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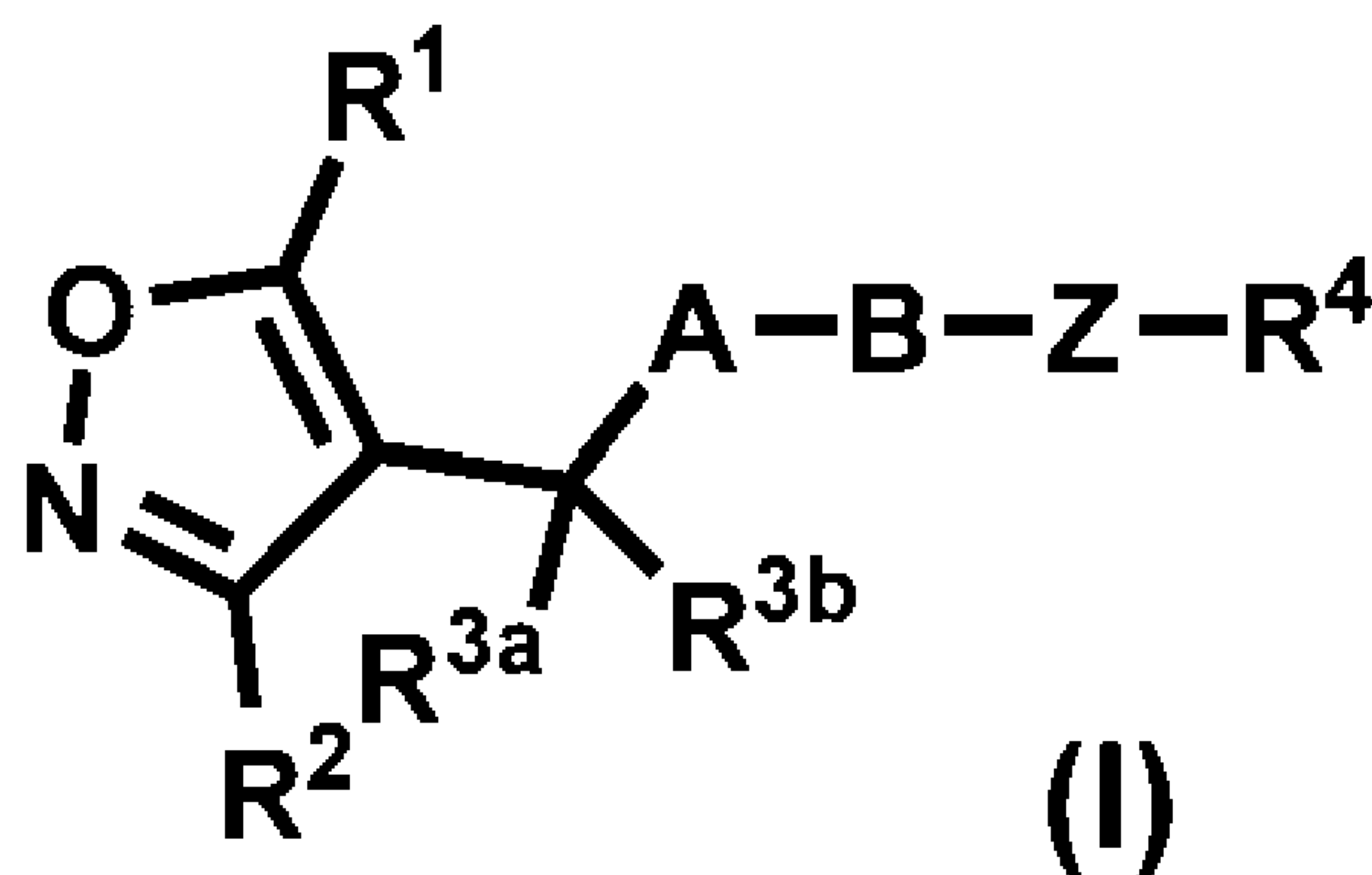
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(57) **Abrégé/Abstract:**

The present invention provides compounds of Formula I, pharmaceutical compositions comprising these compounds and methods of using these compounds to prevent or treat FXR-mediated or TGR5-mediated diseases or conditions.

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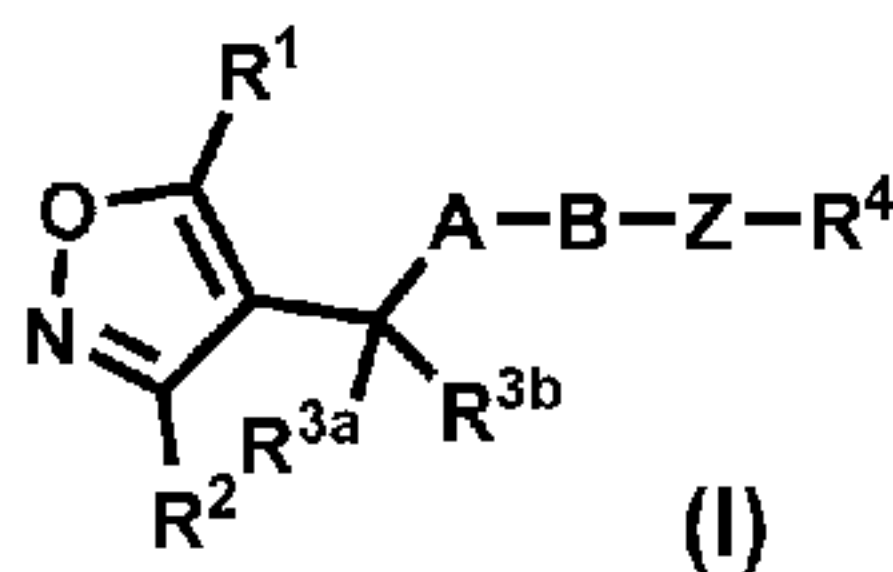
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(54) Title: ISOXAZOLE ANALOGS AS FXR AGONISTS AND METHODS OF USE THEREOF



(57) Abstract: The present invention provides compounds of Formula I, pharmaceutical compositions comprising these compounds and methods of using these compounds to prevent or treat FXR-mediated or TGR5-mediated diseases or conditions.

WO 2018/067704 A1

ISOXAZOLE ANALOGS AS FXR AGONISTS AND METHODS OF USE THEREOF**RELATED APPLICATIONS**

This application claims the benefit of U.S. Provisional Application No. 62/404,059, filed on October 4, 2016. The entire teachings of the above application are incorporated herein by reference.

5

TECHNICAL FIELD

The present invention relates generally to compounds and pharmaceutical compositions useful as FXR modulators. Specifically, the present invention relates to isoxazole derivatives useful as agonists for FXR, and methods for their preparation and use.

BACKGROUND OF THE INVENTION

10

Farnesoid X Receptor (FXR) is an orphan nuclear receptor initially identified from a rat liver cDNA library (BM. Forman, et al., *Cell*, **1995**, 81(5), 687-693) that is most closely related to the insect ecdysone receptor. FXR is a member of the nuclear receptor family of ligand-activated transcription factors that includes receptors for the steroid, retinoid, and thyroid hormones (DJ. Mangelsdorf, et al., *Cell*, **1995**, 83(6), 841-850). The relevant physiological ligands of FXR are bile acids (D. Parks et al., *Science*, 1999, 284(5418), 1362-1365). The most potent one is chenodeoxycholic acid (CDCA), which regulates the expression of several genes that participate in bile acid homeostasis. Farnesol and derivatives, together called farnesoids, are originally described to activate the rat orthologue at high concentration but they do not activate the human or mouse receptor. FXR is expressed in the liver, throughout the entire gastrointestinal tract including the esophagus, stomach, duodenum, small intestine, colon, ovary, adrenal gland and kidney. Beyond controlling intracellular gene expression, FXR seems to be also involved in paracrine and endocrine signaling by upregulating the expression of the cytokine Fibroblast Growth Factor (J. Holt et al., *Genes Dev.*, **2003**, 17(13), 1581-1591; T. Inagaki et al., *Cell Metab.*, **2005**, 2(4), 217-225).

25

Small molecule compounds which act as FXR modulators have been disclosed in the following publications: WO 2000/037077, WO 2002/072598, WO 2003/015771, WO 2003/099821, WO 2004/00752, WO 2004/048349, WO 2005/009387, WO 2005/082925, US 2005/0054634, WO 2007/052843, WO 2007/070796, WO 2007/076260, WO 2007/092751, WO 2007/095174, WO 2007/140174, WO 2007/140183, US 2007/0142340, WO 2008/000643, WO 2008/002573, WO 2008/025539, WO 2008/025540, WO 2008/051942,

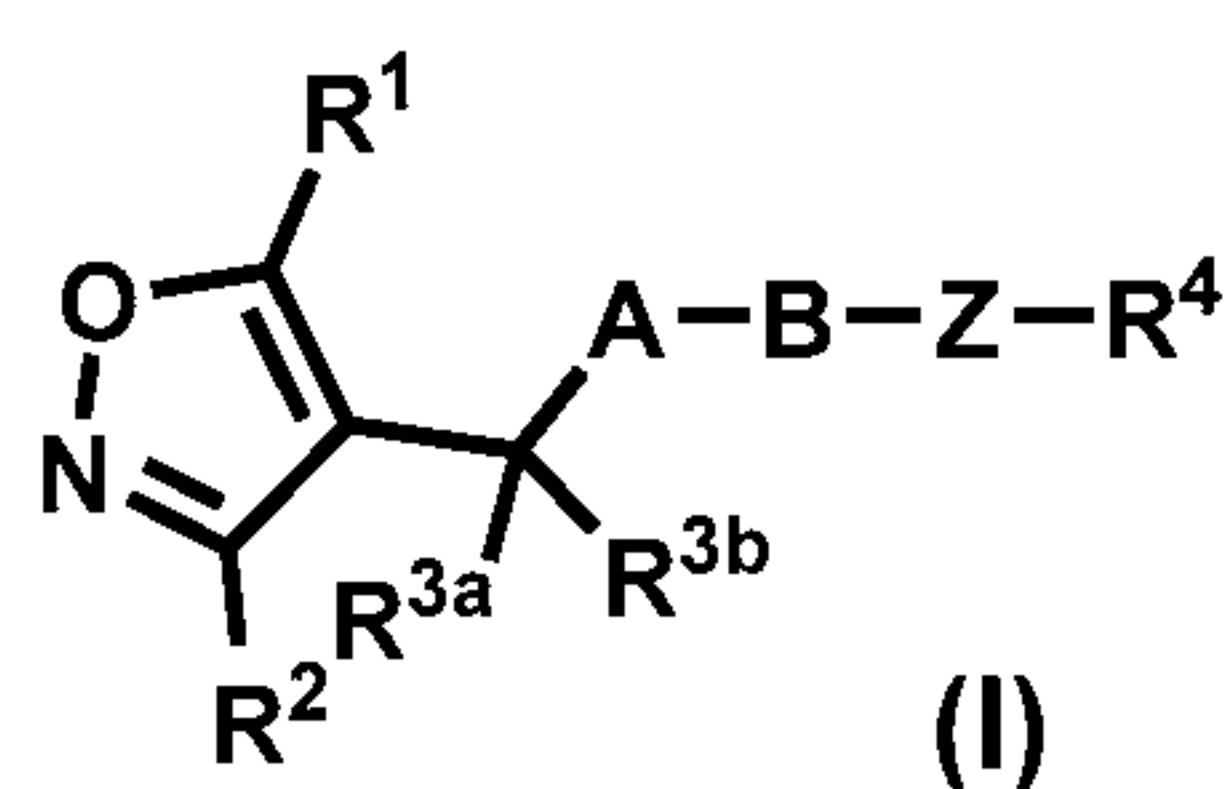
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WO 2008/073825, WO 2008/157270, US 2008/0299118, US 2008/0300235, WO
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 5 WO 2012/087519, WO 2012/087520, WO 2012/087521, WO 2013/007387, WO
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 US 2014/0187633, WO 2015/017813, WO 2015/069666, WO 2016/116054,
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 10 WO 2017/062763, WO 2017/053826, CN 106518708, CN 106518946, CN 106478759, CN
 106478447, CN 106478453, WO 2017/027396, WO 2017/049172, WO 2017/049173, WO
 2017/049176, WO 2017/049177, WO 2017/118294, WO 2017/128896, WO 2017/133521,
 WO 2017/156024. Further small molecule FXR modulators have been recently reviewed (R.
 C. Buijsman, et al., *Curr. Med. Chem.* **2005**, 12(9), 1017-1075; Crawley, M. L. *Expert Opin.*
 15 *Ther. Patents* **2010**, 20(8), 1047-1057; V. Sepe, et al., *Expert Opin. Ther. Patents* **2015**,
 25(8), 885-896.

There is a need for the development of FXR modulators for the treatment and
 prevention of disease. The present invention has identified compounds which modulate FXR
 as well as methods of using these compounds to treat disease.

20 SUMMARY OF THE INVENTION

In one aspect, the invention provides compounds represented by Formula I, and
 pharmaceutically acceptable salts thereof:

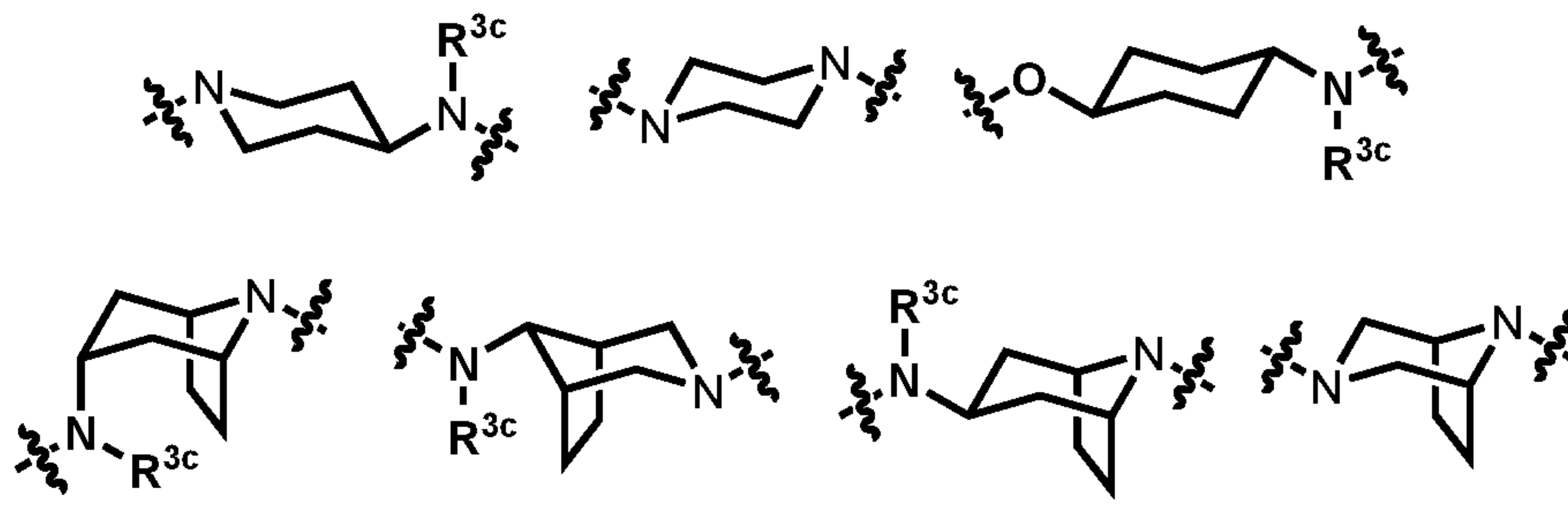


wherein:

- 25 R¹ is hydrogen, halogen, cyano, optionally substituted -C₁-C₆ alkyl, optionally substituted -
 C₂-C₆ alkenyl, optionally substituted -C₂-C₆ alkynyl, optionally substituted C₃-C₆ cycloalkyl
 or optionally substituted 3- to 6- membered heterocycloalkyl. Preferably, R¹ is isopropyl,
tert-butyl, or cyclopropyl.
- R² is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted -C₃-
 30 C₁₂ cycloalkyl or optionally substituted 3- to 12- membered heterocycloalkyl;

R^{3a} and R^{3b} are independently selected from group consisting of hydrogen, halogen, -C₁-C₆ alkyl, halo-C₁-C₆ alkyl, -C₁-C₆ alkoxy or halo-C₁-C₆ alkoxy, -C₃-C₆ cycloalkyl, halo-C₃-C₆ cycloalkyl. Alternatively, R^{3a} and R^{3b} are taken together with the carbon atom to which they are attached to form an optionally substituted -C₃-C₆ cycloalkyl, optionally substituted 3- to 6- membered heterocycloalkyl, or optionally substituted -C₃-C₆ cycloalkenyl.

A is selected from the group consisting of:



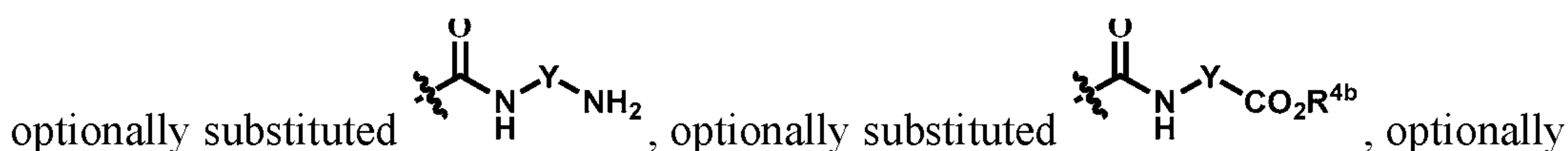
wherein one of the indicated valences is the point of attachment to the carbon atom of - $CHR^{3a}R^{3b}$ and the other is the point of attachment to B; R^{3c} is selected from group consisting of hydrogen, optionally substituted -C₁-C₆ alkyl, optionally substituted -C₃-C₆ cycloalkyl, formyl, and acetyl;

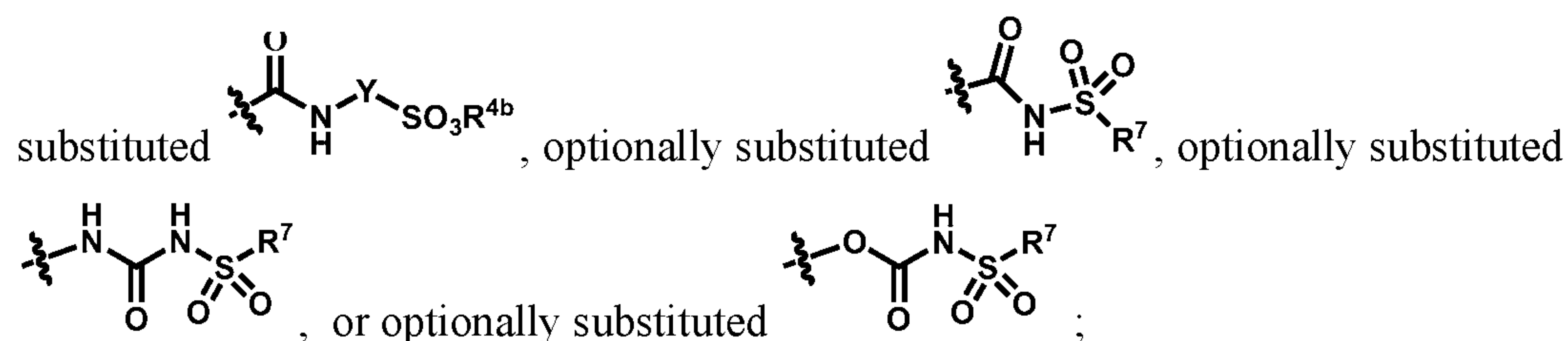
B is optionally substituted aryl, optionally substituted biaryl, optionally substituted 3- to 12 membered heterocycle or optionally substituted heteroaryl;

Z is selected from the group consisting of:

- 1) Absent;
- 2) Optionally substituted -C₁-C₆ alkyl;
- 3) Optionally substituted -C₂-C₆ alkenyl;
- 4) Optionally substituted -C₂-C₆ alkynyl;
- 5) Optionally substituted -C₃-C₈ cycloalkyl;
- 6) Optionally substituted 3- to 8- membered heterocycloalkyl;
- 7) Optionally substituted -C₃-C₈ cycloalkenyl;
- 8) Optionally substituted aryl; and
- 9) Optionally substituted heteroaryl;

R^4 is hydroxy, protected hydroxy, -O-(hydroxy prodrug group), tetrazolyl, cyano, -CO₂R⁵, -





wherein,

Y is absent or optionally substituted -C₁-C₆ alkyl;

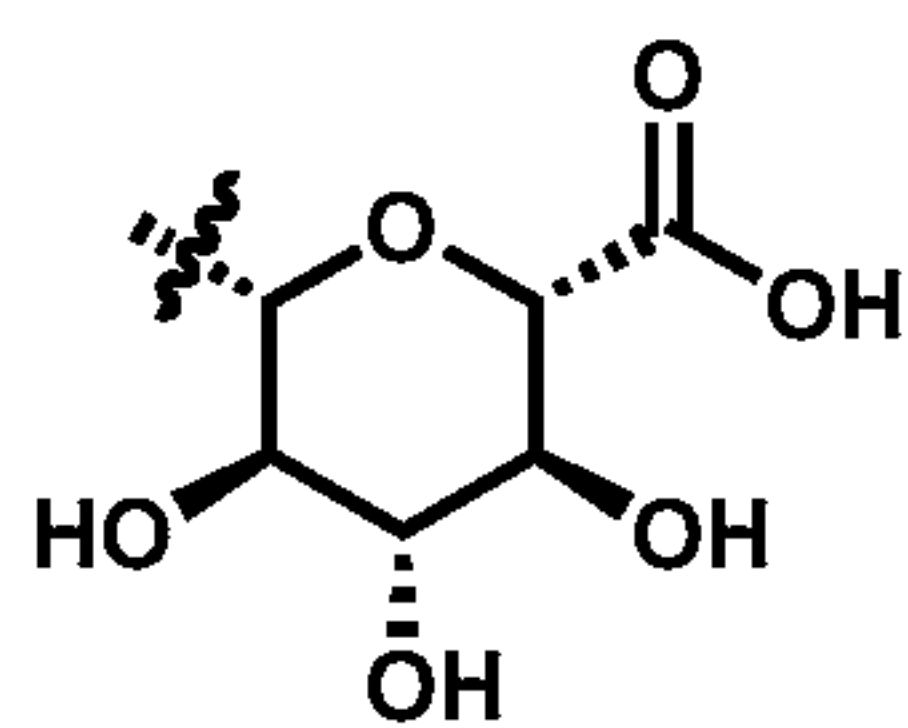
5 R^{4a} and R^{4b} are independently selected from the group consisting of:

- 1) Hydrogen;
- 2) Optionally substituted -C₁-C₈ alkyl;
- 3) Optionally substituted -C₂-C₈ alkenyl;
- 4) Optionally substituted -C₂-C₈ alkynyl; and

10 5) Optionally substituted -C₃-C₈ cycloalkyl;

R⁵ is selected from the group consisting of:

- 1) Hydrogen;



- 3) Optionally substituted -C₁-C₈ alkyl;
- 4) Optionally substituted -C₂-C₈ alkenyl;
- 5) Optionally substituted -C₂-C₈ alkynyl; and
- 6) Optionally substituted -C₃-C₈ cycloalkyl;

R⁷ is selected from the groups consisting of:

- 1) Optionally substituted -C₁-C₈ alkyl;
- 20 2) Optionally substituted -C₂-C₈ alkenyl;
- 3) Optionally substituted -C₂-C₈ alkynyl;
- 4) Optionally substituted -C₃-C₈ cycloalkyl;
- 5) Optionally substituted -C₃-C₈ cycloalkenyl;
- 6) Optionally substituted 3- to 8-membered heterocycloalkyl;
- 25 7) Optionally substituted 3- to 8- membered heterocycloalkenyl;
- 8) Optionally substituted aryl;
- 9) Optionally substituted -C₁-C₈ arylalkyl;

10) Optionally substituted heteroaryl;

11) Optionally substituted $-C_1-C_8$ heteroarylalkyl; and

12) NR^9R^{10} ; wherein R^9 and R^{10} are each independently selected from hydrogen, optionally substituted $-C_1-C_8$ alkyl, optionally substituted $-C_2-C_8$ alkenyl, optionally substituted $-C_2-C_8$ alkynyl, optionally substituted $-C_3-C_8$ cycloalkyl, optionally substituted aryl, optionally substituted alkylaryl, optionally substituted 3- to 8- membered heterocycloalkyl, optionally substituted heteroaryl, optionally substituted alkylheteroaryl; alternatively, R^9 and R^{10} are taken together with the nitrogen atom to which they are attached to form a heterocyclic ring.

10 In certain embodiments, the said hydroxy prodrug group is phosphate or sulfamate. In certain embodiments, the said hydroxy prodrug group is an acyl group derived from an amino acid, preferably an α -amino acid.

15 In another embodiment, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound or combination of compounds of the present invention, or a pharmaceutically acceptable salt form, stereoisomer, solvate, hydrate or combination thereof, in combination with a pharmaceutically acceptable carrier or excipient.

20 In another embodiment, the present invention provides a method for the prevention or treatment of an FXR mediated disease or condition. The method comprises administering a therapeutically effective amount of a compound of Formula (I). The present invention also provides the use of a compound of Formula (I) for the preparation of a medicament for the prevention or treatment of an FXR mediated disease or condition.

DETAILED DESCRIPTION OF THE INVENTION

25 In one embodiment the present invention provides a compound of Formula (I) as described above, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein R^1 is optionally substituted isopropyl, cyclopropyl, or *tert*-butyl.

30 In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein R^2 is optionally substituted cyclohexyl, cyclopentyl, or cyclopropyl.

In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein R^2 is cyclohexyl or cyclopentyl, each

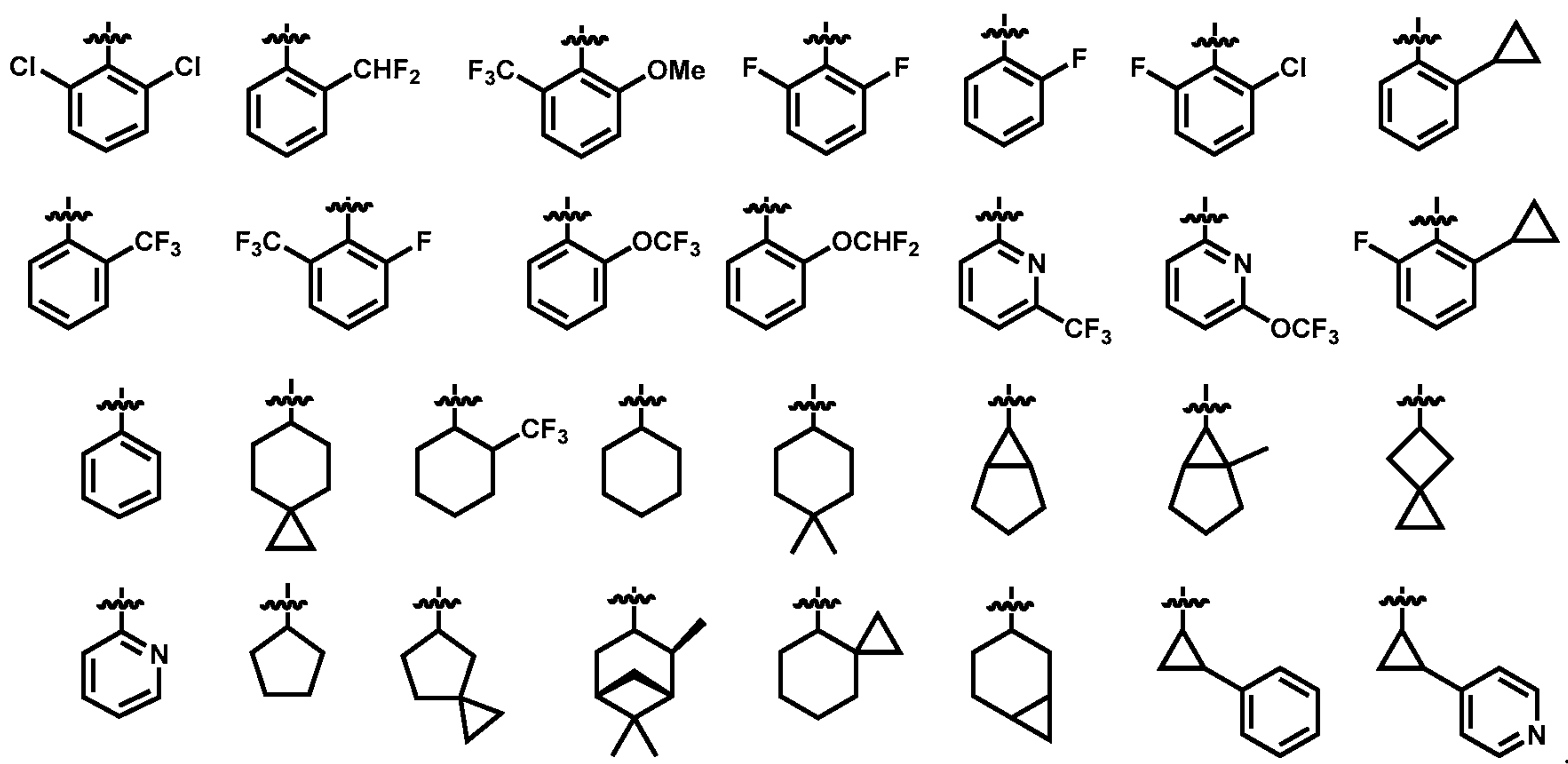
of which is optionally substituted with up to 3 groups which are independently selected from of halogen, -C₁-C₆ alkyl, halo-C₁-C₆ alkyl, -C₁-C₆ alkoxy, halo-C₁-C₆ alkoxy, -C₃-C₆ cycloalkyl, halo-C₃-C₆ cycloalkyl, -C₃-C₆ cycloalkenyl, halo-C₃-C₆ cycloalkenyl, optionally substituted aryl, or optionally substituted heteroaryl.

5 In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein R² is cyclopropyl which is optionally substituted with up to 2 groups which are independently selected from of halogen, -C₁-C₆ alkyl, halo-C₁-C₆ alkyl, -C₁-C₆ alkoxy, halo-C₁-C₆ alkoxy, -C₃-C₆ cycloalkyl, halo-C₃-C₆ cycloalkyl, -C₃-C₆ cycloalkenyl, or halo-C₃-C₆ cycloalkenyl, optionally substituted aryl, or
10 optionally substituted heteroaryl.

In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein R² is optionally substituted phenyl.

In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein R² is optionally substituted heteroaryl.

15 In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein R² is selected from the groups set forth below:

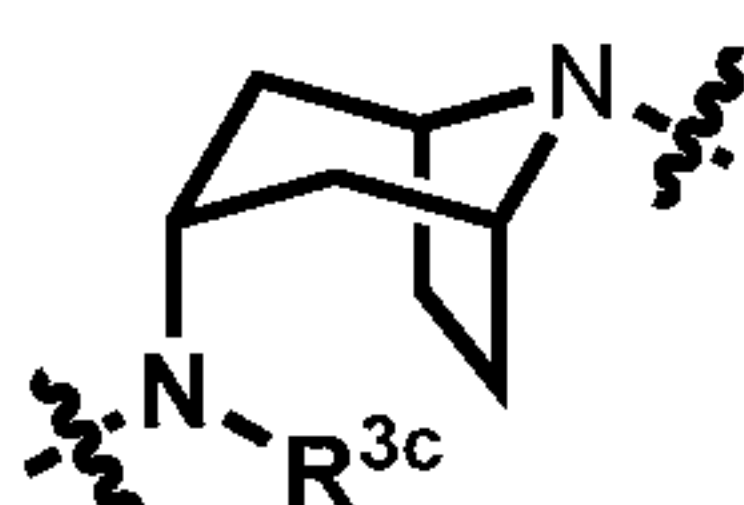


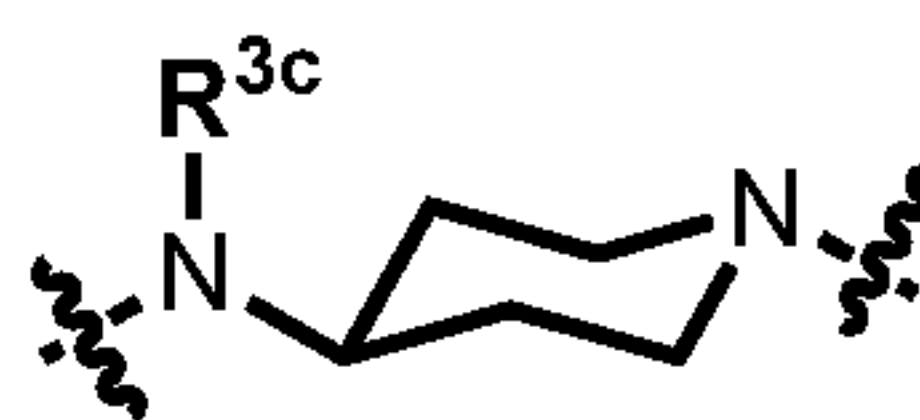
wherein each of above groups can be optionally further substituted. The preferred
20 substituents are halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkenyl, optionally substituted aryl, and optionally substituted heteroaryl.

In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein one of R^{3a} and R^{3b} is hydrogen or

halogen; In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein both R^{3a} and R^{3b} are independently hydrogen or halogen.

In certain embodiments, the present invention relates to compounds of Formula (I),

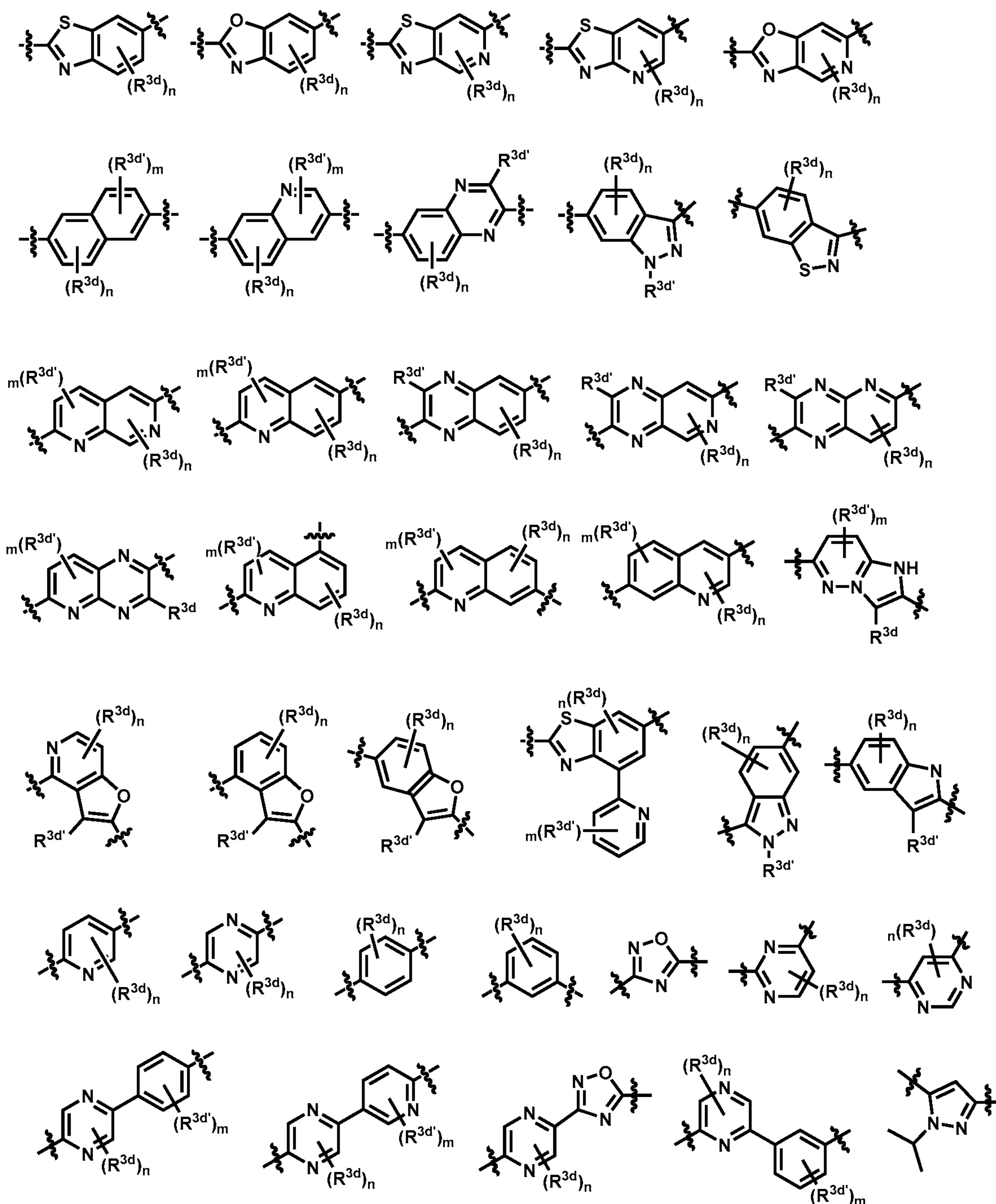
5 and pharmaceutically acceptable salts thereof, wherein A is  or

, and R^{3c} is as previously defined; preferably, R^{3c} is hydrogen, methyl, or formyl.

In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein B is optionally substituted phenyl,
 10 pyridyl, pyrimidinyl, pyrazolyl, thienyl, thiazolyl, triazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxazolyl, oxadiazolyl, imidazolyl, furanyl, indolyl, benzothienyl, naphthyl, quinolyl, naphthyridyl, quinoxalyl, pyridopyrazolyl, pyridooxazolyl, pyridothiazolyl, isoquinolyl, pyridofuranyl, indazolyl, benzisoxazolyl, benzofuranyl, benzotriazolyl, or benzothiazolyl. Preferred substituents include halogen, -CN, -NO₂, -NH₂, optionally substituted C₁-C₆ alkyl,
 15 optionally substituted C₁-C₆ alkoxy, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkenyl, optionally substituted aryl, and optionally substituted heteroaryl.

In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein B is an optionally substituted biaryl
 20 group. In this embodiment, A and Z, or R^4 when Z is absent, are attached to atoms of different rings in the biaryl group. In certain embodiments, B is optionally substituted pyrimidylphenyl, pyrimidylpyridyl, pyrimidyloxadiazolyl. Preferred substituents include halogen, -CN, -NO₂, -NH₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkenyl,
 25 optionally substituted aryl, and optionally substituted heteroaryl.

In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein B is selected from, but not limited to the groups set forth below:

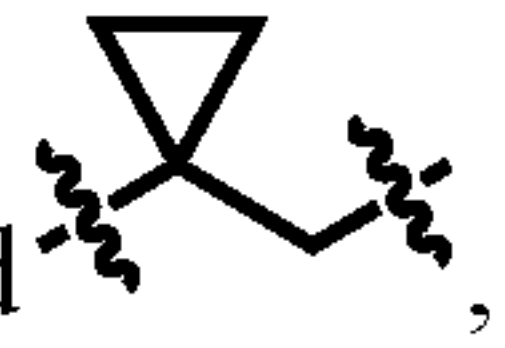


wherein, one of the indicated valences is the point of attachment to A and the other is the point of attachment to Z; R^{3d} and $R^{3d'}$ are independently selected from the group consisting of

5 halogen, -CN, -NO₂, -NH₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkenyl, optionally substituted aryl, and optionally substituted heteroaryl; m and n are independently

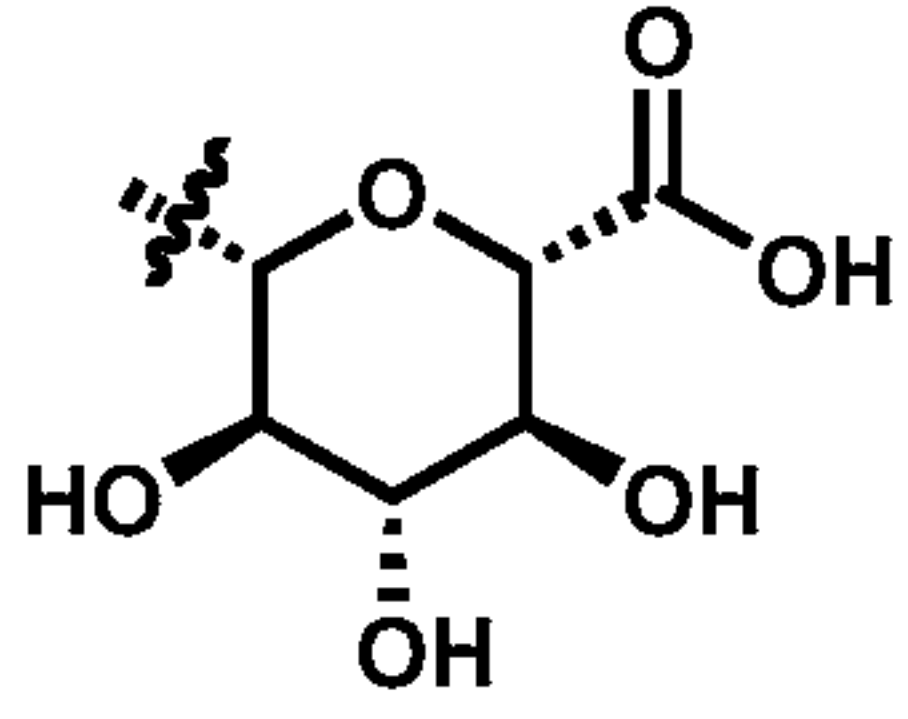
0, 1, 2 or 3, preferably, m and n are independently 0 or 1, more preferably, m and n are both 0.

In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein Z is absent. In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein Z is optionally substituted $-\text{CH}_2-$; preferably, Z is $-\text{CH}_2-$, $-\text{CHF}-$, or $-\text{CF}_2-$. In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein Z is optionally substituted $-\text{CH}_2\text{CH}_2-$. In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein Z is optionally substituted cyclopropyl or cyclohexyl.

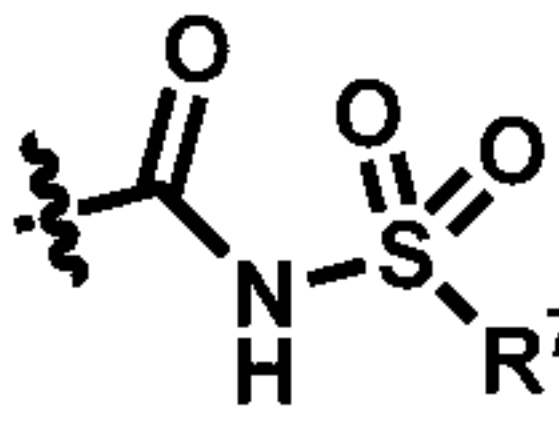
In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein Z is optionally substituted , wherein, one of the indicated valences is the point of attachment to B and the other is the point of attachment to R^4 .

In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein Z is optionally substituted aryl; preferably Z is optionally substituted phenyl. In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein Z is optionally substituted heteroaryl; preferably Z is optionally substituted pyridyl.

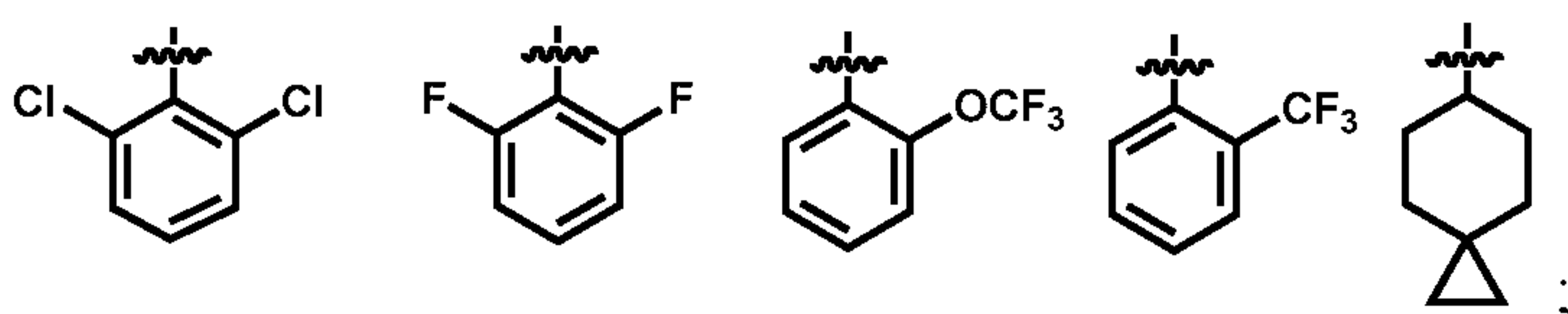
In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein R^4 is $-\text{CO}_2\text{R}^5$, and R^5 is previously

defined. Preferably R^5 is hydrogen, methyl, ethyl, t-butyl, or .

In certain embodiments, the present invention relates to compounds of Formula (I),

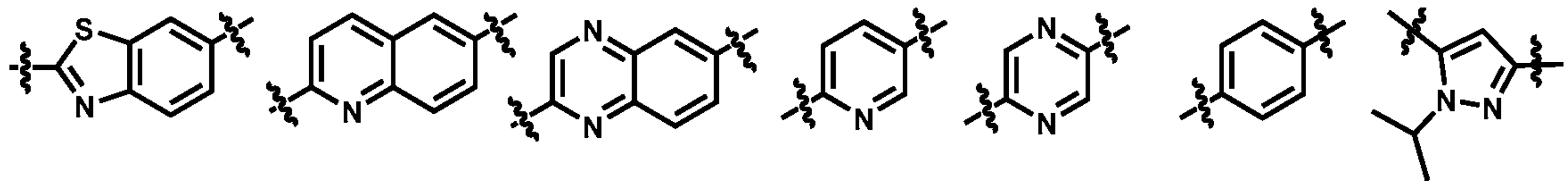
and pharmaceutically acceptable salts thereof, wherein R^4 is , and R^7 is previously defined.

In certain embodiments, the present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein R^1 is optionally substituted



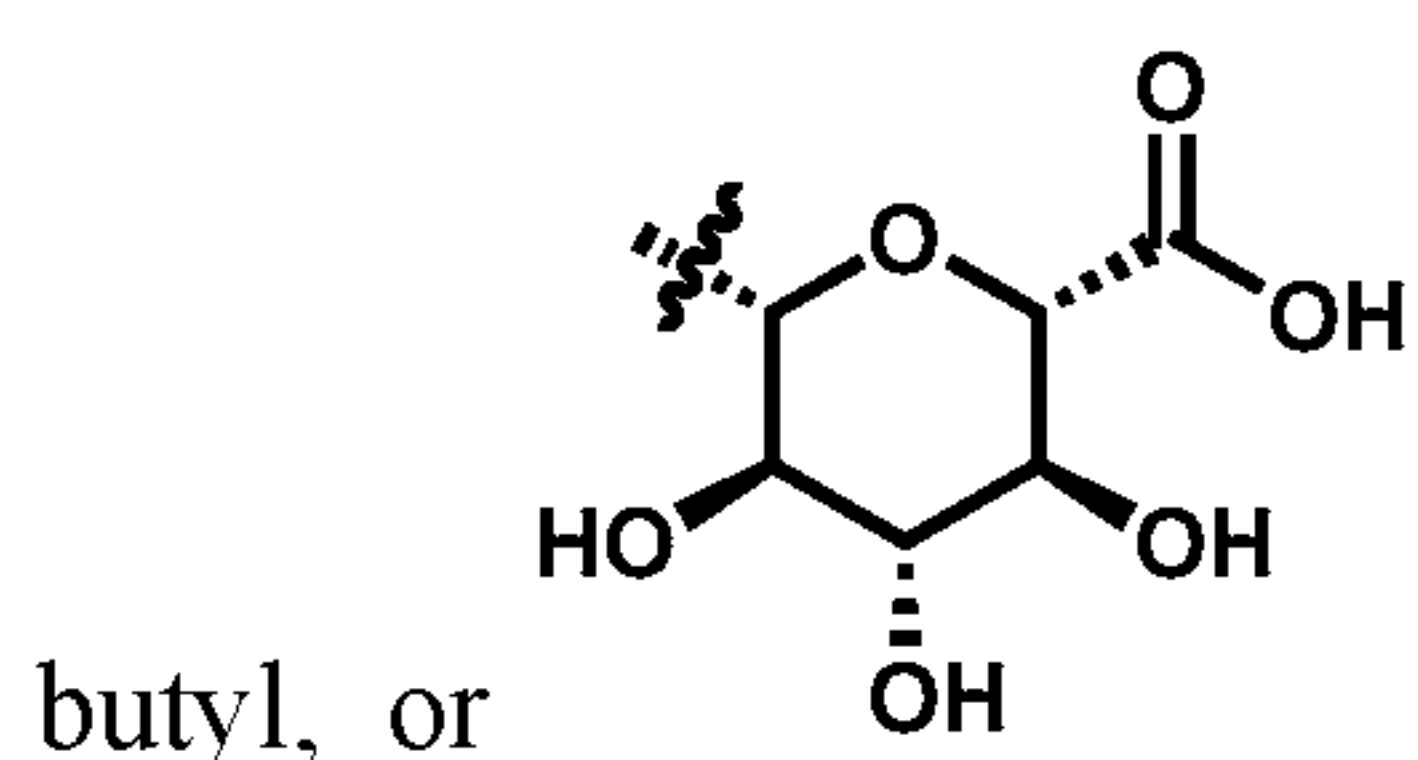
cyclopropyl; R^2 is selected from

R^{3a} is hydrogen; R^{3b} is hydrogen; A is or , R^{3c} is hydrogen, or methyl; B is selected from:



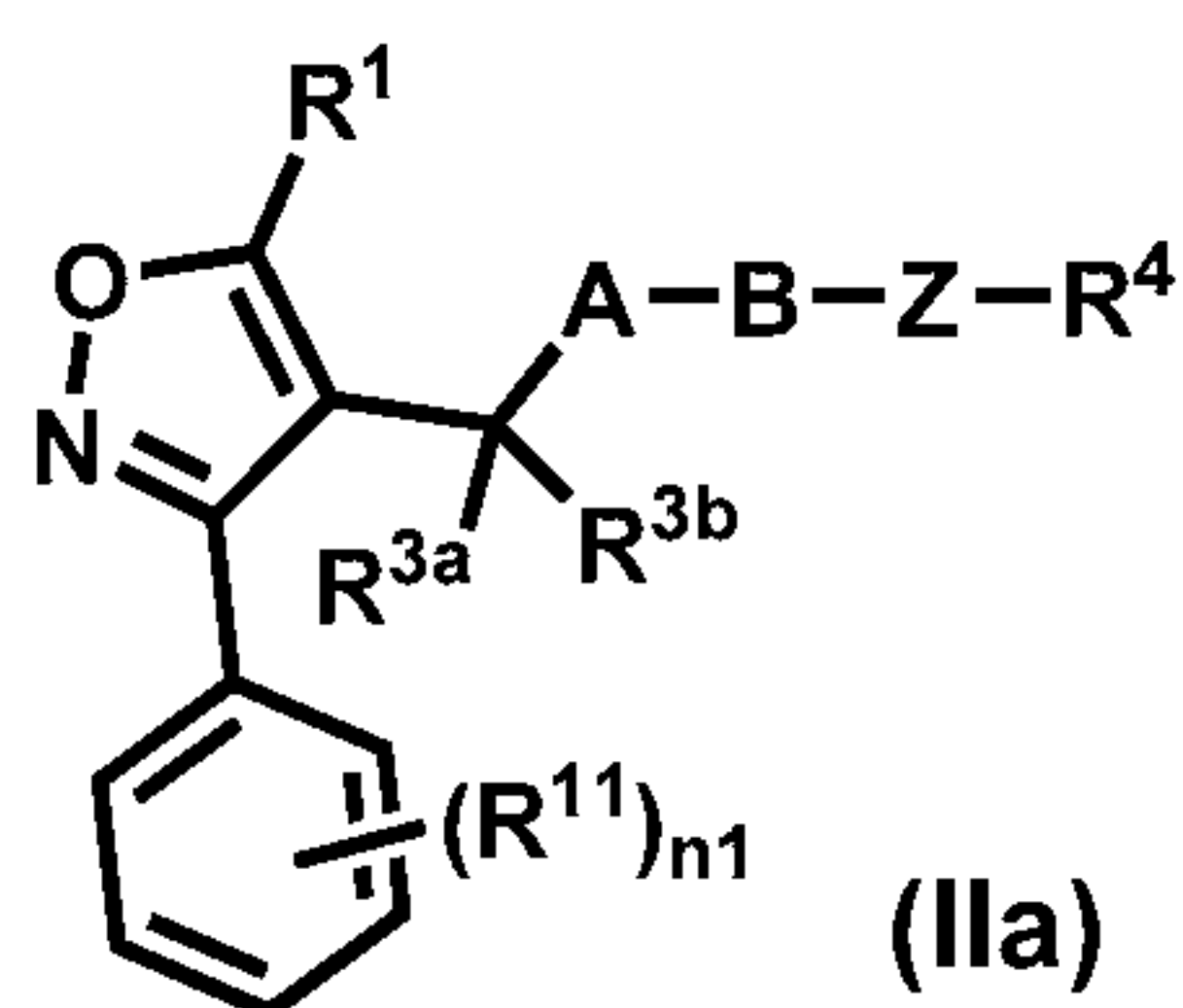
5 and B is optionally substituted; Z is absent; and R^4 is or ,

or $-\text{CO}_2R^5$; R^7 is as previously defined and R^5 is hydrogen, methyl, ethyl, t-

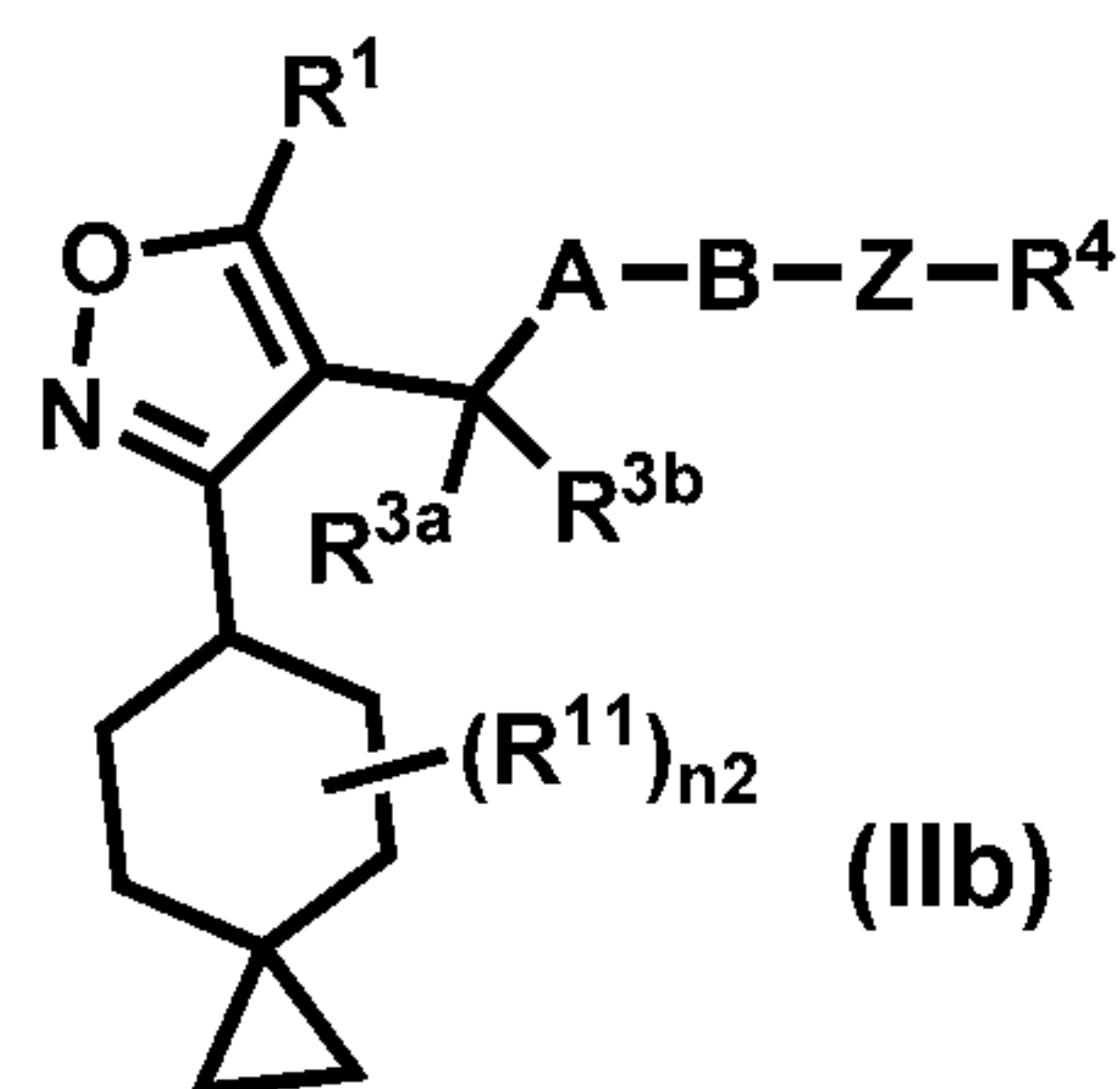


butyl, or

In another embodiment, the compound of Formula (I) is represented by Formula (IIa) or Formula (IIb) or a pharmaceutically acceptable salt thereof:



(IIa)



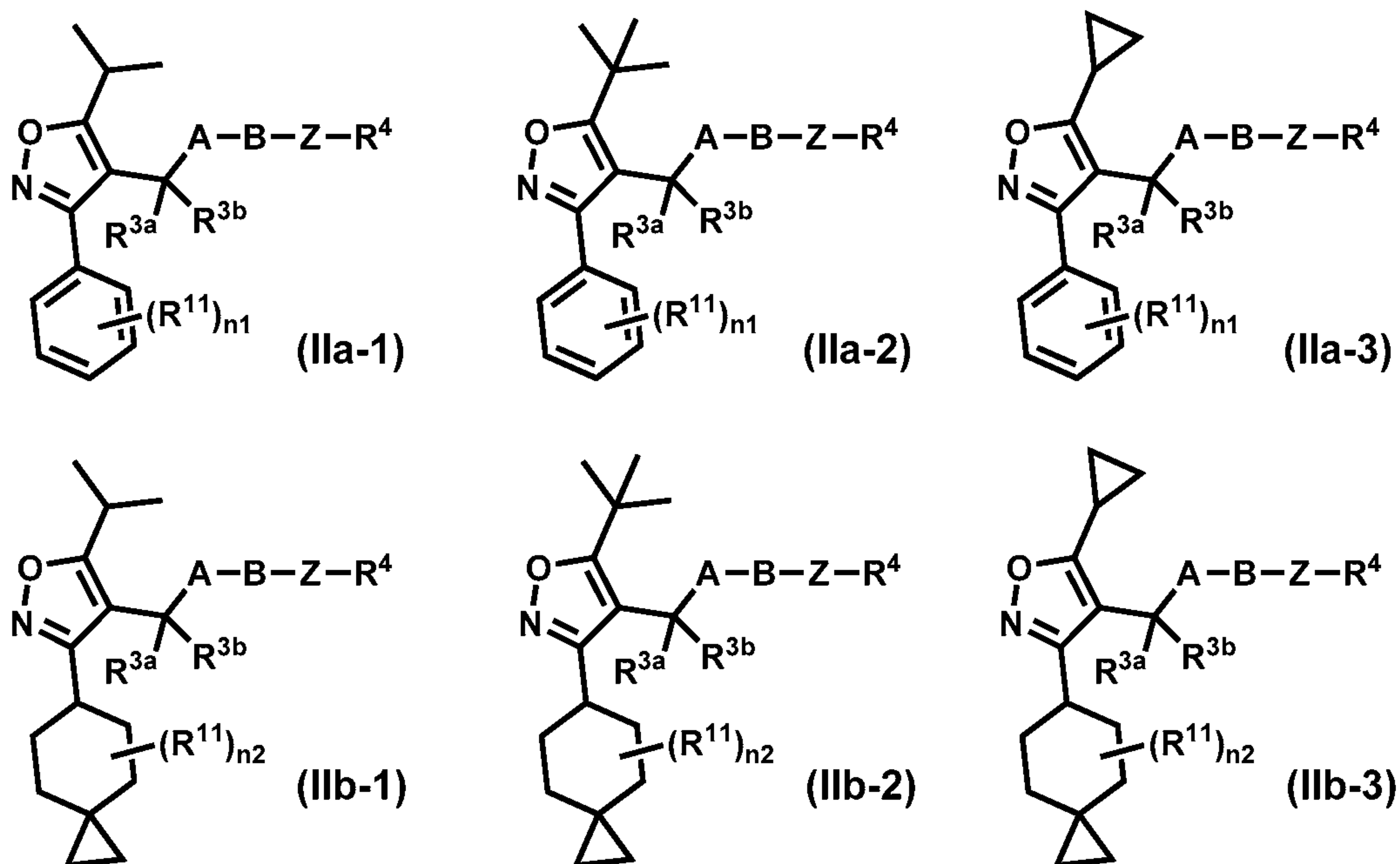
(IIb)

10

wherein R^1 , R^{3a} , R^{3b} , A, B, Z and R^4 are as previously defined; R^{11} at each occurrence is independently selected from the group consisting of halogen, optionally substituted $-\text{C}_1-\text{C}_6$ alkyl, optionally substituted $-\text{C}_1-\text{C}_6$ alkoxy, optionally substituted $-\text{C}_3-\text{C}_6$ cycloalkyl, optionally substituted $-\text{C}_3-\text{C}_6$ cycloalkenyl, optionally substituted aryl, or optionally substituted heteroaryl; n_1 is 0, 1, 2, 3, 4, or 5; and n_2 is 0, 1, or 2.

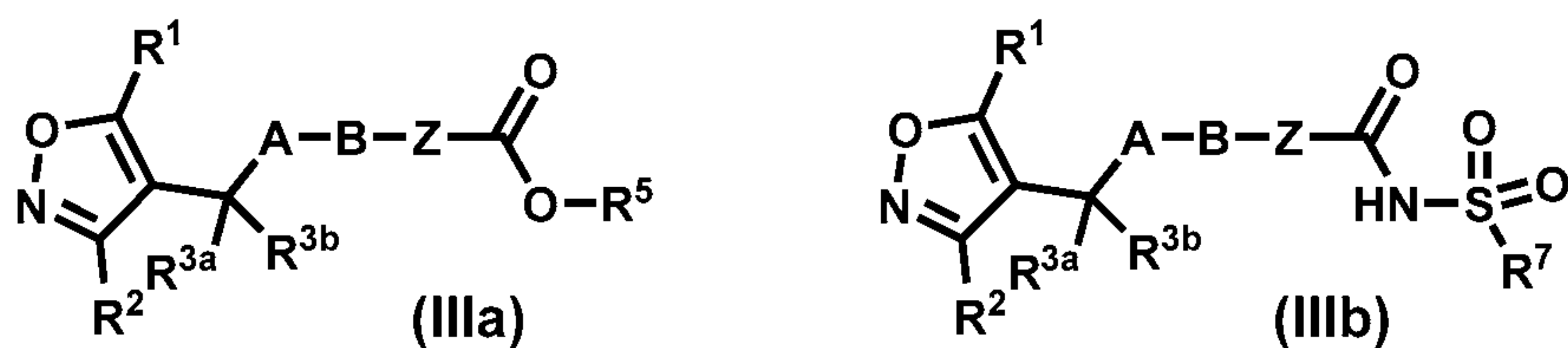
15

In another embodiment, the compound of Formula (I) is represented by Formula (IIa-1), (IIa-2), (IIa-3), (IIb-1), (IIb-2), (IIb-3), or a pharmaceutically acceptable salt thereof:



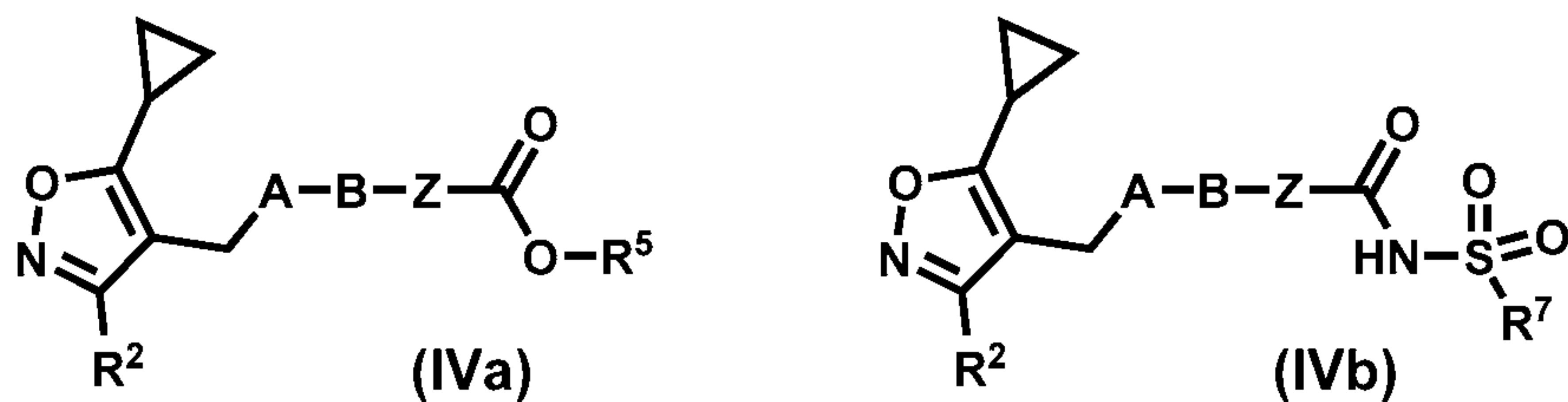
5 wherein R^{3a} , R^{3b} , A, B, Z, R^4 , R^{11} , n_1 and n_2 are as previously defined.

In another embodiment, the compound of Formula (I) is represented by Formula (IIIa) or Formula (IIIb) or a pharmaceutically acceptable salt thereof:



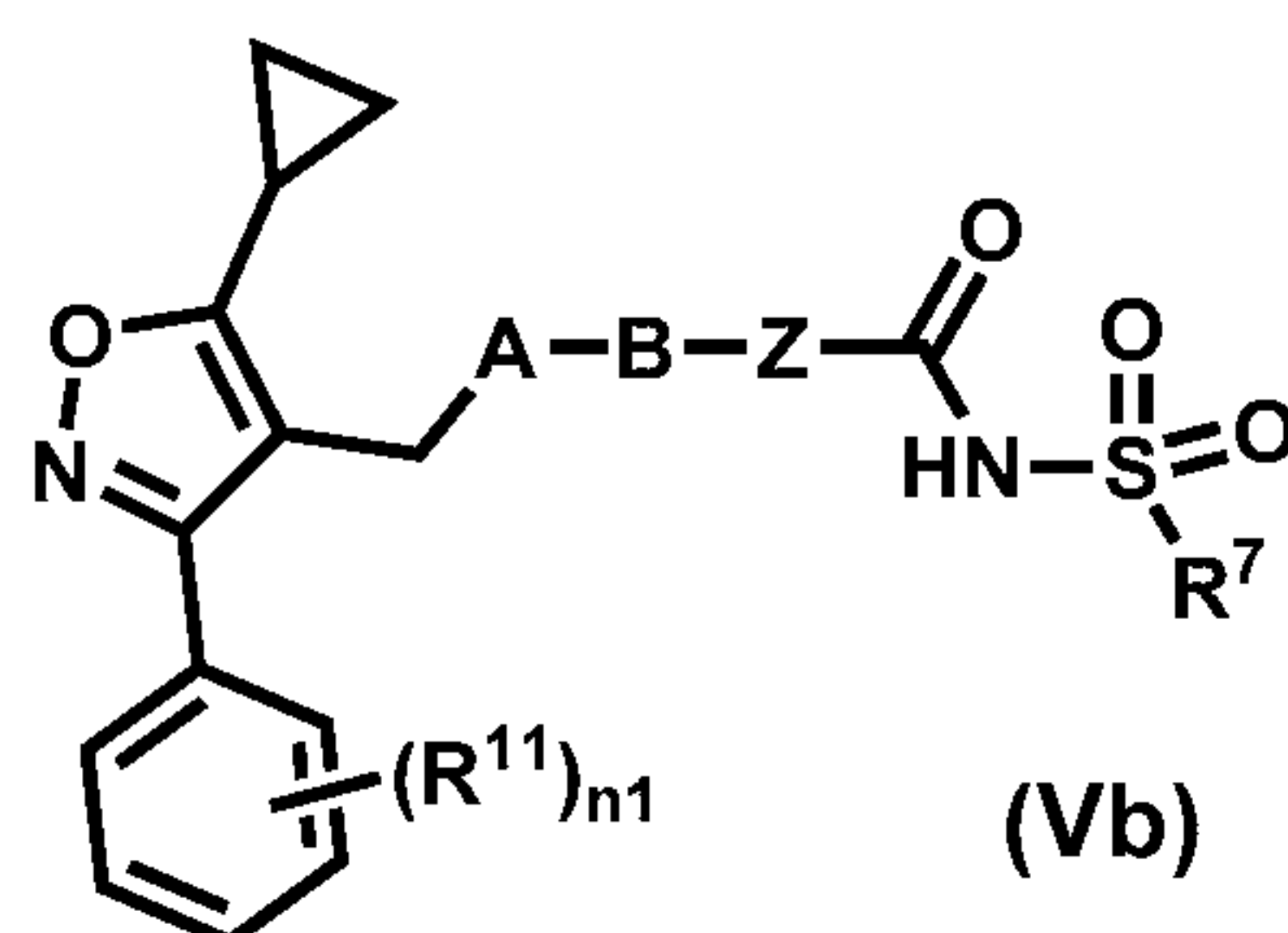
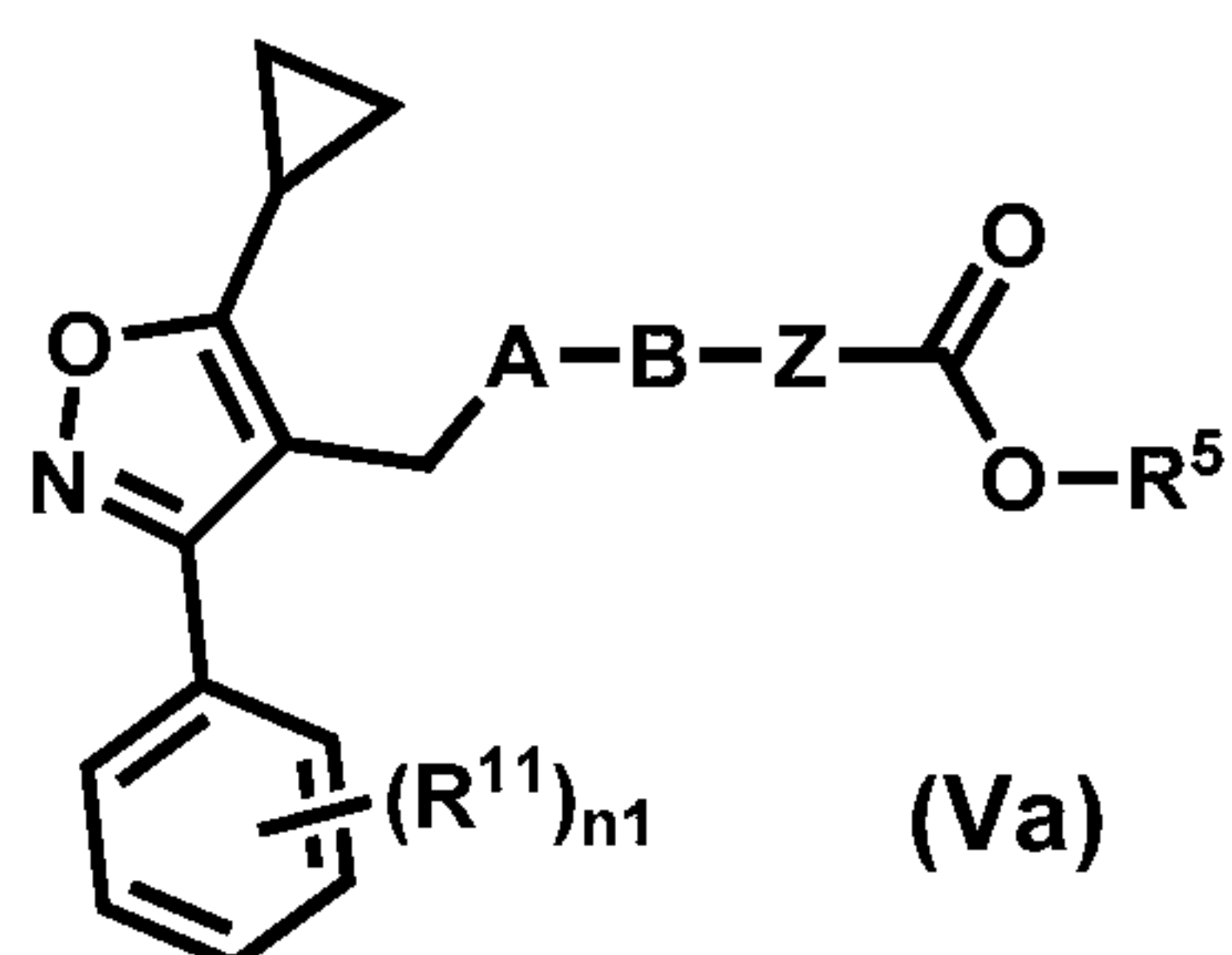
wherein A, B, Z, R^1 , R^2 , R^{3a} , R^{3b} , R^5 , and R^7 are as previously defined.

10 In another embodiment, the compound of Formula (I) is represented by Formula (IVa) or Formula (IVb) or a pharmaceutically acceptable salt thereof:



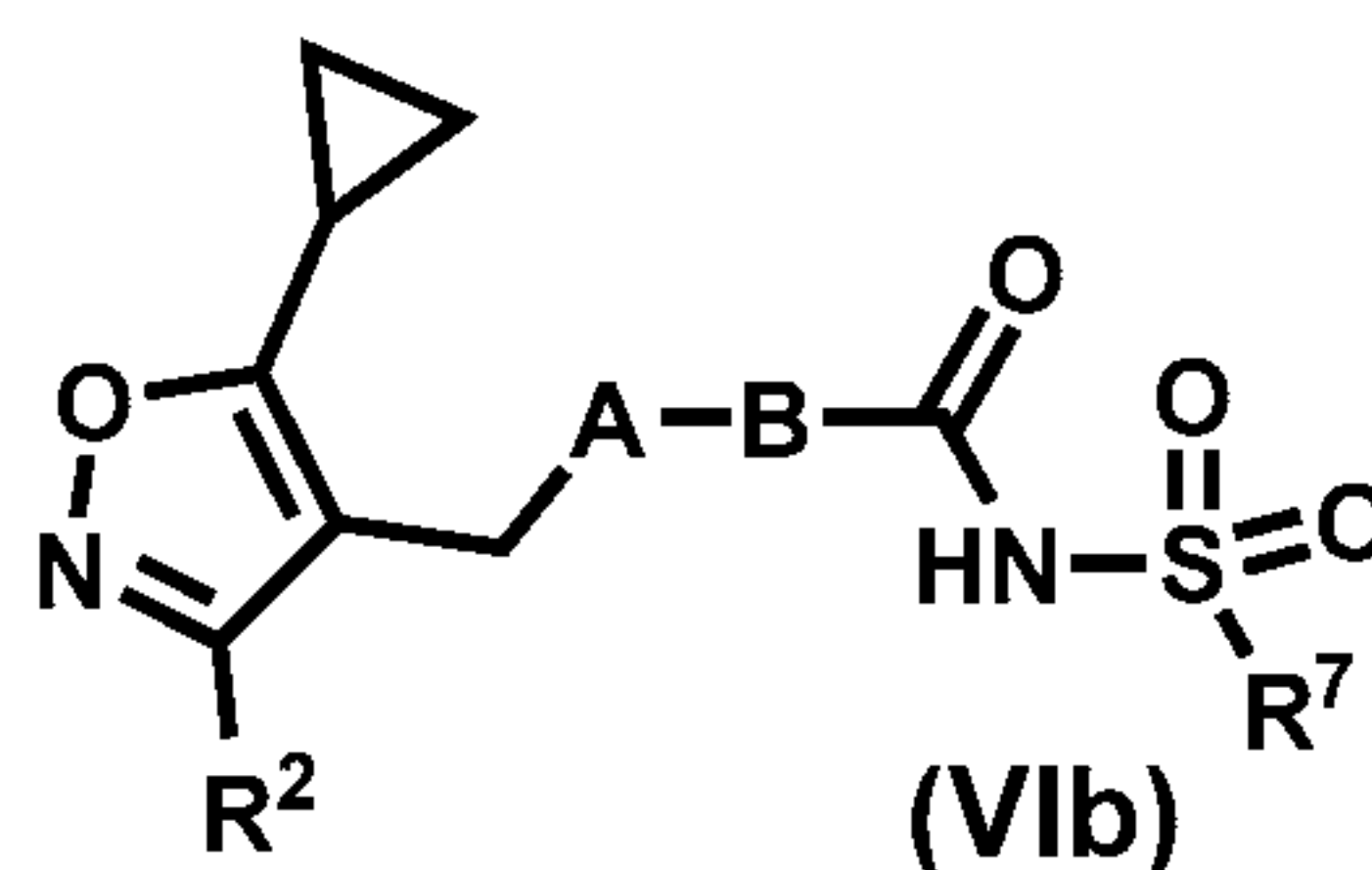
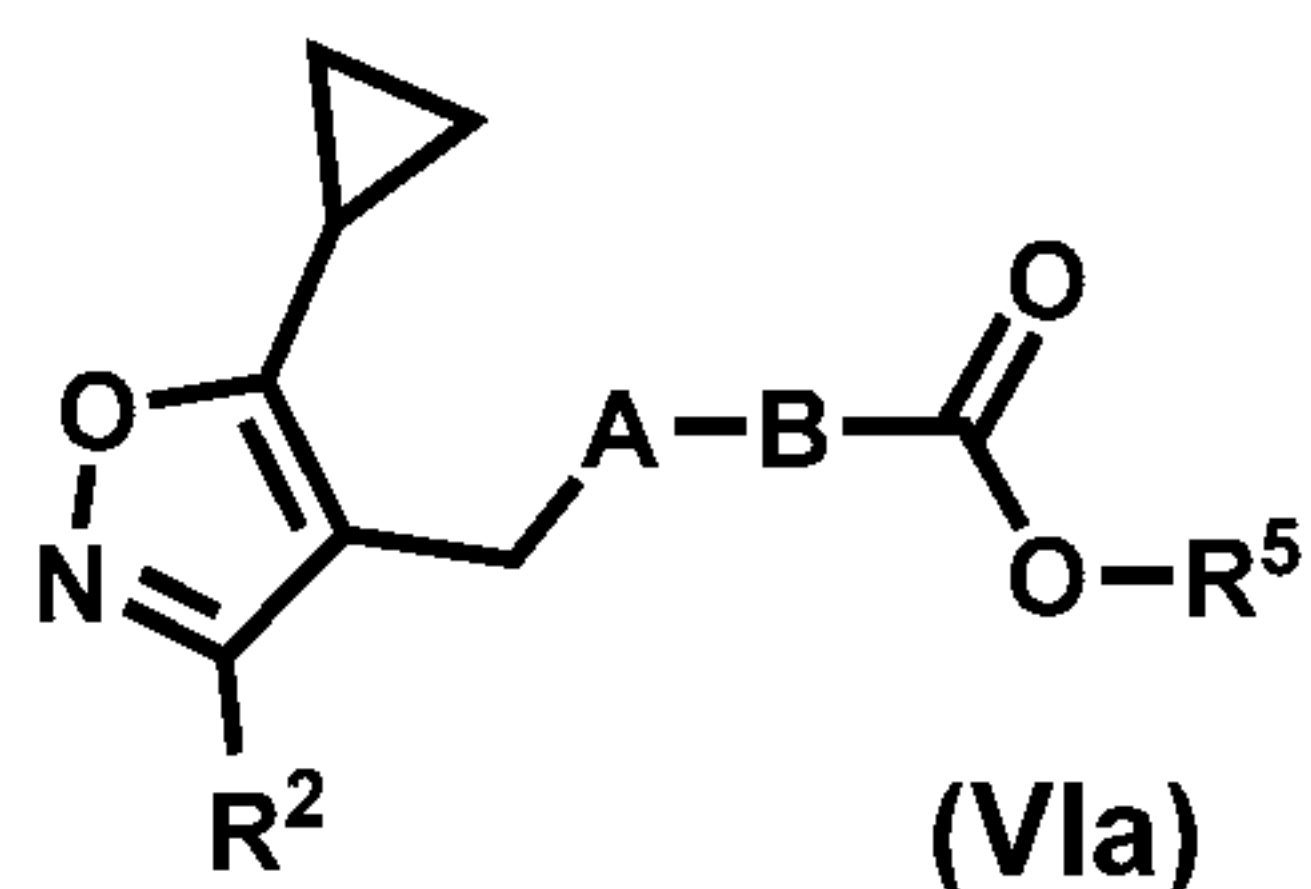
wherein A, B, Z, R^2 , R^5 , and R^7 are as previously defined.

15 In another embodiment, the compound of Formula (I) is represented by Formula (Va) or Formula (Vb) or a pharmaceutically acceptable salt thereof:



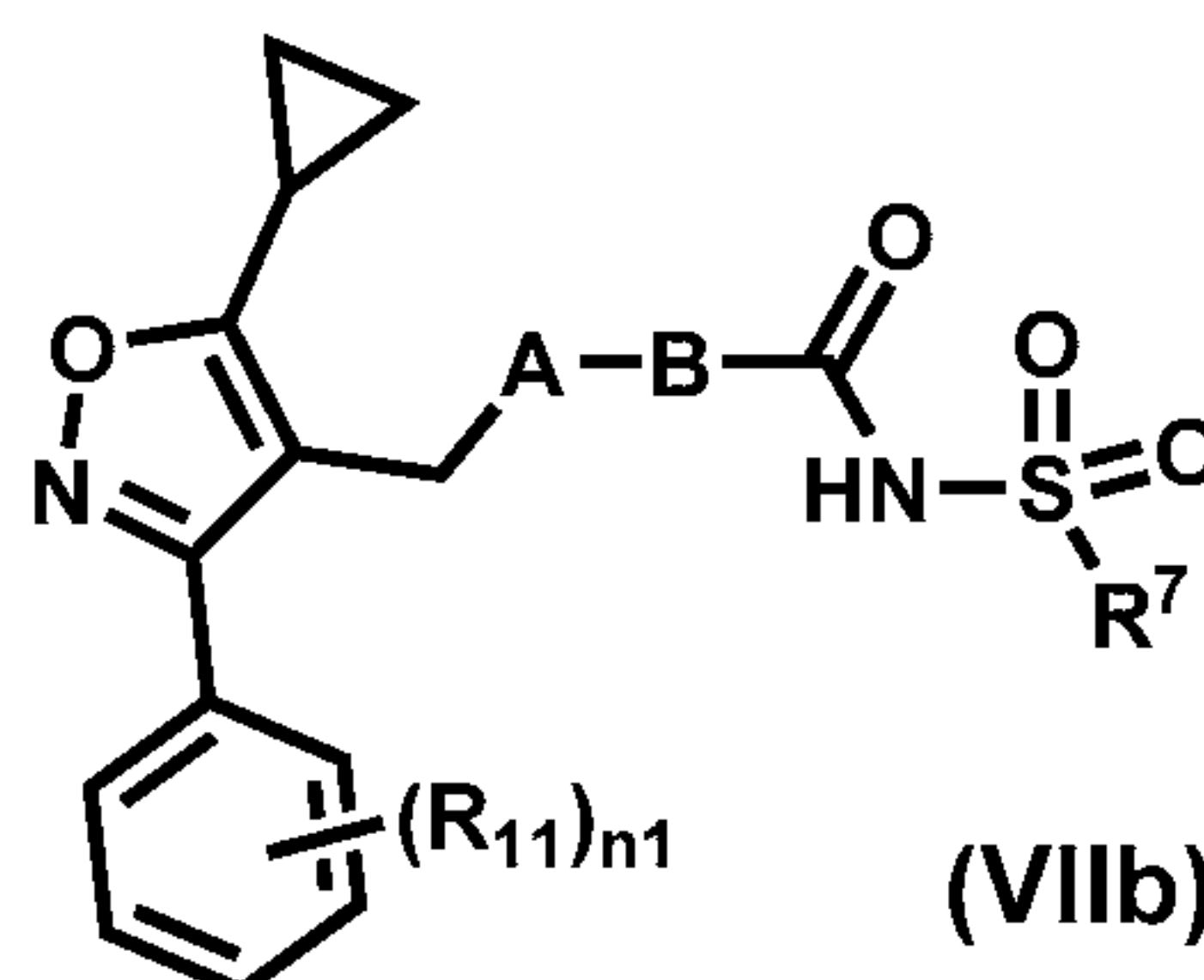
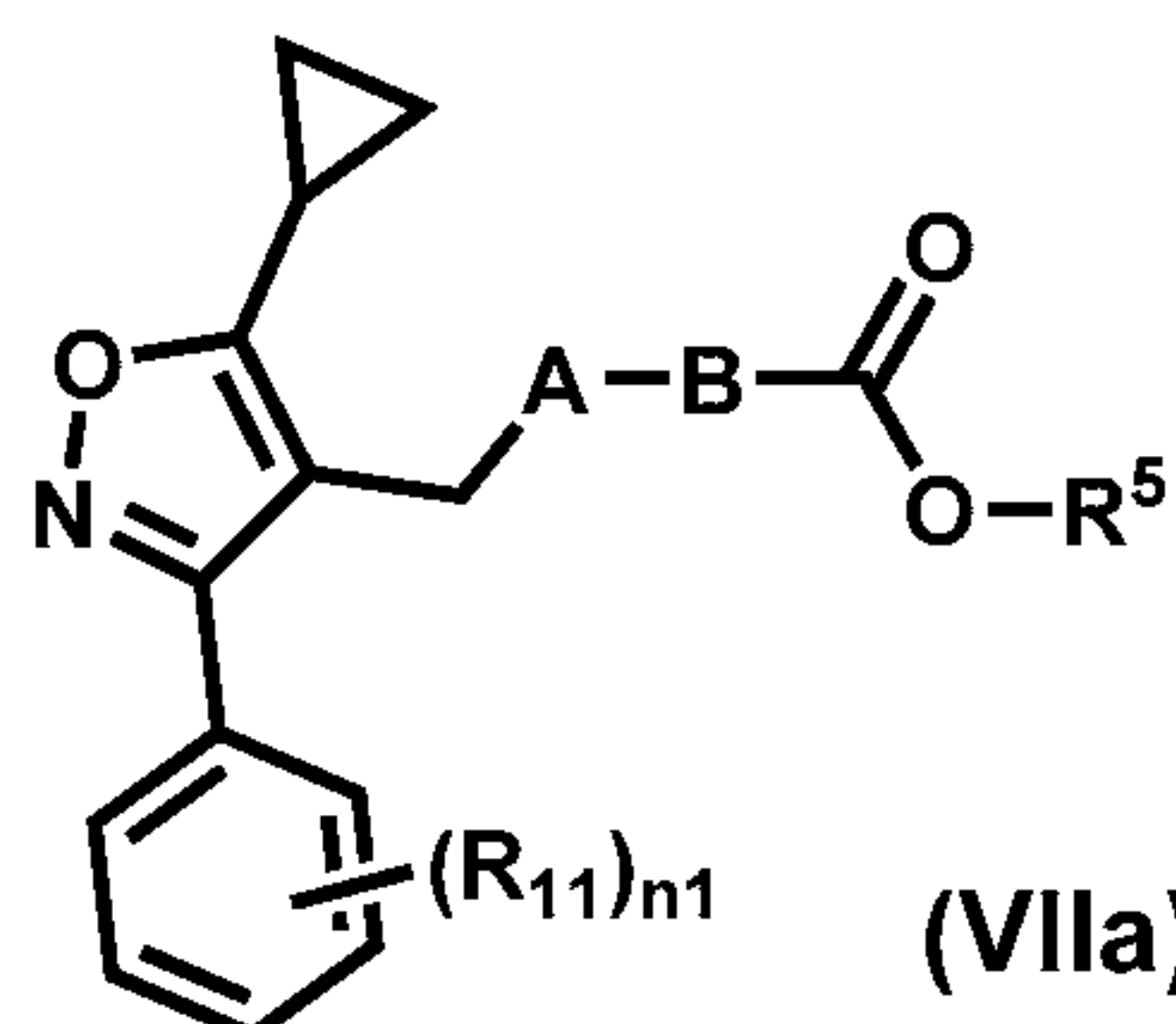
wherein A, B, Z, R^5 , R^7 , R^{11} , and $n1$ are as previously defined.

In another embodiment, the compound of Formula (I) is represented by Formula (VIa) or Formula (VIb) or a pharmaceutically acceptable salt thereof:



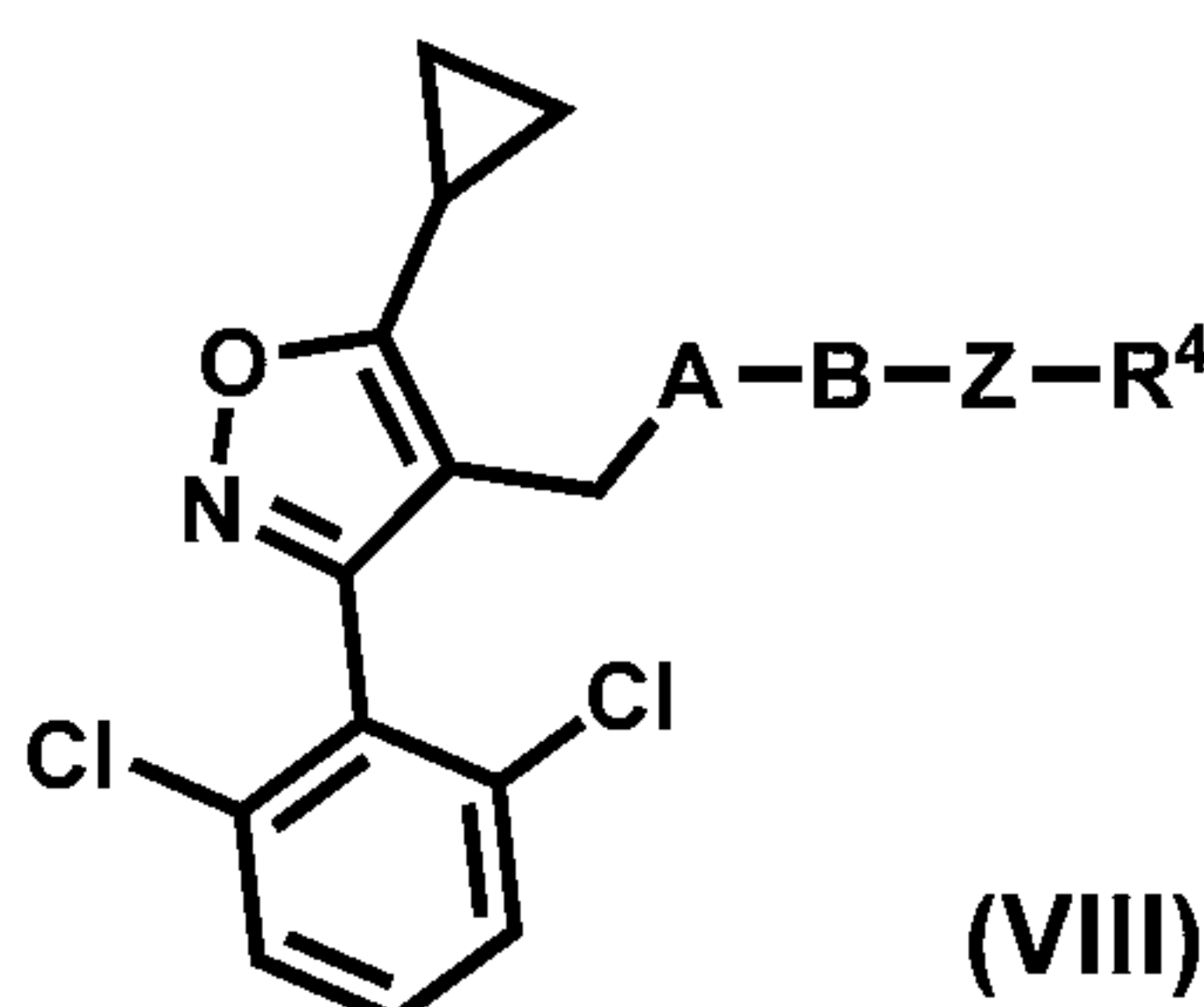
wherein A, B, R^2 , R^5 , and R^7 are as previously defined.

In another embodiment, the compound of Formula (I) is represented by Formula (VIIa) or Formula (VIIb) or a pharmaceutically acceptable salt thereof:



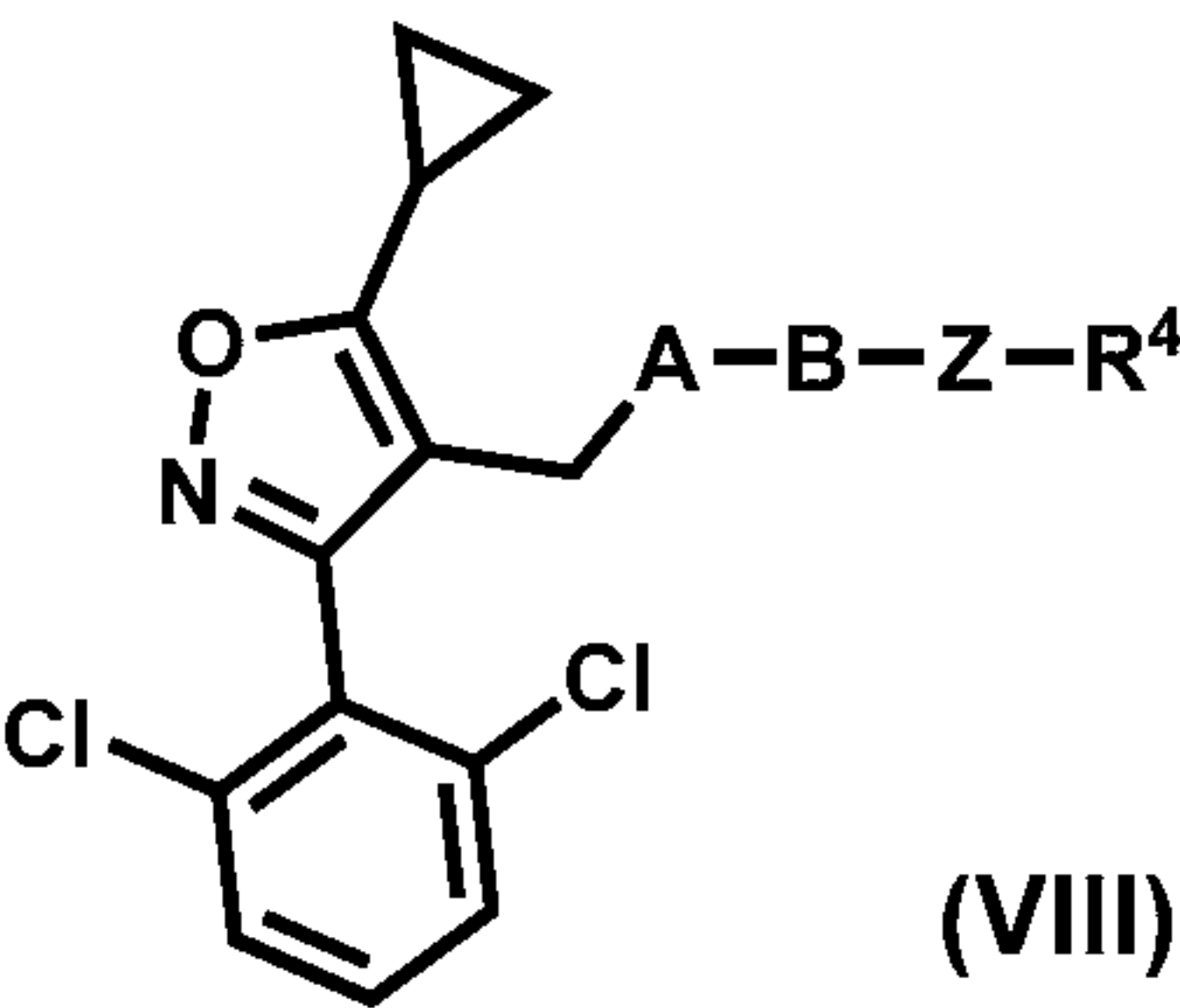
wherein A, B, R^5 , R^7 , R^{11} , and $n1$ are as previously defined.

In another embodiment, the compound of Formula (I) is represented by Formula (VIII) or a pharmaceutically acceptable salt thereof:



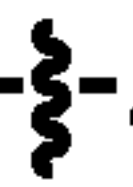
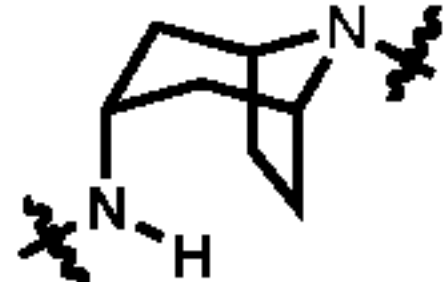
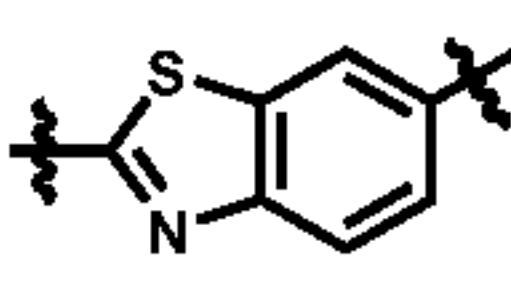
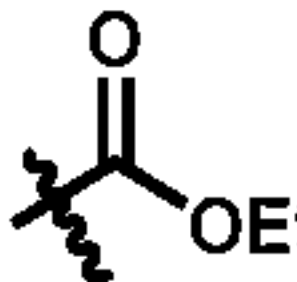
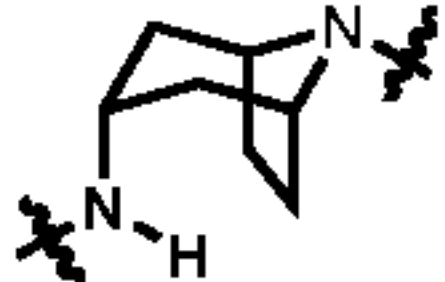
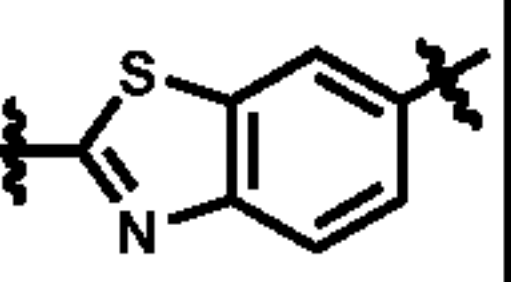
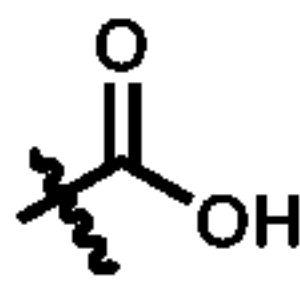
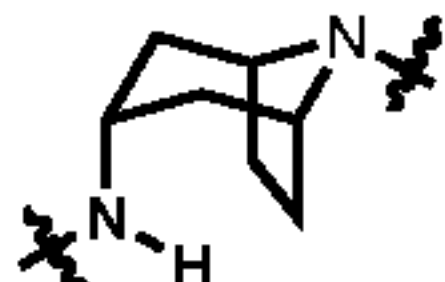
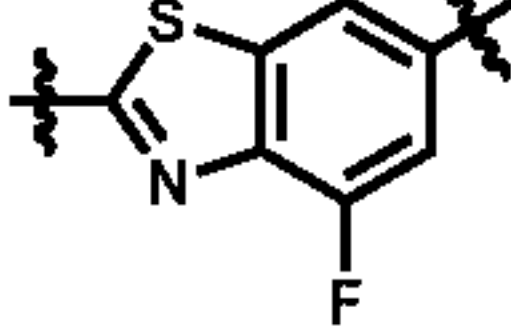
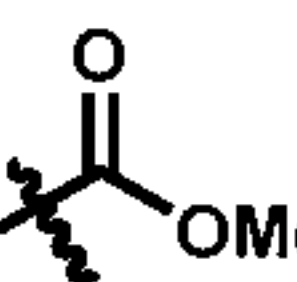
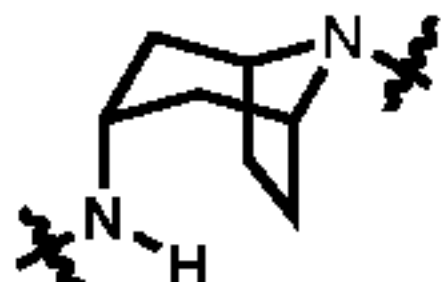
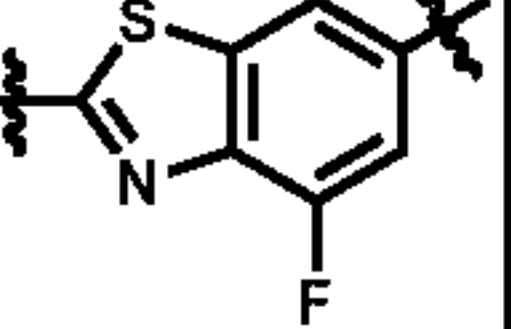
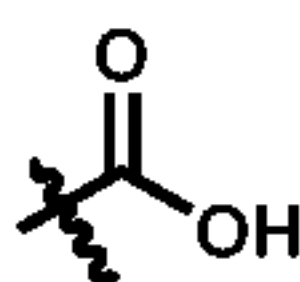
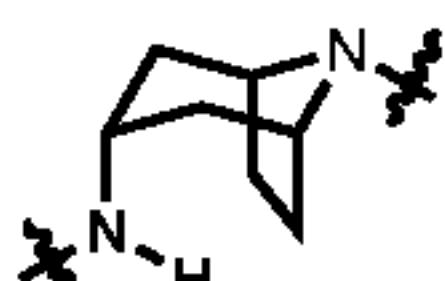
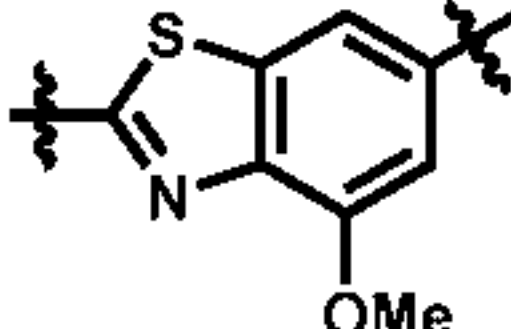
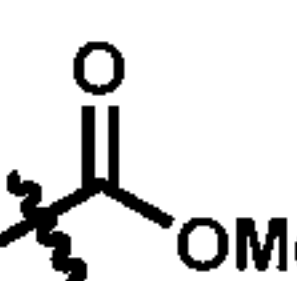
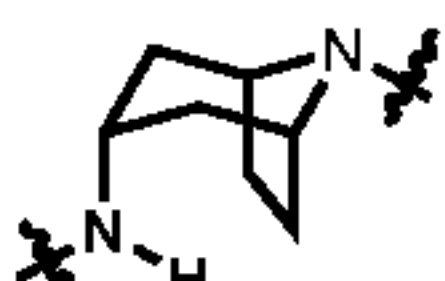
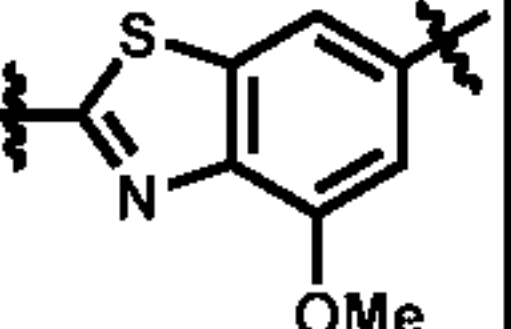
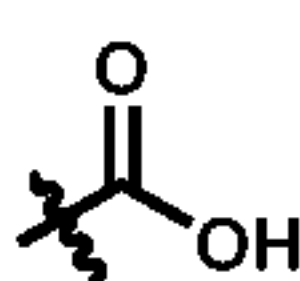
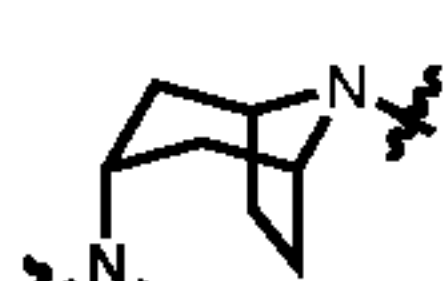
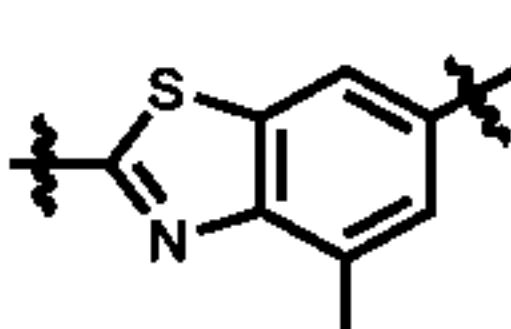
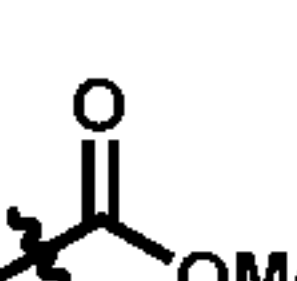
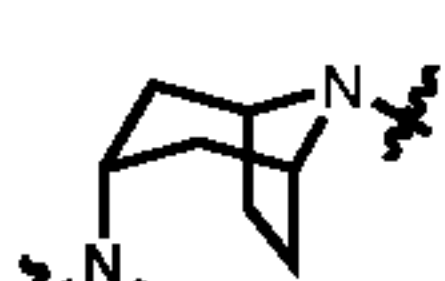
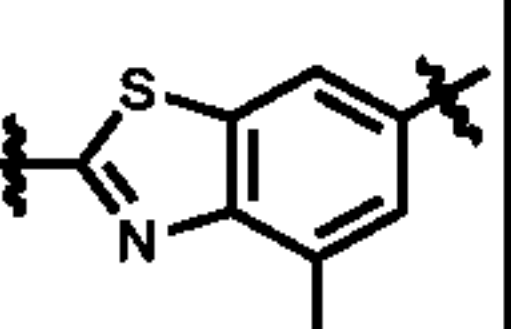
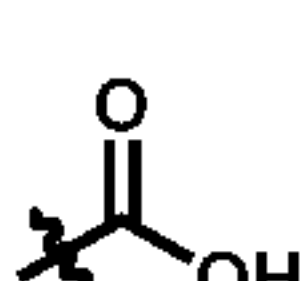
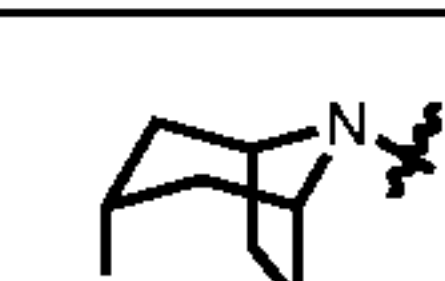
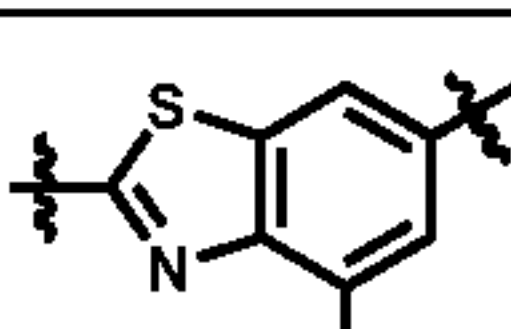
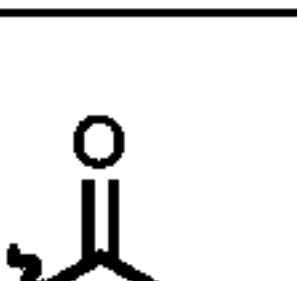
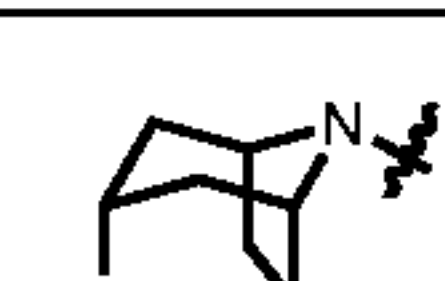
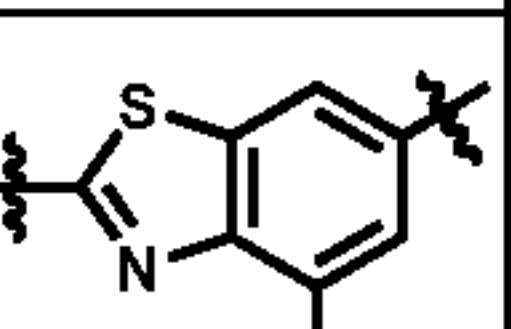
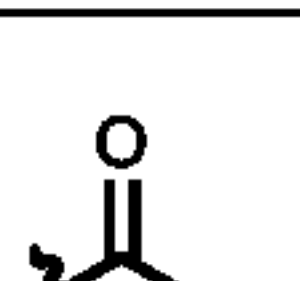
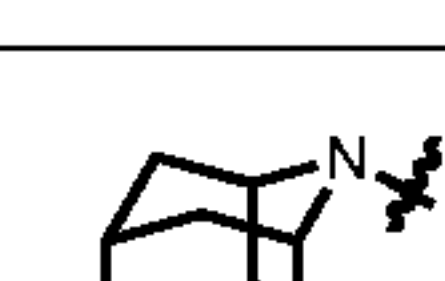
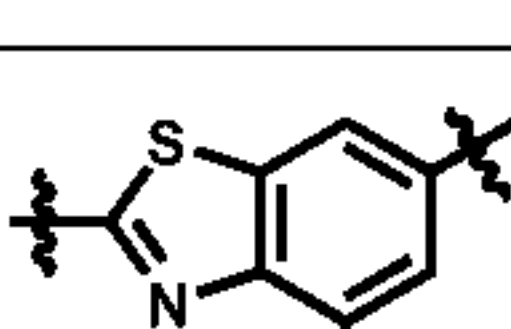
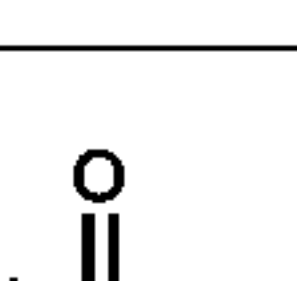
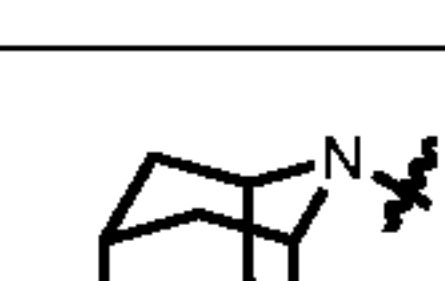
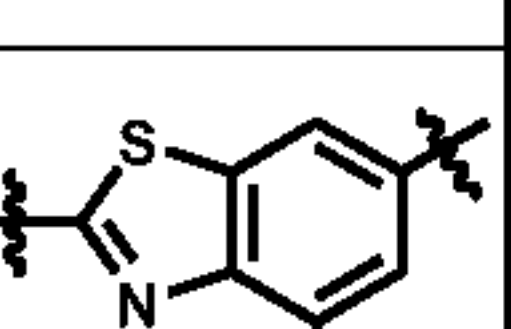
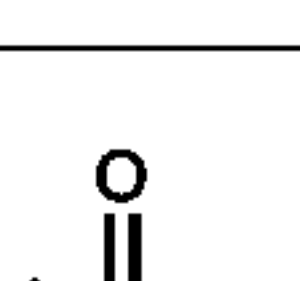
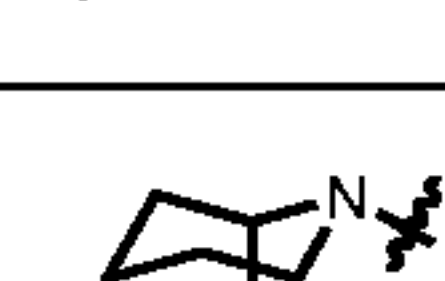
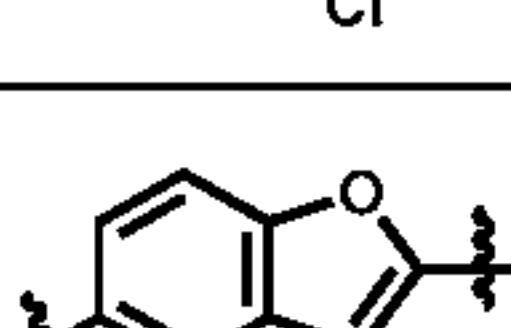
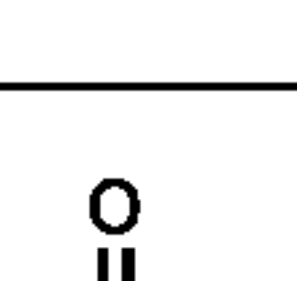
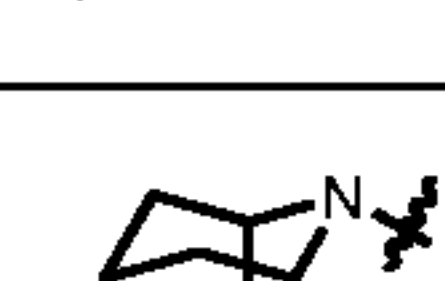
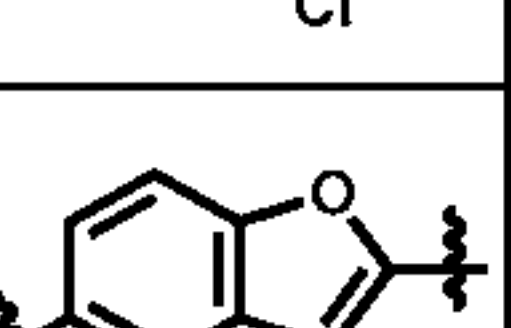
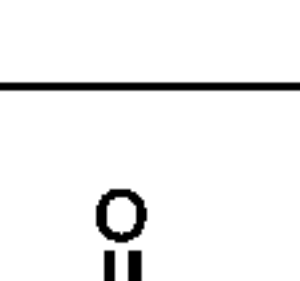
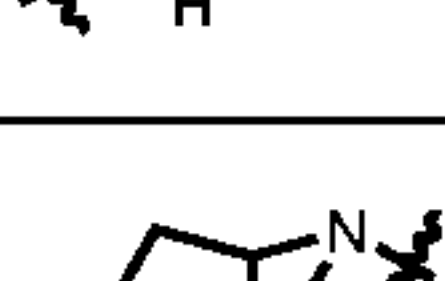
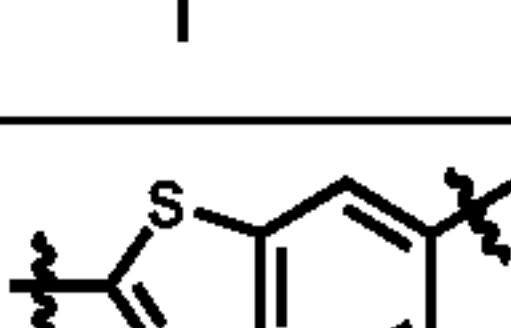
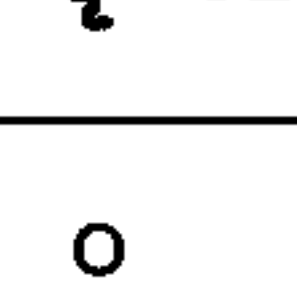
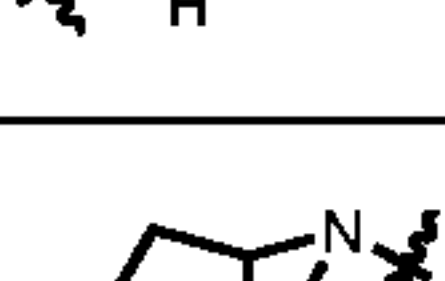
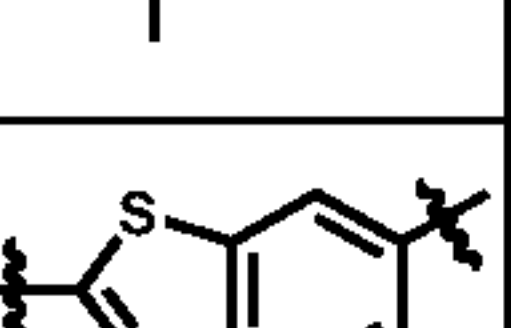
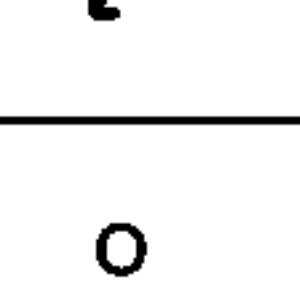
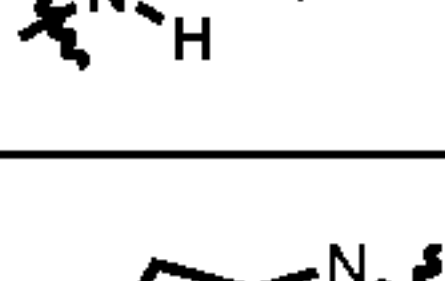
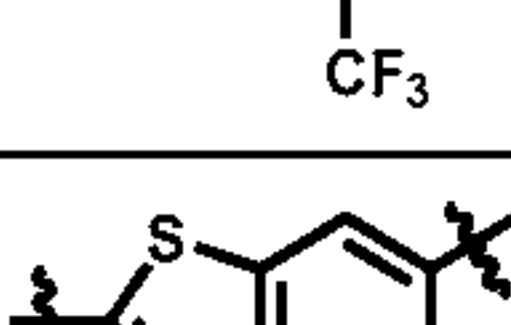
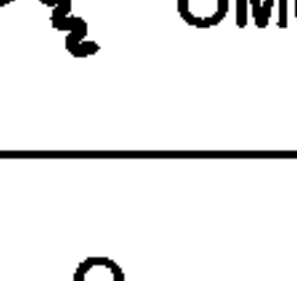
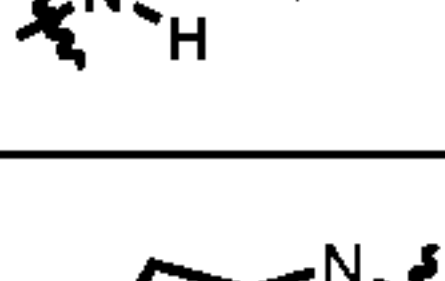
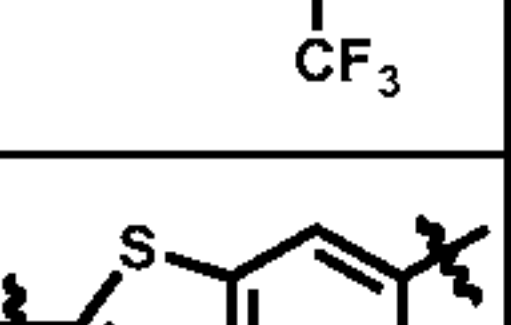
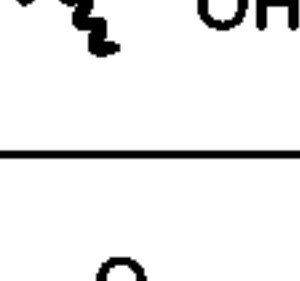
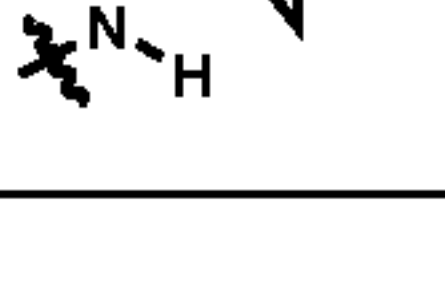
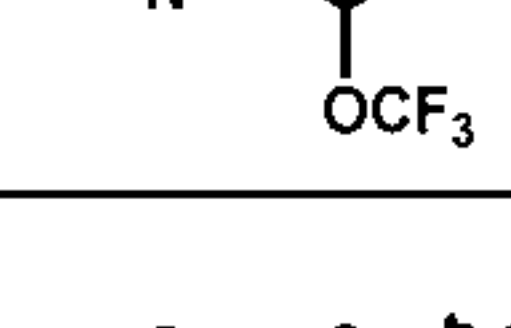
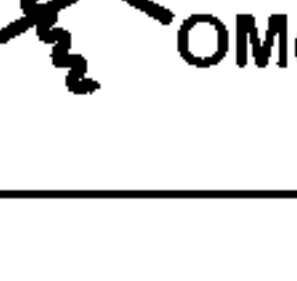
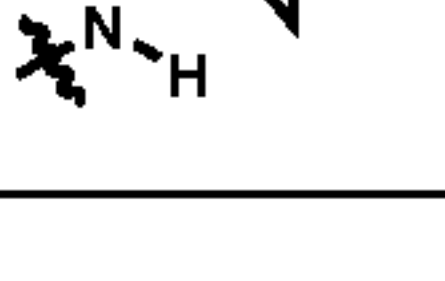
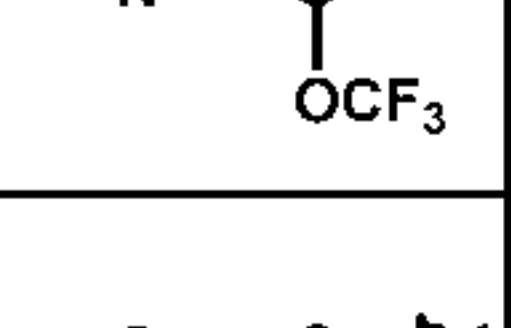
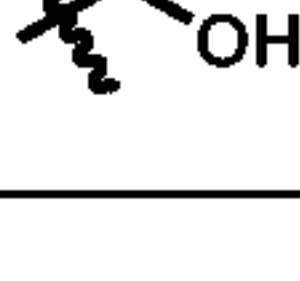
wherein A, B, Z, and R^4 are as previously defined.

Representative compounds of the invention include, but are not limited to, compounds according to Formula (VIII), and pharmaceutically acceptable salts thereof, wherein A, B, and Z-R⁴ are delineated for each compound in Table 1.



5

Table 1

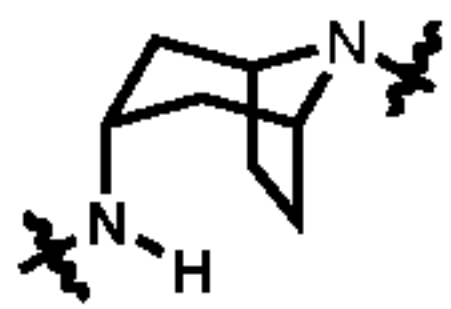
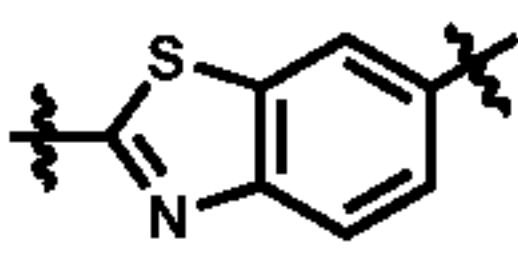
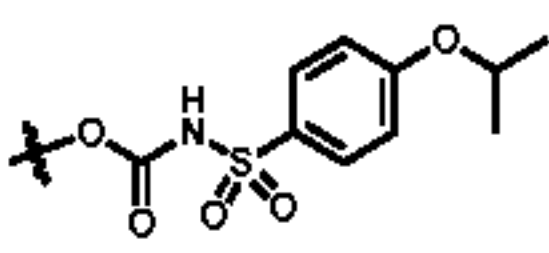
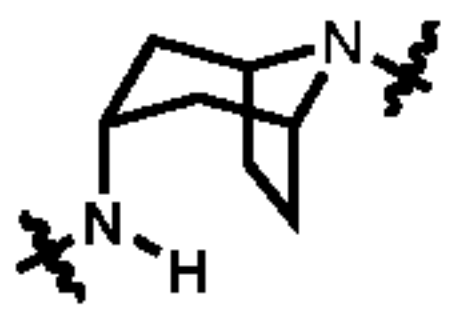
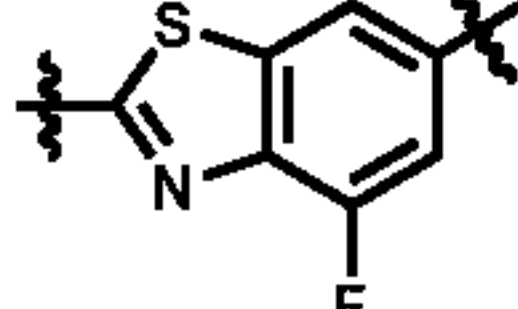
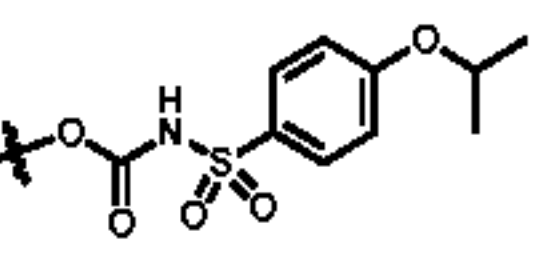
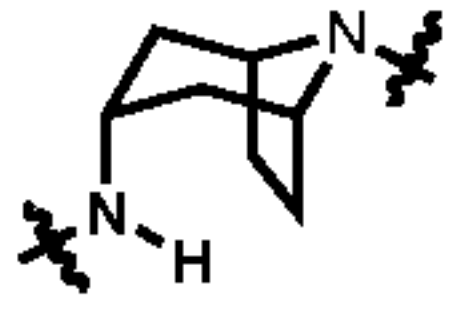
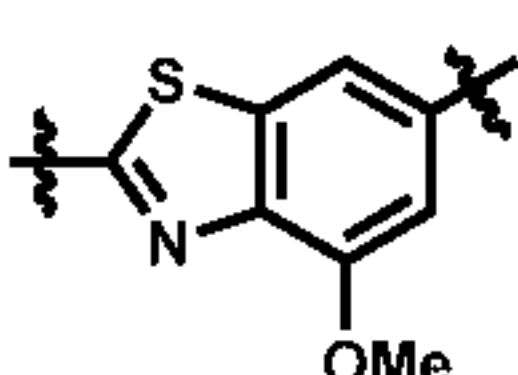
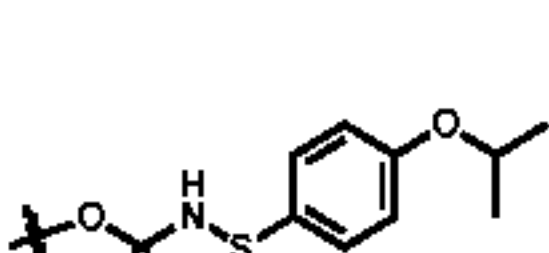
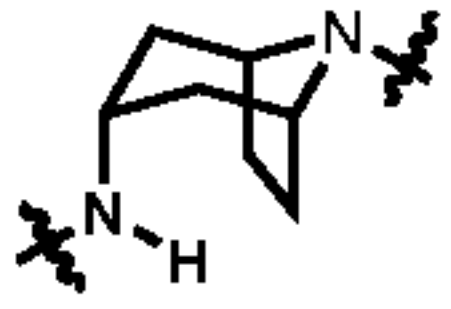
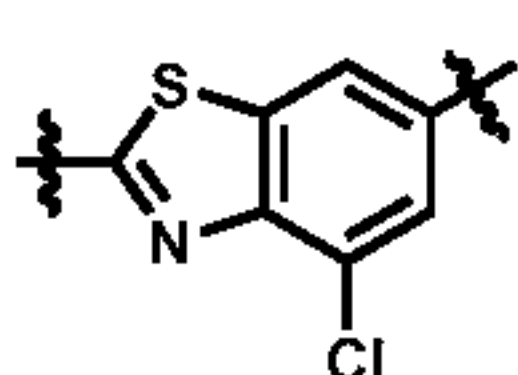
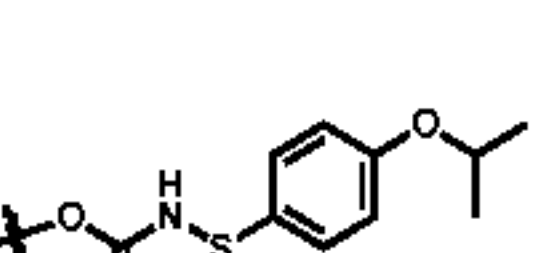
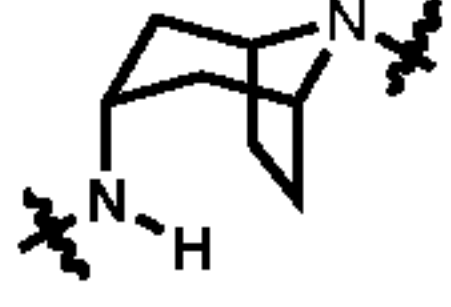
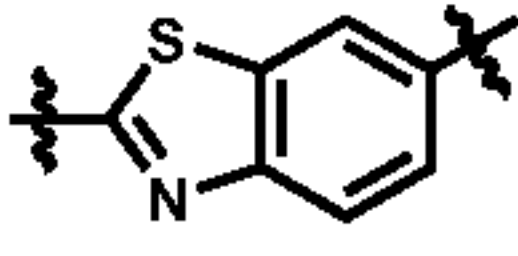
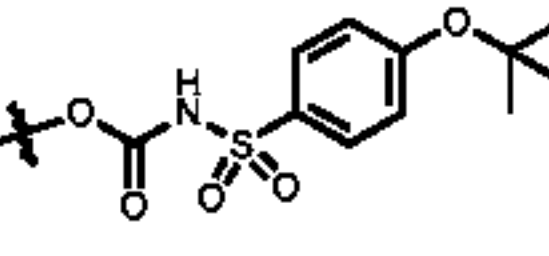
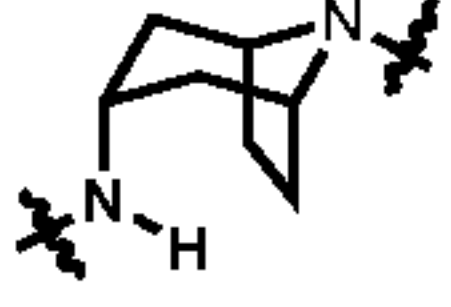
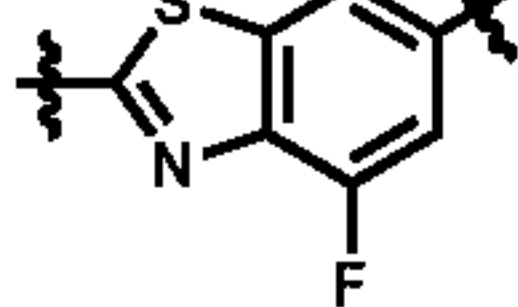
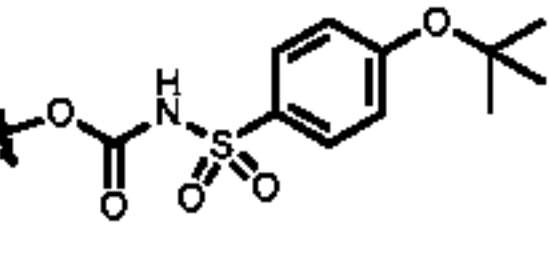
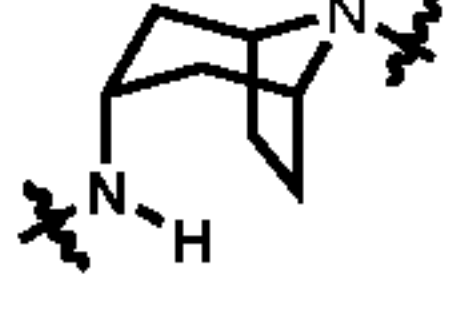
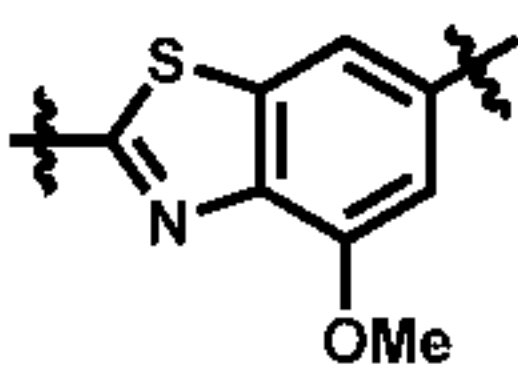
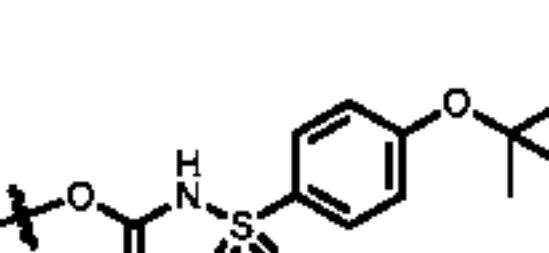
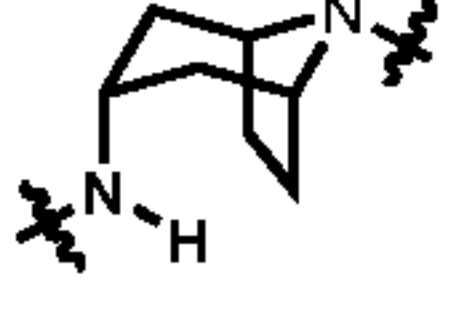
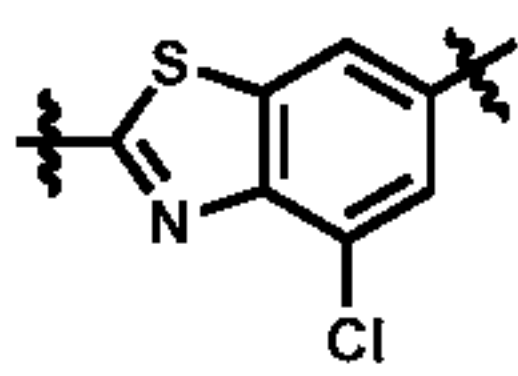
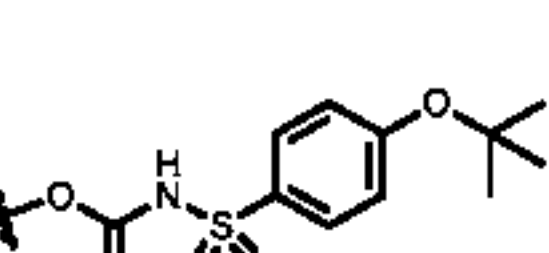
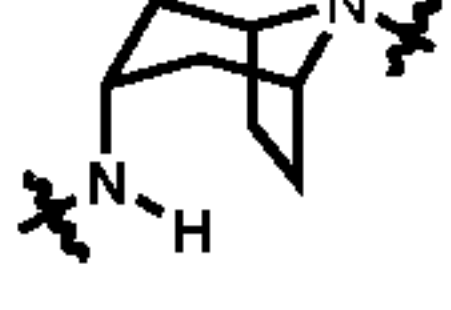
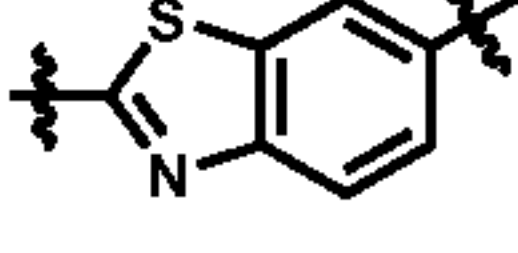
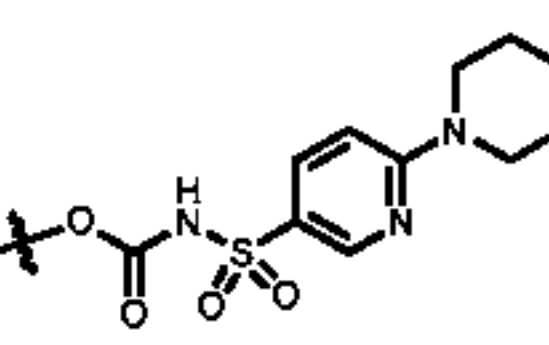
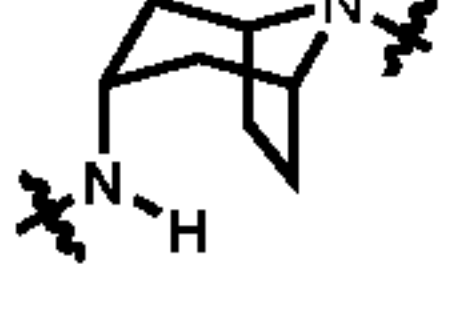
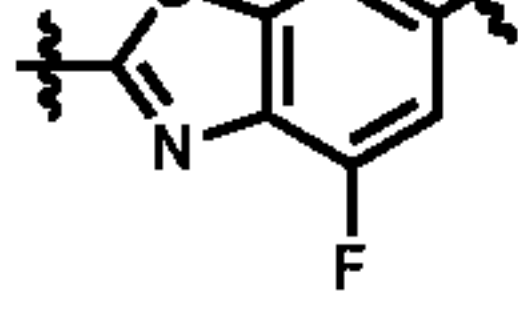
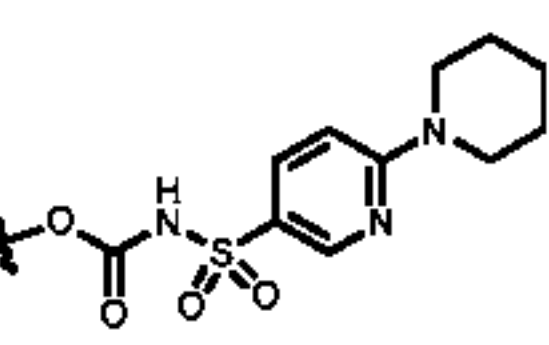
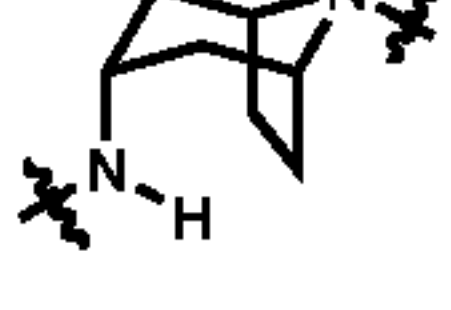
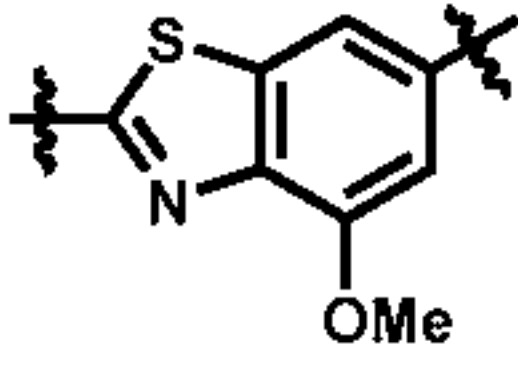
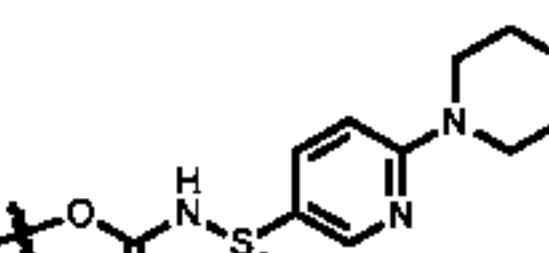
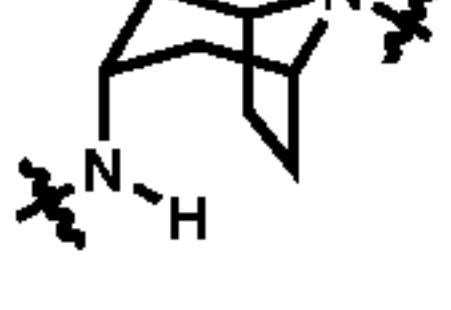
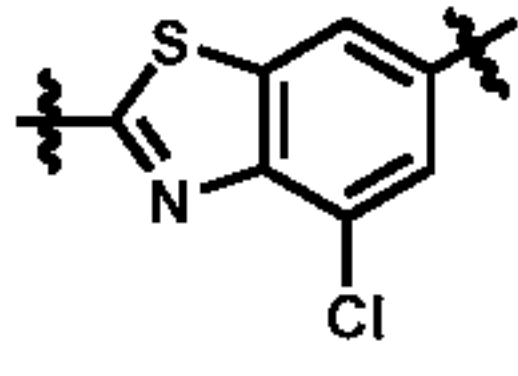
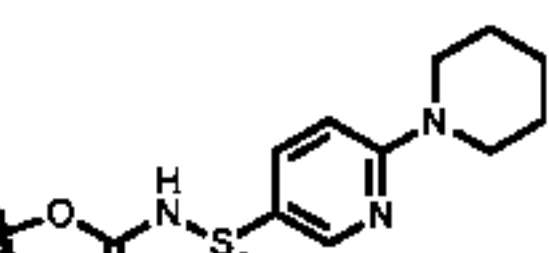
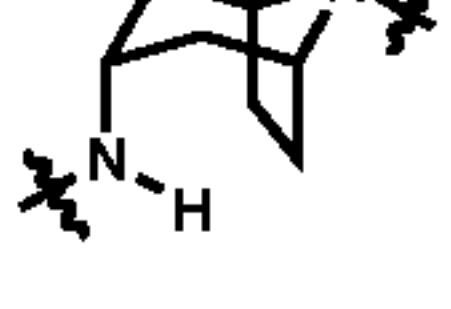
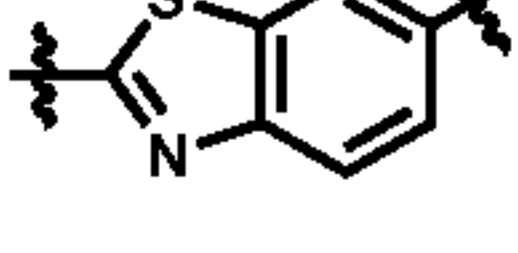
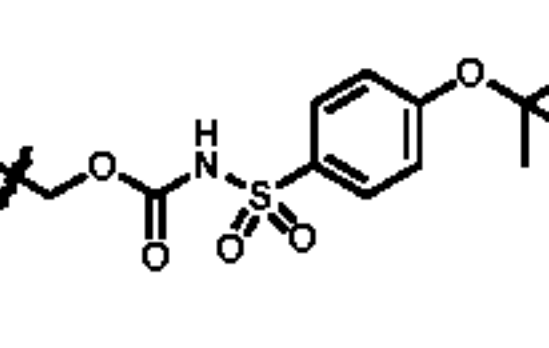
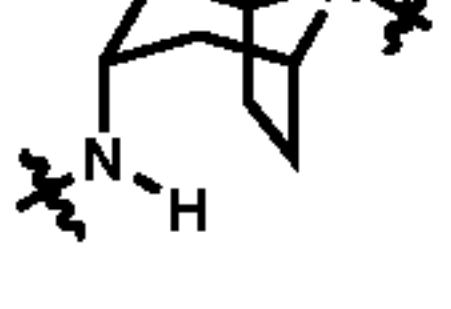
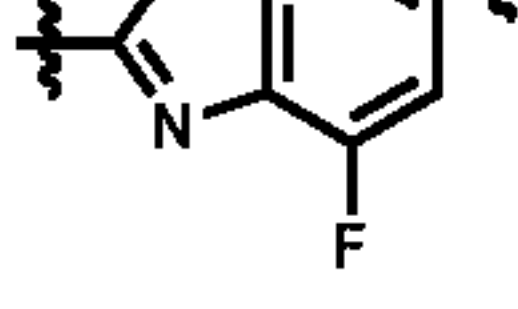
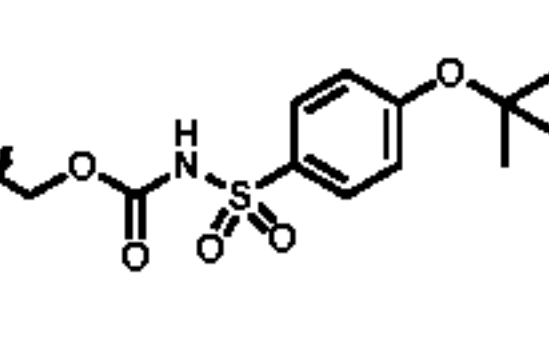
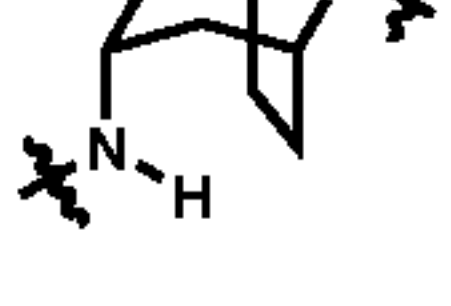
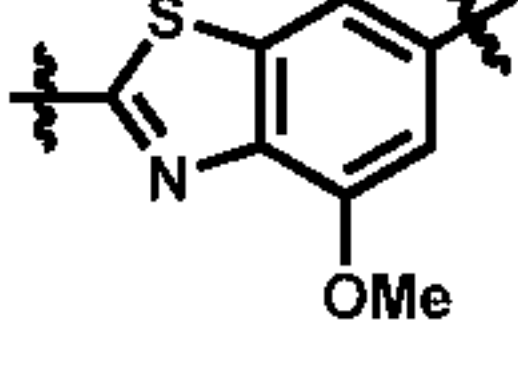
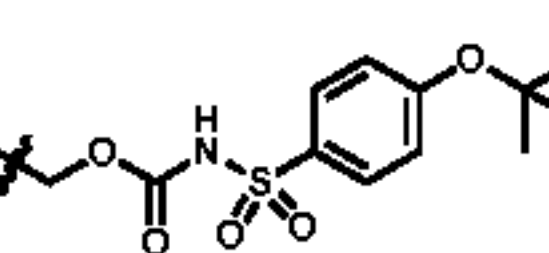
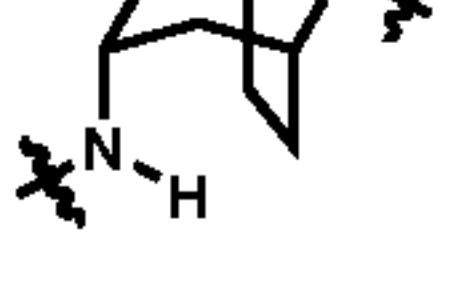
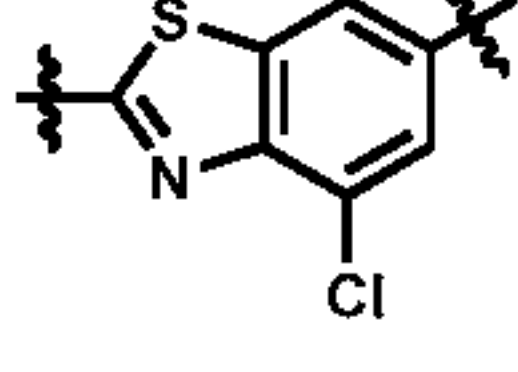
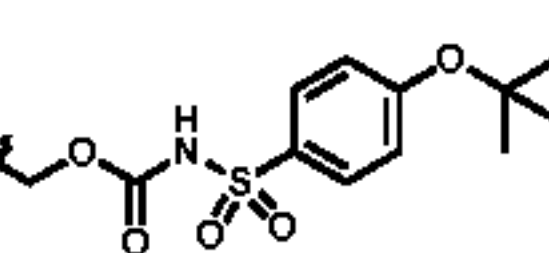
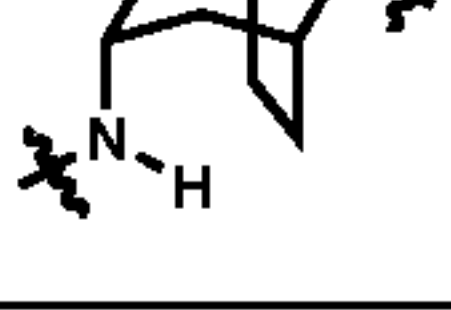
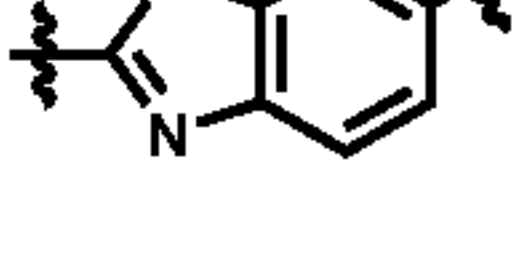
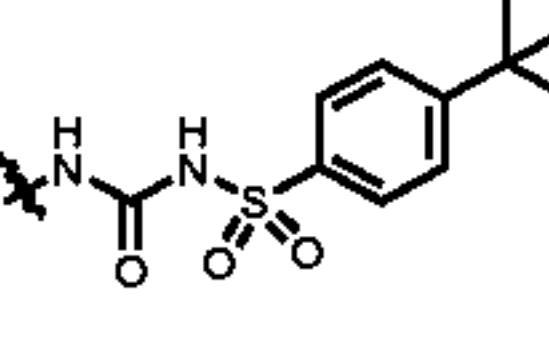
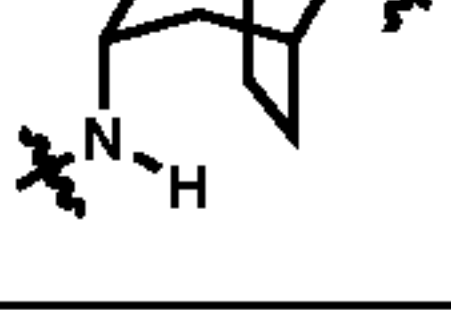
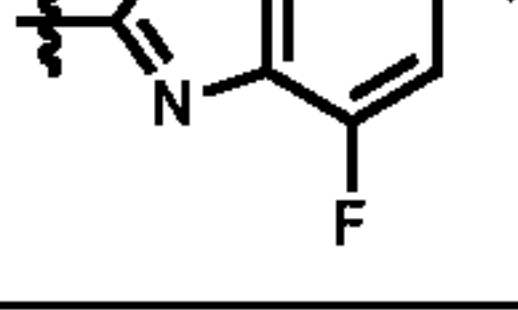
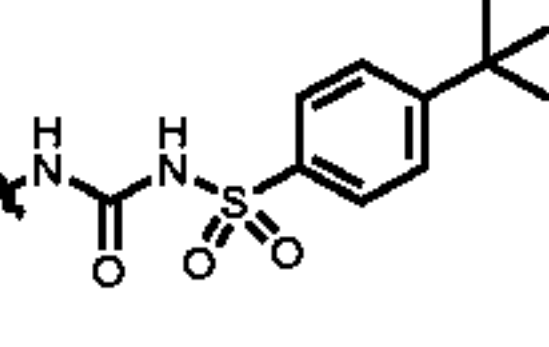
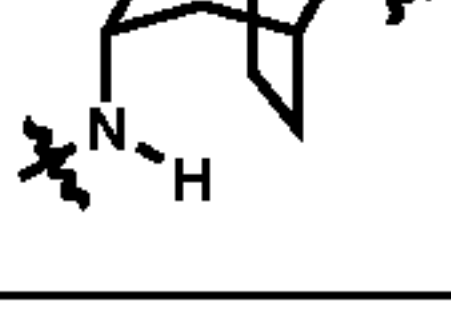
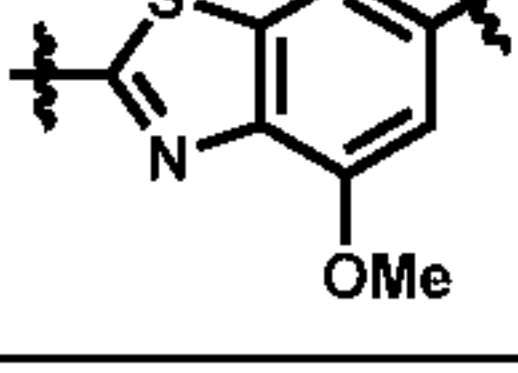
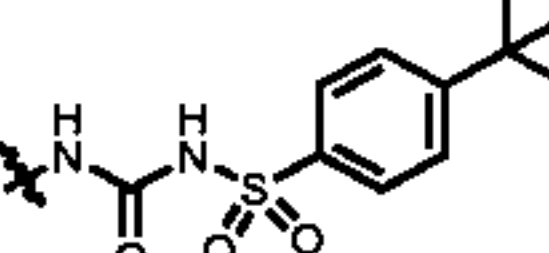
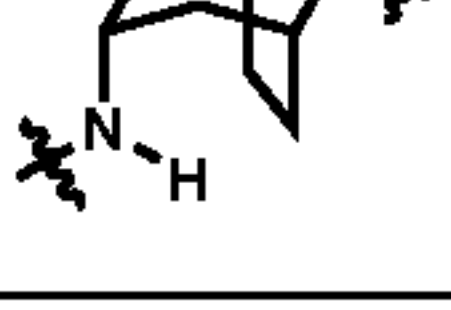
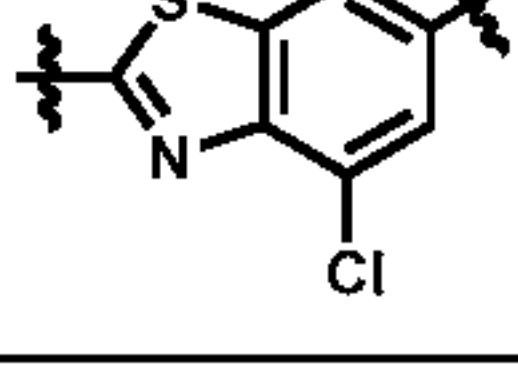
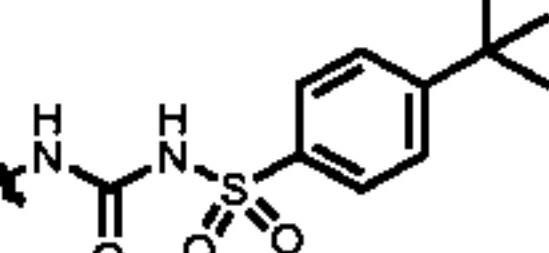
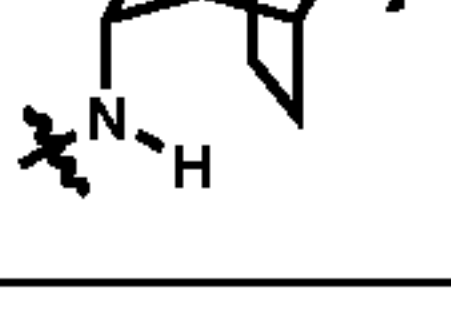
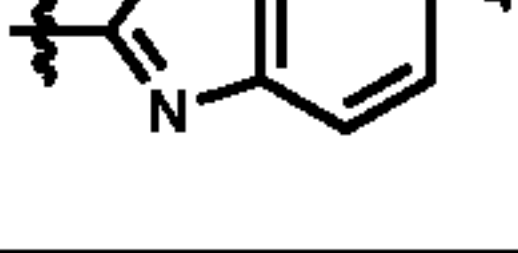
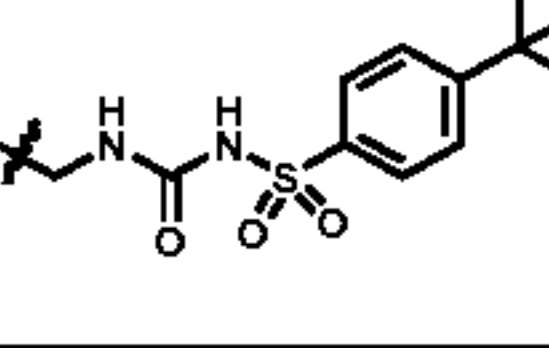
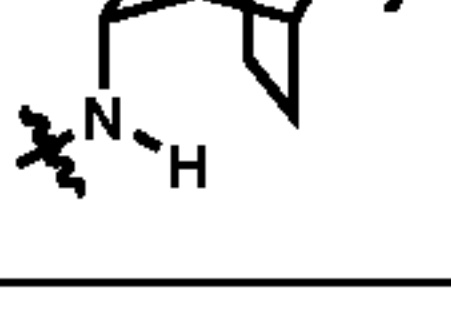
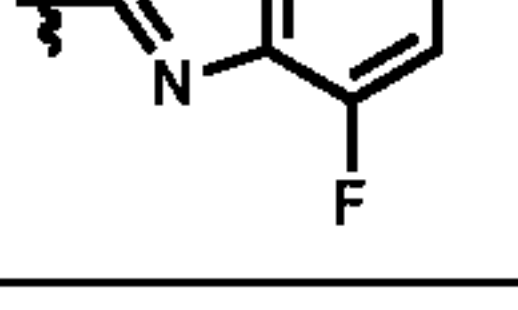
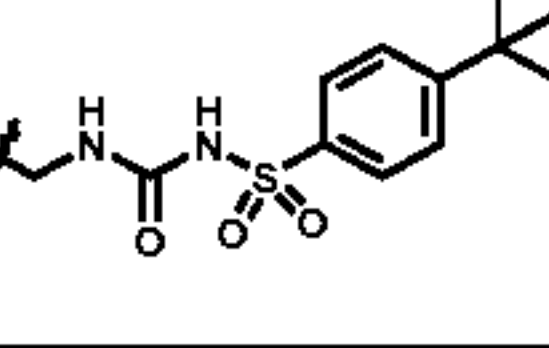
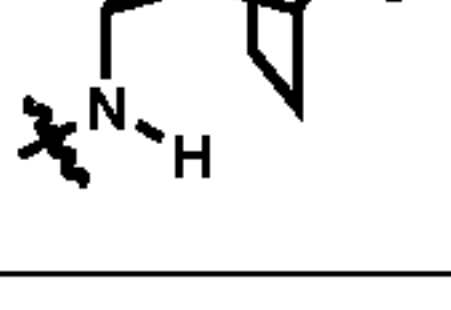
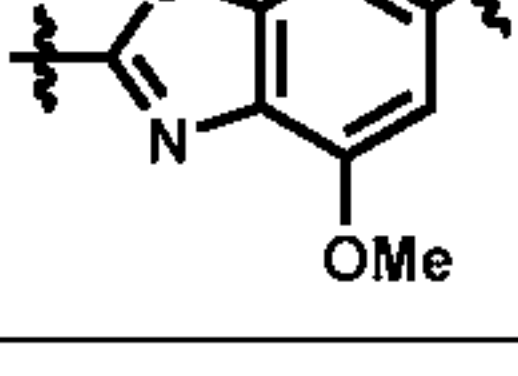
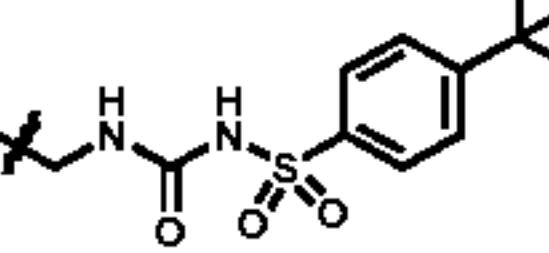
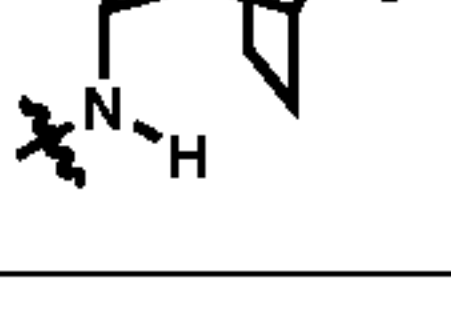
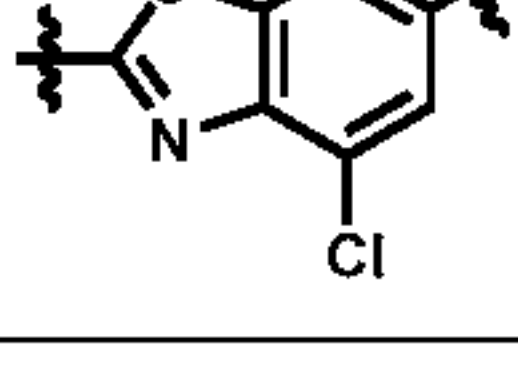
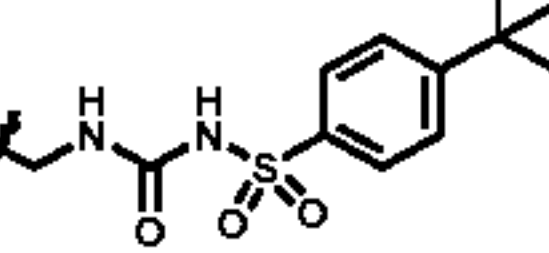
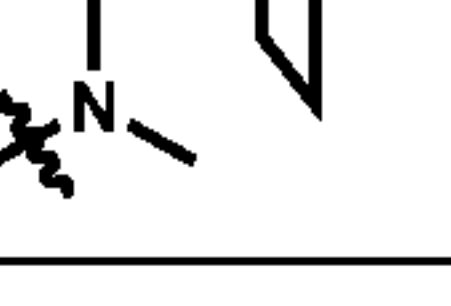
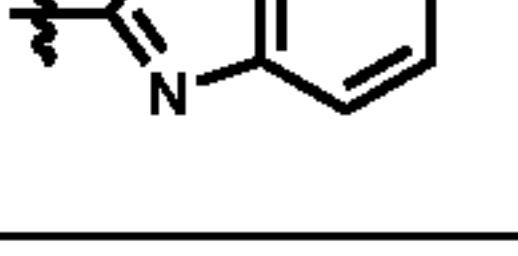
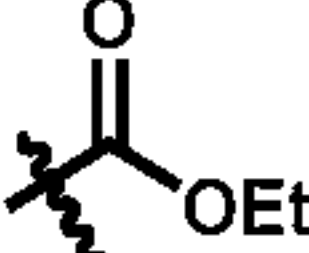
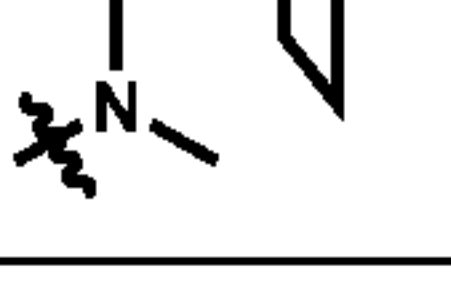
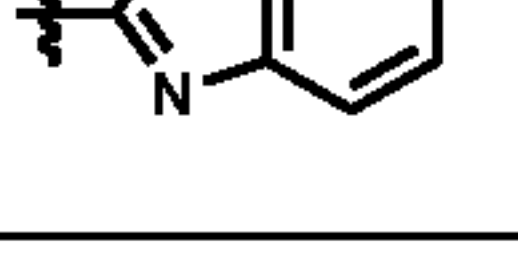
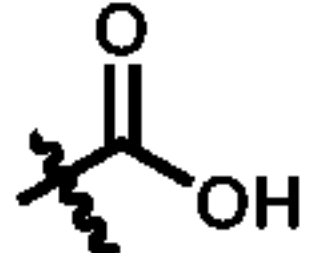
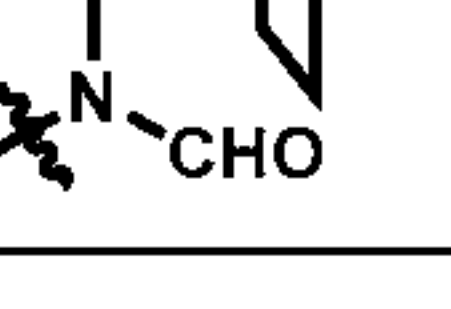
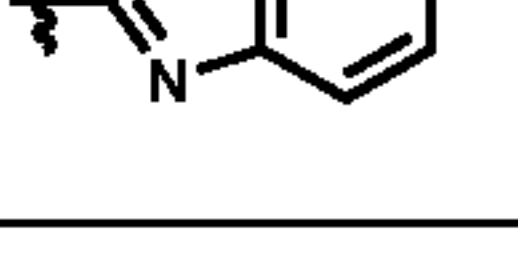
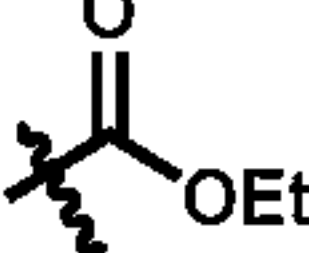
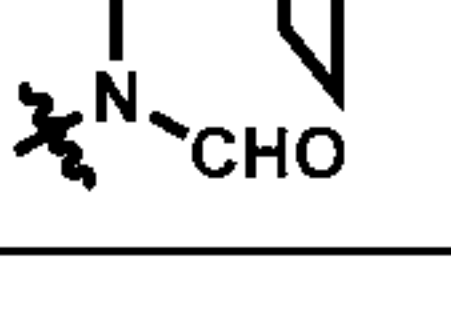
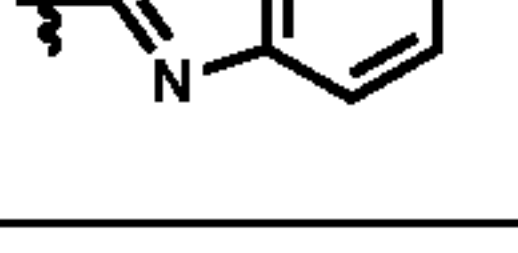
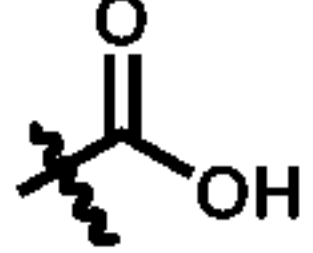
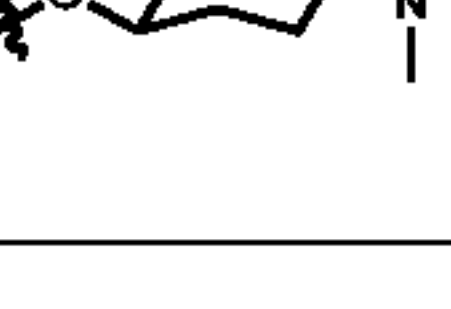
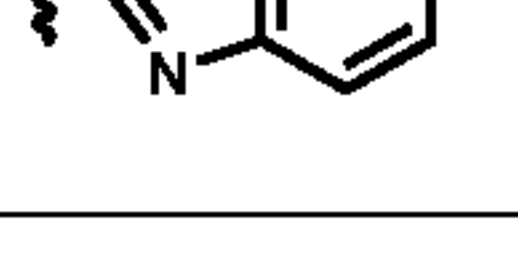
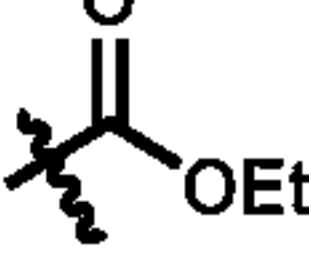
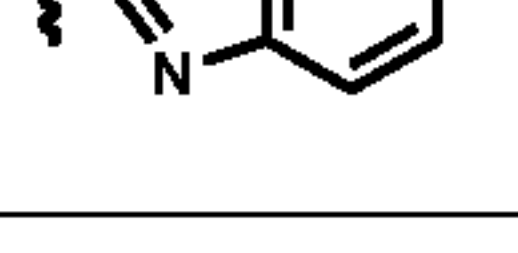
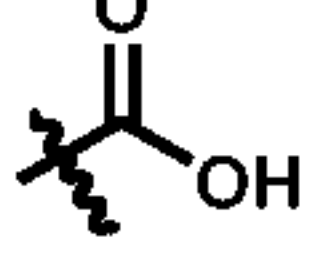
Compound	A	B	 -Z-R ⁴	Compound	A	B	 -Z-R ⁴
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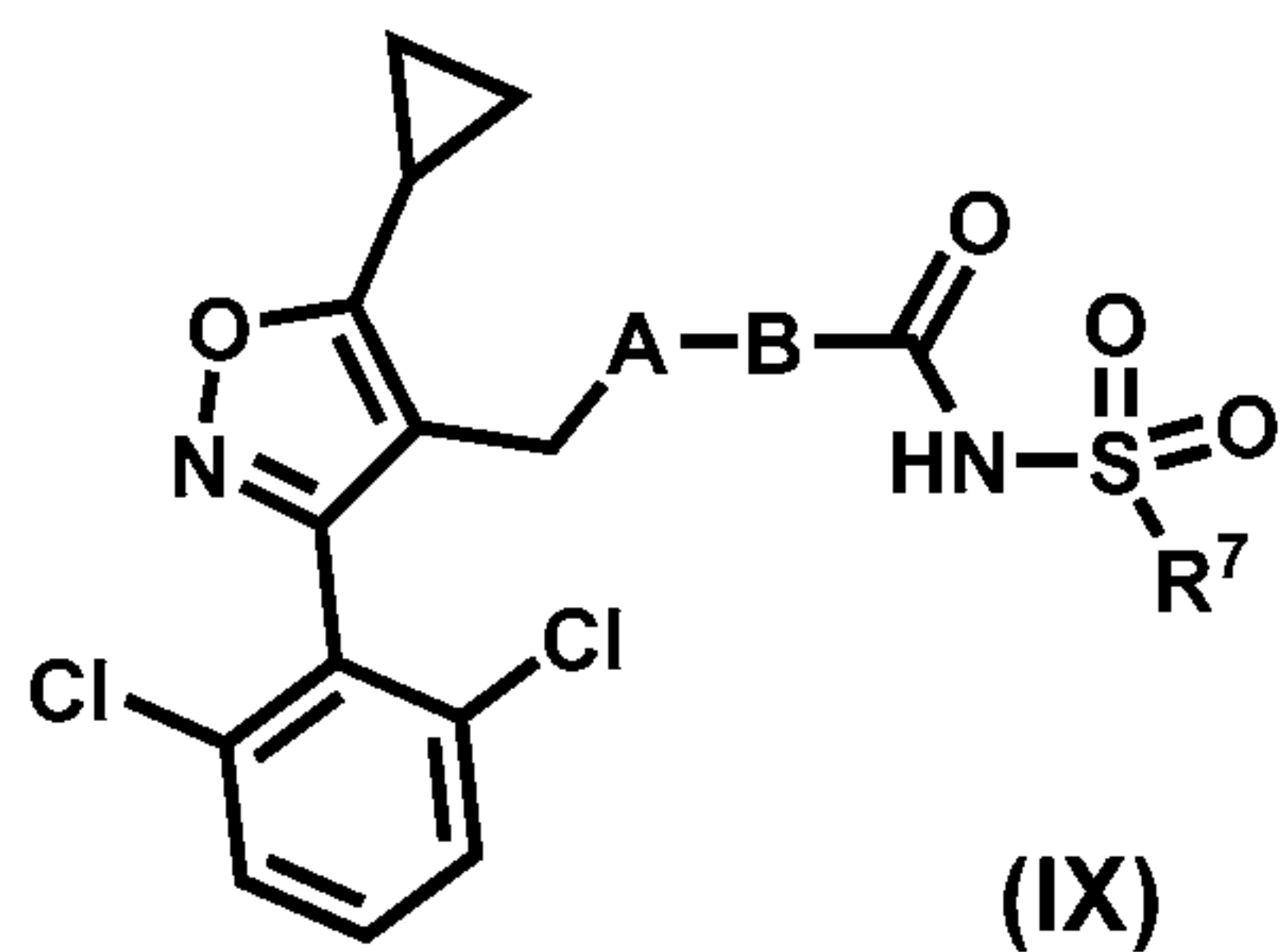
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195				196			
197				198			
199				200			

200-1				200-2			
200-3				200-4			
200-5				200-6			
200-7				200-8			
200-9				200-10			
200-11				200-12			
200-13				200-14			
200-15				200-16			
200-17				200-18			
200-19				200-20			
200-21				200-22			
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200-27				200-28			
200-29				200-30			

200-31				200-32			
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200-43				200-44			
200-45				200-46			
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200-49				200-50			
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200-59				200-60			

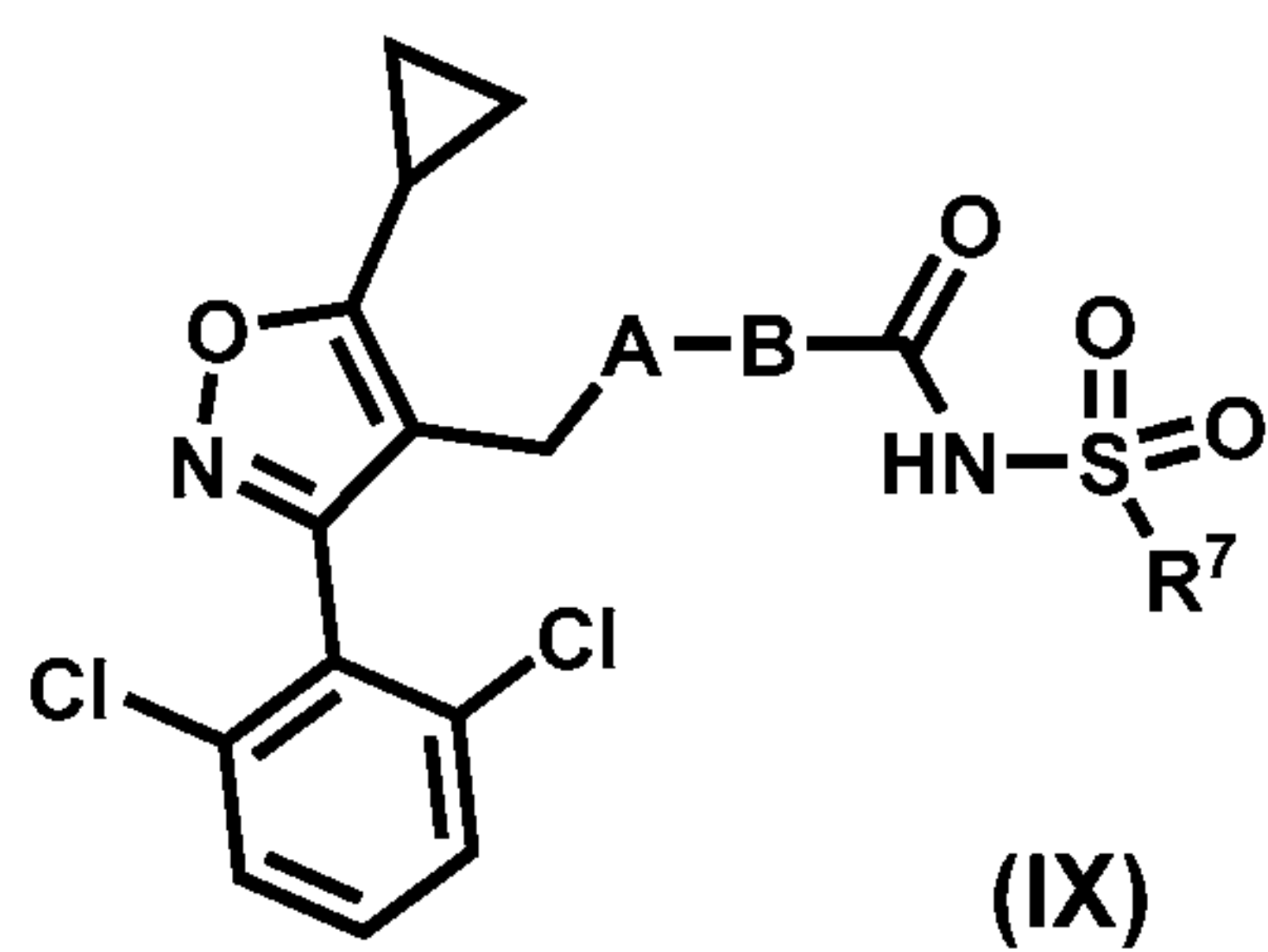
200-61				200-62			
200-63				200-64			
200-65				200-66			
200-67				200-68			
200-69				200-70			
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200-73				200-74			
200-75				200-76			
200-77				200-78			

In another embodiment, the compound of Formula (I) is represented by Formula (IX) or a pharmaceutically acceptable salt thereof:



5 wherein A, B, and R⁷ are as previously defined.

Representative compounds of the invention include, but are not limited to, compounds according to Formula (IX), and pharmaceutically acceptable salts thereof, wherein, A, B, and R⁷ are delineated for each compound in Table 2.

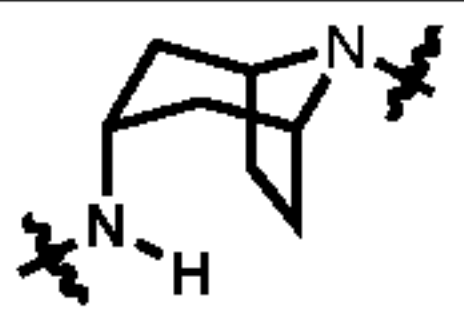
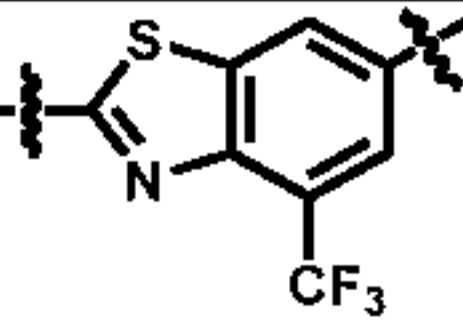
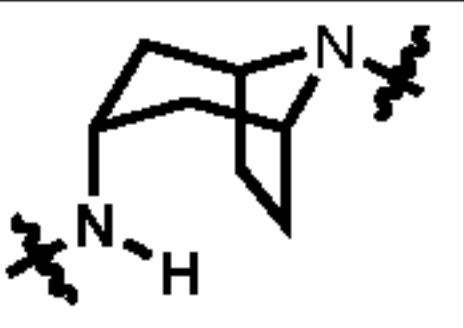
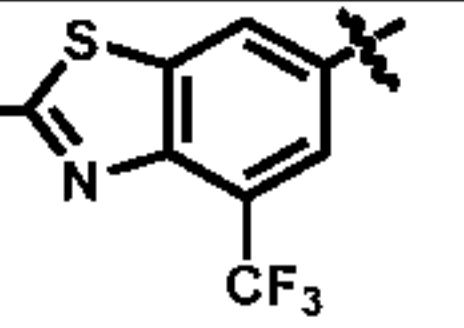
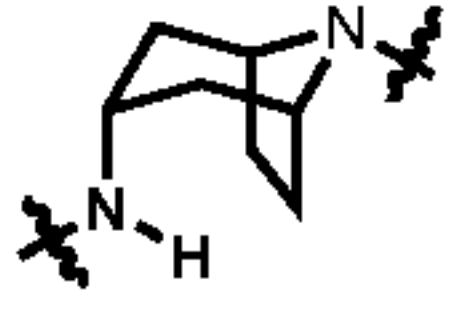
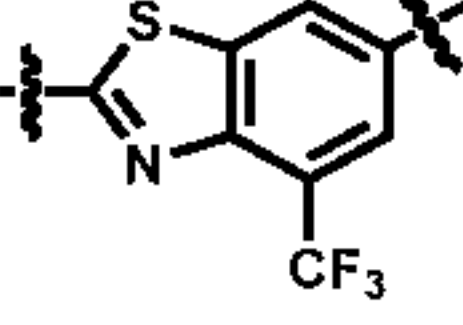
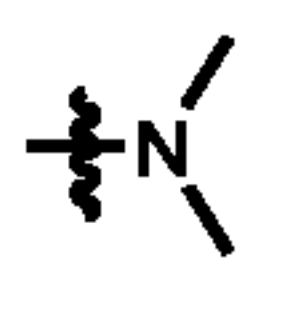
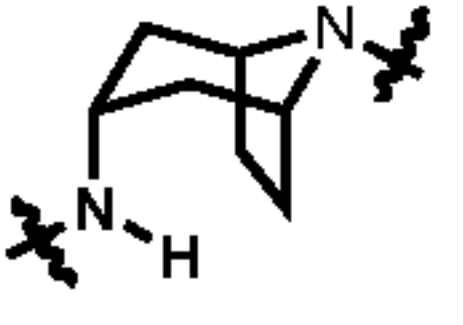
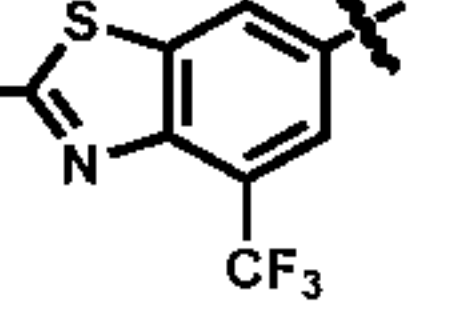
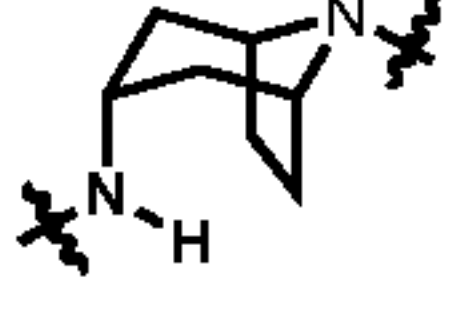
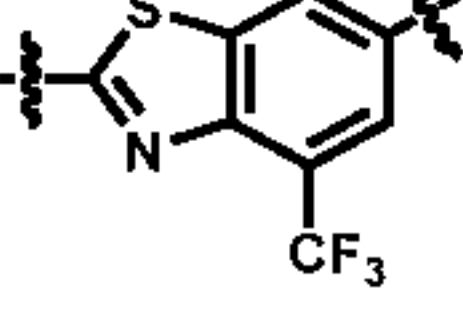
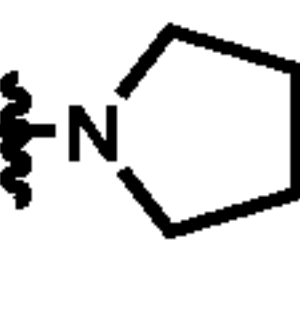
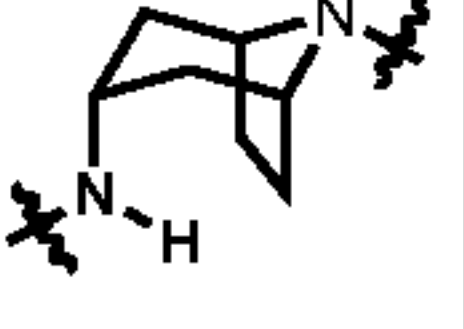
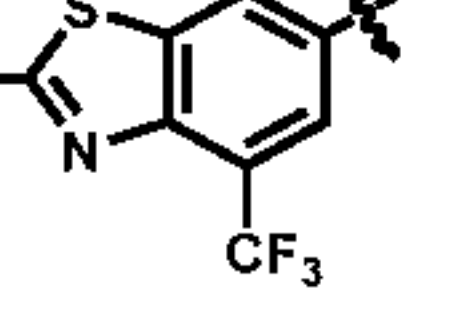
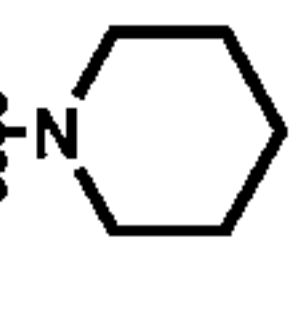
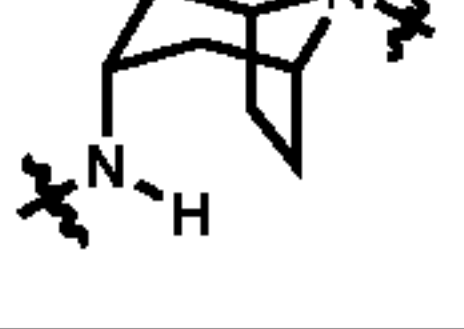
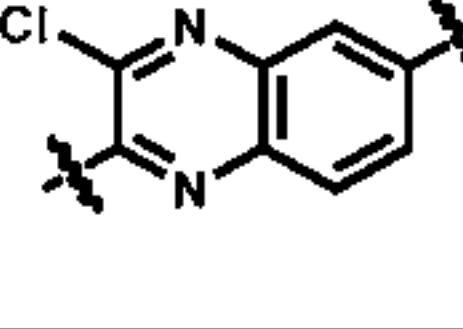
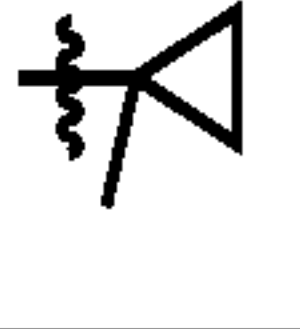
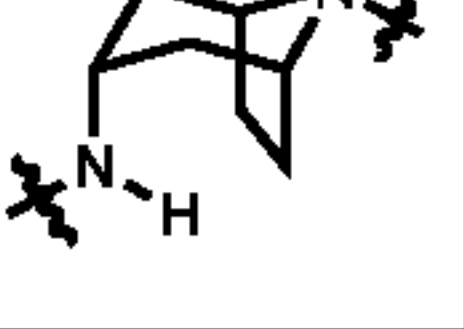
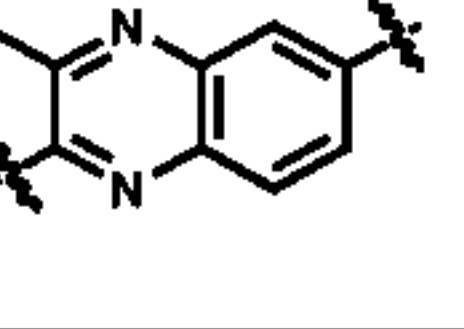
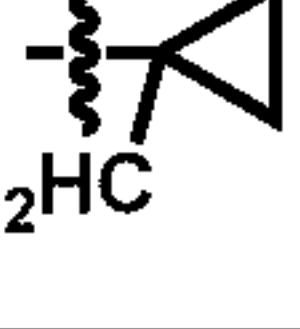
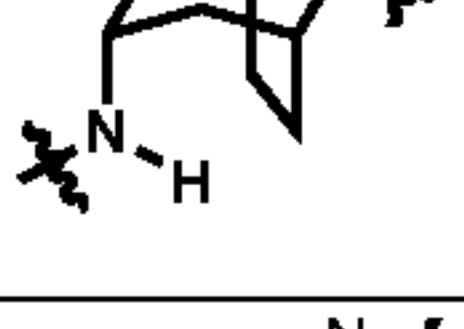
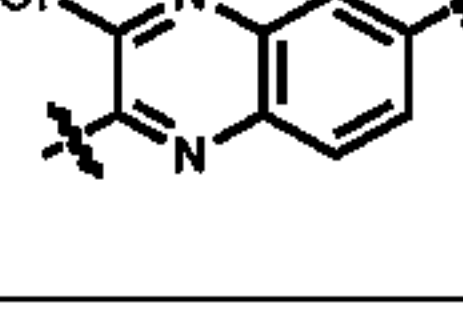
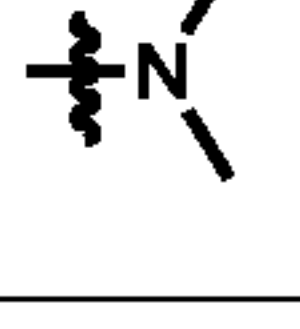
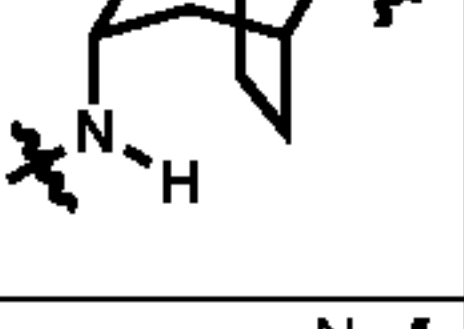
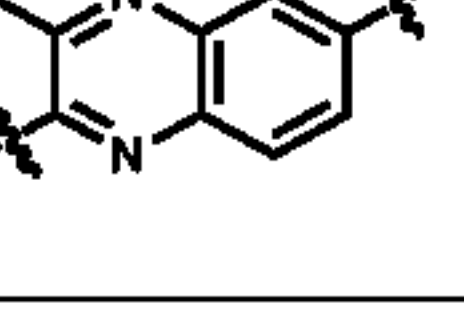
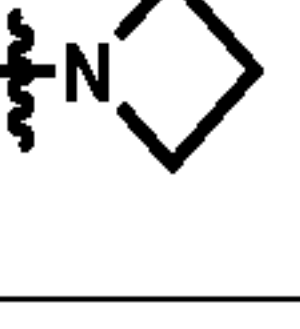
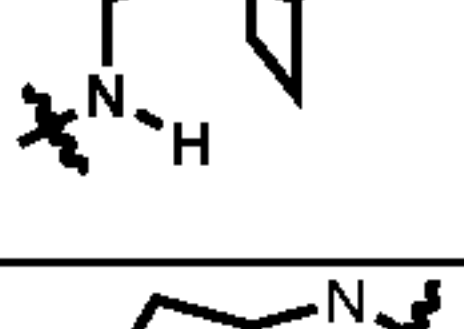
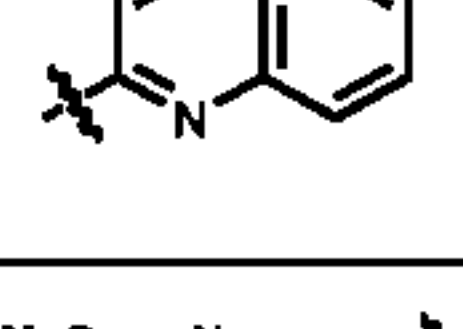
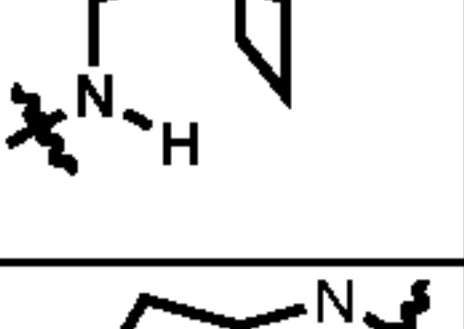
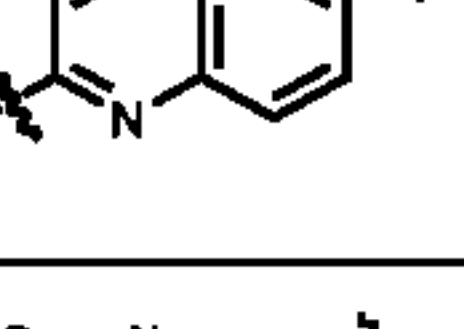
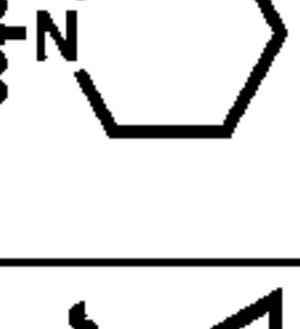
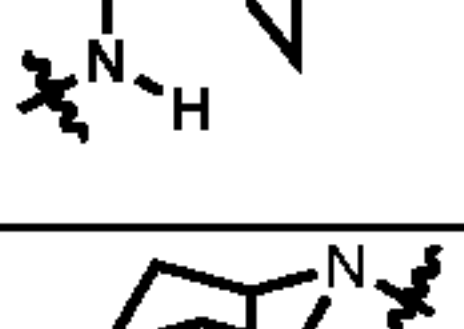
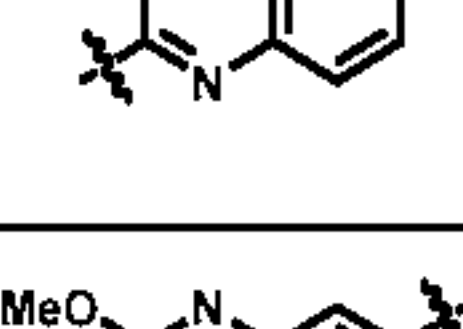
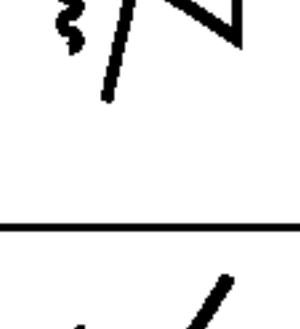
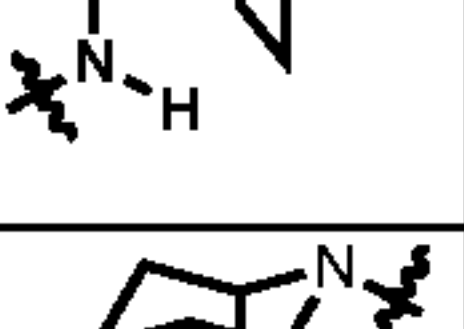
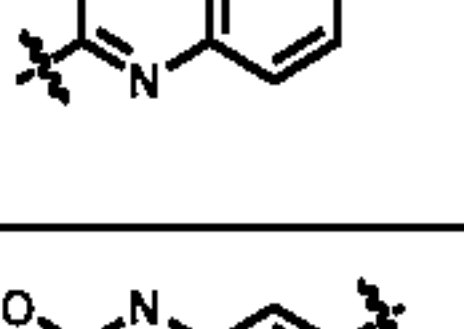
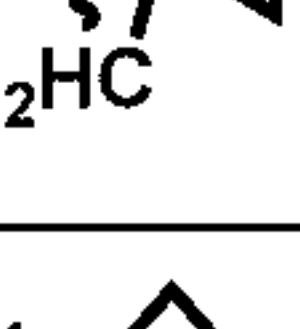
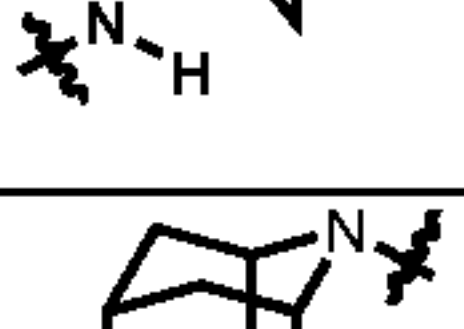
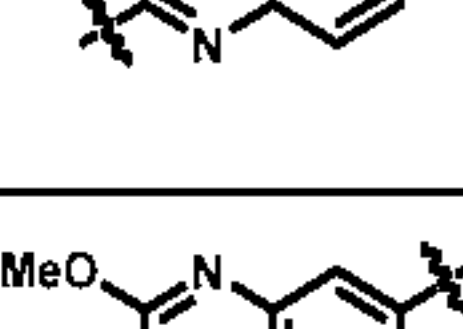
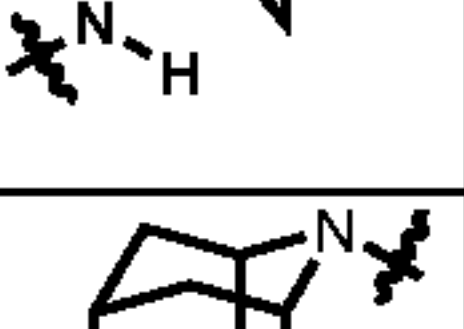
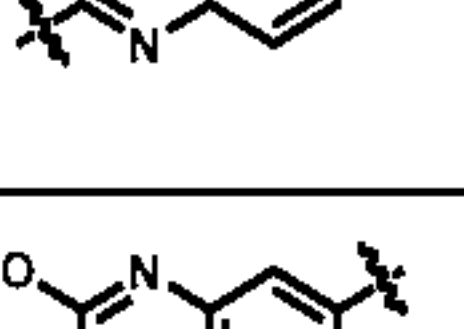
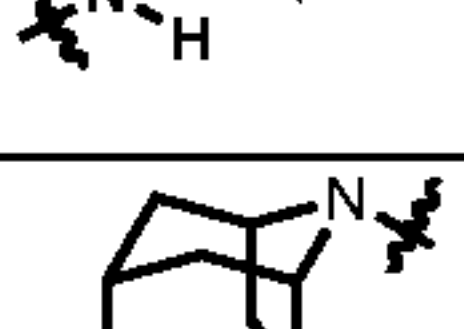
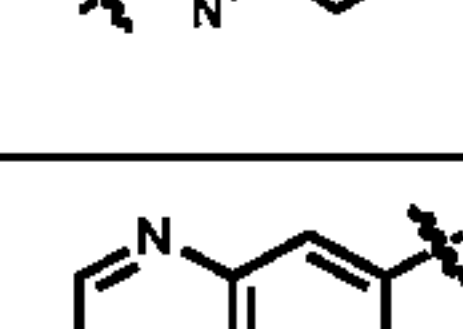
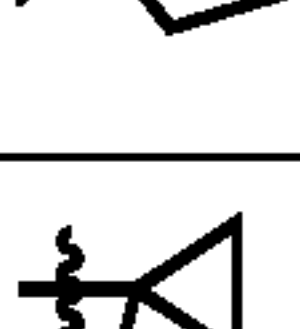
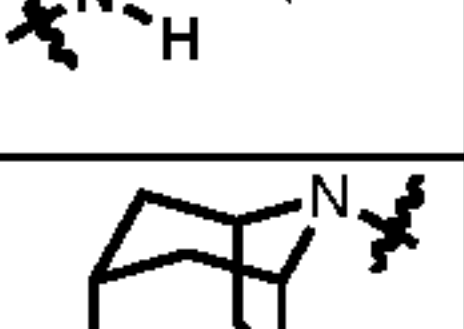
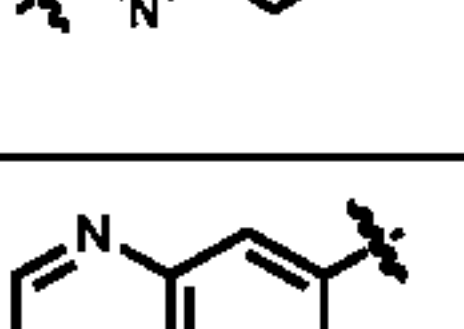
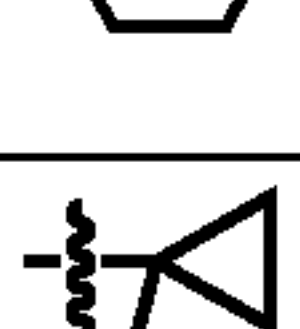
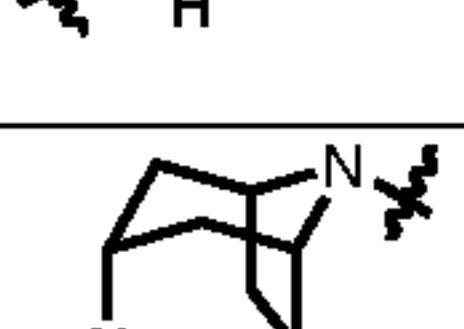
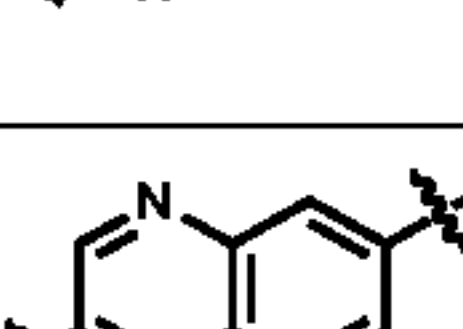
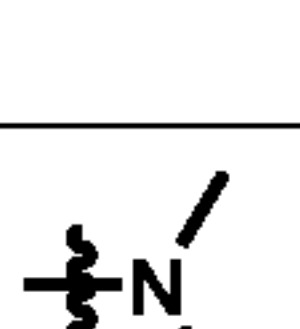
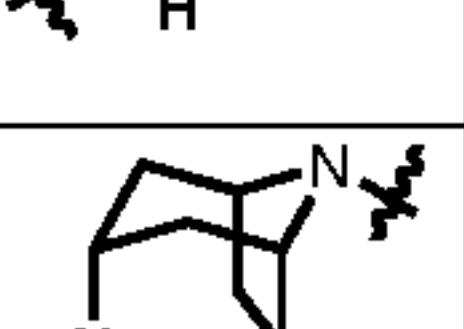
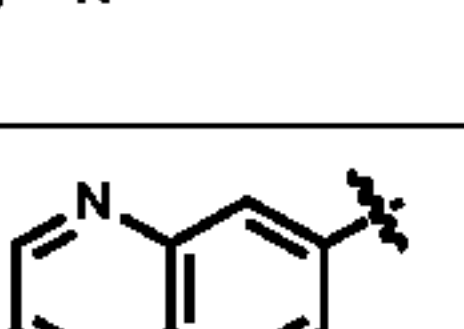
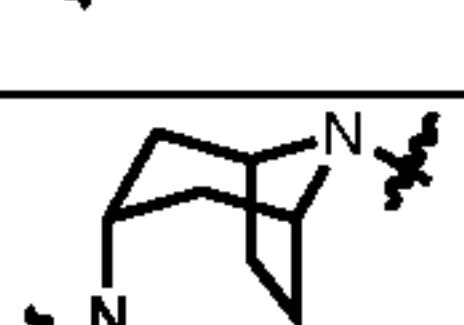
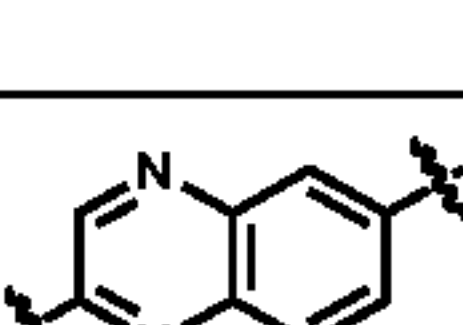
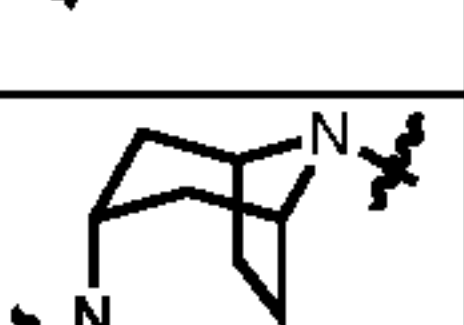
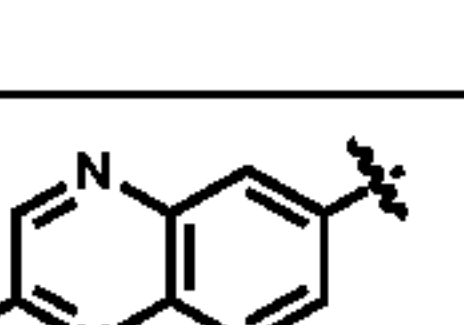
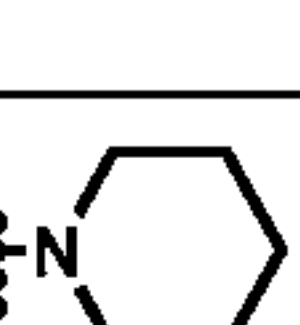
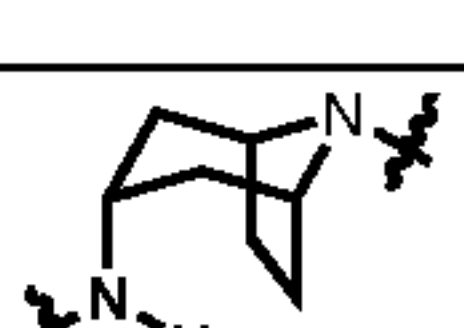
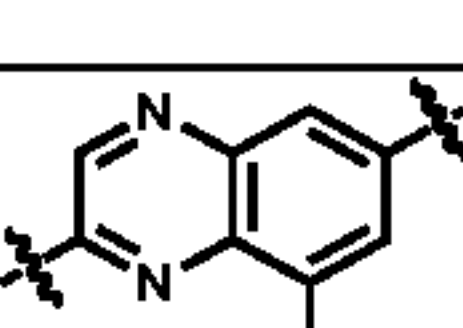
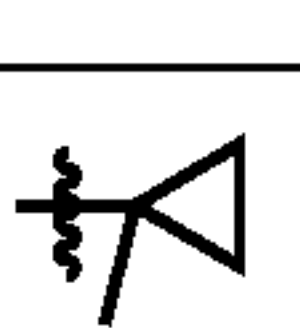
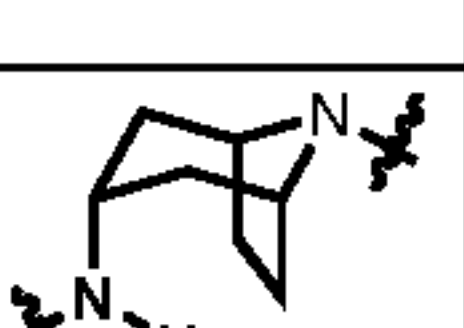
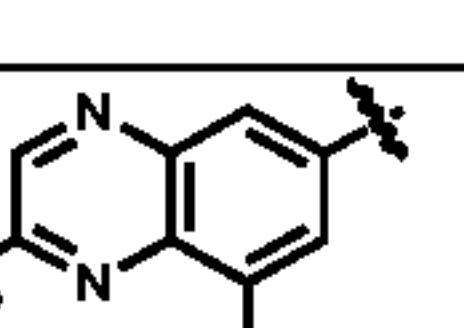
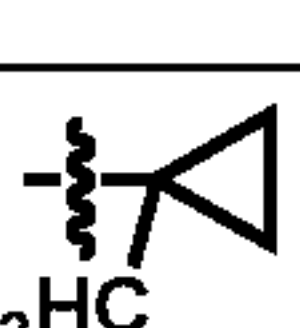
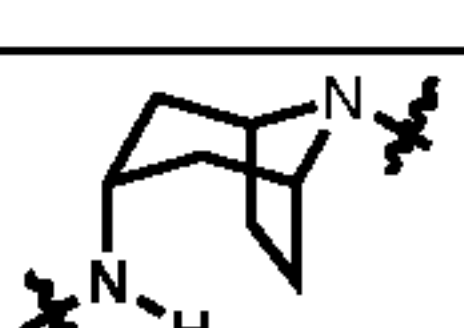
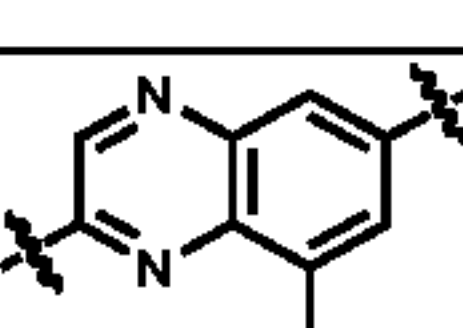
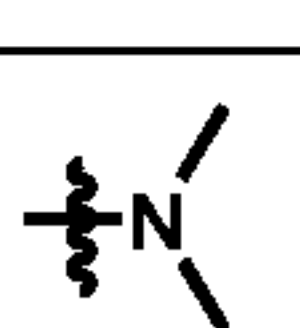
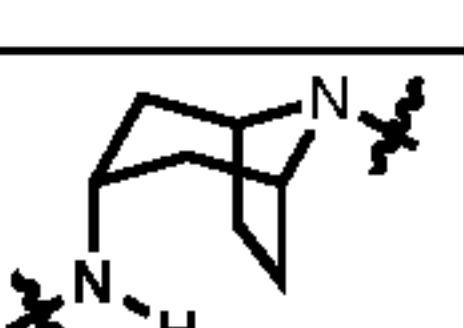
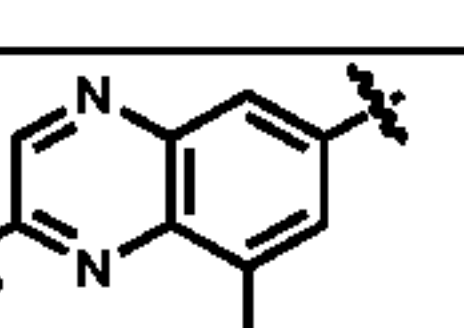
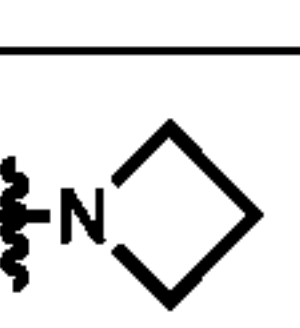
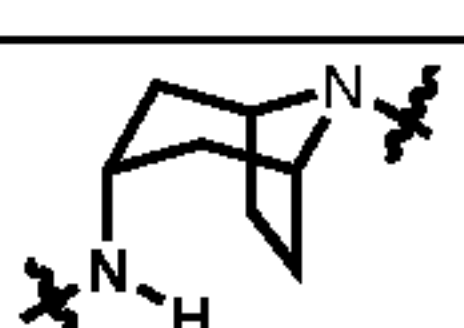
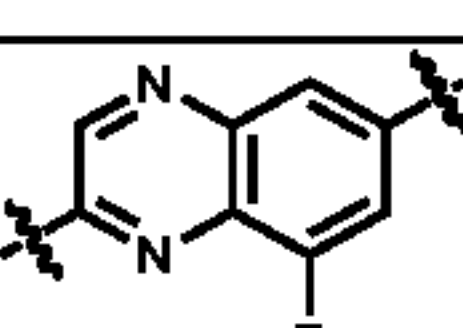
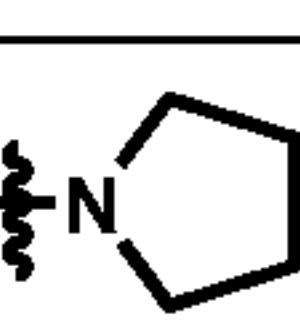
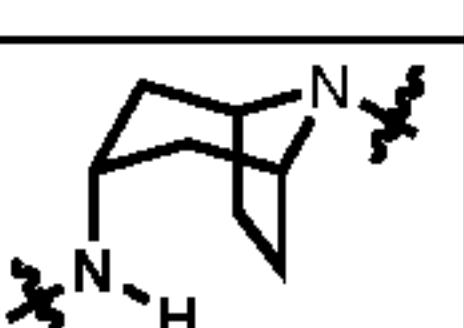
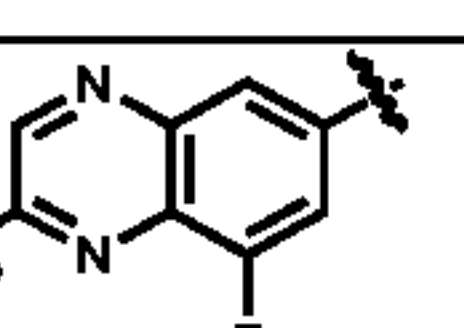
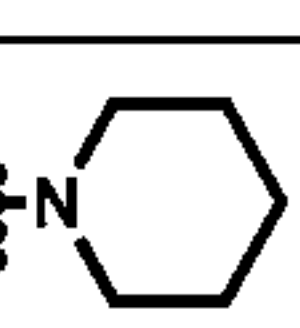
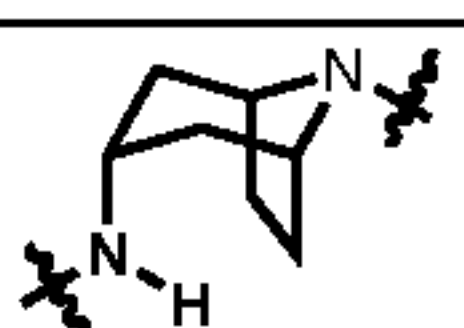
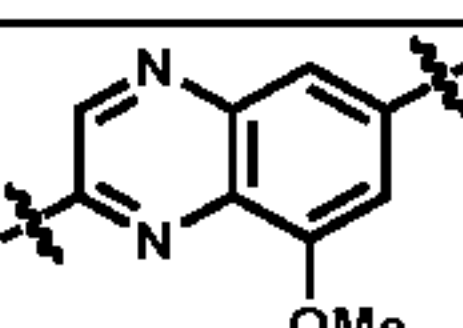
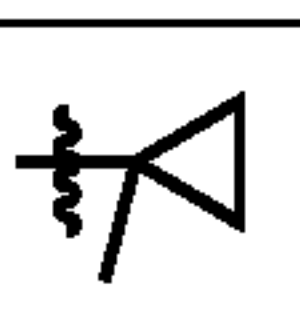
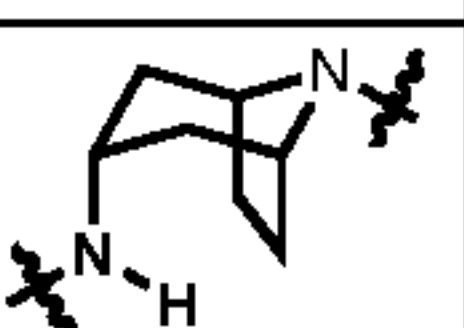
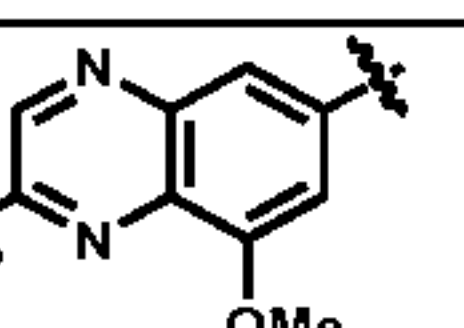
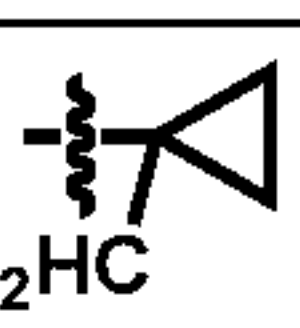
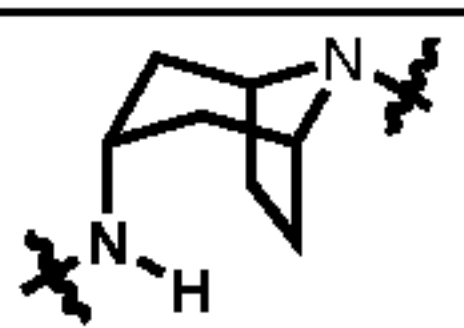
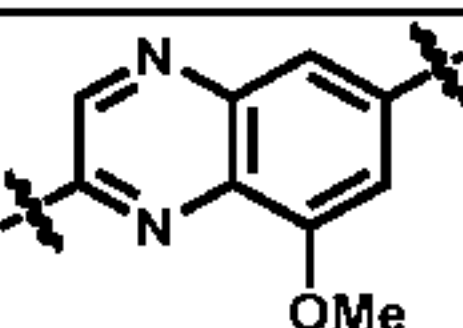
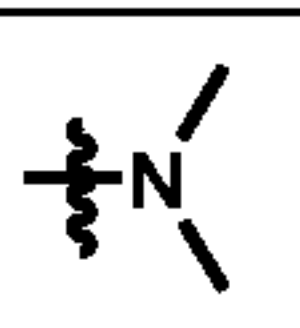
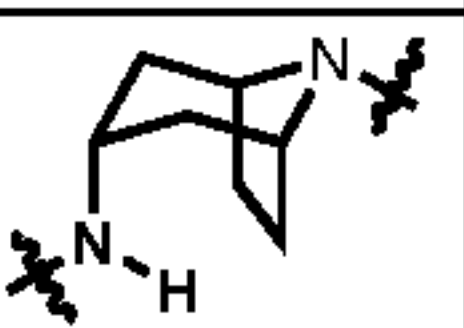
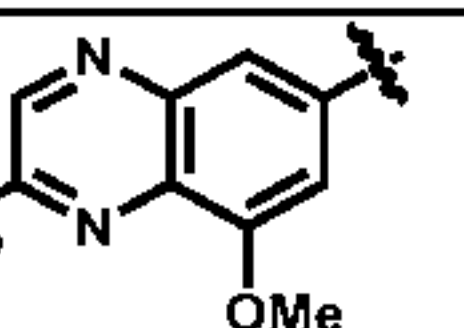
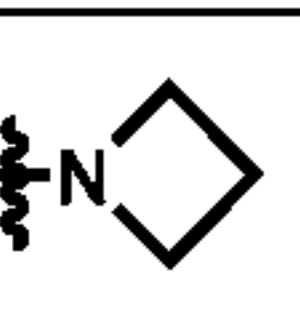
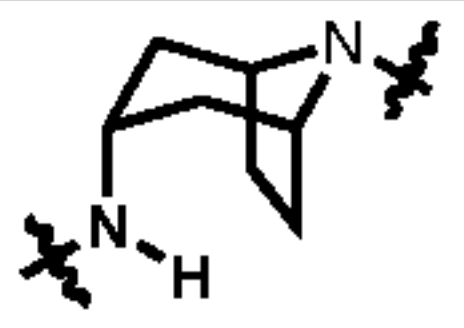
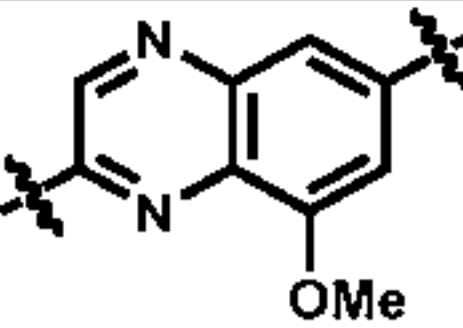
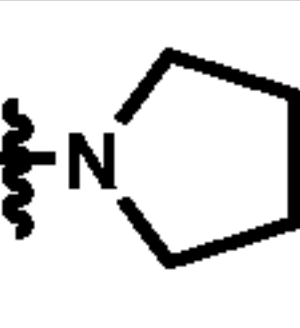
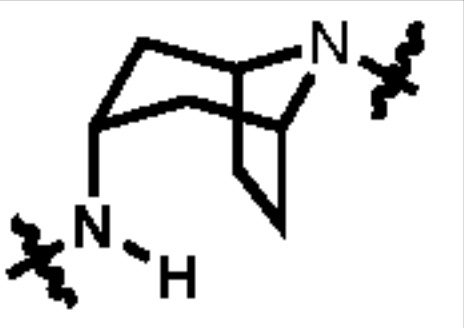
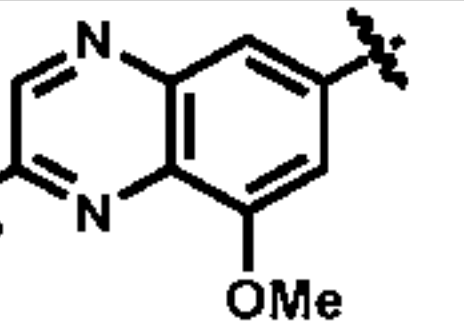
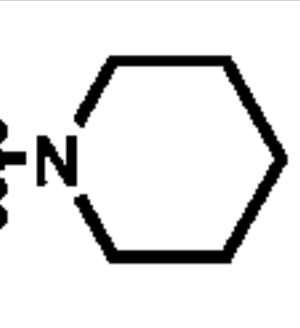
**Table 2**

Compound	A	B	R ⁷	Compound	A	B	R ⁷
201				202			
203				204			
205				206			
207				208			
209				210			
211				212			
213				214			
215				216			
217				218			
219				220			
221				222			
223				224			

225				226			
227				228			
229				230			
231				232			
233				234			
235				236			
237				238			
239				240			
241				242			
243				244			
245				246			
247				248			
249				250			
251				252			
253				254			
255				256			

257				258			
259				260			
261				262			
263				264			
265				266			
267				268			
269				270			
271				272			
273				274			
275				276			
277				278			
279				280			
281				282			
283				284			
285				286			
287				288			
289				290			
291				292			
293				294			

295				296			
297				298			
299				300			
301				302			
303				304			
305				306			
307				308			
309				310			
311				312			
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317				318			
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321				322			
323				324			
325				326			
327				328			

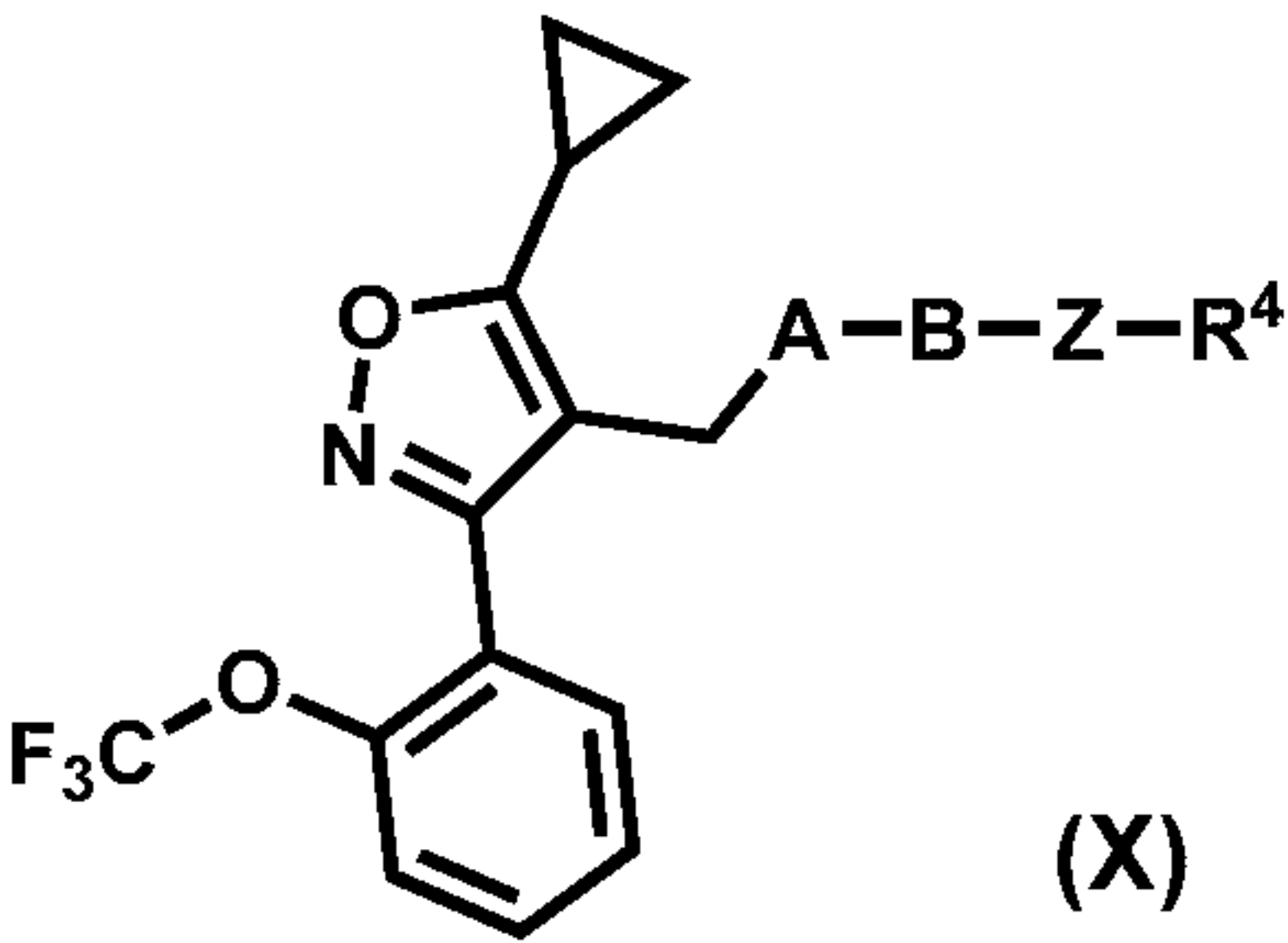
329				330			
331				332			
333				334			
335				336			
337				338			
339				340			
341				342			
343				344			
345				346			
347				348			
349				350			
351				352			
353				354			
355				356			
357				358			
359				360			
361				362			
363				364			

365				366			
367				368			
369				370			
371				372			
373				374			
375				376			
377				378			
379				380			
381				382			
383				384			
385				386			
387				388			
389				390			
391				392			
393				394			
395				396			
397				398			
399				400			

400-1				400-2			
400-3				400-4			
400-5				400-6			
400-7				400-08			
400-9				400-10			
400-11				400-12			
400-13				400-14			
400-15				400-16			
400-17				400-18			
400-19				400-20			
400-21				400-22			
400-23				400-24			
400-25				400-26			
400-27				400-28			
400-29				400-30			
400-31				400-32			
400-33				400-34			

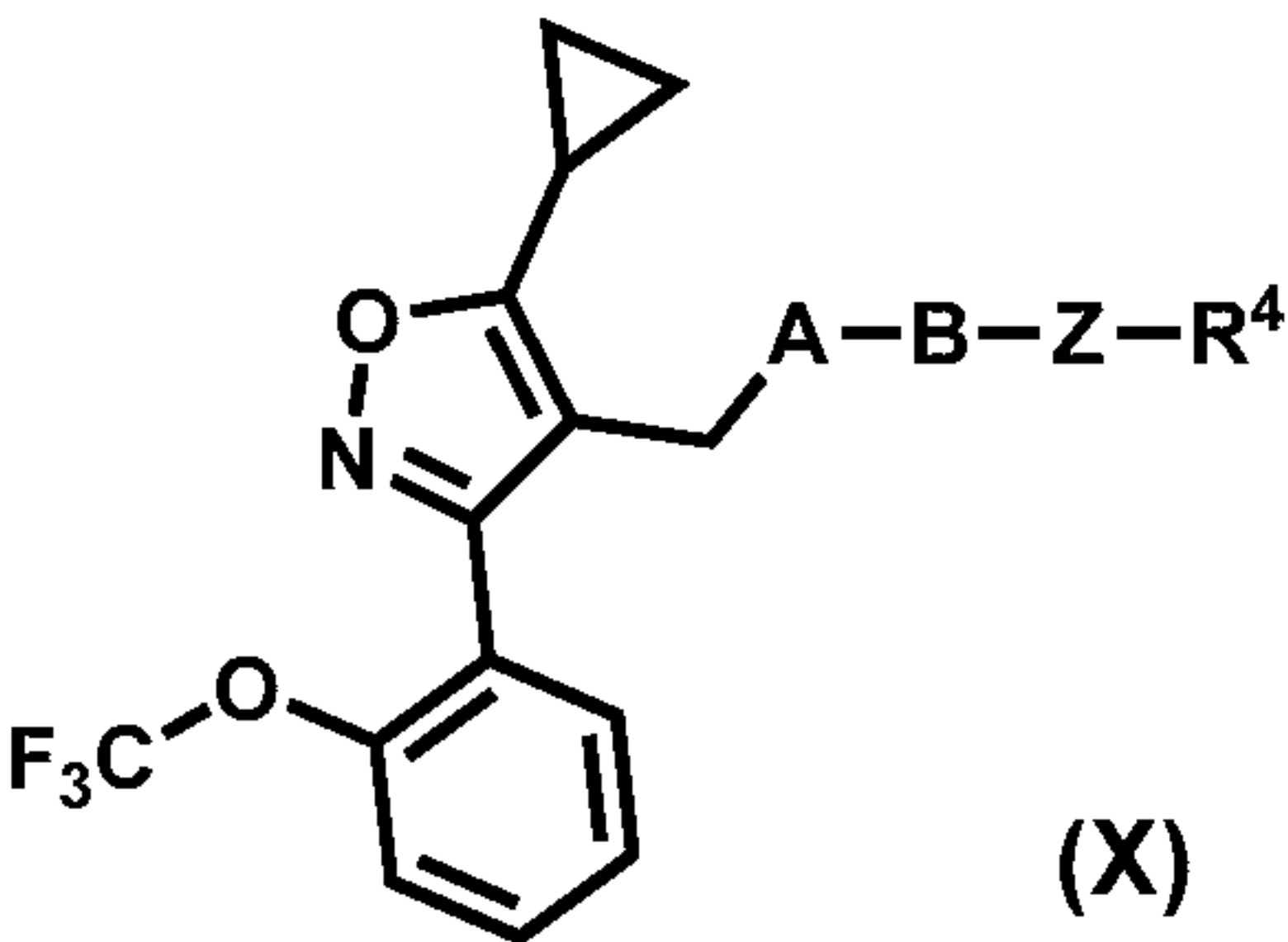
400-35				400-36			
400-37				400-38			
400-39				400-40			

In another embodiment, the compound of Formula (I) is represented by Formula (VIII) or a pharmaceutically acceptable salt thereof:



5 wherein A, B, Z, and R⁴ are as previously defined.

Representative compounds of the invention include, but are not limited to, compounds according to Formula (X), and pharmaceutically acceptable salts thereof, wherein A, B, and Z-R⁴ are delineated for each compound in Table 3.



10

Table 3

Compound	A	B		Compound	A	B	
401				402			
403				404			
405				406			

407				408			
409				410			
411				412			
413				414			
415				416			
417				418			
419				420			
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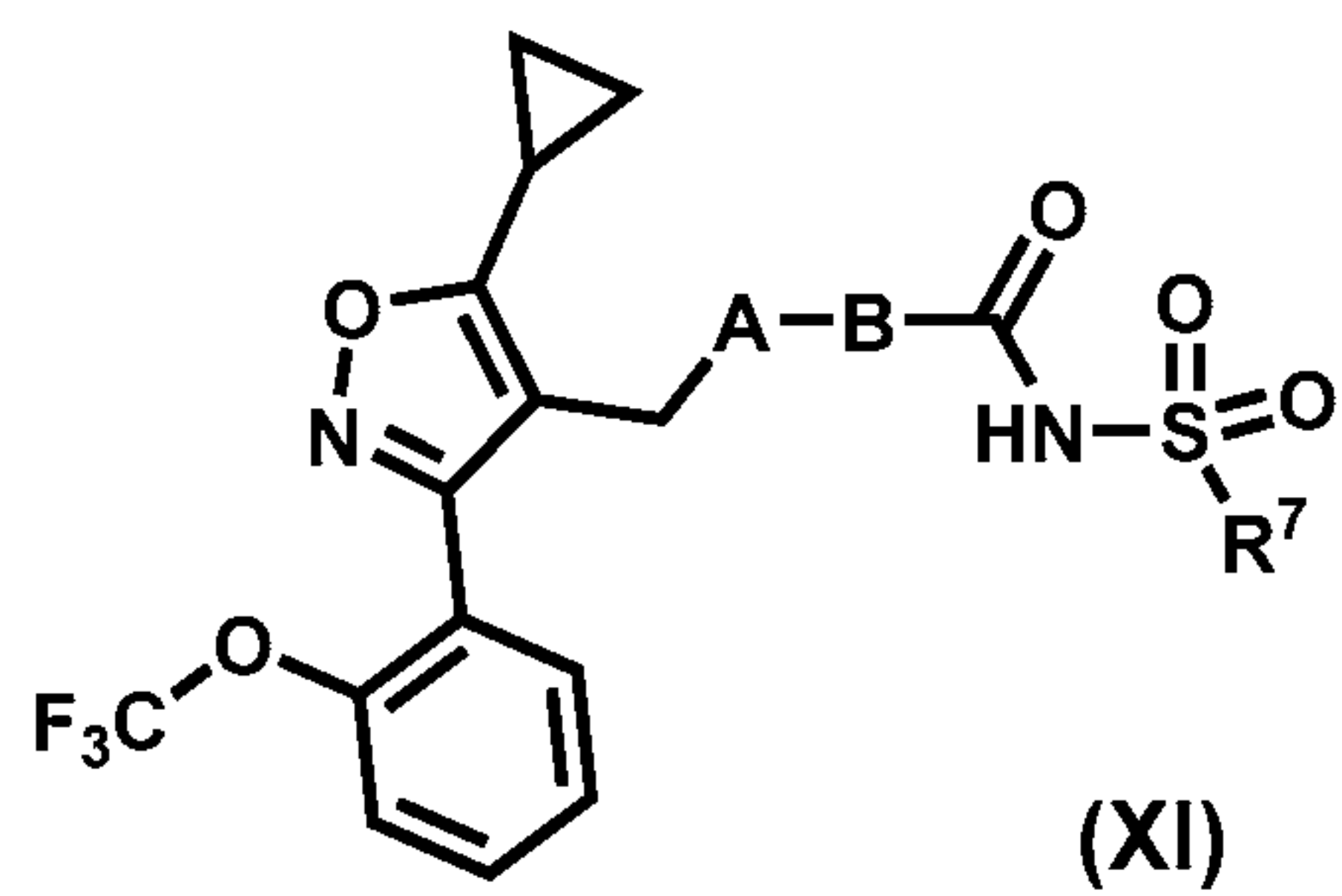
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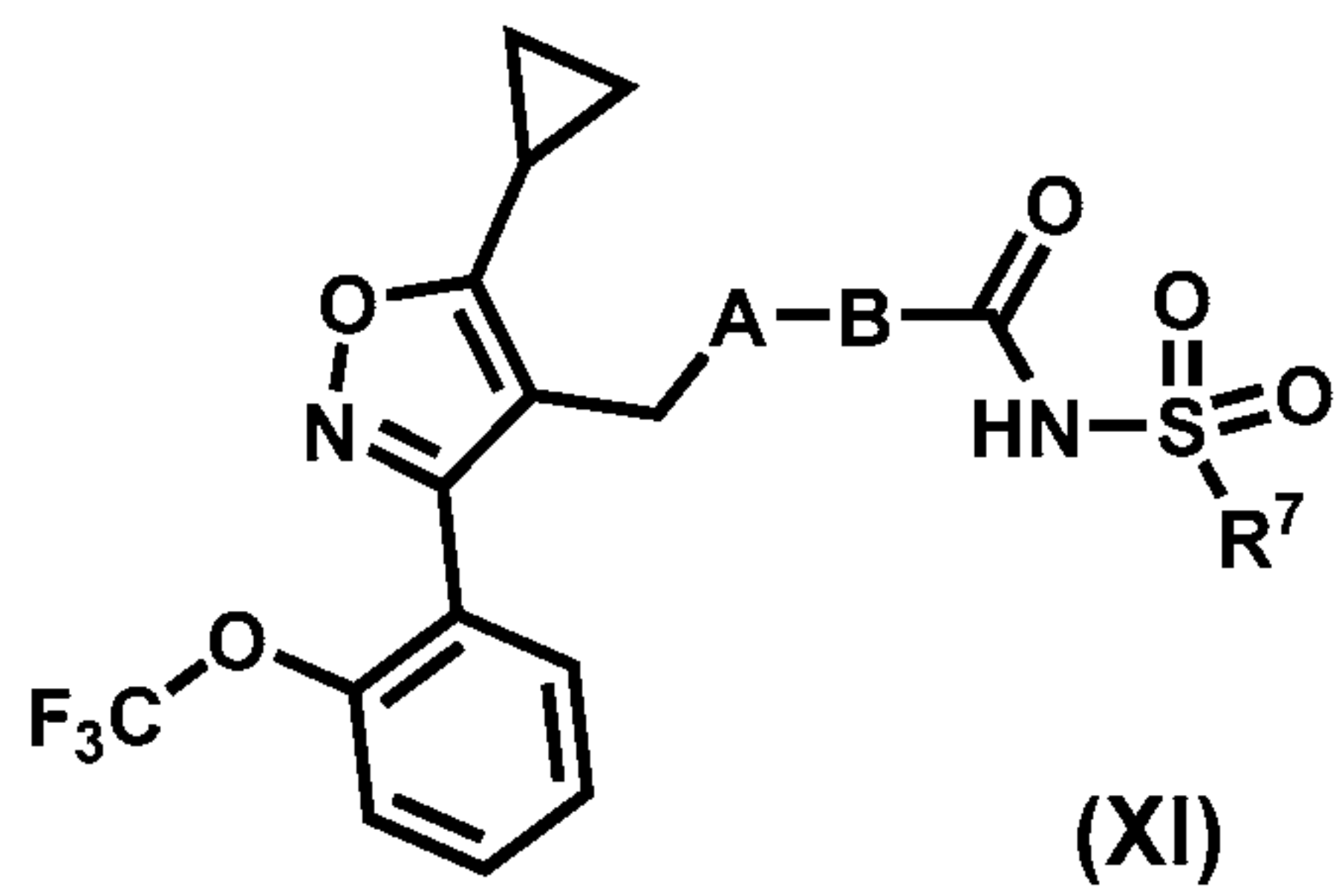
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693				694			
695				696			

In another embodiment, the compound of Formula (I) is represented by Formula (XI) or a pharmaceutically acceptable salt thereof:



5 wherein A, B, and R⁷ are as previously defined.

Representative compounds of the invention include, but are not limited to, compounds according to Formula (XI), and pharmaceutically acceptable salts thereof, wherein, A, B, and R⁷ are delineated for each compound in Table 4.



5

Table 4

Compound	A	B	R ⁷	Compound	A	B	R ⁷
701				702			
703				704			
705				706			
707				708			
709				710			
711				712			
713				714			
715				216			
717				718			
719				720			

721				722			
723				724			
725				726			
727				728			
729				730			
731				732			
733				734			
735				736			
737				738			
739				740			
741				742			
743				744			
745				746			
747				748			
749				750			
751				752			

753				754			
755				756			
757				758			
759				760			
761				762			
763				764			
765				766			
767				768			
769				770			
771				772			
773				774			
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781				782			
783				784			
785				786			
787				788			

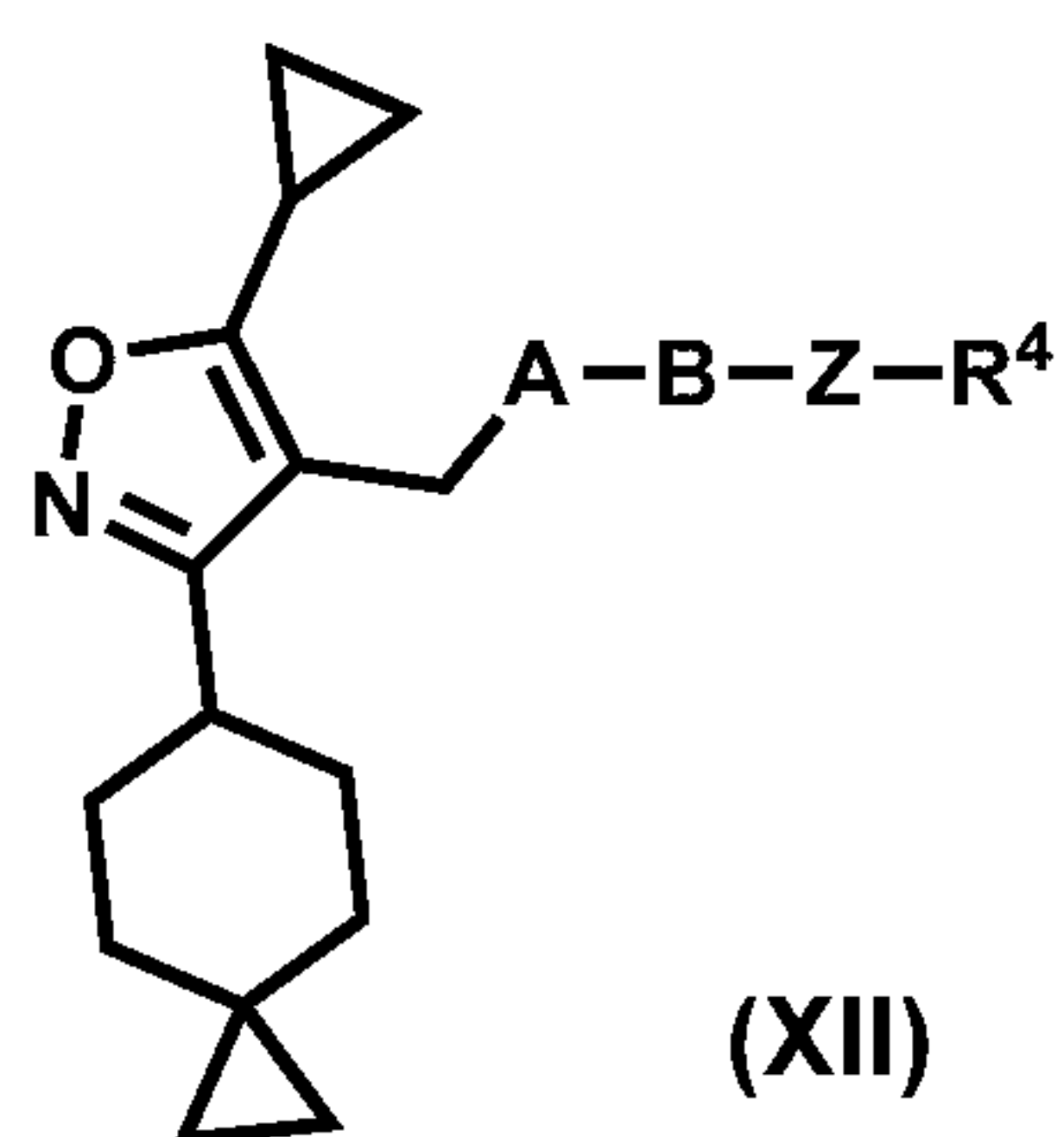
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791				792			
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795				796			
797				798			
799				800			
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805				806			
807				808			
809				810			
811				812			
813				814			
815				816			
817				818			
819				820			
821				822			
823				824			

825				826			
827				828			
829				830			
831				832			
833				834			
835				836			
837				838			
839				840			
841				842			
843				844			
845				846			
847				848			
849				850			
851				852			
853				854			
855				856			
857				858			
859				860			

861				862			
863				864			
865				866			
867				868			
869				870			
871				872			
873				874			
875				876			
877				878			
879				880			
881				882			
883				884			
885				886			
887				888			
889				890			
891				892			
893				894			
895				896			

897				898			
899				900			
900-1				900-2			
900-3				900-4			
900-5				900-6			
900-7				900-8			
900-9				900-10			
900-11				900-12			
900-13				900-14			
900-15							

In another embodiment, the compound of Formula (I) is represented by Formula (XII) or a pharmaceutically acceptable salt thereof:



5 wherein A, B, Z, and R⁴ are as previously defined.

Representative compounds of the invention include, but are not limited to, compounds according to Formula (XII), and pharmaceutically acceptable salts thereof, wherein A, B, and Z-R⁴ are delineated for each compound in Table 5.

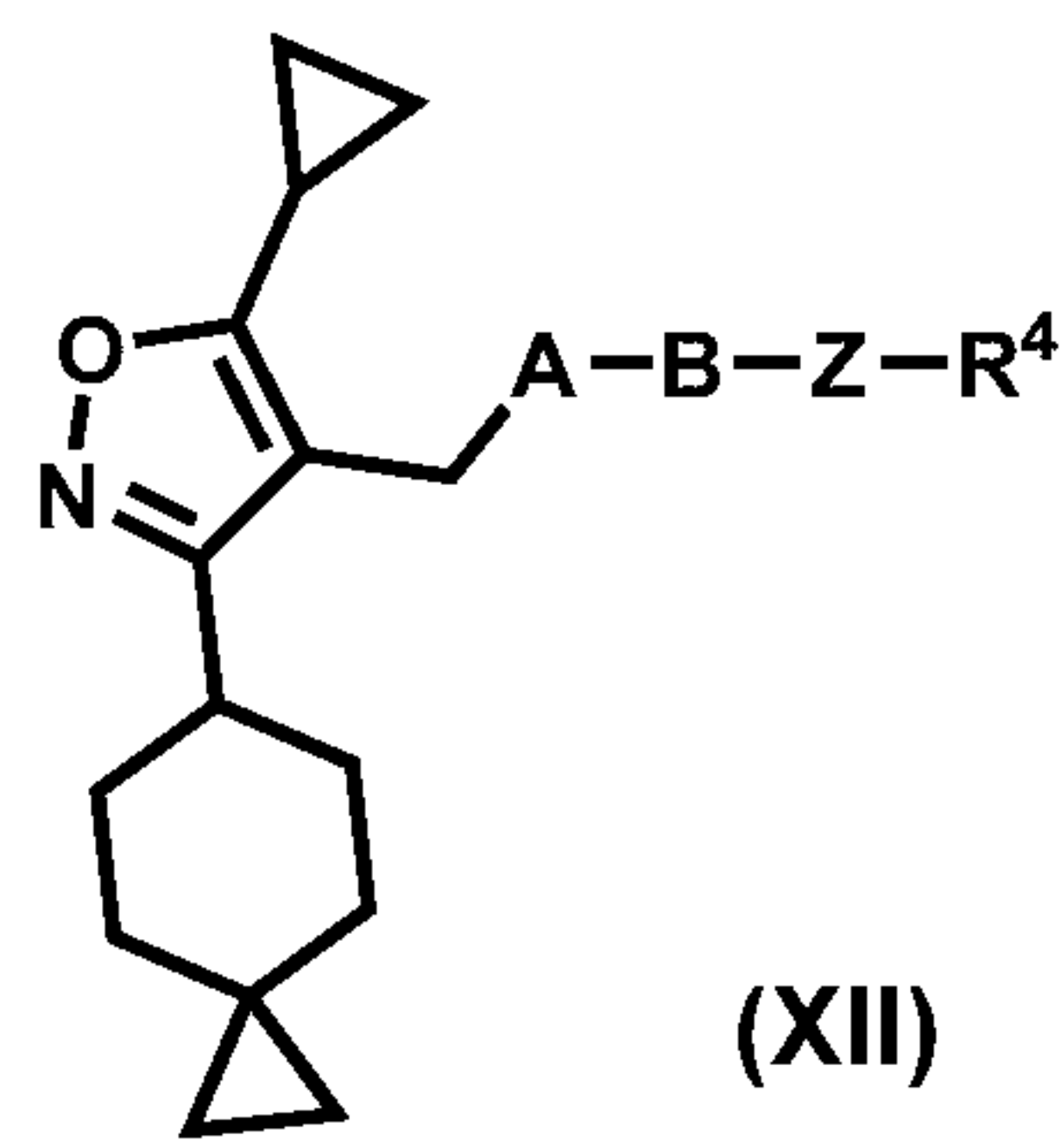
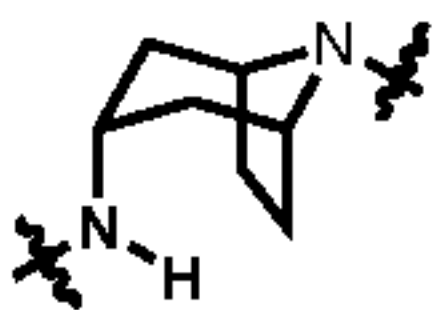
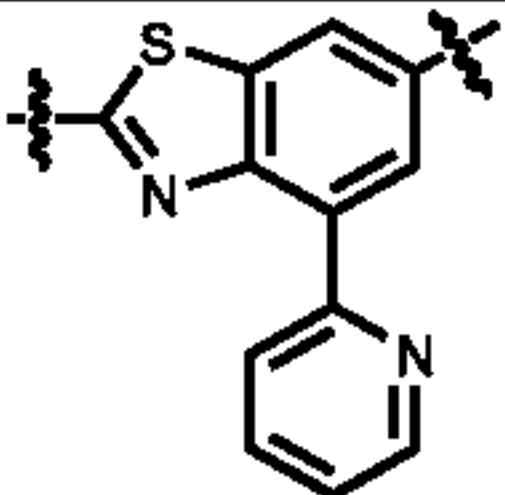
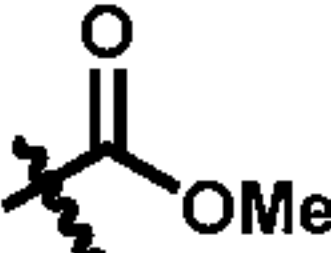
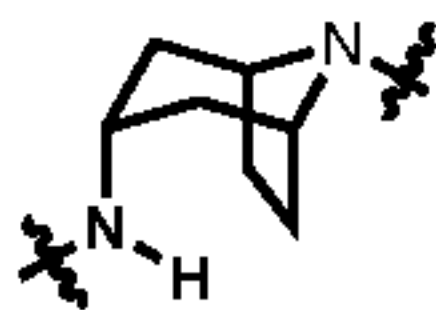
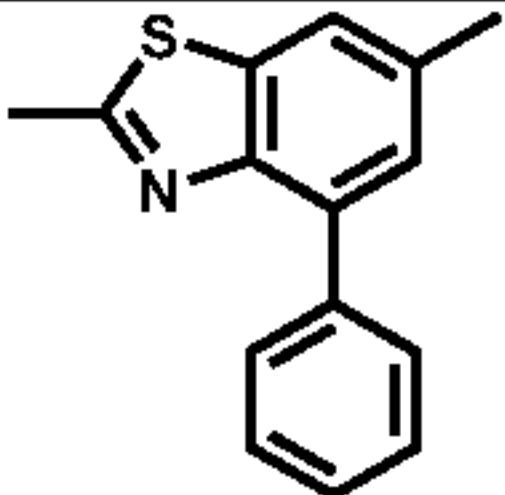
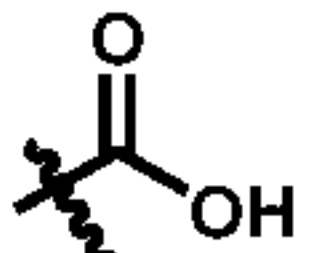
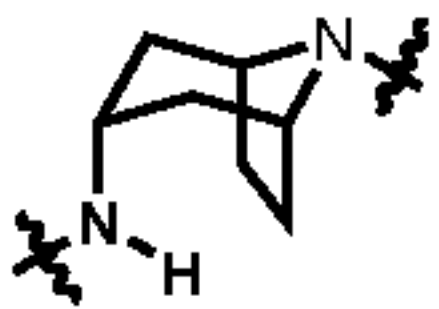
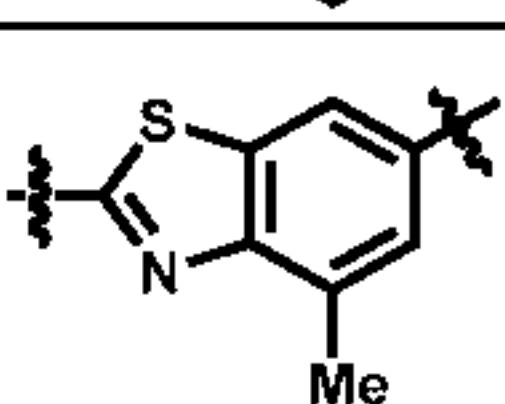
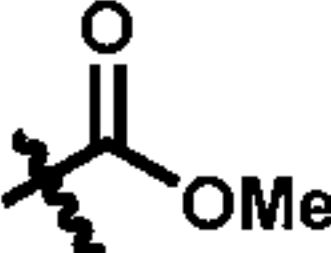
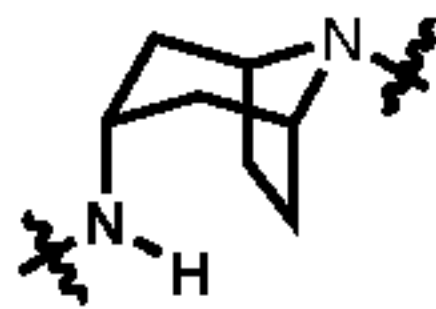
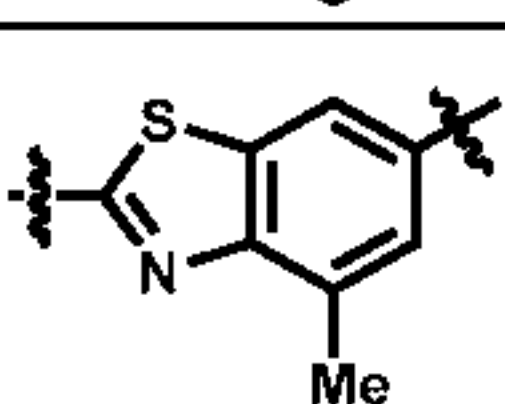
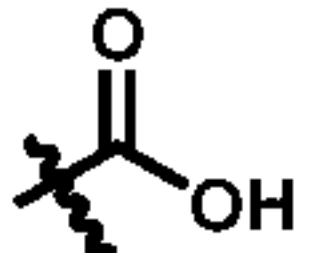
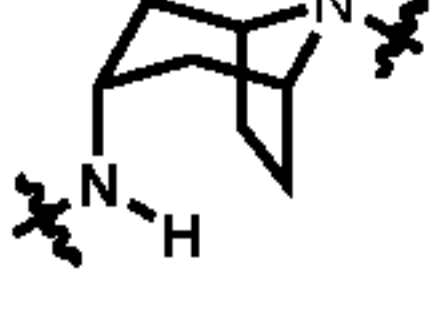
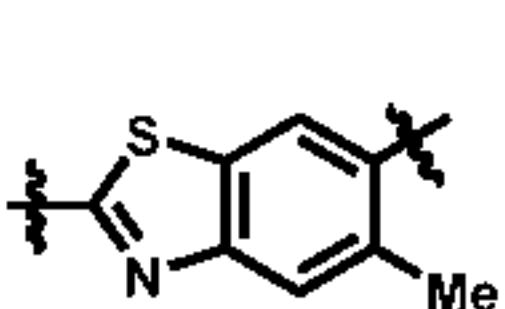
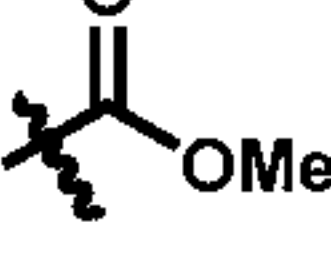
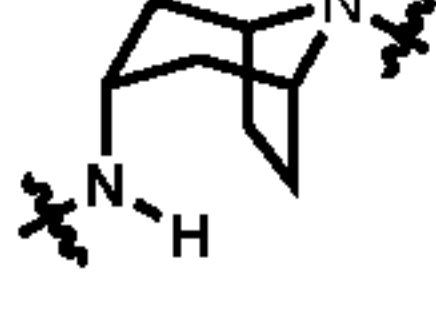
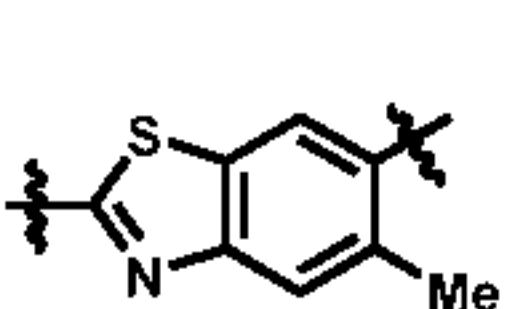
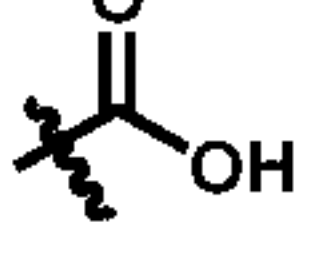
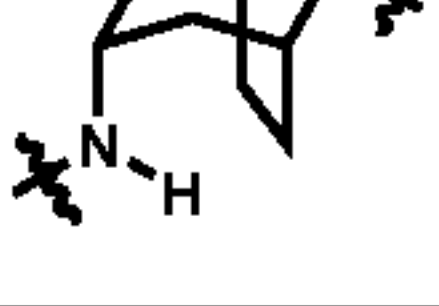
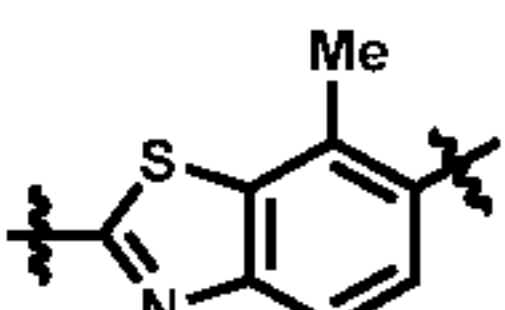
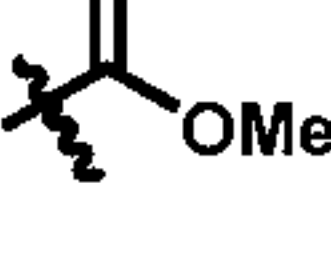
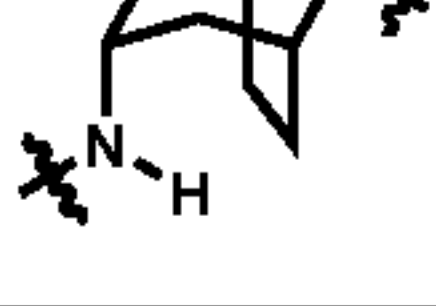
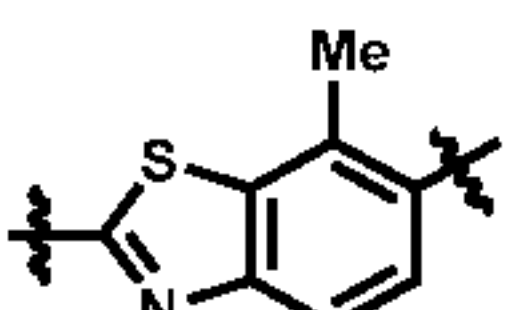
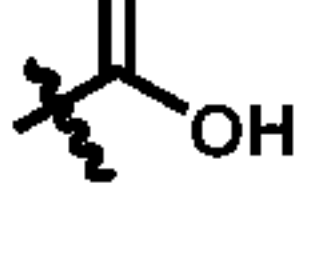
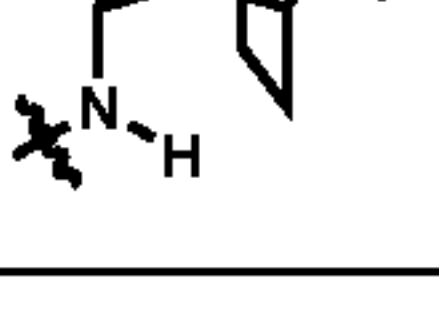
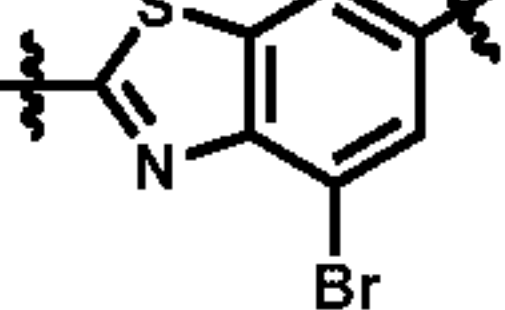
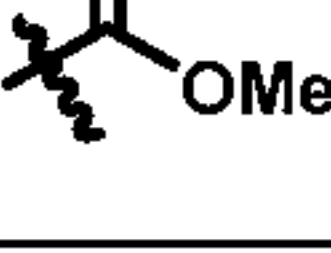
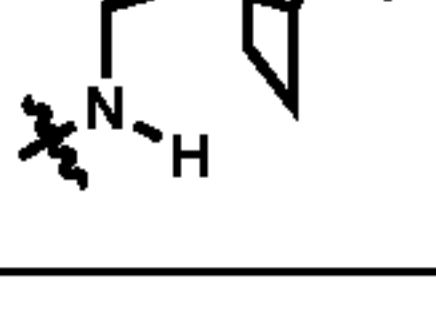
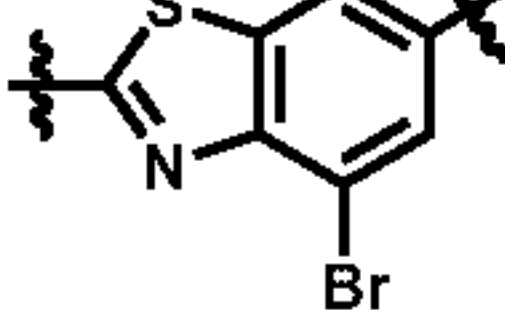
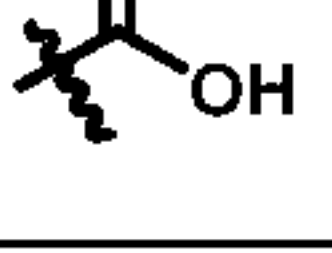
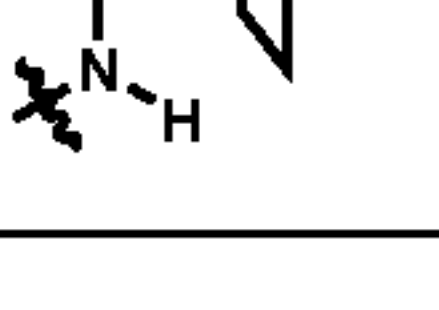
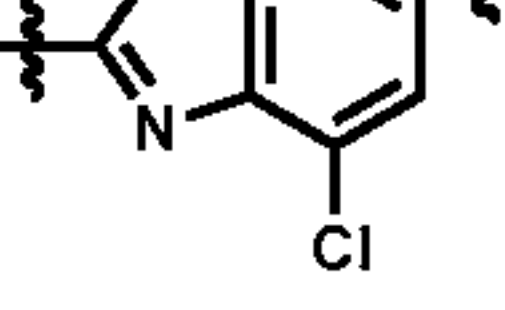
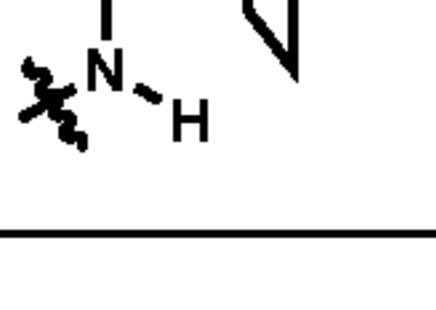
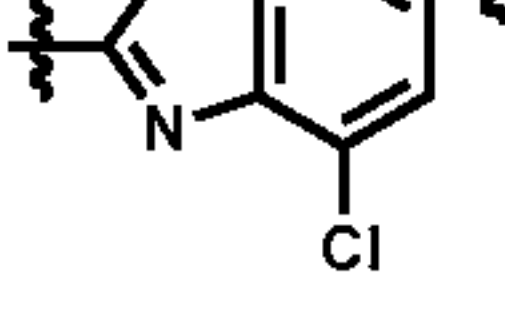
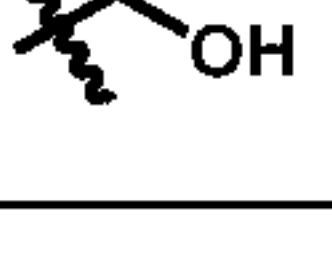
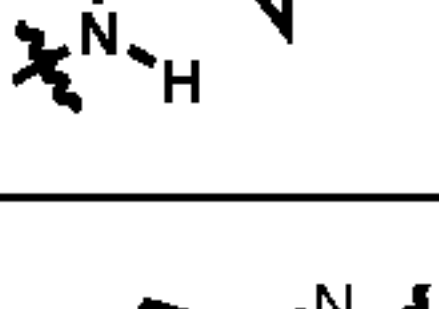
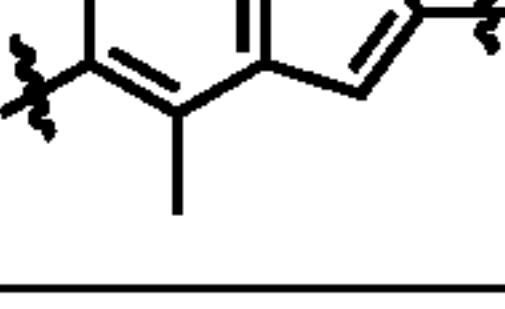
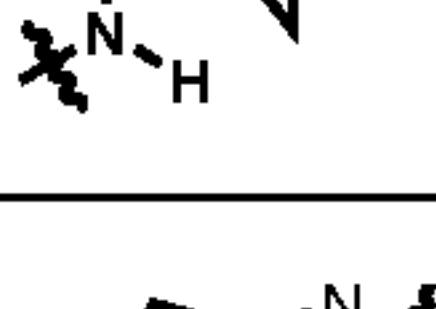
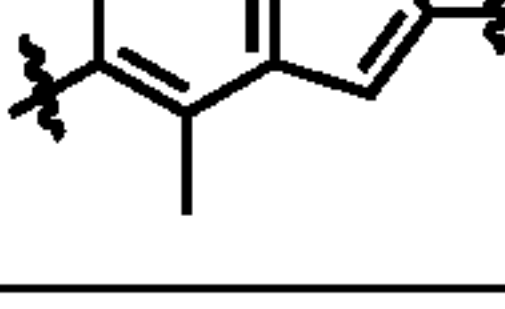
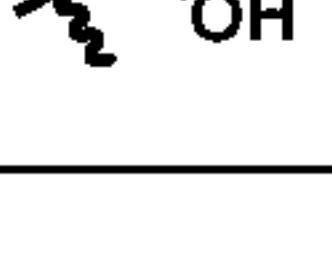
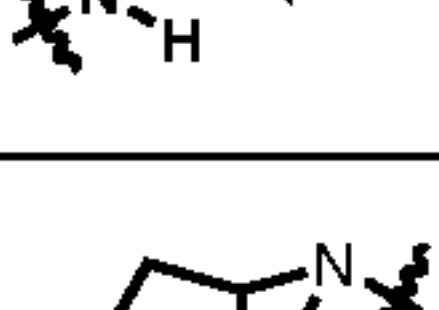
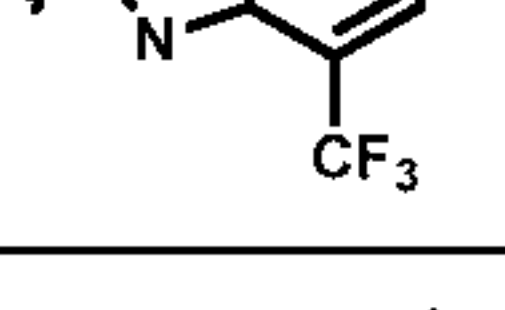
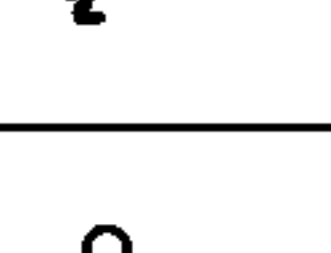
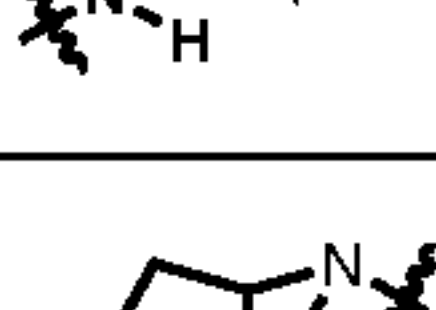
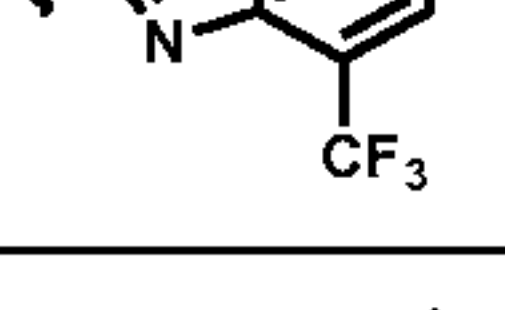
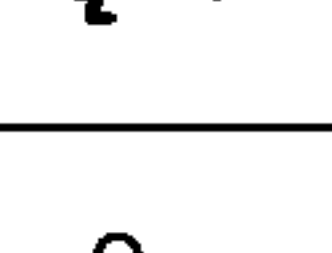
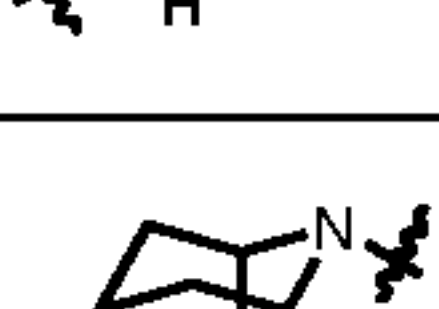
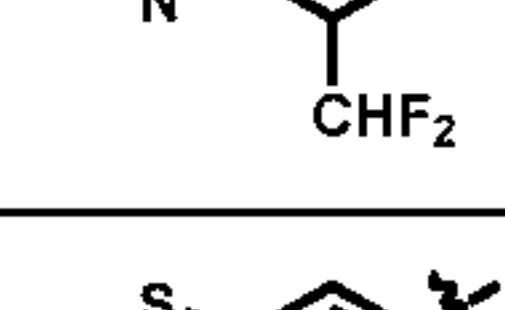
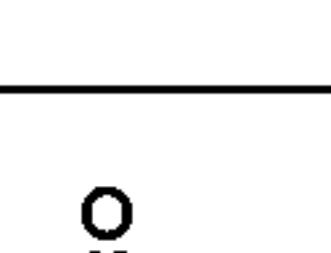
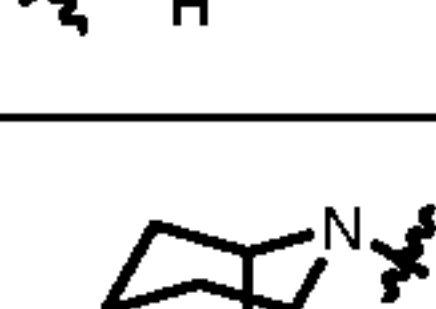
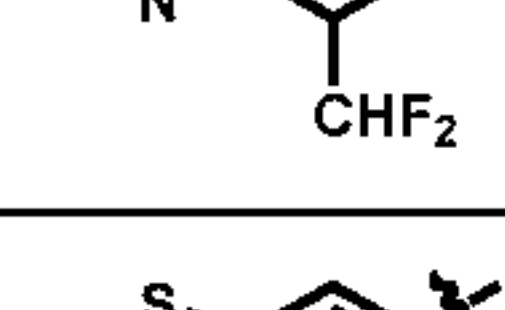
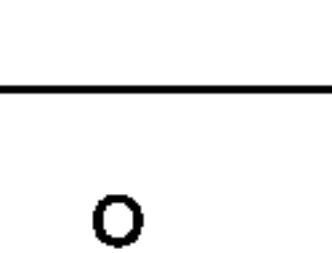
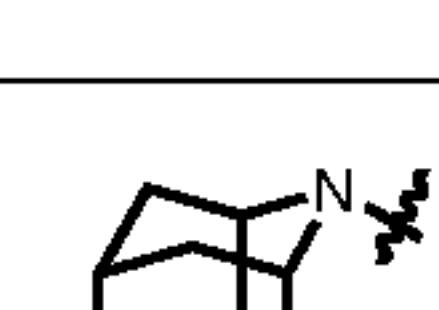
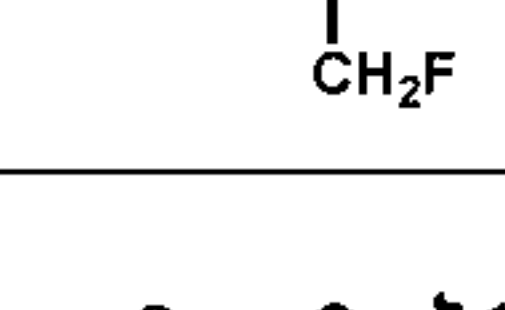
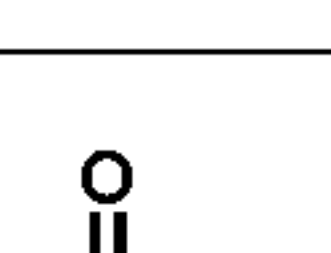
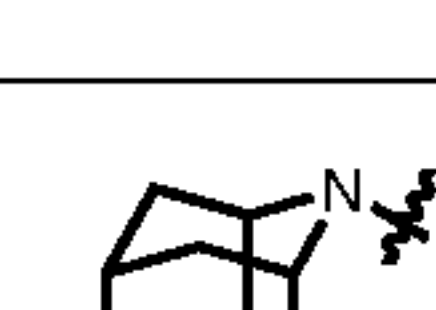
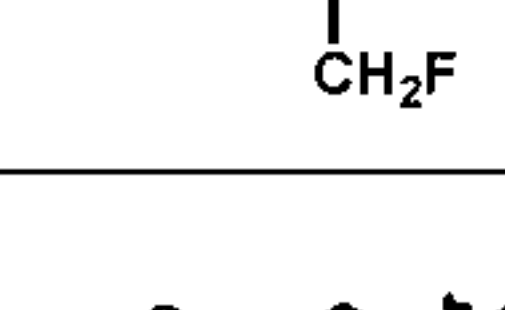
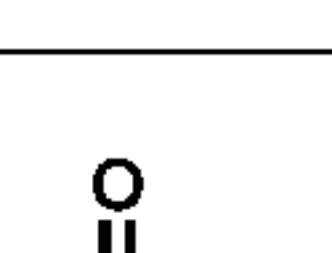
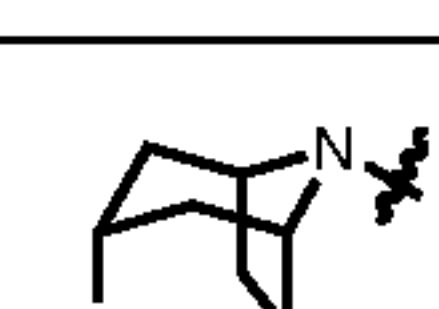
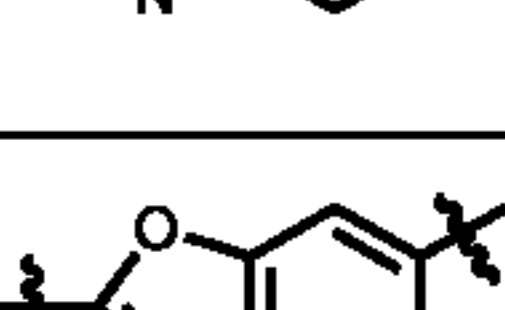
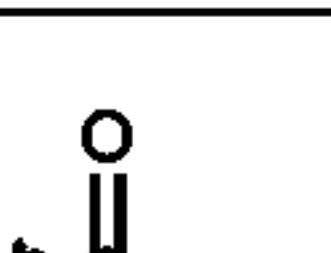
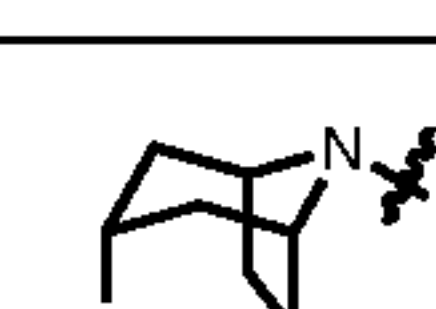
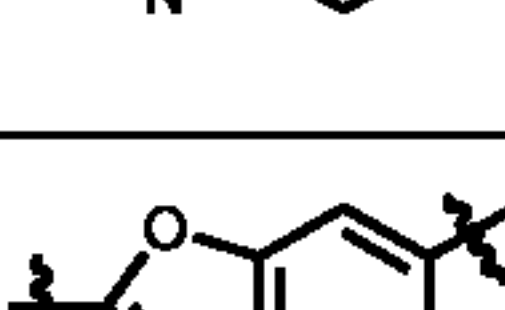
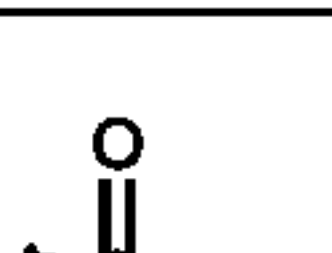
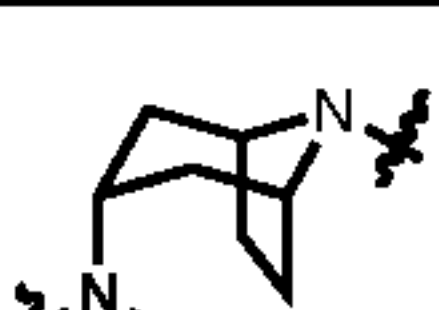
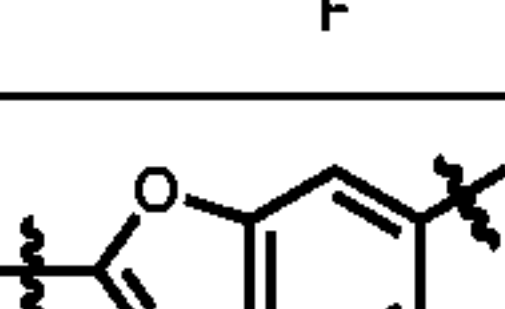
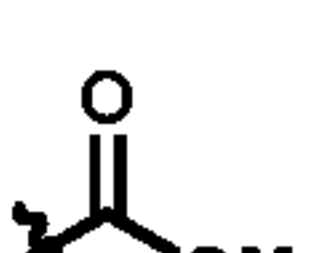
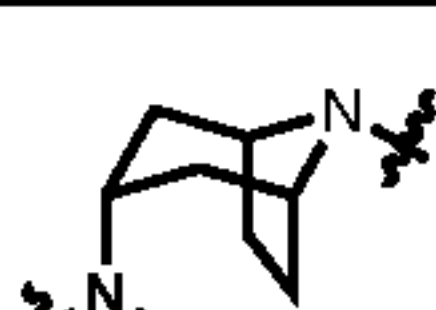
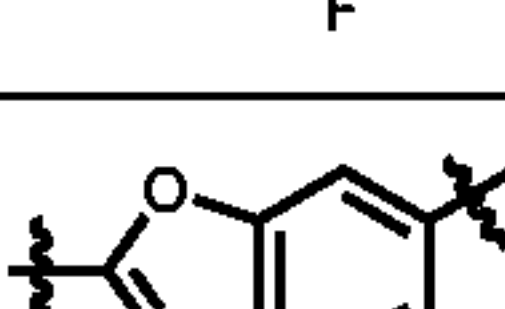
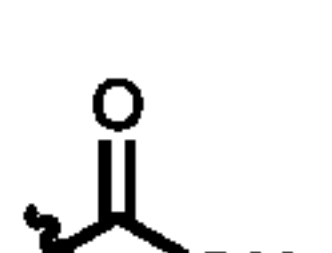
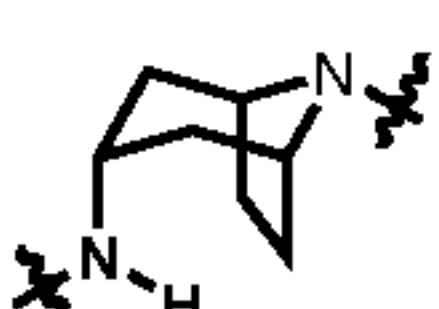
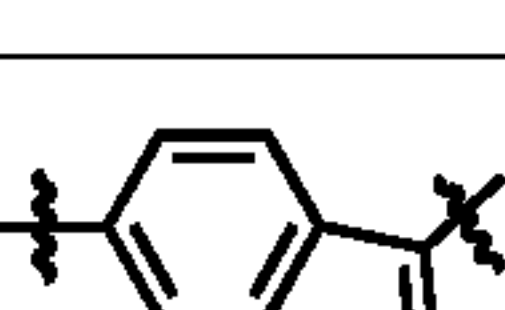
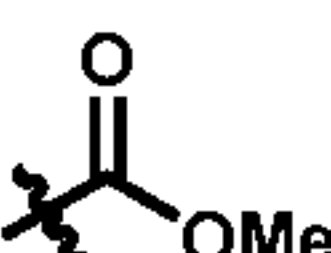
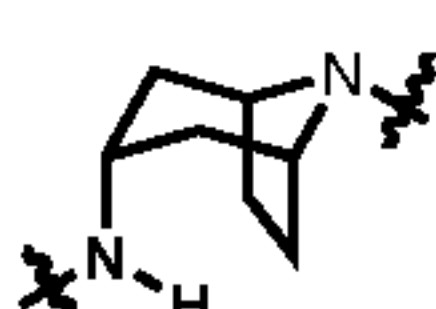
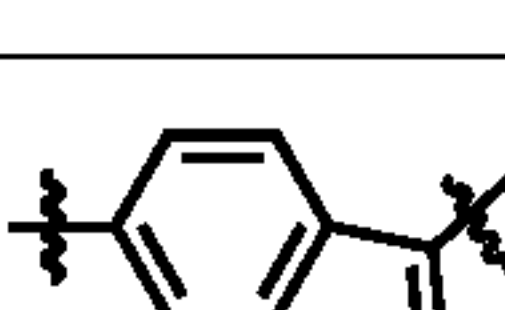
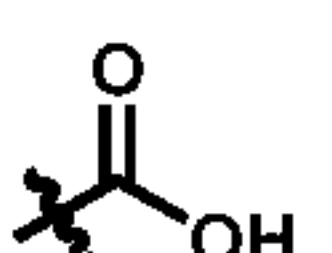
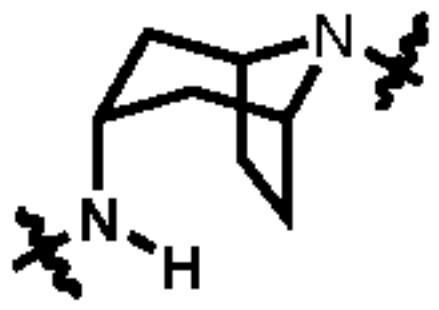
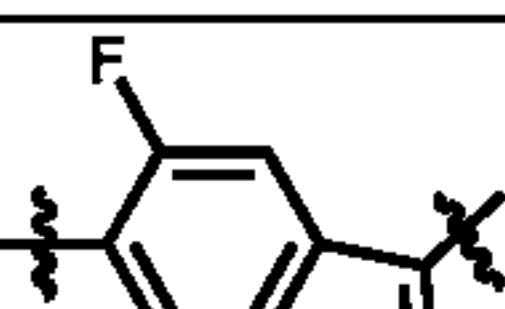
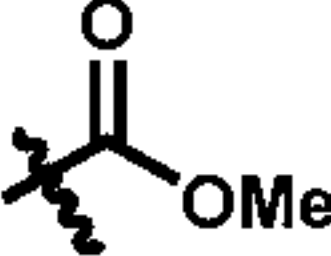
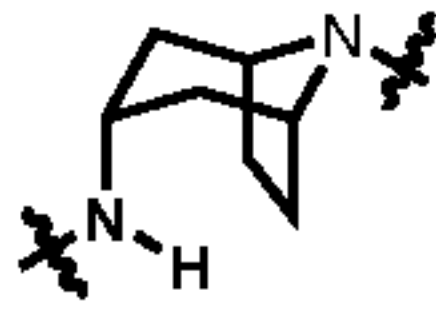
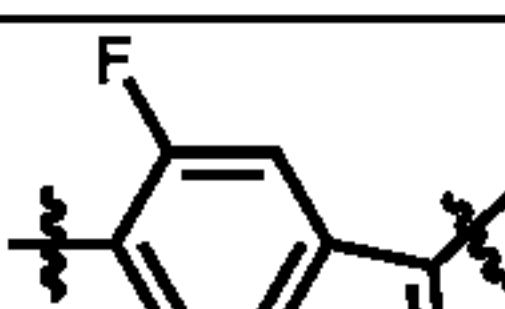
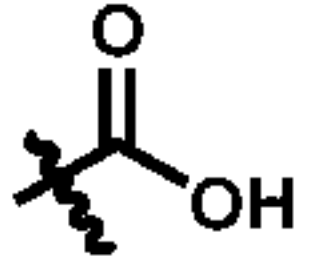


Table 5

Compound	A	B		Compound	A	B	
901				902			
903				904			
905				906			
907				908			
909				910			
911				912			
913				914			
915				916			
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989				990			
991				992			
993				994			
995				996			
997				998			
999				1000			
1001				1002			
1003				1004			
1005				1006			
1007				1008			
1009				1010			
1011				1012			

1013				1014			
1015				1016			
1017				1018			
1019				1020			
1021				1022			
1023				1024			
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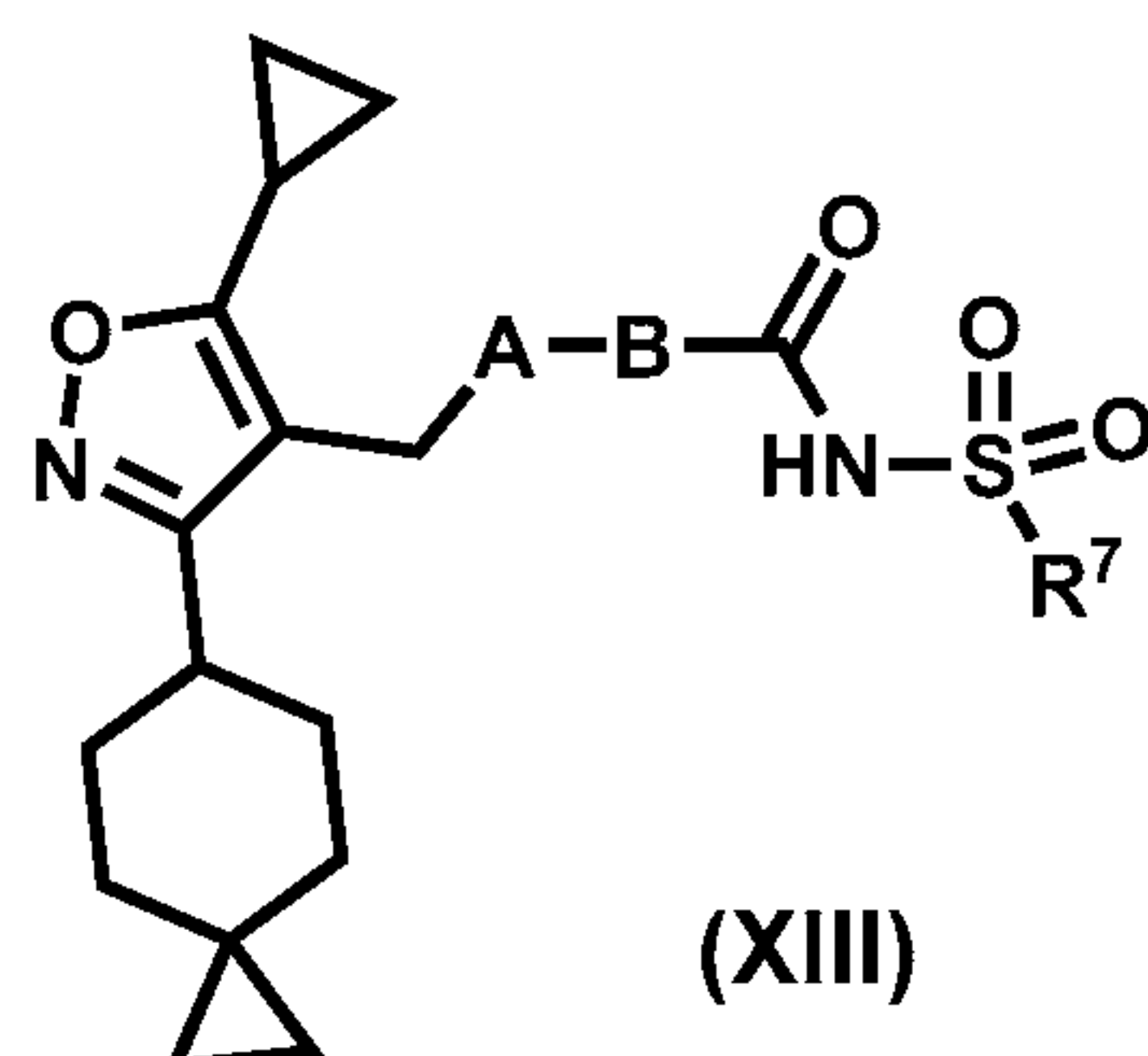
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1099				1100			
1101				1102			

1103				1104			
1105				1106			
1107				1108			
1109				1110			
1111				1112			
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1115				1116			
1117				1118			
1119				1120			
1121				1122			
1123				1124			
1125				1126			
1127				1128			
1129				1130			
1131				1132			

1133				1134			
1135				1136			

In another embodiment, the compound of Formula (I) is represented by Formula (XIII) or a pharmaceutically acceptable salt thereof:



5 wherein A, B, and R⁷ are as previously defined.

Representative compounds of the invention include, but are not limited to, compounds according to Formula (XIII), and pharmaceutically acceptable salts thereof, wherein, A, B, and R⁷ are delineated for each compound in Table 6.

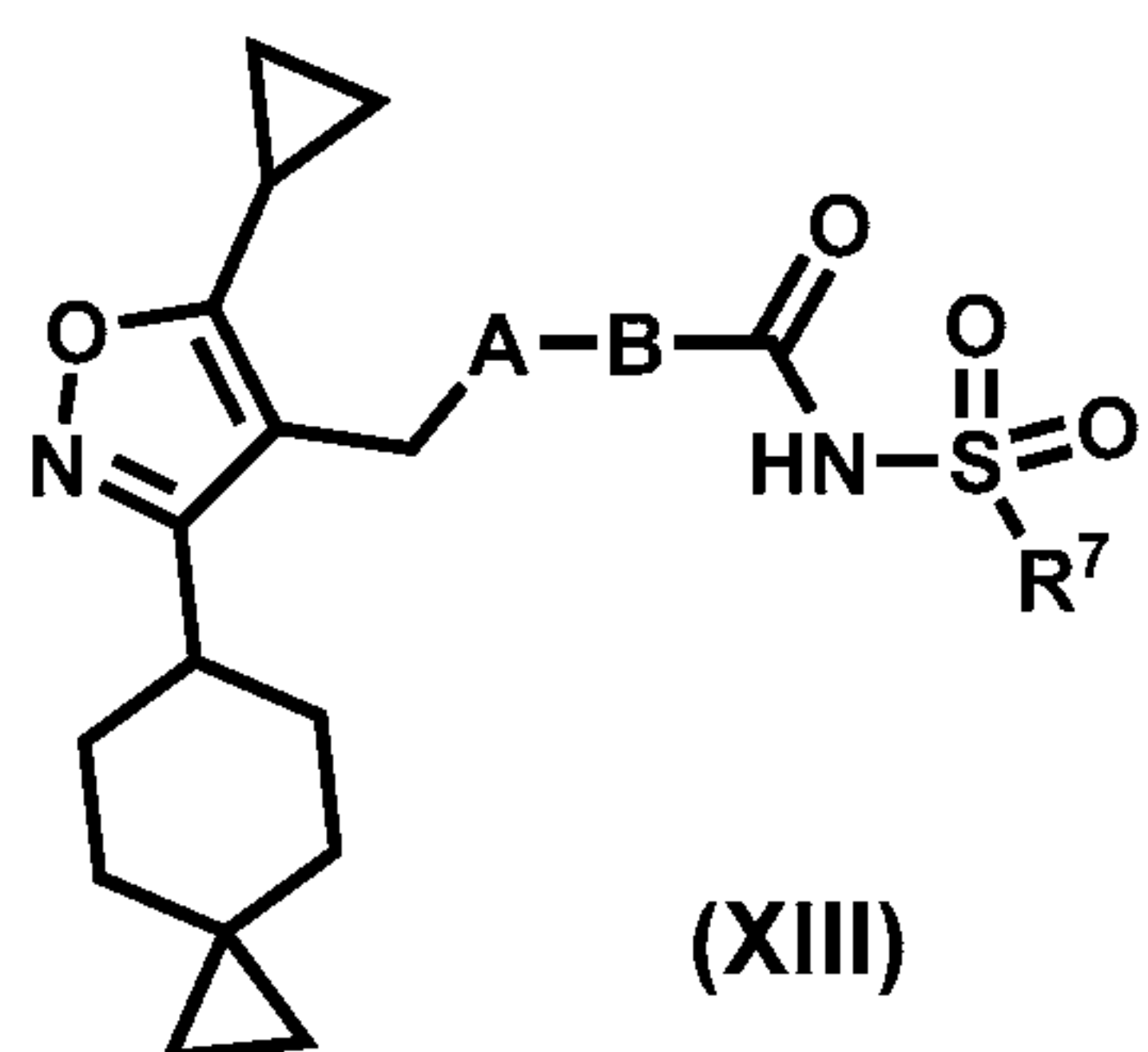


Table 6

Compound	A	B	R ⁷	Compound	A	B	R ⁷
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1203				1204			
1205				1206			

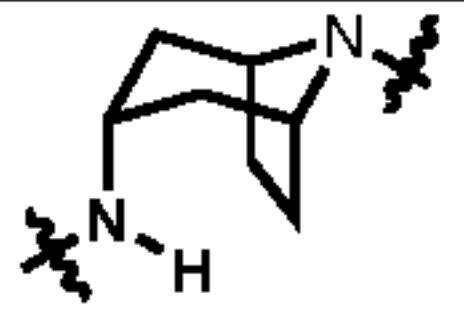
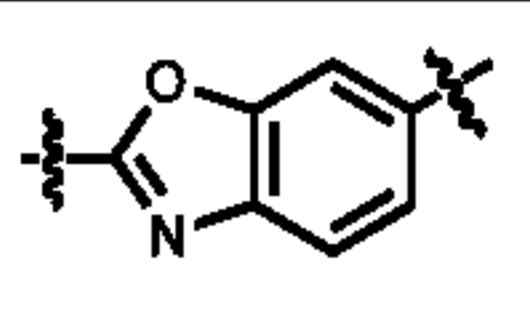
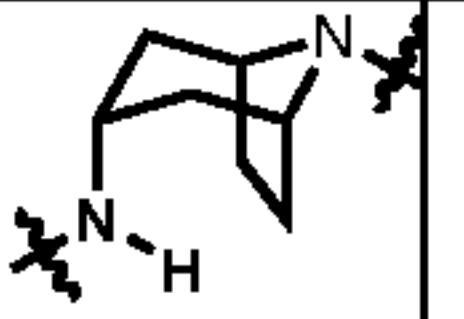
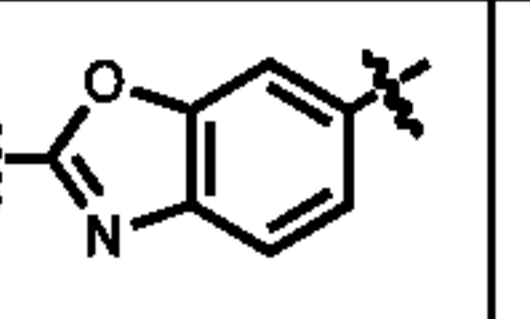
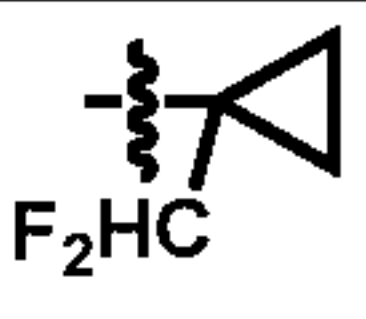
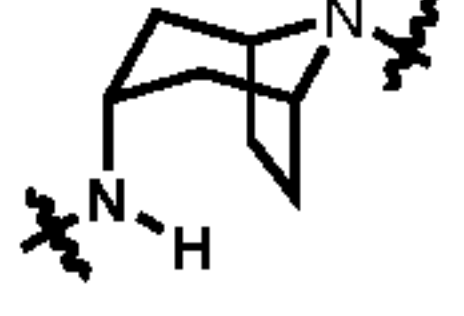
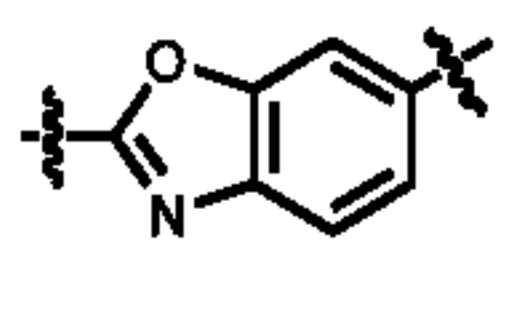
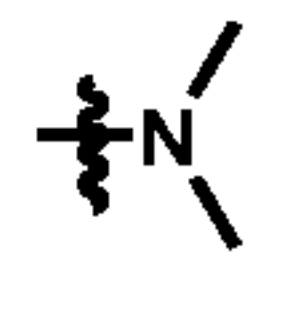
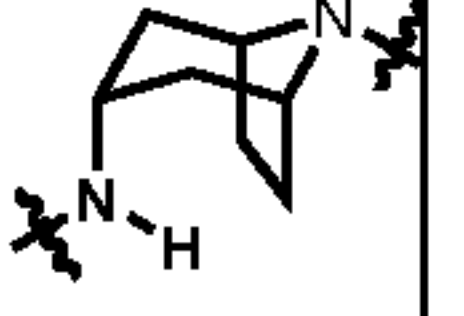
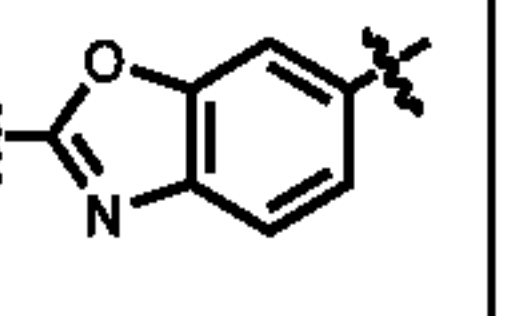
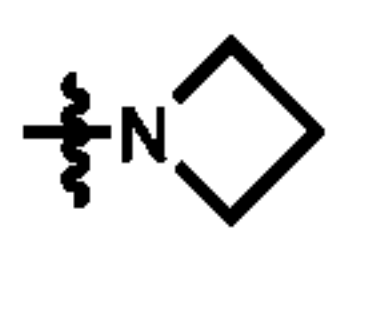
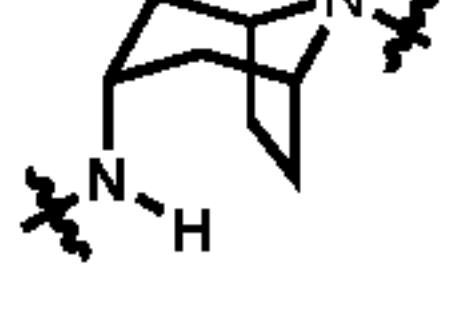
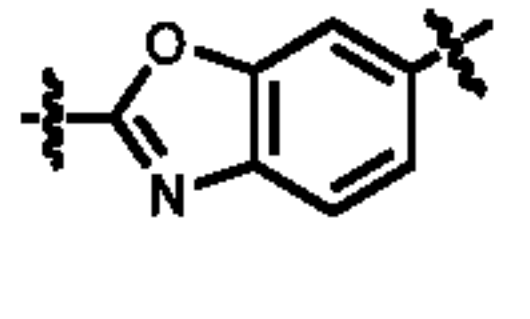
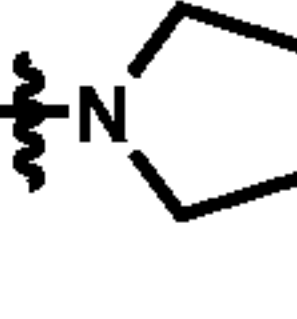
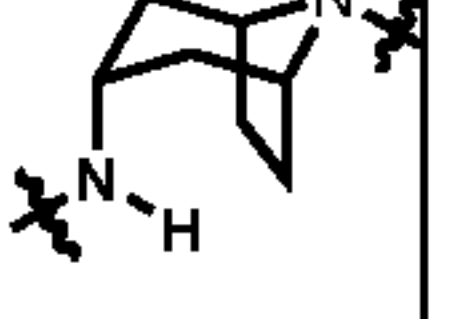
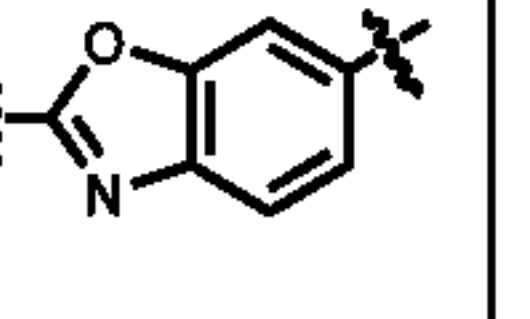
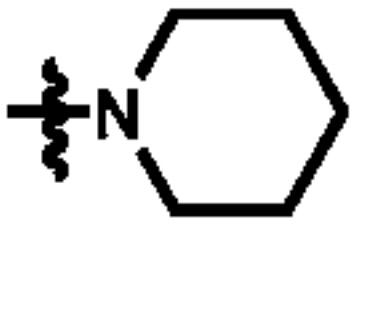
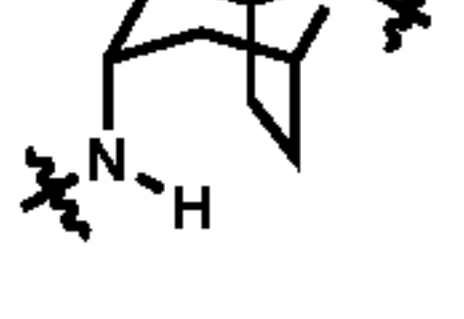
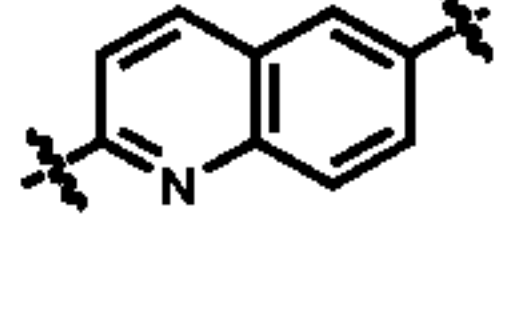
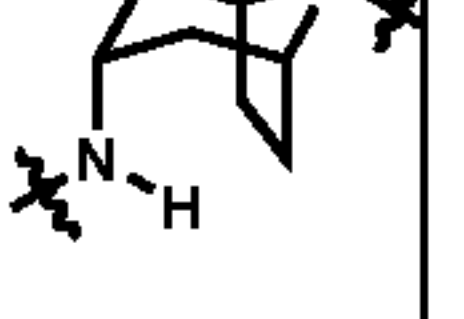
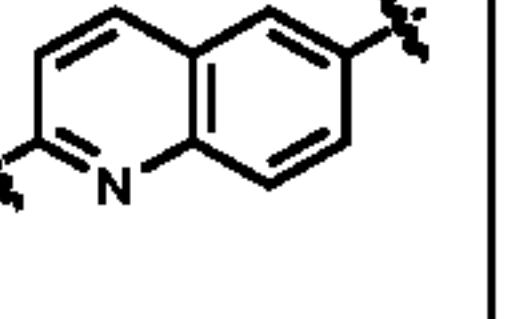
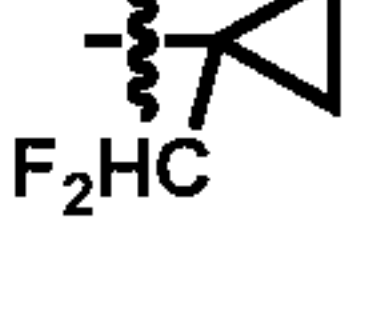
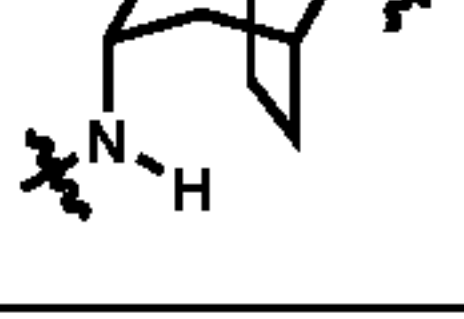
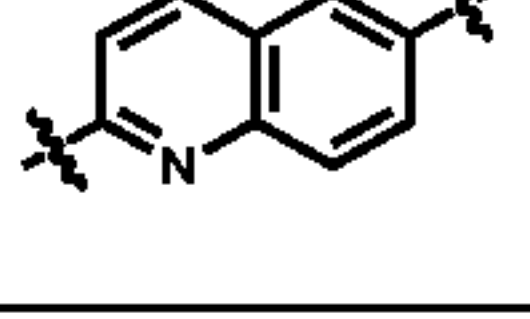
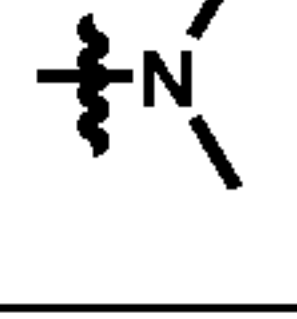
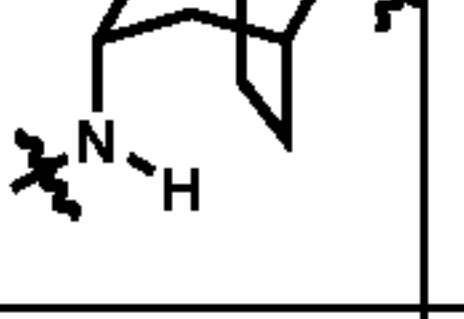
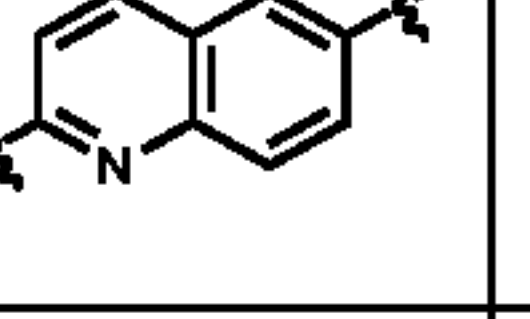
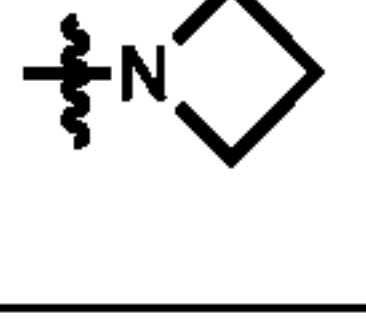
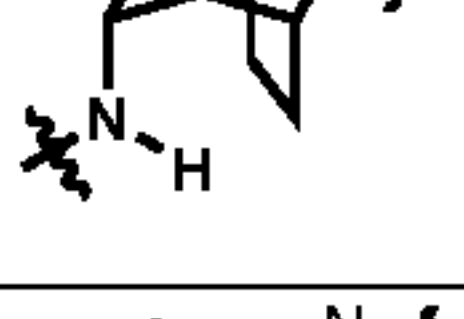
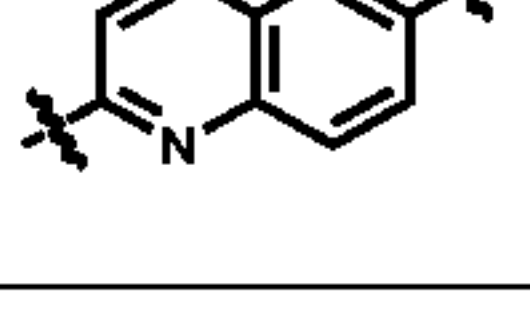
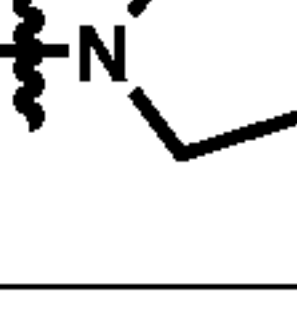
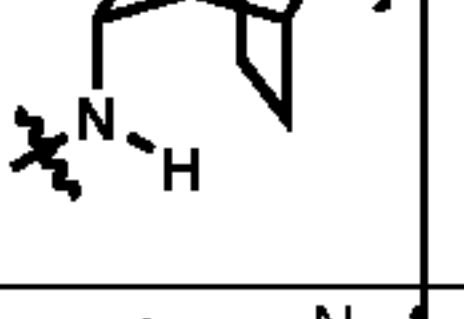
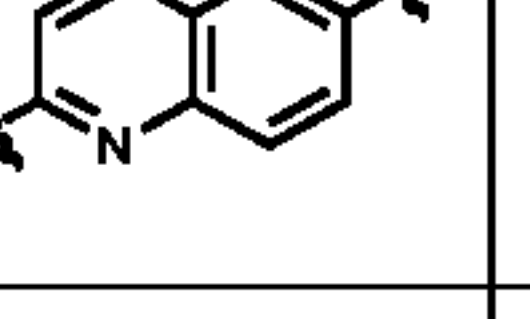
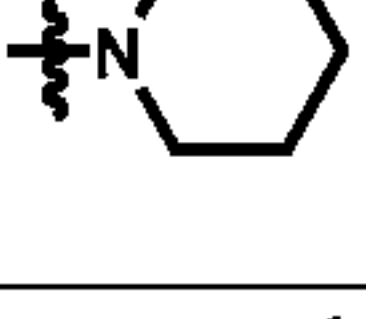
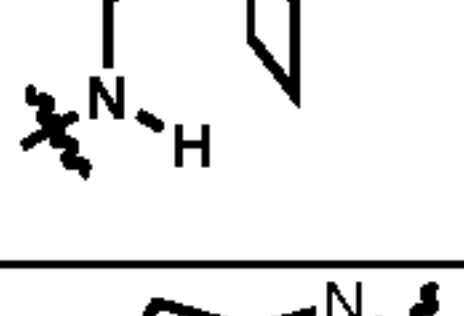
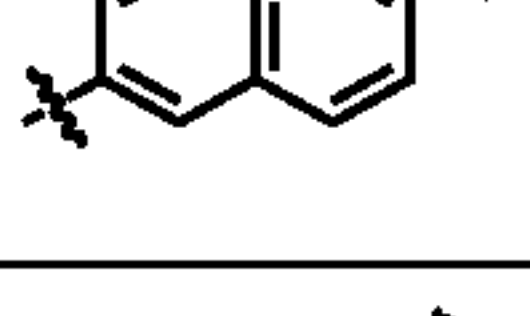
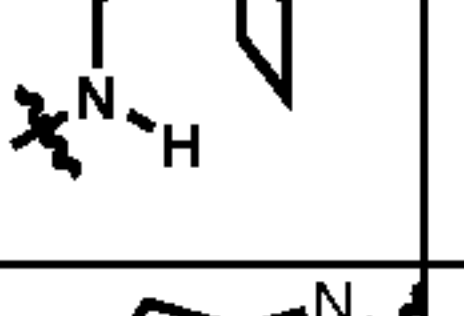
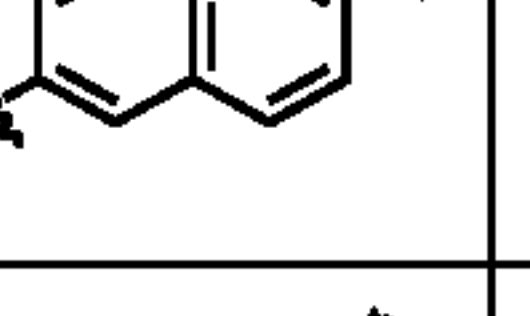
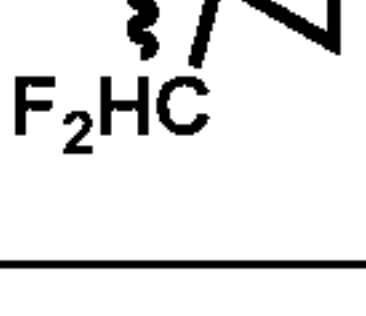
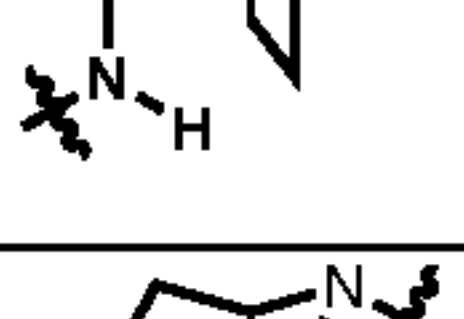
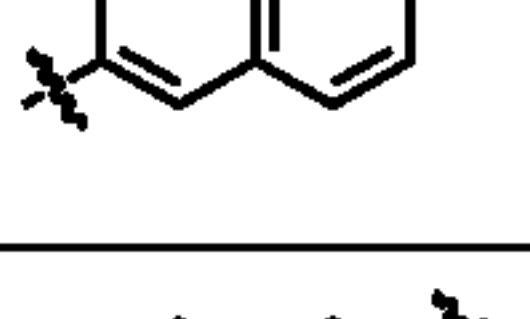
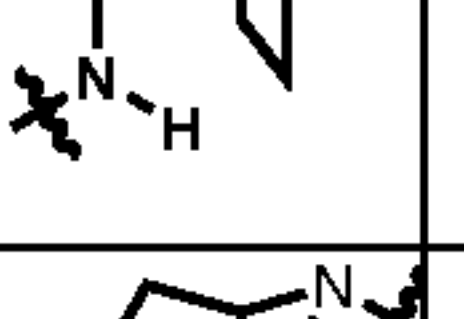
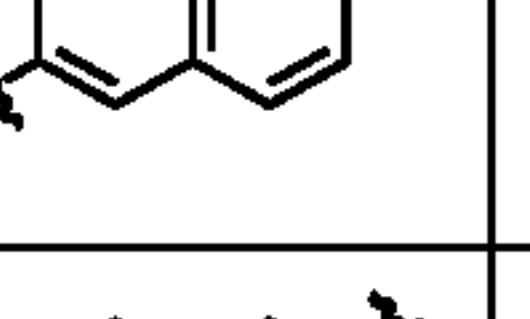
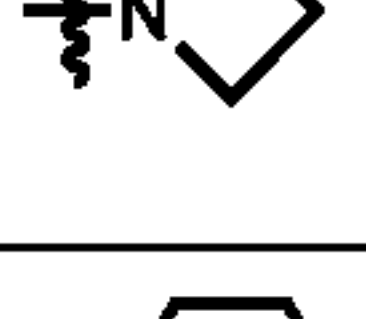
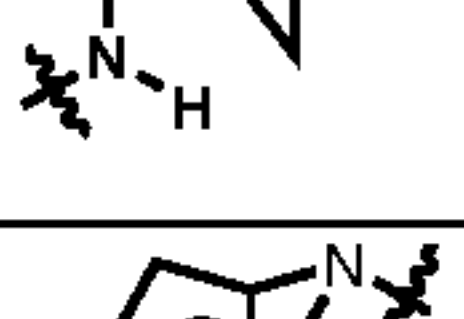
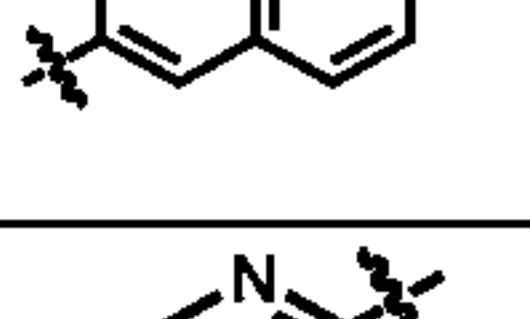
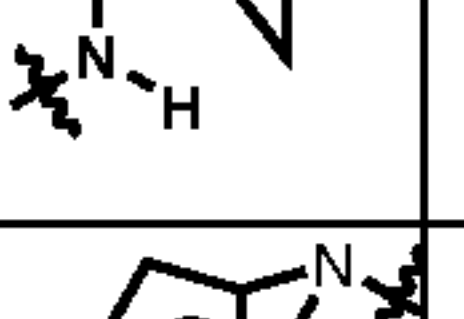
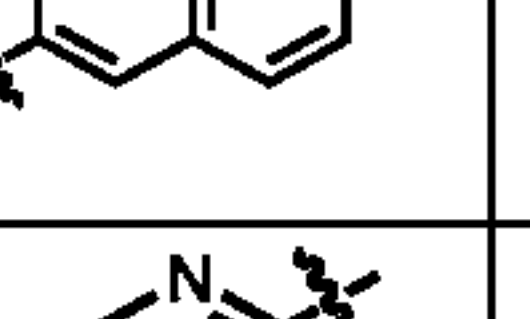
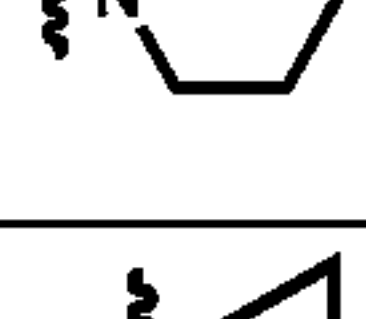
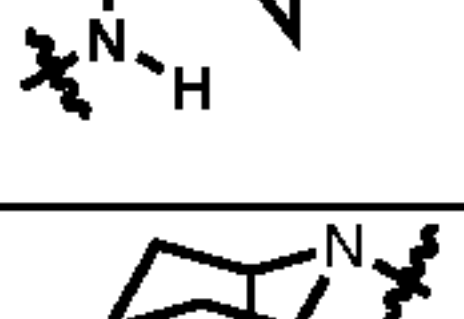
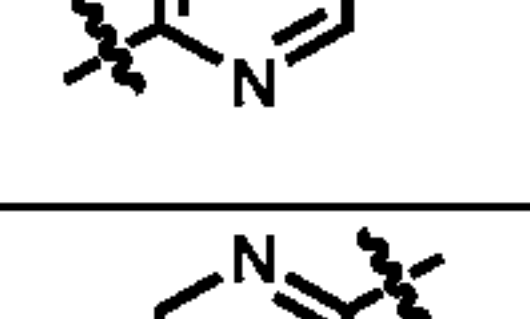
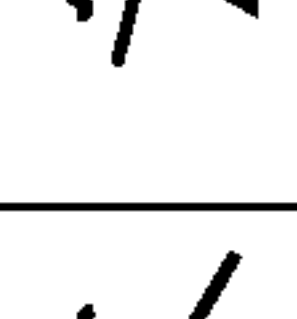
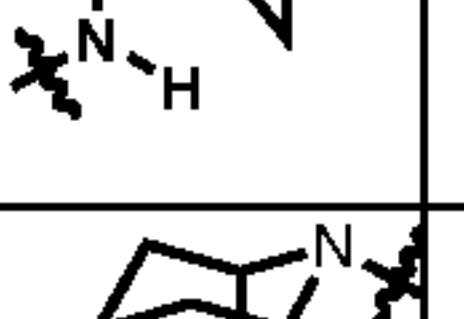
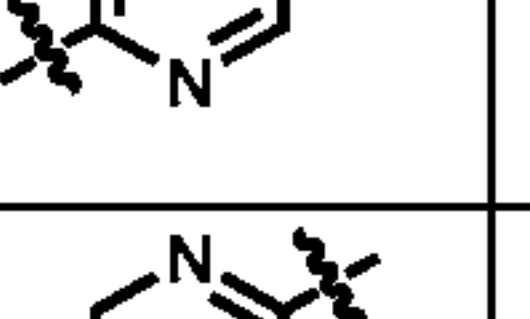
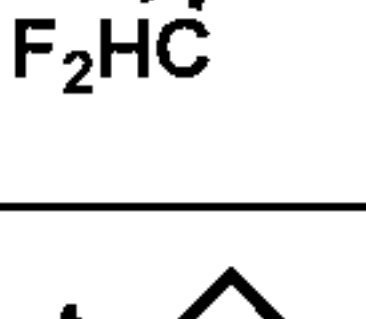
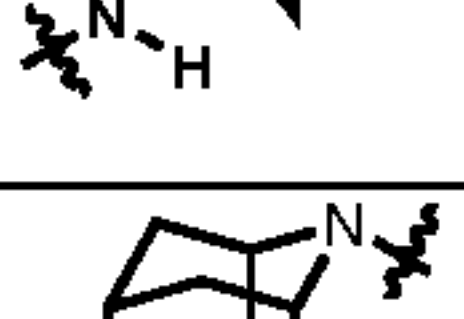
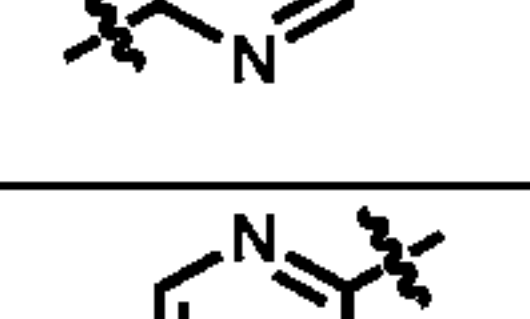
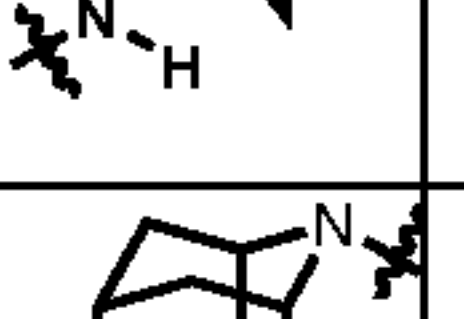
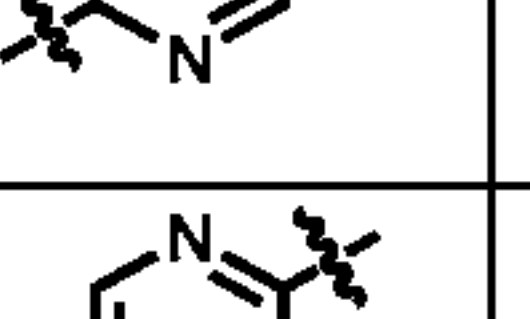
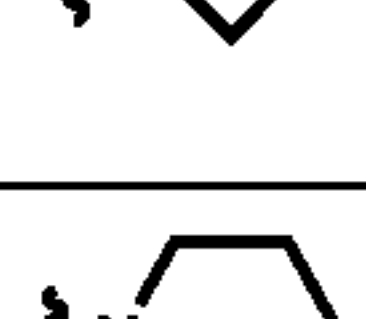
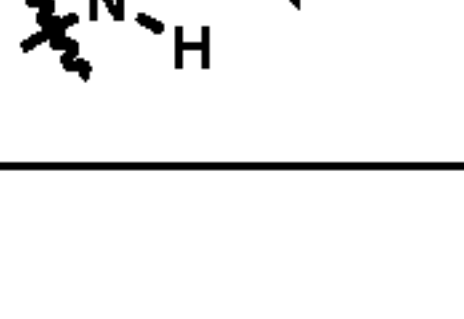
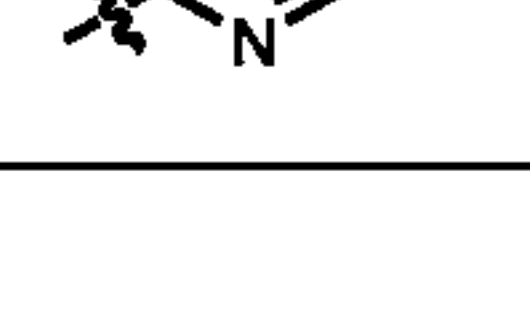
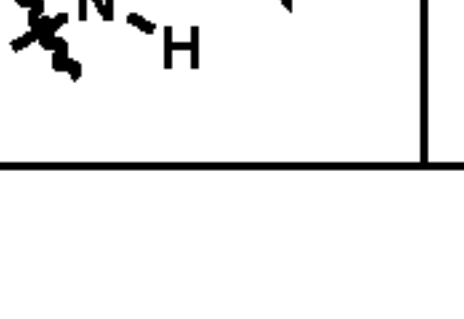
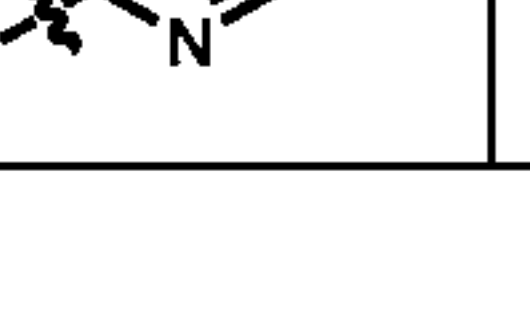
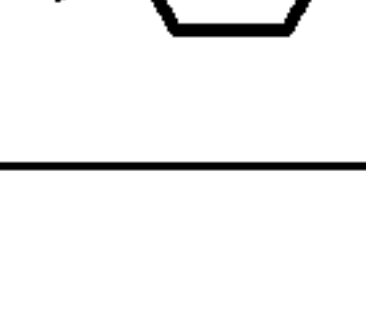
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It will be appreciated that the description of the present invention herein should be construed in congruity with the laws and principles of chemical bonding. In some instances, it may be necessary to remove a hydrogen atom in order to accommodate a substituent at any given location.

It will be yet appreciated that the compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic, diastereoisomeric, and optically active forms. It will still be appreciated that certain compounds of the present invention may exist in different tautomeric forms. All tautomers are contemplated to be within the scope of the present invention.

In certain embodiments, the present invention provides a method for the prevention or treatment of an FXR mediated disease or condition. The method comprises administering

a therapeutically effective amount of a compound of Formula (I). The present invention also provides the use of a compound of Formula (I) for the preparation of a medicament for the prevention or treatment of an FXR mediated disease or condition.

In certain embodiments, the FXR-mediated disease or condition is cardiovascular disease, atherosclerosis, arteriosclerosis, hypercholesterolemia, or hyperlipidemia chronic liver disease, gastrointestinal disease, fibrotic diseases such as primary biliary cirrhosis, primary sclerosing cholangitis, pulmonary fibrosis, renal fibrosis, liver fibrosis, renal disease, metabolic disease, cancer (i.e., colorectal cancer), or neurological indications such as stroke.

In certain embodiments, the chronic liver disease is primary biliary cirrhosis (PBC), cerebrotendinous xanthomatosis (CTX), primary sclerosing cholangitis (PSC), drug induced cholestasis, intrahepatic cholestasis of pregnancy, parenteral nutrition associated cholestasis (PNAC), bacterial overgrowth or sepsis associated cholestasis, autoimmune hepatitis, chronic viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), liver transplant associated graft versus host disease, living donor transplant liver regeneration, congenital hepatic fibrosis, choledocholithiasis, granulomatous liver disease, intra- or extrahepatic malignancy, Sjogren's syndrome, Sarcoidosis, Wilson's disease, Gaucher's disease, hemochromatosis, or alpha 1-antitrypsin deficiency. In certain embodiments, the gastrointestinal disease is inflammatory bowel disease (IBD) (including Crohn's disease and ulcerative colitis), irritable bowel syndrome (IBS), bacterial overgrowth, malabsorption, post-radiation colitis, or microscopic colitis.

In certain embodiments, the renal disease is diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), hypertensive nephrosclerosis, chronic glomerulonephritis, chronic transplant glomerulopathy, chronic interstitial nephritis, or polycystic kidney disease.

In certain embodiments, the cardiovascular disease is atherosclerosis, arteriosclerosis, dyslipidemia, hypercholesterolemia, or hypertriglyceridemia.

In certain embodiments, the metabolic disease is insulin resistance, Type I and Type II diabetes, or obesity.

In one aspect, the compound is a selective FXR agonist over TGR5 activator.

Yet a further aspect of the present invention is a process of making any of the compounds delineated herein employing any of the synthetic means delineated herein.

It should be understood that the compounds encompassed by the present invention are those that are suitably stable for use as pharmaceutical agent.

DEFINITIONS

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

5 The term "alkyl", as used herein, refers to a saturated, monovalent straight- or branched-chain hydrocarbon group. Preferred alkyl radicals include C₁-C₆ alkyl and C₁-C₈ alkyl radicals. Examples of C₁-C₆ alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, *n*-hexyl groups; and examples of C₁-C₈ alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, 10 neopentyl, *n*-hexyl, heptyl, and octyl groups.

 The term "alkenyl", as used herein, denote a monovalent group derived from a hydrocarbon moiety by the removal of a single hydrogen atom wherein the hydrocarbon moiety has at least one carbon-carbon double bond. Preferred alkenyl groups include C₂-C₆ alkenyl and C₂-C₈ alkenyl groups. Alkenyl groups include, but are not limited to, for 15 example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, heptenyl, octenyl and the like.

 The term "alkynyl", as used herein, denotes a monovalent group derived from a hydrocarbon moiety by the removal of a single hydrogen atom wherein the hydrocarbon moiety has at least one carbon-carbon triple bond. Preferred alkynyl groups include C₂-C₆ alkynyl and C₂-C₈ alkynyl groups. Representative alkynyl groups include, but are not limited 20 to, for example, ethynyl, 1-propynyl, 1-butynyl, heptynyl, octynyl and the like.

 The term "cycloalkyl", as used herein, refers to a monocyclic or polycyclic saturated carbocyclic ring or a bi- or tri-cyclic group fused, bridged or spiro system, and the carbon atoms may be optionally oxo-substituted or optionally substituted with exocyclic olefinic double bond. Preferred cycloalkyl groups include C₃-C₈ cycloalkyl and C₃-C₁₂ cycloalkyl 25 groups. Examples of C₃-C₈-cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl and cyclooctyl; and examples of C₃-C₁₂-cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, spiro[2.5]octyl, 3- methylenebicyclo[3.2.1]octyl, spiro[4.4]nonanyl, bicycle[3.1.0]hexanyl, spiro[2.3]hexanyl, 30 bicycle[3.1.1]heptanyl, spiro[2.5]octanyl, bicycle[4.1.0]heptanyl, bicycle[3.1.0]hexan-6-yl, spiro[2.3]hexan-5-yl, bicycle[3.1.1]heptan-3-yl, spiro[2.5]octan-4-yl, and bicycle[4.1.0]heptan-3-yl and the like.

 The term "cycloalkenyl", as used herein, refers to monocyclic or polycyclic carbocyclic ring or a bi- or tri-cyclic group fused, bridged or spiro system having at least one

carbon-carbon double bond and the carbon atoms may be optionally oxo-substituted or optionally substituted with exocyclic olefinic double bond. Preferred cycloalkenyl groups include C₃-C₈ cycloalkenyl and C₃-C₁₂ cycloalkenyl groups. Examples of C₃-C₈-cycloalkenyl include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like; and examples of C₃-C₁₂-cycloalkenyl include, but not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, bicyclo[2.2.1]hept-2-enyl, bicyclo[3.1.0]hex-2-enyl, spiro[2.5]oct-4-enyl, spiro[4.4]non-1-enyl, bicyclo[4.2.1]non-3-en-9-yl, and the like.

The terms "heterocyclic" or "heterocycloalkyl" can be used interchangeably and referred to a non-aromatic ring or a bi- or tri-cyclic group fused, bridged or spiro system, where (i) each ring system contains at least one heteroatom independently selected from oxygen, sulfur and nitrogen, (ii) each ring system can be saturated or unsaturated (iii) the nitrogen and sulfur heteroatoms may optionally be oxidized, (iv) the nitrogen heteroatom may optionally be quaternized, (v) any of the above rings may be fused to an aromatic ring, and (vi) the remaining ring atoms are carbon atoms which may be optionally oxo-substituted or optionally substituted with exocyclic olefinic double bond. Representative heterocycloalkyl groups include, but are not limited to, [1,3]dioxolane, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuryl, 2-azabicyclo[2.2.1]-heptyl, 8-azabicyclo[3.2.1]octyl, 5-azaspiro[2.5]octyl, 1-oxa-7-azaspiro[4.4]nonanyl, 7-oxooxepan-4-yl, and tetrahydrofuryl. Such heterocyclic groups may be further substituted. Heteroaryl or heterocyclic groups can be C-attached or N-attached (where possible).

The term "aryl," as used herein, refers to a mono- or polycyclic carbocyclic ring system comprising at least one aromatic ring, including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, and indenyl. A polycyclic aryl is a polycyclic ring system that comprises at least one aromatic ring. Polycyclic aryls can comprise fused rings, covalently attached rings or a combination thereof.

The term "arylalkyl," as used herein, refers to a functional group wherein an alkylene chain is attached to an aryl group, e.g., -CH₂CH₂-phenyl. The term "substituted arylalkyl" means an arylalkyl functional group in which the aryl group is substituted. Examples include, but are not limited to, benzyl, phenethyl and the like.

The term "heteroaryl," as used herein, refers to a mono-, bi-, or tri-cyclic aromatic radical or ring having from five to ten ring atoms of which at least one ring atom is selected

from S, O and N; wherein any N or S contained within the ring may be optionally oxidized. Preferred heteroaryl groups are monocyclic or bicyclic. Heteroaryl groups include, but are not limited to, pyridinyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, thienyl, triazolyl, isothiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzooxazolyl, benzothienyl, quinoxalinyl, indolyl, indazolyl, benzisoxazolyl, benzofuranyl, benzotriazolyl, benzothiazolyl, and the like.

The term “heteroarylalkyl,” as used herein, refers to an alkylene chain is attached to a heteroaryl group. The tem “substituted heteroarylalkyl” means a heteroarylalkyl functional group in which the heteroaryl group is substituted. Examples include, but are not limited to, pyridinylmethyl, pyrimidinylethyl and the like.

The term “biaryl”, as used herein, refers to a moiety consisting of two aryl groups, two heteroaryl groups or an aryl group and a heteroaryl group, wherein the two groups are connected by a single bond. A substituted biaryl group is a biaryl moiety in which at least one of the connected groups has at least one non-hydrogen substituent. Examples of biaryl groups include bi phenyl, pyrimidylphenyl, pyrimidypyridyl, and pyrimidyloxadizolyl groups.

As used herein, the term “alkoxy” employed alone or in combination with other terms means, unless otherwise stated, an alkyl group having the designated number of carbon atoms connected to the rest of the molecule via an oxygen atom, such as, for example, methoxy, ethoxy, 1-propoxy, 2-propoxy (isopropoxy) and the higher homologs and isomers. Preferred alkoxy are (C₁-C₃) alkoxy.

The term “substituted” refers to substitution by independent replacement of one, two, or three or more of the hydrogen atoms with substituents including, but not limited to, -F, -Cl, -Br, -I, -OH, C₁-C₁₂-alkyl, C₂-C₁₂-alkenyl, C₂-C₁₂-alkynyl, protected hydroxy, -NO₂, -N₃, -CN, -NH₂, protected amino, oxo, thioxo, -NH-C₁-C₁₂-alkyl, -NH-C₂-C₈-alkenyl, -NH-C₂-C₈-alkynyl, -NH-C₃-C₁₂-cycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C₁-C₁₂-alkyl, -O-C₂-C₈-alkenyl, -O-C₂-C₈-alkynyl, -O-C₃-C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)-C₁-C₁₂-alkyl, -C(O)-C₂-C₈-alkenyl, -C(O)-C₂-C₈-alkynyl, -C(O)-C₃-C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂, -CONH-C₁-C₁₂-alkyl, -CONH-C₂-C₈-alkenyl, -CONH-C₂-C₈-alkynyl, -CONH-C₃-C₁₂-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO₂-C₁-C₁₂-alkyl, -OCO₂-C₂-C₈-alkenyl, -OCO₂-C₂-C₈-alkynyl, -OCO₂-C₃-C₁₂-cycloalkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCO₂-

heterocycloalkyl, -CO₂-C₁-C₁₂ alkyl, -CO₂-C₂-C₈ alkenyl, -CO₂-C₂-C₈ alkynyl, CO₂-C₃-C₁₂-cycloalkyl, -CO₂-aryl, CO₂-heteroaryl, CO₂-heterocycloalkyl, -OCONH₂, -OCONH-C₁-C₁₂-alkyl, -OCONH-C₂-C₈-alkenyl, -OCONH-C₂-C₈-alkynyl, -OCONH-C₃-C₁₂-cycloalkyl, -OCONH-aryl, -OCONH-heteroaryl, -OCONH-heterocyclo-alkyl, -NHC(O)H, -NHC(O)-C₁-C₁₂-alkyl, -NHC(O)-C₂-C₈-alkenyl, -NHC(O)-C₂-C₈-alkynyl, -NHC(O)-C₃-C₁₂-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocyclo-alkyl, -NHCO₂-C₁-C₁₂-alkyl, -NHCO₂-C₂-C₈-alkenyl, -NHCO₂-C₂-C₈-alkynyl, -NHCO₂-C₃-C₁₂-cycloalkyl, -NHCO₂-aryl, -NHCO₂-heteroaryl, -NHCO₂-heterocycloalkyl, -NHC(O)NH₂, -NHC(O)NH-C₁-C₁₂-alkyl, -NHC(O)NH-C₂-C₈-alkenyl, -NHC(O)NH-C₂-C₈-alkynyl, -NHC(O)NH-C₃-C₁₂-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, NHC(S)NH₂, -NHC(S)NH-C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₈-alkenyl, -NHC(S)NH-C₂-C₈-alkynyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, -NHC(NH)NH-C₁-C₁₂-alkyl, -NHC(NH)NH-C₂-C₈-alkenyl, -NHC(NH)NH-C₂-C₈-alkynyl, -NHC(NH)NH-C₃-C₁₂-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, -NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₈-alkenyl, -NHC(NH)-C₂-C₈-alkynyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl, -C(NH)NH-C₂-C₈-alkenyl, -C(NH)NH-C₂-C₈-alkynyl, -C(NH)NH-C₃-C₁₂-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C₁-C₁₂-alkyl, -S(O)-C₂-C₈-alkenyl, -S(O)-C₂-C₈-alkynyl, -S(O)-C₃-C₁₂-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocycloalkyl, -SO₂NH₂, -SO₂NH-C₁-C₁₂-alkyl, -SO₂NH-C₂-C₈-alkenyl, -SO₂NH-C₂-C₈-alkynyl, -SO₂NH-C₃-C₁₂-cycloalkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -SO₂NH-heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₈-alkenyl, -NHSO₂-C₂-C₈-alkynyl, -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl, -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C₃-C₁₂-cycloalkyl, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-alkyl, -S-C₂-C₈-alkenyl, -S-C₂-C₈-alkynyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, or methylthio-methyl. It is understood that the aryls, heteroaryls, alkyls, cycloalkyls and the like can be further substituted. In some cases, each substituent in a substituted moiety is additionally optionally substituted with one or more groups, each group being independently selected from C₁-C₄-alkyl, -F, -Cl, -Br, -I, -OH, -NO₂, -CN, or -NH₂.

The term “optionally substituted”, as used herein, means that the referenced group may be substituted or unsubstituted. In one embodiment, the referenced group is optionally

substituted with zero substituents, i.e., the referenced group is unsubstituted. In another embodiment, the referenced group is optionally substituted with one or more additional group(s) individually and independently selected from groups described herein.

In accordance with the invention, any of the aryls, substituted aryls, heteroaryls and substituted heteroaryls described herein, can be any aromatic group. Aromatic groups can be substituted or unsubstituted.

It is understood that any alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl moiety described herein can also be an aliphatic group, an alicyclic group or a heterocyclic group. An "aliphatic group" is non-aromatic moiety that may contain any combination of carbon atoms, hydrogen atoms, halogen atoms, oxygen, nitrogen or other atoms, and optionally contain one or more units of unsaturation, e.g., double and/or triple bonds. An aliphatic group may be straight chained, branched or cyclic and preferably contains between about 1 and about 24 carbon atoms, more typically between about 1 and about 12 carbon atoms. In addition to aliphatic hydrocarbon groups, aliphatic groups include, for example, polyalkoxyalkyls, such as polyalkylene glycols, polyamines, and polyimines, for example. Such aliphatic groups may be further substituted. It is understood that aliphatic groups may be used in place of the alkyl, alkenyl, alkynyl, alkylene, alkenylene, and alkynylene groups described herein.

The term "alicyclic," as used herein, denotes a monovalent group derived from a monocyclic or polycyclic saturated carbocyclic ring compound by the removal of a single hydrogen atom. Examples include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, and bicyclo[2.2.2]octyl. Such alicyclic groups may be further substituted.

It will be apparent that in various embodiments of the invention, the substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, arylalkyl, heteroarylalkyl, and heterocycloalkyl are intended to be monovalent or divalent. Thus, alkylene, alkenylene, and alkynylene, cycloalkylene, cycloalkenylene, cycloalkynylene, arylalkylene, heteroarylalkylene and heterocycloalkylene groups are to be included in the above definitions, and are applicable to provide the Formulas herein with proper valency.

The terms "halo" and "halogen," as used herein, refer to an atom selected from fluorine, chlorine, bromine and iodine.

The term "hydrogen" includes hydrogen and deuterium. In addition, the recitation of an atom includes other isotopes of that atom so long as the resulting compound is pharmaceutically acceptable.

In certain embodiments, the compounds of each formula herein are defined to include isotopically labelled compounds. An “isotopically labelled compound” is a compound in which at least one atomic position is enriched in a specific isotope of the designated element to a level which is significantly greater than the natural abundance of that isotope. For example, one or more hydrogen atom positions in a compound can be enriched with deuterium to a level which is significantly greater than the natural abundance of deuterium, for example, enrichment to a level of at least 1%, preferably at least 20% or at least 50%. Such a deuterated compound may, for example, be metabolized more slowly than its non-deuterated analog, and therefore exhibit a longer half-life when administered to a subject. Such compounds can synthesize using methods known in the art, for example by employing deuterated starting materials. Unless stated to the contrary, isotopically labelled compounds are pharmaceutically acceptable.

The term “hydroxy activating group,” as used herein, refers to a labile chemical moiety which is known in the art to activate a hydroxyl group so that it will depart during synthetic procedures such as in a substitution or an elimination reaction. Examples of hydroxyl activating group include, but not limited to, mesylate, tosylate, triflate, *p*-nitrobenzoate, phosphonate and the like.

The term “activated hydroxyl,” as used herein, refers to a hydroxy group activated with a hydroxyl activating group, as defined above, including mesylate, tosylate, triflate, *p*-nitrobenzoate, phosphonate groups, for example.

The term “hydroxy protecting group,” as used herein, refers to a labile chemical moiety which is known in the art to protect a hydroxyl group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the hydroxy protecting group as described herein may be selectively removed. Hydroxy protecting groups as known in the art are described generally in T.H. Greene and P.G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of hydroxyl protecting groups include benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, tert-butoxycarbonyl, isopropoxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, allyloxycarbonyl, acetyl, formyl, chloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, benzoyl, methyl, *t*-butyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, allyl, benzyl, triphenylmethyl (trityl), methoxymethyl, methylthiomethyl, benzyloxymethyl, 2-(trimethylsilyl)-ethoxymethyl, methanesulfonyl, trimethylsilyl, triisopropylsilyl, and the like.

The term "protected hydroxy," as used herein, refers to a hydroxy group protected with a hydroxy protecting group, as defined above, including benzoyl, acetyl, trimethylsilyl, triethylsilyl, methoxymethyl groups, for example.

5 The term "hydroxy prodrug group," as used herein, refers to a promoietty group which is known in the art to change the physicochemical, and hence the biological properties of a parent drug in a transient manner by covering or masking the hydroxy group. After said synthetic procedure(s), the hydroxy prodrug group as described herein must be capable of reverting back to hydroxy group *in vivo*. Hydroxy prodrug groups as known in the art are described generally in Kenneth B. Sloan, Prodrugs, Topical and Ocular Drug Delivery,
10 (Drugs and the Pharmaceutical Sciences; Volume 53), Marcel Dekker, Inc., New York (1992) and in "Prodrugs of Alcohols and Phenols" by S. S. Dhareshwar and V. J. Stella, in Prodrugs Challenges and Rewards Part-2, (Biotechnology: Pharmaceutical Aspects), edited by V. J. Stella, et al, Springer and AAPSPress, 2007, pp 31-99.

The term "amino protecting group," as used herein, refers to a labile chemical moiety
15 which is known in the art to protect an amino group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the amino protecting group as described herein may be selectively removed. Amino protecting groups as known in the art are described generally in T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of amino protecting
20 groups include, but are not limited to, methoxycarbonyl, t-butoxycarbonyl, 9-fluorenyl-methoxycarbonyl, benzyloxycarbonyl, and the like.

The term "protected amino," as used herein, refers to an amino group protected with an amino protecting group as defined above.

The term "amino acid" refers to naturally occurring and synthetic α , β , γ , or δ amino
25 acids, and includes but is not limited to, amino acids found in proteins or intermediates in metabolism of amino acids or proteins, *i.e.* glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tryptophan, proline, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartate, glutamate, lysine, citrulline, arginine and histidine. In certain embodiments, the amino acid is in the L-configuration. In certain embodiments, the
30 amino acid is in the D-configuration. In certain embodiments, the amino acid is provided as a substituent of a compound described herein, wherein the amino acid is a residue selected from the group consisting of alanyl, valinyl, leucinyl, isoleuccinyl, prolinyl, phenylalaninyl, tryptophanyl, methioninyl, glycyl, serinyl, threoninyl, cysteinyl, tyrosinyl, asparaginyl,

glutaminy, aspartoy, glutaroy, lysiny, argininy, histidiny, β -alany, β -valiny, β -leuciny, β -isoleucciny, β -proliny, β -phenylalaniny, β -tryptophany, β -methioniny, β -glyciny, β -seriny, β -threoniny, β -cysteininy, β -tyrosiny, β -asparaginy, β -glutaminy, β -aspartoy, β -glutaroy, β -lysiny, β -argininy and β -histidiny.

5 The term "amino acid derivative" refers to a group derivable from a naturally or non-naturally occurring amino acid, as described and exemplified herein. Amino acid derivatives are apparent to those of skill in the art and include, but are not limited to, ester, amino alcohol, amino aldehyde, amino lactone, and N-methyl derivatives of naturally and non-naturally occurring amino acids. In an embodiment, an amino acid derivative is
10 provided as a substituent of a compound described herein, wherein the substituent is – $\text{NR}^u\text{-G(S}_c\text{)-C(O)-Q}^1$, wherein Q^1 is -SR^v , $\text{-NR}^v\text{R}^v$ or alkoxyl, R^v is hydrogen or alkyl, S_c is a side-chain of a naturally occurring or non-naturally occurring amino acid, G is $\text{C}_1\text{-C}_2$ alkyl, and R^u is hydrogen; or R^u and S_c are taken together with the atoms to which they are attached to form a five-membered heterocyclic ring. In an embodiment, an amino acid
15 derivative is provided as a substituent of a compound described herein, wherein the substituent is $\text{-O-C(O)-G(S}_c\text{)-NH-Q}^2$, wherein Q^2 is hydrogen or alkoxyl, S_c is a side-chain of a naturally occurring or non-naturally occurring amino acid and G is $\text{C}_1\text{-C}_2$ alkyl. In certain embodiments, Q^2 and S_c are taken together with the atoms to which they are attached to form a five-membered heterocyclic ring. In certain embodiments, G is an
20 optionally substituted methylene and S_c is selected from the group consisting of hydrogen, alkyl, arylalkyl, heterocycloalkyl, carboxylalkyl, heteroarylalkyl, aminoalkyl, hydroxylalkyl, aminoiminoaminoalkyl, aminocarbonylalkyl, sulfanylalkyl, carbamoylalkyl, alkylsulfanylalkyl and hydroxylarylalkyl. In an embodiment, an amino acid derivative is provided as a substituent of a compound described herein, wherein the
25 amino acid derivative is in the D-configuration. In an embodiment, an amino acid derivative is provided as a substituent of a compound described herein, wherein the amino acid derivative is in the L-configuration.

 The term "leaving group" means a functional group or atom which can be displaced by another functional group or atom in a substitution reaction, such as a nucleophilic
30 substitution reaction. By way of example, representative leaving groups include chloro, bromo and iodo groups; sulfonic ester groups, such as mesylate, tosylate, brosylate, nosylate and the like; and acyloxy groups, such as acetoxy, trifluoroacetoxy and the like.

 When the compounds described herein contain one or more asymmetric centers they give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined,

in terms of absolute stereochemistry, as (R)- or (S)-, or as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optical isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques, which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, *et al.*, Enantiomers, Racemates, and Resolutions (John Wiley & Sons, 1981). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text so states; thus a carbon-carbon double bond depicted arbitrarily herein as *trans* may be *cis*, *trans*, or a mixture of the two in any proportion.

The term "subject" as used herein refers to a mammal. A subject therefore refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, and the like. Preferably the subject is a human. When the subject is a human, the subject may be referred to herein as a patient.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts of the compounds formed by the process of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art.

Berge, *et al.* describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reaction of the free base function with a suitable organic acid. Examples of pharmaceutically acceptable salts include, but are not limited to, nontoxic acid addition salts e.g., salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate,

camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-

5 naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when

10 appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

As used herein, the term "pharmaceutically acceptable ester" refers to esters of the compounds formed by the process of the present invention which hydrolyze *in vivo* and

15 include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, formates,

20 acetates, propionates, butyrates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds formed by the process of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like,

25 commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the present invention. "Prodrug", as used herein means a compound, which is convertible *in vivo* by metabolic means (e.g. by hydrolysis) to afford any compound delineated by the Formulae of the instant invention. Various forms of prodrugs are known in the art, for example, as discussed in

30 Bundgaard, (ed.), *Design of Prodrugs*, Elsevier (1985); Widder, *et al.* (ed.), *Methods in Enzymology*, Vol. 4, Academic Press (1985); Krogsgaard-Larsen, *et al.*, (ed). "Design and Application of Prodrugs, *Textbook of Drug Design and Development*, Chapter 5, 113-191 (1991); Bundgaard, *et al.*, *Journal of Drug Deliver Reviews*, 8:1-38(1992); Bundgaard, J. of *Pharmaceutical Sciences*, 77:285 et seq. (1988); Higuchi and Stella (eds.) *Prodrugs as Novel*

Drug Delivery Systems, *American Chemical Society* (1975); and Bernard Testa & Joachim Mayer, "Hydrolysis In Drug And Prodrug Metabolism: Chemistry, Biochemistry And Enzymology," John Wiley and Sons, Ltd. (2002).

5 The term "treating", as used herein, means relieving, lessening, reducing, eliminating, modulating, or ameliorating, i.e. causing regression of the disease state or condition. Treating can also include inhibiting, i.e. arresting the development, of an existing disease state or condition, and relieving or ameliorating, i.e. causing regression of an existing disease state or condition, for example when the disease state or condition may already be present.

10 The term "preventing", as used herein means, to completely or almost completely stop a disease state or condition, from occurring in a patient or subject, especially when the patient or subject is predisposed to such or at risk of contracting a disease state or condition.

Additionally, the compounds of the present invention, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Nonlimiting examples of hydrates include monohydrates,
15 dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

"Solvates" means solvent addition forms that contain either stoichiometric or non-stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water
20 the solvate formed is a hydrate, when the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one of the substances in which the water retains its molecular state as H₂O, such combination being able to form one or more hydrate.

As used herein, the term "analog" refers to a chemical compound that is structurally
25 similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group, or the replacement of one functional group by another functional group). Thus, an analog is a compound that is similar to or comparable in function and appearance to the reference compound.

The term "aprotic solvent," as used herein, refers to a solvent that is relatively inert to
30 proton activity, i.e., not acting as a proton-donor. Examples include, but are not limited to, hydrocarbons, such as hexane and toluene, for example, halogenated hydrocarbons, such as, for example, methylene chloride, ethylene chloride, chloroform, and the like, heterocyclic compounds, such as, for example, tetrahydrofuran and *N*-methylpyrrolidinone, and ethers such as diethyl ether, bis-methoxymethyl ether. Such solvents are well known to those skilled

in the art, and individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of aprotic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: *Organic Solvents Physical Properties and Methods of Purification*, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the *Techniques of Chemistry Series*, John Wiley & Sons, NY, 1986.

The terms "protogenic organic solvent" or "protic solvent" as used herein, refer to a solvent that tends to provide protons, such as an alcohol, for example, methanol, ethanol, propanol, isopropanol, butanol, t-butanol, and the like. Such solvents are well known to those skilled in the art, and individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of protogenic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: *Organic Solvents Physical Properties and Methods of Purification*, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the *Techniques of Chemistry Series*, John Wiley & Sons, NY, 1986.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. In addition, the solvents, temperatures, reaction durations, etc. delineated herein are for purposes of illustration only and variation of the reaction conditions can produce the desired isoxazole products of the present invention. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein include, for example, those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents*

for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995).

The compounds of this invention may be modified by appending various functionalities via synthetic means delineated herein to enhance selective biological properties. Such modifications include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

PHARMACEUTICAL COMPOSITIONS

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention Formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or Formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the Formulator. The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic

pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the Formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the Formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1, 3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The

rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable Formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragées, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical Formulating art. In such solid

dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets
5 and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

10 Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic Formulation, ear drops, eye ointments, powders and solutions are also
15 contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

20 Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a
25 compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Unless otherwise defined, all technical and scientific terms used herein are accorded
30 the meaning commonly known to one with ordinary skill in the art. All publications, patents, published patent applications, and other references mentioned herein are hereby incorporated by reference in their entirety.

ABBREVIATIONS

Abbreviations which have been used in the descriptions of the schemes and the examples that follow are:

- BINAP for 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl;
 5 BrettPhos for 2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-trisopropyl-1,1'-biphenyl;
 BOP-Cl for bis(2-oxo-3-oxazolidinyl)phosphinic chloride;
 CDI for carbonyldiimidazole;
 EDC or EDCI for 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide;
 10 DavePhos for 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl;
 DBU for 1,8-diazabicycloundec-7-ene;
 DCC for *N,N'*-dicyclohexylcarbodiimide;
 DCM for dichloromethane;
 DMA for Dimethylacetamide
 15 DMAP for *N,N*-dimethylaminopyridine;
 DMF for *N,N*-dimethyl formamide;
 DPPA for diphenylphosphoryl azide;
 DPPF for 1,1'-Ferrocenediyl-bis(diphenylphosphine);
 EDC or EDCI for 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride;
 20 Et₃N for triethylamine;
 EtOAc for ethyl acetate;
 HATU for 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate;
 HCl for hydrochloric acid;
 25 LAH for lithium aluminium hydride;
 Mor-Dalpos for Di(1-adamantyl)-2-morpholinophenylphosphine;
 NCS for N-Chlorosuccinimide;
 NMO for N-Methylmorpholine N-oxide;
 PyAOP for 7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium
 30 hexafluorophosphate;
 PyBOP for benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate;
 TBAI for tetrabutylammonium iodide;
 TFA for trifluoroacetic acid;

TFFH for tetramethylfluoroformamidinium hexafluorophosphate;

THF for tetrahydrofuran;

TPAP for Tetrapropylammonium perruthenate;

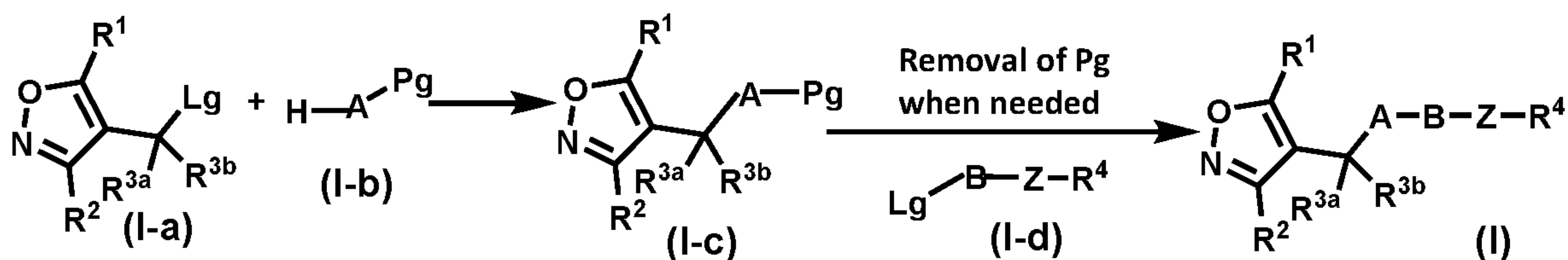
Xantphos for 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene;

5 XPhos for dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphane or
2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl.

SYNTHETIC METHODS

The compounds and processes of the present invention will be better understood in
10 connection with the following synthetic schemes that illustrate the methods by which the
compounds of the invention may be prepared, which are intended as an illustration only and
not to limit the scope of the invention. Various changes and modifications to the disclosed
embodiments will be apparent to those skilled in the art and such changes and modifications
including, without limitation, those relating to the chemical structures, substituents,
15 derivatives, and/or methods of the invention may be made without departing from the spirit
of the invention and the scope of the appended claims.

Scheme 1

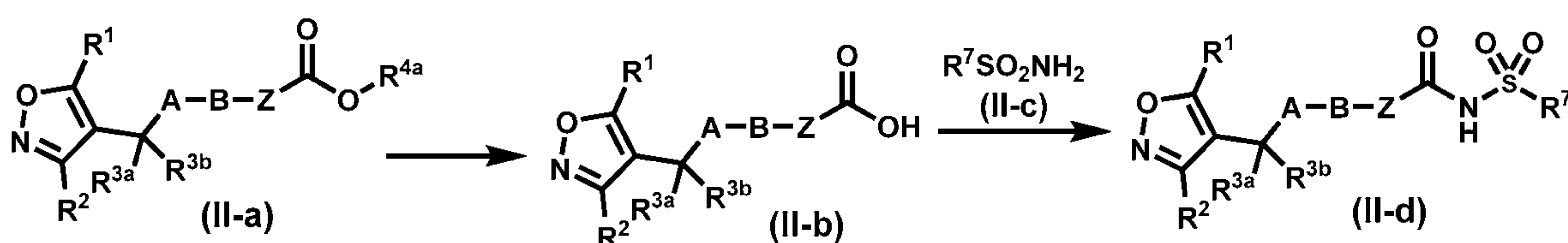


wherein, R^1 , R^2 , R^{3a} , R^{3b} , A, B, Z and R^4 are as previously defined. Lg is a leaving
20 group such as halides, -OMs, -OTf, -OTs, -OAr. Pg is hydrogen or a protecting group for
hydroxyl or amine whenever applicable such as, but not limited to, Boc, Cbz and benzyl. The
protecting groups are common practices in organic synthesis (see T.W. Greene and P.G.M
Wuts, "protective Groups in Organic Chemistry", 4th Ed., Wiley-Interscience, 2006).

As shown in Scheme 1, the compounds of formula (I-c) can be obtained through the
25 coupling between the compounds of formula (I-a) and compounds of formula (I-b)
employing suitable base such as but not limited to sodium *tert*-butoxide, potassium *tert*-
butoxide, or cesium carbonate in the presence or absence of phase transfer reagent such as
but not limited to 18-Crown-6, 15-Crown-5 or tetrabutylammonium iodide. The reaction
temperature is from -20 °C to 140 °C. The protecting group in compounds of formula (I-c)

can be removed whenever applicable and coupled with the compounds of formula (I-d) to afford the compounds of formula (I). This coupling can be achieved employing suitable base such as but not limited to sodium tert-butoxide, potassium tert-butoxide, or cesium carbonate in the presence or absence of phase transfer reagent such as but not limited to 18-Crown-6, 15-Crown-5 or tetrabutylammonium iodide. Alternatively, the compounds of formula (I) could also be prepared from the deprotected form of compounds of formula (I-c) and the compounds of formula (I-d) via Buchwald-Hartwig amination. This process employing suitable palladium catalysts such as but not limited to Pd(OAc)₂, Pd₂(dba)₃, PdCl₂(P(o-Tolyl)₃)₂, PdCl₂(DPPF) and Pd(PPh₃)₄ in presence or absence of a suitable ligand such as but not limited to XPhos, Xantphos, BINAP, BrettPhos, DavePhos, DPPF, P(t-Bu)₃, P(o-tolyl)₃ and Mor-Dalphos. This amination process may use a suitable base such as but not limited to K₃PO₄, Cs₂CO₃, NaOtBu, LiHMDS and NaHMDS. This amination process is carried out in a suitable solvent such as, but not limited to, toluene, dioxane or THF and the temperature can vary from -20 °C to 120 °C. More detail about Buchwald-Hartwig amination could be found in literature. (Buchwald, S.L. et al., *Topics in Curr. Chem.*, **2002**, 219, 131; Lundgren, R. J. et al., *Aldrichimica Acta*, **2012**, 45, 59; Senra, J. D. et al., *Current Organic Synthesis*, **2011**, 81, 53).

Scheme 2

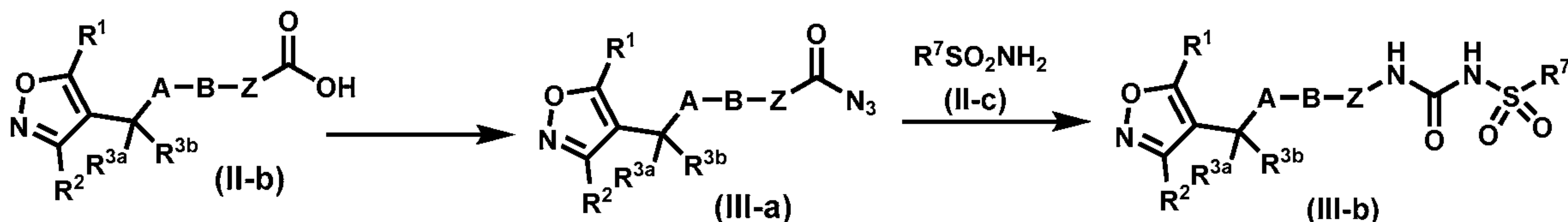


wherein, R¹, R², R^{3a}, R^{3b}, Z, R^{4a}, R⁷, A and B are as previously defined.

As shown in Scheme 2, the hydrolysis of compounds of Formula (II-a) to the acids of Formula (II-b) can be achieved in the presence of suitable bases such as but not limited to sodium hydroxide, lithium hydroxide or potassium hydroxide. The novel isoxazole acylsulfonamide analogs of the compounds of Formula (II-d) can be prepared from the coupling between compounds of Formula (II-b) and sulfonamide (II-c) using suitable coupling reagents in presence of suitable bases. The coupling reagent can be selected from, but not limited to, DCC, EDCI, CDI, diisopropyl carbodiimide, BOP-Cl, PyBOP, PyAOP, TFFH and HATU. Suitable bases include, but are not limited to, triethylamine, diisopropylethylamine, DBU, N-methylmorpholine and DMAP. The coupling reaction is

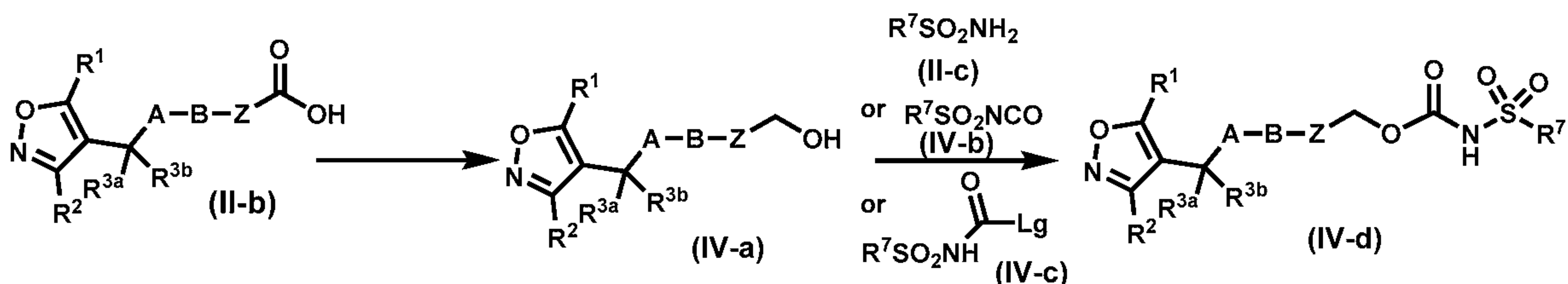
carried out in an aprotic solvent such as, but not limited to, DCM, DMF or THF. The reaction temperature can vary from -20 °C to 120 °C.

Scheme 3



5 As shown in Scheme 3, novel isoxazole sulfonyl urea analogs of the compound of formula (III-b) are prepared from the compounds of formula (II-b), wherein R^1 , R^2 , R^{3a} , R^{3b} , R^7 , Z, A and B are as previously defined. Thus, the compounds of formula (II-b) can be converted to the acyl azide compounds of formula (III-a) using suitable reagents such as, but not limited to, DPPA. The reaction solvents can be, but are not limited to, THF, DCM and
10 toluene. The reaction temperature is from -20°C to 80°C. Alternatively, the acids of formula (II-b) could be transformed to the acyl azides of formula (III-a) via activated acid derivatives such as acyl chlorides or anhydrides in presence of azide source. The reagents for activation of acid includes, but not limited to, tetramethylfluoroformadinium hexafluorophosphate, phenyl dichlorophosphate, SOCl_2 -DMF, triphosgene, cyanuric chloride, NCS- Ph_3P and
15 $\text{Cl}_3\text{CCN-Ph}_3\text{P}$. The azide source includes, but not limited to, sodium azide, tetrabutylammonium azide, trimethylsilyl azide and N,N,N',N' -tetramethylguanidinium azide. Curtius rearrangement of the compounds of formula (III-a) at elevated temperature preferably from 50 °C to 120 °C can lead to the isocyanate intermediates, which then can react with sulfonamides compound of formula (II-c) to afford the compounds of formula (III-
20 b).

Scheme 4



As shown in Scheme 4, the compounds of formula (IV-d) can be prepared from the compounds of formula (II-b), wherein R^1 , R^2 , R^{3a} , R^{3b} , R^7 , Z, A and B are as previously
25 defined and Lg is a leaving group such as halides, -OMs, -OTf, -OTs, -OAr. Thus, the compounds of formula (II-b) can be converted to alcohols of formula (IV-a) using suitable

reducing reagents such as, but not limited to, LAH, LiBH₄, BH₃. Alternatively, the alcohols of formula (IV-a) can also be synthesized via the reduction of the derivatives of acid of formula (II-V). Such derivatives include, but not limited to, acyl chloride, mixed anhydride or ester derivatives of acids (II-b). The compounds of formula (IV-a) could be transformed to the carbamates of formula (IV-d) via coupling with sulfonamides of formula (II-C) employing CDI or phosgene as coupling reagent with or without addition of suitable bases such as, but not limited to, triethylamine, diisopropylethylamine, DBU, *N*-methylmorpholine and DMAP. Alternatively, this transformation could be achieved via direct coupling of alcohols of formula (IV-a) with isocyanates of formula (IV-b) in the presence or absence of suitable bases such as, but not limited to, triethylamine, diisopropylethylamine, DBU, *N*-methylmorpholine and DMAP. Moreover, the isocyanates of formula (IV-b) could be generated in situ from compounds of formula (IV-c).

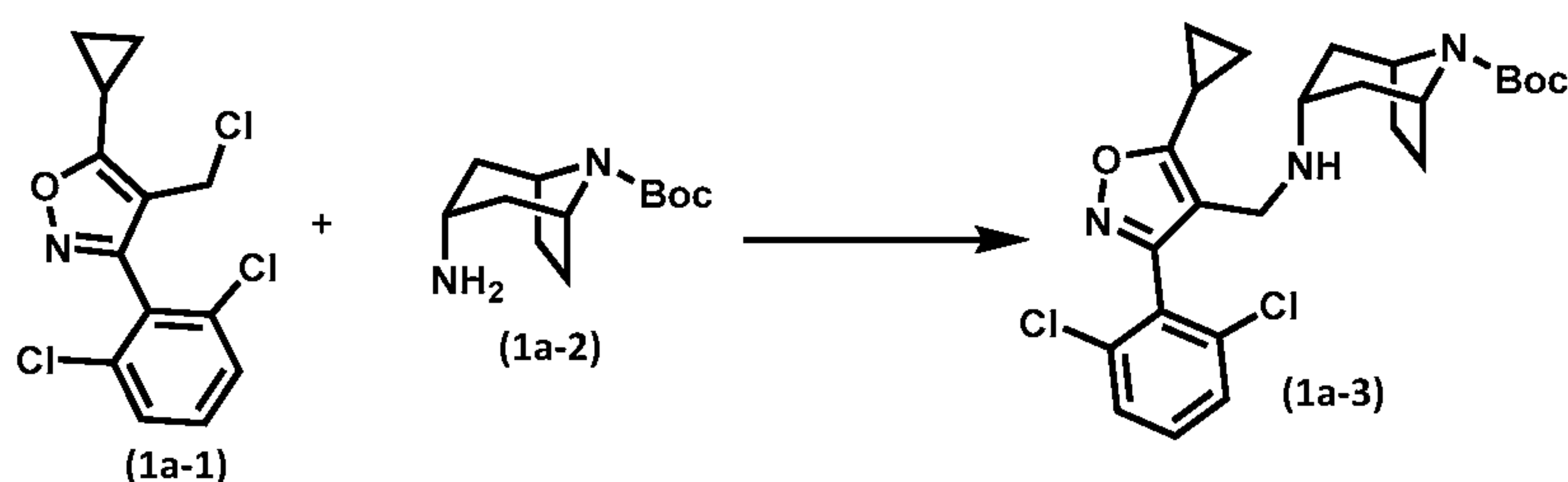
In the reactions described, reactive functional groups such as hydroxyl, amino, imino, thio or carboxy groups, may be protected to avoid unwanted participation in the reactions. These protecting groups may be removed at suitable steps via solvolysis, reduction, photolysis. The protection and deprotection are common practices in organic synthesis (see T.W. Greene and P.G.M Wuts, "protective Groups in Organic Chemistry", 4th Ed., Wiley-Interscience, 2006).

Preparations and Examples

The following preparations and examples are intended for further illustrate the invention only and are not intended to limit the scope of the invention in any way.

Example 1

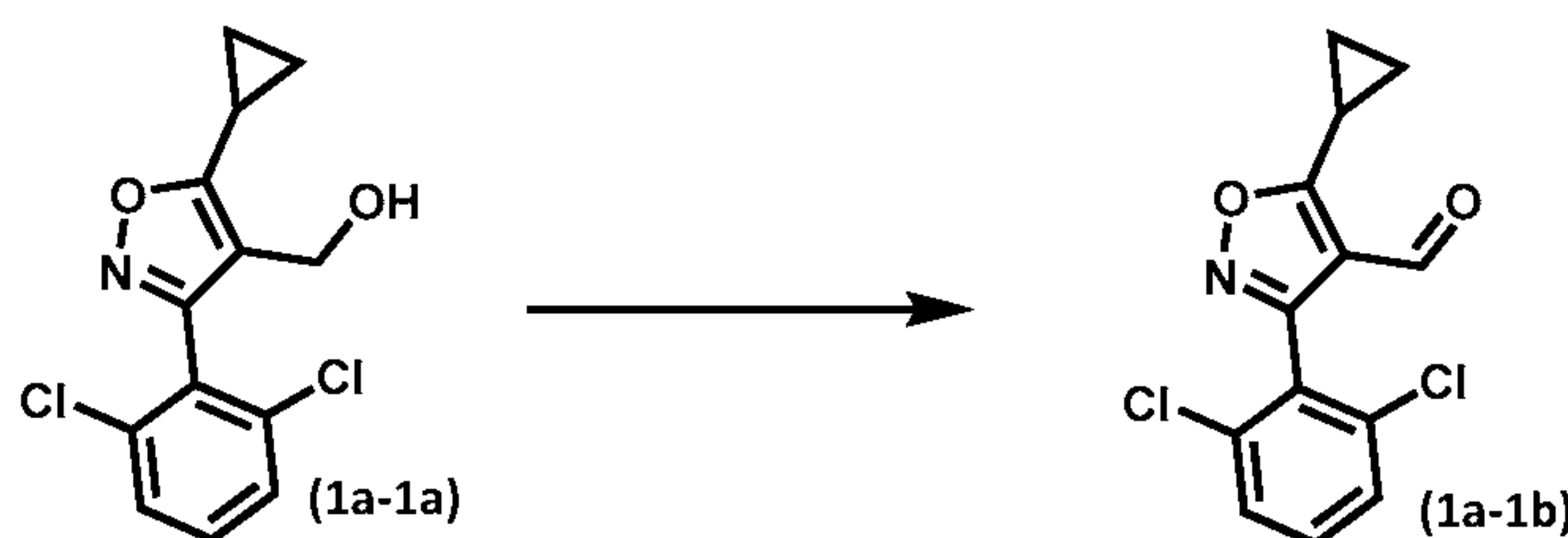
Step 1a



To *tert*-butyl (1*R*,3*R*,5*S*)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (1a-1) (5 g, 22.09 mmol) and 4-(chloromethyl)-5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazole (1a-2) (7.35 g, 24.30 mmol) in Acetonitrile (50 ml) was added TBAI (0.816 g, 2.209 mmol) and

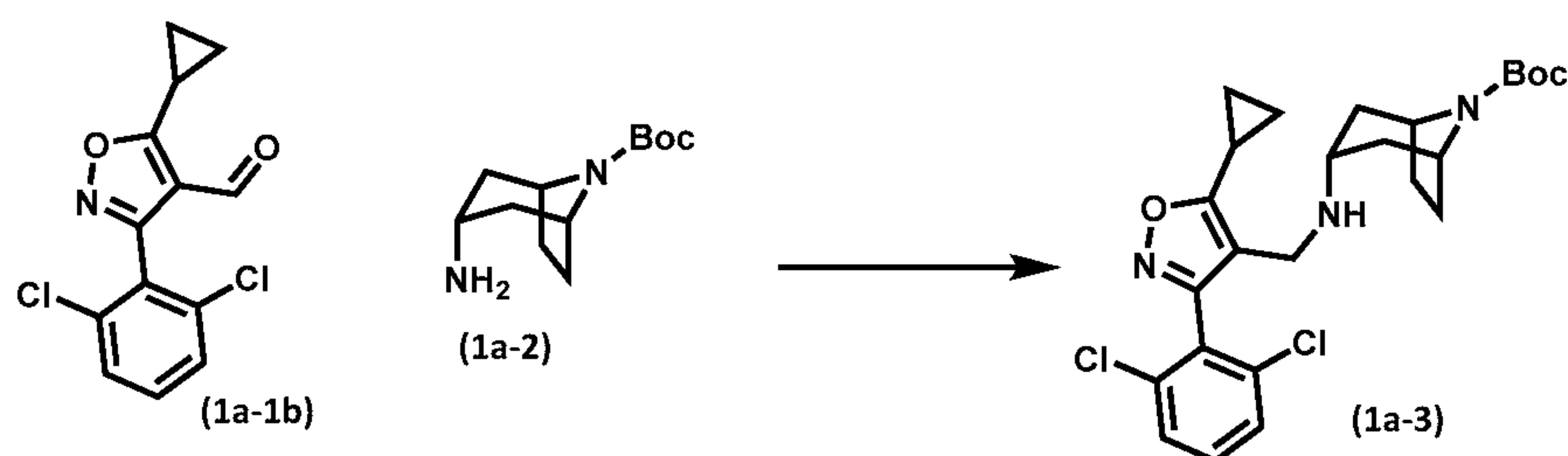
cesium carbonate (18.00 g, 55.2 mmol). The resulting mixture was stirred at 65 °C for 16 h and then concentrated under vacuo to remove most of the solvents. The mixture was diluted with ethyl acetate, washed with water, brine, dried, filtered, and concentrated. The residue was chromatographed by CombiFlash eluting with hexane to 50% acetone/ hexane to give
 5 *tert*-butyl (1R,3R,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (1a-3) (4.12 g). LC/MS observed [M+H], 492.19; 494.17.

Step 1a-1



To (5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methanol (1a-1a) (50 g, 176 mmol) in DCM (503 ml) at room temperature was added TPAP (3.09 g, 8.80 mmol) and NMO (51.5 g, 440 mmol). The mixture was stirred for 30 min, and then filtered through a SiO₂ pad. The filtrate was concentrated to ~ 200 mL left, and heptane (300 mL) was added. The mixture was heated at 45 °C under vacuum to remove most of the DCM and colorless
 15 solid precipitate was formed. The crystalline product was collected by filtration and rinsed with heptane to give 5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazole-4-carbaldehyde (1a-1b) (42 g, 85%). ¹H NMR (400 MHz, Chloroform-d) δ 9.94 – 9.47 (m, 1H), 7.68 – 7.38 (m, 3H), 2.84 (tt, J = 8.8, 4.9 Hz, 1H), 1.75 – 1.29 (m, 4H).

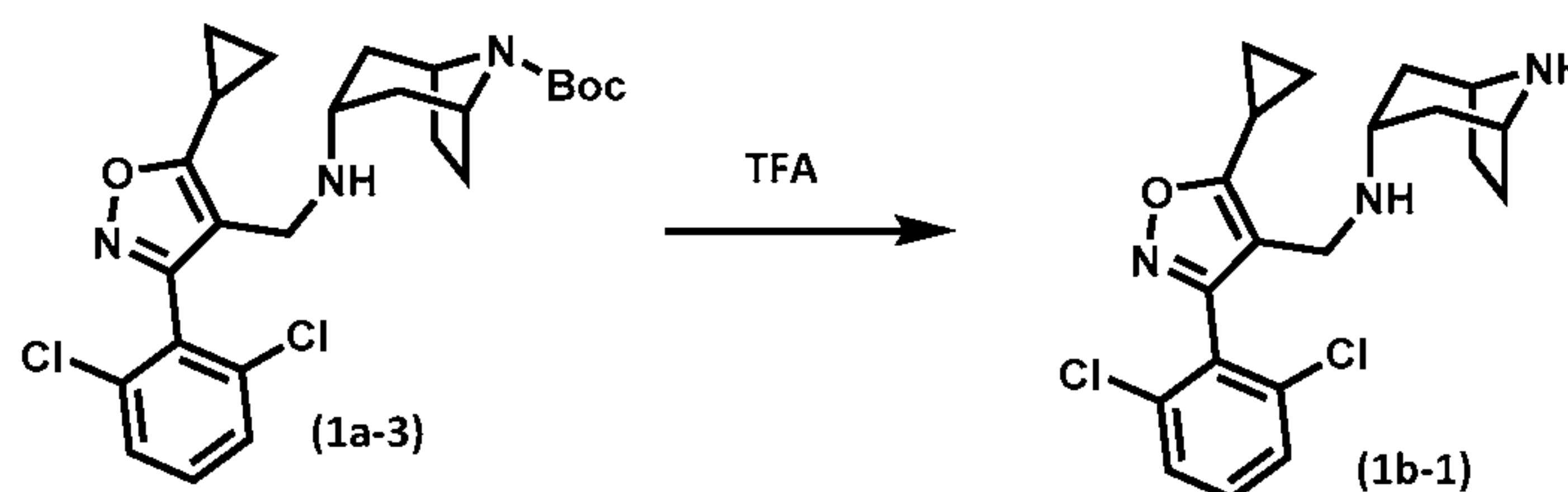
Step 1a-2



To 5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazole-4-carbaldehyde (1a-1b) (50.1g, 178 mmol) and *tert*-butyl (1R,3r,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (38.2 g, 169 mmol) was added 2,2,2-trifluoroethanol (259 ml, 3552 mmol) and the suspension was heated up to 45 °C for 60 min to form a light yellow solution. To this mixture was added
 25 sodium borohydride (8.06 g, 213 mmol) in portions over 45 min. The mixture was stirred at

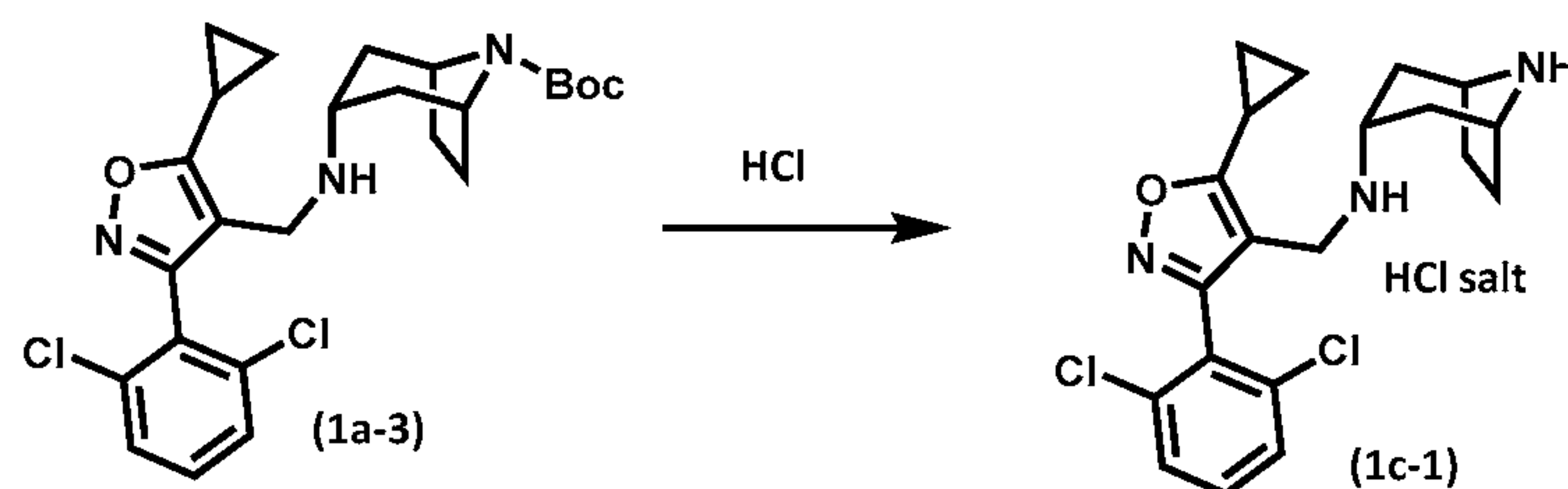
45 °C for 16 h, and the mixture was cooled down and concentrated under vacuum. The filtrate cake was participated in EtOAc/water, organic layer was separated, washed with potassium sodium tartrate, water and brine. The organic layer was combined with the filtrate and concentrated to give crude product. To the crude product was added 20% acetone in heptane (350 ml) and the suspension was heated up to gentle reflux until most of the solid went into solution. The suspension was cooled down to 45 °C and aging for 16h. Then cooled down to room temperature and the solid was collected by filtration to give *tert*-butyl (1R,3r,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (1a-3) (41.5 g). The mother liquor was concentrated and then recrystallized from acetone/Heptane (1:4) to give another crop of product (1a-3) (21.74 g). LC/MS observed [M+H], 492.18; ¹H NMR (500 MHz, Chloroform-d) δ 7.47 – 7.37 (m, 2H), 7.37 – 7.29 (m, 1H), 4.03 (d, J = 45.6 Hz, 2H), 3.50 (s, 2H), 2.88 (t, J = 5.9 Hz, 1H), 2.08 (tt, J = 8.4, 5.1 Hz, 1H), 1.93 (d, J = 43.8 Hz, 2H), 1.66 (td, J = 10.9, 9.8, 6.1 Hz, 4H), 1.44 (s, 9H), 1.31 – 1.19 (m, 3H), 1.19 – 1.06 (m, 2H).

Step 1b



To *tert*-butyl (1R,3R,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (1a-3) (1.43 g, 2.90 mmol) in DCM (8 ml) was added TFA (4.47 ml, 58.1 mmol) and the resulting mixture was stirred at room temperature for 16 h and then concentrated under vacuo. The mixture was diluted with ethyl acetate, washed with 1N NaOH solution, brine, dried, filtered, and concentrated to afford (1R,3R,5S)-N-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octan-3-amine (1b-1) (1.08 g). LC/MS observed [M+H], 392.12.

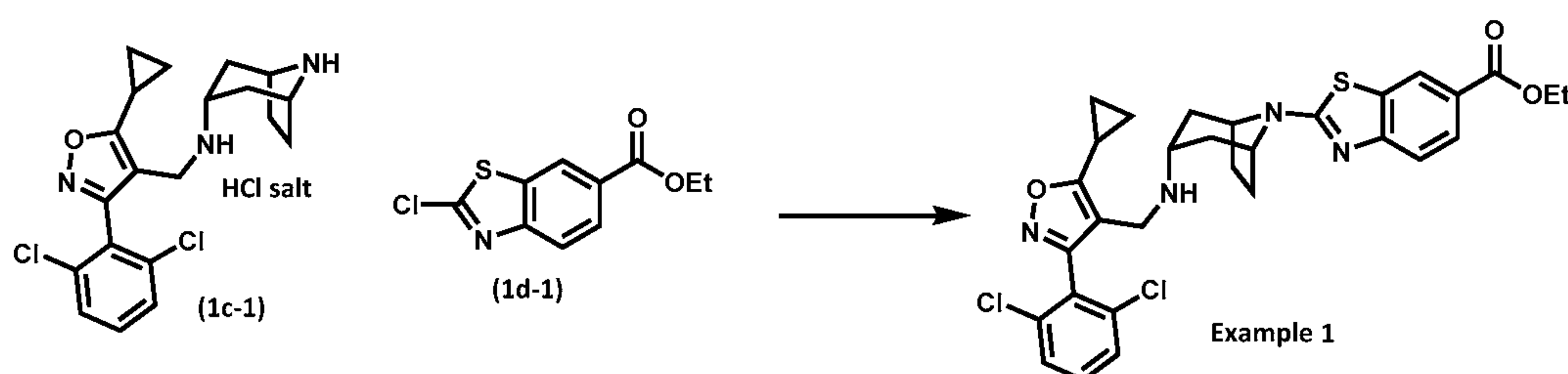
Step 1c



To *tert*-butyl (1R,3R,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (1a-3) (758 mg, 1.539 mmol) in DCM (4 ml) was added HCl (3.85 ml, 15.39 mmol, 4 M in dioxane) and the resulting mixture was stirred at room temperature for 3 h. The mixture was concentrated under vacuo and chased with DCM to afford (1R,3R,5S)-N-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)-8-azabicyclo[3.2.1]octan-3-amine (1c-1) (785 mg) as HCl salt. LC/MS observed [M+H], 392.13.

10

Step 1d

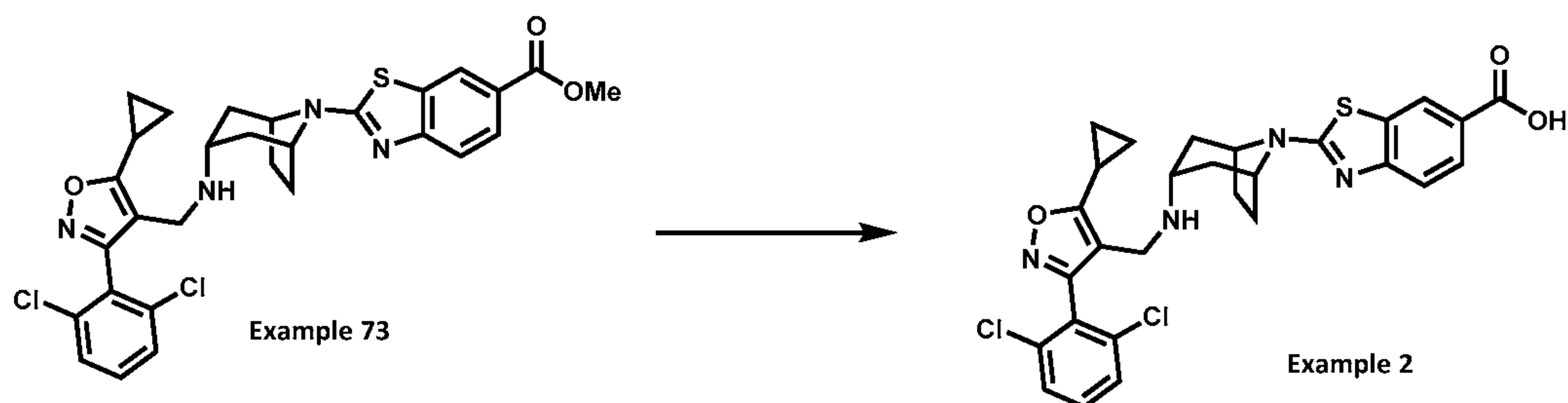


To ethyl 2-chlorobenzo[d]thiazole-6-carboxylate (1d-1) (305 mg, 1.263 mmol) and (1R,3R,5S)-N-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)-8-azabicyclo[3.2.1]octan-3-amine hydrochloride (1c-1) (430 mg, 0.842 mmol, ~84% by weight) in DMA (5 ml) was added cesium carbonate (686 mg, 2.105 mmol). The resulting mixture was heated up to 60 °C for 16 h, cooled down to room temperature. The mixture was diluted with ethyl acetate, washed with water (4X), brine, dried, filtered, and concentrated. The residue was chromatographed by CombiFlash eluting with hexane to 70% ethyl acetate/hexane to give ethyl 2-((1R,3R,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octan-8-yl)benzo[d]thiazole-6-carboxylate (Example 1) (198 mg). LC/MS observed [M+H], 597.15.

20

Example 2

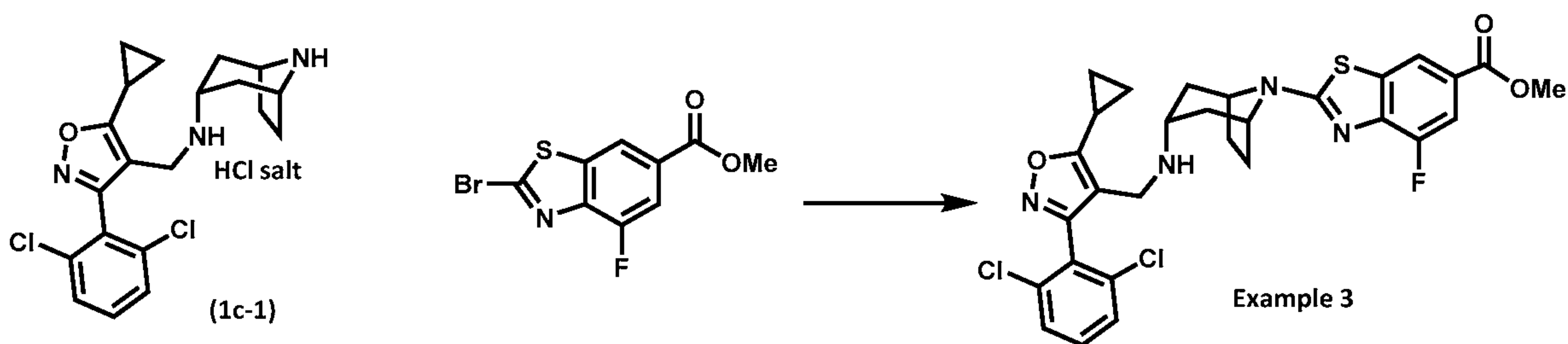
Step 2a



To a suspension of methyl 2-(((1R,3R,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-
 5 4-yl)methyl)amino)-8-azabicyclo[3.2.1]octan-8-yl)benzo[d]thiazole-6-carboxylate Example
 73 (215 mg, 0.368 mmol) in MeOH (3ml), THF (3 ml) and Water (0.5 ml) was added
 potassium hydroxide (0.368 ml, 0.737 mmol, 2 M in water), the mixture was stirred at 70 °C
 for 8 h. Another portion of KOH (0.37 mL), stir at 60 °C for 60 h. The mixture was acidified
 to slightly acidic with 2N HCl, extracted with EA (3X), organic layer combined, and
 10 concentrated under vacuo to give a yellow solid. To this yellow solid was added 20%
 MeOH/DCM, sonicated for 3 min, filtered, and filtrate was collected and concentrated to give
 2-(((1R,3R,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-
 azabicyclo[3.2.1]octan-8-yl)benzo[d]thiazole-6-carboxylic acid (Example 2) (201 mg).
 LC/MS observed [M+H], 569.12.

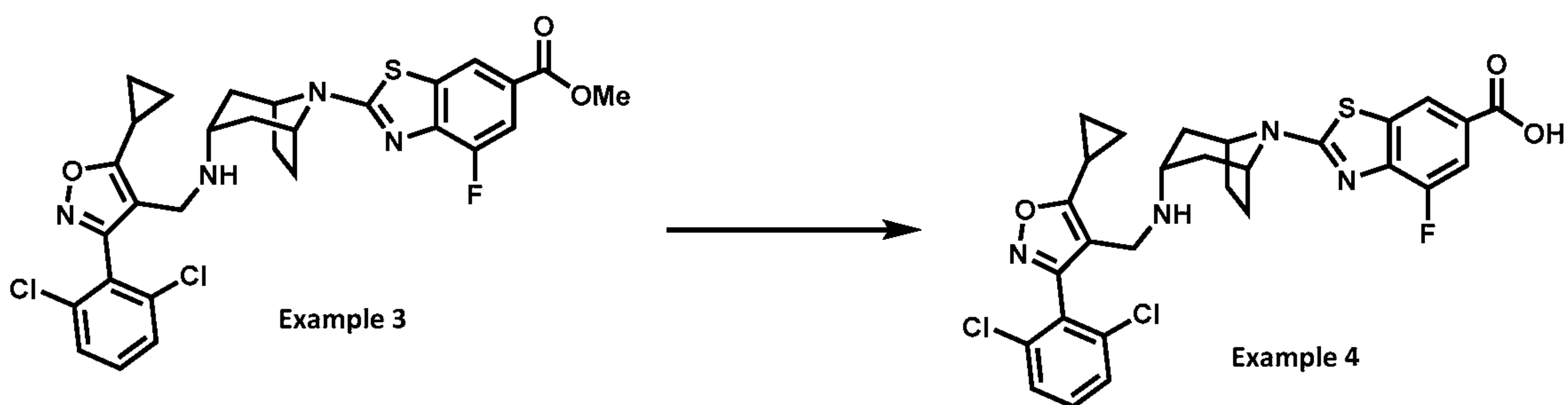
15 A portion of the crude product (35 mg) was purified by CombiFlash DCM to 15%
 MeOH/DCM to afford Example 2 (24.1 mg). LC/MS observed [M+H], 569.12.

Example 3



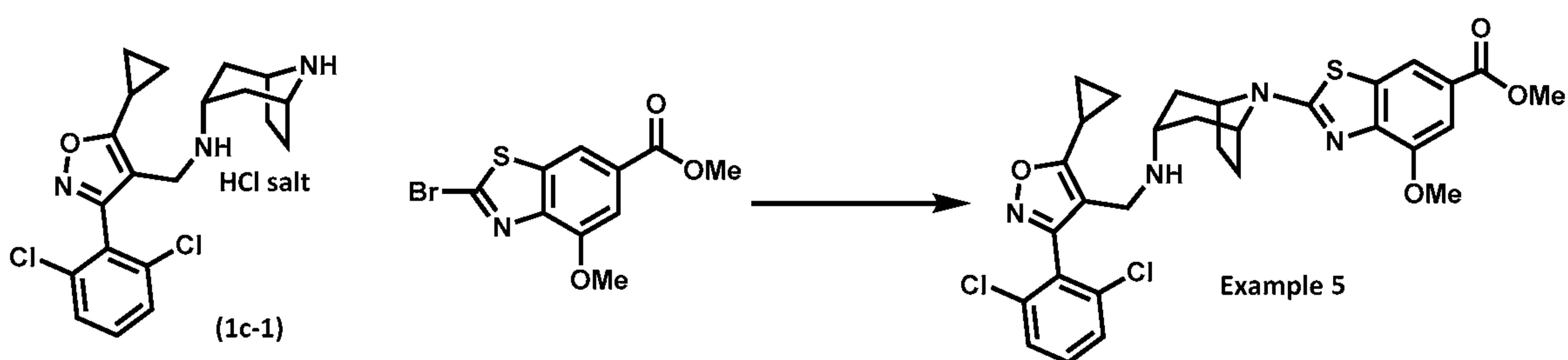
20 Example 3 was prepared from compound (1c-1) and methyl 2-bromo-4-
 fluorobenzo[d]thiazole-6-carboxylate according to the analogous procedure as in step 1d
 described for the preparation of Example 1. LC/MS observed [M+H], 601.13.

Example 4



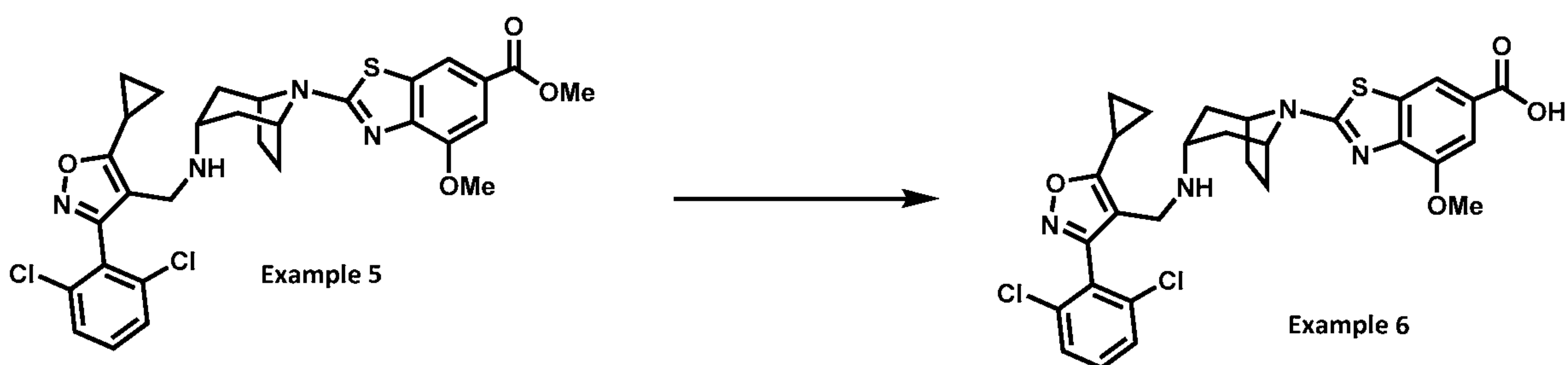
Example 4 was prepared from the hydrolysis of Example 3 according to the analogous procedure as in step 2a described for the preparation of Example 2. LC/MS observed [M+H], 587.11.

Example 5



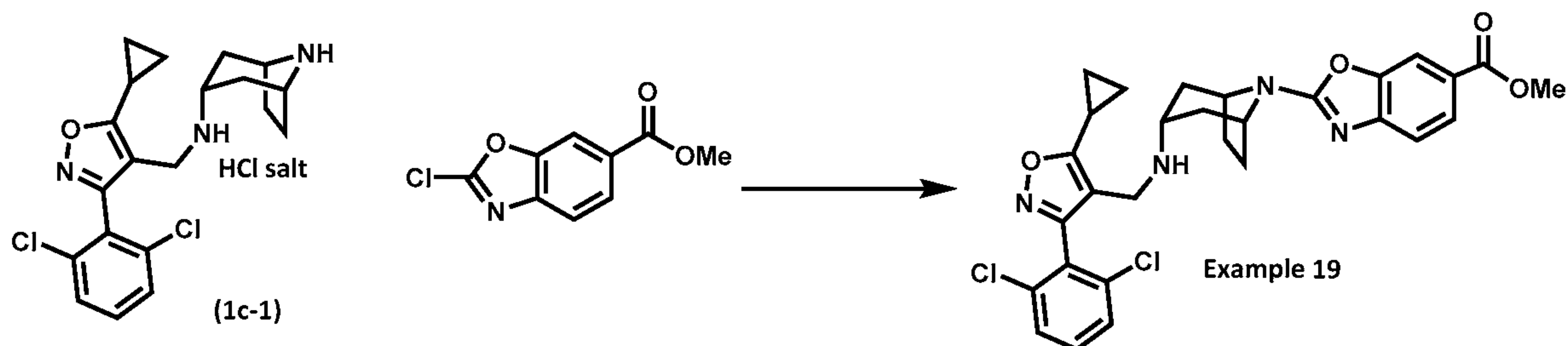
Example 5 was prepared from compound (1c-1) and methyl 2-bromo-4-methoxybenzo[d]thiazole-6-carboxylate according to the analogous procedure as in step 1d described for the preparation of Example 1. LC/MS observed [M+H], 613.15.

Example 6



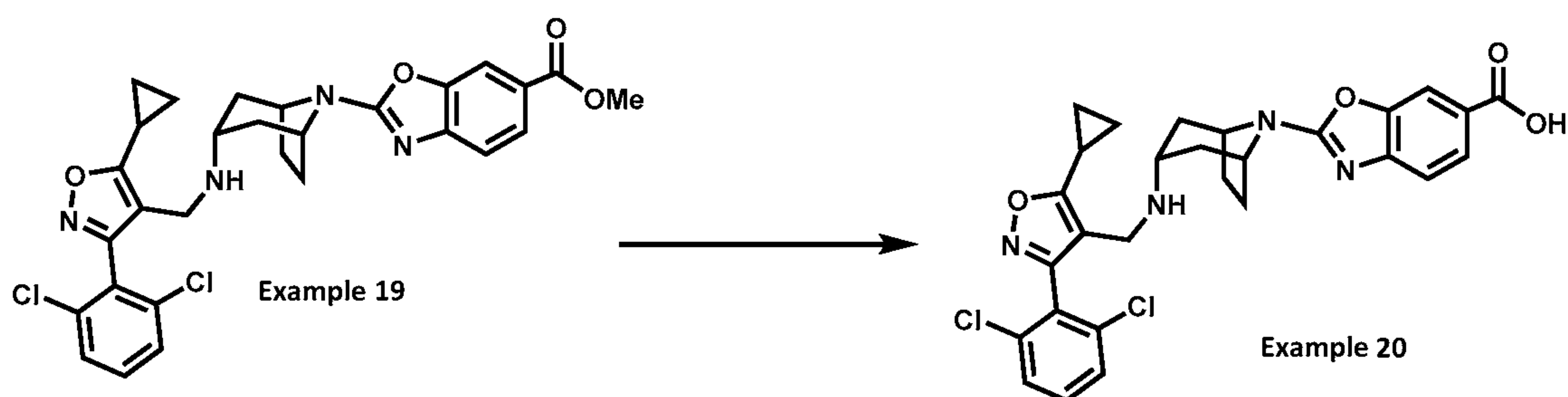
Example 6 was prepared according to the analogous procedure as in step 2a described for the preparation of Example 2. LC/MS observed [M+H], 599.13

Example 19



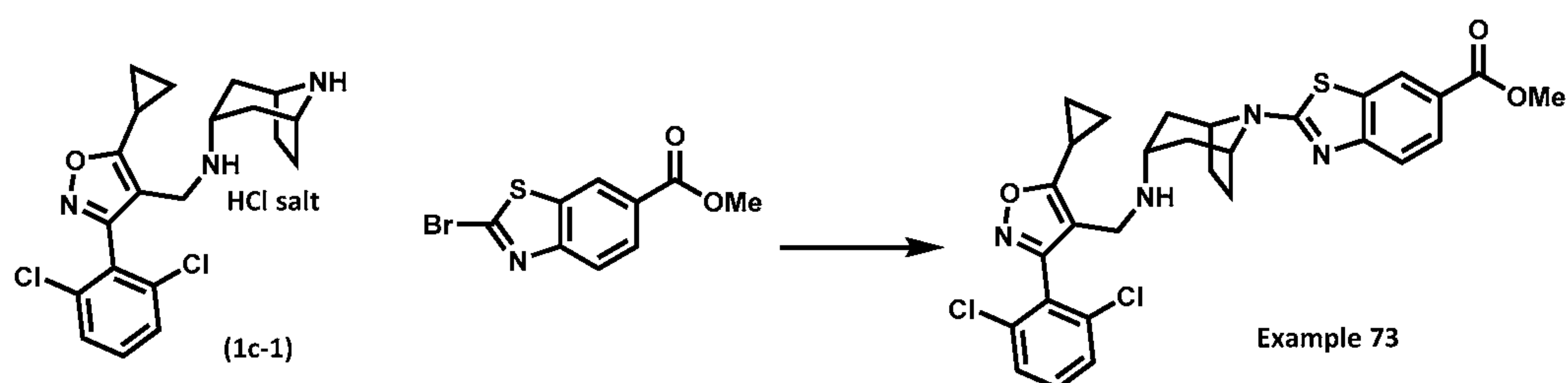
Example 19 was prepared from compound (1c-1) and methyl 2-chlorobenzo[d]oxazole-6-carboxylate according to the analogous procedure as in step 1d described for the preparation of Example 1. LC/MS observed $[M+H]^+$, 567.16.

Example 20



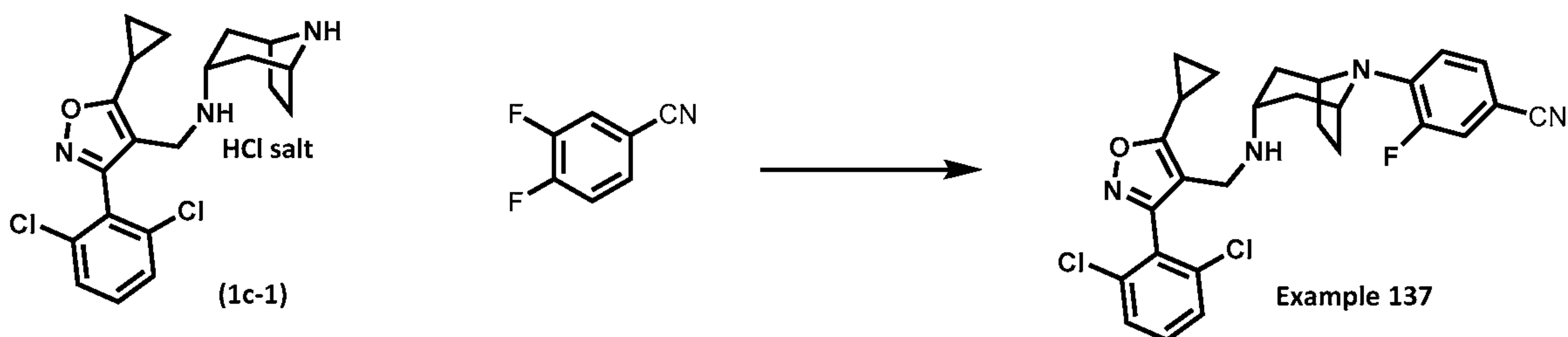
Example 20 was prepared according to the analogous procedure as in step 2a described for the preparation of Example 2. LC/MS observed $[M+H]^+$, 553.15.

10 Example 73

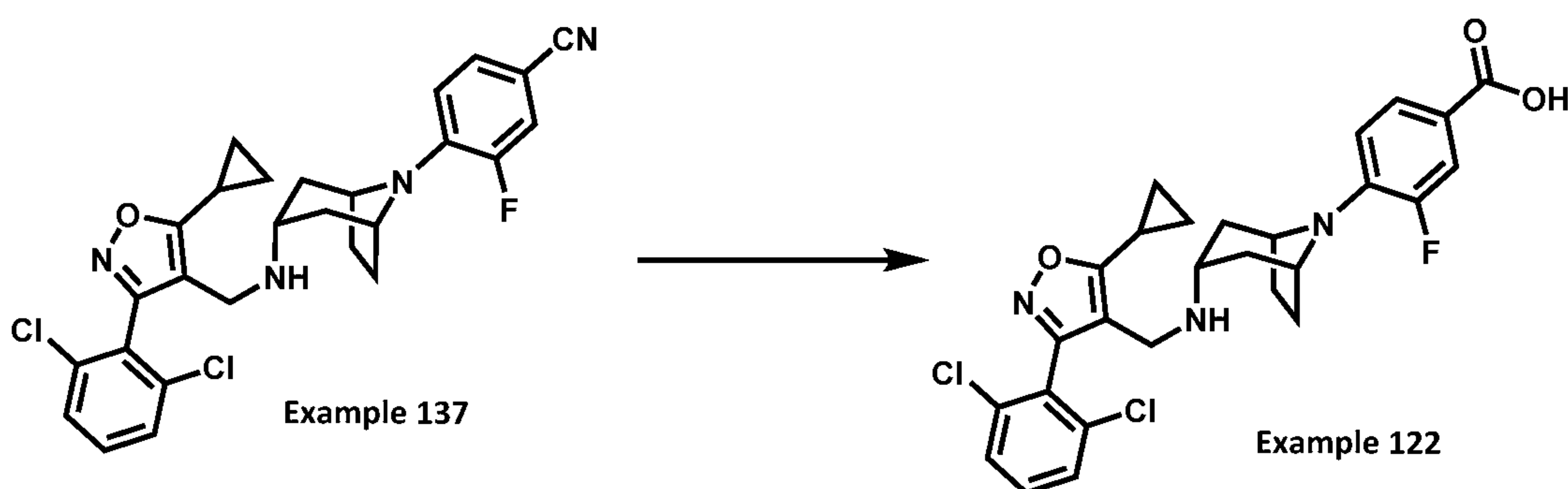


Example 73 was prepared from compound (1c-1) and methyl 2-bromobenzo[d]thiazole-6-carboxylate according to the analogous procedure as in step 1d described for the preparation of Example 1. LC/MS observed $[M+H]^+$, 583.14.

Example 137



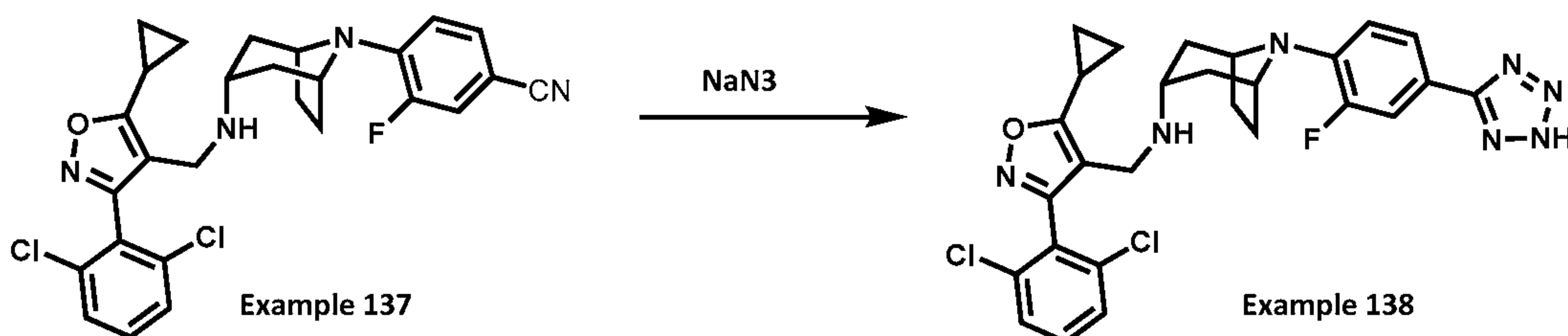
To a vial containing compound (1c-1) (123 mg, 0.229 mmol), 3,4-difluorobenzonitrile (958 mg, 6.88 mmol), and cesium carbonate (224 mg, 0.688 mmol), was added N,N-dimethylacetamide (1.4 ml). The mixture was stirred at 110 °C for 24h. The mixture was treated with water (10 ml), extracted by TBME (3 X 15ml). The combined organic layer was dried over Na₂SO₄, filtered, concentrated to give a crude mixture. The crude mixture was purified by combiflash (20 g silica gel, 0-50% EtOAc in hexane) to give Example 137 as mild yellow syrup (115 mg, 98% yield). LC/MS observed [M+H], 511.14; ¹H NMR (400 MHz, Chloroform-d) δ 7.27 – 6.99 (m, 5H), 6.56 (t, J = 8.8 Hz, 1H), 4.12 – 4.04 (m, 2H), 3.35 (s, 2H), 2.67 (t, J = 5.9 Hz, 1H), 1.92 (ddd, J = 8.5, 5.1, 3.3 Hz, 1H), 1.83 (ddd, J = 14.7, 5.9, 3.6 Hz, 2H), 1.67 – 1.55 (m, 4H), 1.28 (d, J = 15.0 Hz, 2H), 1.09 – 1.04 (m, 2H), 0.97 – 0.90 (m, 2H).



To a slurry of Example 137 (47 mg, 0.092 mmol) in MeOH (1 ml), was added aqueous sodium hydroxide solution (50%w, 146 µl, 2.76 mmol) at room temperature and the mixture was stirred at 65 °C for 16h. Another portion of NaOH (1M, 1 ml), EtOH (2ml) and DMA (2 ml) was added and the mixture was stirred at 65 °C for 51h. Reaction mixture was neutralized with HCl (1M) to pH=5. The solvent was removed and then diluted with EtOAc and Water. The organic layer was separated and aqueous layer was extracted by EtOAc (2X). The combined organic layers were washed by Brine, dried (Na₂SO₄), filtered, and concentrated. The residue was purified by prepHPLC to 4-((1R,3r,5S)-3-(((5-cyclopropyl-3-(2,6-

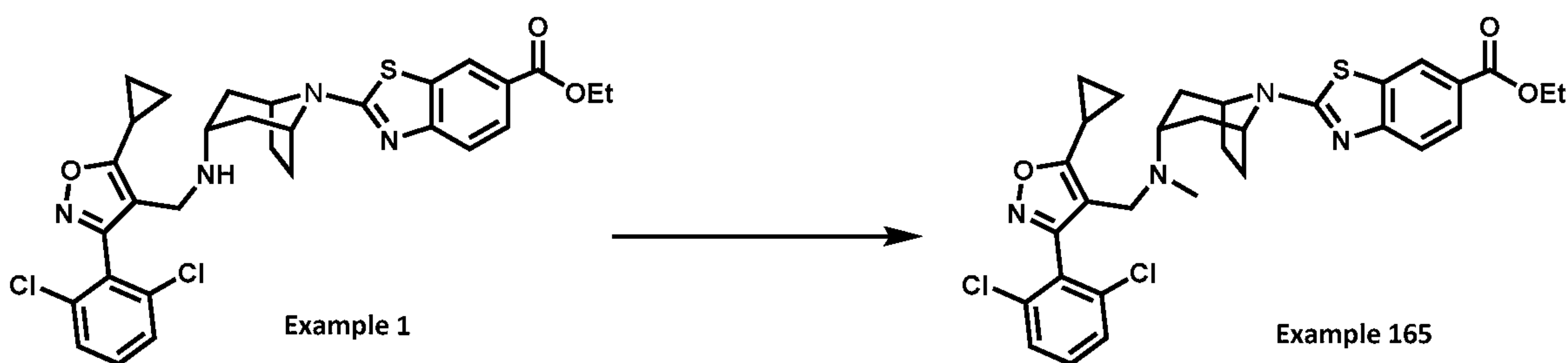
dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octan-8-yl)-3-fluorobenzoic acid (Example 122) (12 mg) as a white solid. LC/MS observed [M+H], 530.16; ¹H NMR (400 MHz, Methanol-d₄) δ 7.62 – 7.38 (m, 5H), 6.88 (t, J = 8.8 Hz, 1H), 4.21 (m, 2H), 3.55 (s, 2H), 2.85 – 2.75 (m, 1H), 2.32 – 2.19 (m, 1H), 2.11 – 1.99 (m, 2H), 1.86 – 1.68 (m, 4H), 1.52 – 1.39 (m, 2H), 1.17 – 1.14 (m, 2H), 1.14 – 1.11 (m, 2H).

Example 138



To a vial containing Example 137 (62 mg, 0.121 mmol), sodium azide (79 mg, 1.212 mmol), and ammonium chloride (64.8 mg, 1.212 mmol), was added DMA (1.7 ml). The mixture was stirred at 120 °C for 20 h. Upon cooling to room temperature, the reaction mixture was diluted by EtOAc (25 ml), washed by water (2x 10 ml). The organic layers was separated, dried, filtered and concentrated to give a crude oil. 1/3 of crude mixture was purified by prepHPLC (reverse column, 0.1% FA in ACN; 0.1% FA in water) to afford Example 138 (9 mg) as a white solid. LC/MS observed [M+H], 554.16; ¹H NMR (400 MHz, Chloroform-d) δ 7.97 (bs, 1H), 7.65 – 7.56 (m, 2H), 7.40 (d, J = 7.6 Hz, 2H), 7.32 (dd, J = 9.1, 7.0 Hz, 1H), 6.83 (t, J = 8.6 Hz, 1H), 4.22 (s, 2H), 3.57 – 3.43 (m, 2H), 2.88 – 2.79 (m, 1H), 2.12 – 2.01 (m, 3H), 1.97 – 1.50 (m, 4H), 1.43 (d, J = 14.4 Hz, 2H), 1.26 – 1.18 (m, 2H), 1.13 – 1.03 (m, 2H).

Example 165

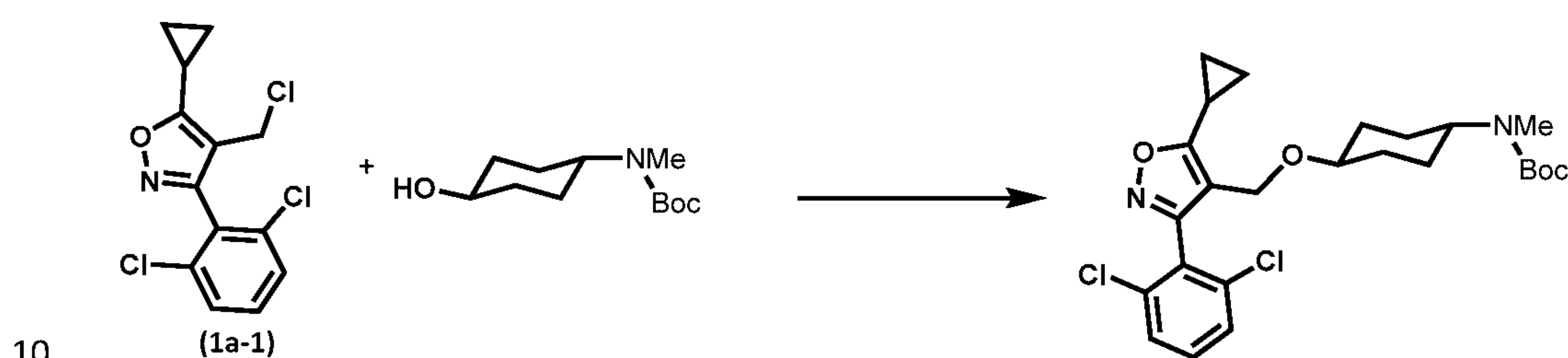


To ethyl 2-((1R,3R,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octan-8-yl)benzo[d]thiazole-6-carboxylate (Example 1) (28 mg, 0.047 mmol) in trifluoroethanol (2 ml) was added paraformaldehyde (2.81 mg, 0.094

mmol) and the resulting mixture was heated up to 45 °C. Sodium borohydride (3.55 mg, 0.094 mmol) was added and stirred for 30 mins. The mixture was concentrated under vacuo and diluted with ethyl acetate, then washed with 1 N NaOH solution, water, and brine. The organic layer was dried, filtered, and concentrated and the residue was purified by

5 CombiFlash eluting with hexane to 40% ethyl acetate in hexane to give ethyl 2-((1R,3R,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)(methyl)amino)-8-azabicyclo[3.2.1]octan-8-yl)benzo[d]thiazole-6-carboxylate (Example 165) (28 mg). LC/MS observed [M+H], 611.17.

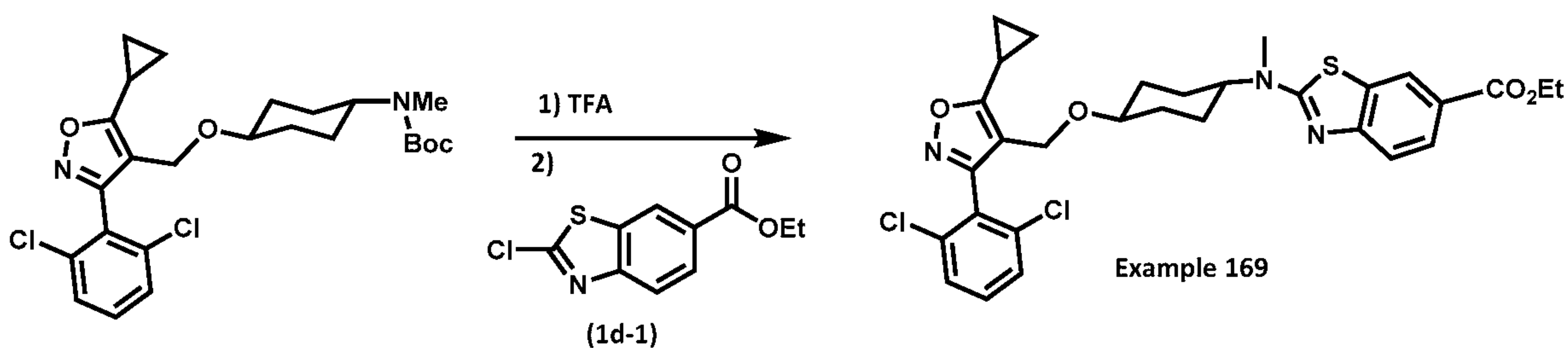
Example 169



To a solution of *tert*-butyl ((1R,4R)-4-hydroxycyclohexyl)(methyl)carbamate (182 mg, 0.793 mmol) in THF (3 ml) was added 18-crown-6 (210 mg, 0.793 mmol) and potassium *tert*-butoxide (104 mg, 0.925 mmol). The resulting mixture was stirred at room temperature for 1 h and to this mixture was added 4-(chloromethyl)-5-cyclopropyl-3-(2,6-

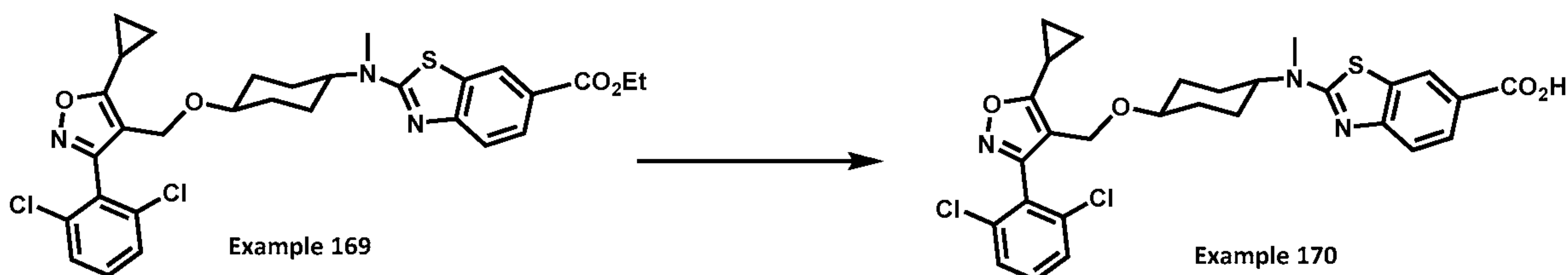
15 dichlorophenyl)isoxazole (1a-1) (200 mg, 0.661 mmol) in THF (2 mL). The resulting mixture was stirred at room temperature for 6 h and was quenched with water and extracted with MTBE (3X). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo and the residue was purified by CombiFlash eluting with hexane to 30% EtOAc in hexane to give *tert*-butyl ((1R,4R)-4-((5-cyclopropyl-3-(2,6-

20 dichlorophenyl)isoxazol-4-yl)methoxy)cyclohexyl)(methyl)carbamate (141.2 mg). LC/MS observed [M-tBu+H], 439.12.



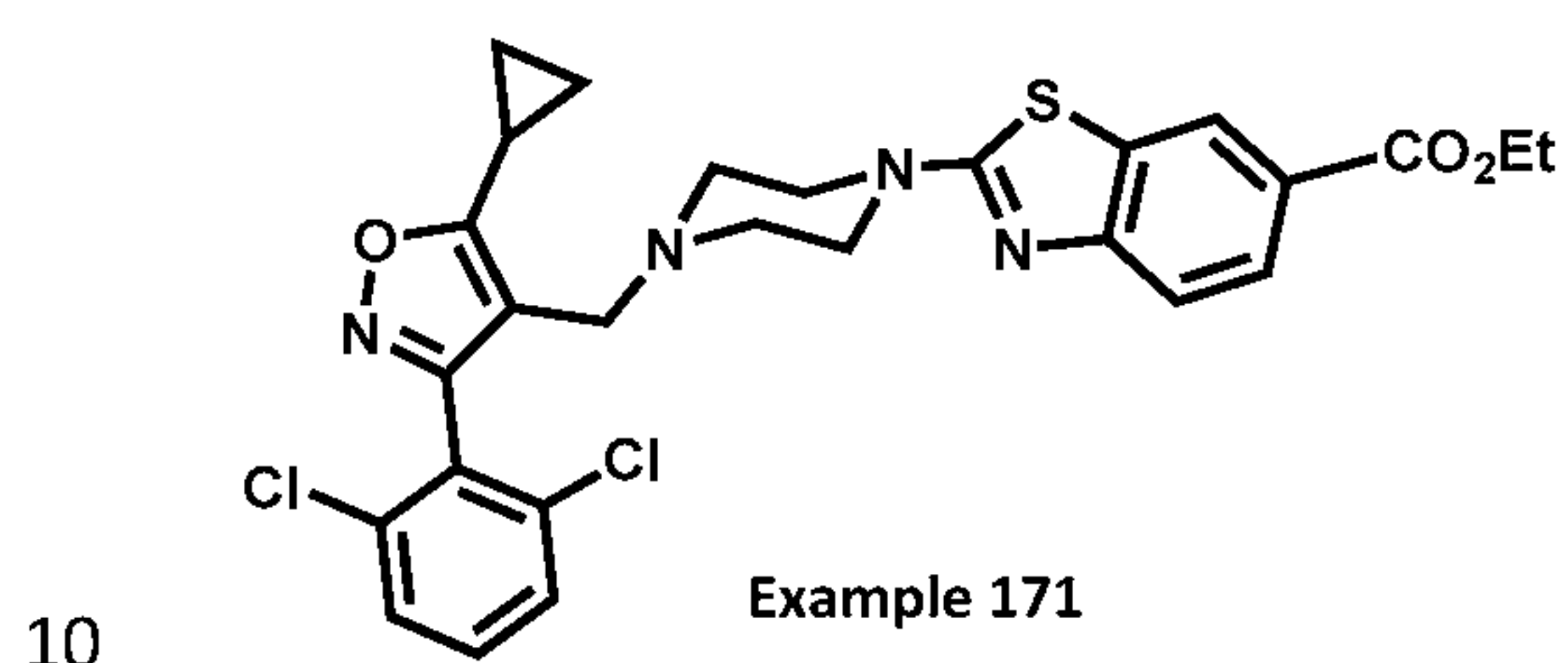
Example 169 was prepared from *tert*-butyl ((1*R*,4*R*)-4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)cyclohexyl)(methyl)carbamate according to the analogous procedures as in step 1b and step 1d described for the preparation of Example 1. LC/MS observed [M+H], 600.15.

5 Example 170



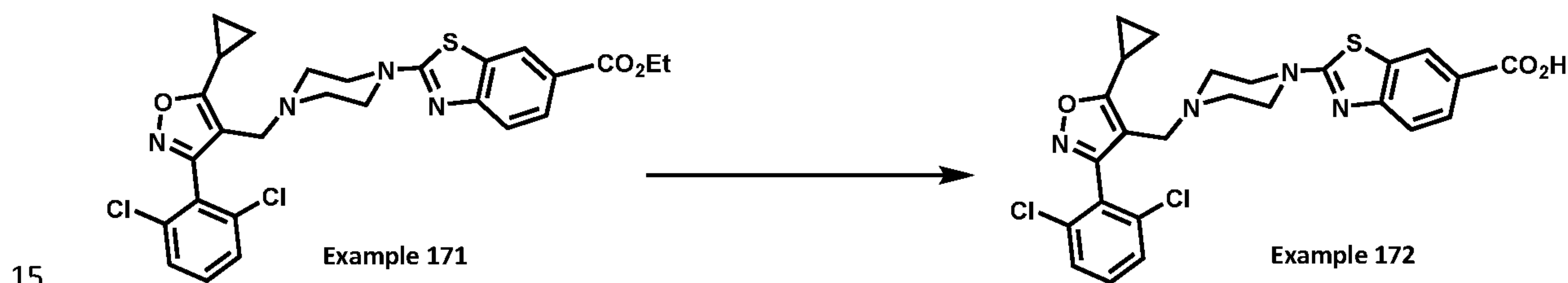
Example 170 was prepared according to the analogous procedure as in step 2a described for the preparation of Example 2. LC/MS observed [M+H], 572.12.

Example 171



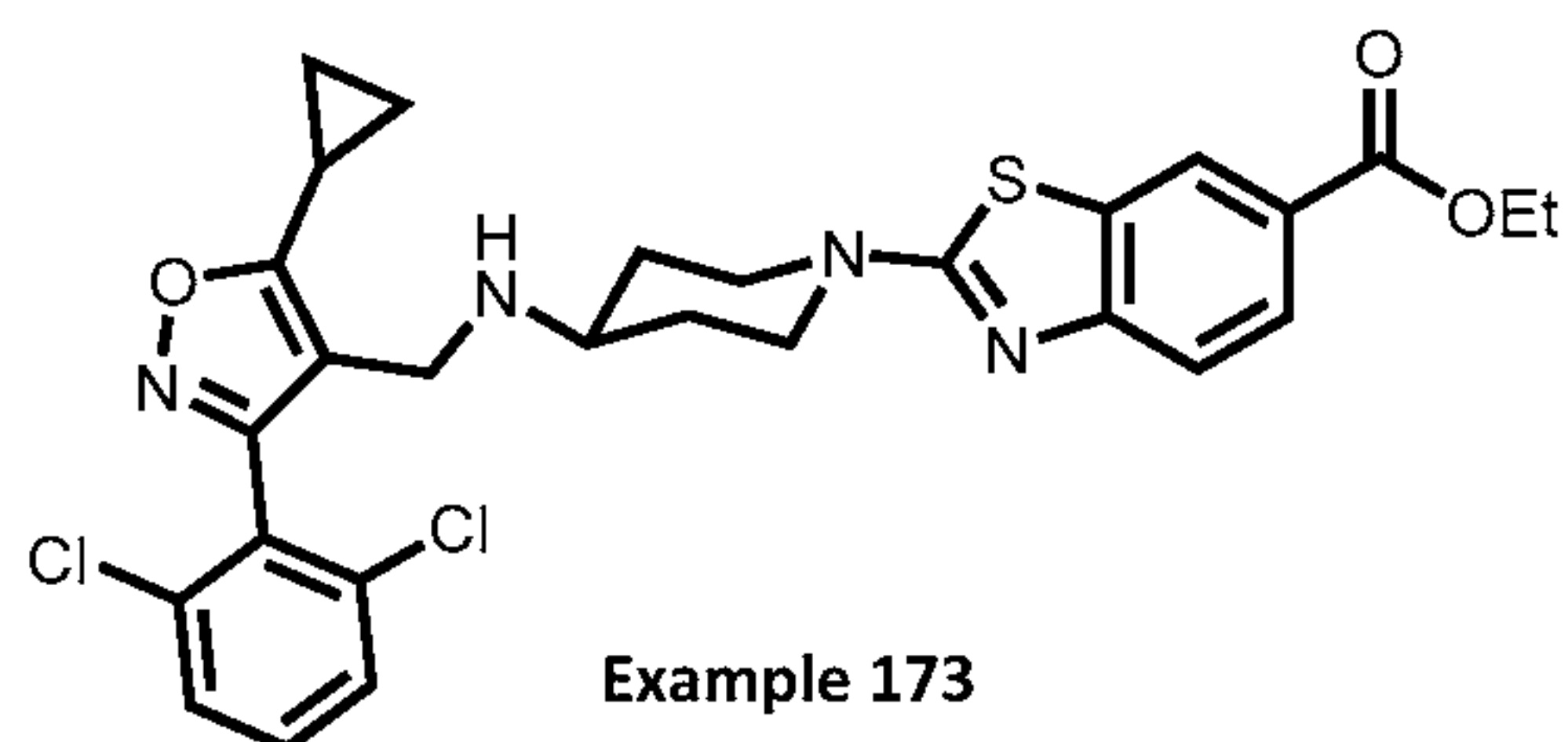
Example 171 was prepared from *tert*-butyl piperazine-1-carboxylate according to the analogous procedures as in step 1a, step 1b and step 1d described for the preparation of Example 1. LC/MS observed [M+H], 557.16.

Example 172



Example 172 was prepared according to the analogous procedure as in step 2a described for the preparation of Example 2. LC/MS observed [M+H], 529.13.

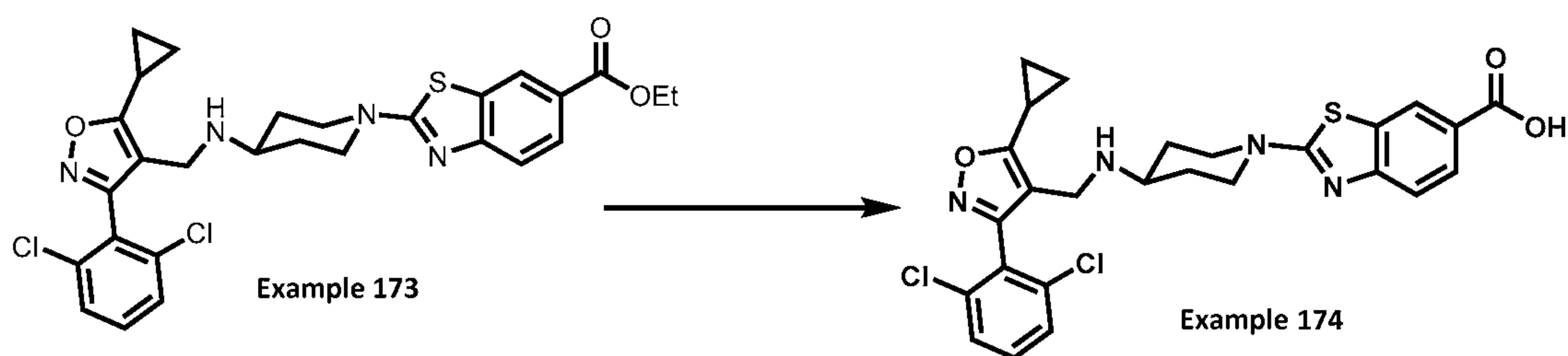
Example 173



Example 173 was prepared from *tert*-butyl 4-aminopiperidine-1-carboxylate according to the analogous procedures as in step 1a, step 1b and step 1d described for the preparation of

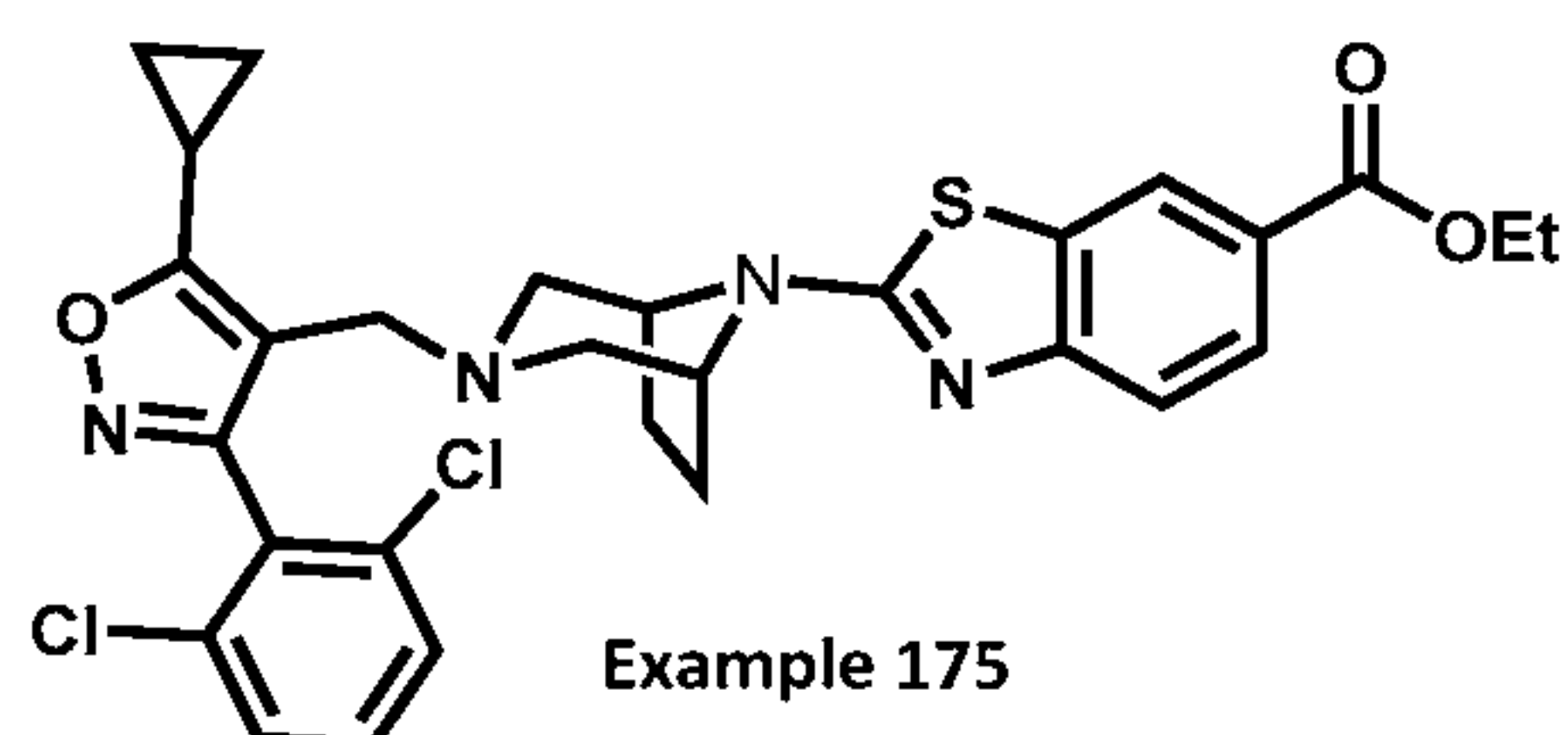
5 Example 1. LC/MS observed [M+H], 571.13.

Example 174



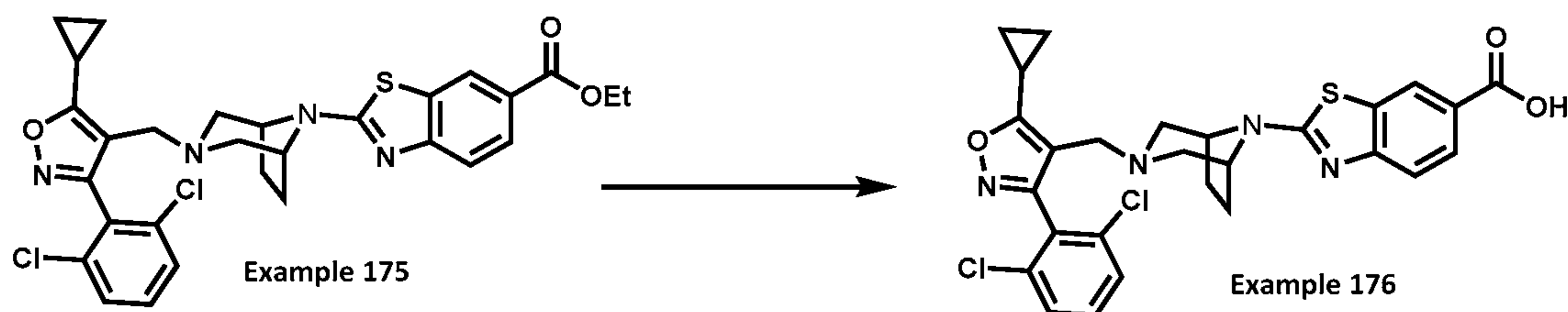
Example 174 was prepared according to the analogous procedure as in step 2a described for the preparation of Example 2. LC/MS observed [M+H], 543.18.

10 Example 175



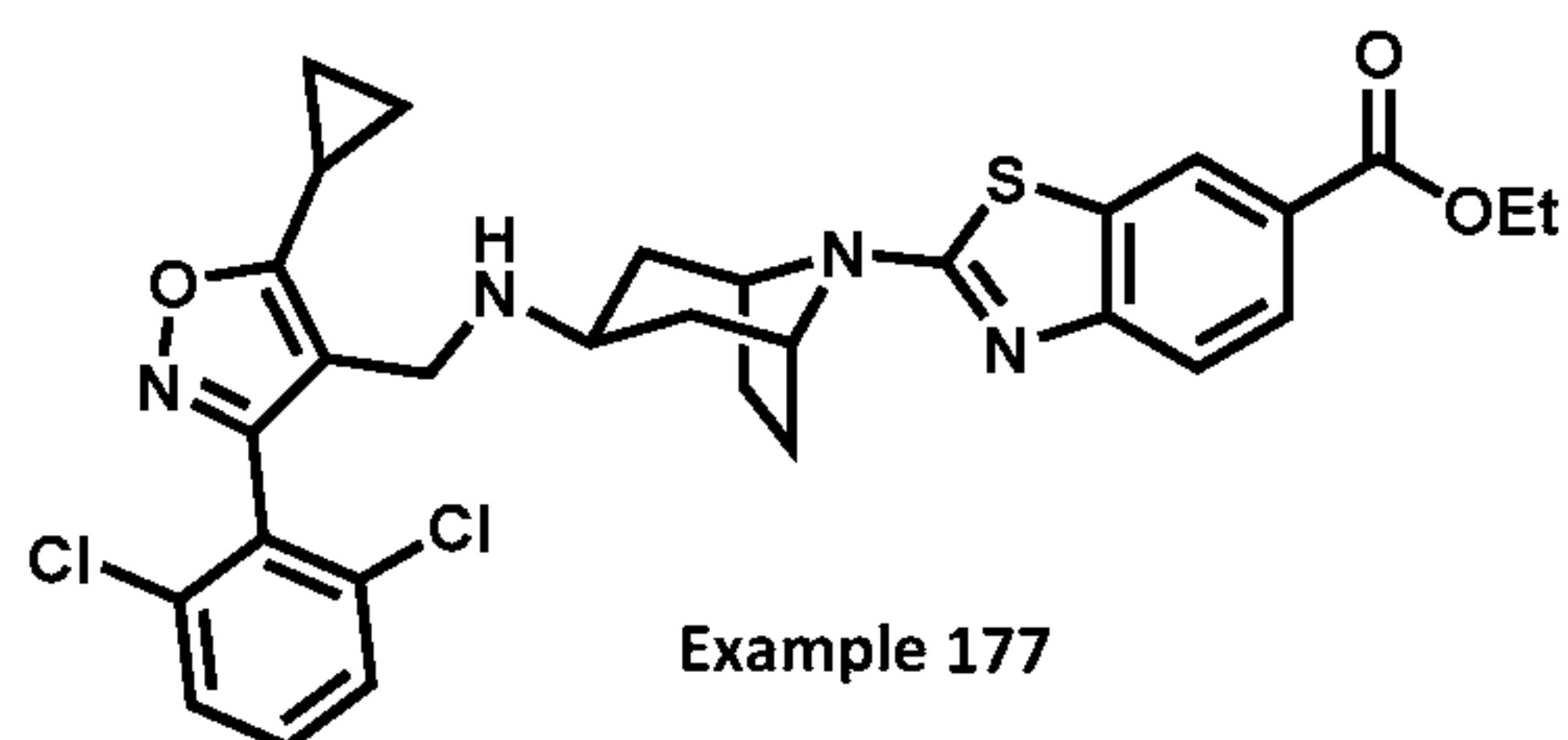
Example 175 was prepared from *tert*-butyl (1R,5S)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate according to the analogous procedures as in step 1a, step 1b and step 1d described for the preparation of Example 1. LC/MS observed [M+H], 571.13.

Example 176



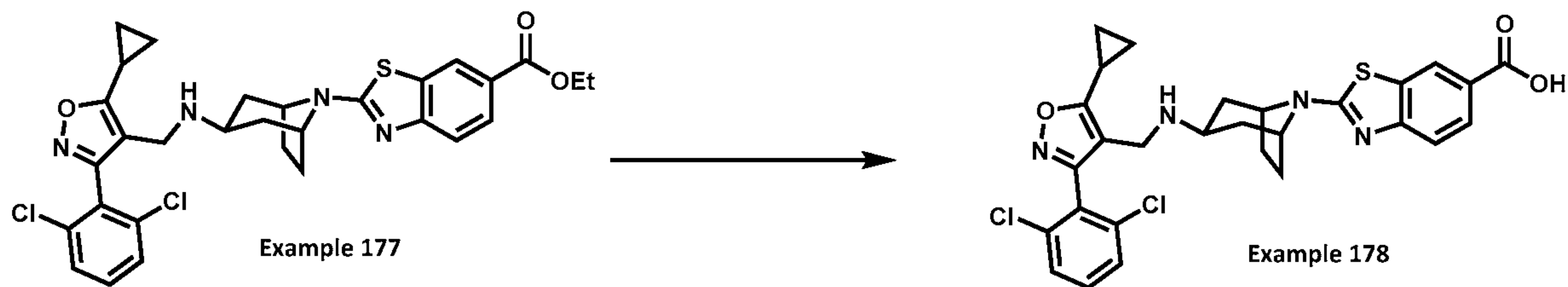
Example 176 was prepared according to the analogous procedure as in step 2a described for the preparation of Example 2. LC/MS observed $[M+H]^+$, 555.10.

5 Example 177



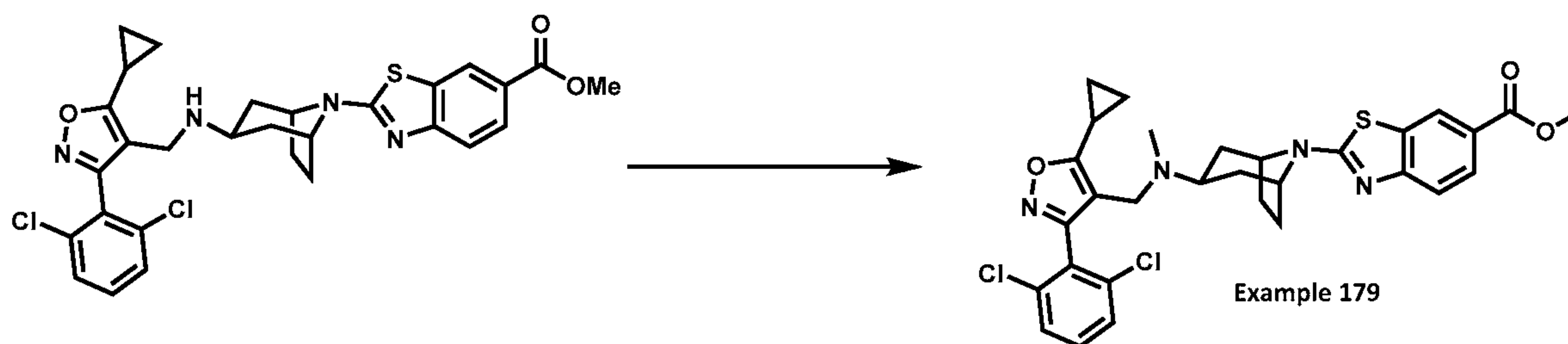
Example 177 was prepared from tert-butyl (1R,3S,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate according to the analogous procedures as in step 1a, step 1b and step 1d described for the preparation of Example 1. LC/MS observed $[M+H]^+$, 597.15.

10 Example 178



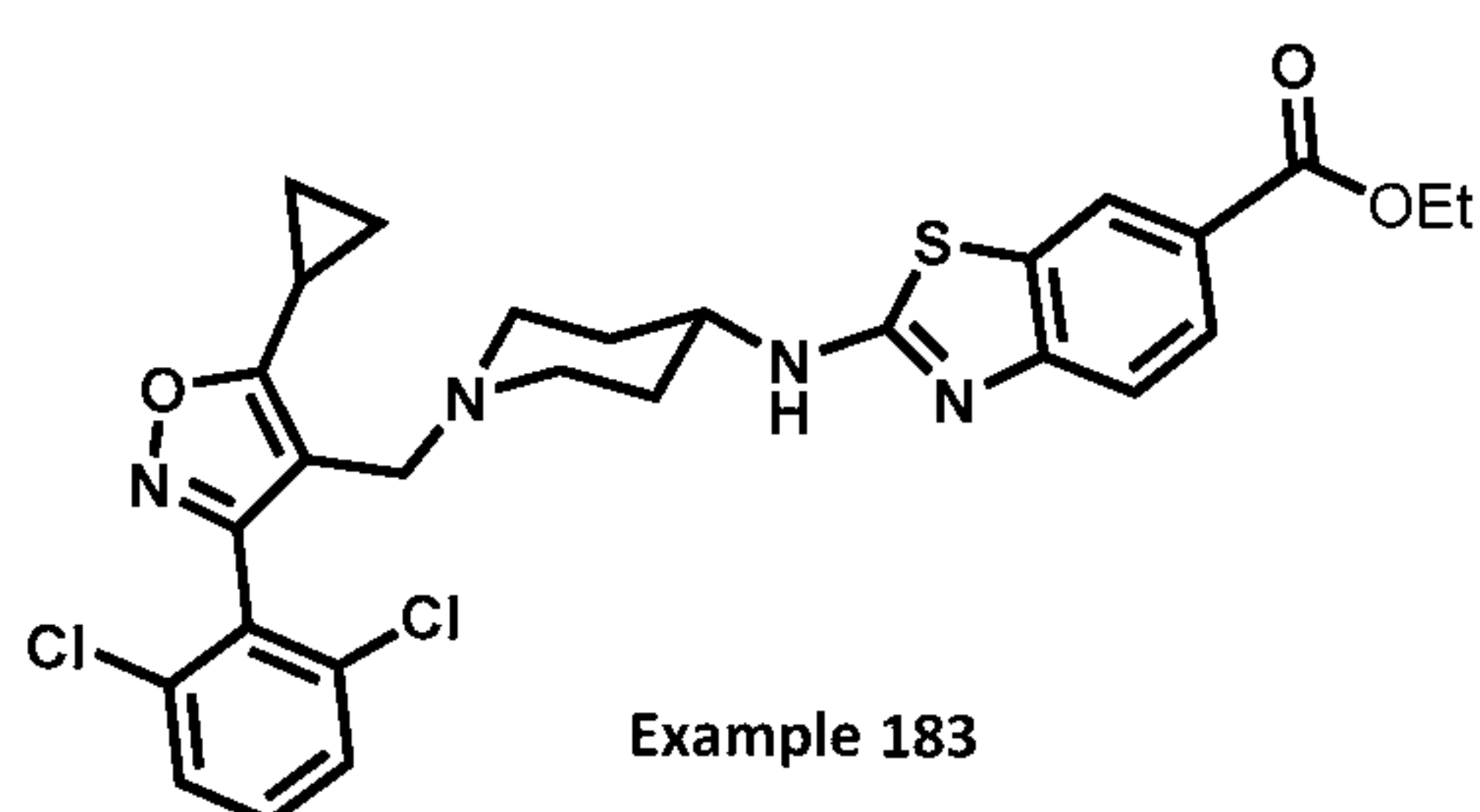
Example 178 was prepared according to the analogous procedure as in step 2a described for the preparation of Example 2. LC/MS observed $[M+H]^+$, 569.12.

Example 179



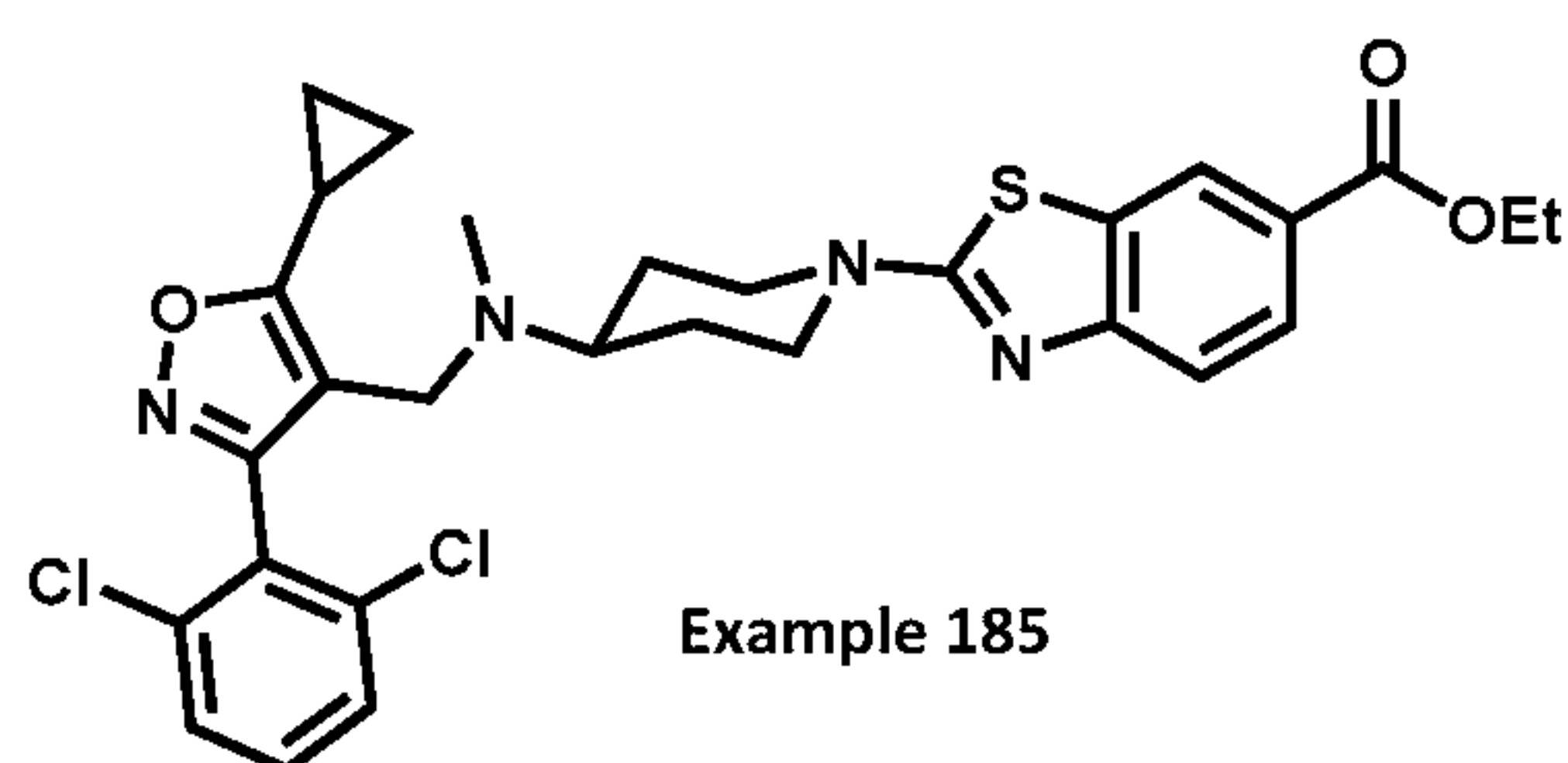
To methyl 2-((1R,3S,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octan-8-yl)benzo[d]thiazole-6-carboxylate (17.4 mg, 0.030 mmol) in DCM (0.3 ml) was added MeI (0.019 ml, 0.298 mmol) and Et₃N (0.062 ml, 0.447 mmol). The resulting mixture was stirred at room temperature for 20h and then concentrated. The residue was purified by CombiFlash Purification eluting with Hexane to 40% Acetone in Hexane to give Example 179 (9.5 mg). LC/MS observed [M+H], 597.15.

Example 183



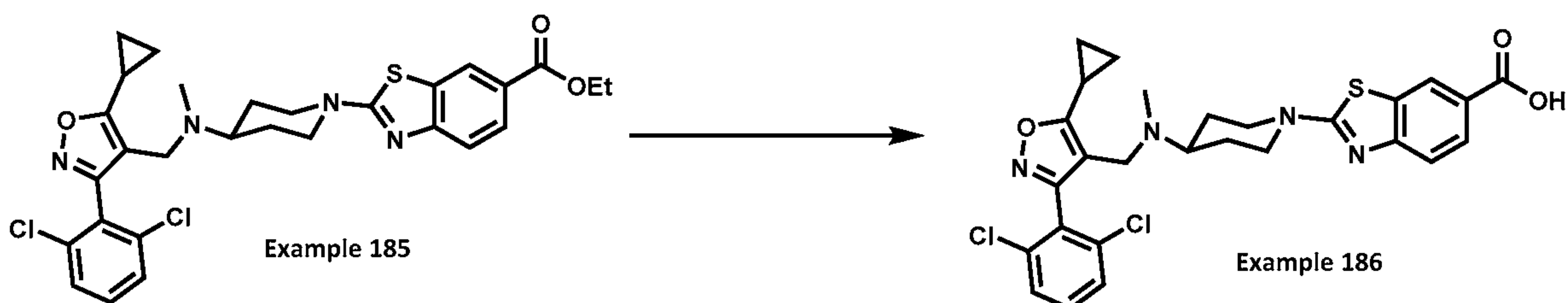
Example 183 was prepared from *tert*-butyl piperidin-4-ylcarbamate according to the analogous procedures as in step 1a, step 1b and step 1d described for the preparation of Example 1. LC/MS observed [M+H], 571.13.

Example 185



Example 185 was prepared from *tert*-butyl 4-(methylamino)piperidine-1-carboxylate according to the analogous procedures as in step 1a, step 1b and step 1d described for the preparation of Example 1. LC/MS observed [M+H], 585.15.

Example 186



Example 186 was prepared according to the analogous procedure as in step 2a described for the preparation of Example 2. LC/MS observed $[M+H]^+$, 557.12.

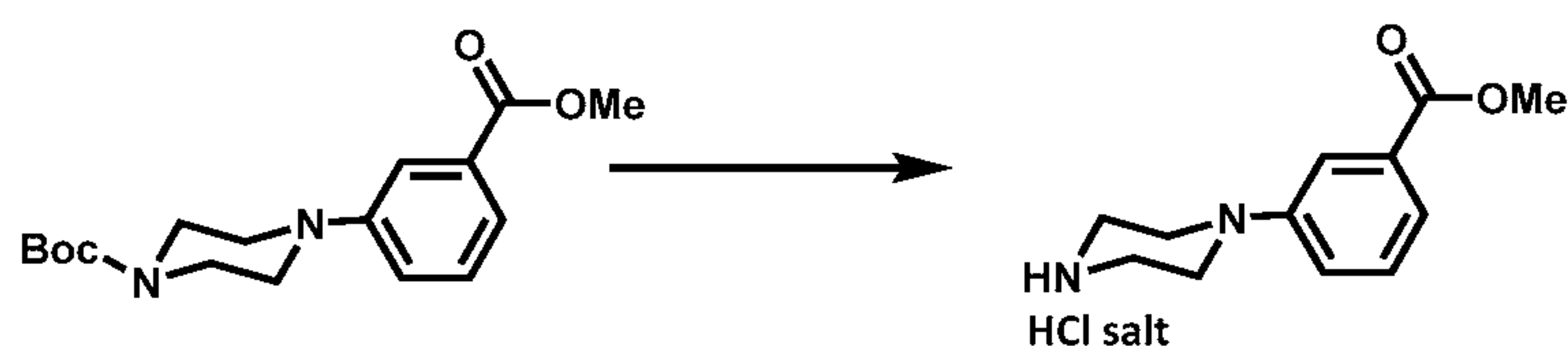
5 Example 187

Step 187-a



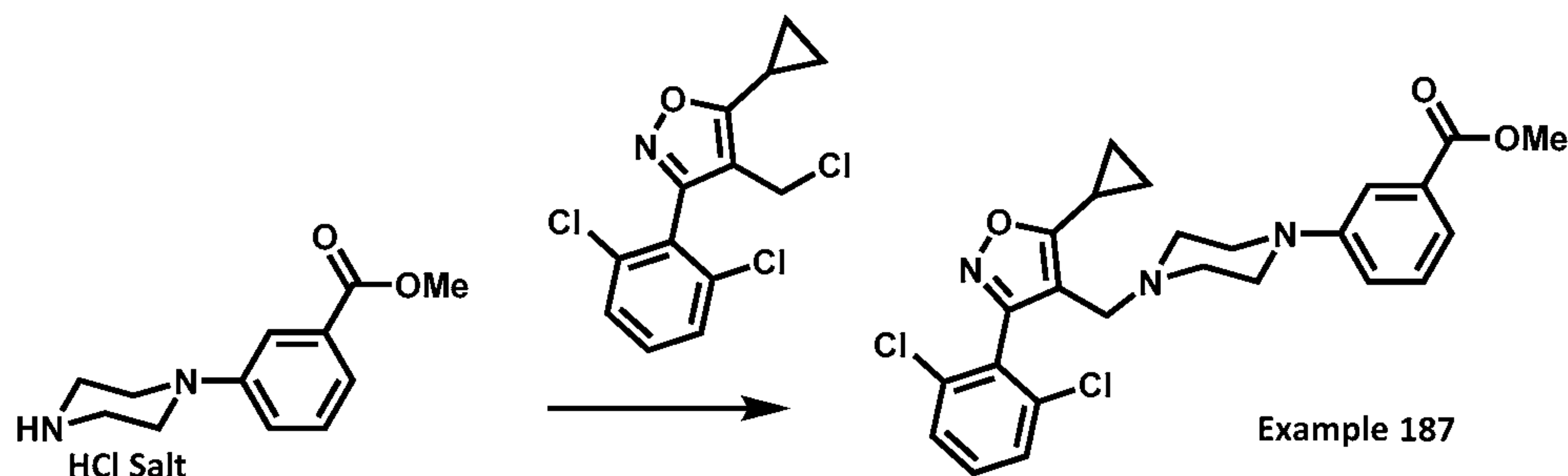
To *tert*-butyl piperazine-1-carboxylate (500 mg, 2.68 mmol), methyl 3-iodobenzoate (1055 mg, 4.03 mmol), L-proline (124 mg, 1.074 mmol), copper(I) iodide (102 mg, 0.537 mmol) and cesium carbonate (2187 mg, 6.71 mmol) was added DMSO (6 ml) and the resulting mixture was heated up at 90 °C for 7 h. The mixture was diluted with ethyl acetate and filtered through celite. The filtrate was collected and concentrated under vacuo. The residue was purified by CombiFlash eluting with hexane to 40% ethyl acetate in hexane to give *tert*-butyl 4-(3-(methoxycarbonyl)phenyl)piperazine-1-carboxylate (182 mg). LC/MS observed $[M-Boc+H]^+$, 221.13.

Step 187-b



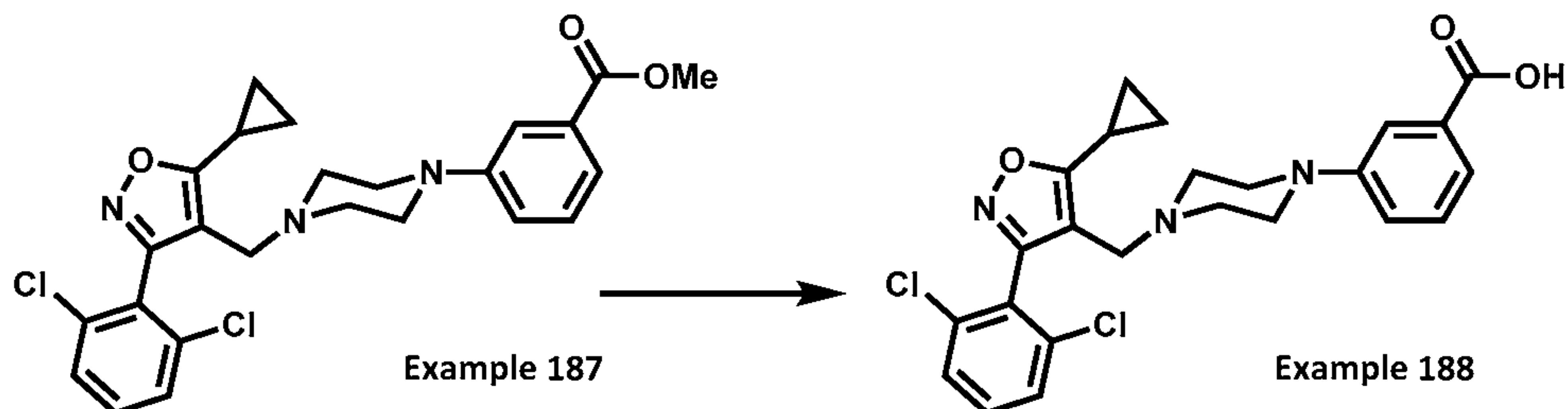
To *tert*-butyl 4-(3-(methoxycarbonyl)phenyl)piperazine-1-carboxylate (282 mg, 0.880 mmol) in DCM (3ml) was added HCl (0.267 ml, 8.80 mmol, 4M in dioxane) and the resulting mixture was stirred at RT for 4h. The mixture was concentrated under vacuo and chased with DCM to give methyl 3-(piperazin-1-yl)benzoate hydrochloride (292 mg).

Step 187-c



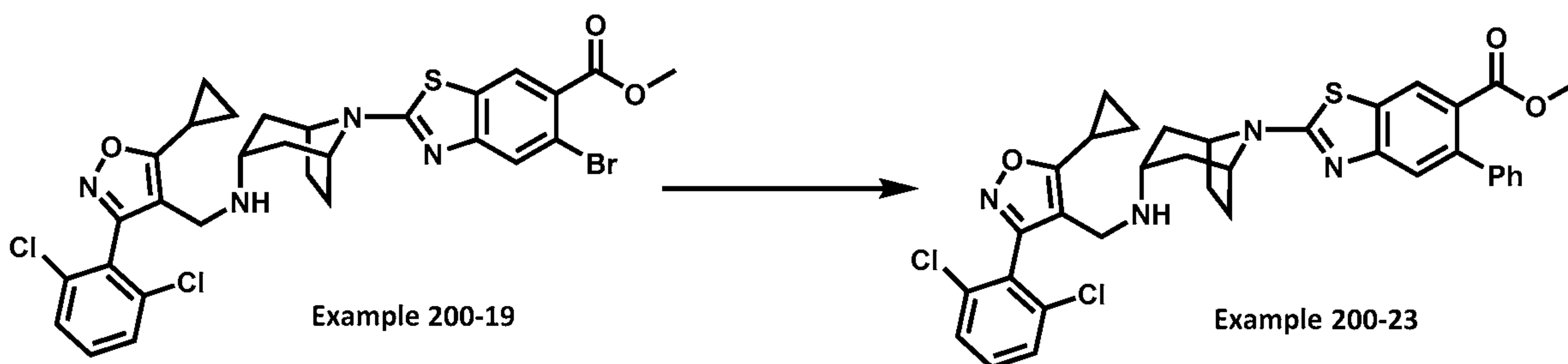
To methyl 3-(piperazin-1-yl)benzoate hydrochloride (226 mg, 0.88 mmol), 4-(chloromethyl)-5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazole (306 mg, 1.012 mmol), TBAI (65.0 mg, 0.176 mmol) in Acetonitrile (4 ml) was added cesium carbonate (717 mg, 2.200 mmol) and the resulting mixture was stirred at 60 °C for 24 h. The mixture was concentrated and the residue was diluted with DCM and filtered. The filtrate was collected and concentrated and the residue was purified by CombiFlash eluting with hexane to 35% ethyl acetate in hexane to give Example 187 (170 mg). LC/MS observed [M+H], 486.14.

10 Example 188



Example 188 was prepared according to the analogous procedure as in step 2a described for the preparation of Example 2. LC/MS observed [M+H], 472.12.

Example 200-23

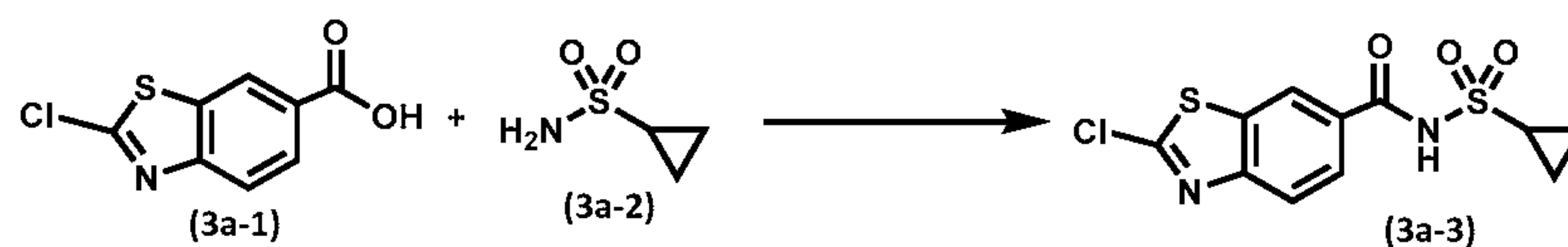


A mixture of phenylboronic acid (7.90 mg, 0.065 mmol), Example 200-19 (33 mg, 0.050 mmol), cesium carbonate (32.5 mg, 0.100 mmol) and bis(triphenylphosphine)palladium(II)

chloride (1.748 mg, 2.491 μ mol) in DMF (1 ml) was stirred under argon atmosphere at 80 °C overnight. After cooling down, the most of DMF was removed by N₂ blowing. The residue was diluted with ethyl acetate and water and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na₂SO₄), filtered and concentrated. The residue was purified by Combiflash (8 g silica gel, 0-50% EtOAc-Hexane) to give a Example 200-23 (10 mg) as colorless oil. LC/MS observed [M+H], 659.17; ¹H NMR (500 MHz, Chloroform-d) δ 8.11 (s, 1H), 7.47 – 7.27 (m, 9H), 4.29 – 4.17 (m, 2H), 3.59 (s, 3H), 3.52 (s, 2H), 2.92 – 2.87 (m, 1H), 2.21 – 2.12 (m, 2H), 2.10 – 1.99 (m, 1H), 1.89 – 1.80 (m, 4H), 1.60 – 1.54 (m, 2H), 1.27 – 1.18 (m, 2H), 1.12 – 1.04 (m, 2H).

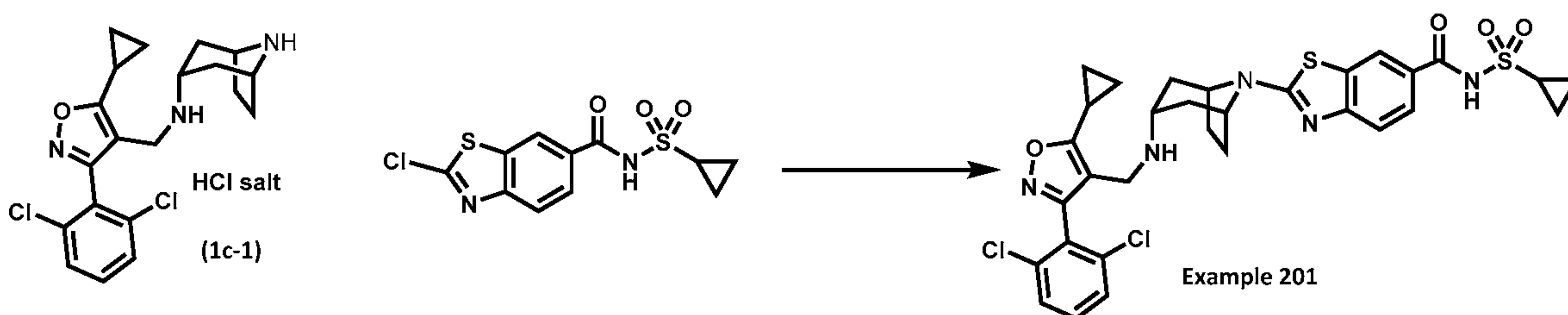
Example 201

Step 201-a



To 2-chlorobenzo[d]thiazole-6-carboxylic acid (200 mg, 0.936 mmol) and cyclopropanesulfonamide (113 mg, 0.936 mmol) in DCM (2 ml) was added EDCI (197 mg, 1.030 mmol) and DMAP (252 mg, 2.060 mmol). The resulting mixture was stirred at room temperature for 16 hrs and then concentrated. The residue was diluted with ethyl acetate and washed with 1N HCl, water. The organic layer contains some white solid and was filtered. The filtrate was collected, dried, and concentrated to give 2-chloro-N-(cyclopropylsulfonyl)benzo[d]thiazole-6-carboxamide (232 mg). This material was used directly to next step without further purification.

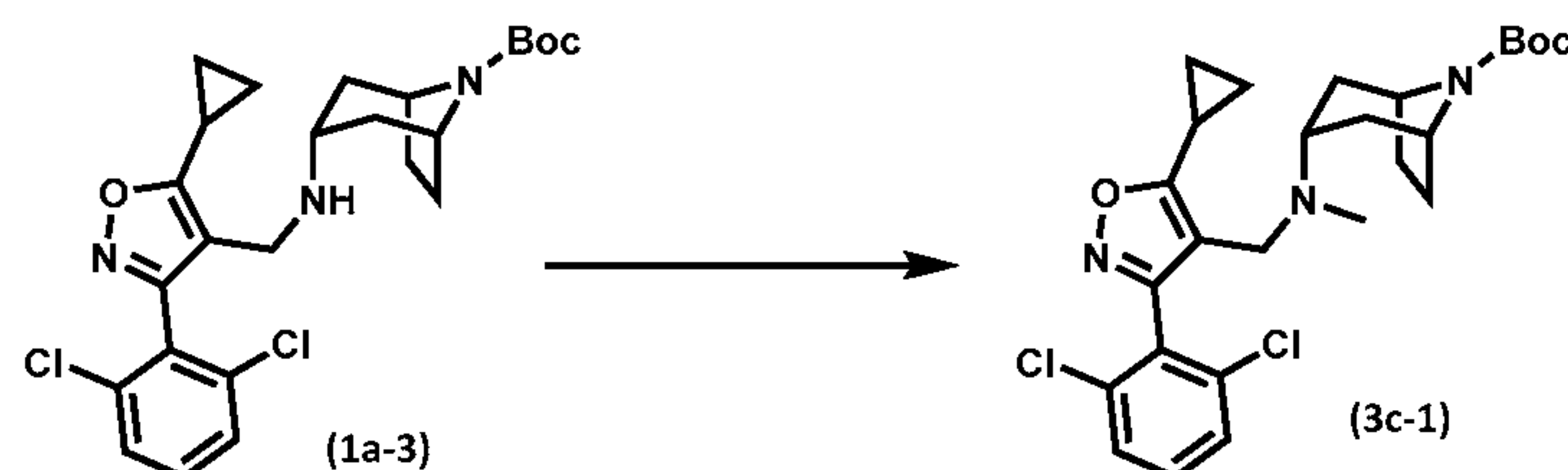
Step 201-b



To 2-chloro-N-(cyclopropylsulfonyl)benzo[d]thiazole-6-carboxamide (32.5 mg, 0.103 mmol) and (1R,3r,5S)-N-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)-8-azabicyclo[3.2.1]octan-3-amine hydrochloride (1c-1) (54.4 mg, ~0.093 mmol, ~74% purity by weight) in DMA (1.5 ml) was added cesium carbonate (60.8 mg, 0.187 mmol). The mixture was added stirred at 65 °C for 18 h, then diluted with ethyl acetate, washed with water. The aq. layer was separated, neutralized with 1 N HCl, then extracted extracted back with with ethyl acetate. All the organic lyaer was combined, washed with water, brine, dried, filtered and concentrated. The residue was purified by CombiFlash eluting with DCM to 40% Acetone/DCM to give Example 201 (20.2 mg). LC/MS observed [M+H], 672.14.

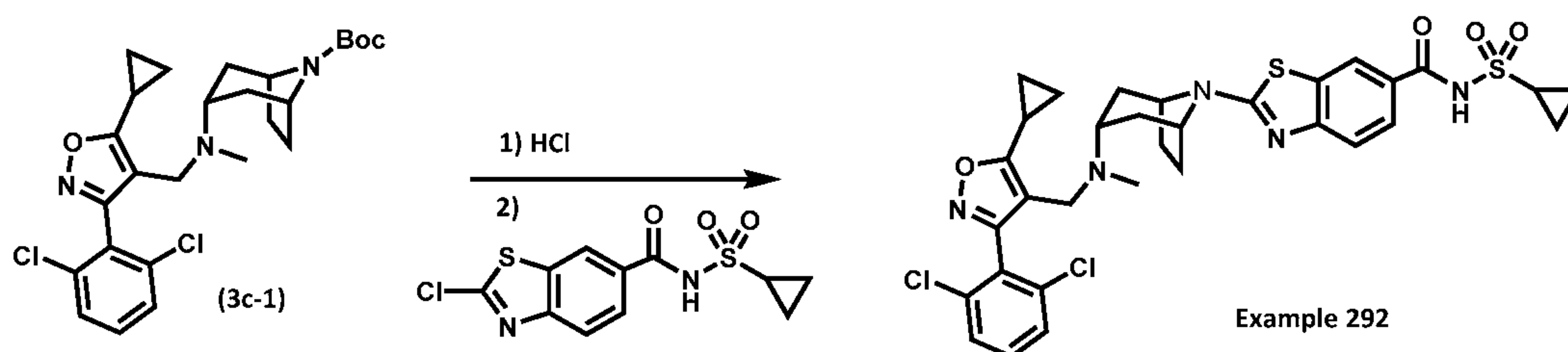
10 Example 292

Step 292-a



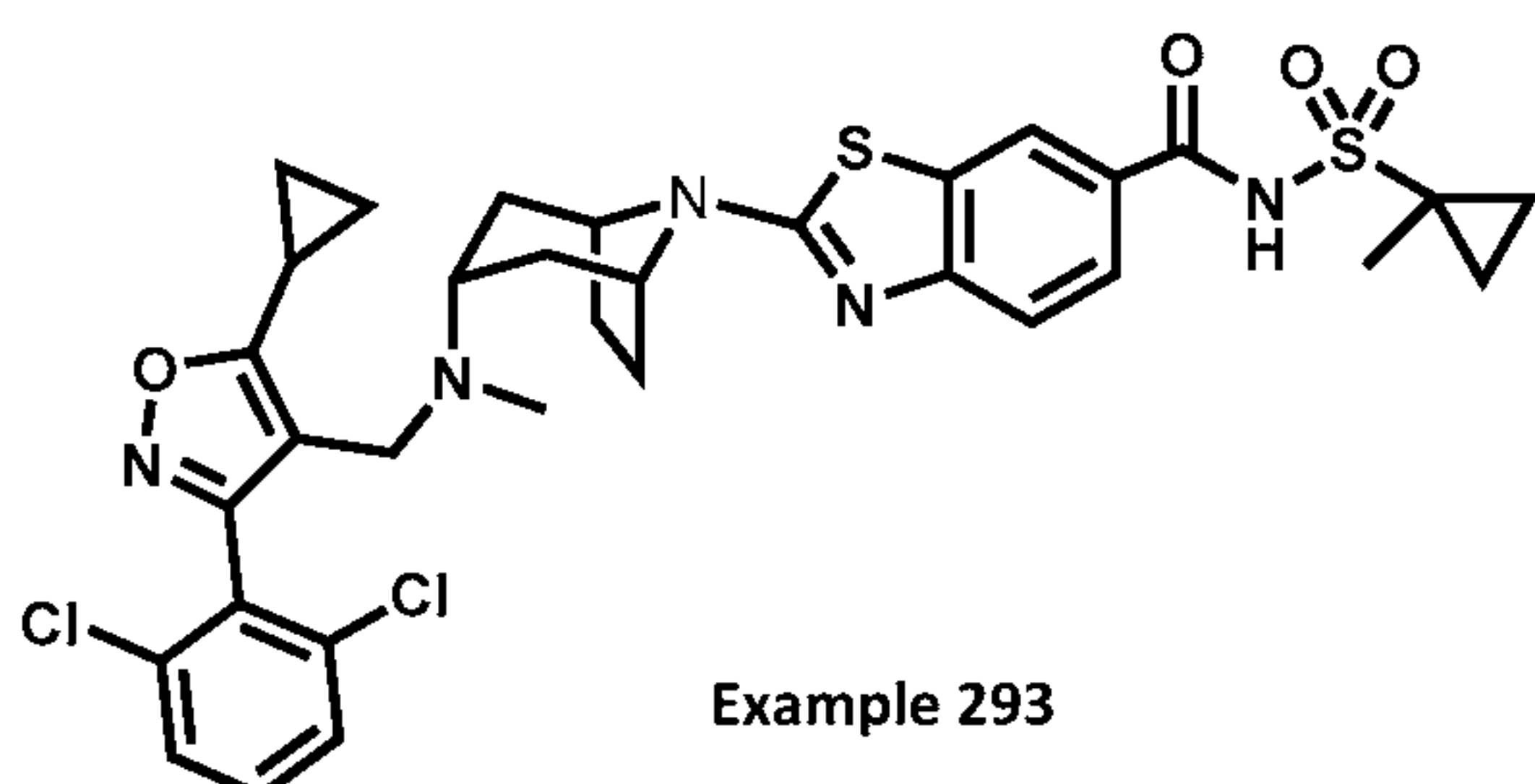
To paraformaldehyde (4.27 mg, 0.142 mmol) and *tert*-butyl (1R,3R,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (1a-3) (35 mg, 0.071 mmol) in 2,2,2-trifluoroethan-1-ol (1.5 ml, 0.071 mmol) at 45 °C was added sodium borohydride (5.38 mg, 0.142 mmol). The reaction mixture was stirred at 45 °C for 30 min, and then quenched with 1 drop of 1 N HCl. The reaction mixture was concentrated under vacuo and the residue was diluted with ethyl acetate and washed ith 1 N NaOH solution, water, brine, dried, filtered, and concentrated to give *tert*-butyl (1R,3R,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (3c-1) (39.2 mg). LC/MS observed [M+H], 506.09.

Step 292-b



Example 292 was prepared from *tert*-butyl (1R,3R,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (3c-1) following the analogous procedures described as in step 201-a and step 201-b for the synthesis of Example 201. LC/MS observed [M+H], 686.15.

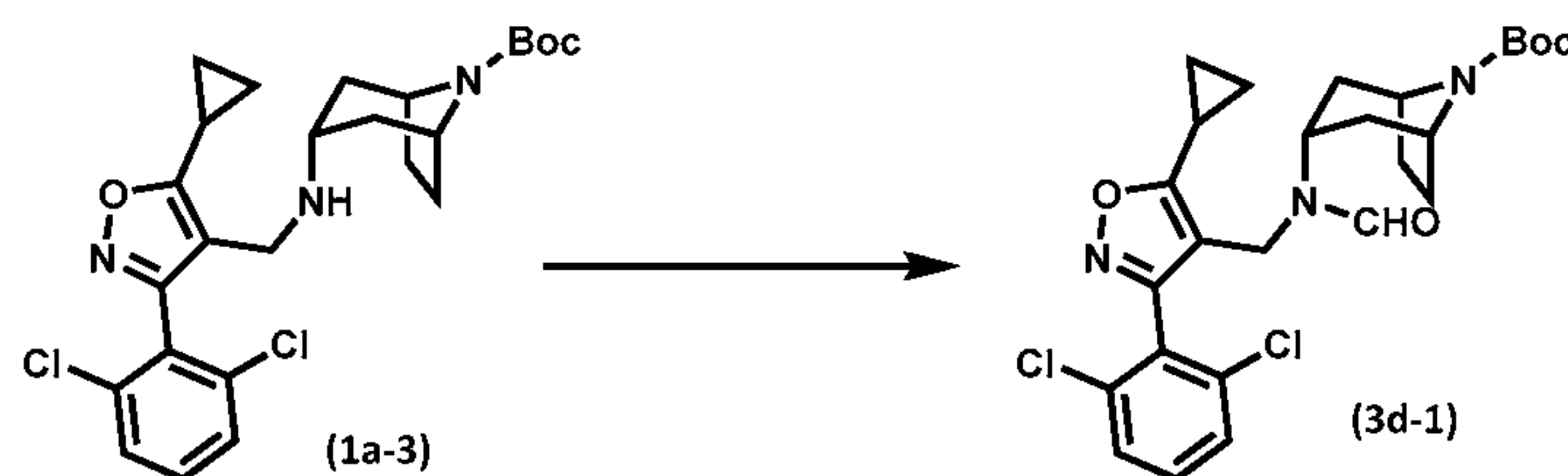
5 Example 293



Example 293 was prepared from *tert*-butyl (1R,3R,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (3c-1) following the analogous procedures described as in step 201-a and step 201-b for the synthesis of Example 201. LC/MS observed [M+H], 700.17.

Example 294

Step 294-a

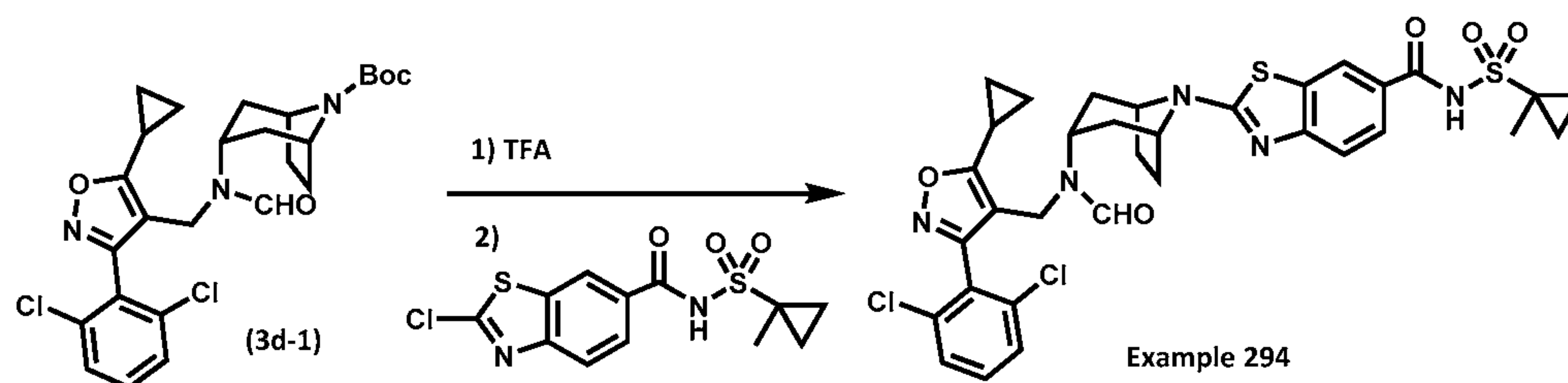


15 To acetic anhydride (2 ml, 21.20 mmol) was added formic acid (0.88 ml, 22.94 mmol) and the mixture was stirred at reflux for 3 h, cooled down to give the crude acetic formic anhydride (AFA) solution.

To *tert*-butyl (1R,3r,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (1a-3) (150 mg, 0.305 mmol) in DCM (1 ml) was added the AFA solution (0.5 ml) and DMAP (74.4 mg, 0.609 mmol). The resulting mixture was stirred at 60 °C for 1.5 h. Volatile was removed under vacuo and chased with ACN. The residue was diluted with ethyl acetate, washed with 1N NaOH, water,

brine, dried, filtered, and concentrated. The residue was purified by CombiFlash eluting with hexane to 50% acetone in hexane to give *tert*-butyl (1R,3R,5S)-3-(N-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)formamido)-8-azabicyclo[3.2.1]octane-8-carboxylate (3d-1) (125 mg). LC/MS observed [M-*t*Bu+H], 464.10.

5 Step 294-b

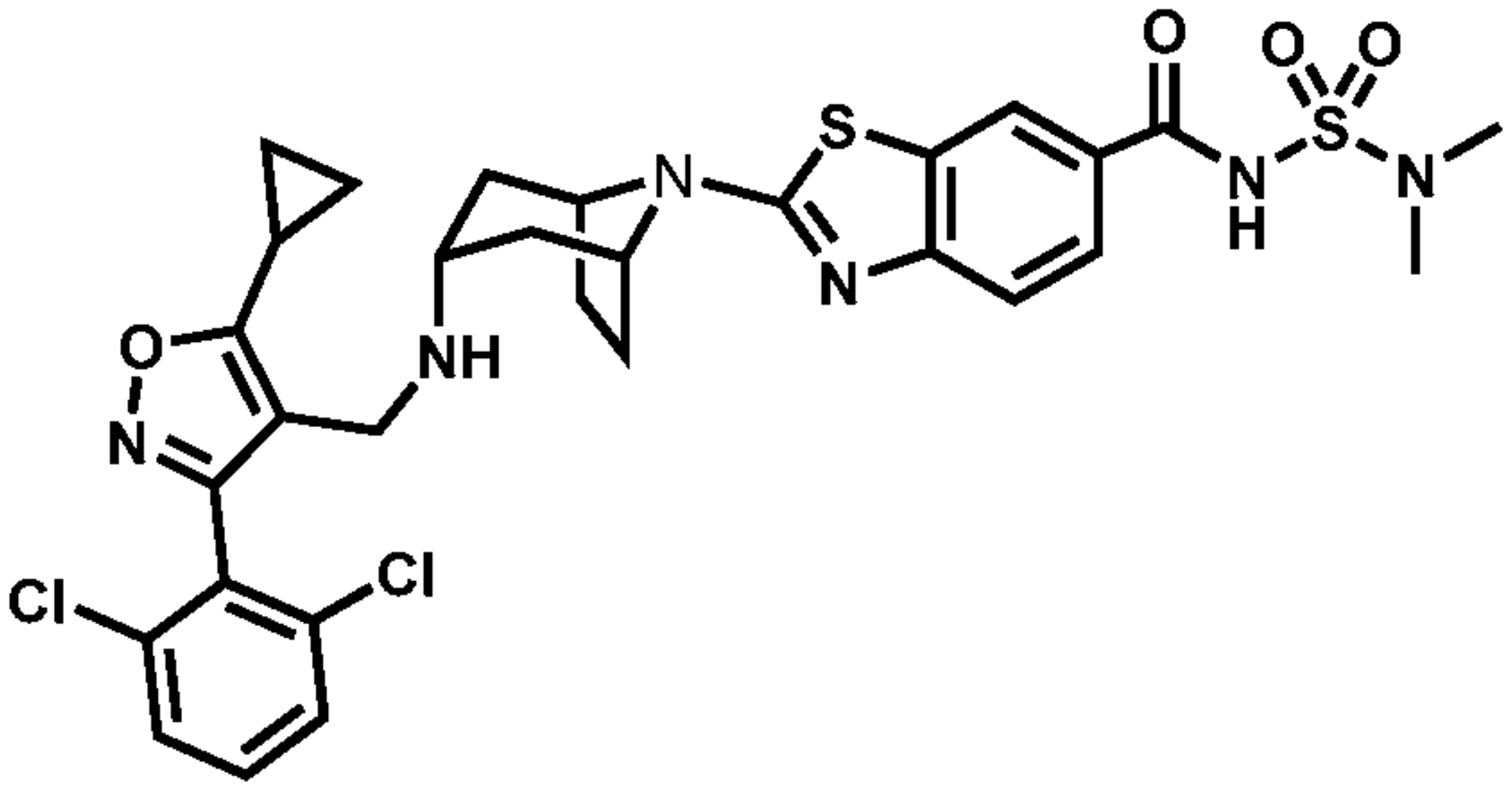
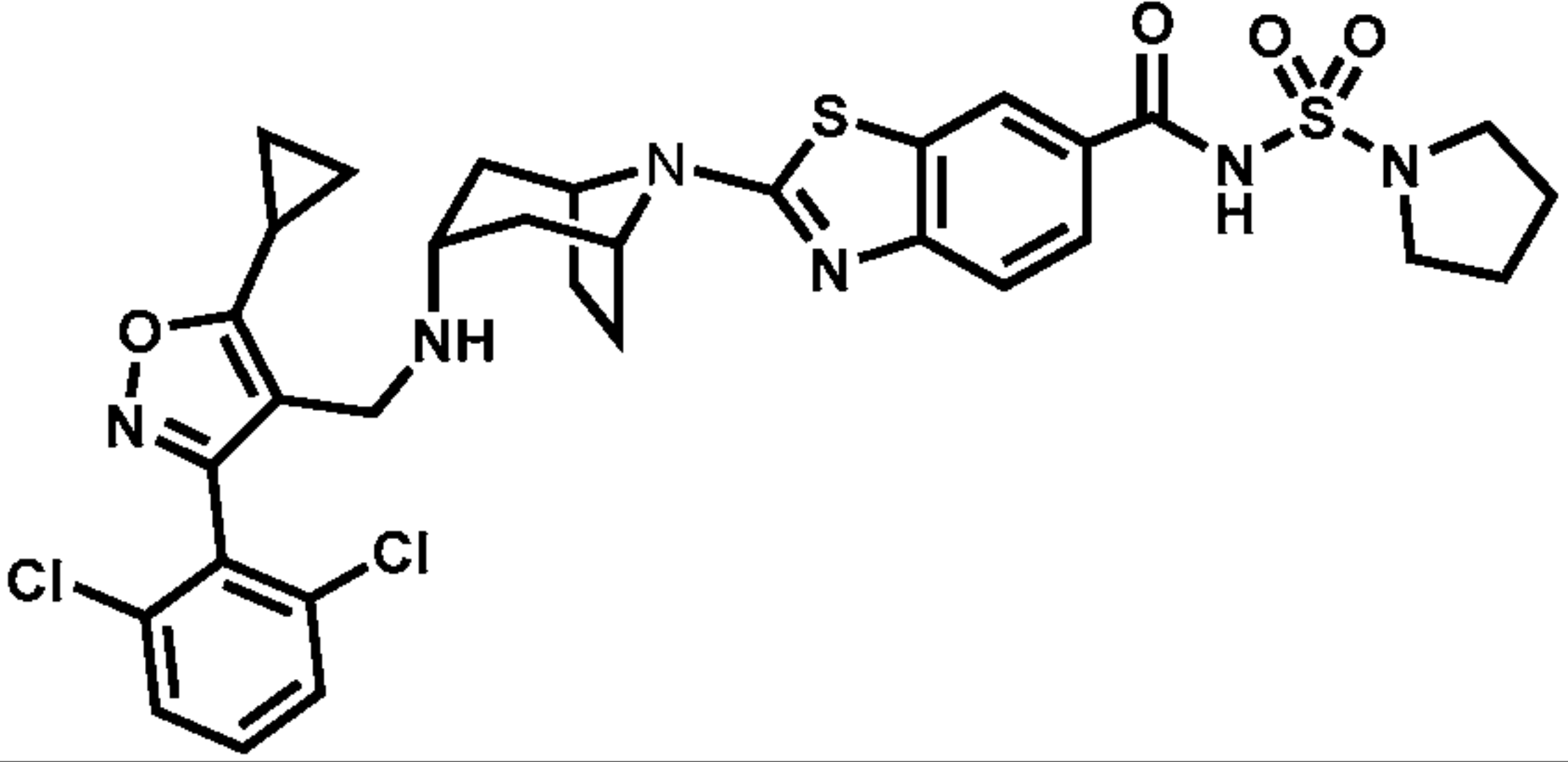
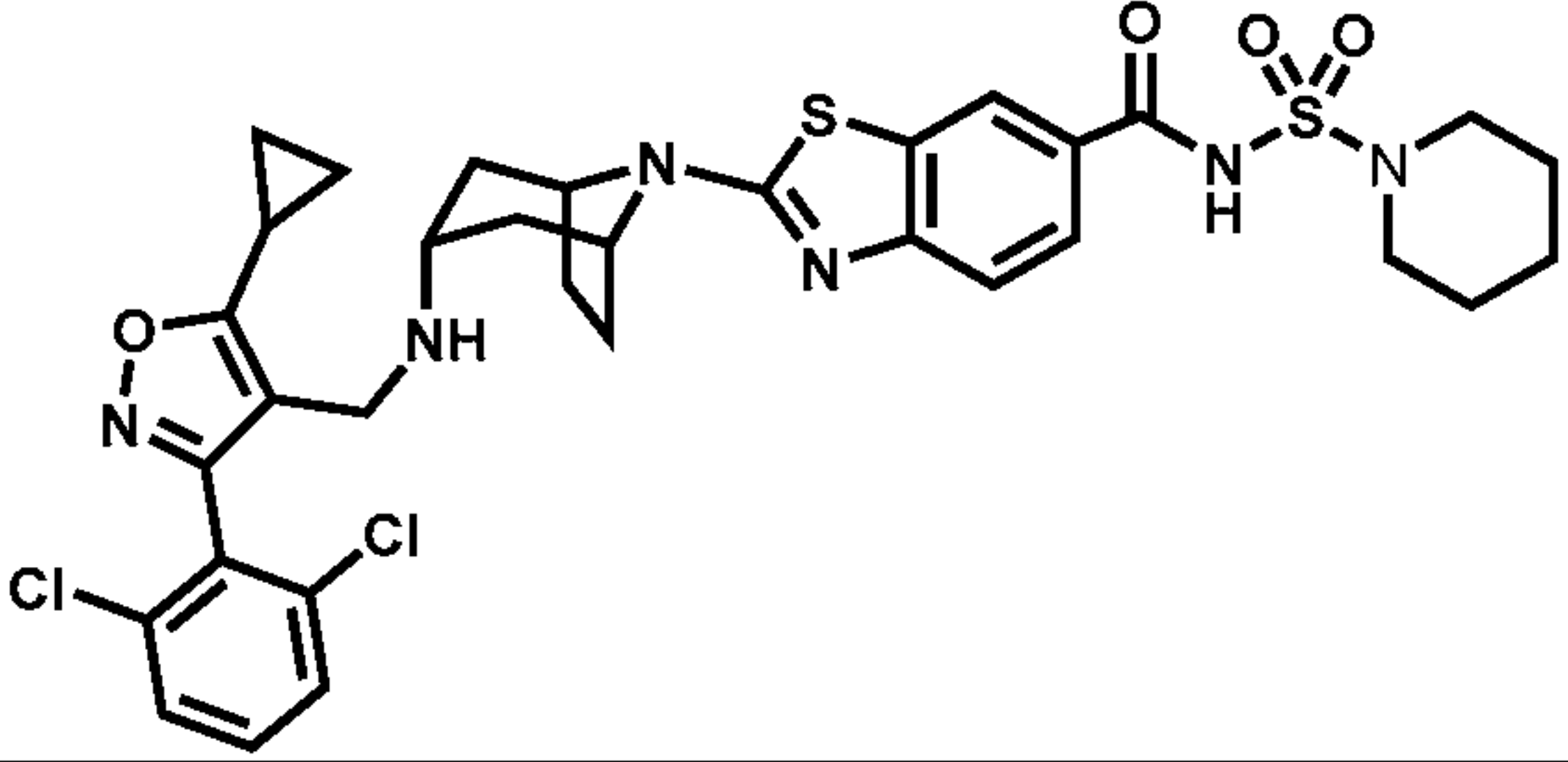
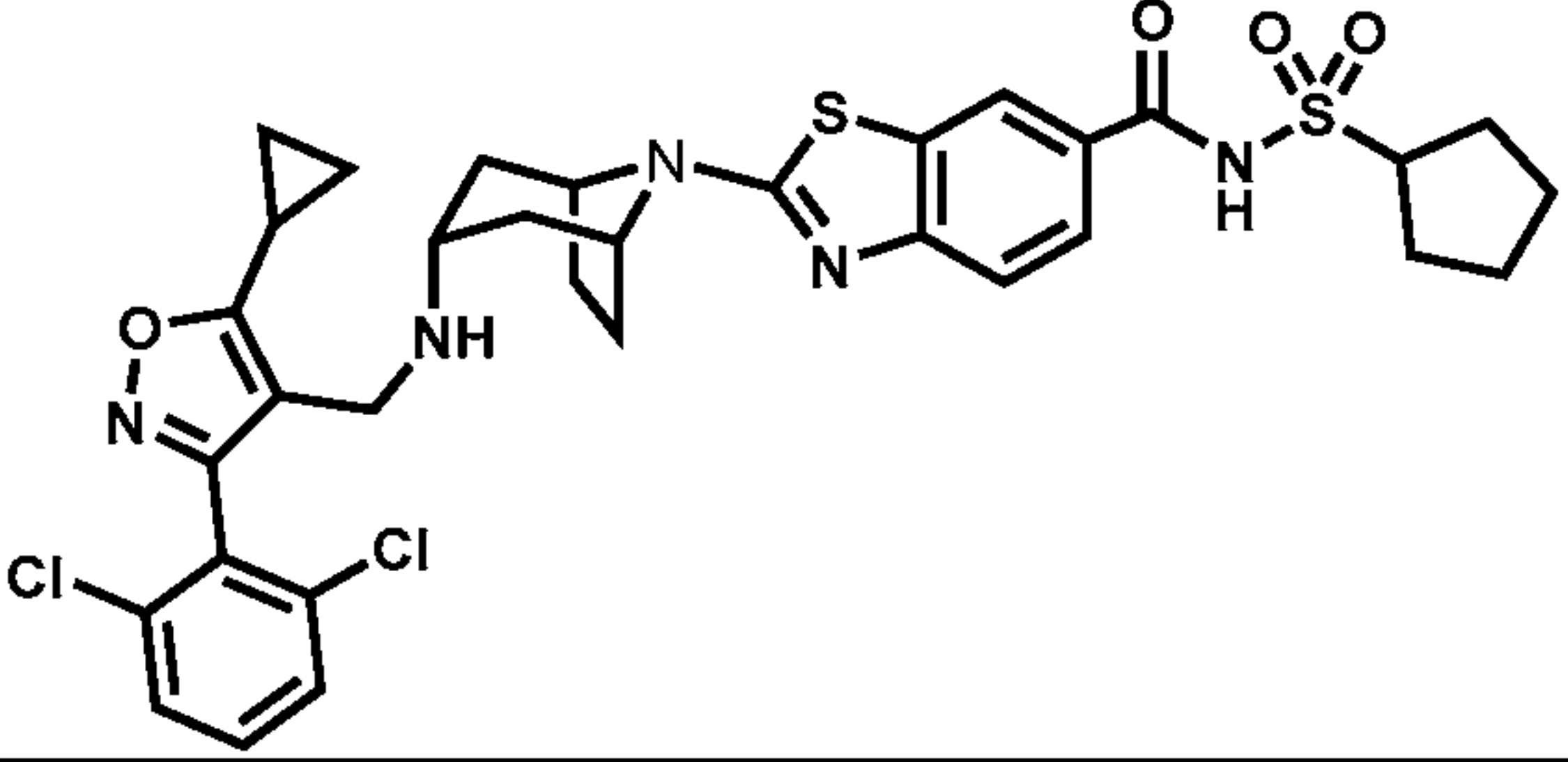
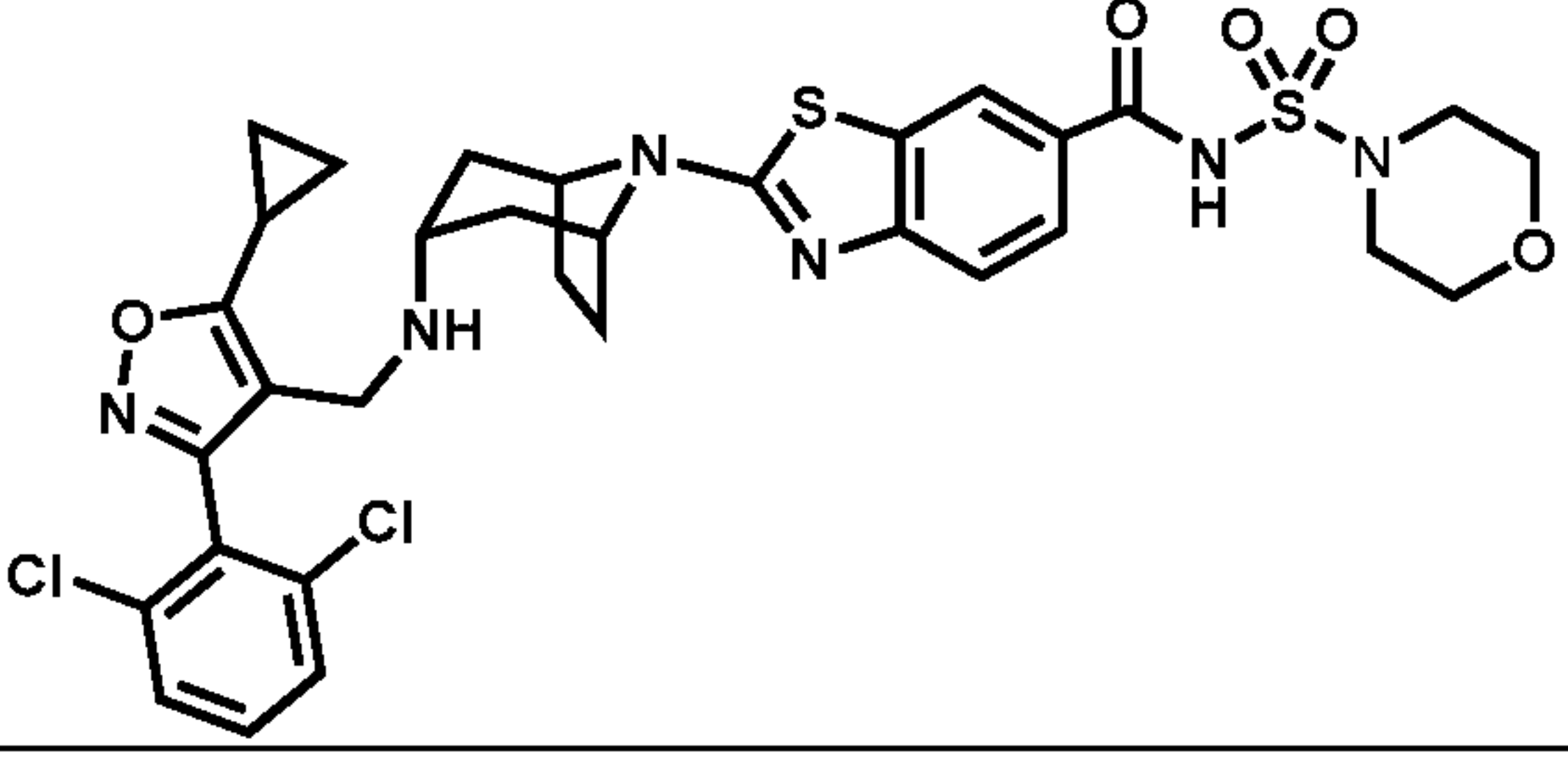
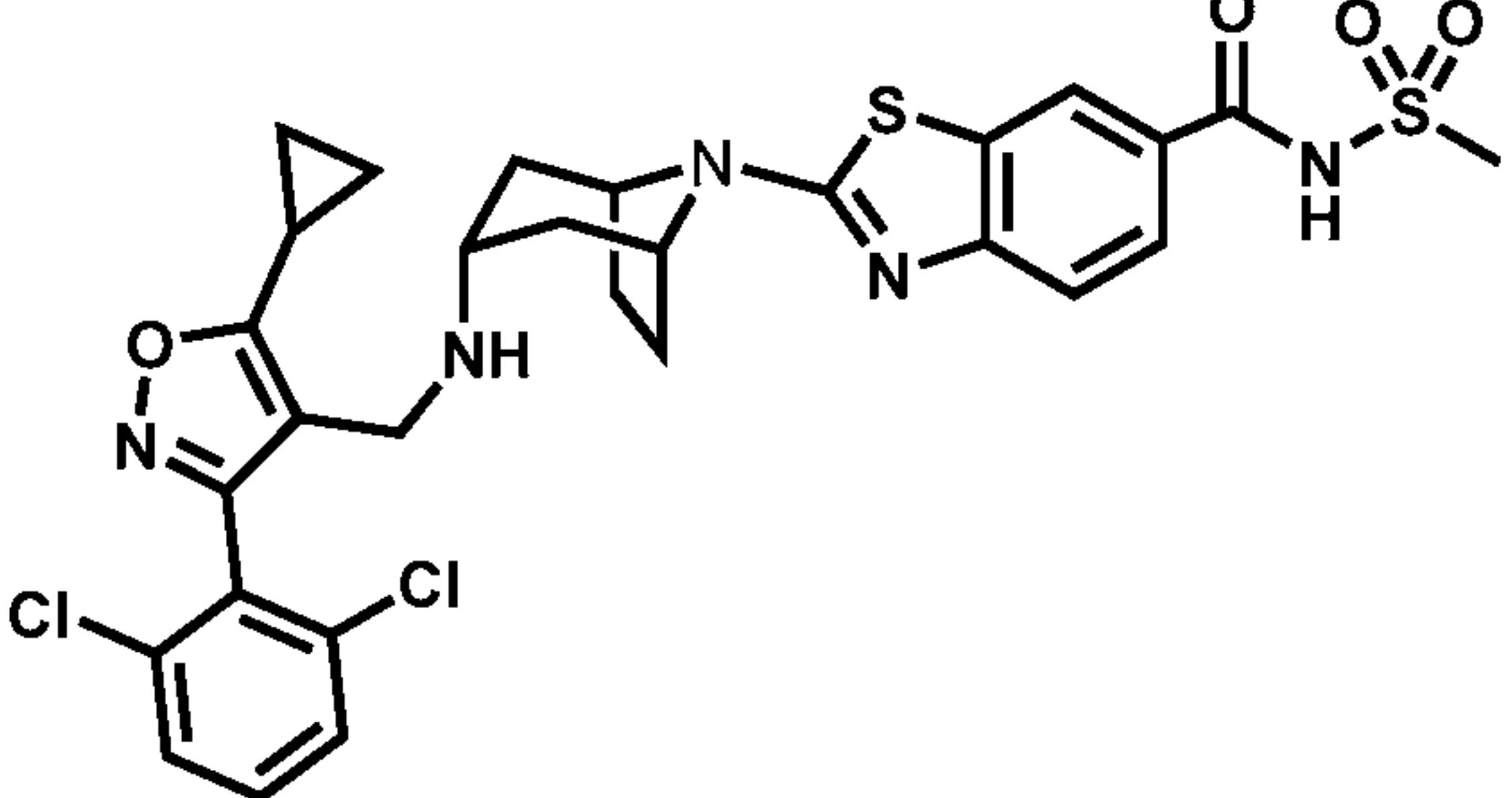


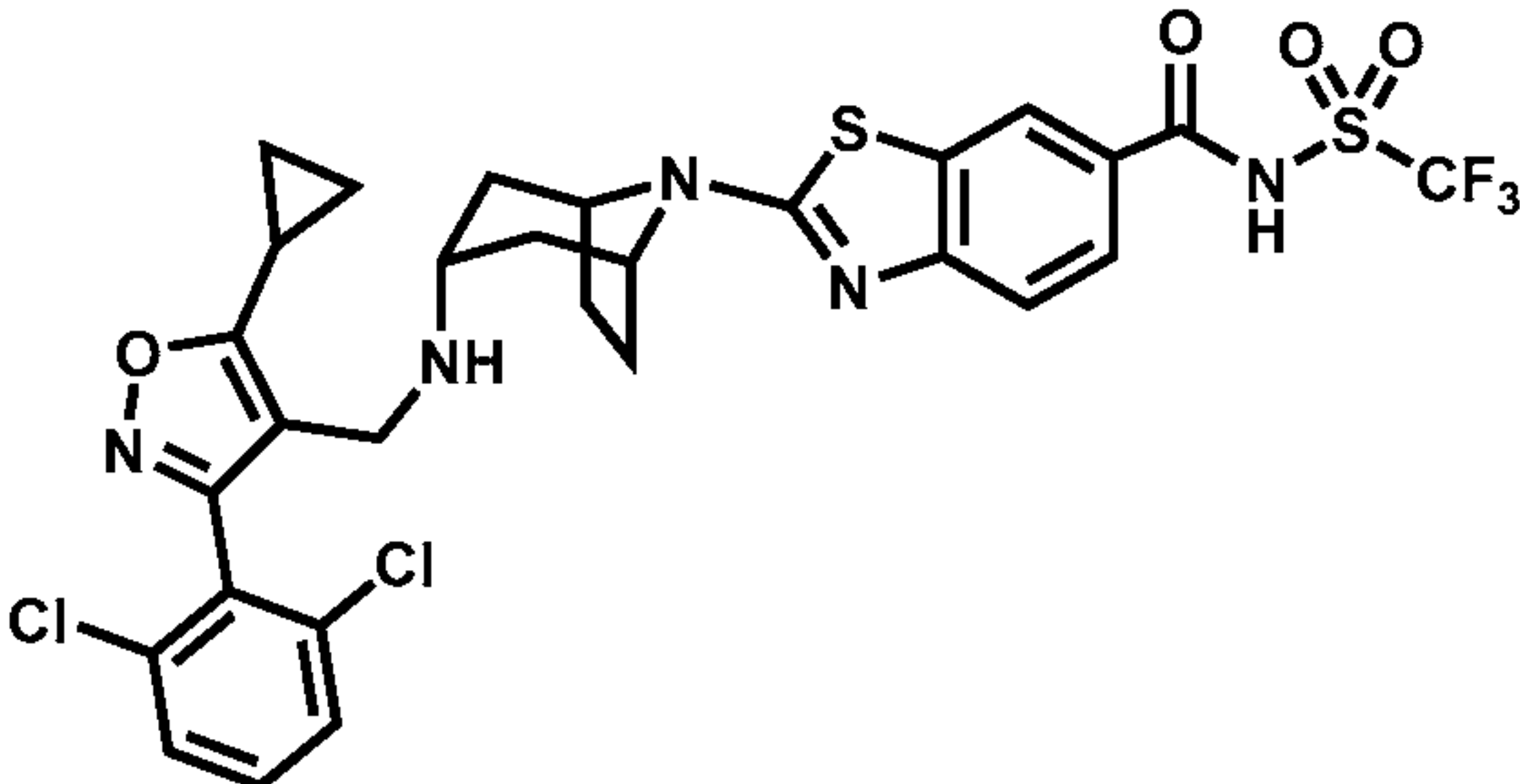
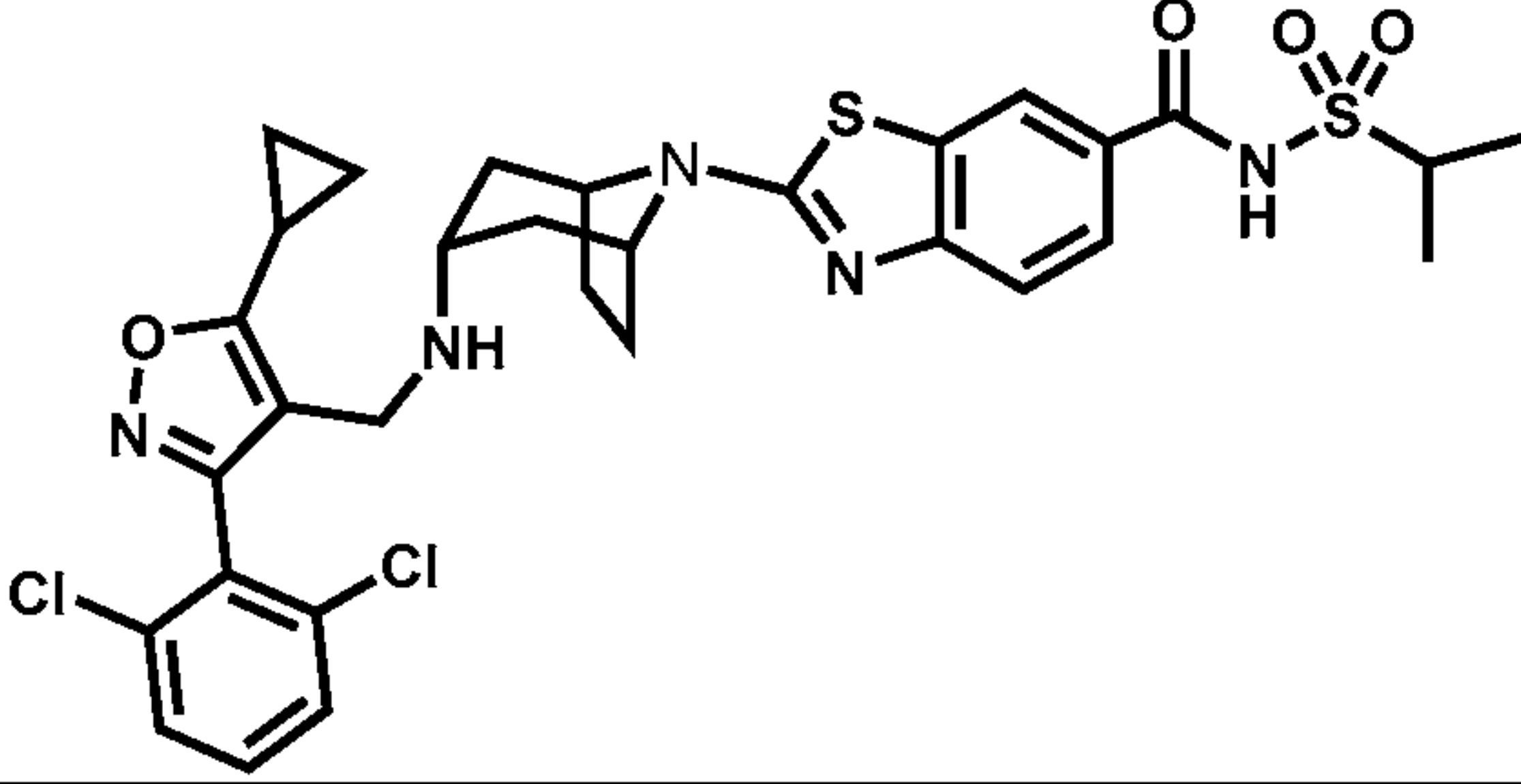
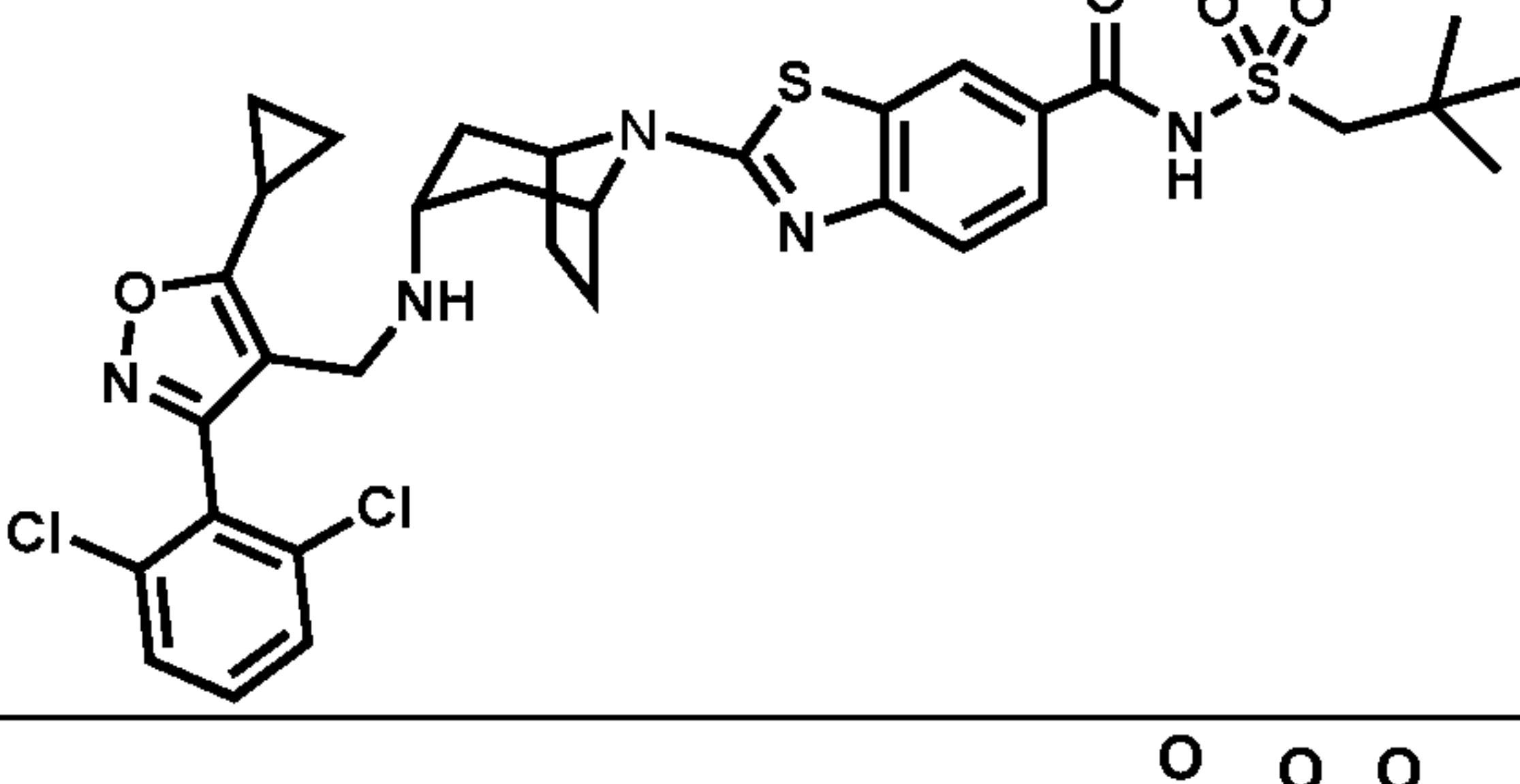
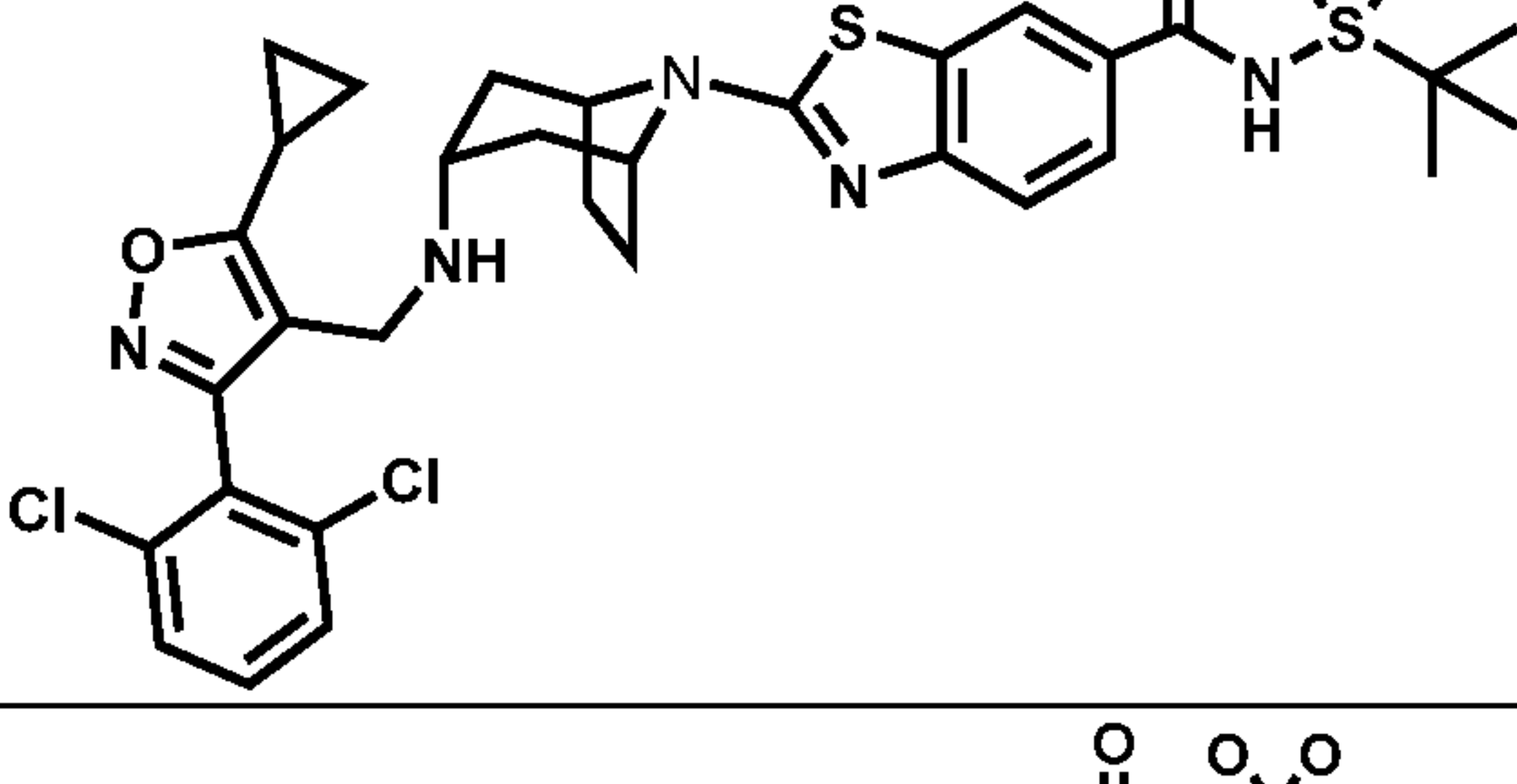
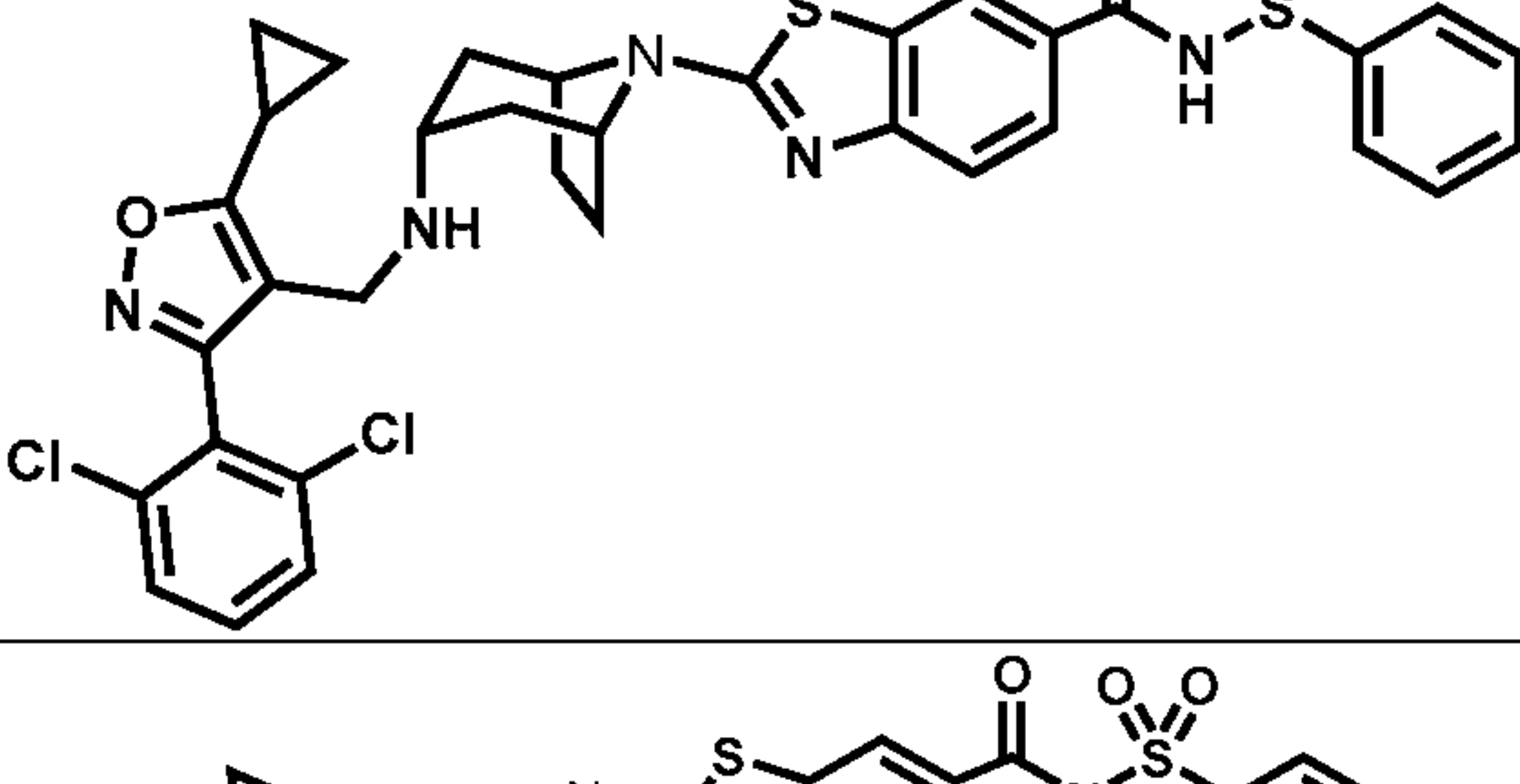
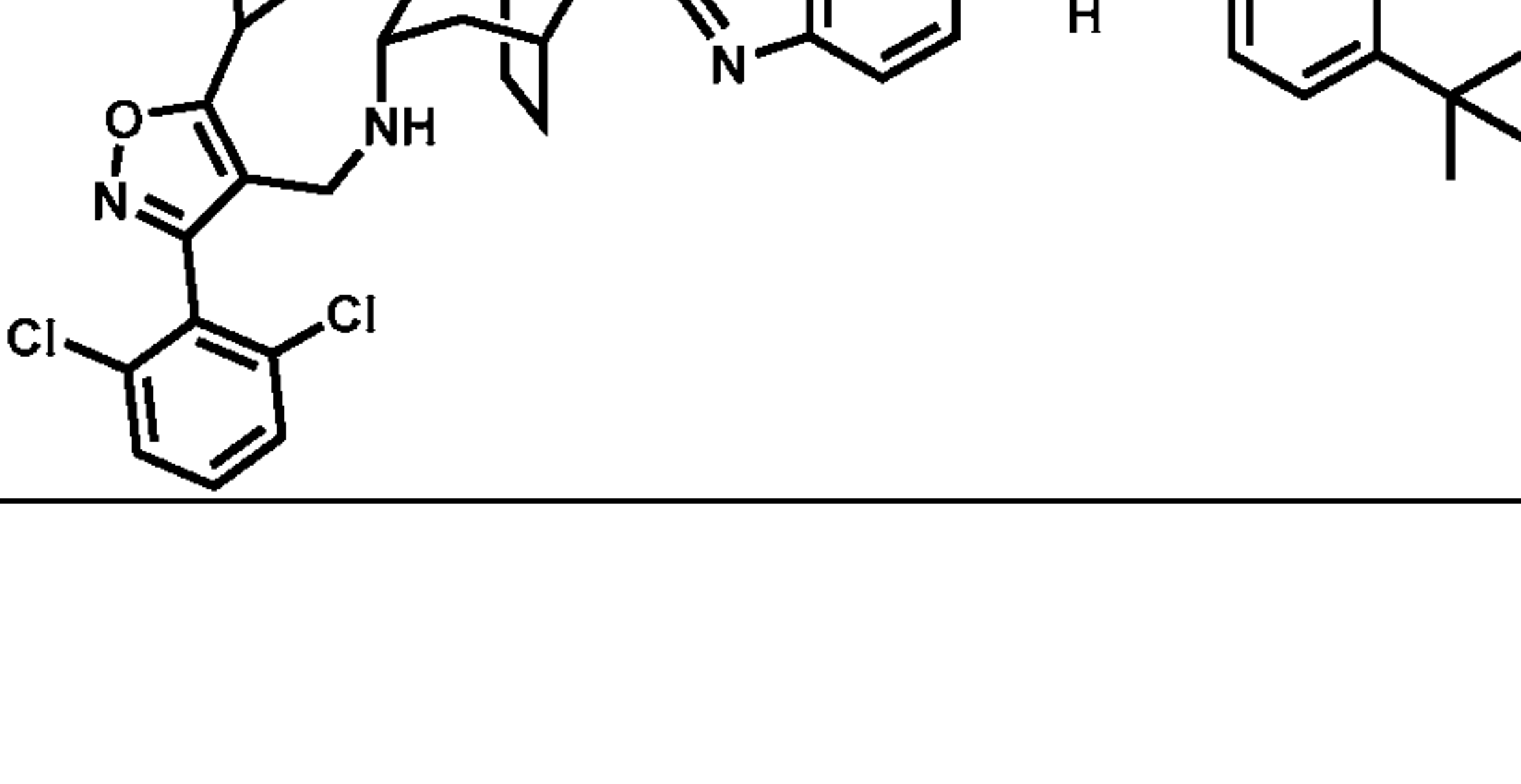
Example 294 was prepared from (1R,3r,5S)-3-(N-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)formamido)-8-azabicyclo[3.2.1]octane-8-carboxylate (3d-1) following the analogous procedures described as in step 201-a and step 201-b for the synthesis of Example 201. LC/MS observed [M+H], 714.16.

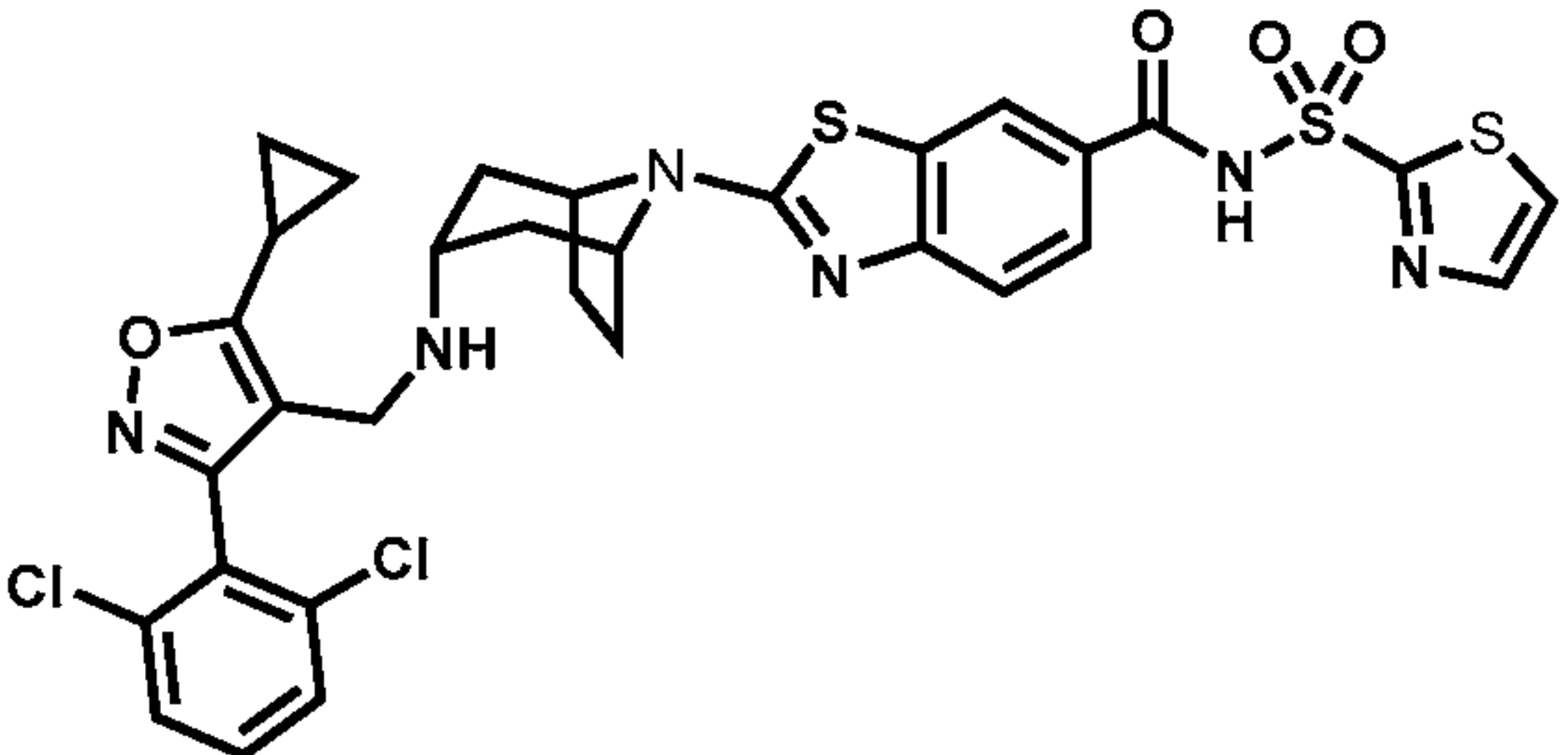
The following examples listed in Table 7 were prepared from (1R,3r,5S)-N-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)-8-azabicyclo [3.2.1]octan-3-amine hydrochloride (1c-1), 2-chlorobenzo[d]thiazole-6-carboxylic acid and the corresponding sulfonamides following the analogous procedures described as in step 201-a and step 201-b for the synthesis of Example 294.

Table 7

Example #	Structure	MS Data
202		686.16 (M+H)

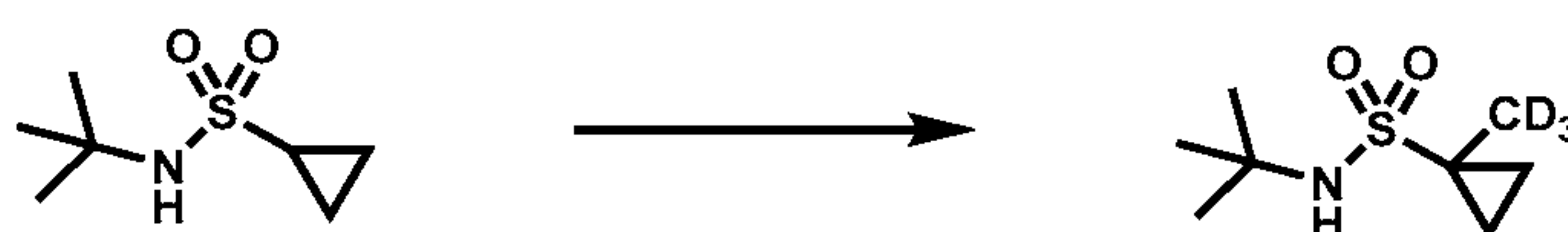
225		675.15 (M+H)
227		701.16 (M+H)
228		715.19 (M+1)
231		700.00 (M+H)
234		717.17 (M+1)
235		672.14 (M+H)

236		700.10 (M+1)
237		674.08 (M+H)
239		702.11 (M+H)
240		688.17 (M+H)
257		708.14 (M+H)
262		764.04 (M+H)

268		715.10 (M+1)
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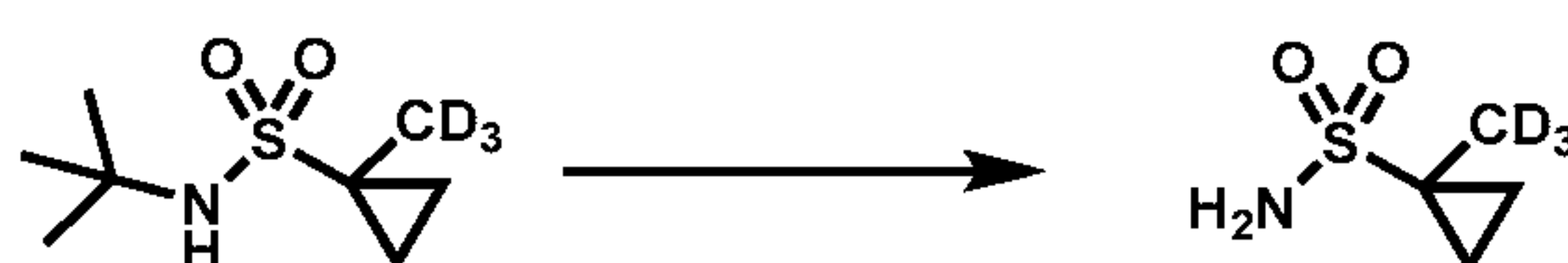
Example 296

Step 296-a



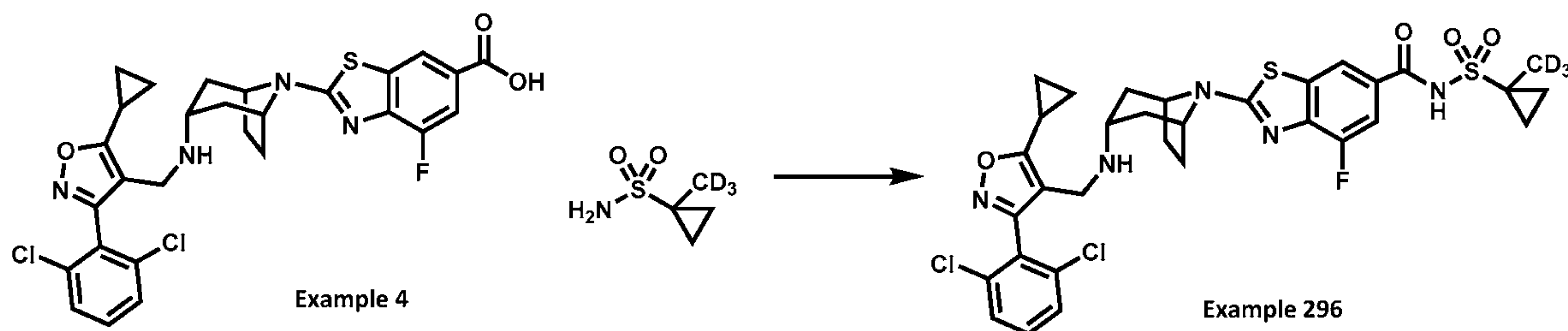
- 5 To N-(*tert*-butyl)cyclopropanesulfonamide (1g, 5.64 mmol) in Tetrahydrofuran (8 ml) at -78 °C was added butyllithium (8.81 ml, 14.10 mmol) dropwise, and the resulting mixture was stirred at -78 °C for 1h. To the reaction mixture was added iodomethane-d₃ (0.430 ml, 6.77 mmol) and the resulting mixture was stirred at -78 °C for 2h. The cooling bath was removed and mixture was allowed to warm up to 0 °C, quenched with NH₄Cl solution. The mixture
- 10 was diluted with ethyl acetate, washed with water, brine, dried, and concentrated. The residue purified by CombiFlash eluting with hexane to 40% acetone in hexane to give 1-(methyl-d₃)cyclopropane-1-sulfonamide (704 mg).

Step 296-b



- 15 To N-(*tert*-butyl)-1-(methyl-d₃)cyclopropane-1-sulfonamide (500 mg, 2.57 mmol) in DCM (6 ml) was added TFA (3 ml, 38.9 mmol), and the resulting mixture was stirred at RT for 16h. The mixture was concentrated under vacuo and the residue was chased with DCM to give 1-(methyl-d₃)cyclopropane-1-sulfonamide (378 mg). This material was directly used to next step without further purification.

Step 296-c

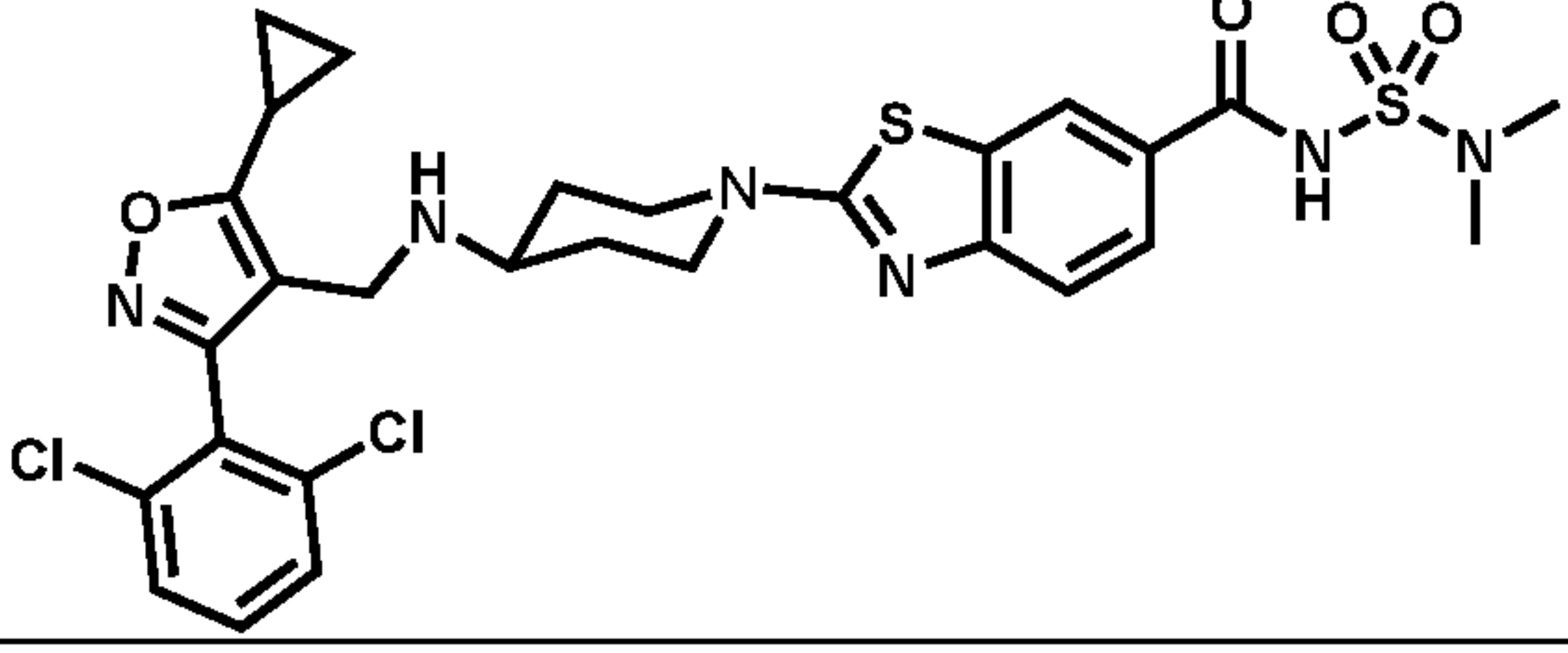
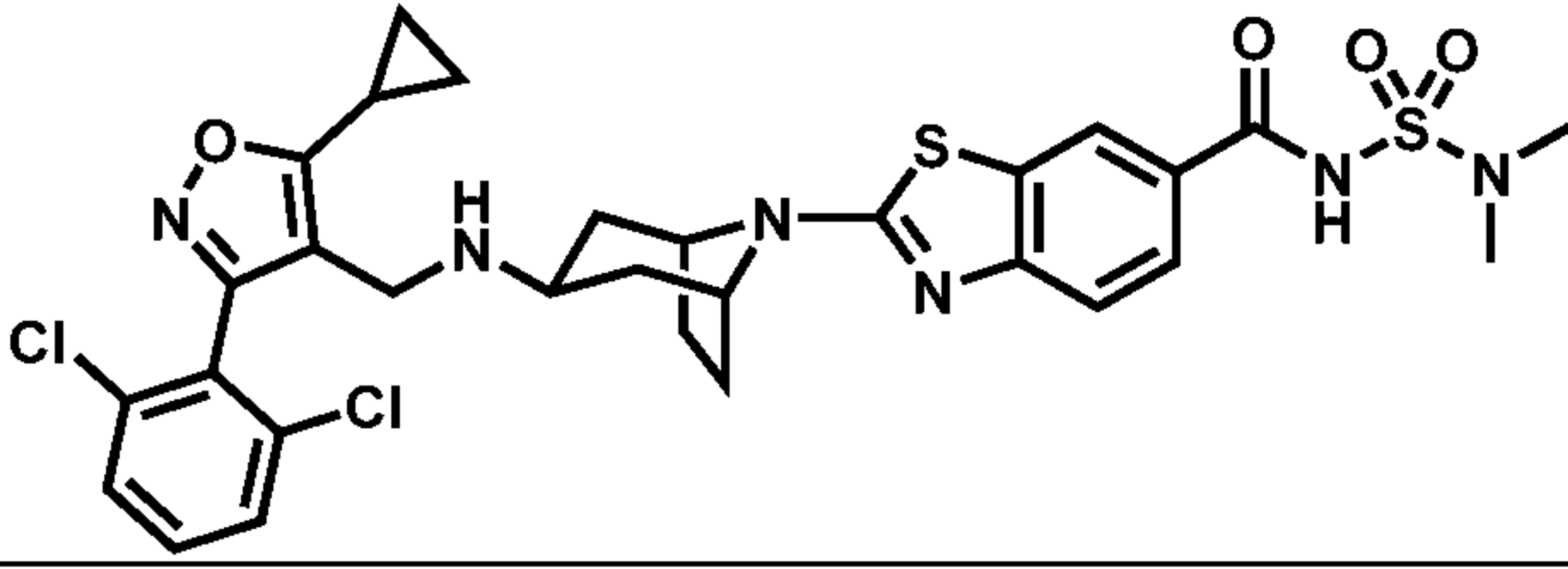
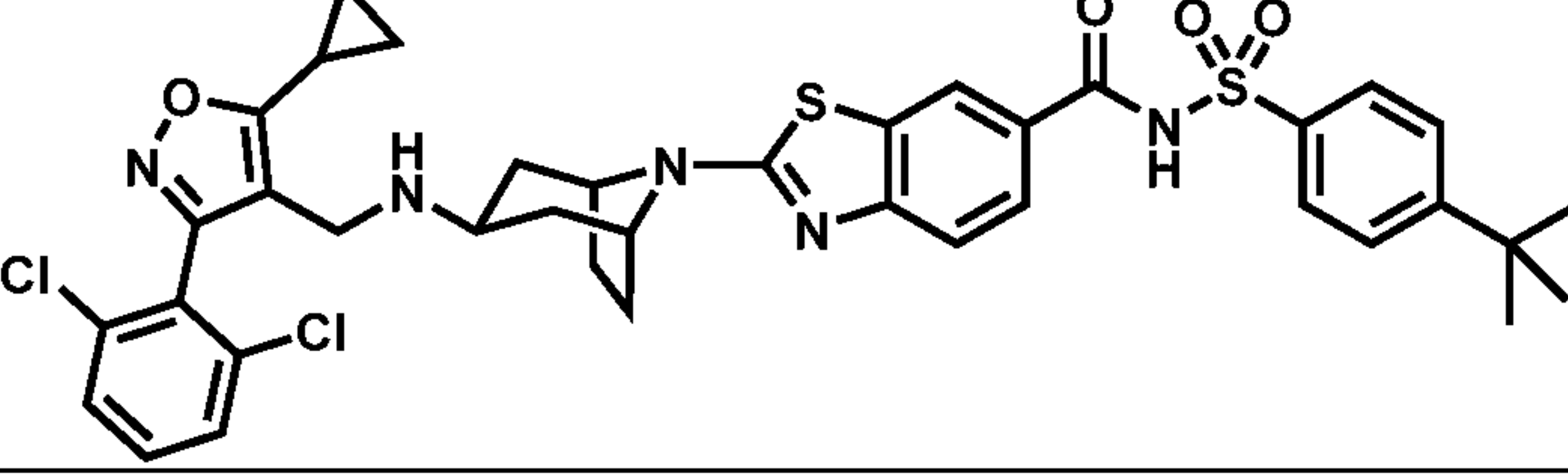
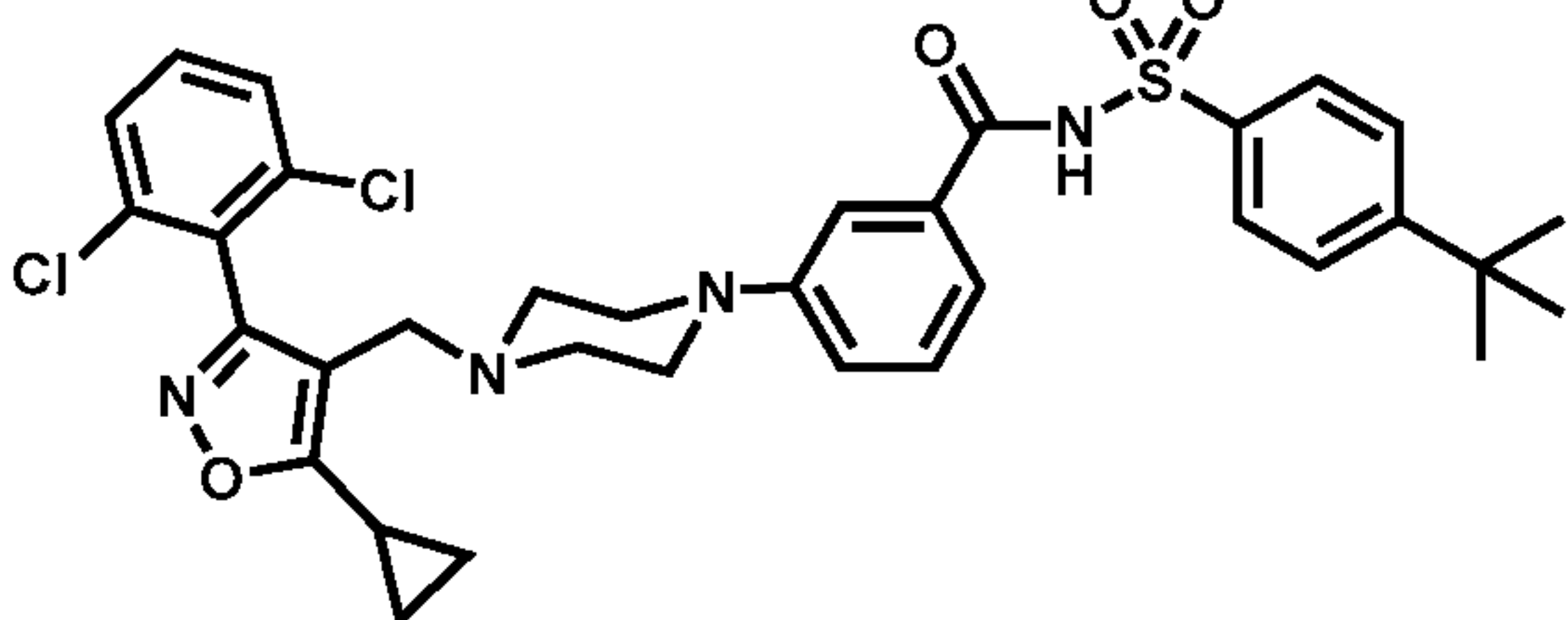
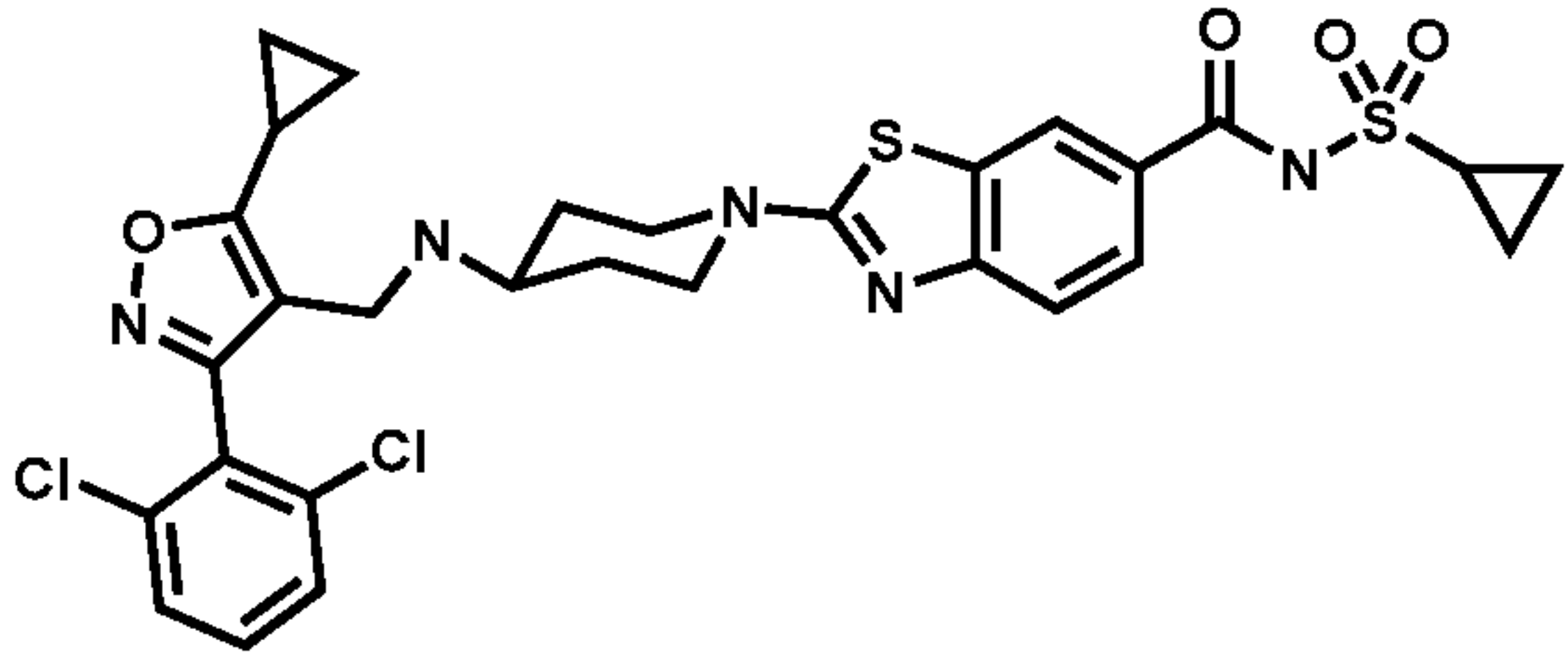
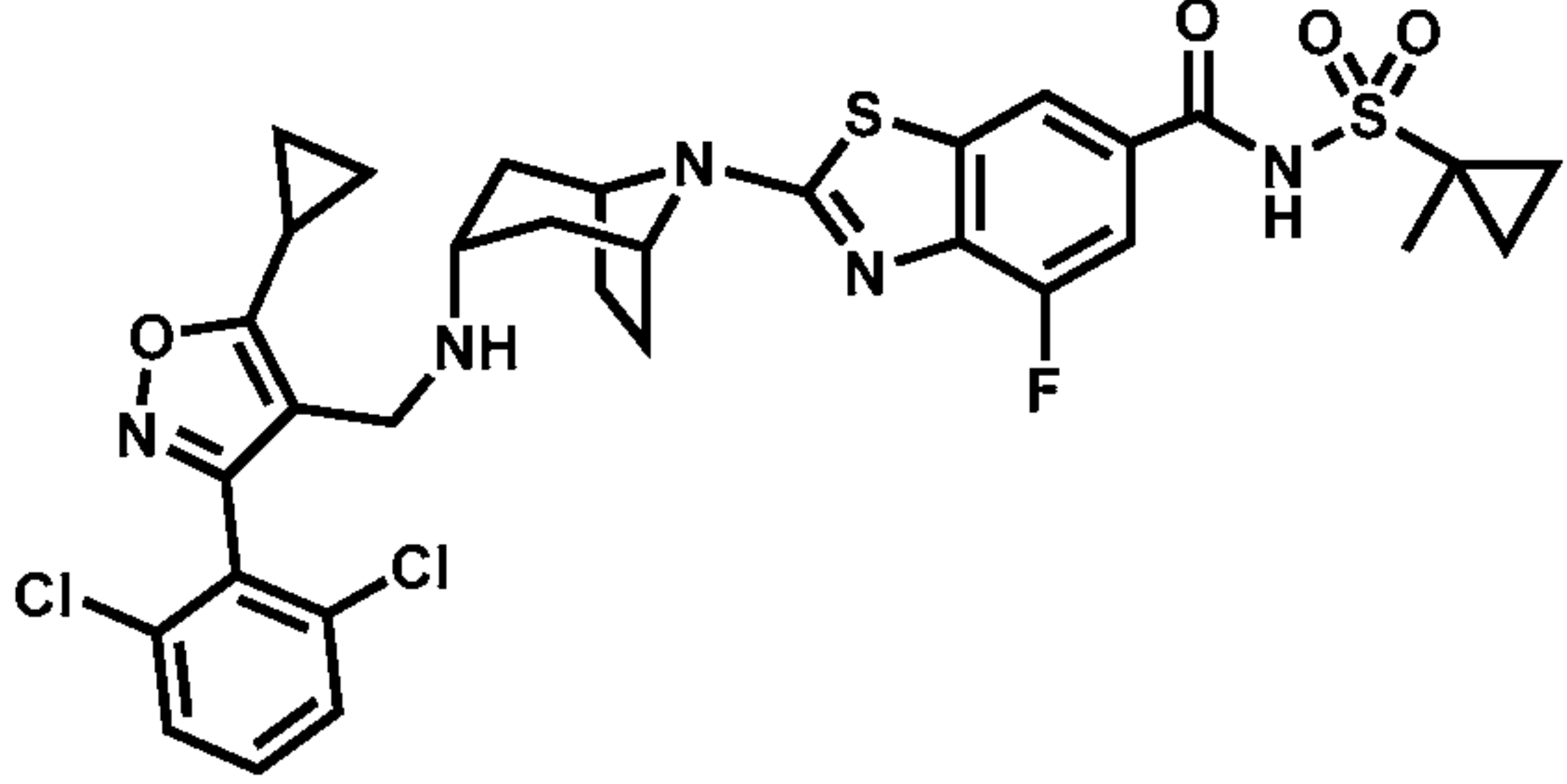
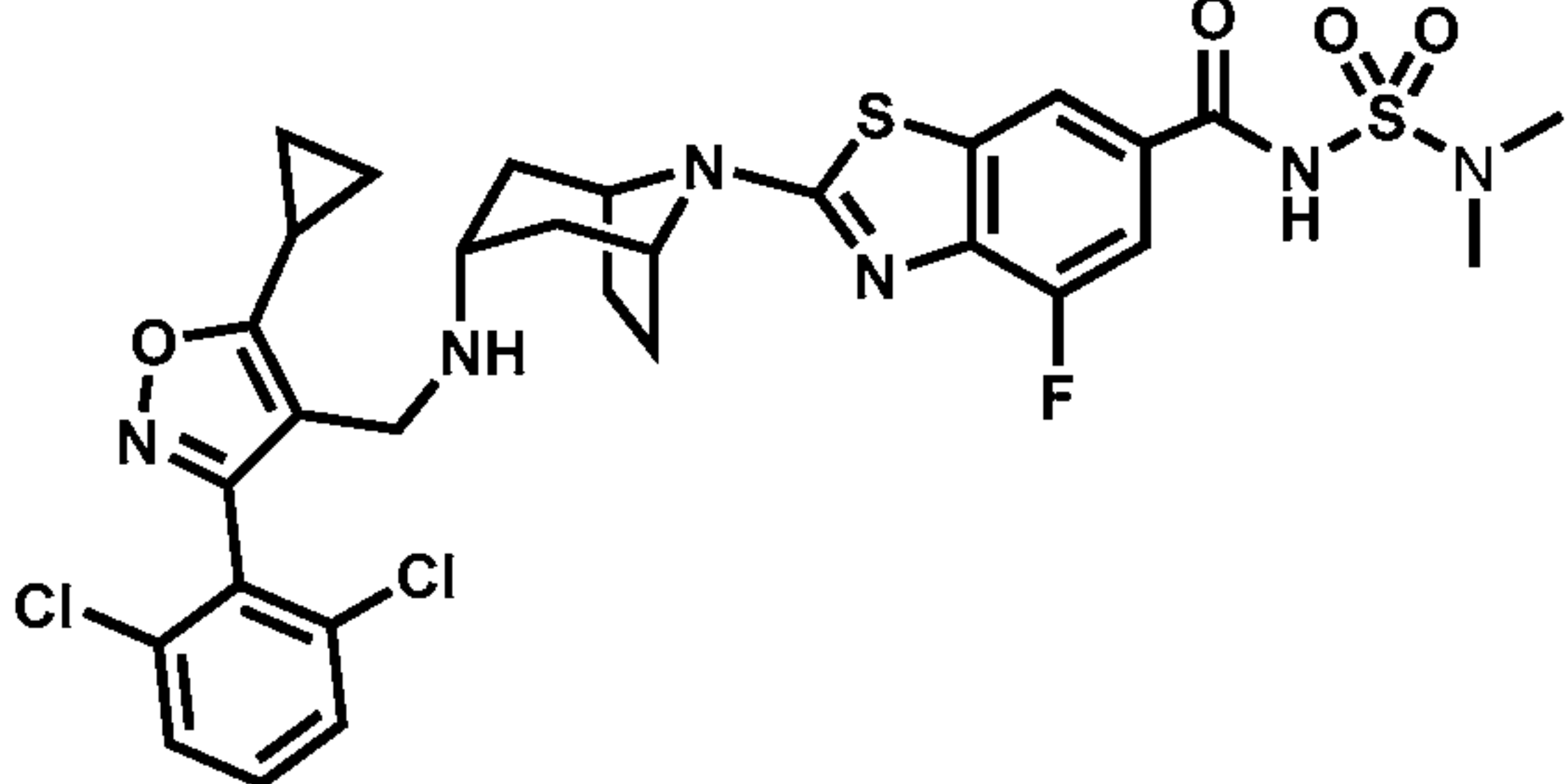


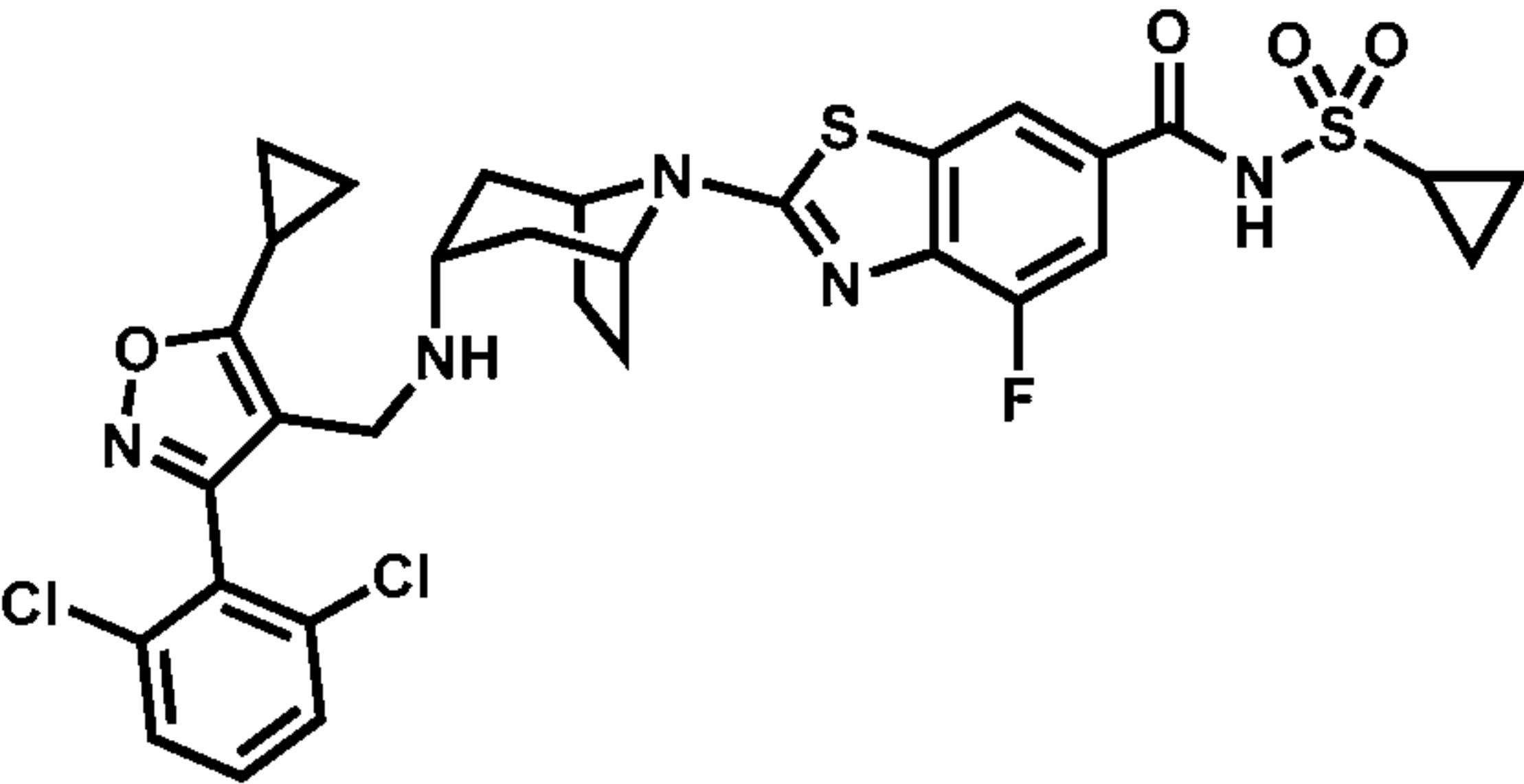
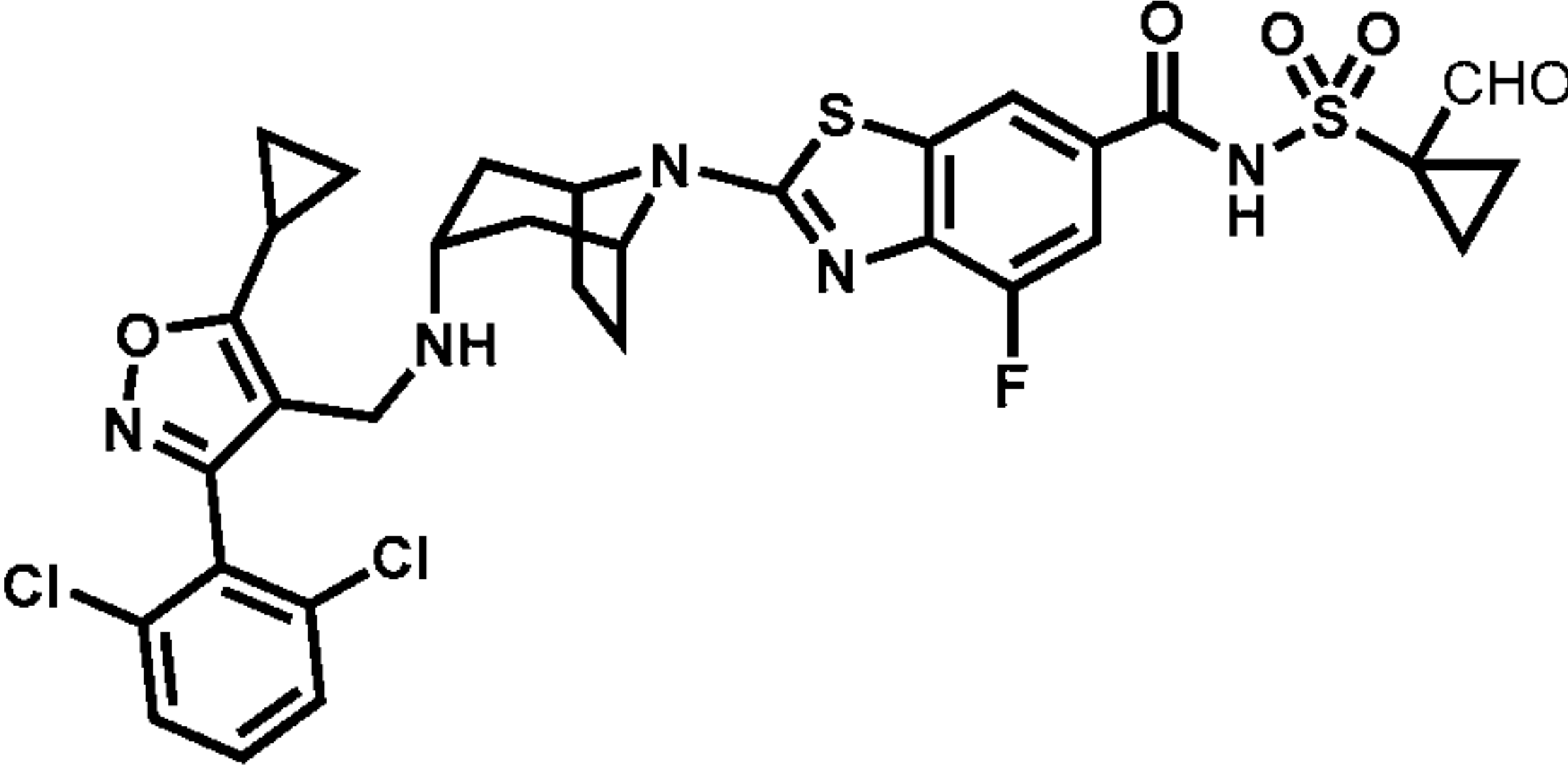
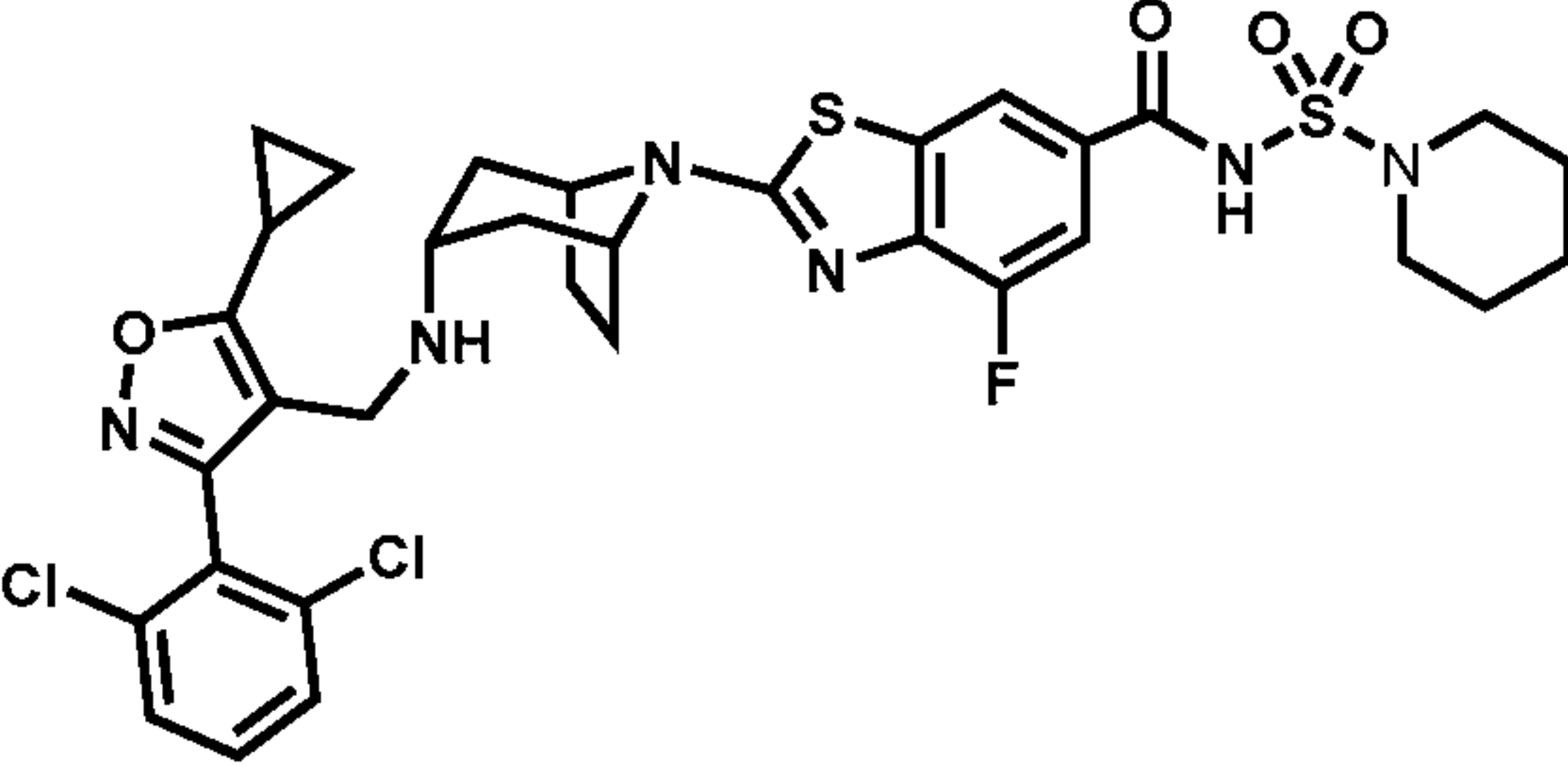
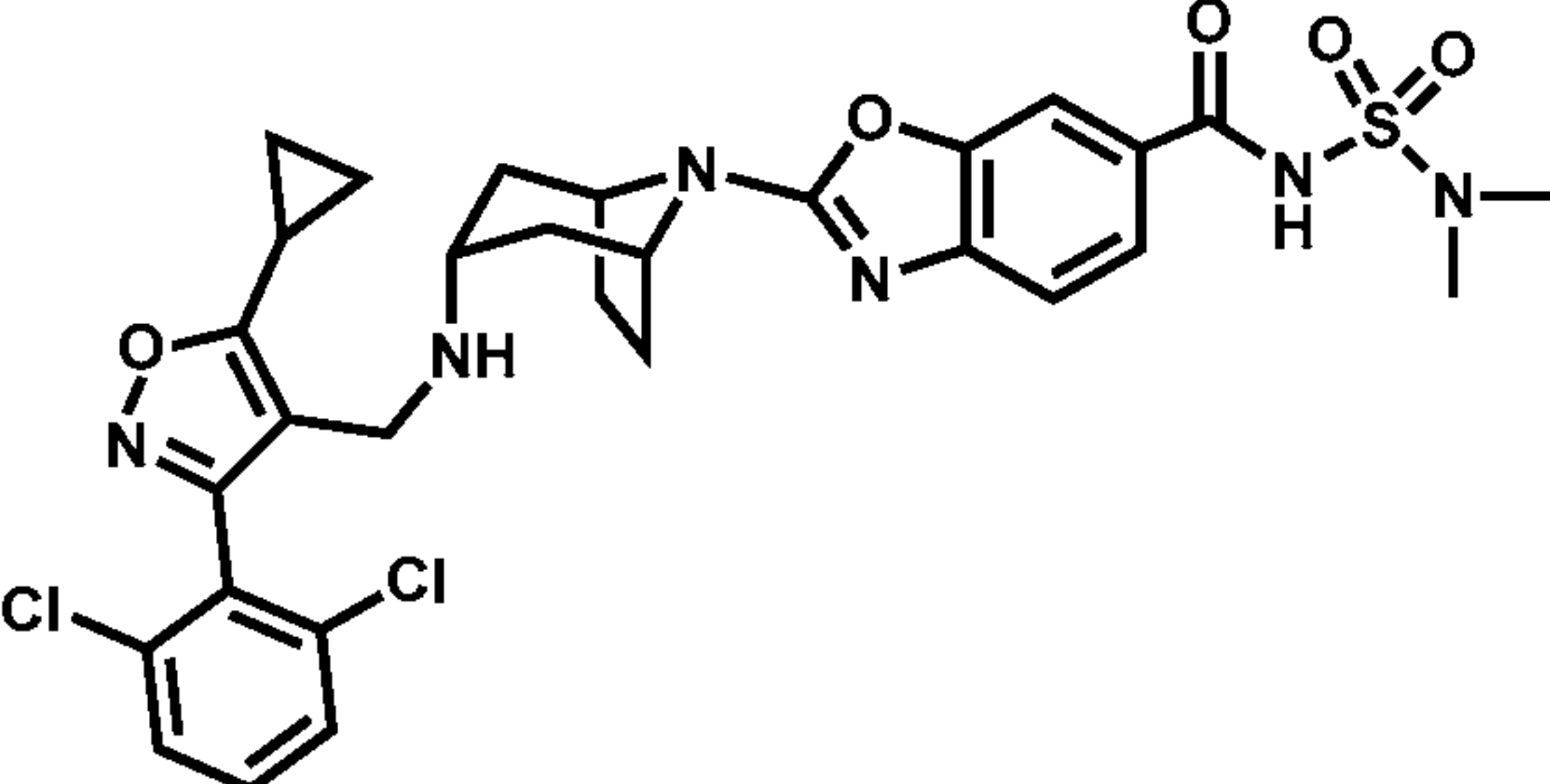
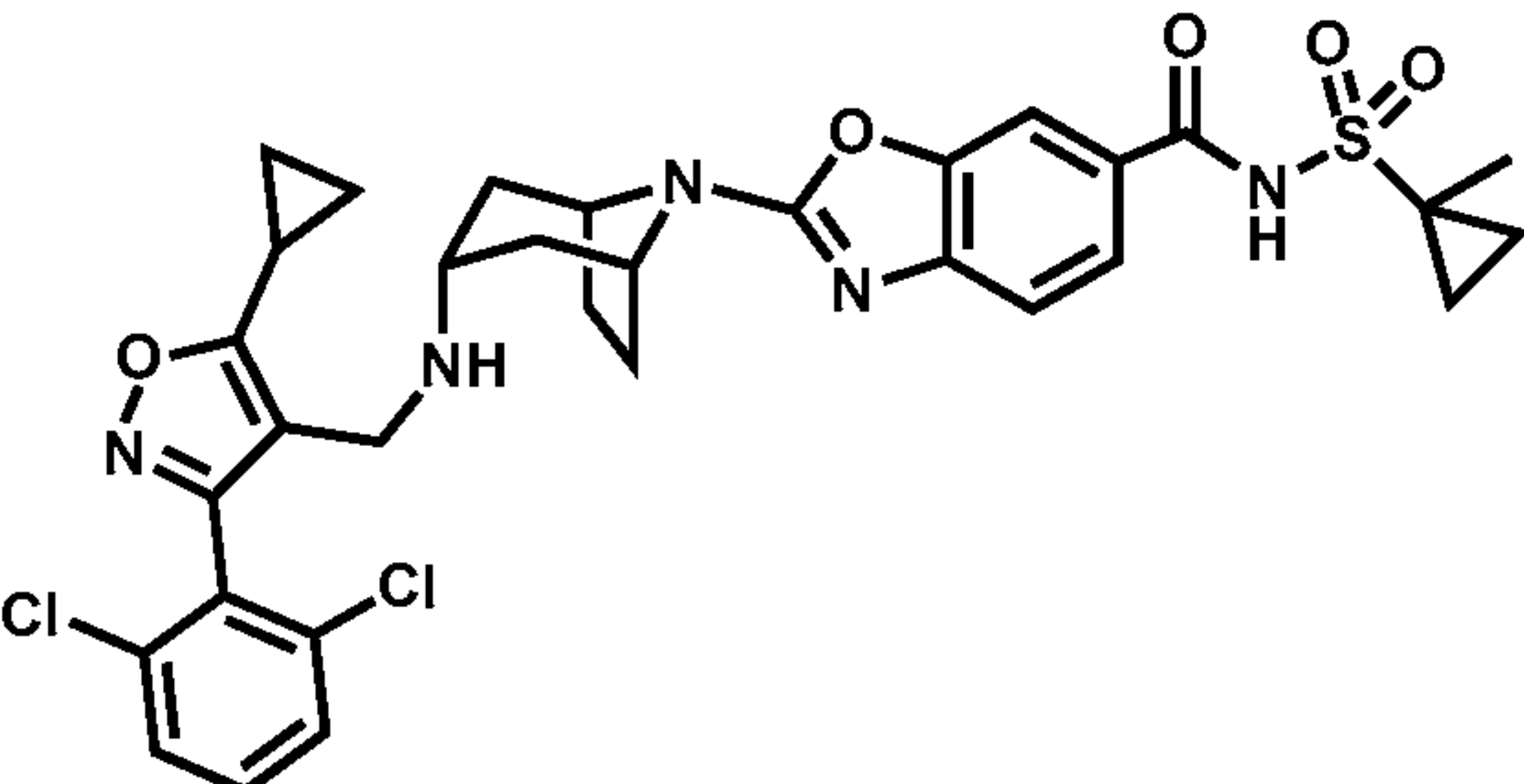
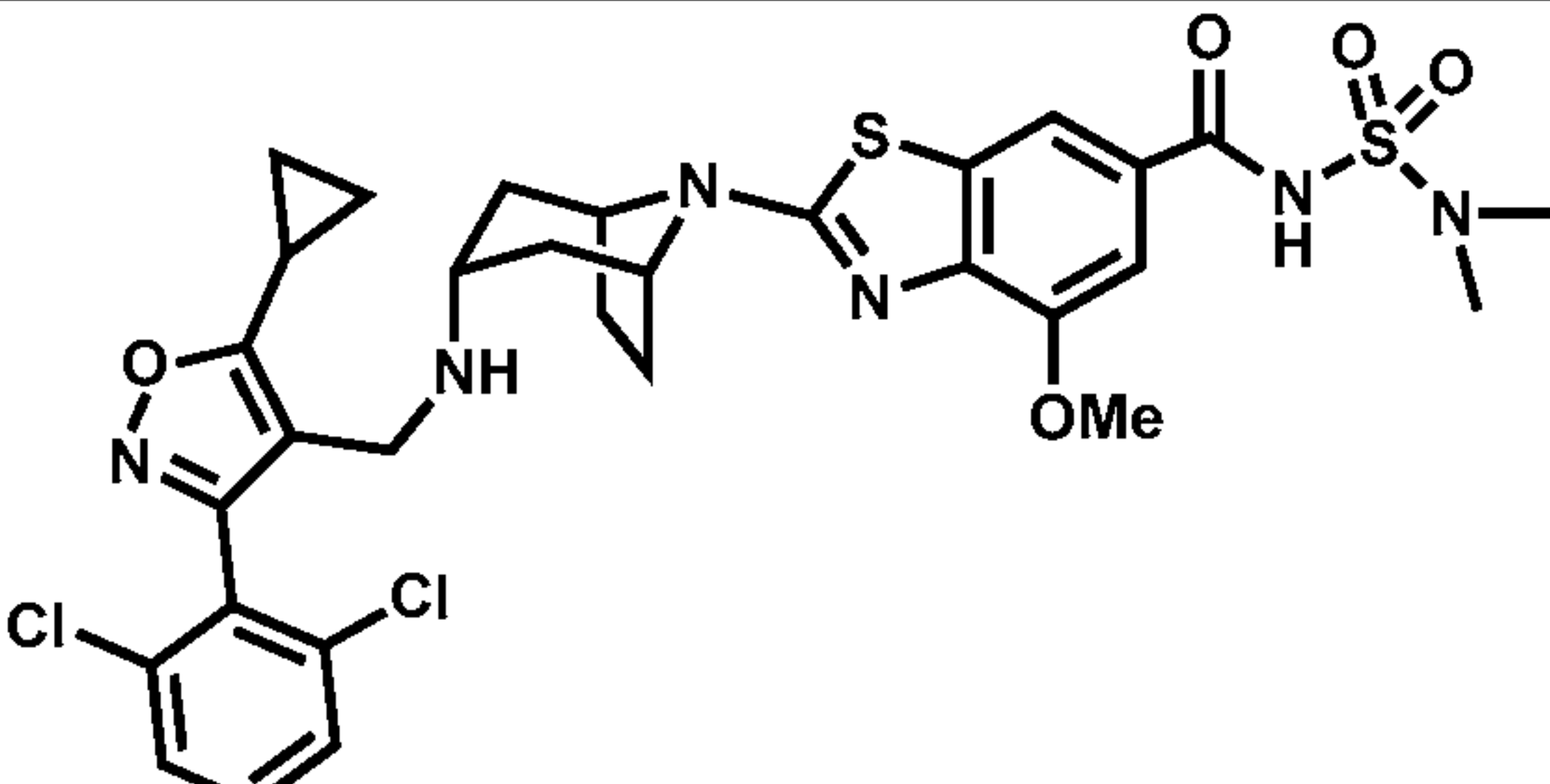
To 2-(((1R,3R,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octan-8-yl)-4-fluorobenzo[d]thiazole-6-carboxylic acid (Example 4) (42mg, 0.071 mmol) and 1-(methyl-d3)cyclopropane-1-sulfonamide (14.82 mg, 0.107 mmol) in DCM (1 ml) was added EDCI (21.93 mg, 0.114 mmol) and DMAP (17.47 mg, 0.143 mmol). The resulting mixture was stirred at RT for 16 h, and then concentrated under vacuo. The residue was purified by CombiFlash eluting with DCM to 50% acetone/DCM to give Example 296 (29.2 mg). LC/MS observed [M+H], 707.17.

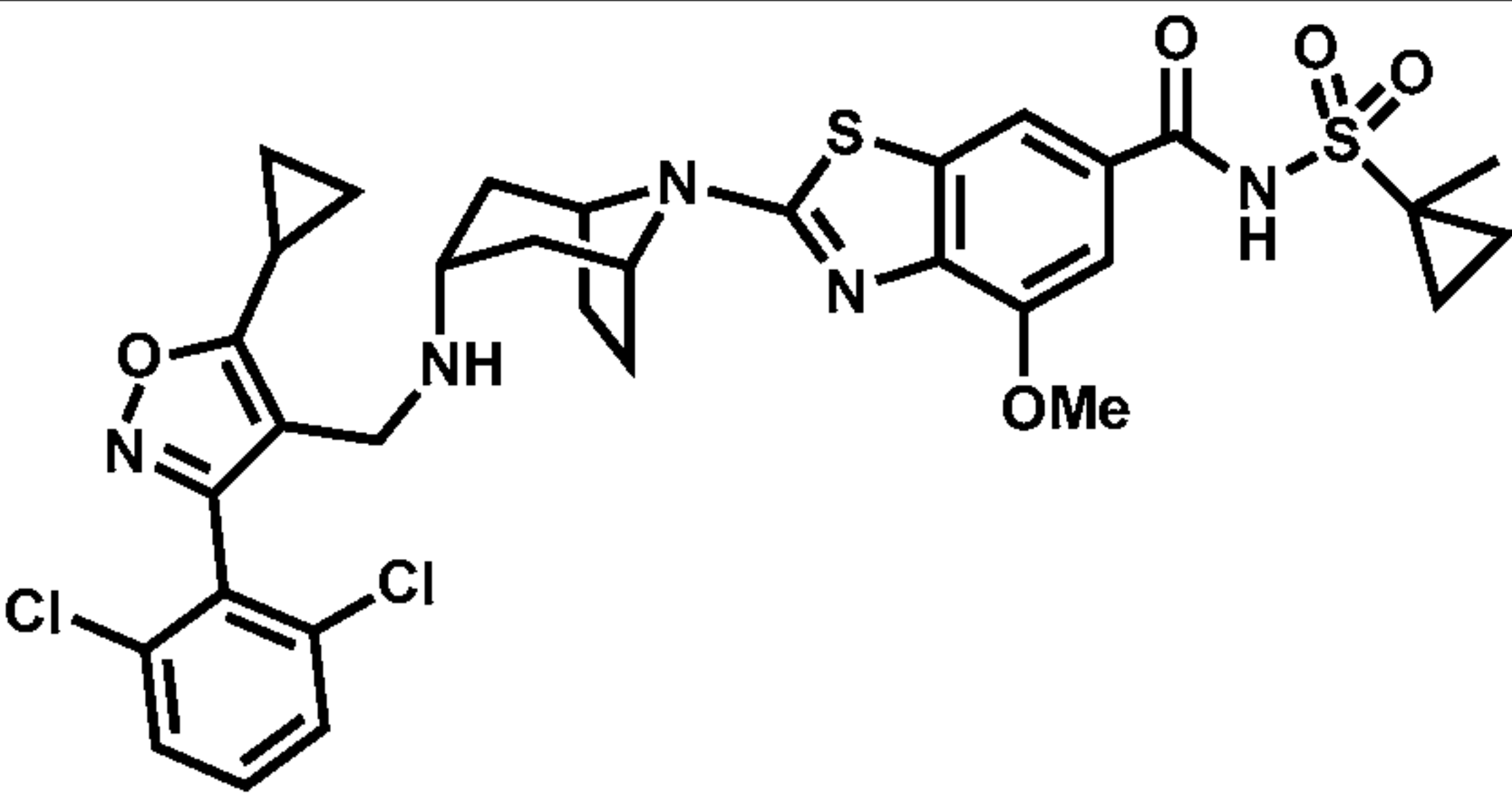
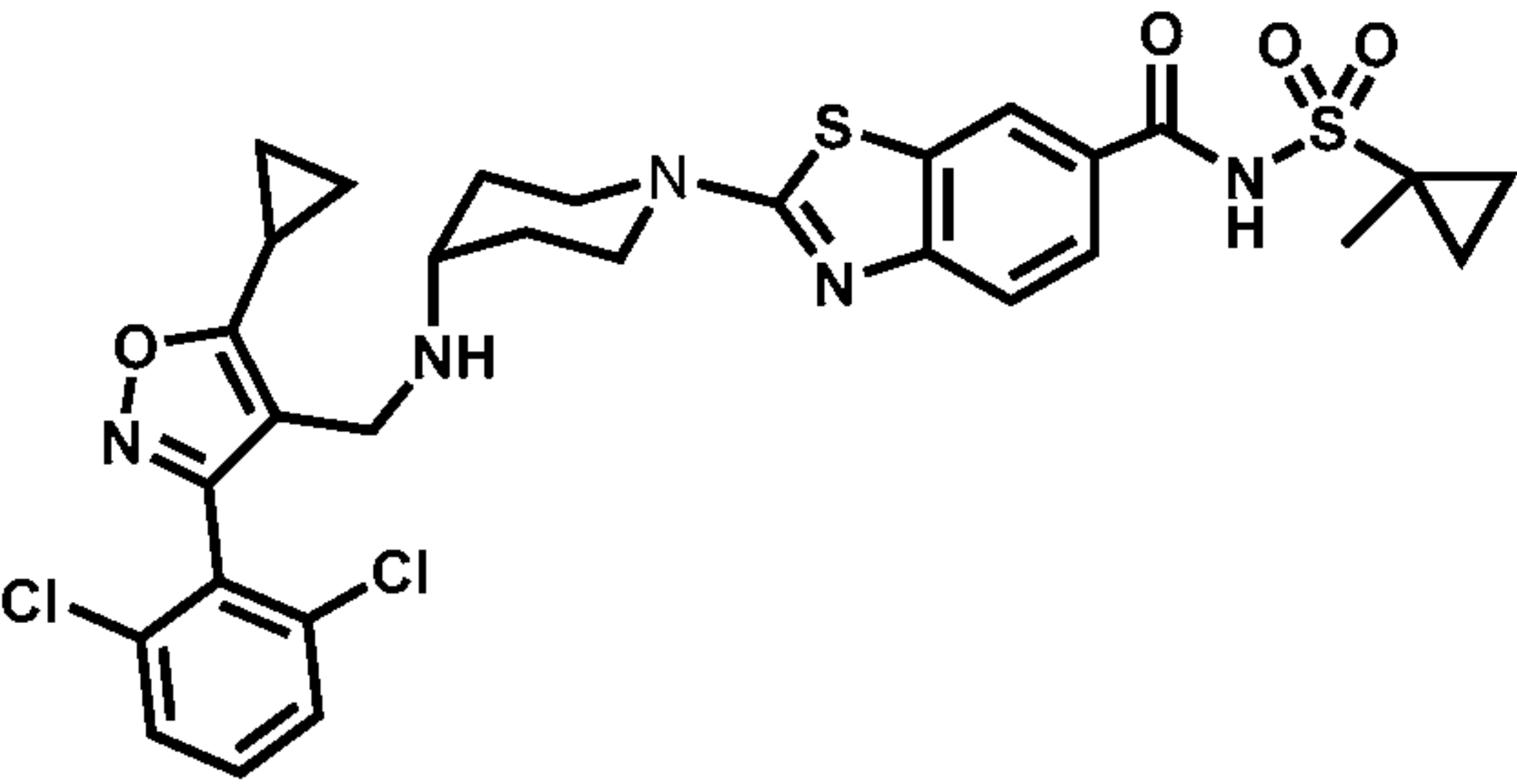
- 10 The following examples listed in Table 8 were prepared from the corresponding acids and sulfonamides following the analogous procedures described as in step 296-c for the synthesis of Example 296.

Table 8

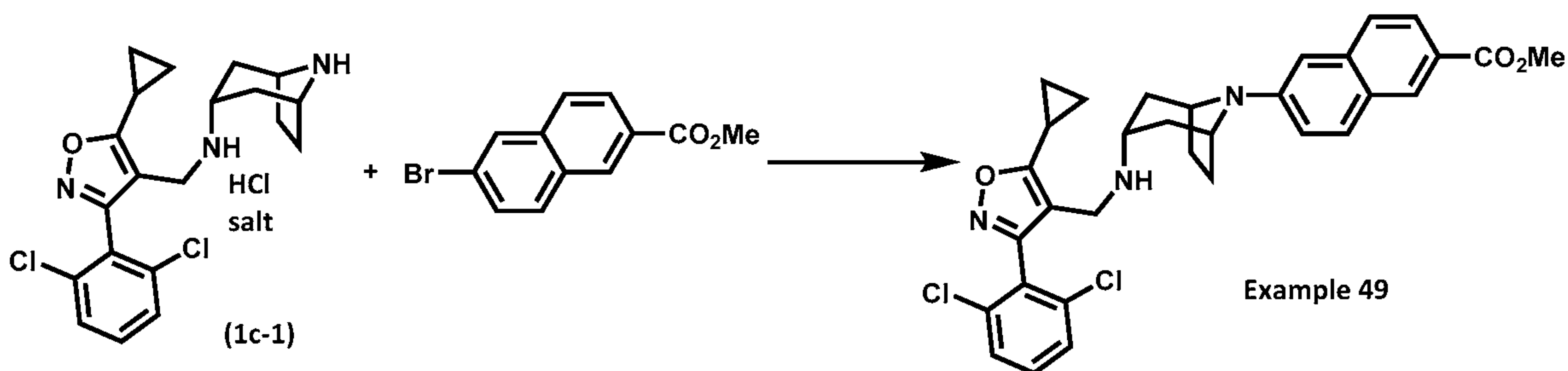
Example #	Structure	MS Data
279		678.13 (M+H)
280		661.13 (M+H)
281		635.11 (M+H)

282		649.12 (M+H)
283		675.13 (M+H)
284		764.18 (M+H)
285		667.19 (M+H)
291		646.11 (M+H)
295		704.15 (M+1)
297		693.14 (M+H)

298		690.13 (M+H)
299		718.13 (M+H)
300		733.18 (M+H)
301		657.15 (M- H)
302		668.15 (M- H)
303		716.17 (M+H)

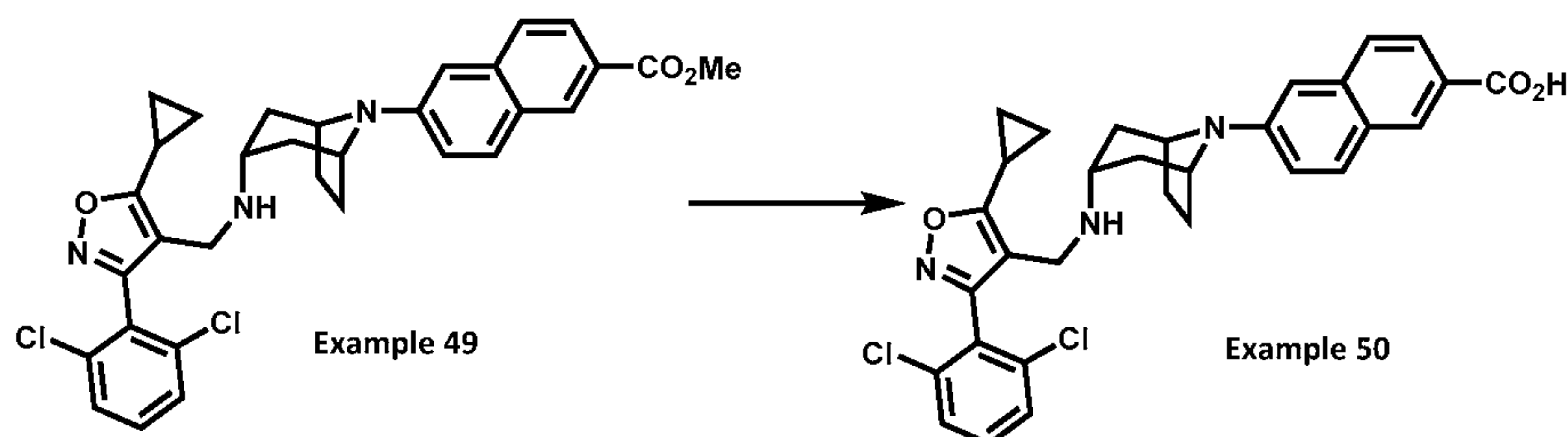
304		716.17 (M+H)
305		660.14 (M+H)

Example 49



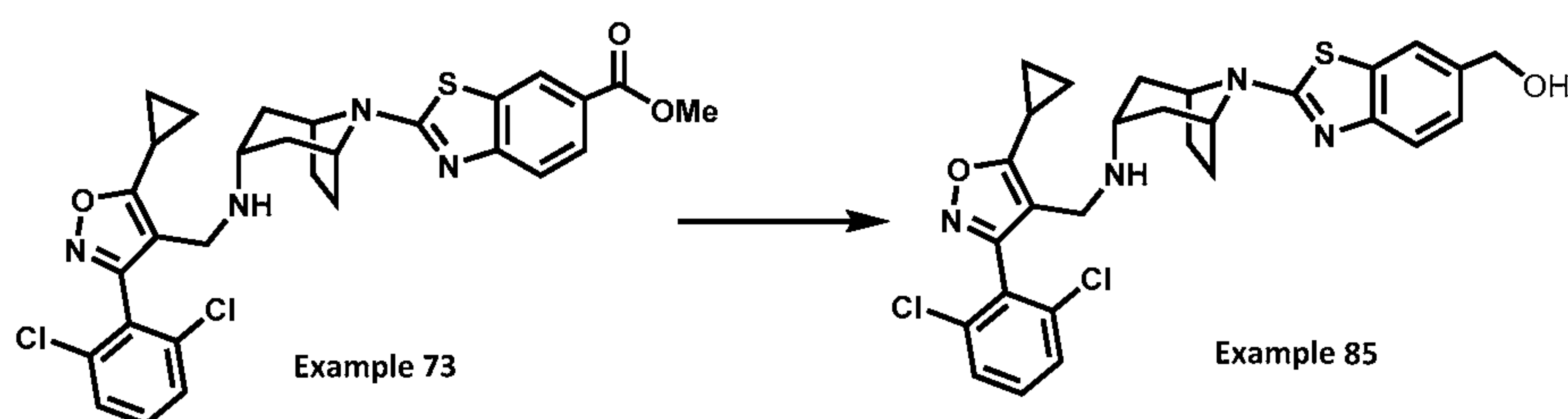
A mixture of Pd₂(dba)₃ (20.42 mg, 0.022 mmol), dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphane (XPhos) (21.26 mg, 0.045 mmol), methyl 6-bromo-2-naphthoate (177 mg, 0.669 mmol), cesium carbonate (581 mg, 1.784 mmol) and (1R,3r,5S)-N-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)-8-azabicyclo[3.2.1]octan-3-amine (175 mg, 0.446 mmol) in toluene (4 ml) was degassed, and then heated to 100 °C under N₂ atmosphere. The mixture was stirred for 16 h before cooled down to room temperature. The mixture was diluted with ethyl acetate and filtered through a celite pad. The filtrate was concentrated and the residue was purified by chromatography on silica gel eluting with Hexane to 40% acetone/hexane. The fractions containing Example 49 were combined, concentrated, and further purified by HPLC (0.1% Formic acid in Water/ACN) to give methyl 6-((1R,3R,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octan-8-yl)-2-naphthoate (58 mg, 0.101 mmol, 22.55 % yield). LC/MS observed [M+H], 576.18.

Example 50



Example 50 was prepared according to the analogous procedure as in step 2a described for the preparation of Example 2. LC/MS observed $[M+H]^+$, 562.17.

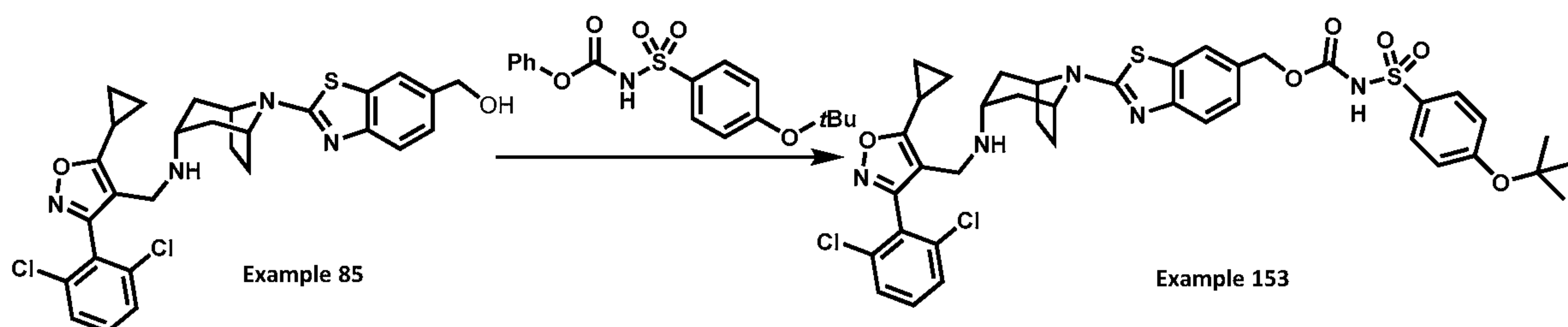
5 Example 85



To methyl 2-((1R,Rr,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octan-8-yl)benzo[d]thiazole-6-carboxylate (77 mg, 0.132 mmol) in THF (1 ml) was added LAH (0.264 ml, 0.264 mmol, 1 M in THF) at 0 °C.

- 10 The resulting mixture was stirred at 0 °C for 4 h and was then quenched with water, NaHCO₃ solution. The mixture was diluted with ethyl acetate and filtered through celite. Organic layer was separated and washed with brine, dried, filtered, and concentrated to Example 85 (68 mg, 0.122 mmol, 93 % yield). LC/MS observed $[M+H]^+$, 555.14.

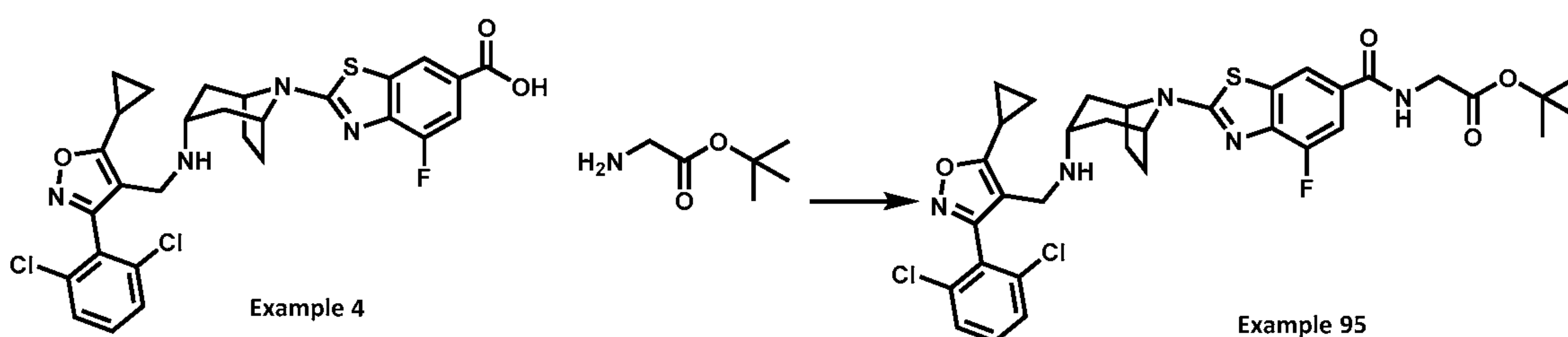
15 Example 153



To (2-((1R,3R,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octan-8-yl)benzo[d]thiazol-6-yl)methanol (28 mg, 0.050 mmol) in THF (2

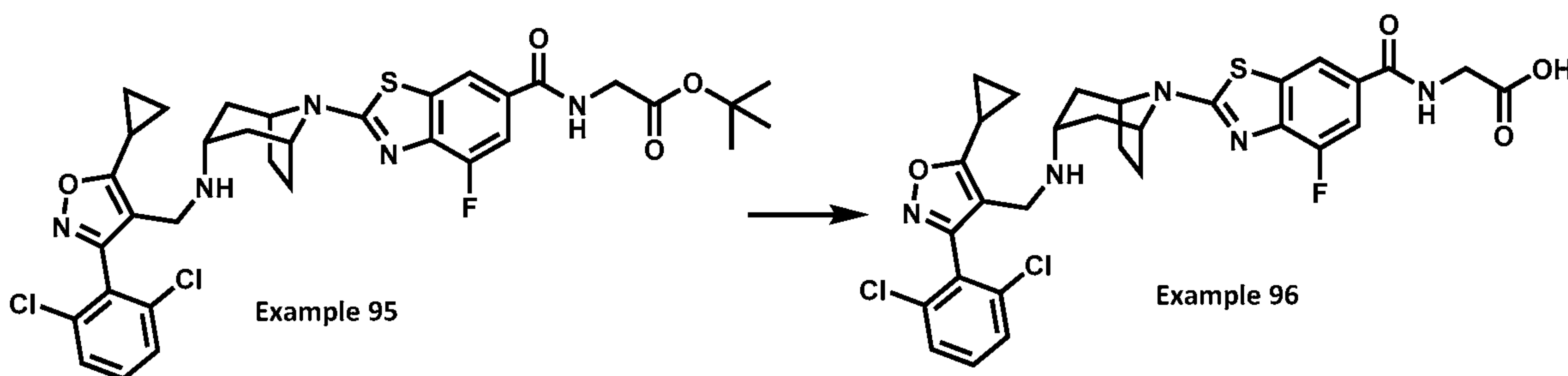
ml) was added triethylamine (0.018 ml, 0.126 mmol), phenyl((4-(*tert*-butoxy)phenyl)sulfonyl)carbamate (21.13 mg, 0.060 mmol) and DMAP (1.232 mg, 10.08 μ mol). The resulting solution was heated up to 50 °C for 16 h. Another portion of phenyl ((4-(*tert*-butoxy)phenyl)sulfonyl)carbamate (21.13 mg, 0.060 mmol) and DMAP (12 mg) was added and the mixture was stirred at 50 °C for another 4 h. The mixture was concentrated under vacuo and the residue was purified by HPLC (0.1% formic acid in water/ACN) to give Example 153 (11 mg, 0.014 mmol, 26.9 % yield). LC/MS observed [M+H], 810.24.

Example 95



To 2-((1R,3R,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octan-8-yl)-4-fluorobenzo[d]thiazole-6-carboxylic acid (Example 4) (50 mg, 0.085 mmol) and tert-butyl glycinate (16.75 mg, 0.128 mmol) in DCM (1 ml) was added EDC (26.1 mg, 0.136 mmol) and DMAP (20.80 mg, 0.170 mmol). The resulting mixture was stirred at RT for 16 h, and concentrated under vacuo. The residue was purified by CombiFlash eluting with DCM to 40% (10% MeOH in EA) to give Example 95 (31 mg). LC/MS observed [M+H], 700.19.

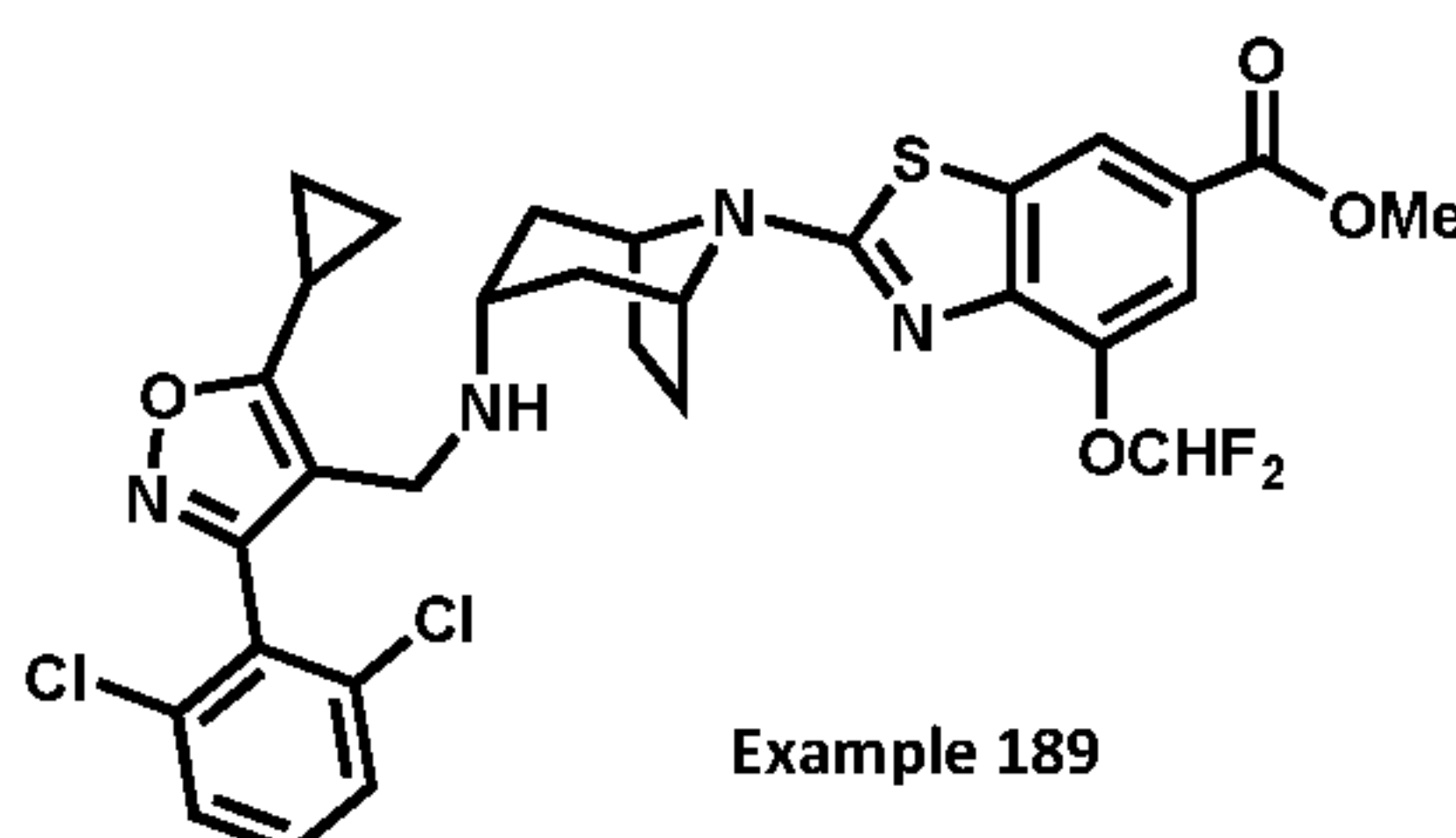
Example 96



To *tert*-butyl (2-((1R,3r,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octan-8-yl)-4-fluorobenzo[d]thiazole-6-carboxyl)glycinate (16 mg, 0.023 mmol) in DCM (1 ml) was added HCl (0.228 ml, 0.913

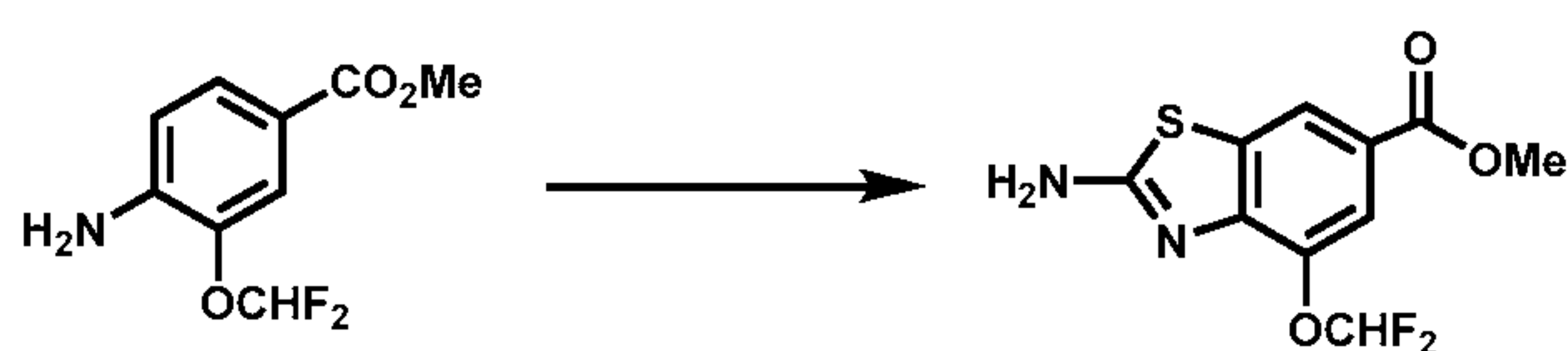
mmol, 4 M in dioxane) and the resulting mixture was stirred at rt for 4h. The mixture was concentrated under vacuo and chased with DCM to give Example 96 (17 mg). LC/MS observed $[M+H]^+$, 644.13.

Example 189



5

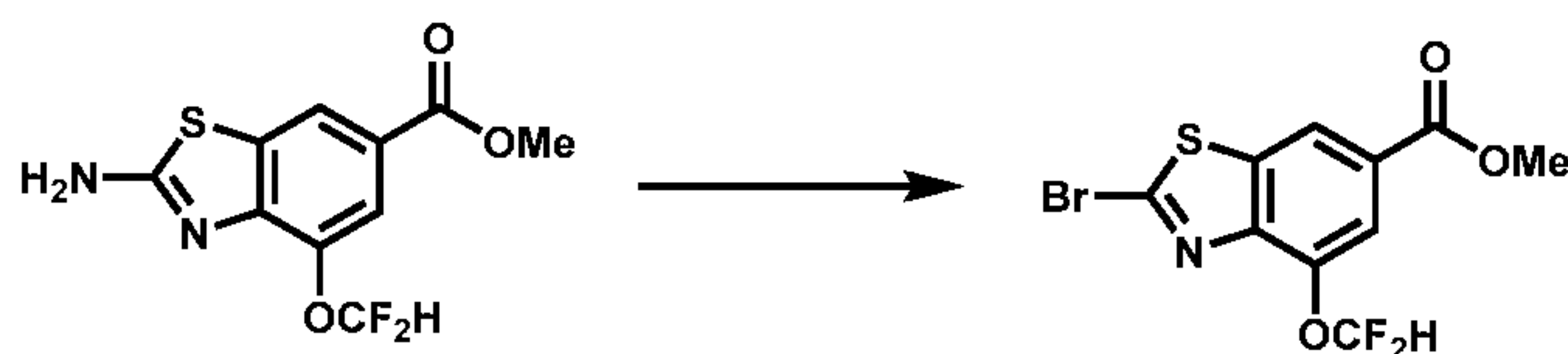
Step 189-a



To a solution of sodium thiocyanate (4.78 g, 58.9 mmol) in AcOH (8.67 ml), was added a solution of methyl 4-amino-3-(difluoromethoxy)benzoate (3.2 g, 14.73 mmol) in AcOH (17.34 ml) between 0 °C and rt. Br₂ (0.835 ml, 16.21 mmol) in AcOH (3.47 ml) was added to this mixture dropwise at 0 °C and the resulting mixture was stirred at 0 °C for 15 min. The mixture was allowed to warm up and stirred for 48h at room temperature. A quarter of reaction mixture was diluted with water (50 ml) and the pH was adjusted to 7 with addition of Na₂CO₃. The resulted yellow slurry was filtered, washed with water and dried under vacuo to give methyl 2-amino-4-(difluoromethoxy)benzo[d]thiazole-6-carboxylate (0.726 g).

10

Step 189-b

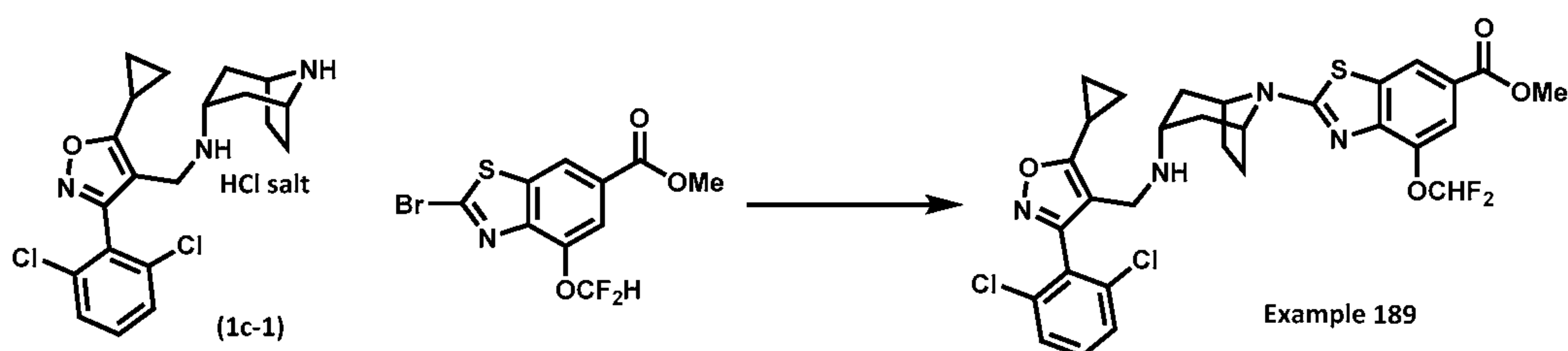


20

To a suspension of methyl 2-amino-4-(difluoromethoxy)benzo[d]thiazole-6-carboxylate (0.726 g, 2.65 mmol) in acetonitrile (15.57 ml) was added copper(II) bromide (0.887 g, 3.97 mmol). The mixture was cooled down to 0 °C and tert-butyl nitrite (0.734 ml, 6.17 mmol was slowly added) over 10 min. The mixture was warmed up to room temperature and stirred for 15h. The mixture was diluted with EtOAc (30 ml) and water (20 ml) then filtered through celite. Organic layer was separated and washed with water, brine, dried,

filtered, concentrated. The residue was purified by CombiFlash eluting with hexane to 30% EtOAc/hexane to give methyl 2-bromo-4-(difluoromethoxy)benzo[d]thiazole-6-carboxylate (0.4 g) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.37 (d, $J = 1.4$ Hz, 1H), 7.91 (dt, $J = 1.5, 0.7$ Hz, 1H), 7.03 (t, $J = 73.6$ Hz, 1H), 3.96 (s, 3H).

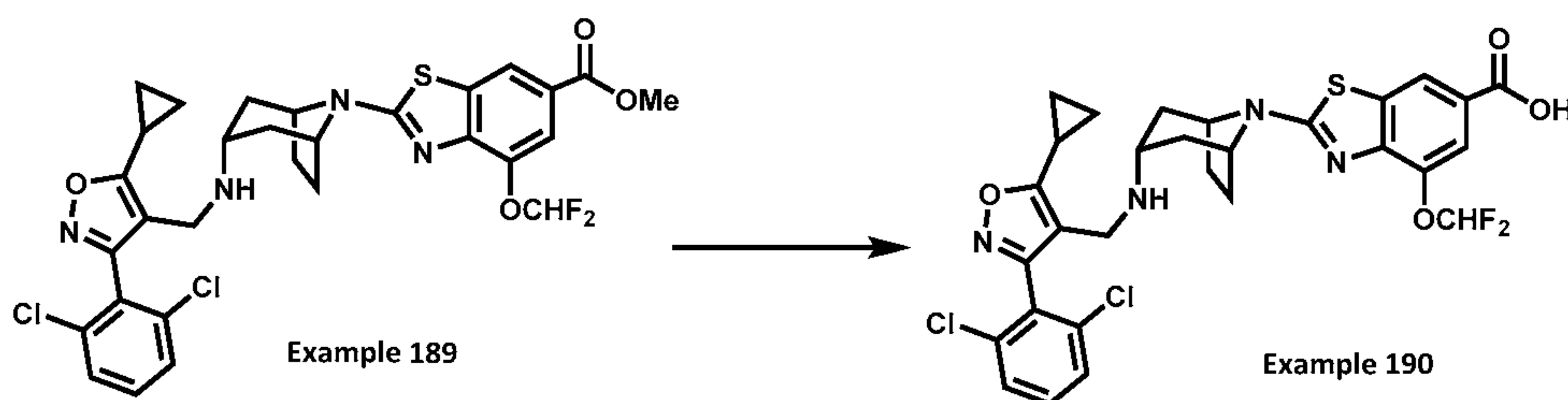
5 Step 189-c



Example 189 was prepared from compound (1c-1) and methyl 2-bromo-4-(difluoromethoxy)benzo[d]thiazole-6-carboxylate according to the analogous procedure as in step 1d described for the preparation of Example 1. LC/MS observed $[M+H]$, 649.13.

10

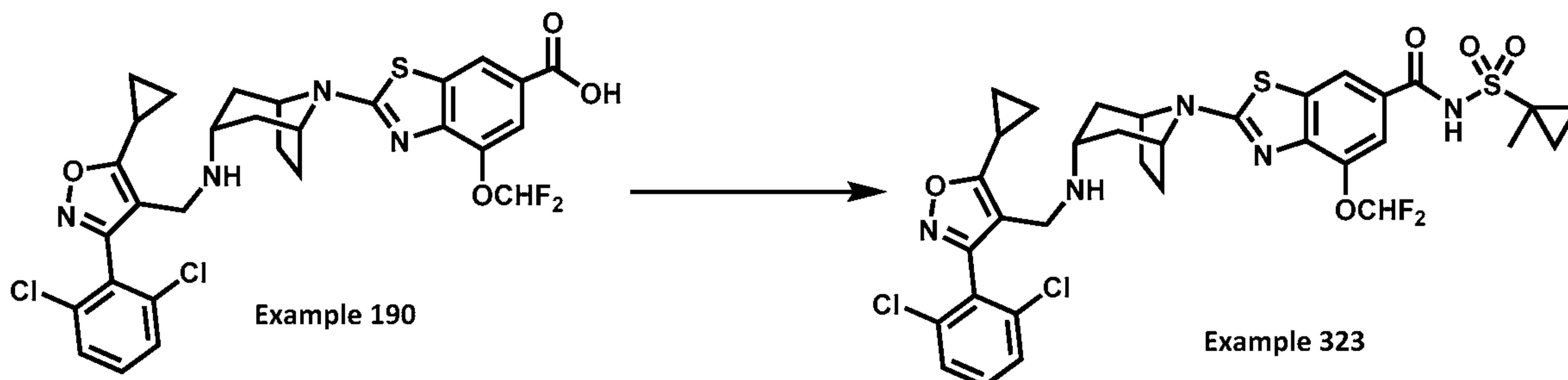
Example 190



Example 190 was prepared according to the analogous procedure as in step 2a described for the preparation of Example 2. LC/MS observed $[M+H]$, 635.11.

15

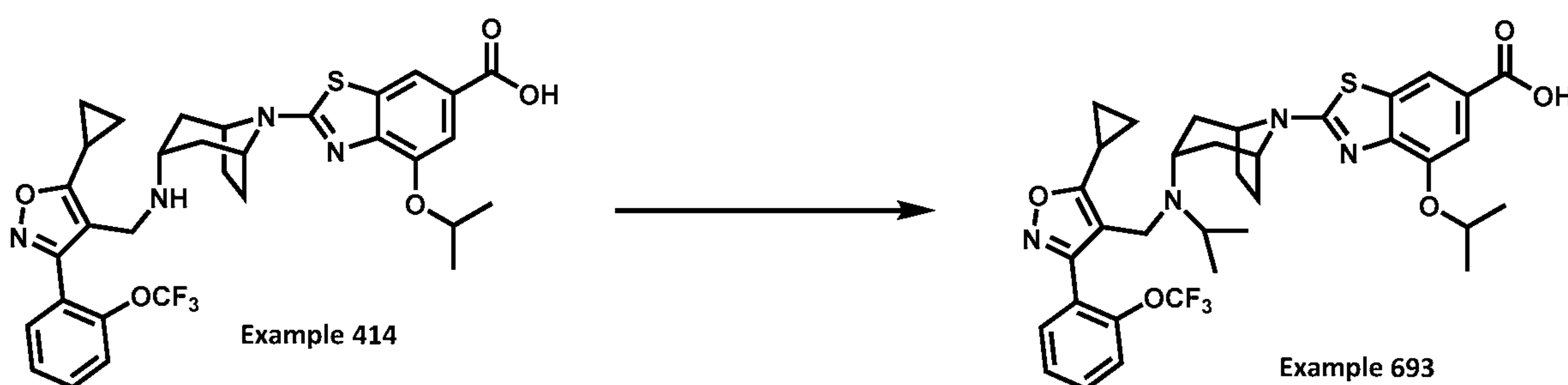
Example 323



To 2-((1R,3r,5S)-3-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octan-8-yl)-4-(difluoromethoxy)benzo[d]thiazole-6-carboxylic acid

(Example 190) (20 mg, 0.031 mmol), DMAP (9.61 mg, 0.079 mmol), and 1-methylcyclopropane-1-sulfonamide (8.51 mg, 0.063 mmol) in DCM (0.629 ml), was added EDC (9.05 mg, 0.047 mmol). The resulting mixture was stirred at rt for 24 h and the volatiles were removed and the residue was purified by HPLC purification (0.1%FA in ACN and water) to give 2-((1R,3r,5S)-3-(((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)amino)-8-azabicyclo[3.2.1]octan-8-yl)-4-(difluoromethoxy)-N-((1-methylcyclopropyl)sulfonyl)benzo[d]thiazole-6-carboxamide (Example 323) (11 mg). LC/MS observed [M+H], 781.16.

10 Example 693



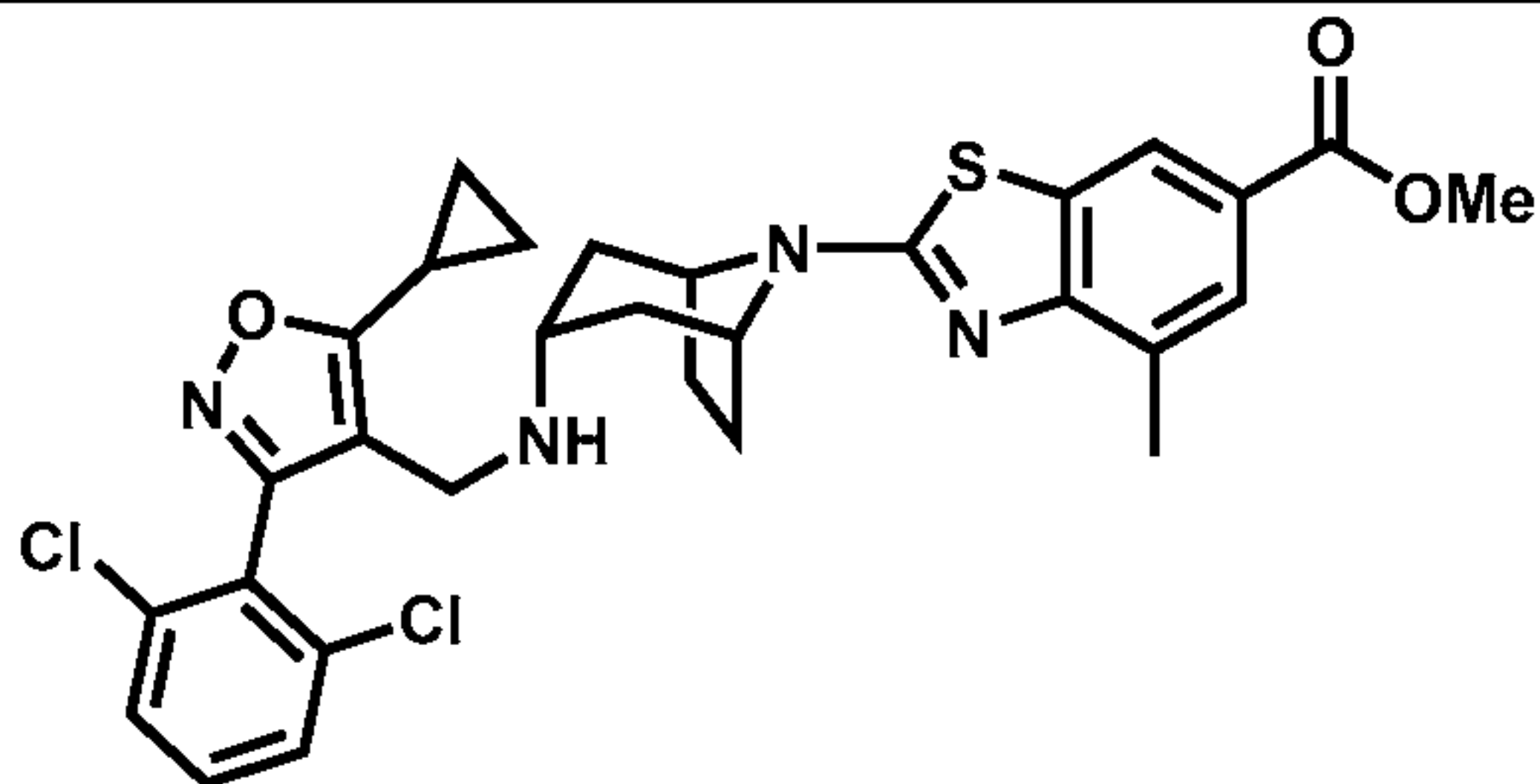
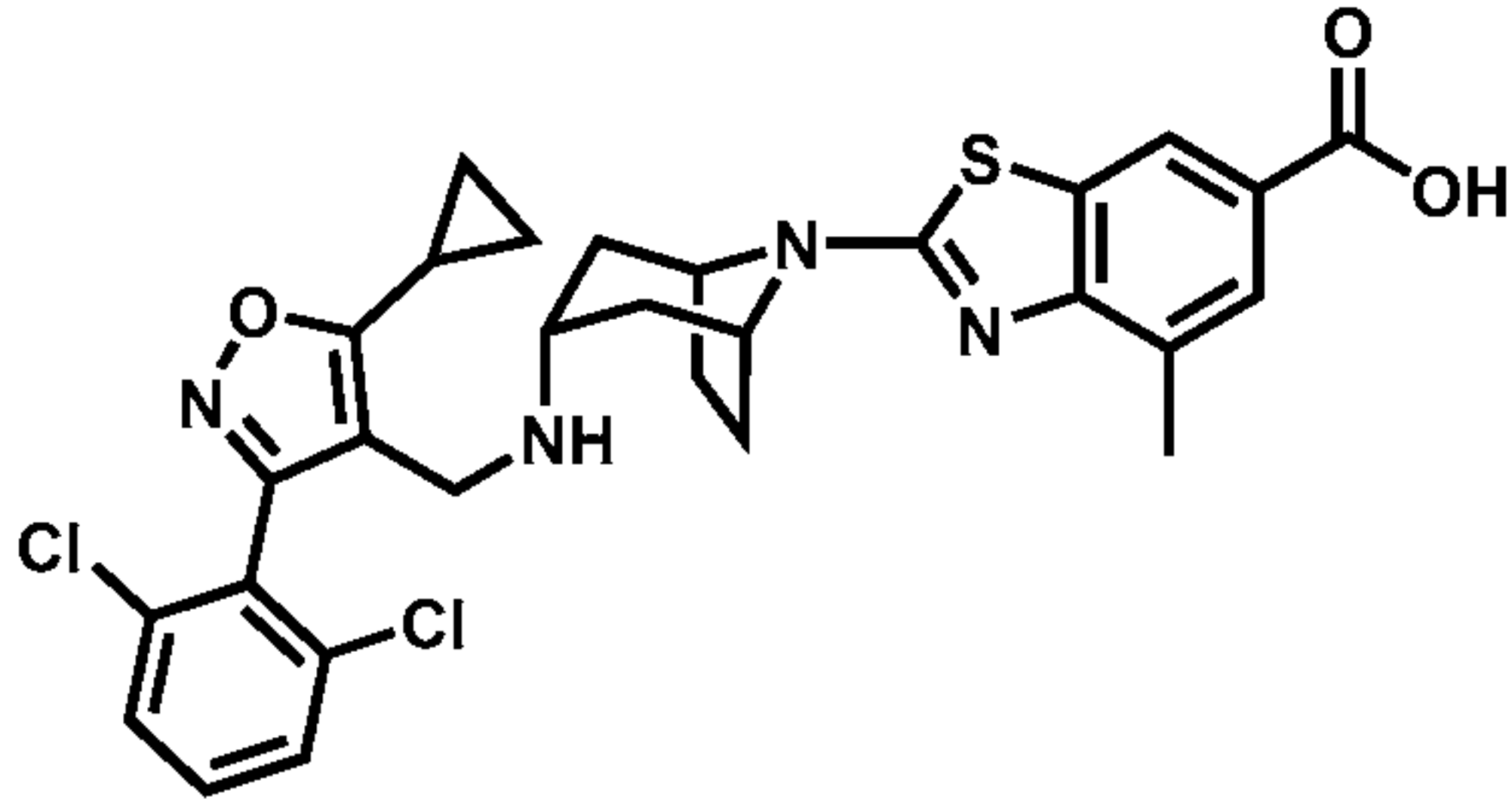
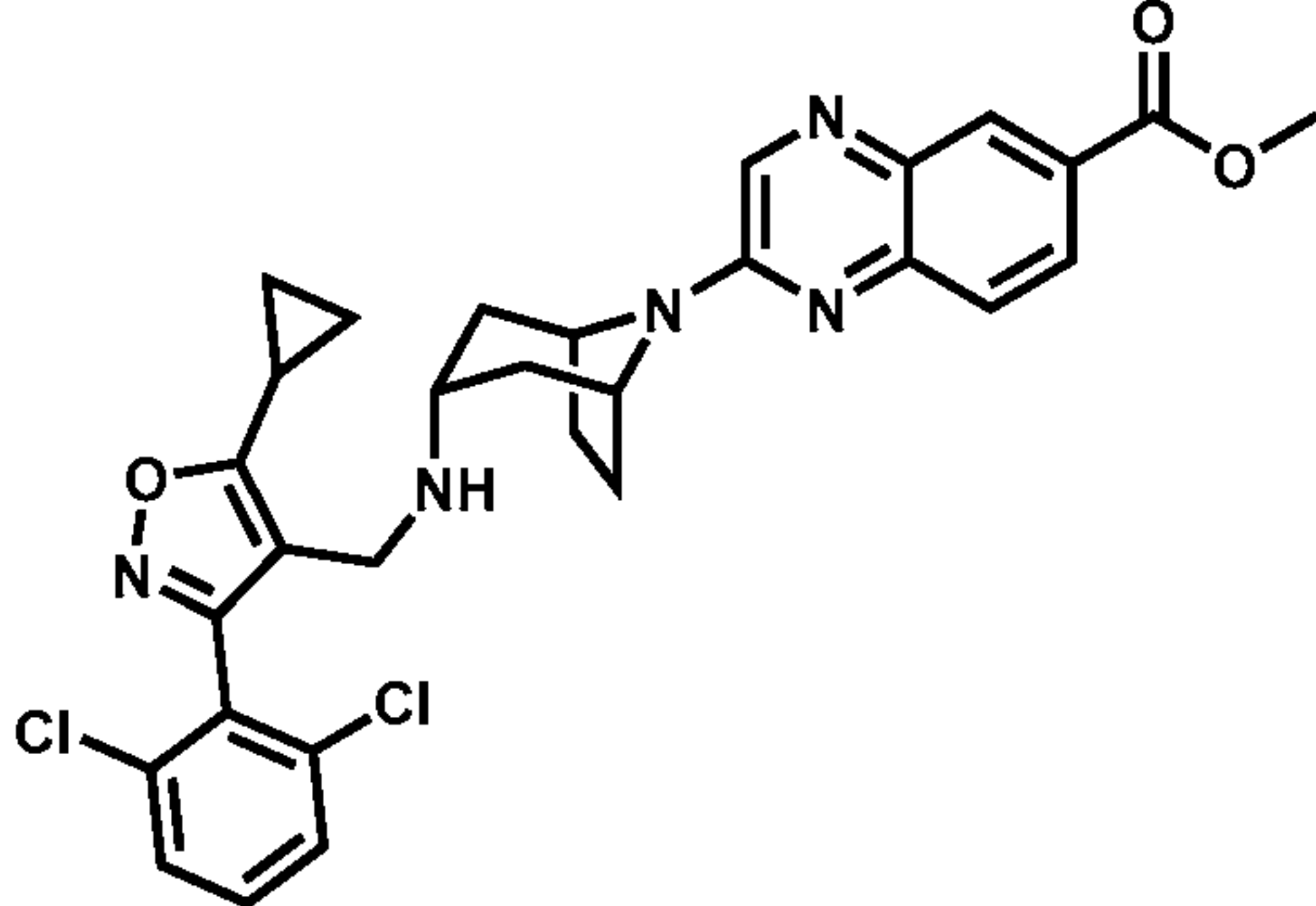
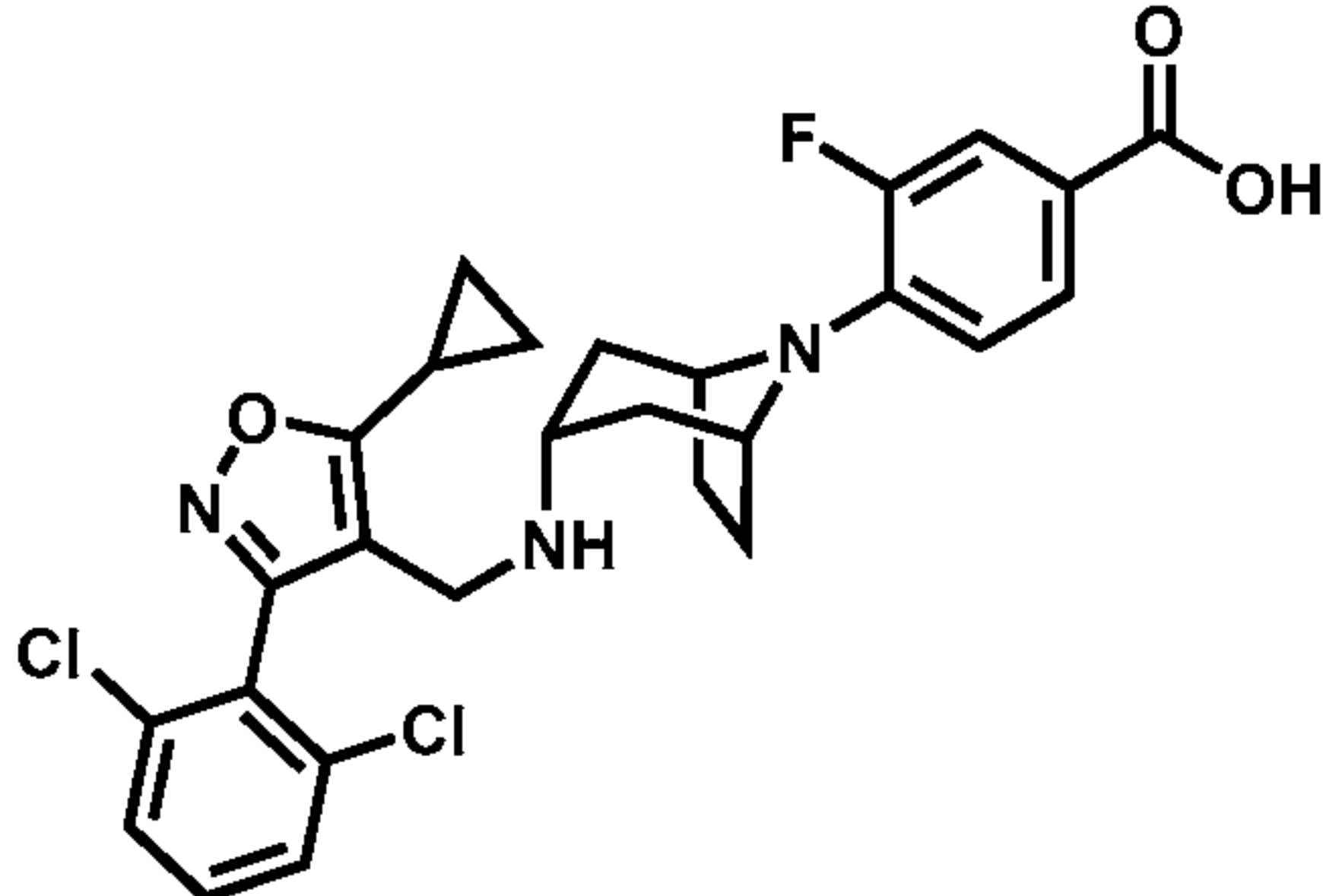
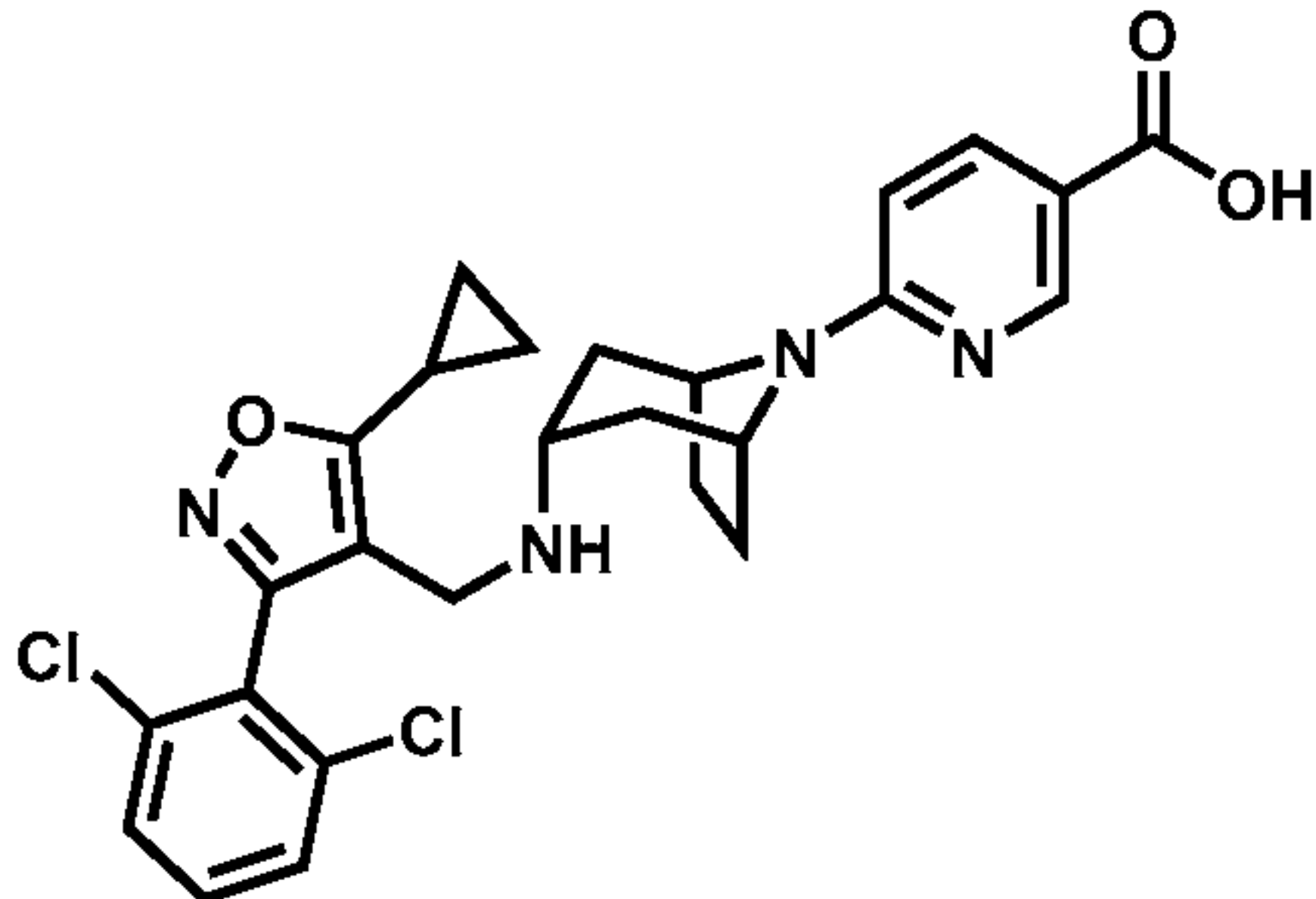
To a solution of Example 414 (200 mg, 0.311 mmol) in ACN (1.0 ml) were added acetone (0.12 mL, 1.56 mmol), acetic acid (178 μ l, 3.11 mmol) and NaBH₃CN (47.8 mg, 0.622 mmol) at 0 °C. The resulting mixture was stirred at 0 °C to room temperature for 16 h.

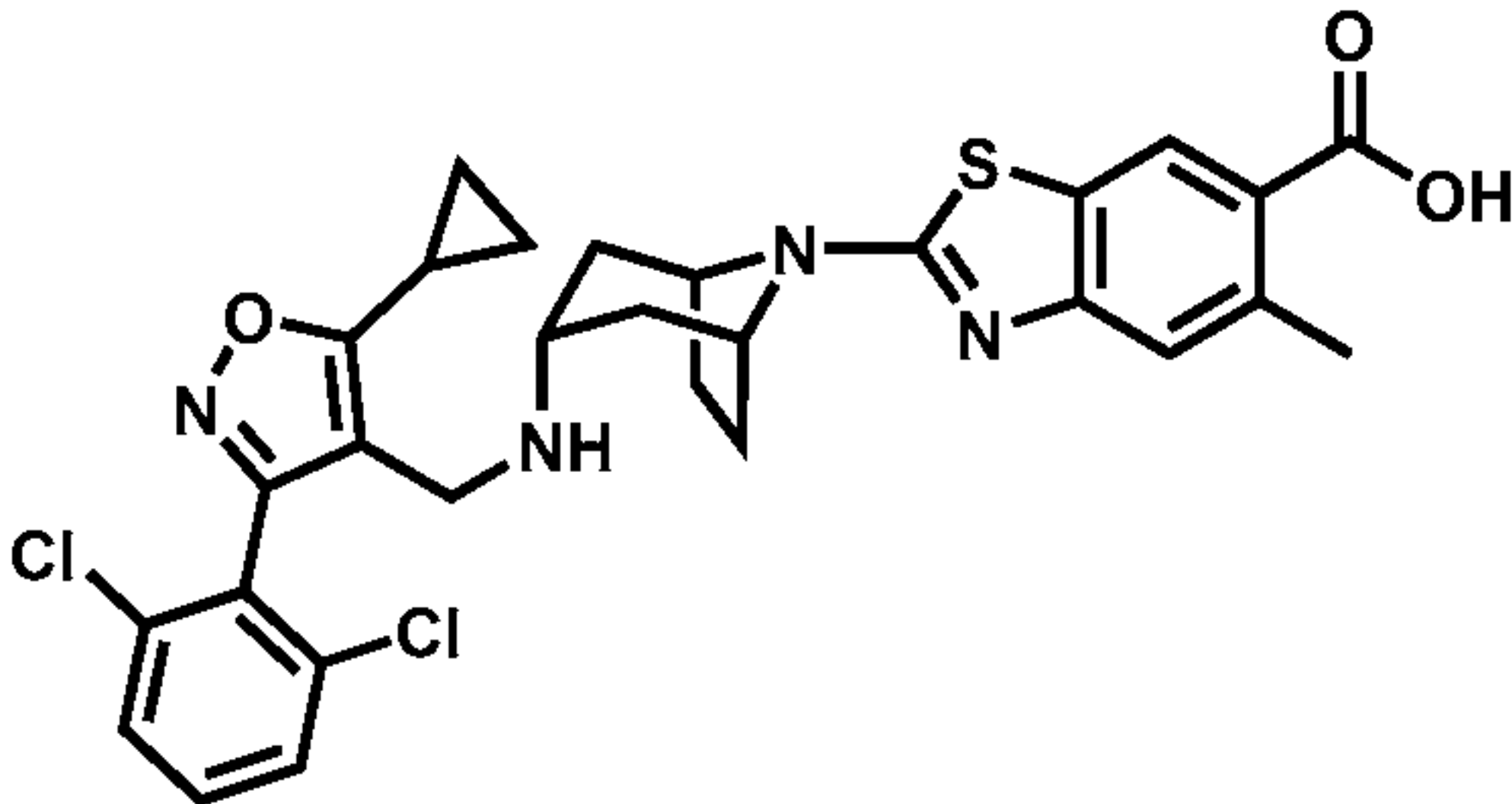
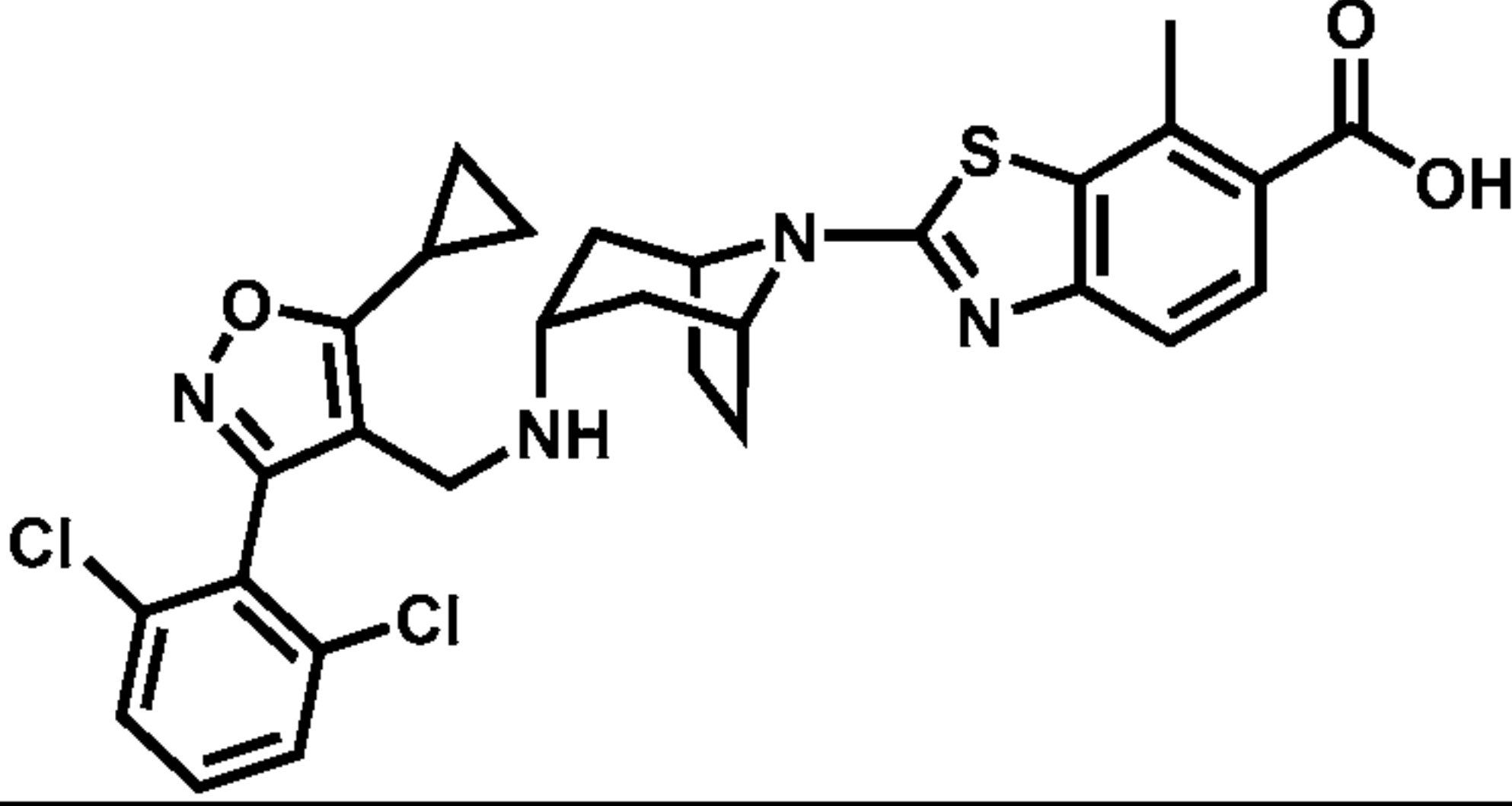
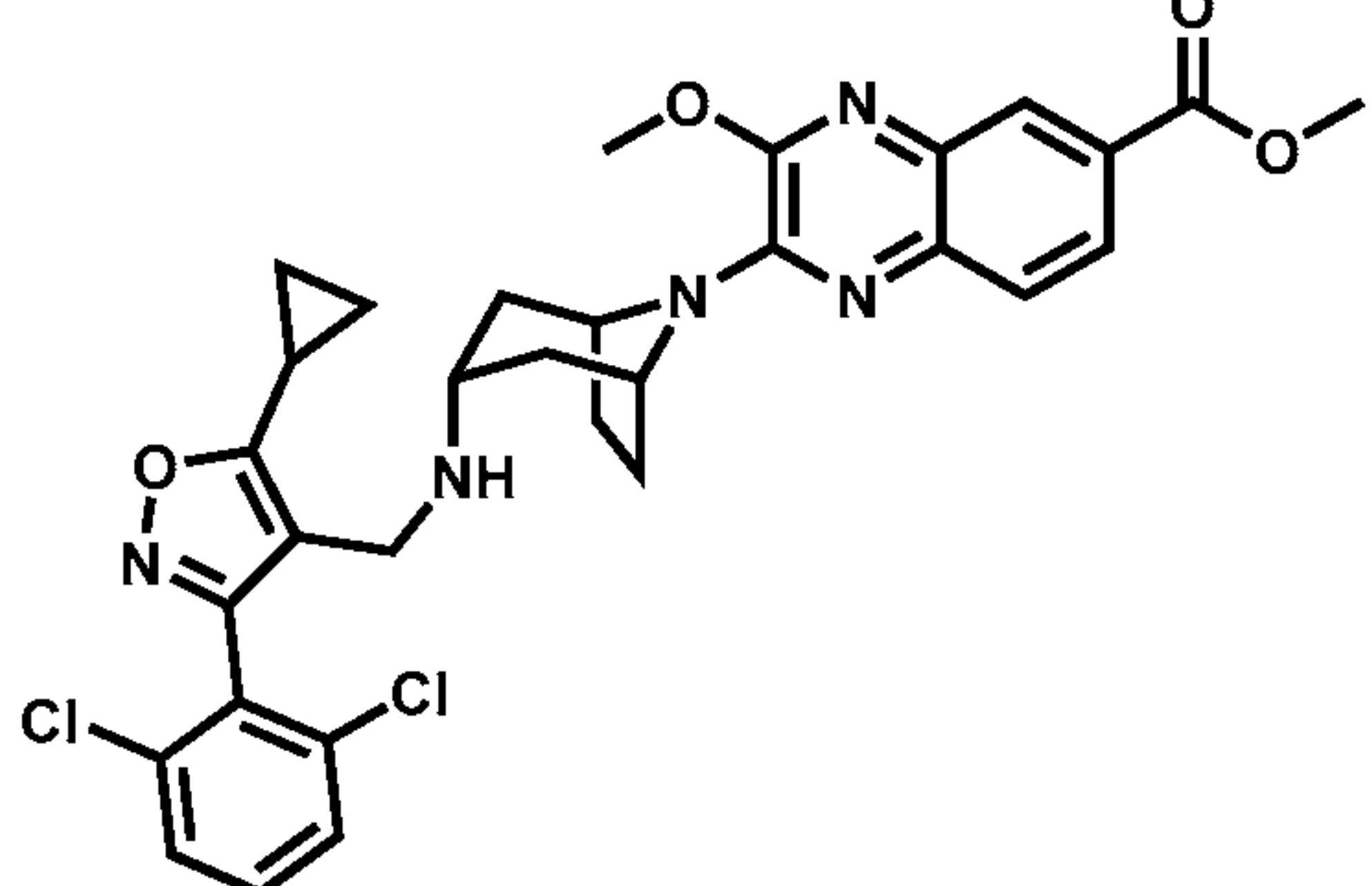
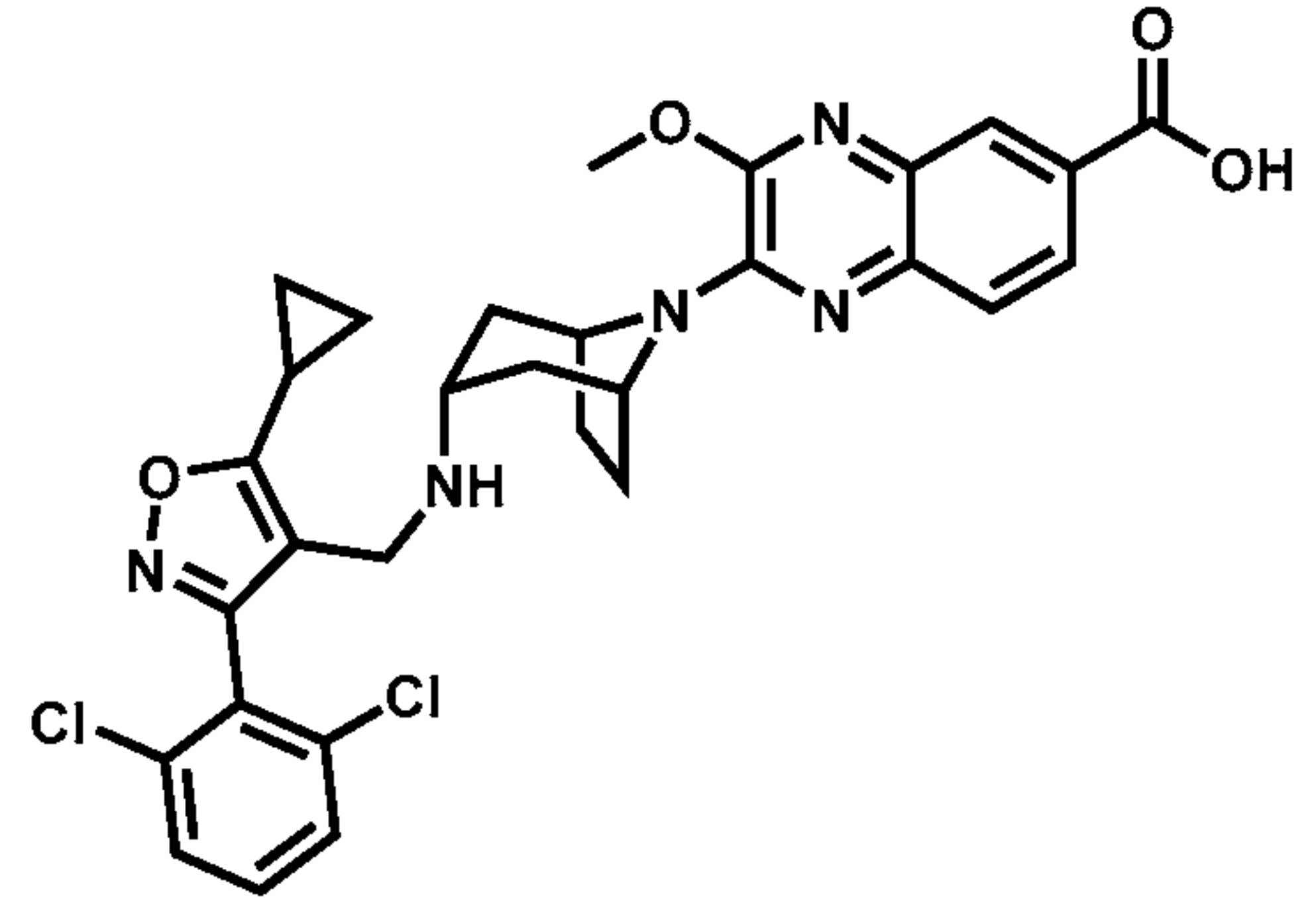
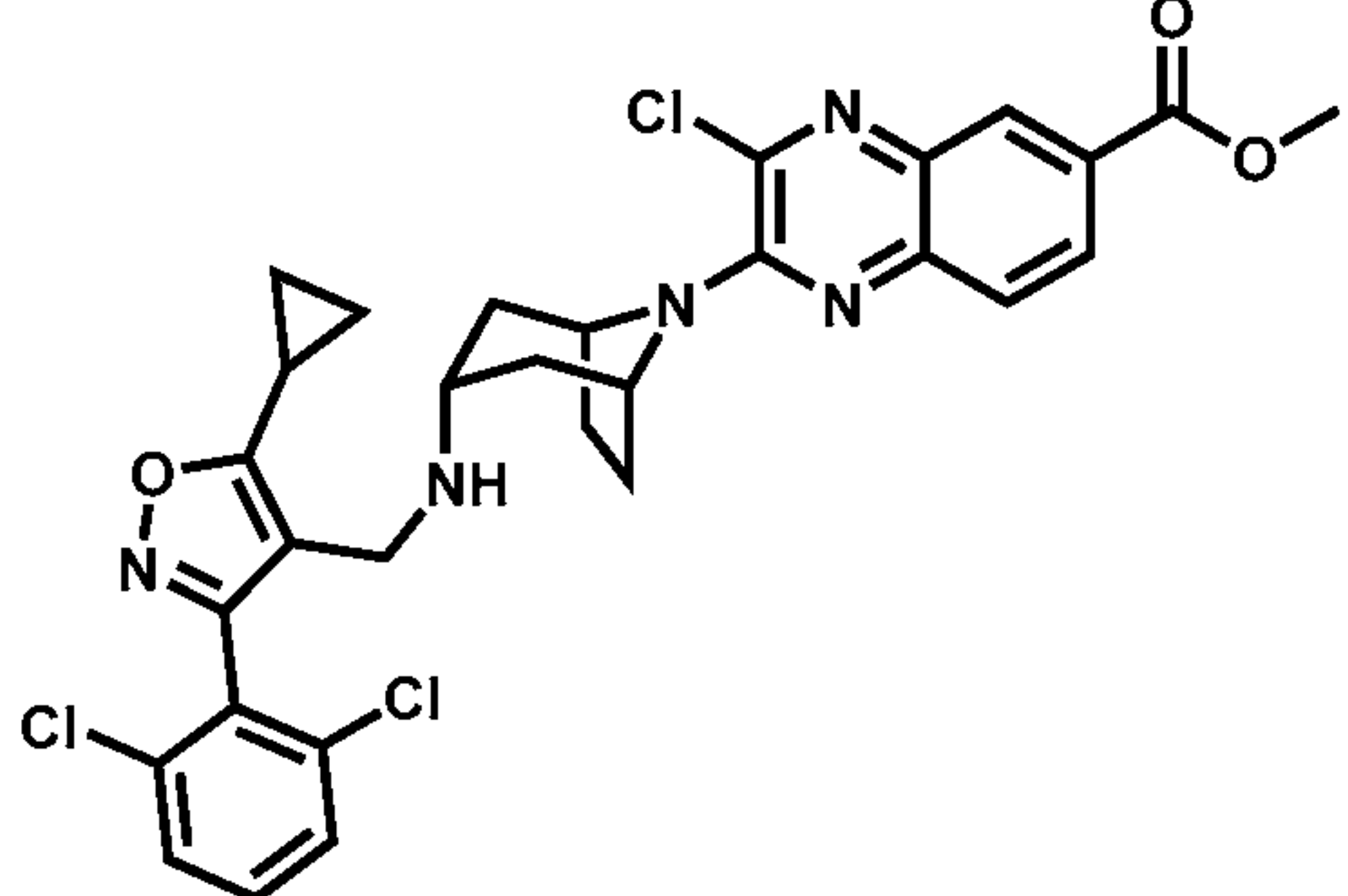
15 Additional portions of acetone (0.12 mL, 1.56 mmol), acetic acid (178 μ l, 3.11 mmol) and NaBH₃CN (47.8 mg, 0.622 mmol) were added and the reaction mixture continued stirring for another 18 h. The reaction mixture was diluted with EtOAc, washed with water (2x), brine, dried (Na₂SO₄), and concentrated. The crude sample was purified by reverse phase preparative HPLC using water acetonitrile as mobile phase (solvent A: water with 0.5% formic acid; solvent B: acetonitrile with 0.5% formic acid). The desired product was

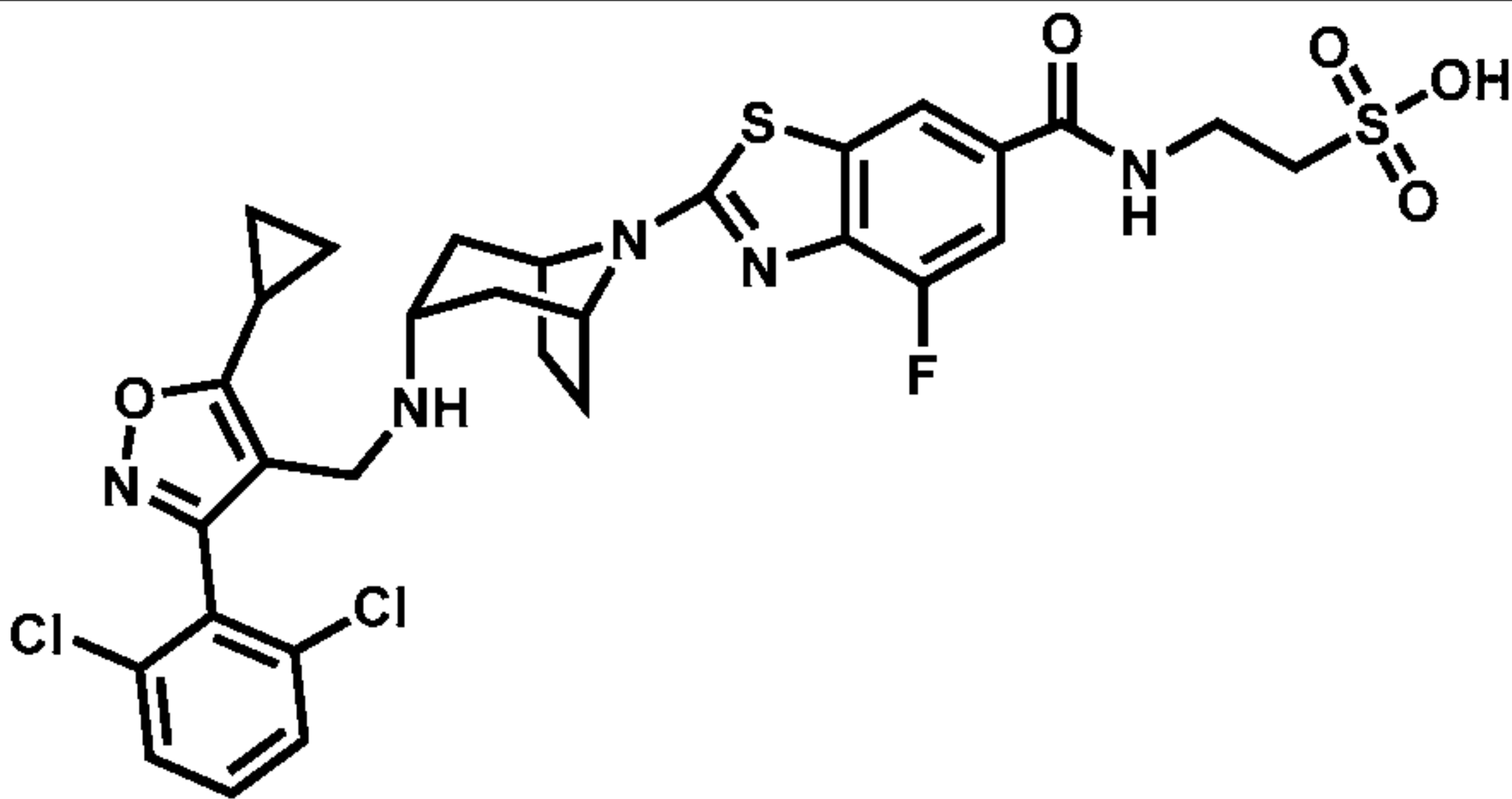
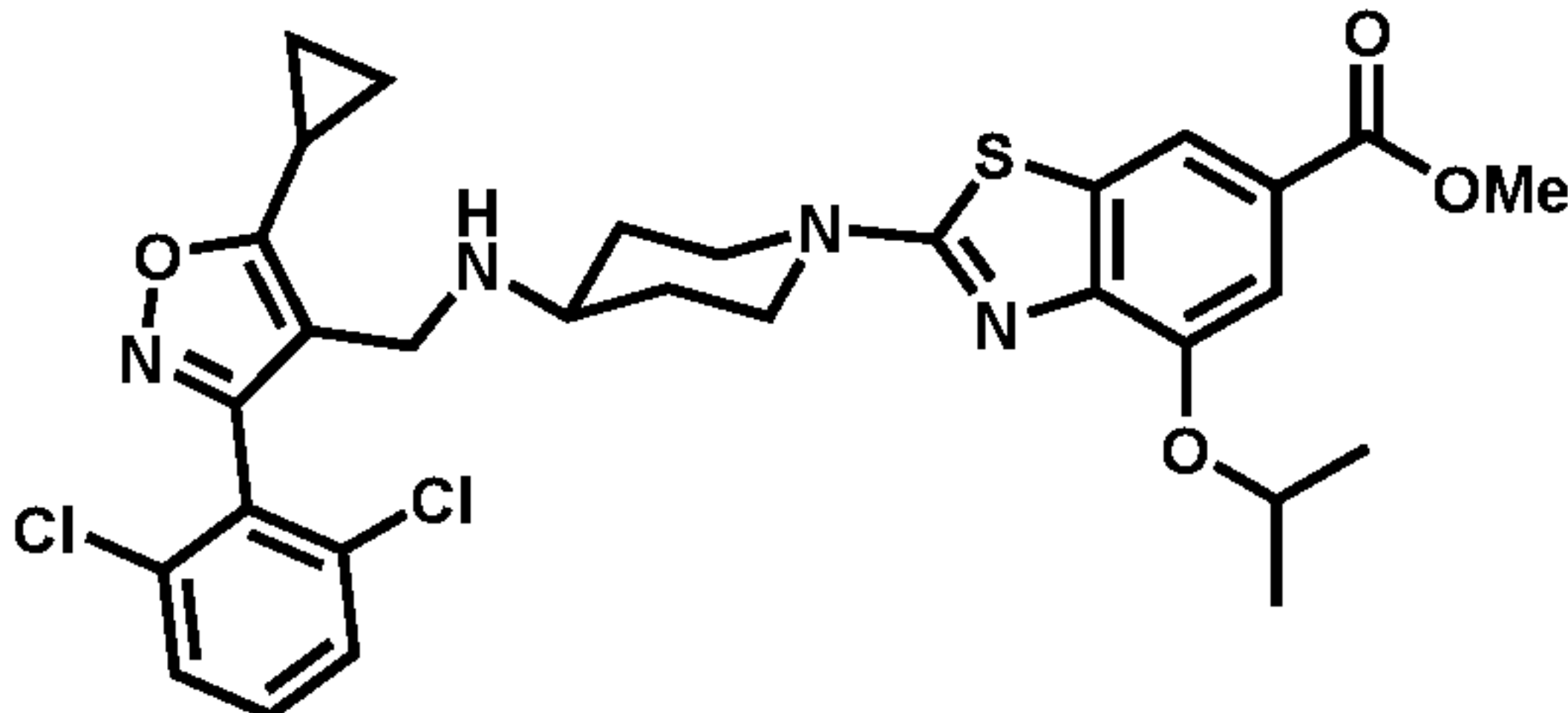
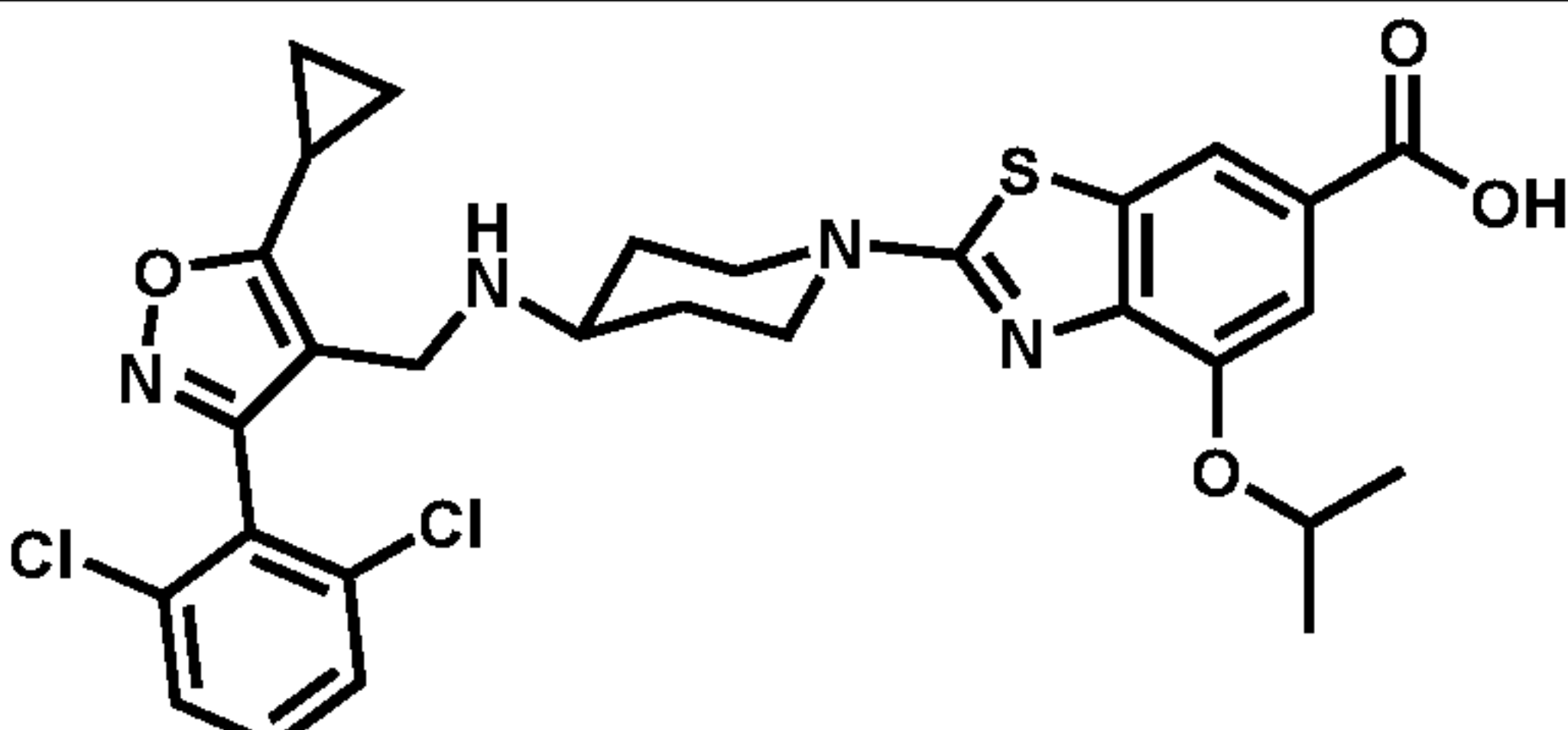
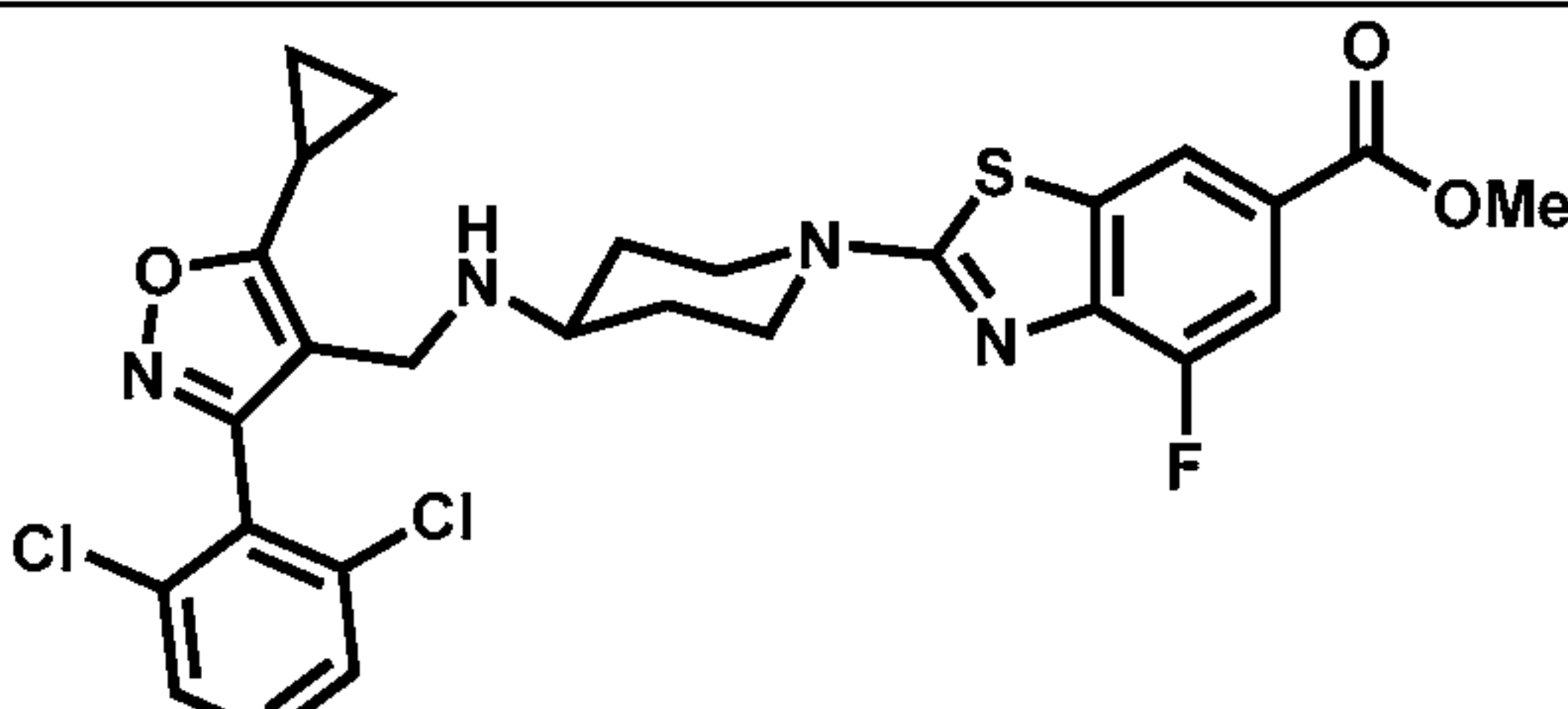
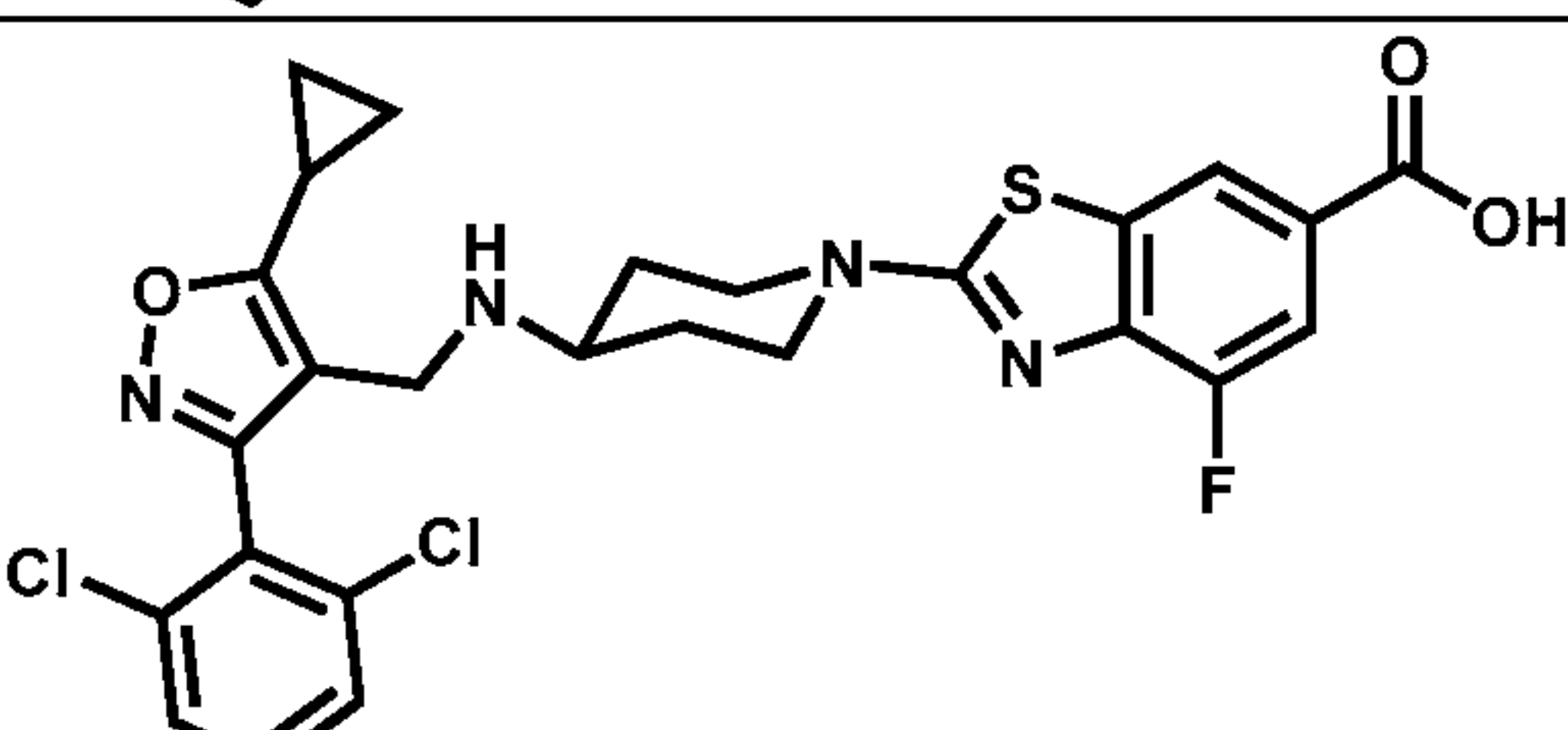
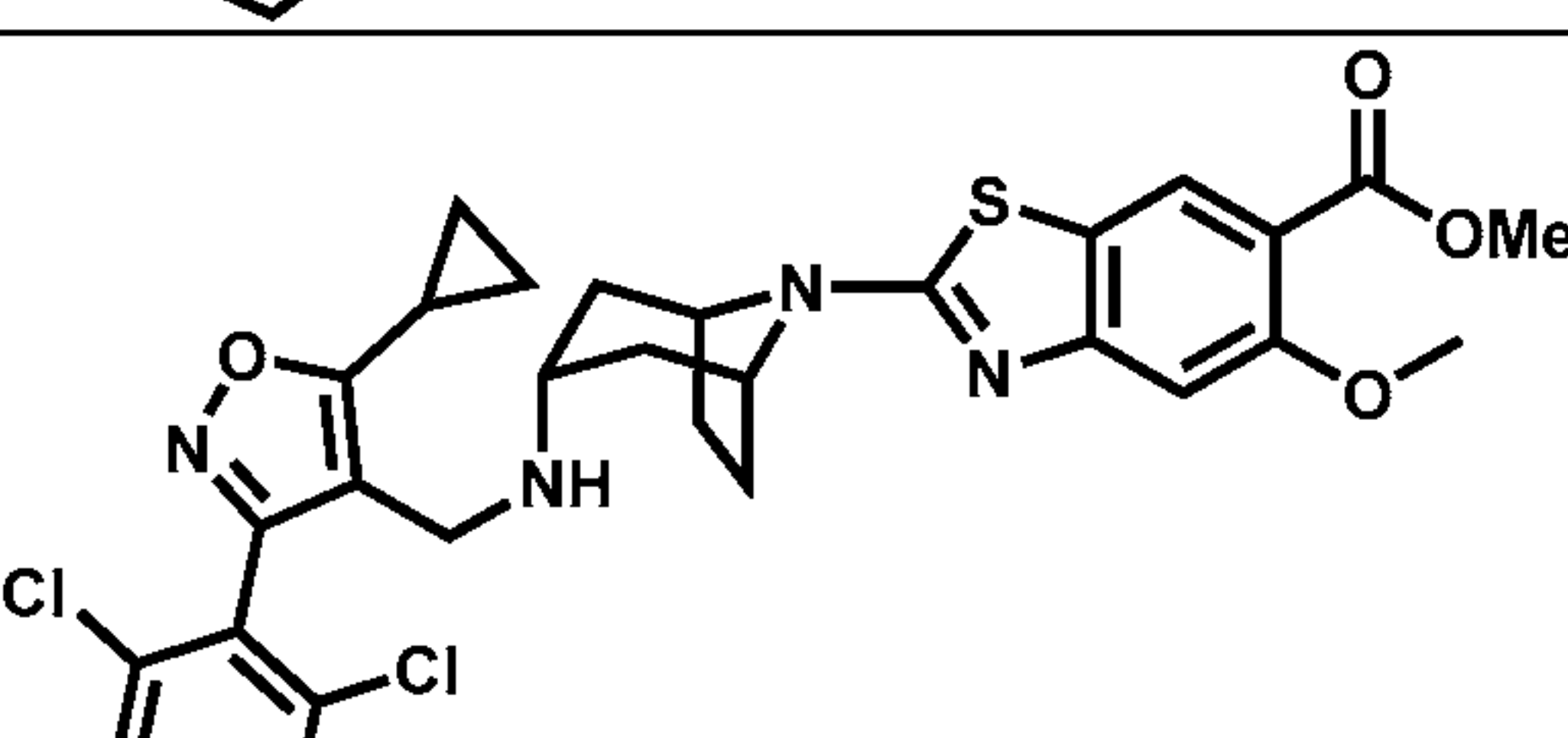
20 lyophilized to afford Example 693 as a white solid. LC-MS: 685.29 ([M+1].

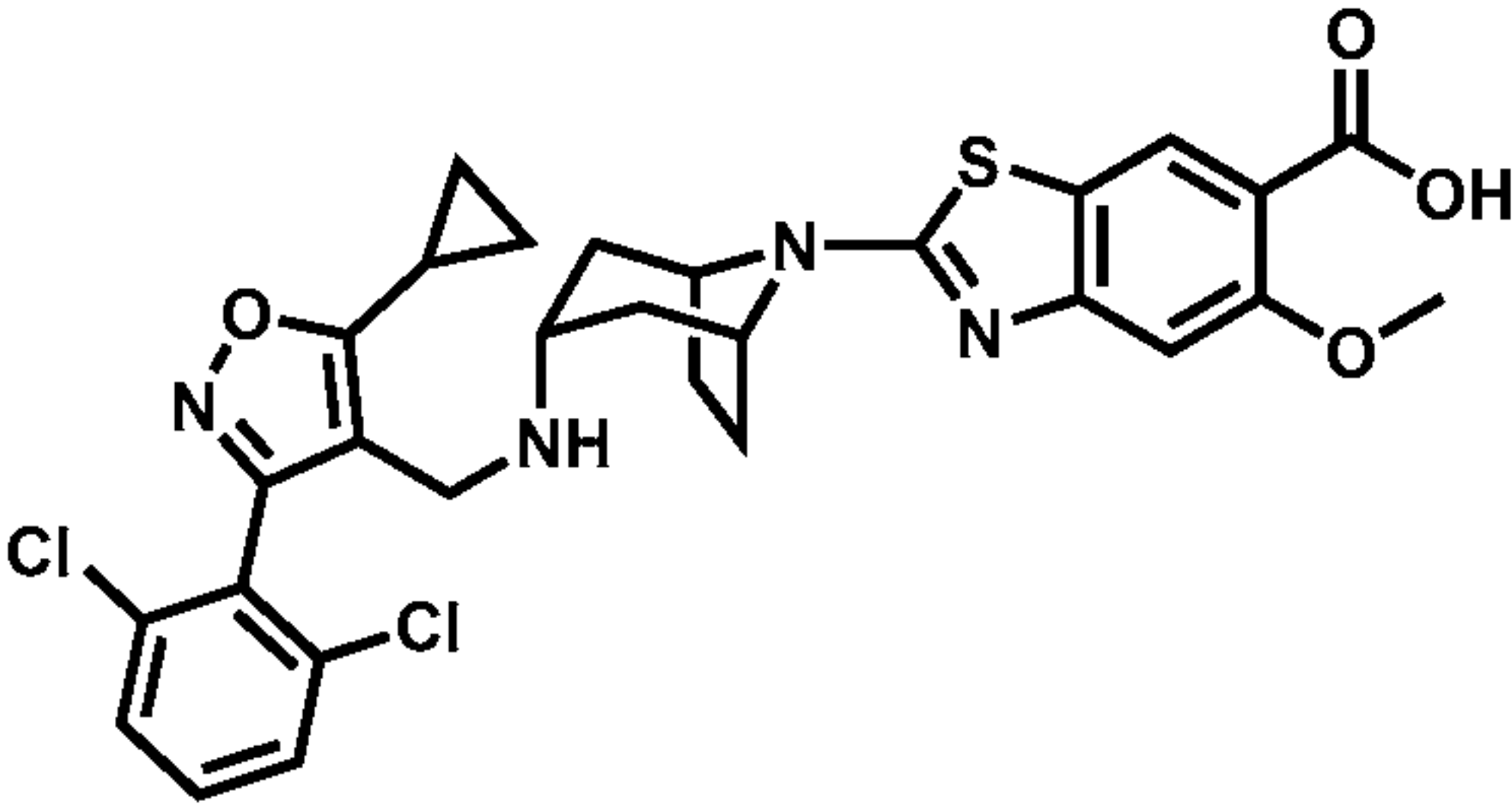
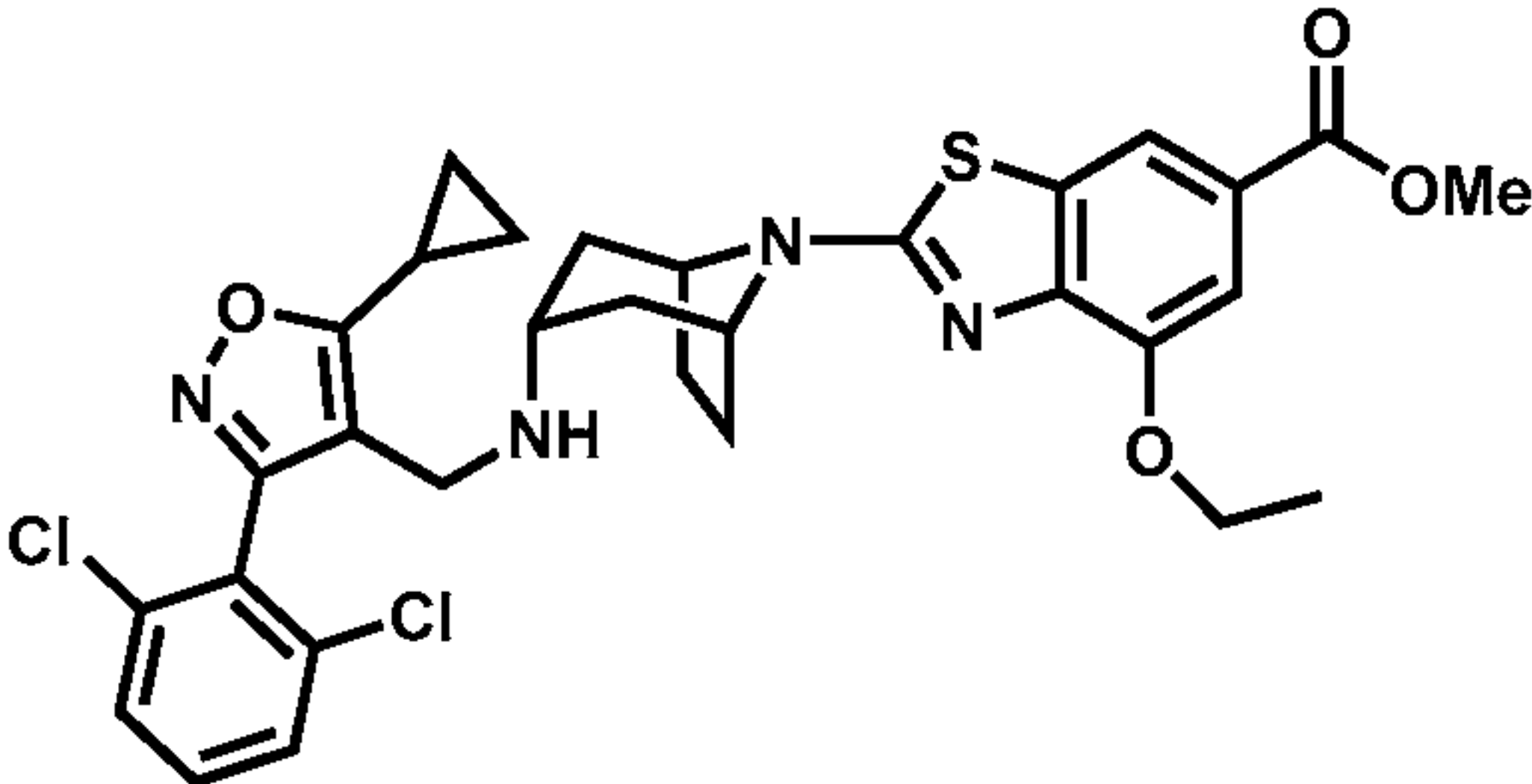
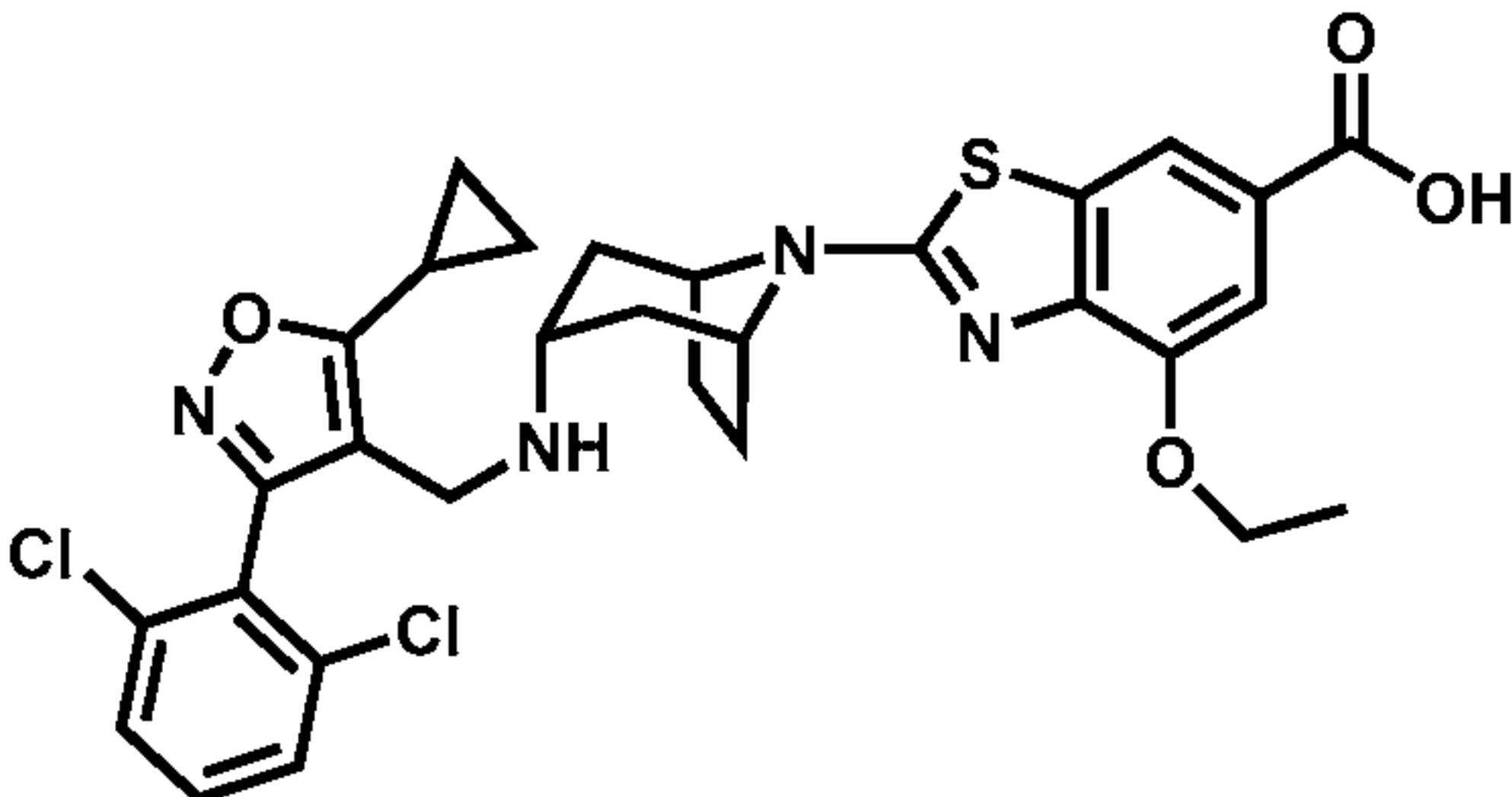
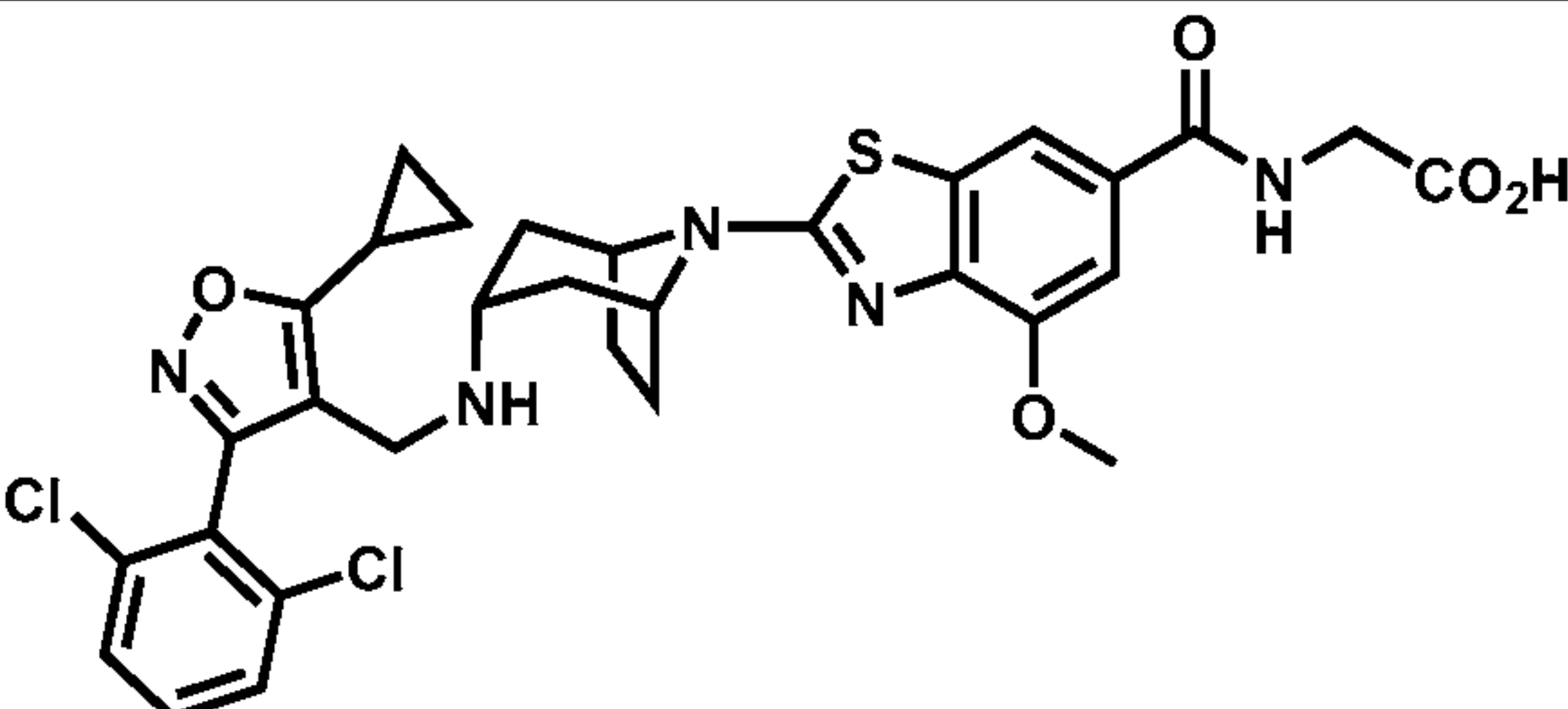
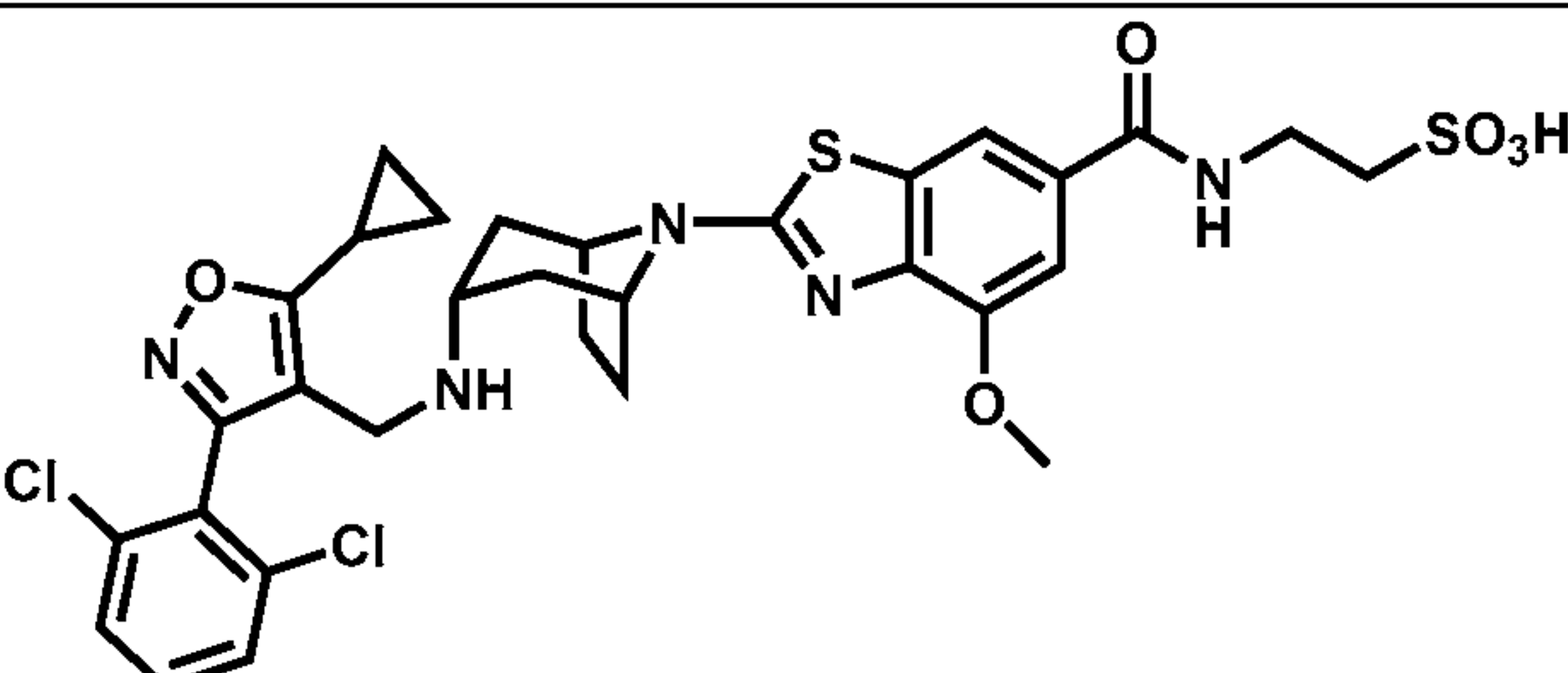
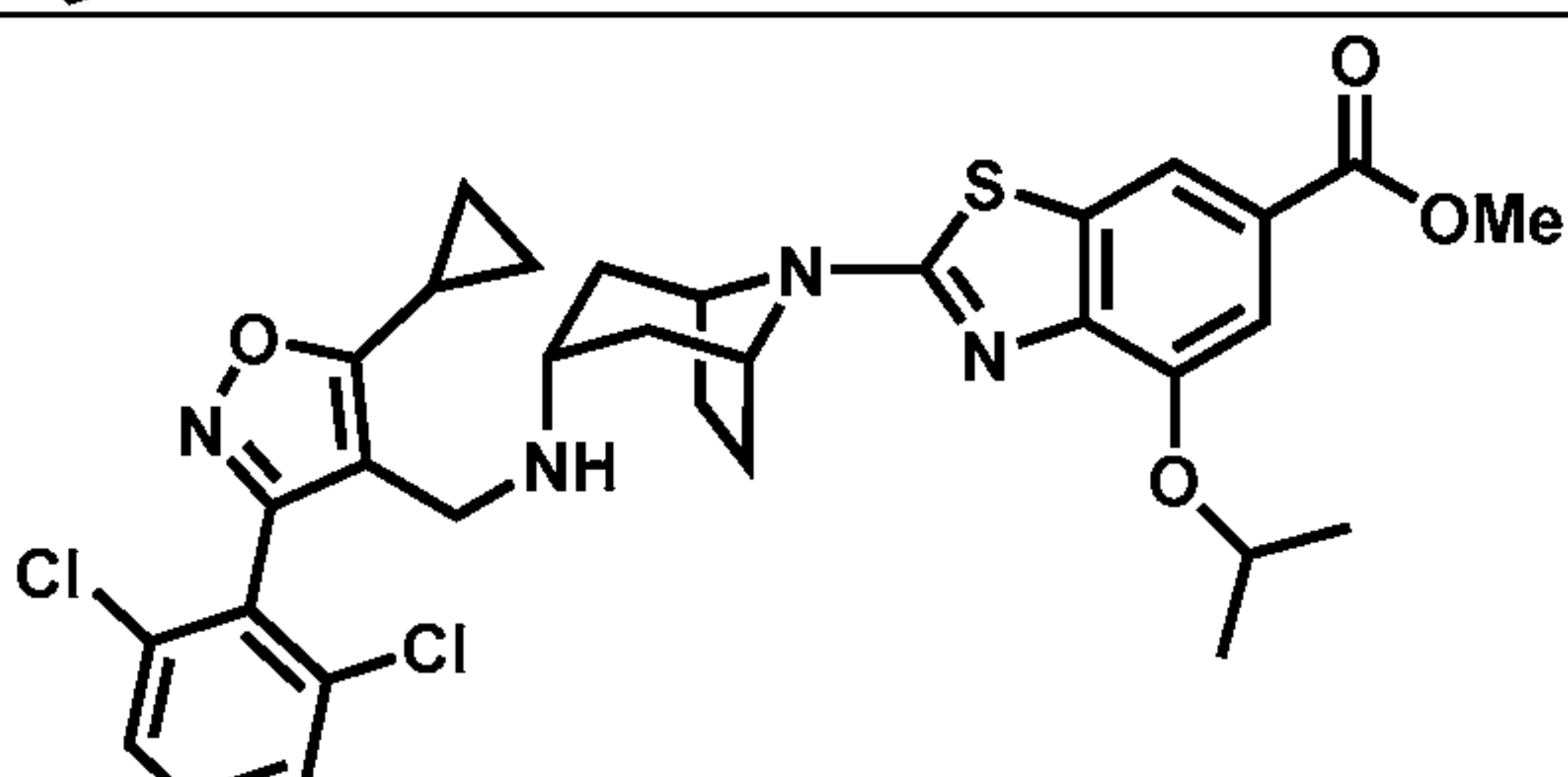
Table 8a

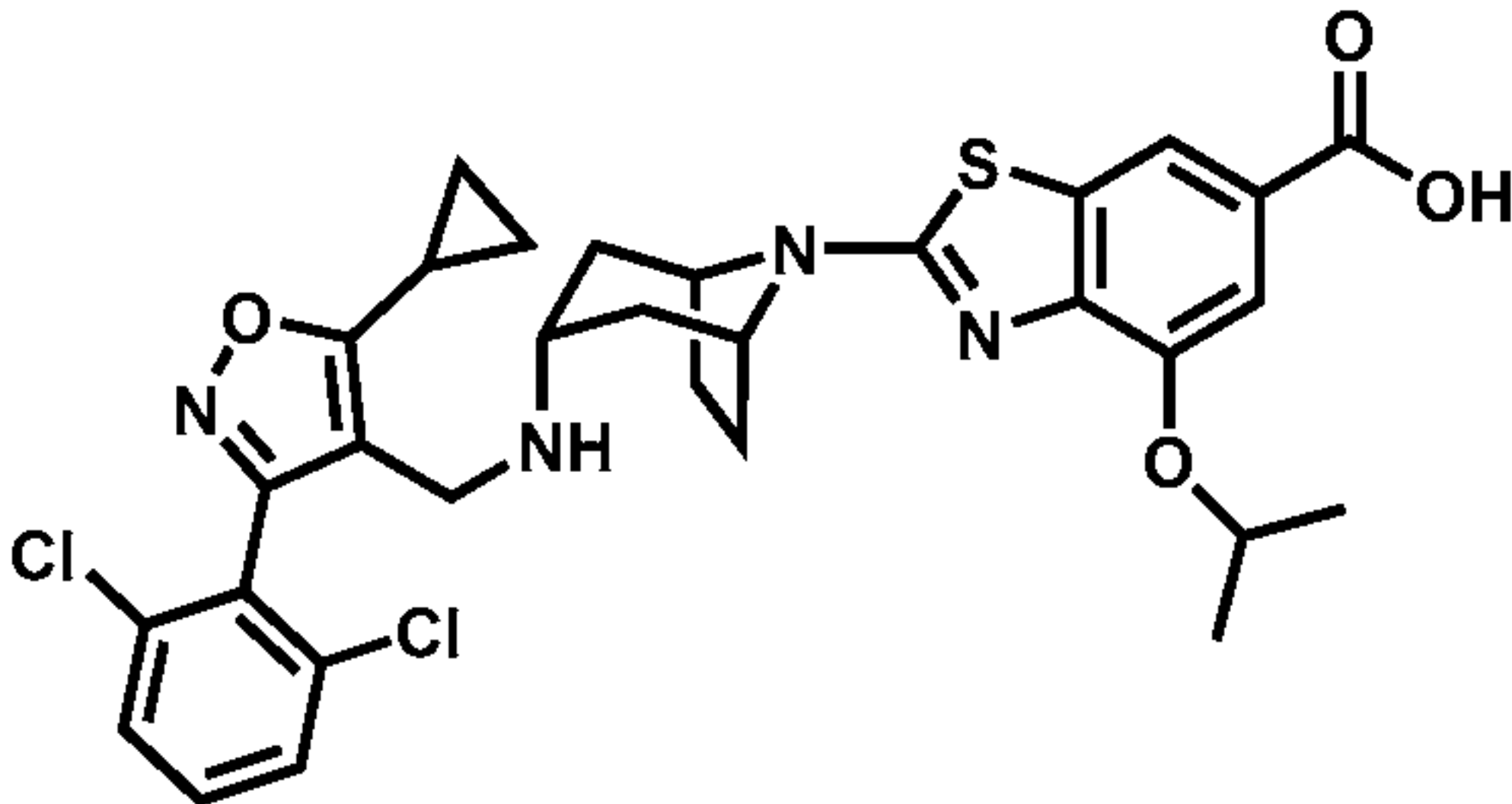
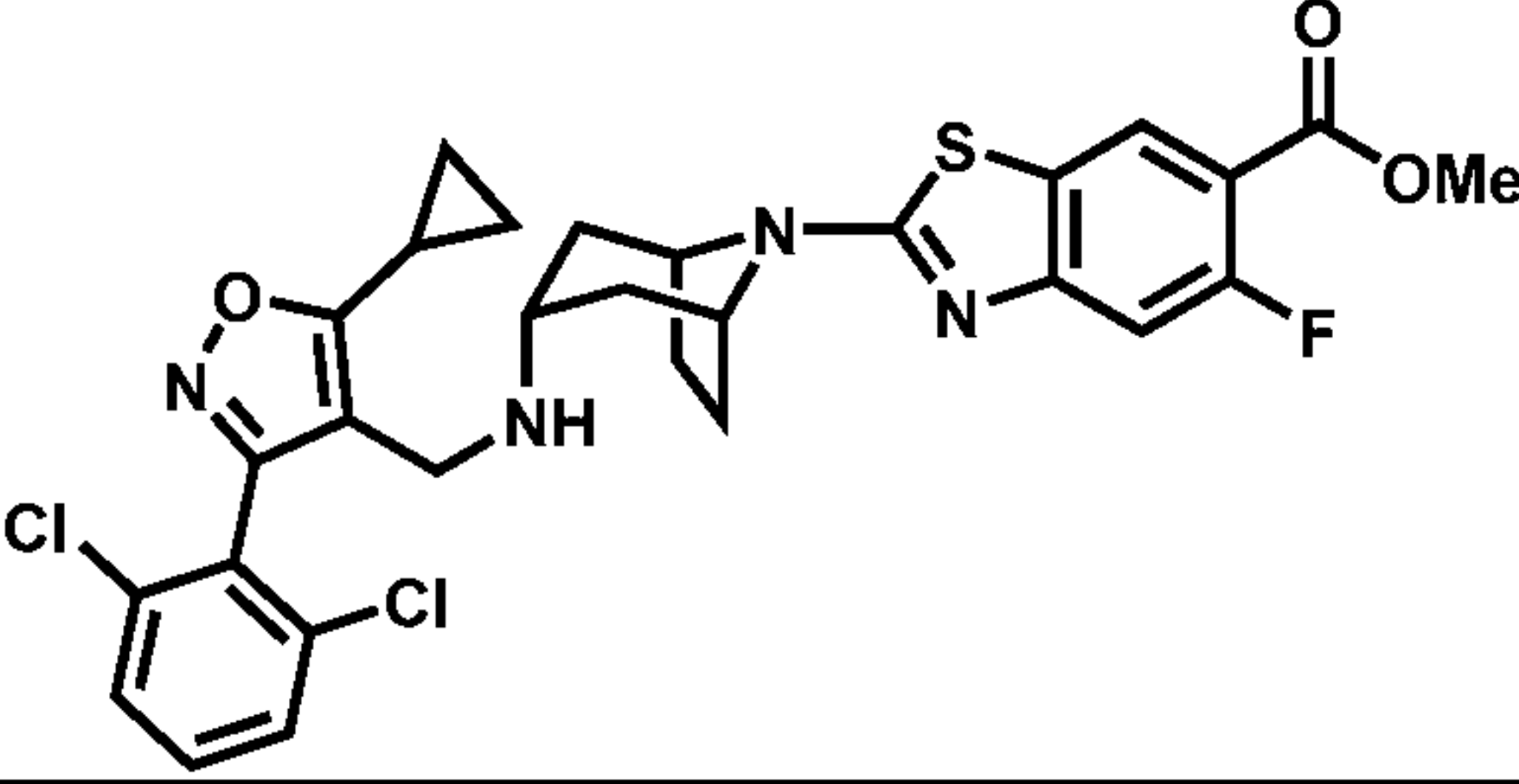
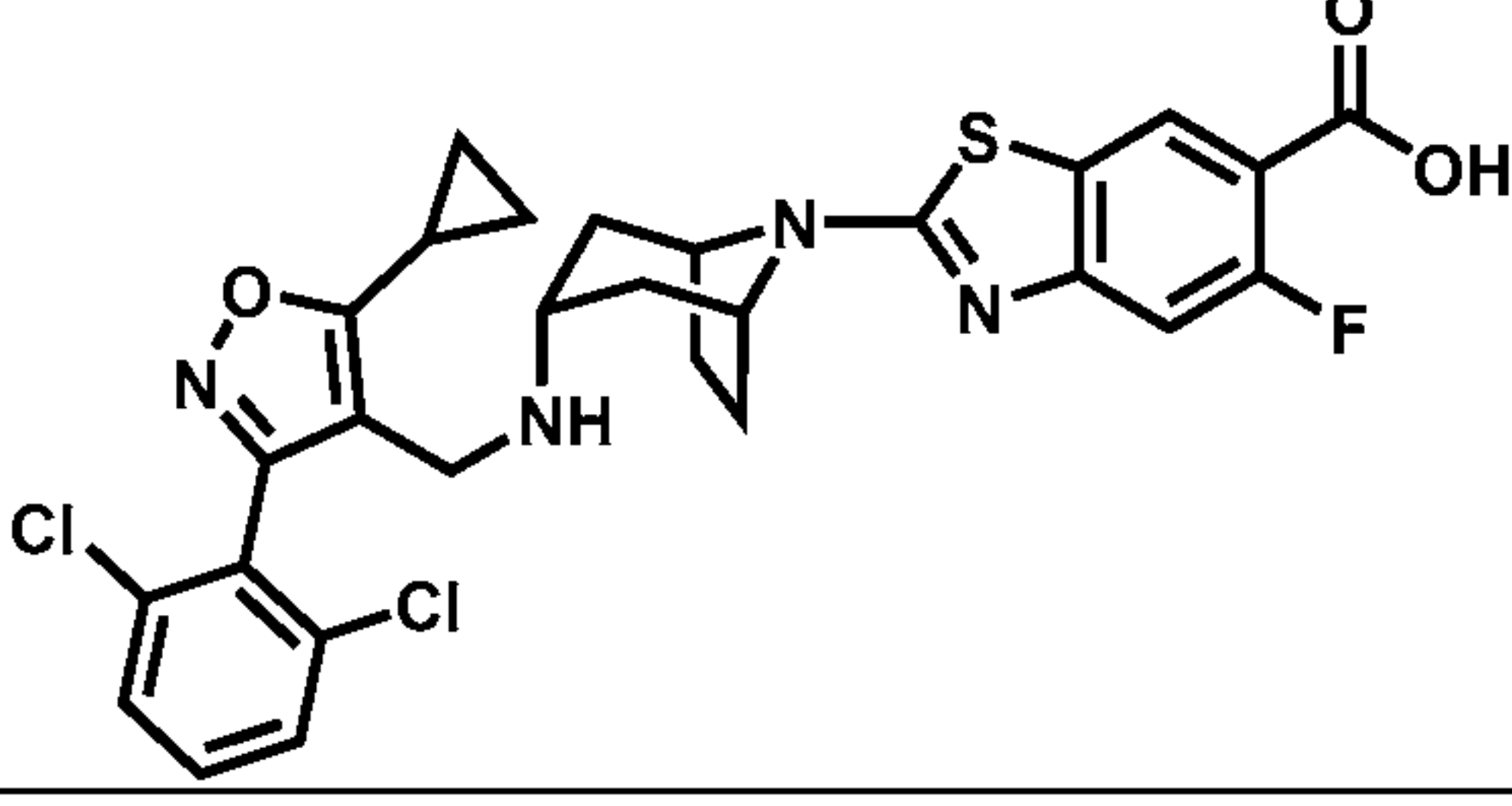
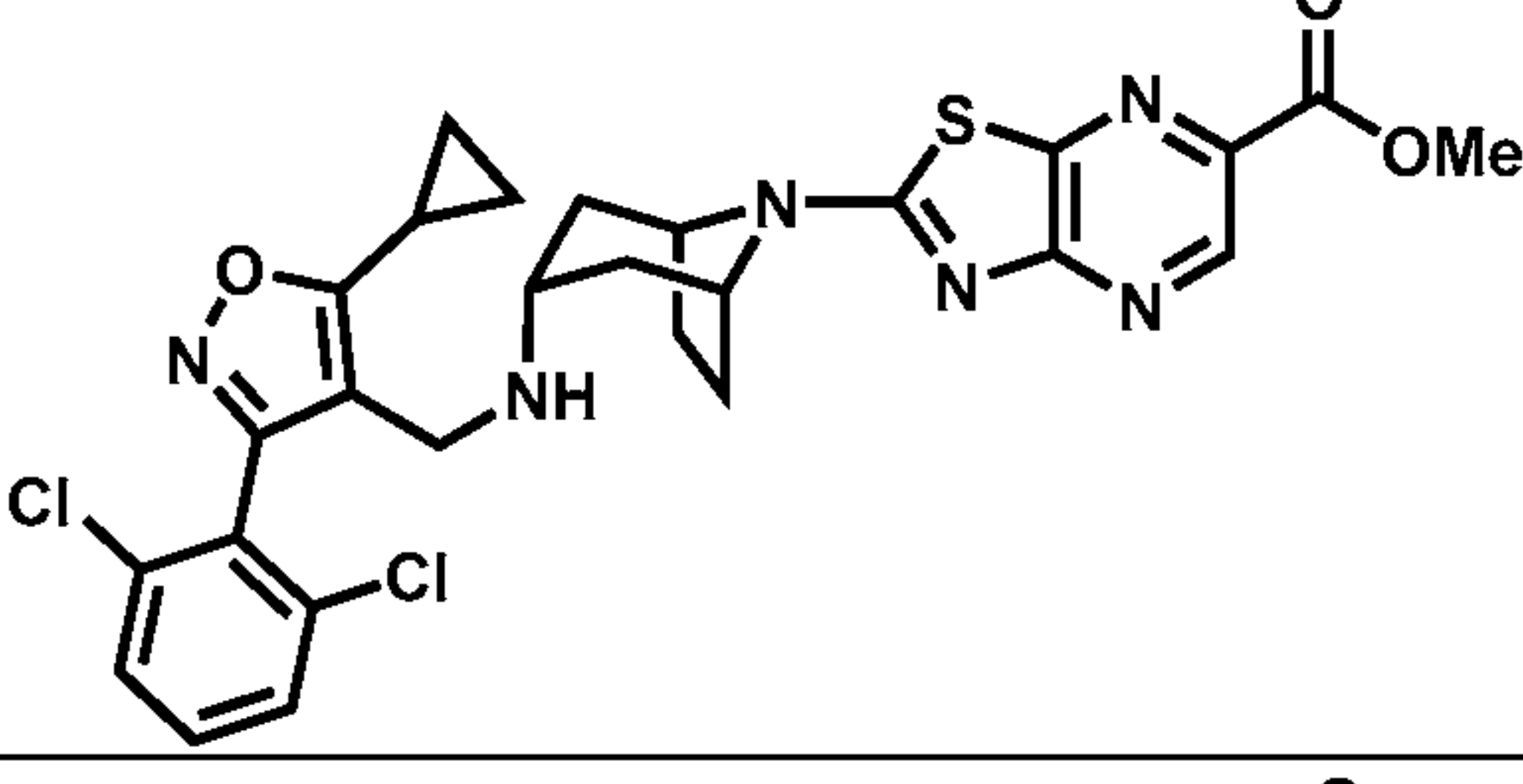
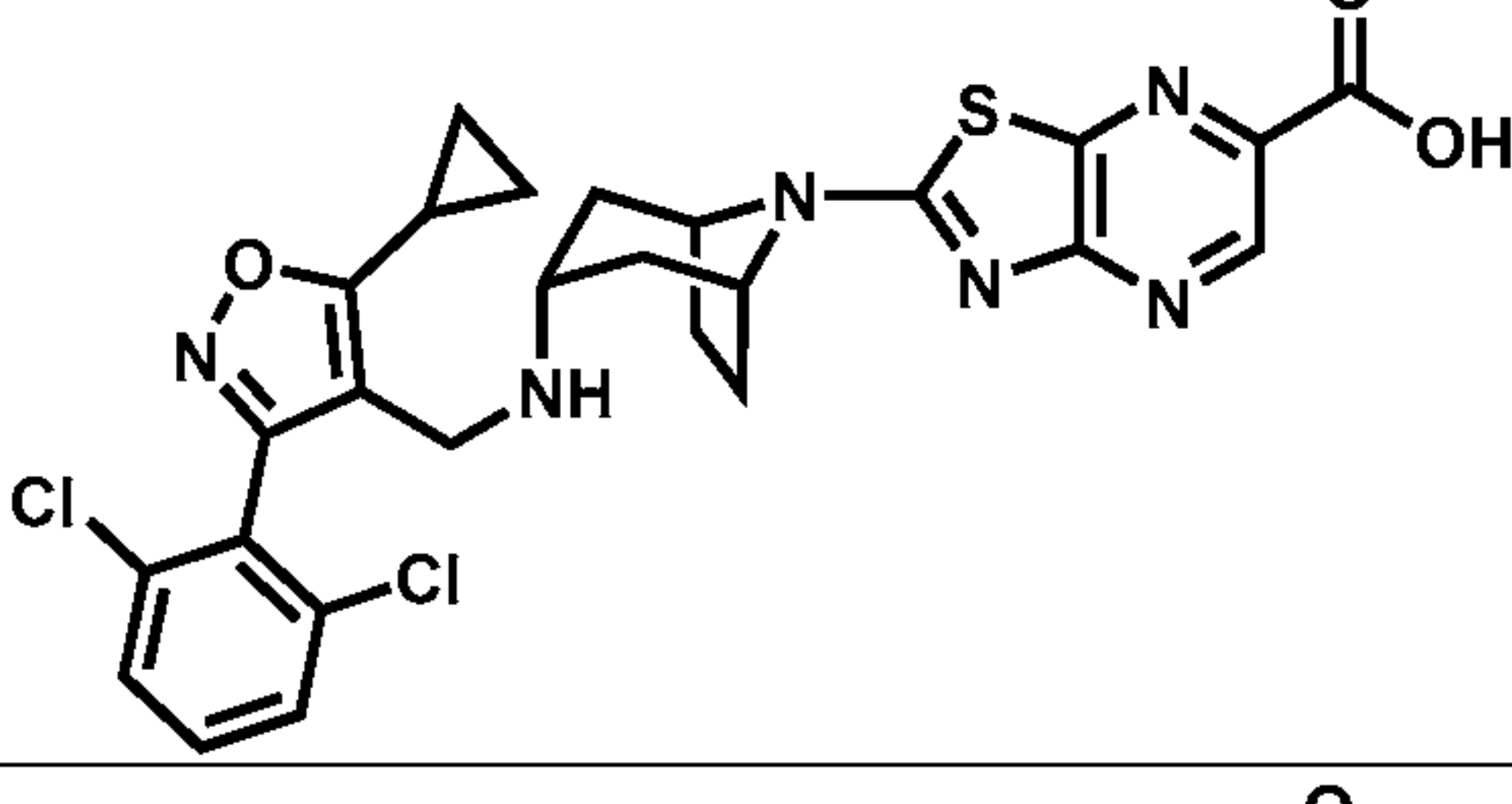
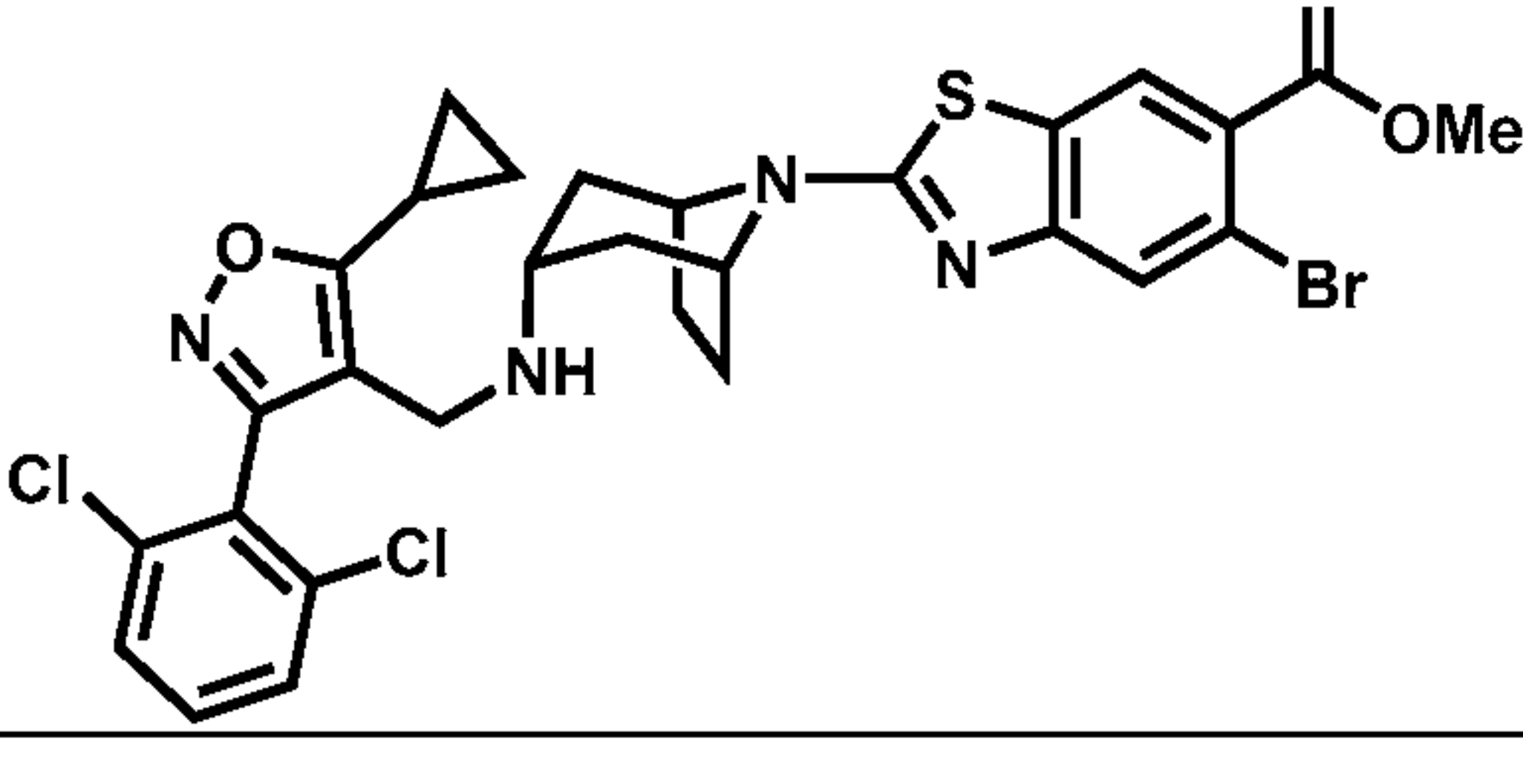
The following examples listed in Table 8a were prepared according to the procedures described for Example 189, Example 190 and Example 323.

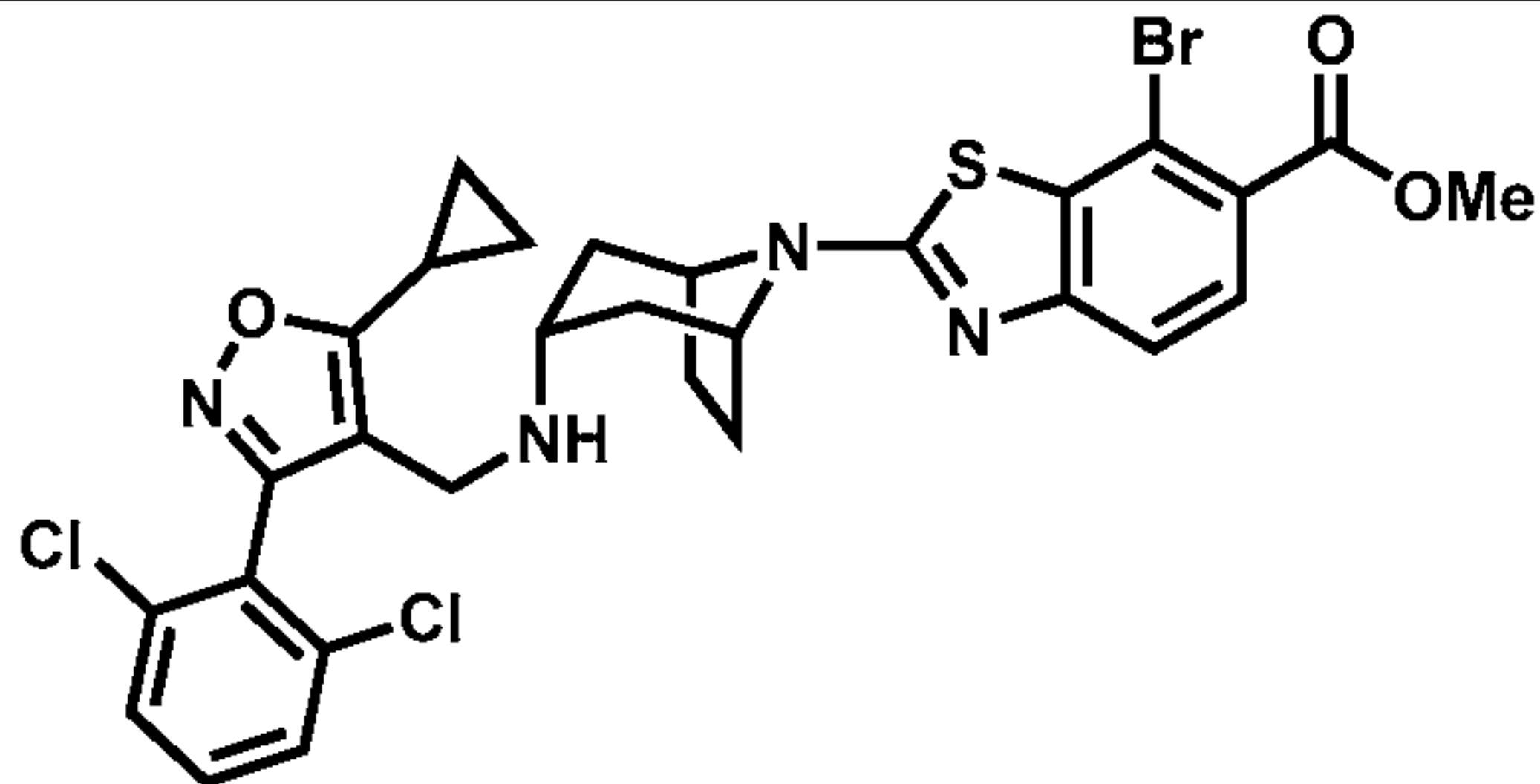
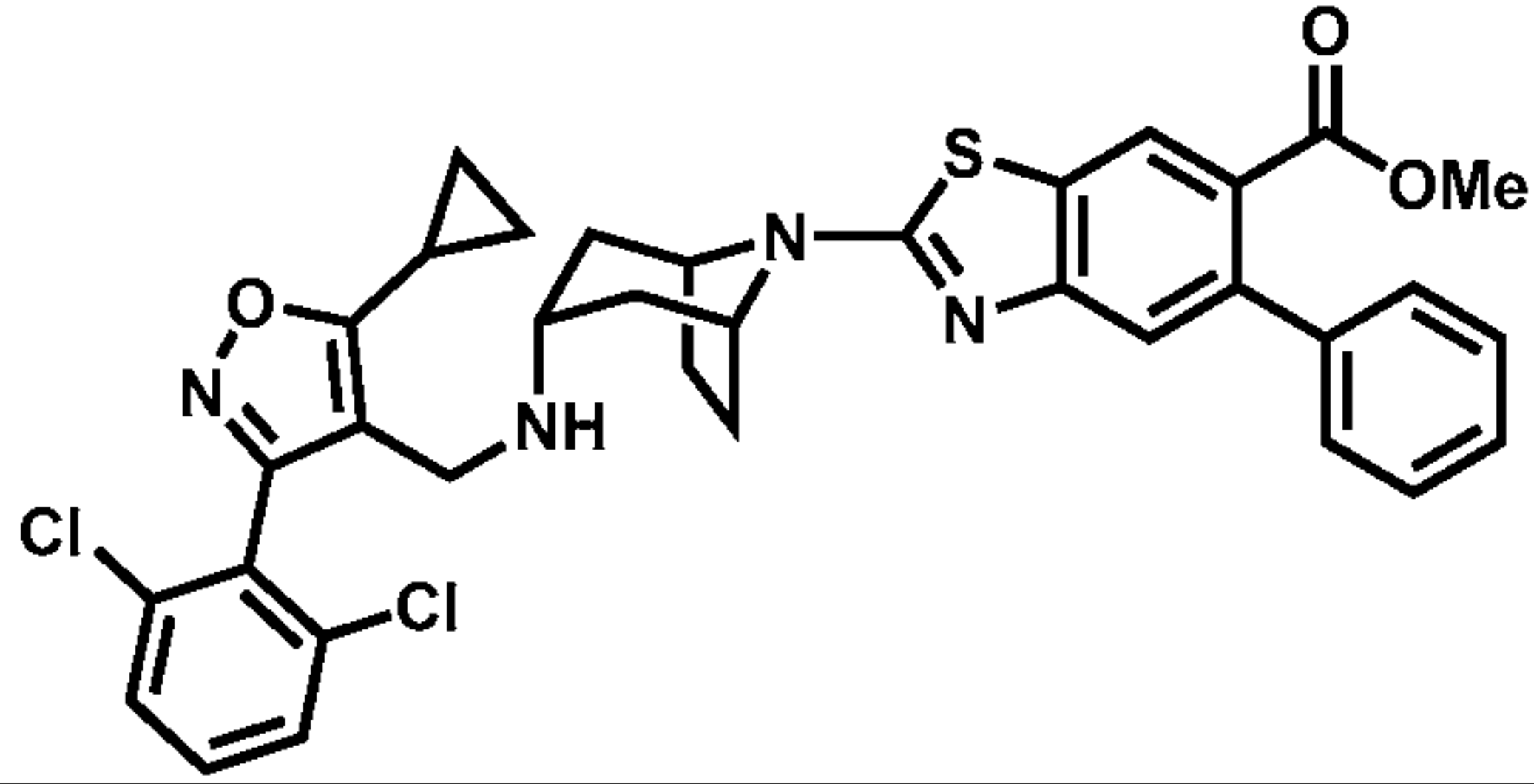
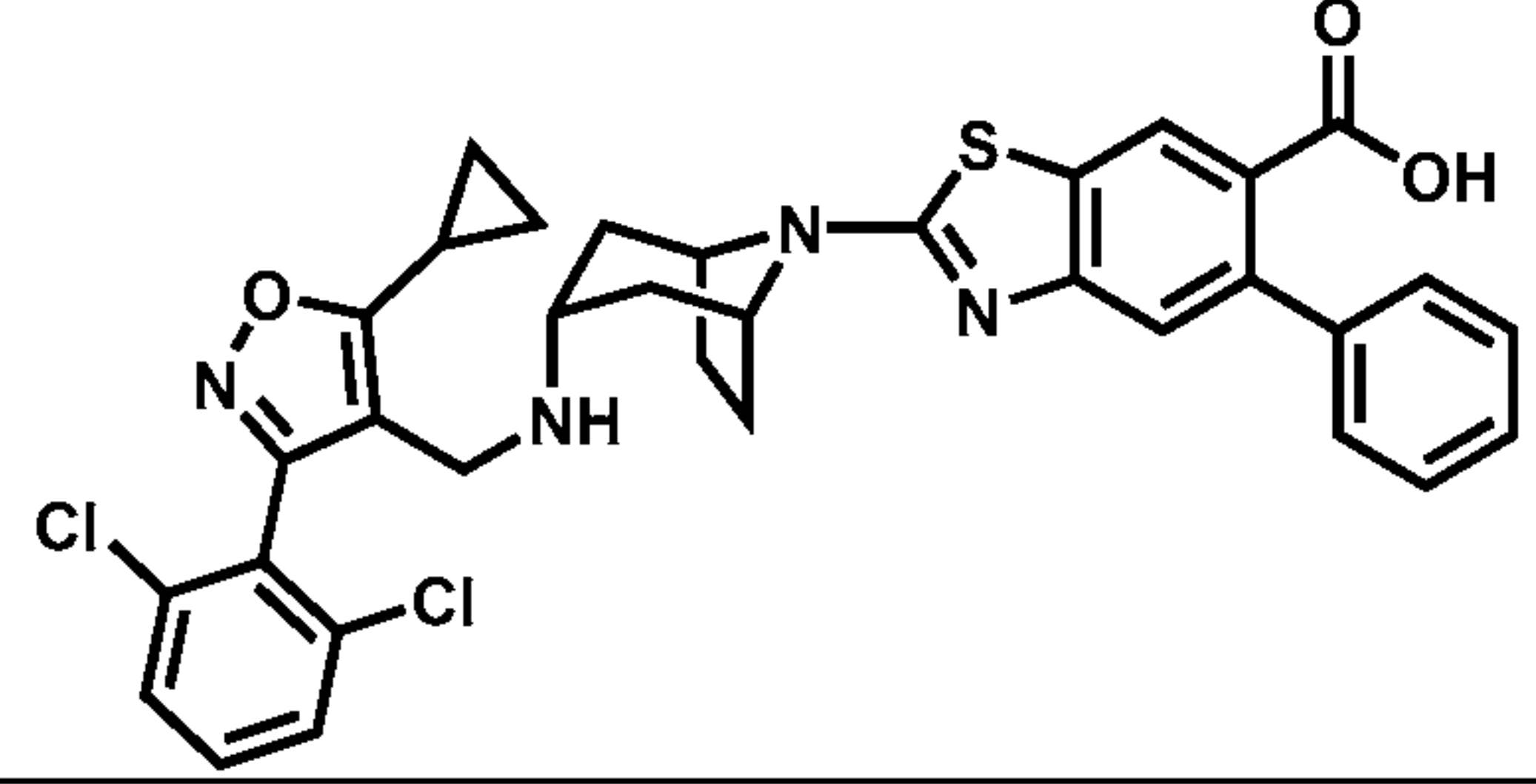
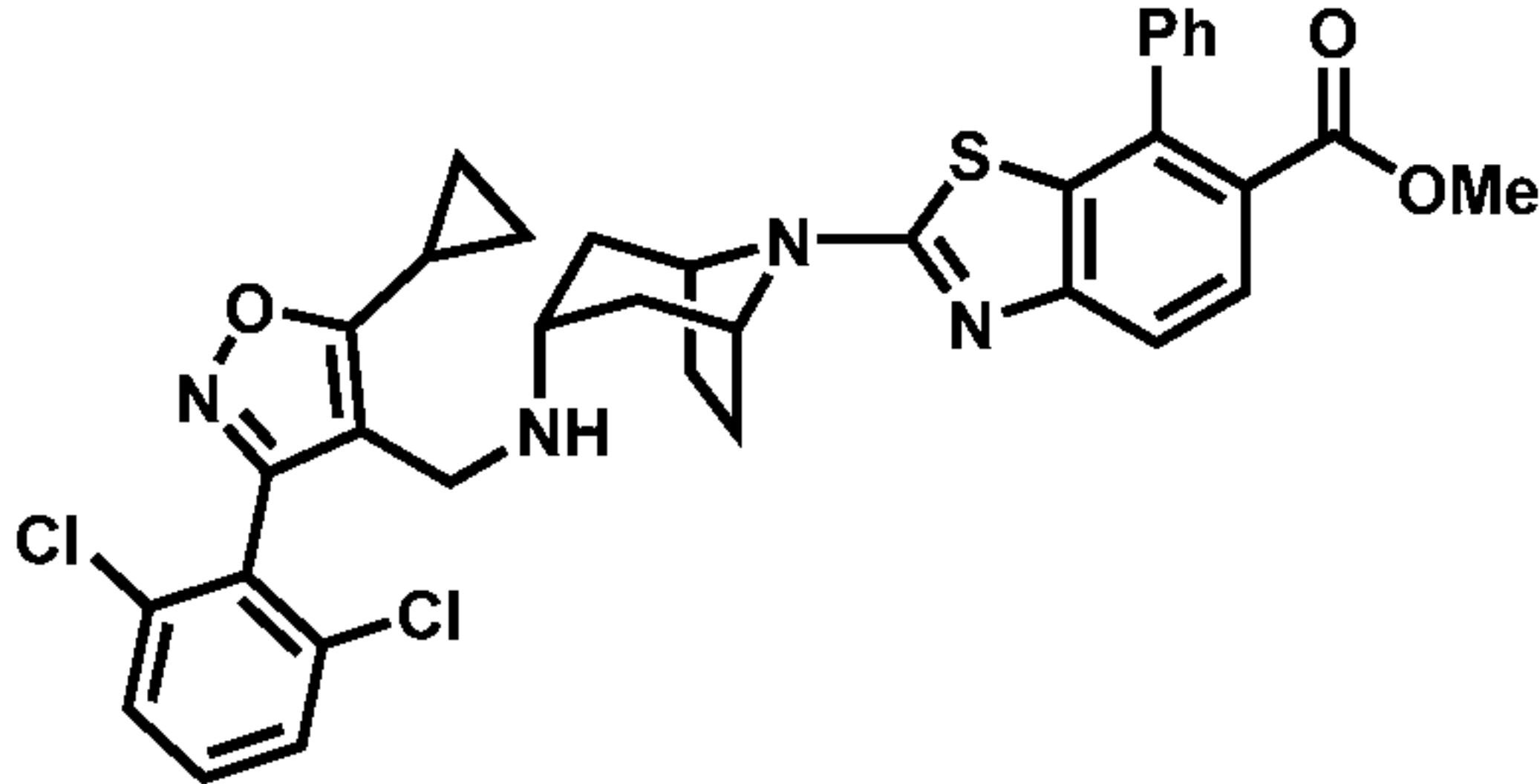
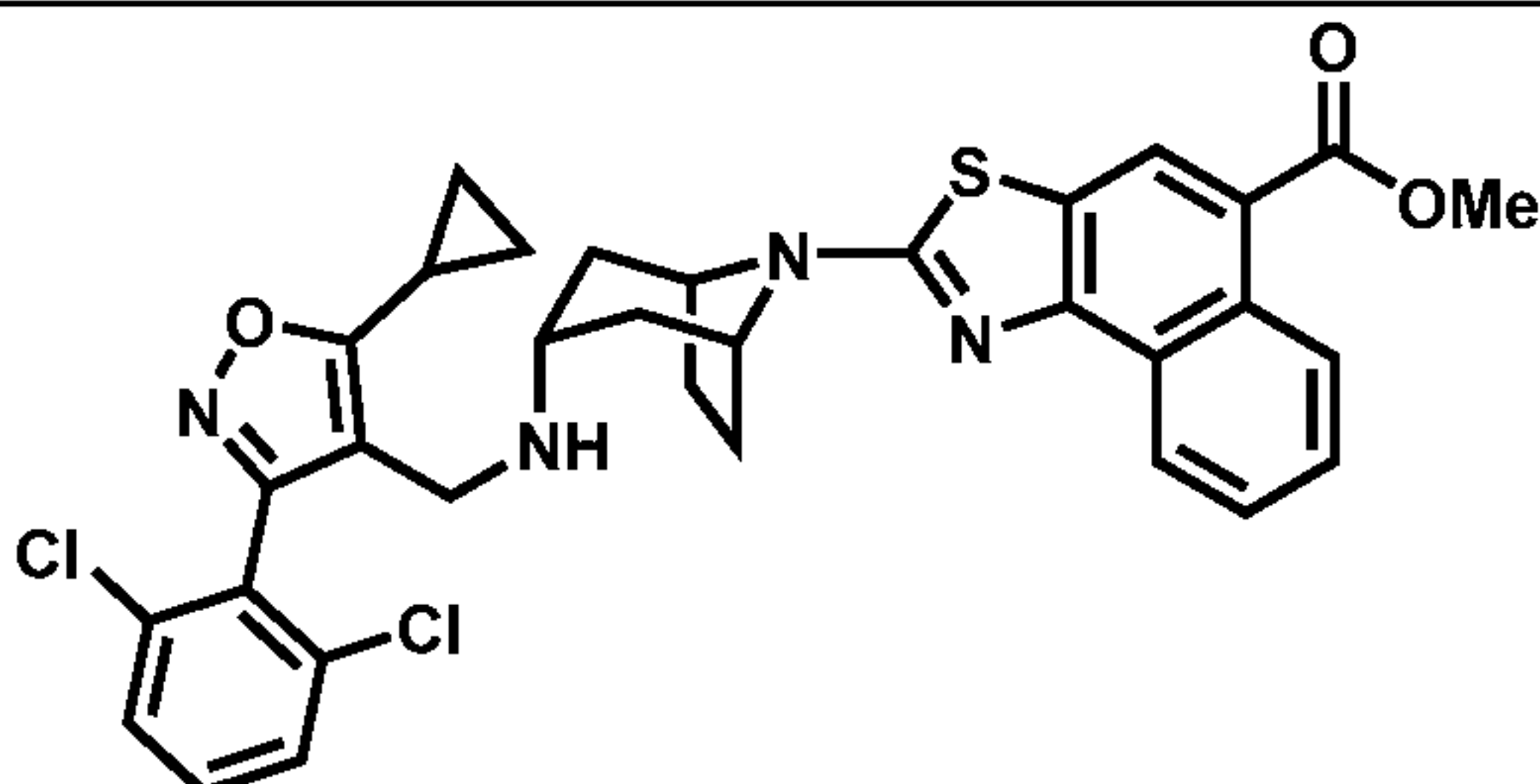
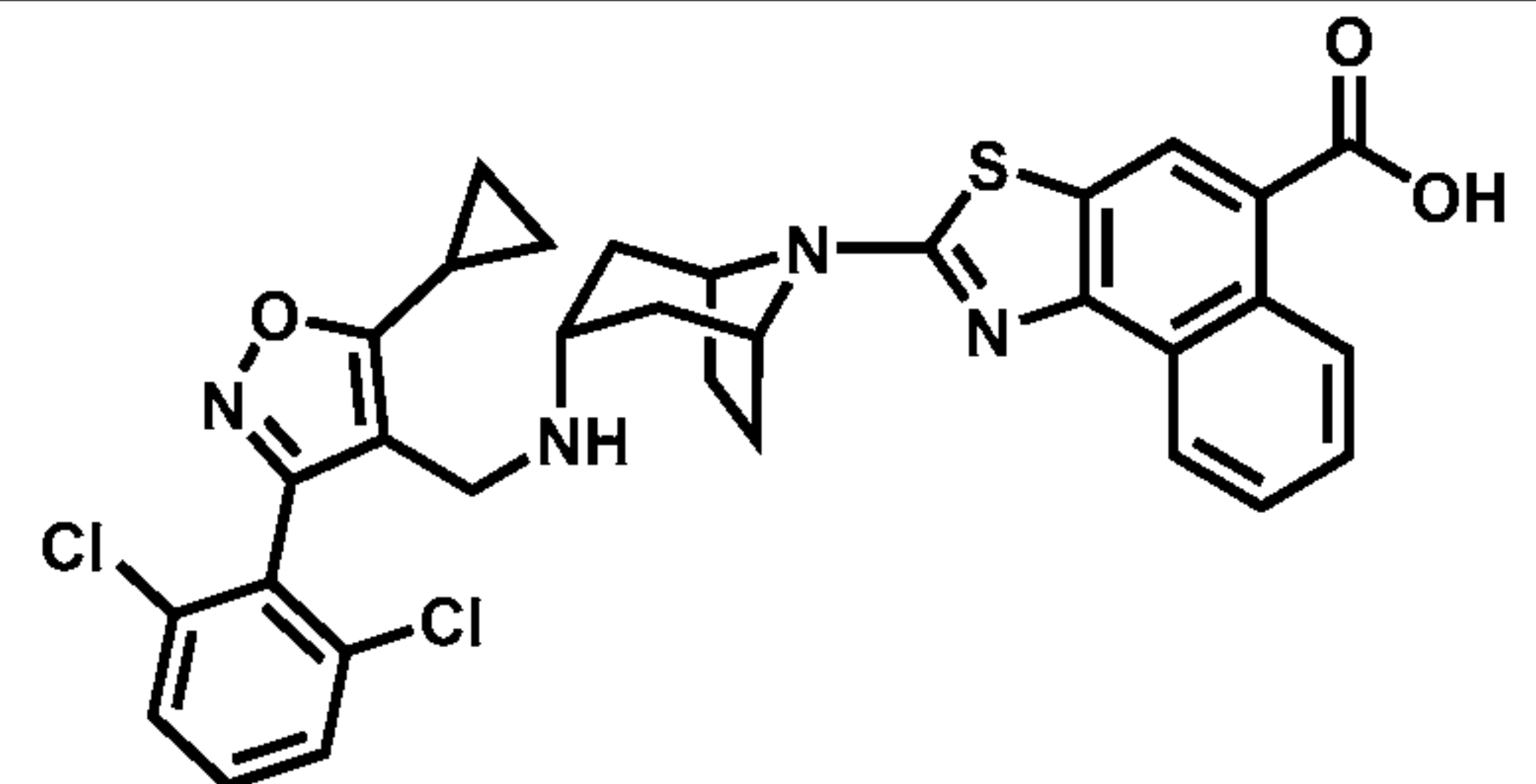
Example	Structure	MS Data
7		597.15 (M+H)
8		583.13 (M+H)
64		578.33 (M+H)
122		530.15 (M+H)
125		513.14 (M+H)

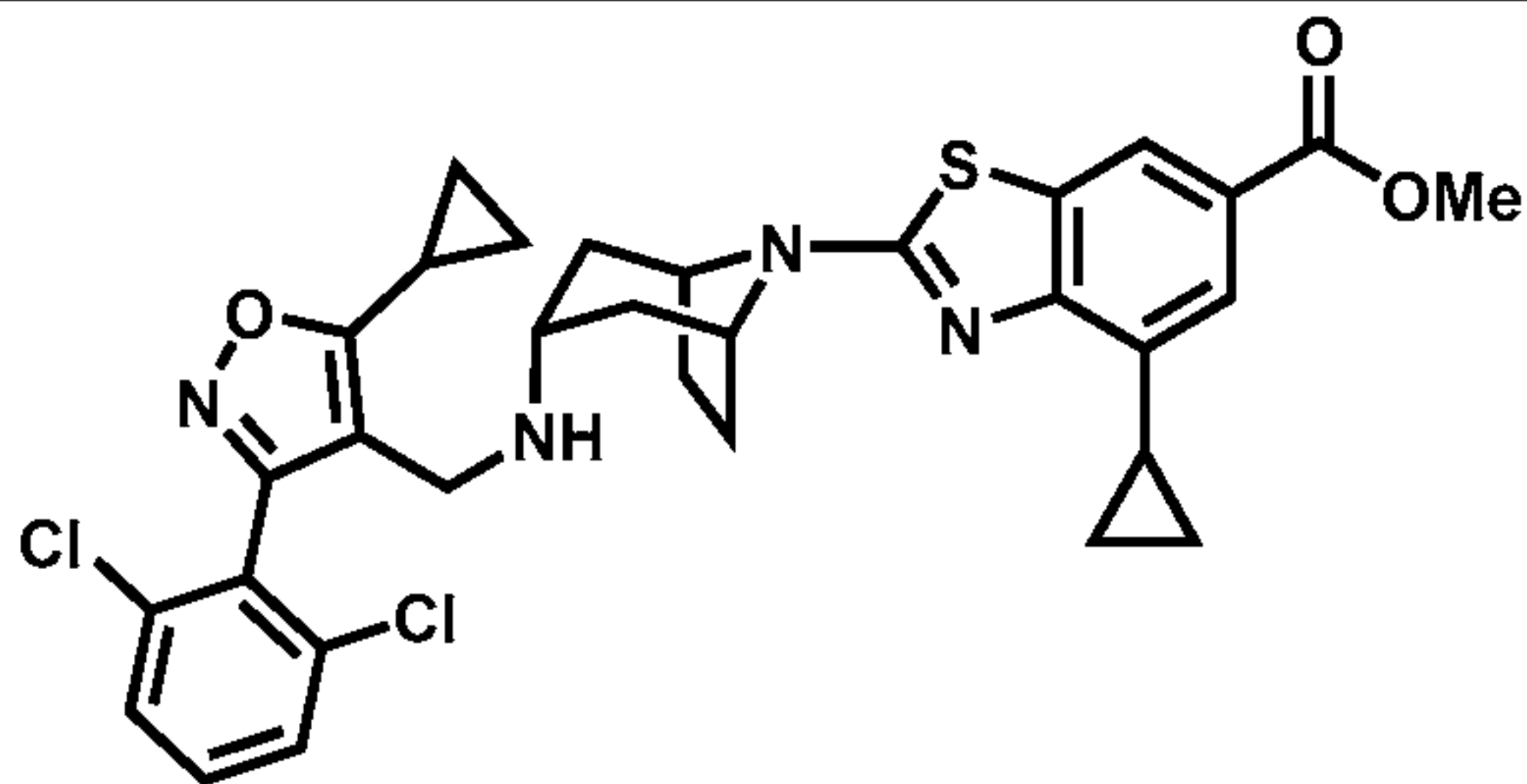
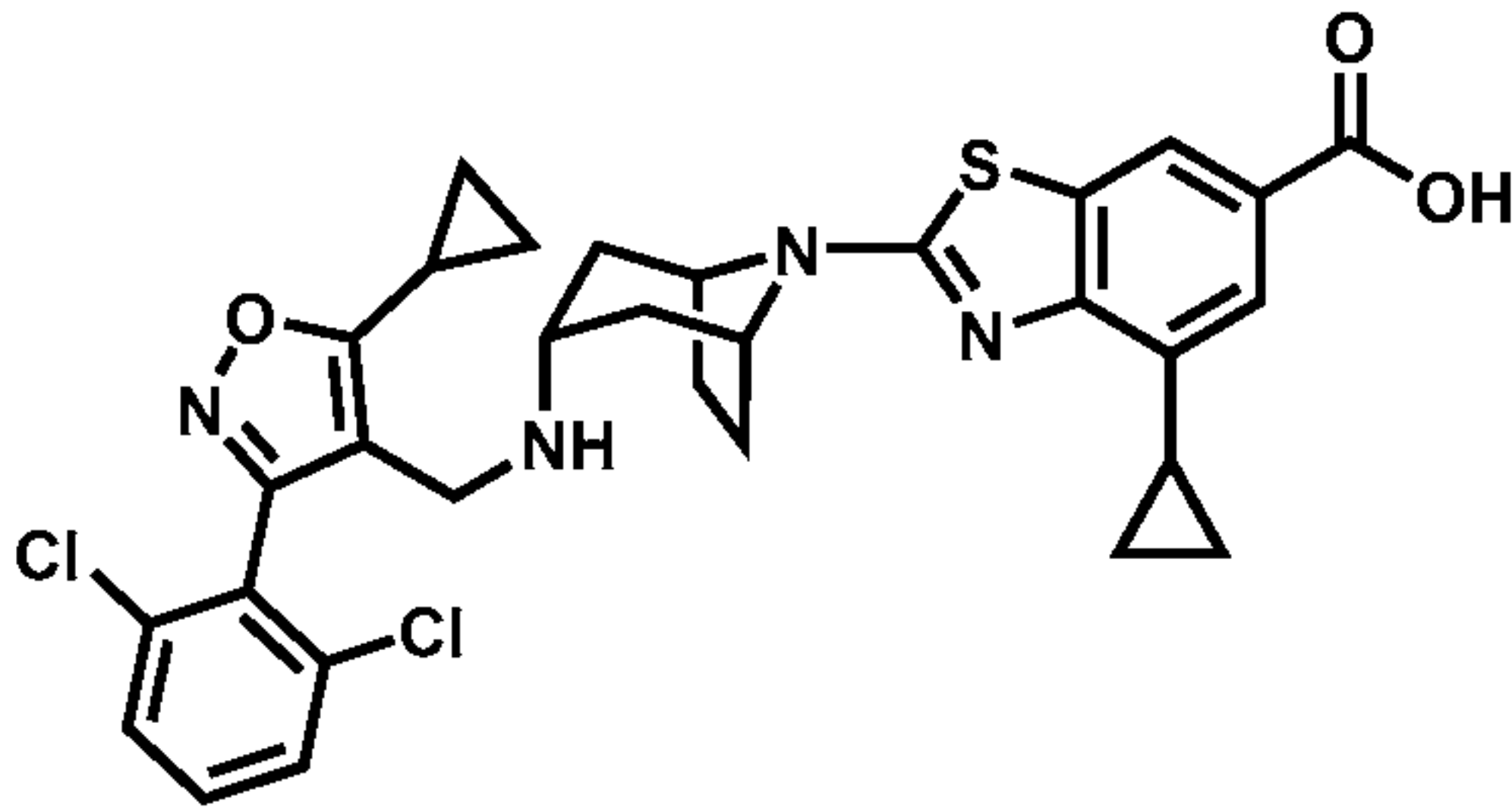
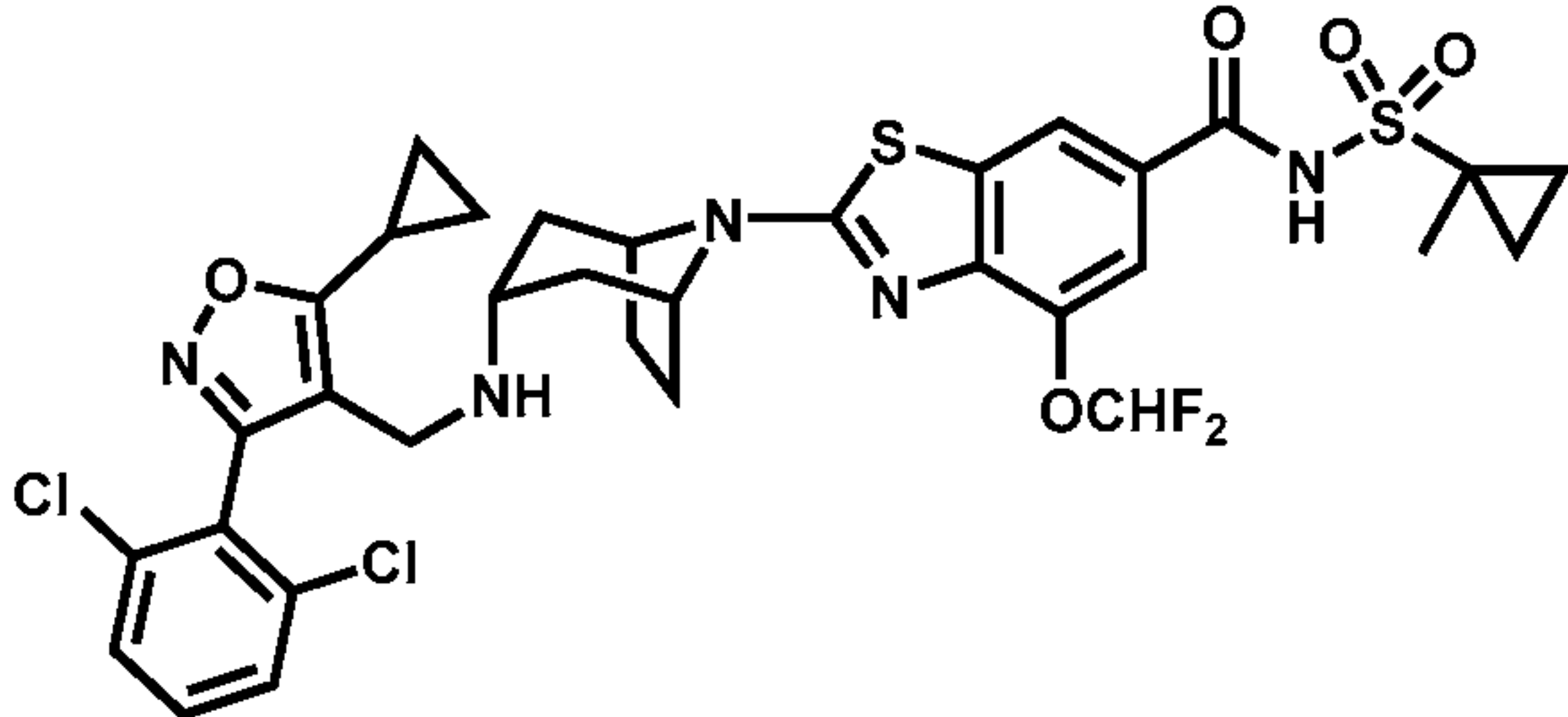
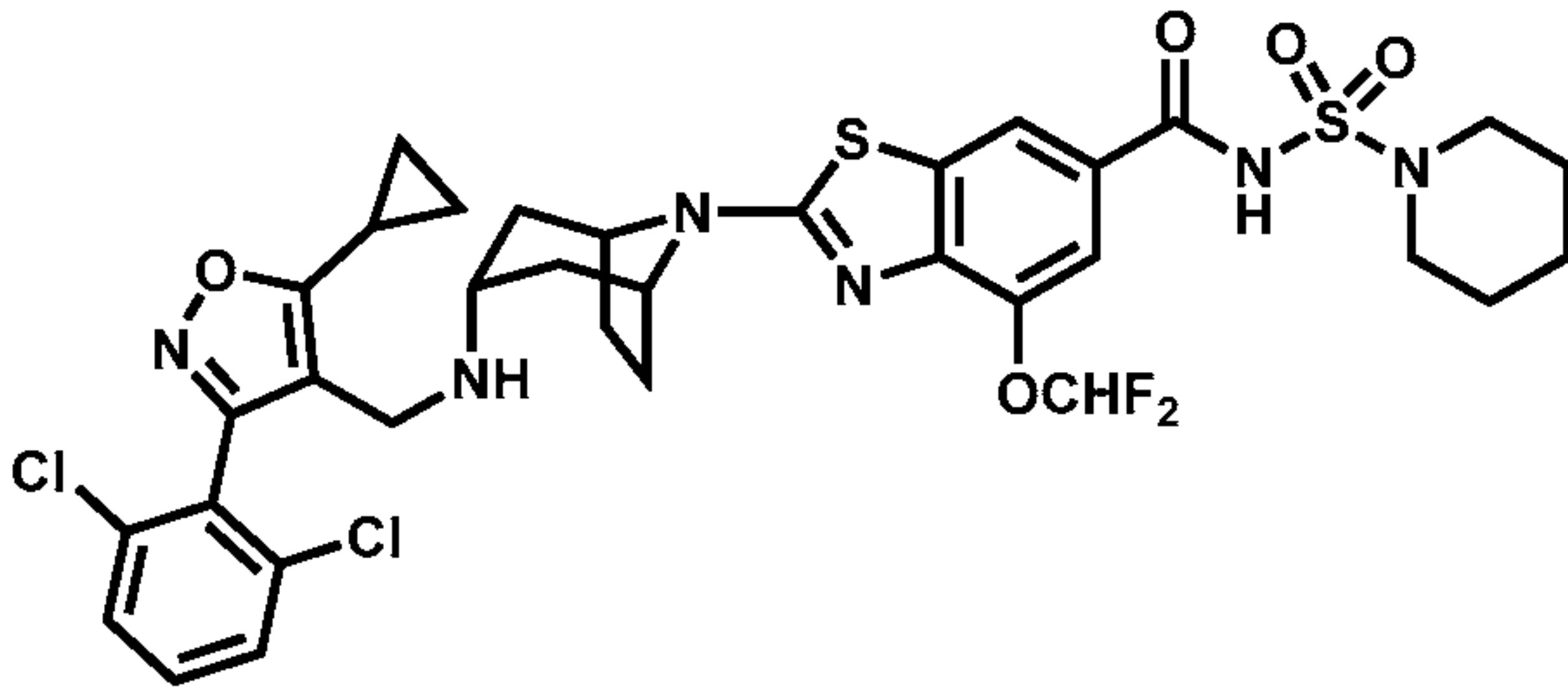
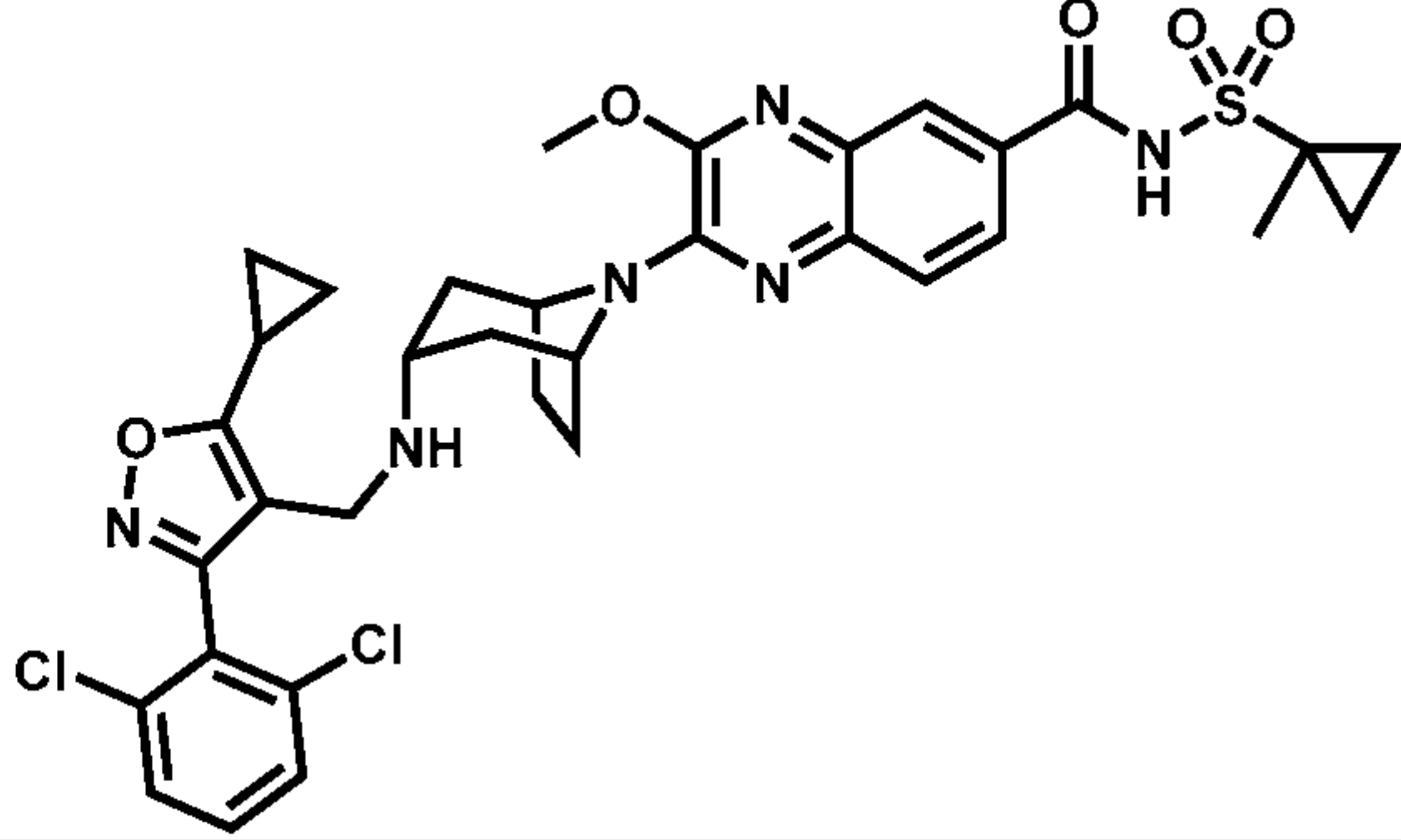
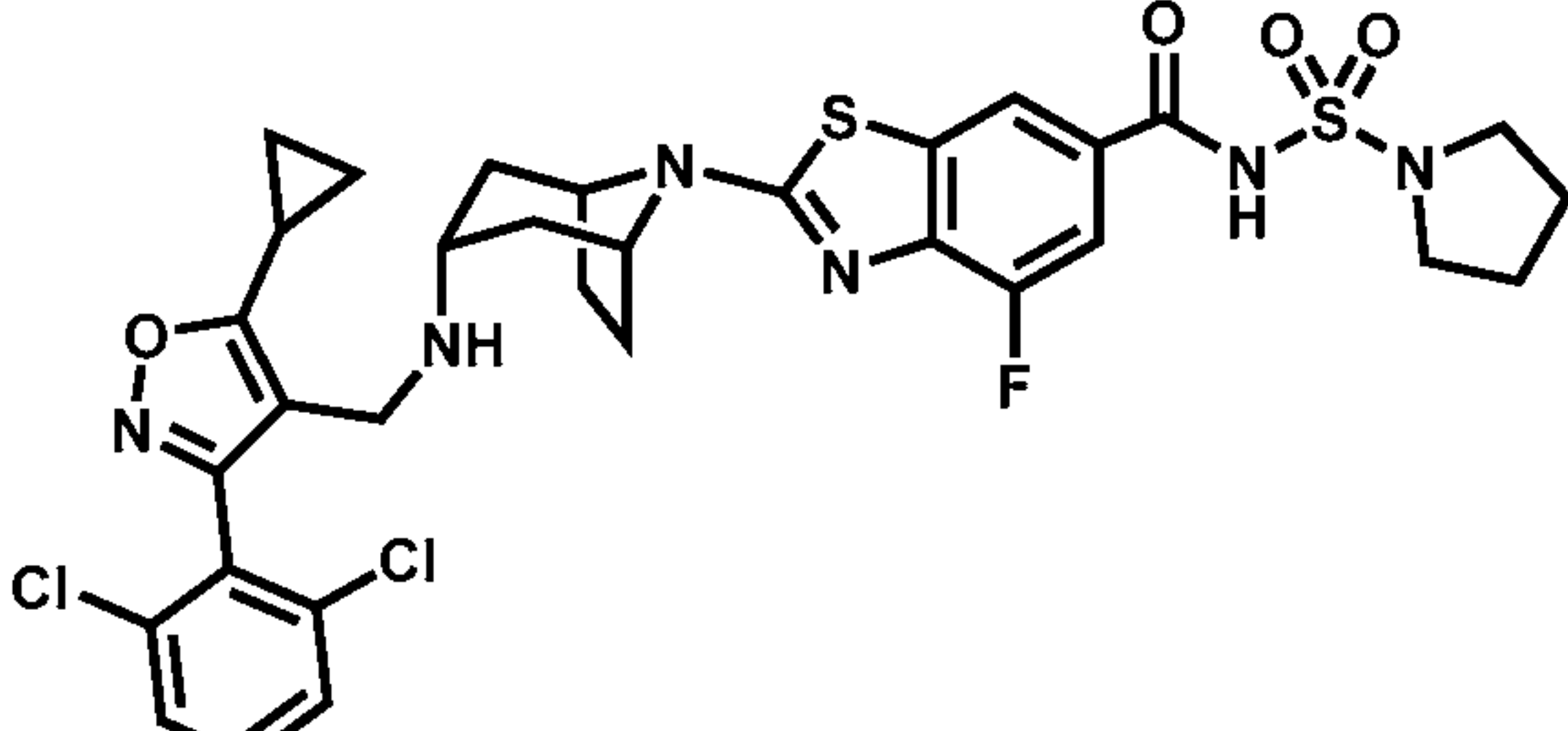
194		583.14 (M+H)
196		583.14 (M+H)
197		608.18 (M+H)
198		594.17 (M+H)
199		614.13 (M+H)

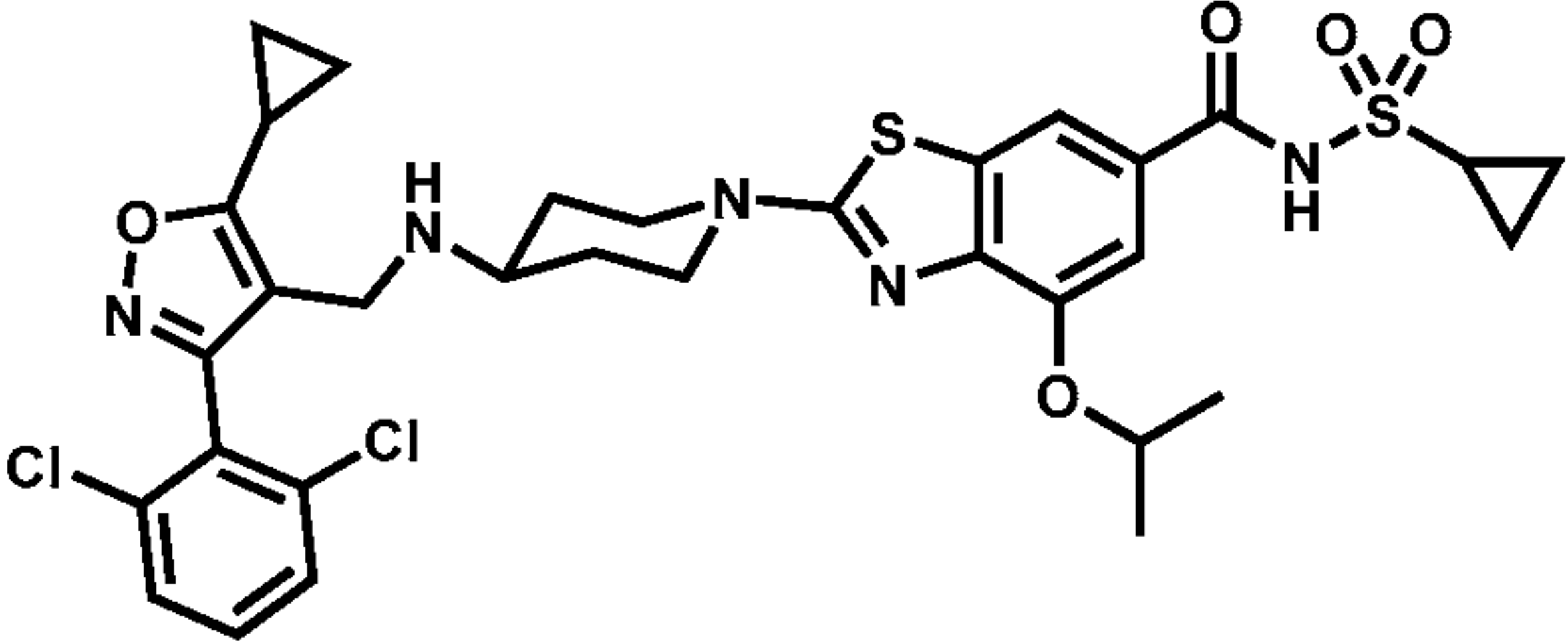
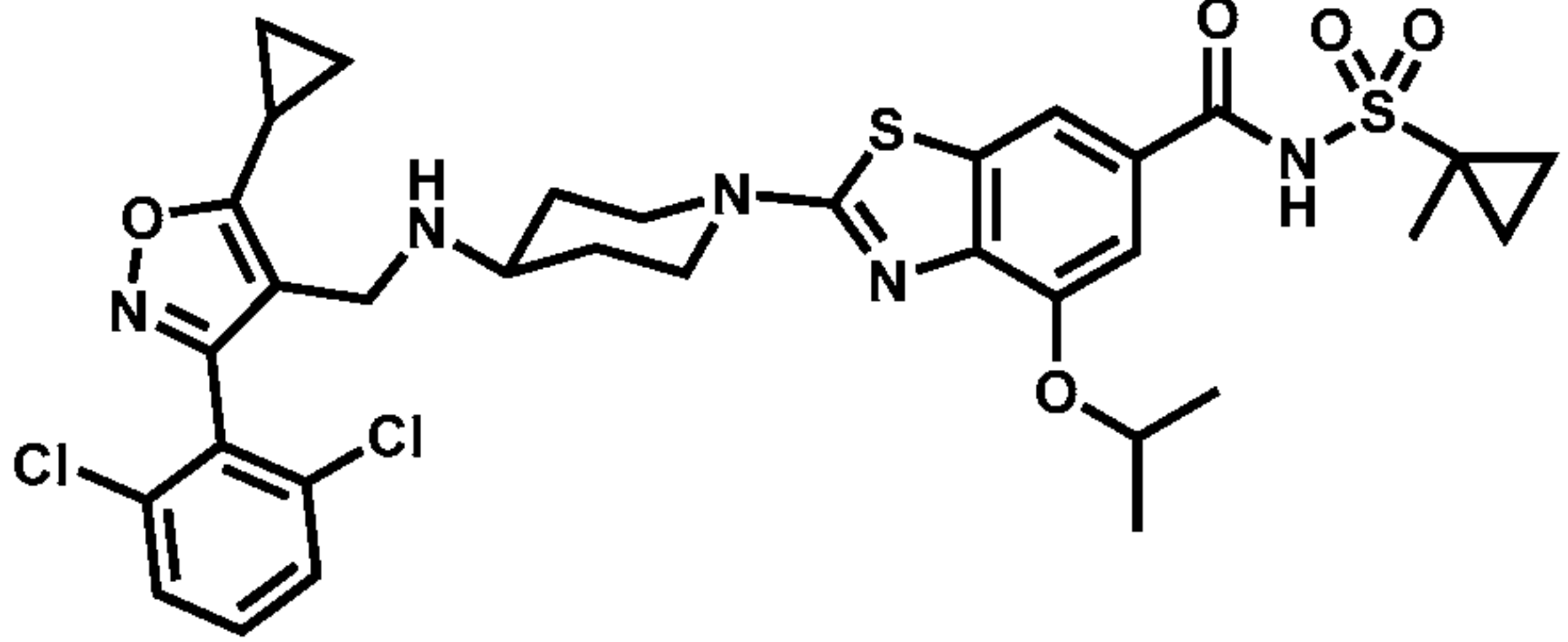
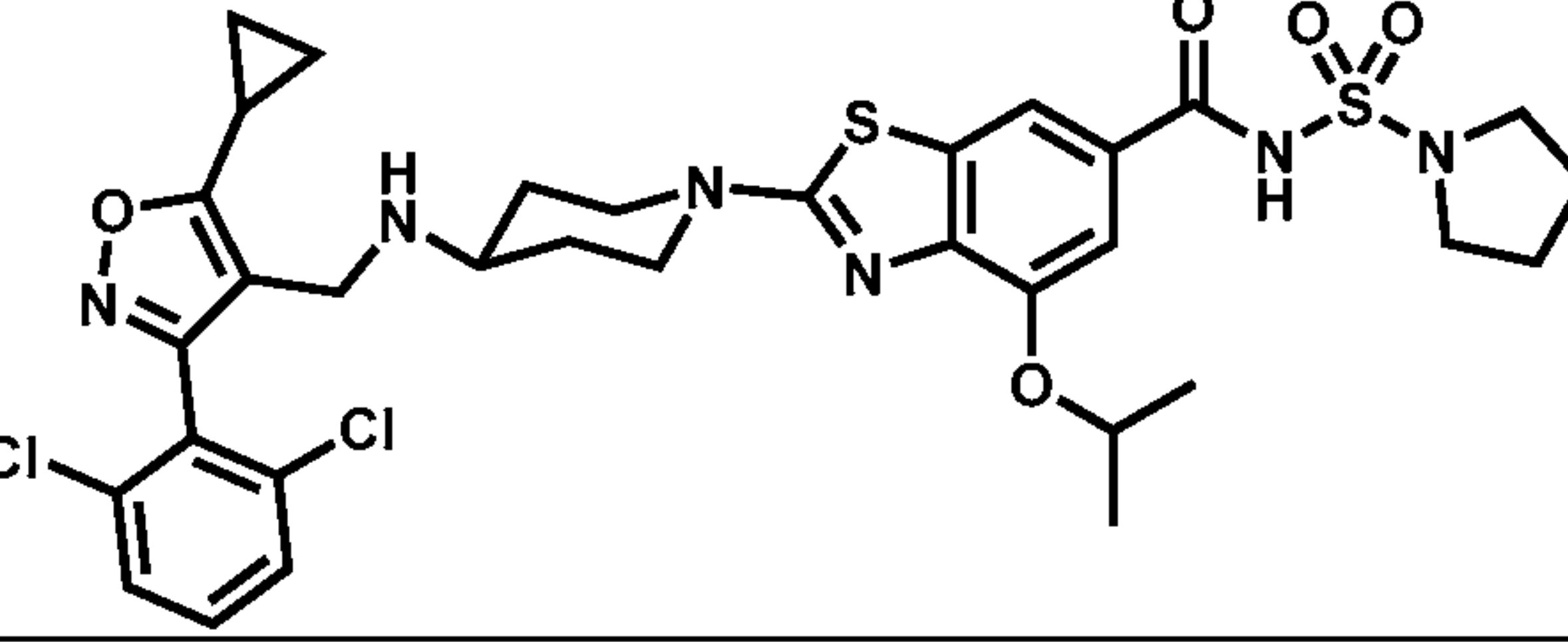
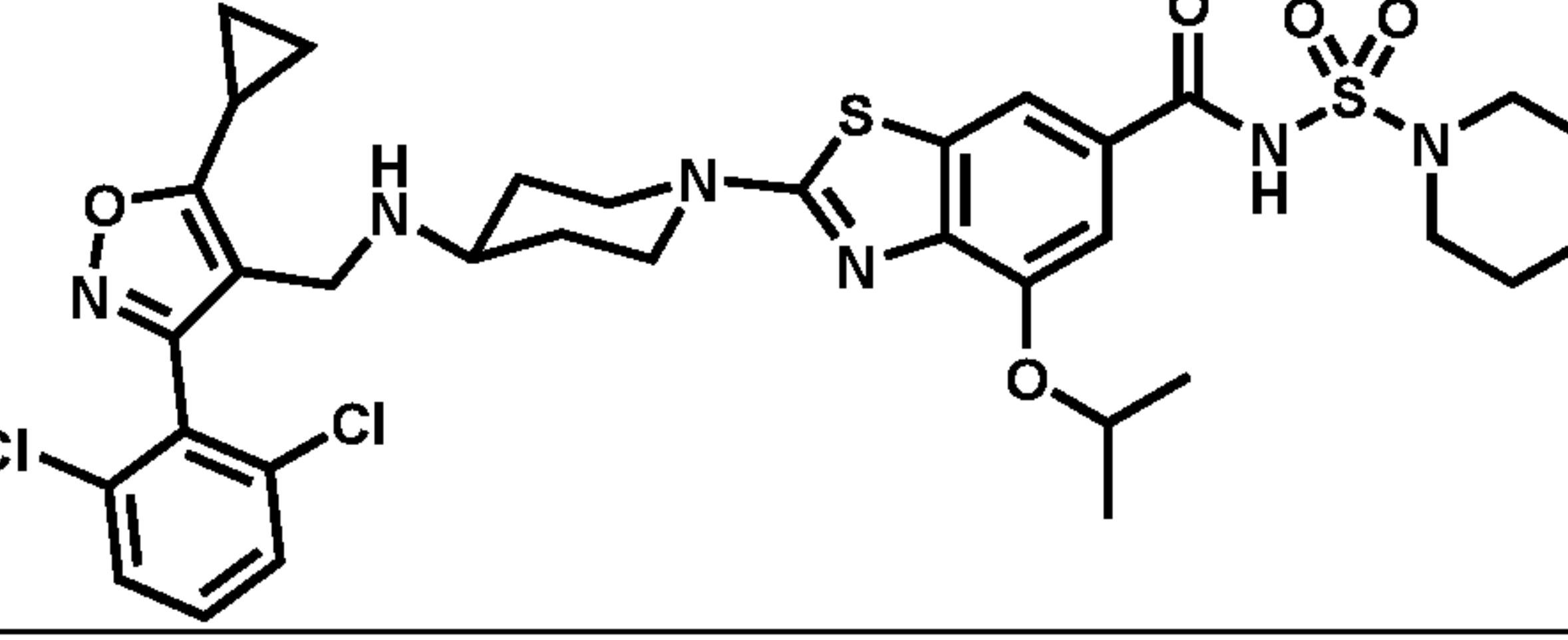
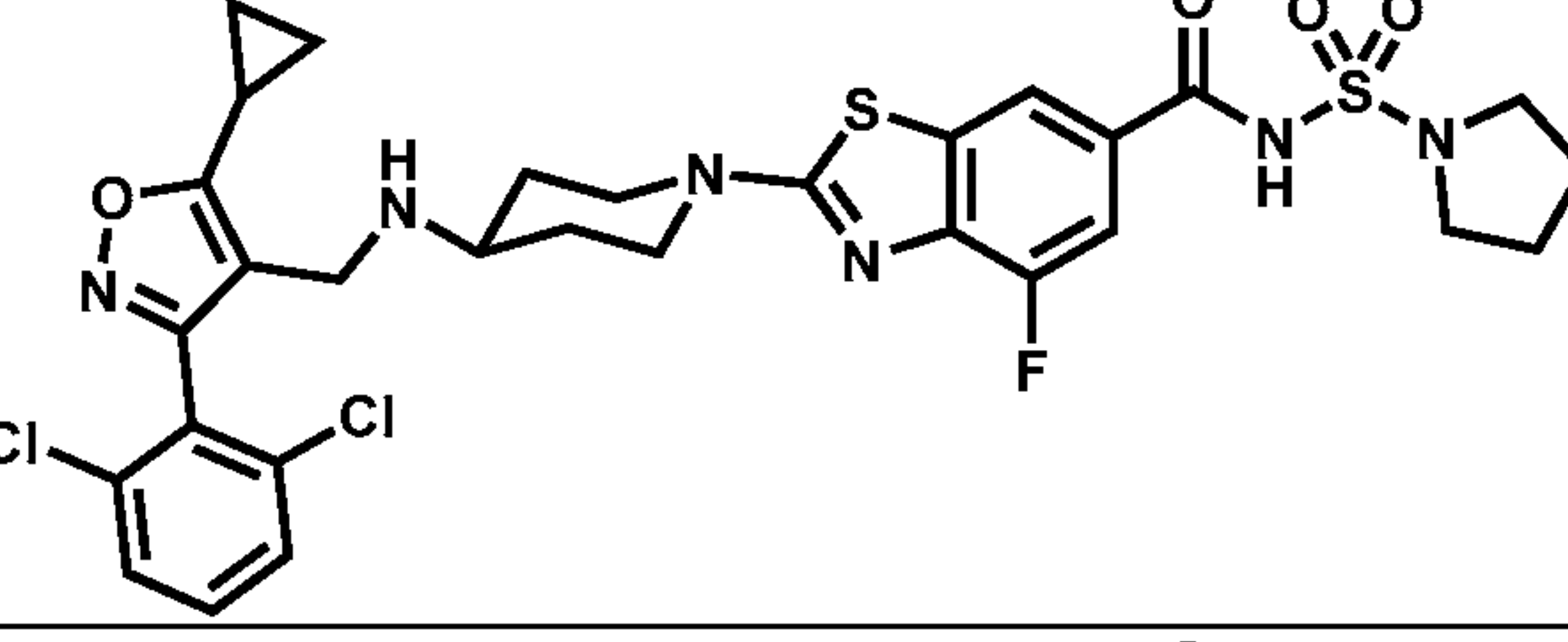
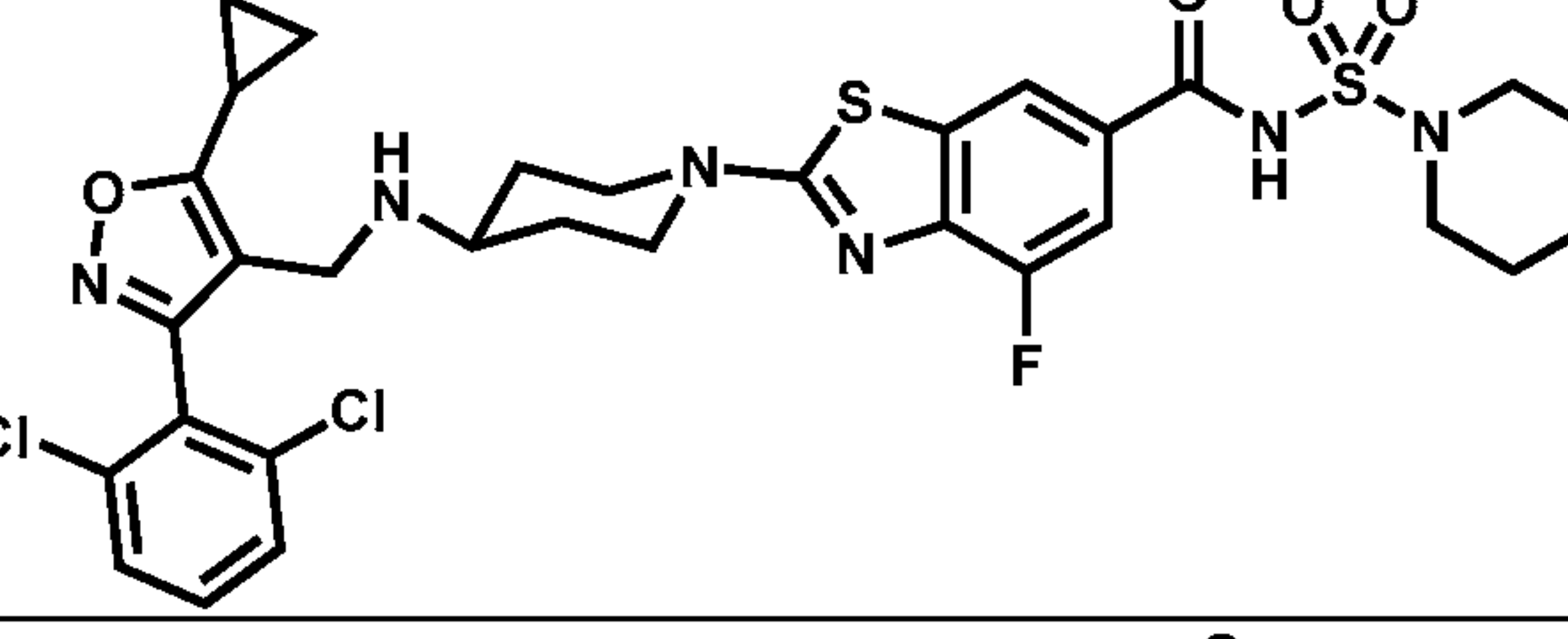
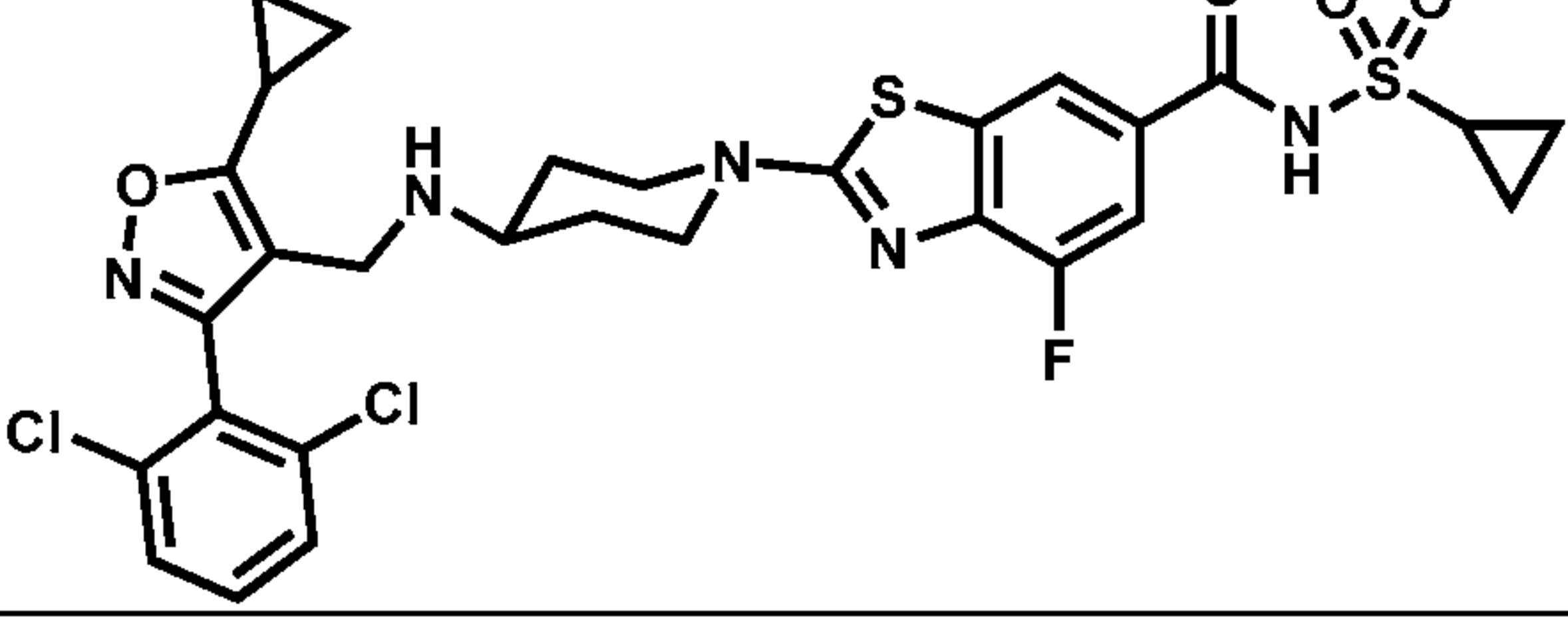
200-1		694.11 (M+H)
200-3		615.17 (M+H)
200-4		601.15 (M+H)
200-5		575.11 (M+H)
200-6		561.09 (M+H)
200-7		613.15 (M+H)

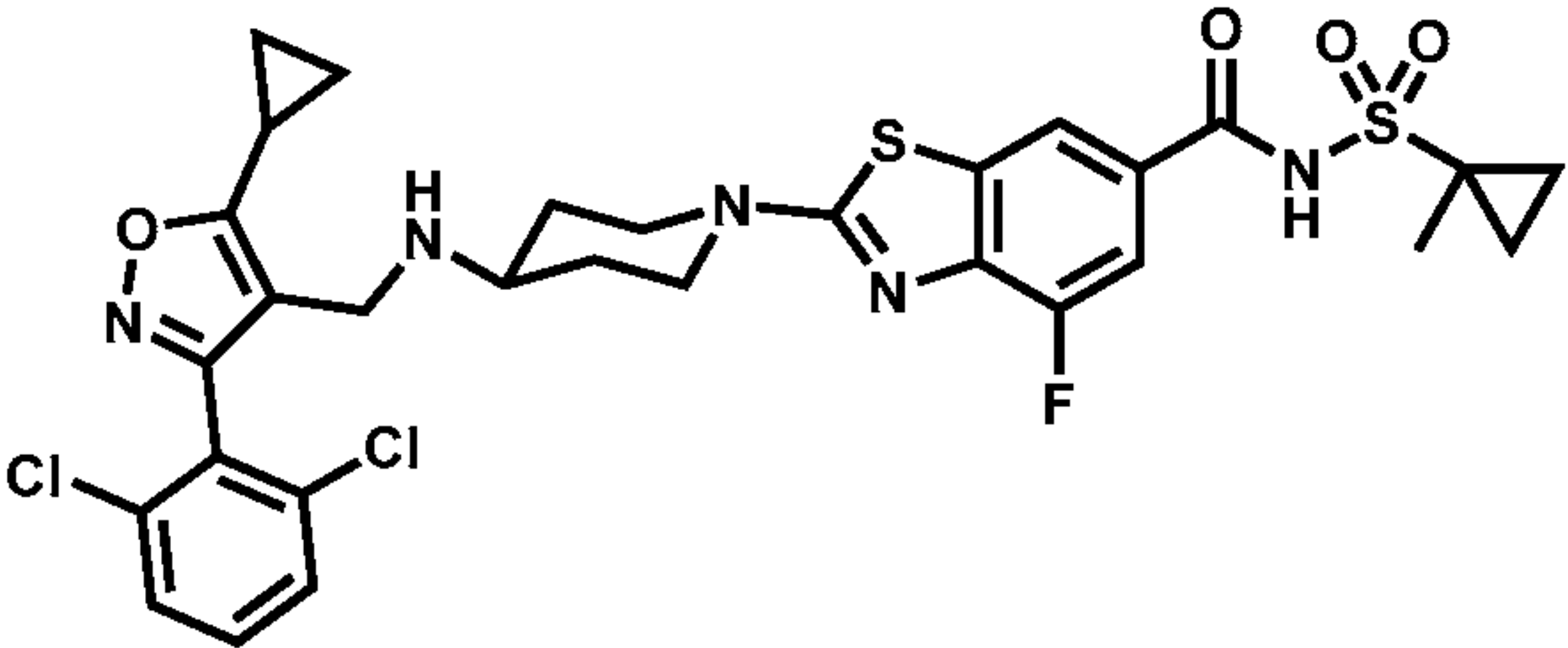
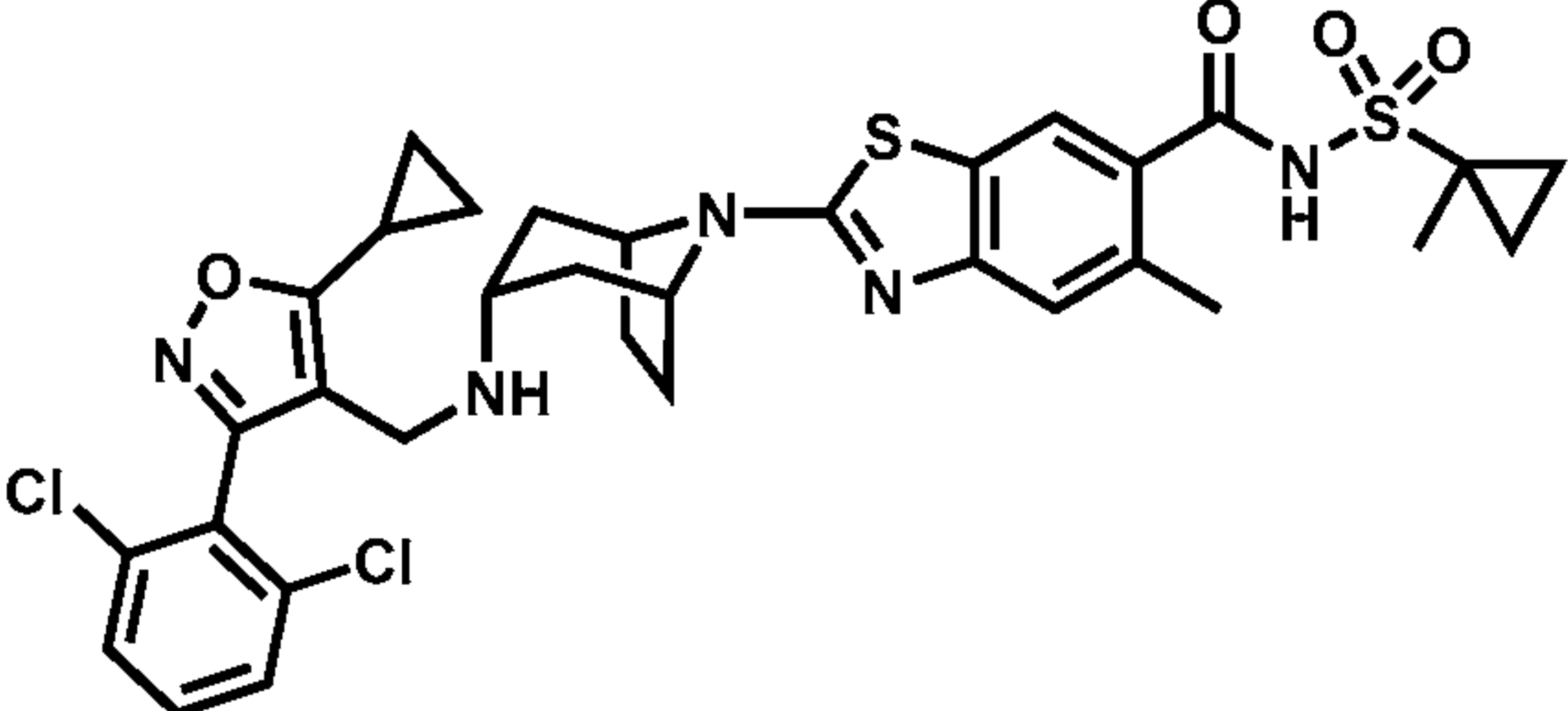
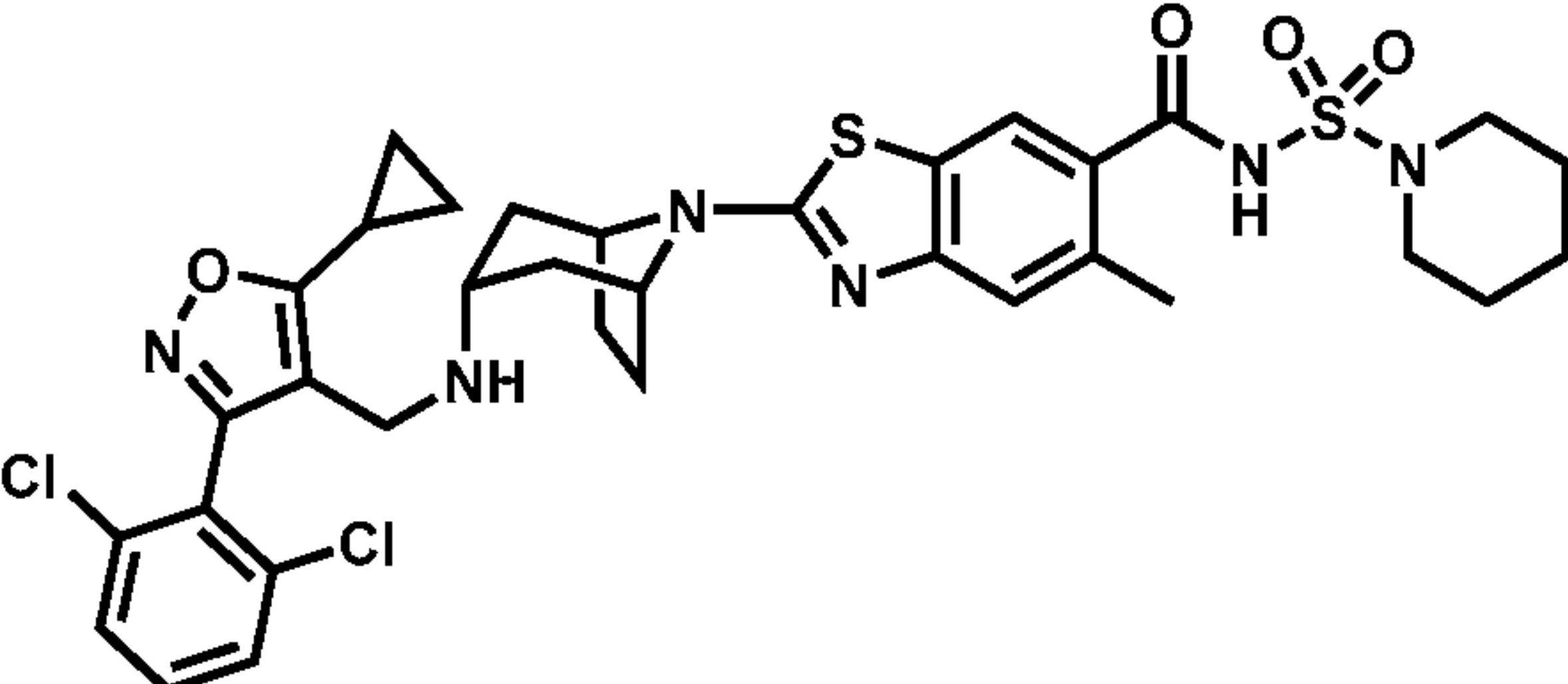
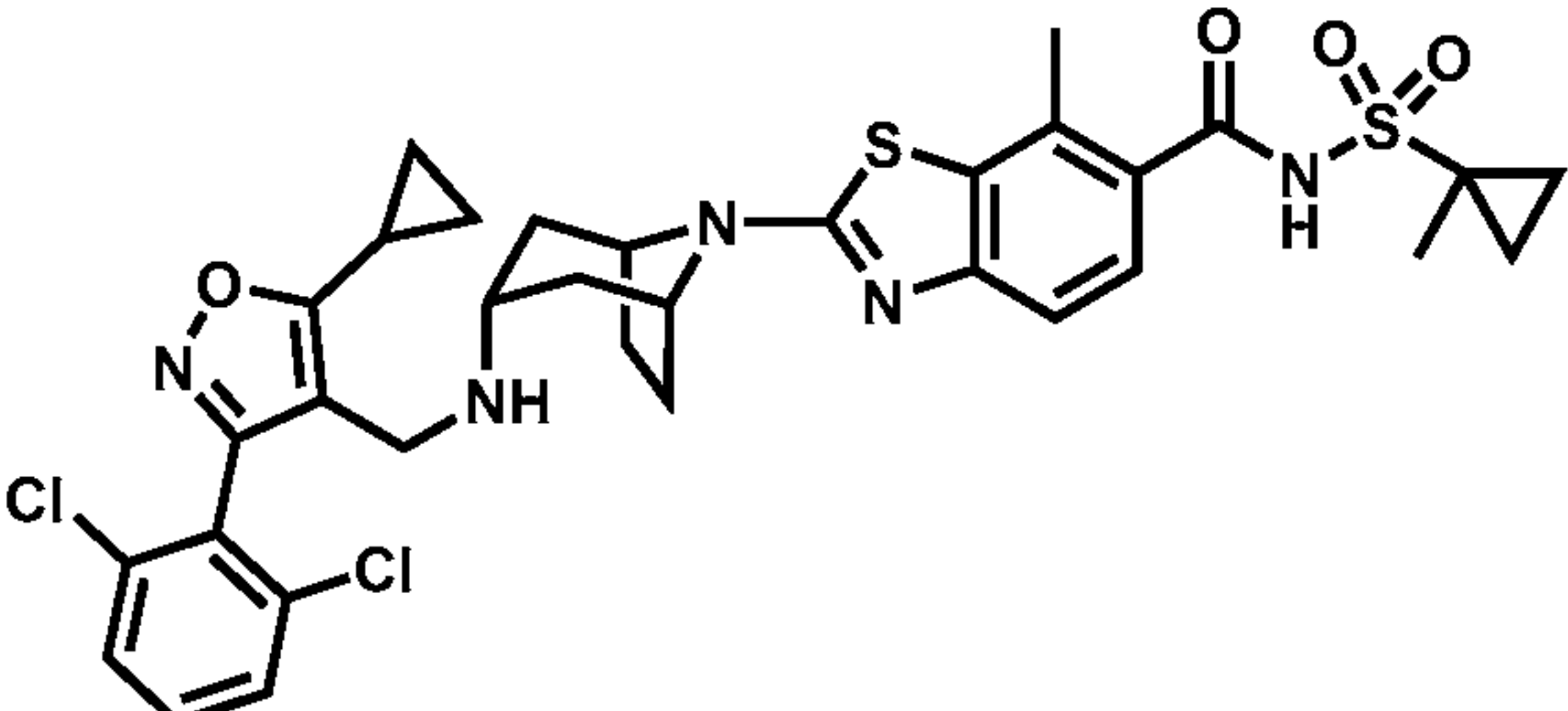
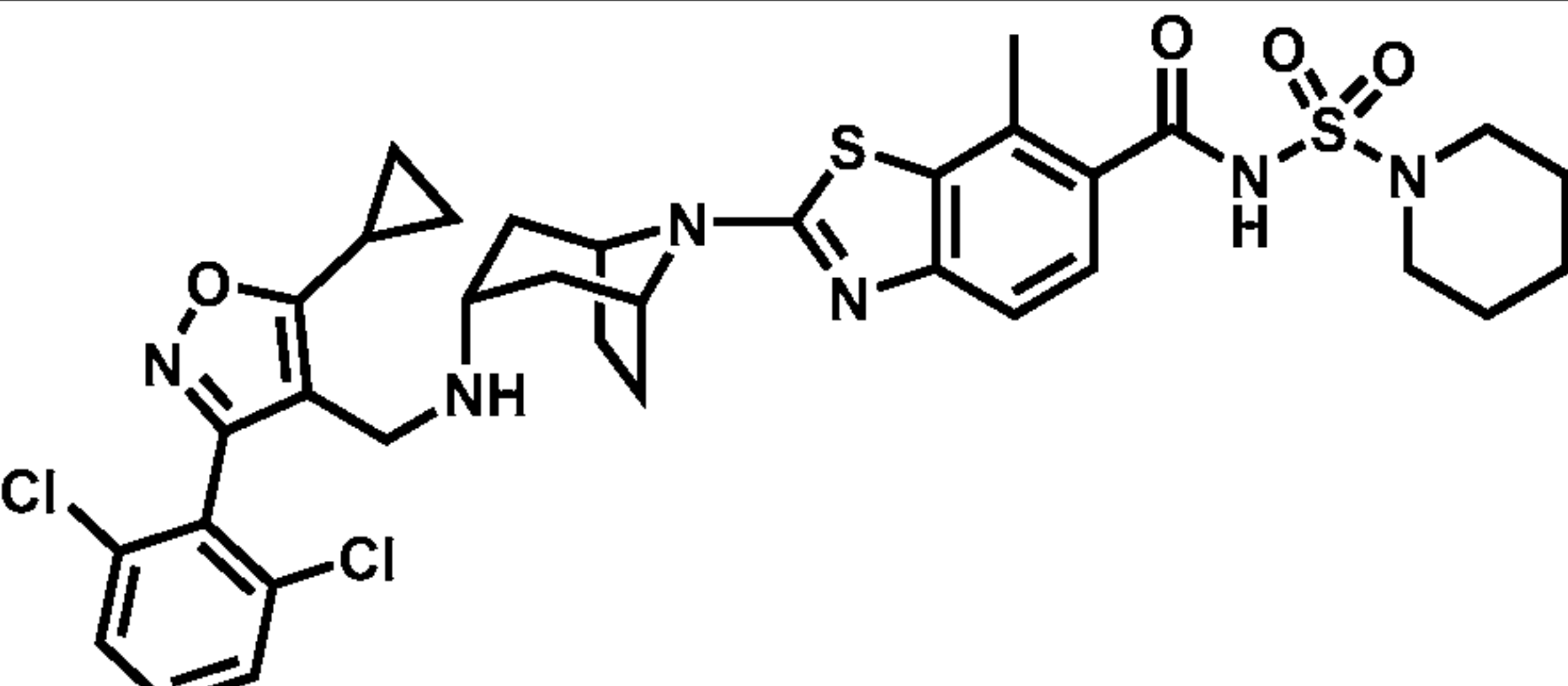
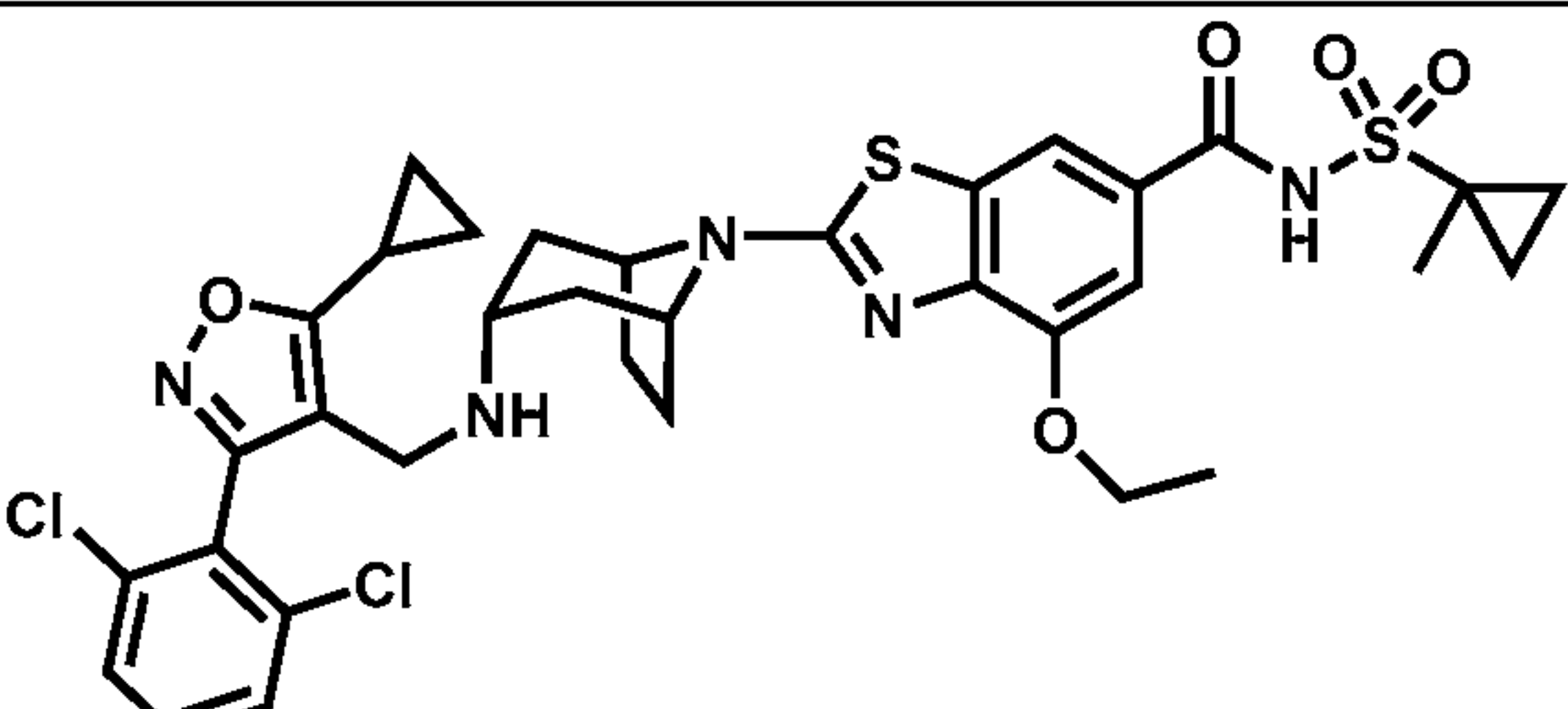
200-8		599.18 (M+H)
200-9		627.16 (M+H)
200-10		613.15 (M+H)
200-11		656.15 (M+H)
200-12		706.13 (M+H)
200-13		641.18 (M+H)

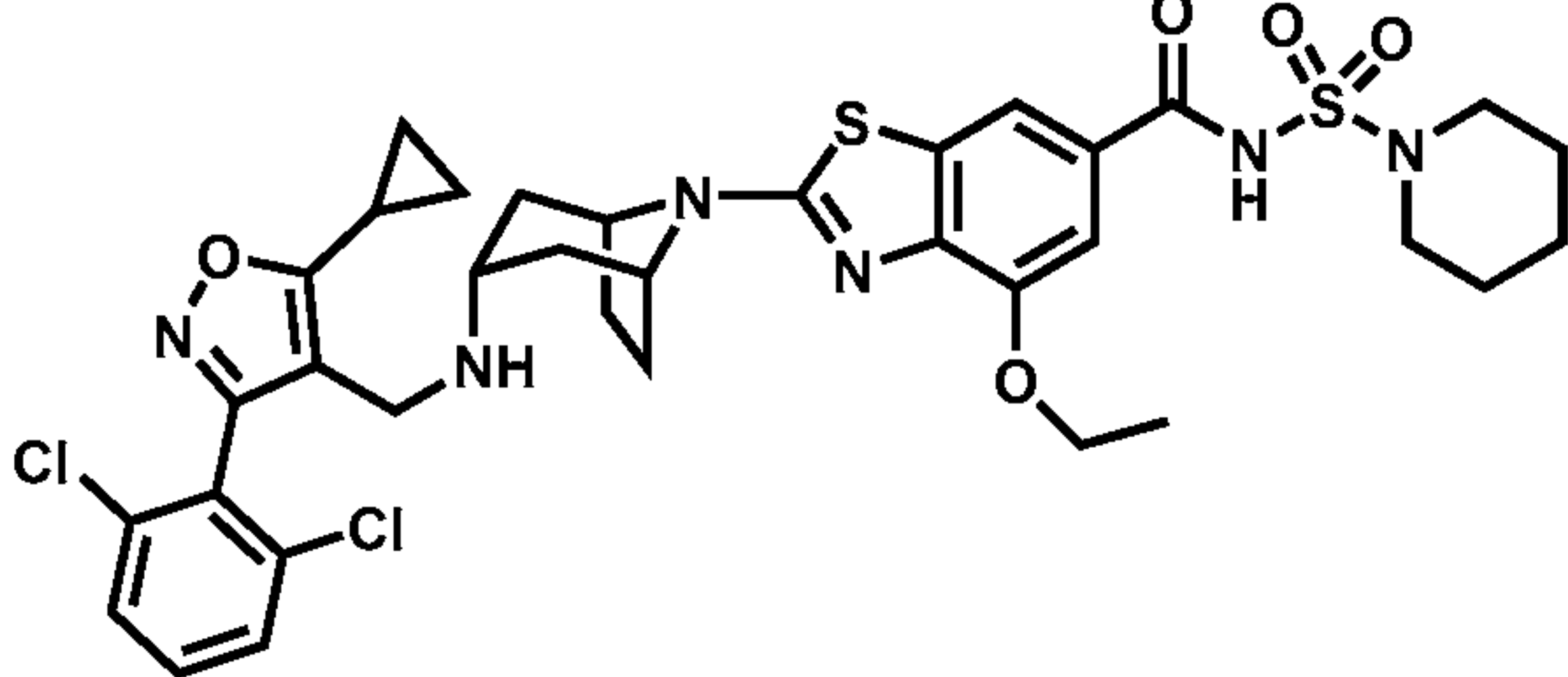
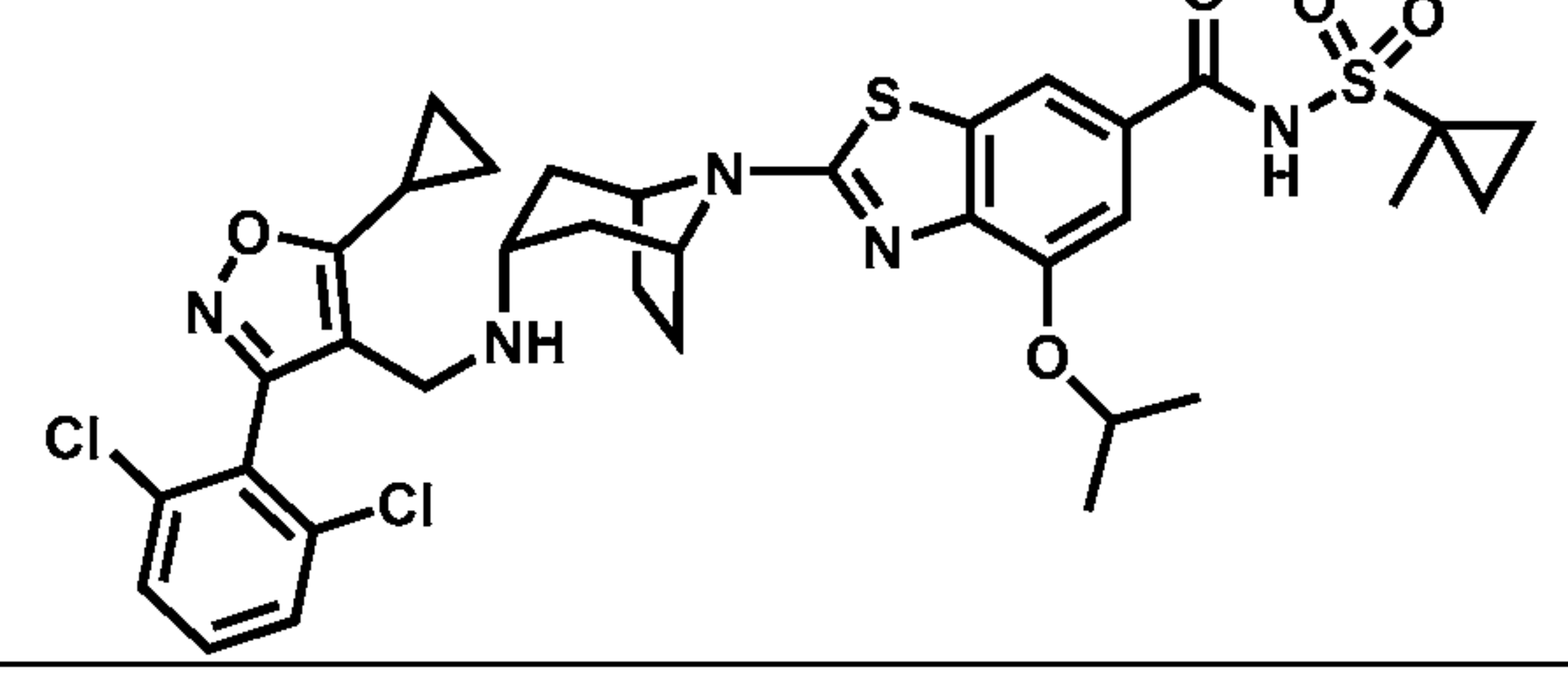
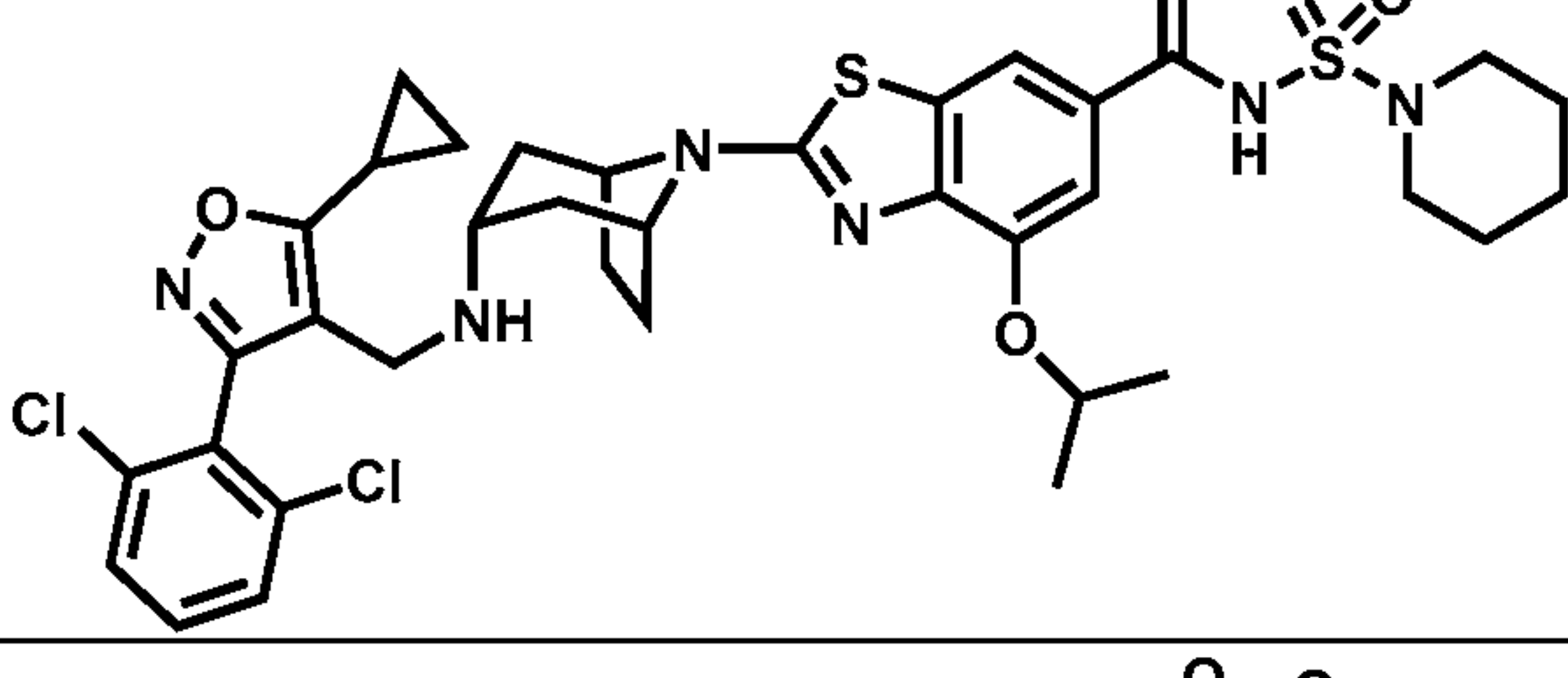
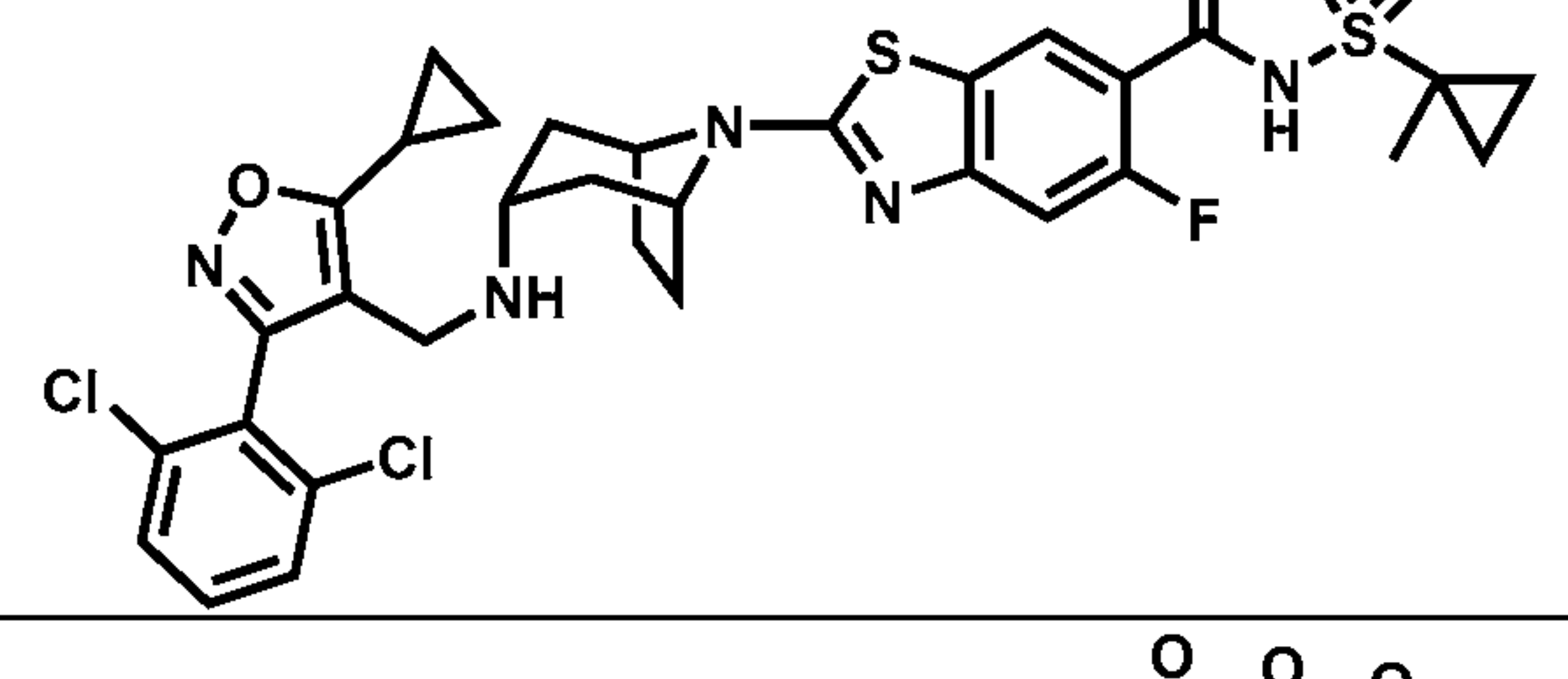
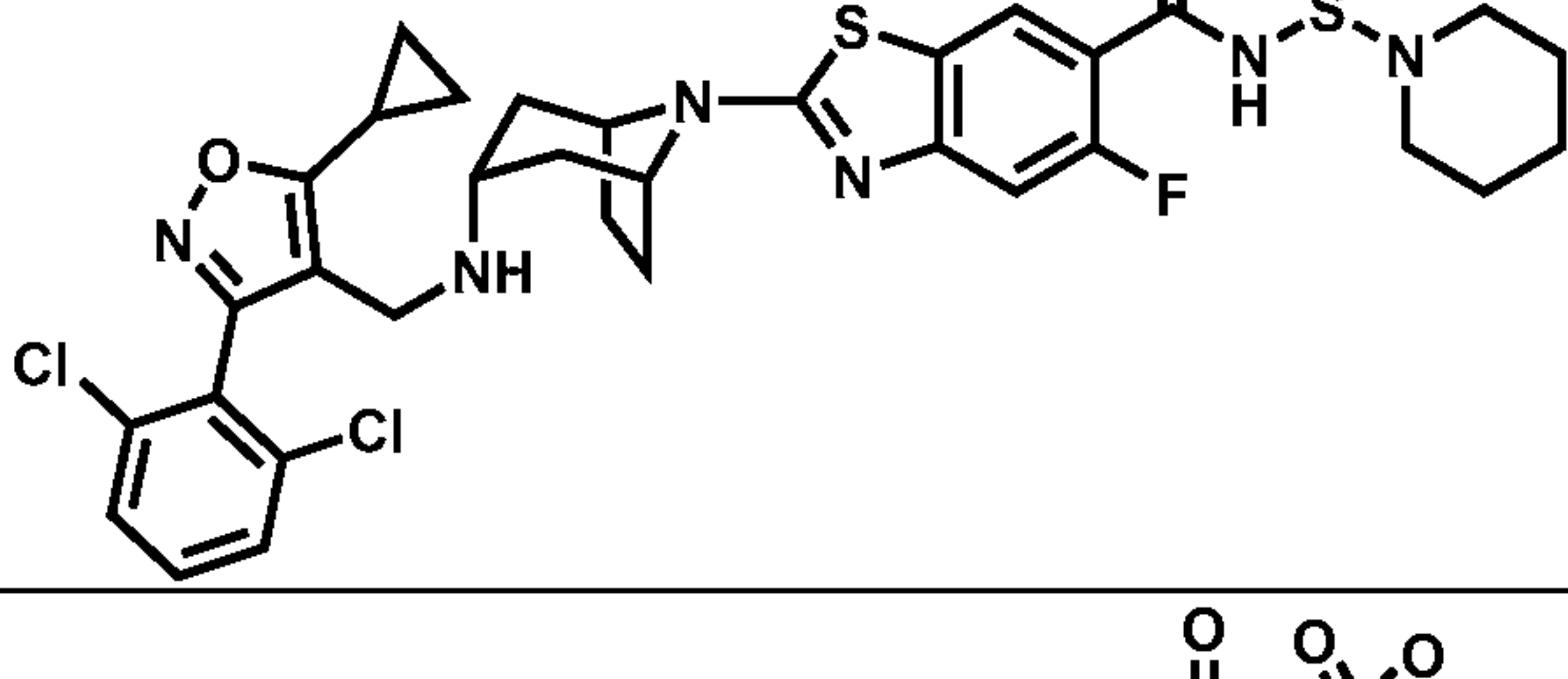
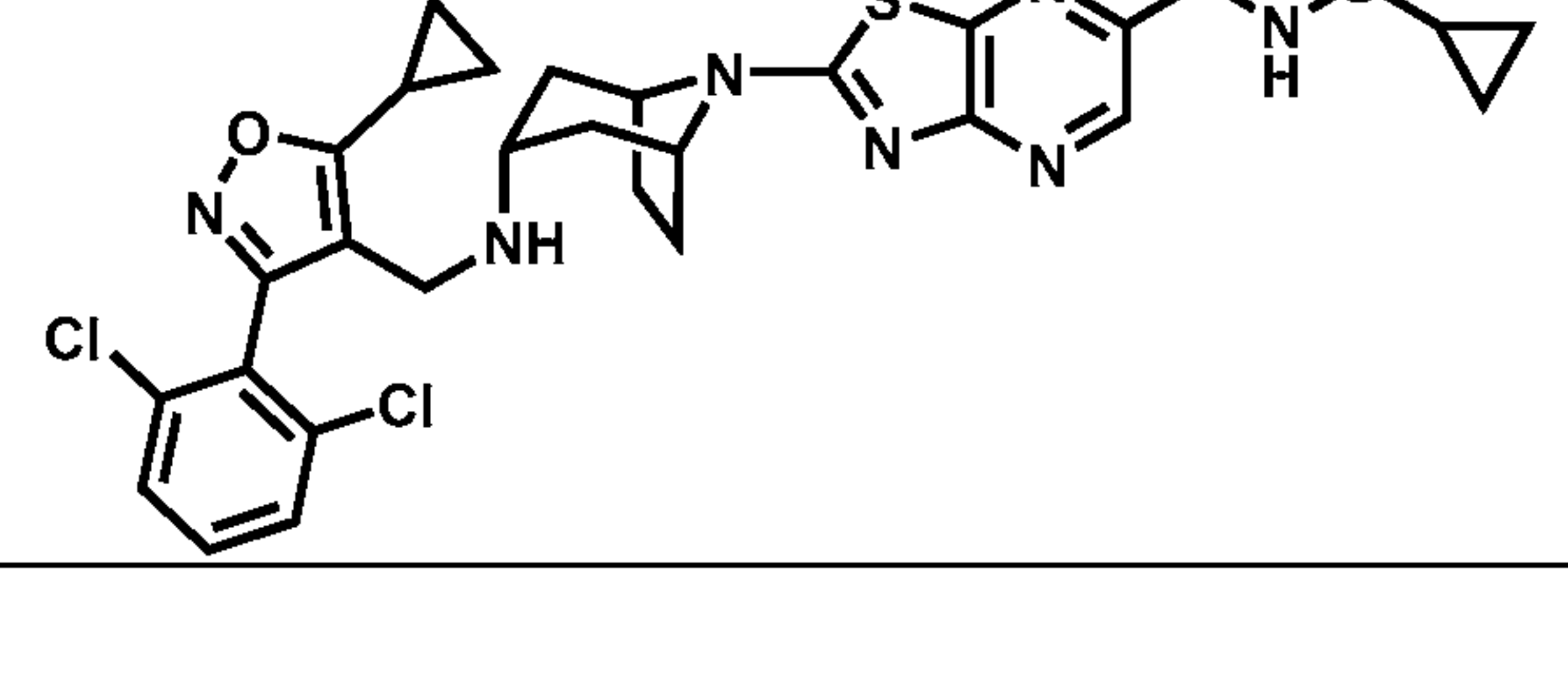
200-14		627.19 (M+H)
200-15		601.13 (M+H)
200-16		587.11 (M+H)
200-17		583.13 (M-H)
200-18		571.11 (M+H)
200-19		663.10 (M+H)

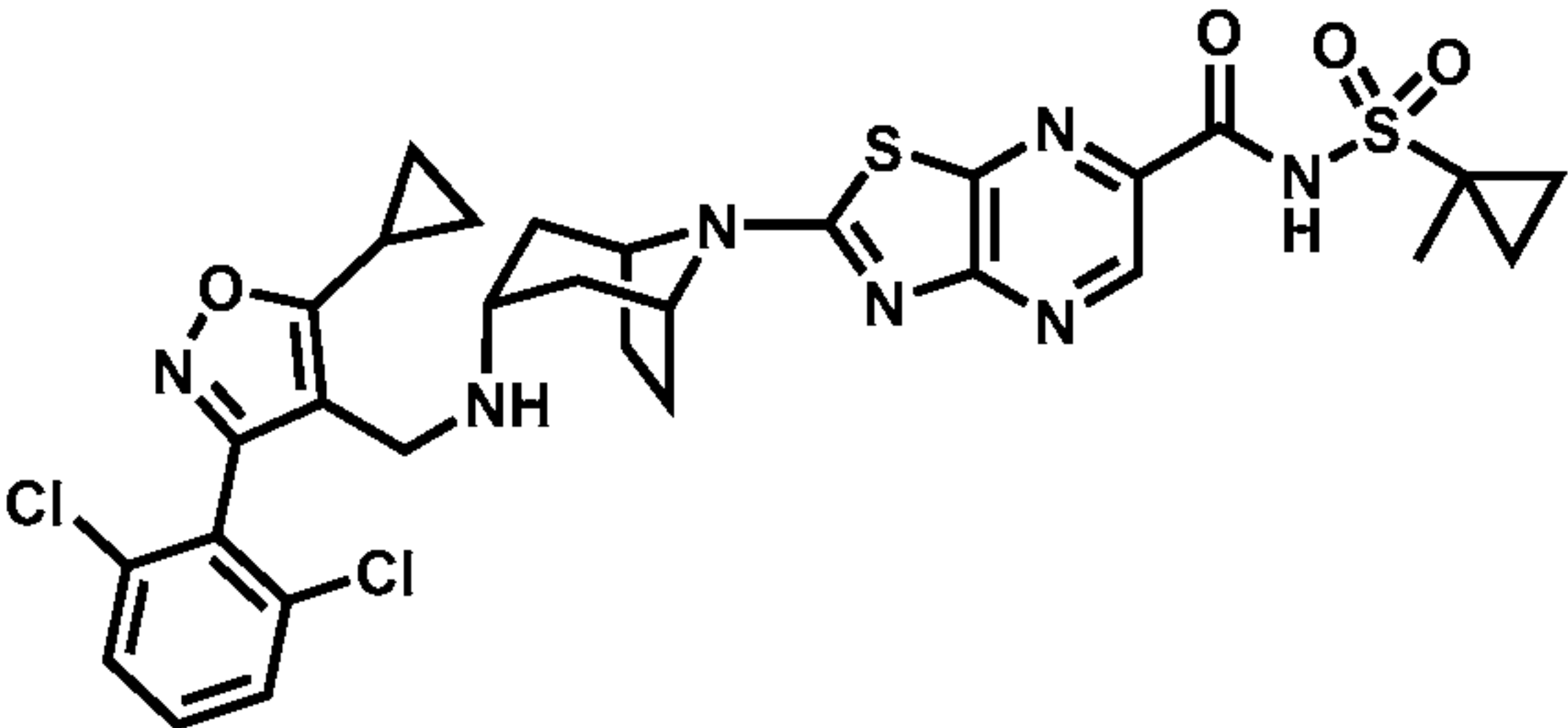
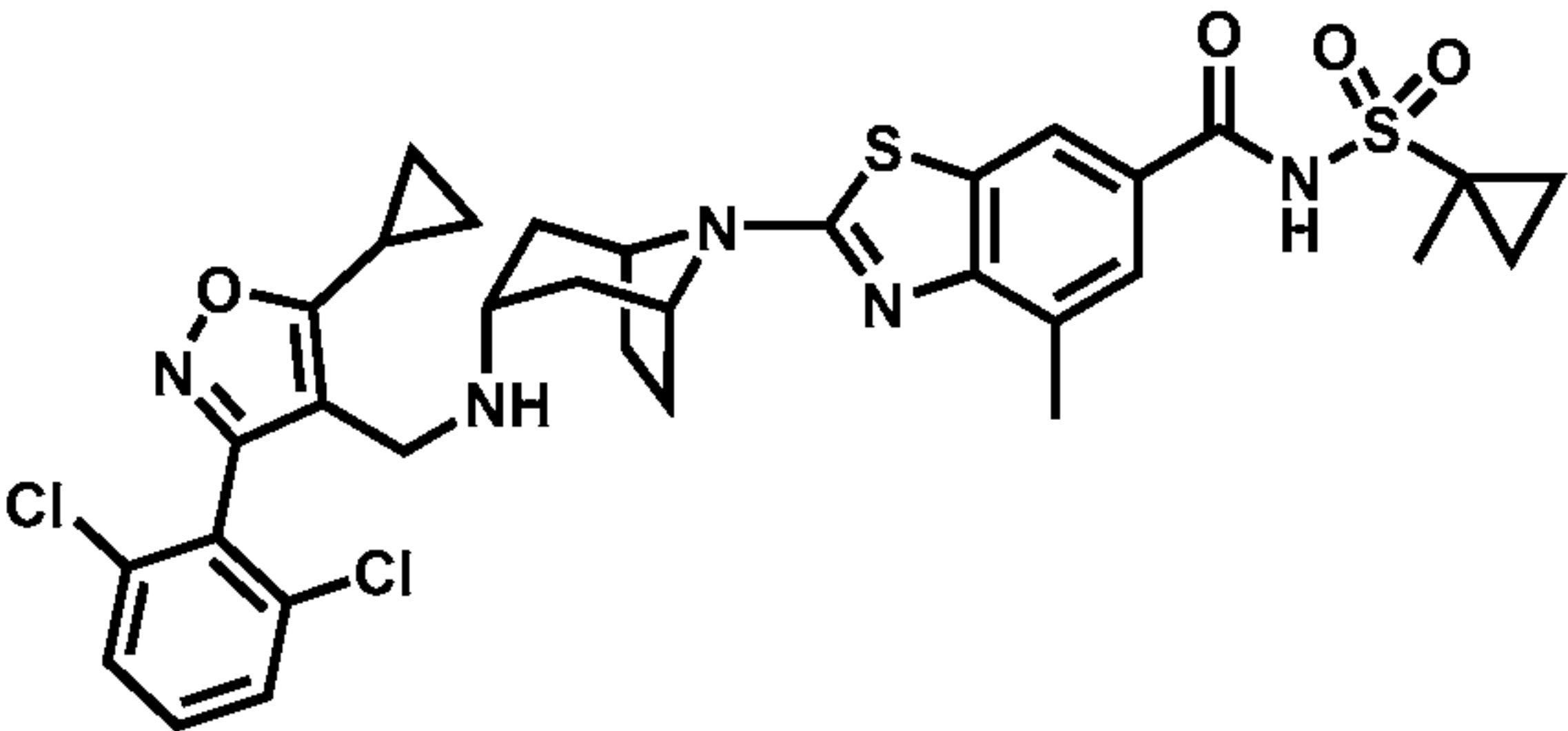
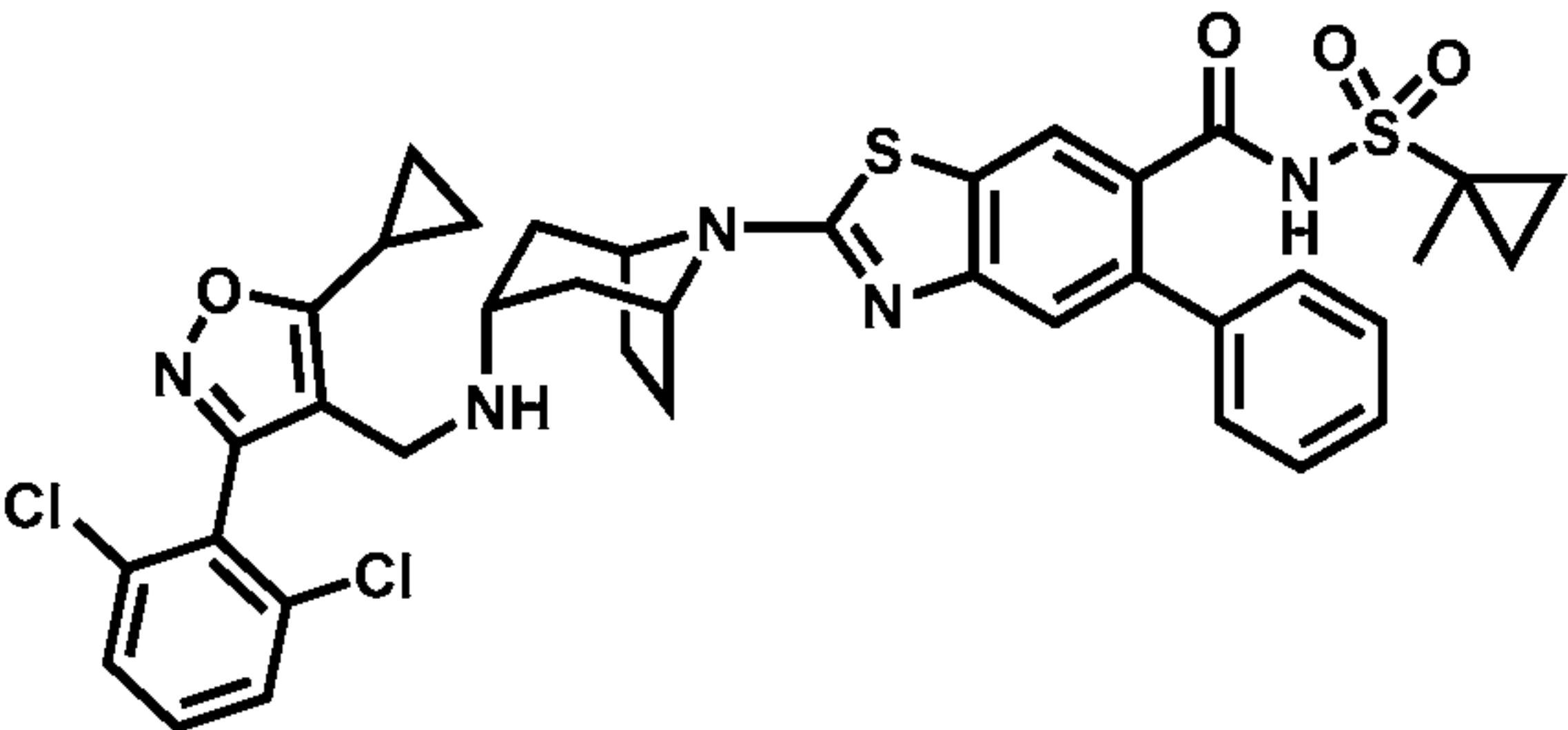
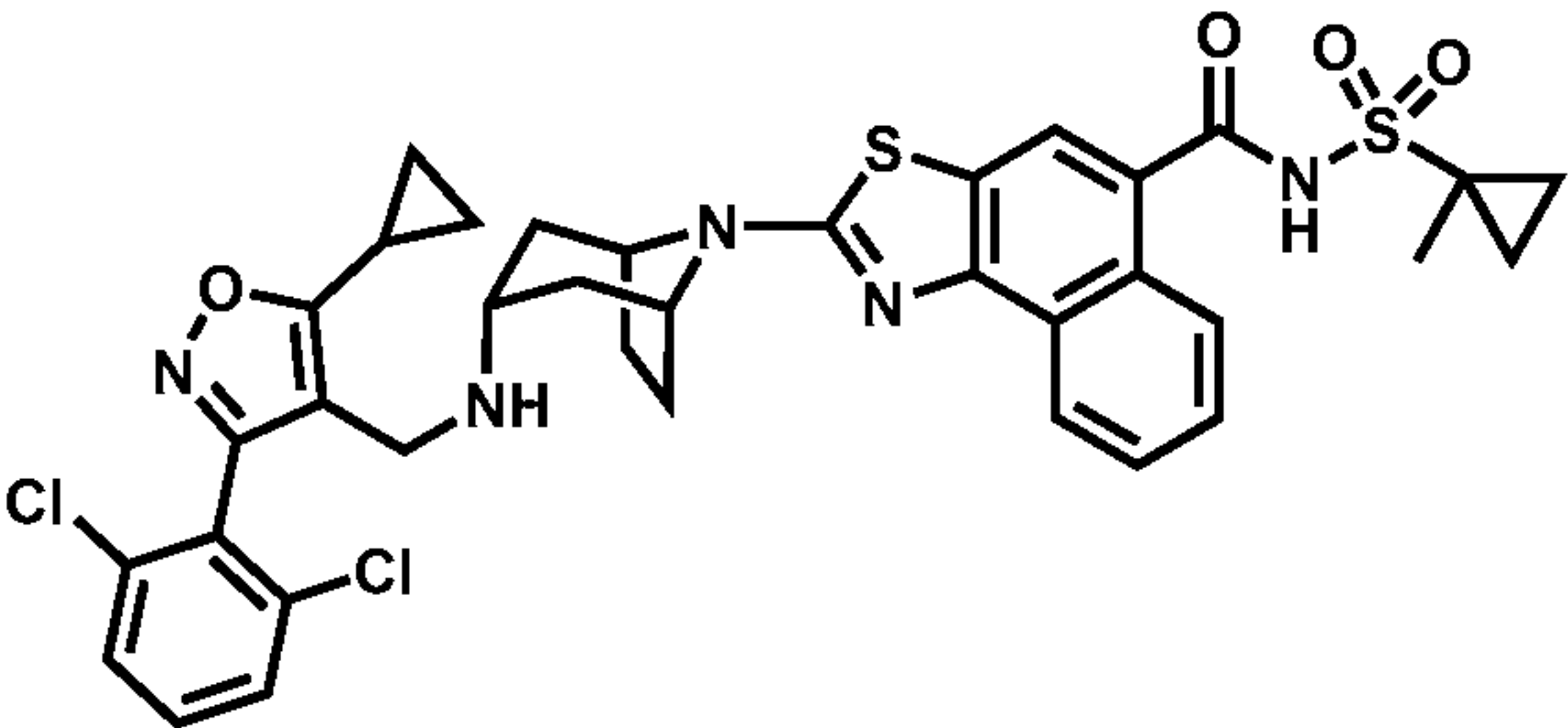
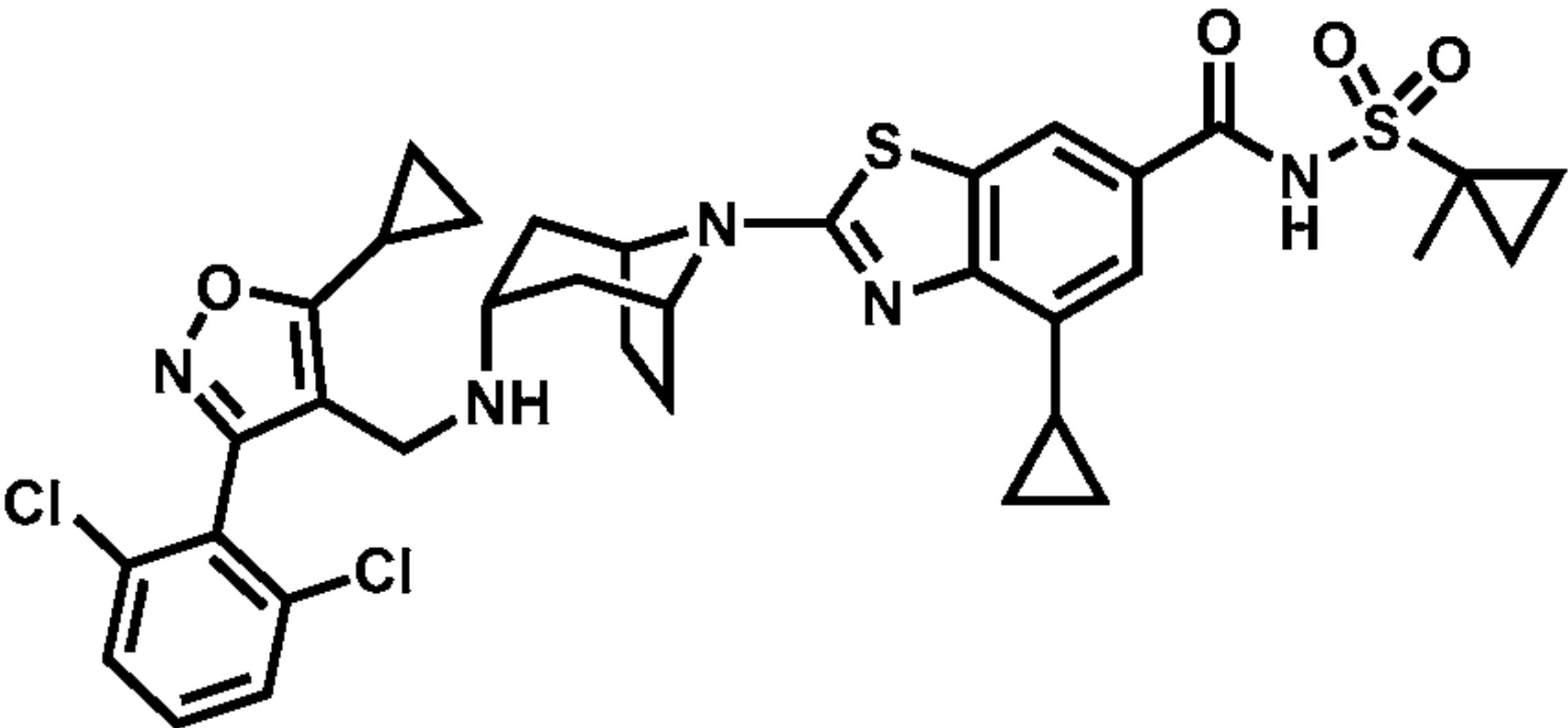
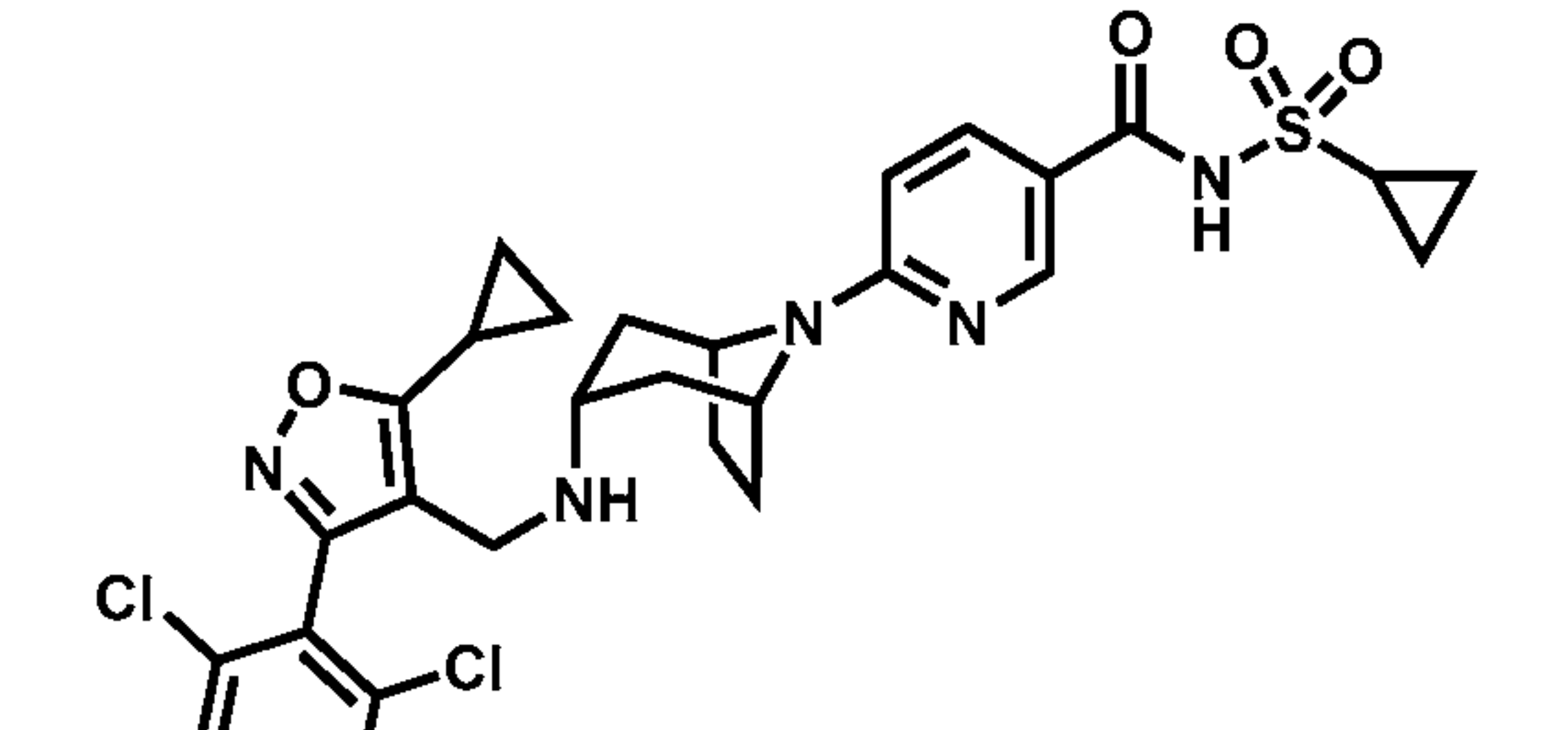
200-21		663.10, (M+H)
200-23		659.17 (M+H)
200-24		645.15 (M+H)
200-25		659.17 (M+H)
200-27		633.15 (M+H)
200-28		619.13 (M+H)

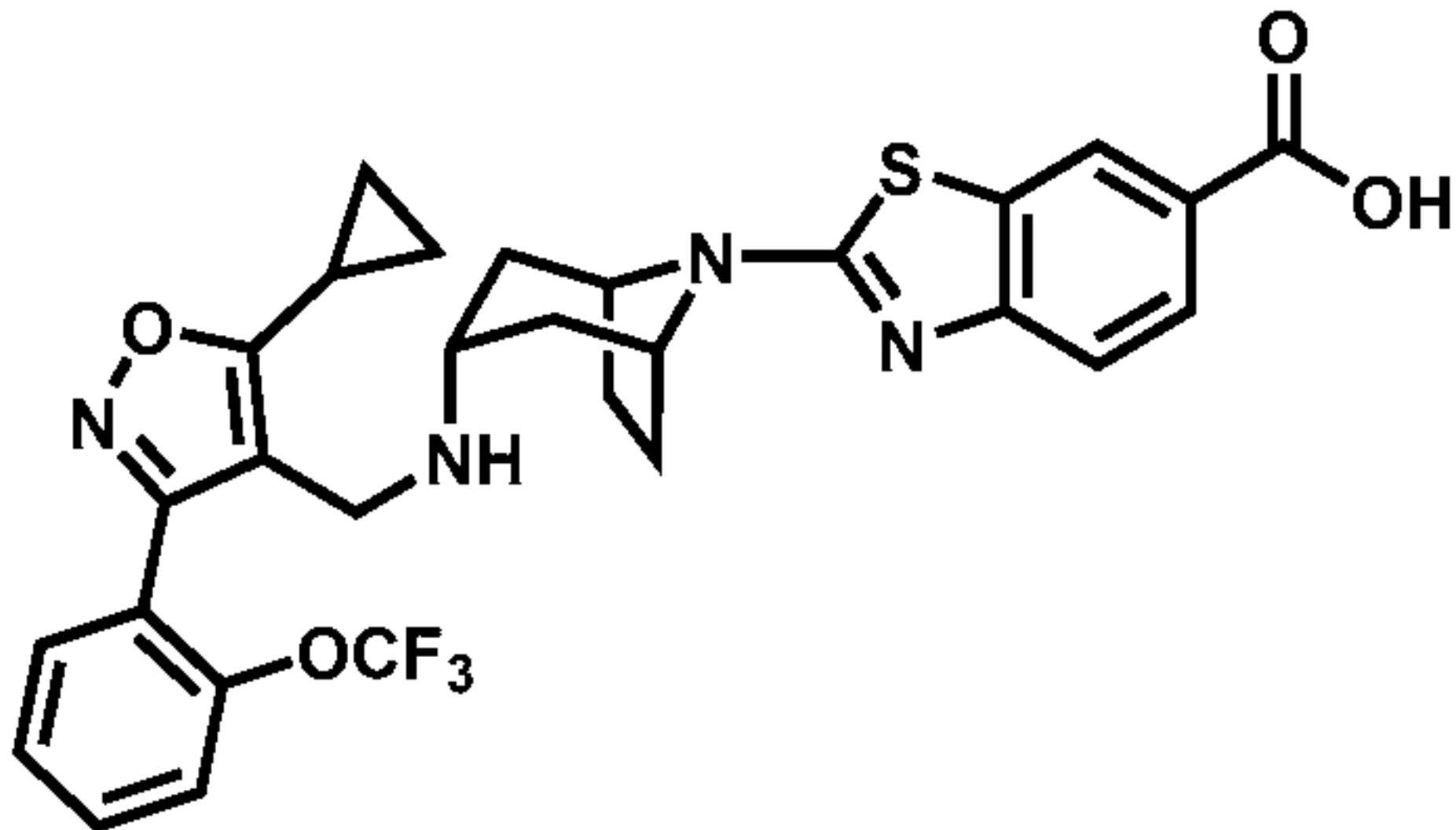
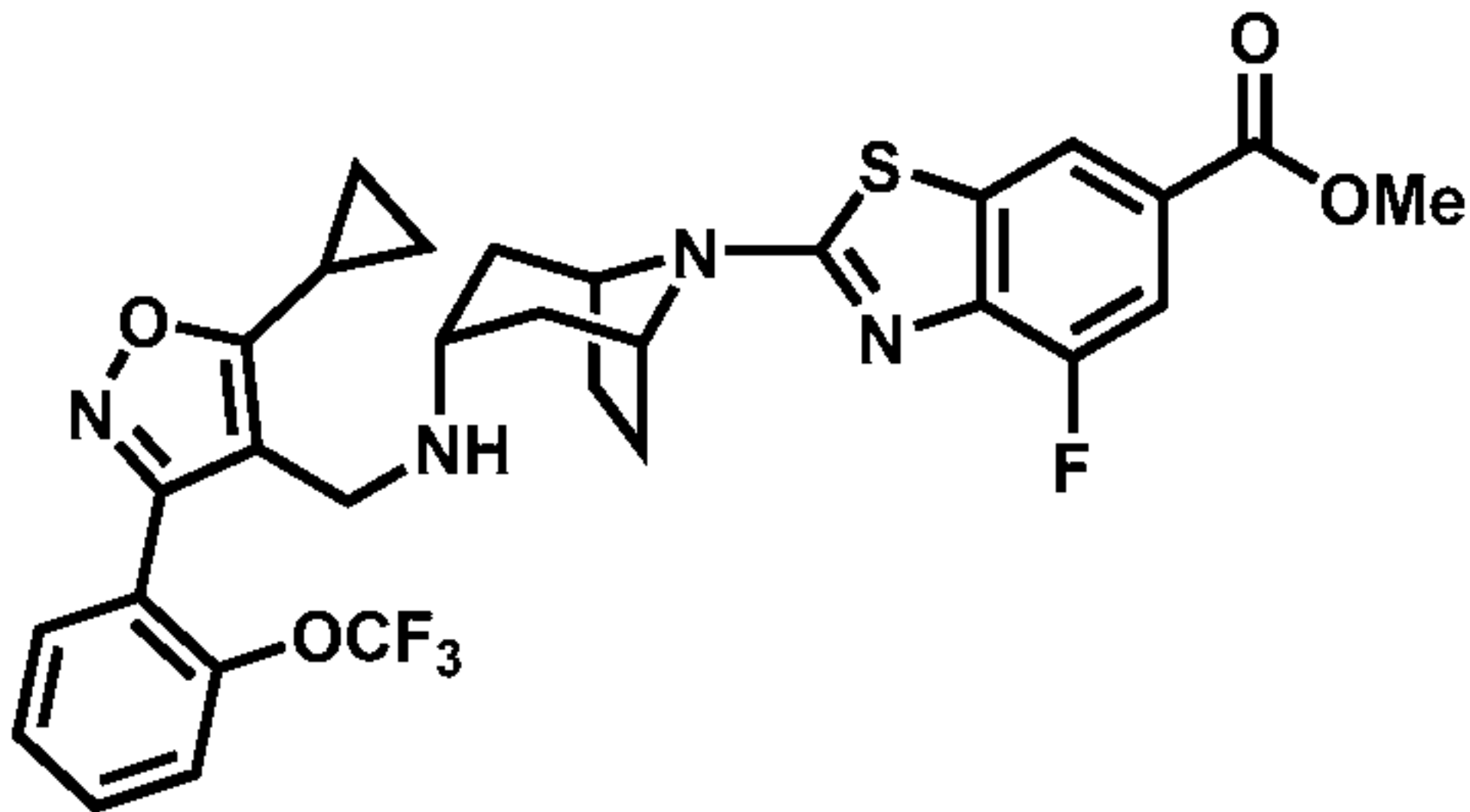
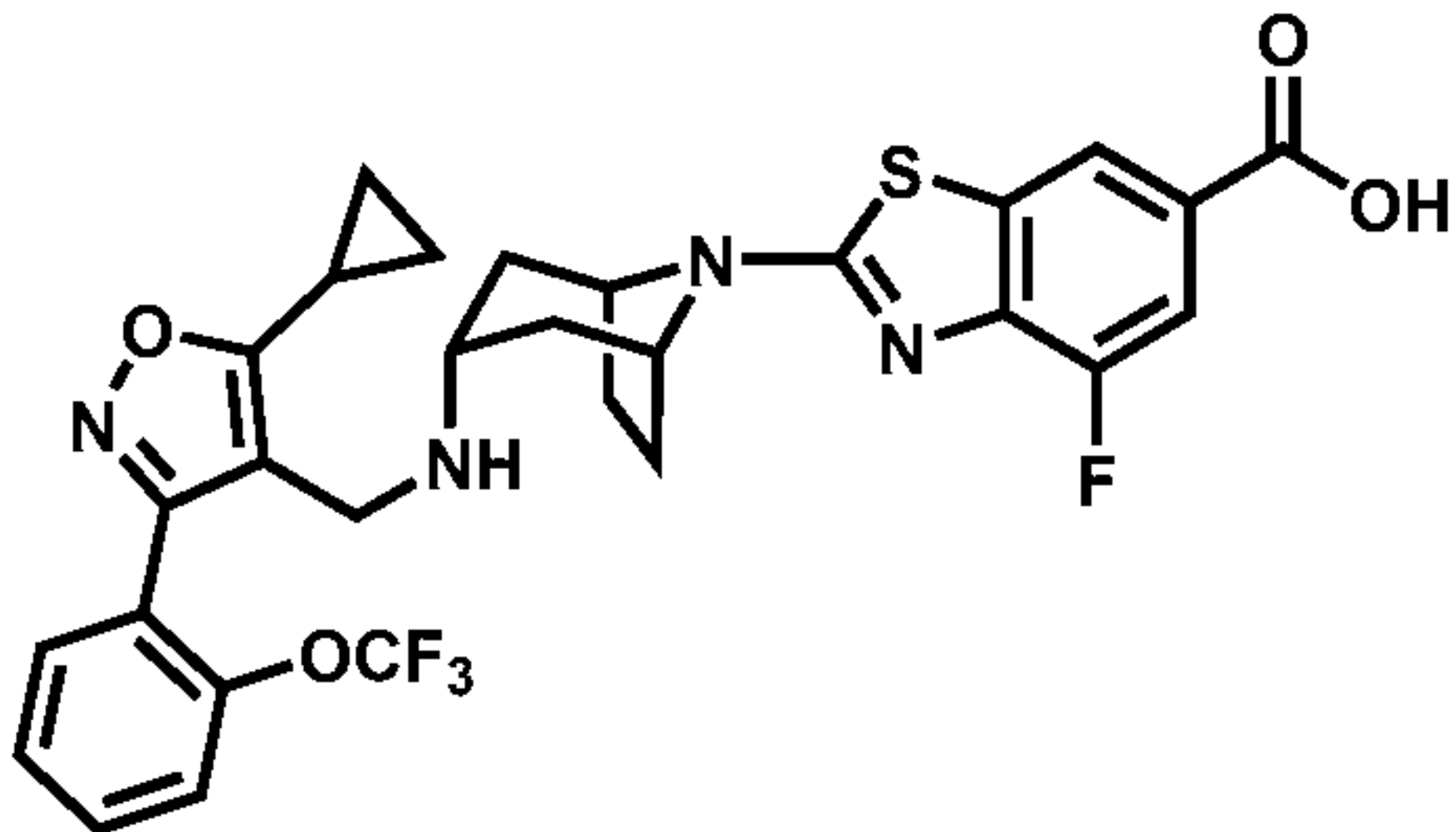
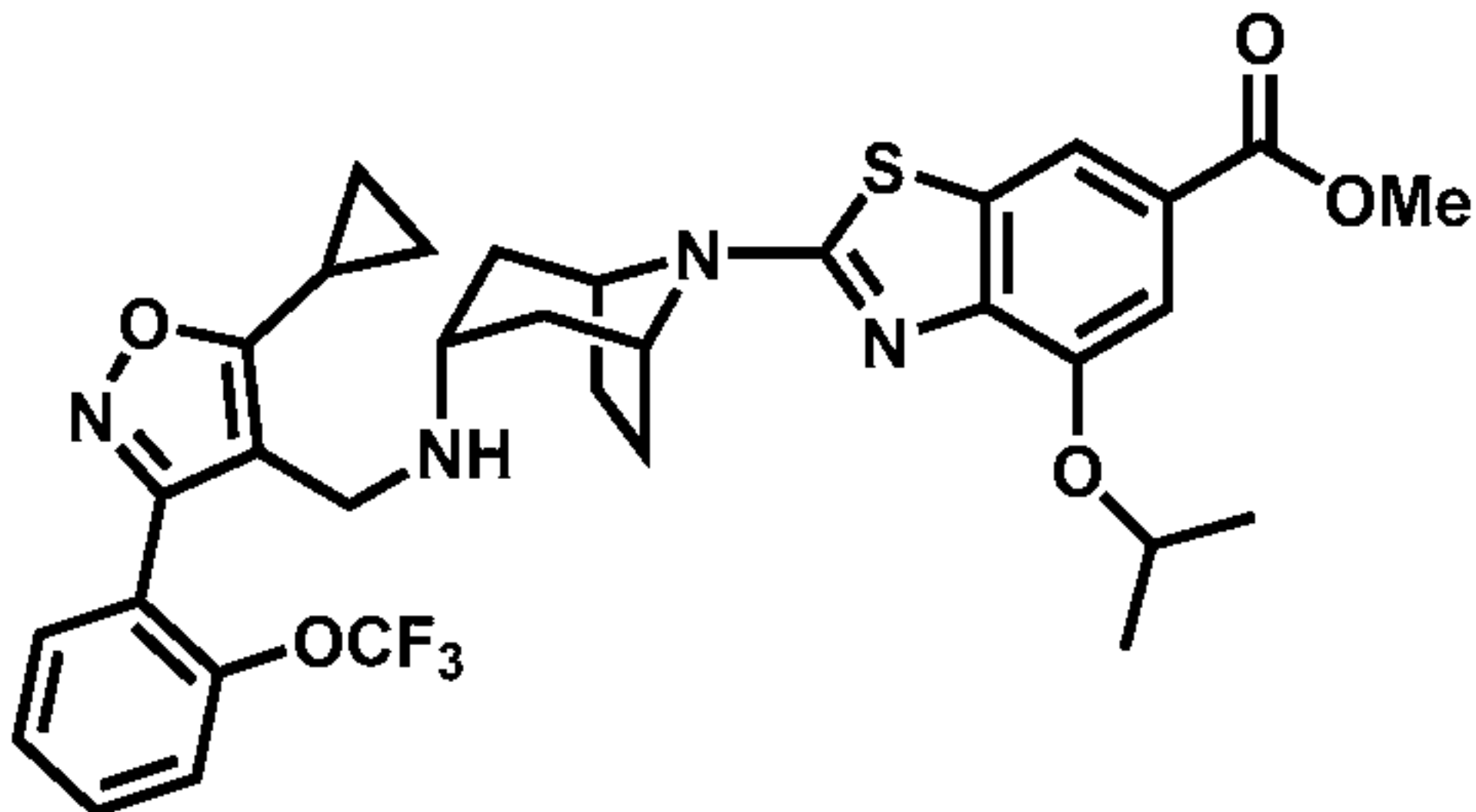
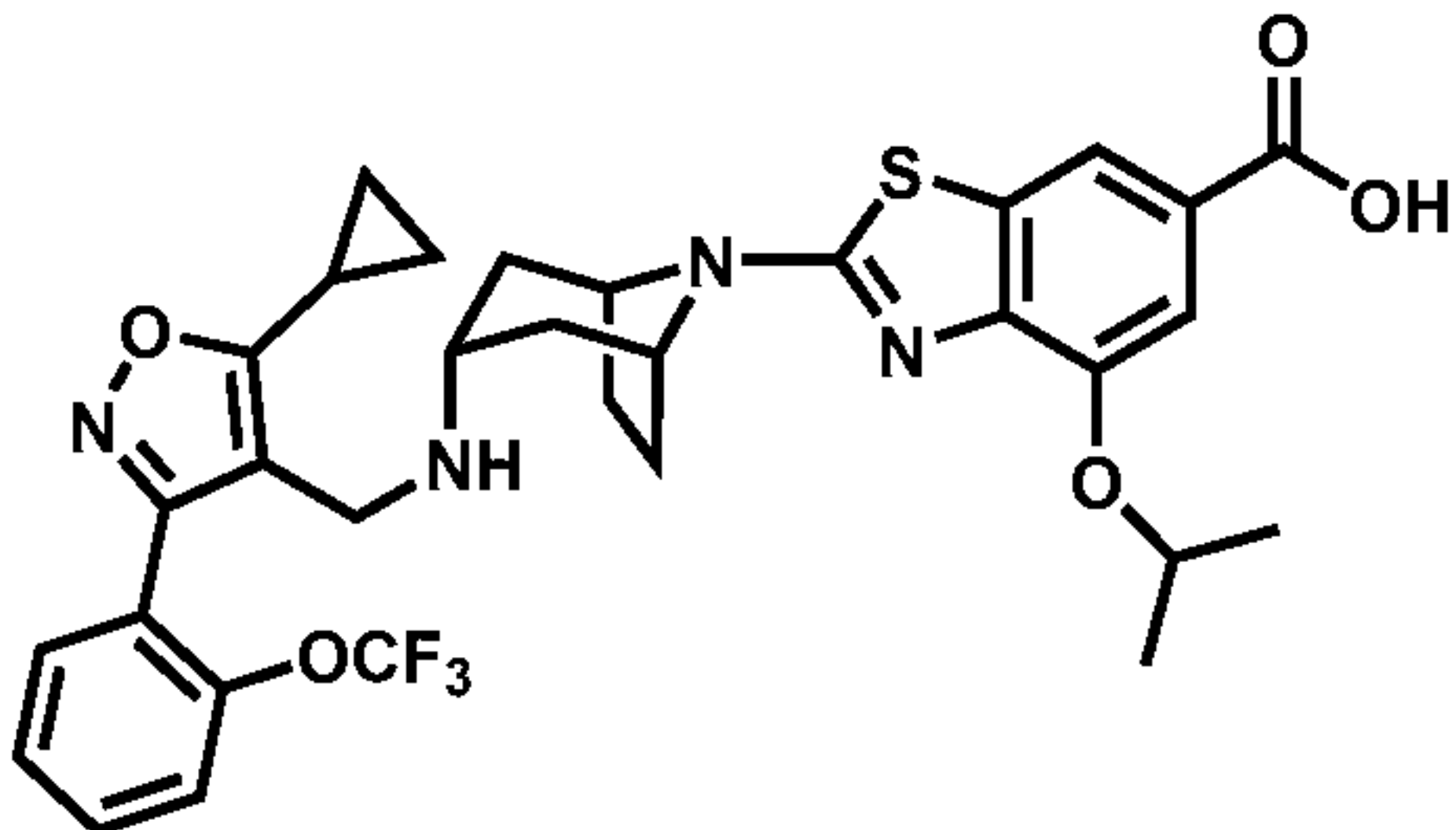
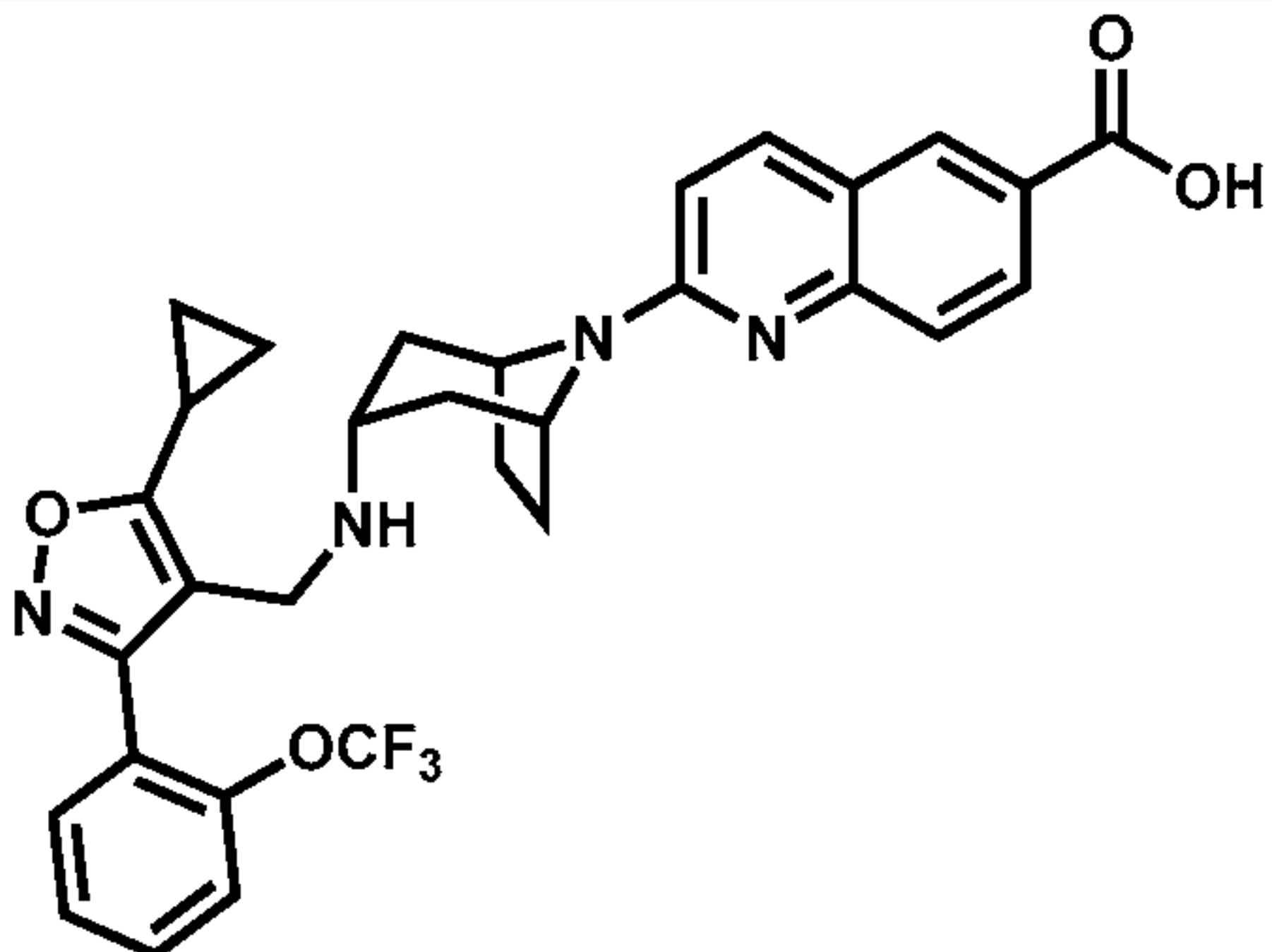
200-29		623.17 (M+H)
200-30		609.15 (M+H)
323		752.14 (M+H)
328		781.16 (M+H)
342		711.22 (M+H)
400-1		719.14 (M+H)

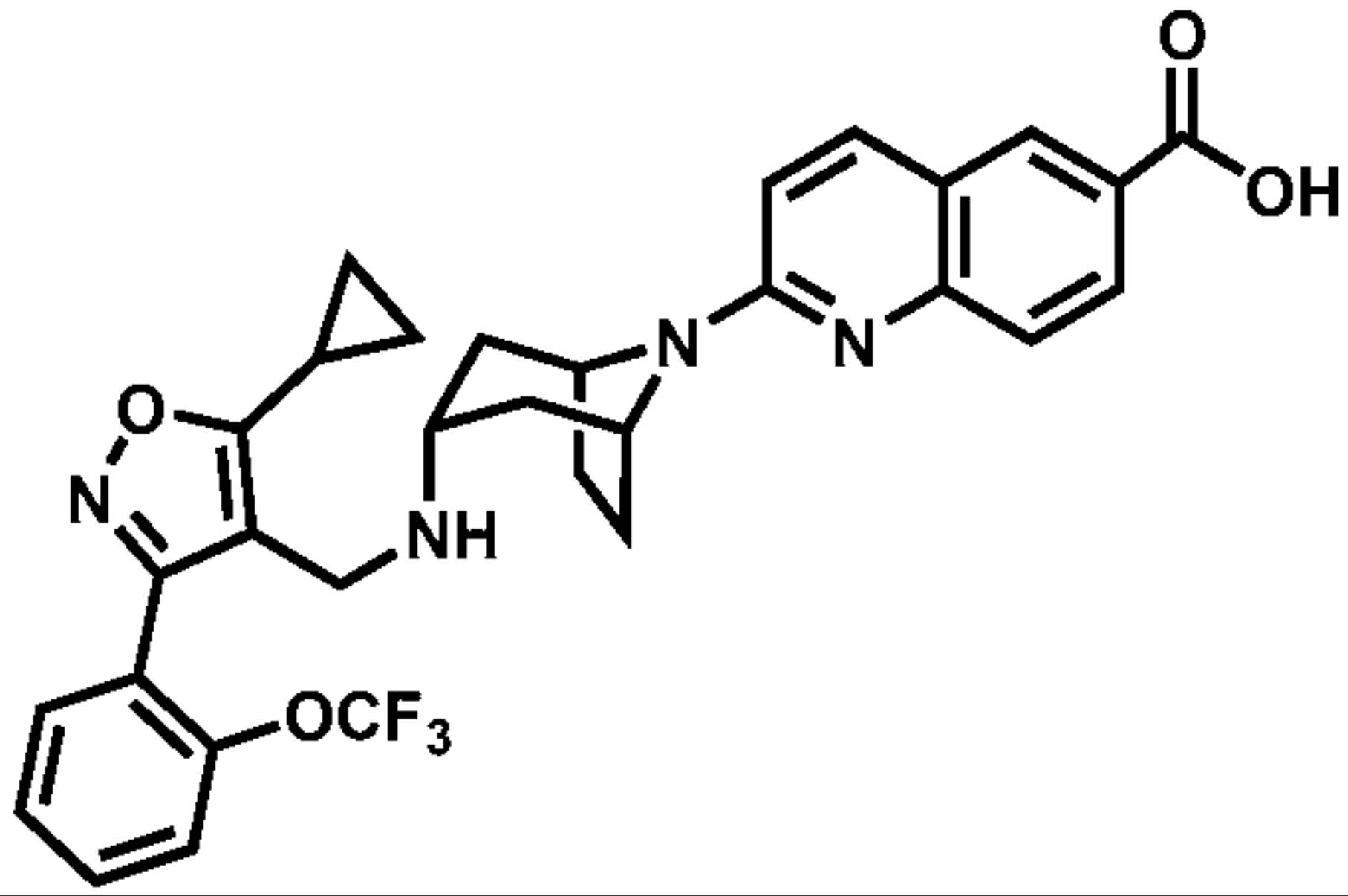
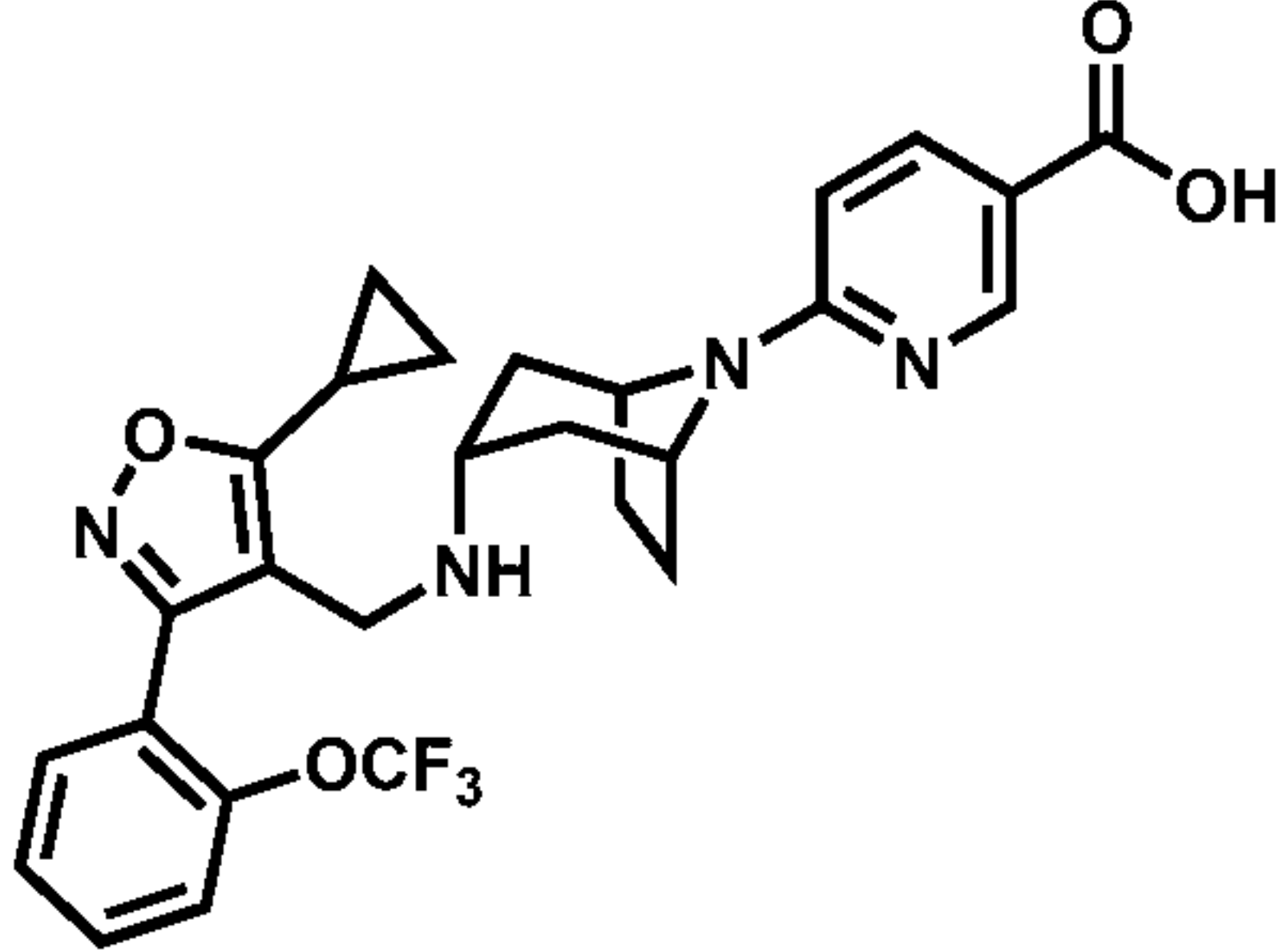
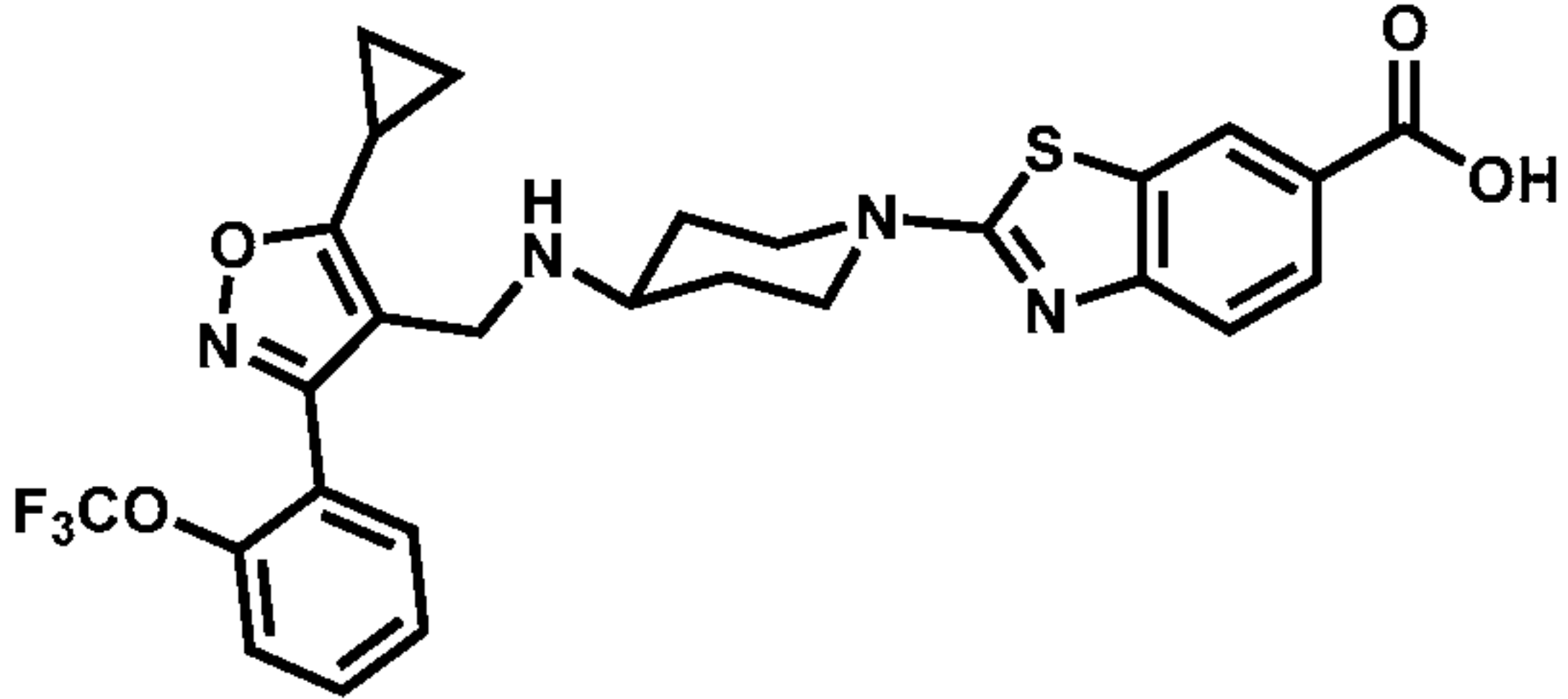
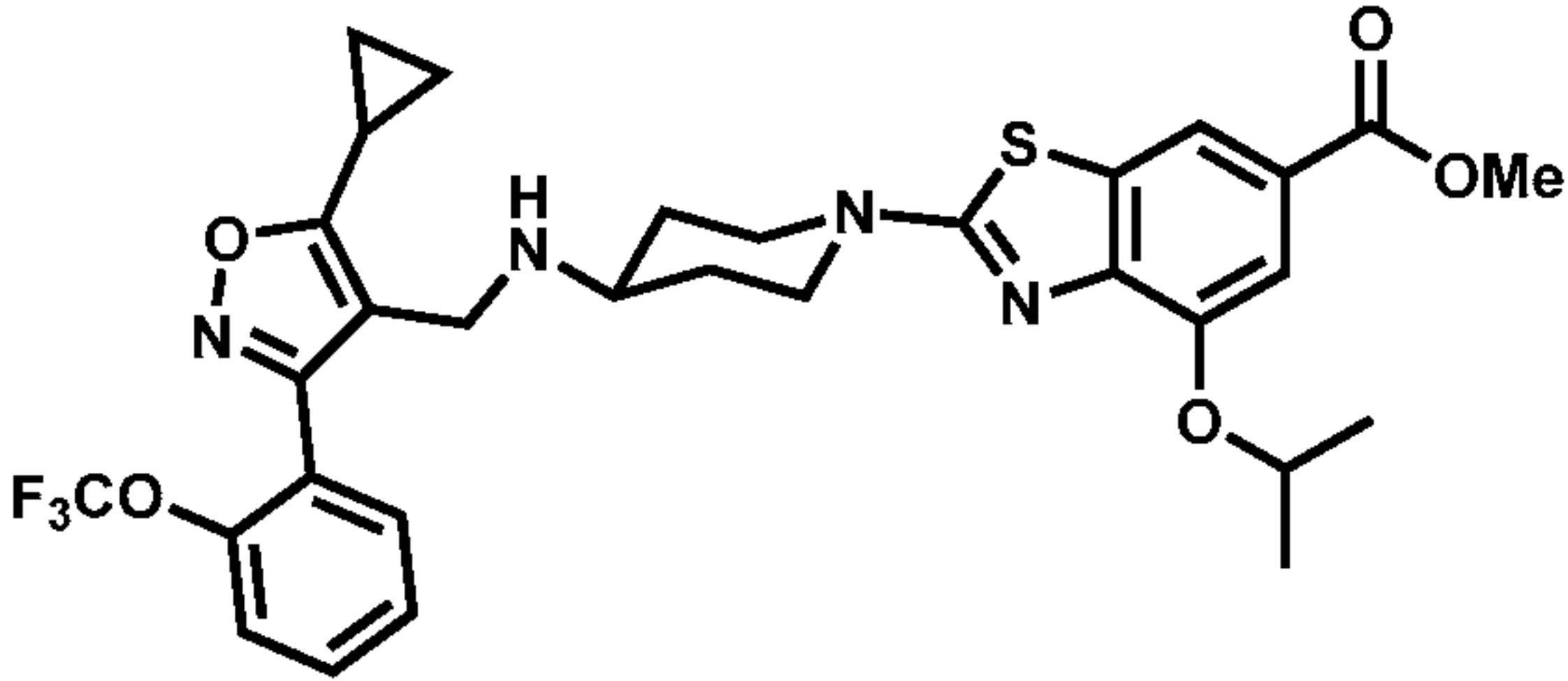
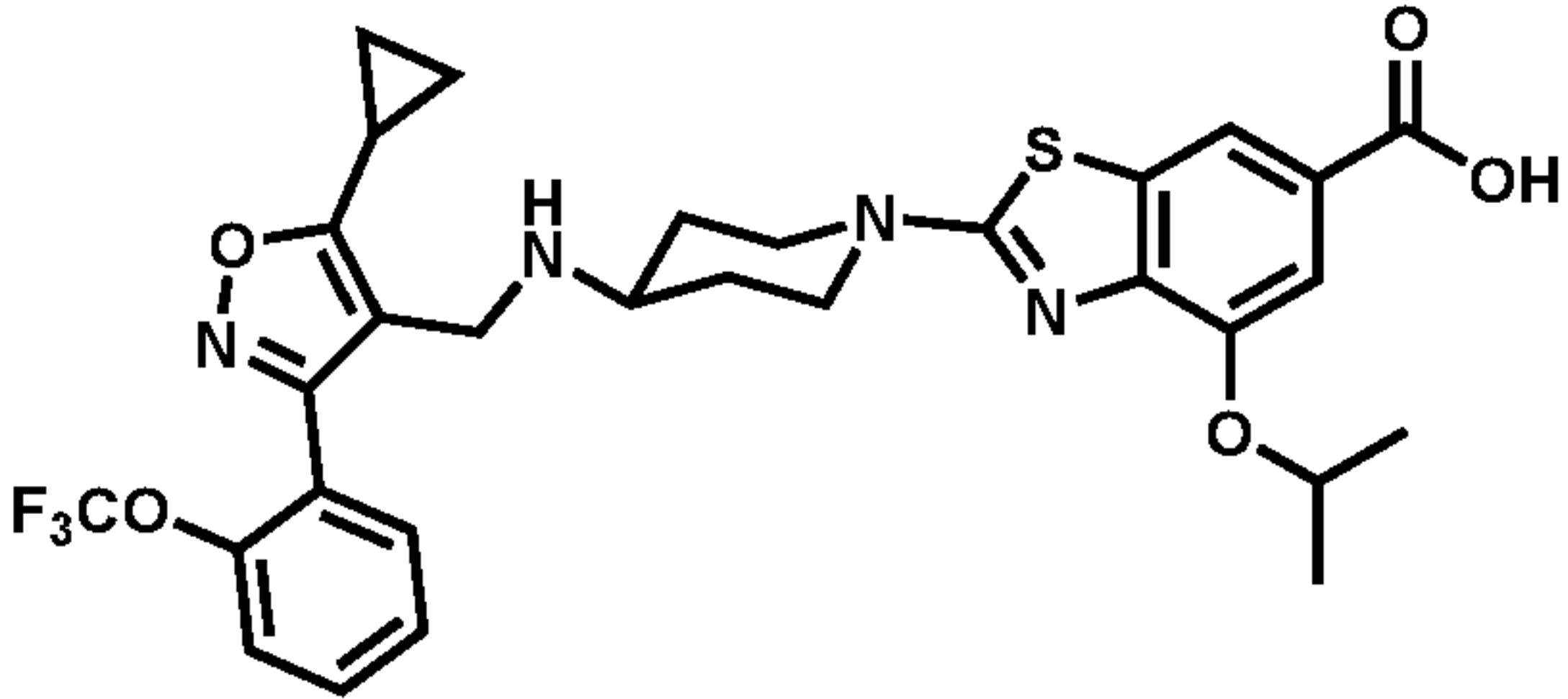
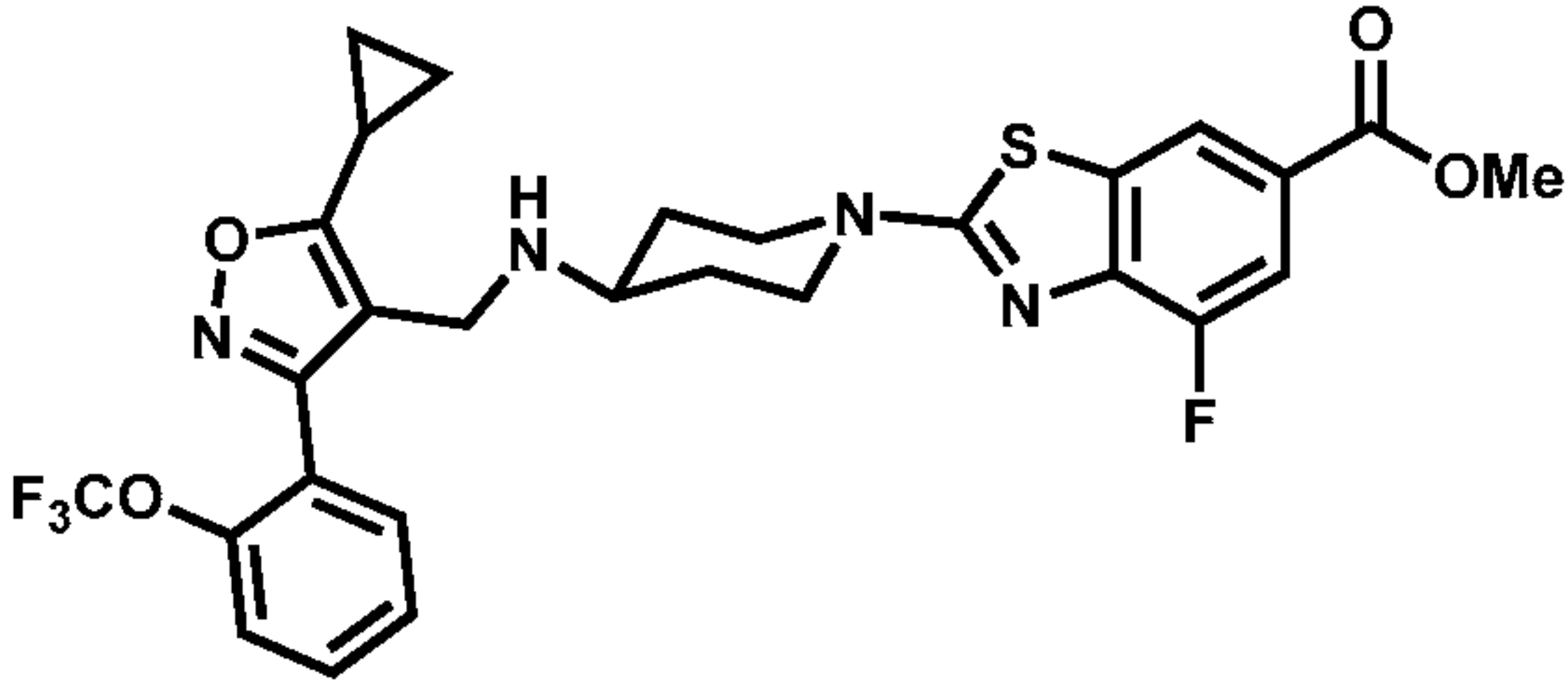
400-3		704.17 (M+H)
400-4		718.19 (M+H)
400-5		733.20 (M+H)
400-6		747.22 (M+H)
400-7		693.15 (M+H)
400-8		707.16 (M+H)
400-9		664.12 (M+H)

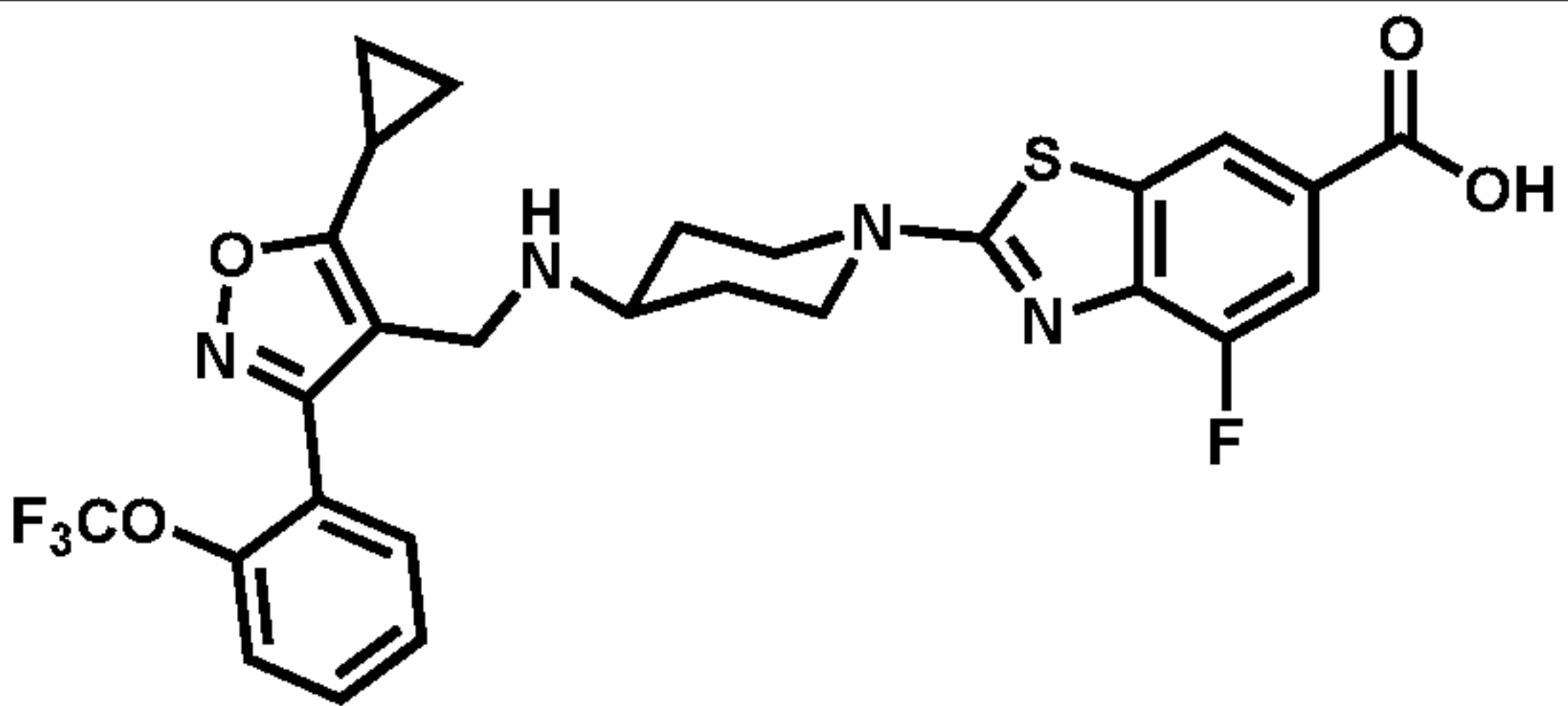
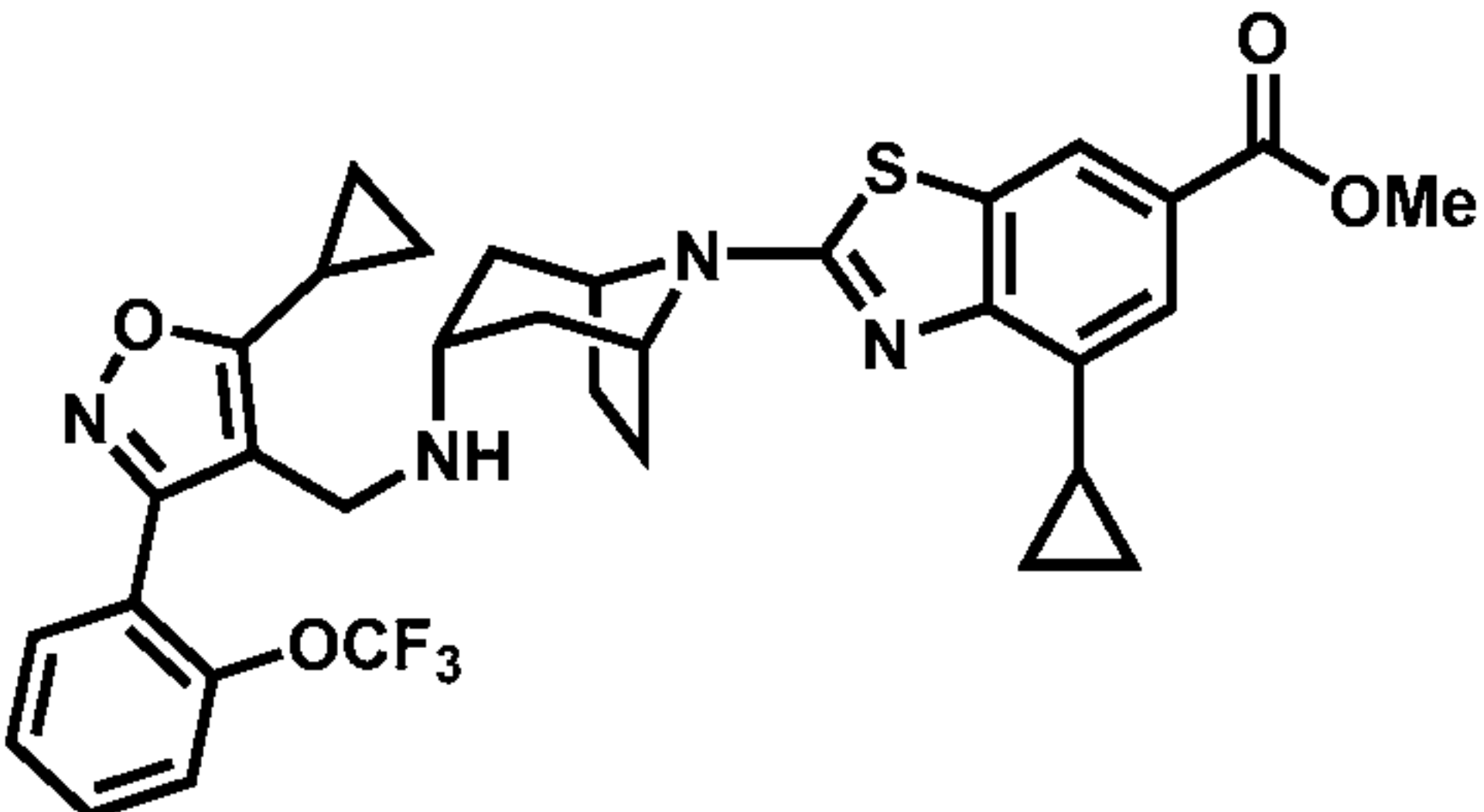
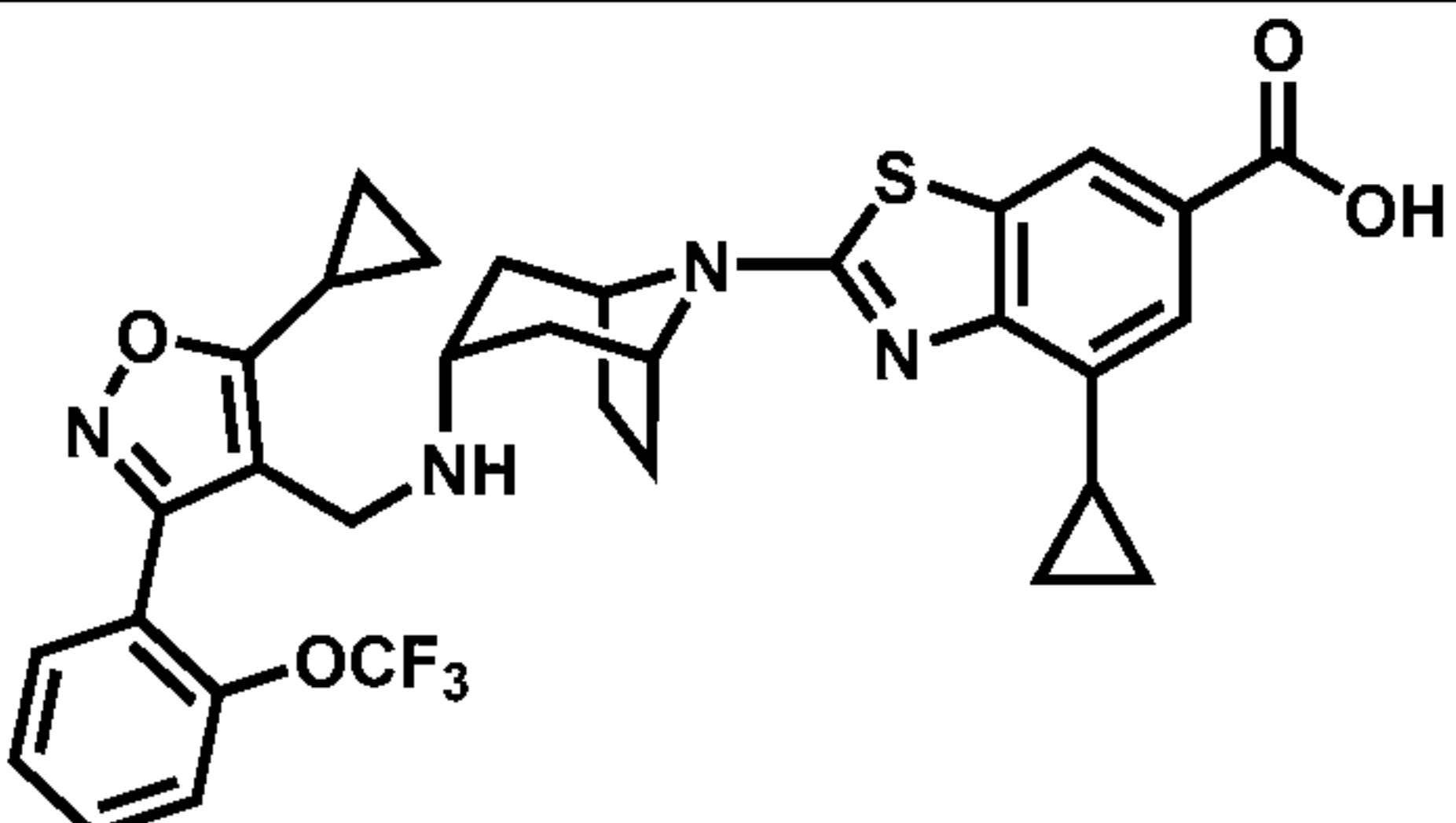
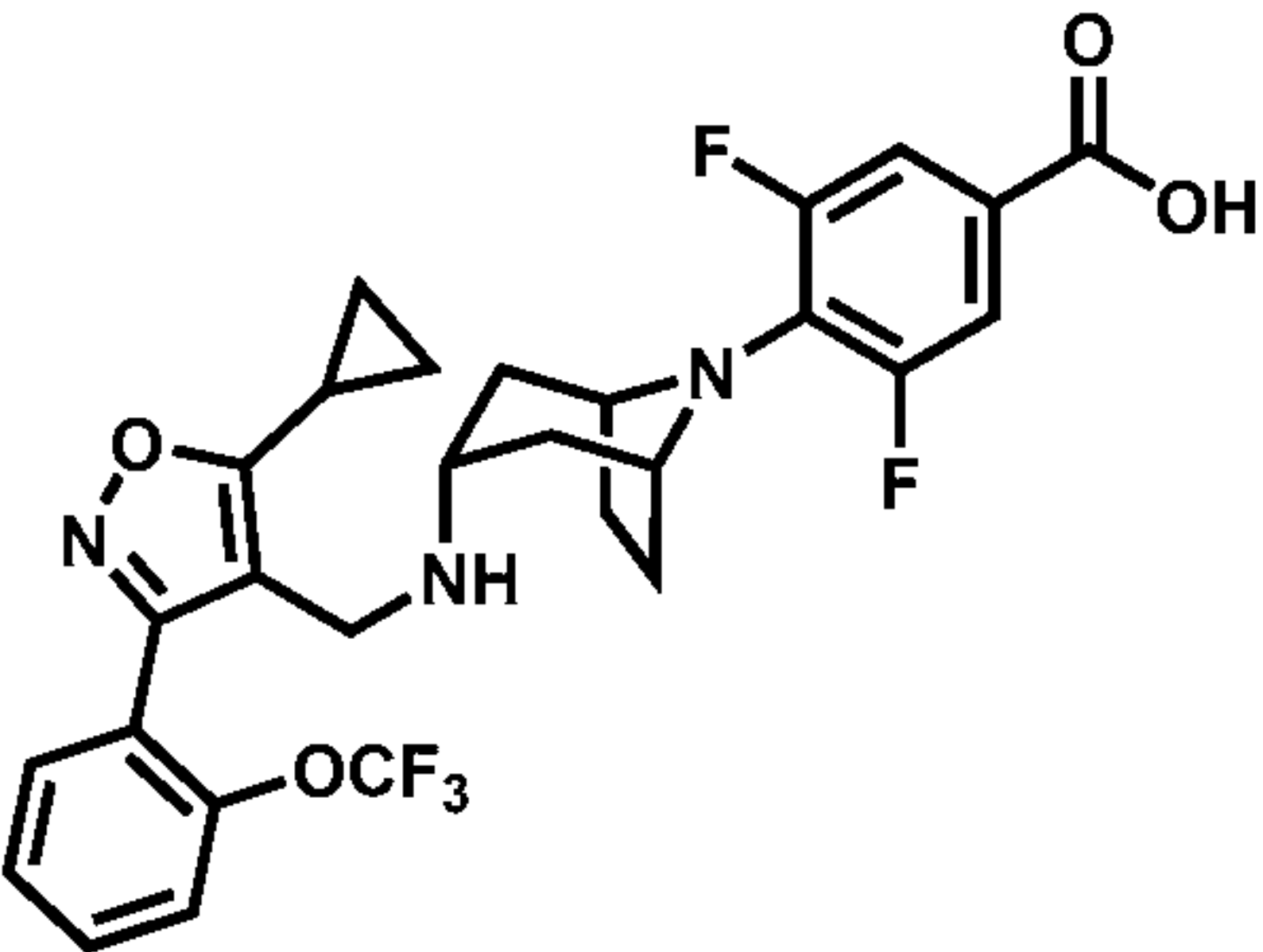
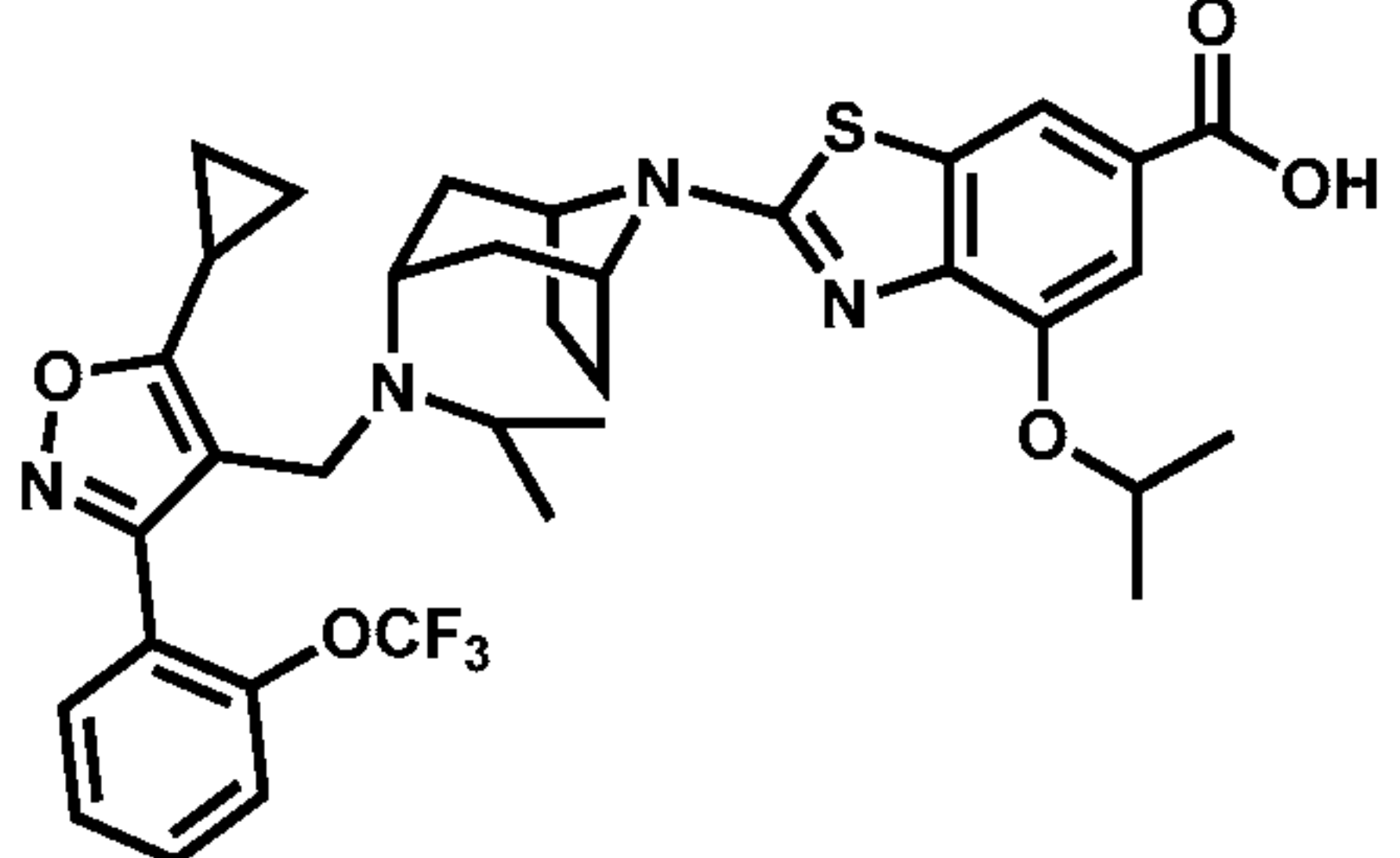
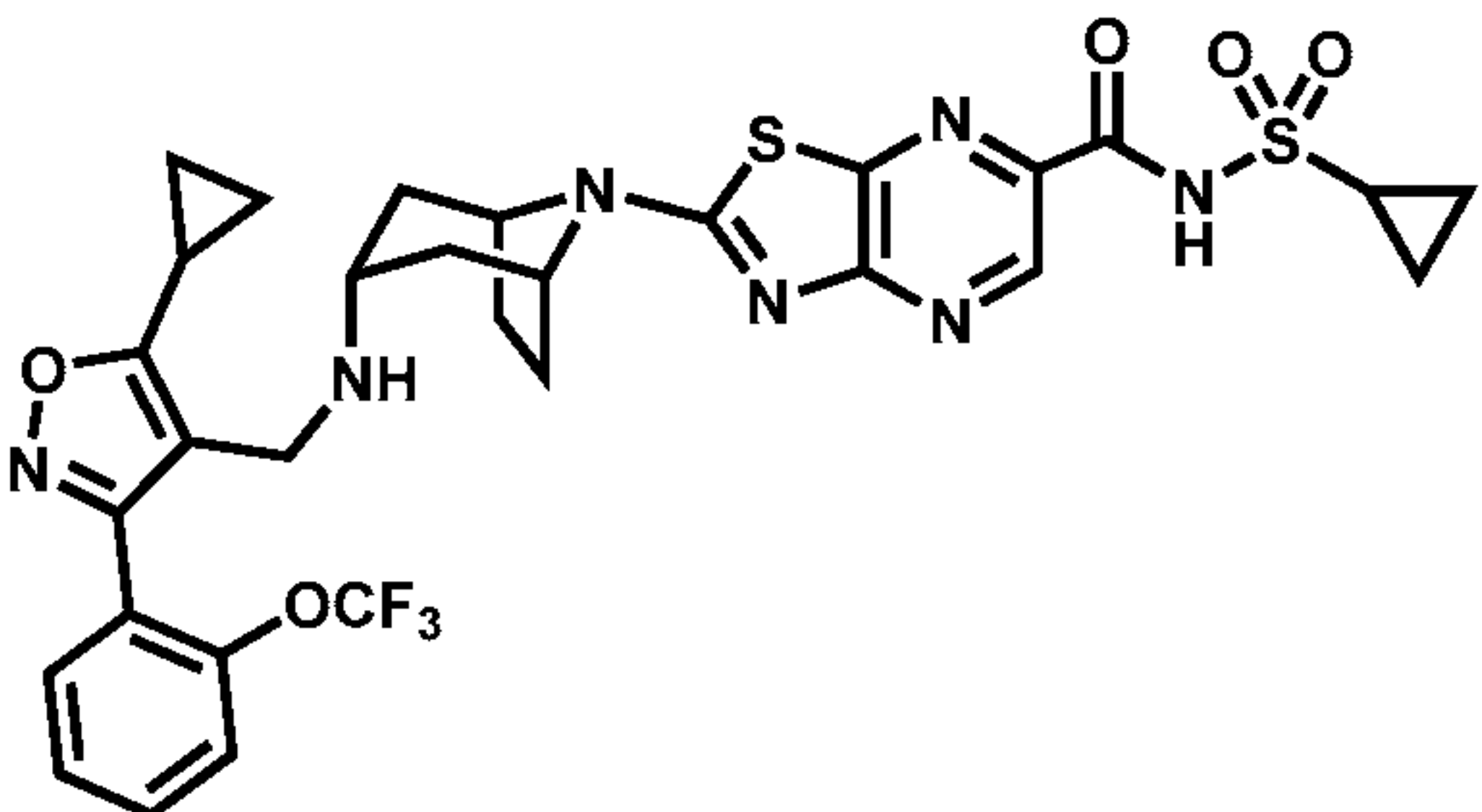
400-10		678.14 (M+H)
400-11		700.19 (M+H)
400-12		729.22 (M+H)
400-13		700.19 (M+H)
400-14		729.22 (M+H)
400-15		730.17 (M+H)

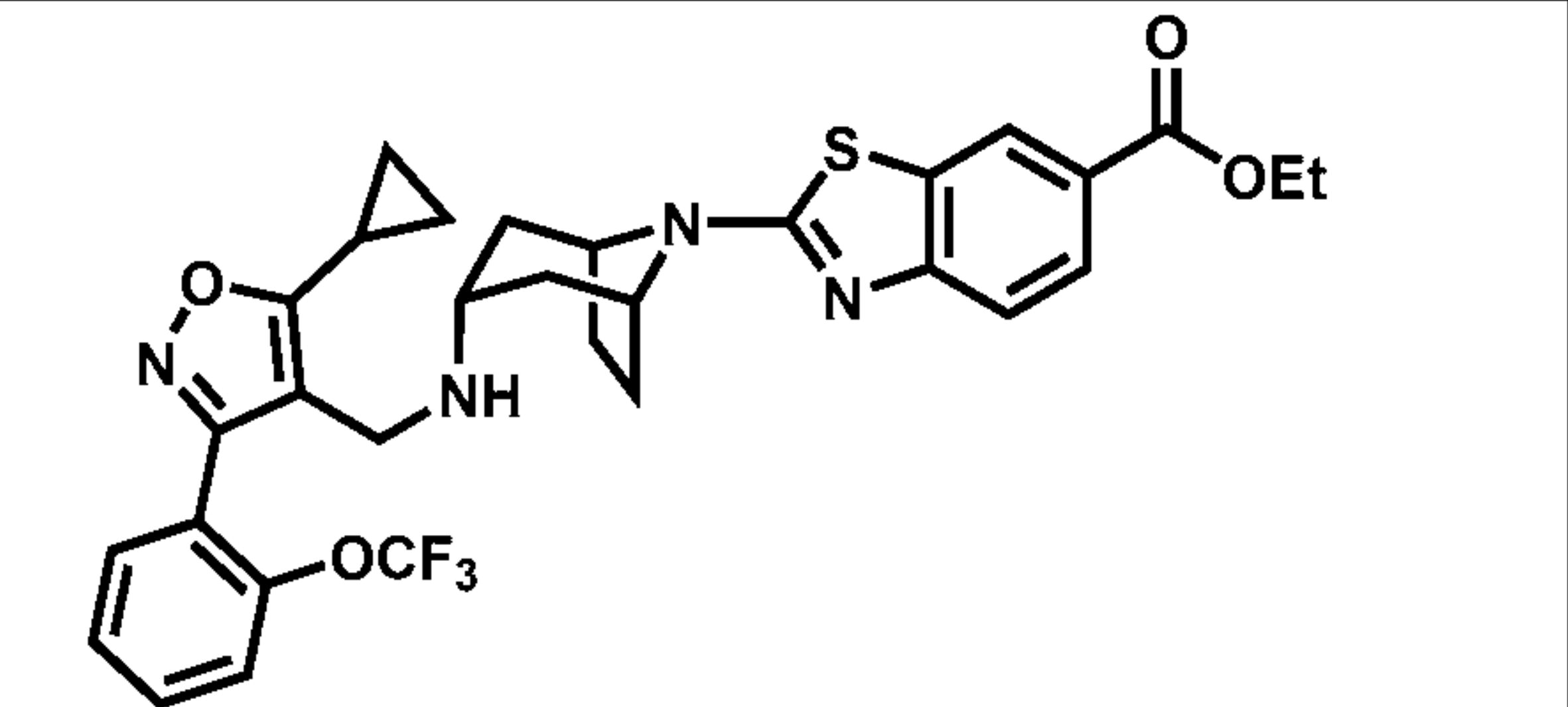
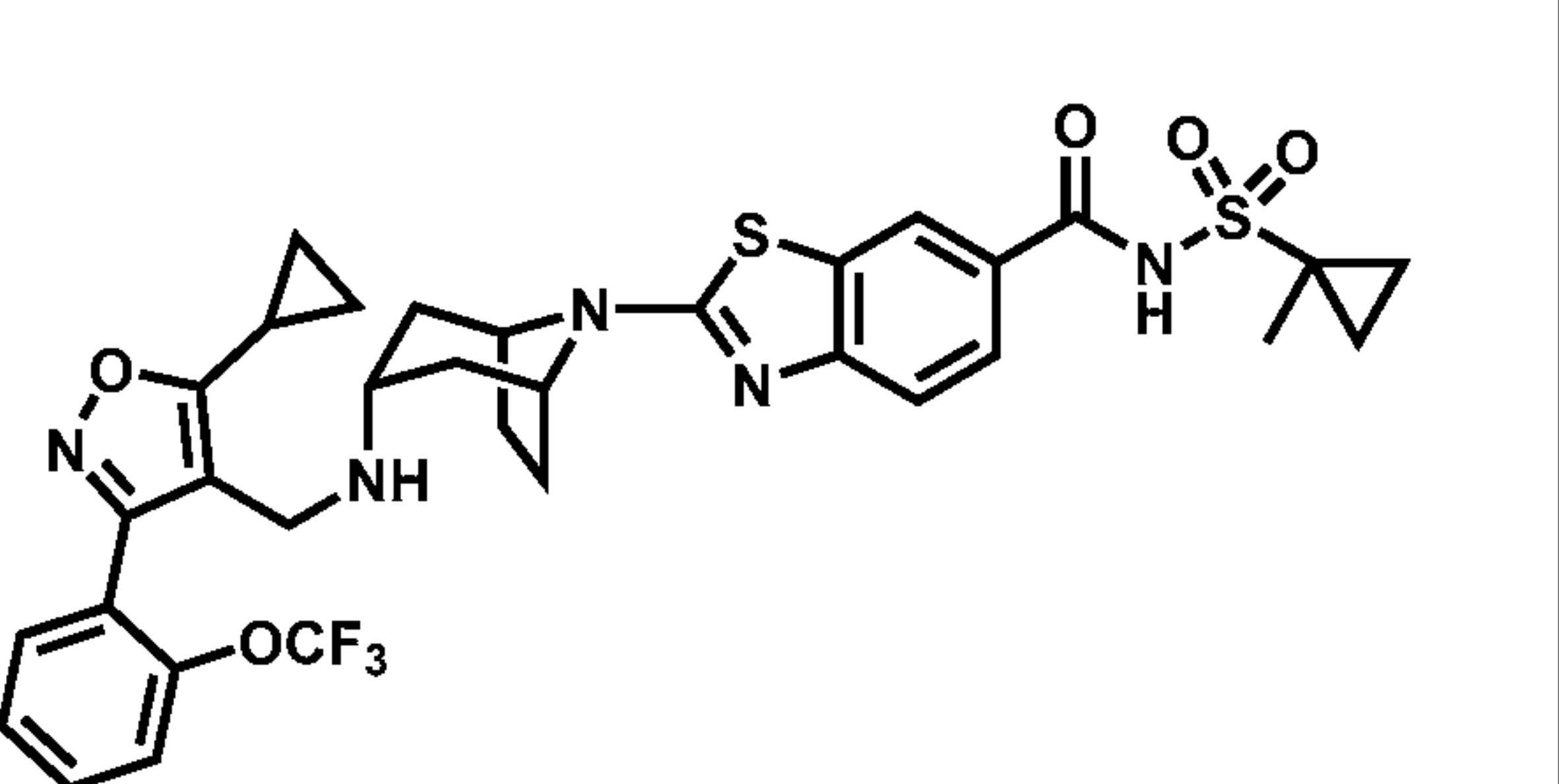
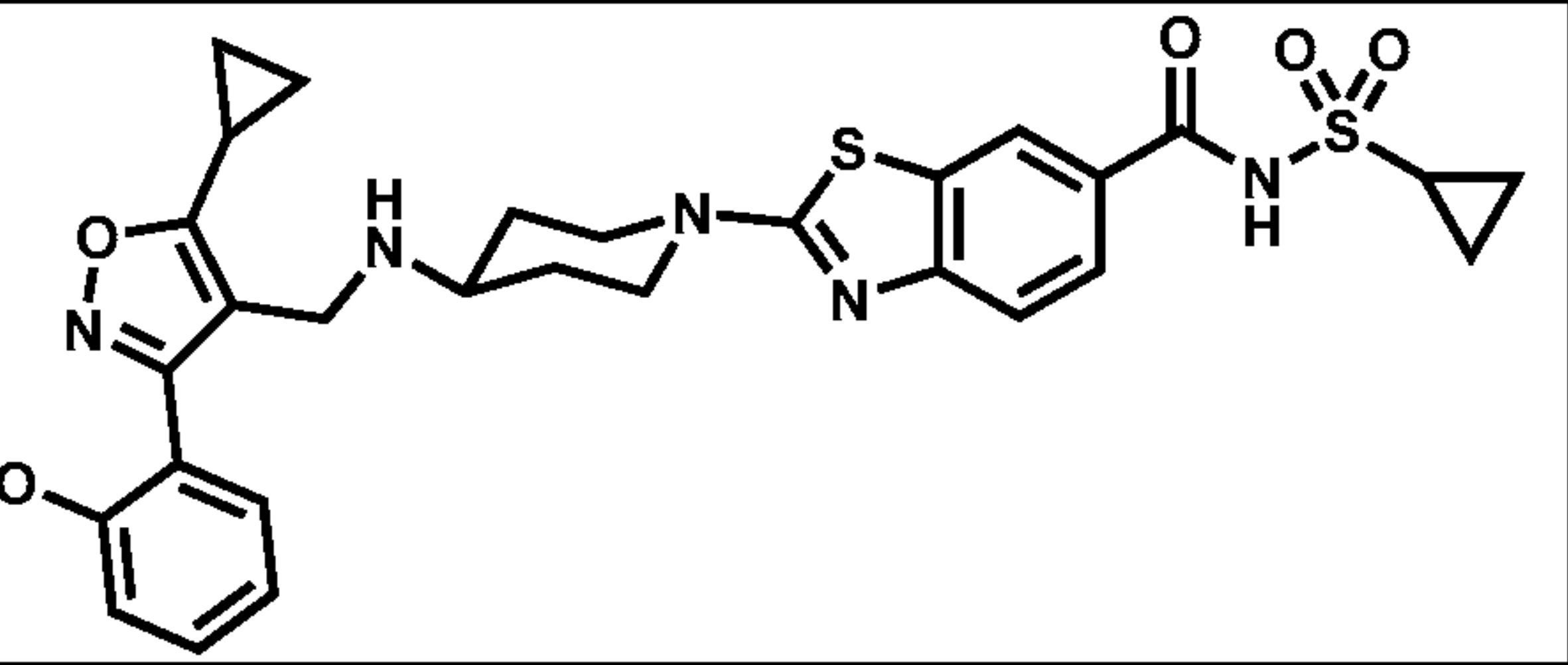
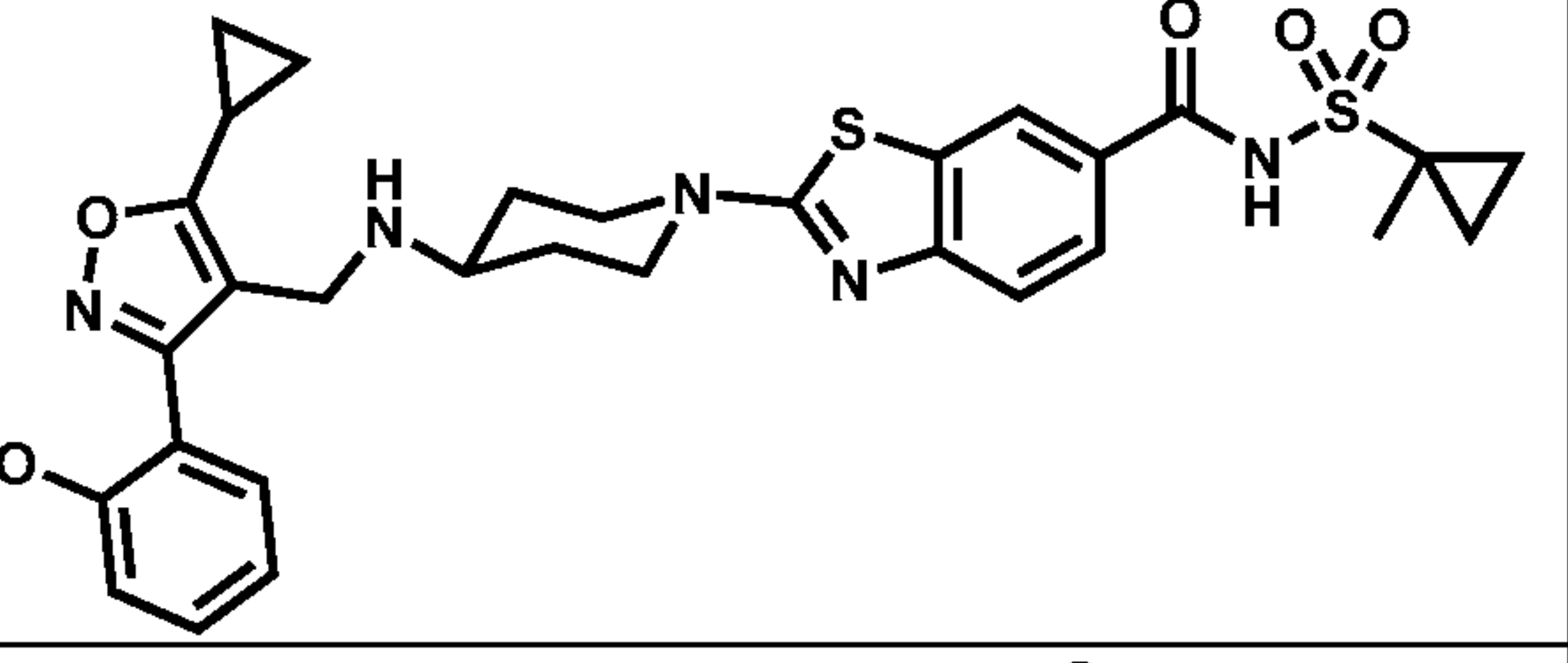
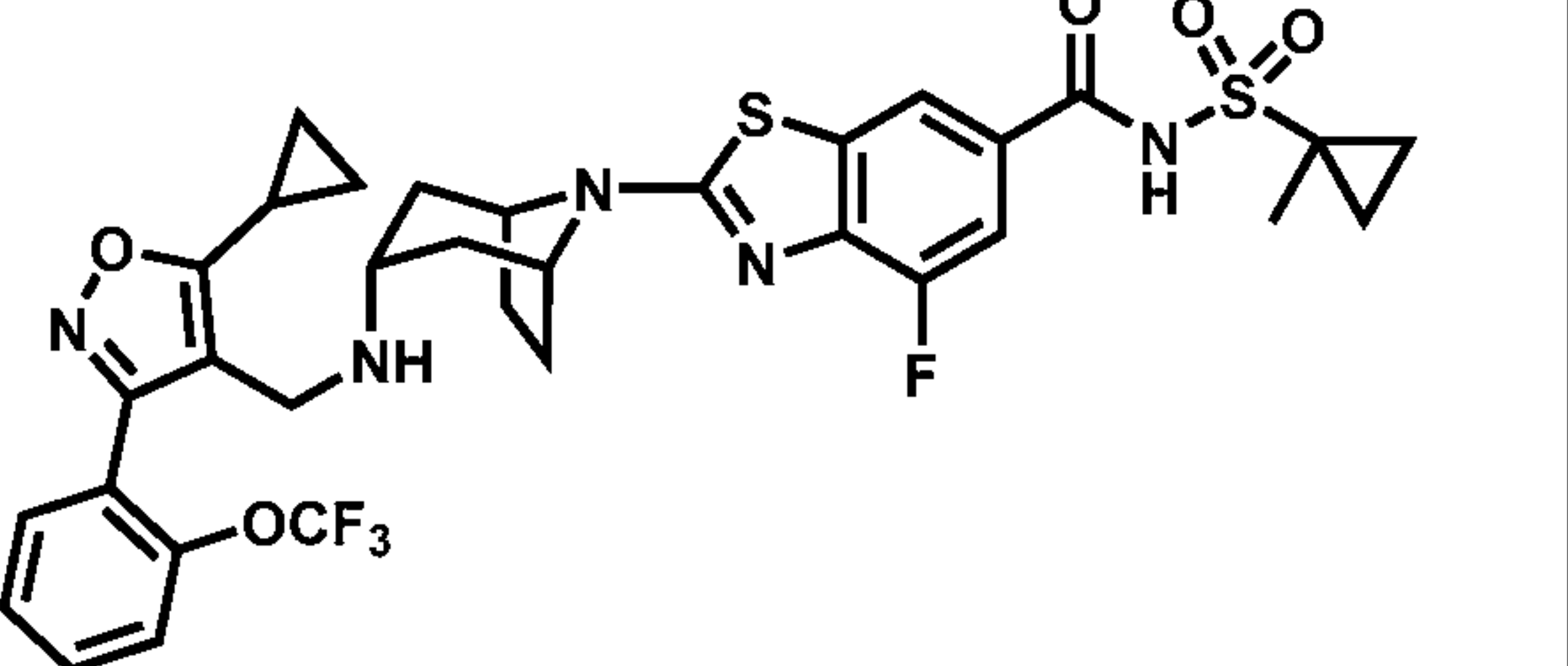
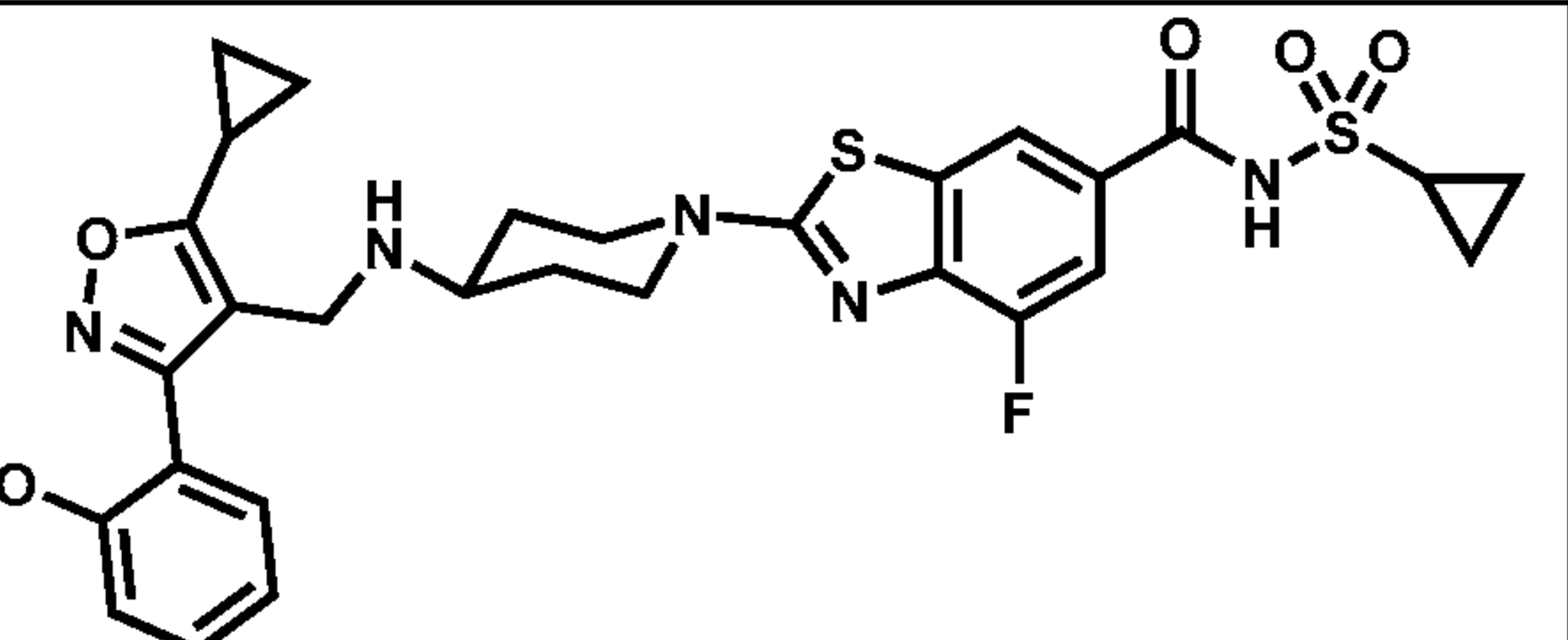
400-16		759.20 (M+H)
400-18		744.19 (M+H)
400-20		773.21 (M+H)
400-22		704.14 (M+H)
400-24		733.16 (M+H)
400-25		674.13 (M+H)

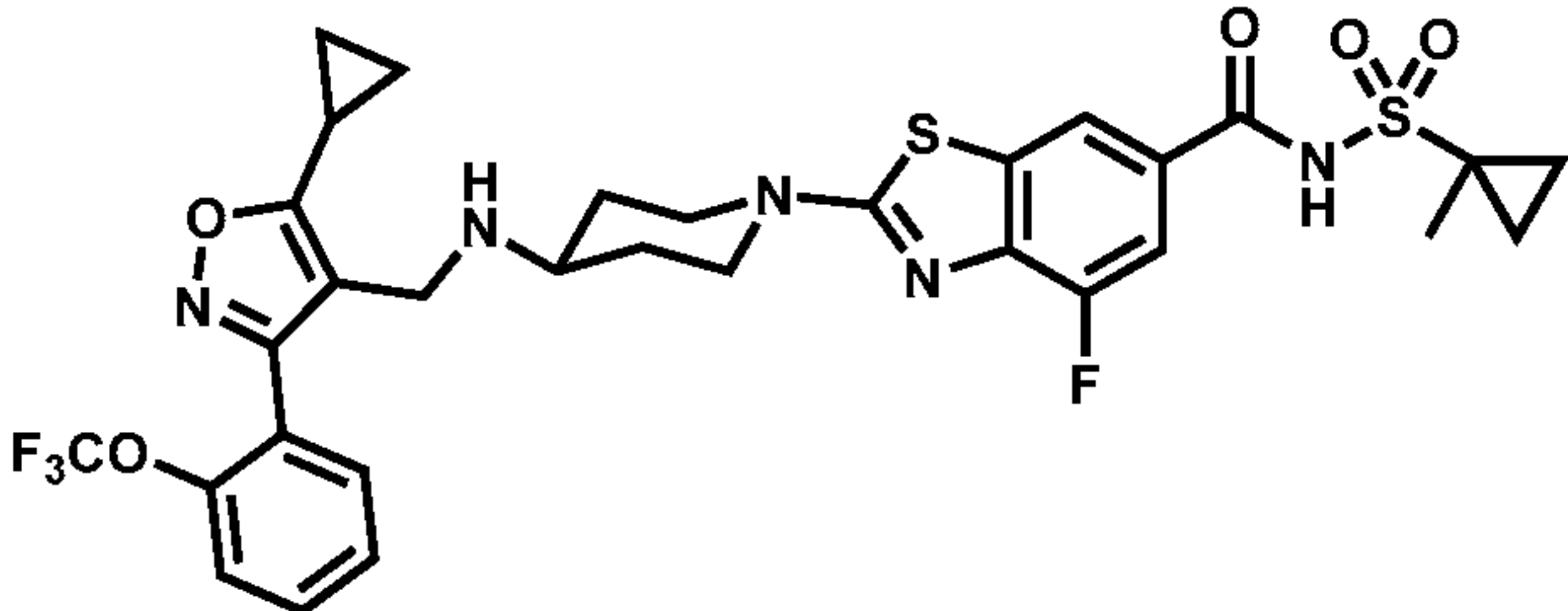
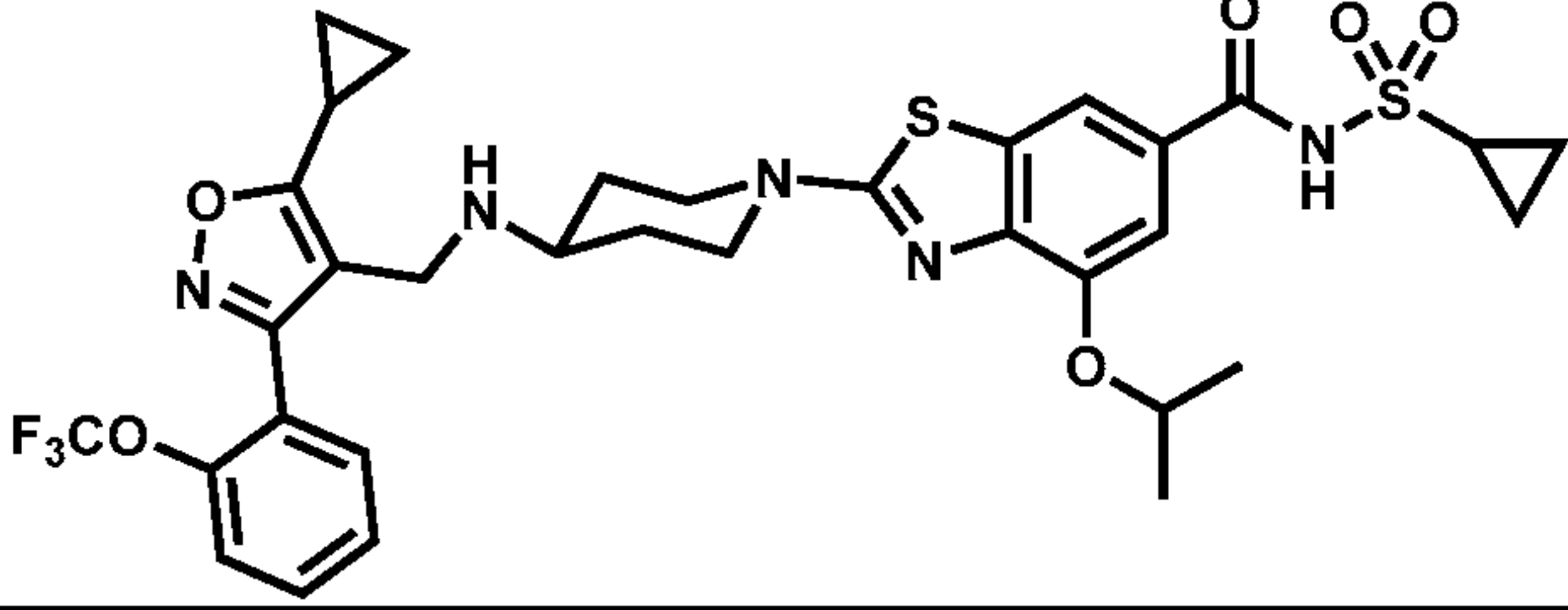
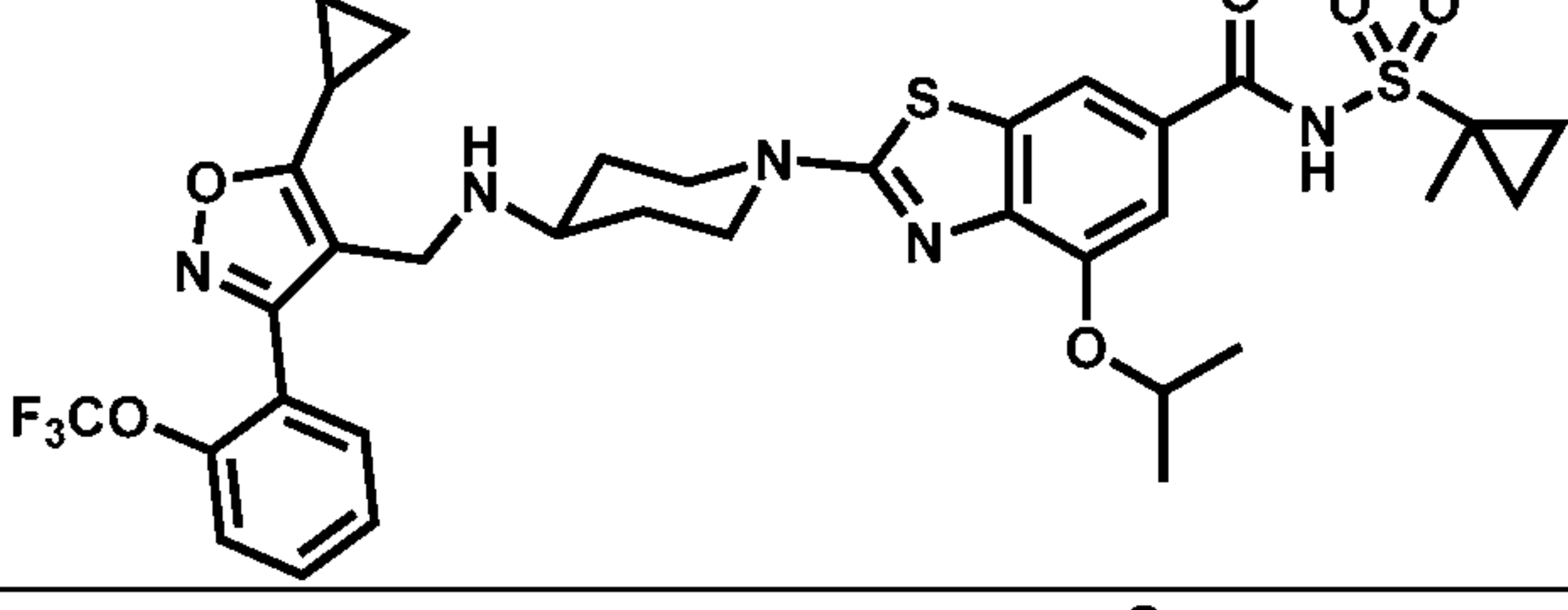
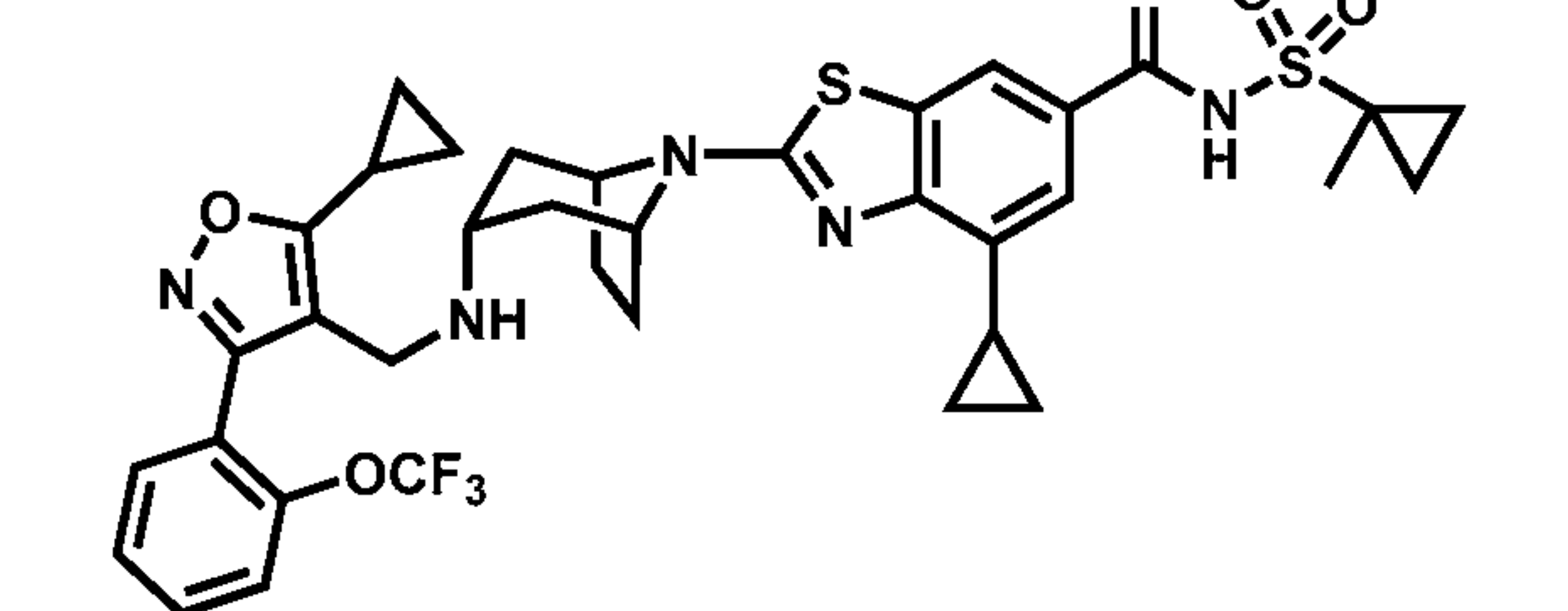
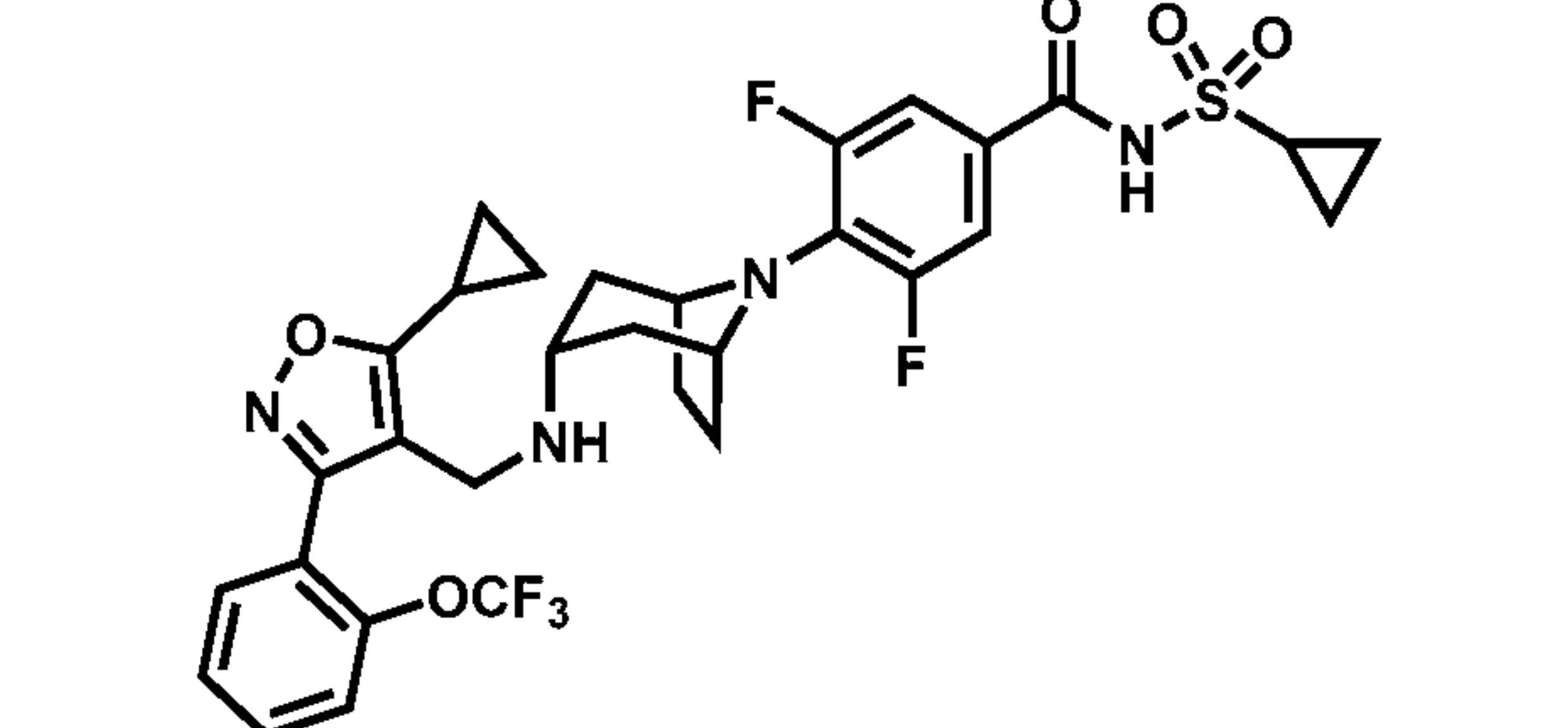
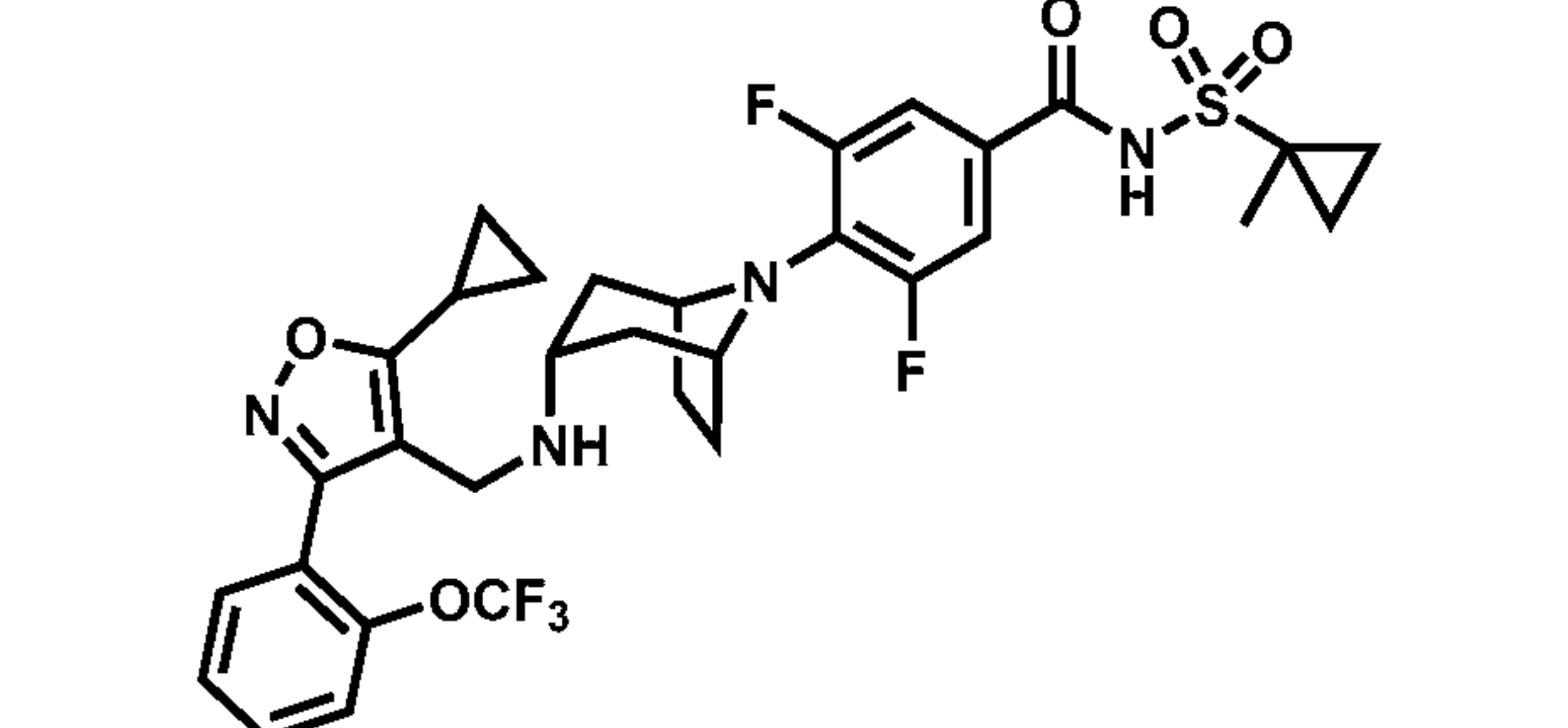
400-26		688.14 (M+H)
400-29		700.16 (M+H)
400-32		762.18 (M+H)
400-33		736.16 (M+H)
400-35		726.19 (M+H)
400-37		616.16 (M+H)

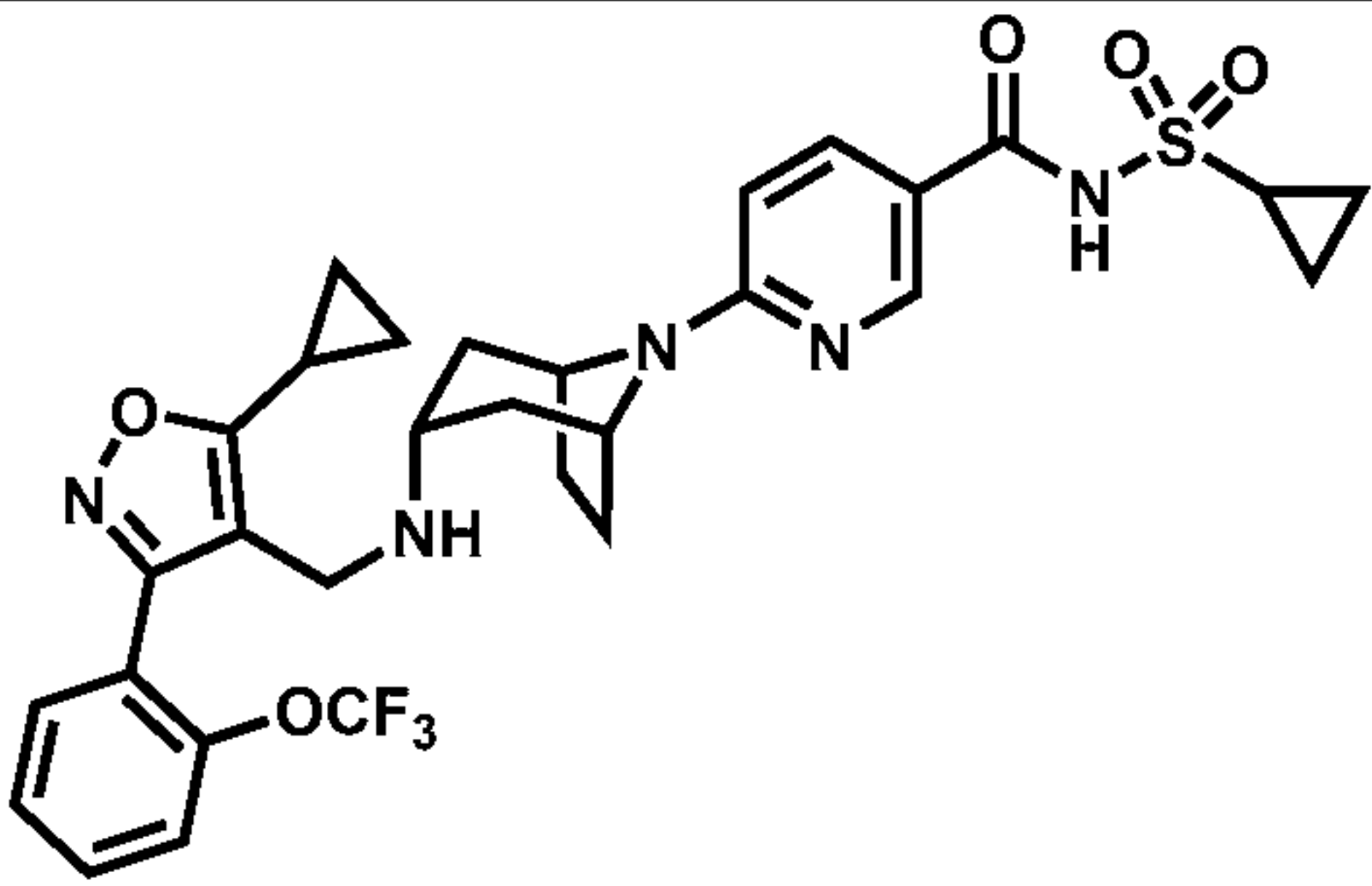
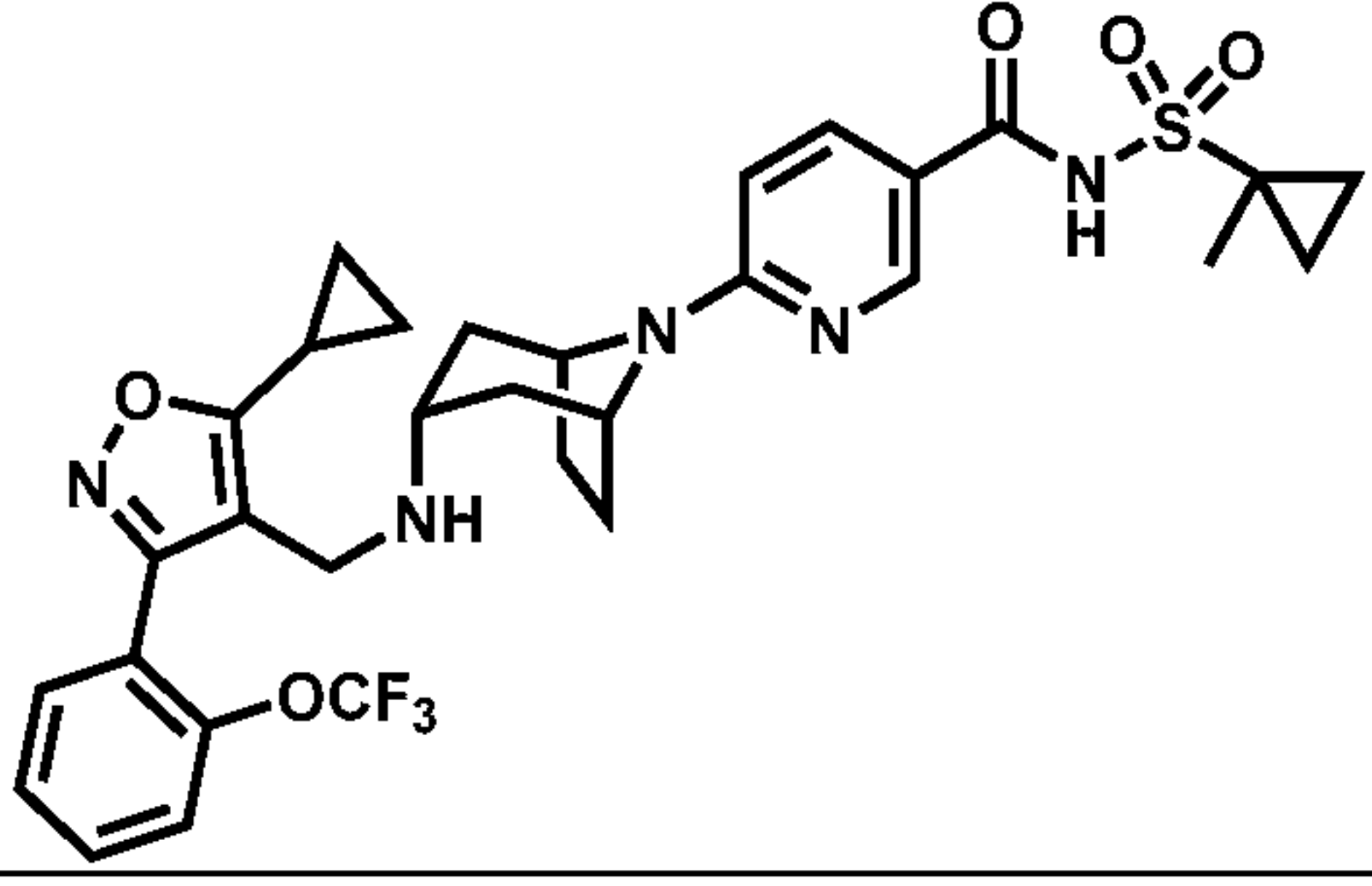
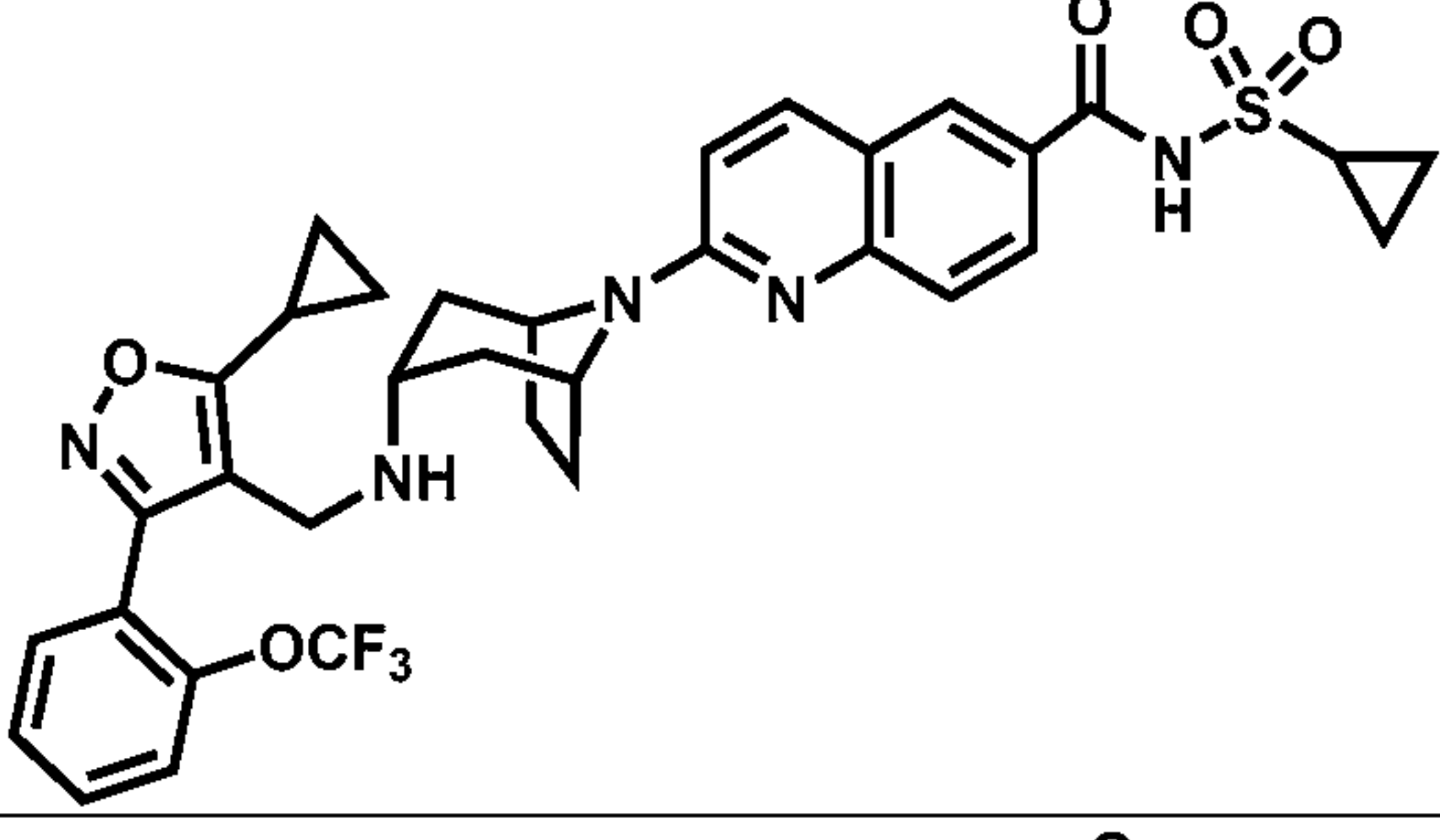
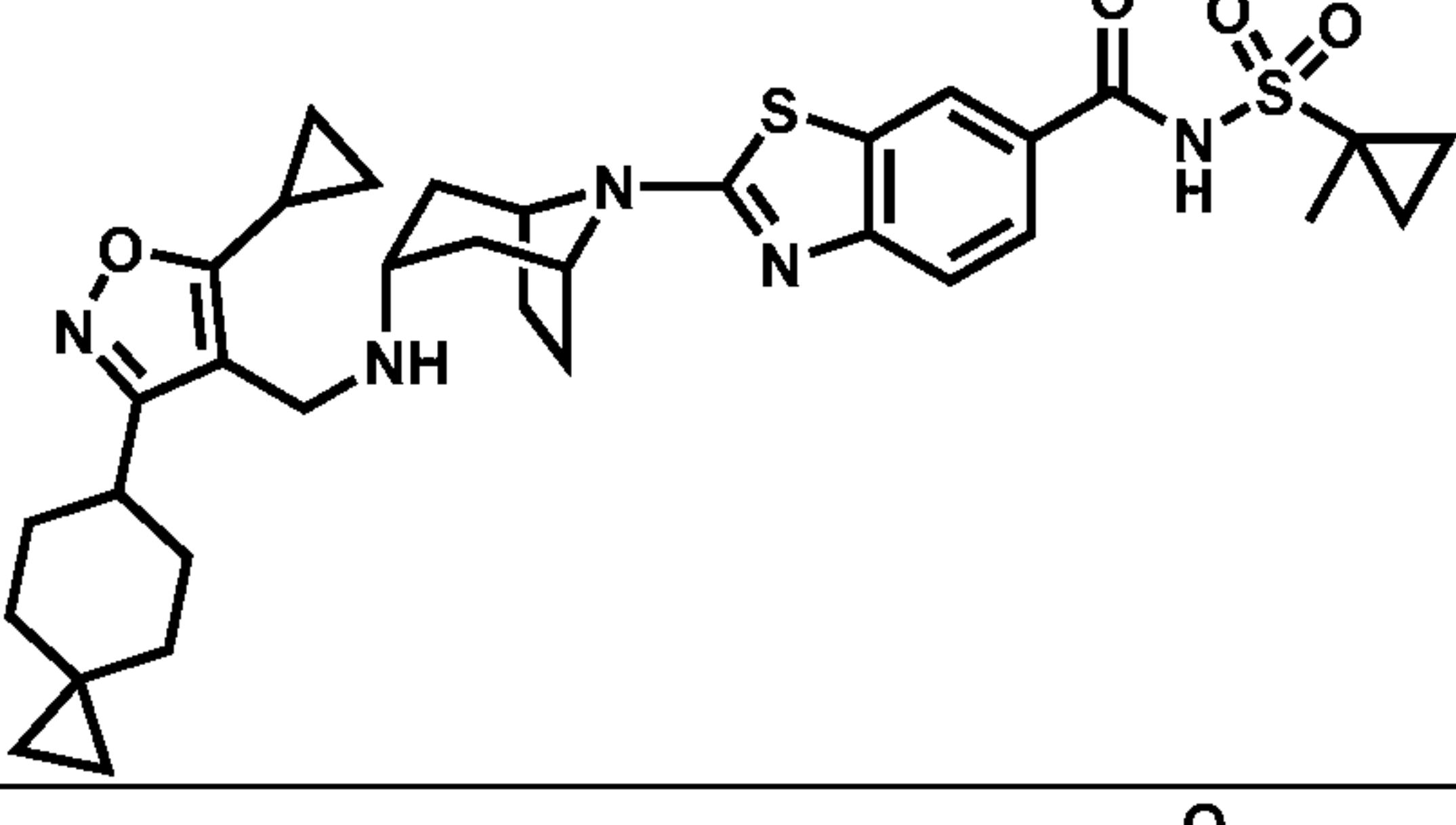
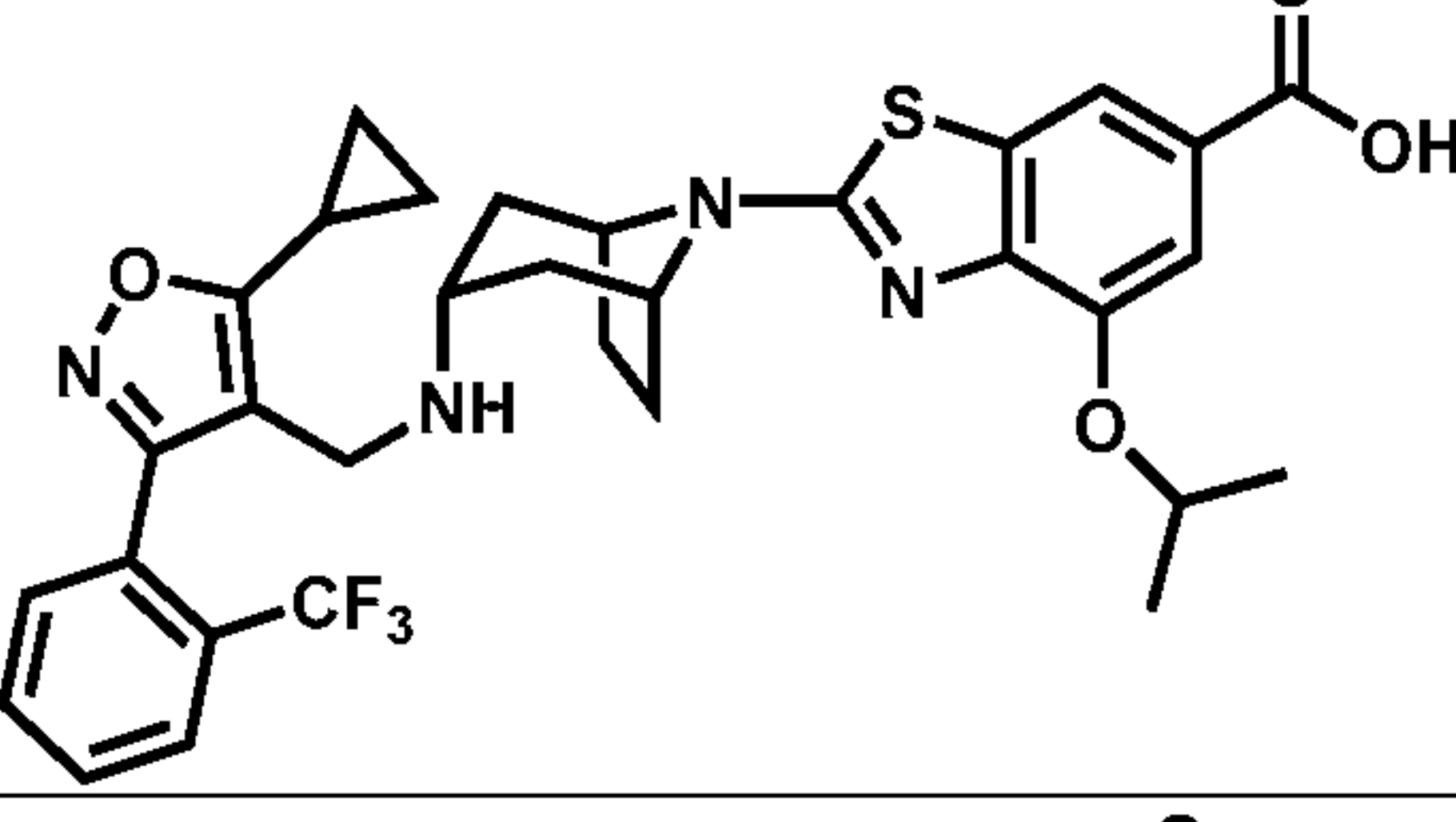
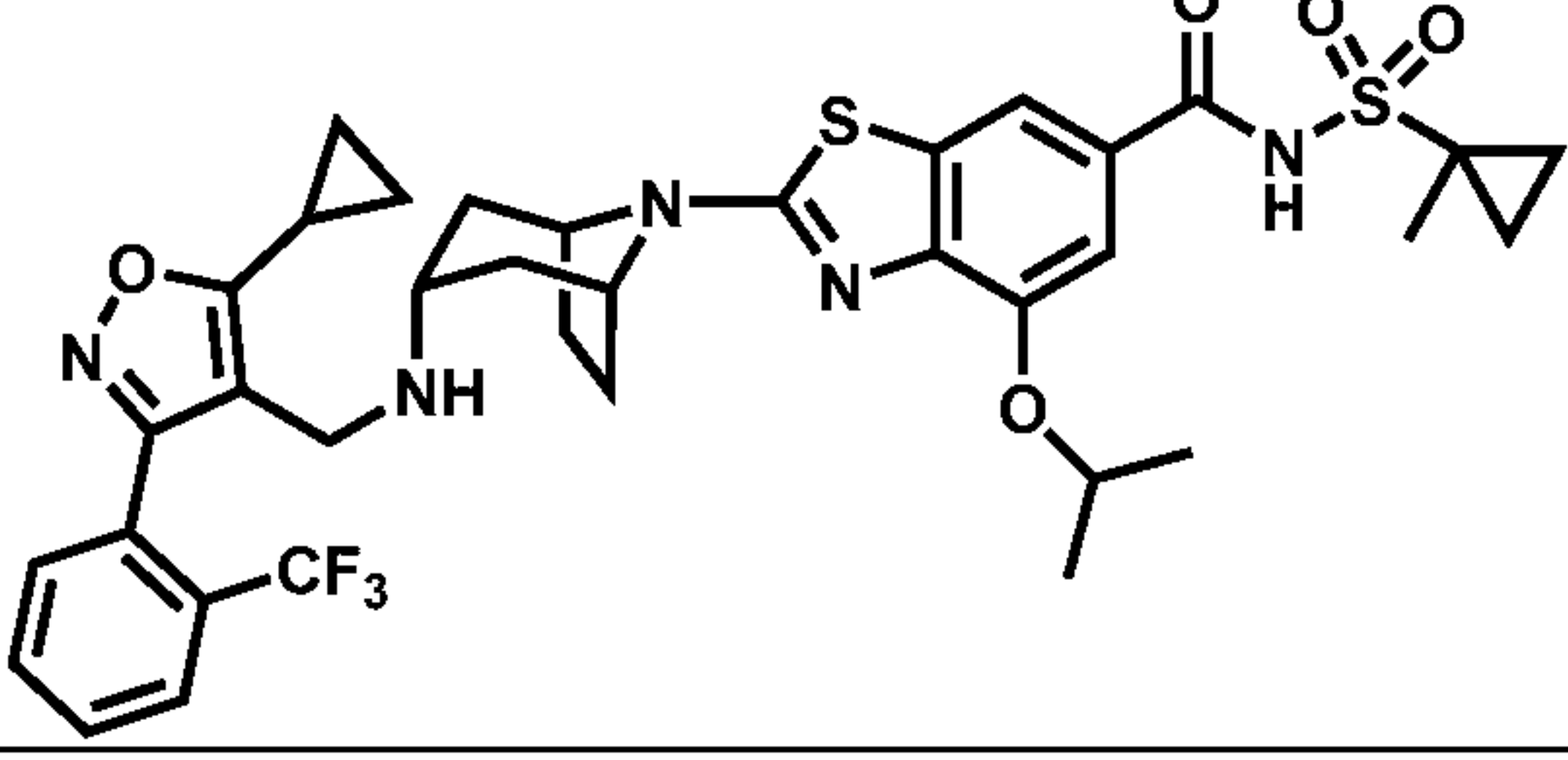
402		585.18 (M+H)
403		617.19 (M+H)
404		603.17 (M+H)
413		657.24 (M+H)
414		643.22 (M+H)
510		587.17 (M+H)

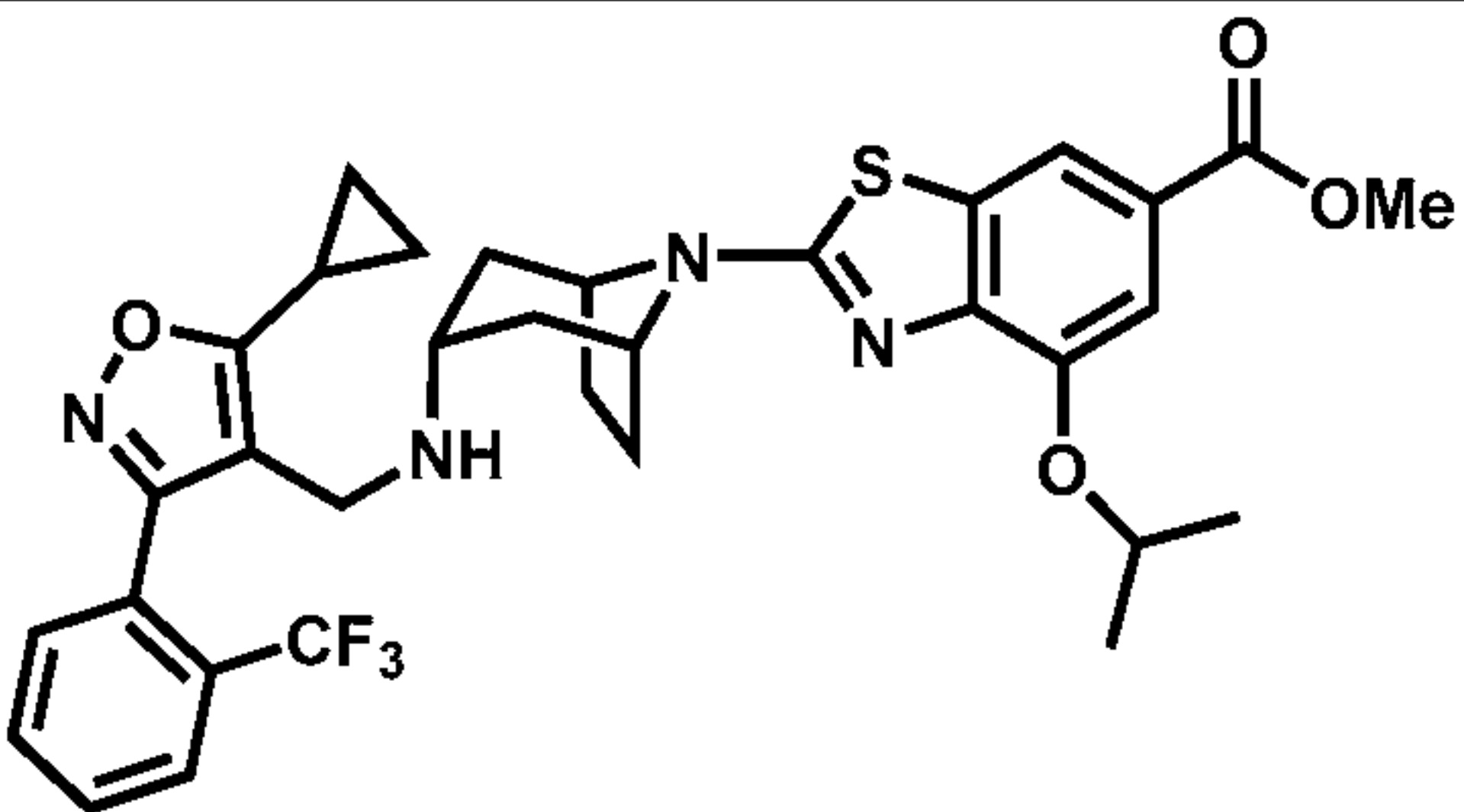
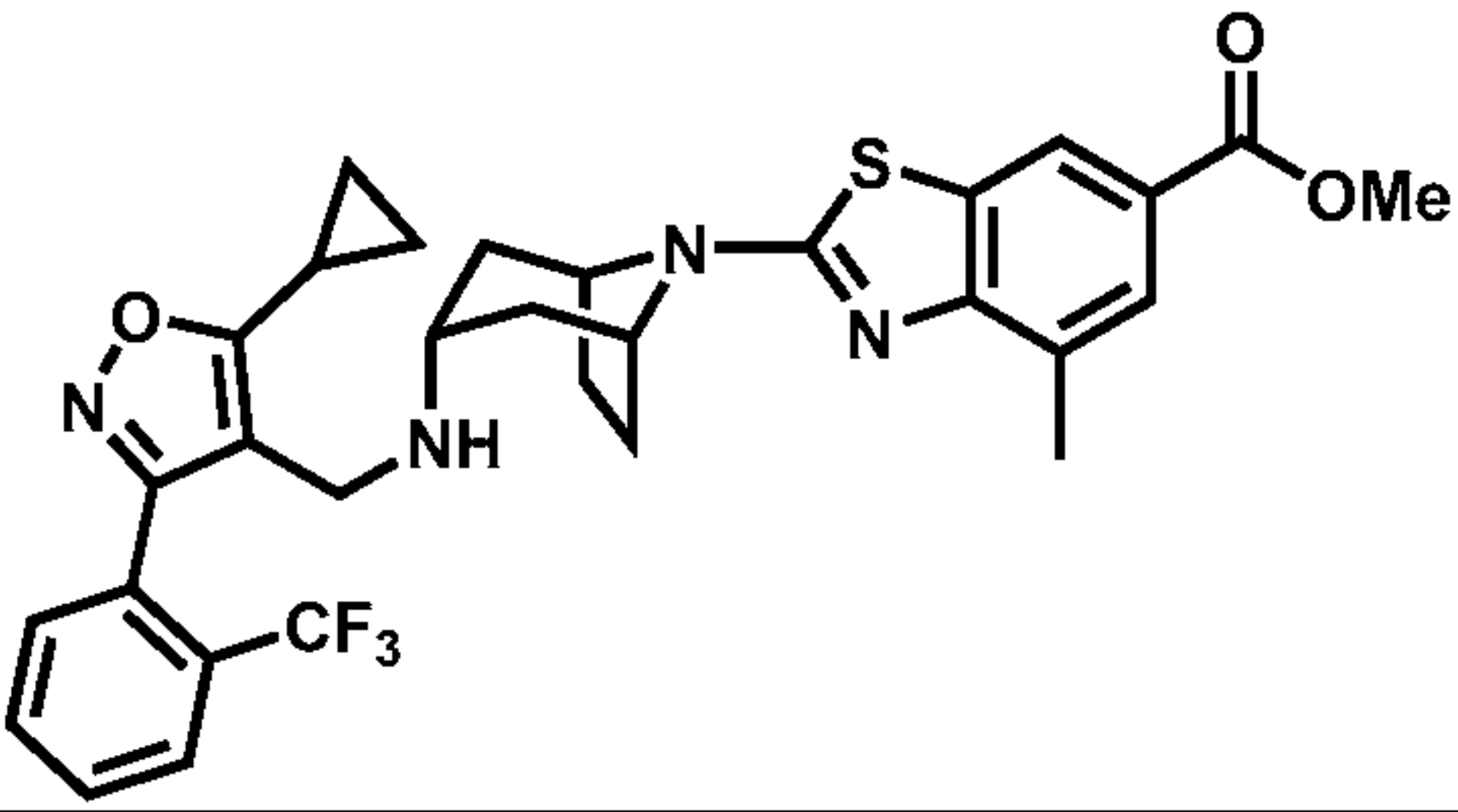
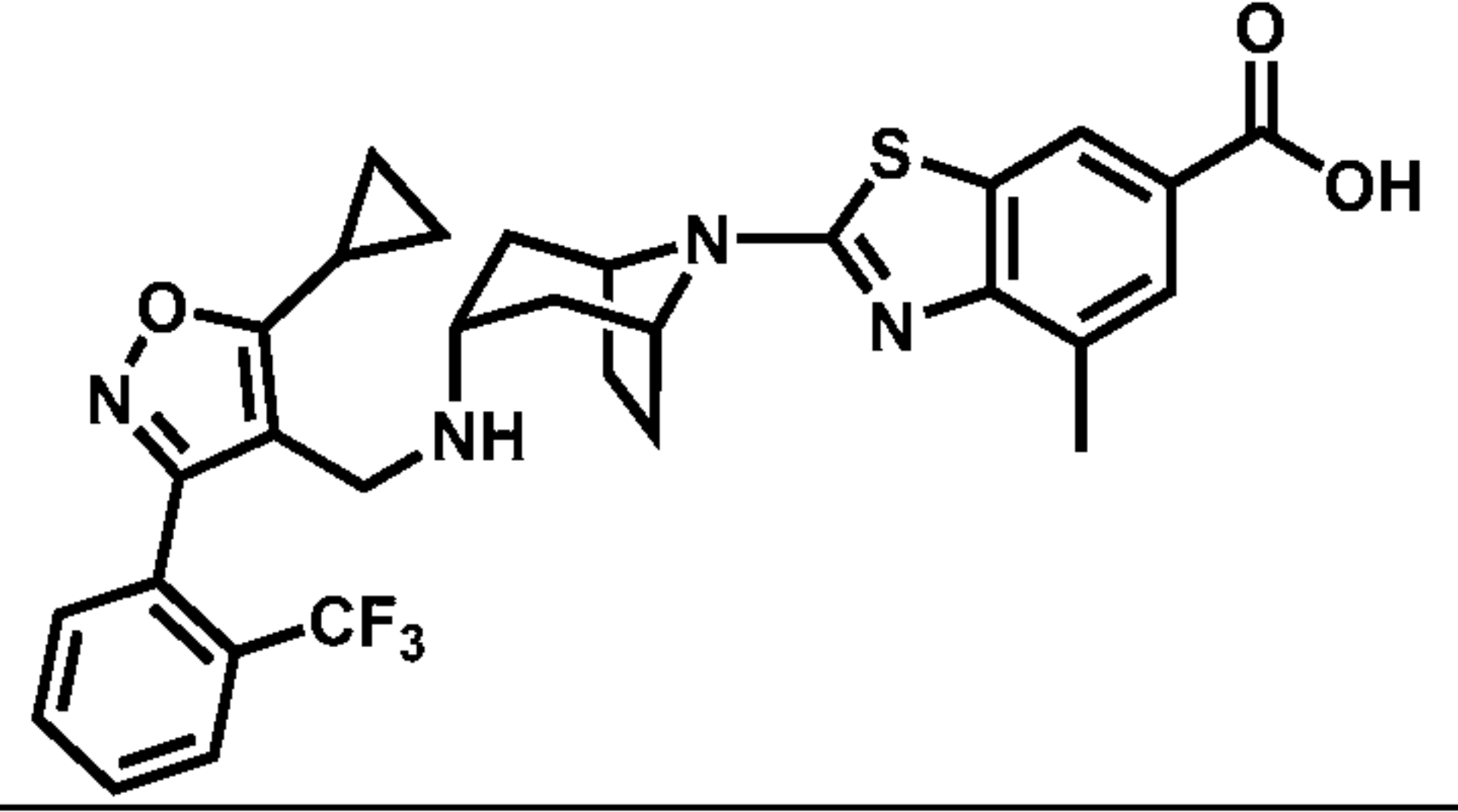
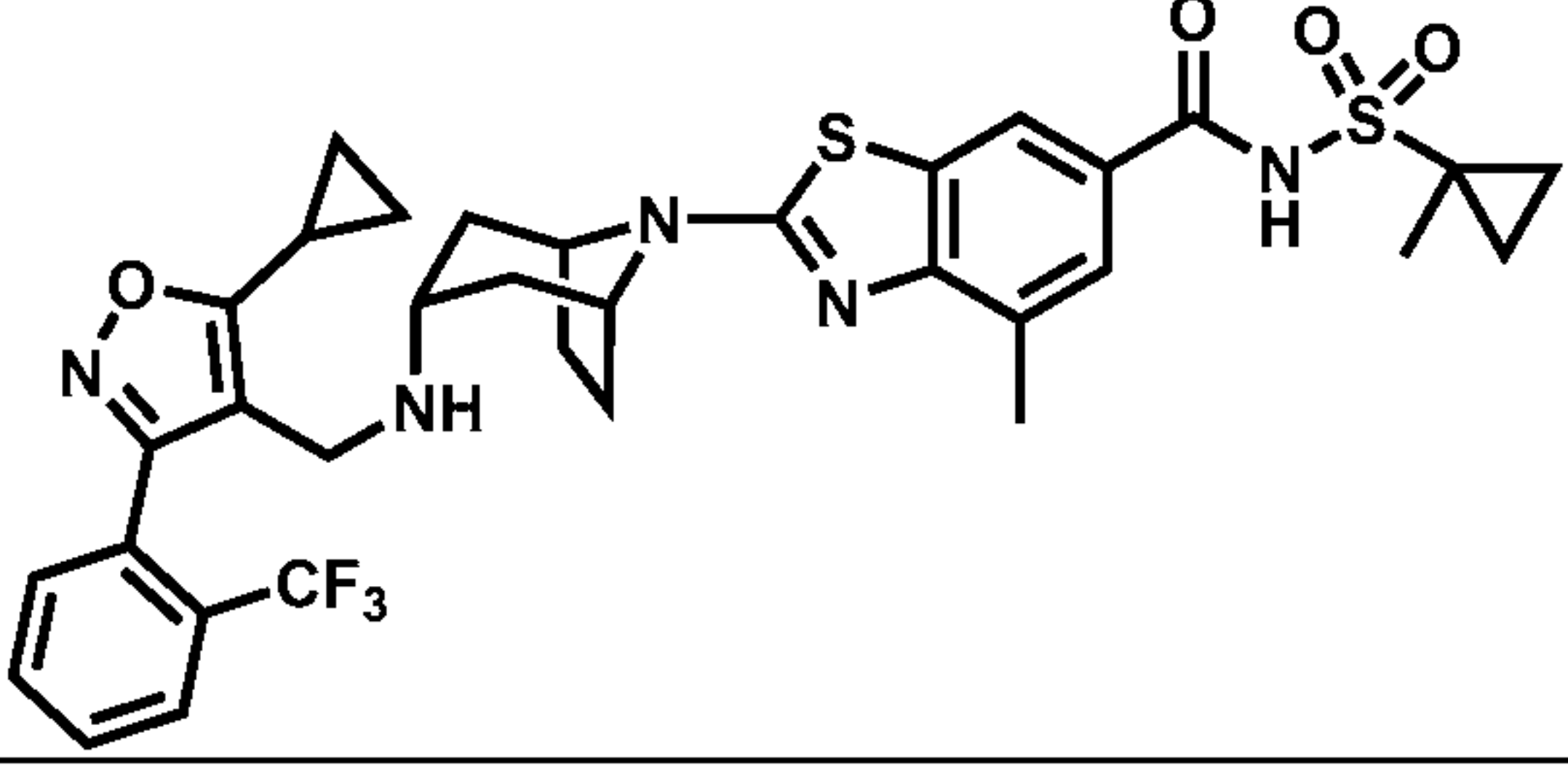
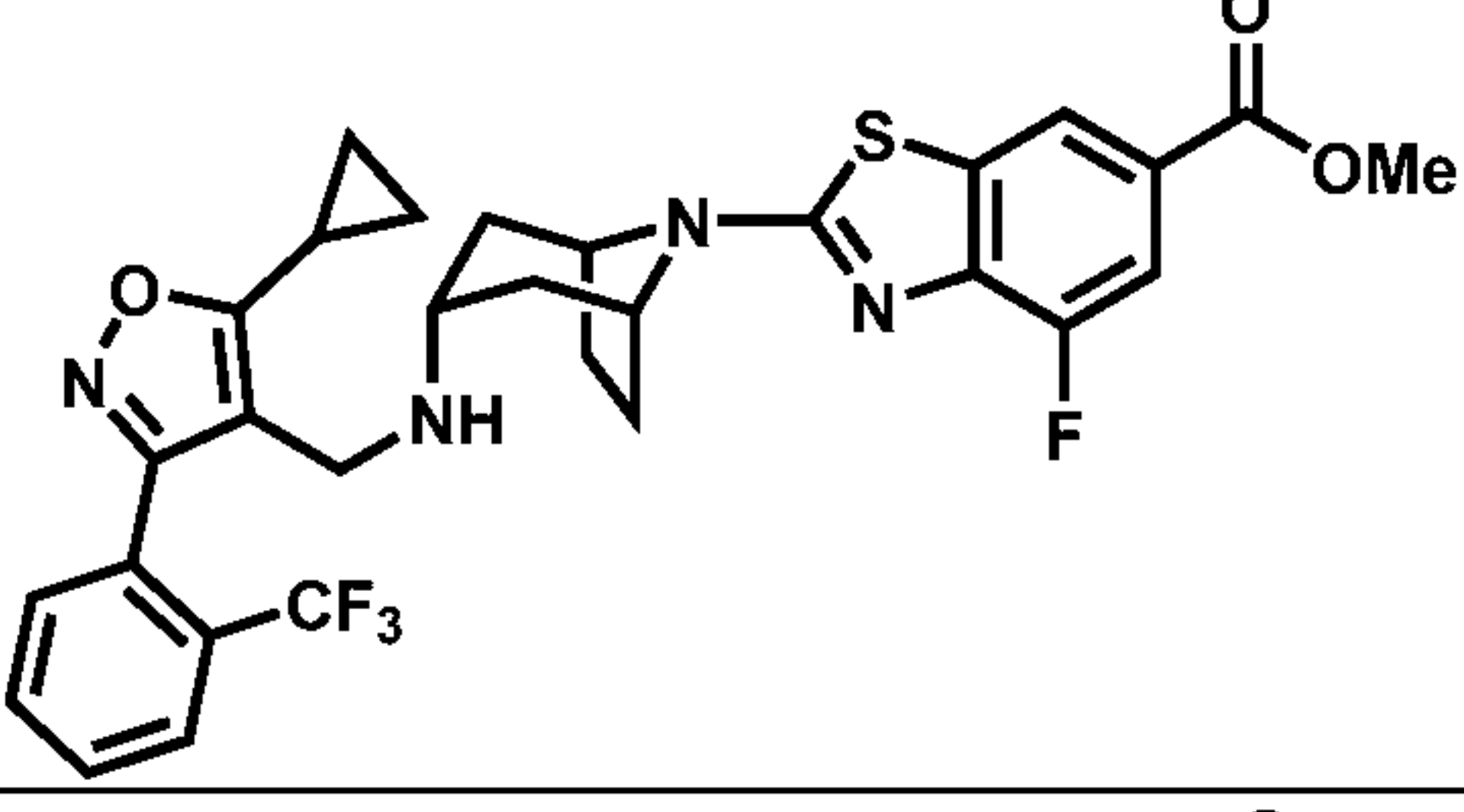
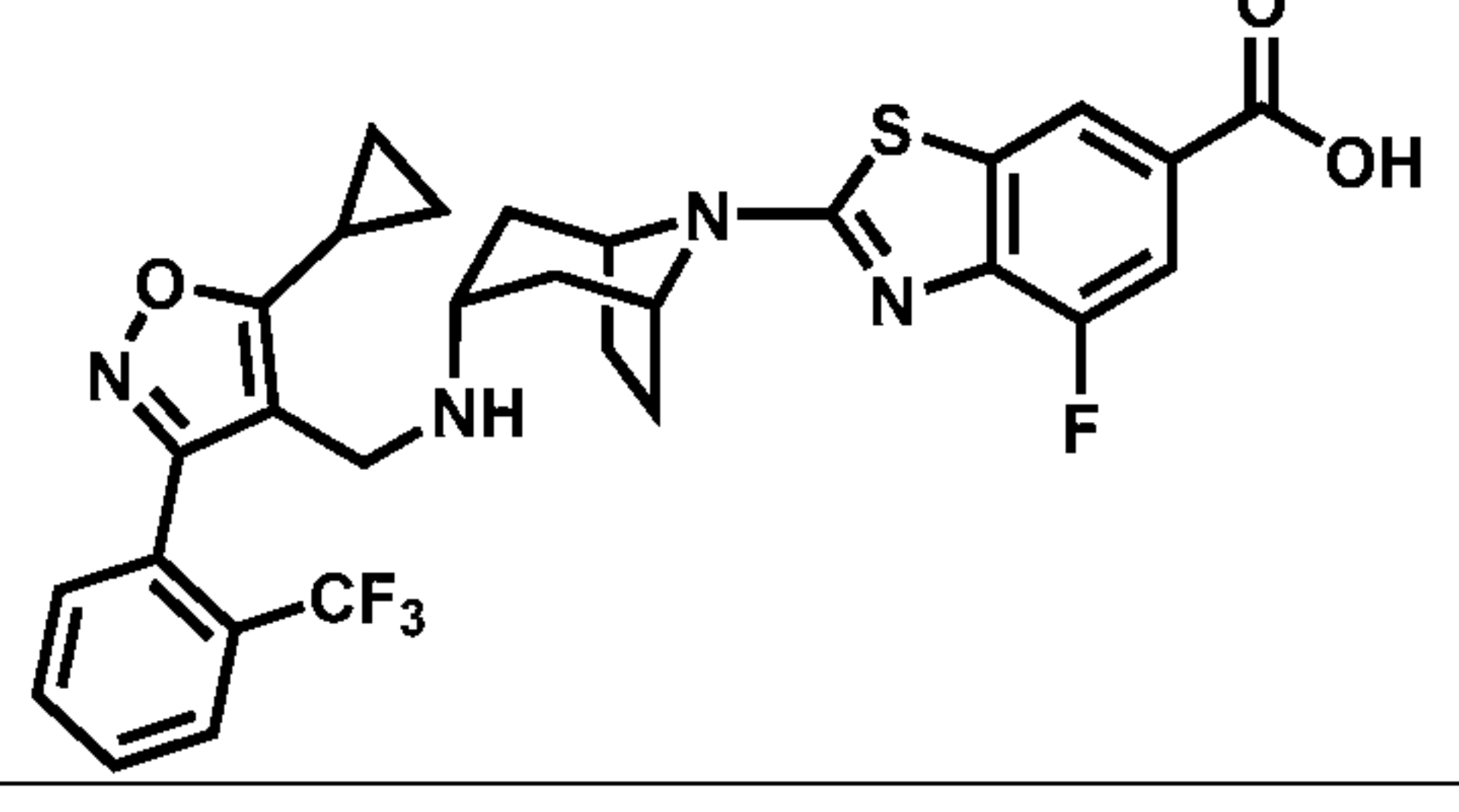
514		579.22 (M+H)
597		528.52 (M+H)
638		559.16 (M+H)
639		631.23 (M+H)
640		617.21 (M+H)
641		591.17 (M+H)

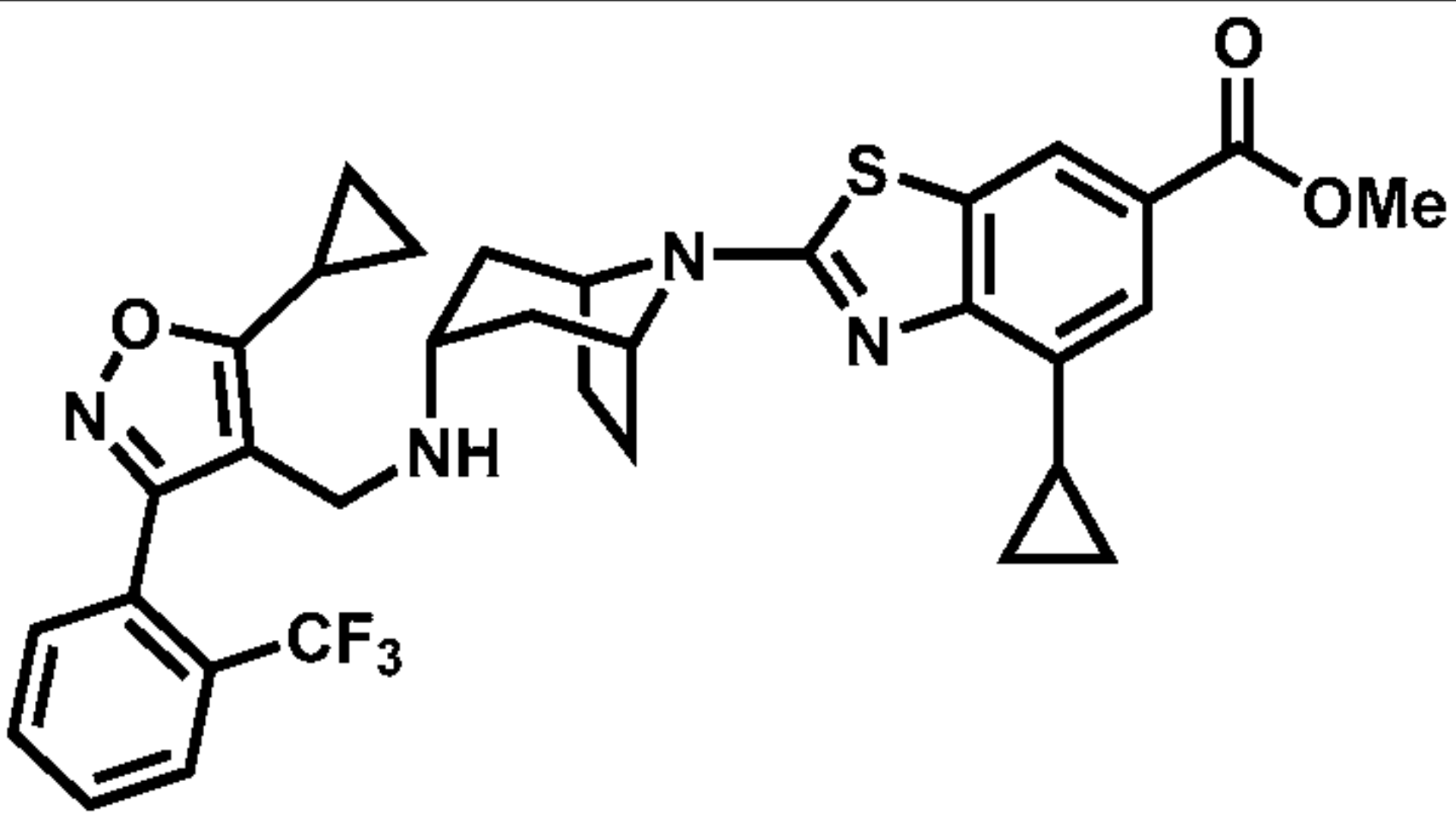
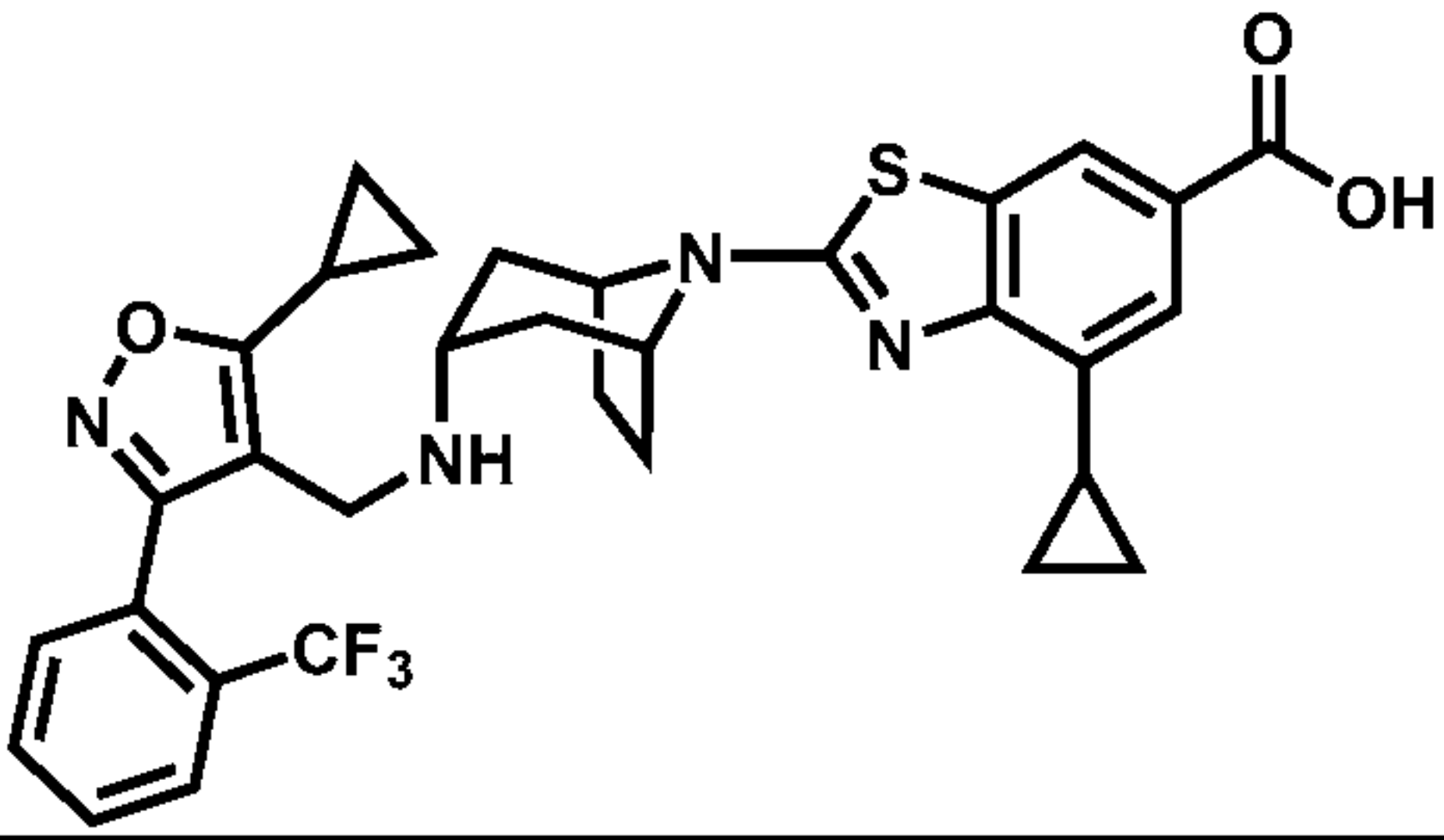
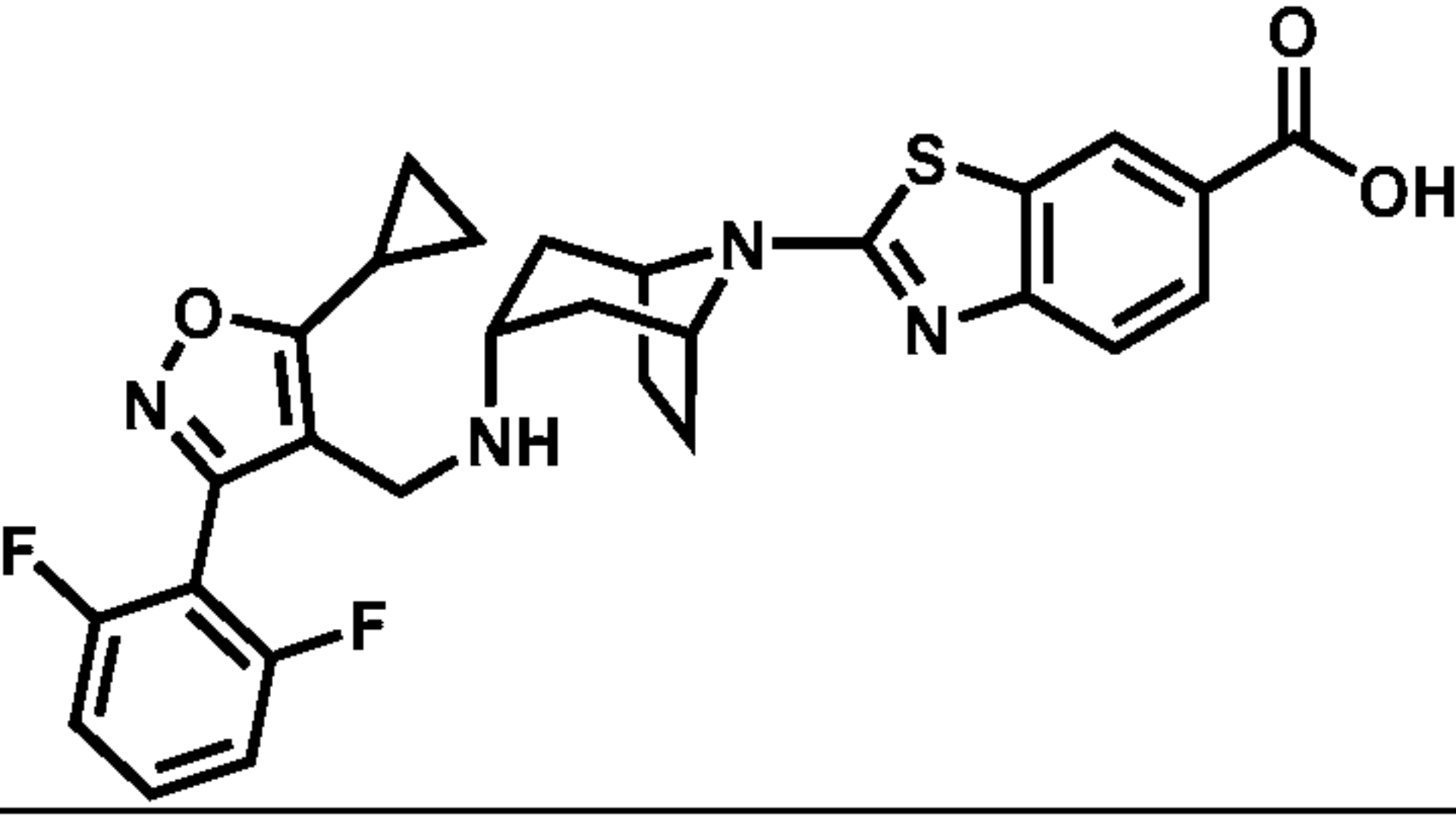
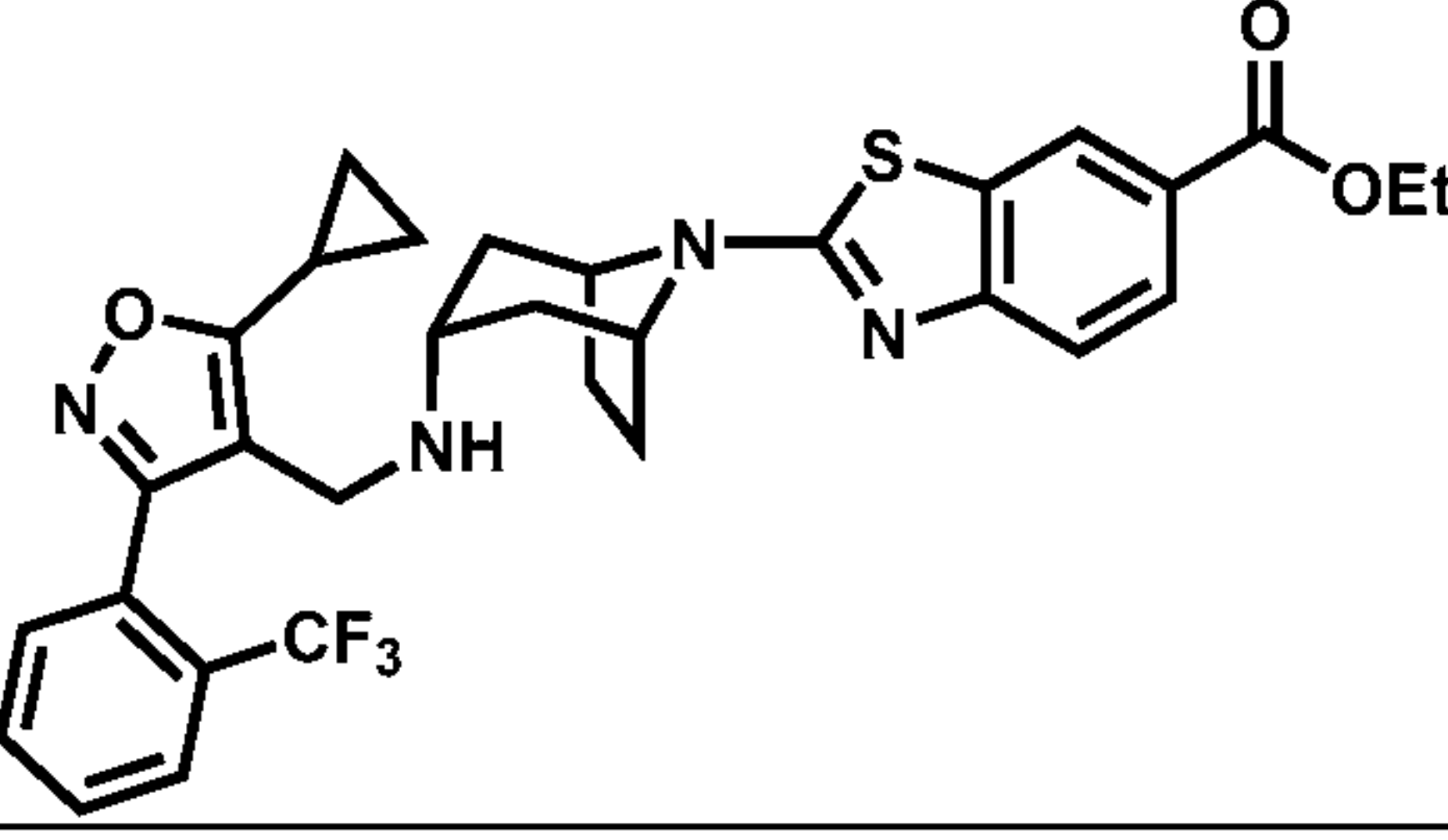
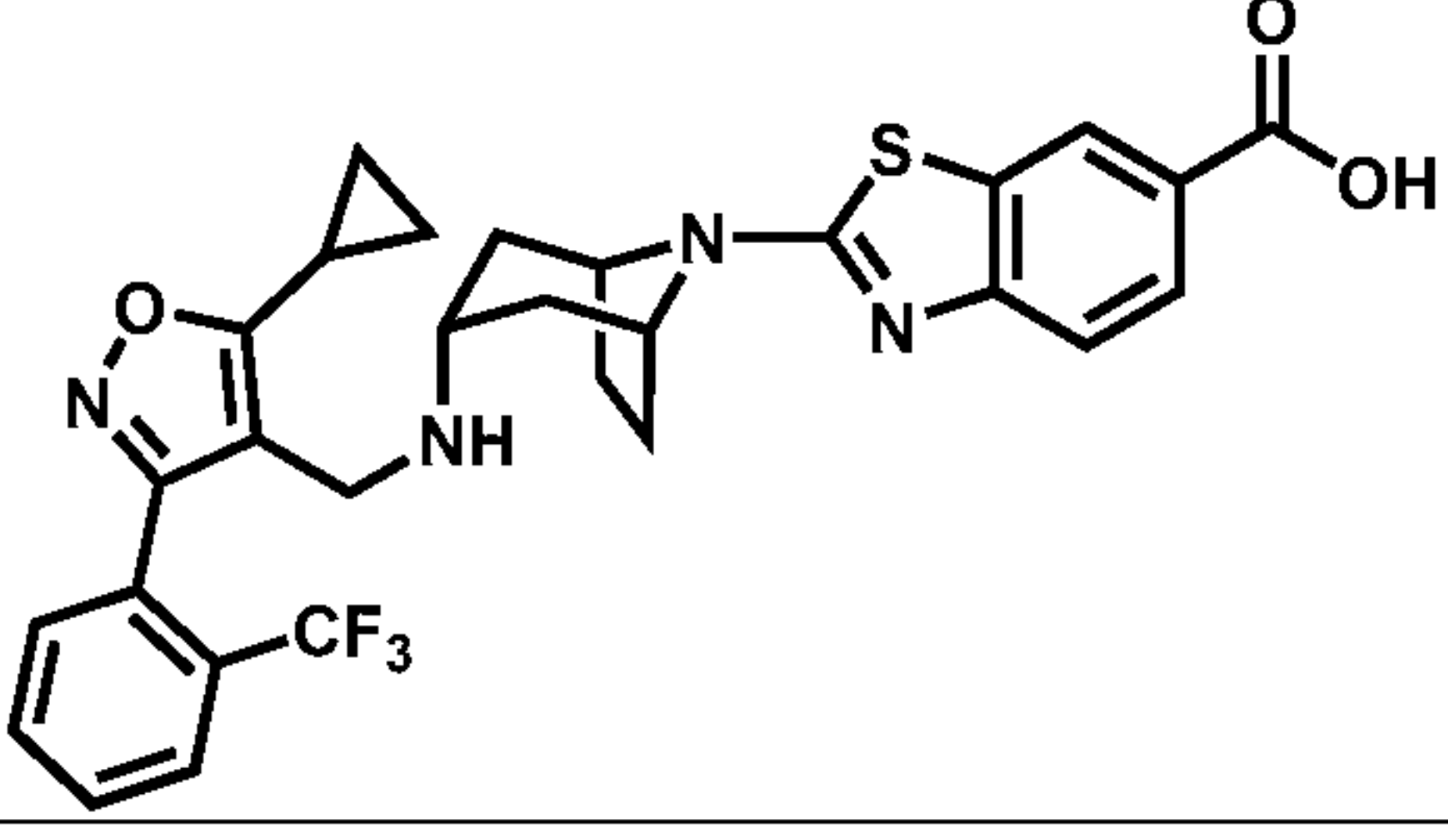
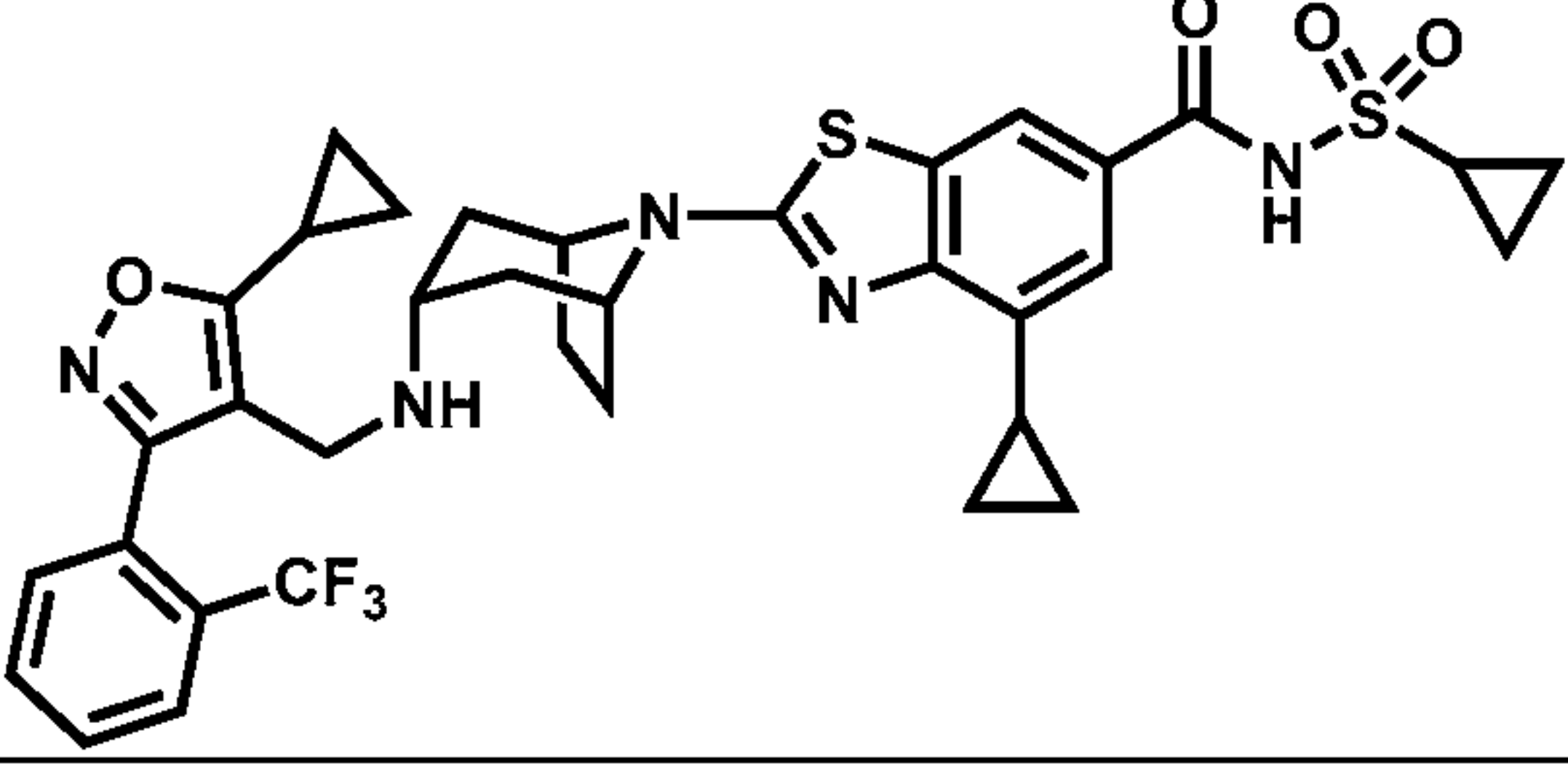
642		577.15 (M+H)
643		639.22 (M+H)
644		625.21 (M+H)
646		564.19 (M+H)
693		685.25 (M+H)
695		688.16 (M-H)

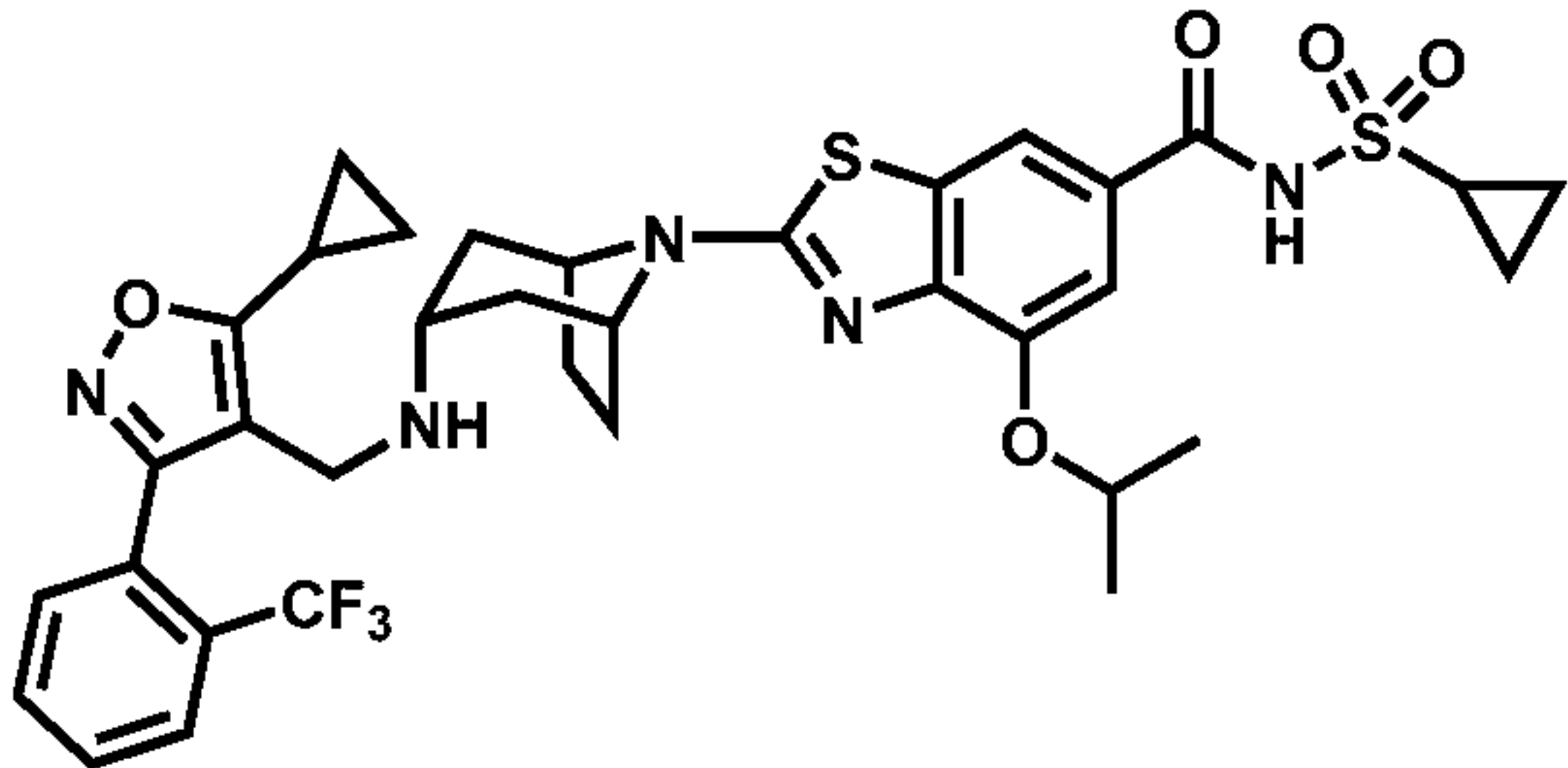
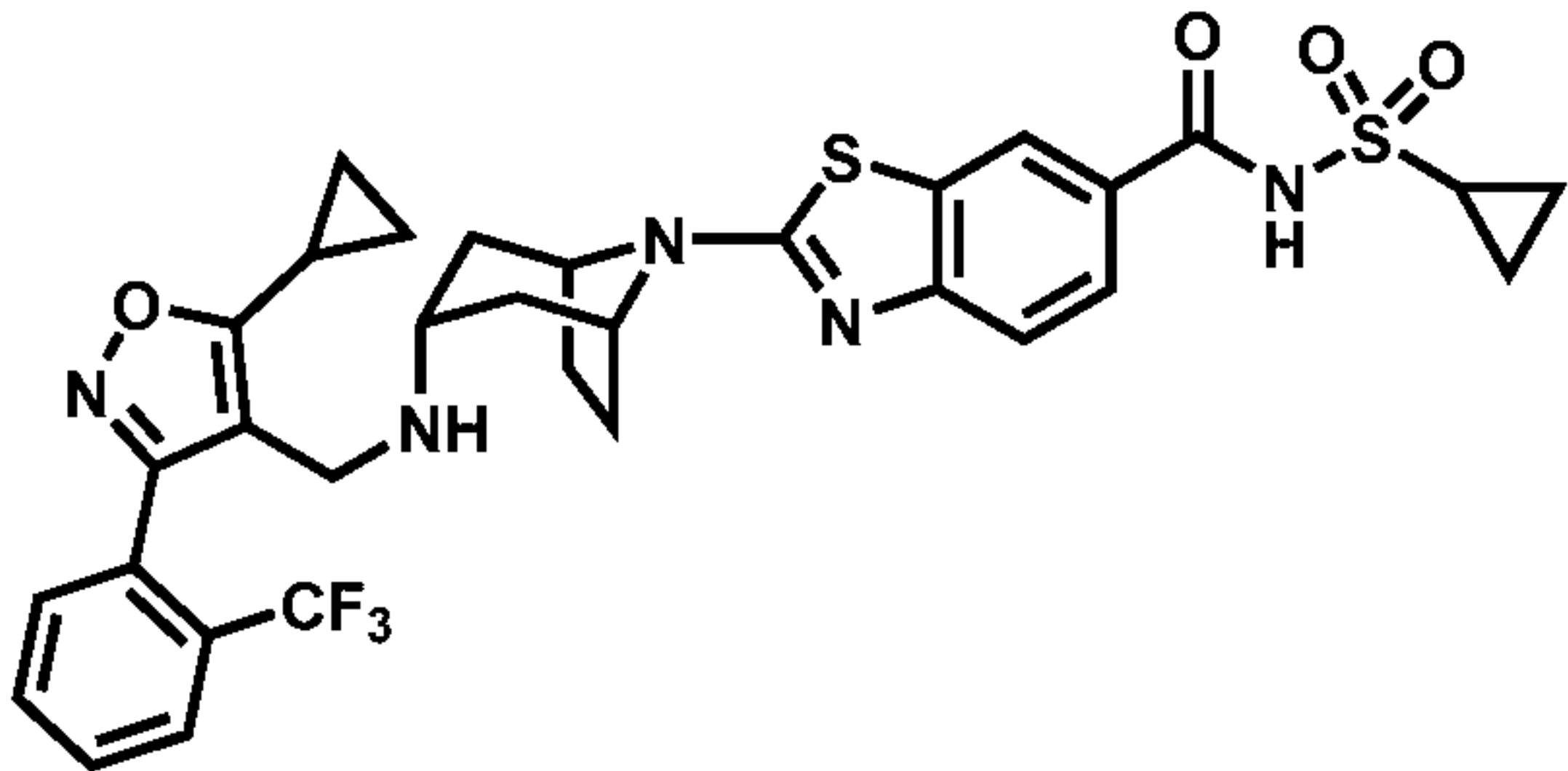
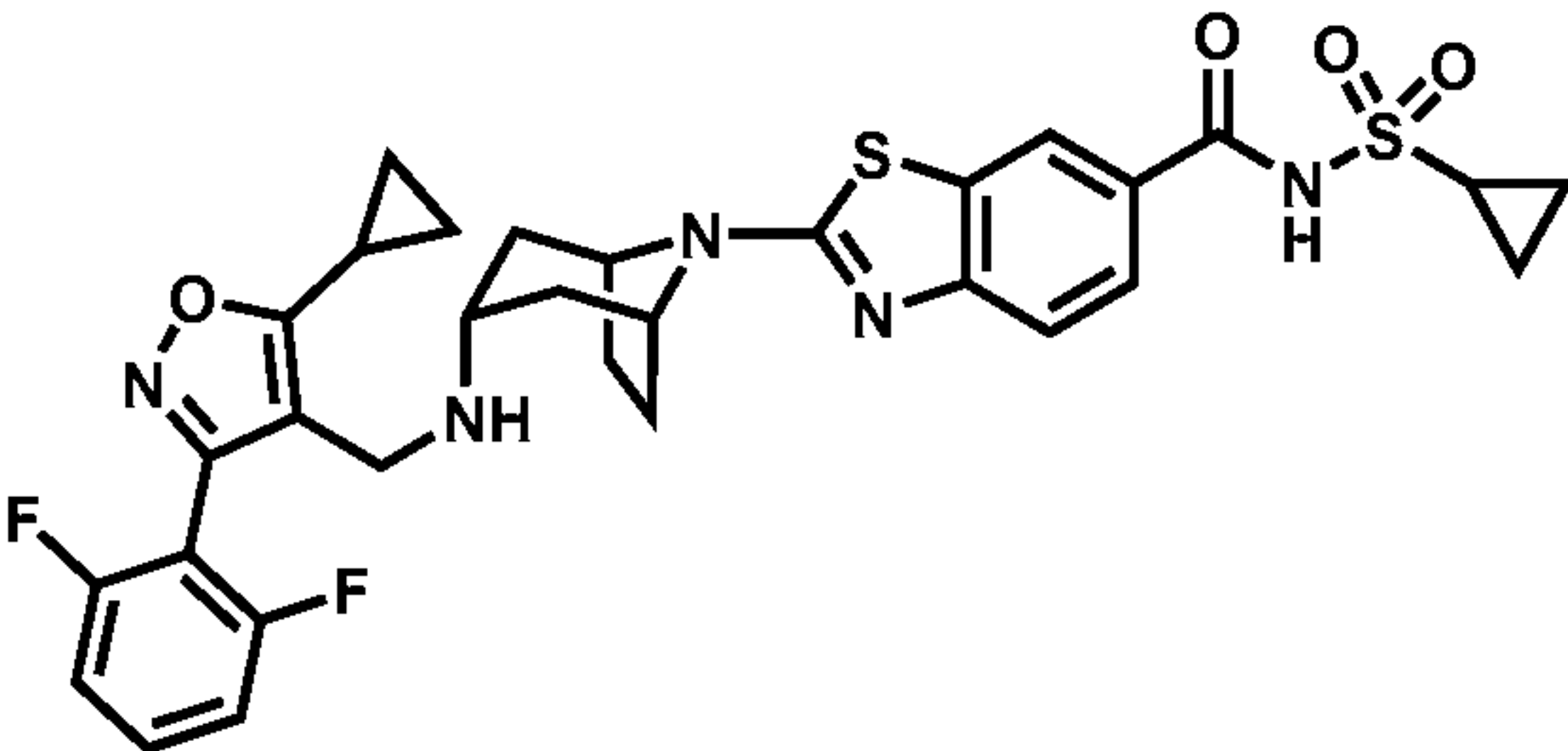
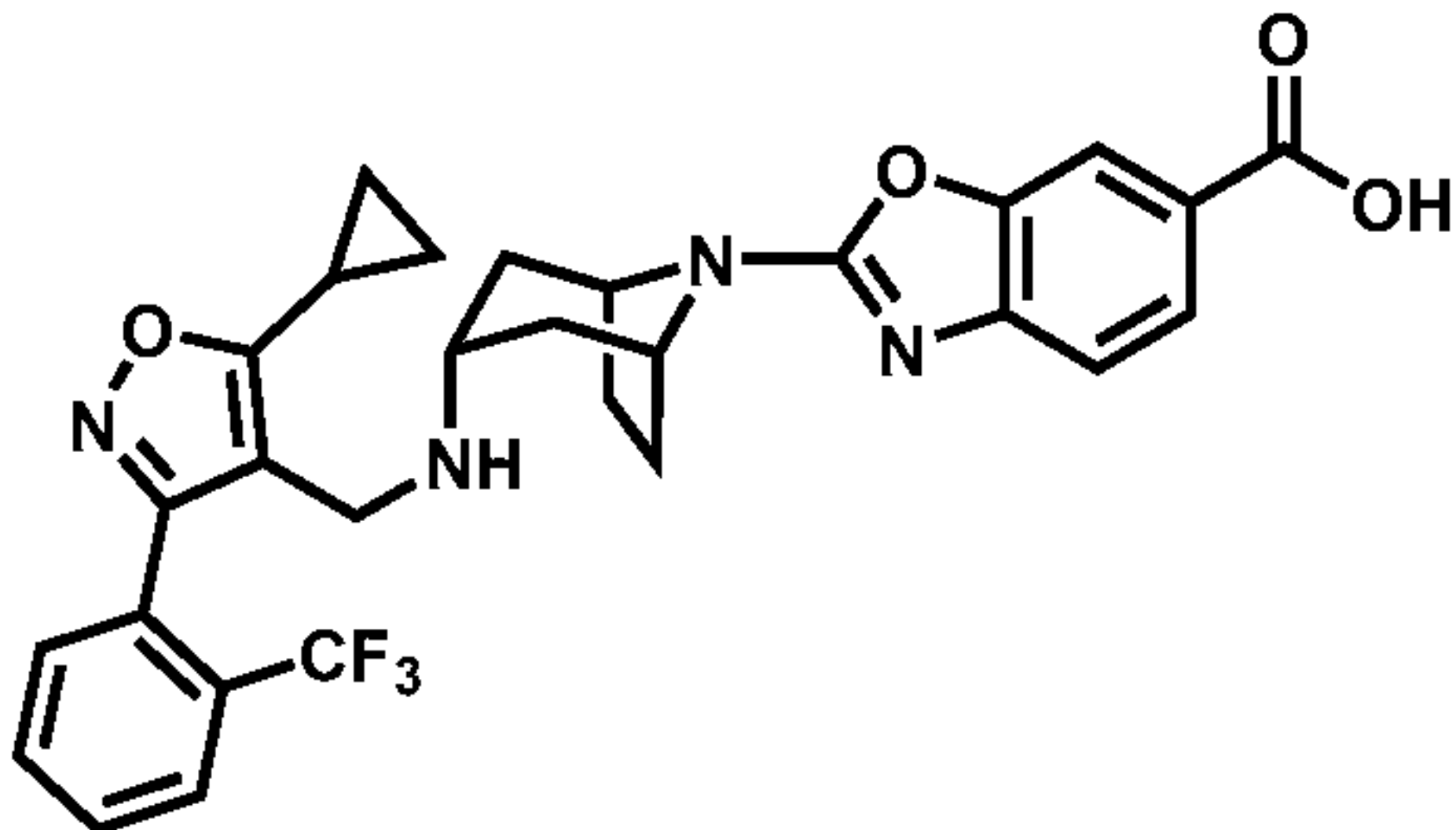
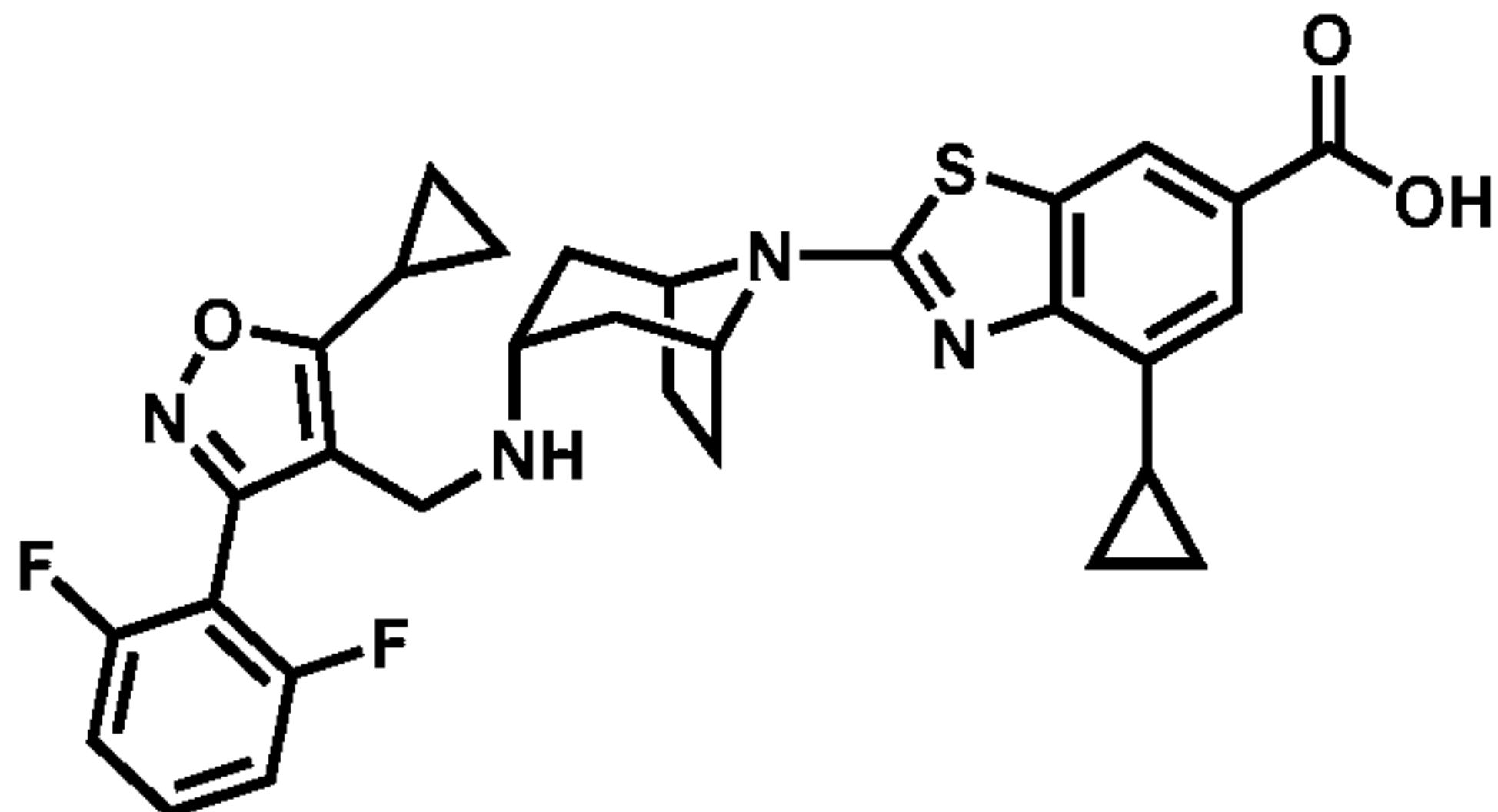
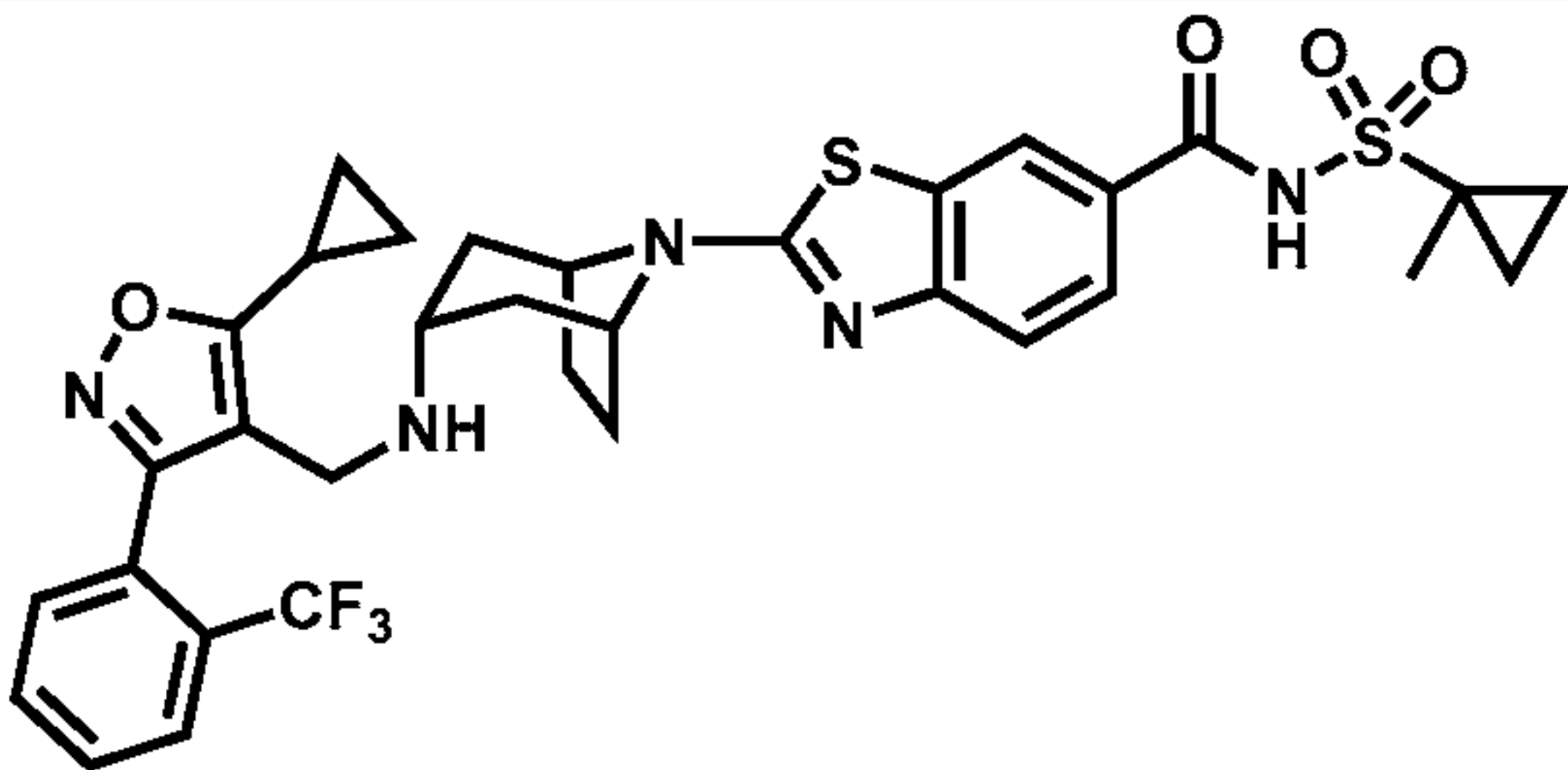
696		613.21 (M+H)
702		700.45 (M-H)
791		662.19 (M+H)
900-1		676.20 (M+H)
900-2		720.23 (M+H)
900-3		680.18 (M+H)

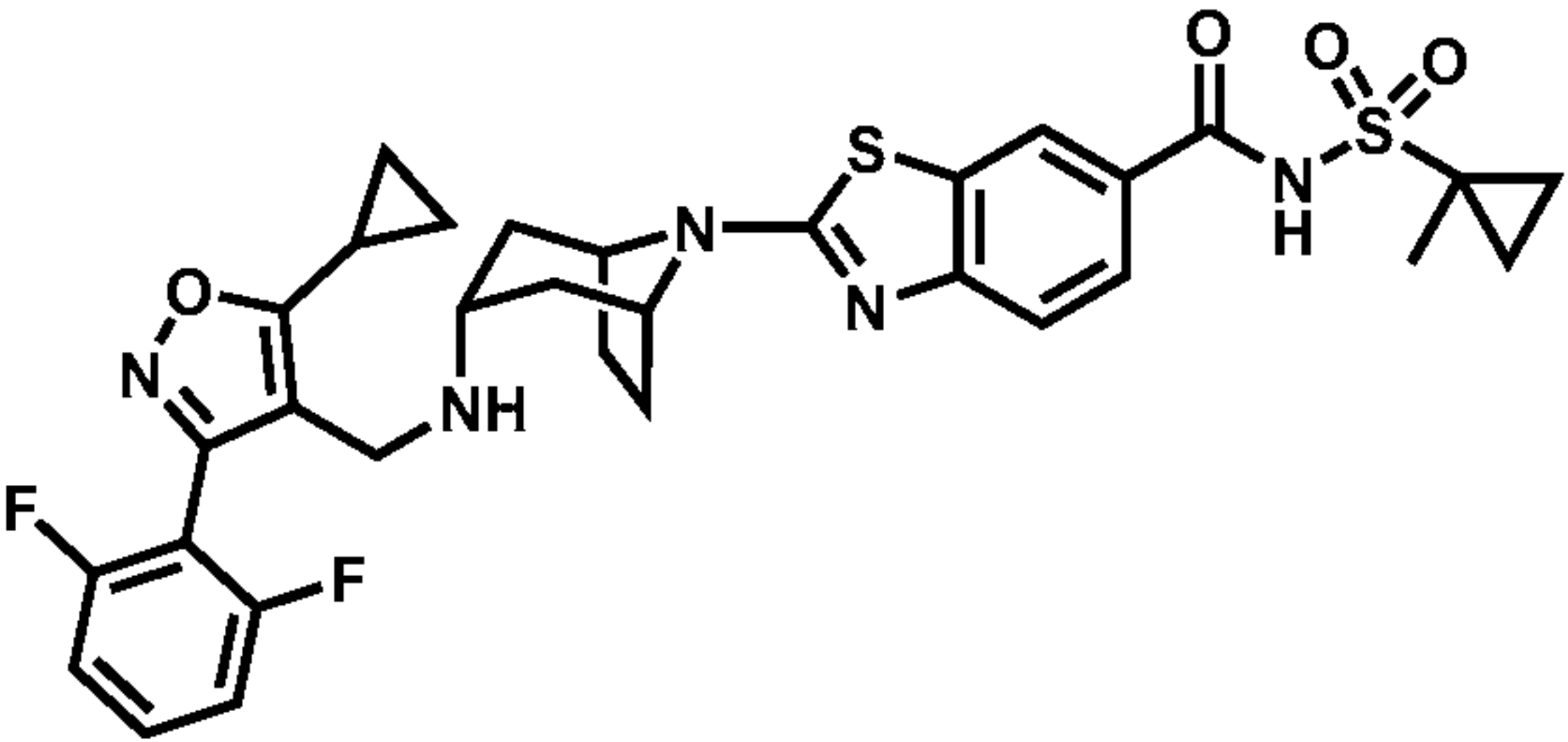
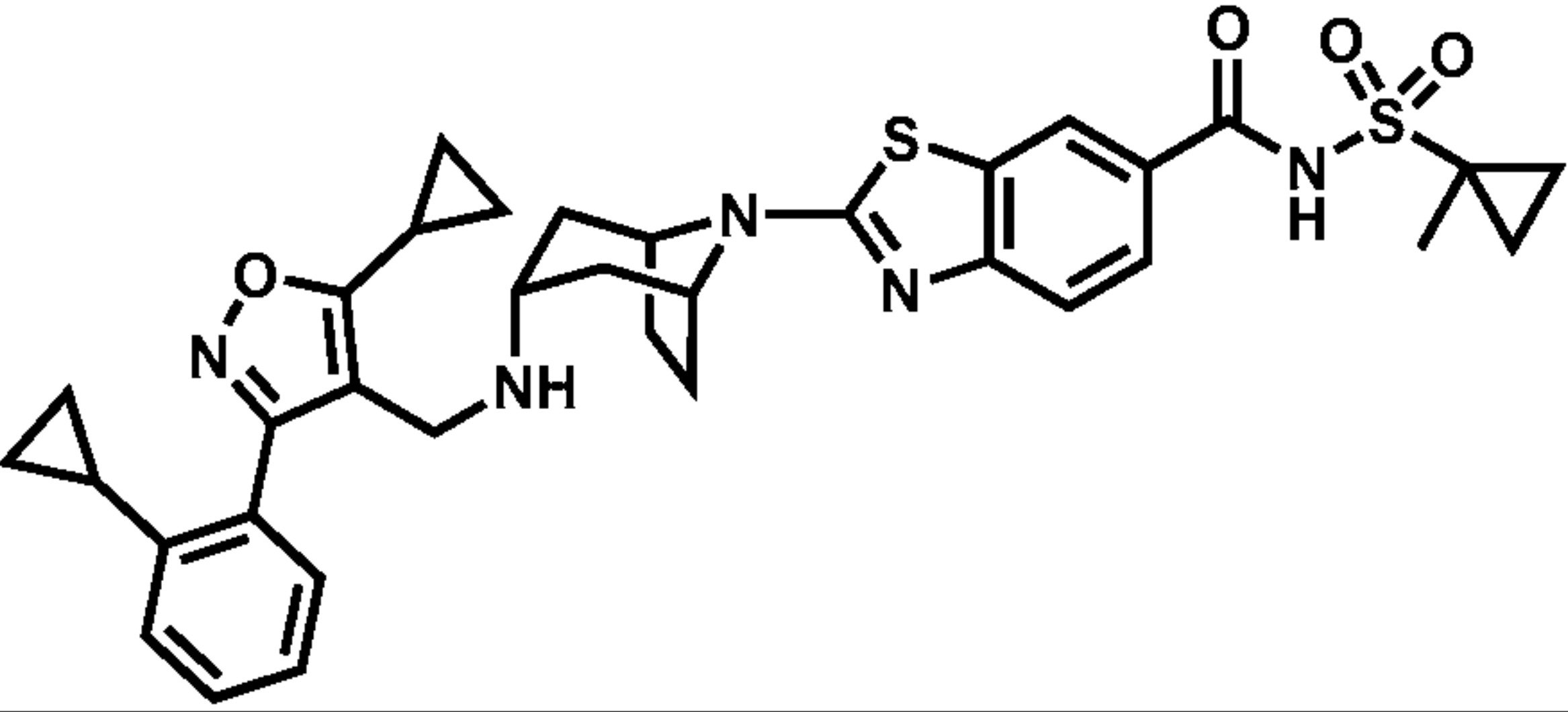
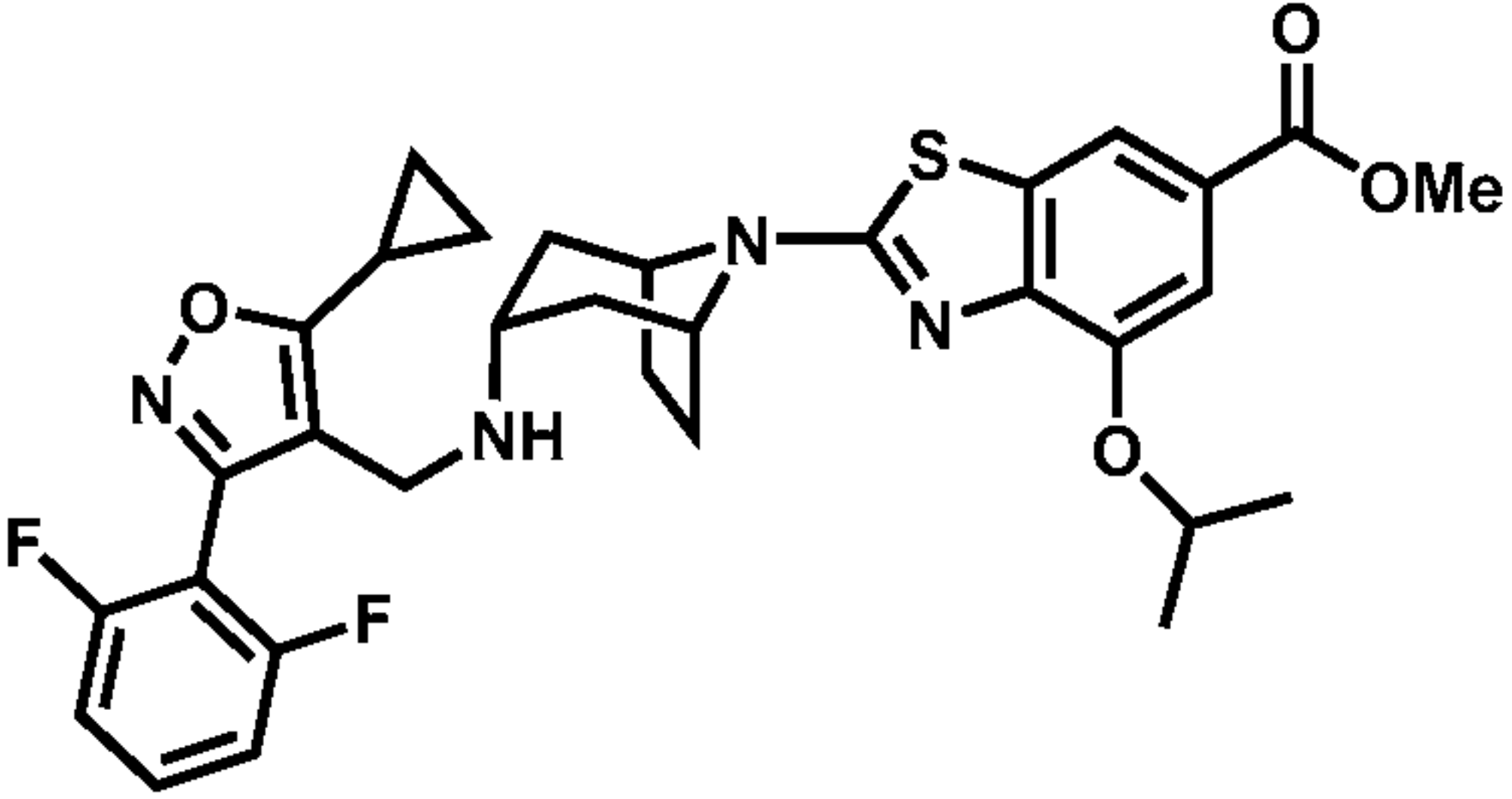
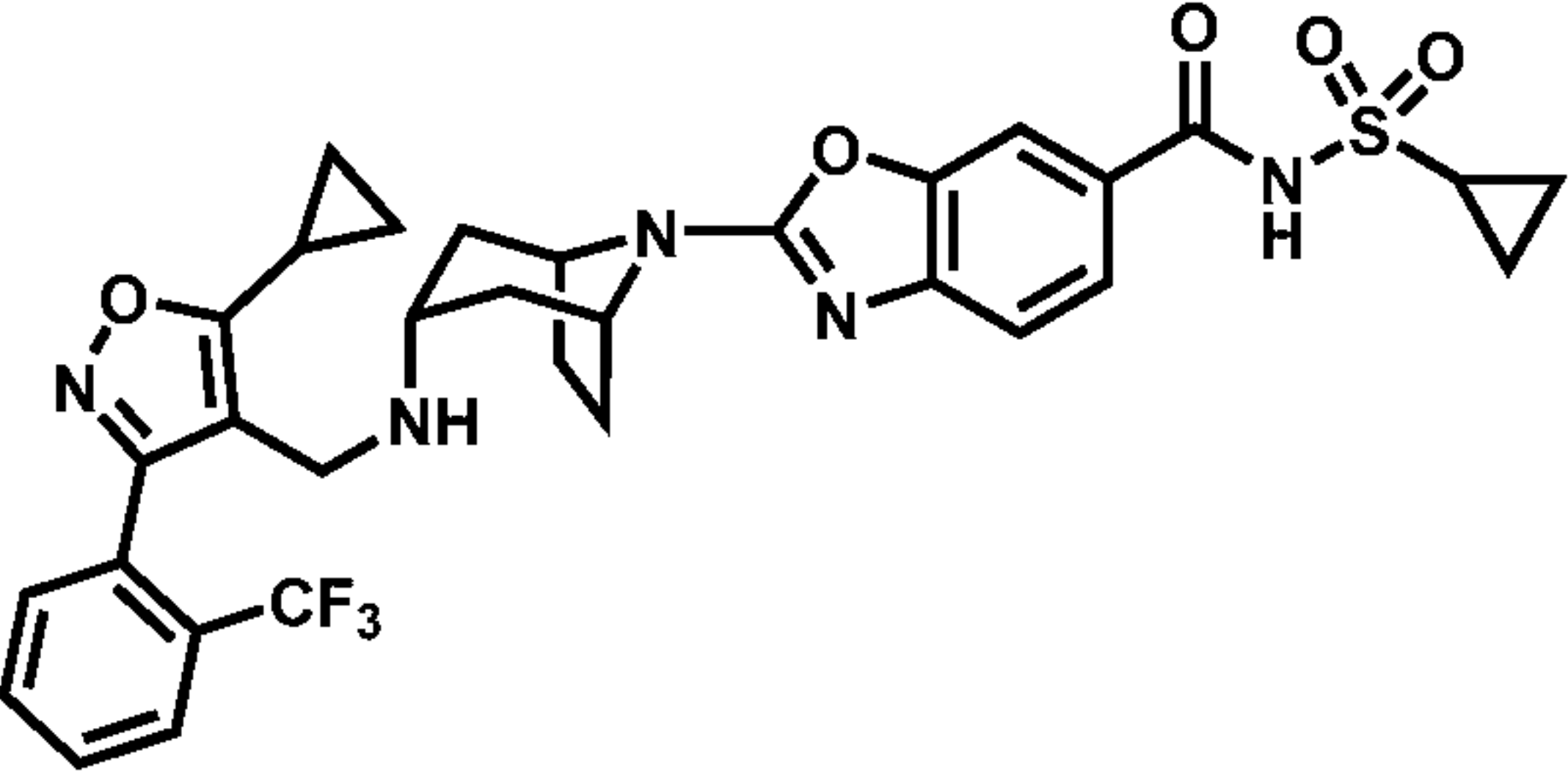
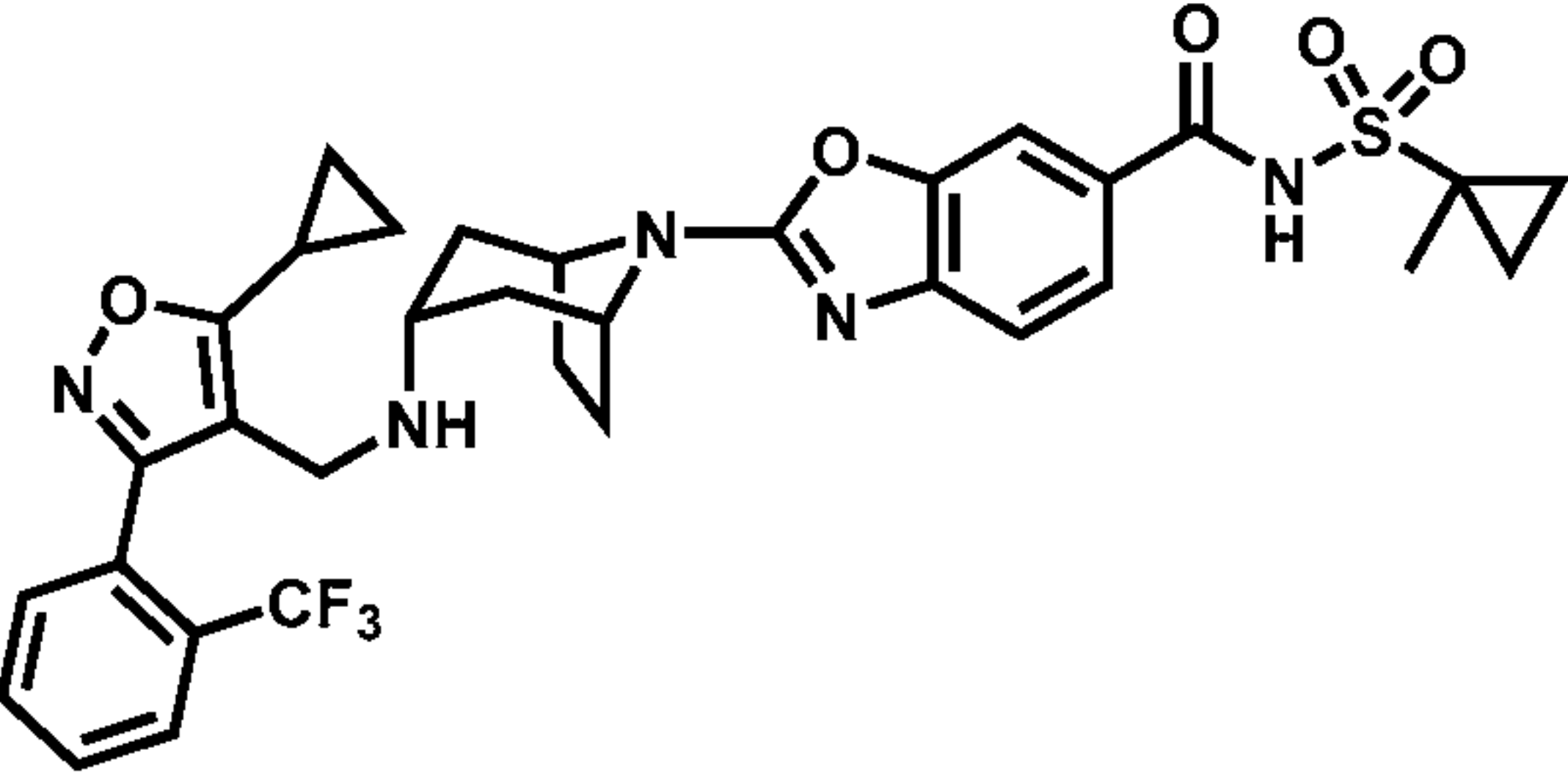
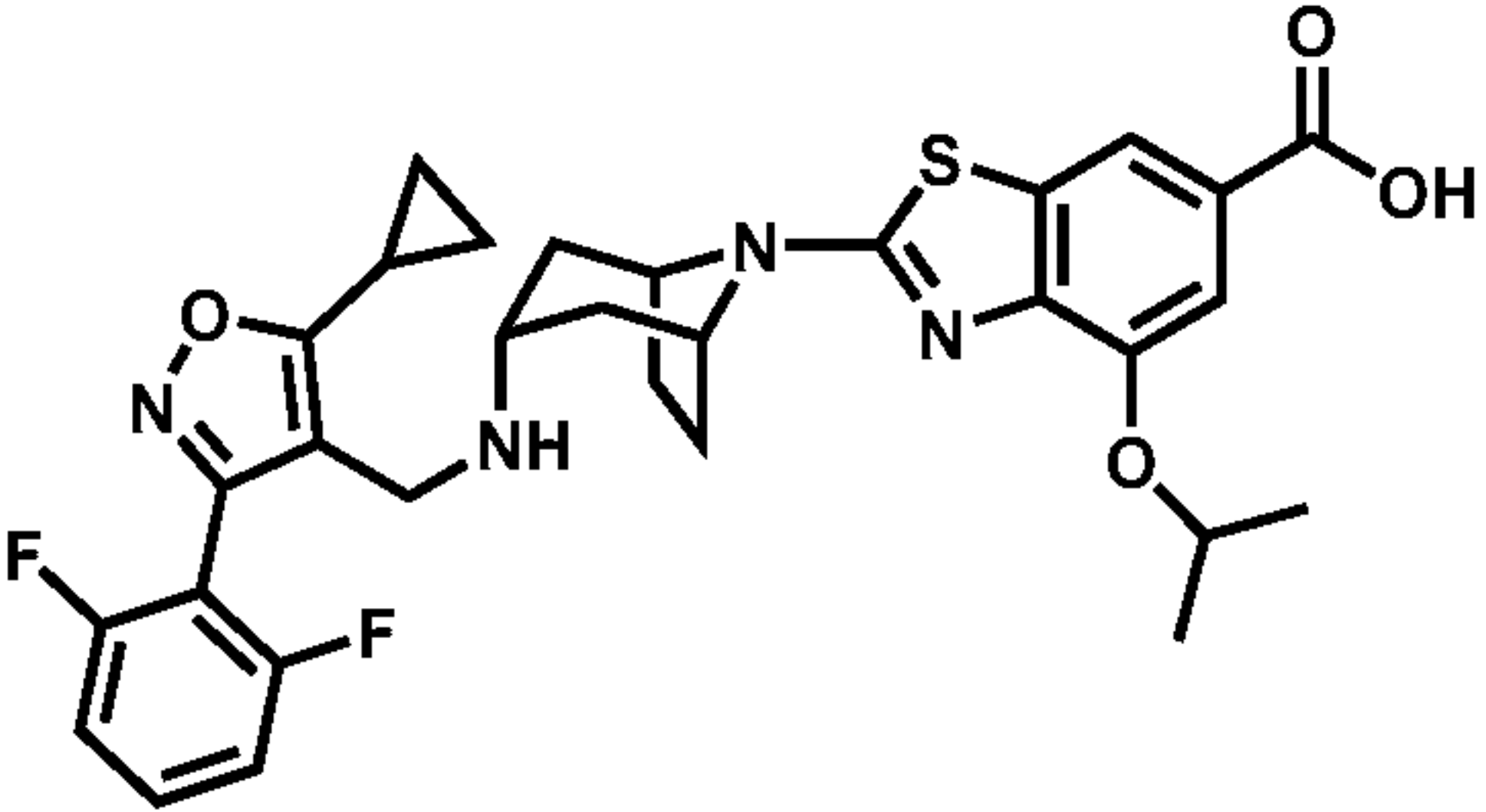
900-4		694.20 (M+H)
900-5		720.24 (M+H)
900-6		734.25 (M+H)
900-9		742.26 (M+H)
900-11		667.22 (M+H)
900-12		681.23 (M+H)

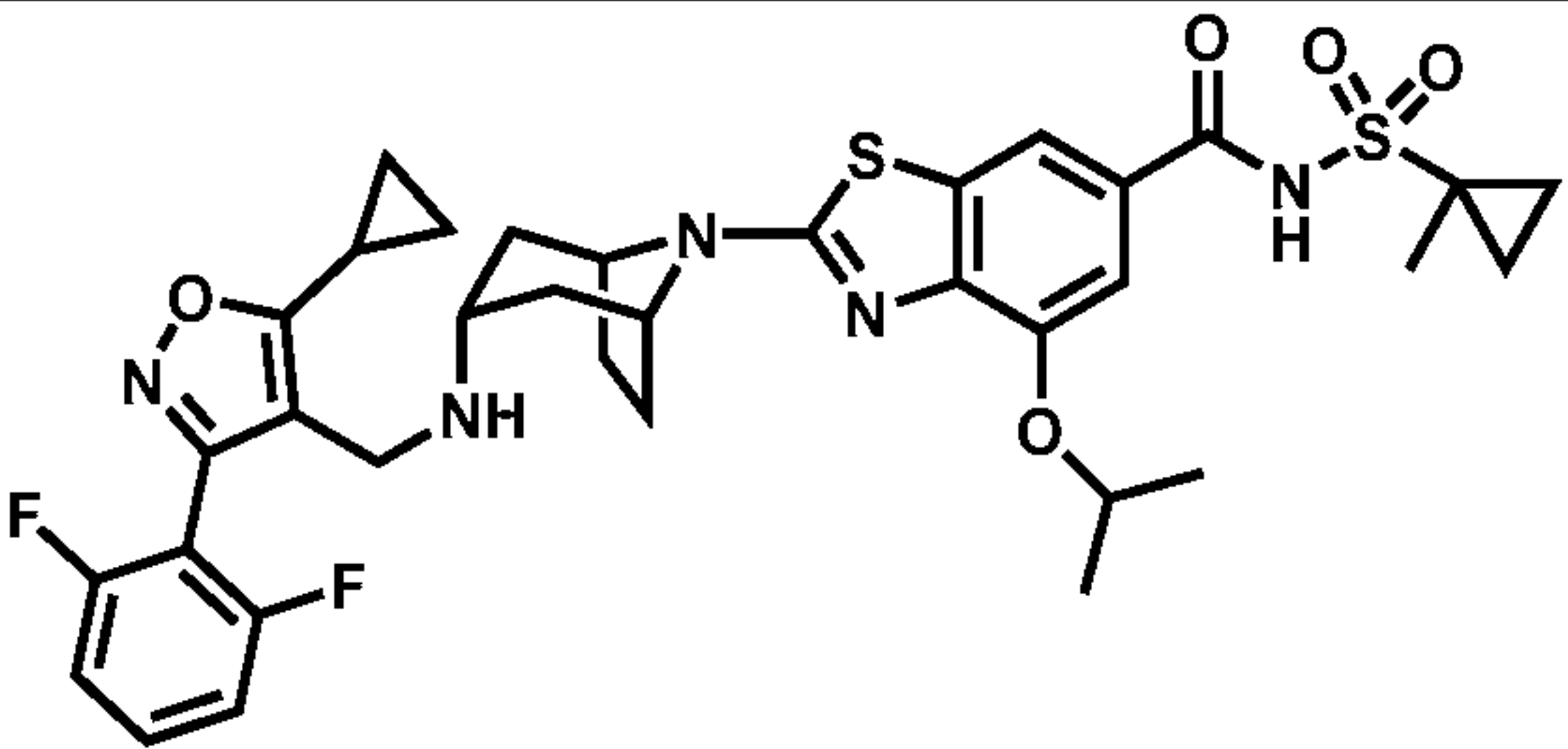
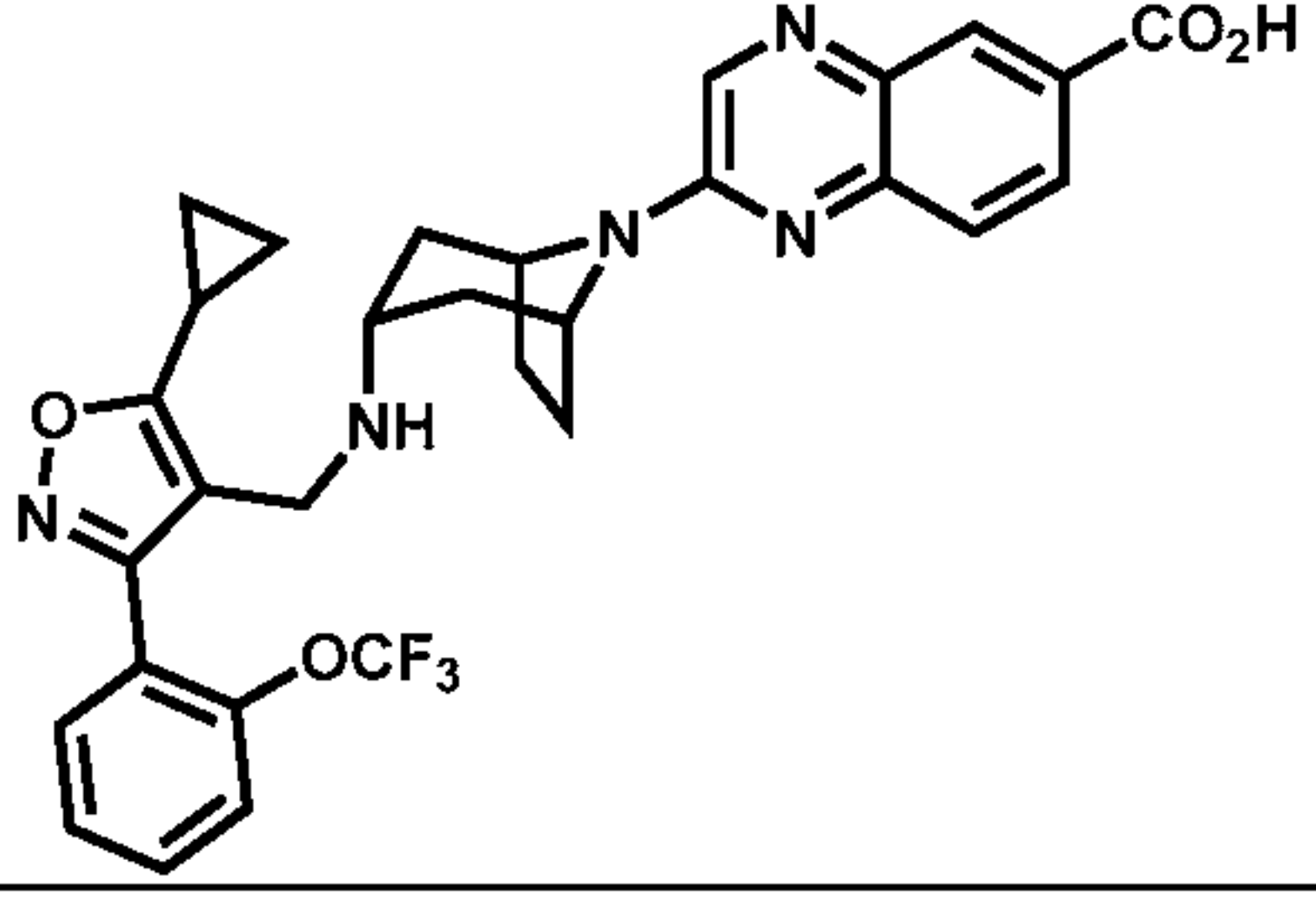
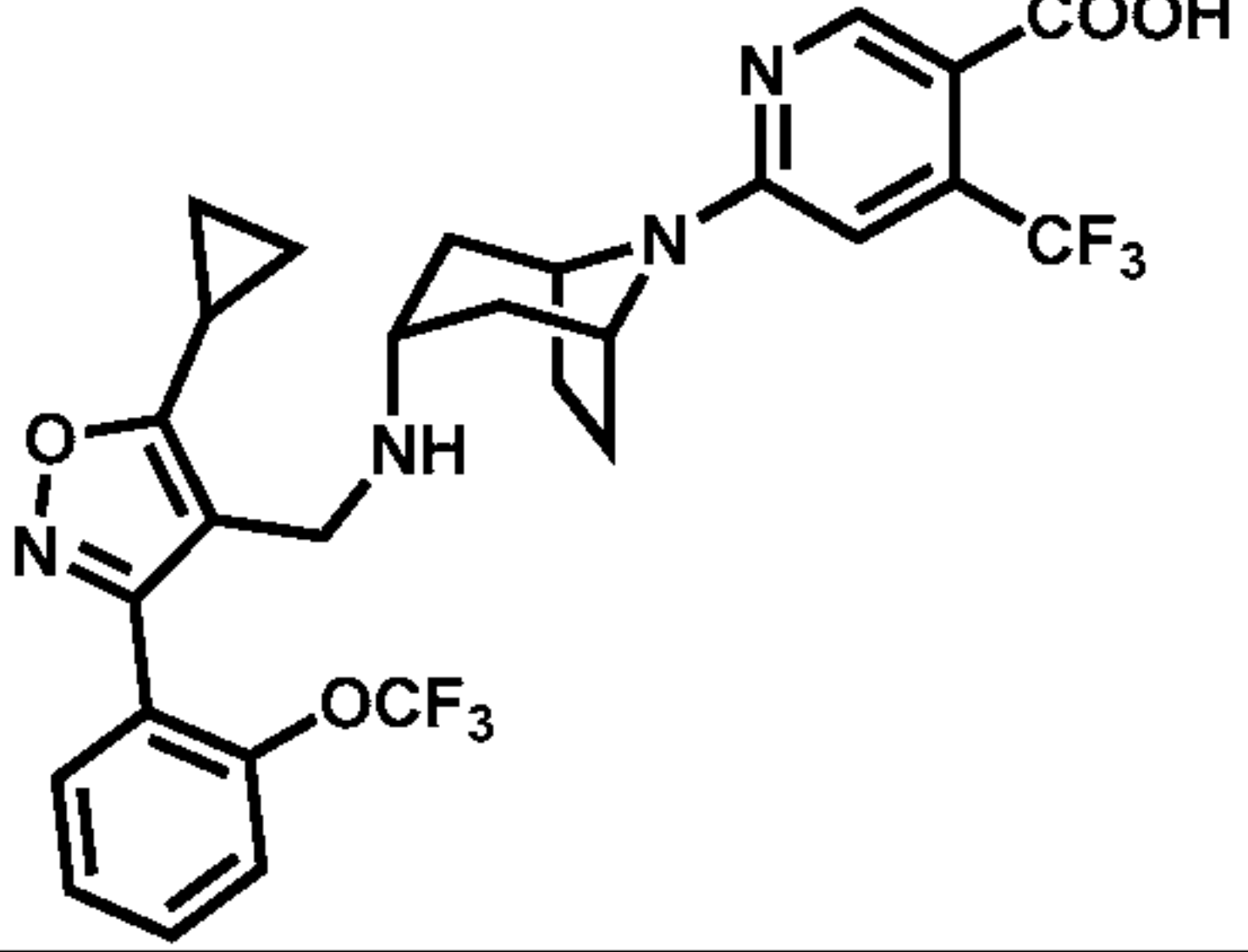
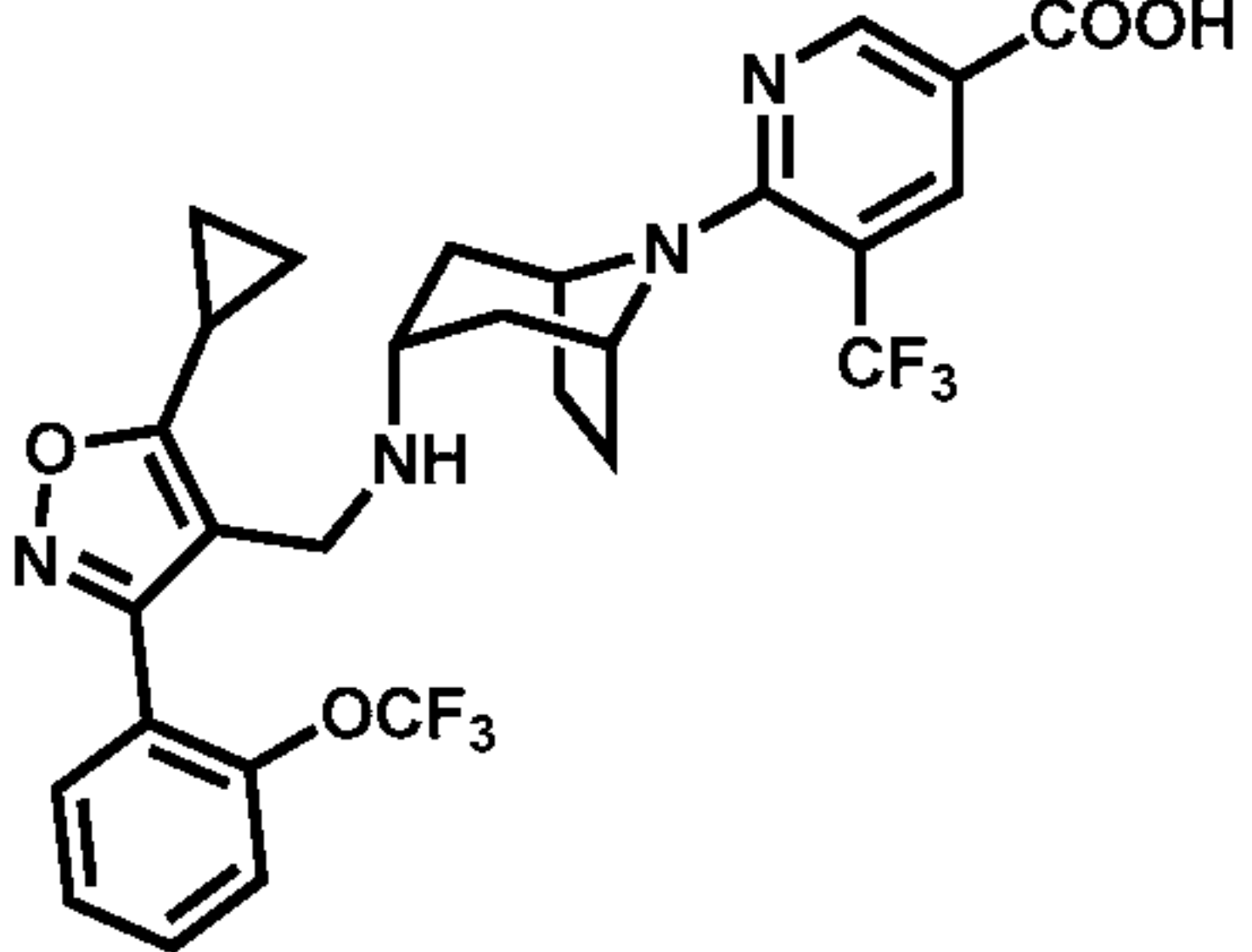
900-13		632.23 (M+H)
900-14		646.24 (M+H)
900-15		682.25 (M+H)
1202		650.55 (M+H)
1401		627.24 (M+H)
1402		744.28 (M+H)

1403		641.25 (M+H)
1404		597.22 (M+H)
1405		583.20 (M+H)
1406		700.25 (M+H)
1407		601.20 (M+H)
1408		587.18 (M+H)

1409		623.24 (M+H)
1410		609.22 (M+H)
1411		537.17 (M+H)
1412		597.22 (M+H)
1413		569.19 (M+H)
1414		712.25 (M+H)

1415		730.26 (M+H)
1416		672.21 (M+H)
1417		640.20 (M+H)
1418		553.21 (M+H)
1419		577.21 (M+H)
1420		686.45 (M+H)

1421		652.40 (M-H)
1422		658.5 (M+H)
1423		609.23 (M+H)
1424		656.23 (M+H)
1425		670.00 (M+H)
1426		595.22 (M+H)

1428		712.24 (M+H)
1429		580.22 (M+H)
1430		597.20 (M+H)
1431		597.20 (M+H)

ASSAYS

Human FXR (NR1H4) Assay

Determination of a ligand mediated Gal4 promoter driven transactivation to quantify ligand binding mediated activation of FXR. FXR Reporter Assay kit purchased from Indigo Bioscience (Catalogue number: IB00601) to determine the potency and efficacy of compound developed by Enanta that can induce FXR activation. The principle application of this reporter assay system is to quantify functional activity of human FXR. The assay utilizes non-human mammalian cells, CHO (Chinese hamster ovary) cells engineered to express human NR1H4 protein (referred to as FXR). Reporter cells also incorporate the cDNA encoding beetle luciferase which catalyzes the substrates and yields photon emission. Luminescence intensity of the reaction is quantified using a plate-reading luminometer,

Envision. Reporter Cells include the luciferase reporter gene functionally linked to an FXR responsive promoter. Thus, quantifying changes in luciferase expression in the treated reporter cells provides a sensitive surrogate measure of the changes in FXR activity. EC₅₀ and efficacy (normalize to CDCA set as 100%) is determined by XLFit. The assay is according to the manufacturer's instructions. In brief, the assay was performed in white, 96 well plates using final volume of 100ul containing cells with different doses of compounds. Retrieve Reporter Cells from -80°C storage. Perform a rapid thaw of the frozen cells by transferring a 10 ml volume of 37°C cell recovery medium into the tube of frozen cells. Recap the tube of Reporter Cells and immediately place it in a 37°C water bath for 5 - 10 minutes. Retrieve the tube of Reporter Cell Suspension from the water bath. Sanitize the outside surface of the tube with a 70% alcohol swab, and then transfer it into the cell culture hood. Dispense 90 µl of cell suspension into each well of the 96-well Assay Plate. Transfer the plate into 37°C incubator, allowing the cells adherent to the bottom of the well. Dilute compounds in Dilution Plate (DP), and administrate to cells at Assay Plate (AP). DMSO content of the samples was kept at 0.2%. Cells were incubated for additional 22 hours before luciferase activities were measured. Thirty minutes before intending to quantify FXR activity, remove Detection Substrate and Detection Buffer from the refrigerator and place them in a low-light area so that they may equilibrate to room temperature. Remove the plate's lid and discard all media contents by ejecting it into an appropriate waste container. Gently tap the inverted plate onto a clean absorbent paper towel to remove residual droplets. Cells will remain tightly adhered to well bottoms. Add 100 µl of luciferase detection reagent to each well of the assay plate. Allow the assay plate to rest at room temperature for at least 5 minutes following the addition of LDR. Set the instrument (Envision) to perform a single 5 second "plate shake" prior to reading the first assay well. Read time may be 0.5 second (500mSec) per well. EC₅₀ and Efficacy (normalize to CDCA set as 100%) is determined by XLFit.

To assess the FXR agonistic potency of the example compounds as well as for reference compound, potency ranges were determined in the Human FXR (NR1H4) Assay as listed below in Table 9. The efficacy was normalized to CDCA set as 100%. (A = EC₅₀ < 0.001 µM; B = 0.001 µM < EC₅₀ < 0.1 µM; C = 0.1µM < EC₅₀ < 1.0 µM; D= EC₅₀ > 1.0 µM)

Table 9

Example	EC ₅₀	Efficacy (%)
CDCA	D	100
6-ECDCA	C	223

1	D	74%
2	B	244%
3	B	137%
4	A	169%
5	B	145%
6	A	153%
19	C	78%
20	B	56%
49	B	135%
50	A	186%
95	B	128%
96	B	136%
138	A	155%
153	B	113%
165	B	236%
169	D	38%
170	C	105%
172	C	257%
173	D	116%
174	B	132%
176	C	228%
178	D	108%
179	C	148%
183	D	119%
186	D	45%
187	D	64%
188	D	15%
189	B	73%
190	A	96%
201	A	282%
202	A	279%
225	A	126%
227	A	256%
228	B	140%
231	A	277%
234	C	146%
235	B	240%
236	B	75%
237	B	226%
239	B	201%
240	A	245%
257	B	203%
262	A	289%
268	C	129%
279	C	158%
280	B	242%
281	B	171%
282	B	142%

283	D	246%
284	D	54%
285	C	126%
286	D	67%
287	D	98%
288	C	114%
289	D	207%
290	D	85%
291	B	171%
292	B	212%
293	B	92%
294	D	130%
295	B	152%
296	A	184%
297	A	150%
298	B	155%
299	B	154%
300	A	143%
301	A	63%
302	B	62%
303	A	175%
304	A	139%
305	C	139%
7	B	37%
8	A	109%
64	B	40%
122	B	90%
125	B	86.5%
194	A	81%
196	B	83.5%
197	C	115%
198	B	140%
199	C	58%
200-1	B	10%
200-3	C	35%
200-4	B	106%
200-5	C	72%
200-6	B	86.5%
200-7	B	74.5%
200-8	A	73.5%
200-9	B	81%
200-10	A	92.5%
200-11	B	75%
200-12	B	16.5%
200-13	A	96%
200-14	A	93.5%
200-15	B	75.8%
200-16	B	109%

200-17	B	51.5%
200-18	B	91.3%
200-19	B	50.5%
200-21	B	58%
200-23	B	76.5%
200-24	B	96.2%
200-25	B	58.5%
200-27	B	28.3%
200-28	A	132%
200-29	B	94%
200-30	A	108%
323	A	150%
328	A	146%
342	B	76%
400-1	B	210%
400-3	B	104%
400-4	B	97.5%
400-5	B	110%
400-6	B	73.5%
400-7	B	91%
400-8	B	79%
400-9	C	37.5%
400-10	C	68%
400-11	A	79.3%
400-12	A	115%
400-13	B	83.3%
400-14	A	119%
400-15	A	104%
400-16	A	87.3%
400-18	A	98%
400-20	B	43.6%
400-22	A	83.2%
400-24	A	88.2%
400-25	B	72%
400-26	A	97.2%
400-29	A	118%
400-32	A	116%
400-33	A	91%
400-35	B	117%
400-37	B	82.5%
402	B	112%
403	B	61%
404	B	88%
413	B	118%
414	A	121%
510	B	41%
514	B	100%
597	B	83.5%

638	C	107%
639	C	13%
640	B	92.3%
641	C	40%
642	C	85.3%
643	B	52%
644	A	94.5%
646	B	105%
695	B	75%
696	B	59.1%
702	B	113%
791	D	63%
900-1	C	80.5%
900-2	B	109%
900-3	C	44.8%
900-4	D	84.8%
900-5	C	68.5%
900-6	B	112%
900-9	A	122%
900-11	B	70.5%
900-12	B	67%
900-13	B	59.5%
900-14	C	46.5%
900-15	B	82.5%
1202	B	85.5%
1401	C	125%
1402	B	136%
1403	B	119%
1404	C	46%
1405	B	125%
1406	A	133%
1407	B	92.5%
1408	B	103%
1409	B	52%
1410	A	74.5%
1411	B	94.7%
1412	C	75%
1413	B	90.7%
1414	A	89.5%
1415	B	106%
1416	B	87.5%
1417	B	69%
1418	B	102%
1419	B	107%
1420	B	91%
1421	B	101%
1422	B	94%
1423	D	78%

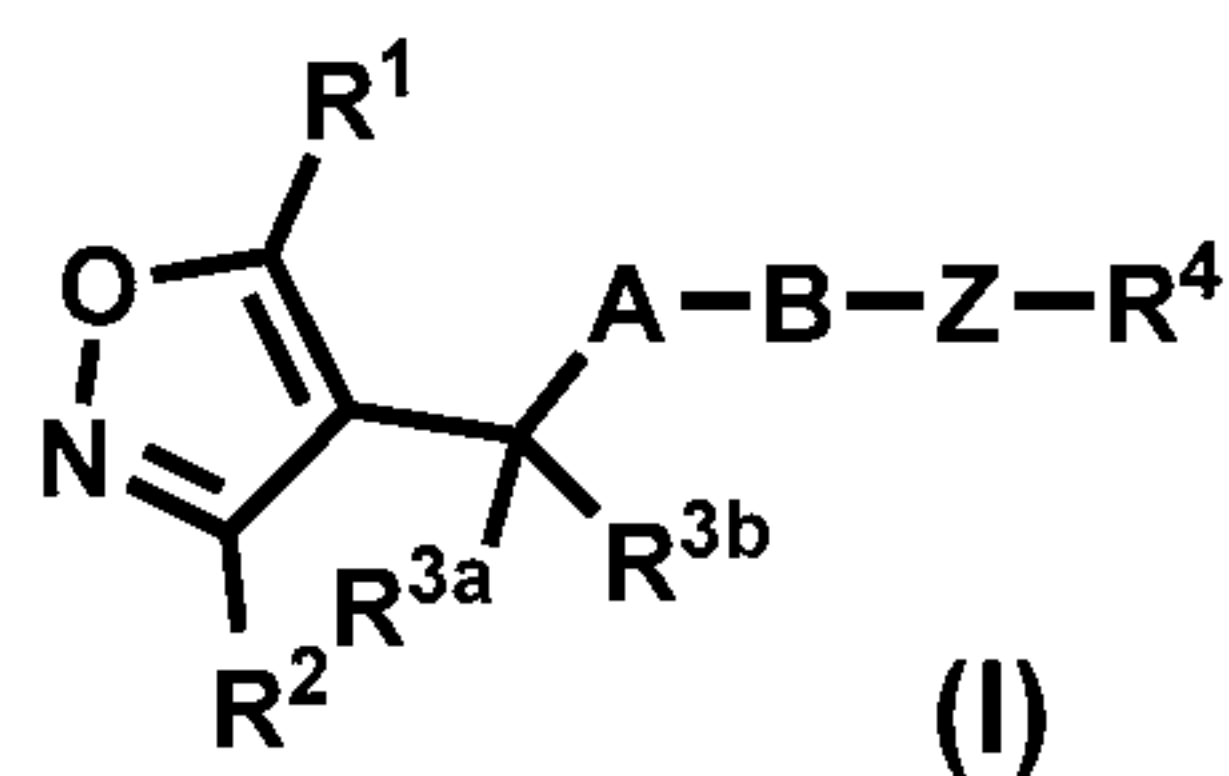
1424	B	148%
1425	C	74%
1426	C	73.2%
1428	B	86%

5 While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound represented by Formula (I):



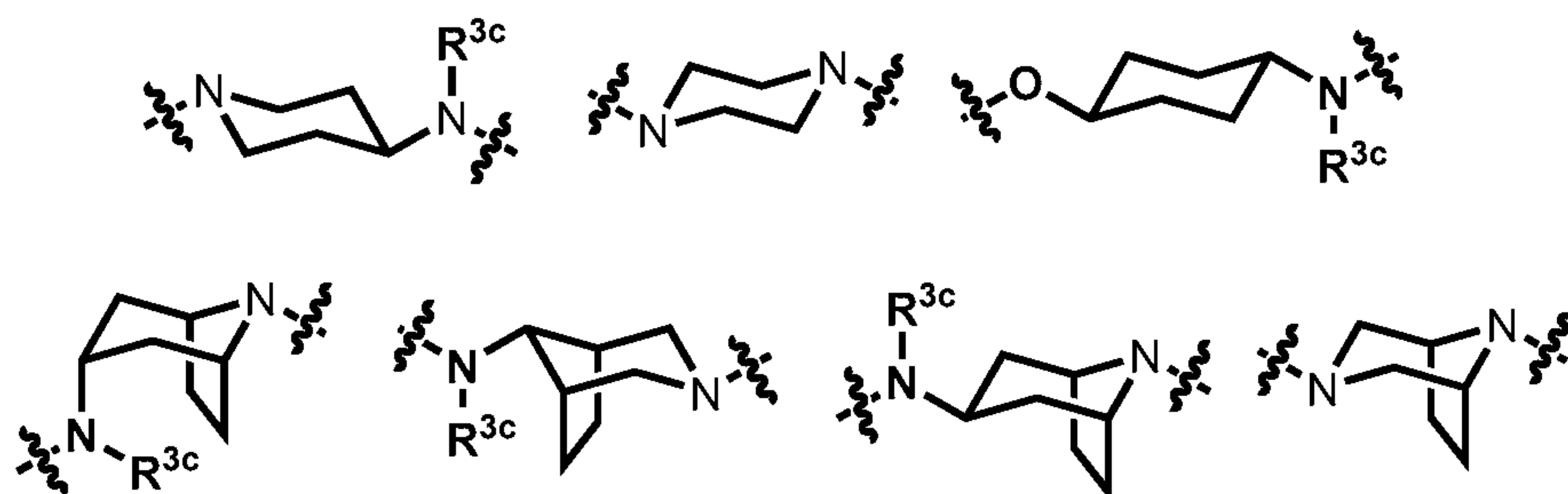
5 or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen, halogen, cyano, optionally substituted $-C_1-C_6$ alkyl, optionally substituted $-C_2-C_6$ alkenyl, optionally substituted $-C_2-C_6$ alkynyl, optionally substituted C_3-C_6 cycloalkyl or optionally substituted 3- to 6- membered heterocycloalkyl;

10 R^2 is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted $-C_3-C_{12}$ cycloalkyl or optionally substituted 3- to 12- membered heterocycloalkyl;

R^{3a} , R^{3b} are independently selected from group consisting of hydrogen, halogen, $-C_1-C_6$ alkyl, halo- $-C_1-C_6$ alkyl, $-C_1-C_6$ alkoxy or halo- $-C_1-C_6$ alkoxy, $-C_3-C_6$ cycloalkyl, and halo- $-C_3-C_6$ cycloalkyl; alternatively, R^{3a} and R^{3b} are taken together with the carbon atom to which they are attached to form an optionally substituted $-C_3-C_6$ cycloalkyl, optionally substituted 3- to 15 6- membered heterocycloalkyl, or optionally substituted $-C_3-C_6$ cycloalkenyl;

A is selected from the group consisting of:



wherein one of the indicated valences is the point of attachment to carbon atom of $-CHR^{3a}R^{3b}$ and the other is the point of attachment to B; R^{3c} is selected from the group consisting of

20 hydrogen, optionally substituted $-C_1-C_6$ alkyl, optionally substituted $-C_3-C_6$ cycloalkyl, formyl, and acetyl;

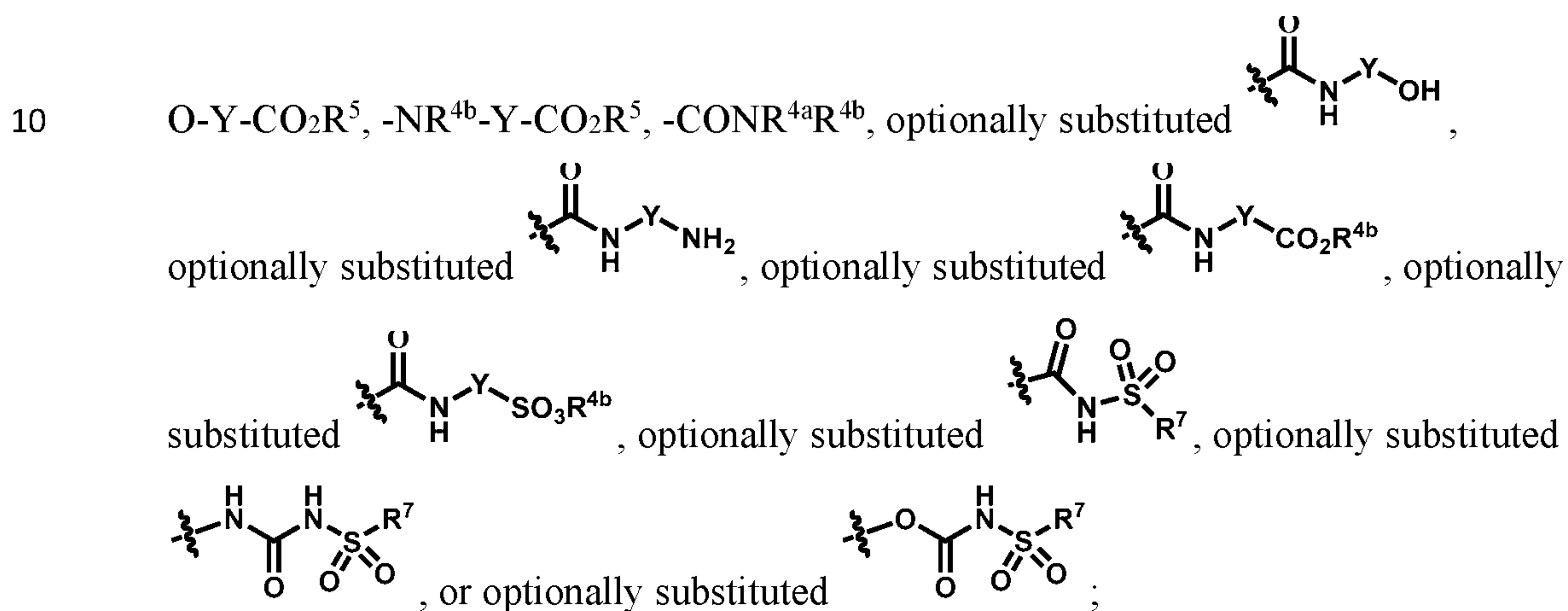
B is optionally substituted aryl, optionally substituted biaryl, optionally substituted 3- to 12 membered heterocycle or optionally substituted heteroaryl;

Z is selected from the group consisting of:

25 1) Absent;

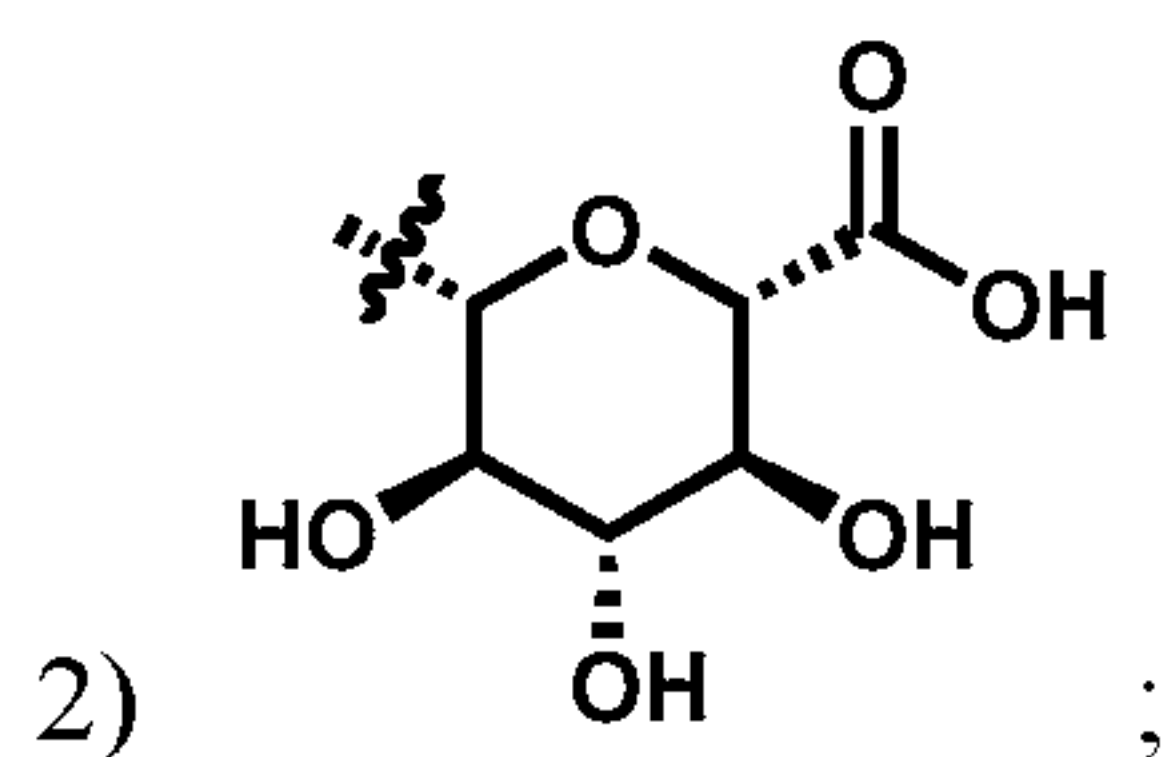
- 2) Optionally substituted $-C_1-C_6$ alkyl;
- 3) Optionally substituted $-C_2-C_6$ alkenyl;
- 4) Optionally substituted $-C_2-C_6$ alkynyl;
- 5) Optionally substituted $-C_3-C_8$ cycloalkyl;
- 6) Optionally substituted 3- to 8- membered heterocycloalkyl;
- 7) Optionally substituted $-C_3-C_8$ cycloalkenyl;
- 8) Optionally substituted aryl; and
- 9) Optionally substituted heteroaryl;

R^4 is hydroxy, protected hydroxy, $-O$ -(hydroxy prodrug group), tetrazolyl, cyano, $-CO_2R^5$, -



wherein,

- 15 Y is absent or optionally substituted $-C_1-C_6$ alkyl;
- R^{4a} and R^{4b} are independently selected from the group consisting of:
- 1) Hydrogen;
 - 2) Optionally substituted $-C_1-C_8$ alkyl;
 - 3) Optionally substituted $-C_2-C_8$ alkenyl;
 - 4) Optionally substituted $-C_2-C_8$ alkynyl; and
 - 5) Optionally substituted $-C_3-C_8$ cycloalkyl;
- R^5 is selected from the group consisting of:
- 1) Hydrogen;



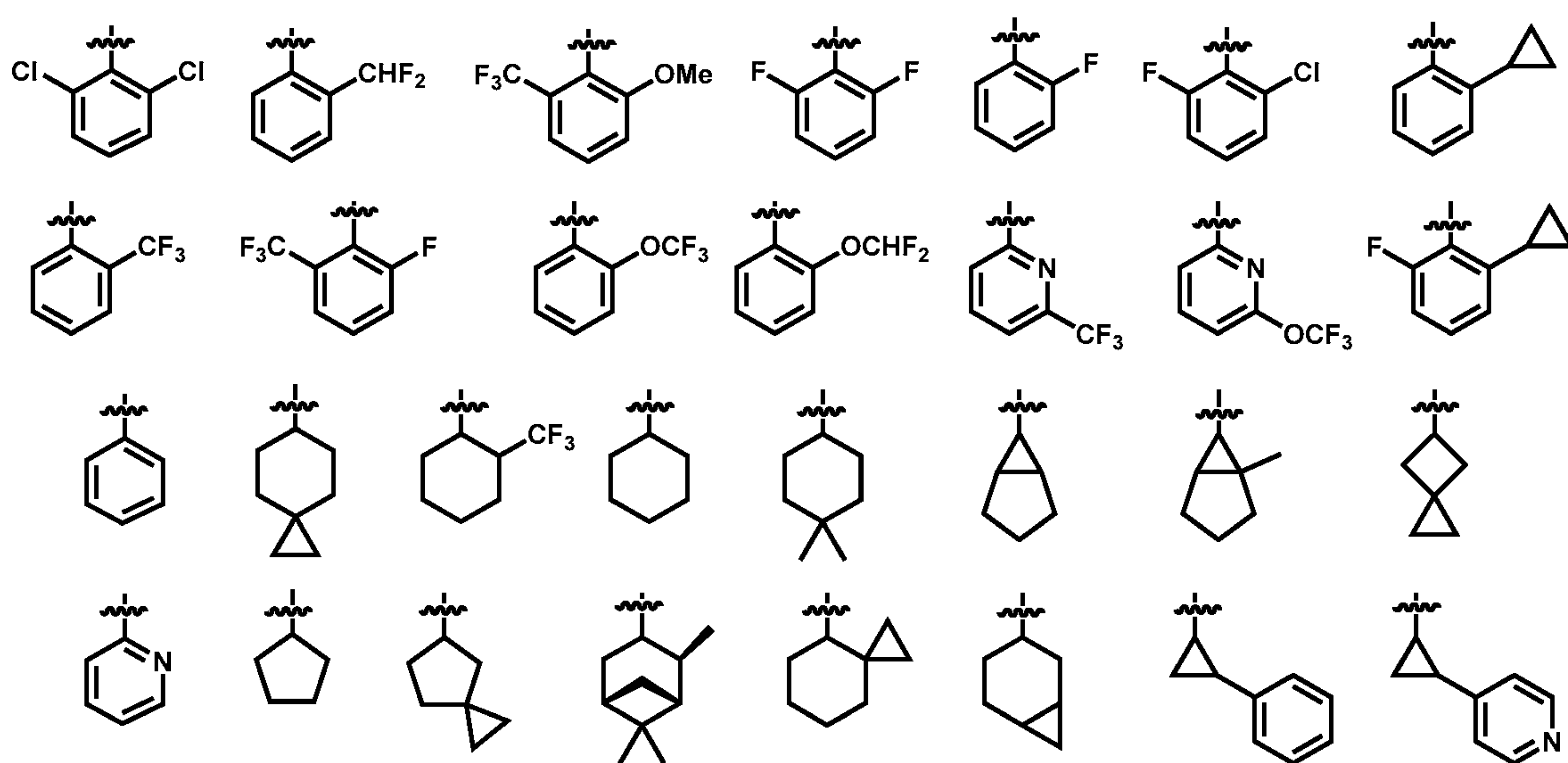
- 25 3) Optionally substituted $-C_1-C_8$ alkyl;

- 4) Optionally substituted $-C_2-C_8$ alkenyl;
- 5) Optionally substituted $-C_2-C_8$ alkynyl; and
- 6) Optionally substituted $-C_3-C_8$ cycloalkyl;

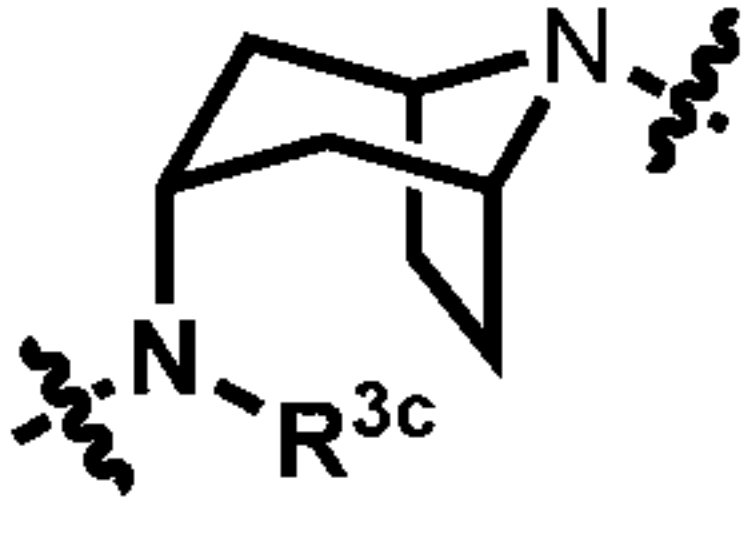
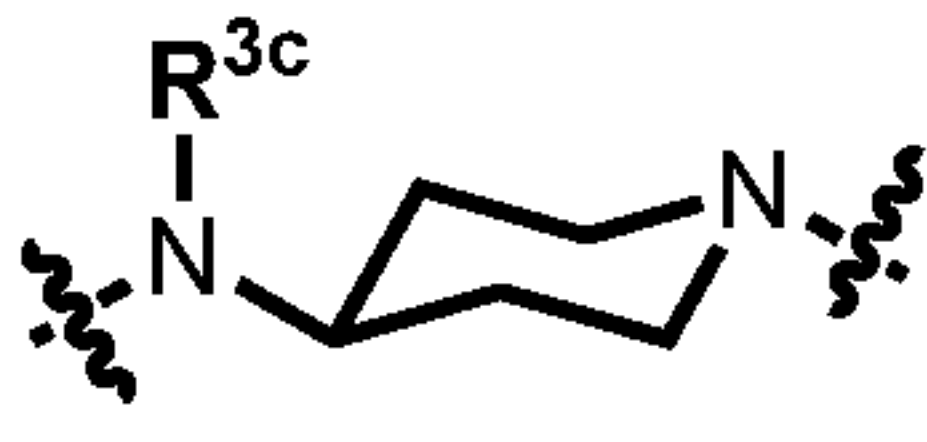
R^7 is selected from the groups consisting of:

- 5 1) Optionally substituted $-C_1-C_8$ alkyl;
- 2) Optionally substituted $-C_2-C_8$ alkenyl;
- 3) Optionally substituted $-C_2-C_8$ alkynyl;
- 4) Optionally substituted $-C_3-C_8$ cycloalkyl;
- 5) Optionally substituted $-C_3-C_8$ cycloalkenyl;
- 10 6) Optionally substituted 3- to 8-membered heterocycloalkyl;
- 7) Optionally substituted 3- to 8- membered heterocycloalkenyl;
- 8) Optionally substituted aryl;
- 9) Optionally substituted $-C_1-C_8$ arylalkyl;
- 10) Optionally substituted heteroaryl;
- 15 11) Optionally substituted $-C_1-C_8$ heteroarylalkyl; and
- 12) NR^9R^{10} ; wherein R^9 and R^{10} are each independently selected from hydrogen,
 optionally substituted $-C_1-C_8$ alkyl, optionally substituted $-C_2-C_8$ alkenyl, optionally
 substituted $-C_2-C_8$ alkynyl, optionally substituted $-C_3-C_8$ cycloalkyl, optionally
 substituted aryl, optionally substituted alkylaryl, optionally substituted 3- to 8-
 20 membered heterocycloalkyl, optionally substituted heteroaryl, and optionally
 substituted alkylheteroaryl; alternatively, R^9 and R^{10} are taken together with the
 nitrogen atom to which they are attached to form a heterocyclic ring.

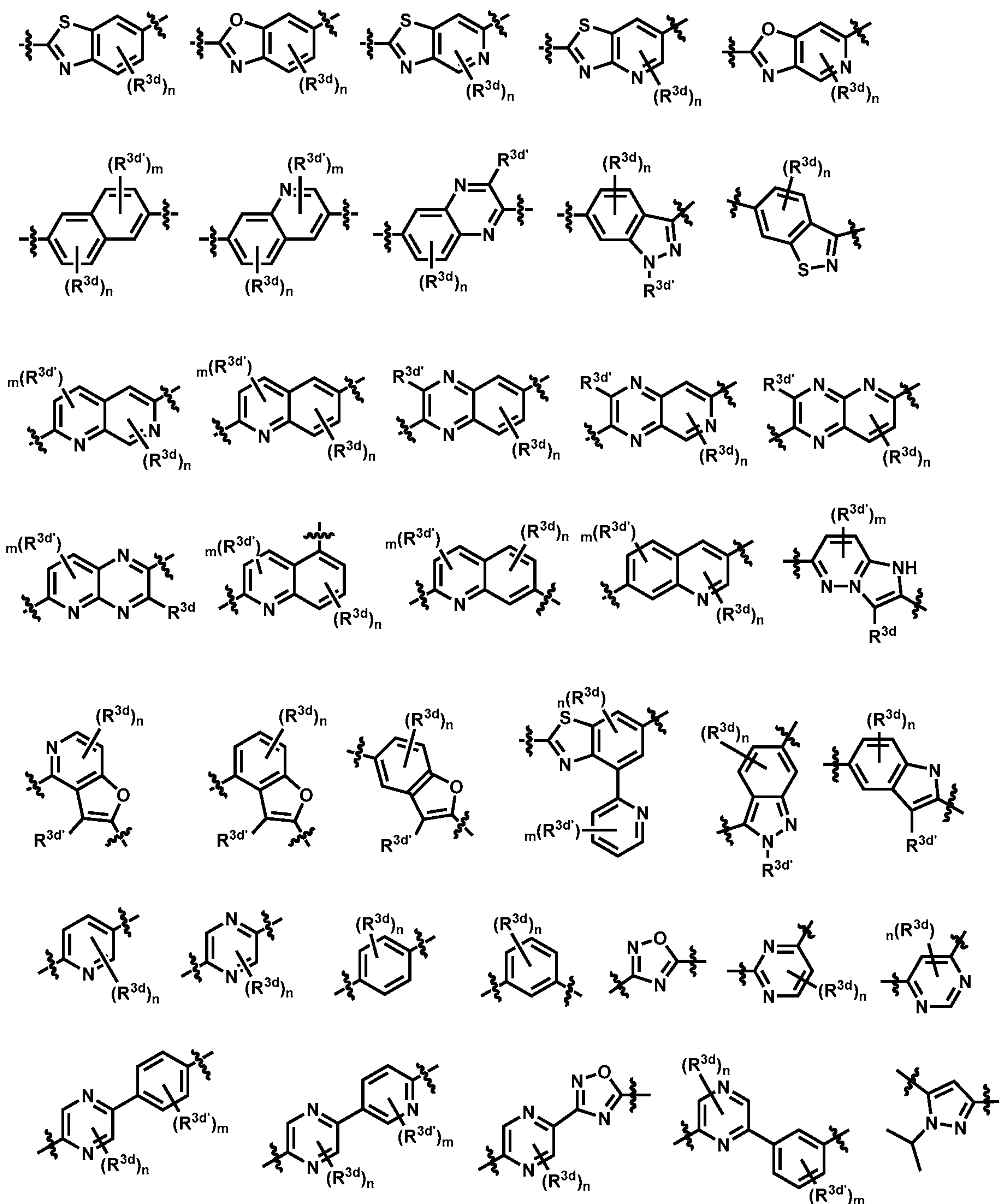
2. The compound of claim 1, wherein R^2 is selected from the groups set forth below:



wherein each of above groups is optionally further substituted.

- 5 3. The compound of claim 1, wherein A is  or , and R^{3c} is as defined in claim 1.

4. The compound of claim 1, wherein B is selected from the groups set forth below:

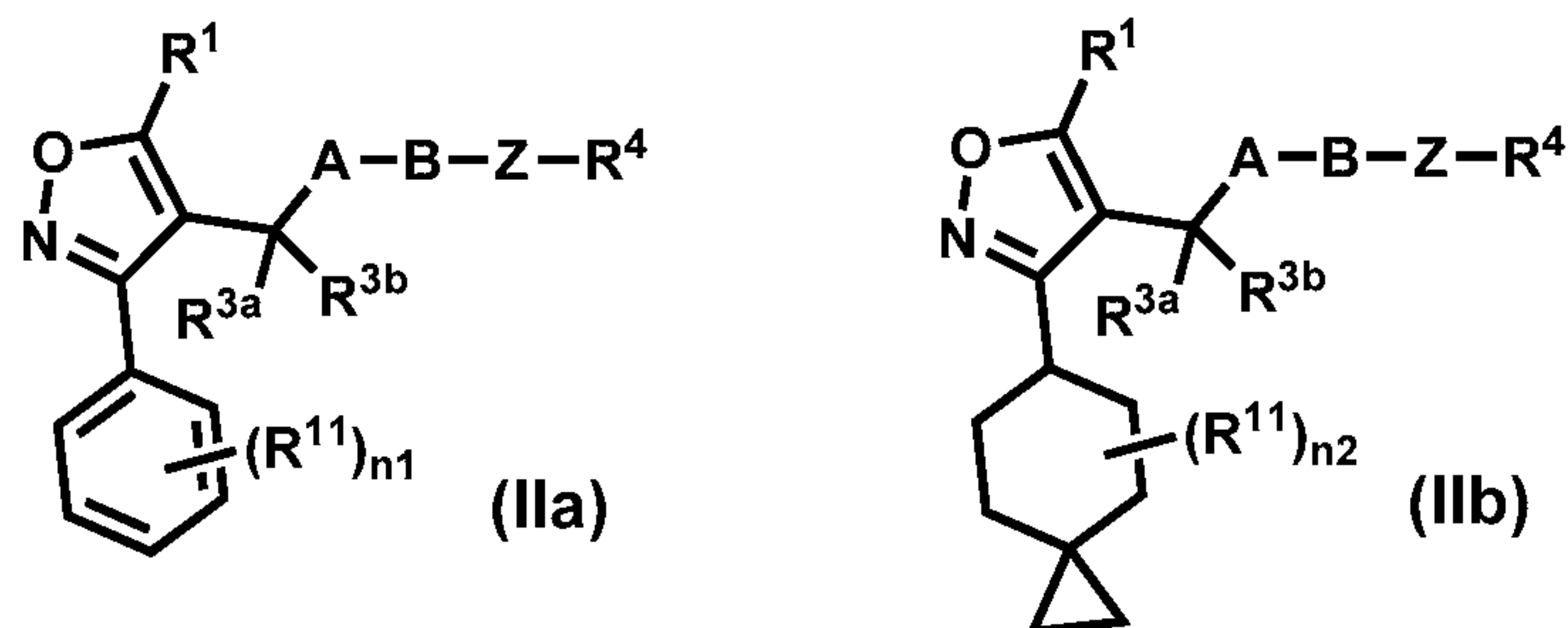


wherein, one of the indicated valences is the point of attachment to A and the other is the point of attachment to the Z; R^{3d} and $R^{3d'}$ are independently selected from the group

5 consisting of hydrogen, halogen, -CN, -NO₂, -NH₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₃-C₆ cycloalkyl, optionally

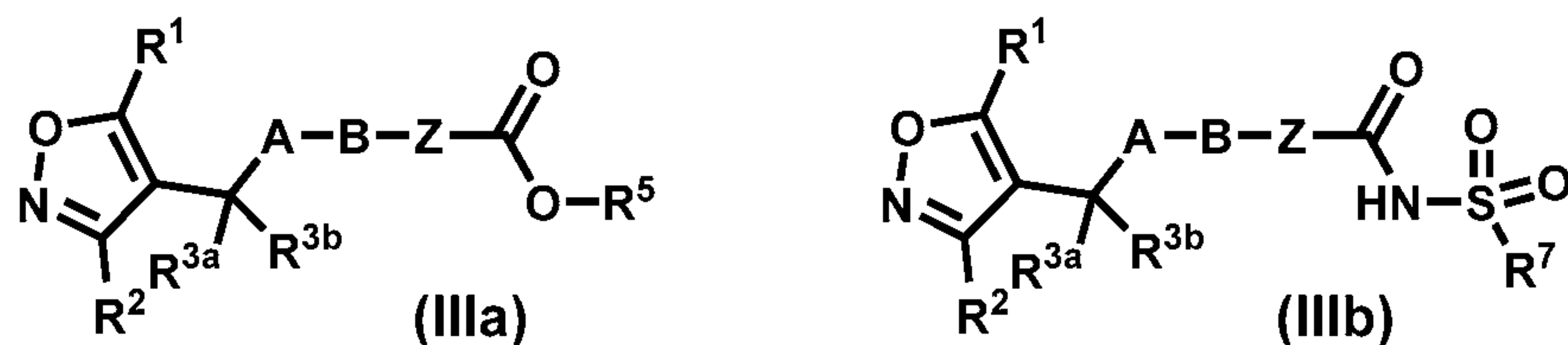
substituted C₃-C₆ cycloalkenyl, optionally substituted aryl, and optionally substituted heteroaryl; and m and n are independently 0, 1 2 or 3.

5. The compound of claim 1, represented by Formula (IIa), or Formula (IIa), or a pharmaceutically acceptable salt thereof:



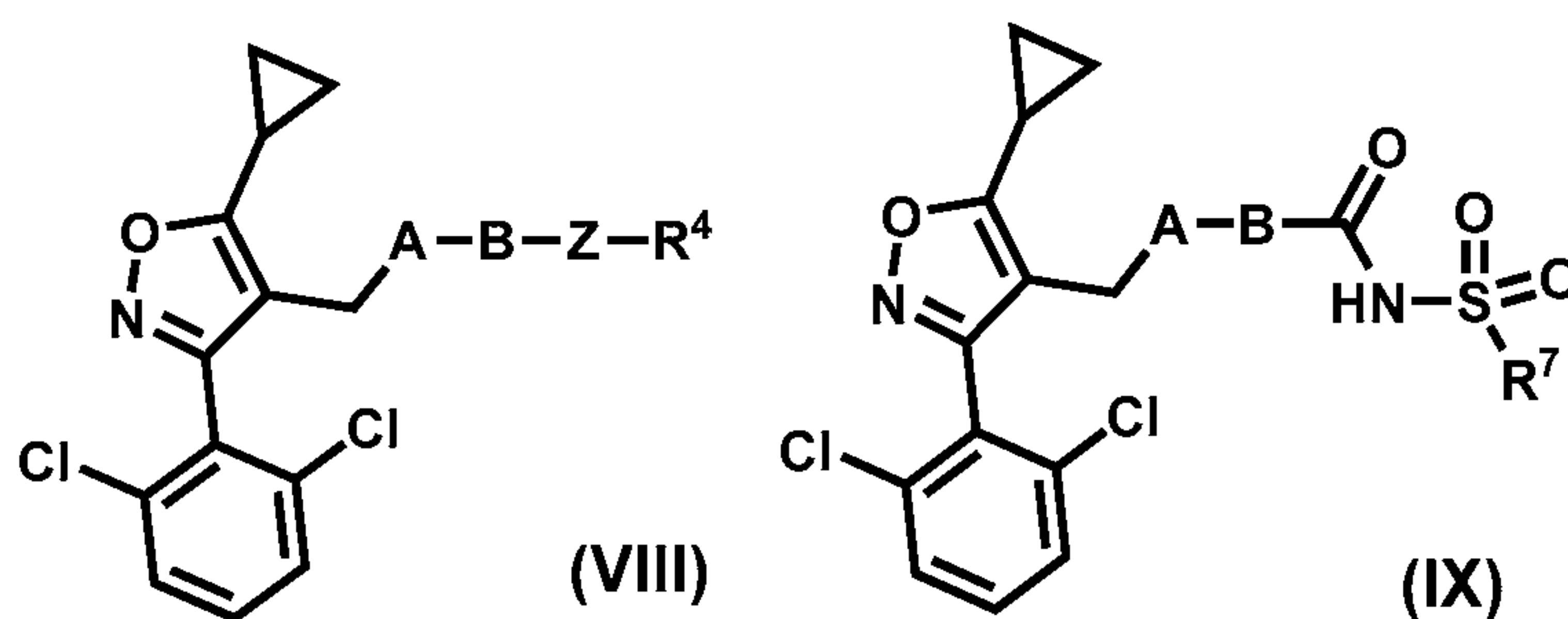
wherein R¹, R^{3a}, R^{3b}, A, B, Z and R⁴ are as defined in claim 1; R¹¹ at each occurrence is independently selected from the group consisting of halogen, optionally substituted -C₁-C₆ alkyl, optionally substituted -C₁-C₆ alkoxy, optionally substituted -C₃-C₆ cycloalkyl, optionally substituted -C₃-C₆ cycloalkenyl, , optionally substituted aryl, or optionally substituted heteroaryl; n₁ is 0, 1, 2, 3, 4, or 5; and n₂ is 0, 1, or 2.

6. The compound of claim 1, represented by Formula (IIIa), or Formula (IIIb), or a pharmaceutically acceptable salt thereof:



wherein A, B, Z, R¹, R², R^{3a}, R^{3b}, R⁵, and R⁷ are as defined in claim 1.

7. The compound of claim 1, represented by Formula (VIII), or Formula (IX), or a pharmaceutically acceptable salt thereof:



wherein A, B, Z, R⁴ and R⁷ are as defined in claim 1.

8. A compound according to claim 1, selected from:

(A) Compounds according to Formula (VIII), wherein A, B, and Z-R⁴ are delineated for each compound in Table 1:

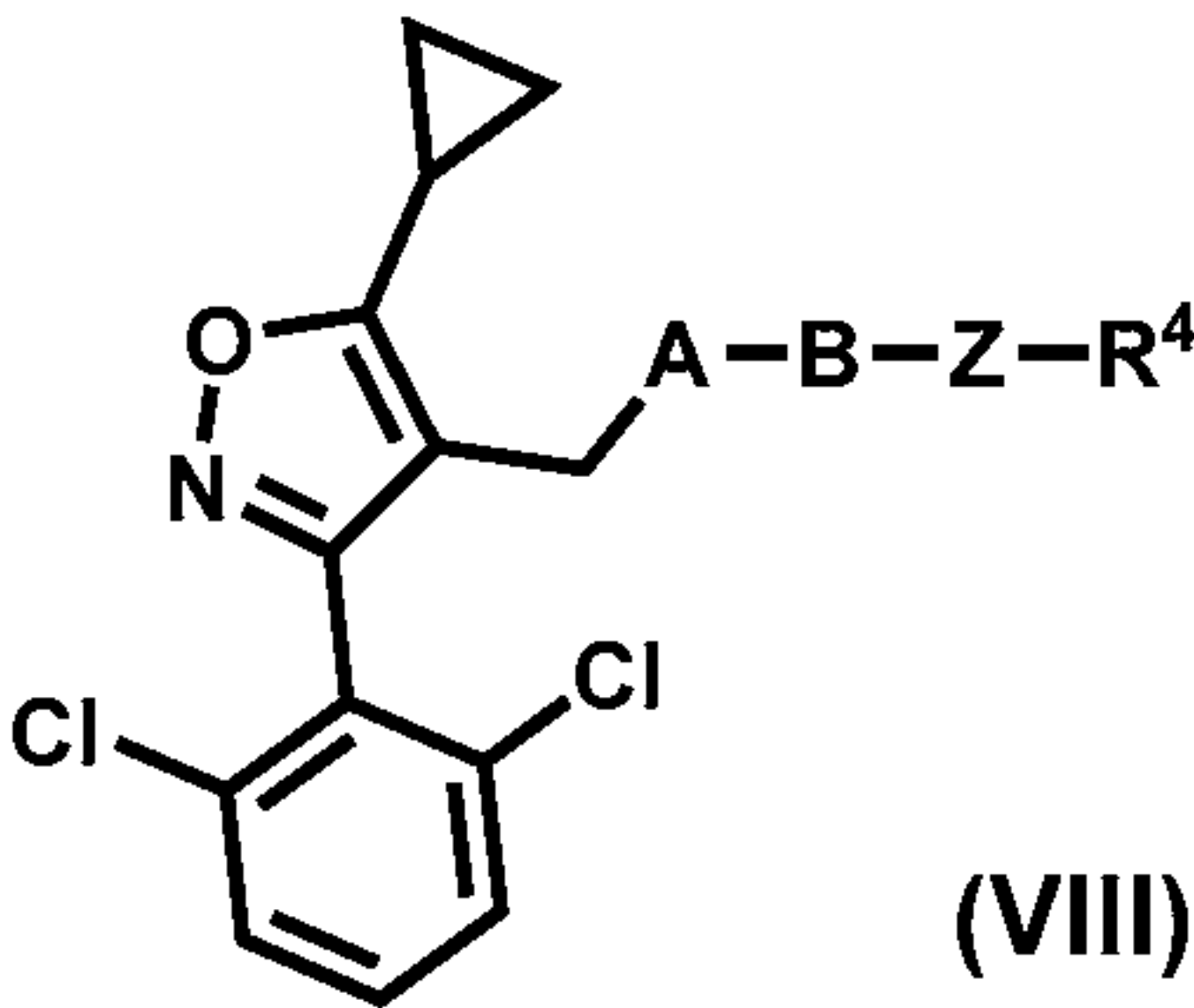


Table 1

Compound	A	B	-Z-R ⁴	Compound	A	B	-Z-R ⁴
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				36			
37				38			
39				40			
41				42			
43				44			
45				46			
47				48			

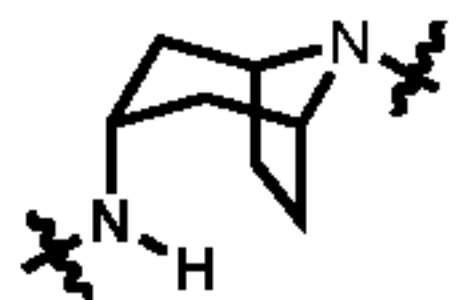
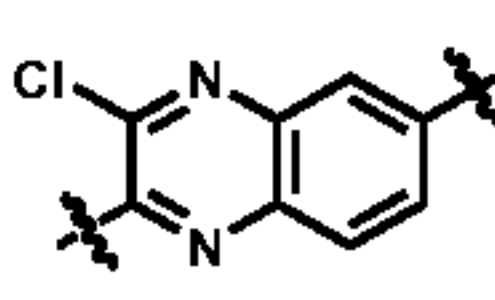
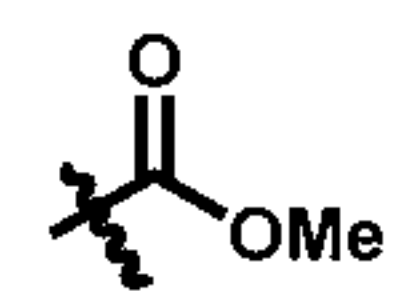
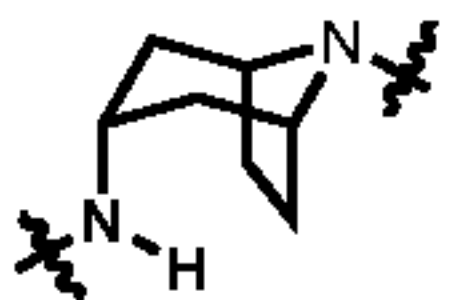
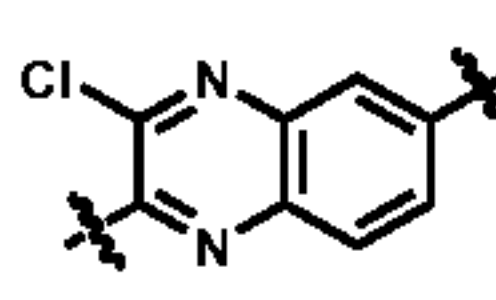
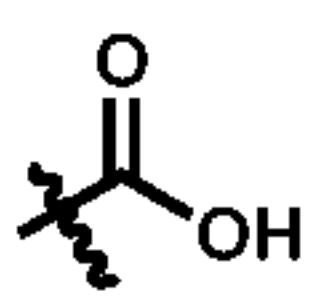
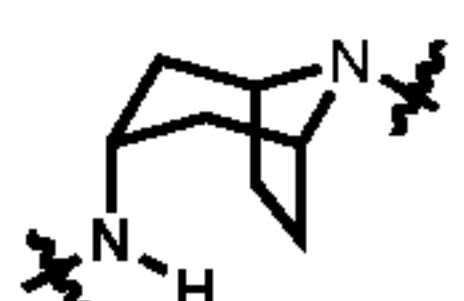
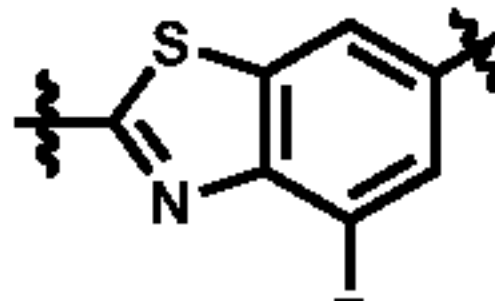
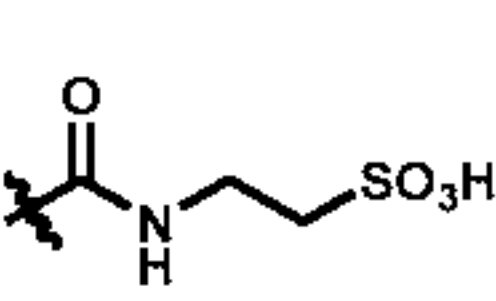
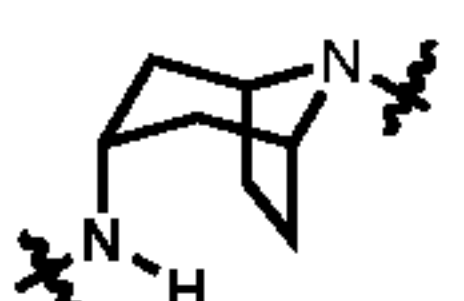
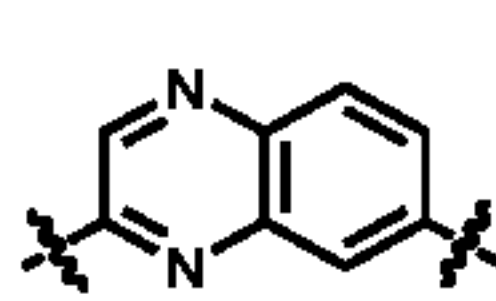
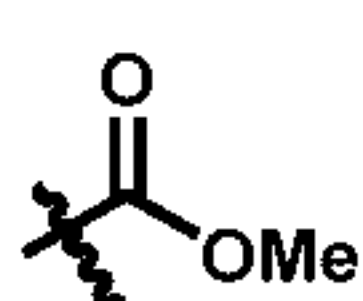
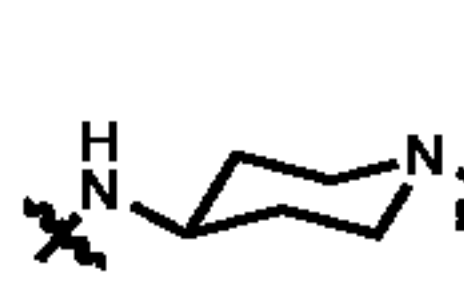
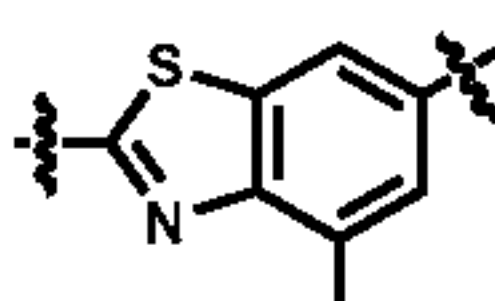
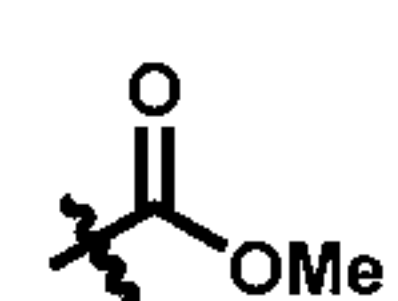
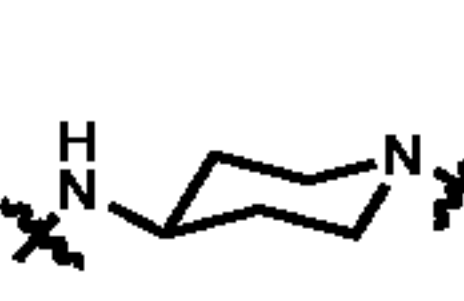
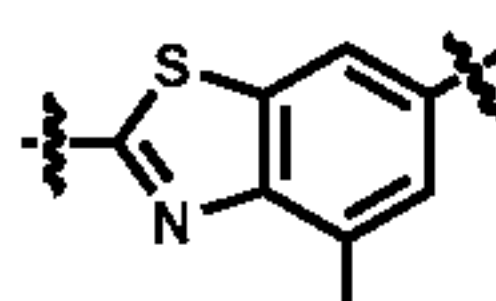
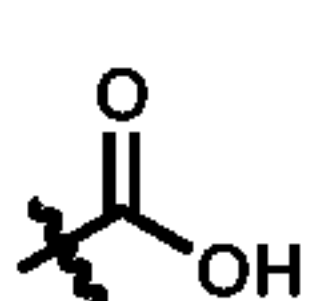
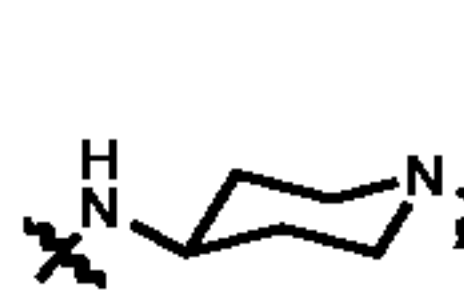
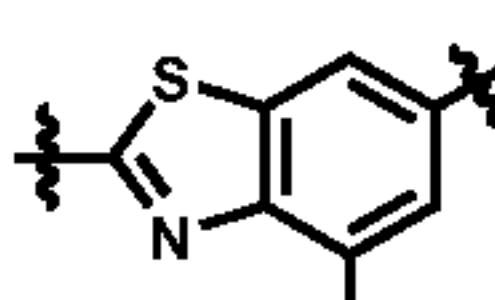
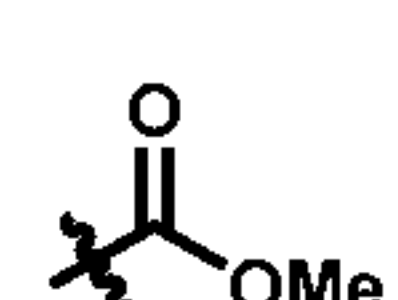
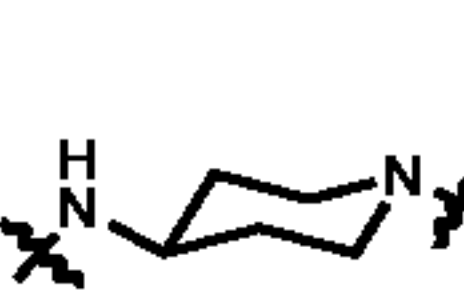
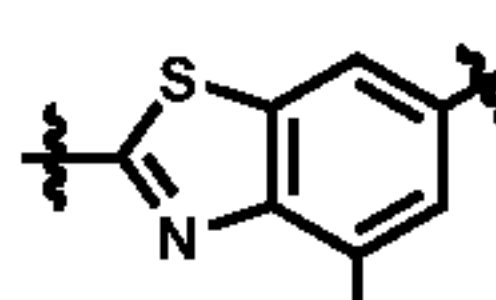
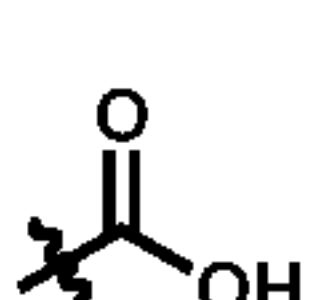
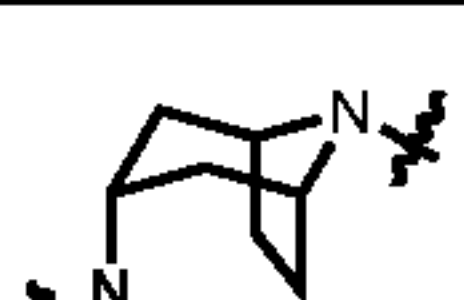
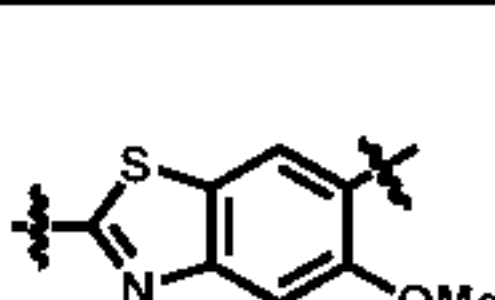
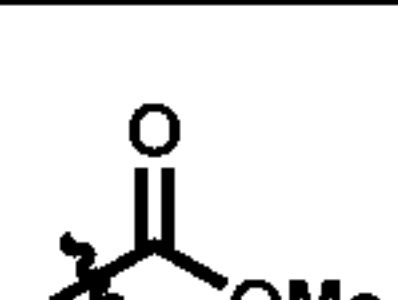
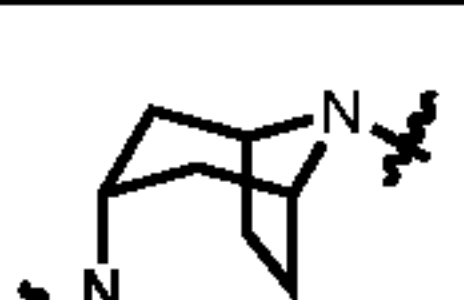
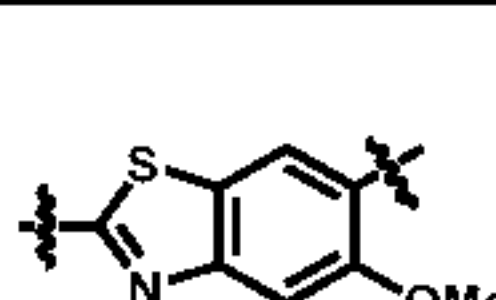
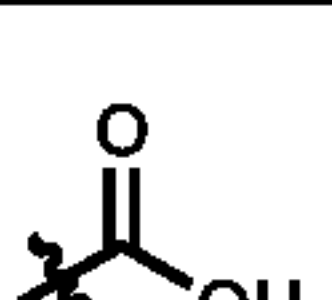
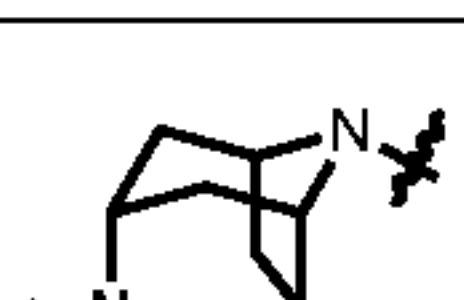
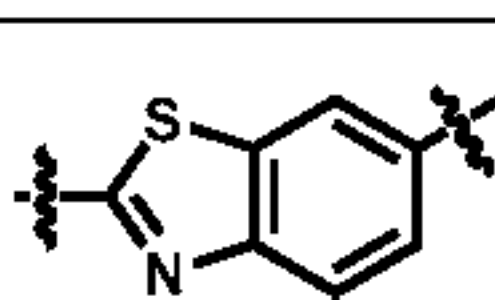
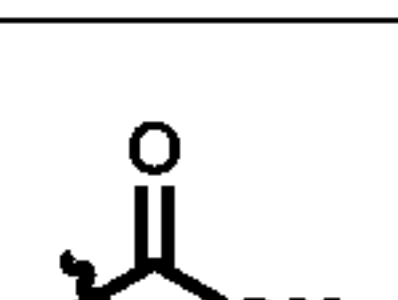
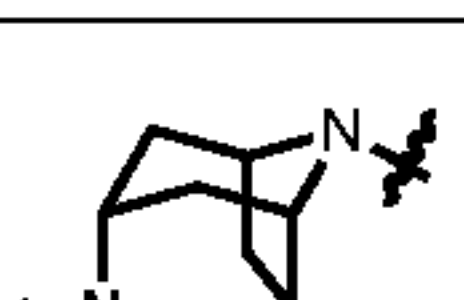
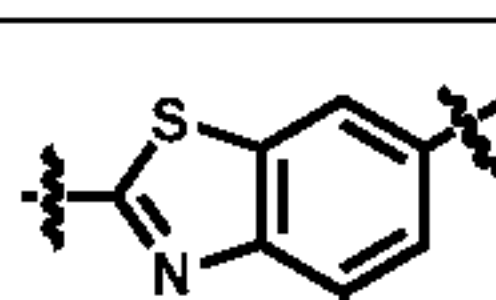
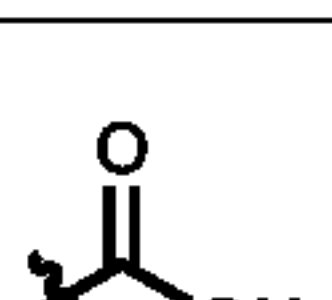
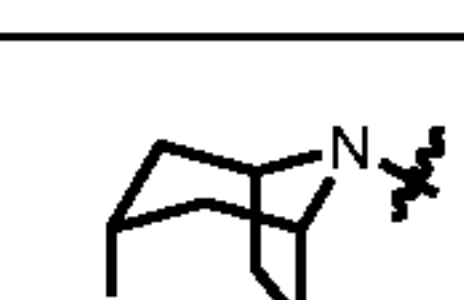
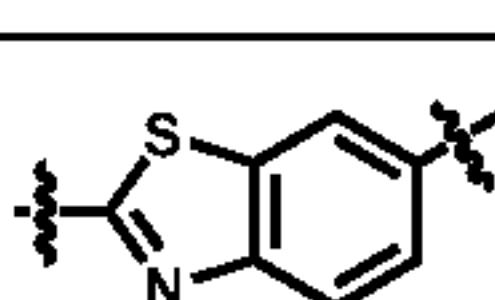
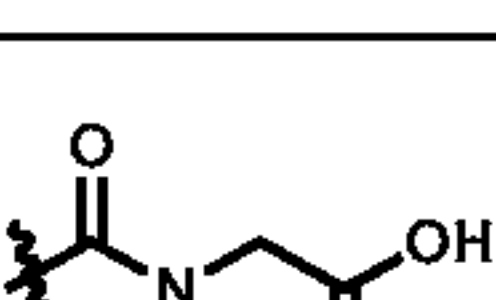
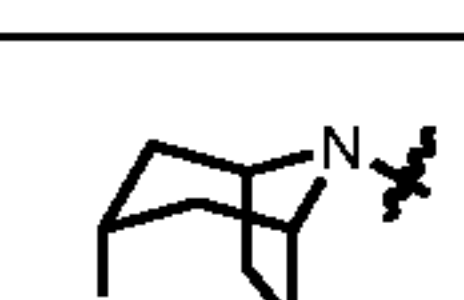
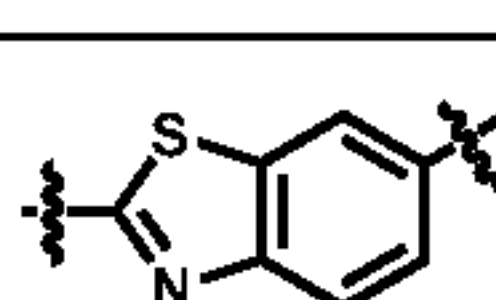
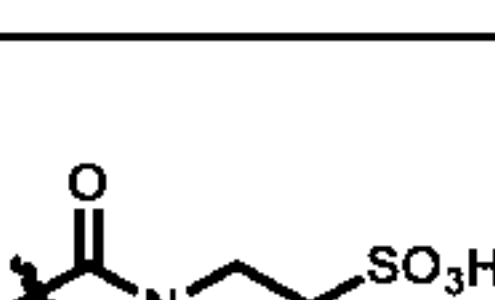
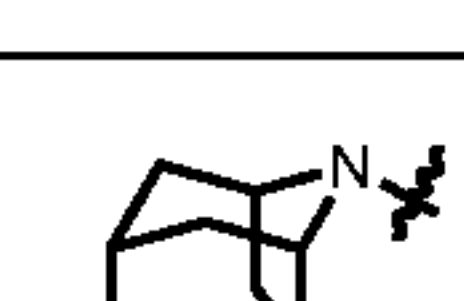
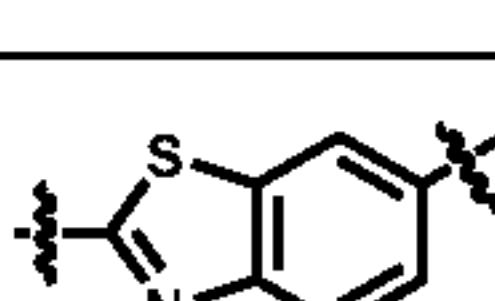
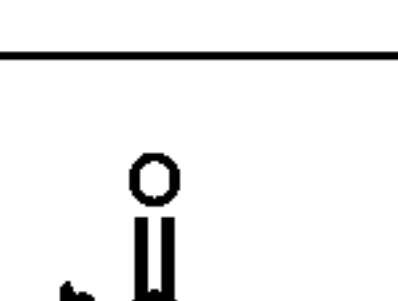
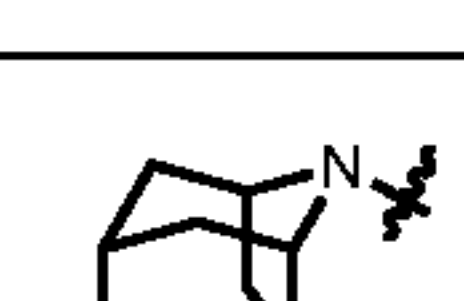
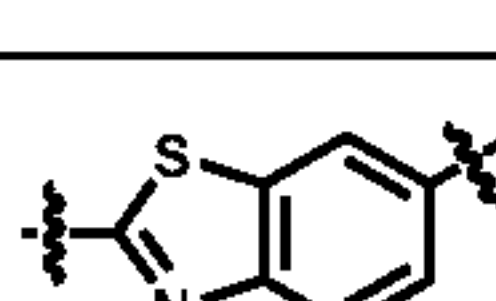
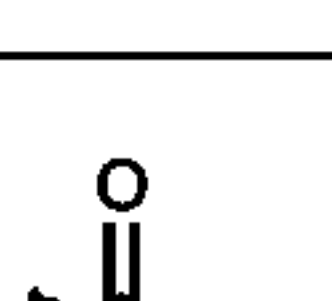
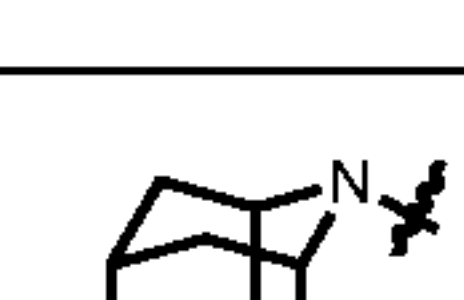
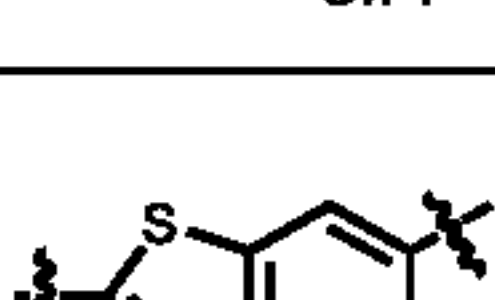
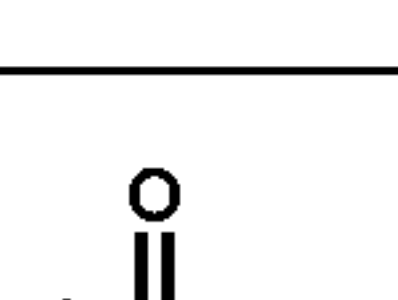
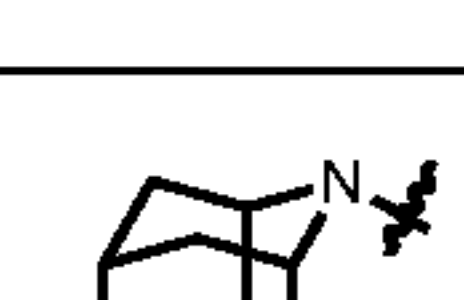
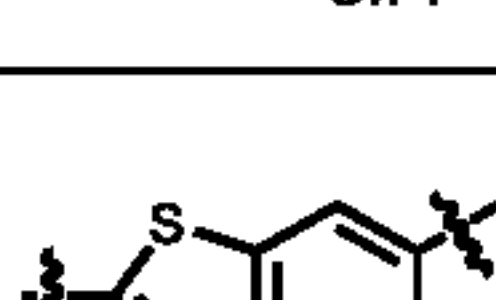
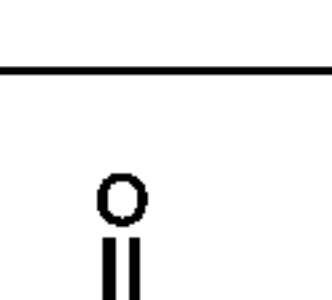
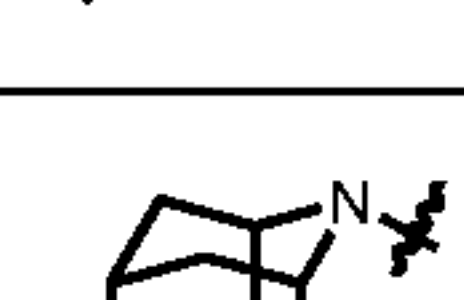
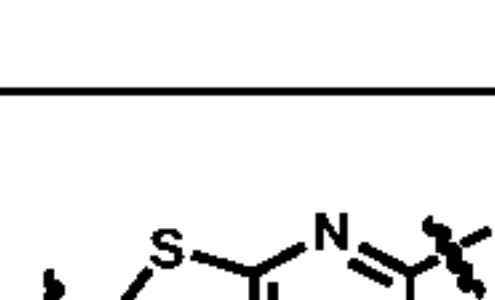
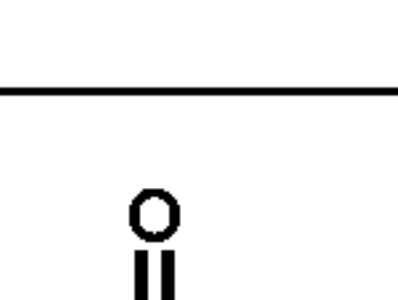
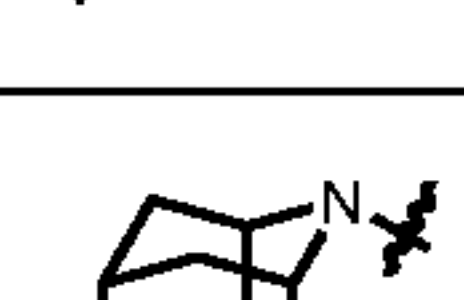
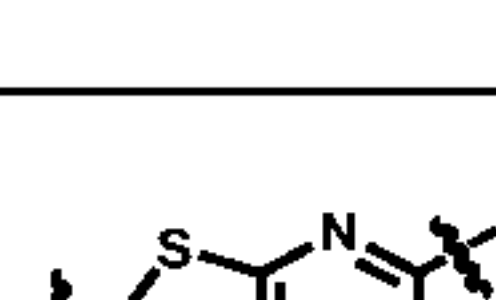
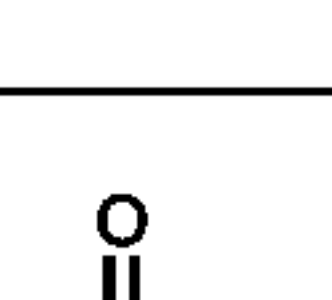
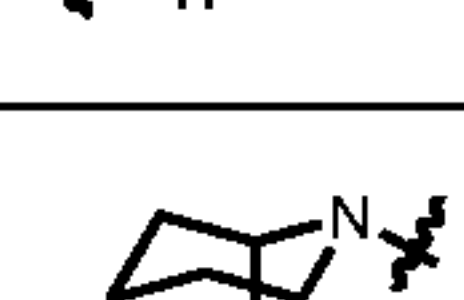
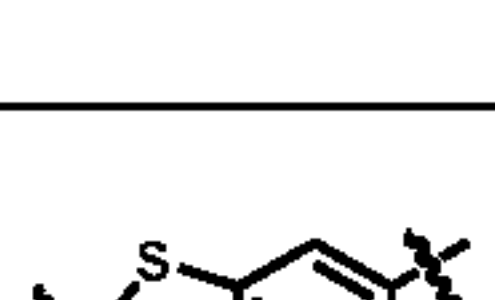
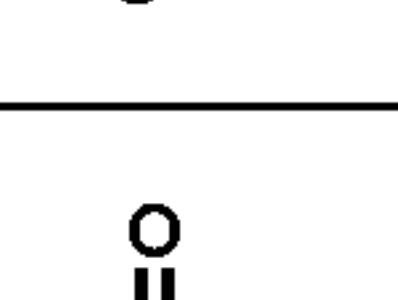
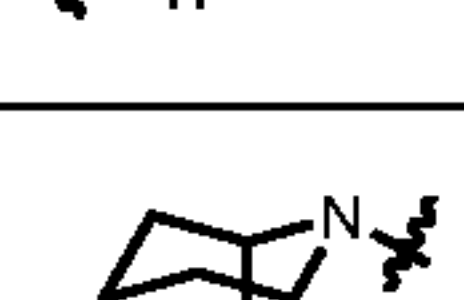
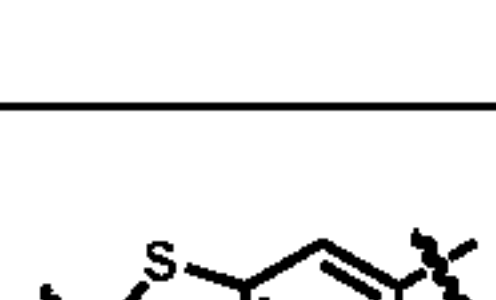
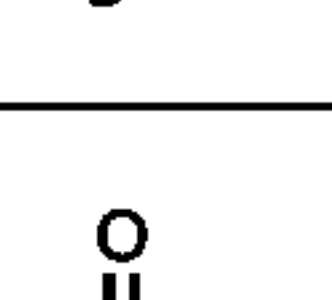
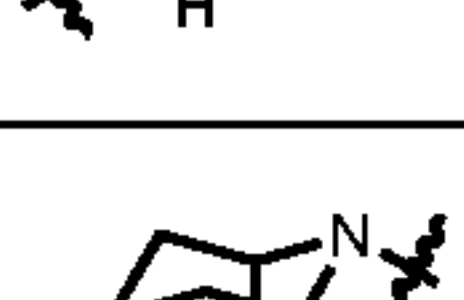
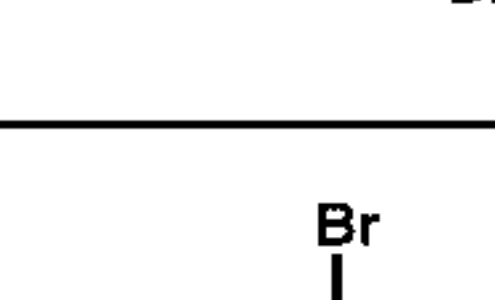
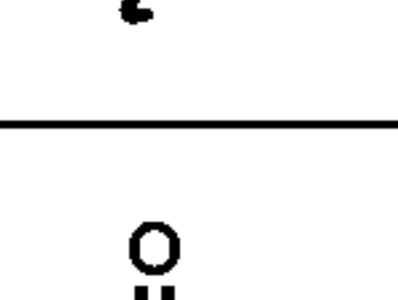
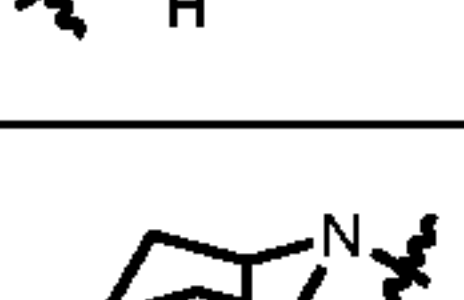
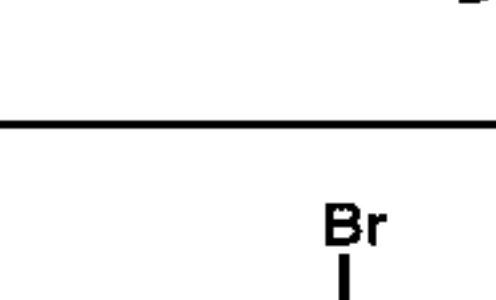
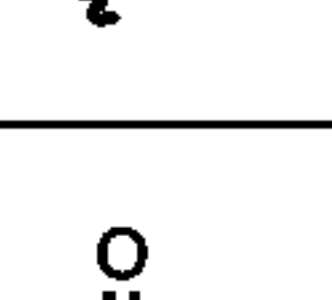
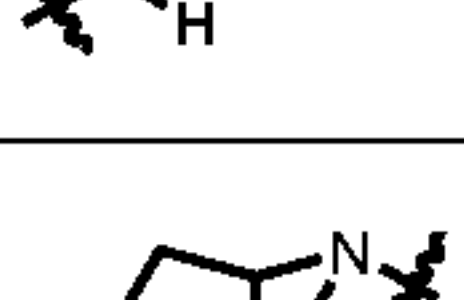
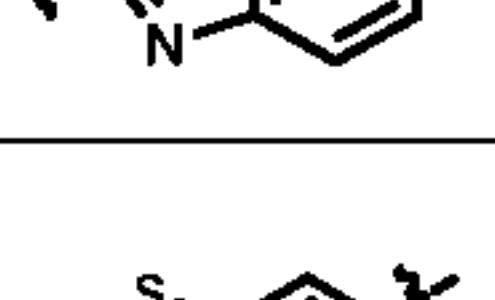
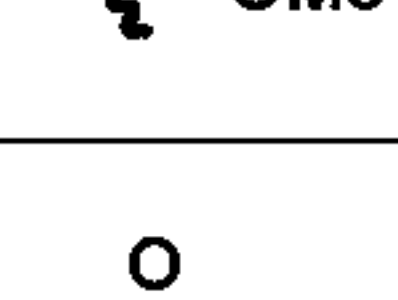
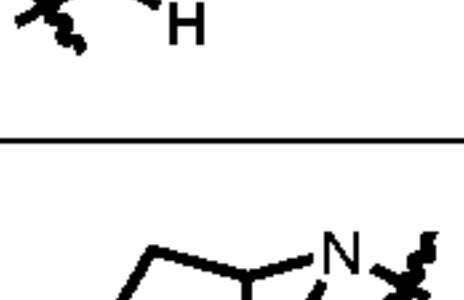
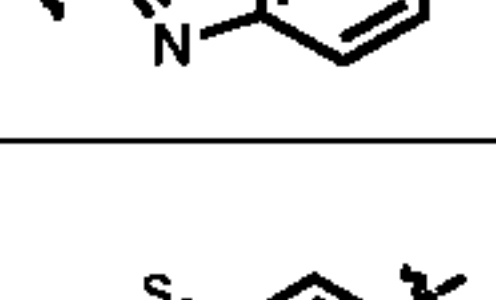
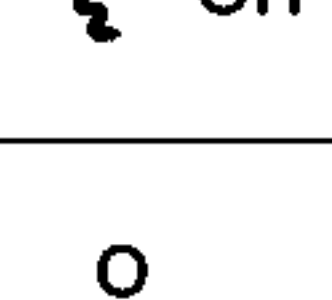
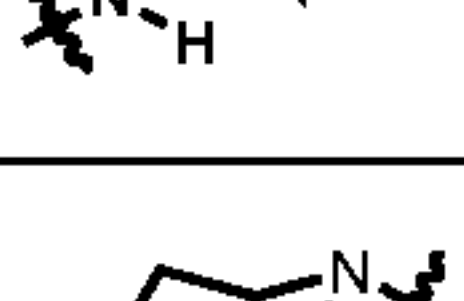
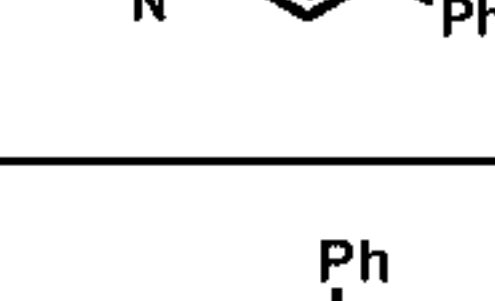
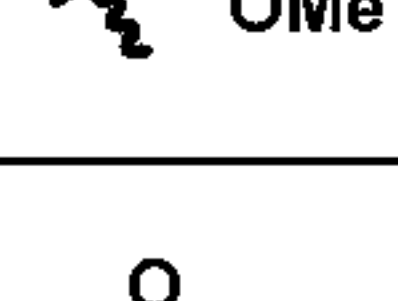
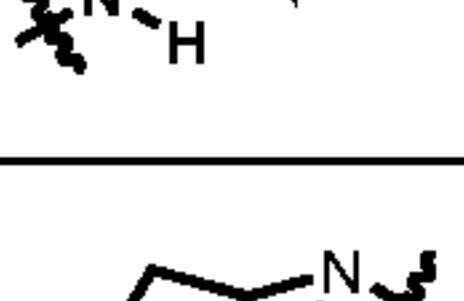
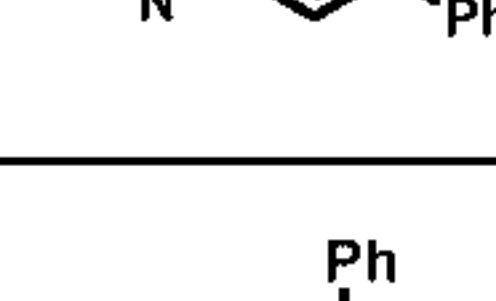
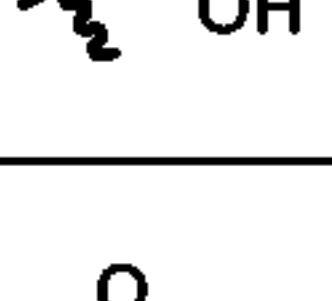
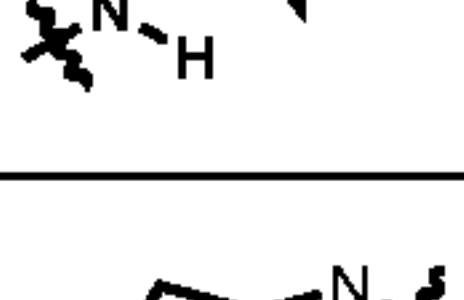
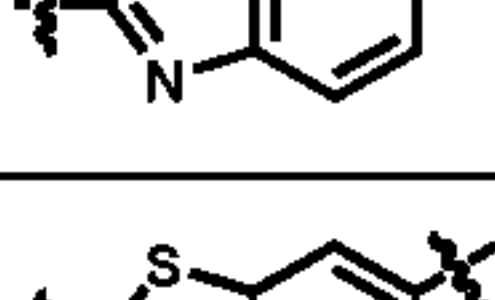
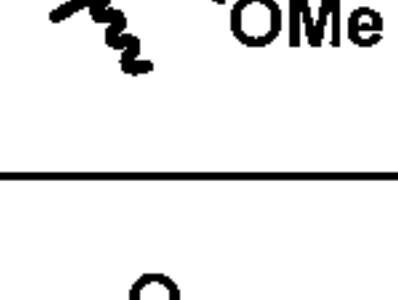
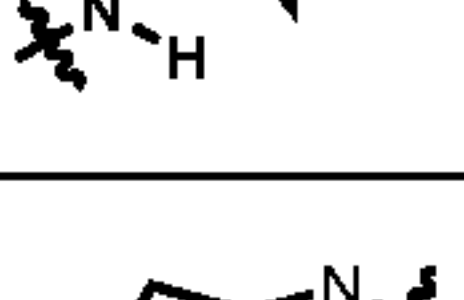
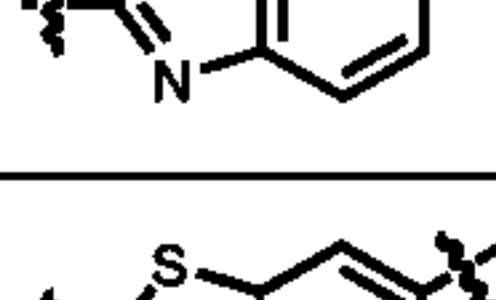
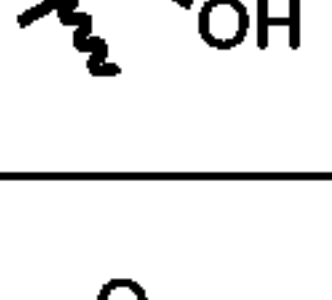
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and

(B) Compounds according to Formula (IX), wherein A, B, and R⁷ are delineated for each compounds in Table 2:

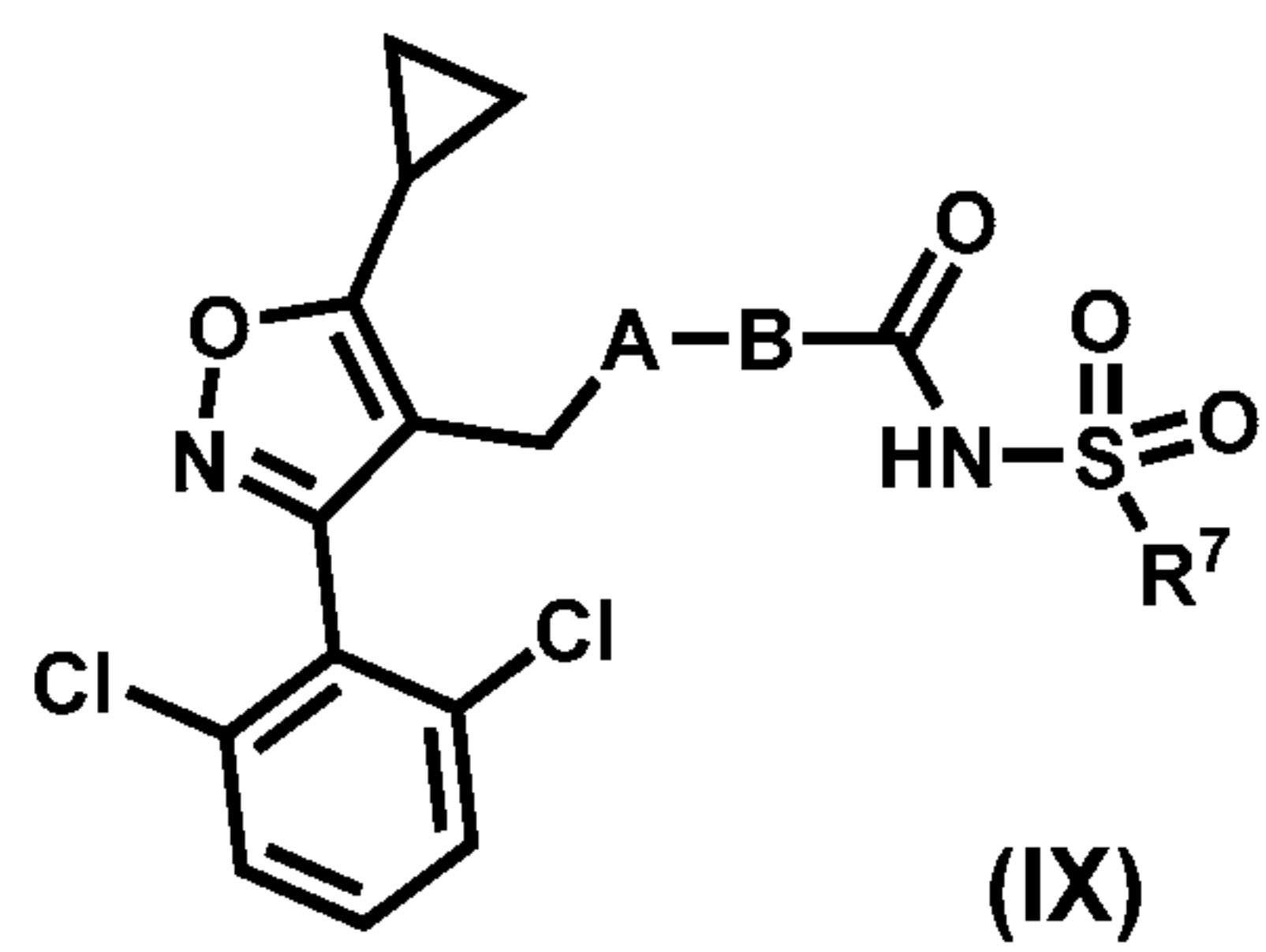
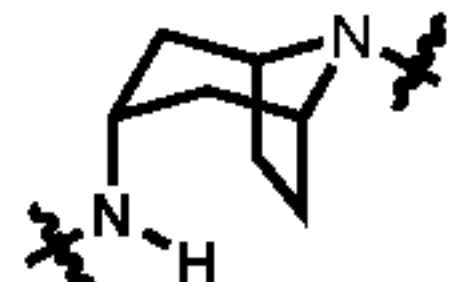
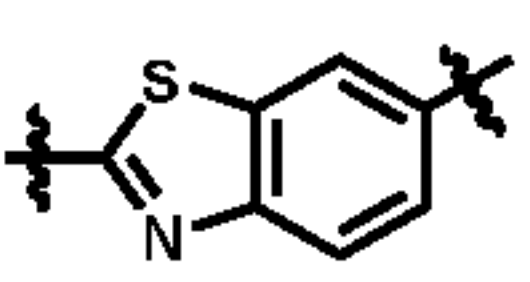
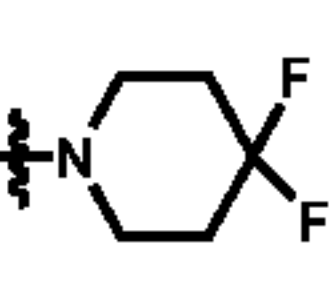
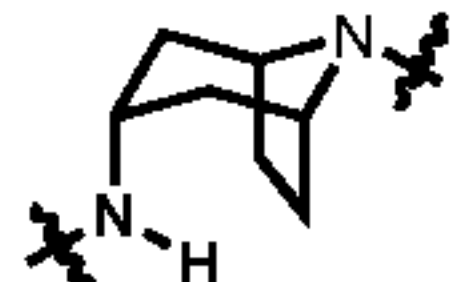
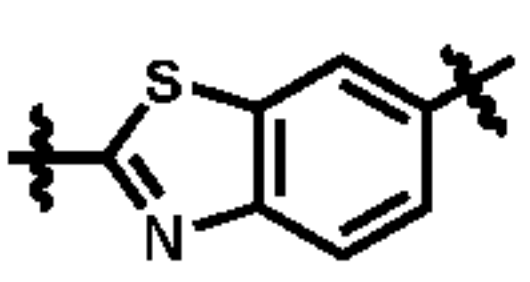
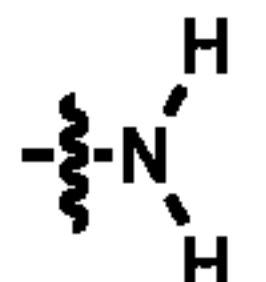
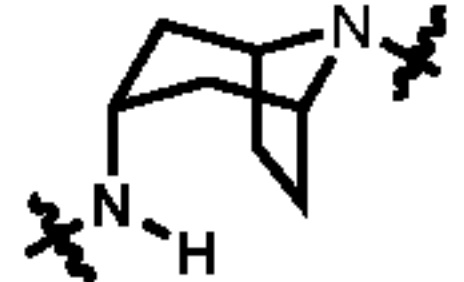
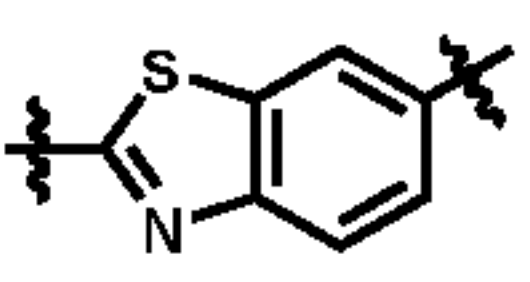
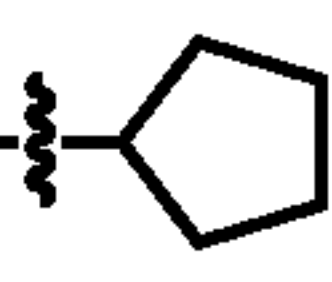
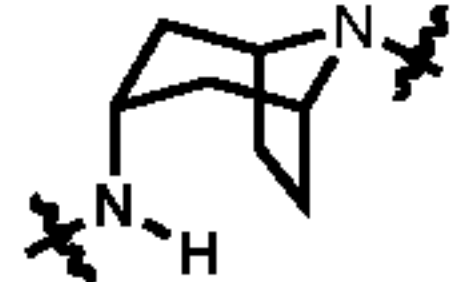
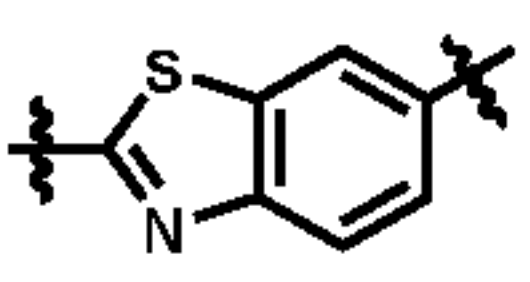
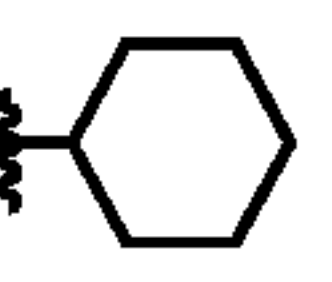
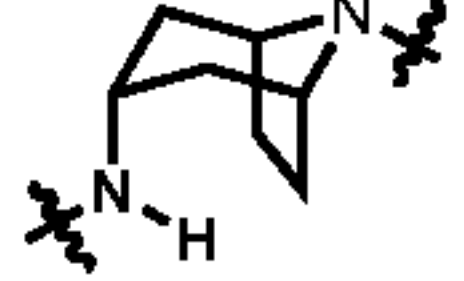
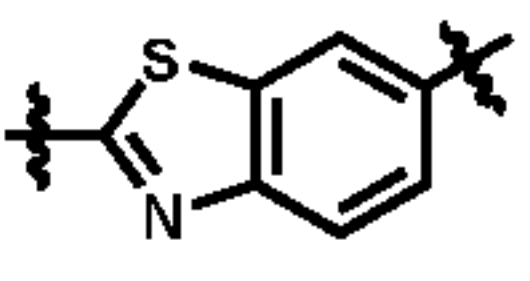
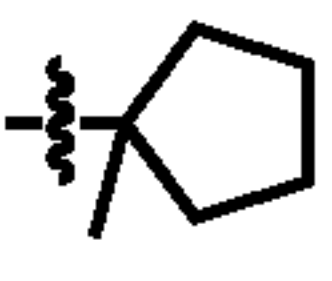
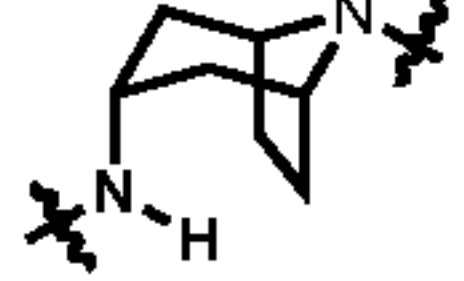
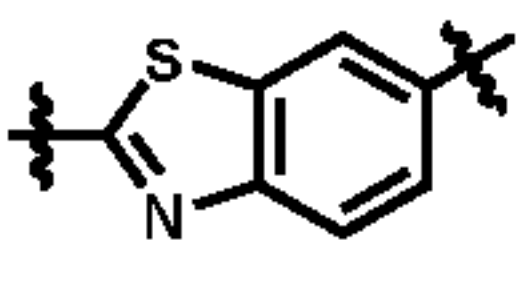
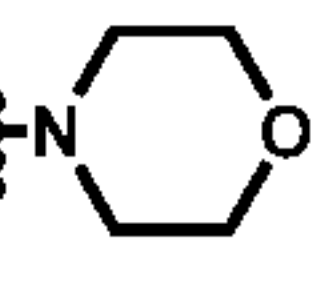
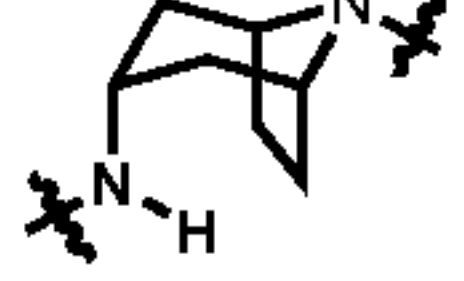
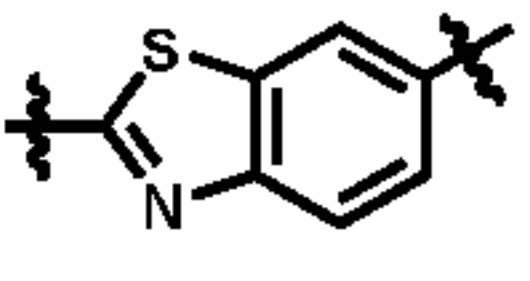
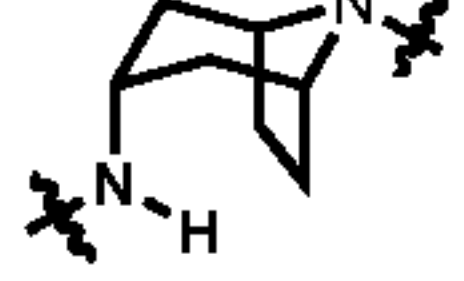
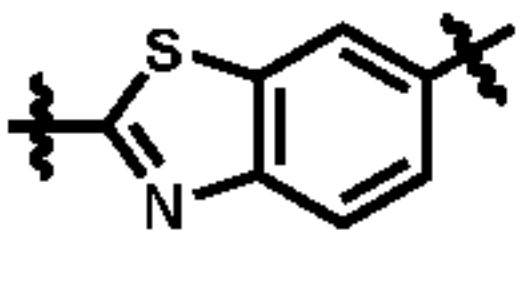
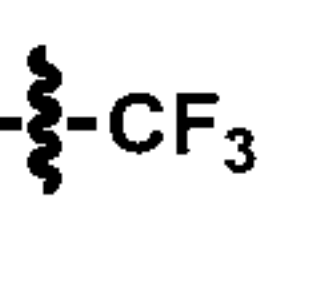
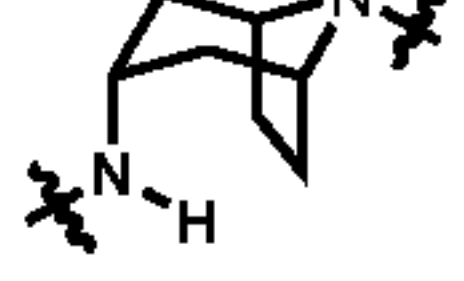
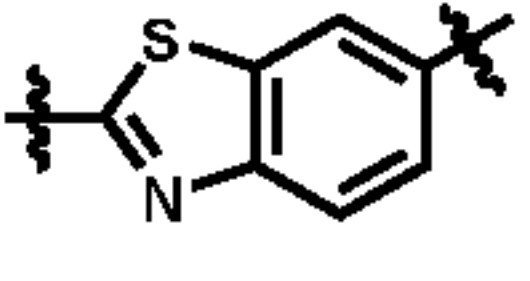
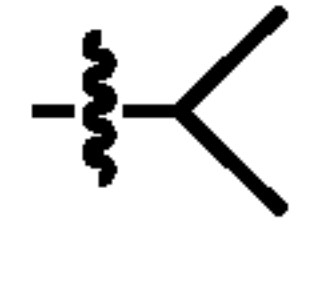
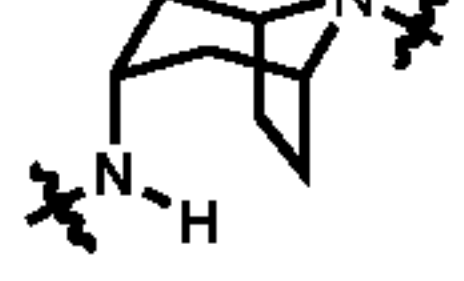
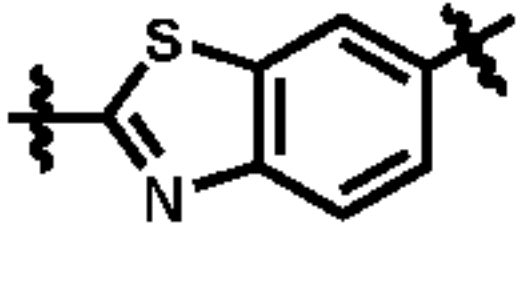
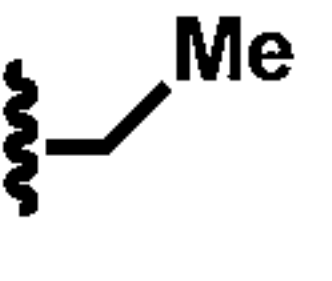
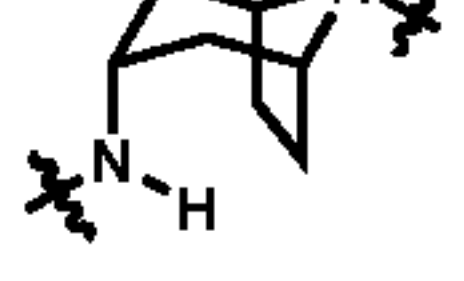
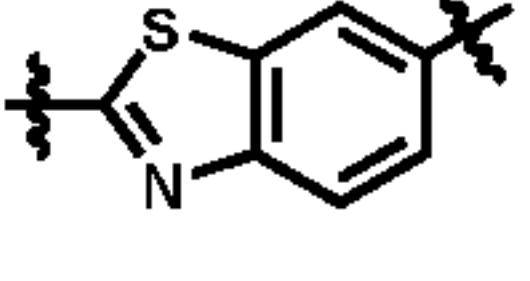
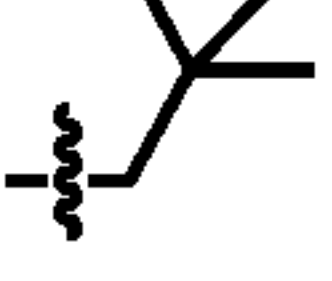
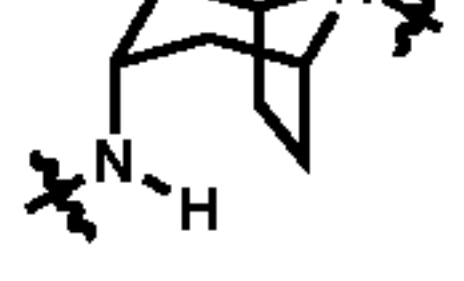
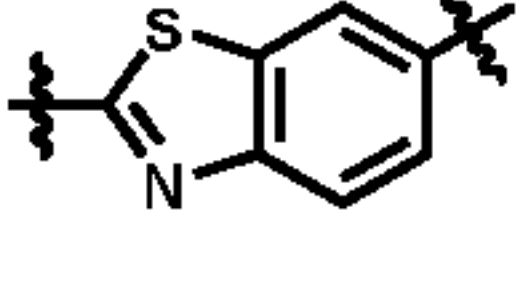
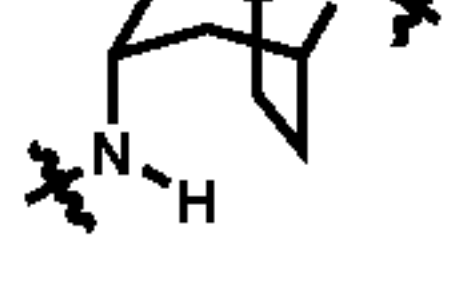
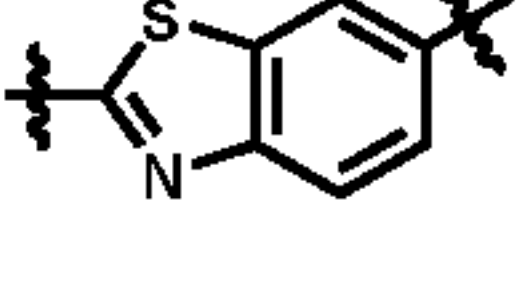
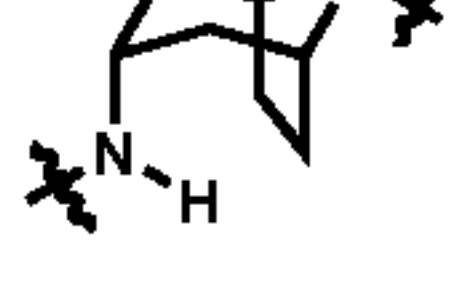
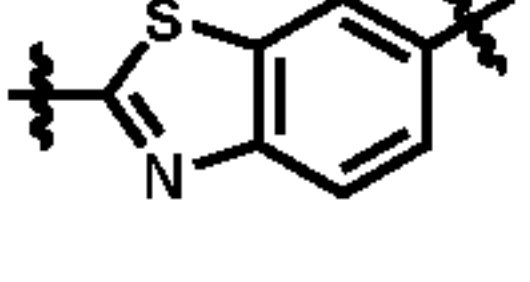
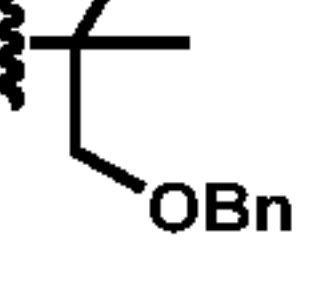
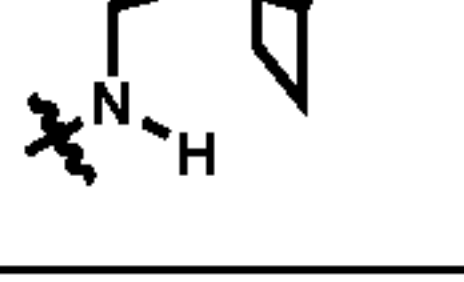
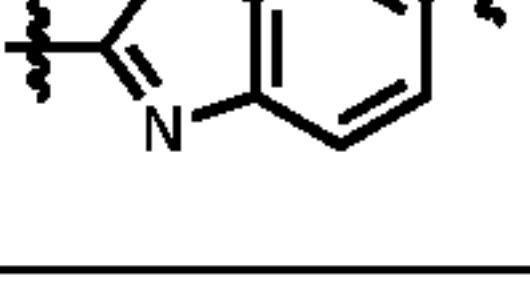
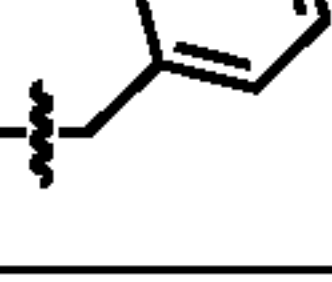
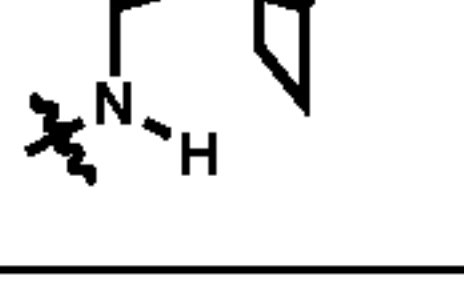
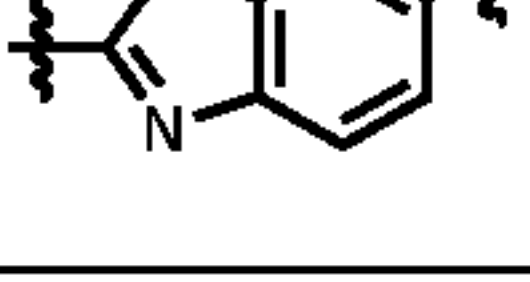
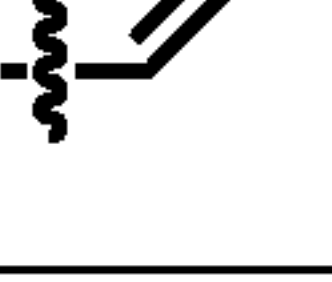
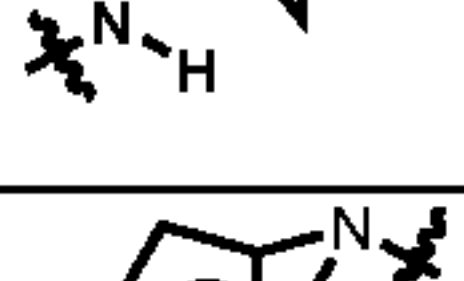
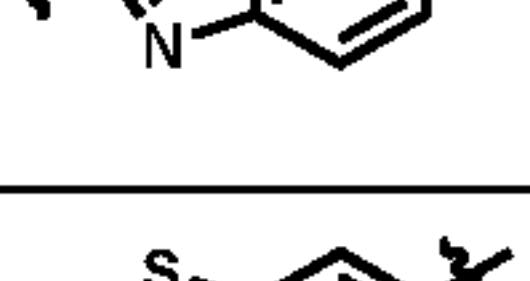
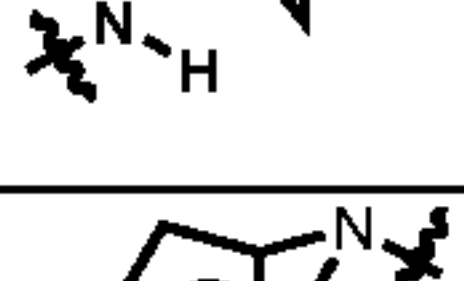
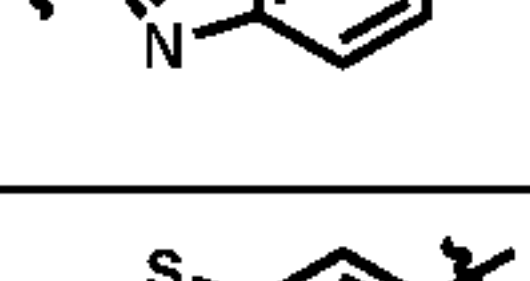
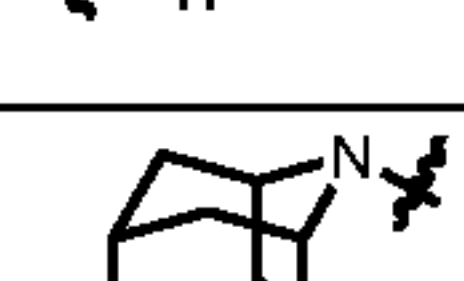
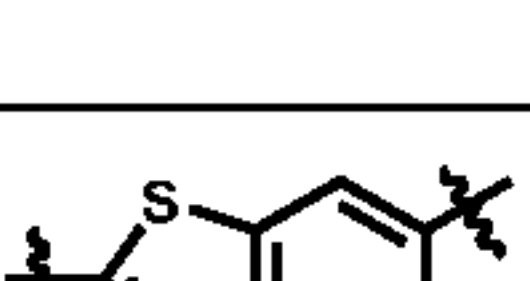
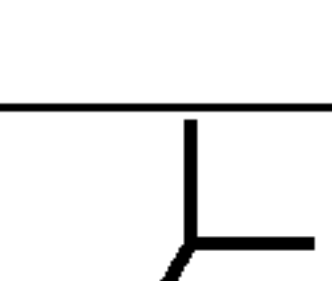
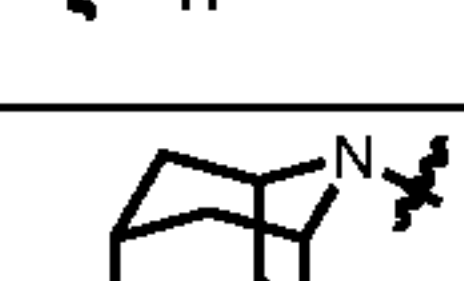
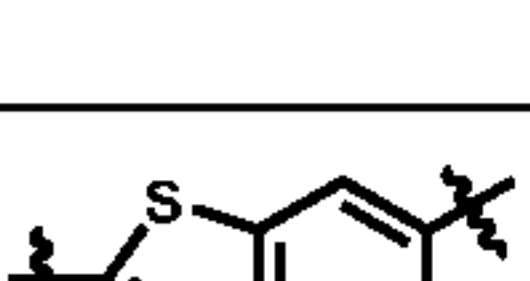
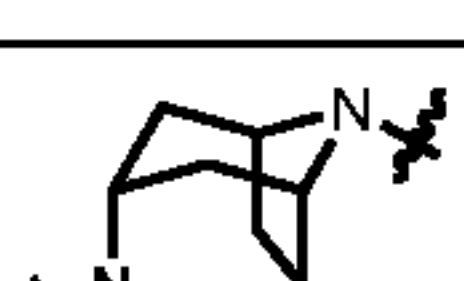
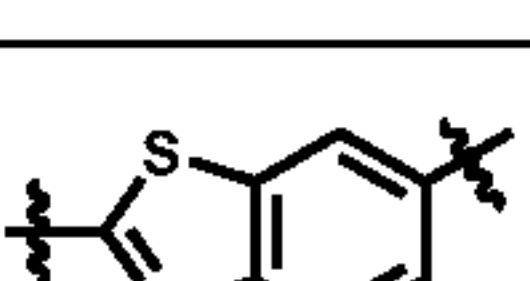
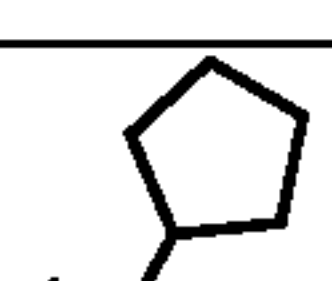
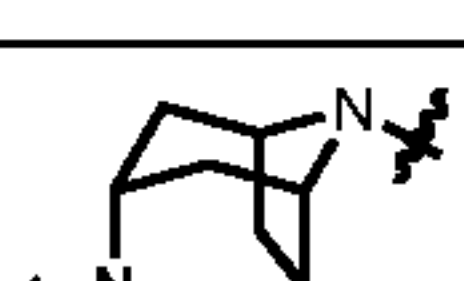
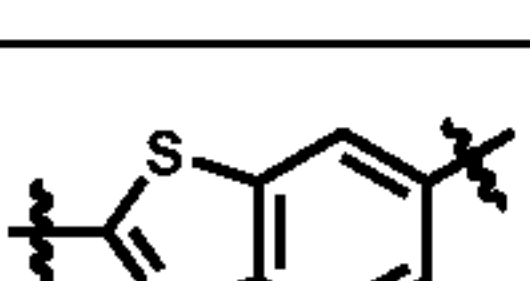
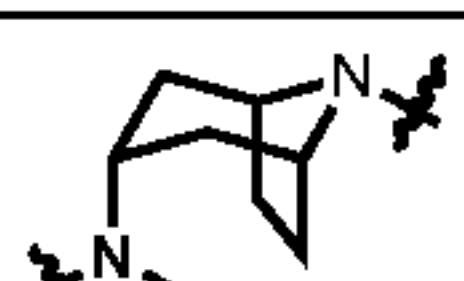
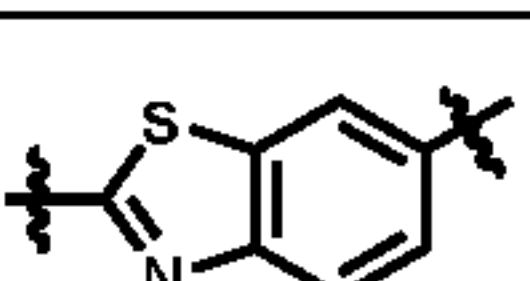
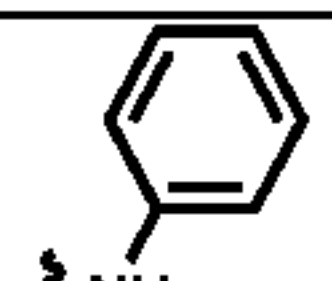
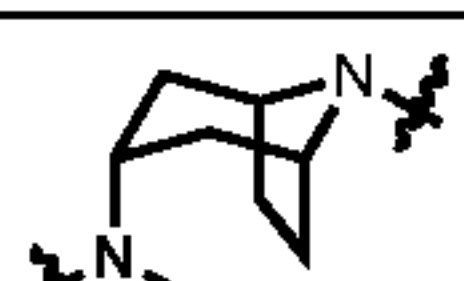
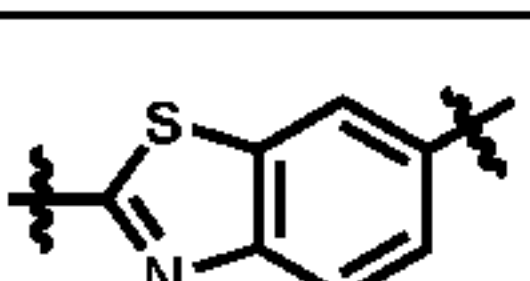
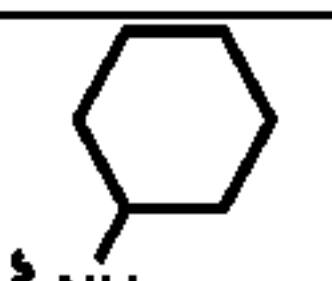
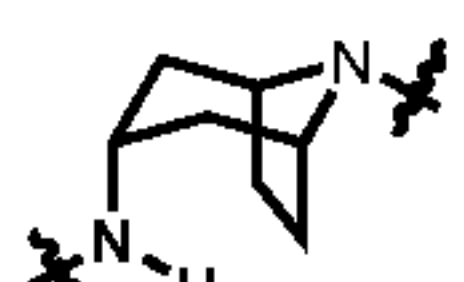
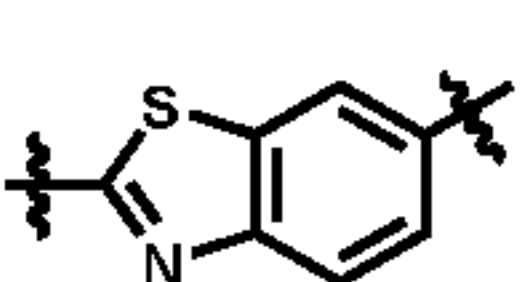
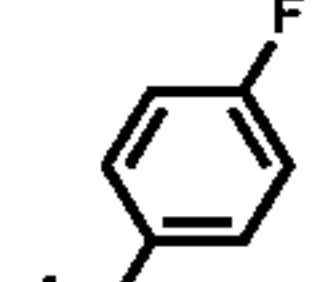
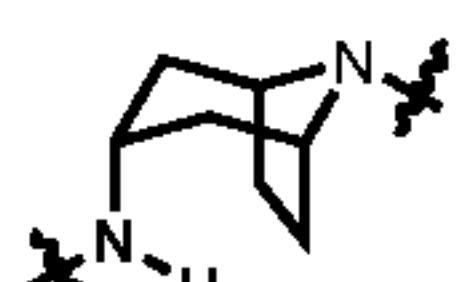
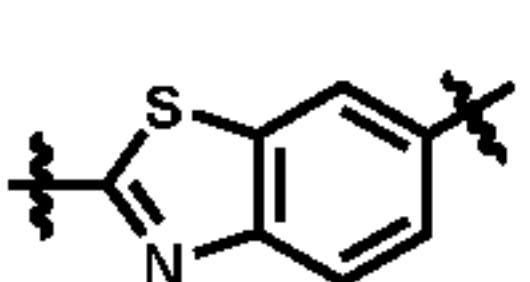
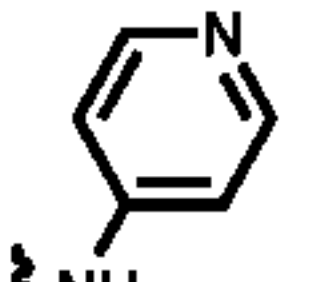
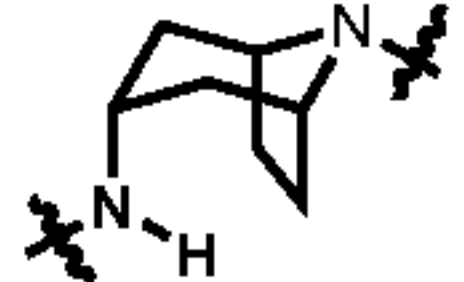
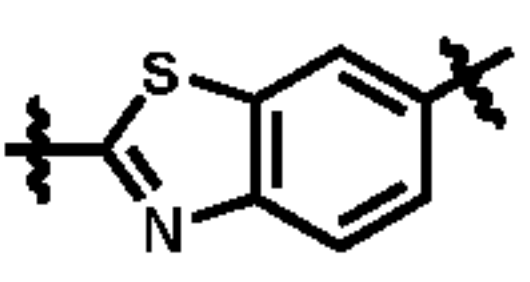
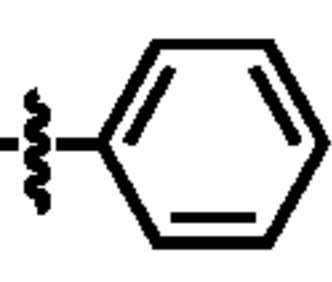
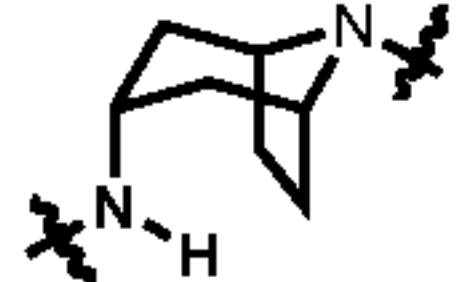
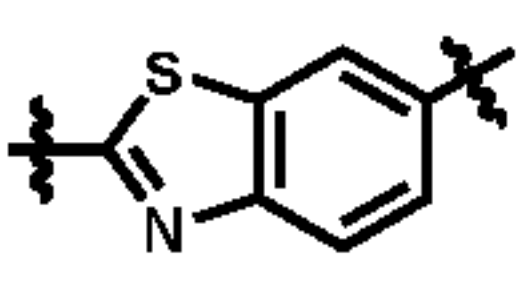
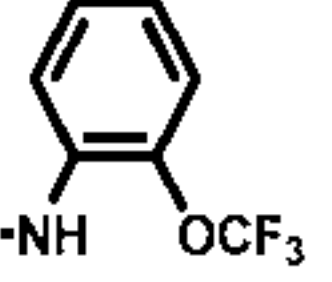
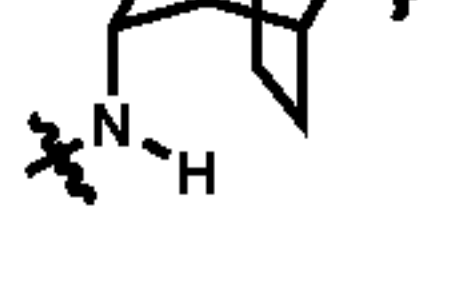
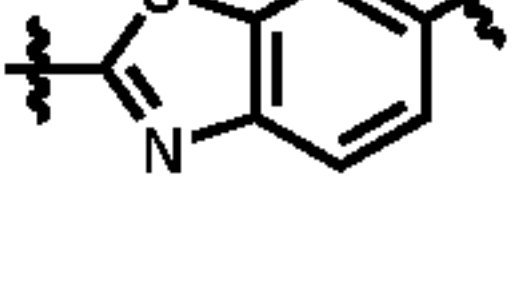
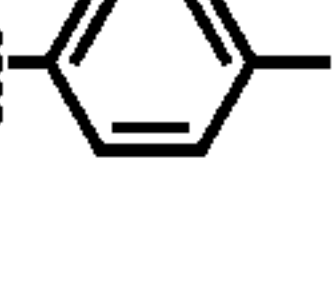
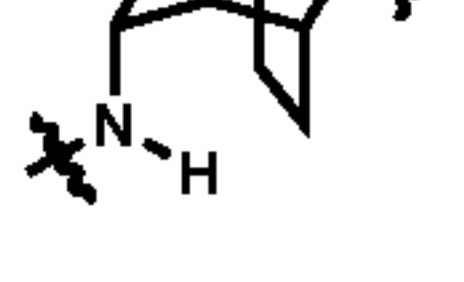
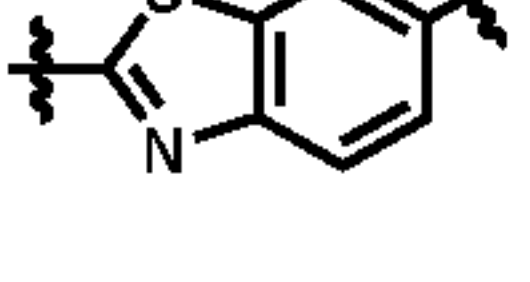
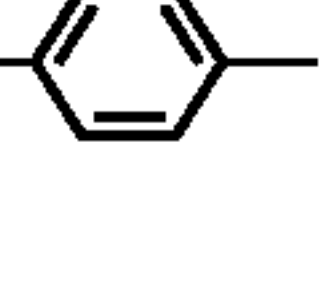
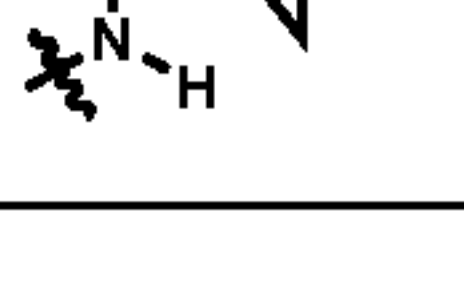
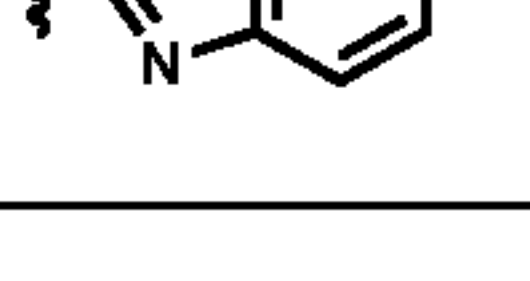
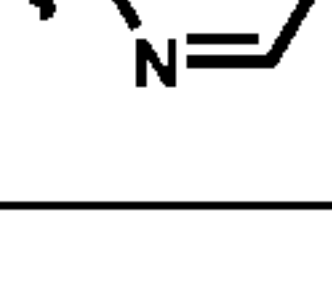
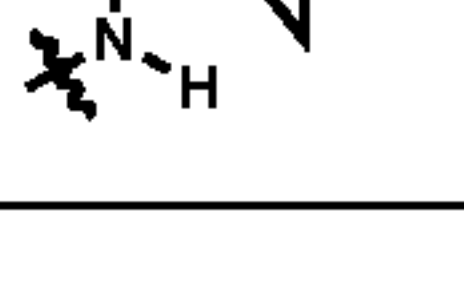
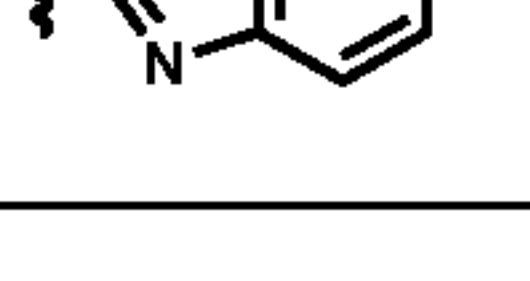


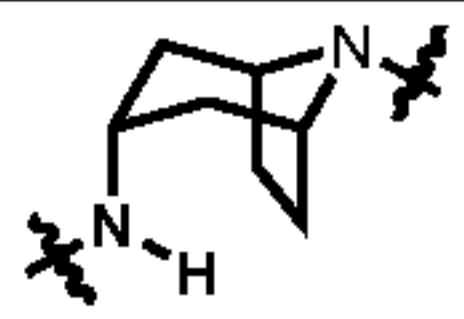
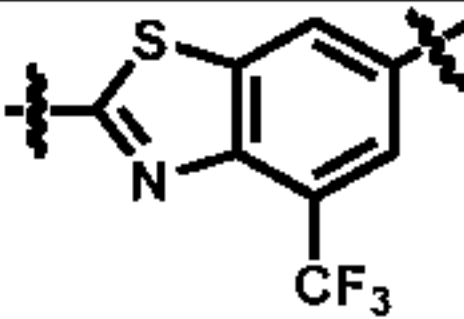
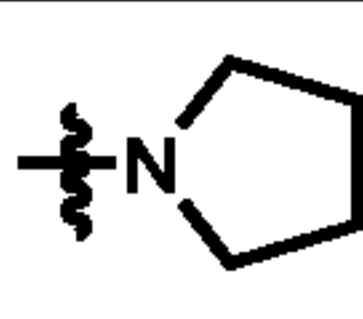
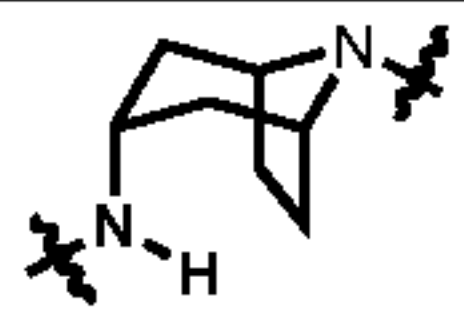
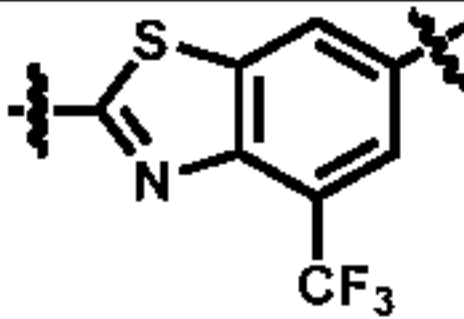
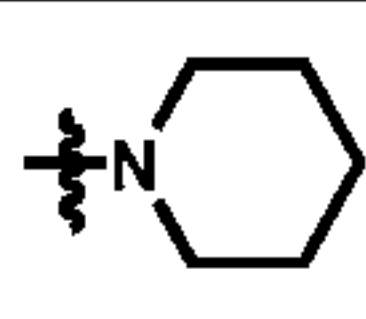
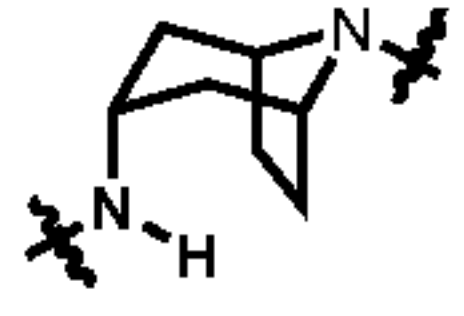
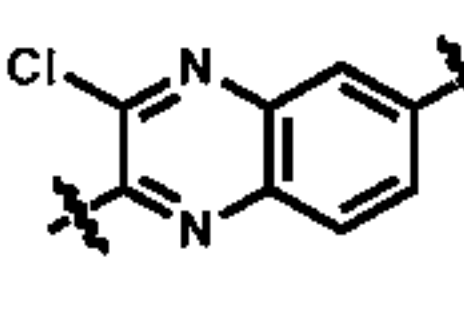
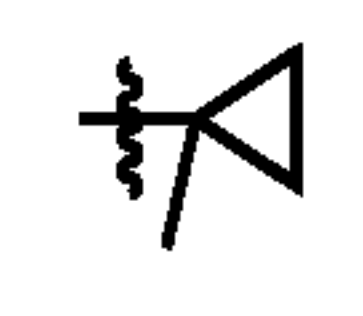
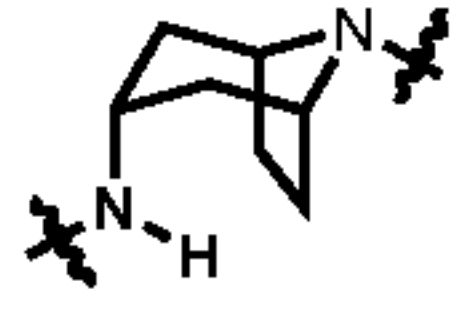
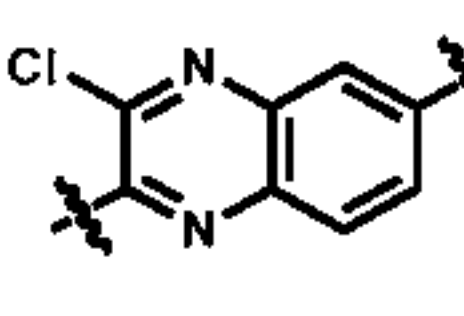
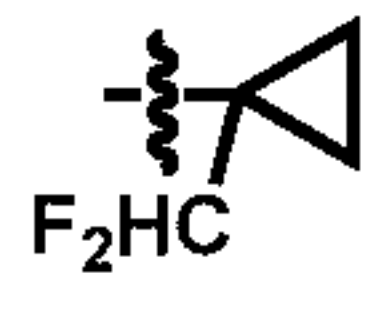
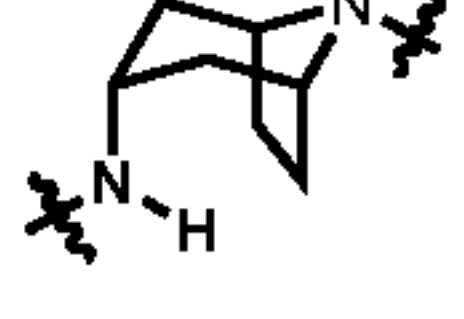
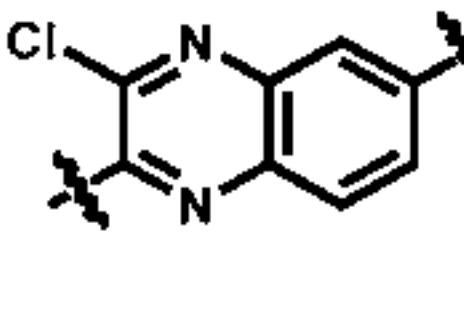
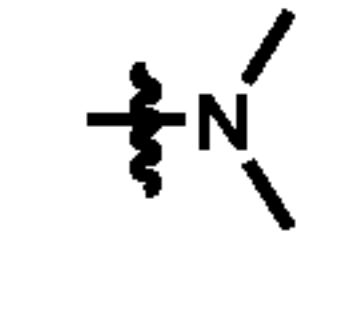
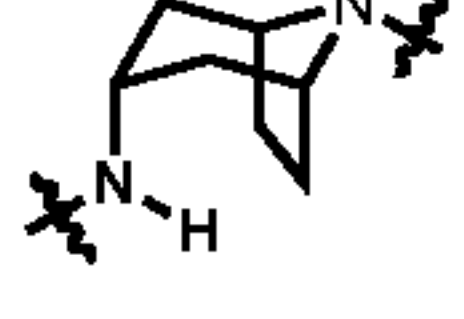
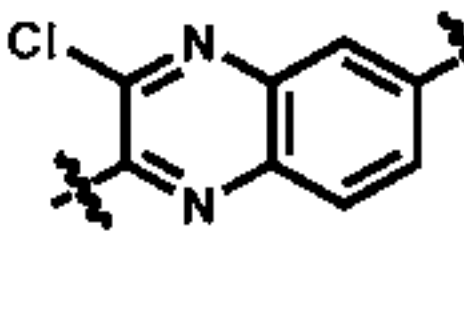
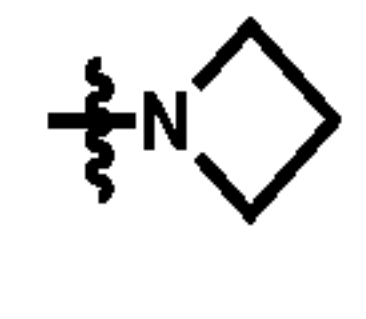
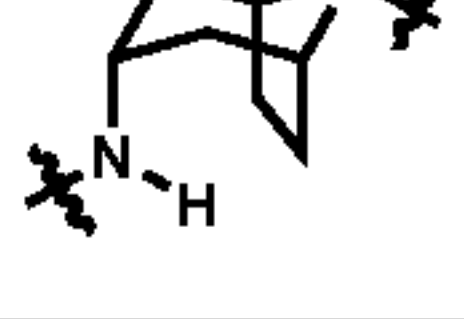
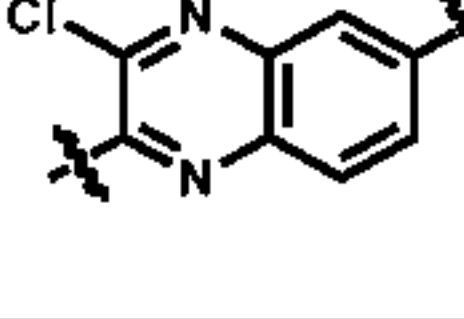
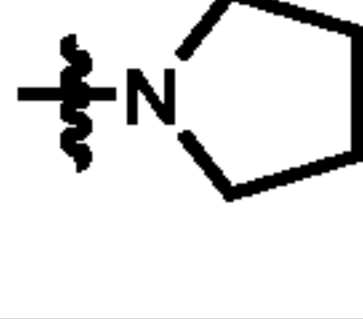
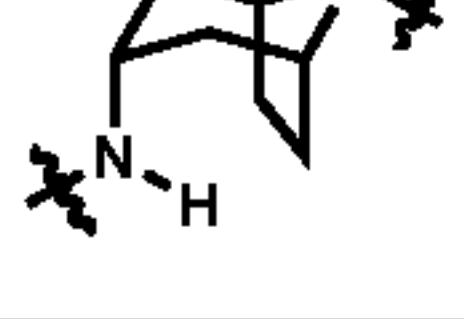
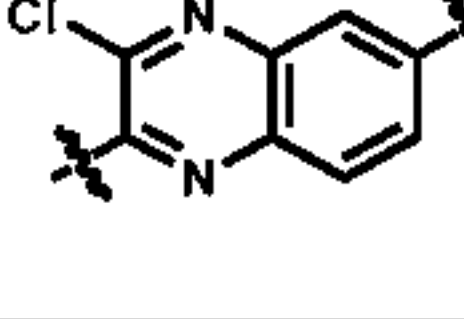
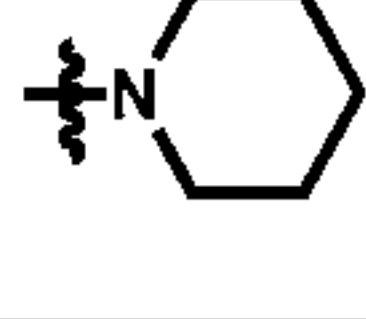
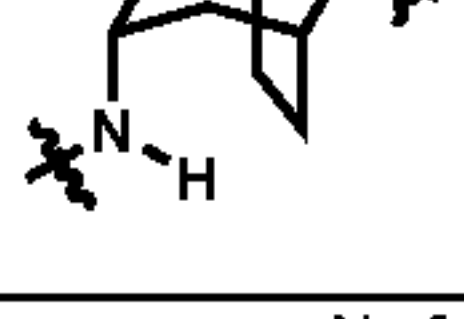
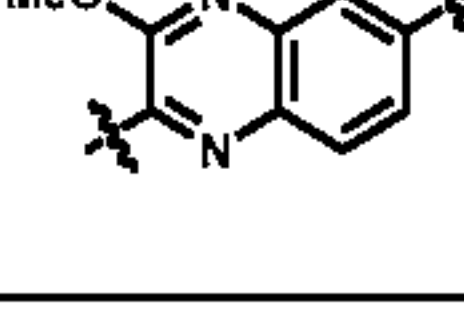
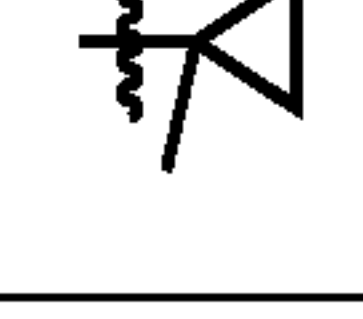
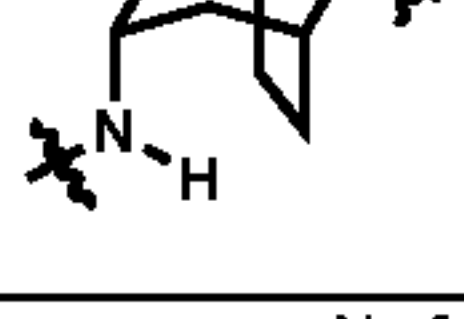
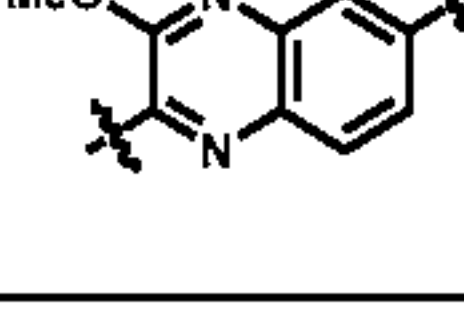
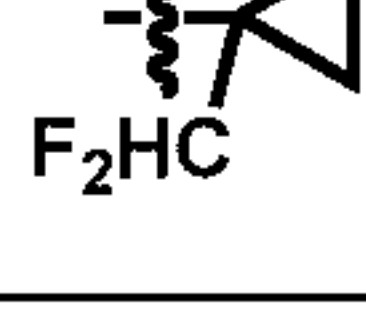
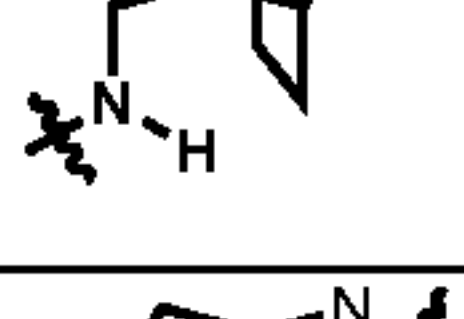
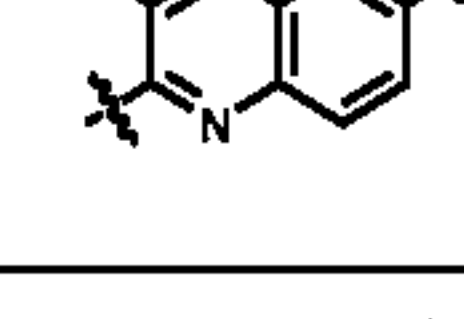
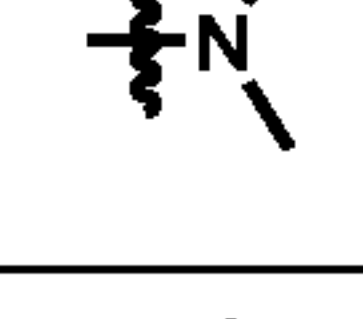
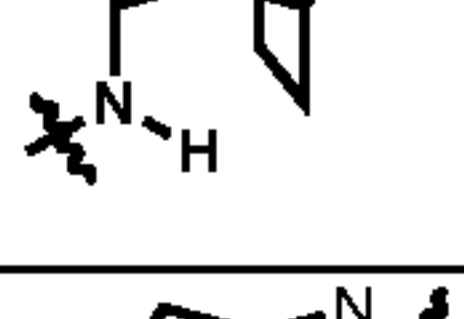
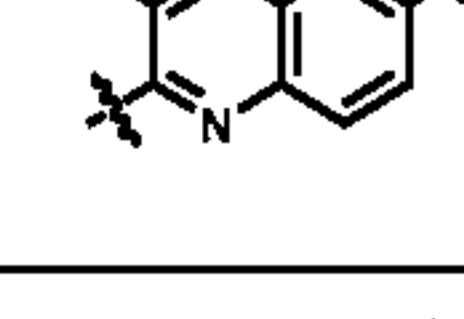
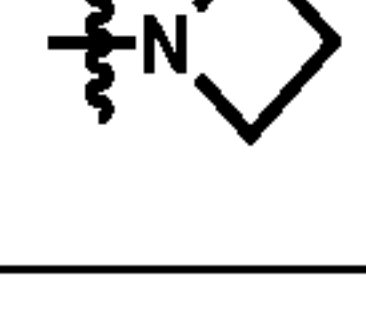
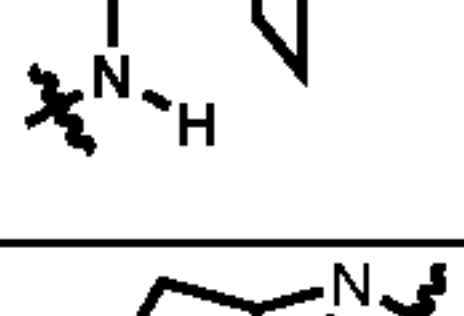
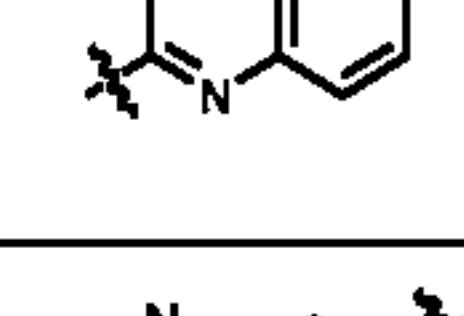
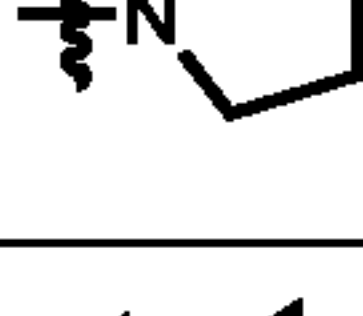
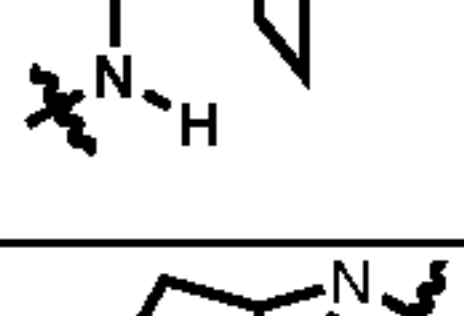
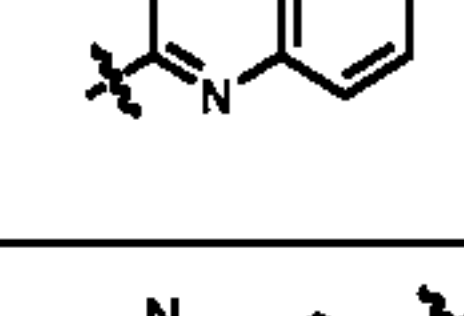
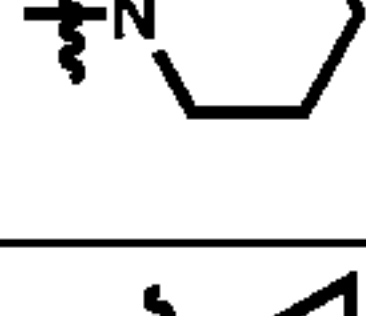
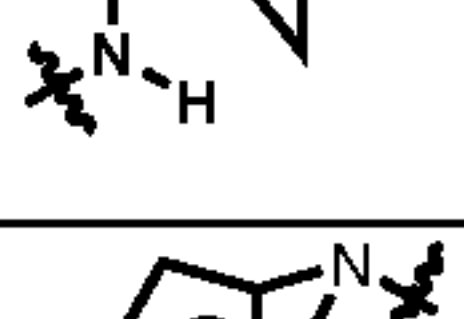
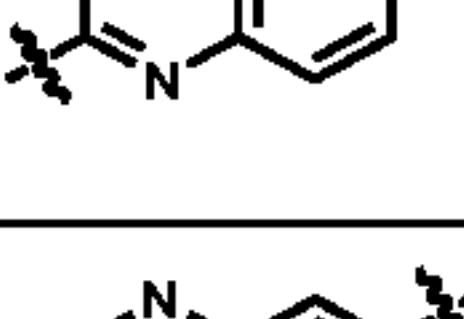
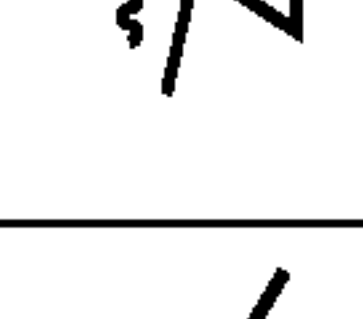
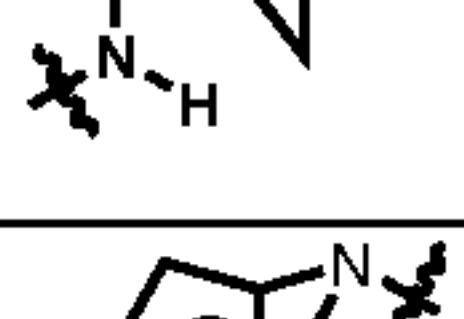
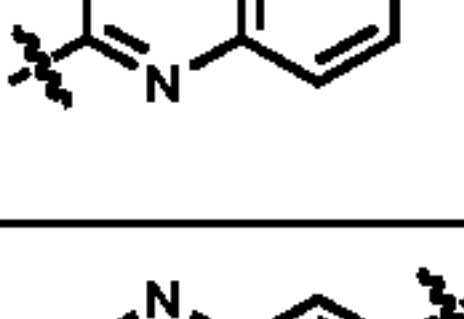
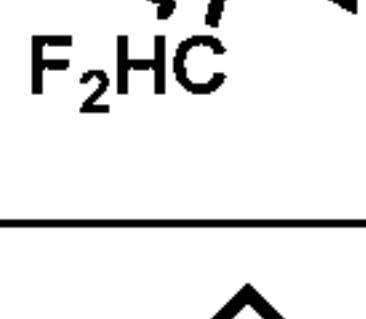
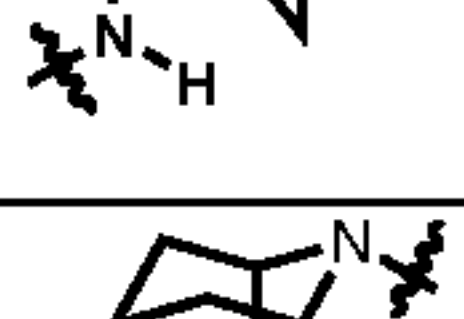
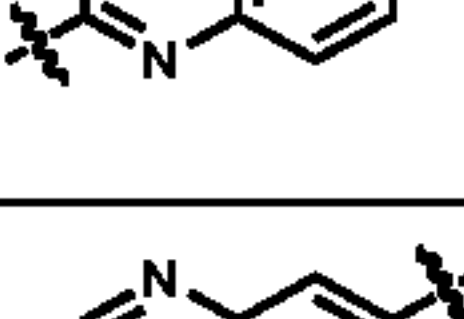
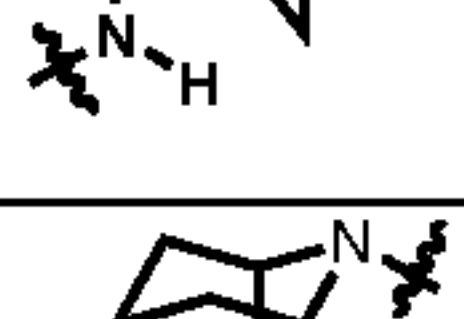
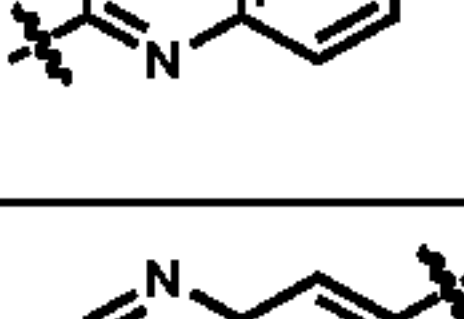
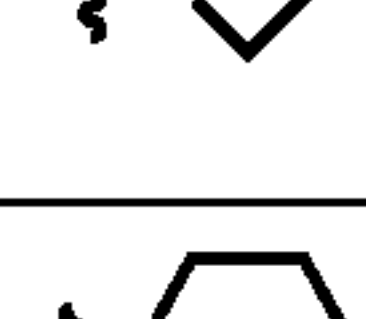
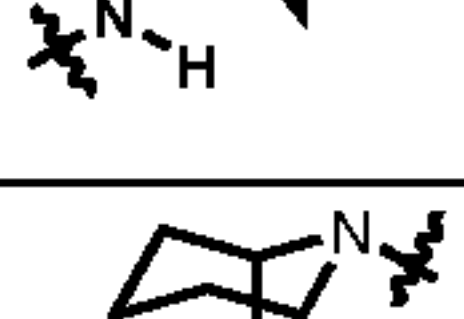
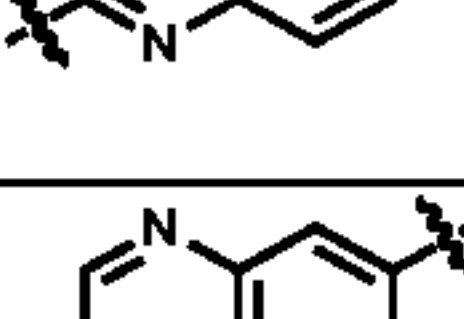
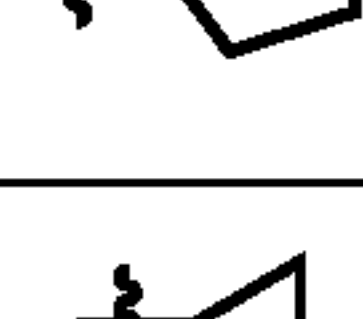
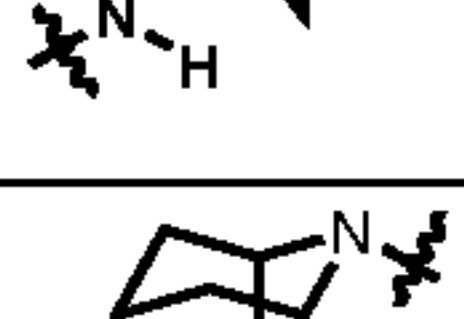
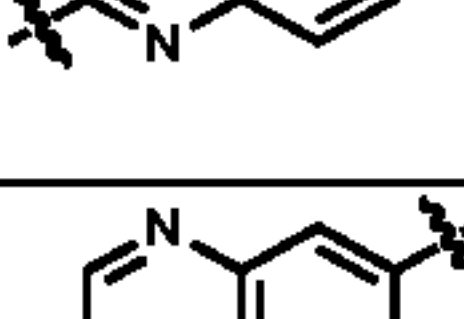
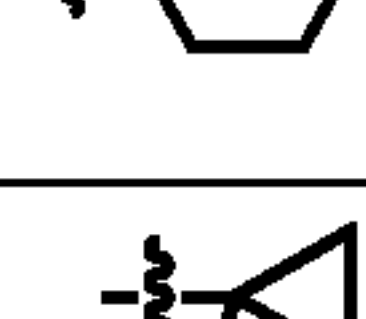
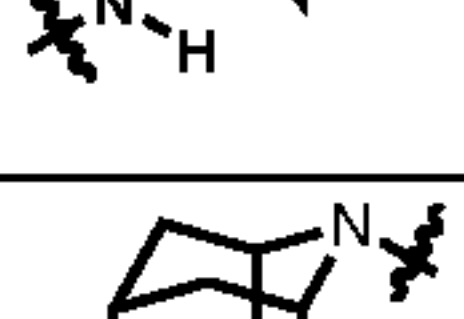
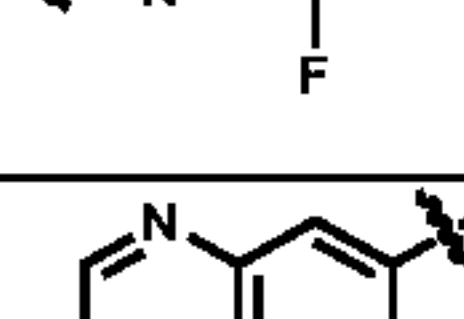
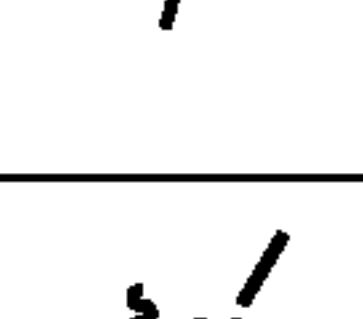
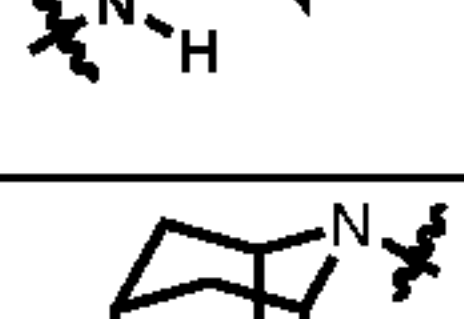
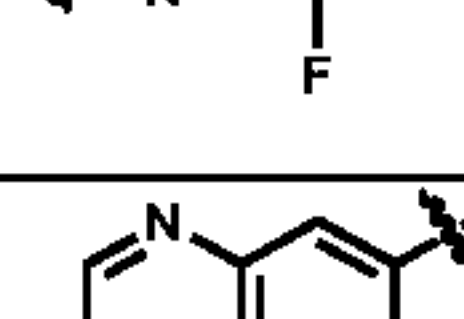
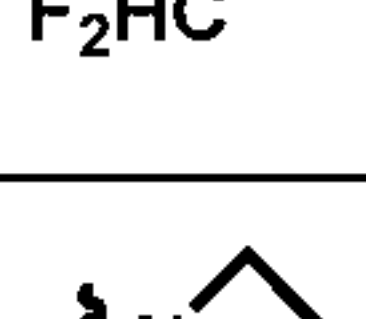
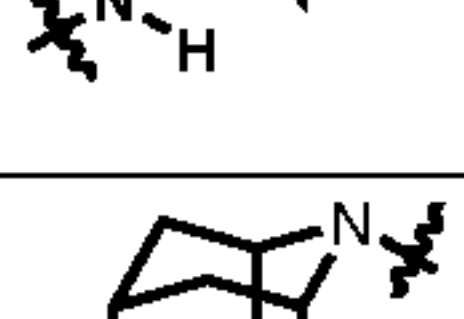
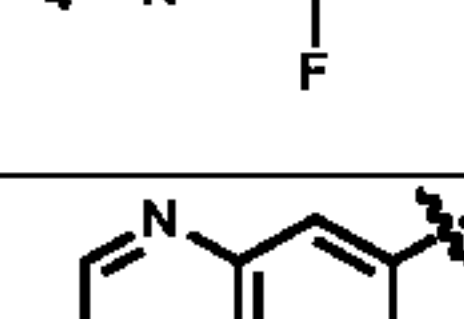
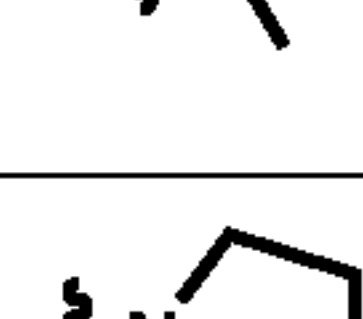
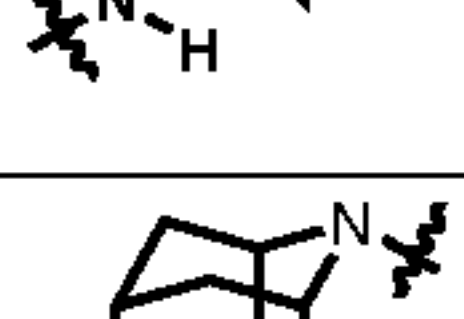
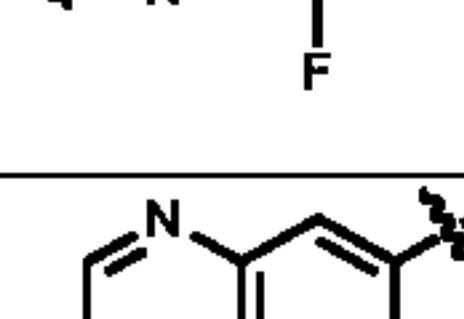
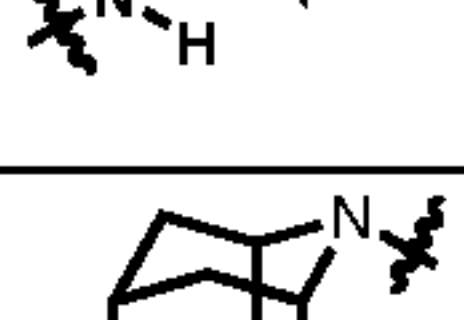
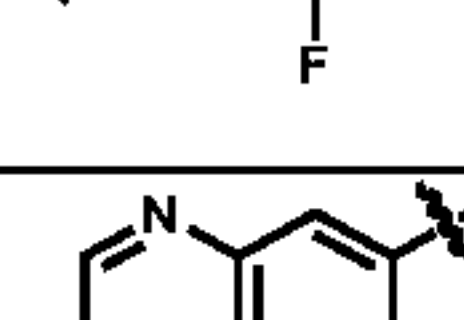
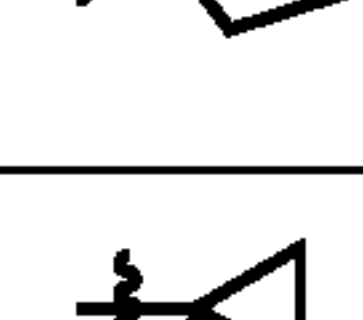
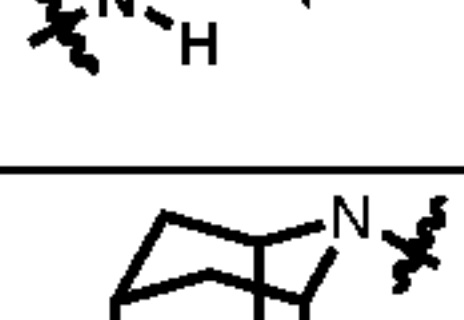
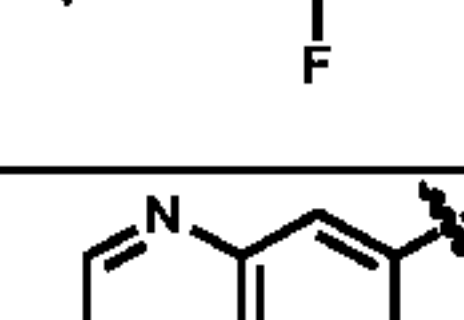
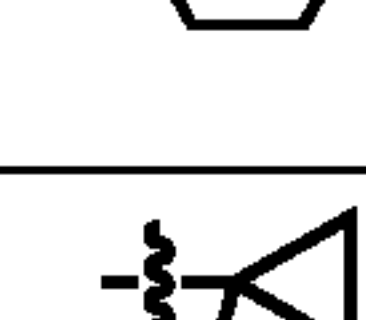
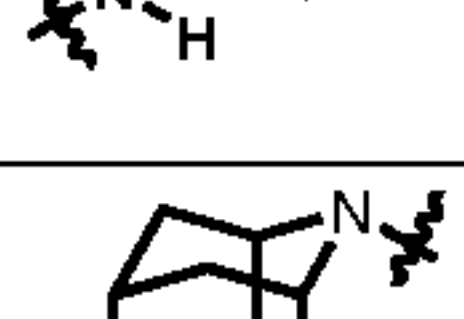
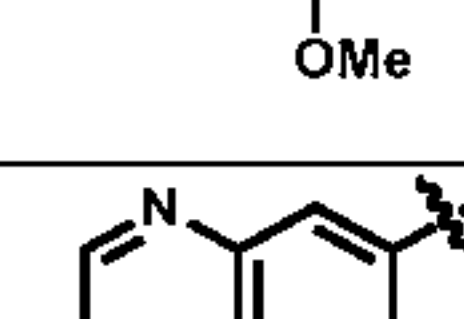
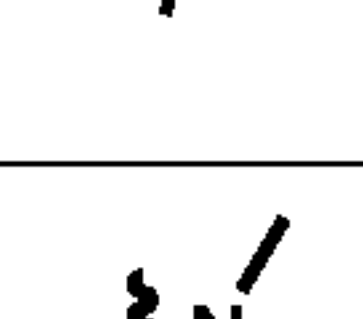
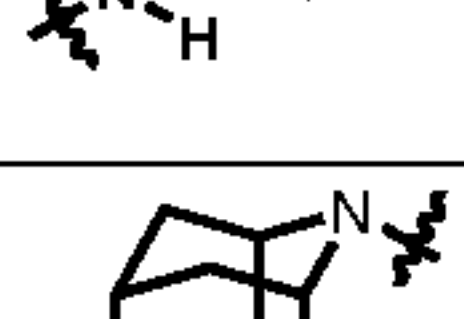
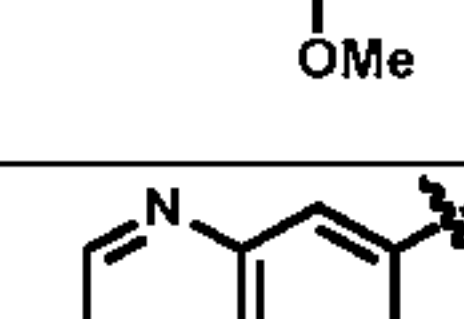
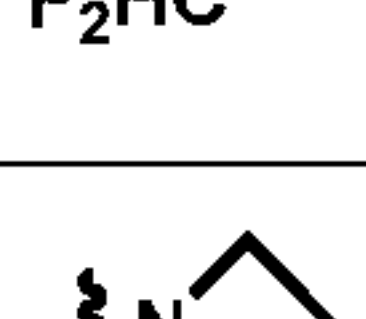
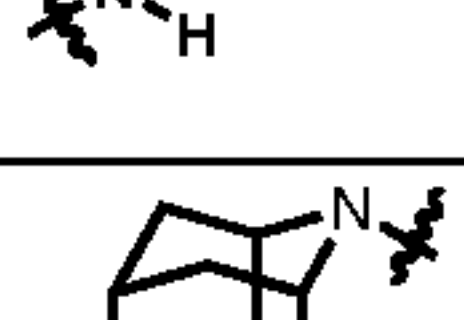
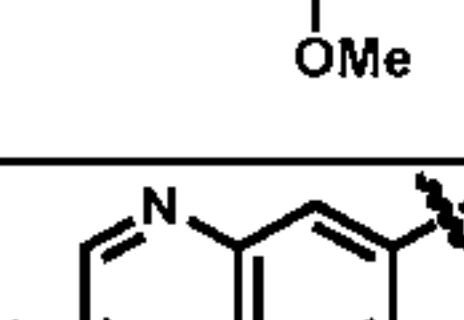
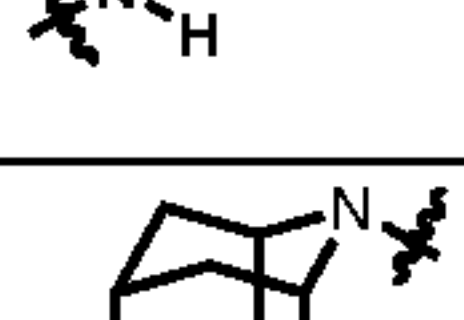
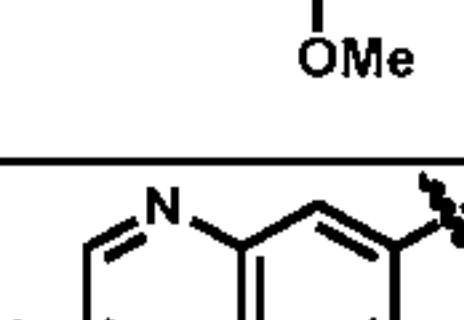
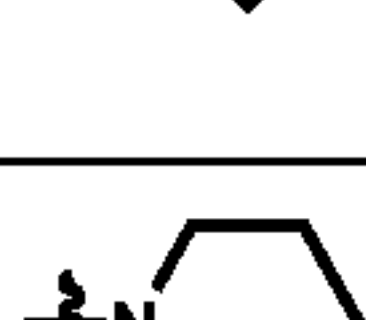
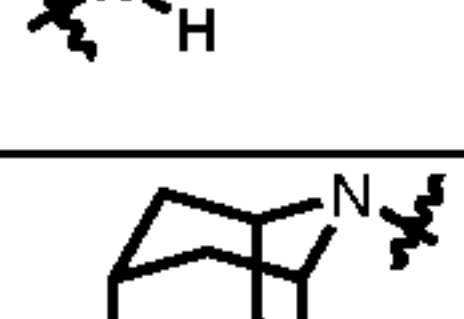
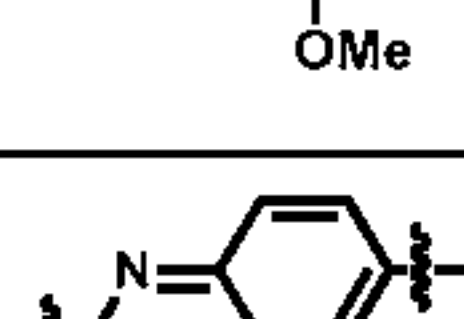
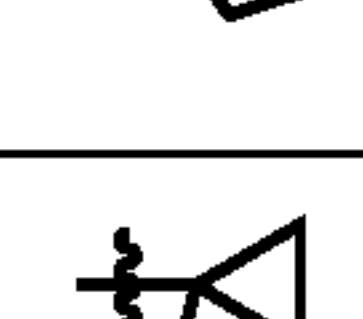
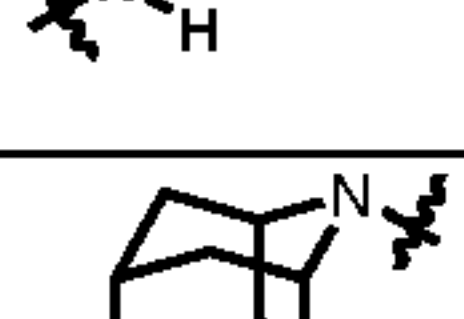
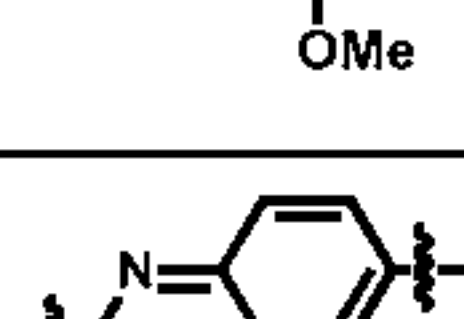
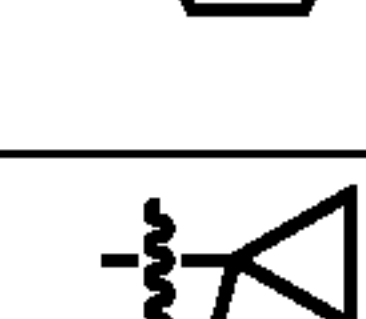
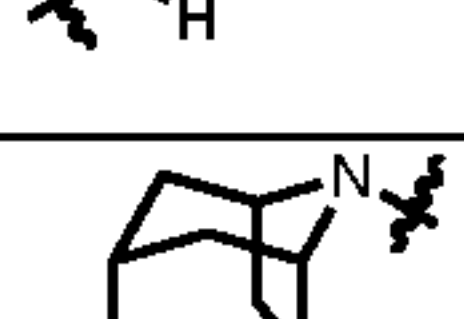
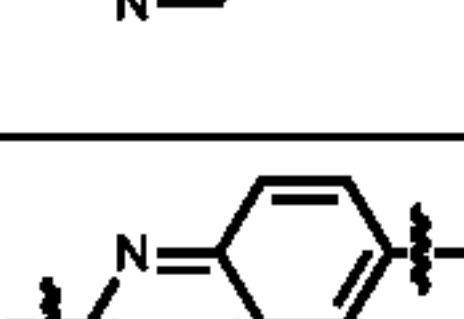
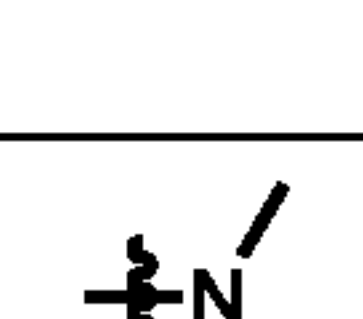
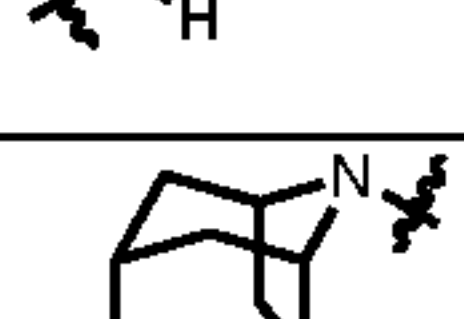
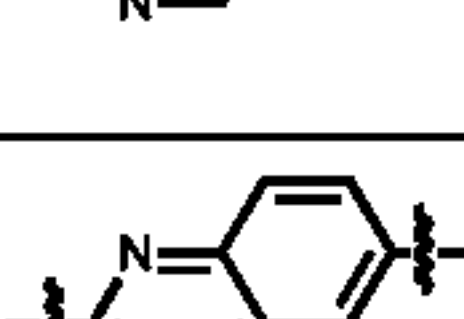
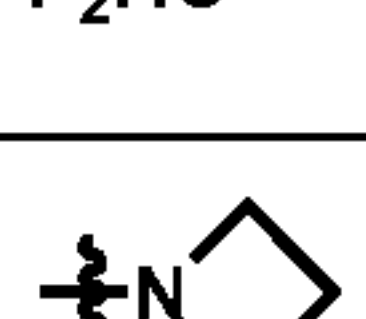
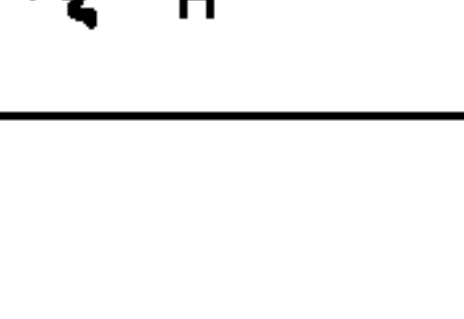
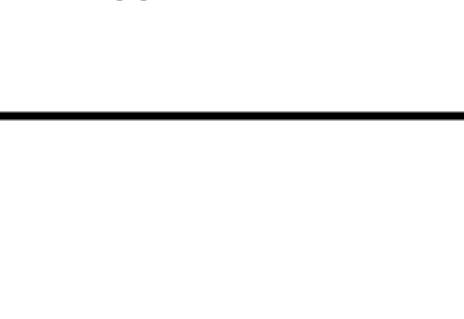
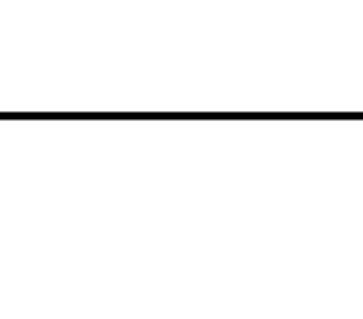
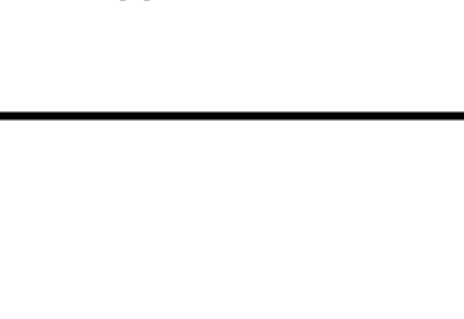
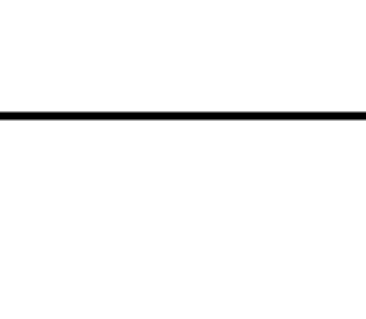
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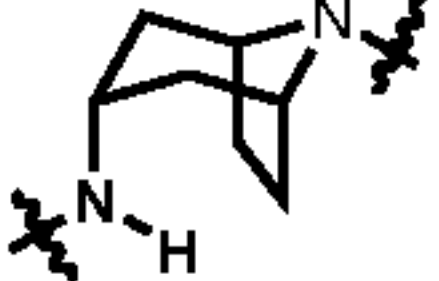
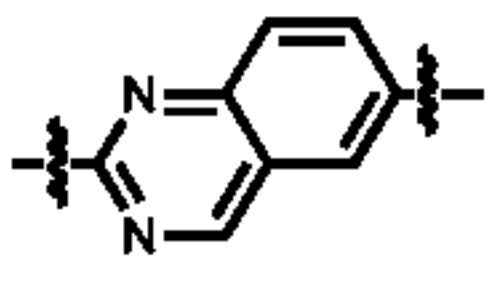
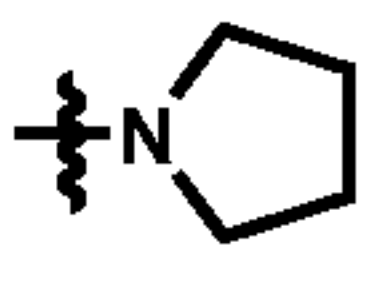
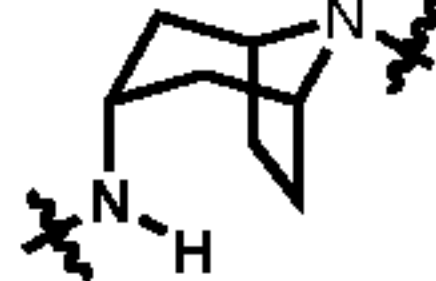
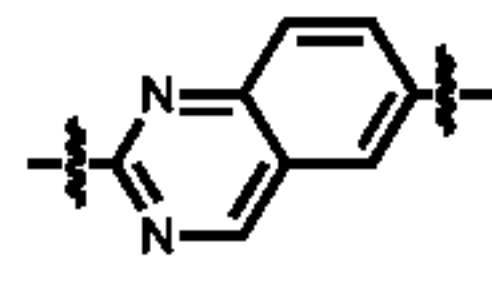
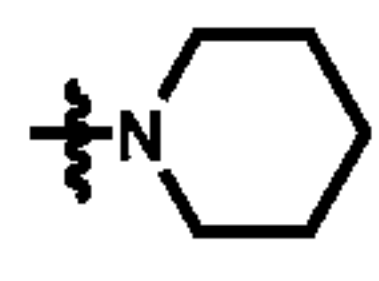
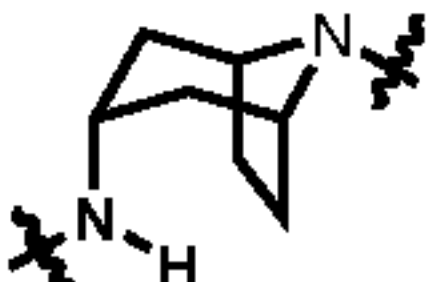
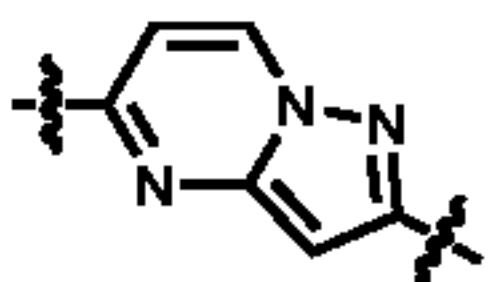
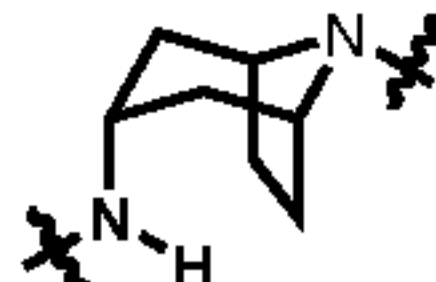
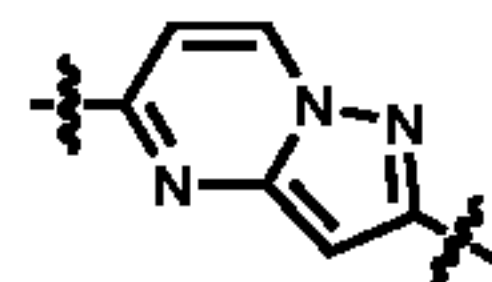
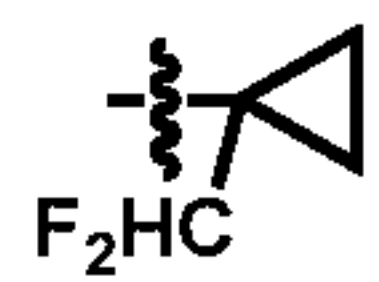
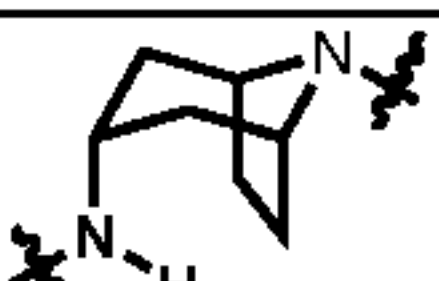
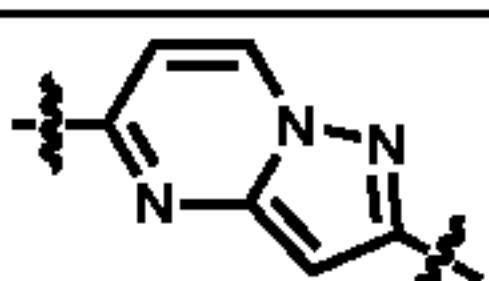
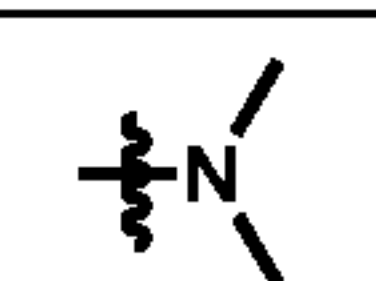
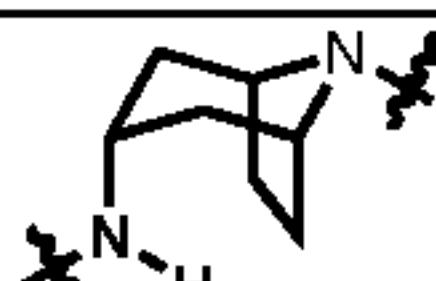
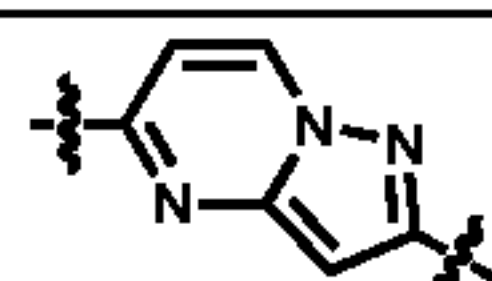
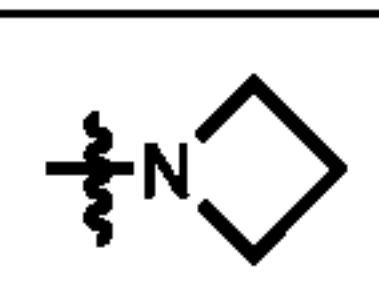
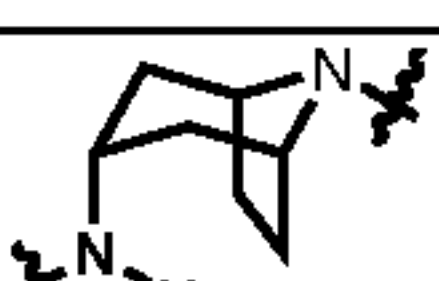
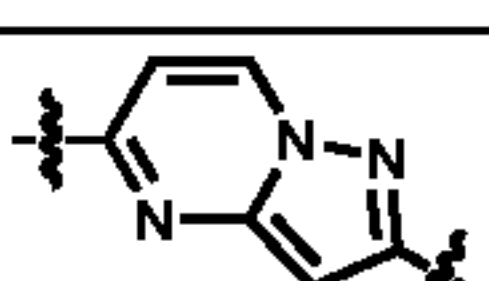
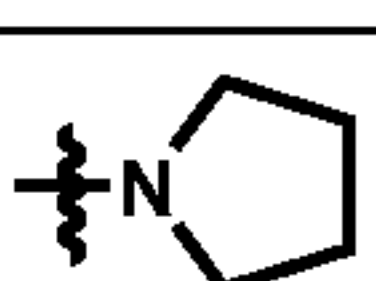
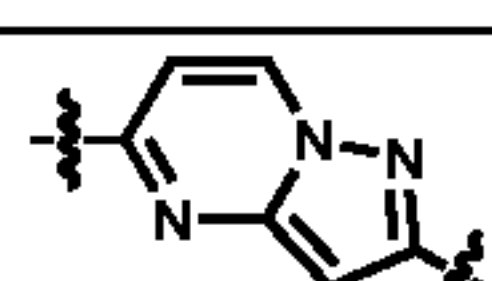
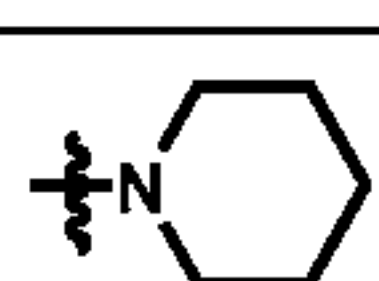
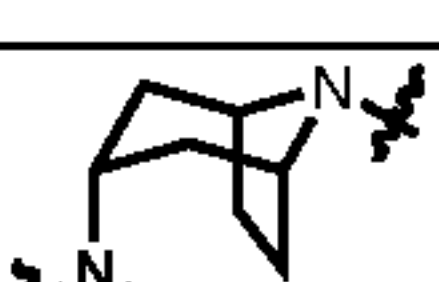
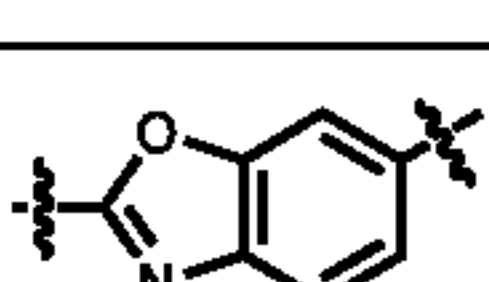
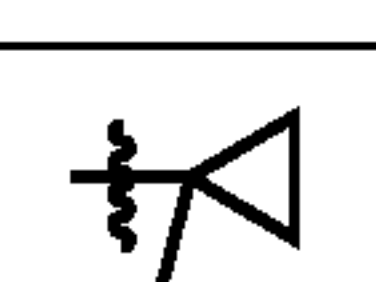
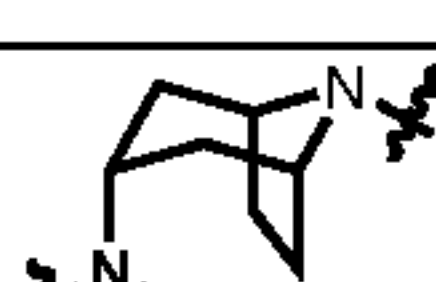
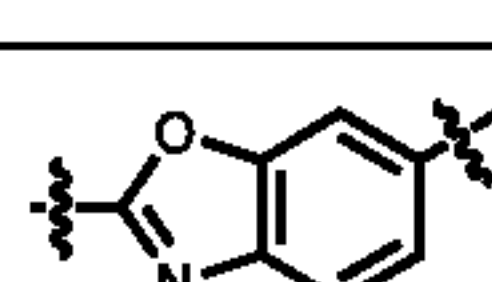
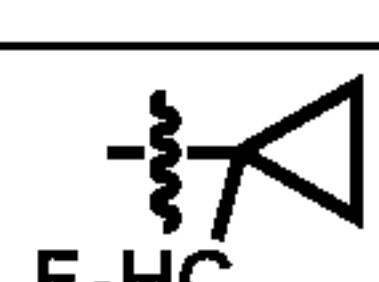
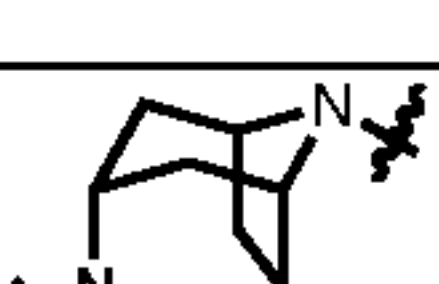
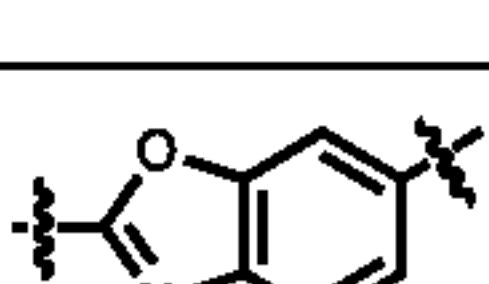
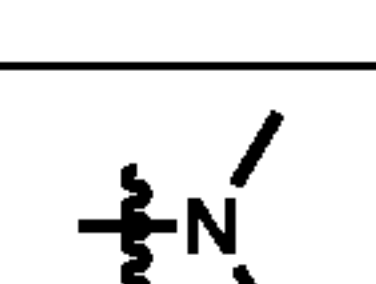
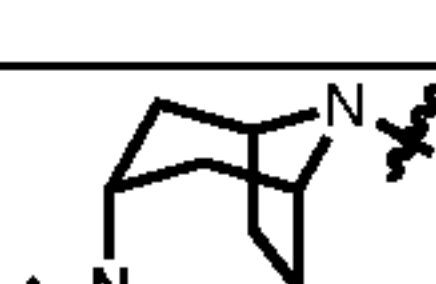
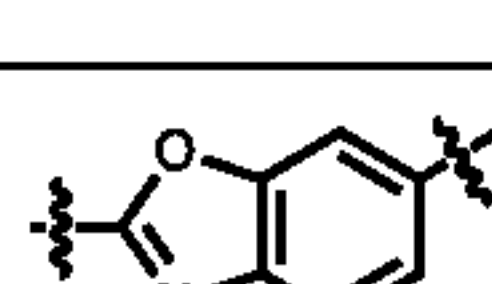
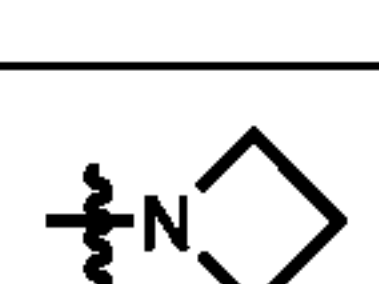
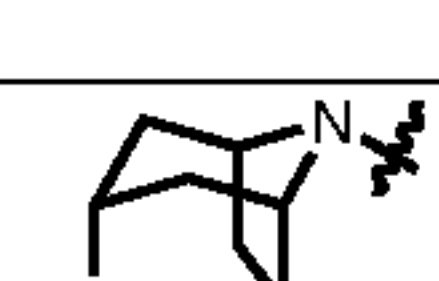
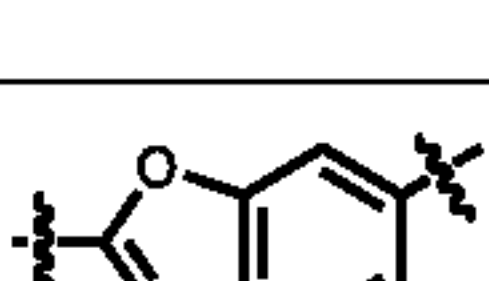
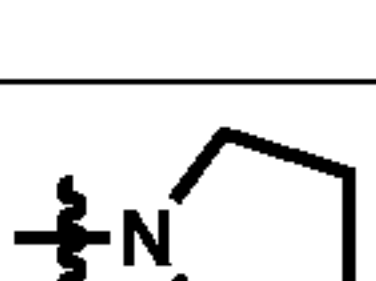
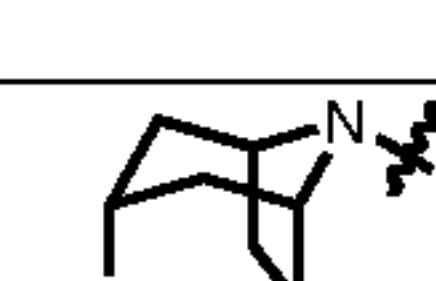
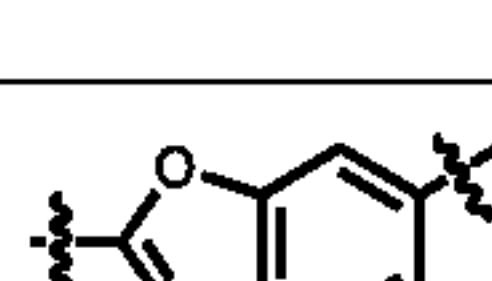
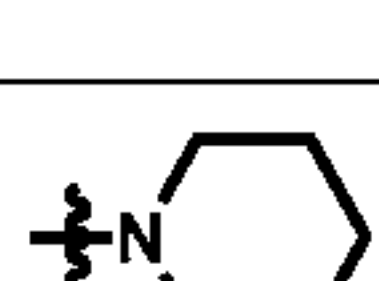
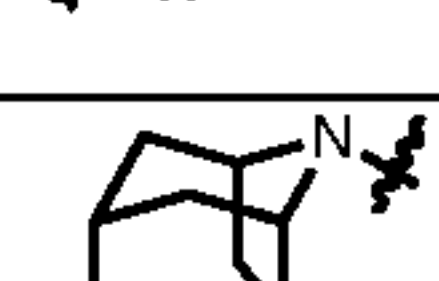
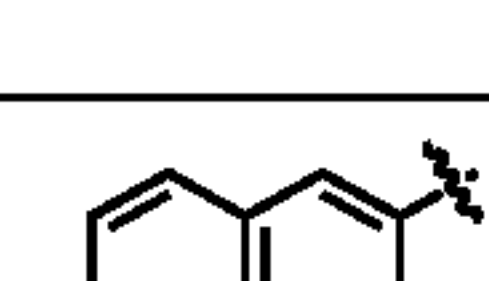
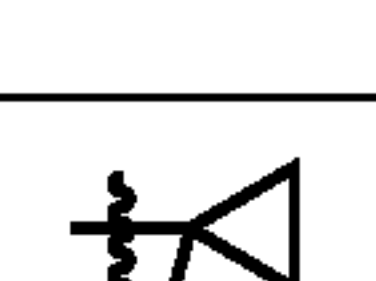
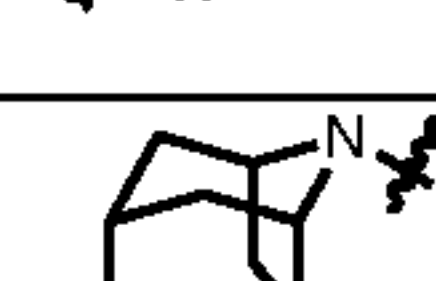
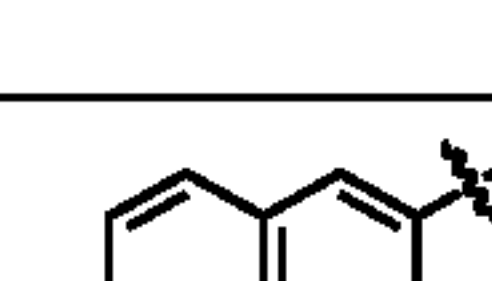
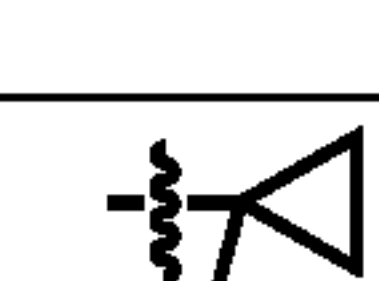
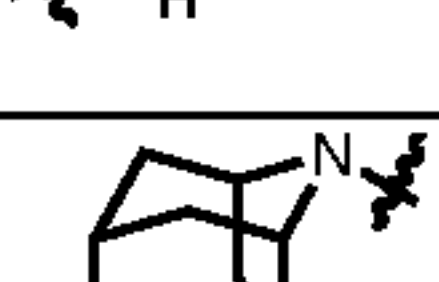
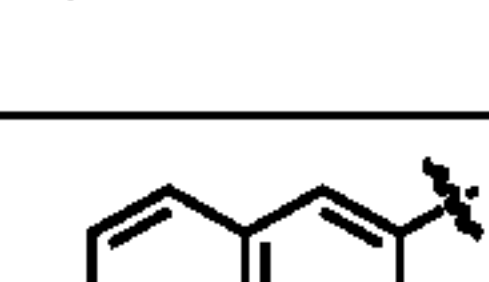
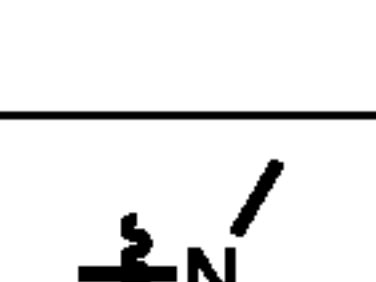
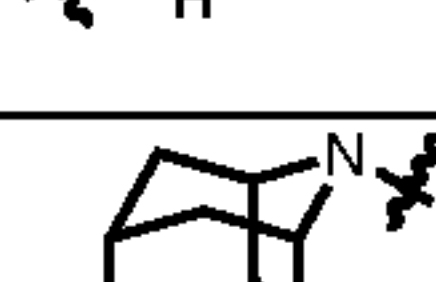
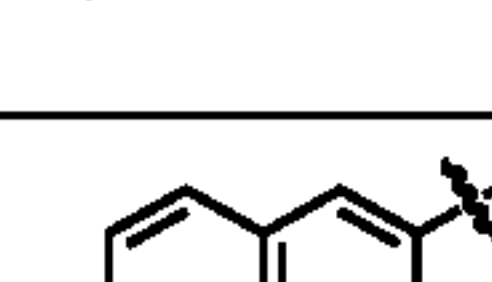
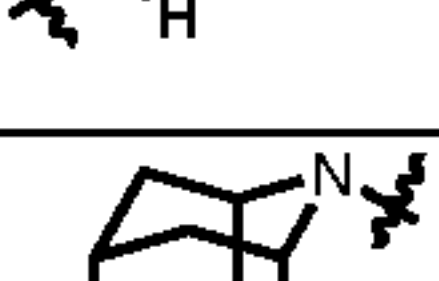
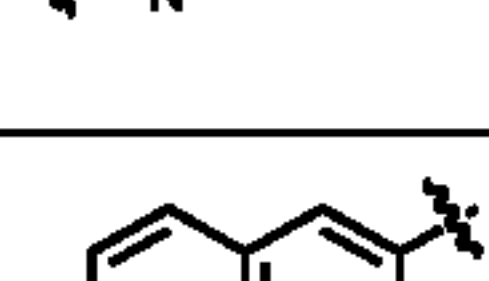
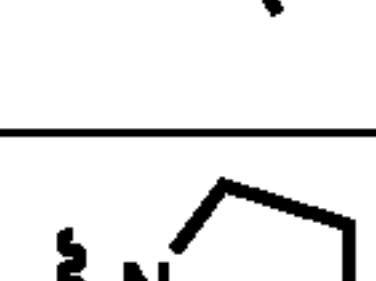
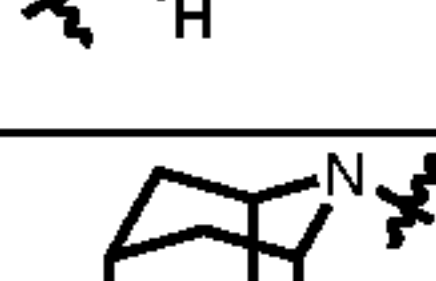
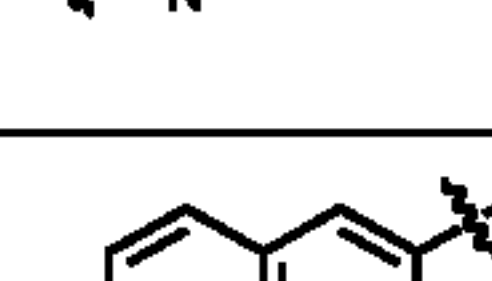
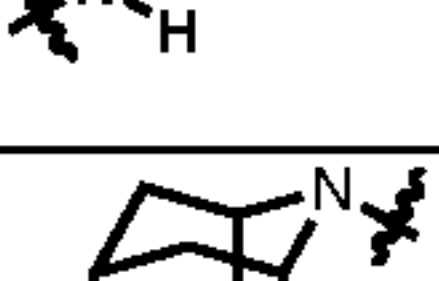
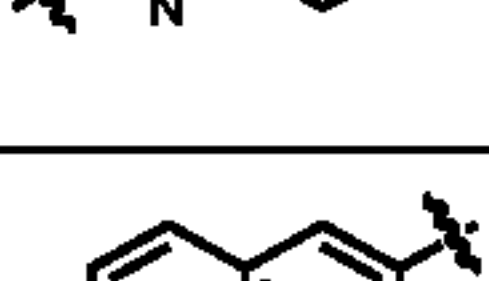
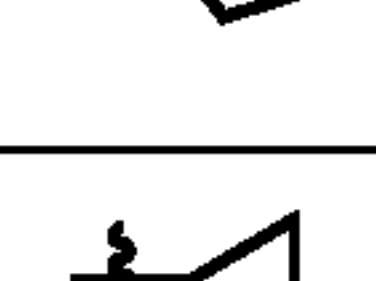
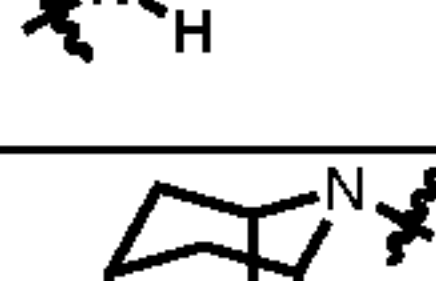
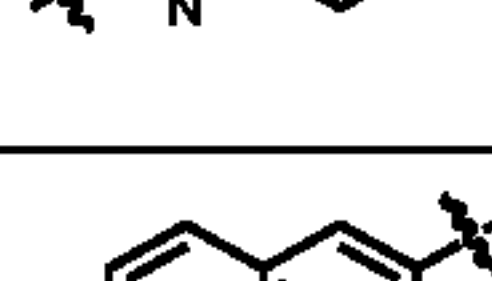
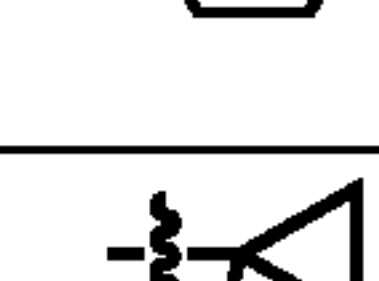
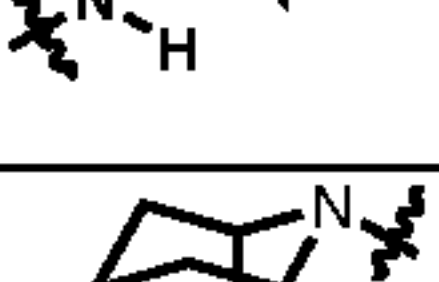
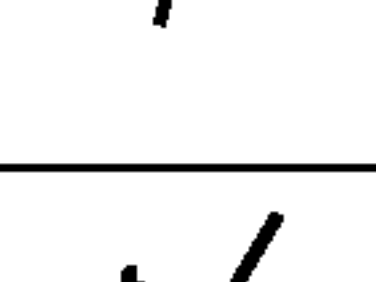
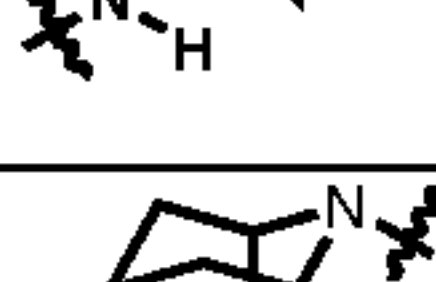
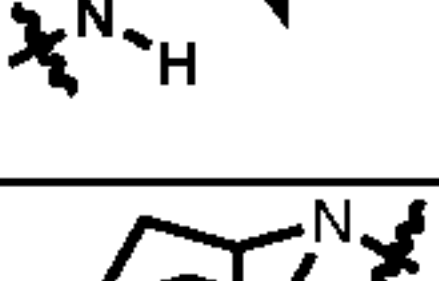
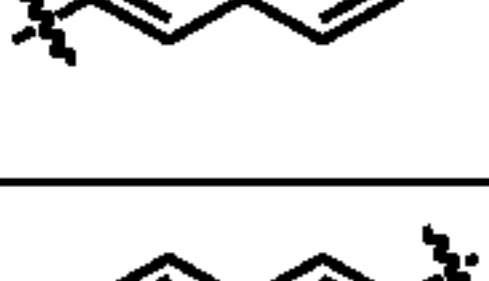
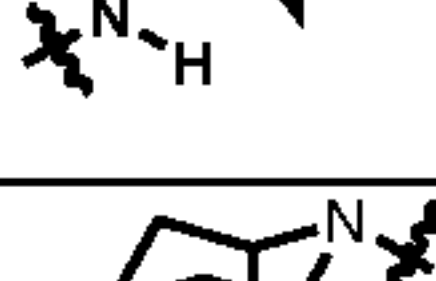
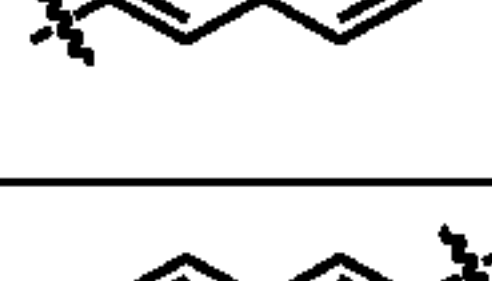
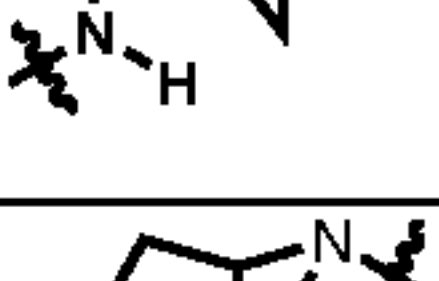
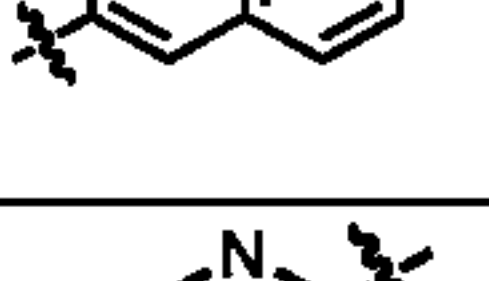
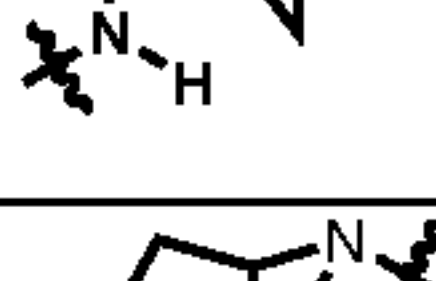
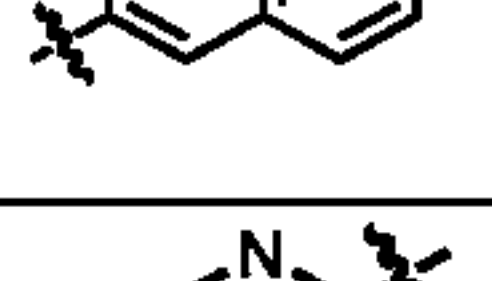
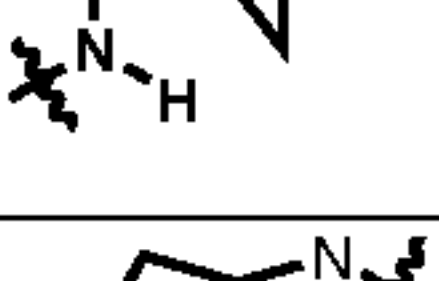
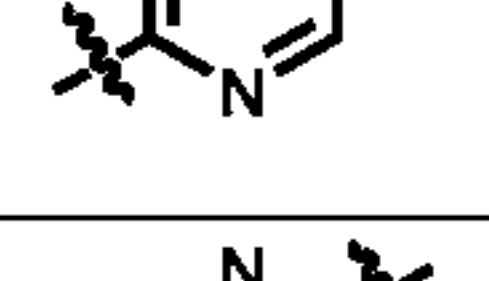
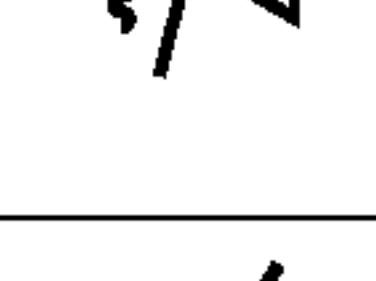
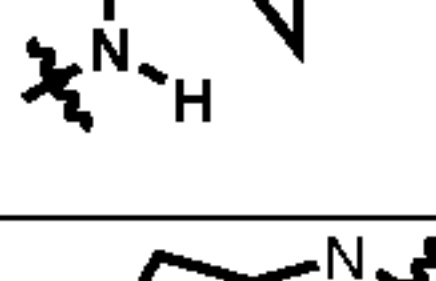
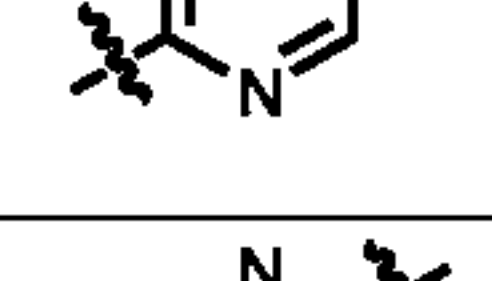
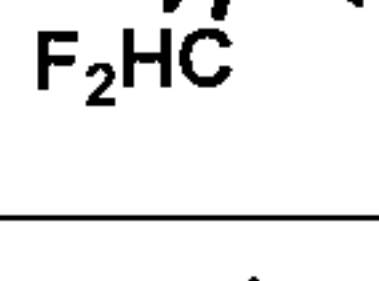
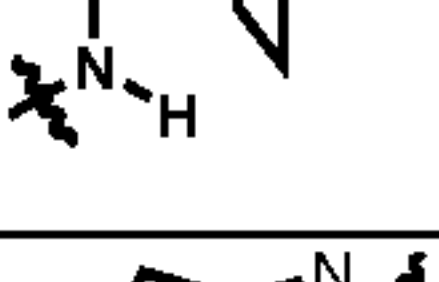
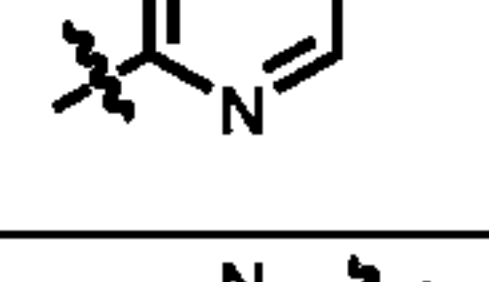
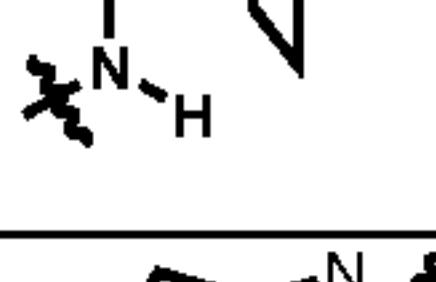
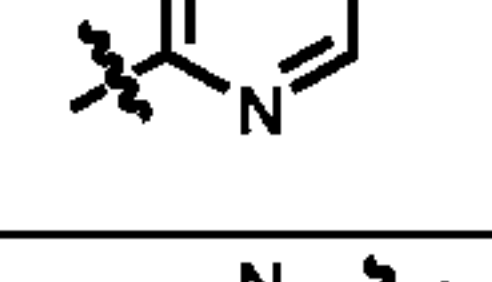
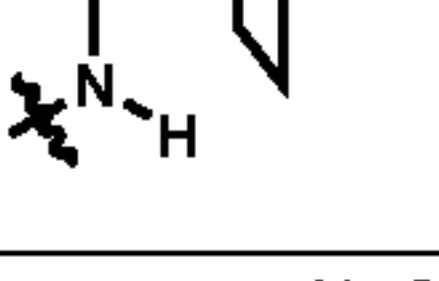
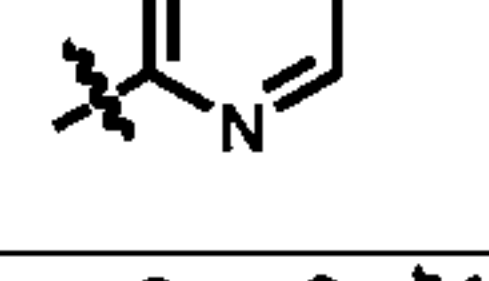
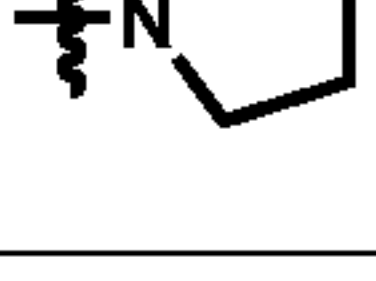
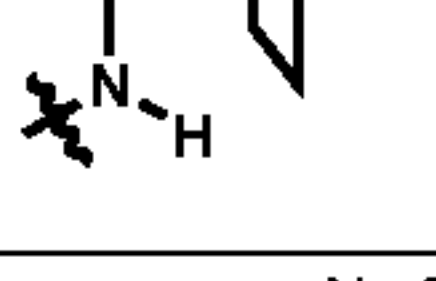
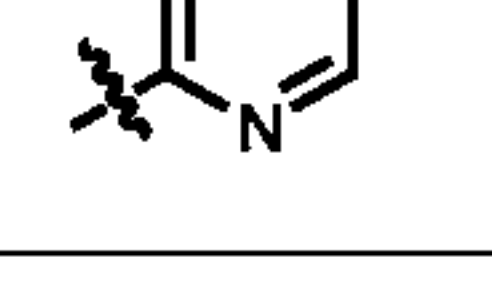
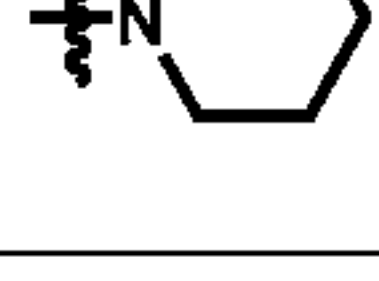
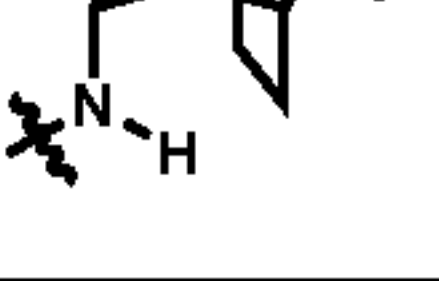
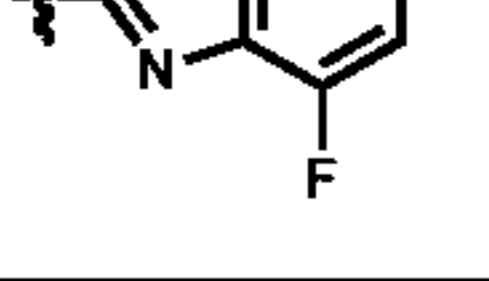
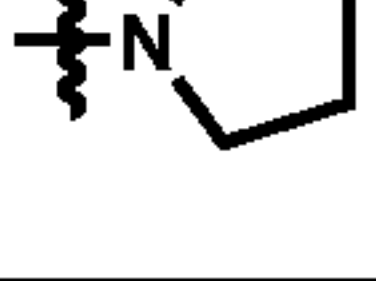
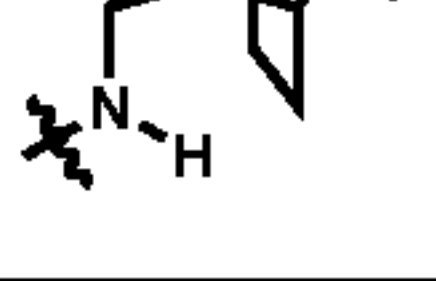
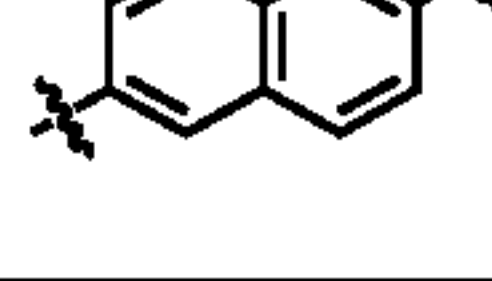
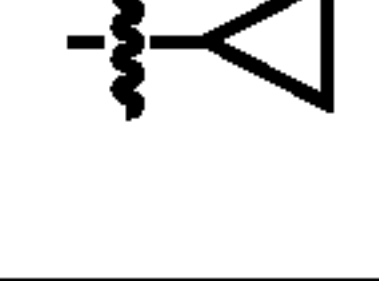
Compound	A	B	R ⁷	Compound	A	B	R ⁷
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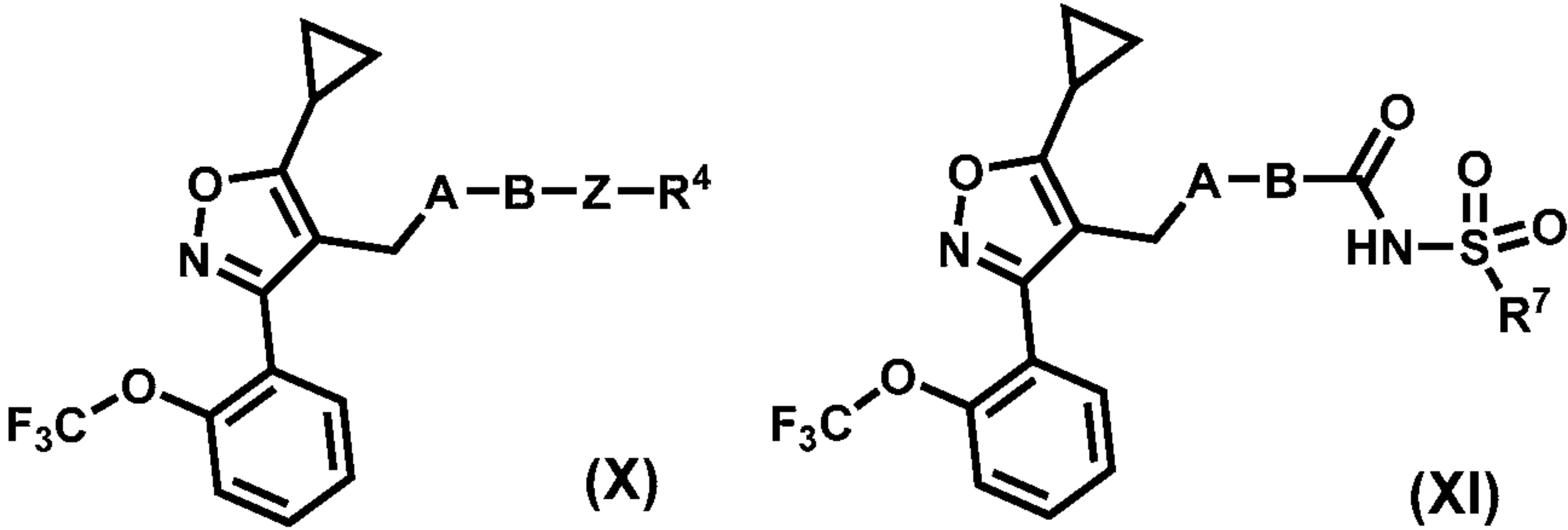
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400-1				400-2			
400-3				400-4			

400-5				400-6			
400-7				400-08			
400-9				400-10			
400-11				400-12			
400-13				400-14			
400-15				400-16			
400-17				400-18			
400-19				400-20			
400-21				400-22			
400-23				400-24			
400-25				400-26			
400-27				400-28			
400-29				400-30			
400-31				400-32			
400-33				400-34			
400-35				400-36			
400-37				400-38			

400-39				400-40			
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or a pharmaceutically acceptable salt thereof.

9. A compound of claim 1, represented by Formula (X), or Formula (XI), or a pharmaceutically acceptable salt thereof:



5 wherein R⁴ and R⁷ are as defined in claim 1.

10. A compound according to claim 1, selected from:
(A) Compounds according to Formula (X), wherein A, B, and Z-R⁴ are delineated for each compound in Table 3:

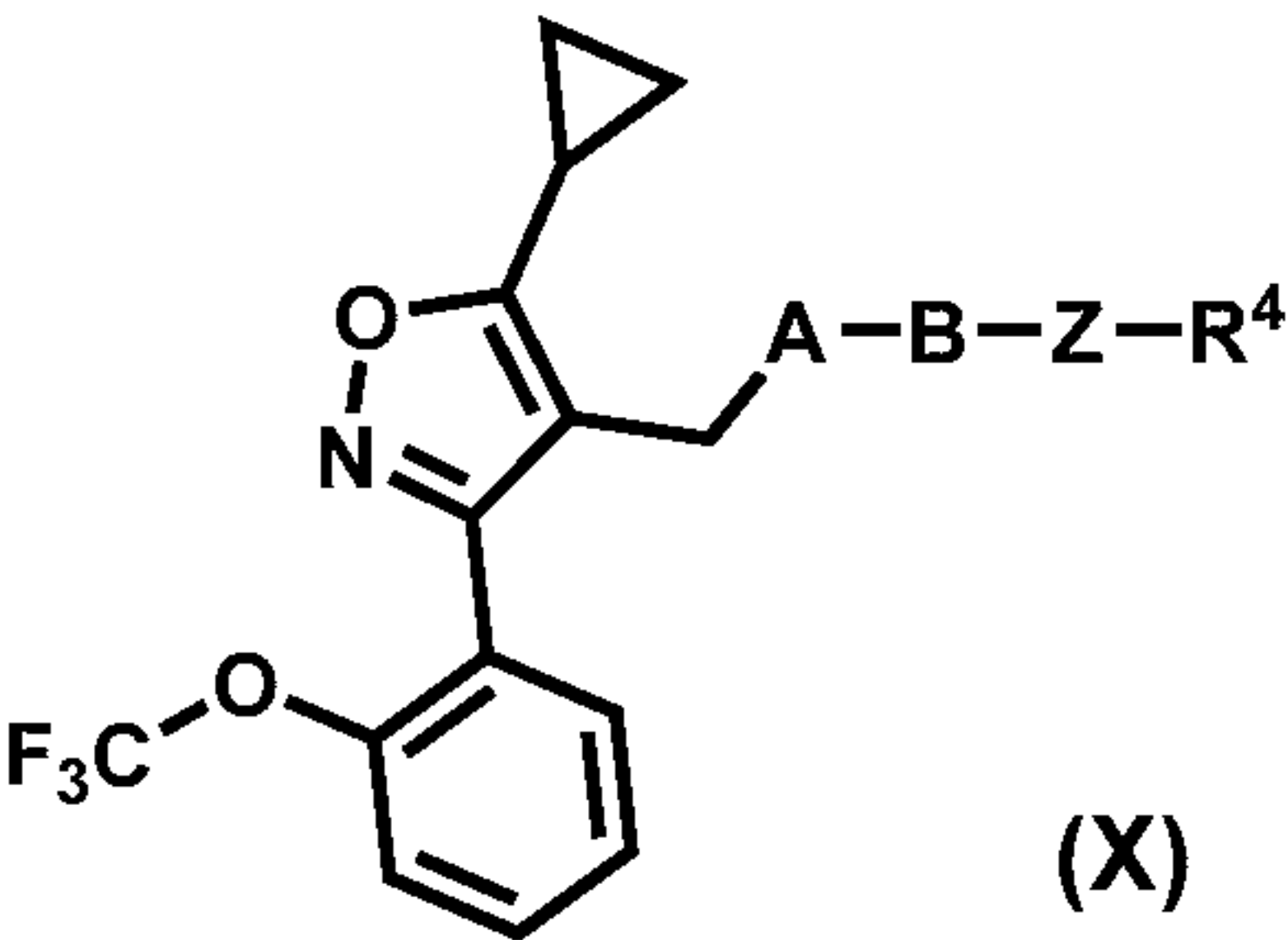
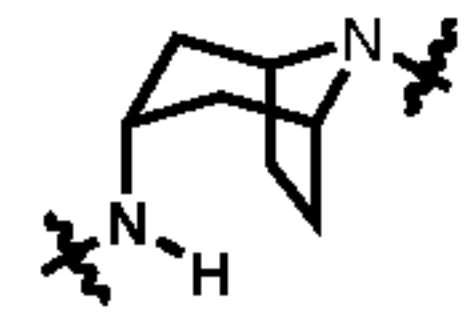
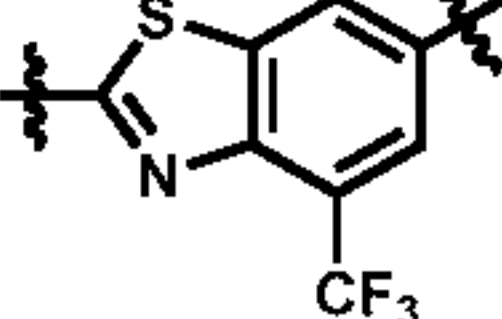
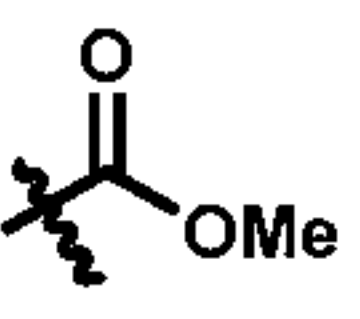
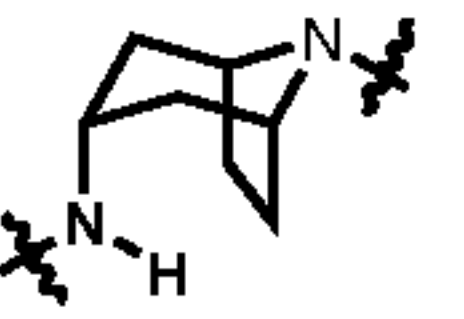
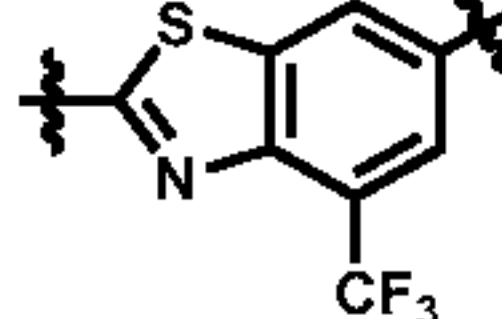
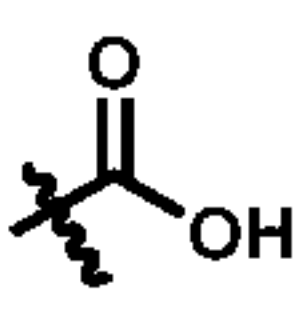
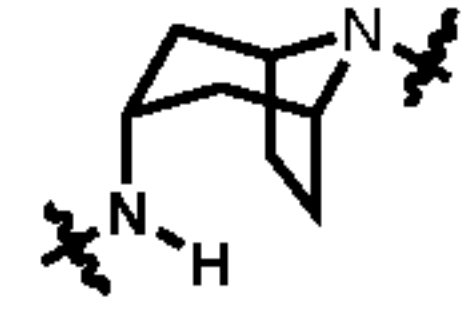
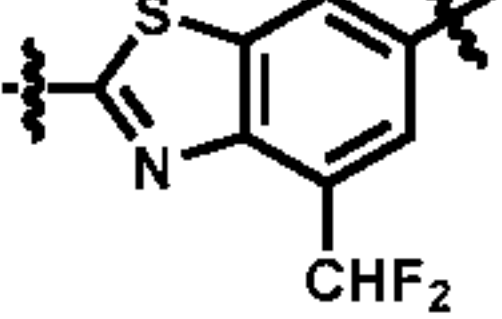
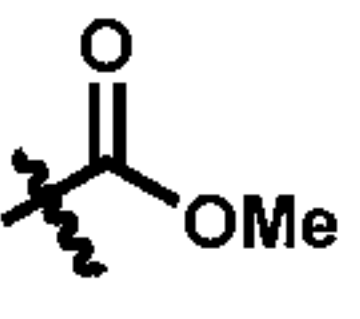
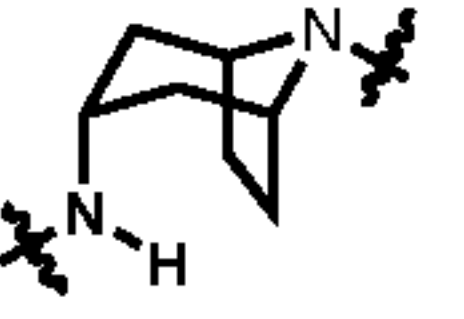
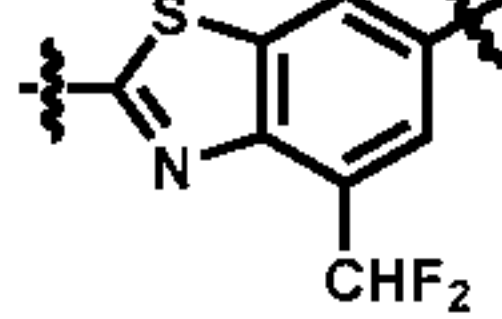
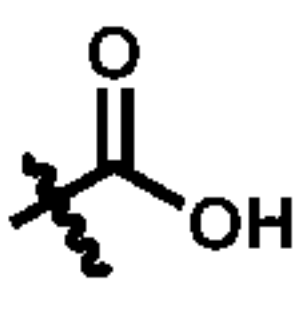
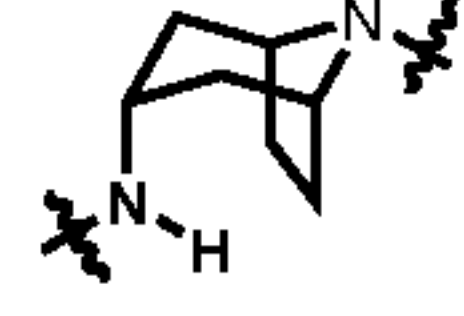
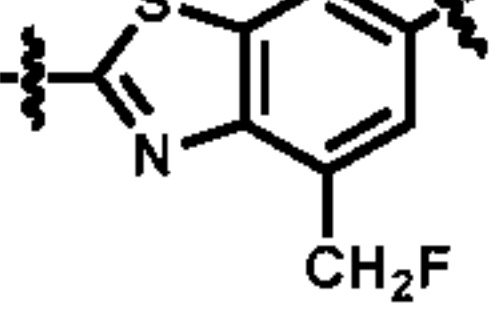
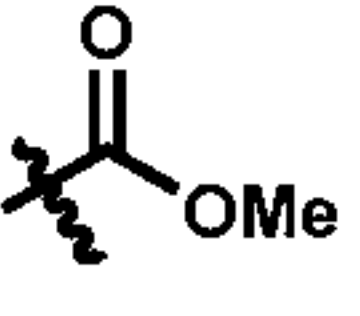
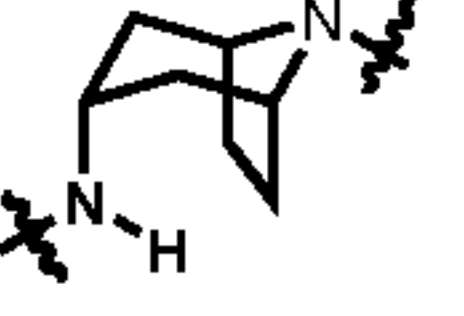
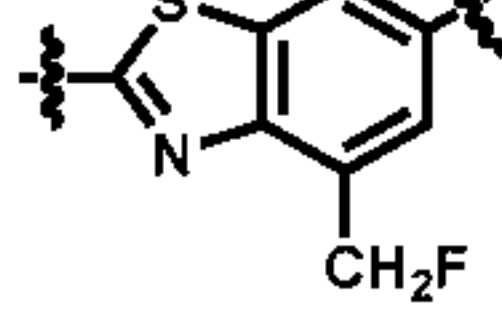
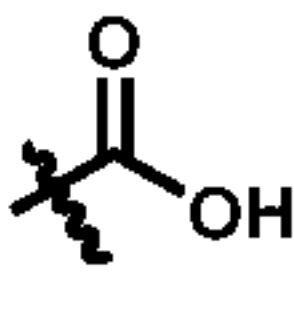
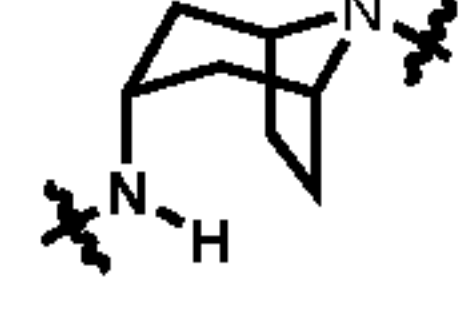
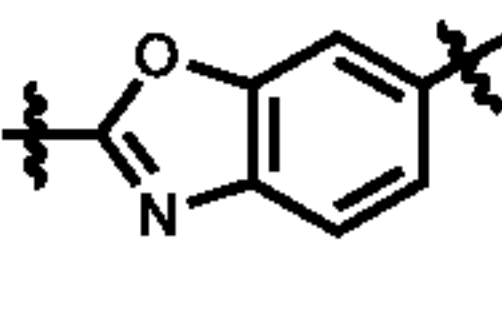
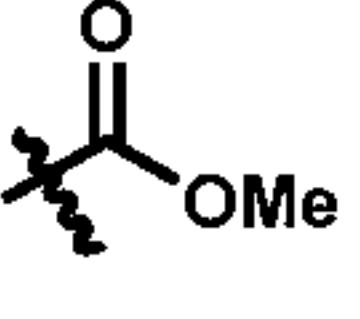
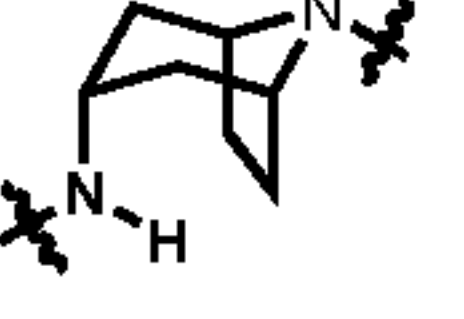
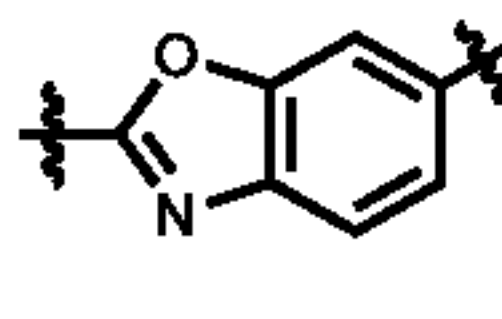
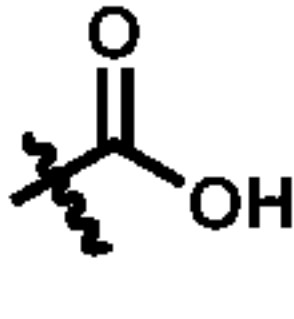
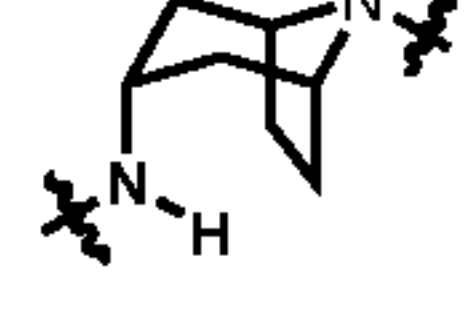
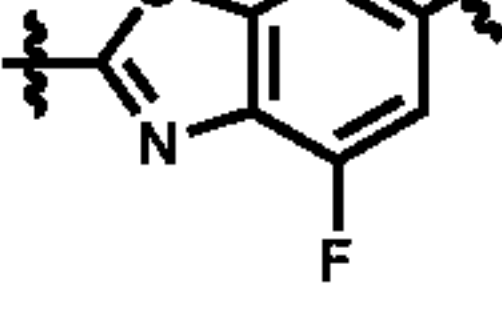
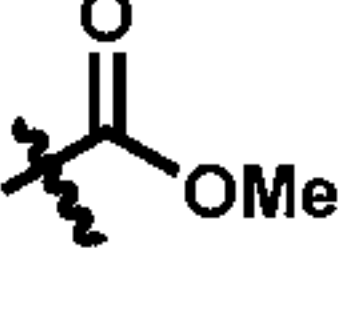
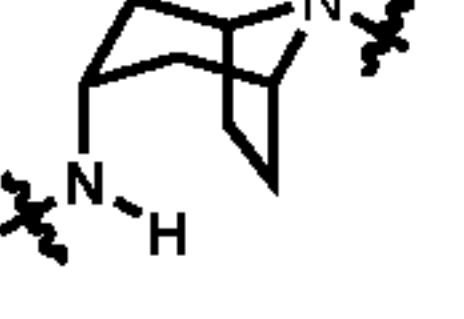
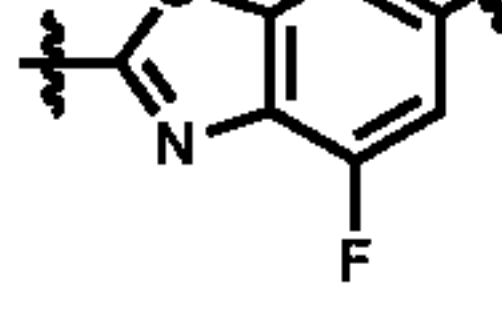
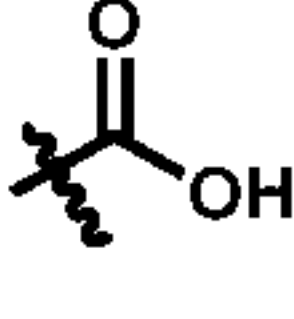
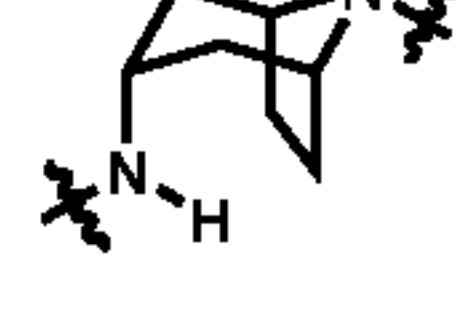
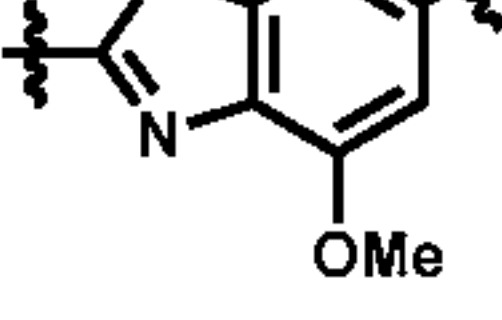
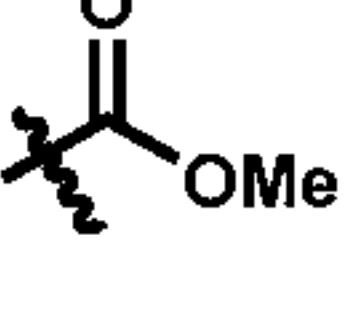
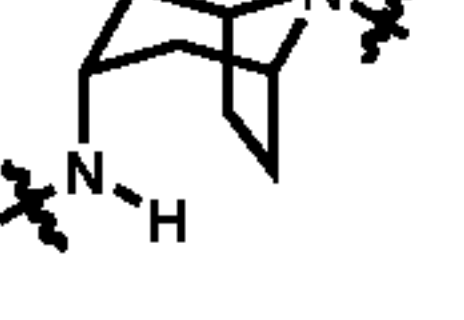
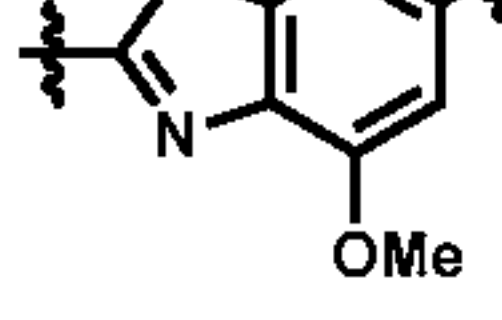
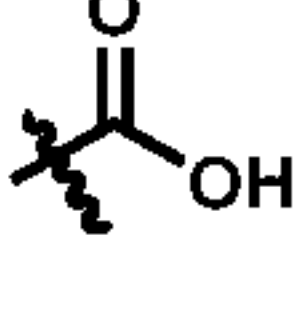
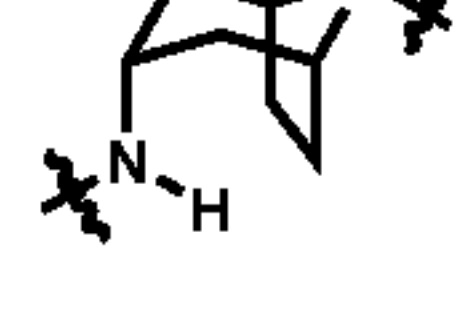
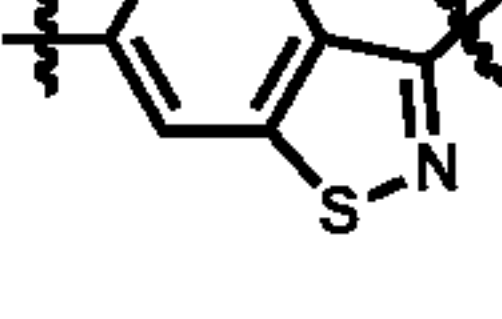
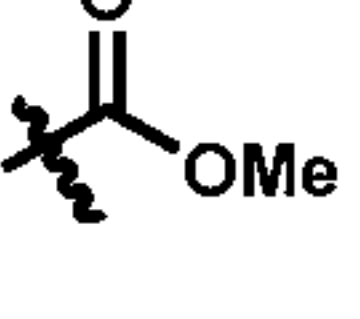
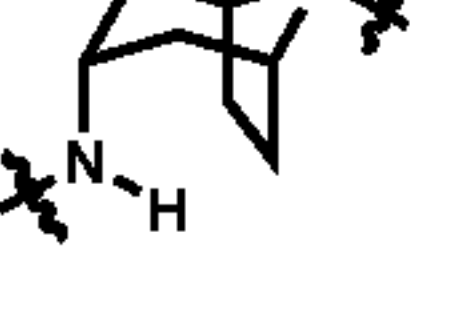
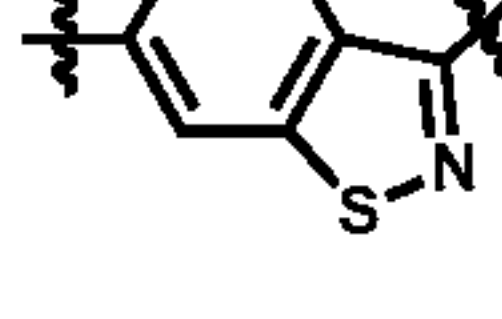
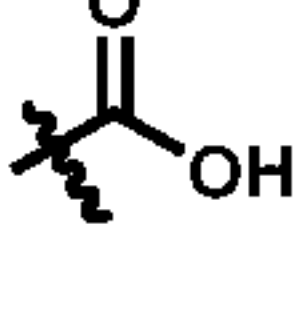
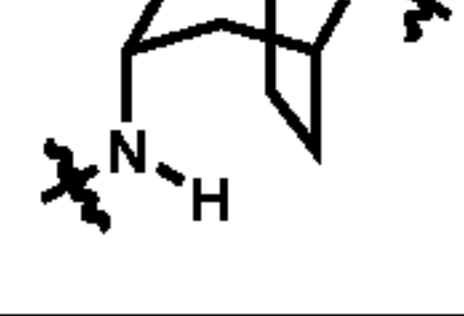
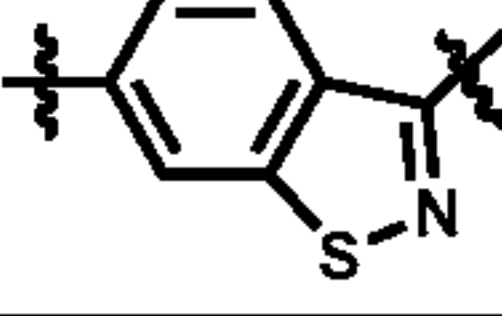
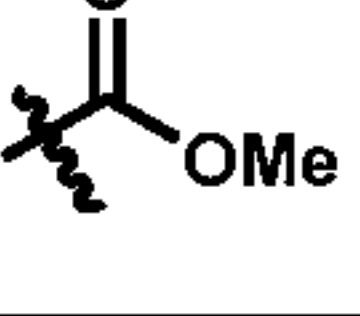
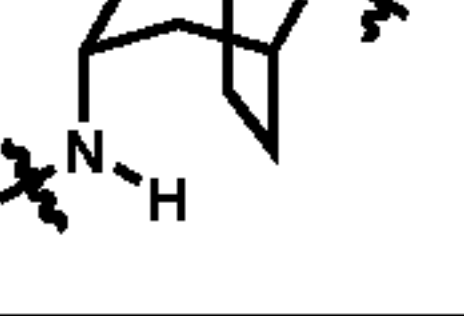
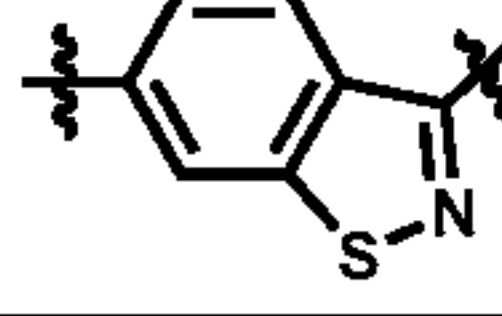
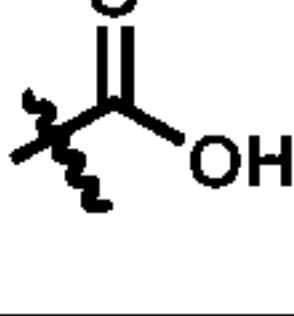
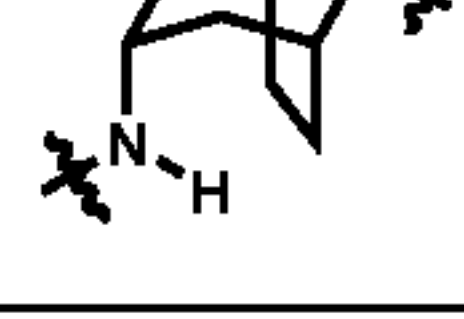
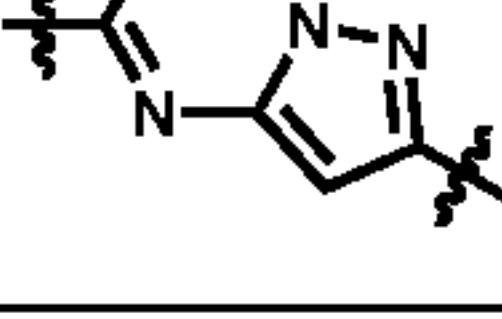
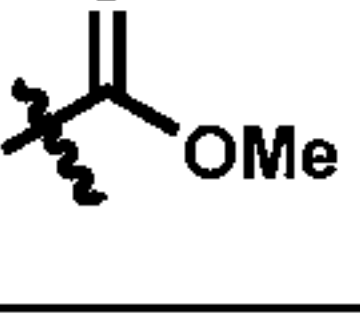
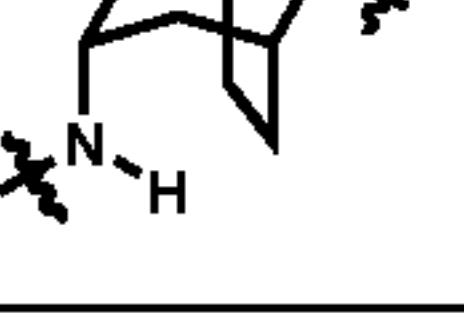
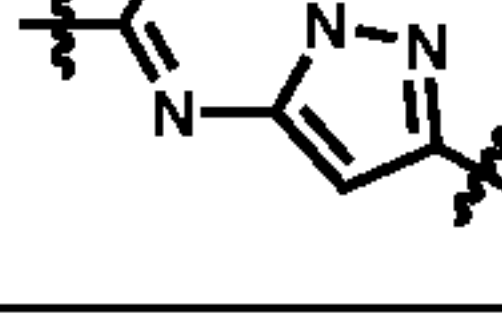
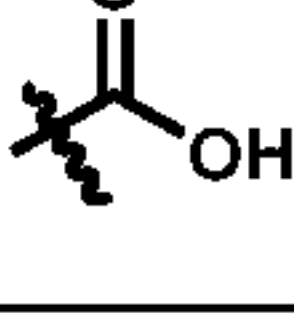
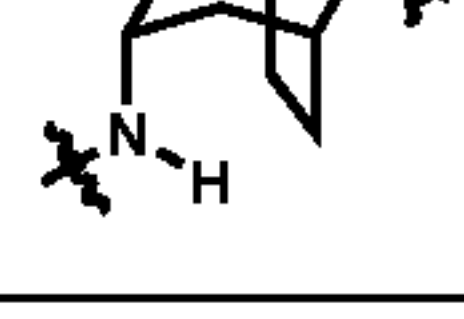
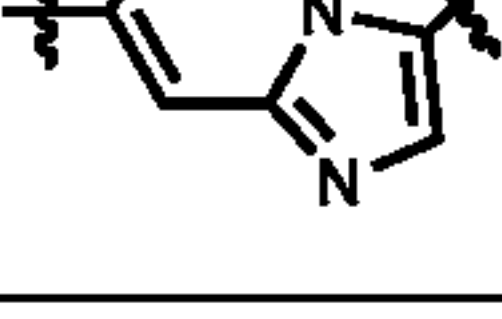
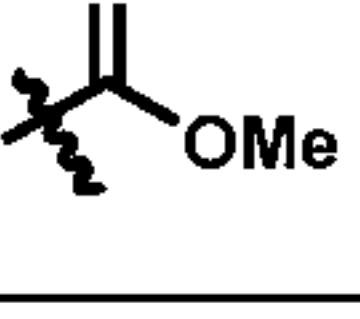
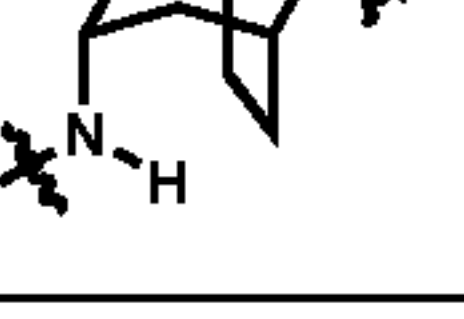
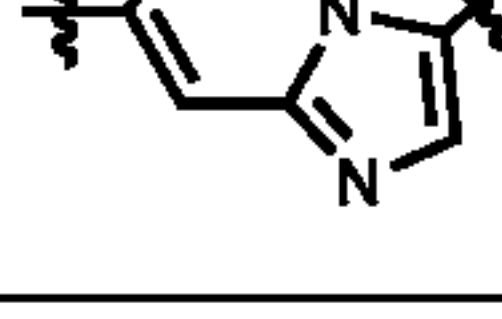
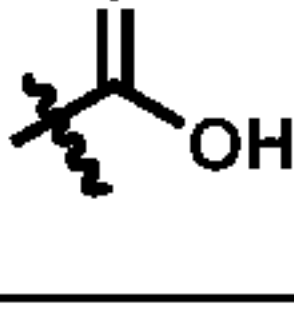
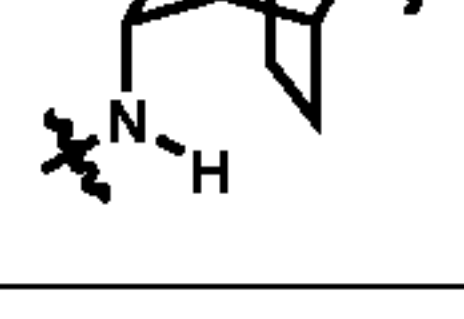
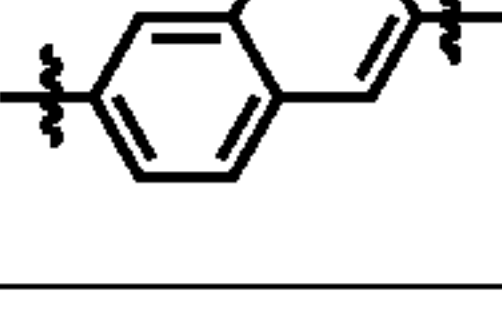
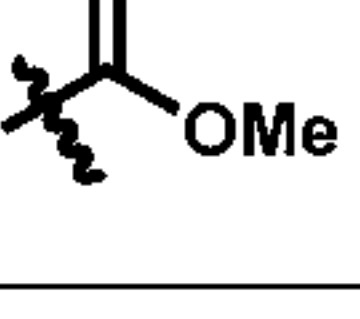
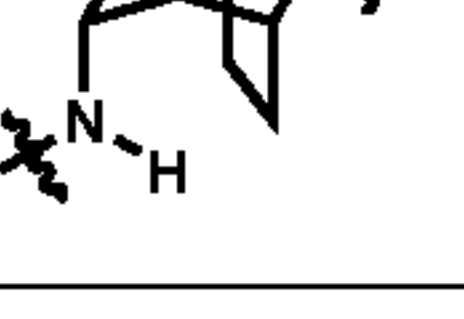
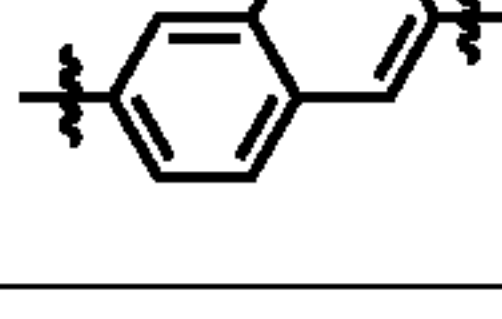
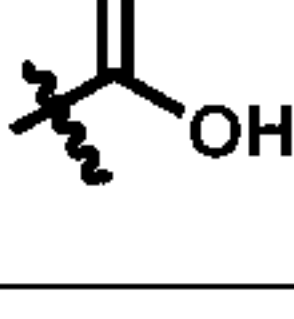
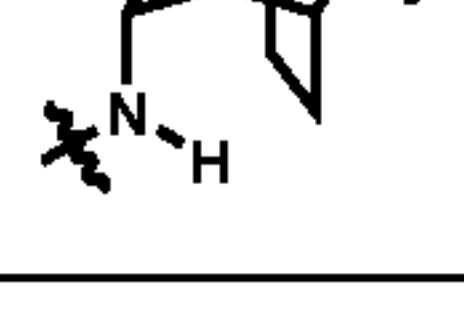
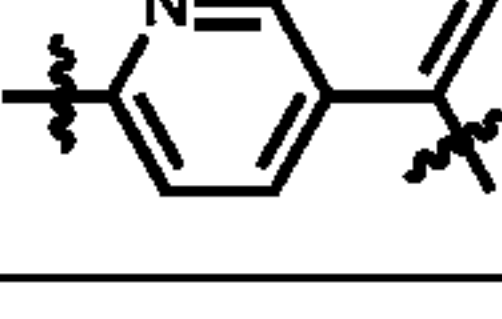
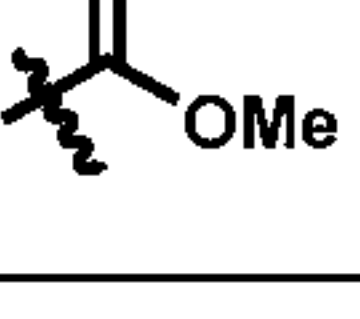
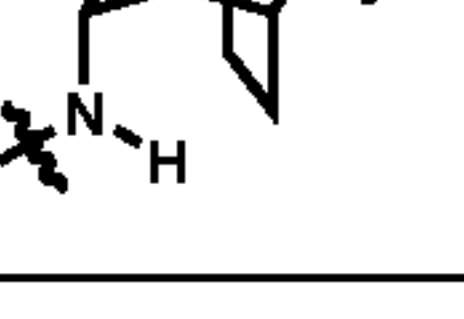
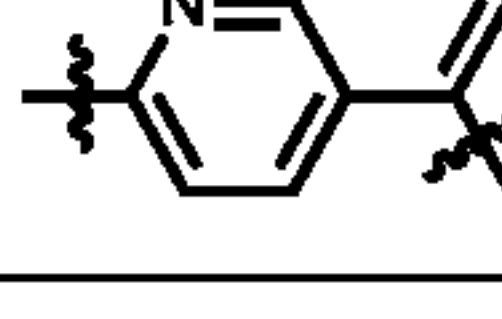
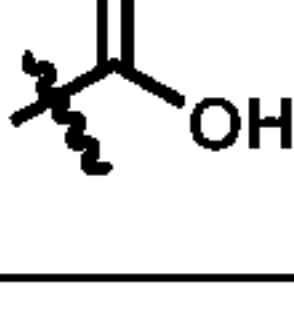
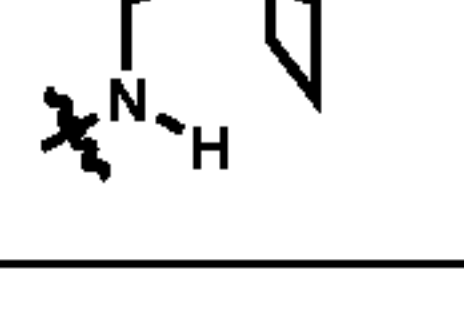
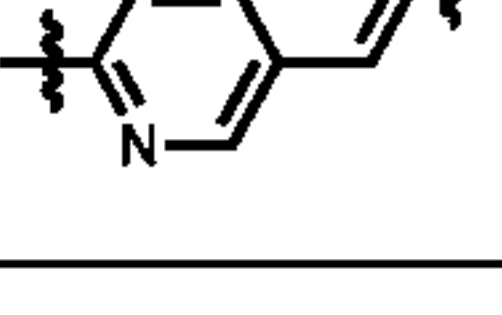
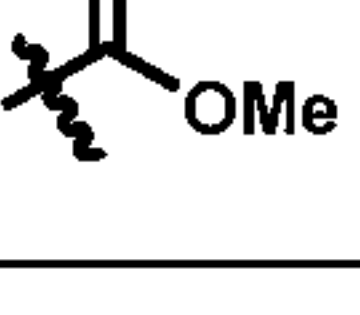
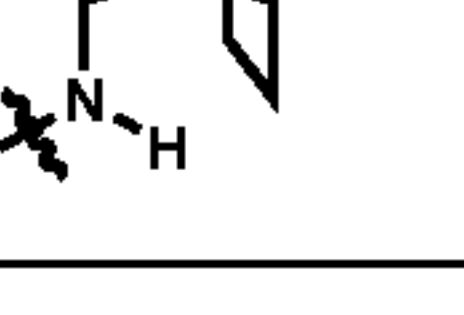
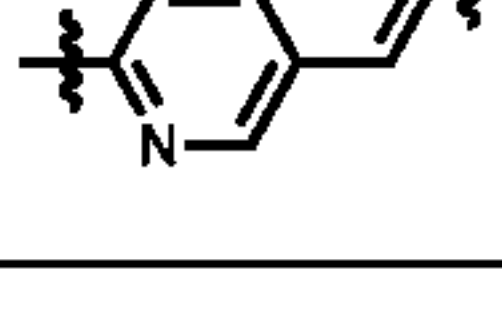
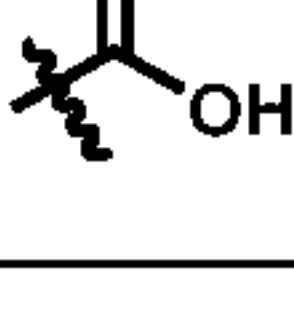
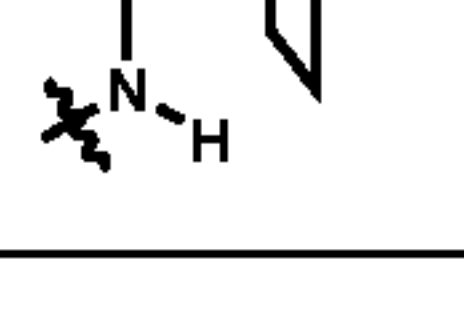
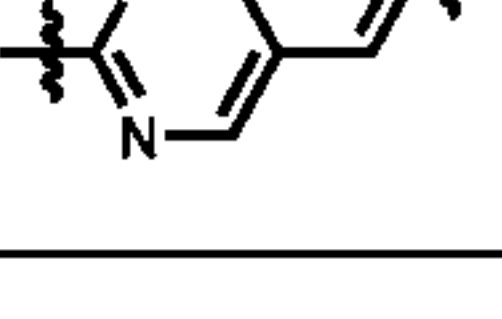
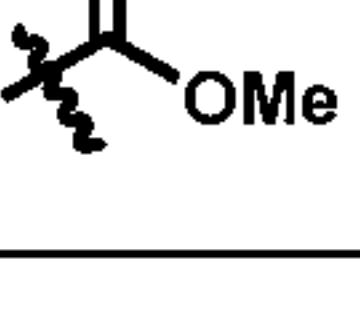
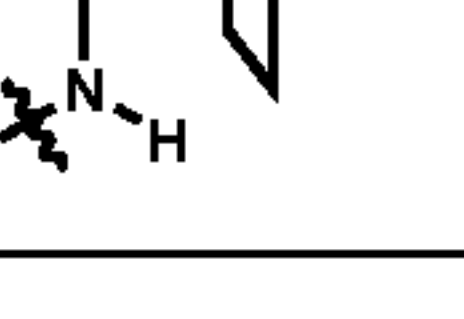
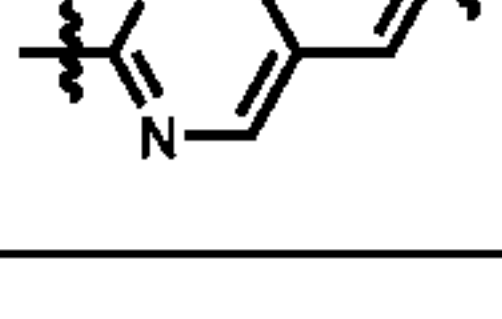
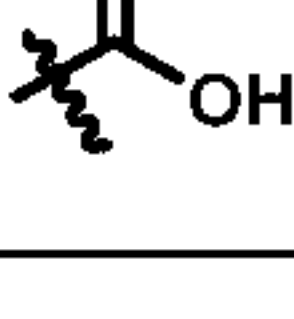
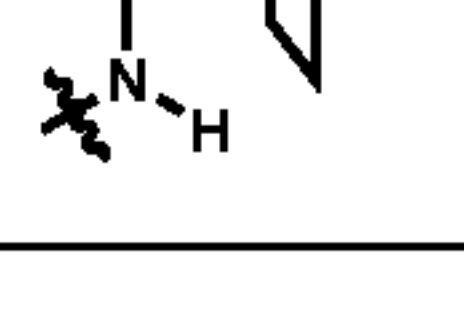
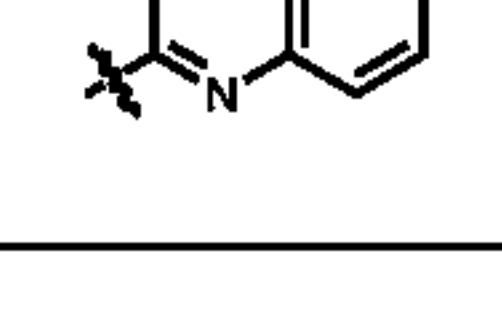
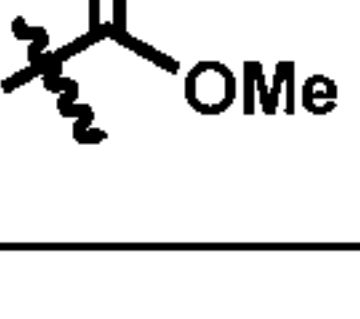
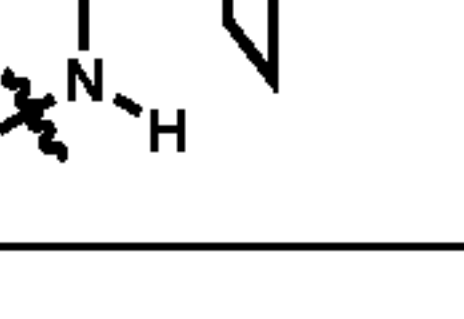
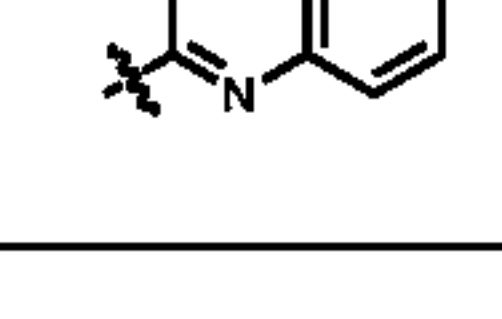
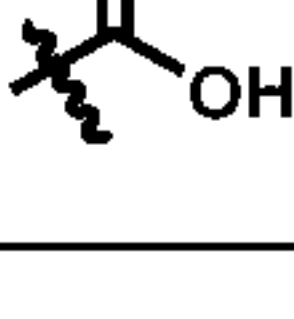


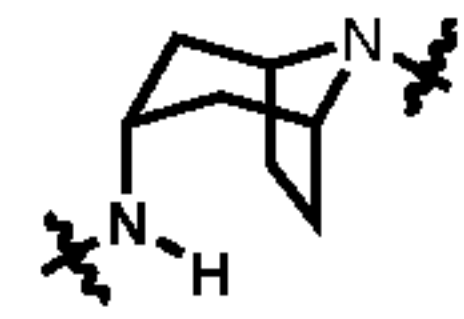
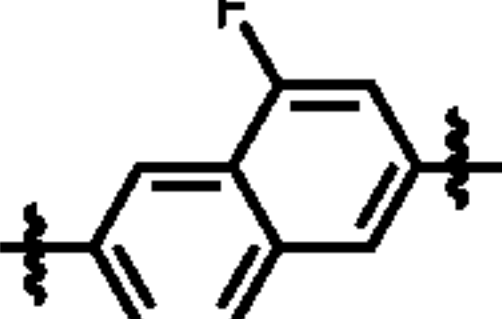
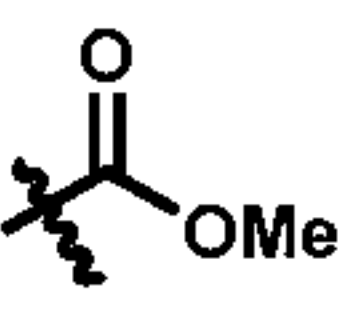
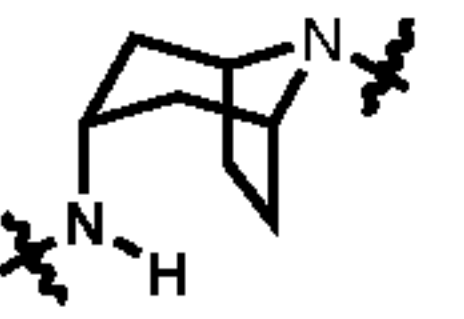
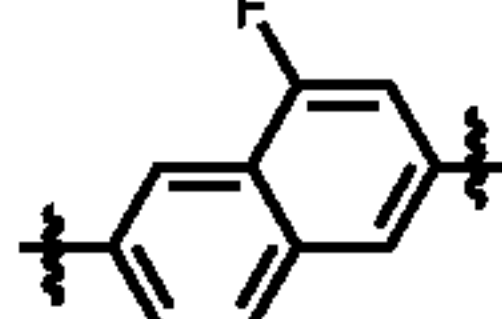
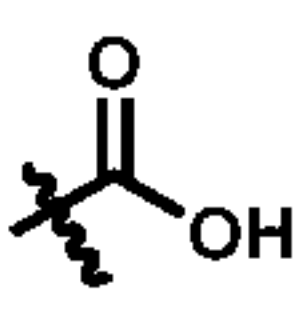
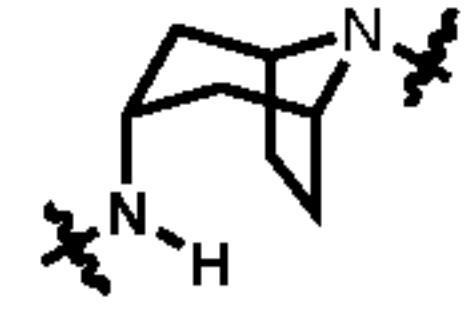
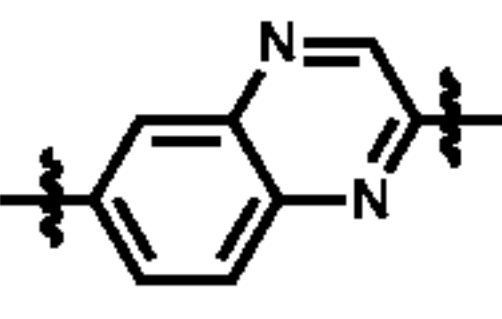
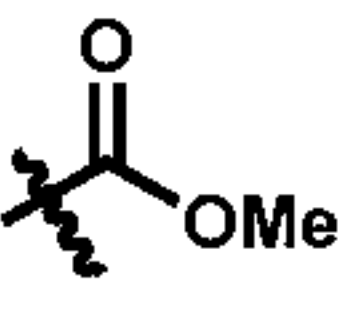
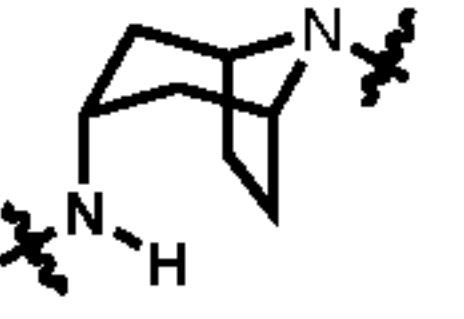
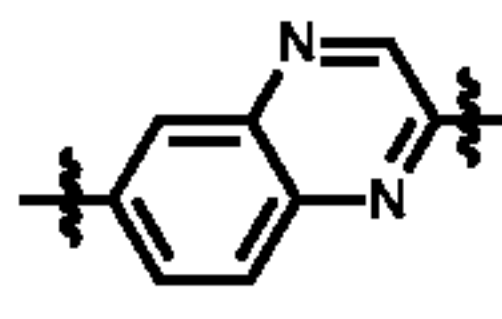
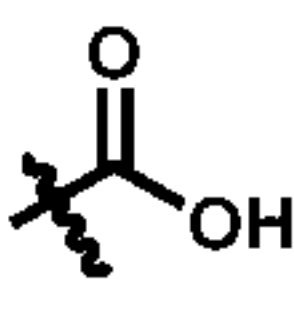
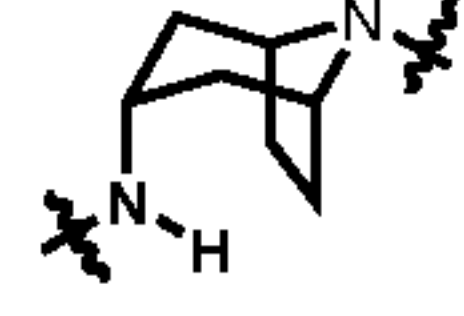
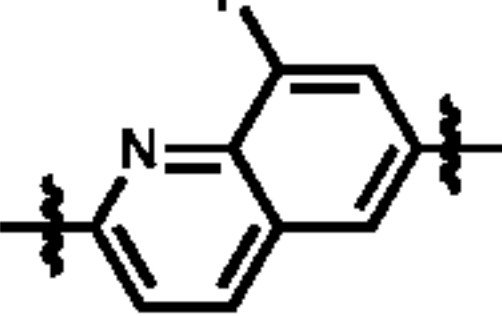
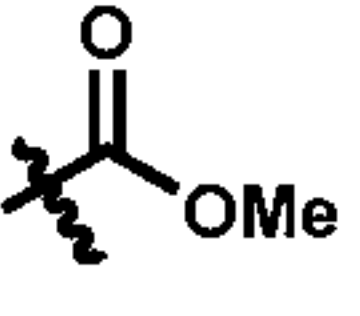
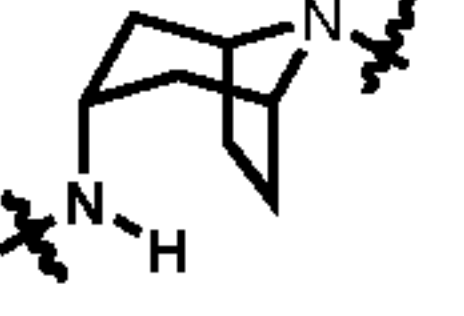
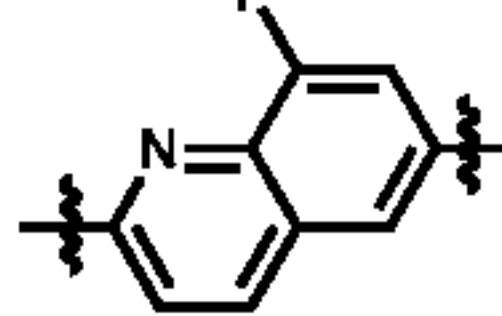
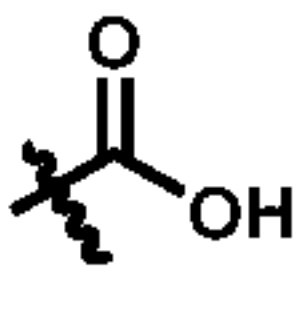
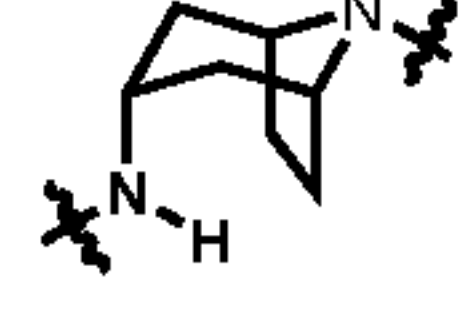
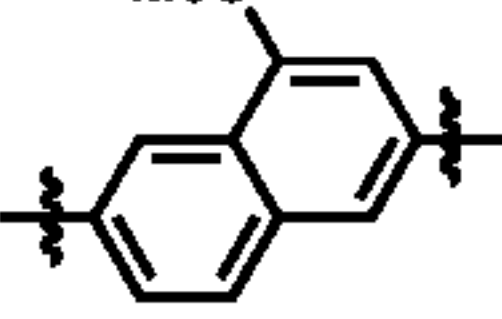
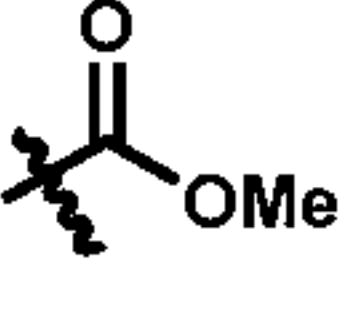
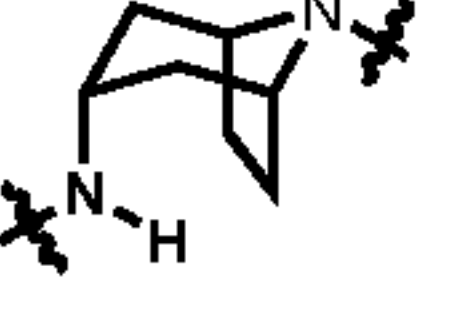
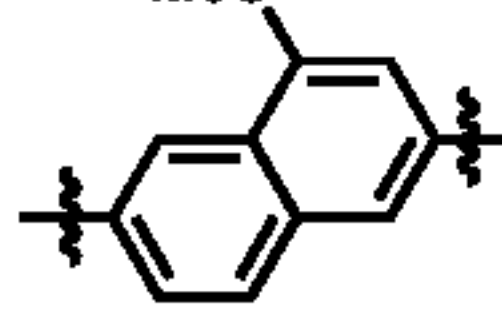
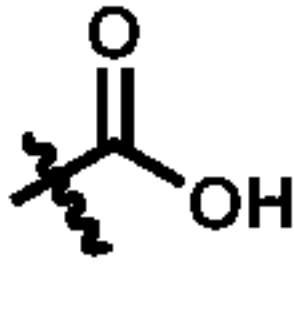
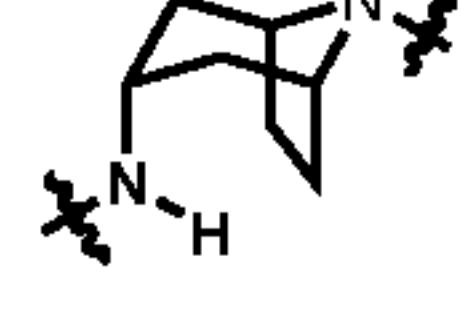
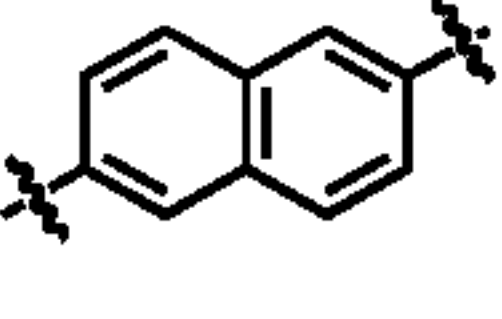
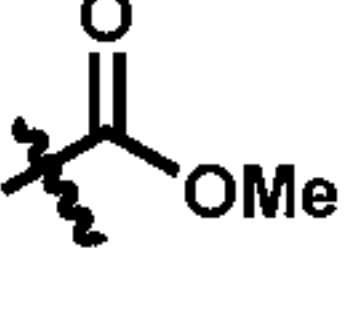
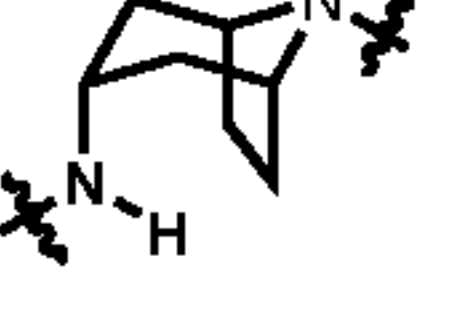
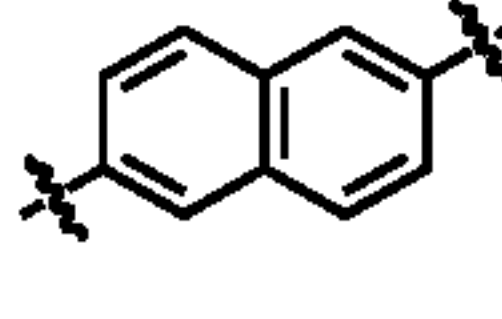
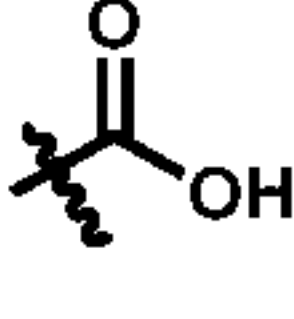
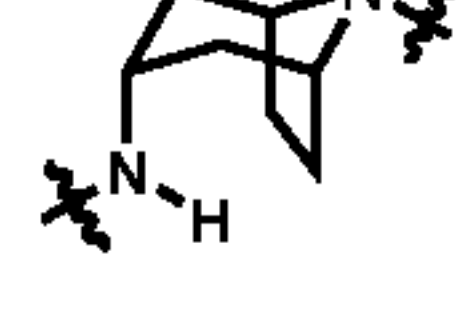
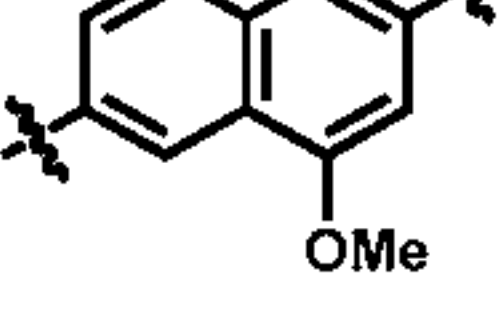
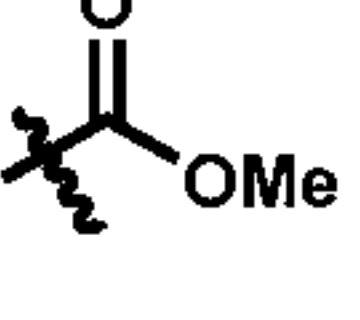
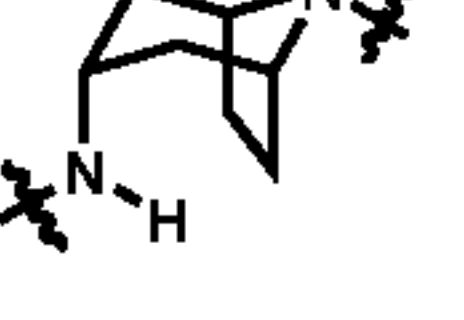
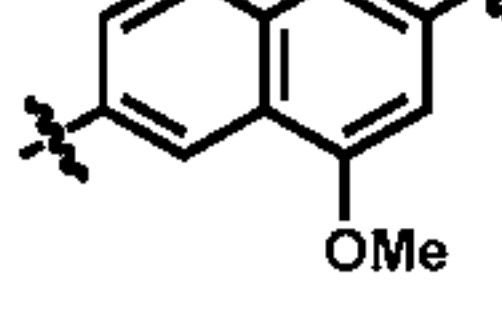
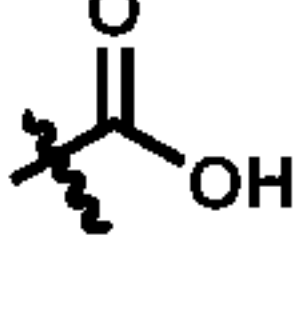
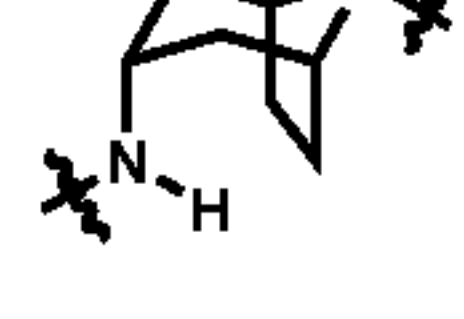
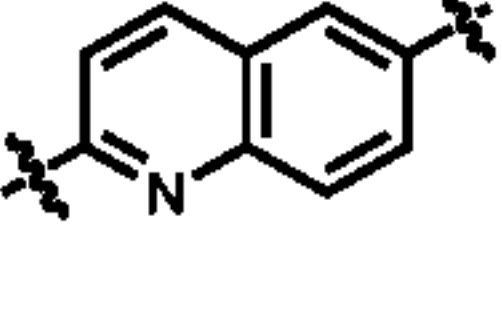
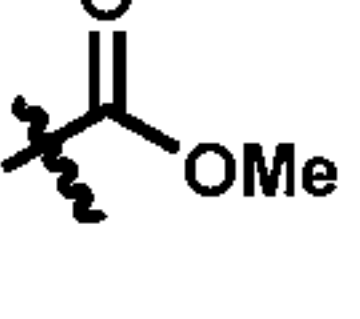
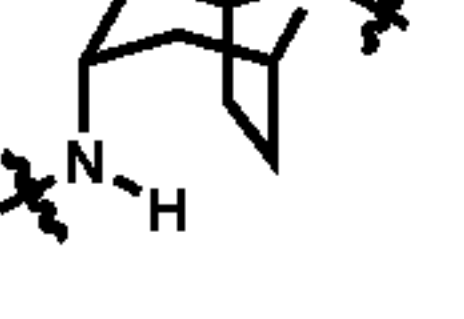
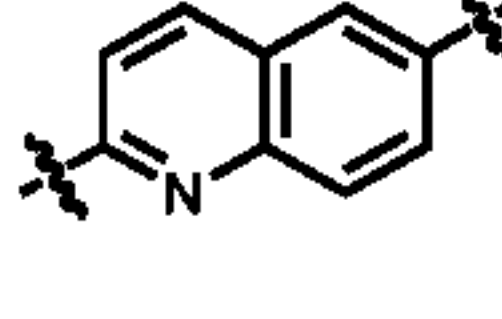
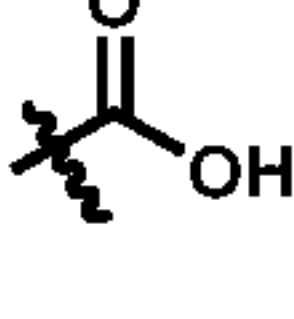
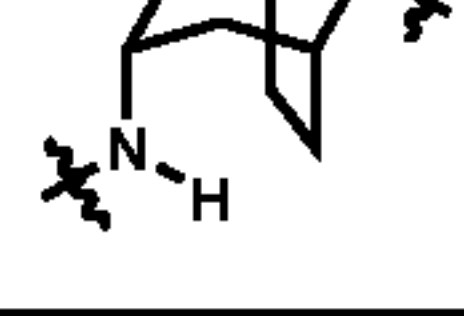
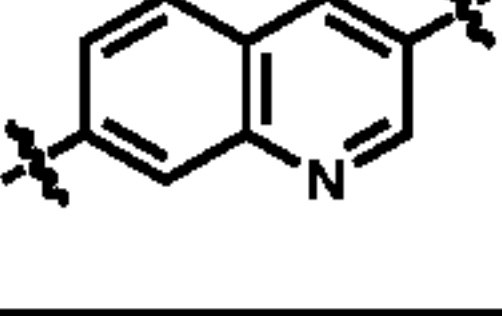
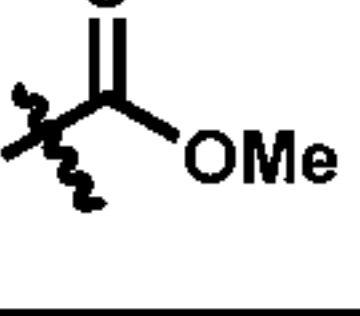
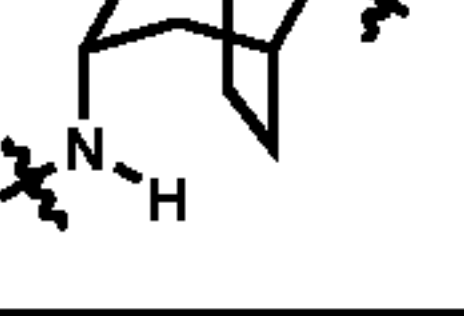
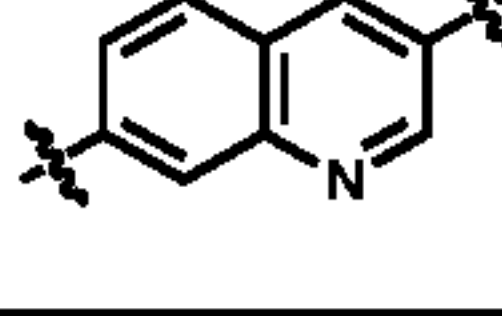
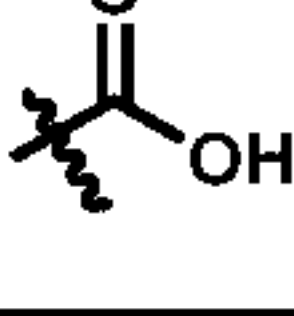
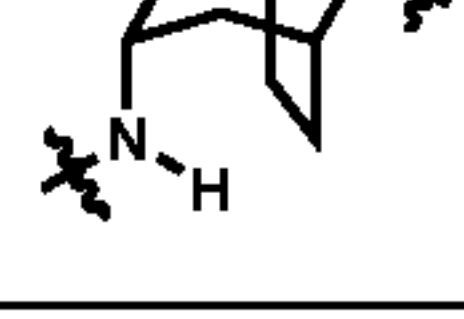
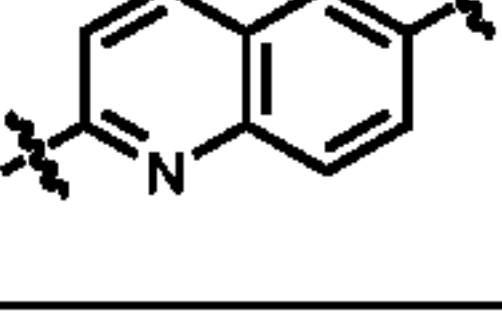
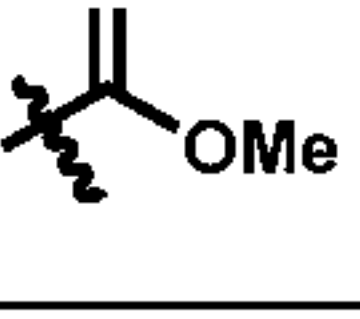
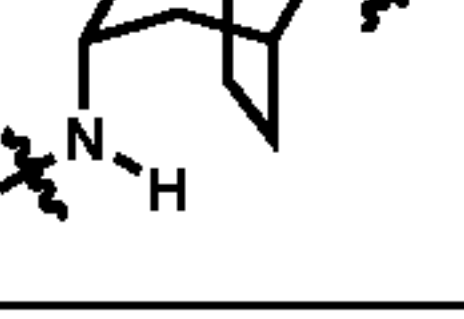
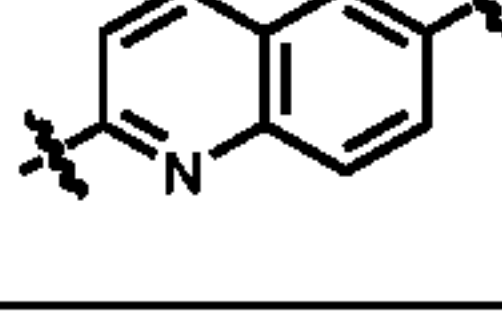
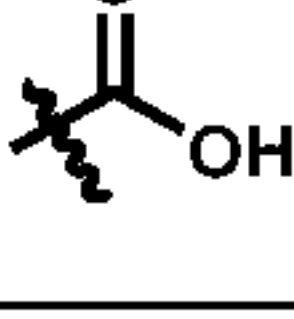
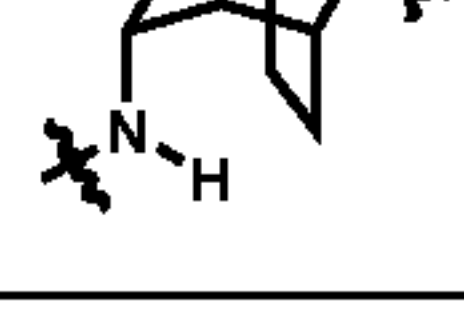
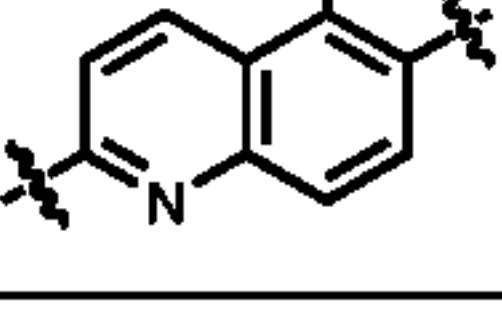
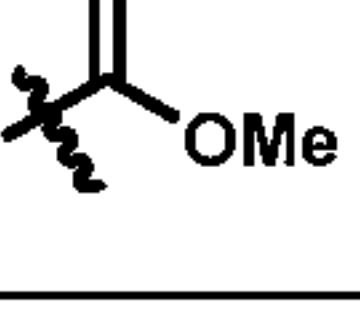
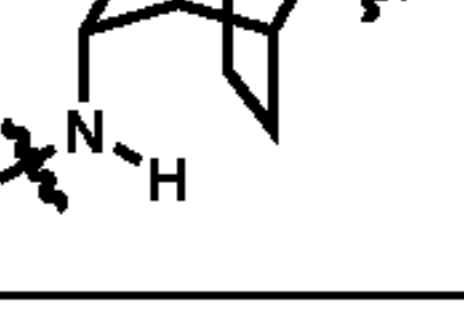
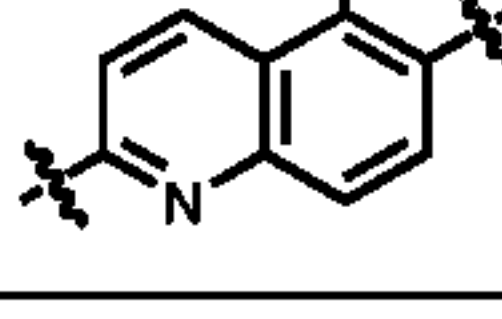
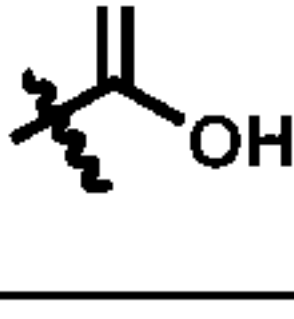
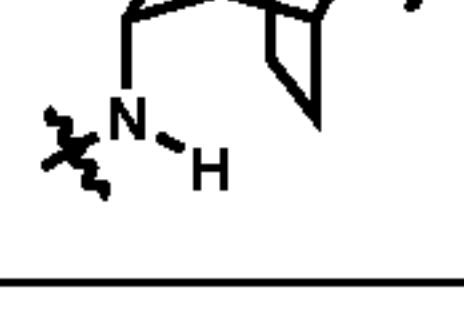
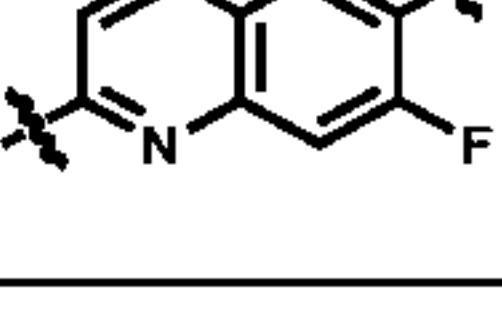
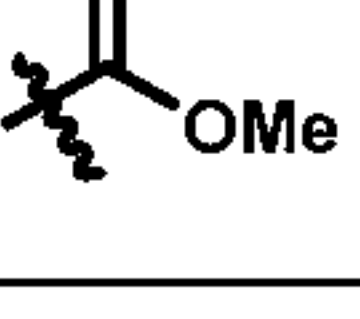
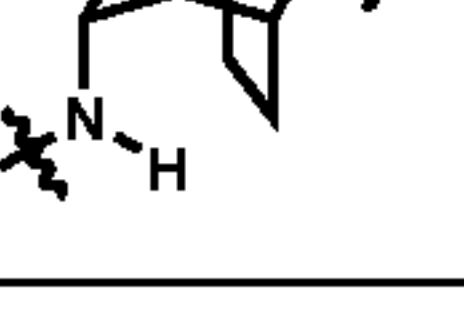
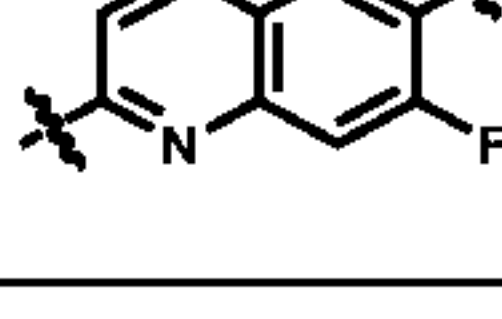
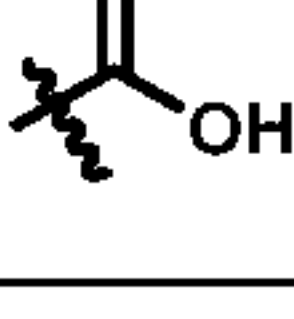
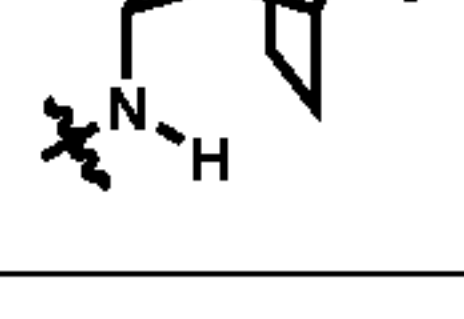
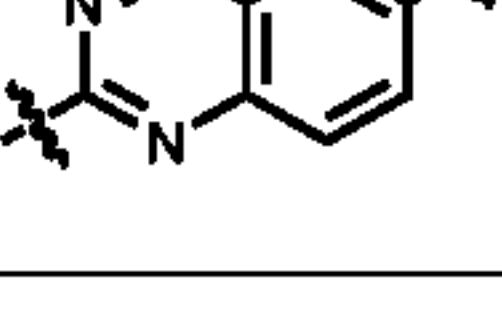
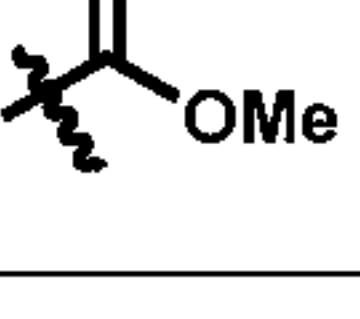
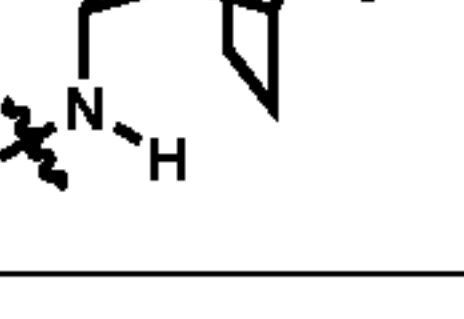
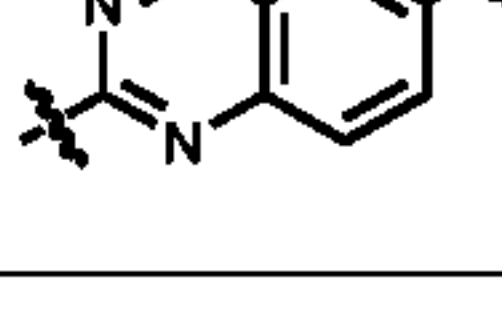
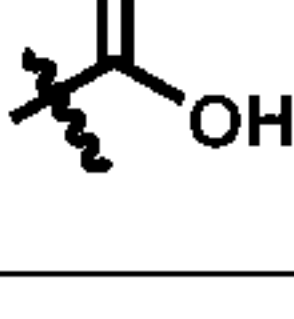
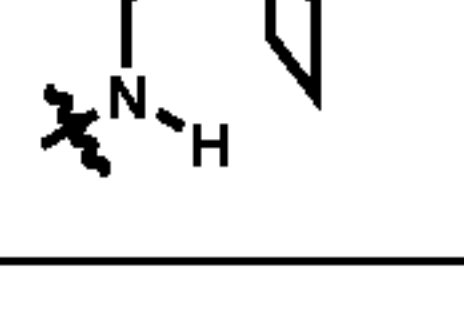
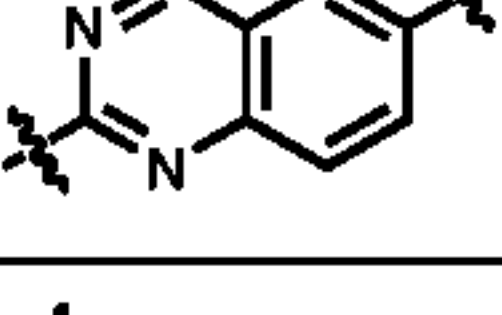
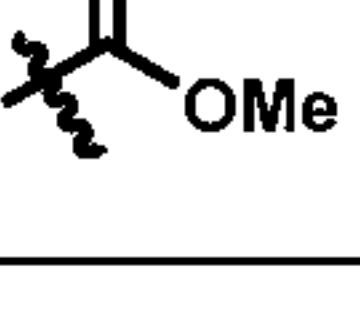
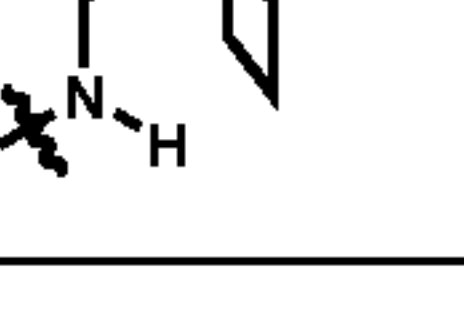
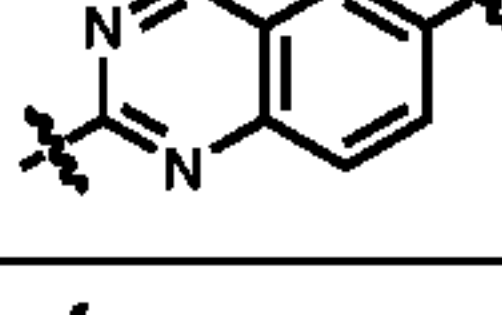
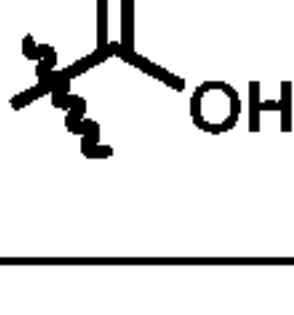
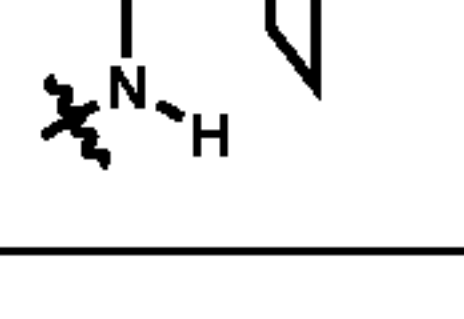
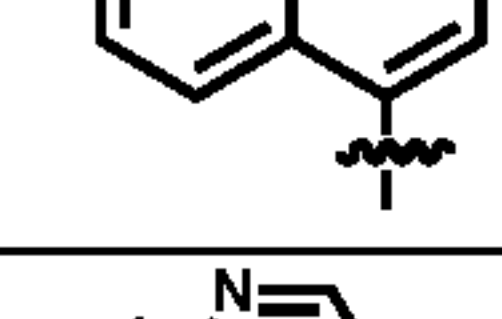
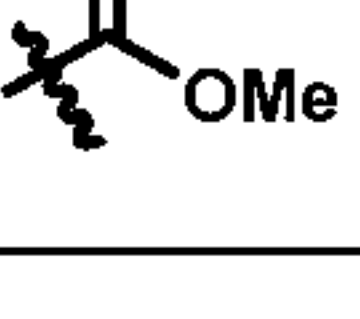
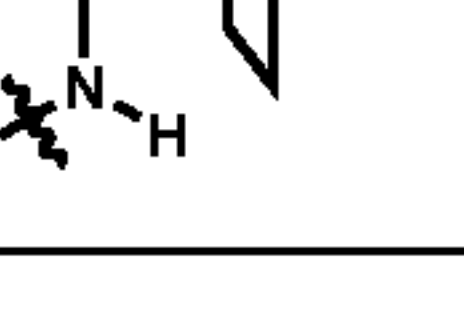
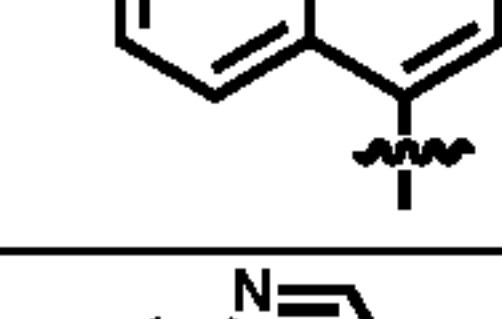
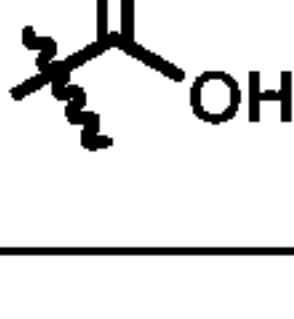
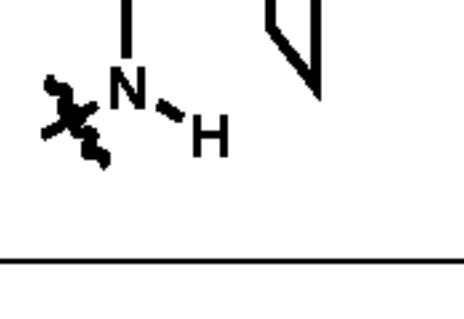
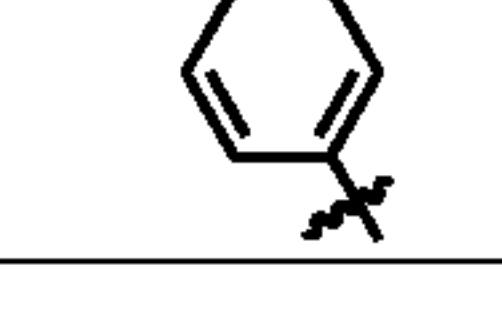
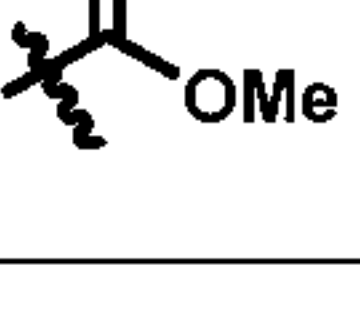
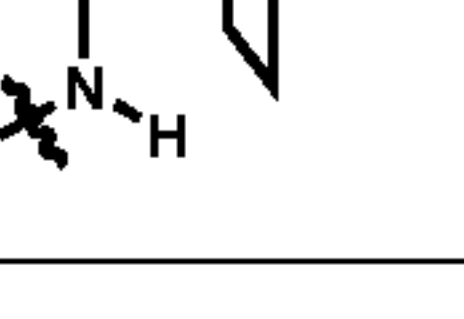
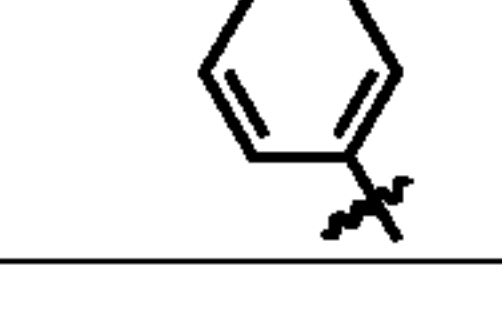
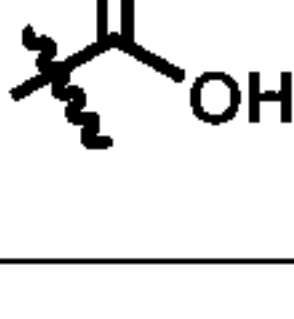
Table 3

Compound	A	B		Z-R ⁴	Compound	A	B		Z-R ⁴
401					402				
403					404				
405					406				

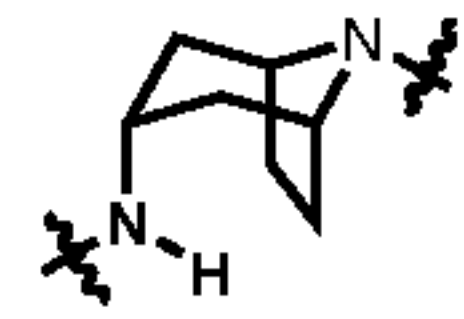
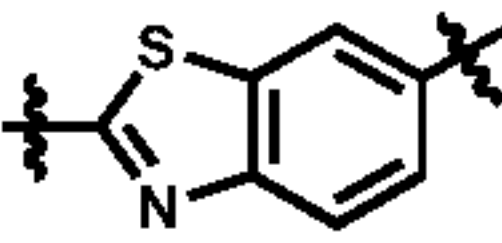
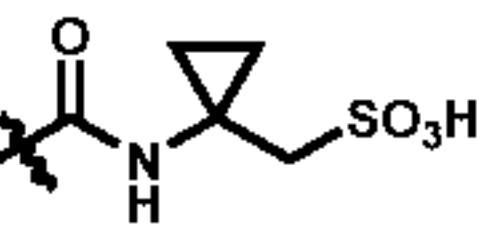
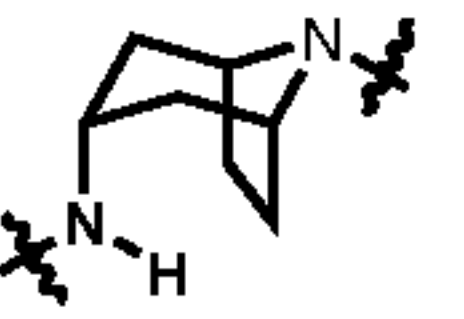
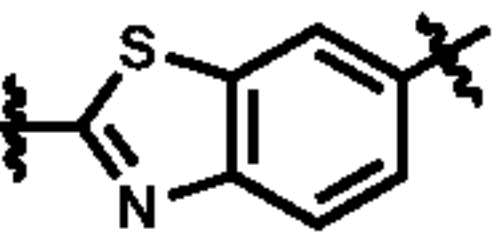
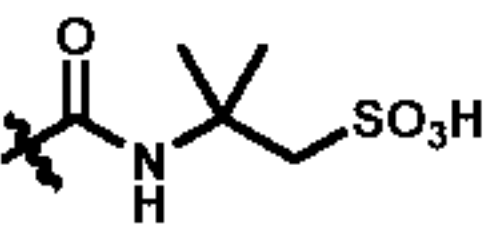
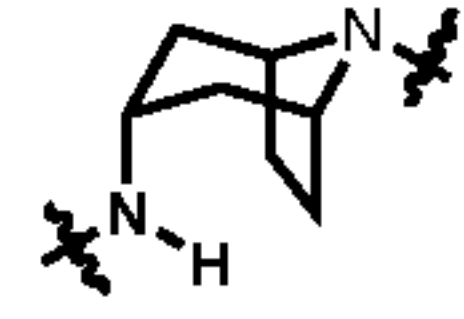
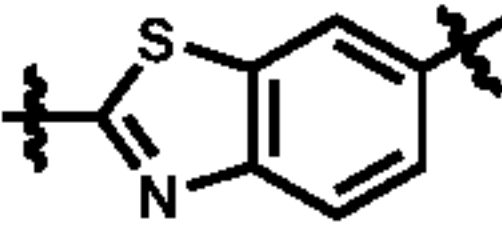
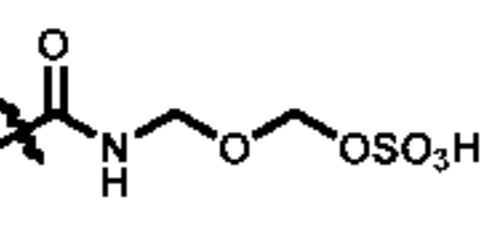
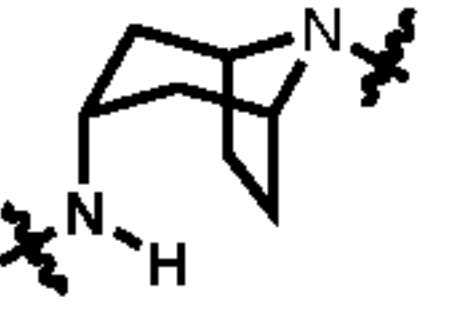
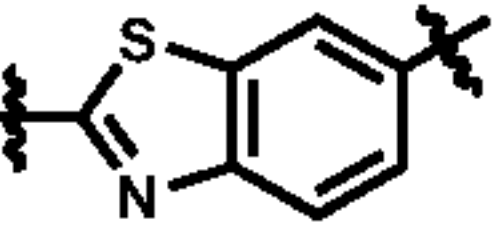
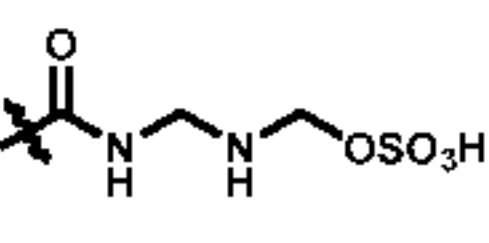
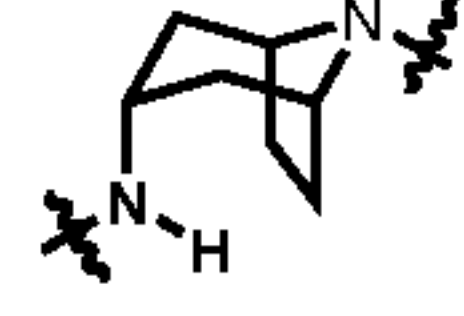
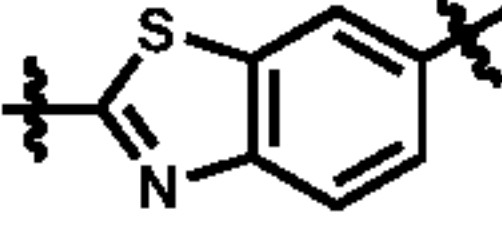
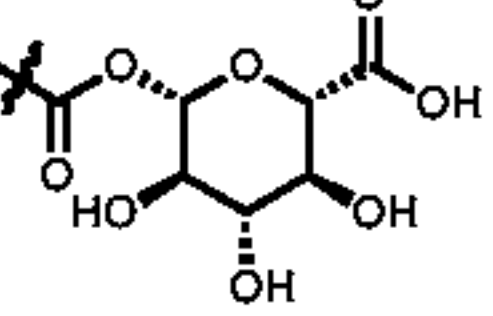
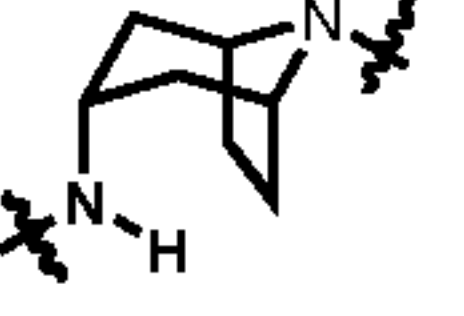
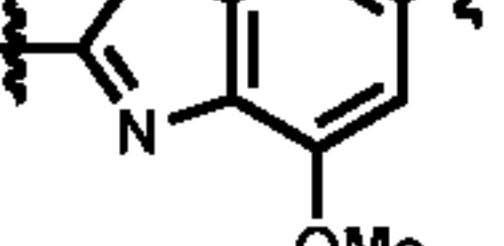
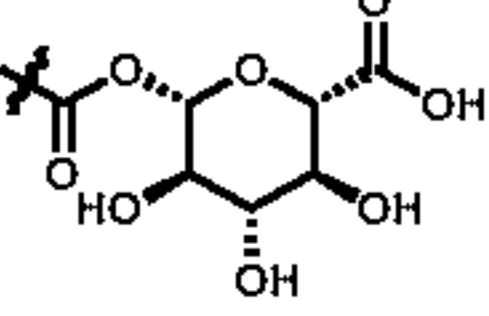
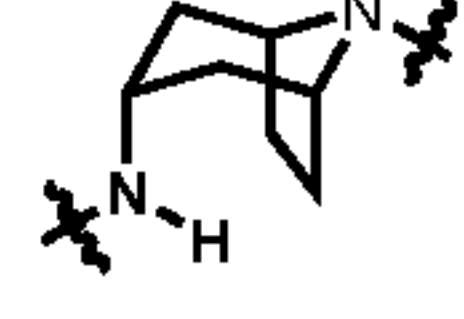
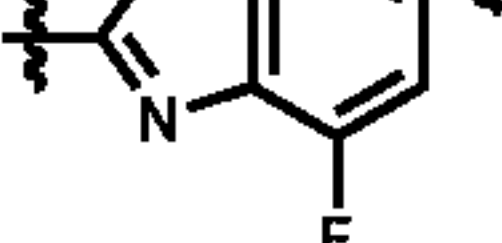
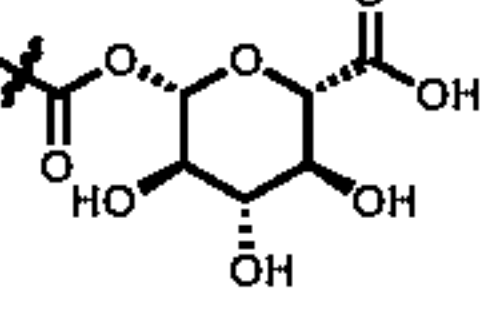
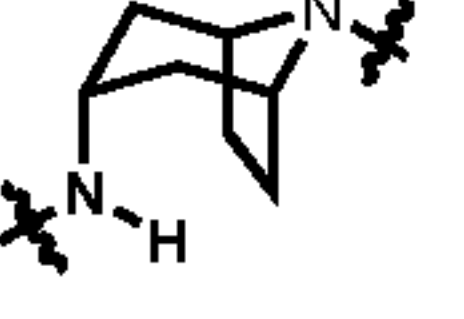
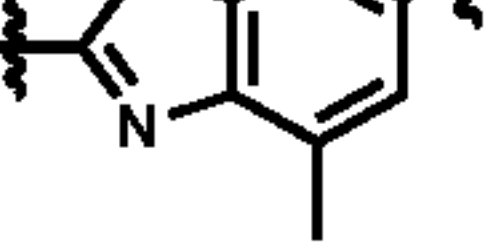
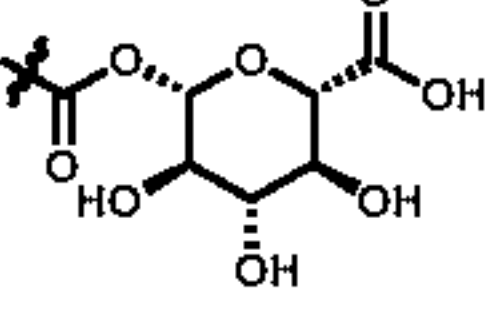
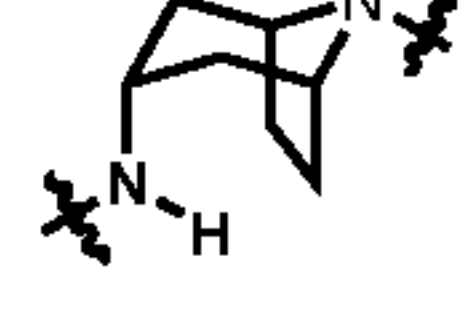
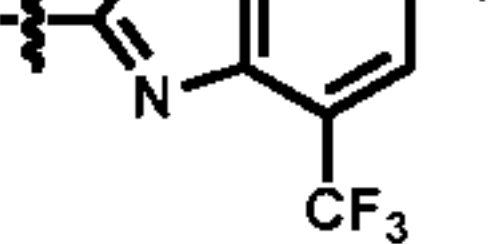
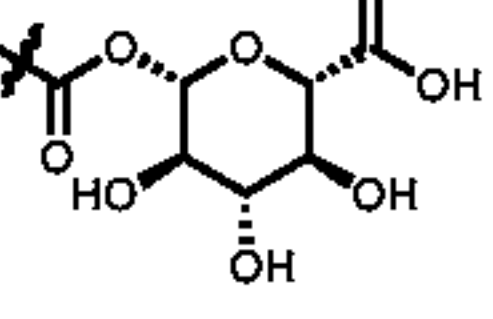
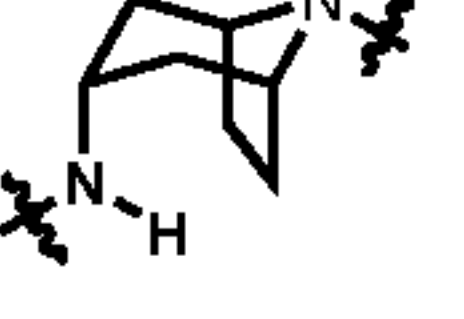
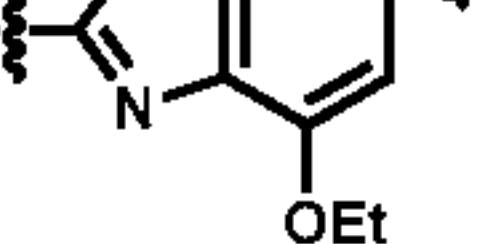
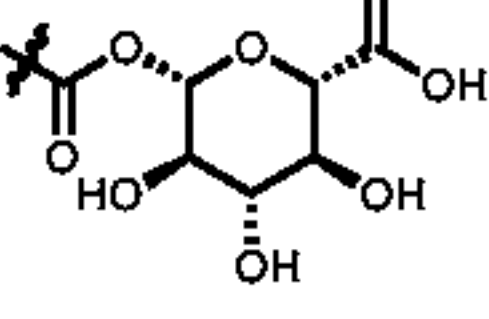
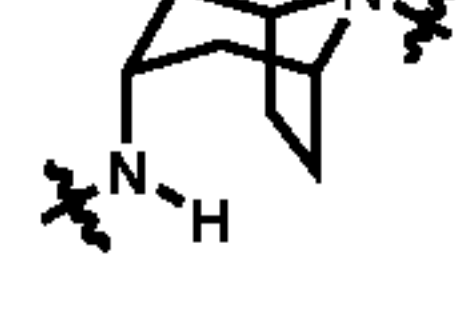
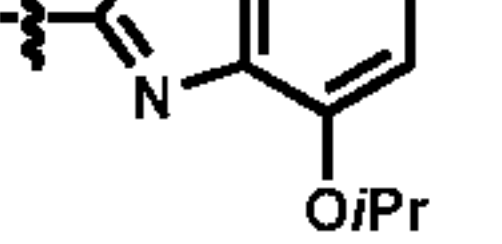
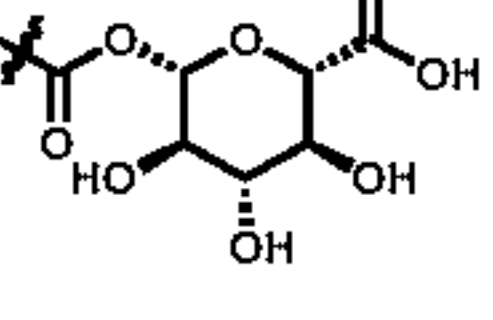
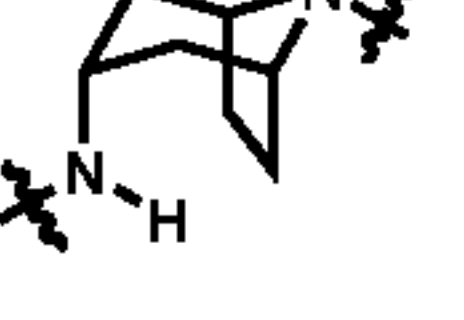
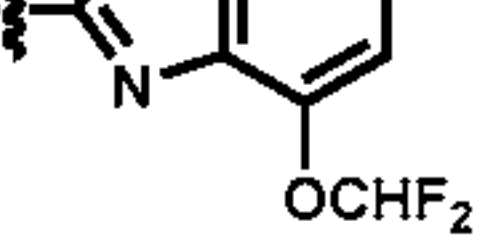
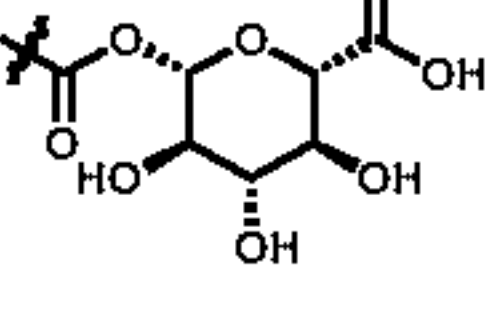
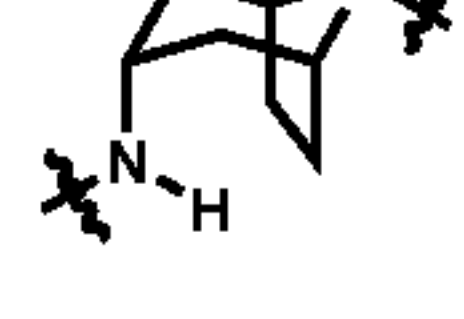
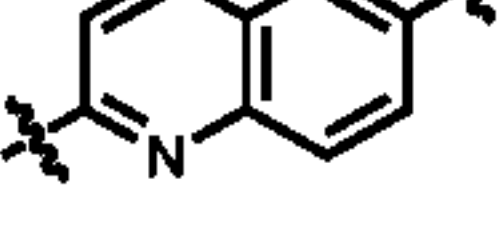
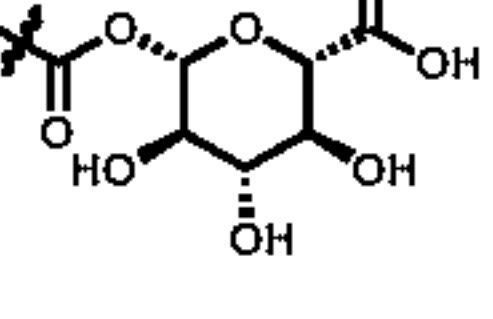
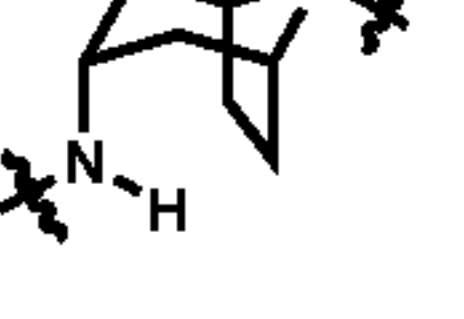
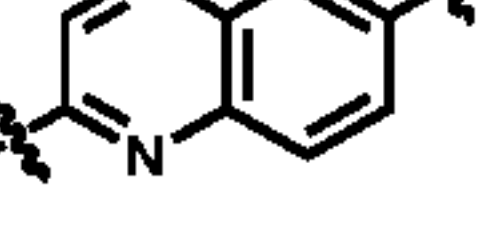
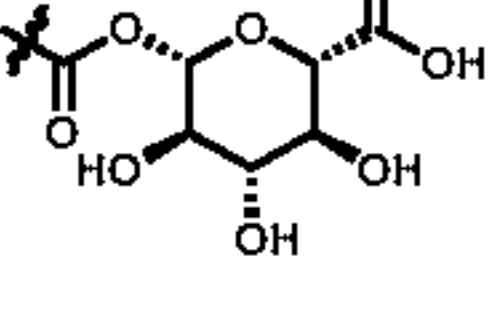
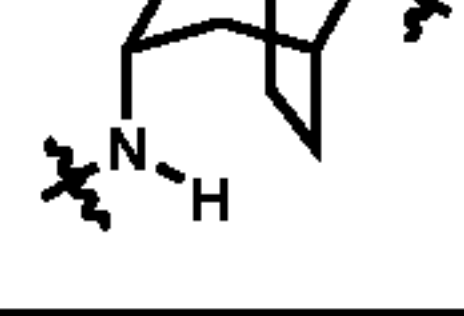
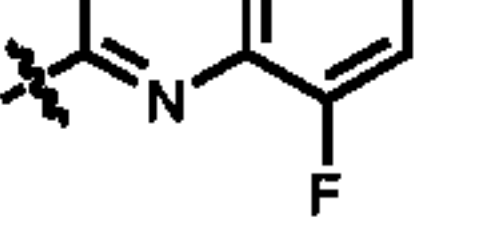
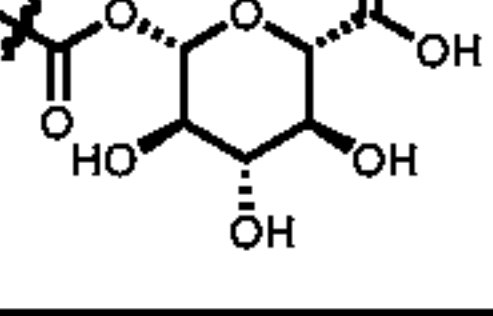
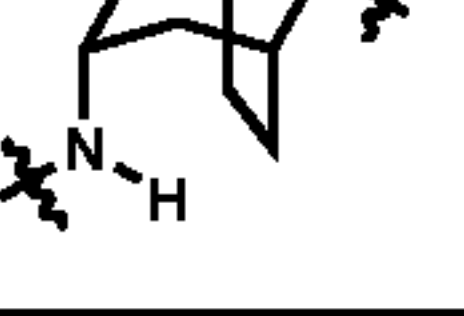
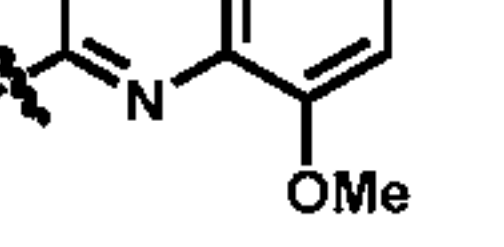
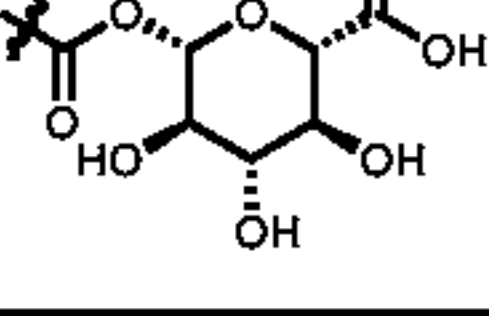
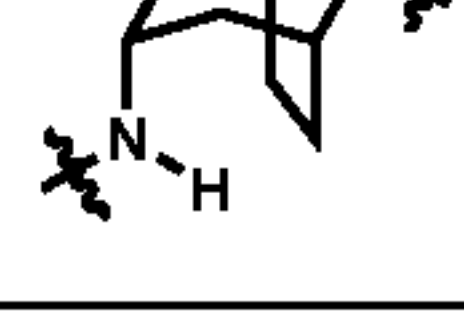
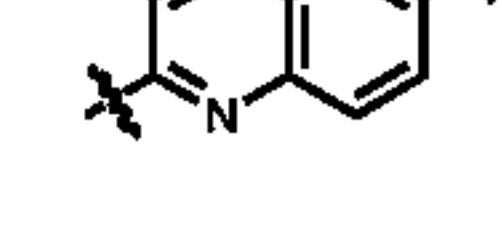
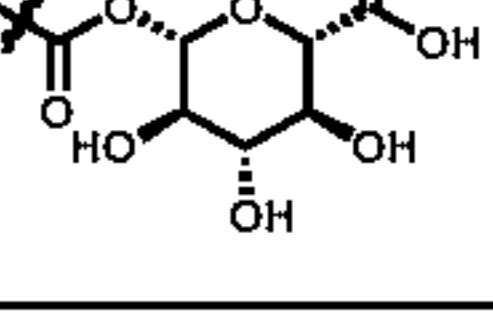
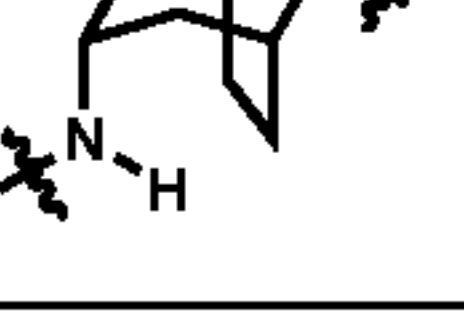
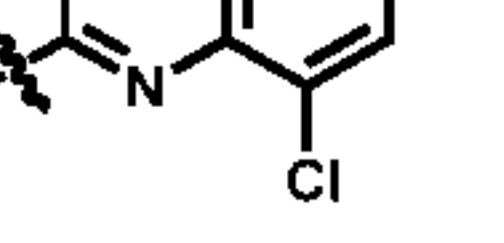
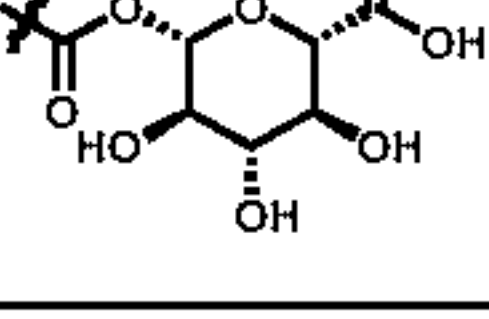
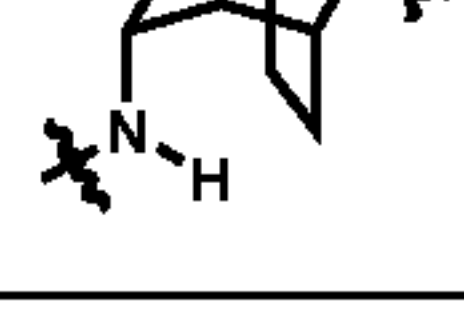
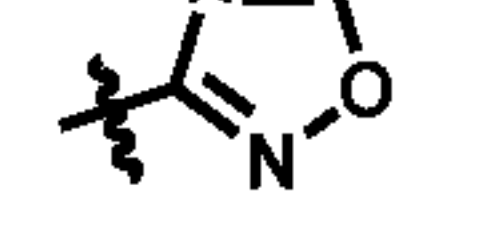
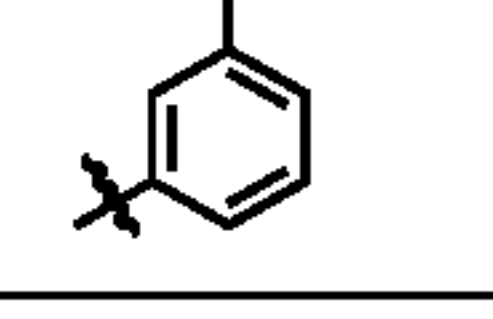
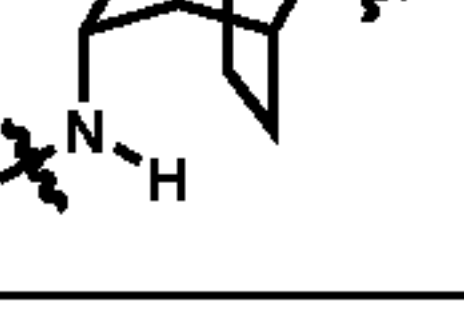
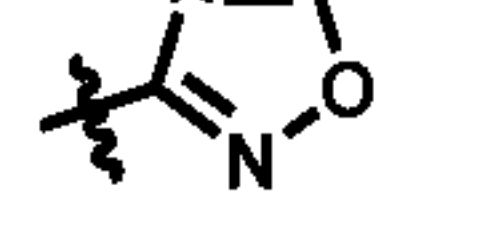
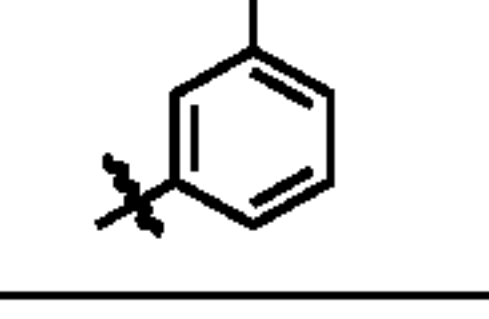
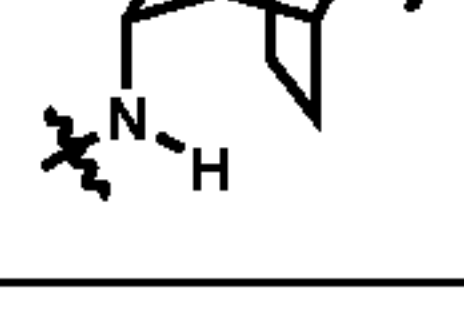
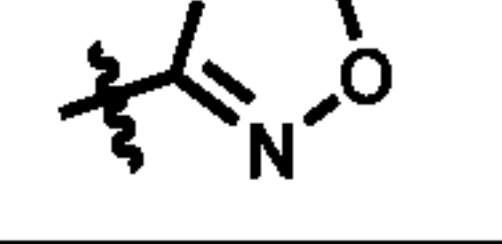
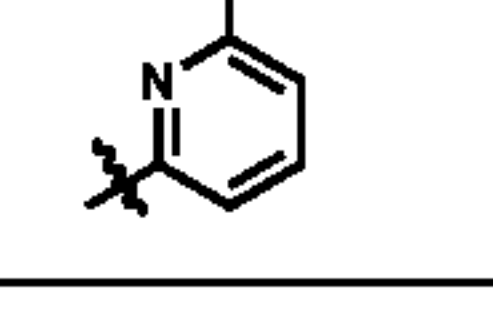
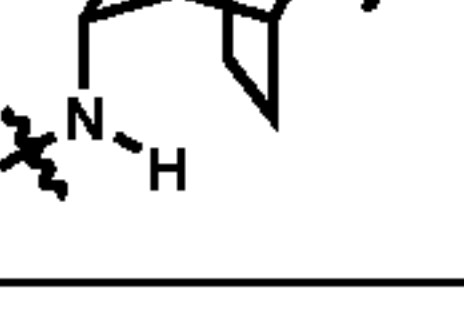
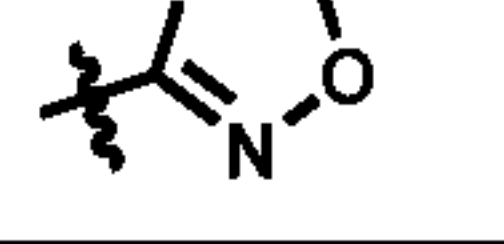
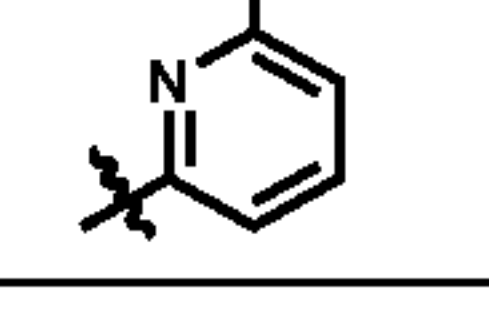
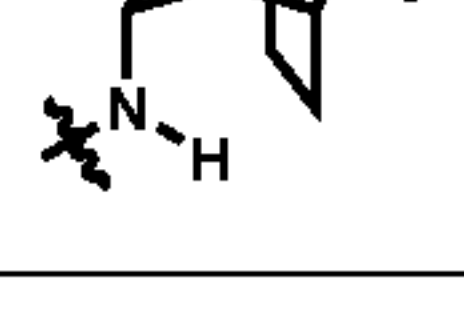
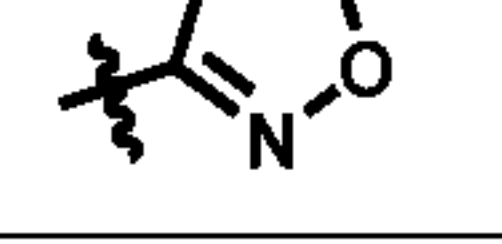
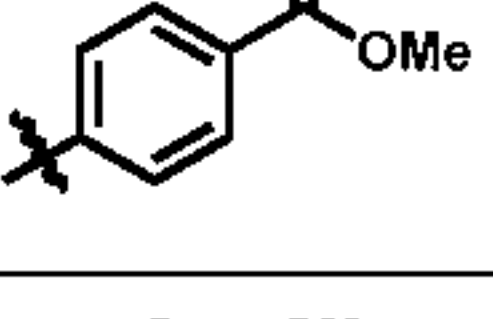
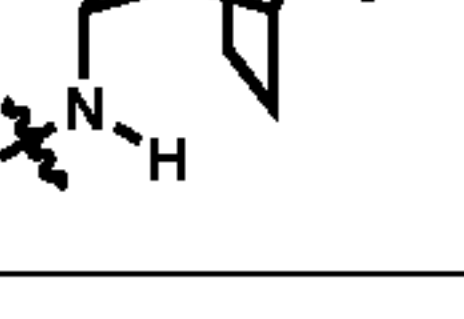
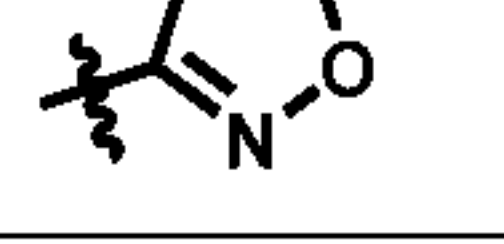
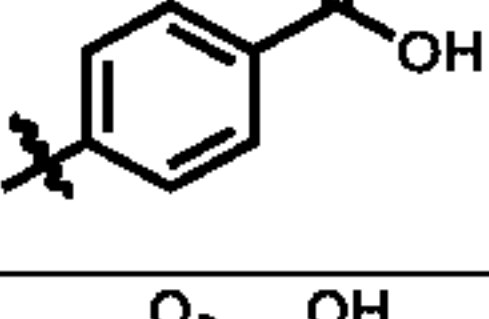
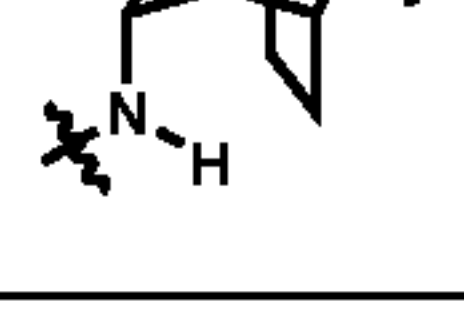
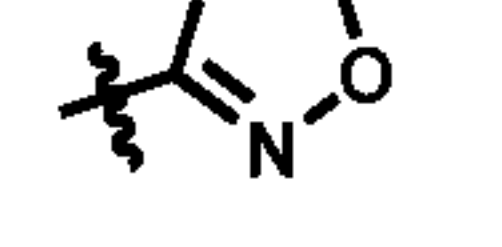
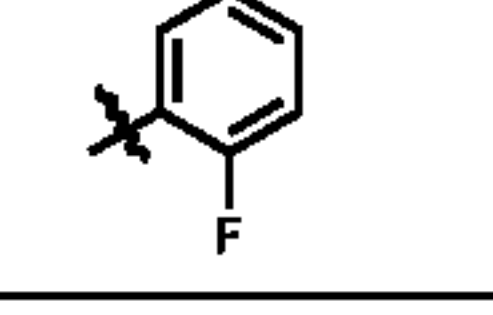
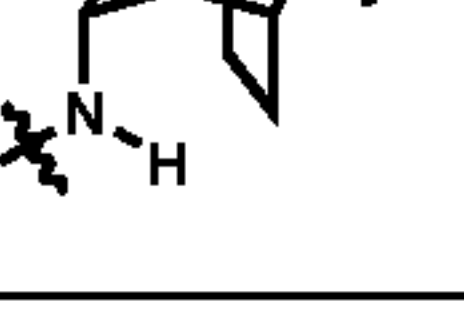
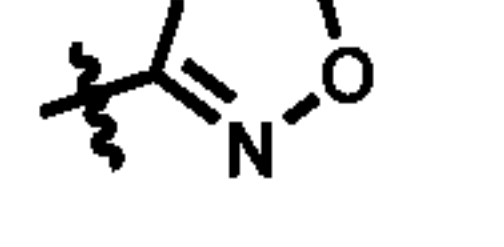
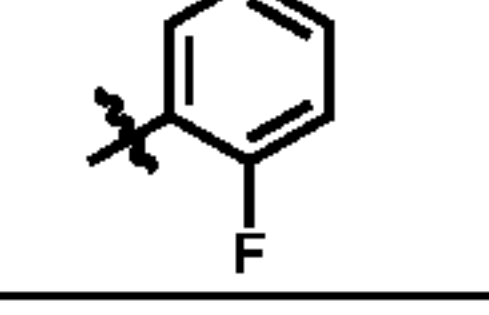
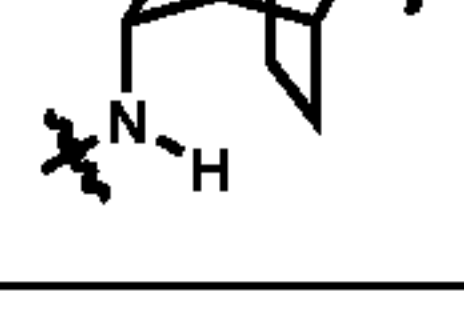
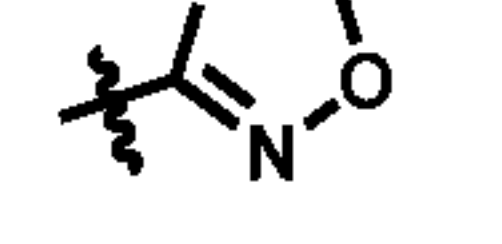
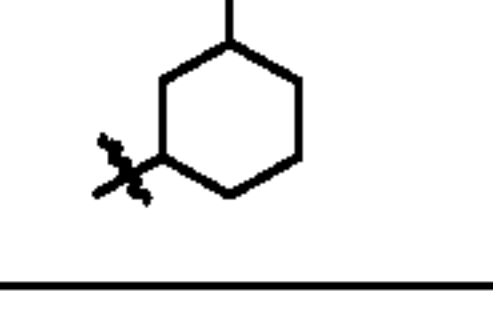
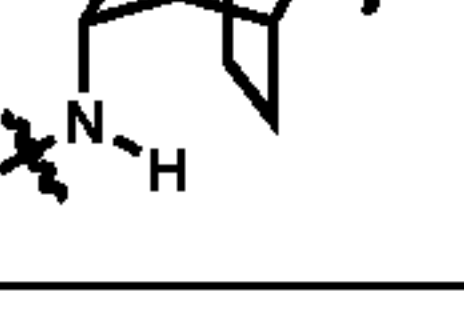
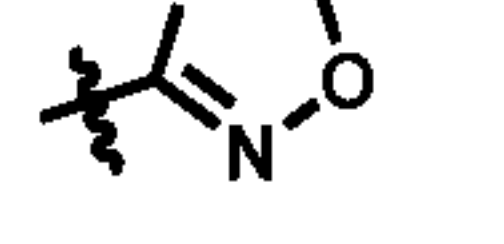
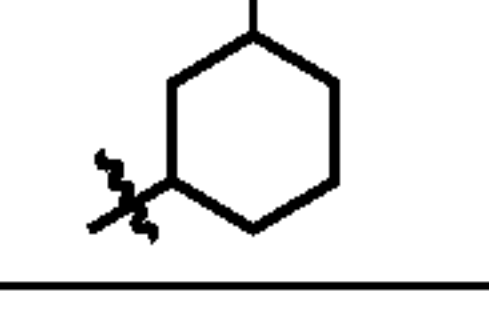
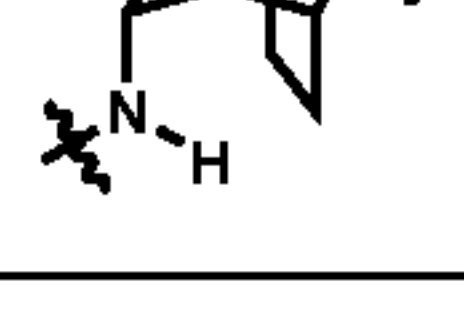
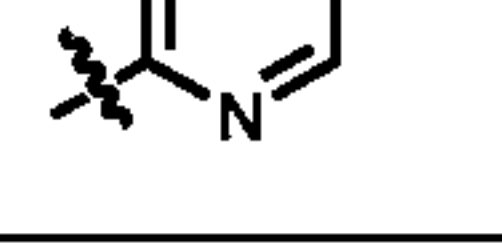
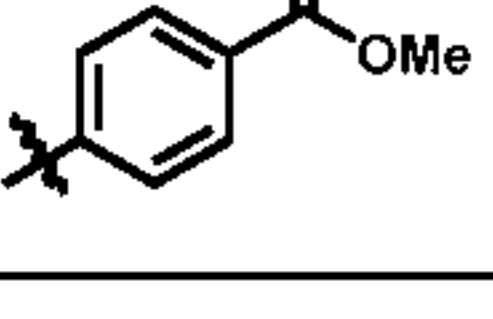
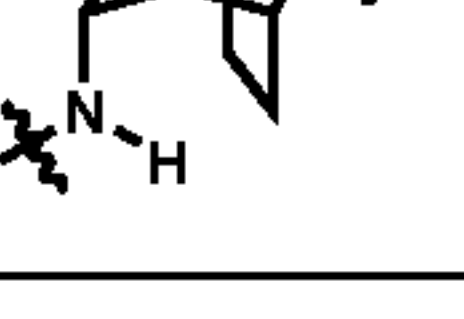
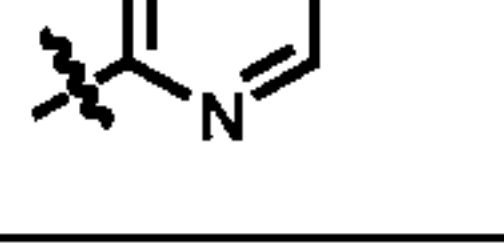
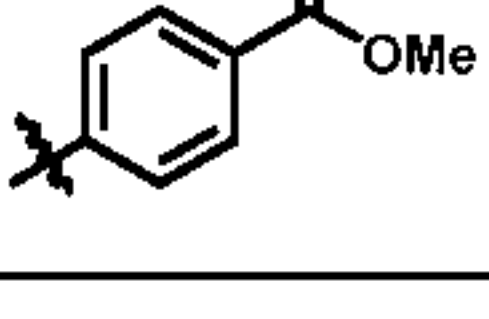
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and

(B) Compounds according to Formula (XI), wherein A, B, and R⁷ are delineated for each compounds in Table 4:

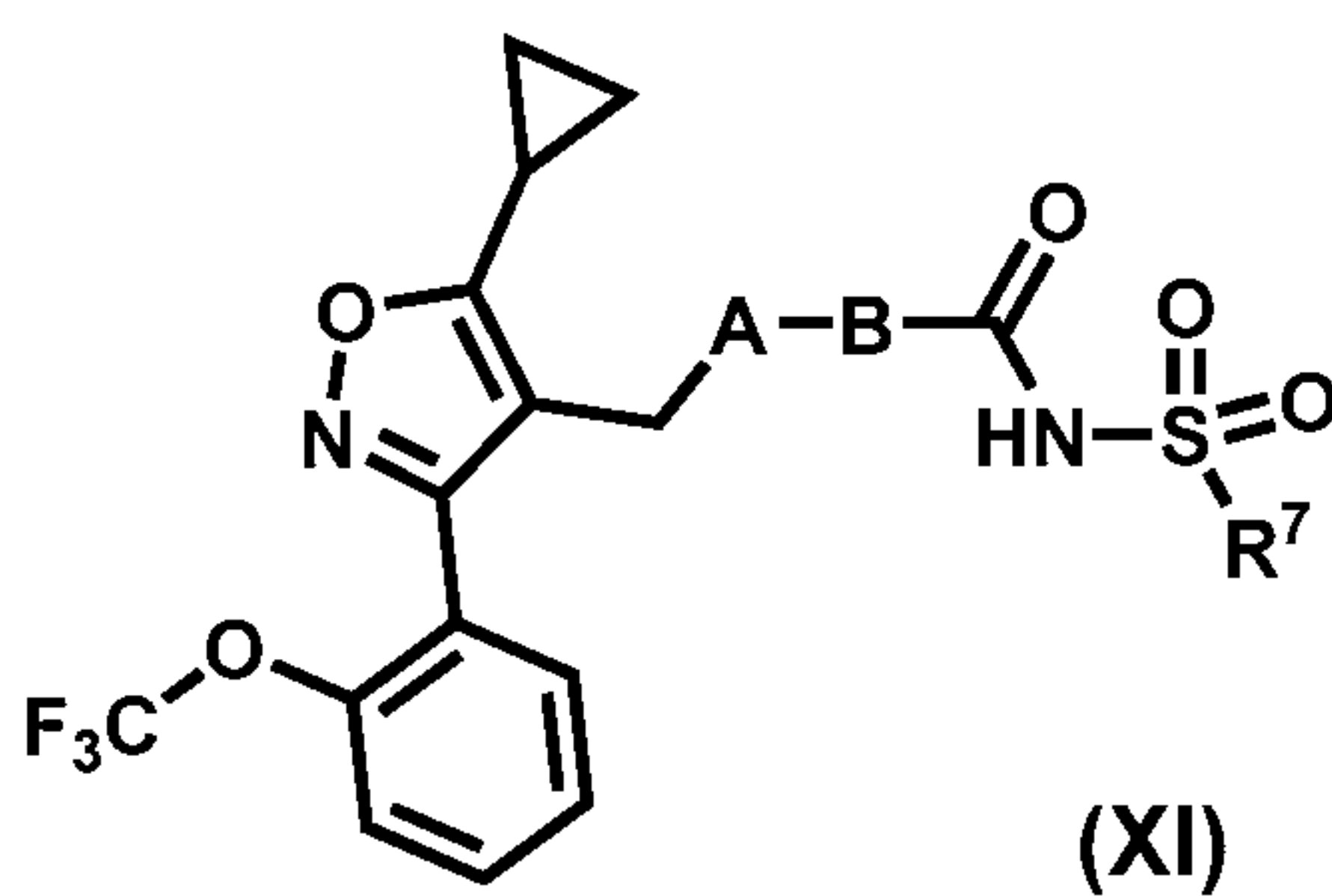


Table 4

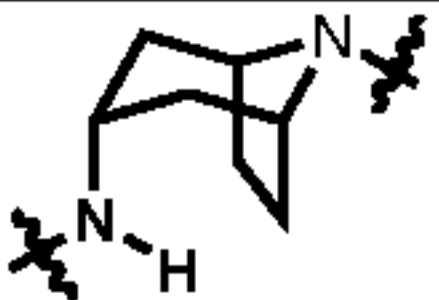
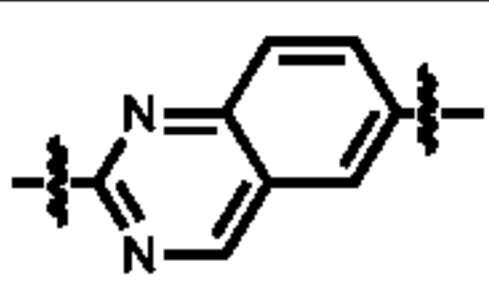
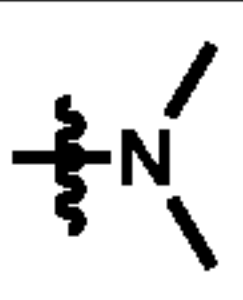
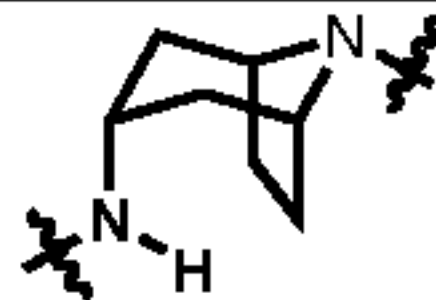
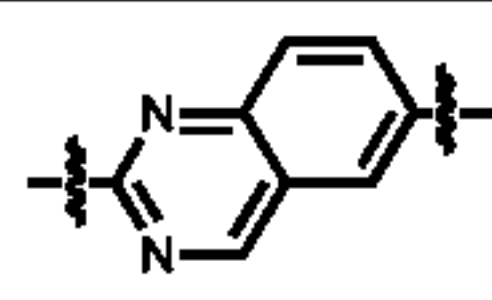
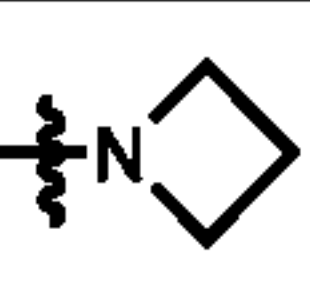
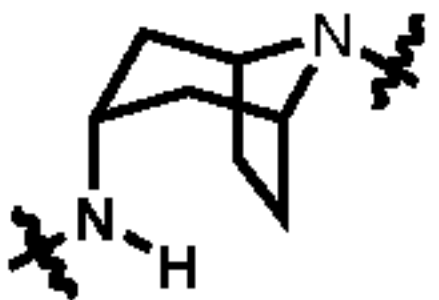
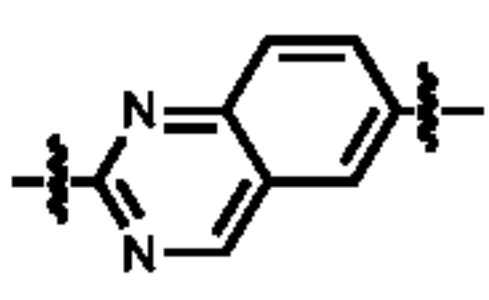
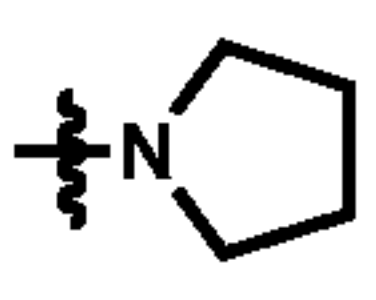
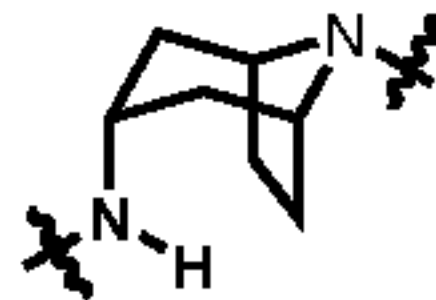
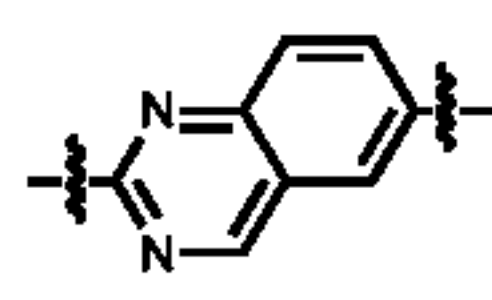
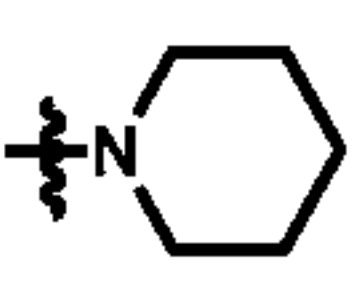
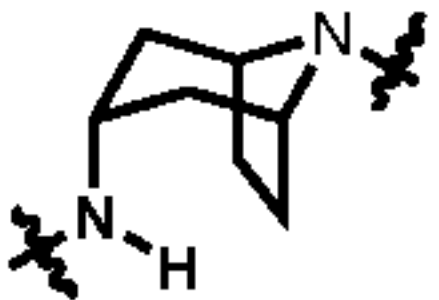
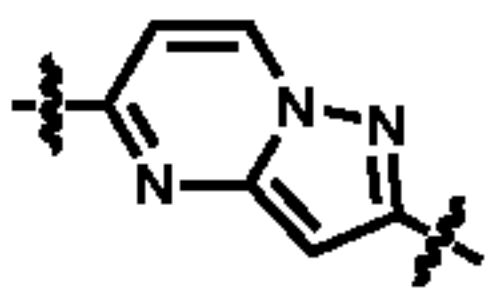
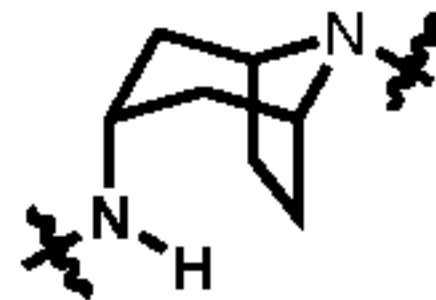
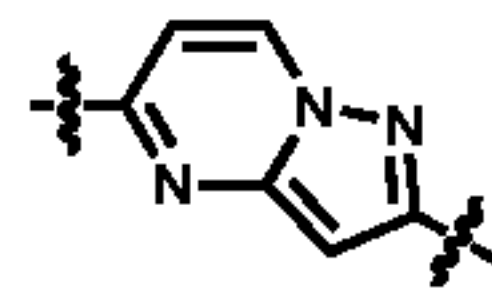
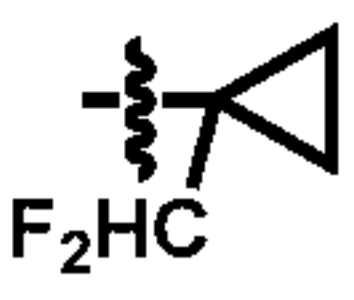
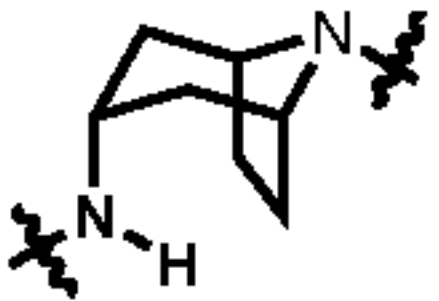
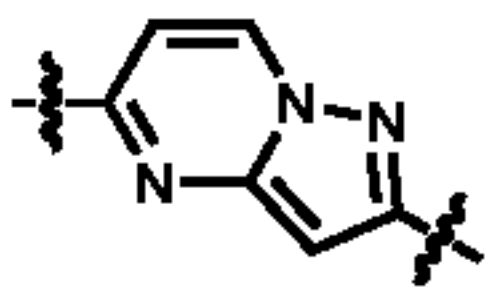
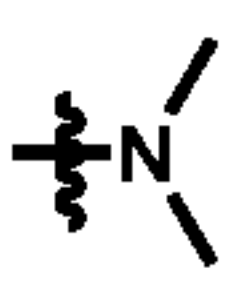
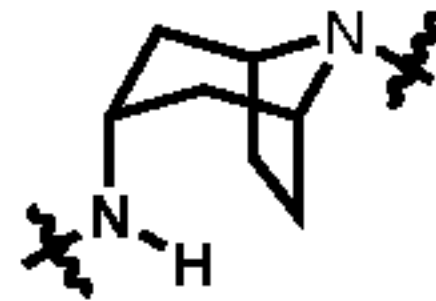
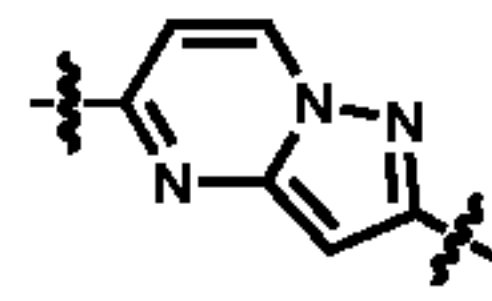
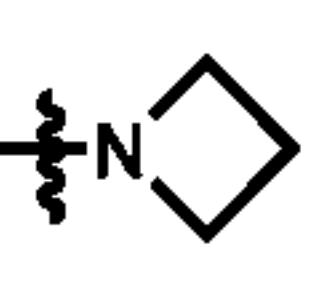
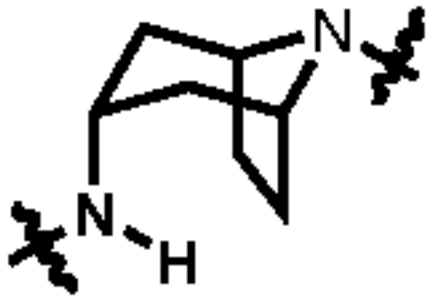
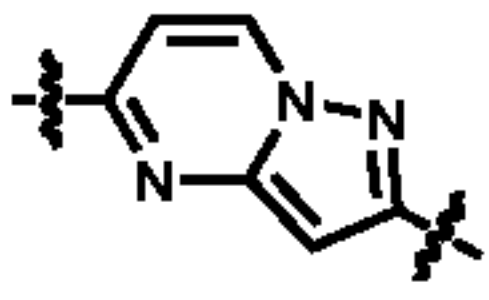
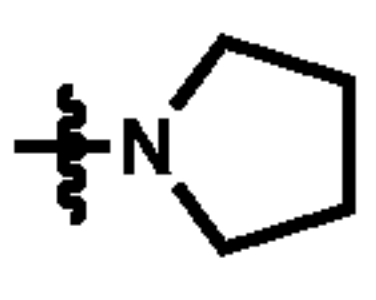
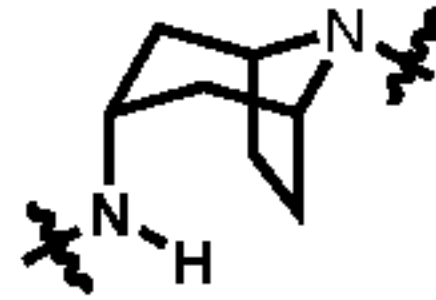
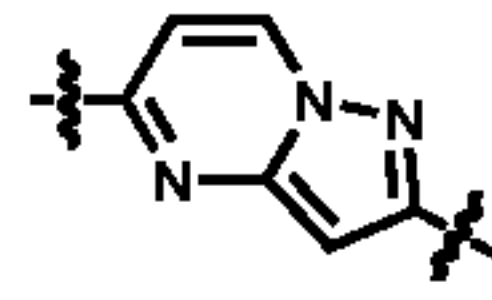
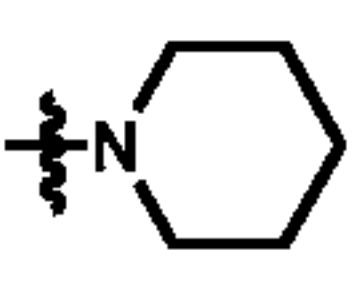
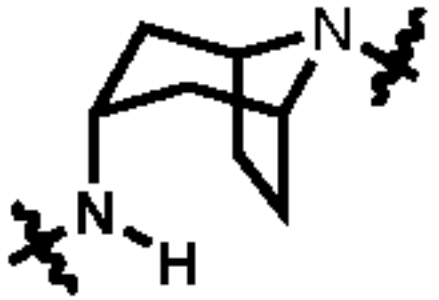
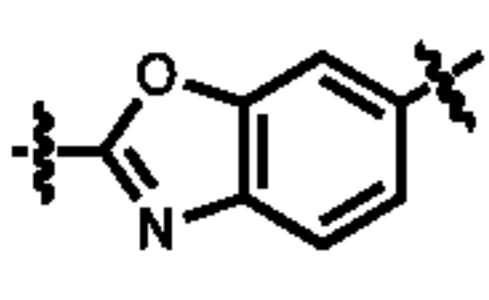
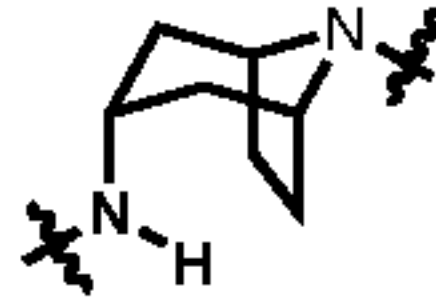
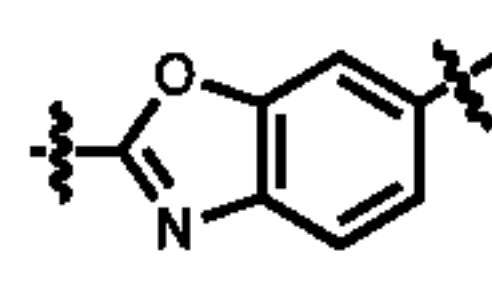
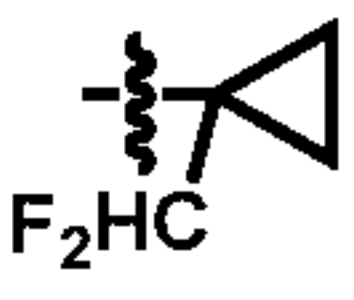
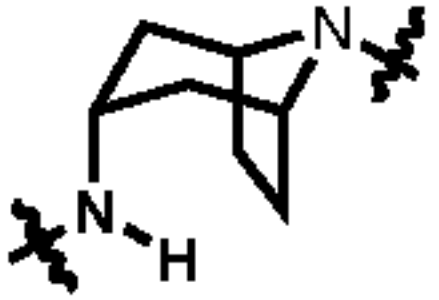
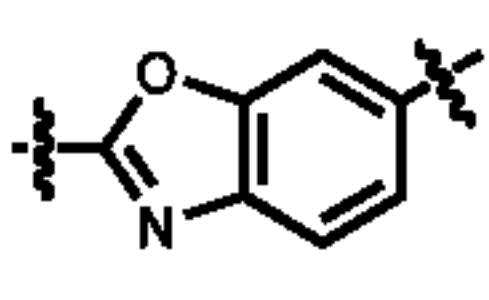
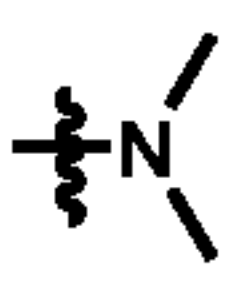
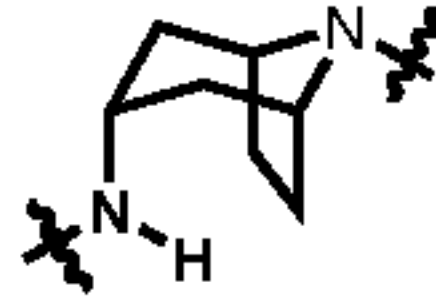
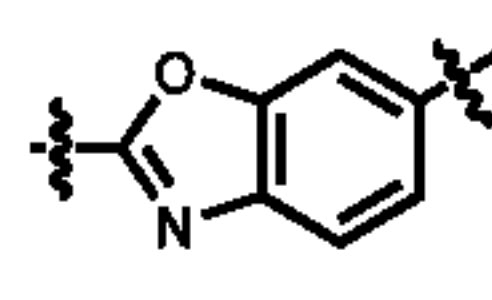
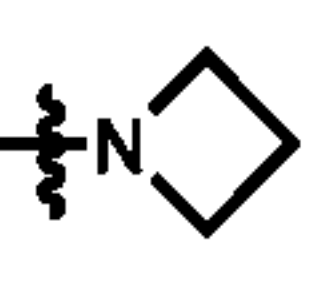
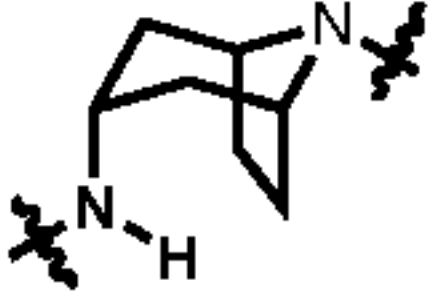
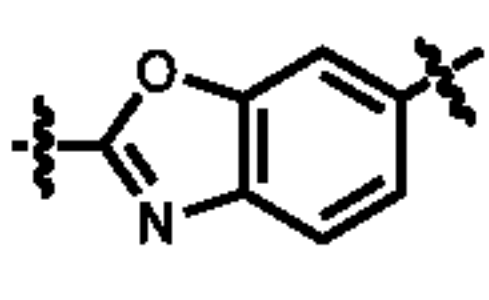
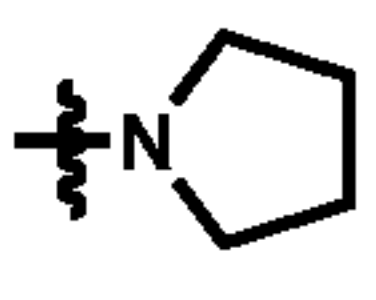
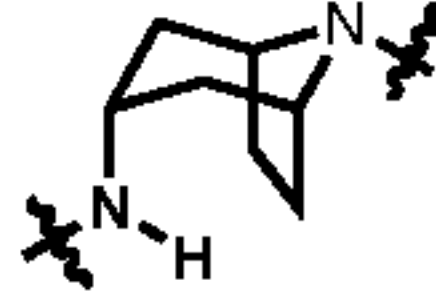
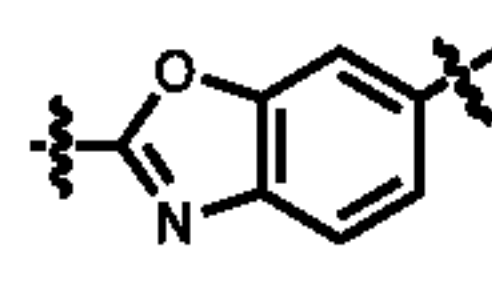
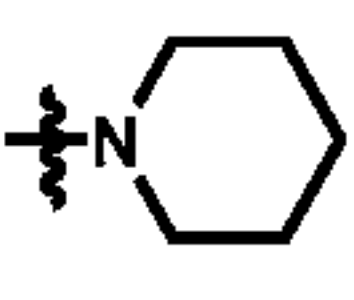
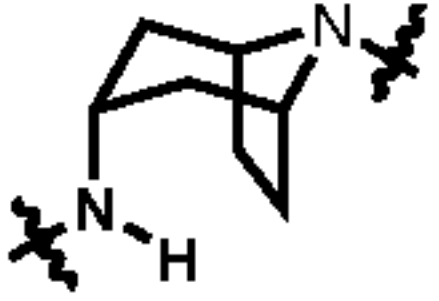
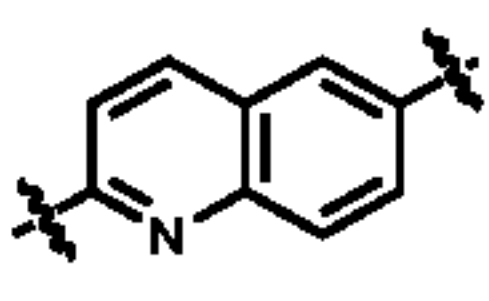
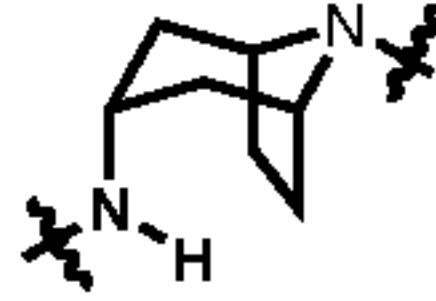
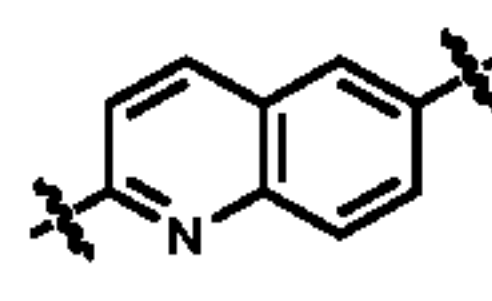
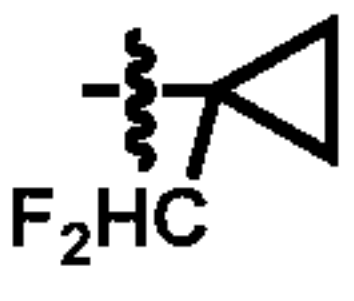
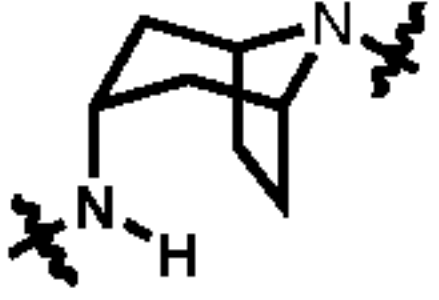
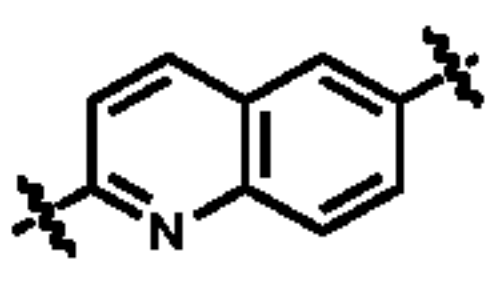
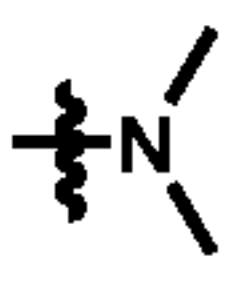
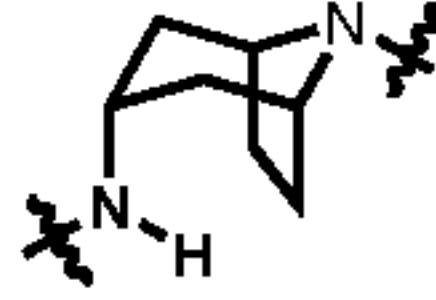
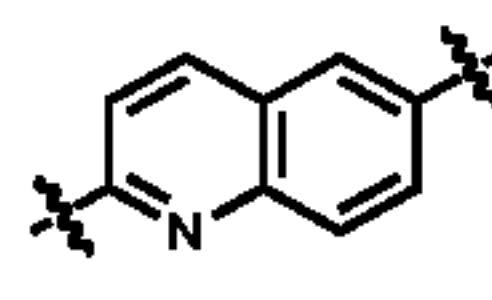
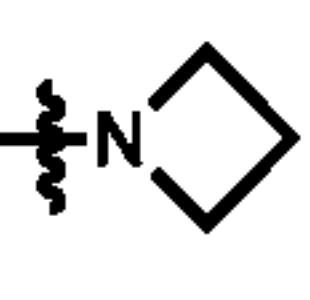
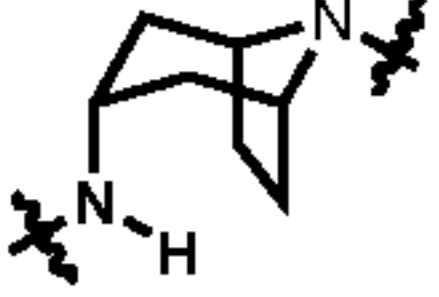
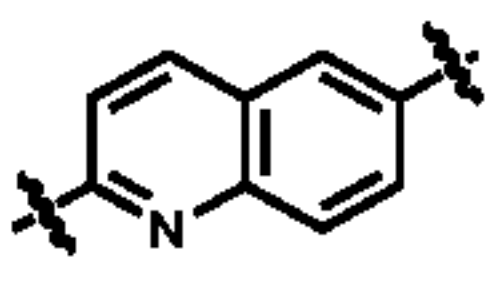
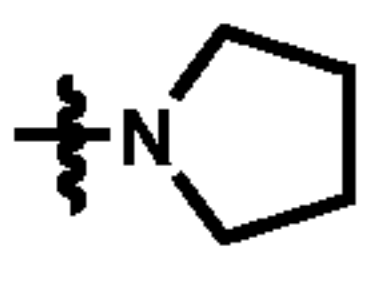
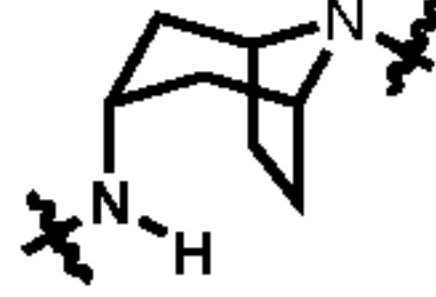
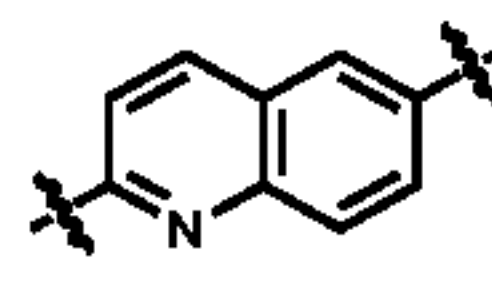
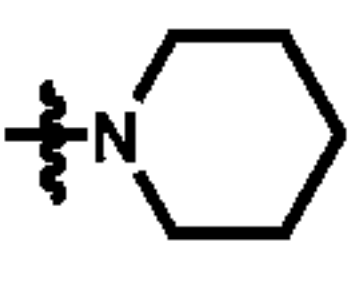
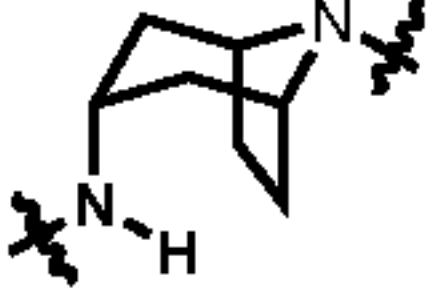
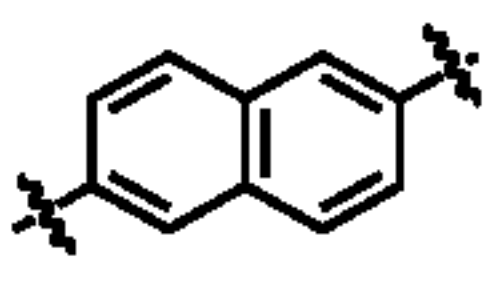
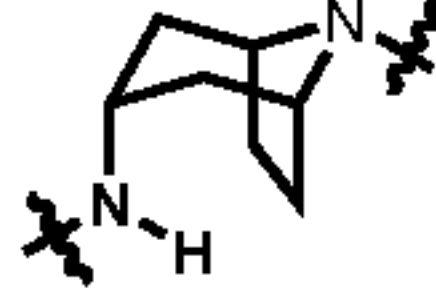
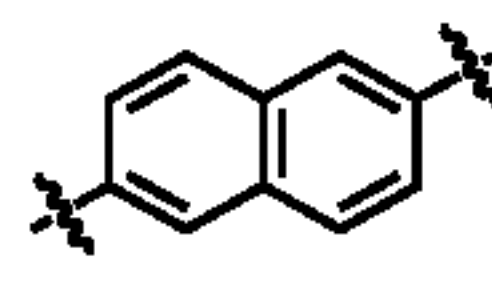
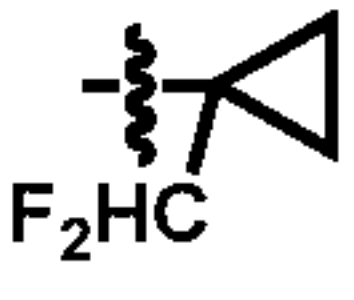
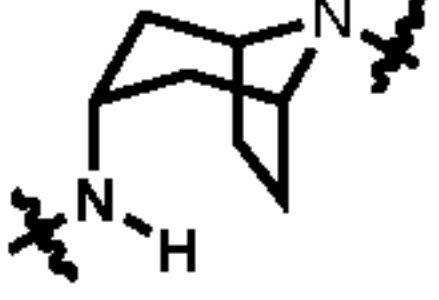
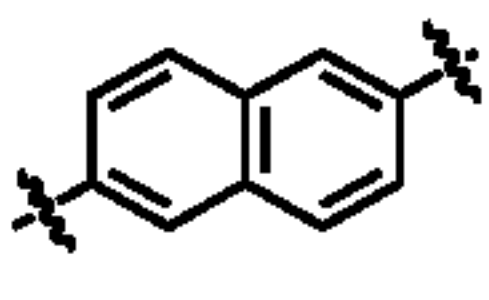
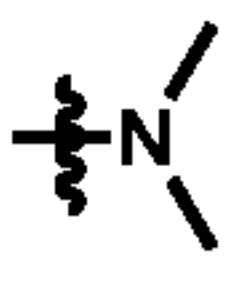
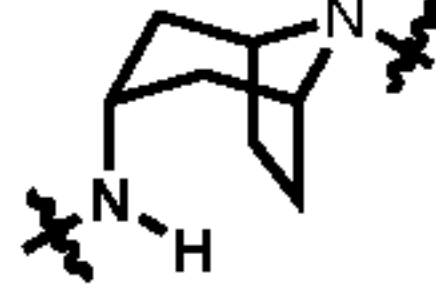
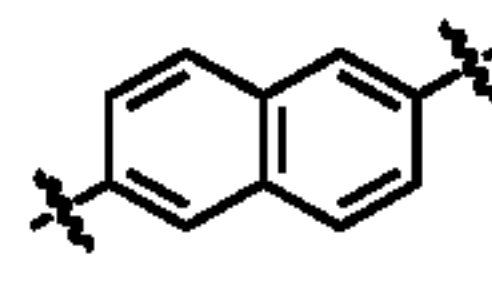
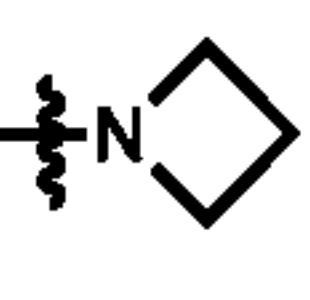
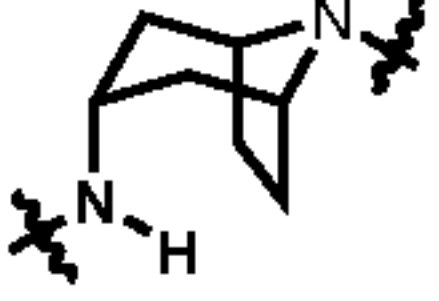
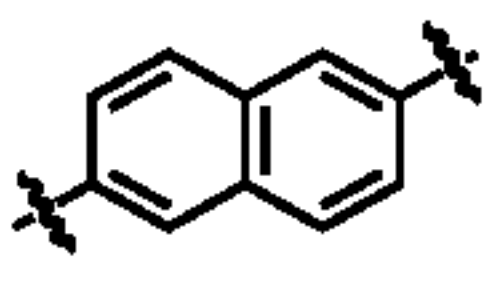
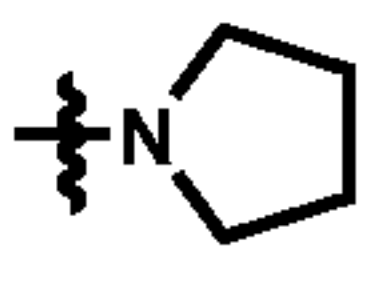
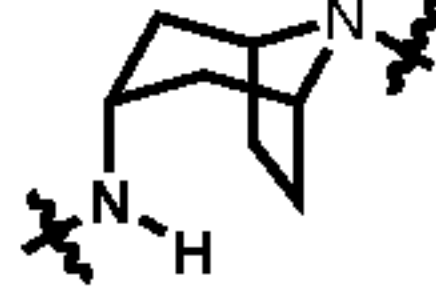
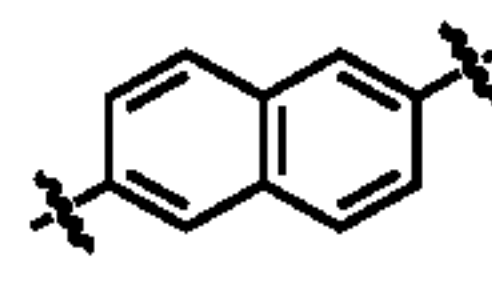
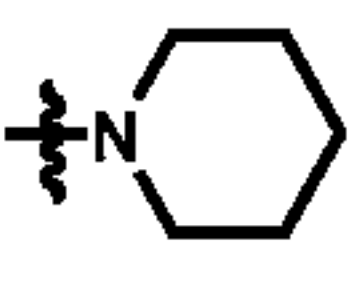
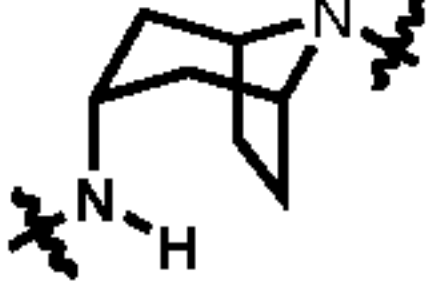
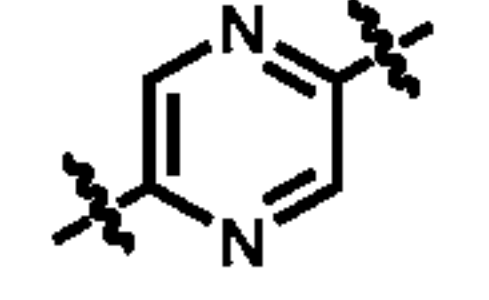
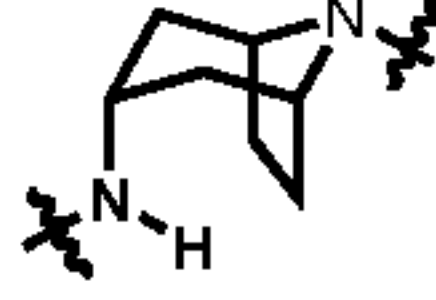
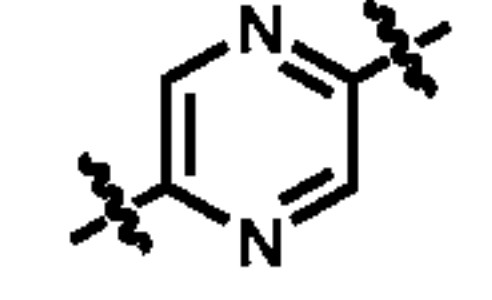
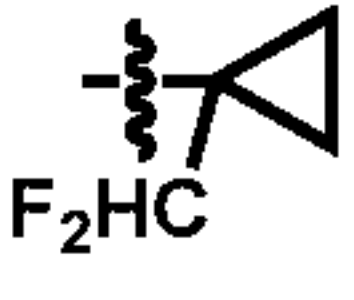
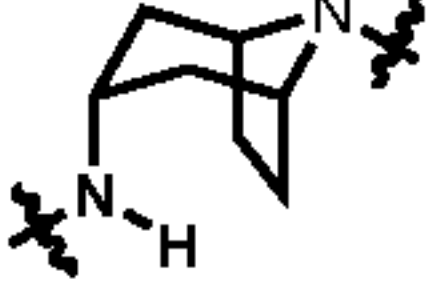
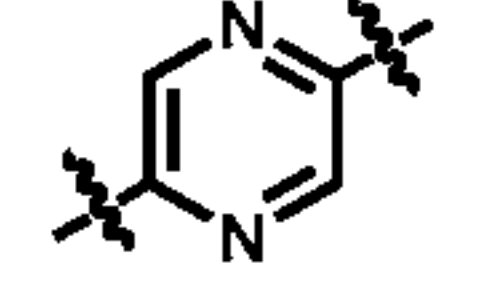
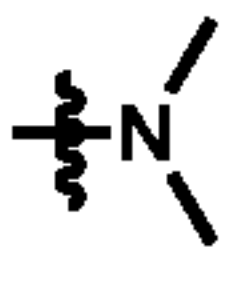
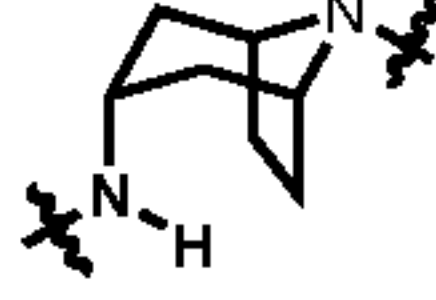
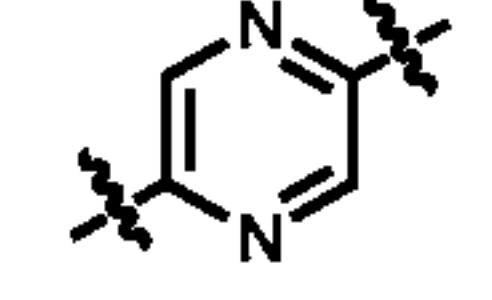
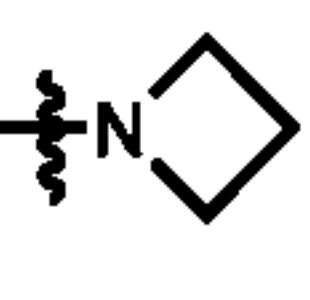
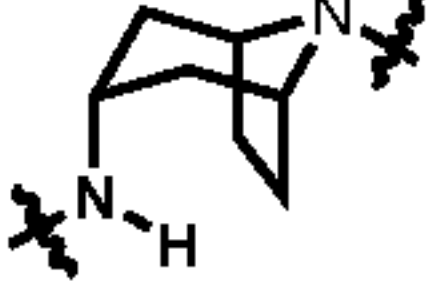
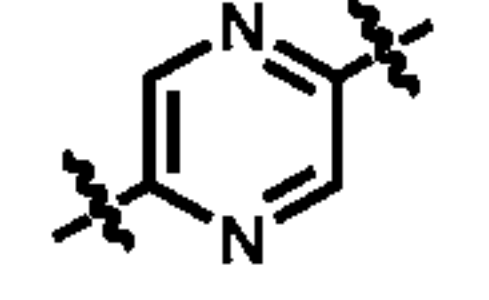
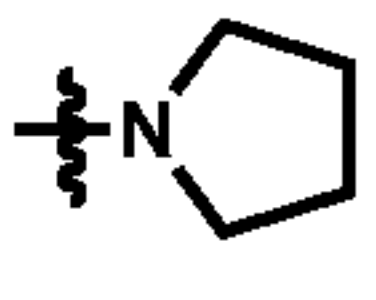
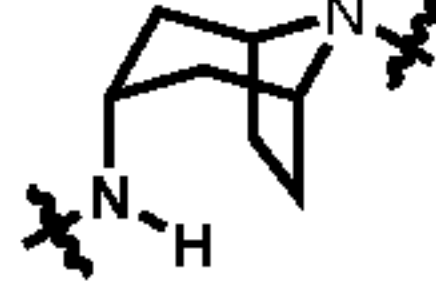
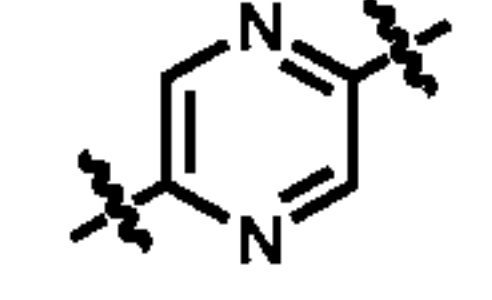
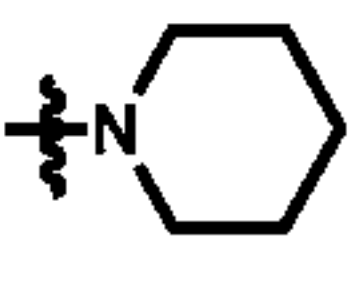
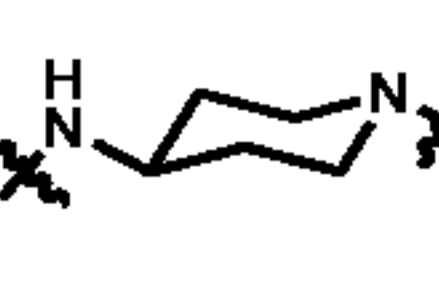
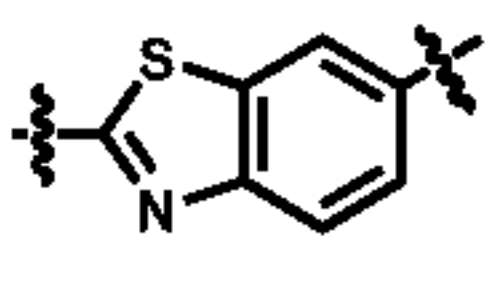
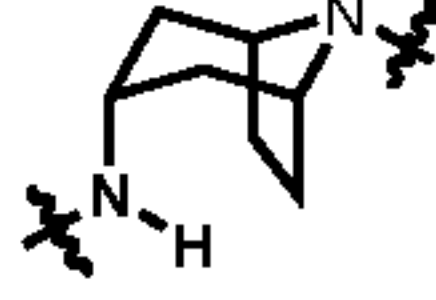
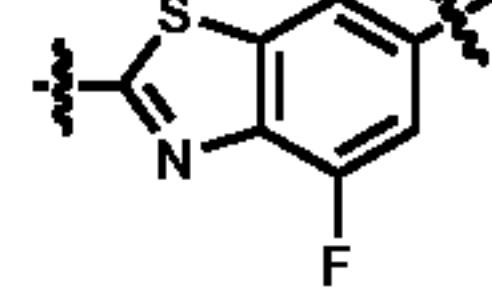
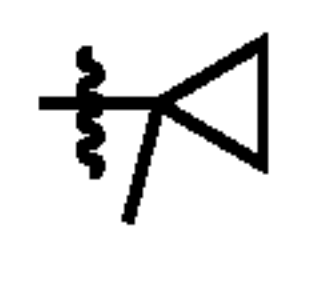
Compound	A	B	R ⁷	Compound	A	B	R ⁷
701				702			
703				704			
705				706			
707				708			
709				710			
711				712			
713				714			
715				216			
717				718			
719				720			
721				722			
723				724			
725				726			
727				728			

729				730			
731				732			
733				734			
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737				738			
739				740			
741				742			
743				744			
745				746			
747				748			
749				750			
751				752			
753				754			
755				756			
757				758			
759				760			

761				762			
763				764			
765				766			
767				768			
769				770			
771				772			
773				774			
775				776			
777				778			
779				780			
781				782			
783				784			
785				786			
787				788			
789				790			
791				792			
793				794			
795				796			

797				798			
799				800			
801				802			
803				804			
805				806			
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809				810			
811				812			
813				814			
815				816			
817				818			
819				820			
821				822			
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825				826			
827				828			
829				830			

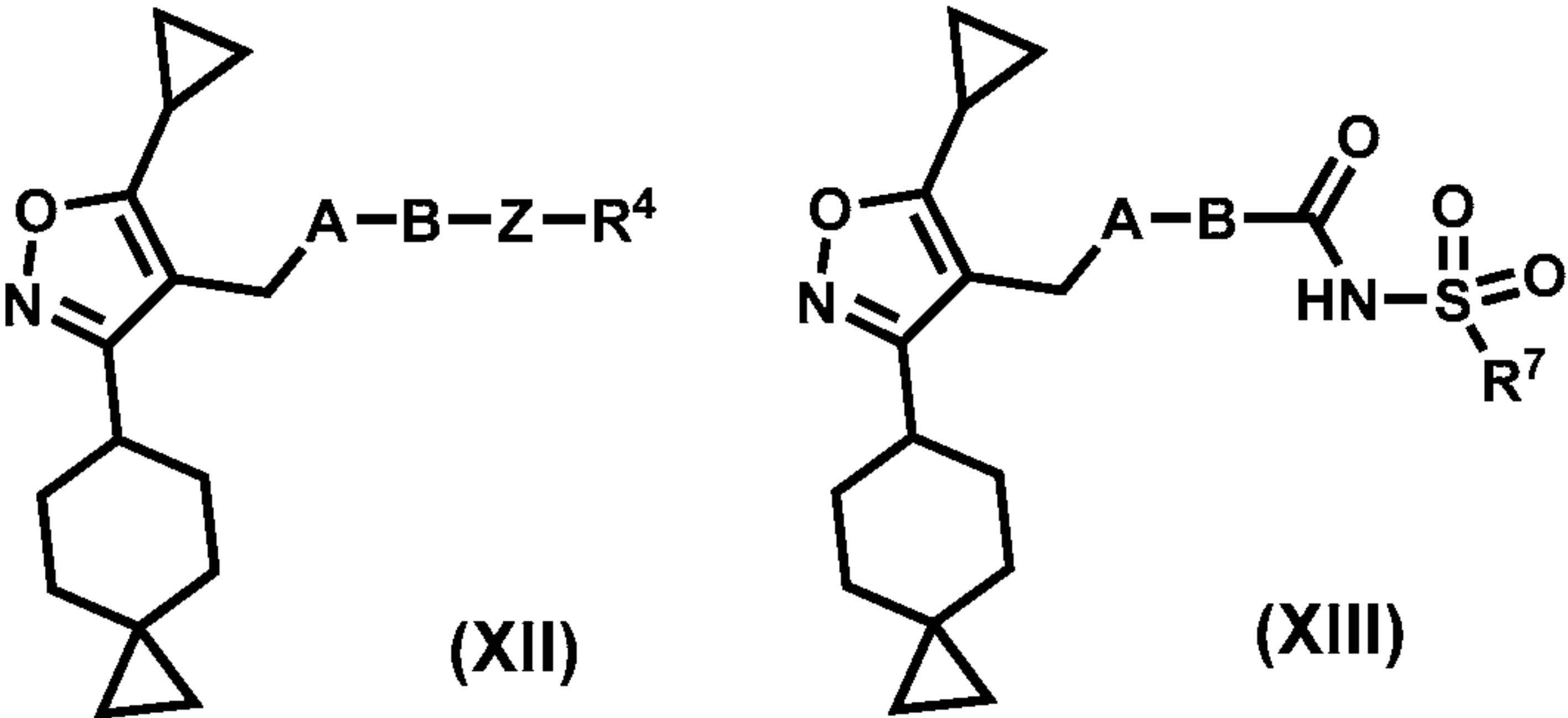
831				832			
833				834			
835				836			
837				838			
839				840			
841				842			
843				844			
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847				848			
849				850			
851				852			
853				854			
855				856			
857				858			
859				860			
861				862			
863				864			
865				866			

867				868			
869				870			
871				872			
873				874			
875				876			
877				878			
879				880			
881				882			
883				884			
885				886			
887				888			
889				890			
891				892			
893				894			
895				896			
897				898			
899				900			
900-1				900-2			

900-3				900-4			
900-5				900-6			
900-7				900-8			
900-9				900-10			
900-11				900-12			
900-13				900-14			
900-15							

or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1, represented by Formula (XII), or Formula (XIII), or a pharmaceutically acceptable salt thereof:



wherein A, B, Z, R⁴ and R⁷ are as defined in claim 1.

12. The compound according to claim 1, selected from:
(A) Compounds according to Formula (XII), wherein A, B, and Z-R⁴ are delineated for each compound in Table 5:

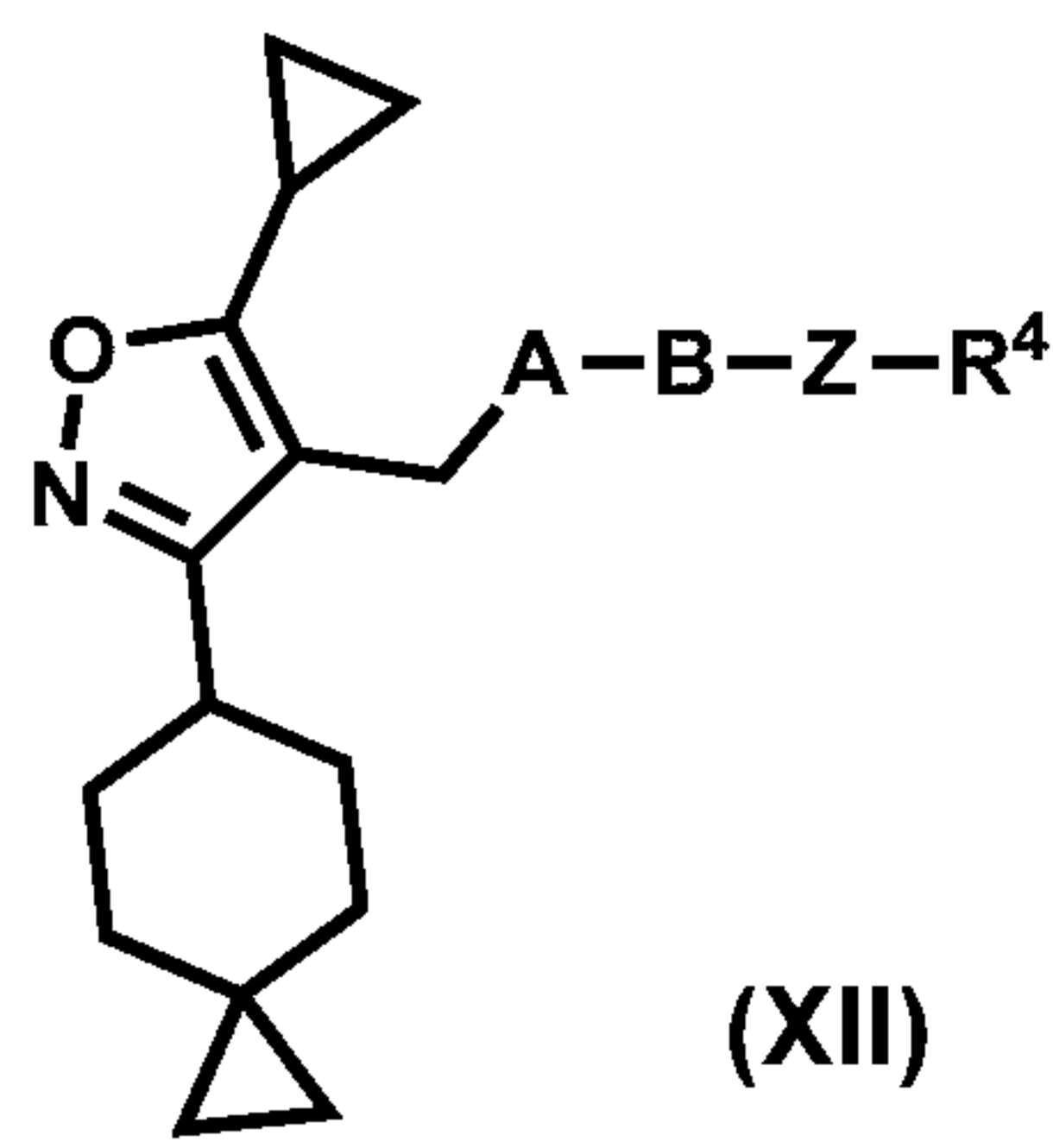
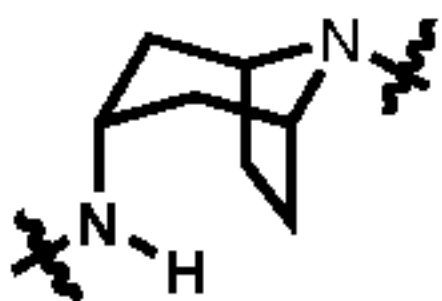
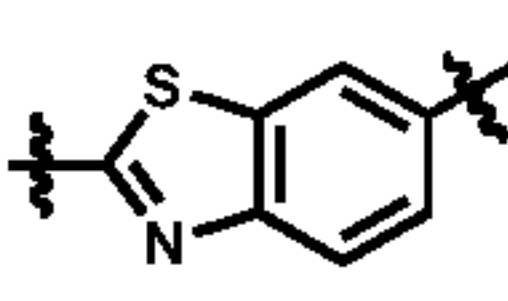
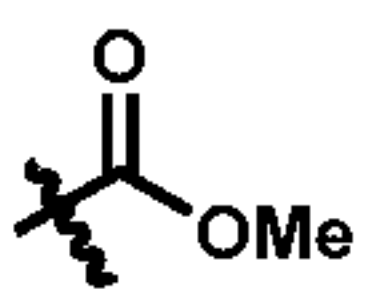
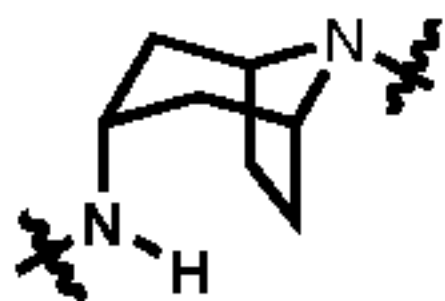
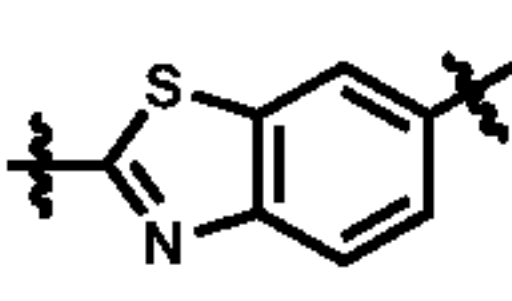
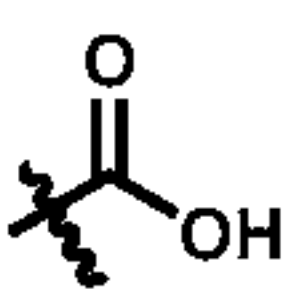
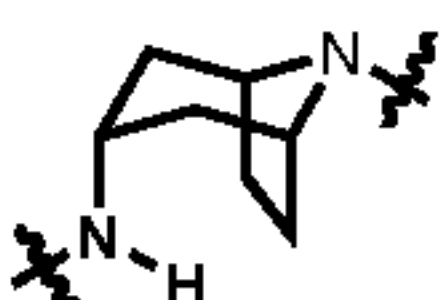
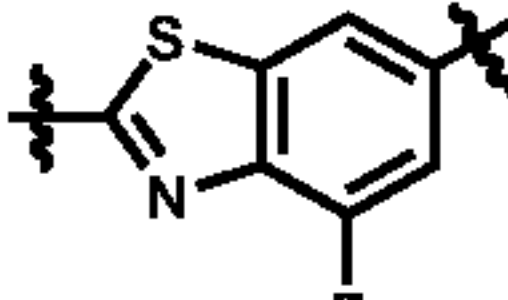
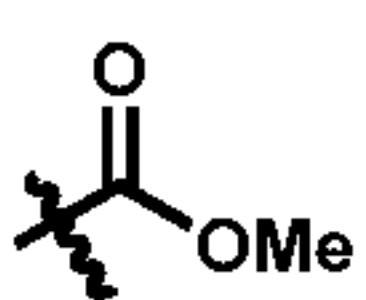
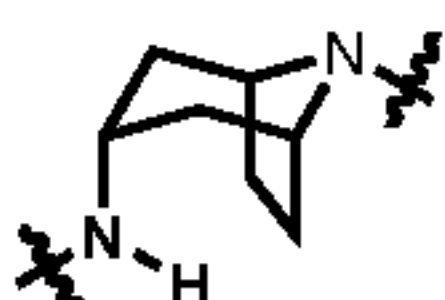
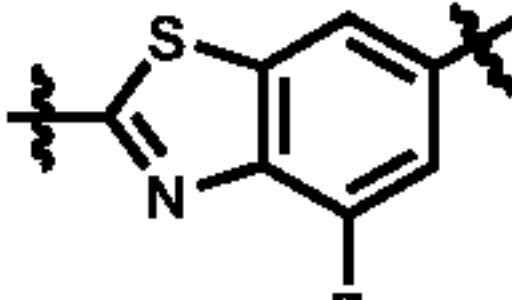
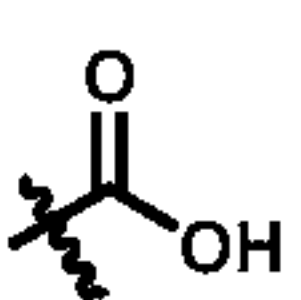
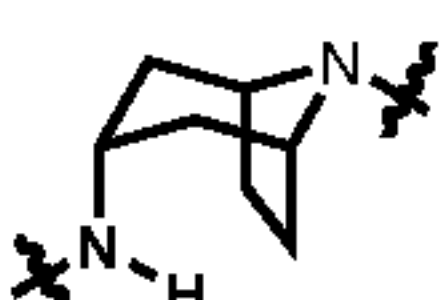
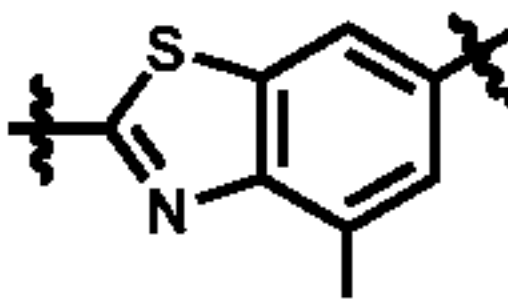
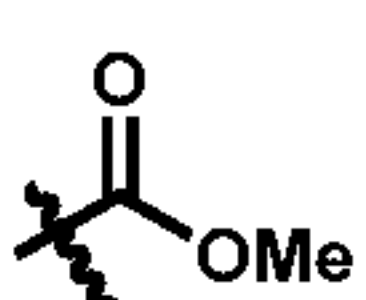
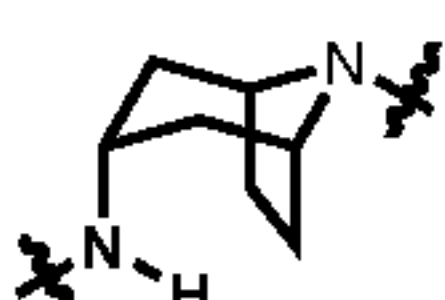
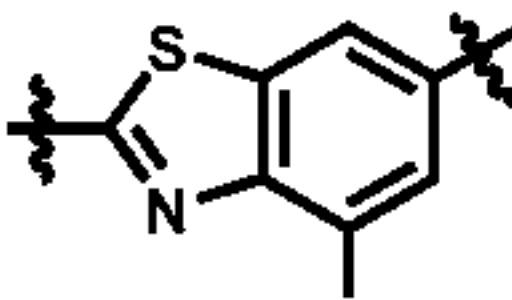
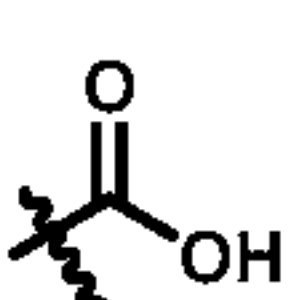
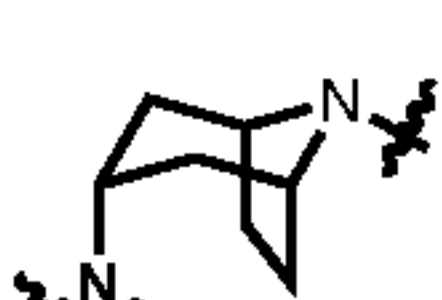
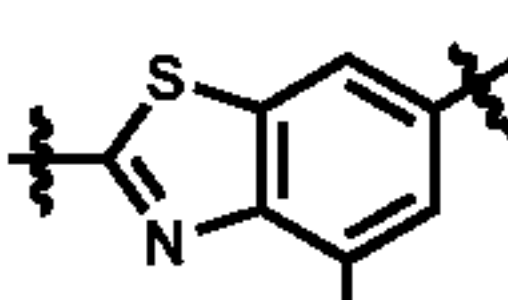
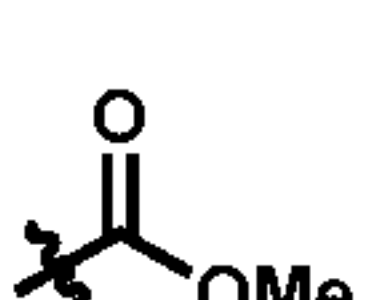
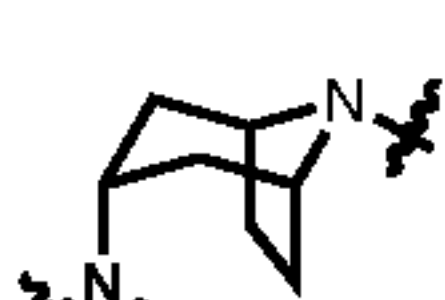
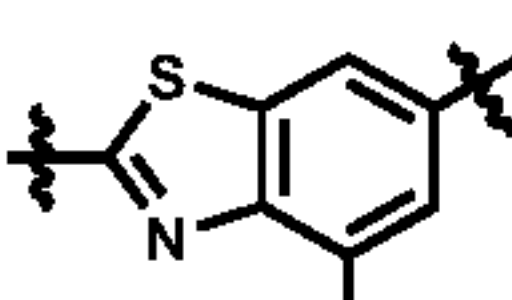
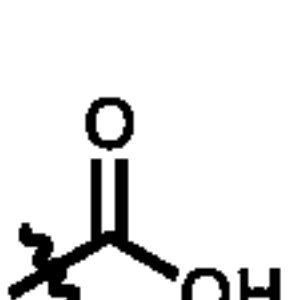
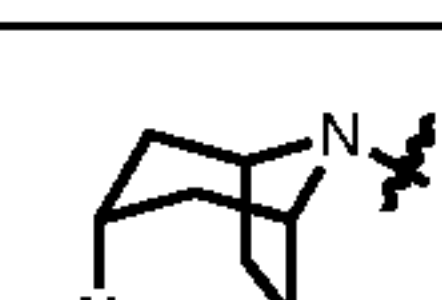
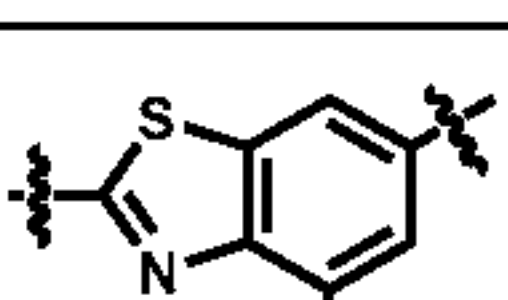
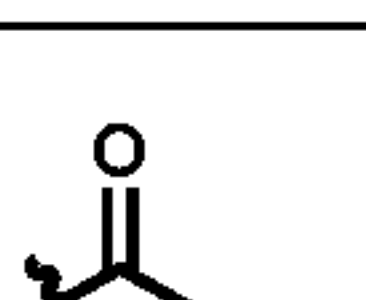
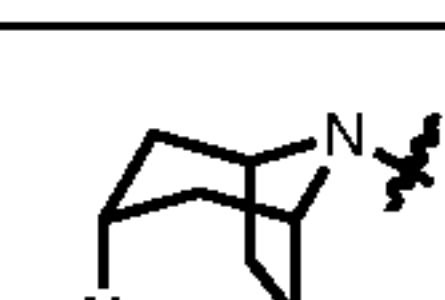
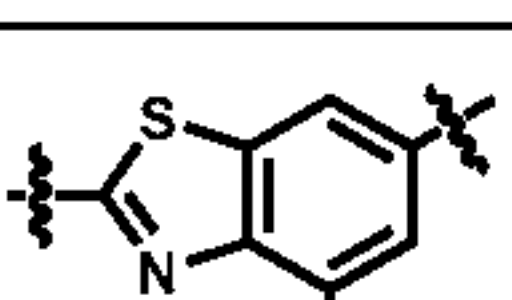
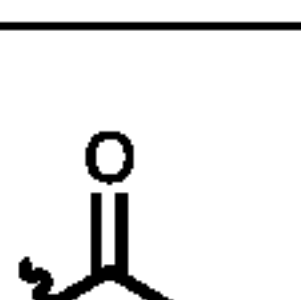
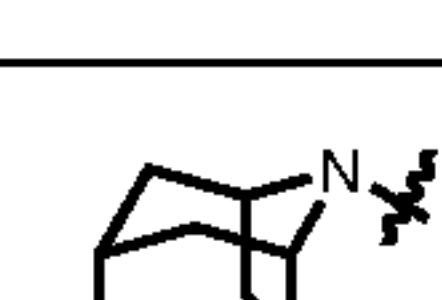
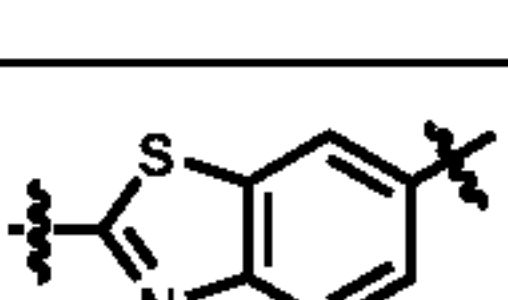
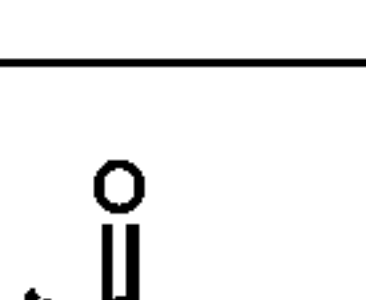
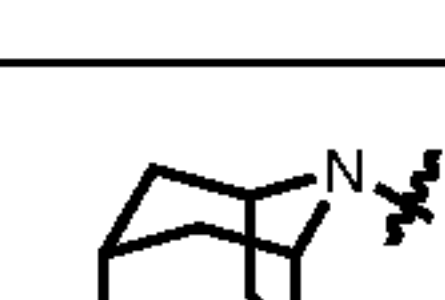
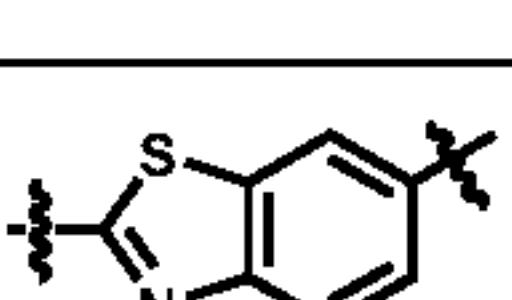
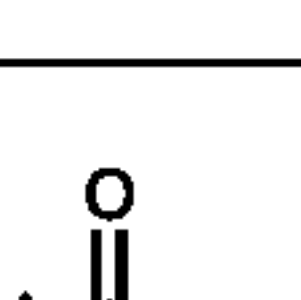
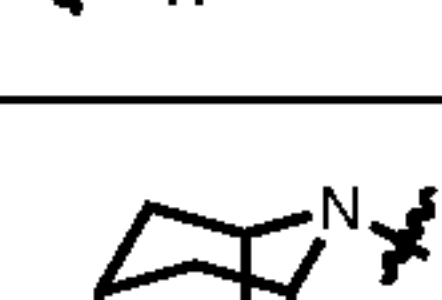
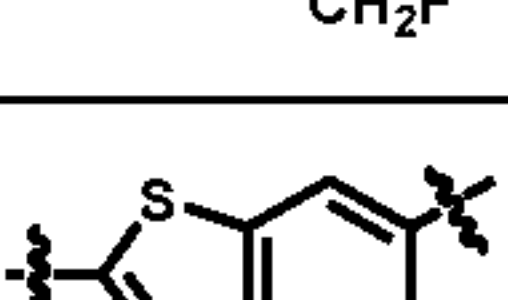
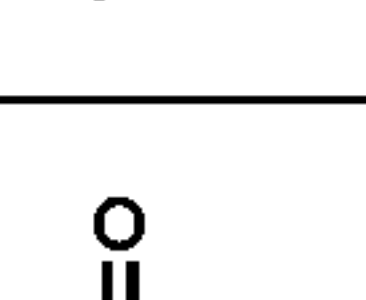
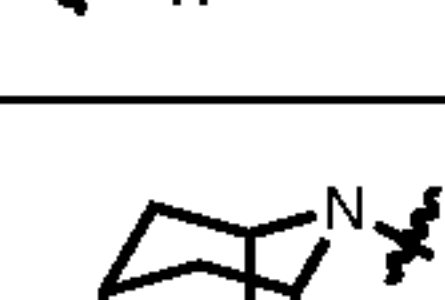
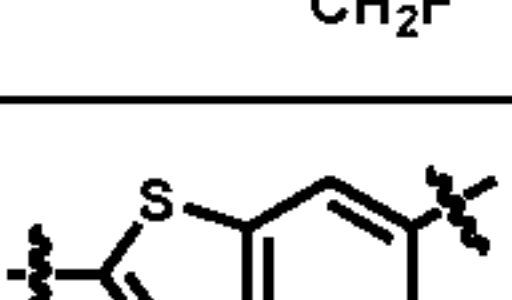
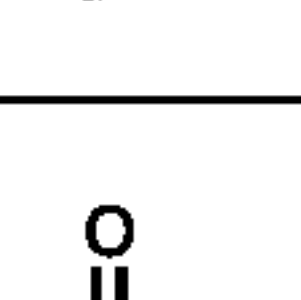
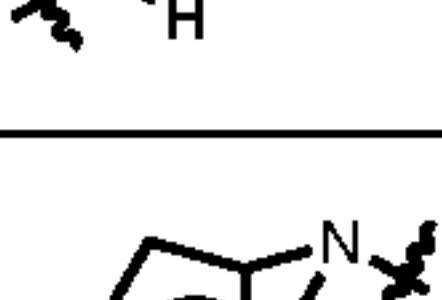
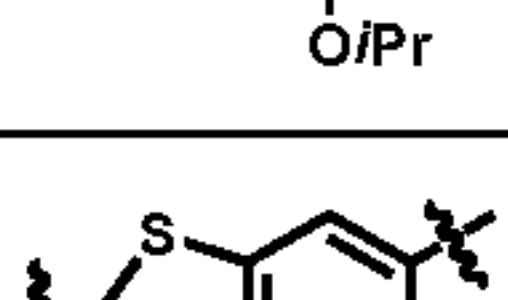
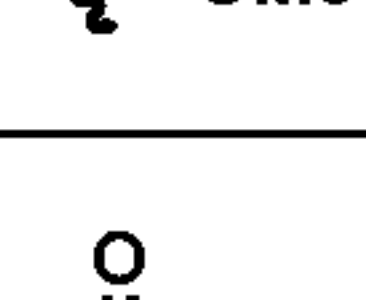
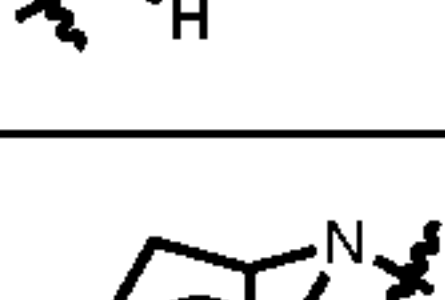
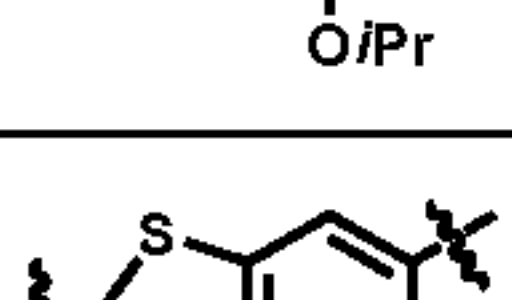
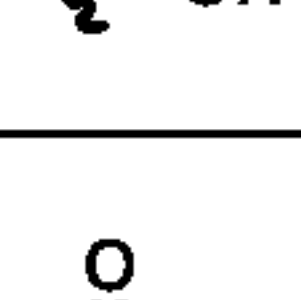
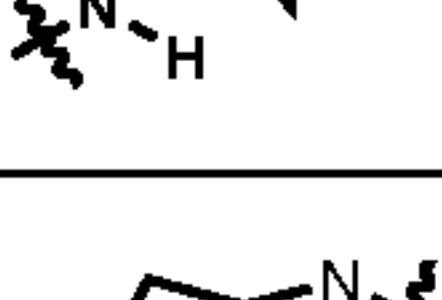
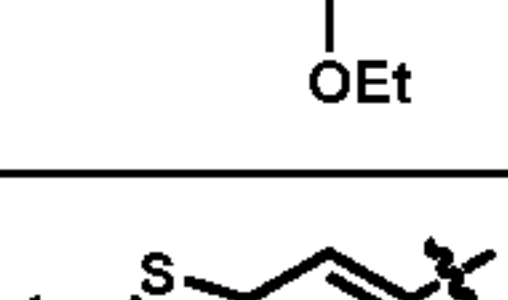
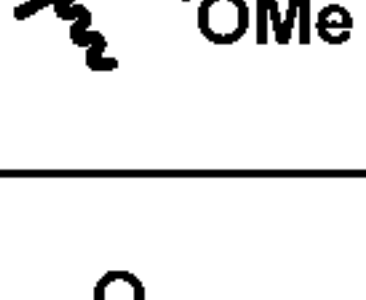
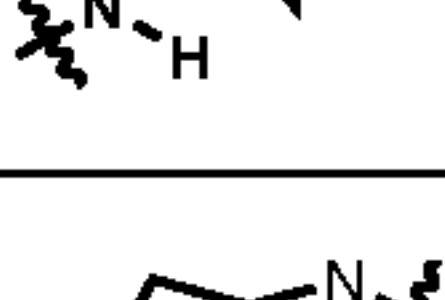
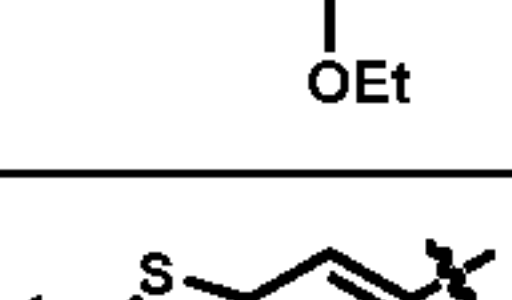
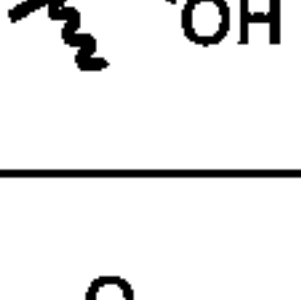
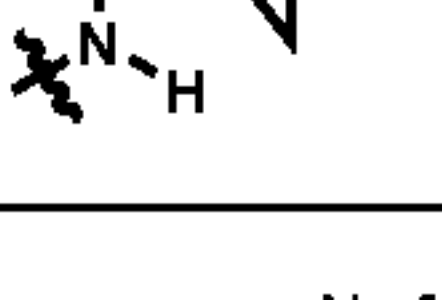
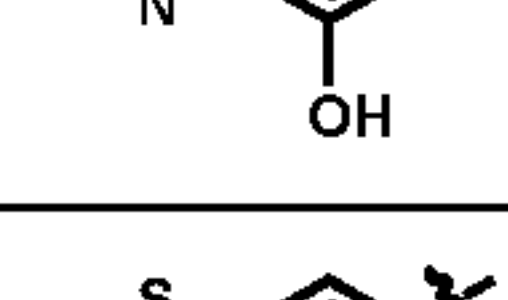
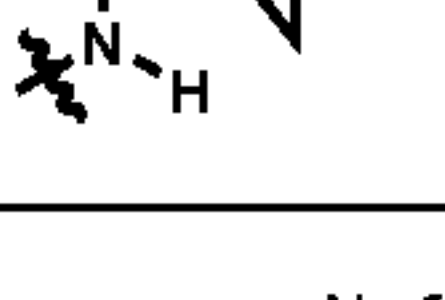
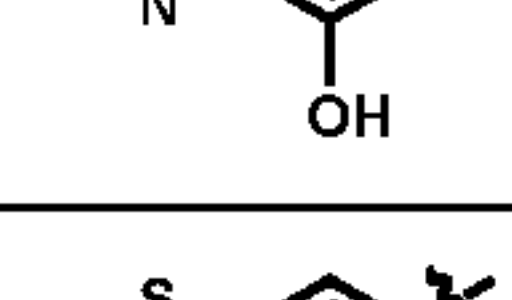
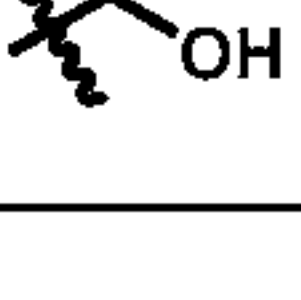
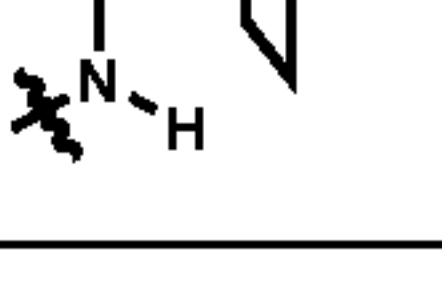
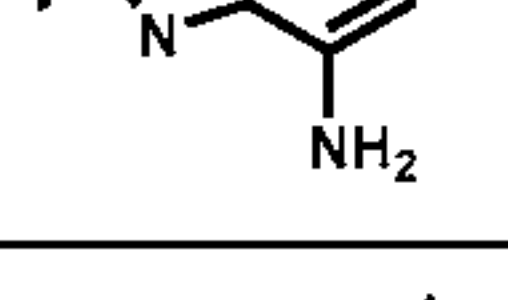
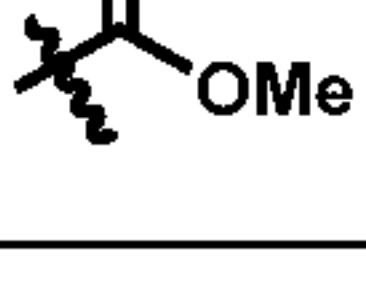
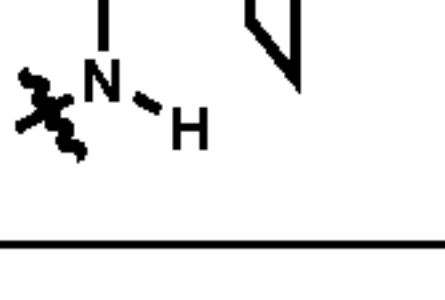
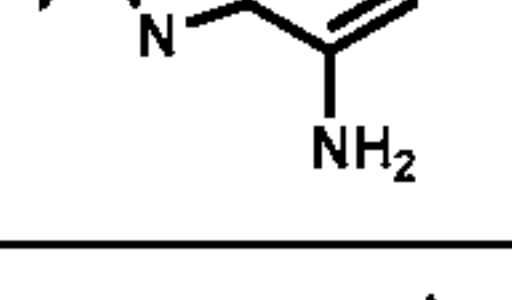
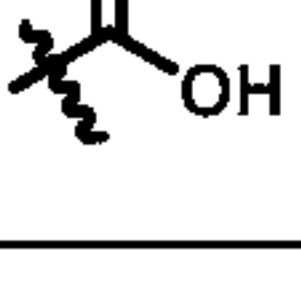
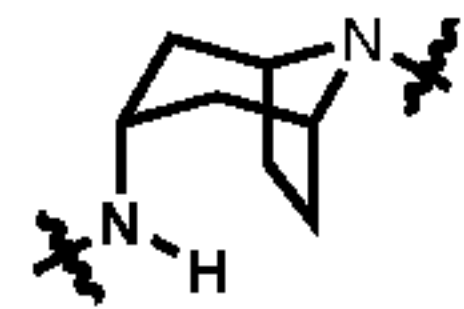
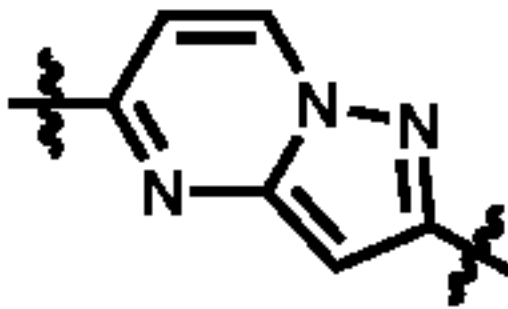
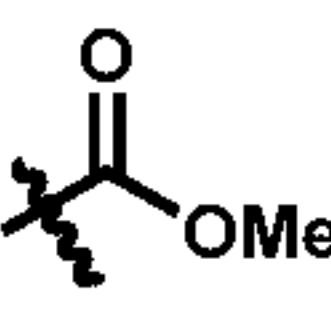
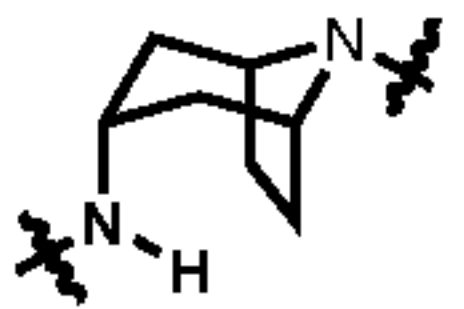
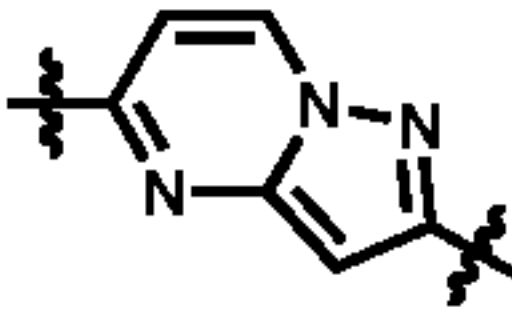
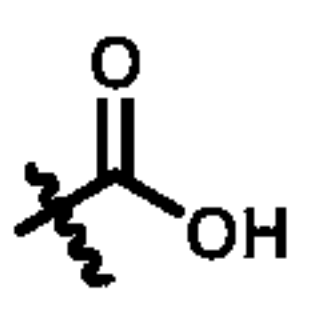
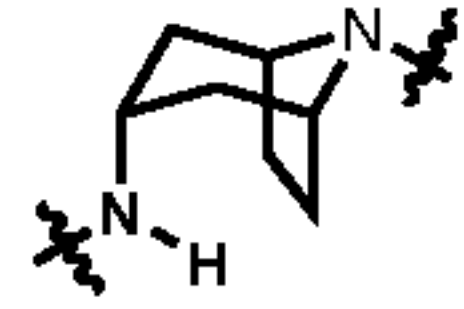
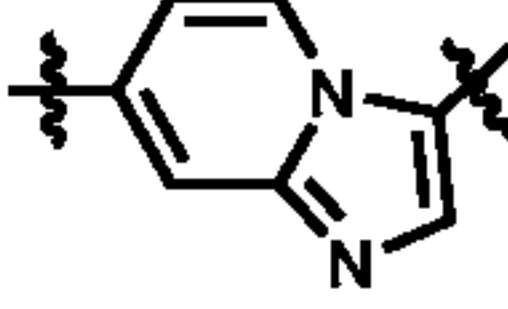
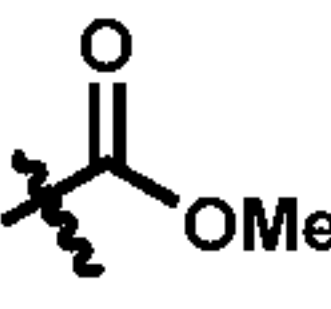
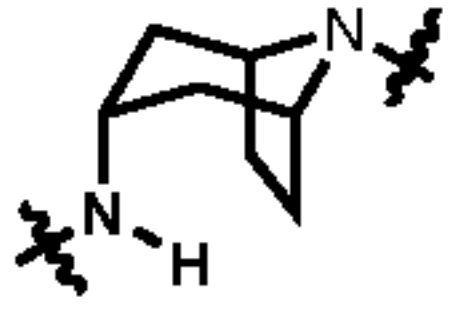
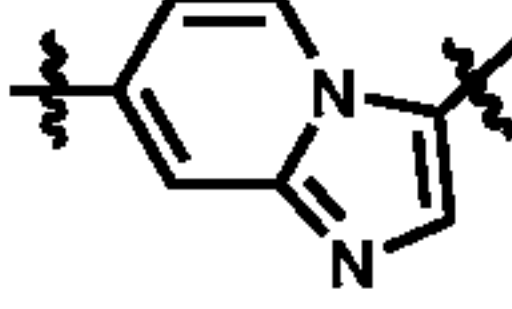
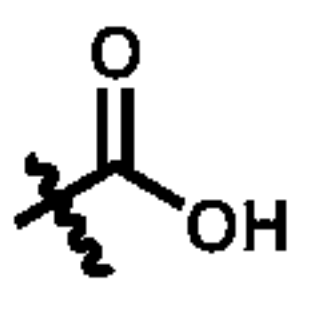
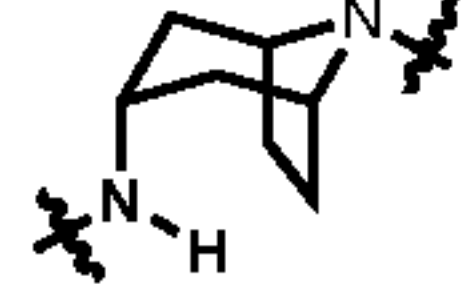
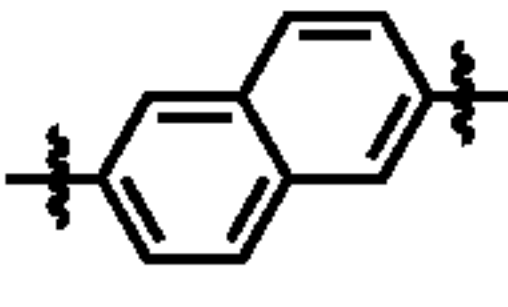
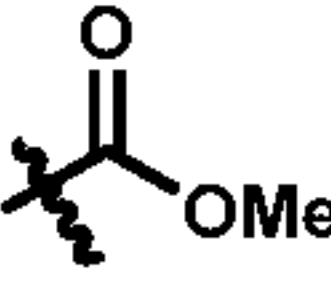
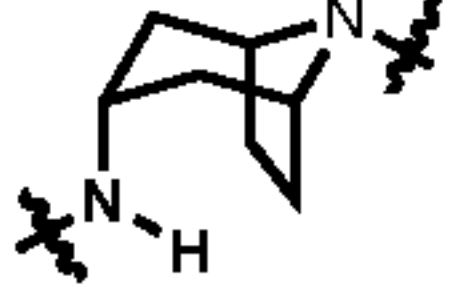
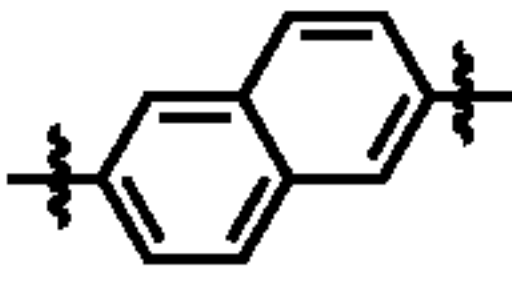
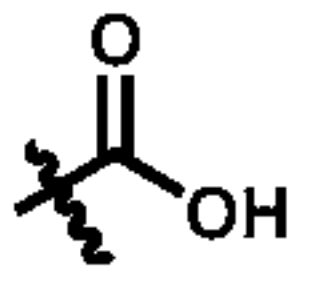
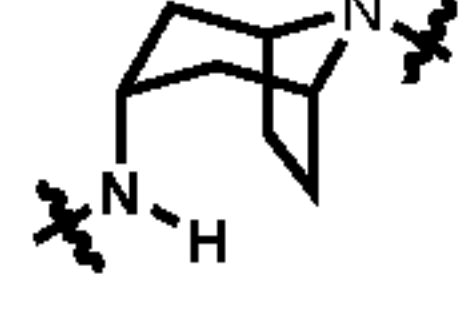
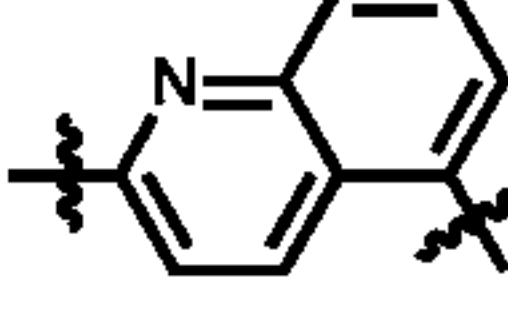
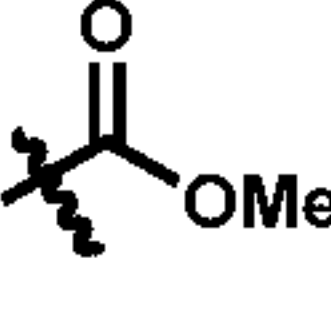
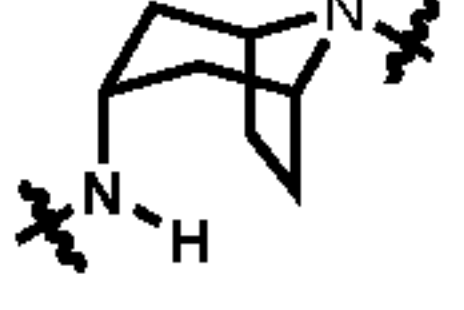
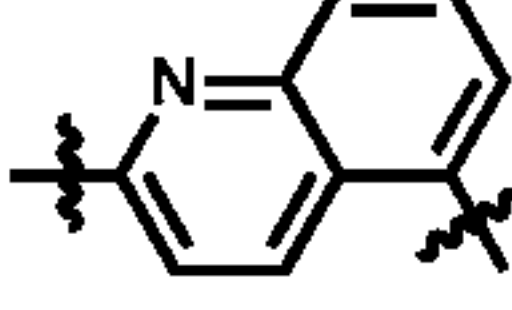
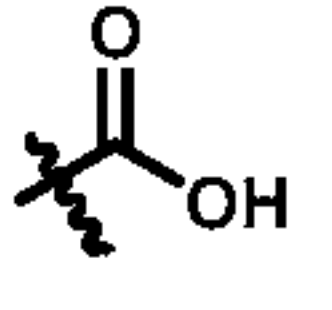
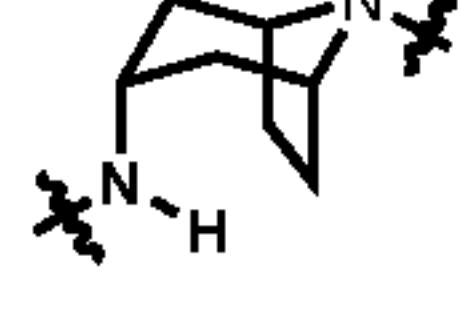
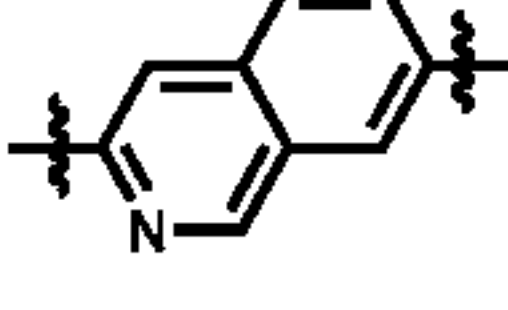
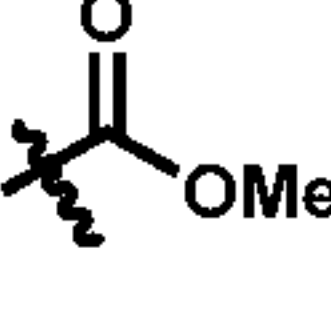
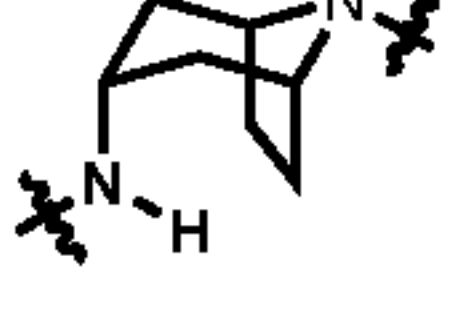
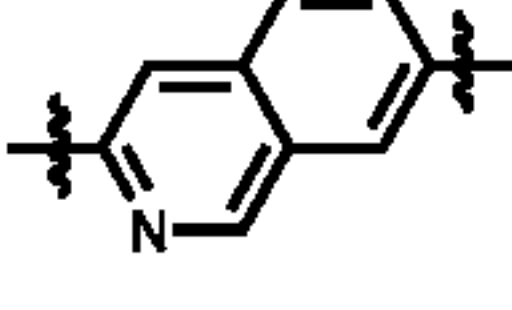
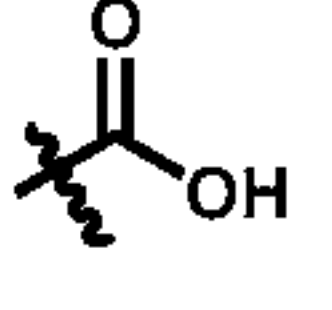
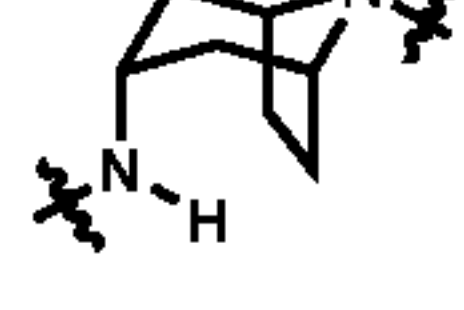
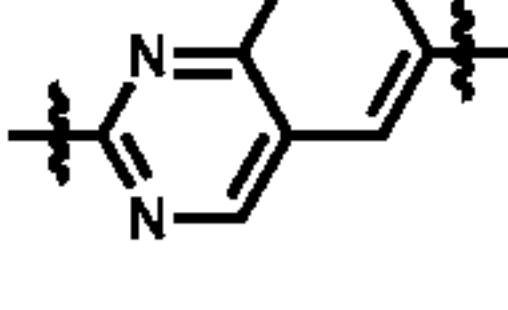
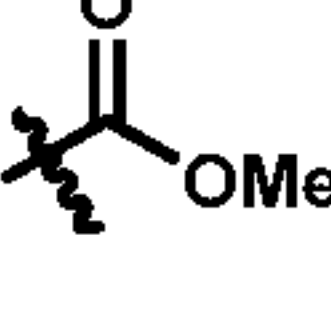
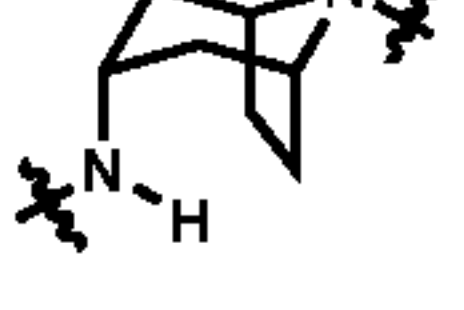
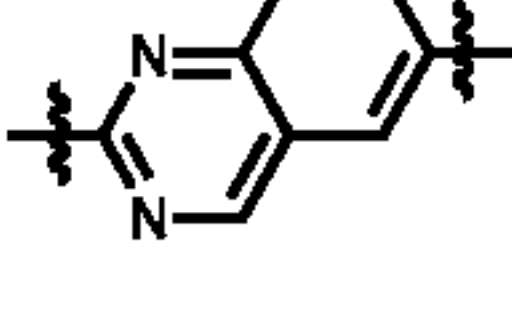
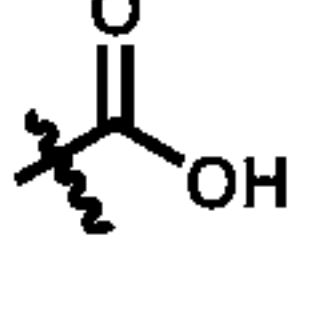
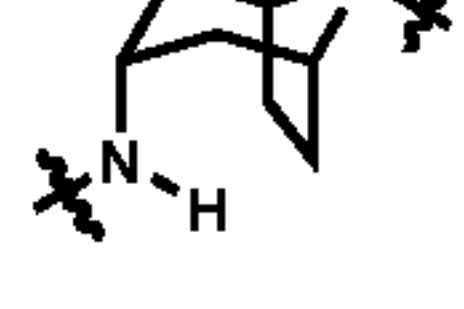
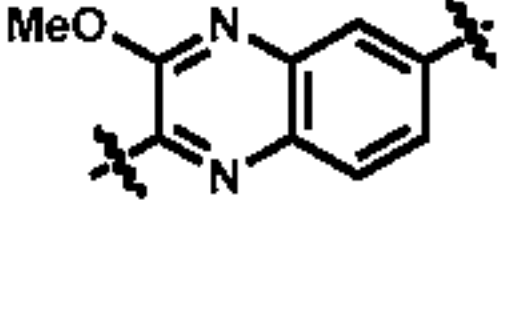
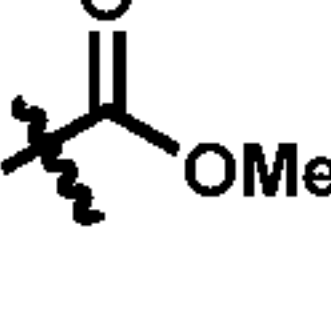
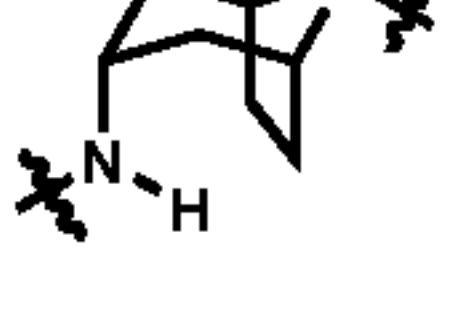
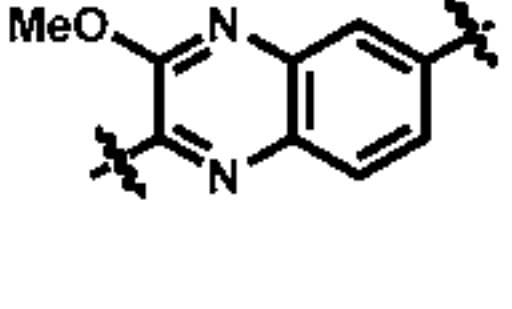
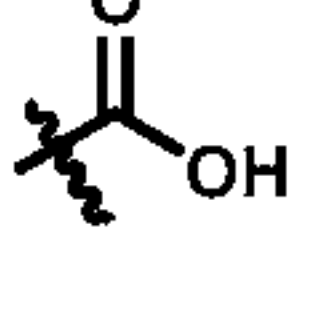
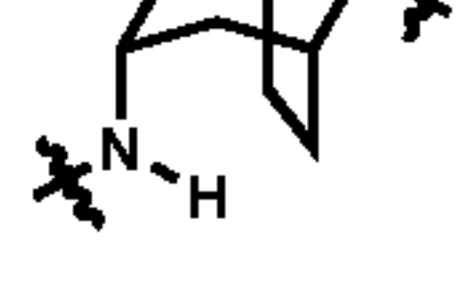
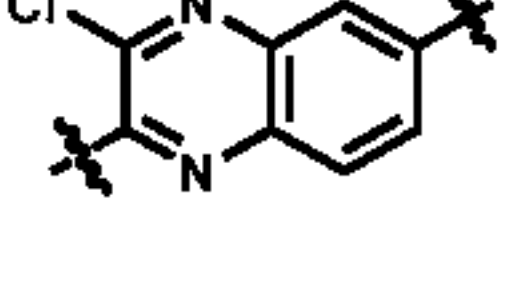
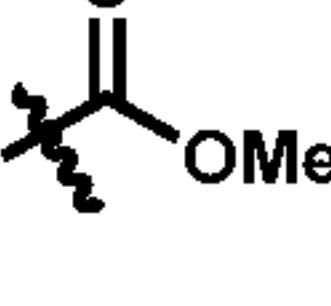
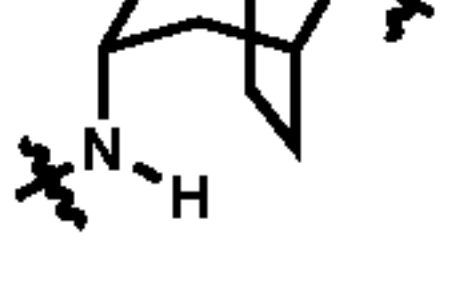
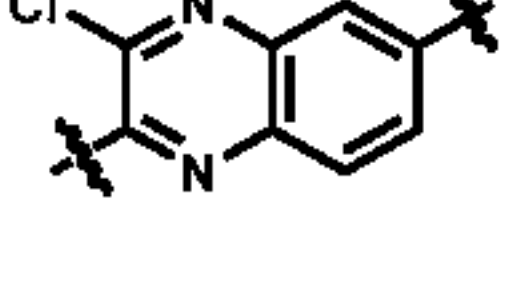
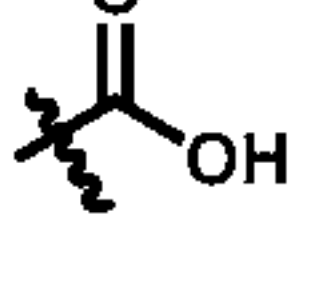
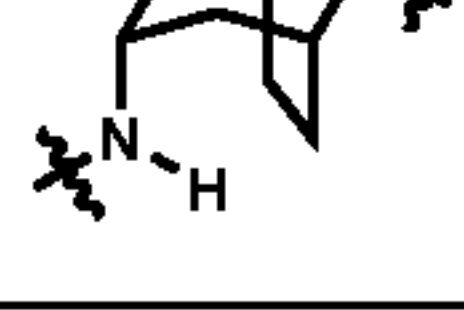
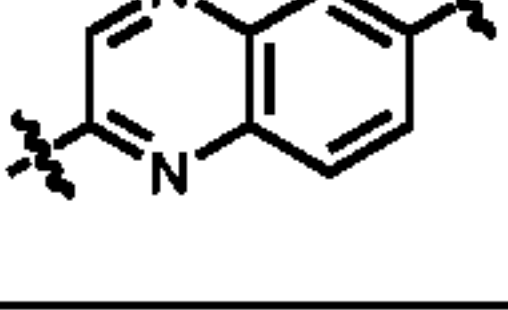
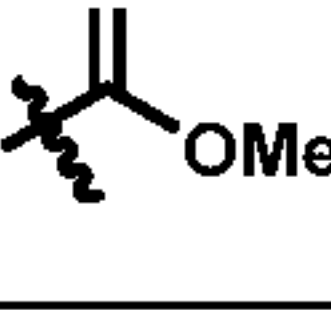
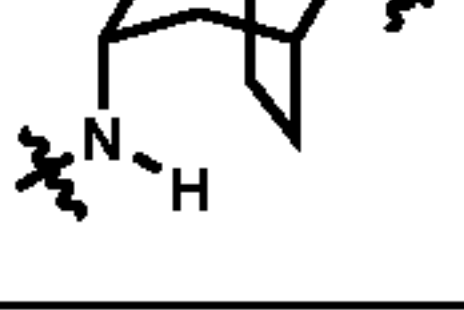
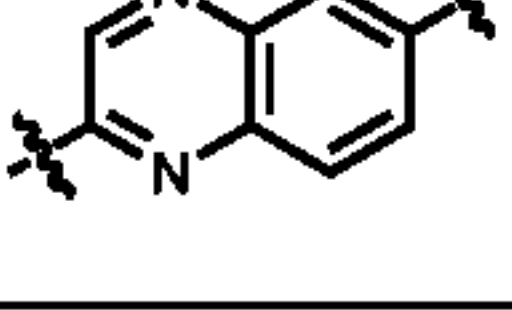
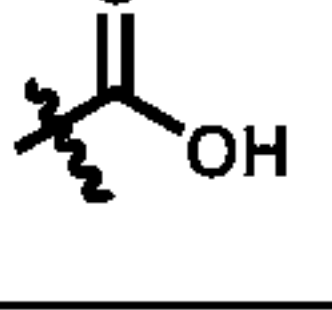
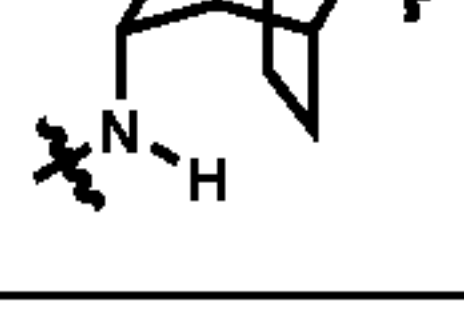
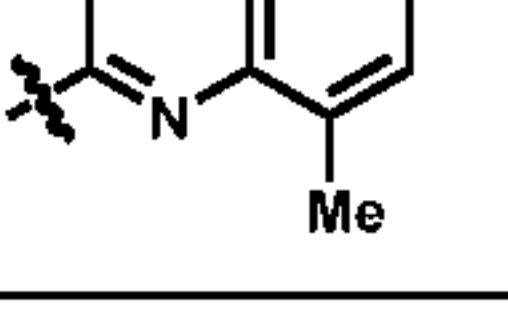
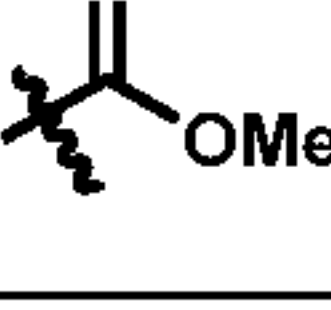
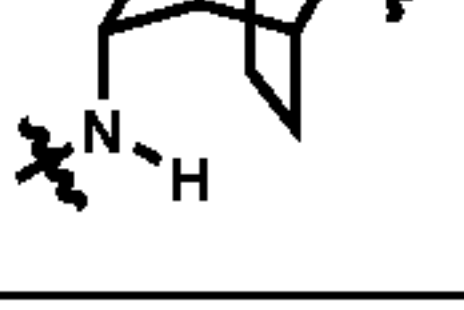
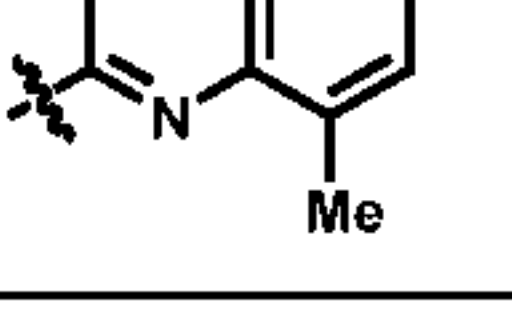
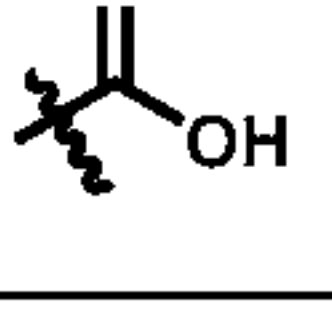
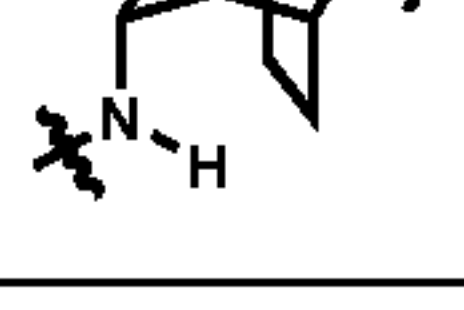
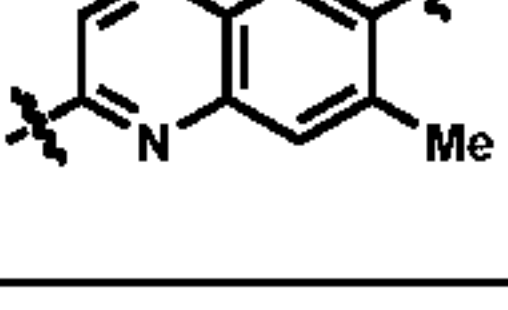
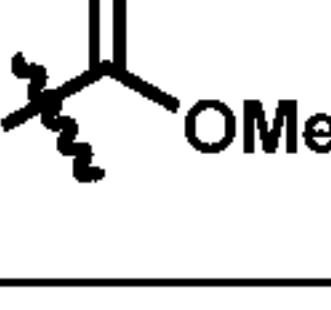
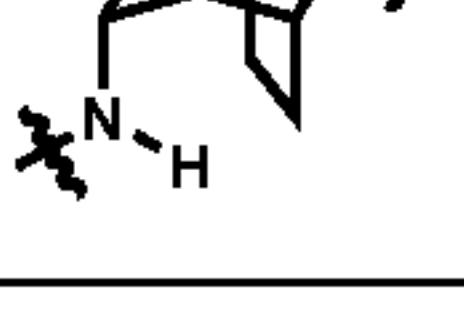
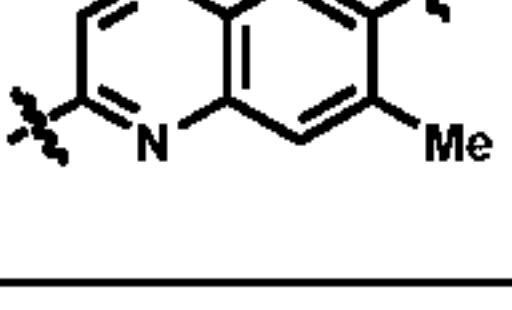
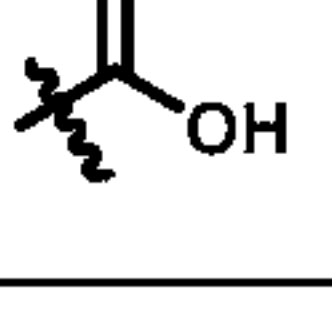
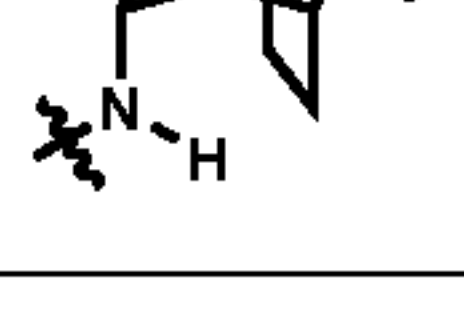
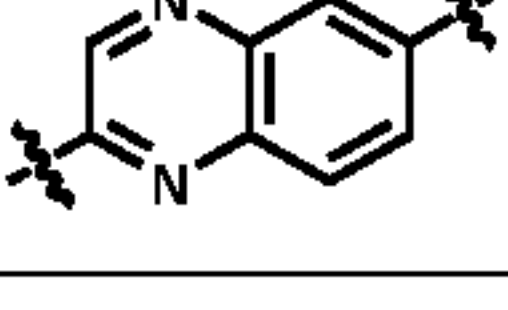
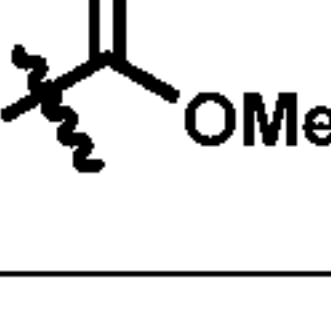
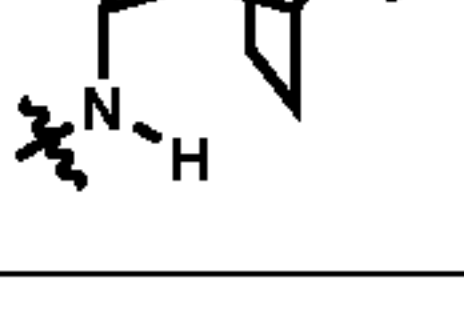
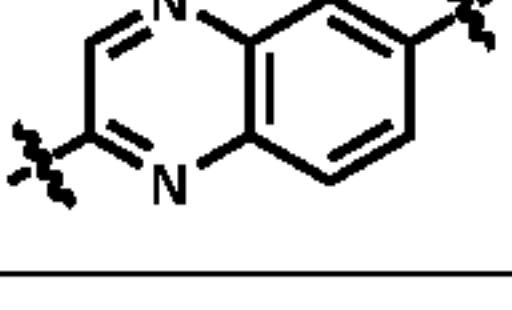
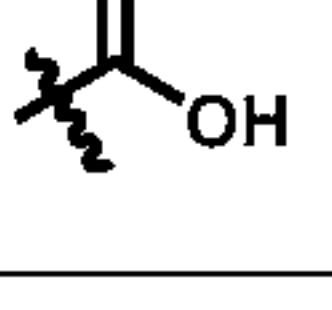
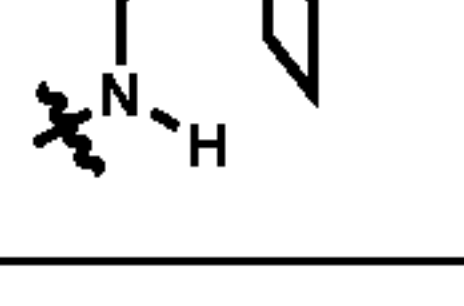
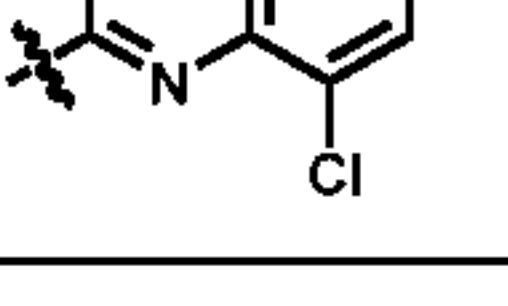
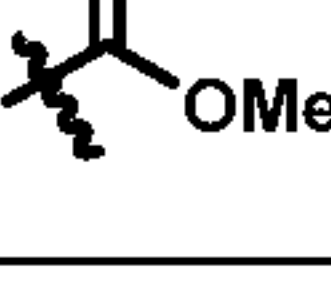
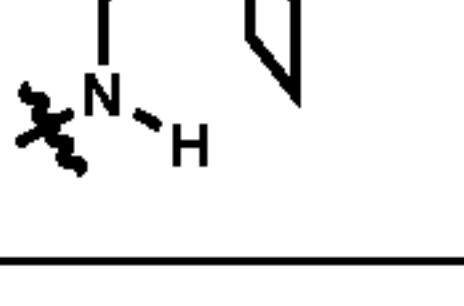
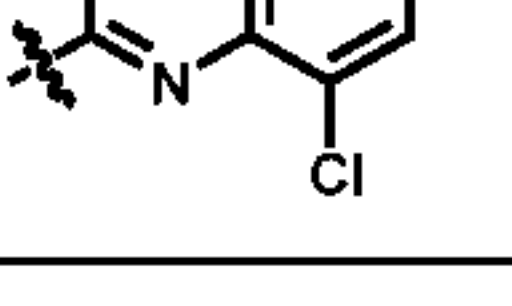
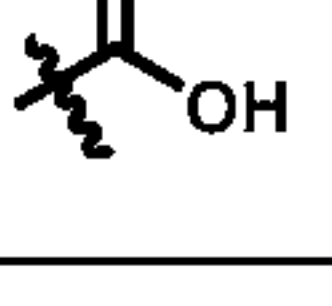
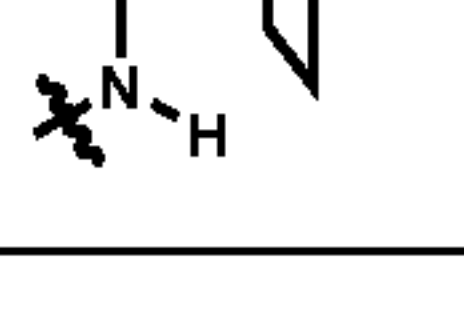
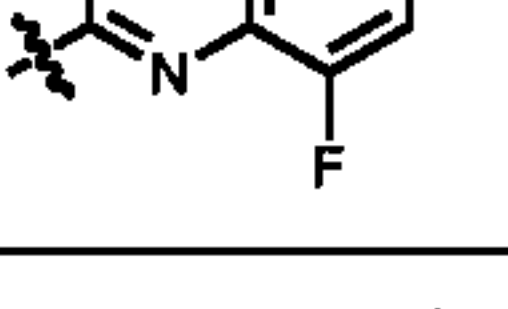
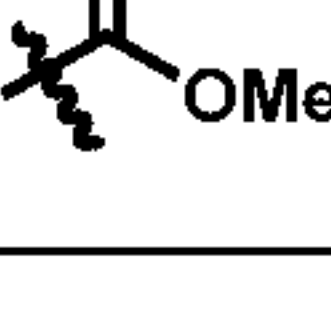
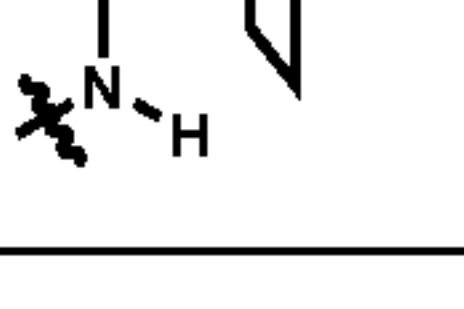
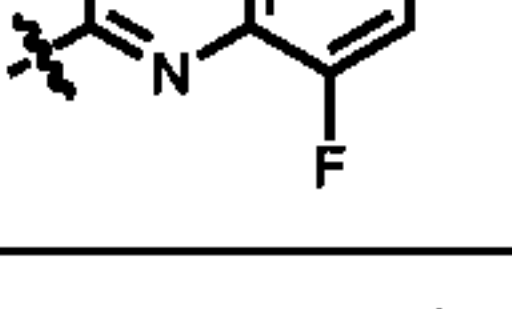
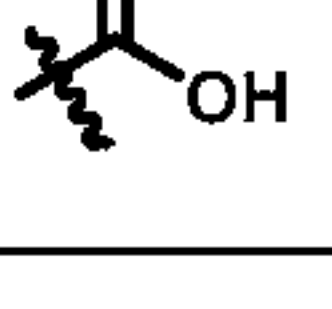
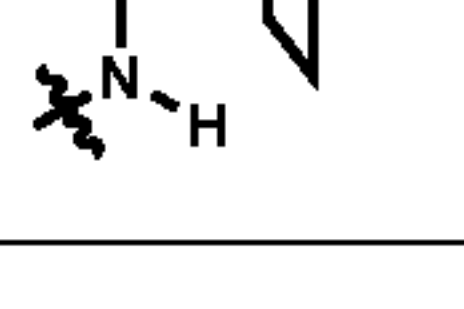
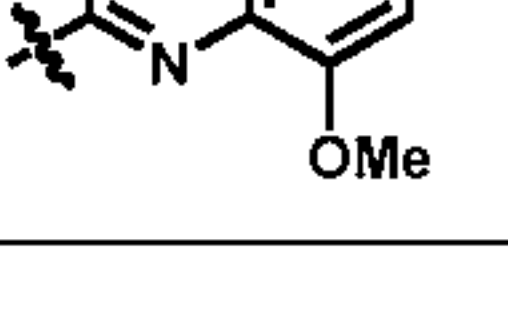
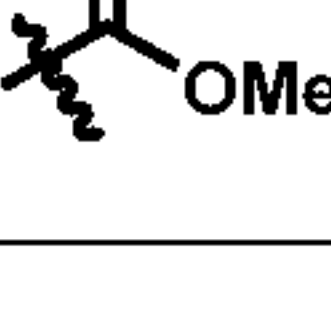
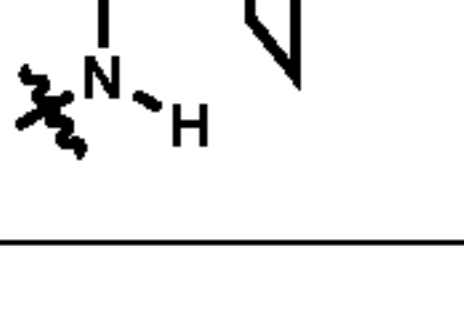
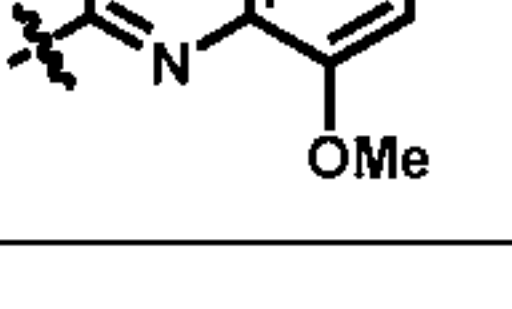
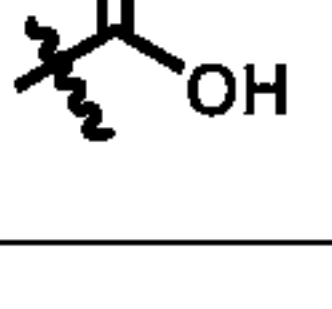
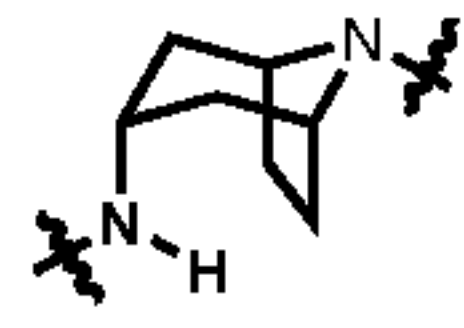
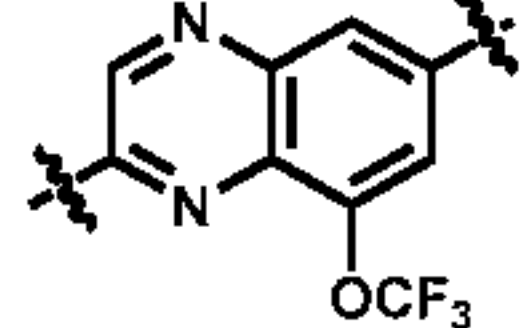
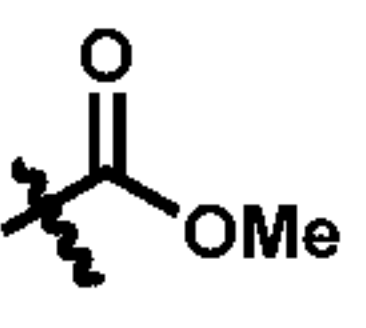
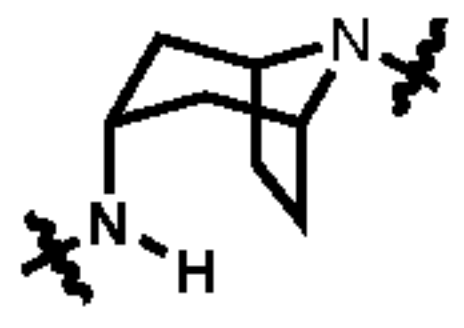
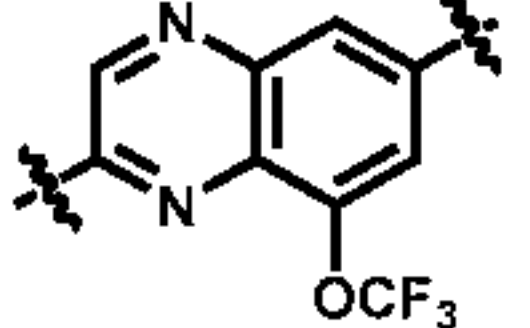
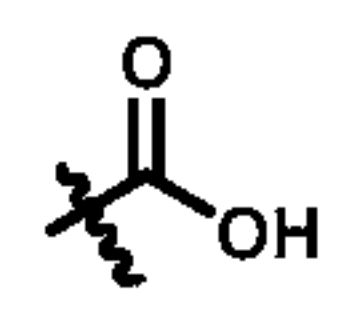
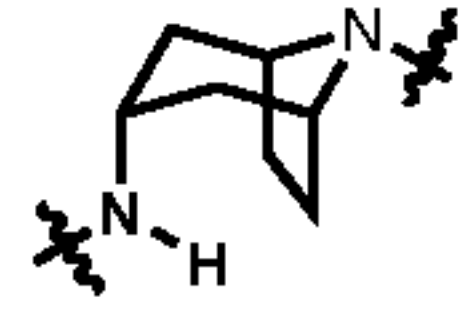
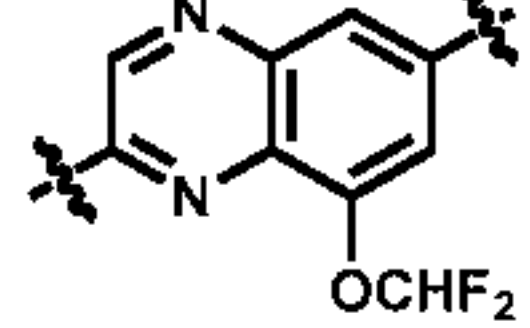
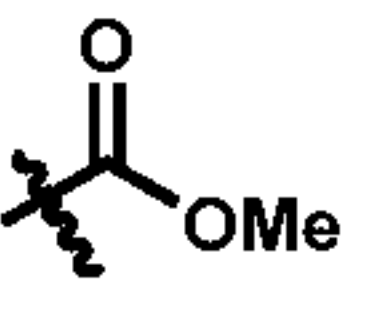
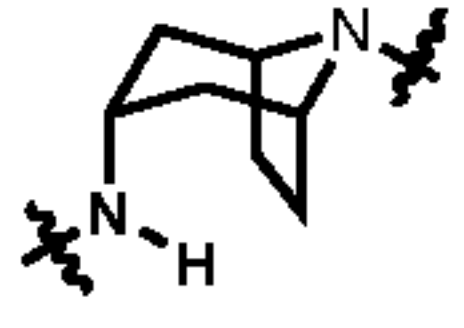
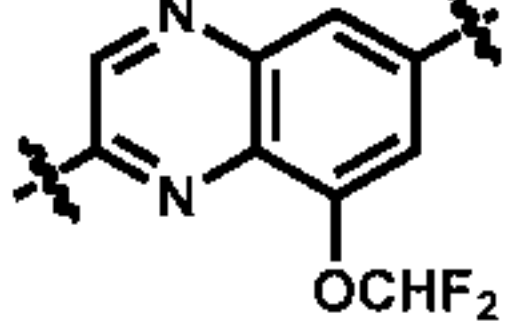
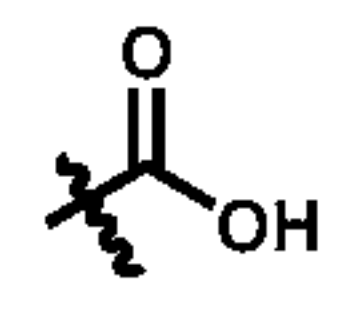
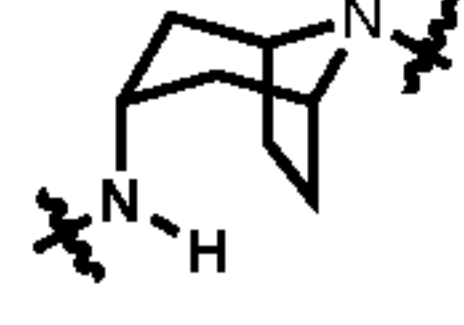
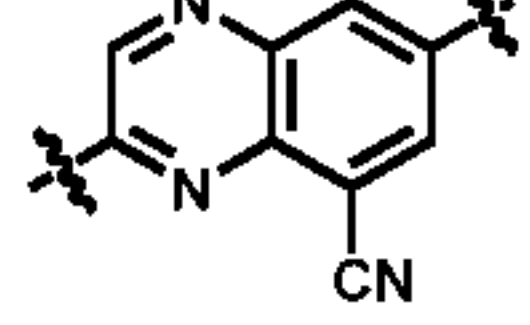
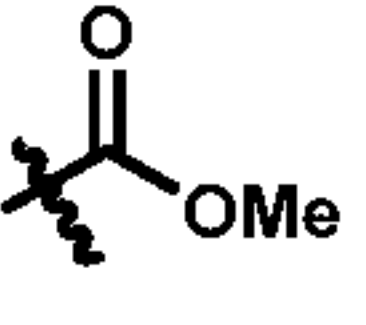
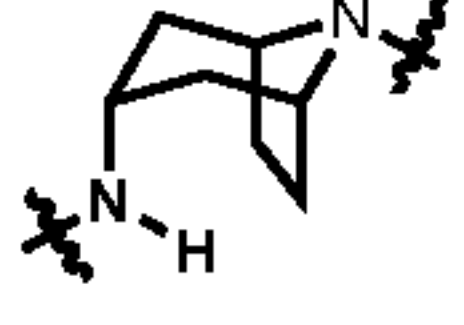
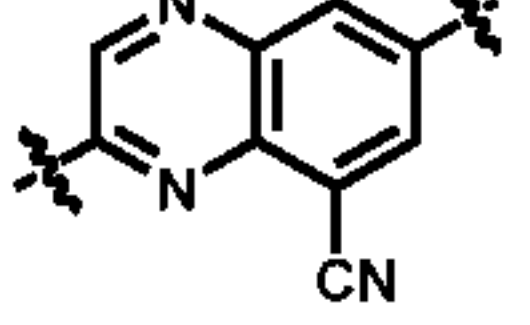
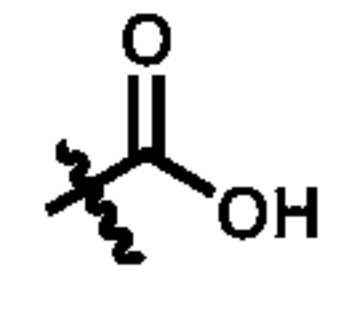
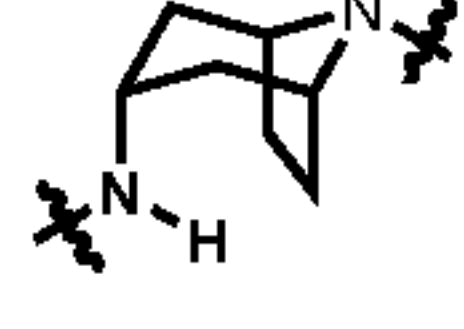
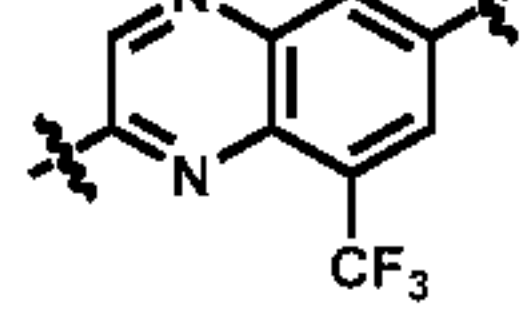
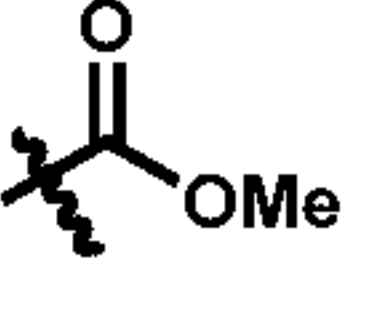
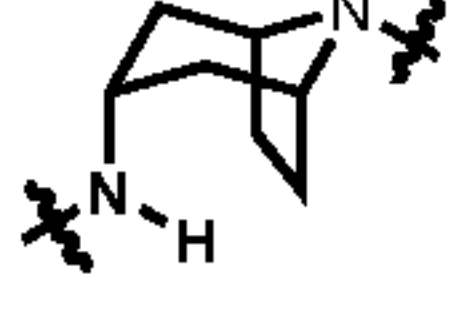
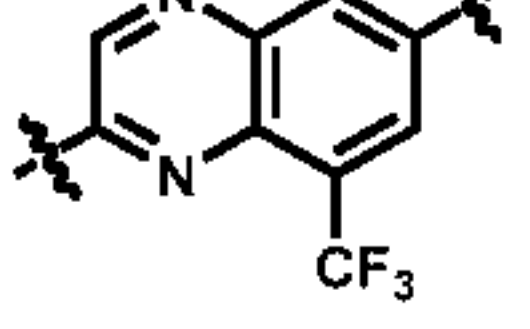
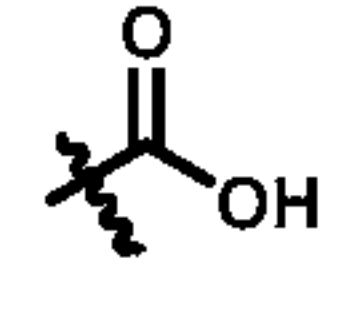
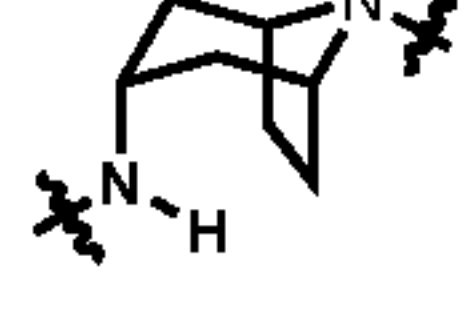
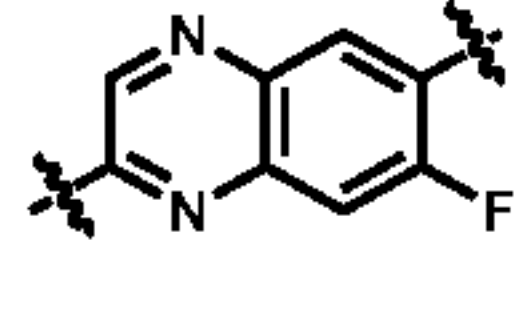
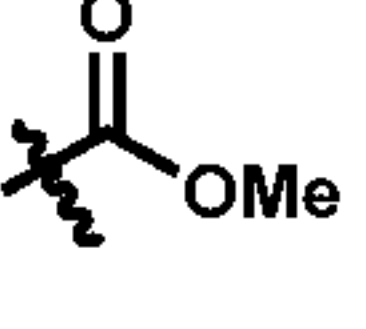
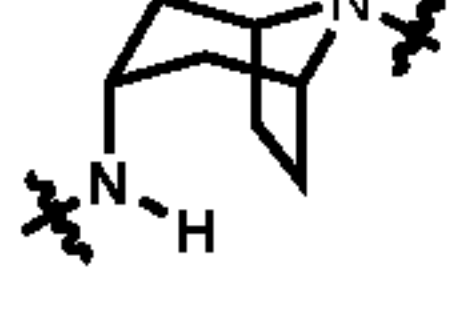
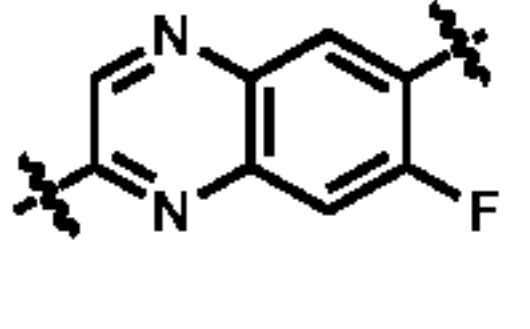
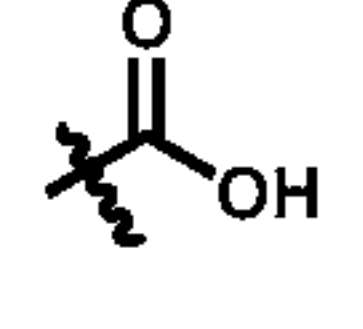
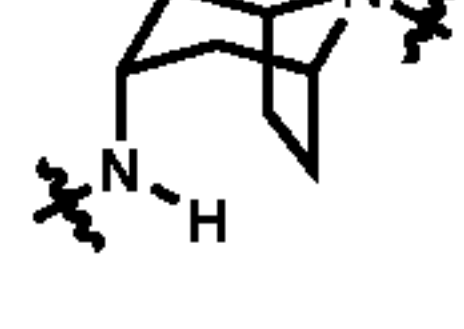
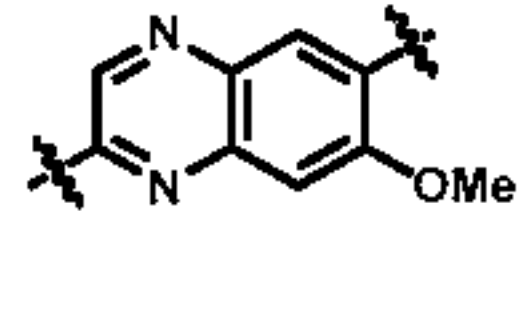
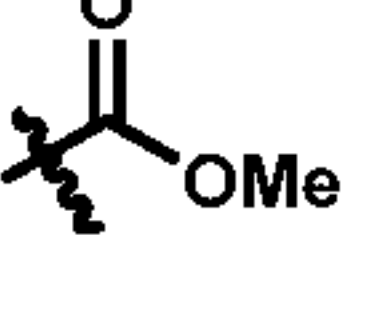
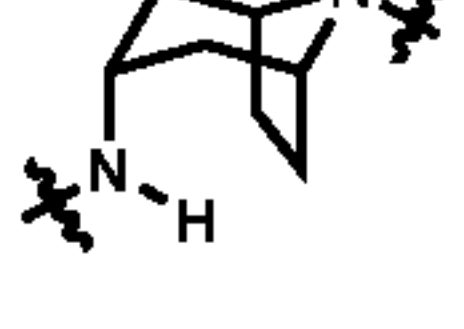
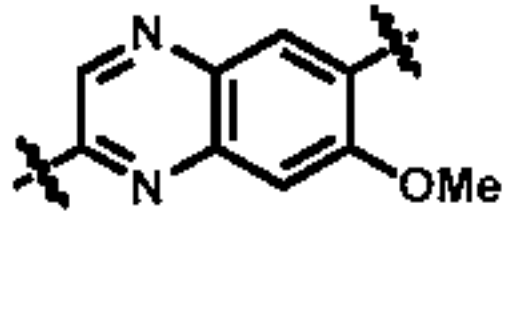
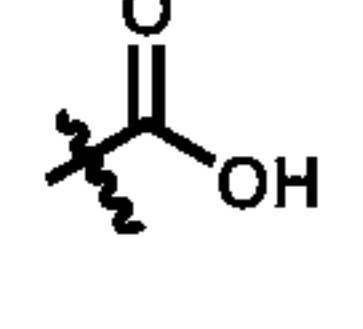
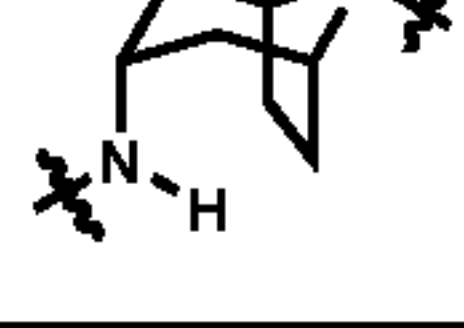
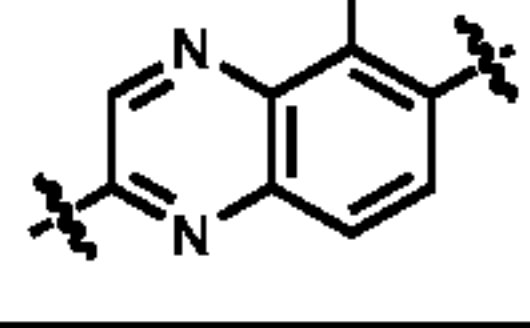
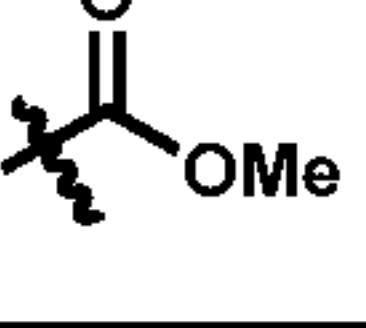
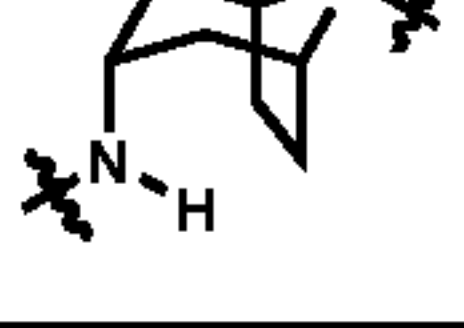
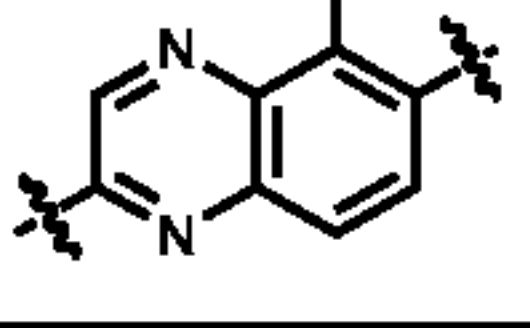
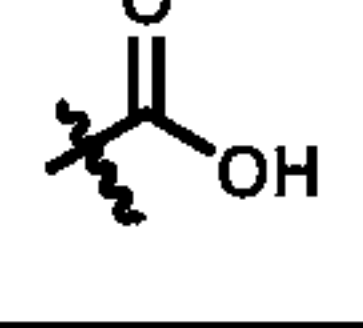
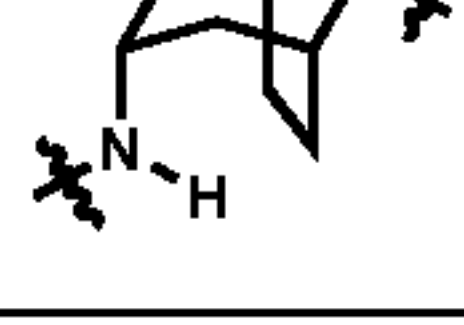
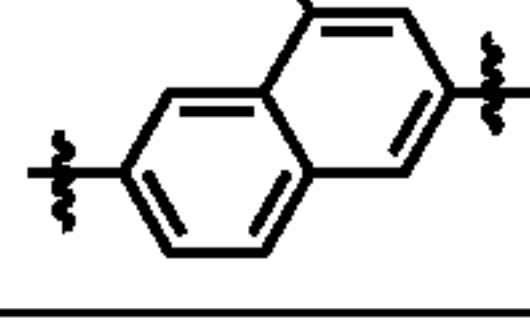
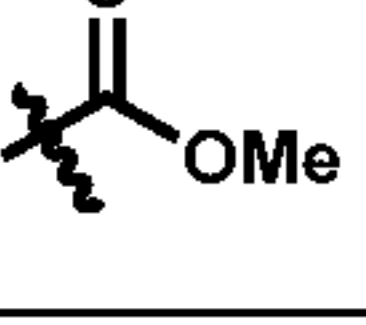
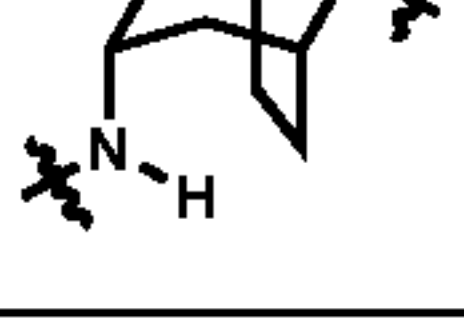
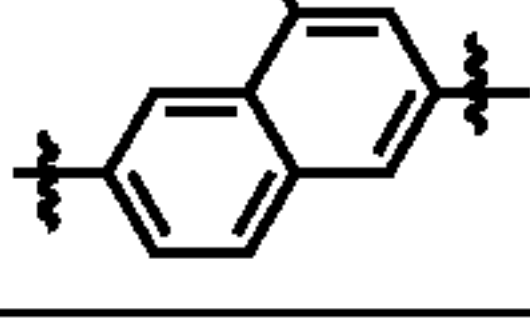
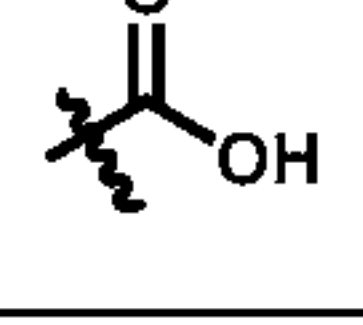
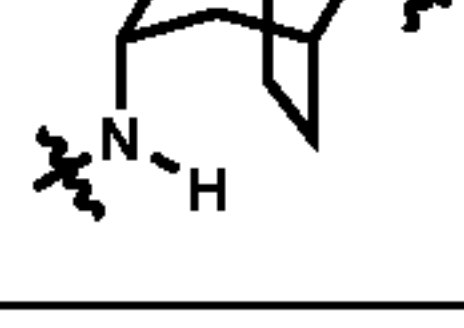
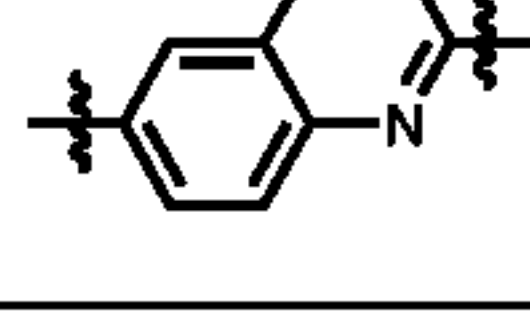
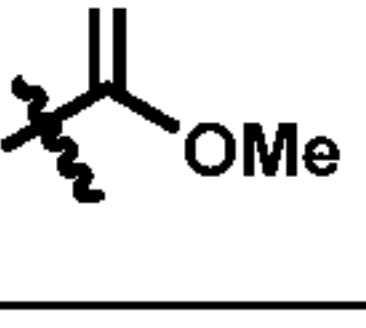
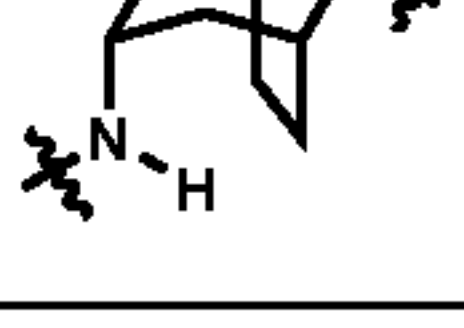
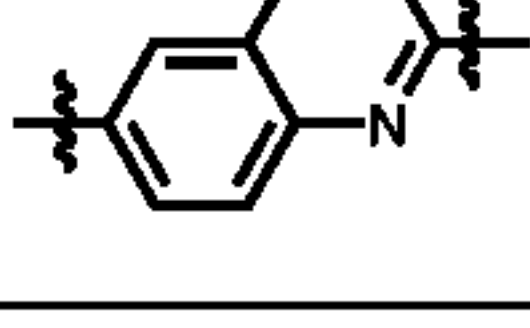
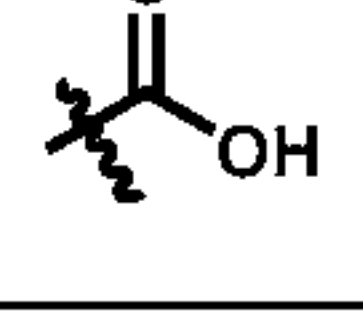
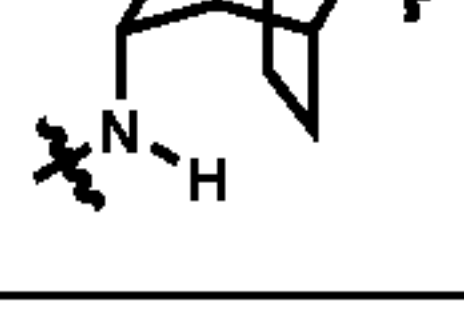
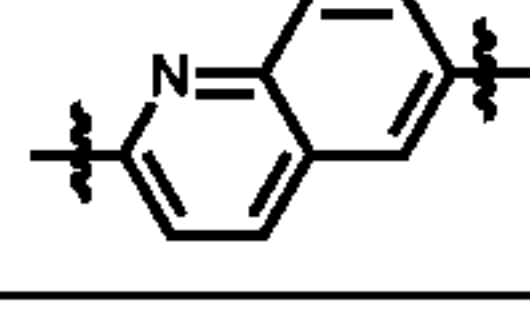
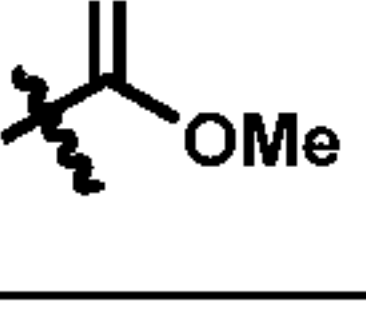
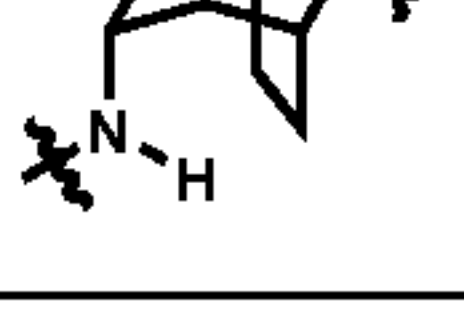
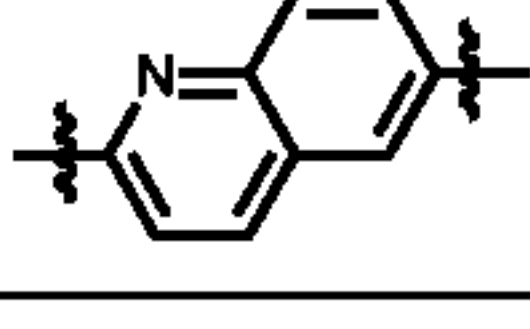
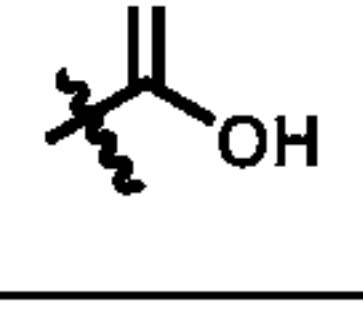
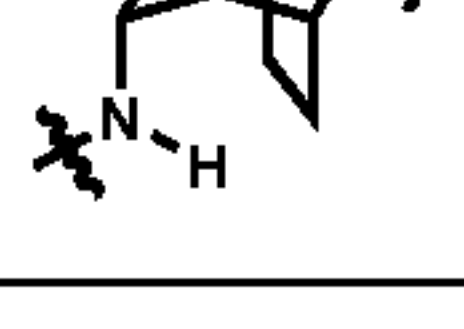
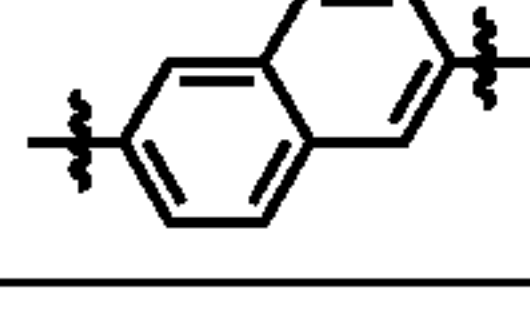
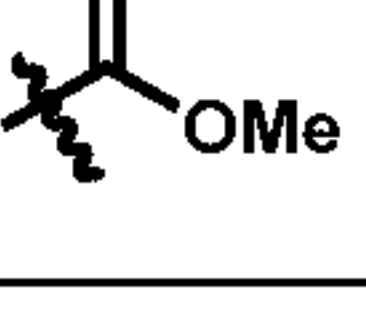
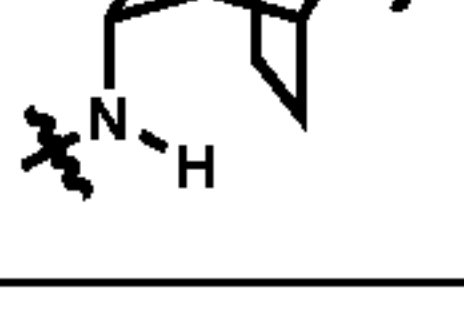
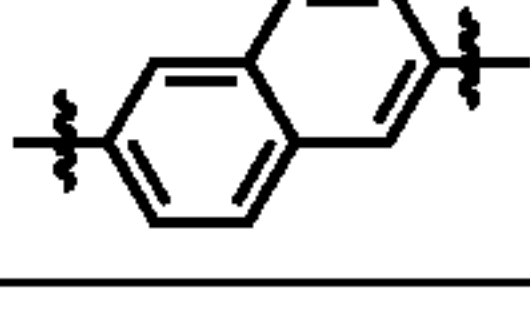
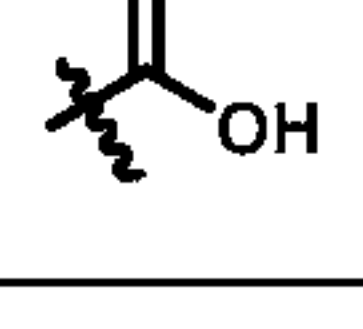
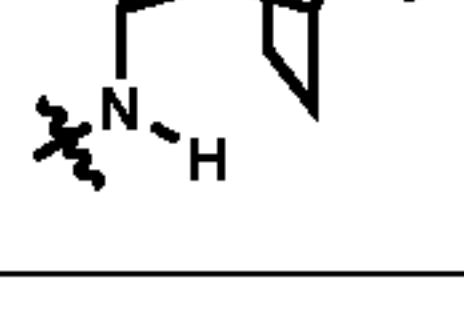
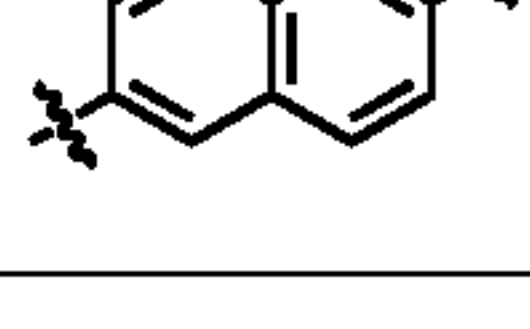
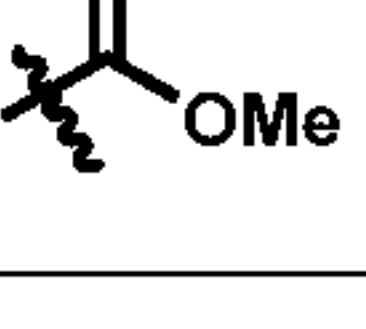
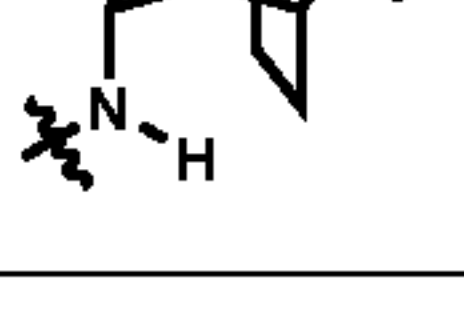
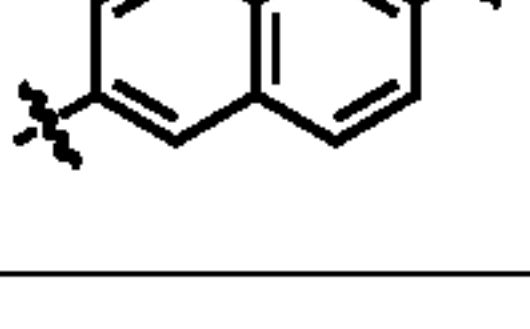
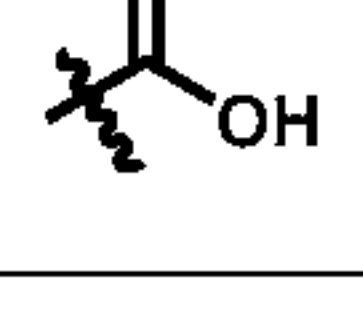
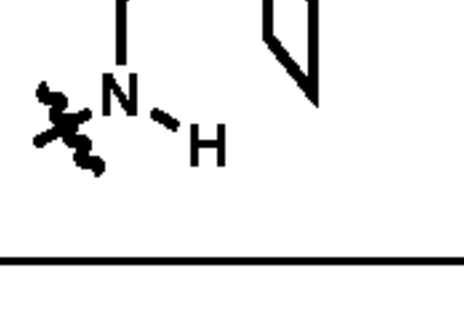
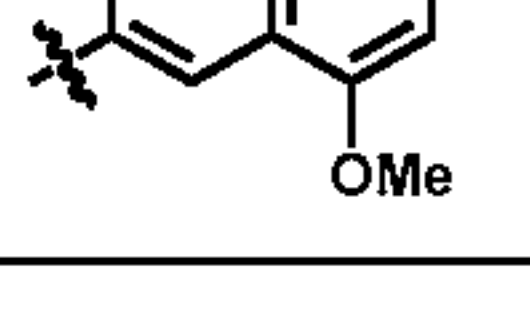
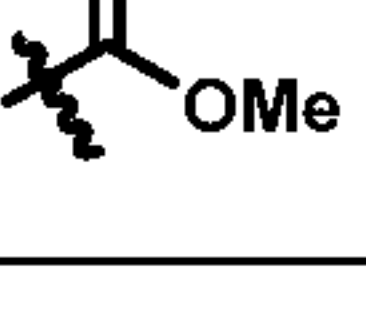
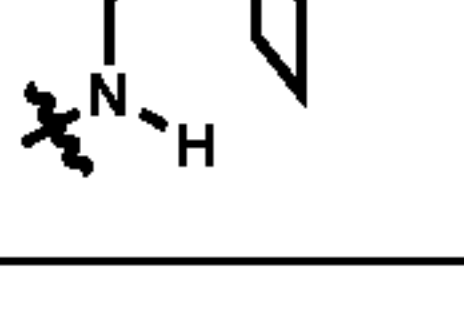
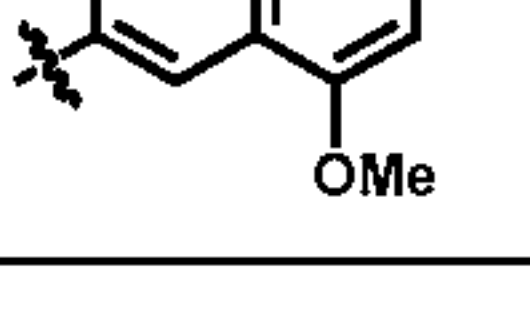
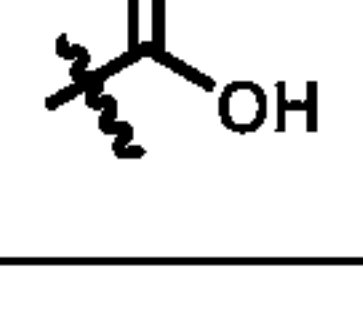
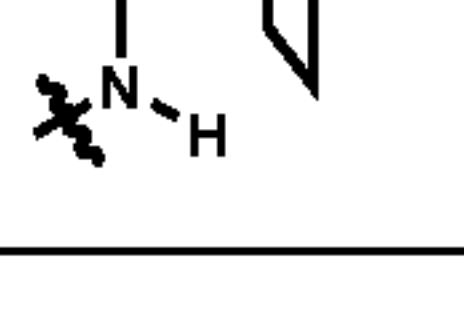
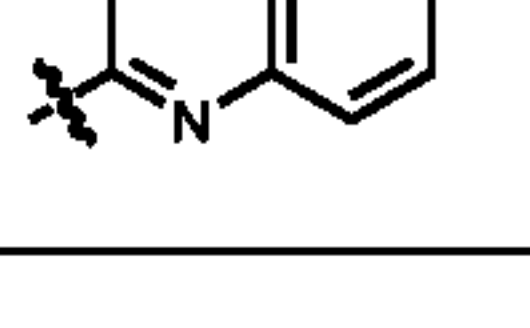
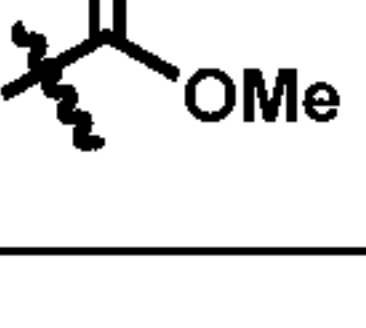
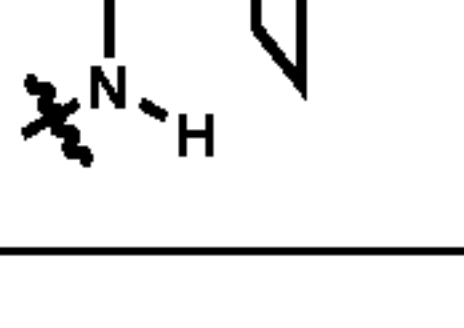
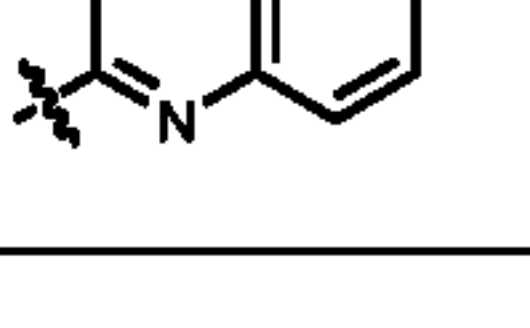
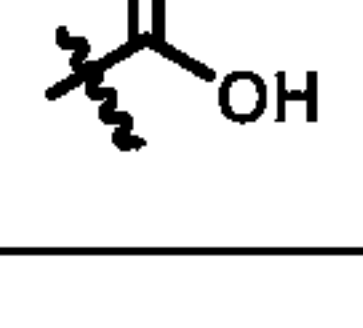
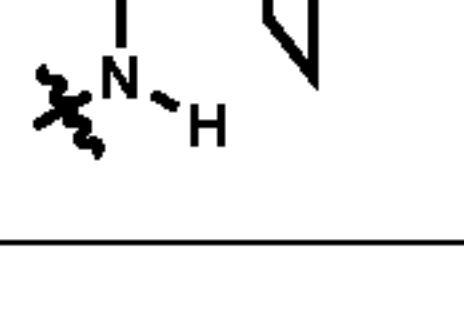
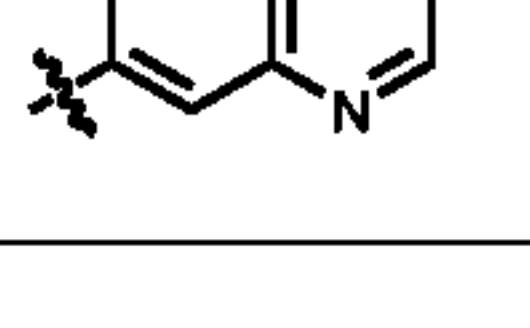
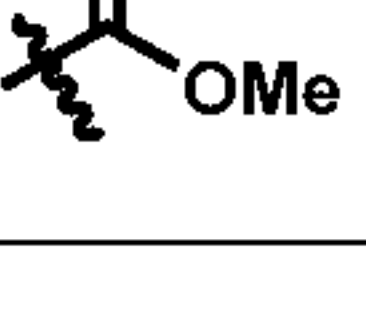
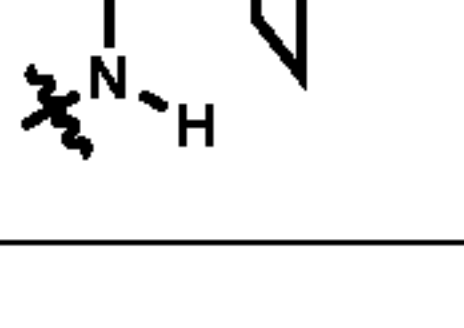
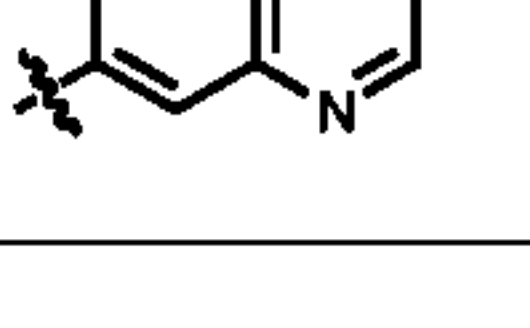
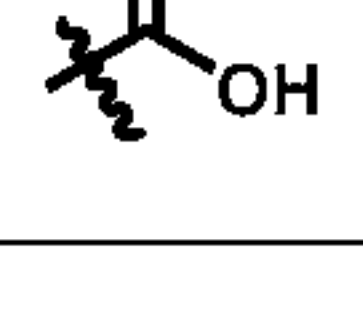


Table 5

Compound	A	B	 -Z-R ⁴	Compound	A	B	 -Z-R ⁴
901				902			
903				904			
905				906			
907				908			
909				910			
911				912			
913				914			
915				916			
917				918			
919				920			
921				922			

923				924			
925				926			
927				928			
929				930			
931				932			
933				934			
935				936			
937				938			
939				940			
941				942			
943				944			
945				946			
947				948			
949				950			
951				952			

953				954			
955				956			
957				958			
959				960			
961				962			
963				964			
965				966			
967				968			
969				970			
971				972			
973				974			
975				976			
977				978			
979				980			
981				982			

983				984			
985				986			
987				988			
989				990			
991				992			
993				994			
995				996			
997				998			
999				1000			
1001				1002			
1003				1004			
1005				1006			
1007				1008			
1009				1010			
1011				1012			

1013				1014			
1015				1016			
1017				1018			
1019				1020			
1021				1022			
1023				1024			
1025				1026			
1027				1028			
1029				1030			
1031				1032			
1033				1034			
1035				1036			
1037				1038			
1039				1040			
1041				1042			

1043				1044			
1045				1046			
1047				1048			
1049				1050			
1051				1052			
1053				1054			
1055				1056			
1057				1058			
1059				1060			
1061				1062			
1063				1064			
1065				1066			
1067				1068			
1069				1070			
1071				1072			

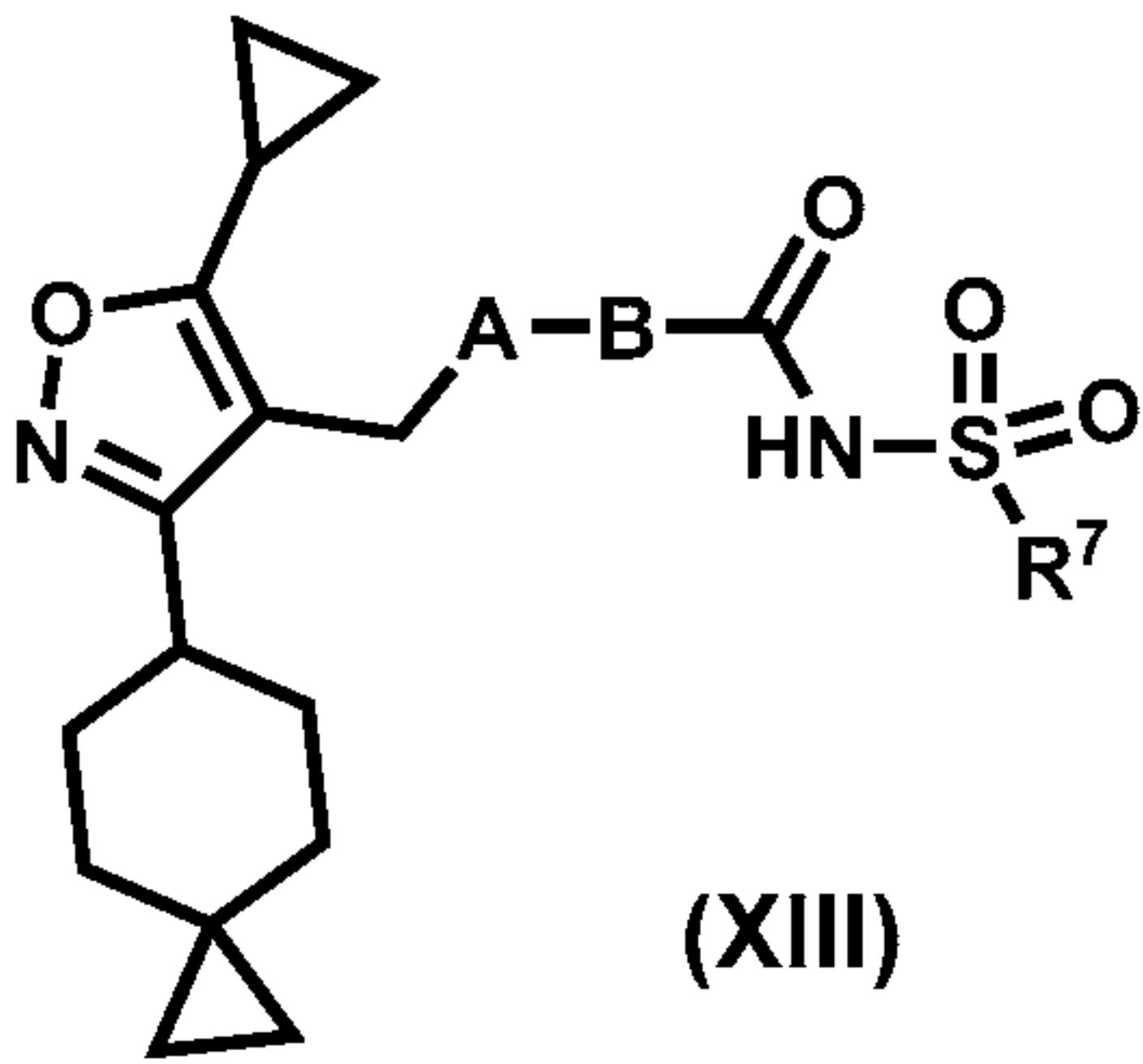
1073				1074			
1075				1076			
1077				1078			
1079				1080			
1081				1082			
1083				1084			
1085				1086			
1087				1088			
1089				1090			
1091				1092			
1093				1094			
1095				1096			
1097				1098			
1099				1100			
1101				1102			

1103				1104			
1105				1106			
1107				1108			
1109				1110			
1111				1112			
1113				1114			
1115				1116			
1117				1118			
1119				1120			
1121				1122			
1123				1124			
1125				1126			
1127				1128			
1129				1130			
1131				1132			

1133				1134			
1135				1136			

and

(B) Compounds according to Formula (XIII), wherein A, B, and R⁷ are delineated for each compounds in Table 6:



5

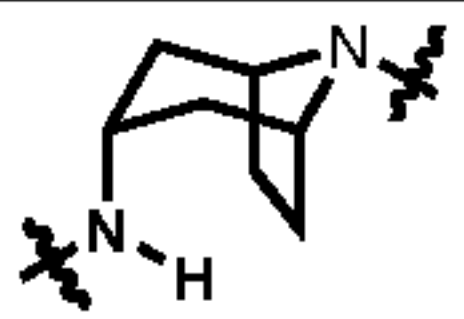
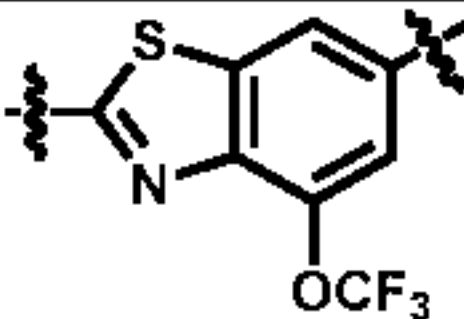
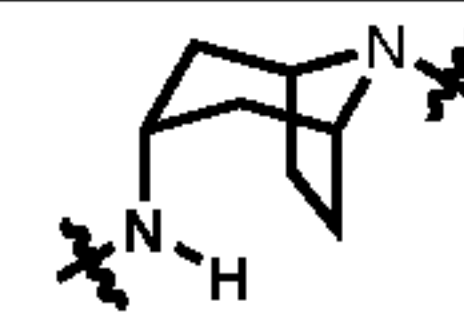
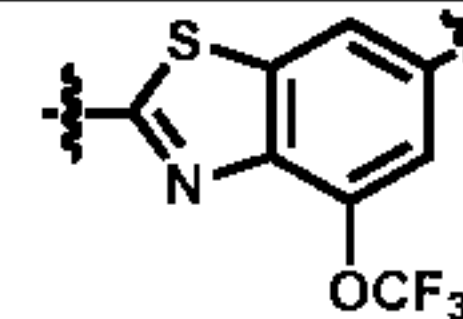
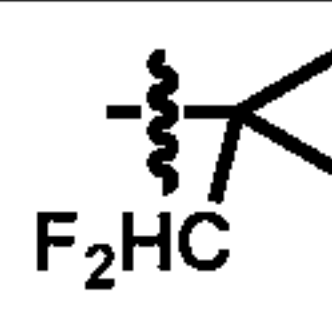
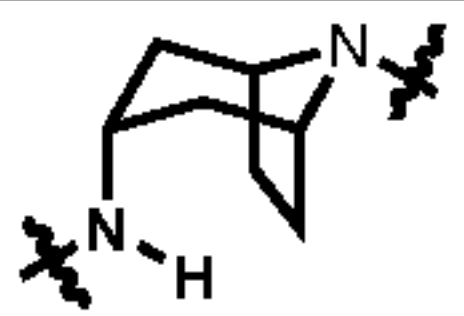
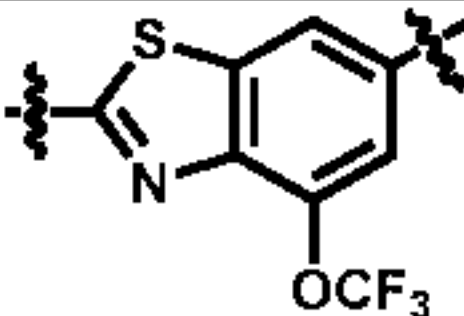
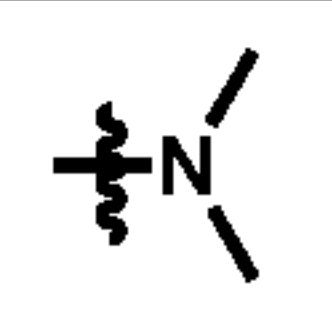
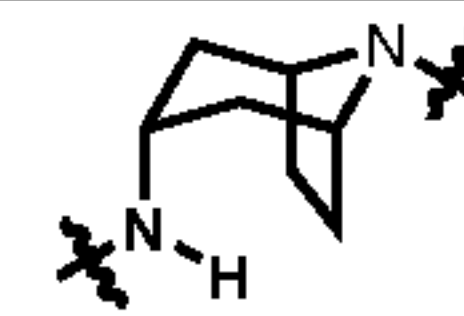
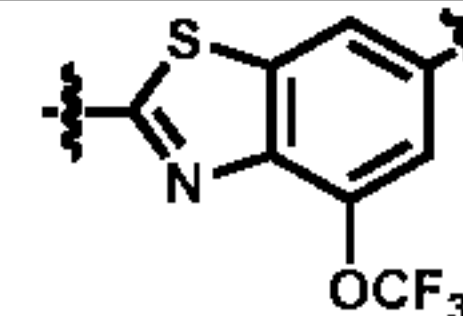
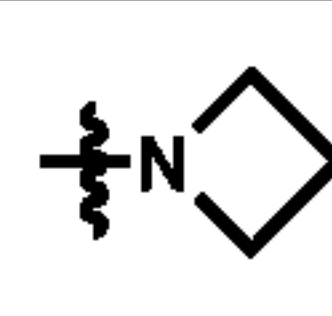
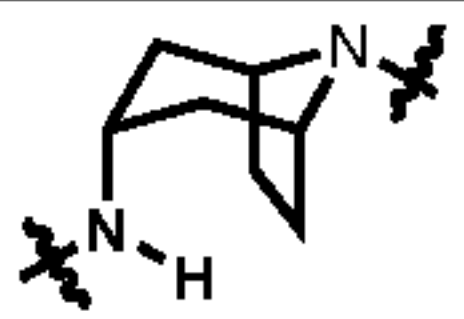
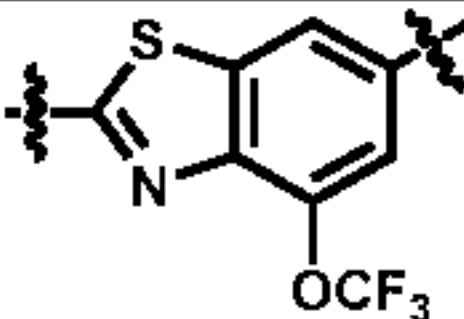
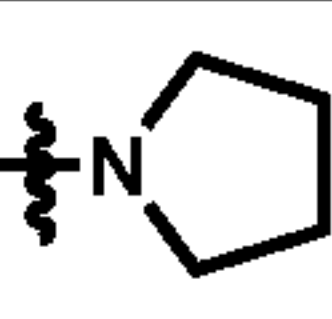
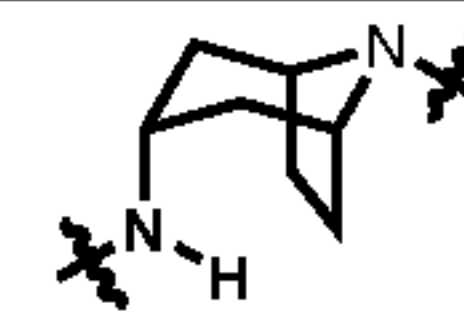
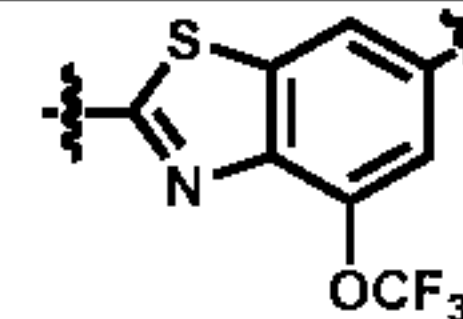
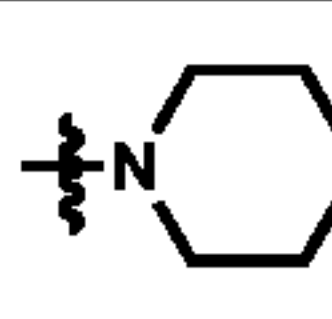
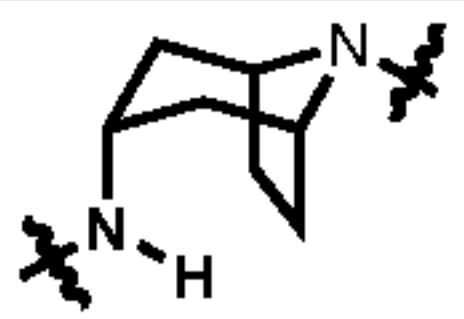
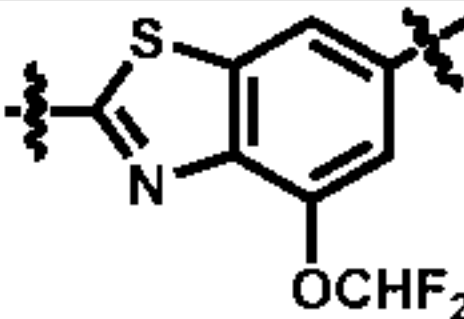
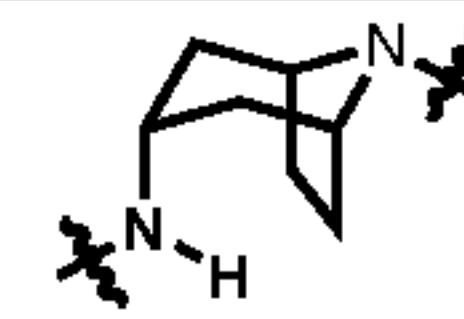
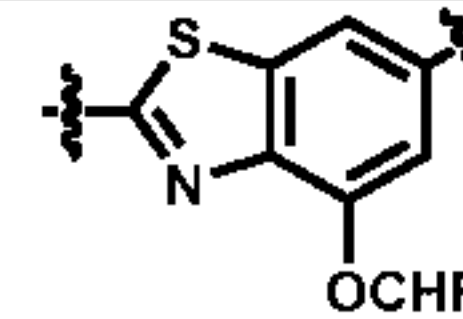
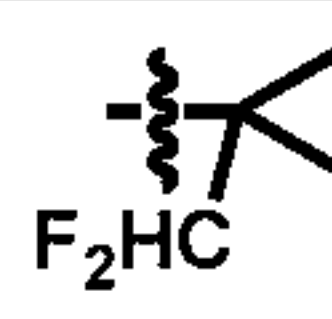
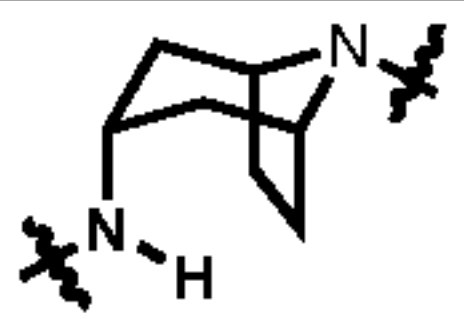
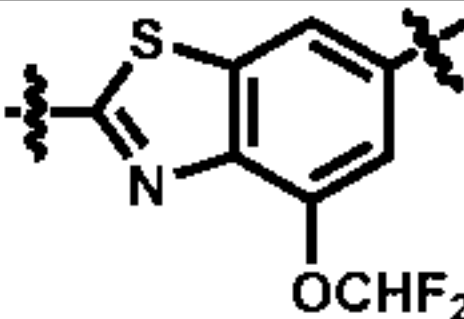
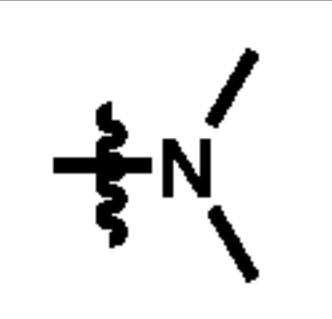
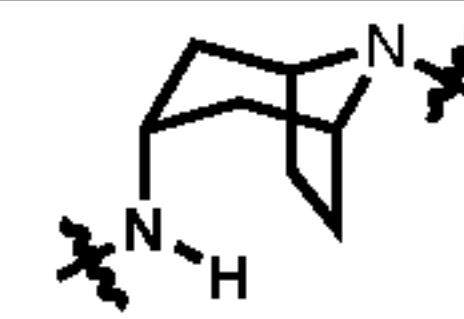
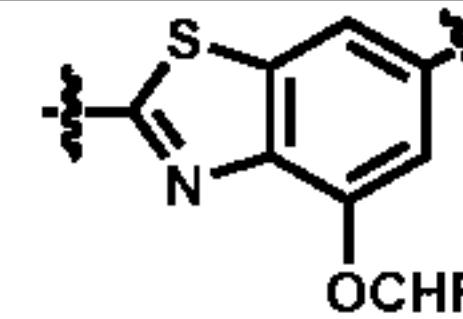
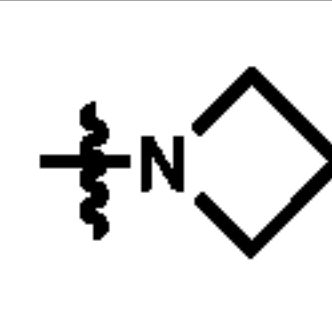
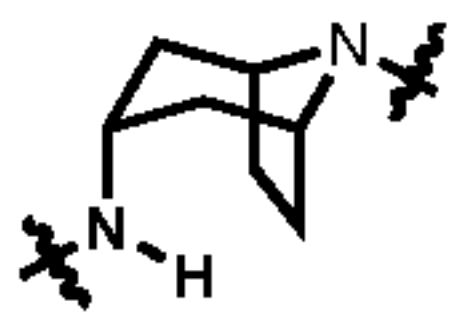
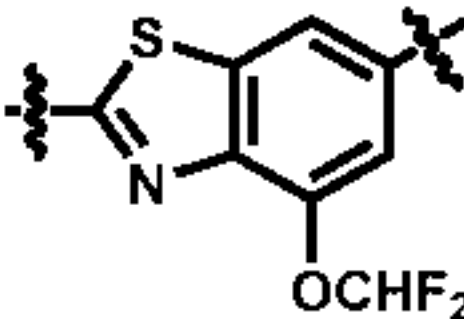
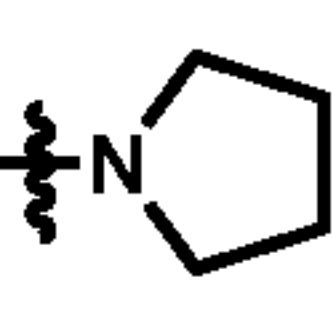
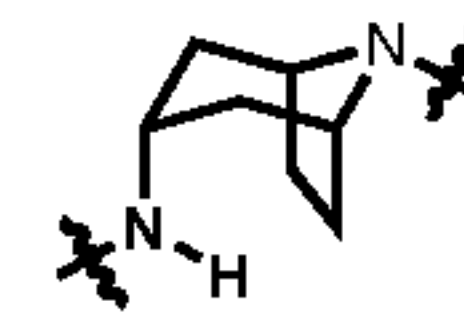
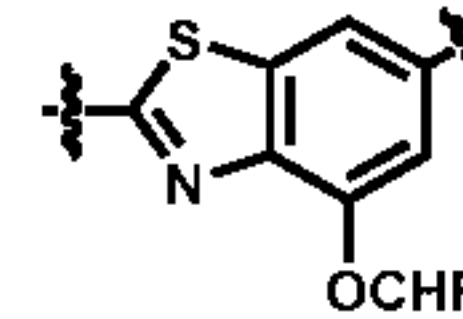
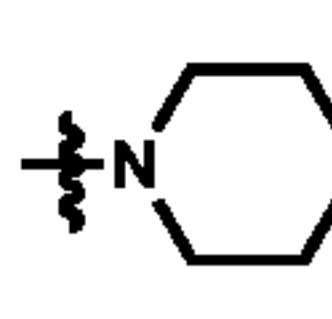
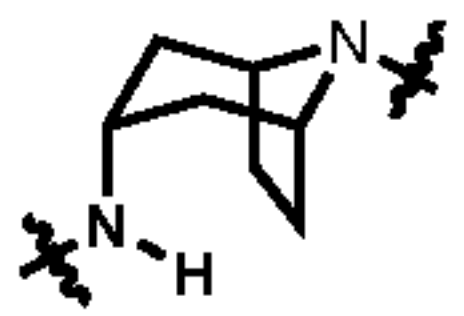
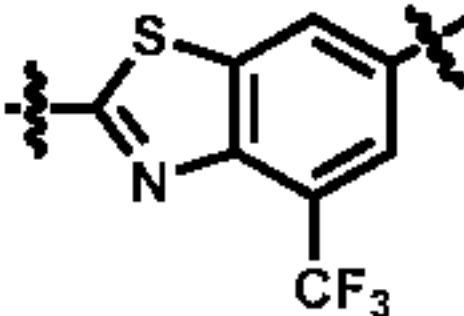
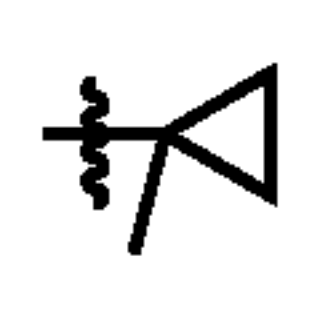
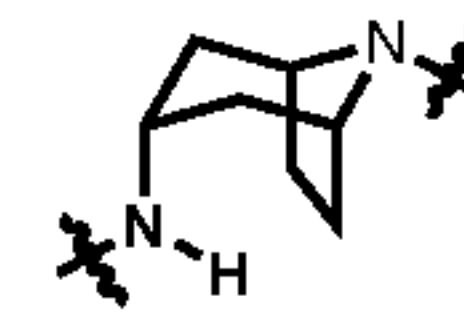
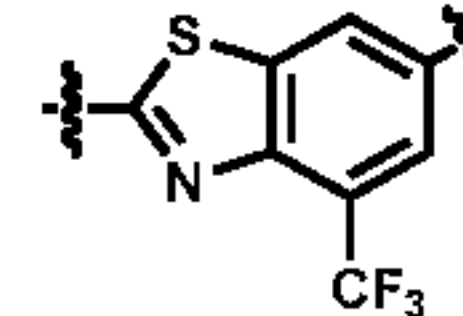
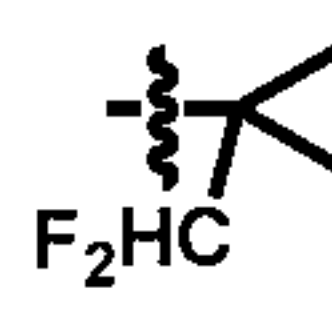
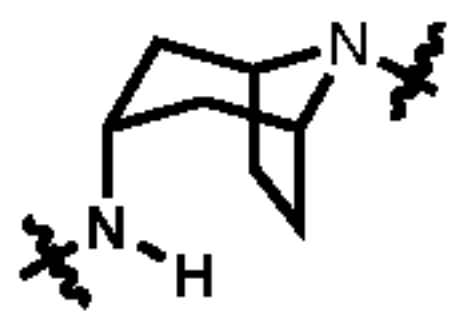
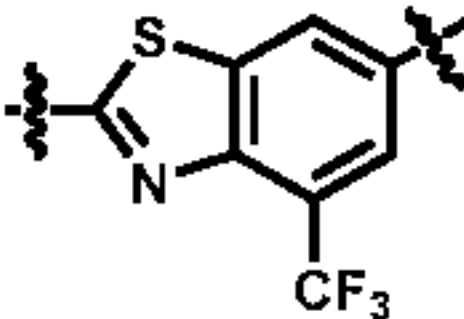
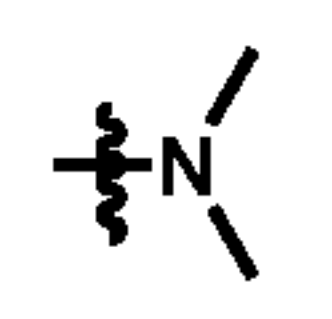
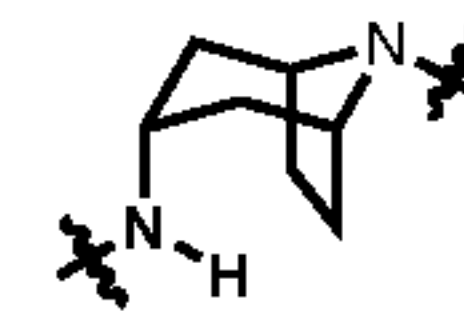
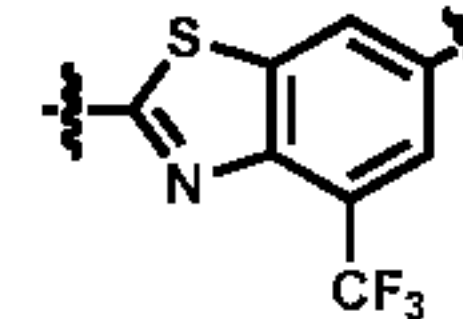
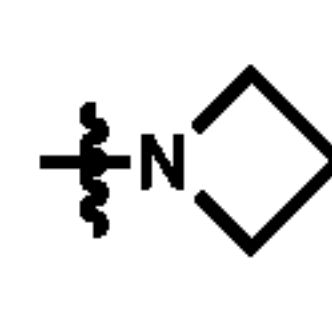
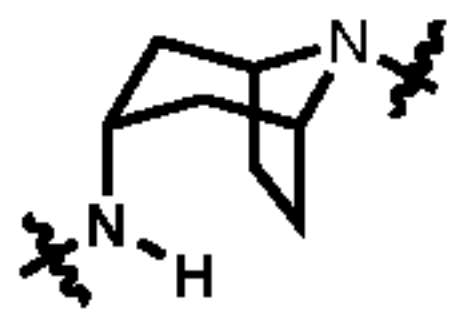
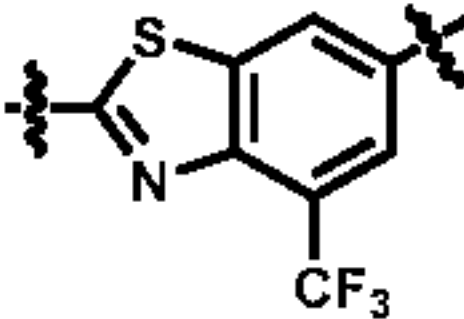
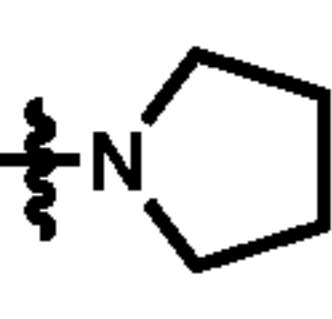
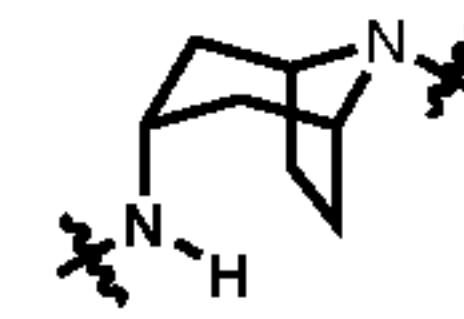
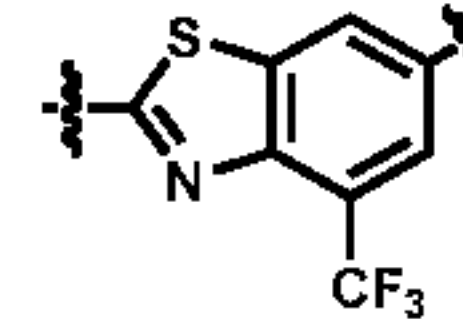
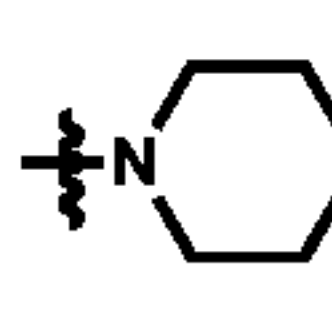
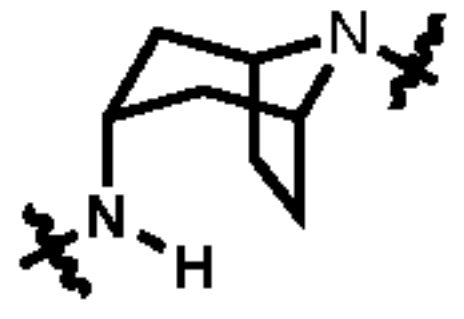
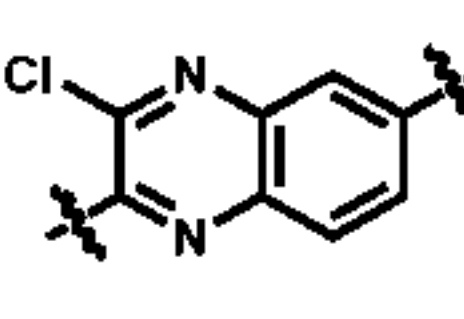
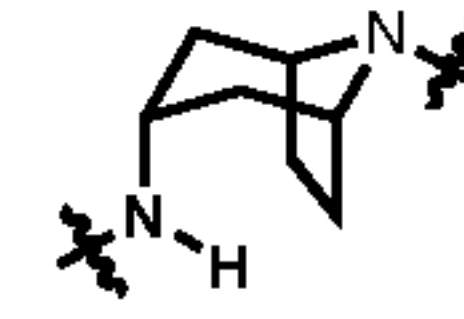
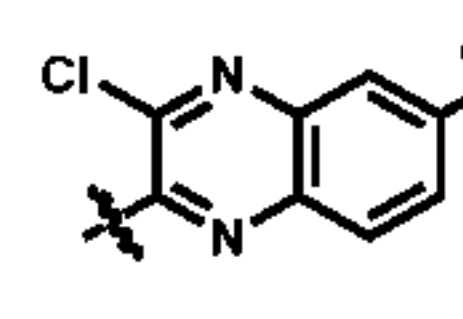
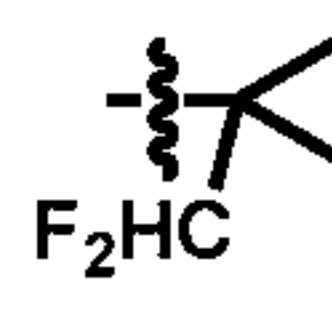
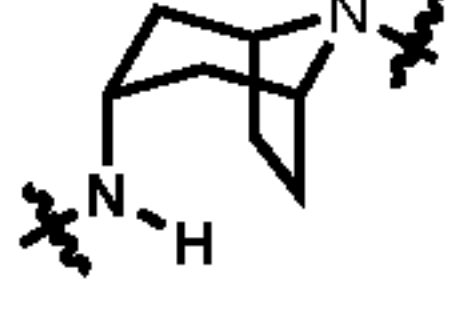
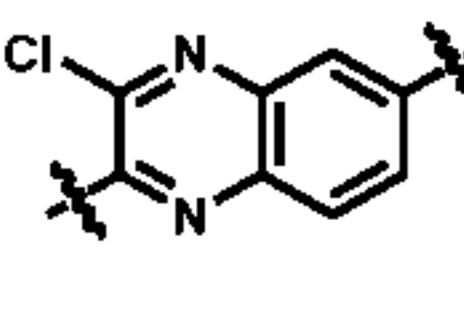
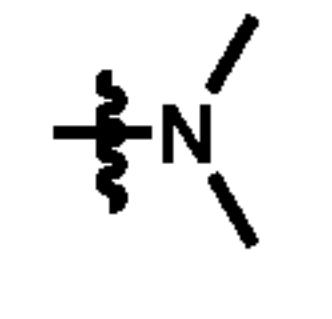
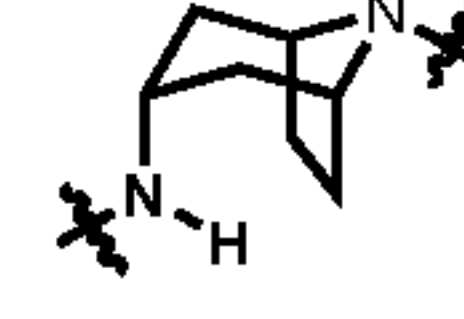
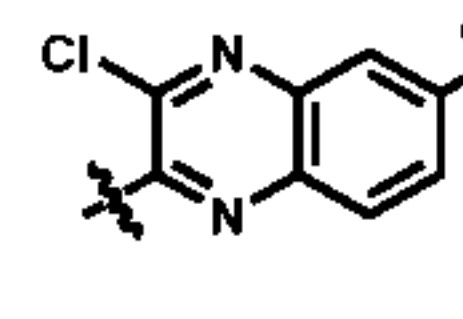
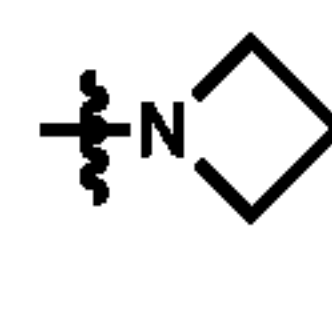
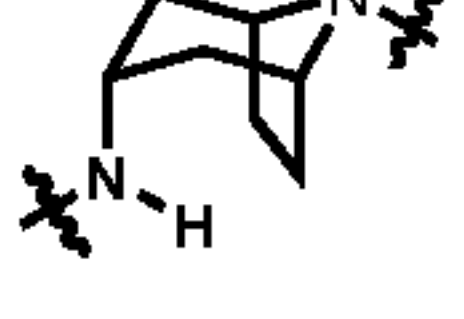
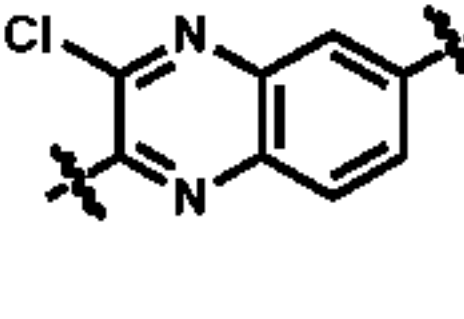
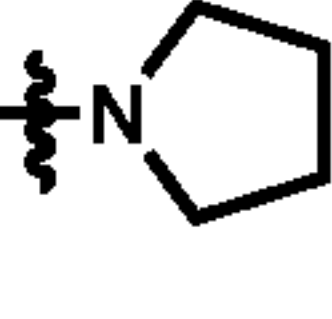
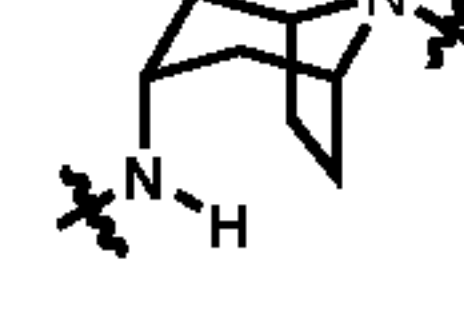
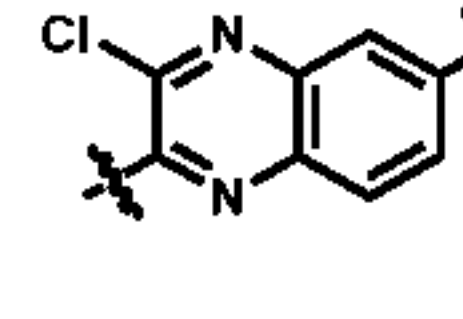
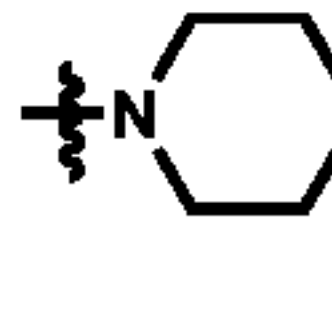
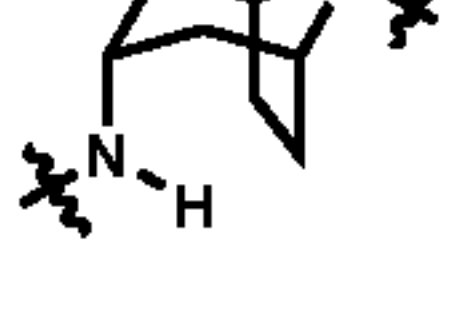
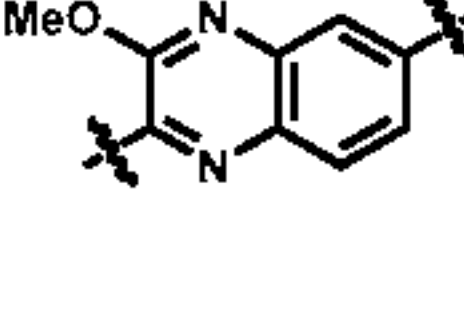
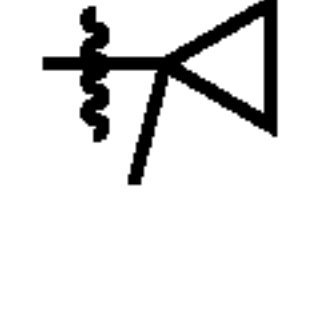
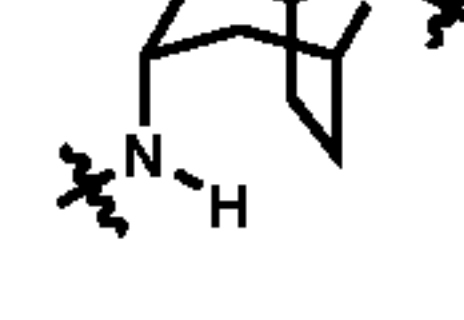
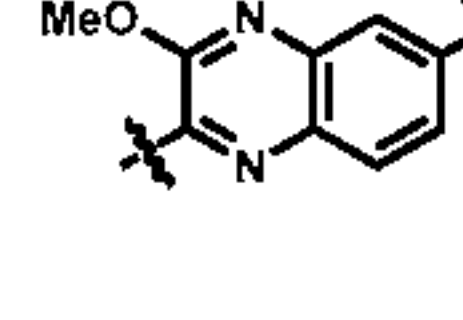
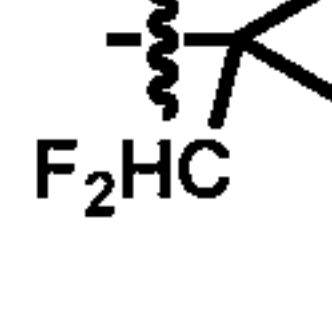
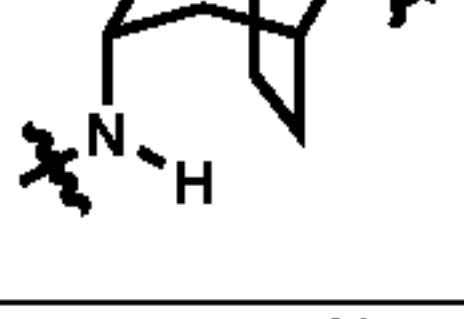
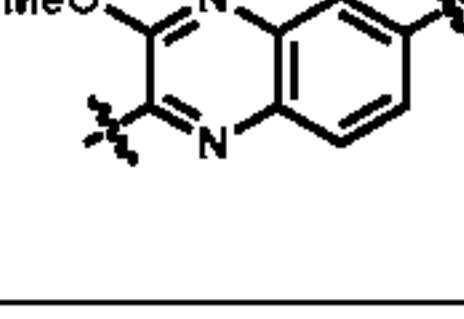
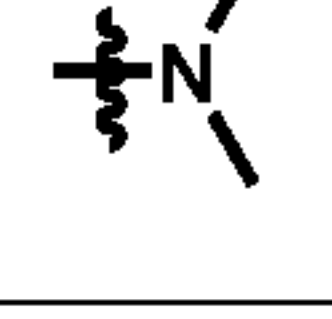
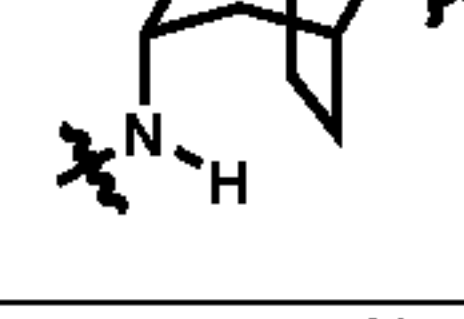
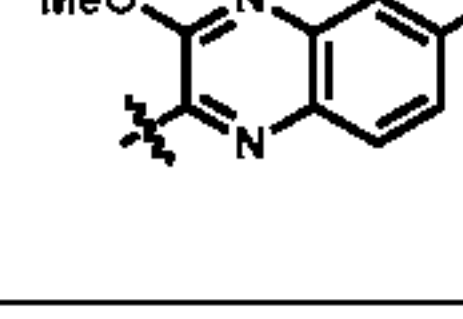
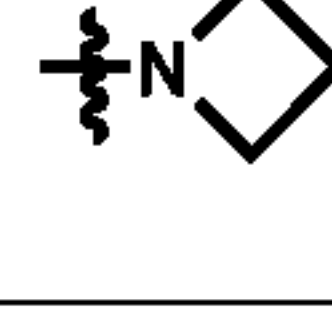
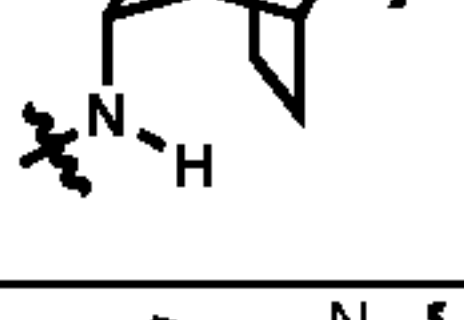
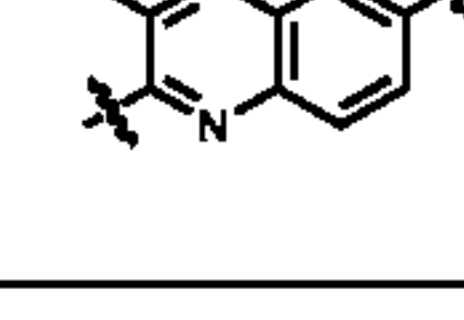
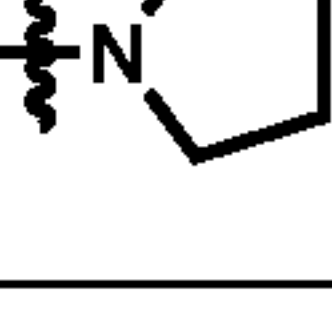
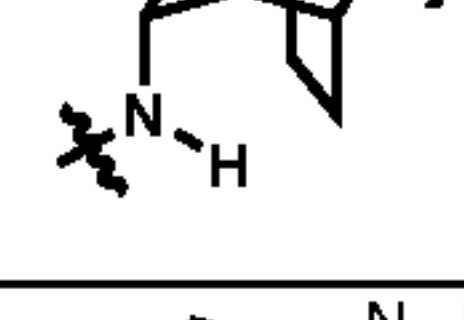
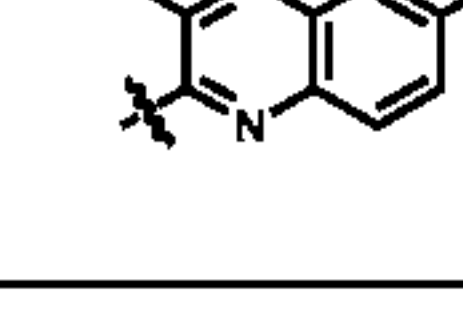
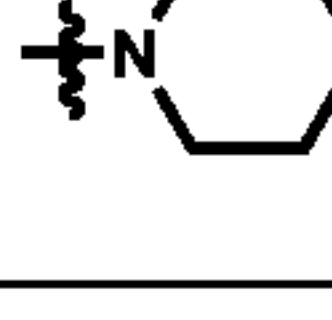
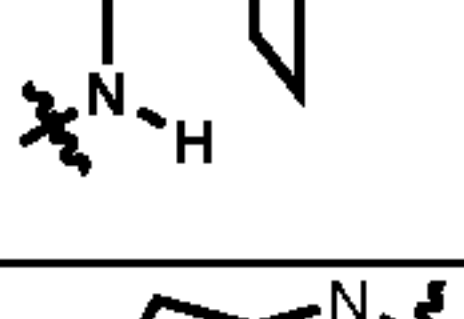
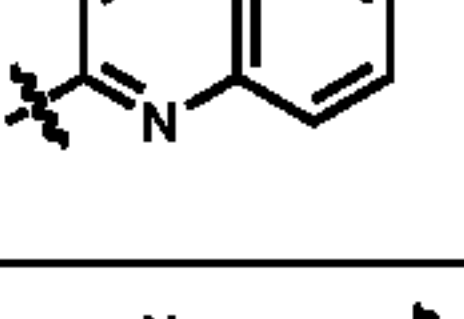
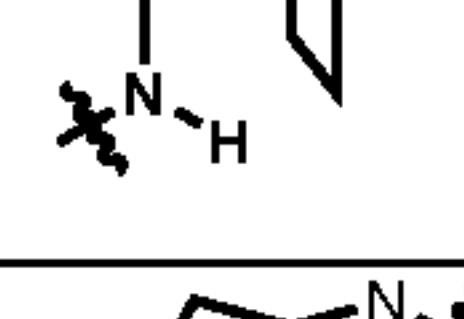
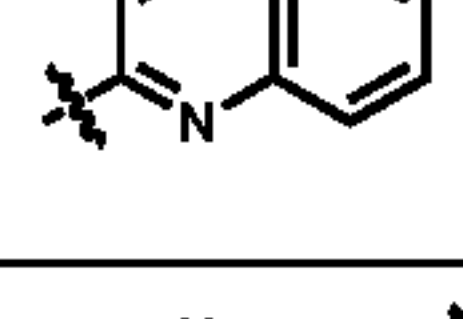
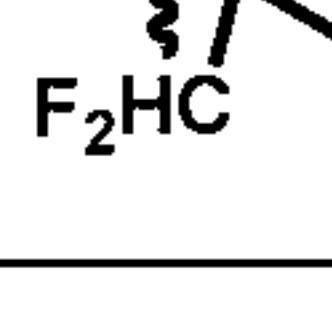
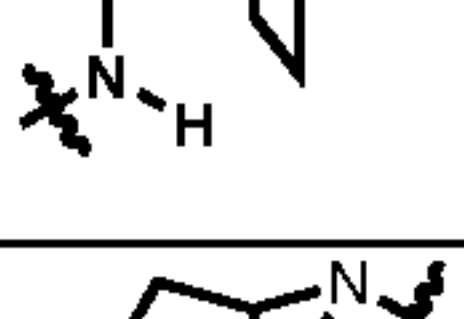
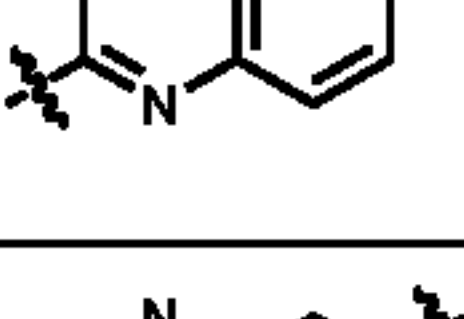
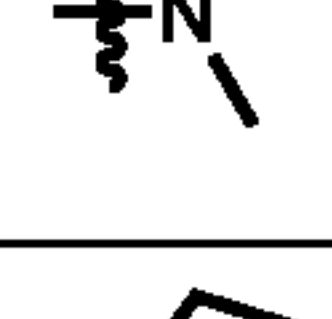
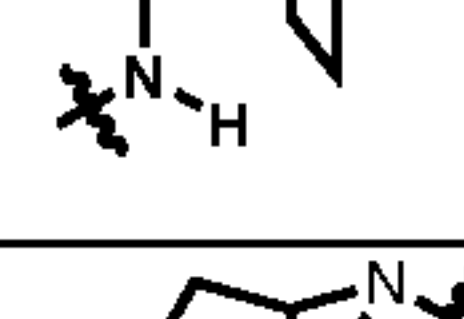
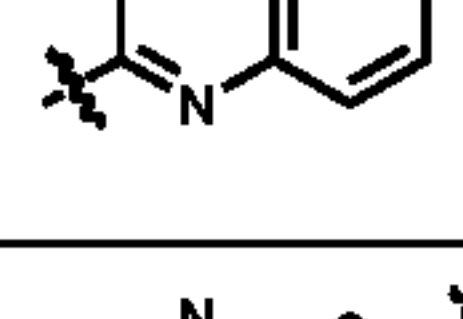
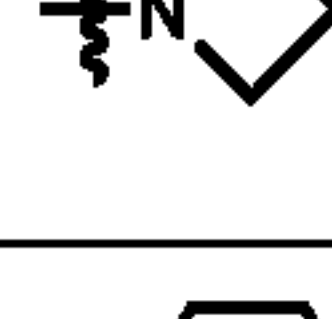
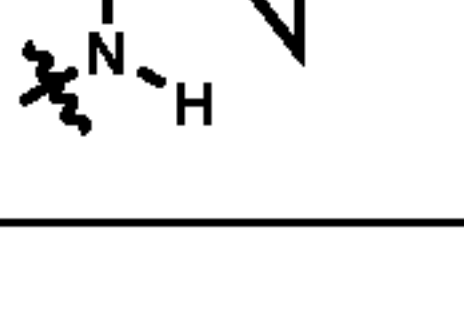
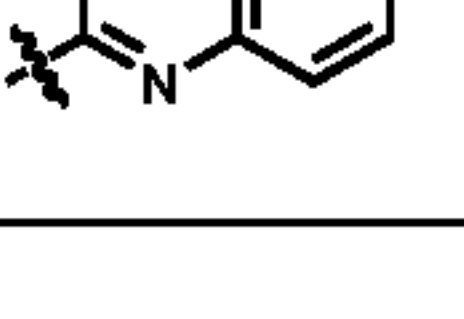
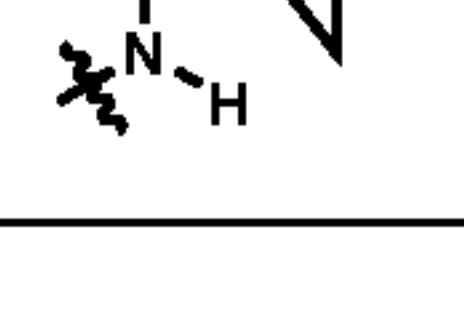
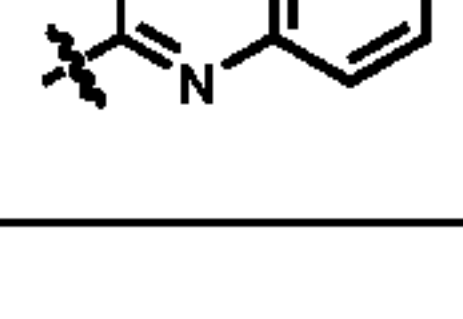
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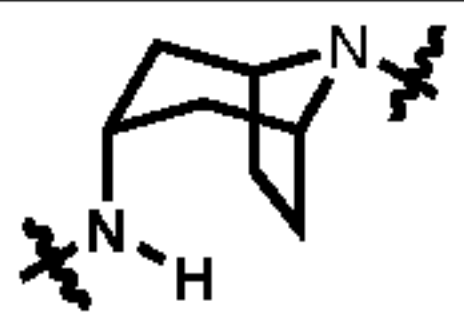
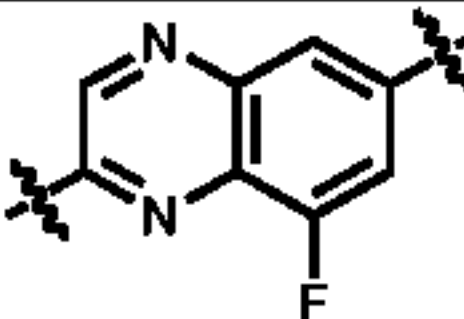
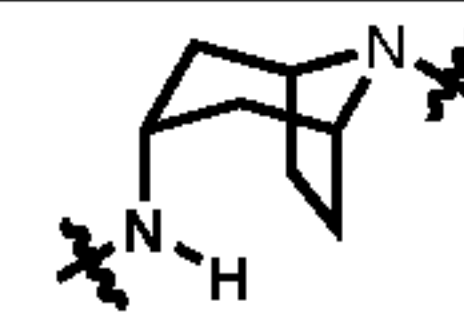
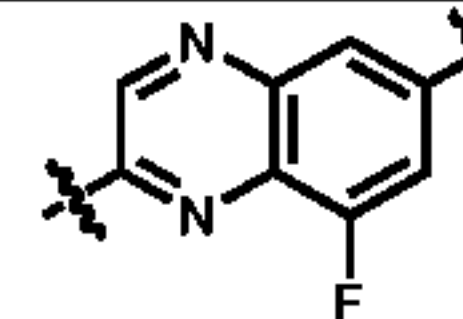
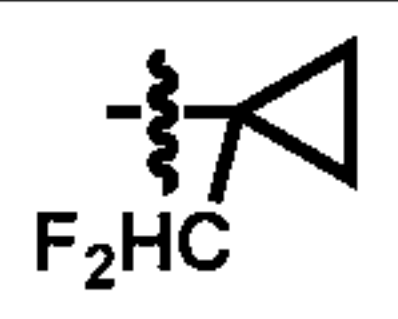
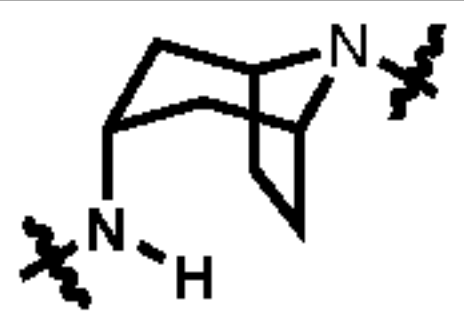
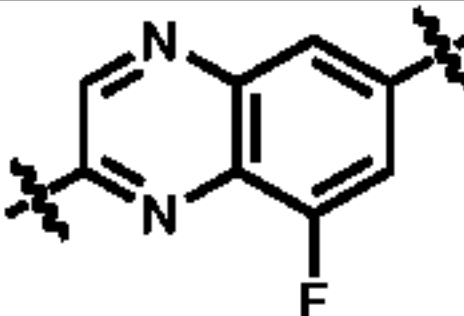
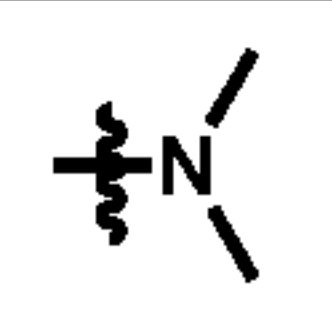
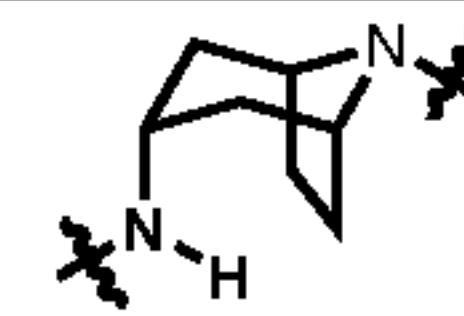
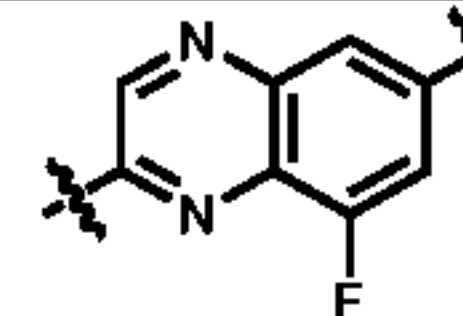
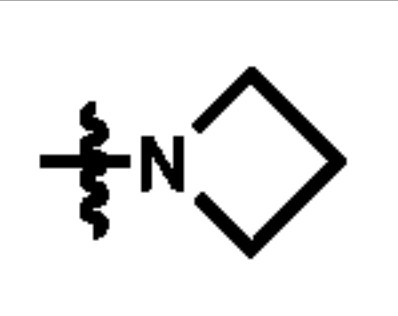
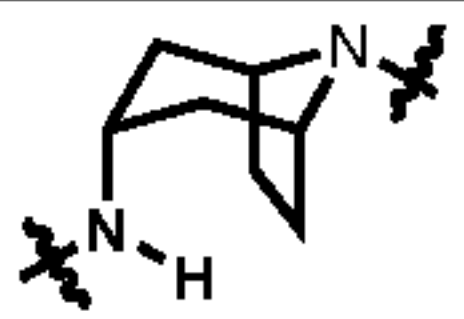
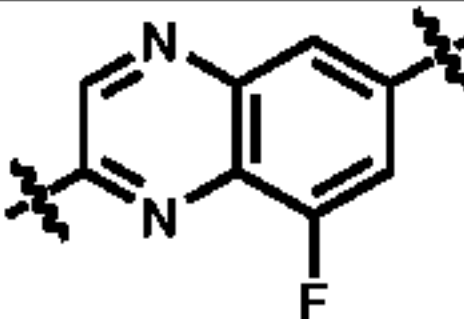
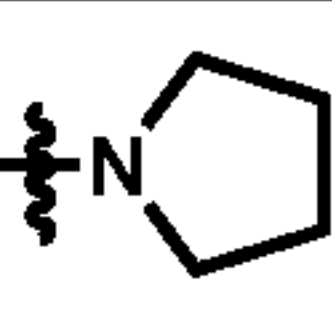
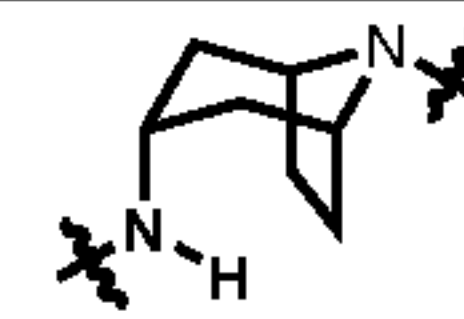
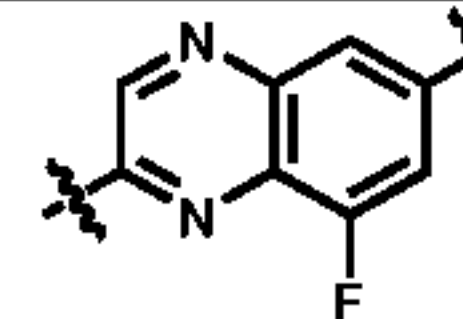
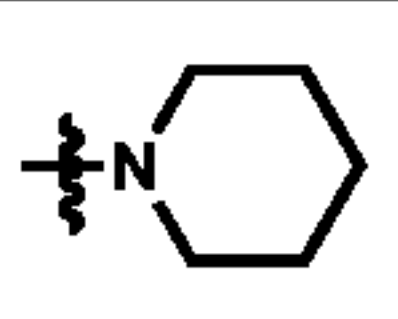
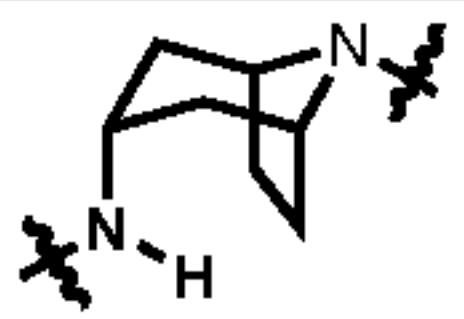
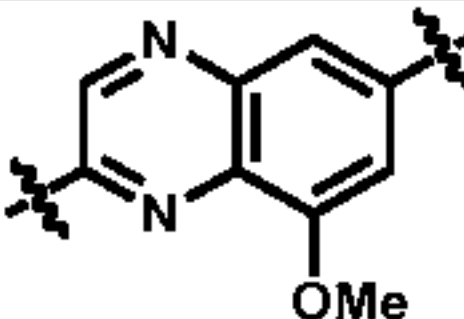
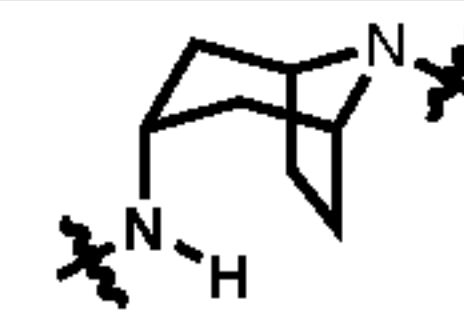
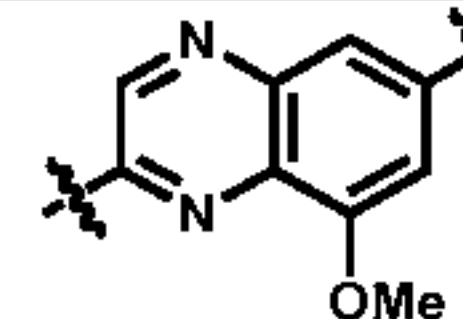
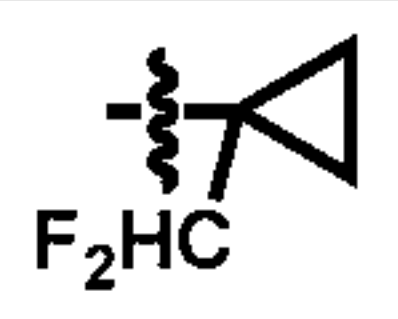
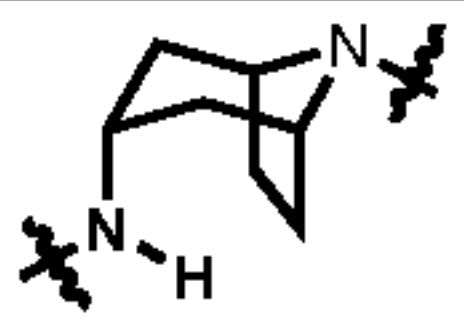
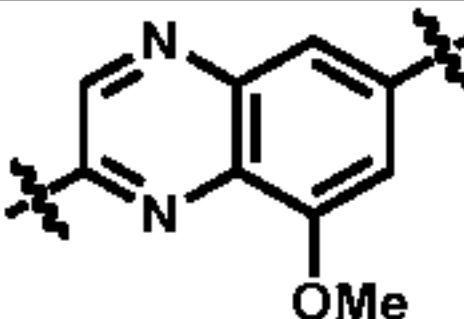
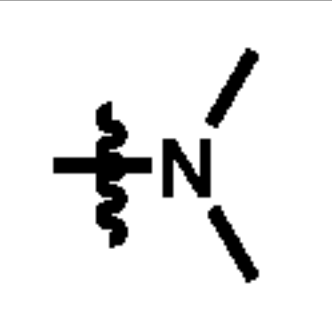
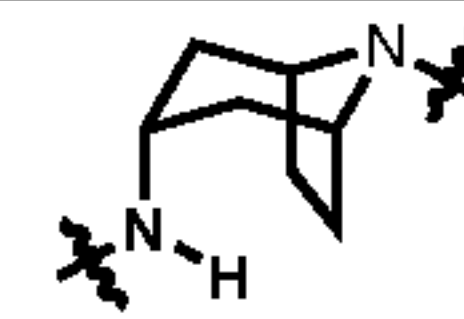
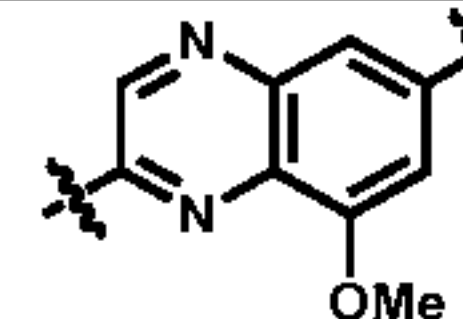
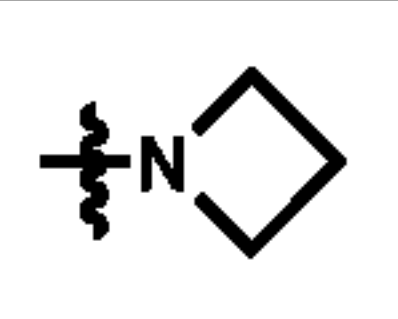
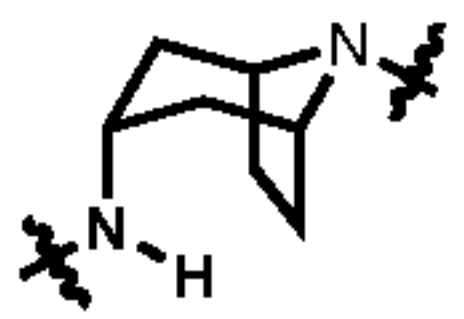
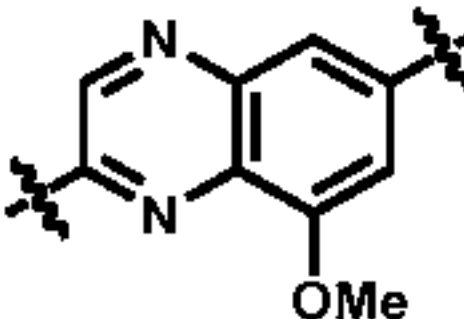
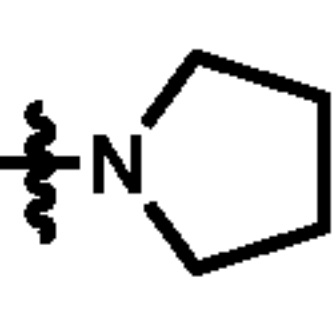
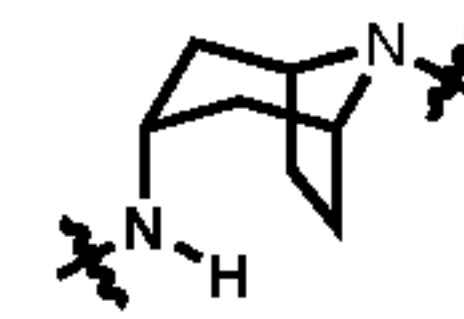
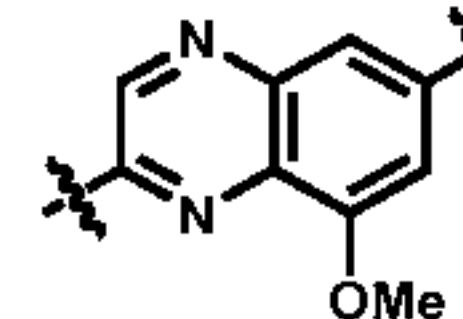
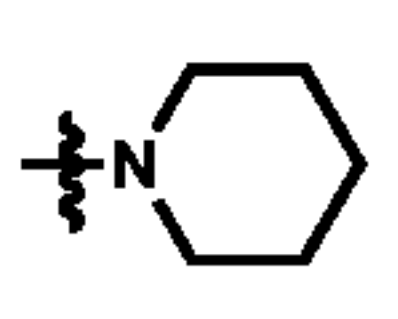
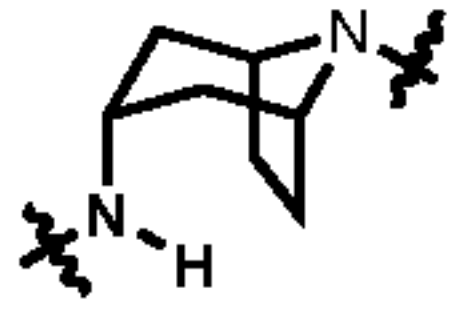
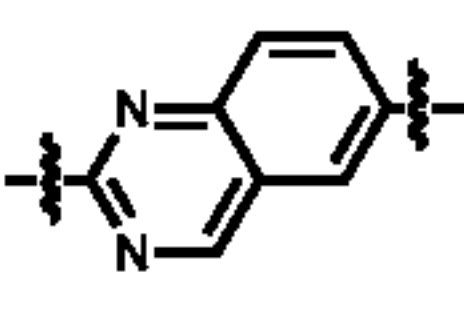
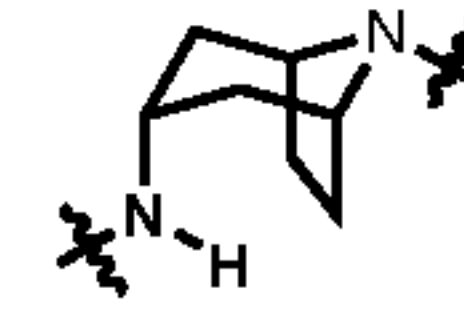
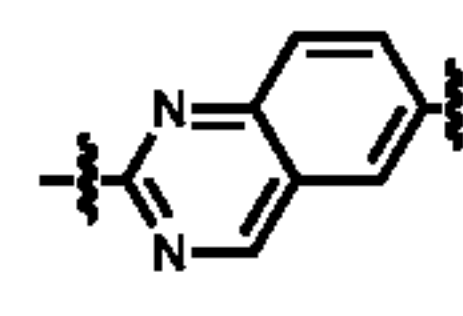
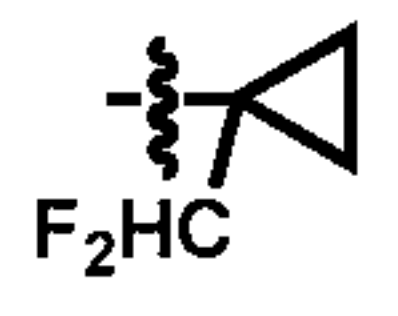
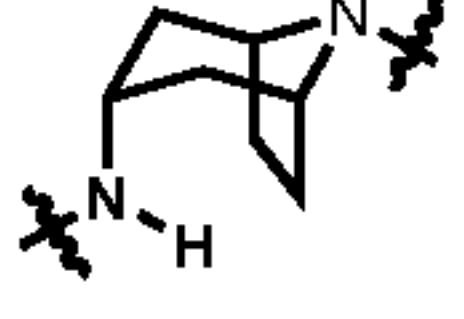
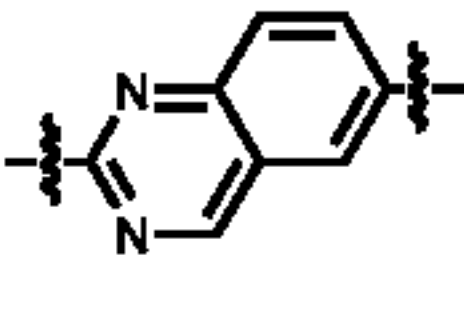
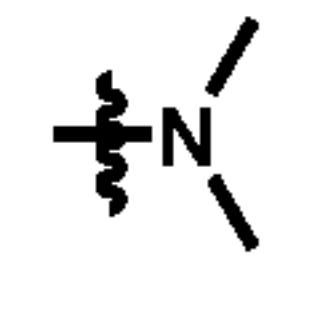
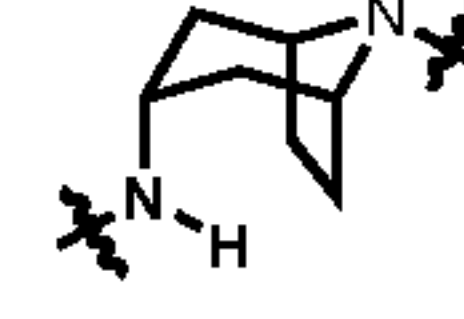
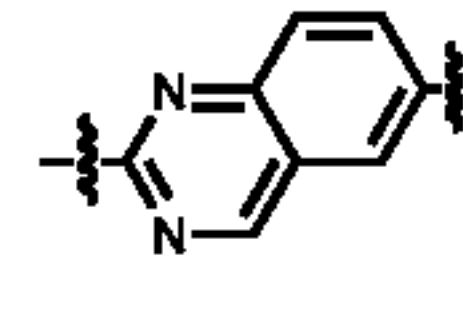
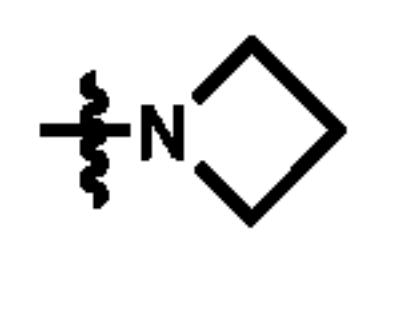
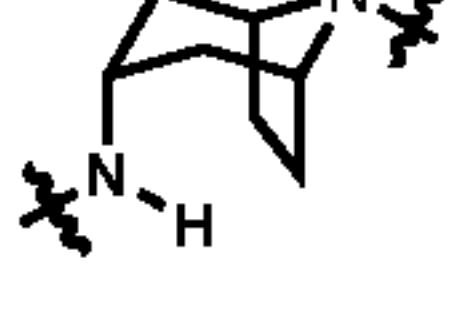
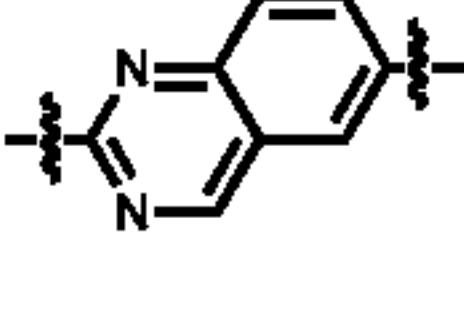
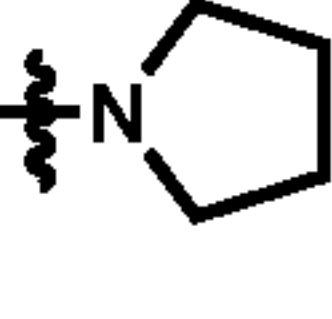
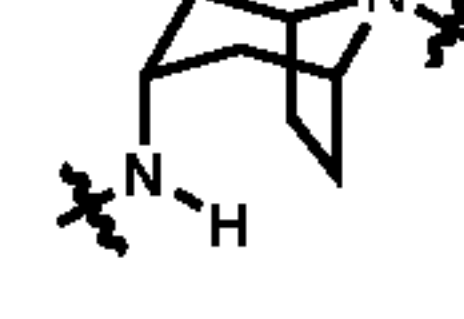
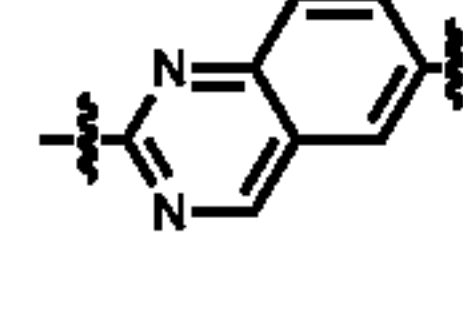
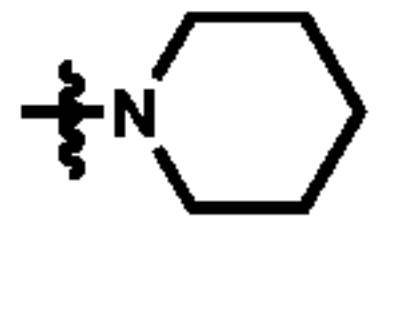
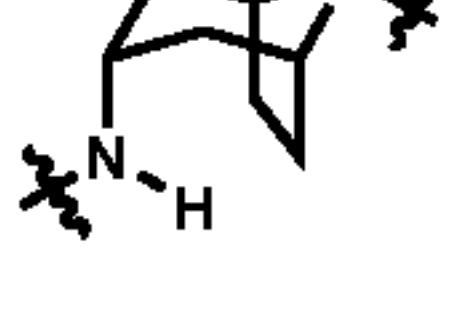
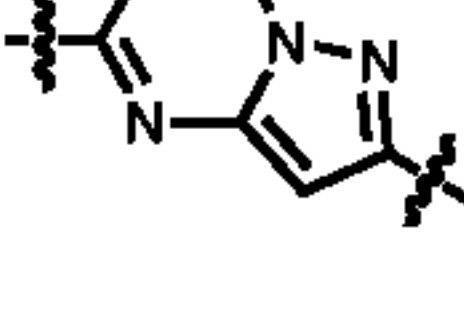
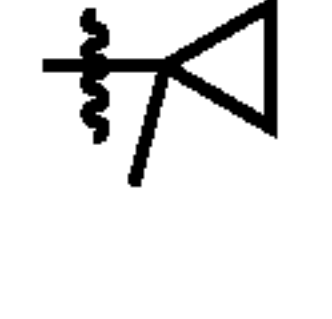
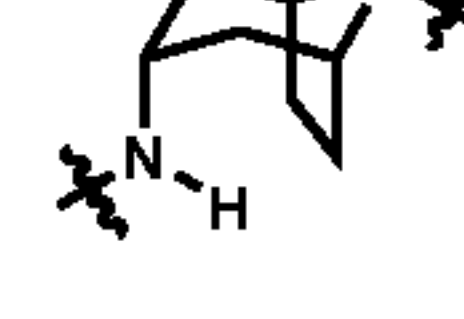
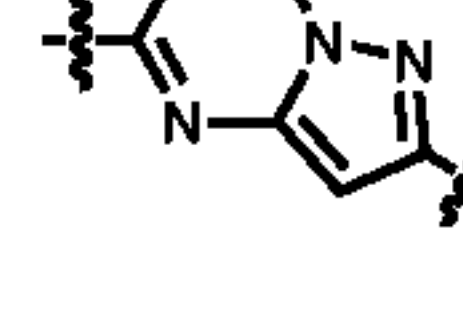
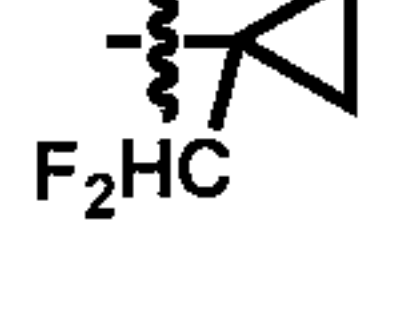
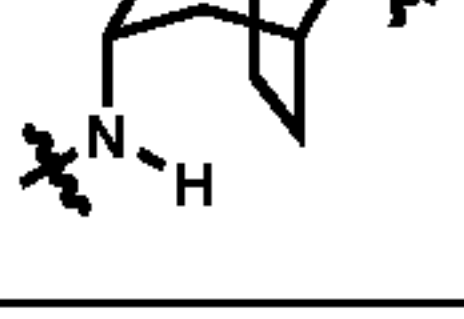
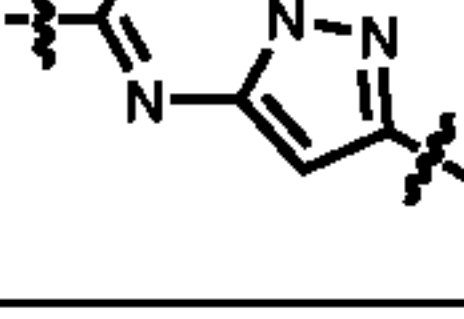
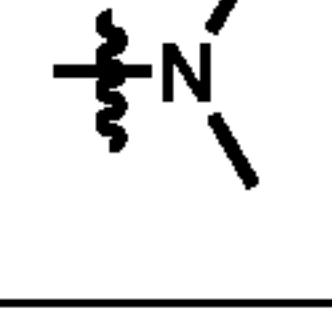
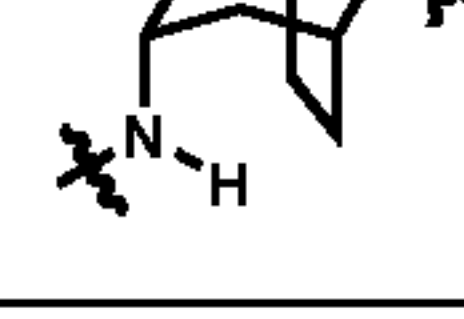
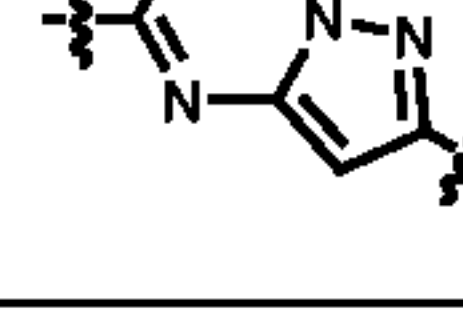
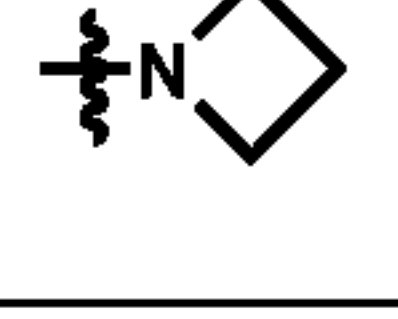
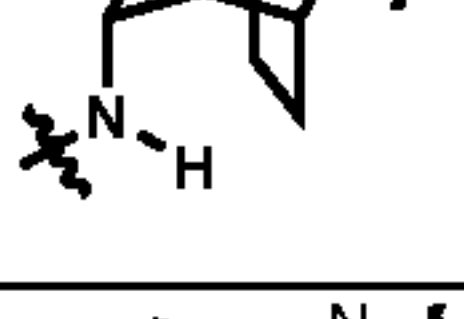
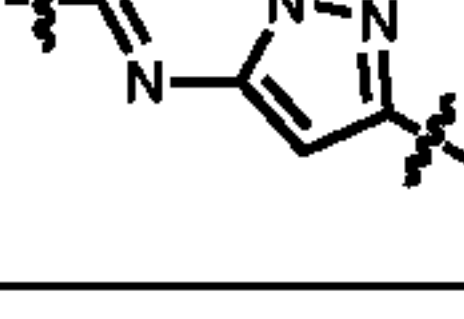
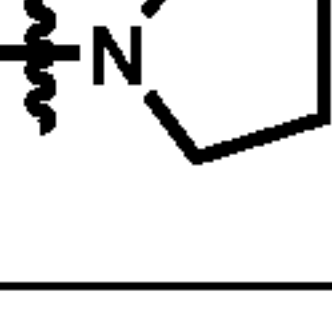
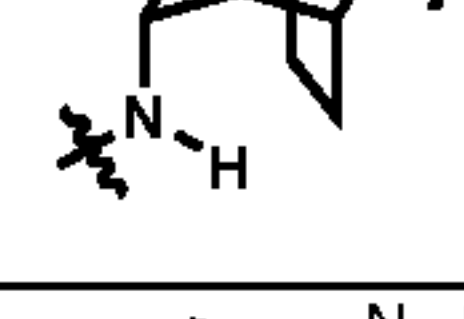
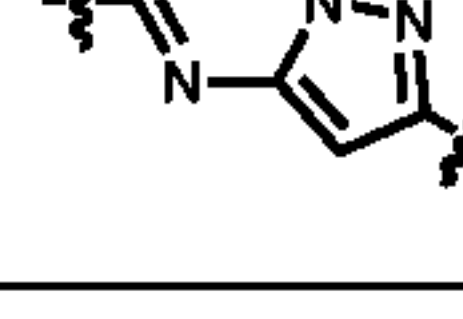
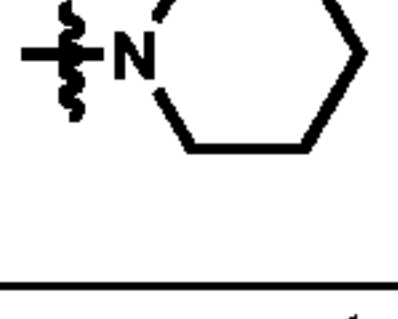
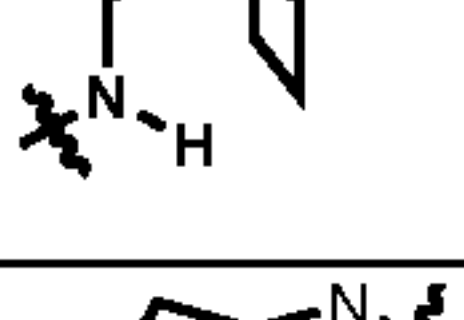
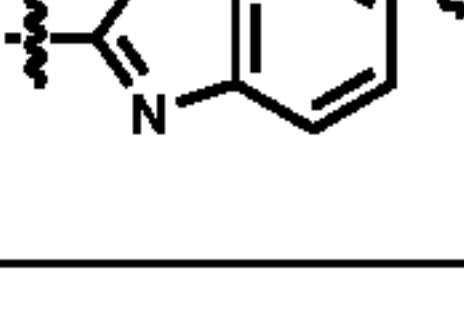
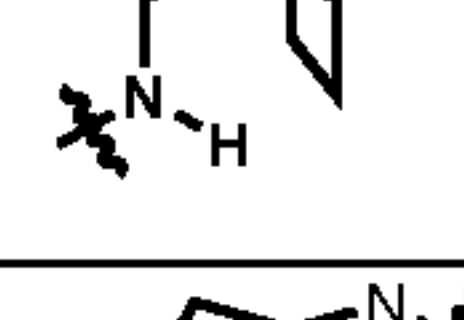
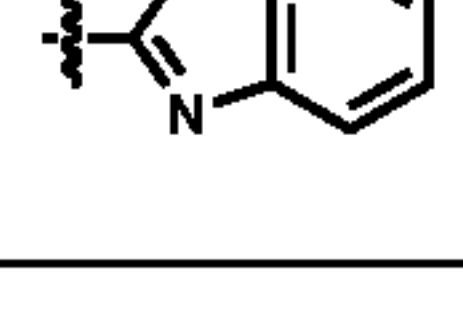
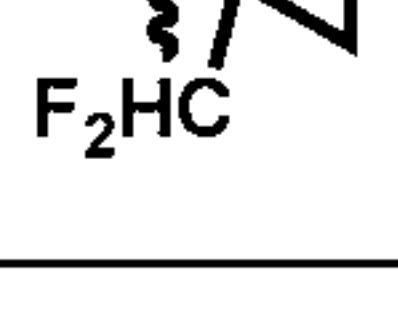
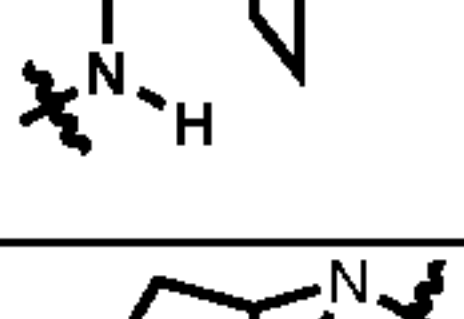
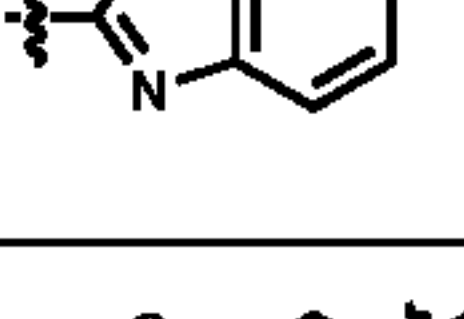
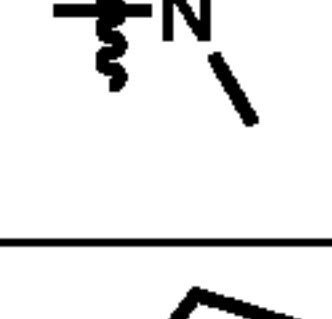
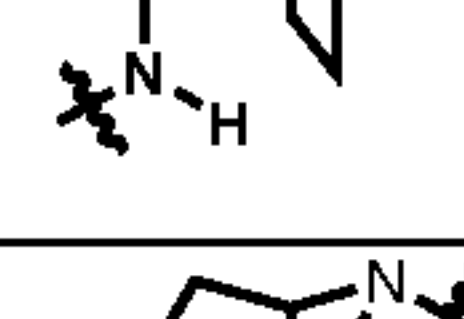
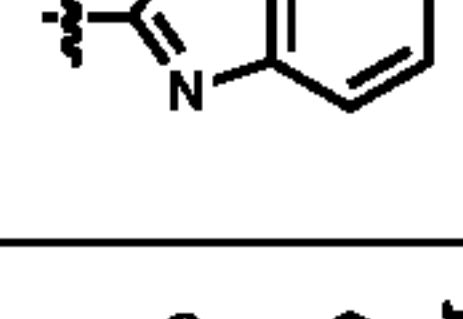
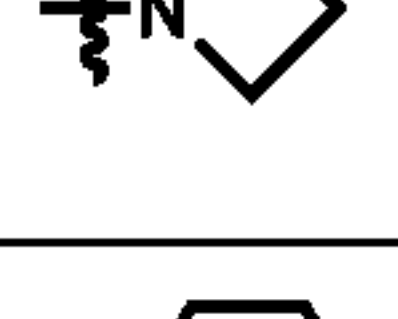
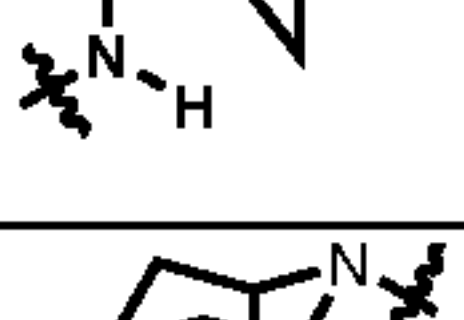
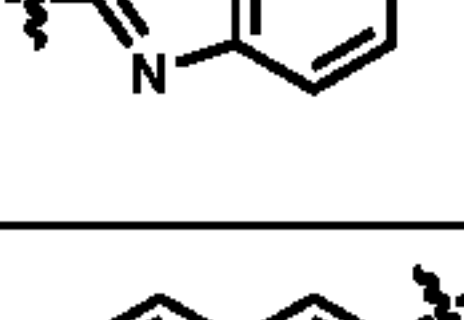
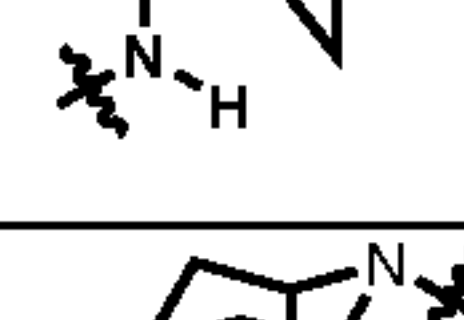
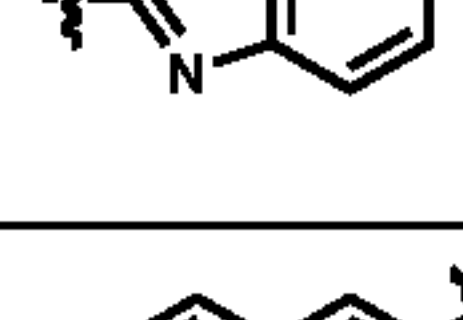
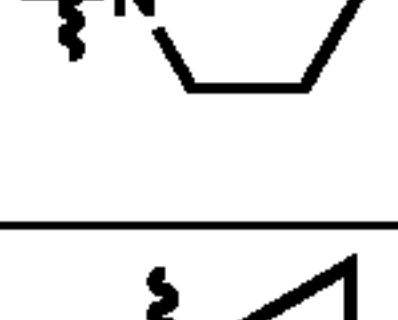
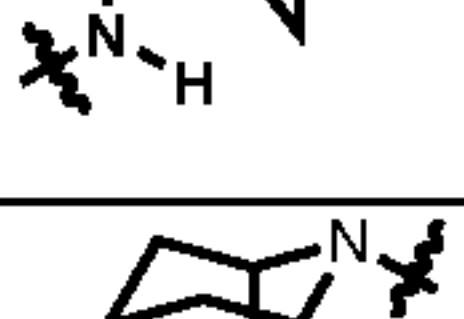
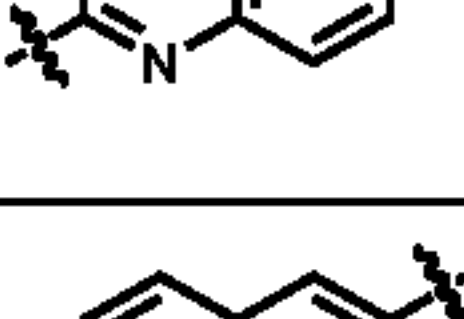
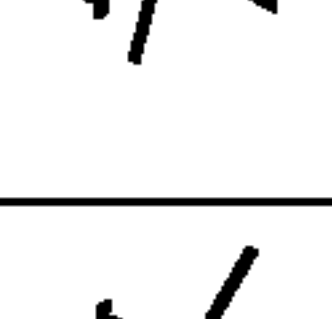
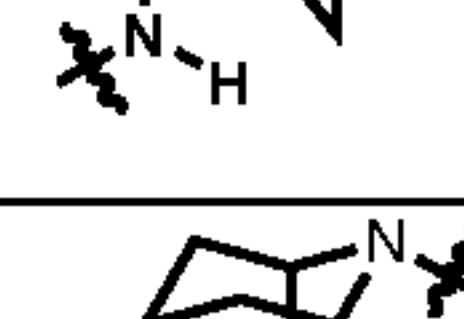
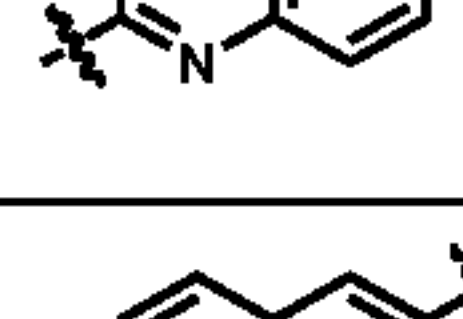
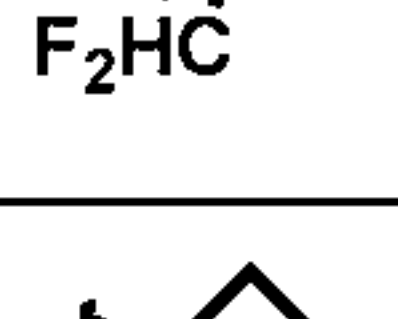
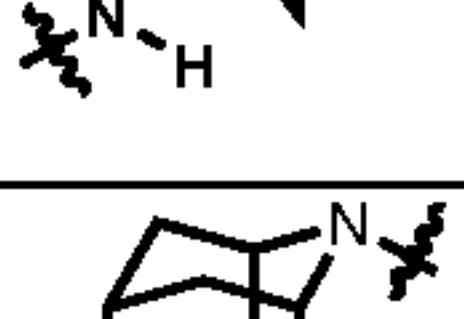
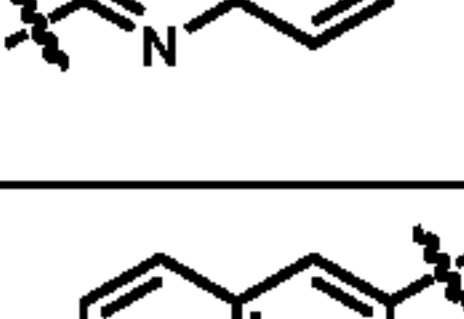
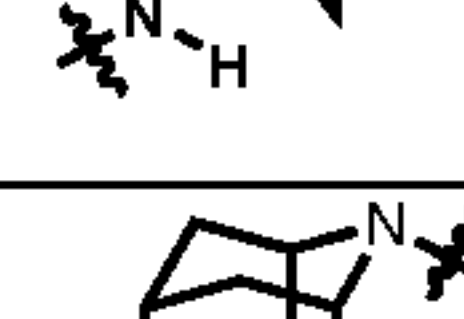
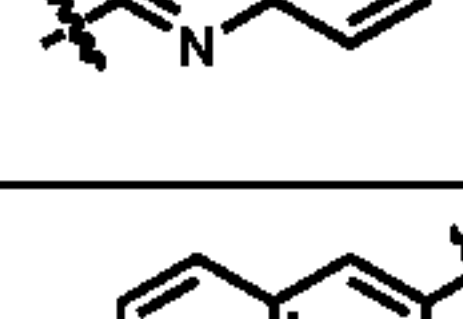
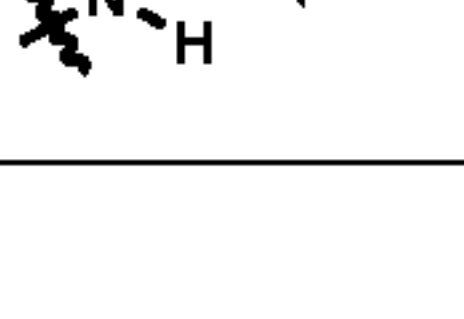
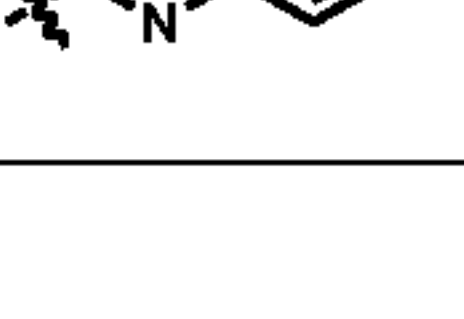
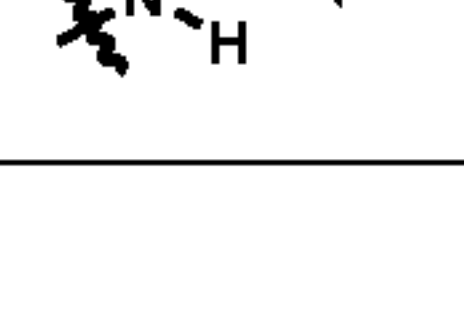
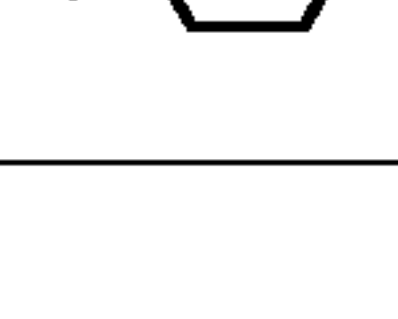
Compound	A	B	R ⁷	Compound	A	B	R ⁷
1201				1202			
1203				1204			
1205				1206			
1207				1208			
1209				1210			
1211				1212			
1213				1214			

1215				1216			
1217				1218			
1219				1220			
1221				1222			
1223				1224			
1225				1226			
1227				1228			
1229				1230			
1231				1232			
1233				1234			
1235				1236			
1237				1238			
1239				1240			
1241				1242			
1243				1244			
1245				1246			

1247				1248			
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1293				1294			
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1297				1298			
1299				1300			
1301				1302			
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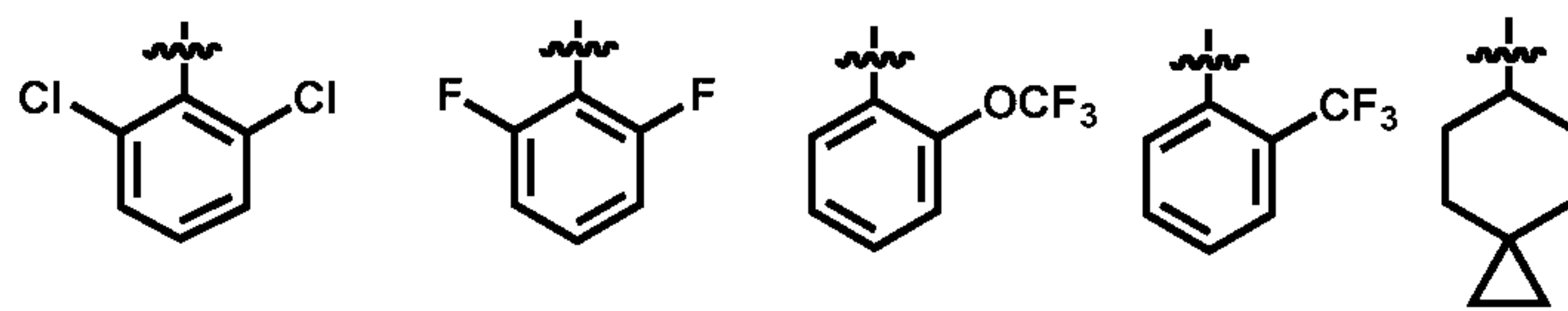
1317				1318			
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1371				1372			
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1397				1398			
1399				1400			

or a pharmaceutically acceptable salt thereof.

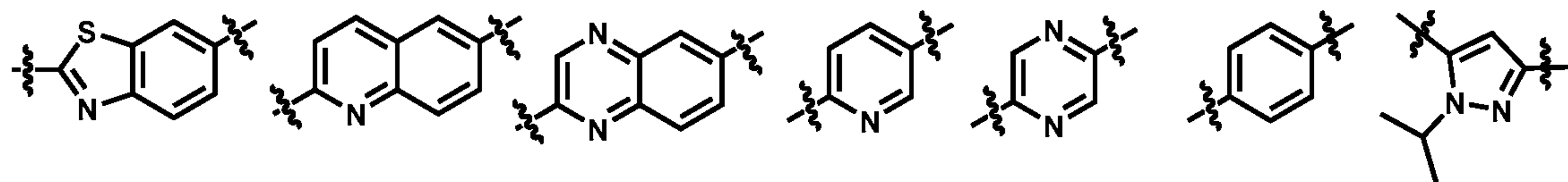
13. The compound of claim 1, wherein R^1 is optionally substituted cyclopropyl; R^2 is



selected from

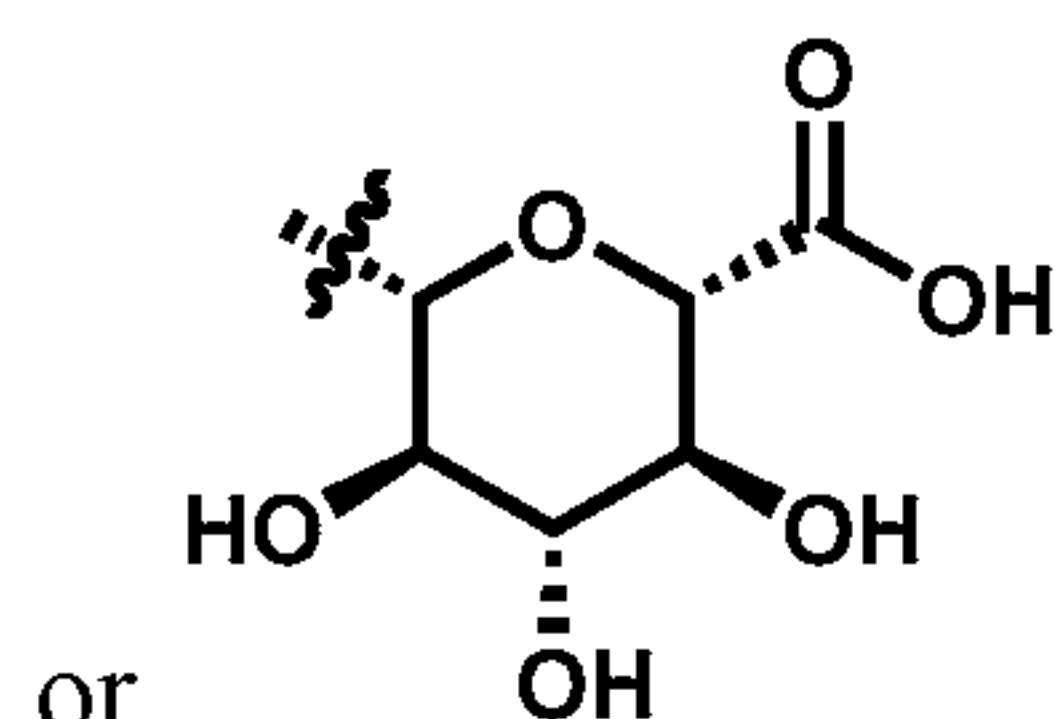
; R^{3a} is hydrogen; R^{3b}

5 is hydrogen; A is or , R^{3c} is hydrogen, or methyl; B is selected from:



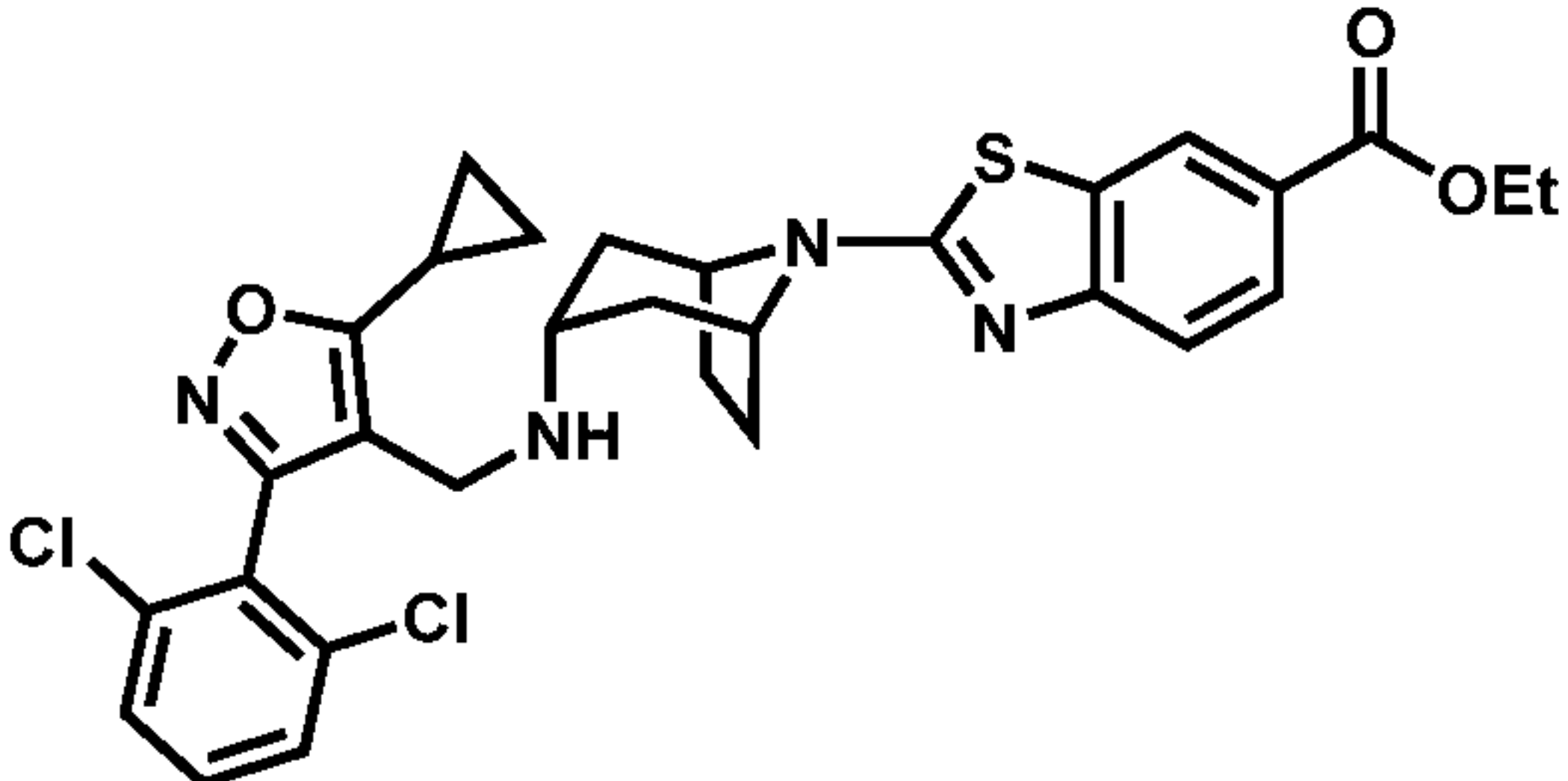
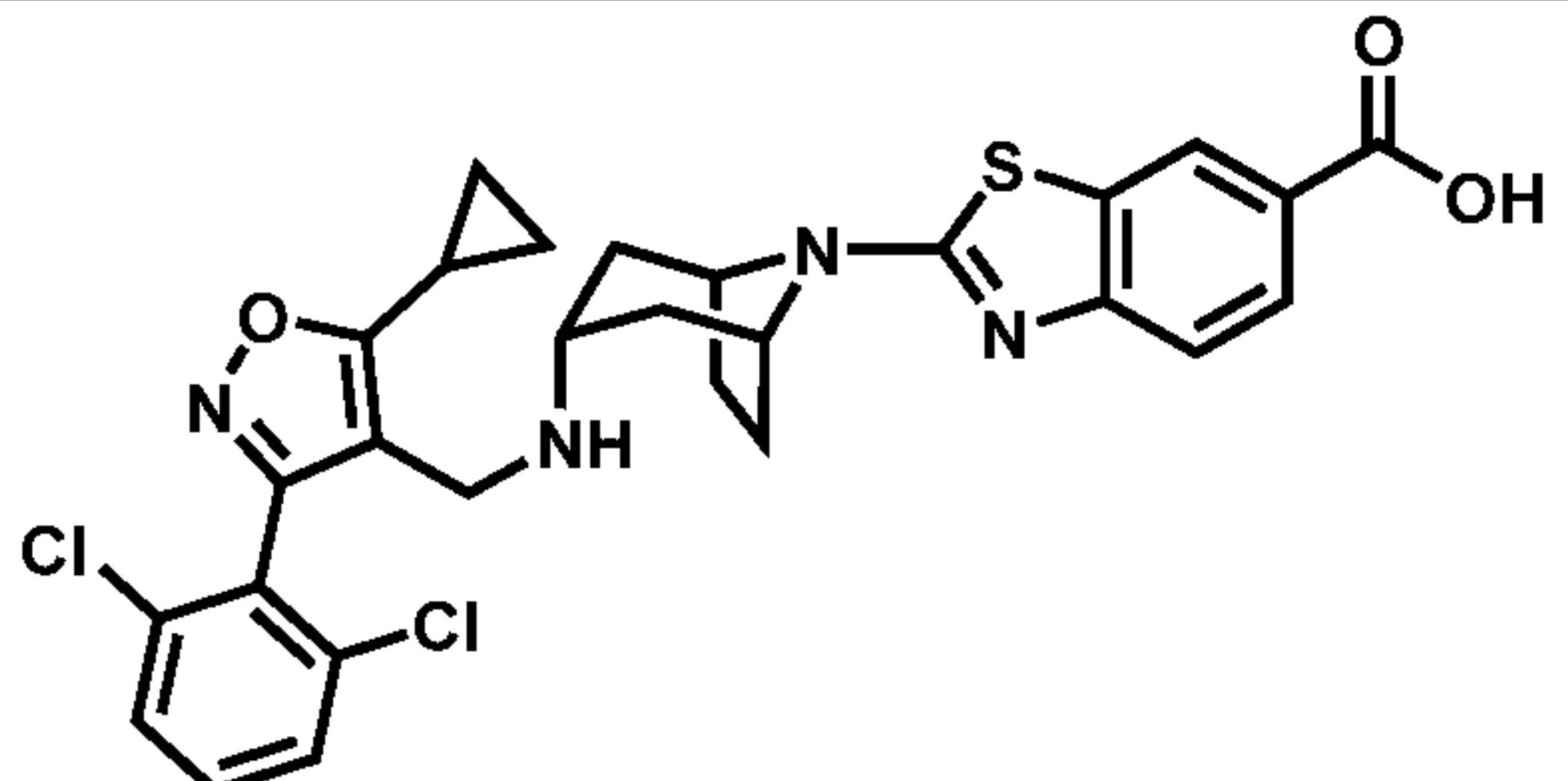
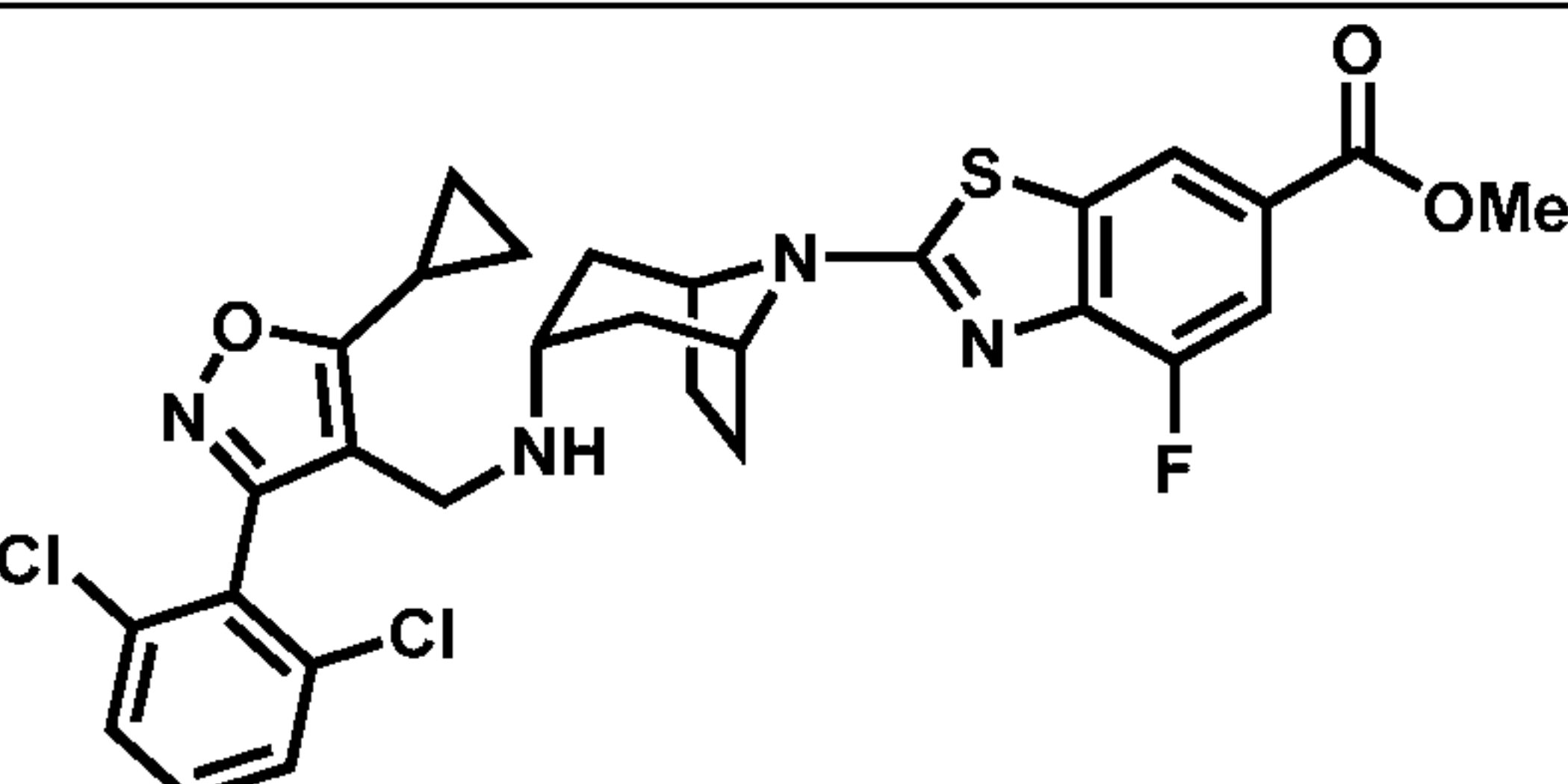
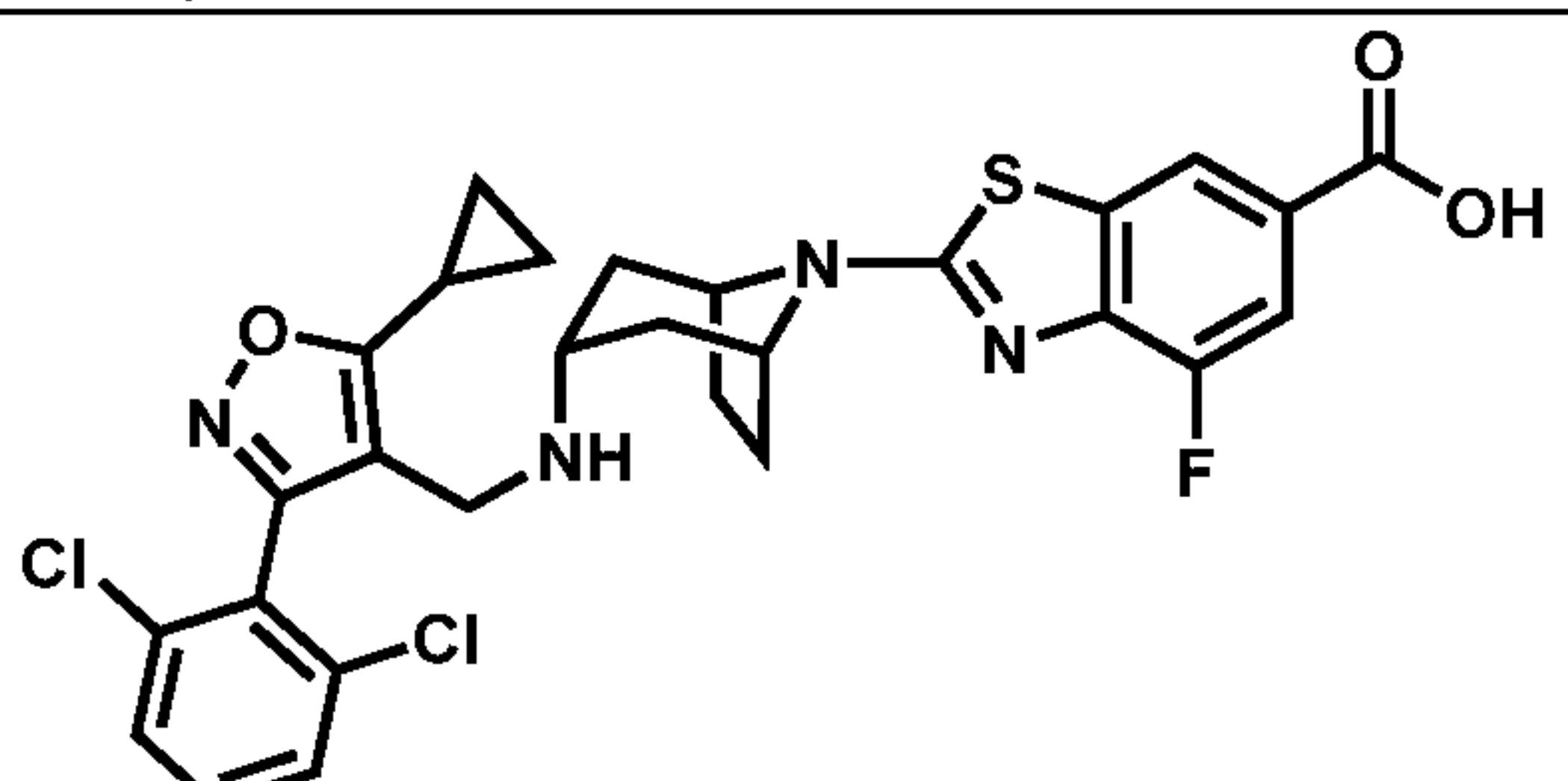
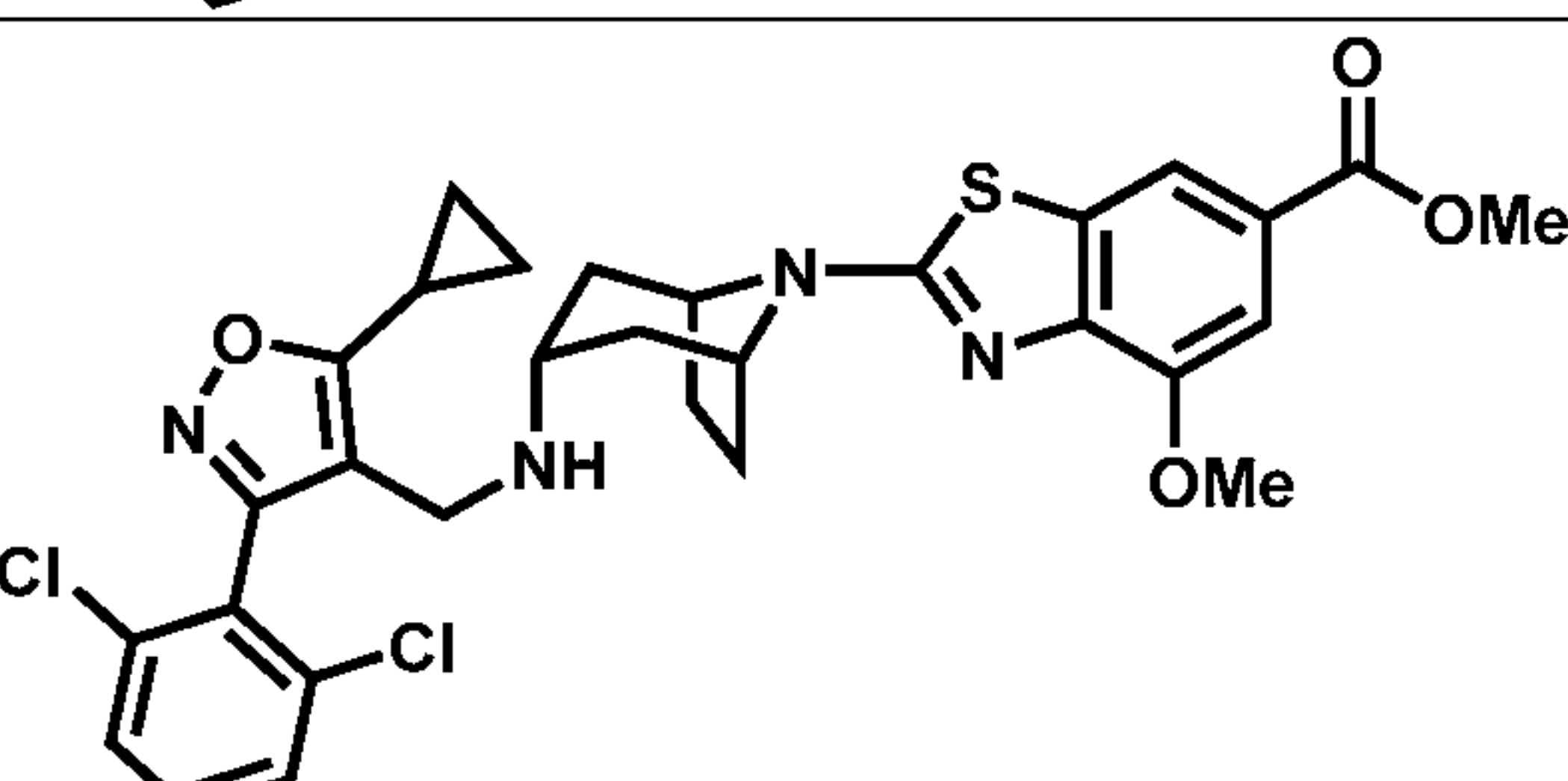
and B is optionally substituted; Z is absent; and R^4 is , ,

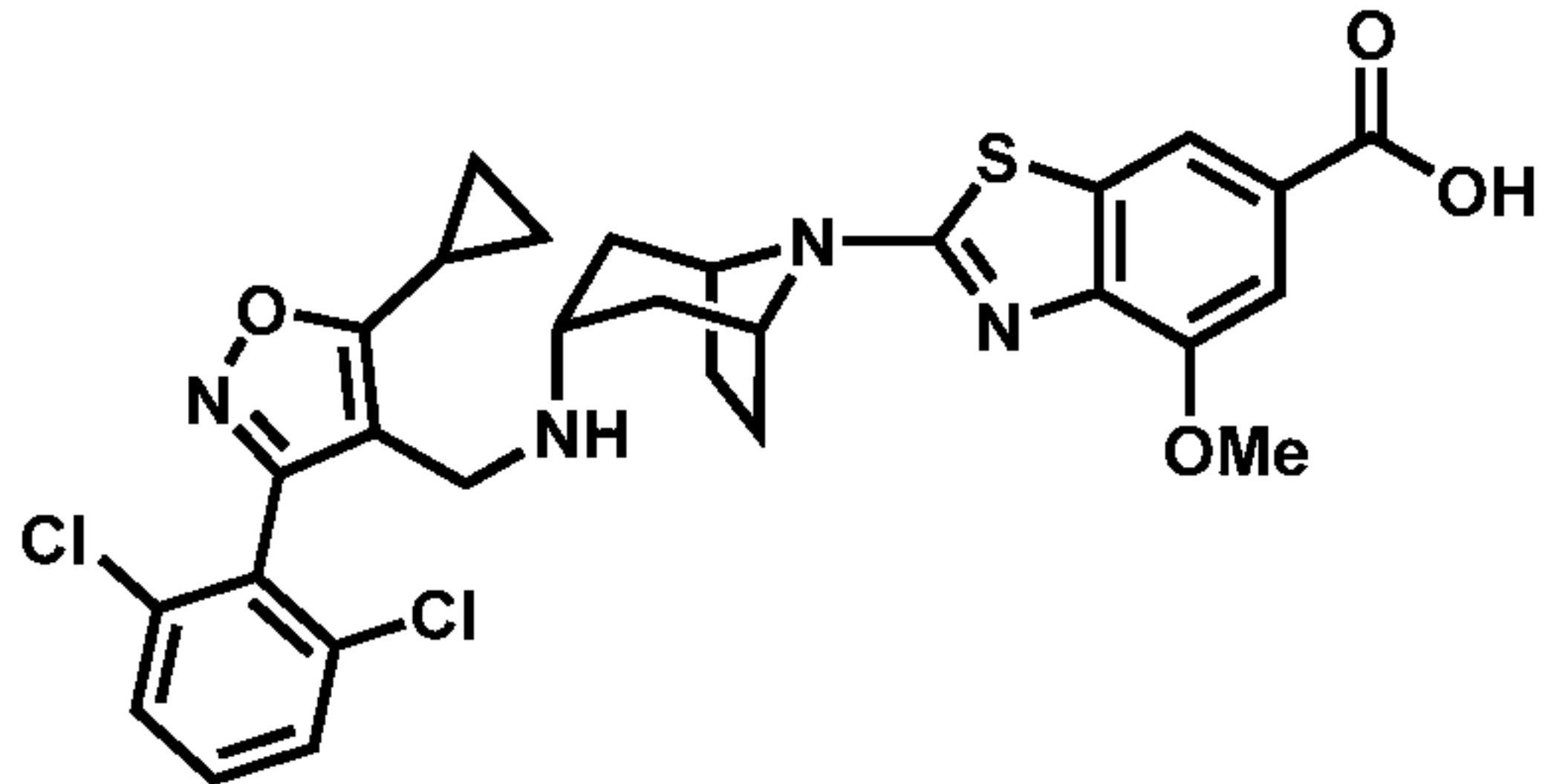
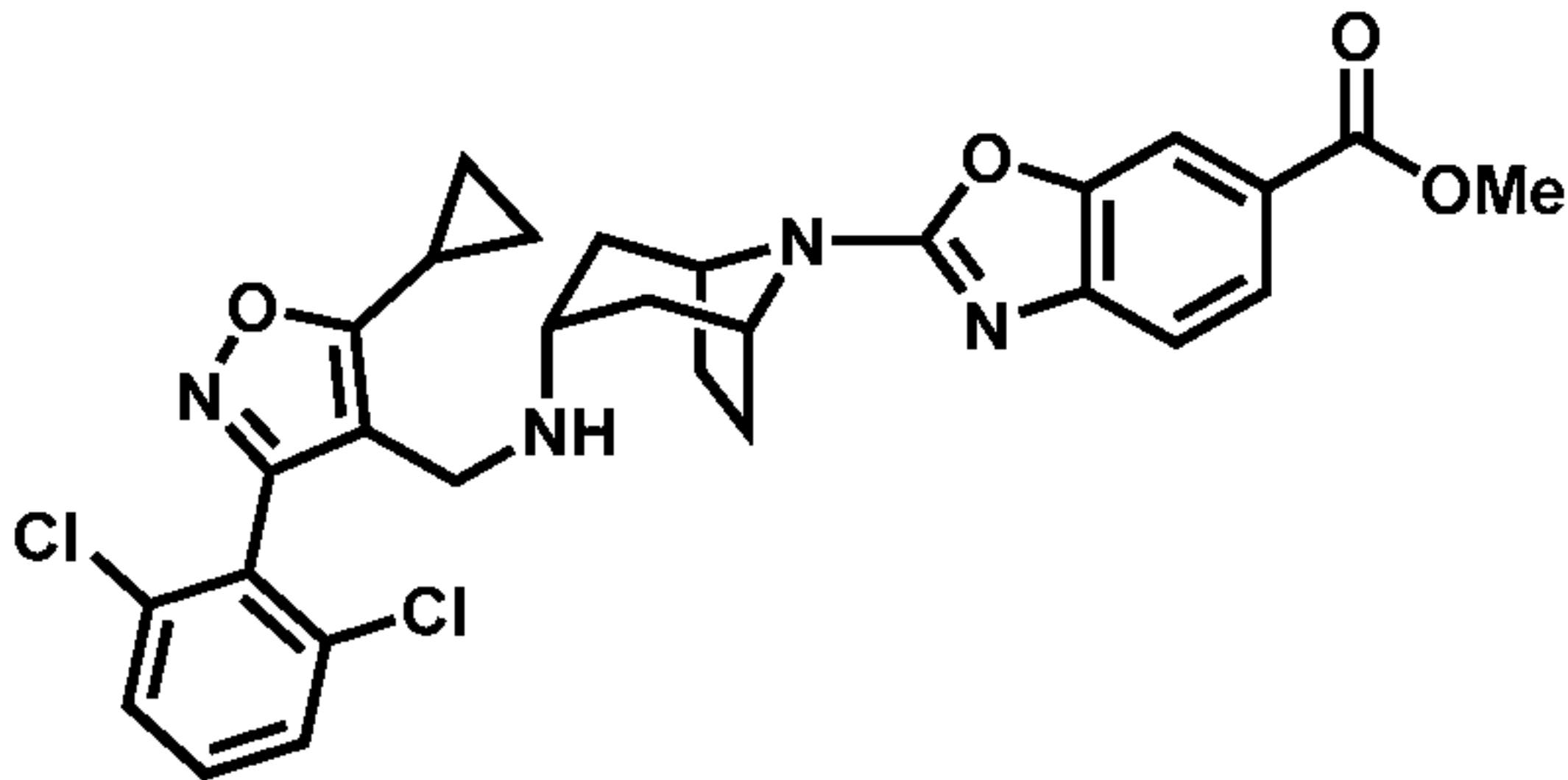
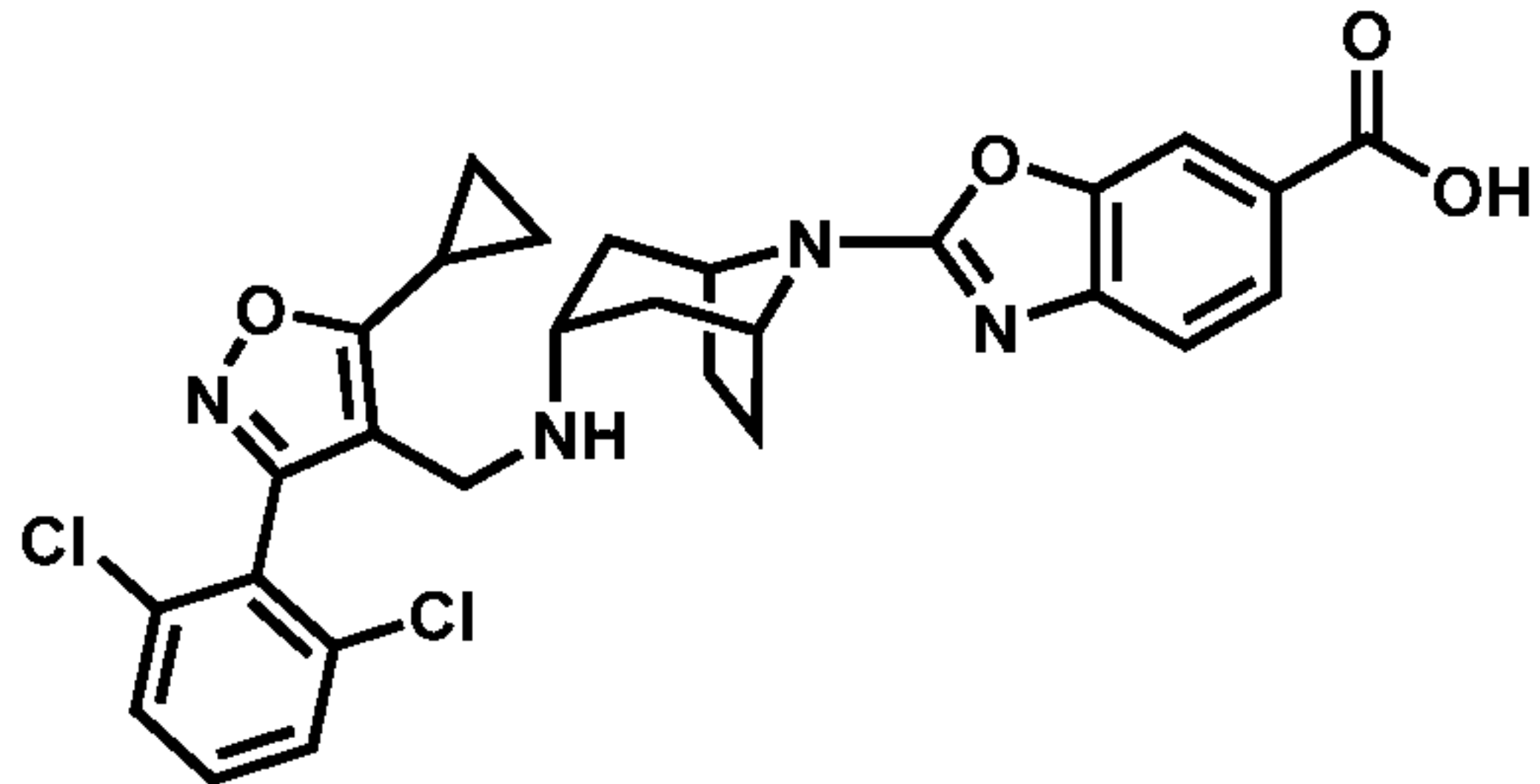
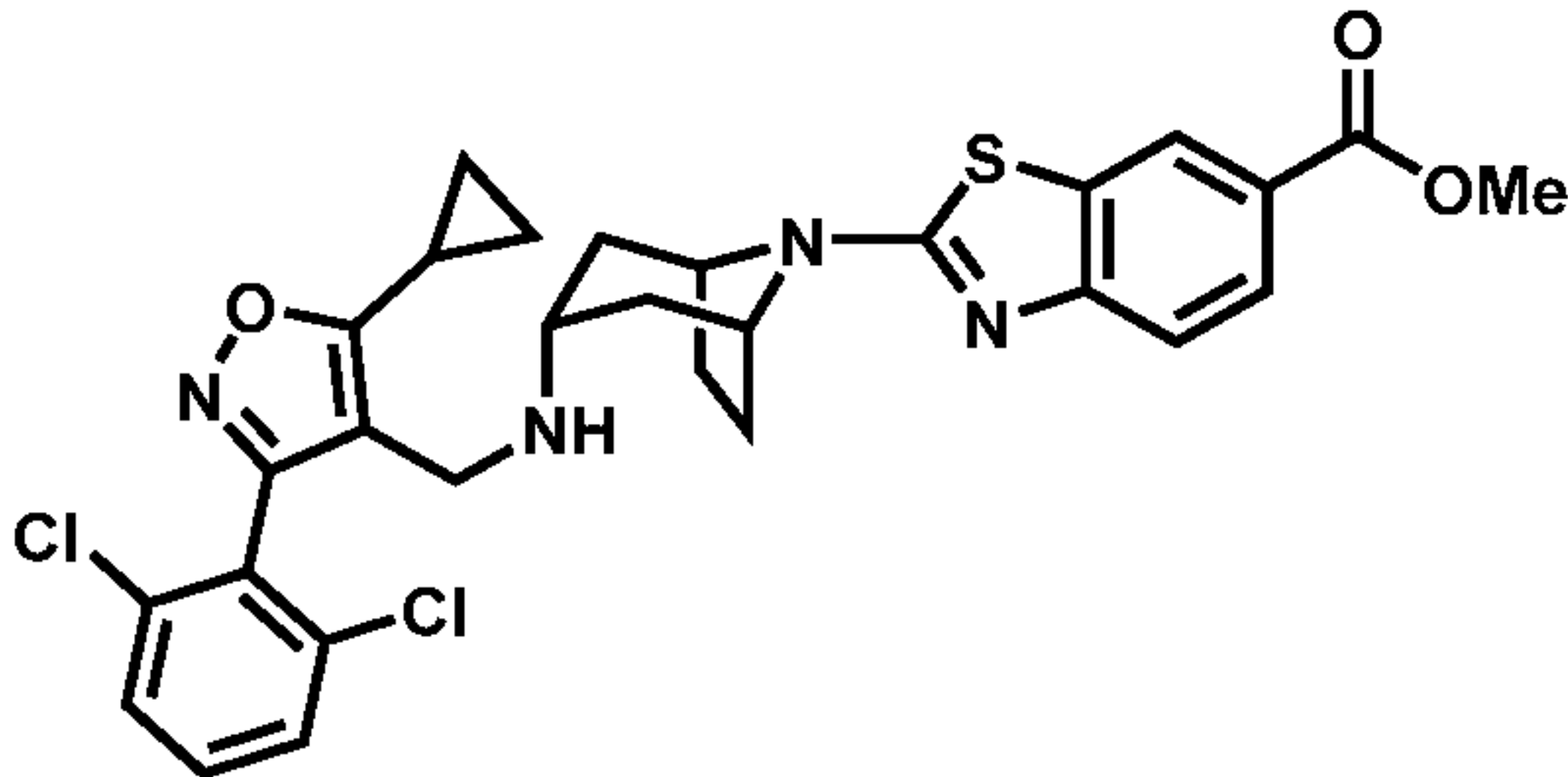
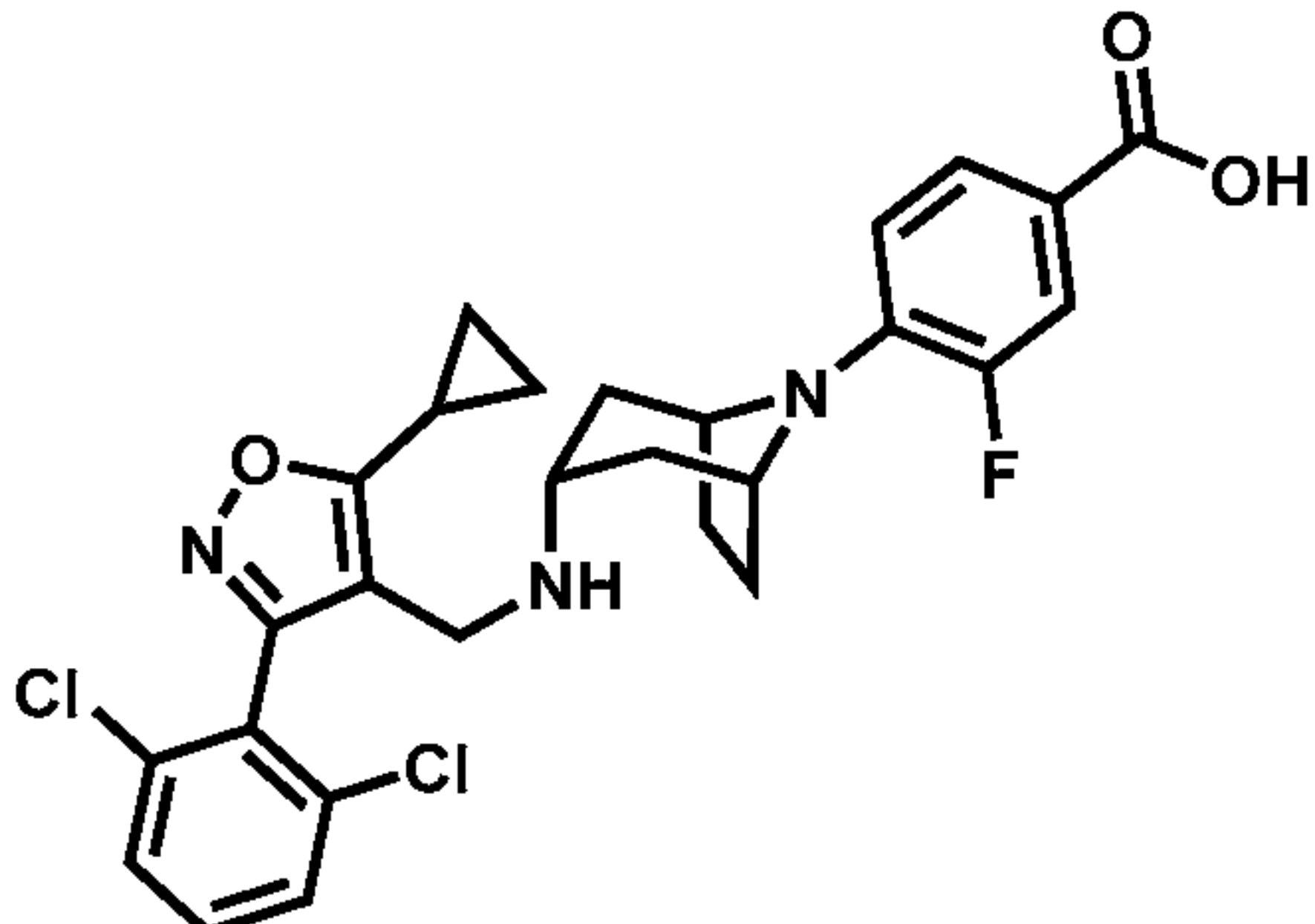
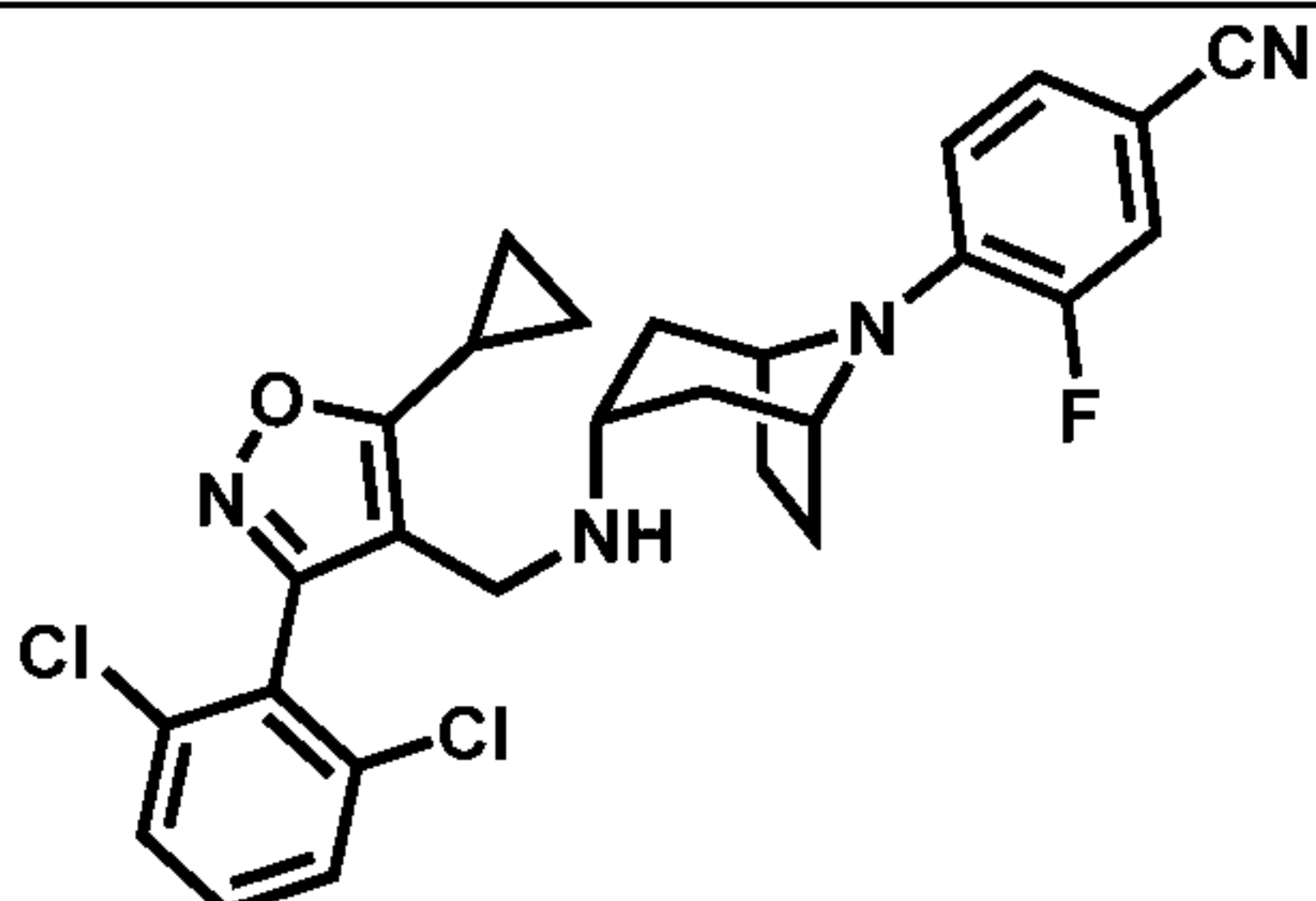
or $-\text{CO}_2R^5$; R^7 is defined in claim 1, and R^5 is hydrogen, methyl, ethyl, t-butyl,



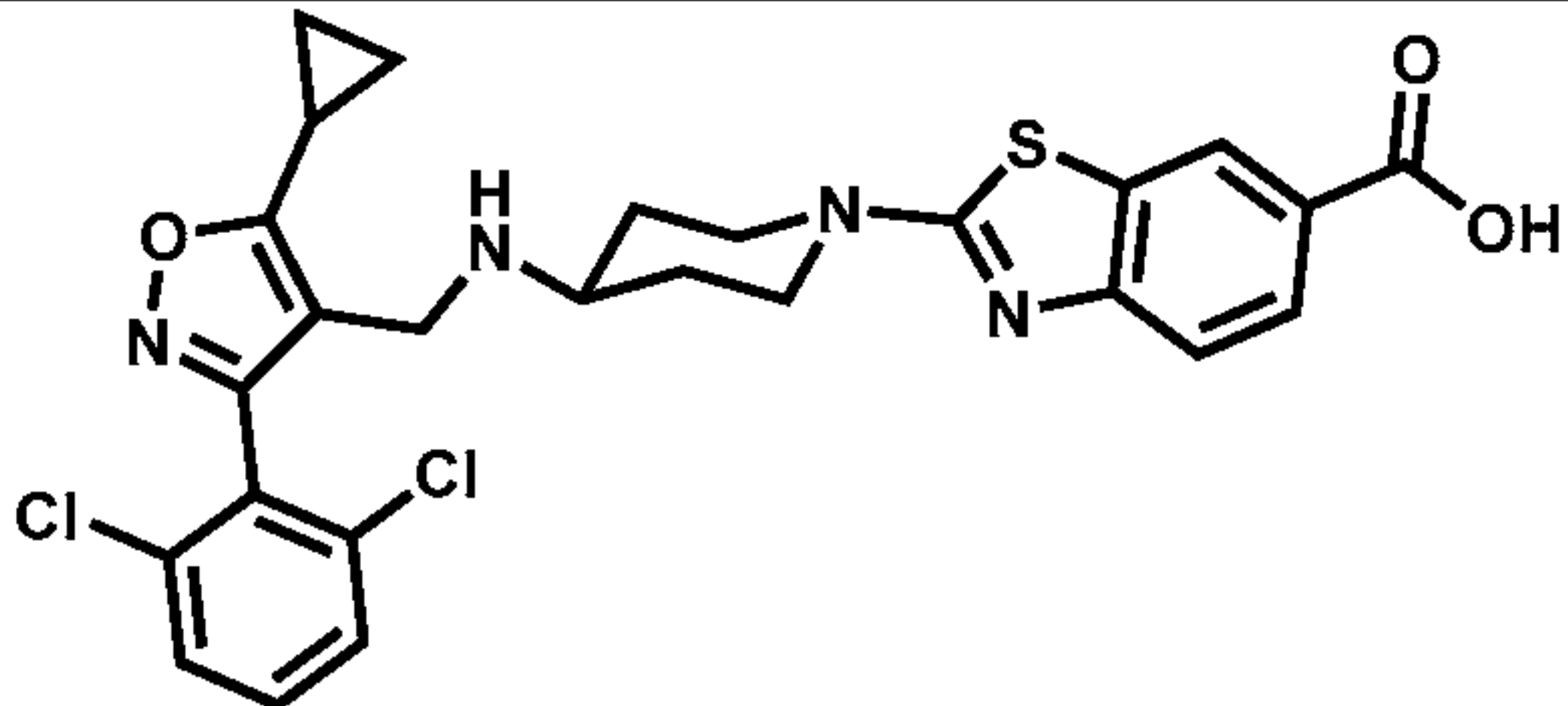
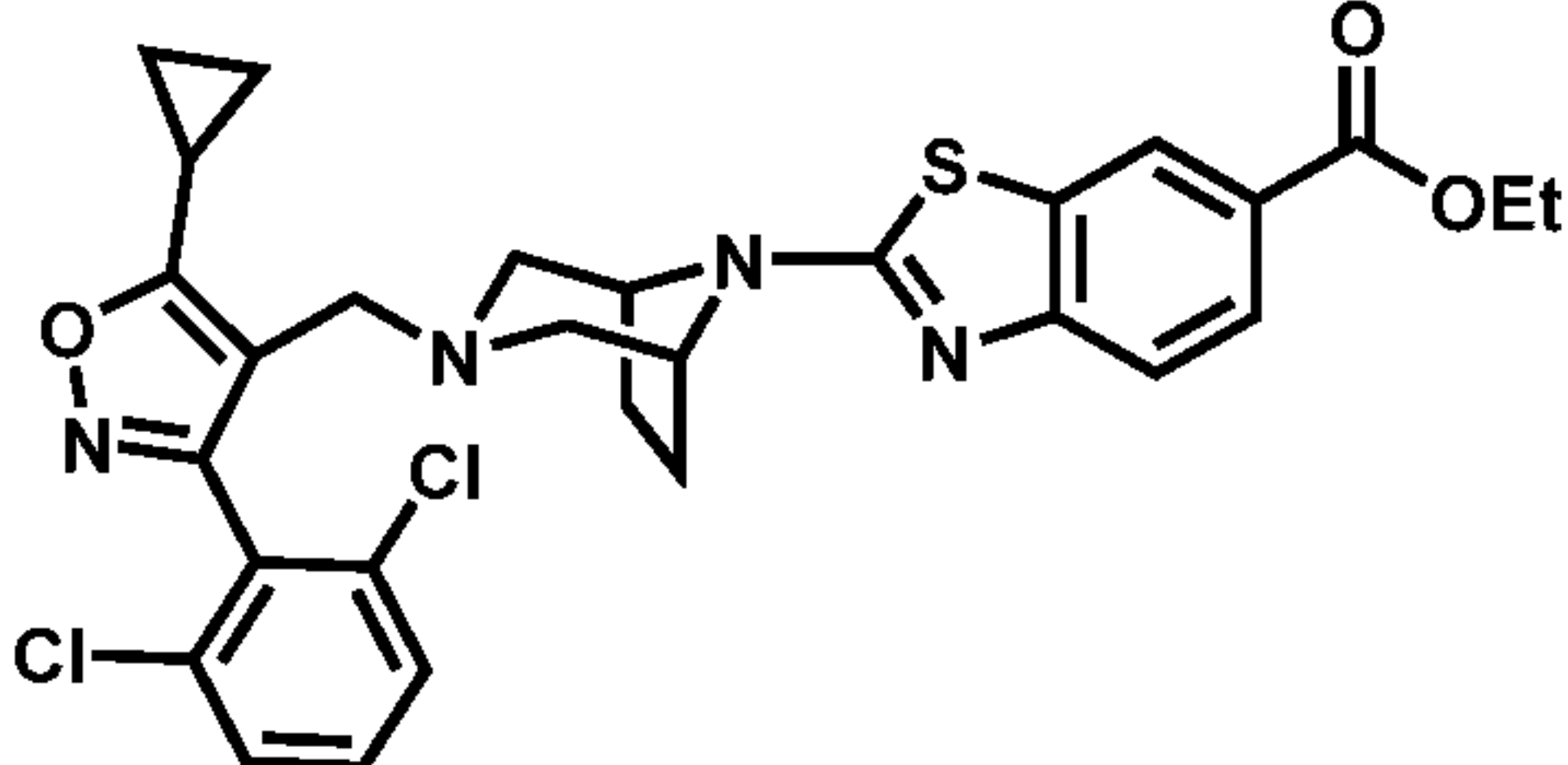
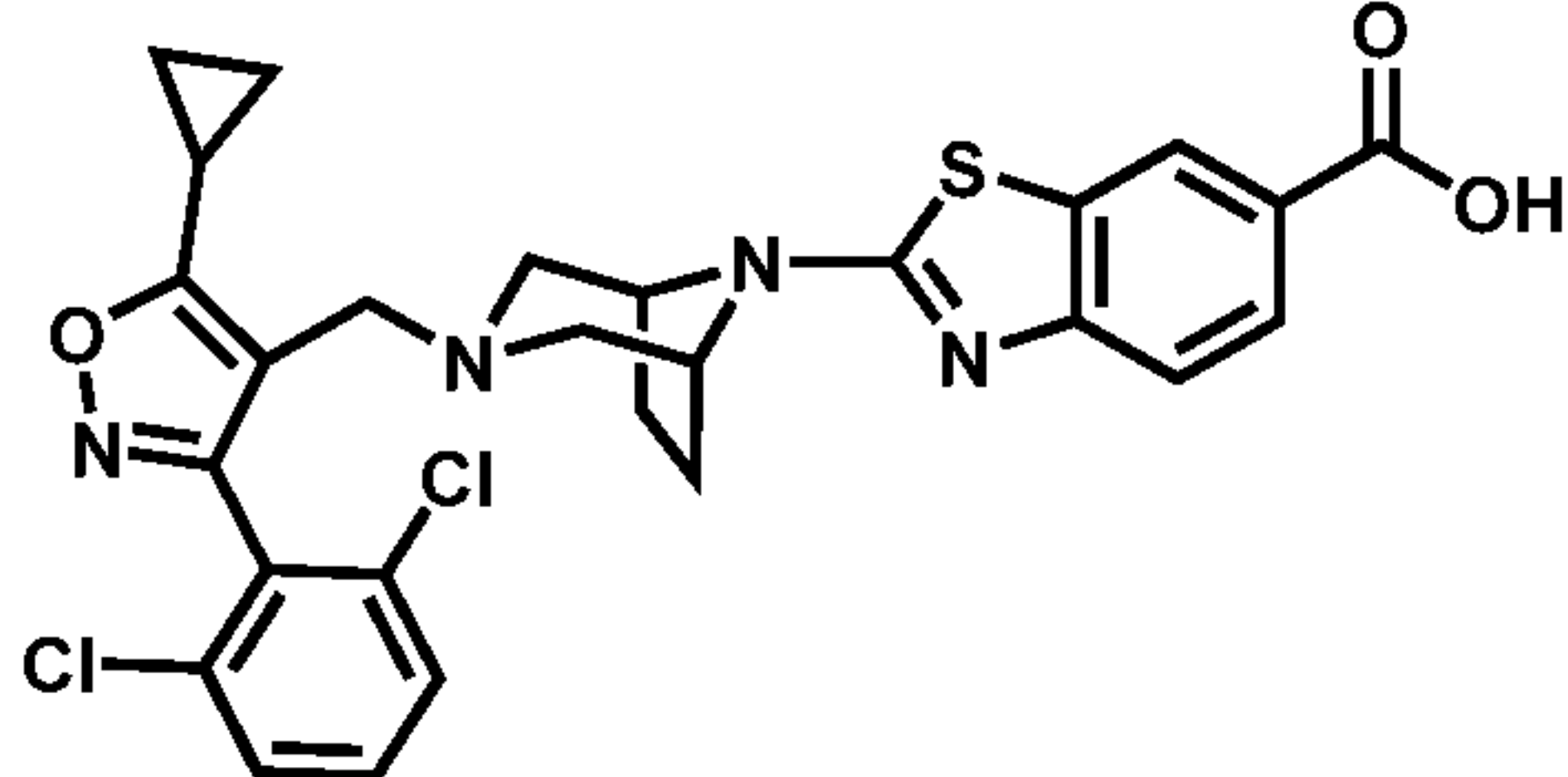
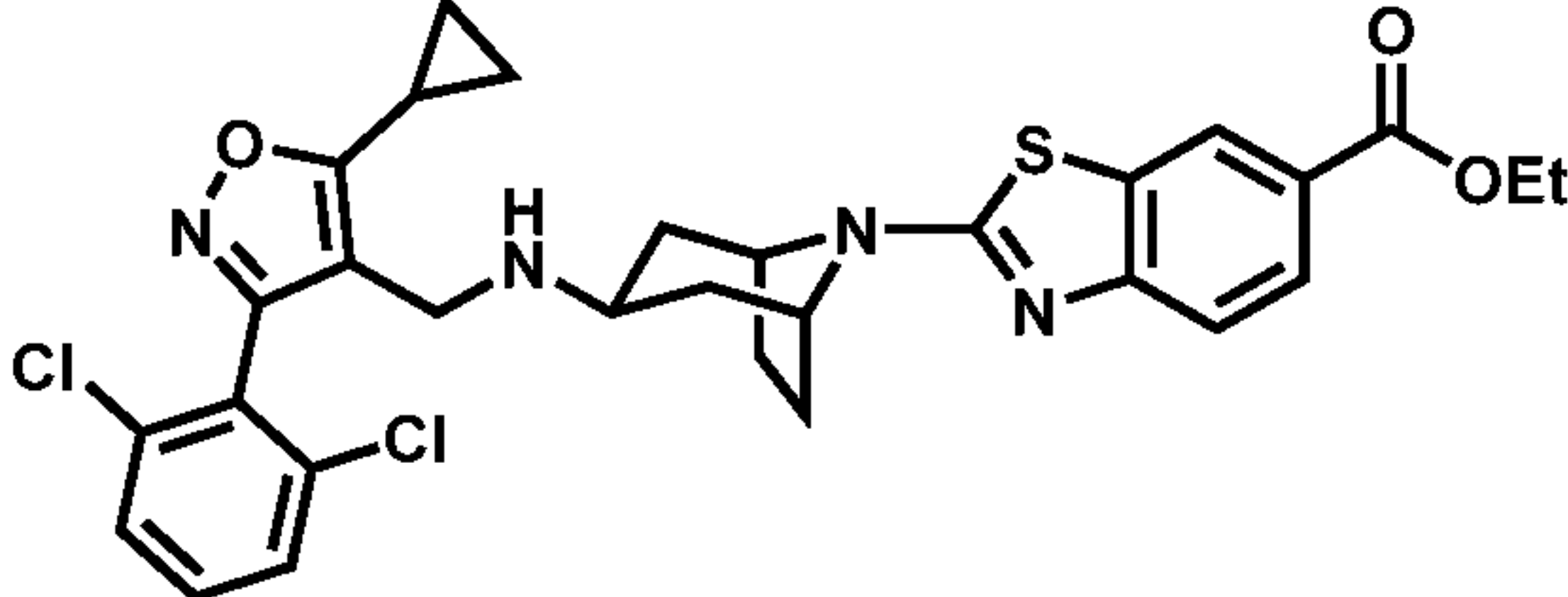
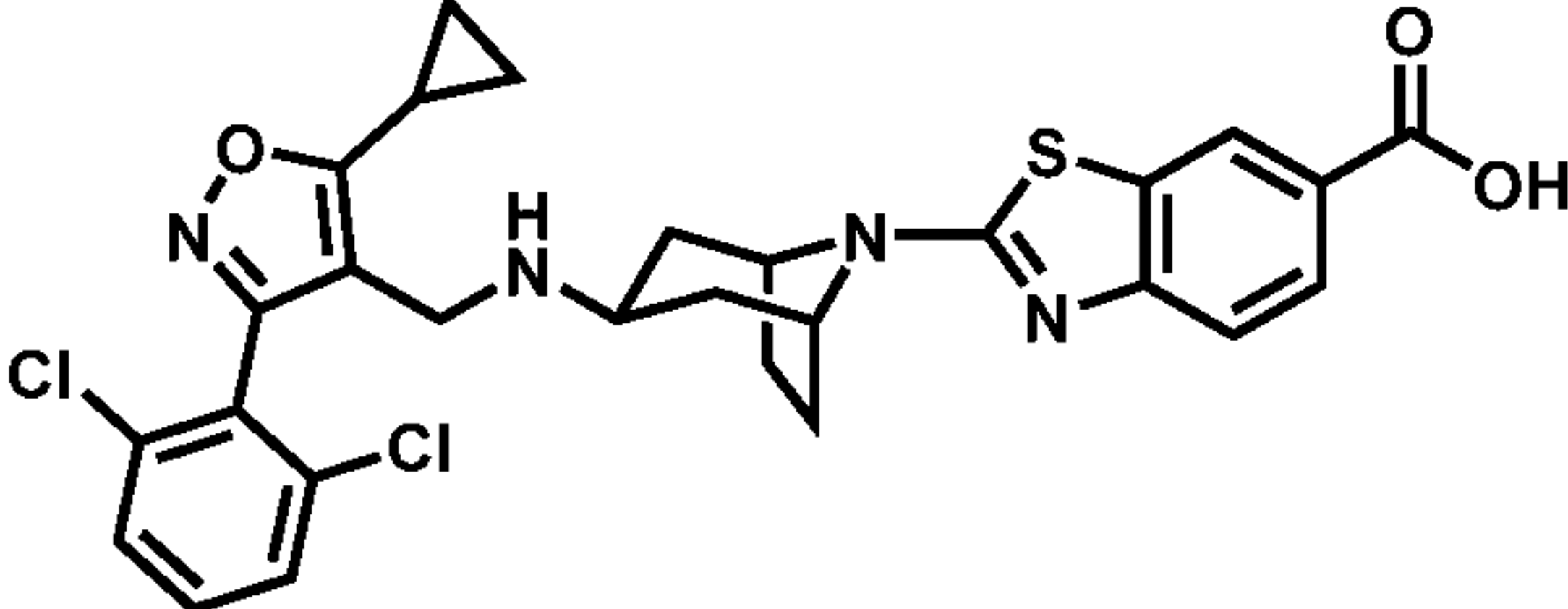
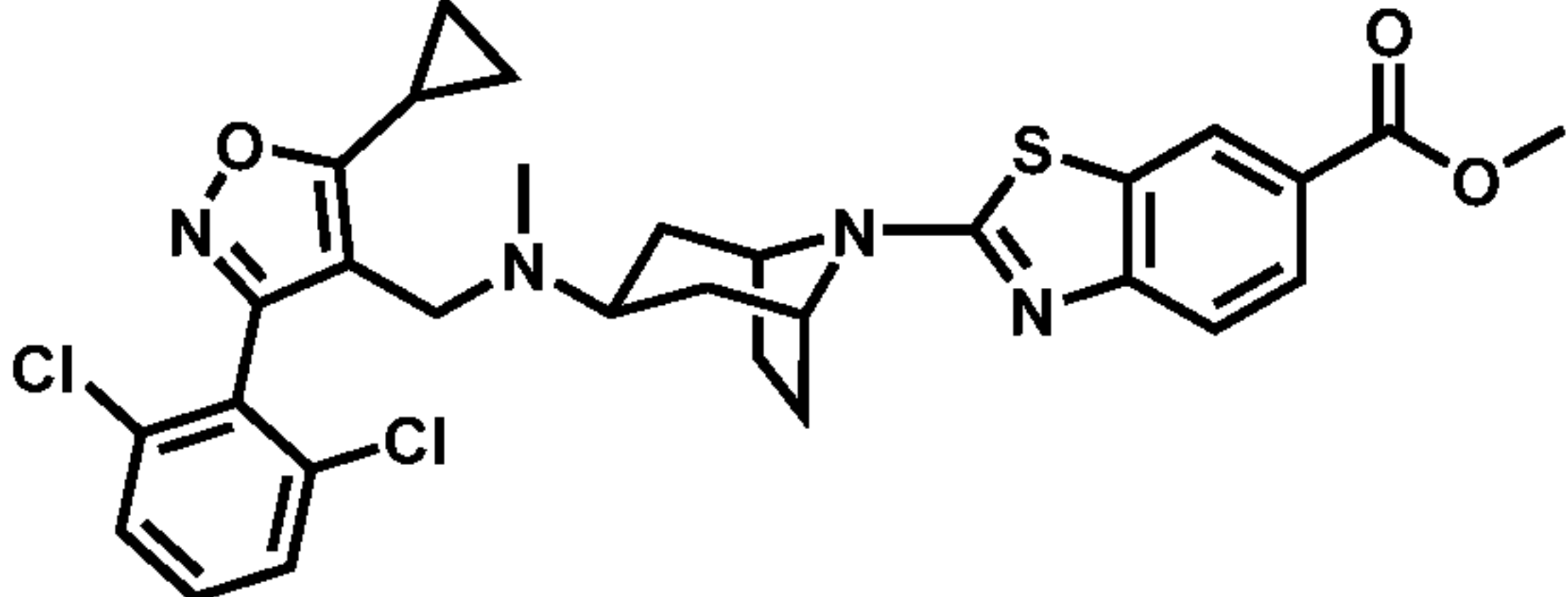
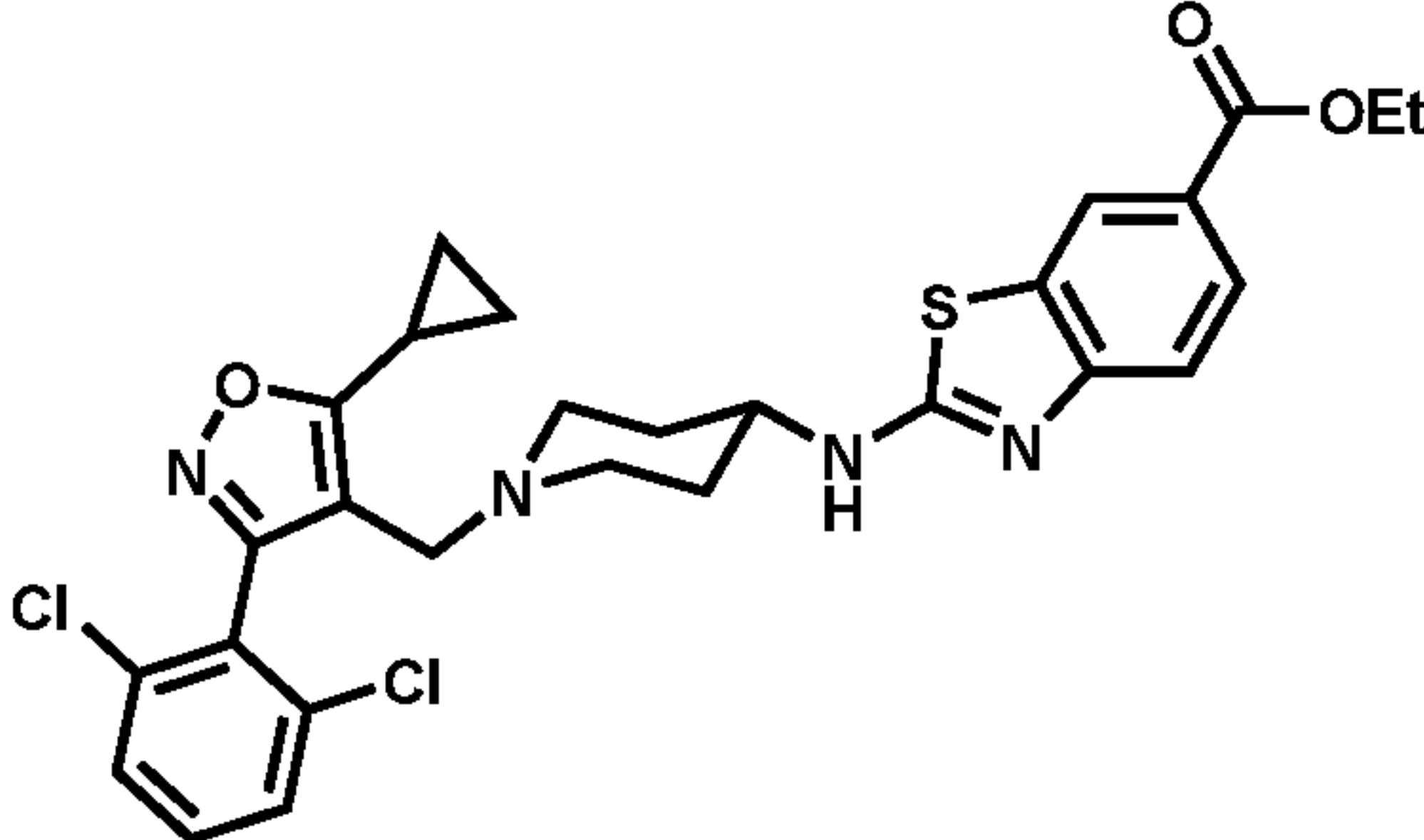
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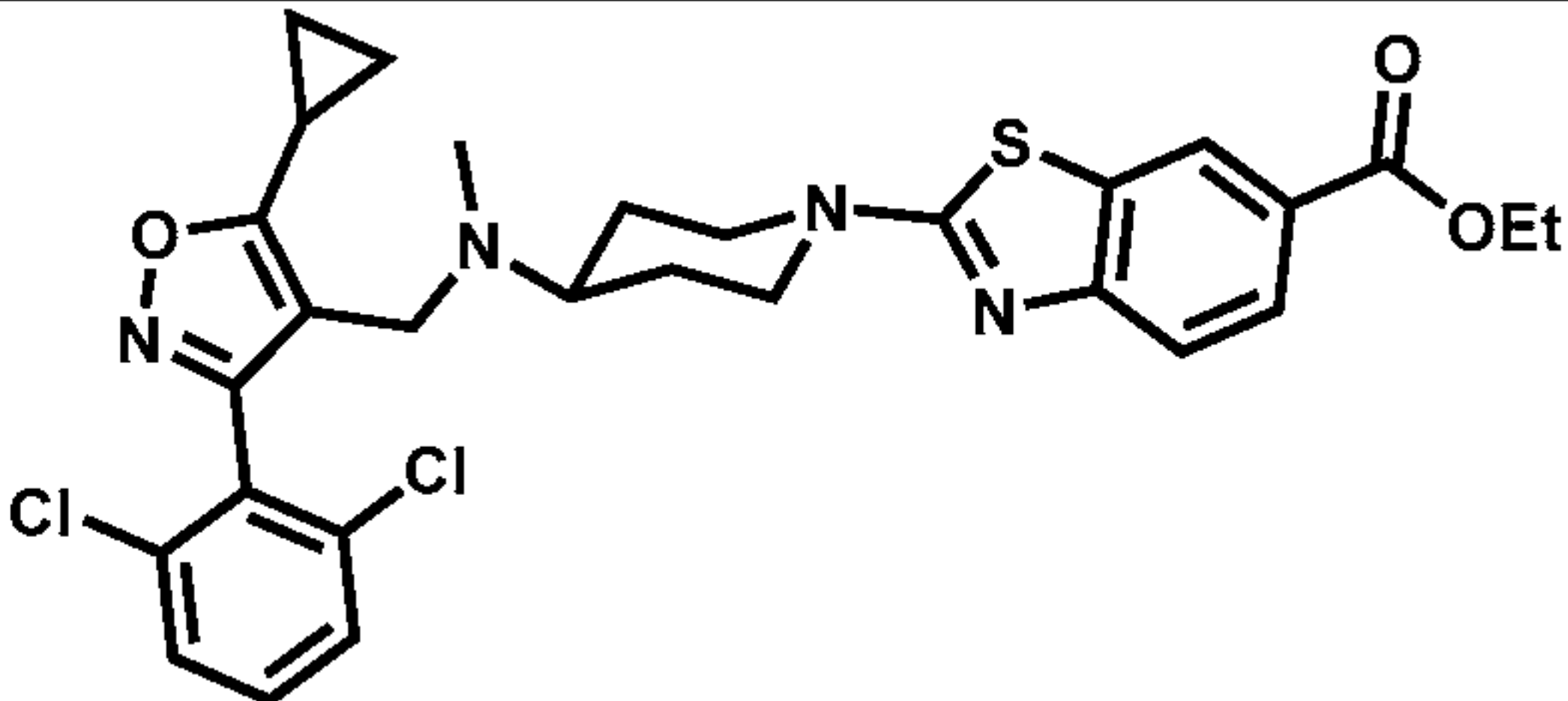
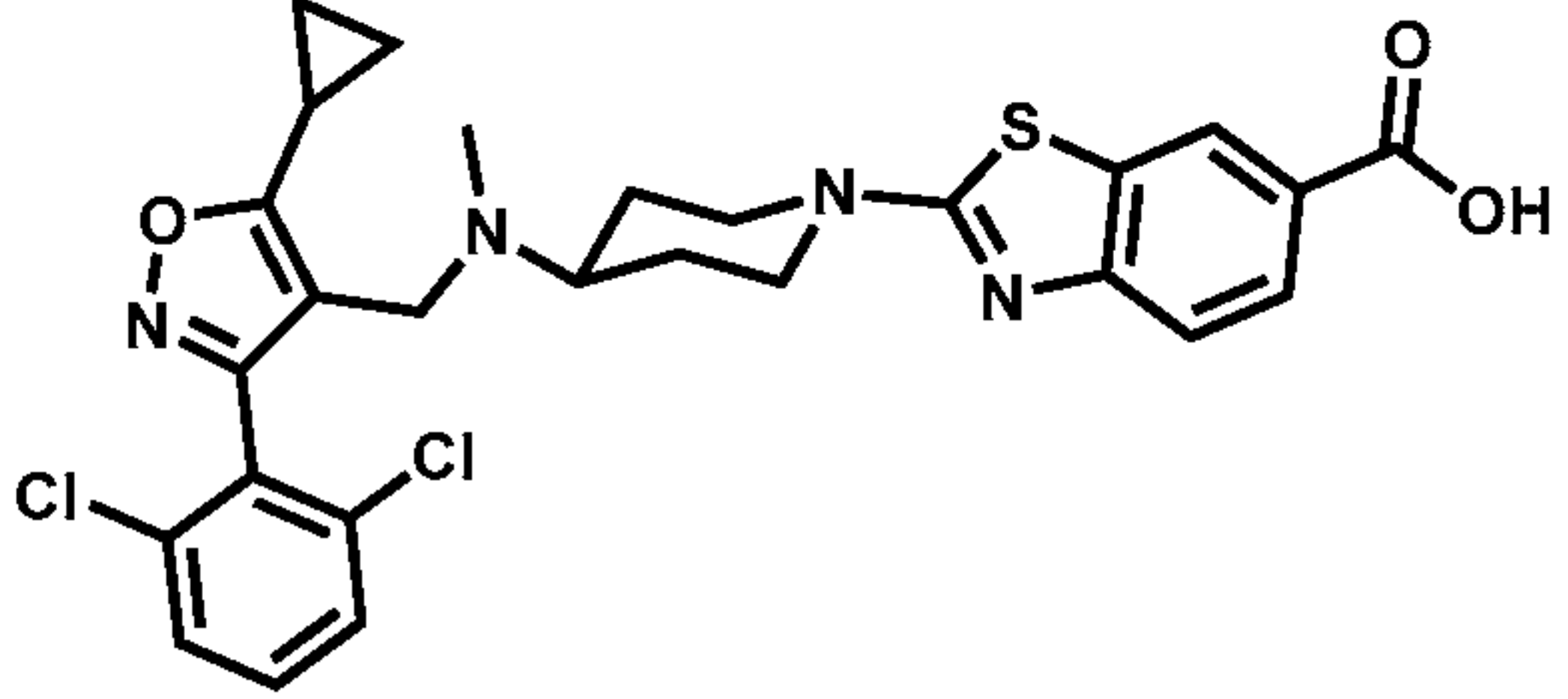
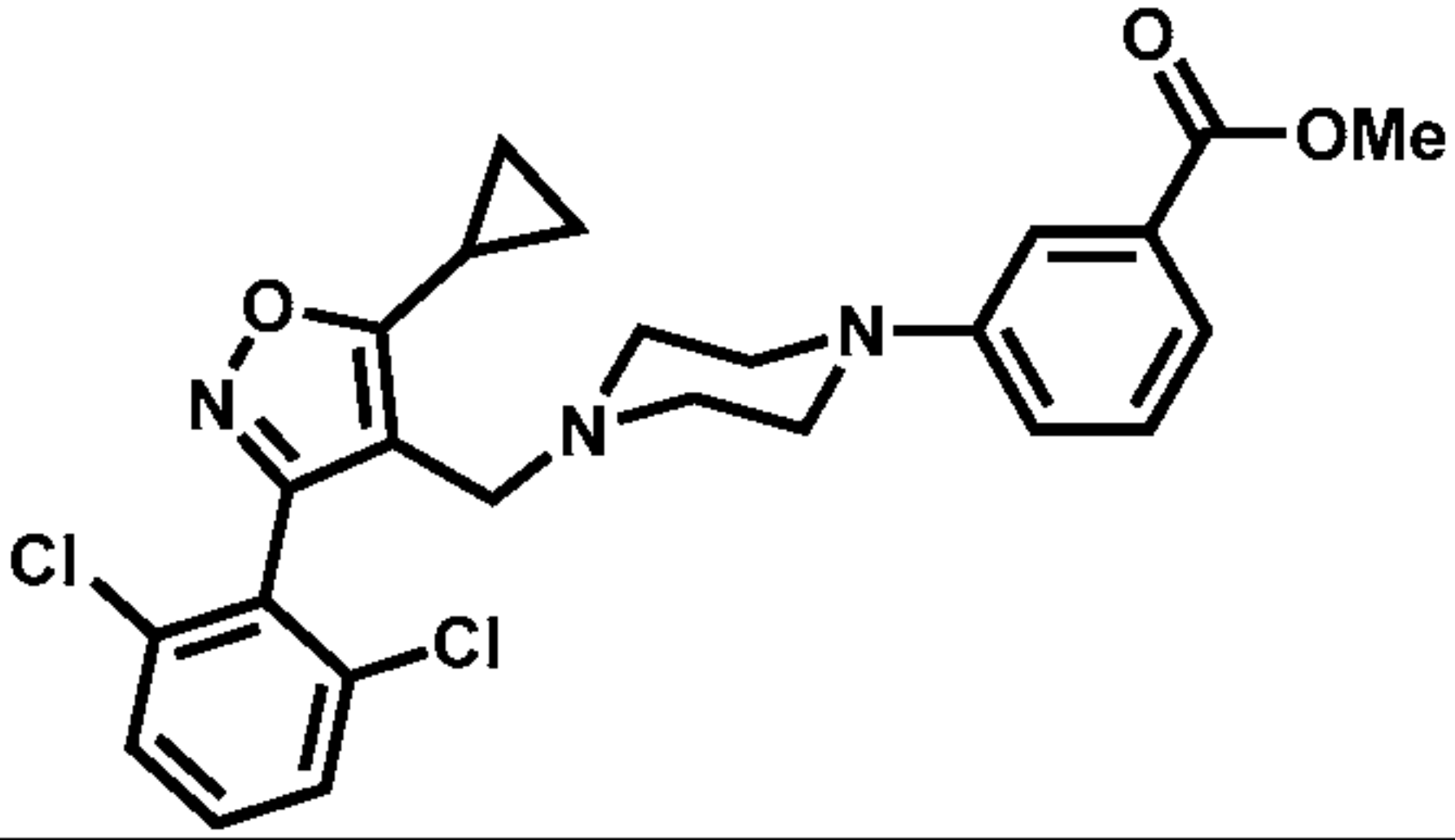
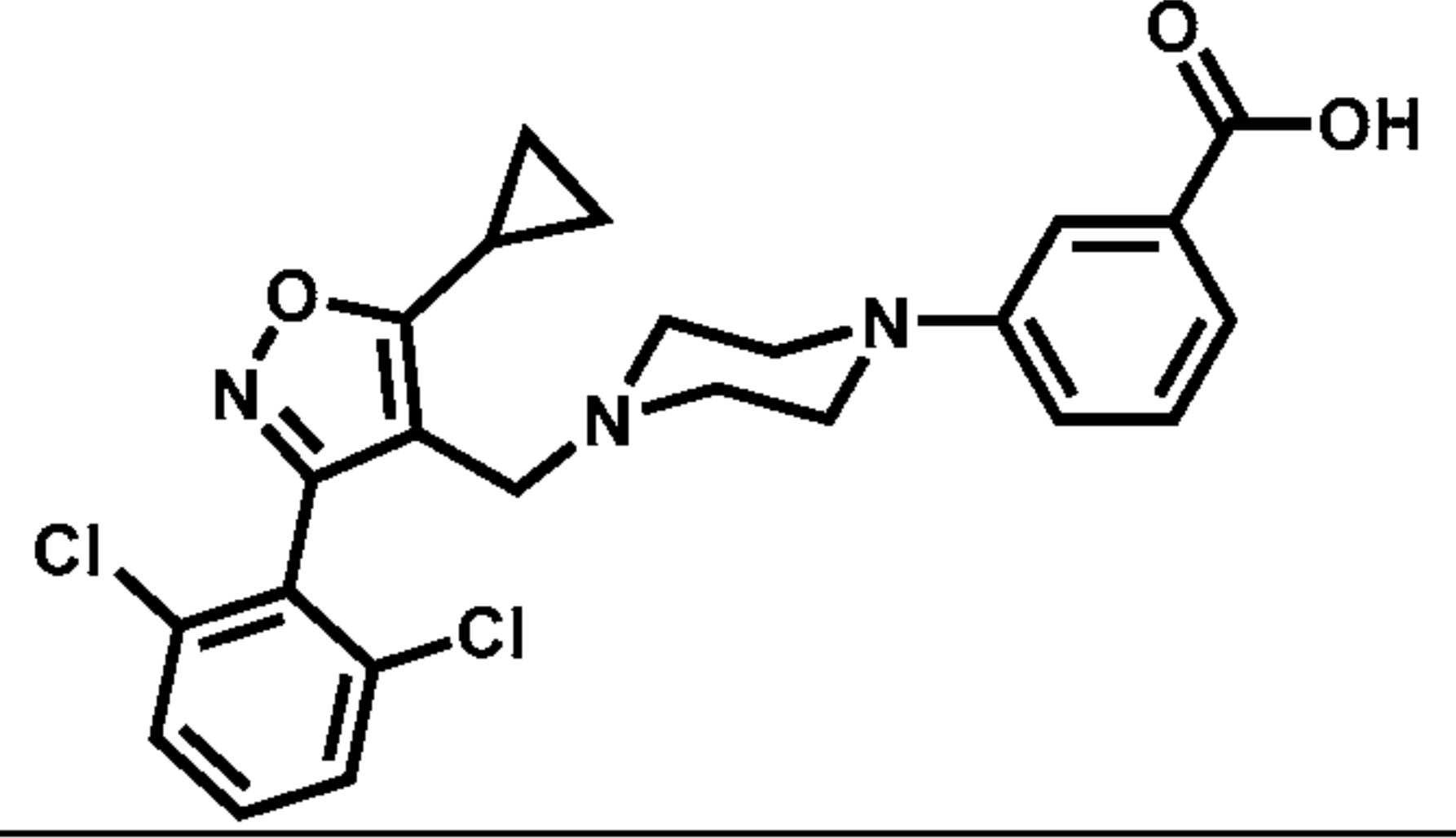
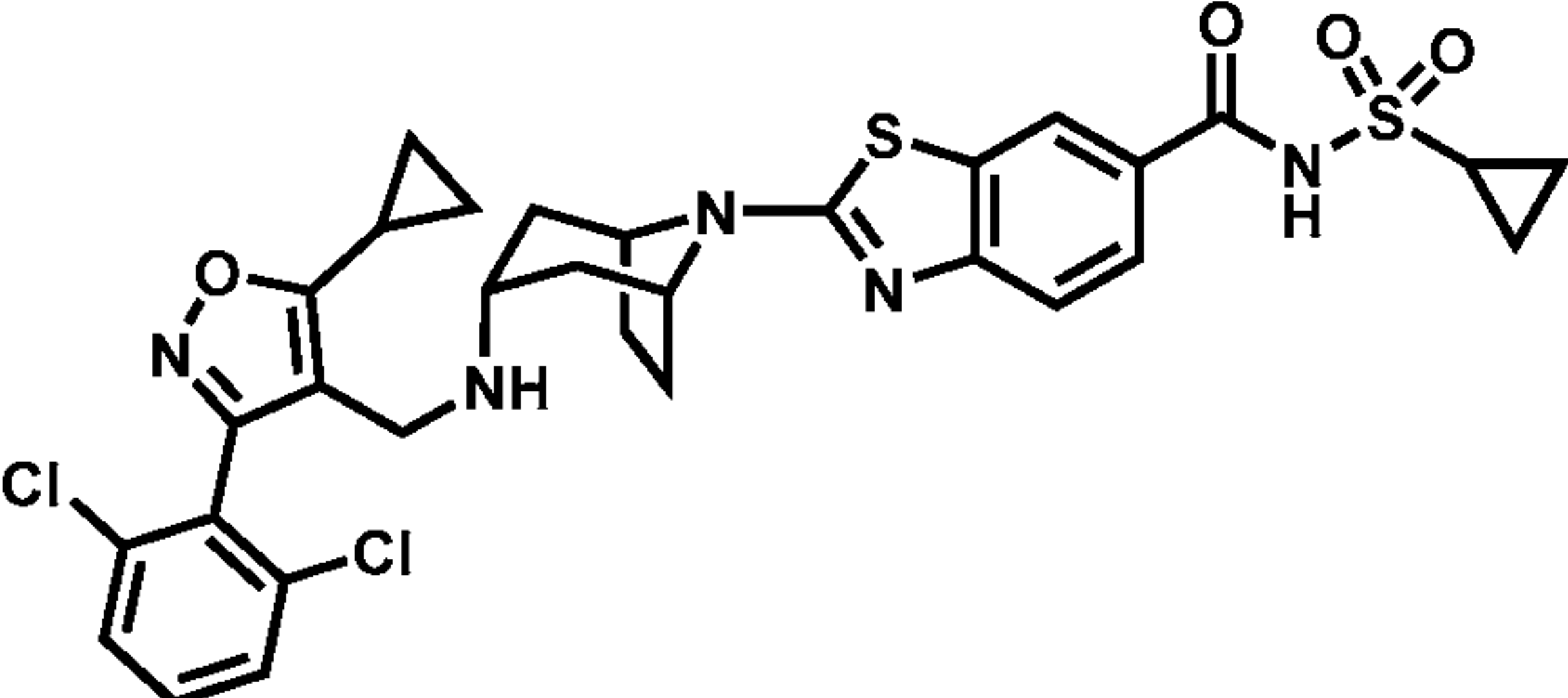
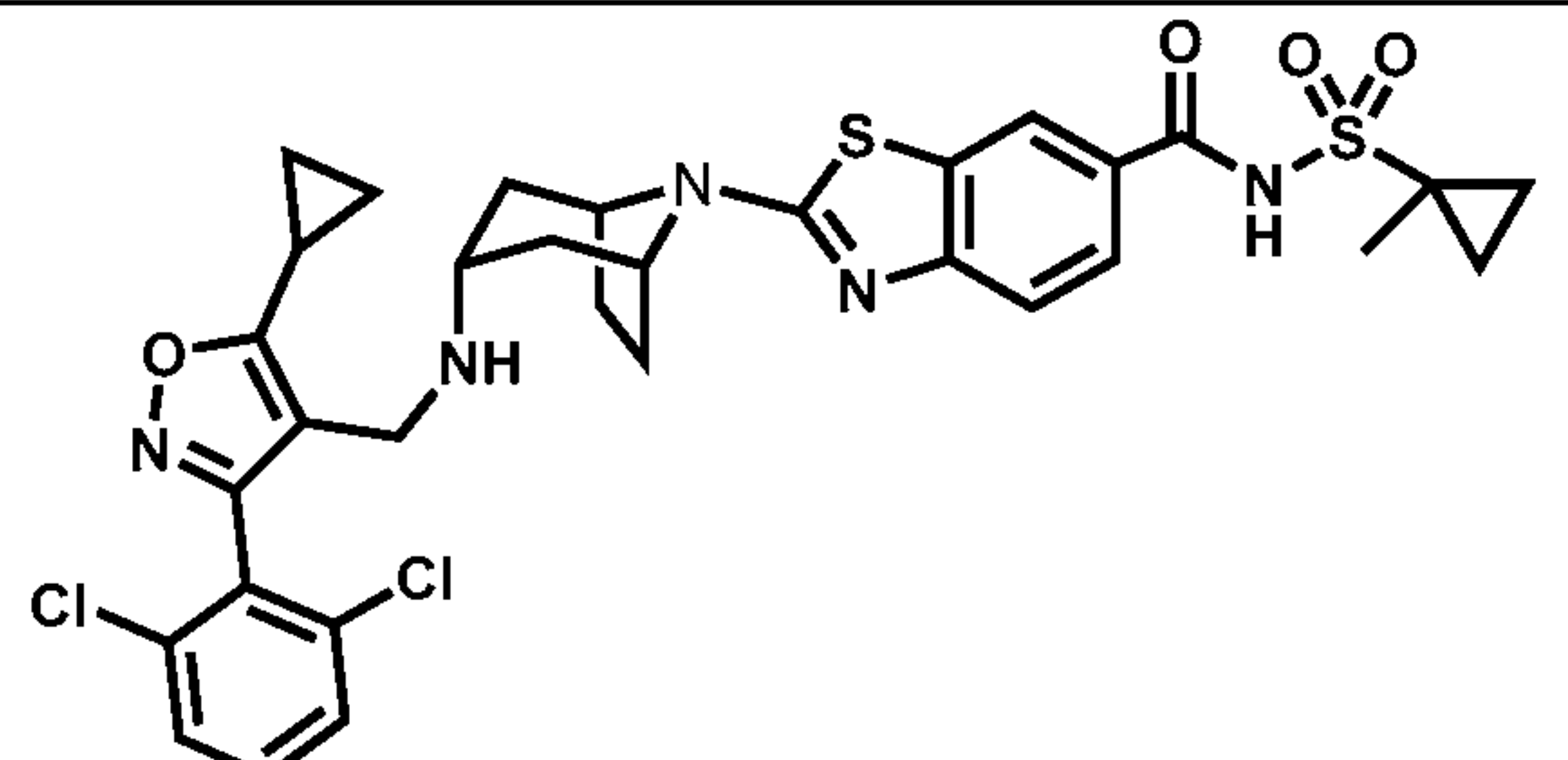
14. The compound of claim 1, selected from the compounds set forth below or a pharmaceutically acceptable salt thereof:

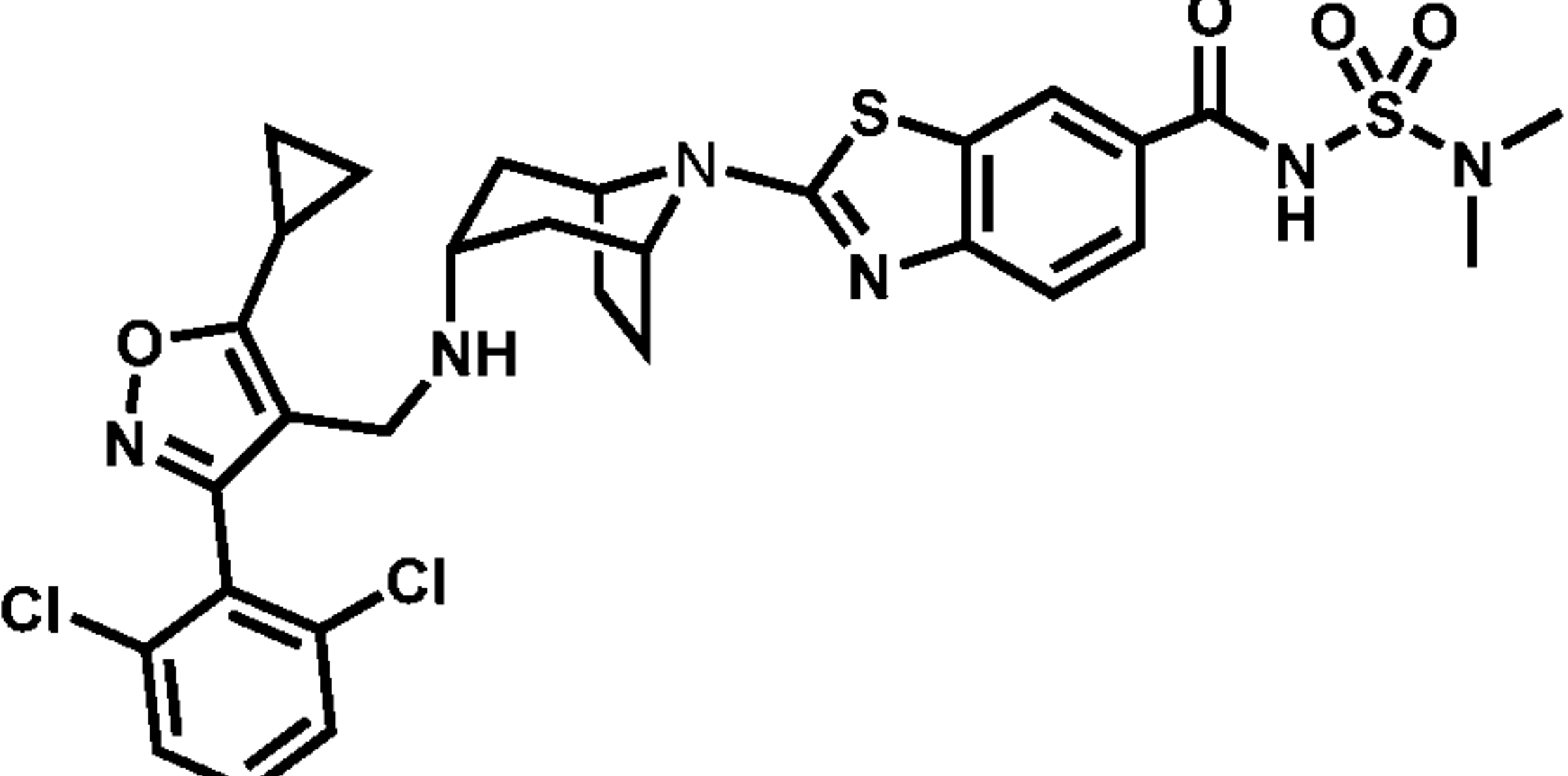
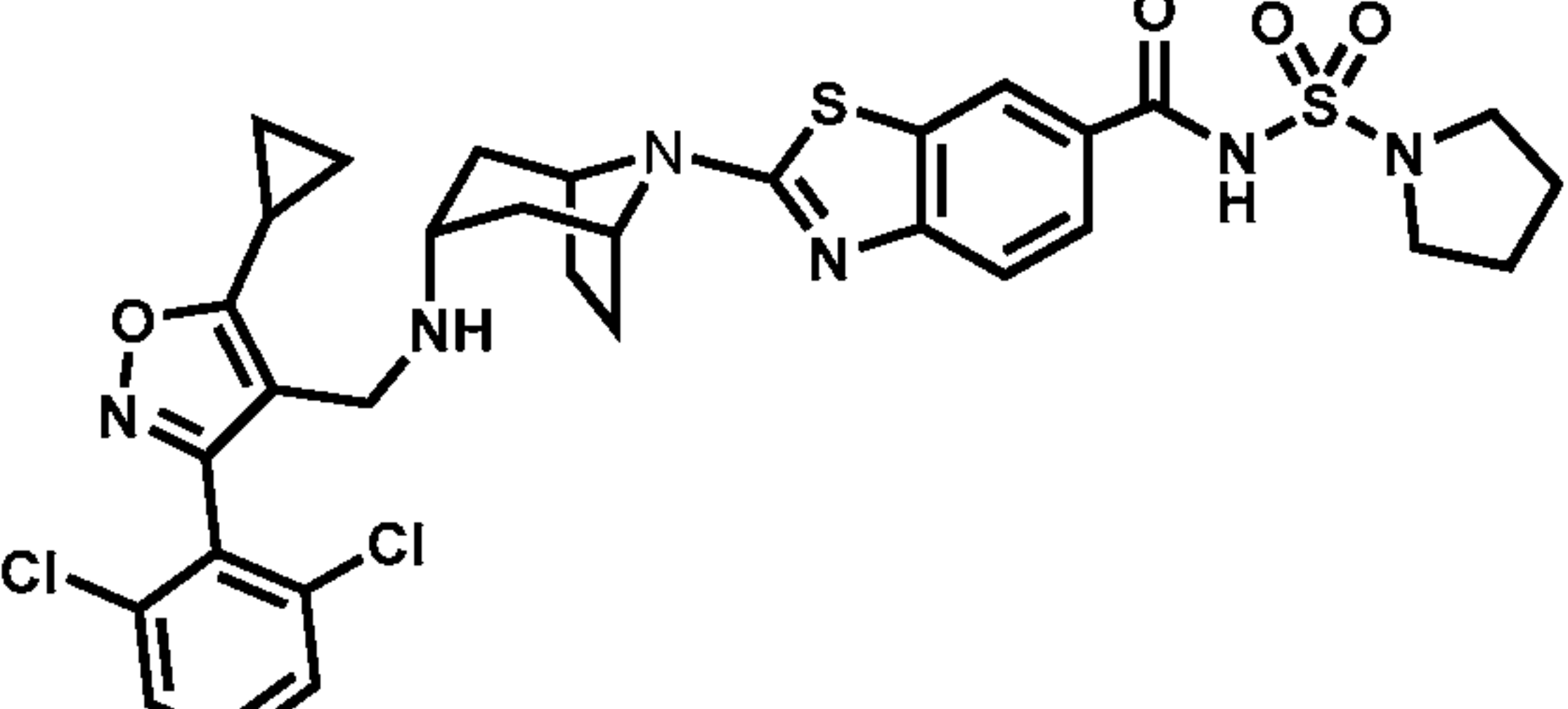
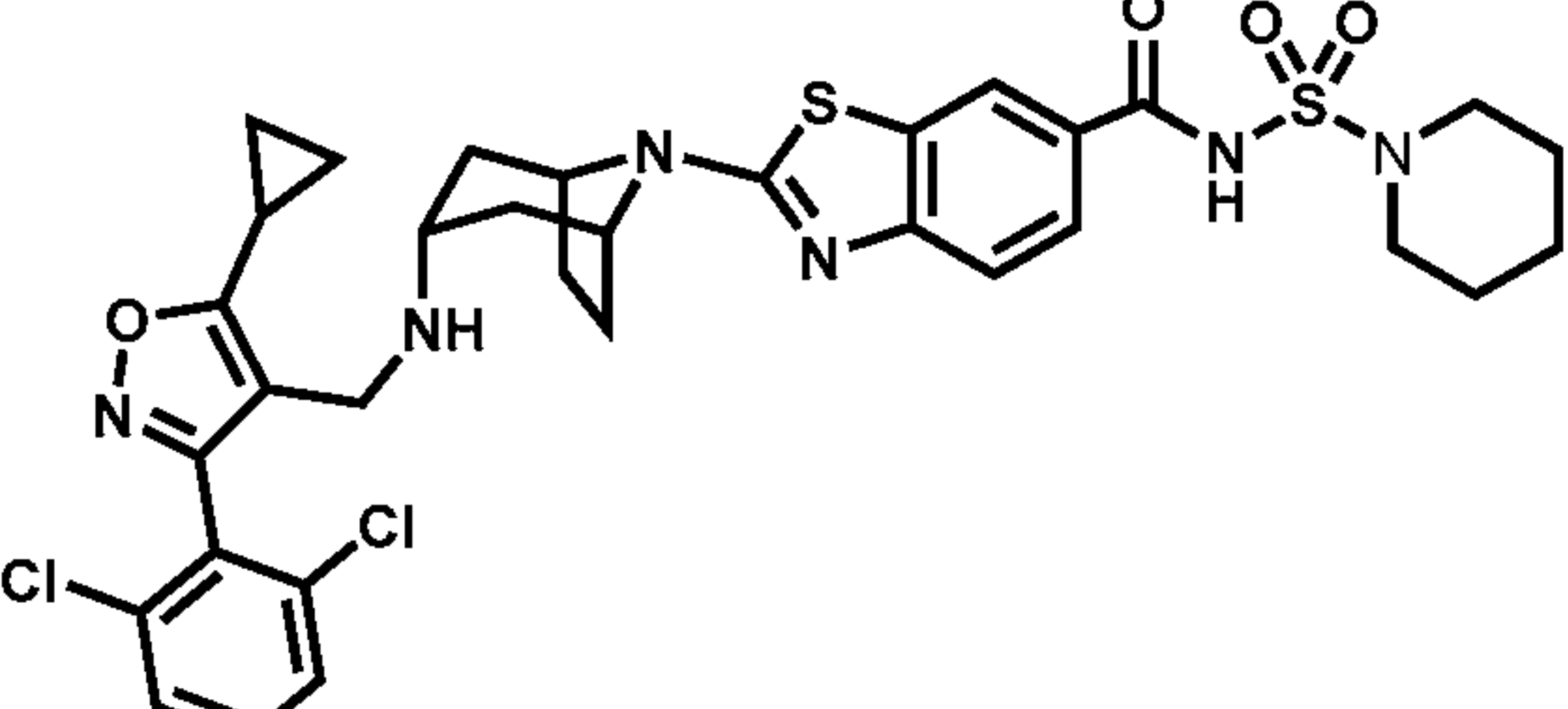
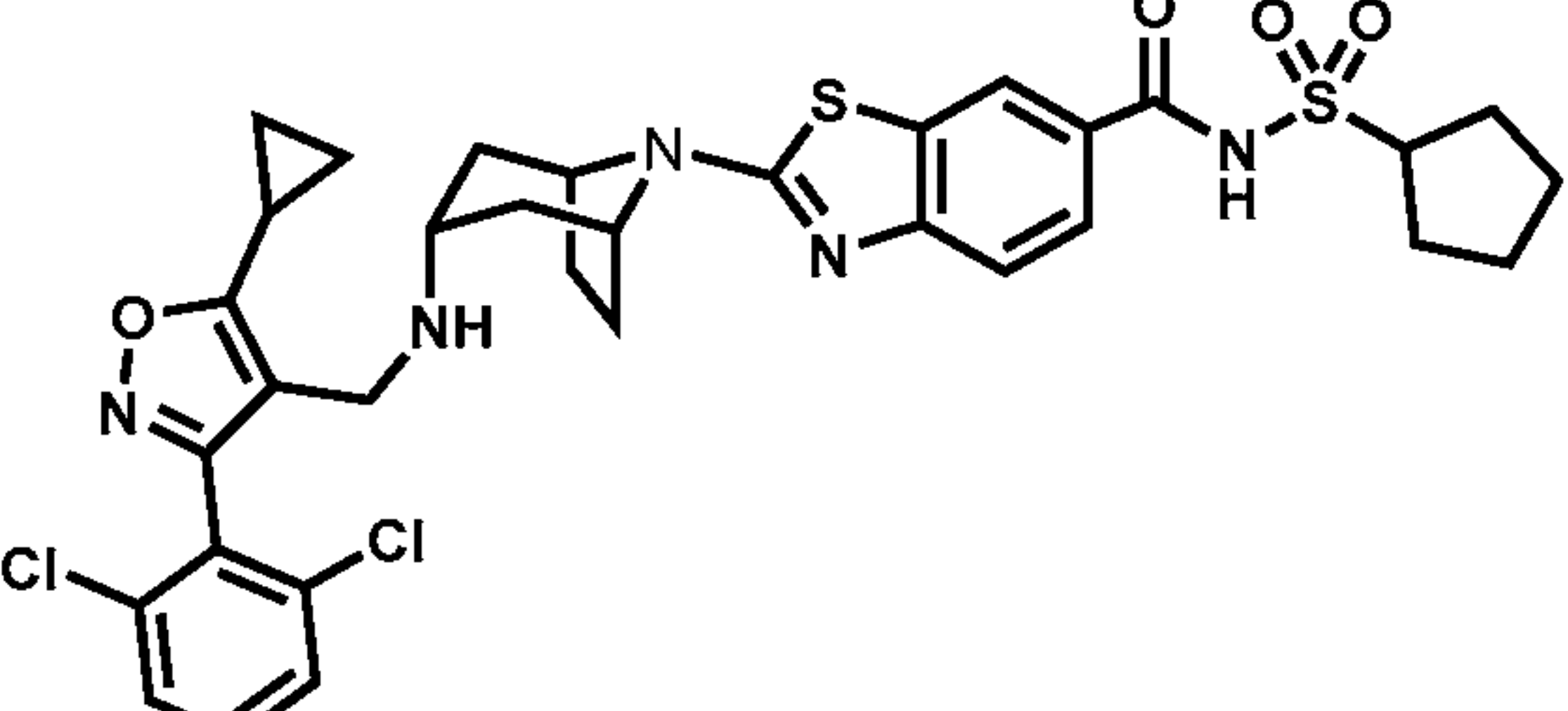
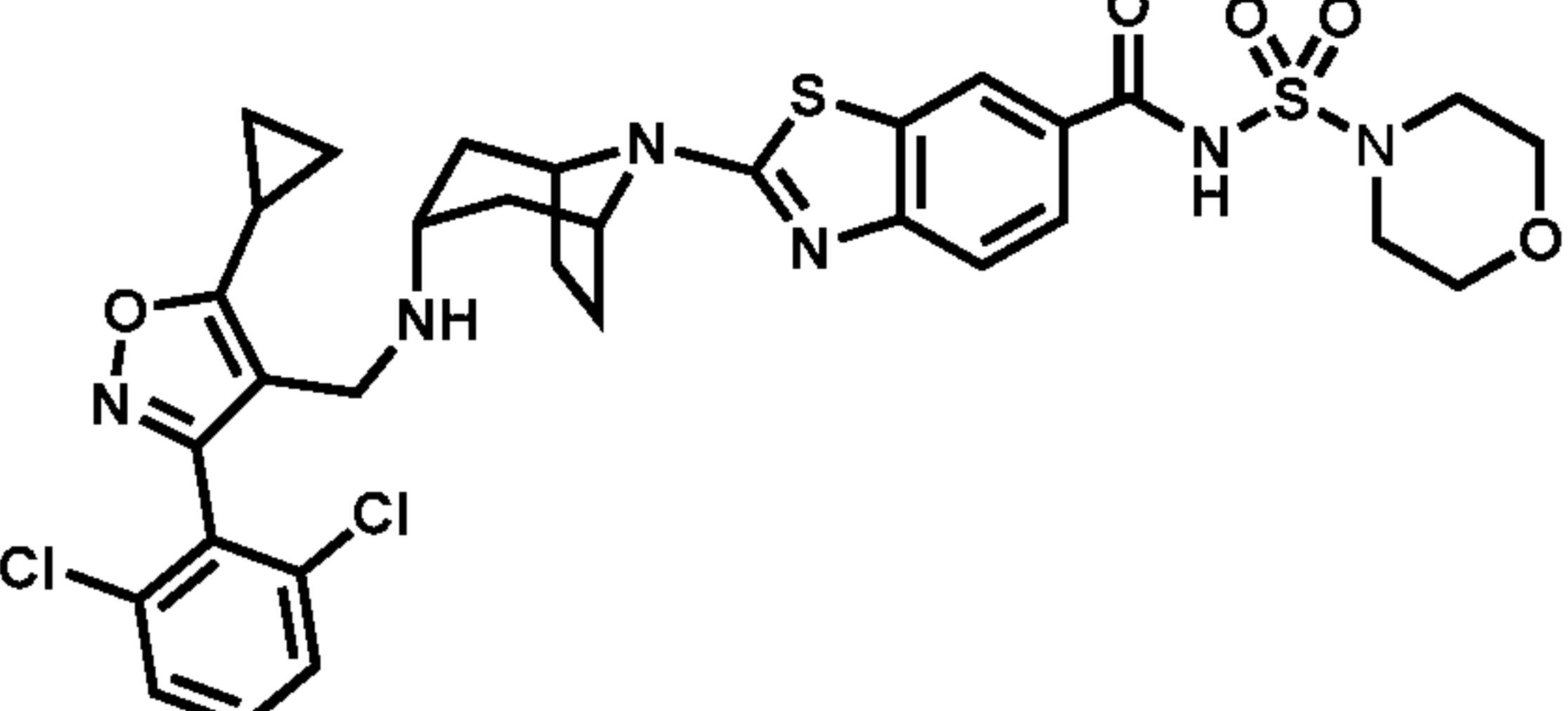
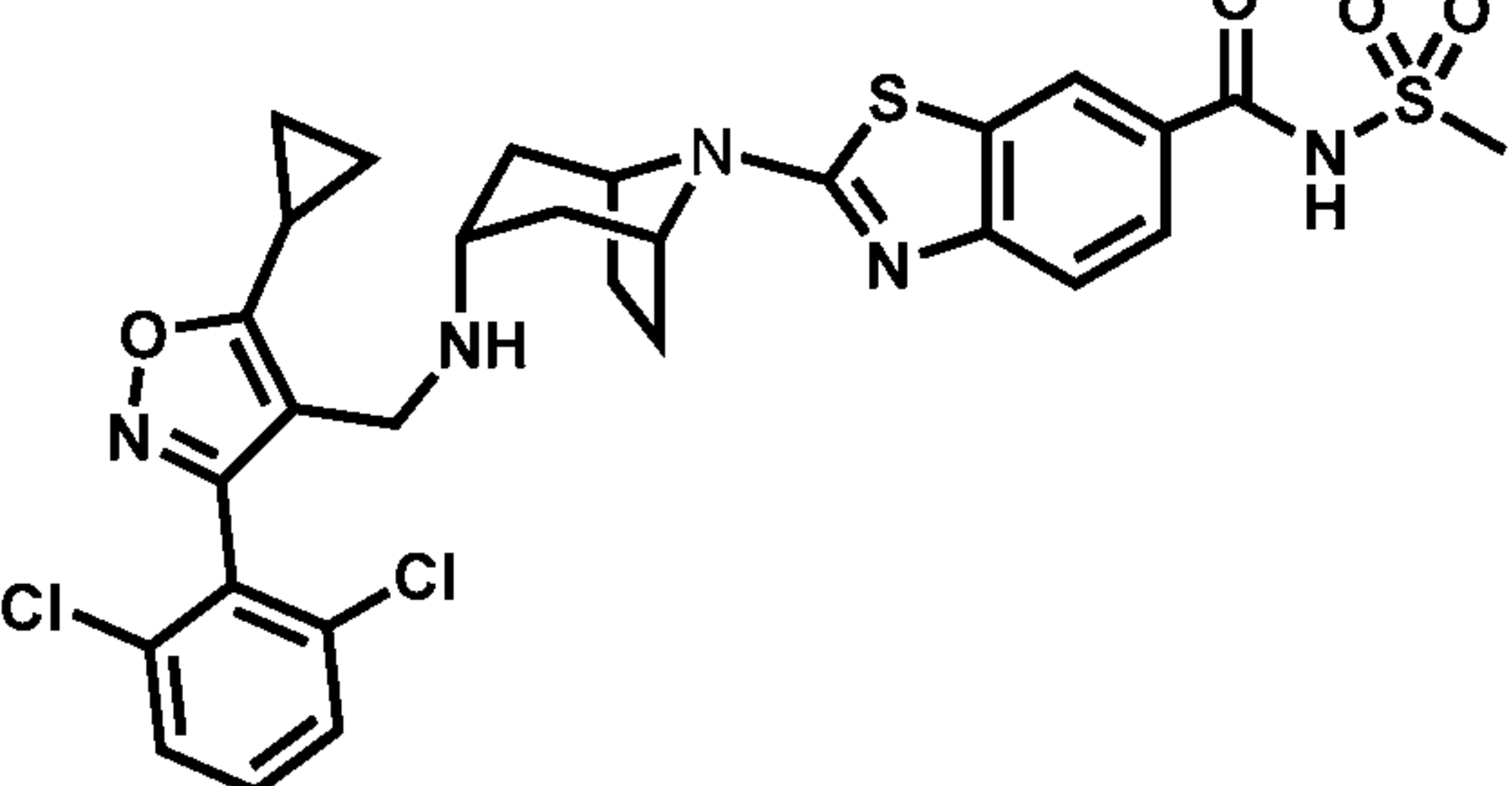
Compound No.	Structure
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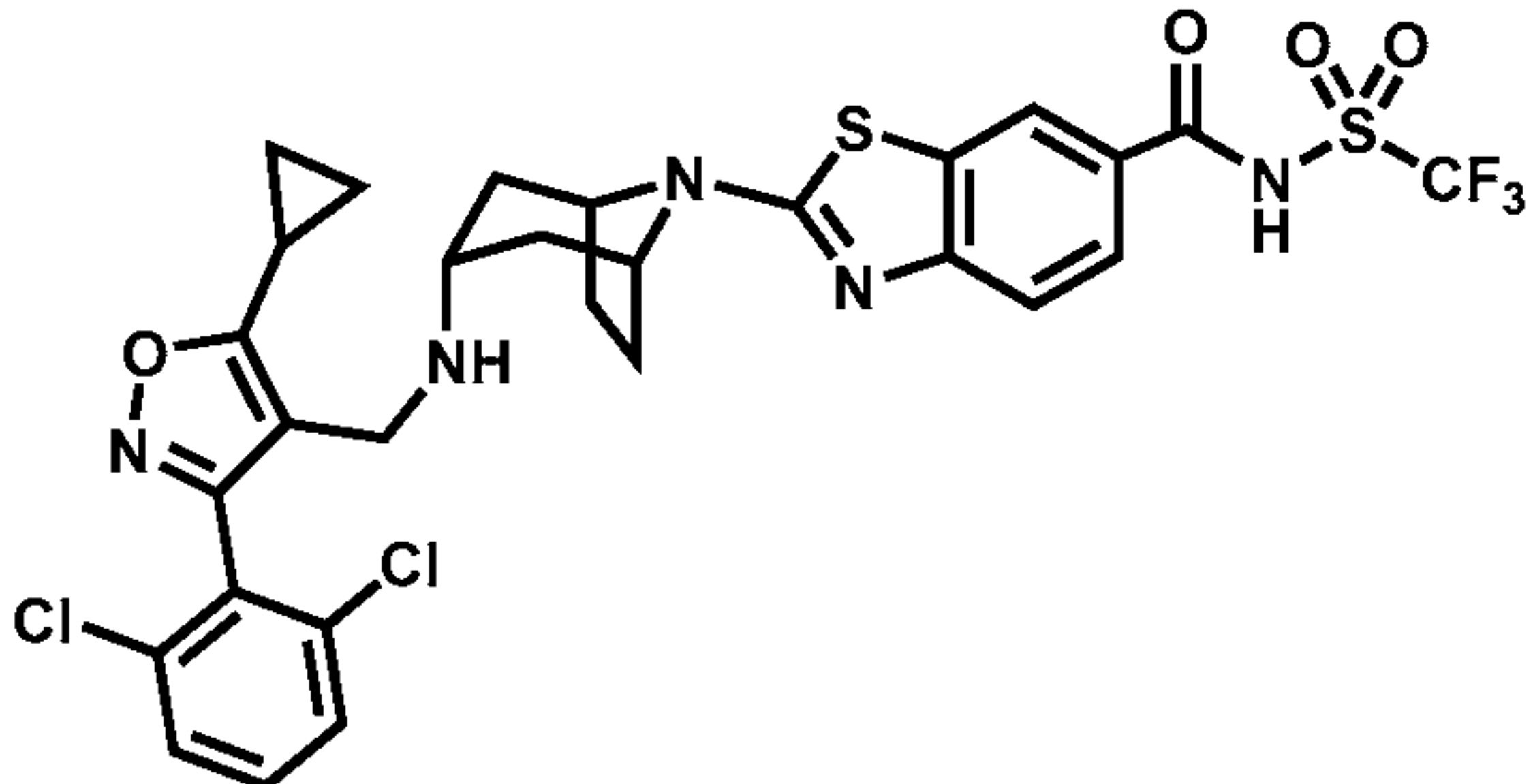
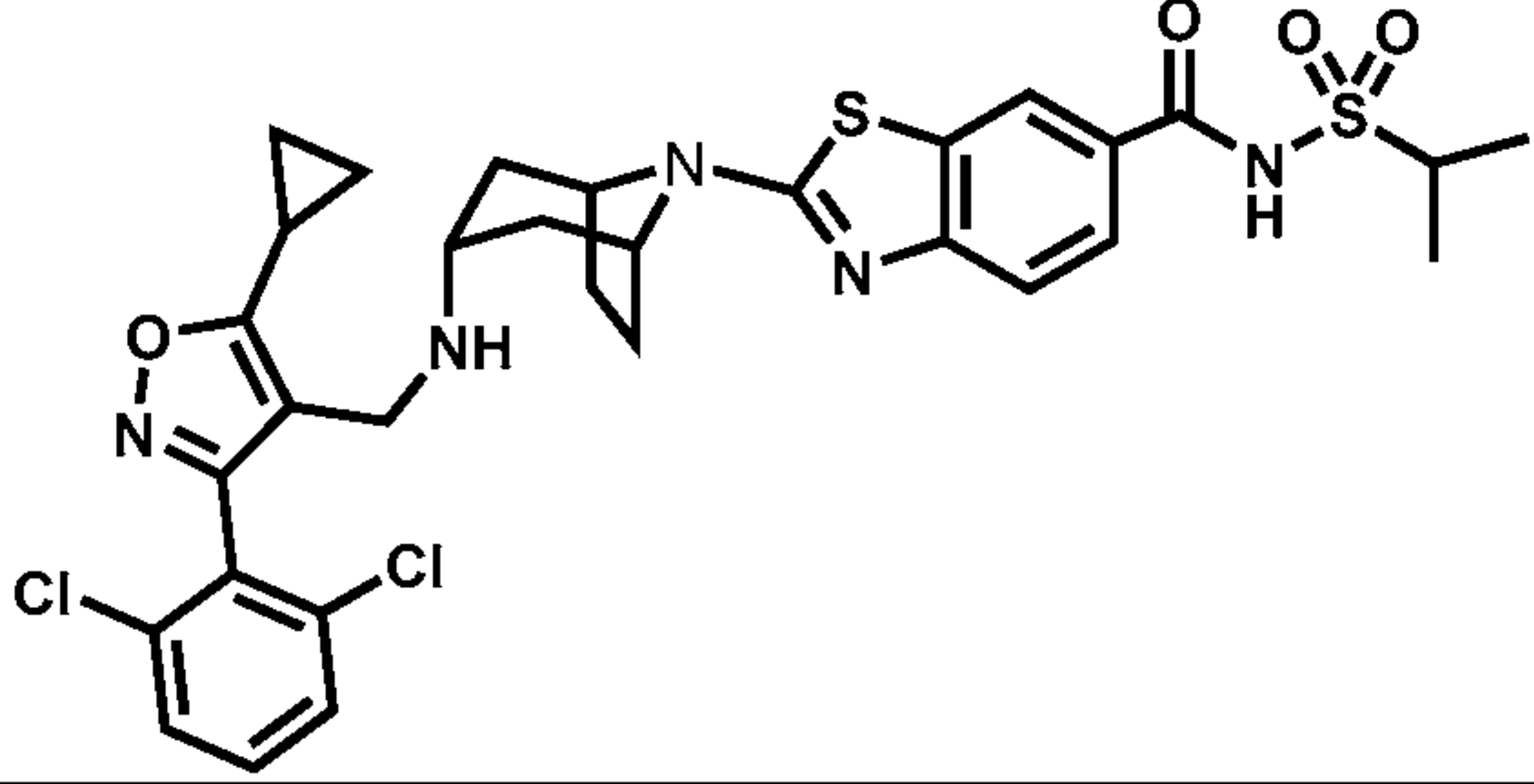
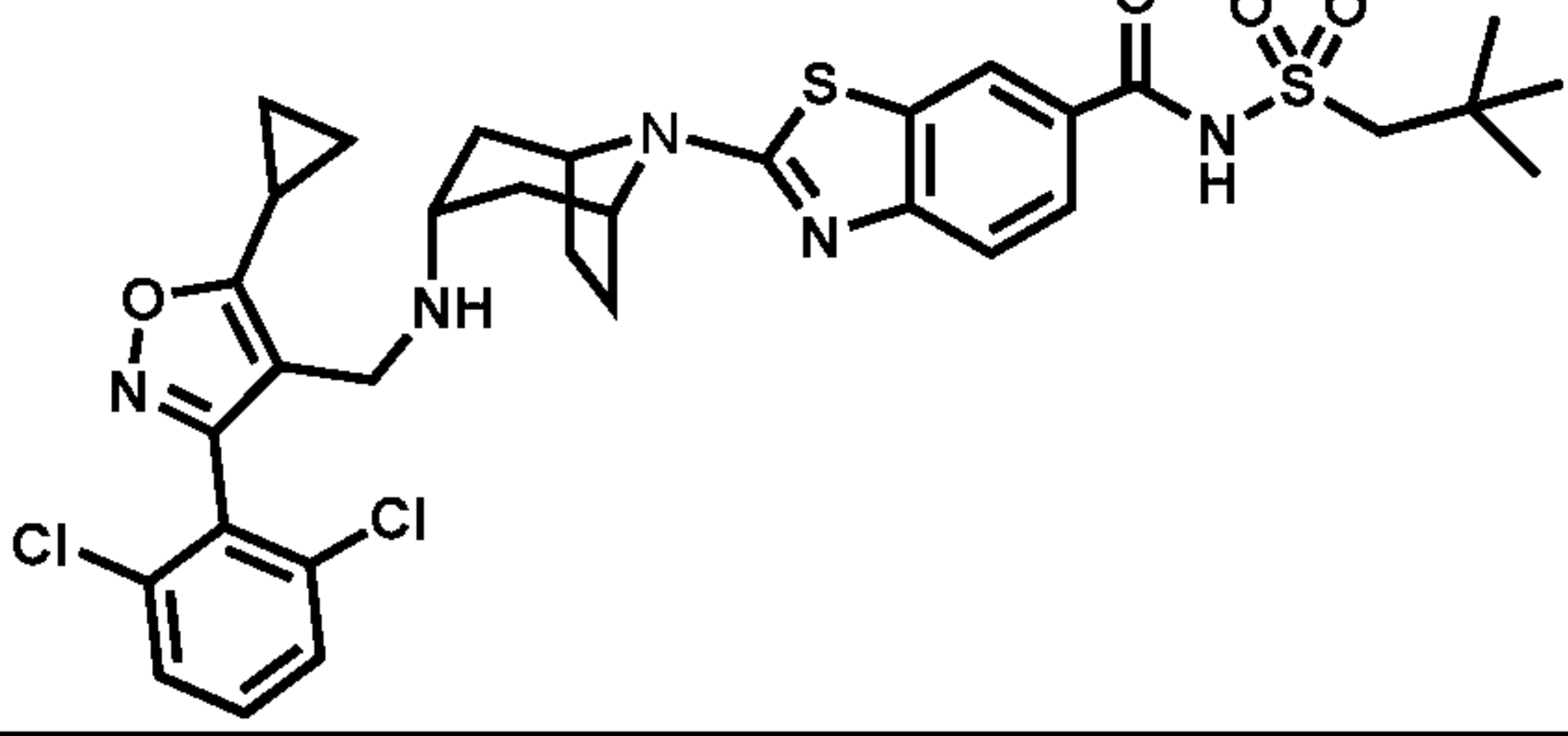
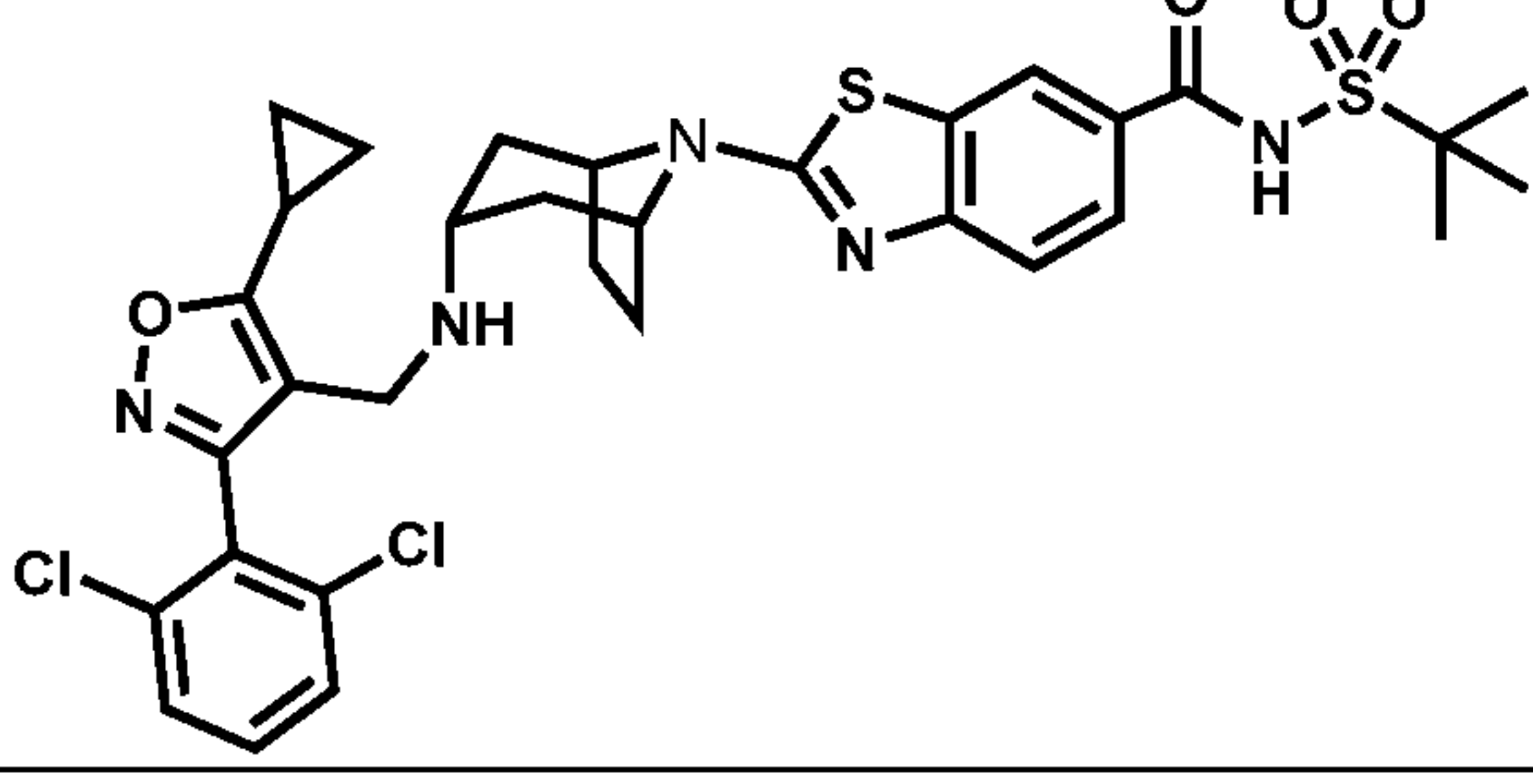
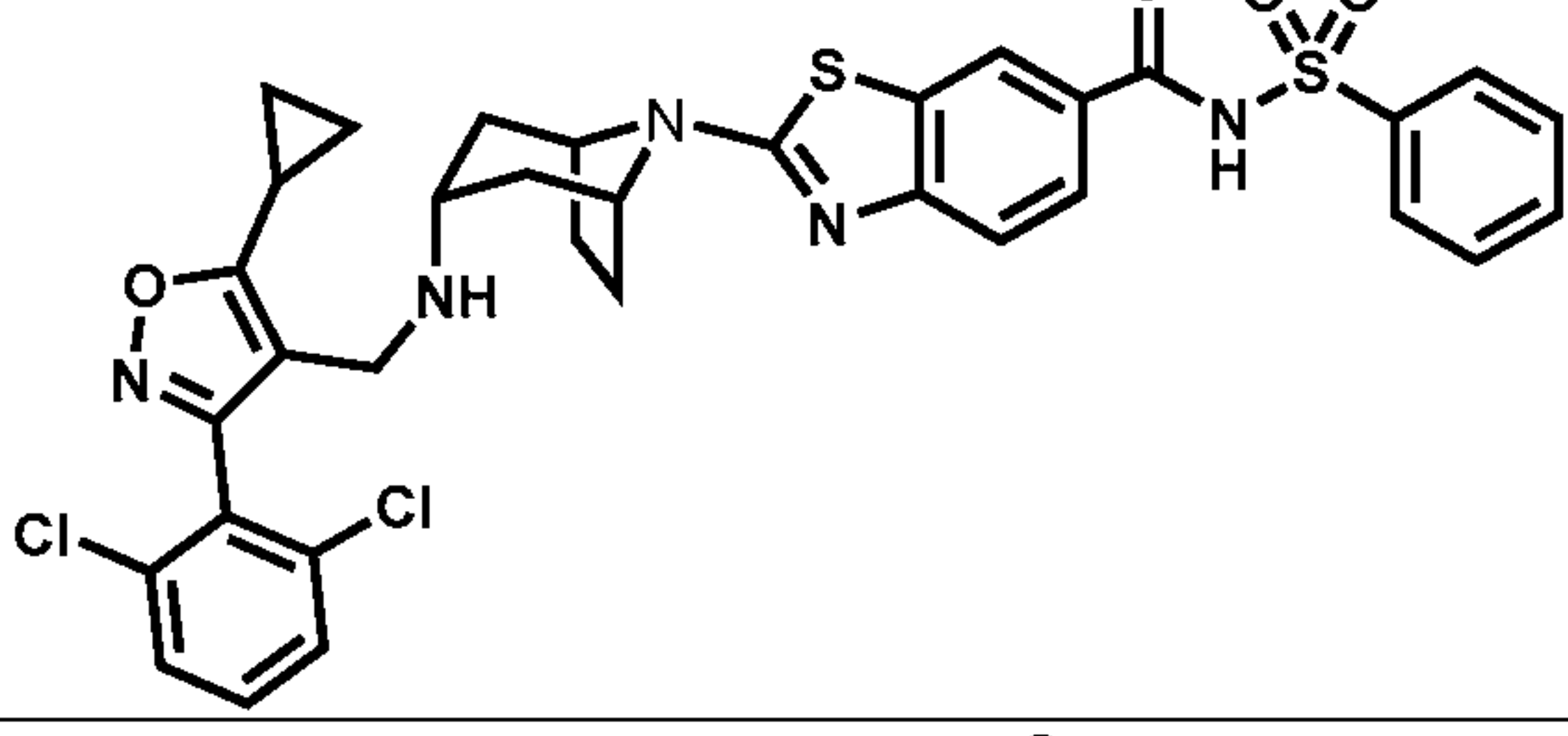
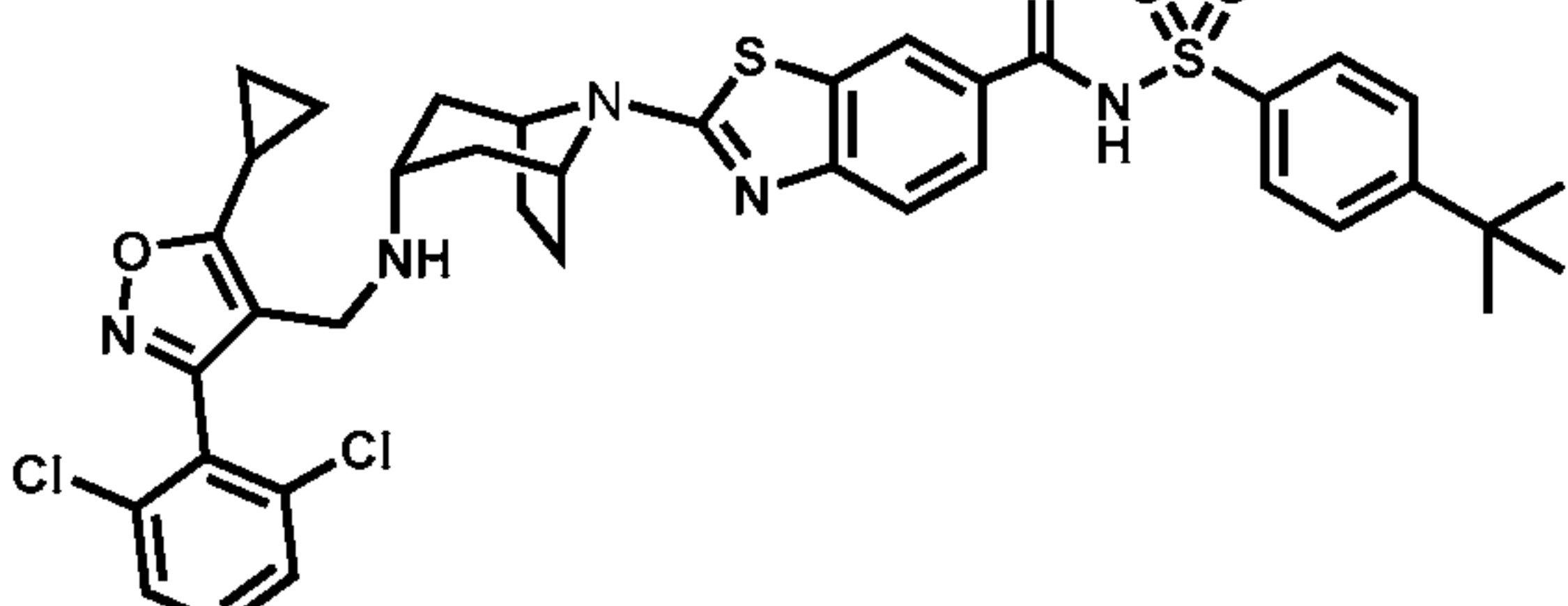
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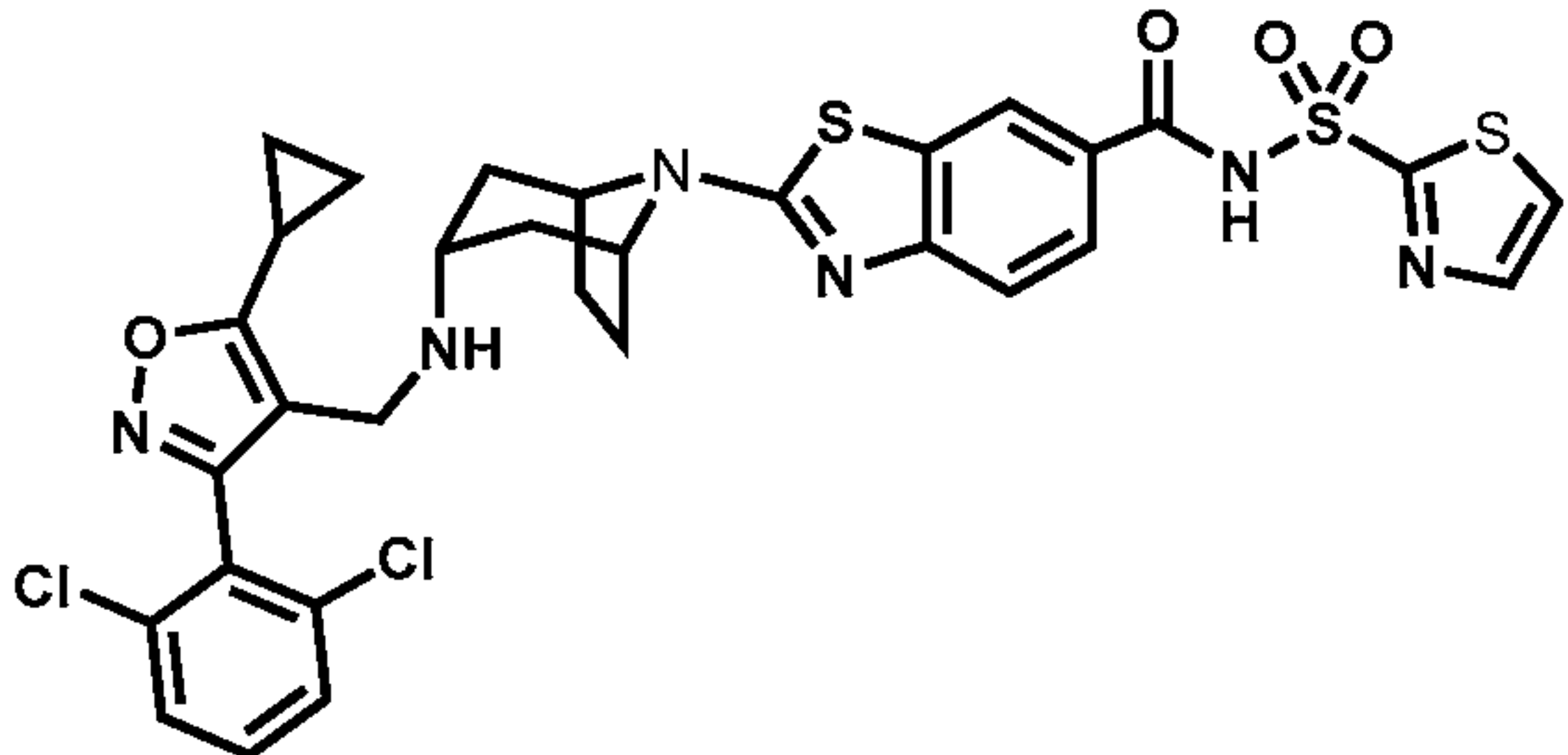
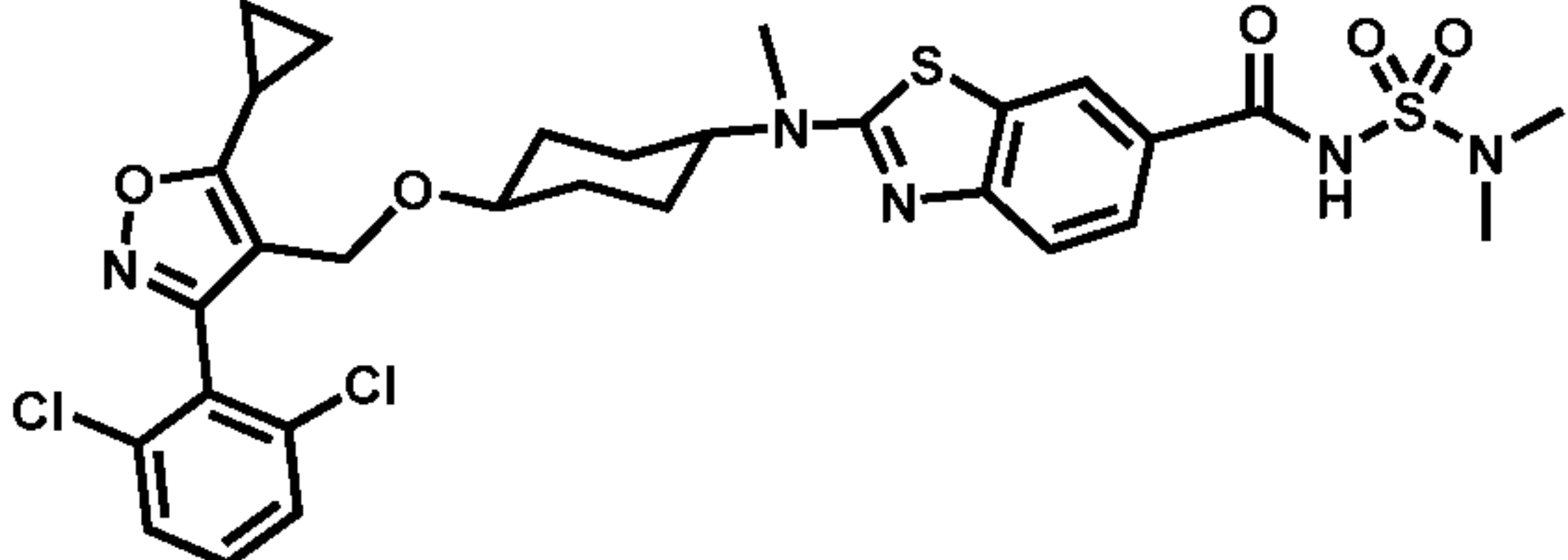
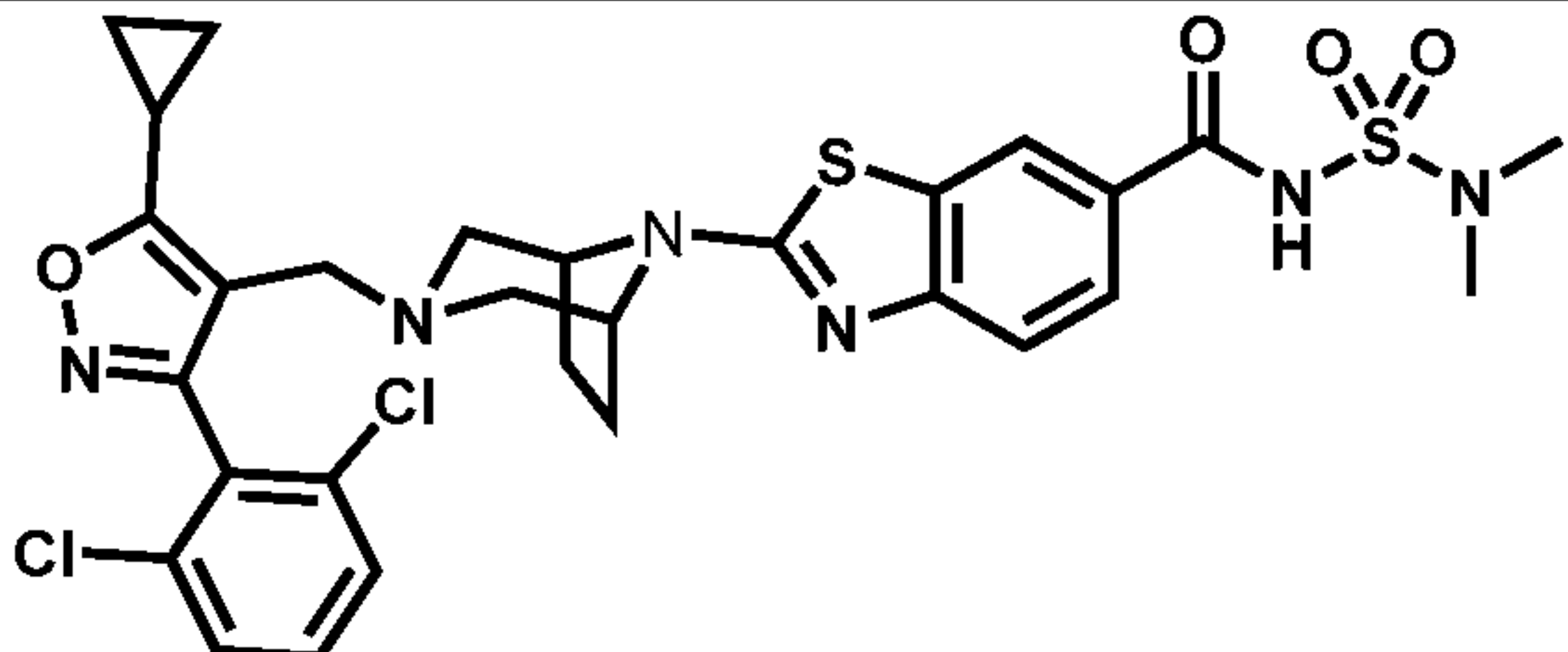
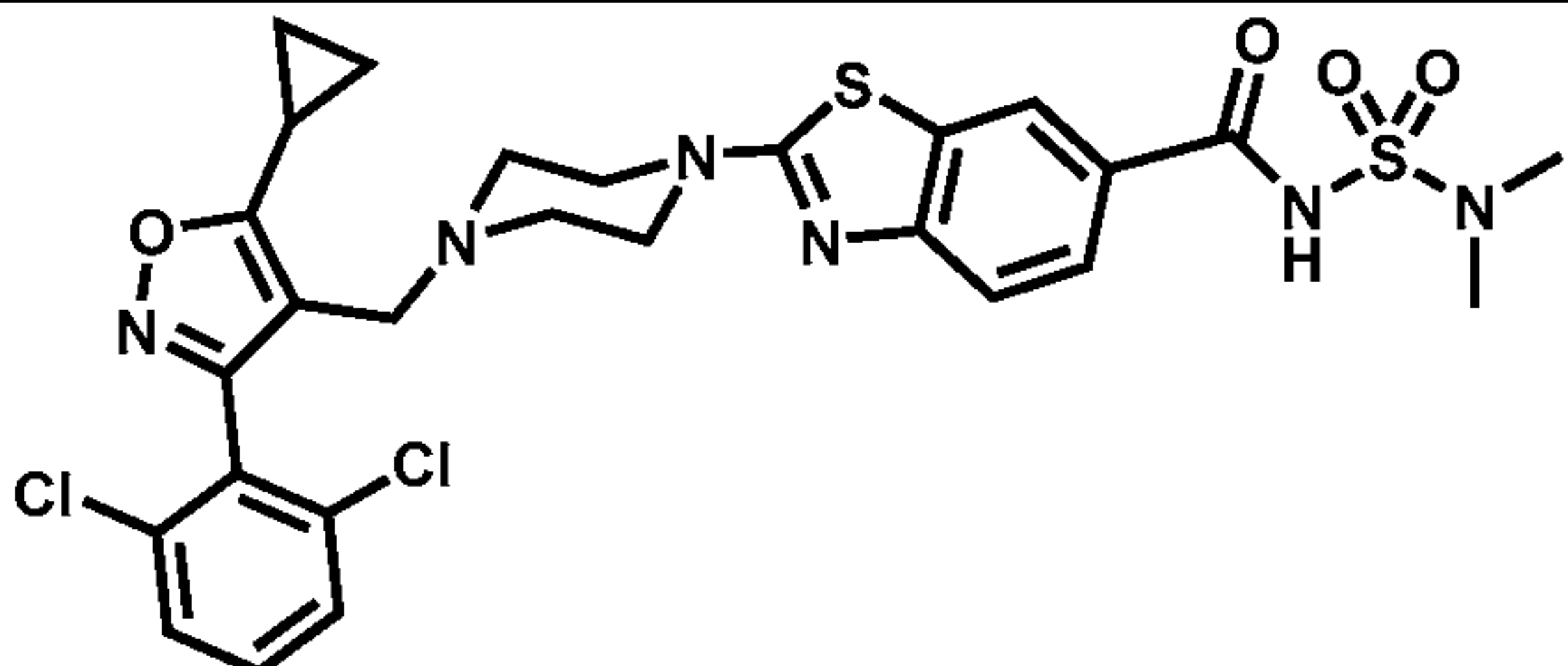
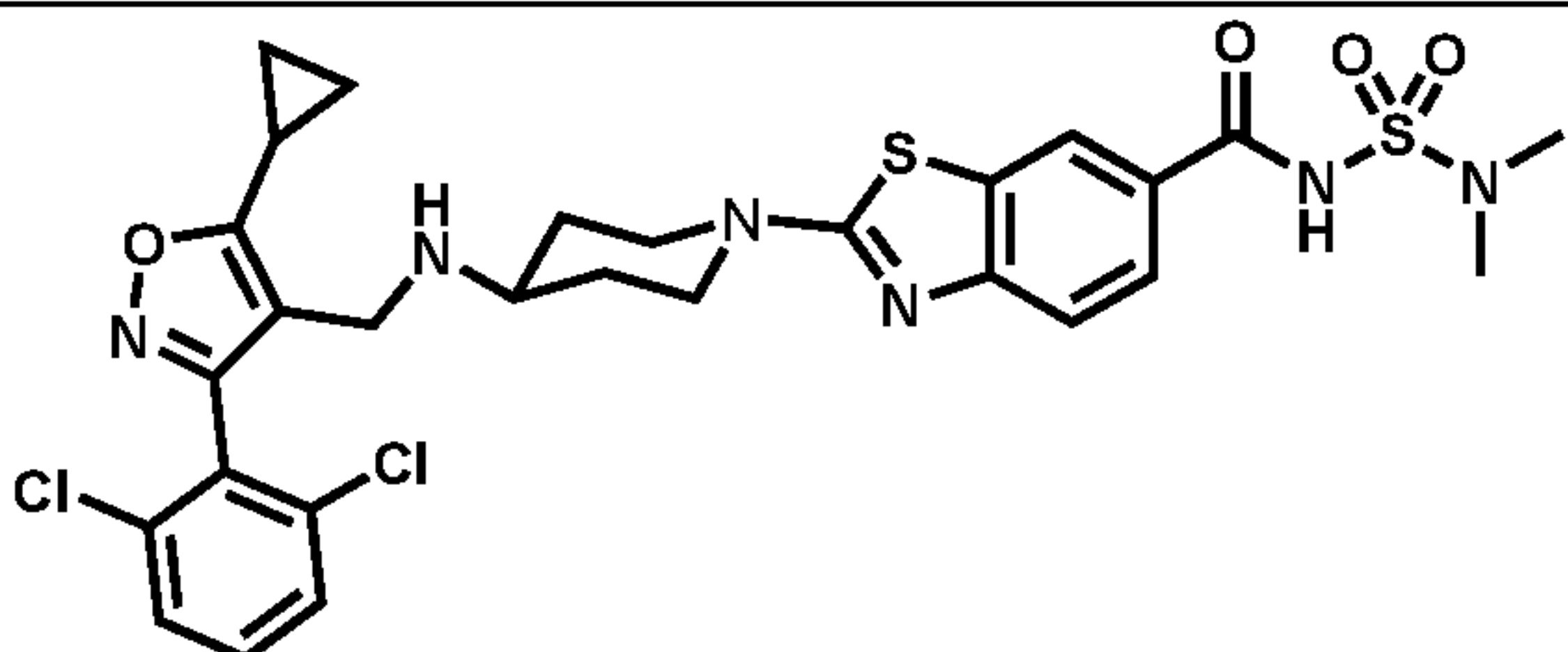
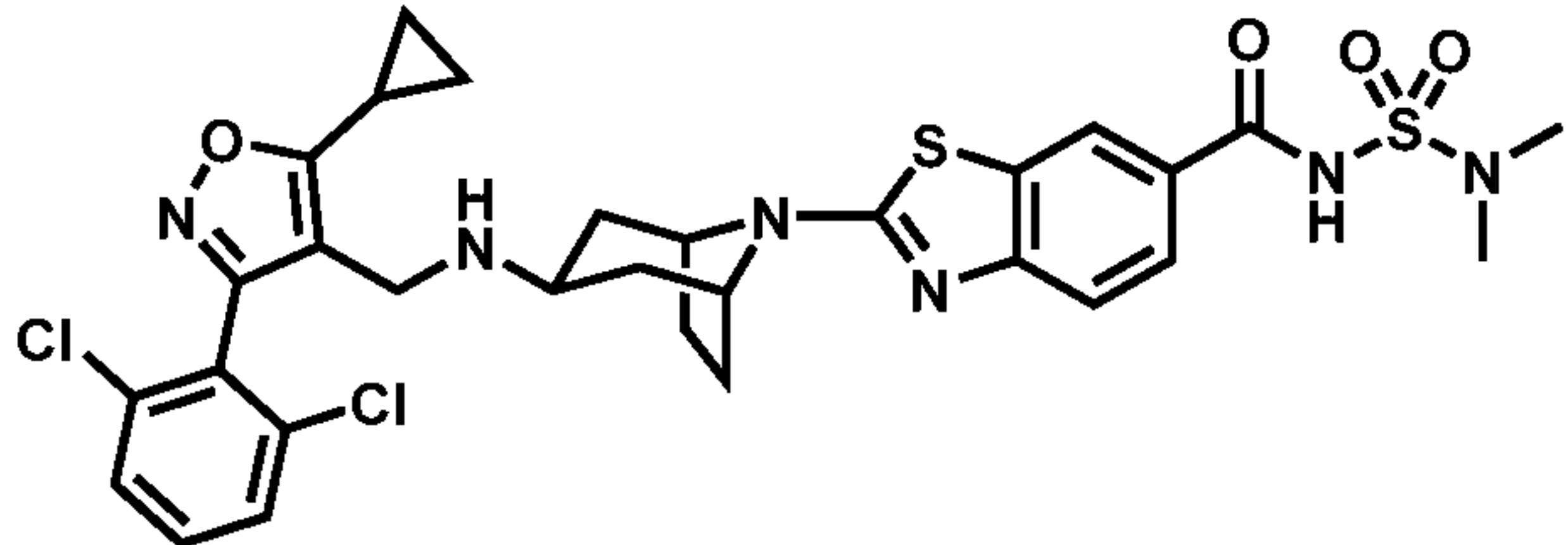
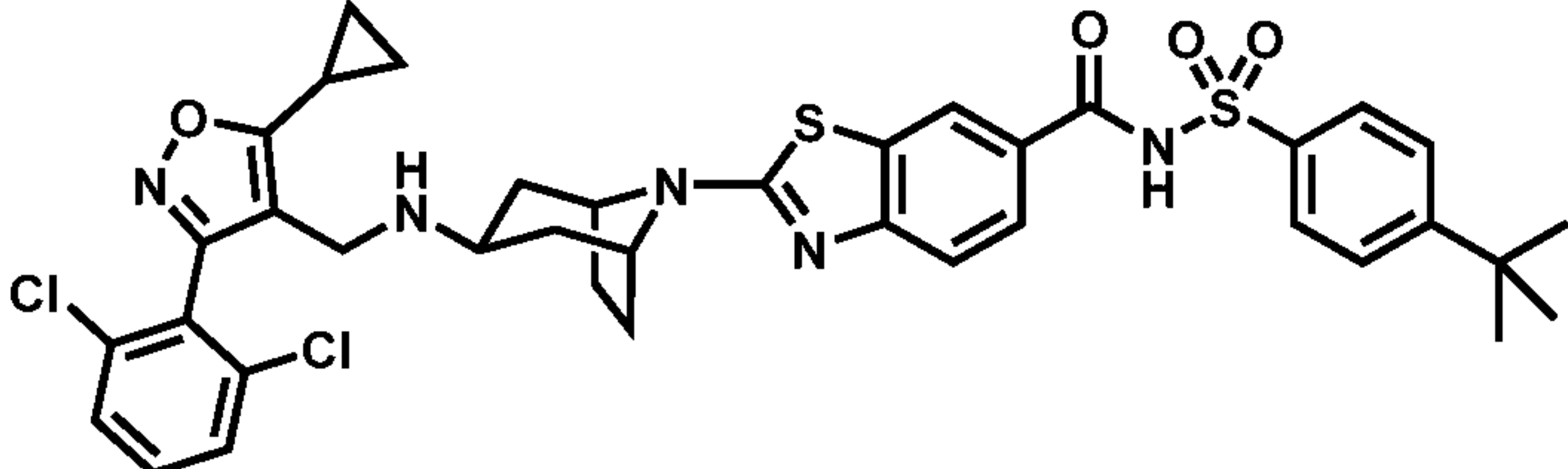
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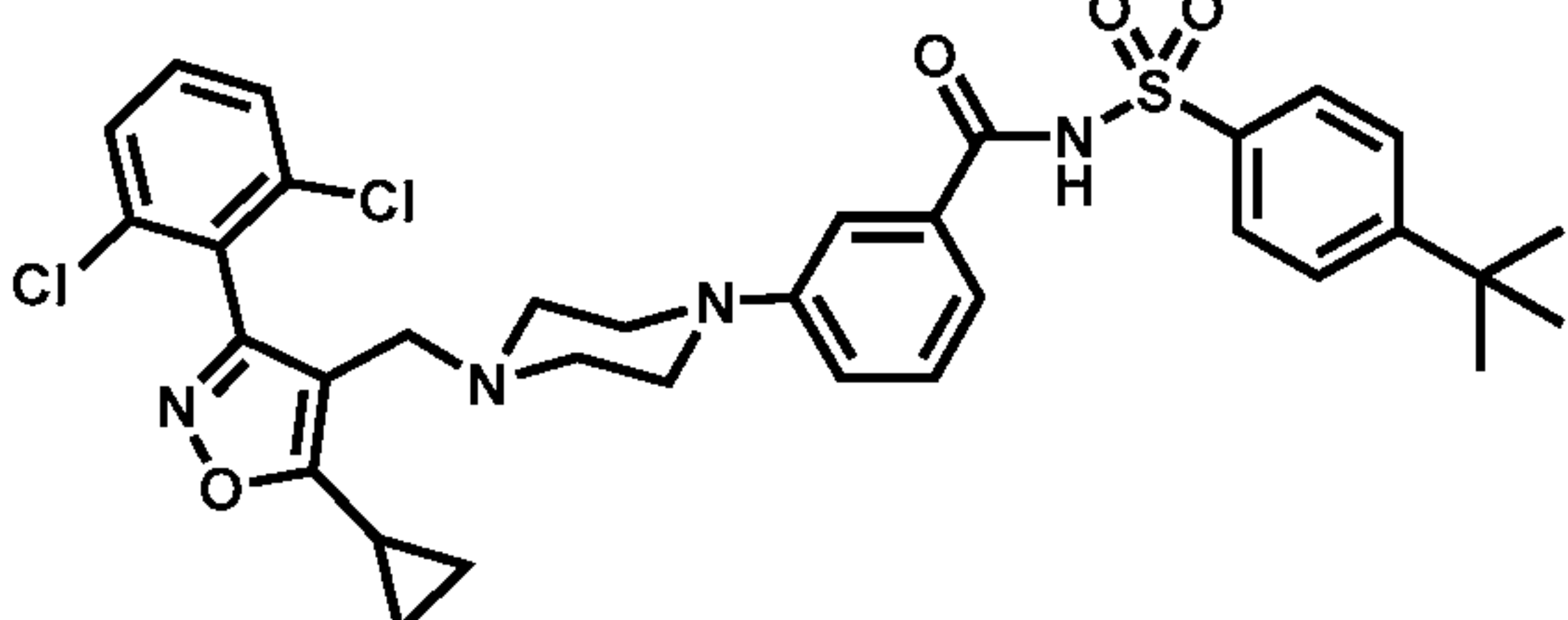
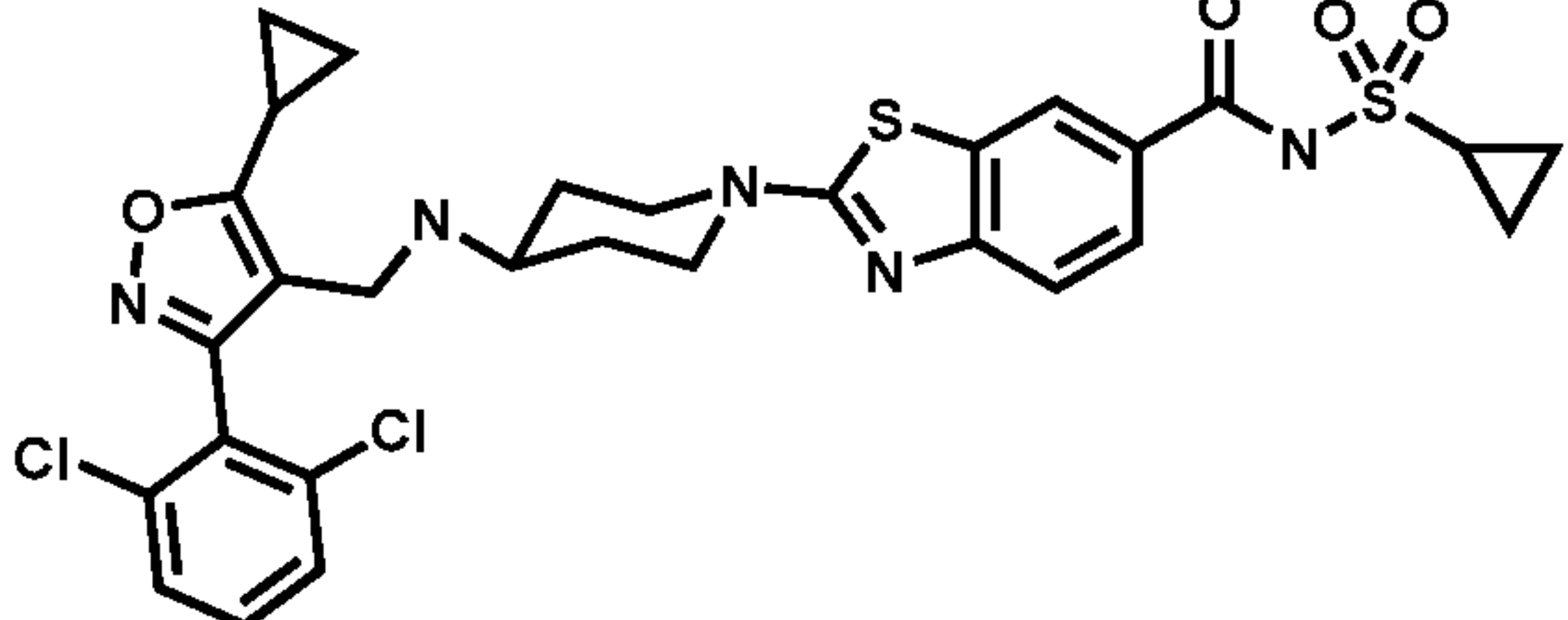
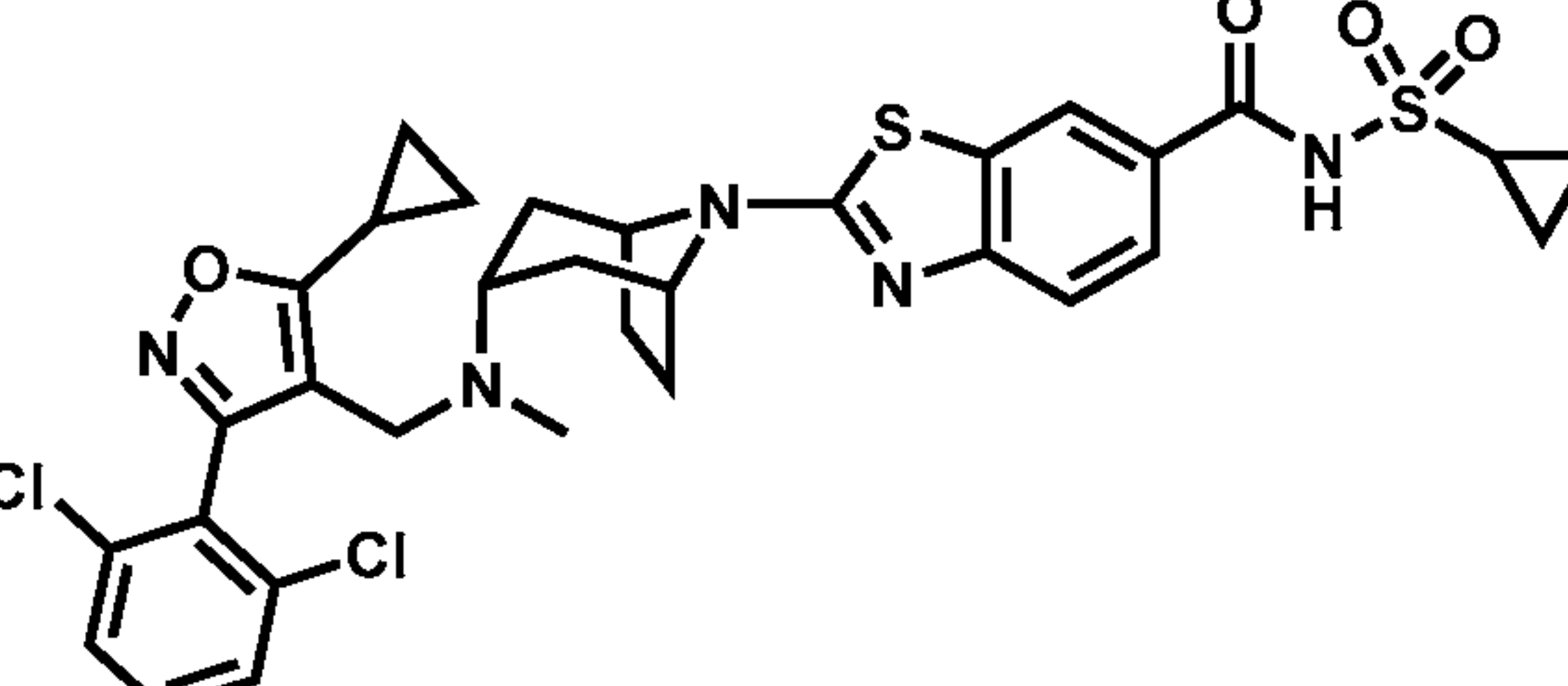
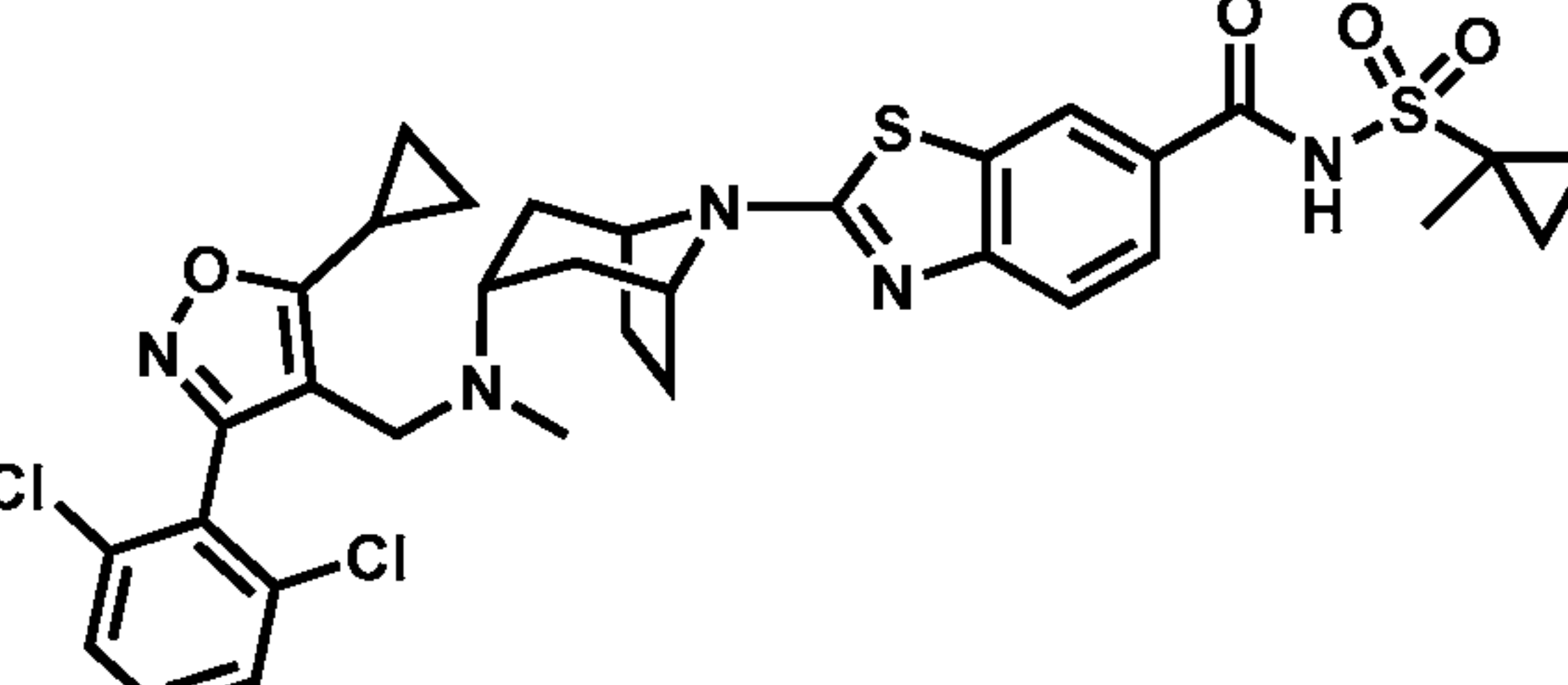
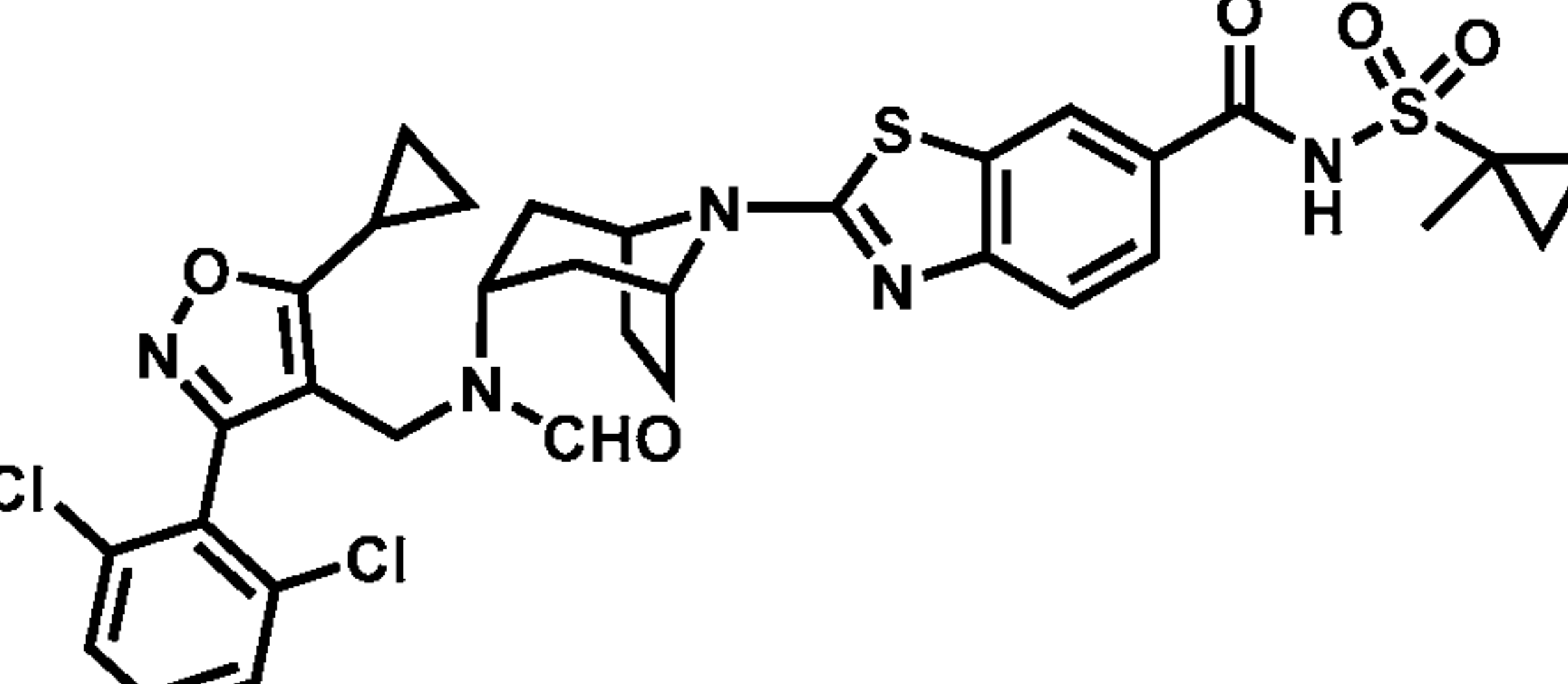
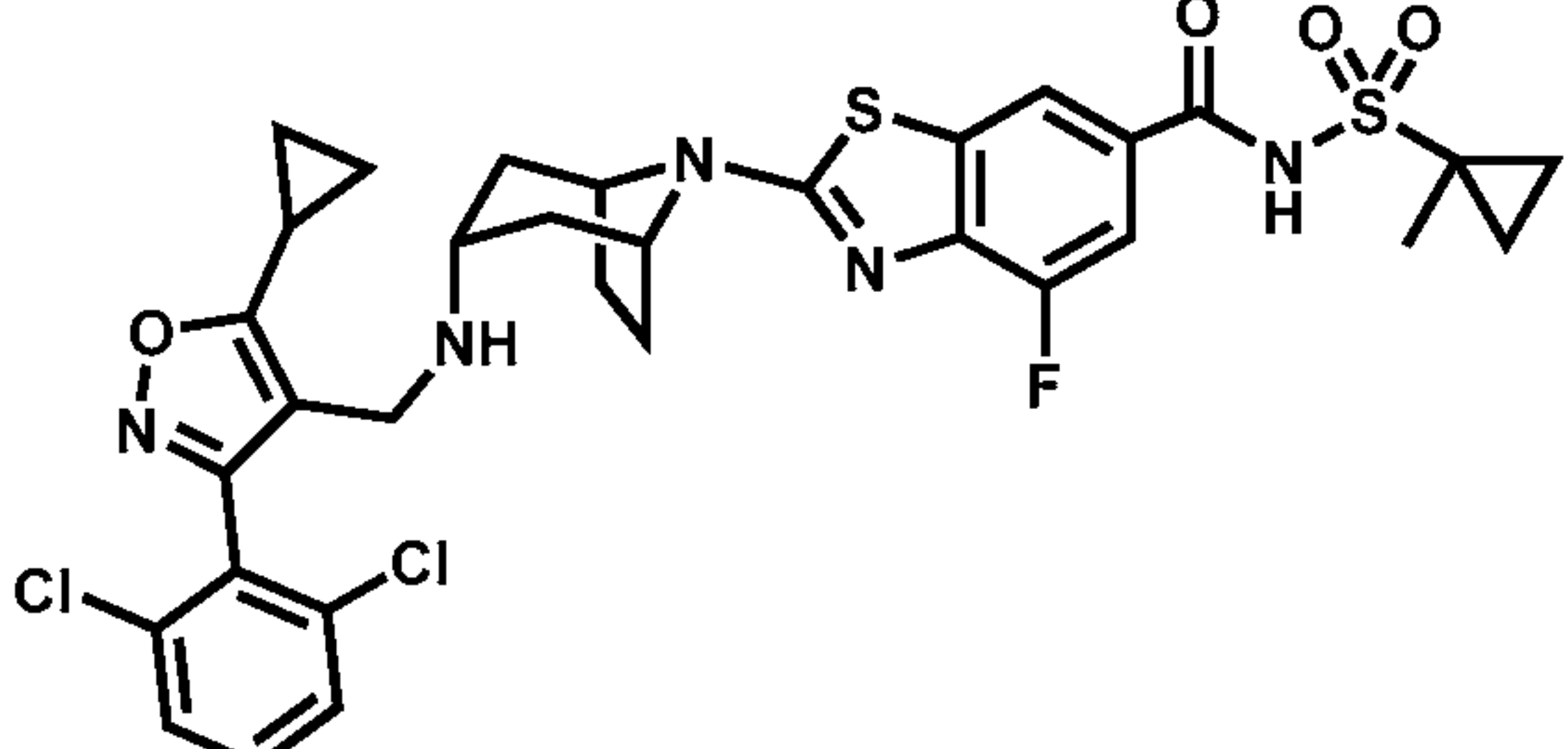
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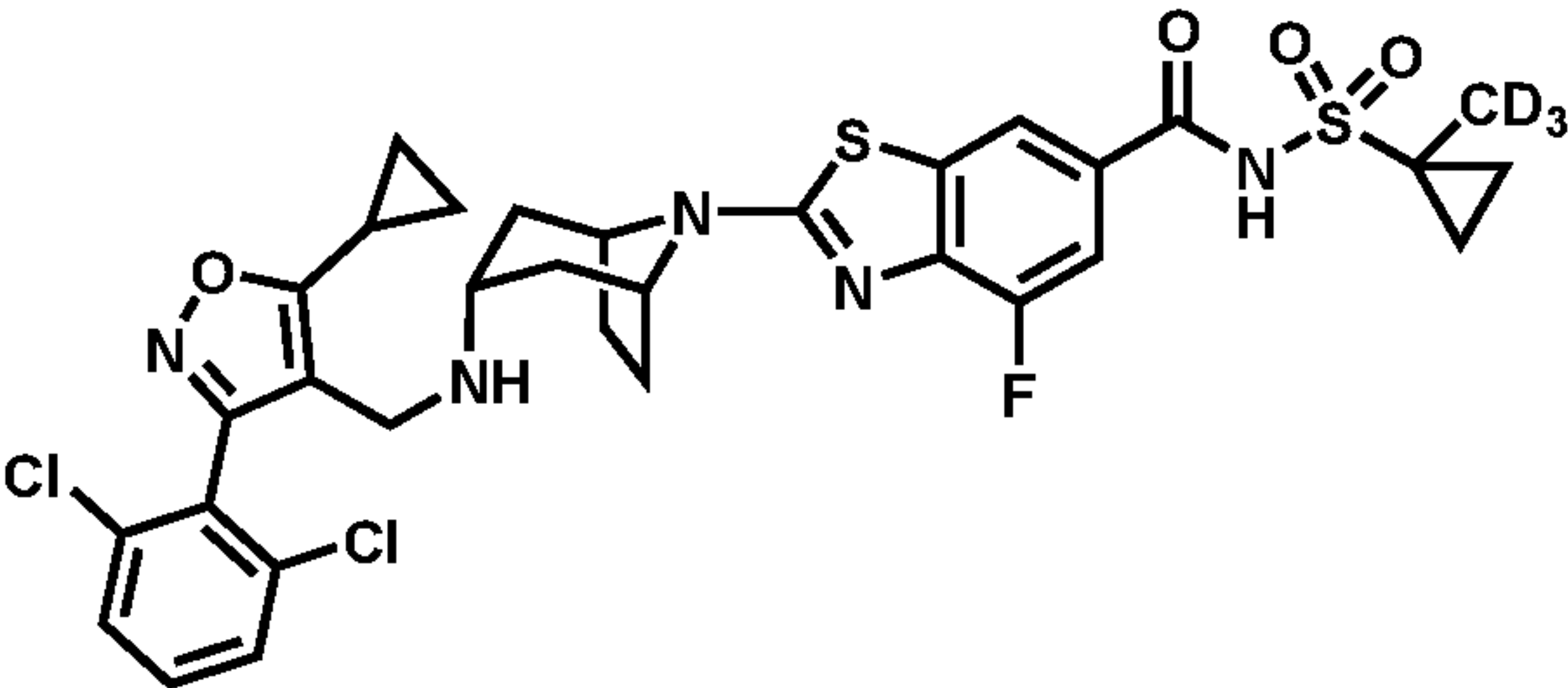
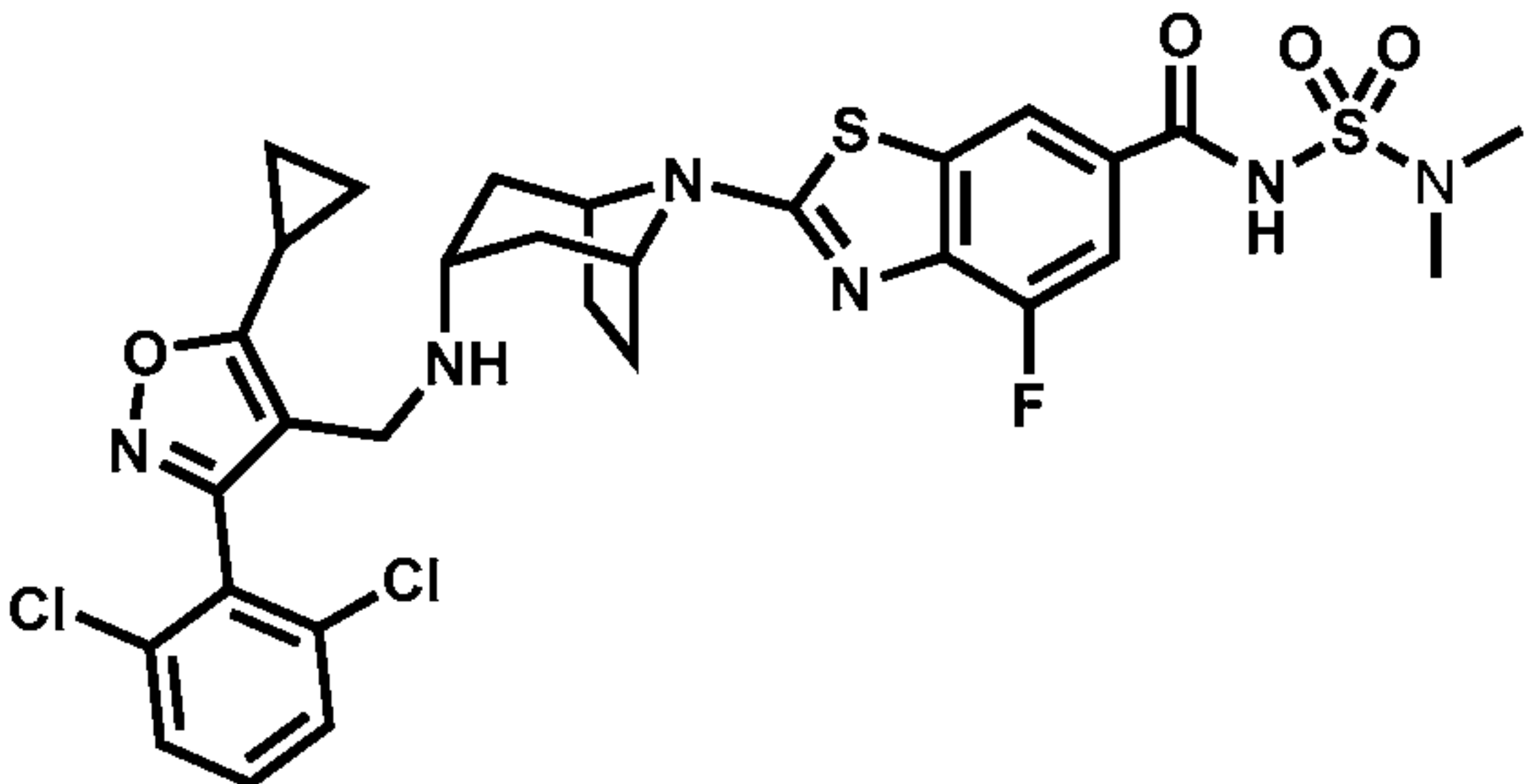
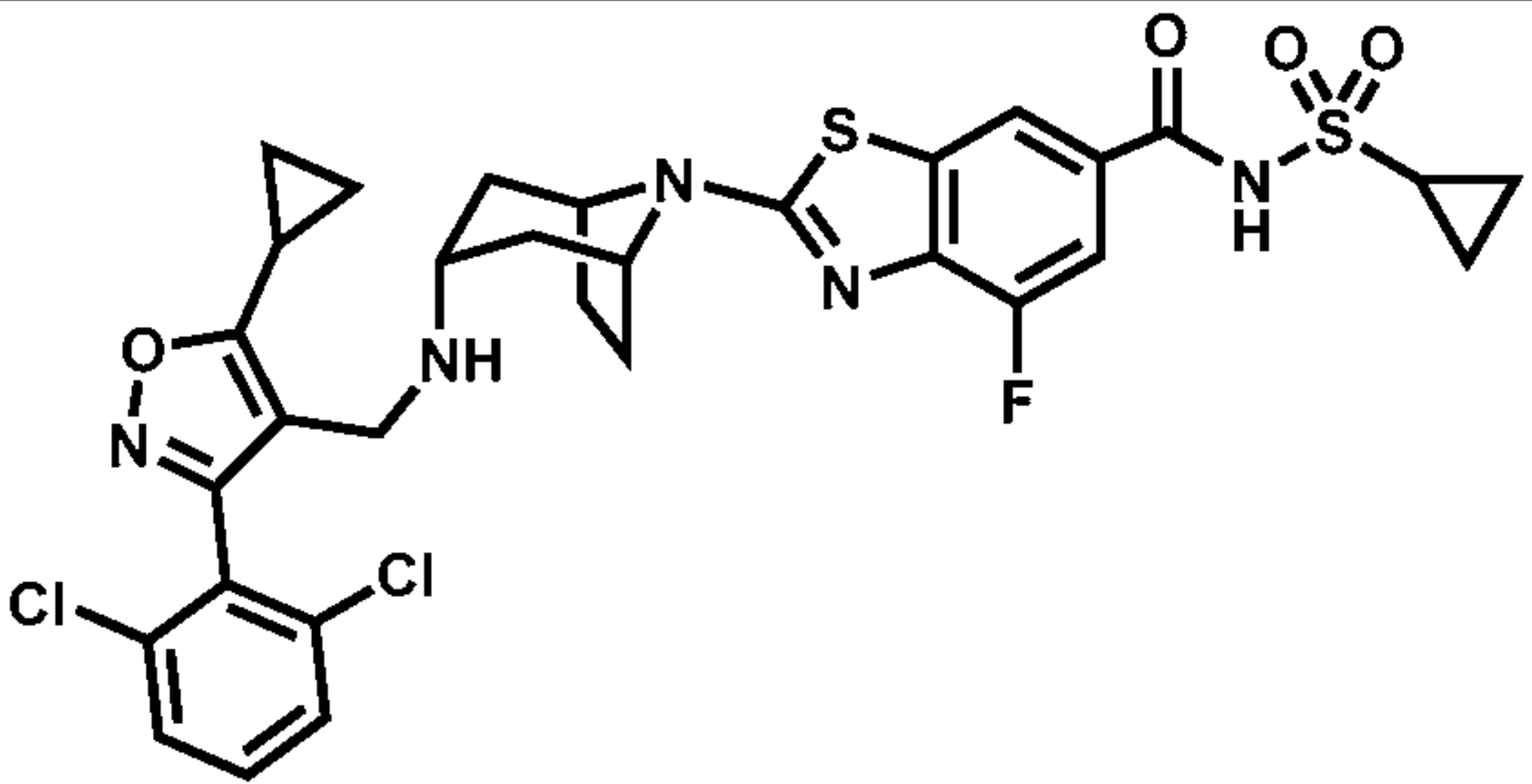
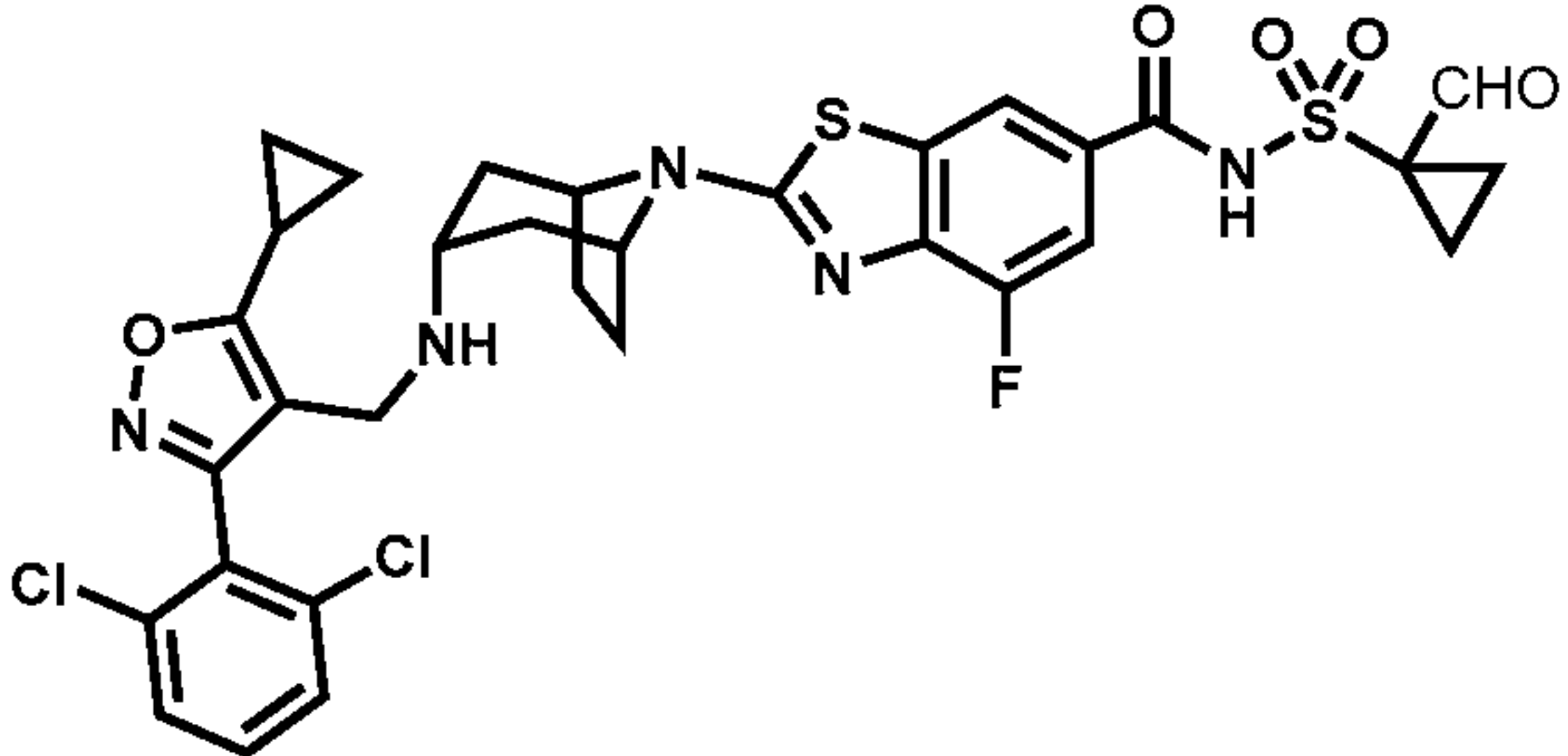
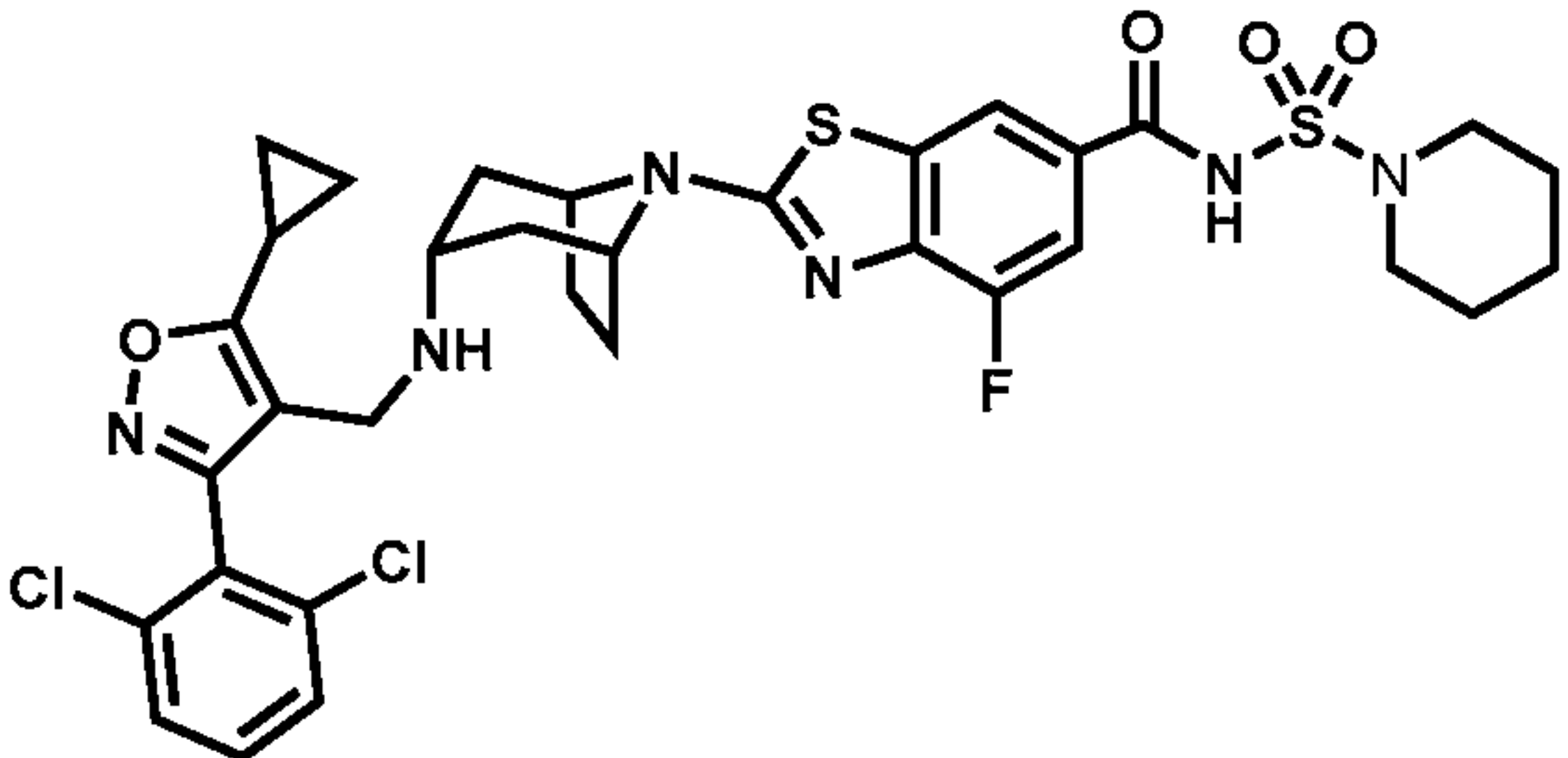
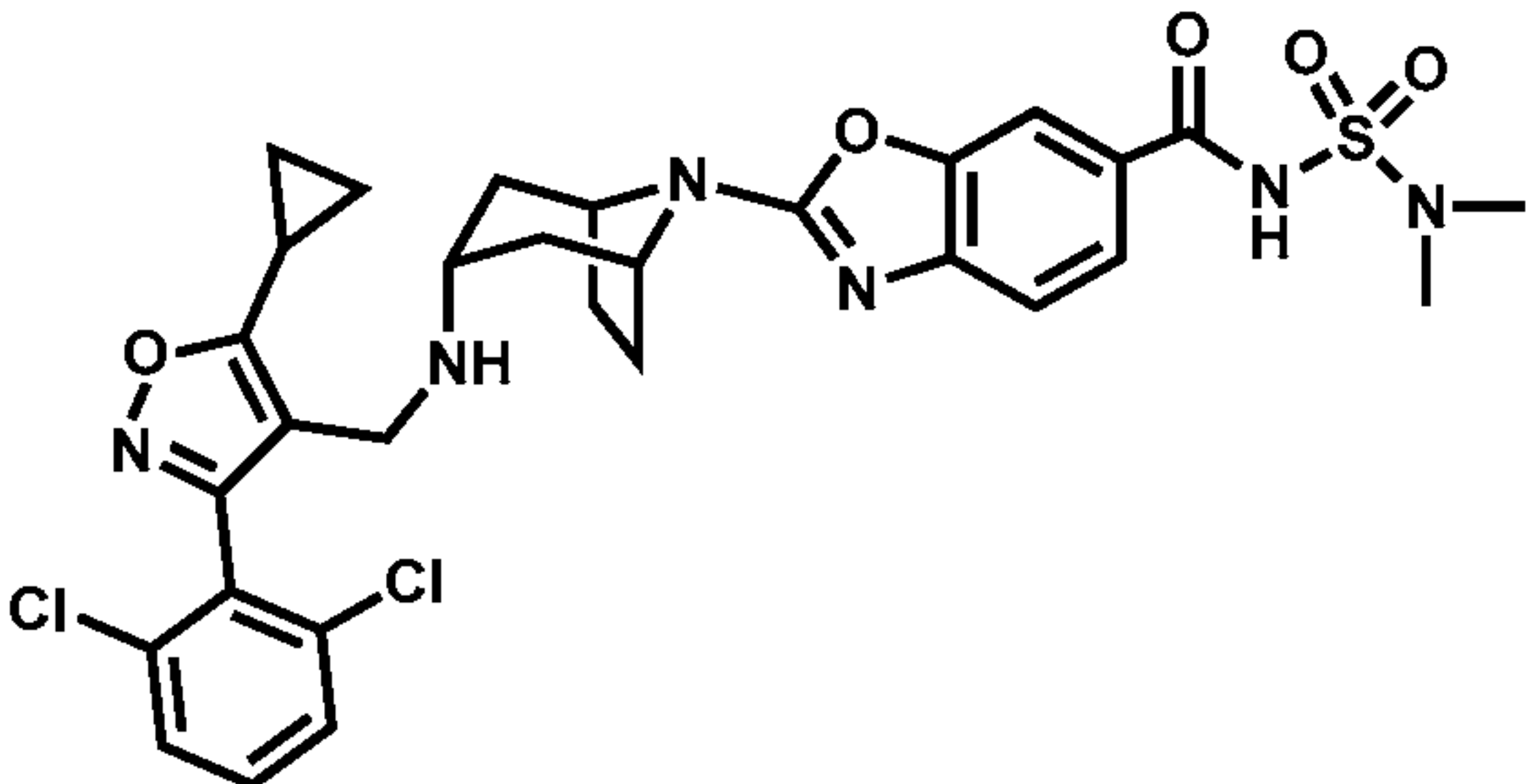
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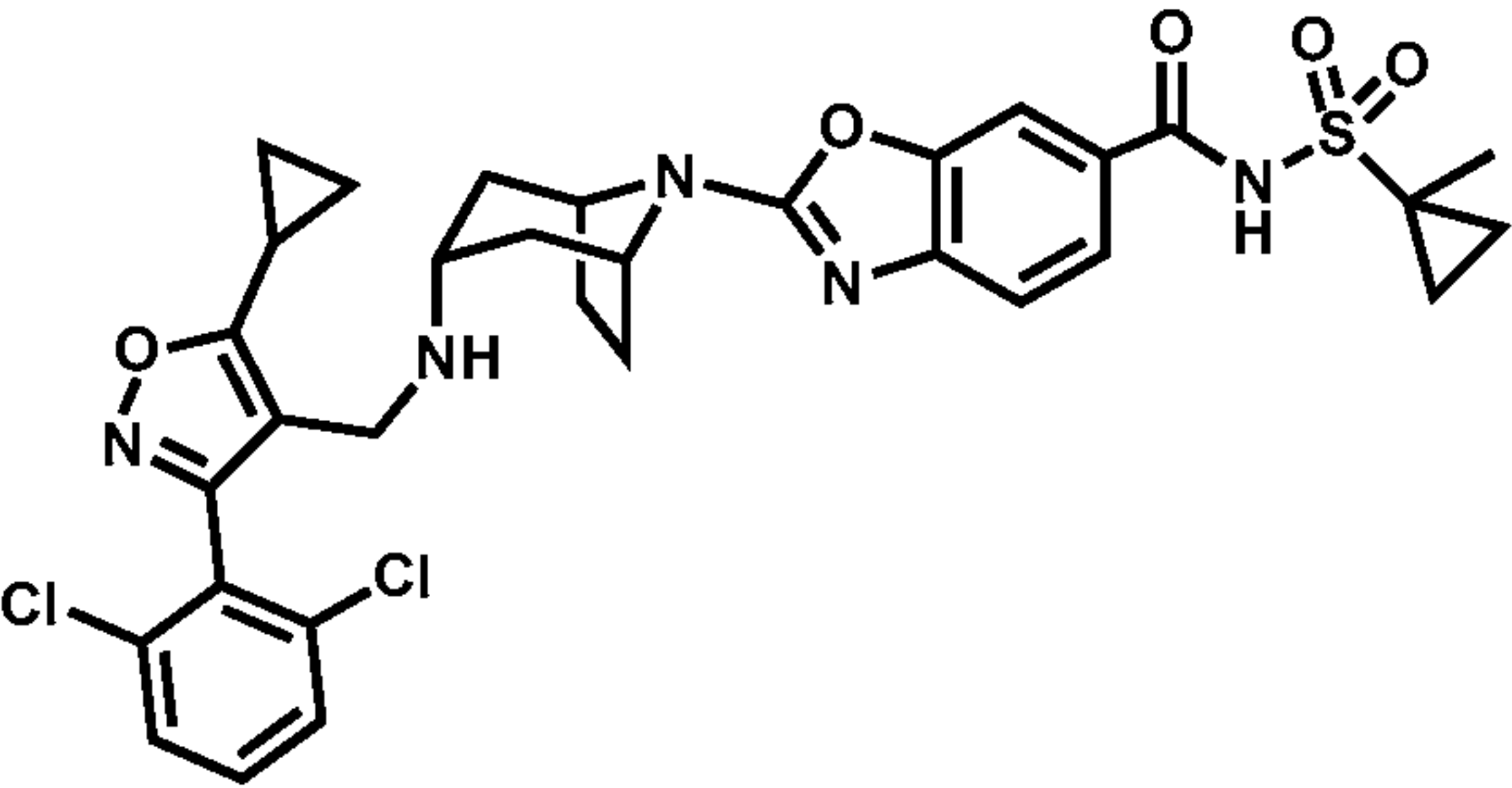
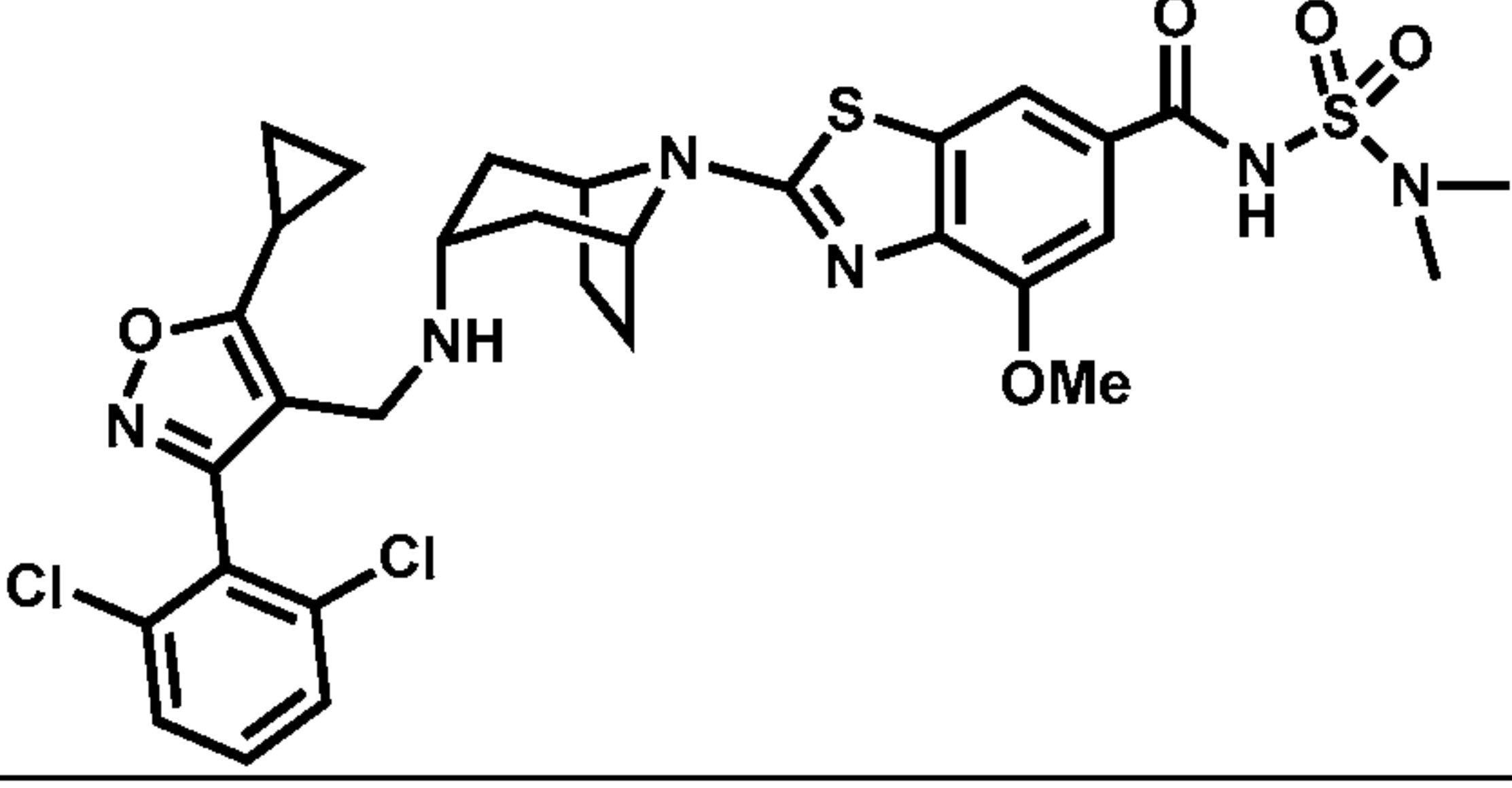
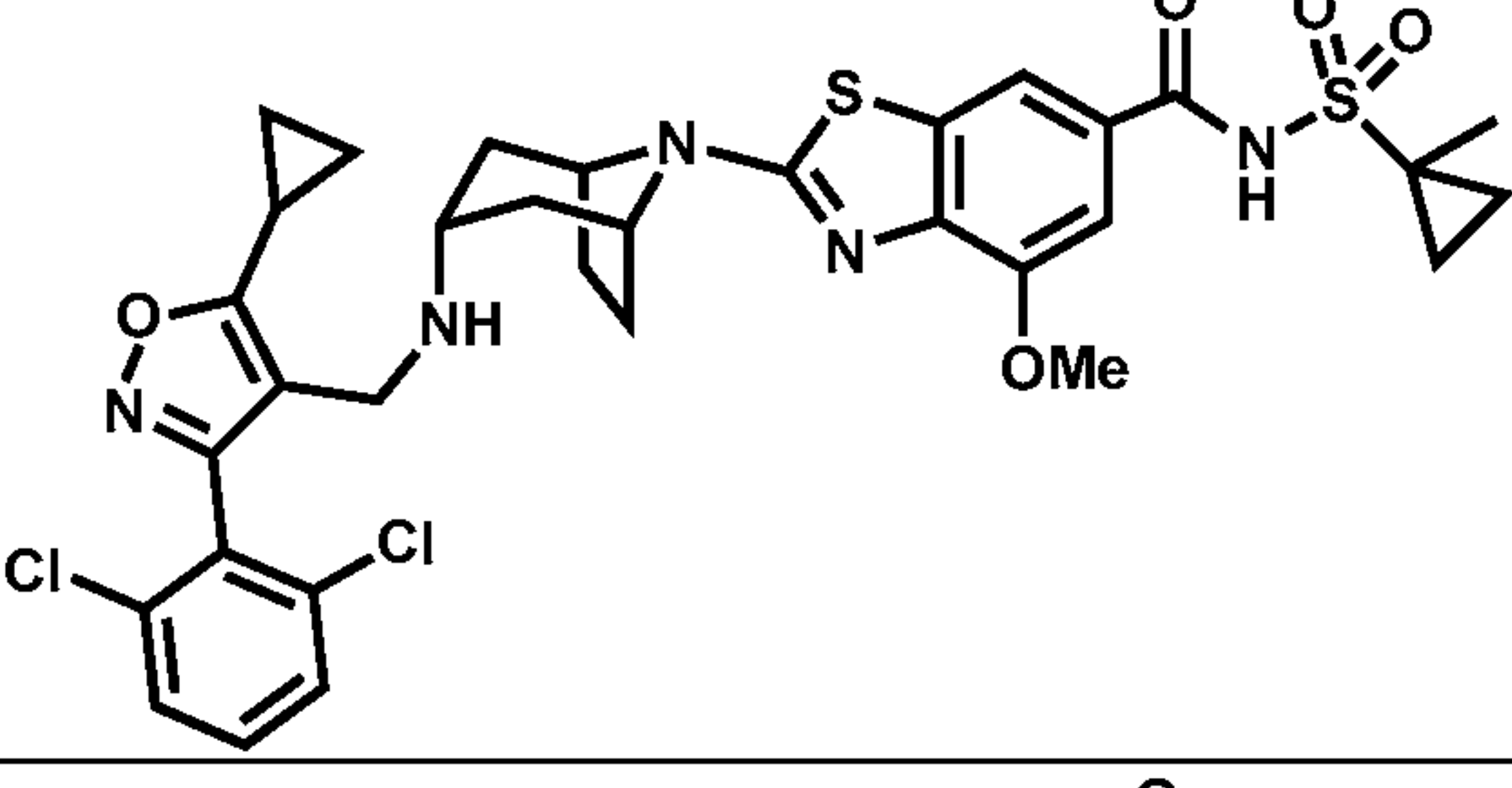
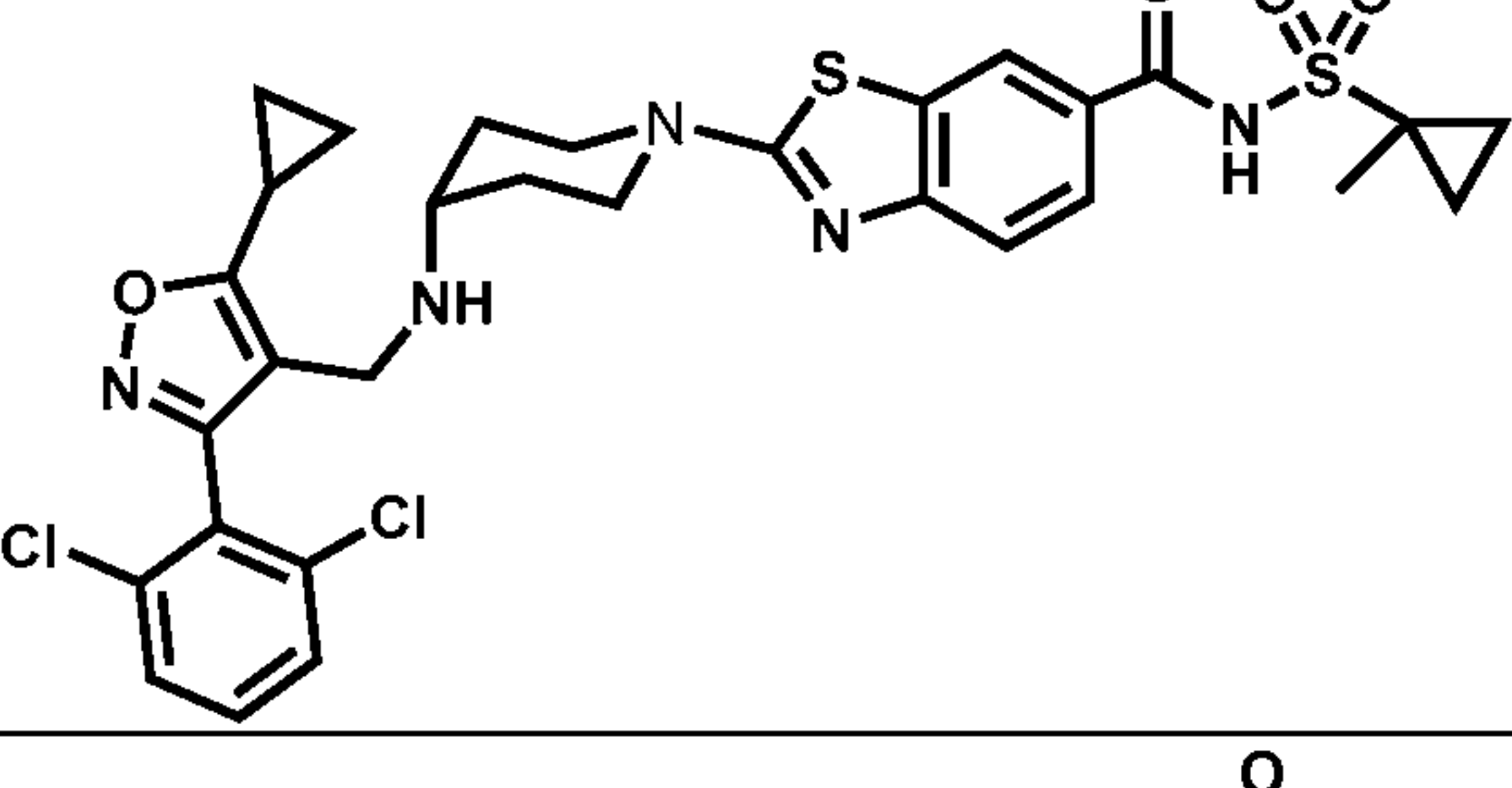
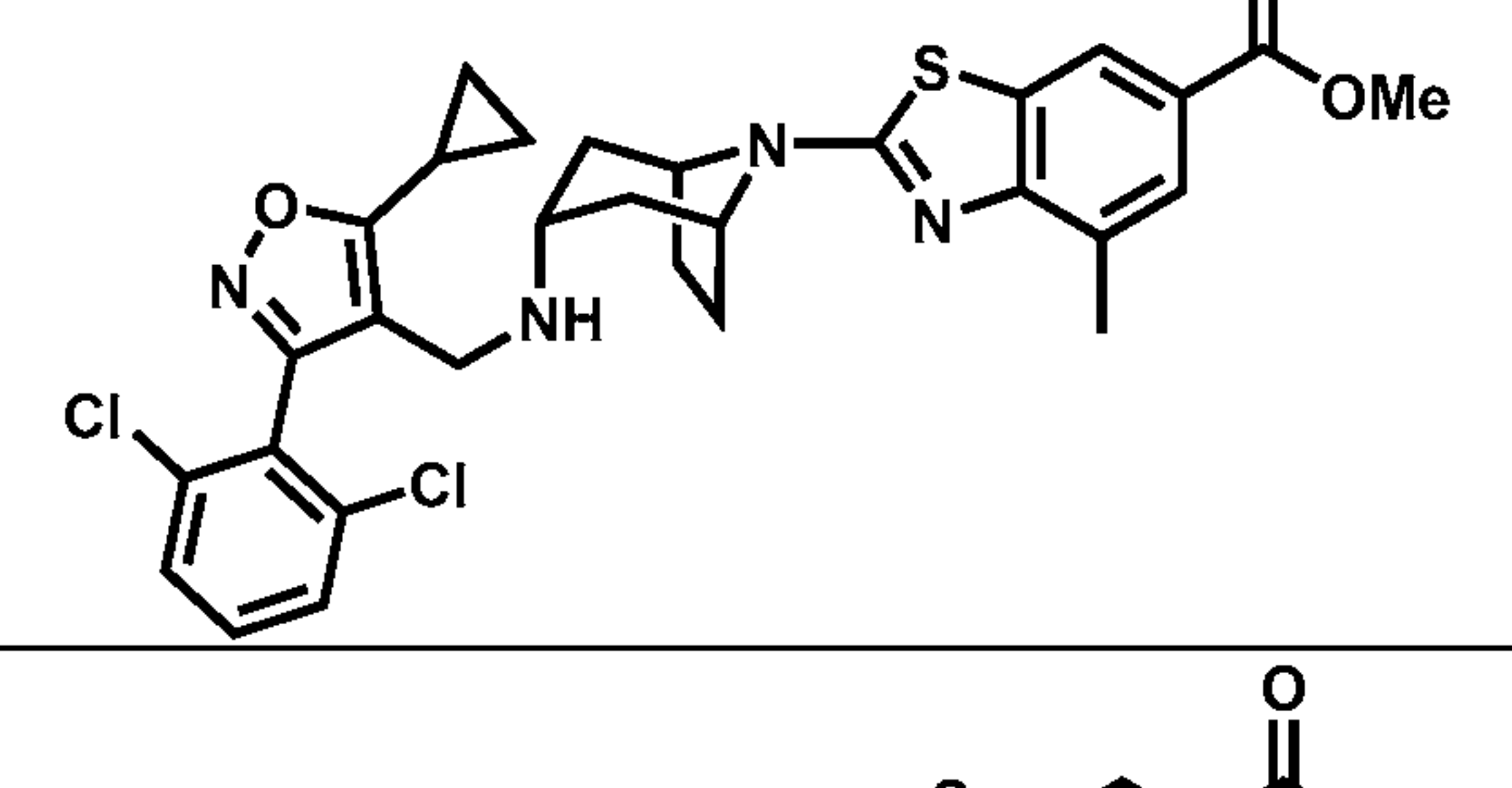
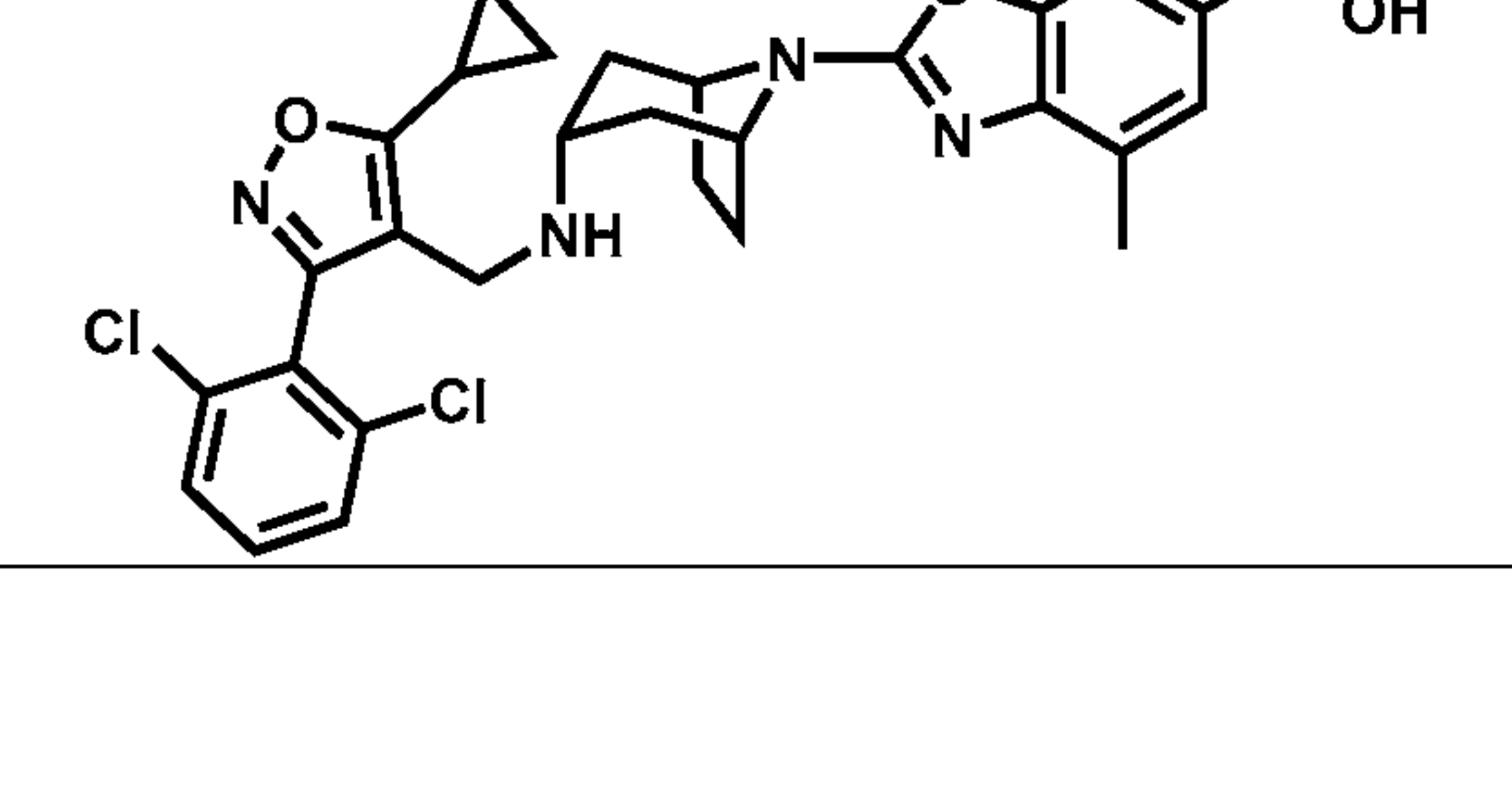
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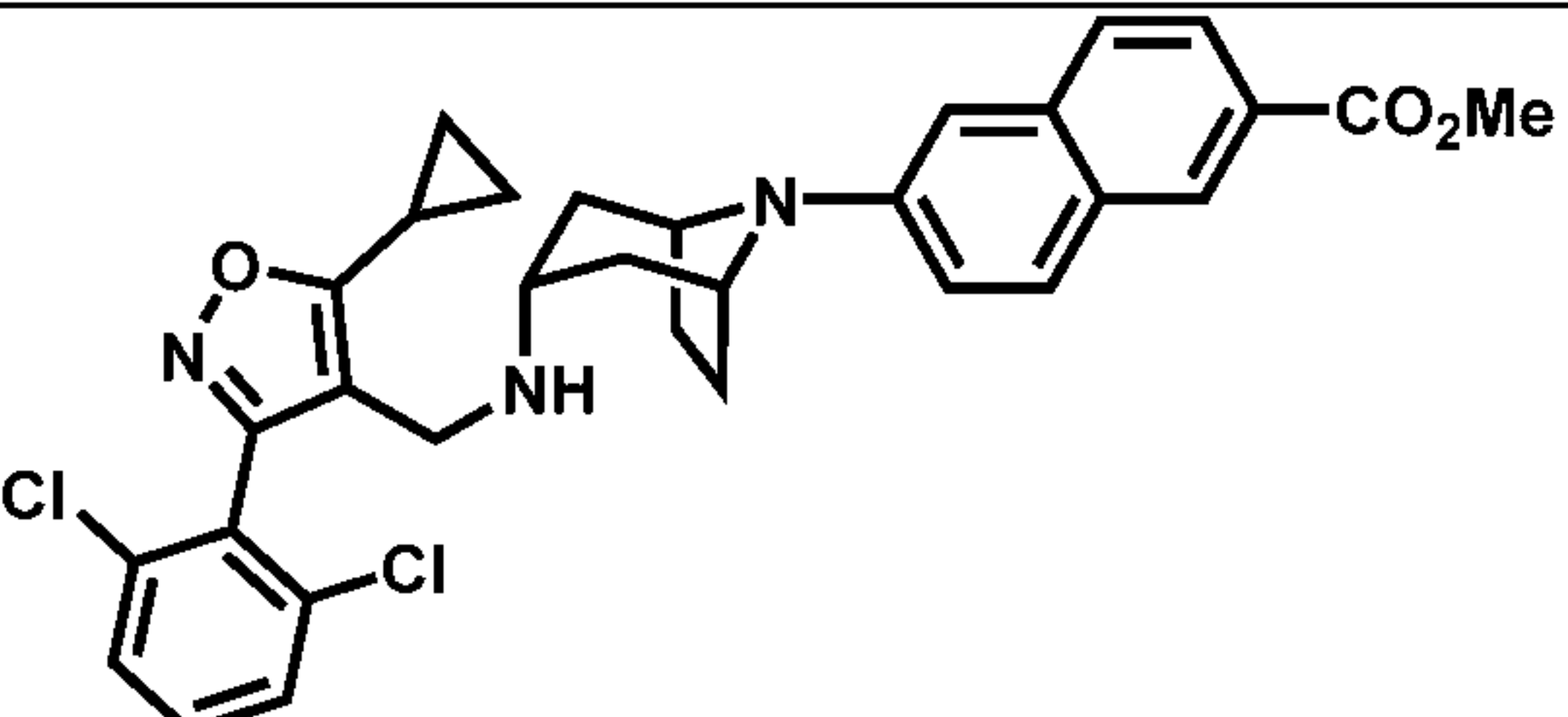
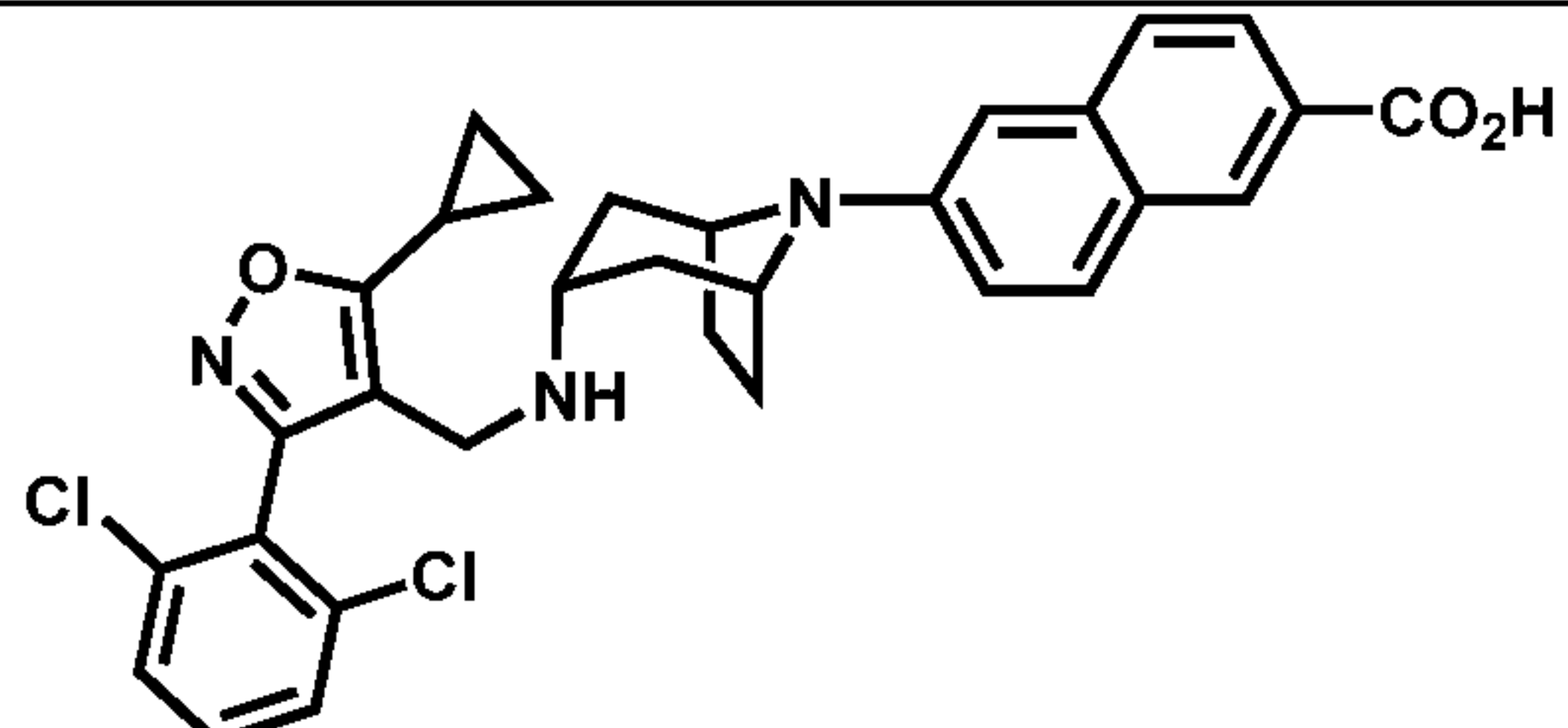
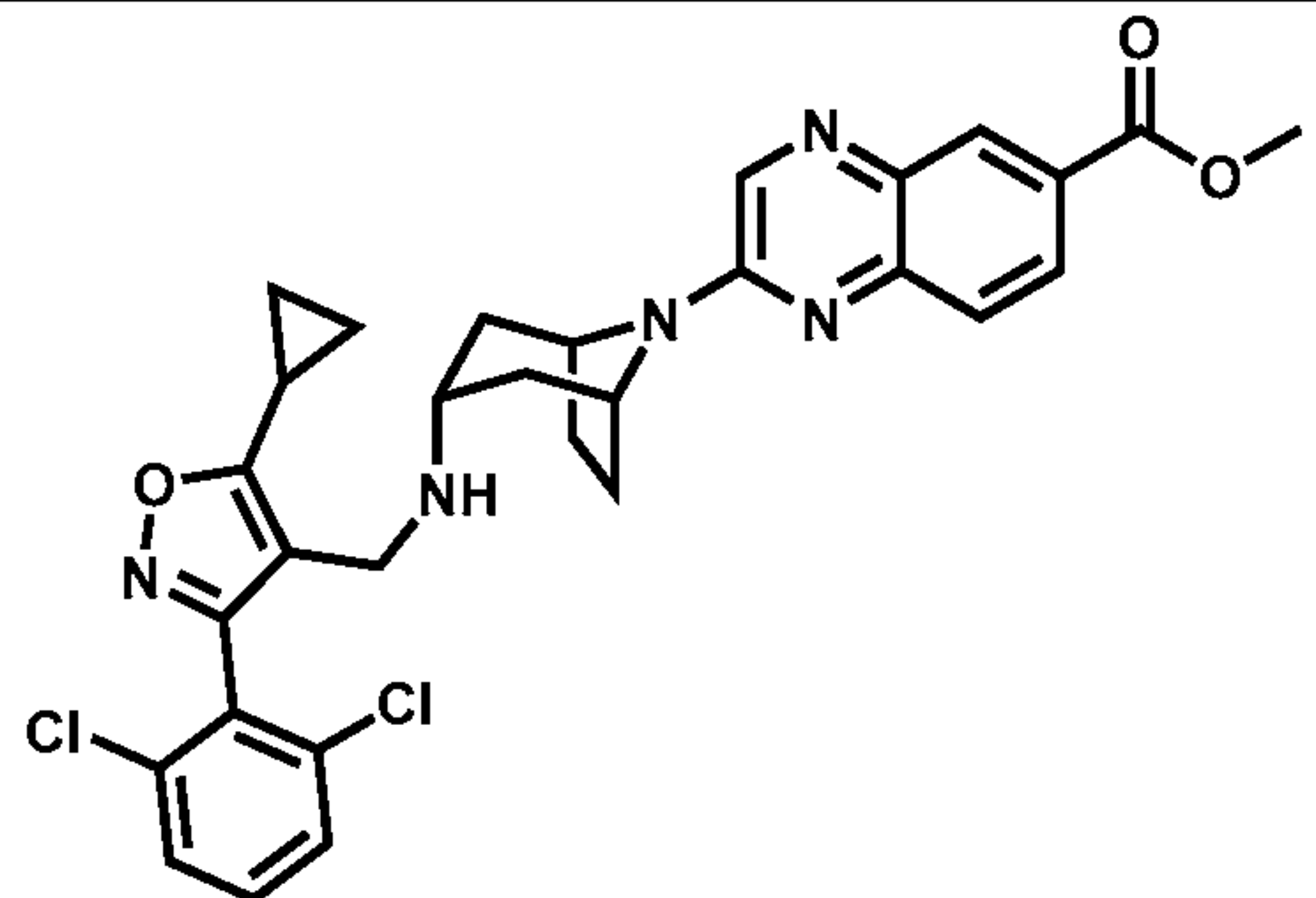
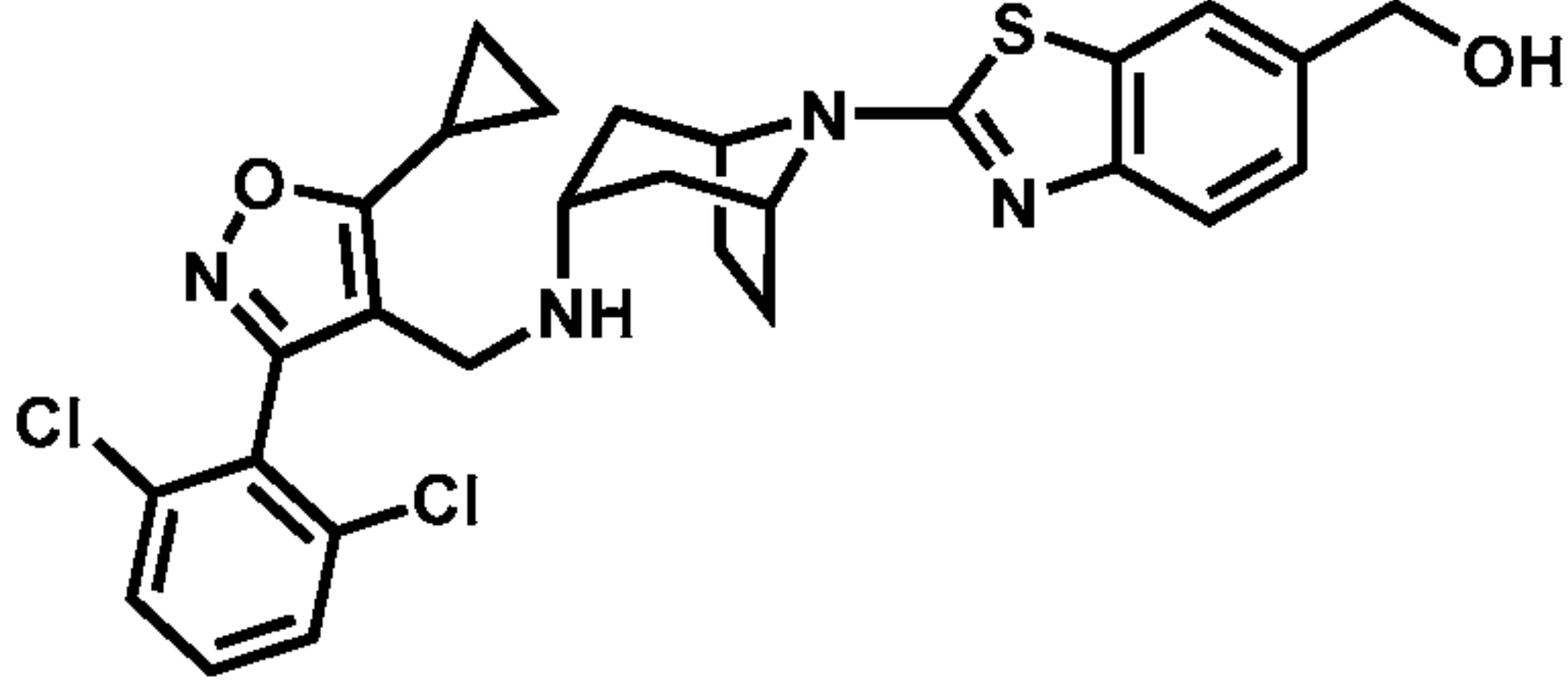
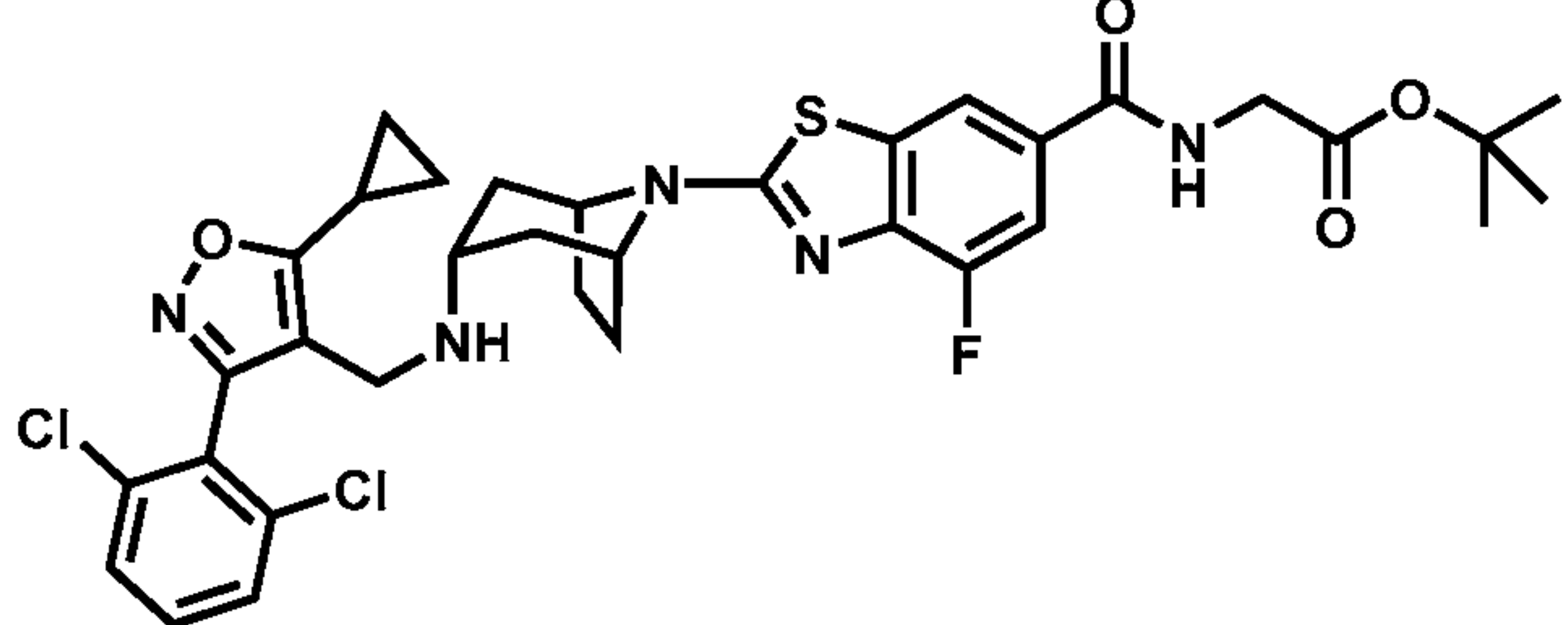
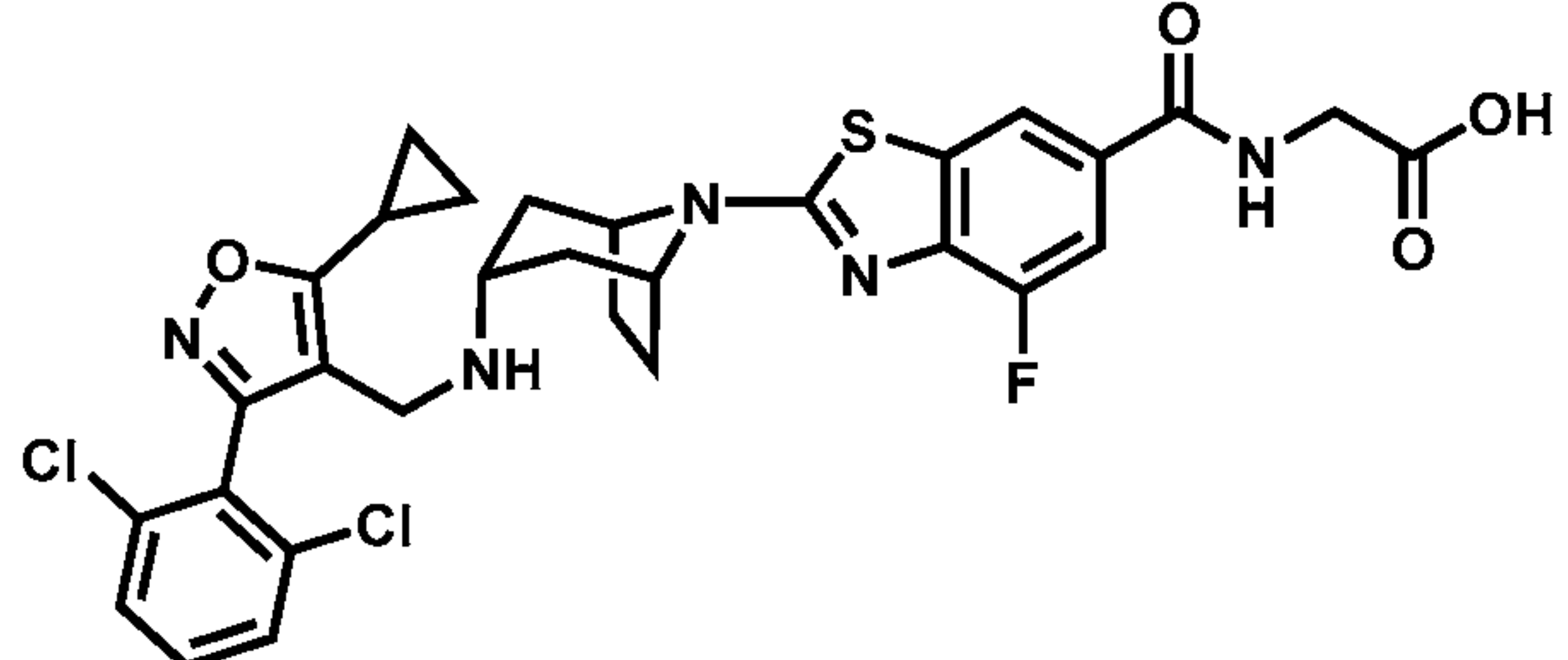
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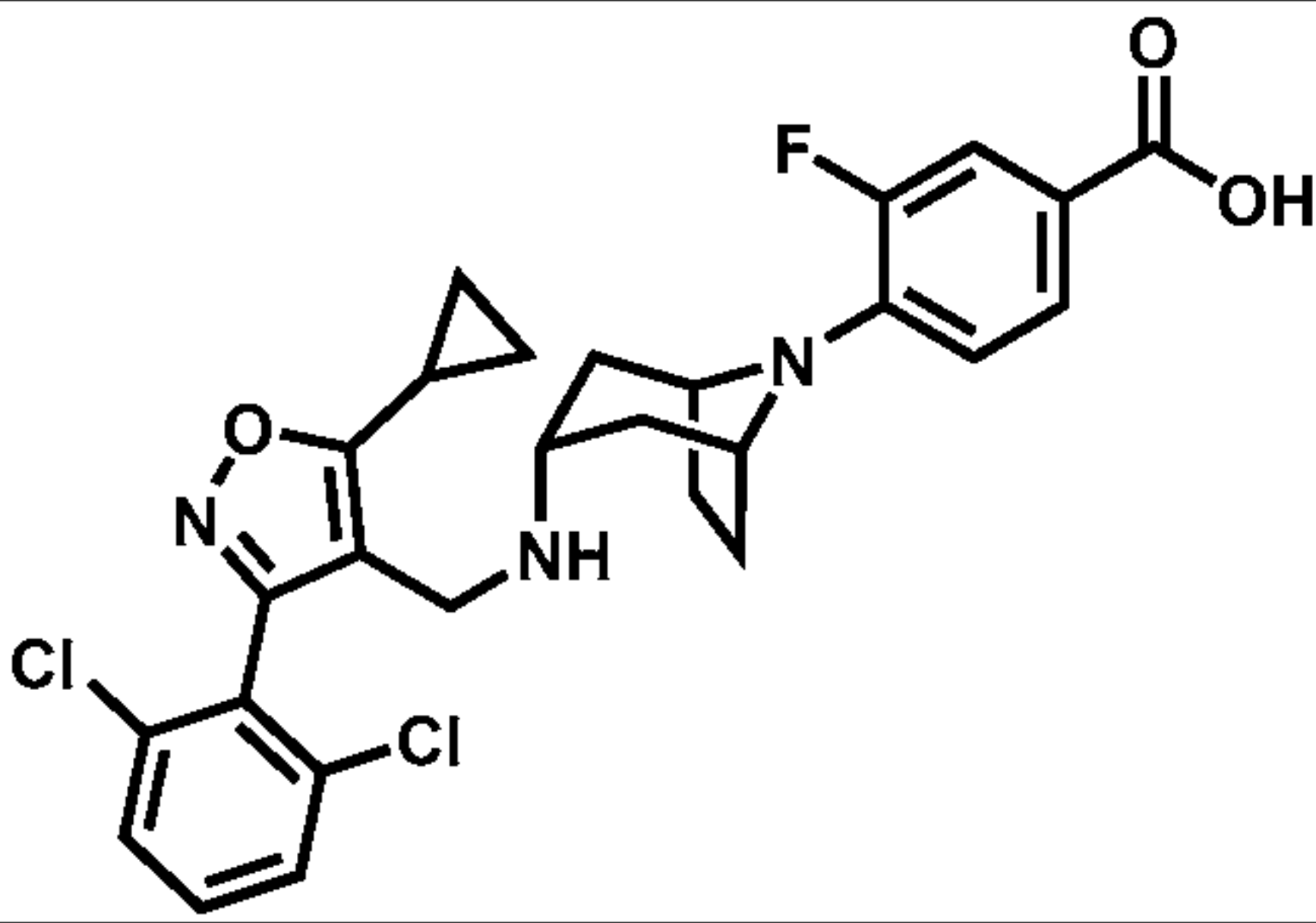
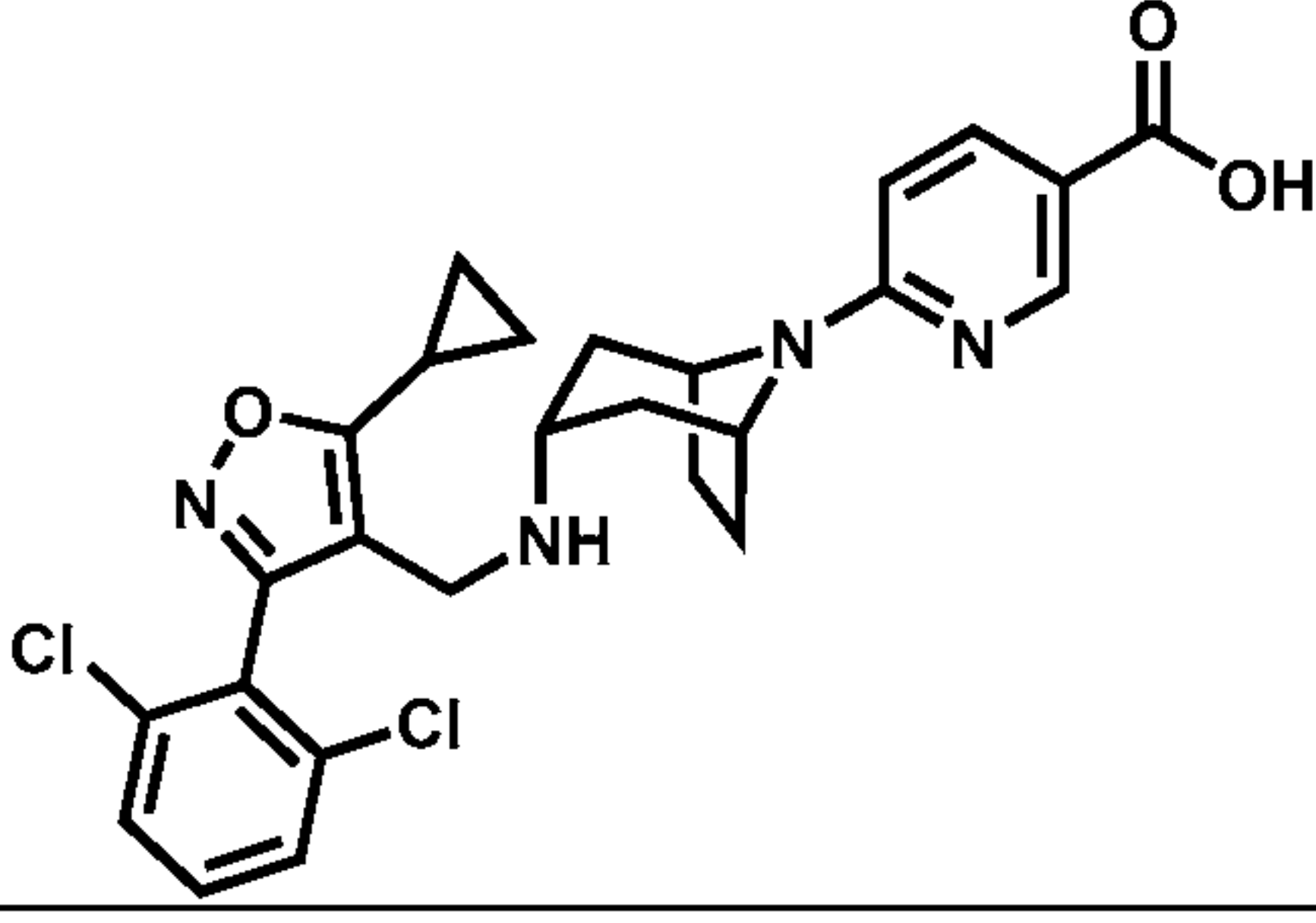
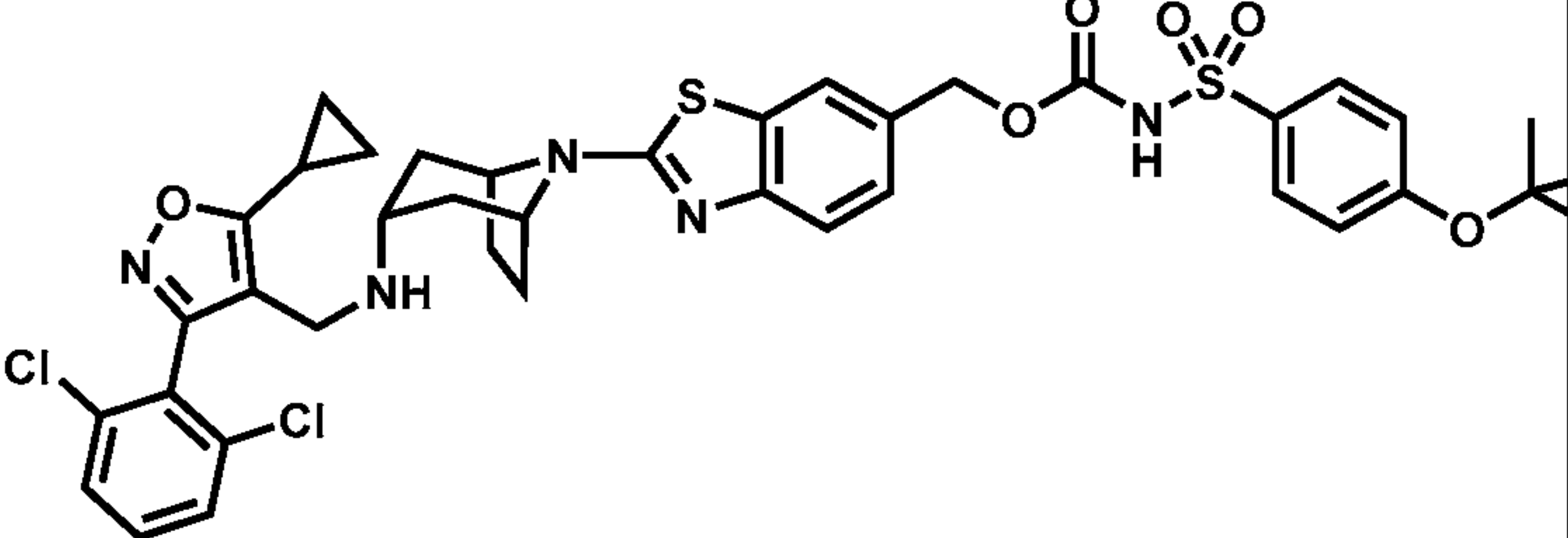
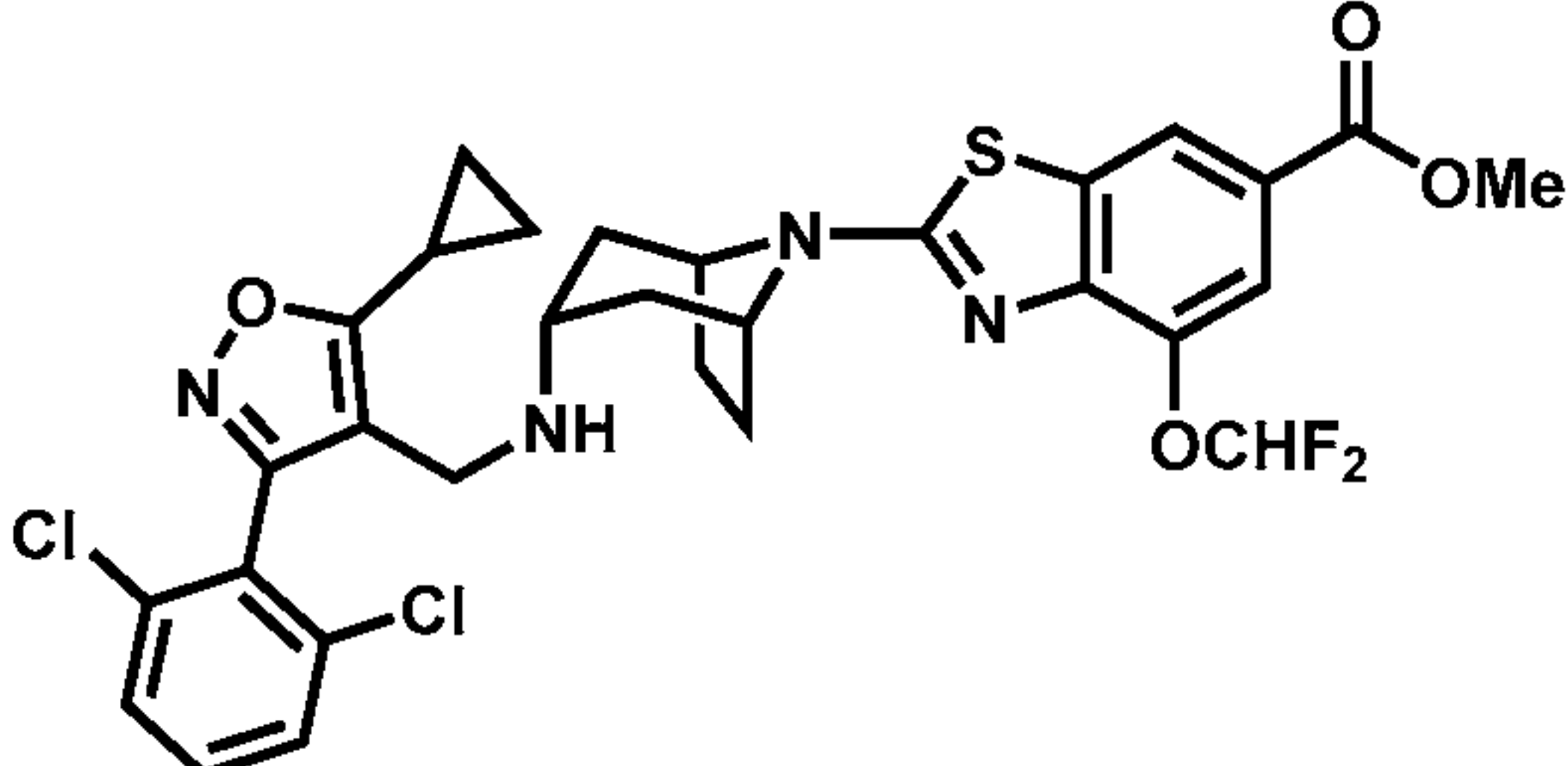
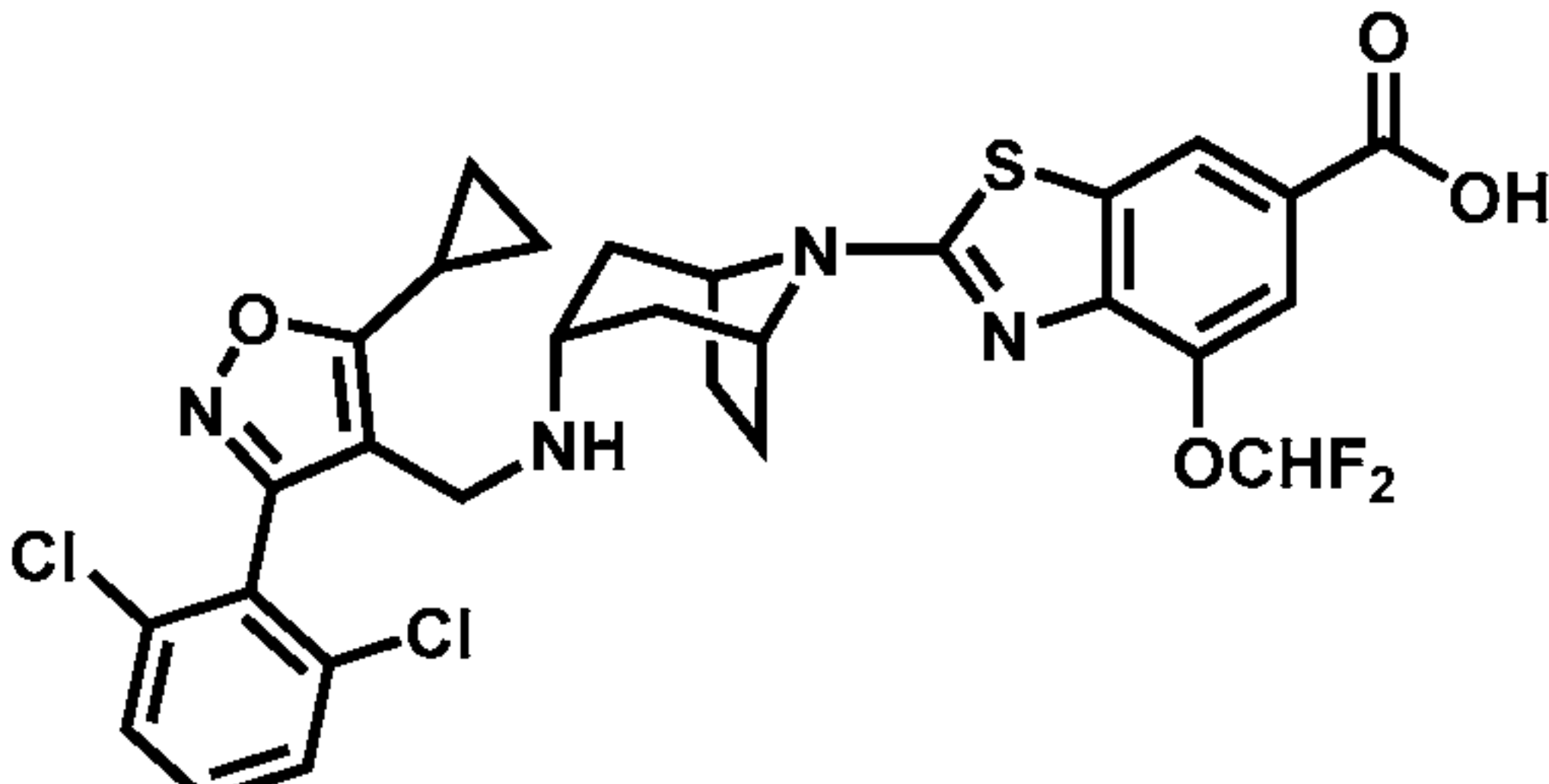
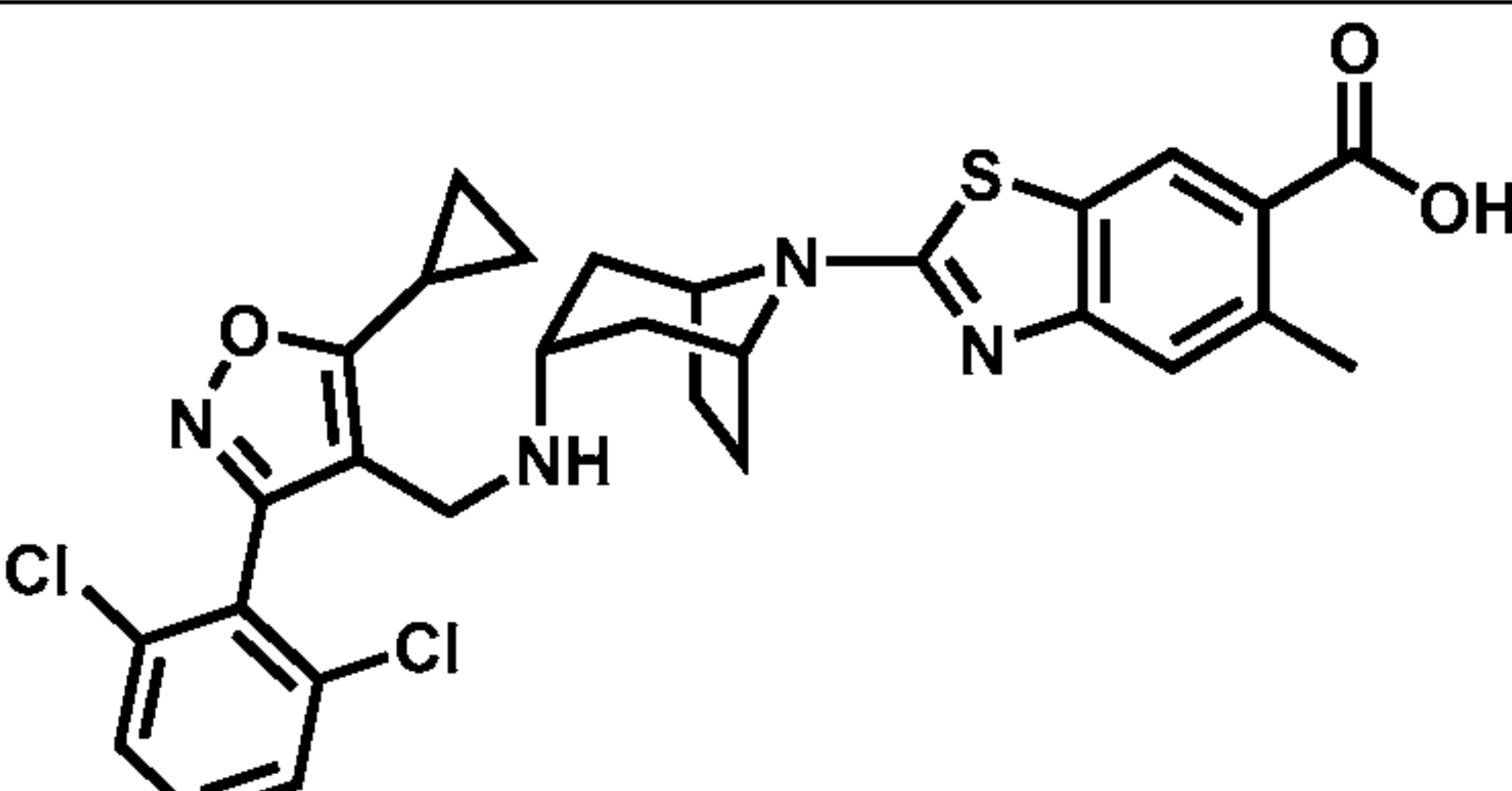
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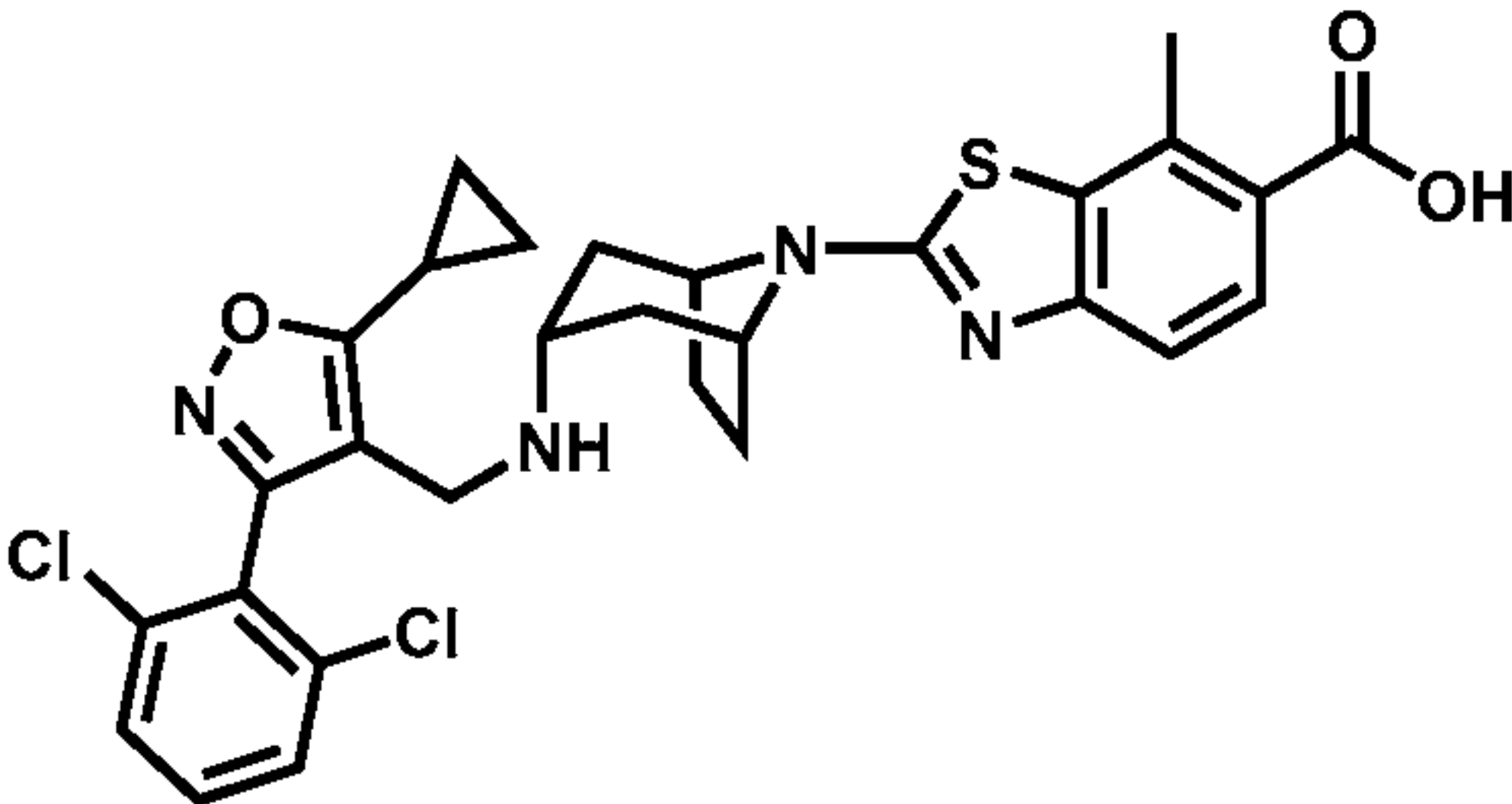
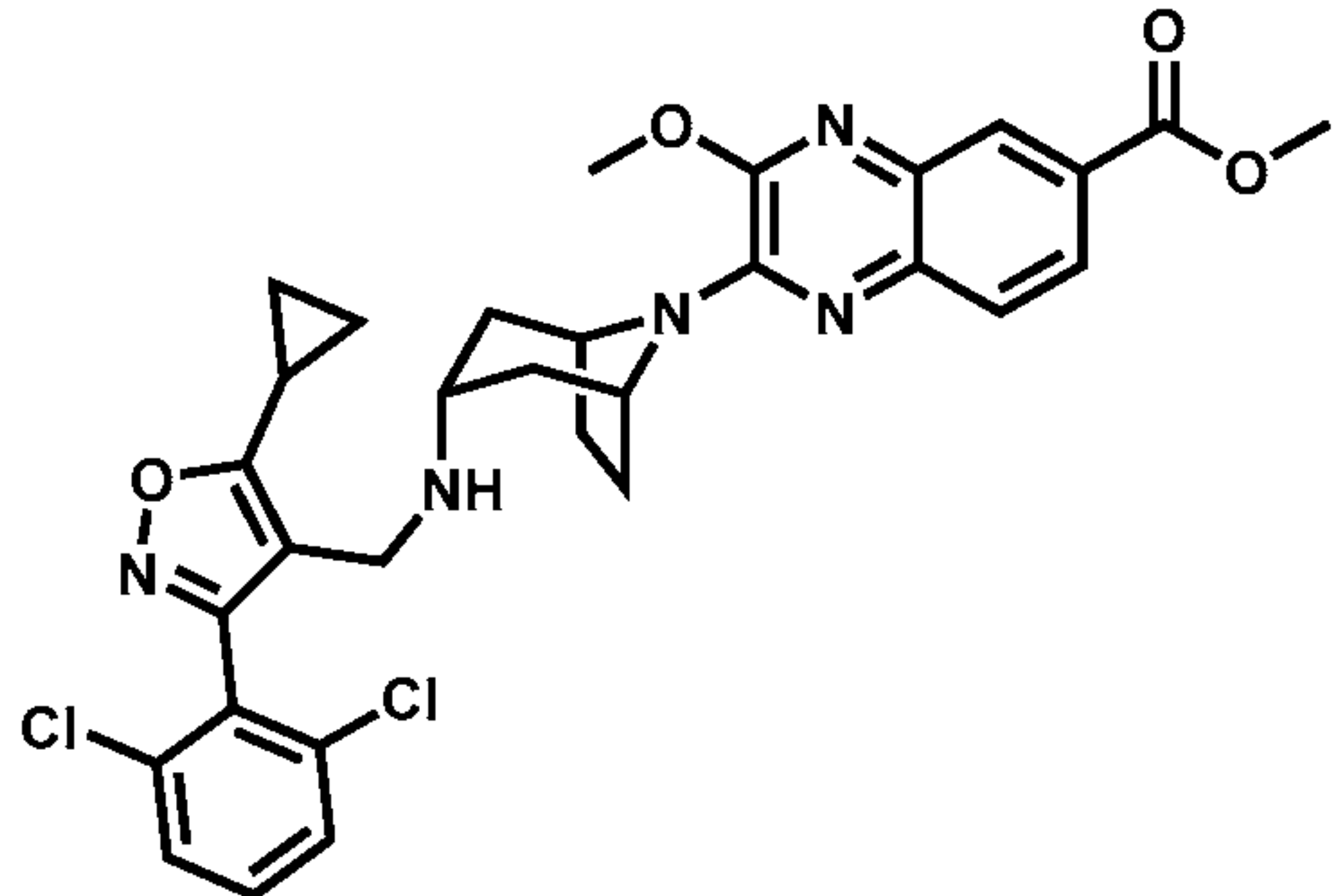
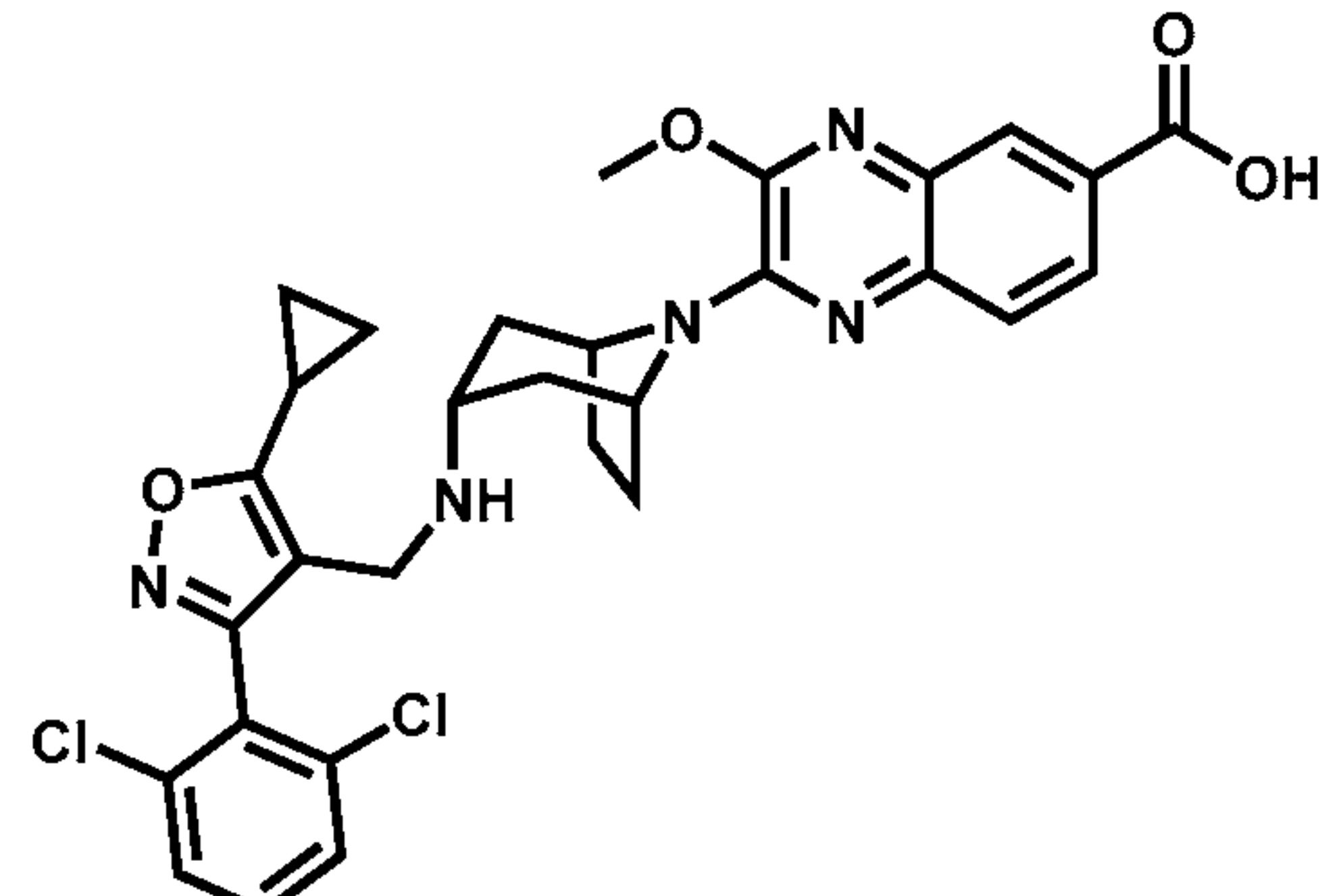
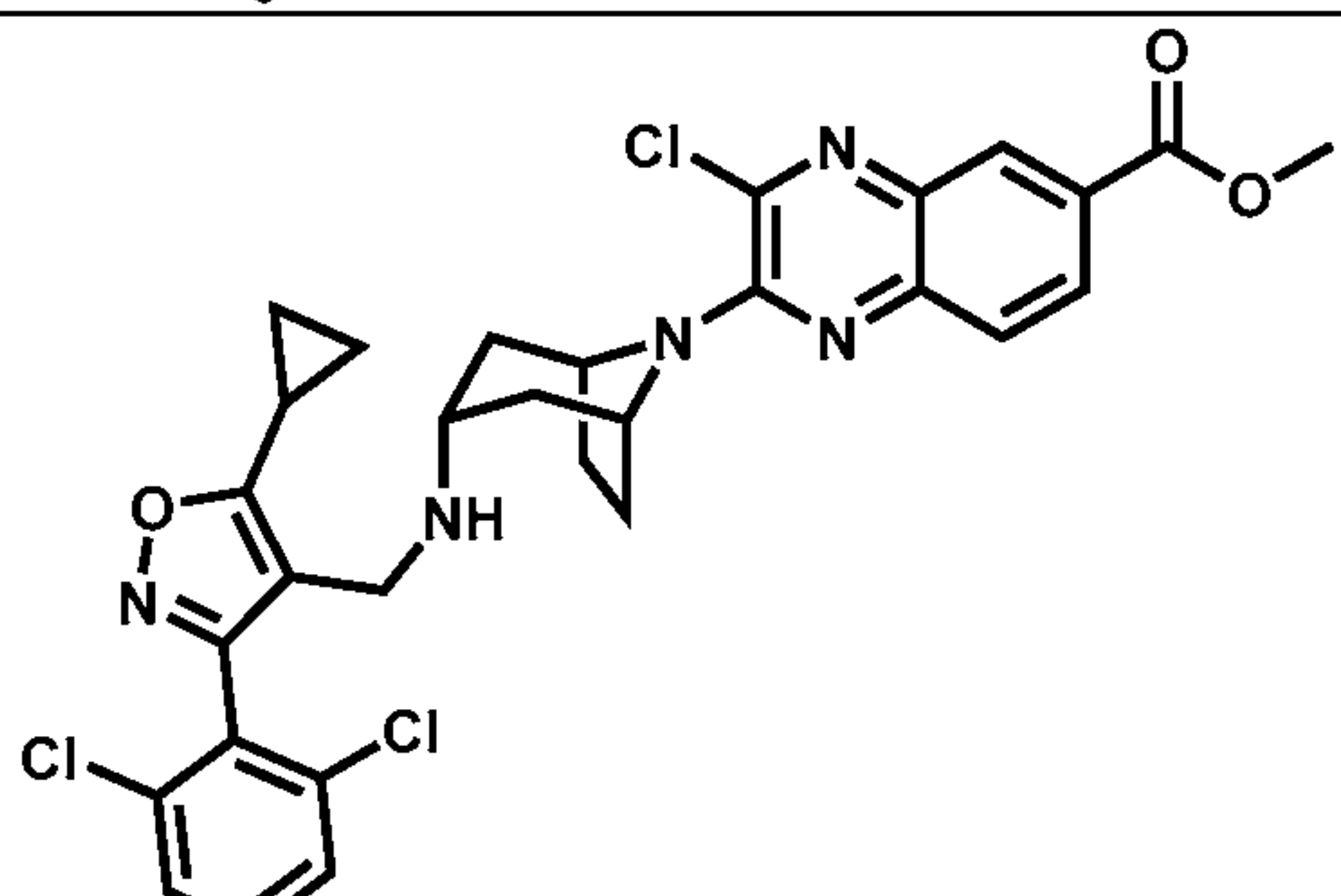
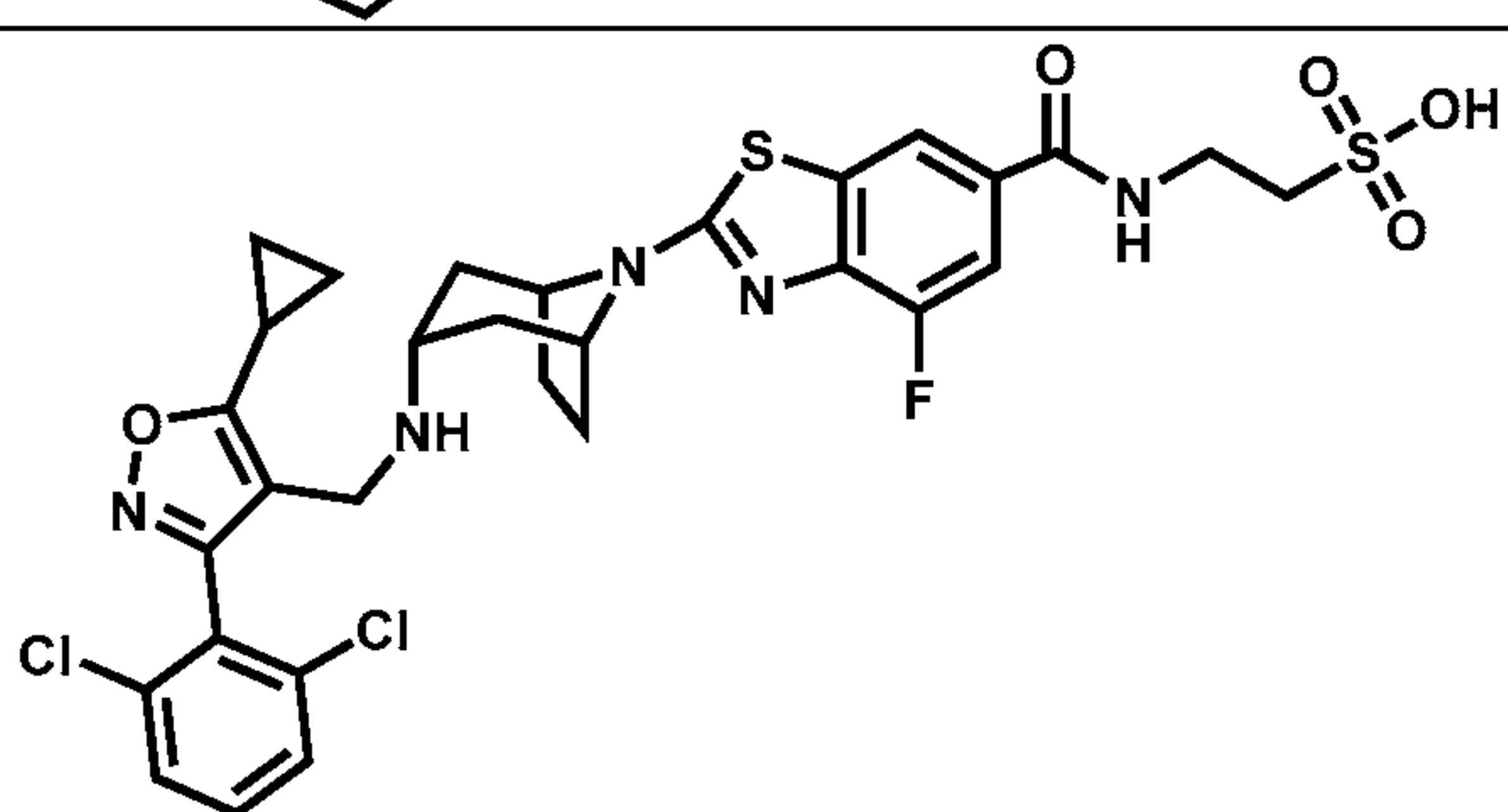
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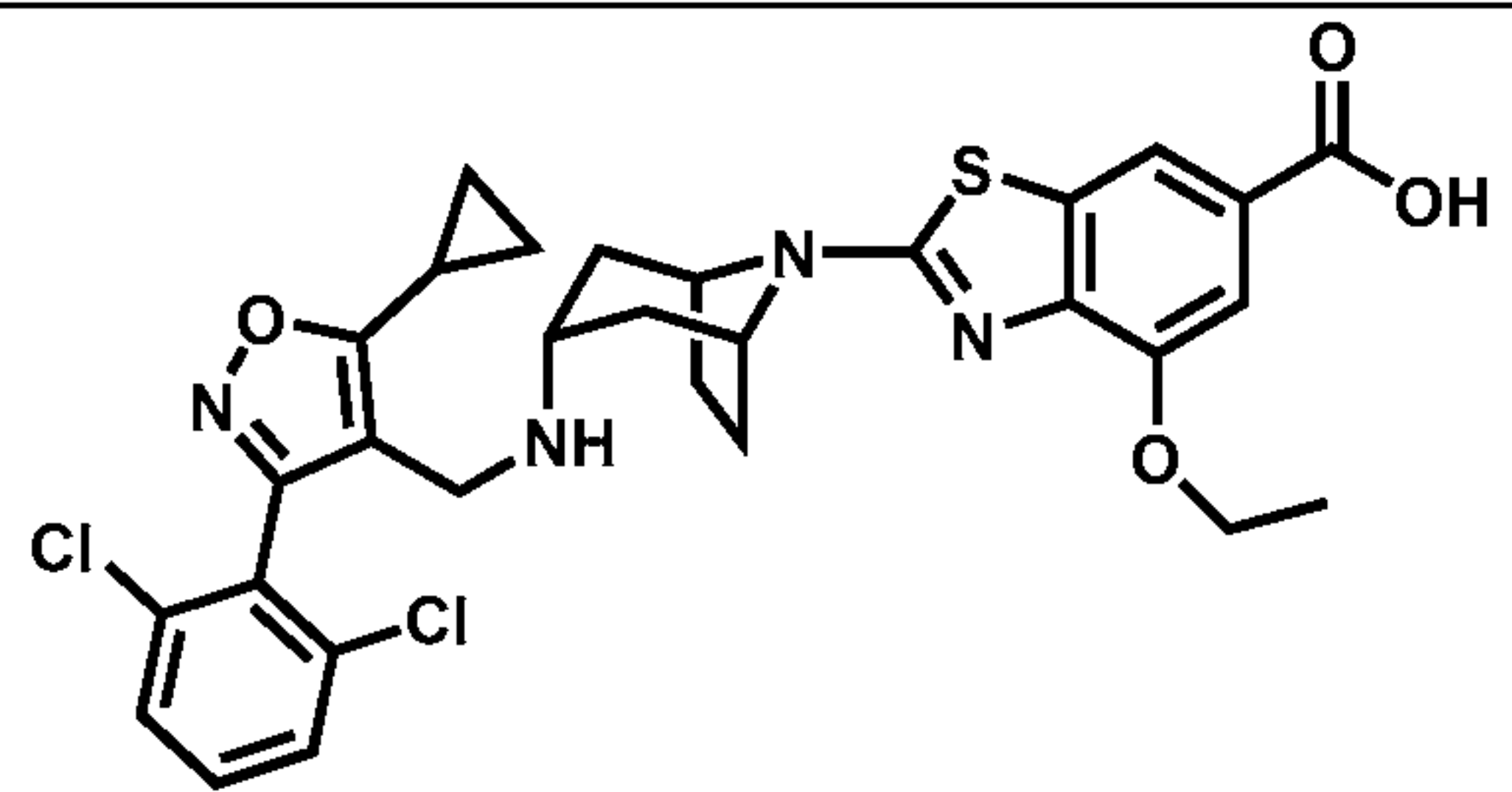
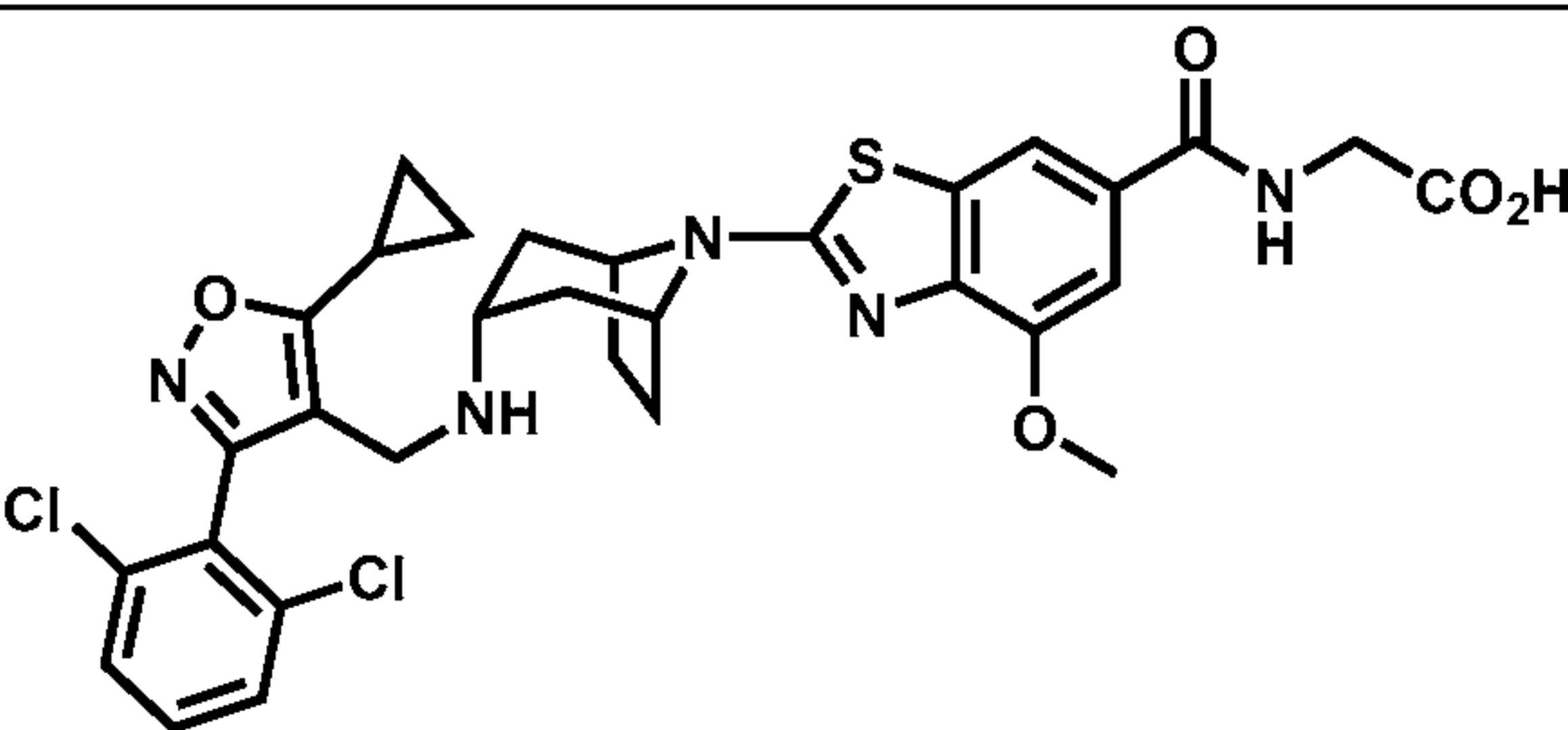
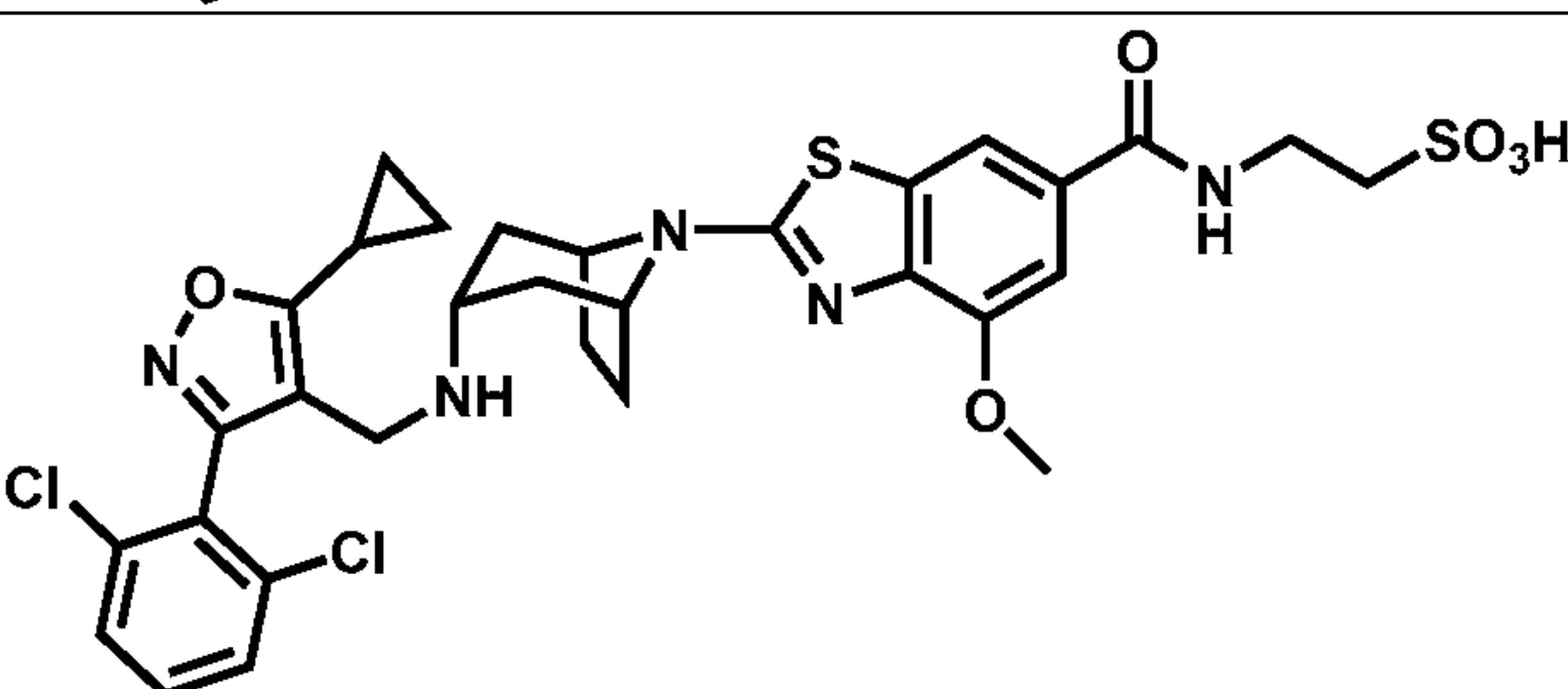
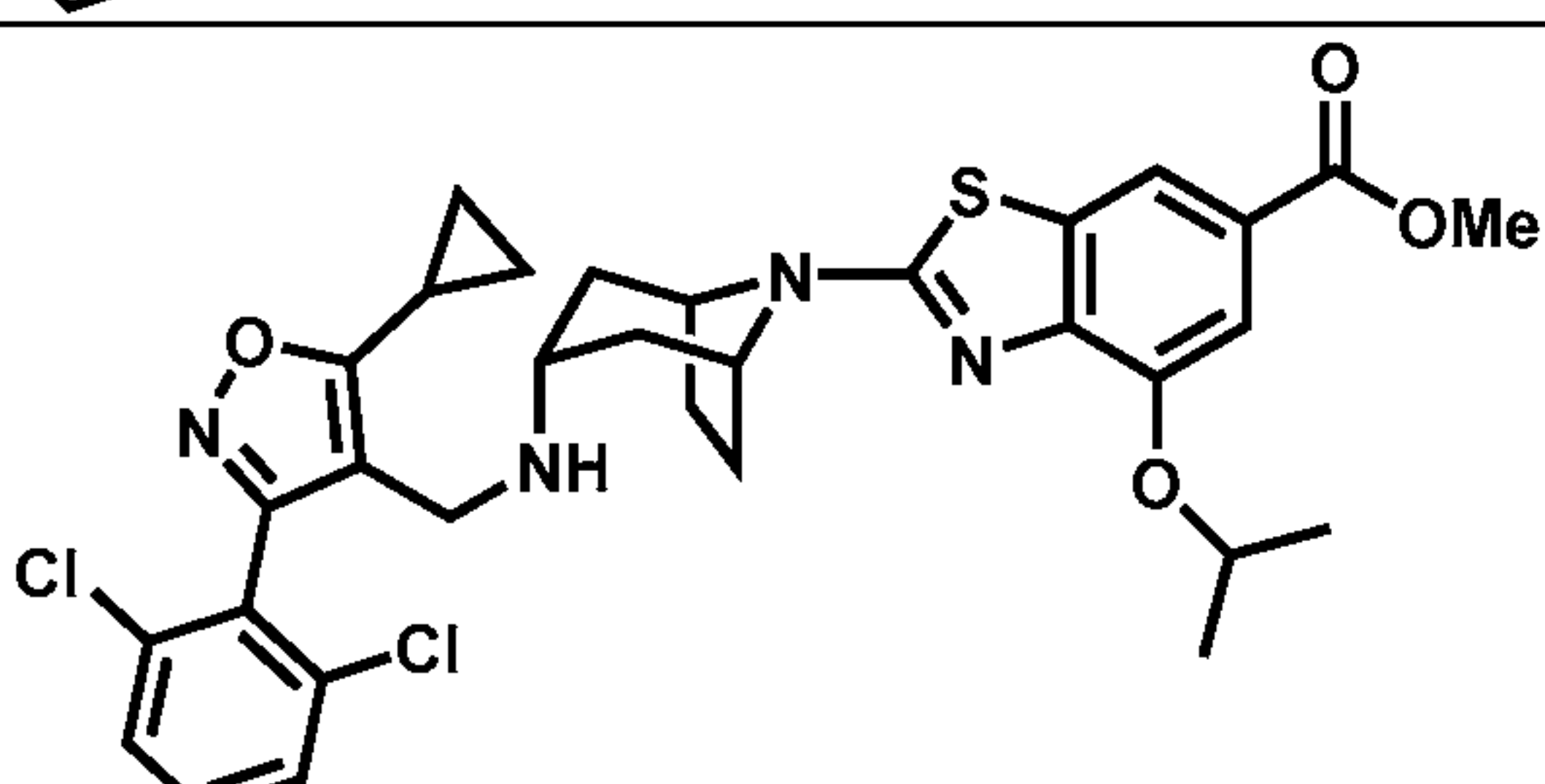
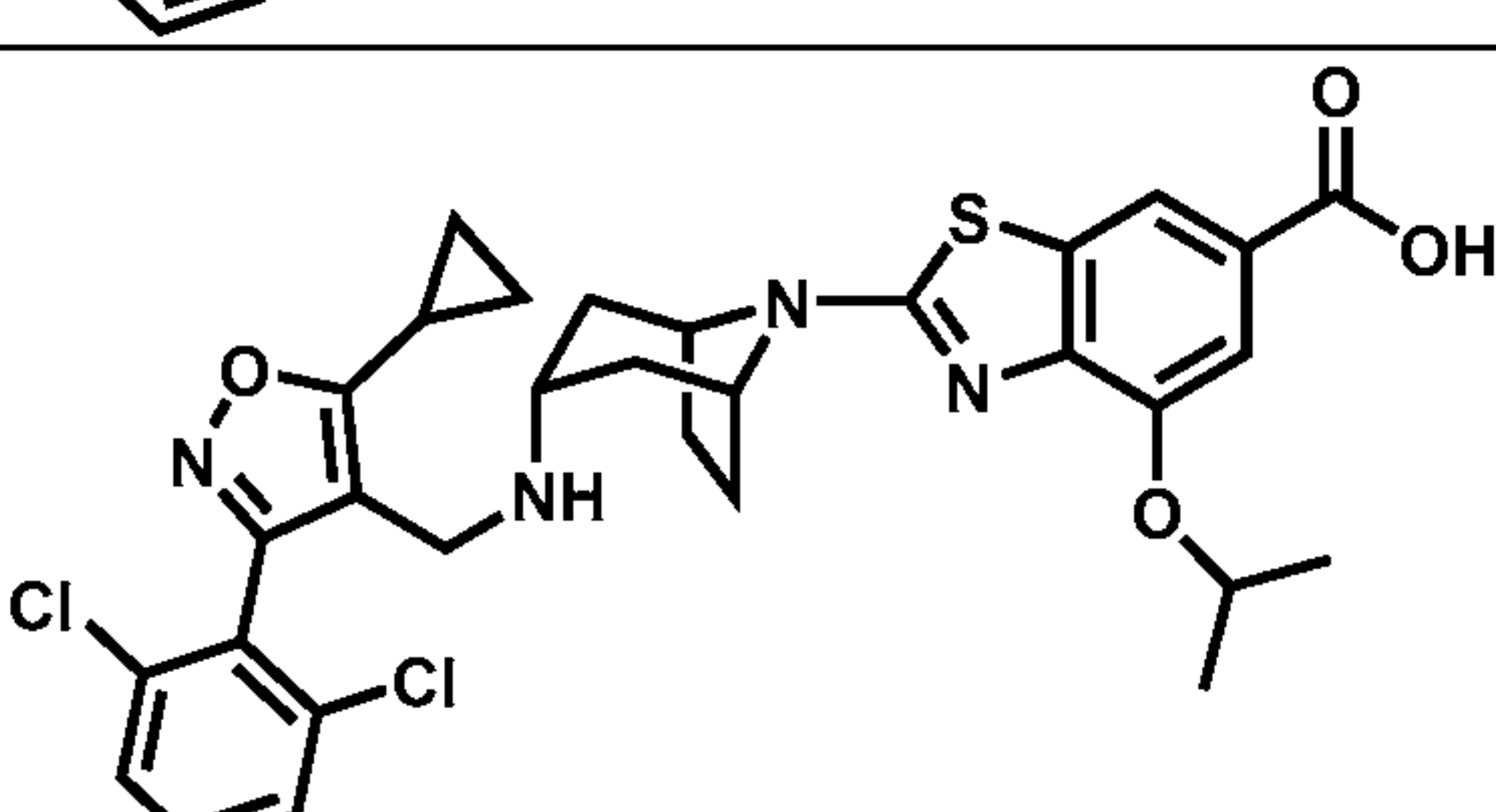
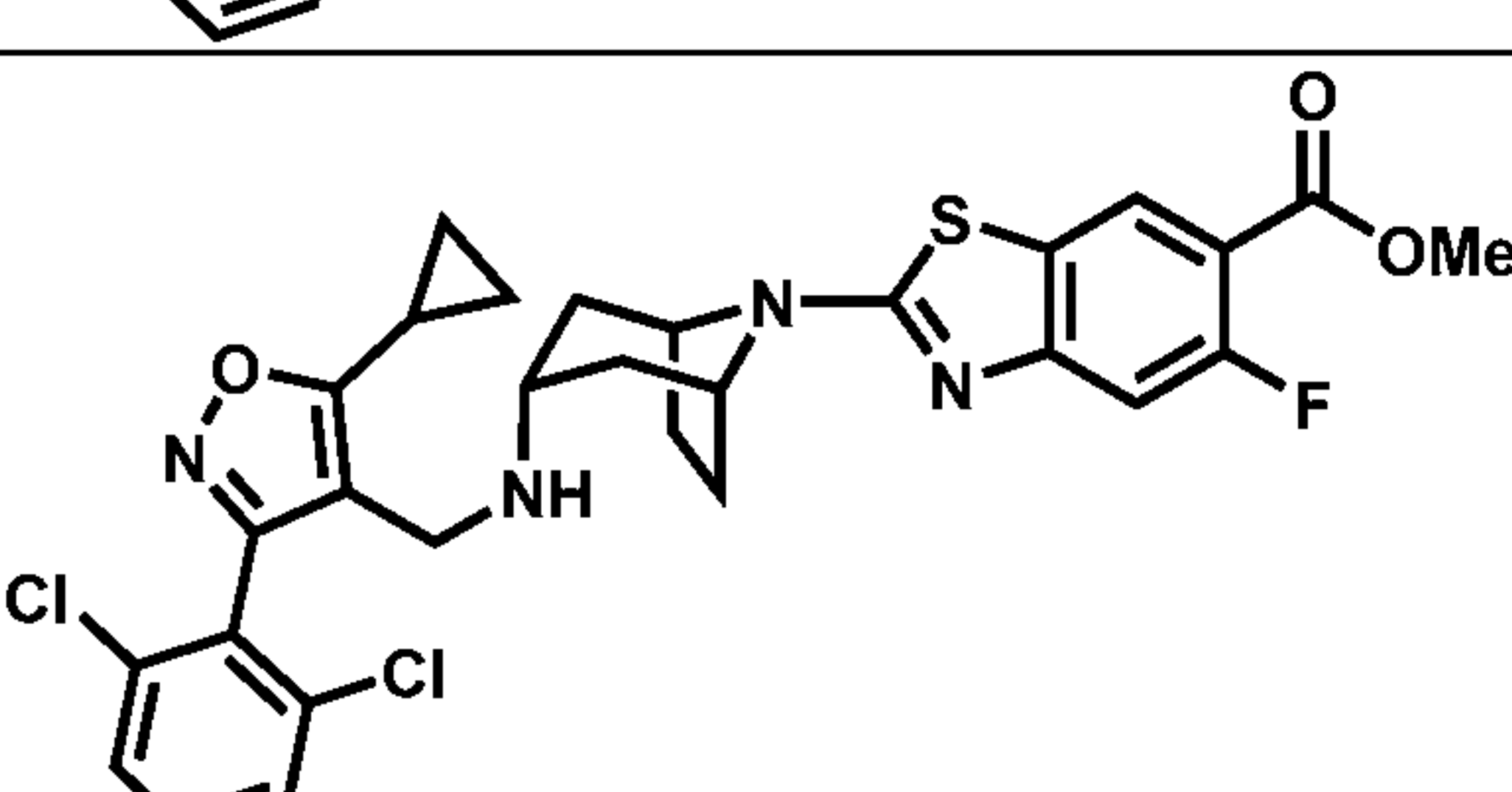
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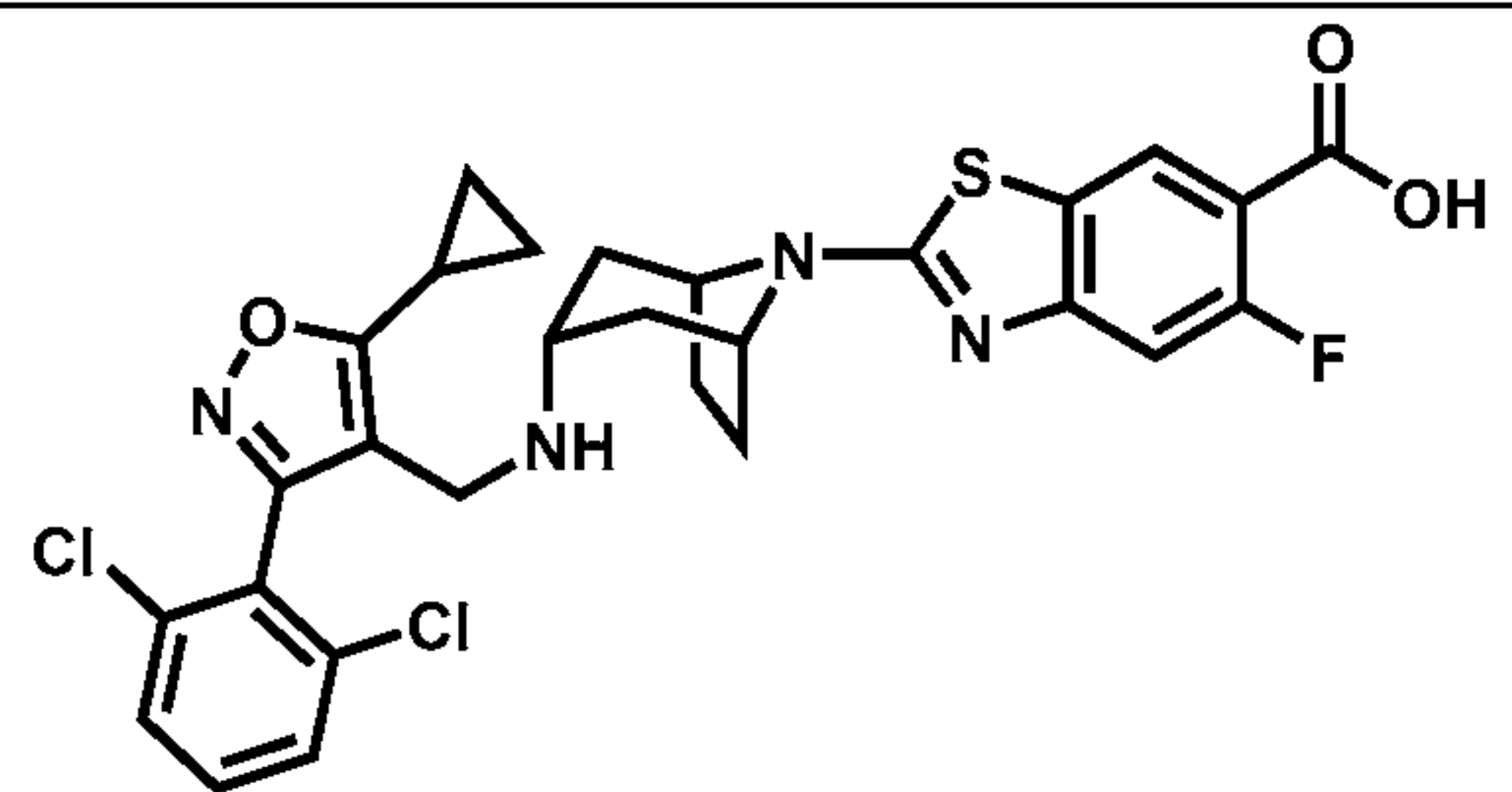
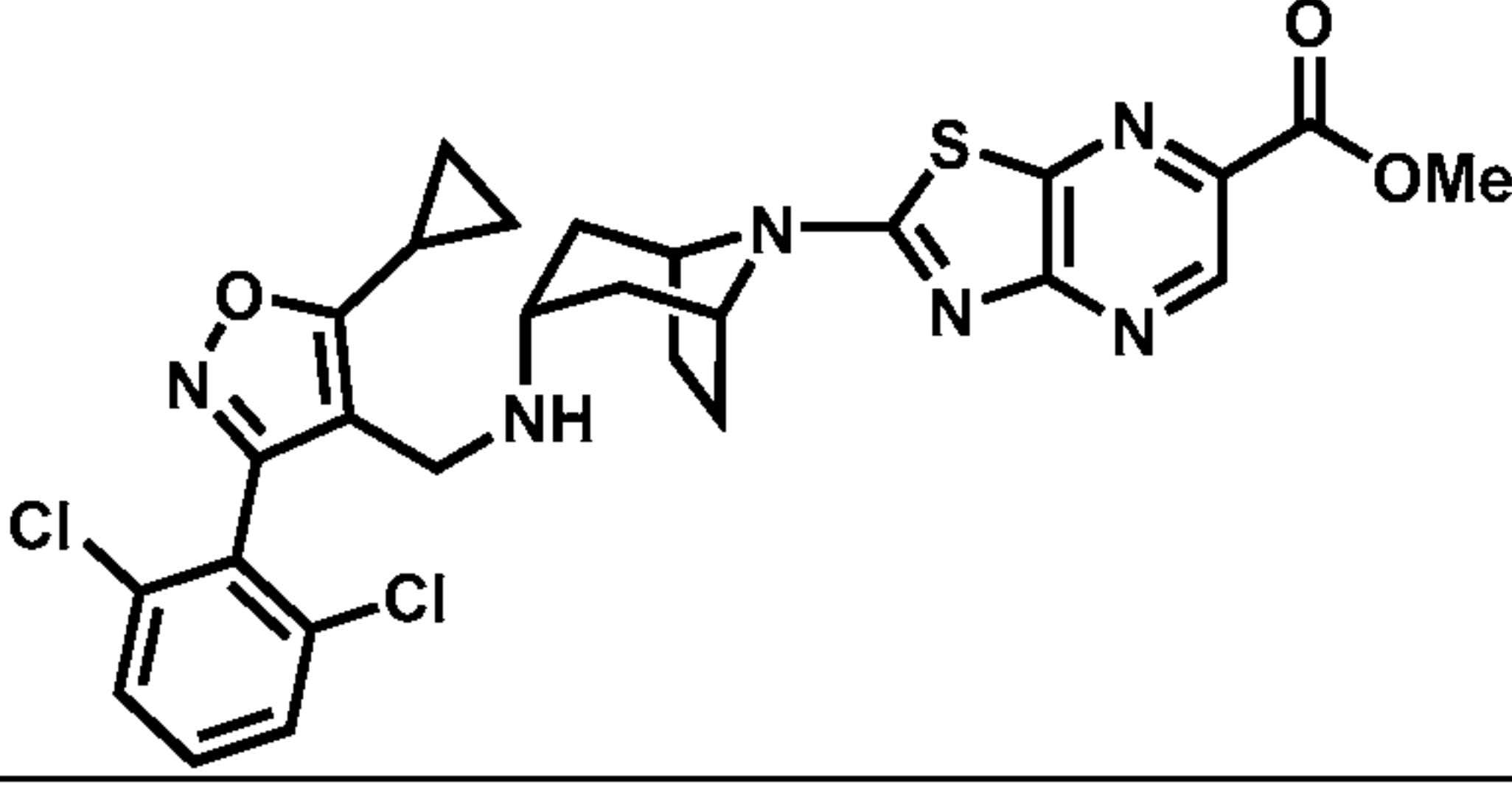
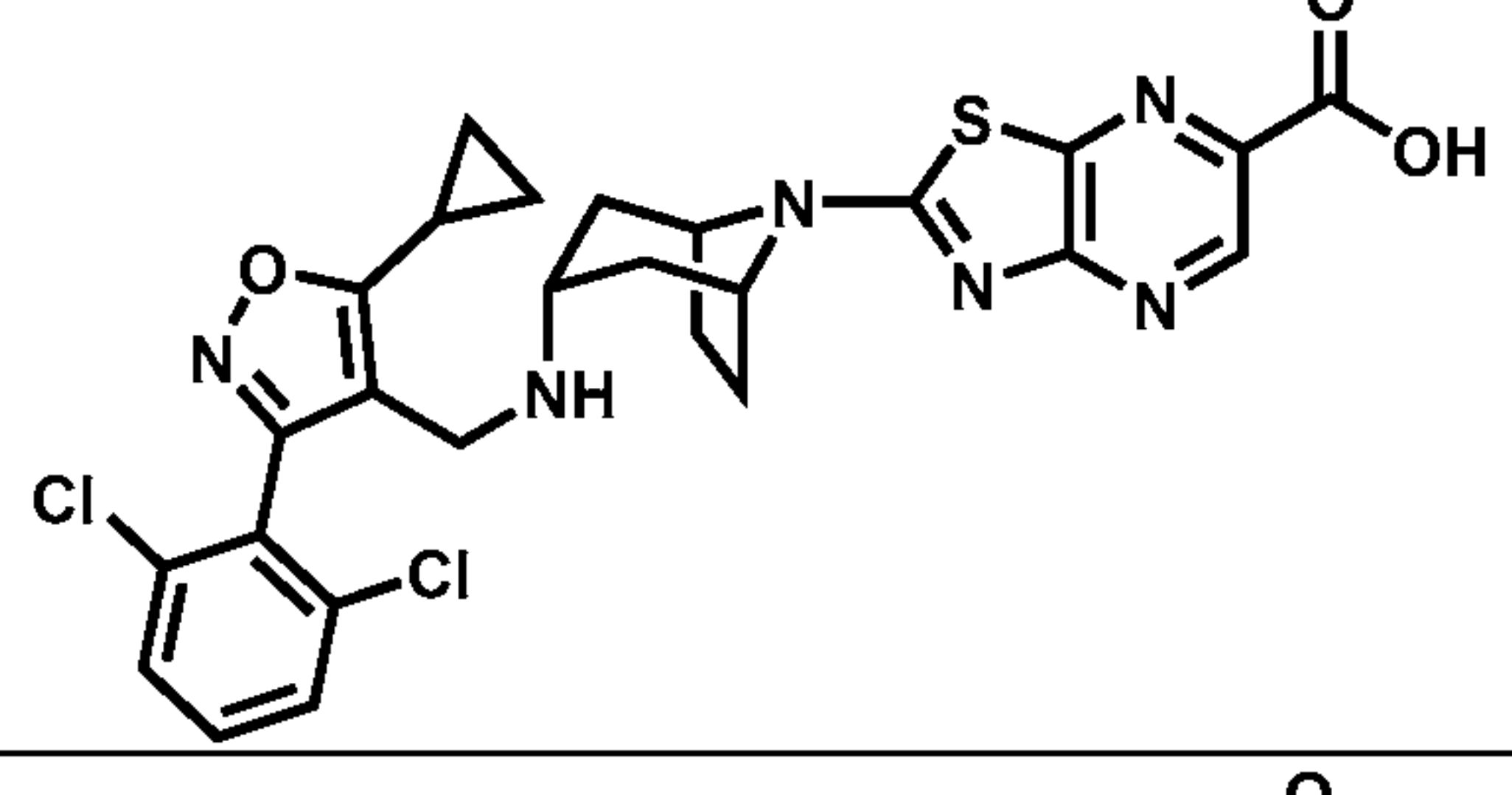
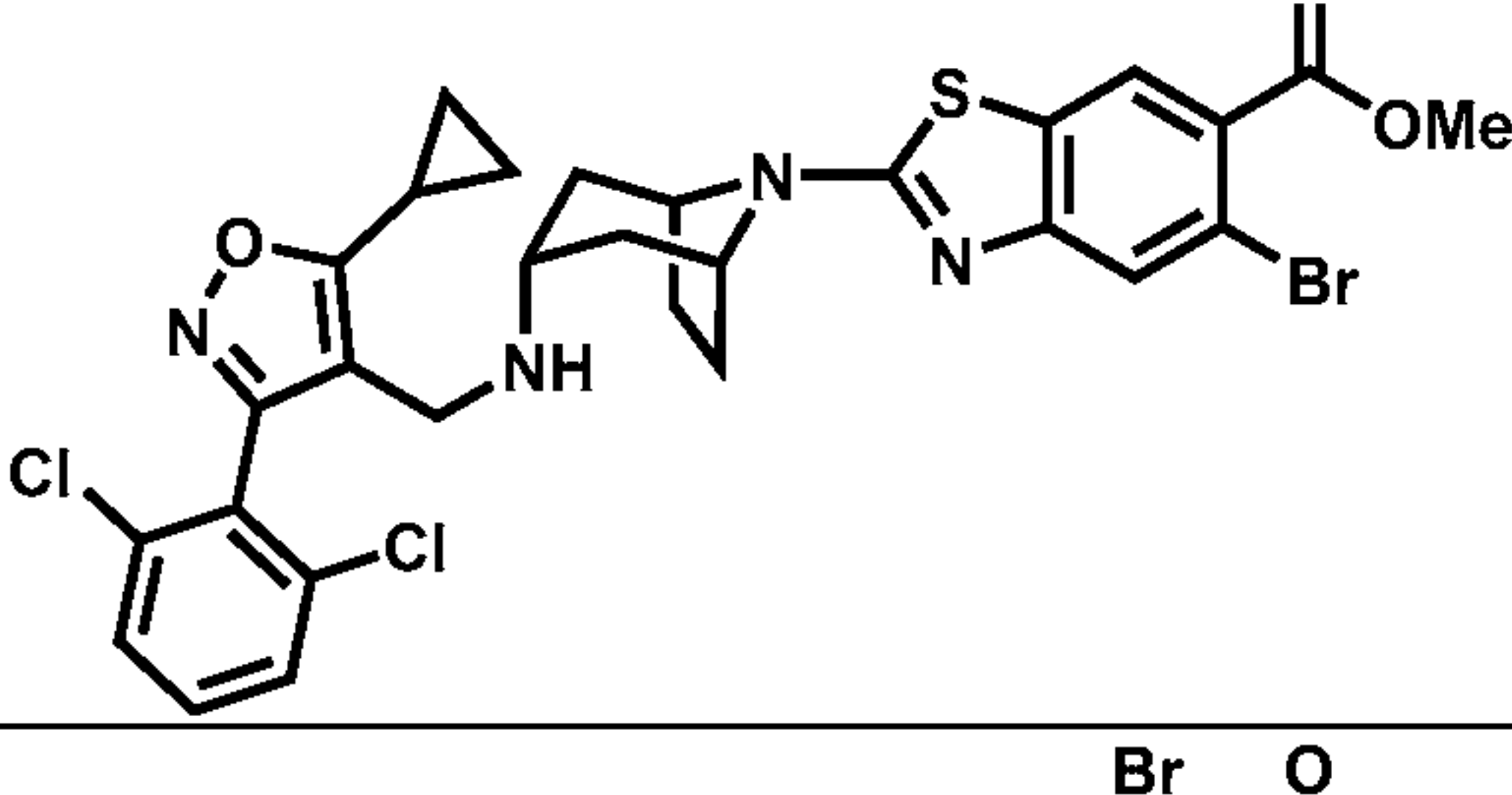
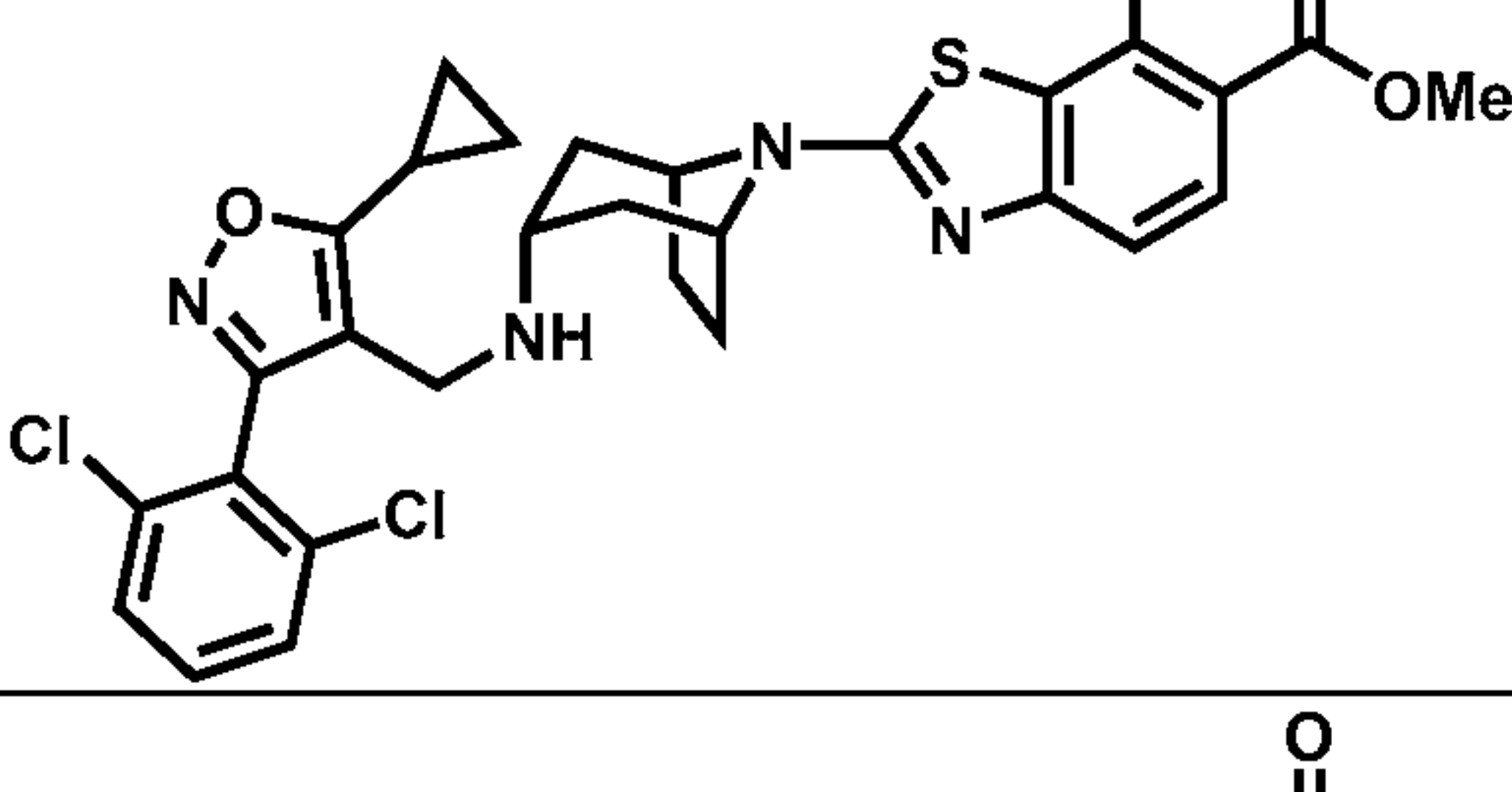
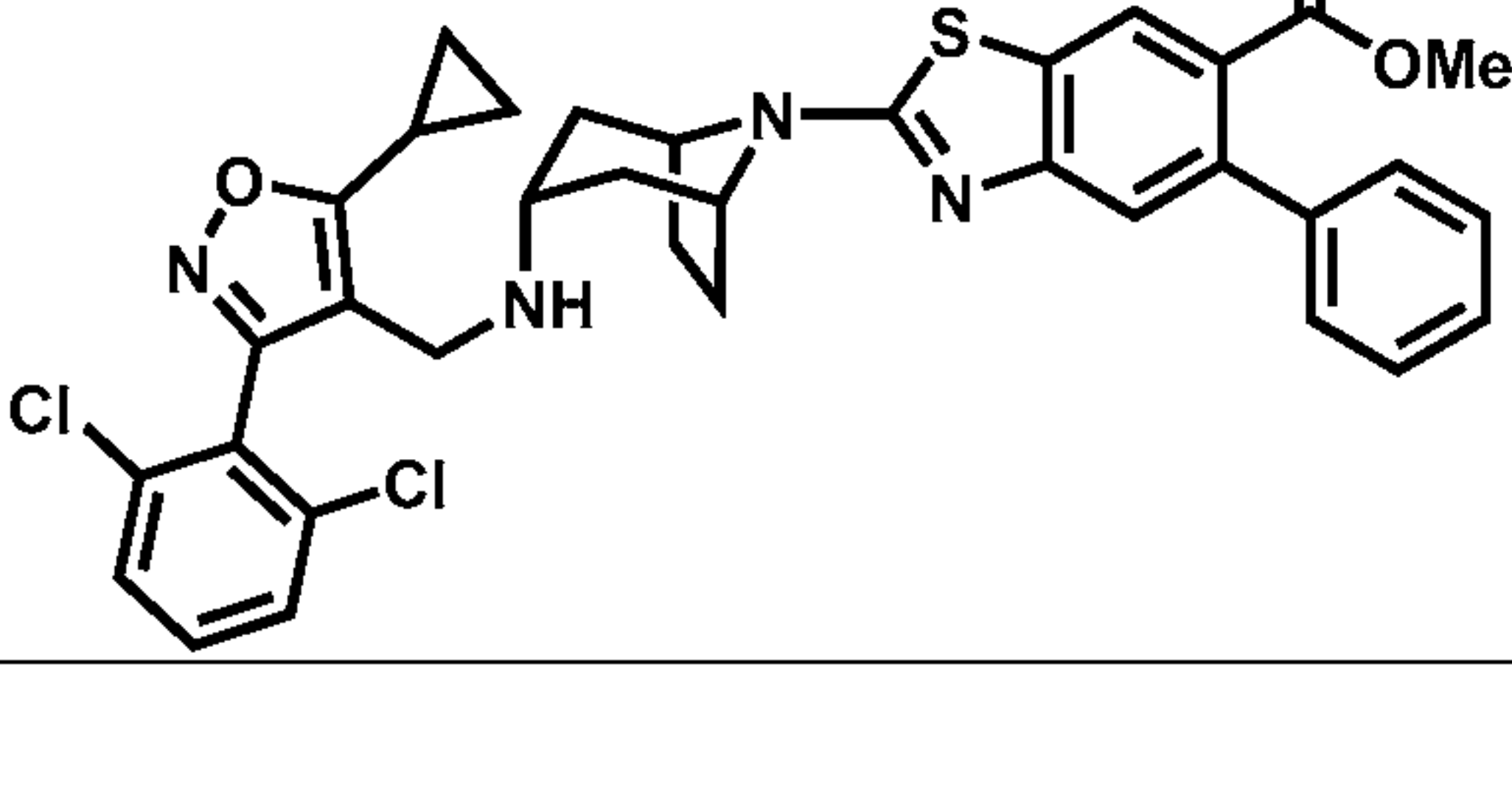
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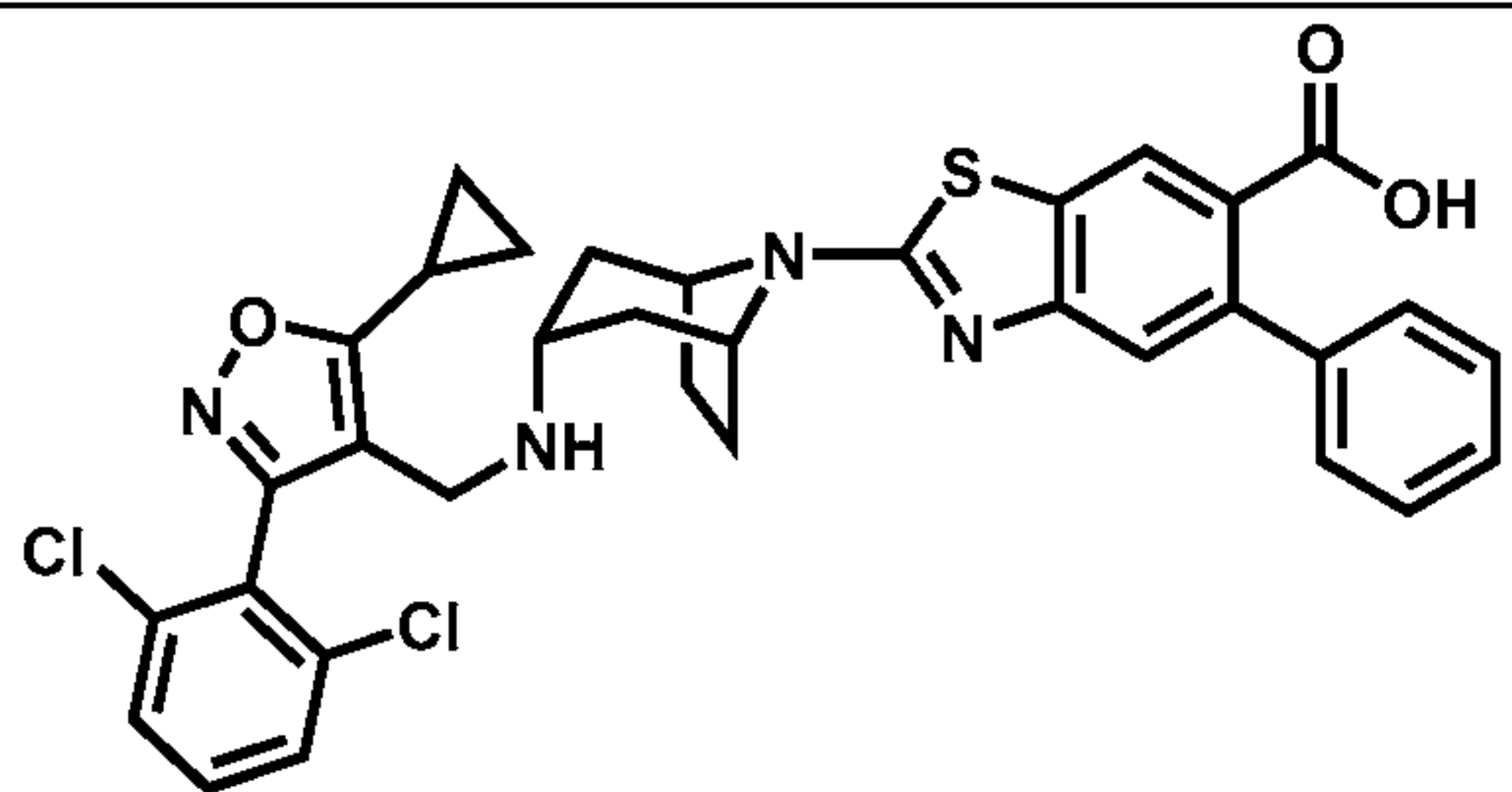
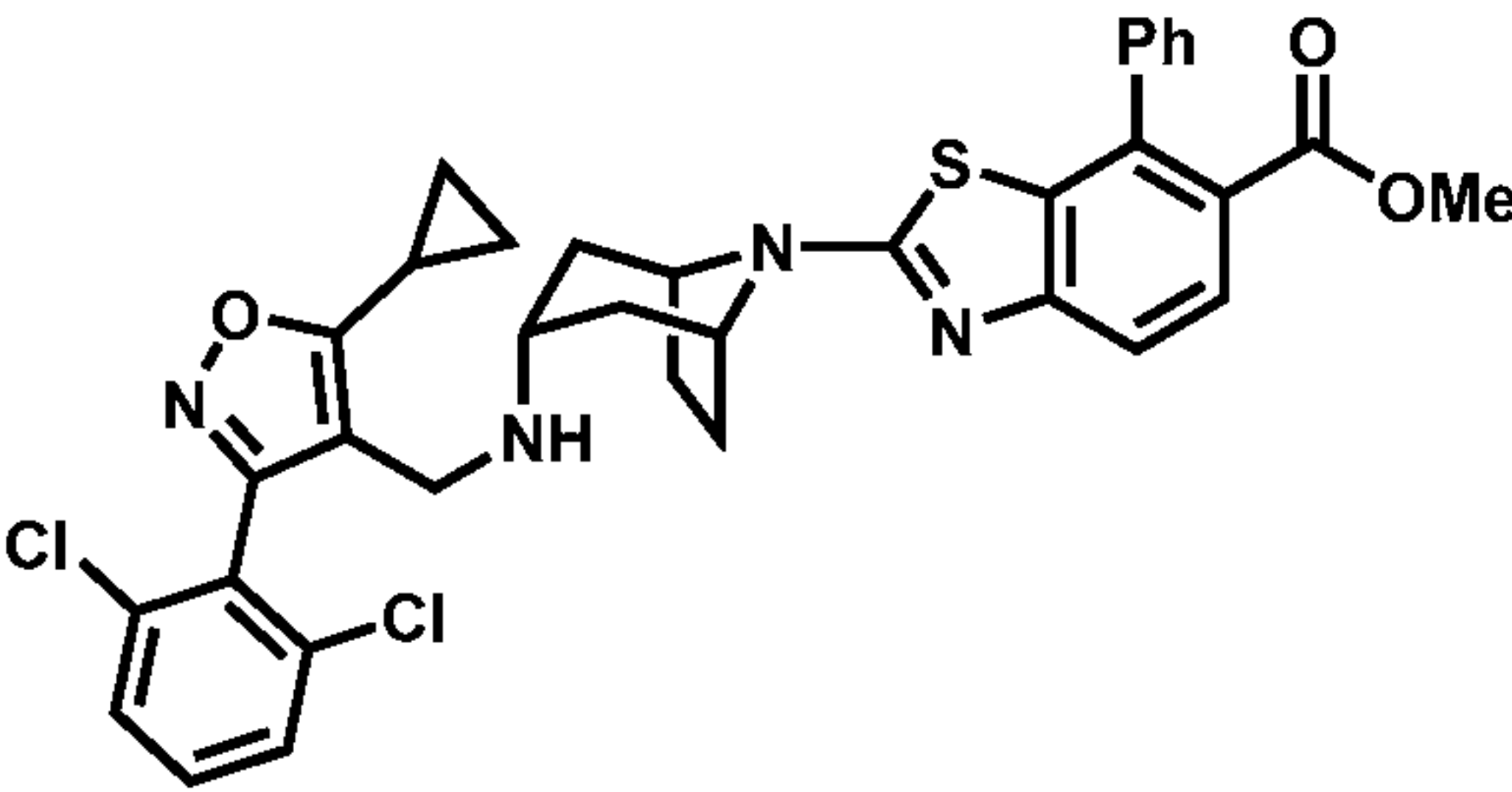
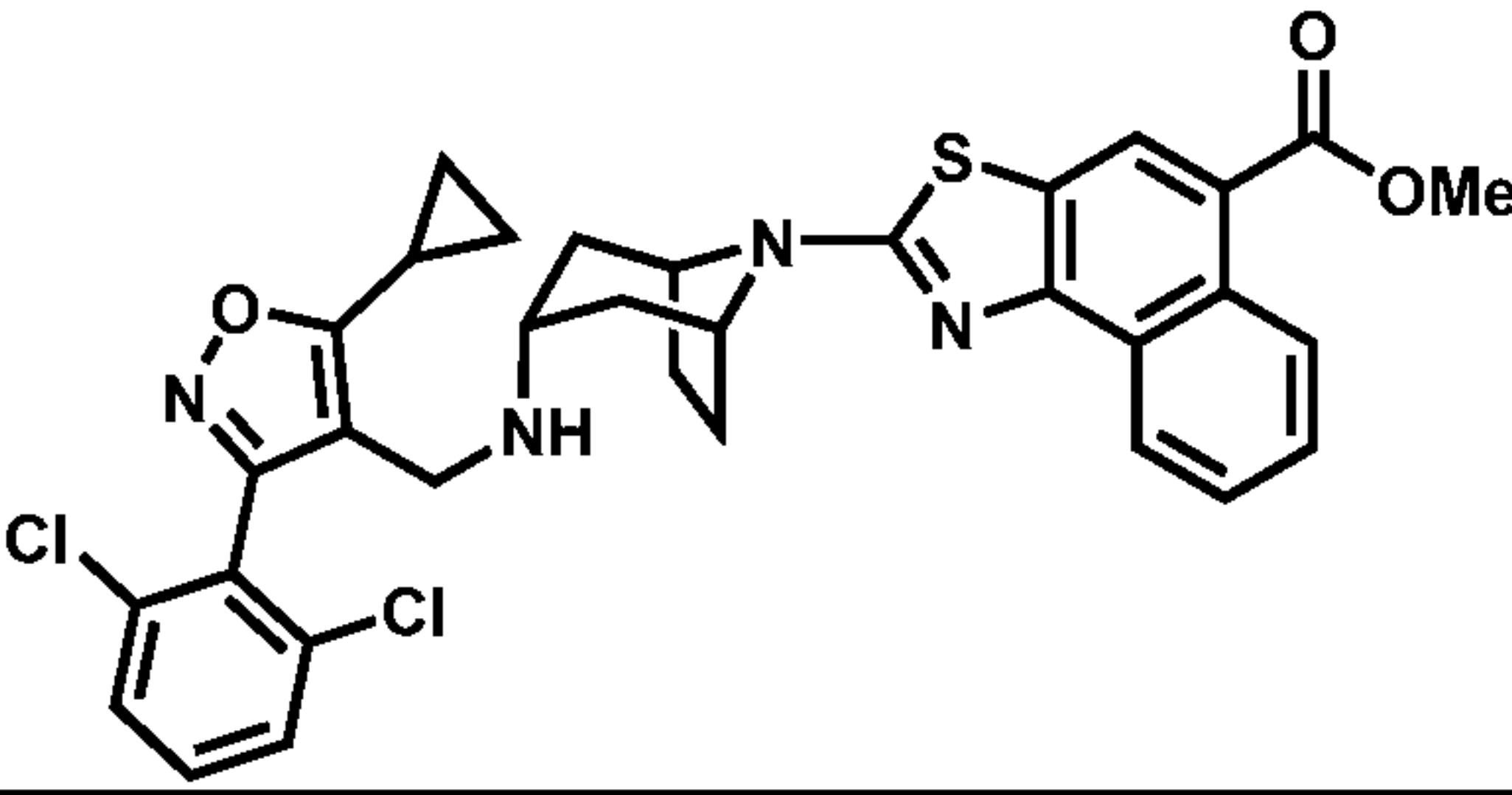
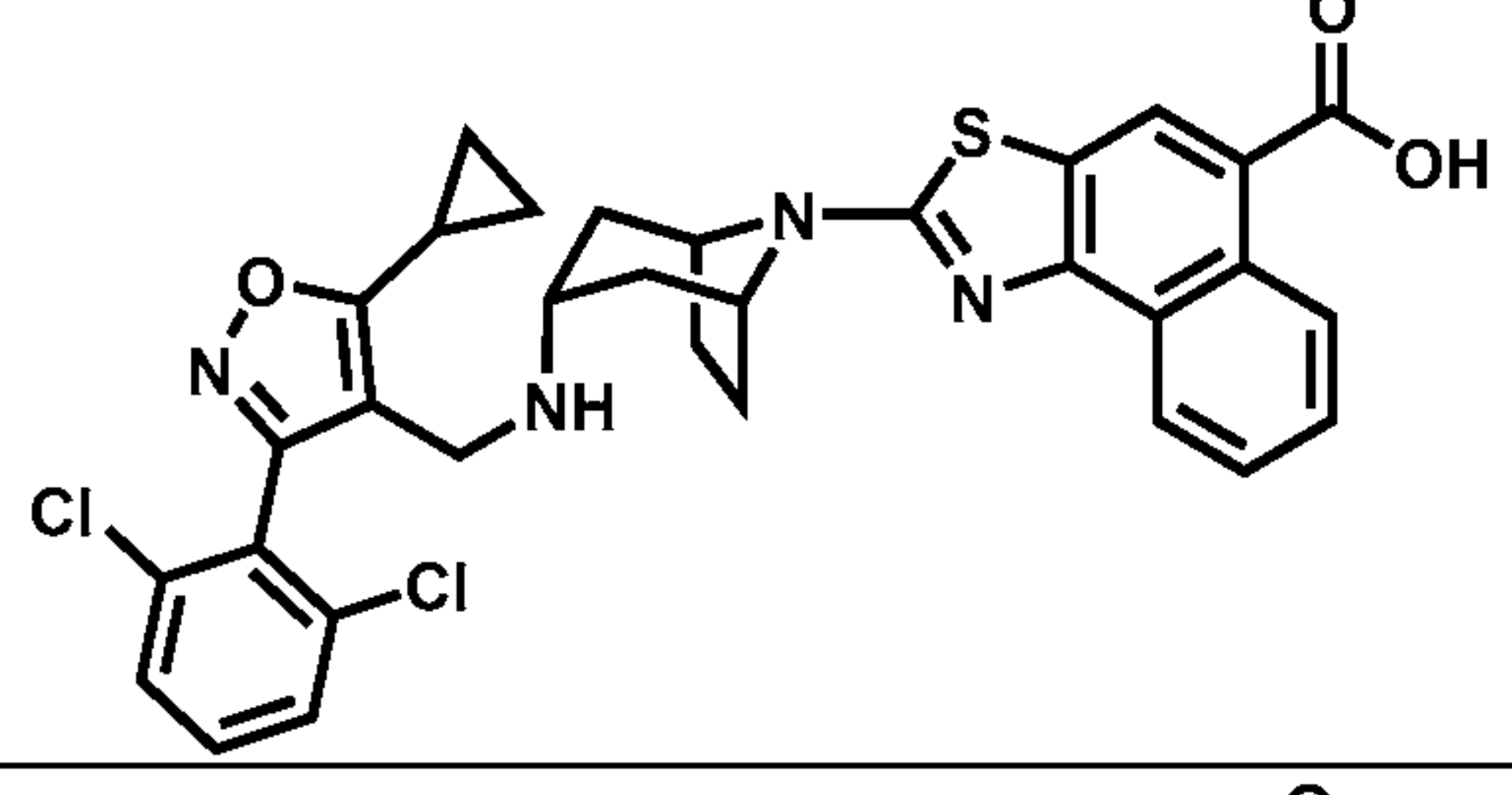
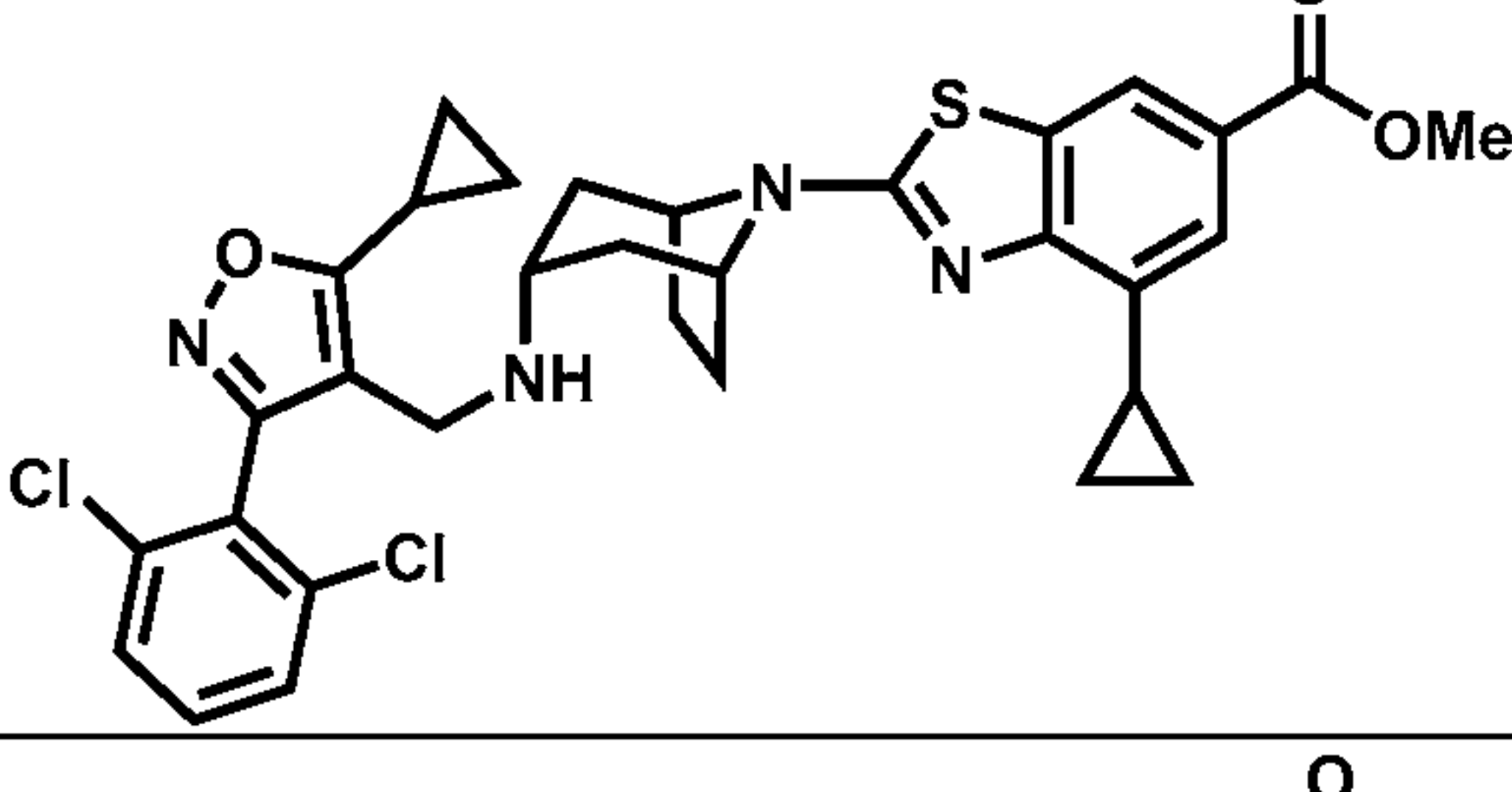
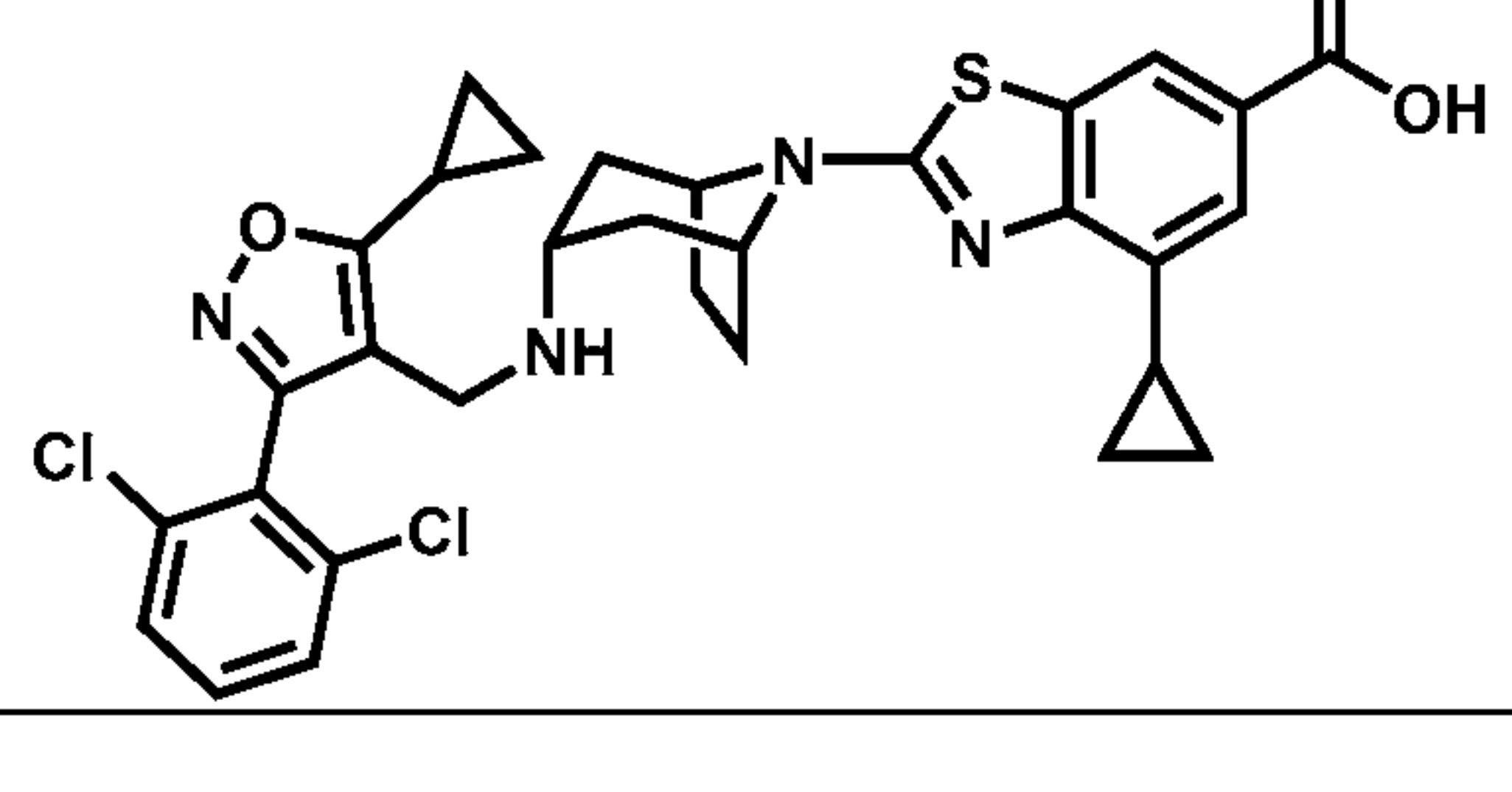
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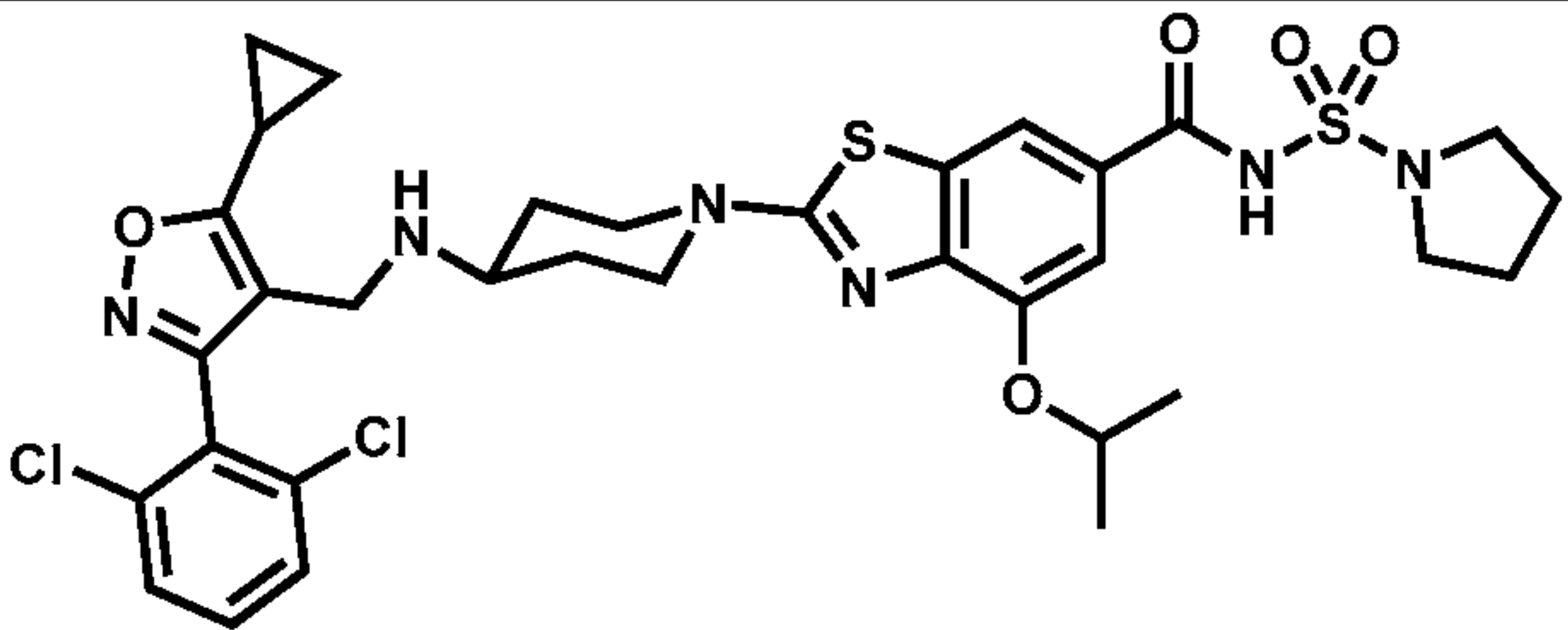
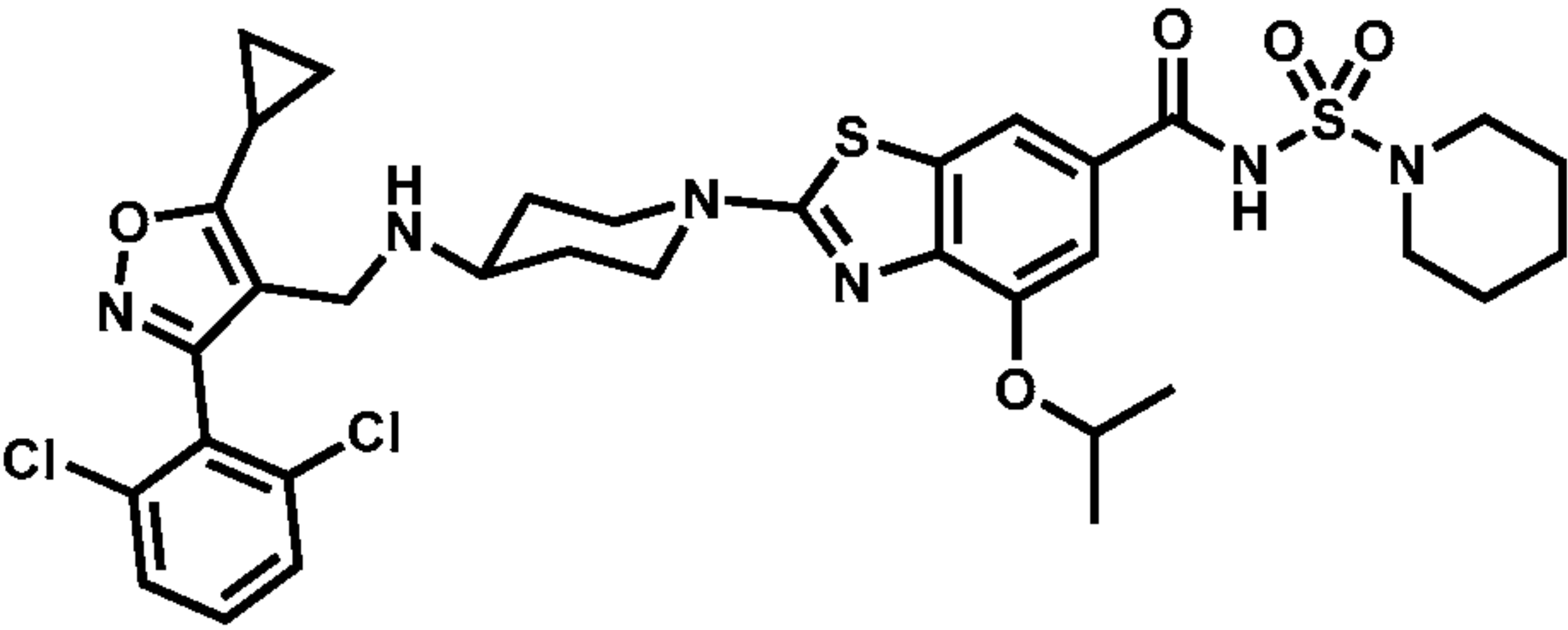
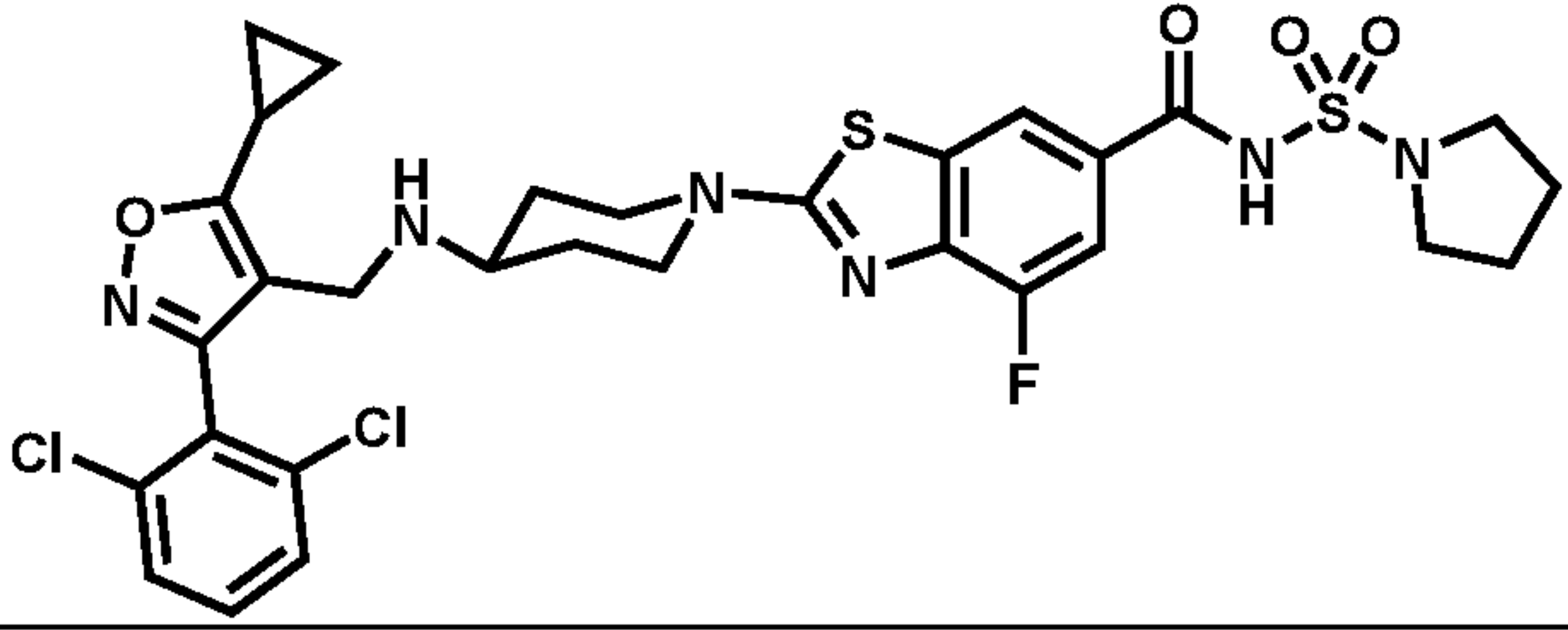
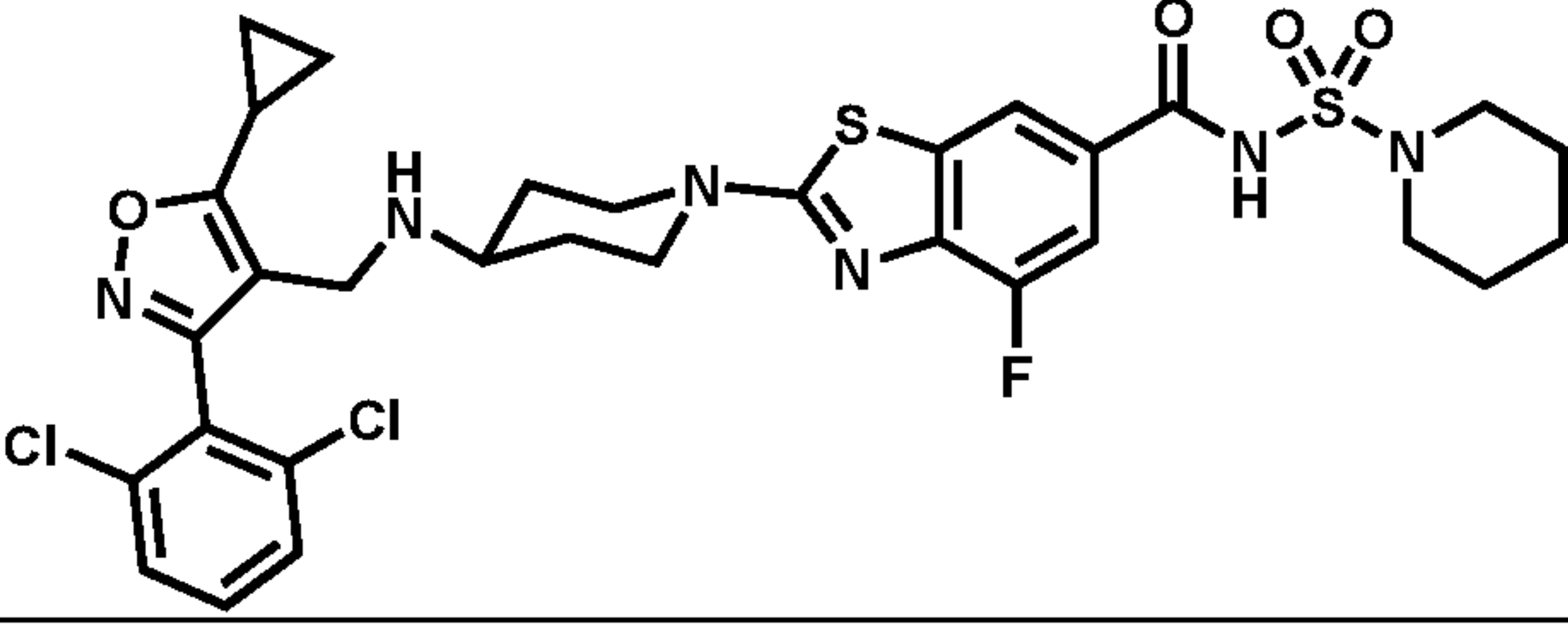
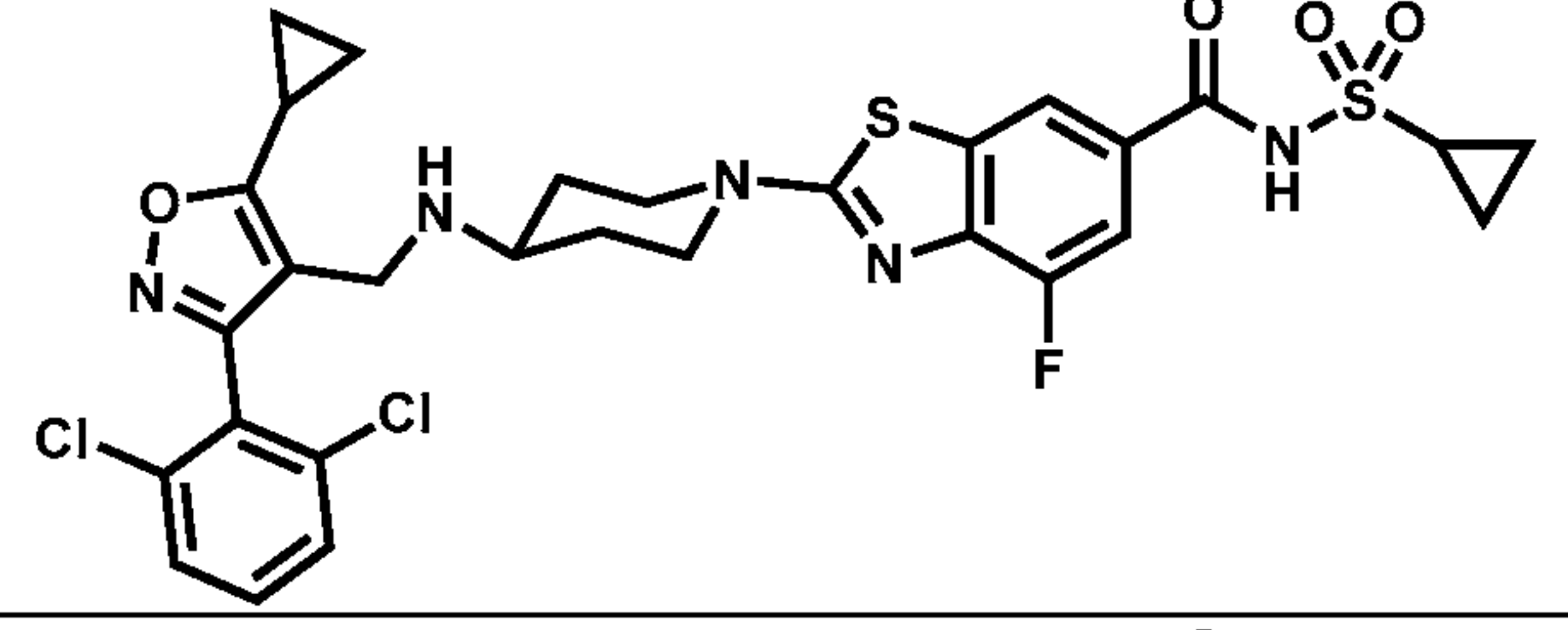
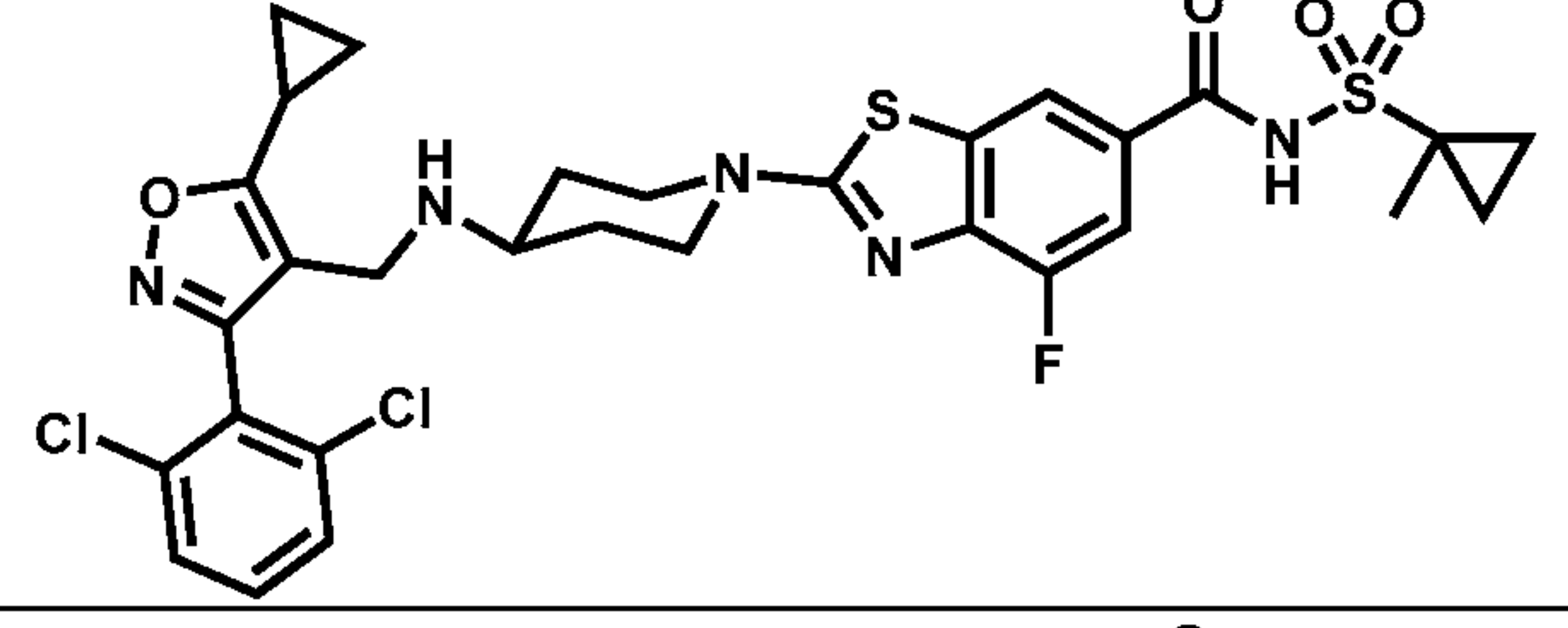
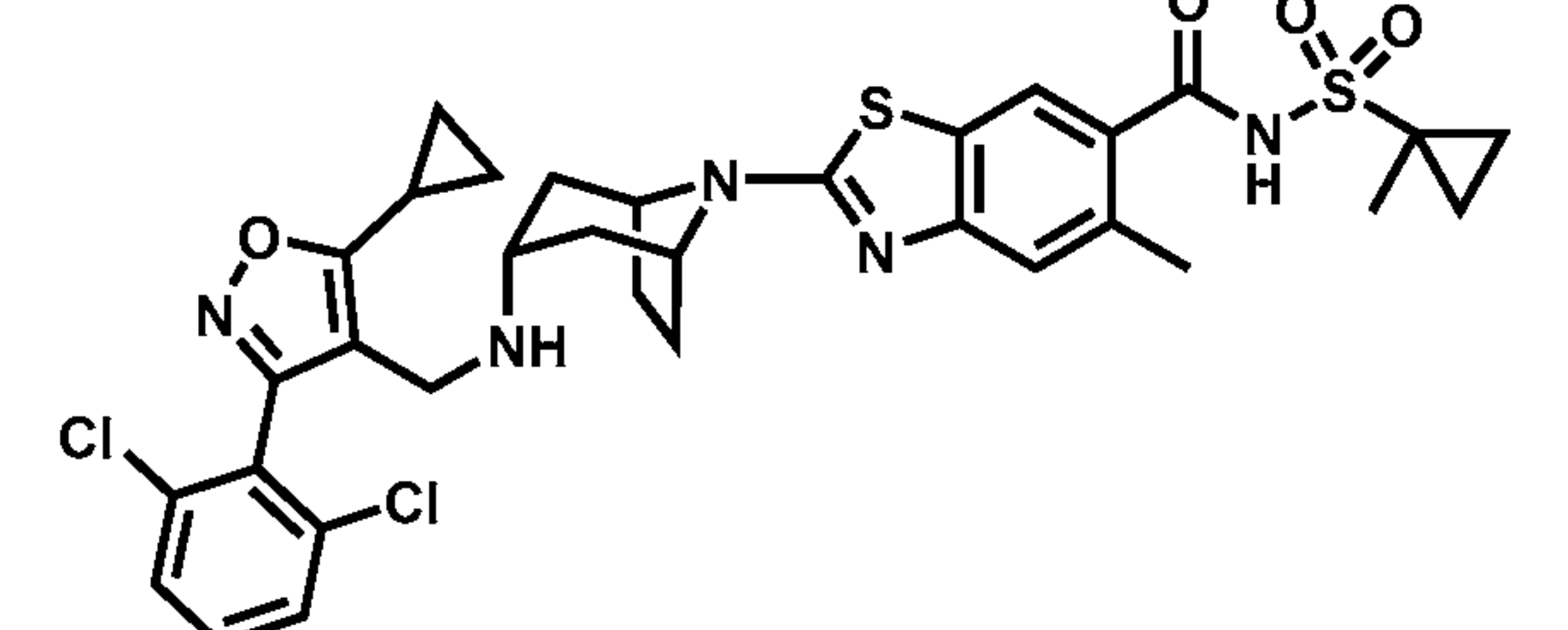
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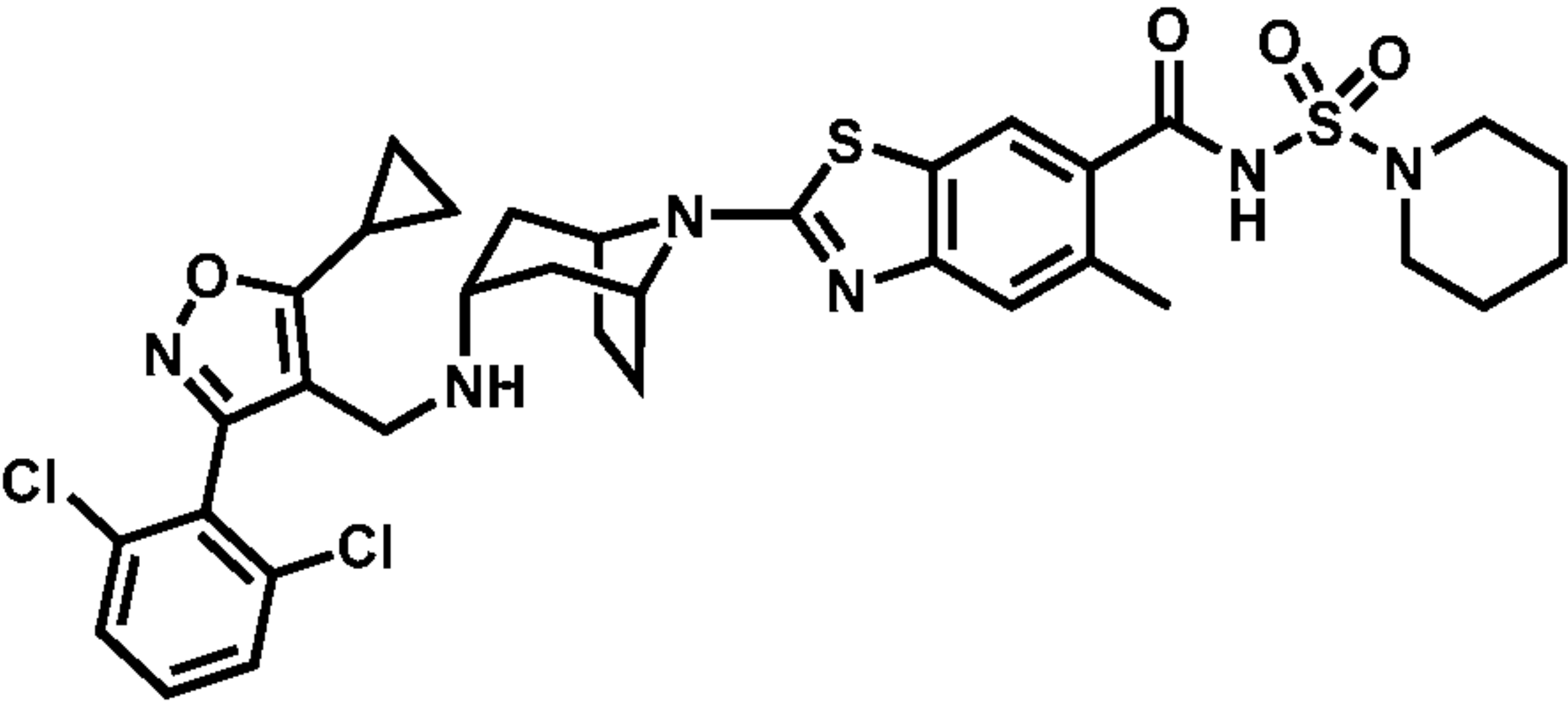
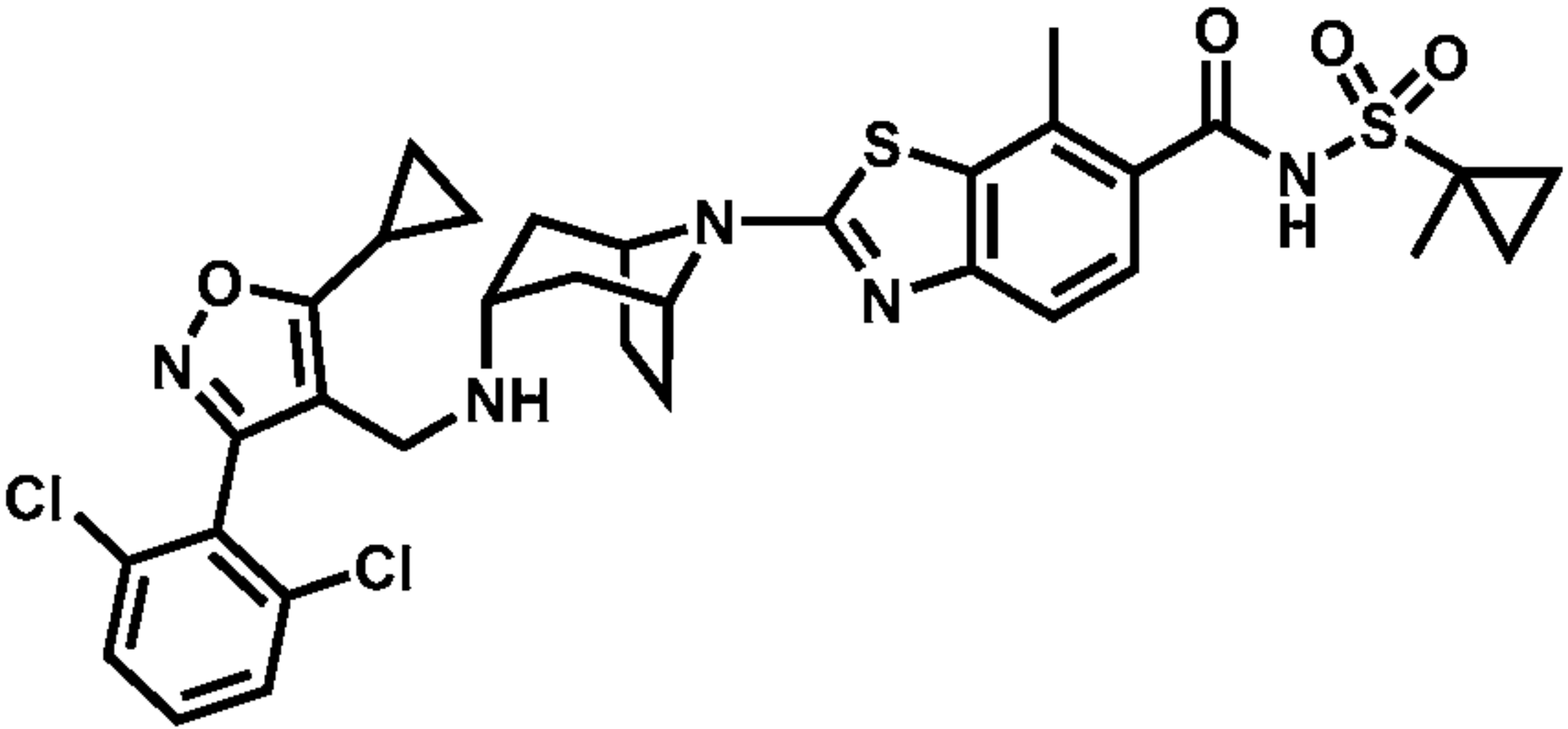
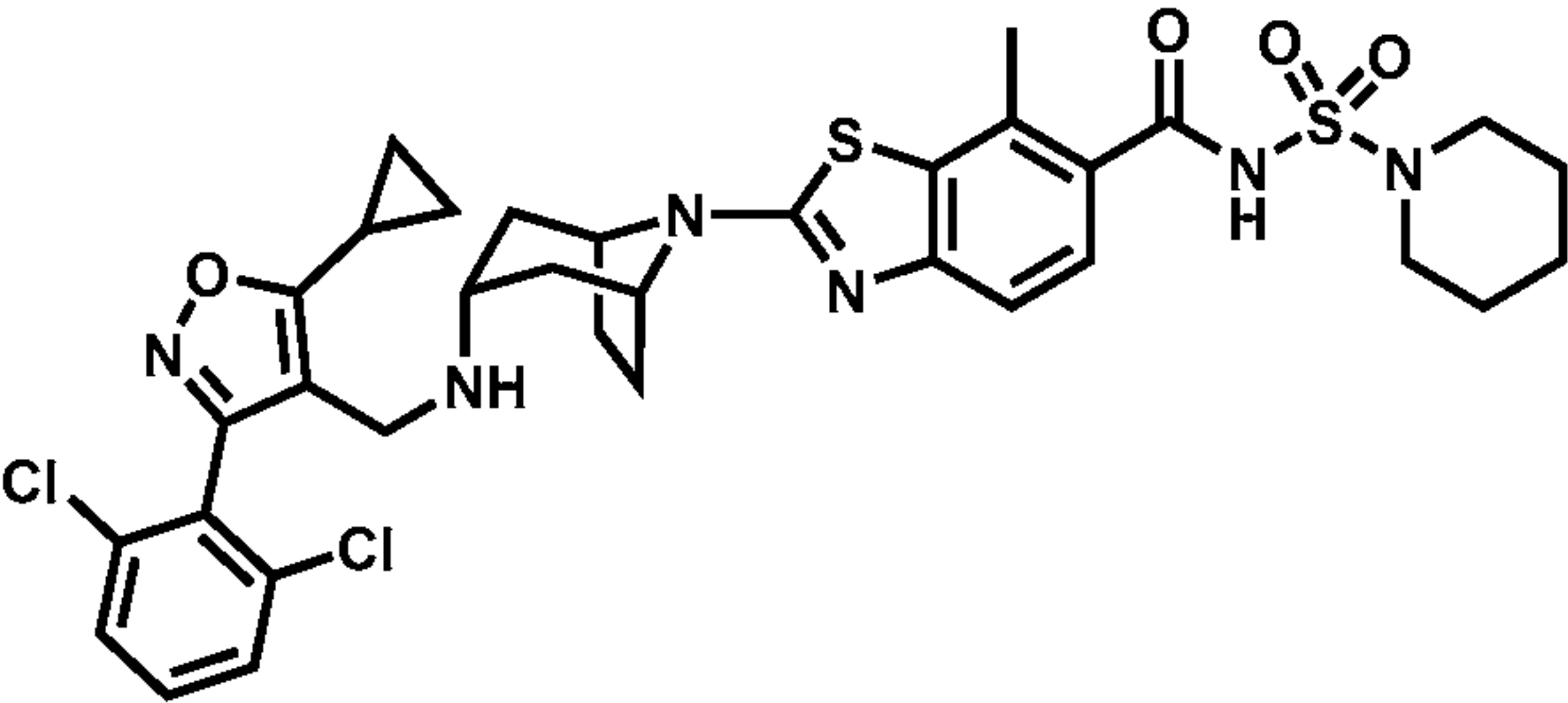
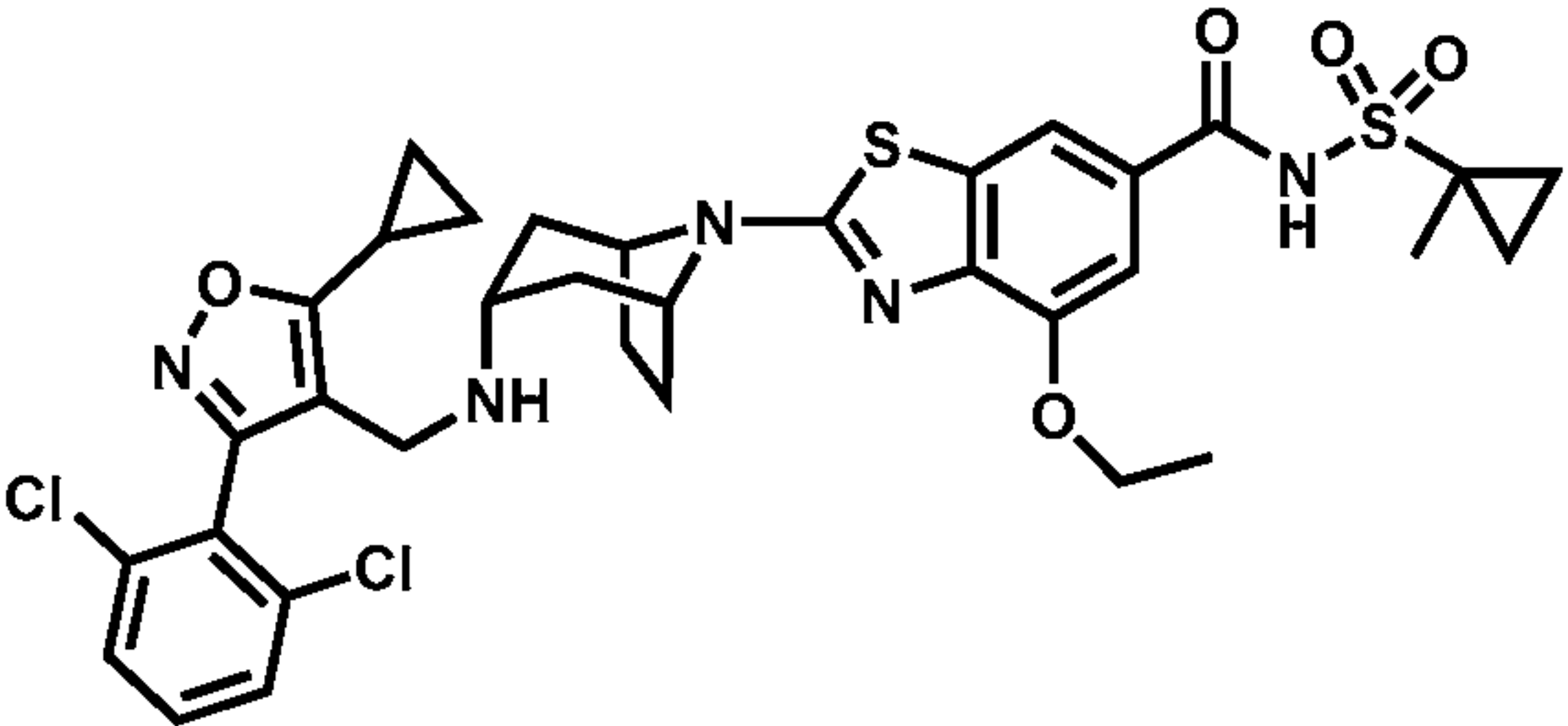
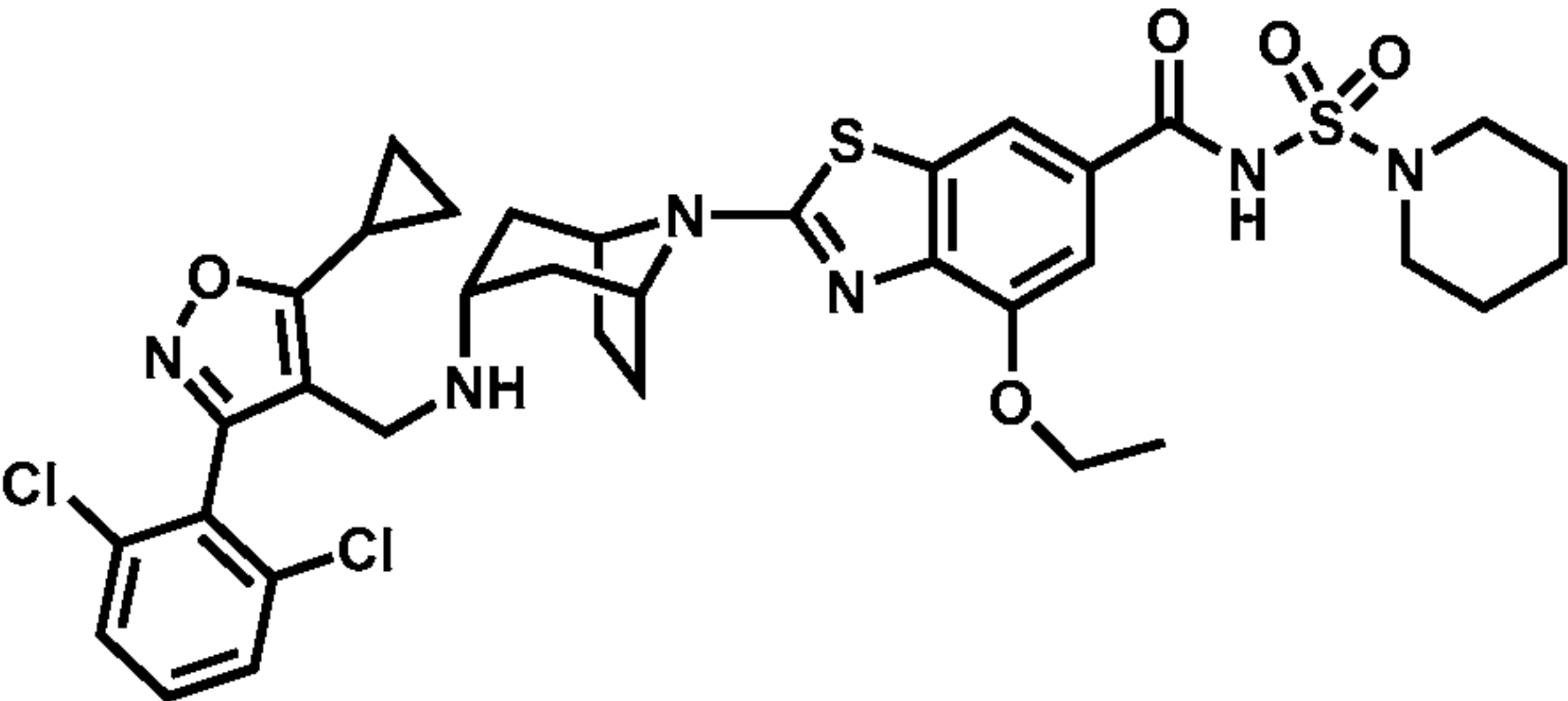
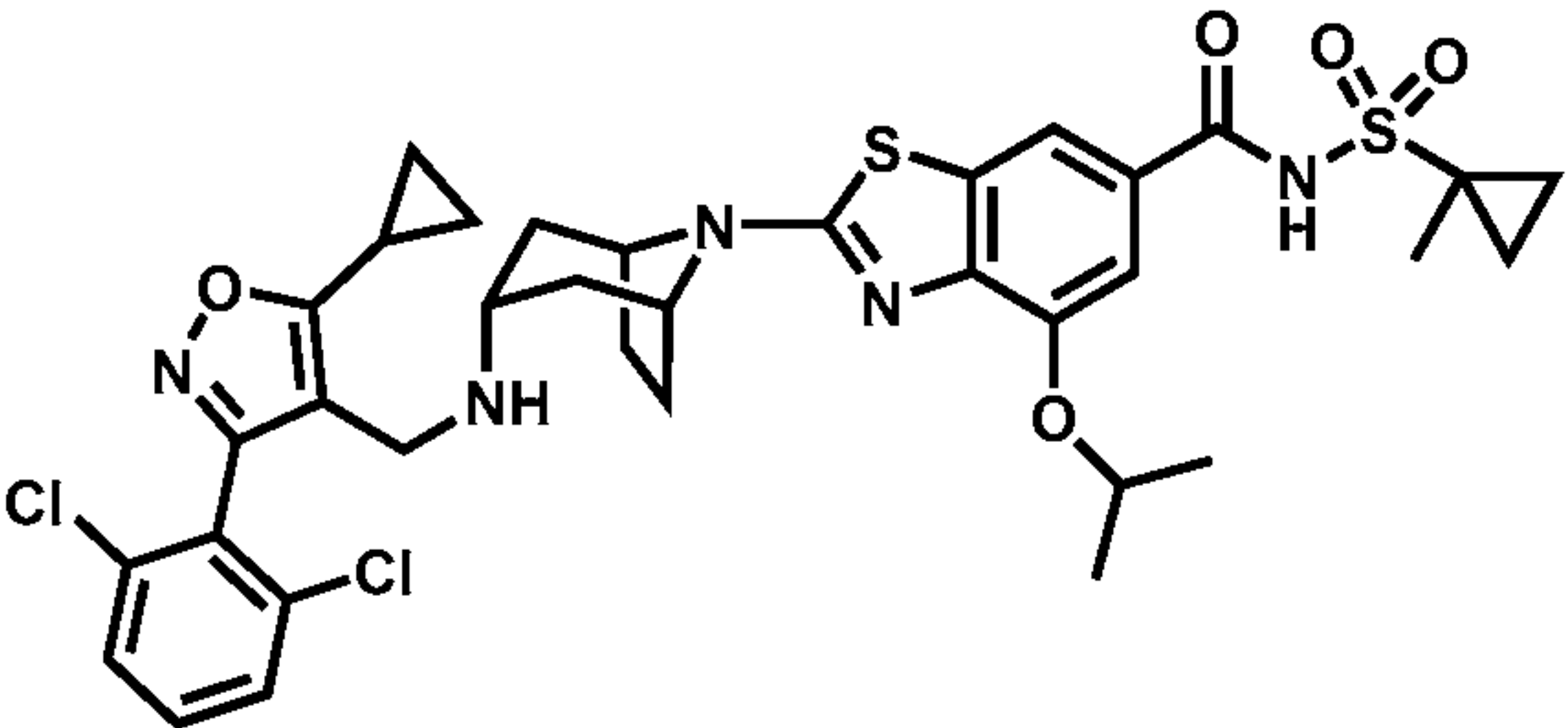
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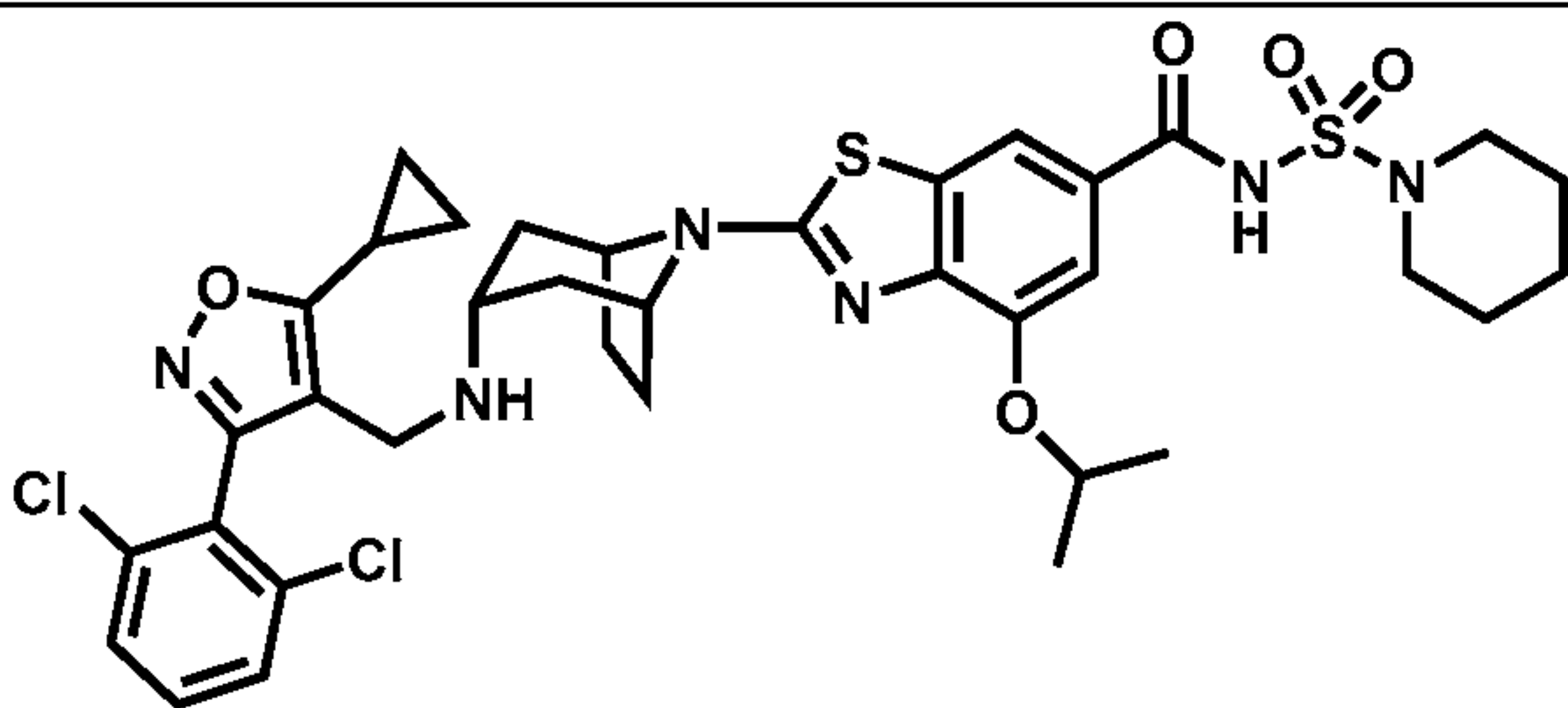
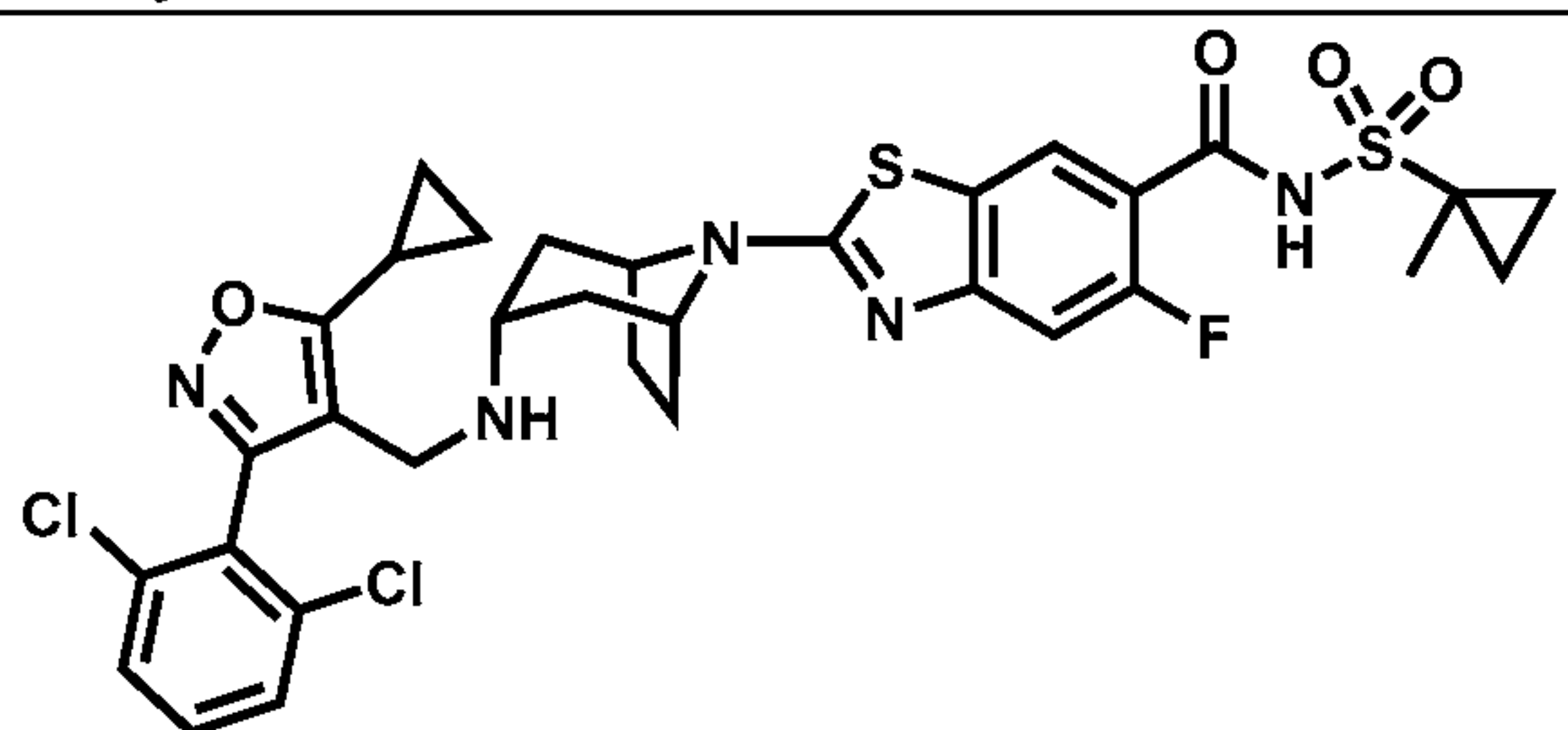
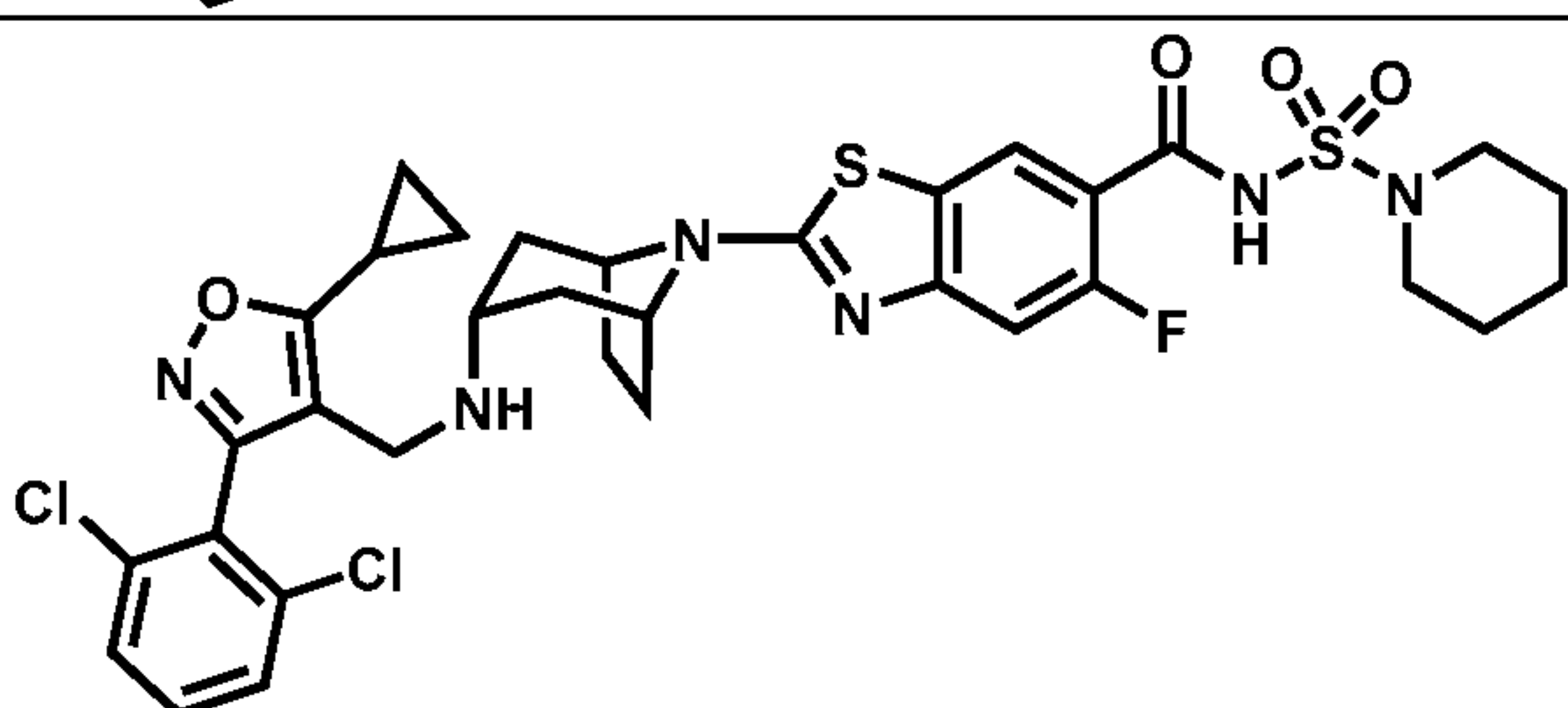
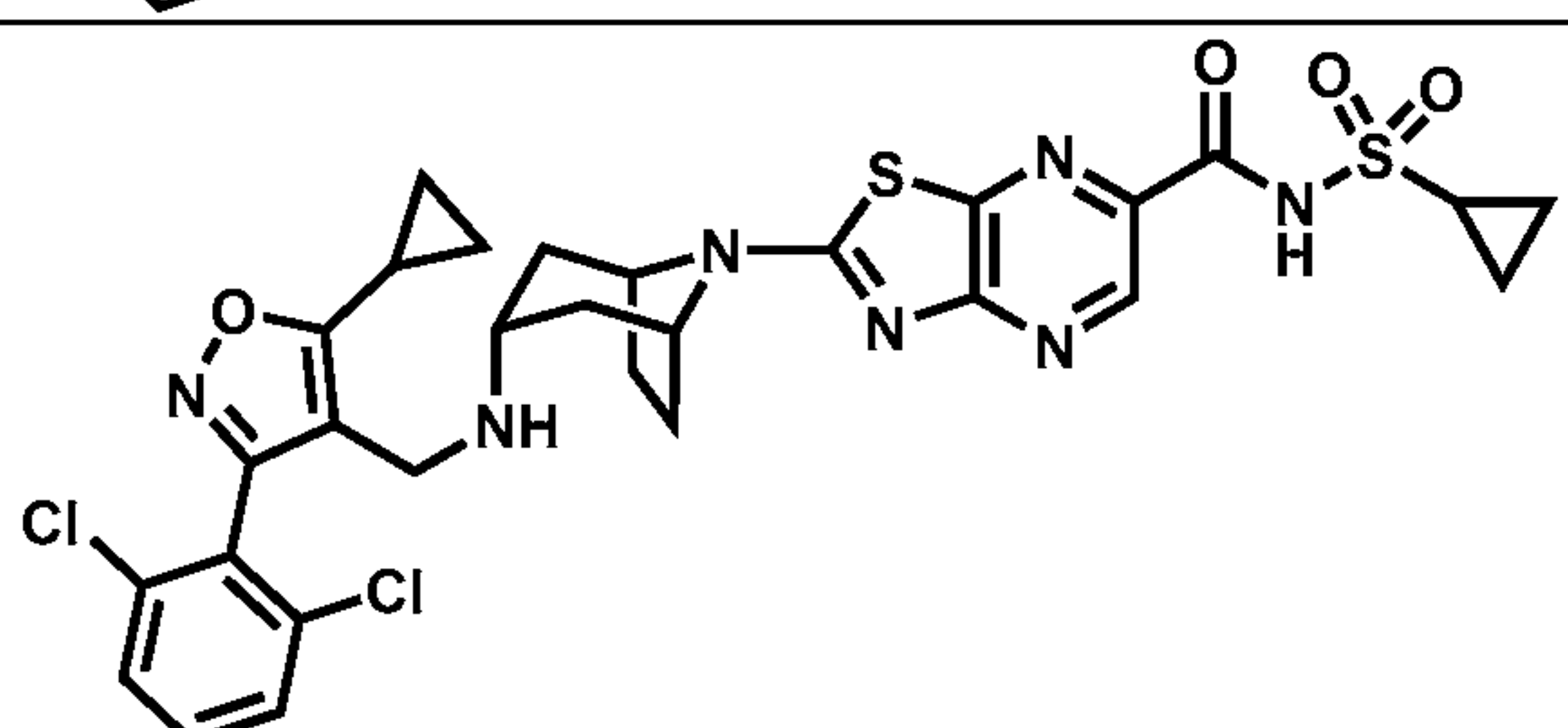
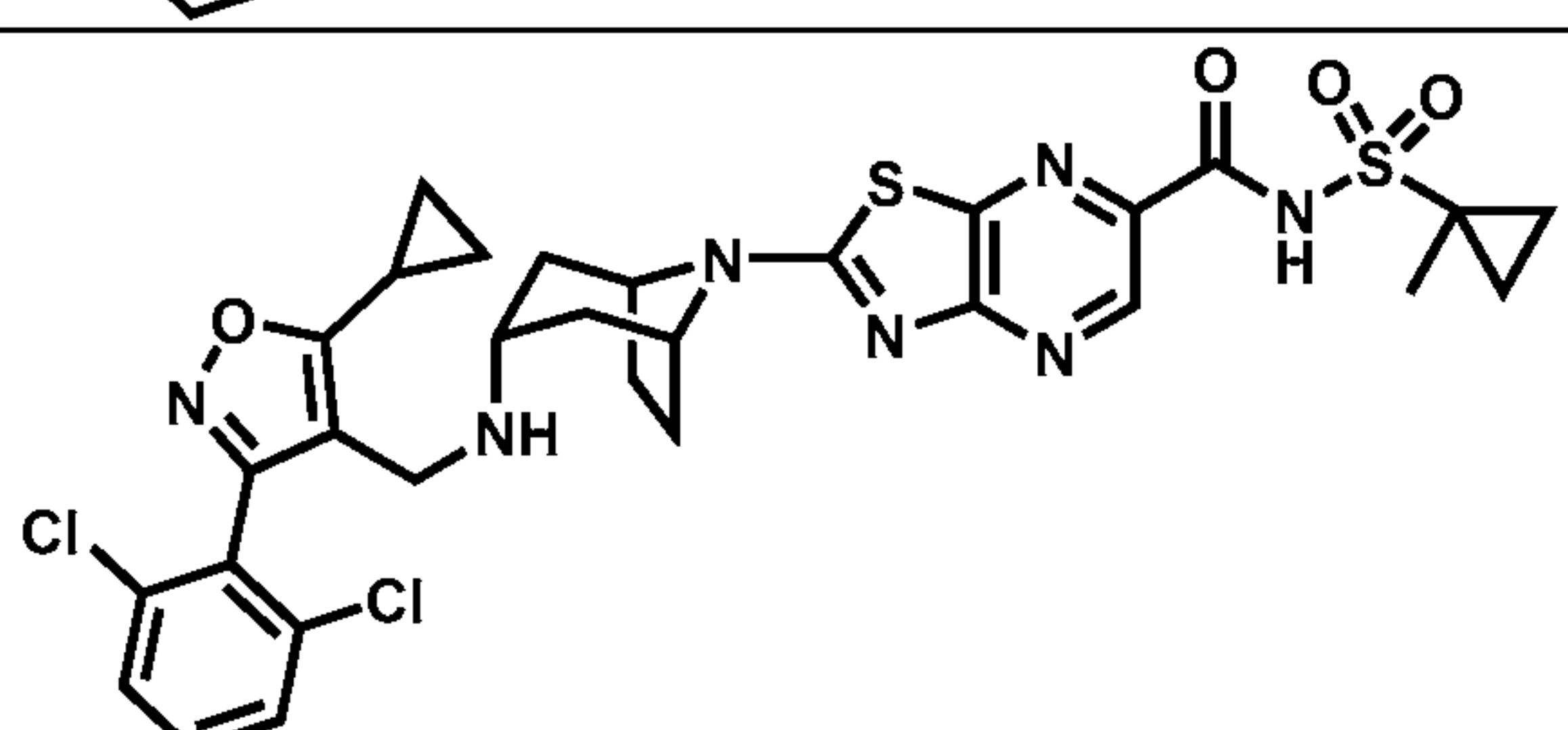
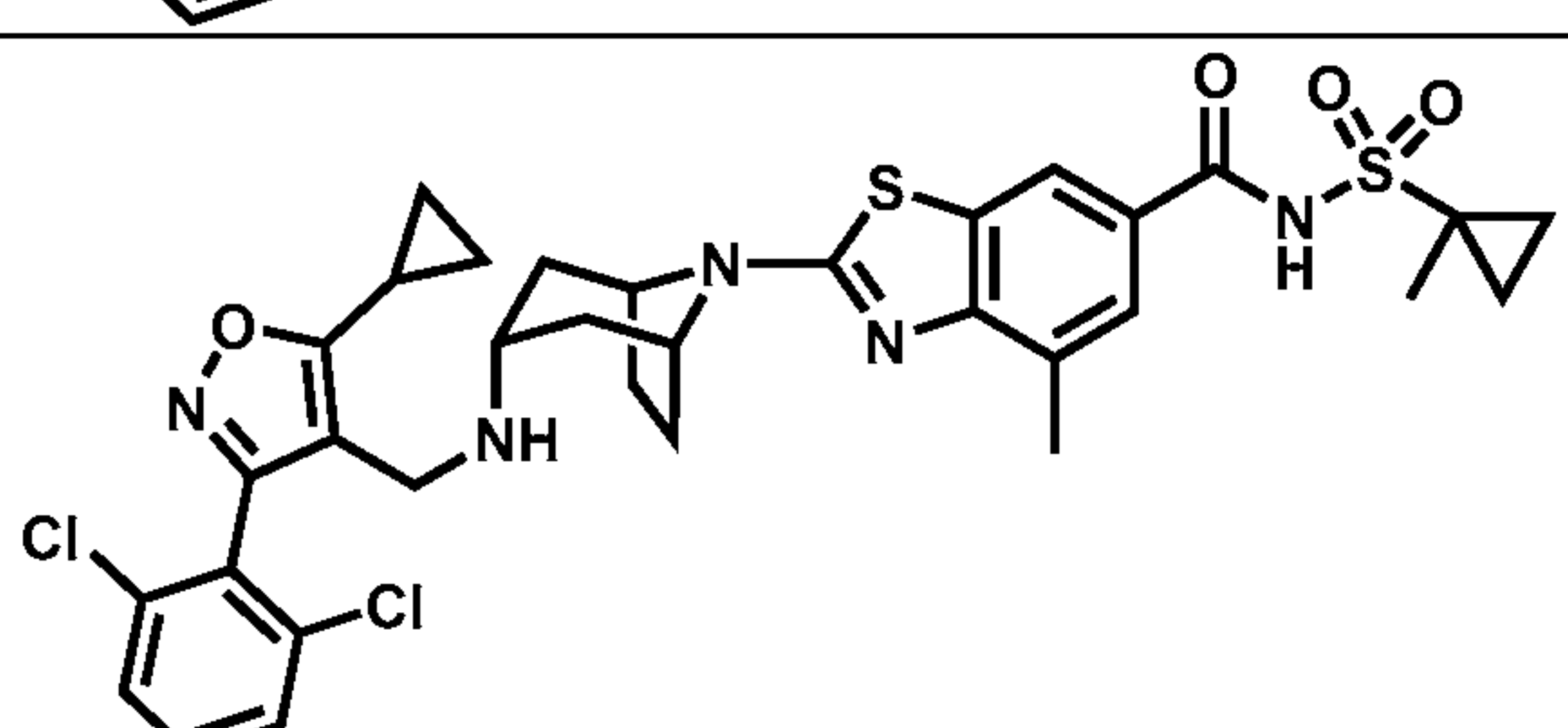
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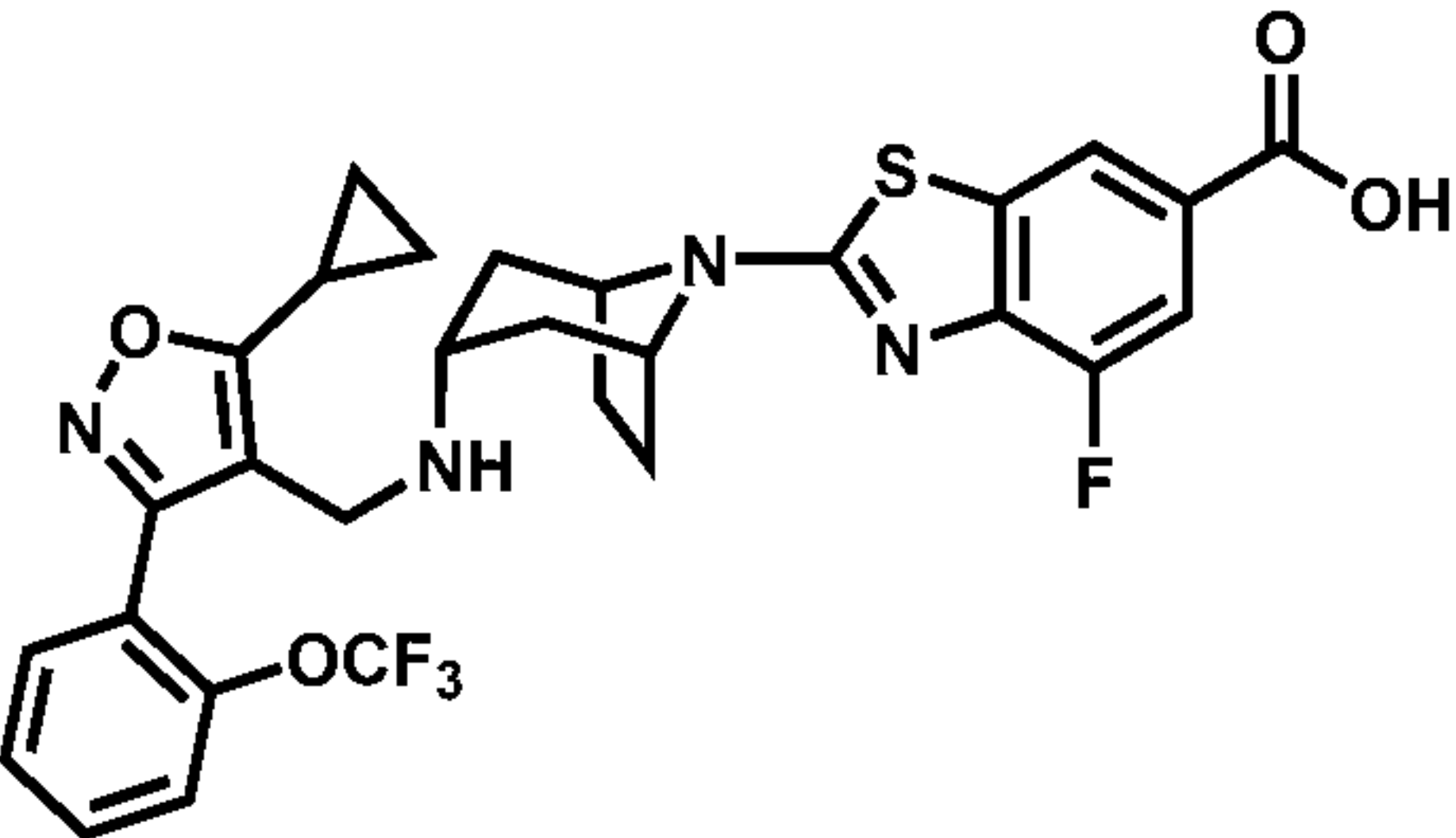
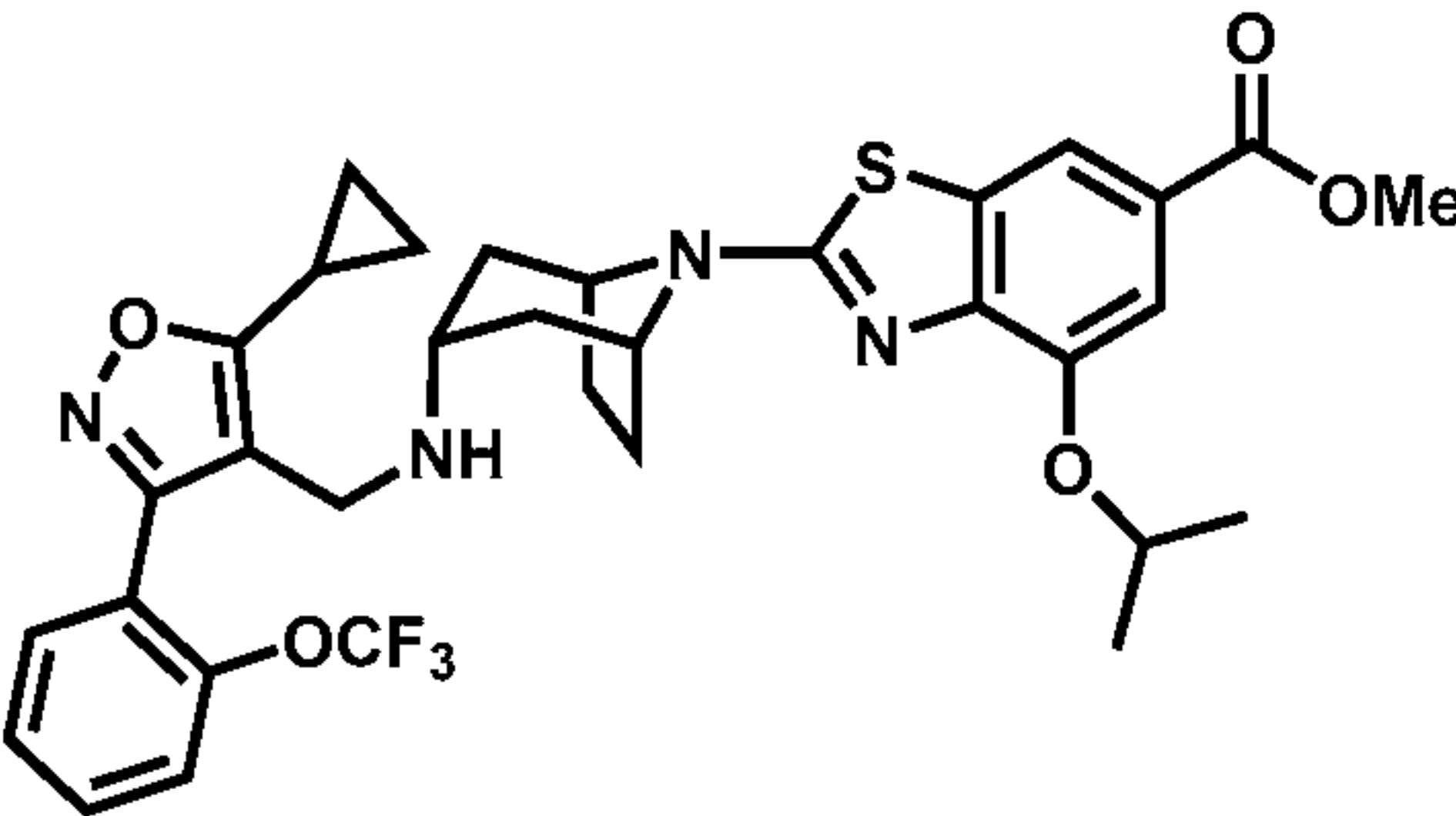
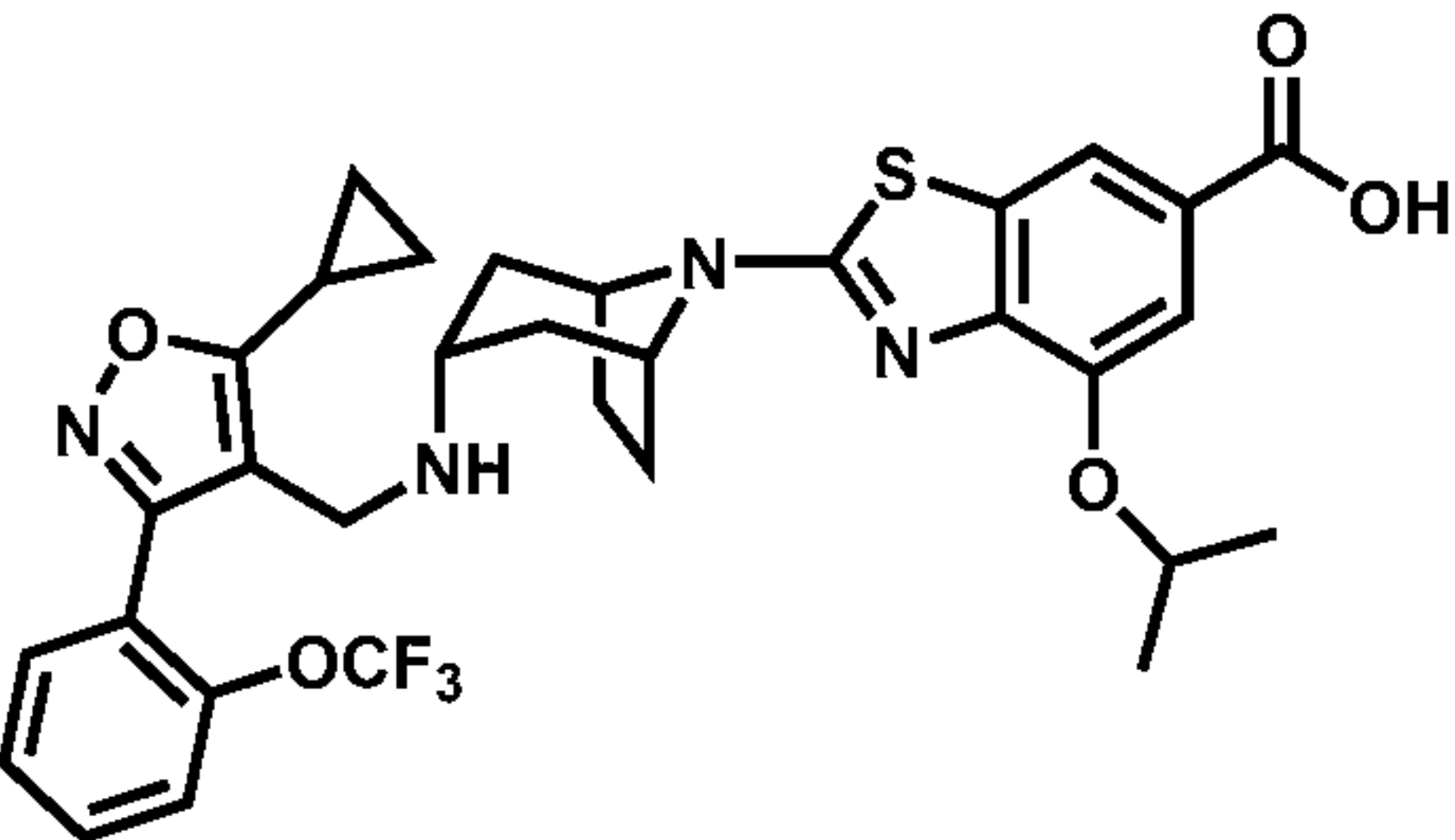
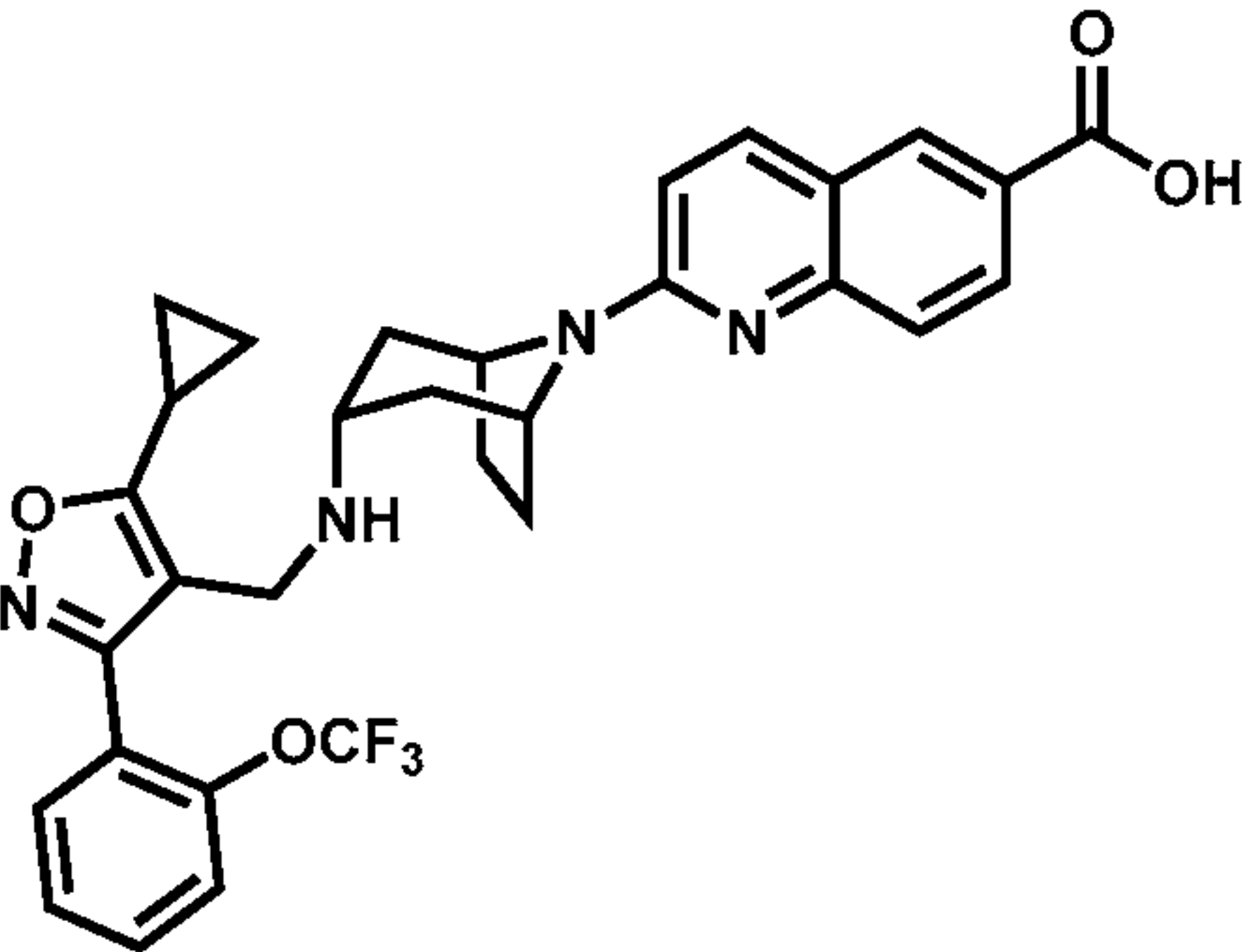
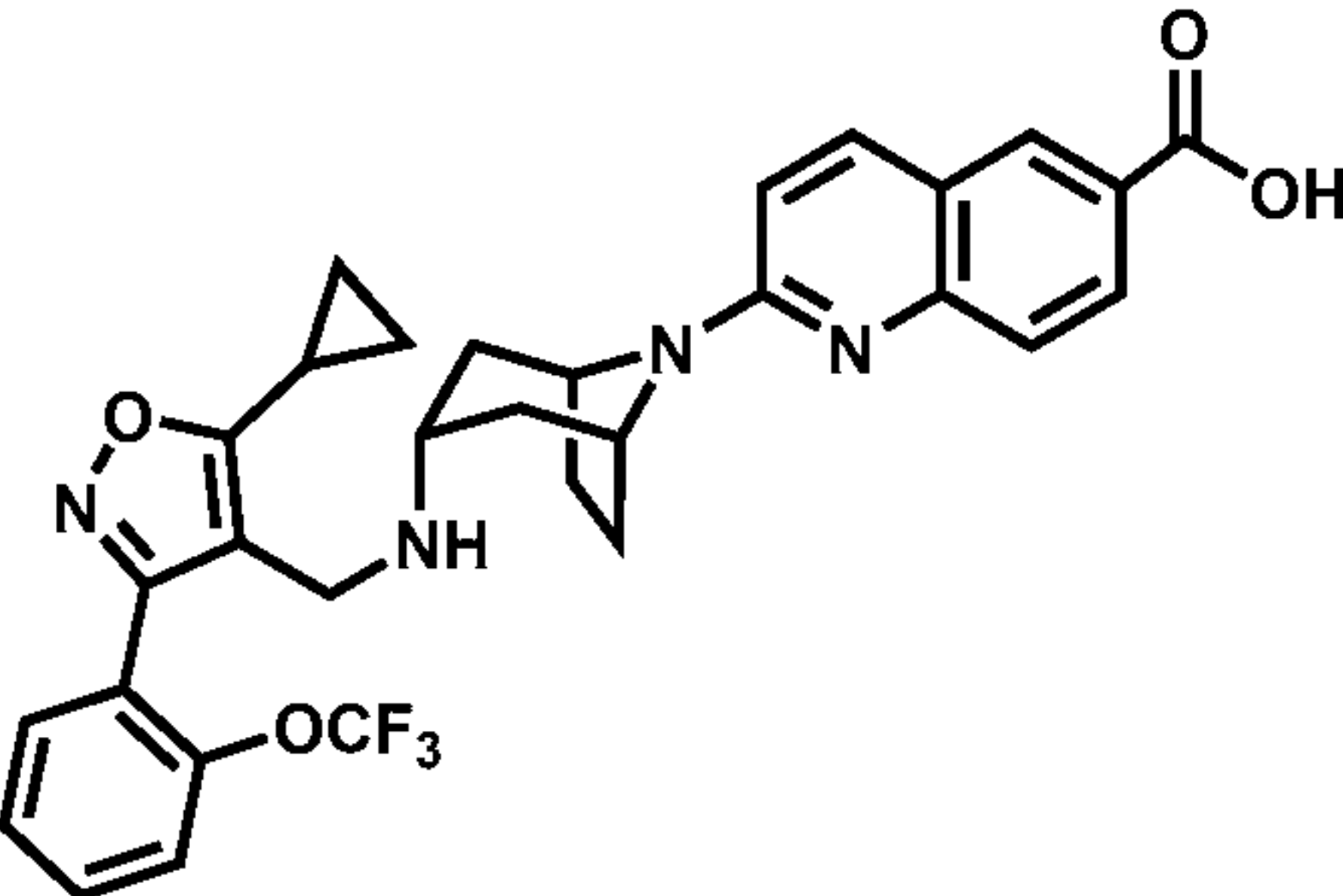
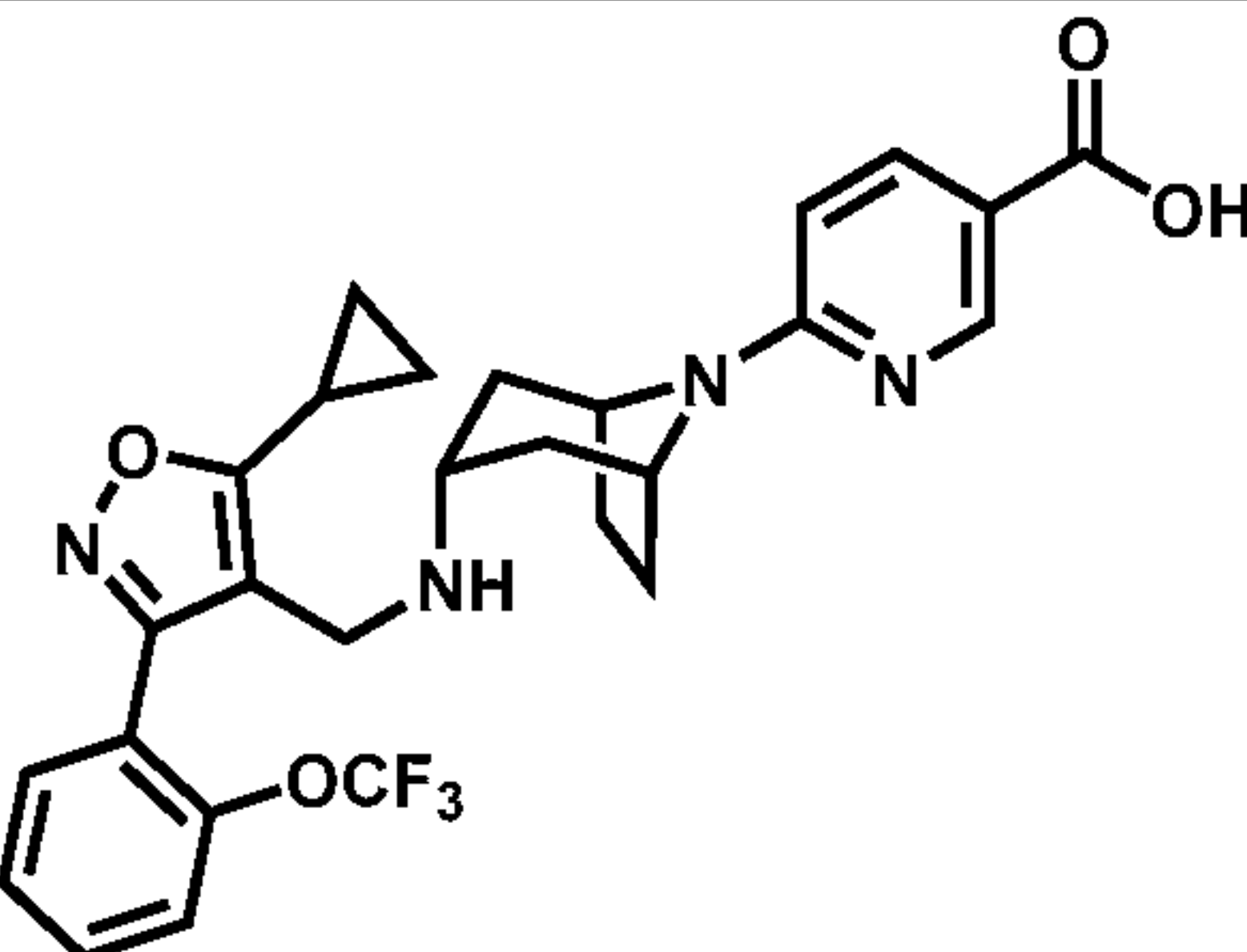
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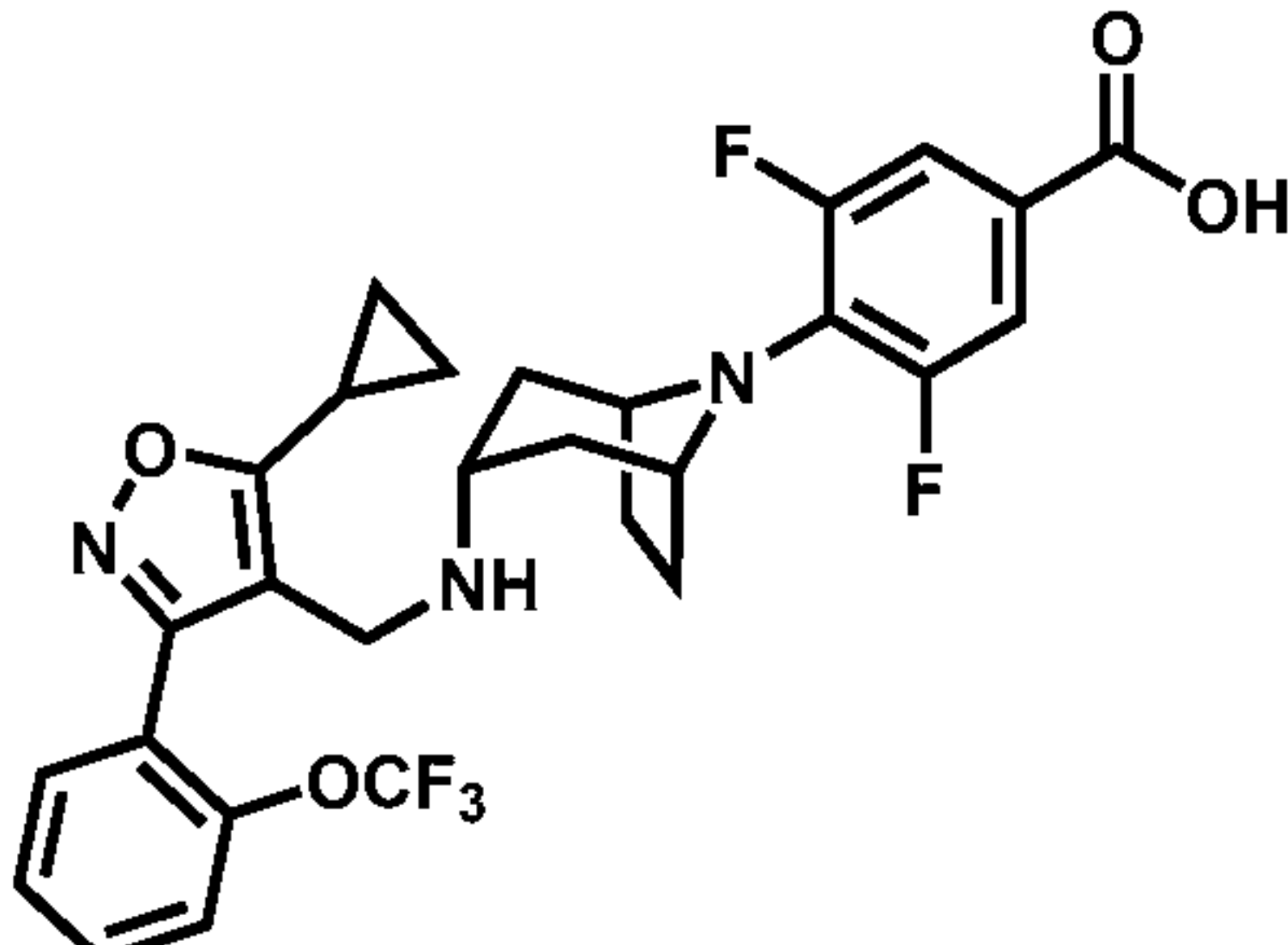
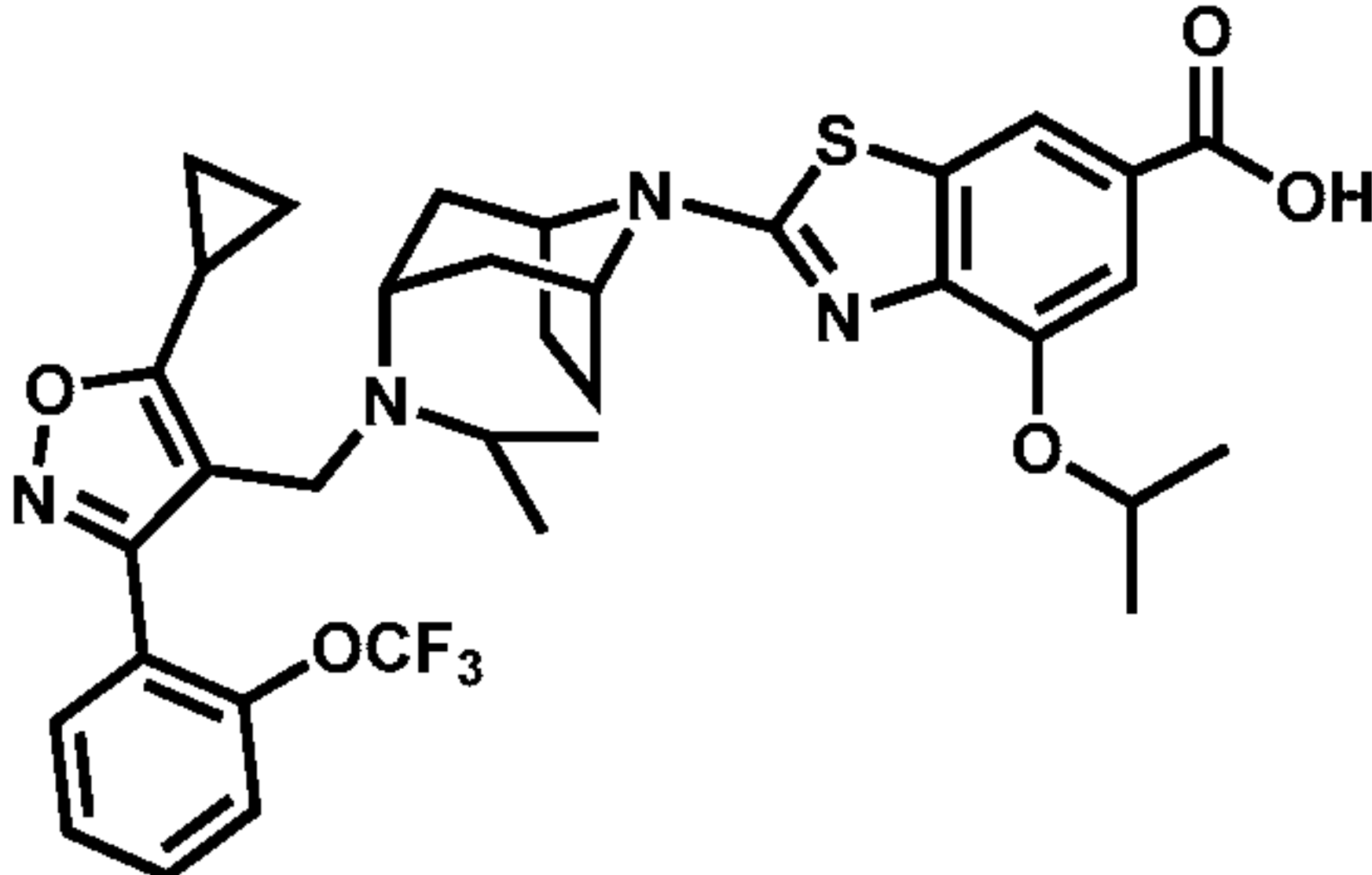
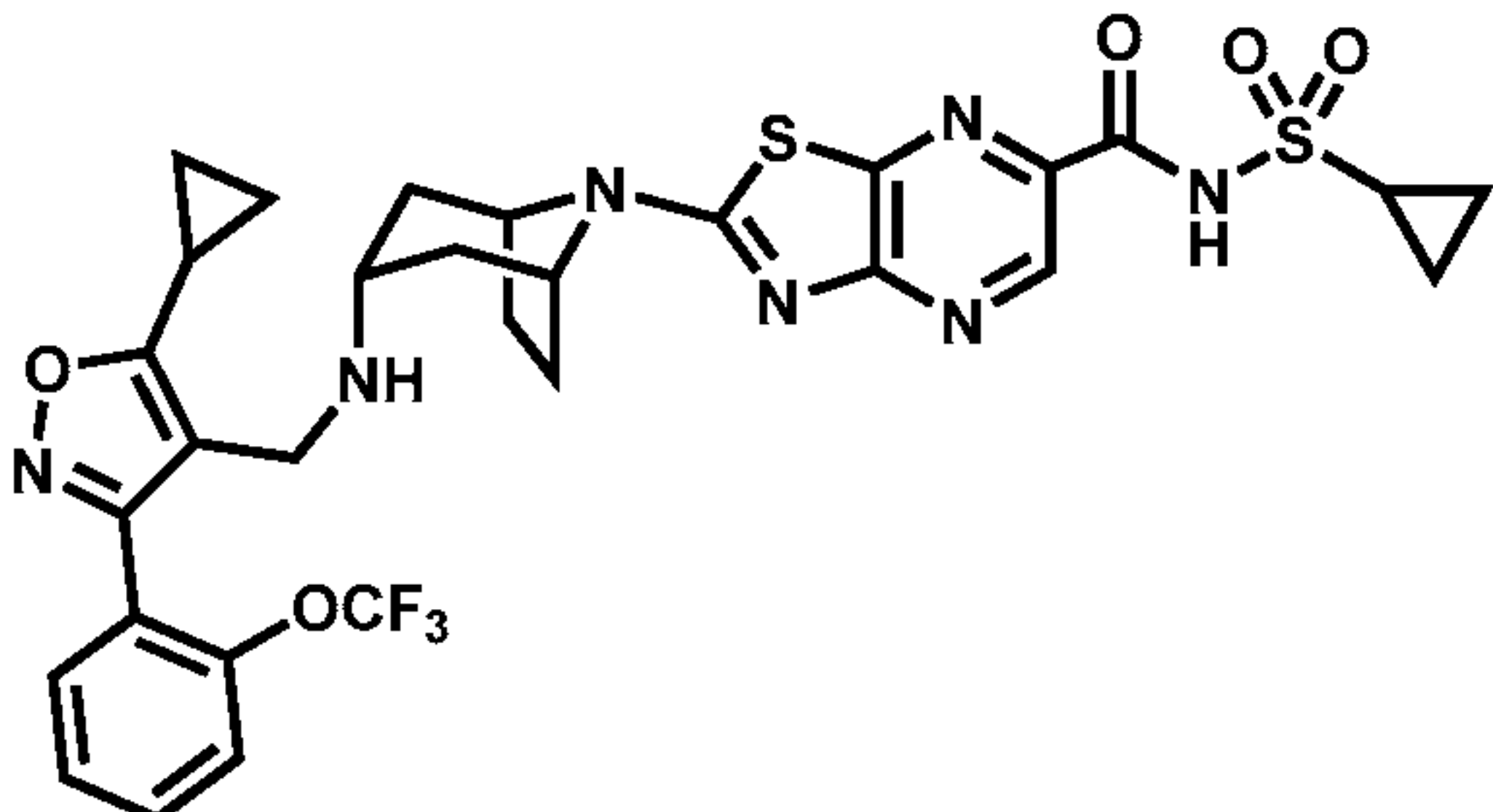
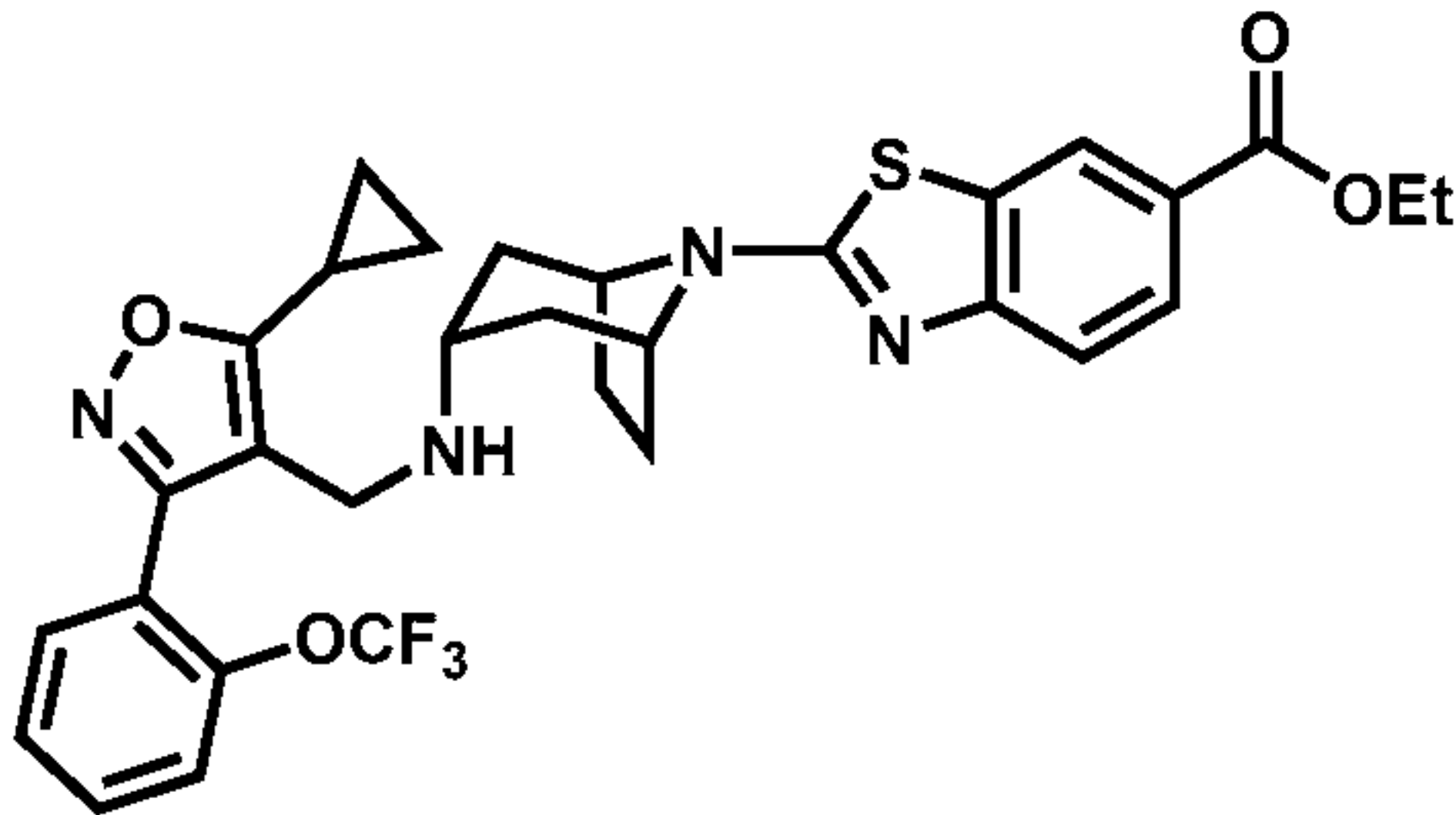
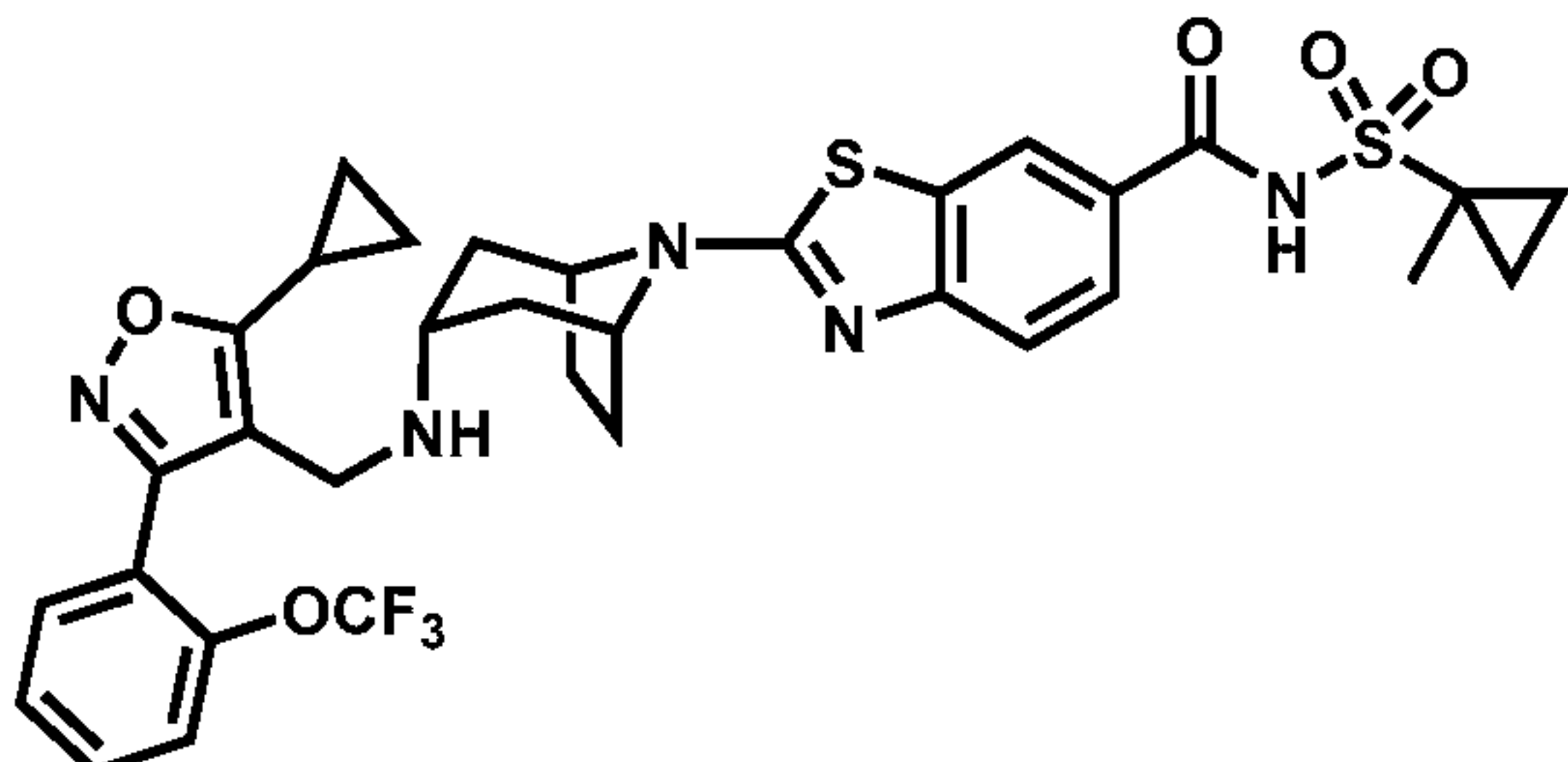
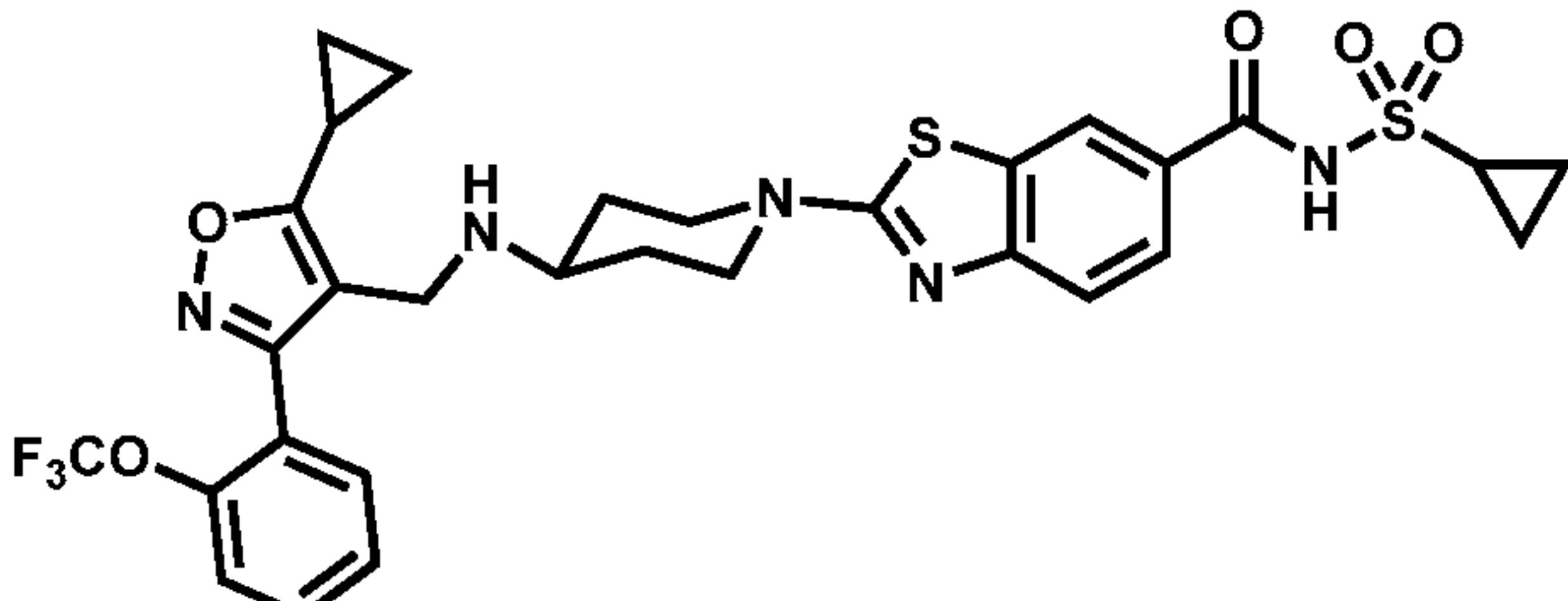
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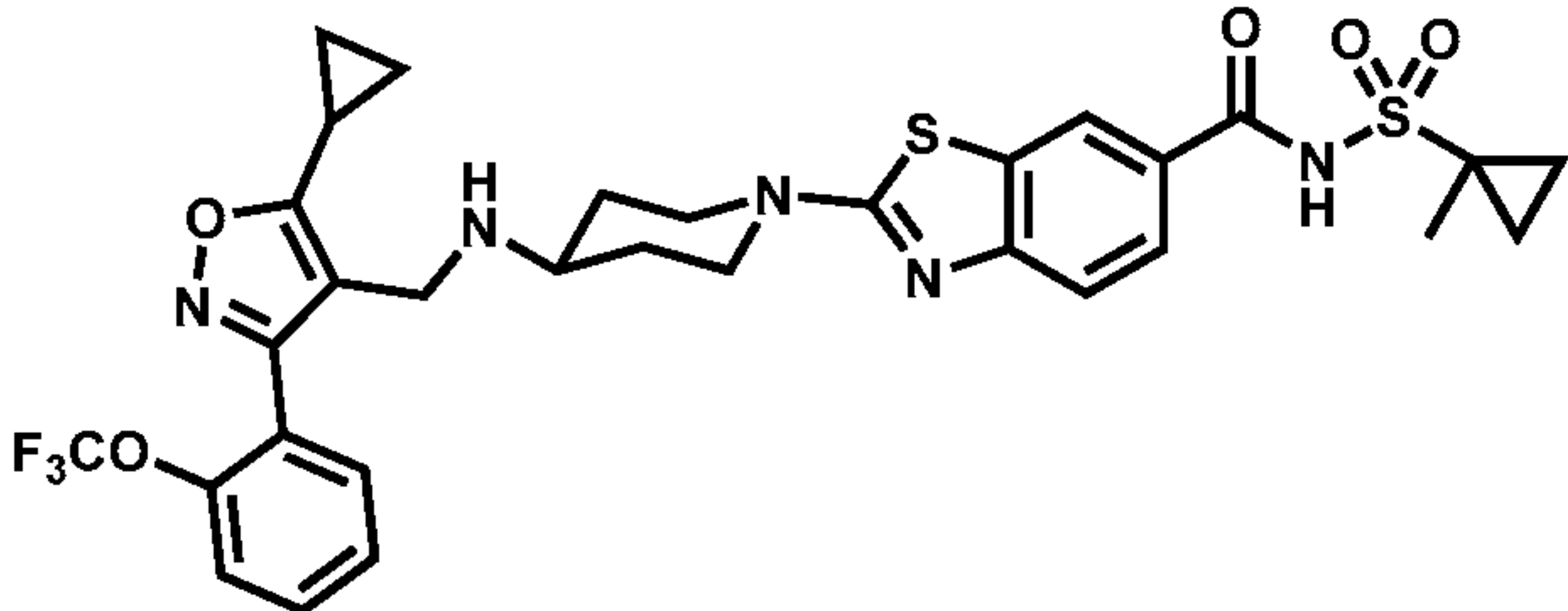
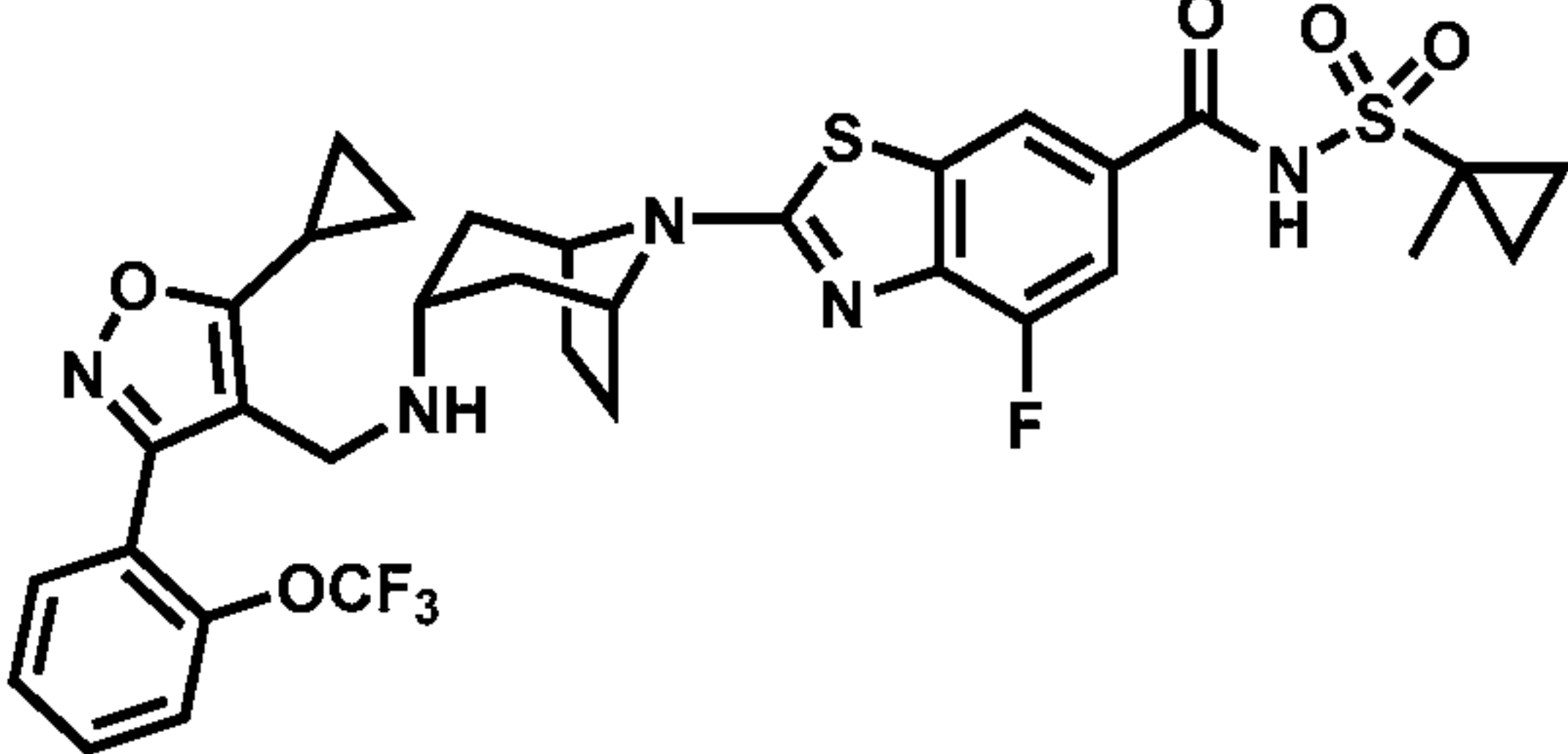
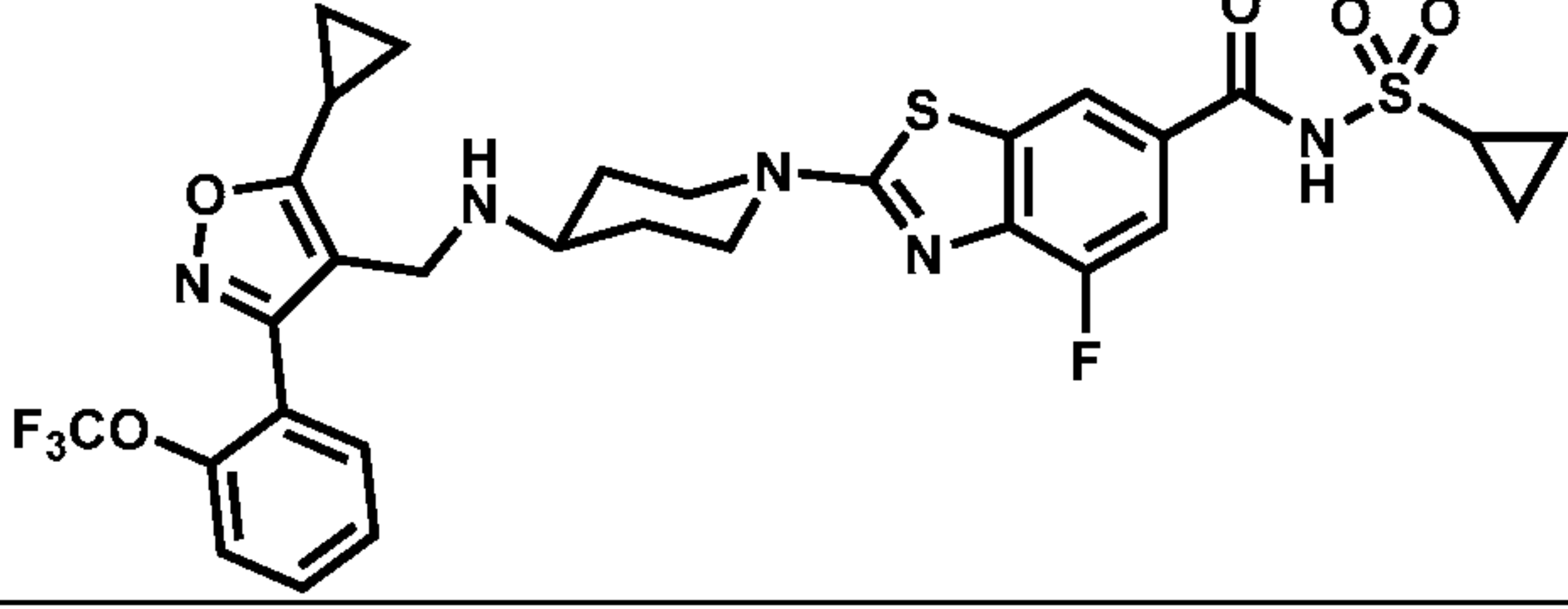
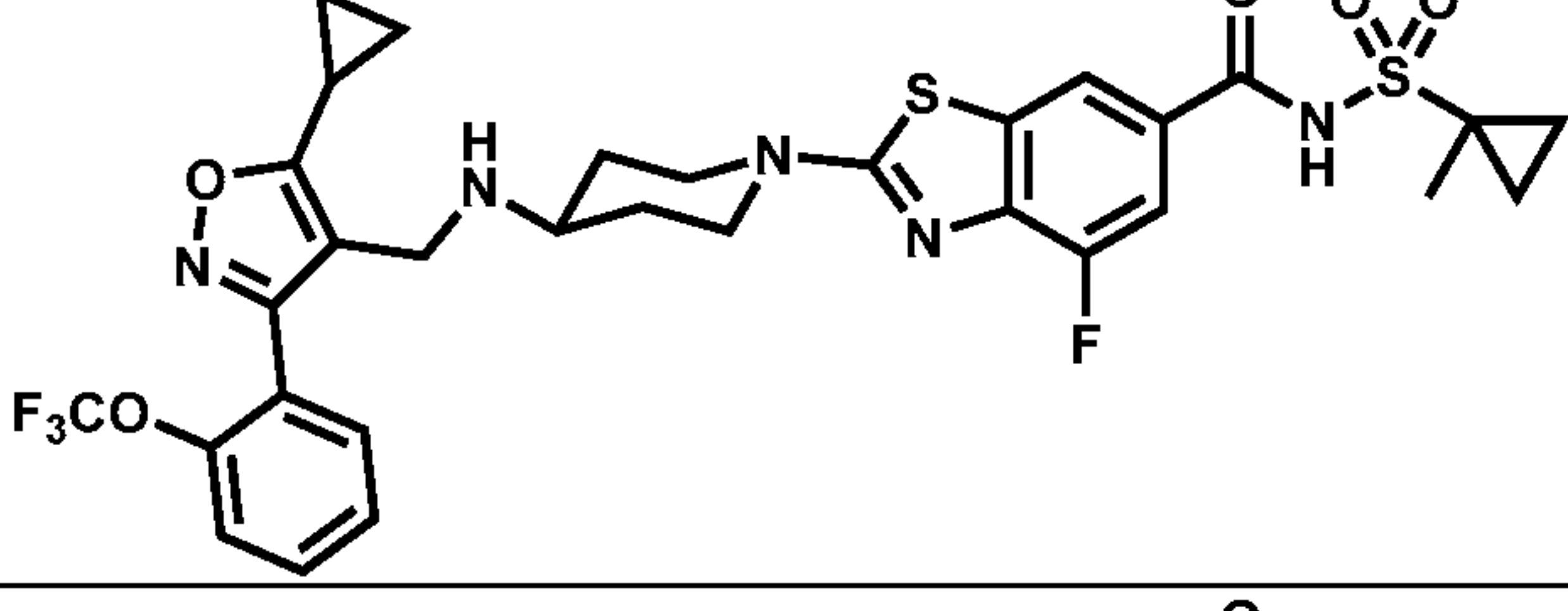
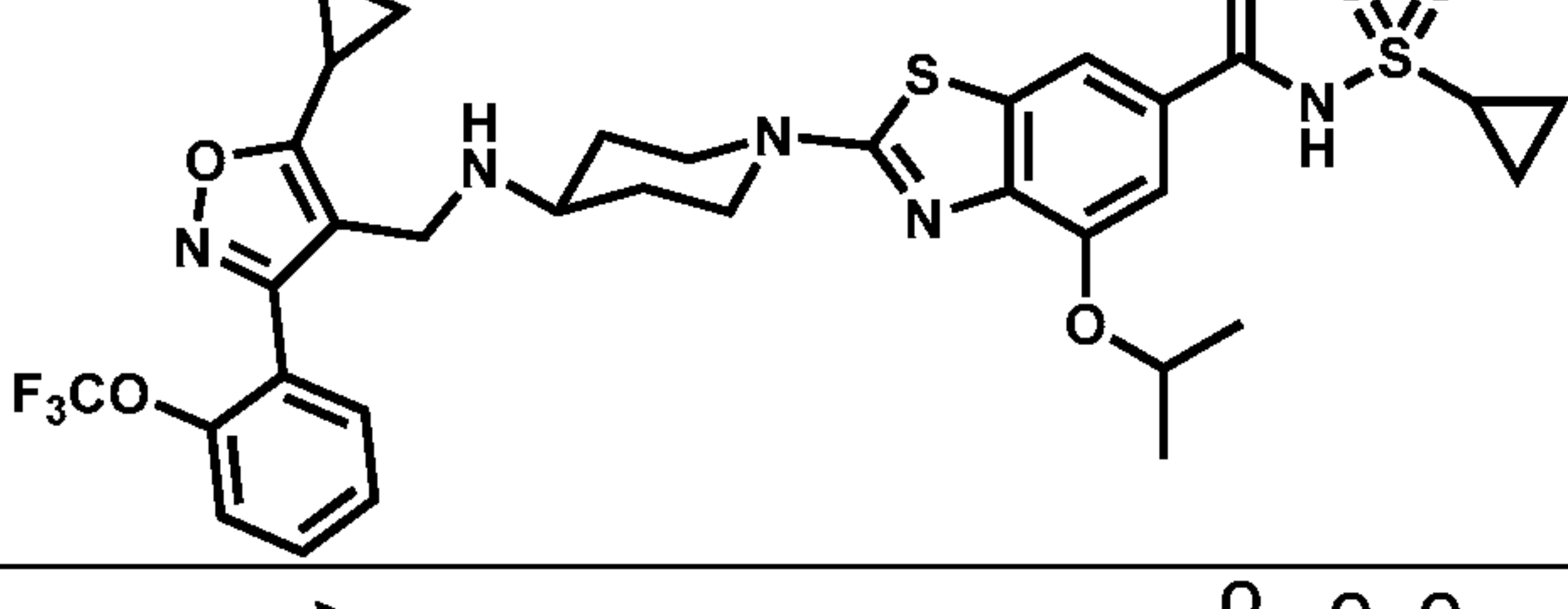
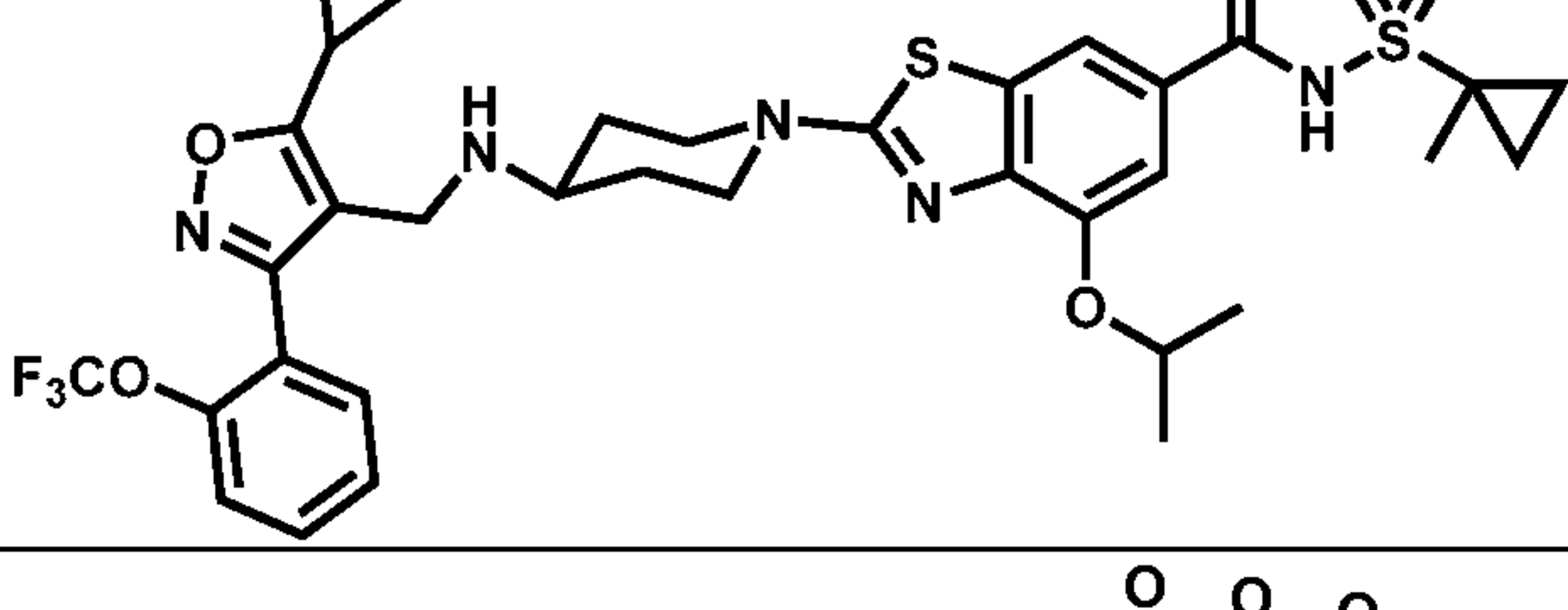
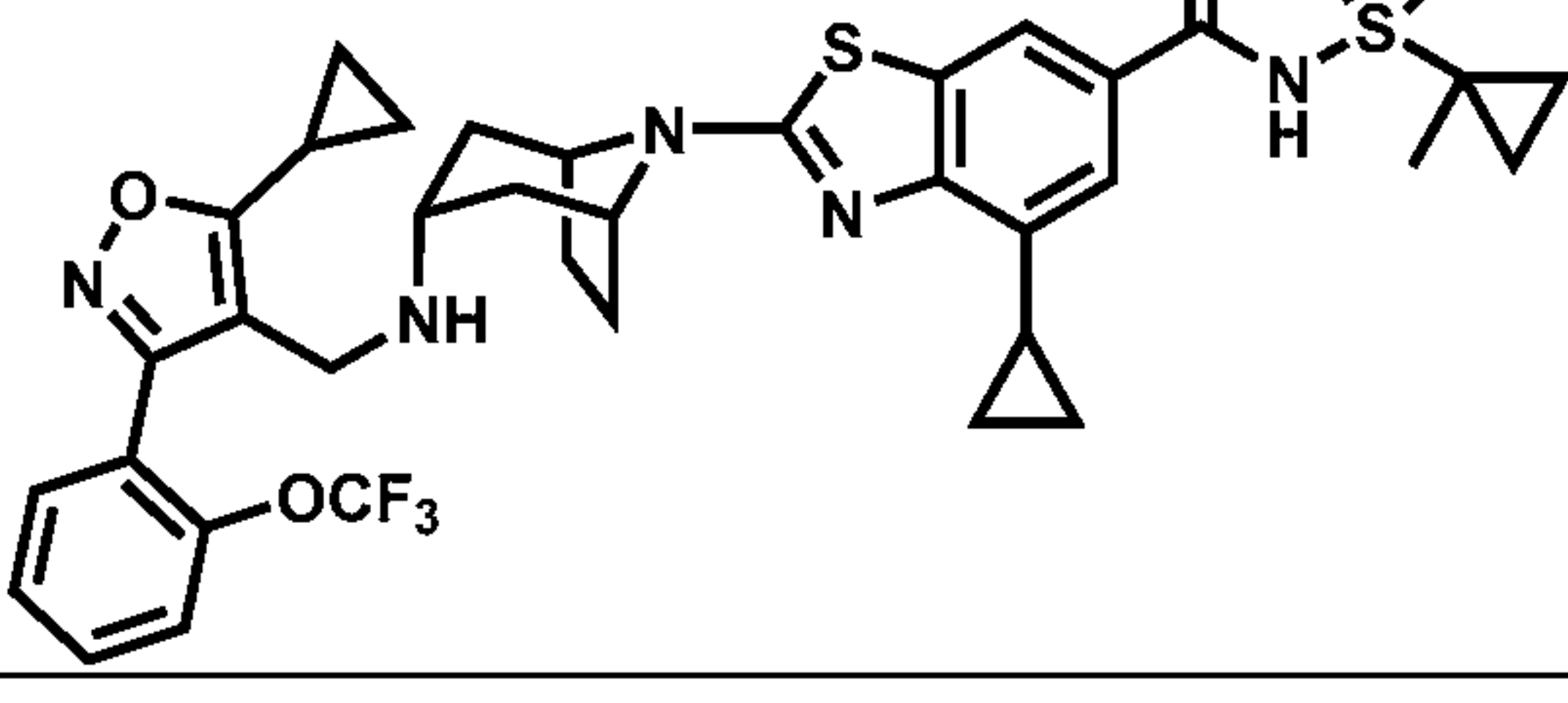
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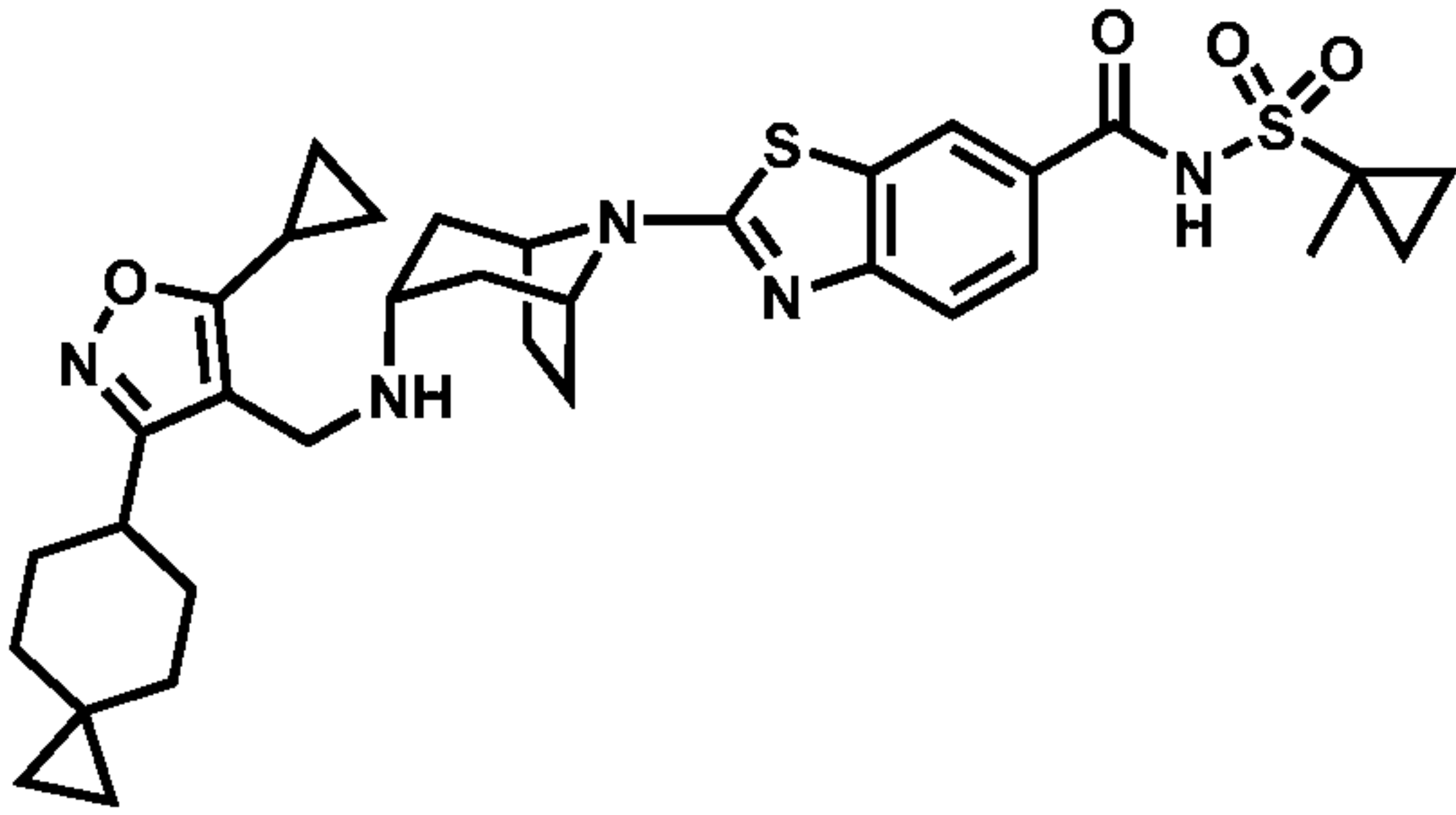
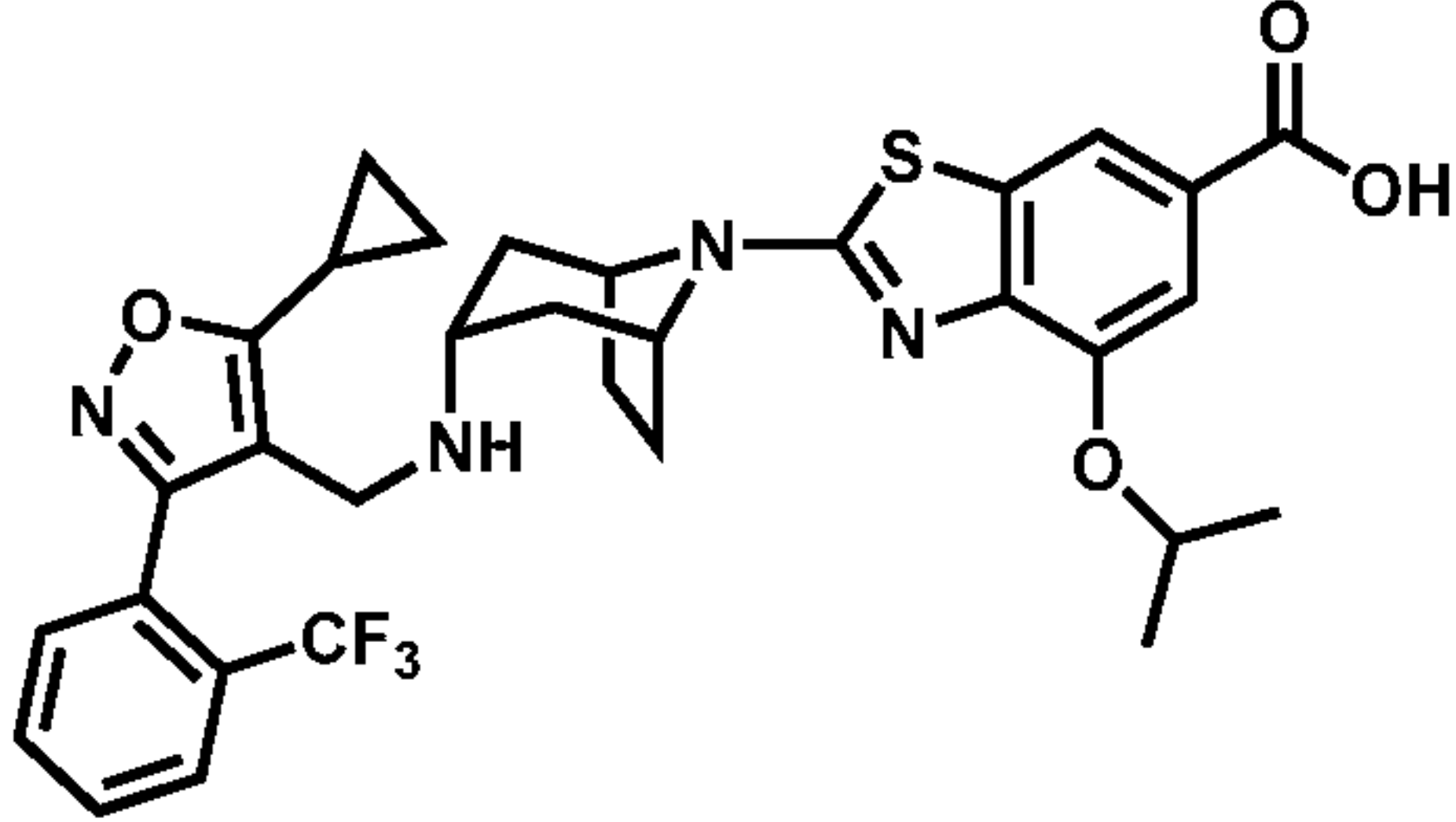
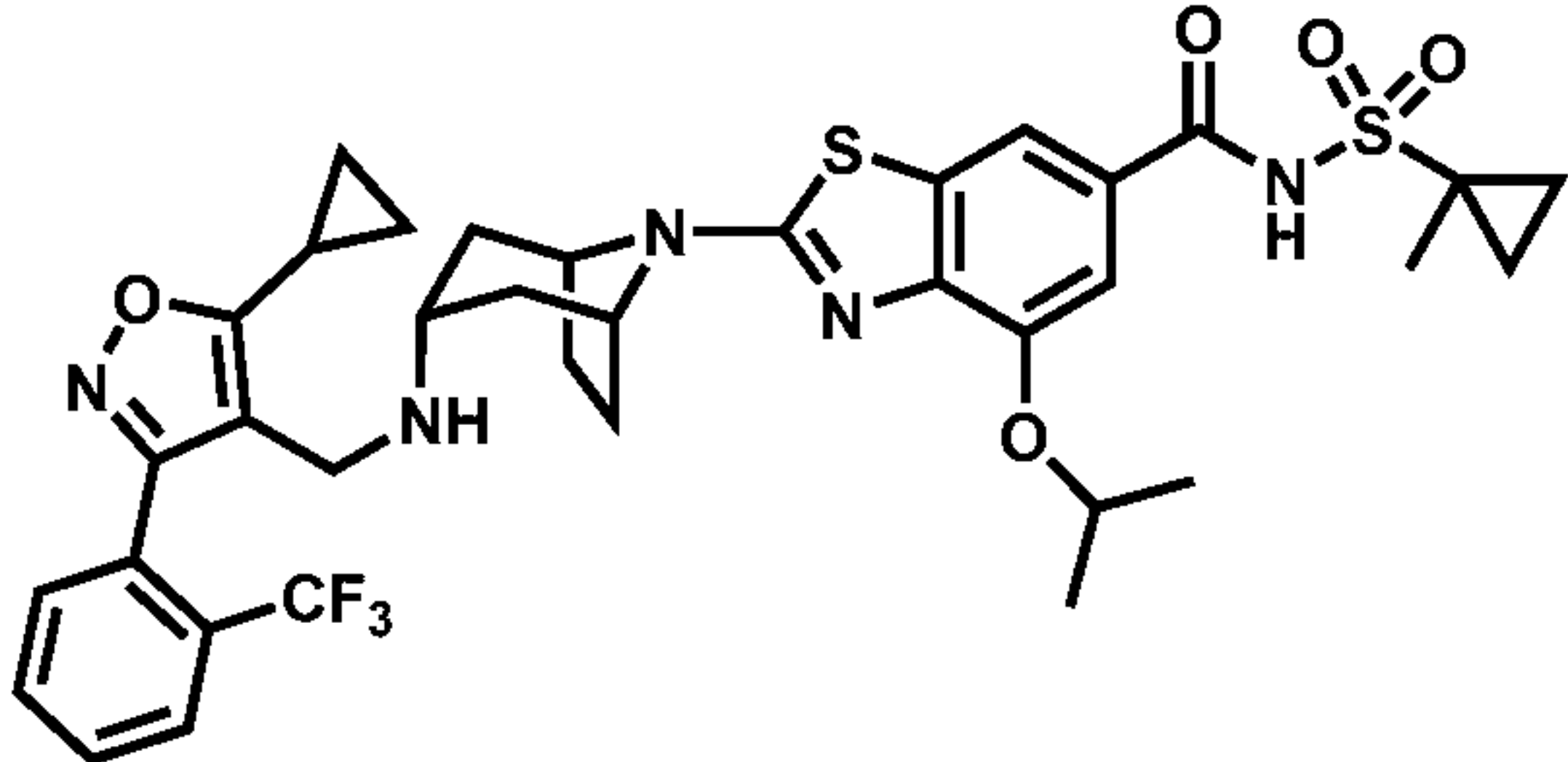
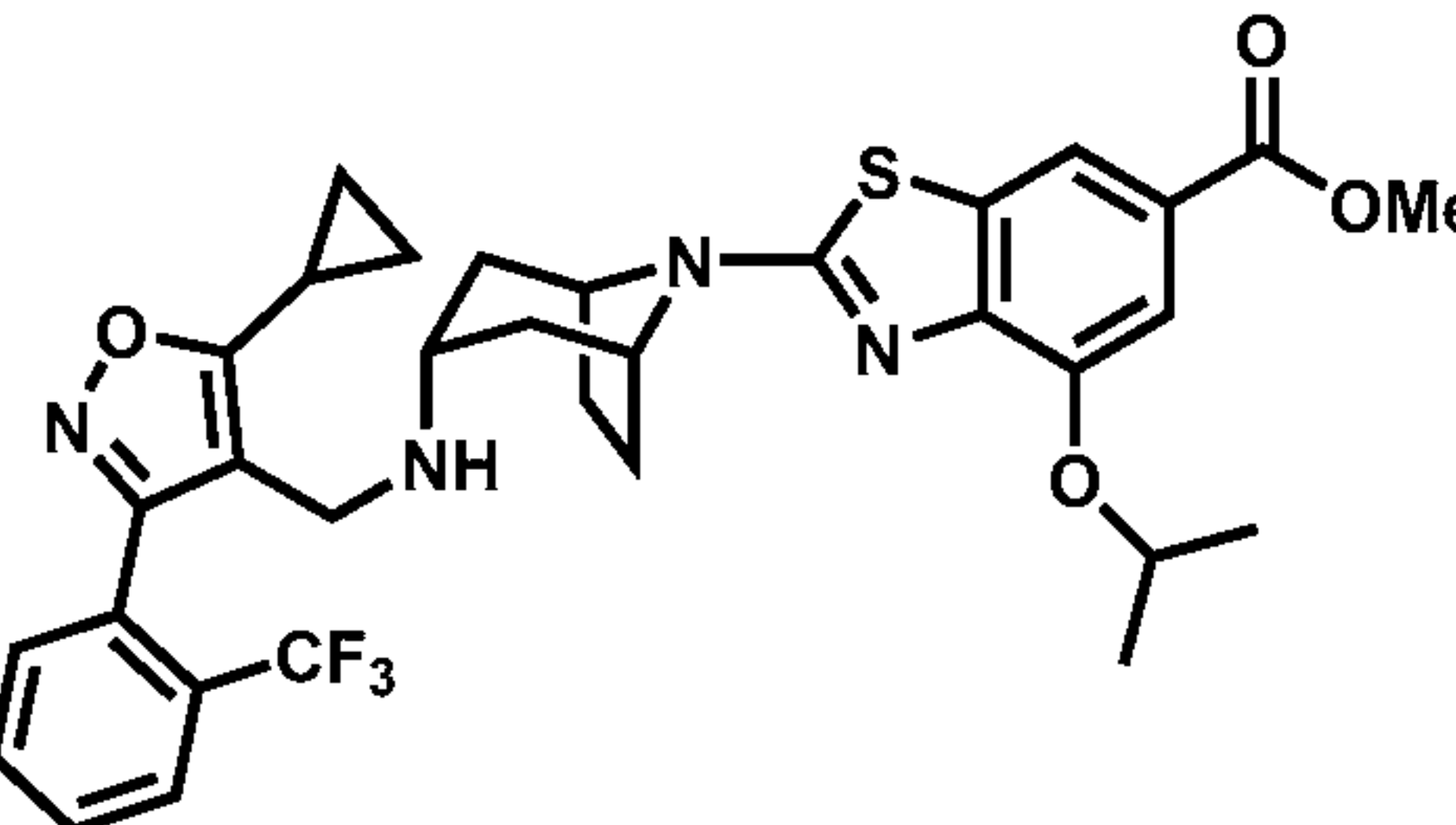
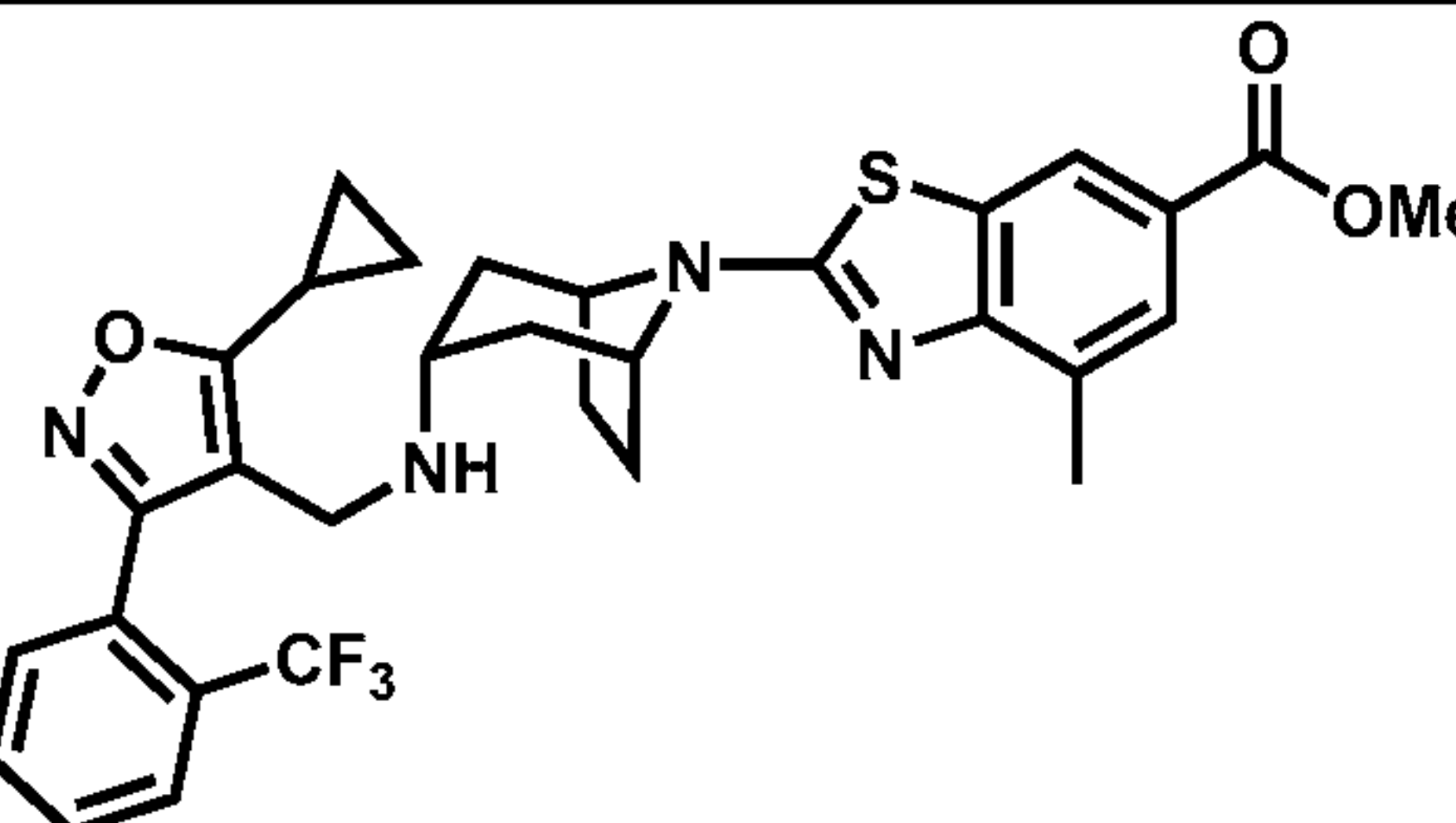
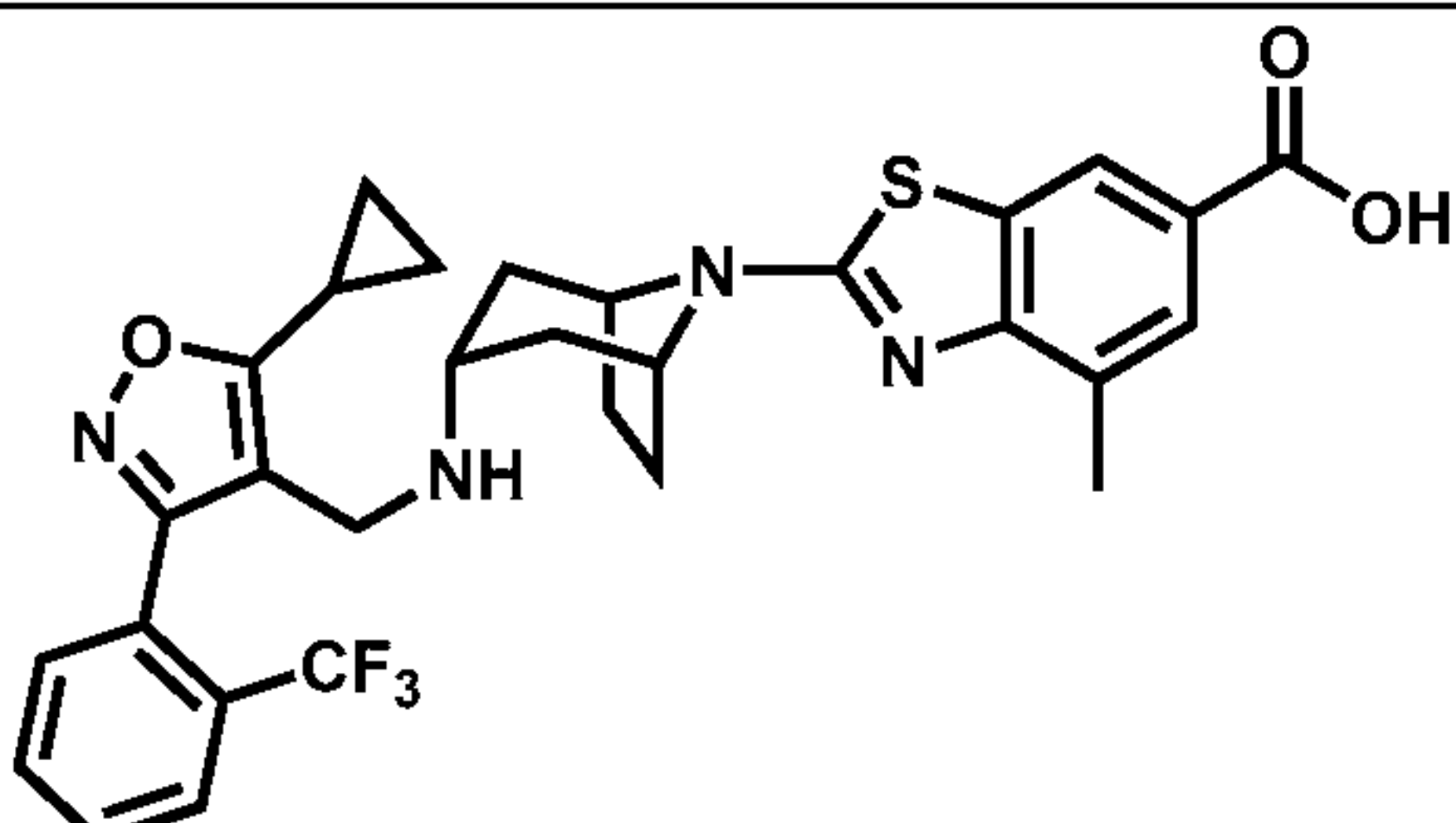
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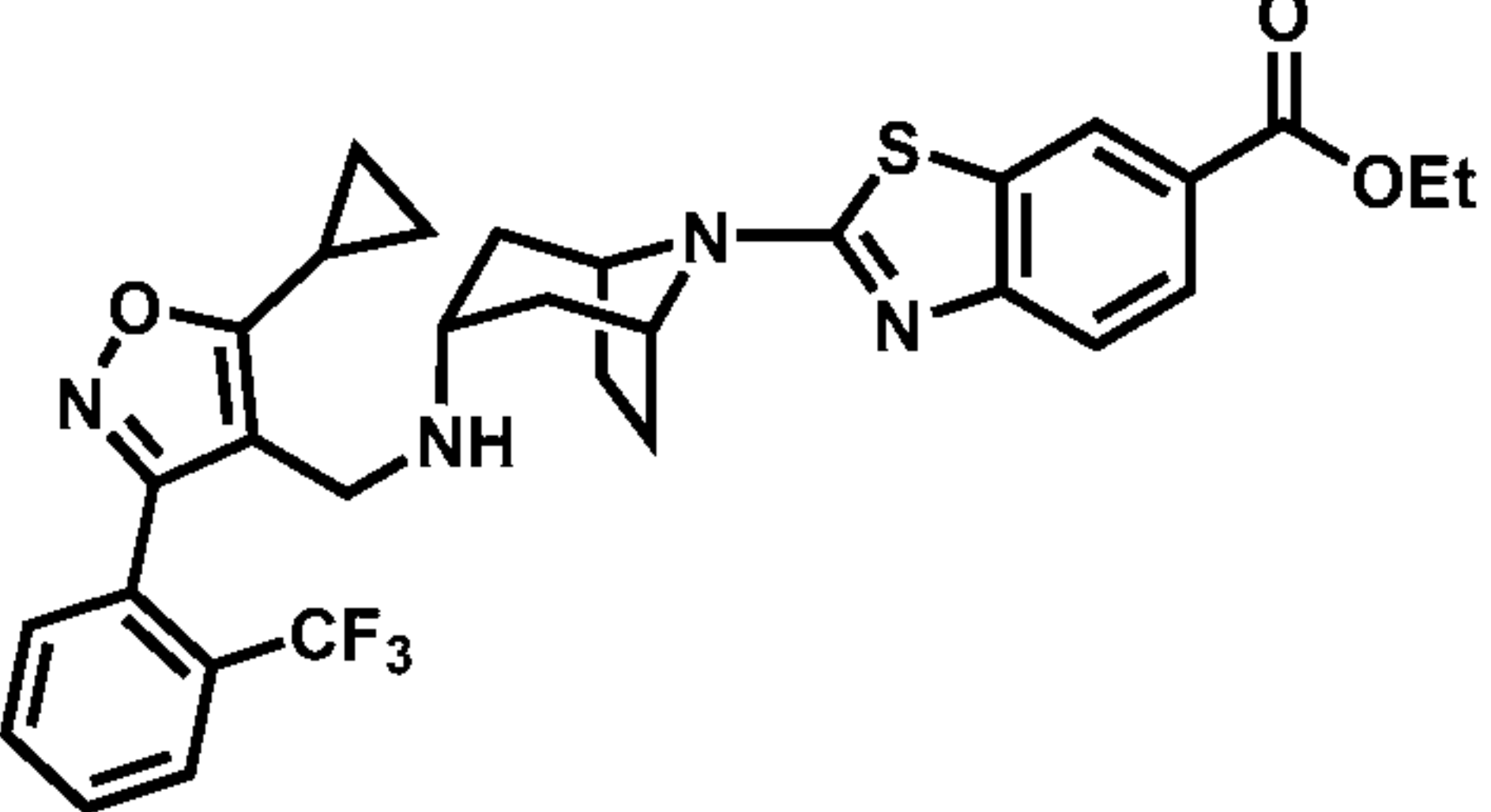
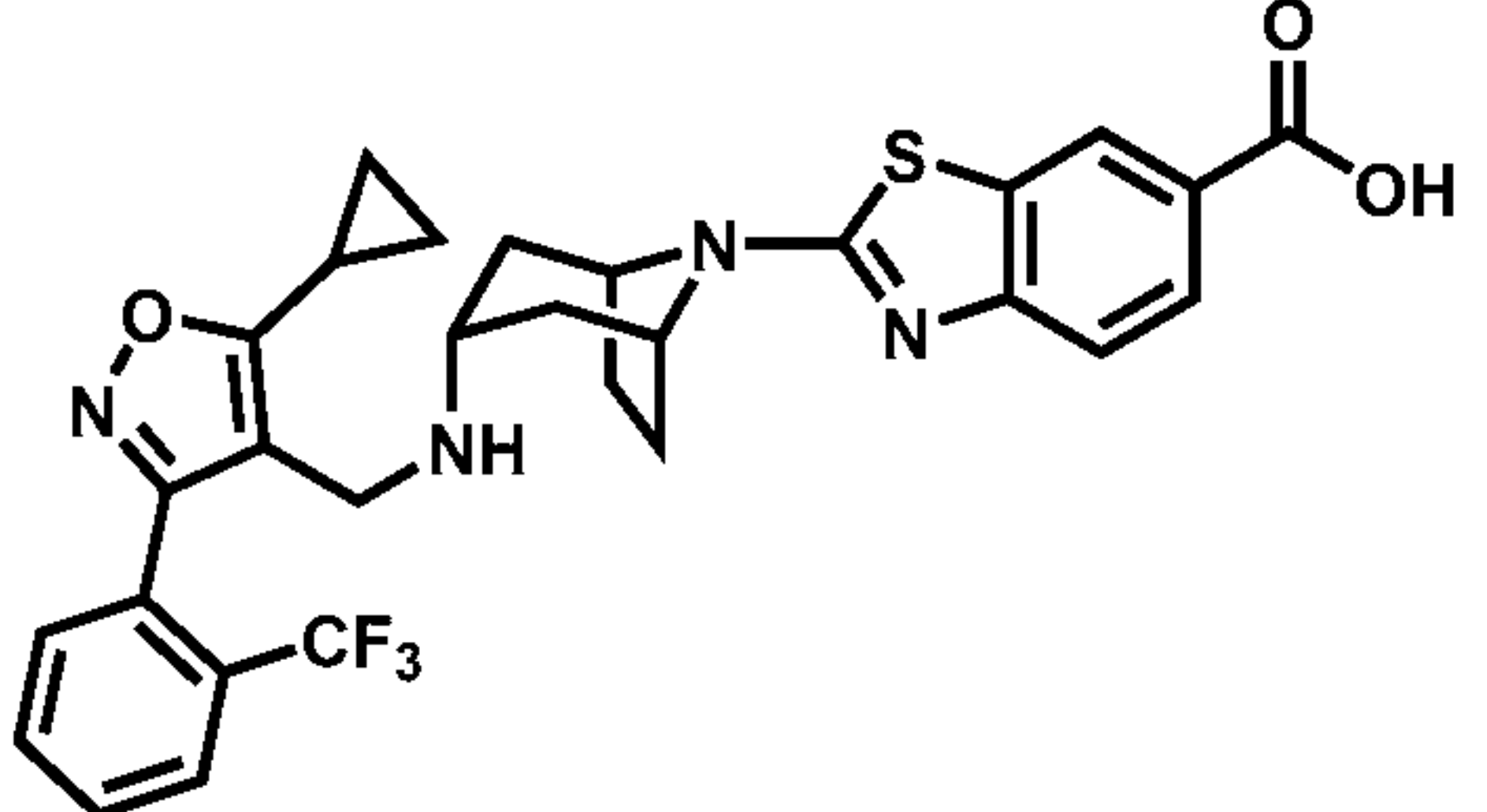
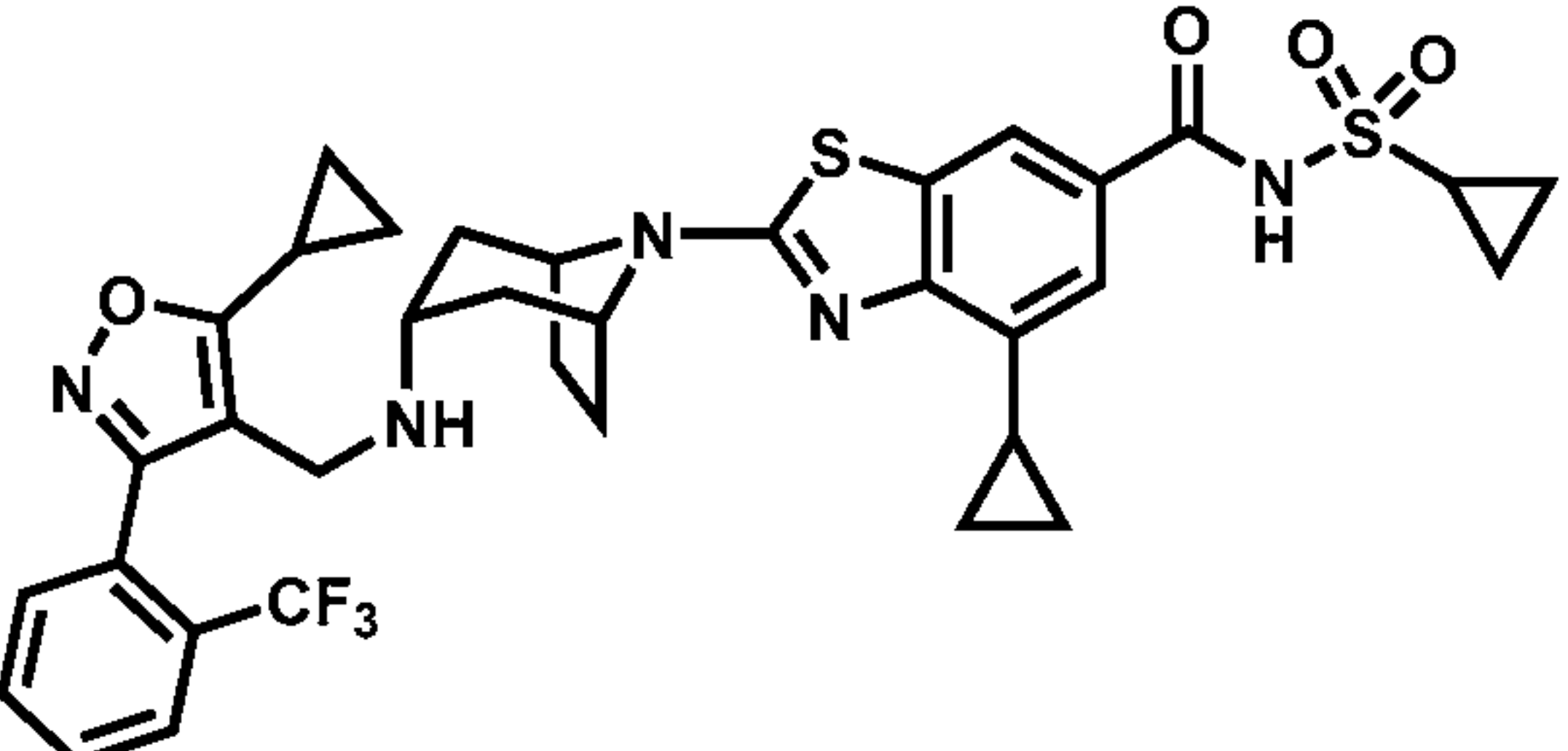
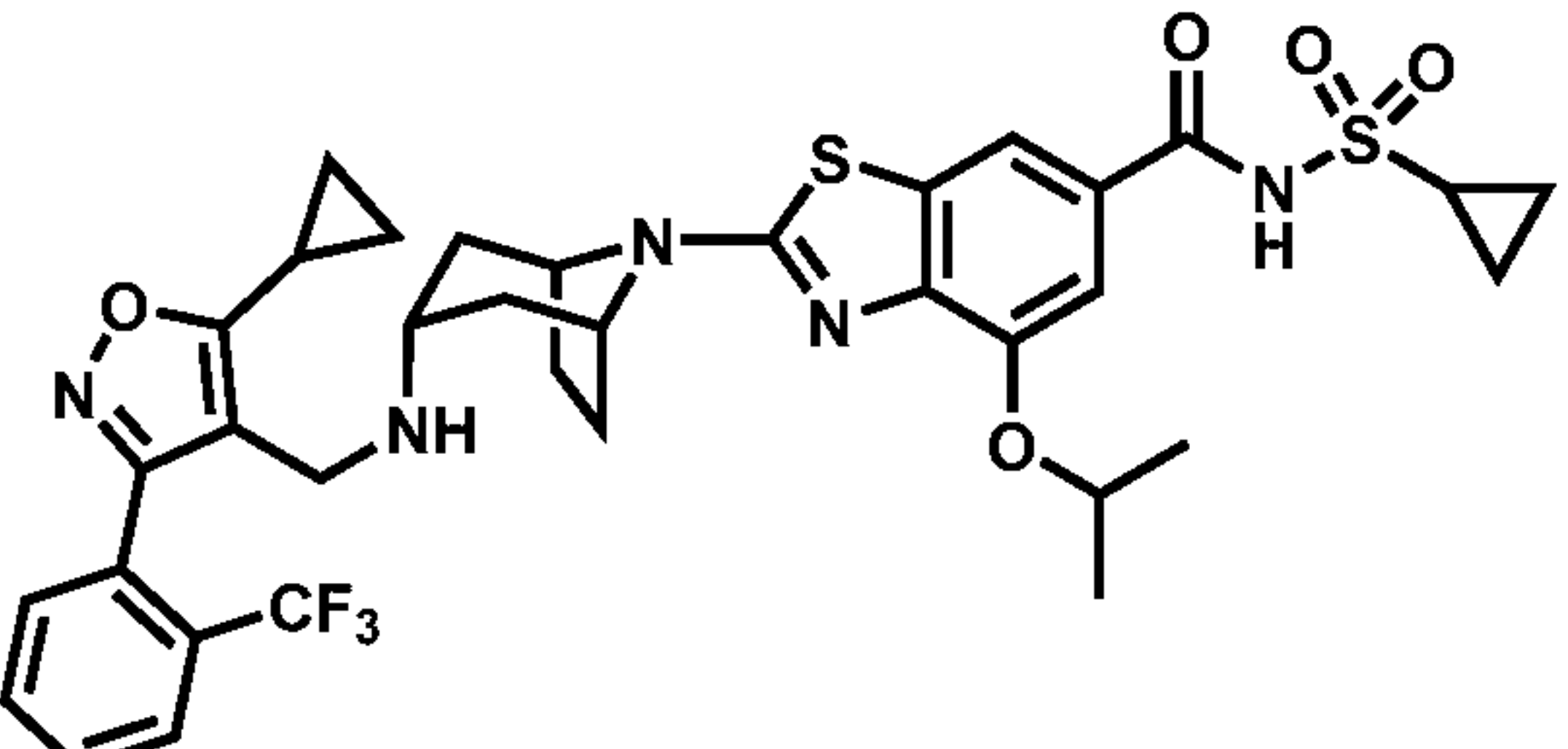
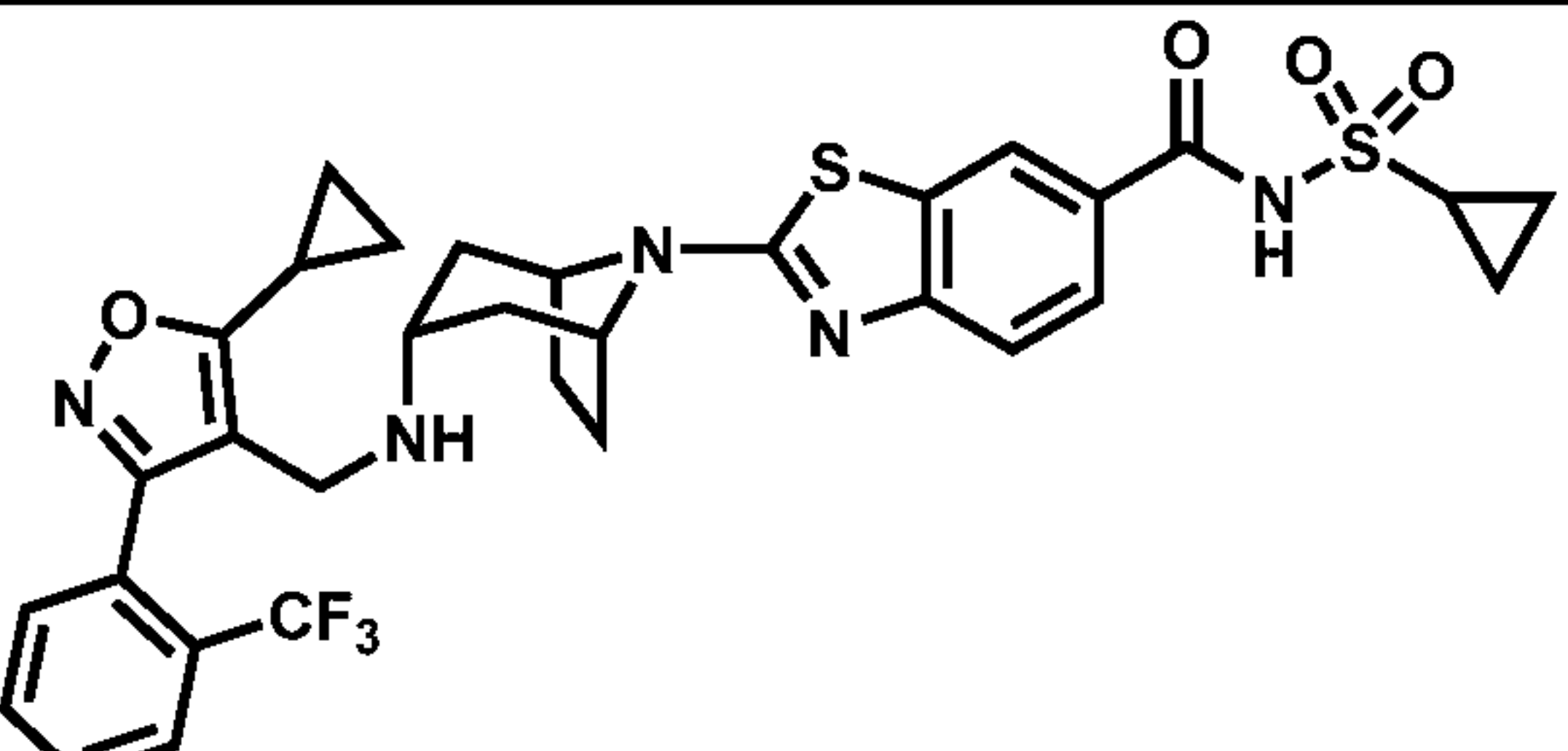
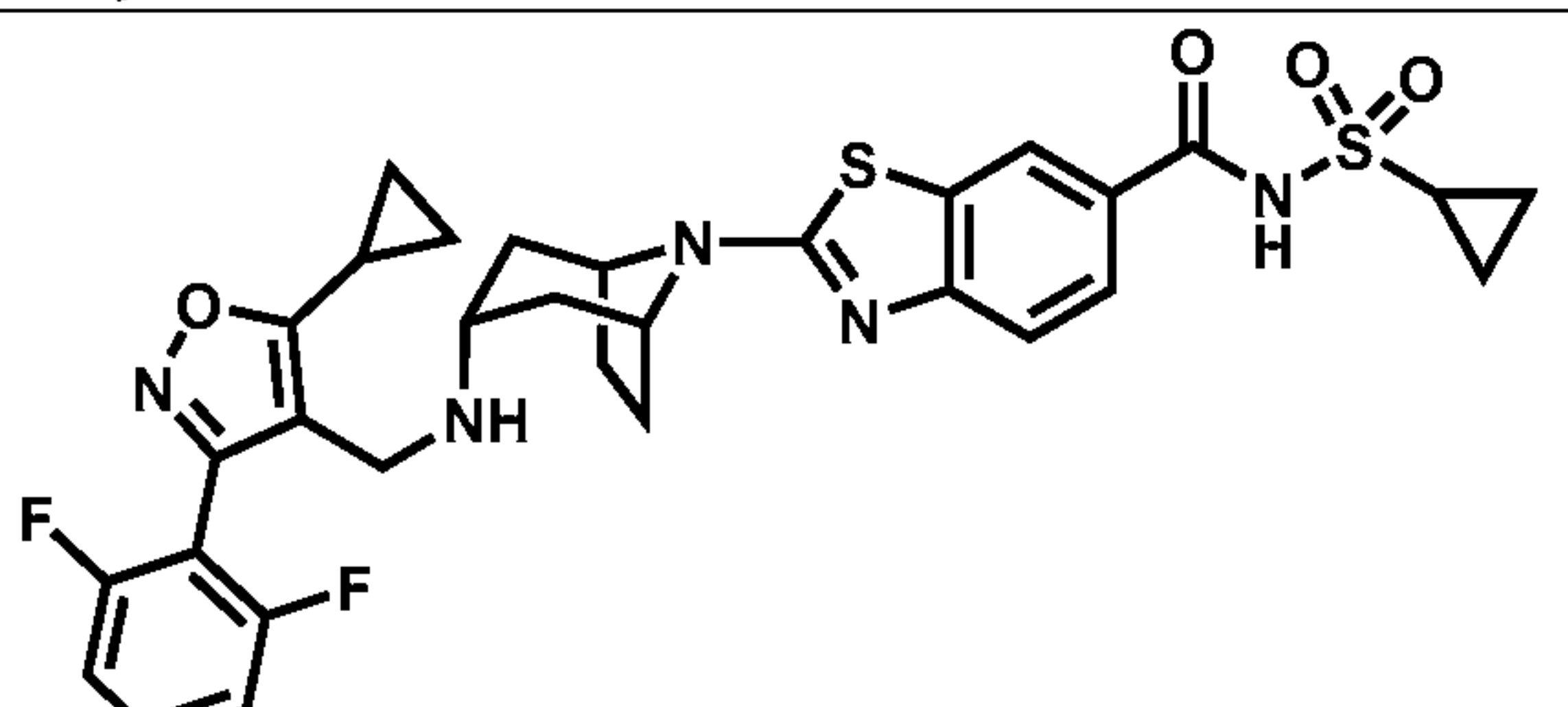
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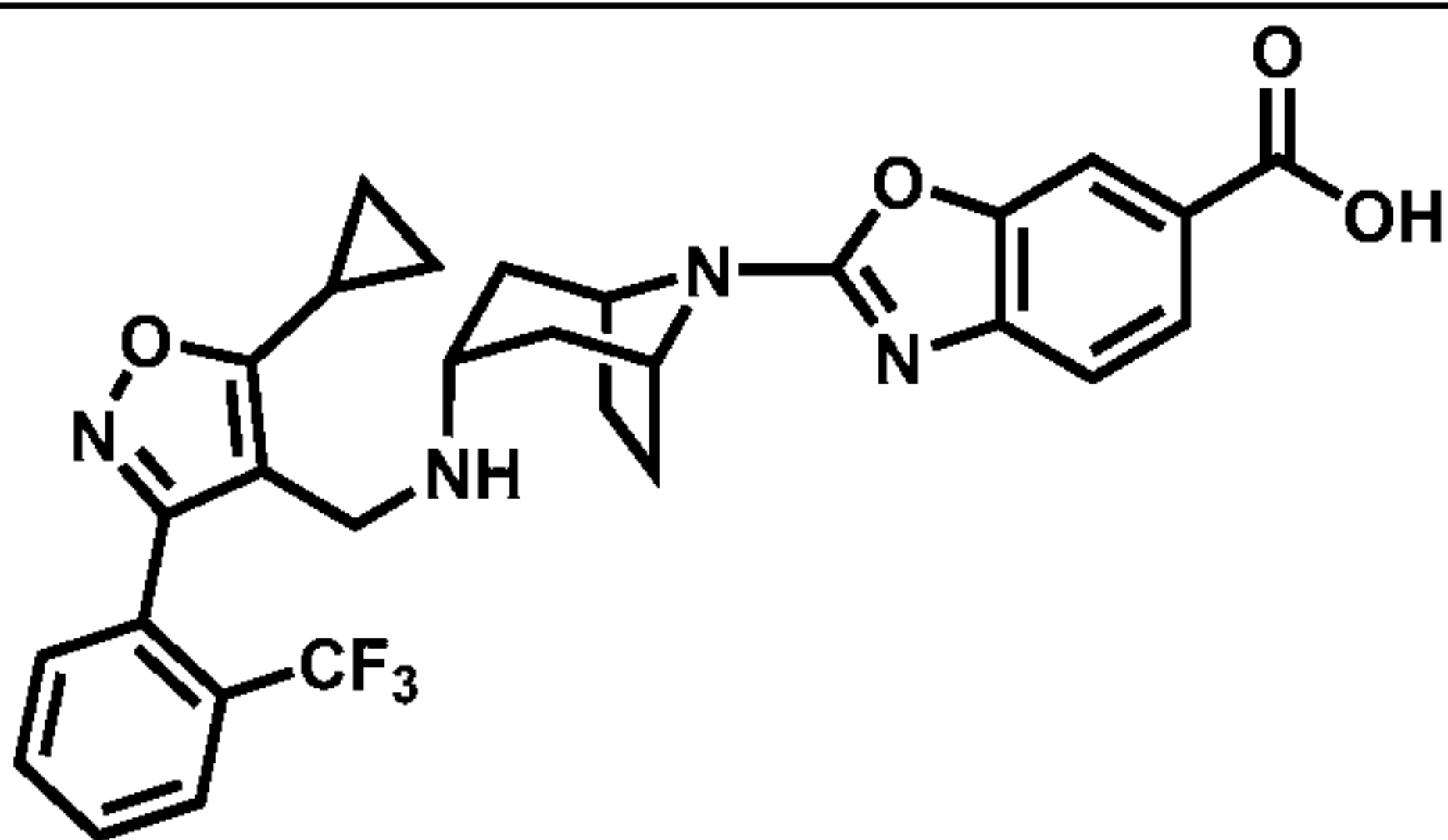
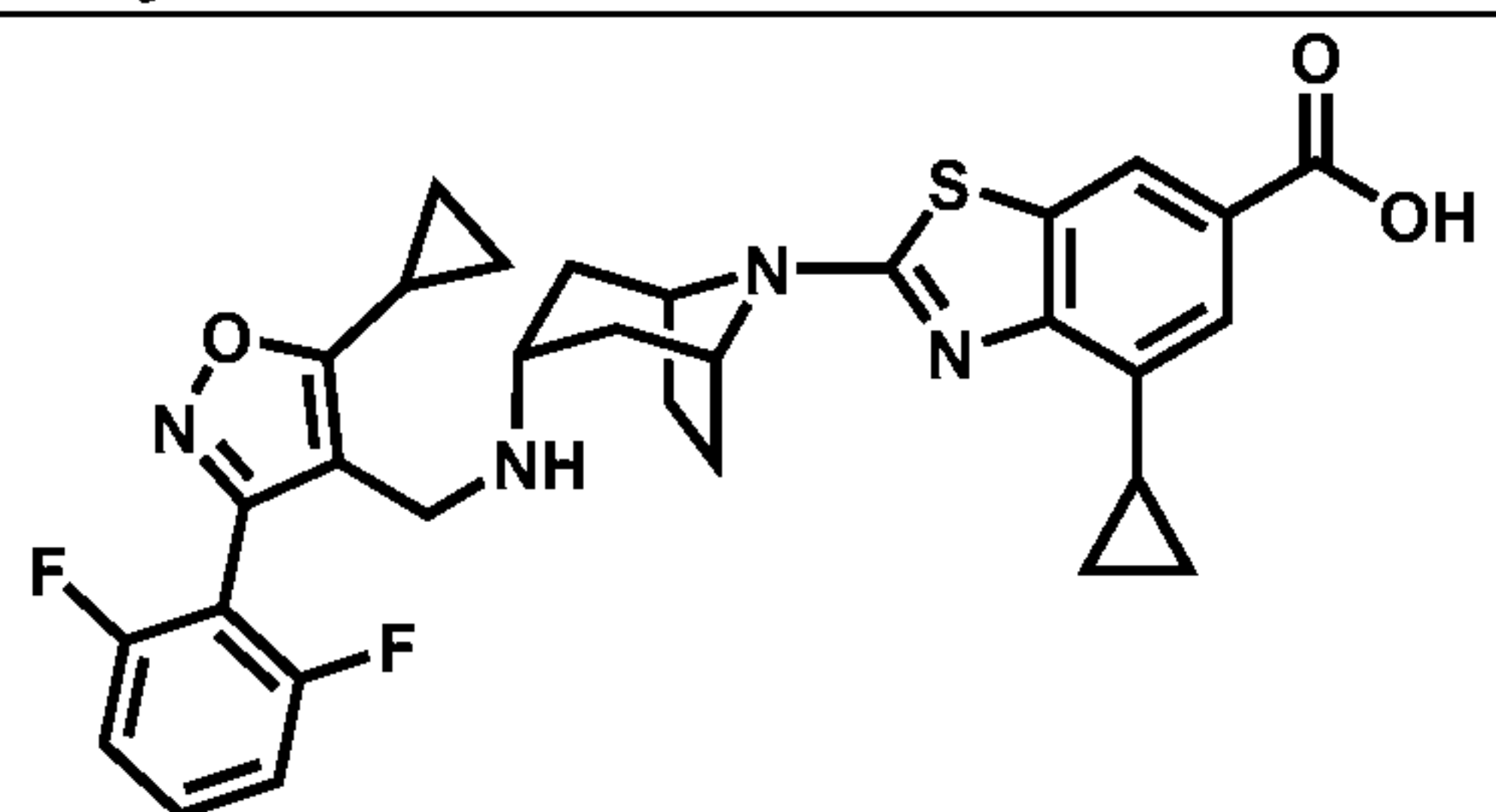
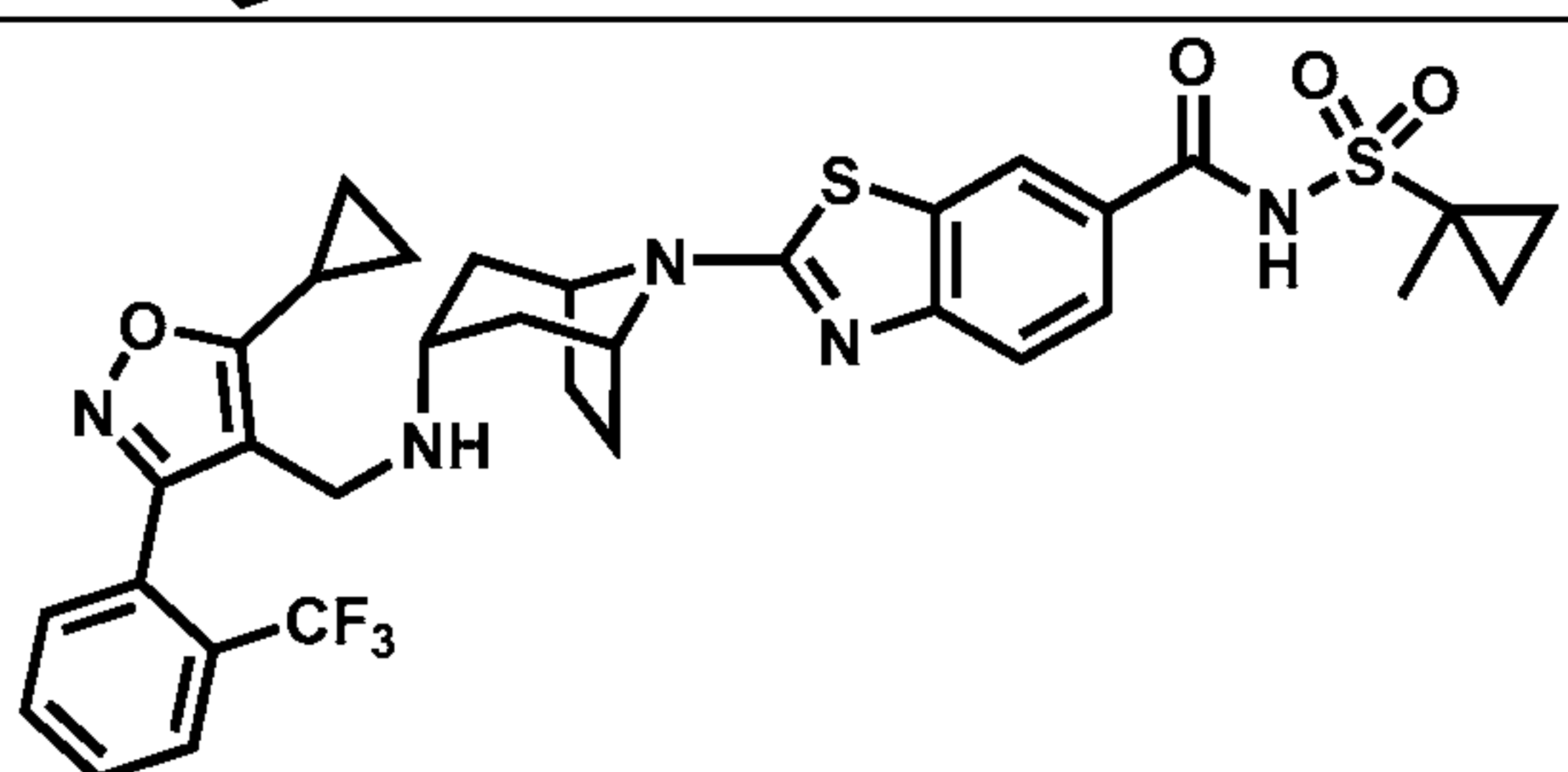
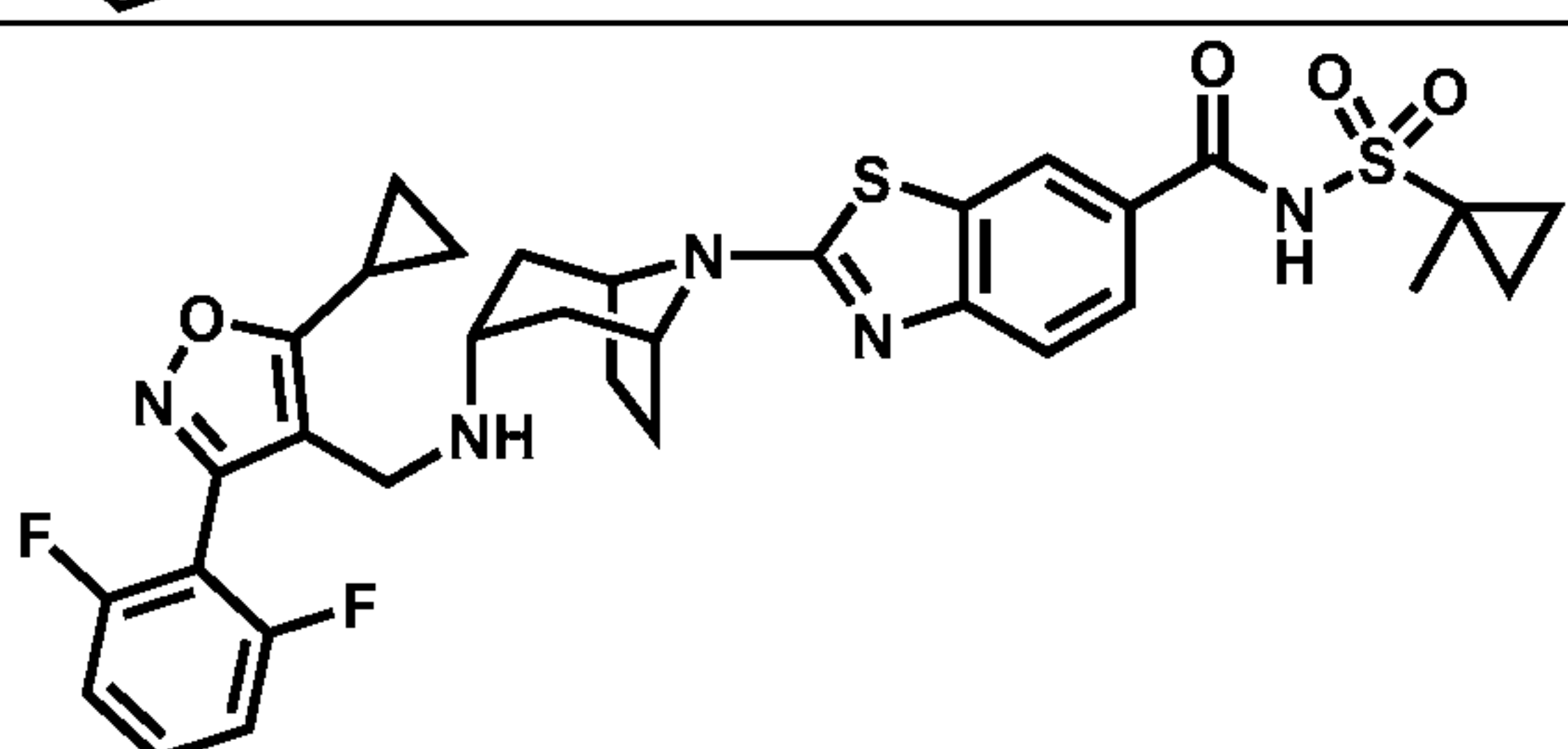
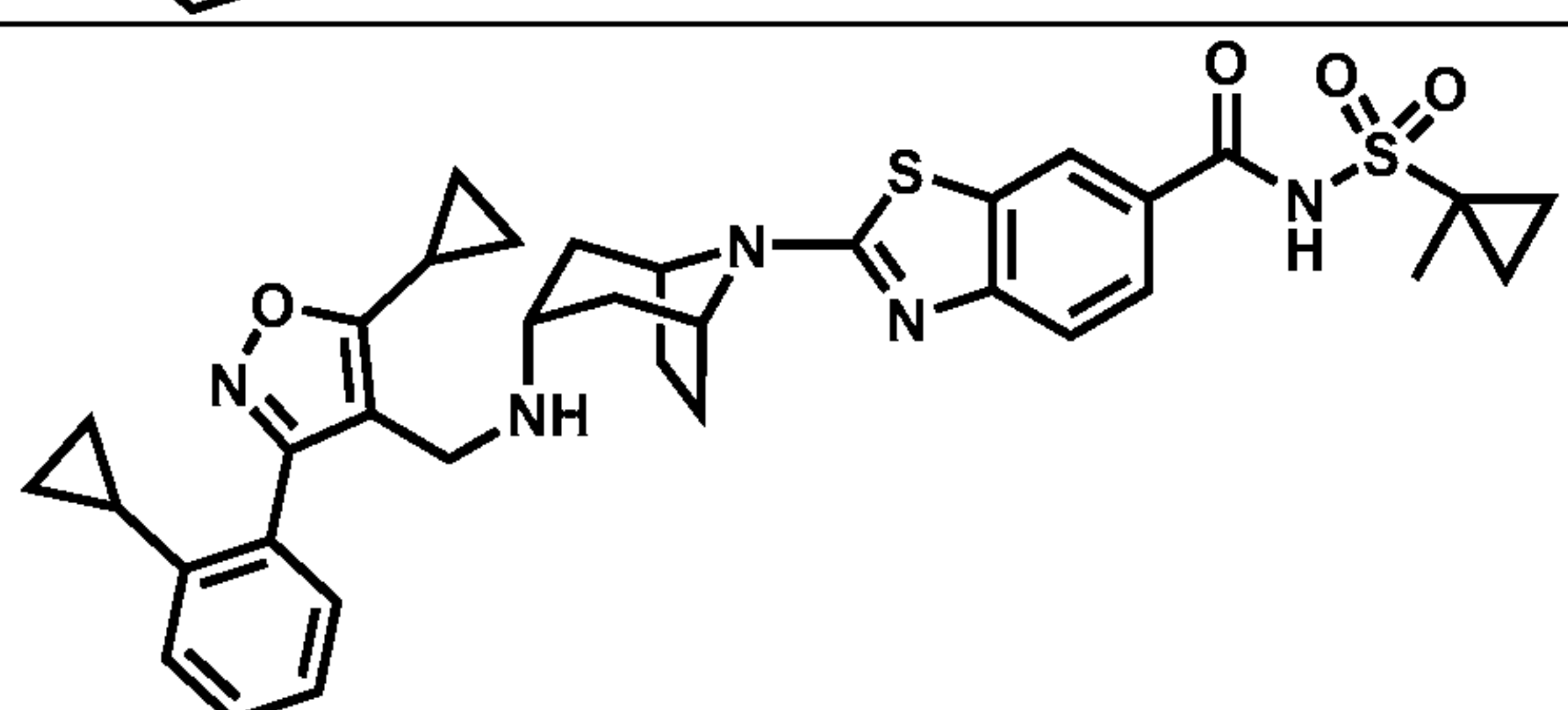
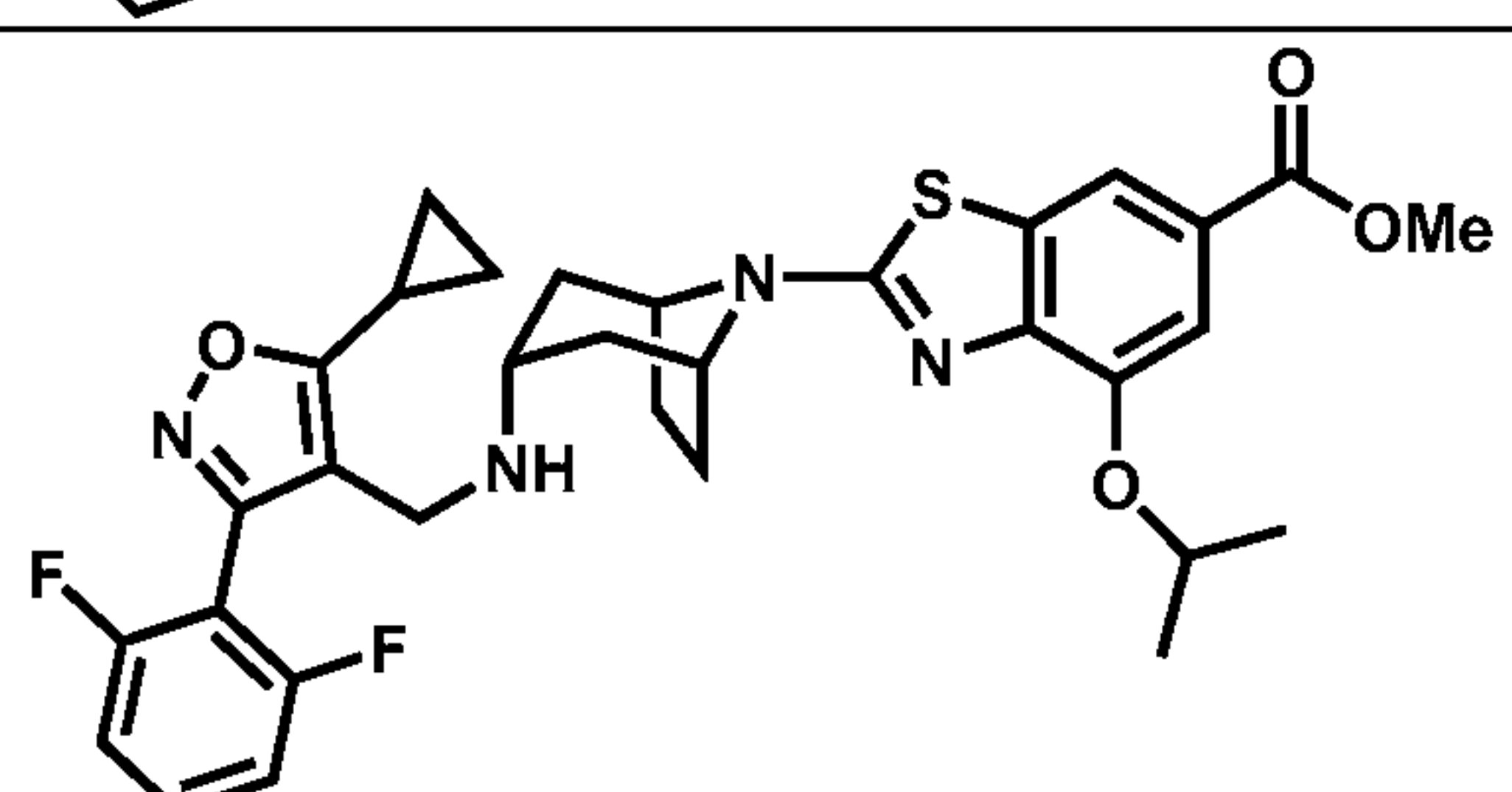
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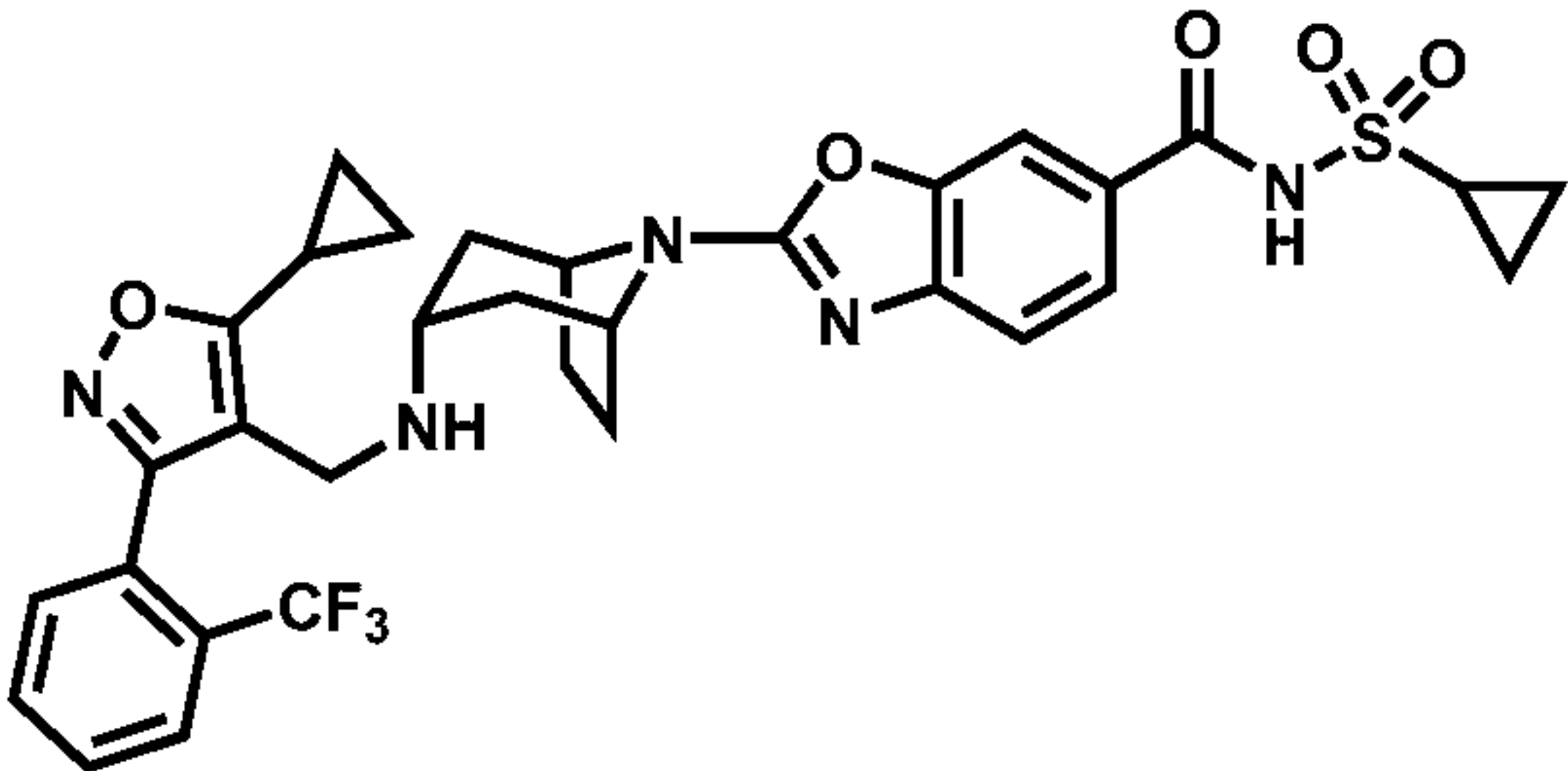
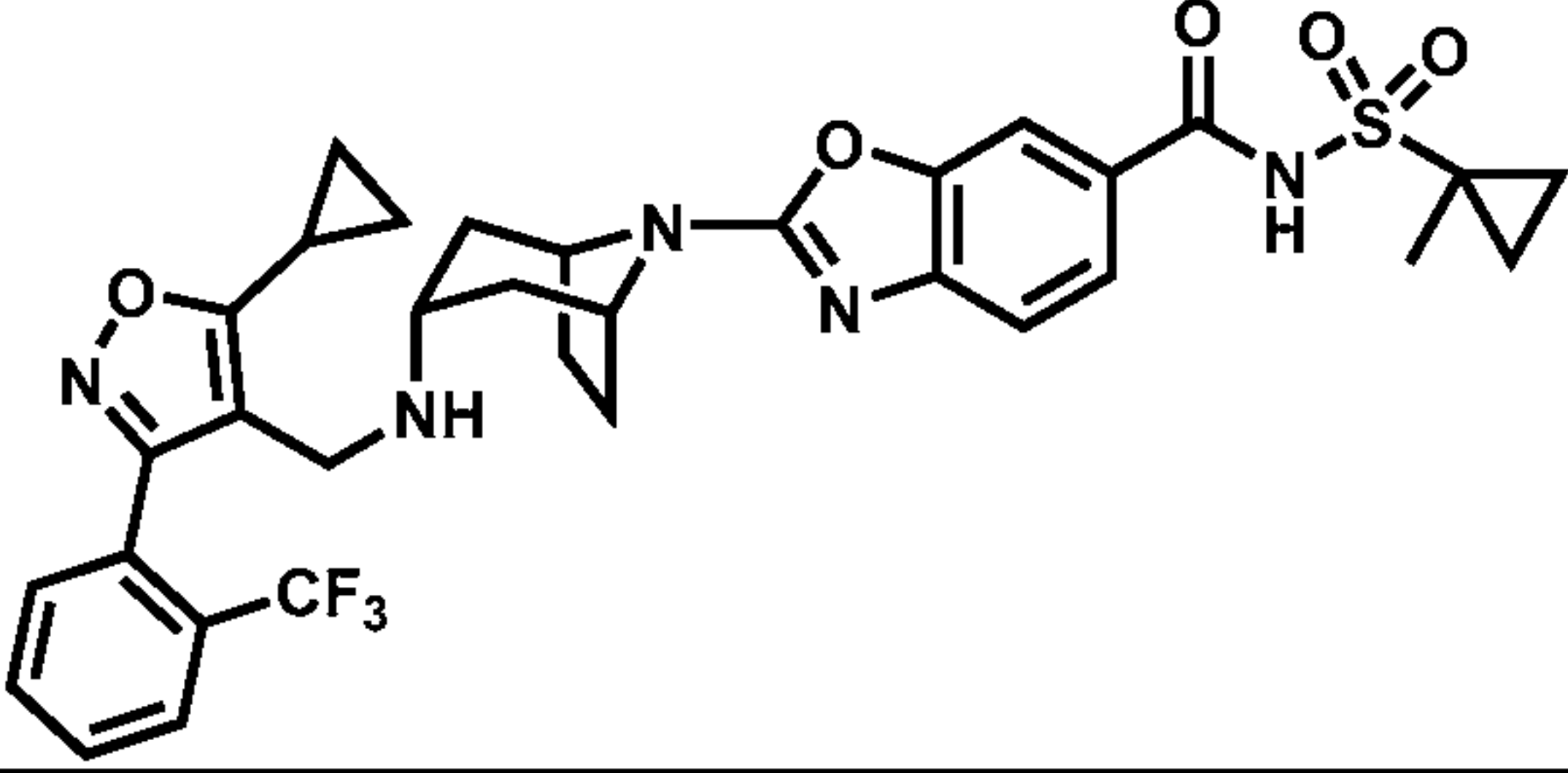
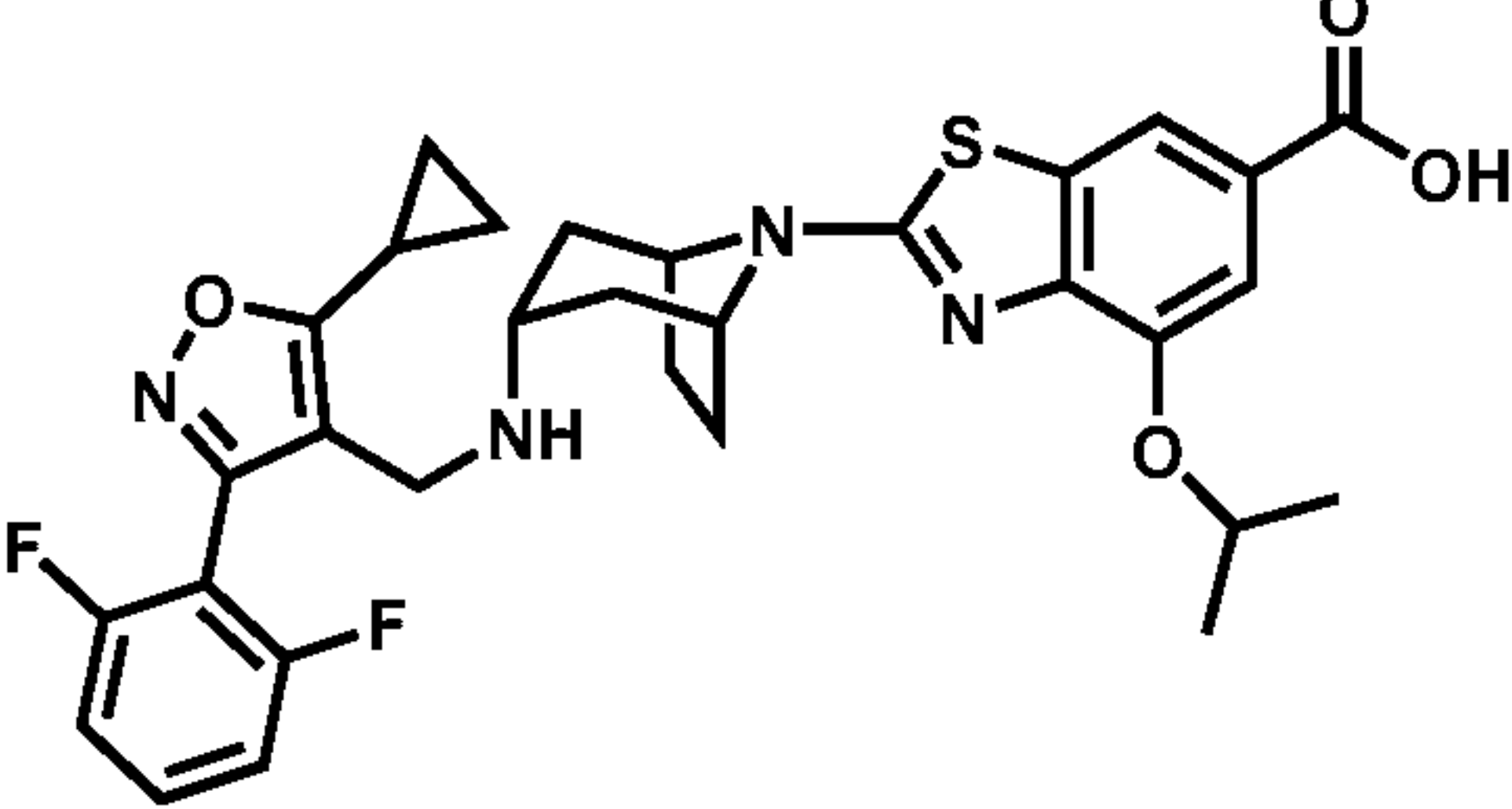
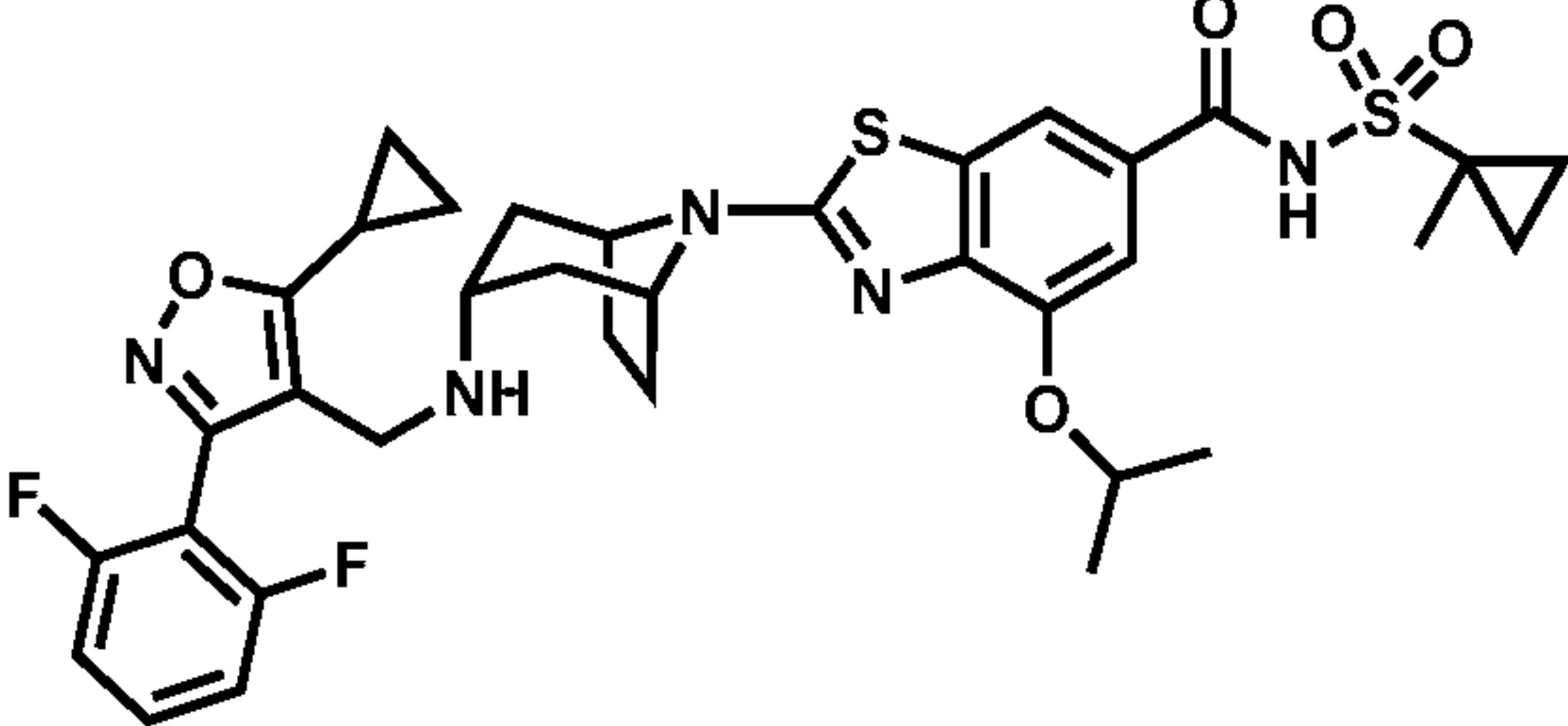
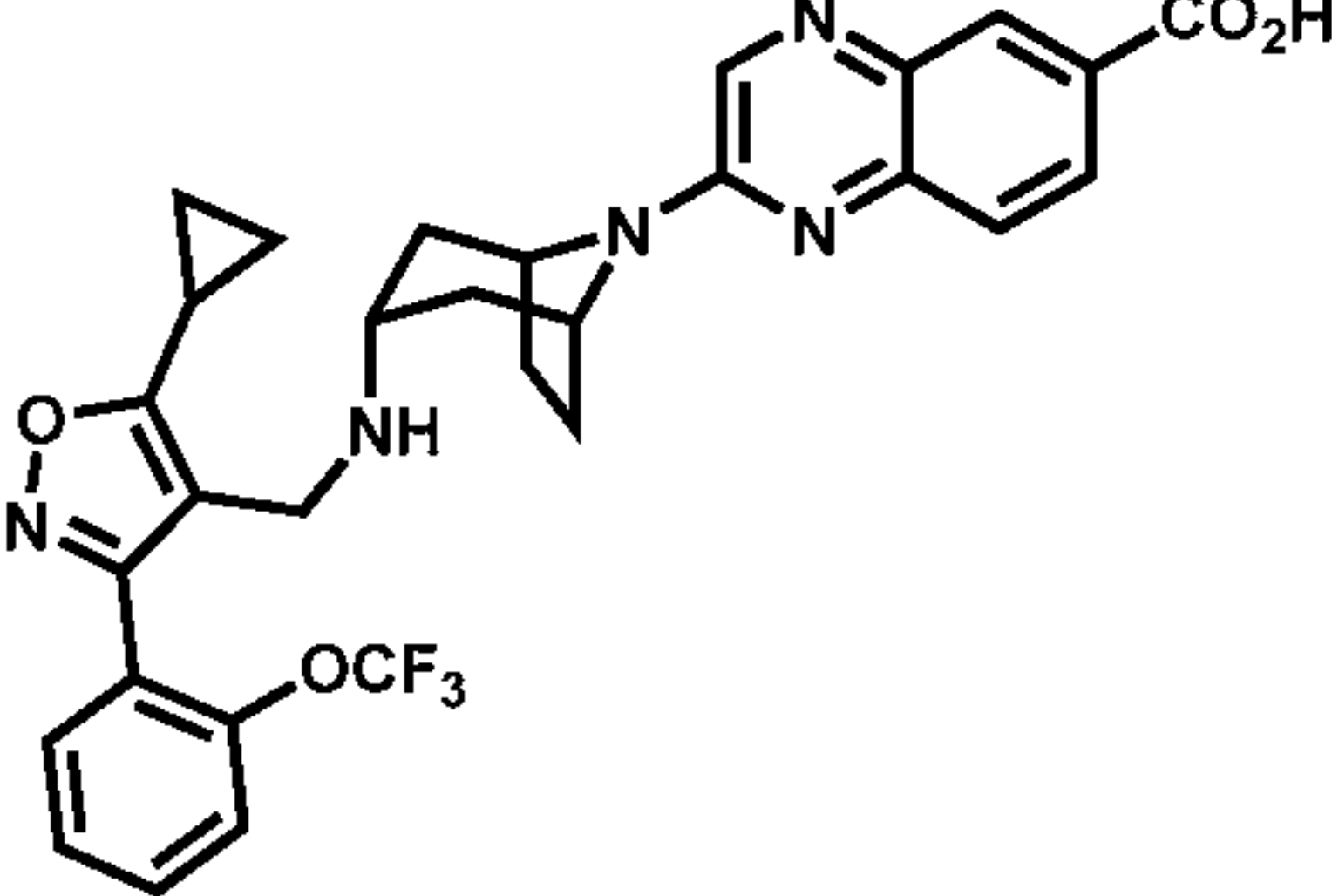
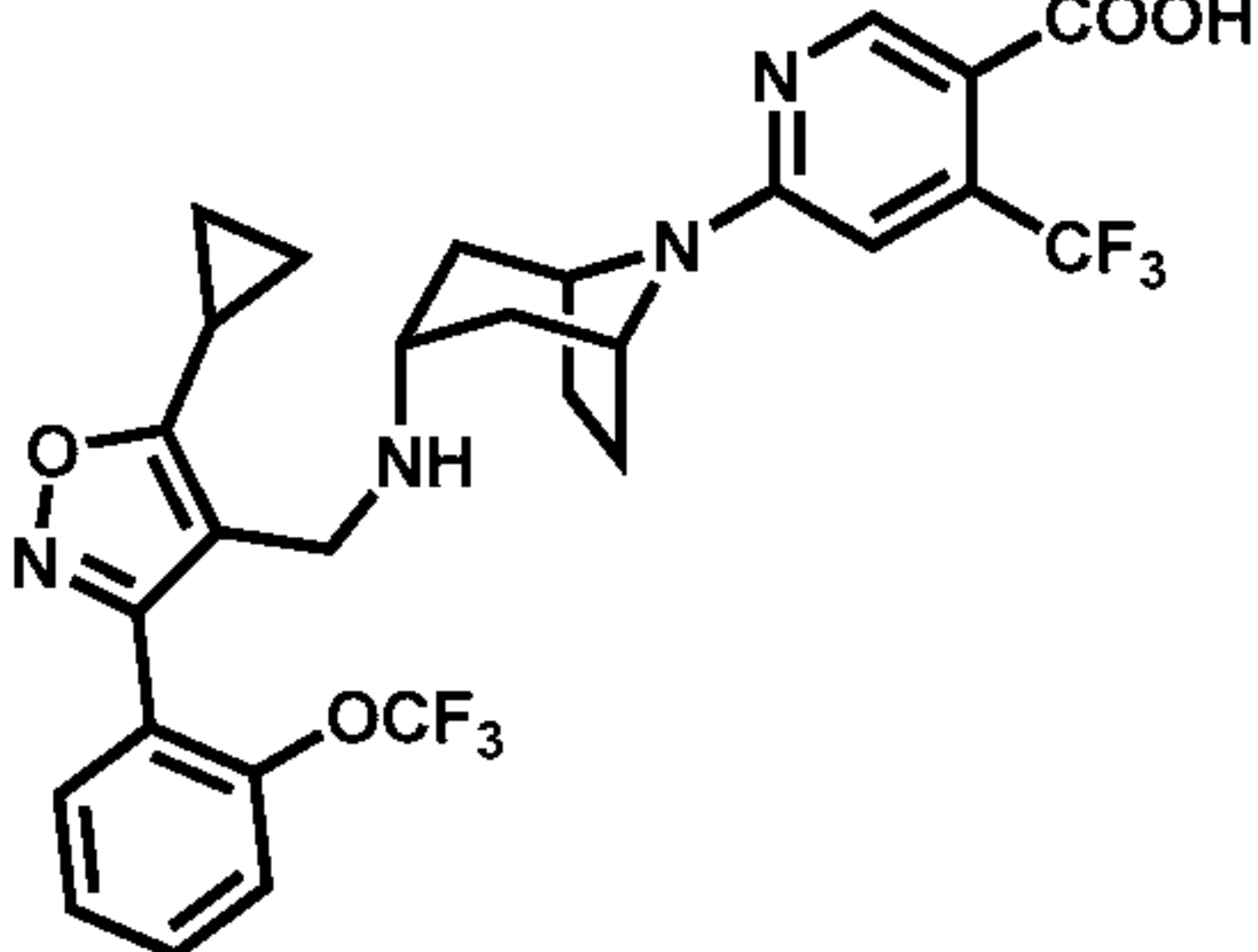
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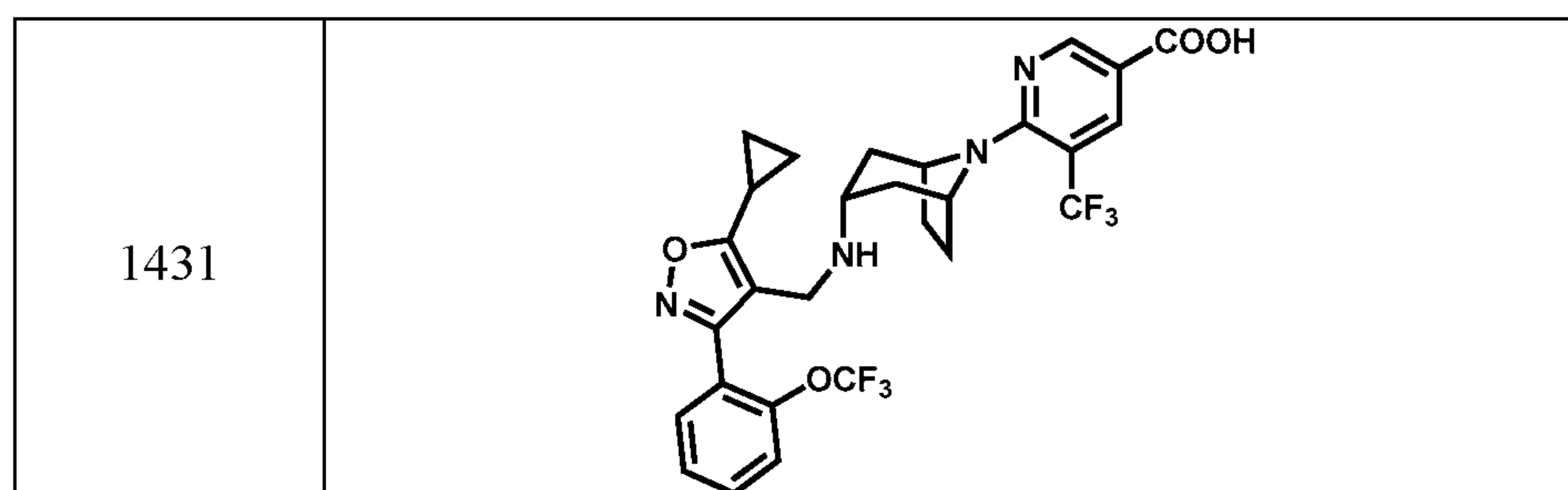
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15. A method for preventing or treating an FXR-mediated disease or condition in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-14.
16. The method according to claim 15, wherein the FXR-mediated disease or condition is selected from the group consisting of chronic liver disease, gastrointestinal disease, renal disease, cardiovascular disease, fibrotic diseases, and metabolic disease.
17. The method according to claim 16, wherein the fibrotic diseases is selected from primary biliary cirrhosis, primary sclerosing cholangitis, pulmonary fibrosis, renal fibrosis, and liver fibrosis.
18. The method according to claim 16, wherein the chronic liver disease is selected from the group consisting of primary biliary cirrhosis (PBC), cerebrotendinous xanthomatosis (CTX), primary sclerosing cholangitis (PSC), drug induced cholestasis, intrahepatic cholestasis of pregnancy, parenteral nutrition associated cholestasis (PNAC), bacterial overgrowth or sepsis associated cholestasis, autoimmune hepatitis, chronic viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), liver transplant associated graft versus host disease, living donor transplant liver regeneration, congenital hepatic fibrosis, choledocholithiasis, granulomatous liver disease, intra- or extrahepatic malignancy, Sjogren's syndrome, Sarcoidosis, Wilson's disease, Gaucher's disease, hemochromatosis, and alpha 1-antitrypsin deficiency.
19. The method according to claim 16, wherein the renal disease is selected from the group consisting of diabetic nephropathy, focal segmental glomerulosclerosis (FSGS),

hypertensive nephrosclerosis, chronic glomerulonephritis, chronic transplant glomerulopathy, chronic interstitial nephritis, and polycystic kidney disease.

20. The method according to claim 16, wherein the cardiovascular disease is selected
5 from the group consisting of atherosclerosis, arteriosclerosis, dyslipidemia, hypercholesterolemia, and hypertriglyceridemia.

21. A method according to claim 16, wherein the metabolic disease is selected from the
10 group consisting of insulin resistance, Type I and Type II diabetes, and obesity.

22. A pharmaceutical composition comprising a compound according to any one of
claims 1-14 and a pharmaceutically acceptable carrier.

23. Use of a compound of any one of claims 1-14 for the preparation of a medicament for
15 preventing or treating a FXR-mediated disease or condition.

