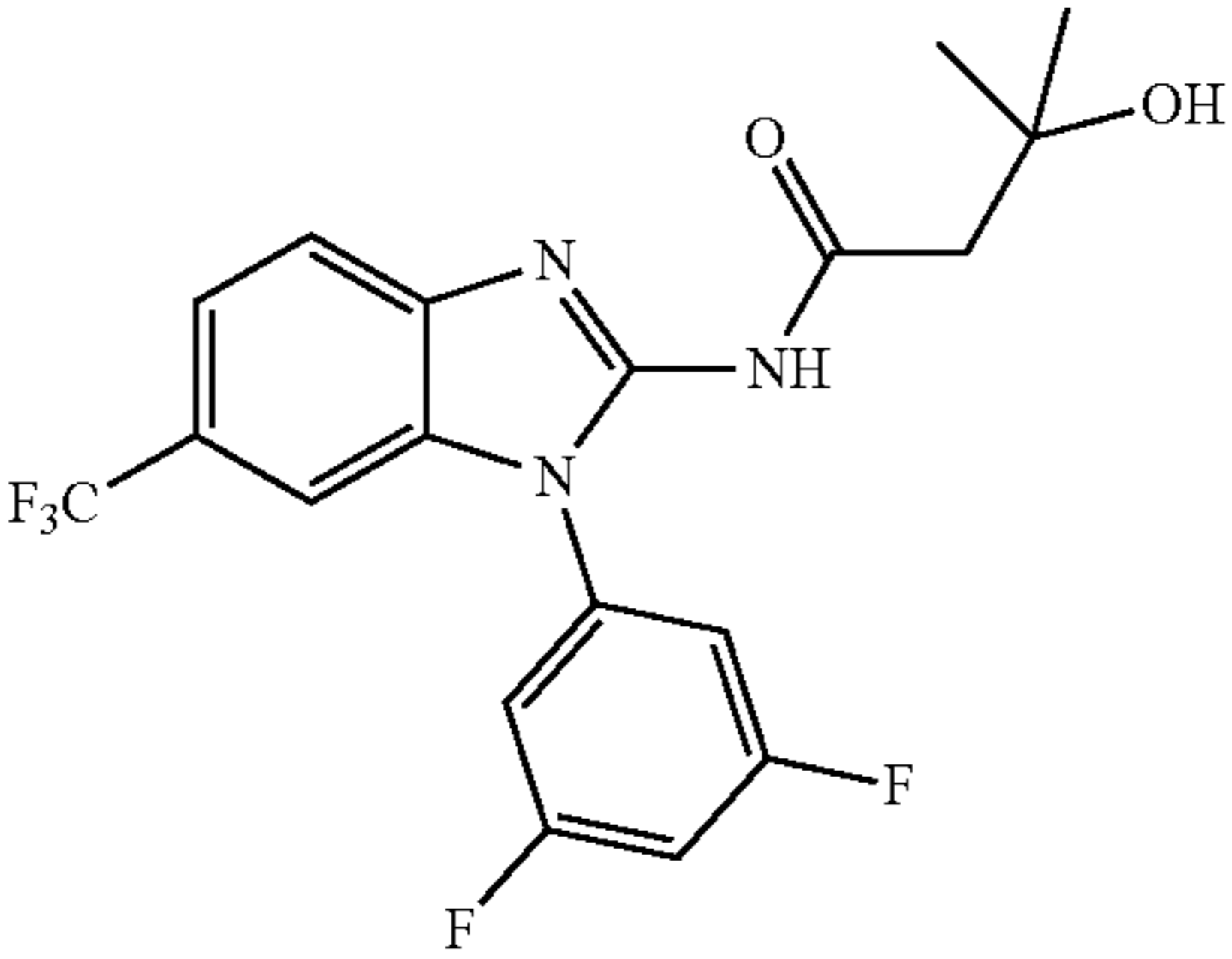
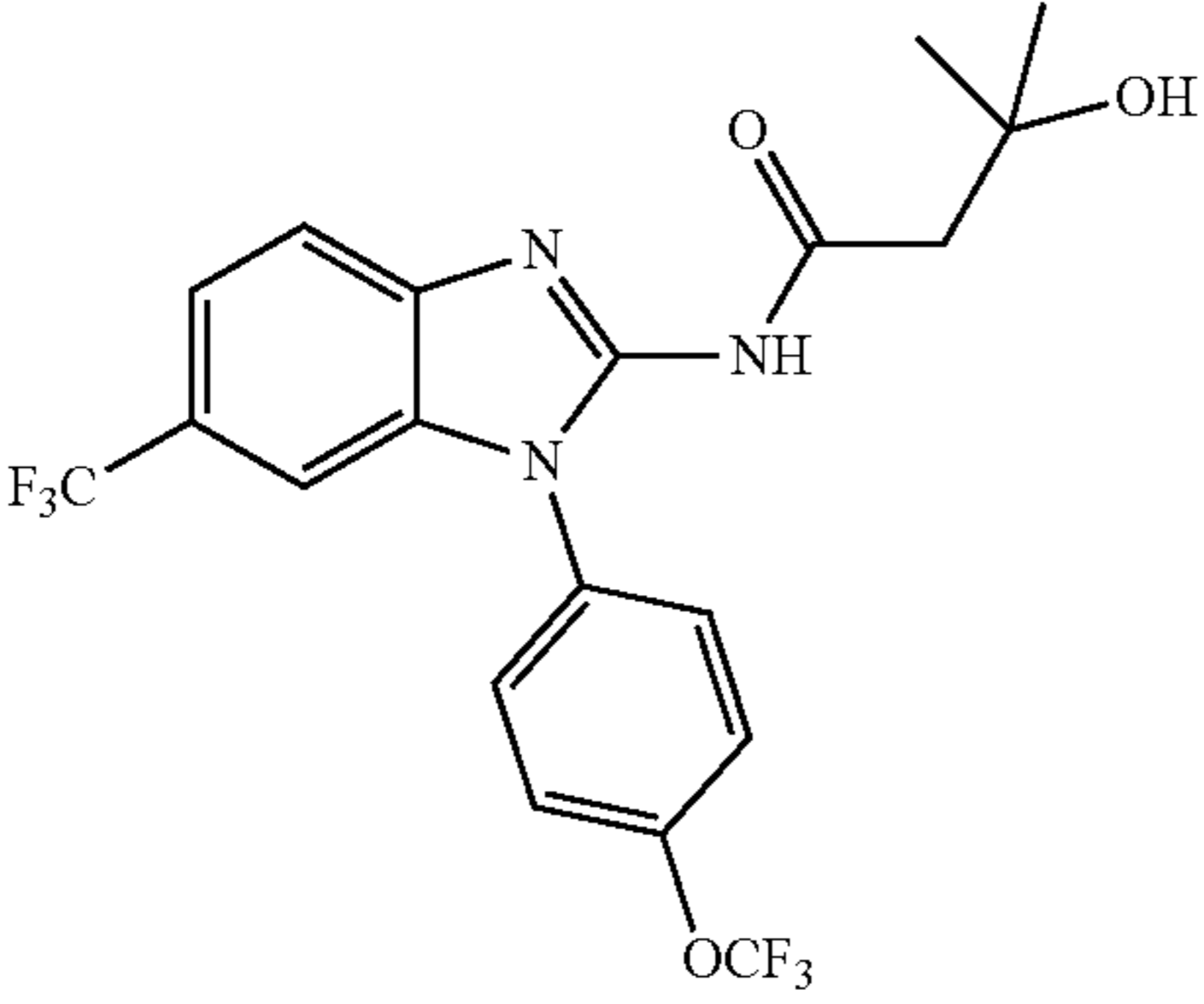
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z
134	 <chem>CC1=CN(C(C)(C)C)C2=CC=C(C#N)C=C12C(=O)N[C@@H](C)C(O)C(F)(F)F</chem> $C_{18}H_{21}F_3N_4O_2$	(S)-N-(1-(tert-butyl)-6-cyano-5-methyl-1H-benzo[d]imidazol-2-yl)-4,4,4-trifluoro-3-hydroxy-3-methylbutanamide	7	B	3.8	383
135	 <chem>CC1=CN(C(C)(C)C)C2=CC=C(C#N)C=C12C(=O)N[C@@H](C)C(O)C(F)(F)F</chem> $C_{18}H_{21}F_3N_4O_2$	(R)-N-(1-(tert-butyl)-6-cyano-5-methyl-1H-benzo[d]imidazol-2-yl)-4,4,4-trifluoro-3-hydroxy-3-methylbutanamide	7	B	3.8	383
136	 <chem>CC(C)(C)C(O)C(=O)N[C@@H]1C=NC2=CC=C(C(F)(F)F)C=C12C3=CC=C(F)C=C3F</chem> $C_{19}H_{16}F_5N_3O_2$	N-(1-(3,5-difluorophenyl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-methylbutanamide	7	B	3.4	414
137	 <chem>CC(C)(C)C(O)C(=O)N[C@@H]1C=NC2=CC=C(C(F)(F)F)C=C12C3=CC=C(OC(F)(F)F)C=C3</chem> $C_{20}H_{17}F_6N_3O_3$	3-hydroxy-3-methyl-N-(1-(4-(trifluoromethoxy)phenyl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)butanamide	7	B	3.5	462

TABLE 1-continued

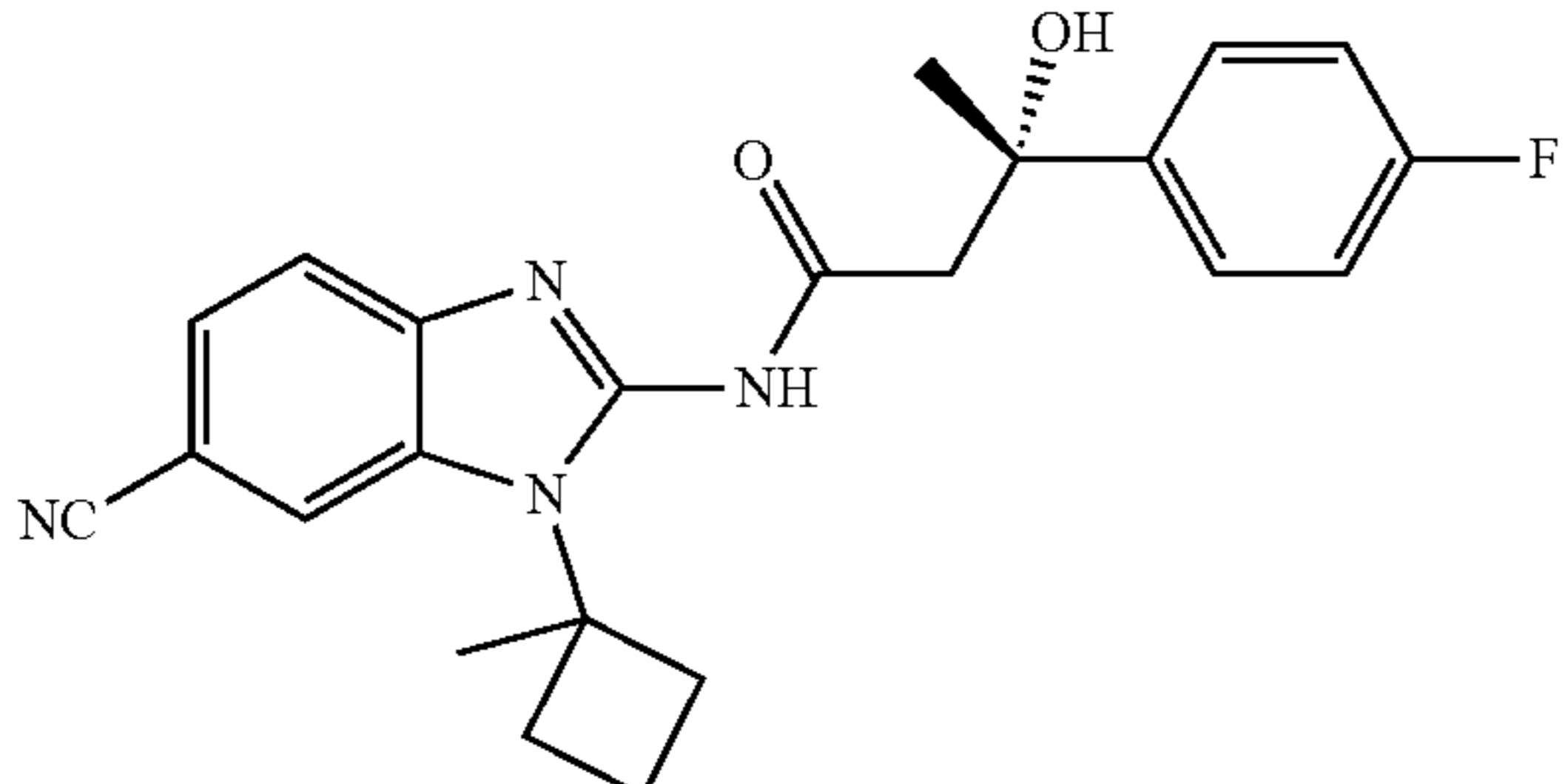
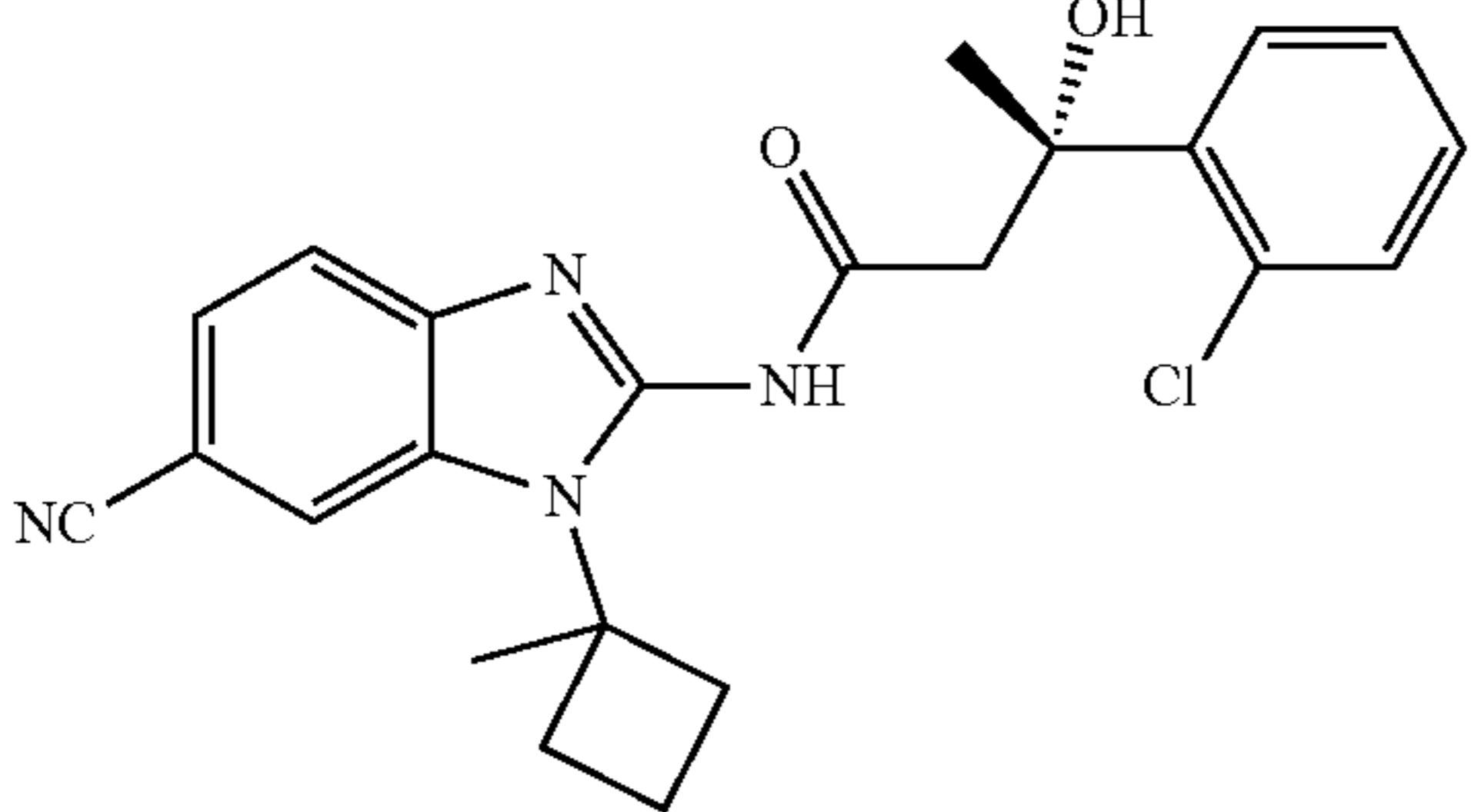
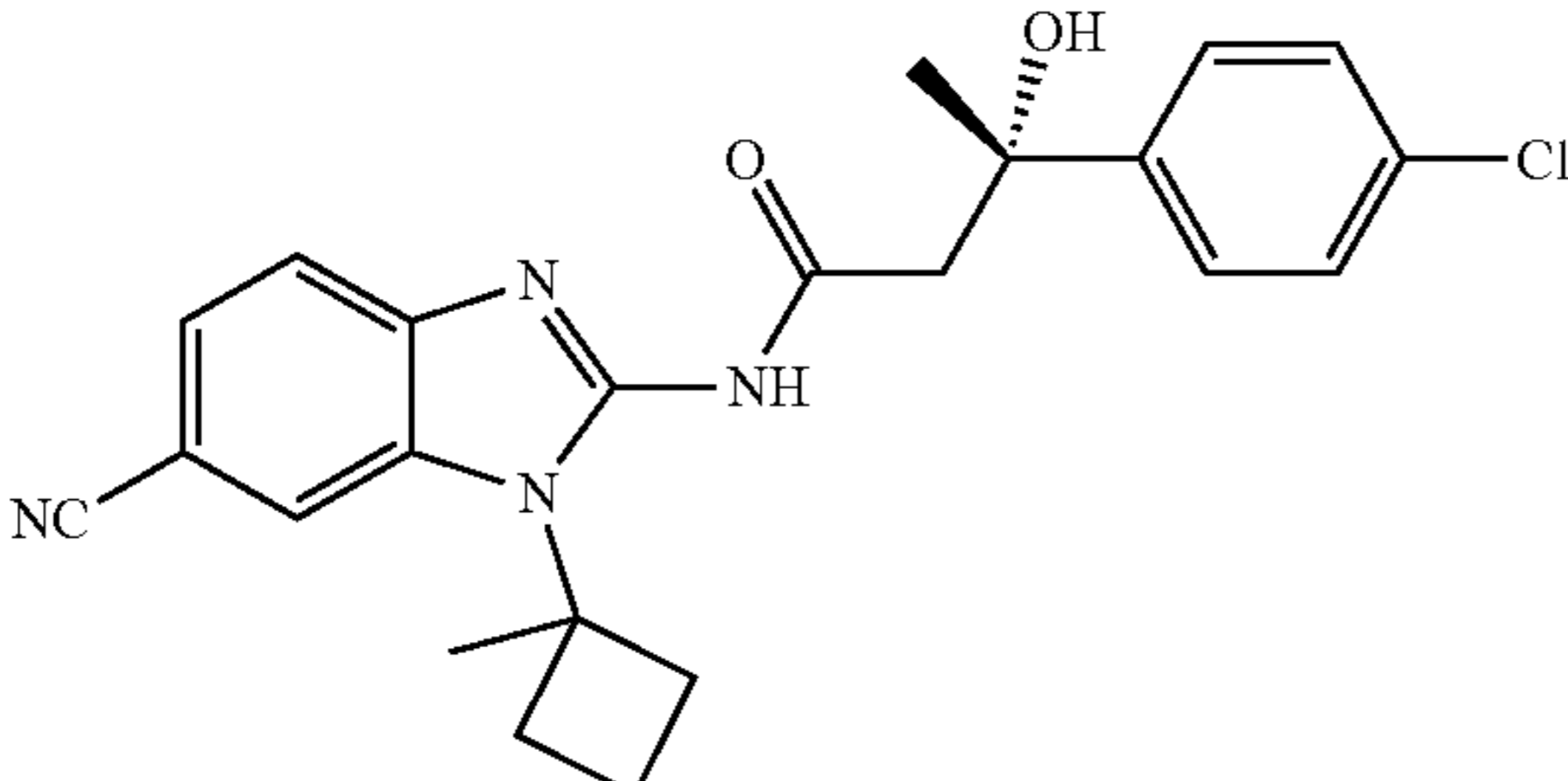
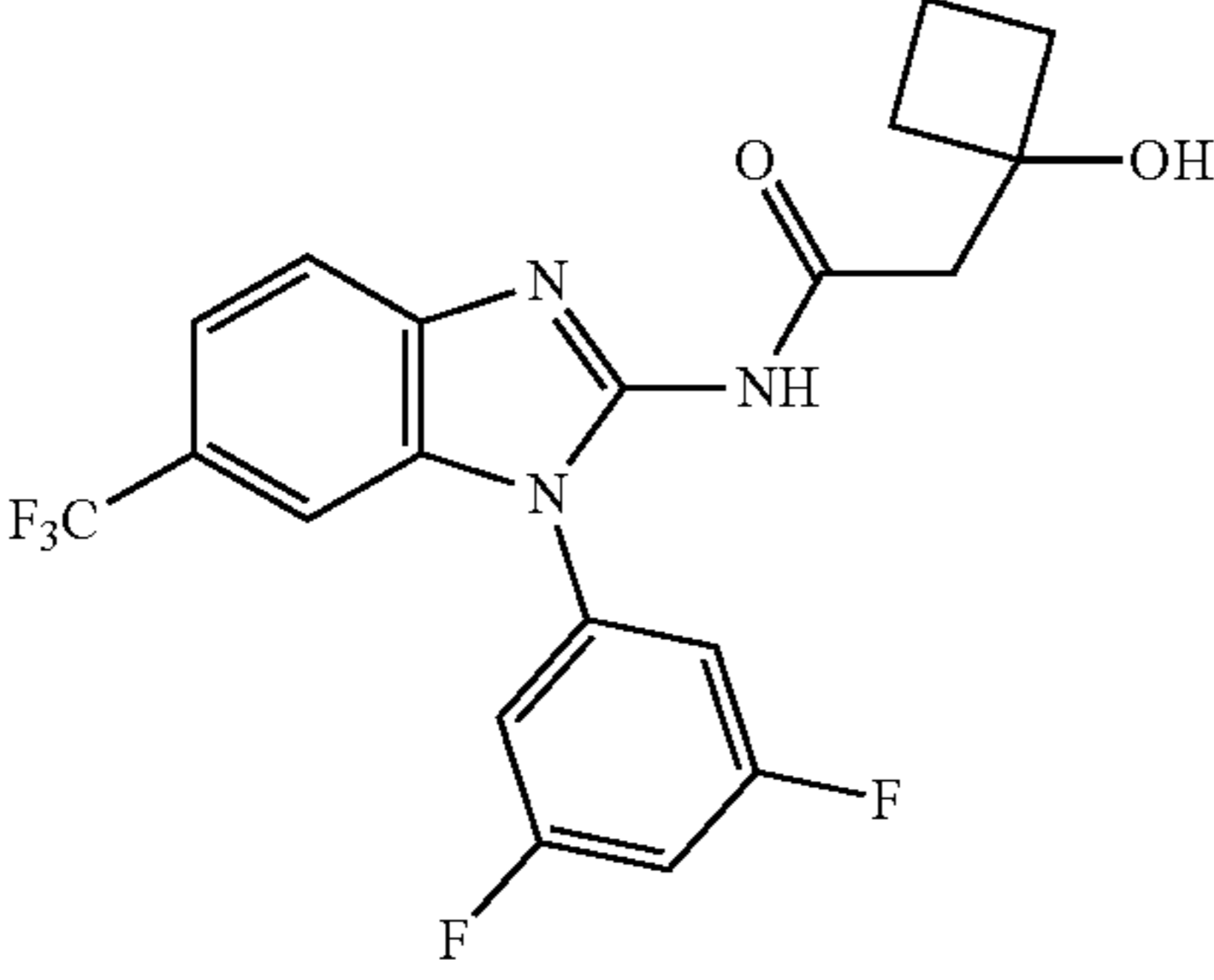
List of Examples, Synthetic Routes and Analytical Data							
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Retention time (min)	LCMS m/z	
138	 $C_{23}H_{23}FN_4O_2$	(S)-N-(6-cyano-1-(1-methylcyclobutyl)-1H-benzo[d]imidazol-2-yl)-3-(4-fluorophenyl)-3-hydroxybutanamide	7	B	3.7	407	
139	 $C_{23}H_{23}ClN_4O_2$	(S)-3-(2-chlorophenyl)-N-(6-cyano-1-(1-methylcyclobutyl)-1H-benzo[d]imidazol-2-yl)-3-hydroxybutanamide	7	B	4.0	423	
140	 $C_{23}H_{23}ClN_4O_2$	(S)-3-(4-chlorophenyl)-N-(6-cyano-1-(1-methylcyclobutyl)-1H-benzo[d]imidazol-2-yl)-3-hydroxybutanamide	7	A	5.7	423	
141	 $C_{20}H_{16}F_5N_3O_2$	N-(1-(3,5-difluorophenyl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-2-(1-hydroxycyclobutyl)acetamide	7	B	3.6	426	

TABLE 1-continued

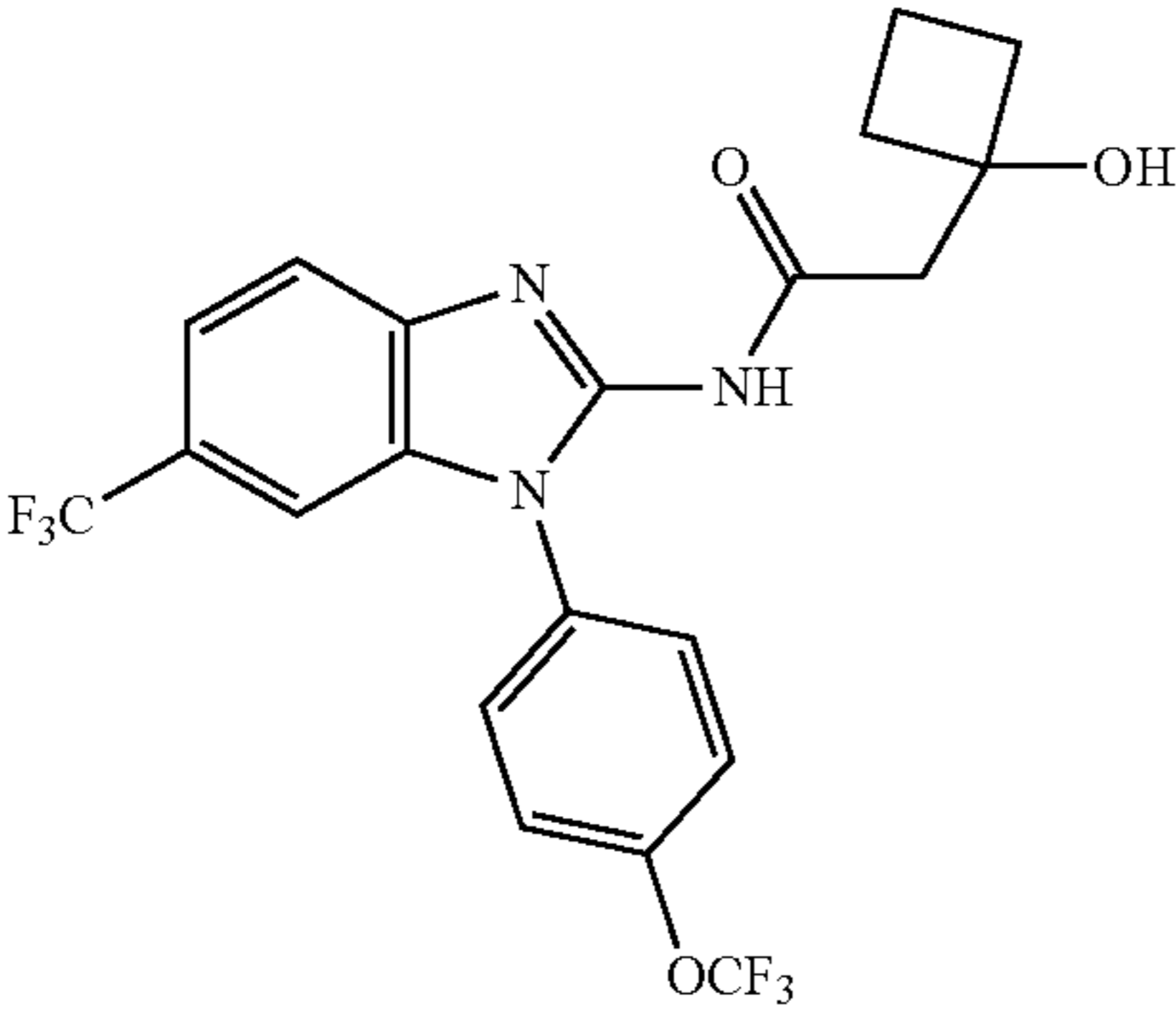
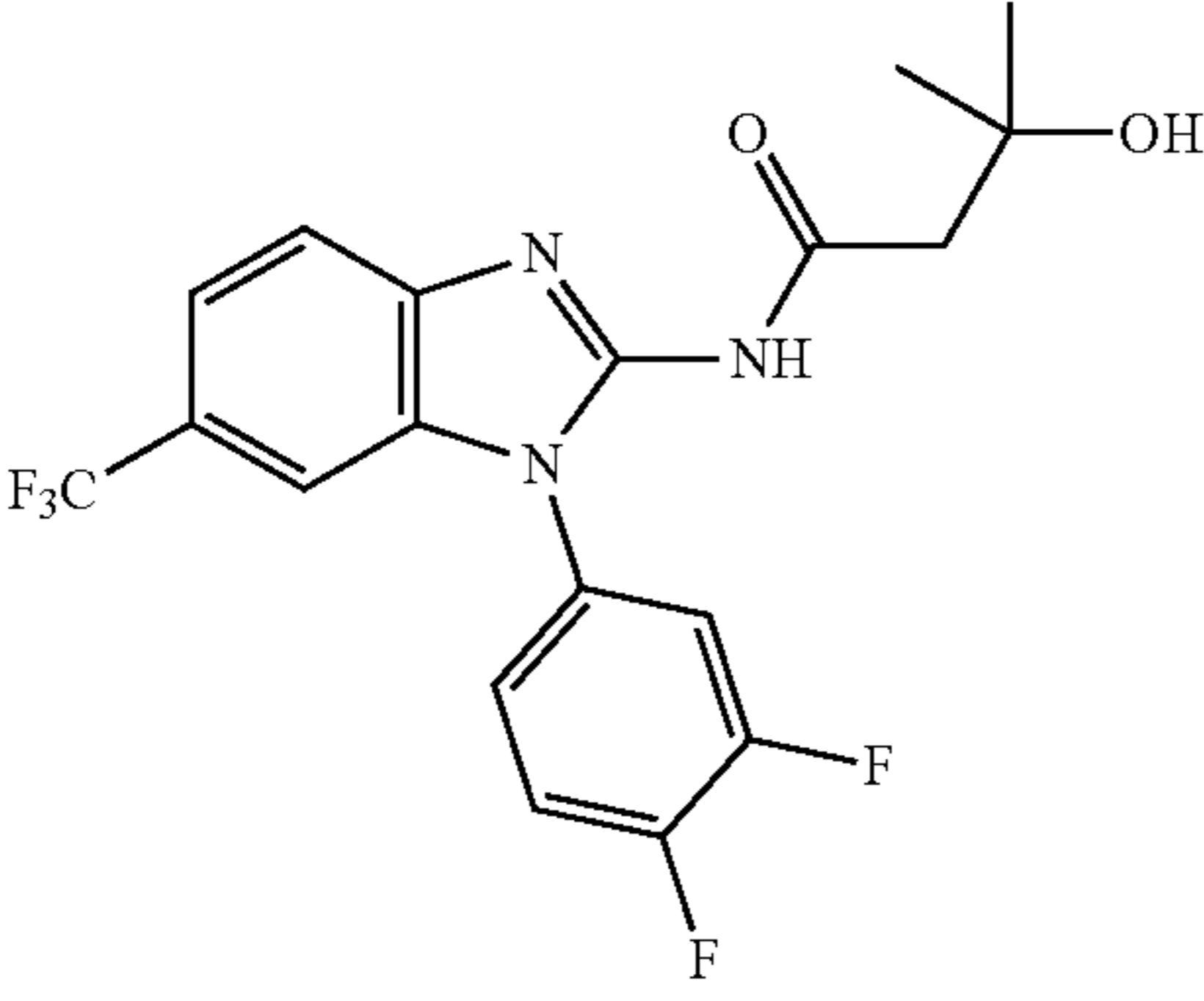
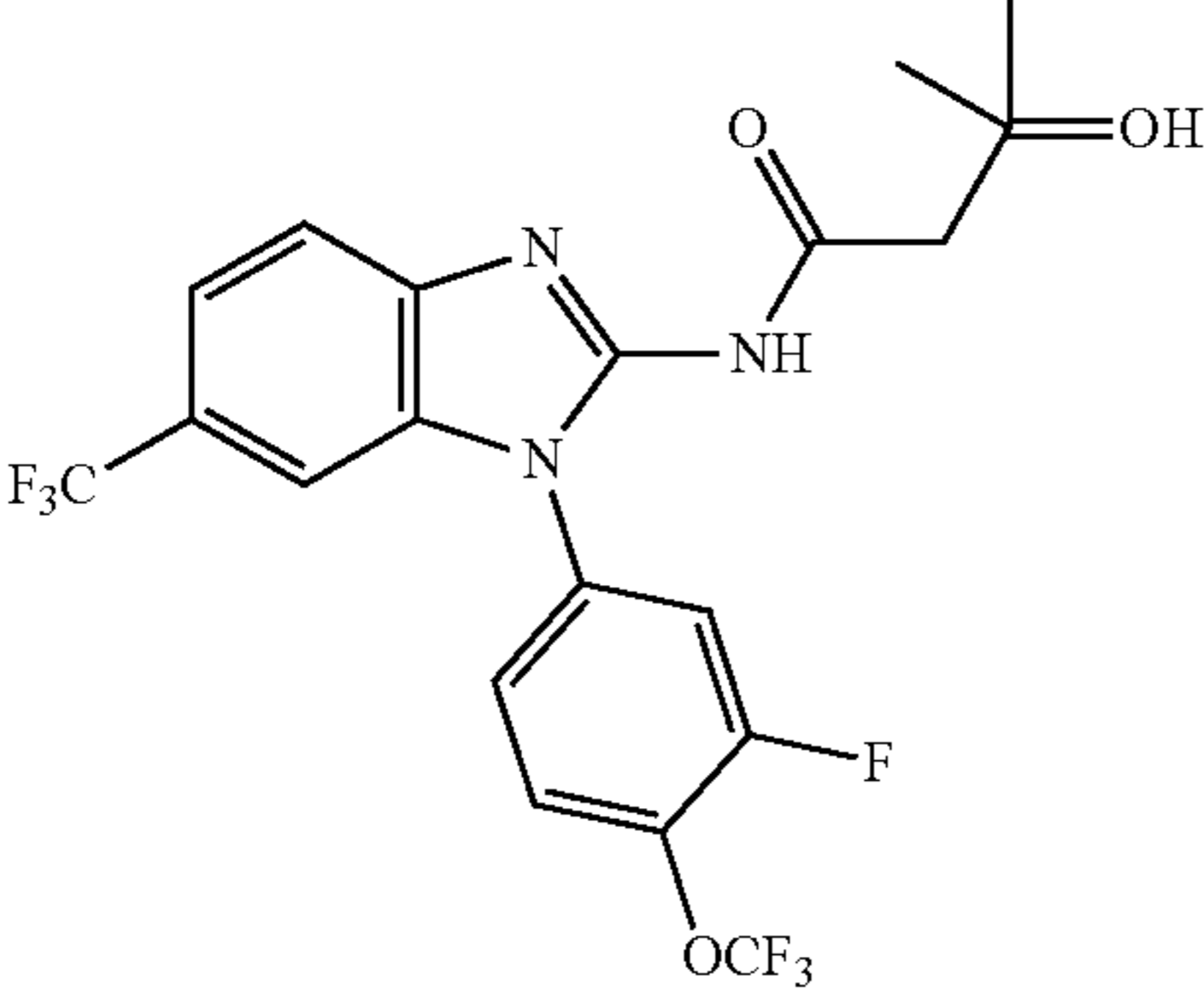
List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Re-tension time (min)	LCMS m/z
142	 <p style="text-align: center;">$C_{21}H_{17}F_6N_3O_3$</p>	2-(1-hydroxycyclobutyl)-N-(1-(4-(trifluoromethoxy)phenyl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)acetamide	7	B	3.8	474
143	 <p style="text-align: center;">$C_{19}H_{16}F_5N_3O_2$</p>	N-(1-(3,4-difluorophenyl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-methylbutanamide	7	B	3.4	414
144	 <p style="text-align: center;">$C_{20}H_{16}F_7N_3O_3$</p>	N-(1-(3-fluoro-4-(trifluoromethoxy)phenyl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-3-hydroxy-3-methylbutanamide	7	B	3.8	480

TABLE 1-continued

List of Examples, Synthetic Routes and Analytical Data						
Ex.	Structure	Name	Coupling Method/ final step	HPLC Method	HPLC Re-tension time (min)	LCMS m/z
145	<p style="text-align: center;">$C_{21}H_{16}F_7N_3O_3$</p>	N-(1-(3-fluoro-4-(trifluoromethoxy)phenyl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-2-(1-hydroxycyclobutyl)acetamide	7	B	3.9	492

Biological Assay Methods

Kv7.2/7.3 Activation Assay

The ability of compounds to potentiate K-currents in Kv7.2/7.3 containing HEK cells was assessed using planar patch-clamp on the QPatch automated screening platform.

Cell Line:

The hKv7.2/7.3 cell line was obtained from Chantest (Cleveland, Ohio 44128) cat. #CT6147. These HEK cells will express the Kv7.2/7.3 ion channels when induced.

Cell Culture:

Cells were maintained in a media containing DMEM/F12; 50/50 (GIBCO cat. #11330), 10% Fetal Bovine Serum (FBS) (GIBCO cat. #26140), 100 units/mL Penicillin-Streptomycin (GIBCO cat. #15140), 0.005 mg/mL Blastocidin (INVIVOGEN cat. # ant-bl-1), 0.5 mg/mL Geneticin (GIBCO cat. #10131), 0.1 mg/mL Zeocin (GIBCO cat. #R25001). Cells used in the electrophysiology assay were maintained in a media without Blastocidin, Geneticin and Zeocin for 2 days and channel expression was induced by adding tetracycline (BIOLINE cat. # BIO-87030) at a final concentration of 1 mg/mL. Cells were grown in T-175 flask to ~75% confluency. Currents were recorded 24 hours after channel induction.

Compound Plates:

Test compounds were prepared by performing serial dilutions on a Biomek NX^P (BECKMAN COULTER). Final dilutions were made in external recording solution with a final DMSO concentration of 0.1% DMSO. For single concentration screens each plate had 10 μ M retigabine as a positive control and 0.1% DMSO as a negative control.

Electrophysiology:

On the day of the experiment cells were washed with Hank's Balanced Salt Solution (HBBS) (GIBCO cat. #14175) and harvested with Tryple (GIBCO cat. #12604). Cells were then centrifuged at 2000 rpm for 5 minutes and resuspended in CHO—S—SFM (GIBCO cat. #12052) at $\sim 3 \times 10^6$ cells/mL. Cells were stirred for 30 minutes before experiments were started. External recording solution contained (in mM): NaCl (145), KCl (4), CaCl₂ (2), MgCl₂ (1), HEPES (10) and Glucose (10); pH was adjusted to 7.4 with NaOH and the osmolarity was adjusted to 300-305 mOsM with sucrose if necessary. Internal solution contained (in

25

mM): KCl (125), KF (10), EGTA (5), Na₂ATP (5), MgCl₂ (3.2), HEPES (5); pH was adjusted to 7.2 with KOH and the osmolarity was adjusted to 298-302 mOsM with sucrose.

30

Potassium channel activity was measured on the QPatch HTX (Sophion Bioscience) using QPlates with 48-wells/plate. Each cell was taken as an independent experiment and only one compound was tested per well. Potassium channel activity was elicited by holding at -80 mV and stepping to -30 mV for 2 s followed by a 100 ms pulse to -120 mV.

35

Single Concentration Screen:

Baseline conditions were obtained by recording 5 sweeps in the external solution only, this was repeated for three applications of the external solution. The effect of test compounds on elicited current was then assessed by recording 5 sweeps in the presence of a 3 μ M compound solution. The steady-state current at the end of the 2 s pulse to -30 mV was measured to determine the fold increase from baseline.

45

TABLE 2

Kv7.2/7.3 Single Concentration Screen Results.	
Example	Kv7.2/7.3 Activity*
1	+
2	+
3	+++
4	+/-
5	+++
6	+
7	+
8	+
9	+
10	+
11	++
12	+/-
13	+/-
14	+/-
15	+/-
16	+/-
17	++
18	+
19	+
20	+
21	+/-
22	+/-

65

187

TABLE 2-continued

Kv7.2/7.3 Single Concentration Screen Results.		
Example	Kv7.2/7.3 Activity*	
23	++	5
24	+	
25	+/-	
26	+/-	
27	+/-	
28	+/-	10
29	+	
30	+	
31	+	
32	+	
33	+	
34	++	15
35	+	
36	+	
37	+	
38	+/-	
39	+	
40	+	
41	+/-	20
42	+/-	
43	+/-	
44	+	
45	+	
46	+	
47	+	25
48	+++	
49	+	
50	+/-	
51	+	
52	+/-	
53	+	30
54	++	
55	+	
56	++	
57	+	
58	+	
59	+	35
60	+	
61	+	
62	+	
63	++	
64	++	
65	+	
66	++	40
67	+/-	
68	+	
69	+	
70	+/-	
71	+	
72	+/-	45
73	+/-	
74	+	
75	++	
76	+	
77	+	
78	+	50
79	+	
80	+	
81	+	
82	+/-	
83	++	
84	+	55
85	+/-	
86	+++	
87	++	
88	+	
89	++	
90	+/-	60
91	+/-	
92	+	
93	+	
94	+/-	
95	++	
96	++	65
97	+/-	
98	+	

188

TABLE 2-continued

Kv7.2/7.3 Single Concentration Screen Results.		
Example	Kv7.2/7.3 Activity*	
99	+	
100	+	
101	+	
102	+/-	
103	+	
104	+ (@ 1 μM)	10
105	+	
106	+/-	
107	+	
108	+/-	
109	+	
110	+	15
111	+	
112	++	
113	+	
114	+	
115	+	
116	+	
117	+/-	20
118	+	
119	+/-	
120	+	
121	+	
122	++	
123	+/-	25
124	+/-	
125	+/-	
126	++	
127	+	
128	+/-	
129	+/-	30
130	+/-	
131	+/-	
132	+/-	
133	+	
134	+/-	
135	+/-	35
136	+	
137	+	
138	+	
139	+	
140	+/-	
141	+	
142	++	40
143	++	
144	+	
145	++	

*Increase in current from Kv7.2/Kv7.3 co-expressing HEK cells, measured at compound concentration of 3 μM, as a range from <1.2-fold increase over baseline (-) up to >6-fold increase over baseline (+++).

Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

The terms "a," "an," "the" and similar referents used in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or

189

exemplary language (e.g., "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of any claim. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

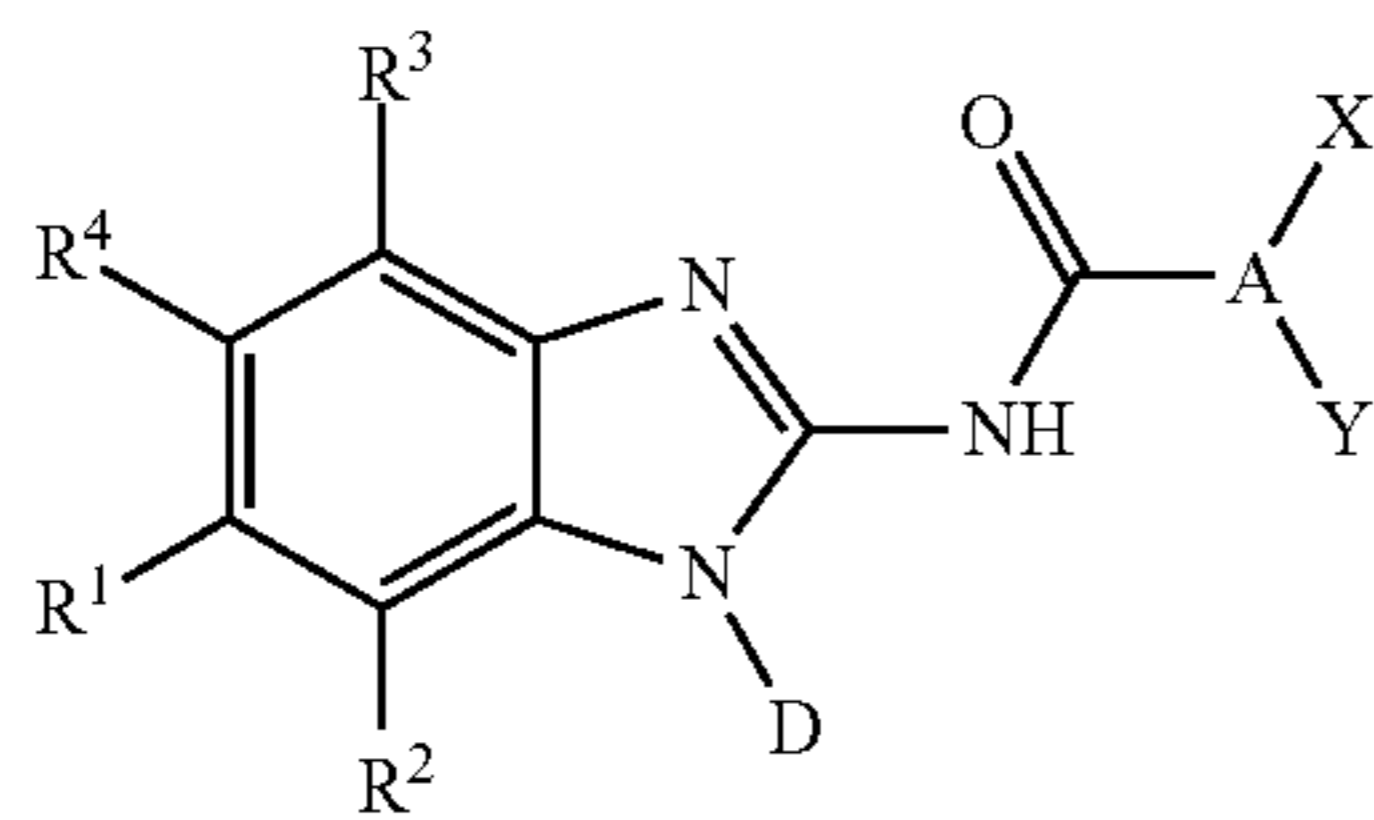
Groupings of alternative elements or embodiments disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

Certain embodiments are described herein, including the best mode known to the inventors for carrying out the invention. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than specifically described herein. Accordingly, the claims include all modifications and equivalents of the subject matter recited in the claims as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is contemplated unless otherwise indicated herein or otherwise clearly contradicted by context.

In closing, it is to be understood that the embodiments disclosed herein are illustrative of the principles of the claims. Other modifications that may be employed are within the scope of the claims. Thus, by way of example, but not of limitation, alternative embodiments may be utilized in accordance with the teachings herein. Accordingly, the claims are not limited to embodiments precisely as shown and described.

The invention claimed is:

1. A compound represented by a formula:



wherein:

D is cyclobutyl;

A is C₁₋₈ alkyl;

X is CF₃;

Y is H;

R¹ is H, Cl, Br, CN, OCH₃, CF₃, —CO₂CH₂CH₃, C₁₋₄ alkyl, or C₁₋₄ hydroxyalkyl;

R² is H, F, —CH₂OH, —CO₂Me, or —C(CH₃)₂OH;

R³ is H, F, Cl, Br, I, or a substituent having a molecular weight of 15 Da to 200 Da and consisting of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br; and

R⁴ is H, —CH₃, or —CF₃.

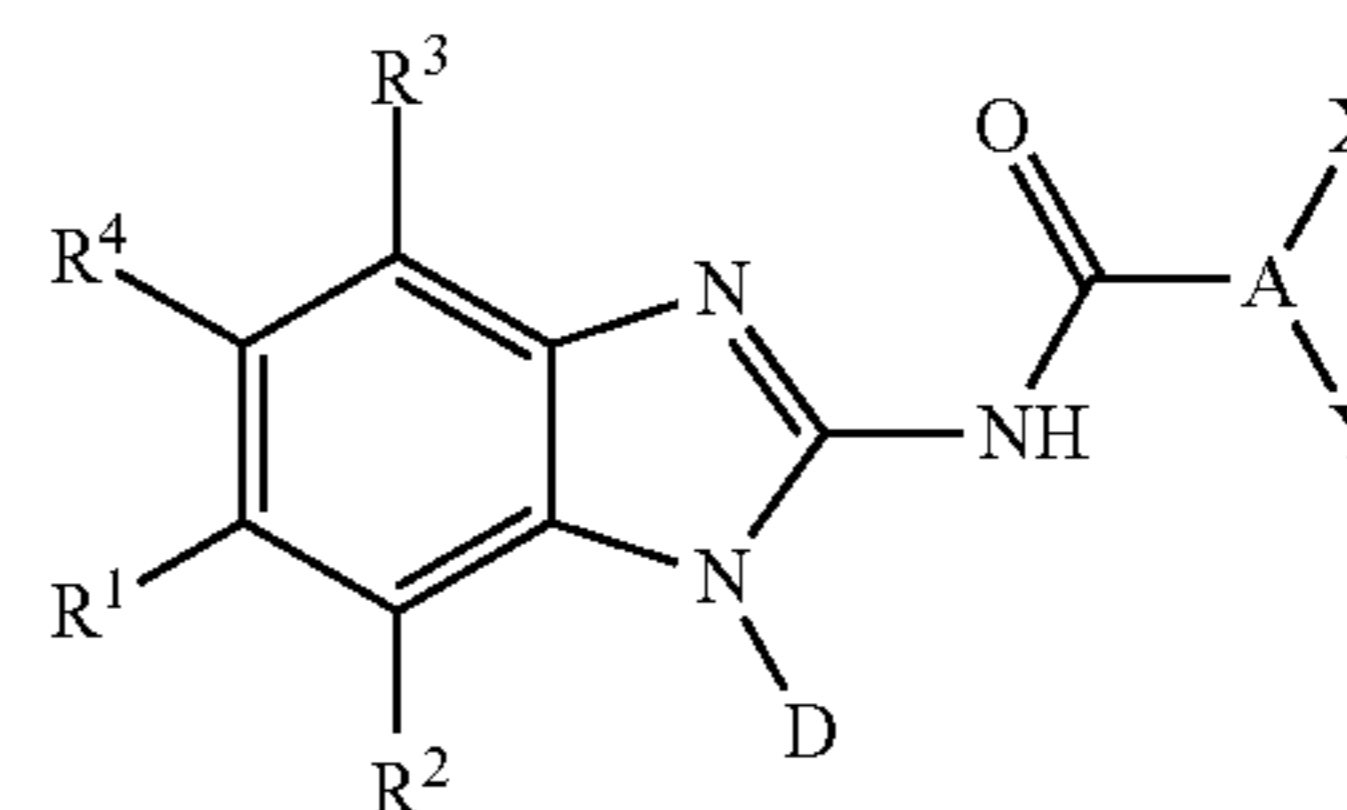
190

2. A composition comprising a compound of claim 1, wherein the composition is pharmaceutically acceptable and further comprises a pharmaceutically acceptable excipient.

3. A method of treating a disease selected from epilepsy, pain, migraine, and tinnitus comprising administering an effective amount of a compound of claim 1 to a mammal in need thereof.

4. The method of claim 3, wherein the pain is selected from neuropathic pain, inflammatory pain, persistent pain, cancer pain and postoperative pain.

5. A compound represented by a formula:



wherein:

D is optionally substituted cyclobutyl;

A is C₁₋₈ alkyl;

X is CF₃;

Y is H;

R¹ is H, Cl, Br, CN, OCH₃, CF₃, —CO₂CH₂CH₃, C₁₋₄ alkyl, or C₁₋₄ hydroxyalkyl;

R² is H, F, —CH₂OH, —CO₂Me, or —C(CH₃)₂OH;

R³ is H; and

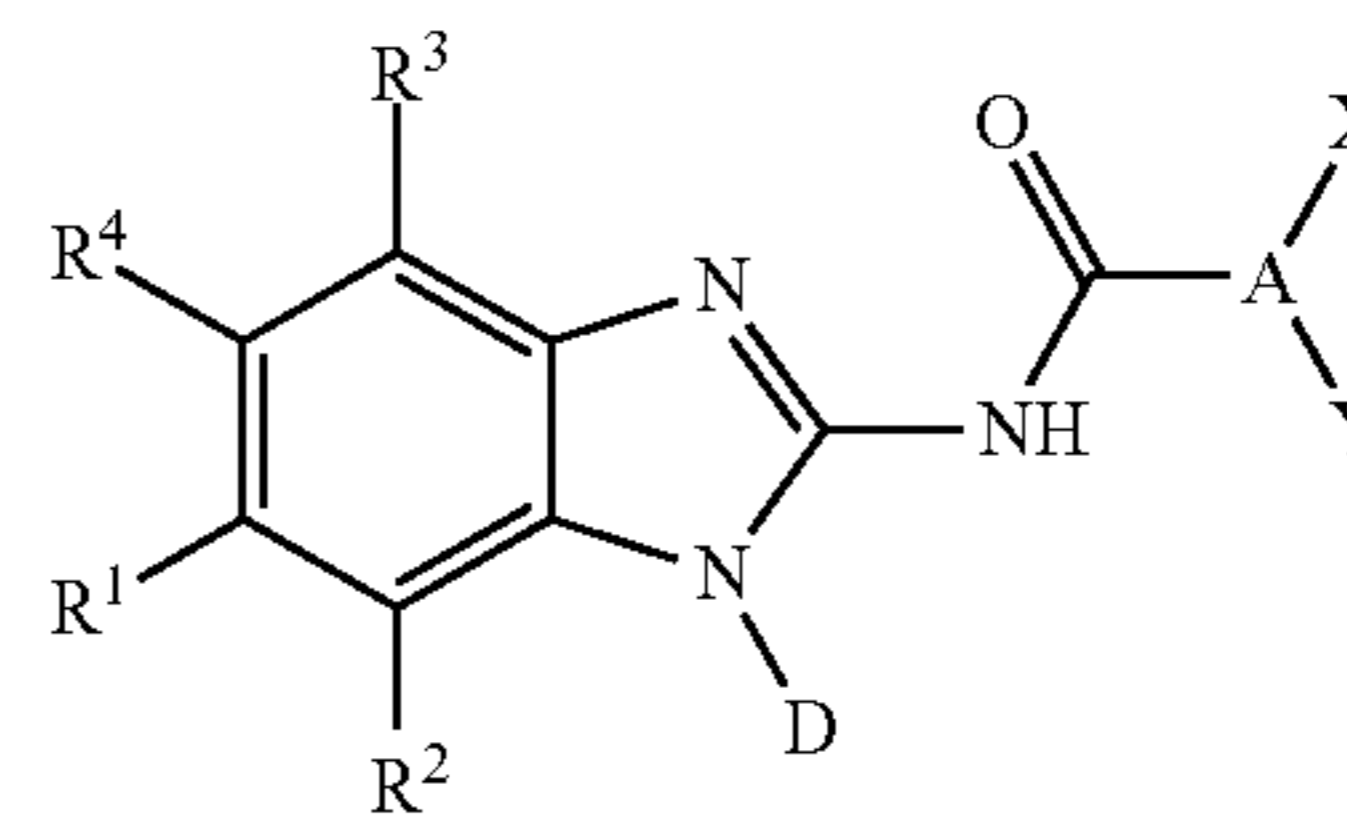
R⁴ is H, —CH₃, or —CF₃.

6. A composition comprising a compound of claim 5, wherein the composition is pharmaceutically acceptable and further comprises a pharmaceutically acceptable excipient.

7. A method of treating a disease selected from epilepsy, pain, migraine, and tinnitus comprising administering an effective amount of a compound of claim 5 to a mammal in need thereof.

8. The method of claim 7, wherein the pain is selected from neuropathic pain, inflammatory pain, persistent pain, cancer pain and postoperative pain.

9. A compound represented by a formula:



wherein:

D is t-butyl;

A is C₁₋₈ alkyl;

X is H;

Y is H;

R¹ is Cl, Br, CN, OCH₃, CF₃, —CO₂CH₂CH₃, C₁₋₄ alkyl, or C₁₋₄ hydroxyalkyl;

R² is H, F, —CH₂OH, —CO₂Me, or —C(CH₃)₂OH;

R³ is H, F, Cl, Br, I, or a substituent having a molecular weight of 15 Da to 200 Da and consisting of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br; and

R⁴ is H, —CH₃, or —CF₃.

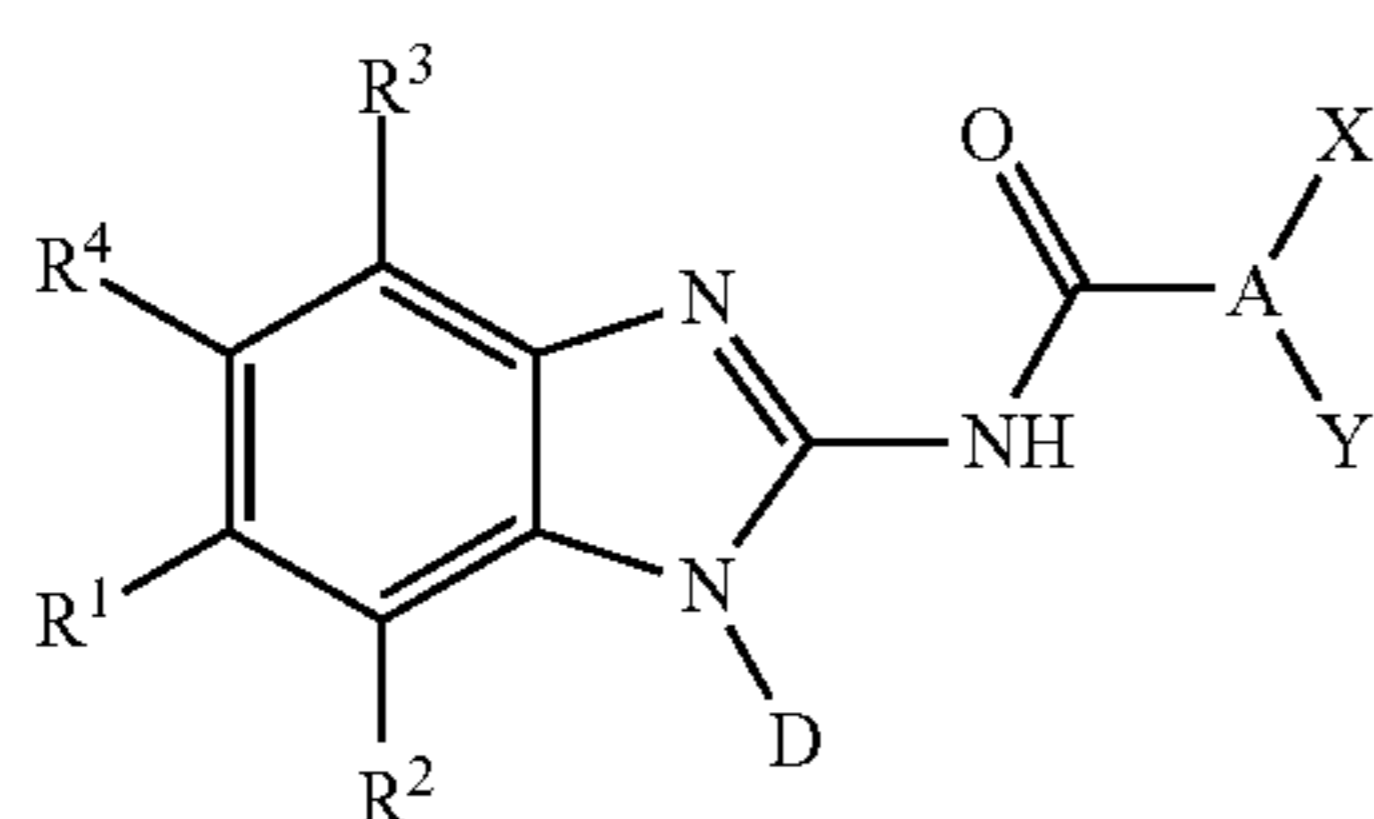
191

10. A composition comprising a compound of claim 9, wherein the composition is pharmaceutically acceptable and further comprises a pharmaceutically acceptable excipient.

11. A method of treating a disease selected from epilepsy, pain, migraine, and tinnitus comprising administering an effective amount of a compound of claim 9 to a mammal in need thereof.

12. The method of claim 11, wherein the pain is selected from neuropathic pain, inflammatory pain, persistent pain, cancer pain and postoperative pain.

13. A compound represented by a formula:



wherein:

192

D is t-butyl;

A is C₁₋₈ alkyl;

X is CF₃;

Y is H;

R¹ is H, Cl, Br, CN, OCH₃, CF₃, —CO₂CH₂CH₃, C₁₋₄ alkyl, or C₁₋₄ hydroxyalkyl;

R² is H, F, —CH₂OH, —CO₂Me, or —C(CH₃)₂OH;

R³ is H, F, Cl, Br, I, or a substituent having a molecular weight of 15 Da to 200 Da and consisting of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, S, F, Cl, or Br; and

R⁴ is H, —CH₃, or —CF₃.

14. A composition comprising a compound of claim 13, wherein the composition is pharmaceutically acceptable and further comprises a pharmaceutically acceptable excipient.

15. A method of treating a disease selected from epilepsy, pain, migraine, and tinnitus comprising administering an effective amount of a compound of claim 13 to a mammal in need thereof.

16. The method of claim 15, wherein the pain is selected from neuropathic pain, inflammatory pain, persistent pain, cancer pain and postoperative pain.

* * * * *