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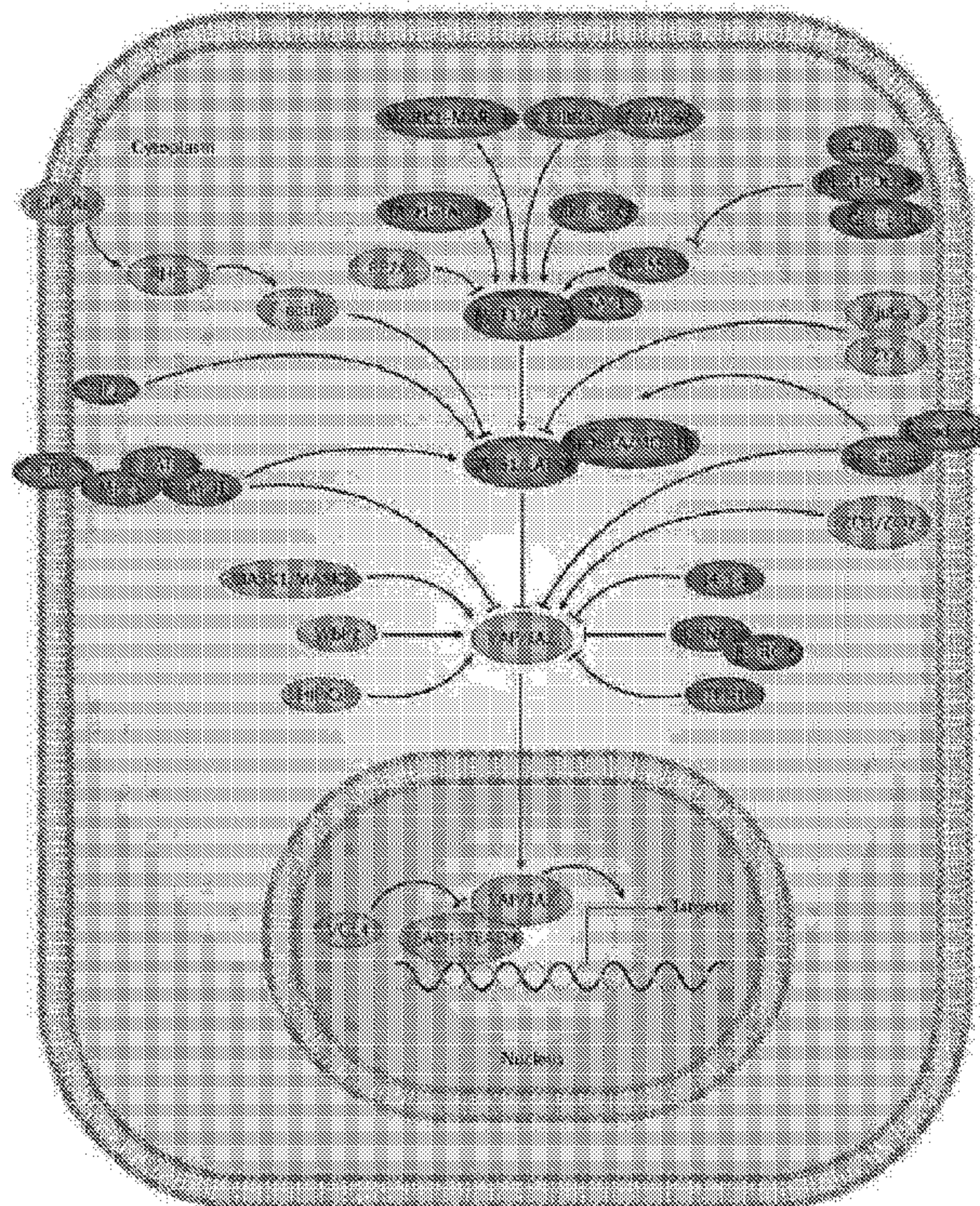
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(72) Inventeurs/Inventors:

(54) Titre : COMPOSES TRICYCLIQUES NON FUSIONNES
(54) Title: NON-FUSED TRICYCLIC COMPOUNDS

FIG.1



(57) **Abrégé/Abstract:**

Provided herein are compounds and pharmaceutical compositions comprising said compounds that are useful for treating cancers. Specific cancers include those that are mediated by YAP/TAZ or those that are modulated by the interaction between YAP/TAZ and TEAD.

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KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME,

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EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,

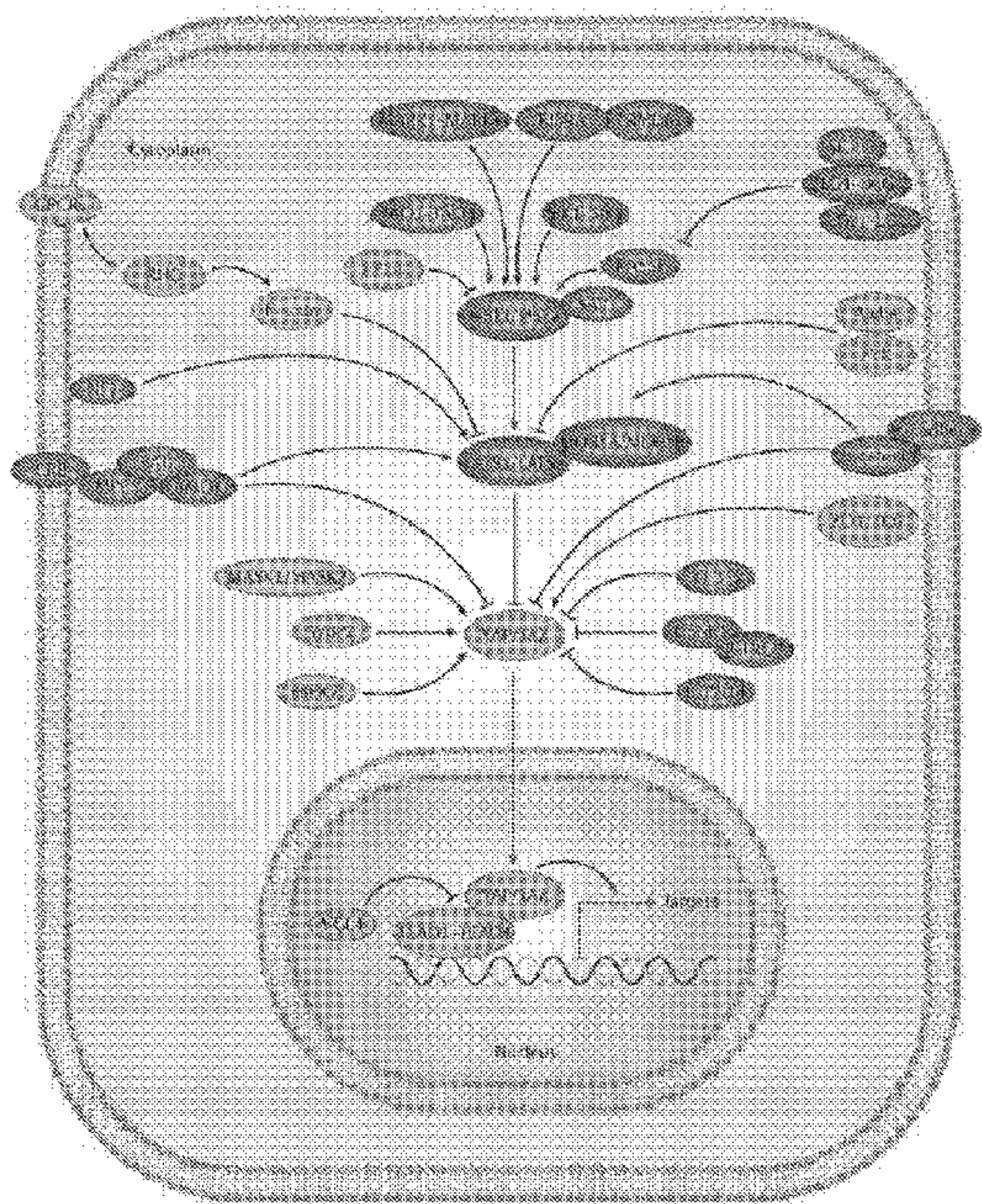
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,

KM, ML, MR, NE, SN, TD, TG).

(54) Title: NON-FUSED TRICYCLIC COMPOUNDS

FIG.1



(57) Abstract: Provided herein are compounds and pharmaceutical compositions comprising said compounds that are useful for treating cancers. Specific cancers include those that are mediated by YAP/TAZ or those that are modulated by the interaction between YAP/TAZ and TEAD.

WO 2018/204532 A1

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- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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- *with international search report (Art. 21(3))*
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DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 317

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 317

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

NON-FUSED TRICYCLIC COMPOUNDS

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Patent Application No. 62/500,937 filed on May 3, 2017, which is incorporated herein by reference in its entirety.

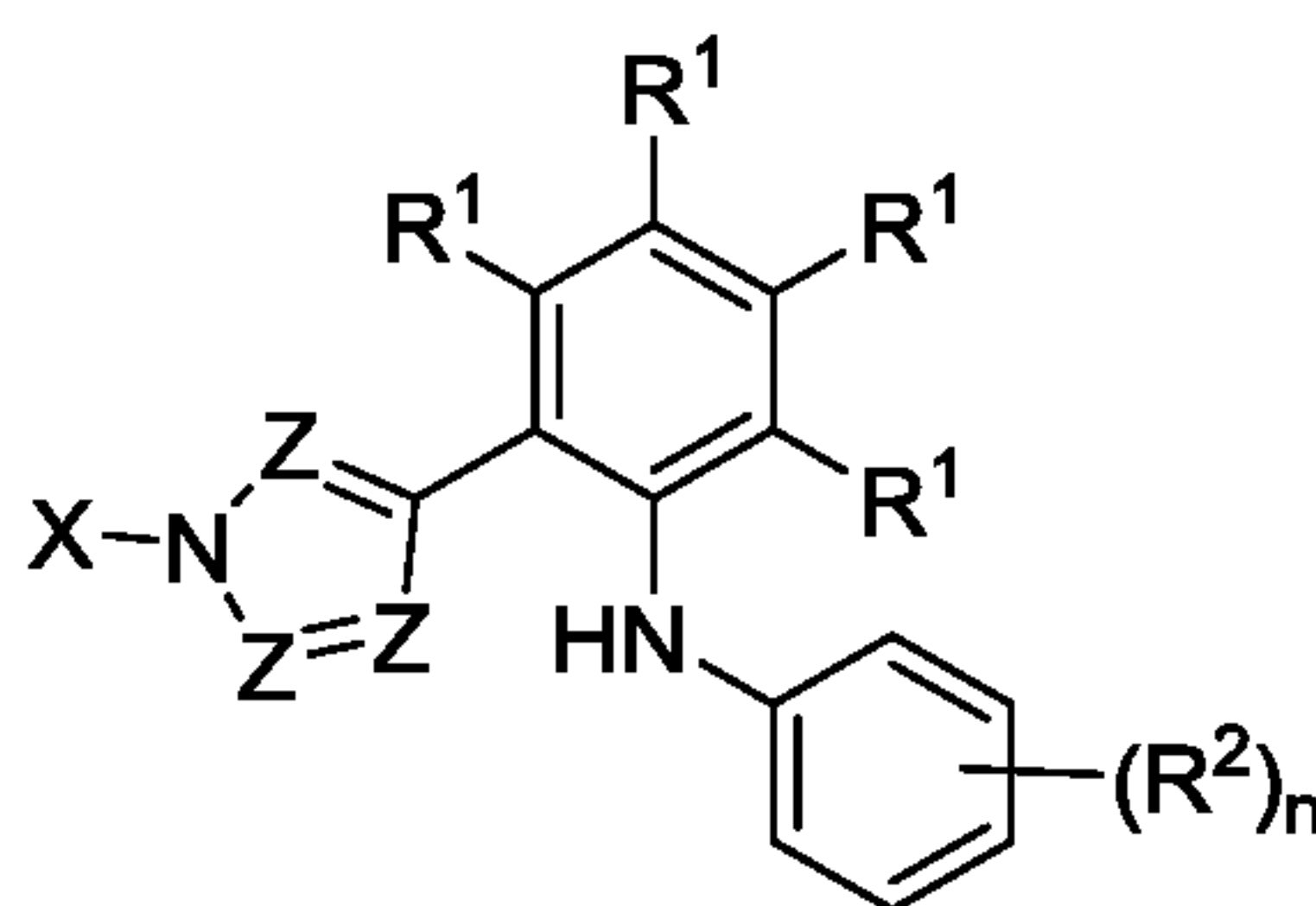
BACKGROUND OF THE DISCLOSURE

[0002] YAP and TAZ are transcriptional co-activators of the Hippo pathway network and regulate cell proliferation, migration, and apoptosis. Inhibition of the Hippo pathway promotes YAP/TAZ translocation to the nucleus, wherein YAP/TAZ interact with transcriptional enhancer associate domain (TEAD) transcription factors and coactivate the expression of target genes and promote cell proliferation. Hyperactivation of YAP and TAZ and/or mutations in one or more members of the Hippo pathway network have been implicated in numerous cancers. Described herein are inhibitors associated with one or more members of the Hippo pathway network, such as inhibitors of YAP/TAZ or inhibitors that modulate the interaction between YAP/TAZ and TEAD.

SUMMARY OF THE DISCLOSURE

[0003] Provided herein are substituted tetrazole compounds and pharmaceutical compositions comprising said compounds. In some embodiments, the subject compounds are useful for the treatment of cancer.

[0004] Provided in one aspect is a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein:

each Z is independently N or CR^Z;

each R^Z is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

X is substituted or unsubstituted C₂-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, unsubstituted aryl, substituted or unsubstituted heteroaryl, -L¹-Y¹, or -L²-L³-Y²;

L¹ is substituted or unsubstituted C₁-C₆alkylene;

Y¹ is substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L² is absent or substituted or unsubstituted C₁-C₆alkylene;

L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -O-NR³(C=O)-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)-, -(SO₂)NR³-(C=O)O-, -O(C=O)-NR³(SO₂)-, -NR³(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)NR³-, -O(C=O)-NR³(SO₂)-NR³-, or -NR³(SO₂)NR³-(C=O)O-;

each R³ is independently H or substituted or unsubstituted C₁-C₆alkyl;

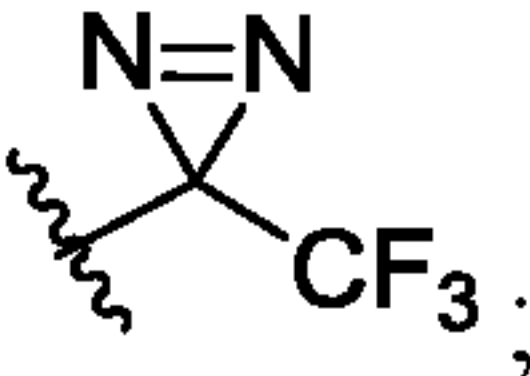
Y² is H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or R³ and Y² on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

each R¹ is independently H, halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

n is 1, 2, 3, 4 or 5;

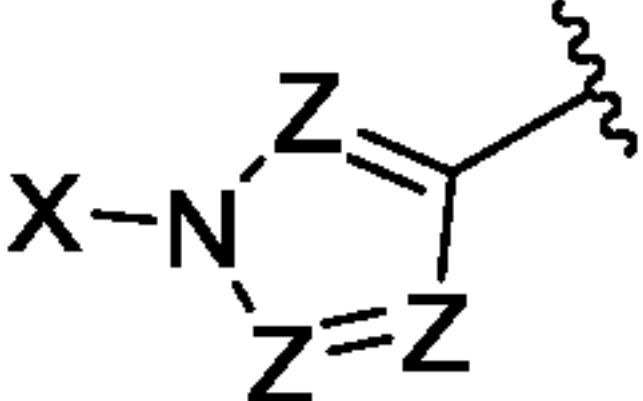
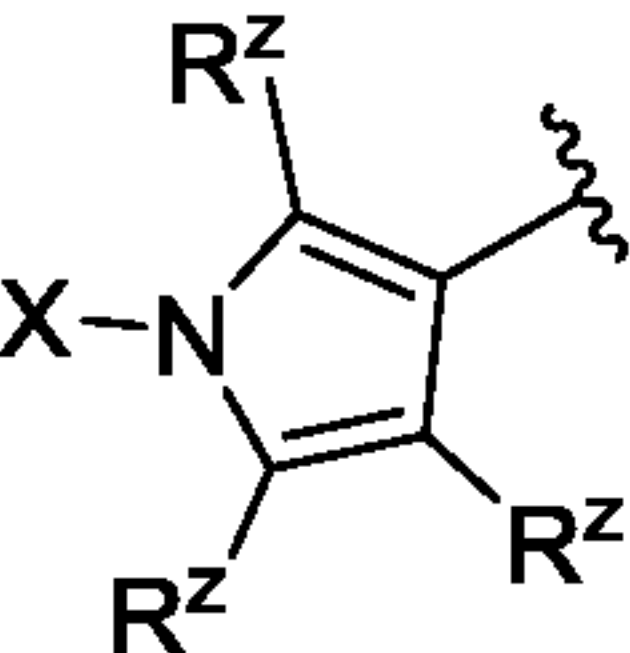
each R² is independently halogen, -N₃, -CN, -OR⁵, -SR⁵, -(SO₂)R⁵, -N(R⁵)₂, -CO₂R⁵, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or

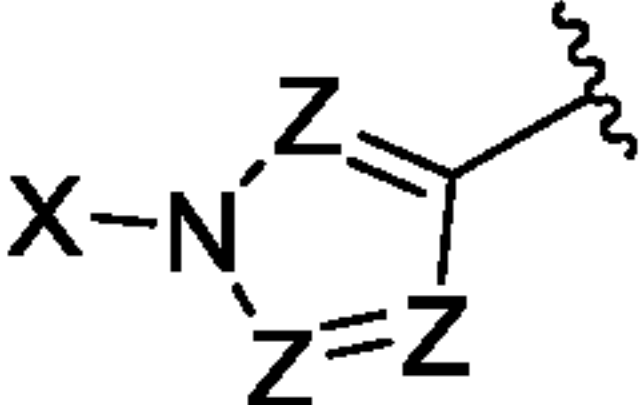
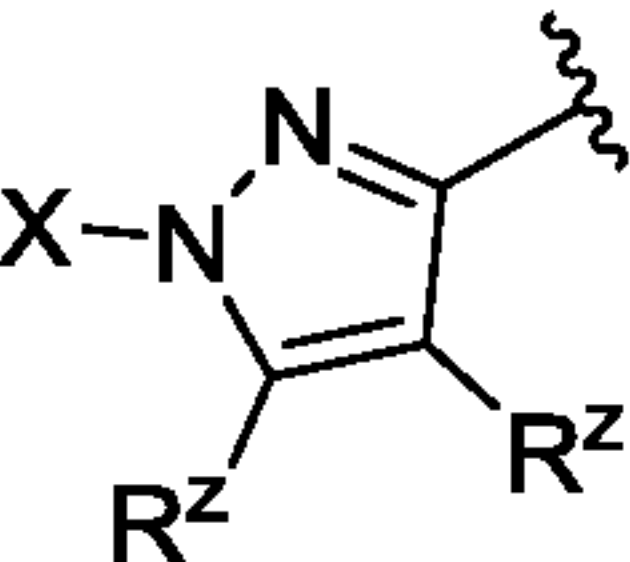
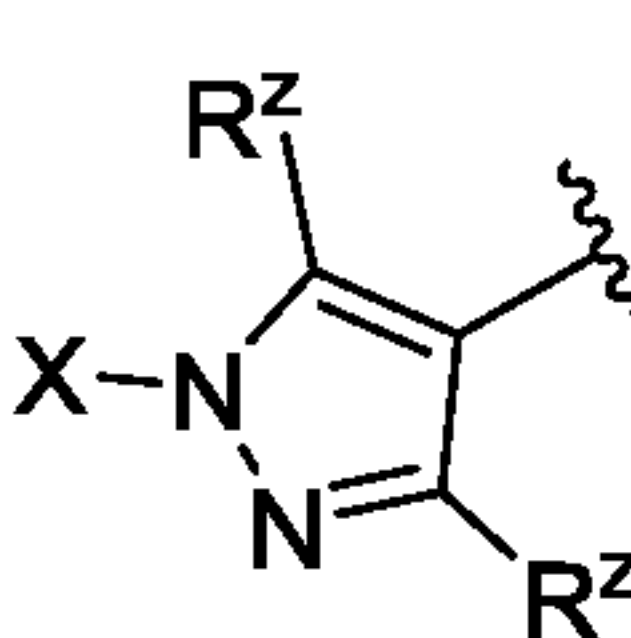
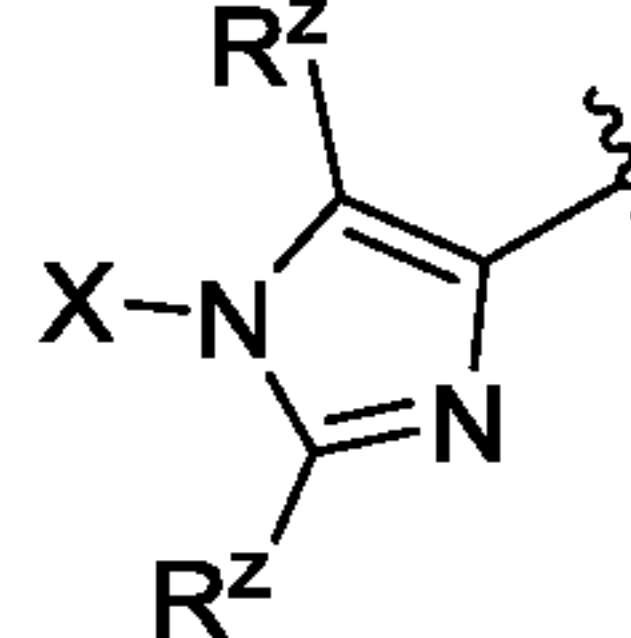
unsubstituted aryl, substituted or unsubstituted heteroaryl, or ;

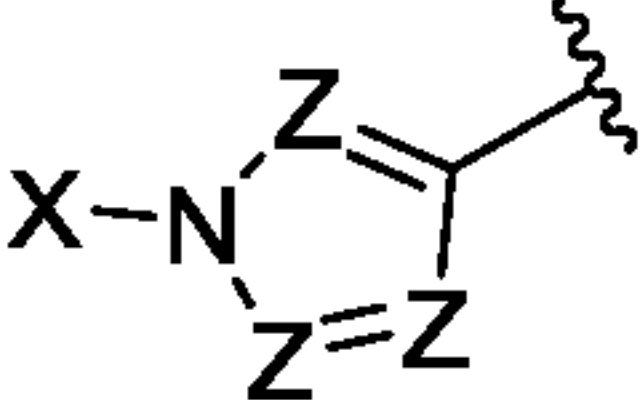
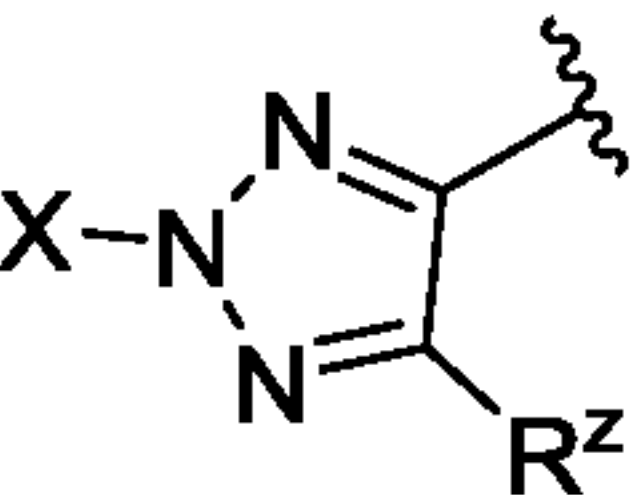
each R⁴ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted

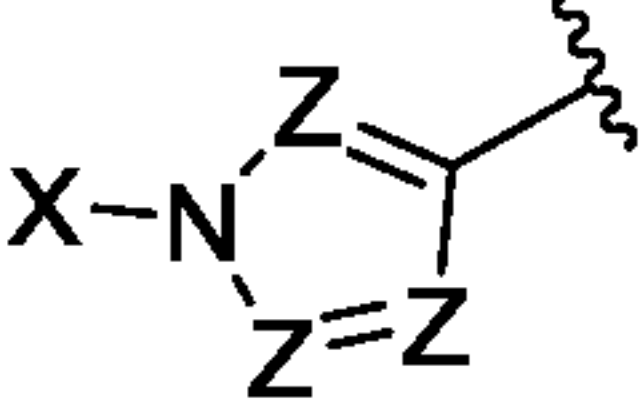
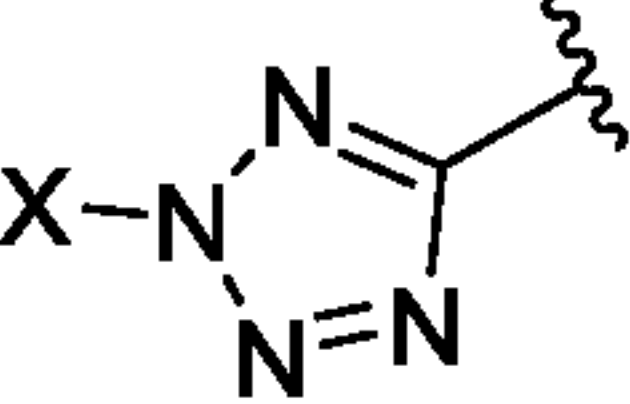
C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

each R⁵ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0005] In some embodiments,  is .

[0006] In some embodiments,  is , , or .

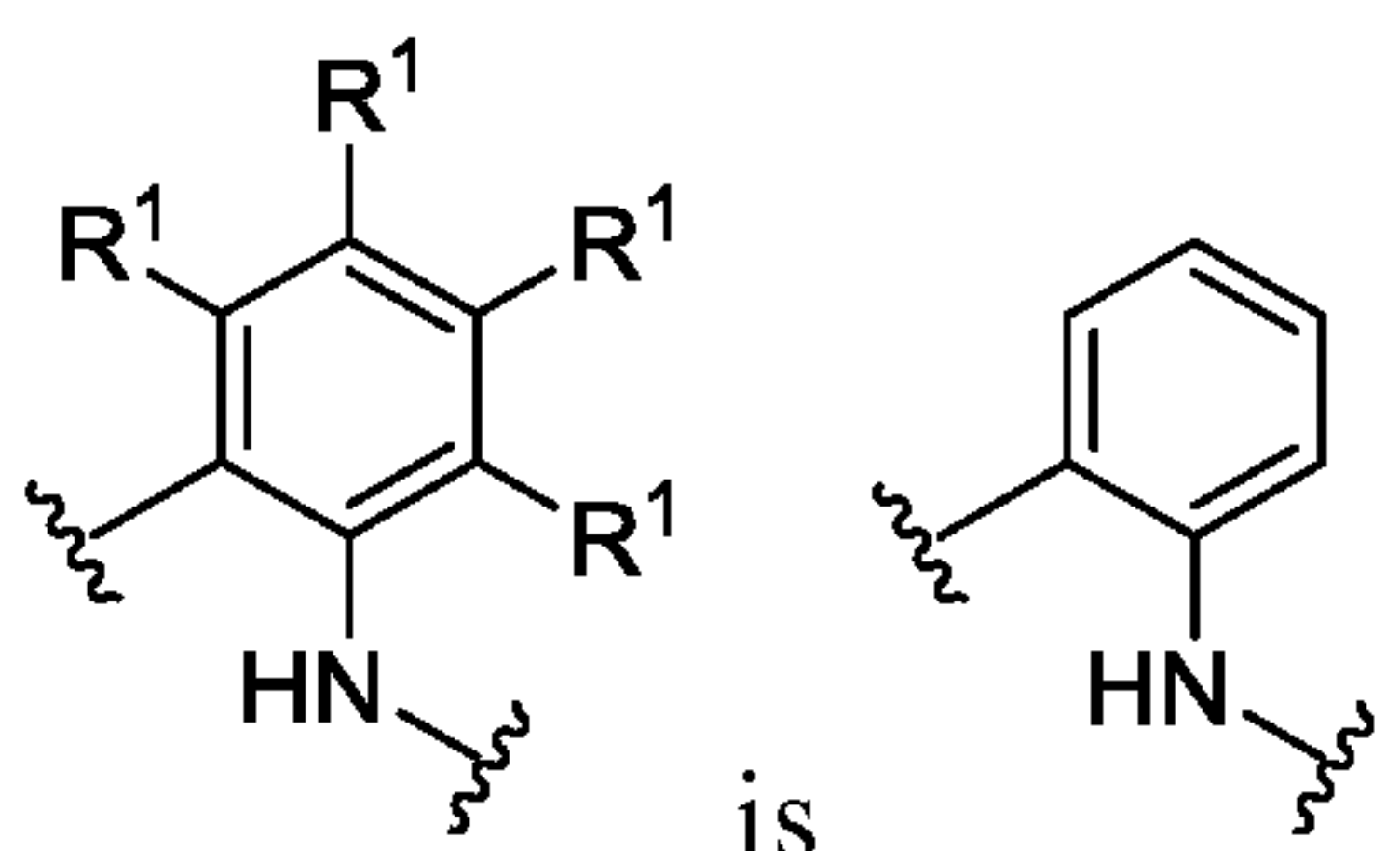
[0007] In some embodiments,  is  or .

[0008] In some embodiments,  is .

[0009] In some embodiments, each R^z is independently H or substituted or unsubstituted C₁-C₆alkyl.

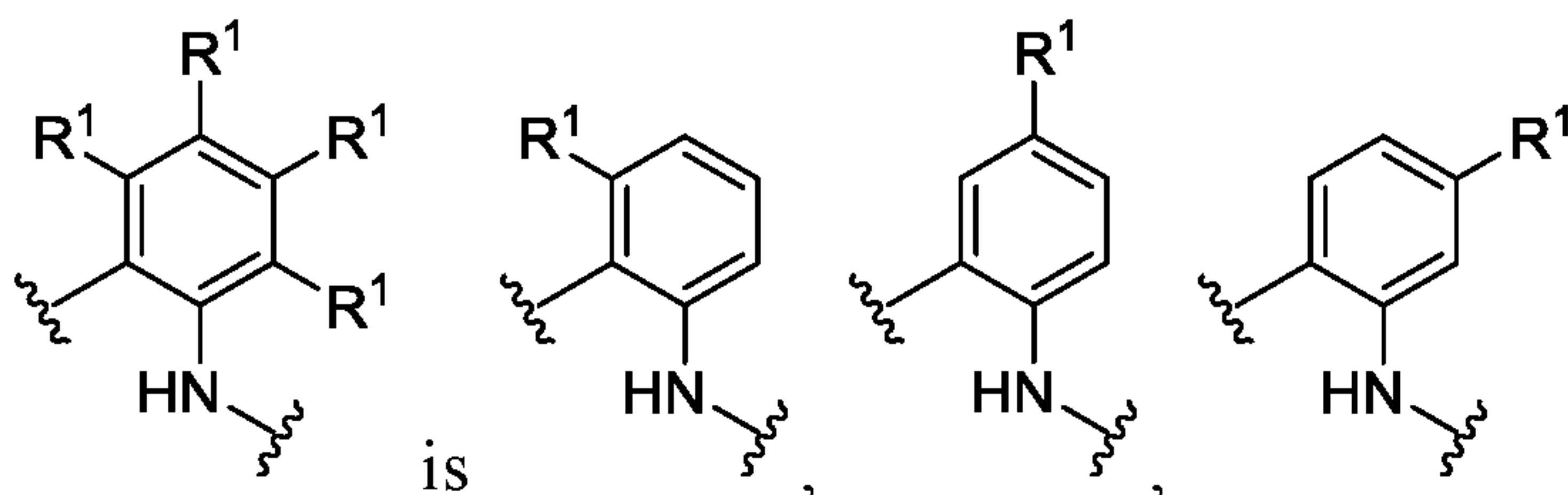
In some embodiments, X is substituted or unsubstituted C₂-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, X is substituted or unsubstituted C₂-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, or substituted or unsubstituted heteroaryl. In some embodiments, X is -L¹-Y¹. In some embodiments, L¹ is substituted or unsubstituted C₁-C₄alkylene; and Y¹ is substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀ heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, L¹ is substituted or unsubstituted C₁-C₄alkylene; and Y¹ is substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆ heterocycloalkyl, substituted or unsubstituted phenyl, or

substituted or unsubstituted monocyclic heteroaryl. In some embodiments, X is $-L^2-L^3-Y^2$. In some embodiments, L^2 is substituted or unsubstituted C_1-C_6 alkylene; L^3 is $-O-$, $-S-$, $-(S=O)-$, $-(SO_2)-$, $-NR^3-$, $-(C=O)-$, $-(C=O)O-$, $-O(C=O)-$, $-(C=O)NR^3-$, $-(C=O)NR^3-O-$, $-NR^3(C=O)-$, $-NR^3(C=O)NR^3-$, $-O(C=O)NR^3-$, $-NR^3(C=O)O-$, $-NR^3(SO_2)NR^3-$, $-NR^3(SO_2)-$, $-(SO_2)NR^3-$, $-(SO_2)NR^3-(C=O)-$, $-(SO_2)NR^3-(C=O)O-$, $-NR^3(SO_2)NR^3-(C=O)-$, or $-NR^3(SO_2)NR^3-(C=O)O-$; each R^3 is independently H or substituted or unsubstituted C_1-C_6 alkyl; and Y^2 is H, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted C_2-C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, L^2 is substituted or unsubstituted C_1-C_4 alkylene; L^3 is $-O-$, $-S-$, $-(S=O)-$, $-(SO_2)-$, $-NR^3-$, $-(C=O)-$, $-(C=O)O-$, $-O(C=O)-$, $-(C=O)NR^3-$, $-(C=O)NR^3-O-$, $-NR^3(C=O)-$, $-NR^3(C=O)NR^3-$, $-O(C=O)NR^3-$, $-NR^3(C=O)O-$, $-NR^3(SO_2)NR^3-$, $-NR^3(SO_2)-$, $-(SO_2)NR^3-$, $-(SO_2)NR^3-(C=O)-$, $-(SO_2)NR^3-(C=O)O-$, $-NR^3(SO_2)NR^3-(C=O)-$, or $-NR^3(SO_2)NR^3-(C=O)O-$; each R^3 is independently H or substituted or unsubstituted C_1-C_4 alkyl; and Y^2 is H, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 haloalkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl.



[0010] In some embodiments,

is



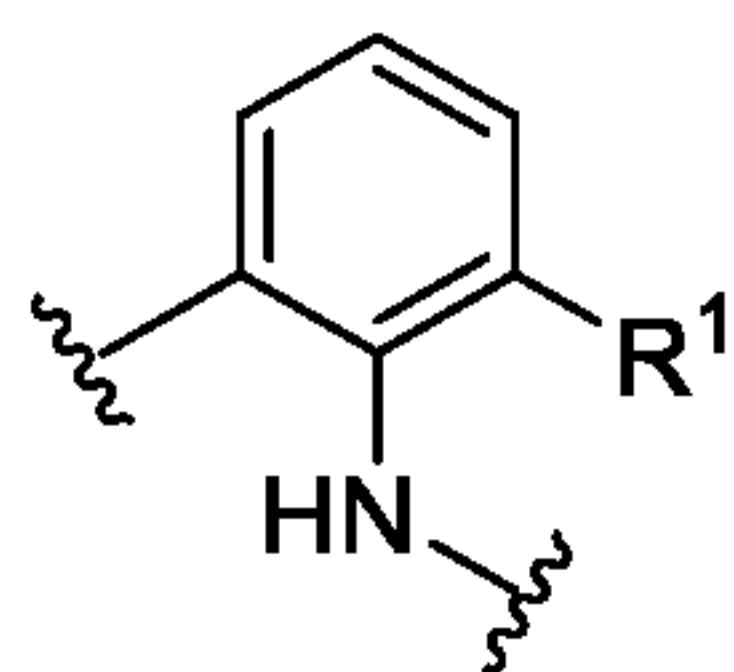
[0011] In some embodiments,

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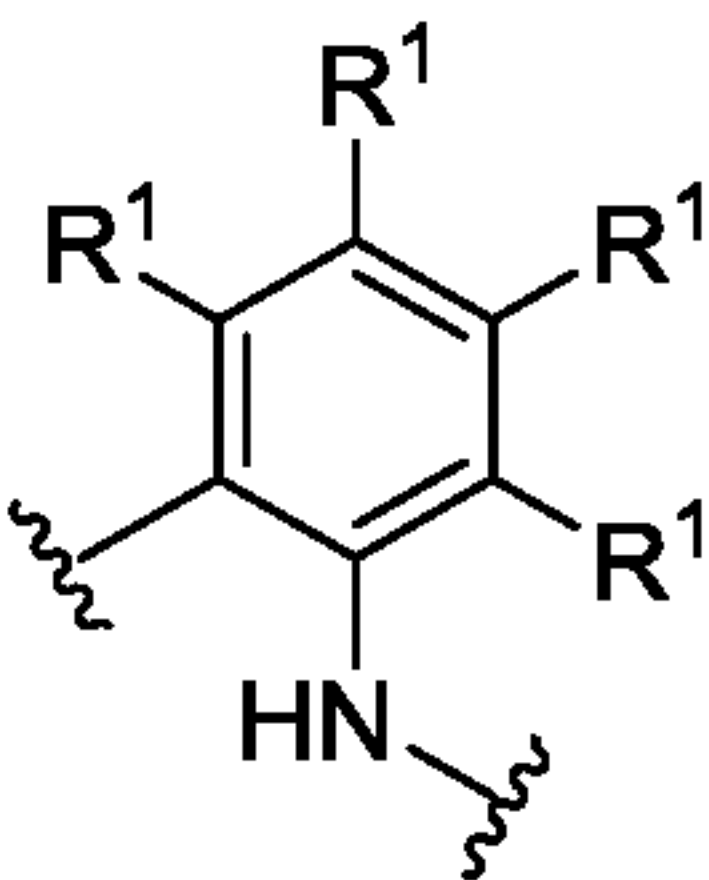
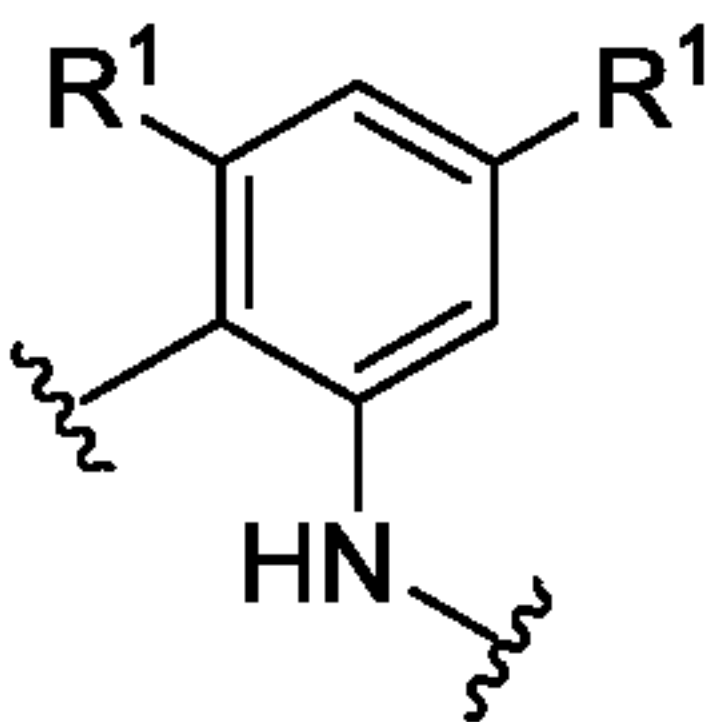
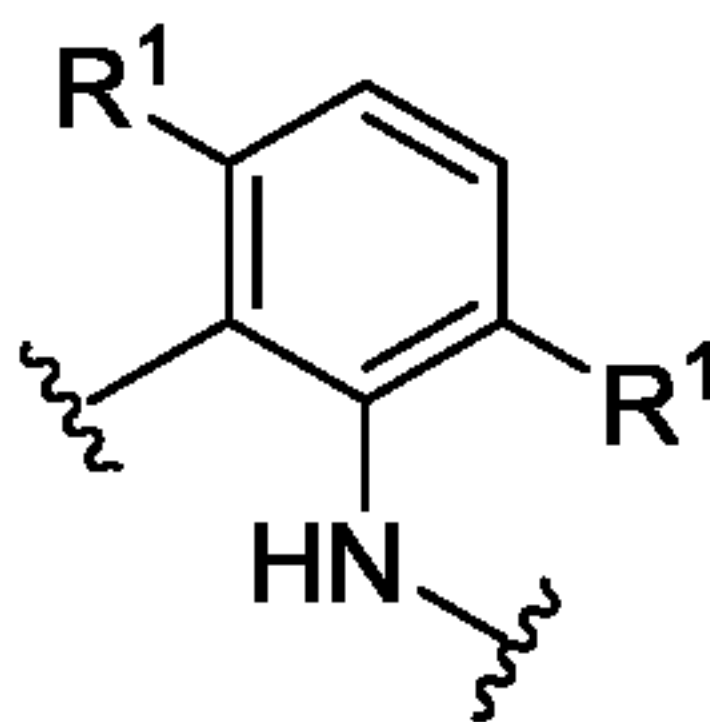
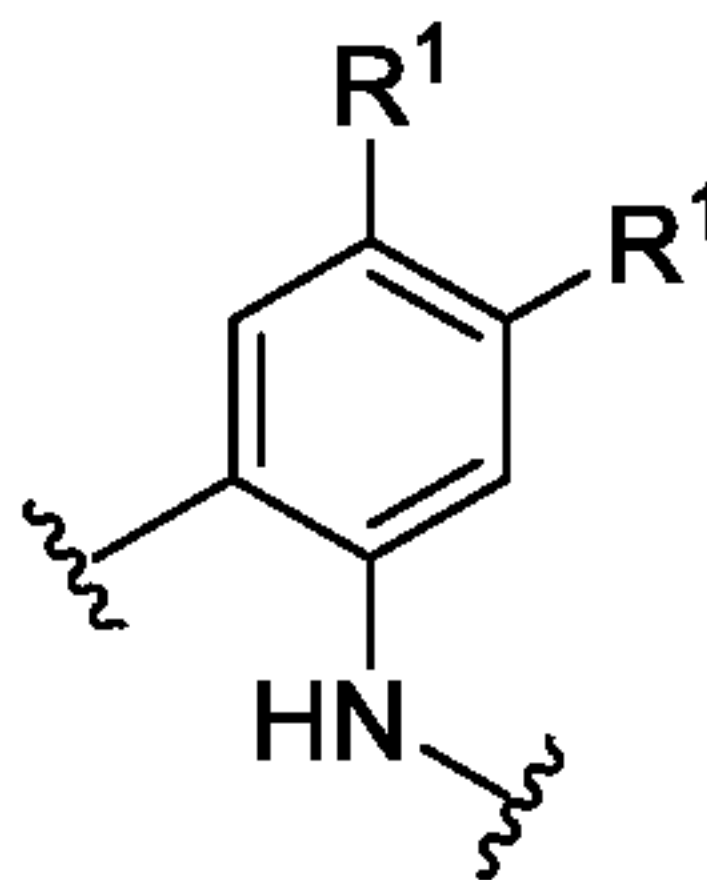
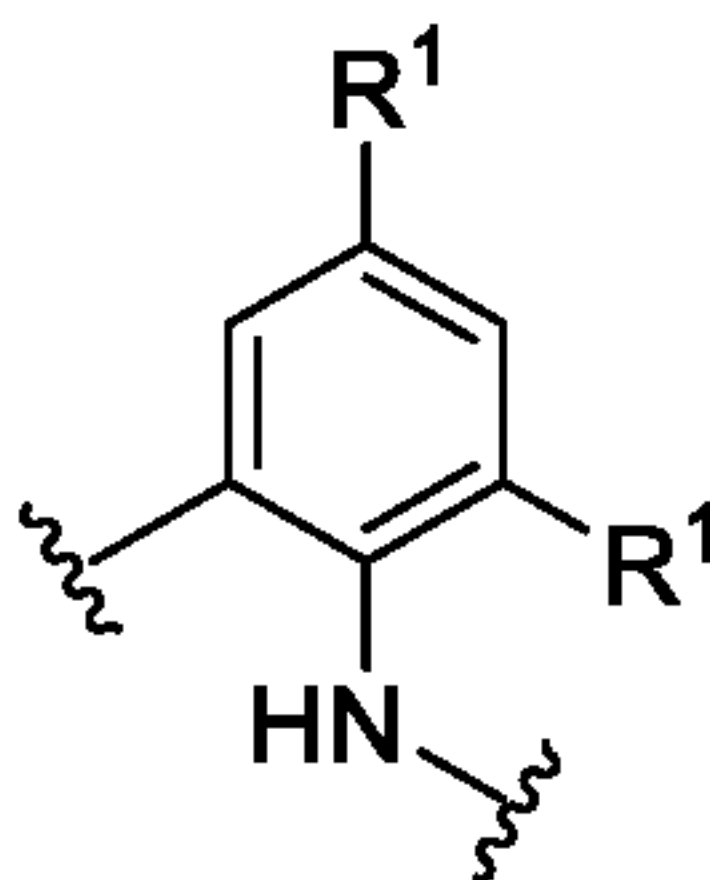
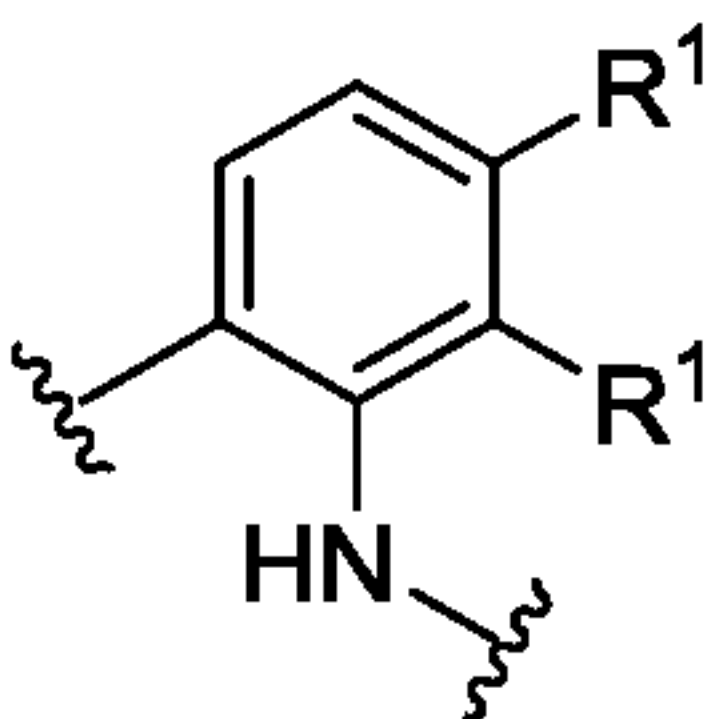
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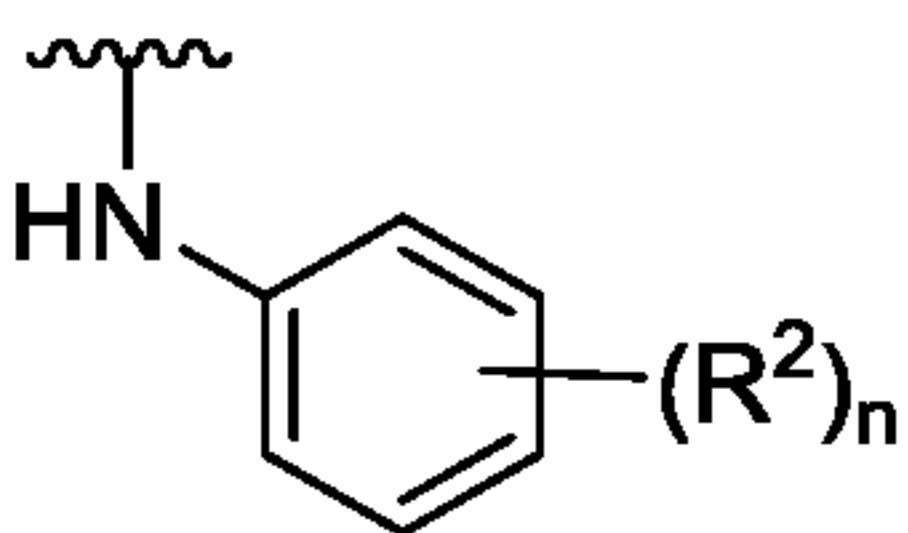
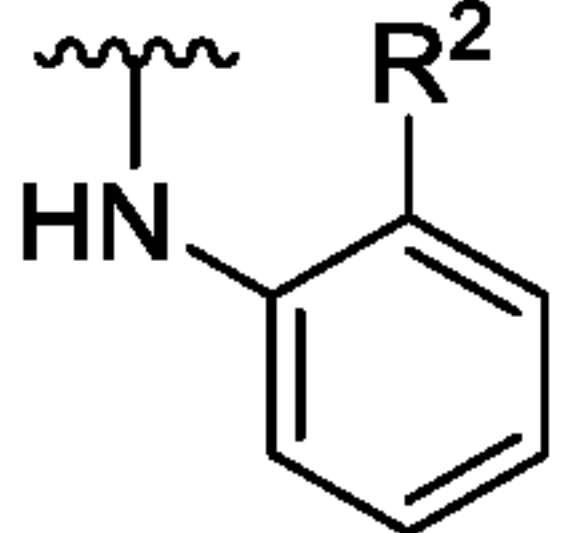
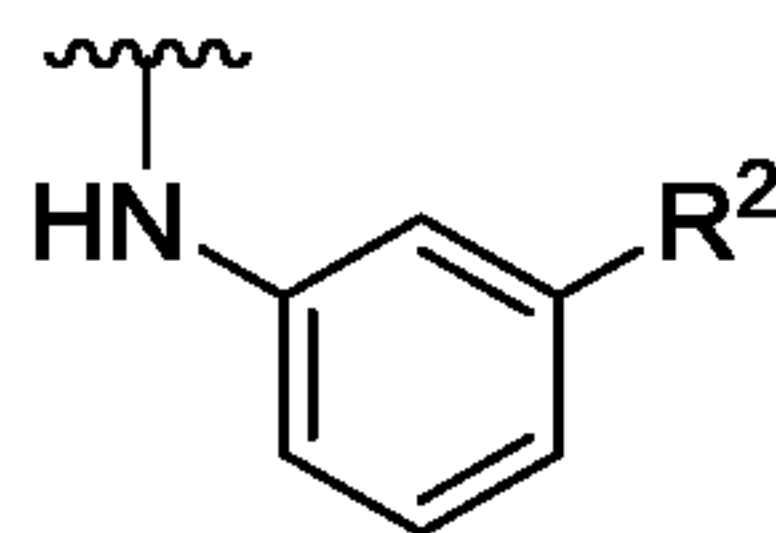
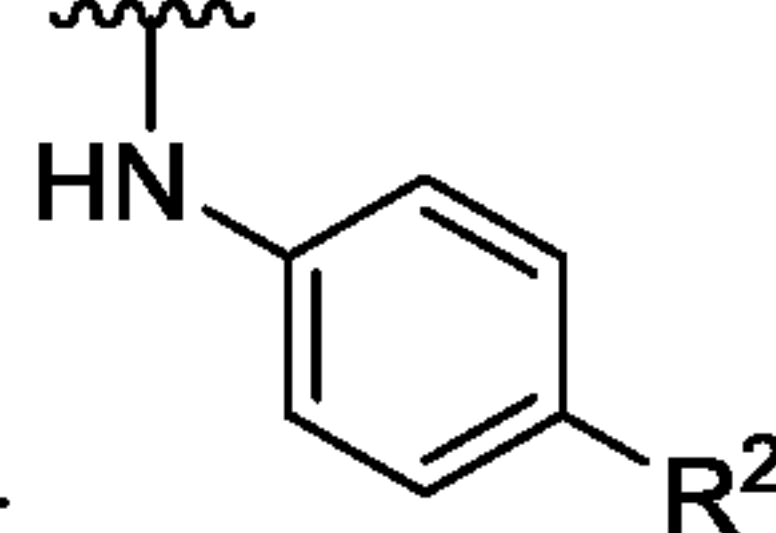
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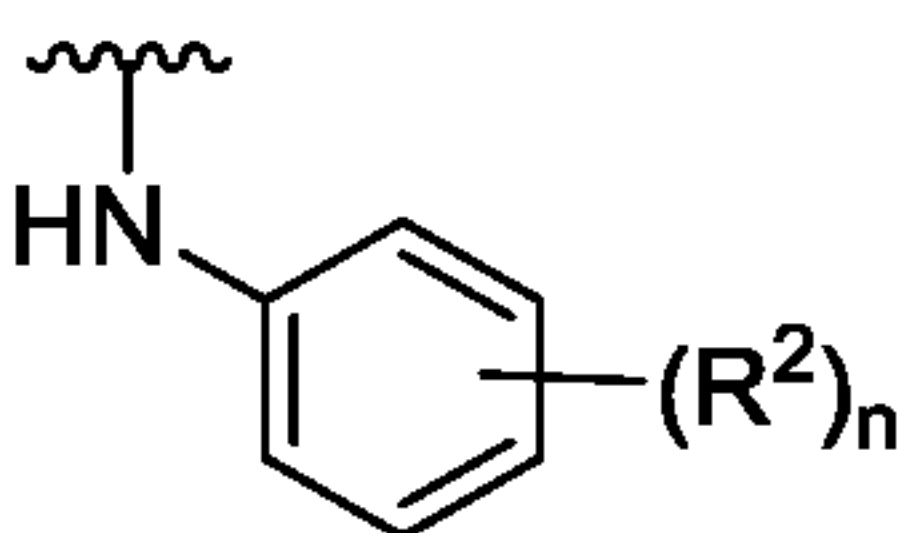
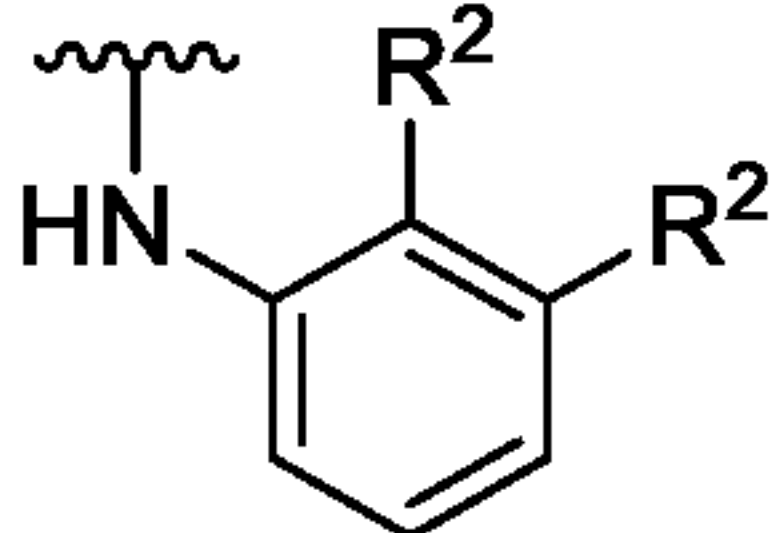
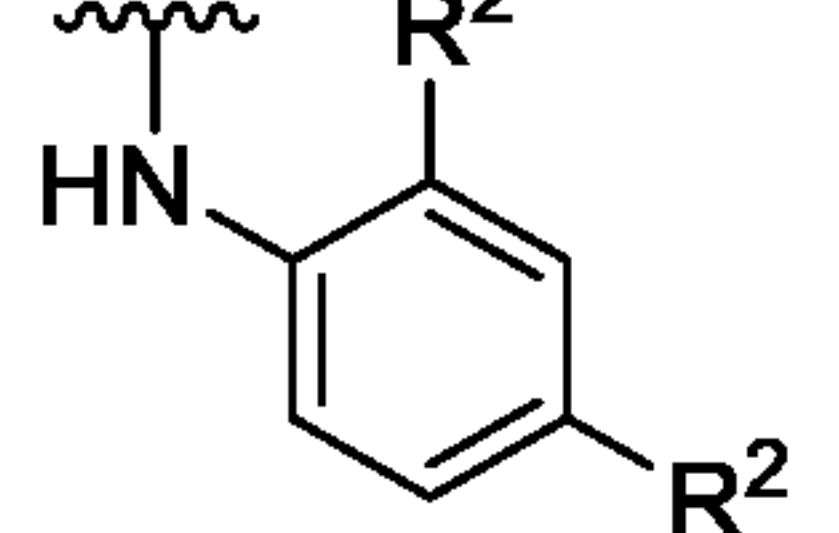
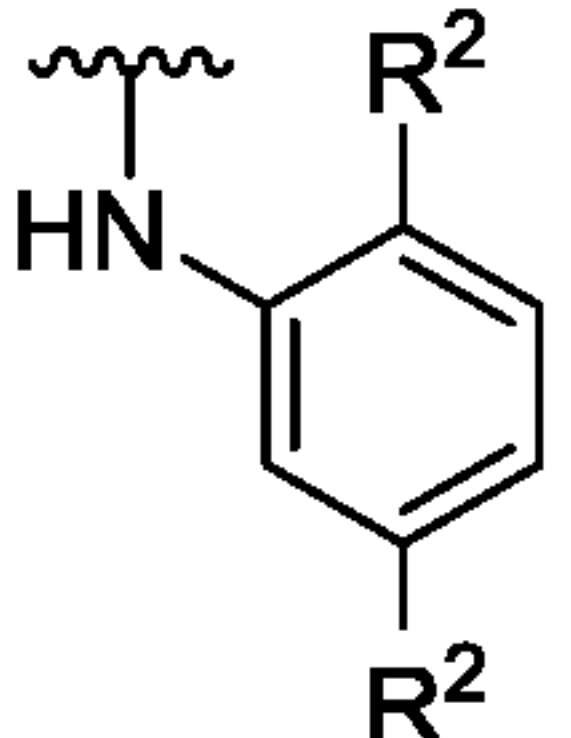


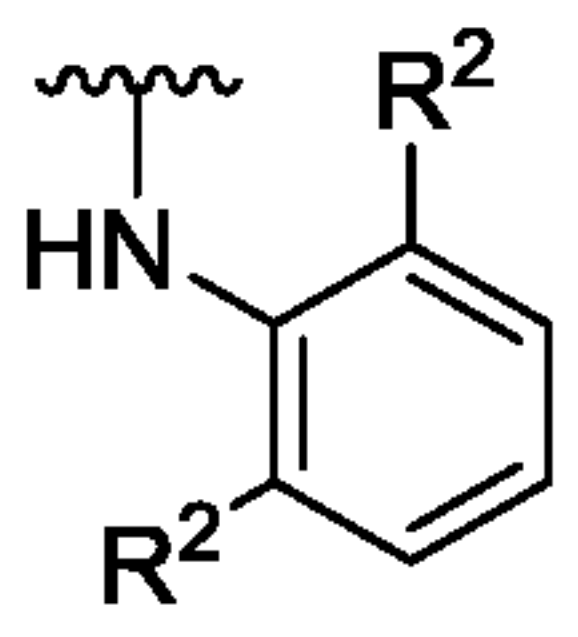
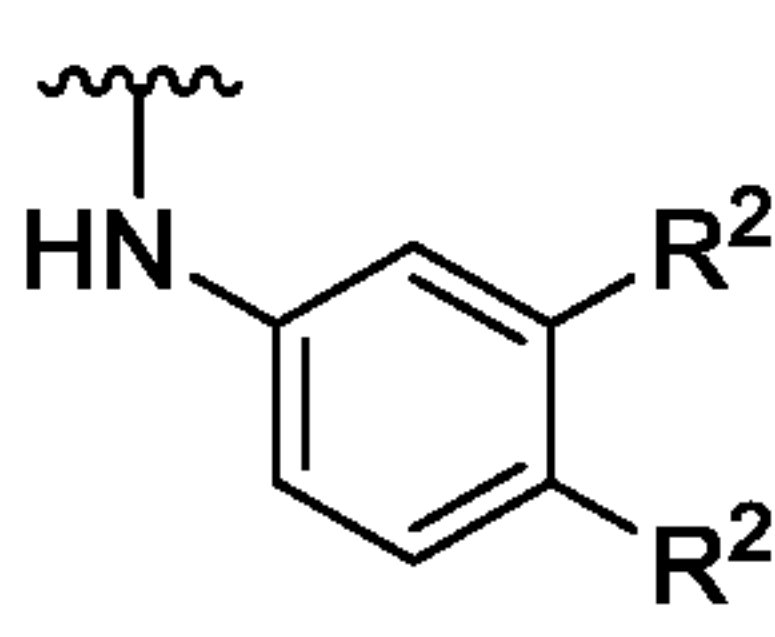
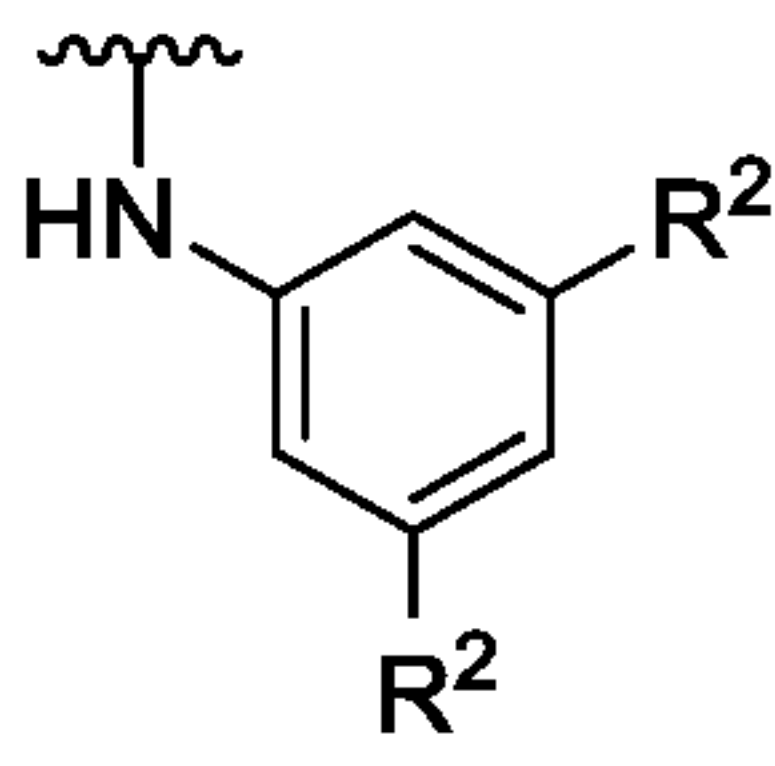
; and R^1 is halogen, $-CN$, $-OR^4$, $-SR^4$, $-N(R^4)_2$, substituted or unsubstituted C_1-

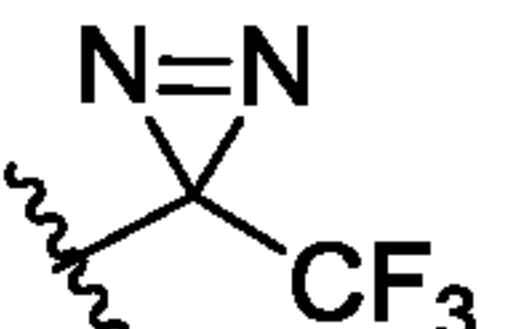
C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0012] In some embodiments,  is , , , , or ; and each R¹ is independently halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

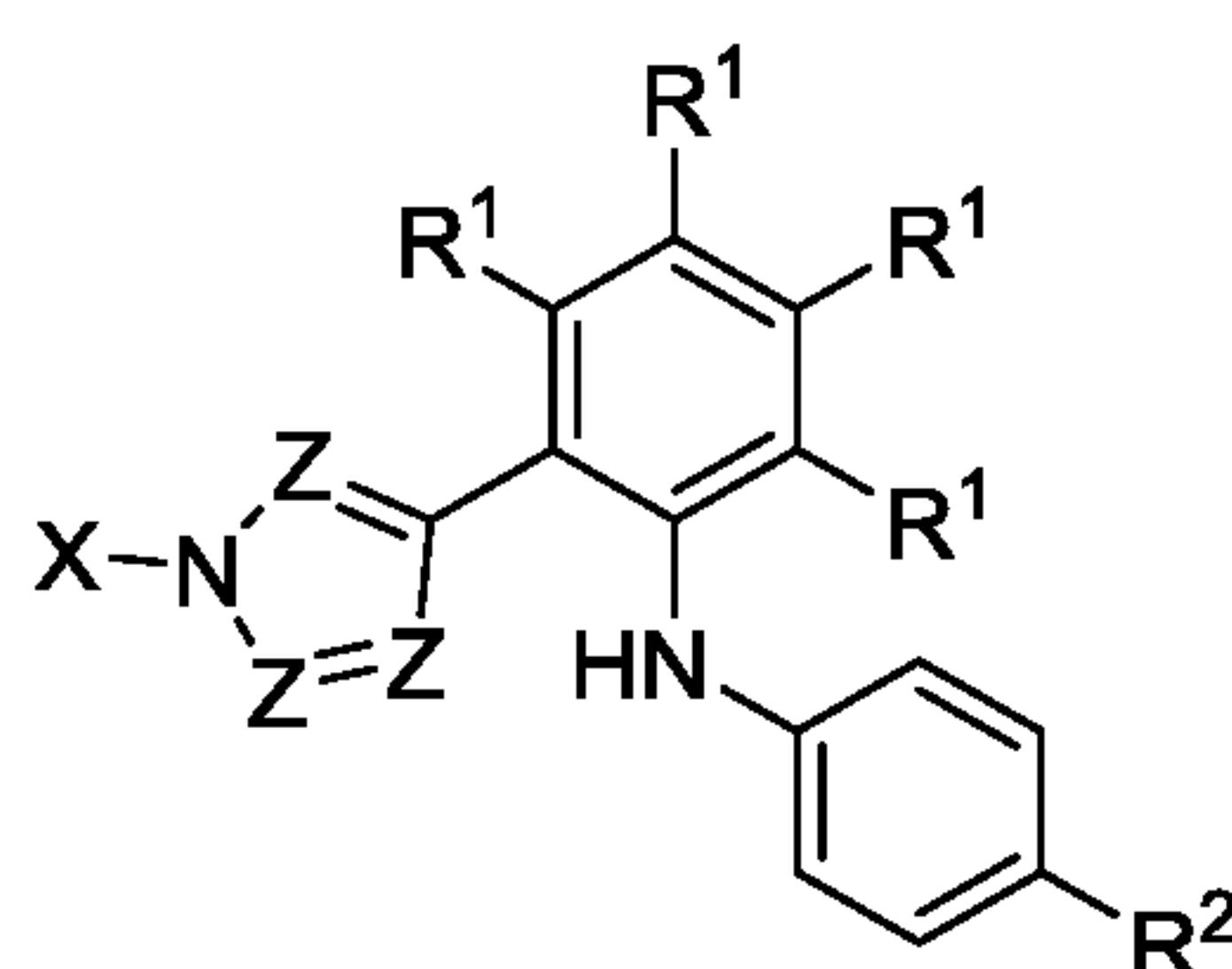
[0013] In some embodiments,  is , , or .

[0014] In some embodiments,  is , , ,

, , or .

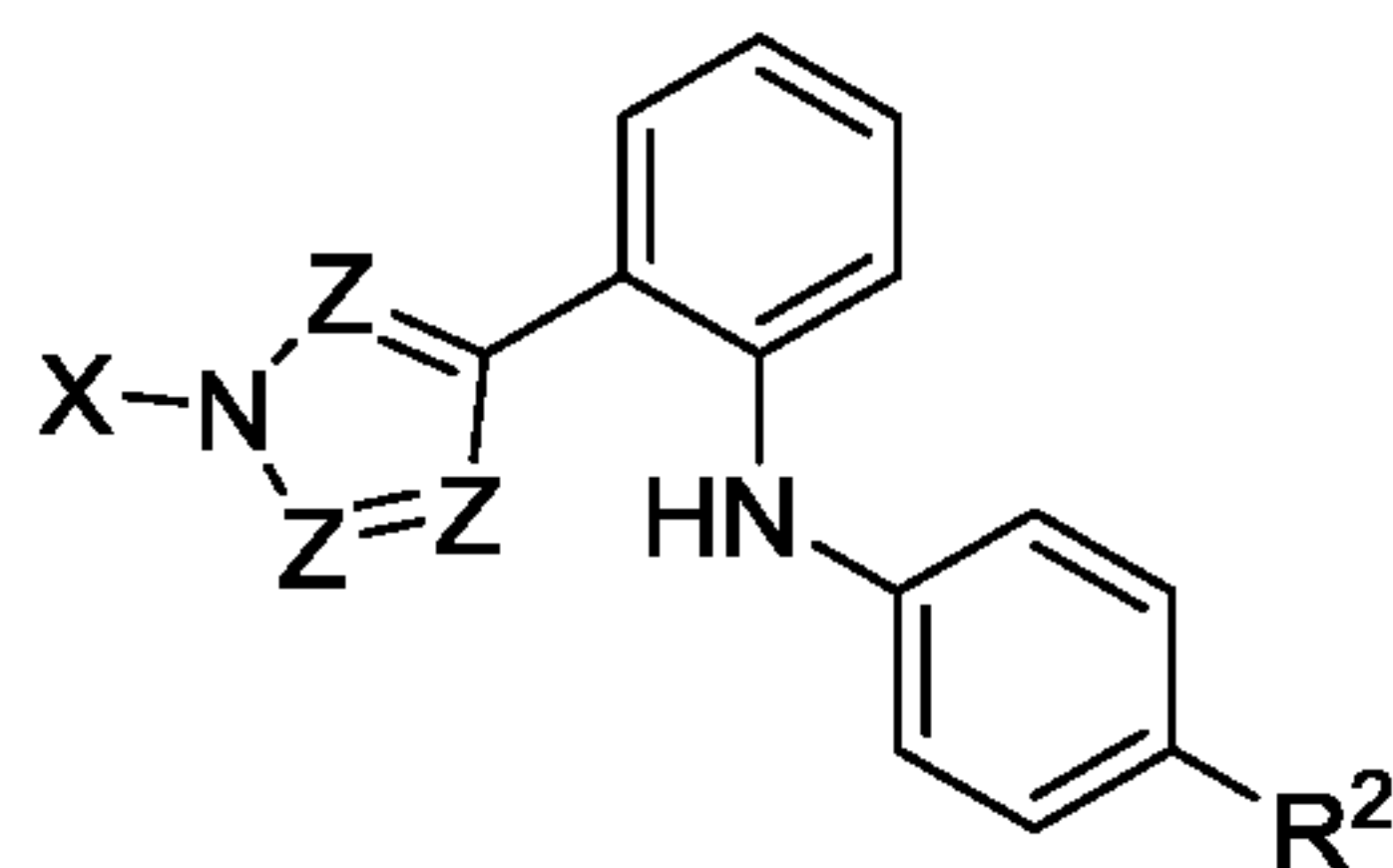
[0015] In some embodiments, each R² is independently halogen, -N₃, -OR⁵, -(SO₂)R⁵, -CO₂R⁵, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, or .

[0016] In some embodiments, the compound has the structure of Formula (Ia), or a pharmaceutically acceptable salt thereof:



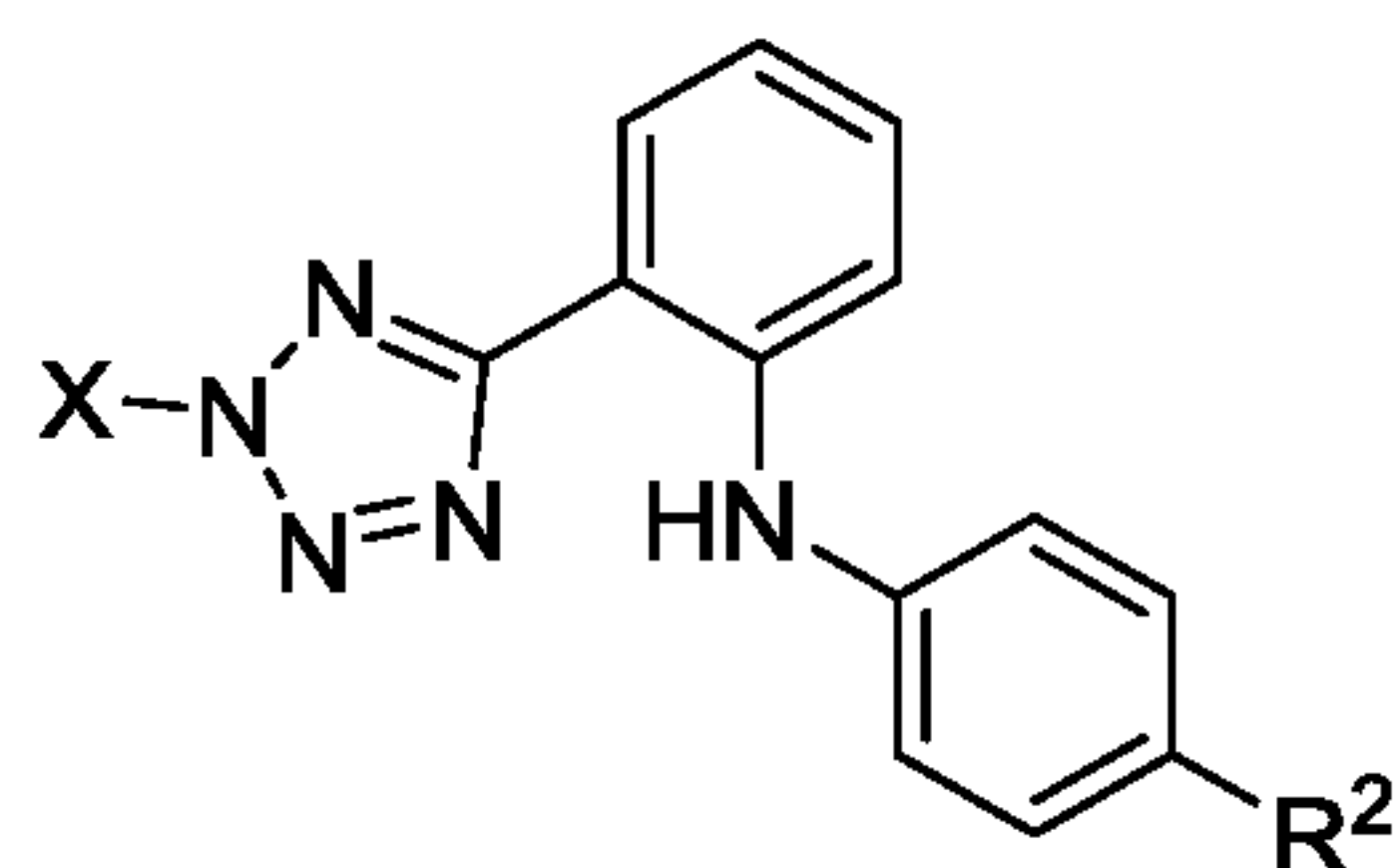
Formula (Ia).

[0017] In some embodiments, the compound has the structure of Formula (Ib), or a pharmaceutically acceptable salt thereof:



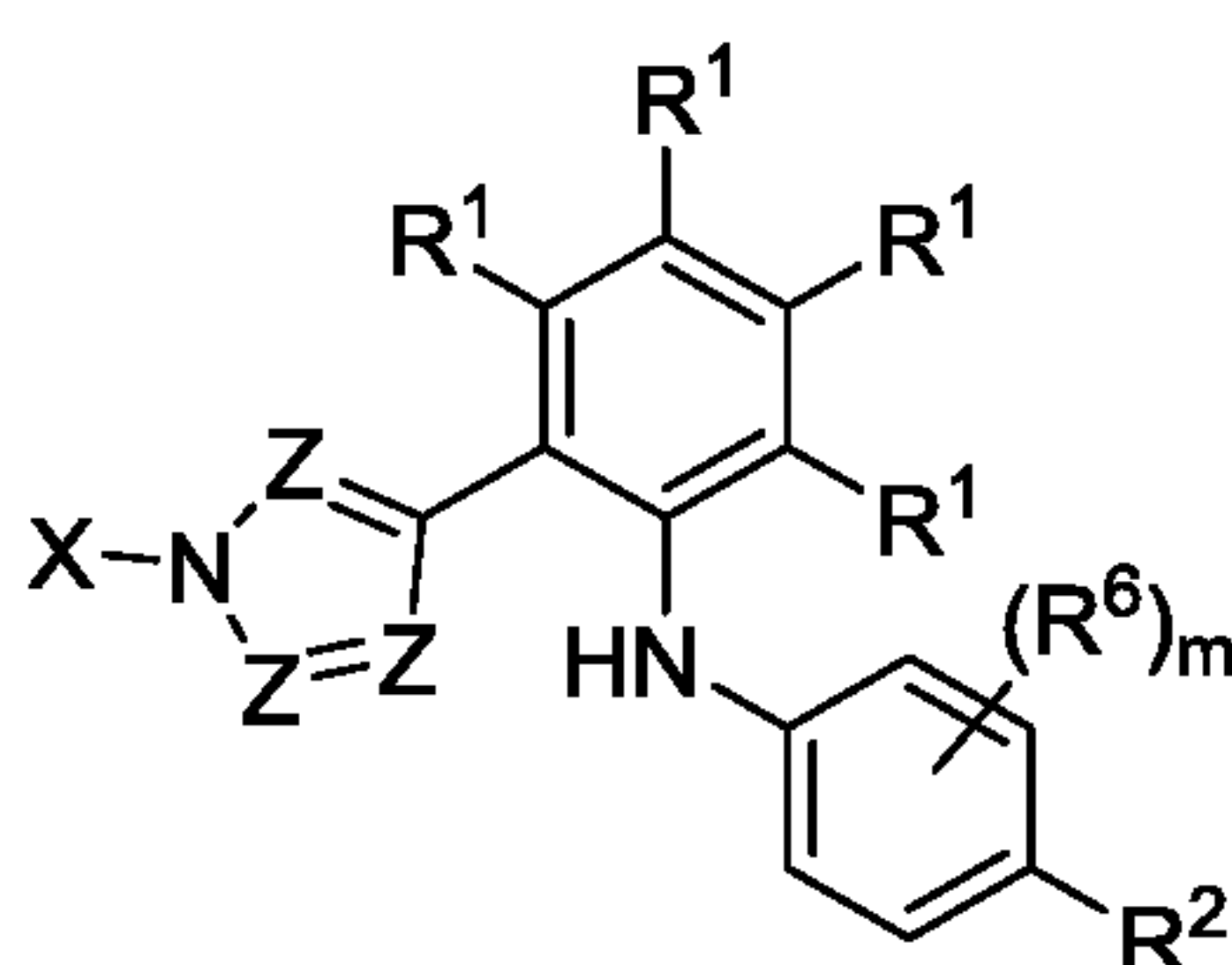
Formula (Ib).

[0018] In some embodiments, the compound has the structure of Formula (Ic), or a pharmaceutically acceptable salt thereof:



Formula (Ic).

[0019] Provided in another aspect is a compound of Formula (II), or a pharmaceutically acceptable salt thereof:



Formula (II)

wherein:

each Z is independently N or CR^Z;

each R^Z is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

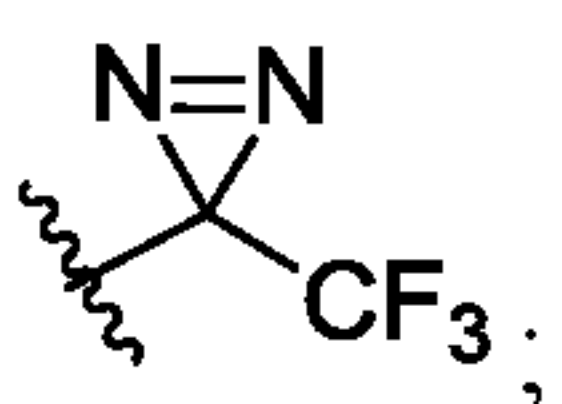
X is methyl;

each R¹ is independently H, halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-

C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R² is halogen, -N₃, -CN, -OR⁵, -SR⁵, -(SO₂)R⁵, -N(R⁵)₂, -CO₂R⁵, substituted or unsubstituted

C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted

aryl, substituted or unsubstituted heteroaryl, or ;

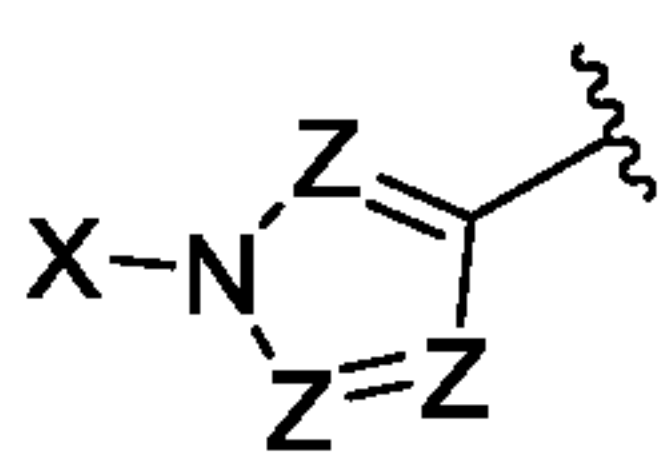
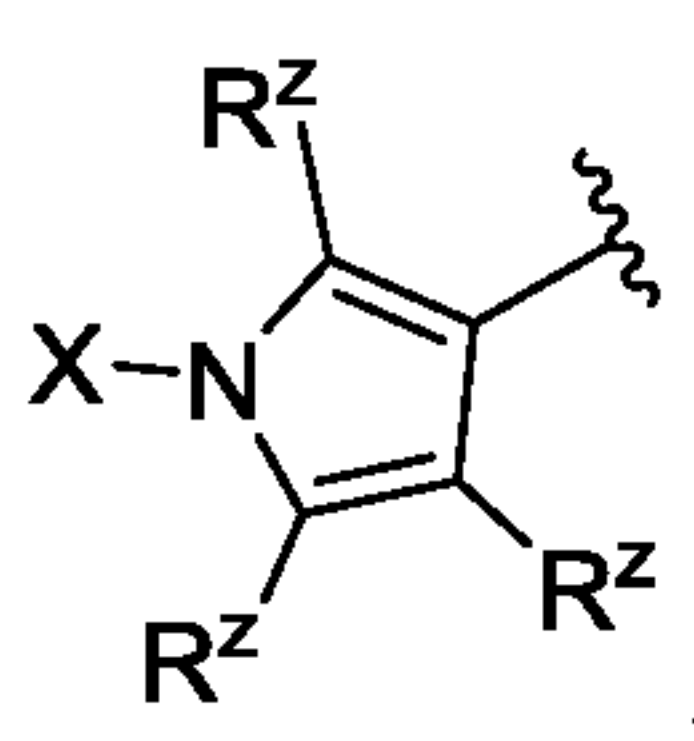
each R⁶ is independently H, halogen, -N₃, -CN, -OR⁷, -SR⁷, -(SO₂)R⁷, -N(R⁷)₂, -CO₂R⁷, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R⁴ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

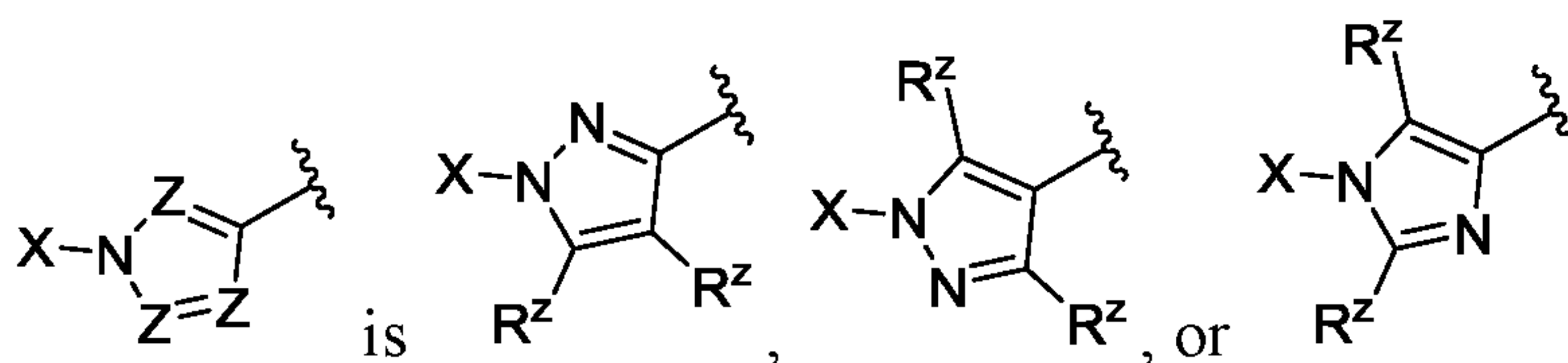
each R⁵ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R⁷ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

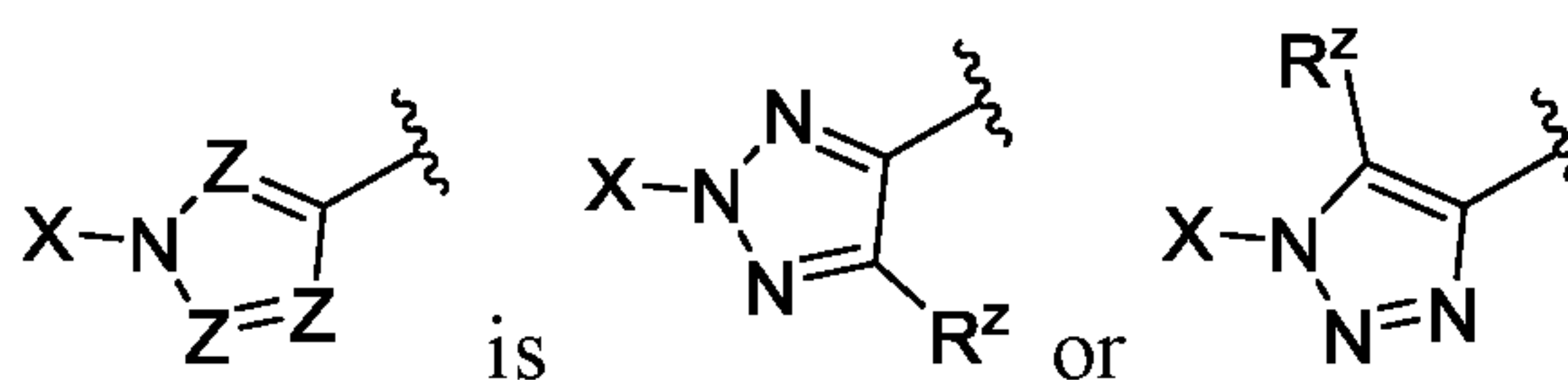
m is 0, 1, 2, 3, or 4.

[0020] In some embodiments,  is .

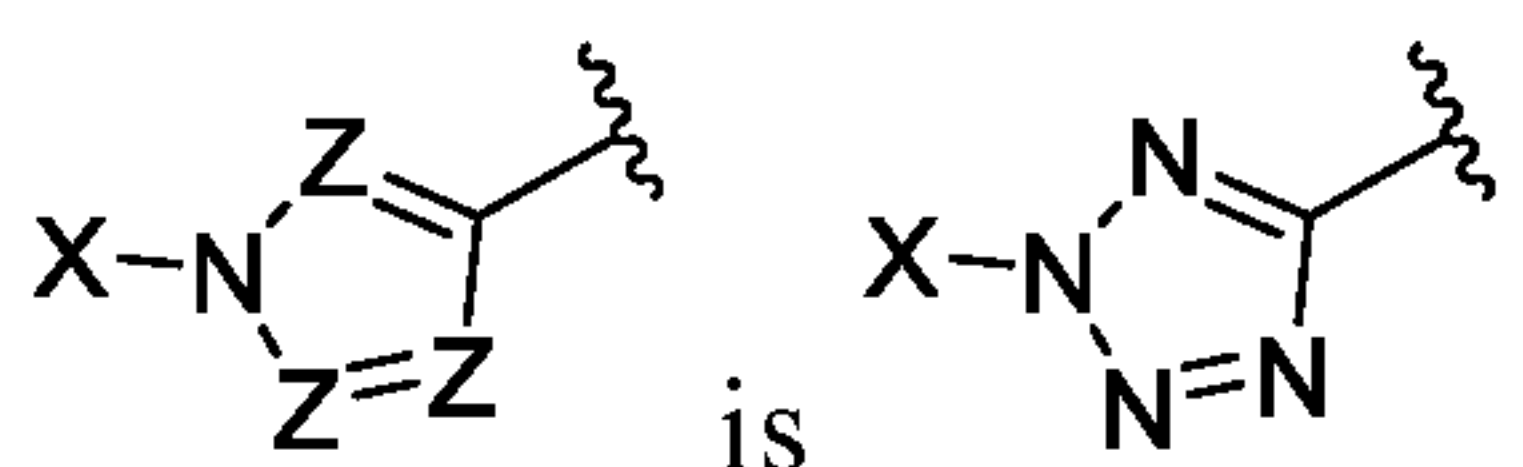
[0021] In some embodiments,



[0022] In some embodiments,

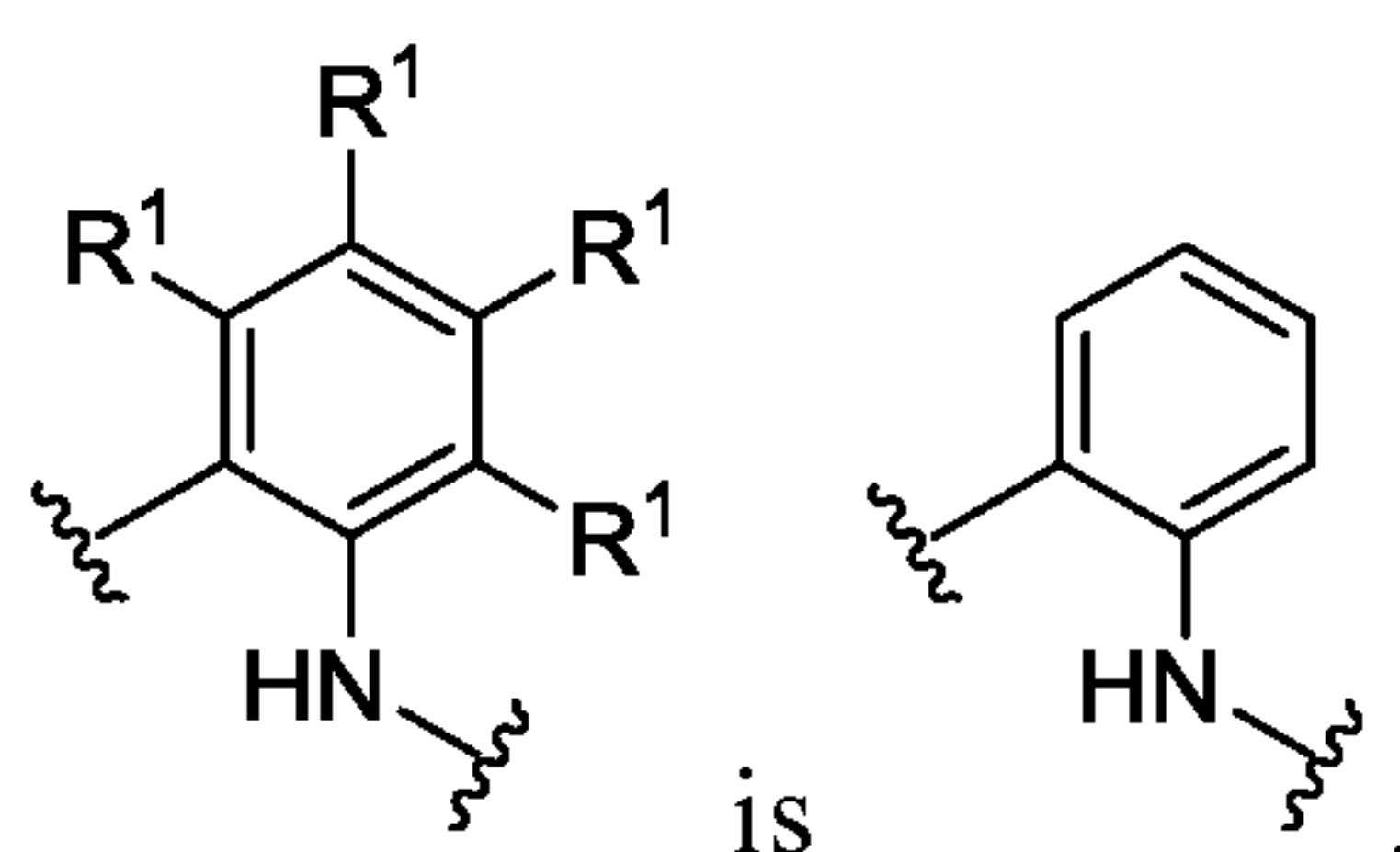


[0023] In some embodiments,

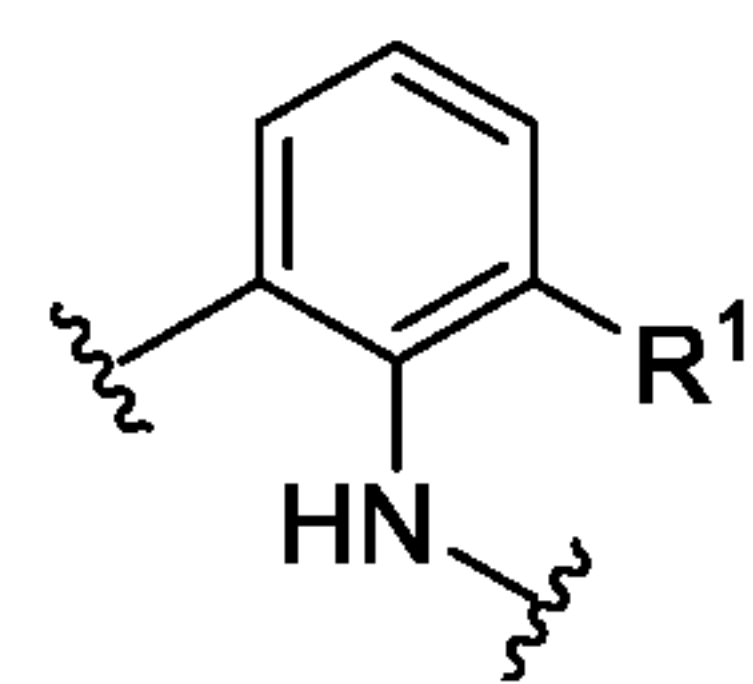
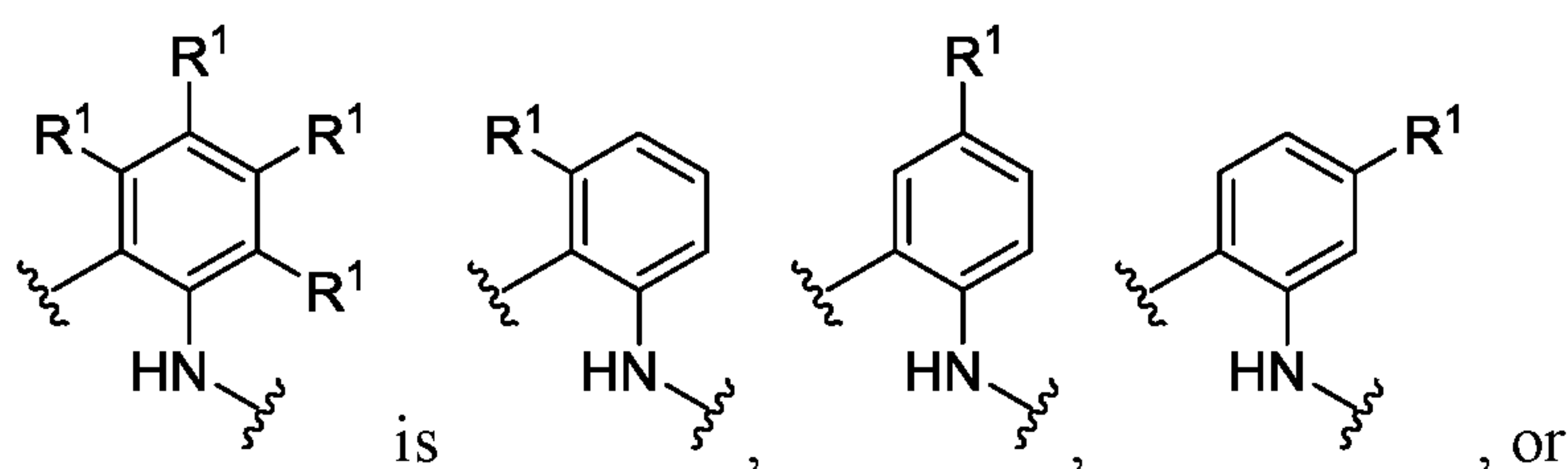


[0024] In some embodiments, each R^Z is independently H or substituted or unsubstituted C_1 - C_6 alkyl.

[0025] In some embodiments,

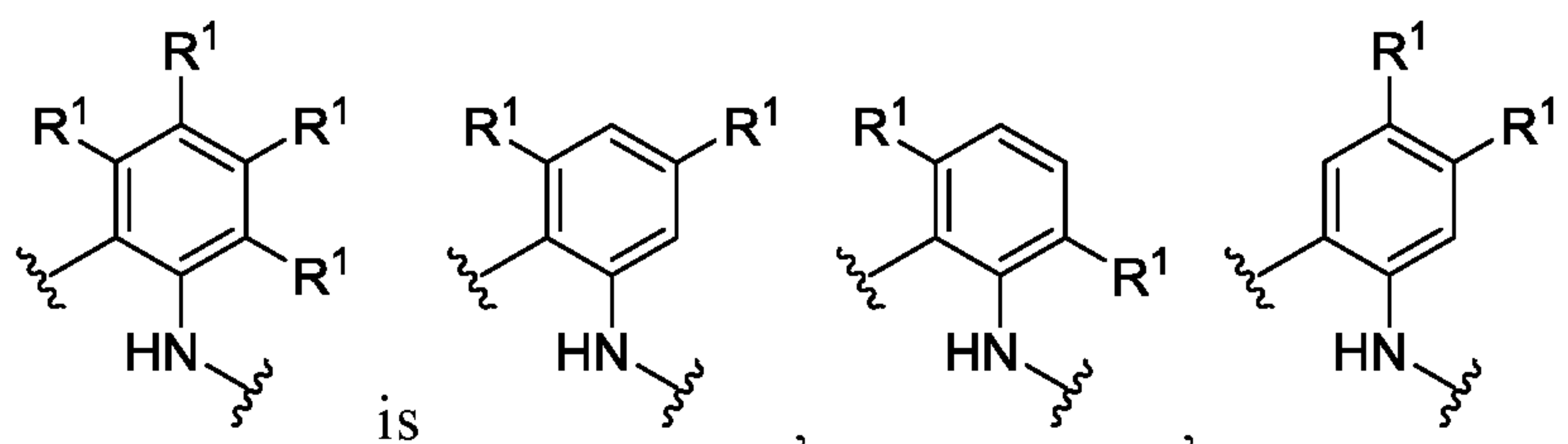


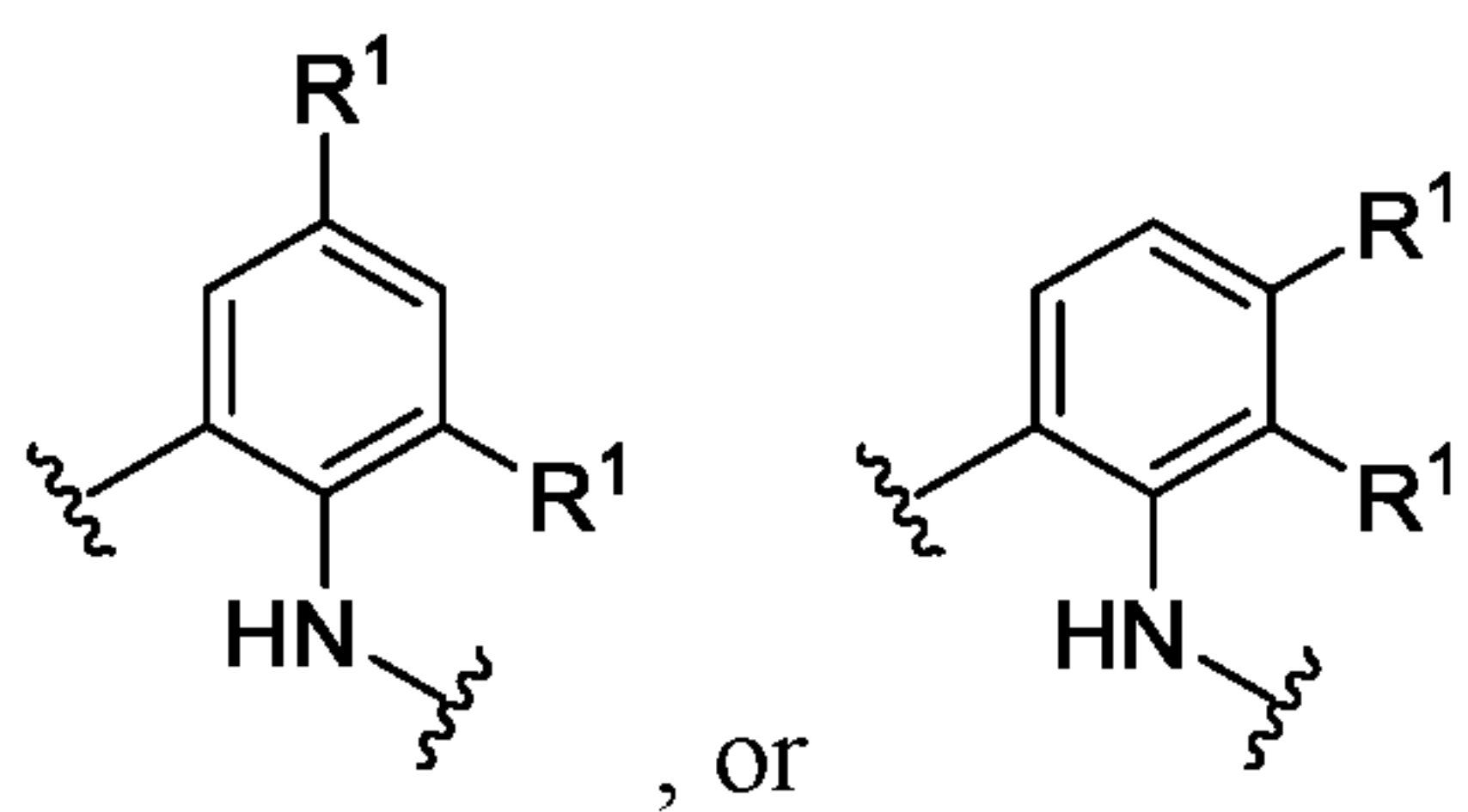
[0026] In some embodiments,



; and R^1 is halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

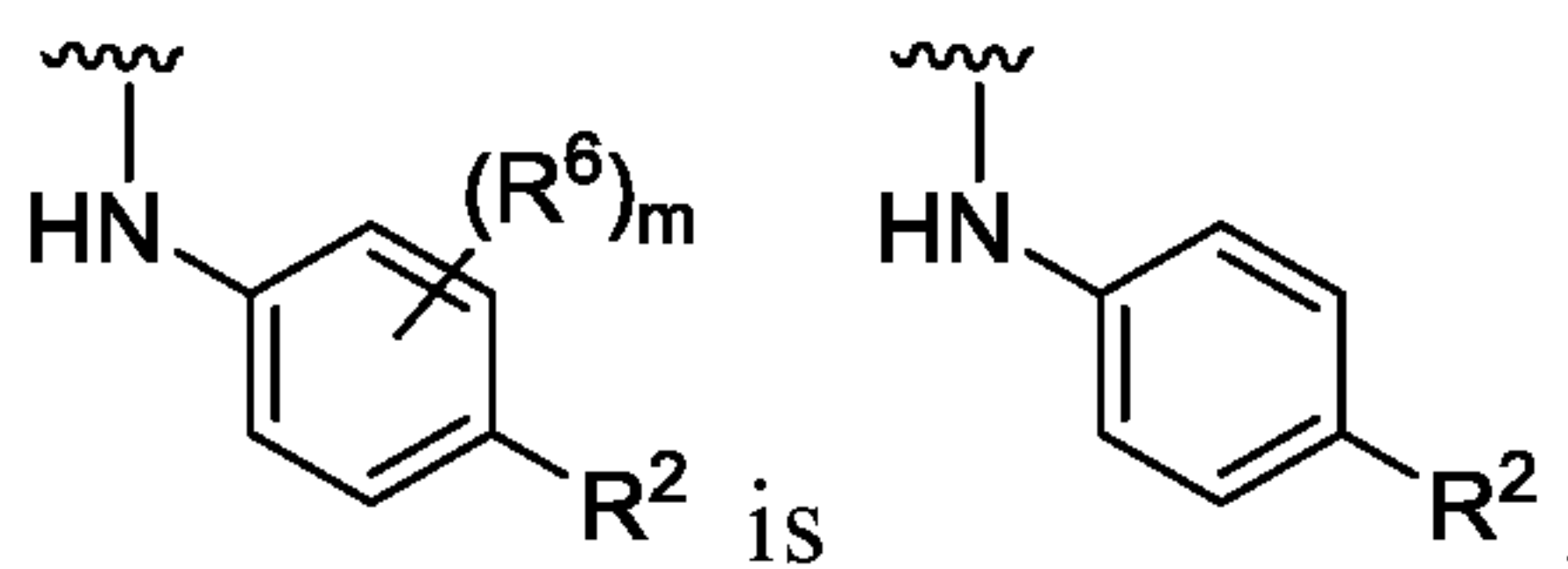
[0027] In some embodiments,



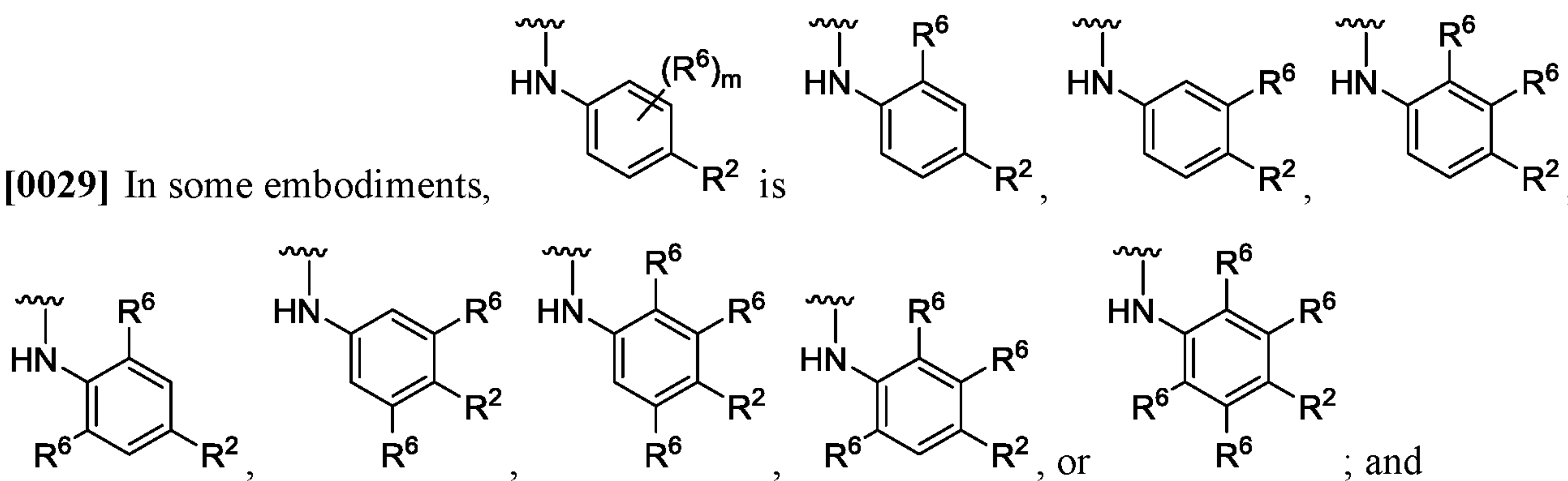


, or ; and each R¹ is independently halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0028] In some embodiments,



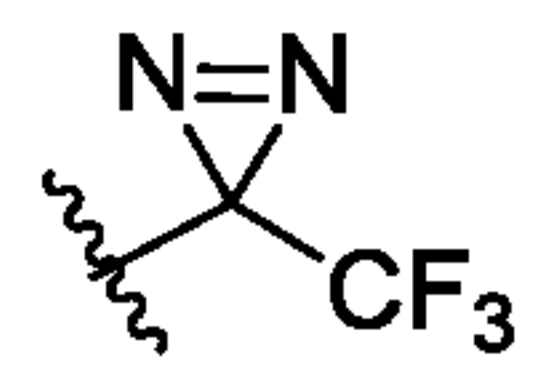
[0029] In some embodiments,



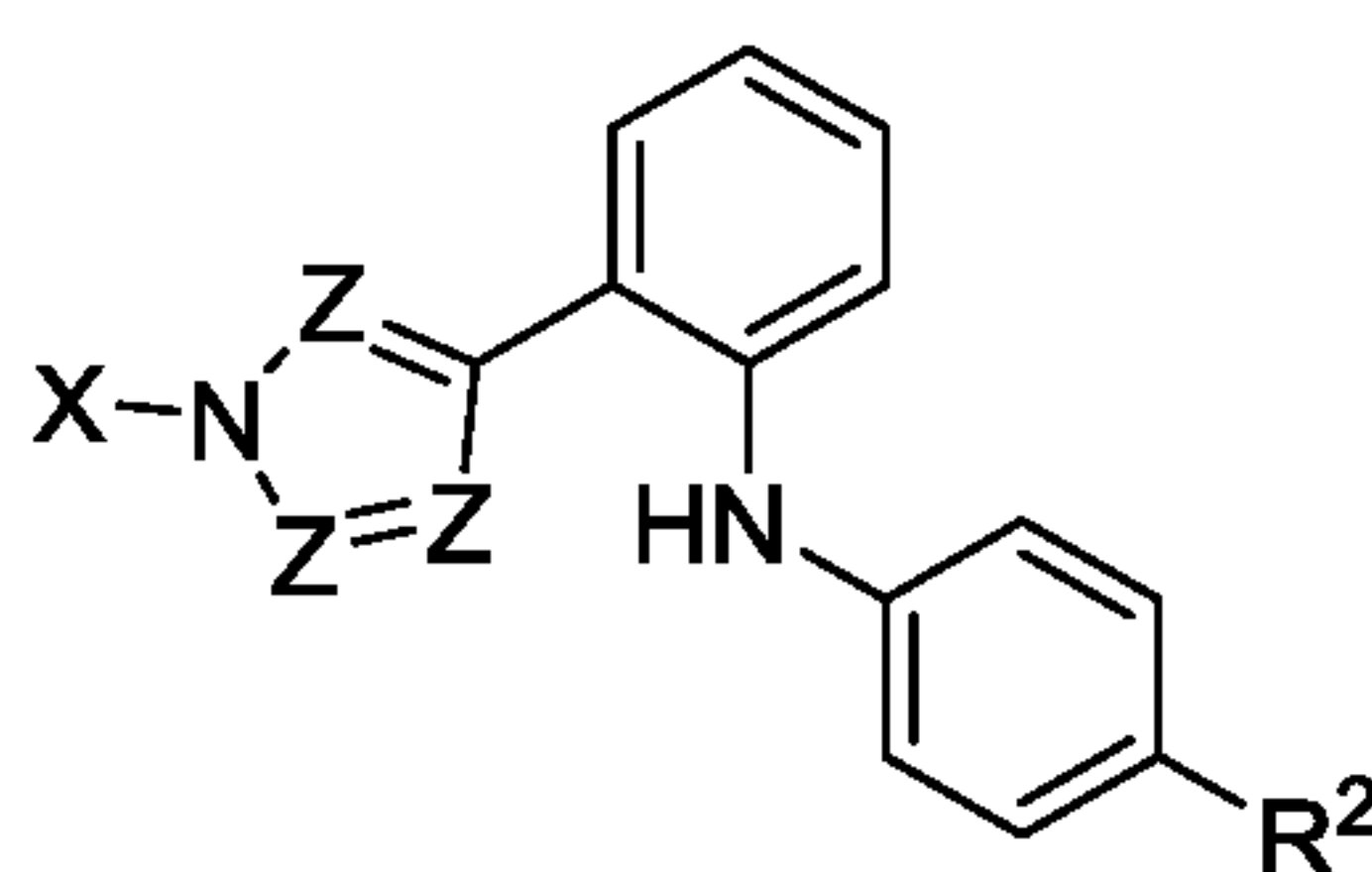
each R⁶ is independently halogen, -N₃, -CN, -OR⁷, -SR⁷, -(SO₂)R⁷, -N(R⁷)₂, -CO₂R⁷, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0030] In some embodiments, R² is halogen, -N₃, -OR⁵, -(SO₂)R⁵, -CO₂R⁵, substituted or

unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, or

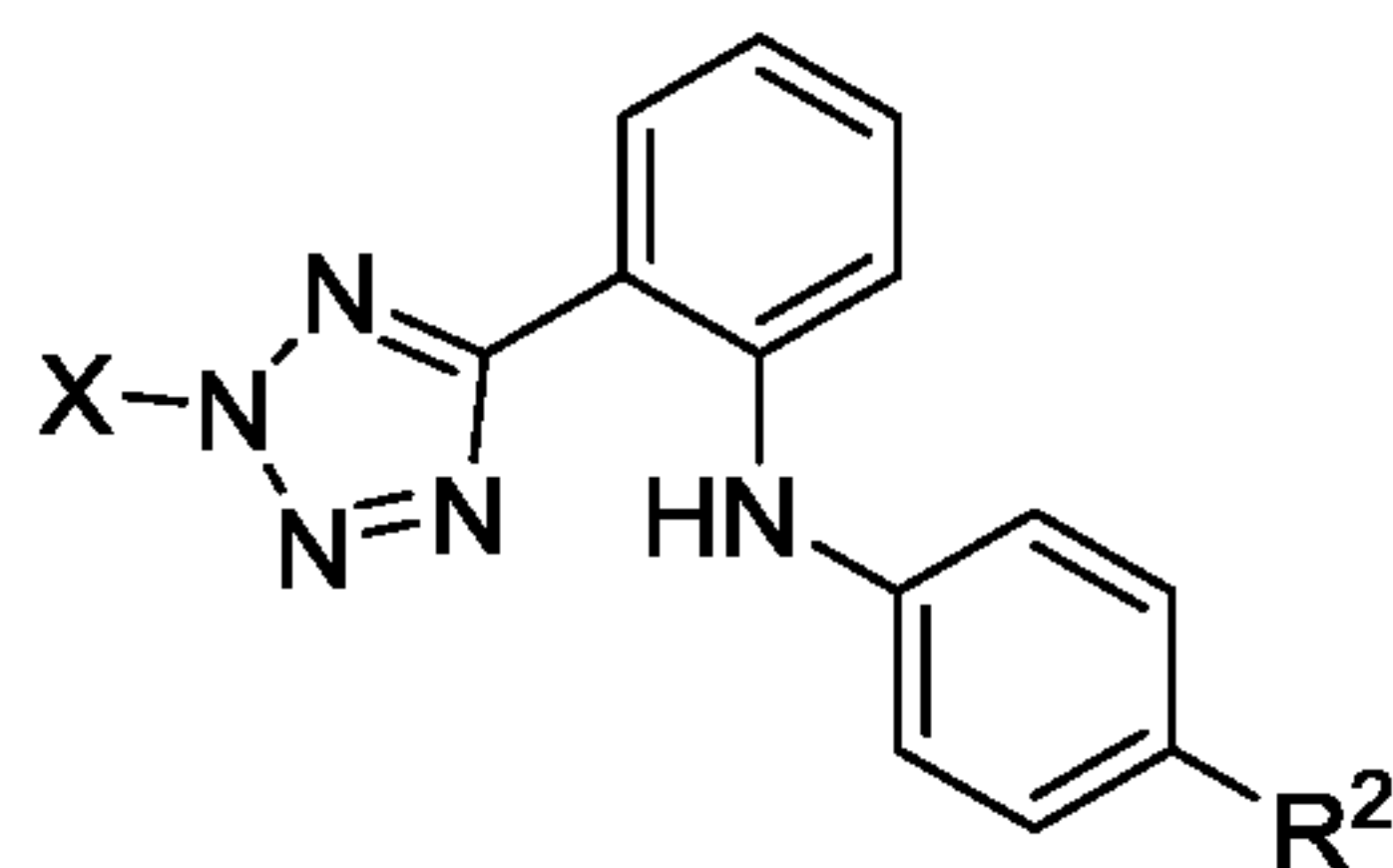


[0031] In some embodiments, the compound has the structure of Formula (IIa), or a pharmaceutically acceptable salt thereof:



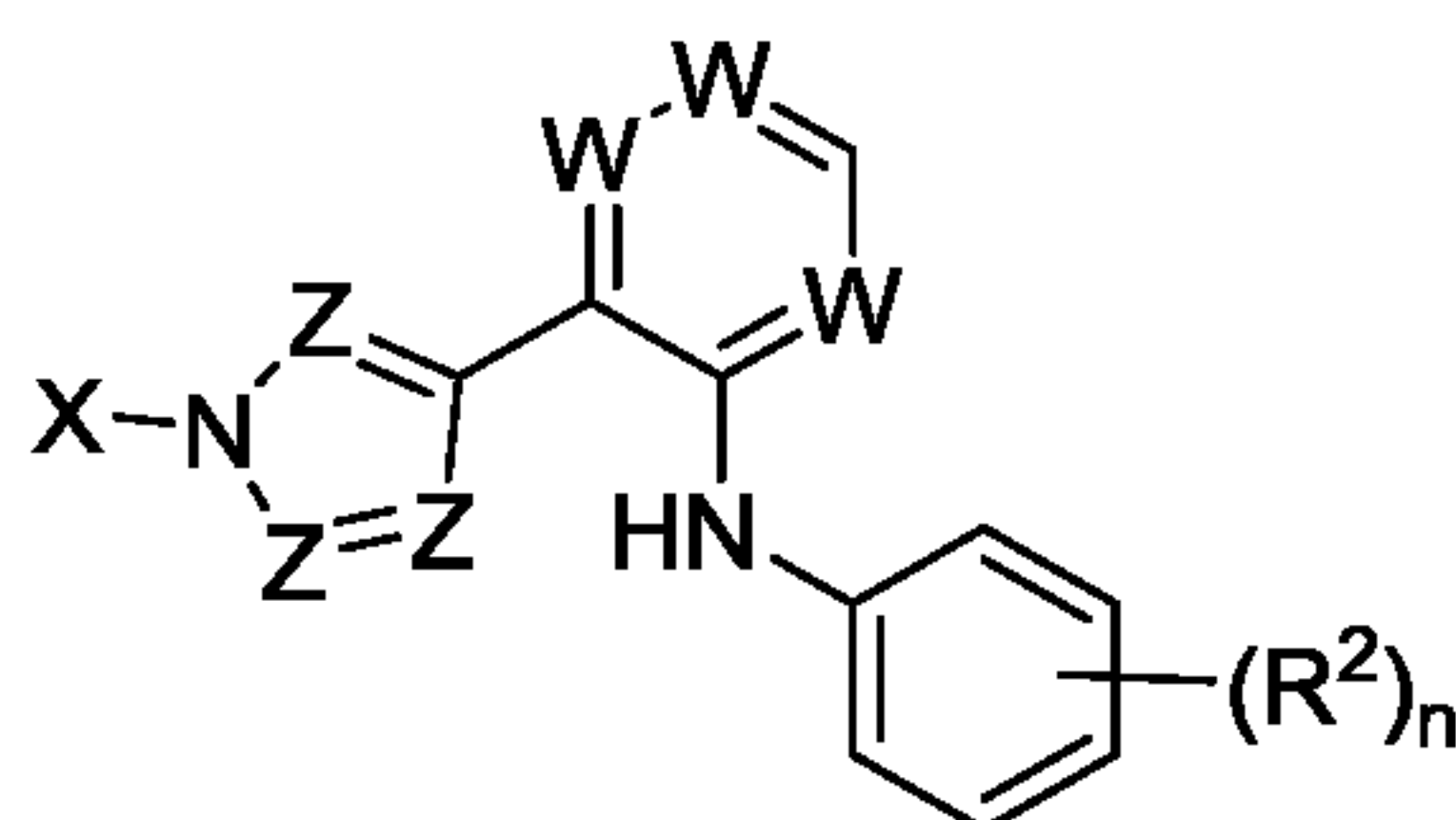
Formula (IIa).

[0032] In some embodiments, the compound has the structure of Formula (IIb), or a pharmaceutically acceptable salt thereof:



Formula (IIb).

[0033] Provided in another aspect is a compound of Formula (III), or a pharmaceutically acceptable salt thereof:



Formula (III)

wherein:

each Z is independently N or CR^Z;

each R^Z is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

X is substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -L¹-Y¹, or -L²-L³-Y²;

L¹ is substituted or unsubstituted C₁-C₆alkylene;

Y¹ is substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L² is absent or substituted or unsubstituted C₁-C₆alkylene;

L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -O-NR³(C=O)-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(C=O)-

$\text{NR}^3(\text{SO}_2)-$, $-(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})\text{O}-$, $-\text{O}(\text{C}=\text{O})-\text{NR}^3(\text{SO}_2)-$, $-\text{NR}^3(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})-$, $-(\text{C}=\text{O})-\text{NR}^3(\text{SO}_2)\text{NR}^3-$, $-\text{O}(\text{C}=\text{O})-\text{NR}^3(\text{SO}_2)-\text{NR}^3-$, or $-\text{NR}^3(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})\text{O}-$;

each R^3 is independently H or substituted or unsubstituted C_1 - C_6 alkyl;

Y^2 is H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

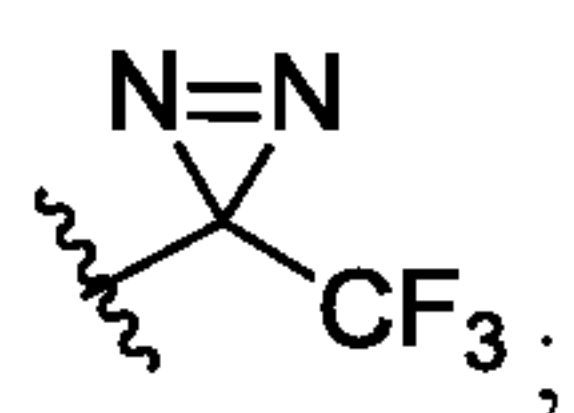
or R^3 and Y^2 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

each W is CR^1 or N with the provision that at least one W is N;

each R^1 is independently H, halogen, $-\text{CN}$, $-\text{OR}^4$, $-\text{SR}^4$, $-\text{N}(\text{R}^4)_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

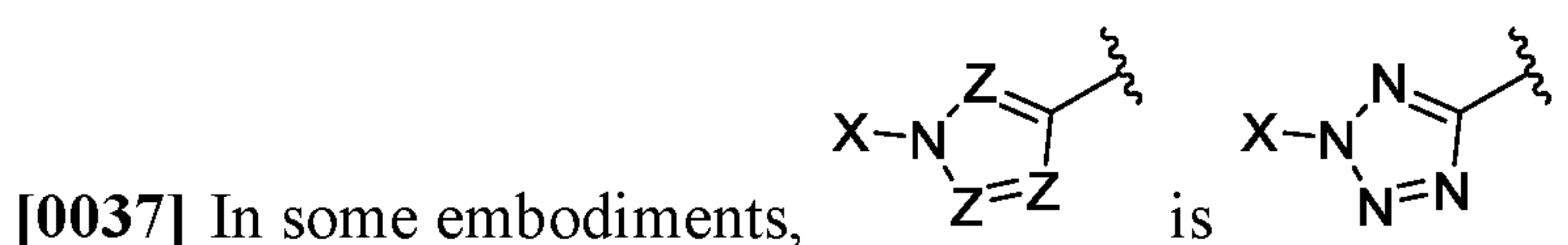
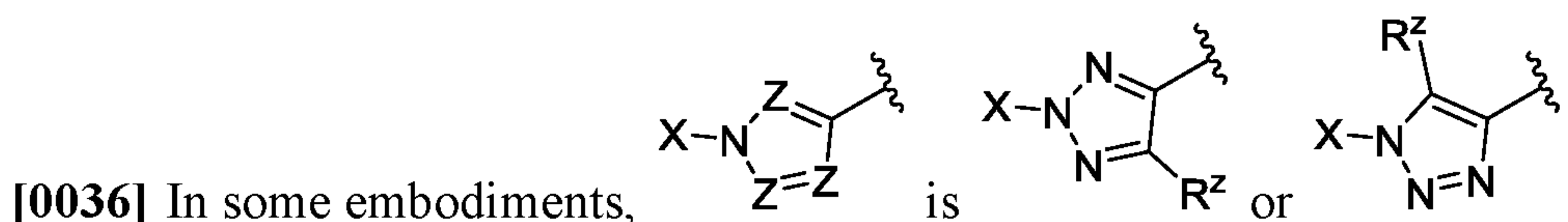
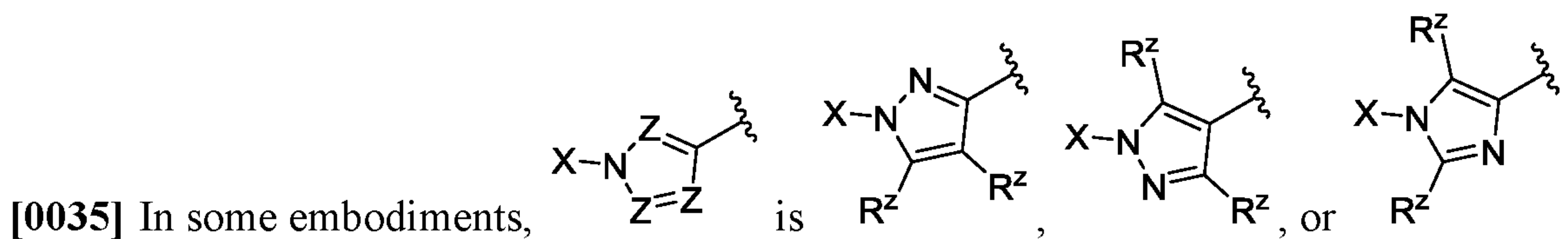
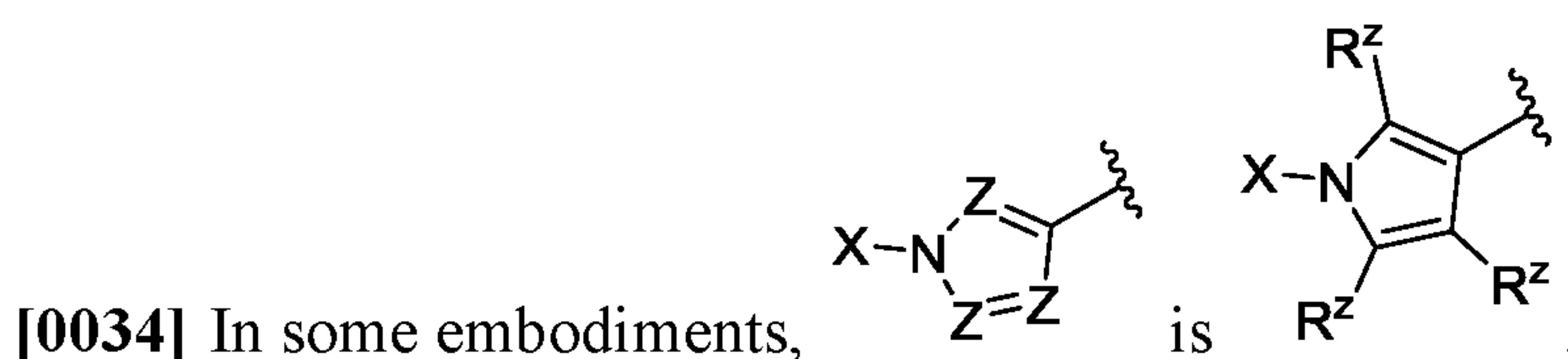
n is 0, 1, 2, 3, 4, or 5;

each R^2 is independently H, halogen, $-\text{N}_3$, $-\text{CN}$, $-\text{OR}^5$, $-\text{SR}^5$, $-(\text{SO}_2)\text{R}^5$, $-\text{N}(\text{R}^5)_2$, $-\text{CO}_2\text{R}^5$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or

unsubstituted aryl, substituted or unsubstituted heteroaryl, or ;

each R^4 is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

each R^5 is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

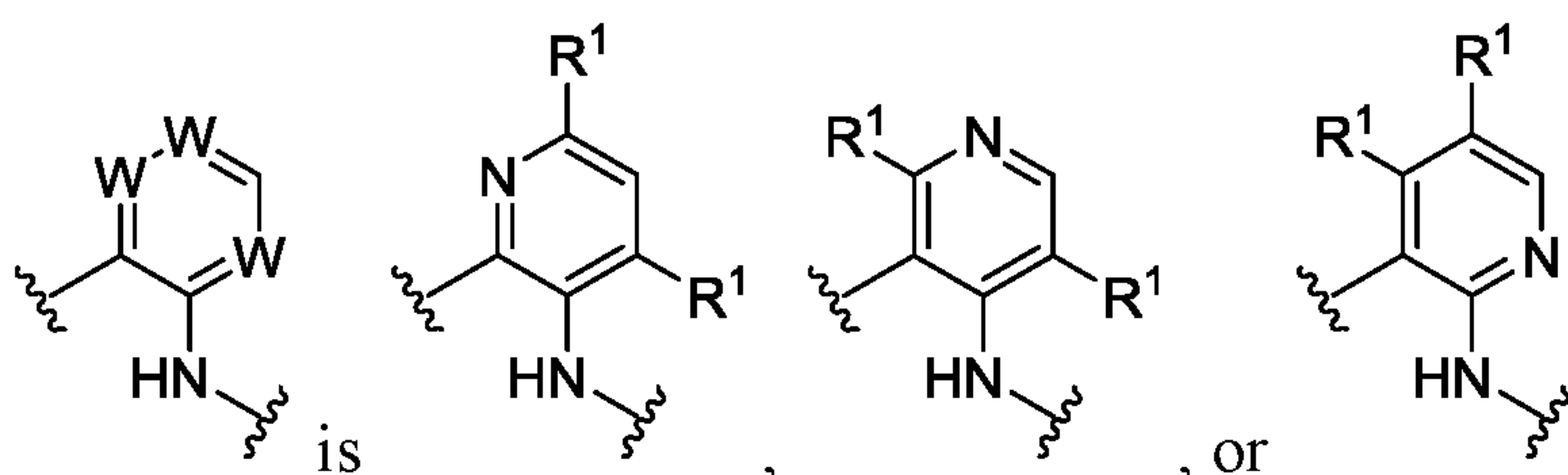


[0038] In some embodiments, each R^Z is independently H or substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, X is substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, X is $-L^1-Y^1$. In some embodiments, L^1 is substituted or unsubstituted C_1 - C_4 alkylene; and Y^1 is substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, L^1 is substituted or unsubstituted C_1 - C_4 alkylene; and Y^1 is substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_6 heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl.

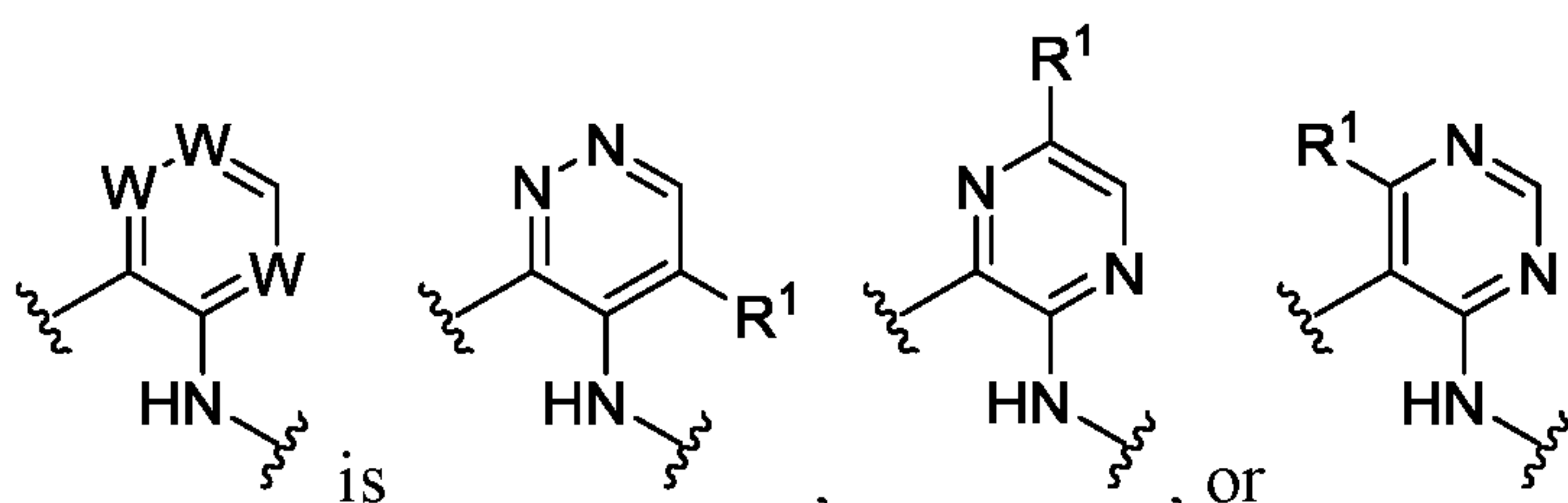
[0039] In some embodiments, X is $-L^2-L^3-Y^2$. In some embodiments, L^2 is substituted or unsubstituted C_1 - C_6 alkylene; L^3 is $-O-$, $-S-$, $-(S=O)-$, $-(SO_2)-$, $-NR^3-$, $-(C=O)-$, $-(C=O)O-$, $-O(C=O)-$, $-(C=O)NR^3-$, $-(C=O)NR^3-O-$, $-NR^3(C=O)-$, $-NR^3(C=O)NR^3-$, $-O(C=O)NR^3-$, $-NR^3(C=O)O-$, $-NR^3(SO_2)NR^3-$, $-NR^3(SO_2)-$, $-(SO_2)NR^3-$, $-(SO_2)NR^3-(C=O)-$, $-(SO_2)NR^3-(C=O)O-$, $-NR^3(SO_2)NR^3-(C=O)-$, or $-NR^3(SO_2)NR^3-(C=O)O-$; each R^3 is independently H or substituted or unsubstituted C_1 - C_6 alkyl; and Y^2 is H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, L^2 is substituted or unsubstituted C_1 - C_4 alkylene; L^3 is $-O-$, $-S-$, $-(S=O)-$, $-(SO_2)-$, $-NR^3-$, $-(C=O)-$, $-(C=O)O-$, $-O(C=O)-$, $-(C=O)NR^3-$, $-(C=O)NR^3-O-$, $-NR^3(C=O)-$, $-NR^3(C=O)NR^3-$, $-O(C=O)NR^3-$, $-NR^3(C=O)O-$, $-NR^3(SO_2)NR^3-$, $-NR^3(SO_2)-$, $-(SO_2)NR^3-$, $-(SO_2)NR^3-(C=O)-$, $-(SO_2)NR^3-(C=O)O-$, $-NR^3(SO_2)NR^3-(C=O)-$, or $-NR^3(SO_2)NR^3-(C=O)O-$.

$\text{NR}^3(\text{SO}_2)\text{NR}^3$ -, $-\text{NR}^3(\text{SO}_2)$ -, $-(\text{SO}_2)\text{NR}^3$ -, $-(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})$ -, $-(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})\text{O}$ -, $-\text{NR}^3(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})$ -, or $-\text{NR}^3(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})\text{O}$ -, each R^3 is independently H or substituted or unsubstituted C_1 - C_4 alkyl; and Y^2 is H, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_6 heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl.

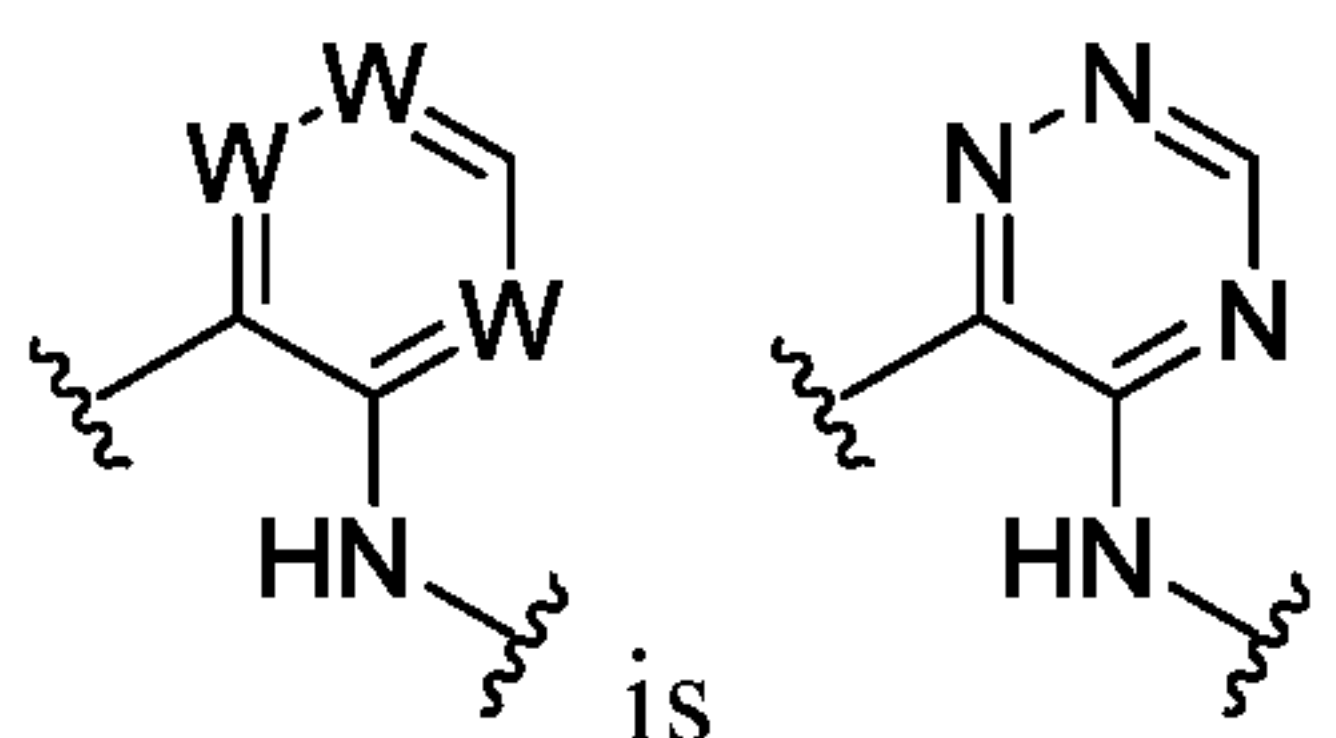
[0040] In some embodiments,



[0041] In some embodiments,

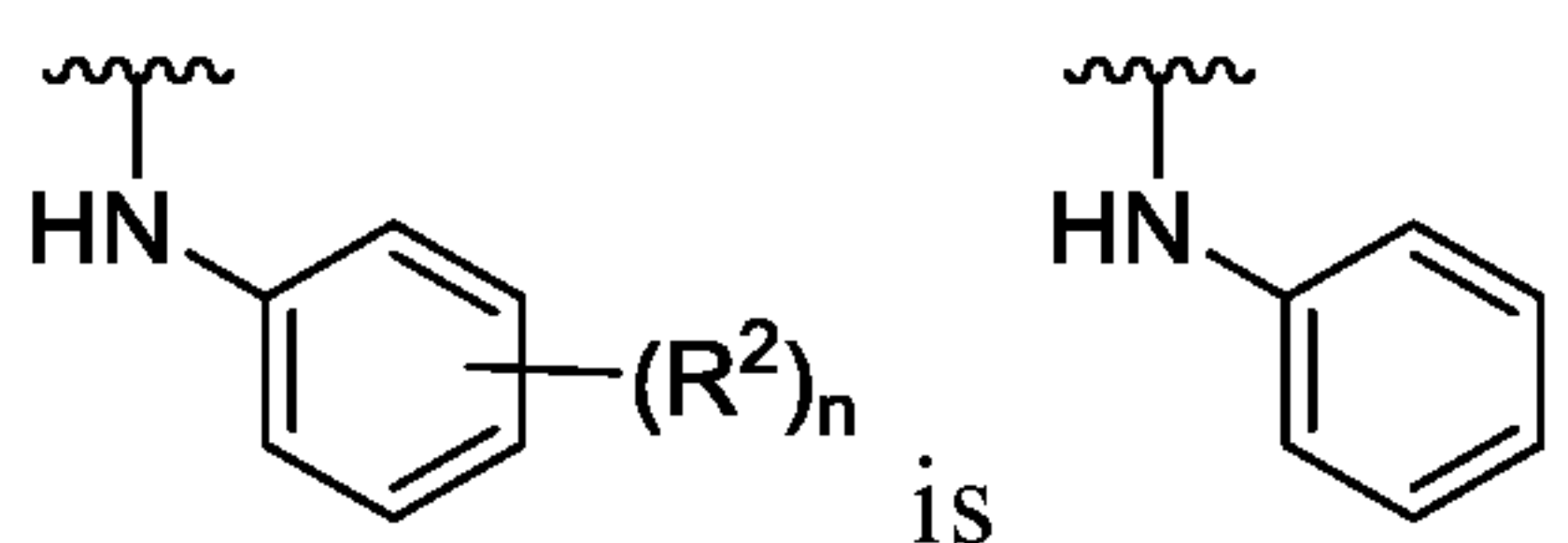


[0042] In some embodiments,

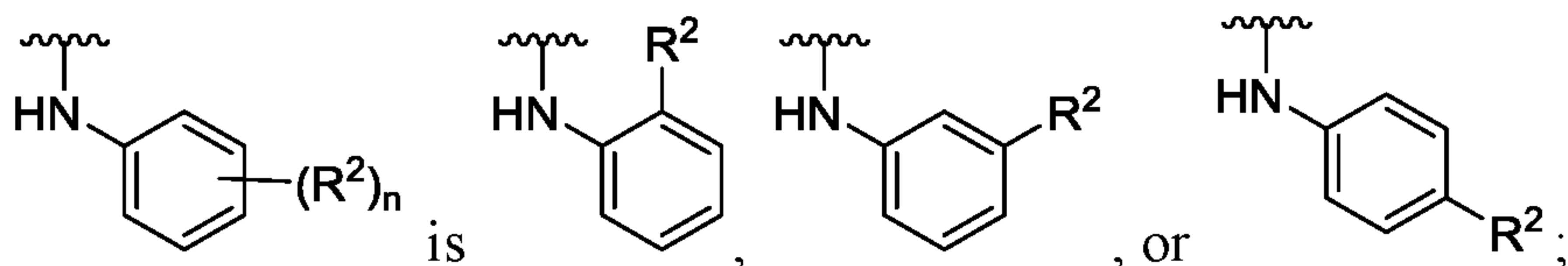


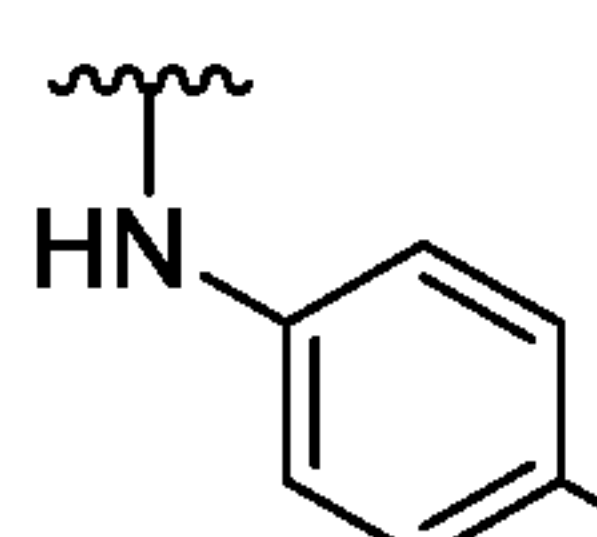
[0043] In some embodiments, each R^1 is independently H, halogen, $-\text{CN}$, $-\text{OR}^4$, $-\text{SR}^4$, $-\text{N}(\text{R}^4)_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

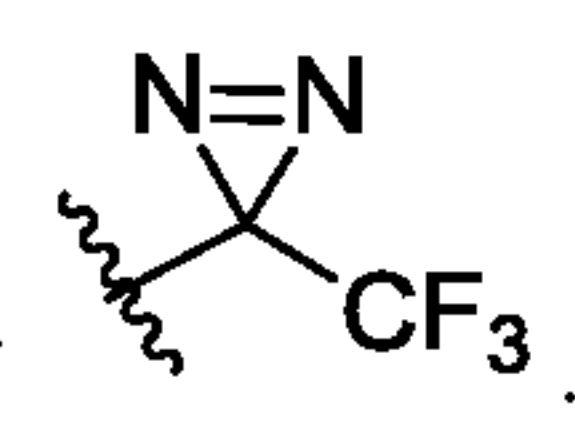
[0044] In some embodiments,

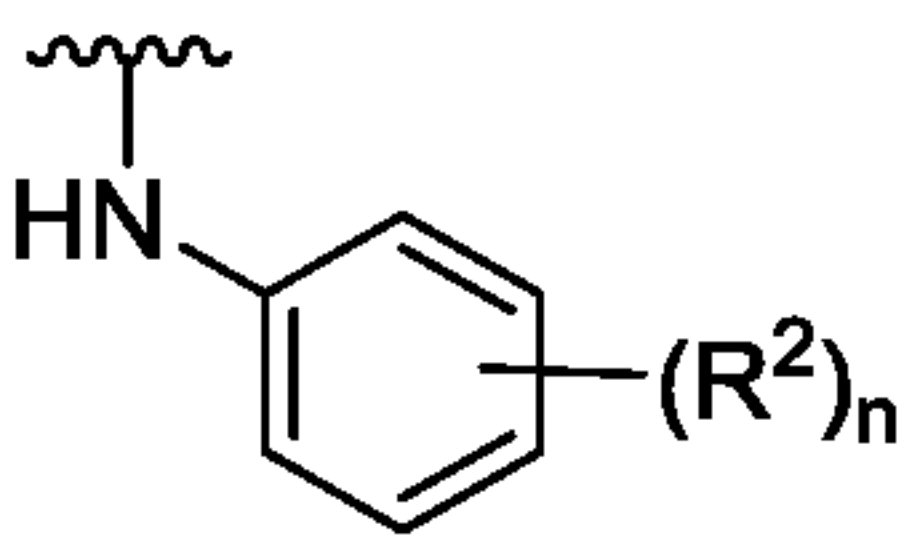
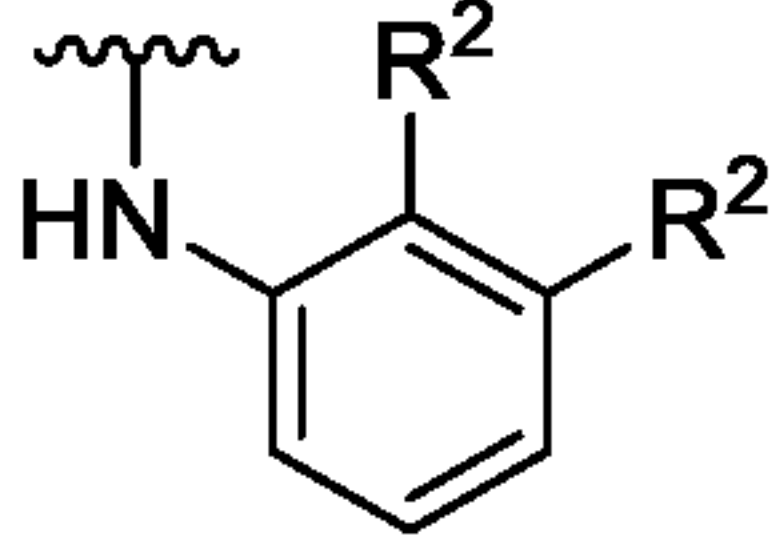
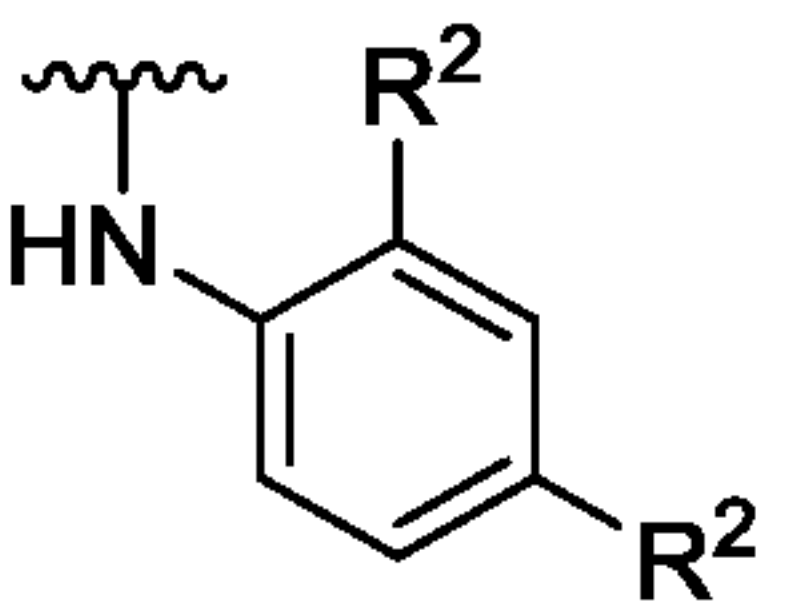
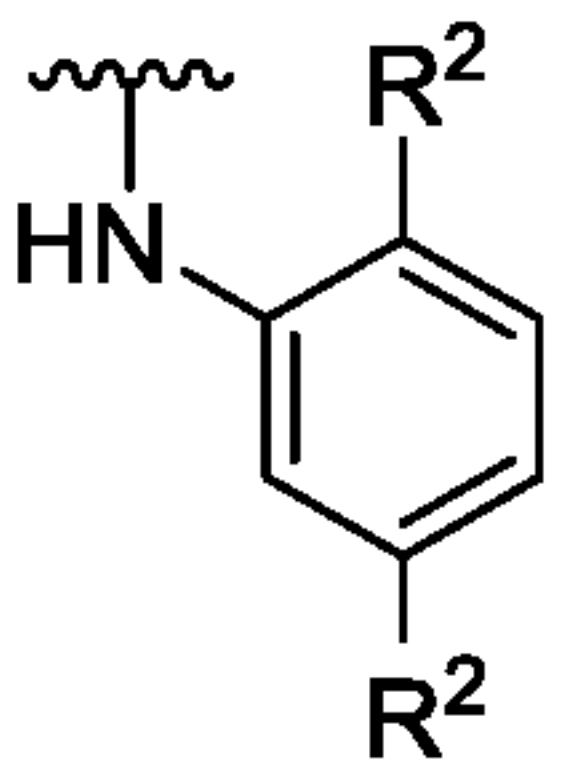
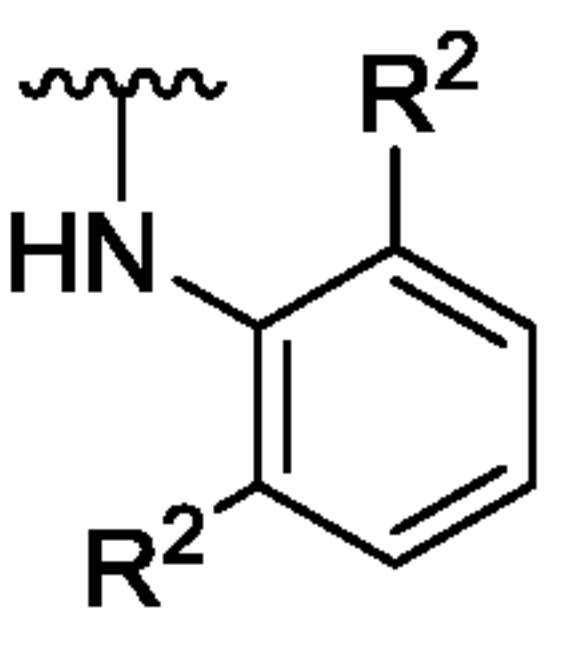
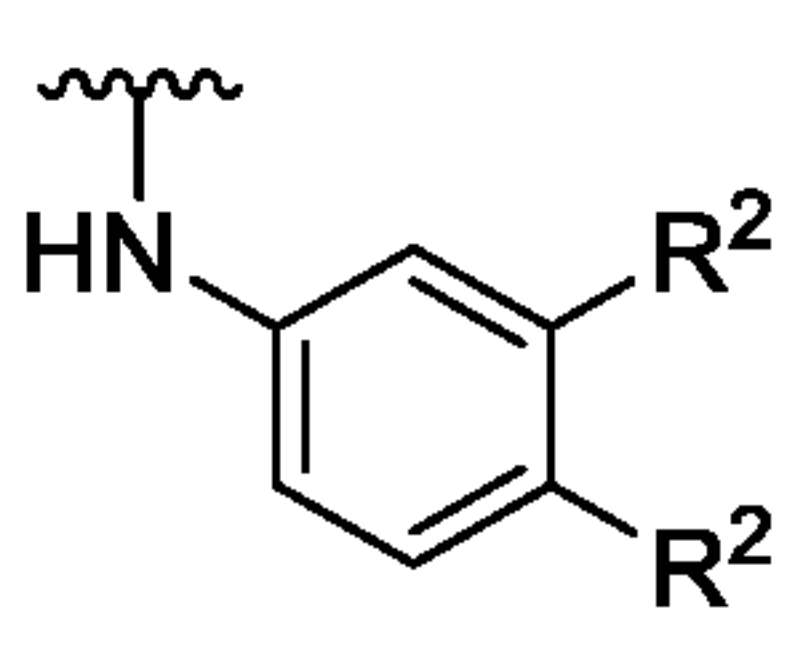
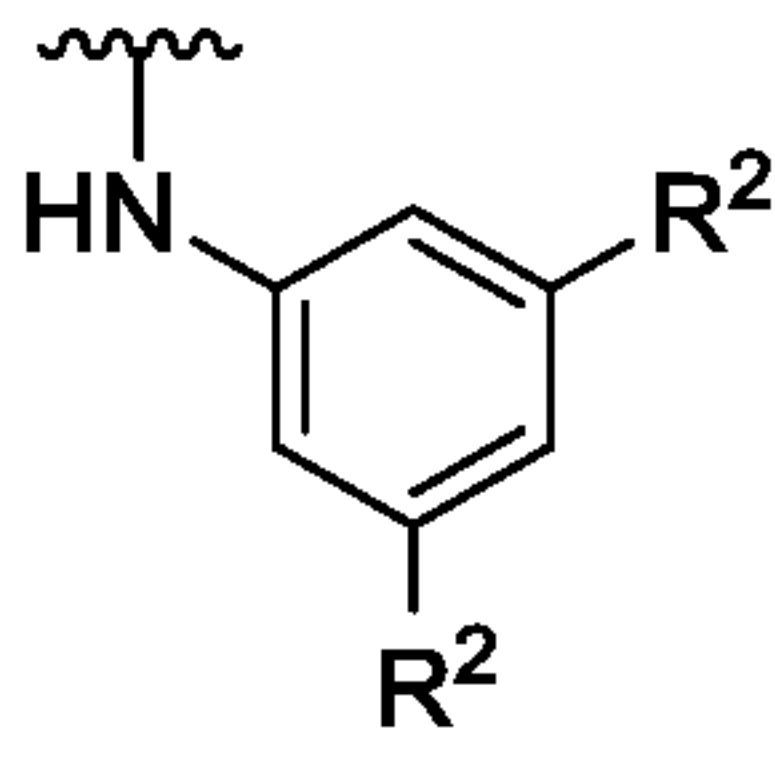
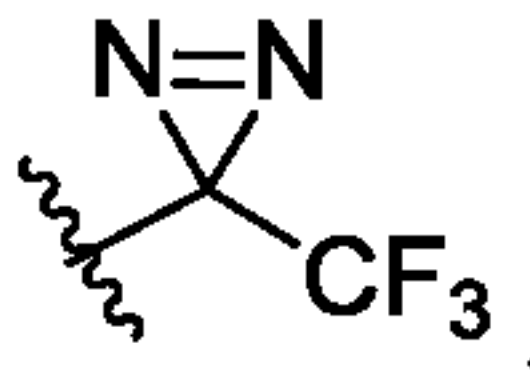


[0045] In some embodiments,

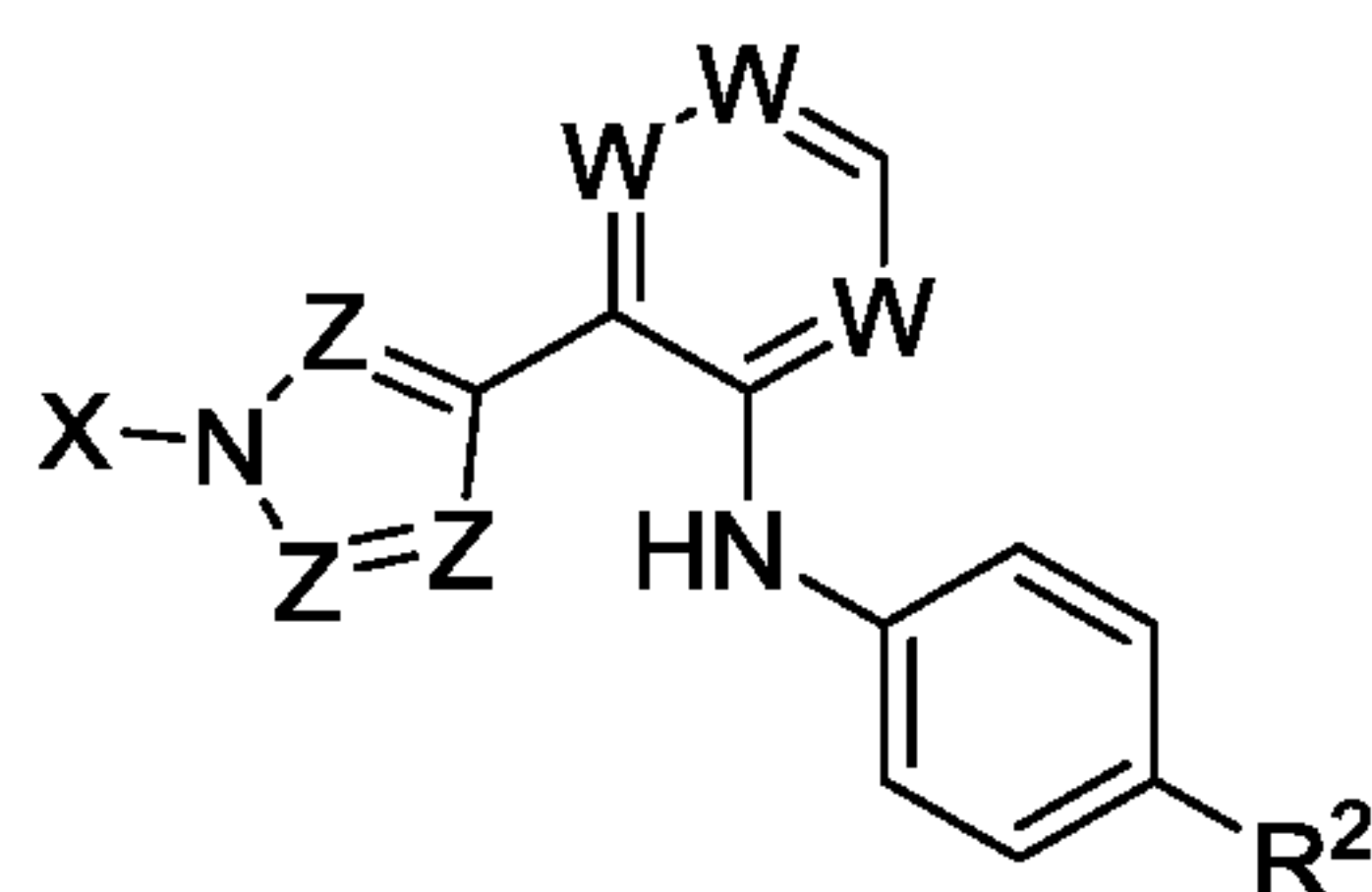


and ; and R^2 is halogen, $-\text{N}_3$, $-\text{OR}^5$, $-(\text{SO}_2)\text{R}^5$, $-\text{CO}_2\text{R}^5$, substituted or unsubstituted

C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, or .

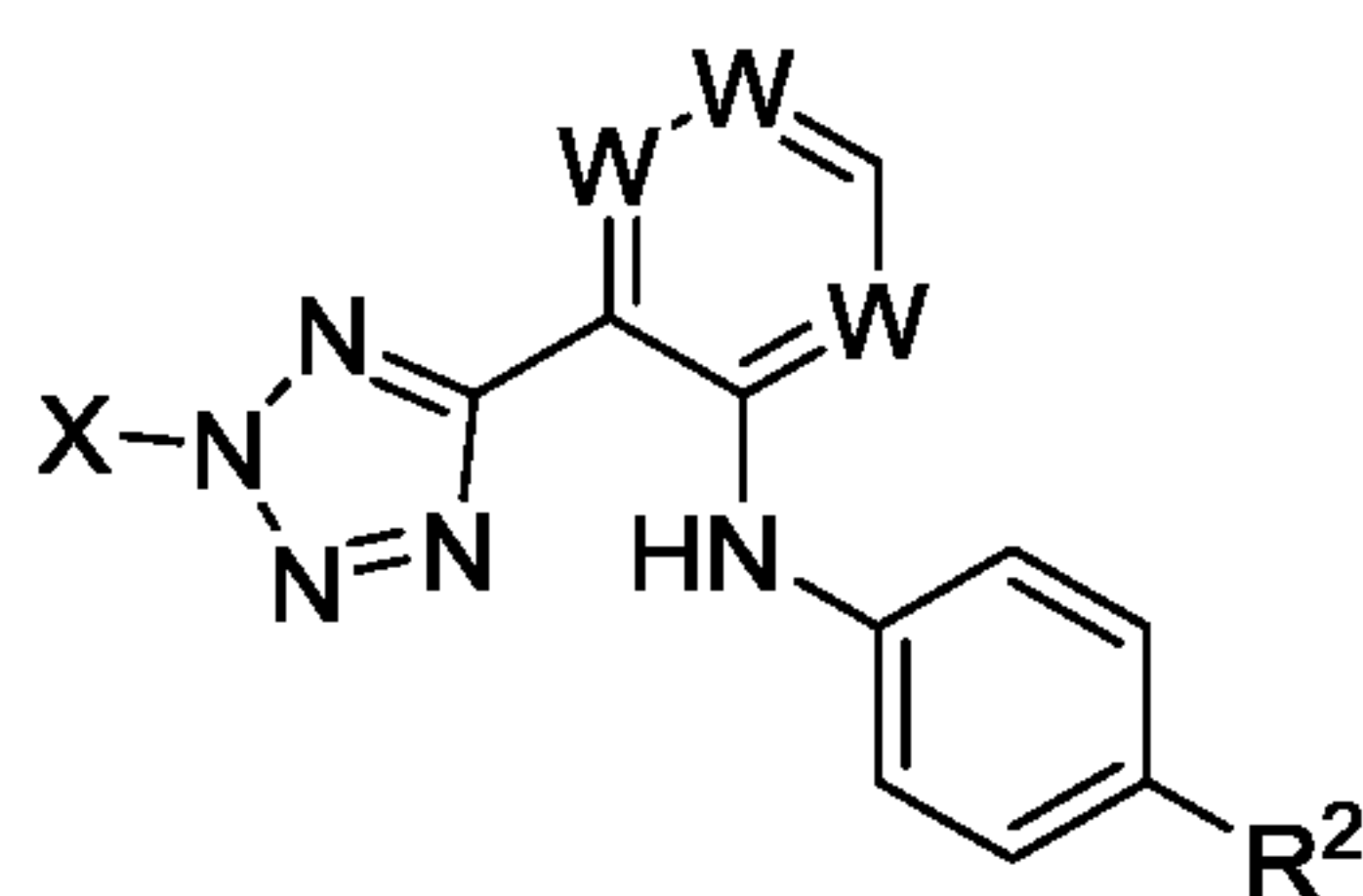
[0046] In some embodiments,  is , , , , , or ; and each R² is independently halogen, -N₃, -OR⁵, -(SO₂)R⁵, -CO₂R⁵, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, or .

[0047] In some embodiments, the compound has the structure of Formula (IIIa), or a pharmaceutically acceptable salt thereof:



Formula (IIIa).

[0048] In some embodiments, the compound has the structure of Formula (IIIb), or a pharmaceutically acceptable salt thereof:



Formula (IIIb).

[0049] In some embodiments, the compound exhibits an IC₅₀ of no more than about 5.000 μM.

[0050] Provided in another aspect is a compound, or pharmaceutically acceptable salt thereof, wherein the compound is a compound from Table 1 or 2, or a pharmaceutically acceptable salt thereof.

[0051] Provided in another aspect is a pharmaceutical composition comprising a pharmaceutically acceptable excipient and any one of the compounds disclosed herein or a pharmaceutically acceptable salt thereof.

[0052] Provided herein is a method for treating a cancer in a subject in need thereof comprising administering a therapeutically effective amount of a compound of any one of the compounds disclosed herein or a pharmaceutically acceptable salt thereof.

INCORPORATION BY REFERENCE

[0053] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0054] Various aspects of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0055] FIG. 1 illustrates a schematic representation of the Hippo signaling network. Hippo pathway components shaded in dark gray indicate components that inhibit YAP/TAZ activity. Hippo pathway components shaded in light gray indicate components that promote YAP/TAZ activity. Pointed and blunt arrowheads indicate activating and inhibitory interactions, respectively. Abbreviations: α -CAT (α -Catenin), AJUB (Ajuba), AMOT (Angiomotin), β -TRCP (β -transducing repeat containing protein), CK1 (Casein Kinase 1), CRB (Crumbs), E-CAD (E-cadherin), EX (Expanded), GPCR (G-protein coupled receptor), HIPK (Homeodomain interacting protein kinase), KIBRA (Kidney brain), LATS (Large tumor suppressor), LGL (Lethal giant larvae), MASK (Multiple ankyrin single KH), MER (Merlin), MOB (Mps one binder), MST (Mammalian sterile 20 like), PALS (Protein Associated with Lin-7), PATJ (Pals1-associated tight junction protein), PP2A (Protein phosphatase 2A), PTPN14 (Protein tyrosine phosphatase non-receptor type 14), RASSF (Ras associated factor), SAV (Salvador), SCRIB (Scribble), SIK (Salt inducible kinase), TAO (Thousand and one amino acid protein), TAZ (transcriptional coactivator with PDZ-binding motif), TEAD (TEA domain protein), VGL4 (Vestigial-like 4), WBP2 (WW domain binding protein 2), YAP (Yes associated protein), ZO (Zonula occludens), ZYX (Zyxin).

[0056] FIG. 2 illustrates a schematic representation of the Hippo signaling pathway regulated by G alpha proteins.

DETAILED DESCRIPTION OF THE DISCLOSURE

Certain Terminology

[0057] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. In this application, the use of “or” means “and/or” unless stated otherwise. Furthermore, use of the term “including” as well as other forms, such as “include,” “includes,” and “included,” is not limiting.

[0058] As used herein, in some embodiments, ranges and amounts are expressed as “about” a particular value or range. About also includes the exact amount. Hence “about 5 μ L” means “about 5 μ L” and also “5 μ L.” Generally, the term “about” includes an amount that is expected to be within experimental error.

[0059] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0060] As used herein, the terms “individual(s),” “subject(s)” and “patient(s)” mean any mammal. In some embodiments, the mammal is a human. In some embodiments, the mammal is a non-human. None of the terms require or are limited to situations characterized by the supervision (e.g. constant or intermittent) of a health care worker (e.g. a doctor, a registered nurse, a nurse practitioner, a physician’s assistant, an orderly, or a hospice worker).

[0061] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0062] "Amino" refers to the $-\text{NH}_2$ radical.

[0063] "Cyano" refers to the $-\text{CN}$ radical.

[0064] "Nitro" refers to the $-\text{NO}_2$ radical.

[0065] "Oxa" refers to the $-\text{O}-$ radical.

[0066] "Oxo" refers to the $=\text{O}$ radical.

[0067] "Thioxo" refers to the $=\text{S}$ radical.

[0068] "Imino" refers to the $=\text{N-H}$ radical.

[0069] "Oximo" refers to the $=\text{N-OH}$ radical.

[0070] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to fifteen carbon atoms (e.g., $\text{C}_1\text{-C}_{15}$ alkyl). In certain embodiments, an alkyl comprises one to thirteen carbon atoms (e.g.,

C₁-C₁₃ alkyl). In certain embodiments, an alkyl comprises one to eight carbon atoms (*e.g.*, C₁-C₈ alkyl). In other embodiments, an alkyl comprises one to five carbon atoms (*e.g.*, C₁-C₅ alkyl). In other embodiments, an alkyl comprises one to four carbon atoms (*e.g.*, C₁-C₄ alkyl). In other embodiments, an alkyl comprises one to three carbon atoms (*e.g.*, C₁-C₃ alkyl). In other embodiments, an alkyl comprises one to two carbon atoms (*e.g.*, C₁-C₂ alkyl). In other embodiments, an alkyl comprises one carbon atom (*e.g.*, C₁ alkyl). In other embodiments, an alkyl comprises five to fifteen carbon atoms (*e.g.*, C₅-C₁₅ alkyl). In other embodiments, an alkyl comprises five to eight carbon atoms (*e.g.*, C₅-C₈ alkyl). In other embodiments, an alkyl comprises two to five carbon atoms (*e.g.*, C₂-C₅ alkyl). In other embodiments, an alkyl comprises three to five carbon atoms (*e.g.*, C₃-C₅ alkyl). In other embodiments, the alkyl group is selected from methyl, ethyl, 1-propyl (*n*-propyl), 1-methylethyl (*iso*-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), 1-pentyl (*n*-pentyl). The alkyl is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -C(O)N(R^a)₂, -N(R^a)C(O)OR^f, -OC(O)-NR^aR^f, -N(R^a)C(O)R^f, -N(R^a)S(O)_tR^f (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tR^f (where t is 1 or 2) and -S(O)_tN(R^a)₂ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl. In some embodiments, an alkyl chain is optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -CN, -R^b-OR^a, -R^b-OC(O)-R^a, -R^b-OC(O)-OR^a, -R^b-OC(O)-N(R^a)₂, -R^b-N(R^a)₂, -R^b-C(O)R^a, -R^b-C(O)OR^a, -R^b-C(O)N(R^a)₂, -R^b-O-R^c-C(O)N(R^a)₂, -R^b-N(R^a)C(O)OR^a, -R^b-N(R^a)C(O)R^a, -R^b-N(R^a)S(O)_tR^a (where t is 1 or 2), -R^b-S(O)_tOR^a (where t is 1 or 2), -R^b-S(O)_tR^a (where t is 1 or 2), and -R^b-S(O)_tN(R^a)₂ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or

alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0071] "Alkoxy" refers to a radical bonded through an oxygen atom of the formula $-O\text{-alkyl}$, where alkyl is an alkyl chain as defined above.

[0072] "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon double bond, and having from two to twelve carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to four carbon atoms. The alkenyl is attached to the rest of the molecule by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^f$, $-OC(O)-NR^aR^f$, $-N(R^a)C(O)R^f$, $-N(R^a)S(O)_tR^f$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^f$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

[0073] "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon triple bond, having from two to twelve carbon atoms. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl has two to four carbon atoms. The alkynyl is attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^f$, $-OC(O)-NR^aR^f$, $-N(R^a)C(O)R^f$, $-N(R^a)S(O)_tR^f$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^f$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

[0074] "Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen,

containing no unsaturation and having from one to twelve carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. In some embodiments, the points of attachment of the alkylene chain to the rest of the molecule and to the radical group are through one carbon in the alkylene chain or through any two carbons within the chain. In certain embodiments, an alkylene comprises one to eight carbon atoms (*e.g.*, C₁-C₈ alkylene). In other embodiments, an alkylene comprises one to five carbon atoms (*e.g.*, C₁-C₅ alkylene). In other embodiments, an alkylene comprises one to four carbon atoms (*e.g.*, C₁-C₄ alkylene). In other embodiments, an alkylene comprises one to three carbon atoms (*e.g.*, C₁-C₃ alkylene). In other embodiments, an alkylene comprises one to two carbon atoms (*e.g.*, C₁-C₂ alkylene). In other embodiments, an alkylene comprises one carbon atom (*e.g.*, C₁ alkylene). In other embodiments, an alkylene comprises five to eight carbon atoms (*e.g.*, C₅-C₈ alkylene). In other embodiments, an alkylene comprises two to five carbon atoms (*e.g.*, C₂-C₅ alkylene). In other embodiments, an alkylene comprises three to five carbon atoms (*e.g.*, C₃-C₅ alkylene). Unless stated otherwise specifically in the specification, an alkylene chain is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -C(O)N(R^a)₂, -N(R^a)C(O)OR^f, -OC(O)-NR^aR^f, -N(R^a)C(O)R^f, -N(R^a)S(O)_tR^f (where *t* is 1 or 2), -S(O)_tOR^a (where *t* is 1 or 2), -S(O)_tR^f (where *t* is 1 or 2), and -S(O)_tN(R^a)₂ (where *t* is 1 or 2) where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl. In some embodiments, an alkylene chain is optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -CN, -R^b-OR^a, -R^b-OC(O)-R^a, -R^b-OC(O)-OR^a, -R^b-OC(O)-N(R^a)₂, -R^b-N(R^a)₂, -R^b-C(O)R^a, -R^b-C(O)OR^a, -R^b-C(O)N(R^a)₂, -R^b-O-R^c-C(O)N(R^a)₂, -R^b-N(R^a)C(O)OR^a, -R^b-N(R^a)C(O)R^a, -R^b-N(R^a)S(O)_tR^a (where *t* is 1 or 2), -R^b-S(O)_tOR^a (where *t* is 1 or 2), -R^b-S(O)_tR^a (where *t* is 1 or 2), and -R^b-S(O)_tN(R^a)₂ (where *t* is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or

alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0075] "Aryl" refers to a radical derived from an aromatic monocyclic or multicyclic hydrocarbon ring system by removing a hydrogen atom from a ring carbon atom. The aromatic monocyclic or multicyclic hydrocarbon ring system contains only hydrogen and carbon from five to eighteen carbon atoms, where at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized $(4n+2)$ π -electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin and naphthalene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-CN$, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl (optionally substituted with one or more halo groups), aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0076] "Aryloxy" refers to a radical bonded through an oxygen atom of the formula $-O$ -aryl, where aryl is as defined above.

[0077] "Aralkyl" refers to a radical of the formula $-R^c$ -aryl where R^c is an alkylene chain as defined above, for example, methylene, ethylene, and the like. The alkylene chain part of the aralkyl radical is optionally substituted as described above for an alkylene chain. The aryl part of the aralkyl radical is optionally substituted as described above for an aryl group.

[0078] "Aralkenyl" refers to a radical of the formula $-R^d$ -aryl where R^d is an alkenylene chain as defined above. The aryl part of the aralkenyl radical is optionally substituted as described above for an aryl group. The alkenylene chain part of the aralkenyl radical is optionally substituted as defined above for an alkenylene group.

[0079] "Aralkynyl" refers to a radical of the formula $-R^e$ -aryl, where R^e is an alkynylene chain as defined above. The aryl part of the aralkynyl radical is optionally substituted as described above for an aryl group. The alkynylene chain part of the aralkynyl radical is optionally substituted as defined above for an alkynylene chain.

[0080] "Carbocyclyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, and in some embodiments, include fused or bridged ring systems, having from three to fifteen carbon atoms. In certain embodiments, a carbocyclyl comprises three to ten carbon atoms. In other embodiments, a carbocyclyl comprises five to seven carbon atoms. The carbocyclyl is attached to the rest of the molecule by a single bond. In some embodiments, the carbocyclyl is saturated, (*i.e.*, containing single C-C bonds only) or unsaturated (*i.e.*, containing one or more double bonds or triple bonds.) A fully saturated carbocyclyl radical is also referred to as "cycloalkyl." Examples of monocyclic cycloalkyls include, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. In certain embodiments, a cycloalkyl comprises three to eight carbon atoms (*e.g.*, C₃-C₈ cycloalkyl). In other embodiments, a cycloalkyl comprises three to seven carbon atoms (*e.g.*, C₃-C₇ cycloalkyl). In other embodiments, a cycloalkyl comprises three to six carbon atoms (*e.g.*, C₃-C₆ cycloalkyl). In other embodiments, a cycloalkyl comprises three to five carbon atoms (*e.g.*, C₃-C₅ cycloalkyl). In other embodiments, a cycloalkyl comprises three to four carbon atoms (*e.g.*, C₃-C₄ cycloalkyl). An unsaturated carbocyclyl is also referred to as "cycloalkenyl." Examples of monocyclic cycloalkenyls include, *e.g.*, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Polycyclic carbocyclyl radicals include, for example, adamantyl, norbornyl (*i.e.*, bicyclo[2.2.1]heptanyl), norbornenyl, decalyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, the term "carbocyclyl" is meant to include carbocyclyl radicals that are optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -CN, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where *t* is 1 or 2), $-R^b-S(O)_tOR^a$ (where *t* is 1 or 2), $-R^b-S(O)_tR^a$ (where *t* is 1 or 2), and $-R^b-S(O)_tN(R^a)_2$ (where *t* is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a

straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0081] "Carbocyclalkyl" refers to a radical of the formula $-R^c$ -carbocyclalkyl where R^c is an alkylene chain as defined above. The alkylene chain and the carbocyclalkyl radical is optionally substituted as defined above.

[0082] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo substituents.

[0083] "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. In some embodiments, the alkyl part of the fluoroalkyl radical is optionally substituted as defined above for an alkyl group.

[0084] "Heterocyclalkyl" or "heterocycle" refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen, and sulfur. Unless stated otherwise specifically in the specification, the heterocyclalkyl radical is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which include fused or bridged ring systems in some embodiments. The heteroatoms in the heterocyclalkyl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocyclalkyl radical is partially or fully saturated. In some embodiments, the heterocyclalkyl is attached to the rest of the molecule through any atom of the ring(s). In some embodiments, the heterocyclalkyl is saturated, (*i.e.*, containing single bonds only) or unsaturated (*i.e.*, containing one or more double bonds or triple bonds.) A fully saturated heterocyclalkyl radical is also referred to as "heterocycloalkyl." Examples of such heterocyclalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranlyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, the term "heterocyclalkyl" is meant to include heterocyclalkyl radicals as defined above that are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclalkyl, optionally substituted carbocyclalkyl, optionally substituted heterocyclalkyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -CN,

$-R^b-CN$, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0085] "Heteroalkyl" refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen (*e.g.* $-NH-$, $-N(alkyl)-$, sulfur, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C_1-C_6 heteroalkyl. In some embodiments, the alkyl part of the heteroalkyl radical is optionally substituted as defined for an alkyl group.

[0086] A "heterocycloalkyl" or "heteroalicyclic" group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. In some embodiments, a heterocycloalkyl is fused with an aryl or heteroaryl. In some embodiments, the heterocycloalkyl is oxazolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidin-2-onyl, pyrrolidine-2,5-dithionyl, pyrrolidine-2,5-dionyl, pyrrolidinonyl, imidazolidinyl, imidazolidin-2-onyl, or thiazolidin-2-onyl. The term heteroalicyclic also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. In one aspect, a heterocycloalkyl is a C_2-C_{10} heterocycloalkyl. In one aspect, a heterocycloalkyl is a C_2-C_6 heterocycloalkyl. In another aspect, a heterocycloalkyl is a C_4-C_{10} heterocycloalkyl. In some embodiments, a heterocycloalkyl contains 0-2 N atoms in the ring. In some embodiments, a heterocycloalkyl contains 0-2 N atoms, 0-2 O atoms and 0-1 S atoms in the ring.

[0087] "Heterocyclalkyl" refers to a radical of the formula $-R^c$ -heterocycl where R^c is an alkylene chain as defined above. If the heterocycl is a nitrogen-containing heterocycl, the heterocycl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclalkyl radical is optionally substituted as defined above for an alkylene chain. The heterocycl part of the heterocyclalkyl radical is optionally substituted as defined above for a heterocycl group.

[0088] "Heterocyclalkoxy" refers to a radical bonded through an oxygen atom of the formula $-O-R^c$ -heterocycl where R^c is an alkylene chain as defined above. If the heterocycl is a

nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heterocyclyl part of the heterocyclylalkoxy radical is optionally substituted as defined above for a heterocyclyl group.

[0089] "Heteroaryl" refers to a radical derived from a 3- to 18-membered aromatic ring radical that comprises two to seventeen carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. As used herein, in some embodiments, the heteroaryl radical is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, wherein at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized $(4n+2)$ π -electron system in accordance with the Hückel theory. Heteroaryl includes fused or bridged ring systems. The heteroatom(s) in the heteroaryl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl is attached to the rest of the molecule through any atom of the ring(s). Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolynyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolynyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolynyl, isoindolynyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolynyl, isoquinolynyl, tetrahydroquinolynyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl,

thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pyridinyl, and thiophenyl (*i.e.* thienyl). In some embodiments, the heteroaryl groups include monocyclic heteroaryls and bicyclic heteroaryls. Monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. Bicyclic heteroaryls include indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. In some embodiments, a heteroaryl contains 0-4 N atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms in the ring. In some embodiments, a heteroaryl contains 0-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. Unless stated otherwise specifically in the specification, the term "heteroaryl" is meant to include heteroaryl radicals as defined above which are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0090] "*N*-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. An *N*-heteroaryl radical is optionally substituted as described above for heteroaryl radicals.

[0091] "*C*-heteroaryl" refers to a heteroaryl radical as defined above and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a carbon atom in the heteroaryl radical. A *C*-heteroaryl radical is optionally substituted as described above for heteroaryl radicals.

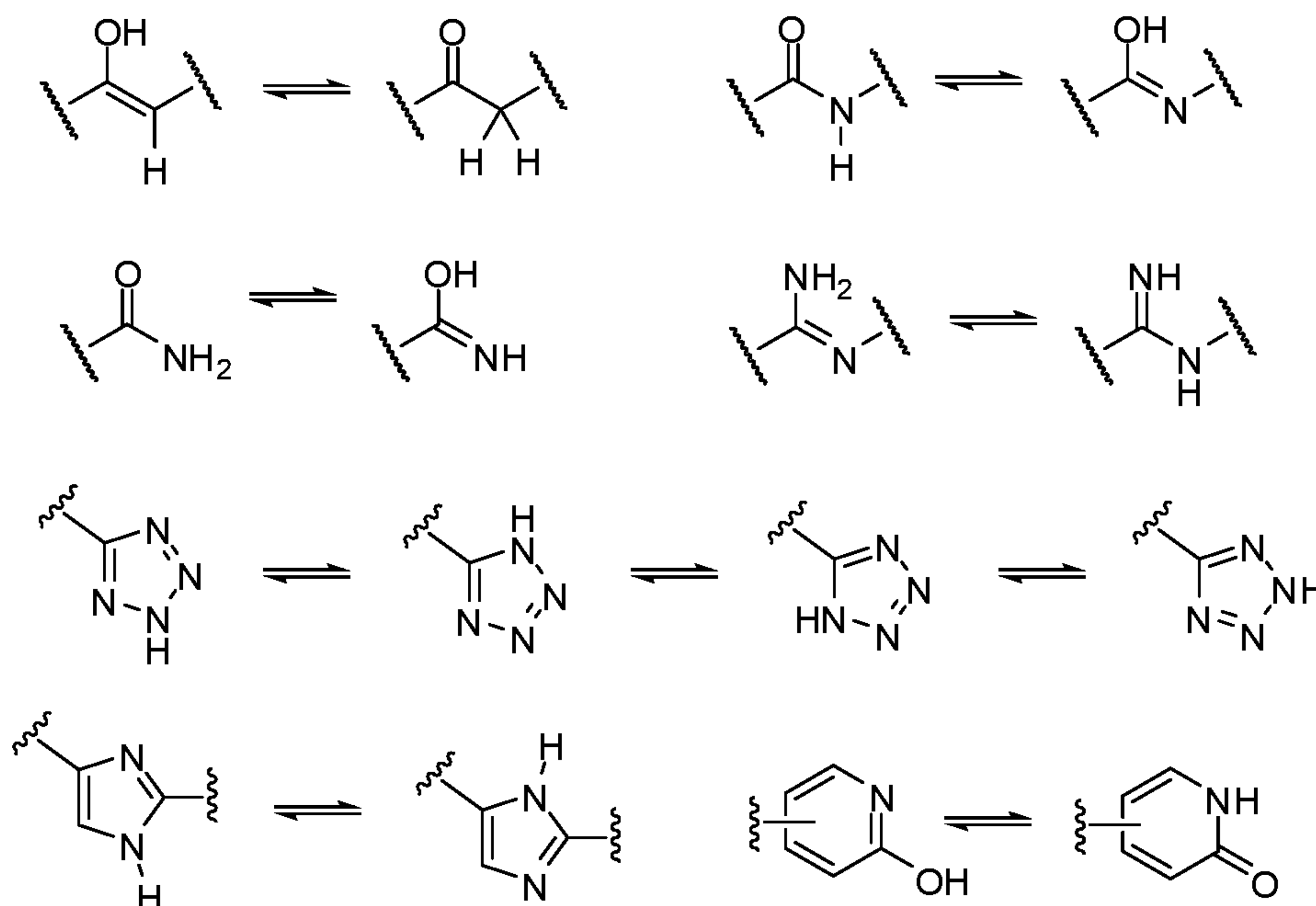
[0092] "Heteroaryloxy" refers to radical bonded through an oxygen atom of the formula –O-heteroaryl, where heteroaryl is as defined above.

[0093] "Heteroarylalkyl" refers to a radical of the formula –R^c-heteroaryl, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkyl radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkyl radical is optionally substituted as defined above for a heteroaryl group.

[0094] "Heteroarylalkoxy" refers to a radical bonded through an oxygen atom of the formula –O-R^c-heteroaryl, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkoxy radical is optionally substituted as defined above for a heteroaryl group.

[0095] In some embodiments, the compounds disclosed herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that are defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. Unless stated otherwise, it is intended that all stereoisomeric forms of the compounds disclosed herein are contemplated by this disclosure. When the compounds described herein contain alkene double bonds, and unless specified otherwise, it is intended that this disclosure includes both *E* and *Z* geometric isomers (*e.g.*, *cis* or *trans*.) Likewise, all possible isomers, as well as their racemic and optically pure forms, and all tautomeric forms are also intended to be included. The term "geometric isomer" refers to *E* or *Z* geometric isomers (*e.g.*, *cis* or *trans*) of an alkene double bond. The term "positional isomer" refers to structural isomers around a central ring, such as *ortho*-, *meta*-, and *para*- isomers around a benzene ring.

[0096] A "tautomer" refers to a molecule wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. The compounds presented herein, in certain embodiments, exist as tautomers. In circumstances where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers depends on several factors, including physical state, temperature, solvent, and pH. Some examples of tautomeric equilibrium include:



[0097] "Optional" or "optionally" means that a subsequently described event or circumstance may or may not occur and that the description includes instances when the event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

[0098] The term "optionally substituted" or "substituted" means that the referenced group is optionally substituted with one or more additional group(s). In some other embodiments, optional substituents are individually and independently selected from D, halogen, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, -OH, -CO₂H, -CO₂alkyl, -C(=O)NH₂, -C(=O)NH(alkyl), -C(=O)N(alkyl)₂, -S(=O)₂NH₂, -S(=O)₂NH(alkyl), -S(=O)₂N(alkyl)₂, -CH₂CO₂H, -CH₂CO₂alkyl, -CH₂C(=O)NH₂, -CH₂C(=O)NH(alkyl), -CH₂C(=O)N(alkyl)₂, -CH₂S(=O)₂NH₂, -CH₂S(=O)₂NH(alkyl), -CH₂S(=O)₂N(alkyl)₂, alkyl, alkenyl, alkynyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some embodiments, optional substituents are individually and independently selected from D, halogen, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, -OH, -CO₂H, -CO₂alkyl, -C(=O)NH₂, -C(=O)NH(alkyl), -C(=O)N(alkyl)₂, -S(=O)₂NH₂, -S(=O)₂NH(alkyl), -S(=O)₂N(alkyl)₂, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some other embodiments, optional substituents are independently selected from D, halogen, -CN, -NH₂, -NH(CH₃), -N(CH₃)₂, -OH, -CO₂H, -CO₂(C₁-C₄alkyl), -C(=O)NH₂, -C(=O)NH(C₁-C₄alkyl), -C(=O)N(C₁-C₄alkyl)₂, -S(=O)₂NH₂, -S(=O)₂NH(C₁-C₄alkyl), -S(=O)₂N(C₁-C₄alkyl)₂, C₁-C₄alkyl, C₃-C₆cycloalkyl, C₁-C₄fluoroalkyl, C₁-

C₄heteroalkyl, C₁-C₄alkoxy, C₁-C₄fluoroalkoxy, -SC₁-C₄alkyl, -S(=O)C₁-C₄alkyl, and -S(=O)₂C₁-C₄alkyl. In some embodiments, optional substituents are independently selected from D, halogen, -CN, -NH₂, -OH, -NH(CH₃), -N(CH₃)₂, -CH₃, -CH₂CH₃, -CF₃, -OCH₃, and -OCF₃. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some embodiments, substituted groups are substituted with one of the preceding groups. In some embodiments, an optional substituent on an aliphatic carbon atom (acyclic or cyclic) includes oxo (=O). In some embodiments, an optional substituent on a sulfur atom includes one or two oxo (=O) groups.

[0099] "Pharmaceutically acceptable salt" includes both acid and base addition salts. A pharmaceutically acceptable salt of any one of the compounds described herein is intended to encompass any and all pharmaceutically suitable salt forms. Pharmaceutically acceptable salts of the compounds described herein are optionally pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts.

[00100] "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like. Also included are salts that are formed with organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Exemplary salts thus include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates, propionates, caprylates, isobutyrate, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science*, 66:1-19 (1997), which is hereby incorporated by reference in its entirety). In some embodiments, acid addition salts of basic compounds are prepared by contacting the free base forms with a sufficient amount of the desired acid to produce the salt according to methods and techniques with which a skilled artisan is familiar.

[00101] "Pharmaceutically acceptable base addition salt" refers to those salts that retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. In some embodiments, pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts, and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, for example, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, *N,N*-dibenzylethylenediamine, chlorprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, *N*-methylglucamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins, and the like. See Berge et al., *supra*.

[00102] As used herein, "treatment" or "treating" or "palliating" or "ameliorating" are used interchangeably herein. These terms refers to an approach for obtaining beneficial or desired results including but not limited to therapeutic benefit and/or a prophylactic benefit. By "therapeutic benefit" is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient is afflicted with the underlying disorder in some embodiments. For prophylactic benefit, in some embodiments, the compositions are administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease has not been made.

[00103] "Prodrug" is meant to indicate a compound that is converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. In some embodiments, a prodrug is inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, e.g., Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam)).

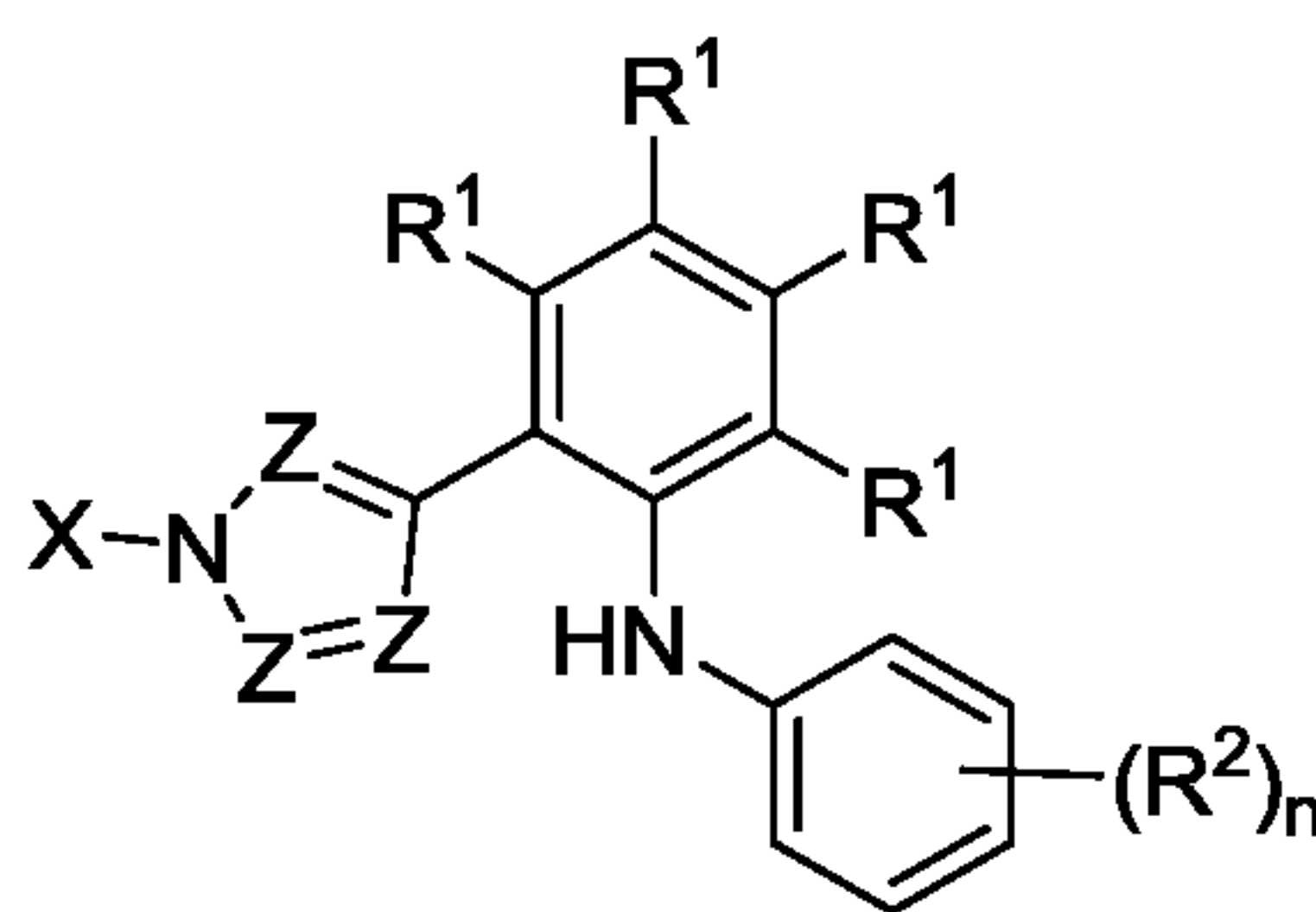
[00104] A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein.

[00105] The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound *in vivo* when such prodrug is administered to a mammalian subject. In some embodiments, prodrugs of an active compound, as described herein, are prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino, or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol or amine functional groups in the active compounds and the like.

Compounds

[00106] In some embodiments, the compounds disclosed herein are tetrazole compounds.

[00107] Provided in one aspect is a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein:

each Z is independently N or CR^Z;

each R^Z is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

X is substituted or unsubstituted C₂-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, unsubstituted aryl, substituted or unsubstituted heteroaryl, -L¹-Y¹,

or $-L^2-L^3-Y^2$;

L^1 is substituted or unsubstituted C_1 - C_6 alkylene;

Y^1 is substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^2 is absent or substituted or unsubstituted C_1 - C_6 alkylene;

L^3 is $-O-$, $-S-$, $-(S=O)-$, $-(SO_2)-$, $-NR^3-$, $-(C=O)-$, $-(C=O)O-$, $-O(C=O)-$, $-(C=O)NR^3-$, $-(C=O)NR^3-O-$, $-O-NR^3(C=O)-$, $-NR^3(C=O)-$, $-NR^3(C=O)NR^3-$, $-O(C=O)NR^3-$, $-NR^3(C=O)O-$, $-NR^3(SO_2)NR^3-$, $-NR^3(SO_2)-$, $-(SO_2)NR^3-$, $-(SO_2)NR^3-(C=O)-$, $-(C=O)-NR^3(SO_2)-$, $-(SO_2)NR^3-(C=O)O-$, $-O(C=O)-NR^3(SO_2)-$, $-NR^3(SO_2)NR^3-(C=O)-$, $-(C=O)-NR^3(SO_2)NR^3-$, $-O(C=O)-NR^3(SO_2)-NR^3-$, or $-NR^3(SO_2)NR^3-(C=O)O-$;

each R^3 is independently H or substituted or unsubstituted C_1 - C_6 alkyl;

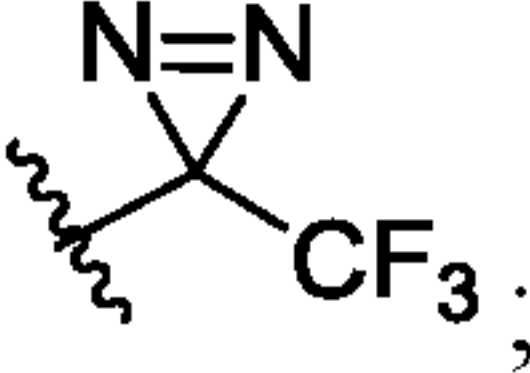
Y^2 is H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or R^3 and Y^2 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

each R^1 is independently H, halogen, $-CN$, $-OR^4$, $-SR^4$, $-N(R^4)_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

n is 1, 2, 3, 4, or 5;

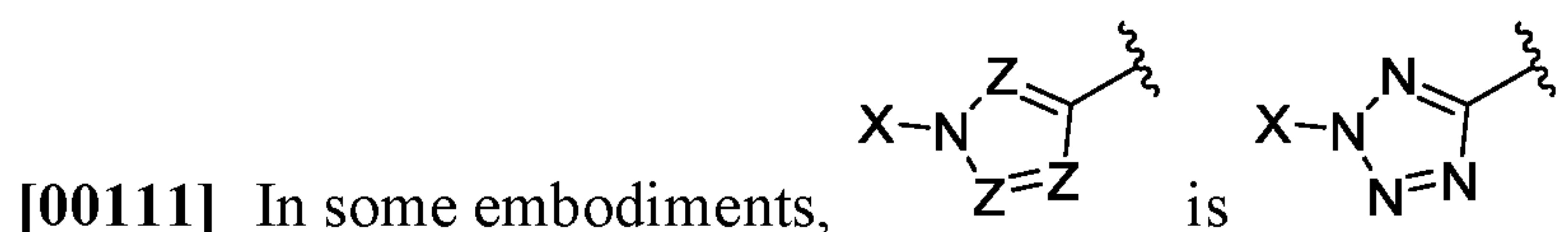
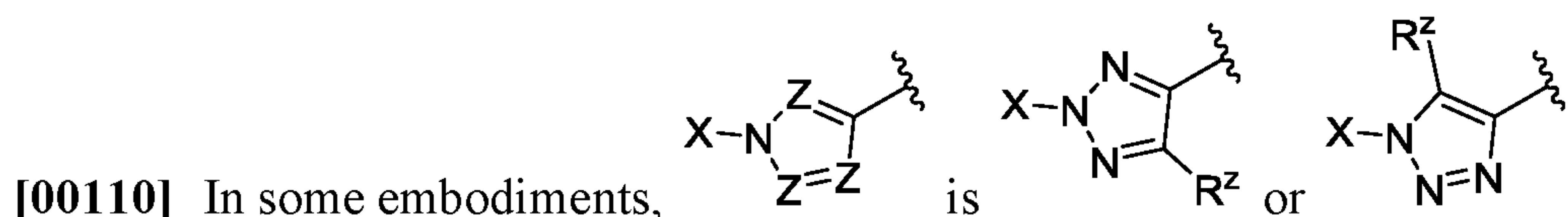
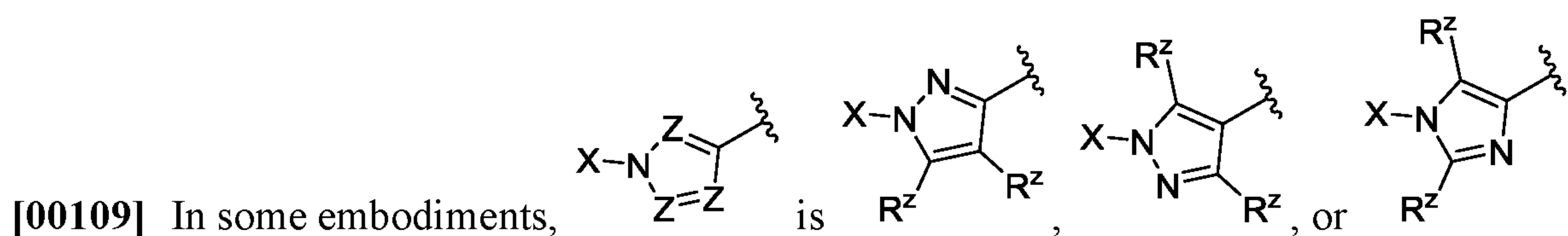
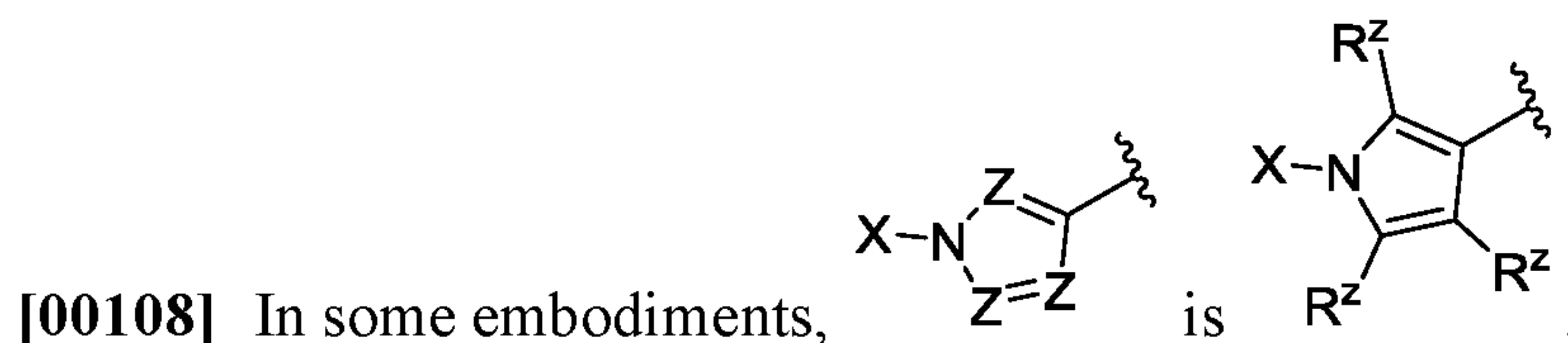
each R^2 is independently halogen, $-N_3$, $-CN$, $-OR^5$, $-SR^5$, $-(SO_2)R^5$, $-N(R^5)_2$, $-CO_2R^5$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or

unsubstituted aryl, substituted or unsubstituted heteroaryl, or ;

each R^4 is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or

unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

each R^5 is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.



[00112] In some embodiments, each R^Z is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, each R^Z is independently H, substituted or unsubstituted C_1 - C_6 alkyl, or substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, each R^Z is independently H or substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^Z is independently H or substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, each R^Z is independently H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-C(CH_3)_3$.

[00113] In some embodiments, each R^Z is independently H. In some embodiments, each R^Z is independently substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, each R^Z is independently $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$. In some embodiments, each R^Z is independently

substituted or unsubstituted C₁-C₆heteroalkyl. In some embodiments, each R^z is independently substituted or unsubstituted C₁-C₄heteroalkyl. In some embodiments, each R^z is independently substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, each R^z is independently substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, each R^z is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R^z is independently substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, each R^z is independently substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, each R^z is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, each R^z is independently substituted or unsubstituted aralkyl. In some embodiments, each R^z is independently substituted or unsubstituted benzyl. In some embodiments, each R^z is independently substituted or unsubstituted aryl. In some embodiments, each R^z is independently substituted or unsubstituted phenyl. In some embodiments, each R^z is independently substituted or unsubstituted heteroaryl. In some embodiments, each R^z is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[00114] In some embodiments, X is substituted or unsubstituted C₂-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00115] In some embodiments, X is substituted or unsubstituted C₂-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, or substituted or unsubstituted heteroaryl.

[00116] In some embodiments, X is substituted or unsubstituted C₂-C₆alkyl. In some embodiments, X is substituted or unsubstituted C₂-C₄alkyl. In some embodiments, X is -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃. In some embodiments, X is substituted or unsubstituted C₁-C₆haloalkyl. In some embodiments, X is substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, X is -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃. In some embodiments, X is substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, X is substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, X is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, X is substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, X is substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, X is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, X is unsubstituted aryl. In some embodiments, X is phenyl. In some embodiments, X is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[00117] In some embodiments, X is -L¹-Y¹. In some embodiments, L¹ is substituted or unsubstituted C₁-C₆alkylene. In some embodiments, L¹ is substituted or unsubstituted C₁-C₄alkylene. In some embodiments, L¹ is -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, or -CH₂CH₂CH₂CH₂-. In some embodiments, Y¹ is substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, Y¹ is substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, Y¹ is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, Y¹ is

substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, Y¹ is substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, Y¹ is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, Y¹ is substituted or unsubstituted aryl. In some embodiments, Y¹ is substituted or unsubstituted phenyl. In some embodiments, Y¹ is substituted or unsubstituted heteroaryl. In some embodiments, Y¹ is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[00118] In some embodiments, L¹ is substituted or unsubstituted C₁-C₄alkylene; and Y¹ is substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀ heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, L¹ is substituted or unsubstituted C₁-C₄alkylene; and Y¹ is substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl.

[00119] In some embodiments, X is -L²-L³-Y². In some embodiments, L² is absent. In some embodiments, L² is substituted or unsubstituted C₁-C₆alkylene. In some embodiments, L² is substituted or unsubstituted C₁-C₄alkylene. In some embodiments, L² is -CH₂-, -CH₂ CH₂-, -CH₂ CH₂ CH₂-, or -CH₂ CH₂ CH₂ CH₂-. In some embodiments, L³ is -O-. In some embodiments, L³ is -S-. In some embodiments, L³ is -(S=O)-. In some embodiments, L³ is -(SO₂)-. In some embodiments, L³ is -NR³-. In some embodiments, L³ is -(C=O)-. In some embodiments, L³ is -(C=O)O-. In some embodiments, L³ is -O(C=O)-. In some embodiments, L³ is -(C=O)NR³-. In some embodiments, L³ is -(C=O)NR³-O-. In some embodiments, L³ is -O-NR³(C=O)-. In some embodiments, L³ is -NR³(C=O)-. In some embodiments, L³ is -NR³(C=O)NR³-. In some

embodiments, L^3 is $-O(C=O)NR^3-$. In some embodiments, L^3 is $-NR^3(C=O)O-$. In some embodiments, L^3 is $-NR^3(SO_2)NR^3-$. In some embodiments, L^3 is $-NR^3(SO_2)-$. In some embodiments, L^3 is $-(SO_2)NR^3-$. In some embodiments, L^3 is $-(SO_2)NR^3-(C=O)-$. In some embodiments, L^3 is $-(C=O)-NR^3(SO_2)-$. In some embodiments, L^3 is $-(SO_2)NR^3-(C=O)O-$. In some embodiments, L^3 is $-O(C=O)-NR^3(SO_2)-$. In some embodiments, L^3 is $-NR^3(SO_2)NR^3-(C=O)-$. In some embodiments, L^3 is $-(C=O)-NR^3(SO_2)NR^3-$. In some embodiments, L^3 is $-O(C=O)-NR^3(SO_2)-NR^3-$. In some embodiments, L^3 is $-NR^3(SO_2)NR^3-(C=O)O-$. In some embodiments, each R^3 is independently H. In some embodiments, each R^3 substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^3 is substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, each R^3 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-C(CH_3)_3$.

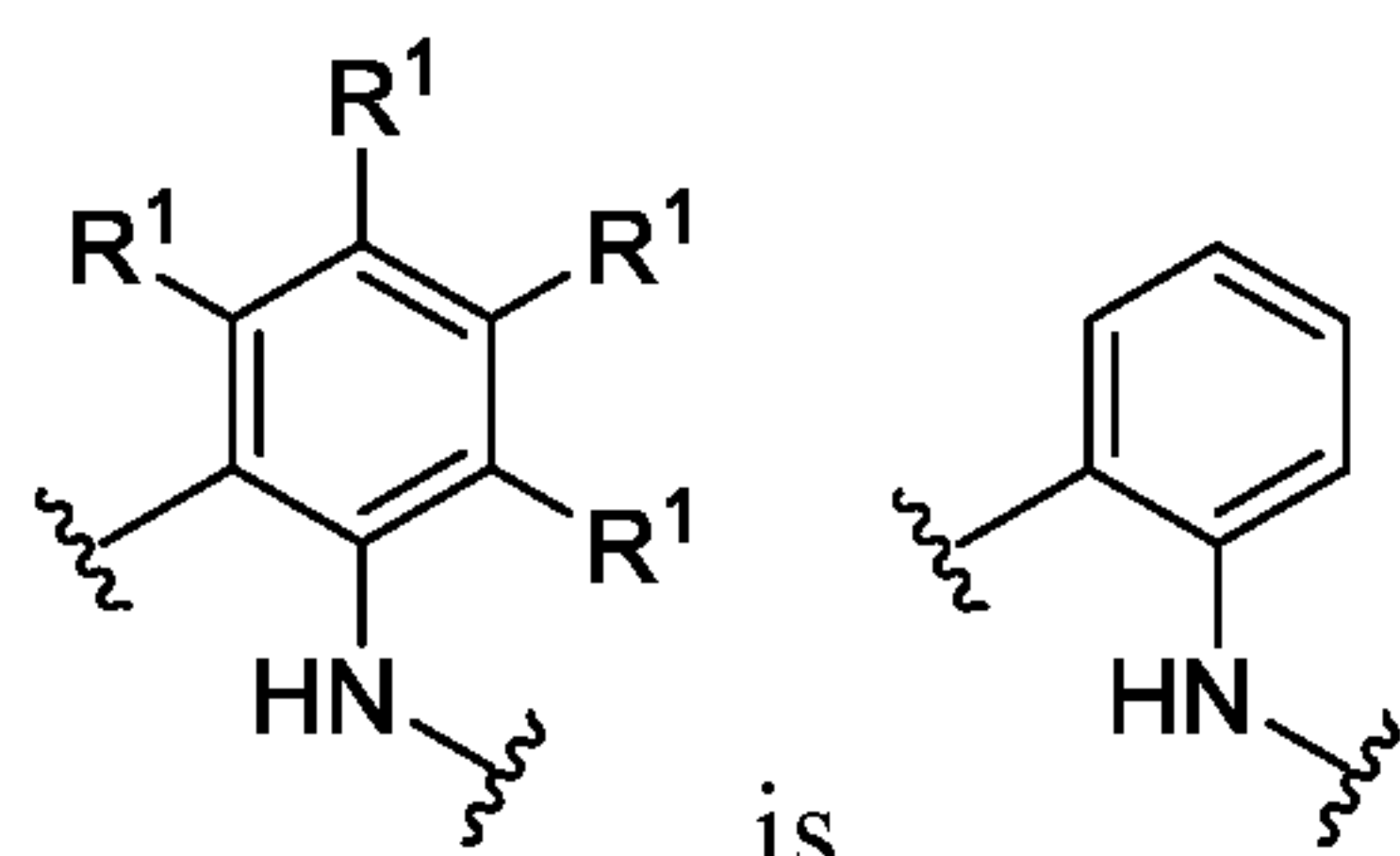
[00120] In some embodiments, Y^2 is H. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, Y^2 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-C(CH_3)_3$. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, Y^2 is $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_6 heteroalkyl. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_4 heteroalkyl. In some embodiments, Y^2 is substituted or unsubstituted C_3 - C_{10} cycloalkyl. In some embodiments, Y^2 is substituted or unsubstituted C_3 - C_6 cycloalkyl. In some embodiments, Y^2 is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, Y^2 is substituted or unsubstituted C_2 - C_{10} heterocycloalkyl. In some embodiments, Y^2 is substituted or unsubstituted C_2 - C_6 heterocycloalkyl. In some embodiments, Y^2 is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, Y^2 is substituted or unsubstituted aryl. In some embodiments, Y^2 is substituted or unsubstituted phenyl. In some embodiments, Y^2 is substituted or unsubstituted heteroaryl. In some embodiments, Y^2 is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or

unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl. In some embodiments, R^3 and Y^2 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

In some embodiments, L^2 is substituted or unsubstituted C_1 - C_6 alkylene; L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -NR³(SO₂)NR³-(C=O)-, or -NR³(SO₂)NR³-(C=O)O-; each R^3 is independently H or substituted or unsubstituted C_1 - C_6 alkyl; and Y^2 is H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, L^2 is substituted or unsubstituted C_1 - C_4 alkylene; L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -NR³(SO₂)NR³-(C=O)-, or -NR³(SO₂)NR³-(C=O)O-; each R^3 is independently H or substituted or unsubstituted C_1 - C_4 alkyl; and Y^2 is H, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_6 heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl.

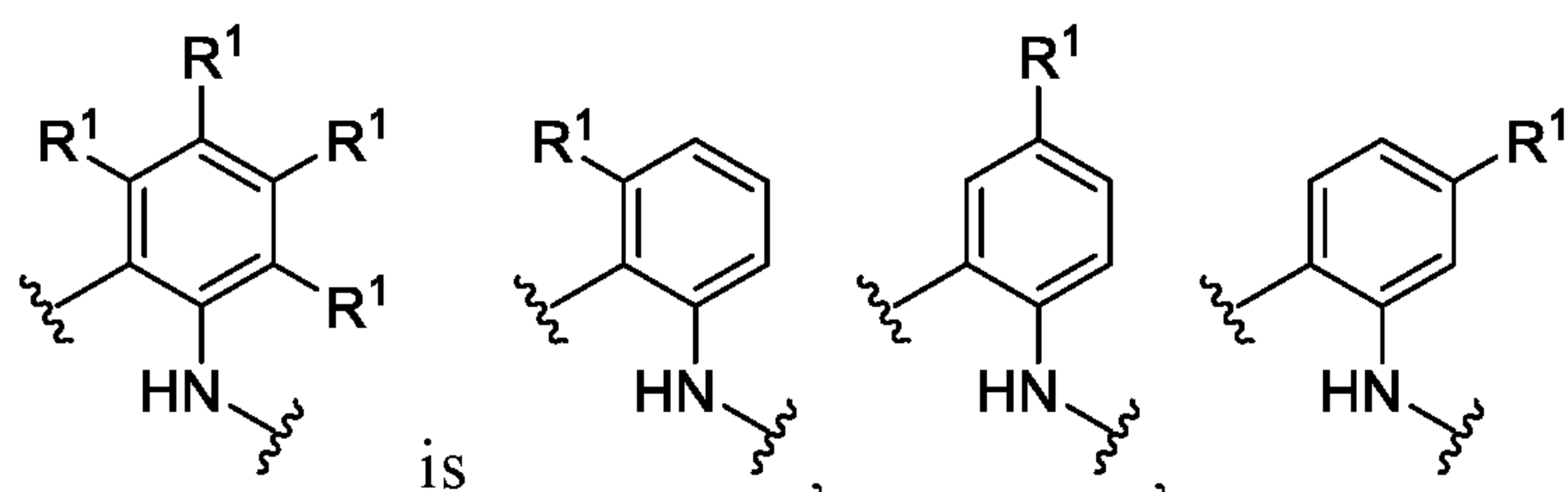
[00121] In some embodiments, each R^1 is independently H. In some embodiments, each R^1 is independently halogen. In some embodiments, each R^1 is independently F, Cl, Br, or I. In some embodiments, each R^1 is independently -CN. In some embodiments, each R^1 is -OR⁴. In some embodiments, each R^1 is -SR⁴. In some embodiments, each R^1 independently is -N(R⁴)₂. In some embodiments, each R^1 is independently substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, R^1 is independently -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃. In some embodiments, each R^1 is independently substituted or

unsubstituted C₁-C₆haloalkyl. In some embodiments, each R¹ is independently substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, each R¹ is independently -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃. In some embodiments, each R¹ is independently substituted or unsubstituted C₁-C₆heteroalkyl. In some embodiments, each R¹ is independently substituted or unsubstituted C₁-C₄heteroalkyl. In some embodiments, each R¹ is independently substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, each R¹ is independently substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, each R¹ is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R¹ is independently substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, each R¹ is independently substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, each R¹ is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, each R¹ is independently substituted or unsubstituted aralkyl. In some embodiments, each R¹ is independently substituted or unsubstituted benzyl. In some embodiments, each R¹ is independently substituted or unsubstituted aryl. In some embodiments, each R¹ is independently substituted or unsubstituted phenyl. In some embodiments, each R¹ is independently substituted or unsubstituted heteroaryl. In some embodiments, each R¹ is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.



[00122] In some embodiments,

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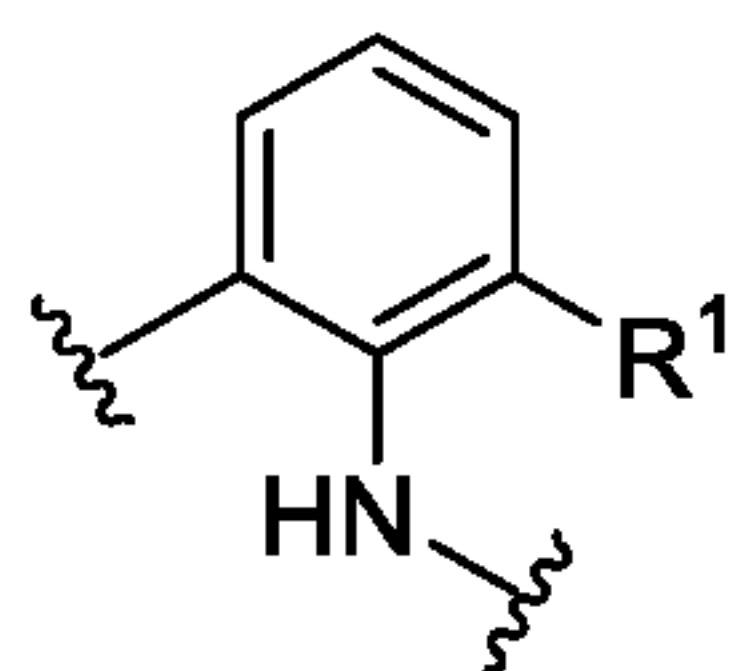
[00123] In some embodiments,

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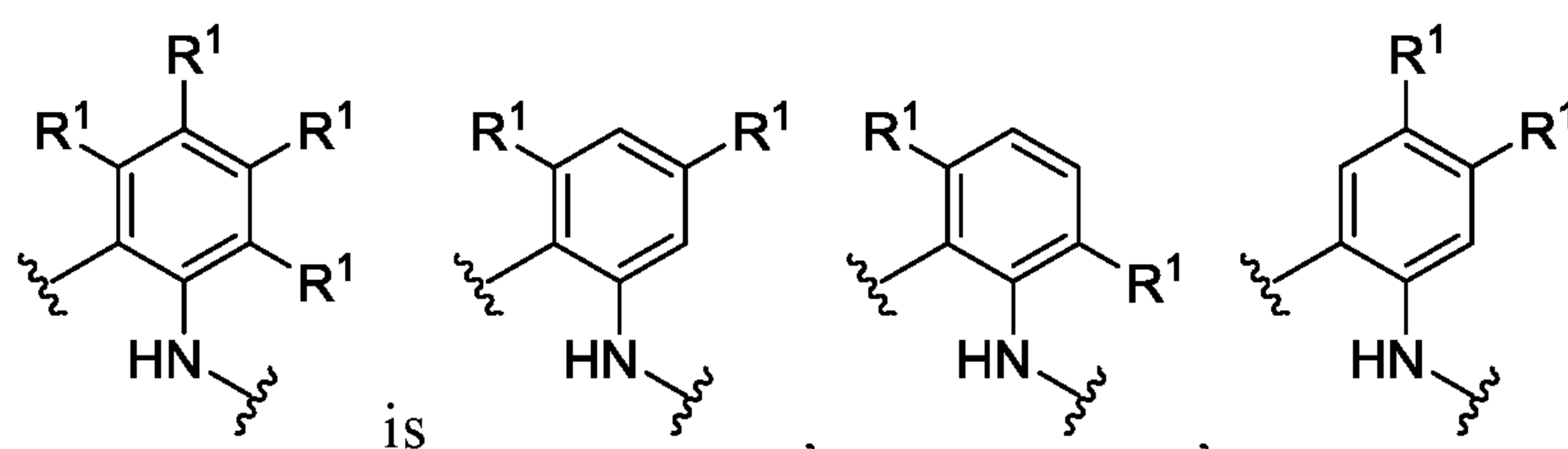
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, or



; and R^1 is halogen, $-\text{CN}$, $-\text{OR}^4$, $-\text{SR}^4$, $-\text{N}(\text{R}^4)_2$, substituted or unsubstituted C_1 -

C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.



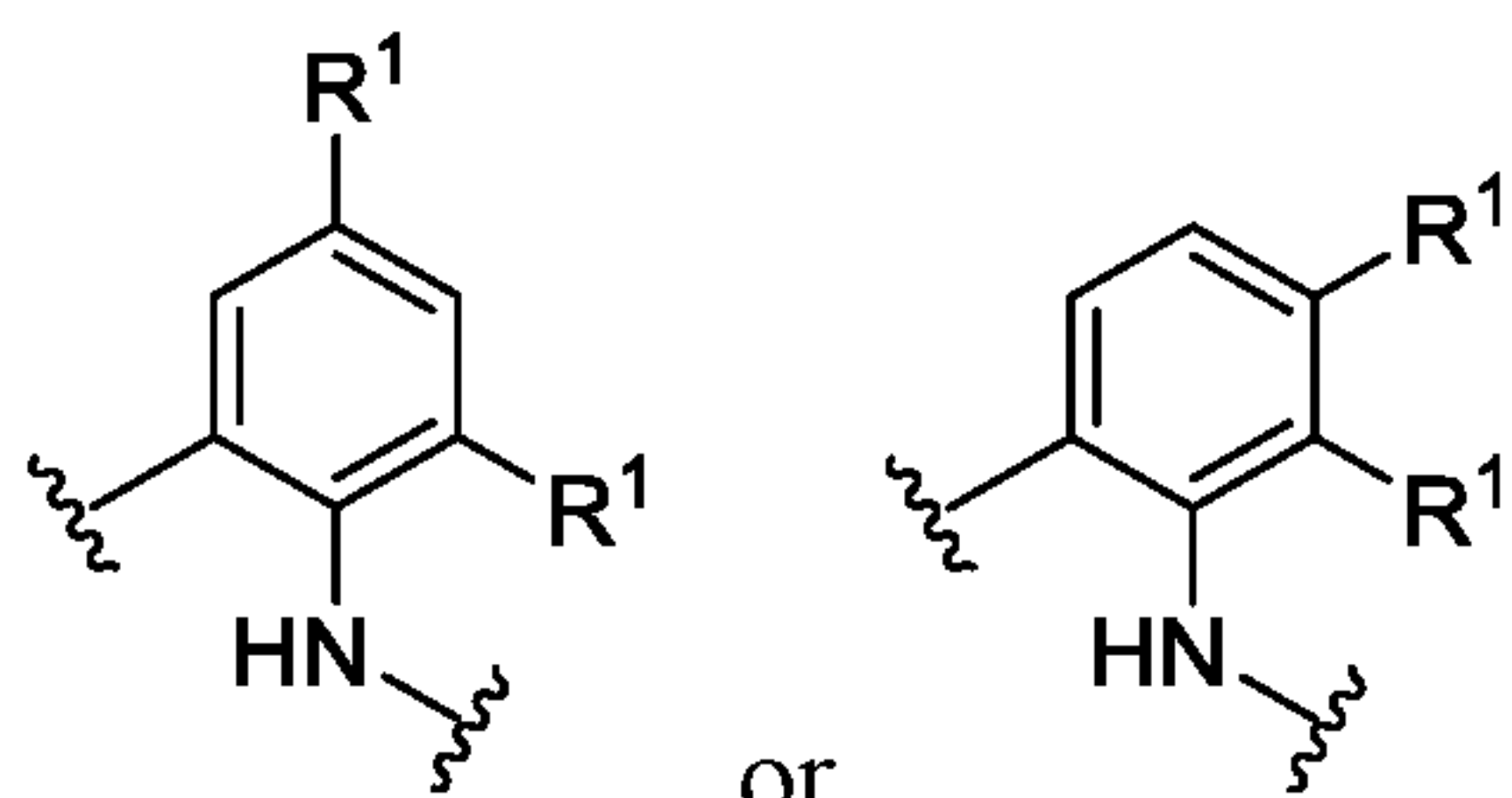
[00124] In some embodiments,

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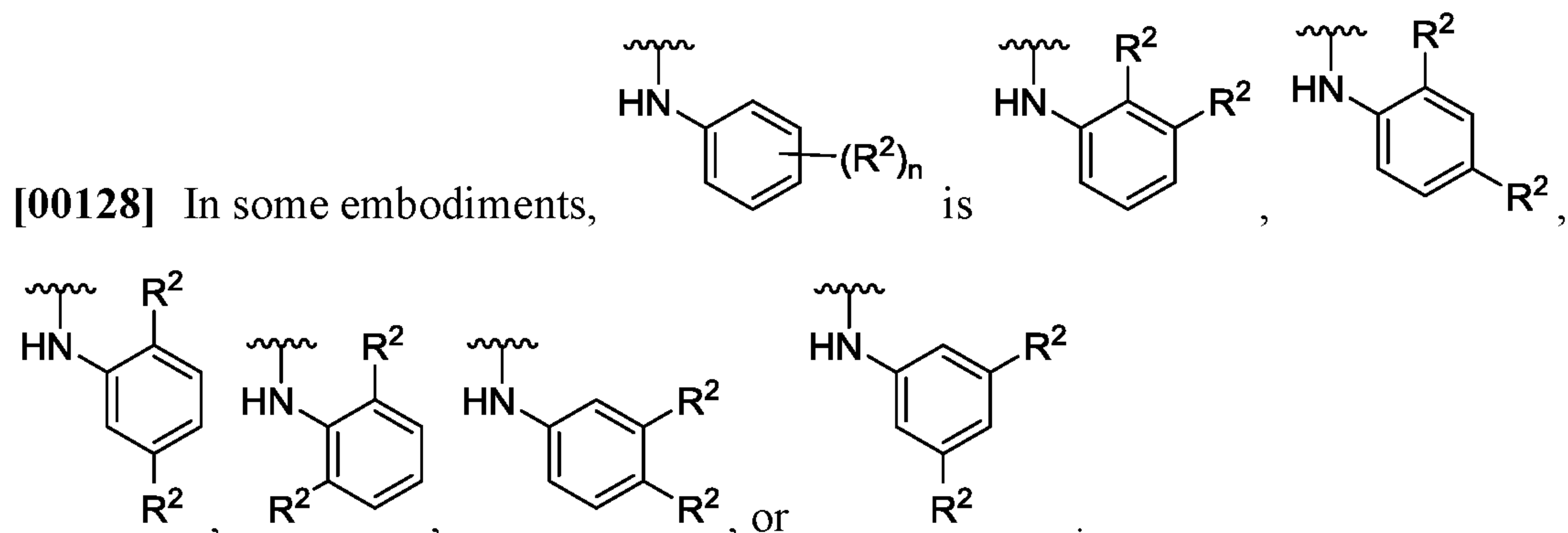
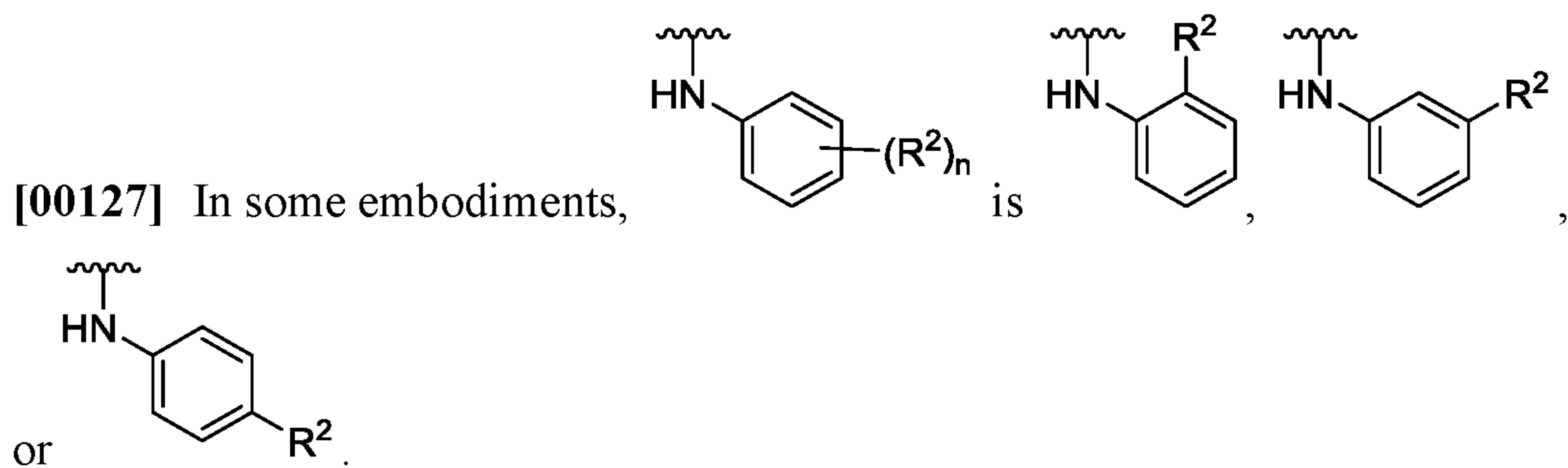
; and each R^1 is independently halogen, $-\text{CN}$, $-\text{OR}^4$, $-\text{SR}^4$, $-\text{N}(\text{R}^4)_2$,

substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00125] In some embodiments, each R^4 is independently H. In some embodiments, each R^4 is independently substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^4 is independently substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, each R^4 is independently $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, or $-\text{C}(\text{CH}_3)_3$. In some embodiments, each R^4 is independently substituted or unsubstituted C_1 -

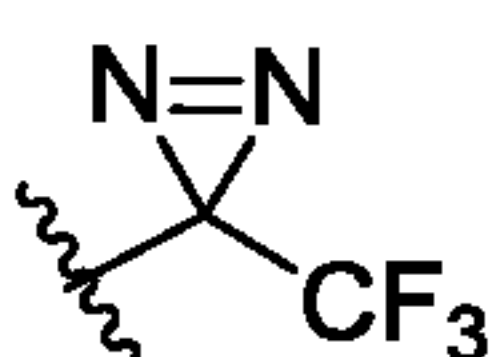
C₆haloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, each R⁴ is independently -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃. In some embodiments, each R⁴ is independently substituted or unsubstituted C₁-C₆heteroalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₁-C₄heteroalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, each R⁴ is independently substituted or unsubstituted aralkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted benzyl. In some embodiments, each R⁴ is independently substituted or unsubstituted aryl. In some embodiments, each R⁴ is independently substituted or unsubstituted phenyl. In some embodiments, each R⁴ is independently substituted or unsubstituted heteroaryl. In some embodiments, each R⁴ is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[00126] In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4. In some embodiments, n is 5.

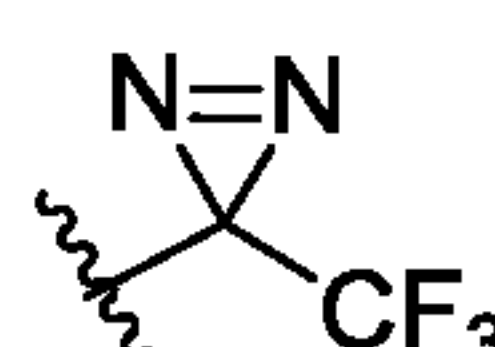


[00129] In some embodiments, each R^2 is independently halogen. In some embodiments, each R^2 is independently F, Cl, Br, or I. In some embodiments, each R^2 is independently $-N_3$. In some embodiments, each R^2 is independently $-CN$. In some embodiments, each R^2 is independently $-OR^5$. In some embodiments, each R^2 is independently $-SR^5$. In some embodiments, each R^2 is independently $-(SO_2)R^5$. In some embodiments, each R^2 is independently $-N(R^5)_2$. In some embodiments, each R^2 is independently $-CO_2R^5$. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, each R^2 is independently $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-C(CH_3)_3$. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, each R^2 is independently $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_6 heteroalkyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_4 heteroalkyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_3 - C_{10} cycloalkyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_3 - C_6 cycloalkyl. In some embodiments, each R^2 is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_2 - C_{10} heterocycloalkyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_2 - C_6 heterocycloalkyl. In some embodiments, each R^2 is independently substituted or unsubstituted aziridinyl, substituted

or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, each R^2 is independently substituted or unsubstituted alkyl. In some embodiments, each R^2 is independently benzyl. In some embodiments, each R^2 is independently substituted or unsubstituted aryl. In some embodiments, each R^2 is independently substituted or unsubstituted phenyl. In some embodiments, each R^2 is independently substituted or unsubstituted heteroaryl. In some embodiments, each R^2 is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl. In some

embodiments, each R^2 is independently .

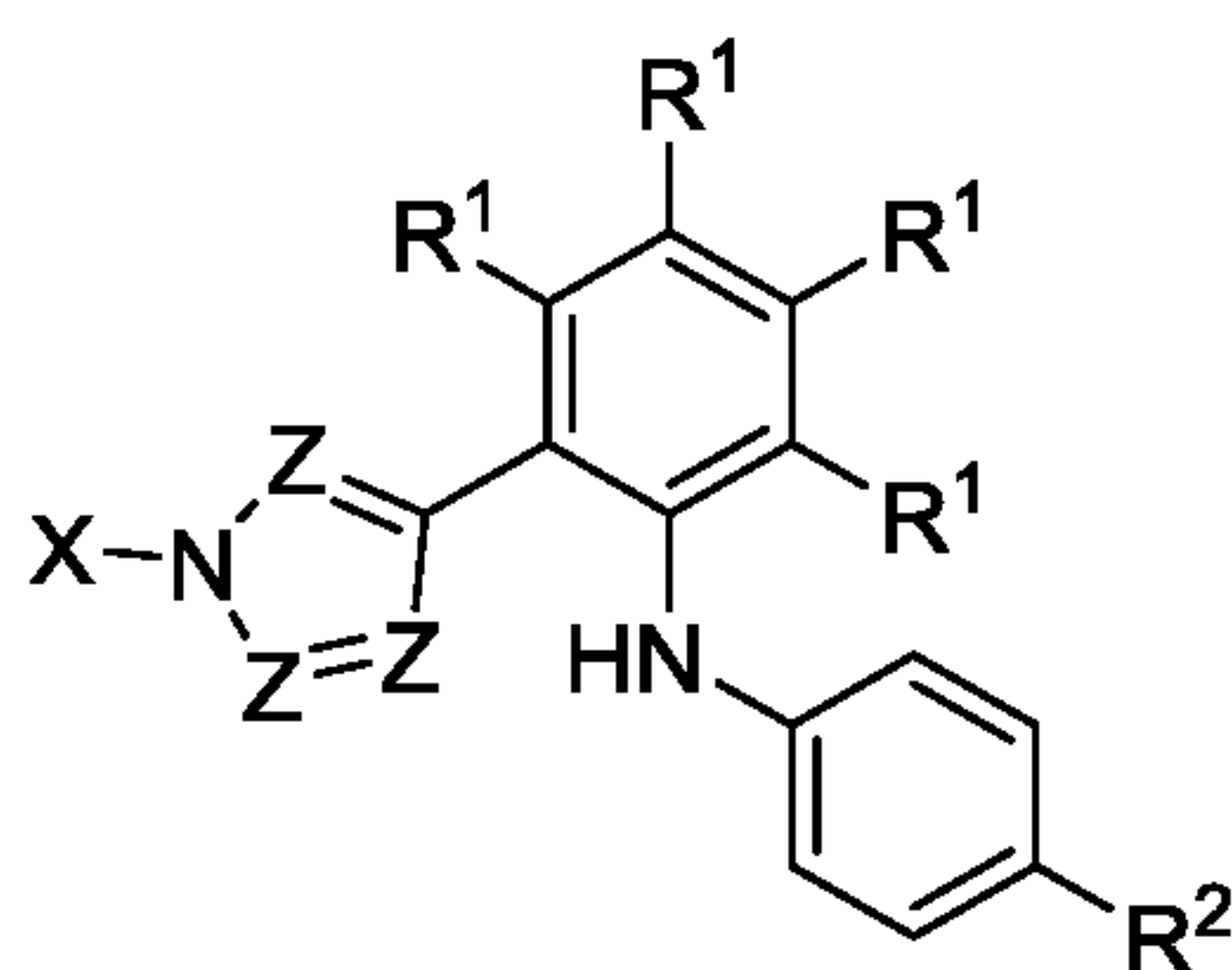
[00130] In some embodiments, each R^2 is independently halogen, $-N_3$, $-OR^5$, $-(SO_2)R^5$, $-CO_2R^5$,

substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, or .

[00131] In some embodiments, each R^5 is independently H. In some embodiments, each R^5 is independently substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^5 is independently substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, each R^5 is independently $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-C(CH_3)_3$. In some embodiments, each R^5 is independently substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, each R^5 is independently substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, each R^5 is independently $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$. In some embodiments, each R^5 is independently substituted or unsubstituted C_1 - C_6 heteroalkyl. In some embodiments, each R^5 is independently substituted or unsubstituted C_1 - C_4 heteroalkyl. In some embodiments, each R^5 is independently substituted or unsubstituted C_3 - C_{10} cycloalkyl. In

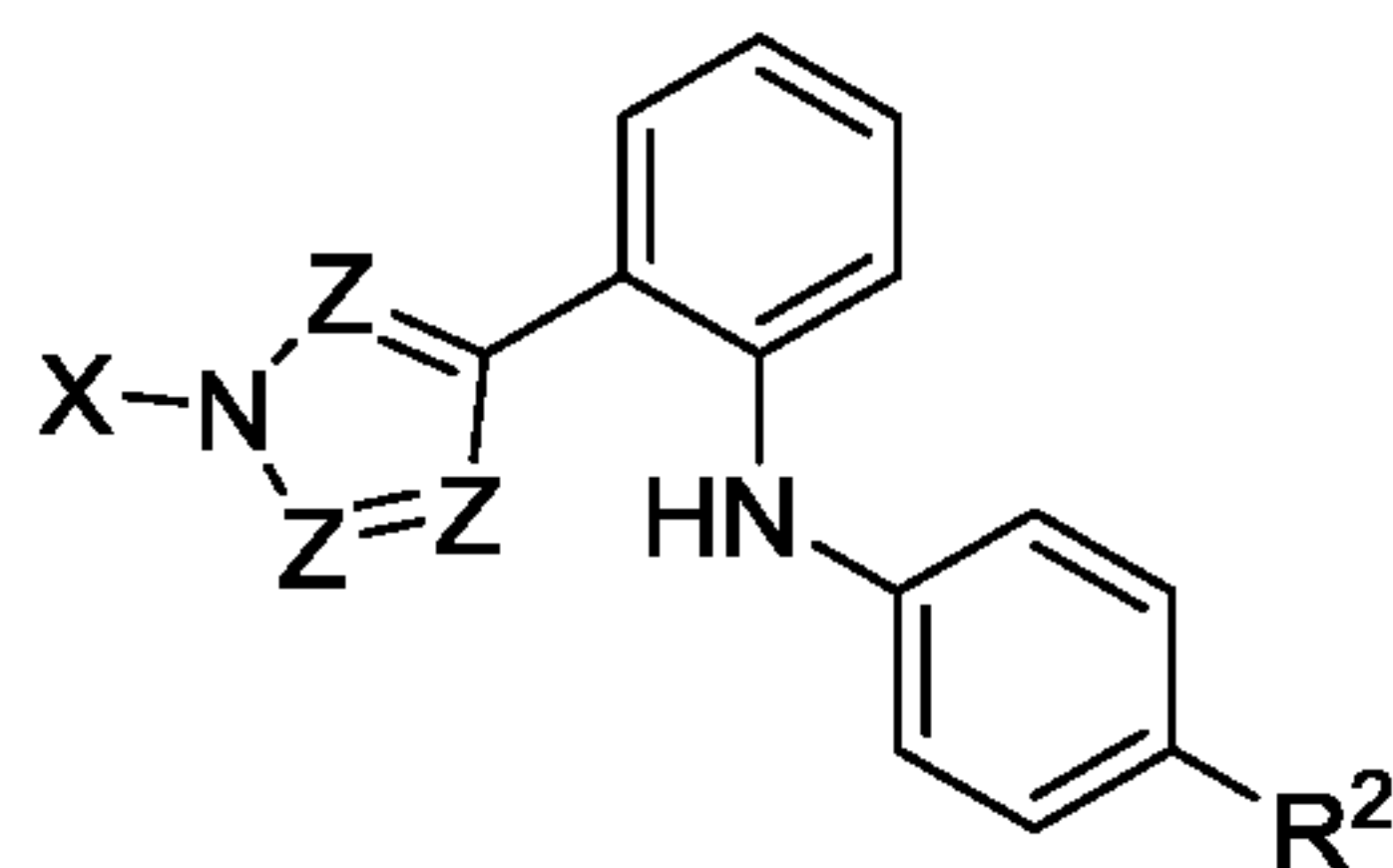
some embodiments, each R^5 is independently substituted or unsubstituted C_3 - C_6 cycloalkyl. In some embodiments, each R^5 is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R^5 is independently substituted or unsubstituted C_2 - C_{10} heterocycloalkyl. In some embodiments, each R^5 is independently substituted or unsubstituted C_2 - C_6 heterocycloalkyl. In some embodiments, each R^5 is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, each R^5 is independently substituted or unsubstituted aralkyl. In some embodiments, each R^5 is independently substituted or unsubstituted benzyl. In some embodiments, each R^5 is independently substituted or unsubstituted aryl. In some embodiments, each R^5 is independently substituted or unsubstituted phenyl. In some embodiments, each R^5 is independently substituted or unsubstituted heteroaryl. In some embodiments, each R^5 is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[00132] In some embodiments, the compound has the structure of Formula (Ia), or a pharmaceutically acceptable salt thereof:



Formula (Ia).

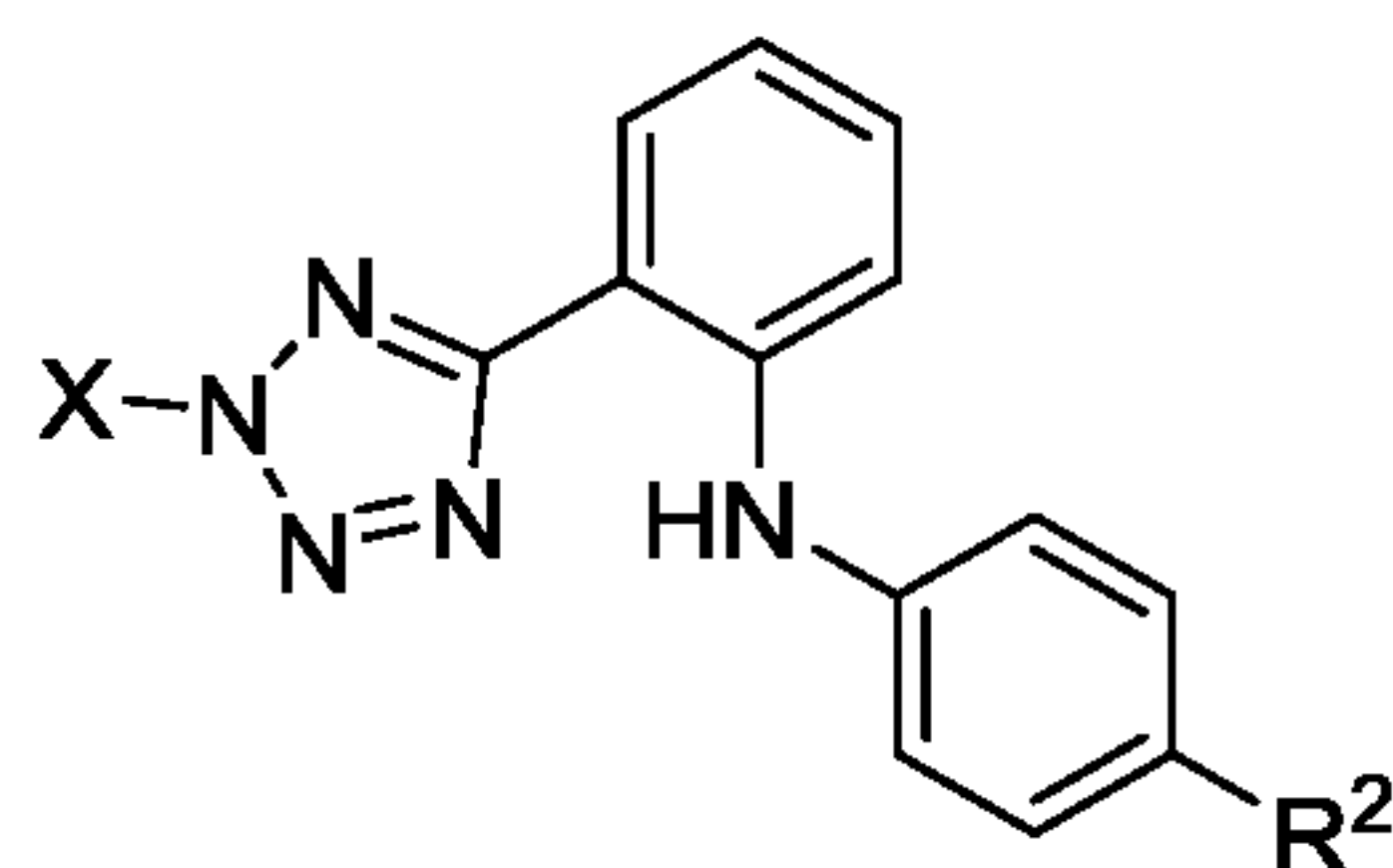
[00133] In some embodiments, the compound has the structure of Formula (Ib), or a pharmaceutically acceptable salt thereof:



Formula (Ib).

[00134] In some embodiments, R^2 is substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, R^2 is substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, R^2 is - CH_2F , - CHF_2 , - CF_3 , or - CH_2CF_3 . In some embodiments, R^2 is - CF_3 .

[00135] In some embodiments, the compound has the structure of Formula (Ic), or a pharmaceutically acceptable salt thereof:

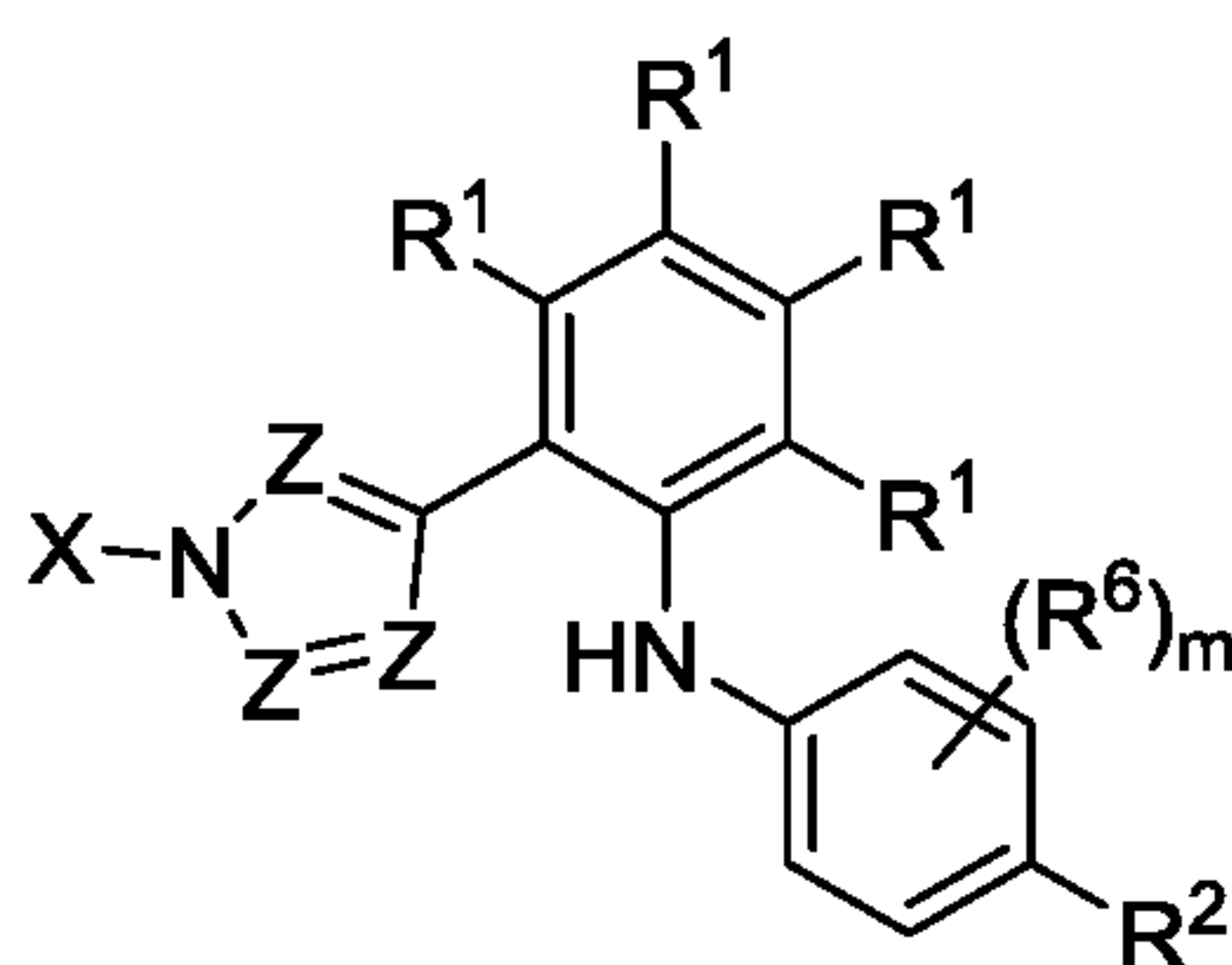


Formula (Ic).

[00136] In some embodiments, R^2 is substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, R^2 is substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, R^2 is - CH_2F , - CHF_2 , - CF_3 , or - CH_2CF_3 . In some embodiments, R^2 is - CF_3 .

[00137] In some embodiments, X is $-(CH_2)_r-OH$, $-(CH_2)_r-OR''$, $-(CH_2)_r-N(R')_2$, $-(CH_2)_r-NR'S(=O)_2R''$, $-(CH_2)_r-S(=O)_2N(R')_2$, $-(CH_2)_r-SR'$, $-(CH_2)_r-S(=O)R''$, $-(CH_2)_r-S(=O)_2R''$, $-(CH_2)_r-C(=O)R''$, $-(CH_2)_r-OC(=O)R''$, $-(CH_2)_r-CO_2H$, $-(CH_2)_r-CO_2R''$, $-(CH_2)_r-OC(=O)OR''$, $-(CH_2)_r-NR'C(=O)R''$, $-(CH_2)_r-C(=O)N(R')_2$, $-(CH_2)_r-NR''C(=O)OR'$, $-(CH_2)_r-OC(=O)N(R'')_2$; r is 1, 2, 3, or 4; each R' is independently H substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and each R'' is independently unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00138] Provided in another aspect is a compound of Formula (II), or a pharmaceutically acceptable salt thereof:



Formula (II)

wherein:

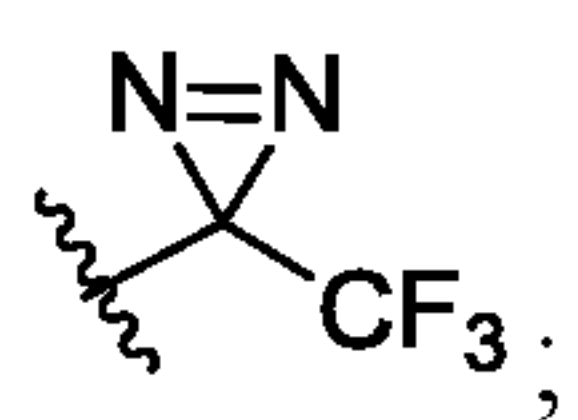
each Z is independently N or CR^Z;

each R^Z is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

X is methyl;

each R¹ is independently H, halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R² is halogen, -N₃, -CN, -OR⁵, -SR⁵, -(SO₂)R⁵, -N(R⁵)₂, -CO₂R⁵, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted

aryl, substituted or unsubstituted heteroaryl, or ;

each R⁶ is independently H, halogen, -N₃, -CN, -OR⁷, -SR⁷, -(SO₂)R⁷, -N(R⁷)₂, -CO₂R⁷, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

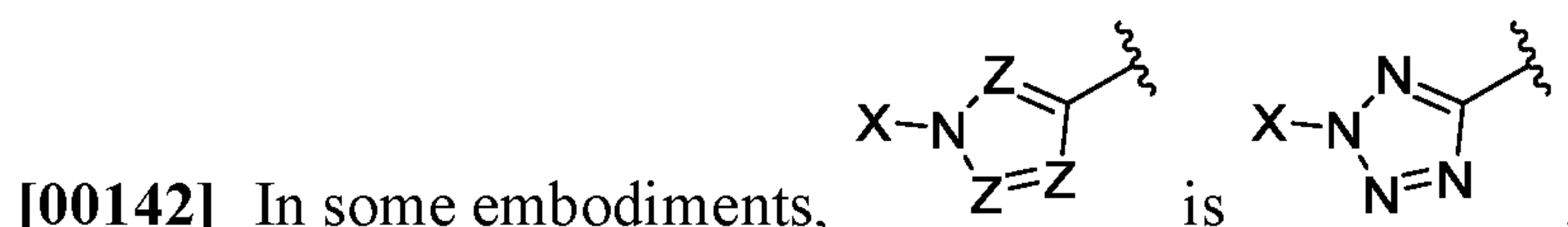
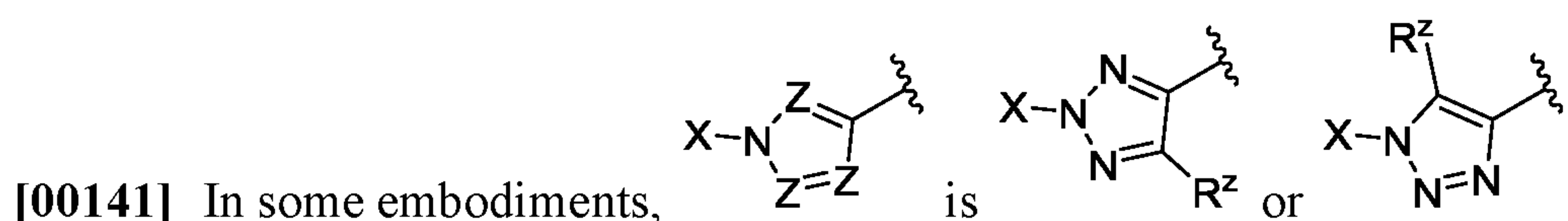
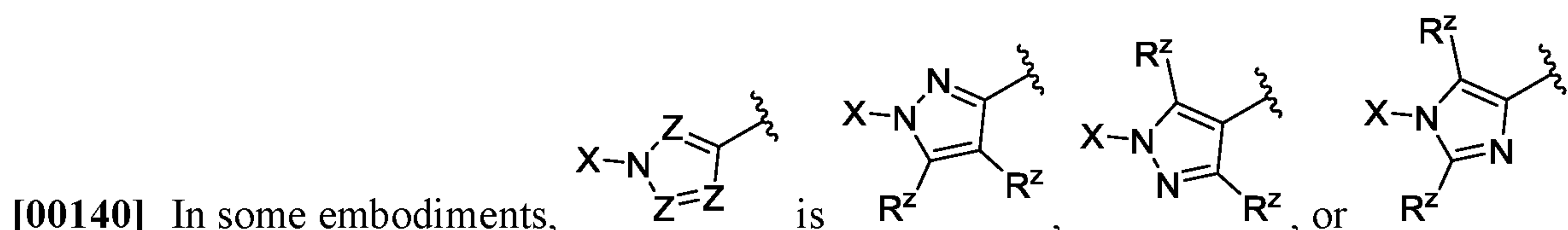
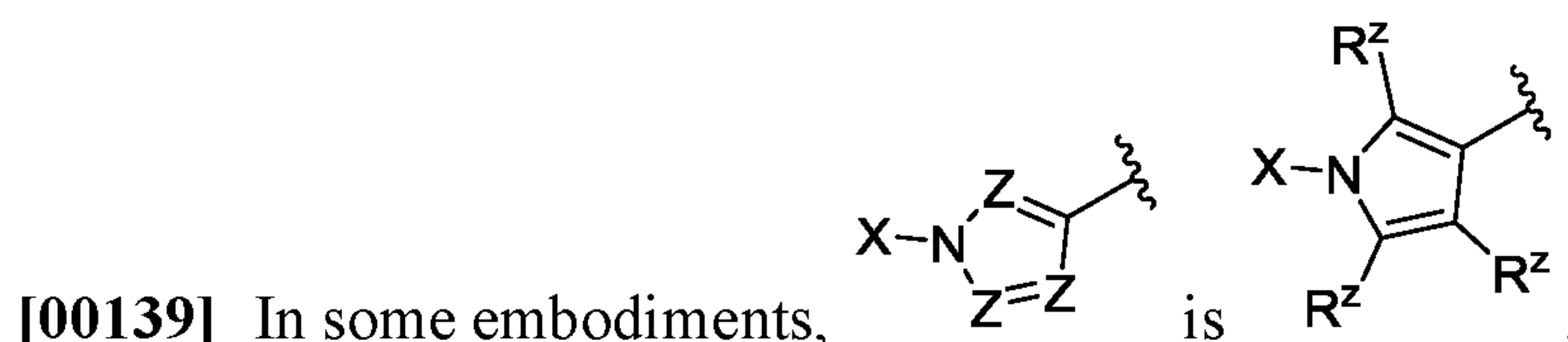
each R⁴ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or

unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^5 is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^7 is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

m is 0, 1, 2, 3, or 4.

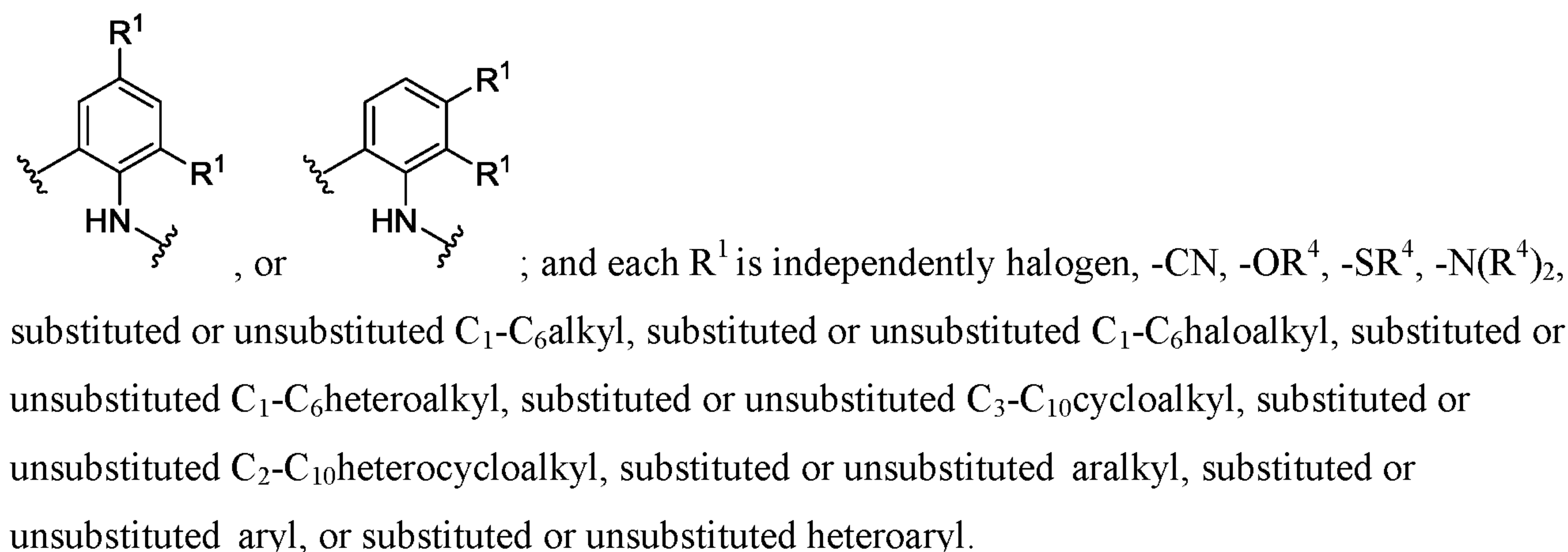
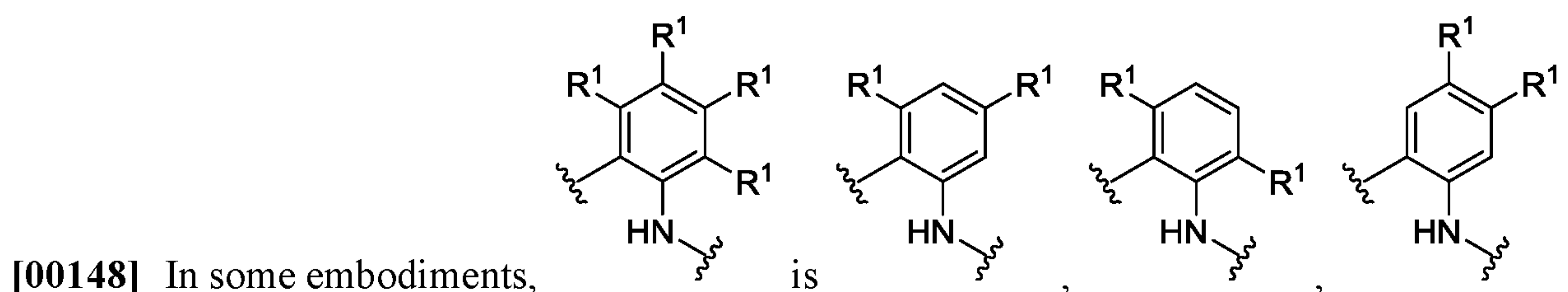
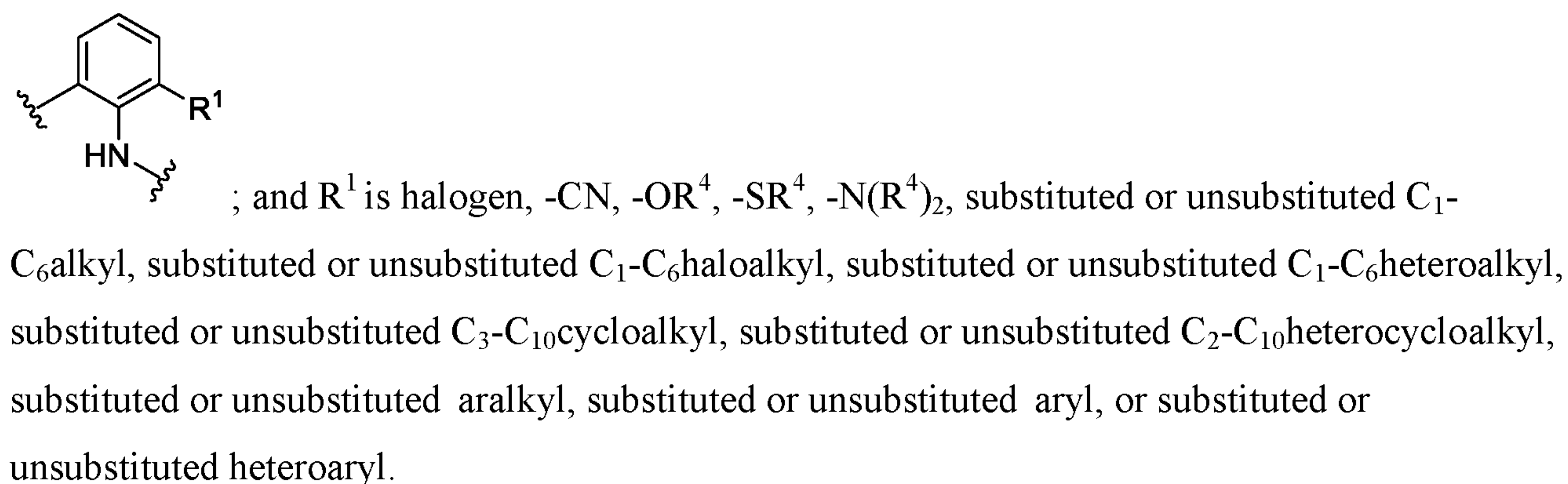
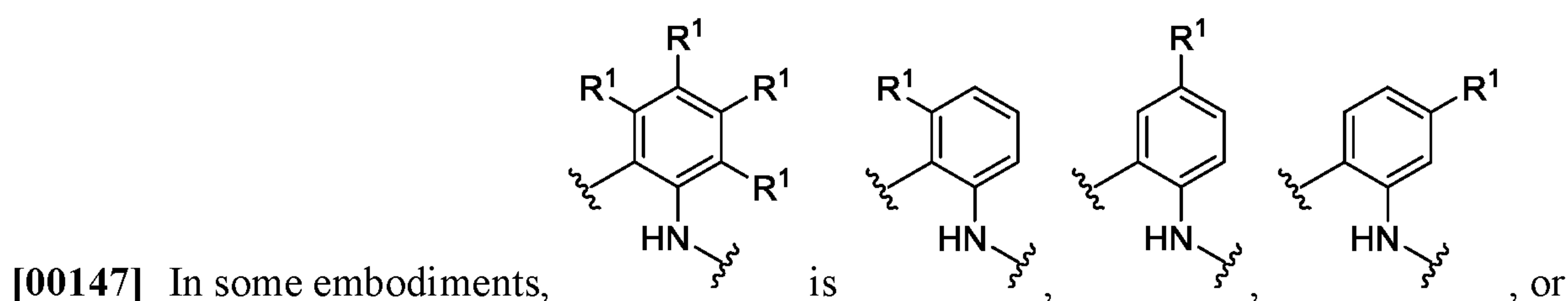
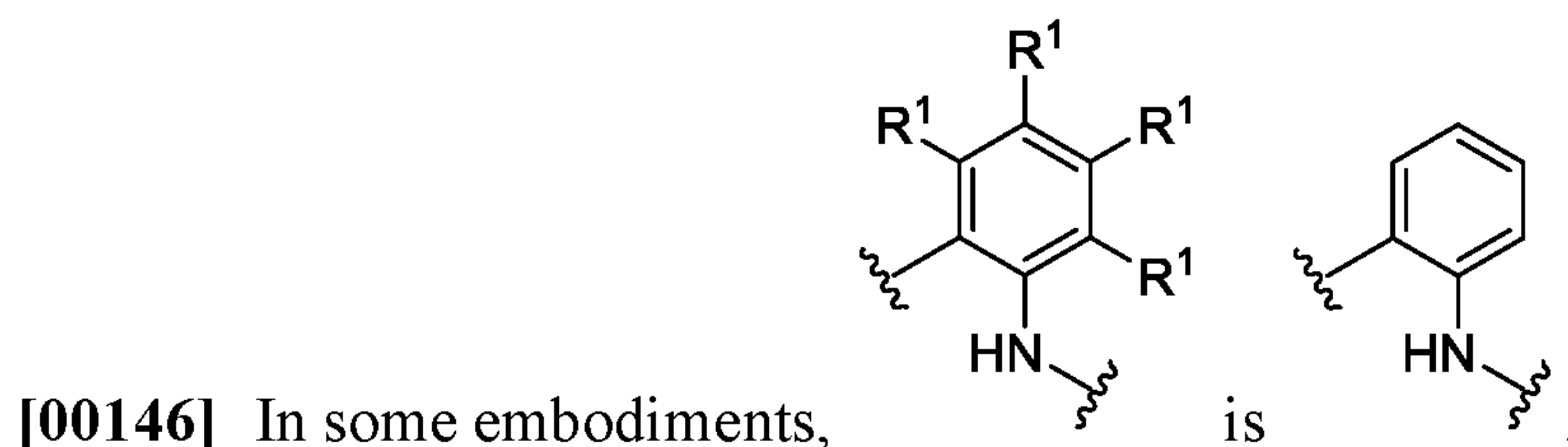


[00143] In some embodiments, each R^Z is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, each R^Z is independently H, substituted or unsubstituted C_1 - C_6 alkyl, or substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, each R^Z is independently H or substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^Z is independently H or substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, each R^Z is independently $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-C(CH_3)_3$.

[00144] In some embodiments, each R^Z is independently H. In some embodiments, each R^Z is independently substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, each R^Z is independently $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$. In some embodiments, each R^Z is independently substituted or unsubstituted C_1 - C_6 heteroalkyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_1 - C_4 heteroalkyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_3 - C_{10} cycloalkyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_3 - C_6 cycloalkyl. In some embodiments, each R^Z is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_2 - C_{10} heterocycloalkyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_2 - C_6 heterocycloalkyl. In some embodiments, each R^Z is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, each R^Z is independently substituted or unsubstituted aralkyl. In some embodiments, each R^Z is independently substituted or unsubstituted benzyl. In some embodiments, each R^Z is independently substituted or unsubstituted aryl. In some embodiments, each R^Z is independently substituted or unsubstituted phenyl. In some embodiments, each R^Z is independently substituted or unsubstituted heteroaryl. In some embodiments, each R^Z is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[00145] In some embodiments, each R^1 is independently H. In some embodiments, each R^1 is independently halogen. In some embodiments, each R^1 is independently F, Cl, Br, or I. In some embodiments, each R^1 is independently -CN. In some embodiments, each R^1 is independently -OR⁴. In some embodiments, each R^1 is independently -SR⁴. In some embodiments, each R^1 is independently -N(R⁴)₂. In some embodiments, each R^1 is independently substituted or unsubstituted C₁-C₆alkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C₁-C₄alkyl. In some embodiments, each R^1 is independently -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃. In some embodiments, each R^1 is independently substituted or unsubstituted C₁-C₆haloalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, each R^1 is independently -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃. In some embodiments, each R^1 is independently substituted or unsubstituted C₁-C₆heteroalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C₁-C₄heteroalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R^1 is independently substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, each R^1 is independently substituted or unsubstituted aralkyl. In some embodiments, each R^1 is independently substituted or unsubstituted benzyl. In some embodiments, each R^1 is independently substituted or unsubstituted aryl. In some embodiments, each R^1 is independently substituted or unsubstituted phenyl. In some embodiments, each R^1 is independently substituted or unsubstituted heteroaryl. In some embodiments, each R^1 is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted

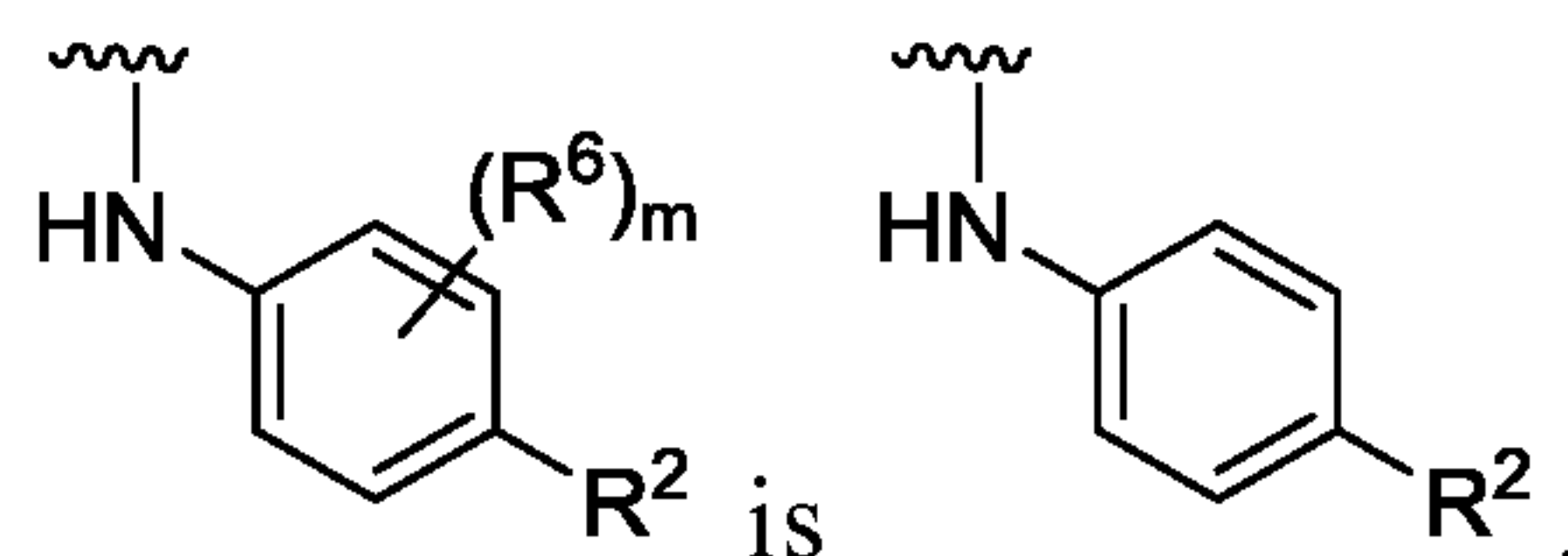
tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.



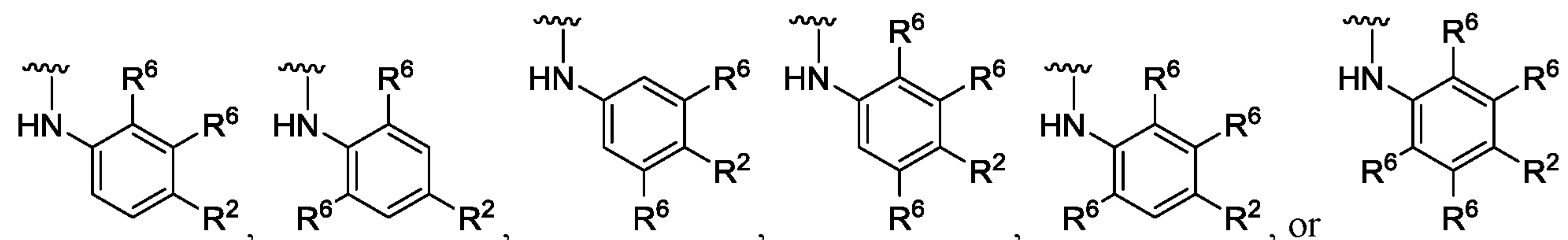
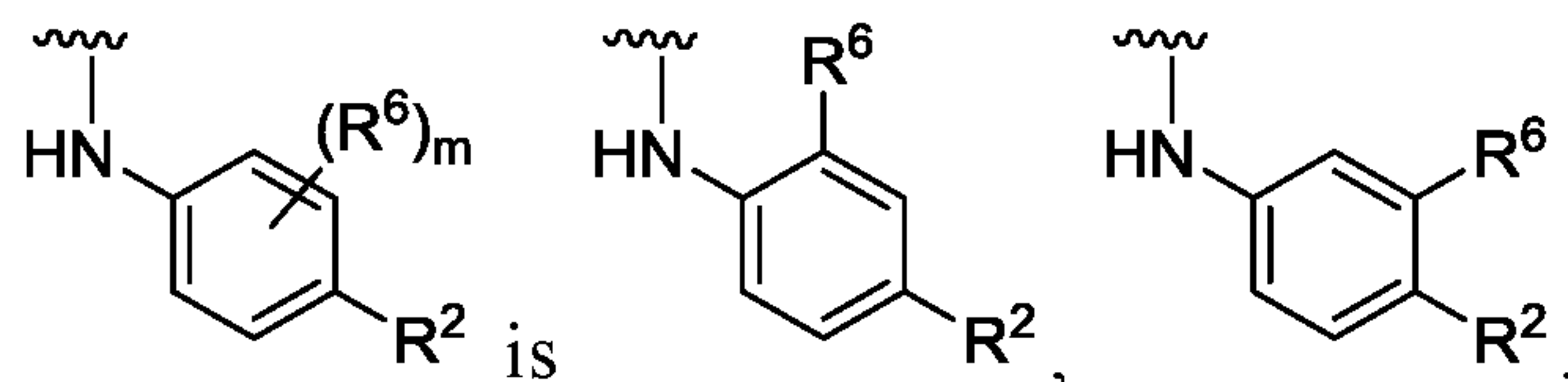
[00149] In some embodiments, each R^4 is independently H. In some embodiments, each R^4 is independently substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^4 is independently substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, each R^4 is independently $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-C(CH_3)_3$. In some embodiments, each R^4 is independently substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, each R^4 is independently substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, each R^4 is independently $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$. In some embodiments, each R^4 is independently substituted or unsubstituted C_1 - C_6 heteroalkyl. In some embodiments, each R^4 is independently substituted or unsubstituted C_1 - C_4 heteroalkyl. In some embodiments, each R^4 is independently substituted or unsubstituted C_3 - C_{10} cycloalkyl. In some embodiments, each R^4 is independently substituted or unsubstituted C_3 - C_6 cycloalkyl. In some embodiments, each R^4 is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R^4 is independently substituted or unsubstituted C_2 - C_{10} heterocycloalkyl. In some embodiments, each R^4 is independently substituted or unsubstituted C_2 - C_6 heterocycloalkyl. In some embodiments, each R^4 is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, each R^4 is independently substituted or unsubstituted aralkyl. In some embodiments, each R^4 is independently substituted or unsubstituted benzyl. In some embodiments, each R^4 is independently substituted or unsubstituted aryl. In some embodiments, each R^4 is independently substituted or unsubstituted phenyl. In some embodiments, each R^4 is independently substituted or unsubstituted heteroaryl. In some embodiments, each R^4 is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted

triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[00150] In some embodiments,

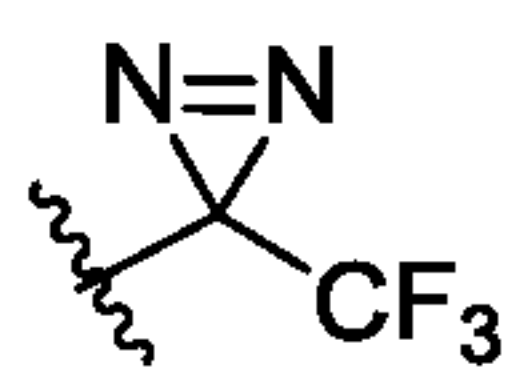


[00151] In some embodiments,

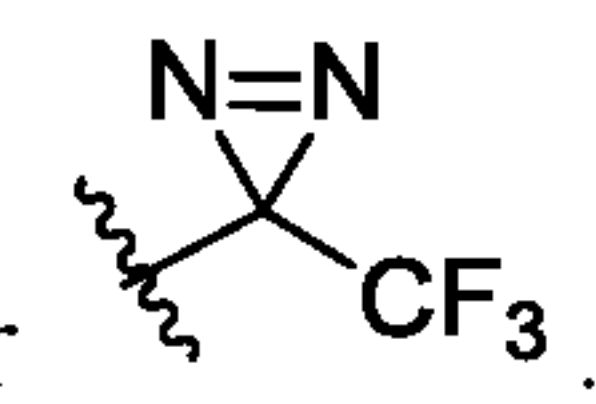


[00152] In some embodiments, R^2 is halogen. In some embodiments, R^2 is F, Cl, Br, or I. In some embodiments, R^2 is $-N_3$. In some embodiments, R^2 is $-CN$. In some embodiments, R^2 is $-OR^5$. In some embodiments, R^2 is $-SR^5$. In some embodiments, R^2 is $-(SO_2)R^5$. In some embodiments, R^2 is $-N(R^5)_2$. In some embodiments, R^2 is $-CO_2R^5$. In some embodiments, R^2 is substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, R^2 is substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, R^2 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-C(CH_3)_3$. In some embodiments, R^2 is substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, R^2 is substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, R^2 is $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$. In some embodiments, R^2 is substituted or unsubstituted C_1 - C_6 heteroalkyl. In some embodiments, R^2 is substituted or unsubstituted C_1 - C_4 heteroalkyl. In some embodiments, R^2 is substituted or unsubstituted C_3 - C_{10} cycloalkyl. In some embodiments, R^2 is substituted or unsubstituted C_3 - C_6 cycloalkyl. In some embodiments, R^2 is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, R^2 is substituted or unsubstituted C_2 - C_{10} heterocycloalkyl. In some embodiments, R^2 is substituted or unsubstituted C_2 - C_6 heterocycloalkyl. In some embodiments, R^2 is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted

oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, R^2 is substituted or unsubstituted aralkyl. In some embodiments, R^2 is substituted or unsubstituted benzyl. In some embodiments, R^2 is substituted or unsubstituted aryl. In some embodiments, R^2 is substituted or unsubstituted phenyl. In some embodiments, R^2 is substituted or unsubstituted heteroaryl. In some embodiments, R^2 is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or

unsubstituted furazanyl. In some embodiments, R^2 is .

[00153] In some embodiments, R^2 is halogen, $-N_3$, $-OR^5$, $-(SO_2)R^5$, $-CO_2R^5$, substituted or

unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, or .

[00154] In some embodiments, each R^5 is independently H. In some embodiments, each R^5 is independently substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^5 is independently substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, each R^5 is independently $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-C(CH_3)_3$. In some embodiments, each R^5 is independently substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, each R^5 is independently substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, each R^5 is independently $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$. In some embodiments, each R^5 is independently substituted or unsubstituted C_1 - C_6 heteroalkyl. In some embodiments, each R^5 is independently substituted or unsubstituted C_1 - C_4 heteroalkyl. In some embodiments, each R^5 is independently substituted or unsubstituted C_3 - C_{10} cycloalkyl. In some embodiments, each R^5 is independently substituted or unsubstituted C_3 - C_6 cycloalkyl. In some embodiments, each R^5 is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R^5 is independently substituted or unsubstituted C_2 - C_{10} heterocycloalkyl. In some embodiments, each R^5 is independently substituted or unsubstituted C_2 - C_6 heterocycloalkyl. In some embodiments, each R^5 is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted

pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, each R^5 is independently substituted or unsubstituted aralkyl. In some embodiments, each R^5 is independently substituted or unsubstituted benzyl. In some embodiments, each R^5 is independently substituted or unsubstituted aryl. In some embodiments, each R^5 is independently substituted or unsubstituted phenyl. In some embodiments, each R^5 is independently substituted or unsubstituted heteroaryl. In some embodiments, each R^5 is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[00155] In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 4.

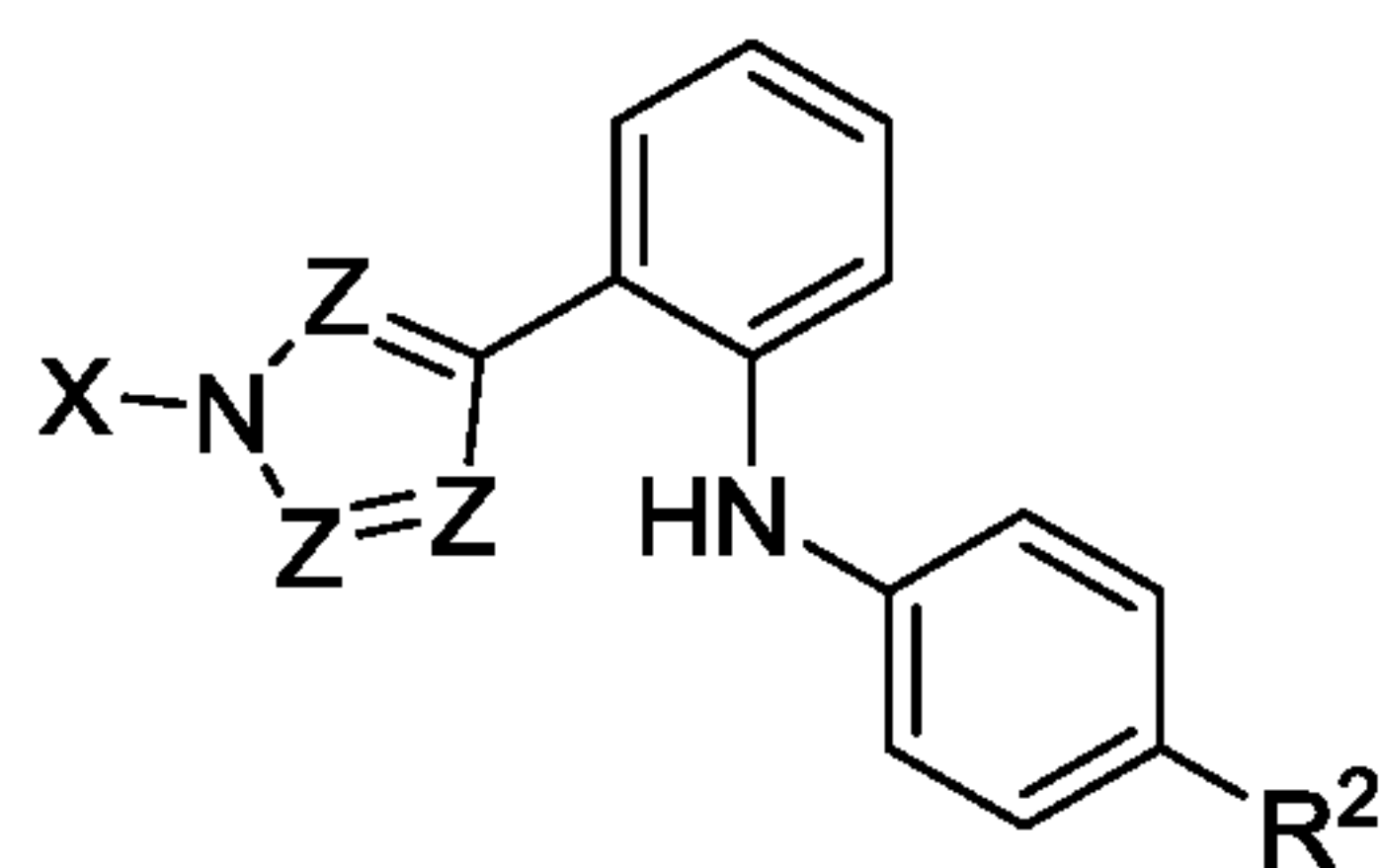
[00156] In some embodiments, each R^6 is independently H. In some embodiments, each R^6 is independently halogen. In some embodiments, each R^6 is independently F, Cl, Br, or I. In some embodiments, each R^6 is independently $-N_3$. In some embodiments, each R^6 is independently $-CN$. In some embodiments, each R^6 is independently $-OR^5$. In some embodiments, each R^6 is independently $-SR^5$. In some embodiments, each R^6 is independently $-(SO_2)R^5$. In some embodiments, each R^6 is independently $-N(R^5)_2$. In some embodiments, each R^6 is independently $-CO_2R^5$. In some embodiments, each R^6 is independently substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^6 is independently substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, each R^6 is independently $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-C(CH_3)_3$. In some embodiments, each R^6 is independently substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, each R^6 is independently substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, each R^6 is independently $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$. In some embodiments, each R^6 is independently substituted or

unsubstituted C₁-C₆heteroalkyl. In some embodiments, each R⁶ is independently substituted or unsubstituted C₁-C₄heteroalkyl. In some embodiments, each R⁶ is independently substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, each R⁶ is independently substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, each R⁶ is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R⁶ is independently substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, each R⁶ is independently substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, each R⁶ is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, each R⁶ is independently substituted or unsubstituted aralkyl. In some embodiments, each R⁶ is independently substituted or unsubstituted benzyl. In some embodiments, each R⁶ is independently substituted or unsubstituted aryl. In some embodiments, each R⁶ is independently substituted or unsubstituted phenyl. In some embodiments, each R⁶ is independently substituted or unsubstituted heteroaryl. In some embodiments, each R⁶ is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[00157] In some embodiments, each R⁷ is independently H. In some embodiments, each R⁷ is independently substituted or unsubstituted C₁-C₆alkyl. In some embodiments, each R⁷ is independently substituted or unsubstituted C₁-C₄alkyl. In some embodiments, each R⁷ is independently -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃. In some embodiments, each R⁷ is independently substituted or unsubstituted C₁-C₆haloalkyl. In some embodiments, each R⁷ is independently substituted or unsubstituted C₁-

C₄haloalkyl. In some embodiments, each R⁷ is independently -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃. In some embodiments, each R⁷ is independently substituted or unsubstituted C₁-C₆heteroalkyl. In some embodiments, each R⁷ is independently substituted or unsubstituted C₁-C₄heteroalkyl. In some embodiments, each R⁷ is independently substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, each R⁷ is independently substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, each R⁷ is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R⁷ is independently substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, each R⁷ is independently substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, each R⁷ is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, each R⁷ is independently substituted or unsubstituted aralkyl. In some embodiments, each R⁷ is independently substituted or unsubstituted benzyl. In some embodiments, each R⁷ is independently substituted or unsubstituted aryl. In some embodiments, each R⁷ is independently substituted or unsubstituted phenyl. In some embodiments, each R⁷ is independently substituted or unsubstituted heteroaryl. In some embodiments, each R⁷ is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

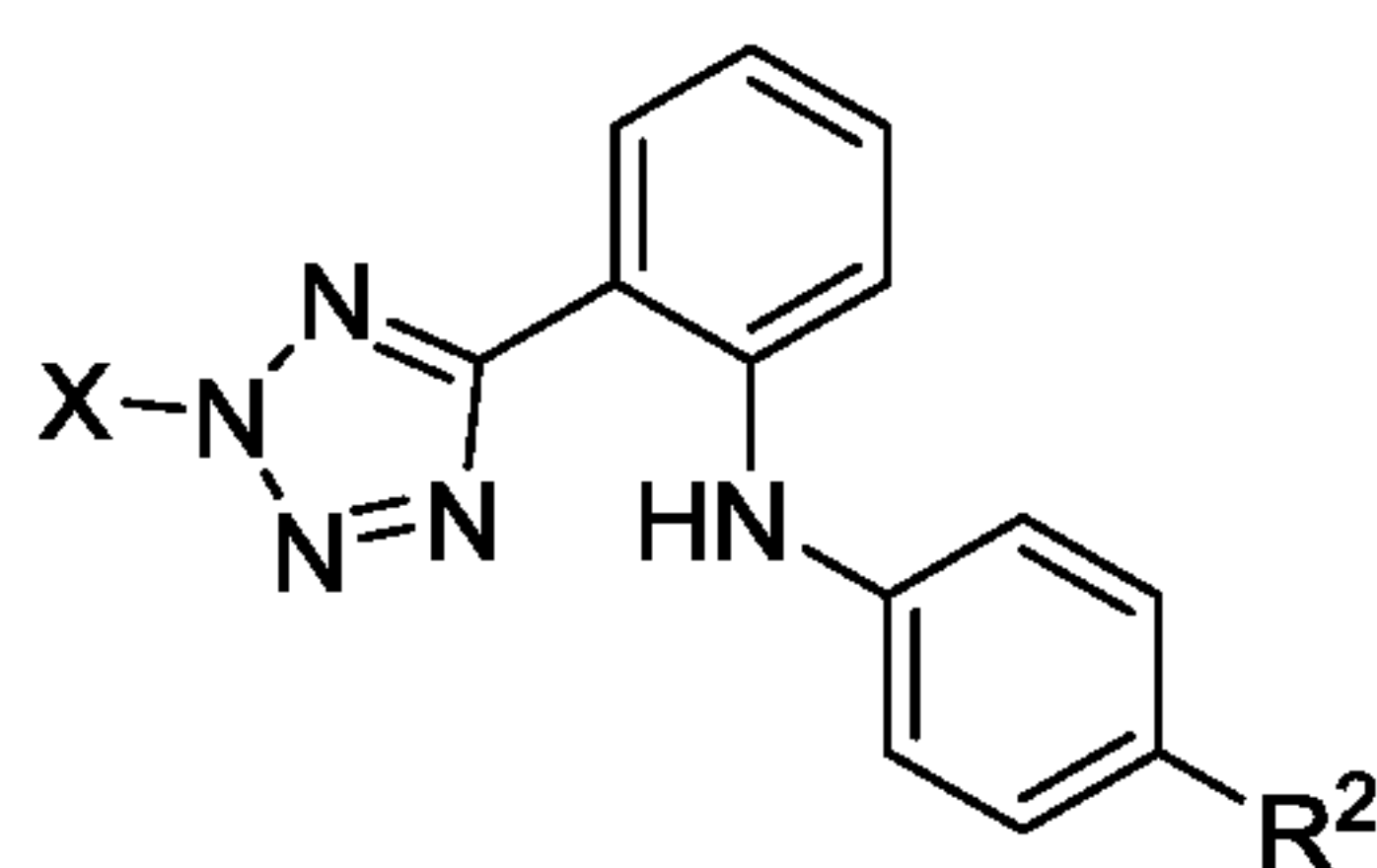
[00158] In some embodiments, the compound has the structure of Formula (IIa), or a pharmaceutically acceptable salt thereof:



Formula (IIa).

[00159] In some embodiments, R^2 is substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, R^2 is substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, R^2 is - CH_2F , - CHF_2 , - CF_3 , or - CH_2CF_3 . In some embodiments, R^2 is - CF_3 .

[00160] In some embodiments, the compound has the structure of Formula (IIb), or a pharmaceutically acceptable salt thereof:

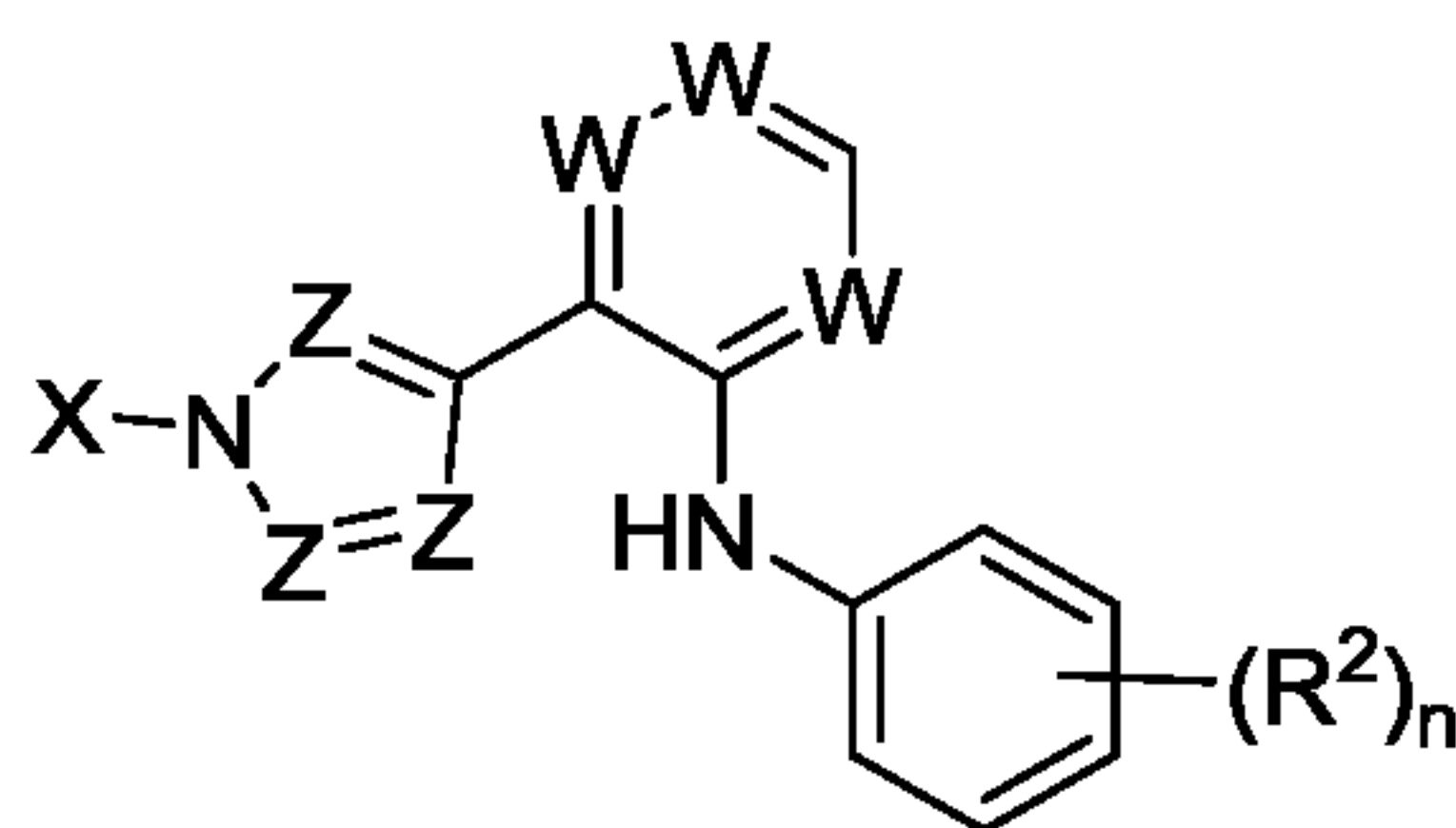


Formula (IIb).

[00161] In some embodiments, R^2 is substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, R^2 is substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, R^2 is - CH_2F , - CHF_2 , - CF_3 , or - CH_2CF_3 . In some embodiments, R^2 is - CF_3 .

[00162] In some embodiments, X is $-(CH_2)_r-OH$, $-(CH_2)_r-OR''$, $-(CH_2)_r-N(R')_2$, $-(CH_2)_r-NR'S(=O)_2R''$, $-(CH_2)_r-S(=O)_2N(R')_2$, $-(CH_2)_r-SR'$, $-(CH_2)_r-S(=O)R''$, $-(CH_2)_r-S(=O)_2R''$, $-(CH_2)_r-C(=O)R''$, $-(CH_2)_r-OC(=O)R''$, $-(CH_2)_r-CO_2H$, $-(CH_2)_r-CO_2R''$, $-(CH_2)_r-OC(=O)OR''$, $-(CH_2)_r-NR'C(=O)R''$, $-(CH_2)_r-C(=O)N(R')_2$, $-(CH_2)_r-NR''C(=O)OR'$, $-(CH_2)_r-OC(=O)N(R'')_2$; r is 1, 2, 3, or 4; each R' is independently H substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and each R'' is independently unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00163] Provided in another aspect is a compound of Formula (III), or a pharmaceutically acceptable salt thereof:



Formula (III)

wherein:

each Z is independently N or CR^Z;

each R^Z is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

X is substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -L¹-Y¹, or -L²-L³-Y²;

L¹ is substituted or unsubstituted C₁-C₆alkylene;

Y¹ is substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L² is absent or substituted or unsubstituted C₁-C₆alkylene;

L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -O-NR³(C=O)-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)-, -(SO₂)NR³-(C=O)O-, -O(C=O)-NR³(SO₂)-, -NR³(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)NR³-, -O(C=O)-NR³(SO₂)-NR³-, or -NR³(SO₂)NR³-(C=O)O-;

each R³ is independently H or substituted or unsubstituted C₁-C₆alkyl;

Y² is H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

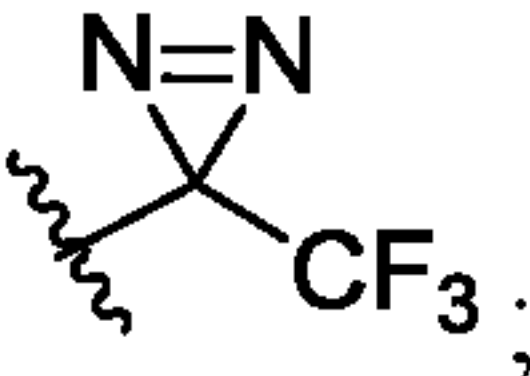
or R³ and Y² on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

each W is CR¹ or N with the provision that at least one W is N;

each R^1 is independently H, halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

n is 0, 1, 2, 3, 4, or 5;

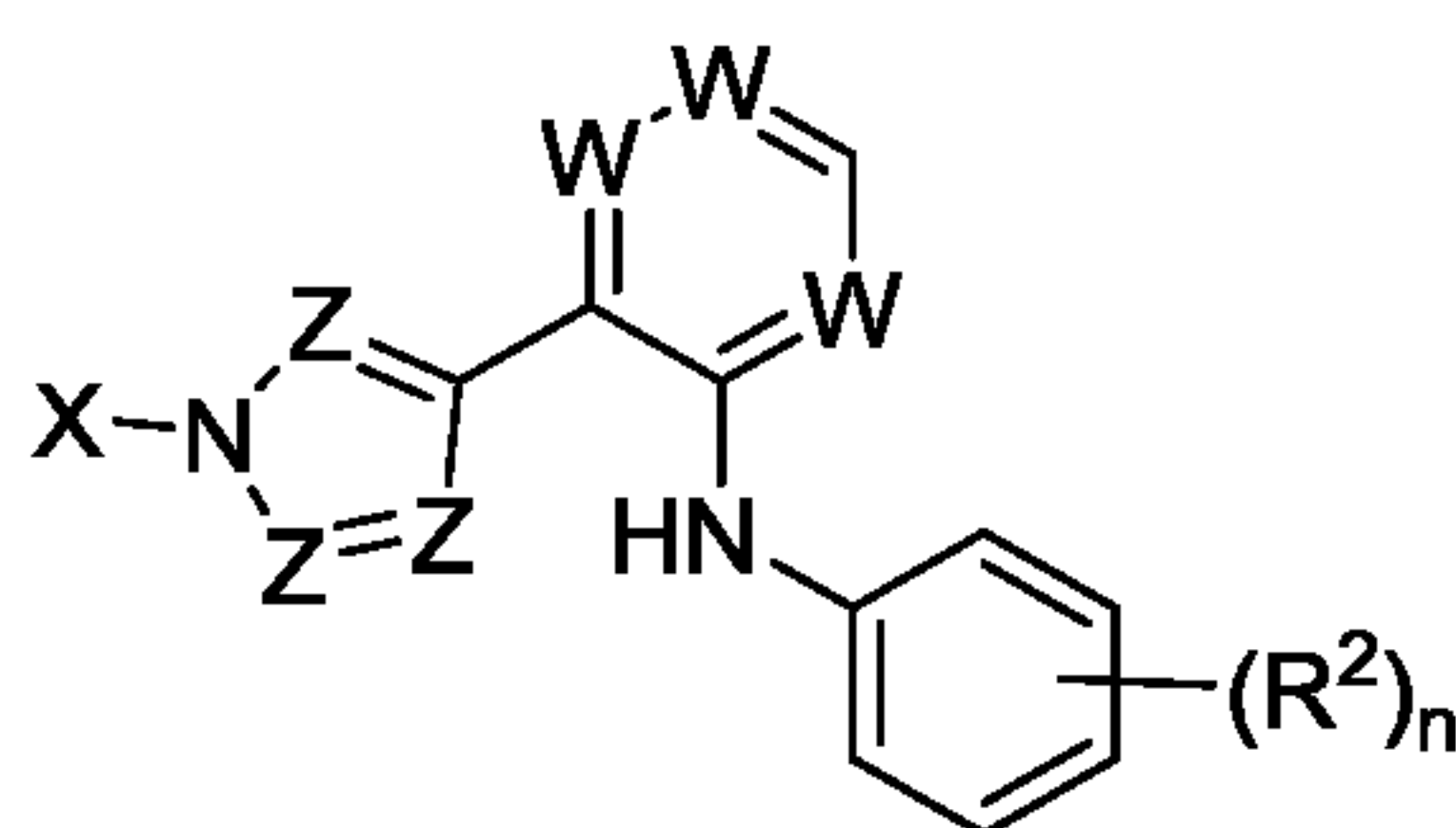
each R^2 is independently H, halogen, -N₃, -CN, -OR⁵, -SR⁵, -(SO₂)R⁵, -N(R⁵)₂, -CO₂R⁵, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or

unsubstituted aryl, substituted or unsubstituted heteroaryl, or ;

each R^4 is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

each R^5 is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00164] Provided in another aspect is a compound of Formula (III), or a pharmaceutically acceptable salt thereof:



Formula (III)

wherein:

each Z is independently N or CR^z;

each R^z is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl,

substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

X is substituted or unsubstituted C₂-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -L¹-Y¹, or -L²-L³-Y²;

L¹ is substituted or unsubstituted C₁-C₆alkylene;

Y¹ is substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L² is absent or substituted or unsubstituted C₁-C₆alkylene;

L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -O-NR³(C=O)-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)-, -(SO₂)NR³-(C=O)O-, -O(C=O)-NR³(SO₂)-, -NR³(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)NR³-, -O(C=O)-NR³(SO₂)-NR³-, or -NR³(SO₂)NR³-(C=O)O-;

each R³ is independently H or substituted or unsubstituted C₁-C₆alkyl;

Y² is H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or R³ and Y² on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

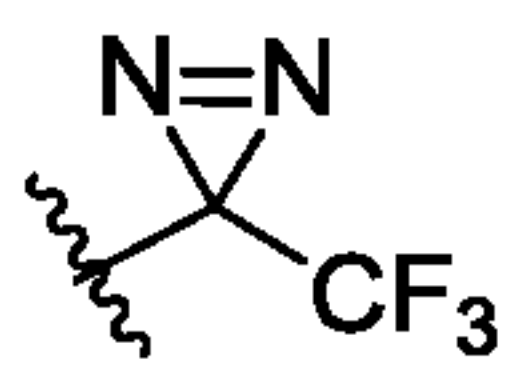
each W is CR¹ or N with the provision that at least one W is N;

each R¹ is independently H, halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

n is 0, 1, 2, 3, 4, or 5;

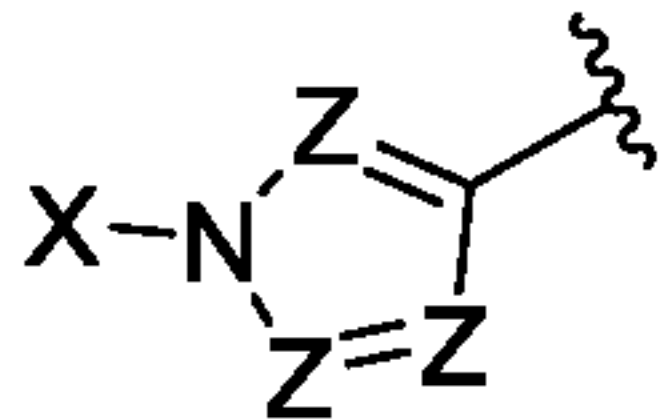
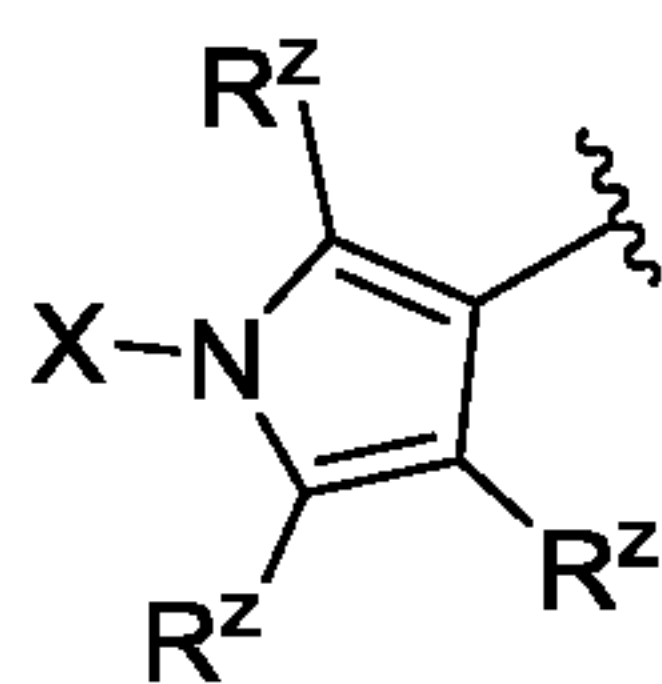
each R² is independently H, halogen, -N₃, -CN, -OR⁵, -SR⁵, -(SO₂)R⁵, -N(R⁵)₂, -CO₂R⁵, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or

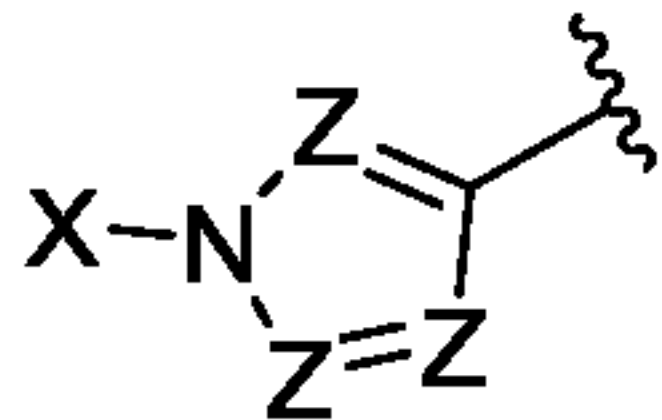
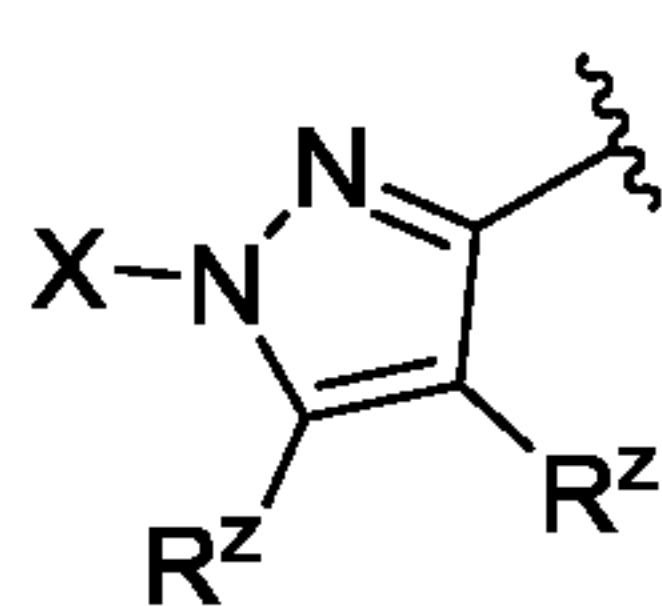
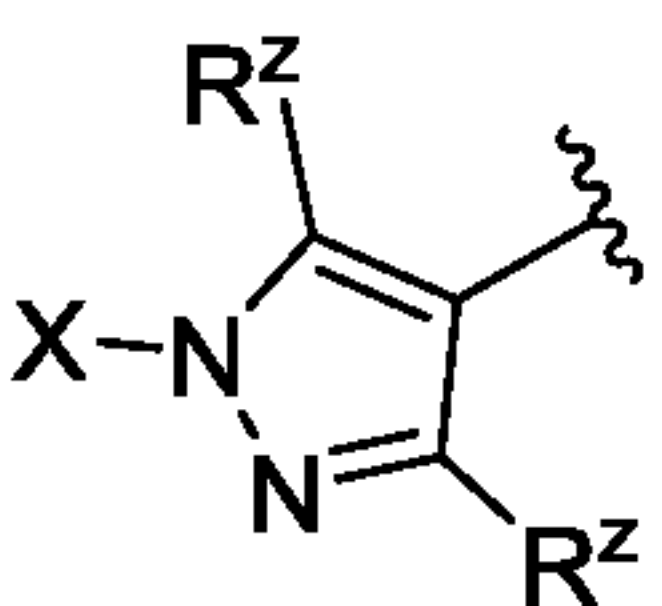
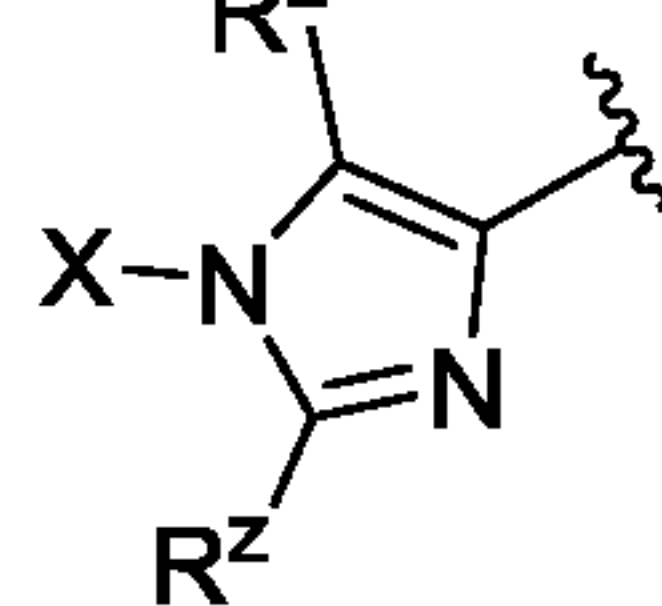
unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or

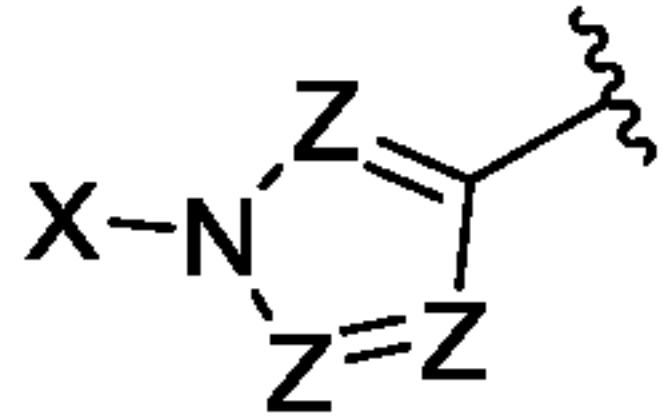
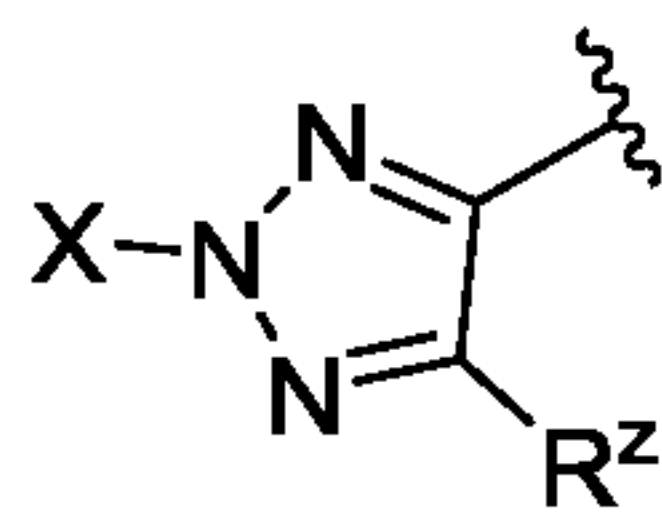
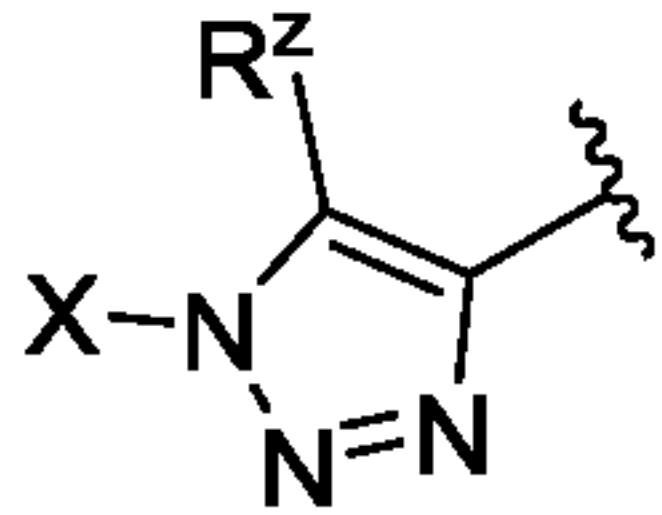
unsubstituted aryl, substituted or unsubstituted heteroaryl, or ;

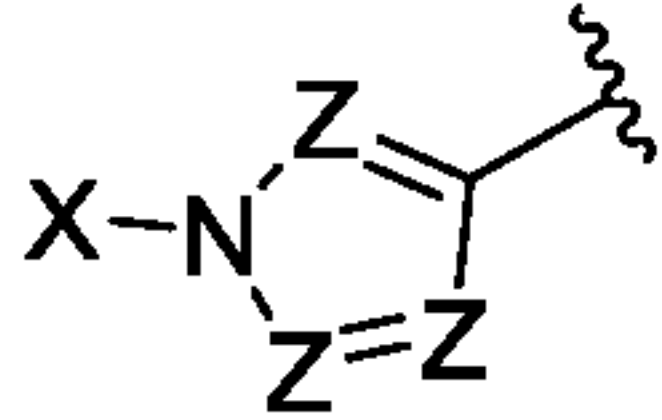
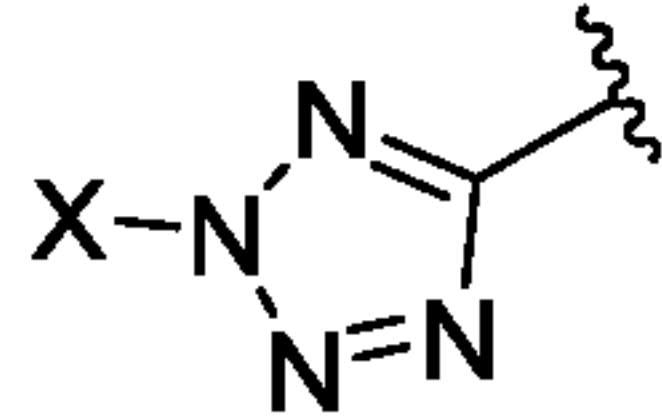
each R⁴ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

each R⁵ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00165] In some embodiments,  is .

[00166] In some embodiments,  is , , or .

[00167] In some embodiments,  is  or .

[00168] In some embodiments,  is .

[00169] In some embodiments, each R^z is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, each R^z is independently H, substituted or unsubstituted C₁-C₆alkyl, or substituted or unsubstituted C₁-C₆haloalkyl. In some embodiments, each R^z is independently H or substituted or unsubstituted C₁-C₆alkyl. In some embodiments, each R^z is independently H or substituted or unsubstituted C₁-C₄alkyl. In some embodiments, each R^z is independently H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃.

[00170] In some embodiments, each R^Z is independently H. In some embodiments, each R^Z is independently substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, each R^Z is independently $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$. In some embodiments, each R^Z is independently substituted or unsubstituted C_1 - C_6 heteroalkyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_1 - C_4 heteroalkyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_3 - C_{10} cycloalkyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_3 - C_6 cycloalkyl. In some embodiments, each R^Z is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_2 - C_{10} heterocycloalkyl. In some embodiments, each R^Z is independently substituted or unsubstituted C_2 - C_6 heterocycloalkyl. In some embodiments, each R^Z is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, each R^Z is independently substituted or unsubstituted aralkyl. In some embodiments, each R^Z is independently substituted or unsubstituted benzyl. In some embodiments, each R^Z is independently substituted or unsubstituted aryl. In some embodiments, each R^Z is independently substituted or unsubstituted phenyl. In some embodiments, each R^Z is independently substituted or unsubstituted heteroaryl. In some embodiments, each R^Z is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[00171] In some embodiments, X is substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00172] In some embodiments, X is substituted or unsubstituted C₂-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00173] In some embodiments, X is substituted or unsubstituted C₁-C₆alkyl. In some embodiments, X is substituted or unsubstituted C₁-C₄alkyl. In some embodiments, X is -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃. In some embodiments, X is substituted or unsubstituted C₂-C₆alkyl. In some embodiments, X is substituted or unsubstituted C₂-C₄alkyl. In some embodiments, X is -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃. In some embodiments, X is substituted or unsubstituted C₁-C₆haloalkyl. In some embodiments, X is substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, X is -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃. In some embodiments, X is substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, X is substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, X is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, X is substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, X is substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, X is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, X is substituted or unsubstituted aryl. In some embodiments, X is substituted or unsubstituted phenyl. In some embodiments, X is substituted or unsubstituted heteroaryl. In some embodiments, X is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or

unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[00174] In some embodiments, X is $-L^1-Y^1$. In some embodiments, L^1 is substituted or unsubstituted C_1-C_6 alkylene. In some embodiments, L^1 is substituted or unsubstituted C_1-C_4 alkylene. In some embodiments, L^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$. In some embodiments, Y^1 is substituted or unsubstituted C_3-C_{10} cycloalkyl. In some embodiments, Y^1 is substituted or unsubstituted C_3-C_6 cycloalkyl. In some embodiments, Y^1 is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, Y^1 is substituted or unsubstituted C_2-C_{10} heterocycloalkyl. In some embodiments, Y^1 is substituted or unsubstituted C_2-C_6 heterocycloalkyl. In some embodiments, Y^1 is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, Y^1 is substituted or unsubstituted aryl. In some embodiments, Y^1 is substituted or unsubstituted phenyl. In some embodiments, Y^1 is substituted or unsubstituted heteroaryl. In some embodiments, Y^1 is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[00175] In some embodiments, L^1 is substituted or unsubstituted C_1-C_4 alkylene; and Y^1 is substituted or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted C_2-C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments,

L^1 is substituted or unsubstituted C_1 - C_4 alkylene; and Y^1 is substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_6 heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl.

[00176] In some embodiments, X is $-L^2-L^3-Y^2$. In some embodiments, L^2 is absent. In some embodiments, L^2 is substituted or unsubstituted C_1 - C_6 alkylene. In some embodiments, L^2 is substituted or unsubstituted C_1 - C_4 alkylene. In some embodiments, L^2 is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, or $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$. In some embodiments, L^3 is $-\text{O}-$. In some embodiments, L^3 is $-\text{S}-$. In some embodiments, L^3 is $-(\text{S}=\text{O})-$. In some embodiments, L^3 is $-(\text{SO}_2)-$. In some embodiments, L^3 is $-\text{NR}^3-$. In some embodiments, L^3 is $-(\text{C}=\text{O})-$. In some embodiments, L^3 is $-(\text{C}=\text{O})\text{O}-$. In some embodiments, L^3 is $-\text{O}(\text{C}=\text{O})-$. In some embodiments, L^3 is $-(\text{C}=\text{O})\text{NR}^3-$. In some embodiments, L^3 is $-(\text{C}=\text{O})\text{NR}^3-\text{O}-$. In some embodiments, L^3 is $-\text{O}-\text{NR}^3(\text{C}=\text{O})-$. In some embodiments, L^3 is $-\text{NR}^3(\text{C}=\text{O})-$. In some embodiments, L^3 is $-\text{NR}^3(\text{C}=\text{O})\text{NR}^3-$. In some embodiments, L^3 is $-\text{O}(\text{C}=\text{O})\text{NR}^3-$. In some embodiments, L^3 is $-\text{NR}^3(\text{C}=\text{O})\text{O}-$. In some embodiments, L^3 is $-\text{NR}^3(\text{SO}_2)\text{NR}^3-$. In some embodiments, L^3 is $-\text{NR}^3(\text{SO}_2)-$. In some embodiments, L^3 is $-(\text{SO}_2)\text{NR}^3-$. In some embodiments, L^3 is $-(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})-$. In some embodiments, L^3 is $-(\text{C}=\text{O})-\text{NR}^3(\text{SO}_2)-$. In some embodiments, L^3 is $-(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})\text{O}-$. In some embodiments, L^3 is $-\text{O}(\text{C}=\text{O})-\text{NR}^3(\text{SO}_2)-$. In some embodiments, L^3 is $-\text{NR}^3(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})-$. In some embodiments, L^3 is $-(\text{C}=\text{O})-\text{NR}^3(\text{SO}_2)\text{NR}^3-$. In some embodiments, L^3 is $-\text{O}(\text{C}=\text{O})-\text{NR}^3(\text{SO}_2)-\text{NR}^3-$. In some embodiments, L^3 is $-\text{NR}^3(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})\text{O}-$. In some embodiments, each R^3 is independently H. In some embodiments, each R^3 substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, R^3 is substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, R^3 is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, or $-\text{C}(\text{CH}_3)_3$.

[00177] In some embodiments, Y^2 is independently H. In some embodiments, Y^2 substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, Y^2 substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, Y^2 is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, or $-\text{C}(\text{CH}_3)_3$. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, Y^2 is $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, or $-\text{CH}_2\text{CF}_3$. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_6 heteroalkyl. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_4 heteroalkyl. In some embodiments, Y^2 is substituted or unsubstituted C_3 - C_{10} cycloalkyl. In some embodiments, Y^2 is substituted or unsubstituted C_3 - C_6 cycloalkyl. In some embodiments, Y^2 is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, Y^2 is

substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, Y² is substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, Y² is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, Y² is substituted or unsubstituted aryl. In some embodiments, Y² is substituted or unsubstituted phenyl. In some embodiments, Y² is substituted or unsubstituted heteroaryl. In some embodiments, Y² is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

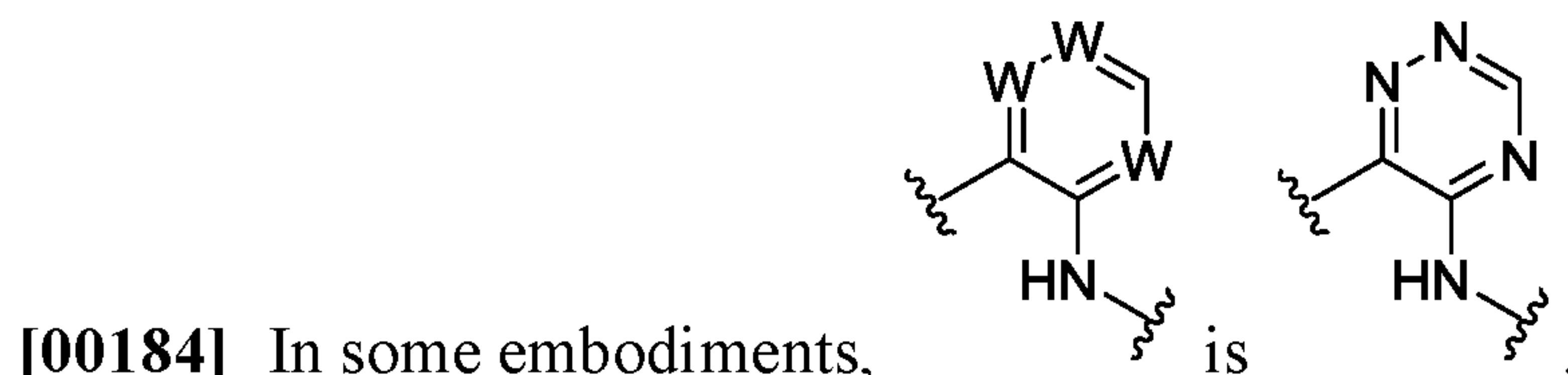
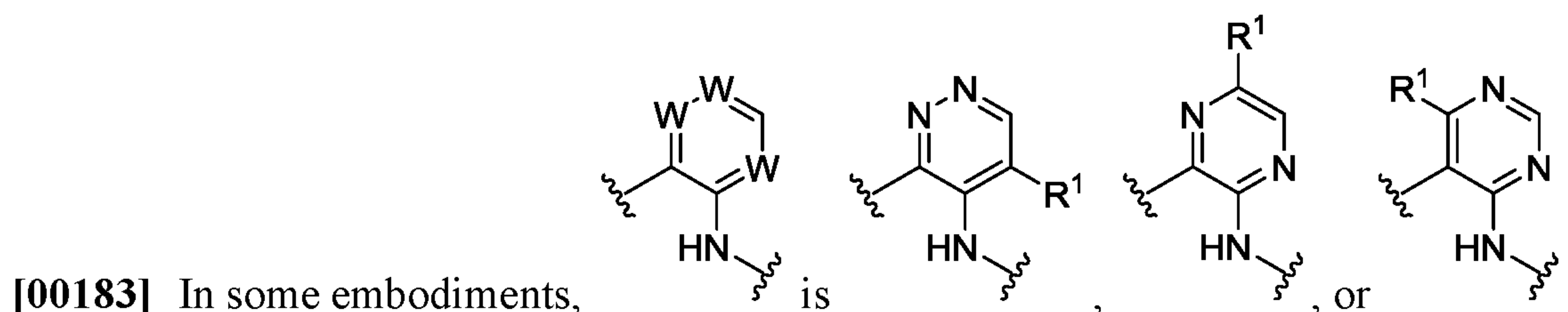
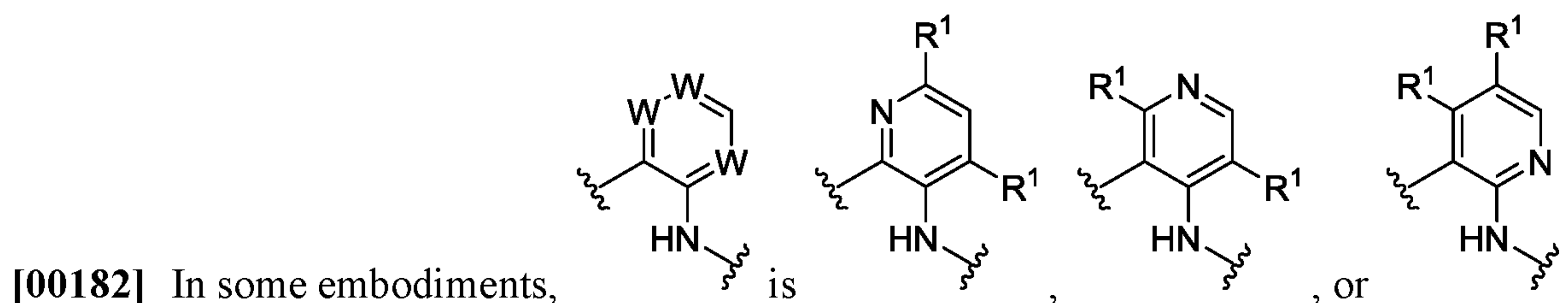
[00178] In some embodiments, R³ and Y² on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00179] In some embodiments, L² is substituted or unsubstituted C₁-C₆alkylene; L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -NR³(SO₂)NR³-(C=O)-, or -NR³(SO₂)NR³-(C=O)O-; each R³ is independently H or substituted or unsubstituted C₁-C₆alkyl; and Y² is H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00180] In some embodiments, L² is substituted or unsubstituted C₁-C₄alkylene; L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -NR³(SO₂)NR³-(C=O)-, or -NR³(SO₂)NR³-(C=O)O-; each R³ is independently H or substituted or unsubstituted C₁-C₄alkyl; and Y² is H, substituted or

unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl.

[00181] In some embodiments, one W is N. In some embodiments, two W are N. In some embodiments, three W are N.



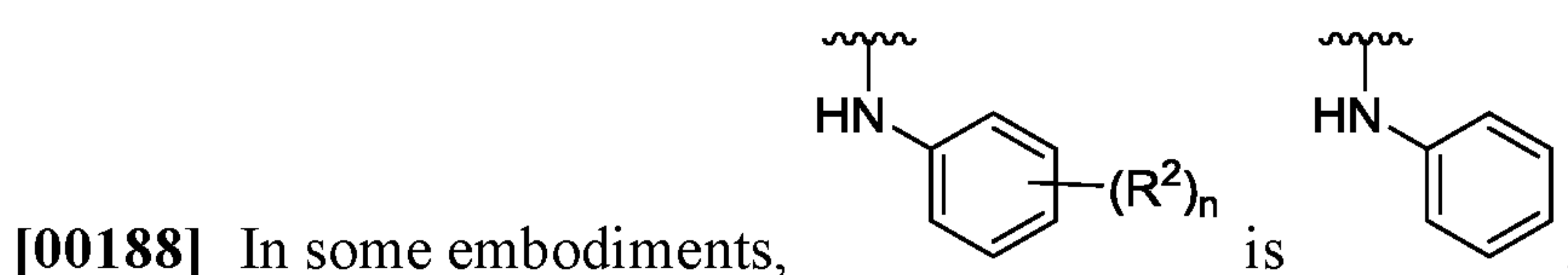
[00185] In some embodiments, each R¹ is independently H. In some embodiments, each R¹ is halogen. In some embodiments, each R¹ is independently F, Cl, Br, or I. In some embodiments, each R¹ is independently -CN. In some embodiments, each R¹ is independently -OR⁴. In some embodiments, each R¹ is independently -SR⁴. In some embodiments, each R¹ is independently -N(R⁴)₂. In some embodiments, each R¹ is independently substituted or unsubstituted C₁-C₆alkyl. In some embodiments, each R¹ is independently substituted or unsubstituted C₁-C₄alkyl. In some embodiments, each R¹ is independently -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃. In some embodiments, each R¹ is independently substituted or unsubstituted C₁-C₆haloalkyl. In some embodiments, each R¹ is independently substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, each R¹ is independently -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃. In some embodiments, each R¹ is independently substituted or unsubstituted C₁-C₆heteroalkyl. In some embodiments, each R¹ is independently substituted or unsubstituted C₁-C₄heteroalkyl. In some embodiments, each R¹ is independently substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, each R¹ is independently substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, each R¹ is independently substituted or

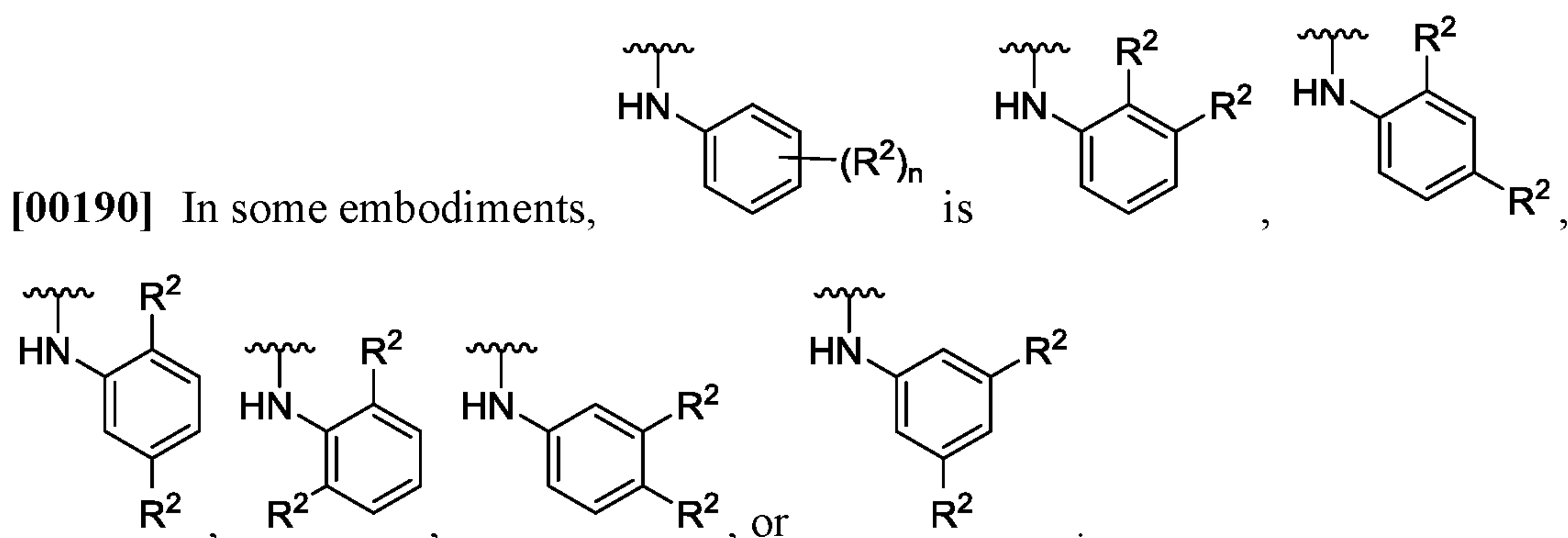
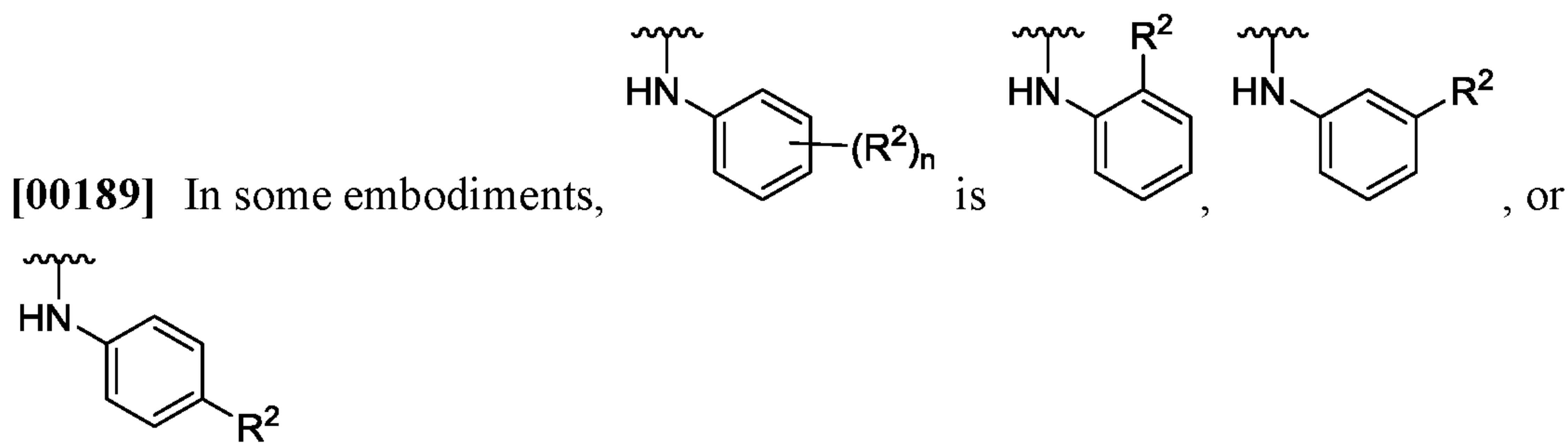
unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_2 - C_{10} heterocycloalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_2 - C_6 heterocycloalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, each R^1 is independently substituted or unsubstituted aralkyl. In some embodiments, each R^1 is independently substituted or unsubstituted benzyl. In some embodiments, each R^1 is independently substituted or unsubstituted aryl. In some embodiments, each R^1 is independently substituted or unsubstituted phenyl. In some embodiments, each R^1 is independently substituted or unsubstituted heteroaryl. In some embodiments, each R^1 is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[00186] In some embodiments, each R^1 is independently H, halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00187] In some embodiments, each R^4 is independently H. In some embodiments, each R^4 is independently substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^4 is independently substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, each R^4 is independently -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃. In some embodiments, each R^4 is independently substituted or unsubstituted C_1 -

C₆haloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, each R⁴ is independently -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃. In some embodiments, each R⁴ is independently substituted or unsubstituted C₁-C₆heteroalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₁-C₄heteroalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, each R⁴ is independently substituted or unsubstituted aralkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted benzyl. In some embodiments, each R⁴ is independently substituted or unsubstituted aryl. In some embodiments, each R⁴ is independently substituted or unsubstituted phenyl. In some embodiments, each R⁴ is independently substituted or unsubstituted heteroaryl. In some embodiments, each R⁴ is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

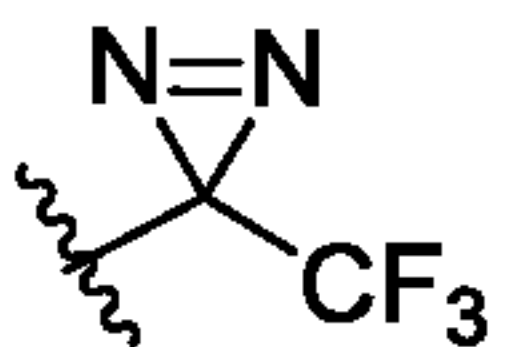




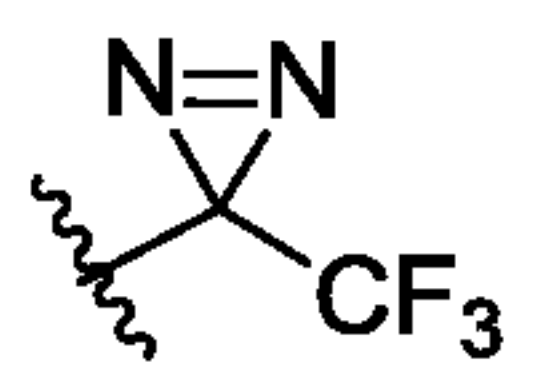
[00191] In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4. In some embodiments, n is 5.

[00192] In some embodiments, each R^2 is independently H. In some embodiments, each R^2 is independently halogen. In some embodiments, each R^2 is independently F, Cl, Br, or I. In some embodiments, each R^2 is independently $-N_3$. In some embodiments, each R^2 is independently $-CN$. In some embodiments, each R^2 is independently $-OR^5$. In some embodiments, each R^2 is independently $-SR^5$. In some embodiments, each R^2 is independently $-(SO_2)R^5$. In some embodiments, each R^2 is independently $-N(R^5)_2$. In some embodiments, each R^2 is independently $-CO_2R^5$. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, each R^2 is independently $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-C(CH_3)_3$. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, each R^2 is independently $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_6 heteroalkyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_4 heteroalkyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_3 - C_{10} cycloalkyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_3 - C_6 cycloalkyl. In some embodiments, each R^2 is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R^2 is

independently substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, each R² is independently substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, each R² is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, each R² is independently substituted or unsubstituted aralkyl. In some embodiments, each R² is independently substituted or unsubstituted benzyl. In some embodiments, each R² is independently substituted or unsubstituted aryl. In some embodiments, each R² is independently substituted or unsubstituted phenyl. In some embodiments, each R² is independently substituted or unsubstituted heteroaryl. In some embodiments, each R² is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl. In

some embodiments, each R² is independently .

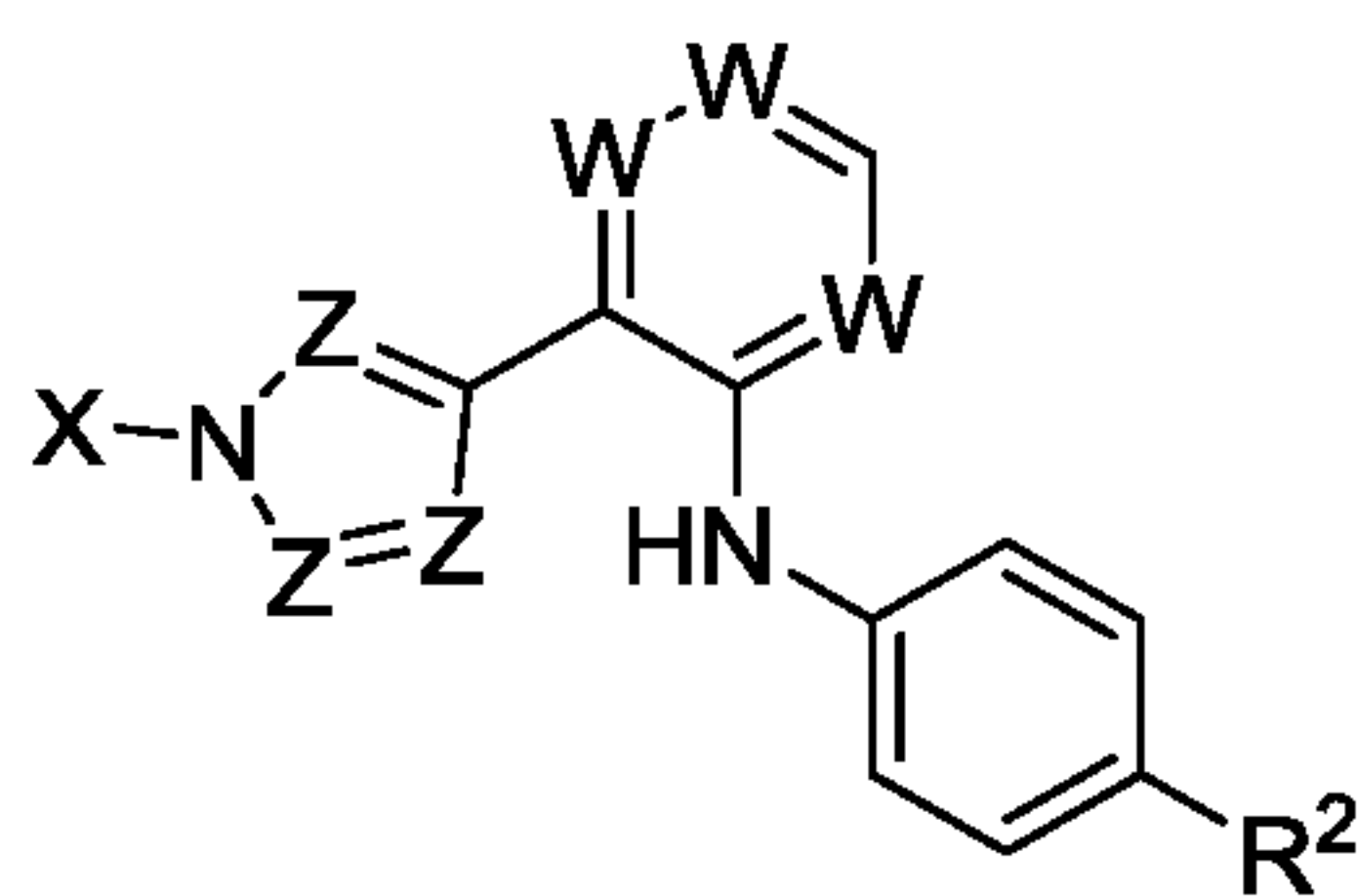
[00193] In some embodiments, each R² is independently H, halogen, -N₃, -OR⁵, -(SO₂)R⁵, -CO₂R⁵, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, or



[00194] In some embodiments, each R⁵ is independently H. In some embodiments, each R⁵ is independently substituted or unsubstituted C₁-C₆alkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₁-C₄alkyl. In some embodiments, each R⁵ is independently -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃. In some embodiments, each R⁵ is independently substituted or unsubstituted C₁-C₆haloalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₁-

C₄haloalkyl. In some embodiments, each R⁵ is independently -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃. In some embodiments, each R⁵ is independently substituted or unsubstituted C₁-C₆heteroalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₁-C₄heteroalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted oxazolidinonyl, or substituted or unsubstituted imidazolidin-2-onyl. In some embodiments, each R⁵ is independently substituted or unsubstituted aralkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted benzyl. In some embodiments, each R⁵ is independently substituted or unsubstituted aryl. In some embodiments, each R⁵ is independently substituted or unsubstituted phenyl. In some embodiments, each R⁵ is independently substituted or unsubstituted heteroaryl. In some embodiments, each R⁵ is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

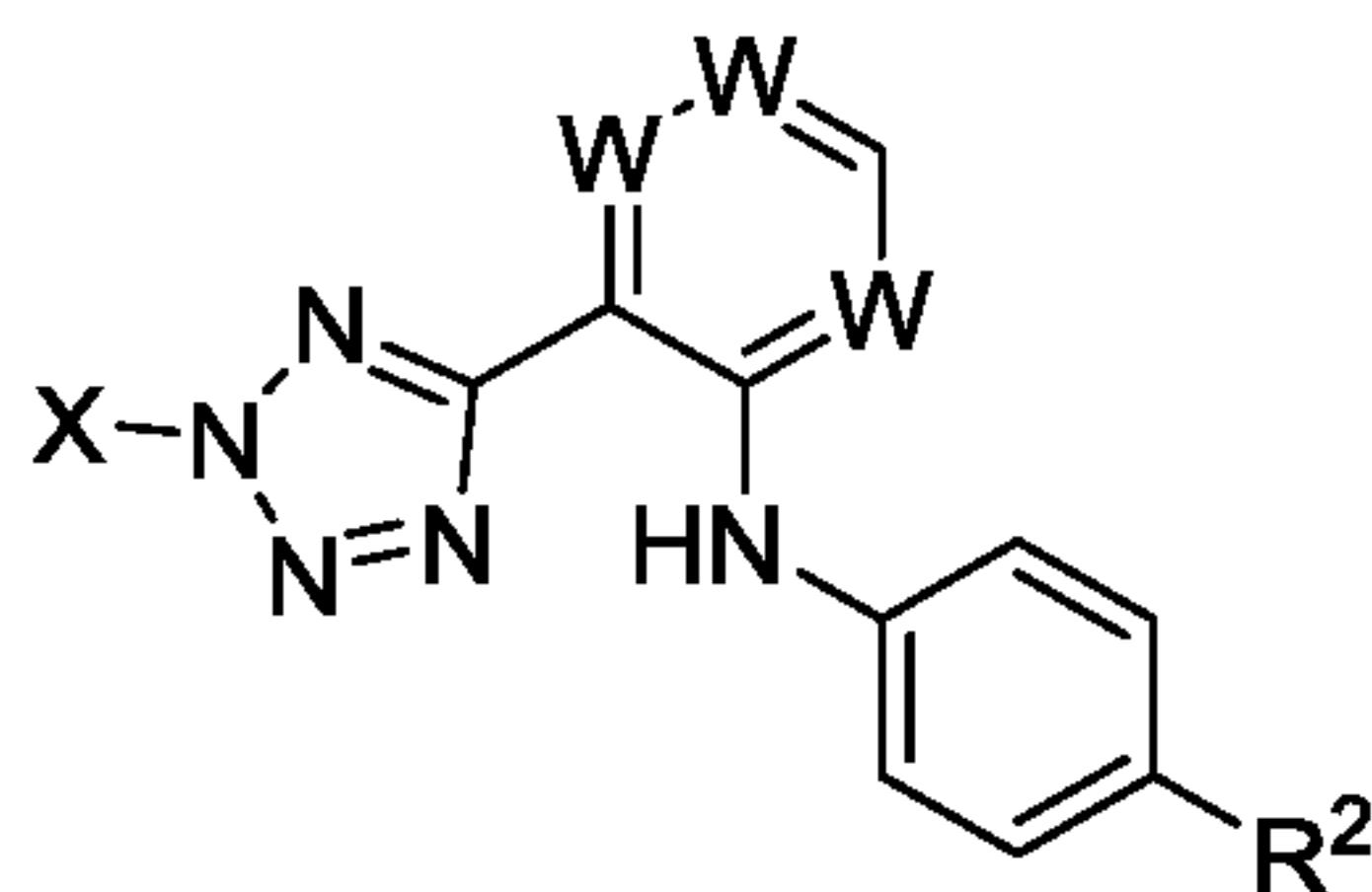
[00195] In some embodiments, the compound has the structure of Formula (IIIa), or a pharmaceutically acceptable salt thereof:



Formula (IIIa).

[00196] In some embodiments, R^2 is substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, R^2 is substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, R^2 is - CH_2F , - CHF_2 , - CF_3 , or - CH_2CF_3 . In some embodiments, R^2 is - CF_3 .

[00197] In some embodiments, the compound has the structure of Formula (IIIb), or a pharmaceutically acceptable salt thereof:



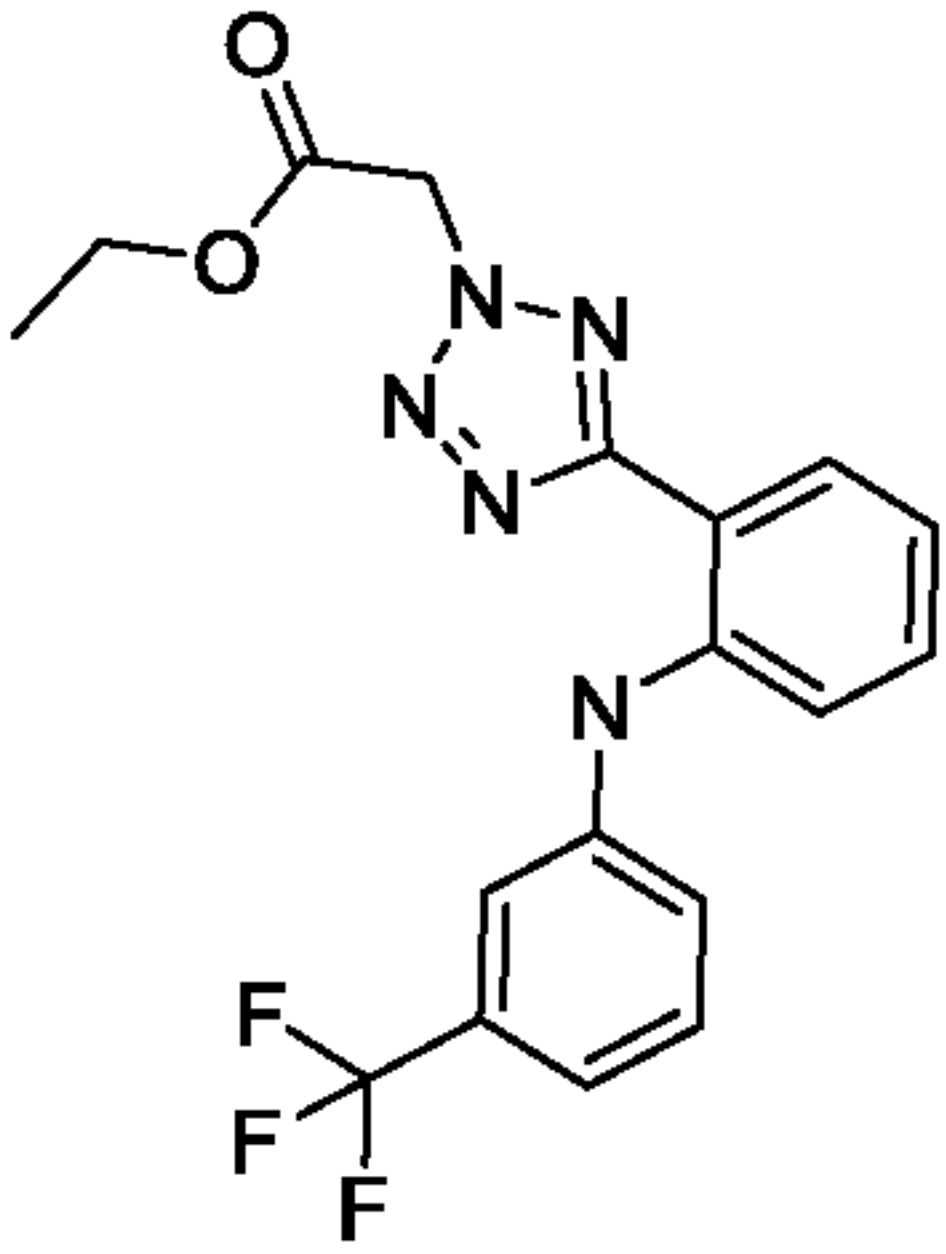
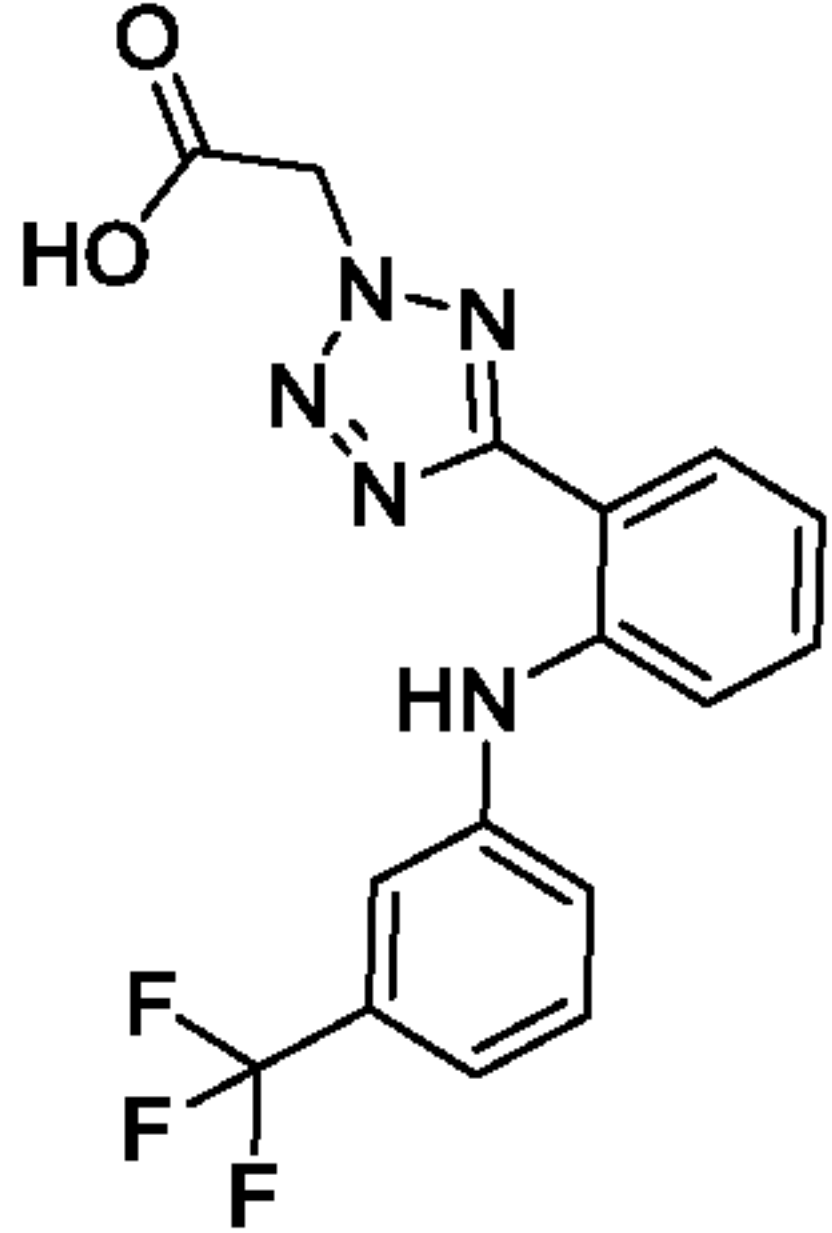
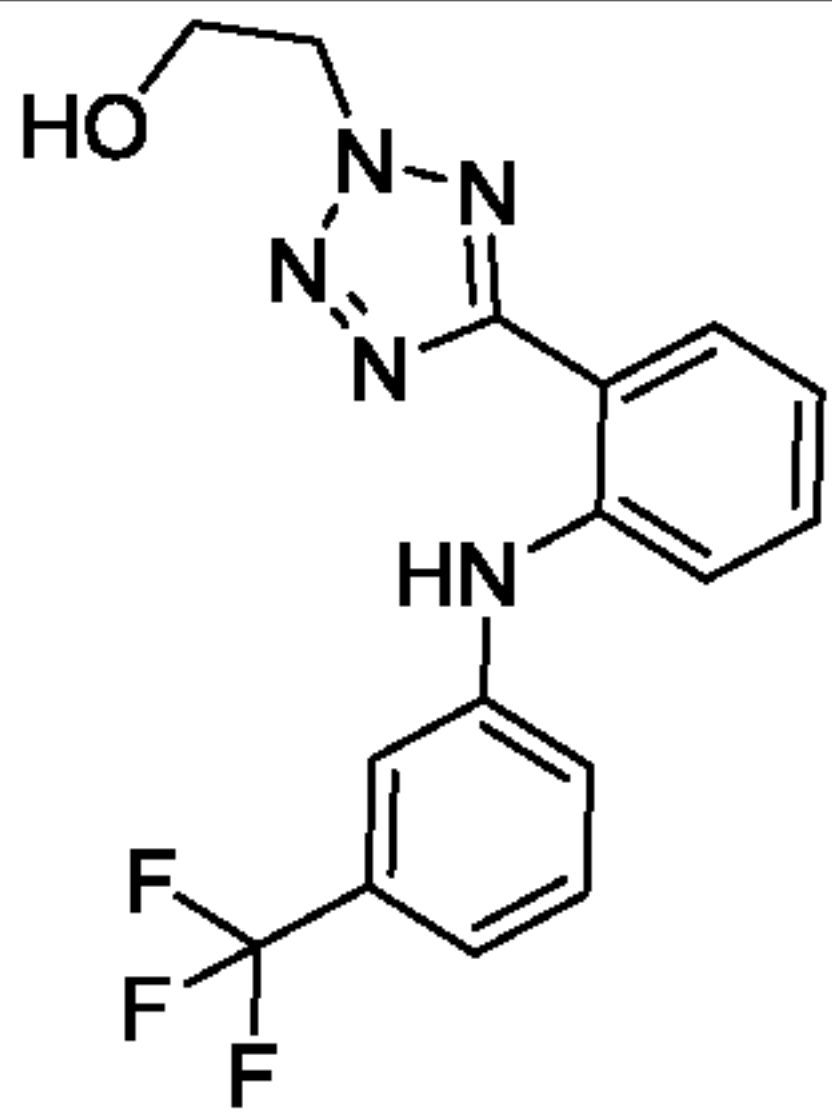
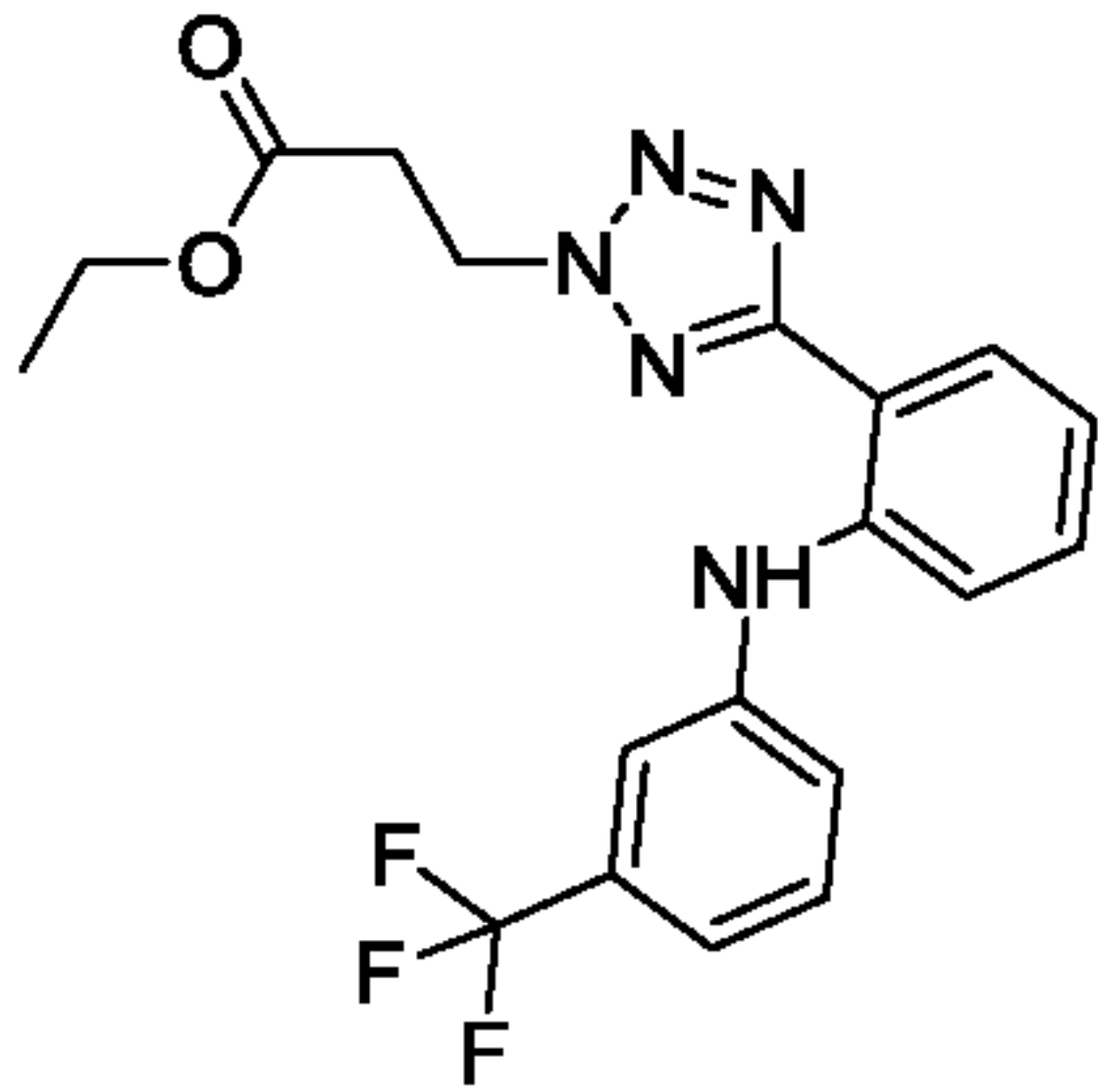
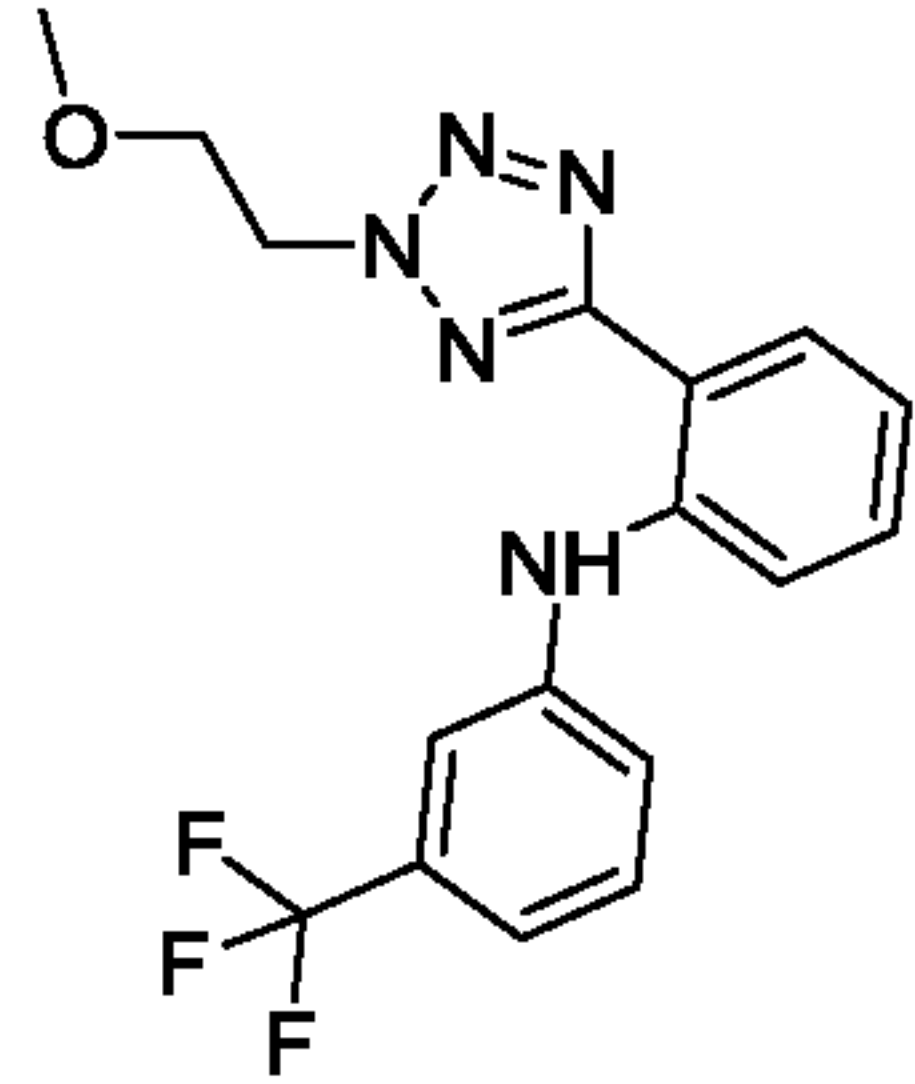
Formula (IIIb).

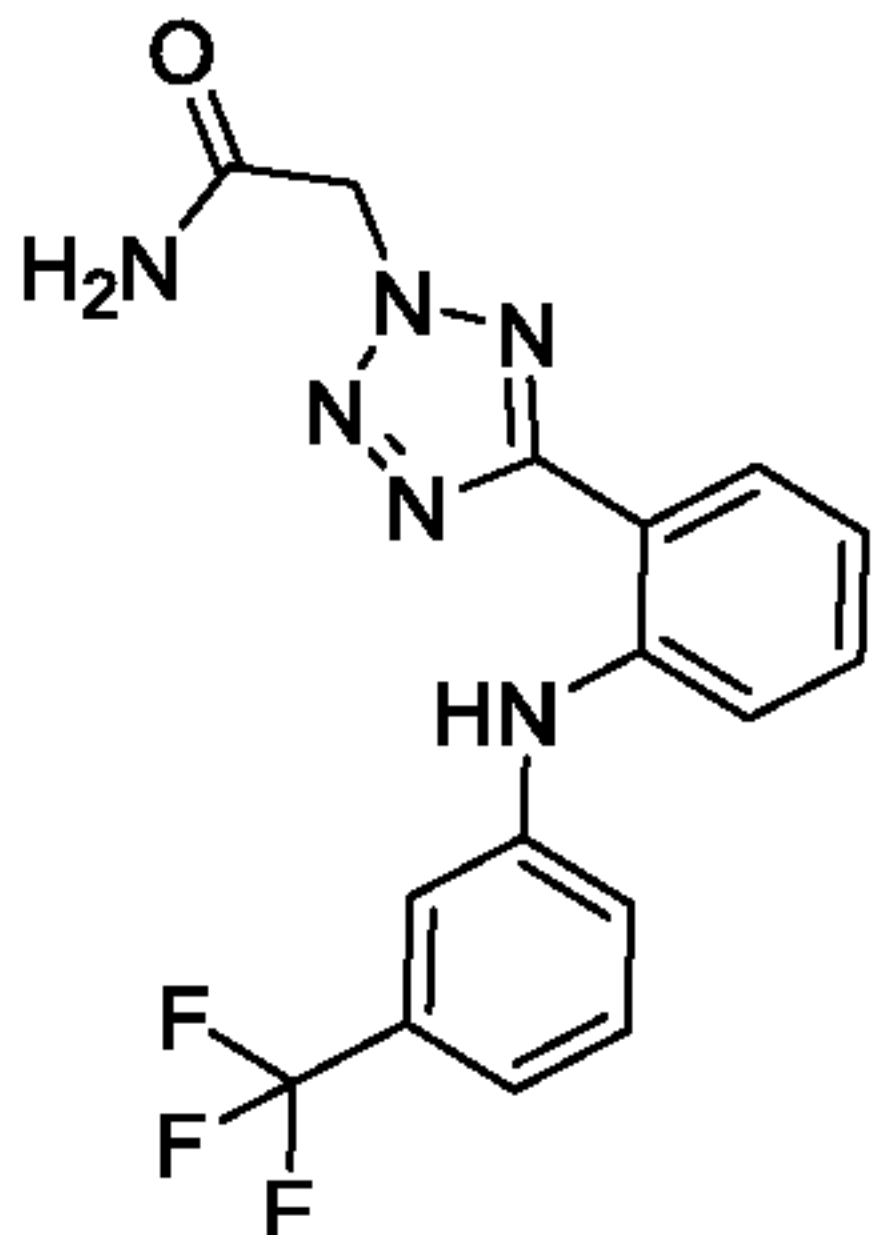
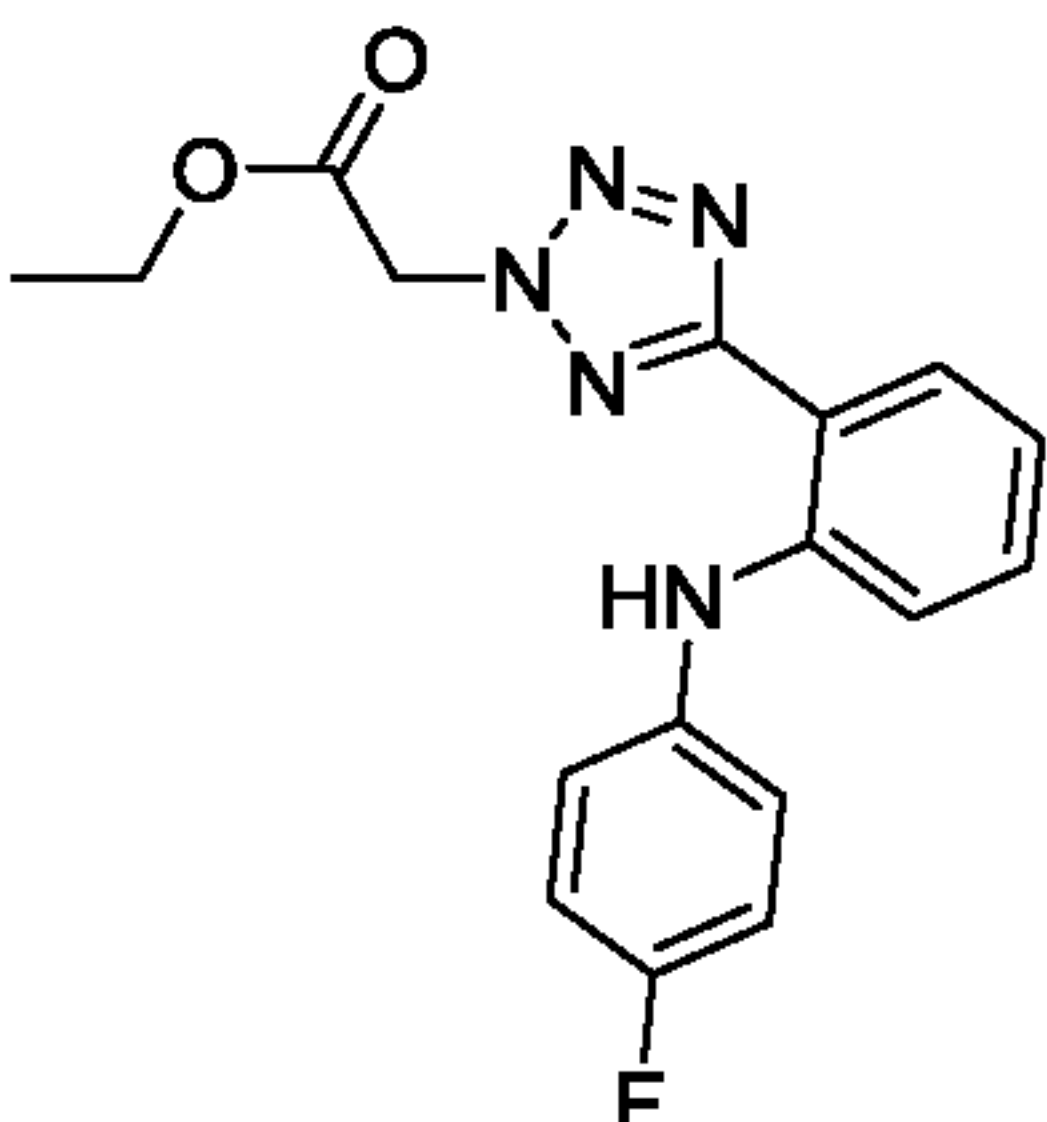
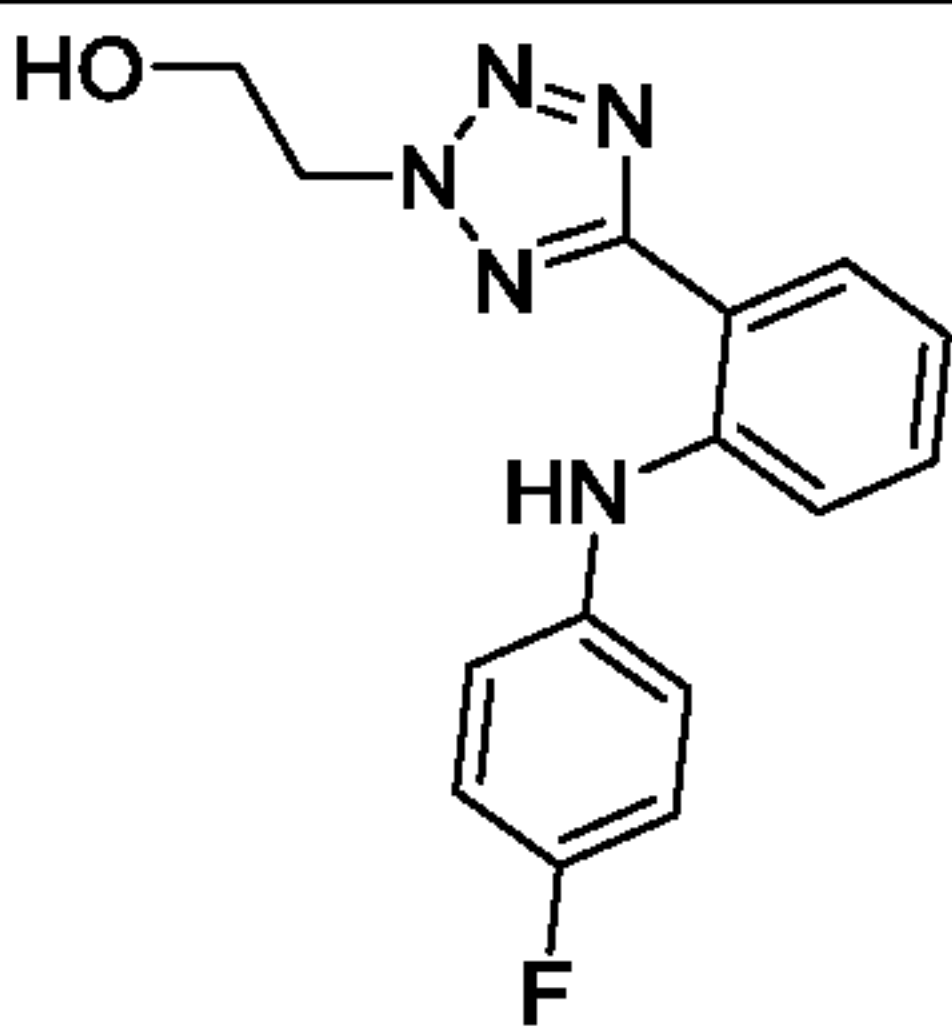
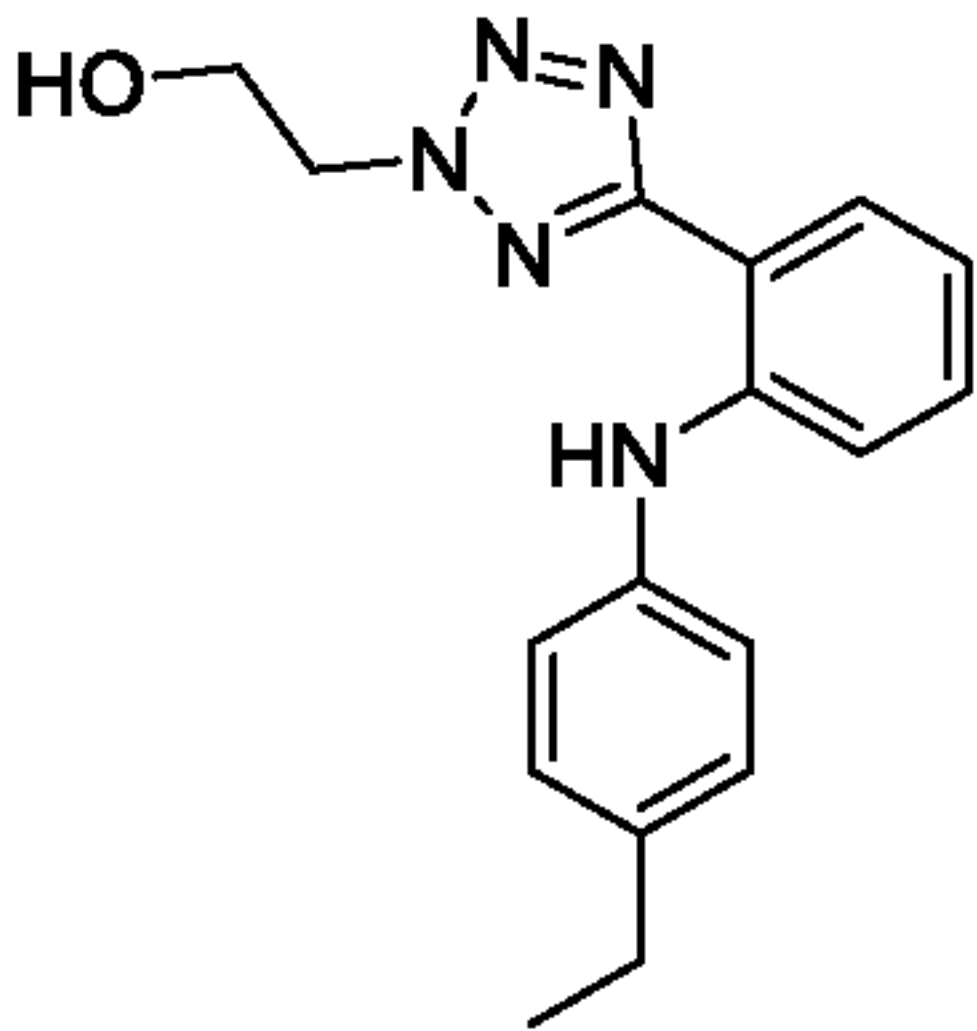
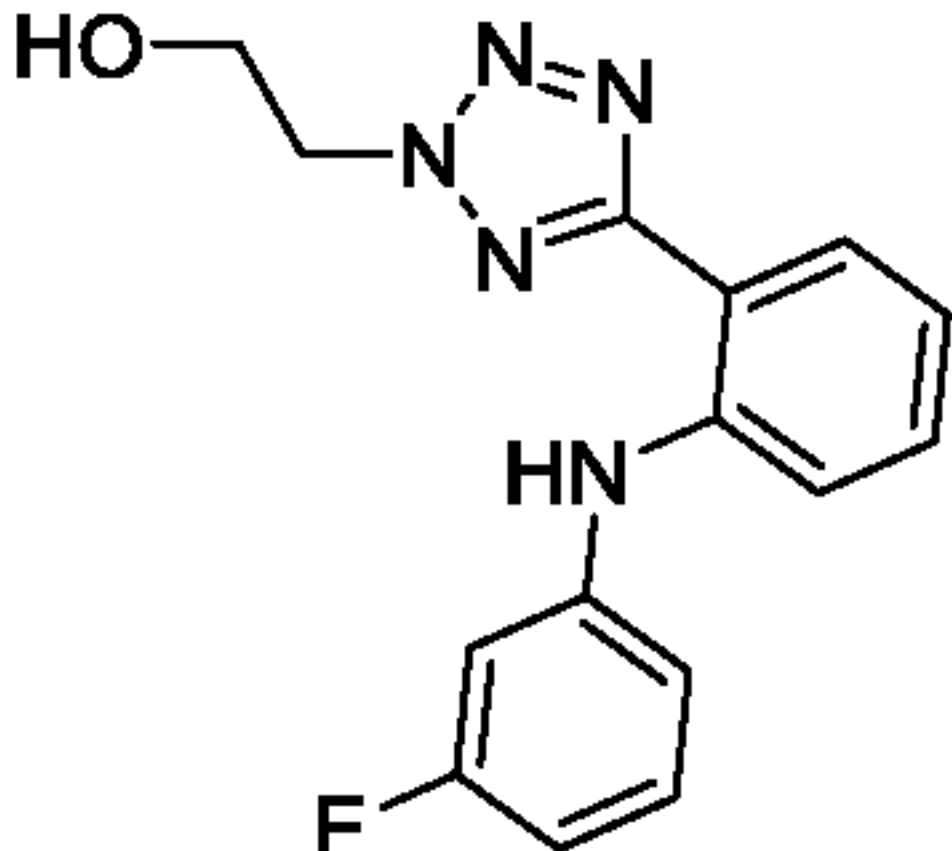
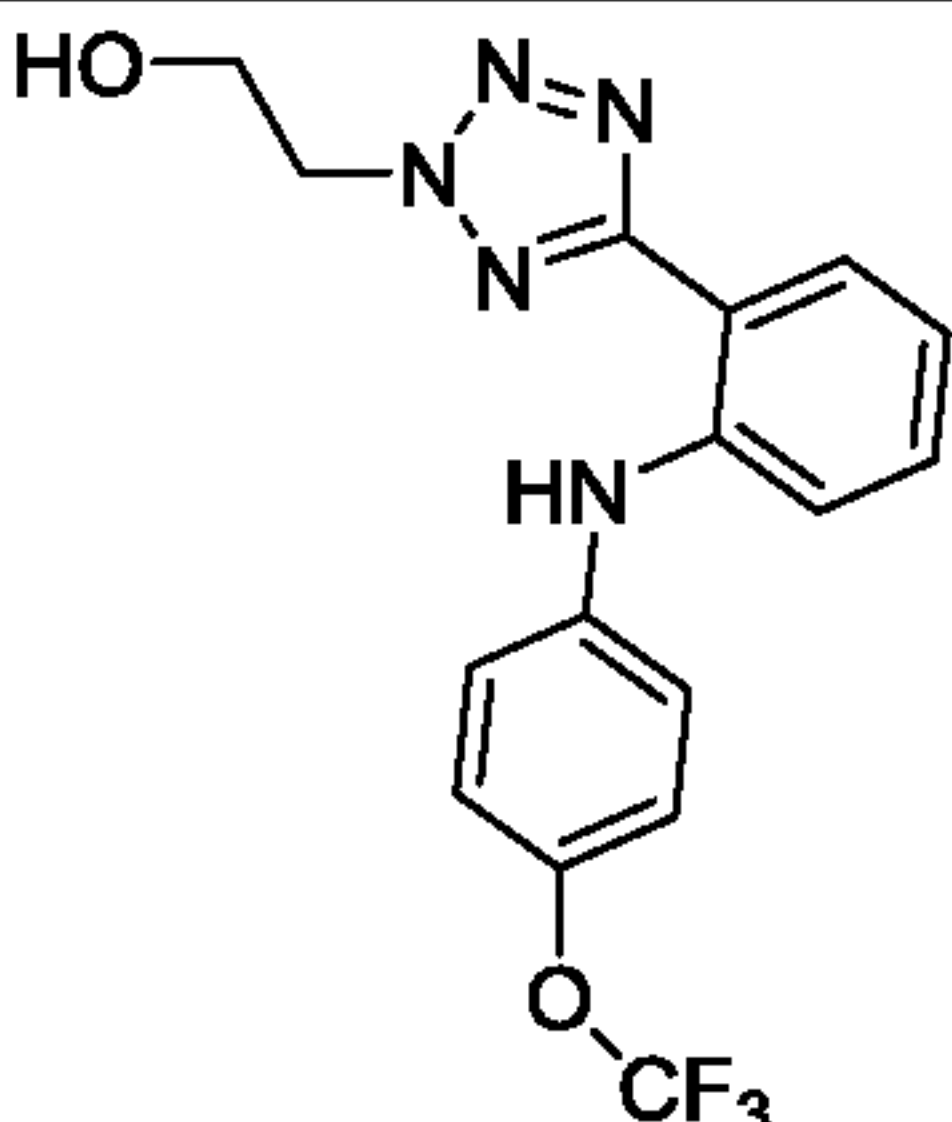
[00198] In some embodiments, R^2 is substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, R^2 is substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, R^2 is - CH_2F , - CHF_2 , - CF_3 , or - CH_2CF_3 . In some embodiments, R^2 is - CF_3 .

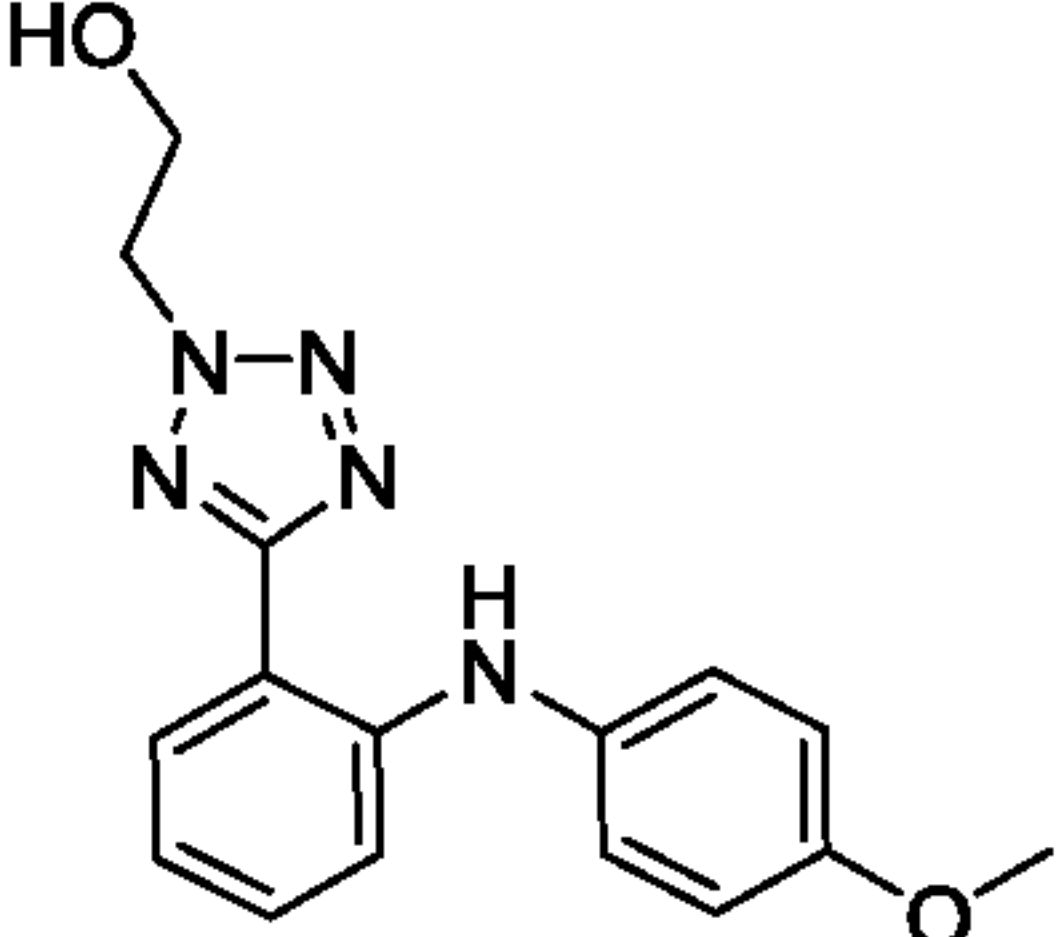
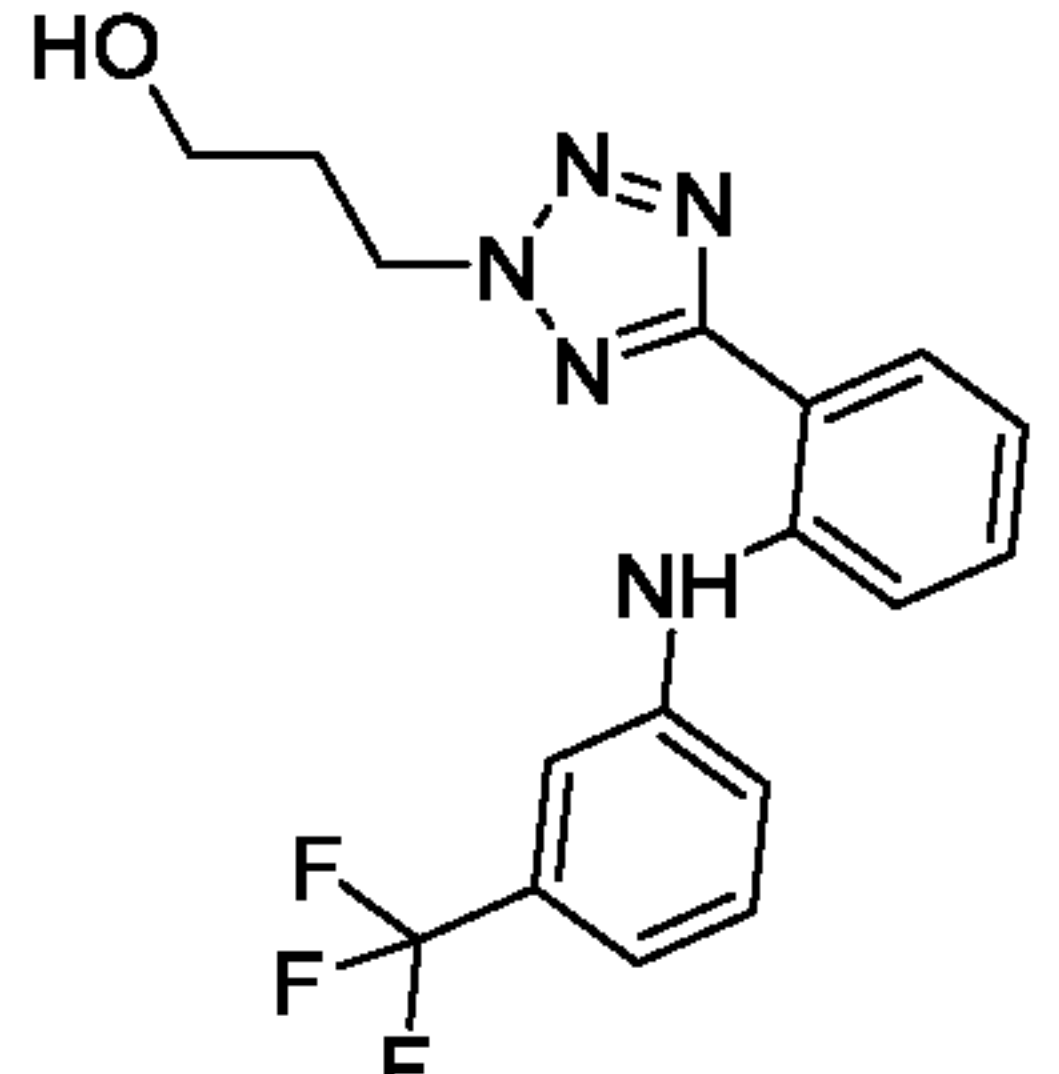
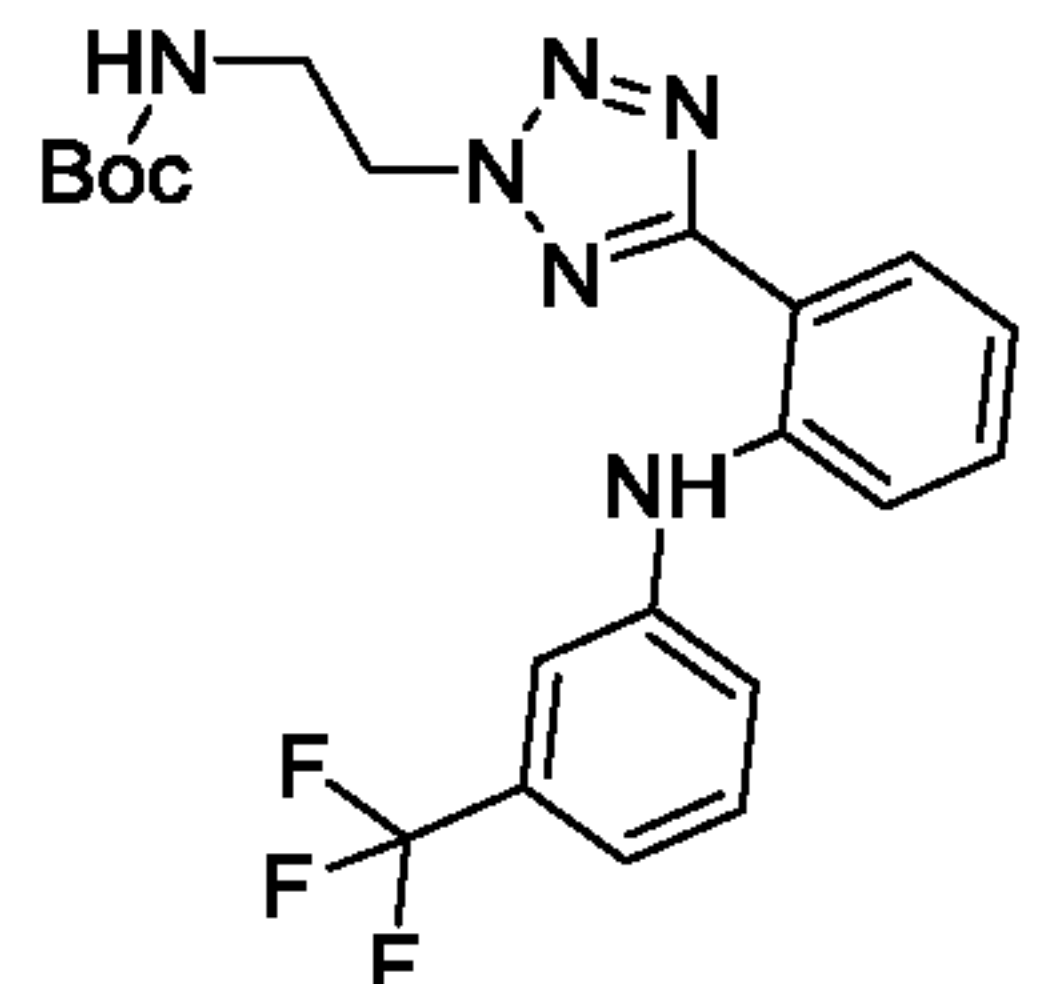
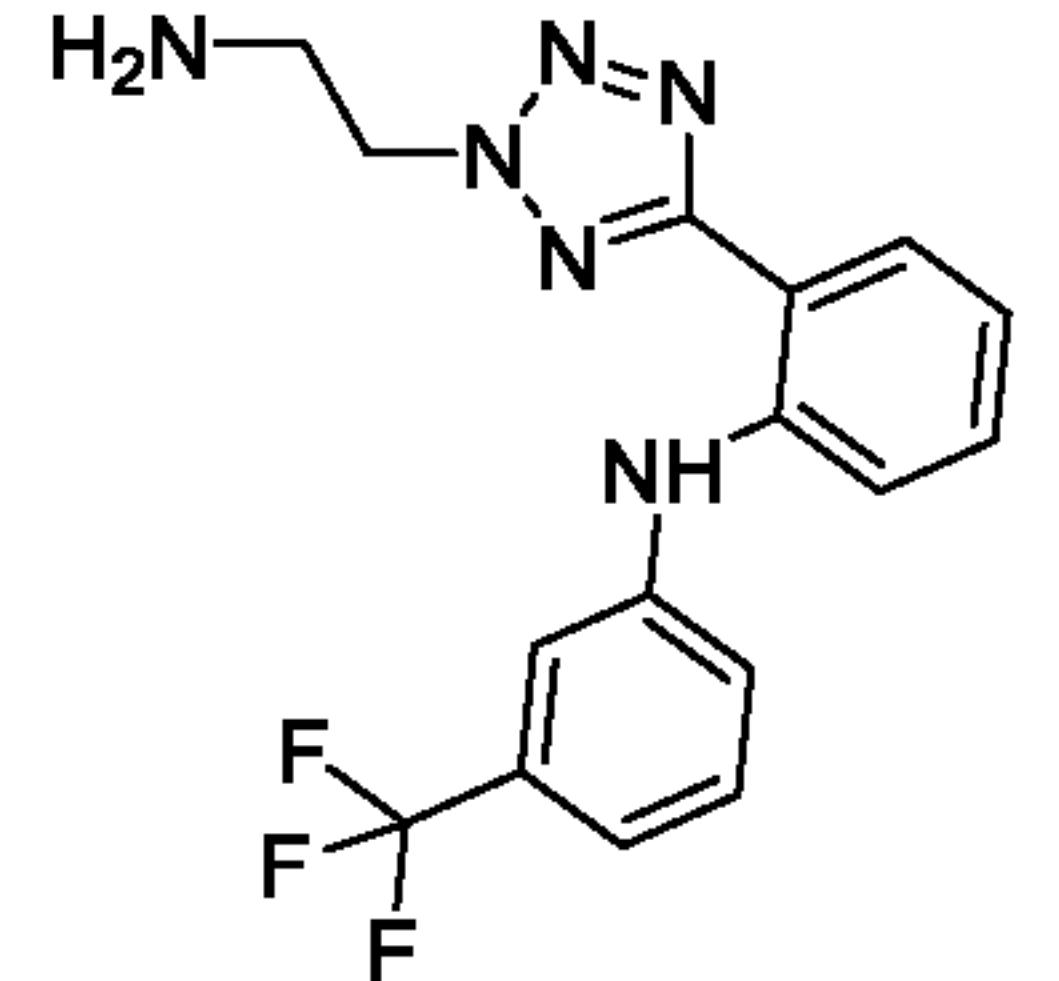
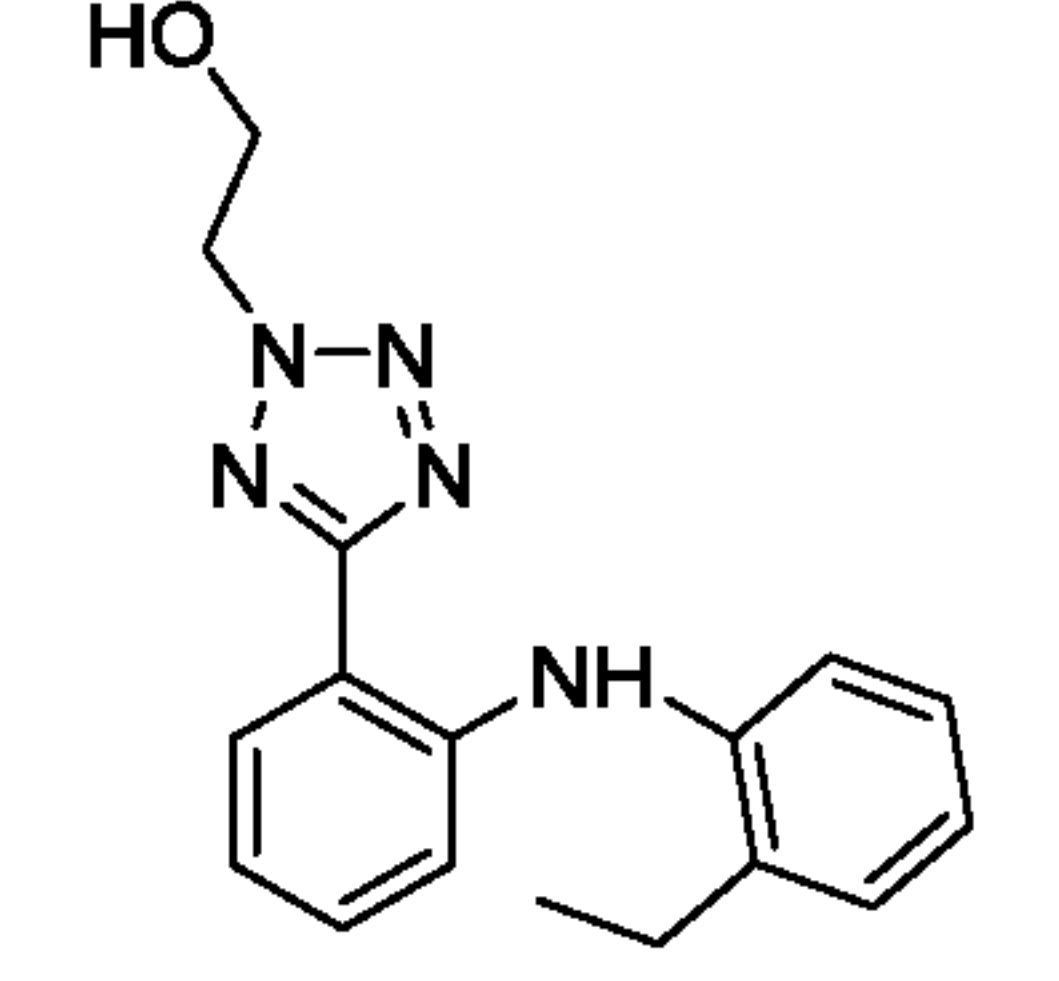
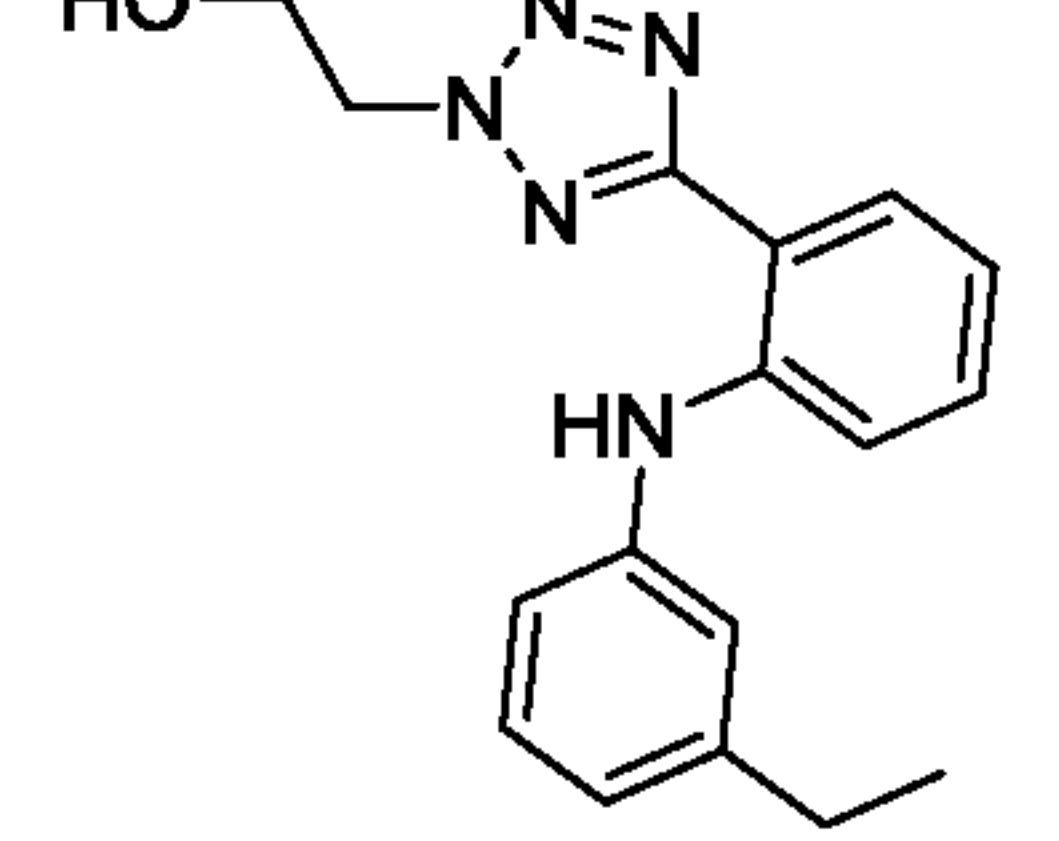
[00199] In some embodiments, X is $-(CH_2)_r-OH$, $-(CH_2)_r-OR''$, $-(CH_2)_r-N(R')_2$, $-(CH_2)_r-NR'S(=O)_2R''$, $-(CH_2)_r-S(=O)_2N(R')_2$, $-(CH_2)_r-SR'$, $-(CH_2)_r-S(=O)R''$, $-(CH_2)_r-S(=O)_2R''$, $-(CH_2)_r-C(=O)R''$, $-(CH_2)_r-OC(=O)R''$, $-(CH_2)_r-CO_2H$, $-(CH_2)_r-CO_2R''$, $-(CH_2)_r-OC(=O)OR''$, $-(CH_2)_r-NR'C(=O)R''$, $-(CH_2)_r-C(=O)N(R')_2$, $-(CH_2)_r-NR''C(=O)OR'$, $-(CH_2)_r-OC(=O)N(R'')_2$; r is 1, 2, 3, or 4; each R' is independently H substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and each R'' is independently unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

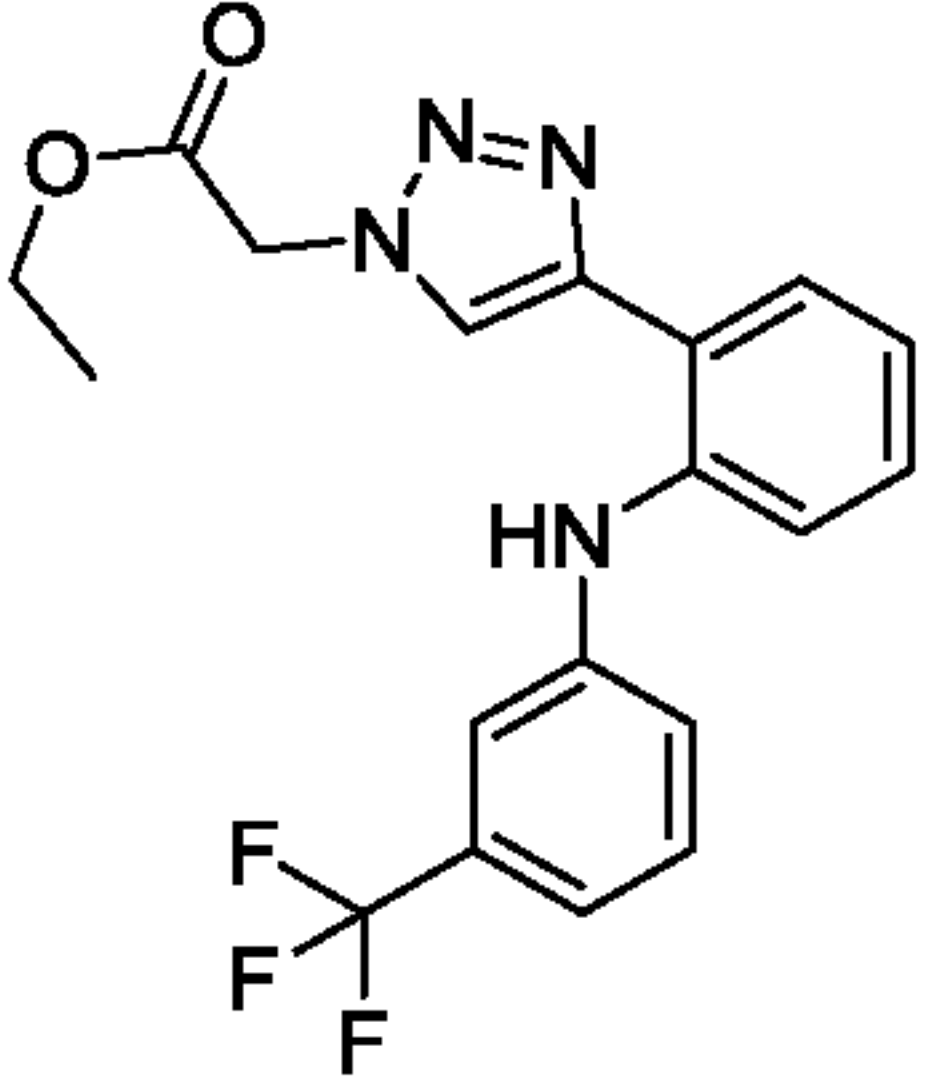
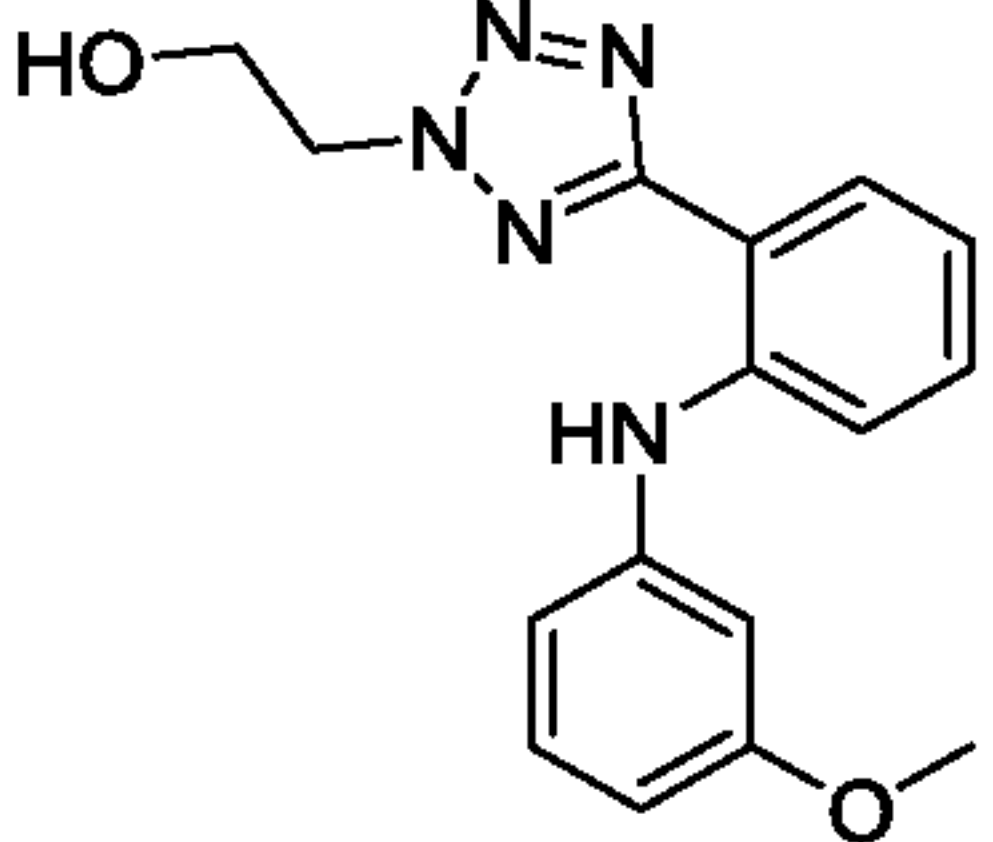
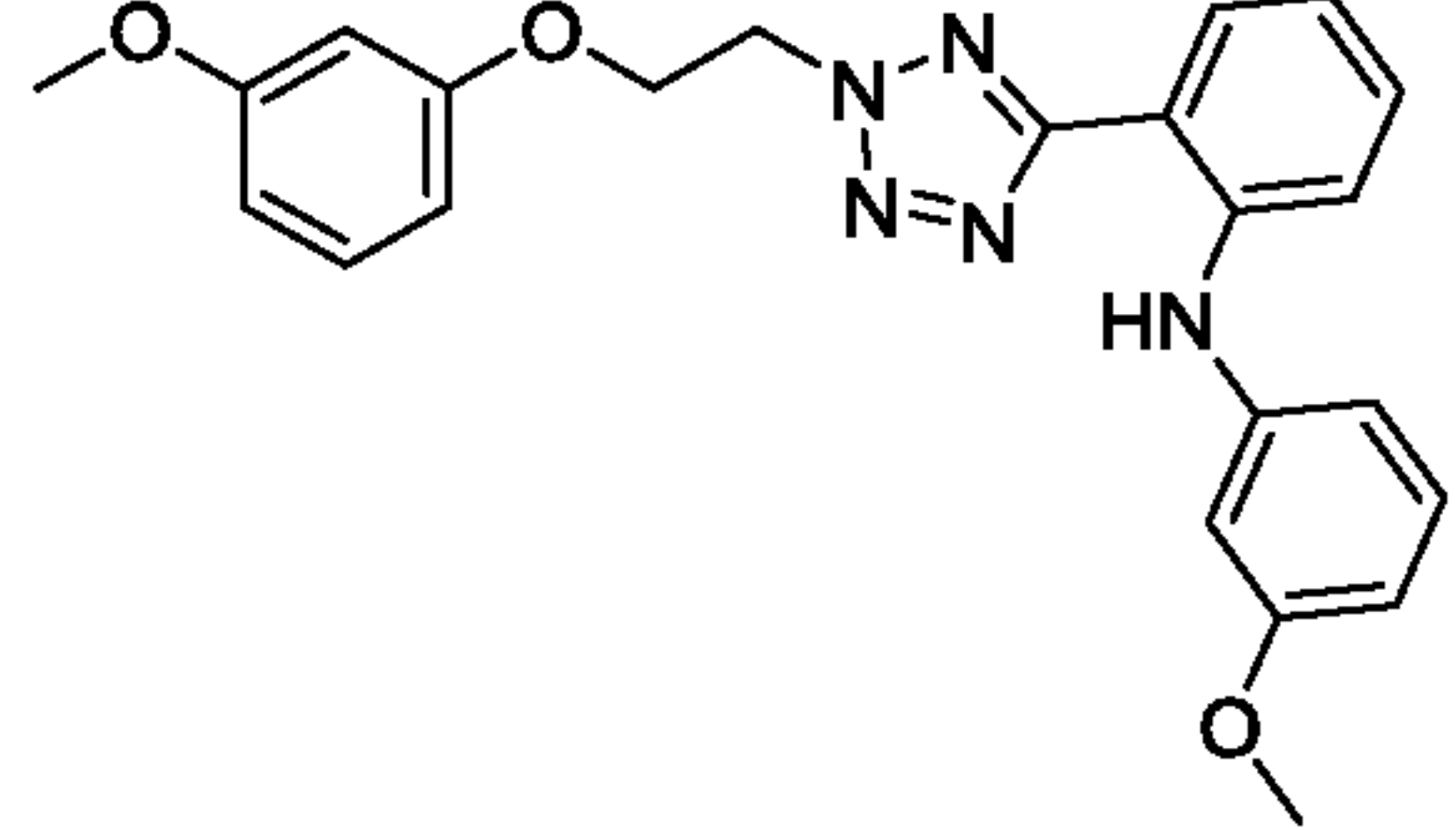
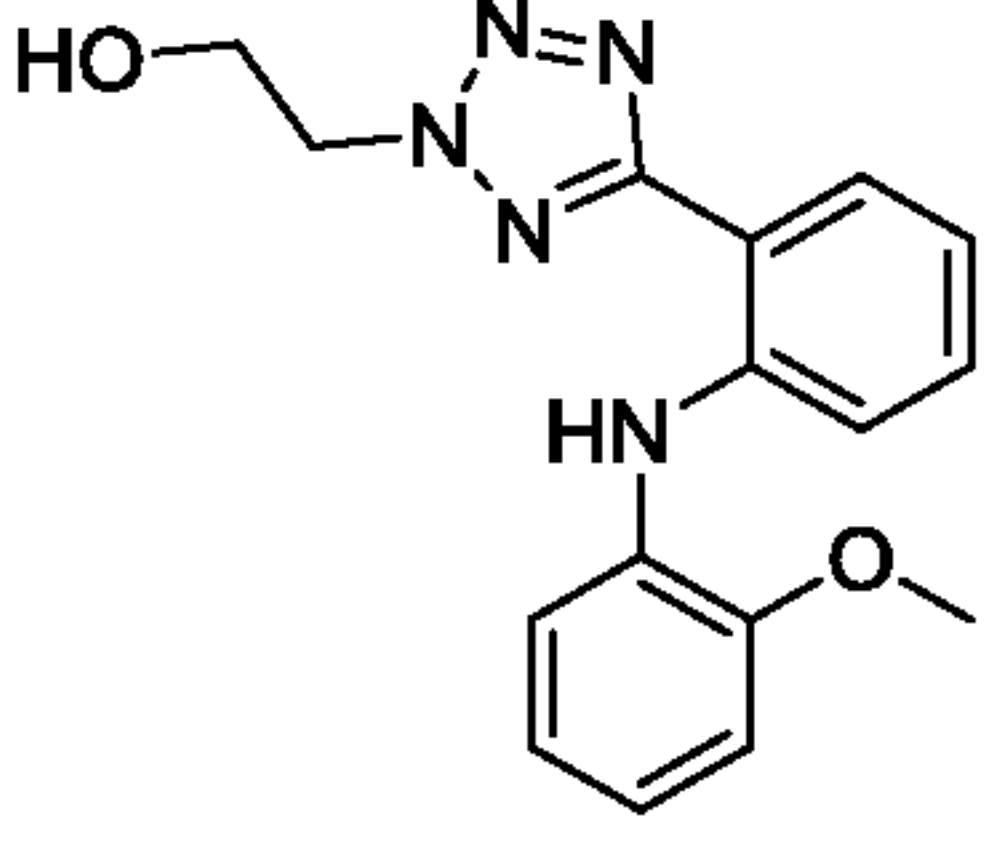
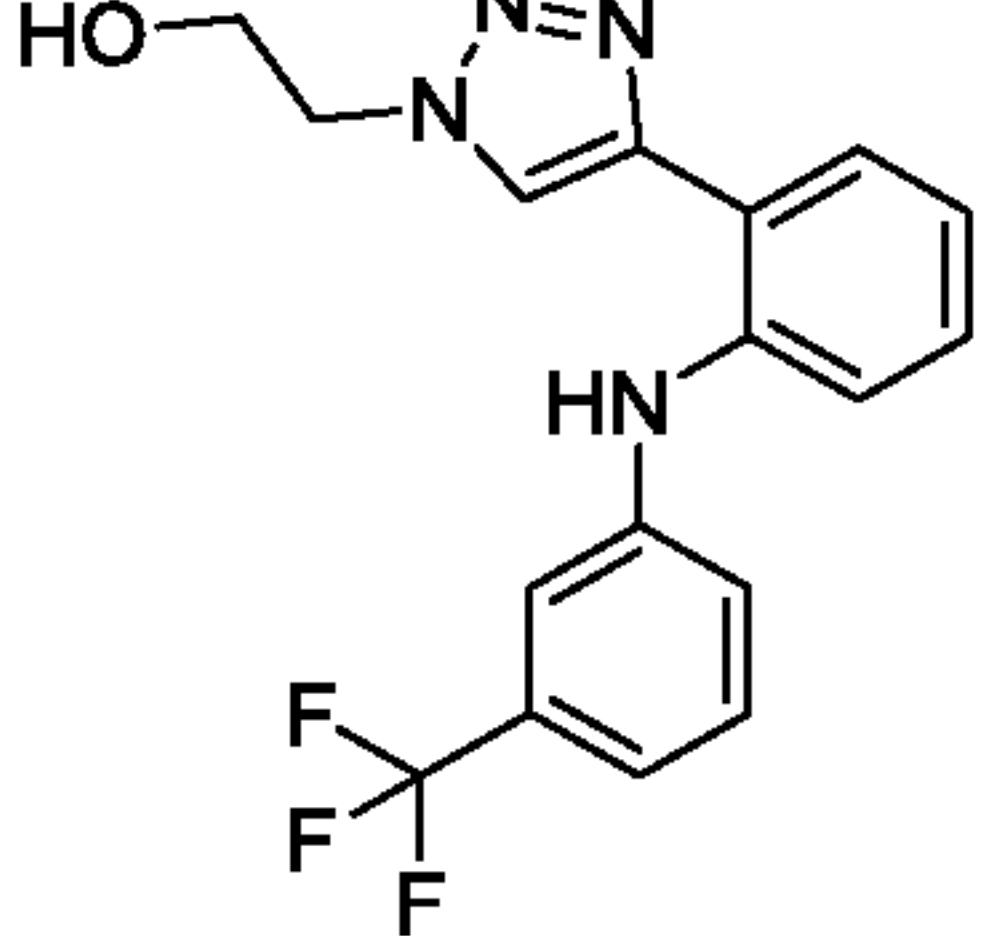
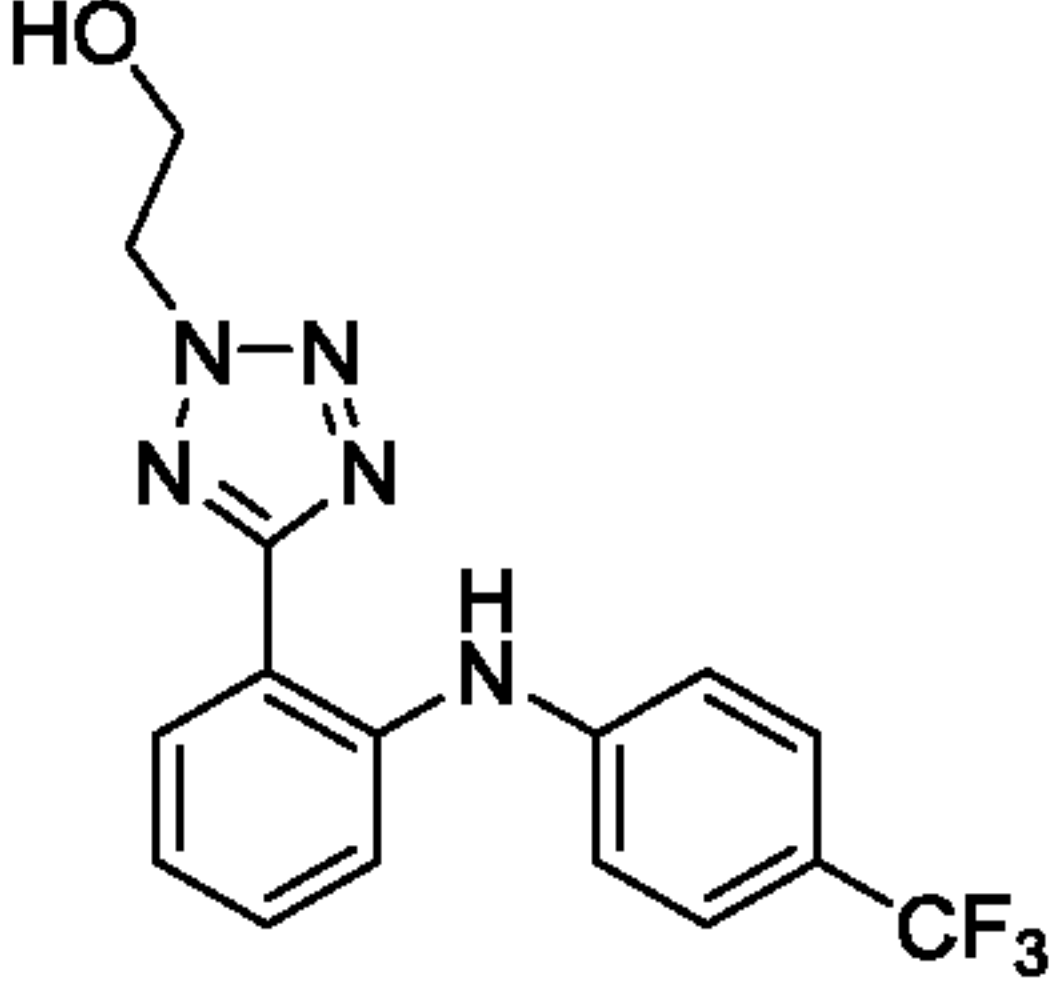
[00200] In some embodiments, the compound disclosed herein has the structure provided in Table 1 or Table 2.

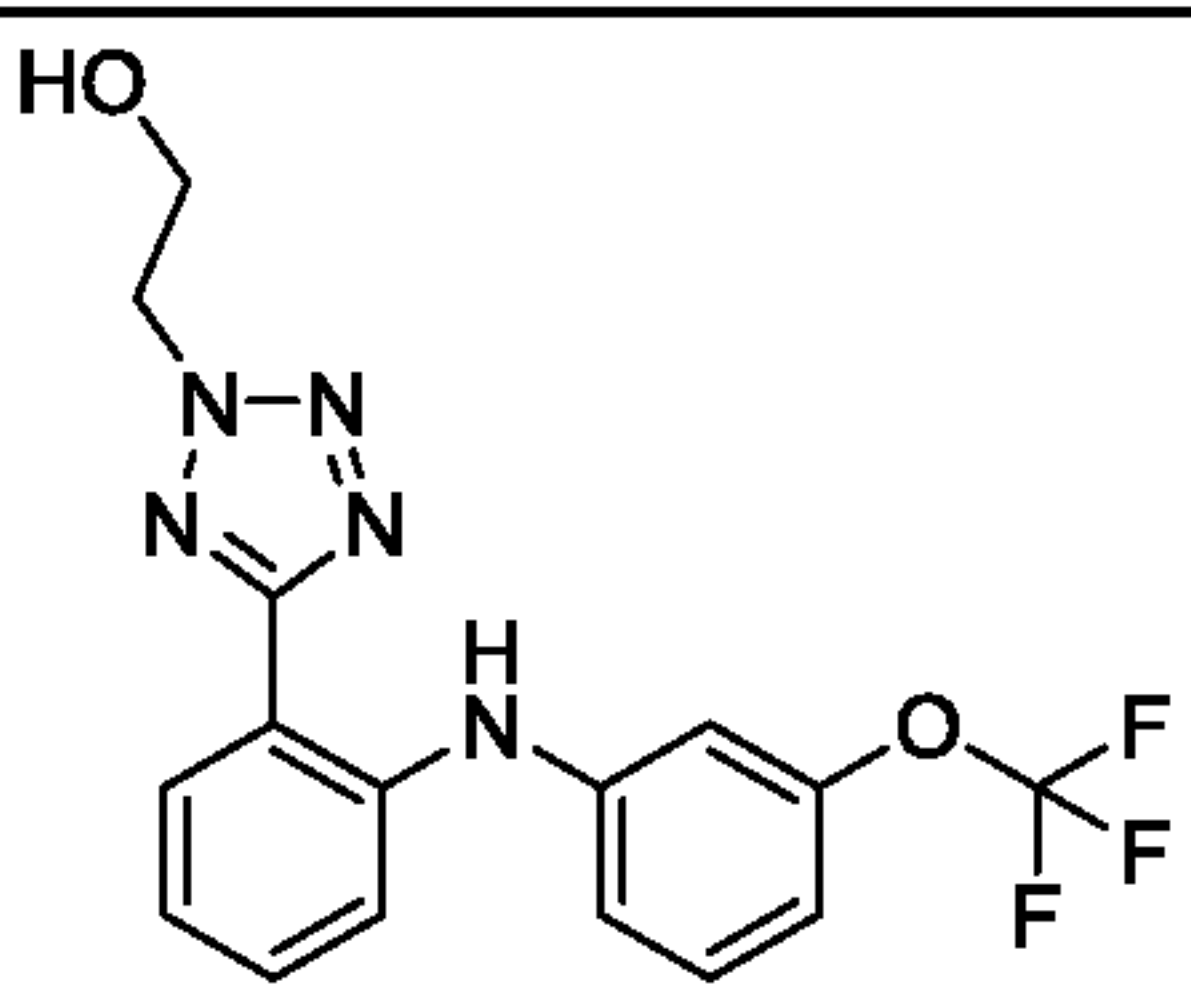
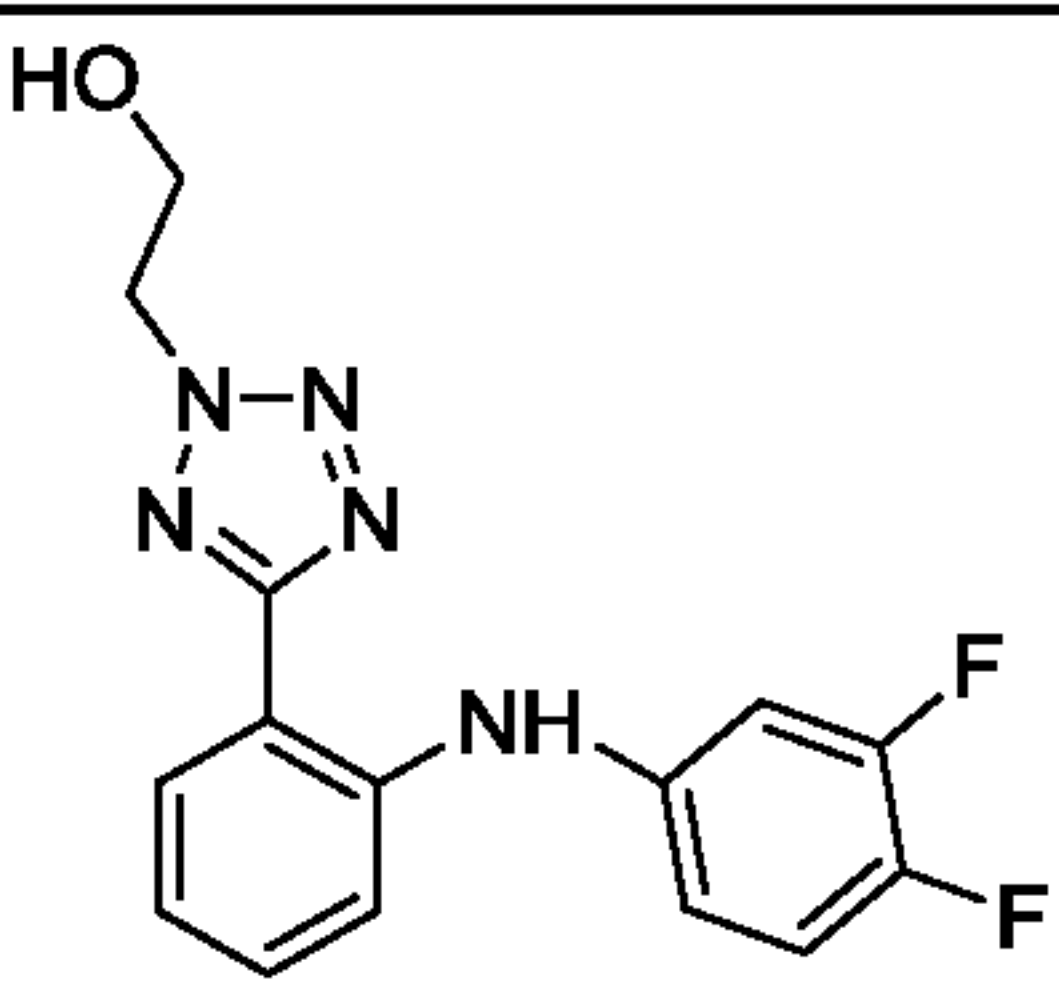
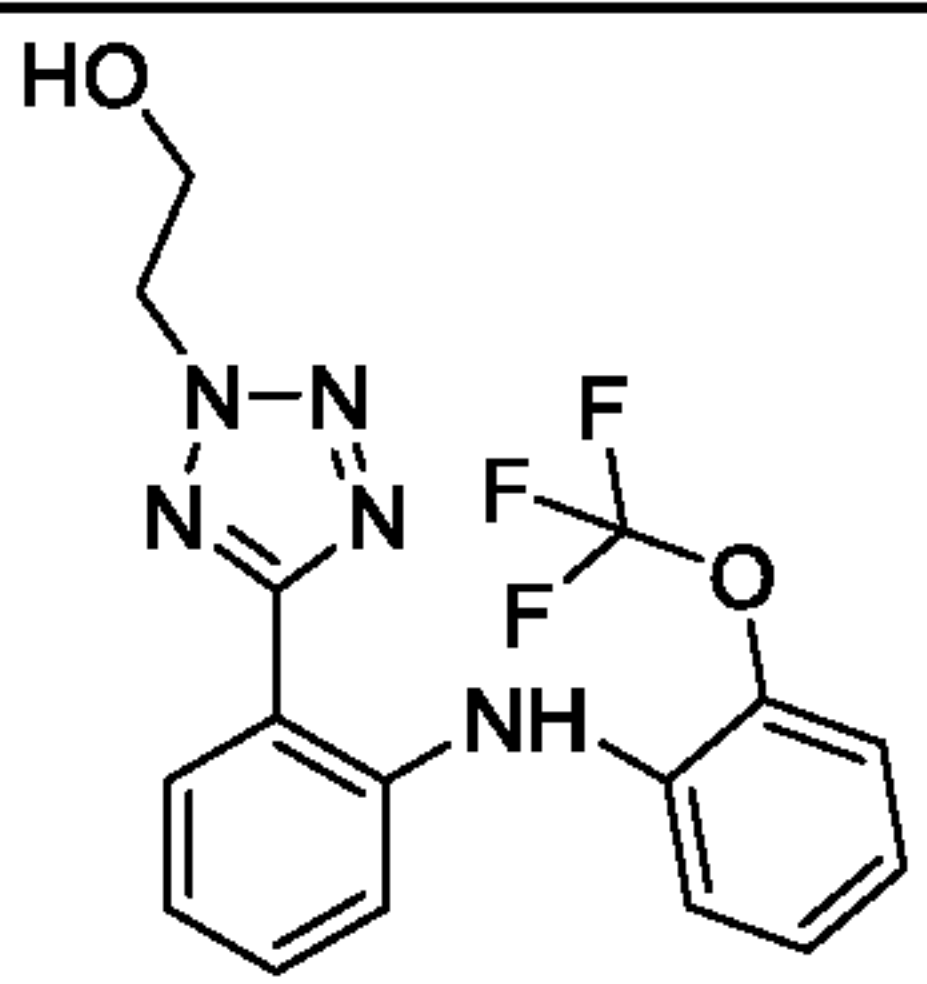
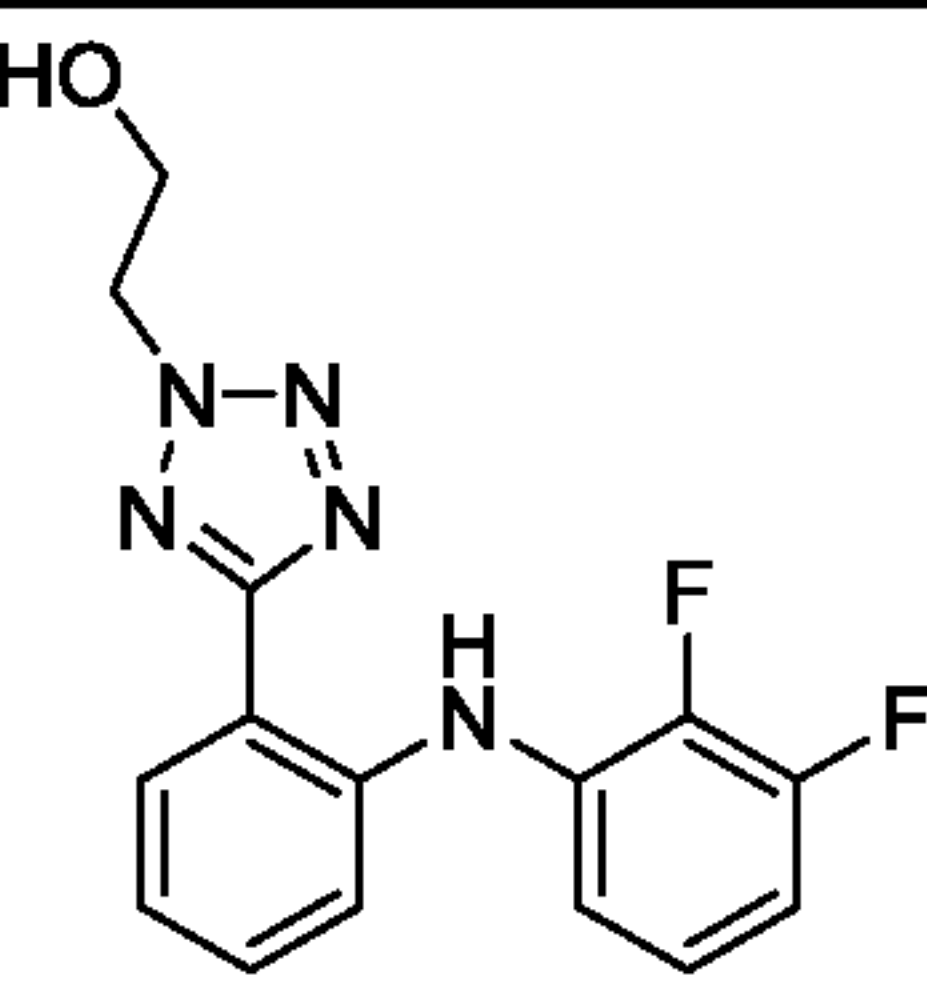
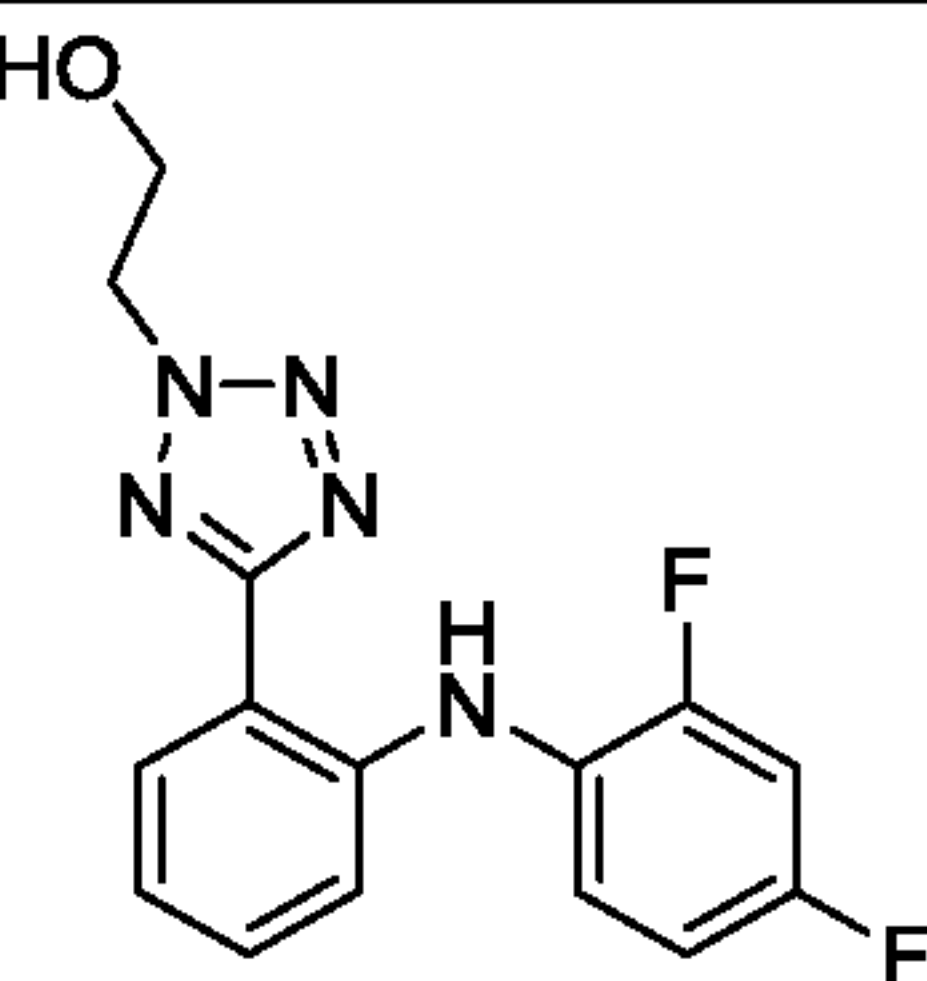
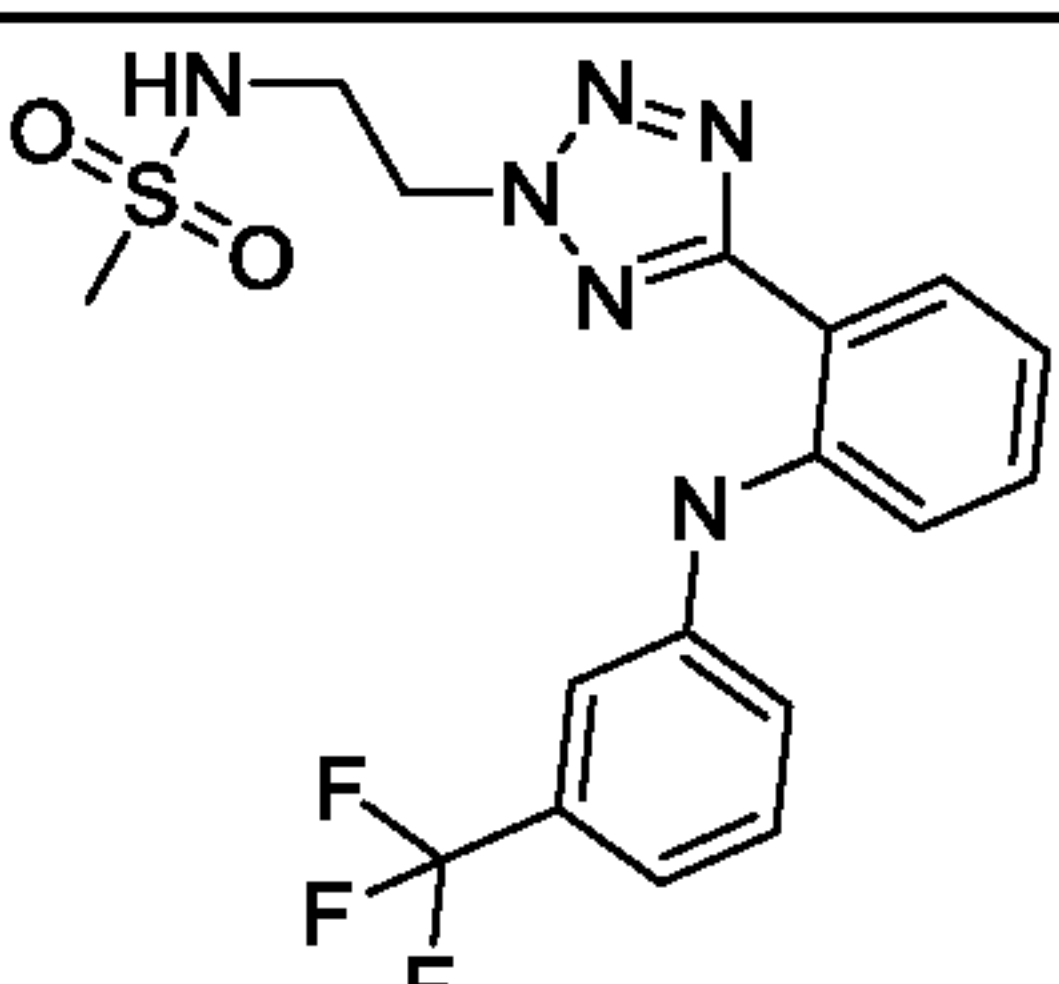
TABLE 1

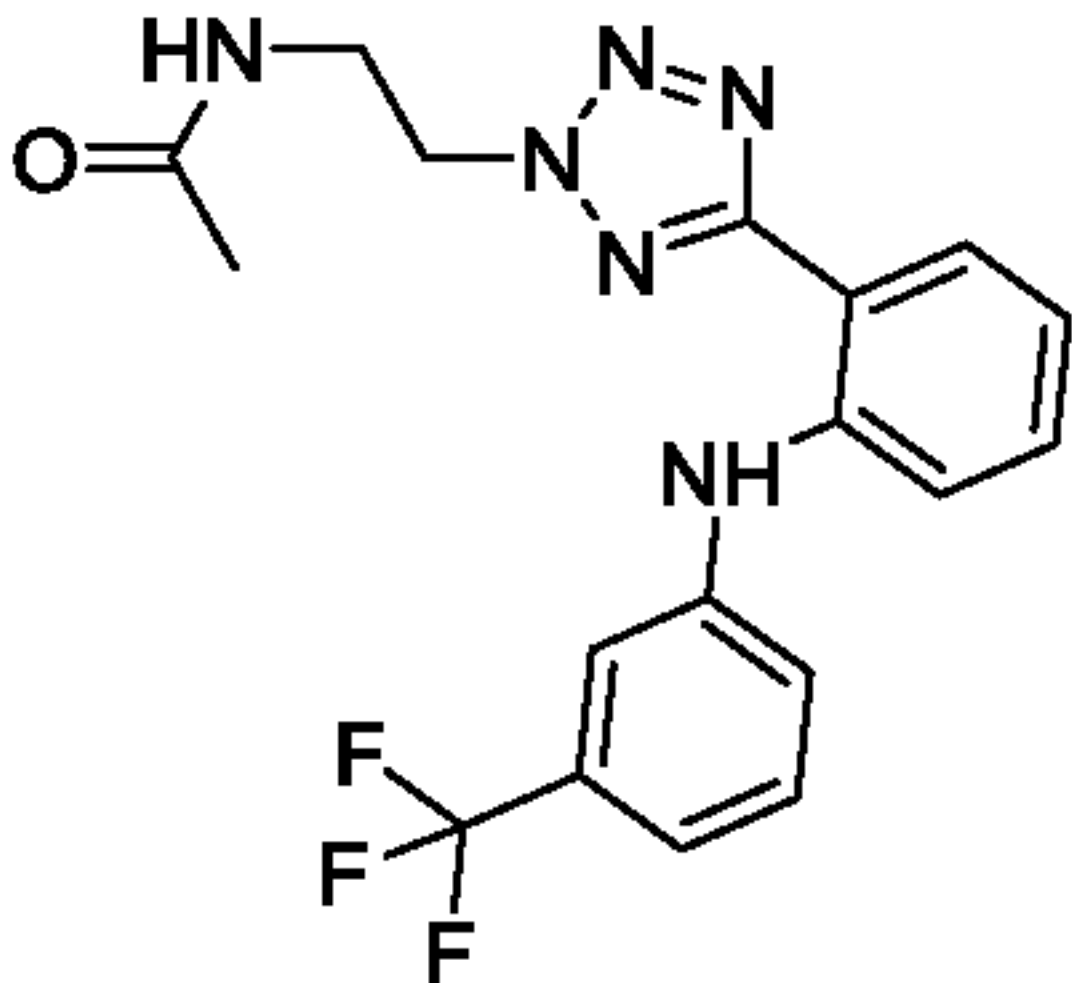
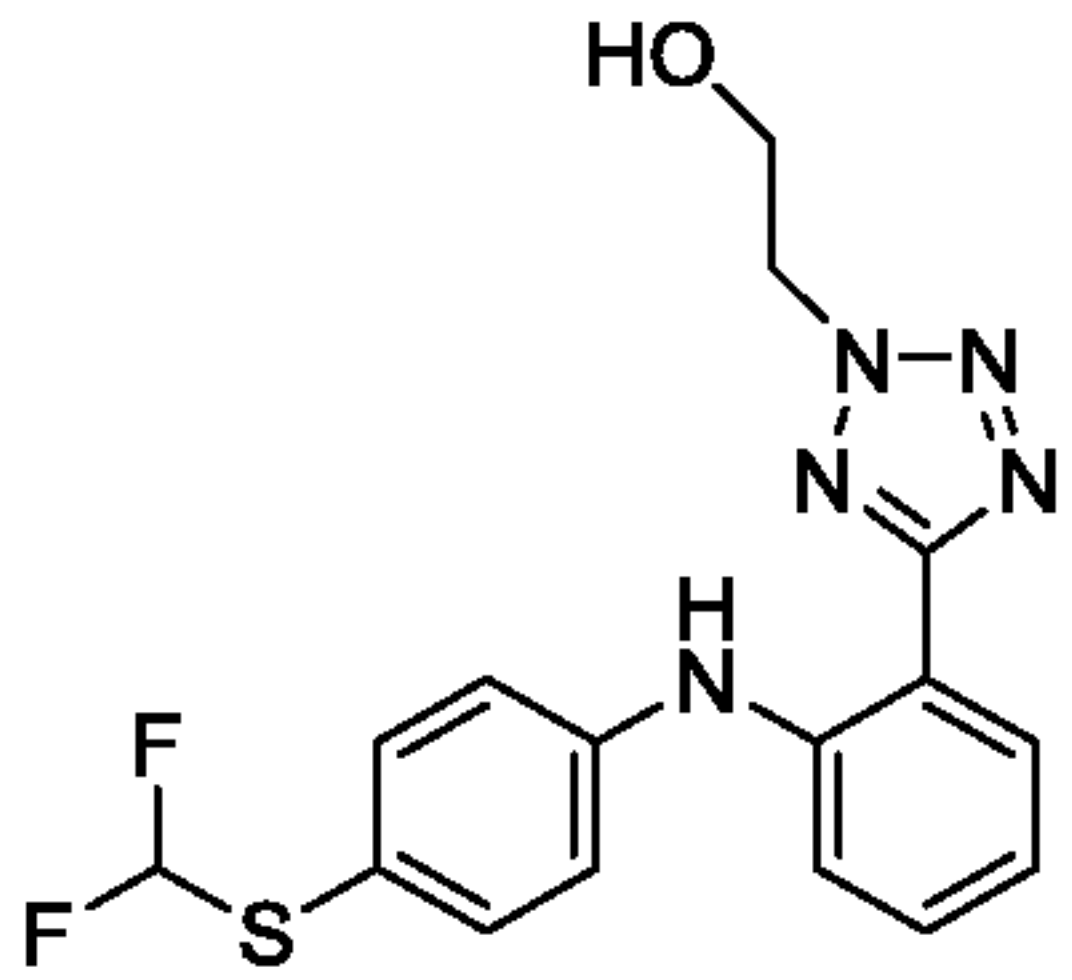
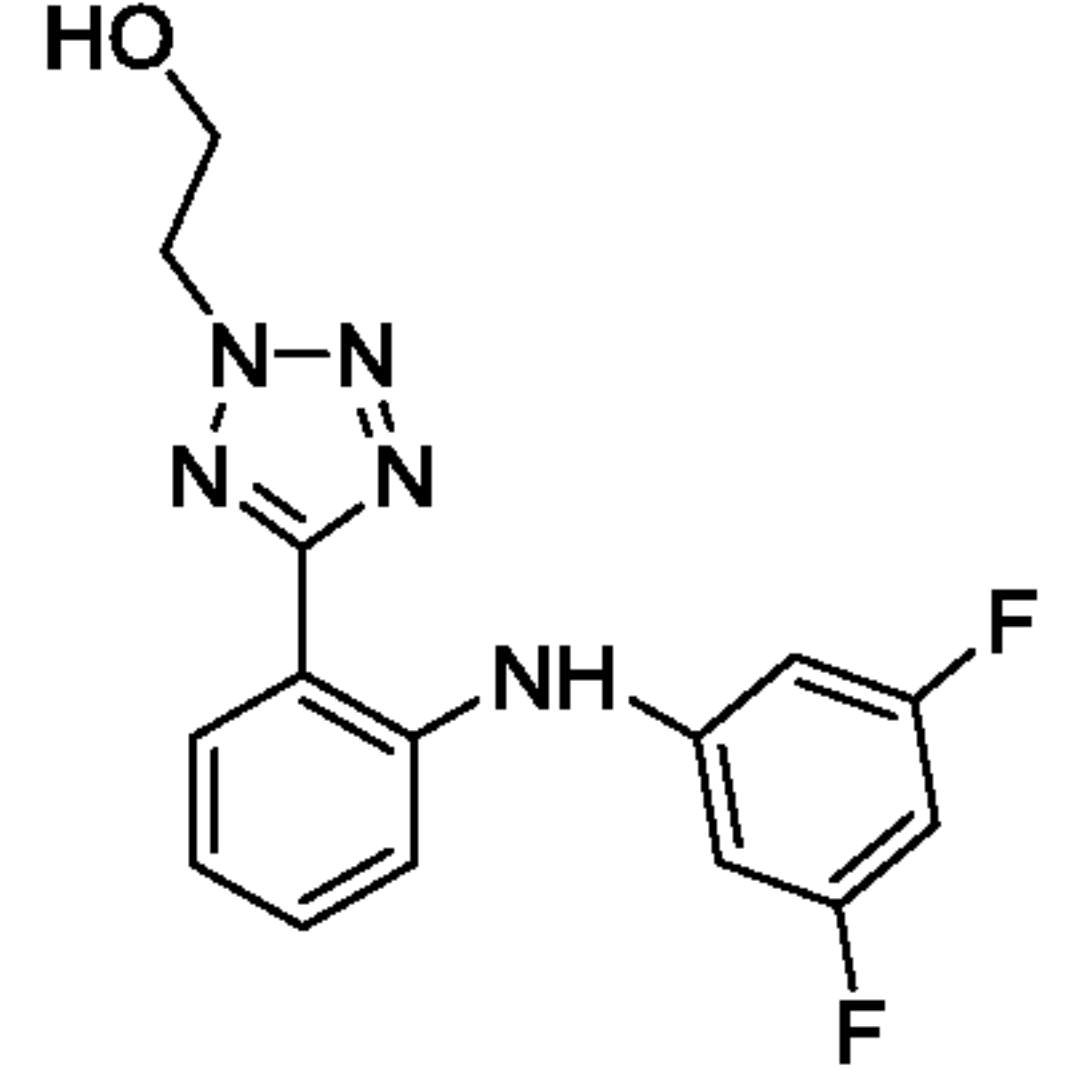
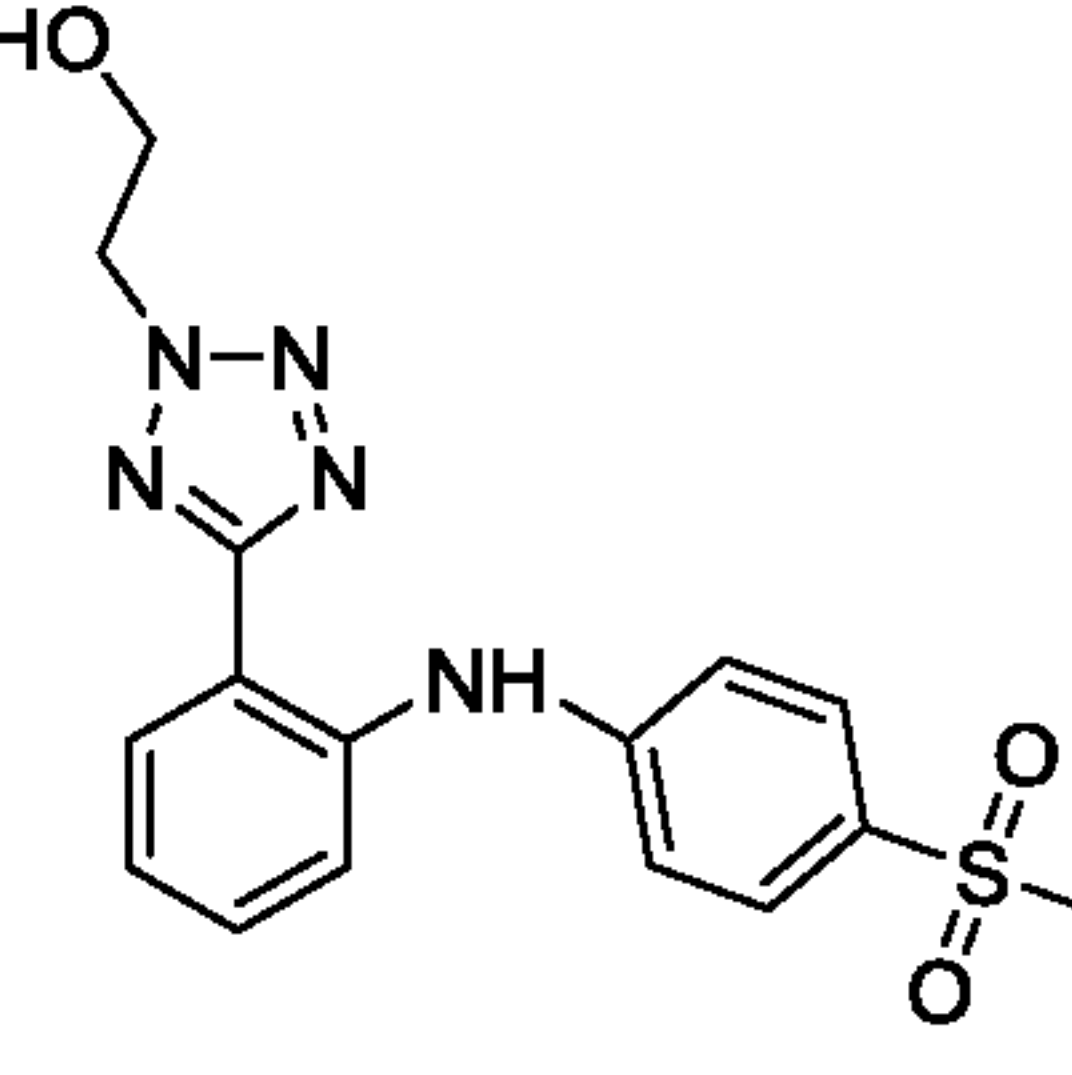
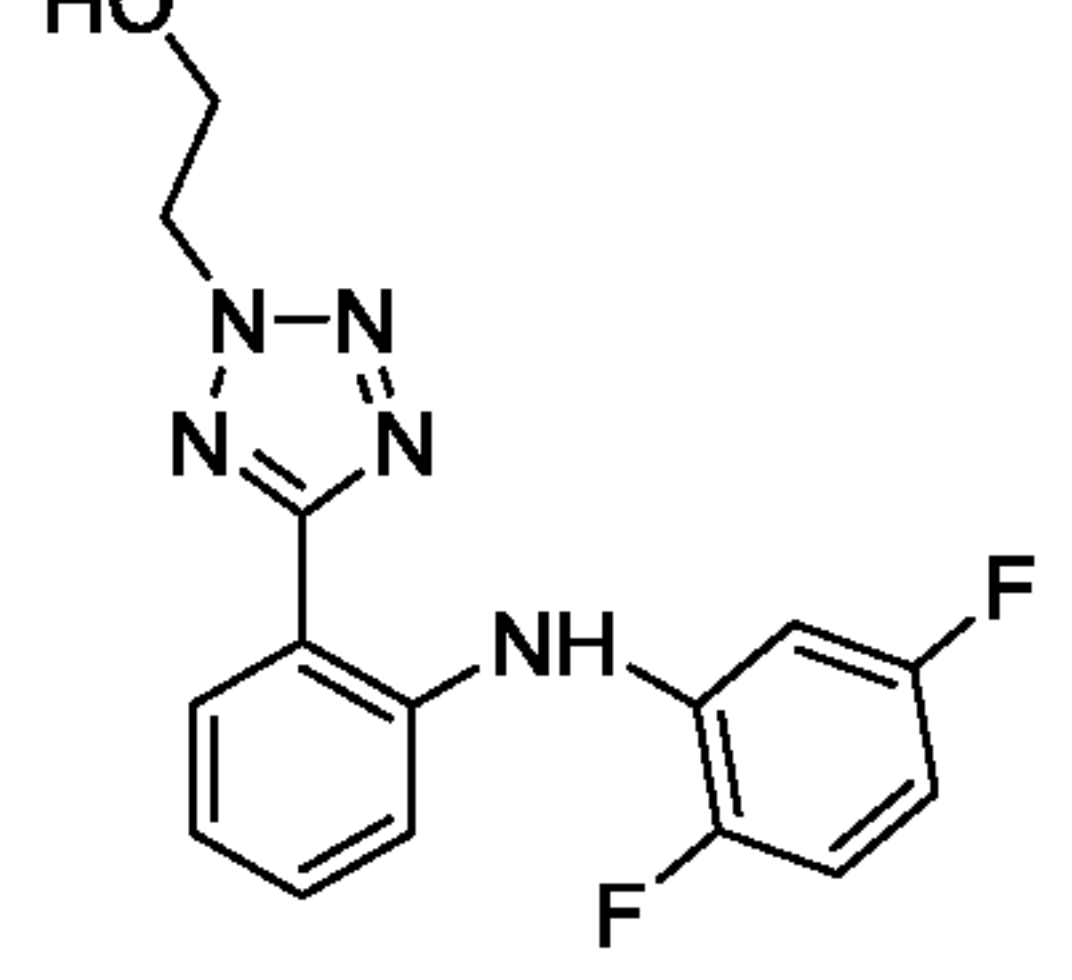
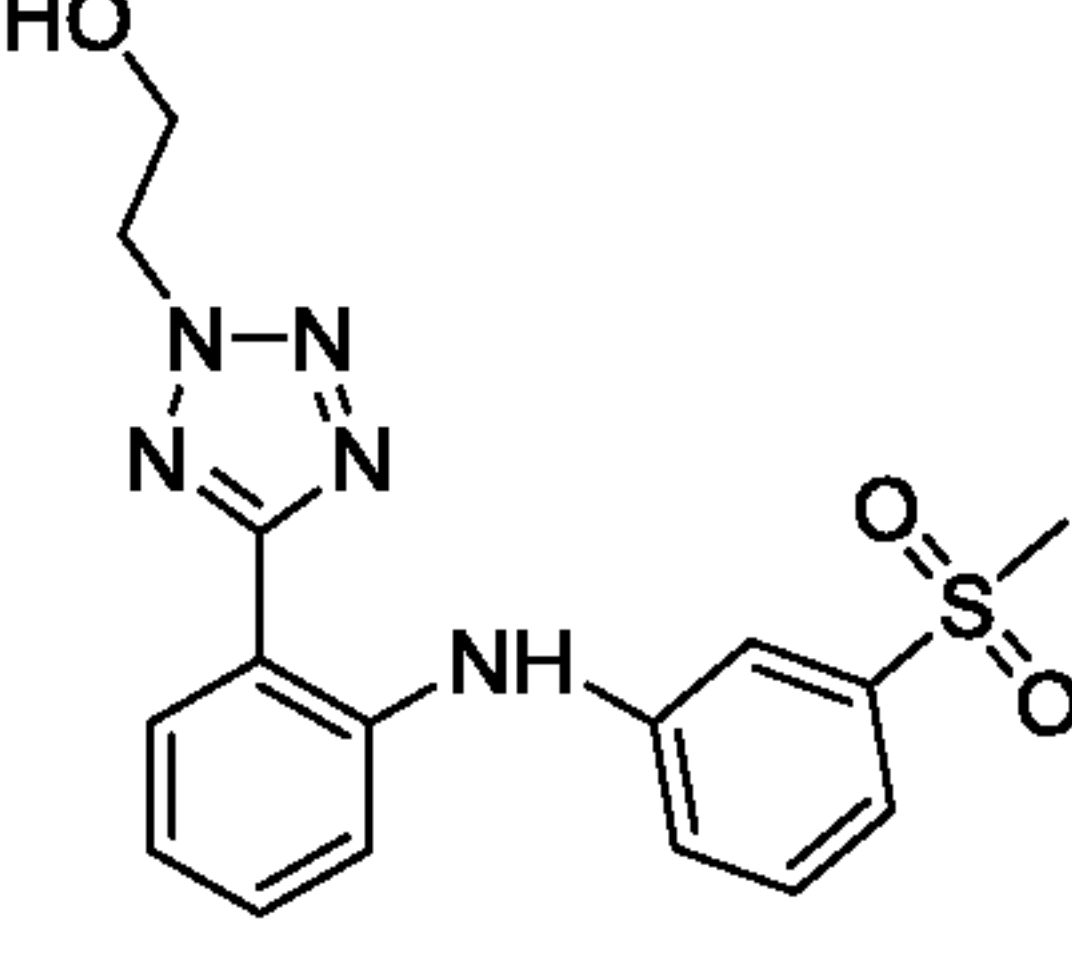
Compound No.	Structure	Name
1		ethyl 2-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetate
2		2-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetic acid
3		2-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol
4		ethyl 3-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propanoate
5		2-[2-(2-methoxyethyl)tetrazol-5-yl]-N-[3-(trifluoromethyl)phenyl]aniline

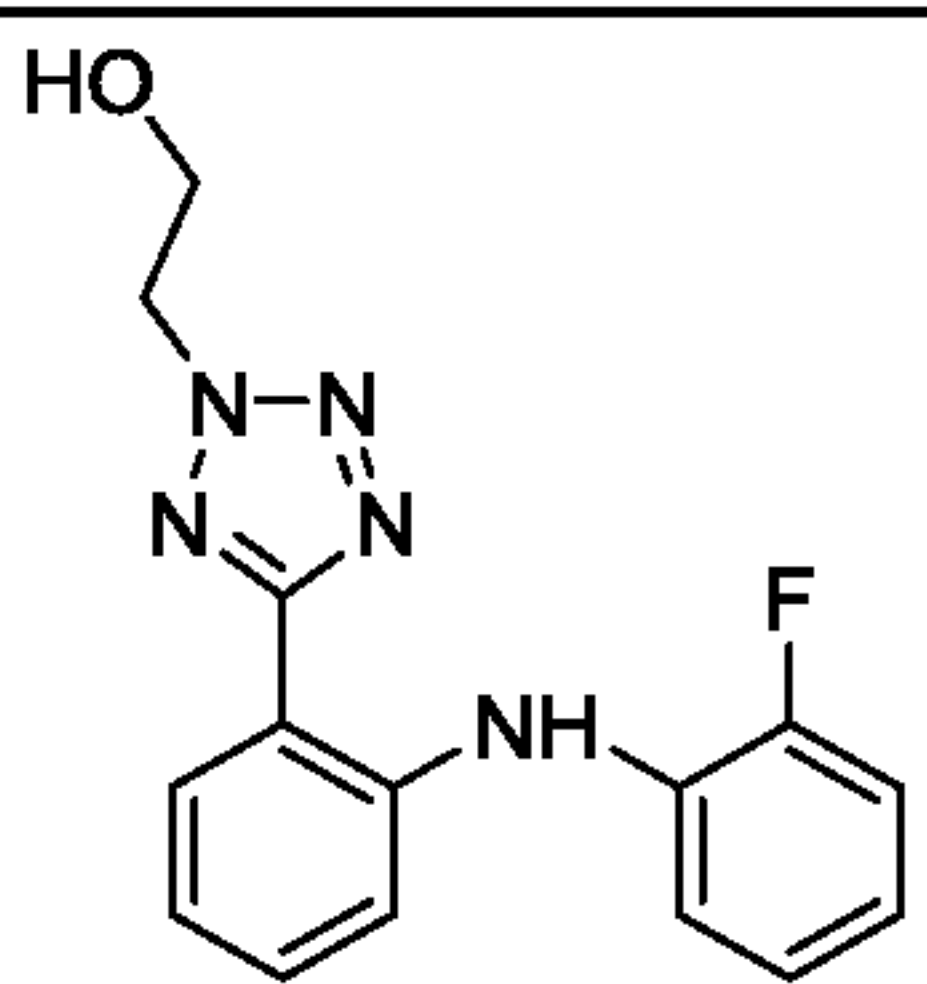
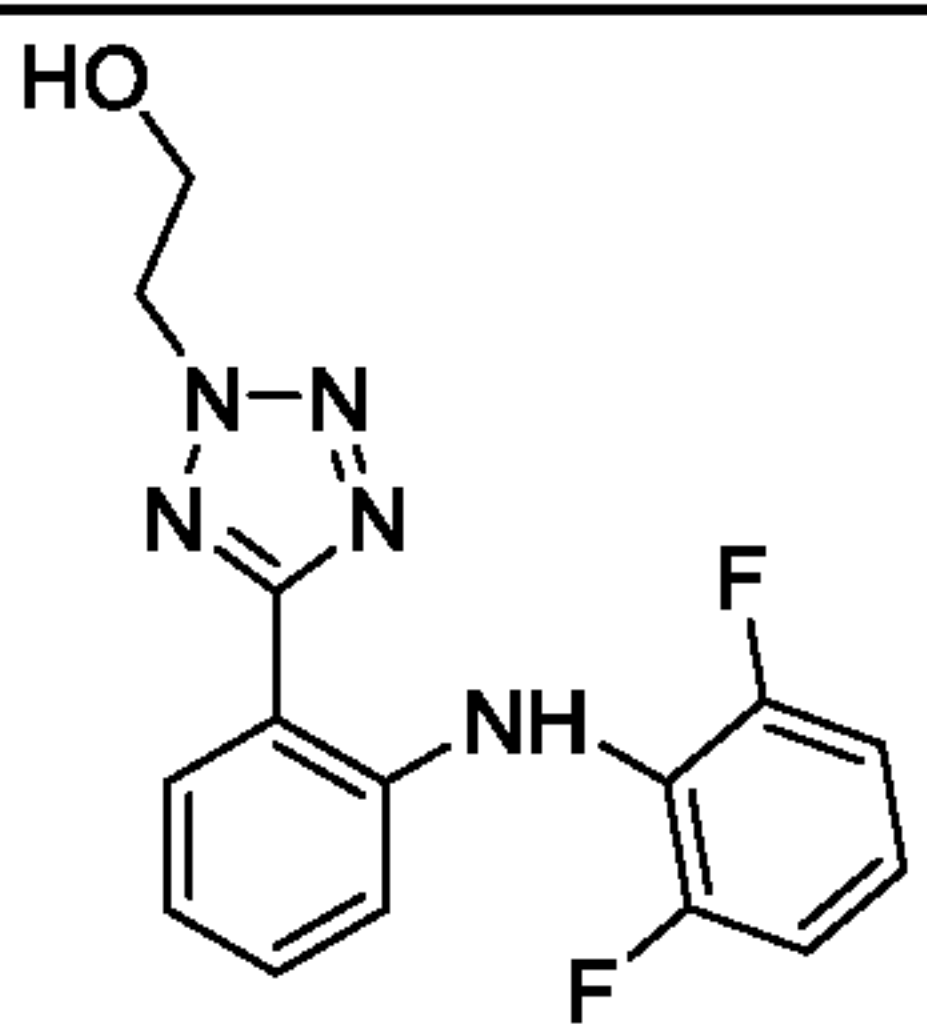
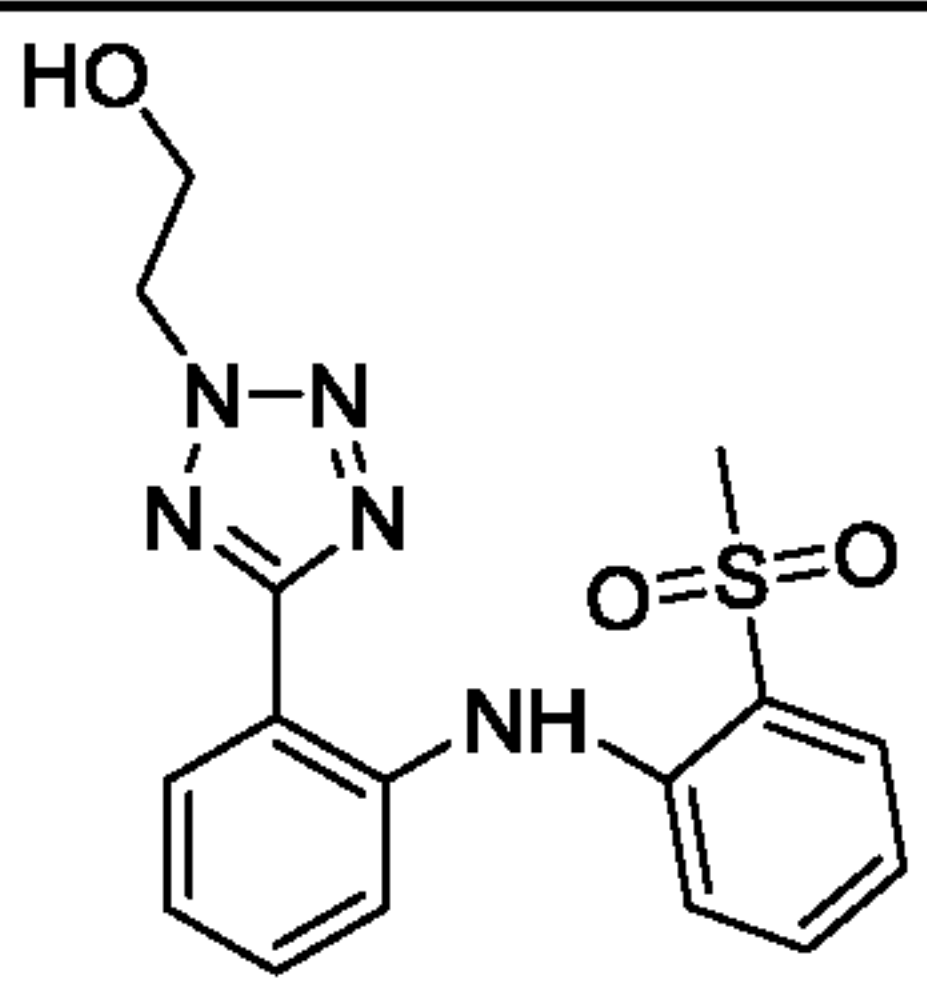
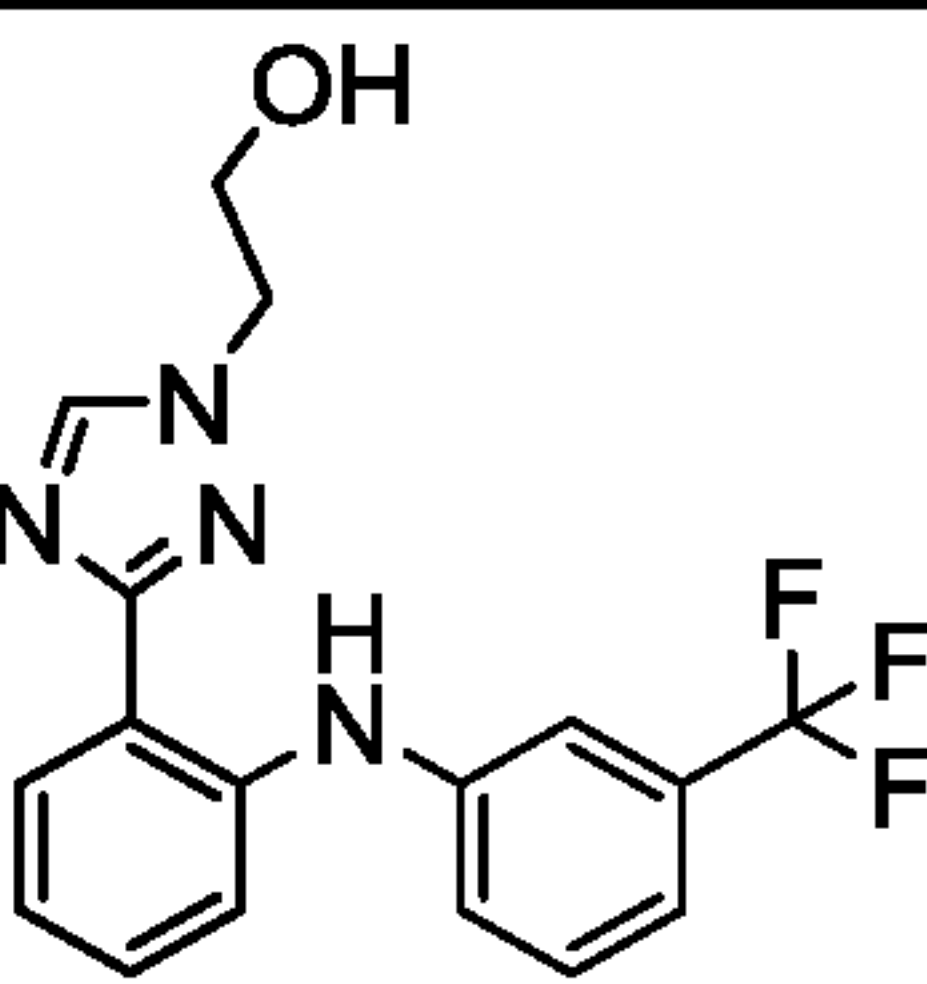
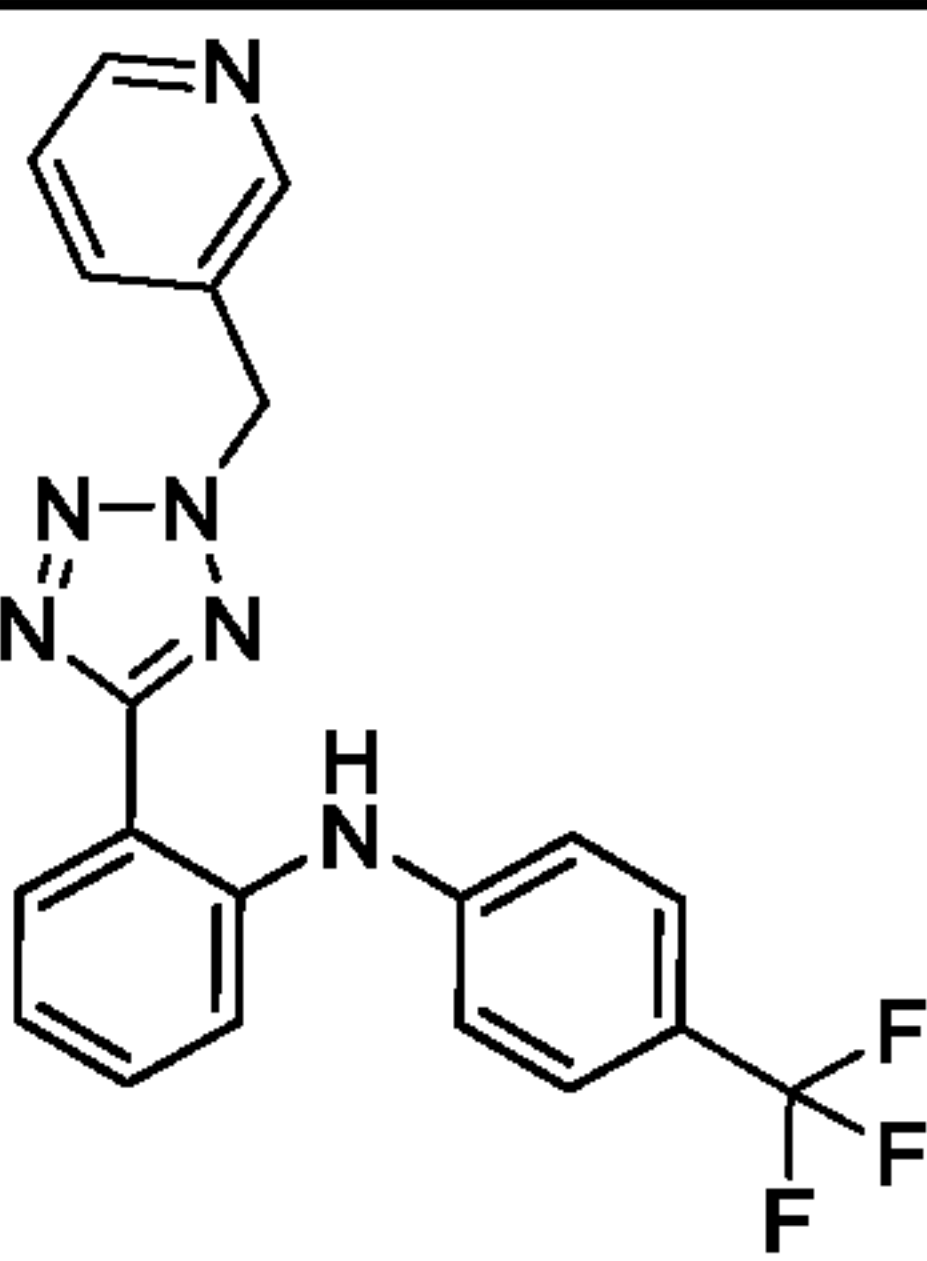
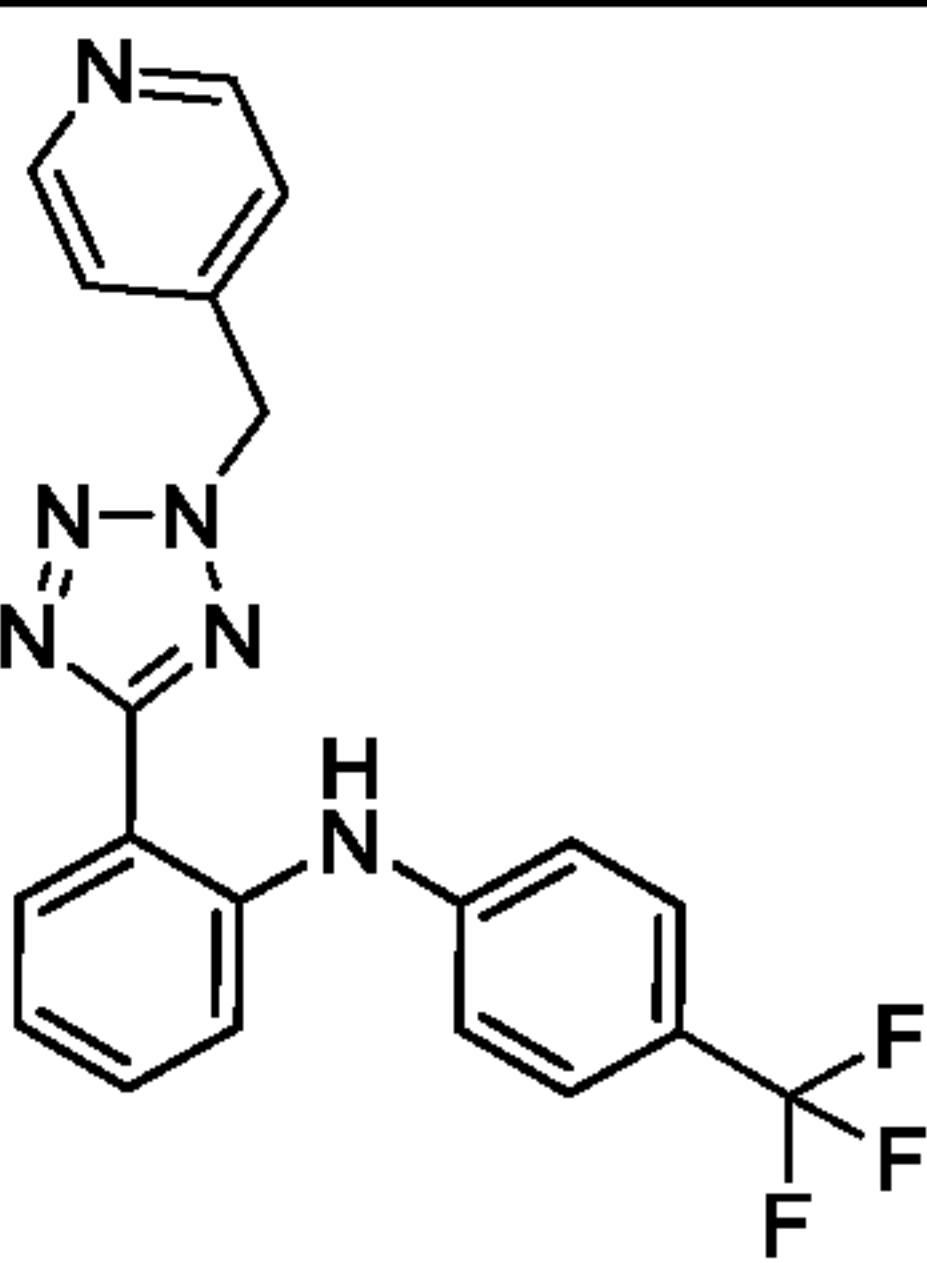
Compound No.	Structure	Name
6		2-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetamide
7		ethyl 2-[5-[2-(4-fluoroanilino)phenyl]tetrazol-2-yl]acetate
8		2-[5-[2-(4-fluoroanilino)phenyl]tetrazol-2-yl]ethanol
9		2-[5-[2-(4-ethylanilino)phenyl]tetrazol-2-yl]ethanol
10		2-(5-(2-((3-fluorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol
11		2-(5-(2-((4-(Trifluoromethoxy)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol

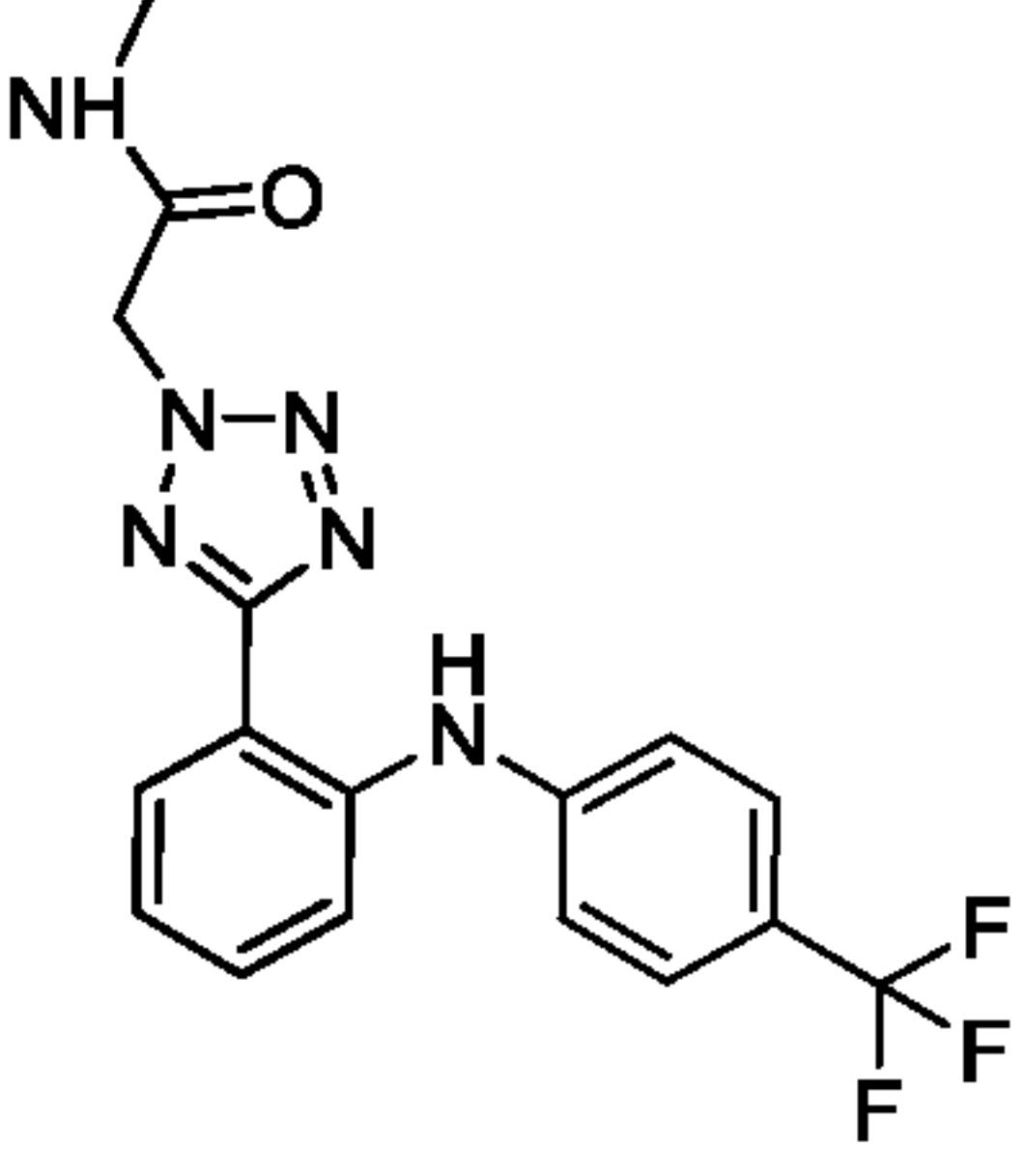
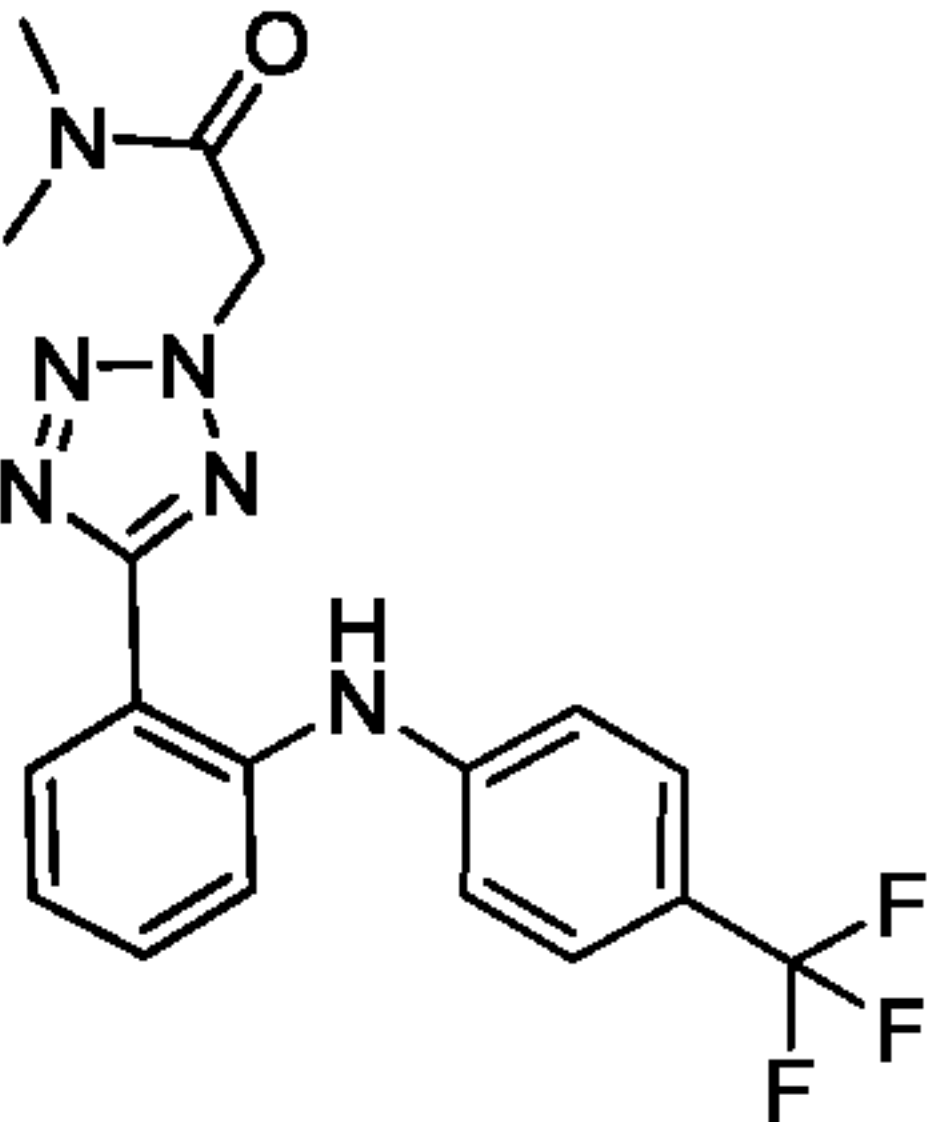
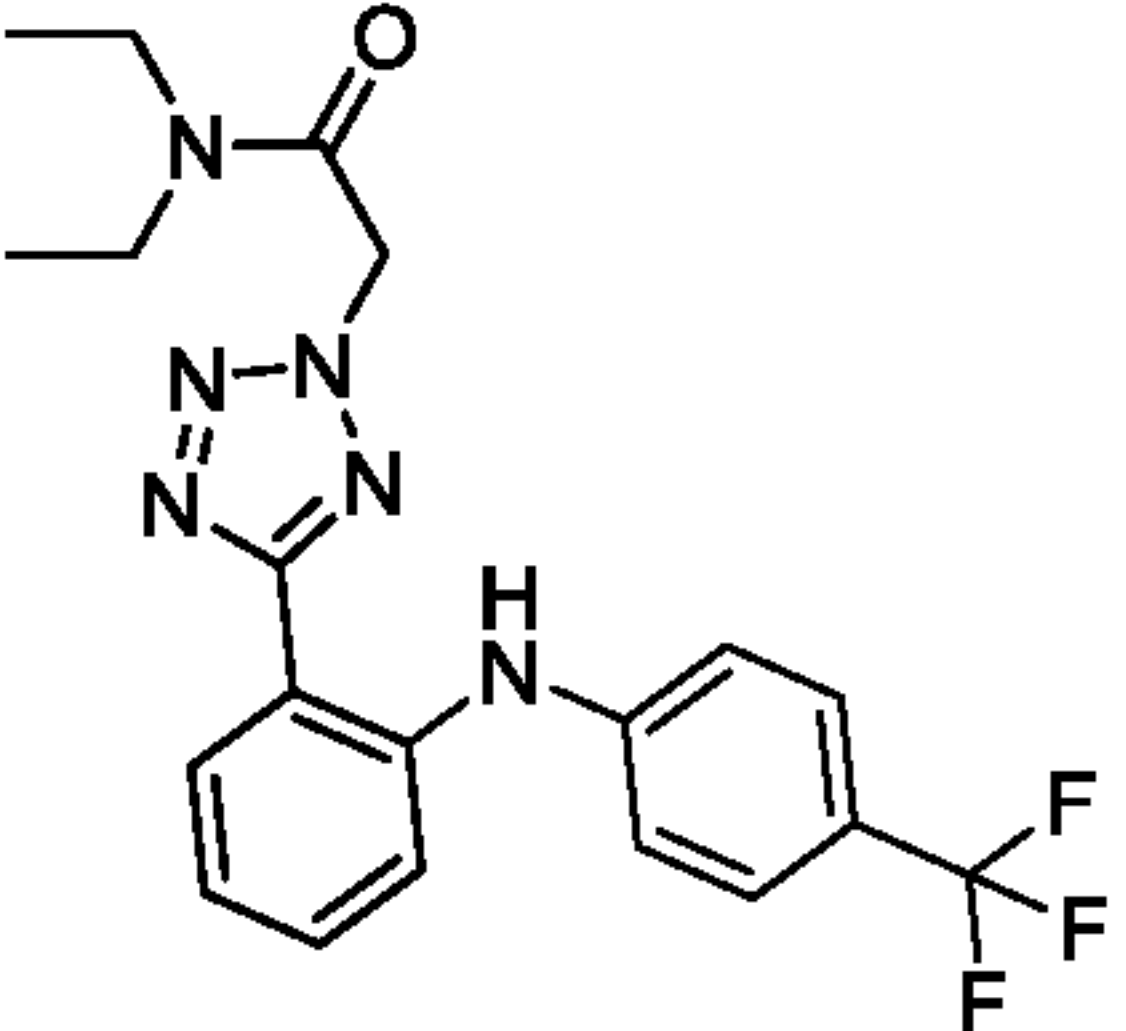
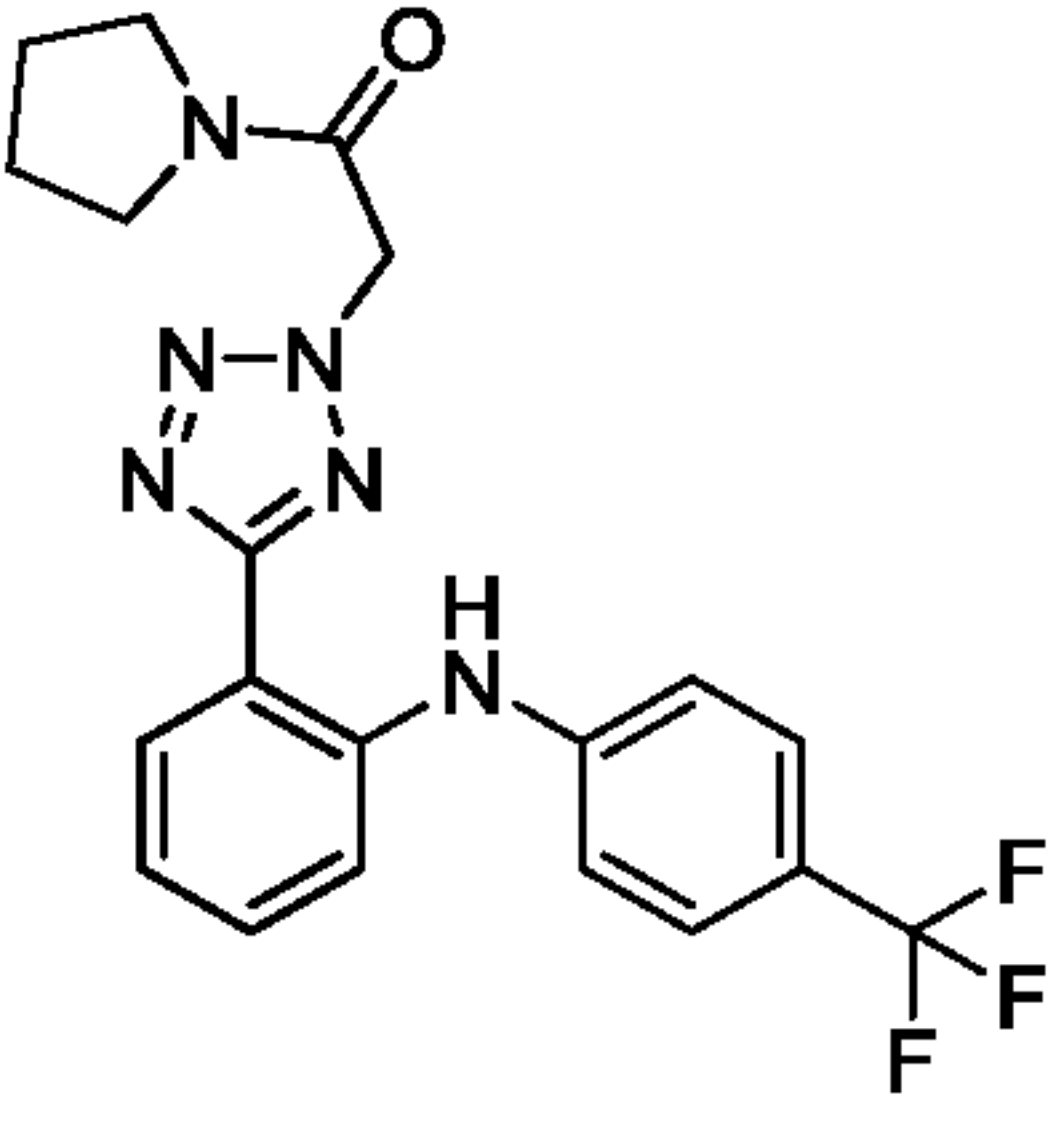
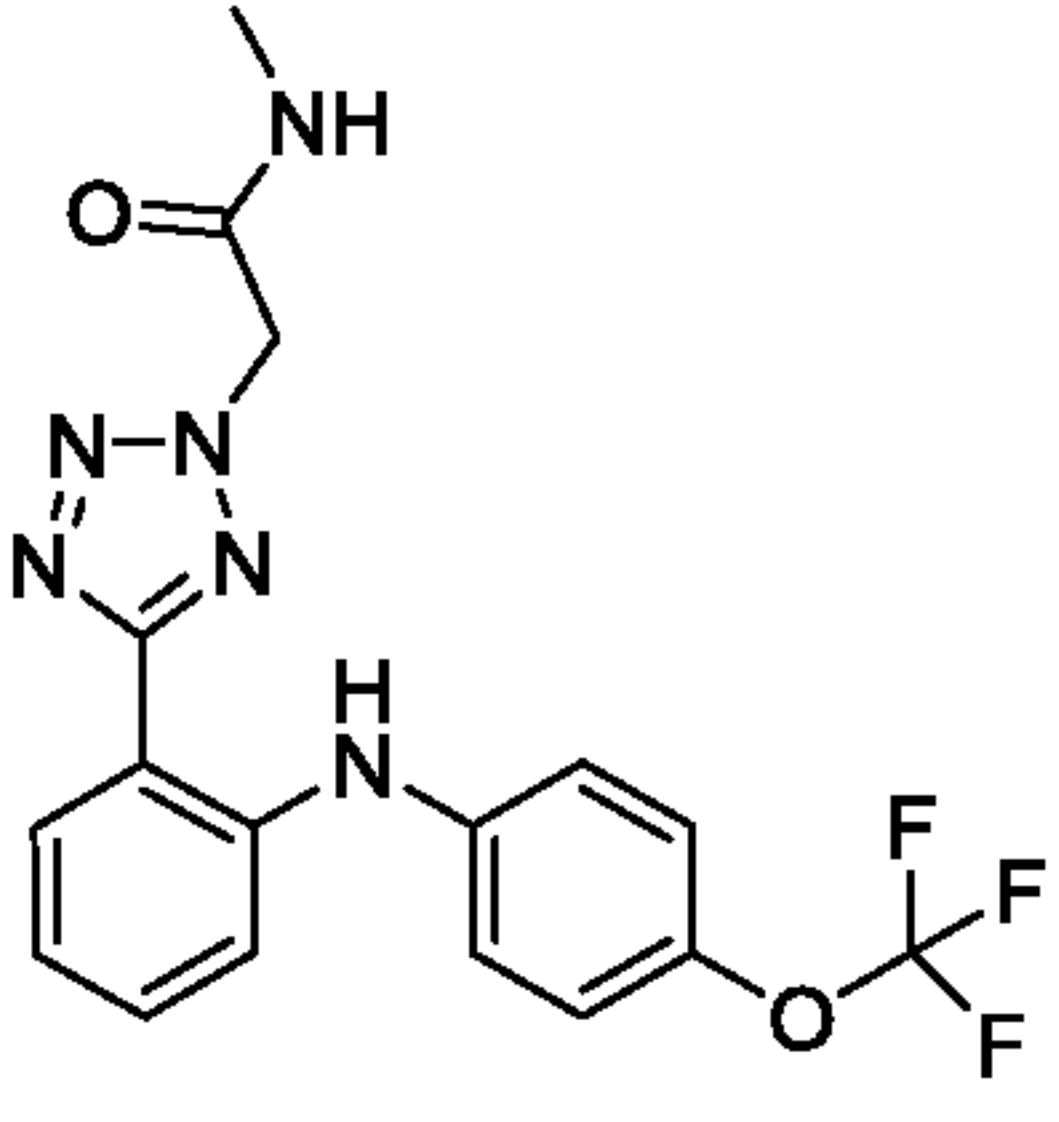
Compound No.	Structure	Name
12		2-[5-[2-(4-methoxyanilino)phenyl]tetrazol-2-yl]ethanol
13		3-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propan-1-ol
14		tert-butyl N-[2-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl]carbamate
15		2-[2-(2-aminoethyl)tetrazol-5-yl]-N-[3-(trifluoromethyl)phenyl]aniline
16		2-[5-[2-(2-ethylanilino)phenyl]tetrazol-2-yl]ethanol
17		2-[5-[2-(3-ethylanilino)phenyl]tetrazol-2-yl]ethanol

Compound No.	Structure	Name
18		Ethyl 2-[4-[2-[3-(trifluoromethyl)anilino]phenyl]triazol-1-yl]acetate
19		2-(5-(2-((3-methoxyphenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-ol
20		2-[2-[2-(3-methoxyphenoxy)ethyl]tetrazol-5-yl]-N-(3-methoxyphenyl)aniline
21		2-[5-[2-(2-methoxyanilino)phenyl]tetrazol-2-yl]ethanol
22		2-[4-[2-[3-(trifluoromethyl)anilino]phenyl]triazol-1-yl]ethanol
23		2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol

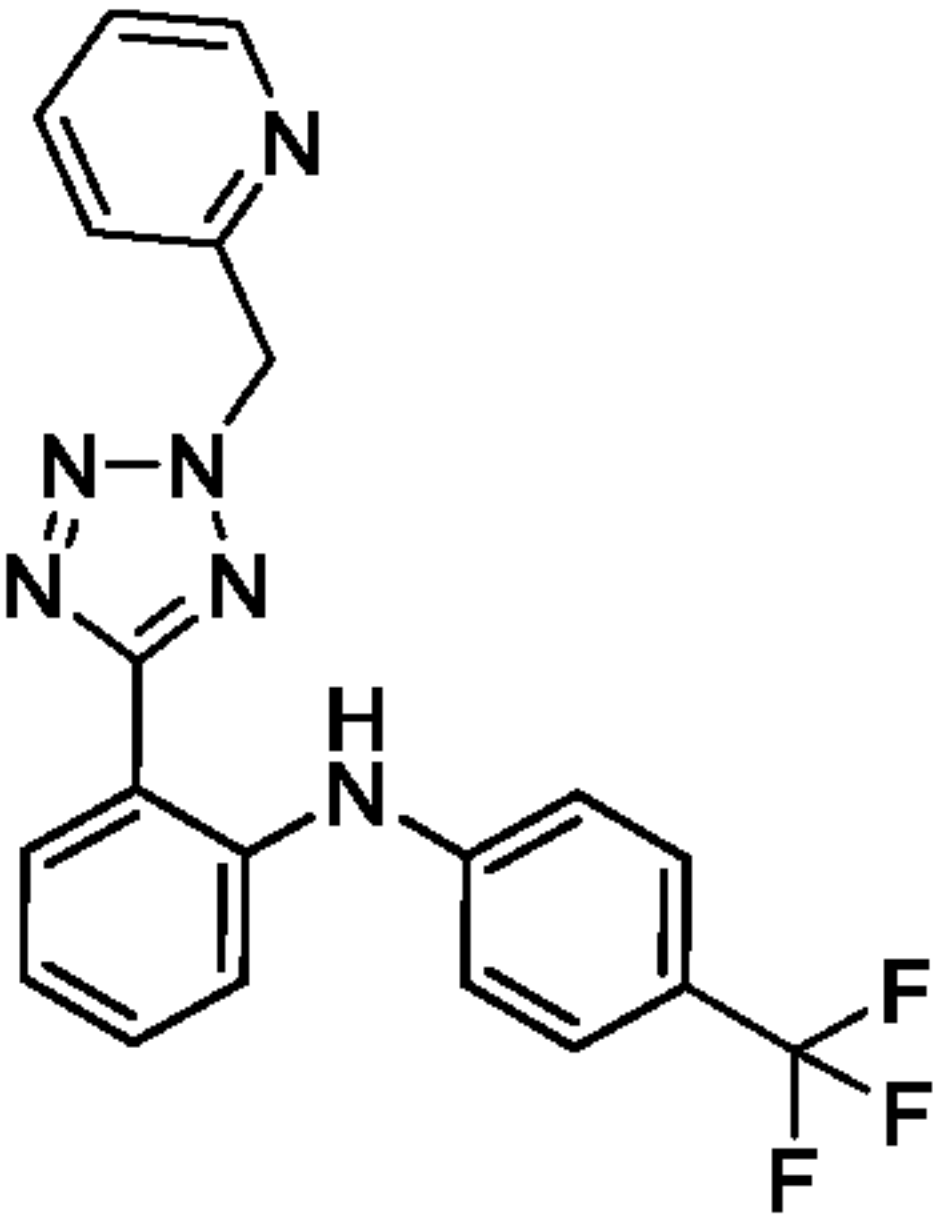
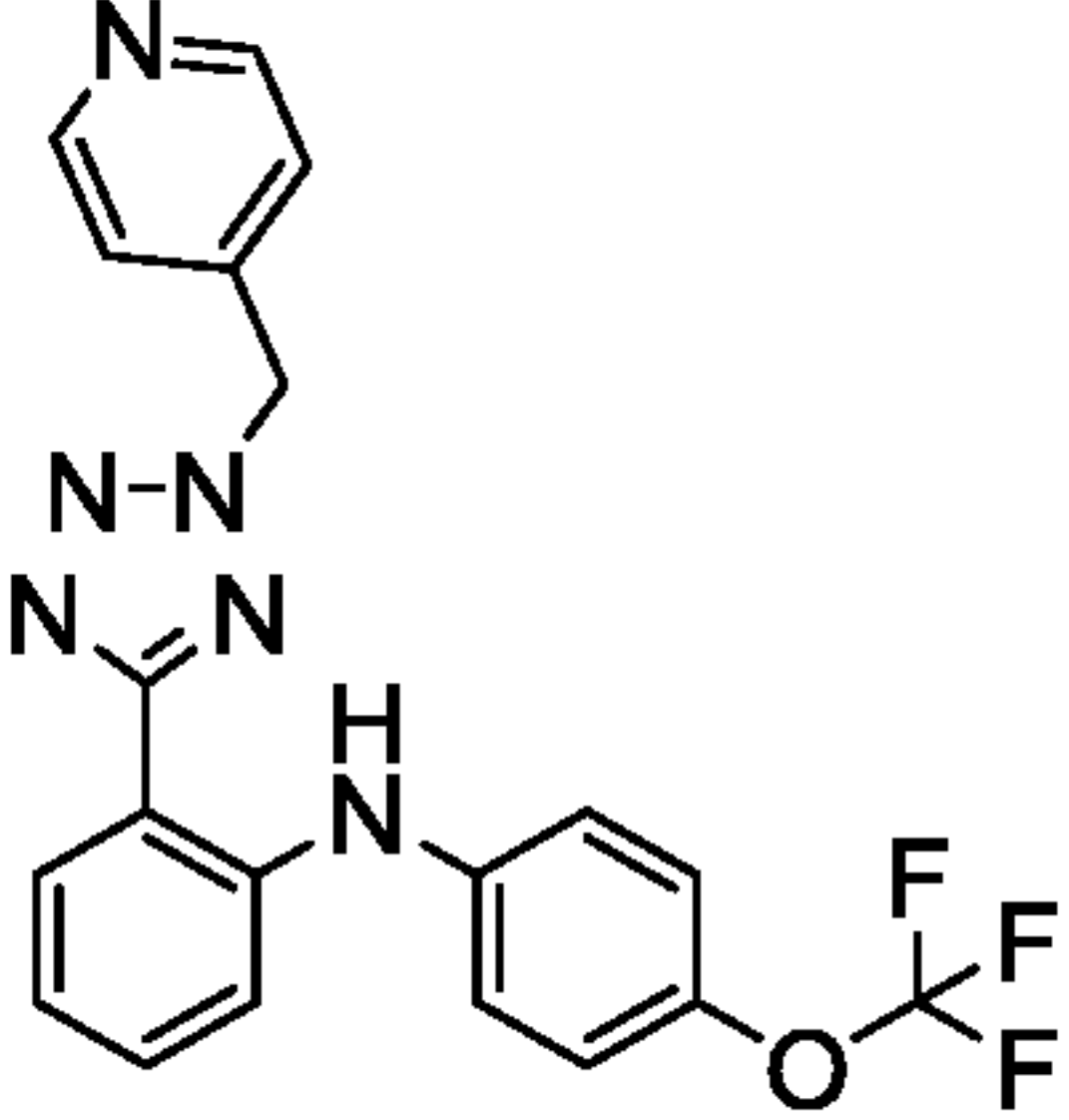
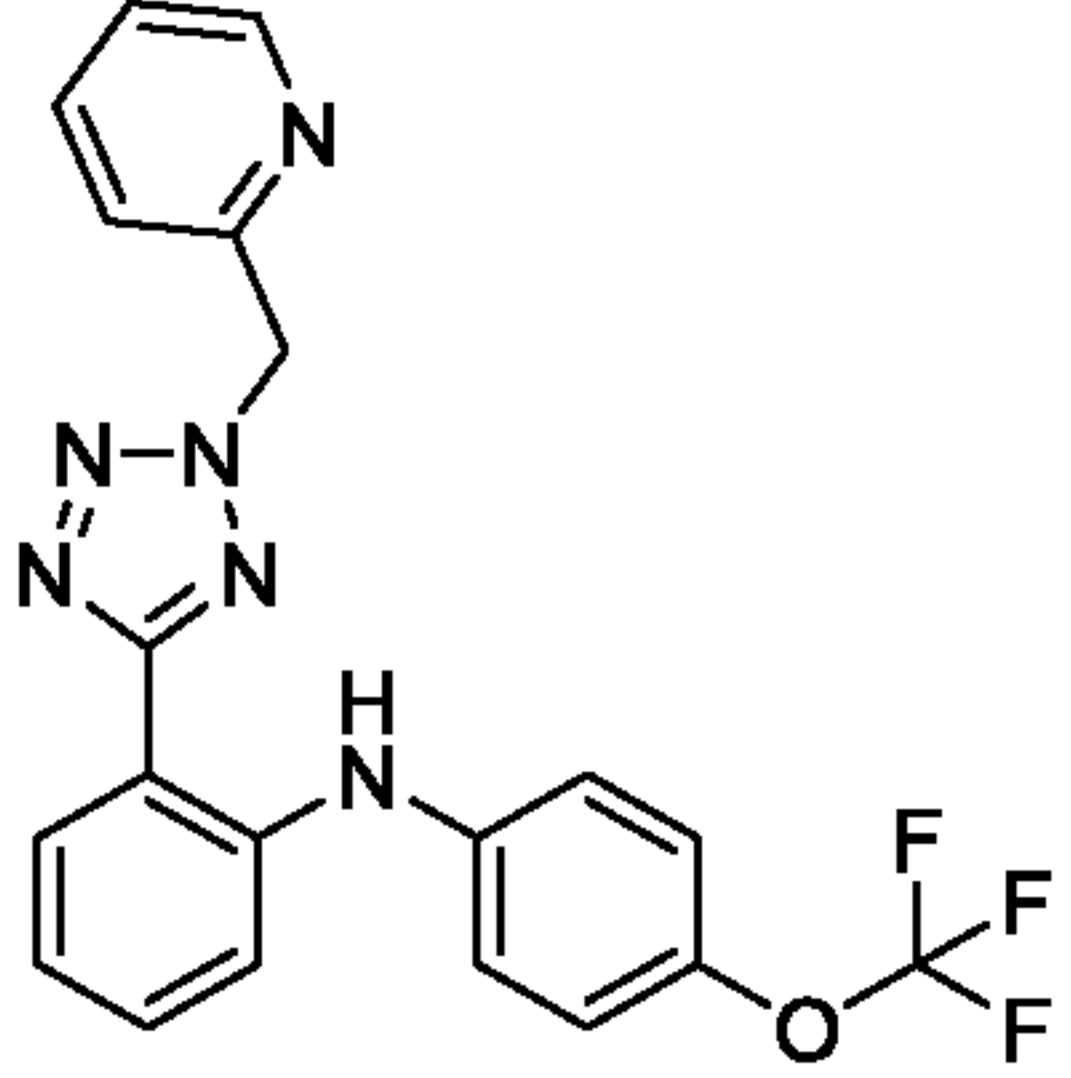
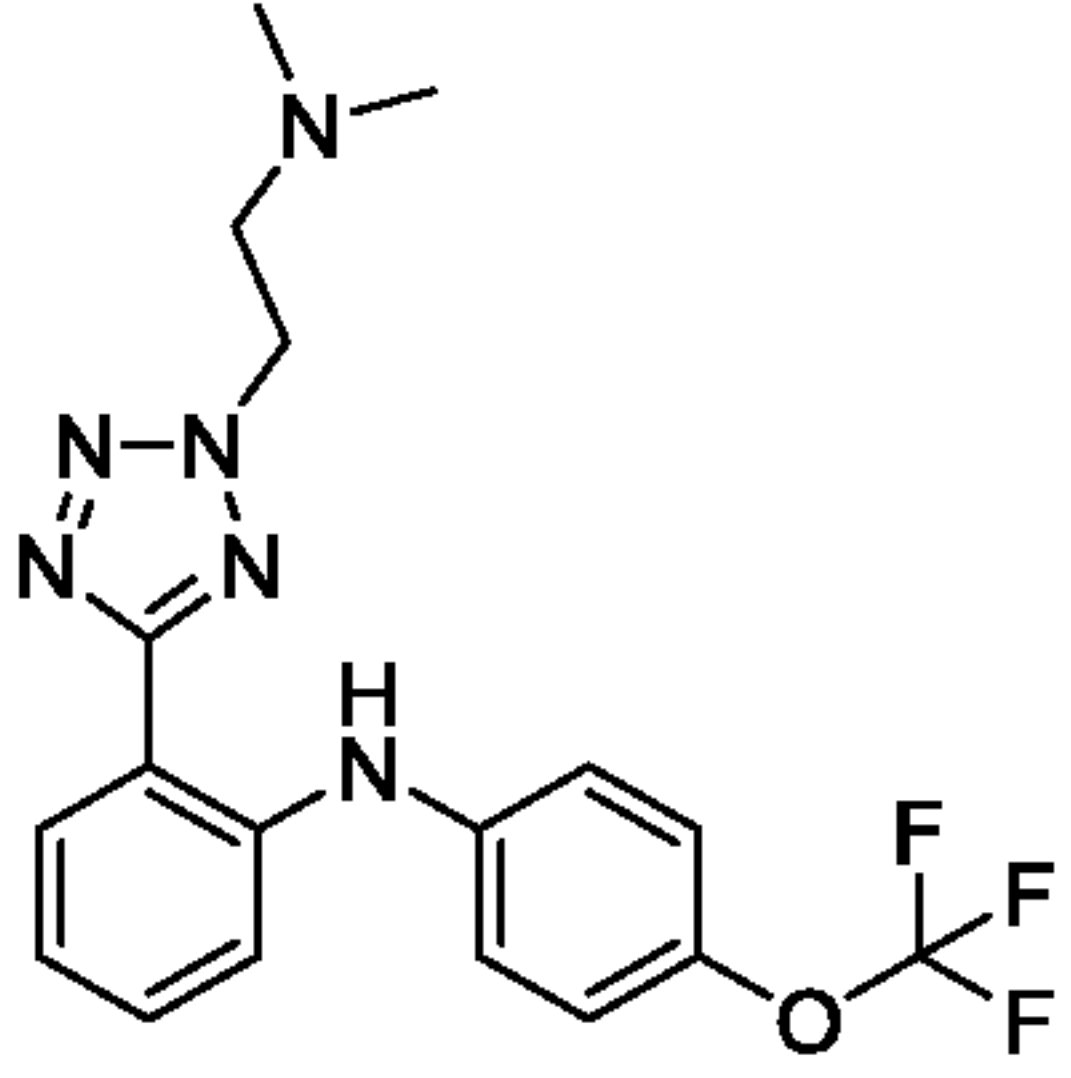
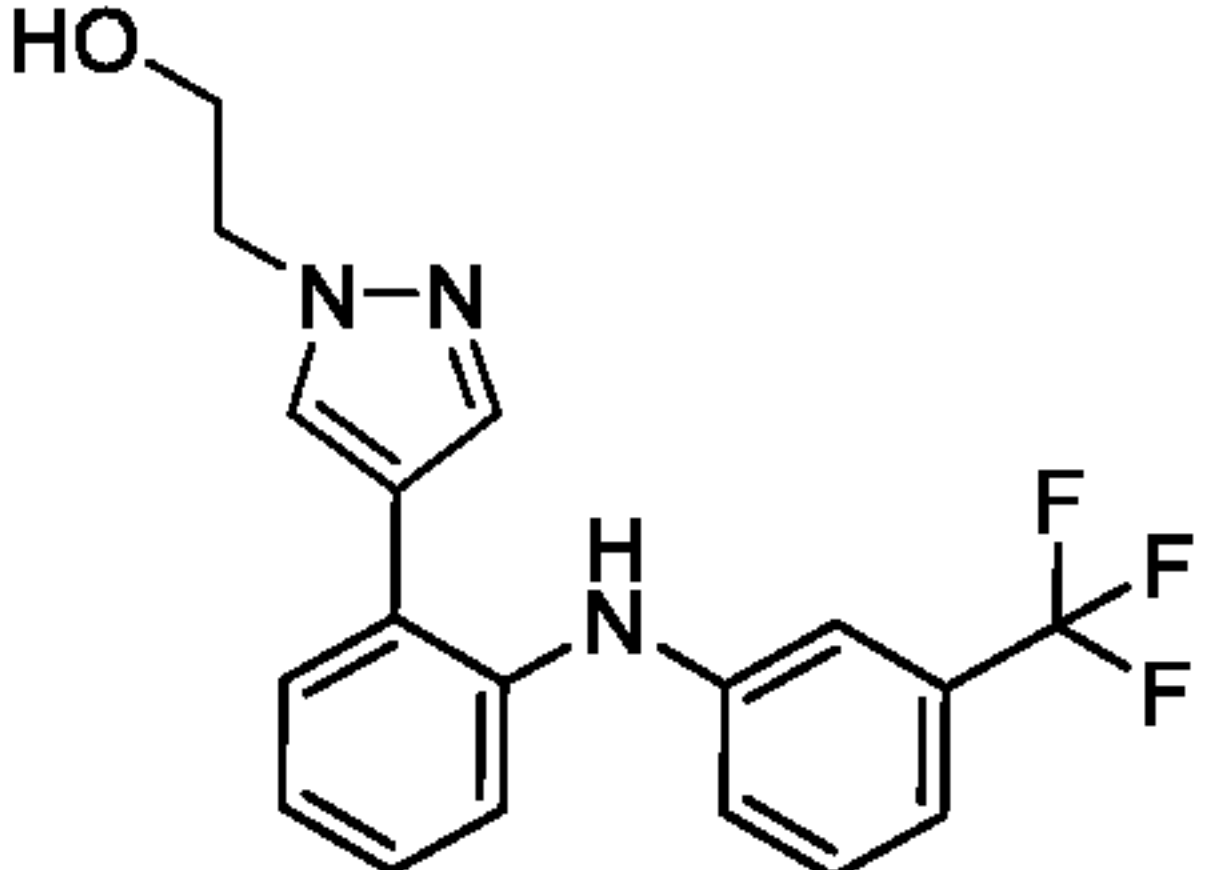
Compound No.	Structure	Name
24		2-(5-(2-((3-(Trifluoromethoxy)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol
25		2-[5-[2-(3,4-difluoroanilino)phenyl]tetrazol-2-yl]ethanol
26		2-[5-[2-[2-(trifluoromethoxy)anilino]phenyl]tetrazol-2-yl]ethanol
27		2-(5-(2-((2,3-difluorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-ol
28		2-(5-(2-((2,4-difluorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-ol
29		N-[2-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl]methanesulfonamide

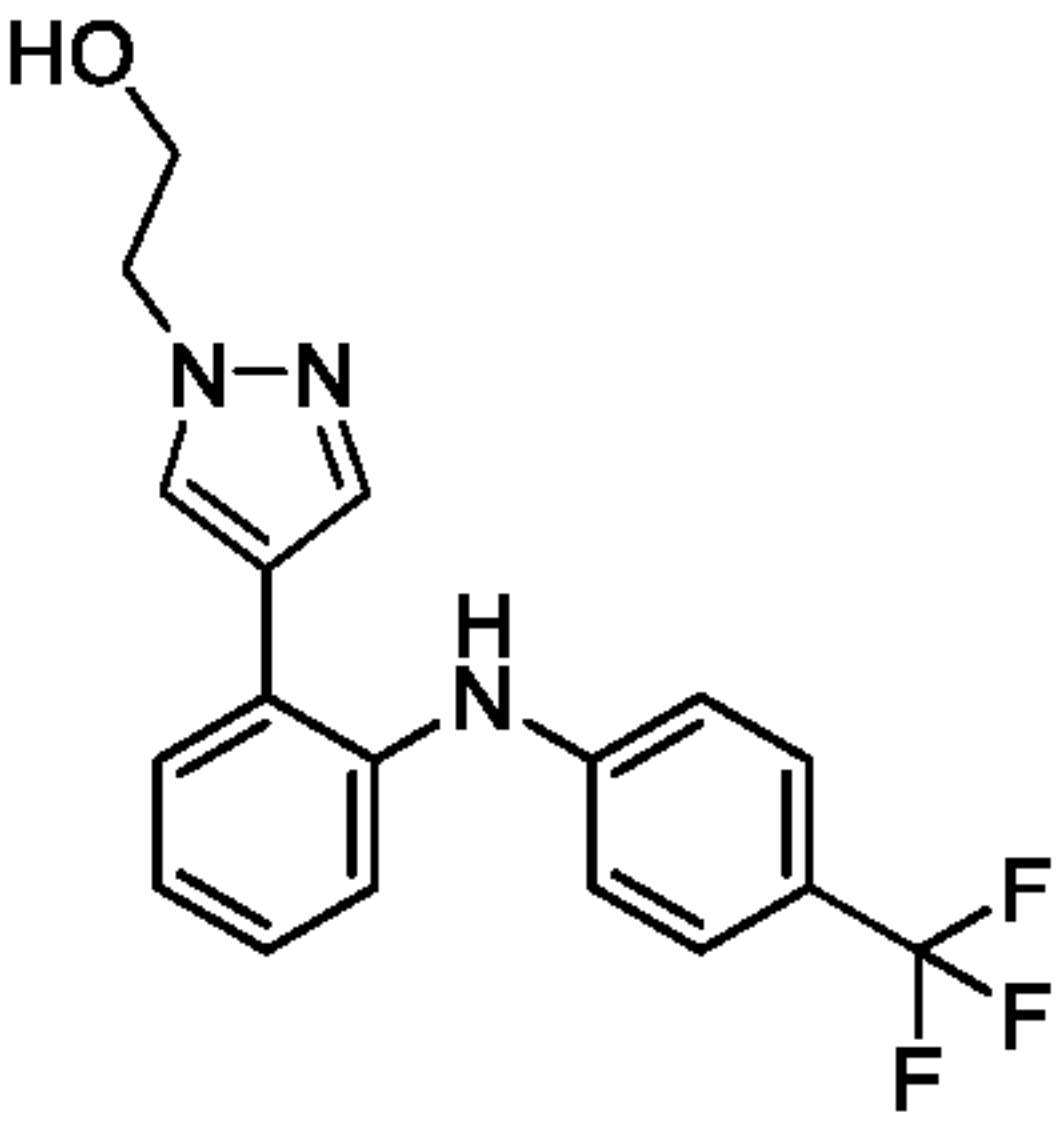
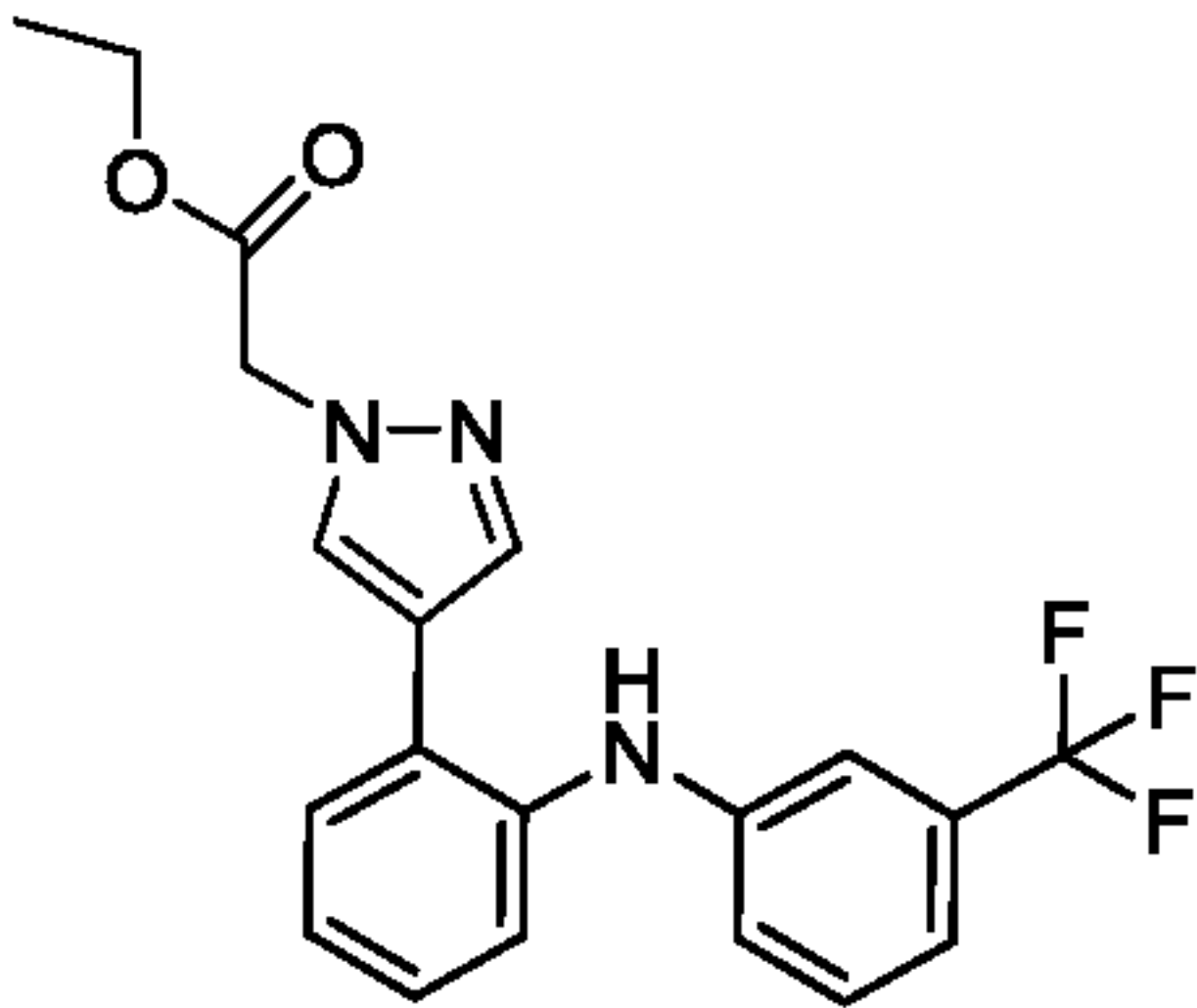
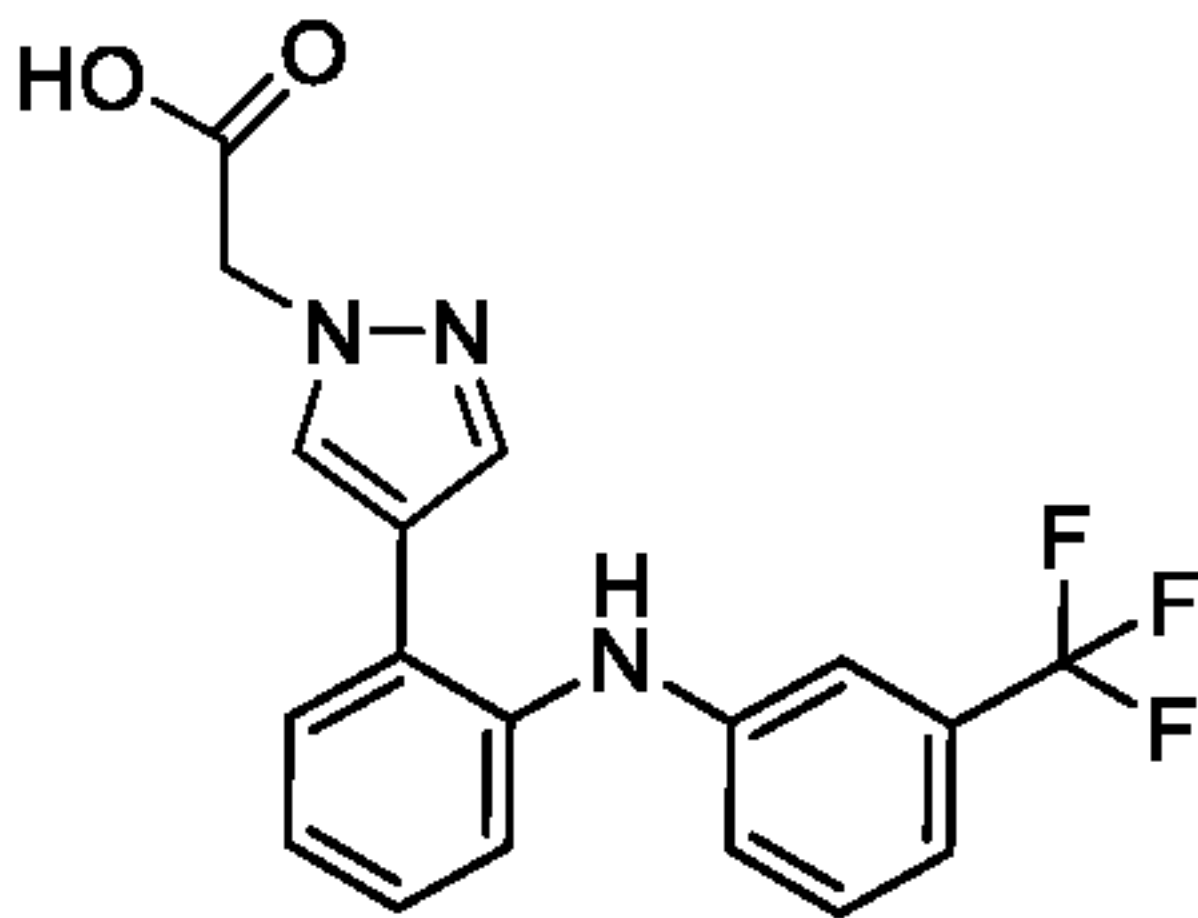
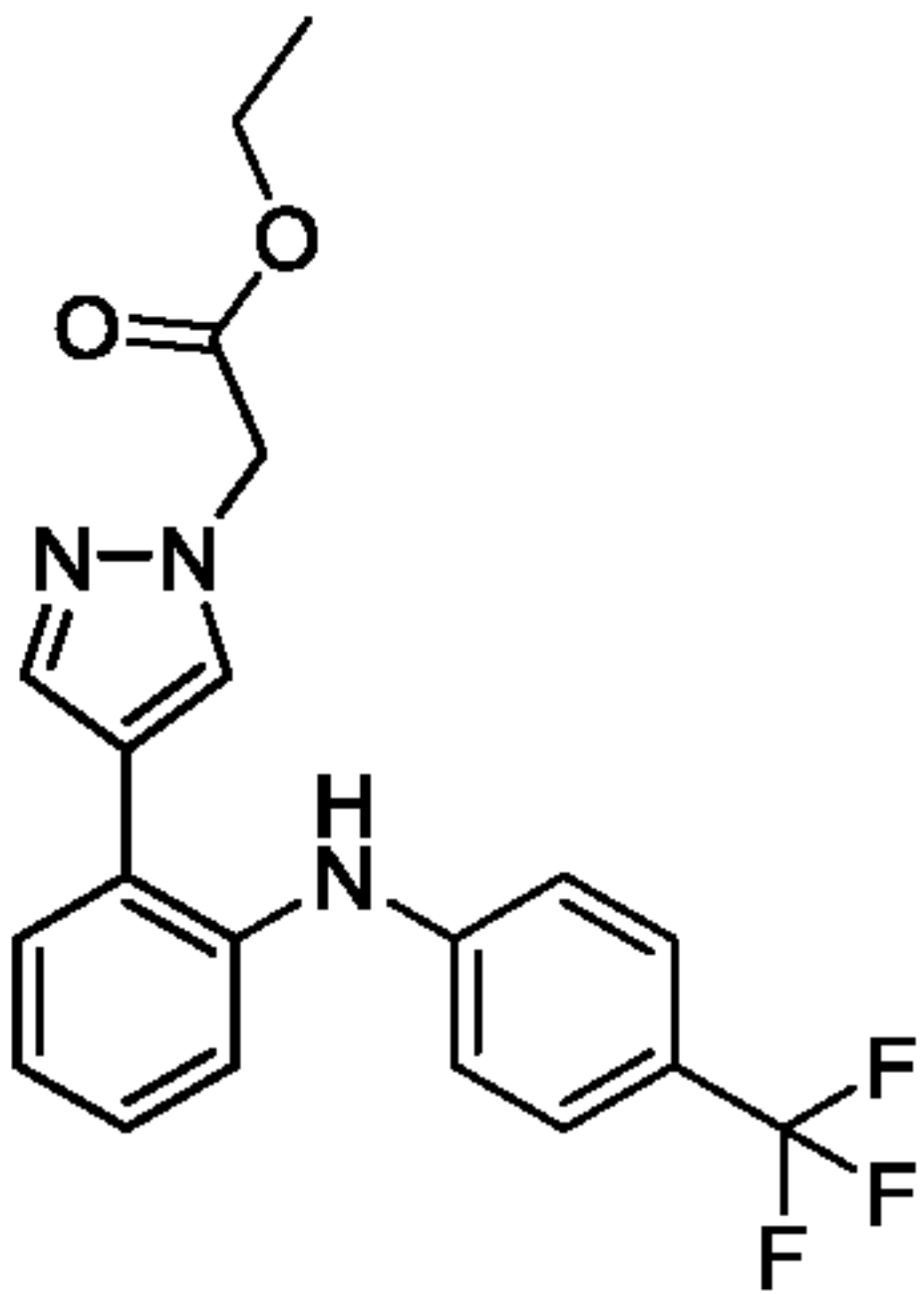
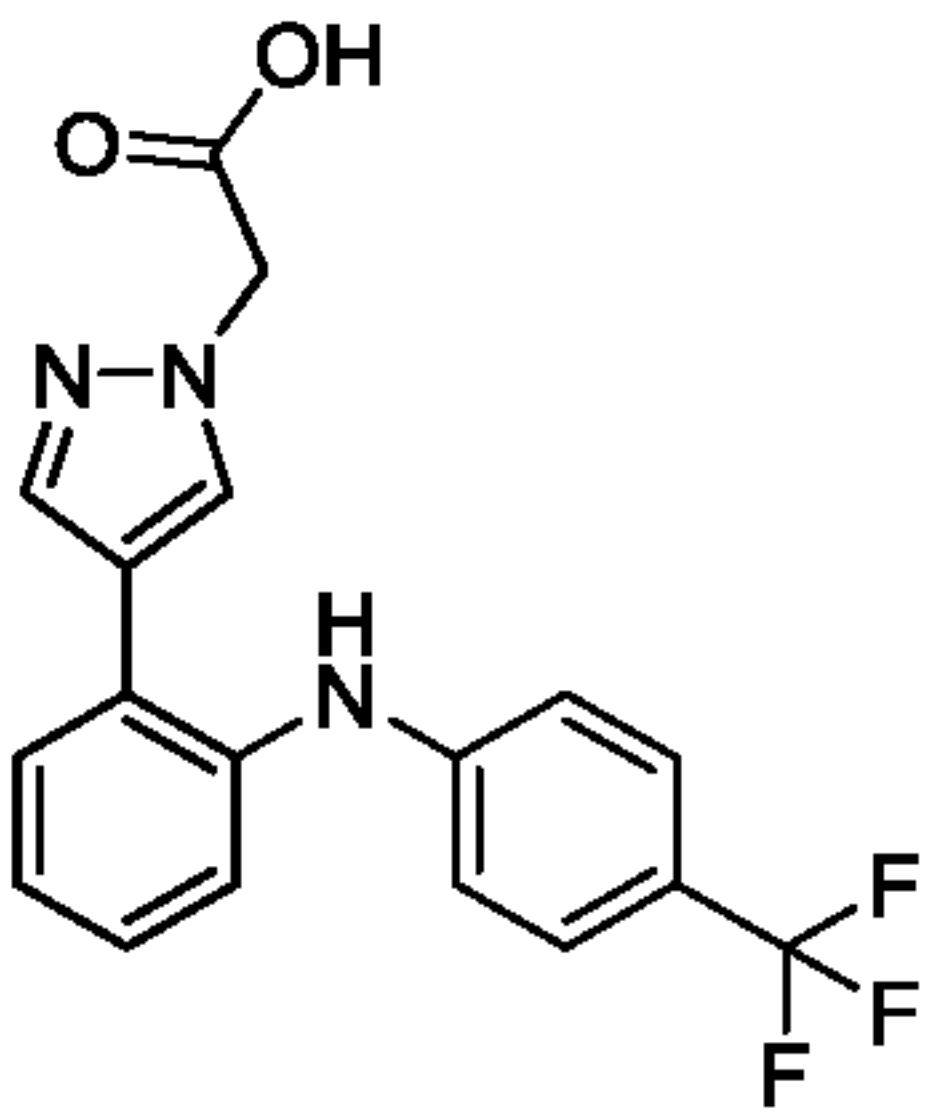
Compound No.	Structure	Name
30		N-[2-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl]acetamide
31		2-[5-[2-[4-(difluoromethylsulfanyl)anilino]phenyl]tetrazol-2-yl]ethanol
32		2-(5-(2-((3,5-difluorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol
33		2-(5-(2-((4-(methylsulfonyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol
34		2-(5-(2-((2,5-difluorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol
35		2-(5-(2-((3-(methylsulfonyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol

Compound No.	Structure	Name
36		2-(5-(2-((2-fluorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol
37		2-[5-[2-(2,6-difluoroanilino)phenyl]tetrazol-2-yl]ethanol
38		2-[5-[2-(2-methylsulfonylanilino)phenyl]tetrazol-2-yl]ethanol
39		2-(3-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-1,2,4-triazol-1-yl)ethanol
40		2-[2-(3-pyridylmethyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline
41		2-[2-(4-pyridylmethyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline

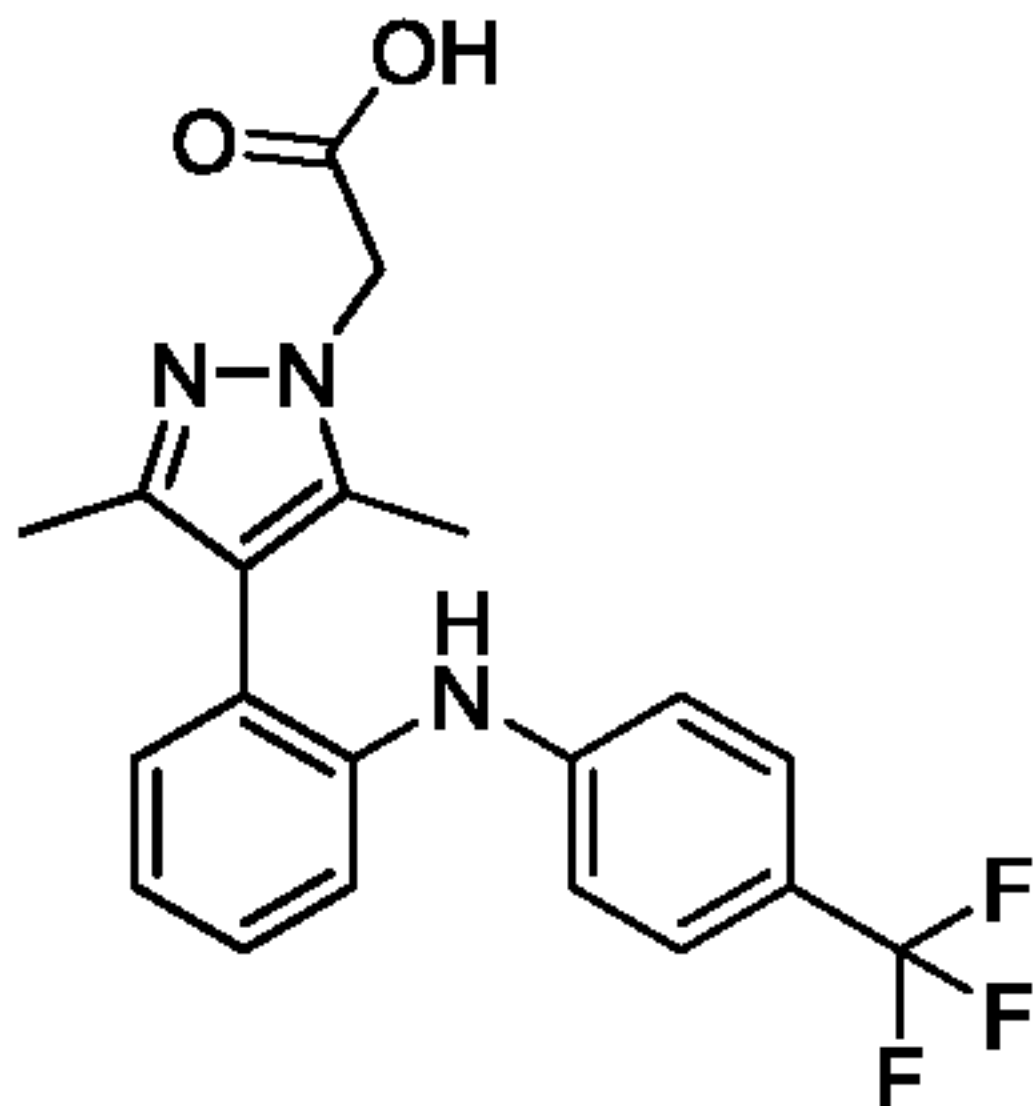
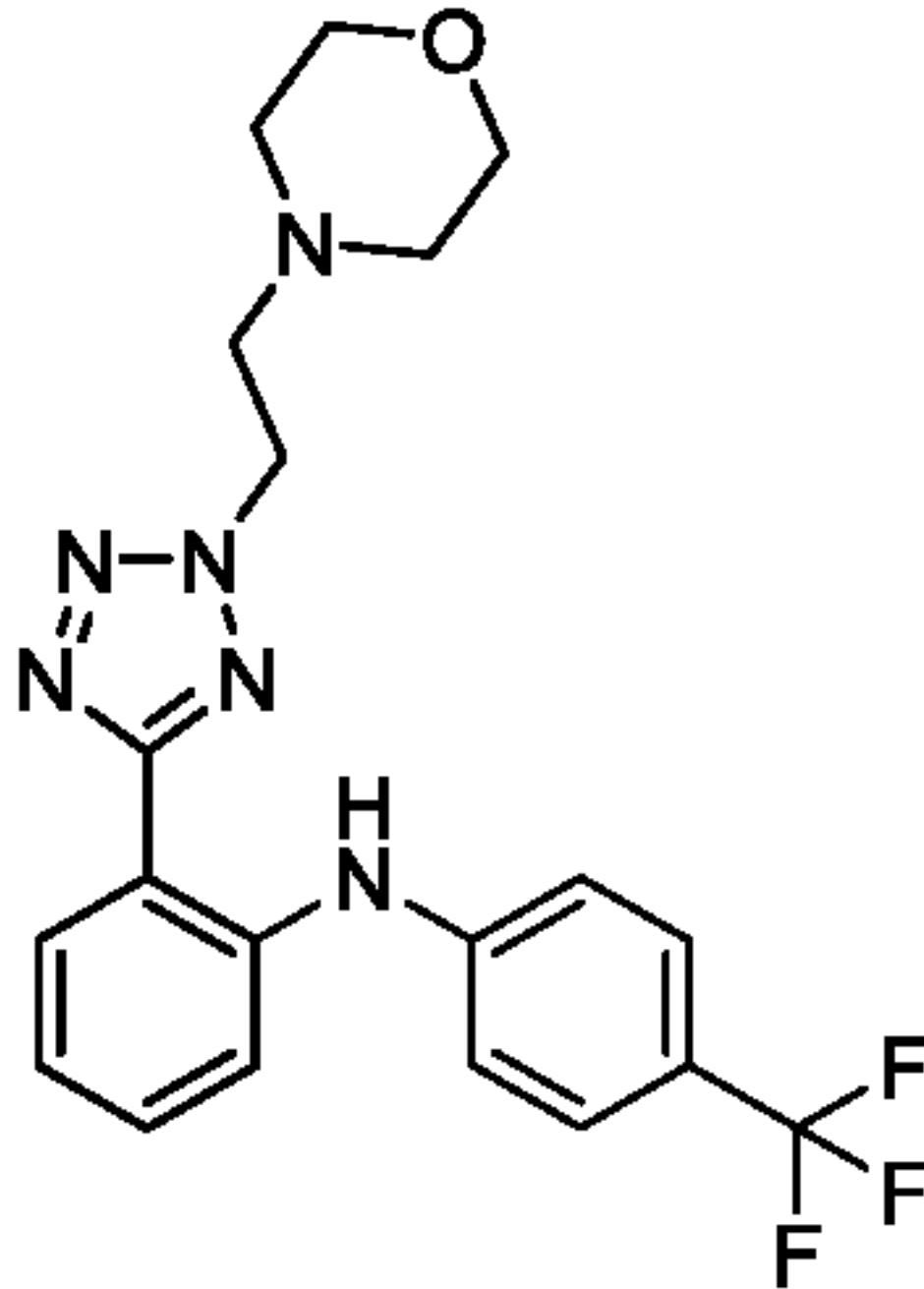
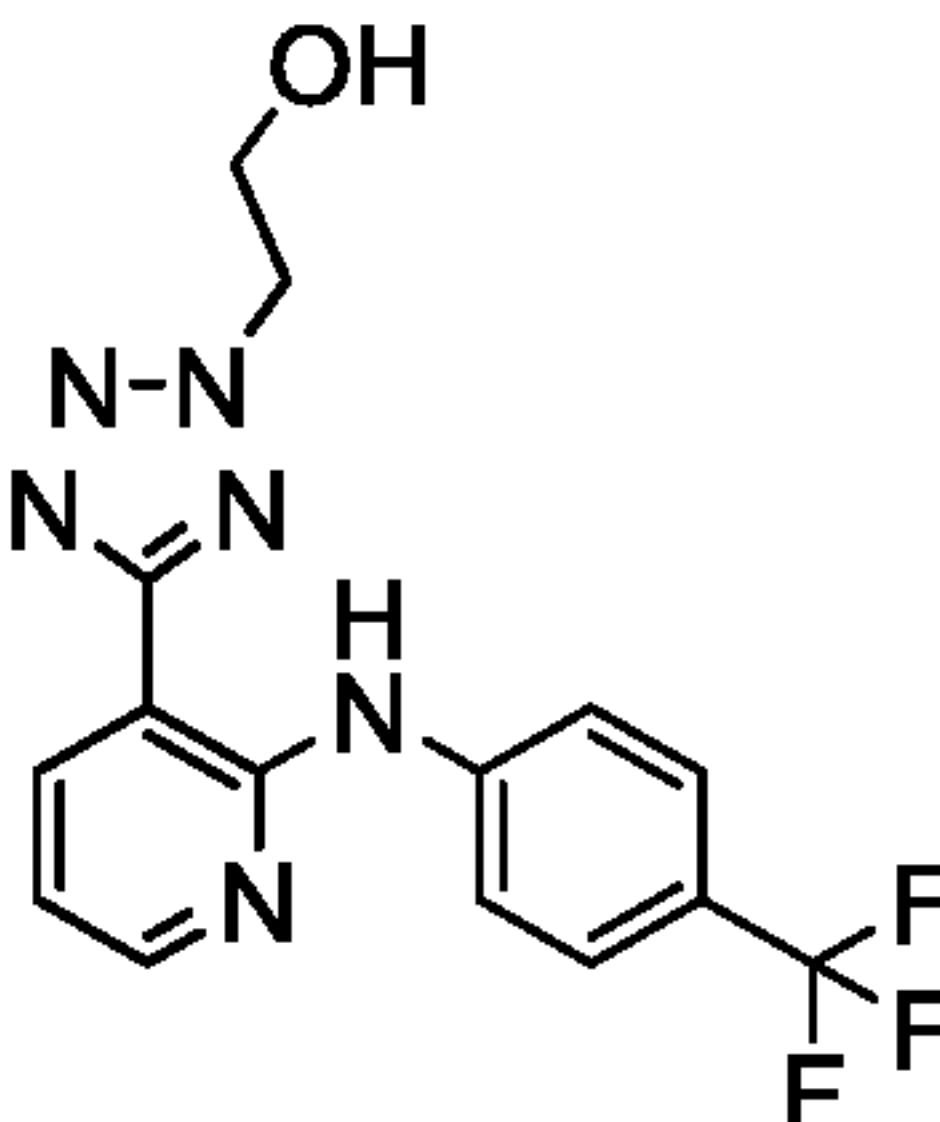
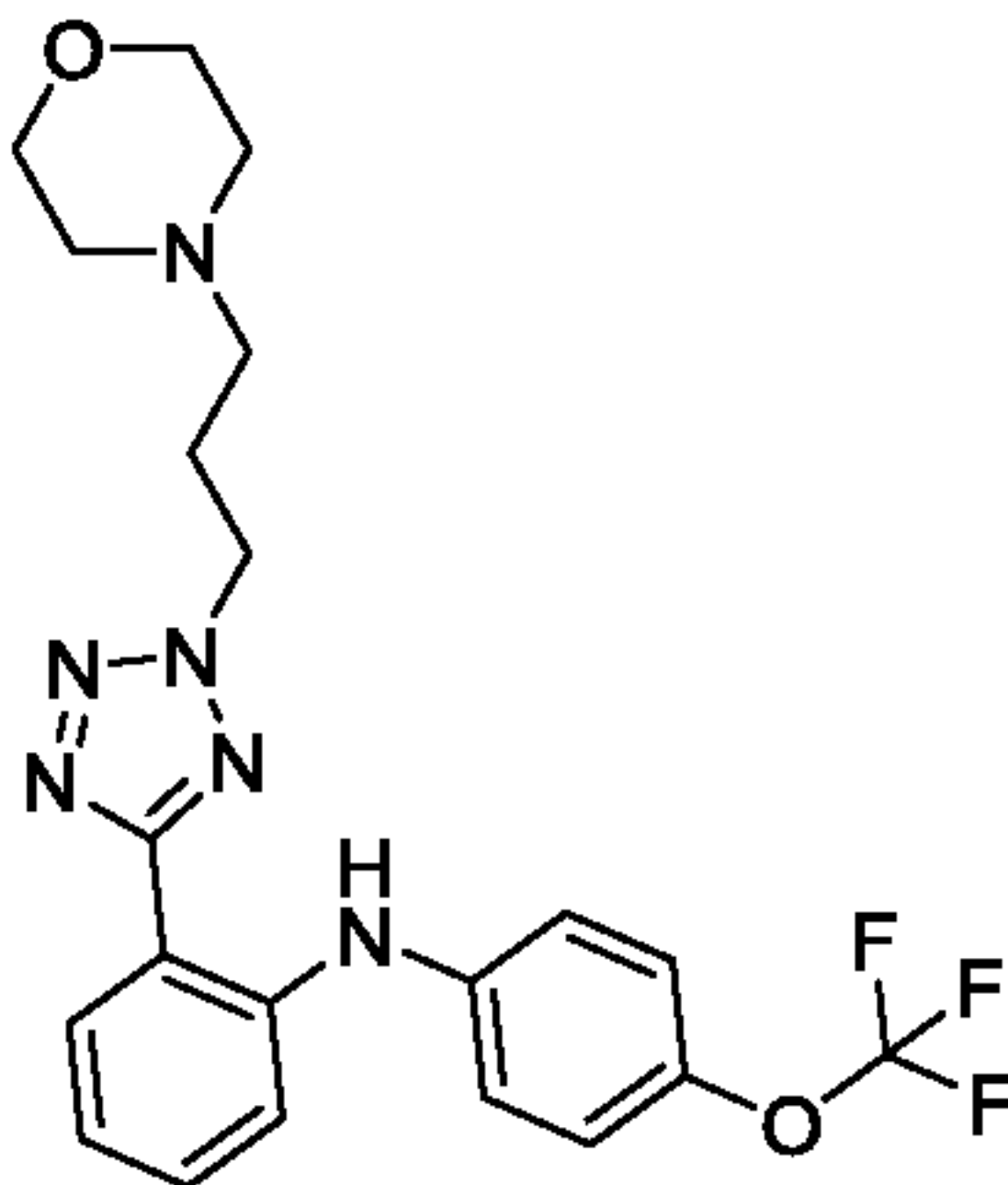
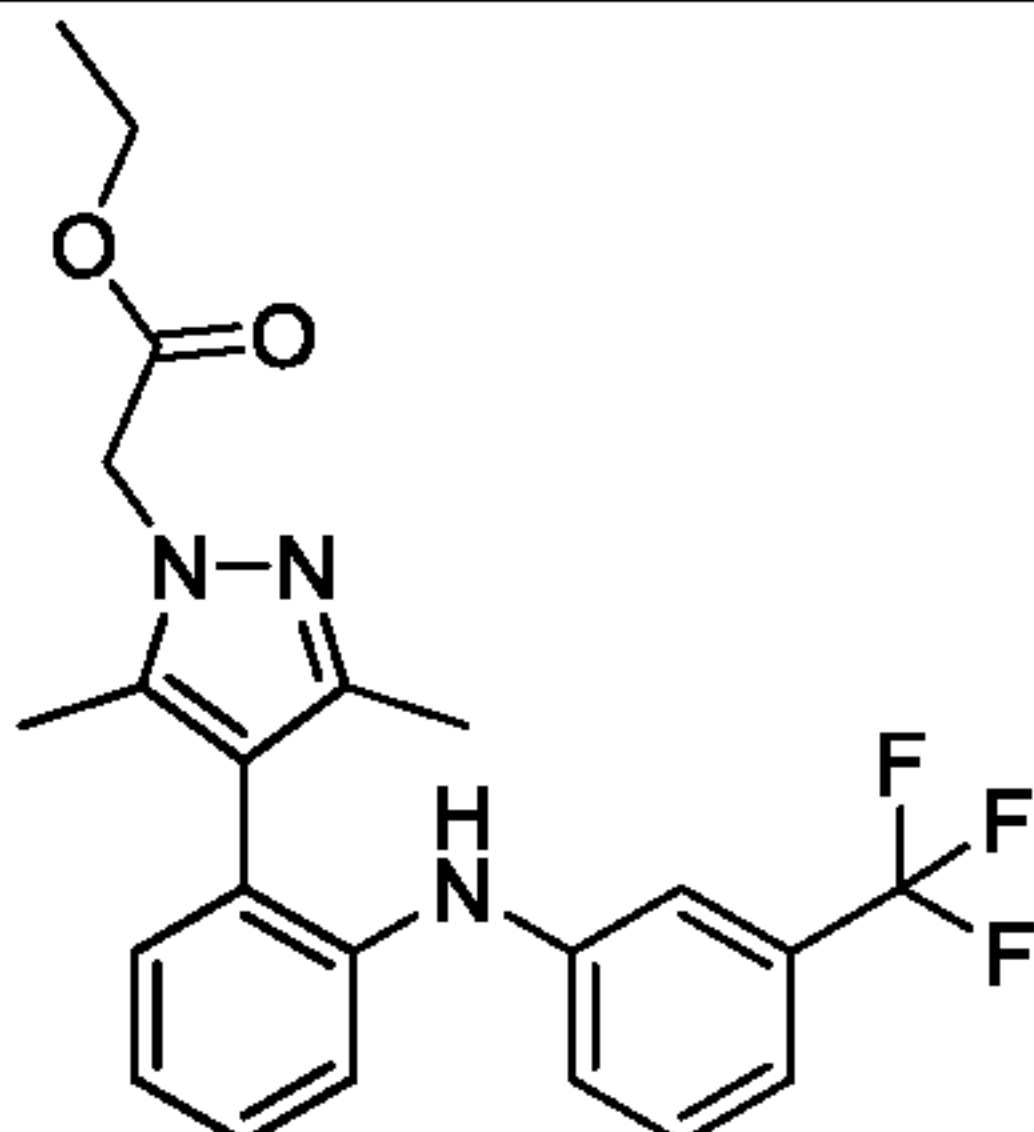
Compound No.	Structure	Name
42		N-methyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetamide
43		N,N-dimethyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetamide
44		N,N-diethyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetamide
45		1-pyrrolidin-1-yl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanone
46		N-methyl-2-[5-[2-[4-(trifluoromethoxy)anilino]phenyl]tetrazol-2-yl]acetamide

Compound No.	Structure	Name
47		N,N-dimethyl-2-[5-[2-[4-(trifluoromethoxy)anilino]phenyl]tetrazol-2-yl]acetamide
48		N,N-diethyl-2-[5-[2-[4-(trifluoromethoxy)anilino]phenyl]tetrazol-2-yl]acetamide
49		1-(pyrrolidin-1-yl)-2-(5-(2-((4-(trifluoromethoxy)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-one
50		2-[2-[2-(dimethylamino)ethyl]tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline
51		2-[2-(3-pyridylmethyl)tetrazol-5-yl]-N-[4-(trifluoromethoxy)phenyl]aniline

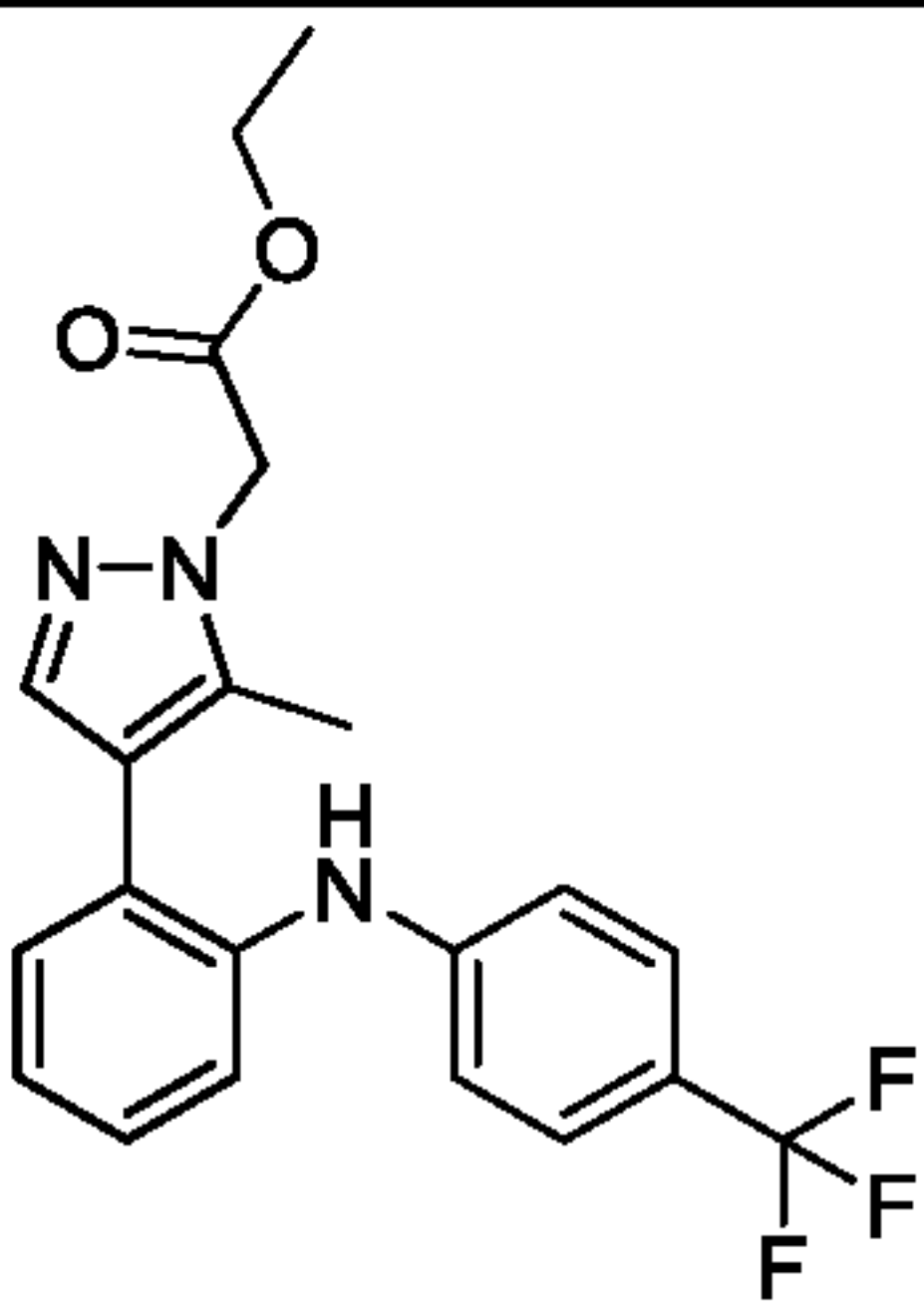
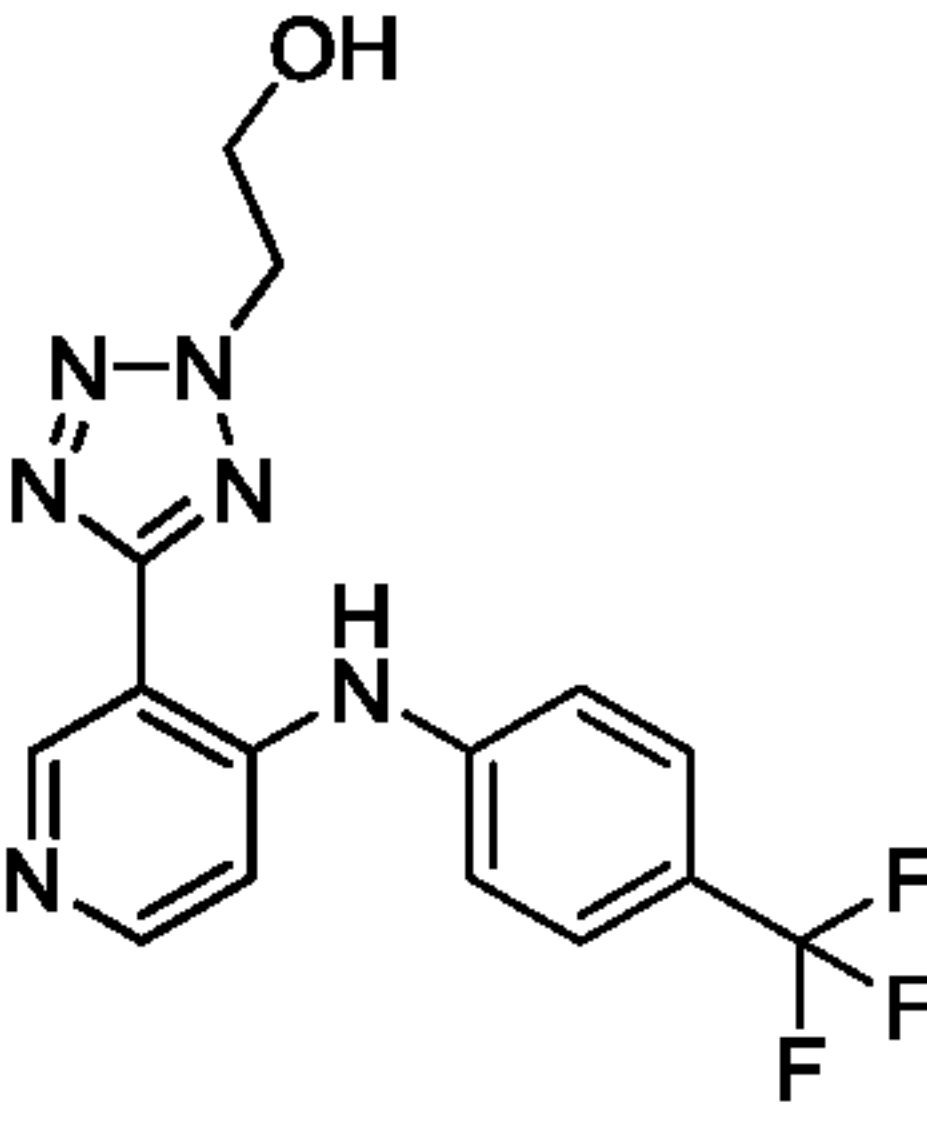
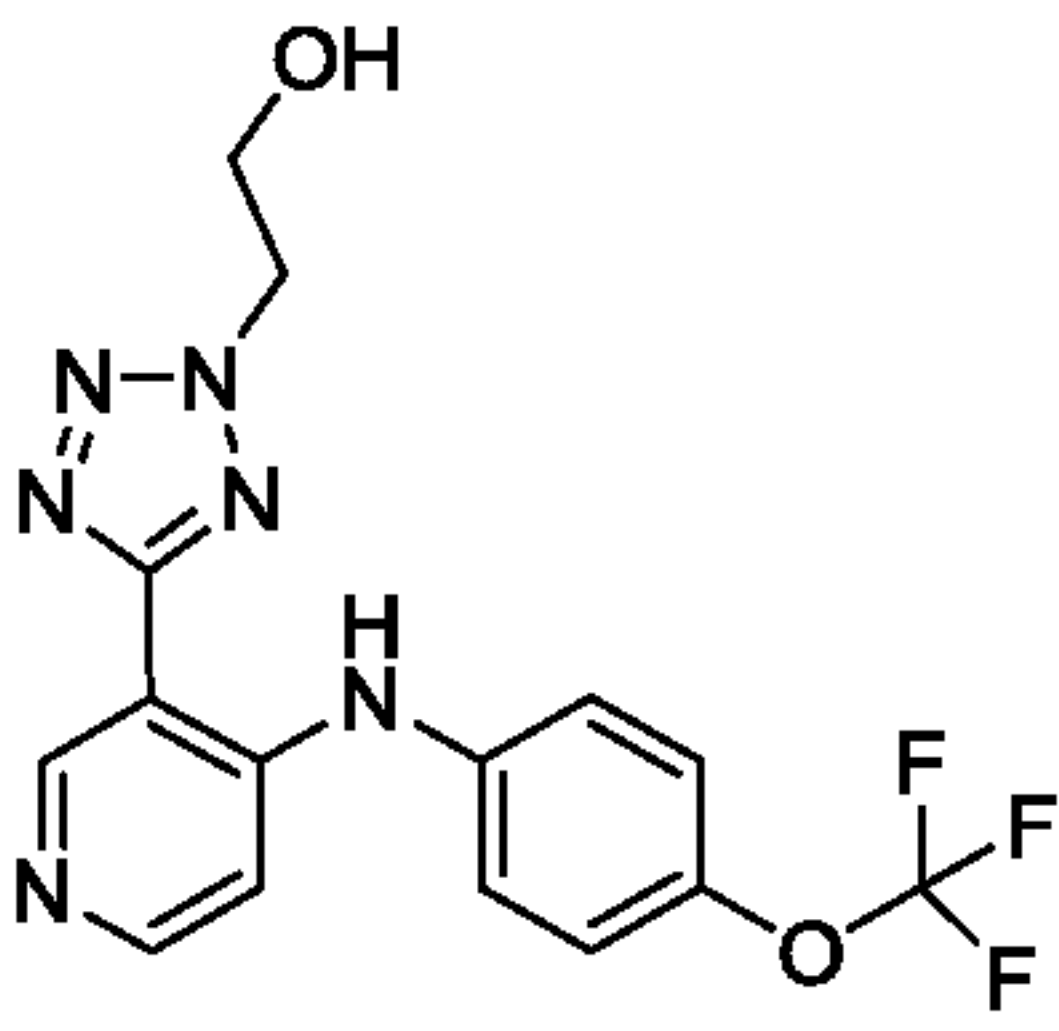
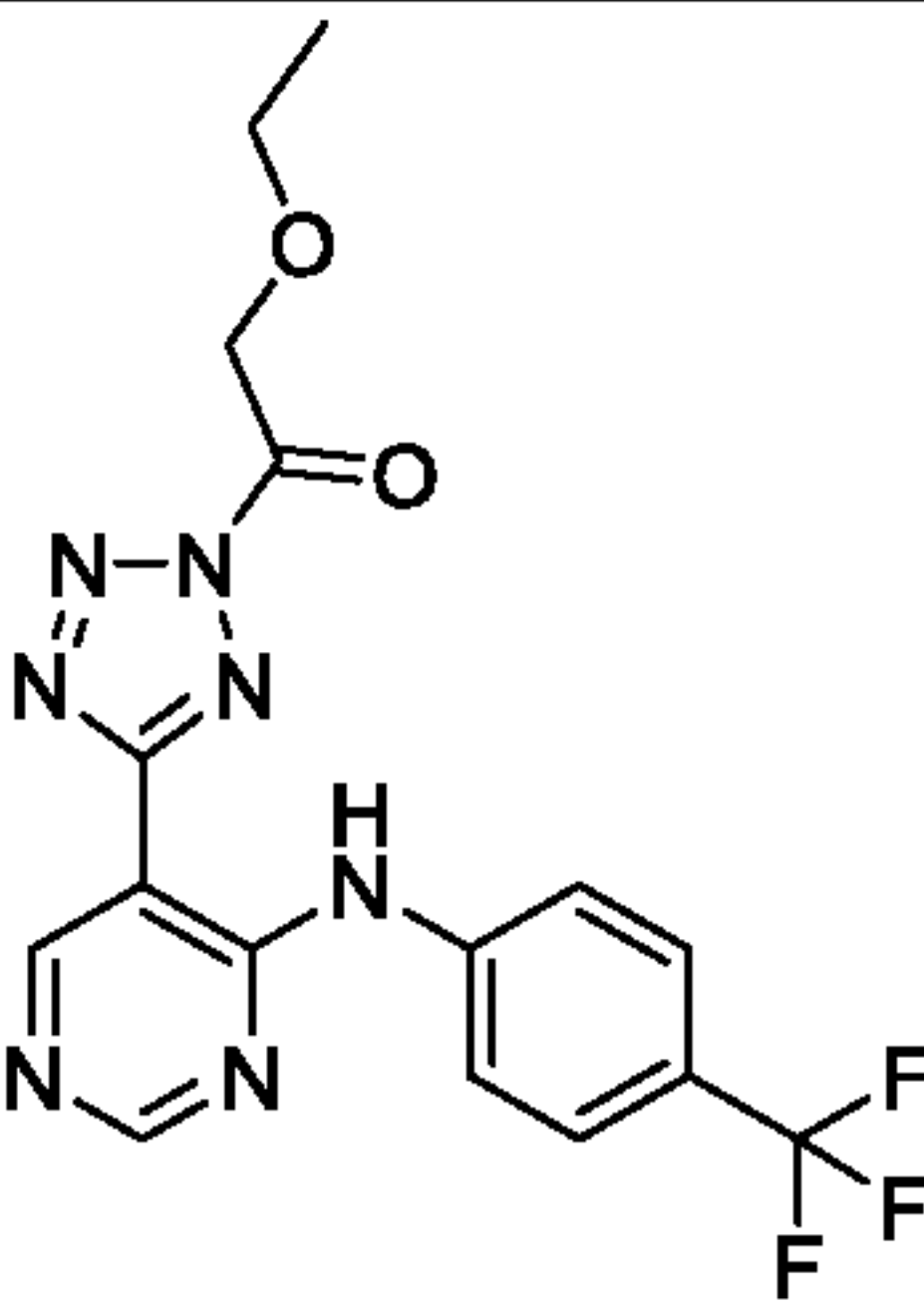
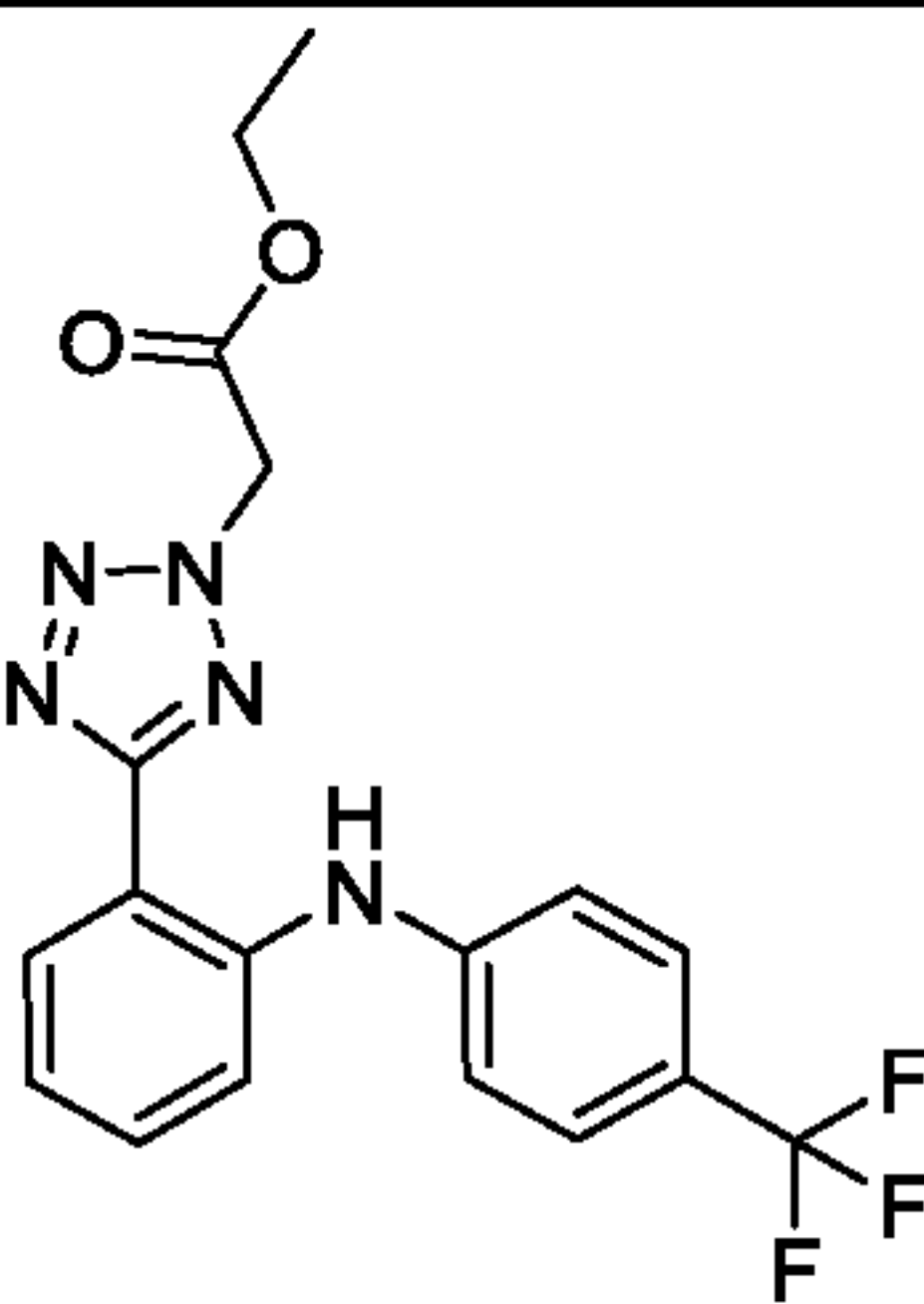
Compound No.	Structure	Name
52		2-[2-(2-pyridylmethyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline
53		2-[2-(4-pyridylmethyl)tetrazol-5-yl]-N-[4-(trifluoromethoxy)phenyl]aniline
54		2-[2-(2-pyridylmethyl)tetrazol-5-yl]-N-[4-(trifluoromethoxy)phenyl]aniline
55		2-[2-[2-(dimethylamino)ethyl]tetrazol-5-yl]-N-[4-(trifluoromethoxy)phenyl]aniline
56		2-[4-[2-[3-(trifluoromethyl)anilino]phenyl]pyrazol-1-yl]ethanol

Compound No.	Structure	Name
57		2-[4-[2-[3-(trifluoromethyl)anilino]phenyl]pyrazol-1-yl]ethanol
58		ethyl 2-(4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetate
59		2-(4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetic acid
60		ethyl 2-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetate
61		2-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetic acid

Compound No.	Structure	Name
62		2-(2-(3-(dimethylamino)propyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
63		2-(2-(3-(dimethylamino)propyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethoxy)phenyl)aniline
64		2-(2-(2-morpholinoethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethoxy)phenyl)aniline
65		2-(2-(3-morpholinopropyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
66		ethyl 2-(3,5-dimethyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetate

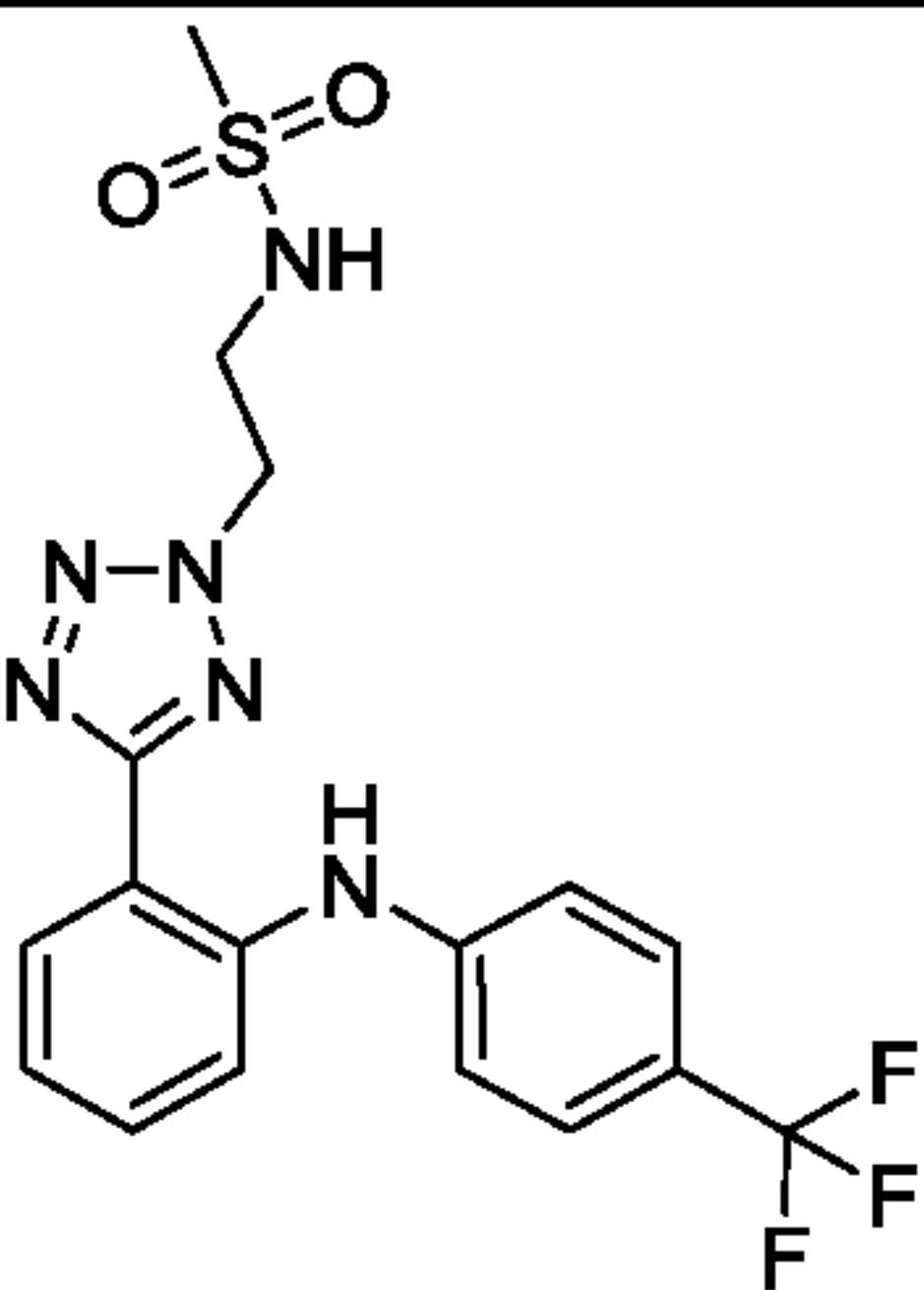
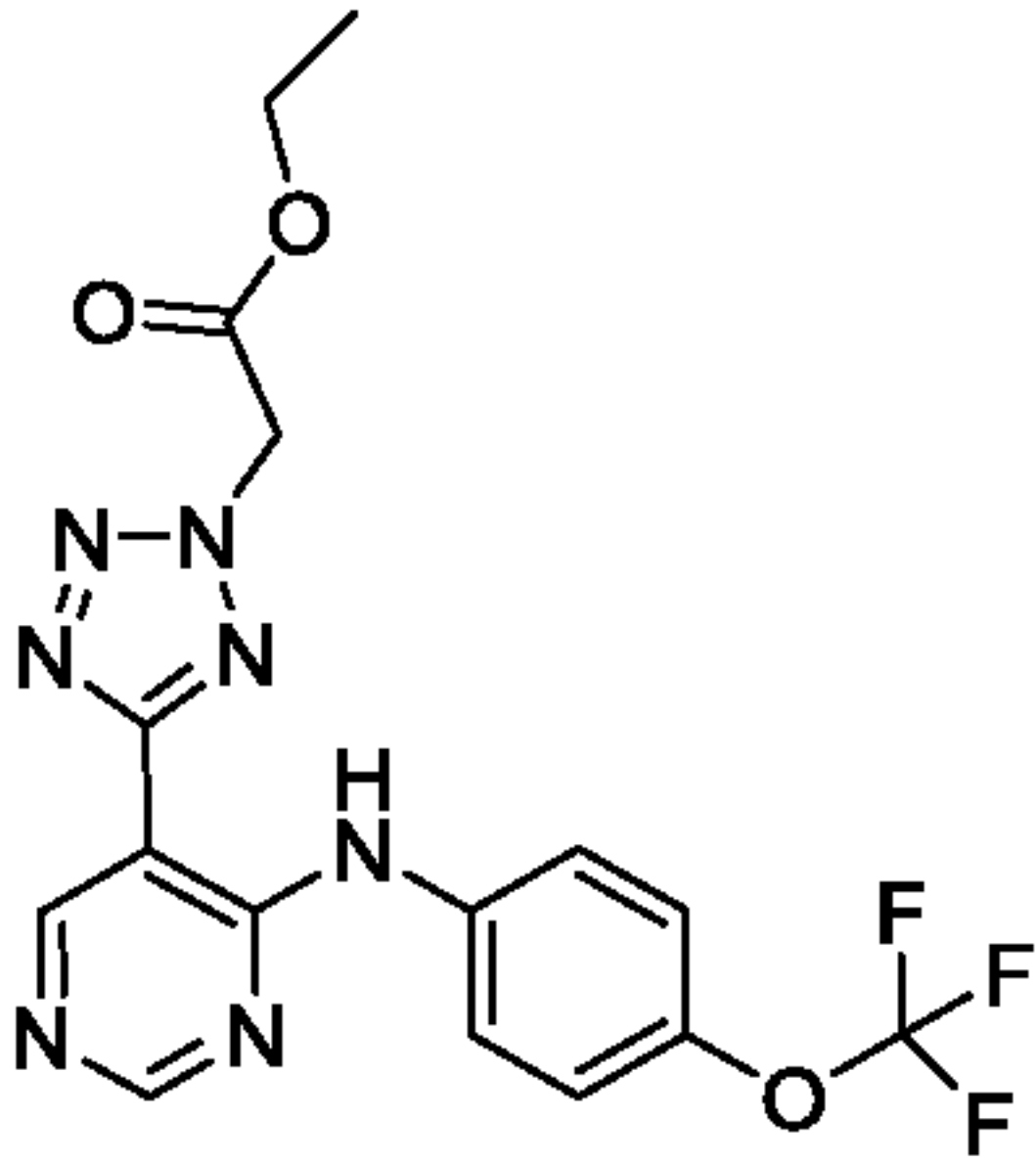
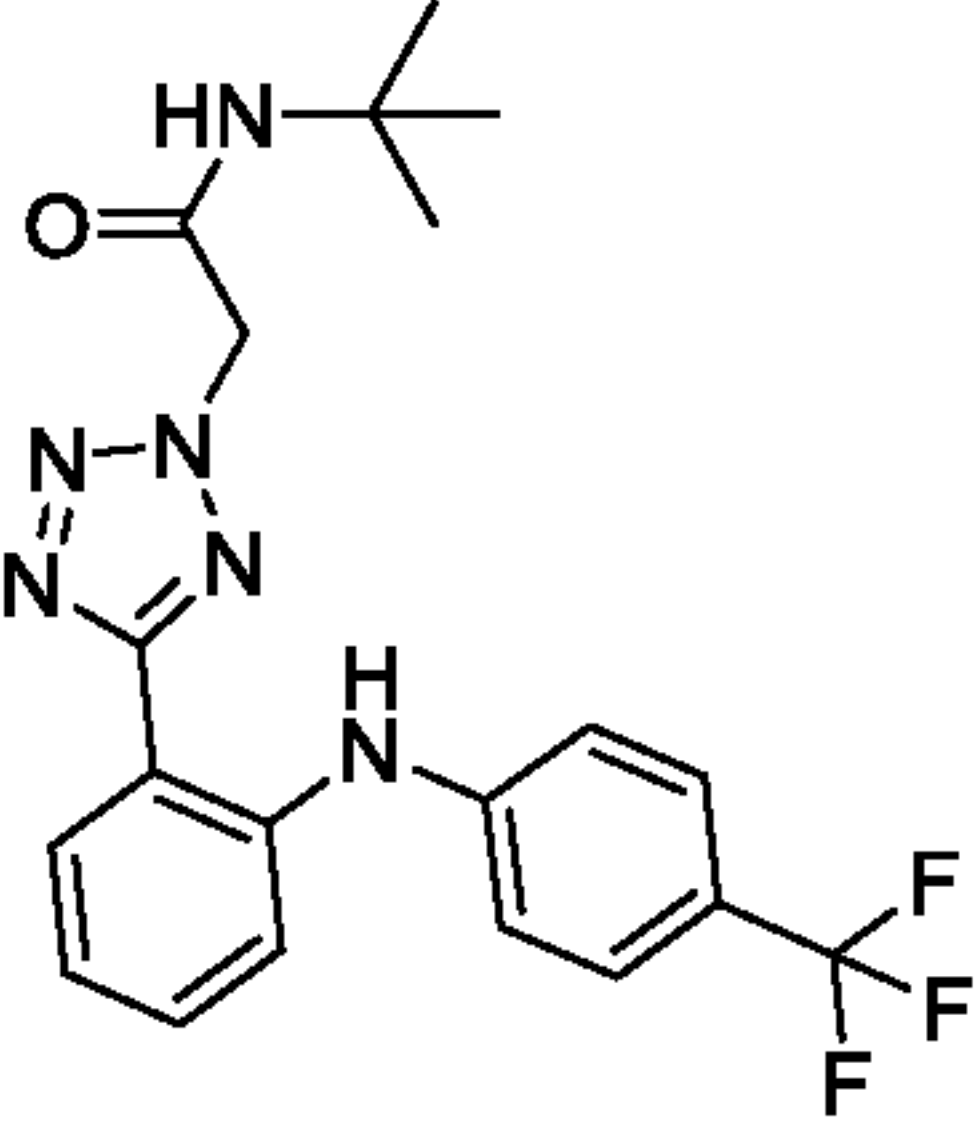
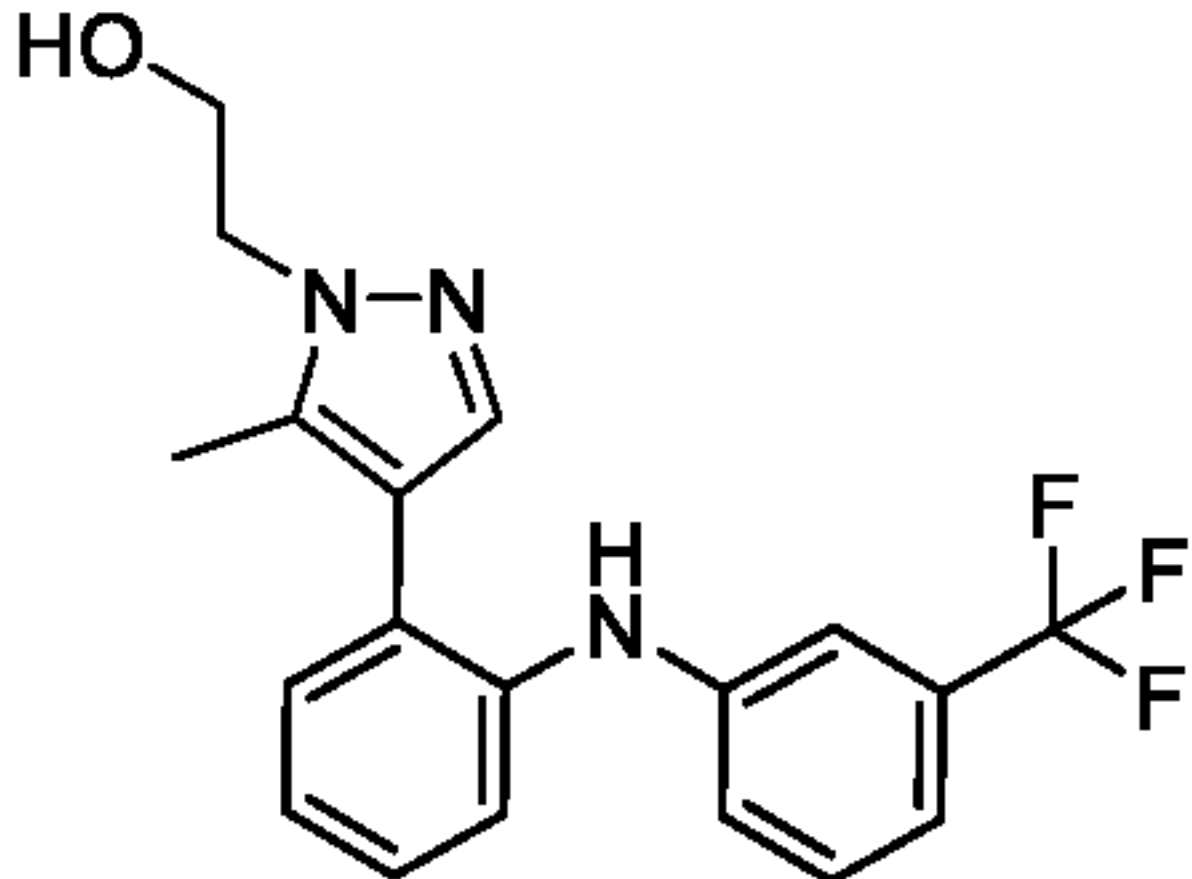
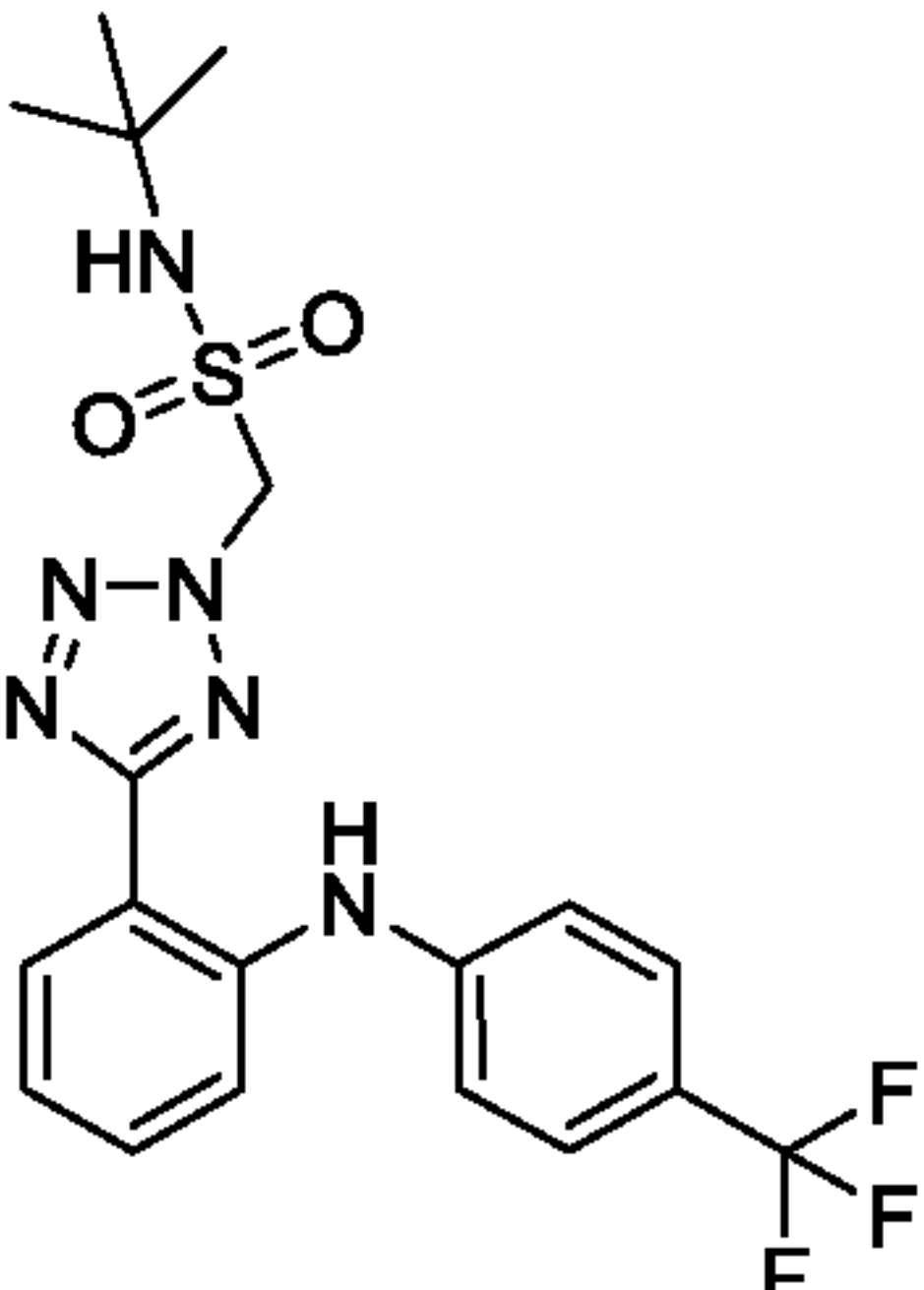
Compound No.	Structure	Name
67		2-(3,5-dimethyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetic acid
68		2-(2-(2-morpholinoethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
69		2-(5-(2-((4-(trifluoromethyl)phenyl)amino)pyridin-3-yl)-2H-tetrazol-2-yl)ethanol
70		2-(2-(3-morpholinopropyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethoxy)phenyl)aniline
71		ethyl 2-(3,5-dimethyl-4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetate

Compound No.	Structure	Name
72		2-(3,5-dimethyl-4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetic acid
73		2-(3,5-dimethyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)ethanol
74		2-(3,5-dimethyl-4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)ethanol
75		2-(5-(2-((4-(trifluoromethoxy)phenyl)amino)pyridin-3-yl)-2H-tetrazol-2-yl)ethanol
76		ethyl 2-[3-methyl-4-[2-[4-(trifluoromethyl)anilino]phenyl]pyrazol-1-yl]acetate

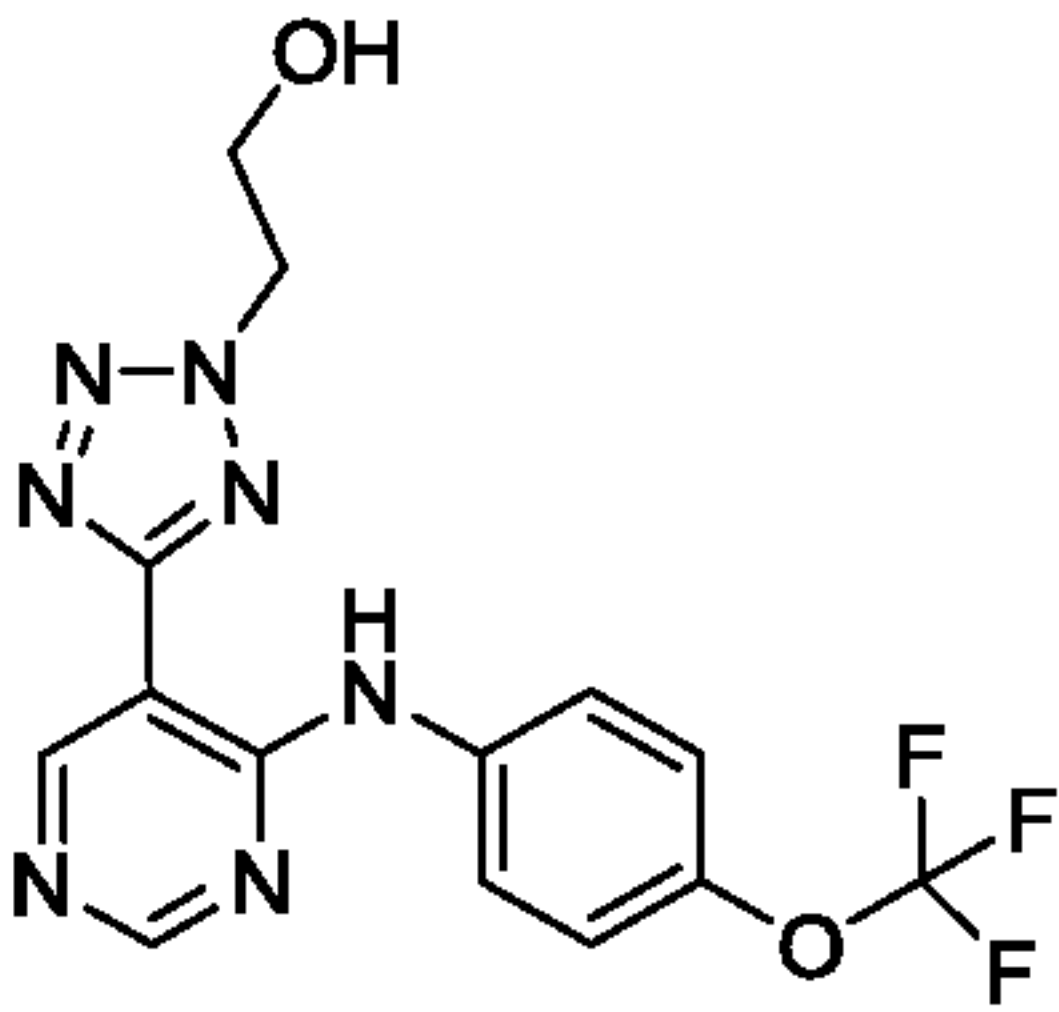
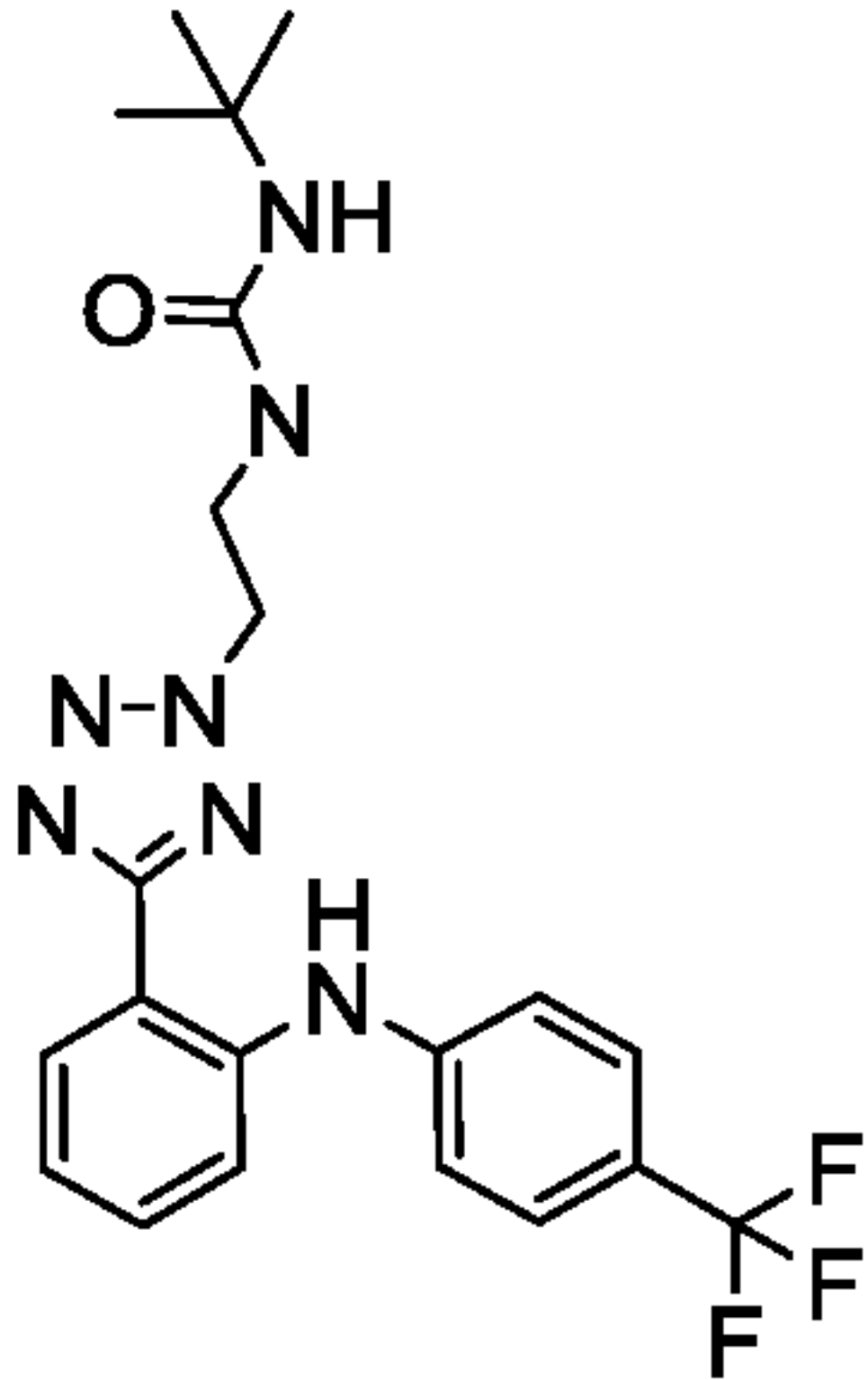
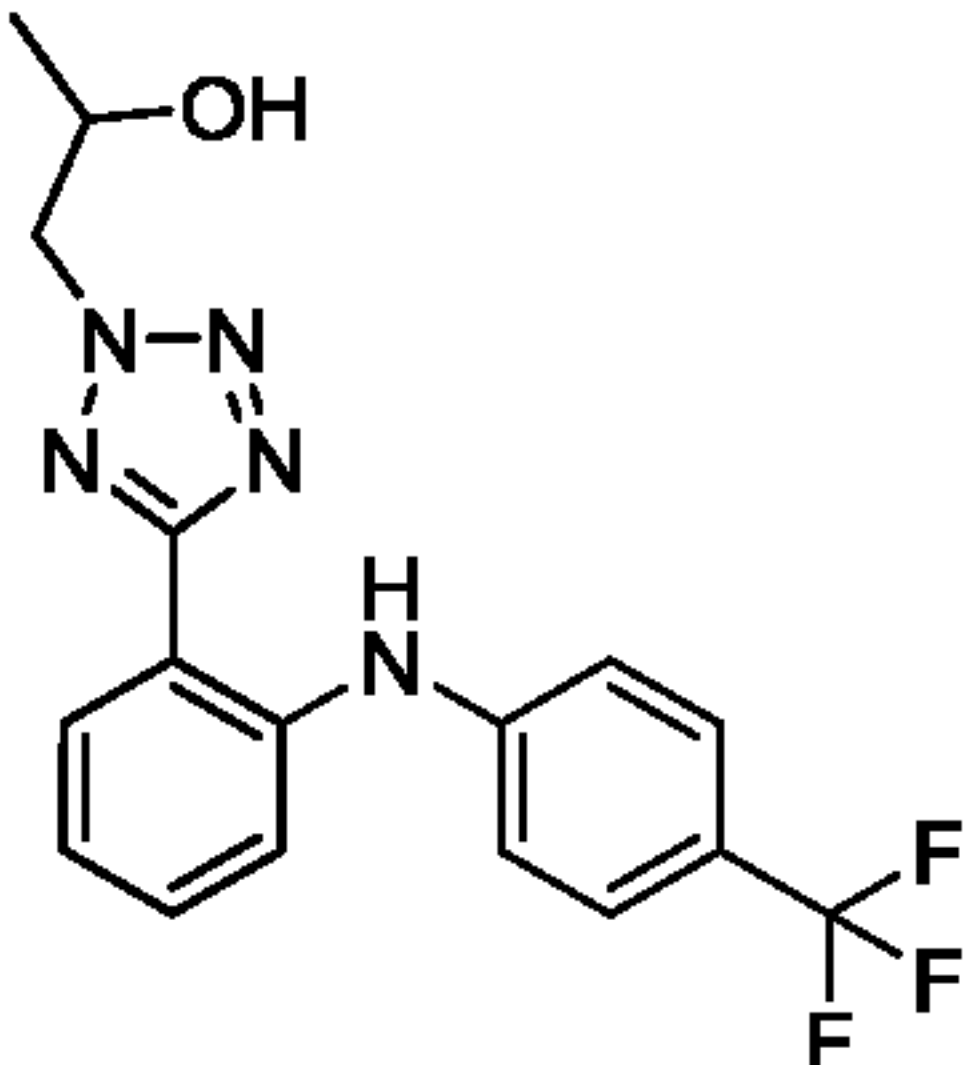
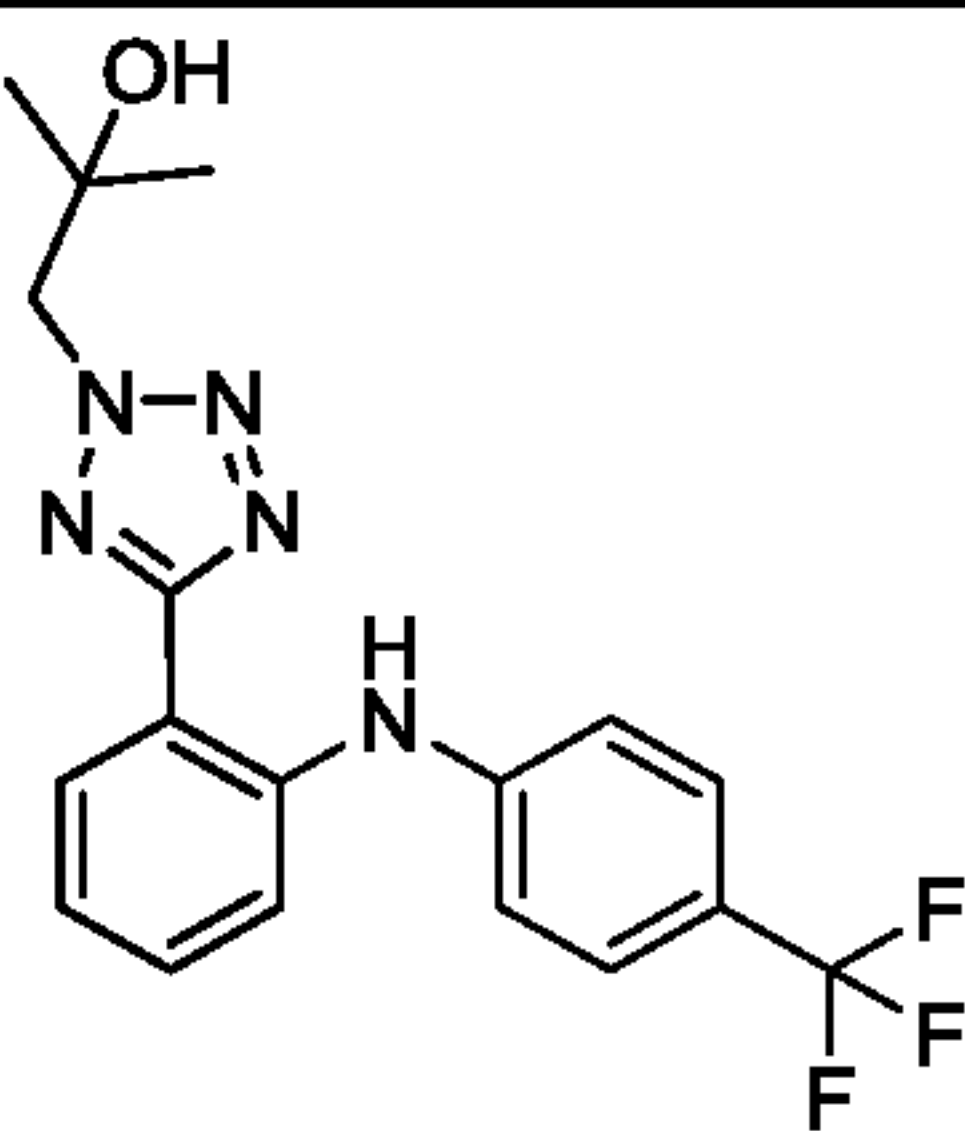
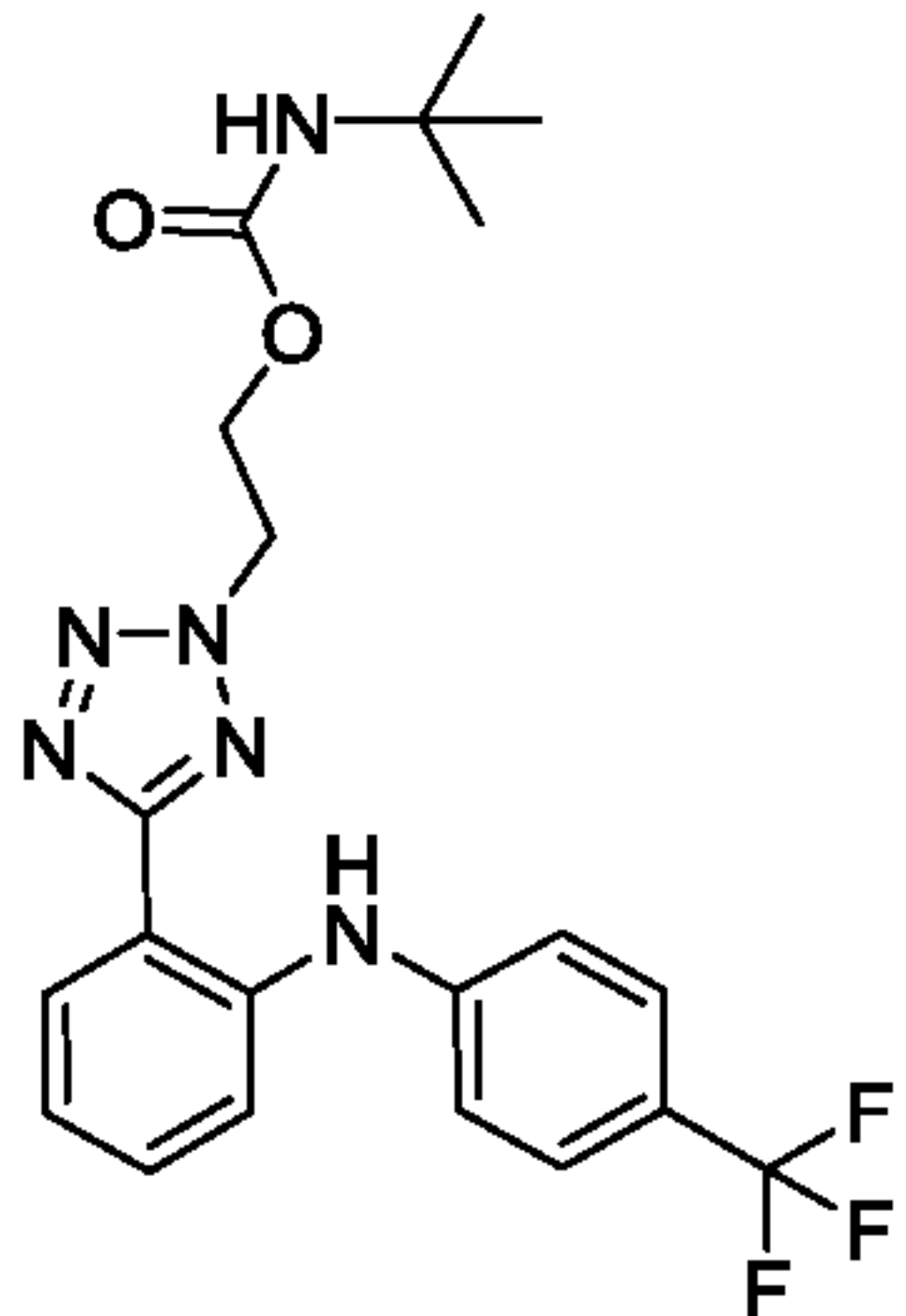
Compound No.	Structure	Name
77		ethyl 2-[5-methyl-4-[2-[4-(trifluoromethyl)anilino]phenyl]pyrazol-1-yl]acetate
78		2-[5-[4-[4-(trifluoromethyl)anilino]-3-pyridyl]tetrazol-2-yl]ethanol
79		2-[5-[4-[4-(trifluoromethoxy)anilino]-3-pyridyl]tetrazol-2-yl]ethanol
80		ethyl 2-[5-[4-[4-(trifluoromethyl)anilino]pyrimidin-5-yl]tetrazol-2-yl]acetate
81		ethyl 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)acetate

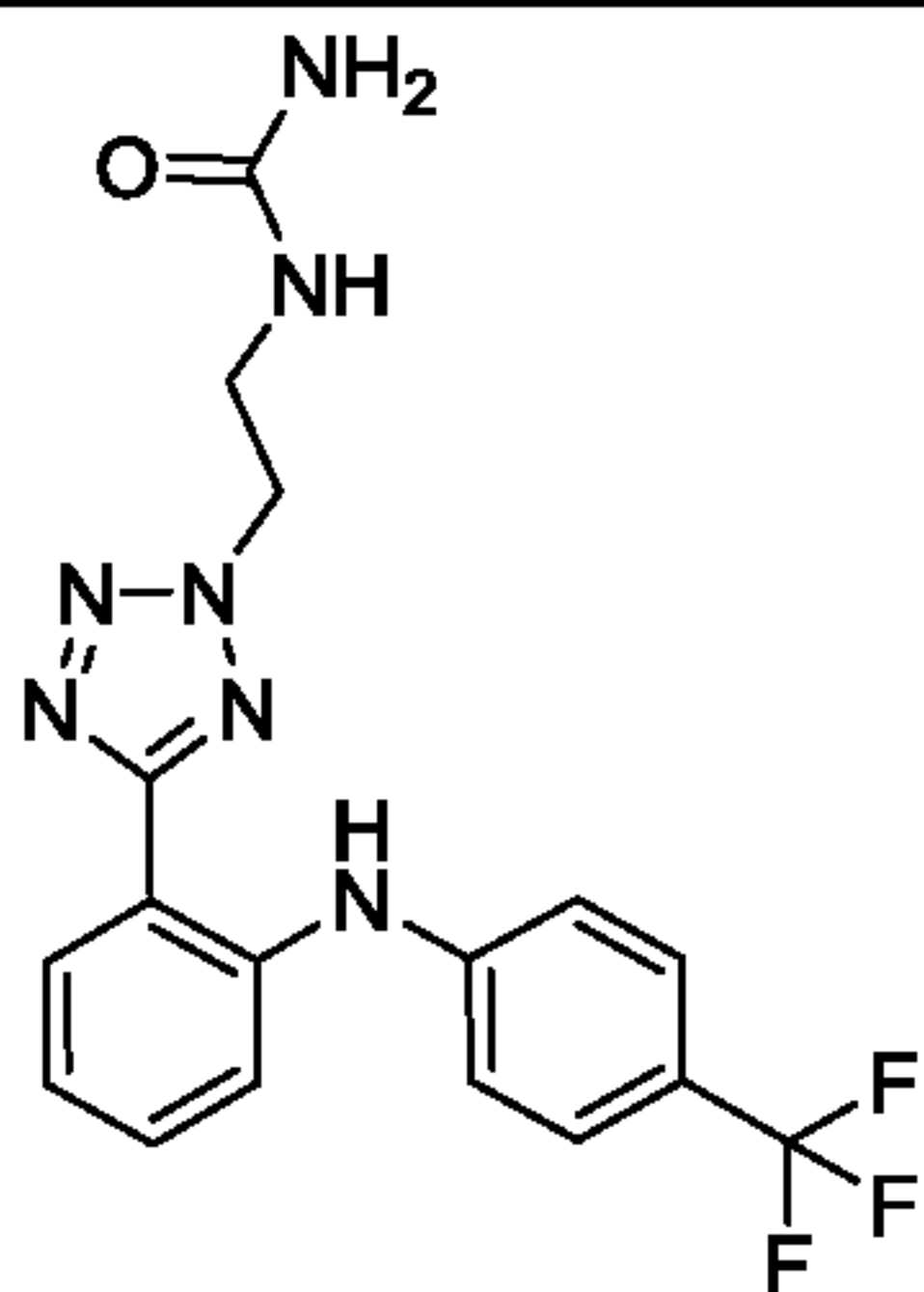
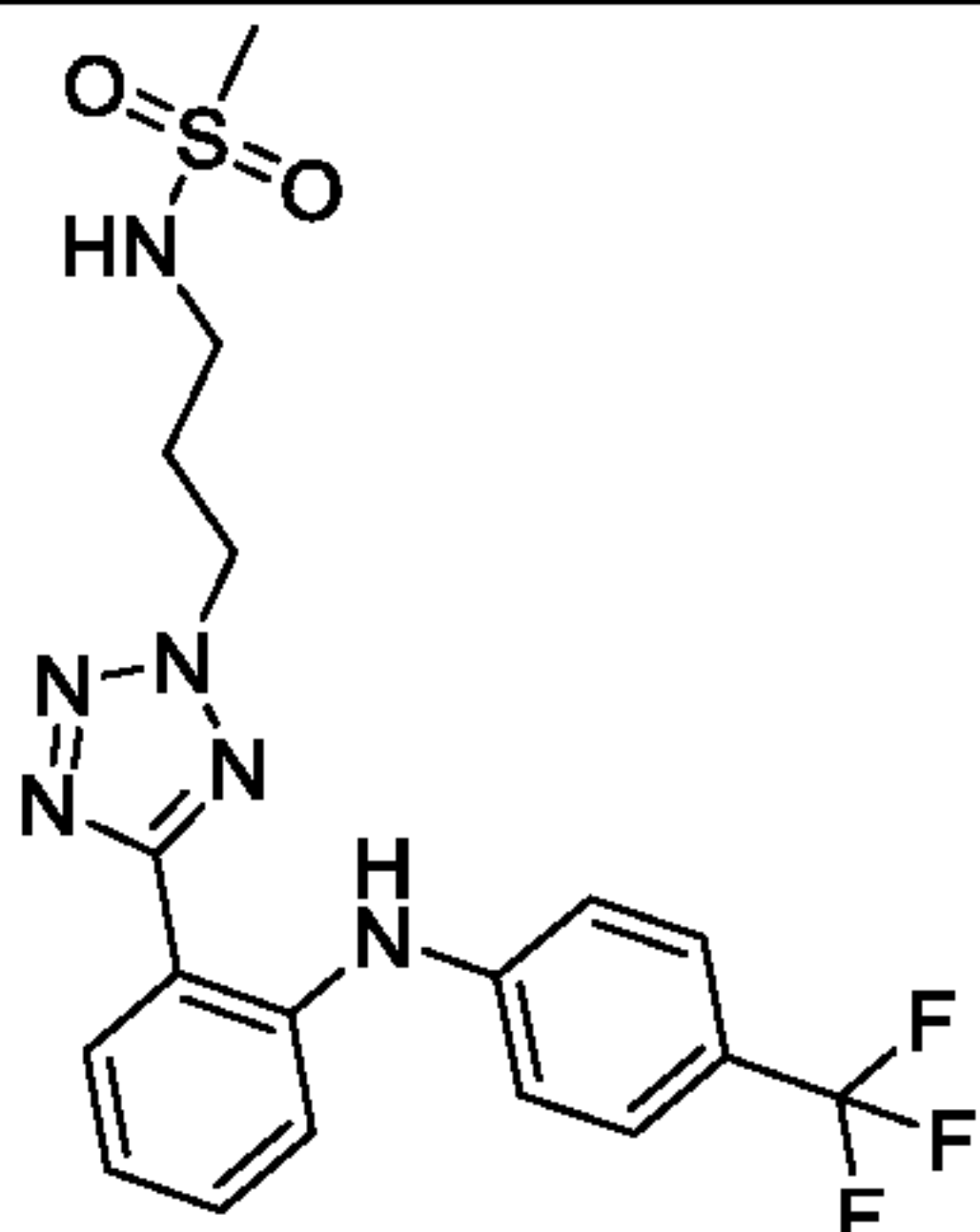
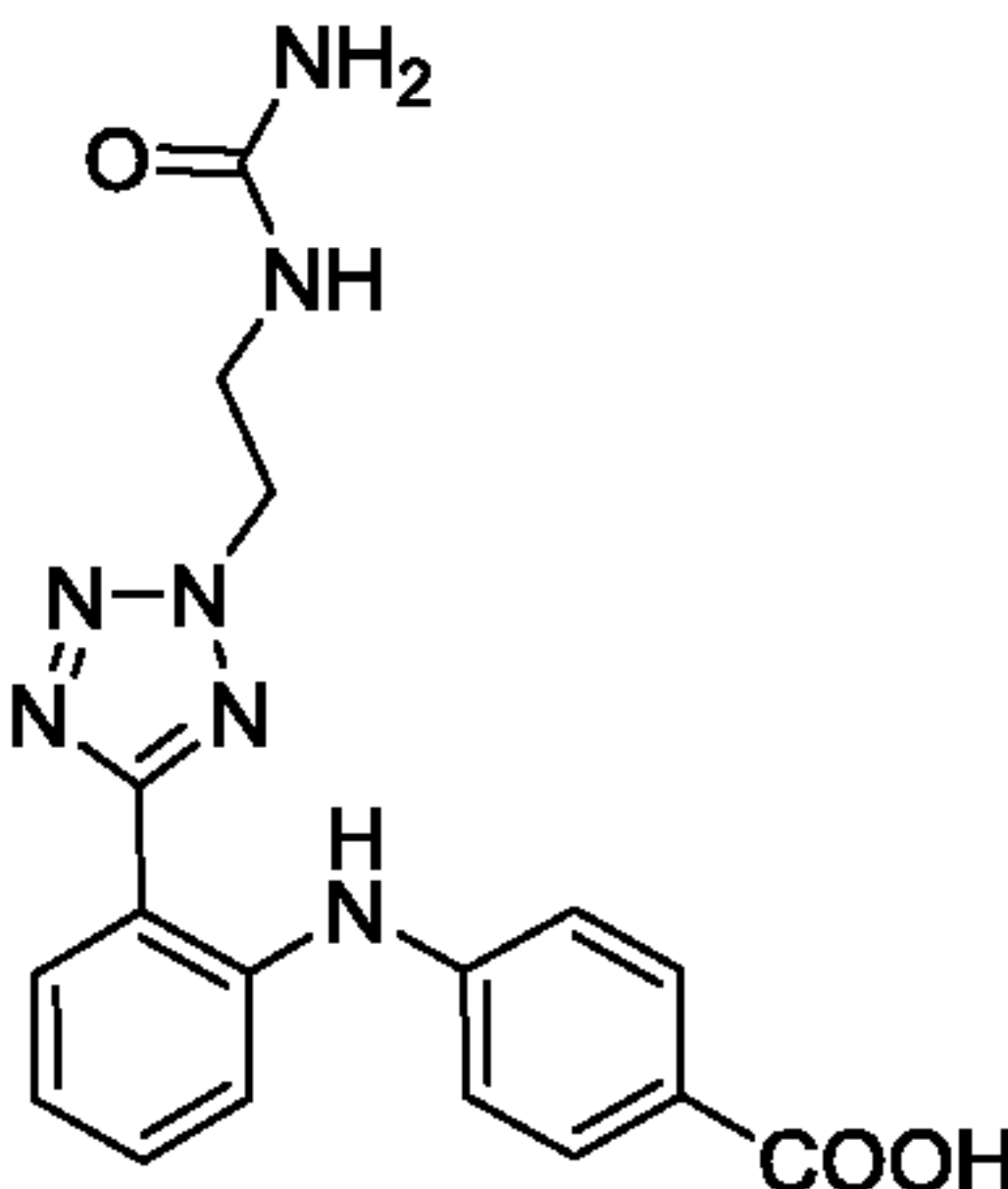
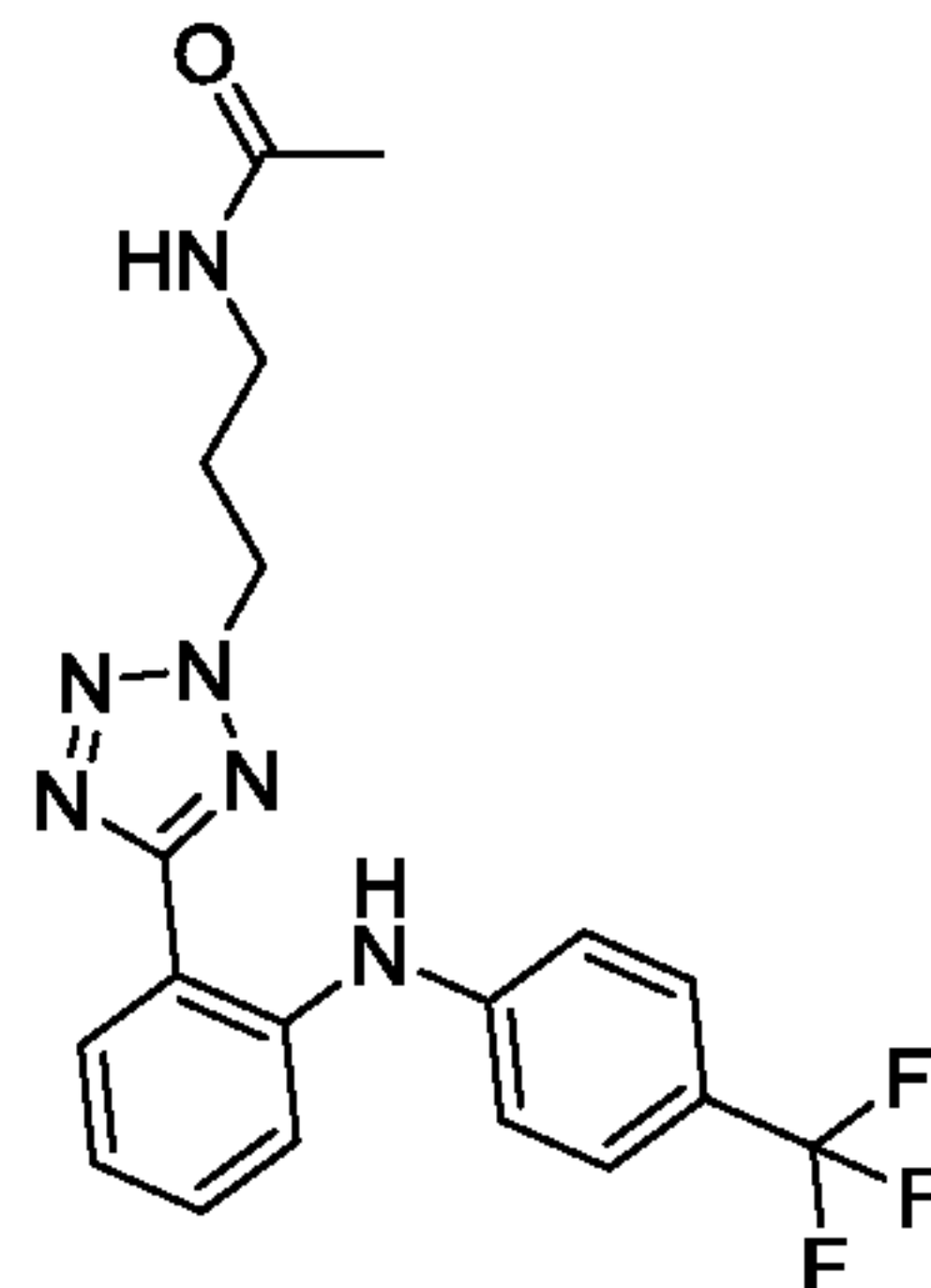
Compound No.	Structure	Name
82		2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetic acid
83		2-[3-methyl-4-[2-[4-(trifluoromethyl)anilino]phenyl]pyrazol-1-yl]ethanol
84		2-[5-methyl-4-[2-[4-(trifluoromethyl)anilino]phenyl]pyrazol-1-yl]ethanol
85		N-methylsulfonyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetamide
86		2-(5-(4-((4-(trifluoromethyl)phenyl)amino)pyrimidin-5-yl)-2H-tetrazol-2-yl)ethan-1-ol

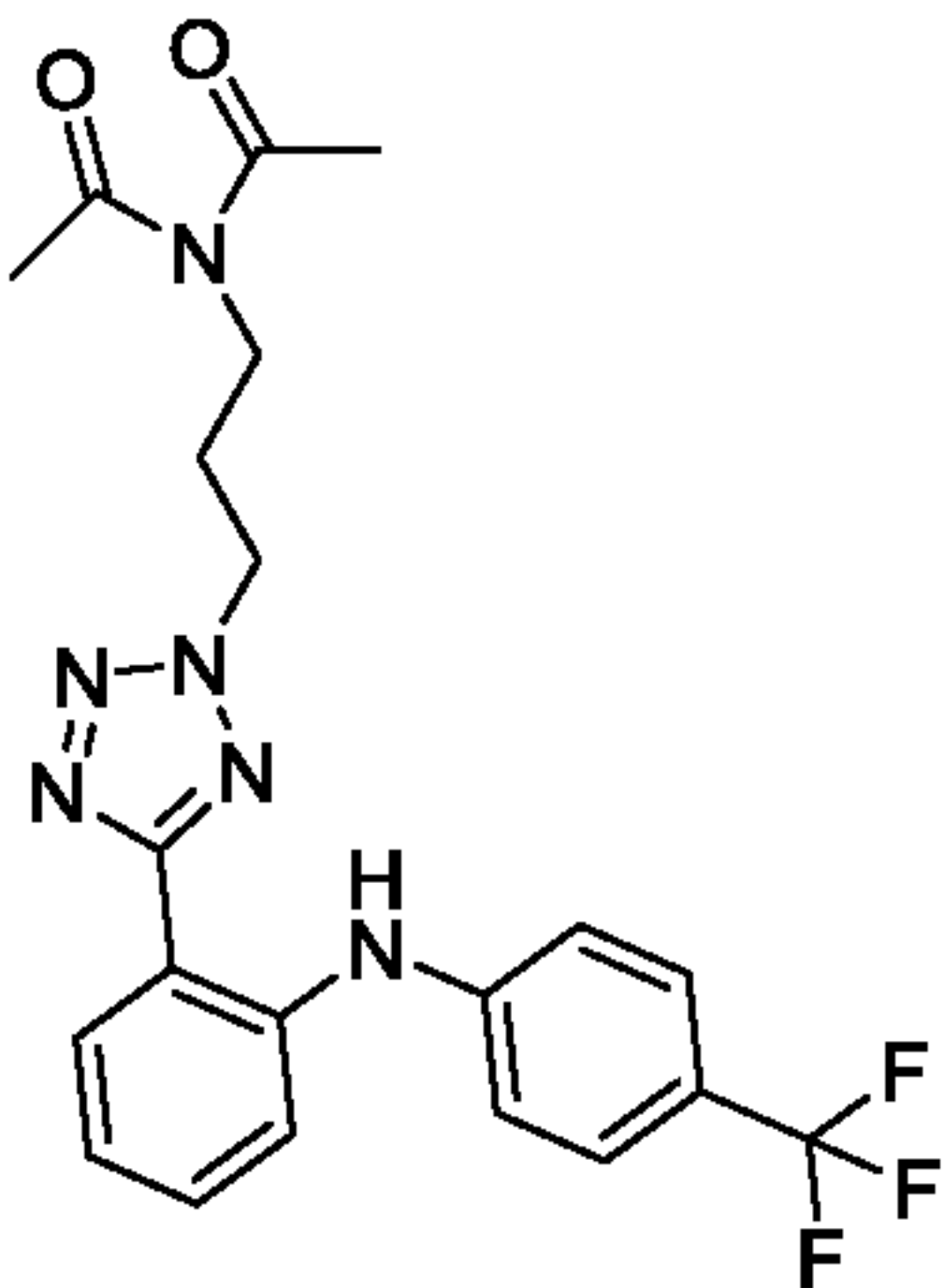
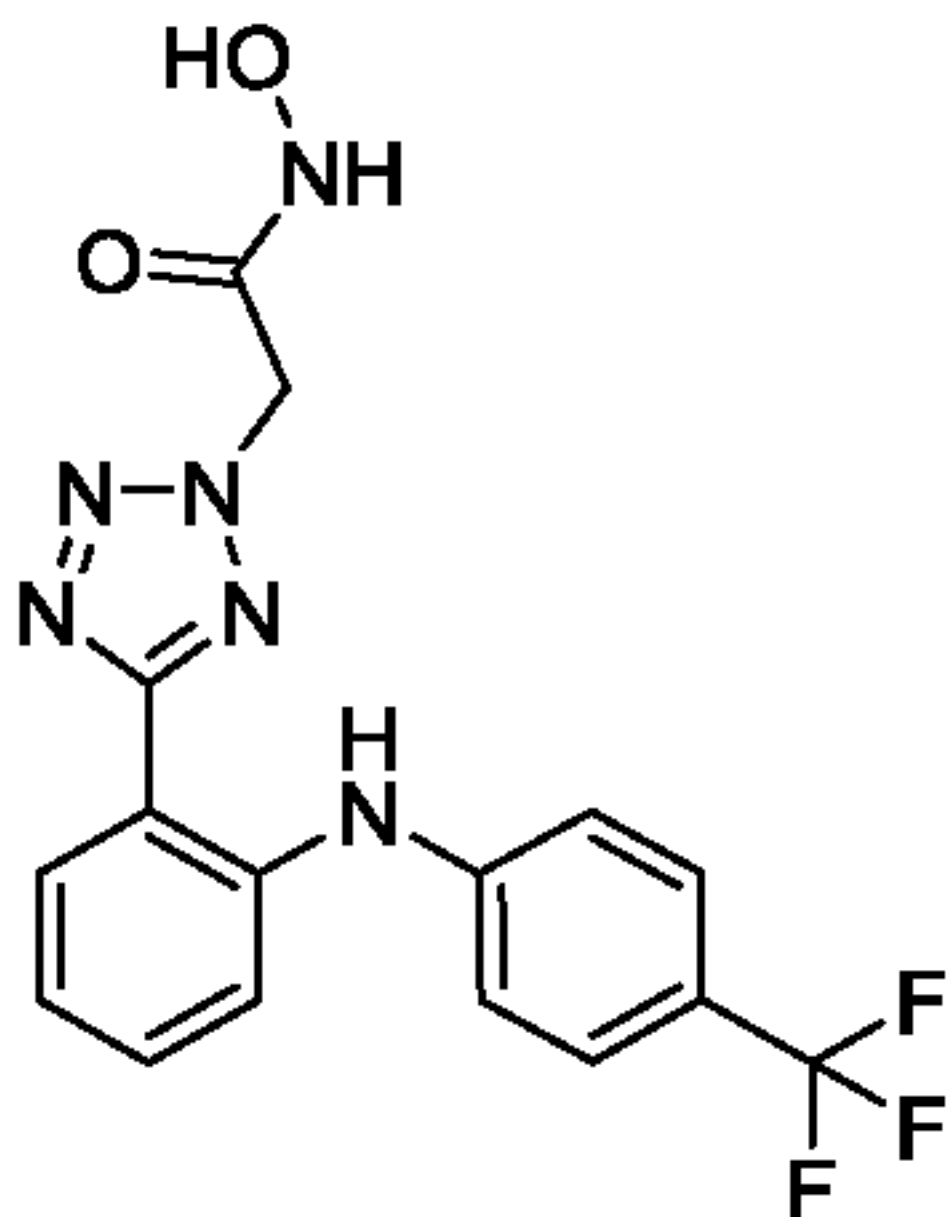
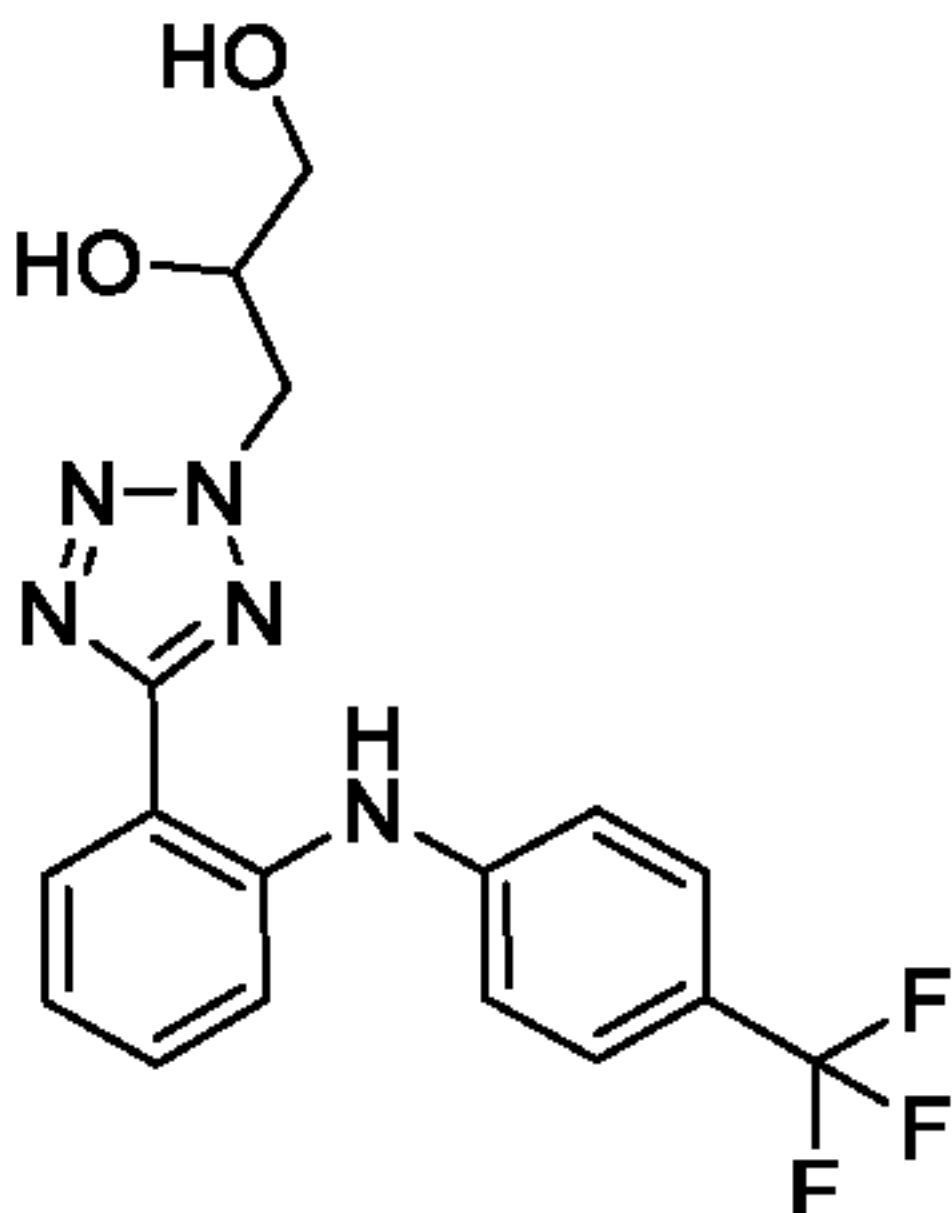
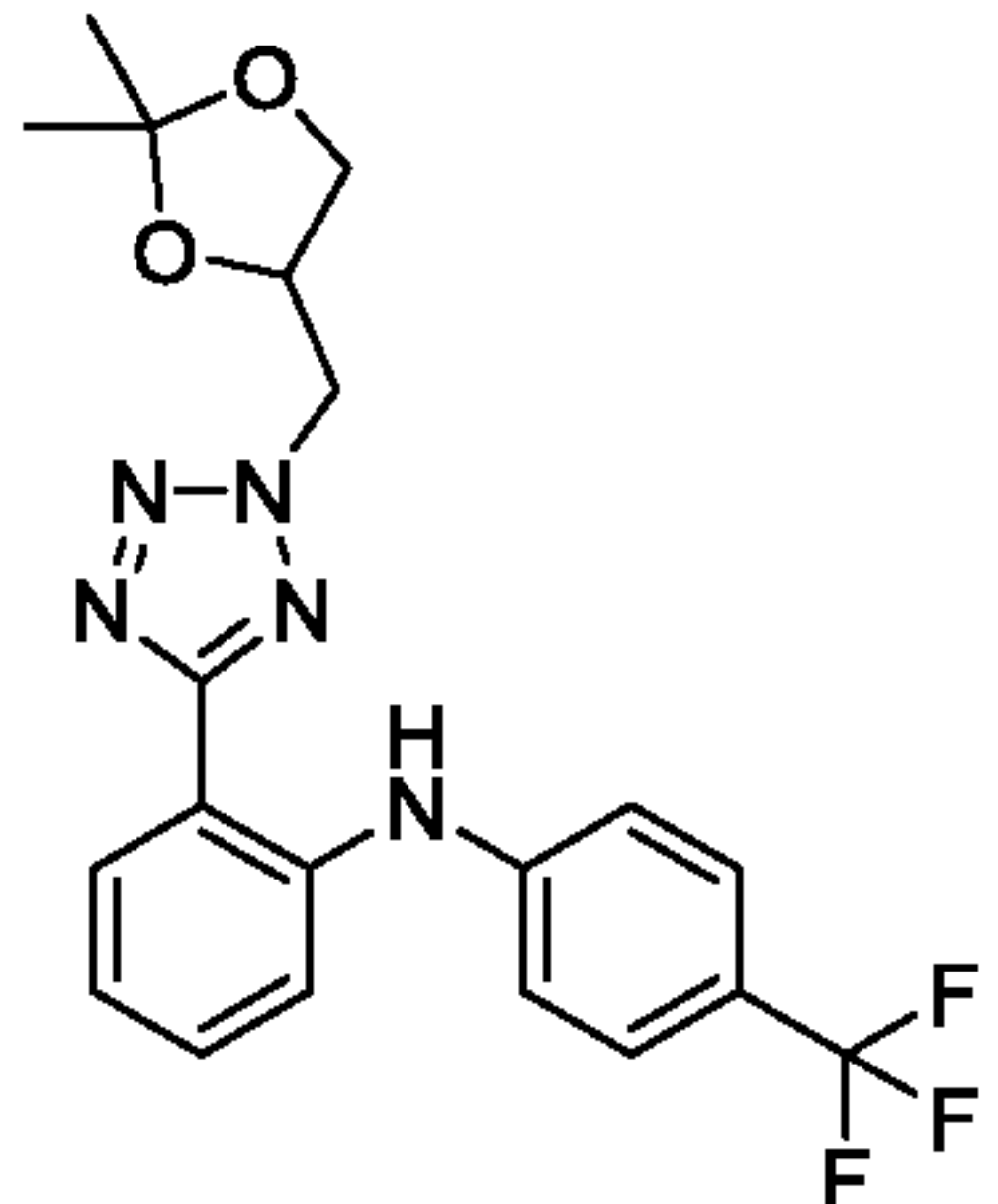
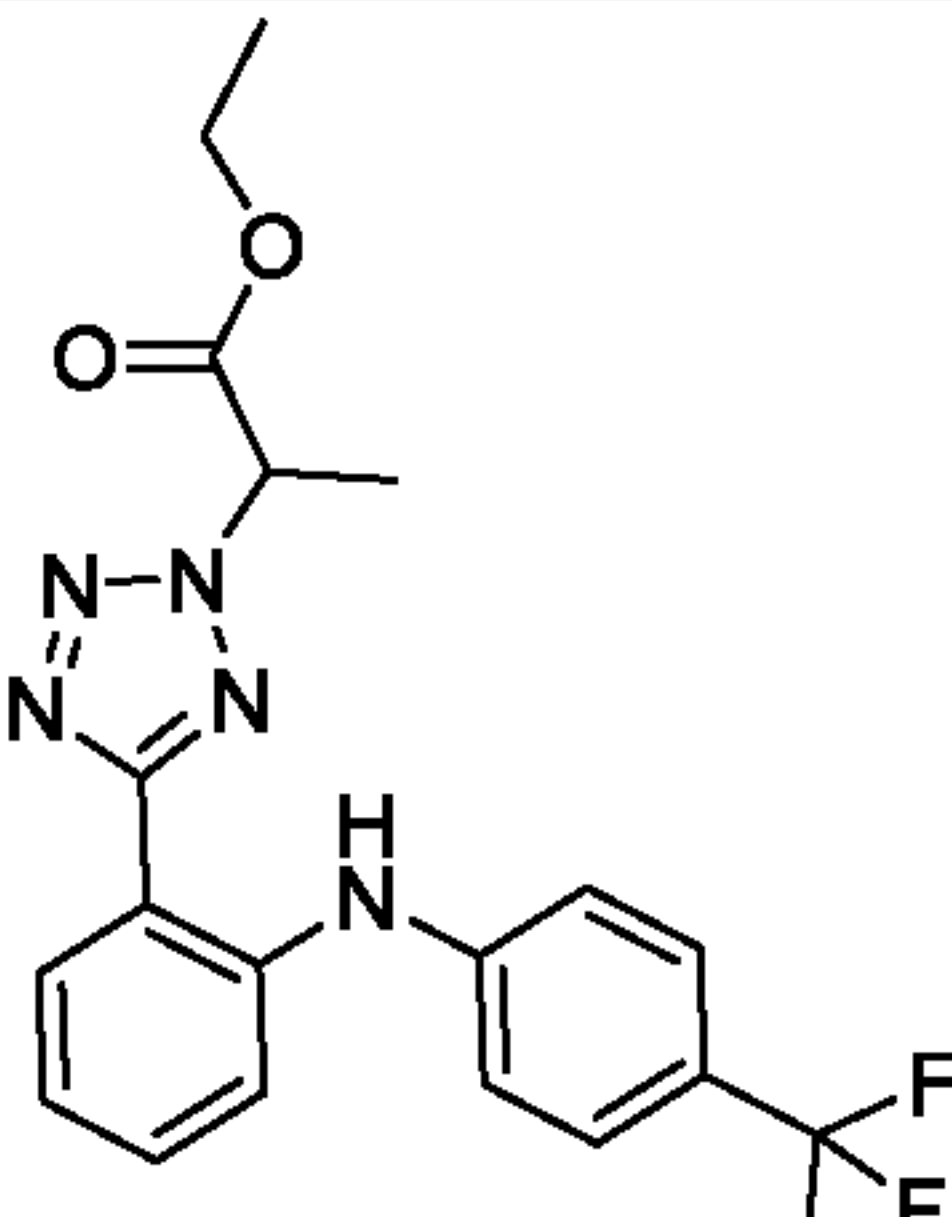
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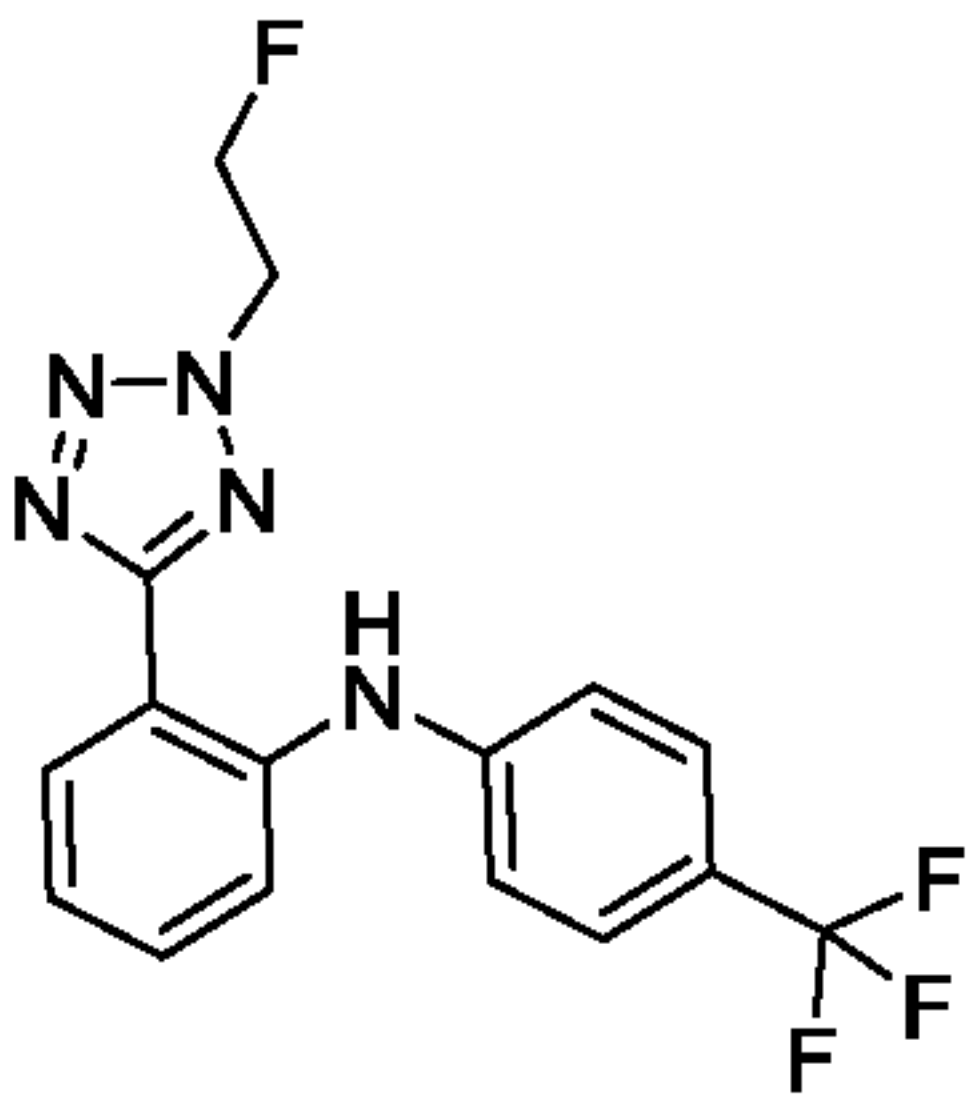
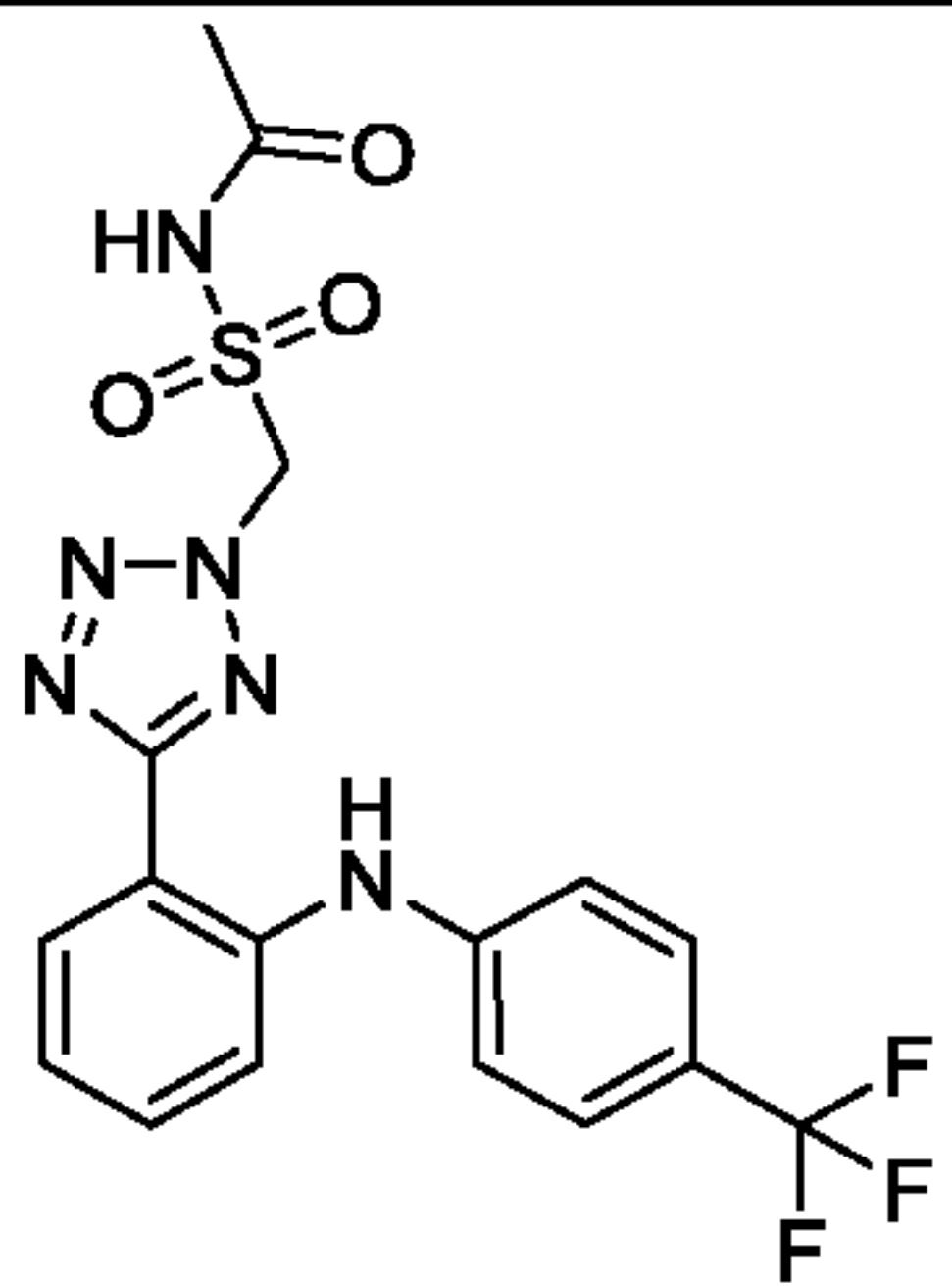
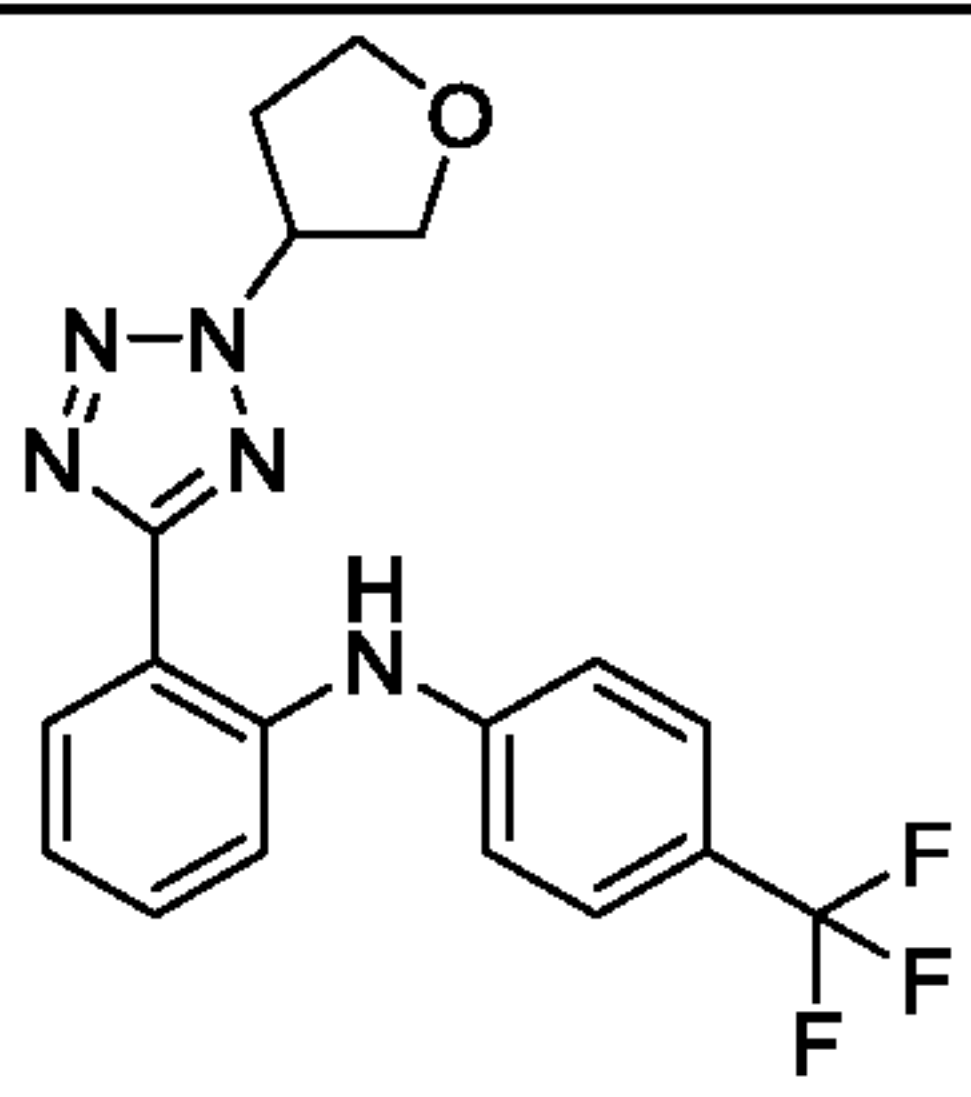
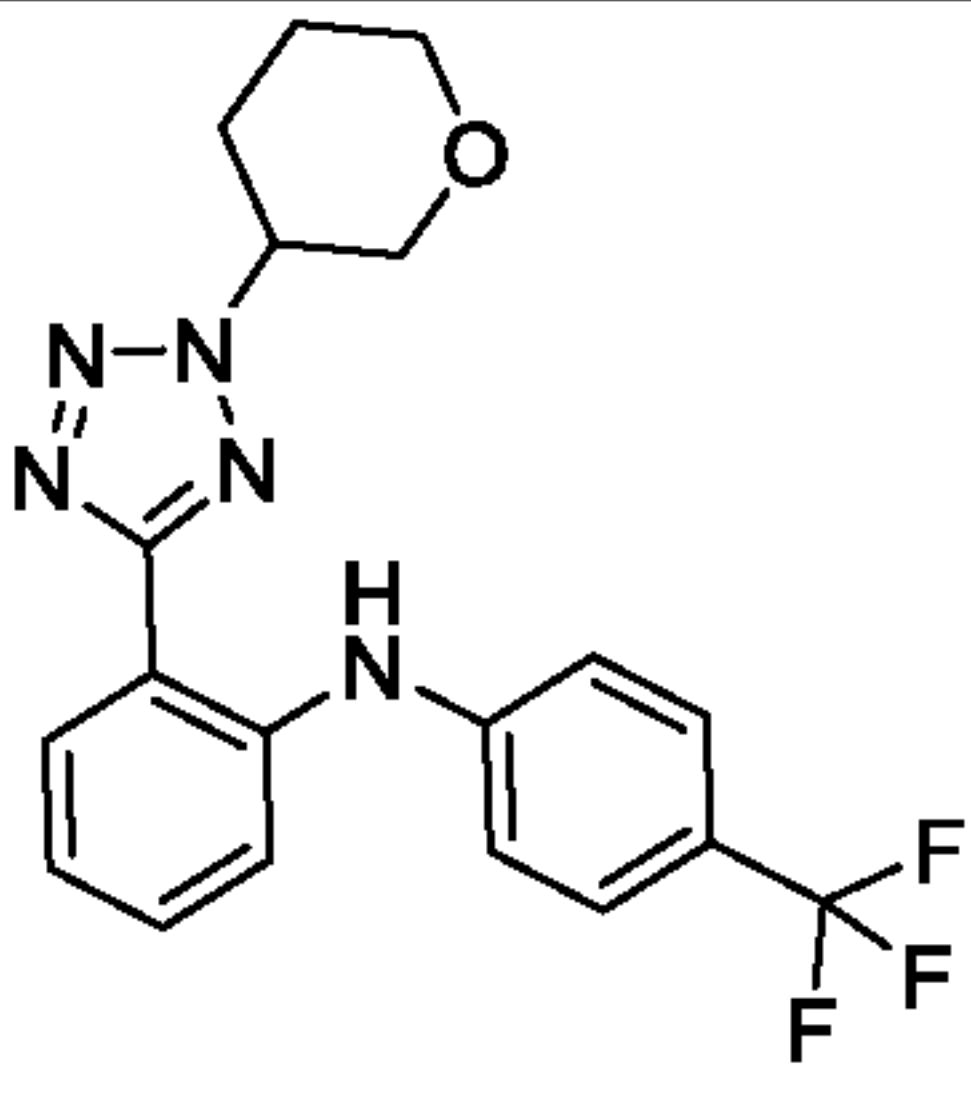
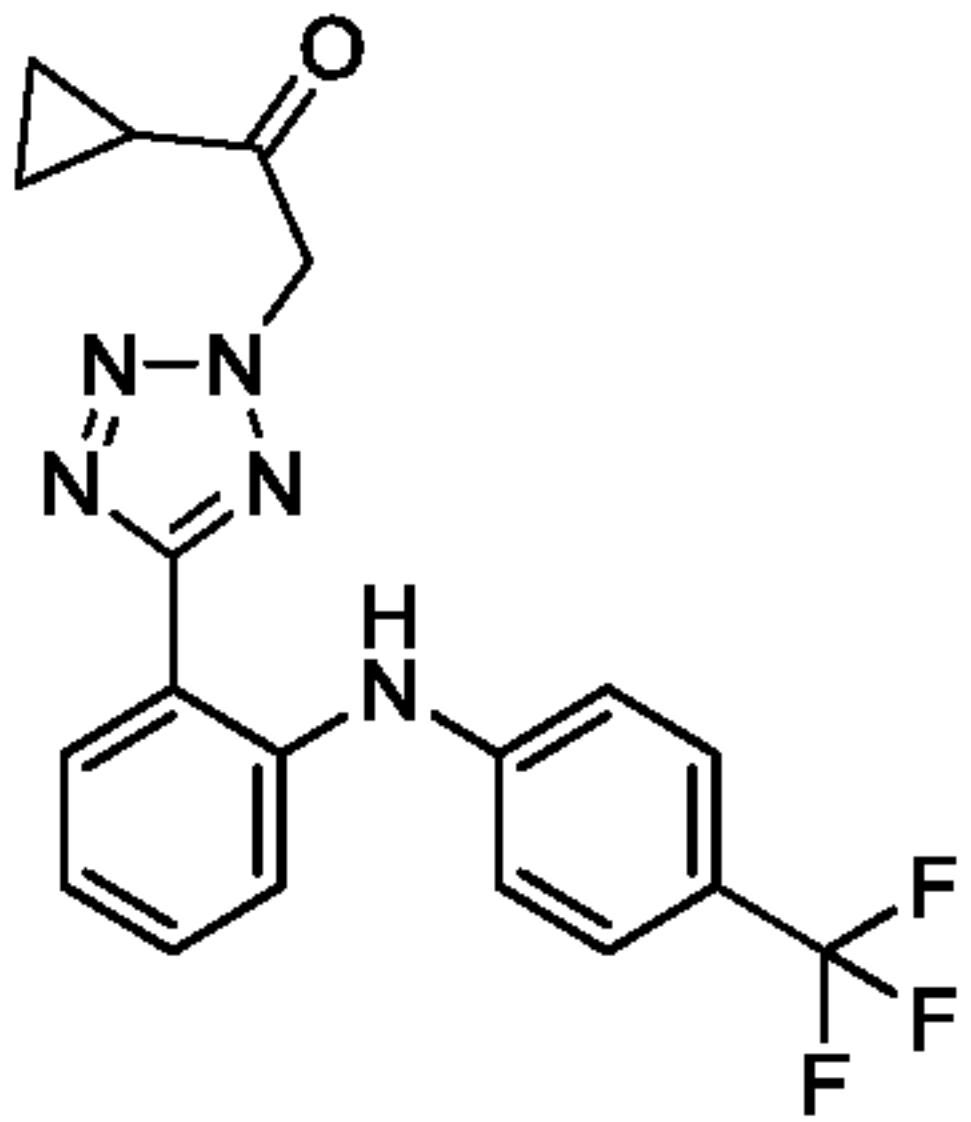
Compound No.	Structure	Name
93		N-[2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl]methanesulfonamide
94		ethyl 2-[5-[4-[4-(trifluoromethoxy)anilino]pyrimidin-5-yl]tetrazol-2-yl]acetate
95		N-tert-butyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetamide
96		2-(5-methyl-4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)ethanol
97		N-tert-butyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methanesulfonamide

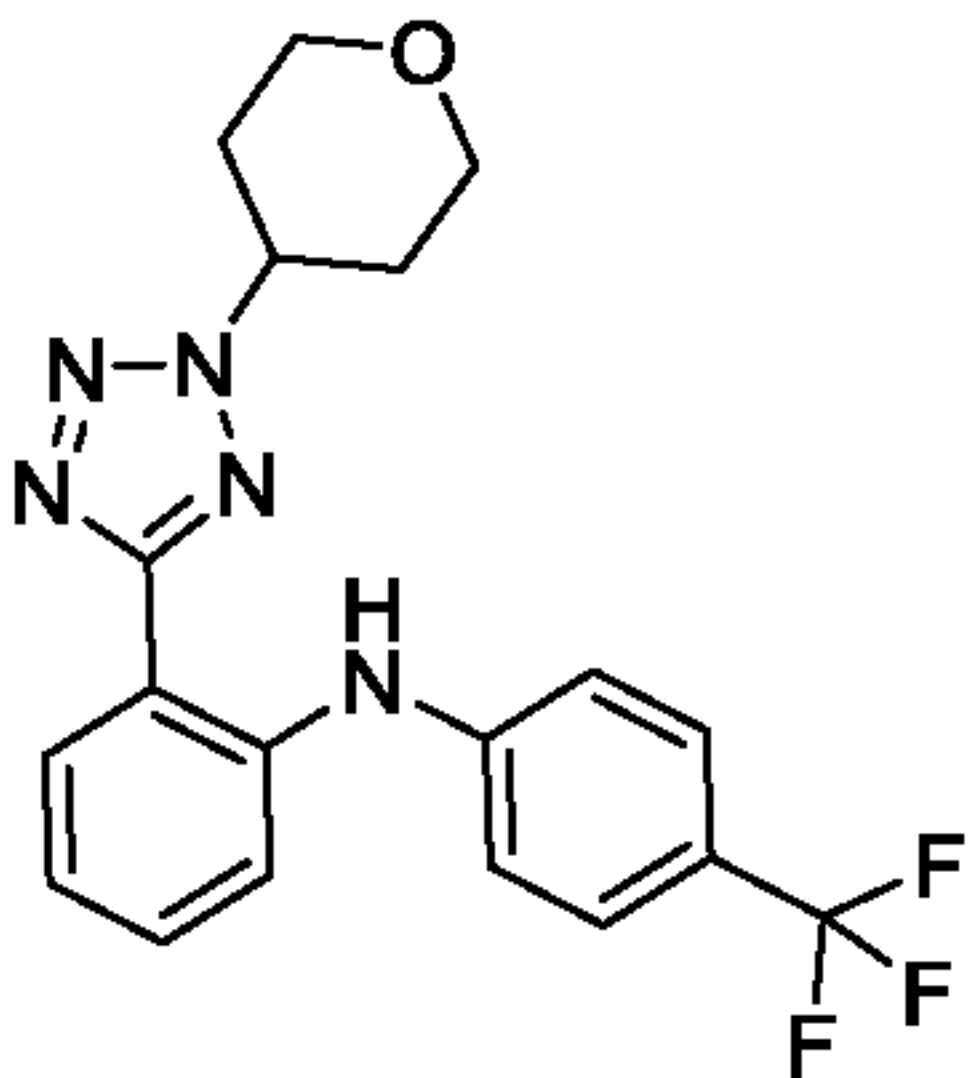
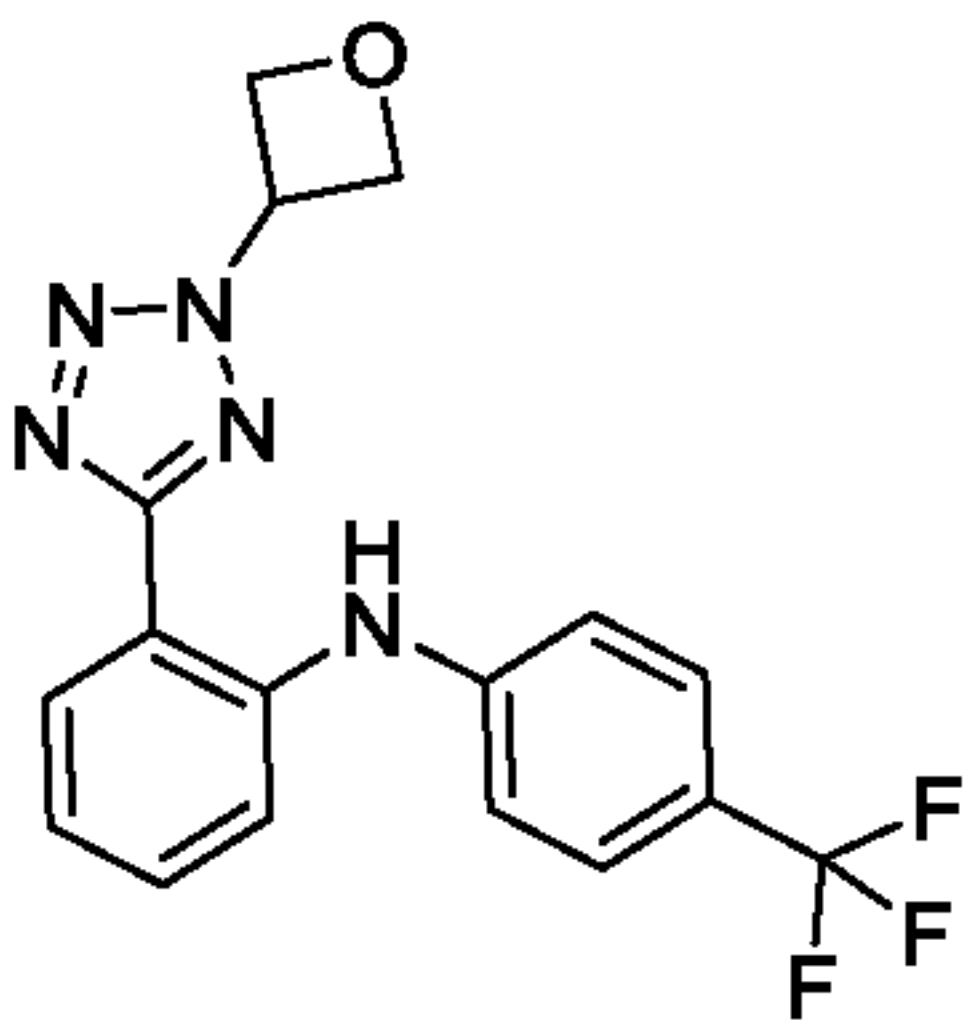
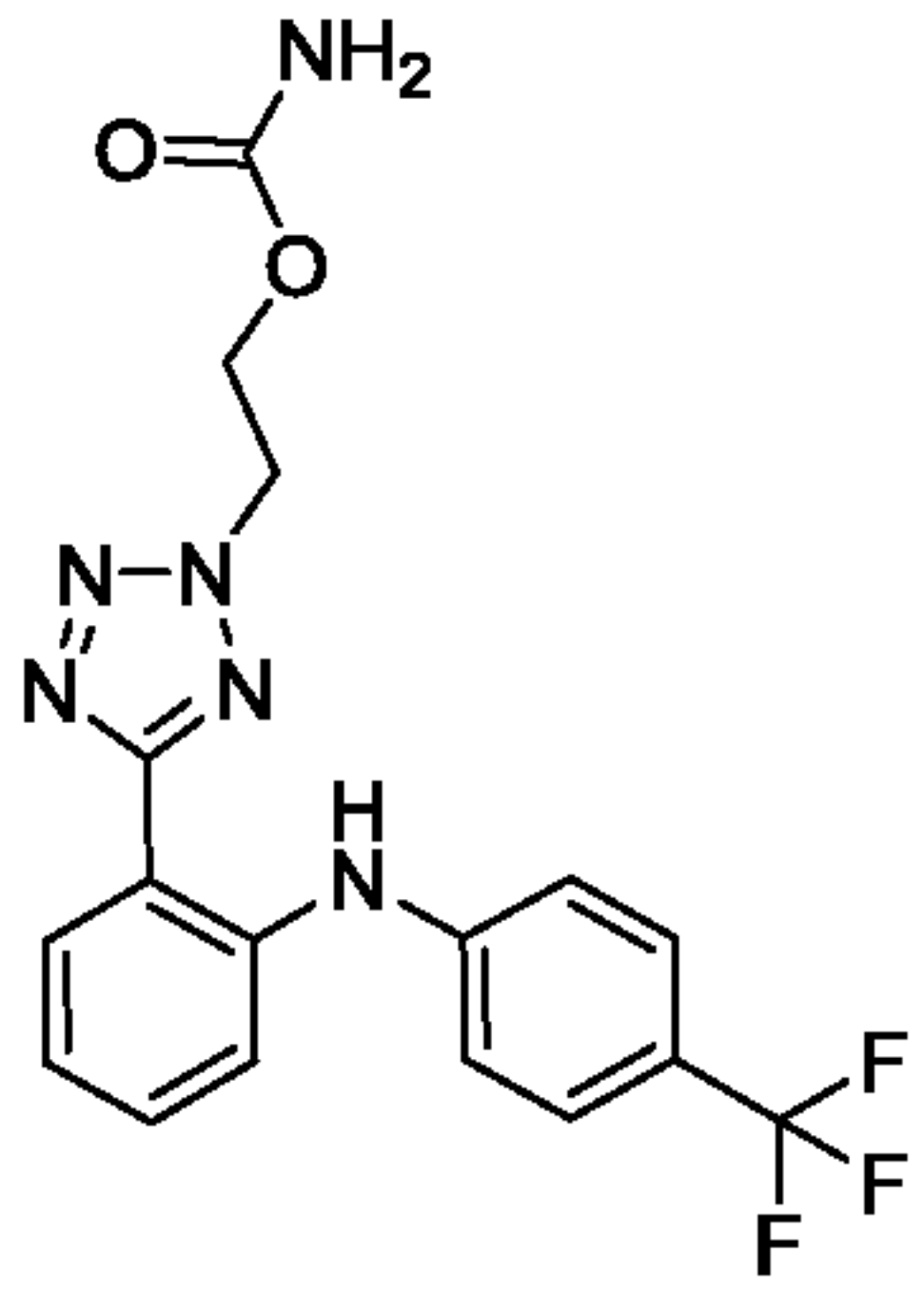
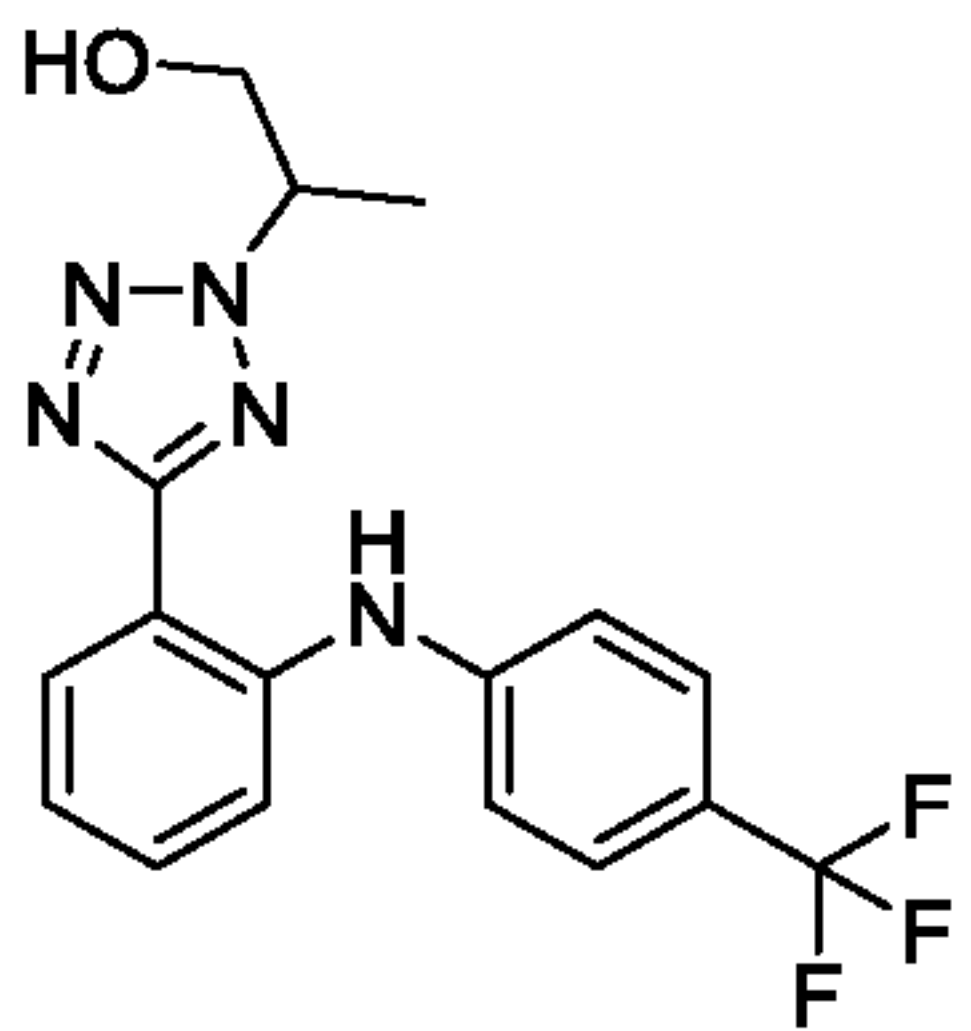
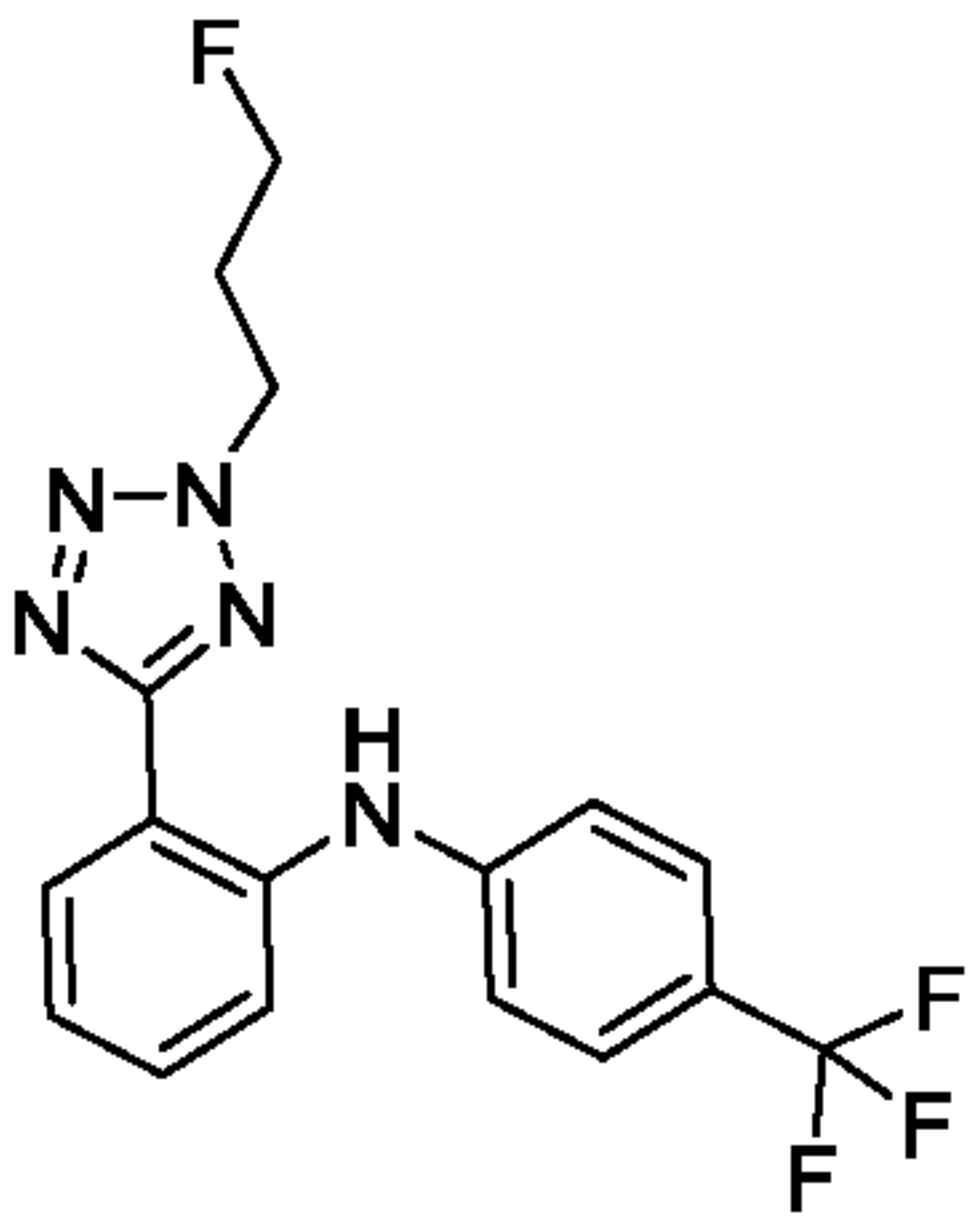
Compound No.	Structure	Name
98		3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propan-1-ol
99		2-[2-(sulfamoylamino)ethyl]-5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazole
100		tert-butyl N-[2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethylsulfamoyl]carbamate
101		(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methanesulfonamide
102		2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetamide

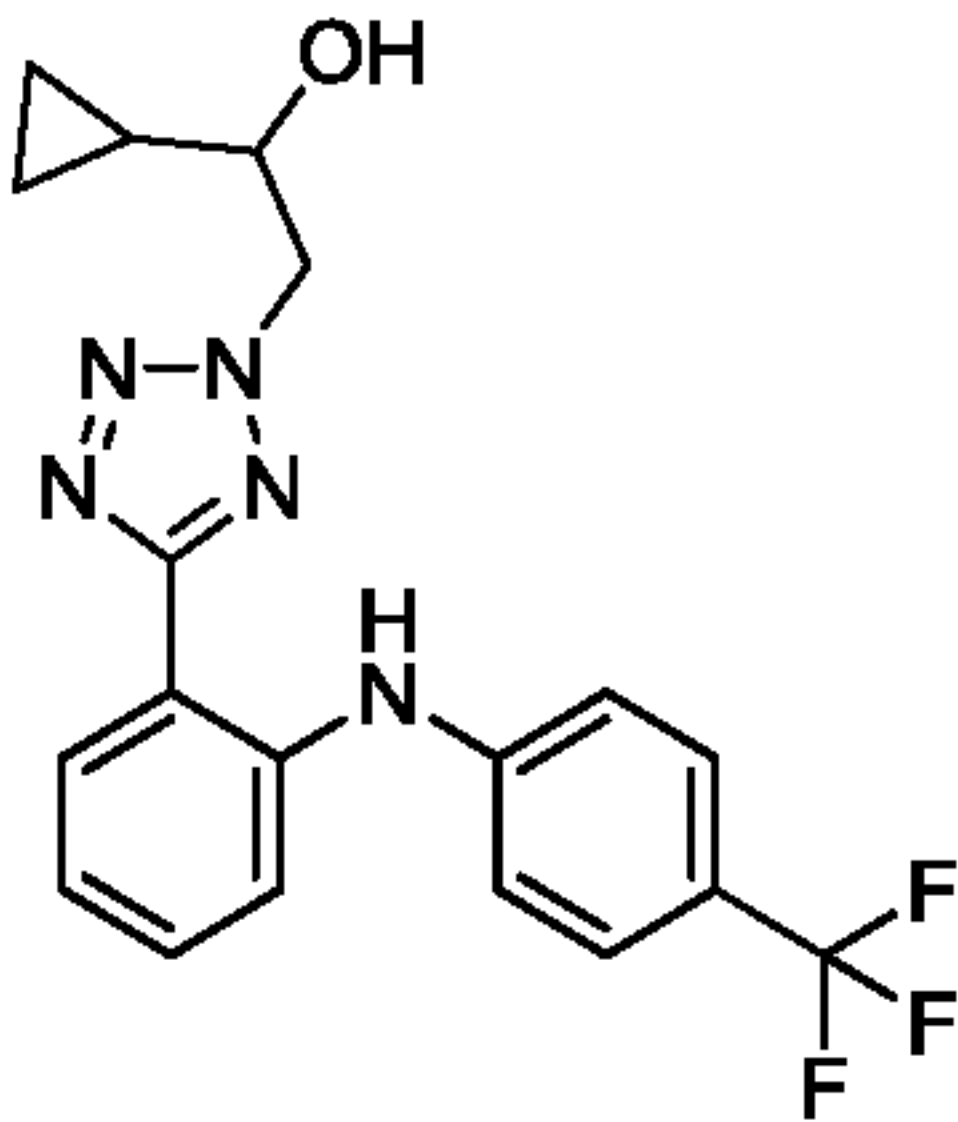
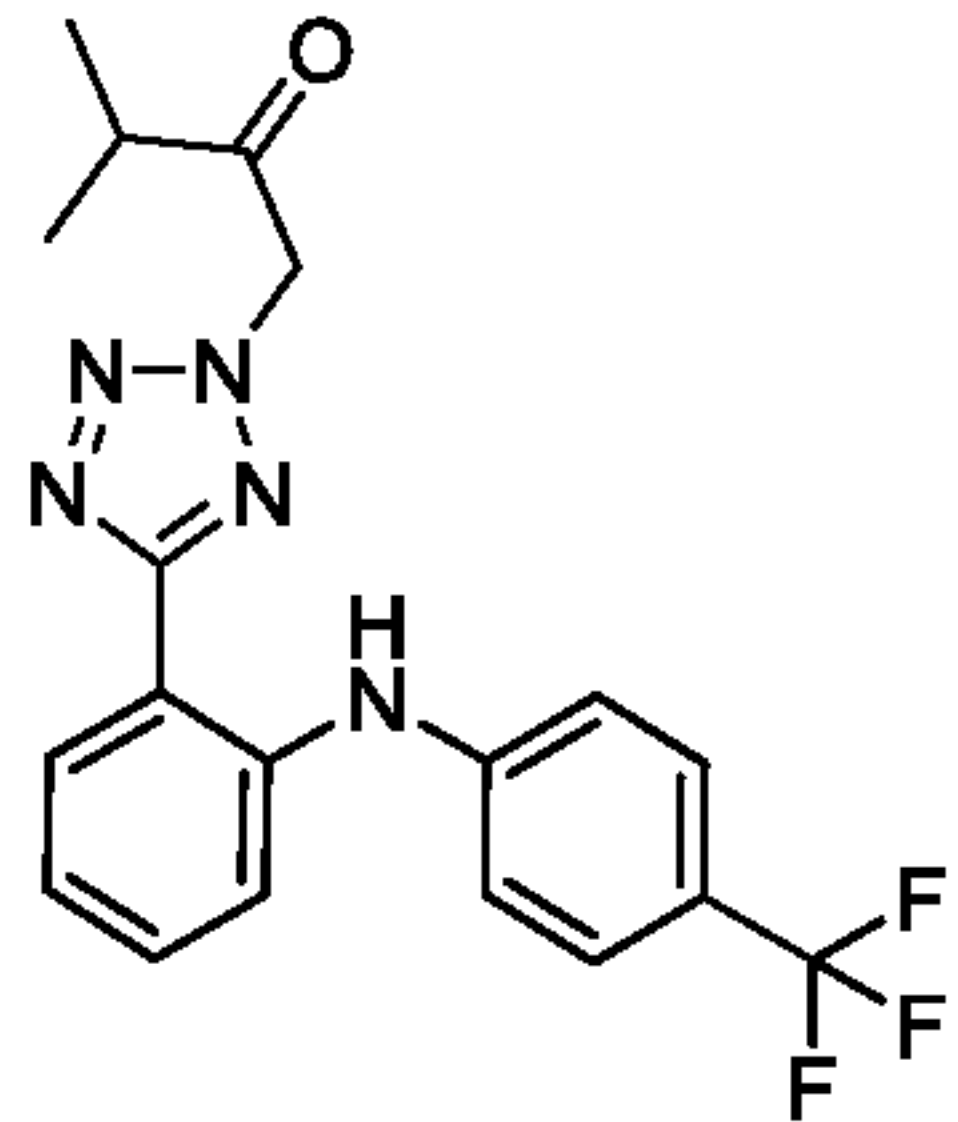
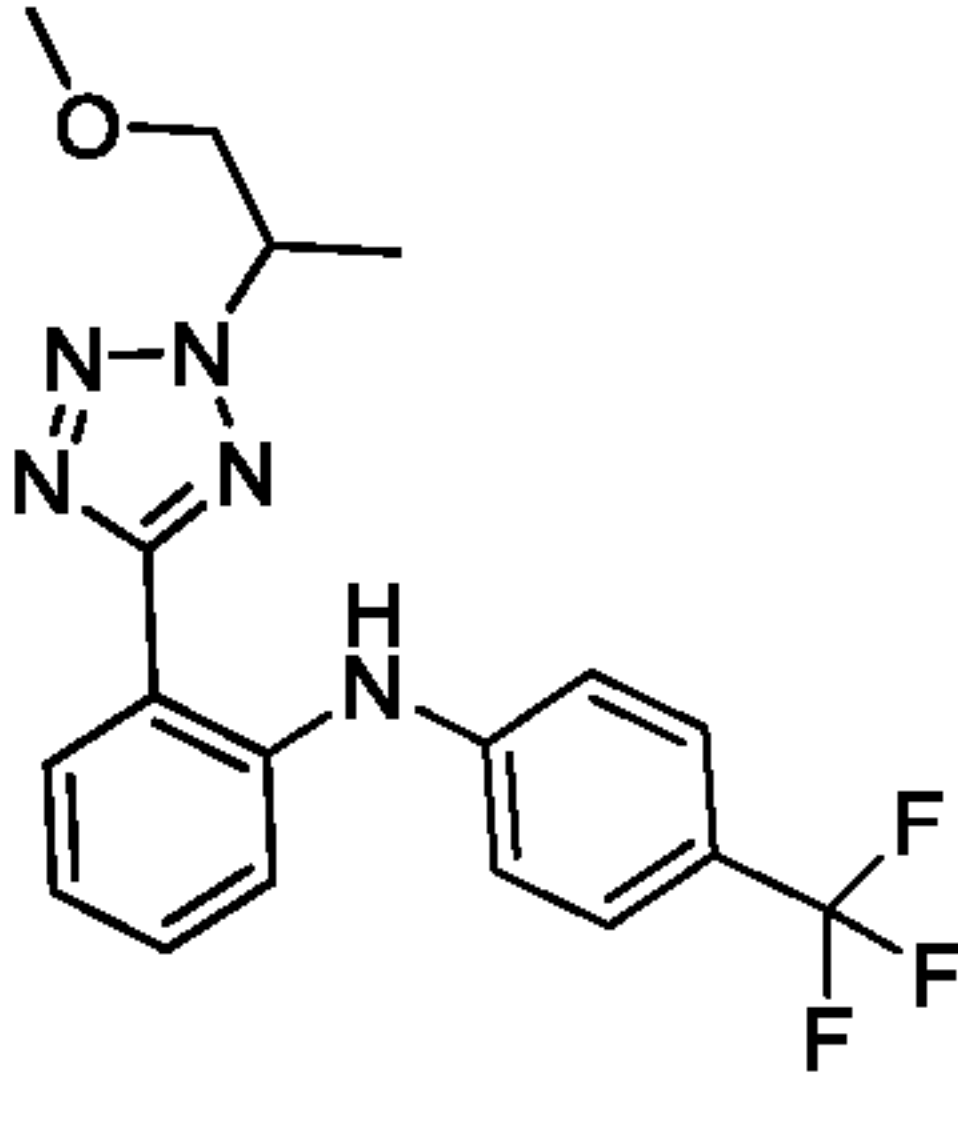
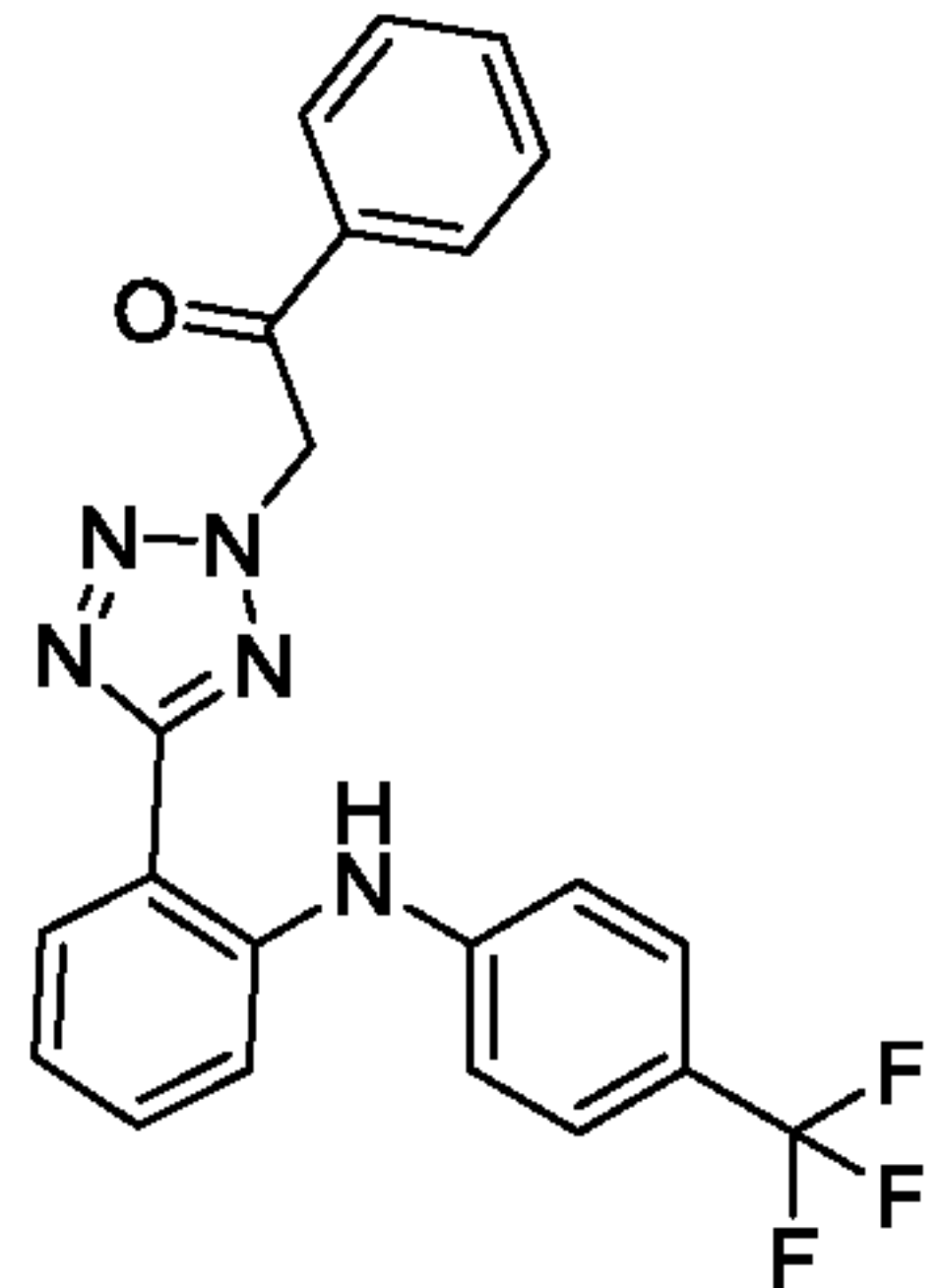
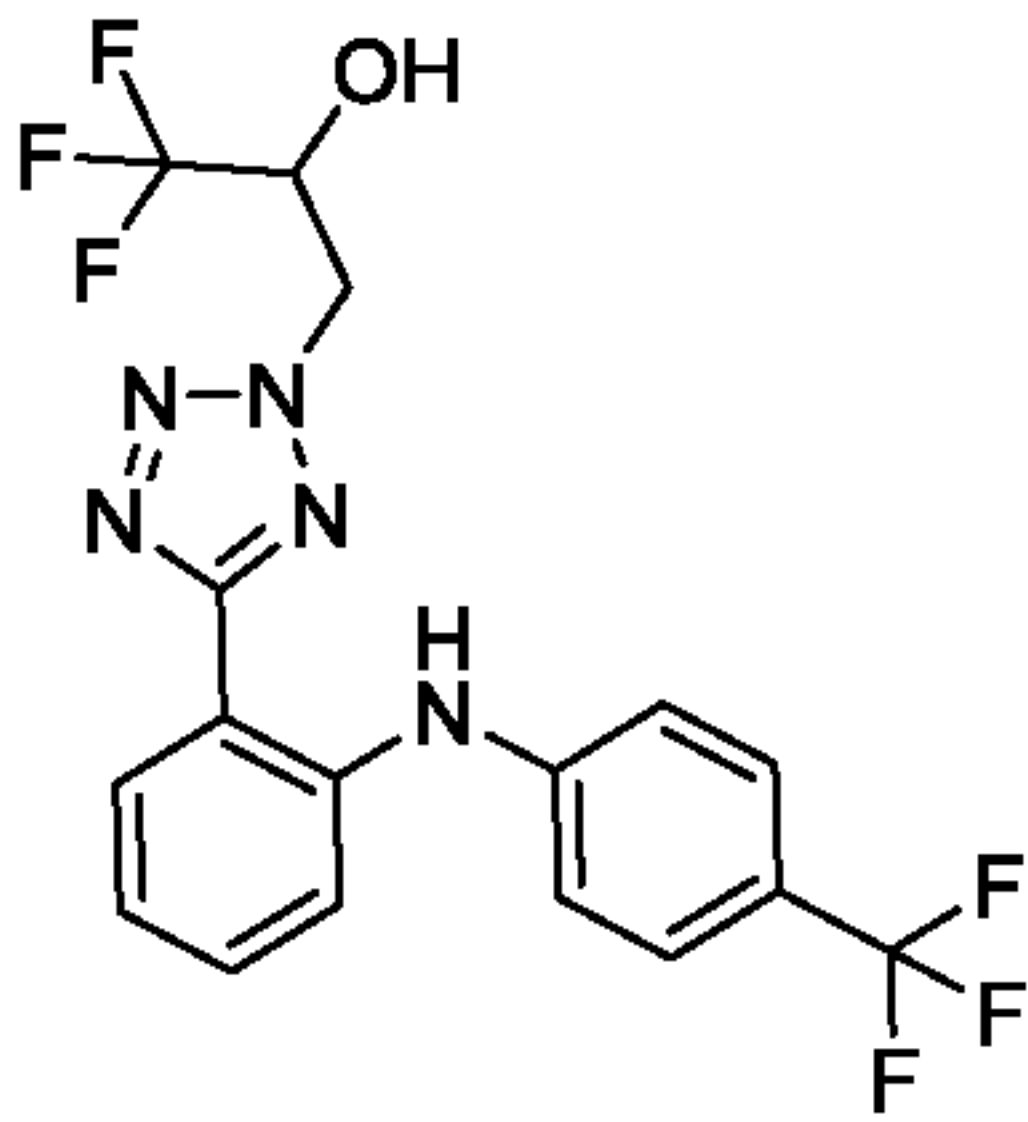
Compound No.	Structure	Name
103		2-[5-[4-[4-(trifluoromethoxy)anilino]pyrimidin-5-yl]tetrazol-2-yl]ethanol
104		1-tert-butyl-3-[2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl]urea
105		1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propan-2-ol
106		1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propan-2-ol
107		2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl N-tert-butylcarbamate

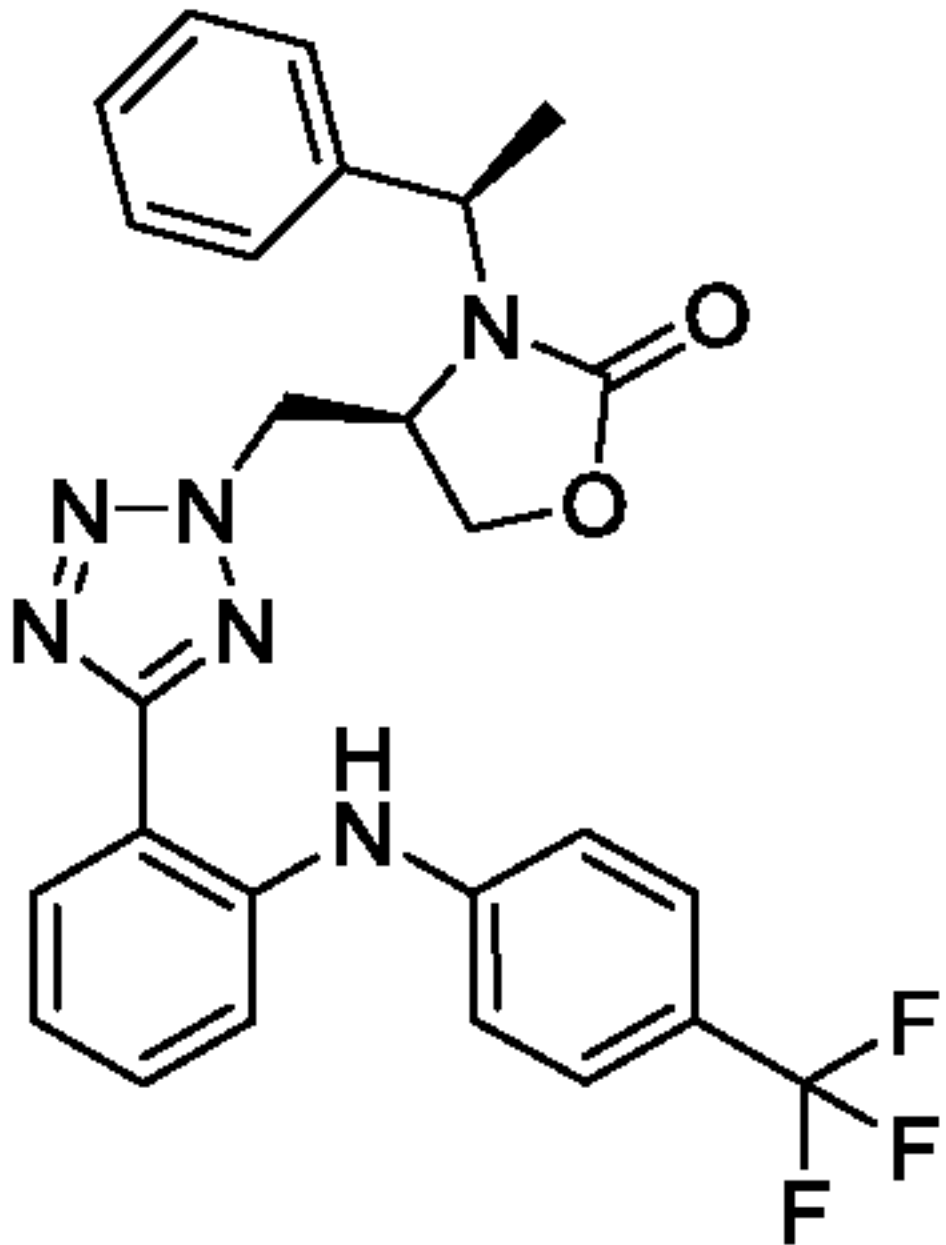
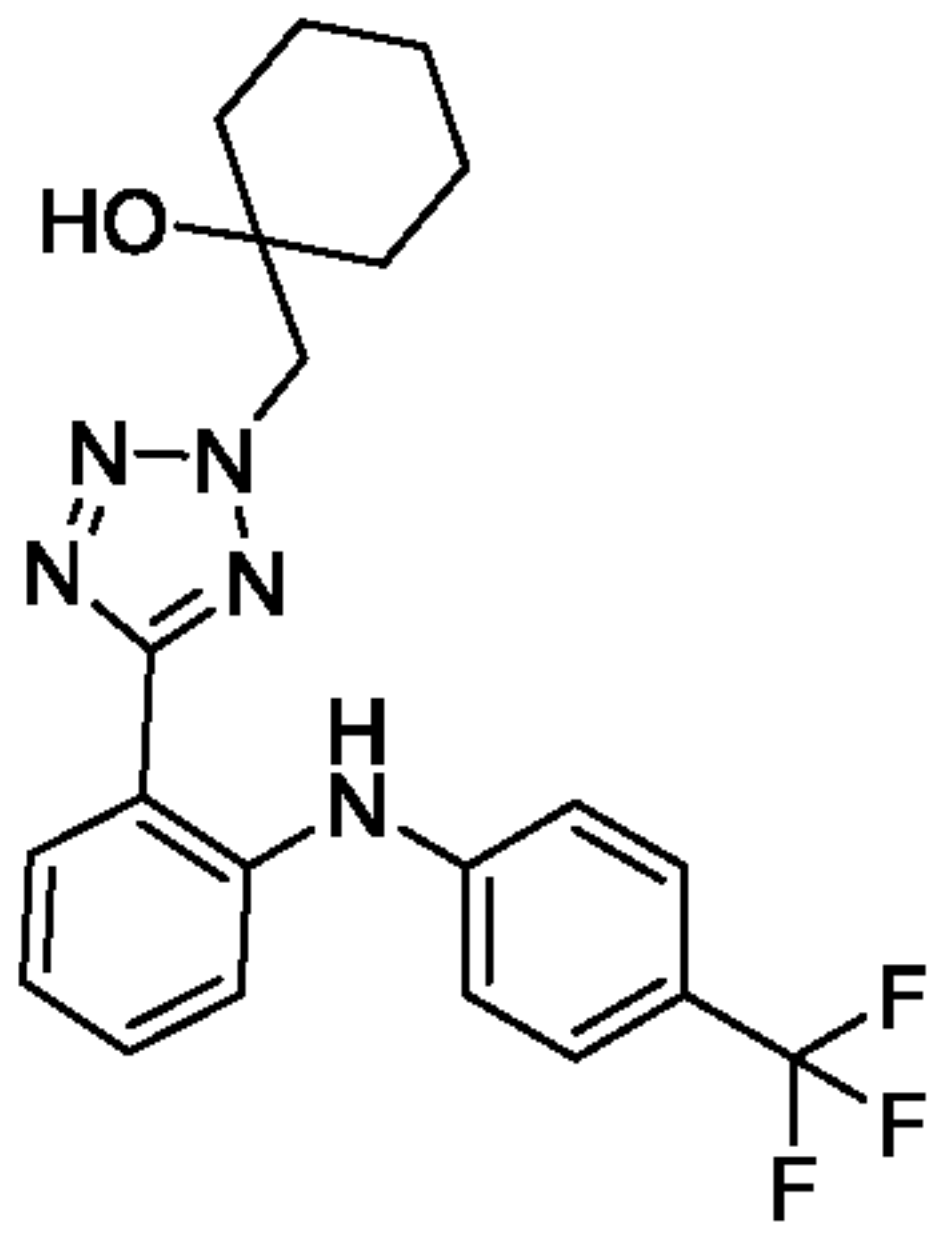
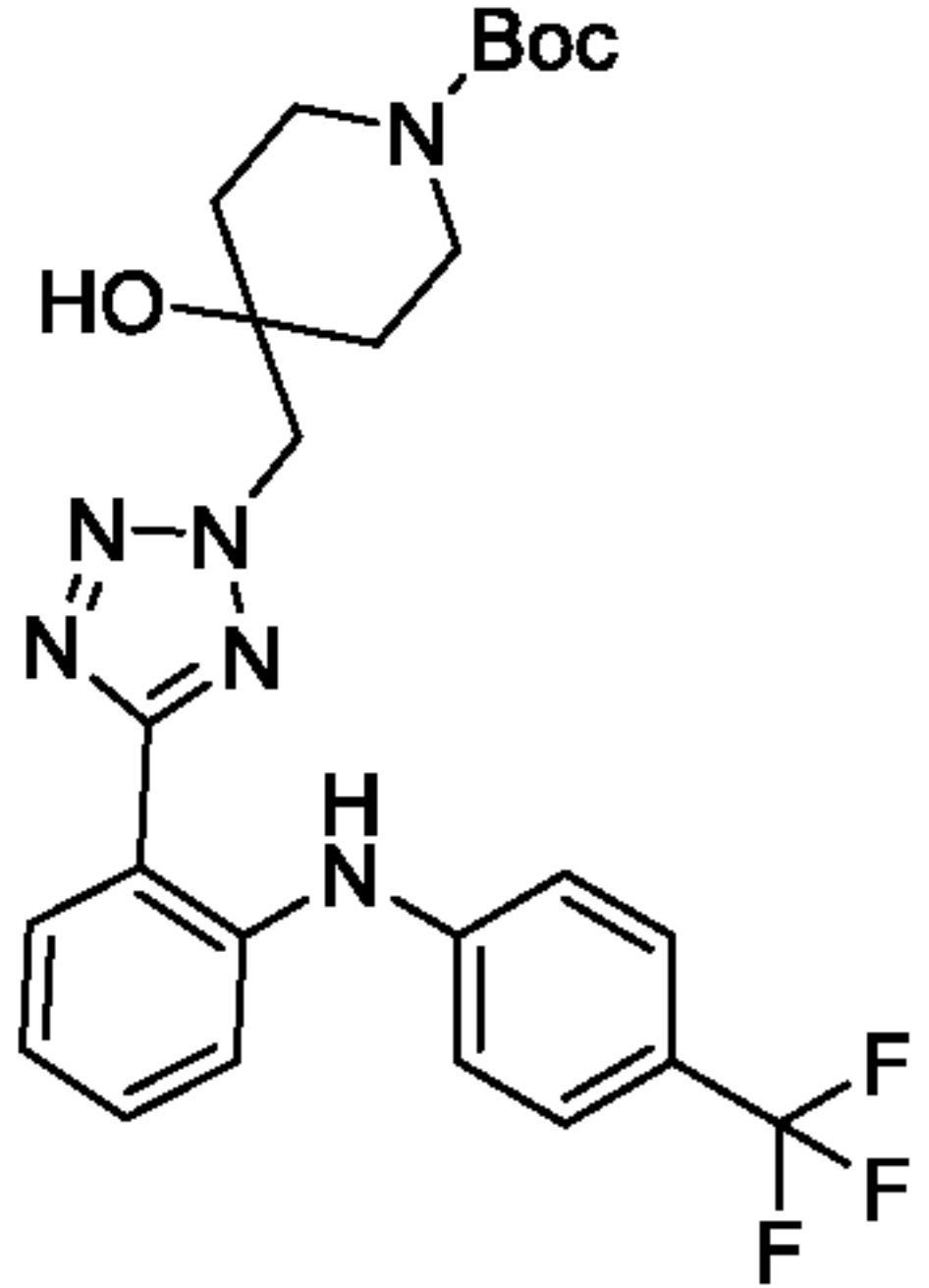
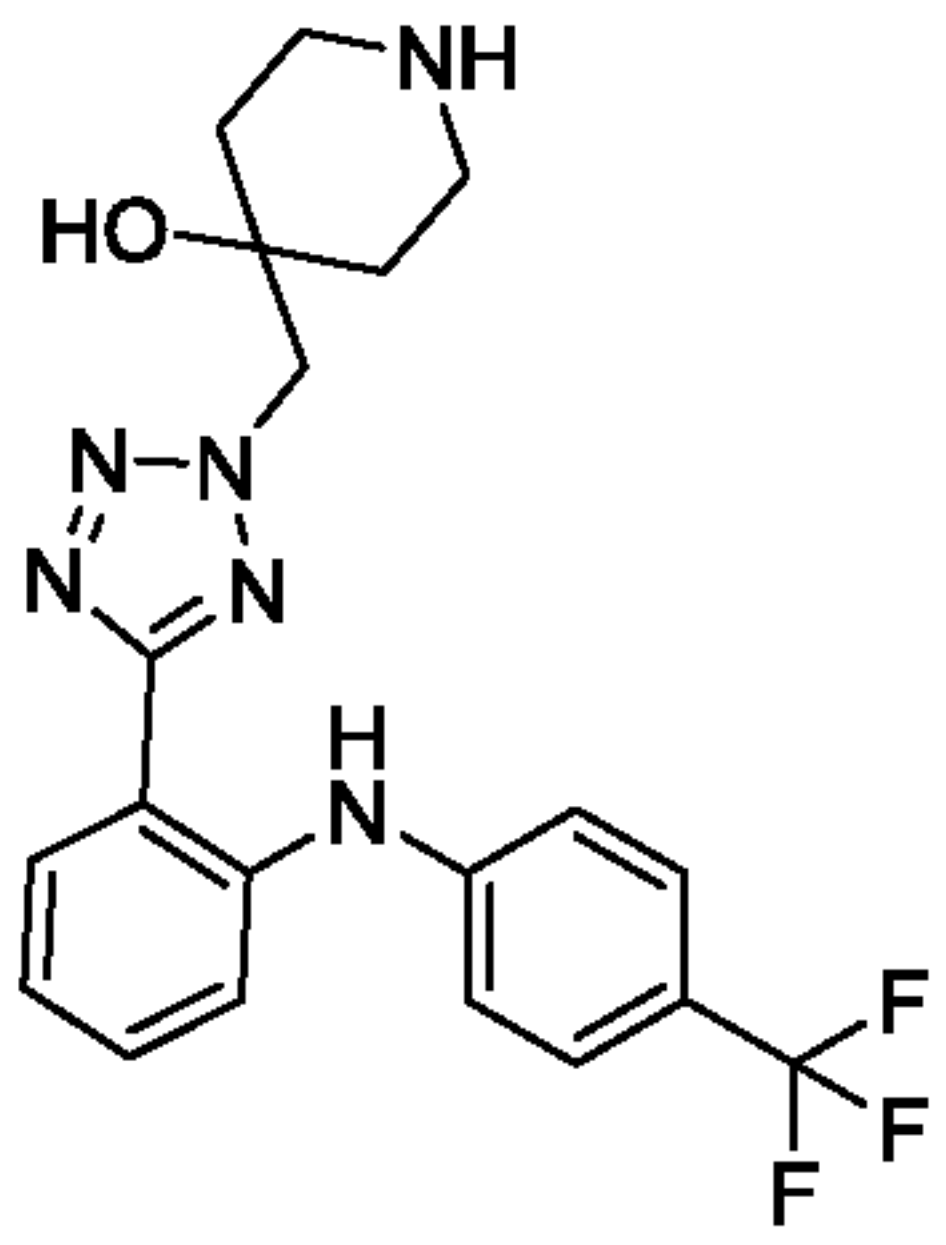
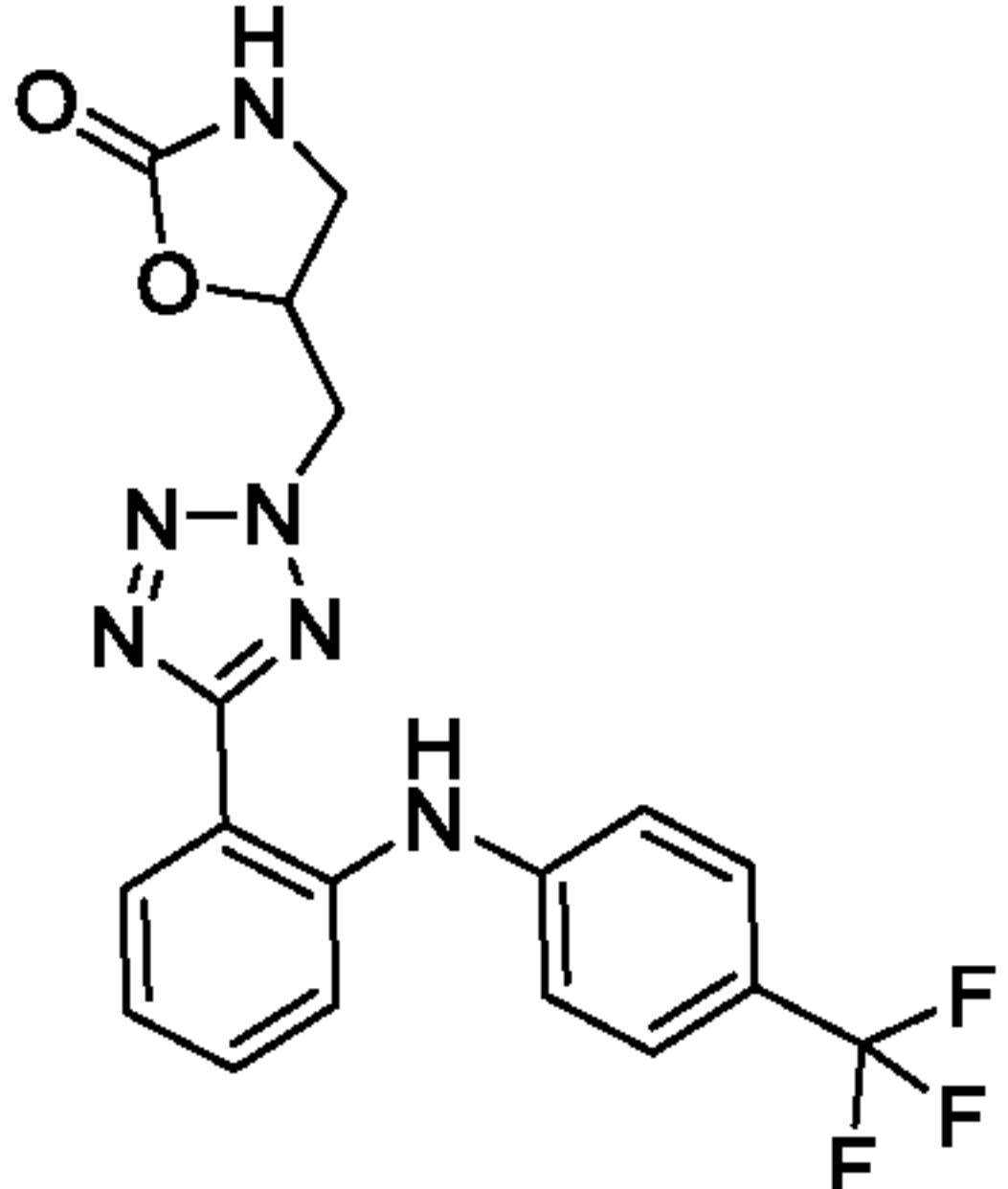
Compound No.	Structure	Name
108		2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethylurea
109		N-(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propyl)methanesulfonamide
110		4-[2-[2-(2-ureidoethyl)tetrazol-5-yl]anilino]benzoic acid
111		N-[3-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propyl]acetamide

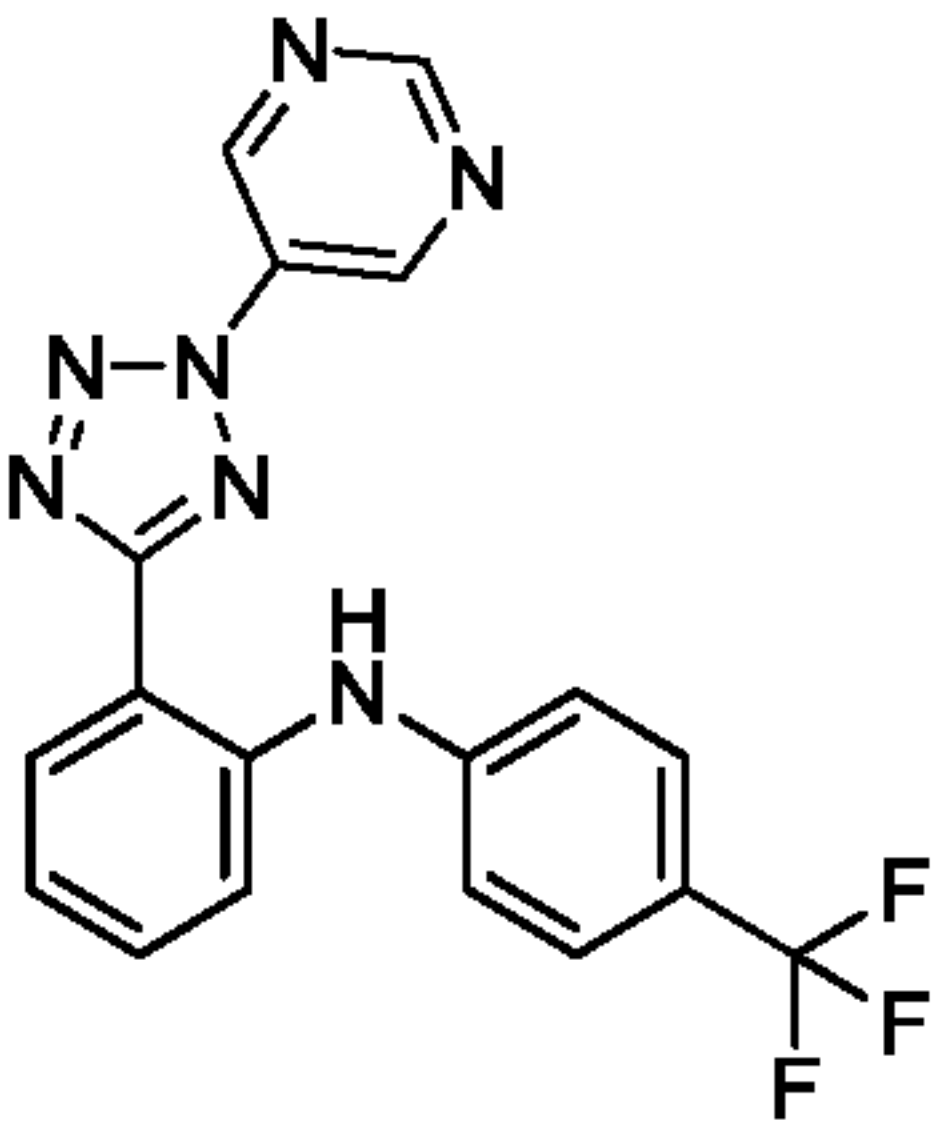
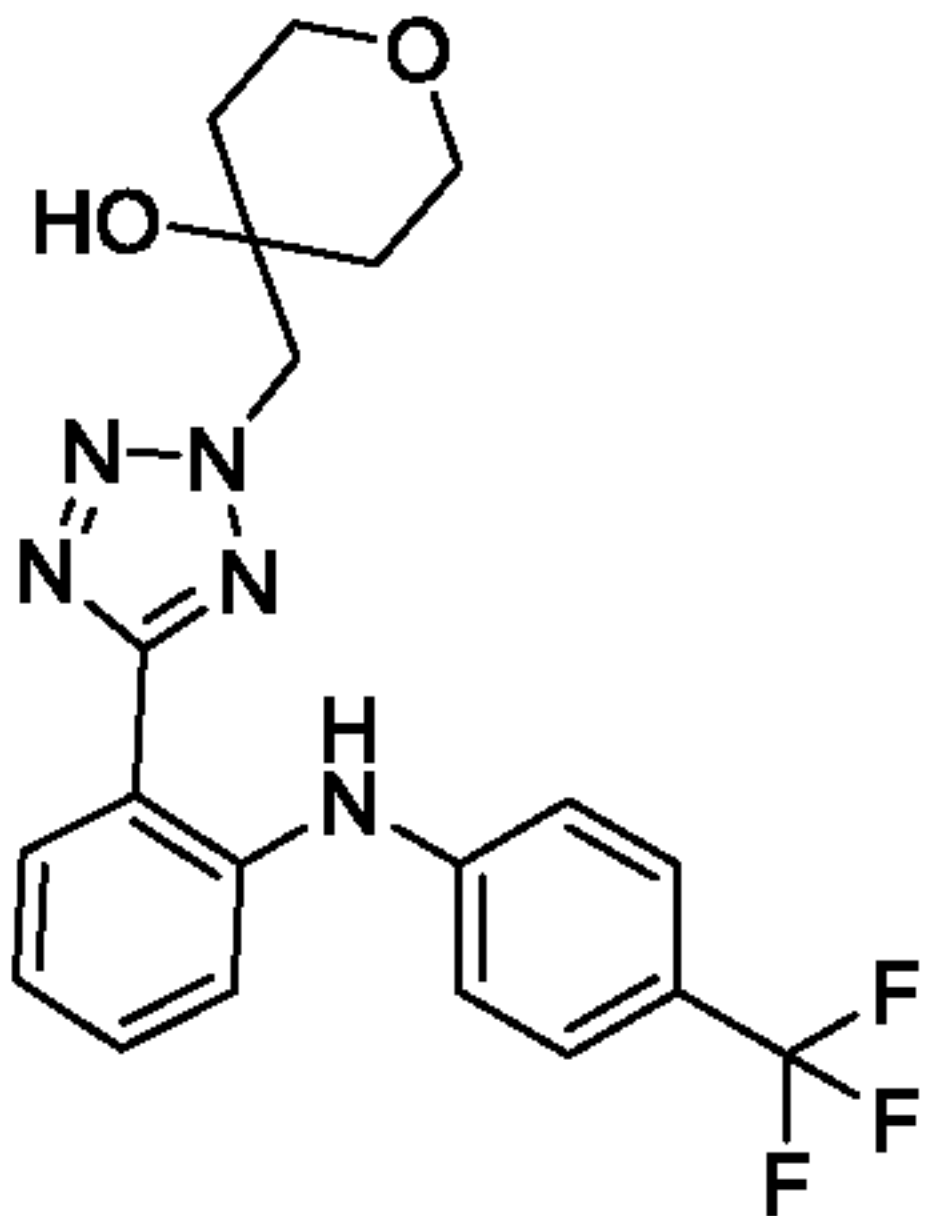
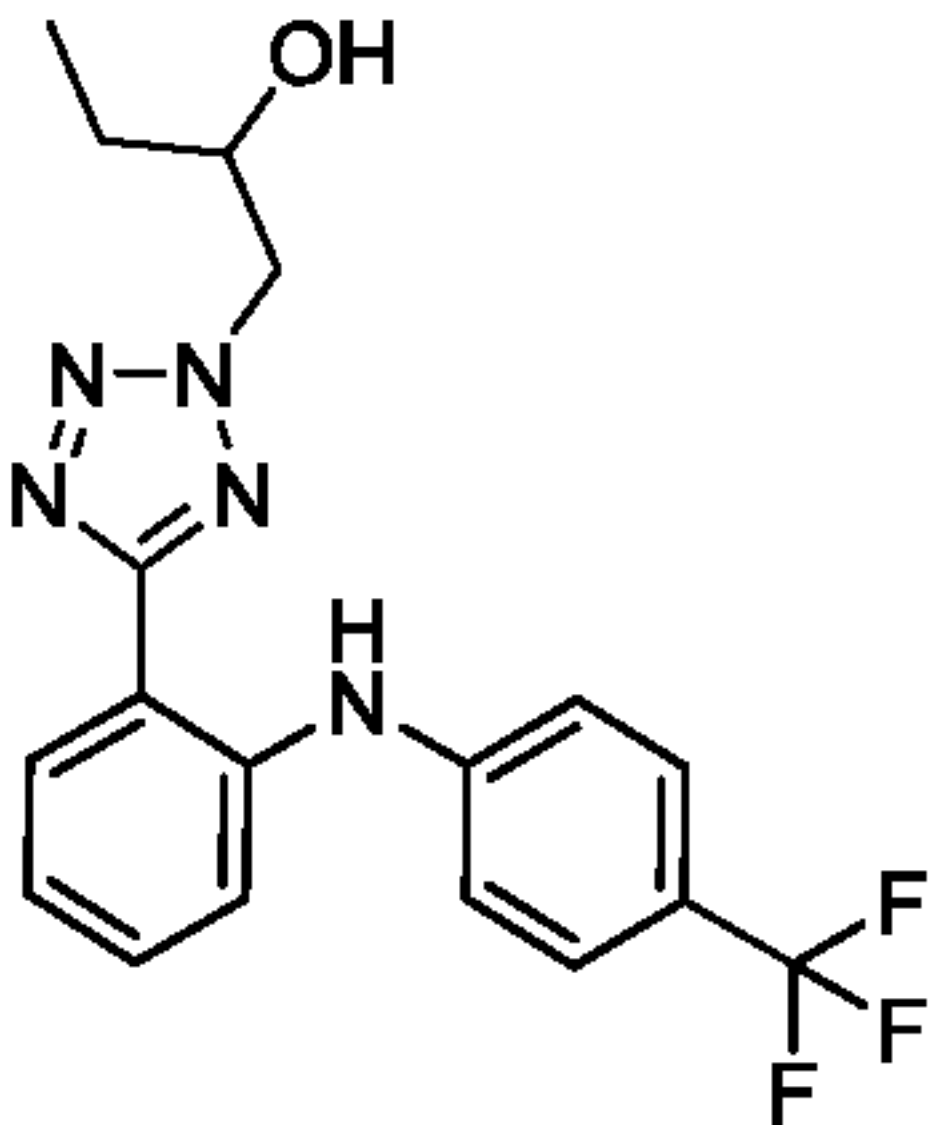
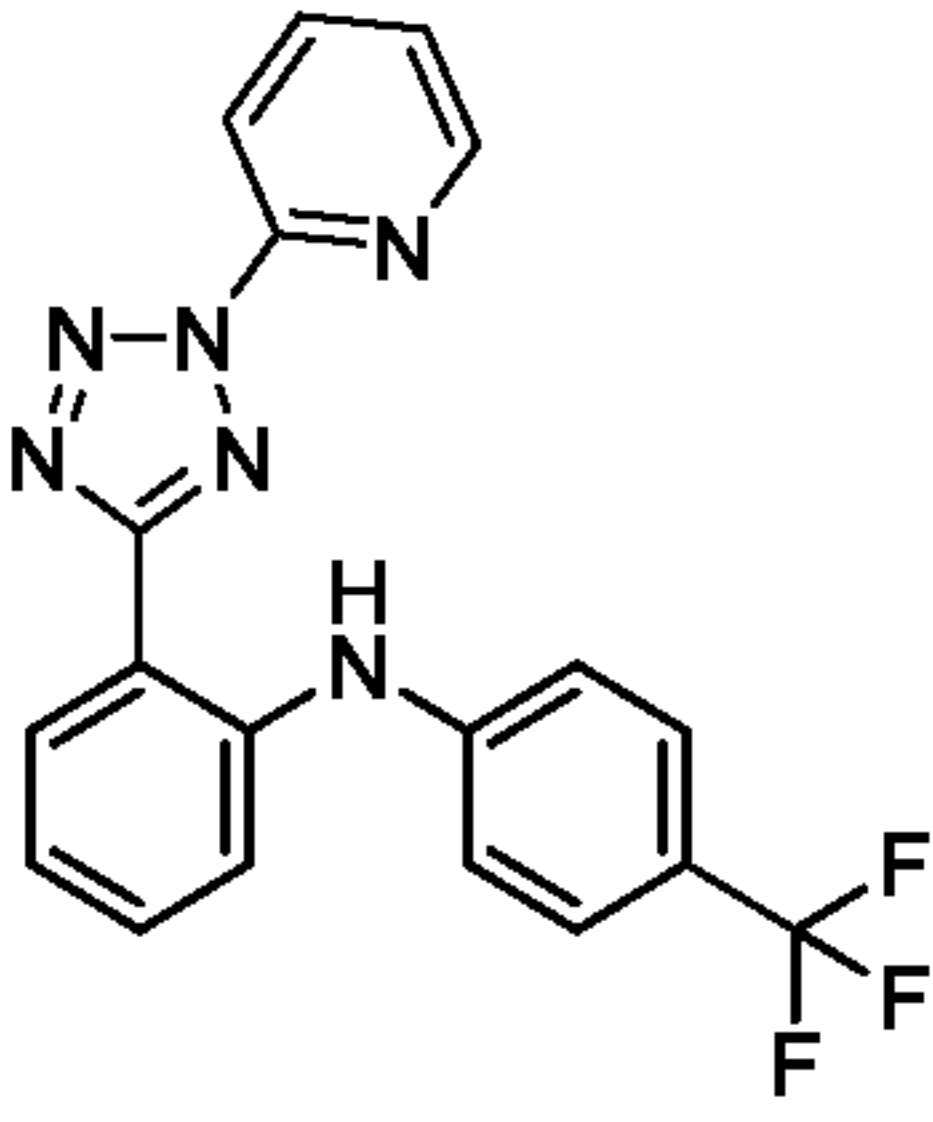
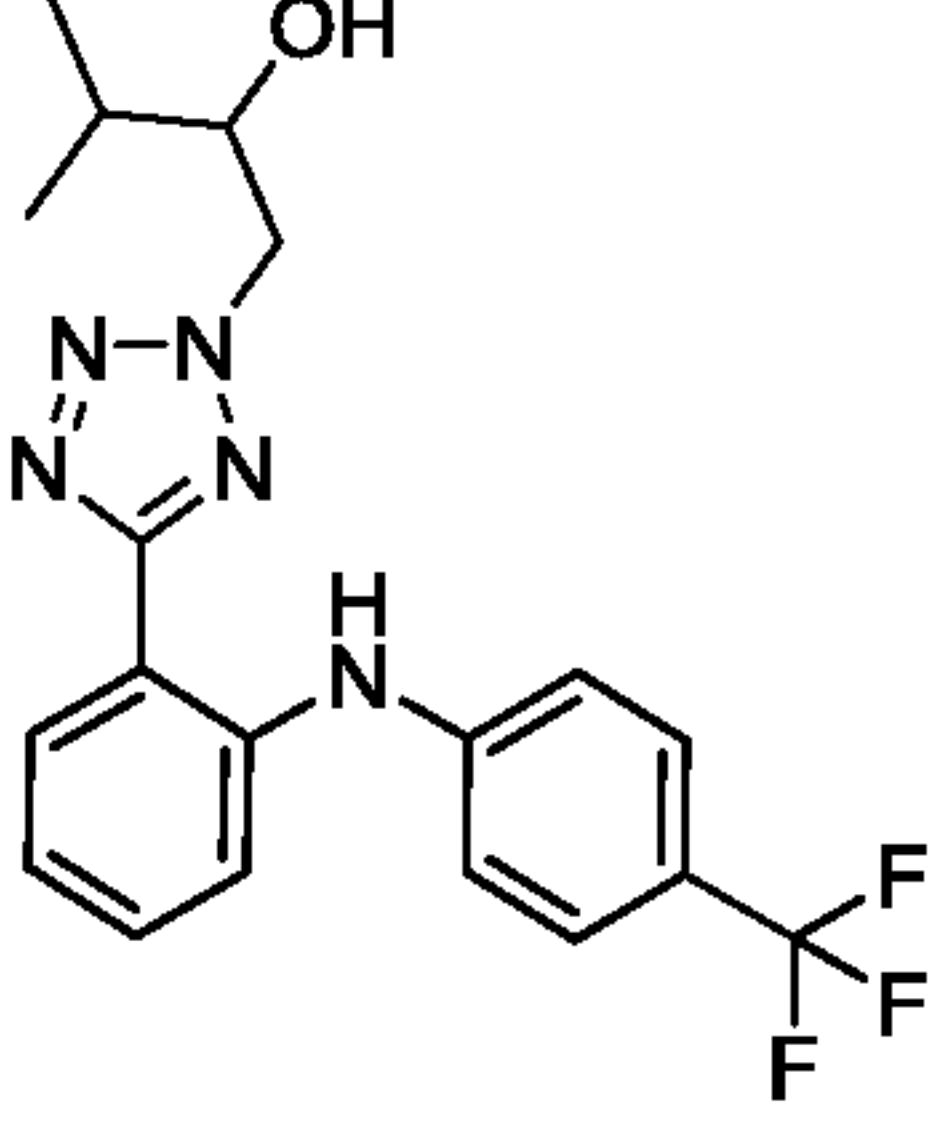
Compound No.	Structure	Name
112		N-acetyl-N-[3-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propyl]acetamide
113		2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanehydroxamic acid
114		3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propane-1,2-diol
115		2-(2-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
116		ethyl 2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propanoate

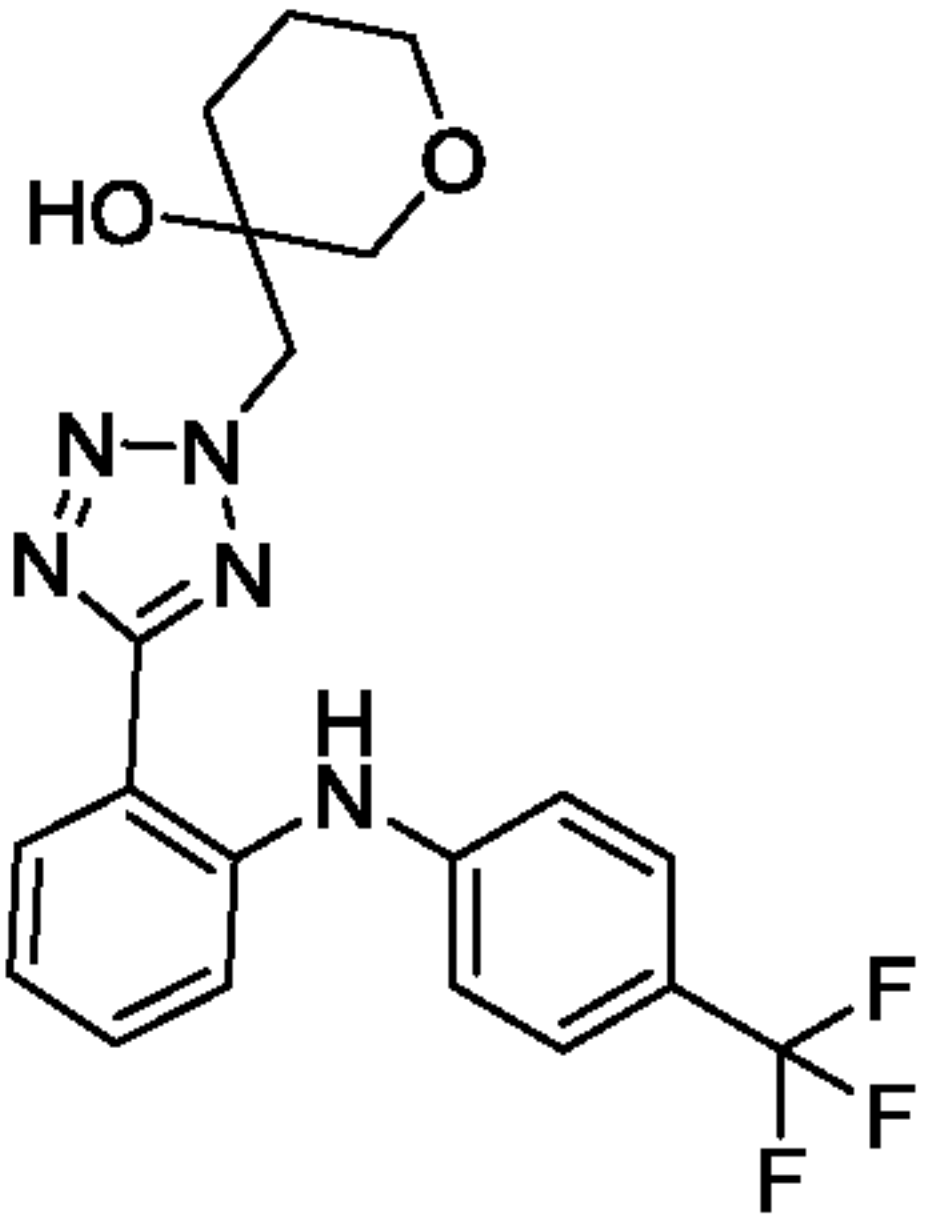
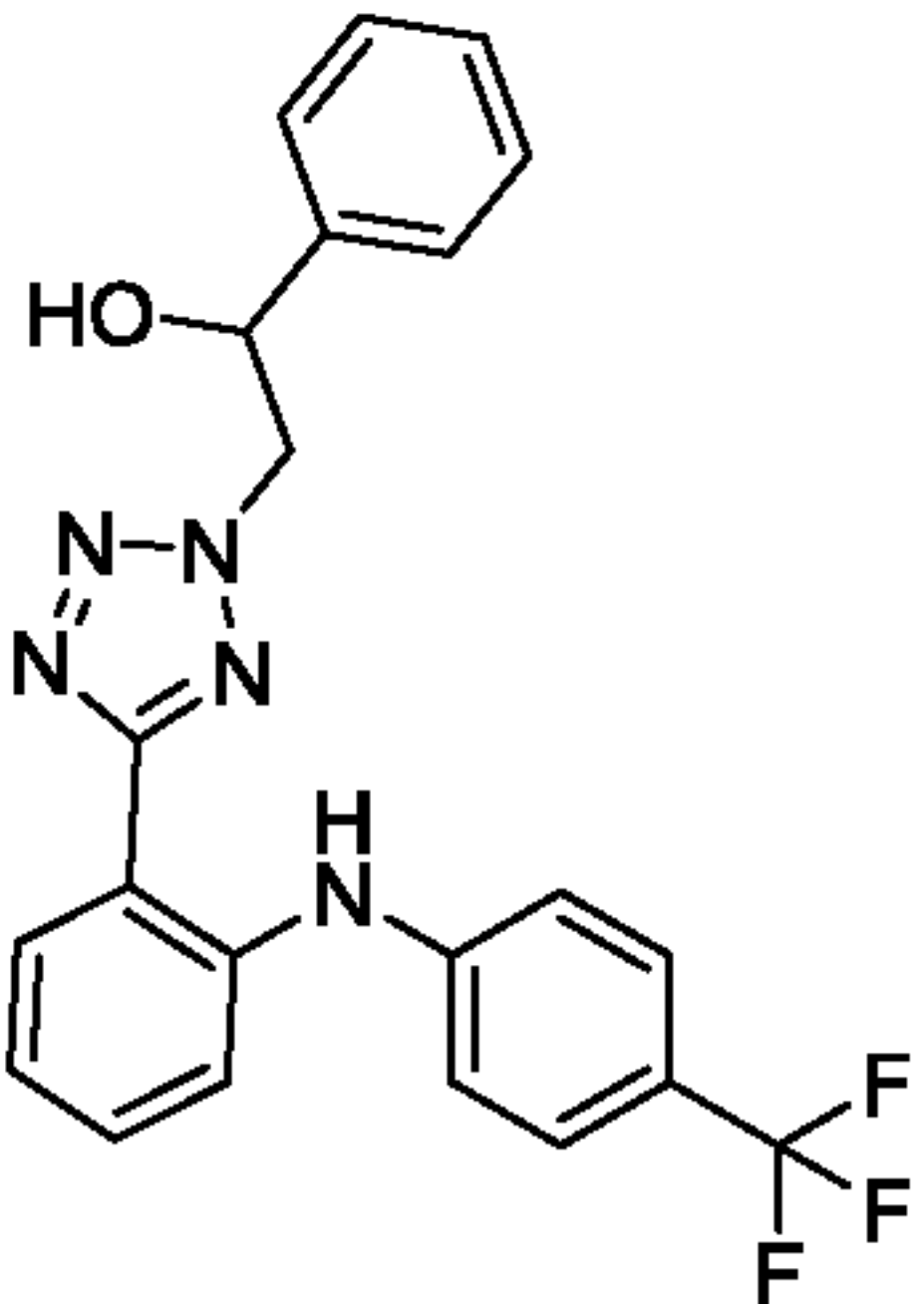
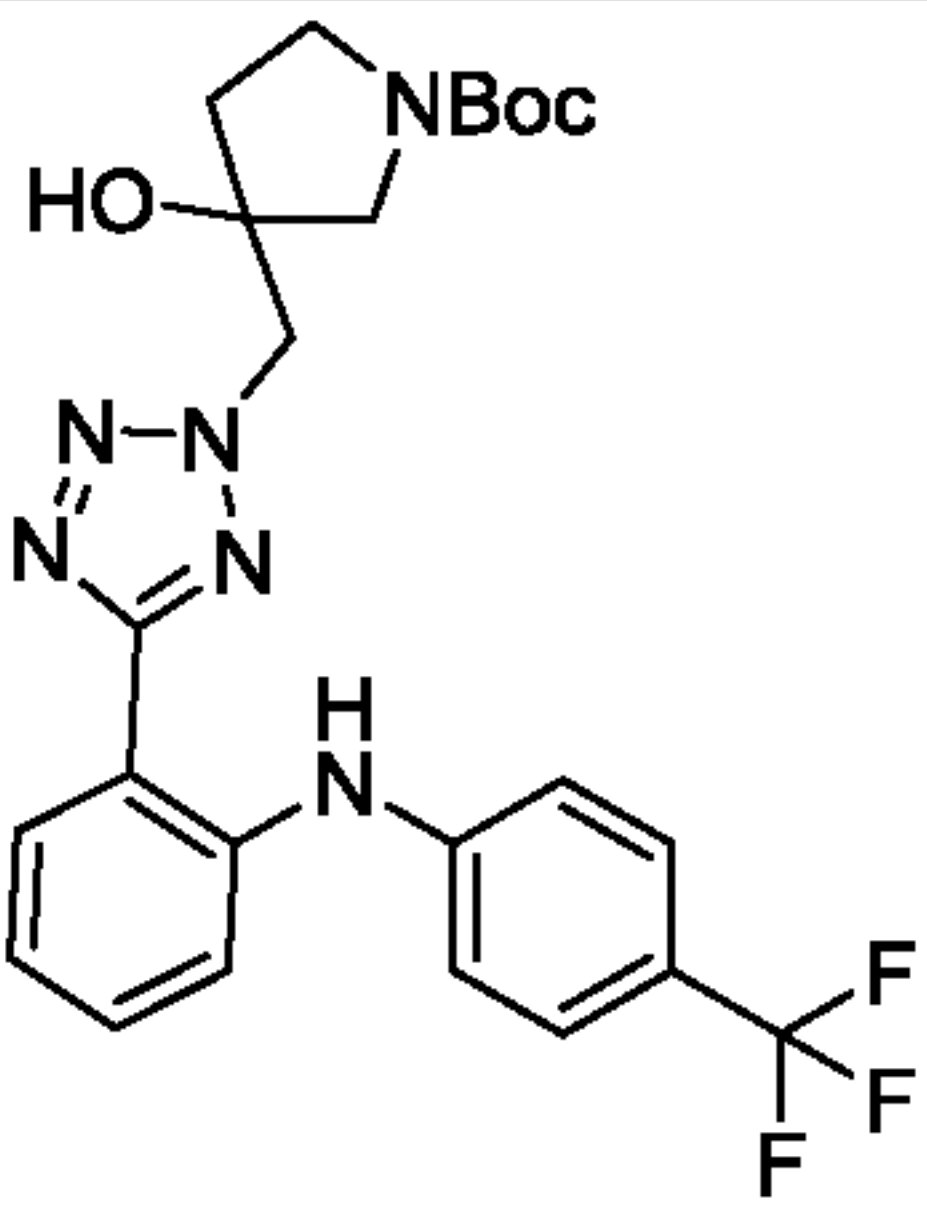
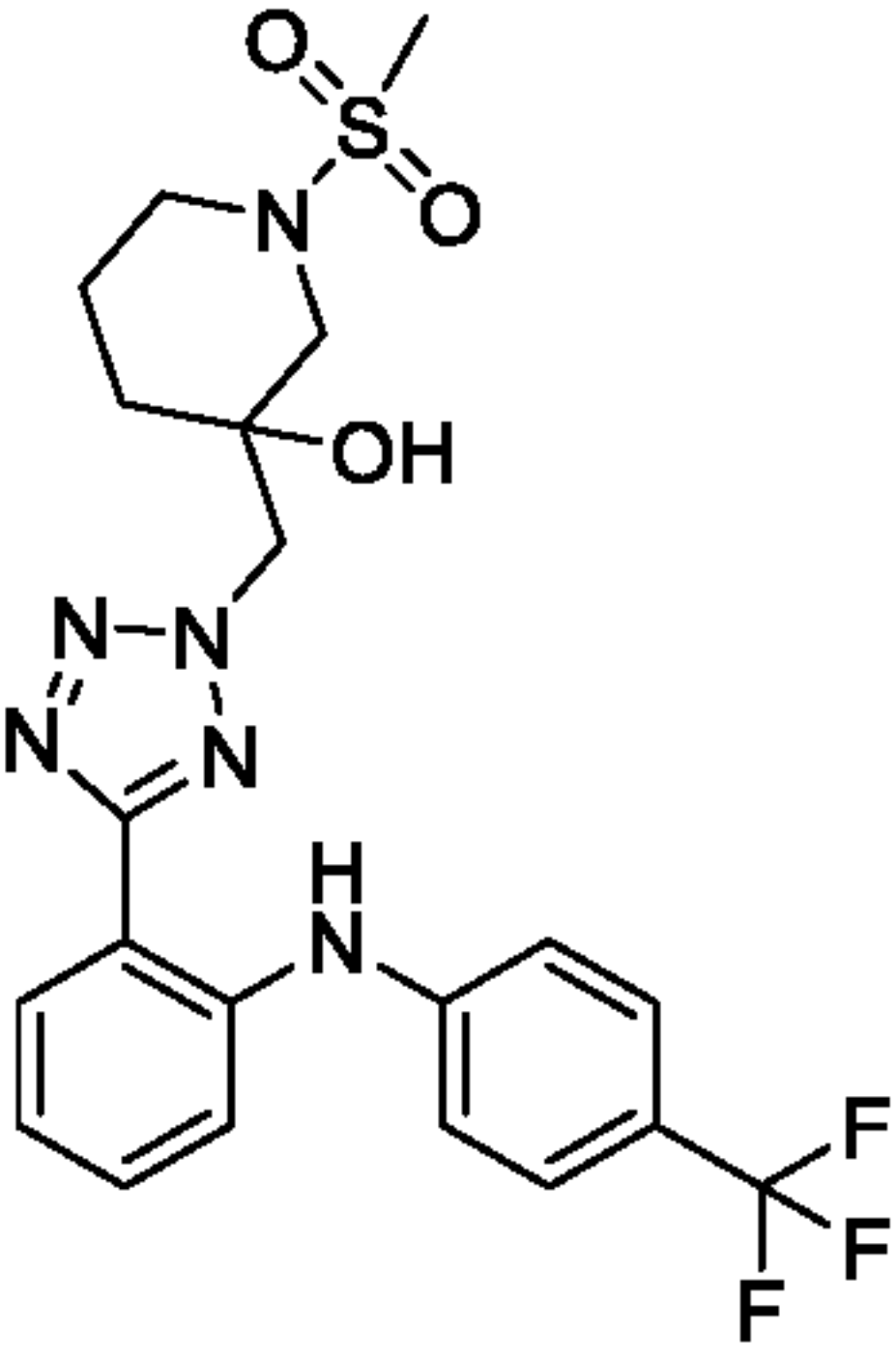
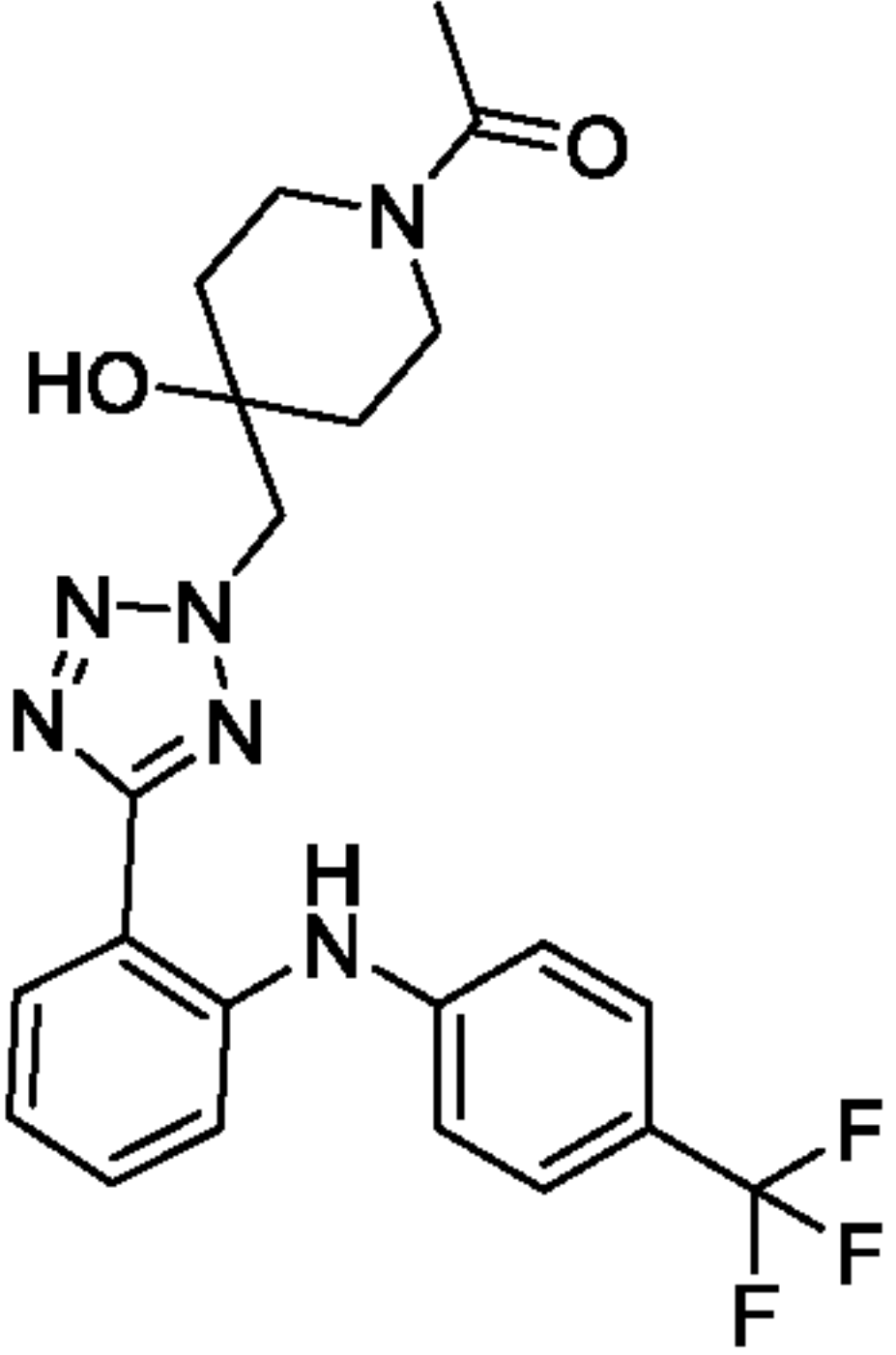
Compound No.	Structure	Name
117		2-[2-(2-fluoroethyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline
118		N-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methylsulfonyl]acetamide
119		2-(2-(tetrahydrofuran-3-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
120		2-(2-tetrahydropyran-3-yl)tetrazol-5-yl)-N-[4-(trifluoromethyl)phenyl]aniline
121		1-cyclopropyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanone

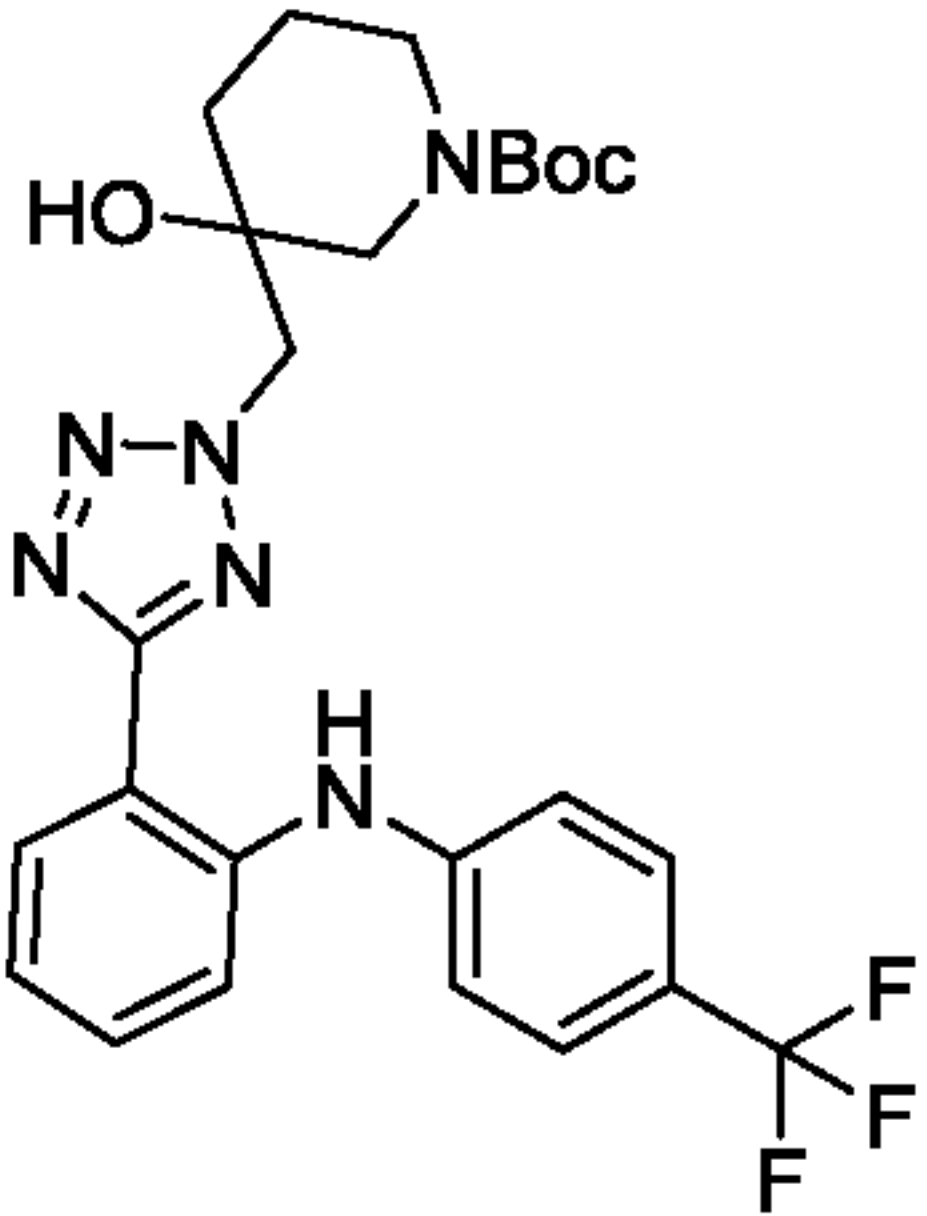
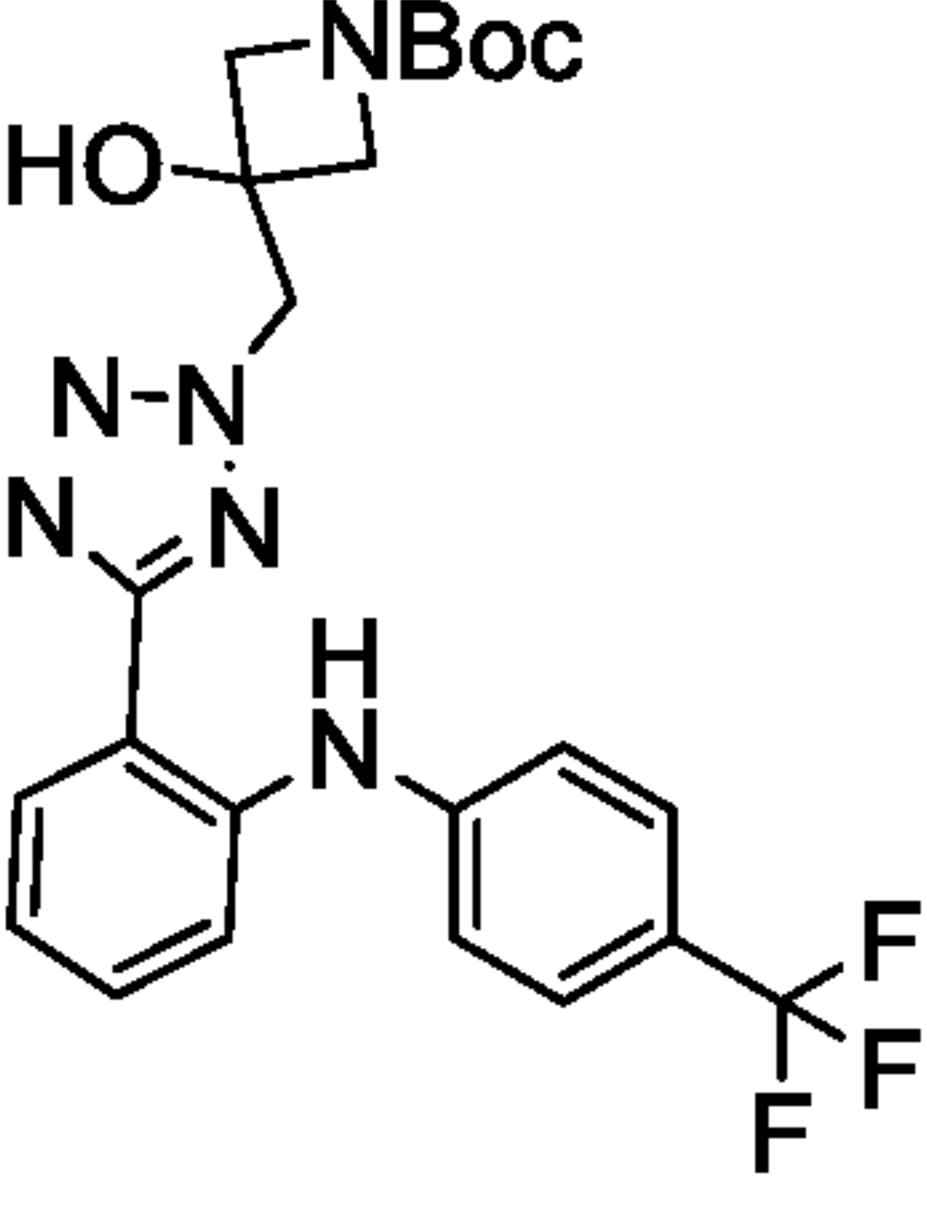
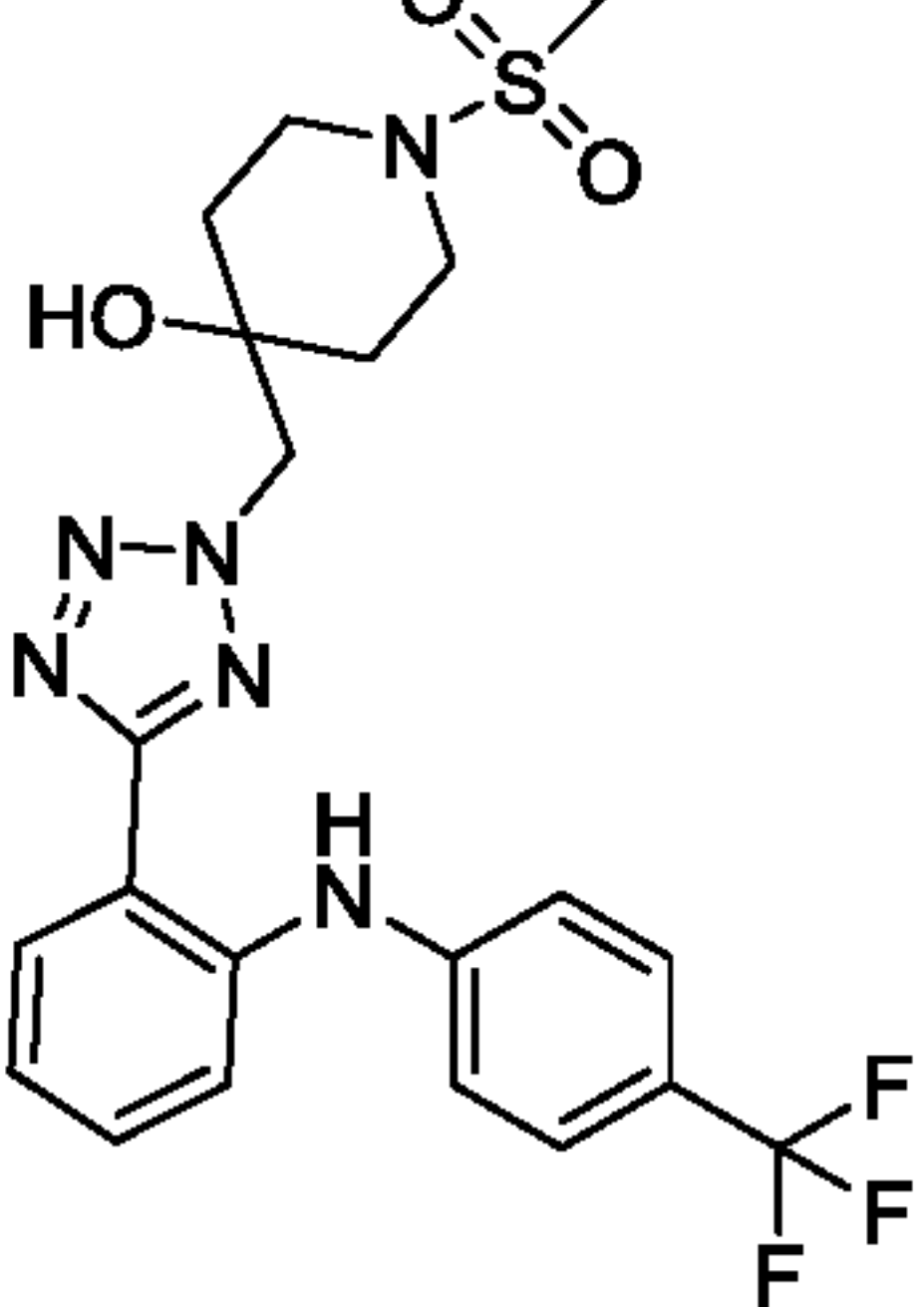
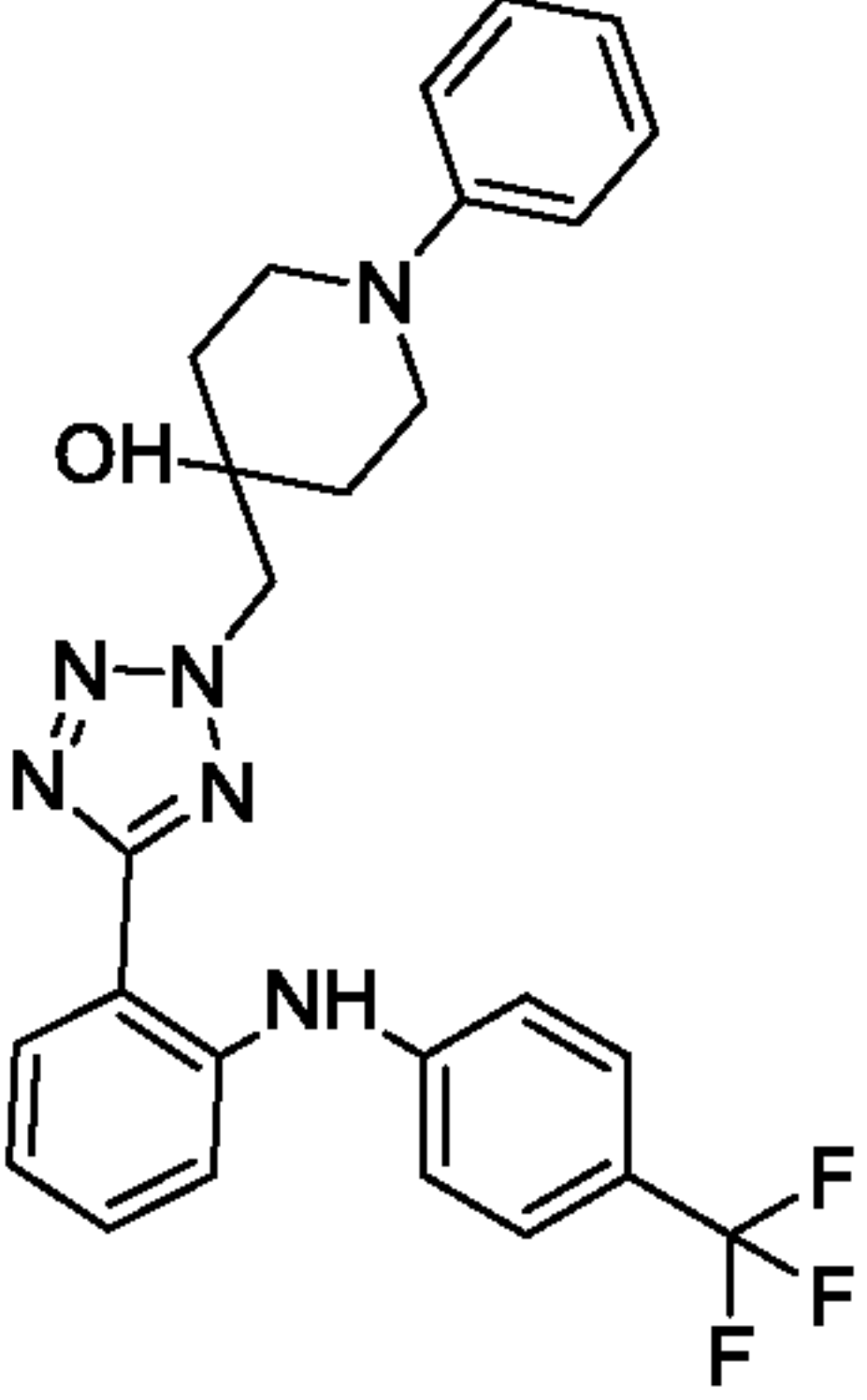
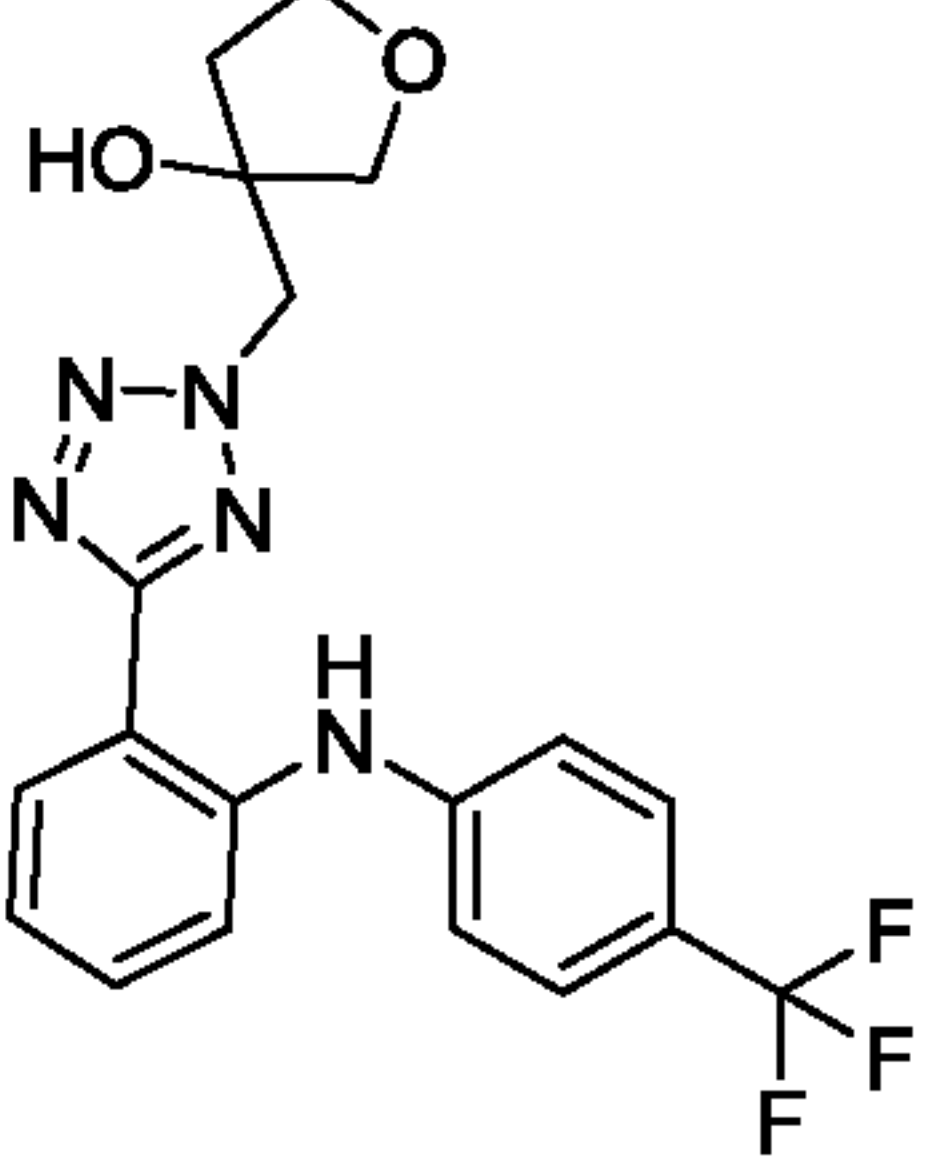
Compound No.	Structure	Name
122		2-(2-tetrahydropyran-4-yltetrazol-5-yl)-N-[4-(trifluoromethyl)phenyl]aniline
123		2-[2-(oxetan-3-yl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline
124		2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl carbamate
125		2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propan-1-ol
126		2-[2-(3-fluoropropyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline

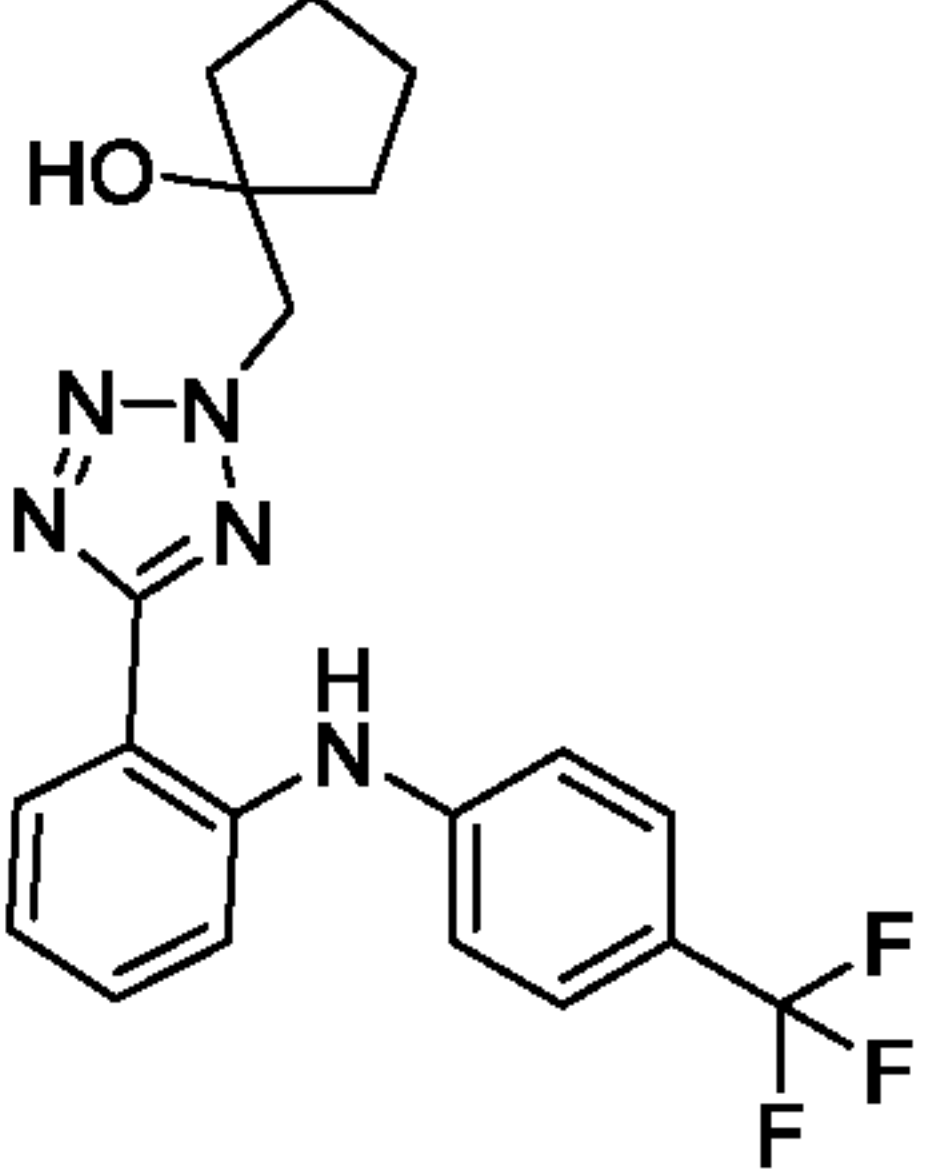
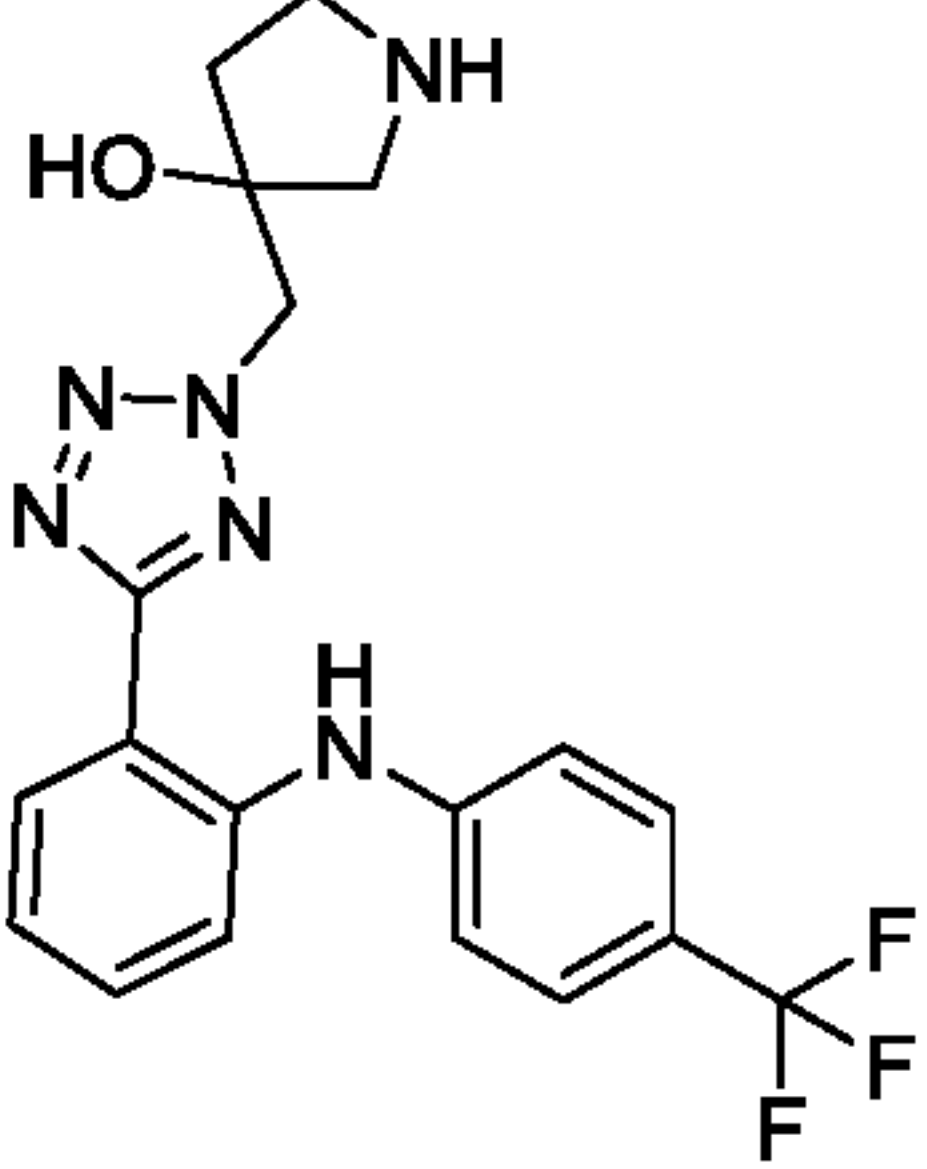
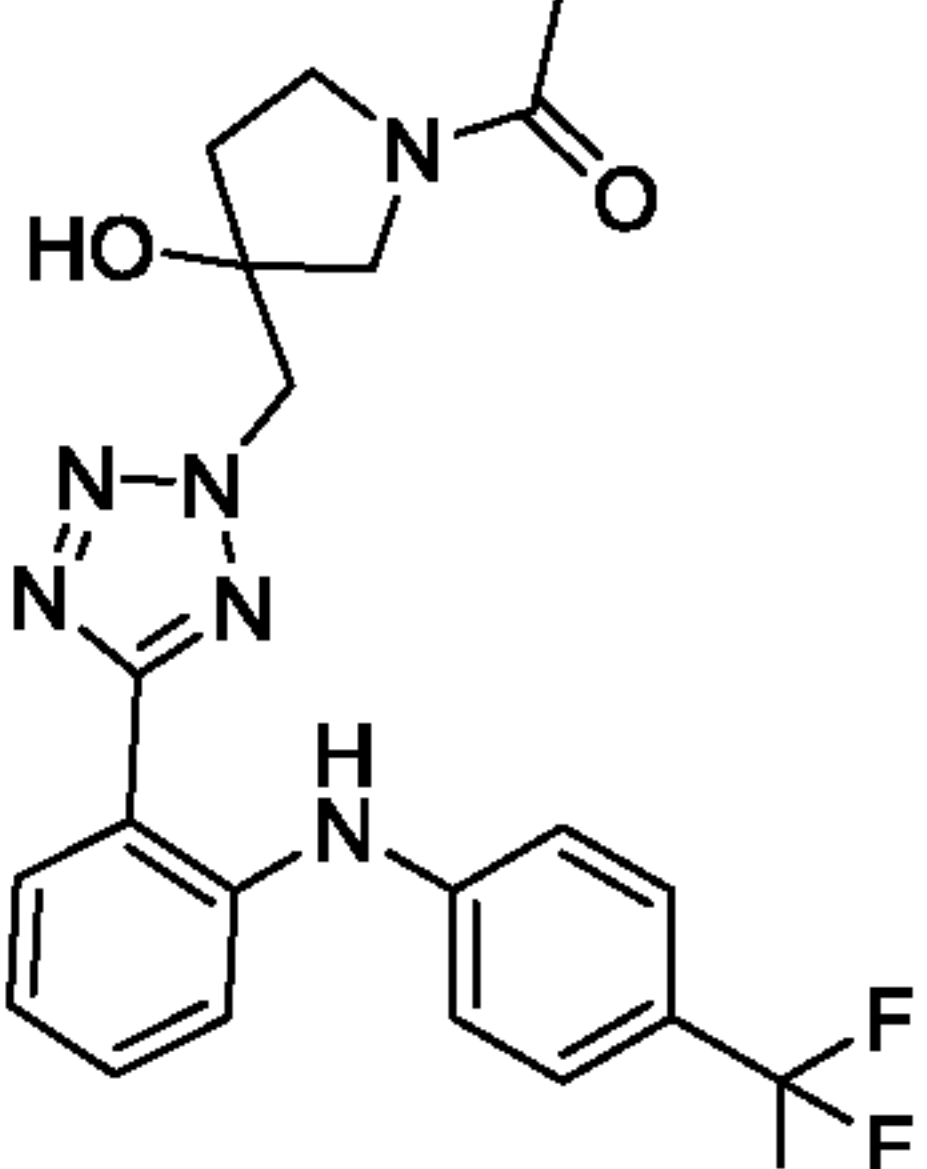
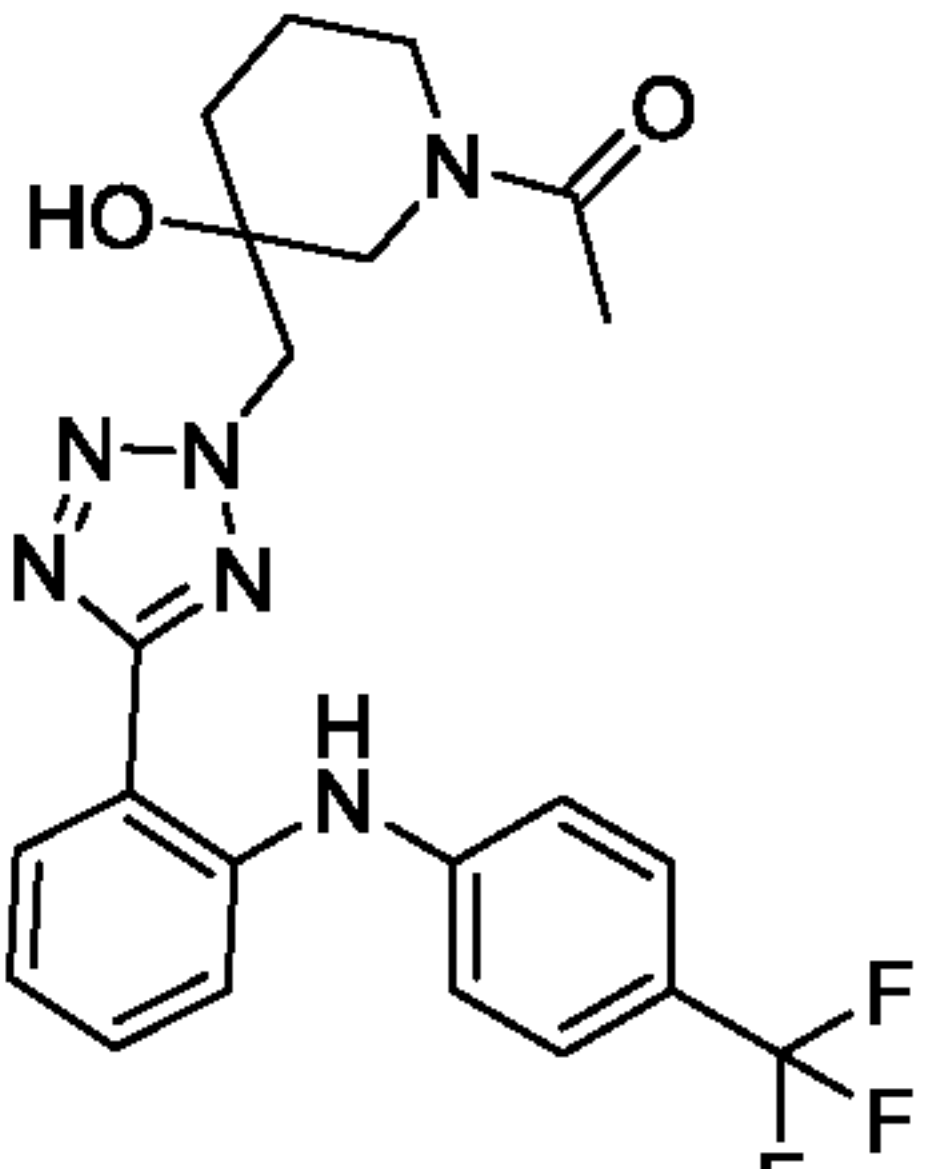
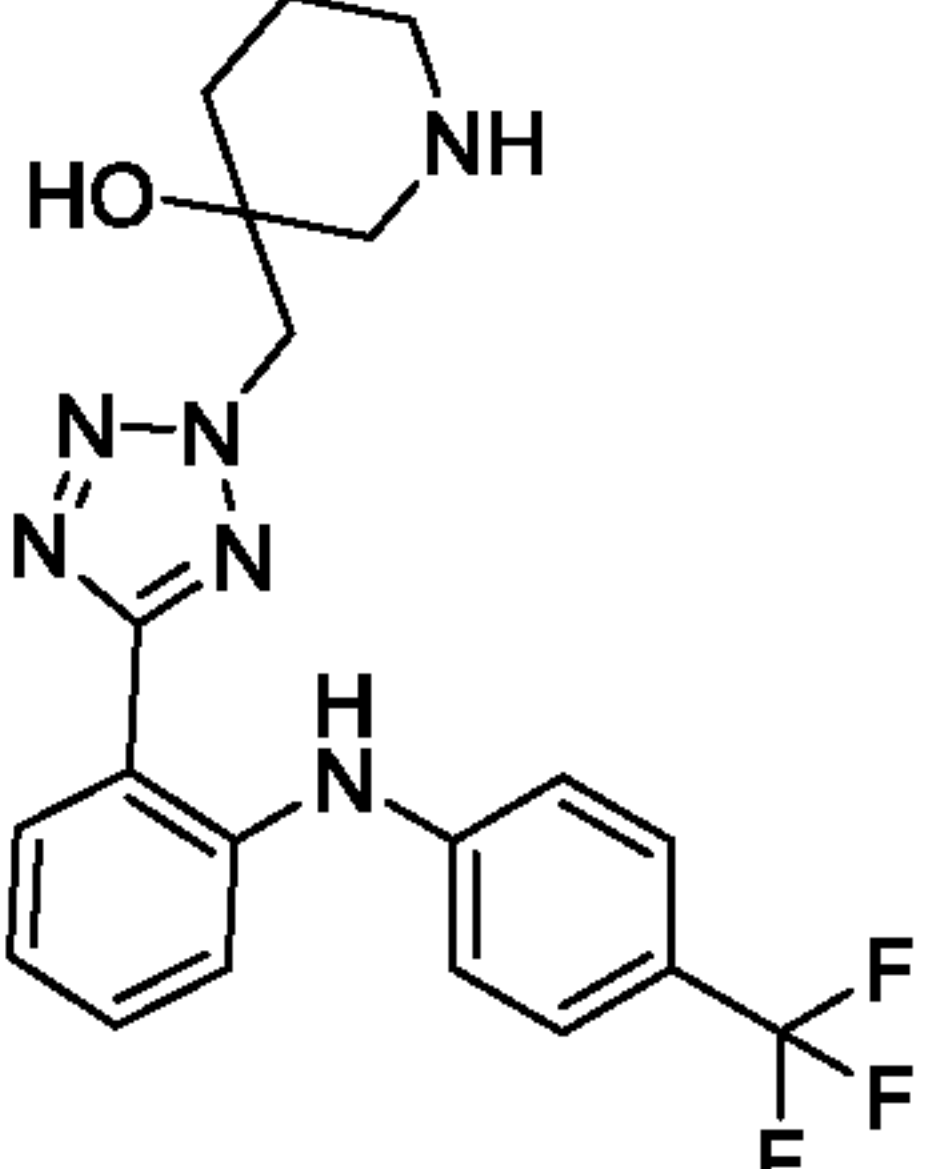
Compound No.	Structure	Name
127		1-cyclopropyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol
128		3-methyl-1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]butan-2-one
129		2-(2-(1-methoxypropan-2-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
130		1-phenyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanone
131		1,1,1-trifluoro-3-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propan-2-ol

Compound No.	Structure	Name
132		(4R)-3-[(1R)-1-phenylethyl]-4-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]oxazolidin-2-one
133		1-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]cyclohexanol
134		tert-butyl 4-hydroxy-4-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]piperidine-1-carboxylate
135		4-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]piperidin-4-ol
136		5-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)oxazolidin-2-one

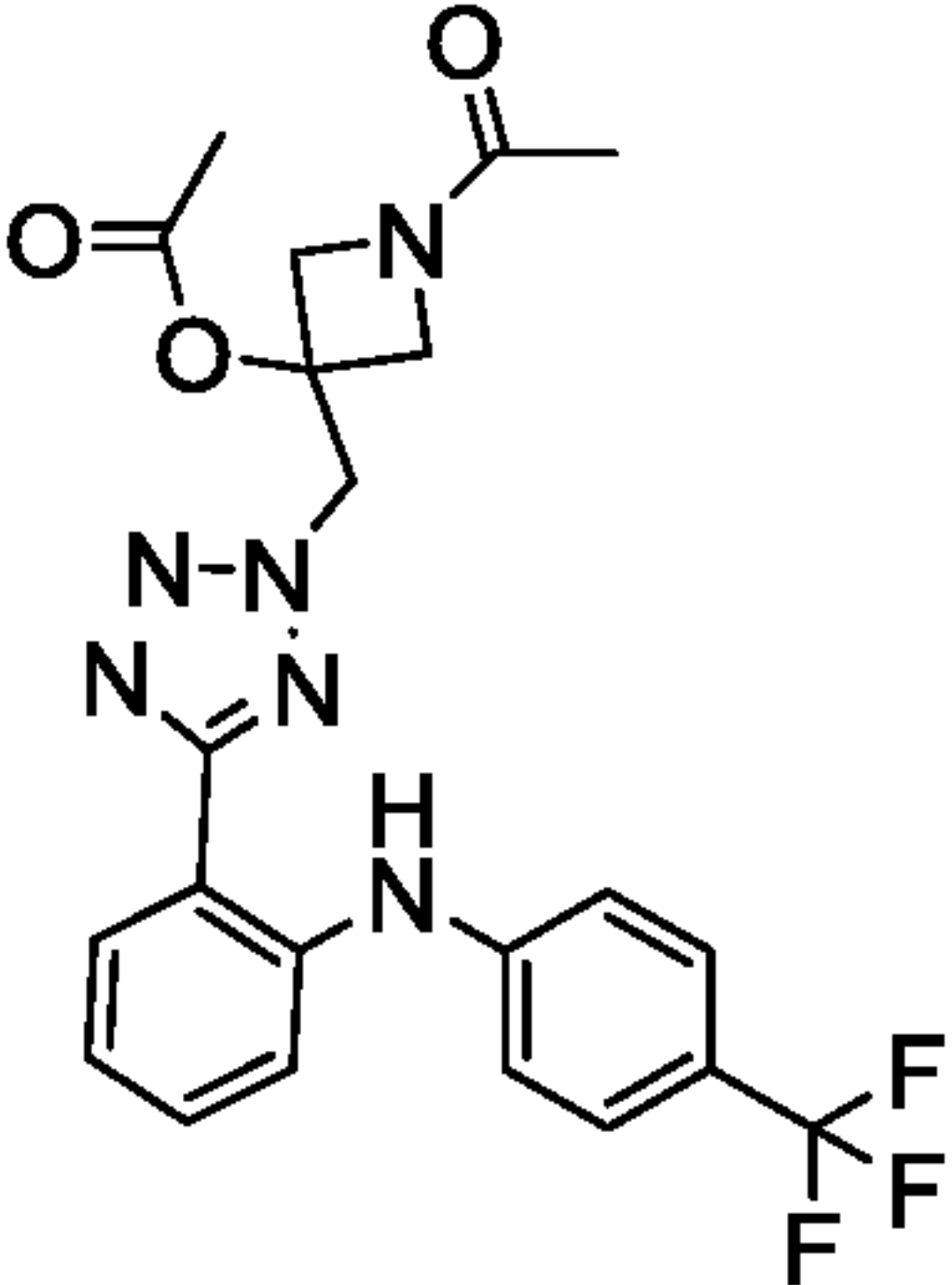
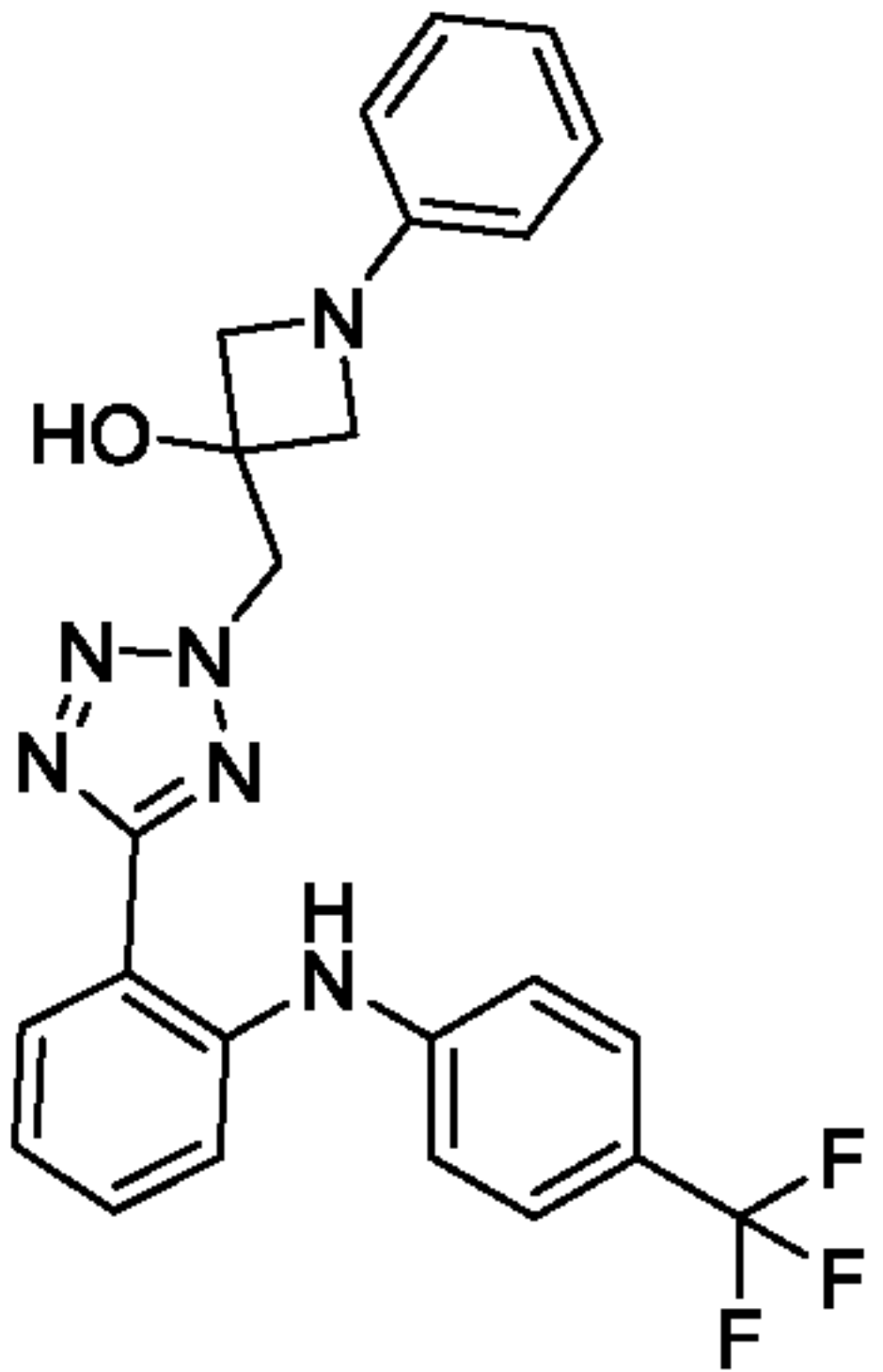
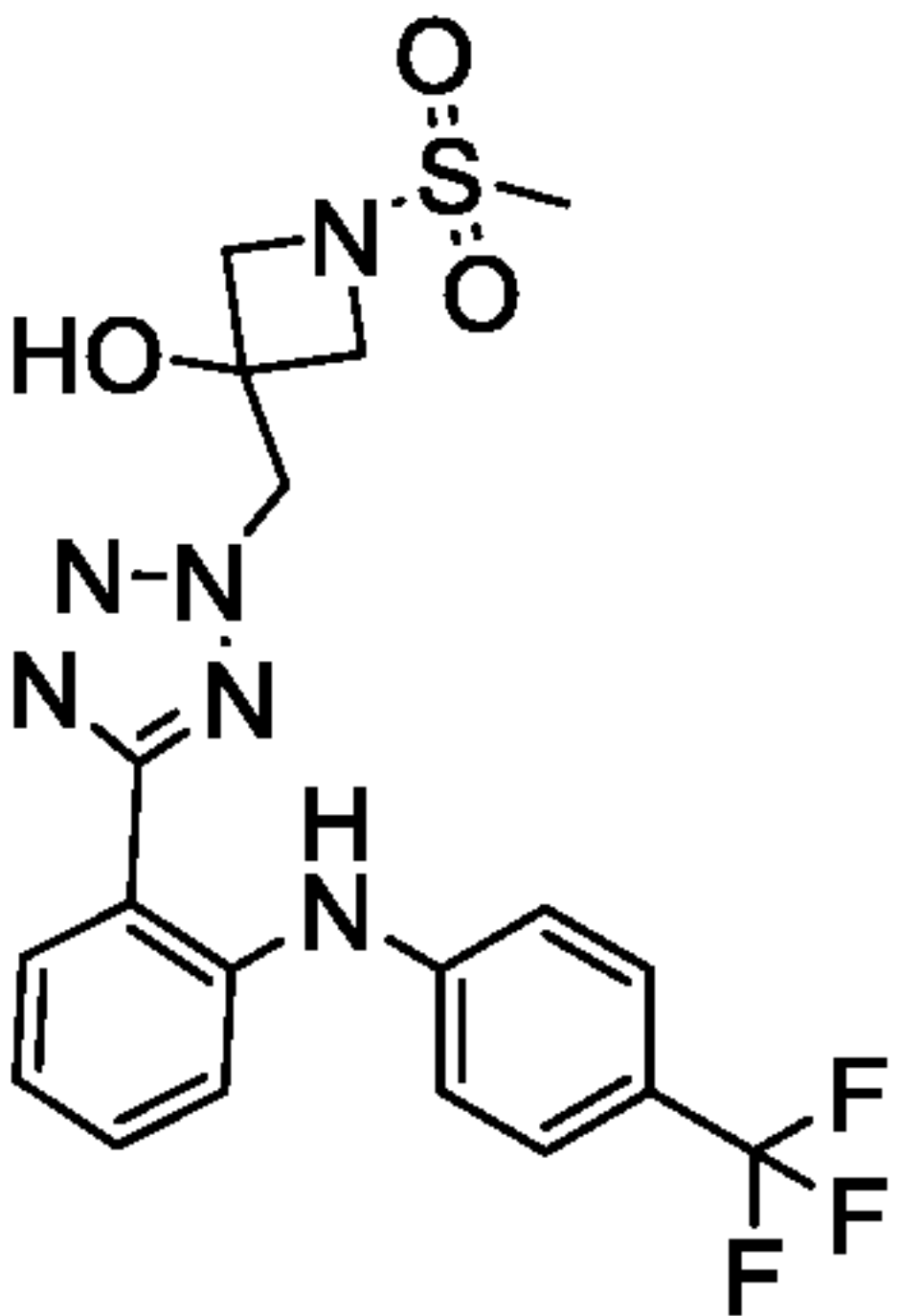
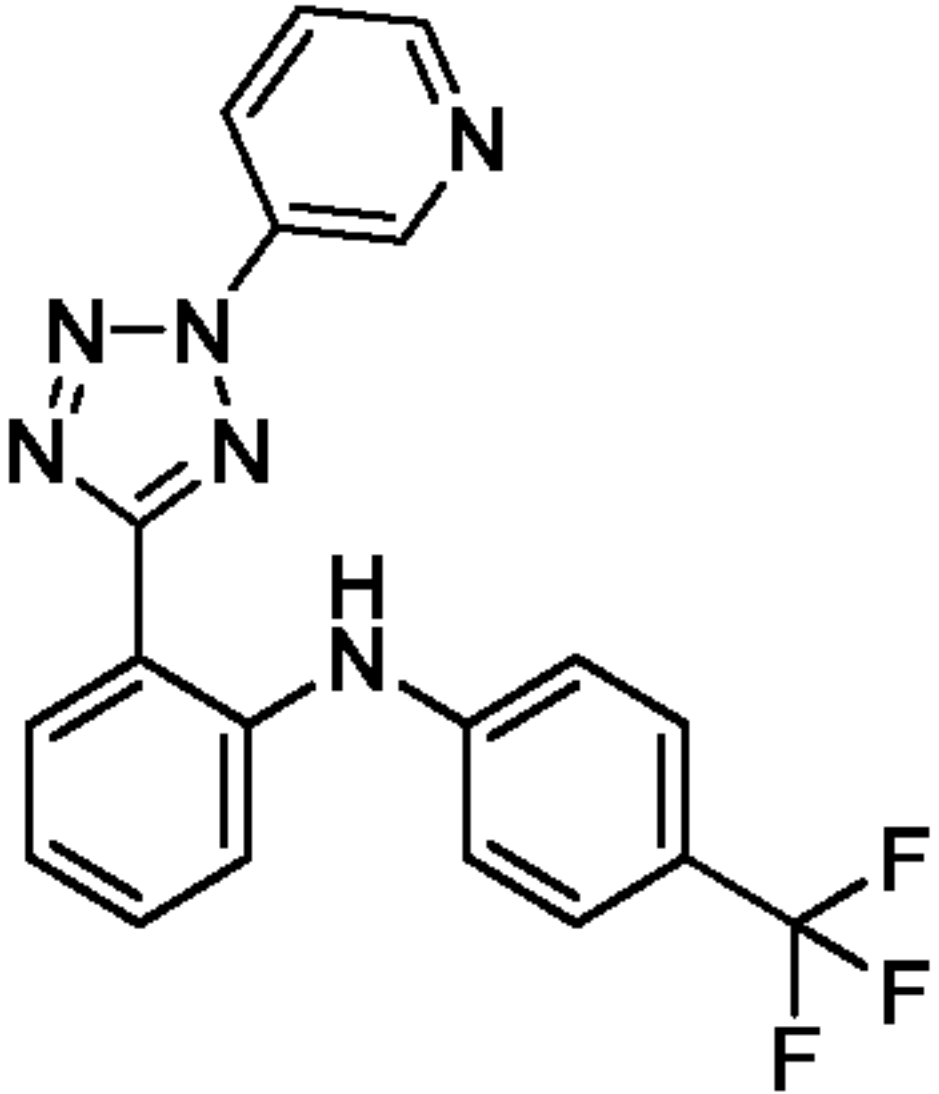
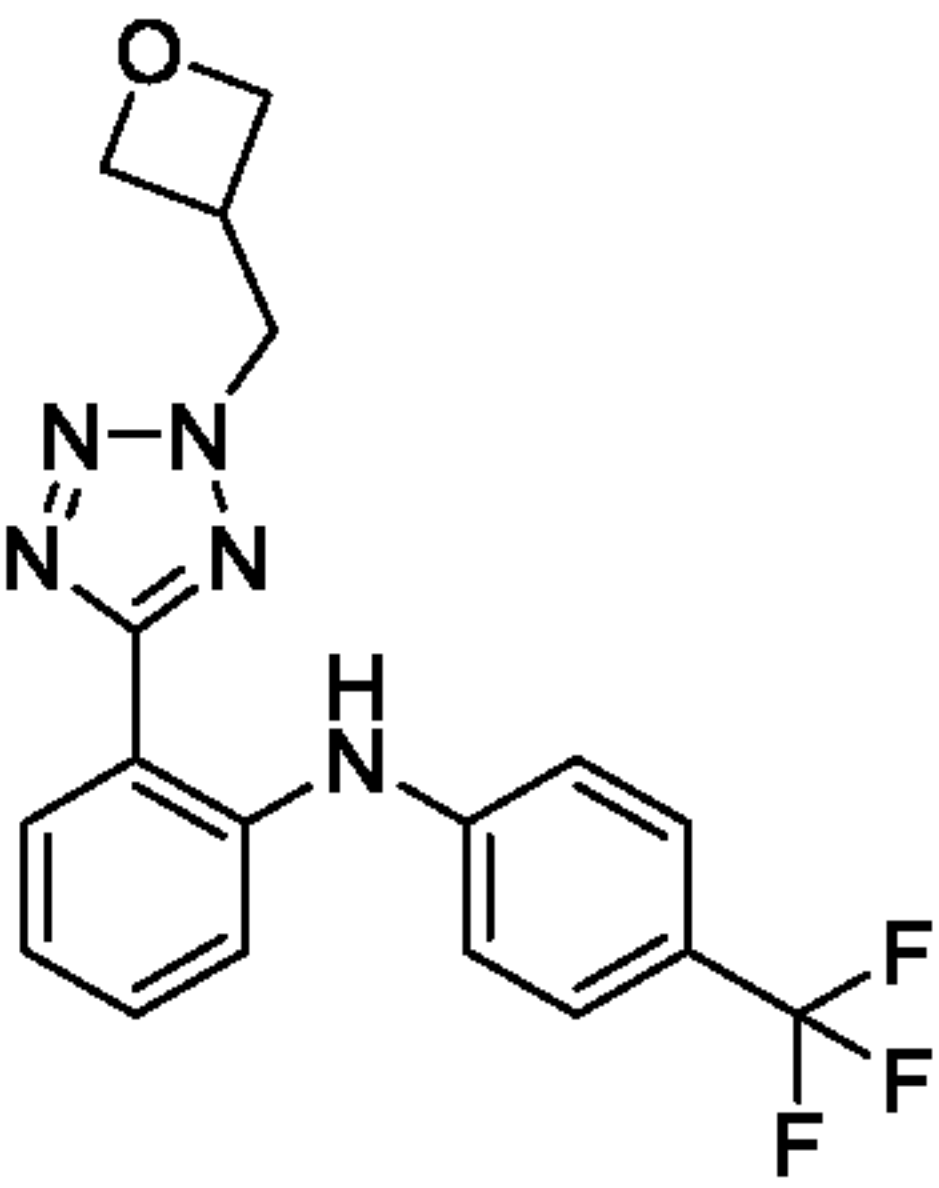
Compound No.	Structure	Name
137		2-(2-pyrimidin-5-yltetrazol-5-yl)-N-[4-(trifluoromethyl)phenyl]aniline
138		4-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]tetrahydropyran-4-ol
139		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)butan-2-ol
140		2-[2-(2-pyridyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline
141		3-methyl-1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]butan-2-ol

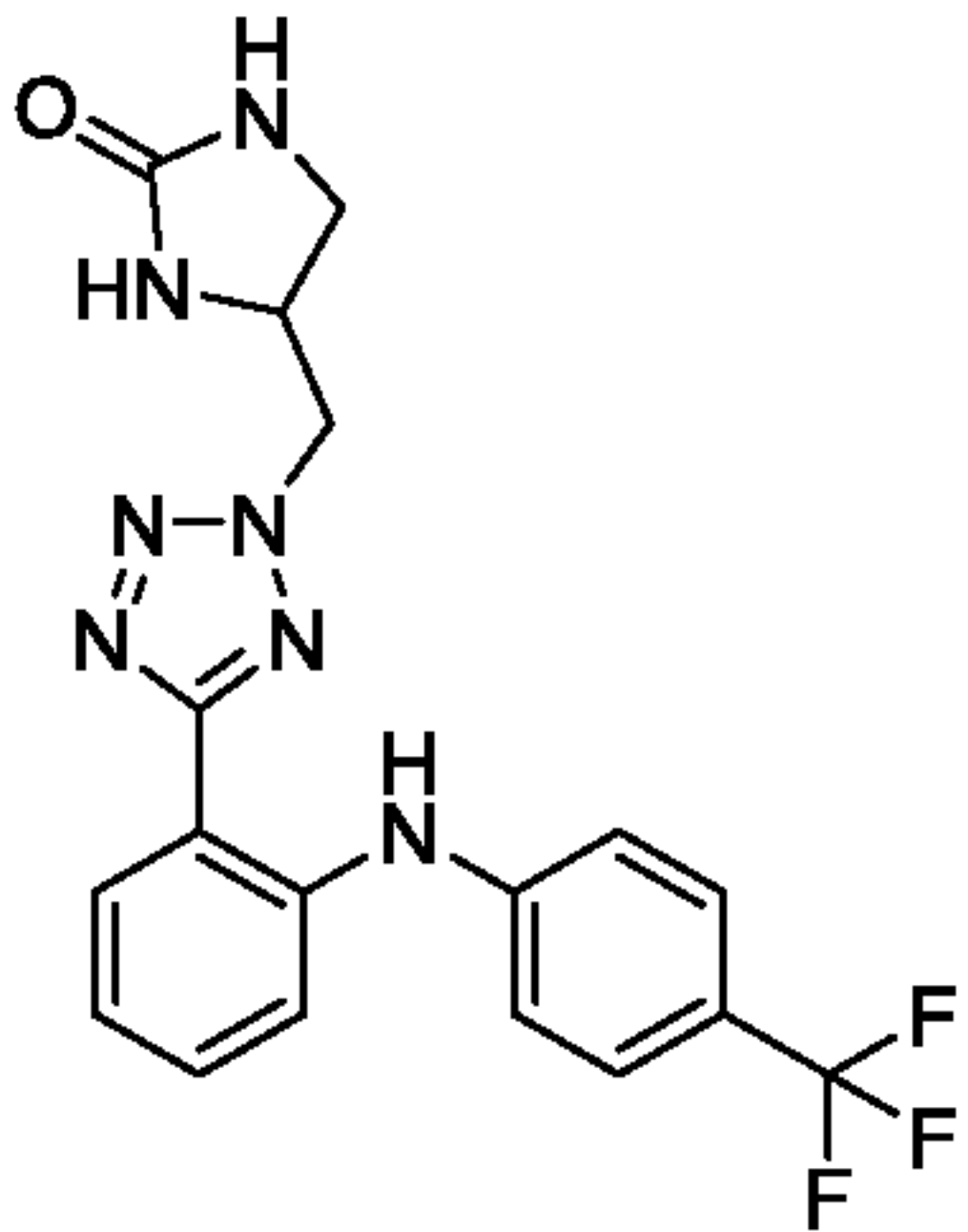
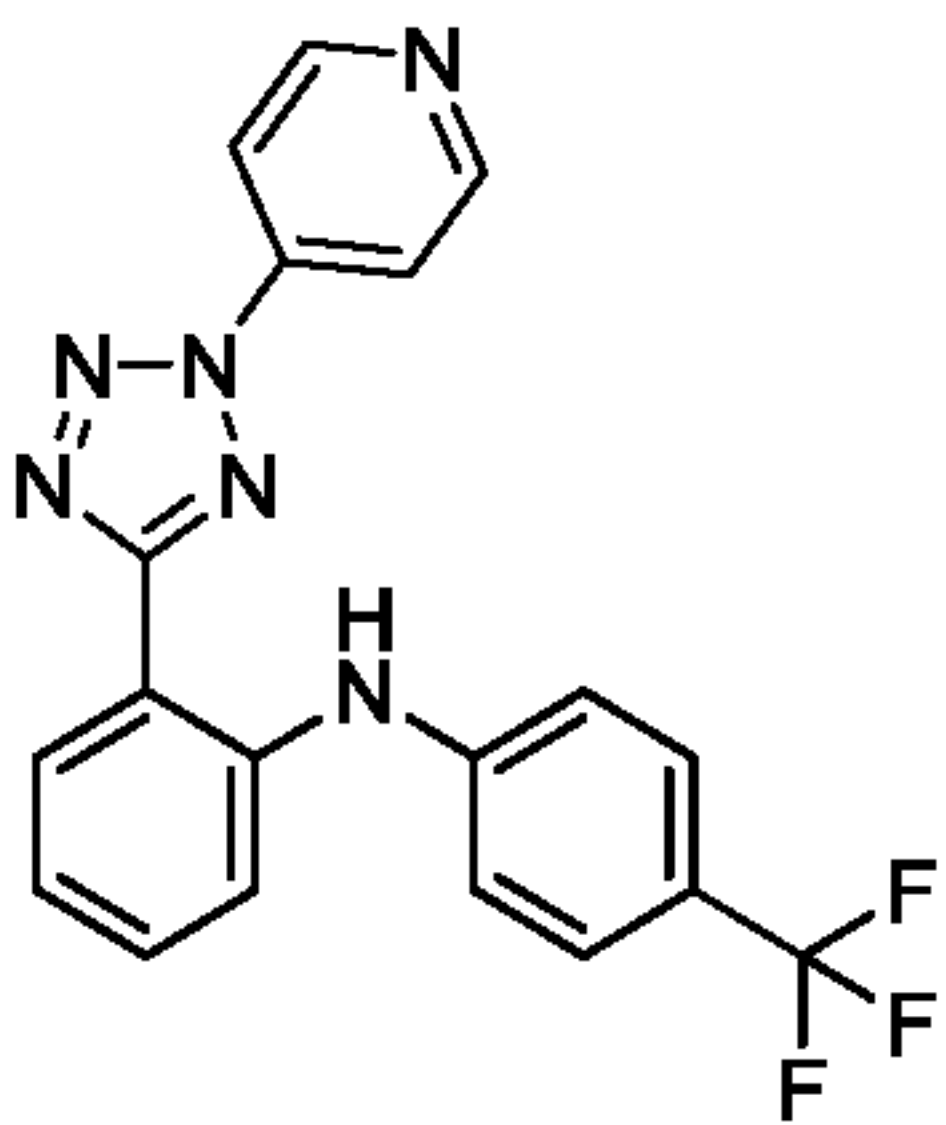
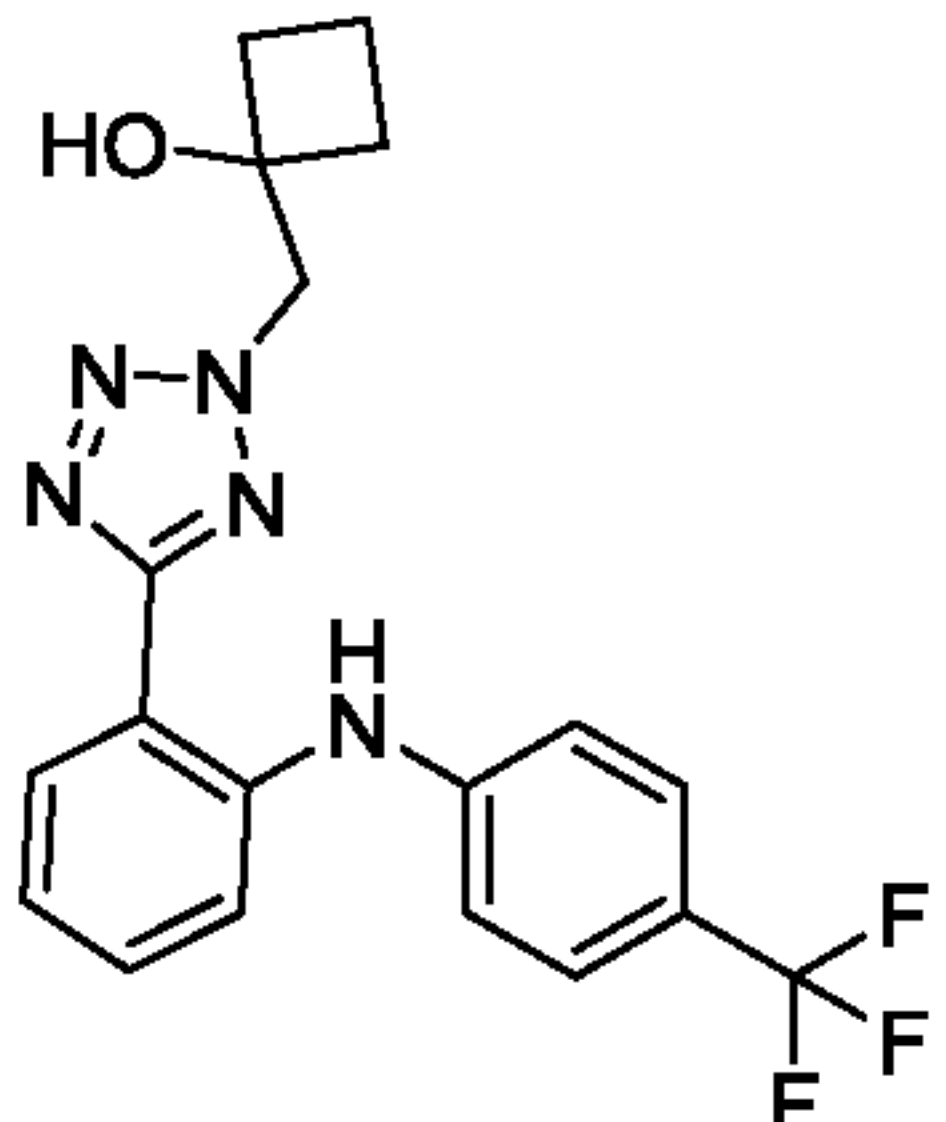
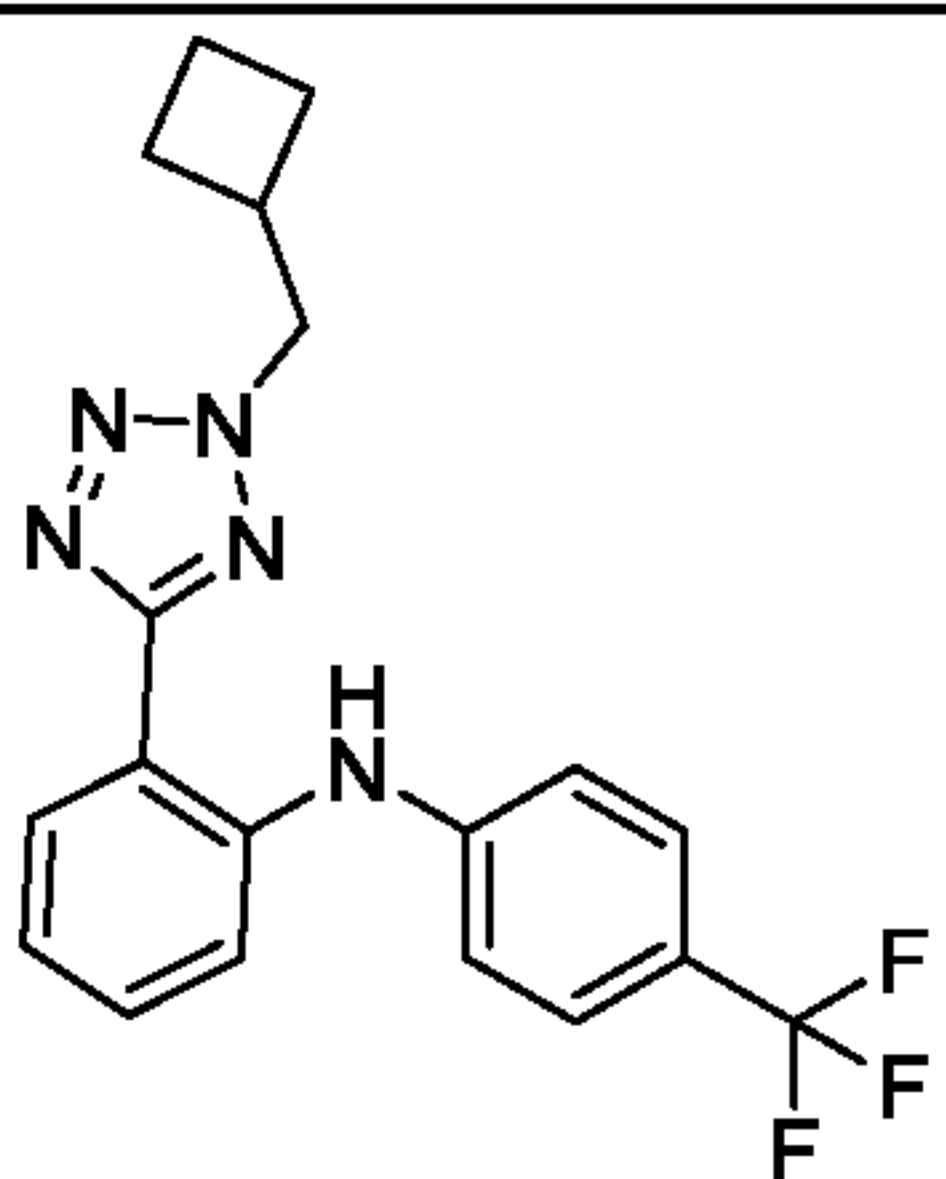
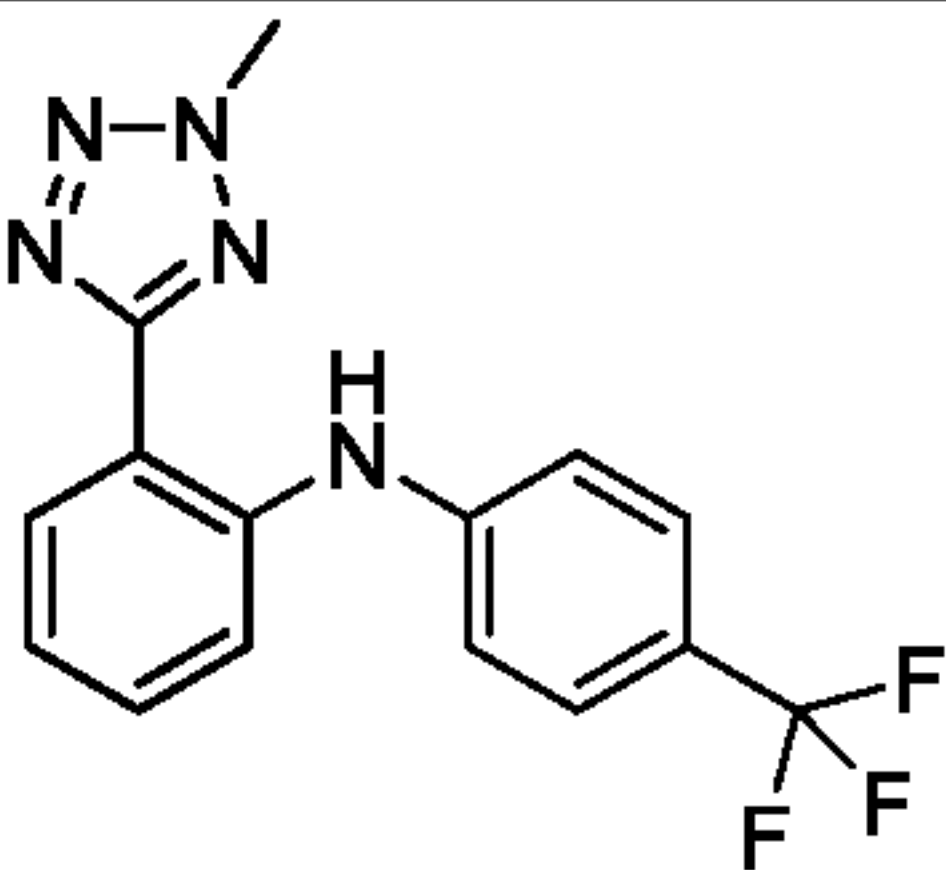
Compound No.	Structure	Name
142		3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]tetrahydropyran-3-ol
143		1-phenyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol
144		tert-butyl 3-hydroxy-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)pyrrolidine-1-carboxylate
145		1-(methylsulfonyl)-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)piperidin-3-ol
146		1-[4-hydroxy-4-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]-1-piperidyl]ethanone

Compound No.	Structure	Name
147		tert-butyl 3-hydroxy-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)piperidine-1-carboxylate
148		tert-butyl 3-hydroxy-3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]azetidine-1-carboxylate
149		1-methylsulfonyl-4-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]piperidin-4-ol;
150		1-phenyl-4-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]piperidin-4-ol
151		3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]tetrahydrofuran-3-ol

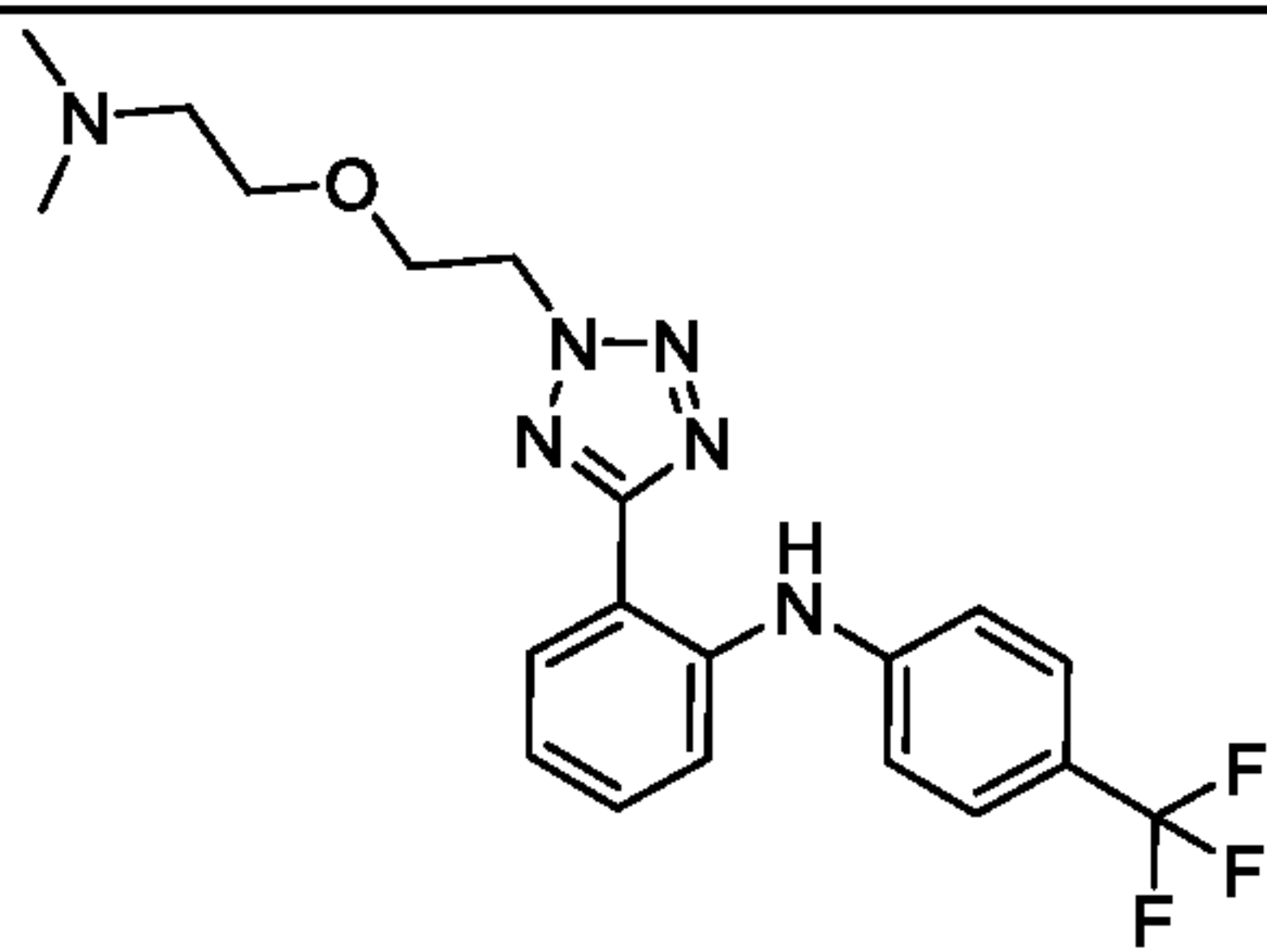
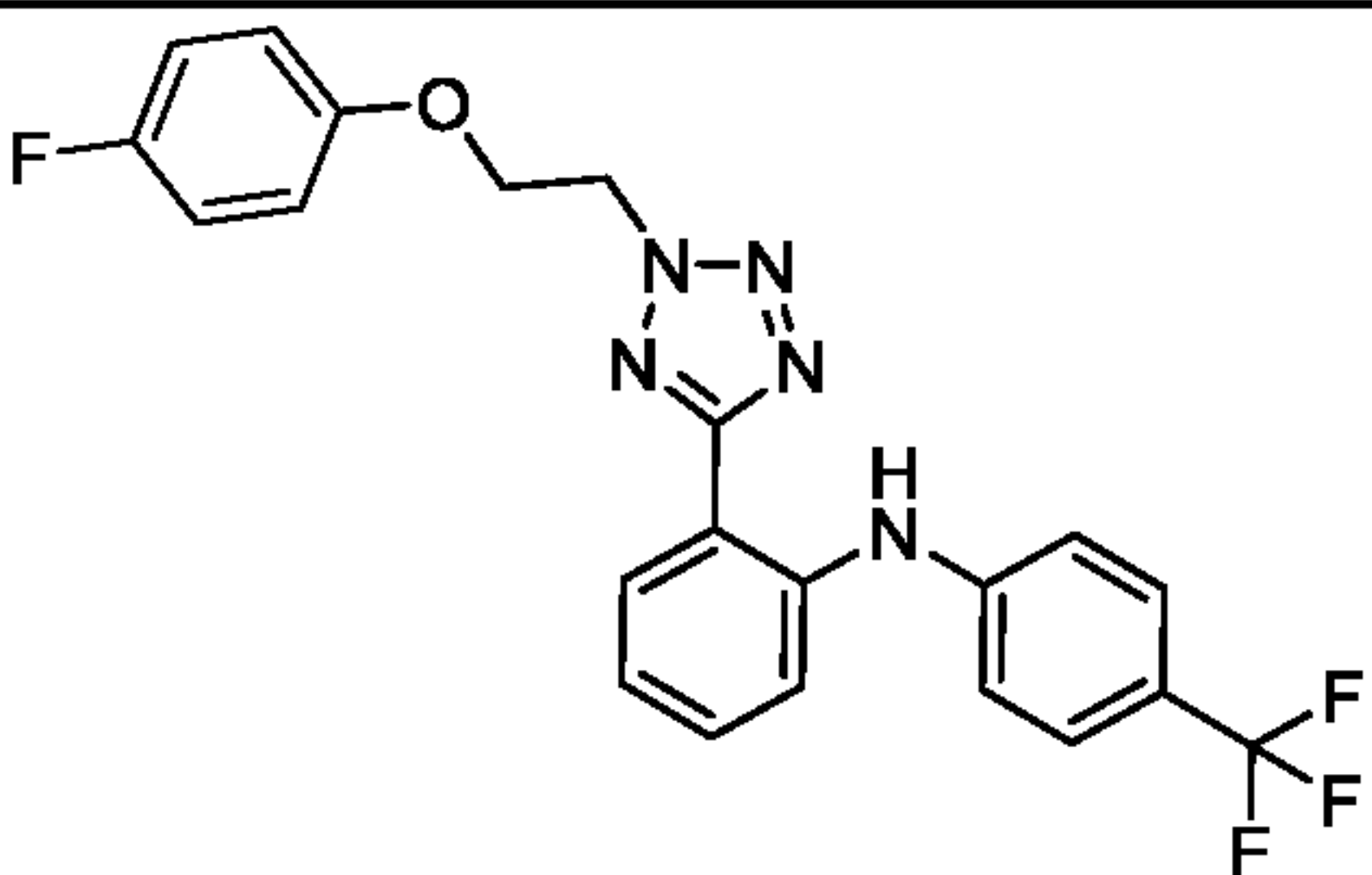
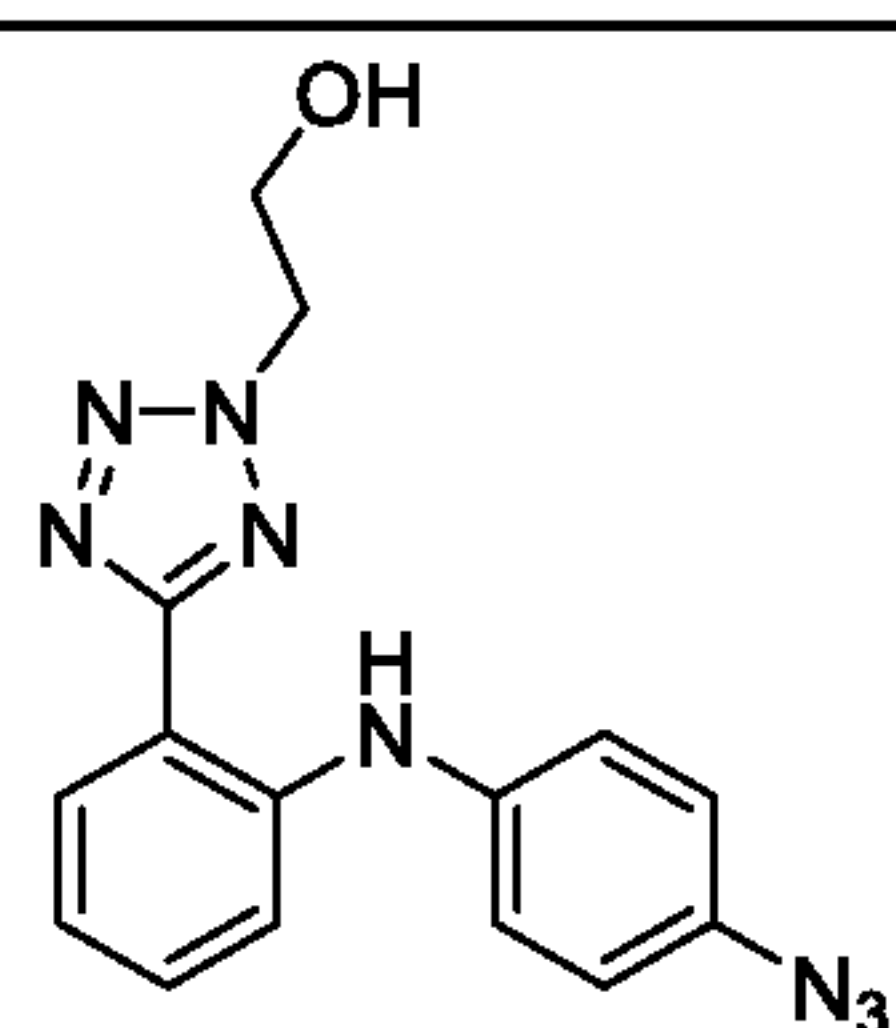
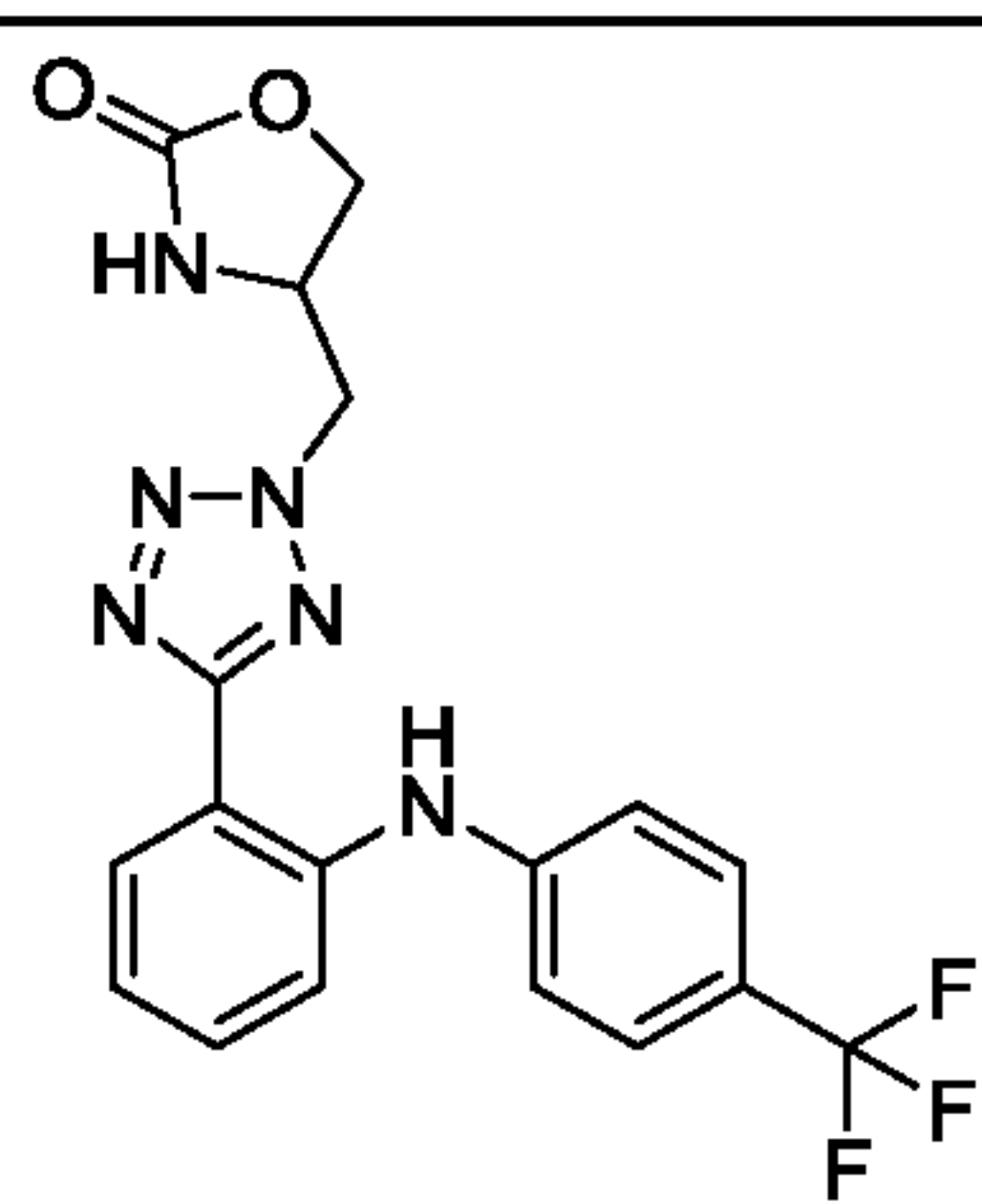
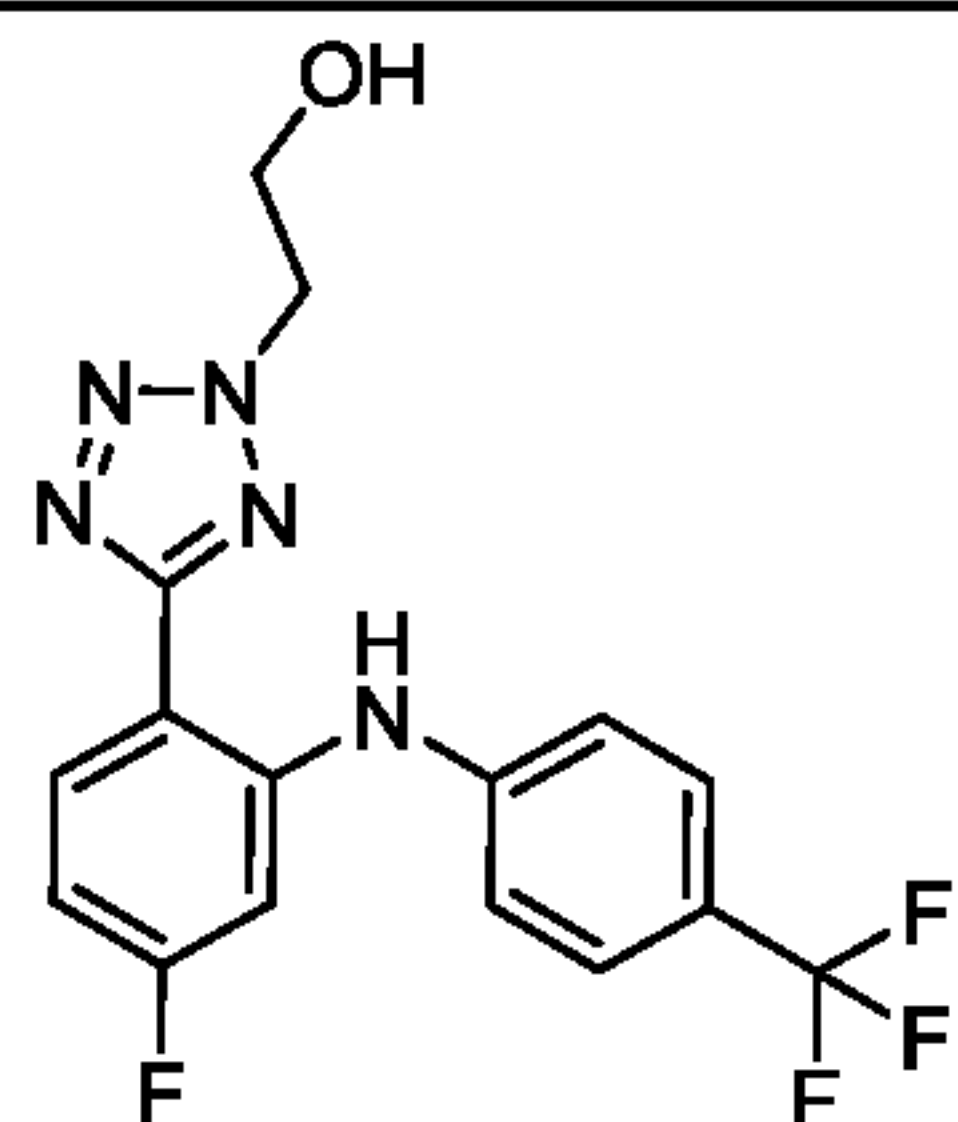
Compound No.	Structure	Name
152		1-((5-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)cyclopentanol
153		3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)pyrrolidin-3-ol
154		1-(3-hydroxy-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)pyrrolidin-1-yl)ethanone
155		1-(3-hydroxy-3-((5-(2-((4-(trifluoromethyl)phenyl) amino) phenyl) -2H-tetrazol-2-yl) methyl) piperidin-1-yl) ethanone
156		3-((5-(2-((4-(trifluoromethyl) phenyl) amino) phenyl)-2H-tetrazol-2-yl) methyl) piperidin-3-ol

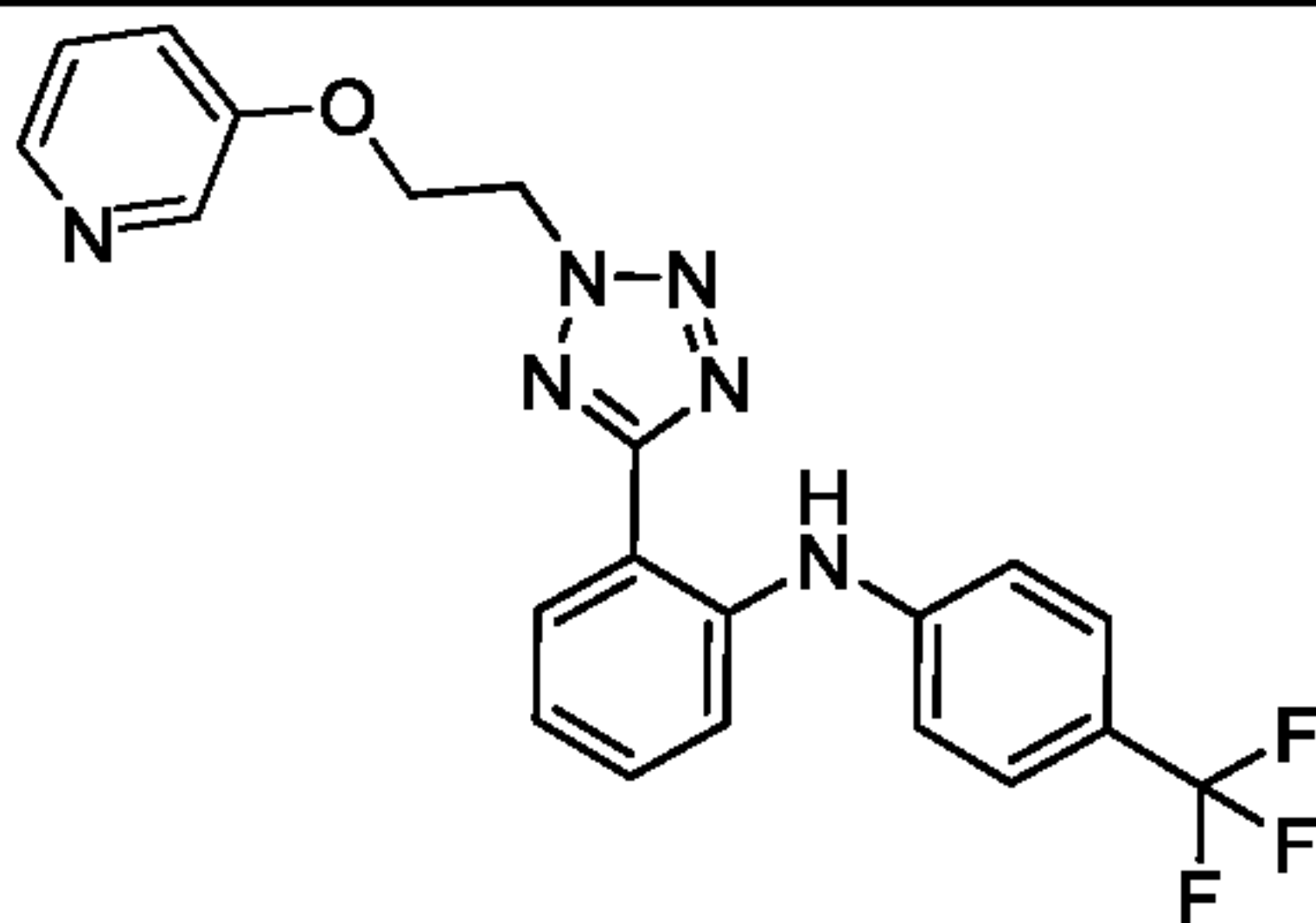
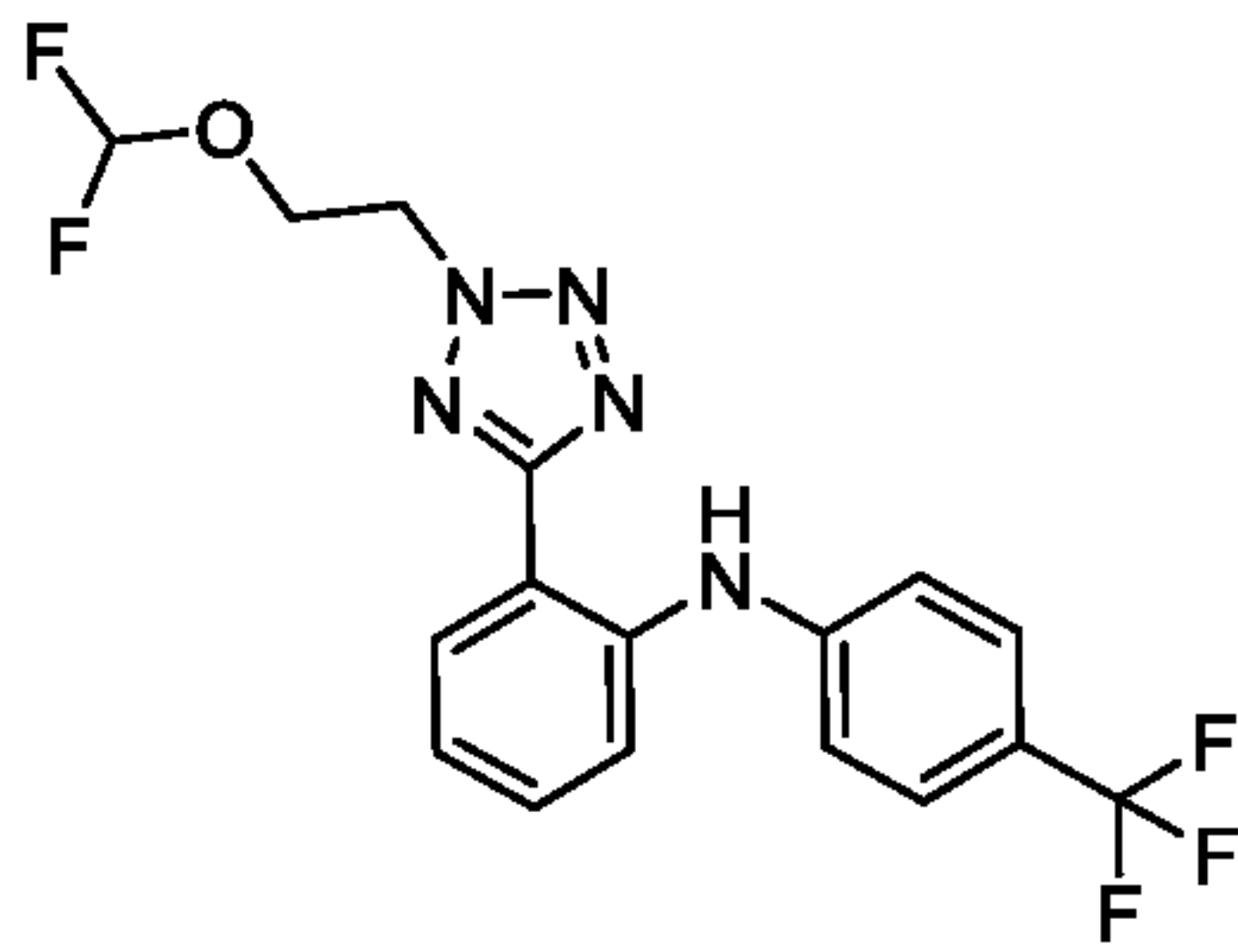
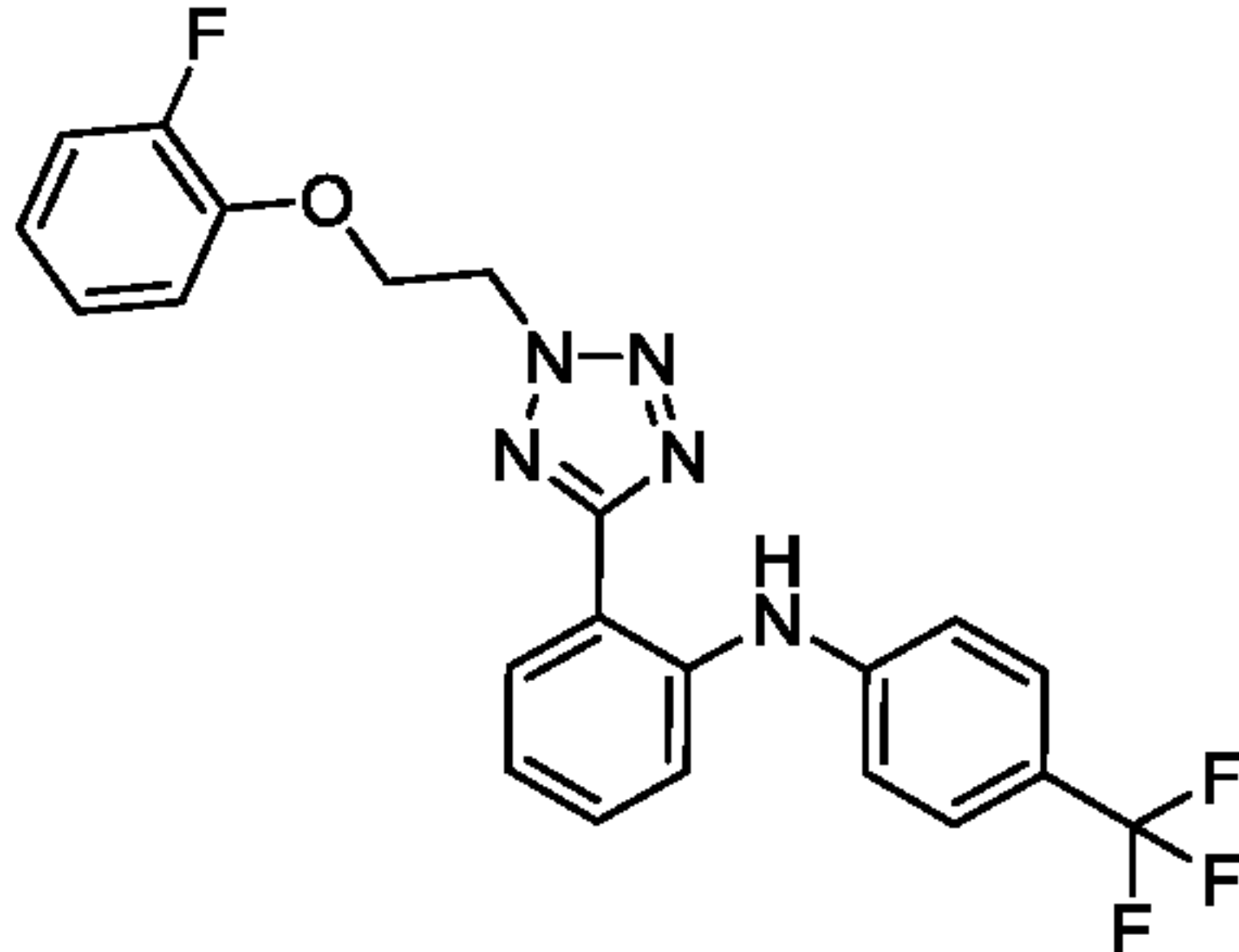
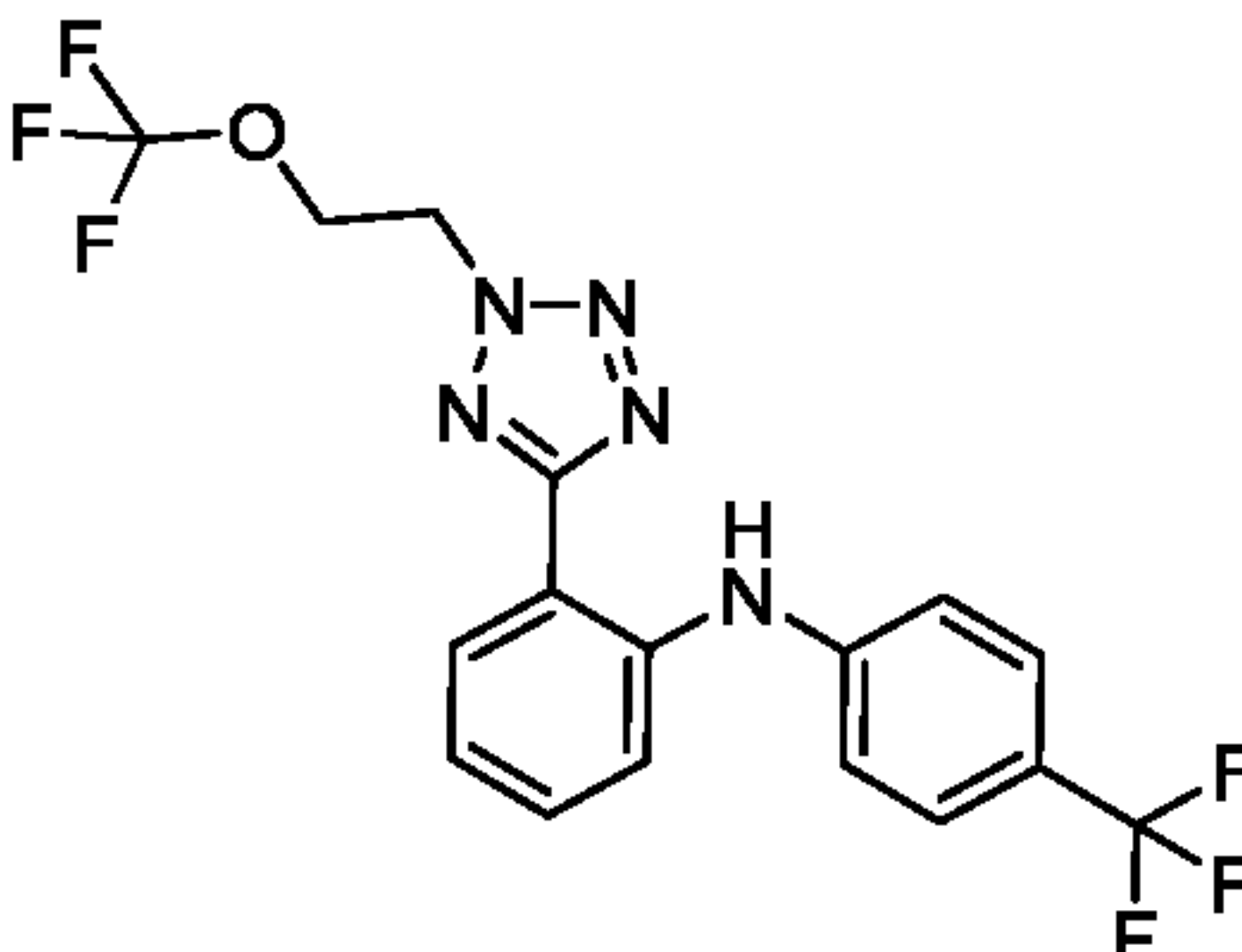
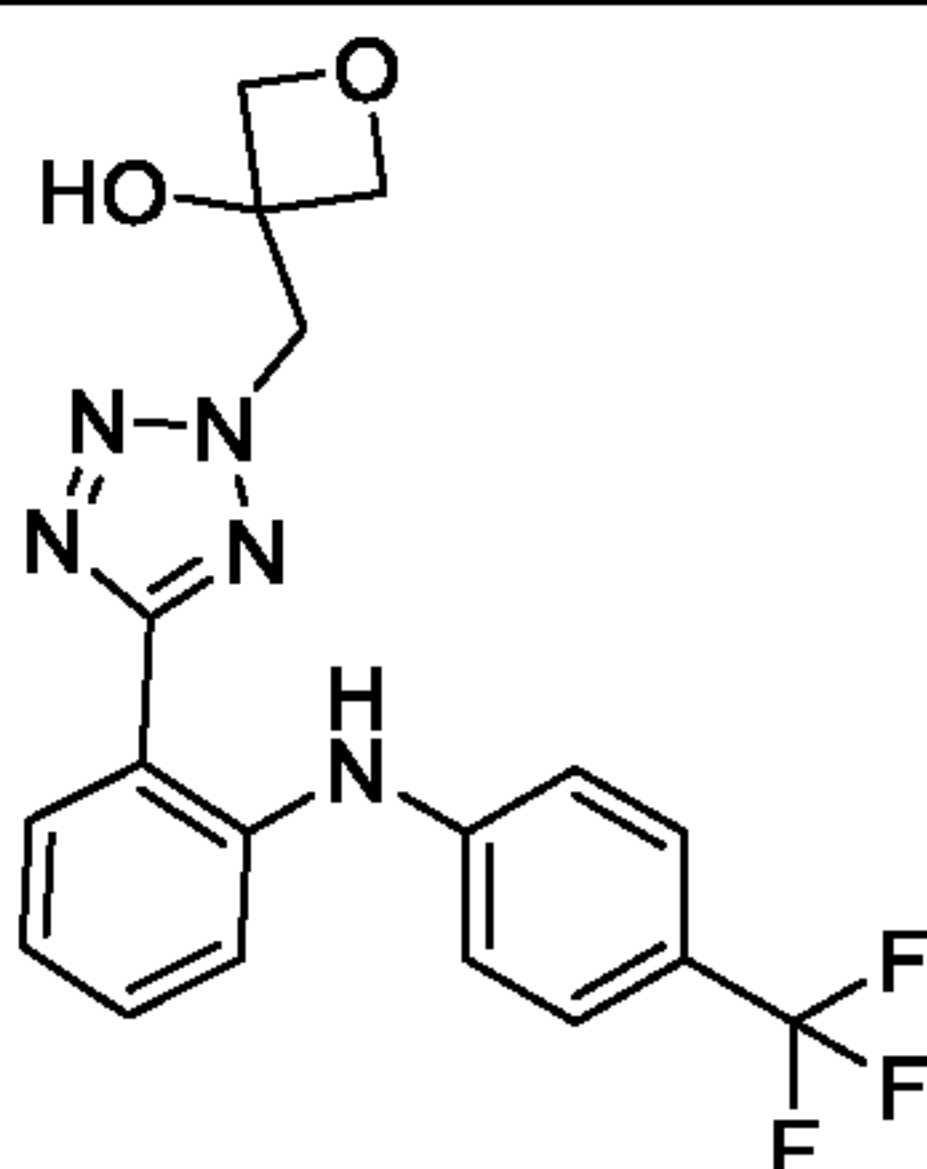
Compound No.	Structure	Name
157		3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]azetidin-3-ol
158		(R)-4-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)oxazolidin-2-one
159		1-(methylsulfonyl)-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)pyrrolidin-3-ol
160		[1-methylsulfonyl-3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]azetidin-3-yl] methanesulfonate
161		1-[3-hydroxy-3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]azetidin-1-yl]ethanone

Compound No.	Structure	Name
162		[1-acetyl-3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]azetidin-3-yl] acetate
163		1-phenyl-3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]azetidin-3-ol
164		1-methylsulfonyl-3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]azetidin-3-ol
165		2-[2-(3-pyridyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline
166		2-(2-(oxetan-3-ylmethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

Compound No.	Structure	Name
167		4-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)imidazolidin-2-one
168		2-[2-(4-pyridyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline
169		1-((5-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)cyclobutanol
170		2-(2-(Cyclobutylmethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
171		2-(2-methyltetrazol-5-yl)-N-[4-(trifluoromethyl)phenyl]aniline

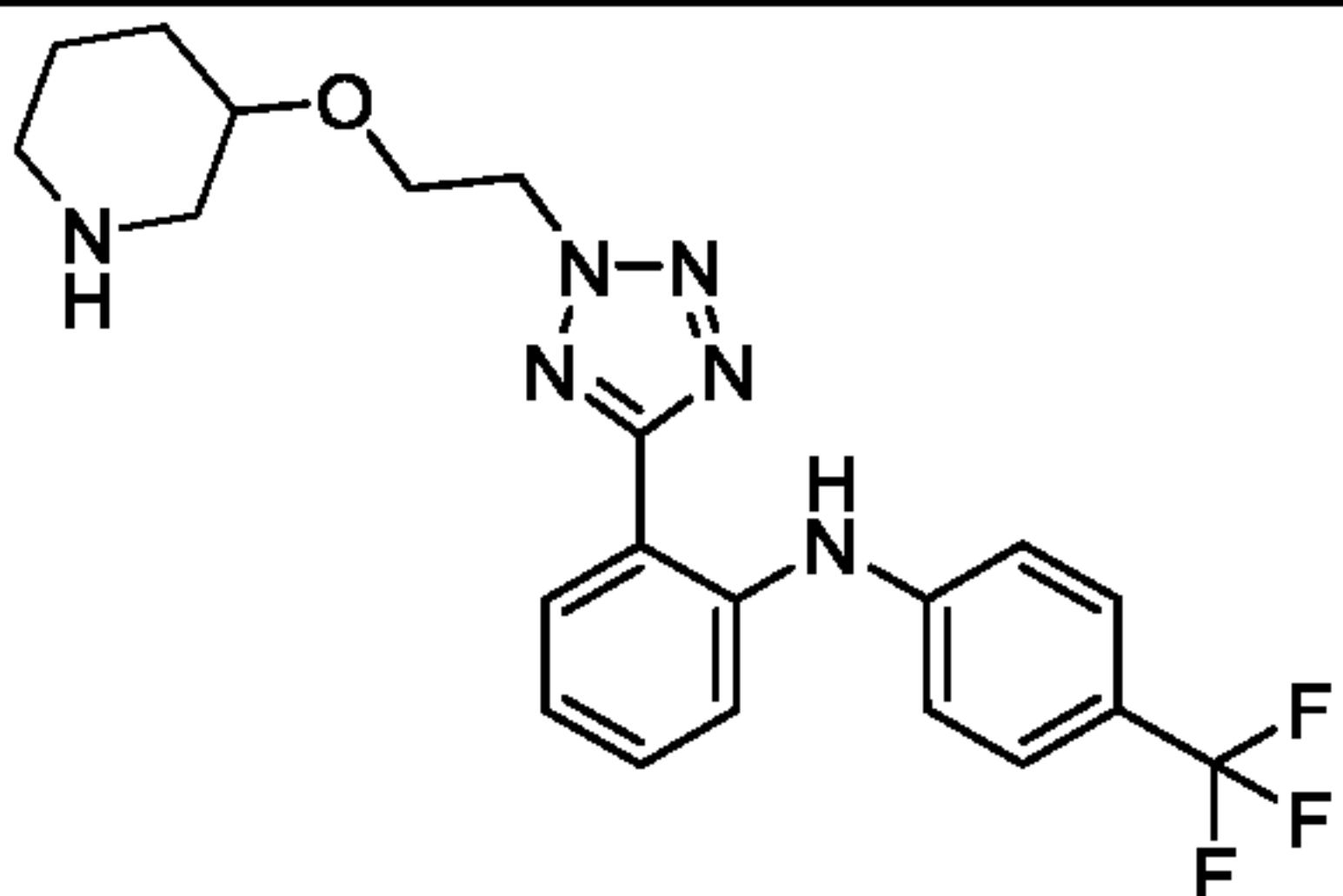
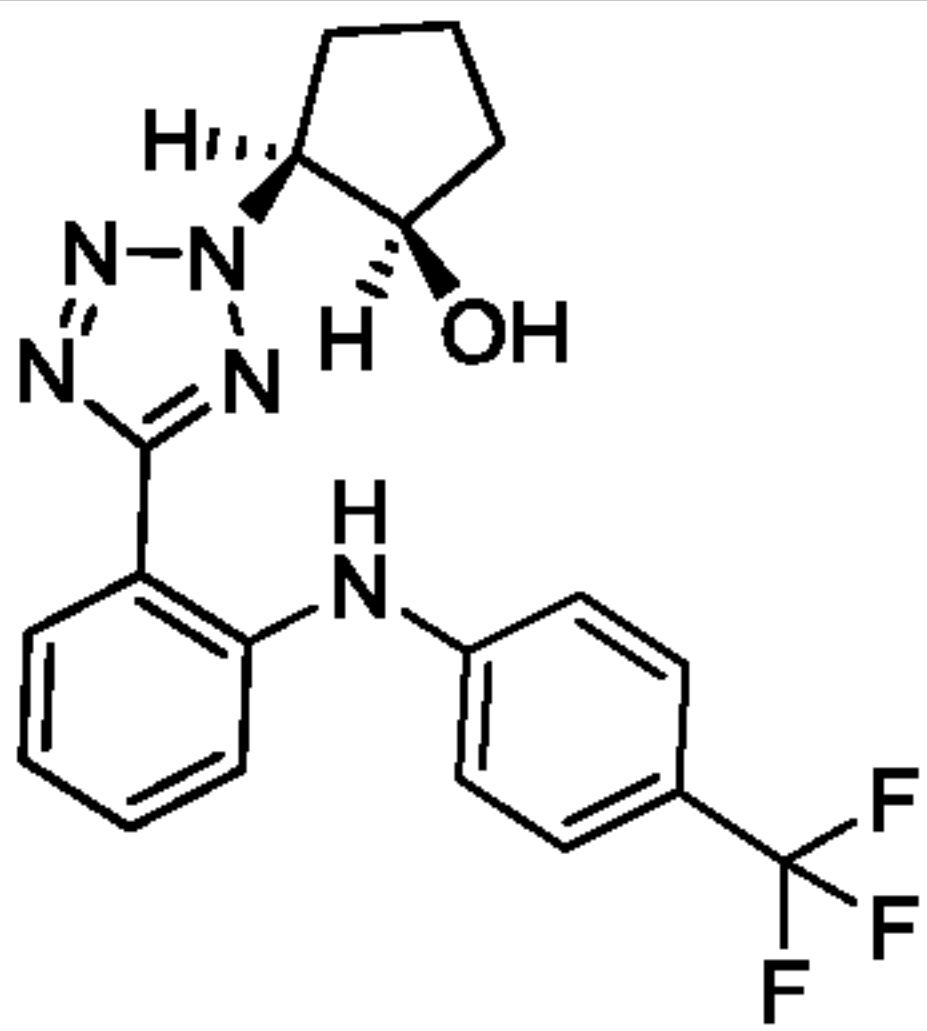
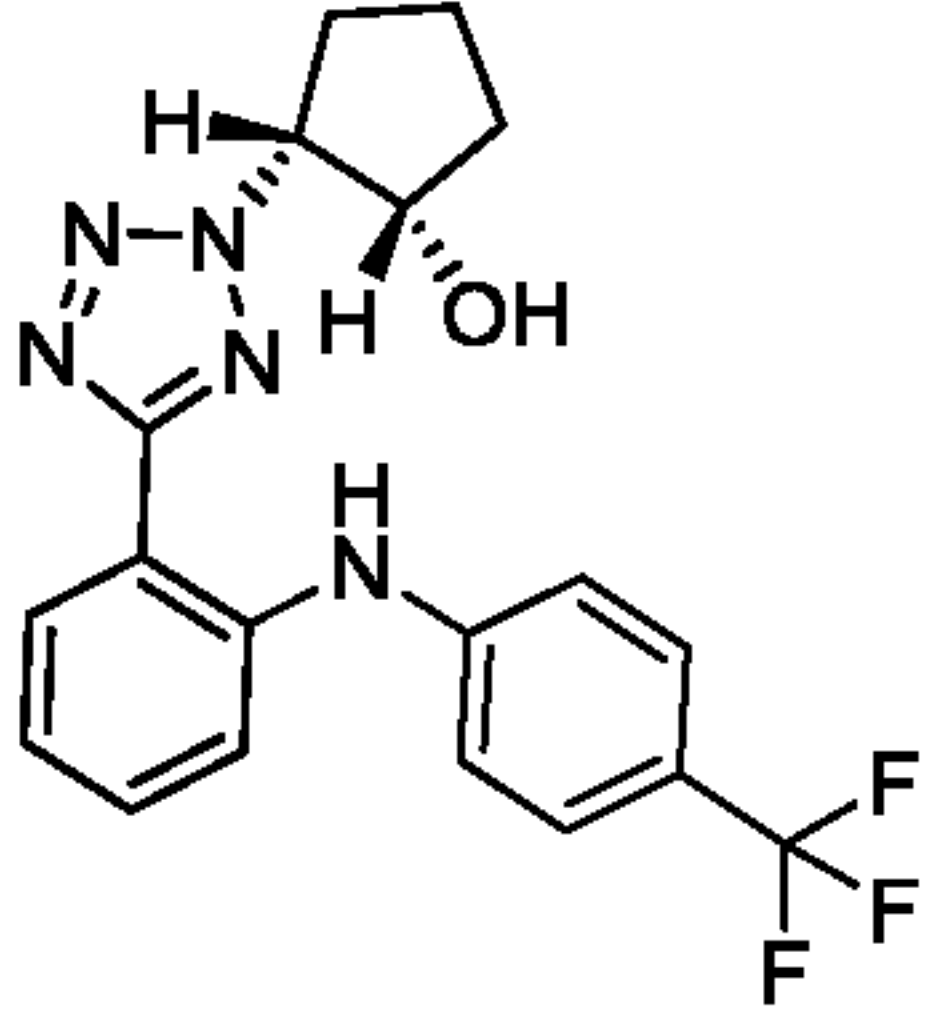
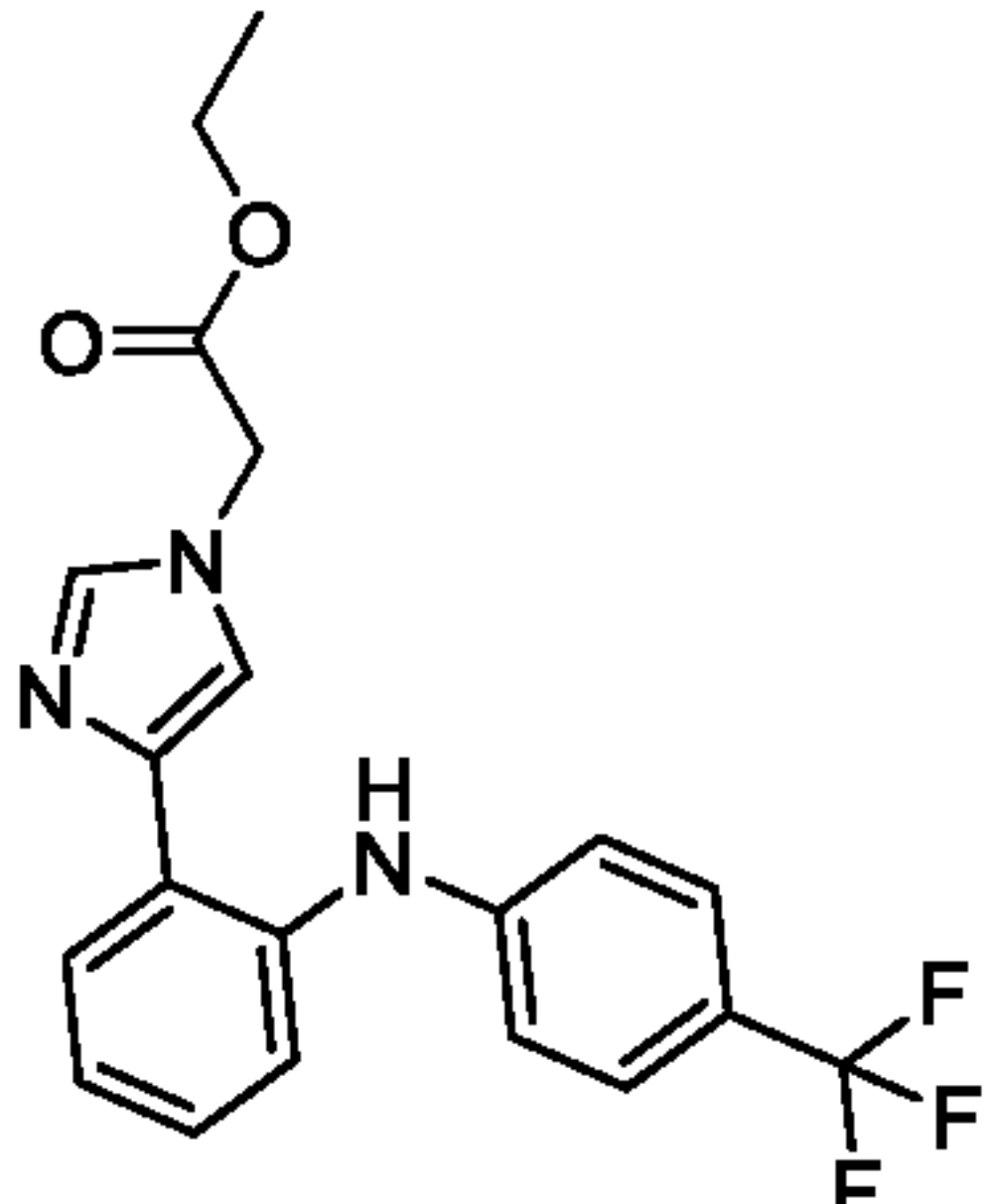
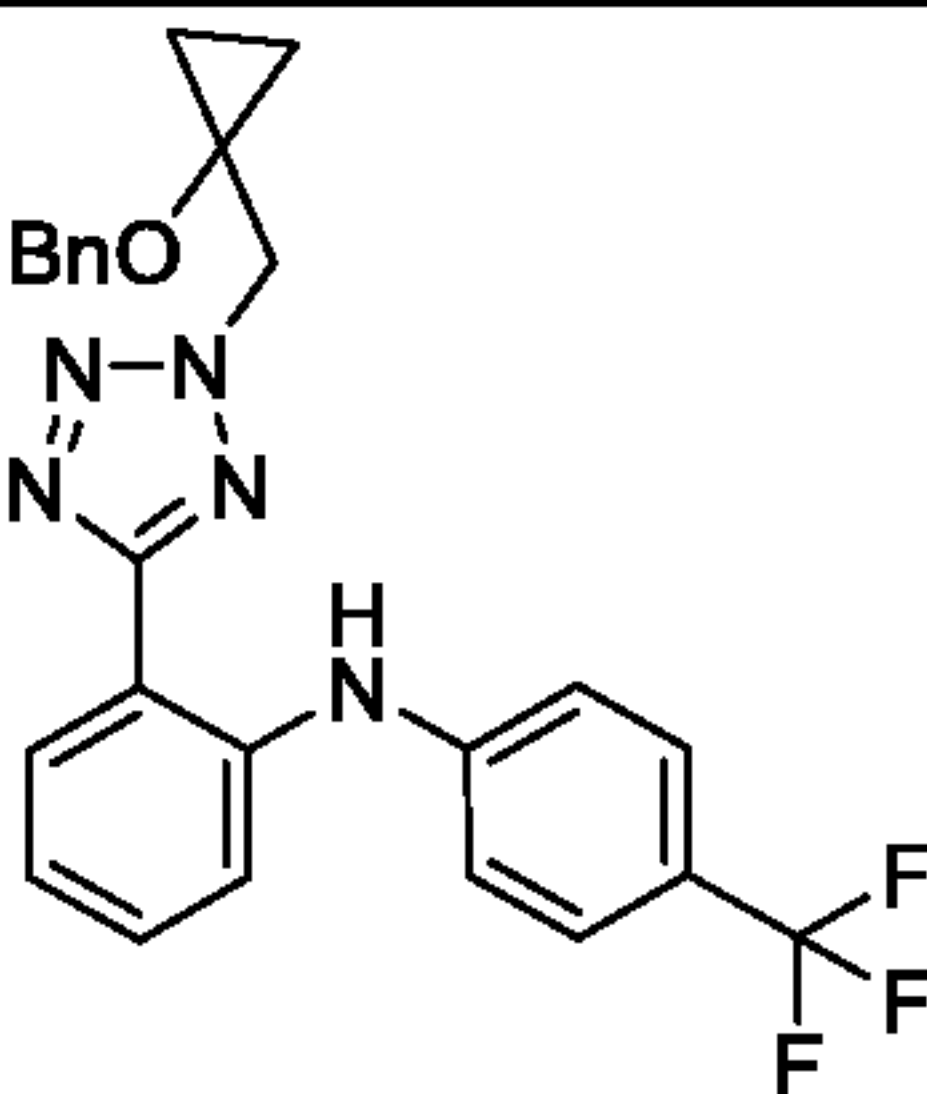
Compound No.	Structure	Name
172		1-phenyl-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)pyrrolidin-3-ol
173		2-(2-(2-methoxyethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
174		2-(2-(2-phenoxyethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
175		2-[5-[5-fluoro-2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol
176		1-phenyl-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)piperidin-3-ol

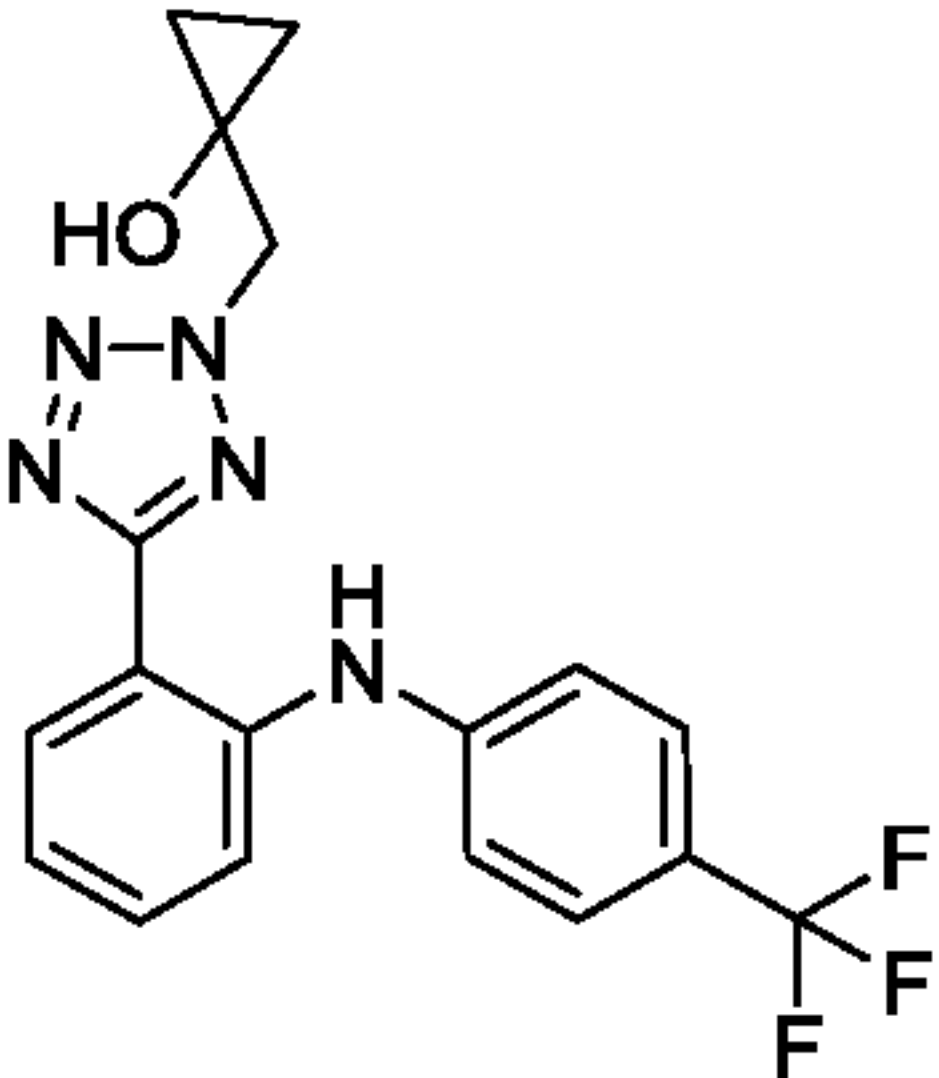
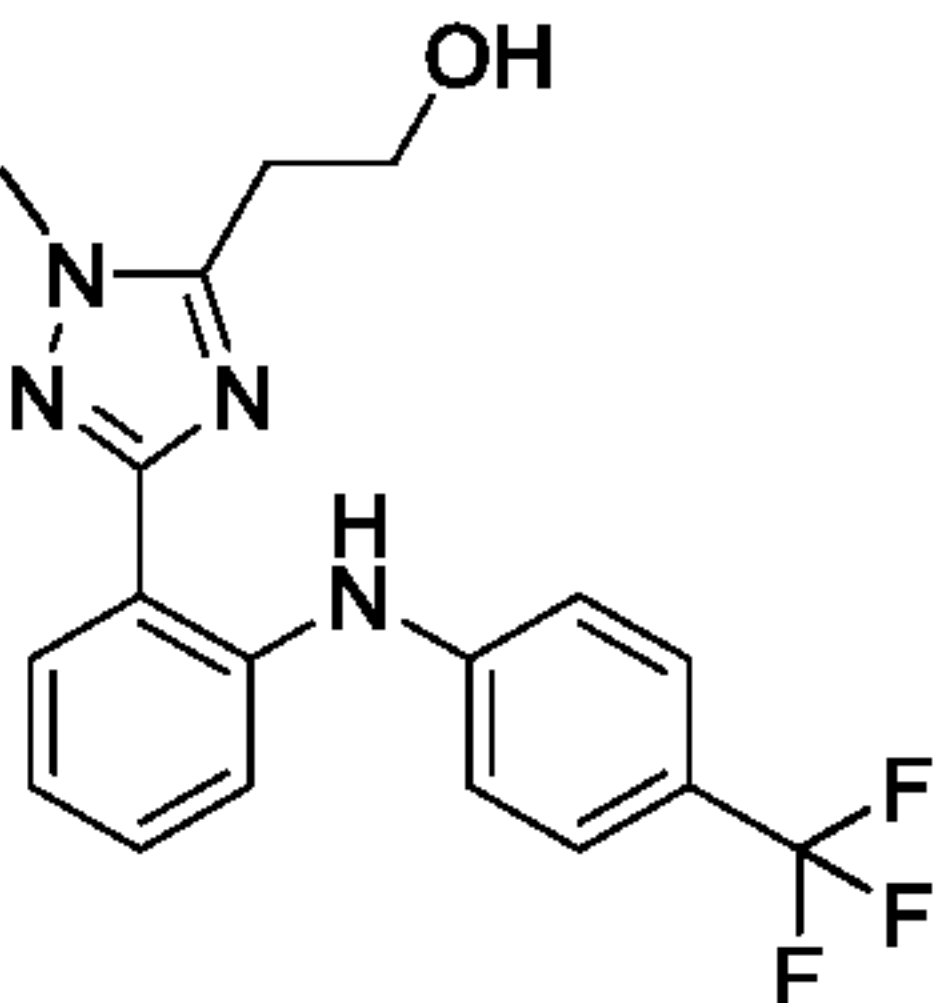
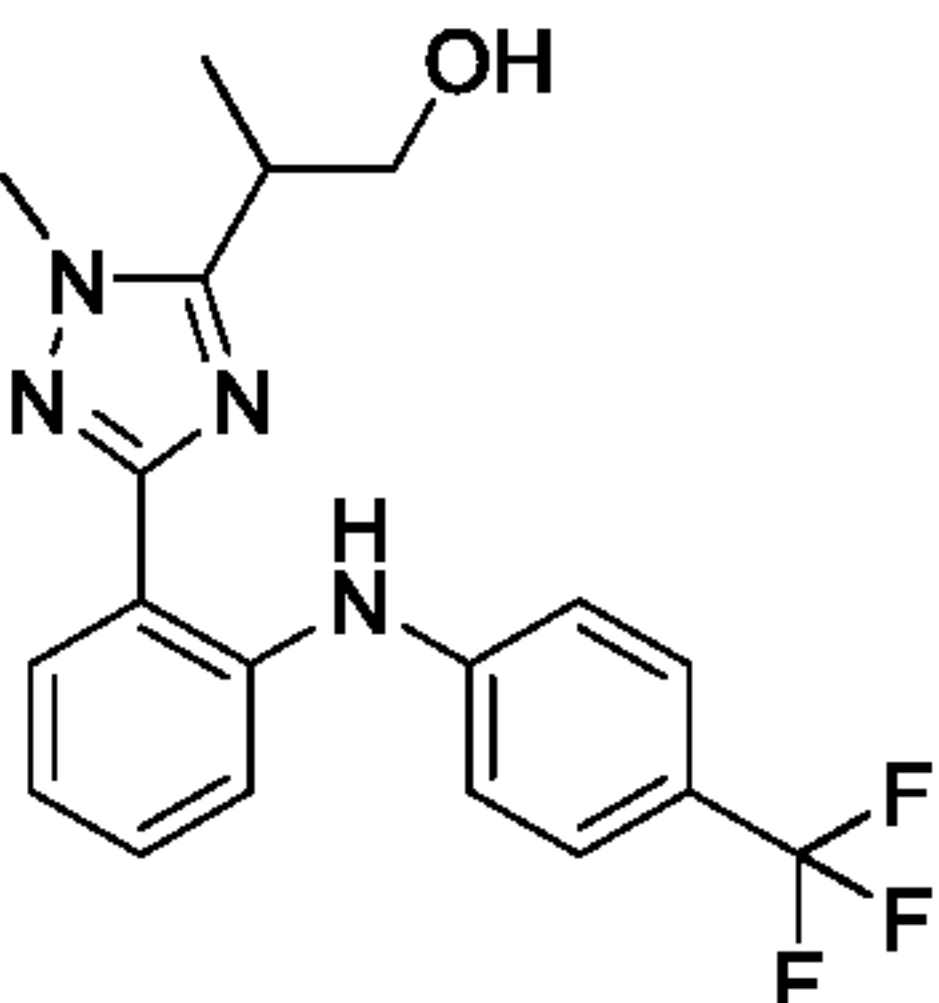
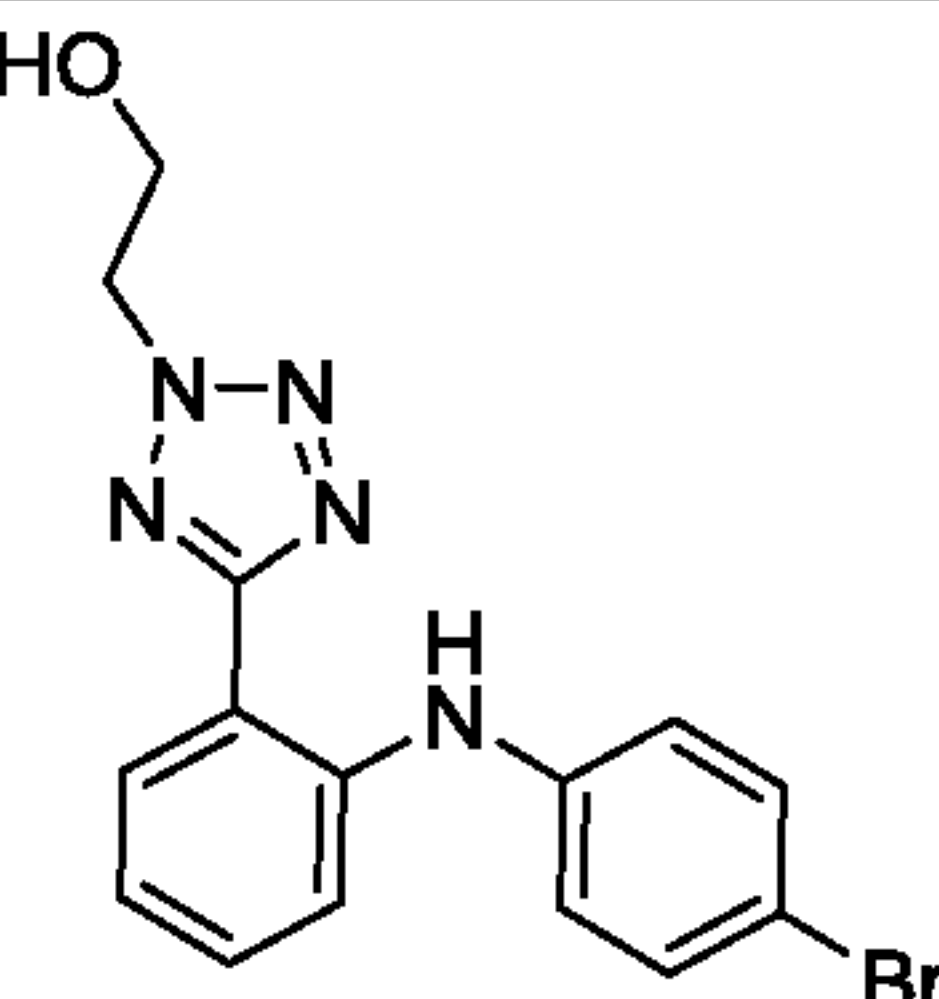
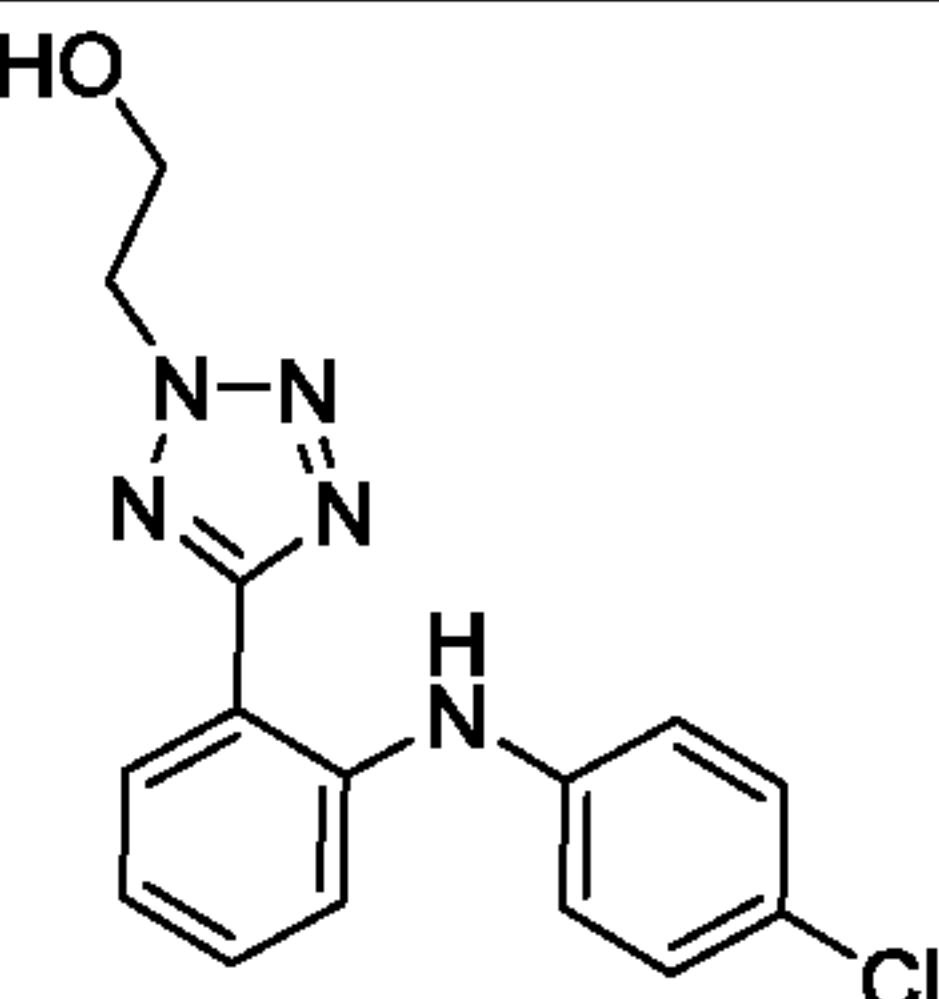
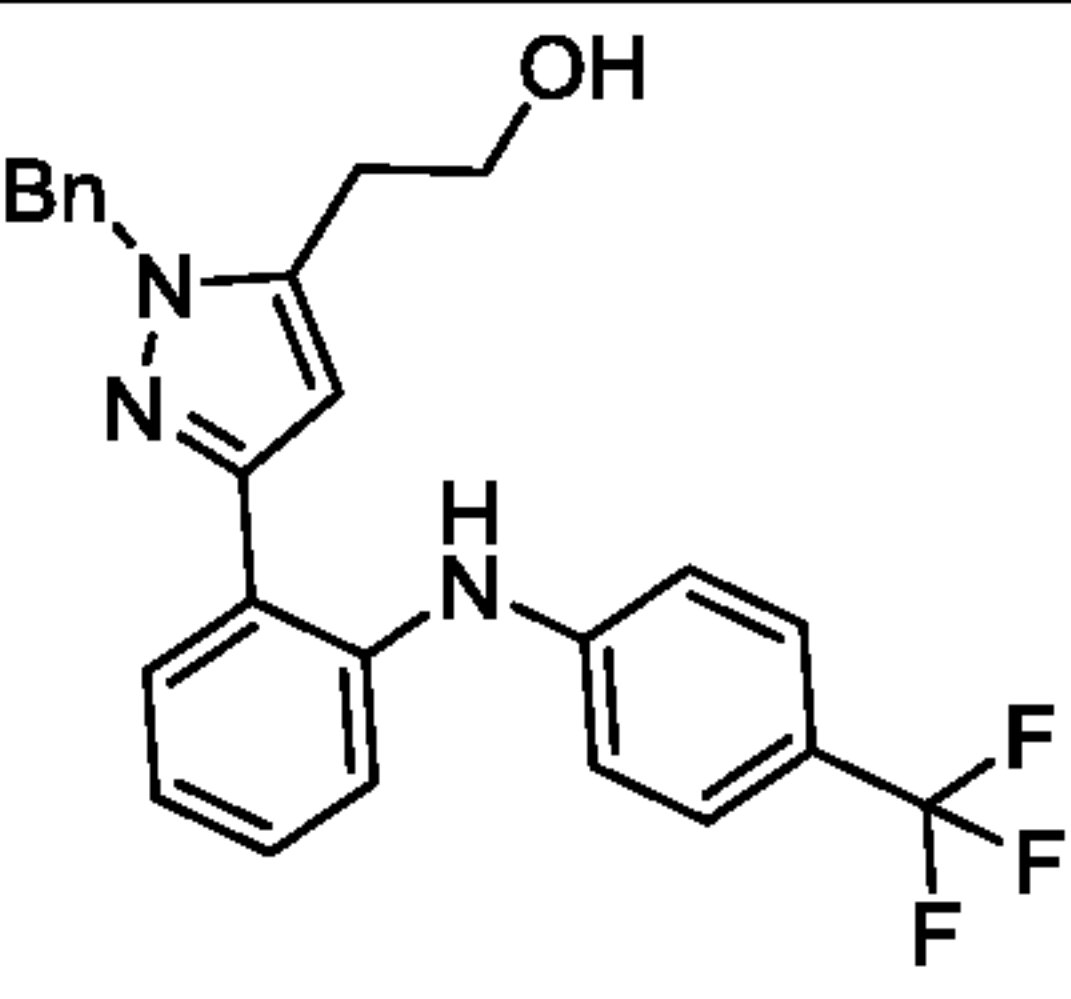
Compound No.	Structure	Name
177		2-(2-(2-(2-(dimethylamino)ethoxy)ethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
178		2-[2-[2-(4-fluorophenoxy)ethyl]tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline
179		2-[5-[2-(4-azidoanilino)phenyl]tetrazol-2-yl]ethanol
180		4-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)oxazolidin-2-one
181		2-[5-[4-fluoro-2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol

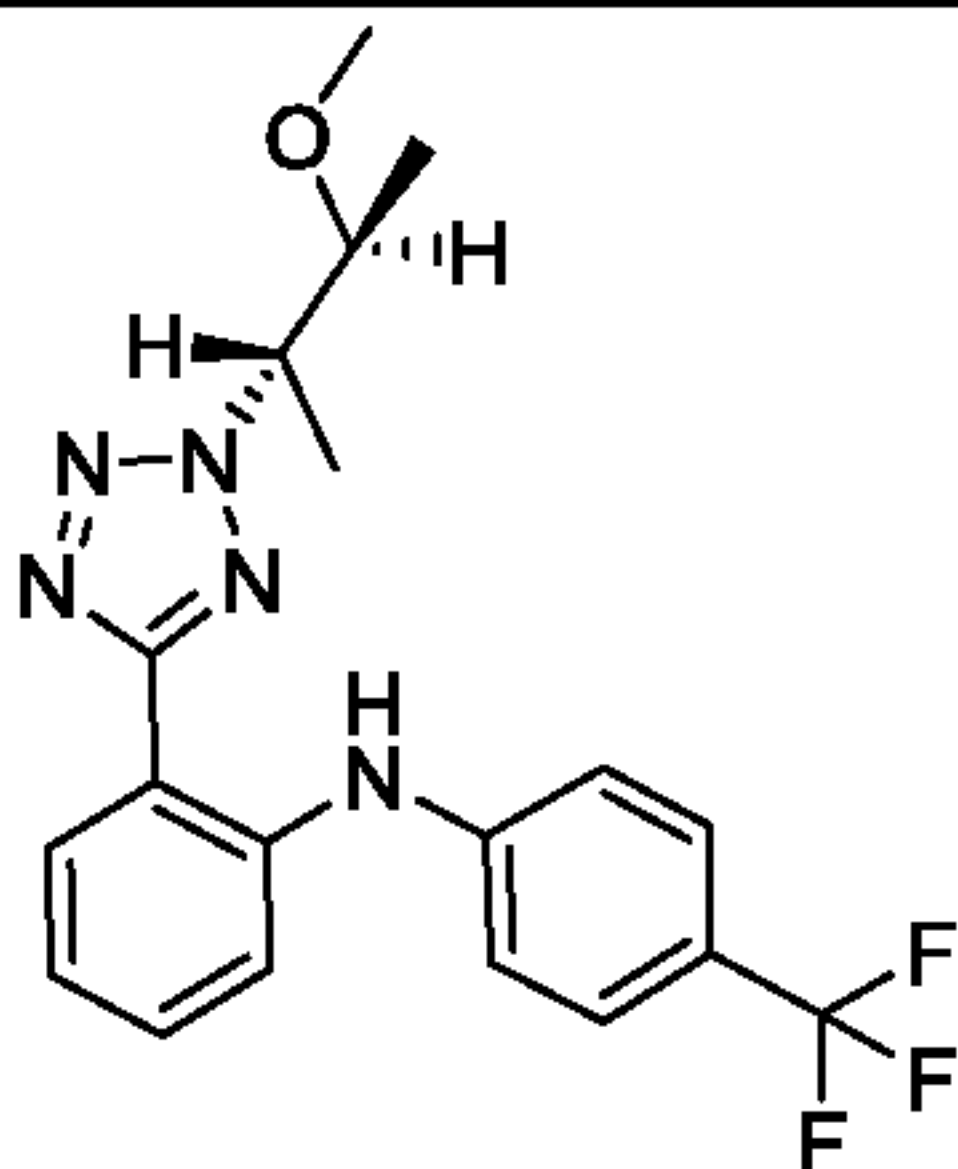
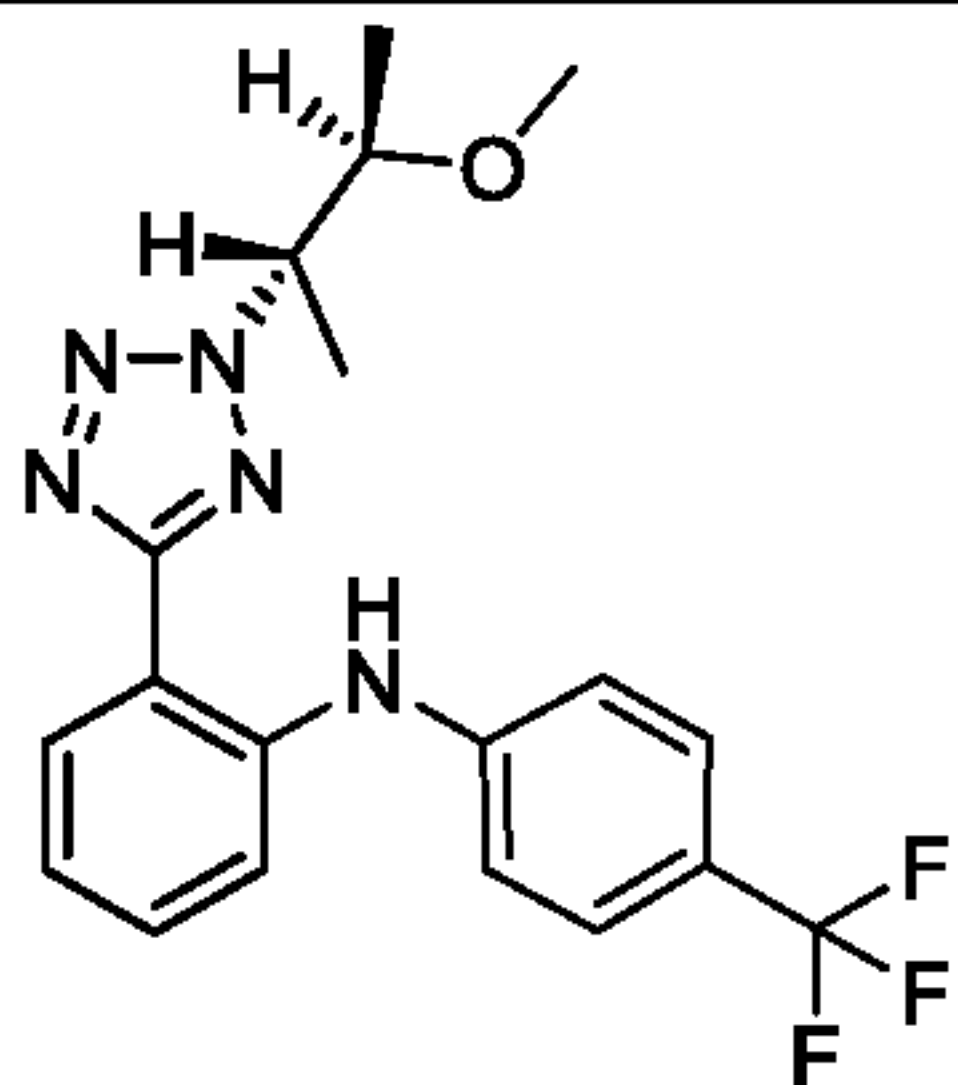
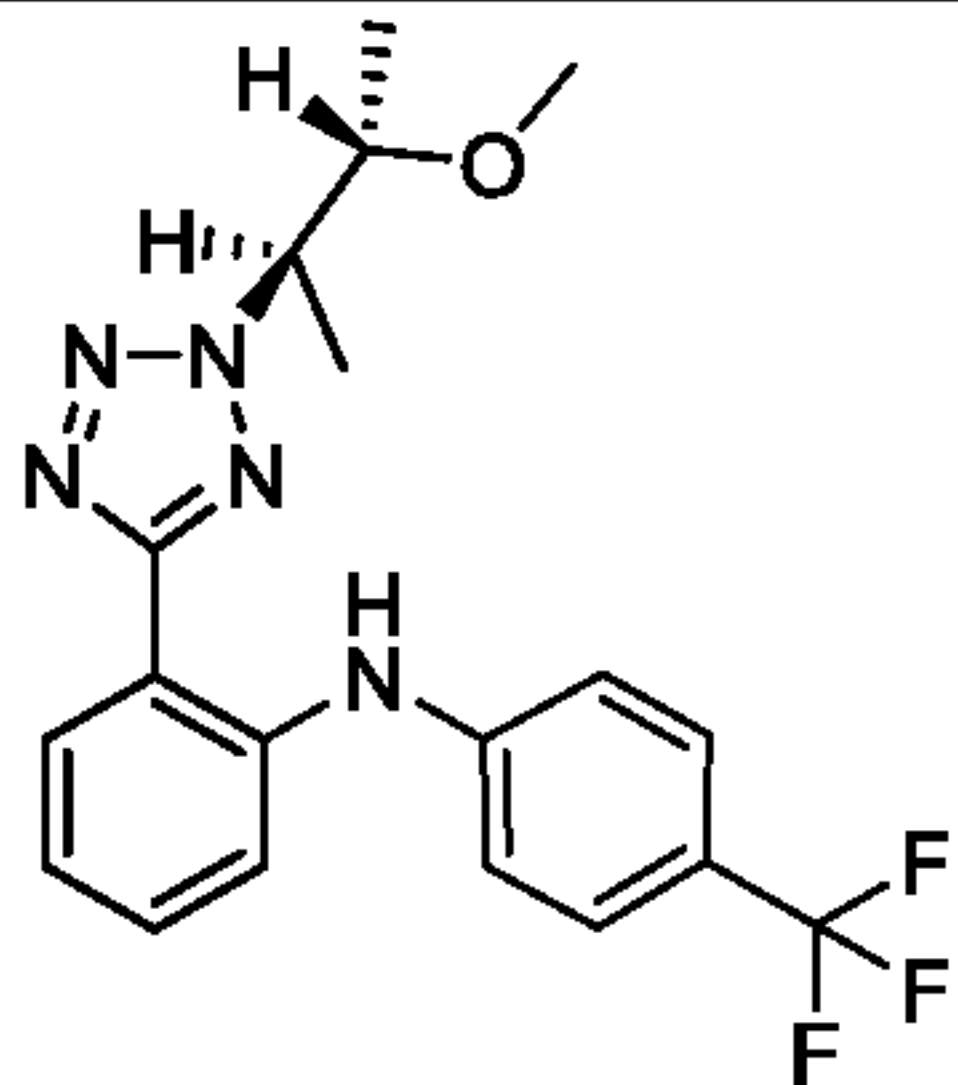
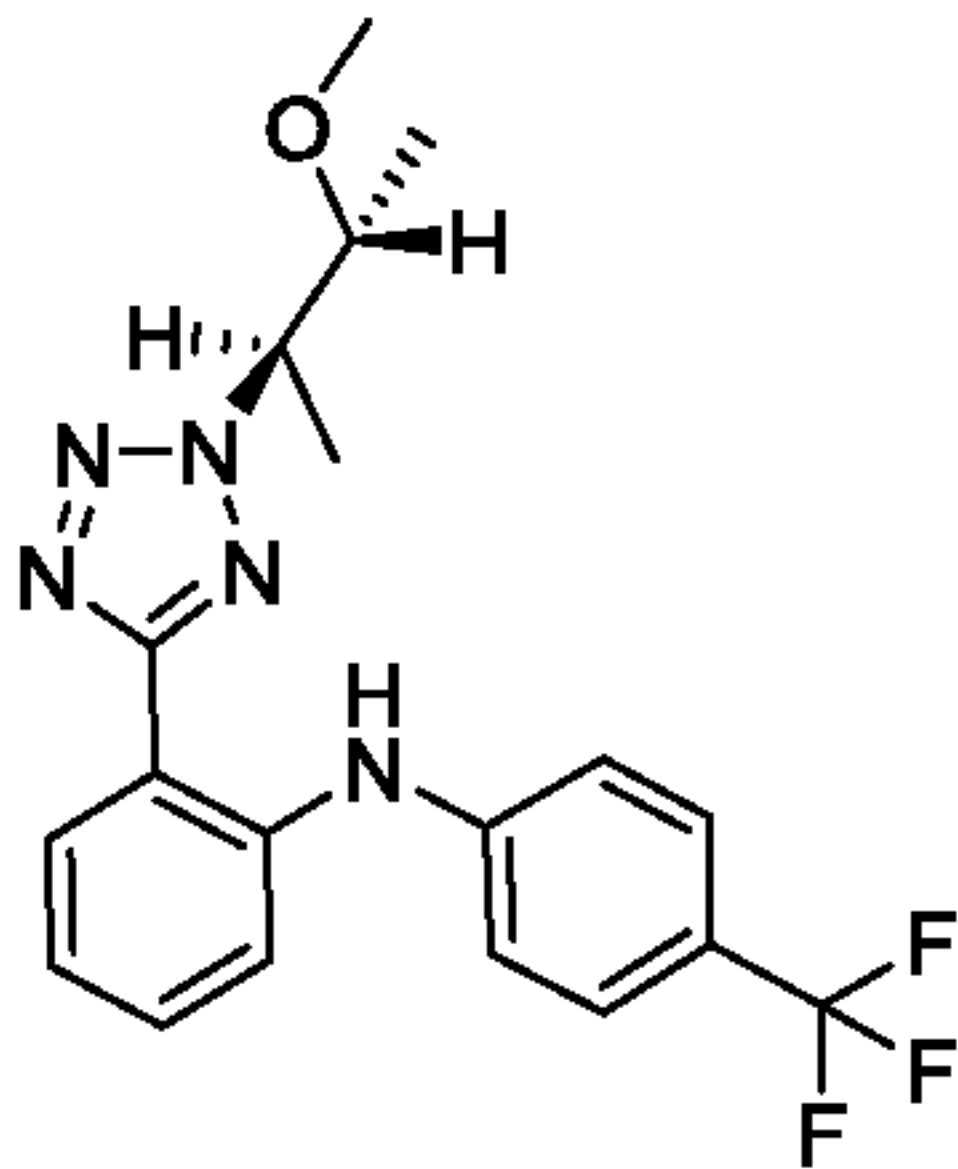
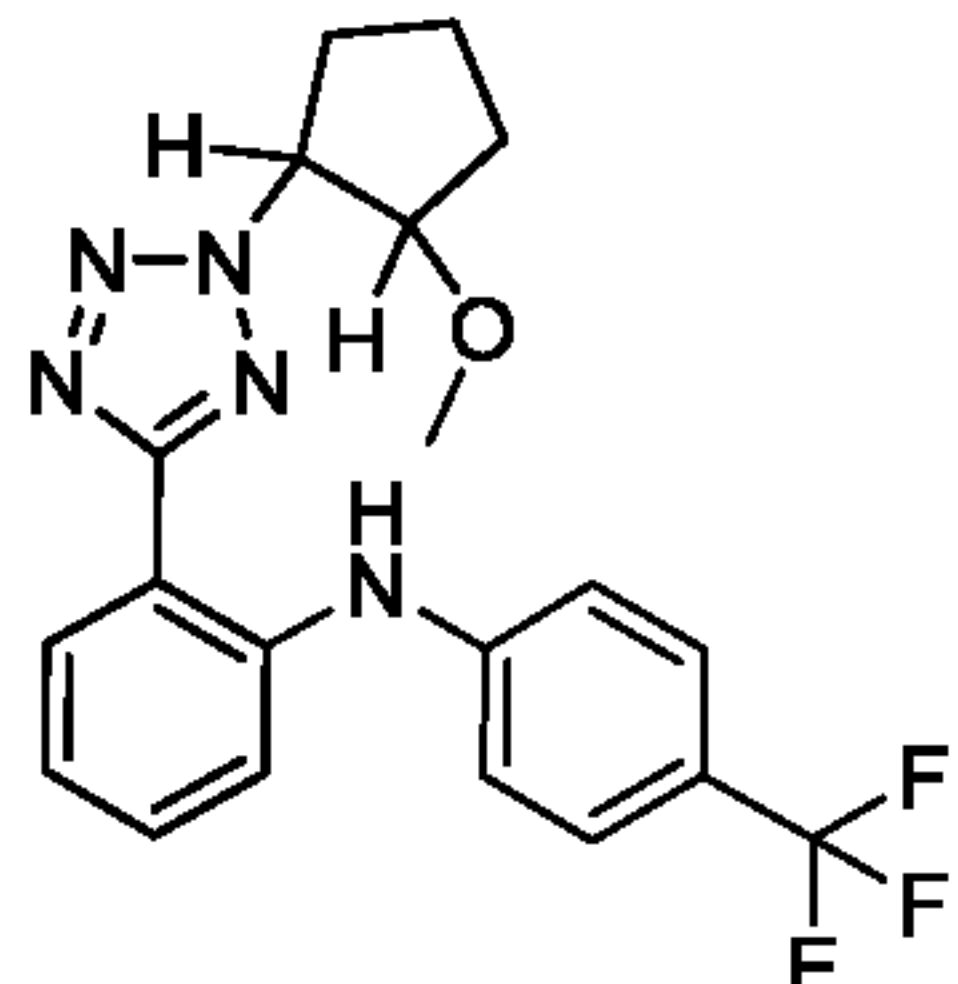
Compound No.	Structure	Name
182		2-[2-[2-(3-pyridyloxy)ethyl]tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline
183		2-(2-(2-(difluoromethoxy)ethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
184		2-[2-[2-(2-fluorophenoxy)ethyl]tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline
185		2-(2-(2-(trifluoromethoxy)ethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
186		3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)oxetan-3-ol

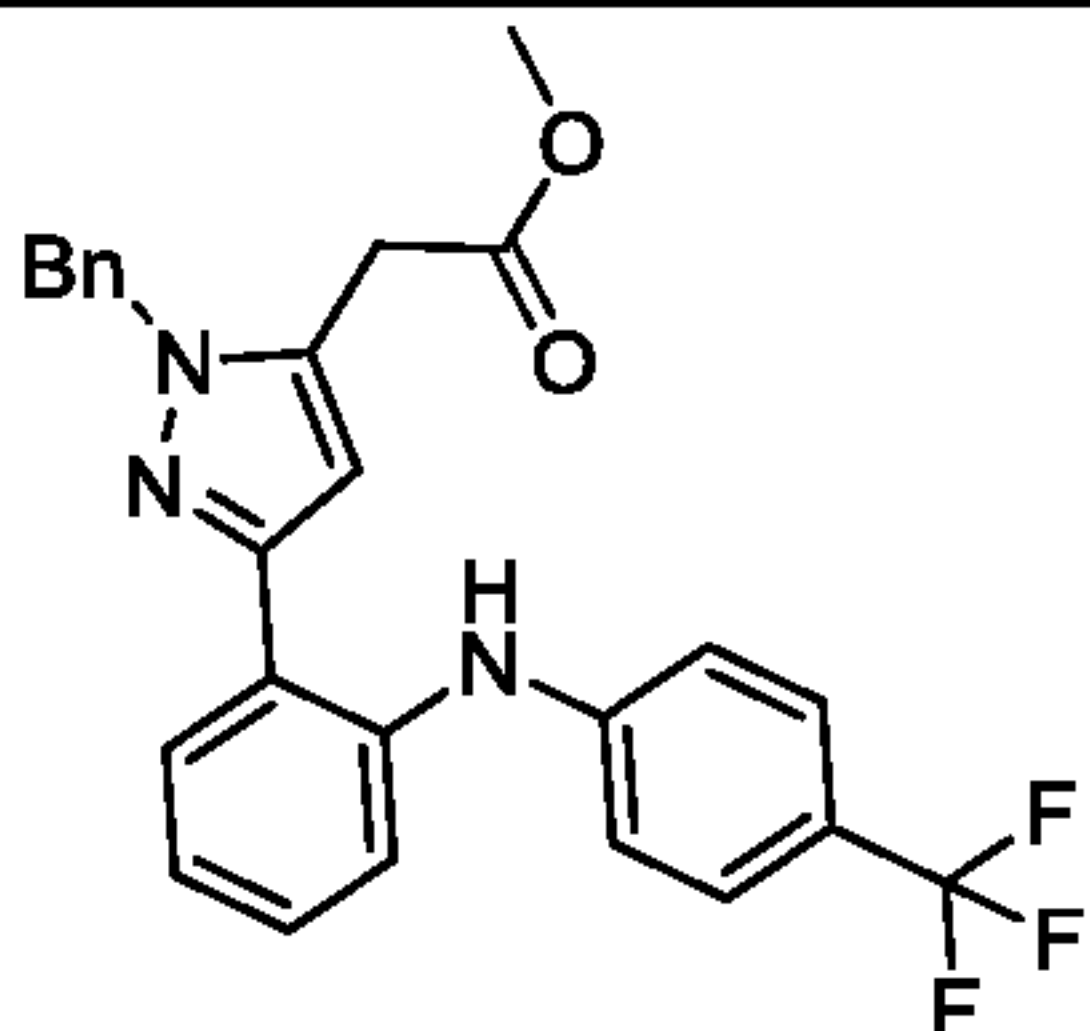
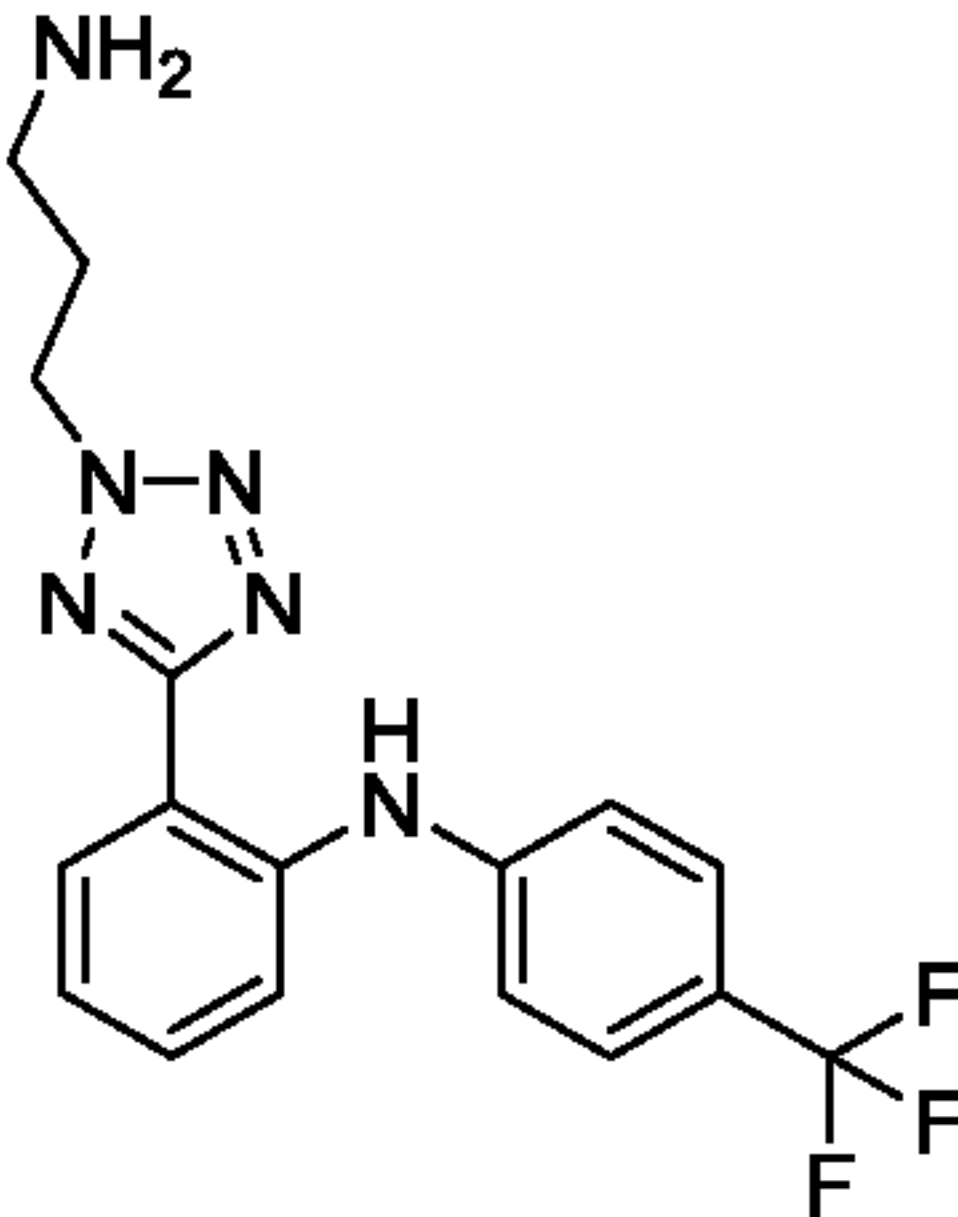
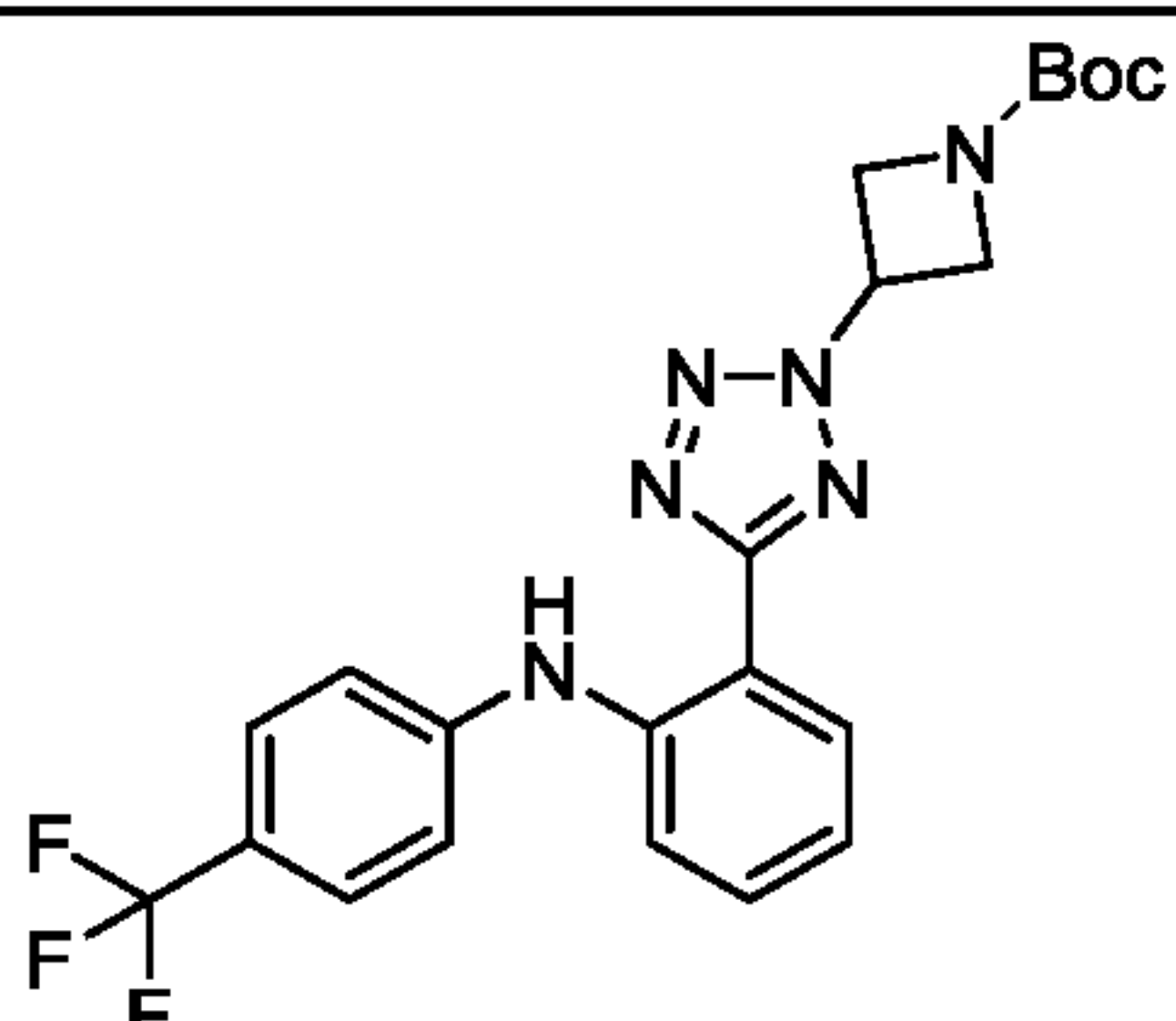
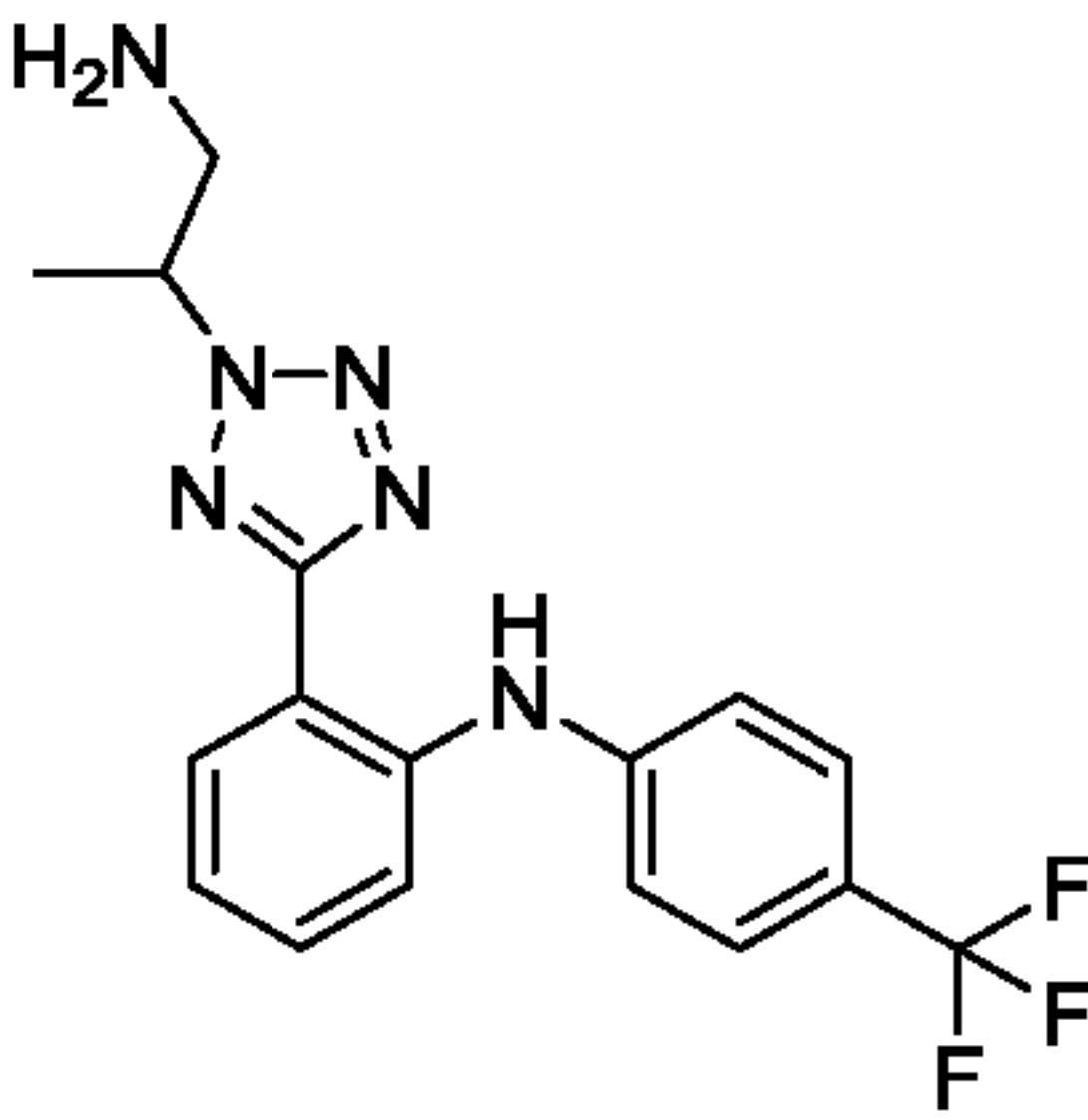
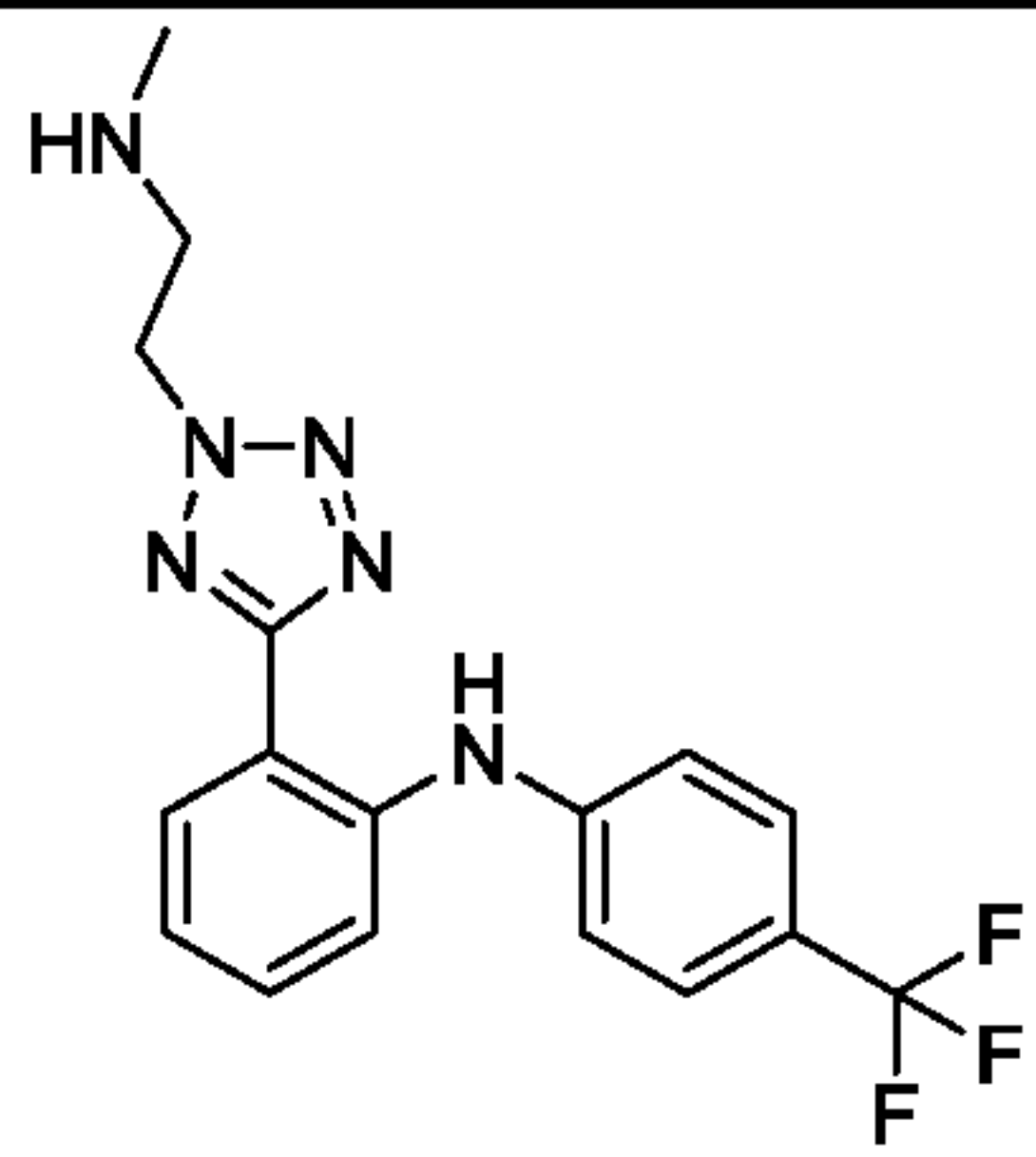
Compound No.	Structure	Name
187		2-(5-(2-fluoro-6-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-ol
188		2-(5-(3-fluoro-2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol
189		2-(5-(2-((3-heptylphenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-ol
190		tert-butyl 3-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethoxy)piperidine-1-carboxylate
191		2-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-1,2,3-triazol-1-yl)ethan-1-ol
192		(2S,3S)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)butan-2-ol

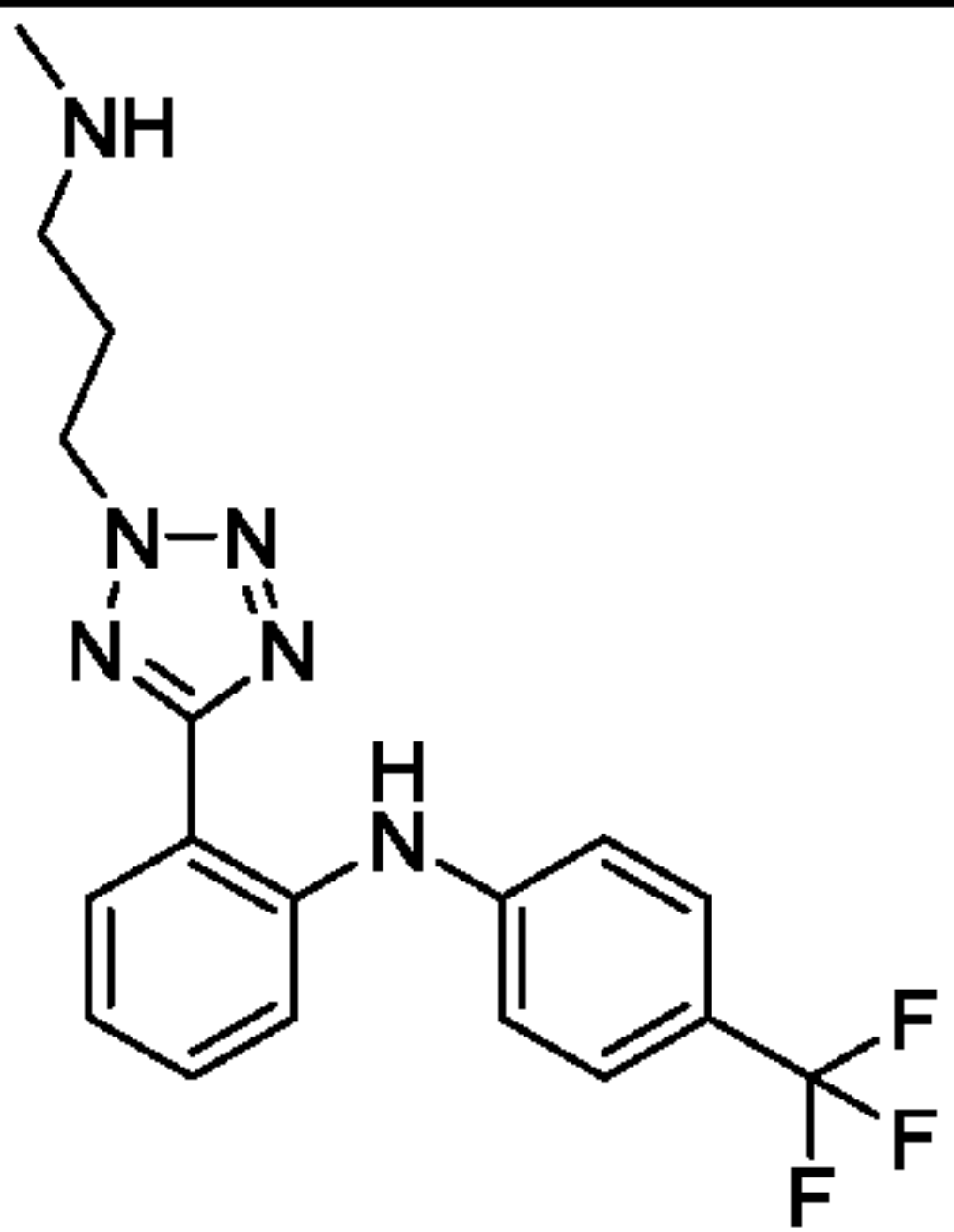
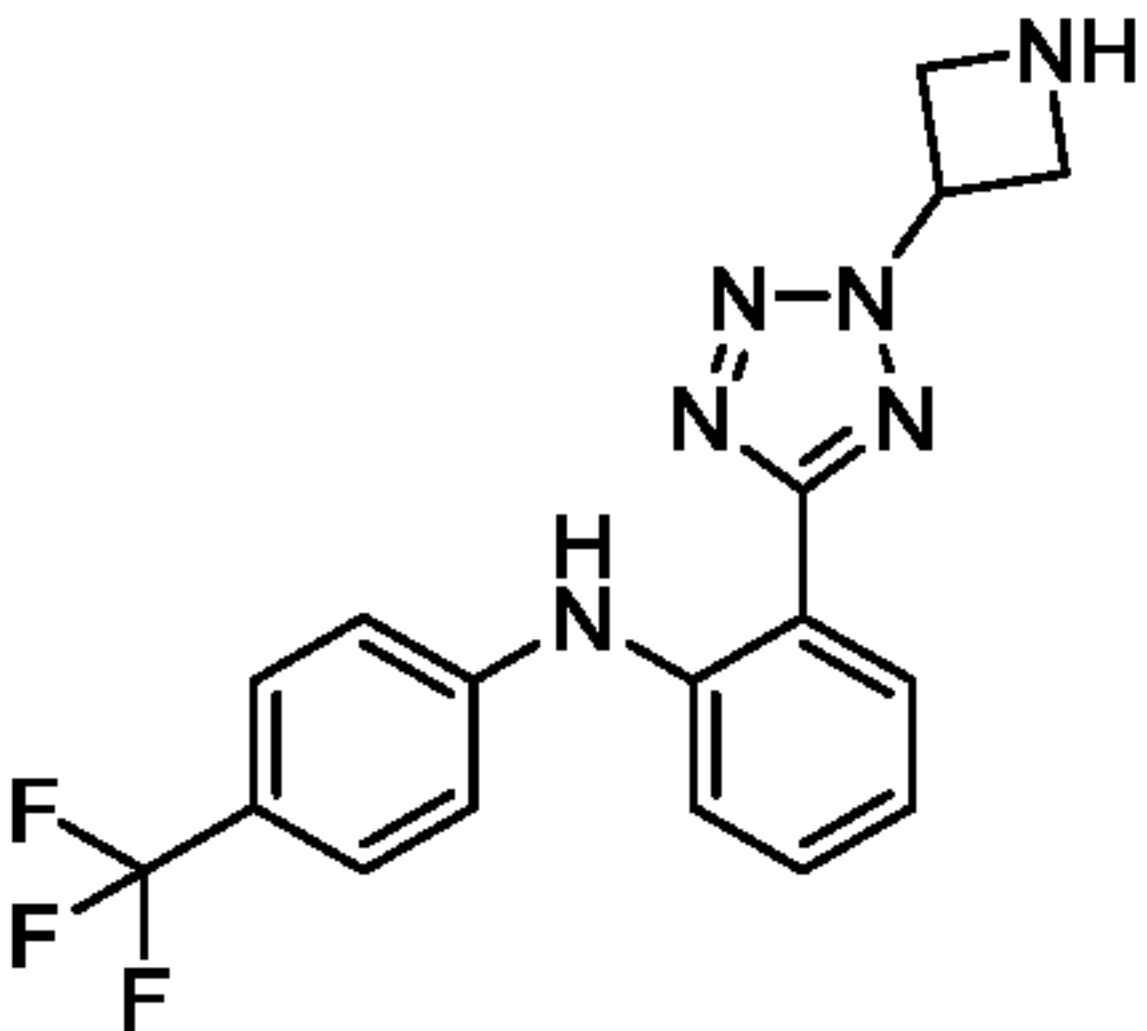
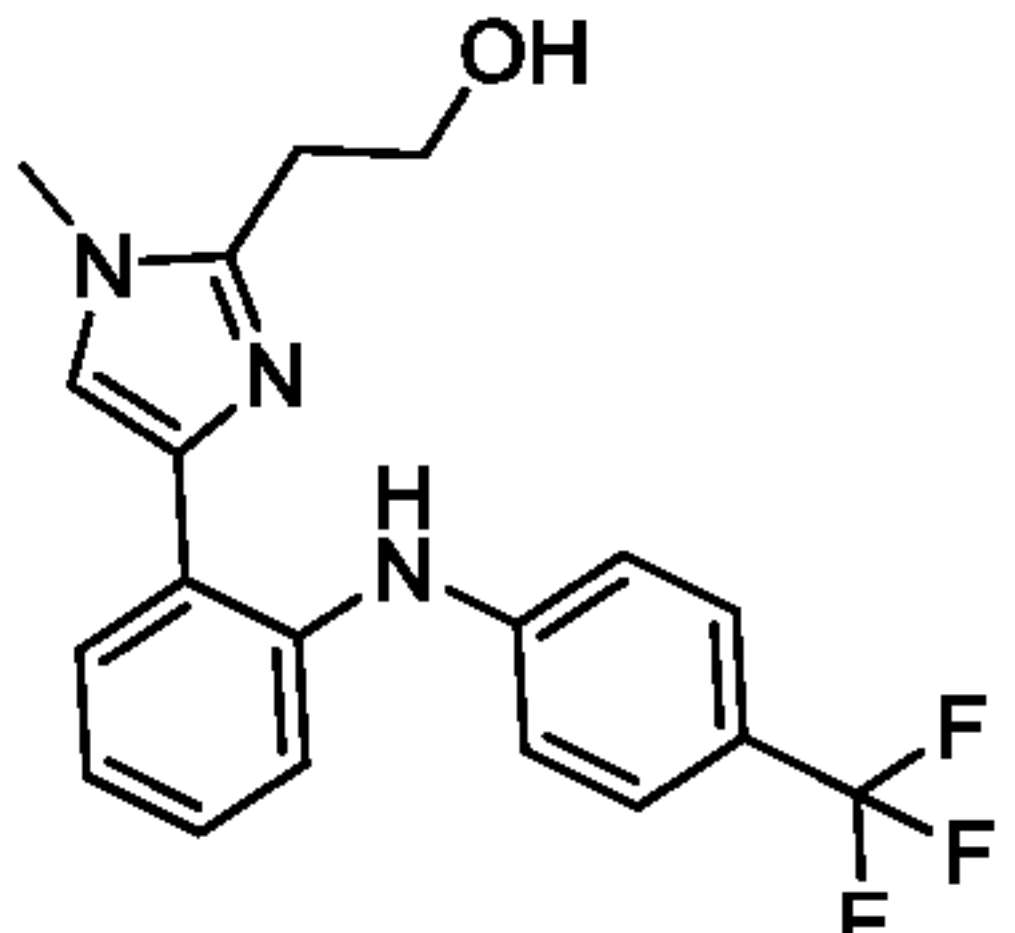
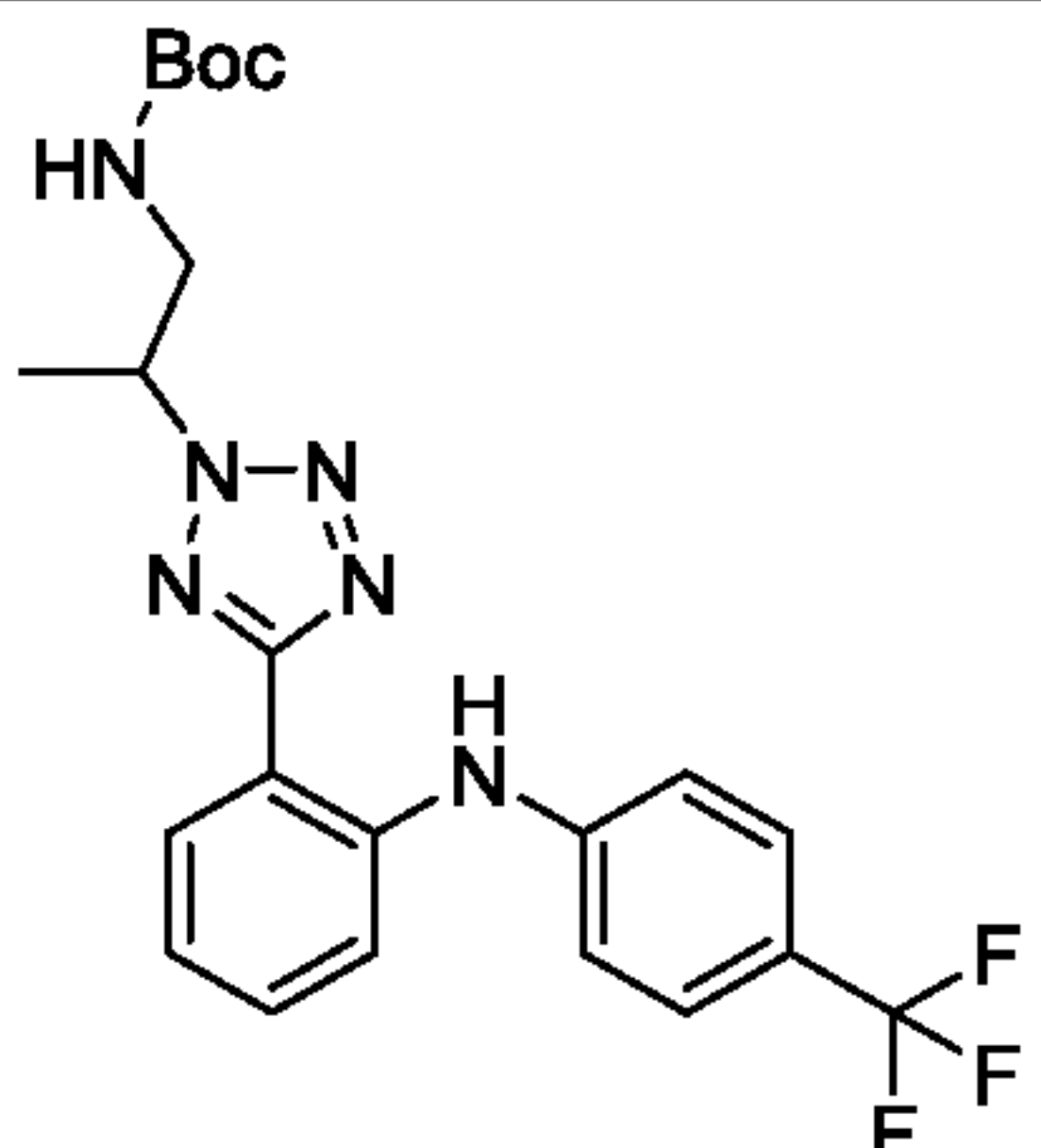
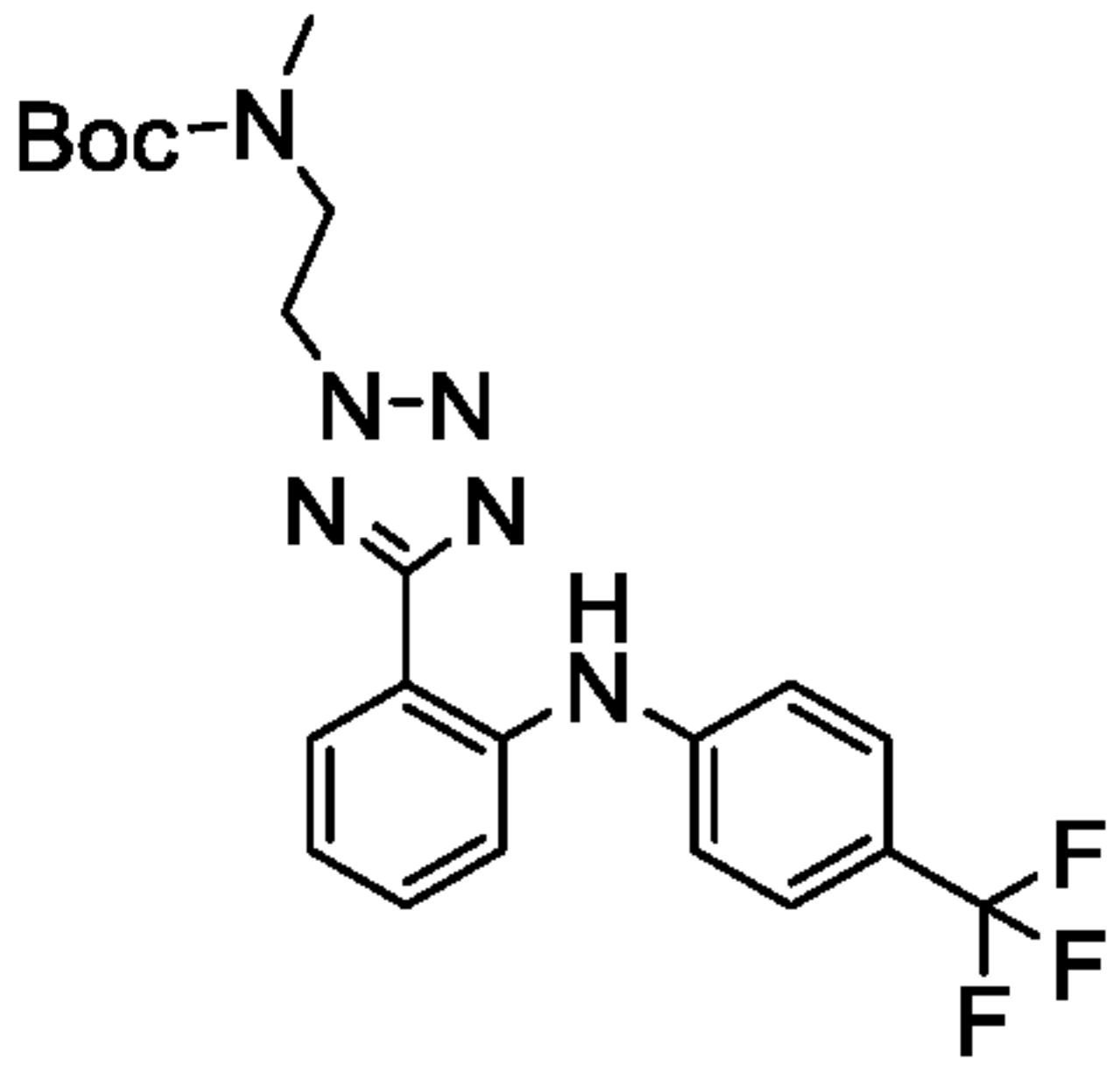
Compound No.	Structure	Name
193		(2R,3R)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)butan-2-ol
194		(2R,3S)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)butan-2-ol
195		(2S,3R)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)butan-2-ol
196		2-(1-methyl-3-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-5-yl)ethan-1-ol
197		2-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-imidazol-1-yl)ethan-1-ol
198		2-(2-(2-(piperidin-4-yloxy)ethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

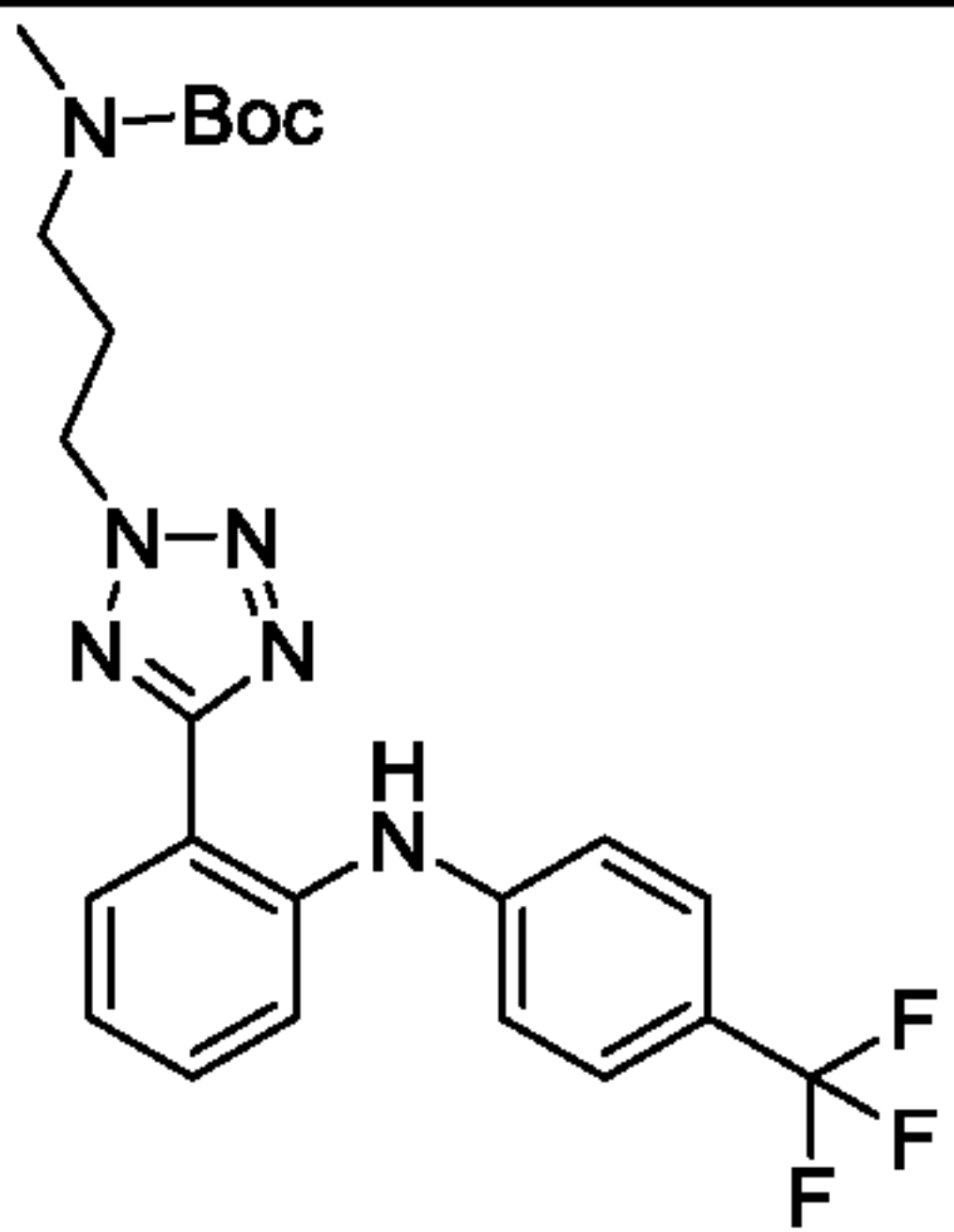
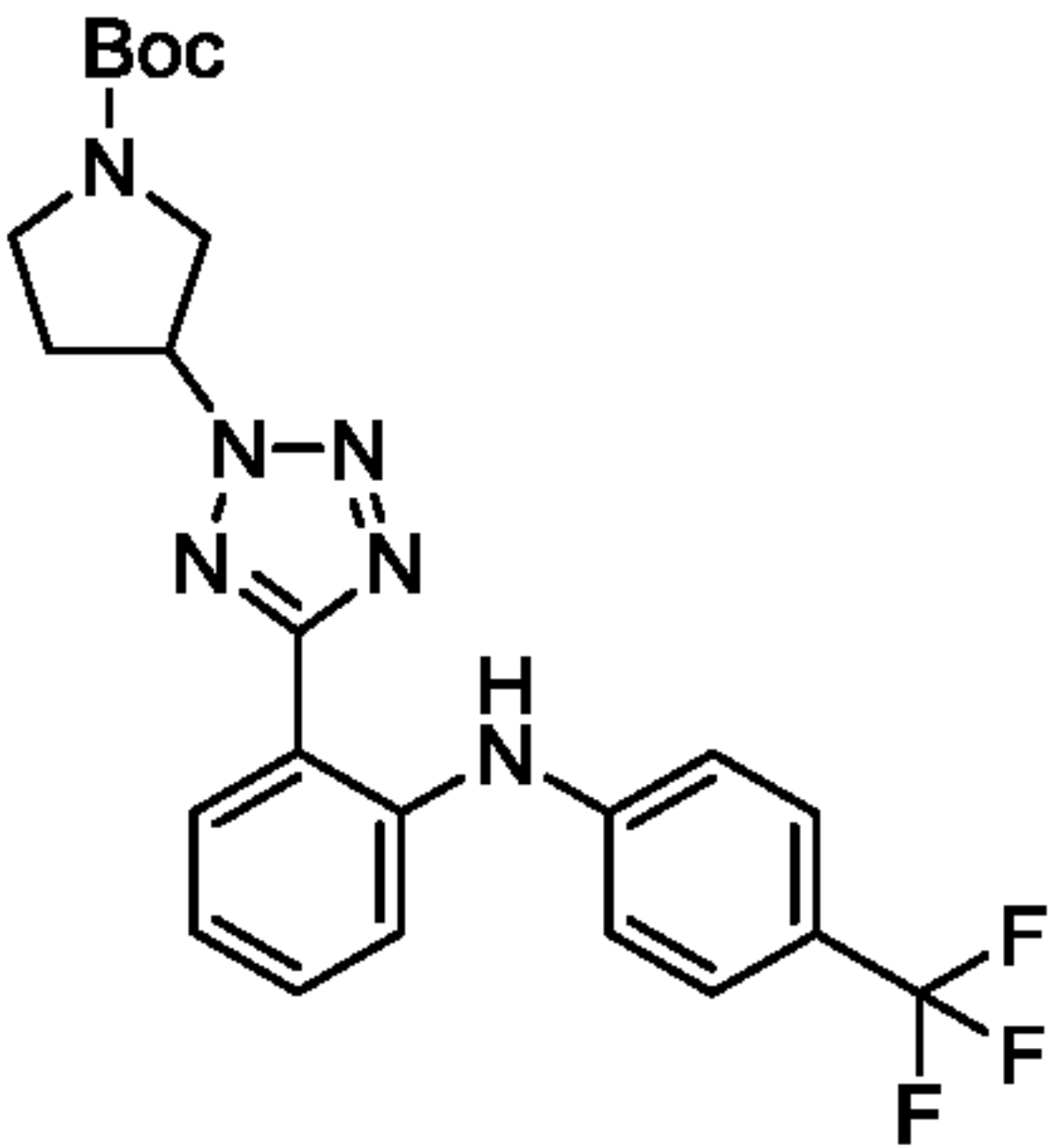
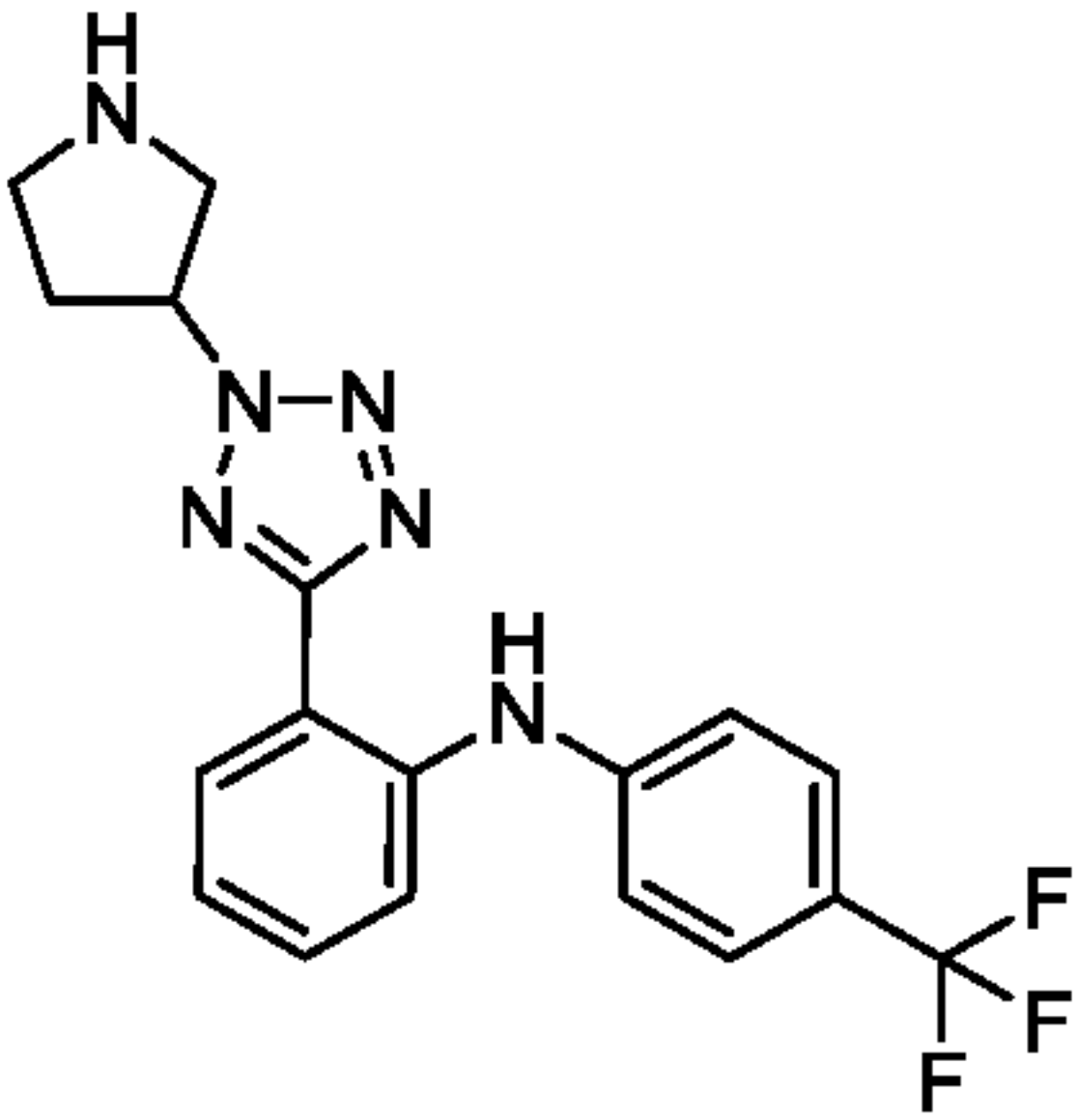
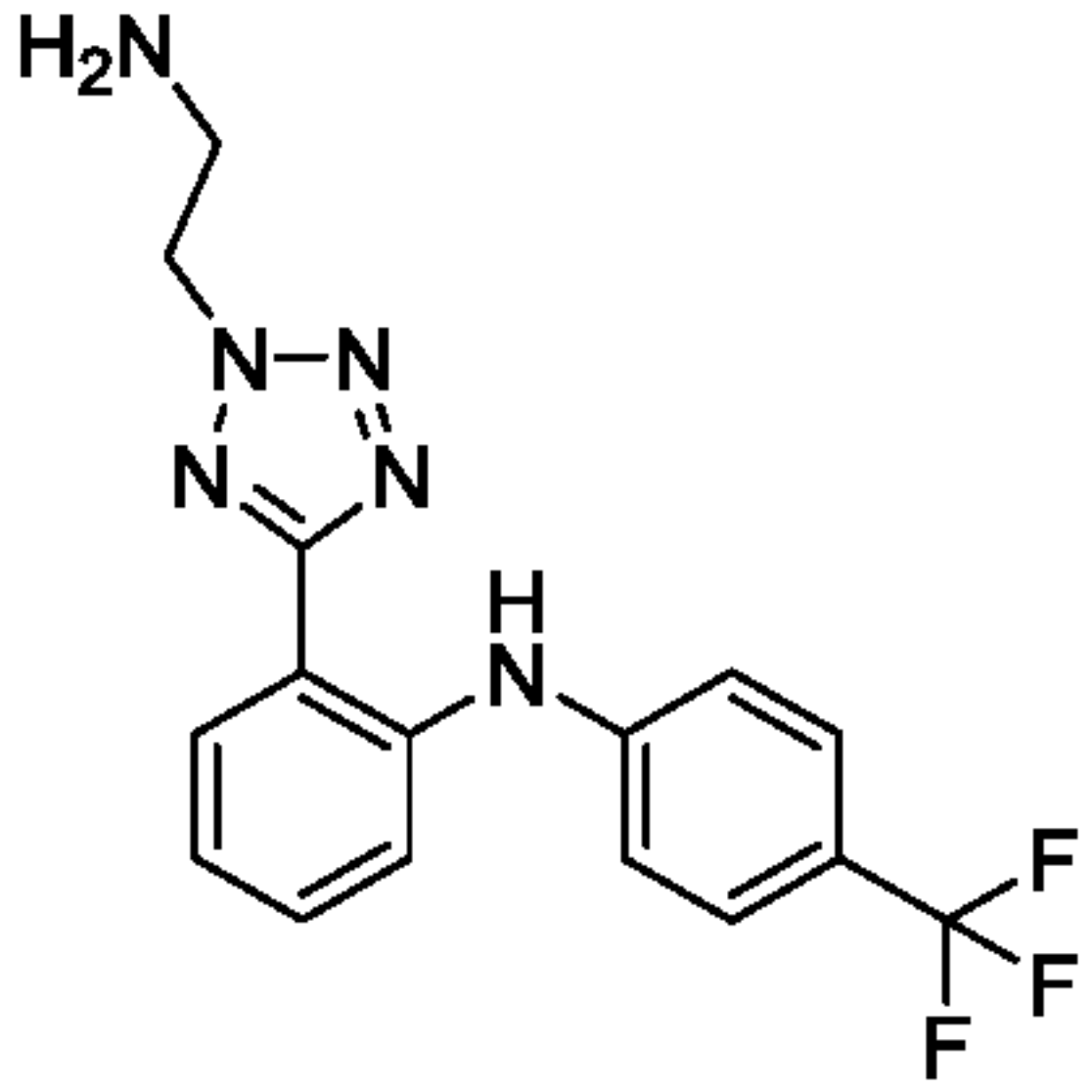
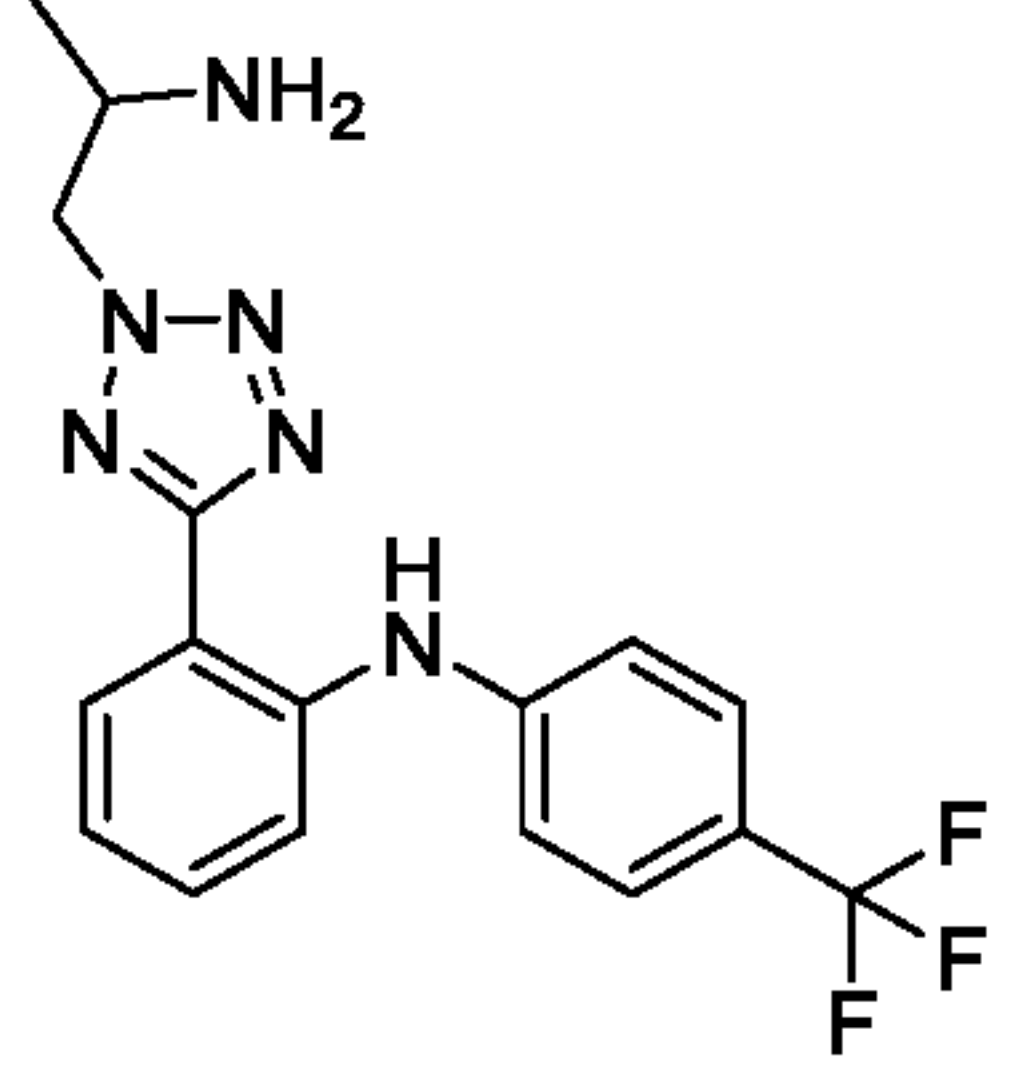
Compound No.	Structure	Name
199		2-(2-(2-(piperidin-3-yloxy)ethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
200		(1R,2S)-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)cyclopentan-1-ol
201		(1S,2R)-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)cyclopentan-1-ol
202		ethyl 2-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-imidazol-1-yl)acetate
203		2-(2-((1-(benzyloxy)cyclopropyl)methyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

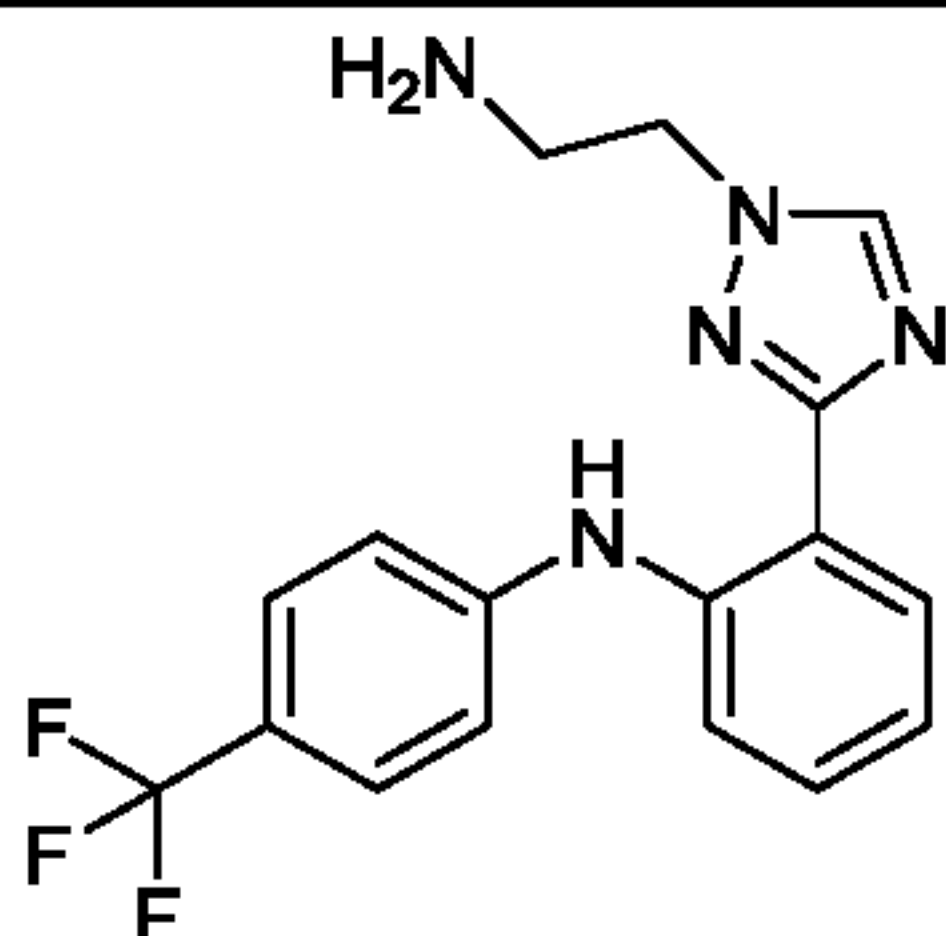
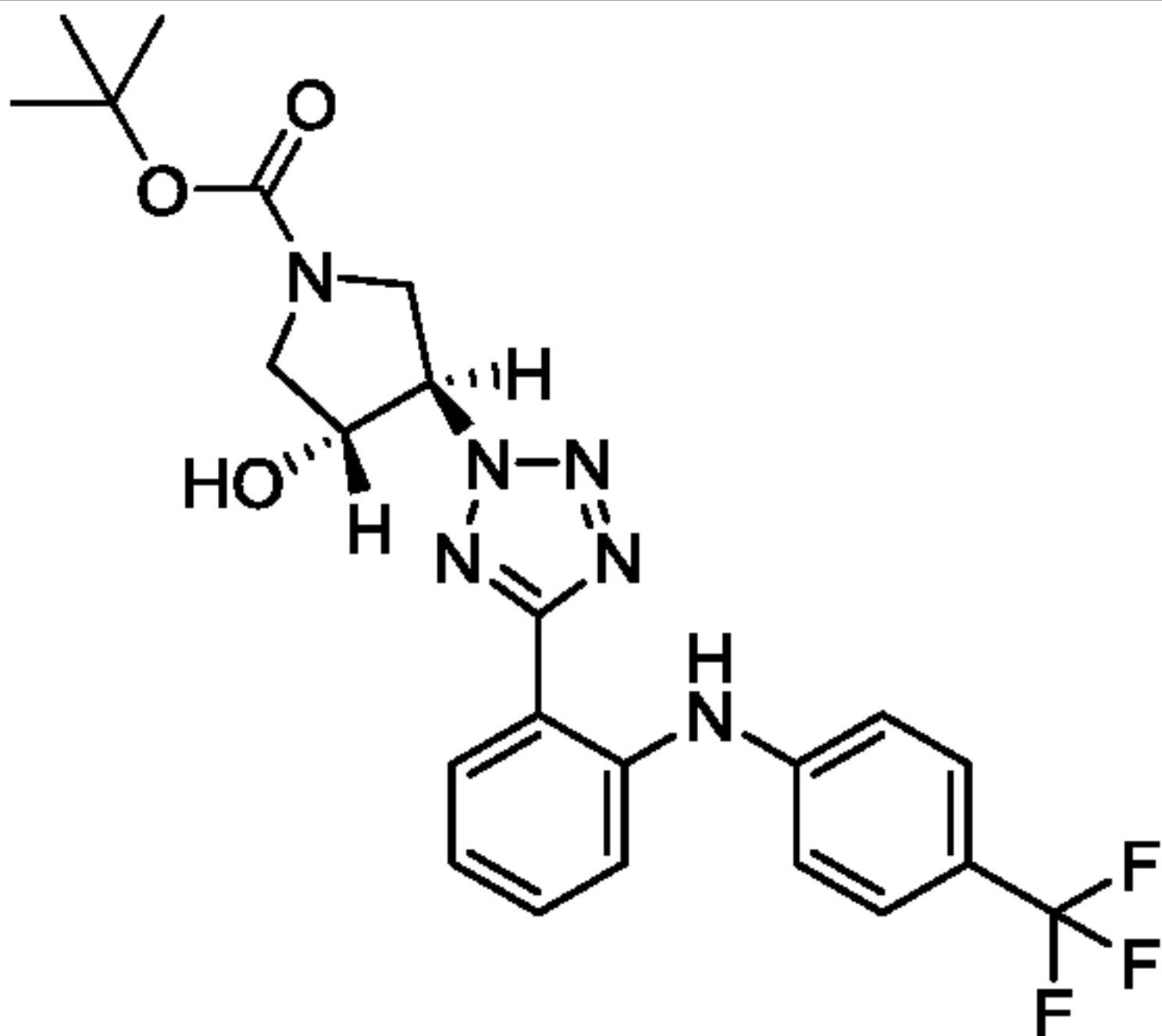
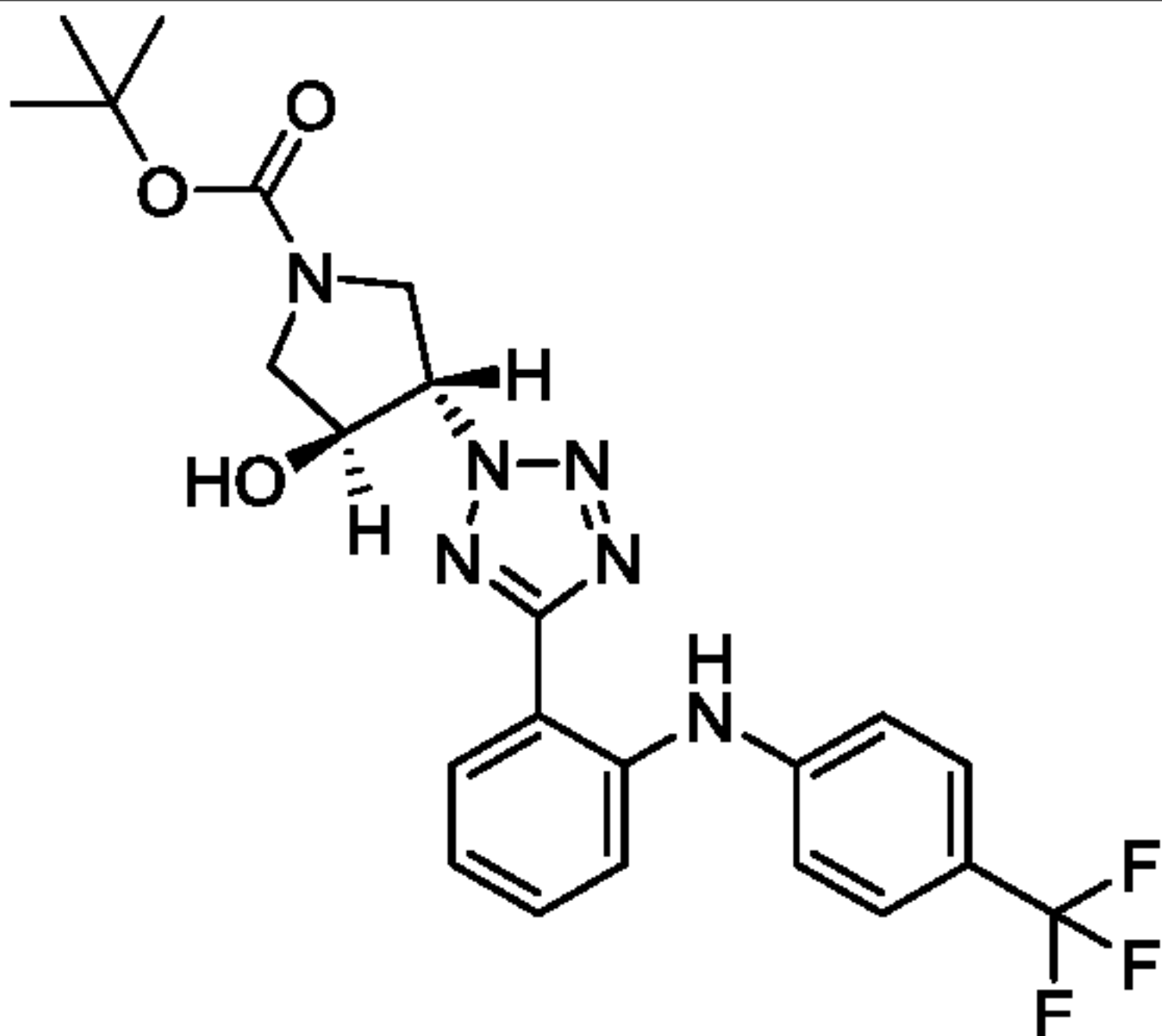
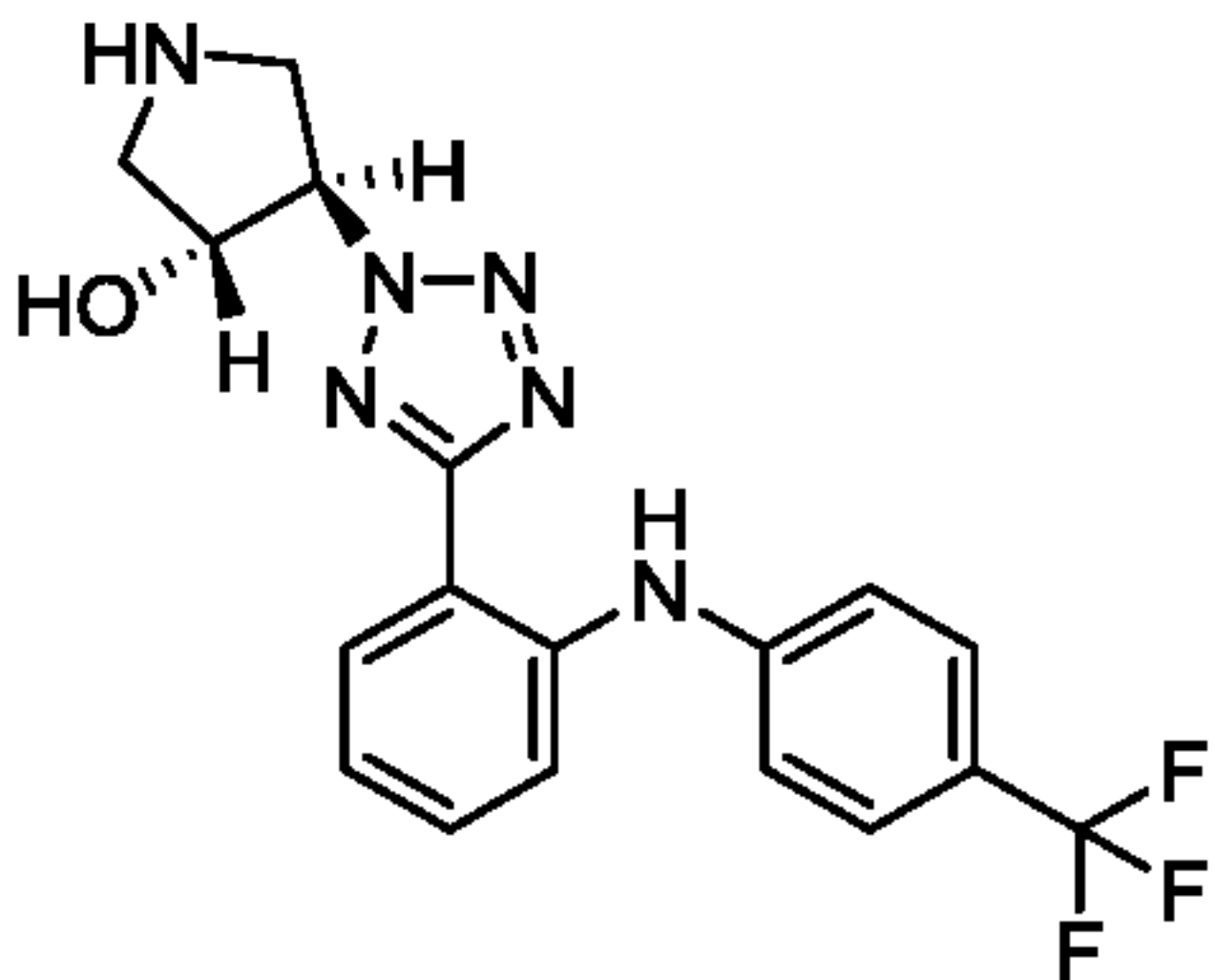
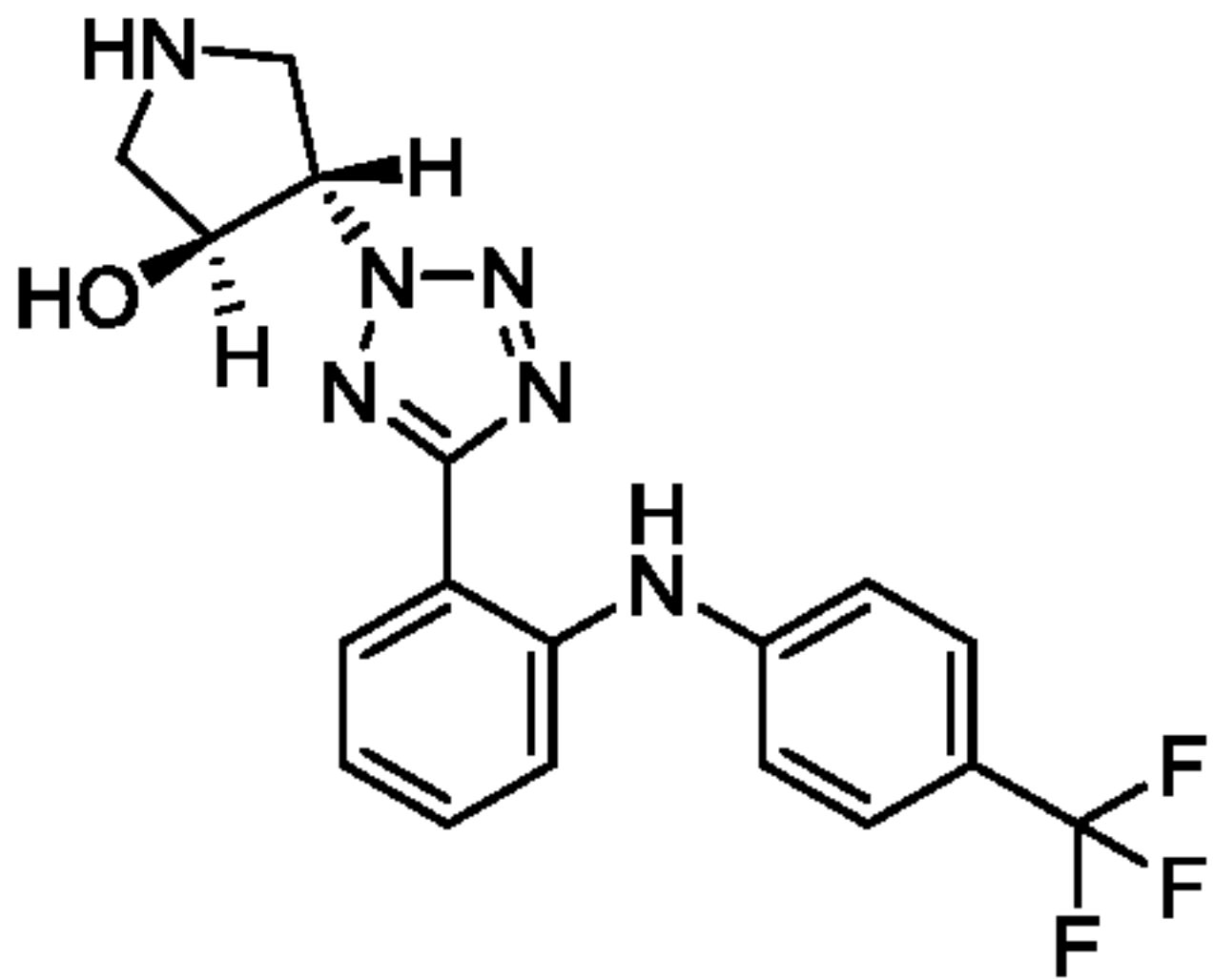
Compound No.	Structure	Name
204		1-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)cyclopropan-1-ol
205		2-(1-methyl-3-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-1,2,4-triazol-5-yl)ethan-1-ol
206		2-(1-methyl-3-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-1,2,4-triazol-5-yl)propan-1-ol
207		2-(5-(2-((4-bromophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-ol
208		2-(5-(2-((4-chlorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-ol
209		2-(1-benzyl-3-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-5-yl)ethan-1-ol

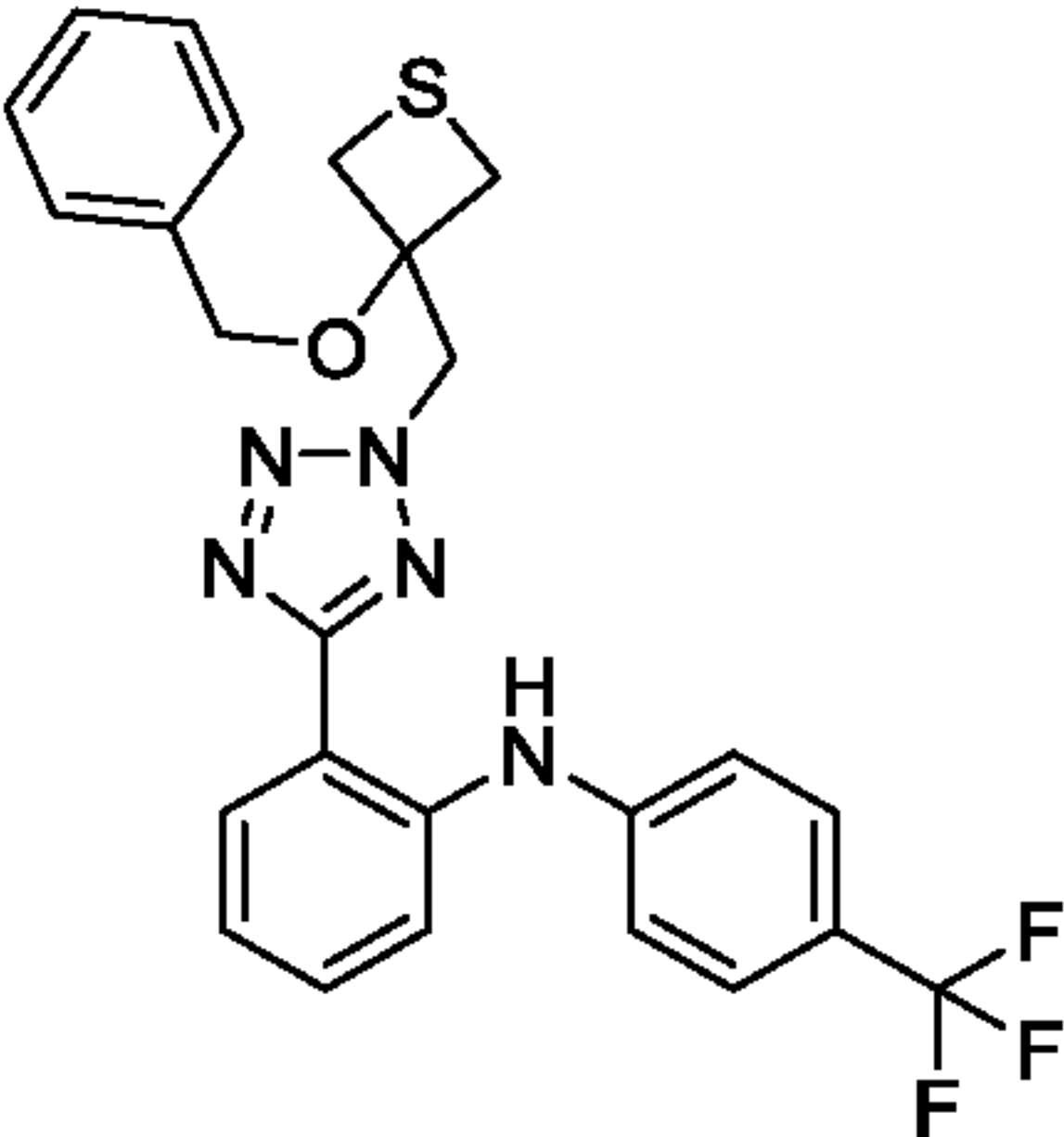
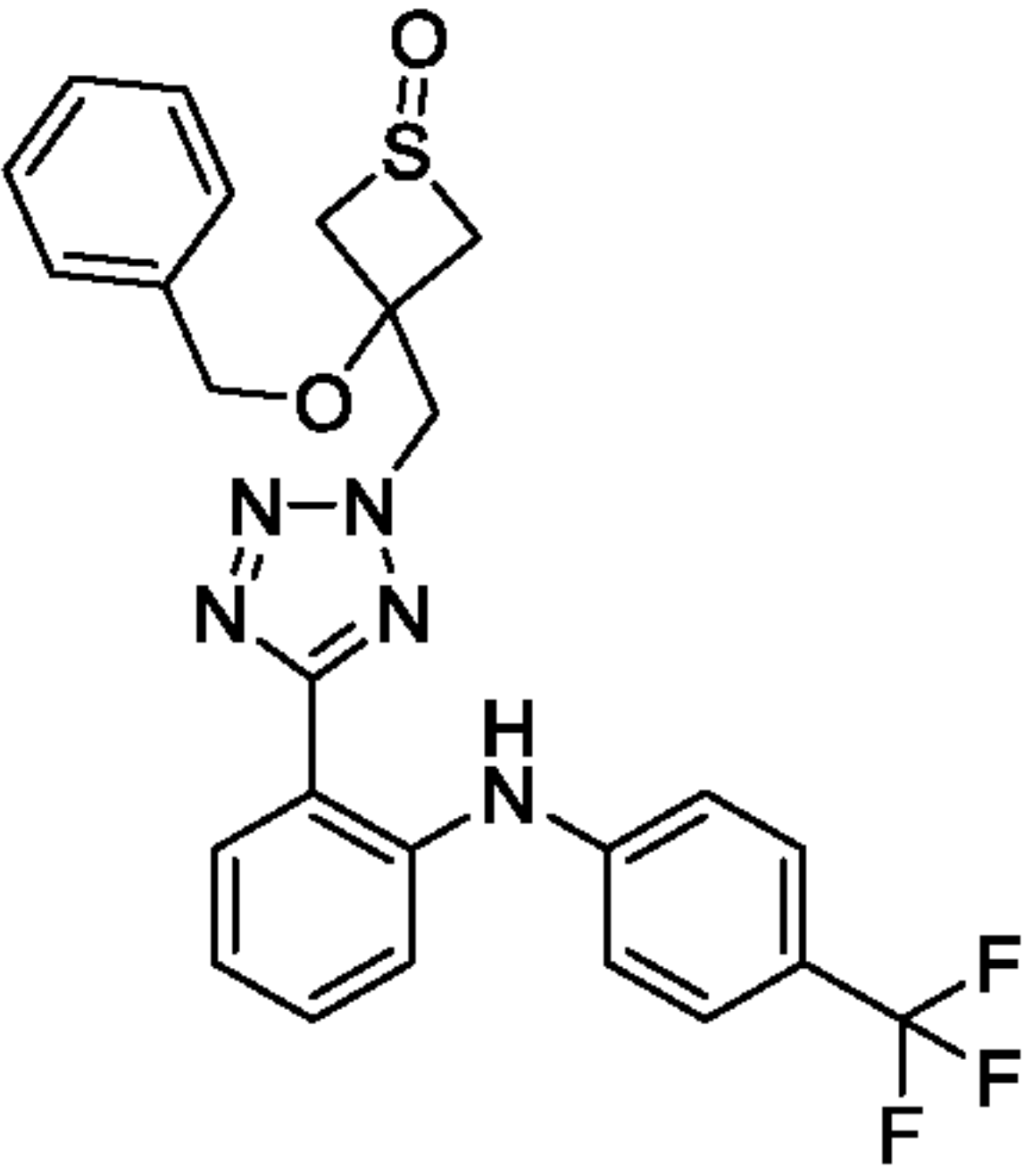
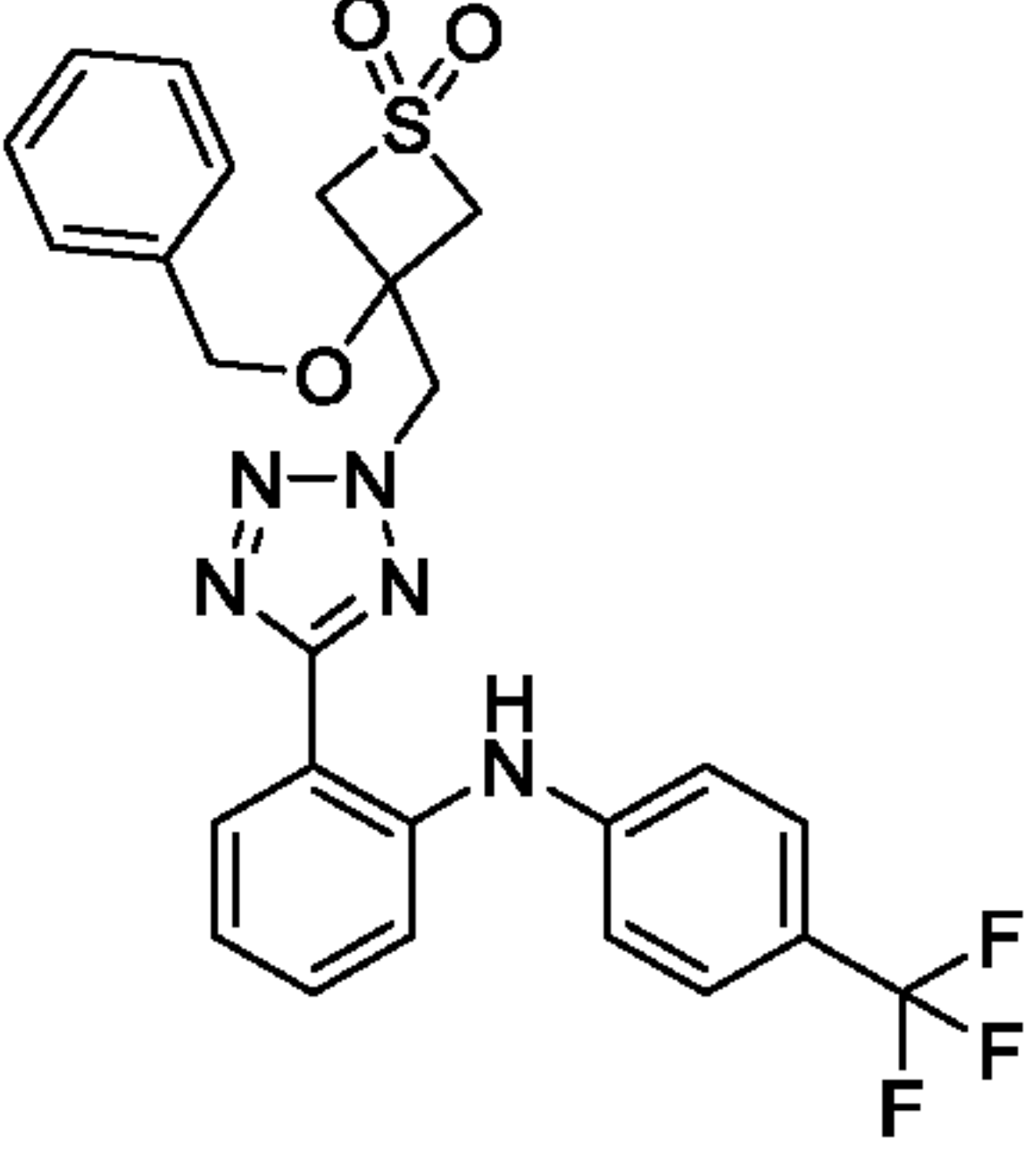
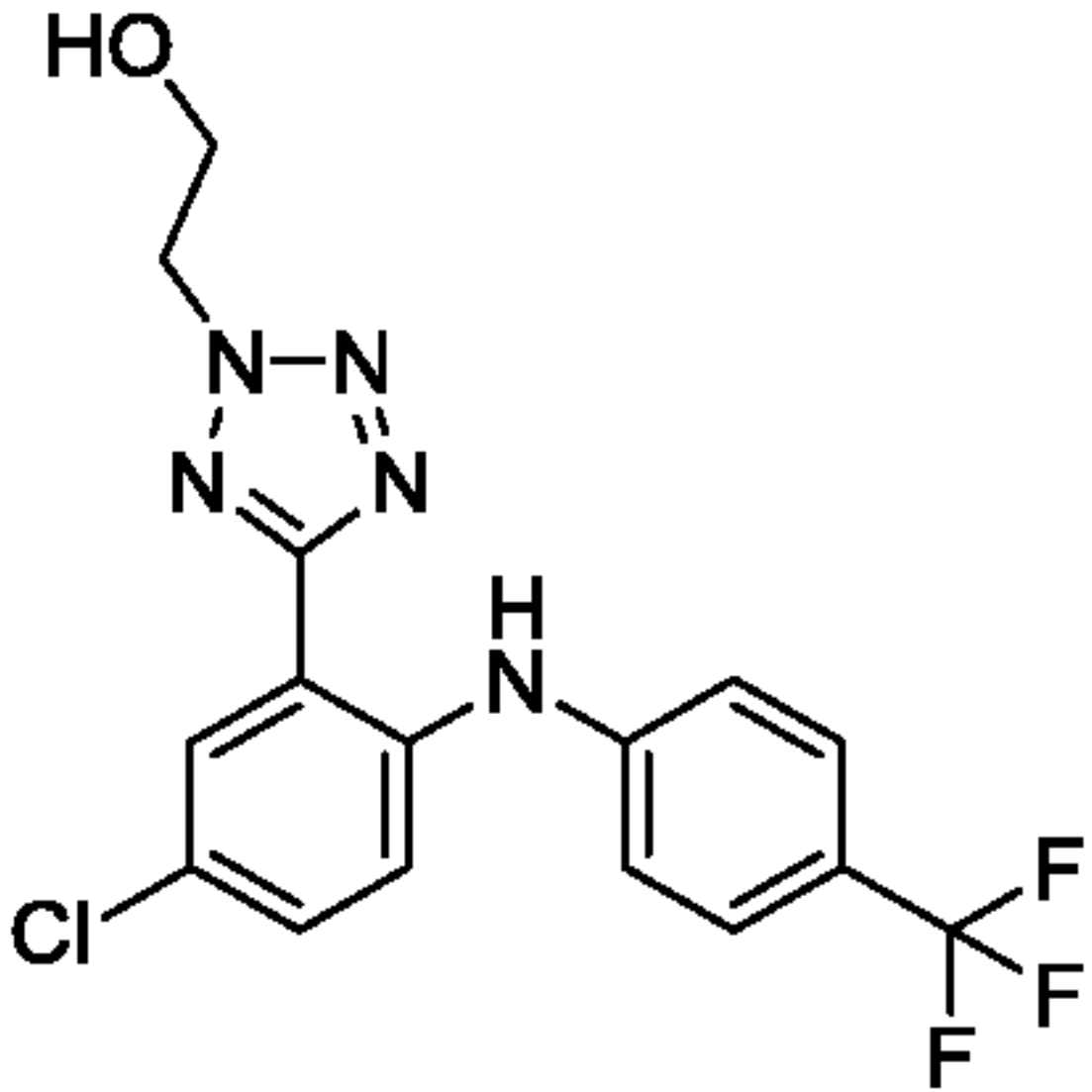
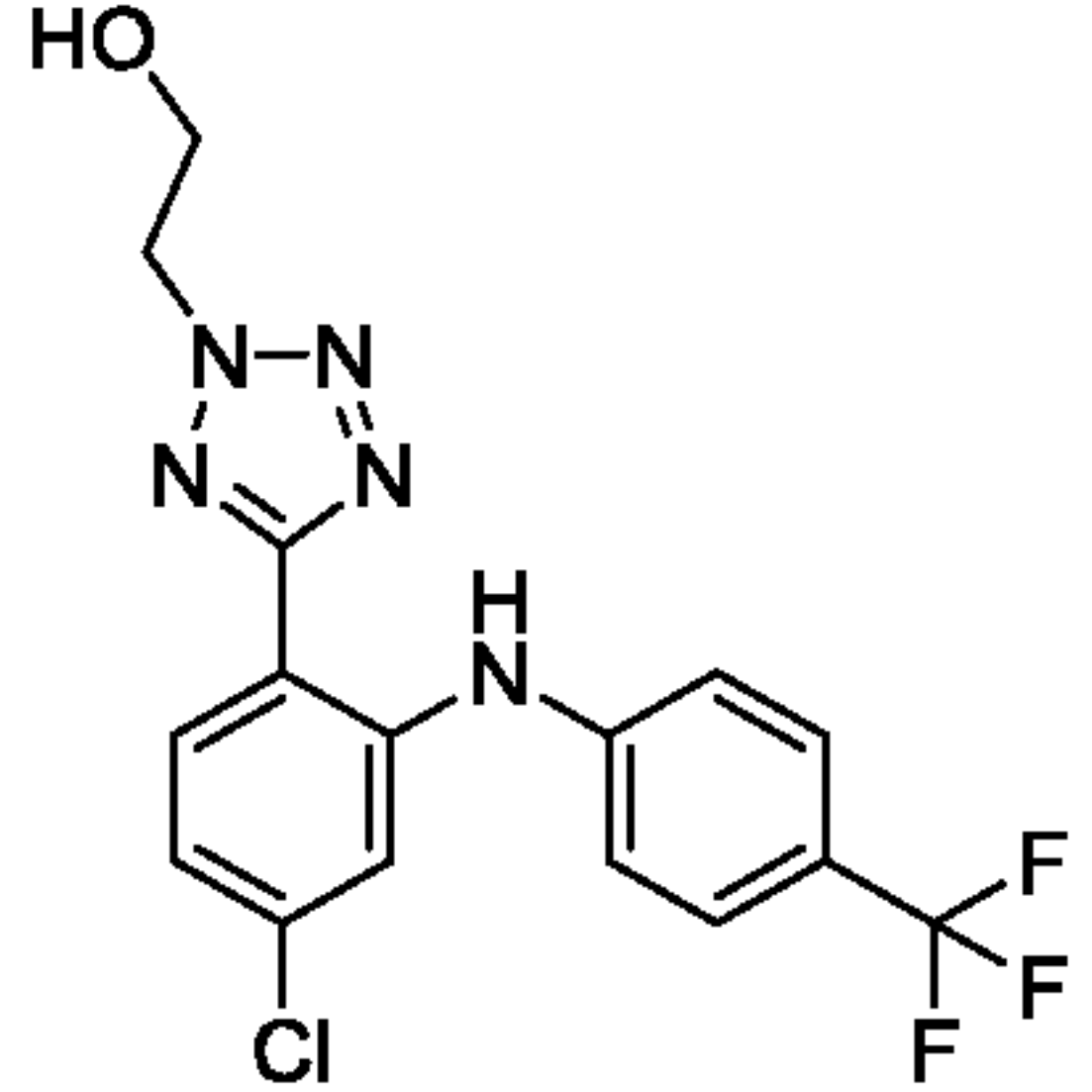
Compound No.	Structure	Name
210		2-(2-((2S,3S)-3-methoxybutan-2-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
211		2-(2-((2S,3R)-3-methoxybutan-2-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
212		2-(2-((2R,3S)-3-methoxybutan-2-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
213		2-(2-((2R,3R)-3-methoxybutan-2-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
214		2-(2-(2-methoxycyclopentyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

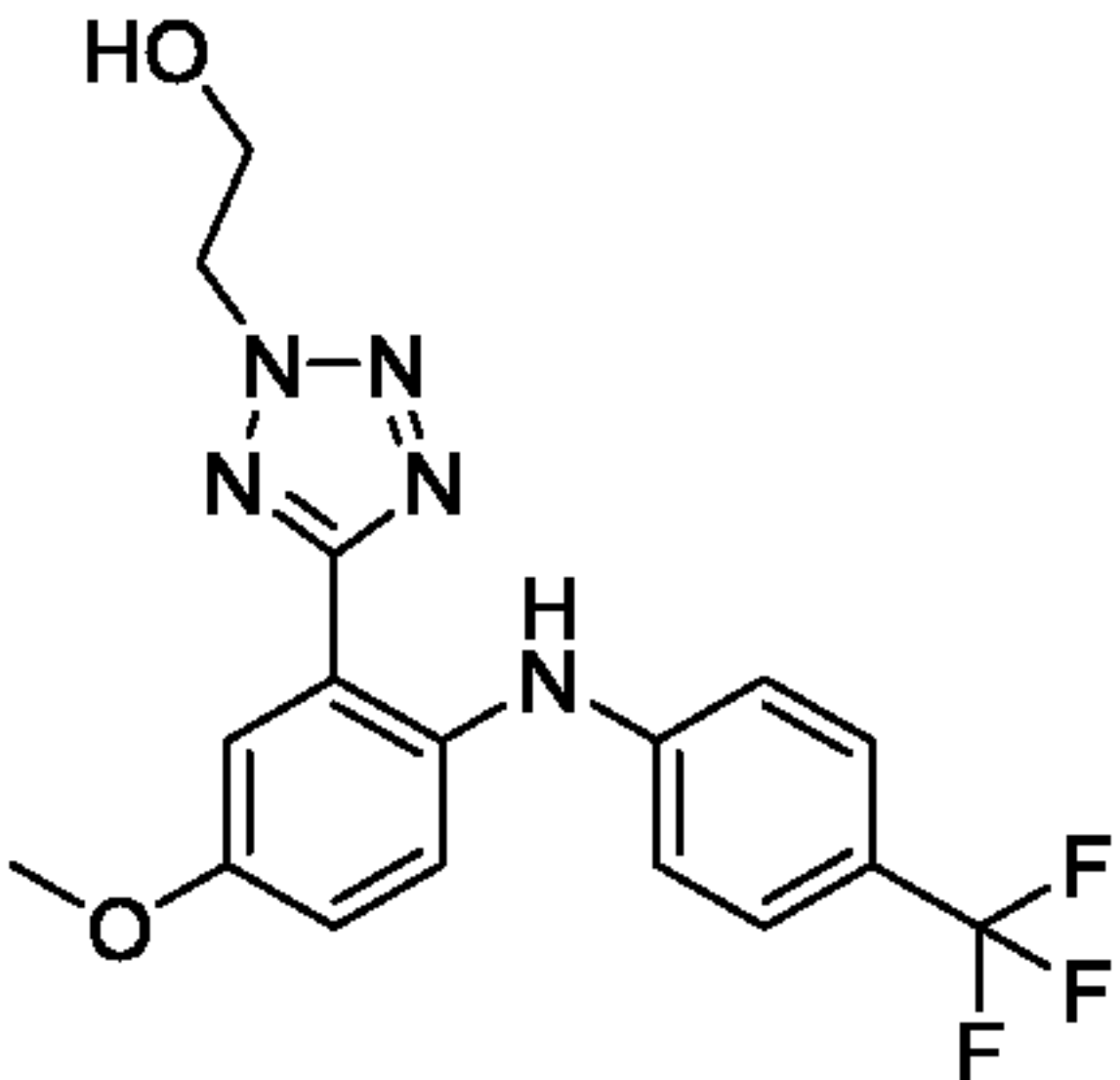
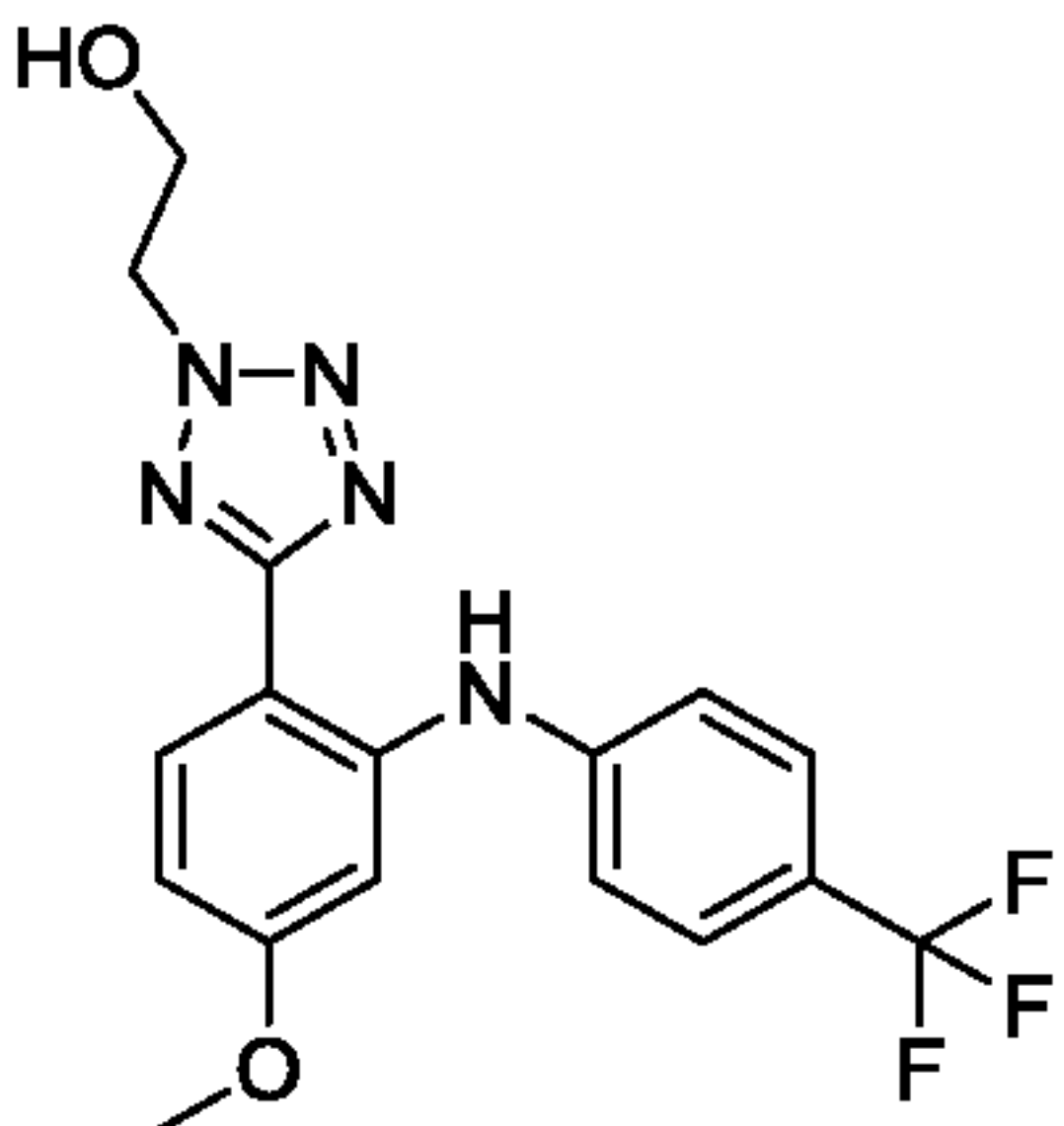
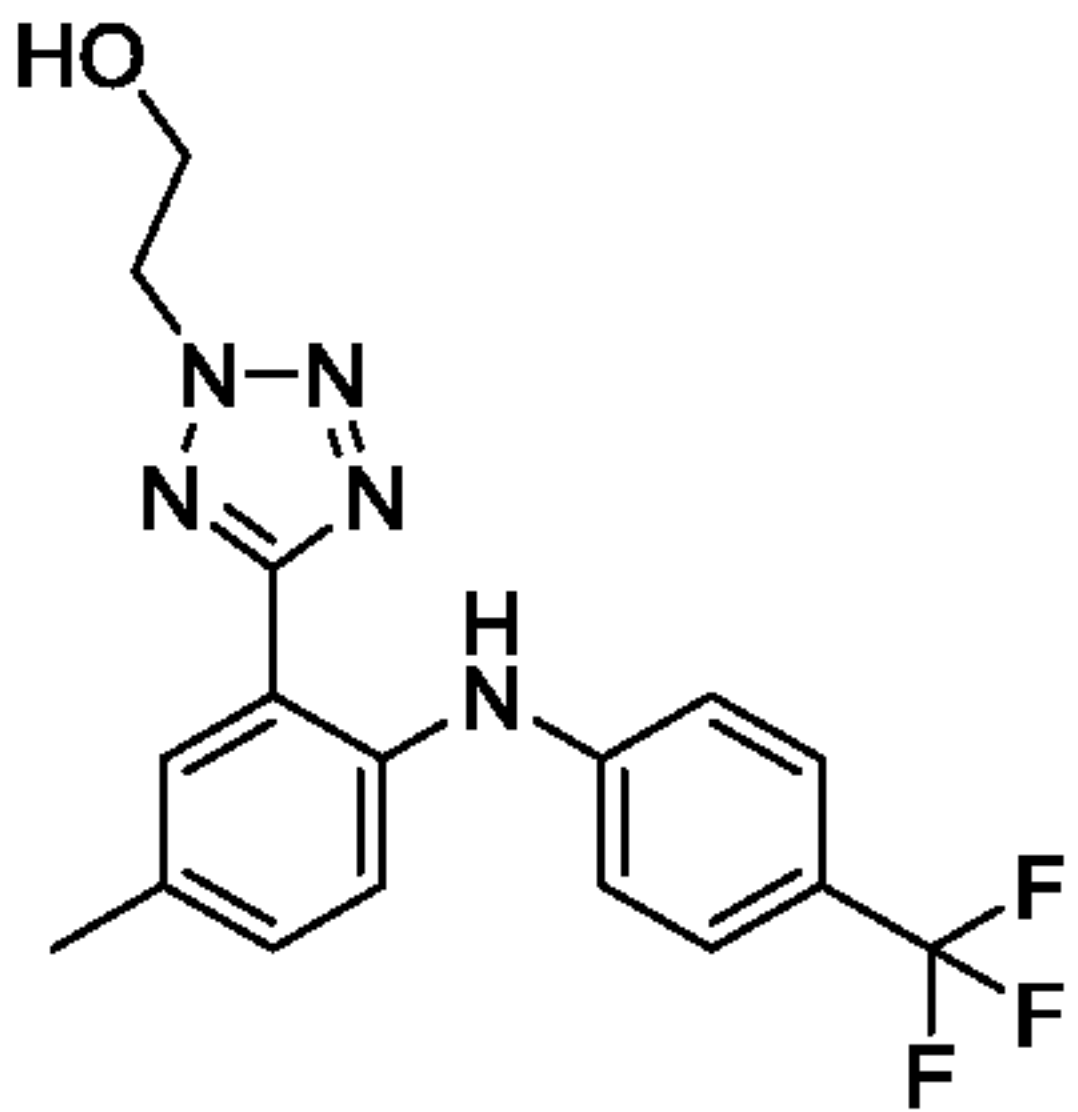
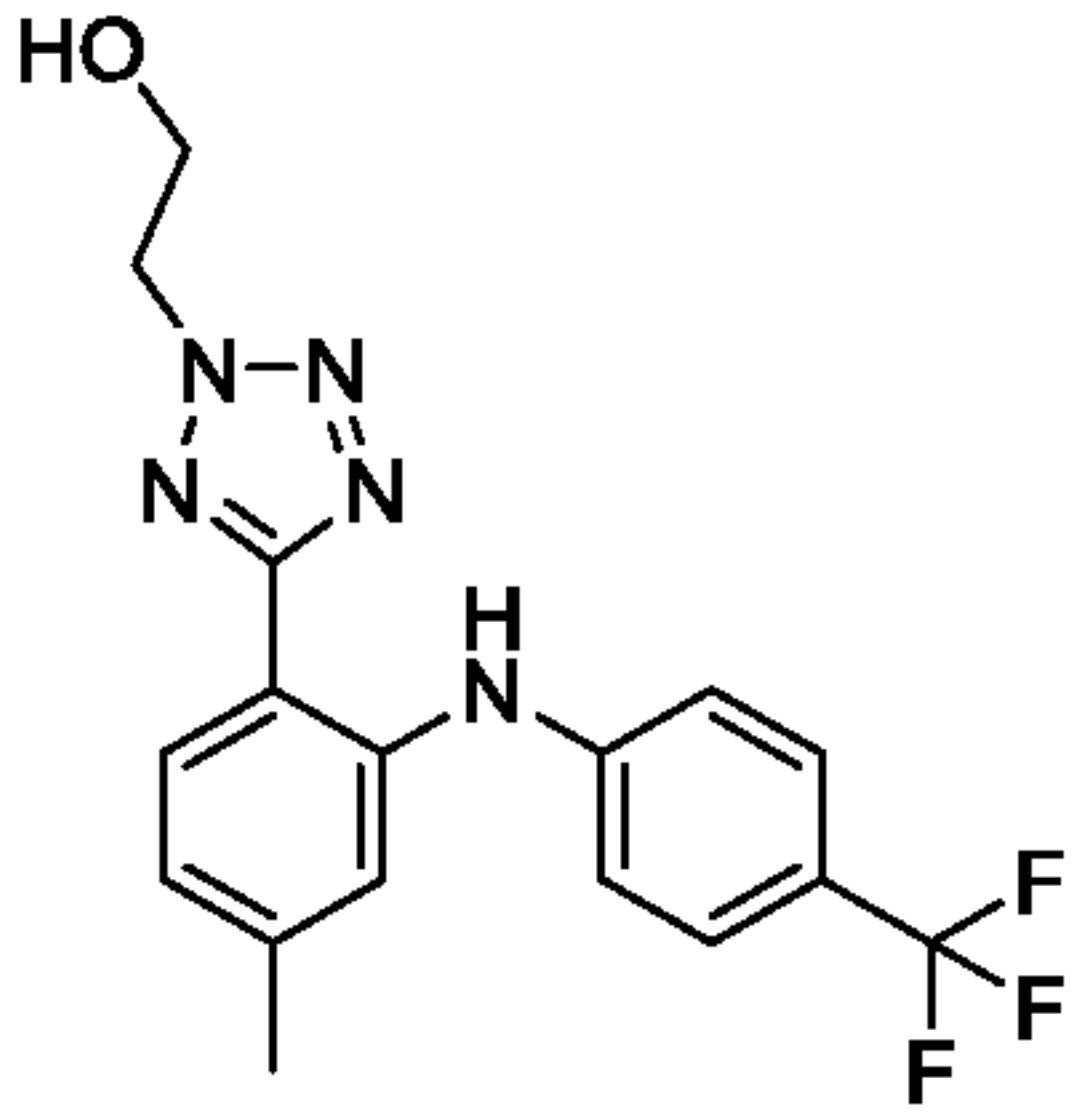
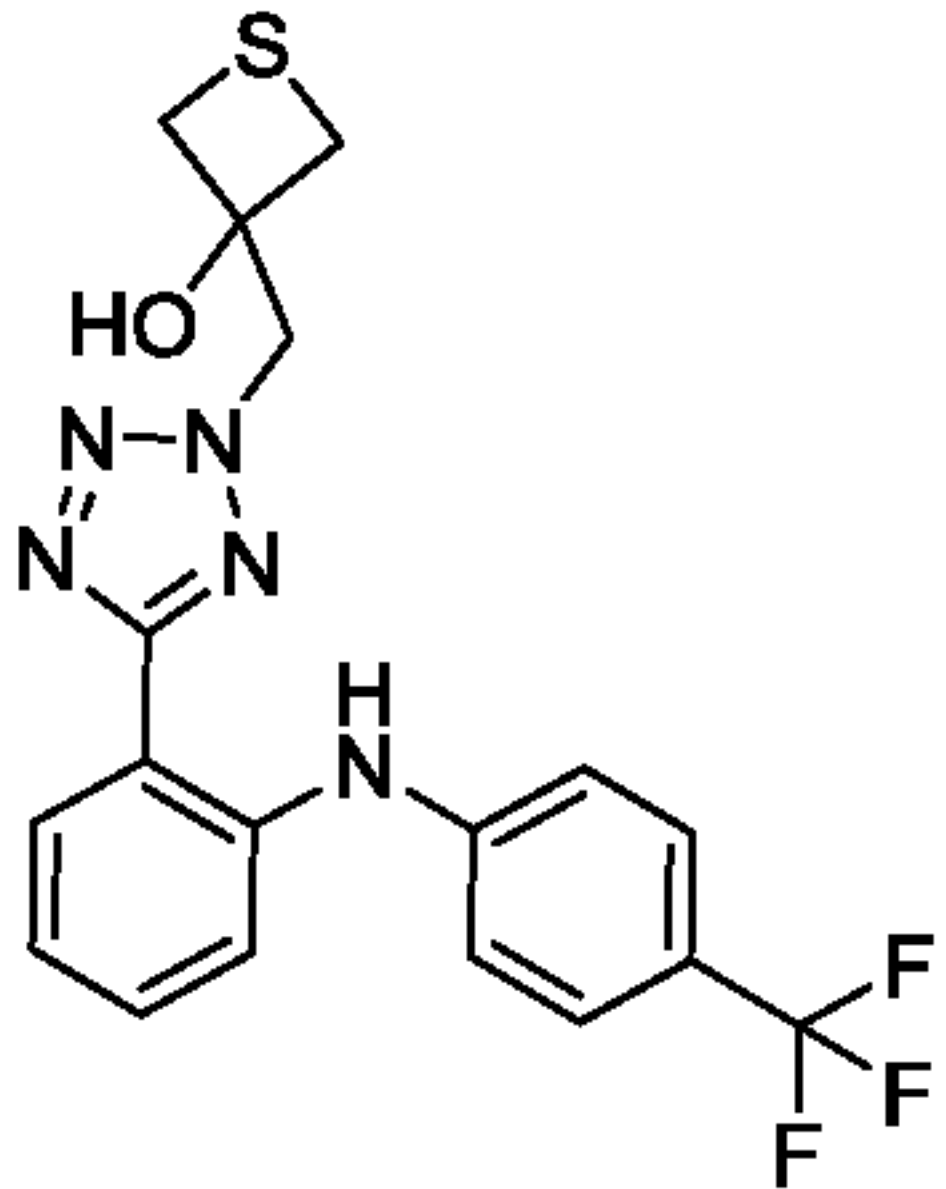
Compound No.	Structure	Name
215		methyl 2-(1-benzyl-3-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-5-yl)acetate
216		2-(2-(3-aminopropyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
217		tert-butyl 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)azetidine-1-carboxylate
218		2-(2-(1-aminopropan-2-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
219		2-(2-(2-(methylamino)ethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

Compound No.	Structure	Name
220		2-(2-(3-(methylamino)propyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
221		2-(2-(azetidin-3-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
222		2-(1-methyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-imidazol-2-yl)ethan-1-ol
223		tert-butyl (2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propyl)carbamate
224		tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethyl)carbamate

Compound No.	Structure	Name
225		tert-butyl methyl(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propyl)carbamate
226		tert-butyl 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)pyrrolidine-1-carboxylate
227		2-(2-(pyrrolidin-3-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
228		2-(2-(2-aminoethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
229		2-(2-(2-aminopropyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

Compound No.	Structure	Name
230		2-(1-(2-aminoethyl)-1H-1,2,4-triazol-3-yl)-N-(4-(trifluoromethyl)phenyl)aniline
231		tert-butyl (3R,4R)-3-hydroxy-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)pyrrolidine-1-carboxylate
232		tert-butyl (3S,4S)-3-hydroxy-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)pyrrolidine-1-carboxylate
233		(3R,4R)-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)pyrrolidin-3-ol
234		(3S,4S)-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)pyrrolidin-3-ol

Compound No.	Structure	Name
235		2-(2-((3-(benzyloxy)thietan-3-yl)methyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
236		3-(benzyloxy)-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)thietane-1-oxide
237		3-(benzyloxy)-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)thietane-1,1-dioxide
238		2-(5-(5-chloro-2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol
239		2-(5-(4-chloro-2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol

Compound No.	Structure	Name
240		2-[5-[5-methoxy-2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol
241		2-[5-[4-methoxy-2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol
242		2-(5-(5-methyl-2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol
243		2-(5-(4-methyl-2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol
244		3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]thietan-3-ol

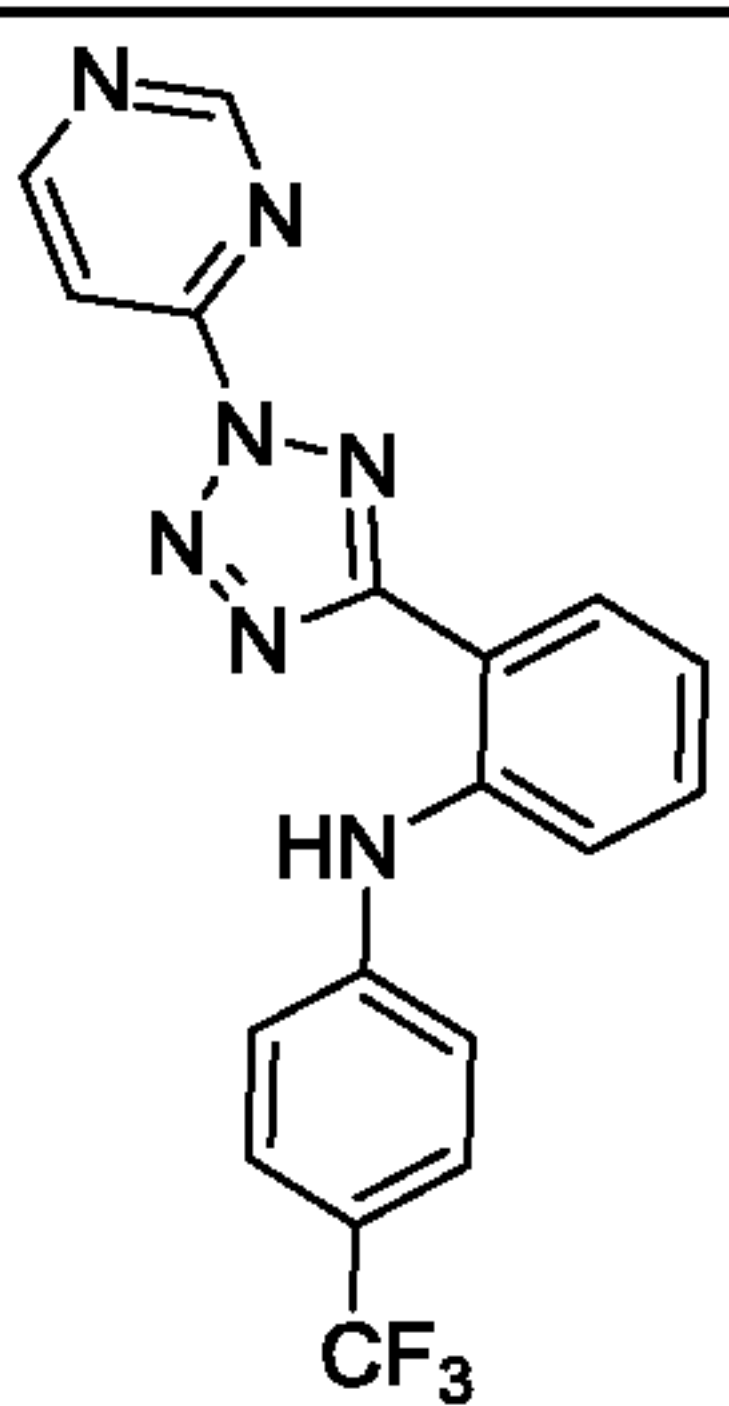
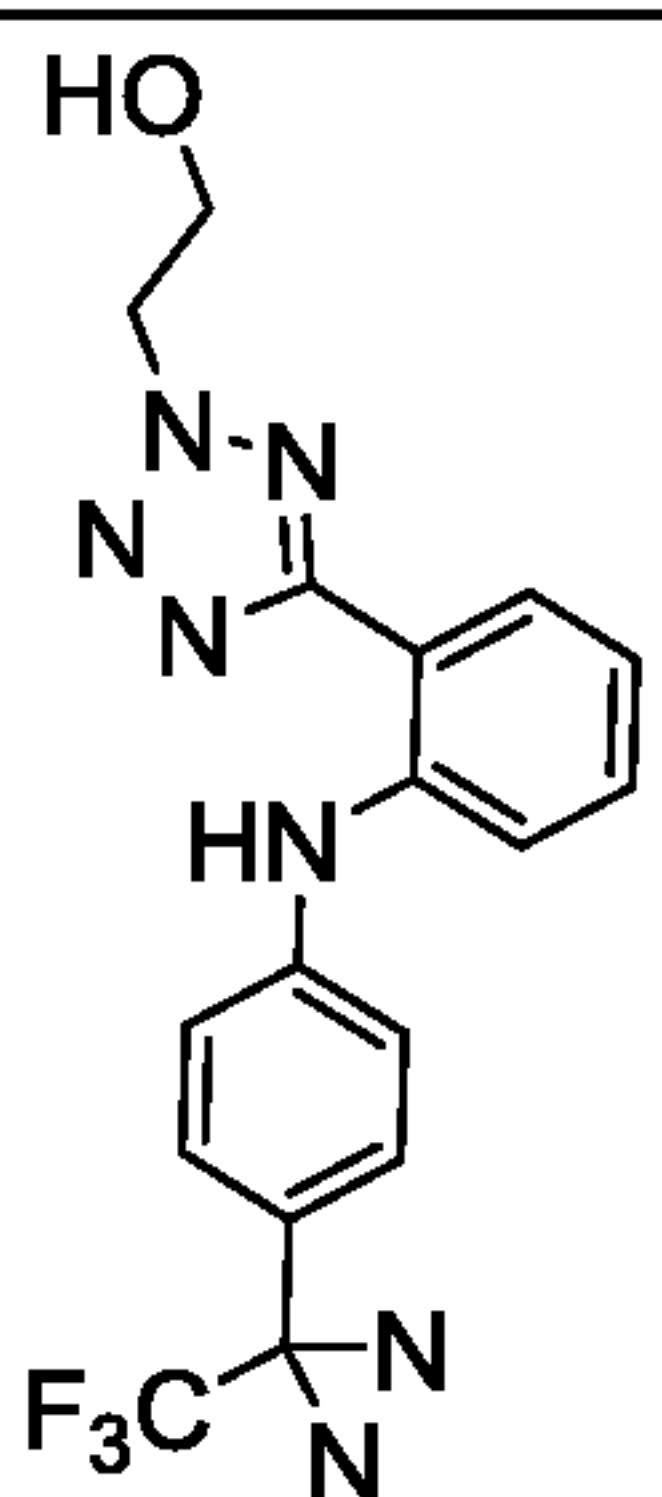
Compound No.	Structure	Name
245		1-oxo-3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]thietan-3-ol
246		2-(5-(2-((3-chloro-4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol
247		1,1-dioxo-3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]thietan-3-ol
248		2-(5-(2-((4-((trifluoromethyl)thio)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol
249		2-[5-[2-[3,5-bis(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol
250		2-(5-(2-((3-chlorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol

Compound No.	Structure	Name
251		2-(5-(2-((3,4-dichlorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol
252		2-(5-(2-((3,5-dichlorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol
253		2-(5-(2-((3,4,5-trichlorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol
254		2-[5-[5-bromo-2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol
255		2-(5-(5-cyclopropyl-2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol
256		2-[5-[5-ethyl-2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol

Compound No.	Structure	Name
257		methyl 3-((tert-butoxycarbonyl)amino)-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propanoate
258		tert-butyl (3-hydroxy-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propyl)carbamate
259		3-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propan-1-ol
260		2-(5-(5-(difluoromethoxy)-2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol
261		2-(5-(5-(trifluoromethoxy)-2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol

Compound No.	Structure	Name
262		2-(5-(5-(trifluoromethyl)-2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol
263		2-(2-(1,3-dioxan-5-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
264		2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propane-1,3-diol
265		2-(2-(1-methyl-1H-pyrazol-4-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
266		2-[5-[5-(difluoromethyl)-2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol

TABLE 2

Structure	Name
	2-(2-(pyrimidin-4-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline
	2-(5-(2-(((4-(3-(trifluoromethyl)-3H-diazirin-3-yl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-ol

Preparation of the Compounds

[00201] The compounds used in the reactions described herein are made according to organic synthesis techniques known to those skilled in this art, starting from commercially available chemicals and/or from compounds described in the chemical literature. "Commercially available chemicals" are obtained from standard commercial sources including Acros Organics (Pittsburgh, PA), Aldrich Chemical (Milwaukee, WI, including Sigma Chemical and Fluka), Apin Chemicals Ltd. (Milton Park, UK), Avocado Research (Lancashire, U.K.), BDH Inc. (Toronto, Canada), Bionet (Cornwall, U.K.), Chemservice Inc. (West Chester, PA), Crescent Chemical Co. (Hauppauge, NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester, NY), Fisher Scientific Co. (Pittsburgh, PA), Fisons Chemicals (Leicestershire, UK), Frontier Scientific (Logan, UT), ICN Biomedicals, Inc. (Costa Mesa, CA), Key Organics (Cornwall, U.K.), Lancaster Synthesis (Windham, NH), Maybridge Chemical Co. Ltd. (Cornwall, U.K.), Parish Chemical Co. (Orem, UT), Pfaltz & Bauer, Inc. (Waterbury, CN), Polyorganix (Houston, TX), Pierce Chemical Co. (Rockford, IL), Riedel de Haen AG (Hanover, Germany), Spectrum Quality Product, Inc. (New Brunswick, NJ), TCI America (Portland, OR), Trans World Chemicals, Inc. (Rockville, MD), and Wako Chemicals USA, Inc. (Richmond, VA).

[00202] Methods known to one of ordinary skill in the art are identified through various reference books and databases. Suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th Ed., Wiley-Interscience, New York, 1992. Additional suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, Fuhrhop, J. and Penzlin G. "Organic Synthesis: Concepts, Methods, Starting Materials", Second, Revised and Enlarged Edition (1994) John Wiley & Sons ISBN: 3-527-29074-5; Hoffman, R.V. "Organic Chemistry, An Intermediate Text" (1996) Oxford University Press, ISBN 0-19-509618-5; Larock, R. C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" 2nd Edition (1999) Wiley-VCH, ISBN: 0-471-19031-4; March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" 4th Edition (1992) John Wiley & Sons, ISBN: 0-471-60180-2; Otera, J. (editor) "Modern Carbonyl Chemistry" (2000) Wiley-VCH, ISBN: 3-527-29871-1; Patai, S. "Patai's 1992 Guide to the Chemistry of Functional Groups" (1992) Interscience ISBN: 0-471-93022-9; Solomons, T. W. G. "Organic Chemistry" 7th Edition (2000) John Wiley & Sons, ISBN: 0-471-19095-0; Stowell, J.C., "Intermediate Organic Chemistry" 2nd Edition (1993) Wiley-Interscience, ISBN: 0-471-57456-2; "Industrial Organic Chemicals: Starting Materials and Intermediates: An Ullmann's Encyclopedia" (1999) John Wiley & Sons, ISBN: 3-527-29645-X, in 8 volumes; "Organic Reactions" (1942-2000) John Wiley & Sons, in over 55 volumes; and "Chemistry of Functional Groups" John Wiley & Sons, in 73 volumes.

[00203] In some instances, specific and analogous reactants are identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as through on-line databases (the American Chemical Society, Washington, D.C., is contacted for more details). Chemicals that are known but not commercially available in catalogs are prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (*e.g.*, those listed above) provide custom synthesis services. A reference for the preparation and selection of pharmaceutical salts of the compounds described herein is P. H. Stahl & C. G. Wermuth "Handbook of Pharmaceutical Salts", Verlag Helvetica Chimica Acta, Zurich, 2002.

[00204] In some embodiments, the compounds disclosed herein are prepared as described in the Examples section.

Further Forms of Compounds Disclosed Herein

Isomers

[00205] Furthermore, in some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all cis, trans, syn, anti, entgegen (*E*), and zusammen (*Z*) isomers as well as the corresponding mixtures thereof. In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the R configuration, or S configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers, and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization.

Labeled compounds

[00206] In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. In some embodiments, examples of

isotopes that are incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds described herein, and the metabolites, pharmaceutically acceptable salts, esters, prodrugs, solvates, hydrates or derivatives thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this disclosure. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i. e., ^3H and carbon-14, i. e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavy isotopes such as deuterium, i. e., ^2H , produces certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. In some embodiments, the isotopically labeled compounds, pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof is prepared by any suitable method.

[00207] In some embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Pharmaceutically acceptable salts

[00208] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[00209] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds of the disclosure, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

Solvates

[00210] In some embodiments, the compounds described herein exist as solvates. The disclosure provides for methods of treating diseases by administering such solvates. The disclosure further provides for methods of treating diseases by administering such solvates as pharmaceutical compositions.

[00211] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. In some embodiments, solvates of the compounds described herein are conveniently prepared or formed during the processes described herein. By way of example only, hydrates of the compounds described herein are conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran or methanol. In some embodiments, the compounds provided herein exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Prodrugs

[00212] In some embodiments, the compounds described herein exist in prodrug form. The disclosure provides for methods of treating diseases by administering such prodrugs. The disclosure further provides for methods of treating diseases by administering such prodrugs as pharmaceutical compositions.

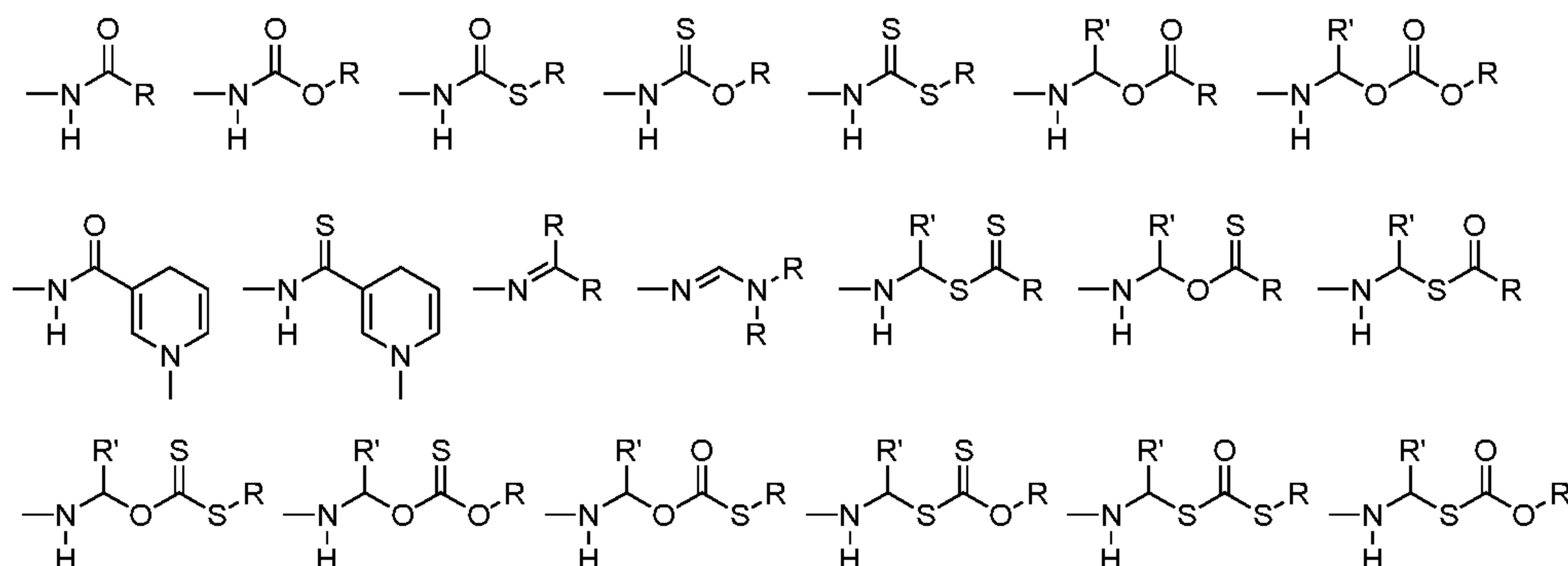
[00213] In some embodiments, prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e. g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy, or carboxylic acid group of compounds of the present disclosure. The amino acid residues include but are not limited to the 20 naturally occurring amino acids and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvaline, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. In other embodiments, prodrugs include compounds wherein a nucleic acid residue, or an oligonucleotide of two or more (e. g., two, three or four) nucleic acid residues is covalently joined to a compound of the present disclosure.

[00214] Pharmaceutically acceptable prodrugs of the compounds described herein also include, but are not limited to, esters, carbonates, thiocarbonates, N-acyl derivatives, N-acyloxyalkyl derivatives, quaternary derivatives of tertiary amines, N-Mannich bases, Schiff bases, amino acid conjugates, metal salts and sulfonate esters. In some embodiments, compounds having free amino, amido, hydroxy, or carboxylic groups are converted into prodrugs. For instance, free carboxyl groups are derivatized as amides or alkyl esters. In certain instances, all of these prodrug moieties incorporate groups including but not limited to ether, amine, and carboxylic acid functionalities.

[00215] Hydroxy prodrugs include esters, such as though not limited to, acyloxyalkyl (e.g. acyloxymethyl, acyloxyethyl) esters, alkoxycarbonyloxyalkyl esters, alkyl esters, aryl esters,

sulfonate esters, sulfate esters and disulfide containing esters; ethers, amides, carbamates, hemisuccinates, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in *Advanced Drug Delivery Reviews* **1996**, *19*, 115.

[00216] Amine derived prodrugs include, but are not limited to, the following groups and combinations of groups:



as well as sulfonamides and phosphonamides.

[00217] In certain instances, sites on any aromatic ring portions are susceptible to various metabolic reactions, therefore incorporation of appropriate substituents on the aromatic ring structures, reduce, minimize, or eliminate this metabolic pathway.

Metabolites

[00218] In some embodiments, compounds described herein are susceptible to various metabolic reactions. Therefore, in some embodiments, incorporation of appropriate substituents into the structure will reduce, minimize, or eliminate a metabolic pathway. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of an aromatic ring to metabolic reactions is, by way of example only, a halogen, or an alkyl group.

[00219] In additional or further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

Pharmaceutical Compositions

[00220] In certain embodiments, the compound as described herein is administered as a pure chemical. In other embodiments, the compound described herein is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)), the disclosure of which is hereby incorporated herein by reference in its entirety.

[00221] Accordingly, provided herein is a pharmaceutical composition comprising at least one compound described herein, or a stereoisomer, pharmaceutically acceptable salt, hydrate, solvate, or N-oxide thereof, together with one or more pharmaceutically acceptable carriers. The carrier(s) (or excipient(s)) is acceptable or suitable if the carrier is compatible with the other ingredients of the composition and not deleterious to the recipient (*i.e.*, the subject) of the composition.

[00222] One embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[00223] One embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (II), or a pharmaceutically acceptable salt thereof.

[00224] One embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (III), or a pharmaceutically acceptable salt thereof.

[00225] Another embodiment provides a pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. Another embodiment provides a pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and a compound of Formula (II), or a pharmaceutically acceptable salt thereof. Another embodiment provides a pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and a compound of Formula (III), or a pharmaceutically acceptable salt thereof.

[00226] In certain embodiments, the compound as described herein is substantially pure, in that it contains less than about 5%, or less than about 1%, or less than about 0.1%, of other organic small molecules, such as contaminating intermediates or by-products that are created, for example, in one or more of the steps of a synthesis method.

[00227] These formulations include those suitable for oral, rectal, topical, buccal, parenteral (*e.g.*, subcutaneous, intramuscular, intradermal, or intravenous), rectal, vaginal, or aerosol administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used. For example, disclosed compositions are formulated as a unit dose, and/or are formulated for oral or subcutaneous administration.

[00228] In some instances, exemplary pharmaceutical compositions are used in the form of a pharmaceutical preparation, for example, in solid, semisolid, or liquid form, which includes one or more of a disclosed compound, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral, or parenteral applications. In some embodiments, the active ingredient is compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions,

and any other form suitable for use. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

[00229] For preparing solid compositions such as tablets in some instances, the principal active ingredient is mixed with a pharmaceutical carrier, *e.g.*, conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, *e.g.*, water, to form a solid preformulation composition containing a homogeneous mixture of a disclosed compound or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition is readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[00230] In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions also comprise buffering agents in some embodiments. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[00231] In some instances, a tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets are prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets are made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, are optionally be scored or prepared with coatings and

shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

[00232] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms contain optionally 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, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

[00233] Suspensions, in addition to the subject composition, optionally contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[00234] In some embodiments, formulations for rectal or vaginal administration are presented as a suppository, which are prepared by mixing a subject composition with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent.

[00235] Dosage forms for transdermal administration of a subject composition include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component is optionally mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which are required in some embodiments.

[00236] In some embodiments, the ointments, pastes, creams and gels contain, in addition to a subject composition, 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.

[00237] In some embodiments, powders and sprays contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[00238] Compositions and compounds disclosed herein are alternatively administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (*e.g.*, fluorocarbon propellant) suspension could be used. Sonic nebulizers are used because they minimize exposing the agent to shear, which result in degradation of the compounds contained in the subject compositions in some embodiments. Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[00239] Pharmaceutical compositions suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which are reconstituted into sterile injectable solutions or dispersions just prior to use, which optionally contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[00240] Examples of suitable aqueous and non-aqueous carriers employed in the pharmaceutical compositions include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. In some embodiments, proper fluidity is maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[00241] Also contemplated are enteral pharmaceutical formulations including a disclosed compound and an enteric material; and a pharmaceutically acceptable carrier or excipient thereof. Enteric materials refer to polymers that are substantially insoluble in the acidic environment of the stomach, and that are predominantly soluble in intestinal fluids at specific pHs. The small intestine is the part of the gastrointestinal tract (gut) between the stomach and the large intestine, and includes the duodenum, jejunum, and ileum. The pH of the duodenum is about 5.5, the pH of the jejunum is about 6.5 and the pH of the distal ileum is about 7.5. Accordingly, enteric materials are not soluble, for example, until a pH of about 5.0, of about 5.2, of about 5.4, of about 5.6, of about 5.8, of about 6.0, of about 6.2, of about 6.4, of about 6.6, of about 6.8, of about 7.0, of about 7.2, of about 7.4, of about 7.6, of about 7.8, of about 8.0, of about 8.2, of about 8.4, of about 8.6, of about

8.8, of about 9.0, of about 9.2, of about 9.4, of about 9.6, of about 9.8, or of about 10.0. Exemplary enteric materials include cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, natural resins such as zein, shellac and copal colophonium, and several commercially available enteric dispersion systems (*e.g.*, Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric). The solubility of each of the above materials is either known or is readily determinable *in vitro*. The foregoing is a list of possible materials, but one of skill in the art with the benefit of the disclosure would recognize that it is not comprehensive and that there are other enteric materials that would meet the objectives of the present disclosure.

[00242] In some embodiments, the dose of the composition comprising at least one compound as described herein differ, depending upon the patient's (*e.g.*, human) condition, that is, stage of the disease, general health status, age, and other factors that a person skilled in the medical art will use to determine dose.

[00243] In some instances, pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented) as determined by persons skilled in the medical arts. An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (*e.g.*, an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. In some embodiments, the optimal dose depends upon the body mass, weight, or blood volume of the patient.

[00244] In some embodiments, oral doses typically range from about 1.0 mg to about 1000 mg, one to four times, or more, per day.

The Hippo Signaling Network

[00245] The Hippo signaling network (also known as the Salvador/Warts/Hippo (SWH) pathway) is a master regulator of cell proliferation, death, and differentiation. In some embodiments, the main function of the Hippo signaling pathway is to regulate negatively the transcriptional co-activators Yes-associated protein (YAP) and its paralogue, the transcriptional co-activator with PDZ-binding motif (TAZ; also known as WWTR1) (**FIG. 1**). The Hippo kinase cascade phosphorylates and inhibits YAP/TAZ by promoting its cytoplasmic retention and degradation, thereby inhibiting the growth promoting function regulated under the YAP/TAZ control. In an un-phosphorylated/de-phosphorylated state, YAP, also known as YAP1 or YAP65, together with TAZ, are transported into the nucleus where they interact with TEAD family of transcription factors to upregulate genes that promote proliferation and migration, and inhibit apoptosis. In some instances, unregulated upregulation of these genes involved in proliferation, migration, and anti-apoptosis leads to development of cancer. In some instances, overexpression of YAP/TAZ is associated with cancer.

[00246] Additional core members of the Hippo signaling pathway comprise the serine/threonine kinases MST1/2 (homologues of *Hippo/Hpo* in *Drosophila*), Lats1/2 (homologues of *Warts/Wts*), and their adaptor proteins Sav1 (homologue of *Salvador/Sav*) and Mob (MOBKL1A and MOBKL1B; homologues of *Mats*), respectively (**FIG. 1**). In general, MST1/2 kinase complexes with the scaffold protein Sav1, which in turn phosphorylates and activates Lats1/2 kinase. Lats1/2 is also activated by the scaffold protein Mob. The activated Lats1/2 then phosphorylates and inactivates YAP or its paralog TAZ. The phosphorylation of YAP/TAZ leads to their nuclear export, retention within the cytoplasm, and degradation by the ubiquitin proteasome system.

[00247] In some instances, Lats1/2 phosphorylates YAP at the [HXRXXS] consensus motifs. YAP comprises five [HXRXXS] consensus motifs, wherein X denotes any amino acid residue. In some instances, Lats1/2 phosphorylates YAP at one or more of the consensus motifs. In some instances, Lats1/2 phosphorylates YAP at all five of the consensus motifs. In some instances, Lats1/2 phosphorylate at the S127 amino acid position. The phosphorylation of YAP S127 promotes 14-3-3 protein binding and results in cytoplasmic sequestration of YAP. Mutation of YAP at the S127 position thereby disrupts its interaction with 14-3-3 and subsequently promotes nuclear translocation.

[00248] Additional phosphorylation occurs at the S381 amino acid position in YAP. Phosphorylation of YAP at the S381 position and on the corresponding site in TAZ primes both proteins for further phosphorylation events by CK1 δ/ϵ in the degradation motif, which then signals for interaction with the β -TRCP E3 ubiquitin ligase, leading to polyubiquitination and degradation of YAP.

[00249] In some instances, Lats1/2 phosphorylates TAZ at the [HXRXXS] consensus motifs. TAZ comprises four [HXRXXS] consensus motifs, wherein X denotes any amino acid residues. In some instances, Lats1/2 phosphorylates TAZ at one or more of the consensus motifs. In some instances, Lats1/2 phosphorylates TAZ at all four of the consensus motifs. In some instances, Lats1/2 phosphorylate at the S89 amino acid position. The phosphorylation of TAZ S89 promotes 14-3-3 protein binding and results in cytoplasmic sequestration of TAZ. Mutation of TAZ at the S89 position thereby disrupts its interaction with 14-3-3 and subsequently promotes nuclear translocation.

[00250] In some embodiments, phosphorylated YAP/TAZ accumulates in the cytoplasm, and undergoes SCF^{β-TRCP}-mediated ubiquitination and subsequent proteasomal degradation. In some instances, the Skp, Cullin, F-box containing complex (SCF complex) is a multi-protein E3 ubiquitin ligase complex that comprises a F-box family member protein (e.g. Cdc4), Skp1, a bridging protein, and RBX1 which contains a small RING Finger domain which interacts with E2-ubiquitin conjugating enzyme. In some cases, the F-box family comprises more than 40 members, in which exemplary members include F-box/WD repeat-containing protein 1A (FBXW1A, βTrCP1, Fbxw1, hsSlimb, plkappaBalpha-E3 receptor subunit) and S-phase kinase-associated proteins 2 (SKP2). In some embodiments, the SCF complex (e.g. SCF^{βTrCP1}) interacts with an E1 ubiquitin-activating enzyme and an E2 ubiquitin-conjugating enzyme to catalyze the transfer of ubiquitin to the YAP/TAZ substrate. Exemplary E1 ubiquitin-activating enzymes include those encoded by the following genes: *UBA1*, *UBA2*, *UBA3*, *UBA5*, *UBA5*, *UBA7*, *ATG7*, *NAE1*, and *SAE1*. Exemplary E2 ubiquitin-conjugating enzymes include those encoded by the following genes: *UBE2A*, *UBE2B*, *UBE2C*, *UBE2D1*, *UBE2D2*, *UBE2D3*, *UBE2E1*, *UBE2E2*, *UBE2E3*, *UBE2F*, *UBE2G1*, *UBE2G2*, *UBE2H*, *UBE2I*, *UBE2J1*, *UBE2J2*, *UBE2K*, *UBE2L3*, *UBE2L6*, *UBE2M*, *UBE2N*, *UBE2O*, *UBE2Q1*, *UBE2Q2*, *UBE2R1*, *UBE2R2*, *UBE2S*, *UBE2T*, *UBE2U*, *UBE2V1*, *UBE2V2*, *UBE2Z*, *ATG2*, *BIRC5*, and *UFC1*. In some embodiments, the ubiquitinated YAP/TAZ further undergoes the degradation process through the 26S proteasome.

[00251] In some embodiments, the Hippo pathway is regulated upstream by several different families of regulators (**FIG. 1**). In some instances, the Hippo pathway is regulated by the G-protein and its coupled receptors, the Crumbs complex, regulators upstream of the MST kinases, and the adherens junction.

YAP/TAZ Interaction with TEAD

[00252] In some embodiments, un-phosphorylated and/or dephosphorylated YAP/TAZ accumulates in the nucleus. Within the nucleus, YAP/TAZ interacts with the TEAD family of

transcription factors (e.g. TEAD1, TEAD2, TEAD3, or TEAD4) to activate genes involved in anti-apoptosis and proliferation, such as for example *CTFG*, *Cyr61*, and *FGF1*.

[00253] In some embodiments, the compounds disclosed herein modulate the interaction between YAP/TAZ and TEAD. In some embodiments, the compounds disclosed herein bind to TEAD, YAP, or TAZ and prevent the interaction between YAP/TAZ and TEAD.

YAP/TAZ regulation mediated by G-proteins/GPCRs

[00254] In some embodiments, the Hippo pathway is regulated by the G protein-coupled receptor (GPCR) and G protein (also known as guanine nucleotide-binding proteins) family of proteins (**FIG. 2**). G proteins are molecular switches that transmit extracellular stimuli into the cell through GPCRs. In some instances, there are two classes of G proteins: monomeric small GTPases; and heterotrimeric G protein complexes. In some instances, the latter class of complexes comprise of alpha (G_α), beta (G_β), and gamma (G_γ) subunits. In some cases, there are several classes of G_α subunits: $G_{q/11}\alpha$, $G_{12/13}\alpha$, $G_{i/o}\alpha$ (G inhibitory, G other), and $G_s\alpha$ (G stimulatory).

[00255] In some instances, $G_i\alpha$ (G inhibitory), $G_o\alpha$ (G other), $G_{q/11}\alpha$, and $G_{12/13}\alpha$ coupled GPCRs activate YAP/TAZ and promote nuclear translocation. In other instances, $G_s\alpha$ (G stimulatory) coupled GPCRs suppress YAP/TAZ activity, leading to YAP/TAZ degradation.

[00256] In some cases, $G_i\alpha$ (G inhibitory), $G_o\alpha$ (G other), $G_{q/11}\alpha$, and $G_{12/13}\alpha$ coupled GPCRs activate YAP/TAZ through repression of Lats1/2 activities. In contrast, $G_s\alpha$, in some embodiments, induces Lats1/2 activity, thereby promoting YAP/TAZ degradation.

G_q Family

[00257] $G_{q\alpha}$ (also known as $G_{q/11}$ protein), participates in the inositol trisphosphate (IP_3) signal transduction pathway and calcium (Ca^{2+}) release from intracellular storage through the activation of phospholipase C (PLC). The activated PLC hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to diacyl glycerol (DAG) and IP_3 . In some instances, IP_3 then diffuses through the cytoplasm into the ER or the sarcoplasmic reticulum (SR) in the case of muscle cells, and then binds to inositol trisphosphate receptor ($InsP3R$), which is a Ca^{2+} channel. In some cases, the binding triggers the opening of the Ca^{2+} channel, and thereby increases the release of Ca^{2+} into the cytoplasm.

[00258] In some embodiments, the GPCRs that interact with $G_{q\alpha}$ include, but are not limited to, 5-hydroxytryptamine receptor (5-HT receptor) types 5-HT₂ and 5-HT₃; alpha-1 adrenergic receptor; vasopressin type 1 receptors 1A and 1B; angiotensin II receptor type 1; calcitonin receptor; histamine H1 receptor; metabotropic glutamate receptor, group I; muscarinic receptors M₁, M₃, and M₅; and trace amine-associated receptor 1.

[00259] In some instances, there are several types of $G_q\alpha$: G_q , $G_{q/11}$, $G_{q/14}$, and $G_{q/15}$. The G_q protein is encoded by *GNAQ*. $G_{q/11}$ is encoded by *GNA11*. $G_{q/14}$ is encoded by *GNA14*. $G_{q/15}$ is encoded by *GNA15*.

[00260] In some instances, mutations or modifications of the $G_q\alpha$ genes have been associated with cancer. Indeed, studies have shown that mutations in $G_q\alpha$ promote uveal melanoma (UM) tumorigenesis. In some instances, about 80% of UM cases have been detected to contain a mutation in *GNAQ* and/or *GNA11*.

[00261] In some instances, mutations or modifications of the $G_q\alpha$ genes have been associated with congenital diseases. In some instances, mutations of $G_q\alpha$ have been observed in congenital diseases such as Port-Wine Stain and/or Sturge-Weber Syndrome. In some instances, about 92% of Port-Wine stain cases harbors a mutation in *GNAQ*. In some instances, about 88% of Sturge-Weber Syndrome harbors a mutation in *GNAQ*.

G_{12/13} Family

[00262] $G_{12/13}\alpha$ modulates actin cytoskeletal remodeling in cells and regulates cell processes through guanine nucleotide exchange factors (GEFs). GEFs participate in the activation of small GTPases which acts as molecular switches in a variety of intracellular signaling pathways. Examples of small GTPases include the Ras-related GTPase superfamily (e.g. Rho family such as Cdc42), which is involved in cell differentiation, proliferation, cytoskeletal organization, vesicle trafficking, and nuclear transport.

[00263] In some embodiments, the GPCRs that interact with $G_{12/13}\alpha$ include, but are not limited to, purinergic receptors (e.g. P2Y₁, P2Y₂, P2Y₄, P2Y₆); muscarinic acetylcholine receptors M1 and M3; receptors for thrombin [protease-activated receptor (PAR)-1, PAR-2]; thromboxane (TXA₂); sphingosine 1-phosphate (e.g. S1P₂, S1P₃, S1P₄ and S1P₅); lysophosphatidic acid (e.g. LPA₁, LPA₂, LPA₃); angiotensin II (AT1); serotonin (5-HT_{2c} and 5-HT₄); somatostatin (sst₅); endothelin (ET_A and ET_B); cholecystokinin (CCK₁); V_{1a} vasopressin receptors; D₅ dopamine receptors; fMLP formyl peptide receptors; GAL₂ galanin receptors; EP₃ prostanoid receptors; A₁ adenosine receptors; α_1 adrenergic receptors; BB₂ bombesin receptors; B₂ bradykinin receptors; calcium-sensing receptors; KSHV-ORF74 chemokine receptors; NK₁ tachykinin receptors; and thyroid-stimulating hormone (TSH) receptors.

[00264] In some instances, $G_{12/13}\alpha$ is further subdivided into G_{12} and G_{13} types which are encoded by *GNA12* and *GNA13*, respectively.

G_{i/o} Family

[00265] $G_{i/o}\alpha$ (G inhibitory, G other) (also known as G_i/G_0 or G_i protein) that suppresses the production of 3',5'-cyclic AMP (cAMP) from adenosine triphosphate (ATP) through an inhibition of adenylate cyclase activity, which converts ATP to cAMP.

[00266] In some embodiments, the GPCRs that interact with $G_i\alpha$ include, but are not limited to, 5-hydroxytryptamine receptor (5-HT receptor) types 5-HT₁ and 5-HT₅; muscarinic acetylcholine receptors such as M₂ and M₄; adenosine receptors such as A₁ and A₃; adrenergic receptors such as α_{2A} , α_{2B} , and α_{2C} ; apelin receptors; calcium-sensing receptor; cannabinoid receptors CB1 and CB2; chemokine CXCR4 receptor; dopamines D₂, D₃, and D₄; GABA_B receptor; glutamate receptors such as metabotropic glutamate receptor 2 (mGluR2), metabotropic glutamate receptor 3 (mGluR3), metabotropic glutamate receptor 4 (mGluR4), metabotropic glutamate receptor 6 (mGluR6), metabotropic glutamate receptor 7 (mGluR7), and metabotropic glutamate receptor 8 (mGluR8); histamine receptors such as H₃ and H₄ receptors; melatonin receptors such as melatonin receptor type 1 (MT1), melatonin receptor type 2 (MT2), and melatonin receptor type 3 (MT3); niacin receptors such as NIACR1 and NIACR2; opioid receptors such as δ , κ , μ , and nociceptin receptors; prostaglandin receptors such as prostaglandin E receptor 1 (EP₁), prostaglandin E receptor 3 (EP₃), prostaglandin F receptor (FP), and thromboxane receptor (TP); somatostatin receptors sst1, sst2, sst3, sst4, and sst5; and trace amine-associated receptor 8.

[00267] In some instances, there are several types of $G_i\alpha$: $G_{i1}\alpha$, $G_{i2}\alpha$, $G_{i3}\alpha$, $G_{i4}\alpha$, $G_o\alpha$, G_t , G_{gust} , and G_z . $G_{i1}\alpha$ is encoded by *GNAI1*. $G_{i2}\alpha$ is encoded by *GNAI2*. $G_{i3}\alpha$ is encoded by *GNAI3*. $G_o\alpha$, the a_o subunit, is encoded by *GNAO1*. G_t is encoded by *GNAT1* and *GNAT2*. G_{gust} is encoded by *GNAT3*. G_z is encoded by *GNAZ*.

G_s Family

[00268] $G_s\alpha$ (also known as G stimulatory, G_s alpha subunit, or G_s protein) activates the cAMP-dependent pathway through the activation of adenylate cyclase, which converts adenosine triphosphate (ATP) to 3',5'-cyclic AMP (cAMP) and pyrophosphate. In some embodiments, the GPCRs that interact with $G_s\alpha$ include, but are not limited to, 5-hydroxytryptamine receptor (5-HT receptor) types 5-HT₄, 5-HT₆, and 5-HT₇; adrenocorticotrophic hormone receptor (ACTH receptor) (also known as melanocortin receptor 2 or MC2R); adenosine receptor types A_{2a} and A_{2b}; arginine vasopressin receptor 2 (AVPR2); β -adrenergic receptors β_1 , β_2 , and β_3 ; calcitonin receptor; calcitonin gene-related peptide receptor; corticotropin-releasing hormone receptor; dopamine receptor D₁-like family receptors such as D₁ and D₅; follicle-stimulating hormone receptor (FSH-receptor); gastric inhibitory polypeptide receptor; glucagon receptor; histamine H₂ receptor; luteinizing hormone/choriogonadotropin receptor; melanocortin receptors such as MC1R, MC2R, MC3R, MC4R, and MC5R; parathyroid hormone receptor 1; prostaglandin receptor types D₂ and

I₂; secretin receptor; thyrotropin receptor; trace amine-associated receptor 1; and box jellyfish opsin.

[00269] In some instances, there are two types of G_sα: G_s and G_{olf}. G_s is encoded by *GNAS*. G_{olf} is encoded by *GNAL*.

Additional Regulators of the Hippo signaling network

[00270] In some embodiments, the additional regulator of the Hippo signaling pathway is the Crumbs (Crb) complex. The Crumbs complex is a key regulator of cell polarity and cell shape. In some instances, the Crumbs complex comprises transmembrane CRB proteins which assemble multi-protein complexes that function in cell polarity. In some instances, CRB complexes recruit members of the Angiomotin (AMOT) family of adaptor proteins that interact with the Hippo pathway components. In some instances, studies have shown that AMOT directly binds to YAP, promotes YAP phosphorylation, and inhibits its nuclear localization.

[00271] In some instances, the additional regulator of the Hippo signaling pathway comprises regulators of the MST kinase family. MST kinases monitor actin cytoskeletal integrity. In some instances, the regulators include TAO kinases and cell polarity kinase PAR-1.

[00272] In some instances, the additional regulator of the Hippo signaling pathway comprises molecules of the adherens junction. In some instances, E-Cadherin (E-cad) suppresses YAP nuclear localization and activity through regulating MST activity. In some embodiments, E-cad-associated protein α-catenin regulates YAP through sequestering YAP/14-3-3 complexes in the cytoplasm. In other instances, Ajuba protein family members interact with Lats1/2 kinase activity, thereby preventing inactivation of YAP/TAZ.

[00273] In some embodiments, additional proteins that interact with YAP/TAZ either directly or indirectly include, but are not limited to, Merlin, protocadherin Fat 1, MASK1/2, HIPK2, PTPN14, RASSF, PP2A, Salt-inducible kinases (SIKs), Scribble (SCRIB), the Scribble associated proteins Discs large (Dlg), KIBRA, PTPN14, NPHP3, LKB1, Ajuba, and ZO1/2.

[00274] In some embodiments, the compounds described herein are inhibitors of transcriptional coactivator with PDZ binding motif/Yes- associated protein transcriptional coactivator (TAZ/YAP). In some embodiments, the compounds described herein increase the phosphorylation of transcriptional coactivator with PDZ binding motif/ Yes- associated protein transcriptional coactivator (TAZ/YAP) or decrease the dephosphorylation of transcriptional coactivator with PDZ binding motif/ Yes- associated protein transcriptional coactivator (TAZ/YAP). In some embodiments, the compounds increase the ubiquitination of transcriptional coactivator with PDZ binding motif/ Yes- associated protein transcriptional coactivator (TAZ/YAP) or decrease the

deubiquitination of transcriptional coactivator with PDZ binding motif/ Yes- associated protein transcriptional coactivator (TAZ/YAP).

[00275] In some embodiments, the compounds disclosed herein are inhibitors of one or more of the proteins encompassed by, or related to, the Hippo pathway. In some instances, the one or more proteins comprise a protein shown in Figs. 1 and/or 2. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a G-protein and/or its coupled GPCR. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a G-protein. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of the $G_q\alpha$ family proteins such as G_q , $G_{q/11}$, $G_{q/14}$, and $G_{q/15}$; the $G_{12/13}\alpha$ family of proteins such as G_{12} and G_{13} ; or the $G_i\alpha$ family of proteins such as $G_{i\alpha1}$, $G_{i\alpha2}$, $G_{i\alpha3}$, $G_{i\alpha4}$, $G_o\alpha$, G_t , G_{gust} , and G_z . In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_q . In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{q/11}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{q/14}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{q/15}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_{12} . In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_{13} . In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{i\alpha1}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{i\alpha2}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{i\alpha3}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{i\alpha4}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_o\alpha$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_t . In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_{gust} . In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_z .

[00276] In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a core protein of the Hippo pathway. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of Sav1. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of Mob. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of YAP. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of TAZ. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of TEAD.

[00277] In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a protein associated with the ubiquitination and proteasomal degradation pathway. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a proteasomal degradation pathway protein (e.g. 26S proteasome).

[00278] In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a protein of the Ras superfamily of proteins. In some embodiments, an inhibitor of the Hippo pathway is an

inhibitor of a protein of the Rho family of proteins. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of Cdc42.

[00279] Cdc42 is a member of the Ras superfamily of small GTPases. Specifically, Cdc42 belongs to the Rho family of GTPases, in which the family members participate in diverse and critical cellular processes such as gene transcription, cell-cell adhesion, and cell cycle progression. Cdc42 is involved in cell growth and polarity, and in some instances, Cdc42 is activated by guanine nucleotide exchange factors (GEFs). In some cases, an inhibitor of Cdc42 is a compound disclosed herein.

[00280] In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a deubiquitinating enzyme. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a cysteine protease or a metalloprotease. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of an ubiquitin-specific protease. USP47 is a member of the ubiquitin-specific protease (USP/UBP) superfamily of cysteine proteases. In some embodiments, the compounds disclosed herein are inhibitors of USP47.

[00281] Further embodiments provided herein include combinations of one or more of the particular embodiments set forth above.

Diseases

Cancer

[00282] In some embodiments, the compounds disclosed herein are useful for treating cancer. In some embodiments, the cancer is mediated by activation of transcriptional coactivator with PDZ binding motif/Yes-associated protein transcription coactivator (TAZ/YAP). In some embodiments, the cancer is mediated by modulation of the interaction of YAP/TAZ with TEAD. In some embodiments, the cancer is characterized by a mutant G α -protein. In some embodiments, the mutant G α -protein is selected from G12, G13, Gq, G11, Gi, Go, and Gs. In some embodiments, the mutant G α -protein is G12. In some embodiments, the mutant G α -protein is G13. In some embodiments, the mutant G α -protein is Gq. In some embodiments, the mutant G α -protein is G11. In some embodiments, the mutant G α -protein is Gi. In some embodiments, the mutant G α -protein is Go. In some embodiments, the mutant G α -protein is Gs.

[00283] In some embodiments, the cancer is a solid tumor. In some instances, the cancer is a hematologic malignancy. In some instances, the solid tumor is a sarcoma or carcinoma. In some instances, the solid tumor is a sarcoma. In some instances, the solid tumor is a carcinoma.

[00284] Exemplary sarcoma includes, but is not limited to, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastoma, angiosarcoma, chondrosarcoma, chordoma, clear cell sarcoma of soft tissue, dedifferentiated liposarcoma, desmoid, desmoplastic small round cell tumor, embryonal

rhabdomyosarcoma, epithelioid fibrosarcoma, epithelioid hemangioendothelioma, epithelioid sarcoma, esthesioneuroblastoma, Ewing sarcoma, extrarenal rhabdoid tumor, extraskeletal myxoid chondrosarcoma, extraskeletal osteosarcoma, fibrosarcoma, giant cell tumor, hemangiopericytoma, infantile fibrosarcoma, inflammatory myofibroblastic tumor, Kaposi sarcoma, leiomyosarcoma of bone, liposarcoma, liposarcoma of bone, malignant fibrous histiocytoma (MFH), malignant fibrous histiocytoma (MFH) of bone, malignant mesenchymoma, malignant peripheral nerve sheath tumor, mesenchymal chondrosarcoma, myxofibrosarcoma, myxoid liposarcoma, myxoinflammatory fibroblastic sarcoma, neoplasms with perivascular epithelioid cell differentiation, osteosarcoma, parosteal osteosarcoma, neoplasm with perivascular epithelioid cell differentiation, periosteal osteosarcoma, pleomorphic liposarcoma, pleomorphic rhabdomyosarcoma, PNET/extraskeletal Ewing tumor, rhabdomyosarcoma, round cell liposarcoma, small cell osteosarcoma, solitary fibrous tumor, synovial sarcoma, and telangiectatic osteosarcoma.

[00285] Exemplary carcinoma includes, but is not limited to, adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, anaplastic carcinoma, large cell carcinoma, small cell carcinoma, anal cancer, appendix cancer, bile duct cancer (i.e., cholangiocarcinoma), bladder cancer, brain tumor, breast cancer, cervical cancer, colon cancer, cancer of Unknown Primary (CUP), esophageal cancer, eye cancer, fallopian tube cancer, gastroenterological cancer, kidney cancer, liver cancer, lung cancer, medulloblastoma, melanoma, oral cancer, ovarian cancer, pancreatic cancer, parathyroid disease, penile cancer, pituitary tumor, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, and vulvar cancer. In some instances, the liver cancer is primary liver cancer.

[00286] In some instances, the cancer is selected from uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, and meningioma. In some cases, the cancer is uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, or meningioma. In some cases, the cancer is uveal melanoma, mesothelioma, esophageal cancer, or liver cancer. In some cases, the cancer is uveal melanoma. In some cases, the cancer is mesothelioma. In some cases, the cancer is esophageal cancer. In some cases, the cancer is liver cancer. In some cases, the cancer is primary liver cancer.

[00287] In some instances, the cancer is a hematologic malignancy. In some embodiments, a hematologic malignancy is a leukemia, a lymphoma, a myeloma, a non-Hodgkin's lymphoma, a Hodgkin's lymphoma, a T-cell malignancy, or a B-cell malignancy. In some instances, a hematologic malignancy is a T-cell malignancy. Exemplary T-cell malignancy includes, but is not limited to, peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma, angioimmunoblastic lymphoma, cutaneous T-cell lymphoma, adult T-cell leukemia/lymphoma (ATLL), blastic NK-cell lymphoma, enteropathy-type T-cell lymphoma, hematosplenic gamma-delta T-cell lymphoma, lymphoblastic lymphoma, nasal NK/T-cell lymphomas, and treatment-related T-cell lymphomas.

[00288] In some instances, a hematologic malignancy is a B-cell malignancy. Exemplary B-cell malignancy includes, but is not limited to, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, and a non-CLL/SLL lymphoma. In some embodiments, the cancer is follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, multiple myeloma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, primary mediastinal B-cell lymphoma (PMBL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, or lymphomatoid granulomatosis.

[00289] In some instances, the cancer is a relapsed or refractory cancer. In some embodiments, the relapsed or refractory cancer is a relapsed or refractory solid tumor. In some embodiments, the relapsed or refractory solid tumor is a relapsed or refractory sarcoma or a relapsed or refractory carcinoma. In some embodiments, the relapsed or refractory carcinoma includes adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, anaplastic carcinoma, large cell carcinoma, small cell carcinoma, anal cancer, appendix cancer, bile duct cancer (i.e., cholangiocarcinoma), bladder cancer, brain tumor, breast cancer, cervical cancer, colon cancer, cancer of Unknown Primary (CUP), esophageal cancer, eye cancer, fallopian tube cancer, gastroenterological cancer, kidney cancer, liver cancer, lung cancer, medulloblastoma, melanoma, oral cancer, ovarian cancer, pancreatic cancer, parathyroid disease, penile cancer, pituitary tumor, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, and vulvar cancer.

[00290] In some instances, the relapsed or refractory cancer is selected from relapsed or refractory uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular

carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, or meningioma. In some cases, the relapsed or refractory cancer is relapsed or refractory uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, and meningioma. In some cases, the relapsed or refractory cancer is relapsed or refractory uveal melanoma, mesothelioma, esophageal cancer, or liver cancer. In some cases, the relapsed or refractory cancer is relapsed or refractory uveal melanoma. In some cases, the relapsed or refractory cancer is relapsed or refractory mesothelioma. In some cases, the relapsed or refractory cancer is relapsed or refractory esophageal cancer. In some cases, the relapsed or refractory cancer is relapsed or refractory liver cancer. In some cases, the relapsed or refractory cancer is relapsed or refractory primary liver cancer.

[00291] In some instances, the relapsed or refractory cancer is a relapsed or refractory hematologic malignancy. In some embodiments, a relapsed or refractory hematologic malignancy is a relapsed or refractory leukemia, a relapsed or refractory lymphoma, a relapsed or refractory myeloma, a relapsed or refractory non-Hodgkin's lymphoma, a relapsed or refractory Hodgkin's lymphoma, a relapsed or refractory T-cell malignancy, or a relapsed or refractory B-cell malignancy. In some instances, a relapsed or refractory hematologic malignancy is a relapsed or refractory T-cell malignancy. In some instances, a relapsed or refractory hematologic malignancy is a relapsed or refractory B-cell malignancy, such as for example, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, or a non-CLL/SLL lymphoma. In some embodiments, the cancer is follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, multiple myeloma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, primary mediastinal B-cell lymphoma (PMBL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, or lymphomatoid granulomatosis.

[00292] In some instances, the cancer is a metastasized cancer. In some instances, the metastasized cancer is a metastasized solid tumor. In some instances, the metastasized solid tumor is a metastasized sarcoma or a metastasized carcinoma. In some embodiments, the metastasized

carcinoma includes adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, anaplastic carcinoma, large cell carcinoma, small cell carcinoma, anal cancer, appendix cancer, bile duct cancer (i.e., cholangiocarcinoma), bladder cancer, brain tumor, breast cancer, cervical cancer, colon cancer, cancer of Unknown Primary (CUP), esophageal cancer, eye cancer, fallopian tube cancer, gastroenterological cancer, kidney cancer, liver cancer, lung cancer, medulloblastoma, melanoma, oral cancer, ovarian cancer, pancreatic cancer, parathyroid disease, penile cancer, pituitary tumor, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, and vulvar cancer.

[00293] In some instances, the metastasized cancer is selected from metastasized uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, and meningioma. In some cases, the metastasized cancer is metastasized uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, or meningioma. In some cases, the metastasized cancer is metastasized uveal melanoma, mesothelioma, esophageal cancer, or liver cancer. In some cases, the metastasized cancer is metastasized uveal melanoma. In some cases, the metastasized cancer is metastasized mesothelioma. In some cases, the metastasized cancer is metastasized esophageal cancer. In some cases, the metastasized cancer is metastasized liver cancer. In some cases, the metastasized cancer is metastasized primary liver cancer.

[00294] In some instances, the metastasized cancer is a metastasized hematologic malignancy. In some embodiments, the metastasized hematologic malignancy is a metastasized leukemia, a metastasized lymphoma, a metastasized myeloma, a metastasized non-Hodgkin's lymphoma, a metastasized Hodgkin's lymphoma, a metastasized T-cell malignancy, or a metastasized B-cell malignancy. In some instances, a metastasized hematologic malignancy is a metastasized T-cell malignancy. In some instances, a metastasized hematologic malignancy is a metastasized B-cell malignancy, such as for example, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, or a non-CLL/SLL lymphoma. In some embodiments, the cancer is follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, multiple myeloma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, primary mediastinal B-cell lymphoma (PMBL), immunoblastic large cell

lymphoma, precursor B-lymphoblastic lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, or lymphomatoid granulomatosis.

Congenital Diseases

[00295] In some embodiments, the compounds disclosed herein are useful for treating a congenital disease. In some embodiments, the congenital disease is mediated by activation of transcriptional coactivator with PDZ binding motif/Yes- associated protein transcription coactivator (TAZ/YAP). In some embodiments, the congenital disease is characterized by a mutant Gα-protein. In some embodiments, the mutant Gα-protein is selected from G12, G13, Gq, G11, Gi, Go, and Gs. In some embodiments, the mutant Gα-protein is G12. In some embodiments, the mutant Gα-protein is G13. In some embodiments, the mutant Gα-protein is Gq. In some embodiments, the mutant Gα-protein is G11. In some embodiments, the mutant Gα-protein is Gi. In some embodiments, the mutant Gα-protein is Go. In some embodiments, the mutant Gα-protein is Gs.

[00296] In some embodiments, the congenital disease is the result of a genetic abnormality, an intrauterine environment, errors related to morphogenesis, infection, epigenetic modifications on a parental germline, or a chromosomal abnormality. Exemplary congenital diseases include, but are not limited to, Sturge-Weber Syndrome, Port-Wine stain, Holt-Oram syndrome, abdominal wall defects, Becker muscular dystrophy (BMD), biotinidase deficiency, Charcot-Marie-Tooth (CMT), cleft lip, cleft palate, congenital adrenal hyperplasia, congenital heart defects, congenital hypothyroidism, congenital muscular dystrophy, cystic fibrosis, Down syndrome, Duchenne muscular dystrophy, Fragile X syndrome, Friedreich's ataxia, galactosemia, hemoglobinopathies, Krabbe disease, limb-girdle muscular dystrophy, medium chain acyl-CoA dehydrogenase deficiency, myasthenia gravis, neural tube defects, phenylketonuria, Pompe disease, severe combined immunodeficiency (SCID), Stickler syndrome (or hereditary progressive arthropathopathy), spinal muscular atrophy, and trisomy 18. In some embodiments, the congenital disease is Sturge-Weber Syndrome or Port-Wine stain. In some embodiments, the congenital disease is Sturge-Weber Syndrome. In some embodiments, the congenital disease is Port-Wine stain.

EXAMPLES

[00297] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

List of abbreviations

[00298] As used above, and throughout the disclosure, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

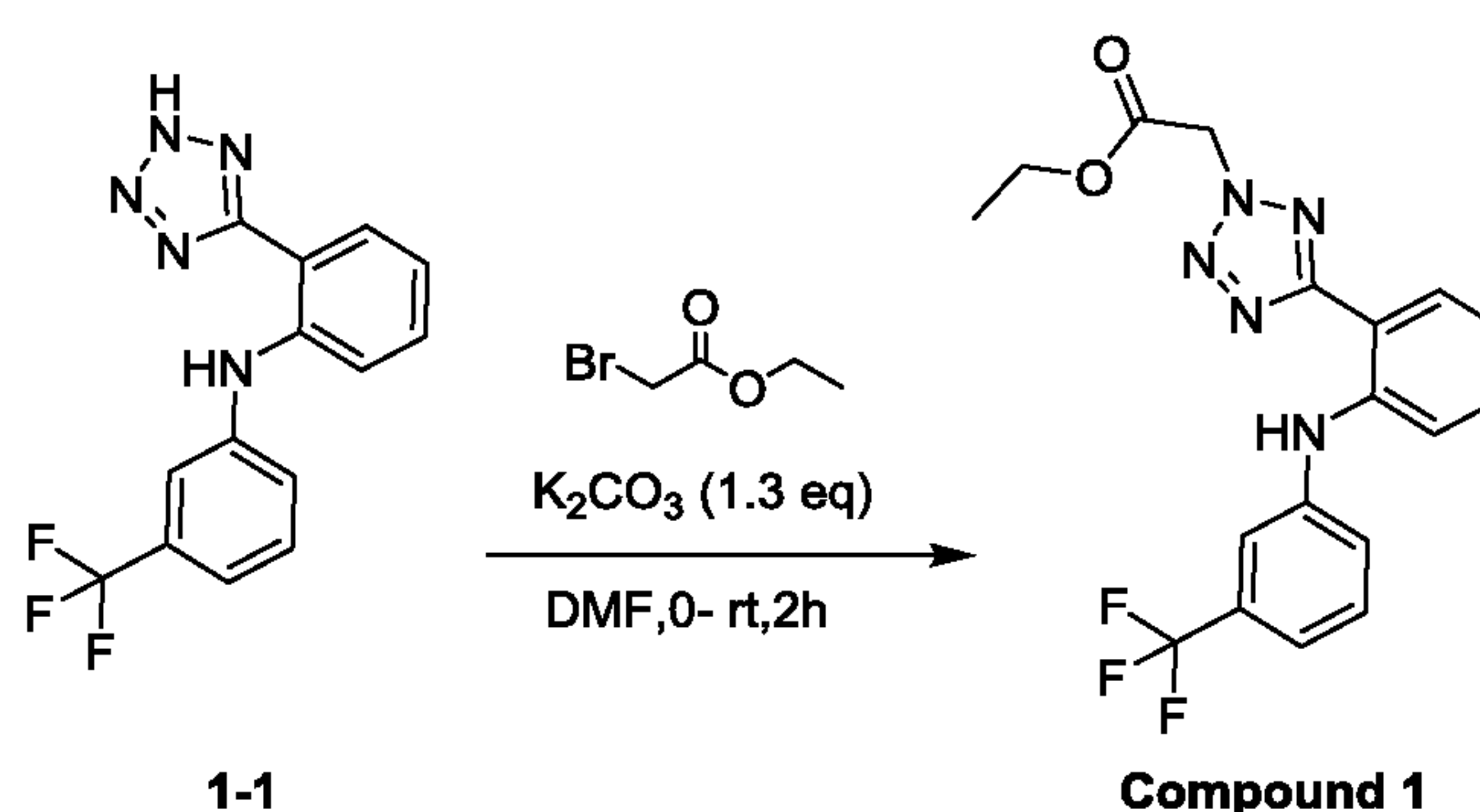
ACN or MeCN	acetonitrile
Bn	benzyl
BOC or Boc	<i>tert</i> -butyl carbamate
t-Bu	<i>tert</i> -butyl
Cy	cyclohexyl
DBA	dibenzylideneacetone
DCE	dichloroethane (ClCH ₂ CH ₂ Cl)
DCM	dichloromethane (CH ₂ Cl ₂)
DIPEA or DIEA	diisopropylethylamine
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DMF	dimethylformamide
DMA	<i>N,N</i> -dimethylacetamide
DMSO	dimethylsulfoxide
Dppf or dppf	1,1'-bis(diphenylphosphino)ferrocene
eq	equivalent(s)
Et	ethyl
Et ₂ O	diethyl ether
EtOH	ethanol
EtOAc	ethyl acetate
HPLC	high performance liquid chromatography
LAH	lithium aluminum anhydride
LCMS	liquid chromatography mass spectrometry
Me	methyl
MeOH	methanol
MS	mass spectroscopy
NMM	<i>N</i> -methyl-morpholine
NMP	<i>N</i> -methyl-pyrrolidin-2-one
NMR	nuclear magnetic resonance
RP-HPLC	reverse phase-high pressure liquid chromatography
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TLC	thin layer chromatography

I. Chemical Synthesis

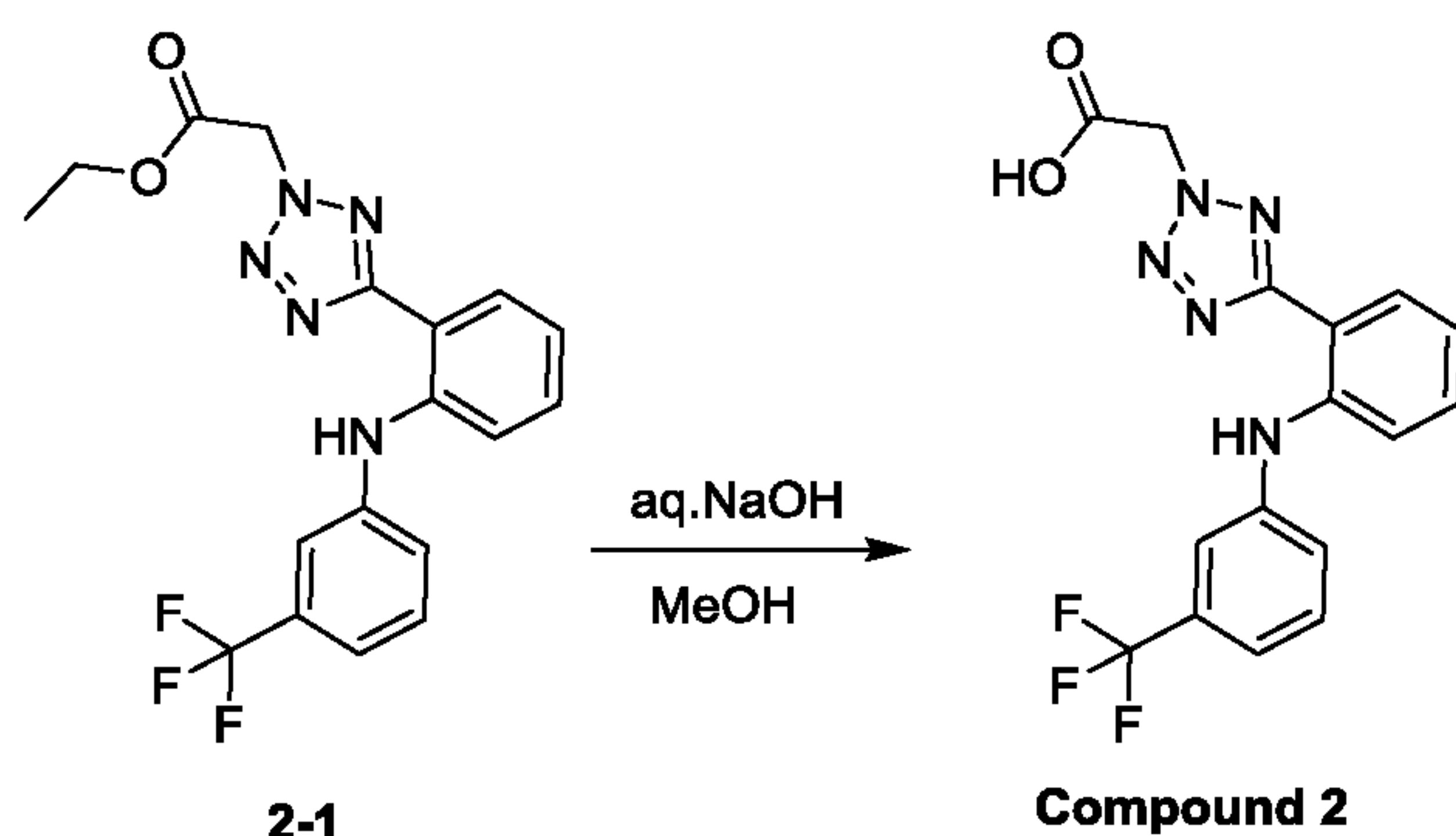
[00299] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Anhydrous solvents and oven-dried glassware were used for synthetic transformations sensitive to moisture and/or oxygen. Yields were not optimized. Reaction times were approximate and were not optimized. Column chromatography and thin layer chromatography (TLC) were performed on silica gel unless otherwise noted.

Example 1: ethyl 2-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetate (Compound 1)



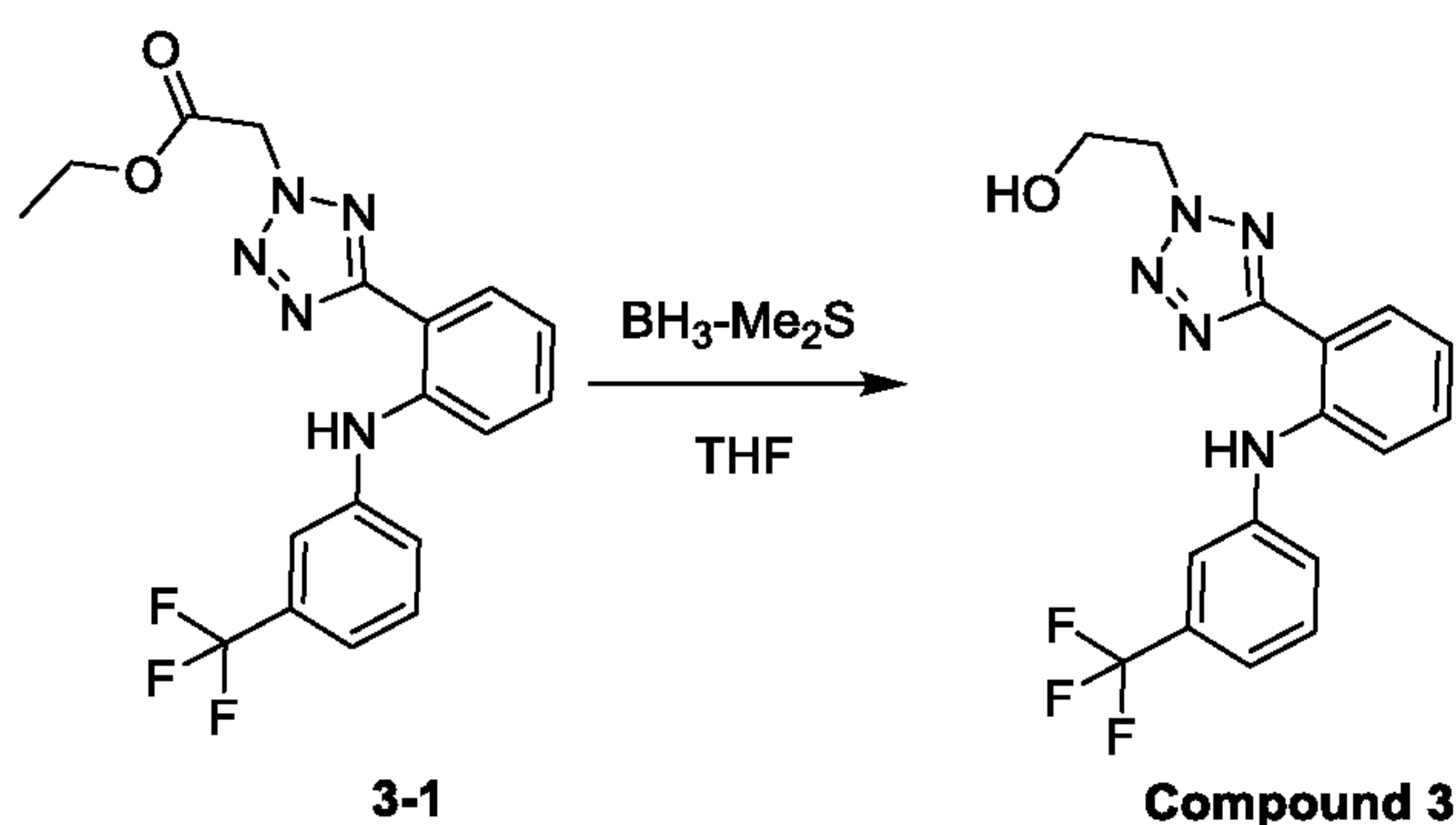
[00300] To a mixture of **1-1** (140 mg, 0.459 mmol, 1.00 *eq*) and K_2CO_3 (84 mg, 0.610 mmol, 1.33 *eq*) in DMF (14 mL) and CH_3CN (2 mL) was stirred at 0 °C for 5 min. The mixture was added ethyl 2-bromoacetate (80 mg, 0.482 mmol, 1.05 *eq*), then warmed to 28 °C and stirred for 2 h. LCMS showed the starting material and one peak with the desired MS was detected. The reaction mixture was stirred for an additional 1 h. TLC indicated the starting material was consumed completely. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography to provide the title compound (140 mg, 0.322 mmol, 70.2% yield). LCMS (ESI): RT = 0.900 min, mass calcd. for $\text{C}_{18}\text{H}_{16}\text{F}_3\text{N}_5\text{O}_2$ 391.13, m/z found 392.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) δ 8.89 (s, 1H), 8.23 (dd, $J = 7.60, 1.40$ Hz, 1H), 7.50 - 7.35 (m, 5H), 7.27 - 7.23 (m, 1H), 7.03 - 6.99 (m, 1H), 5.50 (s, 2H), 4.34 - 4.29 (m, 2H), 1.31 (t, $J = 7.20$ Hz, 3H).

Example 2: 2-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetic acid (Compound 2)



[00301] To a mixture of **2-1** (20 mg, 46 μmol , 1.00 *eq*) in MeOH (1 mL) and H₂O (1 mL) was added NaOH (12 mg, 0.312 mmol, 6.79 *eq*) in one portion at 28°C. The mixture was stirred at 45 °C for 30 min. LCMS showed that compound **2-1** was consumed completely. The reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was adjusted to pH 1 by adding HCl (1M), and filtered under reduced pressure to give a residue. LCMS and ¹H NMR confirmed the title compound (4.89 mg, 13.46 μmol , 29.27% yield). LCMS (ESI): RT = 0.805 min, mass calcd. for C₁₆H₁₂F₃N₅O₂ 363.09, m/z found 363.9[M+H]⁺. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.83 (br s, 1H), 8.22 (d, *J*=7.20 Hz, 1H), 7.49 (s, 1H), 7.43 - 7.34 (m, 4H), 7.27 - 7.26 (m, 1H), 7.01 (t, *J*=7.60 Hz, 1H), 5.55 (s, 2H).

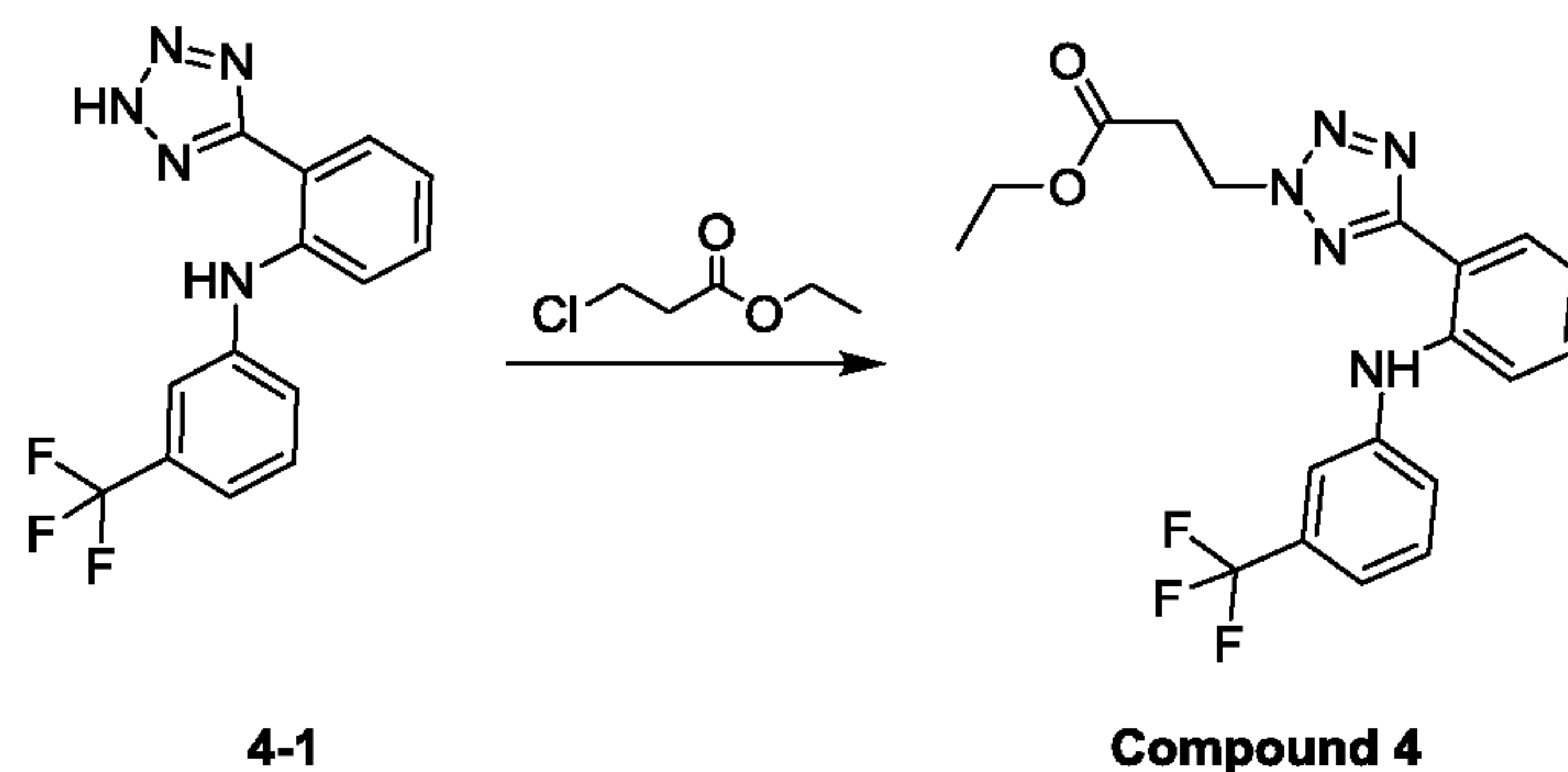
Example 3: 2-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol (Compound 3)



[00302] To a mixture of **3-1** (40 mg, 0.102 mmol, 1.00 *eq*) in THF (5 mL) was added BH₃-Me₂S (10 M, 0.15 mL, 15.00 *eq*) in one portion at 0°C under N₂. The mixture was stirred at 0 °C for 5 min, then heated to 60 °C and stirred for 2 h. LCMS indicated the starting material remained, and one small peak with the desired MS was detected. The reaction mixture was stirred an additional 2 h. LCMS showed 24 % of compound **3-1** remained. Several new peaks were shown on LCMS and 52 % of the desired compound was detected. The reaction mixture was continued by stirring for 1.5 h. LCMS indicated the starting material was consumed completely and one main peak with the desired mass was detected. TLC (Petroleum ether: Ethyl acetate = 5:1) showed one spot had formed. The reaction mixture was quenched with MeOH (5 mL), and then concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to provide the title compound (11.10 mg, 30.82 μmol , 30.2% yield). LCMS (ESI): RT = 0.807 min,

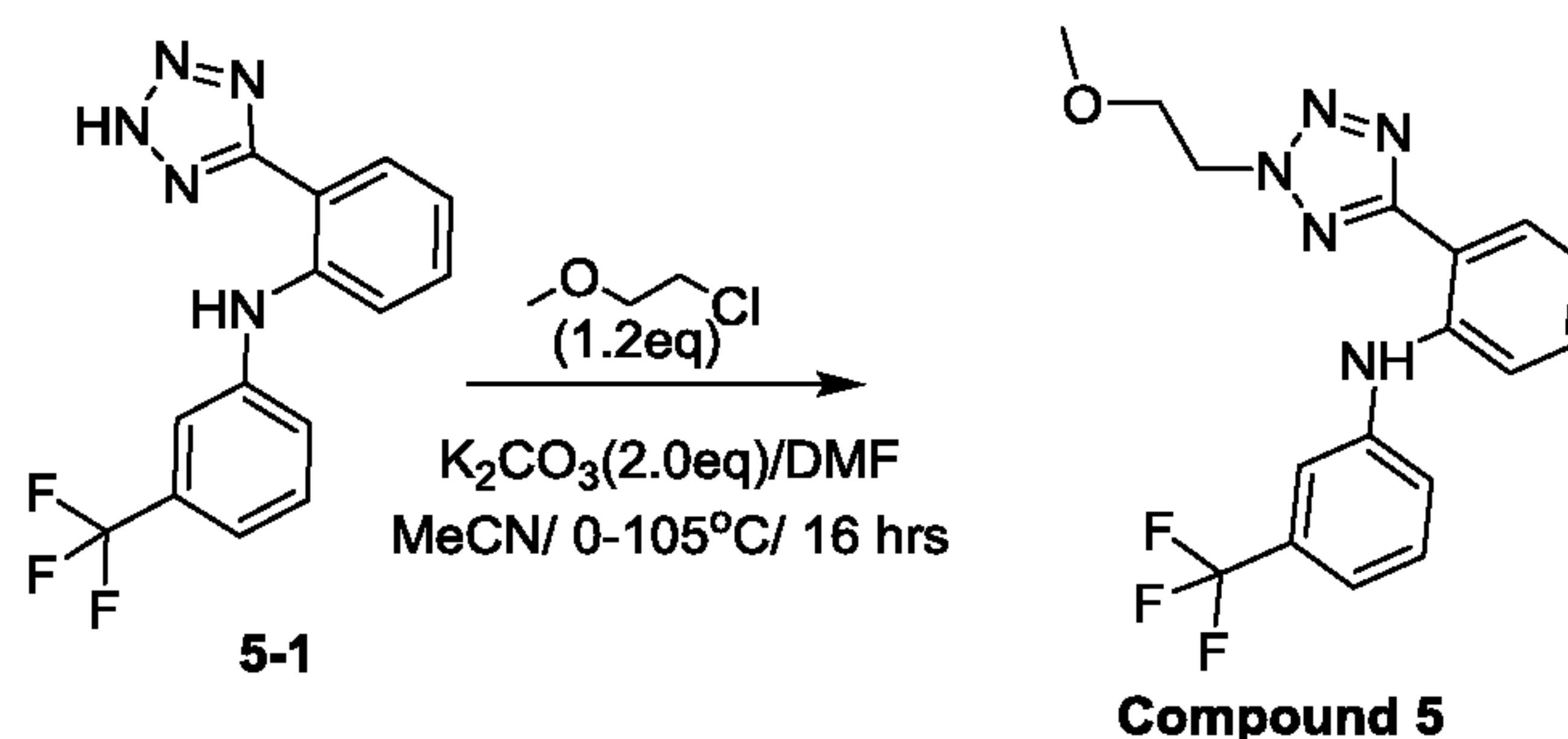
mass calcd. for $C_{16}H_{14}F_3N_5O$ 349.12, m/z found 349.9 $[M+H]^+$. ^1H NMR (400 MHz, $DMSO-d_6$) δ 8.74 (s, 1H), 8.05 (d, $J=7.60$ Hz, 1H), 7.51 - 7.42 (m, 5H), 7.23 (d, $J=7.20$ Hz, 1H), 7.14 - 7.10 (m, 1H), 5.07 (t, $J=5.60$ Hz, 1H), 4.78 (t, $J=5.20$ Hz, 2H), 3.97 - 3.93 (m, 2H).

Example 4: ethyl 3-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propanoate (Compound 4)



[00303] Compound **4-1** (55 mg, 0.18 mmol, 1.00 *eq*), ethyl 3-chloropropanoate (74 mg, 0.541 mmol, 3.00 *eq*) and K_2CO_3 (77 mg, 0.559 mmol, 3.10 *eq*) were taken up into a microwave tube in DMF (3.5 mL). The sealed tube was heated at 130 °C for 30 min under microwave. LCMS showed compound **4-1** remained and one peak with the desired MS was detected. TLC (Ethyl acetate: Petroleum ether = 5:1) indicated one new spot had formed. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (20 mL * 6). The combined organic layers were dried with anhydrous Na_2SO_4 , filtered and concentrated under vacuum. The residue was purified by flash silica gel chromatography to provide the title compound (18.00 mg, 44 μ mol, 12.2% yield). LCMS (ESI): RT = 1.297 min, mass calcd. for $C_{19}H_{18}F_3N_5O_2$ 405.14, m/z found 406.1 $[M+H]^+$. ^1H NMR (400 MHz, $CHLOROFORM-d$) δ 8.94 (s, 1H), 8.30 - 8.19 (m, 1H), 7.50 (s, 1H), 7.44 - 7.36 (m, 4H), 7.27 - 7.25 (m, 1H), 7.02 - 7.00 (m, 1H), 5.01 (t, $J = 6.8$, 2H), 4.22 - 4.16 (m, 2H), 3.15 (t, $J = 6.8$ Hz, 2H), 1.25 (t, $J = 7.2$ Hz, 3H).

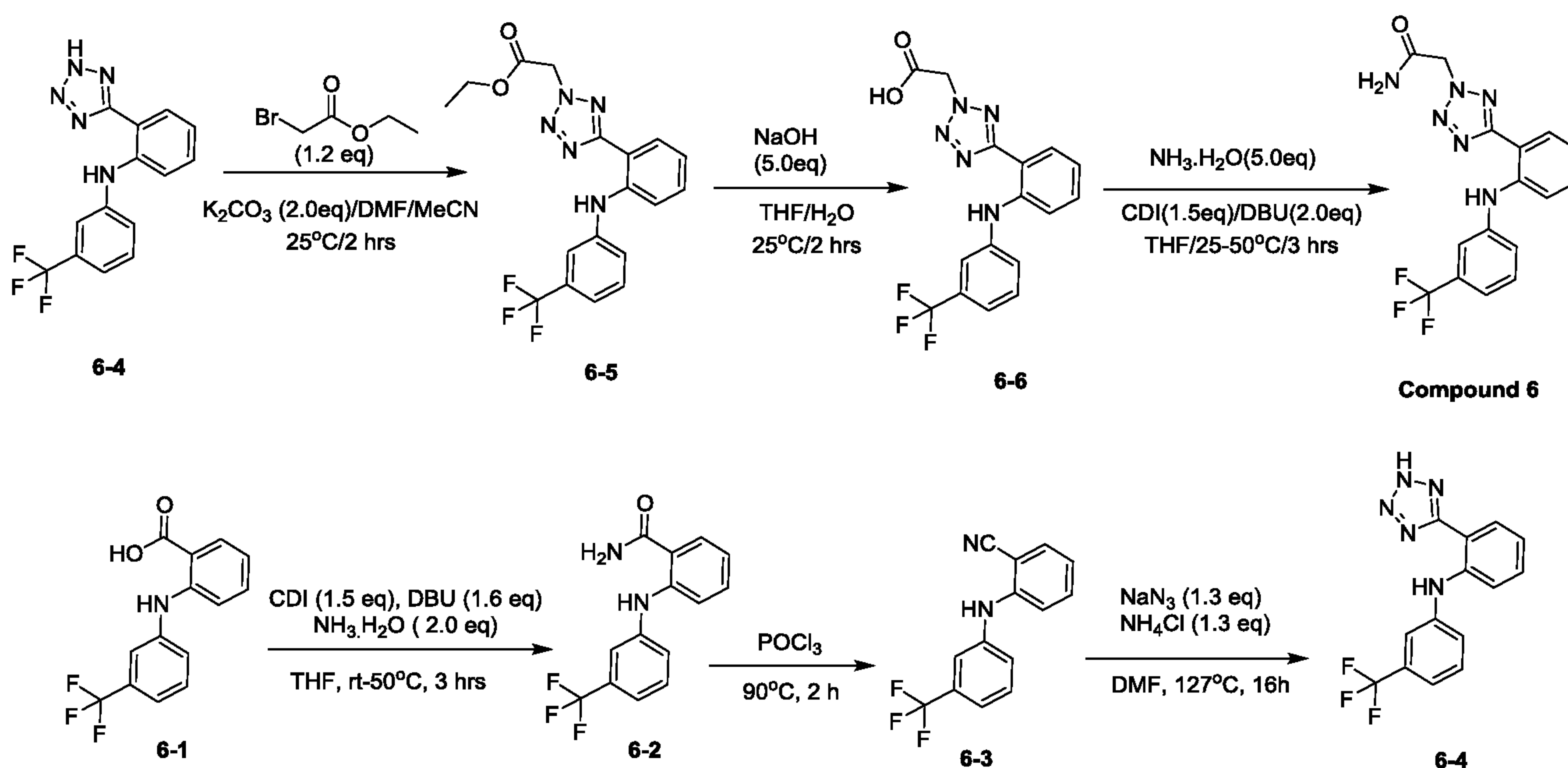
Example 5: 2-[2-(2-methoxyethyl)tetrazol-5-yl]-N-[3-(trifluoromethyl)phenyl]aniline (Compound 5)



[00304] To a solution of **5-1** (50.0 mg, 0.16 mmol, 1.0 *eq*) in DMF (5.0 mL) and MeCN (0.6 mL) was added K_2CO_3 (45.3 mg, 0.33 mmol, 2.0 *eq*) at 0°C. The reaction mixture was stirred at 0°C for 5 min and 1-chloro-2-methoxy-ethane (18.6 mg, 0.20 mmol, 17.9 μ L, 1.20 *eq*) was added. The

reaction mixture was warmed to 25°C and stirred at 105°C for 16 hrs. LCMS showed that **5-1** was consumed completely and the desired product was detected. The reaction mixture was diluted with H₂O (100 mL), extracted with DCM (3*20 mL). The combined organic layers were washed with brine (3*20 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC to obtain the title compound (4.08 mg, 11.23 μ mol, 6.86% yield). LCMS (ESI): RT=0.913 min, mass calc. for C₁₇H₁₆F₃N₅O 363.13, m/z found 364.0 [M+H]⁺. ¹HNMR (400MHz, DMSO-*d*₆) δ 8.75-8.65 (s, 1 H), 8.10-8.00 (d, *J*=7.7 Hz, 1 H), 7.50 - 7.43 (m, 3 H), 7.42-7.30 (br. d, *J*=4.9 Hz, 1 H), 7.26-7.16 (br. d, *J*=7.5 Hz, 1 H), 7.15-7.05 (t, *J*=6.7 Hz, 1 H), 4.95-4.85 (t, *J*=5.1 Hz, 2 H), 3.95-3.85 (t, *J*=5.1 Hz, 2 H), 3.25-3.15 (s, 3 H).

Example 6: 2-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetamide (Compound 6)



Step 1: 2-[3-(trifluoromethyl)anilino]benzamide

[00305] To a suspension of **6-1** (2.00 g, 7.11 mmol, 1.0 *eq*) in THF (100.0 mL) was added CDI (1.73 g, 10.67 mmol, 1.5 *eq*). After stirring at 50°C for 0.5 hr, the reaction mixture was cooled to 25°C and DBU (1.73 g, 11.38 mmol, 1.71 mL, 1.6 *eq*), NH₃.H₂O (1.99 g, 14.22 mmol, 2.19 mL, 2.0 *eq*) was added. The reaction mixture was stirred at 50°C for another 3 hrs. LCMS showed that the desired product was detected. TLC showed that **6-1** was consumed completely and a new spot had formed. The reaction mixture was diluted with H₂O (150 mL), extracted with EtOAc (3*50 mL). The combined organic layers were washed with brine (3*50 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel to obtain **6-2** (1.40 g, 5.00 mmol, 70.3% yield).

Step 2: 2-[3-(trifluoromethyl)anilino]benzonitrile

[00306] **6-2** (1.40 g, 5.00 mmol, 1.00 *eq*) was added to POCl₃ (16.50 g, 107.61 mmol, 10.0 mL, 21.52 *eq*). The reaction mixture was stirred at 90°C for 2 hrs. TLC showed that **6-2** was consumed completely and a new spot had formed. The reaction mixture was dropwise added to 150 mL water at 25°C and stirred vigorously until heat was not given out from the system. Then, the reaction mixture was extracted with EtOAc (3*50 mL) and the combined organic layers were washed with brine (3*50 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to obtain **6-3** (1.29 g, 4.92 mmol, 98.4% yield).

Step 3: 2-(2H-tetrazol-5-yl)-N-[3-(trifluoromethyl)phenyl]aniline

[00307] To a solution of **6-3** (1.09 g, 4.16 mmol, 1.00 *eq*) in DMF (8.0 mL) was added NaN₃ (351.57 mg, 5.41 mmol, 1.30 *eq*) and NH₄Cl (289.27 mg, 5.41 mmol, 189.07 uL, 1.30 *eq*). The reaction mixture was stirred at 127°C for 16 hrs. LCMS showed that **6-3** was consumed completely and the desired product was detected. The reaction mixture was quenched by addition of saturated aq. Na₂CO₃ to adjust the pH to 9, and extracted with EtOAc (3*20 mL). The combined organic layers were washed with brine (3* 20 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure, and a residue was formed. The aqueous layer was quenched by aq. NaClO (200 mL) and stewed for 16 hrs. The residue was purified by flash silica gel chromatography to obtain **6-4** (500.0 mg, 1.64 mmol, 39.4% yield).

Step 4: ethyl 2-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetate

[00308] To a solution of **6-4** (150.0 mg, 0.49 mmol, 1.0 *eq*), K₂CO₃ (135.8 mg, 0.98 mmol, 2.0 *eq*) in MeCN (0.6mL) and DMF (5.0 mL) was added ethyl 2-bromoacetate (98.5 mg, 0.59mmol, 65.2 uL, 1.20 *eq*) at 0°C, and stirred for 5 min. The reaction mixture was then stirred at 25°C for an additional 2 hrs. LCMS showed that the **6-4** was consumed and the desired product was detected. The reaction mixture was diluted with H₂O (30 mL), extracted with EtOAc (3* 15 mL). The combined organic layers were washed with brine (3*15 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residue was used to next step without purification. **6-5** (200.0 mg, crude) was obtained as colorless oil.

Step 5:2-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetic acid

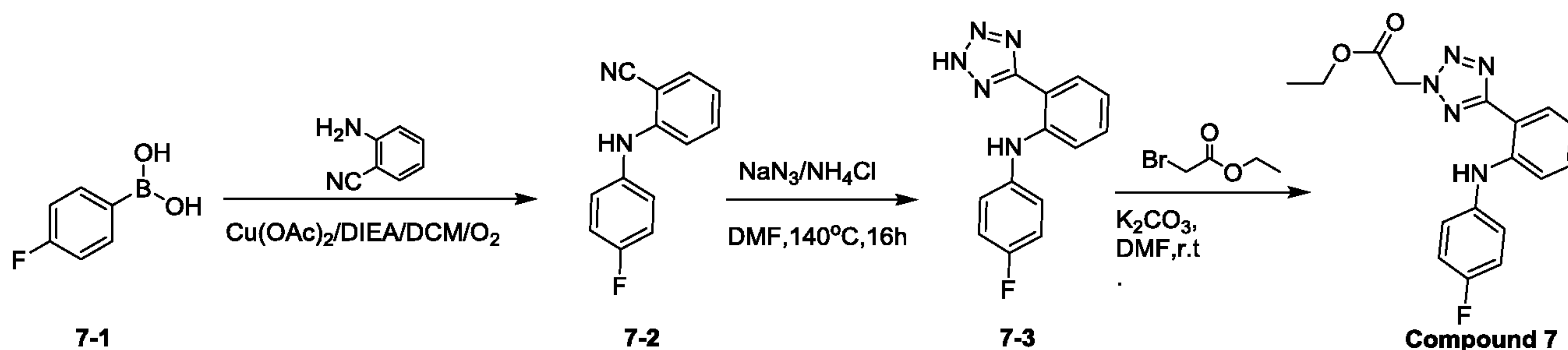
[00309] To a solution of **6-5** (200.0 mg, 0.51 mmol, 1.00 *eq*) in THF (5.0 mL) was added the solution of NaOH (102.2 mg, 2.56 mmol, 5.00 *eq*) in H₂O (2.6 mL). The reaction mixture was stirred at 25°C for 2 hrs. LCMS showed that the **6-5** was consumed and the desired product was detected. The reaction mixture was evaporated to remove THF, 20 mL H₂O was added, and 1N HCl was added to adjust the pH to 1; forming a suspension. Then, the suspension was extracted with EtOAc (3* 15 mL), and the combined organic layers were washed with brine (3*15 mL), dried over

Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residue (**6-6**) was used in the next step without purification (210.0 mg, crude).

Step 6: 2-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetamide

[00310] To a suspension of **6-6** (100.0 mg, 0.28 mmol, 1.0 *eq*) in THF (5.0 mL) was added CDI (67.0 mg, 0.41 mmol, 1.5 *eq*). After stirring at 50°C for 0.5 hr, the reaction mixture was cooled to 25°C and DBU (83.8 mg, 0.55 mmol, 83.0 uL, 2.0 *eq*), NH₃·H₂O (77.2 mg, 0.55 mmol, 84.8 uL, 2.0 *eq*) was added. The reaction mixture was stirred at 50°C for another 3 hrs. LCMS showed that the desired product was detected. The reaction mixture was diluted with H₂O (150 mL), extracted with EtOAc (3*50 mL). The combined organic layers were washed with brine (3*50 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC to obtain **Compound 6** (13.23 mg, 35.42 umol, 12.87% yield). LCMS (ESI): RT = 0.799 min, mass cal.cd for C₁₆H₁₃F₃N₆O 362.11, m/z found 363.0 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.75-8.65 (s, 1 H), 8.10-8.00 (d, *J*=7.5 Hz, 1 H), 7.90-7.80 (br. s, 1 H), 7.60-7.50 (br. s, 1 H), 7.52 - 7.41 (m, 5 H), 7.30-7.20 (d, *J*=7.7 Hz, 1 H), 7.15-7.05 (t, *J*=6.7 Hz, 1 H), 5.60-5.50 (s, 2 H).

Example 7: ethyl 2-[5-[2-(4-fluoroanilino)phenyl]tetrazol-2-yl]acetate (Compound 7)



Step 1: 2-(4-fluoroanilino)benzonitrile

[00311] To a solution of **7-1** (500.0 mg, 3.6 mmol, 1.0 *eq*) and 2-aminobenzonitrile (422.2 mg, 3.6 mmol, 1.00 *eq*) in DCM (10.0 mL) was added Cu(OAc)₂ (649.1 mg, 3.6 mmol, 1.0 *eq*) and DIPEA (748.19 uL, 4.28 mmol, 1.2 *eq*). The mixture was stirred at 20-30 °C for 16 hour under O₂ atmosphere. The reaction was monitored by LC-MS. The reaction mixture was filtered through a Celite pad and washed with DCM (30 mL). The filtrate was concentrated to give a residue. The residue was purified by flash column chromatography to obtain **7-2** (400.0 mg, 1.9 mmol, 52.8% yield). LCMS (ESI): RT = 0.783 min, mass calc. for C₁₃H₉FN₂ 212.07, m/z found 212.8 [M+H]⁺; ¹HNMR (400 MHz, CDCl₃) δ(ppm): 7.55 - 7.46 (m, 1 H) 7.37-7.33 (m, 1 H) 7.22 - 7.14 (m, 2 H) 7.13 - 7.04 (m, 2 H) 7.01-6.99 (m, 1 H) 6.87 - 6.69 (m, 1 H) 6.23 (s, 1 H).

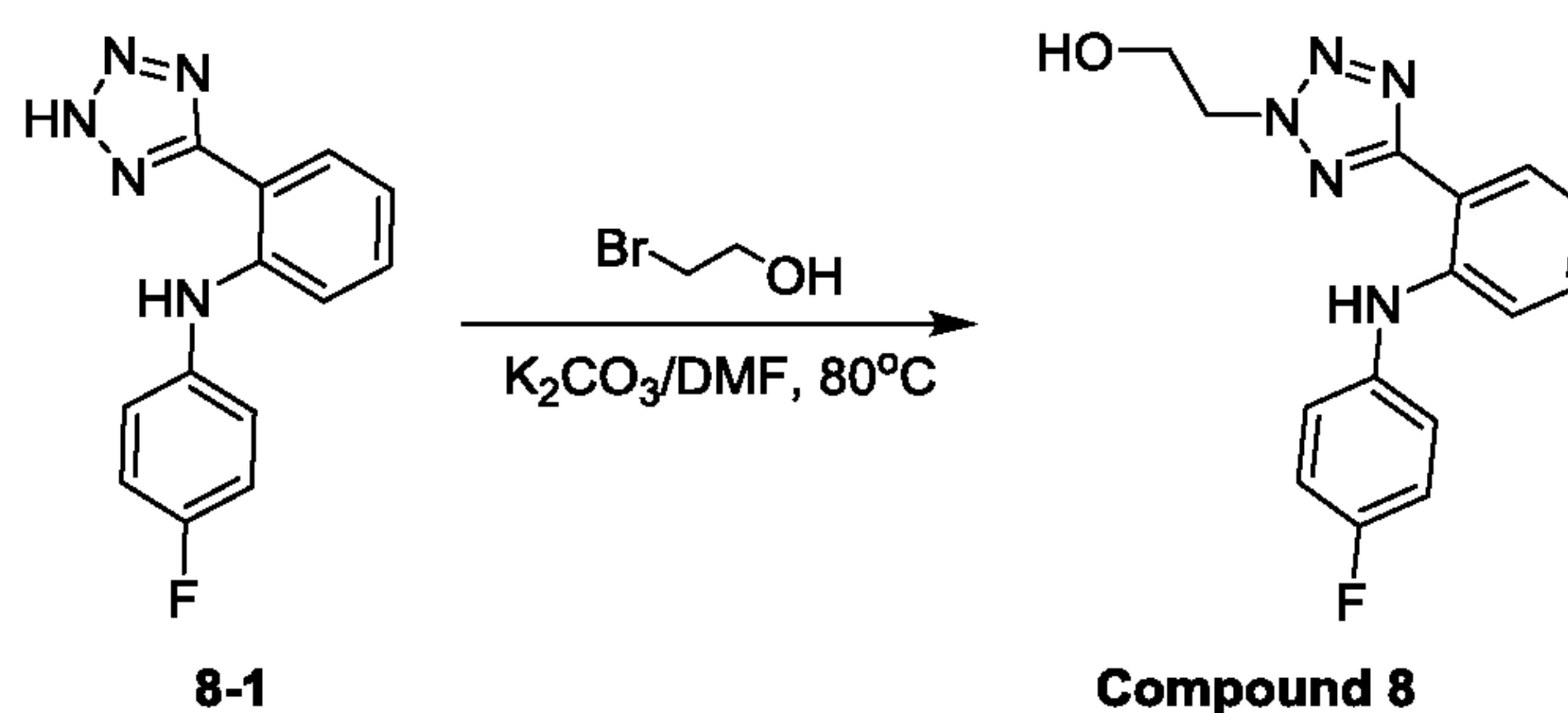
Step 2: N-(4-fluorophenyl)-2-(2H-tetrazol-5-yl)aniline

[00312] To a solution of **7-2** (100.0 mg, 0.47 mmol, 1.0 eq) in DMF (5.0 mL) was added NH_4Cl (65.6 mg, 1.22 mmol, 3.0 eq) and NaN_3 (80.0 mg, 1.22 mmol, 3.0 eq). The mixture was stirred at 120 °C for 16 h under an N_2 atmosphere. TLC showed a trace of reactant remained and one new spot had formed. The reaction mixture was poured into sat. aq. NaHCO_3 (5 mL) and extracted with EtOAc (5 mL*3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated to give a residue. The residue was used in the next step directly without further purification to obtain **7-3** (120.00 mg, crude). LCMS (ESI): RT = 0.768 min, mass calc. for $\text{C}_{13}\text{H}_{10}\text{FN}_5$ 255.09, m/z found 255.9 $[\text{M}+\text{H}]^+$;

Step 3: ethyl 2-[5-[2-(4-fluoroanilino)phenyl]tetrazol-2-yl]acetate

[00313] To a solution of **7-3** (120.0 mg, 0.47 mmol, 1.0 eq) in DMF (5.0 mL) was added K_2CO_3 (130.0 mg, 0.94 mmol, 2.0 eq) and ethyl 2-bromoacetate (78.5 mg, 0.47 mmol, 52.0 uL, 1.00 eq). The mixture was stirred at 20-30 °C for 5 hours to give a brown solution. LCMS indicated the starting material was consumed completely and one main peak with the desired MS was detected on LCMS. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (5 mL*3). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated to give a residue. The residue was purified by prep-HPLC to obtain Compound **7** (25.98 mg, 68.8 umol, 14.6% yield, HCl). LCMS (ESI): RT = 0.883 min, mass calc. for $\text{C}_{17}\text{H}_{16}\text{FN}_5\text{O}_2$ 341.13, m/z found 341.9 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.55 (s, 1 H) 8.09-8.06 (m, 1 H) 7.40 - 7.33 (m, 1 H) 7.30- 7.25 (m, 2 H) 7.23 - 7.16 (m, 3 H) 6.99-6.95 (m, 1 H) 5.94 (s, 2 H) 4.22 (q, $J=7.19$ Hz, 2 H) 1.23 (t, $J=7.03$ Hz, 3 H).

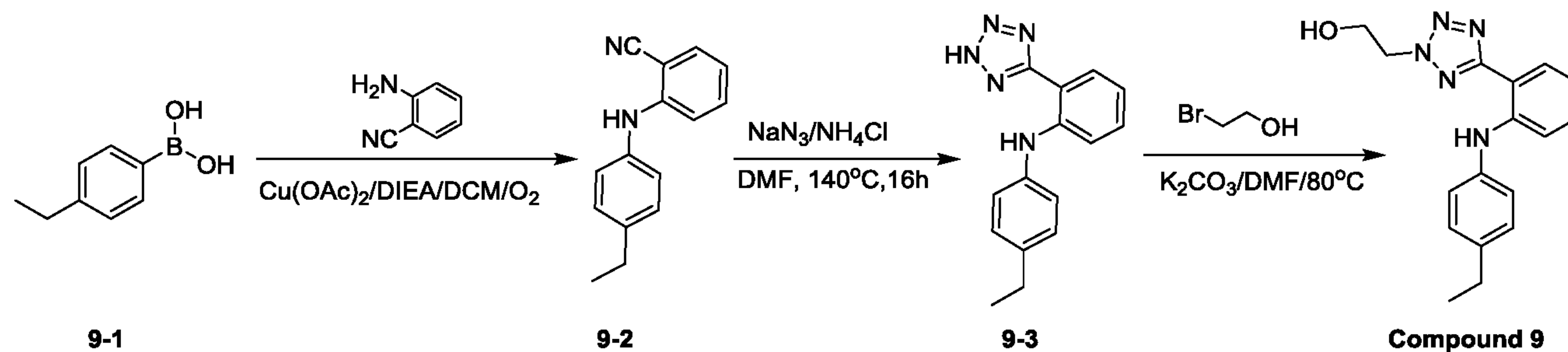
Example 8: 2-[5-[2-(4-fluoroanilino)phenyl]tetrazol-2-yl]ethanol (Compound 8)



[00314] To a solution of **8-1** (150.0 mg, 0.59 mmol, 1.0 eq) in DMF (3.00 mL) was added K_2CO_3 (162.4 mg, 1.18 mmol, 2.0 eq) and 2-bromoethanol (88.13 mg, 0.71 mmol, 50.0 uL, 1.2 eq) and was stirred for 4 h at 80°C. LC-MS showed **8-1** was consumed completely and ~50% of the desired MS was detected. The reaction mixture was filtered and washed with DCM (10 mL). The filtrate was concentrated to give a residue. The residue was purified by prep-HPLC (TFA). The resulting eluent was concentrated to give a residue, and the residue was lyophilized to give the title compound (18.79 mg, 45.46 umol, 7.74% yield, TFA). (LCMS (ESI): RT = 1.998 min, mass calc. for

$C_{15}H_{14}FN_5O$ 299.12, m/z found 300.1 $[M+H]^+$; ^1H NMR (400 MHz, $DMSO-d_6$) δ ppm 8.64 (s, 1 H) 8.06 (d, $J=7.40$ Hz, 1 H) 7.39 - 7.32 (m, 1 H) 7.30- 7.15 (m, 6 H) 6.96 (t, $J=7.40$ Hz, 1 H) 5.13 (s, 1 H) 4.80 (t, $J=5.02$ Hz, 2 H) 3.97 (d, $J=4.52$ Hz, 2 H).

Example 9: 2-[5-[2-(4-ethylanilino)phenyl]tetrazol-2-yl]ethanol (Compound 9)



Step 1: 2-(4-ethylphenyl)-2-(2-aminobenzonitrile)aniline

[00315] To a solution of **9-1** (761.3 mg, 5.08 mmol, 1.2 eq) and 2-aminobenzonitrile (500.0 mg, 4.23 mmol, 1.0 eq) in DCM (20.00 mL) was added $Cu(OAc)_2$ (768.7 mg, 4.23 mmol, 1.0 eq) and DIPEA (820.0 mg, 6.35 mmol, 1.1 mL, 1.5 eq). The mixture was stirred at 20-30 °C for 40 hours under O_2 atmosphere. The reaction was monitored by LC-MS. The reaction mixture was filtered through a Celite pad and washed with DCM (30 mL). The filtrate was concentrated to give a residue. The residue was purified by flash column chromatography to obtain **9-2** (410.0 mg, 1.84 mmol, 43.6% yield) was obtained as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.49-7.47 (m, 1 H) 7.37 - 7.30 (m, 1 H) 7.17 - 7.23 (m, 2 H) 7.15 - 7.08 (m, 3 H) 6.82-6.78 (m, 1 H) 2.65 (q, $J=7.5$ Hz, 2 H) 1.28 - 1.22 (t, $J=7.5$ Hz, 3 H).

Step 2: N-(4-ethylphenyl)-2-(2H-tetrazol-5-yl)aniline

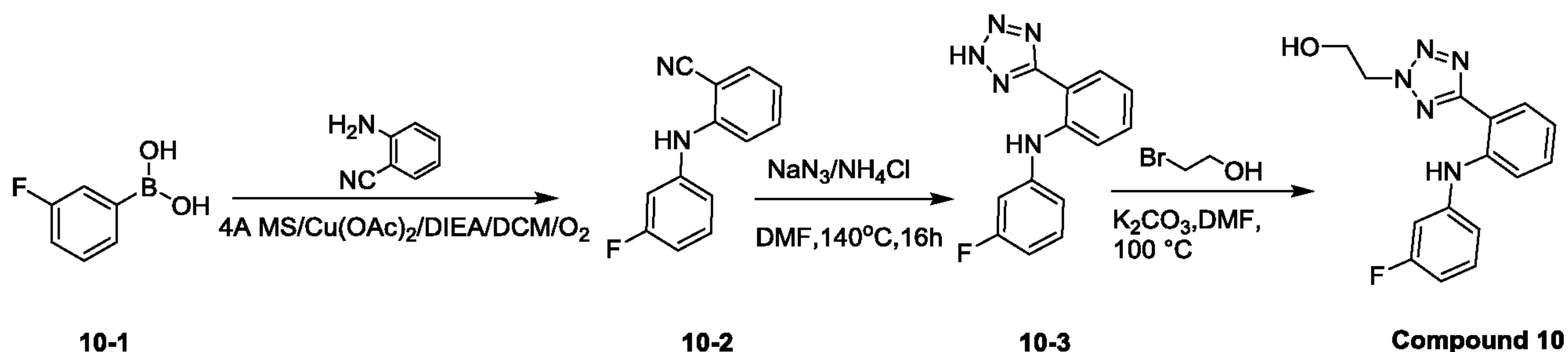
[00316] To a solution of **9-2** (410.0 mg, 1.84 mmol, 1.0 eq) in DMF (5.00 mL) was added NH_4Cl (295.3 mg, 5.52 mmol, 3.0 eq) and NaN_3 (358.9 mg, 5.52 mmol, 3.00eq). The mixture was stirred at 140 °C for 16 h under an N_2 atmosphere. The reaction was monitored by LC-MS, and TLC showed that the starting materials were consumed completely. The reaction mixture was poured into sat. aq. $NaHCO_3$ (5 mL) and extracted with EtOAc (5 mL*3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and filtered. The filtration was concentrated to give a residue. The residue **9-3** (500.0 mg, crude) was used in next step directly without further purification. LCMS (ESI): RT = 0.837 min, mass calc. for $C_{15}H_{15}N_5$ 265.13, m/z found 265.9 $[M+H]^+$.

Step 3: 2-[5-[2-(4-ethylanilino)phenyl]tetrazol-2-yl]ethanol

[00317] To a solution of **9-3** (200.0 mg, 0.75 mmol, 1.0 eq) in DMF (3.0 mL) was added K_2CO_3 (208.4 mg, 1.5 mmol, 2.0 eq) and 2-bromoethanol (113.0 mg, 0.90 mmol, 1.2 eq). The mixture was stirred at 80 °C for 2 hours to give a brown solution. The reaction was monitored by LC-MS. The

reaction mixture was poured into water (10 mL) and extracted with EtOAc (5 mL*3). The combined organic layers were washed with brine(10 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated to give a residue. The residue was purified by prep-HPLC (TFA). The eluent was concentrated to give a residue, and the residue was lyophilized to give **Compound 9** (43.54 mg, 0.10mmol, 13.6% yield, TFA). LCMS (ESI): RT = 2.207 min, mass calc. for C₁₇H₁₉N₅O 309.16, m/z found 310.0 [M+H]⁺; ¹HNMR (400 MHz, DMSO-*d*₆) δ ppm 8.68 (s, 1 H) 8.07 (d, *J*=7.28 Hz, 1 H) 7.41 - 7.25 (m, 2 H) 7.18 (s, 4 H) 6.93 (t, *J*=6.78 Hz, 1 H) 4.80 (s, 2 H) 3.98 (s, 2 H) 2.65 - 2.53 (m, 2 H) 1.18 (t, *J*=7.28 Hz, 3 H).

Example 10: 2-(5-(2-((3-fluorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol (Compound 10)



Step 1: 2-((3-fluorophenyl)amino)benzonitrile

[00318] To the solution of 2-aminobenzonitrile (422 mg, 4.0 mmol, 1.0 *eq*) in DCM (10 mL) was added **10-1** (500 mg, 4.0 mmol, 1.0 *eq*), Cu(OAc)₂ (648 mg, 4.0 mmol, 1.0 *eq*) and DIEA (554 mg, 4 mmol, 748 uL, 1.2 *eq*). The mixture was stirred at 30 °C for 16 hr. The reaction was monitored by TLC. The reaction solution was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂) to give compound **10-2** (343 mg, 1.6 mmol, 45% yield).

Step 2: N-(3-fluorophenyl)-2-(2H-tetrazol-5-yl)aniline

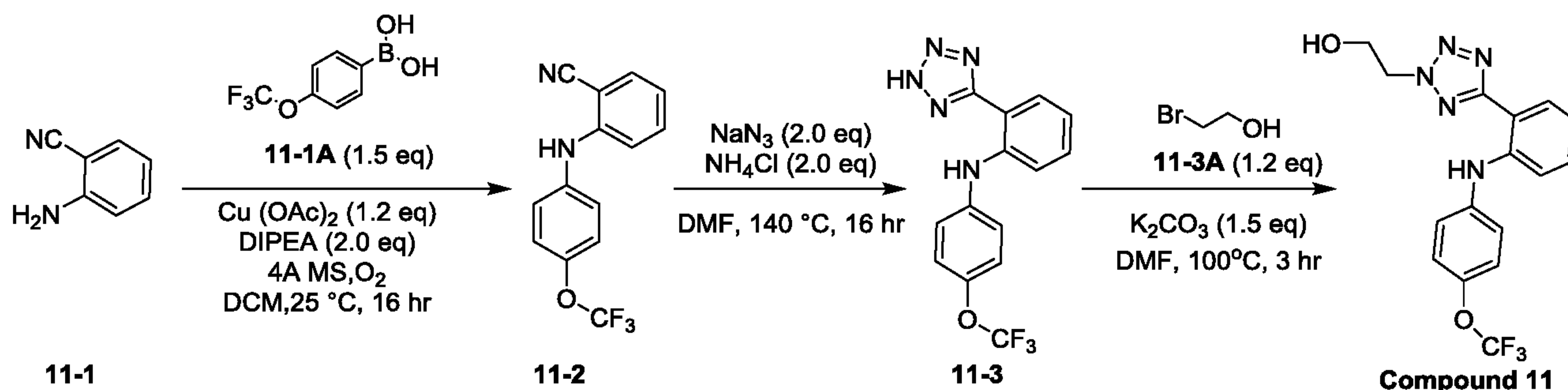
[00319] To the solution of **10-2** (343 mg, 1.6 mmol, 1.0 *eq*) in DMF (2 mL) was added NaN₃ (316 mg, 4.9 mmol, 3.0 *eq*) and NH₄Cl (260 mg, 4.9 mmol, 3.0 *eq*). The mixture was stirred at 140 °C for 16 hr under N₂ atmosphere. The reaction was monitored by LCMS. The reaction solution was poured into HCl aqueous (1M, 20mL). An insoluble solid appeared. The mixture was filtered and the solid was washed with H₂O (20 mL*2) to give **10-3** (357 mg, 1.4 mmol, 86% yield).

Step 3: 2-(5-(2-((3-fluorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol

[00320] To the solution of **10-3** (157 mg, 0.6 mmol, 1.0 *eq*) in DMF (5 mL) was added 2-bromoethanol (92 mg, 0.7 mmol, 52 uL, 1.2 *eq*) and K₂CO₃ (128 mg, 0.9 mmol, 1.5 *eq*). The mixture was stirred at 100 °C for 16 hr. The reaction was monitored by LCMS. The reaction solution was concentrated under reduced pressure. The residue was purified by Prep-HPLC to give **Compound 10** (29.13 mg, 95.4 umol, 15.5% yield). LCMS (ESI): RT = 1.152 min, mass calc. for C₁₅H₁₄FN₅O 299.12, m/z found 300.0 [M+H]⁺, ¹HNMR (400MHz, DMSO-*d*₆) δ 8.72 (s, 1H), 8.10

- 8.03 (m, 1H), 7.50 - 7.42 (m, 2H), 7.34 - 7.28 (m, 1H), 7.12 - 7.06 (m, 1H), 7.04 - 6.97 (m, 2H), 6.78 - 6.70 (m, 1H), 5.08 (t, $J=5.5$ Hz, 1H), 4.80 (t, $J=5.3$ Hz, 2H), 3.97 (q, $J=5.3$ Hz, 2H).

Example 11: 2-(5-(2-((4-(Trifluoromethoxy)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol (Compound 11)



Step 1: 2-((4-(Trifluoromethoxy)phenyl)amino)benzonitrile

[00321] To a solution of **11-1** (500 mg, 4.23 mmol, 1.0 *eq*), **11-1A** (1.3 g, 6.4 mmol, 1.5 *eq*), Cu(OAc)₂ (922 mg, 5.08 mmol, 1.2 *eq*), DIPEA (1.1 g, 8.5 mmol, 2.0 *eq*) in DCM (10 mL) was added 4A MS (200 mg). The reaction mixture was stirred at 25 °C for 16 hours under O₂. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (30 mL) and the resultant mixture was extracted with DCM (50 mL * 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography over silica gel to afford **11-2** (850 mg, 72% yield). LCMS (ESI): RT = 0.862 min, mass calc. for C₁₄H₉F₃N₂O 278.07, m/z found 278.8 [M+H]⁺.

Step 2: 2-(2H-Tetrazol-5-yl)-N-(4-(trifluoromethoxy)phenyl)aniline

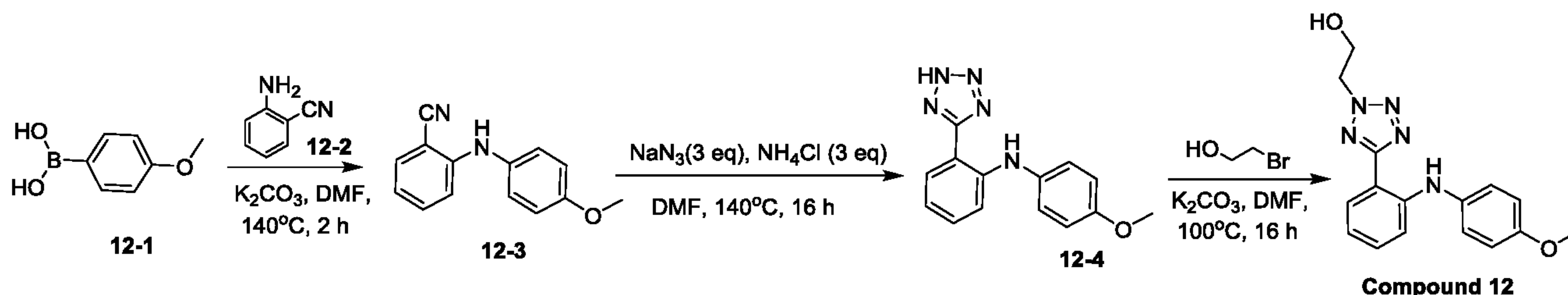
[00322] A solution of **11-2** (300 mg, 1.08 mmol, 1.0 *eq*), NH₄Cl (116 mg, 2.16 mmol, 2.0 *eq*) and NaN₃ (140 mg, 2.16 mmol, 2.0 *eq*) in DMF (4 mL) was stirred at 140 °C for 16 hours. The reaction mixture was acidified with HCl (1M) to pH 2. The mixture was diluted with water (30 mL) and the resultant mixture was extracted with DCM (EtOAc mL * 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography over silica gel to afford **11-3** (210 mg, 59% yield). LCMS (ESI): RT = 1.215 min, mass calc. for C₁₄H₁₀F₃N₅O 321.08, m/z found 321.9 [M+H]⁺, ¹HNMR (400MHz, DMSO-*d*₆) δ 9.09 (s, 1H), 7.89 (d, $J=7.8$ Hz, 1H), 7.48 - 7.41 (m, 2H), 7.33 - 7.25 (m, 4H), 7.11 - 7.04 (m, 1H).

Step 3: 2-(5-(2-((4-(Trifluoromethoxy)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol

[00323] To a solution of **11-3** (100 mg, 0.311 mmol, 1.0 *eq*) and **11-3A** (47 mg, 0.37 mmol, 1.2 *eq*) in DMF (3 mL) was added K₂CO₃ (65 mg, 0.47 mmol, 1.5 *eq*). The reaction mixture was stirred at 100 °C for 3 hours. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (10 mL) and the resultant mixture was extracted with DCM (30 mL * 2).

The combined organic layers were dried over Na_2SO_4 , filtered and concentrated to dryness under reduced pressure. The residue was purified by preparative high performance liquid chromatography. The pure fractions were collected and the volatiles were removed under vacuum. The residue was re-suspended in water (10mL) and the resulting mixture was lyophilized to dryness to remove the solvent residue completely to obtain **Compound 11** (37.94 mg, 33% yield). LCMS (ESI): RT = 2.259 min, mass calc. for $\text{C}_{16}\text{H}_{14}\text{F}_3\text{N}_5\text{O}_2$ 365.11, m/z found 366.0 $[\text{M}+\text{H}]^+$, ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ 8.72 (s, 1H), 8.07 (d, $J=7.5$ Hz, 1H), 7.45 - 7.39 (m, 2H), 7.33 - 7.26 (m, 4H), 7.08 - 7.04 (m, 1H), 5.15-5.02 (m, 1H), 4.80 (t, $J=5.3$ Hz, 2H), 3.97 (t, $J=5.1$ Hz, 2H)

Example 12: 2-[5-[2-(4-methoxyanilino)phenyl]tetrazol-2-yl]ethanol (Compound 12)



Step 1: 2-(4-methoxyanilino)benzonitrile

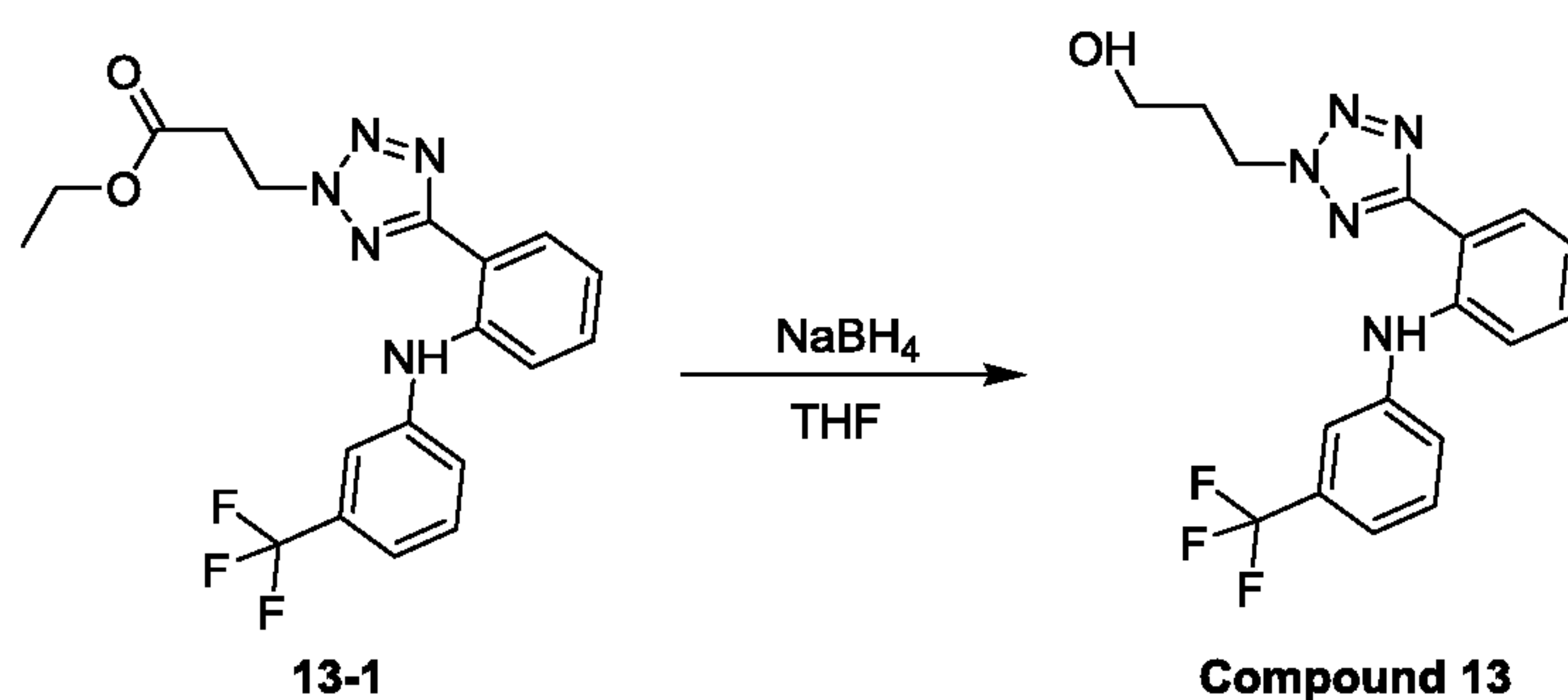
[00324] To a solution of **12-1** (700 mg, 4.61 mmol, 1.0 *eq*) and **12-2** (545 mg, 4.61 mmol, 1.0 *eq*) in DCM (10 mL) was added DIEA (714 mg, 5.53 mmol, 965 μL , 1.2 *eq*), $\text{Cu}(\text{OAc})_2$ (837 mg, 4.61 mmol, 1.0 *eq*) and 4A MS (500 mg, 4.61 mmol, 1.0 *eq*). The resulting mixture was stirred at 30°C for 16 hr under O_2 . LCMS and TLC (Petroleum ether: Ethyl acetate = 10/1) showed the desired compound was found and the starting material remained. The mixture was concentrated in vacuo to give a crude product. The crude product was purified by column chromatography (silica) to give **12-3** (380 mg, 1.57 mmol, 34% yield). LCMS (ESI): RT = 0.790 min, mass calc. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}$ 224.09, m/z found 224.8 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{CHLOROFORM}-d$) δ 7.48 (dd, $J = 1.5, 7.8$ Hz, 1H), 7.33 (ddd, $J = 1.5, 7.4, 8.7$ Hz, 1H), 7.20 - 7.14 (m, 2H), 6.97 - 6.90 (m, 3H), 6.81 - 6.75 (m, 1H), 6.21 (br s, 1H).

Step 2: N-(4-methoxyphenyl)-2-(2H-tetrazol-5-yl)aniline

[00325] To a solution of **12-3** (200 mg, 0.825 mmol, 1.0 *eq*) and NH_4Cl (132 mg, 2.47 mmol, 87 μL , 3.0 *eq*) in DMF (2 mL) was added NaN_3 (161 mg, 2.47 mmol, 3.0 *eq*). The resulting mixture was stirred at 140°C for 16 hr. The reaction was monitored by LCMS. The reaction mixture was poured into cold water (10 mL), HCl (1N, 1 mL) and then extracted by ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL*2) dried over Na_2SO_4 , concentrated under reduced pressure to give **12-4** (300 mg, crude), and the compound was directly used without further purification. LCMS (ESI): RT = 0.762 min, mass calc. for $\text{C}_{14}\text{H}_{13}\text{N}_5\text{O}$ 267.11, m/z found 267.9 $[\text{M}+\text{H}]^+$.

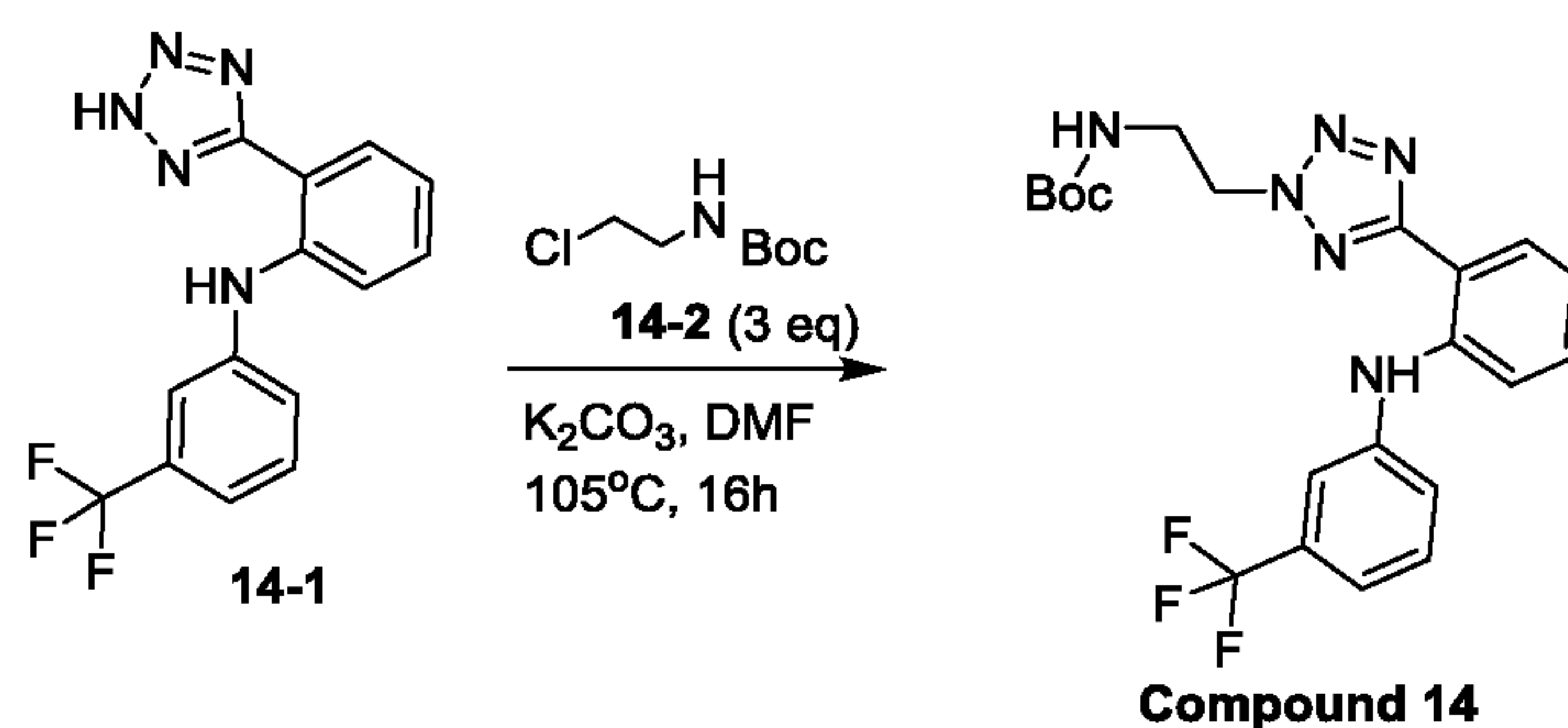
Step 3: 2-[5-[2-(4-methoxyanilino)phenyl]tetrazol-2-yl]ethanol

[00326] To a solution of **12-4** (100 mg, 0.322 mmol, 1.0 *eq*) and 2-bromoethanol (60 mg, 0.483 mmol, 34 μ L, 1.5 *eq*) in DMF (2 mL) was added K_2CO_3 (89 mg, 0.644 mmol, 2.0 *eq*). The resulting mixture was stirred at 100°C for 1 hour. The reaction was monitored by LCMS. The mixture was concentrated in vacuo to give a crude product. The crude product was purified by HPLC to give **Compound 12** (40 mg, 0.128 mmol, 40% yield). LCMS (ESI): RT = 2.023 min, mass calc. for $C_{16}H_{17}N_5O_2$ 311.14, m/z found 312.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ 8.59 (s, 1H), 8.08 (dd, J = 1.5, 7.9 Hz, 1H), 7.34 - 7.28 (m, 1H), 7.22 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.4 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 6.89 (t, J = 7.4 Hz, 1H), 5.11 (t, J = 5.5 Hz, 1H), 4.82 (t, J = 5.3 Hz, 2H), 3.99 (q, J = 5.4 Hz, 2H), 3.78 (s, 3H).

Example 13: 3-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propan-1-ol (Compound 13)

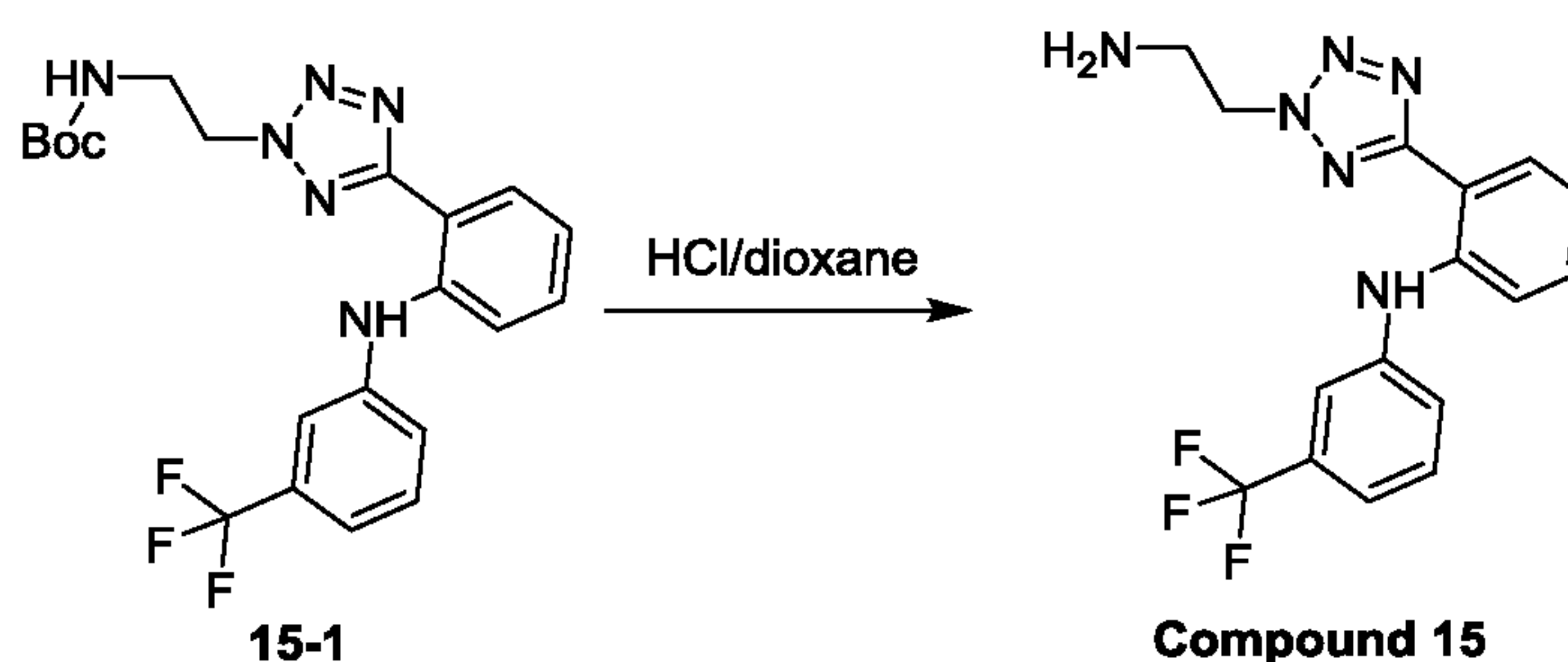
[00327] To a mixture of **13-1** (12.0 mg, 30 μ mol, 1.00 *eq*) in THF (2 mL) was added $NaBH_4$ (4.5 mg, 118 μ mol, 4.00 *eq*) at 28°C under N_2 . The mixture was heated to 60 °C and stirred for 3 h. LCMS showed the starting material was remained and one main peak with the desired MS was detected. The reaction mixture was quenched by addition H_2O (10 mL) at 0 °C and concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC to provide the title compound (4.43 mg, 11.8 μ mol, 39.9% yield). LCMS (ESI): RT = 1.226 min, mass calcd. for $C_{17}H_{16}F_3N_5O$, 363.13 m/z found 364.0 $[M+H]^+$. ^1H NMR (400MHz, CHLOROFORM- d) δ 9.01 (s, 1H), 8.20 (dd, J =7.60, 1.20 Hz, 1H), 7.50 (s, 1H), 7.46 - 7.40 (m, 3H), 7.39 - 7.33 (m, 1H), 7.26 - 7.22 (m, 1H), 7.04 - 6.98 (m, 1H), 4.89 (t, J =6.80 Hz, 2H), 3.77 (t, J =5.60 Hz, 2H), 2.33 (quin, J =6.30 Hz, 2H), 1.72 (br s, 1H).

Example 14: tert-butyl N-[2-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl]carbamate (Compound 14)



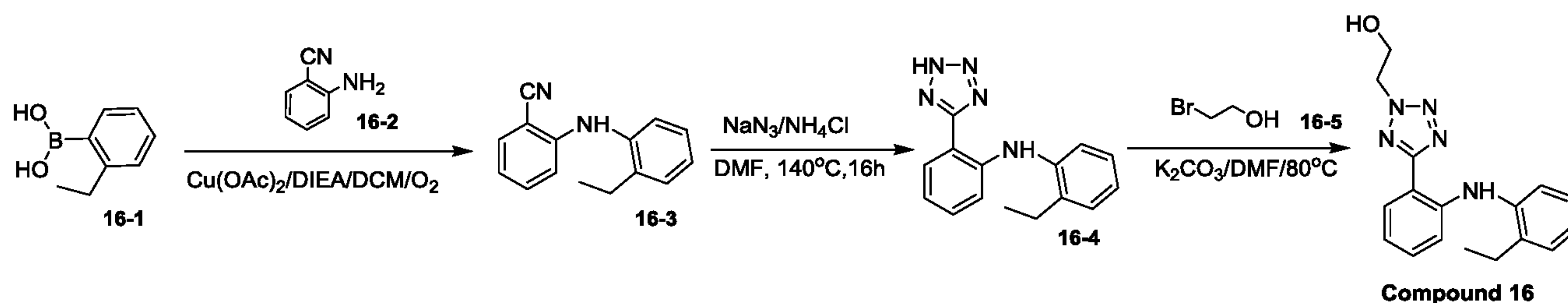
[00328] A mixture of **14-1** (160 mg, 0.524 mmol, 1.00 *eq*) and K_2CO_3 (254 mg, 1.83 mmol, 3.50 *eq*) in DMF (8 mL) was stirred at $28^\circ C$ for 5 min. To the mixture was added **14-2** (282 mg, 1.57 mmol, 3.00 *eq*), and then the mixture was heated to $105^\circ C$ and stirred for 18 h. LCMS showed the starting material was consumed completely and one main peak with the desired MS was detected. TLC indicated one new spot had formed. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL * 6). The combined organic layers were dried with anhydrous Na_2SO_4 , filtered and concentrated under vacuum. The residue was purified by flash silica gel chromatography to provide the title compound (115 mg, 0.250 mmol, 47.7% yield). LCMS (ESI): RT = 1.357 min, mass calcd. for $C_{21}H_{23}F_3N_6O_2$, 448.18 m/z found 393.0[M+H-56]⁺. ^1H NMR (400MHz, CHLOROFORM-*d*) δ 8.94 (s, 1H), 8.20 (dd, $J=7.60, 1.20$ Hz, 1H), 7.51 (s, 1H), 7.47 - 7.41 (m, 3H), 7.39 - 7.34 (m, 1H), 7.26 - 7.23 (m, 1H), 7.01 (t, $J=7.4$ Hz, 1H), 4.90 - 4.77 (m, 3H), 3.87 - 3.78 (m, 2H), 1.42 (s, 9H).

Example 15: 2-[2-(2-aminoethyl)tetrazol-5-yl]-N-[3-(trifluoromethyl)phenyl]aniline (Compound 15)



[00329] Compound **15-1** (100 mg, 0.223 mmol, 1.00 *eq*) in HCl/dioxane (4 M, 2 mL, 35.87 *eq*) was stirred at $28^\circ C$ for 2 h. LCMS showed the starting material was consumed completely and one main peak with the desired MS was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (HCl condition) to provide the title compound (45 mg, 0.115 mmol, 51.4% yield, HCl). LCMS (ESI): RT = 0.705 min, mass calcd. for $C_{16}H_{15}F_3N_6$, 348.13 m/z found 348.9[M+H]⁺. ^1H NMR (400MHz, DMSO-*d*₆) δ 8.71 (s, 1H), 8.33 (br s, 3H), 8.04 (d, $J=7.20$ Hz, 1H), 7.53 - 7.42 (m, 5H), 7.22 (d, $J=7.20$ Hz, 1H), 7.18 - 7.11 (m, 1H), 5.05 (t, $J=6.00$ Hz, 2H), 3.54 - 3.44 (m, 2H).

Example 16: 2-[5-[2-(2-ethylanilino)phenyl]tetrazol-2-yl]ethanol (Compound 16)



Step 1: 2-(2-ethylanilino)benzonitrile

[00330] To a solution of **16-2** (500.0 mg, 4.23 mmol, 1.0 *eq*) and **16-1** (634.4 mg, 4.23 mmol, 1.0 *eq*) in DCM (10.0 mL) was added DIEA (656.0 mg, 5.1 mmol, 886.5 μL , 1.2 *eq*) and $\text{Cu}(\text{OAc})_2$ (768.3 mg, 4.23 mmol, 1.0 *eq*). The mixture was stirred at 30°C for 16 hour under O_2 atmosphere. LCMS showed the desired compound was formed. TLC (30% ethyl acetate in petroleum ether, $R_f = 0.6$) showed a new spot had appeared. The reaction was filtered through celatom and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography over silica gel to give **16-3** (280.0 mg, 1.26 mmol, 29.8% yield) a colourless oil. LCMS (ESI): RT = 0.857 min, mass calc. for $\text{C}_{15}\text{H}_{14}\text{N}_2$ 222.12, m/z found 222.9 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.86 (s, 1H), 7.57 (dd, $J=1.5, 7.8$ Hz, 1H), 7.41 - 7.34 (m, 1H), 7.23 - 7.14 (m, 3H), 7.11 - 7.06 (m, 1H), 6.85 - 6.79 (m, 1H), 6.53 (d, $J=8.5$ Hz, 1H), 2.55 - 2.52 (m, 2H), 1.11 (d, $J=1.5$ Hz, 3H).

Step 2: 2-ethyl-N-[2-(2H-tetrazol-5-yl)phenyl]aniline

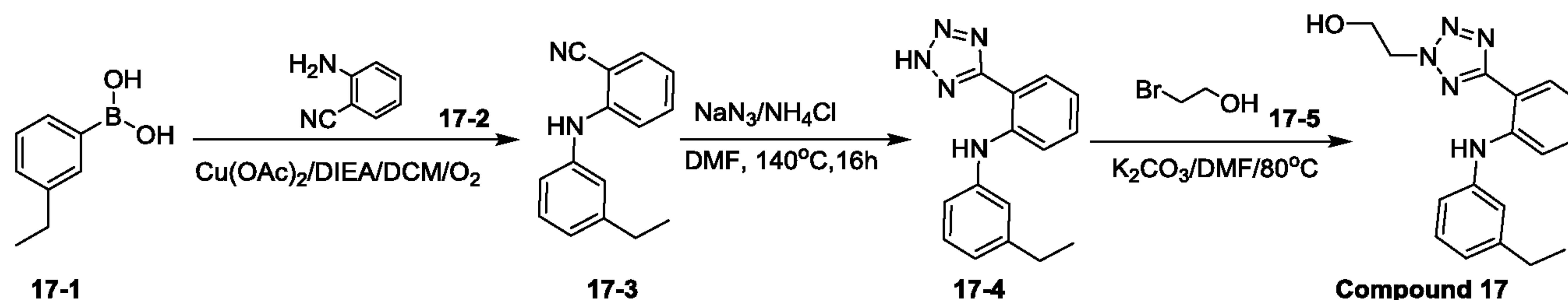
[00331] To a solution of **16-3** (280.0 mg, 1.26 mmol, 1.0 *eq*) in DMF (10.0 mL) was added NH_4Cl (202.4 mg, 3.78 mmol, 0.13 mL, 3.0 *eq*) and NaN_3 (819.1 mg, 12.6 mmol, 10.0 *eq*). The mixture was stirred at 140°C for 16 hour under an N_2 atmosphere. LCMS showed the desired compound had formed. The reaction mixture was poured into sat. aq. NaHCO_3 (5 mL) and extracted with EtOAc (5 mL*2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to afford **16-4** (300.0 mg, 1.13 mmol, 89.7% yield), which was directly used without further purification. LCMS (ESI): RT = 0.819 min, mass calc. for $\text{C}_{15}\text{H}_{15}\text{N}_5$ 265.13, m/z found 265.9 $[\text{M}+\text{H}]^+$.

Step 3: 2-[5-[2-(2-ethylanilino)phenyl]tetrazol-2-yl]ethanol

[00332] To a solution of **16-4** (100.0 mg, 0.38 mmol, 1.0 *eq*) in DMF (5.0 mL) was added K_2CO_3 (78.1 mg, 0.57 mmol, 1.5 *eq*) and **16-5** (56.5 mg, 0.45 mmol, 32.1 μL , 1.2 *eq*). The mixture was stirred at 100°C for 3 hours under an N_2 atmosphere. LCMS showed the desired compound had formed. The reaction was filtered to give a crude product. The crude product was purified by prep-HPLC to give **Compound 16** (21.11 mg, 32.77 μmol , 68.7% yield). LCMS (ESI): RT = 0.832 min, mass calc. for $\text{C}_{17}\text{H}_{19}\text{N}_5\text{O}$ 309.16, m/z found 309.9 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.66

(s, 1H), 8.11 (dd, $J=1.5, 8.0$ Hz, 1H), 7.35 - 7.28 (m, 3H), 7.25 - 7.19 (m, 1H), 7.13 - 7.07 (m, 1H), 7.03 (d, $J=8.3$ Hz, 1H), 6.94 - 6.87 (m, 1H), 5.11 (br s, 1H), 4.81 (t, $J=5.1$ Hz, 2H), 3.98 (t, $J=5.1$ Hz, 2H), 2.65 (q, $J=7.5$ Hz, 2H), 1.19 (t, $J=7.5$ Hz, 3H).

Example 17: 2-[5-[2-(3-ethylanilino)phenyl]tetrazol-2-yl]ethanol (Compound 17)



Step 1: 2-(3-ethylanilino)benzonitrile

[00333] To a solution of **17-2** (500.0 mg, 4.23 mmol, 1.0 *eq*) and **17-1** (634.43 mg, 4.23 mmol, 1.0 *eq*) in DCM (10.0 mL) was added DIEA (656.0 mg, 5.1 mmol, 0.89 mL, 1.2 *eq*) and Cu(OAc)₂ (768.3 mg, 4.23 mmol, 1.0 *eq*). The mixture was stirred at 30 °C for 16 hour under O₂ atmosphere. LCMS showed the desired compound was formed. TLC (30% ethyl acetate in petroleum ether, R_f = 0.6) showed a new spot. The reaction was filtered through celatom and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography over silica gel to provide **17-3** (450.0 mg, 2.02 mmol, 47.9% yield). LCMS (ESI): RT = 0.867 min, mass calc. for C₁₅H₁₄N₂ 222.12, m/z found 222.9 [M+H]⁺; ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.36 (s, 1H), 7.65 (dd, $J=1.5, 7.8$ Hz, 1H), 7.51 - 7.46 (m, 1H), 7.25 - 7.17 (m, 2H), 7.00 - 6.92 (m, 3H), 6.83 (d, $J=7.8$ Hz, 1H), 2.59 - 2.53 (m, 2H), 1.17 (t, $J=7.5$ Hz, 3H).

Step 2: N-(3-ethylphenyl)-2-(2H-tetrazol-5-yl)aniline

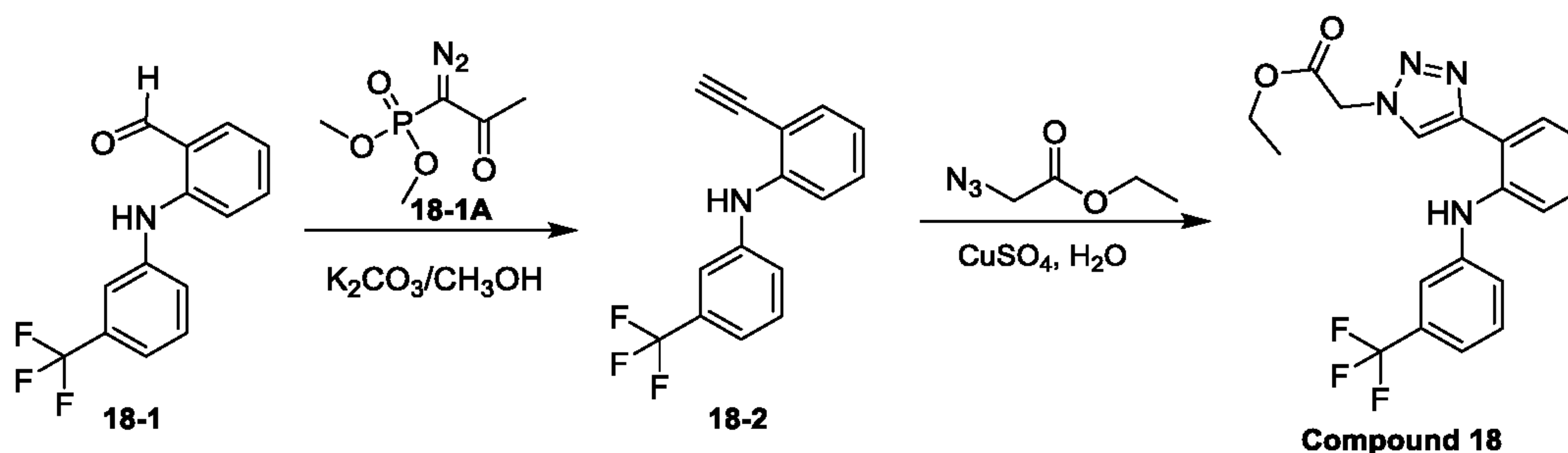
[00334] To a solution of **17-3** (300.0 mg, 1.35 mmol, 1.0 *eq*) in DMF (10.0 mL) was added NH₄Cl (216.6 mg, 4.05 mmol, 0.14 mL, 3.0 *eq*) and NaN₃ (263.3 mg, 4.05 mmol, 3.0 *eq*). The mixture was stirred at 140 °C for 16 hour under an N₂ atmosphere. LCMS showed the desired compound was formed. The reaction mixture was poured into sat. aq. NaHCO₃ (5 mL) and extracted with EtOAc (5 mL*2). The combined organic layer was washed with brine (10 mL), dried over Na₂SO₄, and filtered. The solvent was removed under reduced pressure to afford **17-4** (300.0 mg, 1.13 mmol, 83.8% yield), which was directly used without further purification. LCMS (ESI): RT = 0.826 min, mass calc. for C₁₅H₁₅N₅ 265.13, m/z found 265.9 [M+H]⁺.

Step 3: 2-[5-[2-(3-ethylanilino)phenyl]tetrazol-2-yl]ethanol

[00335] To a solution of **17-4** (100.0 mg, 0.38 mmol, 1.0 *eq*) in DMF (5.0 mL) was added K₂CO₃ (78.1 mg, 0.57 mmol, 1.5 *eq*) and 2-bromoethanol (56.5 mg, 0.45 mmol, 32.1 uL, 1.2 *eq*). The mixture was stirred at 100 °C for 3 hours under an N₂ atmosphere. LCMS showed the desired

compound was formed. The reaction was filtered to give a crude product. The crude product was purified by prep-HPLC to give **Compound 17** (19.79 mg, 63.97 μ mol, 16.97% yield). LCMS (ESI): RT = 0.846 min, mass calc. for $C_{17}H_{19}N_5O$ 309.16, m/z found 309.9 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ 8.69 (s, 1H), 8.06 (d, $J=7.5$ Hz, 1H), 7.39 - 7.35 (m, 2H), 7.24 (t, $J=7.7$ Hz, 1H), 7.08 - 7.03 (m, 2H), 6.99 - 6.94 (m, 1H), 6.87 (d, $J=7.5$ Hz, 1H), 5.10 (br s, 1H), 4.80 (t, $J=5.1$ Hz, 2H), 3.97 (br s, 2H), 2.58 (q, $J=7.5$ Hz, 2H), 1.18 (t, $J=7.5$ Hz, 3H).

Example 18: Ethyl 2-[4-[2-[3-(trifluoromethyl)anilino]phenyl]triazol-1-yl]acetate (Compound 18)



Step 1: 2-ethynyl-N-[3-(trifluoromethyl)phenyl]aniline

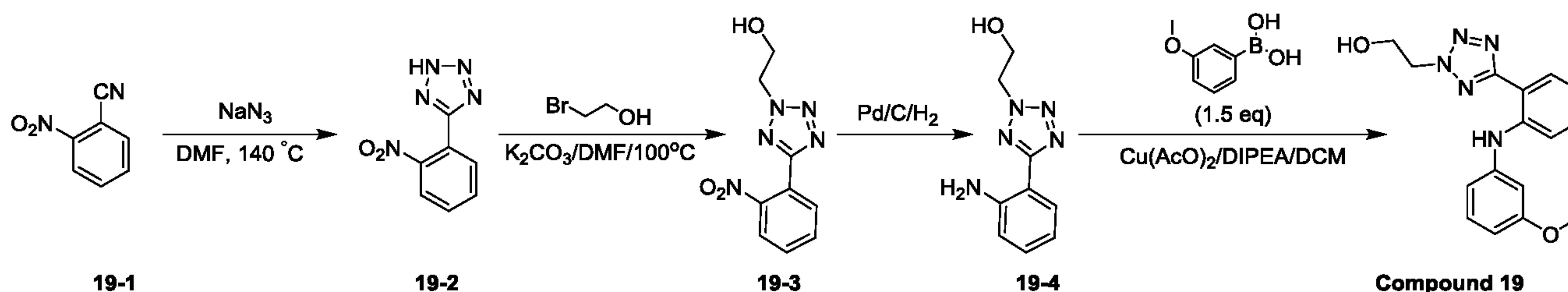
[00336] To a solution of **18-1** (150.0 mg, 0.57 mmol, 1.0 eq) in MeOH (3.00 mL) was added K_2CO_3 (156.3 mg, 1.1 mmol, 2.0 eq) and **18-1A** (108.7 mg, 0.57 mmol, 1.0 eq). The mixture was stirred at 20-30 °C for 16 hour to give a yellow solution. The reaction was monitored by LC-MS and TLC. The reaction mixture was concentrated to give a residue. The residue was purified by flash column chromatography to provide **18-2** (70.0 mg, 0.13 mmol, 23.69% yield) as a light yellow oil. LCMS (ESI): RT = 2.706 min, mass calc. for $C_{15}H_{10}F_3N$ 261.08, m/z found 261.9 $[M+H]^+$.

Step 2: Ethyl 2-[4-[2-[3-(trifluoromethyl)anilino]phenyl]triazol-1-yl]acetate

[00337] To a suspension of ethyl 2-azidoacetate (41.5 mg, 0.32 mmol, 45.1 μ L, 1.2 eq) and **18-2** (70.0 mg, 0.27 mmol, 1.0 eq) in H_2O (2.00 mL) was added $CuSO_4 \cdot 5H_2O$ (669.04 μ g, 2.68 μ mol, 0.01 eq). The mixture was stirred at 100 °C for 6 hour. The reaction was monitored by LC-MS. The reaction mixture was extracted with DCM (5 mL*3). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 18** (50.0 mg, 0.13 mmol, 47.8% yield). LCMS (ESI): RT = 2.323 min, mass calc. for $C_{19}H_{17}F_3N_4O_2$ 390.13, m/z found 391.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.57-7.55(m, 1H), 7.28-7.24 (m, 2H), 7.13-7.10(m, 1H), 3.95-3.88 (m, 2H), 3.06-3.00(m, 2H). LCMS (ESI): RT = 0.856 min, mass calc. for $C_{33}H_{40}N_4O_5S_2$ 636.24, m/z found 637.1 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ (ppm) 9.19 (s, 1H), 7.89 (s, 1H),

7.47-7.45 (m, 1H), 7.40 - 7.34 (m, 2H), 7.29-7.28 (m, 2H), 7.23 - 7.18 (m, 1H), 7.13 - 7.05 (m, 1H), 6.92 - 6.85 (m, 1H), 5.15 (s, 2H), 4.23 (q, $J=7.3$ Hz, 2H), 1.25 (t, $J=7.2$ Hz, 3H)

**Example 19: 2-(5-(2-((3-methoxyphenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-ol
(Compound 19)**



Step 1: 5-(2-nitrophenyl)-2H-tetrazole

[00338] To a solution of **19-1** (400.0 mg, 2.7 mmol, 1.0 eq), sodium azide (1.1 g, 16.2 mmol, 6.0 eq) in DMF (4.0 mL) was added NH_4Cl (866.5 mg, 16.2 mmol, 6.00 eq). The mixture was stirred at 140°C for 16 hour under N_2 atmosphere. Th reaction was monitored by LC-MS. The reaction mixture was poured into 1N HCl (20 mL) and extracted with EtOAc (10 ml*3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , and filtered. The filtrate was concentrated to give **19-2** (550.0 mg, crude) as a yellow oil. The crude product was used in next step directly without further purification. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.00 (d, $J=8.0$ Hz, 1H), 7.98 - 7.95 (m, 1H), 7.90 (dd, $J=1.3, 7.8$ Hz, 1H), 7.71 (dt, $J=1.3, 7.5$ Hz, 1H), 7.67 - 7.61 (m, 1H).

Step 2: 2-[5-(2-nitrophenyl)tetrazol-2-yl]ethanol

[00339] To a solution of **19-2** (250.0 mg, 1.31 mmol, 1.0 eq) in DMF (3.0 mL) was added K_2CO_3 (271.58 mg, 2.0 mmol, 1.5 eq) and 2-bromoethanol (196.5 mg, 1.6 mmol, 111.6 μL , 1.20 eq). The mixture was stirred at 100°C for 16 hours to give a brown suspension. The reaction was monitored by LC-MS. The reaction mixture was poured into water (5 mL) and extracted with EtOAc (5 mL*3). The combined organic layers were dried over Na_2SO_4 , and filtered. The filtrate was concentrated to give a residue. The residue was purified by flash column chromatography to give **19-3** (150.0 mg, 0.64mmol, 48.7% yield) was obtained as a light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.03 (dd, $J=1.4, 7.7$ Hz, 1H), 7.92 (dd, $J=1.3, 8.0$ Hz, 1H), 7.75 (dt, $J=1.3, 7.5$ Hz, 1H), 7.71 - 7.65 (m, 1H), 4.88 - 4.83 (m, 2H), 4.29 - 4.22 (m, 2H), 2.30 (t, $J=6.4$ Hz, 1H).

Step 3: 2-[5-(2-aminophenyl)tetrazol-2-yl]ethanol

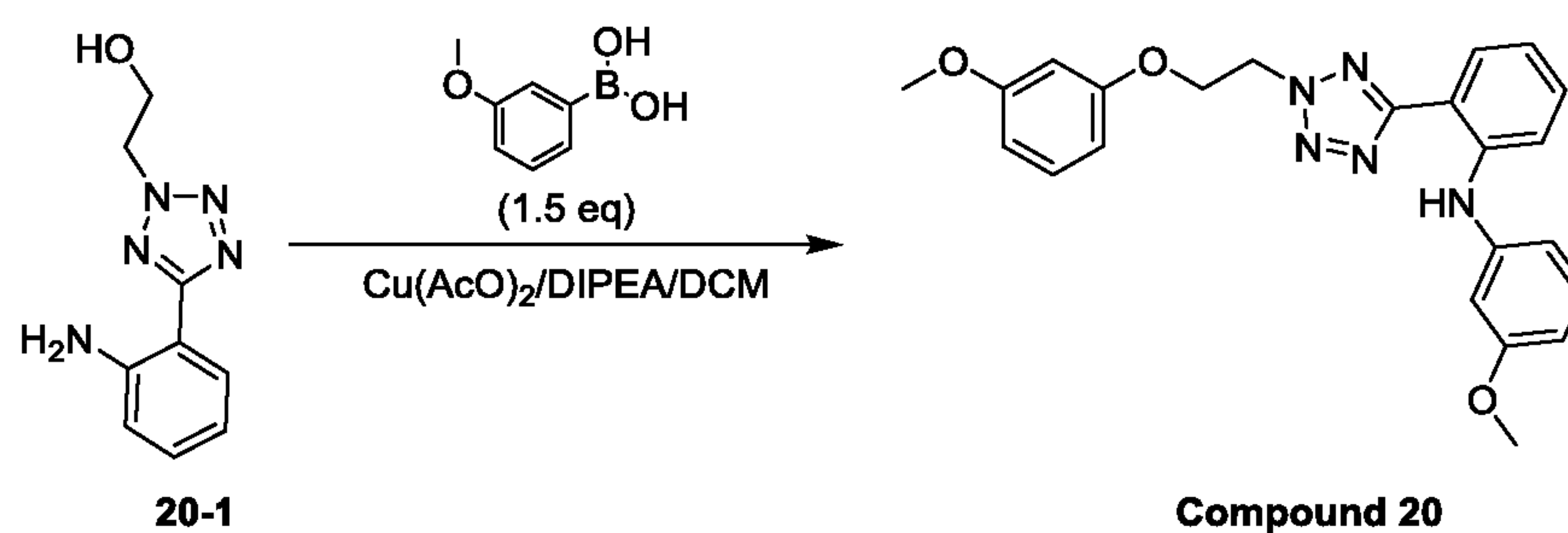
[00340] To a solution of **19-3** (150.0 mg, 0.64 mmol, 1.0 eq) in MeOH (5.0 mL) was added Pd/C (10%, 20 mg) under N_2 . The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at $20\text{-}30^\circ\text{C}$ for 3 hours. LCMS showed the

starting material was consumed completely and one main peak with the desired MS was detected. The reaction mixture was filtered and the filtrate was concentrated to give crude product **19-4** (140.0 mg, crude). The crude product was use in next step directly without further purification. LCMS (ESI): RT = 0.538 min, mass calc. for C₉H₁₁N₅O 205.10, m/z found 205.8 [M+H]⁺.

Step 4: 2-(5-(2-((3-methoxyphenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-ol

[00341] To a solution of (3-methoxyphenyl)boronic acid (155.5 mg, 1.0 mmol, 1.5 eq) and **19-4** (140.0 mg, 0.68 mmol, 1.0 eq) in DCM (20.0 mL) was added Cu(OAc)₂ (136.3 mg, 0.75mmol, 1.10 eq) and DIPEA (132.3 mg, 1.0 mmol, 178.7 uL, 1.5 eq). The mixture was stirred at 20-30 °C for 60 hr under O₂ atmosphere. The reaction was monitored by LCMS. The reaction mixture was filtered through a Celite pad and washed with DCM (30 mL). The filtrate was concentrated to give a residue. The residue was purified by flash column chromatography to provide **Compound 19** (45.31 mg, 0.15 mmol, 21.3% yield). LCMS (ESI): RT = 1.982 min, mass calc. for C₁₆H₁₇N₅O₂ 311.14, m/z found 311.9 [M+H]⁺; ¹HNMR (400 MHz, CDCl₃) δ(ppm): 8.75 (s, 1H), 8.09 (dd, *J*=1.6, 7.9 Hz, 1H), 7.38 (d, *J*=7.8 Hz, 1H), 7.29 - 7.08 (m, 1H), 6.89 - 6.83 (m, 1H), 6.81 - 6.73 (m, 2H), 6.53 (dd, *J*=2.0, 8.0 Hz, 1H), 4.82 - 4.71 (m, 2H), 4.18 (q, *J*=5.3 Hz, 2H), 3.77 - 3.67 (m, 3H), 2.24 (br t, *J*=6.0 Hz, 1H).

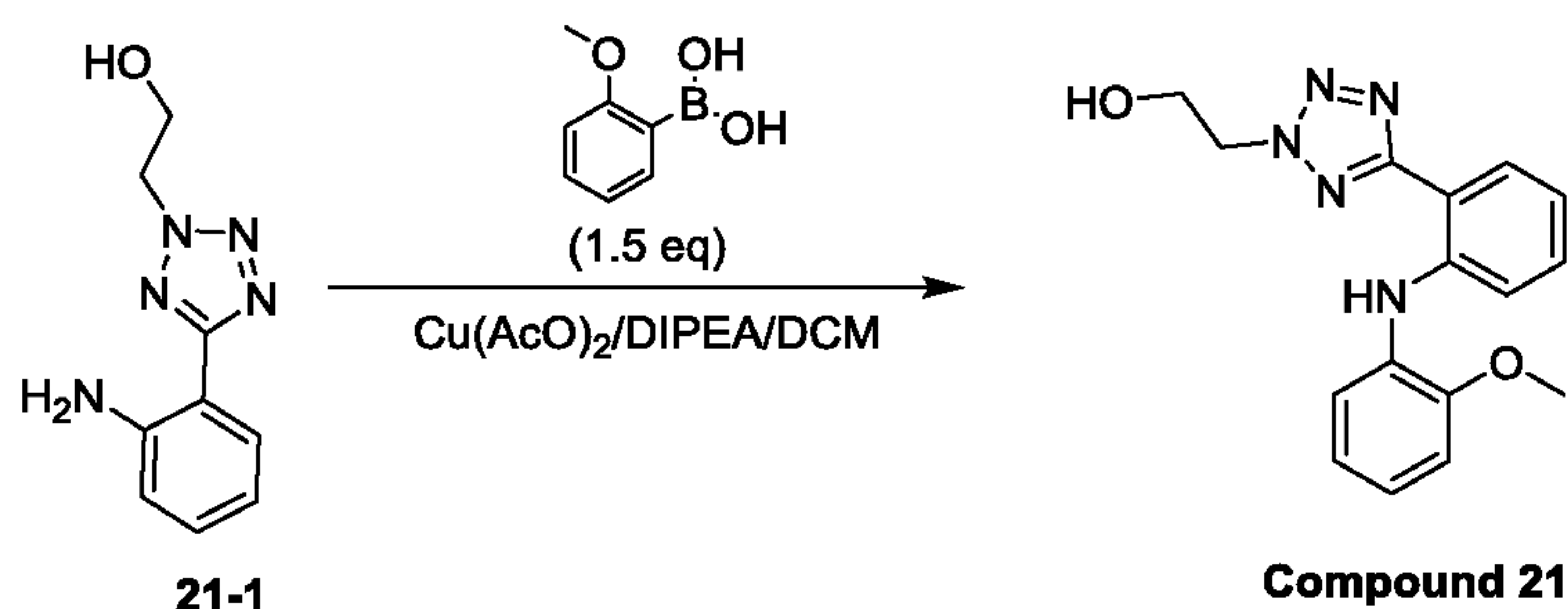
Example 20: 2-[2-[2-(3-methoxyphenoxy)ethyl]tetrazol-5-yl]-N-(3-methoxyphenyl)aniline (Compound 20)



[00342] To a solution of (3-methoxyphenyl)boronic acid (155.5 mg, 1.0 mmol, 1.5 eq) and **20-1** (140.0 mg, 0.68 mmol, 1.0 eq) in DCM (20.0 mL) was added Cu(OAc)₂ (136.3 mg, 0.75 mmol, 1.10 eq) and DIPEA (132.3 mg, 1.0 mmol, 178.7 uL, 1.5 eq). The mixture was stirred at 20-30 °C for 60 hr under O₂ atmosphere. The reaction was monitored by LCMS. The reaction mixture was filtered through a Celite pad and washed with DCM (30 mL). The filtrate was concentrated to give a residue. The residue was purified by flash column chromatography (EtOAc/petroleum ether = 0~20%) to give **Compound 20** (45.11 mg, 0.11 mmol, 15.8% yield). LCMS (ESI): RT = 2.489 min, mass calc. for C₂₃H₂₃N₅O₃ 417.18, m/z found 418.1 [M+H]⁺; ¹HNMR (400 MHz, CDCl₃) δ(ppm): 8.74 (s, 1H), 8.12 (dd, *J*=1.5, 7.8 Hz, 1H), 7.37 (d, *J*=8.3 Hz, 1H), 7.26 - 7.20 (m, 1H), 7.15 (t, *J*=8.0 Hz, 1H), 7.08 (t, *J*=8.3 Hz, 1H), 6.88 - 6.82 (m, 1H), 6.80 - 6.72 (m, 2H), 6.52 (dd,

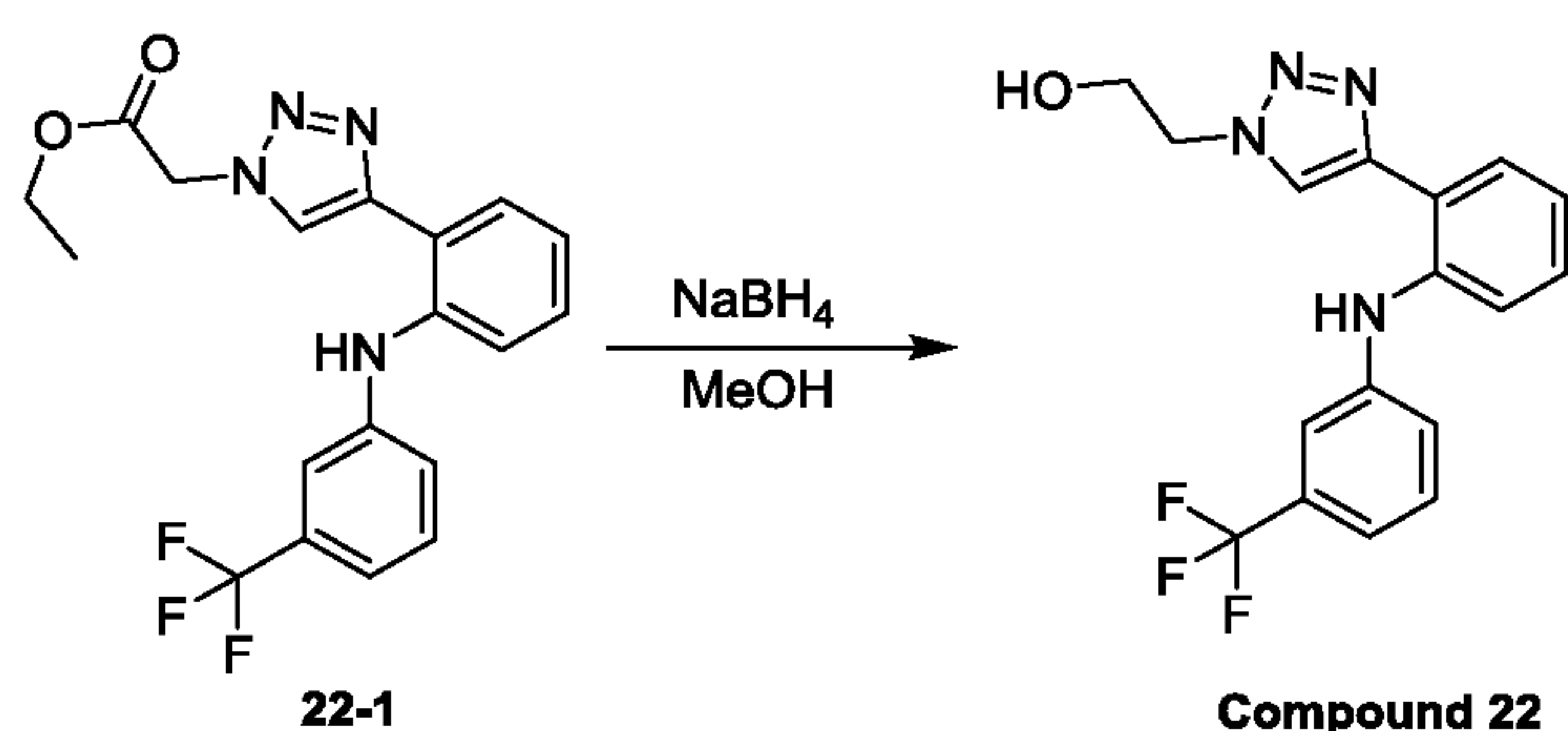
$J=2.0, 8.0$ Hz, 1H), 6.46 (dd, $J=2.3, 8.3$ Hz, 1H), 6.40 (dd, $J=2.0, 8.0$ Hz, 1H), 6.37 - 6.34 (m, 1H), 4.99 (t, $J=5.5$ Hz, 2H), 4.50 (t, $J=5.4$ Hz, 2H), 3.73 (s, 3H), 3.67 (s, 3H).

Example 21: 2-[5-[2-(2-methoxyanilino)phenyl]tetrazol-2-yl]ethanol (Compound 21)



[00343] To a solution of (2-methoxyphenyl)boronic acid (74.1 mg, 0.49 mmol, 1.0 eq) and **21-1** (100.0 mg, 0.49 mmol, 1.0 eq) in DCM (20.0 mL) was added $\text{Cu}(\text{OAc})_2$ (97.36 mg, 536.01 μmol , 1.10 eq) and DIPEA (94.5 mg, 0.73 mmol, 127.7 μL , 1.5 eq). The mixture was stirred at 20-30 °C for 60 hr under O_2 atmosphere. TLC showed most of reactant remained, and one new spot had formed. The reaction mixture was filtered through a Celite pad and washed with DCM (30 mL). The filtrate was concentrated to give a residue. The residue was purified by flash column chromatography and then by prep-HPLC). The resulting eluent was concentrated to remove the organic solvent and the residue was lyophilized to give the title compound (4.23 mg, 13.59 μmol , 2.8% yield). LCMS (ESI): RT = 2.013 min, mass calc. for $\text{C}_{16}\text{H}_{17}\text{N}_5\text{O}_2$ 311.14, m/z found 312.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ ppm: 8.67 (s, 1H), 8.14-8.12 (m, 1H), 7.44 - 7.33 (m, 2H), 7.28 - 7.21 (m, 1H), 6.94 - 6.81 (m, 4H), 4.78 - 4.72 (m, 2H), 4.16-4.15 (m, 2H), 3.85 (s, 3H), 2.57 (s, 1H).

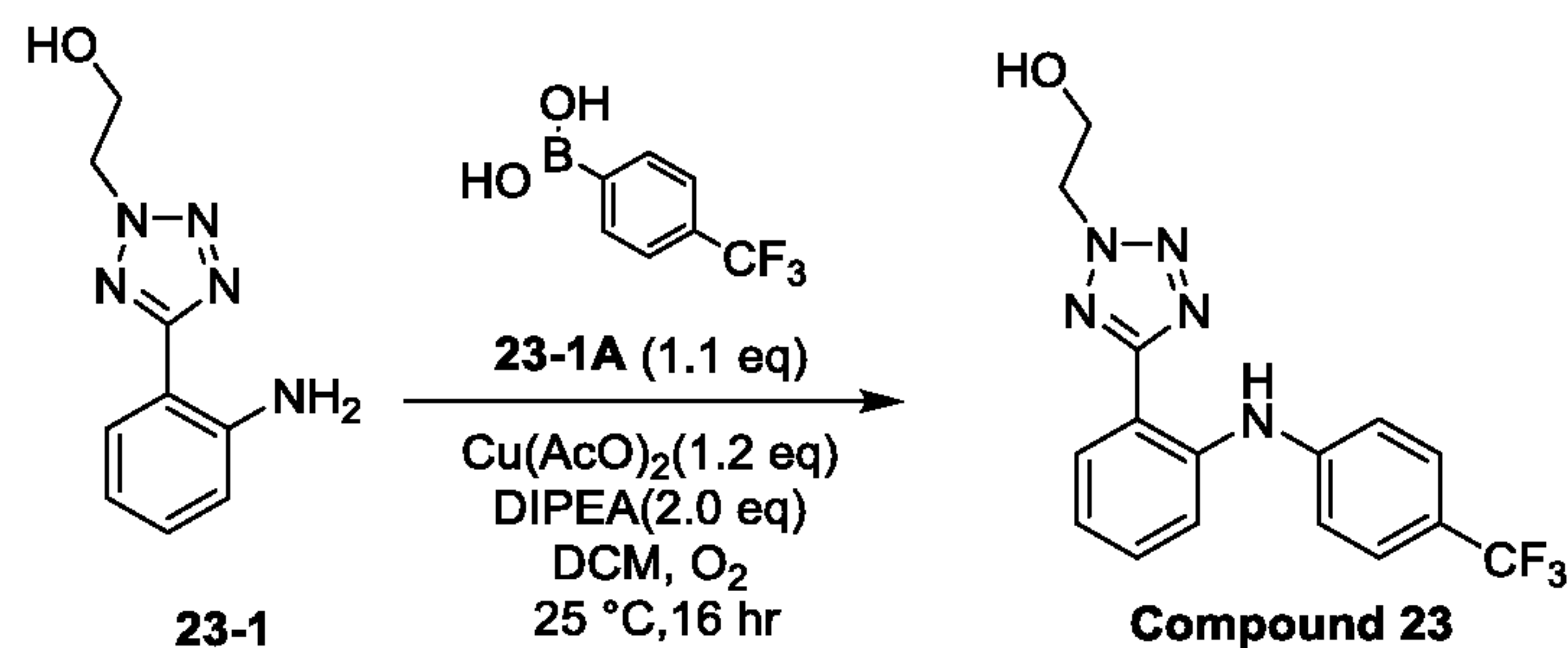
Example 22: 2-[4-[2-[3-(trifluoromethyl)anilino]phenyl]triazol-1-yl]ethanol (Compound 22)



[00344] To a solution of **22-1** (40.0 mg, 0.10 mmol, 1.0 eq) in MeOH (5.0 mL) was added NaBH_4 (38.8 mg, 1.0 mmol, 10.0 eq) at 0°C. The mixture was stirred at 0-30 °C for 2 hour. LC-MS showed reactant was consumed completely and one main peak with the desired MS was detected. The reaction was quenched by adding water (1 mL). The mixture was purified by prep-HPLC. The resulting eluent was concentrated to remove the organic solvent and the residue was lyophilized to give the title compound (5.74 mg, 16.48 μmol , 16.1% yield). LCMS (ESI): RT = 2.068 min, mass calc. for $\text{C}_{17}\text{H}_{15}\text{F}_3\text{N}_4\text{O}$ 348.12, m/z found 349.1 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ (ppm): 9.24

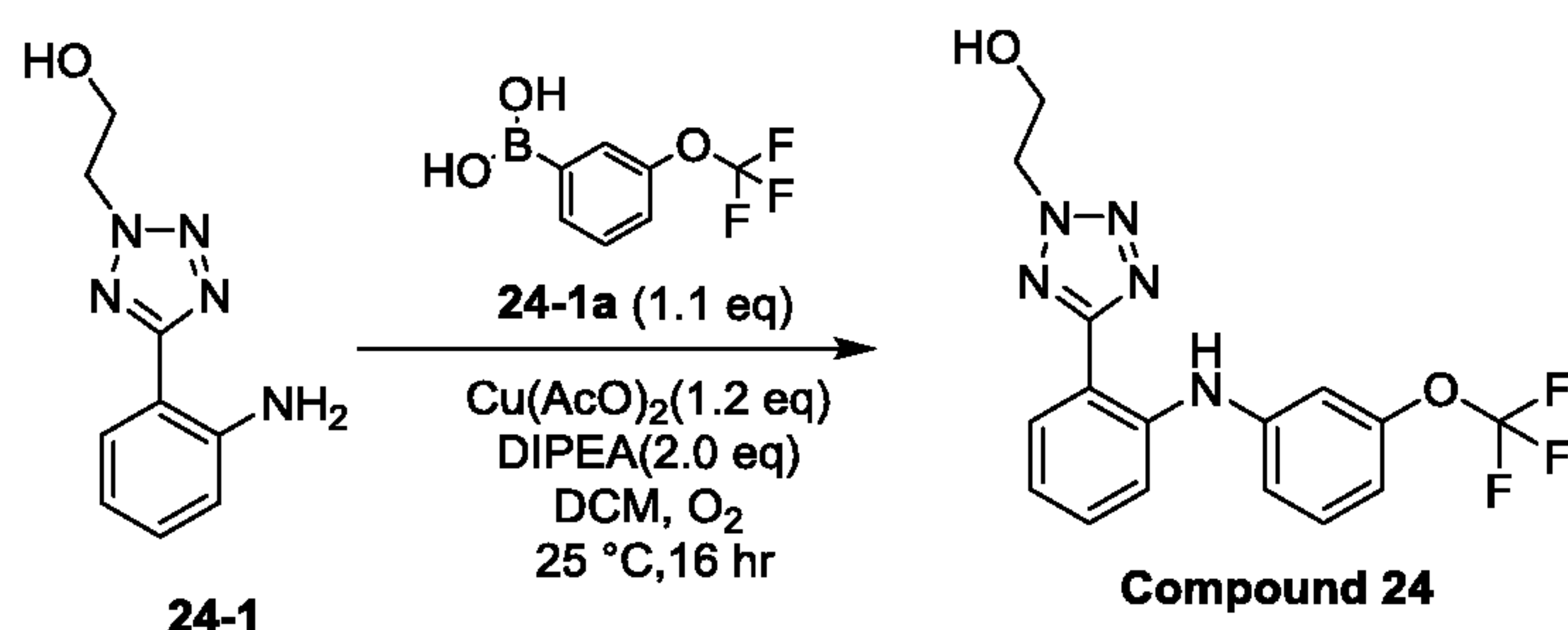
(s, 1 H), 7.86 (s, 1 H), 7.44-7.37 (m, 1 H), 7.40- 7.34 (m, 2 H), 7.31 - 7.26 (m, 2 H), 7.20 - 7.17 (m, 1 H), 7.09-7.08 (m, 1 H), 6.92 - 6.86 (m, 1 H), 4.44 - 4.53 (m, 2 H), 3.99 - 4.09 (m, 2 H).

Example 23: 2-(5-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol (Compound 23)



[00345] To a solution of **23-1** (100 mg, 0.487 mmol, 1.0 *eq*), **23-1A** (110 mg, 0.536 mmol, 1.1 *eq*), Cu(OAc)₂ (106 mg, 0.585 μmol, 1.2 *eq*), DIPEA (126 mg, 0.975 mmol, 2.0 *eq*) in DCM (5 mL) was added 4A MS (50 mg). The reaction mixture was stirred at 25 °C for 16 hours under O₂. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (30 mL) and the resultant mixture was extracted with DCM (50 mL * 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to dryness under reduced pressure. The residue was purified by preparative high performance liquid chromatography. The pure fractions were collected and the volatiles were removed under vacuum. The residue was re-suspended in water (10mL) and the resulting mixture was lyophilized to dryness to remove the solvent residue completely to provide the title compound (80.94 mg, 47% yield). LCMS (ESI): RT = 2.232 min, mass calc. for C₁₆H₁₄F₃N₅O 349.12, m/z found 349.9 [M+H]⁺, ¹HNMR (400MHz, DMSO-*d*₆) δ 8.82 (s, 1H), 8.06 (dd, *J*=1.5, 7.8 Hz, 1H), 7.60 - 7.53 (m, 3H), 7.52 - 7.47 (m, 1H), 7.25 (d, *J*=8.5 Hz, 2H), 7.21 - 7.16 (m, 1H), 5.11 - 5.03 (m, 1H), 4.77 (t, *J*=5.3 Hz, 2H), 4.00 - 3.90 (m, 2H).

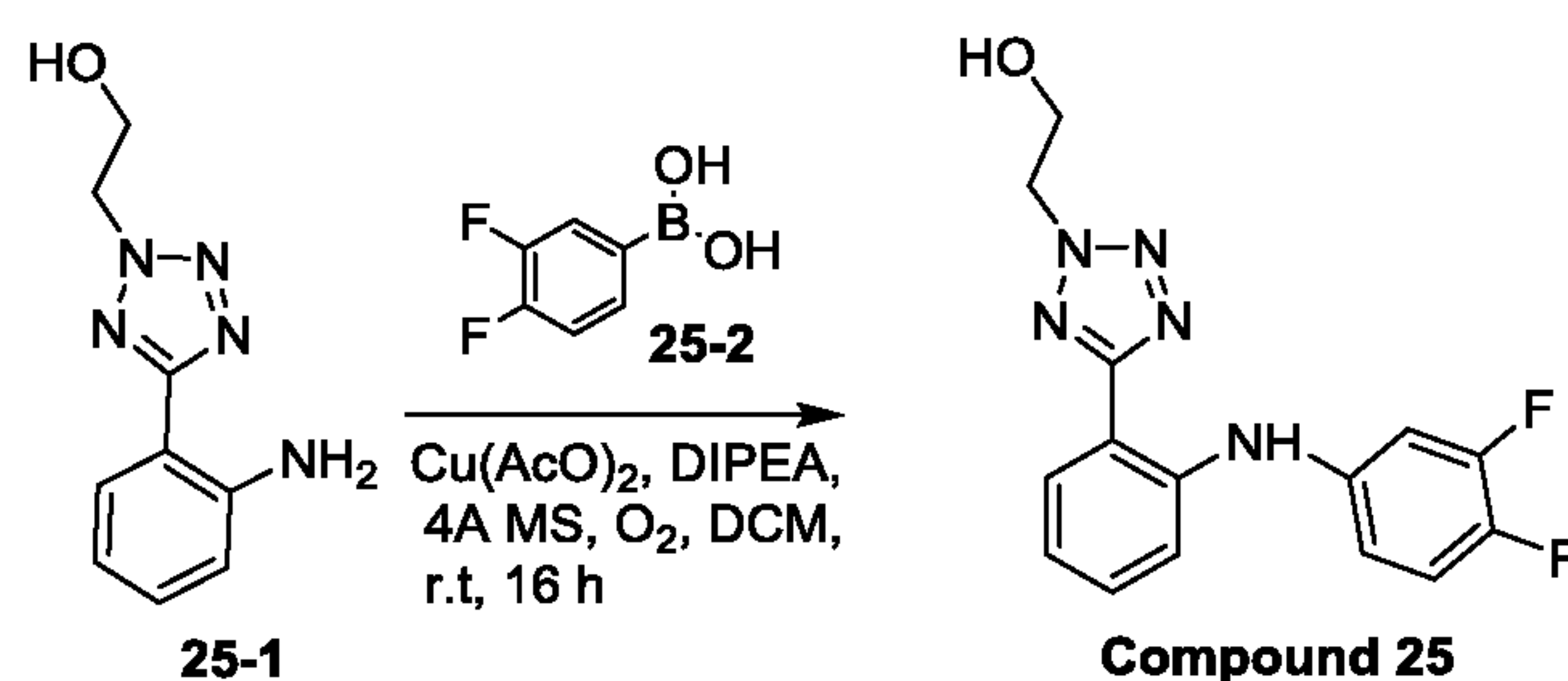
Example 24: 2-(5-(2-((3-(Trifluoromethoxy)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol (Compound 24)



[00346] To a solution of **24-1** (100 mg, 0.487 mmol, 1.0 *eq*), **24-1a** (110 mg, 0.536 mmol, 1.1 *eq*), Cu(OAc)₂ (106 mg, 0.585 μmol, 1.2 *eq*), DIPEA (126 mg, 0.975 mmol, 2.0 *eq*) in DCM (5 mL) was added 4A MS (50 mg). The reaction mixture was stirred at 25 °C for 16 hours under O₂. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (30

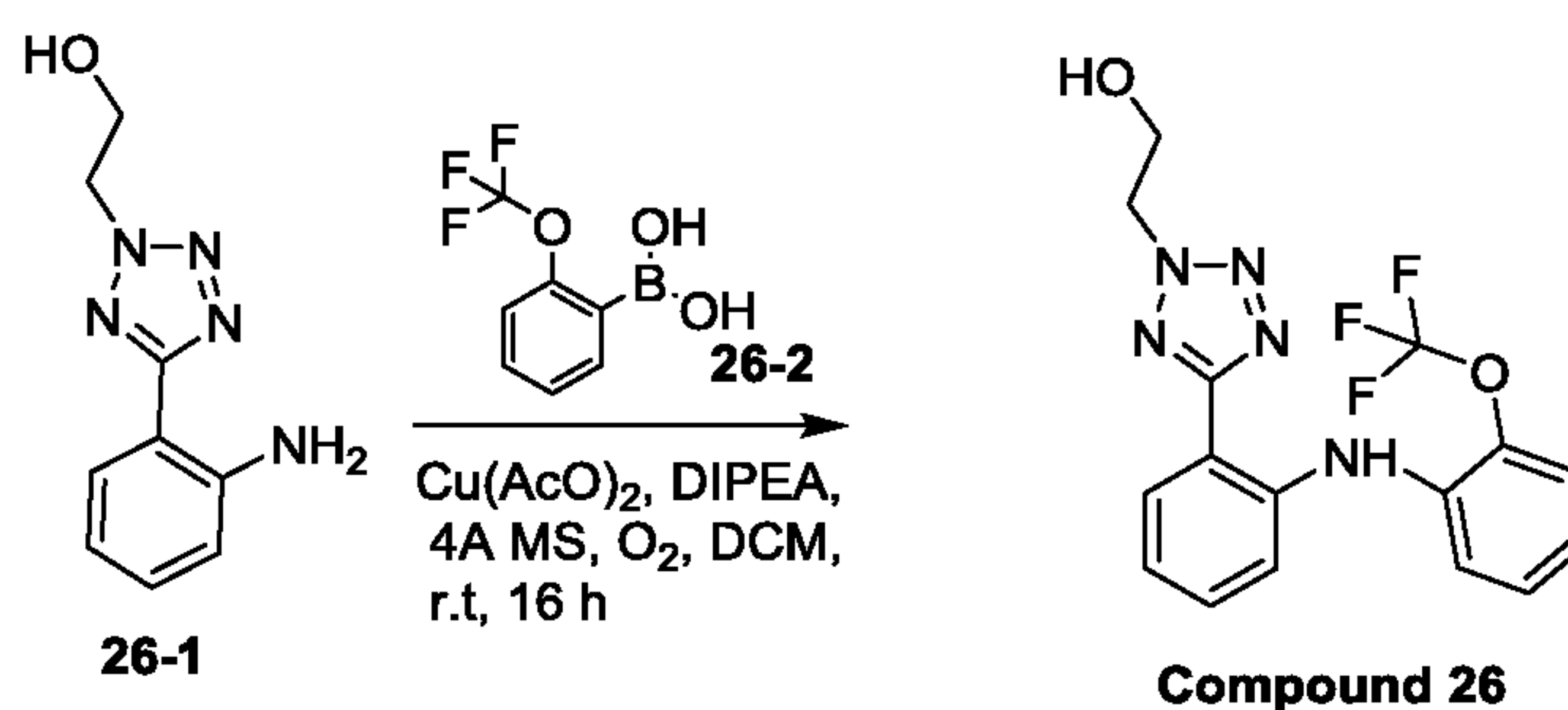
mL) and the resultant mixture was extracted with DCM (50 mL * 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was purified by preparative high performance liquid chromatography. The pure fractions were collected and the volatiles were removed under vacuum. The residue was re-suspended in water (10mL) and the resulting mixture was lyophilized to dryness to remove the solvent residue completely to provide the title compound (77.97 mg, 44% yield). LCMS (ESI): RT = 2.251 min, mass calc. for C₁₆H₁₄F₃N₅O₂ 365.11, m/z found 366.0 [M+H]⁺, ¹HNMR (400MHz, DMSO-*d*₆) δ 8.73 (s, 1H), 8.06 (d, *J*=7.5 Hz, 1H), 7.49 - 7.42 (m, 2H), 7.41 - 7.35 (m, 1H), 7.17 (dd, *J*=1.8, 8.0 Hz, 1H), 7.14 - 7.08 (m, 2H), 6.87 (d, *J*=8.0 Hz, 1H), 5.08 (t, *J*=5.6 Hz, 1H), 4.78 (t, *J*=5.3 Hz, 2H), 3.96 (q, *J*=5.4 Hz, 2H).

Example 25: 2-[5-[2-(3,4-difluoroanilino)phenyl]tetrazol-2-yl]ethanol (Compound 25)



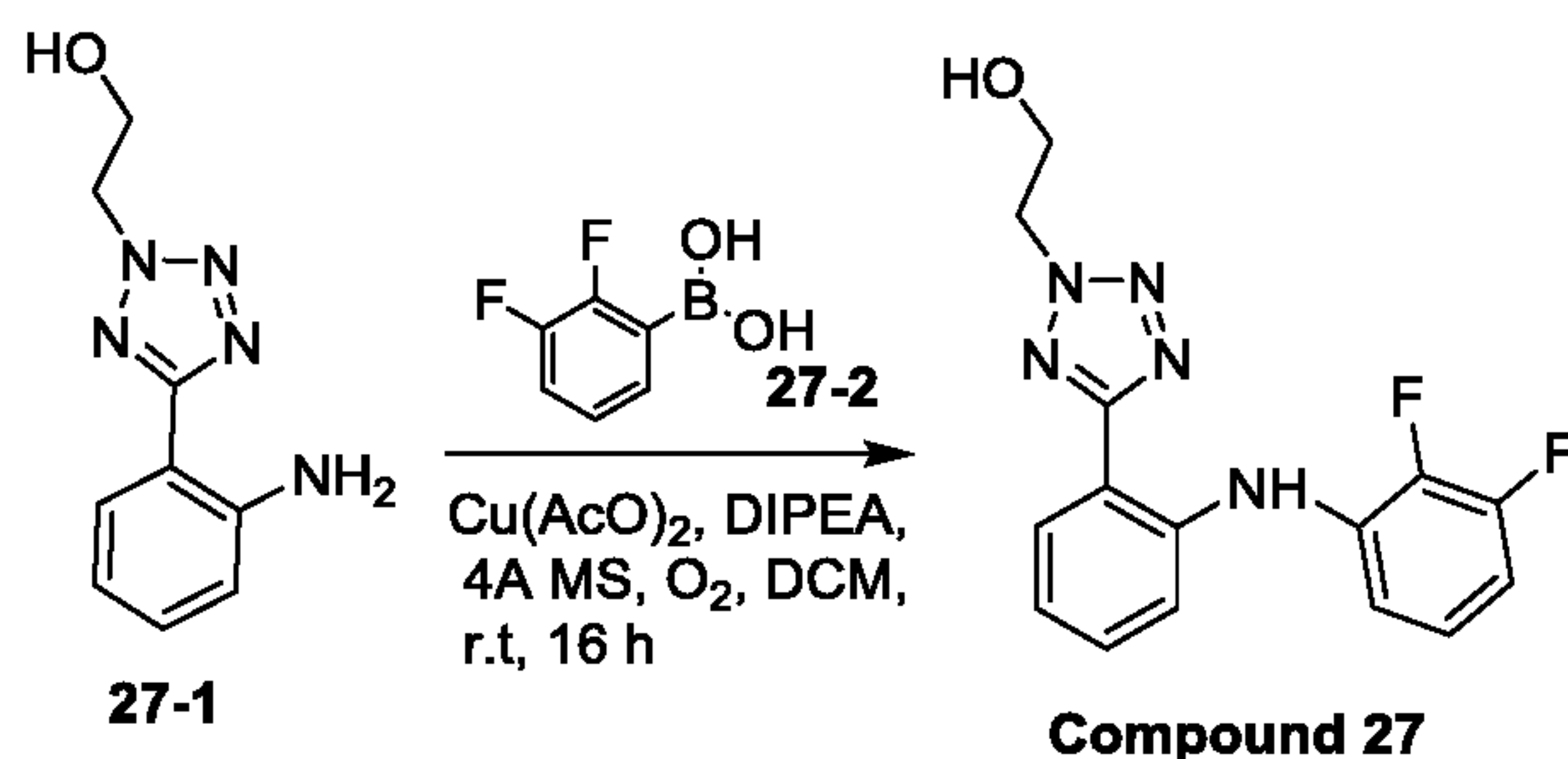
[00347] To a solution of **25-1** (100 mg, 0.487 mmol, 1.0 *eq*) and **25-2** (77 mg, 0.487 mmol, 1.0 *eq*) in DCM (10 mL) was added DIPEA (76 mg, 0.585 mmol, 102 uL, 1.2 *eq*), Cu(OAc)₂ (89 mg, 0.487 mmol, 1.0 *eq*) and 4A MS (100 mg). The resulting mixture was stirred at 30°C for 16 hr under O₂. The reaction was monitored by LCMS and TLC (Petroleum ether: Ethyl acetate = 10/1). The mixture was concentrated in vacuo to give a crude product. The crude product was purified by column chromatography (silica) to give the title compound (110 mg, 0.347 mmol, 71 % yield). LCMS (ESI): RT = 0.809 min, mass calc. for C₁₅H₁₃F₂N₅O 317.11, m/z found 317.9 [M+H]⁺; ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.65 (s, 1H), 8.06 (dd, *J* = 1.3, 7.8 Hz, 1H), 7.45 - 7.31 (m, 3H), 7.26 (ddd, *J* = 2.5, 7.2, 12.7 Hz, 1H), 7.09 - 6.99 (m, 2H), 5.08 (t, *J* = 5.6 Hz, 1H), 4.80 (t, *J* = 5.1 Hz, 2H), 3.97 (q, *J* = 5.5 Hz, 2H).

Example 26: 2-[5-[2-[2-(trifluoromethoxy)anilino]phenyl]tetrazol-2-yl]ethanol (Compound 26)



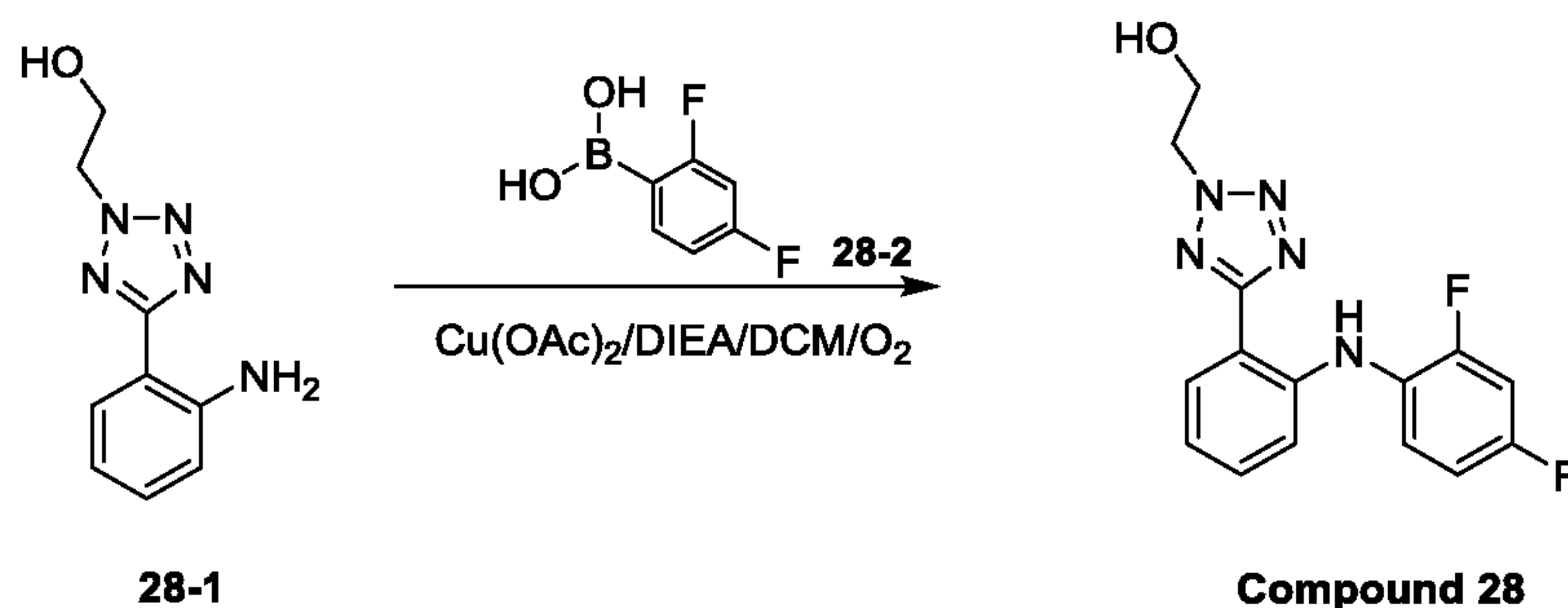
[00348] To a solution of **26-1** (100 mg, 0.487 mmol, 1.0 *eq*) and **26-2** (100 mg, 0.487 mmol, 1.0 *eq*) in DCM (10 mL) was added DIEA (76 mg, 0.585 mmol, 102 μ L, 1.2 *eq*), Cu(OAc)₂ (89 mg, 0.487 mmol, 1.0 *eq*) and 4A MS (100 mg). The resulting mixture was stirred at 30°C for 16 hr under O₂. The reaction was monitored by LCMS and TLC (Petroleum ether: Ethyl acetate =10/1). The mixture was concentrated in vacuo to give a crude product. The crude product was purified by column chromatography (silica) to give the title compound (40 mg, 0.110 mmol, 22% yield). LCMS (ESI): RT = 0.845 min, mass calc. for C₁₆H₁₄F₃N₅O₂ 365.11, m/z found 365.9 [M+H]⁺; ¹HNMR (400 MHz, DMSO-*d*₆) δ 9.07 (s, 1H), 8.14 (d, *J* = 7.5 Hz, 1H), 7.58 (dd, *J* = 1.3, 8.3 Hz, 1H), 7.49 - 7.41 (m, 3H), 7.40 - 7.33 (m, 1H), 7.15 - 7.05 (m, 2H), 5.10 (t, *J* = 5.6 Hz, 1H), 4.79 (t, *J* = 5.3 Hz, 2H), 3.98 (q, *J* = 5.4 Hz, 2H).

Example 27: 2-(5-(2-((2,3-difluorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-ol
(Compound 27)



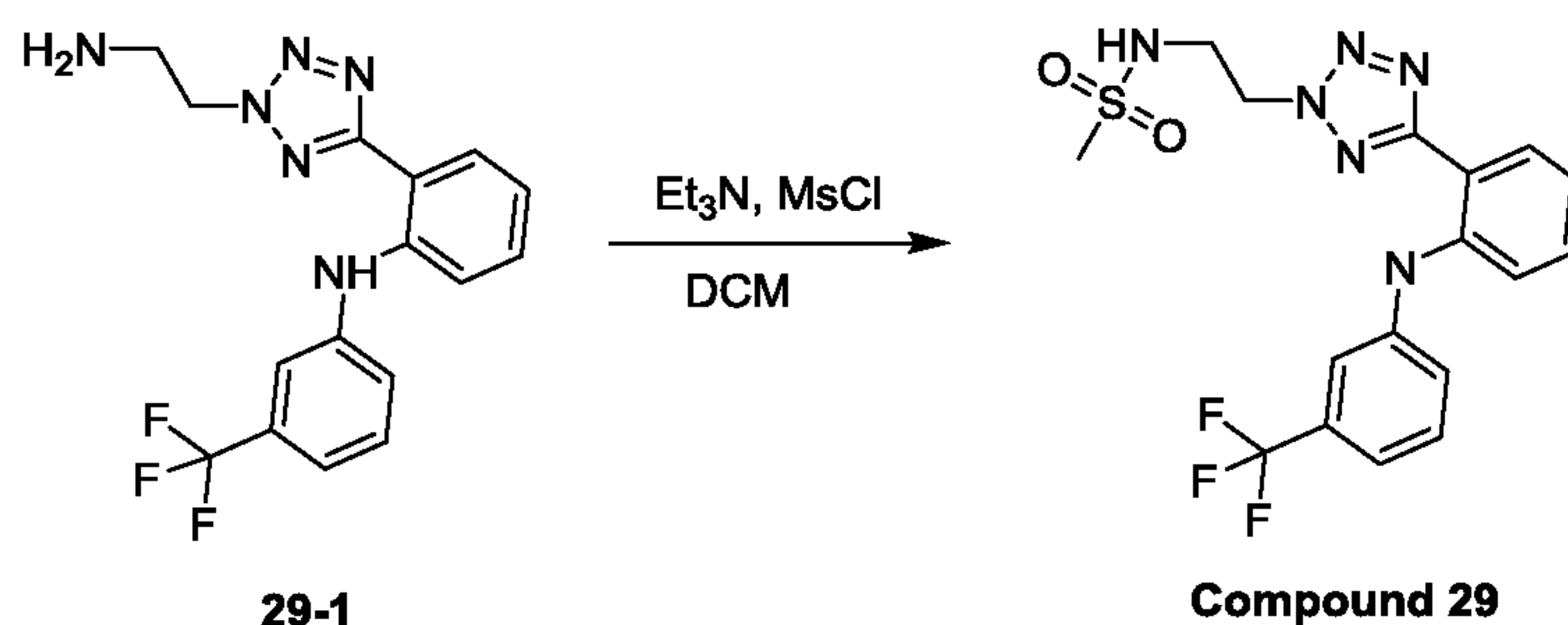
[00349] To a solution of **27-1** (50.0 mg, 0.24 mmol, 1.0 *eq*) and **27-2** (38.5 mg, 0.24 mmol, 1.0 *eq*) in DCM (5.0 mL) was added DIEA (37.8 mg, 0.29 mmol, 51.1 μ L, 1.2 *eq*) and Cu(OAc)₂ (44.3 mg, 0.24 mmol, 1.0 *eq*). The mixture was stirred at 30 °C for 16 hour under O₂ atmosphere. LCMS showed the desired compound was formed. TLC (30% ethyl acetate in petroleum ether, R_f = 0.6) showed a new spot appeared. The reaction was filtered through celatom and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography over silica gel. The crude product was purified by prep-HPLC to obtain the title compound (2.24 mg, 7.06 μ mol, 2.90% yield). LCMS (ESI): RT = 0.795 min, mass calc. for C₁₅H₁₃F₂N₅O 317.11, m/z found 317.9 [M+H]⁺; ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.85 (s, 1H), 8.11 (dd, *J*=1.4, 7.9 Hz, 1H), 7.47 - 7.41 (m, 1H), 7.31 (d, *J*=8.5 Hz, 1H), 7.27 - 7.22 (m, 1H), 7.17 - 7.01 (m, 3H), 5.10 (t, *J*=5.5 Hz, 1H), 4.80 (t, *J*=5.3 Hz, 2H), 3.97 (q, *J*=5.4 Hz, 2H).

Example 28: 2-(5-(2-((2,4-difluorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-ol
(Compound 28)



[00350] To a solution of **28-1** (50.0 mg, 0.24 mmol, 1.0 *eq*) and **28-2** (38.5 mg, 0.24 mmol, 1.0 *eq*) in DCM (10.0 mL) was added DIEA (37.8 mg, 0.29 mmol, 51.1 μ L, 1.2 *eq*) and Cu(OAc)₂ (44.3 mg, 0.24 mmol, 1.0 *eq*). The mixture was stirred at 30 °C for 16 hour under O₂ atmosphere. LCMS showed the desired compound was formed. TLC (30% ethyl acetate in petroleum ether, R_f = 0.6) showed residual starting material and a new spot. The reaction was filtered through celatom and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography over silica gel. The crude product was purified by prep-HPLC to give the title compound (5.76 mg, 18.15 μ mol, 7.45% yield). LCMS (ESI): RT = 0.791 min, mass calc. for C₁₅H₁₃F₂N₅O 317.11, m/z found 317.9 [M+H]⁺; ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.63 (s, 1H), 8.09 (dd, *J*=1.3, 7.8 Hz, 1H), 7.50 (dt, *J*=6.1, 9.1 Hz, 1H), 7.43 - 7.33 (m, 2H), 7.13 - 7.07 (m, 1H), 7.04 - 6.96 (m, 2H), 5.11 (t, *J*=5.6 Hz, 1H), 4.81 (t, *J*=5.1 Hz, 2H), 3.98 (q, *J*=5.4 Hz, 2H).

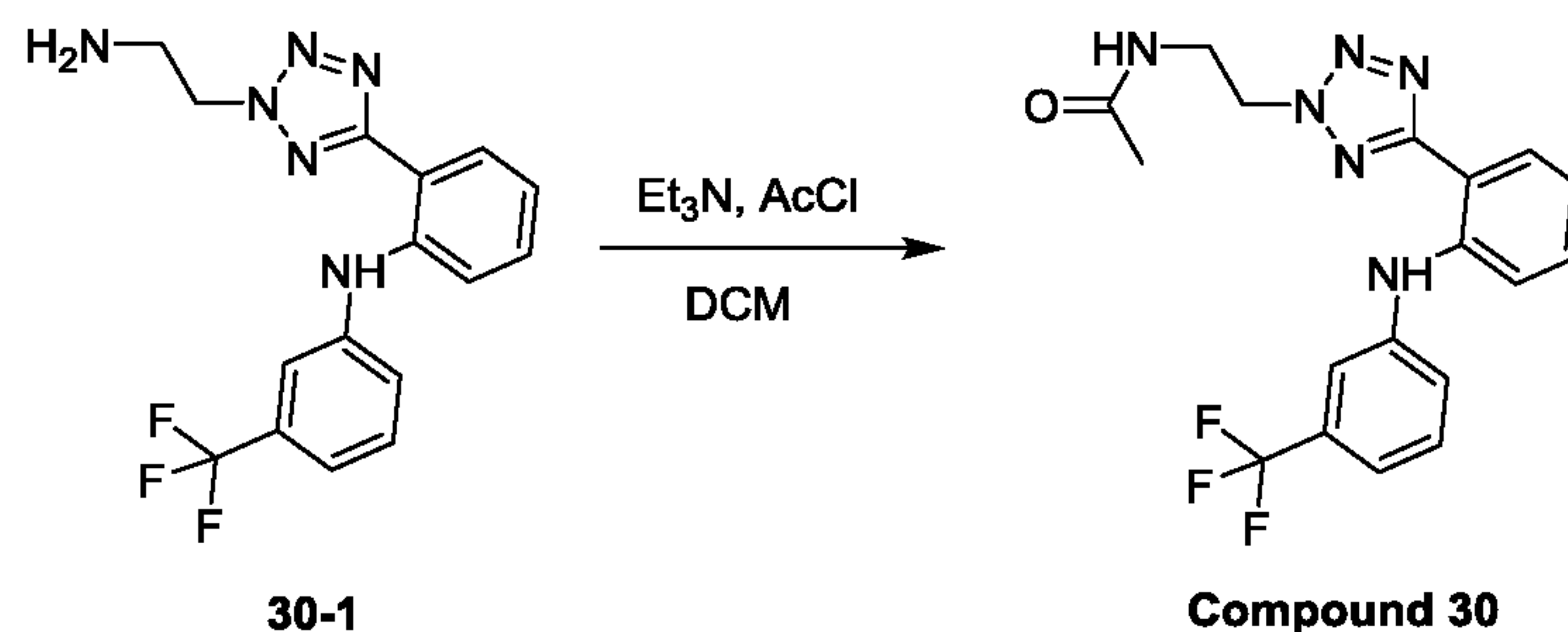
Example 29: N-[2-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl]methane sulfonamide (Compound 29)



[00351] To a mixture of **29-1** (15 mg, 39 μ mol, 1.00 *eq*, HCl) and Et₃N (12 mg, 0.117 mmol, 16 μ L, 3.00 *eq*) in DCM (2 mL) was added MsCl (6.7 mg, 59 μ mol, 5 μ L, 1.50 *eq*) in one portion at 28 °C. The mixture was stirred at 28 °C for 2 h. LCMS showed **29-1** was consumed completely and one main peak with the desired MS was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with water (6 mL) and extracted with EtOAc (8 mL * 6). The combined organic layers were dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by prep-HPLC (basic condition) to provide the title compound (4.57 mg, 9.9 μ mol, 25.3% yield). LCMS (ESI): RT = 0.852 min, mass calcd. for C₁₇H₁₇F₃N₆O₂S, 426.11 m/z found 426.9[M+H]⁺. ¹HNMR (400 MHz, CHLOROFORM-

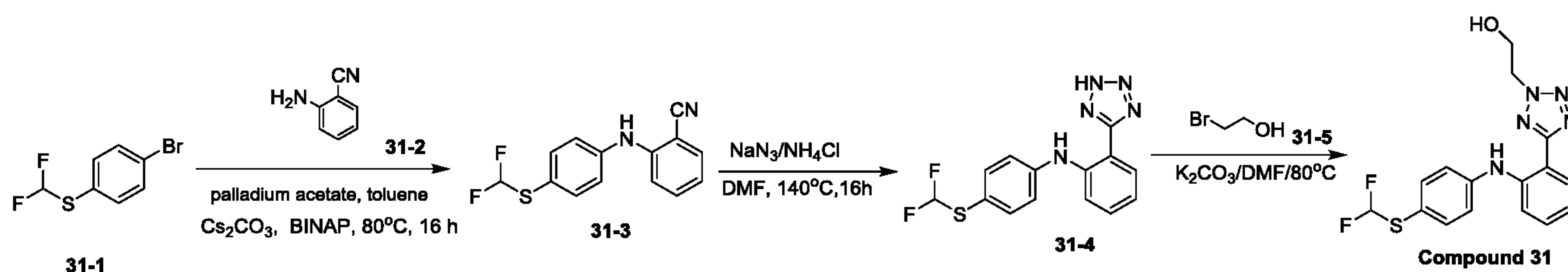
d) δ 8.89 (s, 1H), 8.18 (dd, $J = 7.60, 1.4$ Hz, 1H), 7.50 (s, 1H), 7.44 - 7.42 (m, 3H), 7.40 - 7.35 (m, 1H), 7.27 - 7.26 (m, 1H), 7.04 - 7.00 (m, 1H), 4.93 - 4.90 (m, 3H), 3.83 (t, $J = 5.20$ Hz, 2H), 2.98 (s, 3H).

Example 30: N-[2-[5-[2-[3-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl]acetamide (Compound 30)



[00352] To a mixture of **30-1** (20 mg, 52 μ mol, 1.00 *eq*, HCl) and Et₃N (21 mg, 0.208 mmol, 28 μ L, 4.00 *eq*) in DCM (2 mL) was added AcCl (16 mg, 0.208 mmol, 15 μ L, 4.00 *eq*) in one portion at 28°C. The mixture was stirred at 28 °C for 2 h. LCMS showed **30-1** was consumed completely and one main peak with the desired MS was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with water (6 mL) and extracted with EtOAc (8 mL * 6). The combined organic layers were dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by prep-HPLC (basic condition) to provide the title compound (13.95 mg, 35.7 μ mol, 68.8% yield). LCMS (ESI): RT = 0.835 min, mass calcd. for C₁₈H₁₇F₃N₆O, 390.14 m/z found 391.0[M+H]⁺. ¹HNMR (400 MHz, CHLOROFORM-*d*) δ 8.93 (s, 1H), 8.19 (dd, $J = 7.60, 1.40$ Hz, 1H), 7.50 (s, 1H), 7.45 - 7.43 (m, 3H), 7.40 - 7.36 (m, 1H), 7.27 - 7.26 (m, 1H), 7.02 (t, $J = 7.60$ Hz, 1H), 5.87 (br s, 1H), 4.87 - 4.84 (m, 2H), 3.96 - 3.92 (m, 2H), 1.99 (s, 3H).

Example 31: 2-[5-[2-[4-(difluoromethylsulfanyl)anilino]phenyl]tetrazol-2-yl]ethanol (Compound 31)



Step 1: 2-[4-(difluoromethylsulfanyl)anilino]benzonitrile

[00353] To a solution of **31-1** (400.0 mg, 1.7 mmol, 1.0 *eq*), **31-2** (197.7 mg, 1.7 mmol, 1.0 *eq*) and Cs₂CO₃ (545.1 mg, 1.7 mmol, 1.0 *eq*) in toluene (300.0 mL) was added BINAP (104.18 mg, 167.31 μ mol, 0.10 *eq*) and palladium acetate (37.56 mg, 167.31 μ mol, 0.10 *eq*). The resulting

mixture was stirred at 100 °C under N₂ for 15 hours. LCMS showed the desired compound was formed and the starting material was consumed completely. The reaction mixture was concentrated. The residue crude product was dissolved with CH₂Cl₂ (500 ml) and washed with water (2 × 100 mL). After drying the organic layer over anhydrous Na₂SO₄, the solvent was removed under reduced pressure to afford the crude product. The crude product was purified by column chromatography over silica gel to give **31-3** (100.0 mg, 0.36 mmol, 21.7% yield). LCMS (ESI): RT = 0.832 min, mass calc. for C₁₄H₁₀F₂N₂S 276.05, m/z found 276.8 [M+H]⁺.

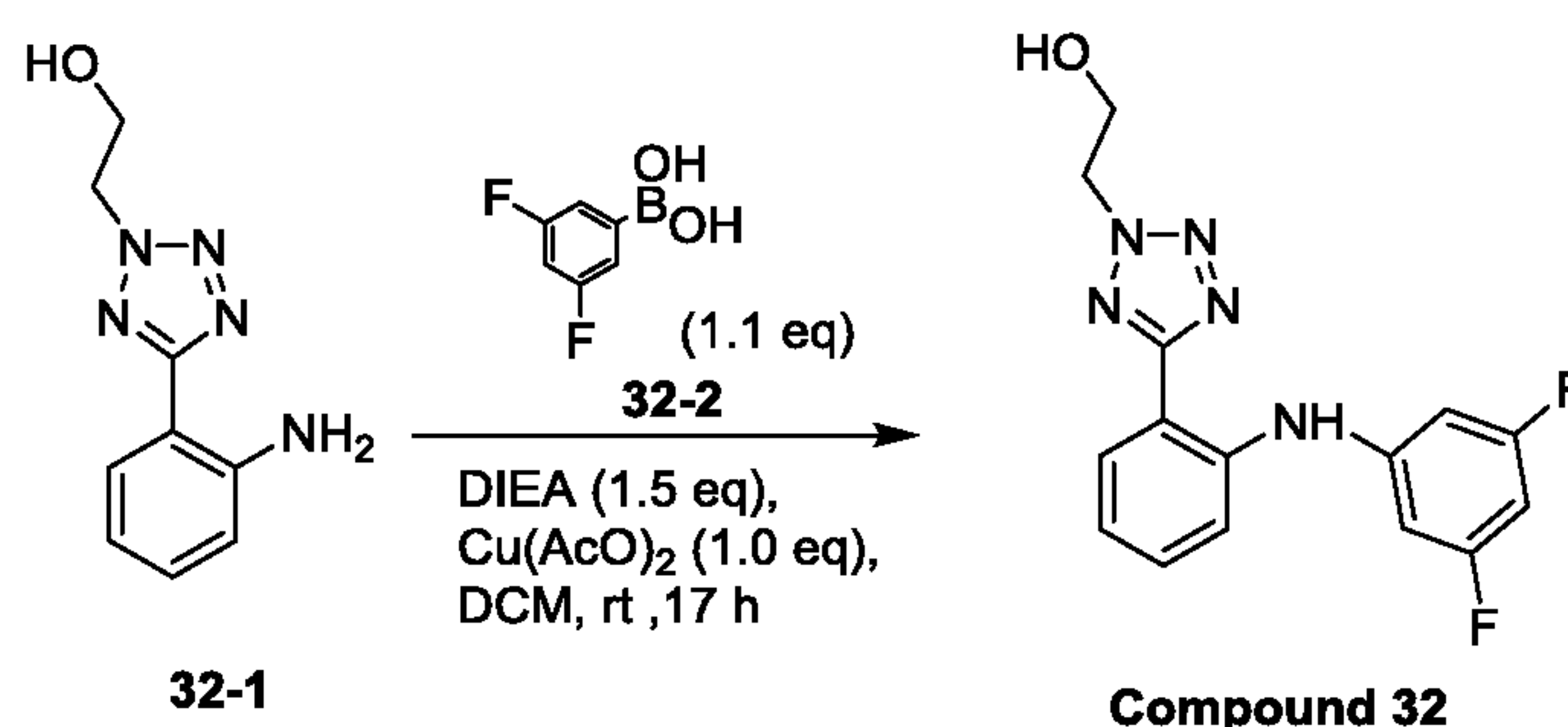
Step 2: N-[4-(difluoromethylsulfanyl)phenyl]-2-(2H-tetrazol-5-yl)aniline

[00354] To a solution of **31-3** (100.0 mg, 0.36 mmol, 1.0 *eq*) in DMF (10.0 mL) was added NH₄Cl (58.1 mg, 1.1 mmol, 38.0 uL, 3.0 *eq*) and NaN₃ (235.3 mg, 3.6 mmol, 10.0 *eq*). The mixture was stirred at 140 °C for 16 hour under N₂ atmosphere. LCMS showed the desired compound was formed. The reaction mixture was poured into sat. aq. NaHCO₃ (5 mL) and extracted with EtOAc (5 mL*2). The combined organic layer was washed with brine (10 mL), dried over Na₂SO₄, and filtered. The solvent was removed under reduced pressure to afford **31-4** (100.0 mg, 0.31 mmol, 86.5% yield) as a yellow oil, which was directly used without further purification. LCMS (ESI): RT = 0.796 min, mass calc. for C₁₄H₁₁F₂N₅S 319.07, m/z found 319.9 [M+H]⁺.

Step 3: 2-[5-[2-[4-(difluoromethylsulfanyl)anilino]phenyl]tetrazol-2-yl]ethanol

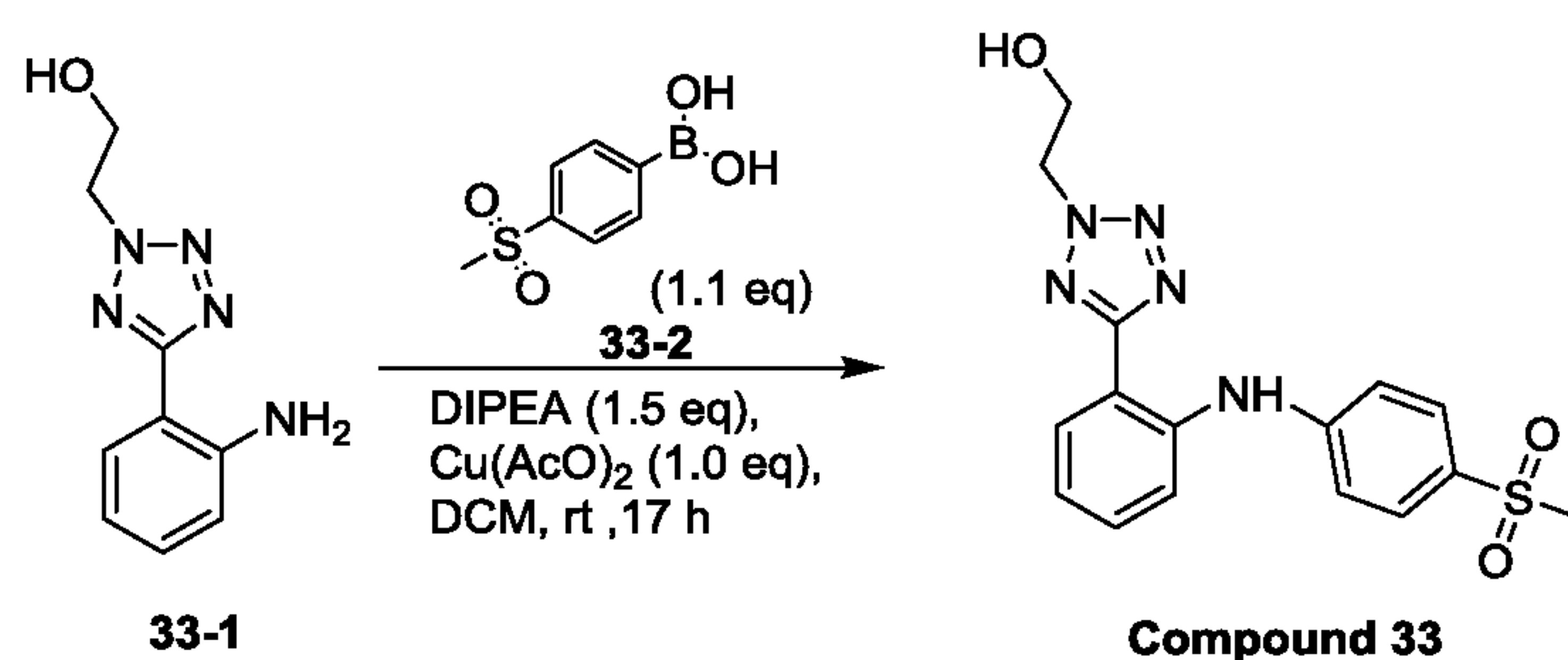
[00355] To a solution of **31-4** (100.0 mg, 0.31 mmol, 1.0 *eq*) in DMF (5.0 mL) was added K₂CO₃ (64.9 mg, 0.47 mmol, 1.5 *eq*) and **31-5** (47.0 mg, 0.38 mmol, 26.7 uL, 1.2 *eq*). The mixture was stirred at 100 °C for 3 hours under N₂ atmosphere. LCMS showed the desired compound was formed. The reaction was filtered to give a crude product. The crude product was purified by prep-HPLC to give **Compound 31** (10.94 mg, 30.11 umol, 9.61% yield). LCMS (ESI): RT = 0.832 min, mass calc. for C₁₆H₁₅F₂N₅OS 363.10, m/z found 363.9 [M+H]⁺; ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.76 (s, 1H), 8.06 (dd, *J*=1.3, 7.8 Hz, 1H), 7.53 - 7.43 (m, 5H), 7.34 (s, 1H), 7.22 (d, *J*=8.8 Hz, 2H), 7.15 - 7.09 (m, 1H), 5.08 (t, *J*=5.6 Hz, 1H), 4.78 (t, *J*=5.3 Hz, 2H), 3.95 (q, *J*=5.5 Hz, 2H).

Example 32: 2-(5-(2-((3,5-difluorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-ol
(Compound 32)



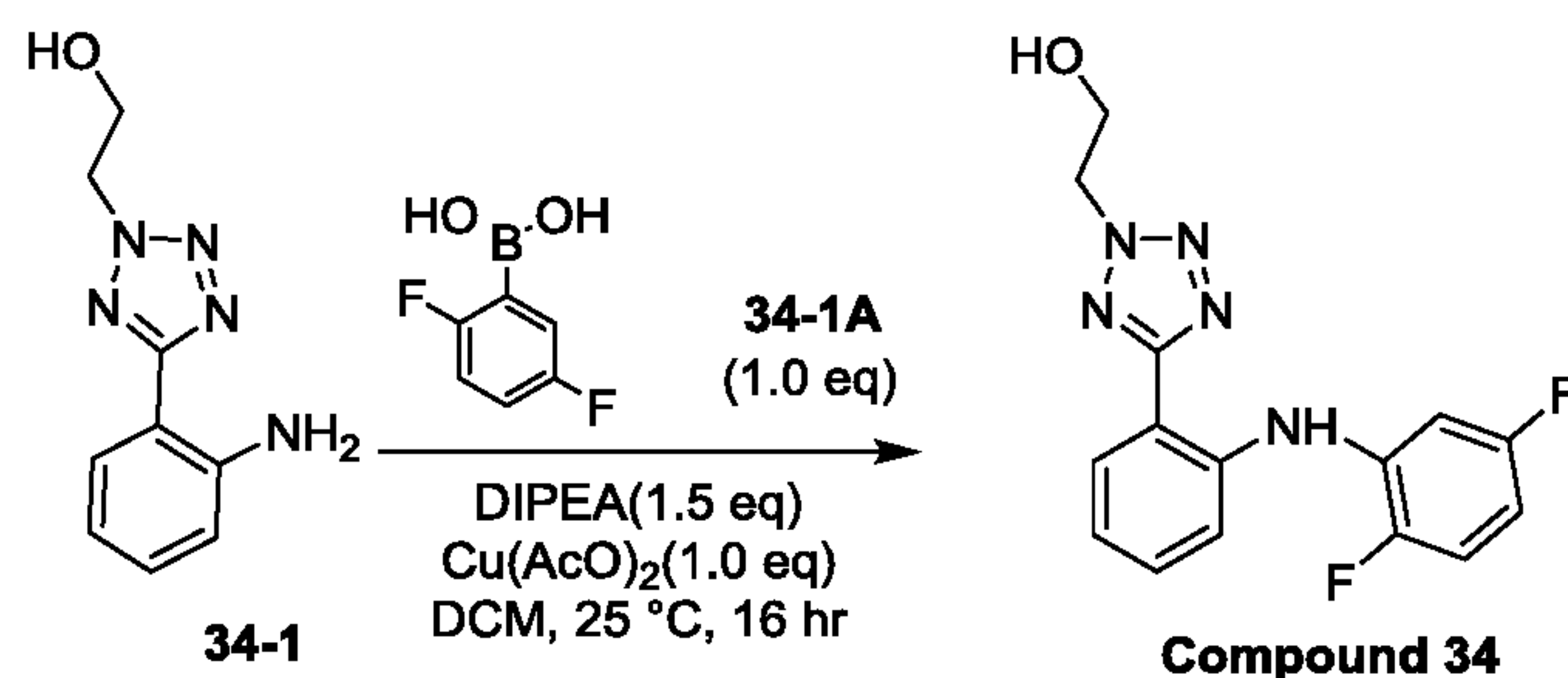
[00356] To a mixture of **32-1** (100.0 mg, 487.3 μmol , 1.00 *eq*), **32-2** (84.6 mg, 536.0 μmol , 1.10 *eq*) and $\text{Cu}(\text{OAc})_2$ (88.5 mg, 487.3 μmol , 1.00 *eq*) in DCM (6.0 mL), was added DIEA (94.7 mg, 732.9 μmol , 1.50 *eq*). The mixture was degassed under vacuum and purged with O_2 3 times. The resulting mixture was stirred at 26 °C under O_2 (15 Psi) for 17 h. LCMS detected about 71% of the desired compound, and about 6% starting material remained. The mixture was filtered, and the solid was washed with DCM (5 mL *2). The filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography to provide the title compound (101.42 mg, 319.6 μmol , 65.6% yield). LCMS (ESI): RT = 0.818 min, mass calc. for $\text{C}_{15}\text{H}_{13}\text{F}_2\text{N}_5\text{O}$ 317.11, m/z found 317.9 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.73 (s, 1 H) 8.04 (dd, $J = 7.8, 1.3$ Hz, 1 H) 7.45 - 7.56 (m, 2 H) 7.15 - 7.23 (m, 1 H) 6.71 - 6.80 (m, 2 H) 6.63 (tt, $J = 9.4, 2.3$ Hz, 1 H) 5.07 (t, $J = 5.7$ Hz, 1 H) 4.78 (t, $J = 5.3$ Hz, 2 H) 3.95 (q, $J = 5.5$ Hz, 2 H).

Example 33: 2-(5-(2-((4-(methylsulfonyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol (Compound 33)



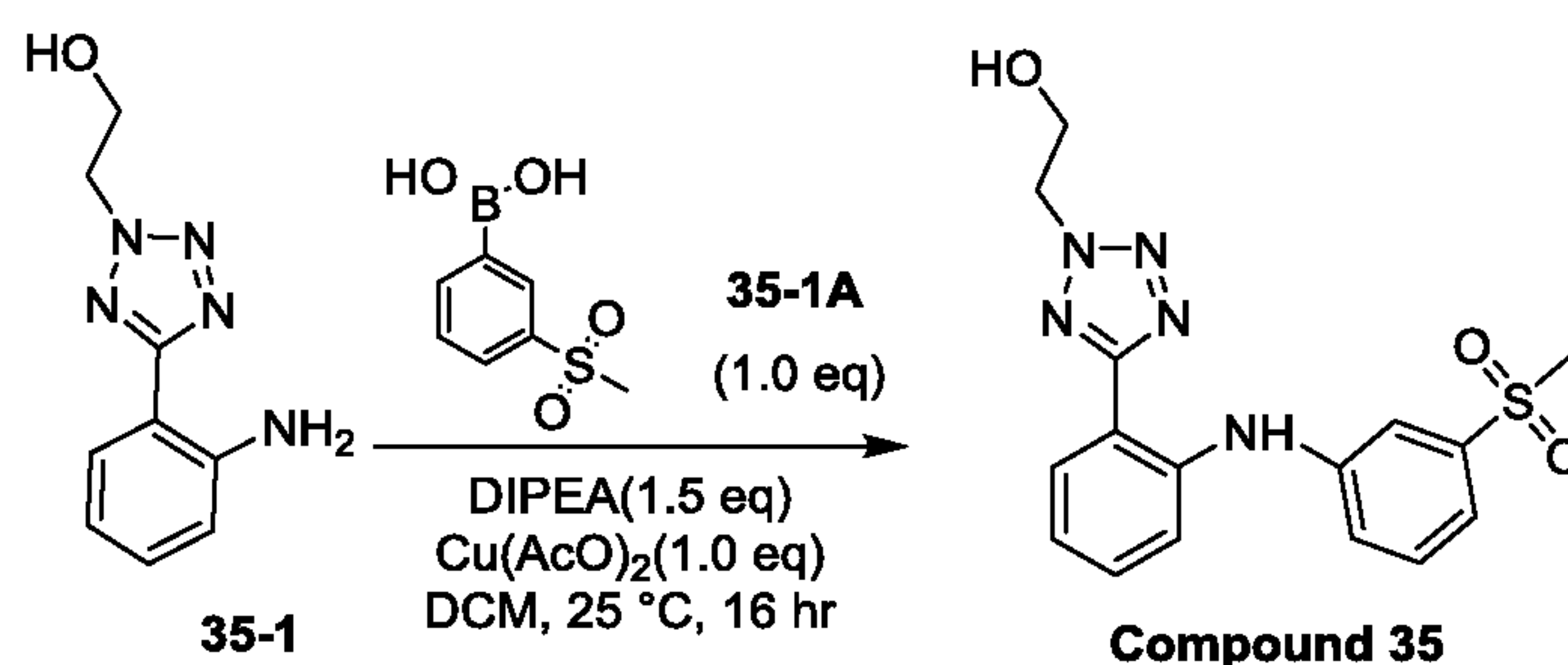
[00357] To a mixture of **33-1** (100.0 mg, 487.3 μmol , 1.00 *eq*), **33-2** (102.3 mg, 511.6 μmol , 1.05 *eq*) and $\text{Cu}(\text{OAc})_2$ (88.5 mg, 487.3 μmol , 1.00 *eq*) in DCM (6.0 mL), was added DIEA (94.5 mg, 730.9 μmol , 1.50 *eq*). The mixture was degassed under vacuum and purged with O_2 for 3 times. The resulting mixture was stirred at 26 °C under O_2 (15 Psi) for 17 h. LCMS detected about 68% of the desired compound, and about 23% starting material remained. The mixture was filtered, and the solid was washed with DCM (5 mL *2). The filtrate was concentrated under vacuum. The residue was purified by prep-HPLC (acidic HCl condition) to provide the title compound (69.93 mg, 194.6 μmol , 39.9% yield). LCMS (ESI): RT = 0.977 min, mass calc. for $\text{C}_{16}\text{H}_{17}\text{N}_5\text{O}_3\text{S}$ 359.11, m/z found 382.0 $[\text{M}+\text{Na}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.89 (s, 1 H) 8.06 (dd, $J = 7.8, 1.3$ Hz, 1 H) 7.72 (d, $J = 8.8$ Hz, 2 H) 7.55 - 7.59 (m, 1 H) 7.49 - 7.55 (m, 1 H) 7.22 - 7.27 (m, 1 H) 7.19 (d, $J = 8.8$ Hz, 2 H) 5.05 (t, $J = 5.8$ Hz, 1 H) 4.75 (t, $J = 5.3$ Hz, 2 H) 3.93 (q, $J = 5.5$ Hz, 2 H) 3.11 (s, 3 H).

Example 34: 2-(5-(2-((2,5-difluorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol (Compound 34)



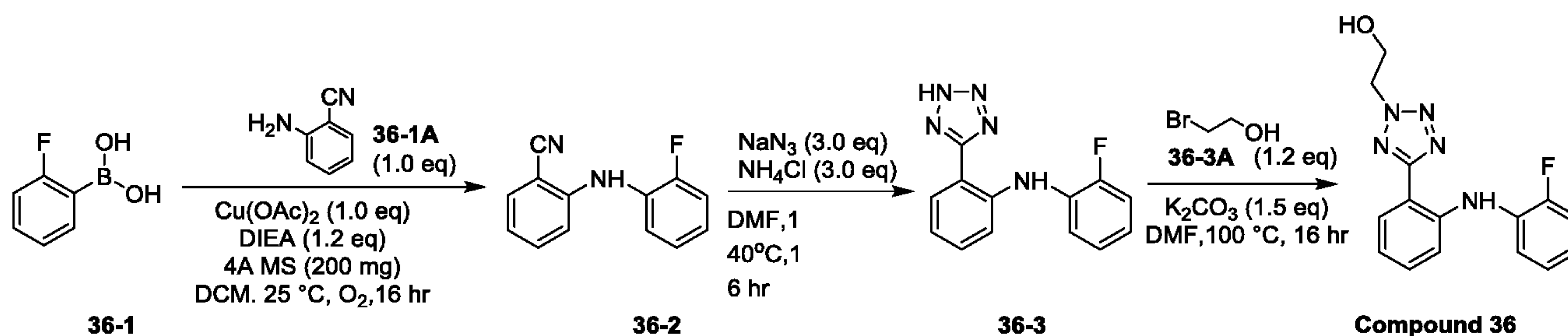
[00358] To the solution of **34-1A** (100 mg, 0.6 mmol, 1.0 *eq*) in DCM (10 mL) was added compound **34-1** (130 mg, 0.6 mmol, 1.0 *eq*), DIPEA (123 mg, 1.0 mmol, 166 μ L, 1.5 *eq*), Cu(OAc)₂ (115 mg, 0.6 mmol, 1.0 *eq*). The mixture was stirred at 25 °C for 16 hr under O₂ atmosphere. The reaction was monitored by LCMS. The reaction solution was washed with H₂O (10 mL). The organic layer was filtered and concentrated under reduced pressure. The residue was purified by Prep-HPLC to give the title compound (5.97 mg, 18.3 μ mol, 2.88% yield). LCMS (ESI): RT = 1.150 min, mass calc. for C₁₅H₁₃F₂N₅O 317.11, *m/z* found 317.9 [M+H]⁺, ¹HNMR (400MHz, CHLOROFORM-*d*) δ 8.89 (s, 1H), 8.29 - 8.15 (m, 1H), 7.51 - 7.38 (m, 2H), 7.23 - 7.11 (m, 1H), 7.11 - 7.03 (m, 2H), 6.64 - 6.57 (m, 1H), 4.89 - 4.83 (m, 2H), 4.33 - 4.23 (m, 2H), 2.32 (br, 1H).

Example 35: 2-(5-(2-((3-(methylsulfonyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol (Compound 35)



[00359] To the solution of **35-1** (103 mg, 0.5 mmol, 1.0 *eq*) in DCM (10 mL) was added **35-1A** (100 mg, 0.5 mmol, 1.0 *eq*), DIPEA (97 mg, 0.7 mmol, 131 μ L, 1.5 *eq*), Cu(OAc)₂ (91 mg, 0.5 mmol, 1.0 *eq*). The mixture was stirred at 25 °C for 16 hr under O₂ atmosphere. The reaction was monitored by LCMS. The reaction solution was washed with H₂O (10 mL). The organic layer was filtered and concentrated under reduced pressure. The residue was purified by Prep-HPLC to provide the title compound (44.72 mg, 117.0 μ mol, 23.4% yield). LCMS (ESI): RT = 0.999 min, mass calc. for C₁₆H₁₇N₅O₃S 359.11, *m/z* found 382.0 [M+Na]⁺, ¹HNMR (400MHz, CHLOROFORM-*d*) δ 9.02 (s, 1H), 8.22 - 8.14 (m, 1H), 7.78 - 7.73 (m, 1H), 7.52 - 7.43 (m, 4H), 7.40 - 7.34 (m, 1H), 7.06 - 7.00 (m, 1H), 4.88 - 4.81 (m, 2H), 4.25 (q, *J*=5.4 Hz, 2H), 3.06 (s, 3H), 2.63 (t, *J*=6.0 Hz, 1H).

Example 36: 2-(5-(2-((2-fluorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol (Compound 36)



Step 1: 2-((2-fluorophenyl)amino)benzonitrile

[00360] To the solution of **36-1** (500 mg, 3.6 mmol, 1.0 eq) in DCM (10 mL) was added **36-1A** (422 mg, 3.6 mmol, 1.0 eq), $\text{Cu}(\text{OAc})_2$ (648 mg, 3.6 mmol, 1.0 eq) and DIEA (554 mg, 4.3 mmol, 748 μL , 1.2 eq), 4A MS (200 mg). The mixture was stirred at 30 °C for 16 hr. The reaction was monitored by TLC. The reaction solution was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2) to give **36-2** (73 mg, 0.3 mmol, 9.6% yield).

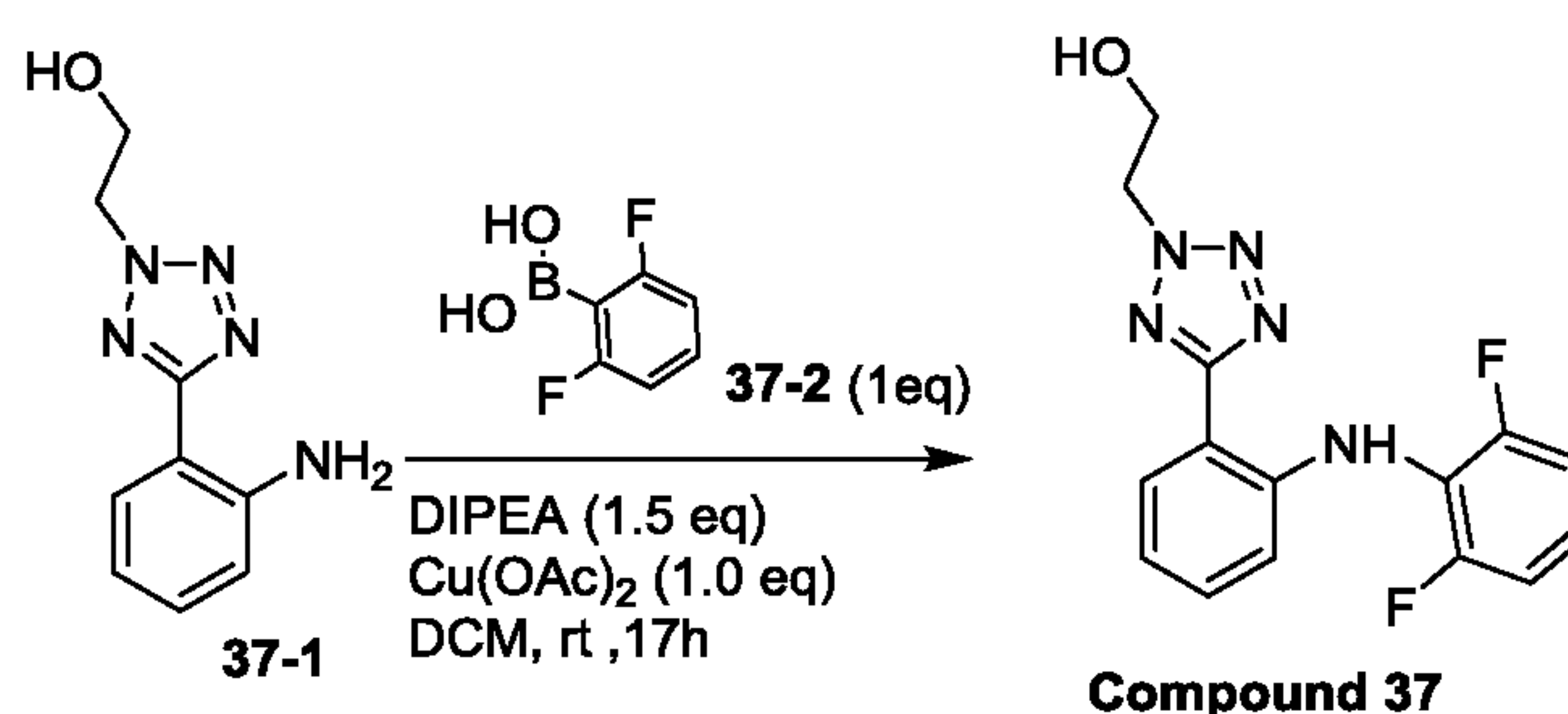
Step 2: N-(2-(2H-tetrazol-5-yl)phenyl)-2-fluoroaniline

[00361] To the solution of **36-2** (73 mg, 0.3 mmol, 1.0 eq) in DMF (2 mL) was added NaN_3 (67 mg, 1.0 mmol, 3.0 eq) and NH_4Cl (55 mg, 1.0 mmol, 3.0 eq). The mixture was stirred at 140 °C for 16 hr under N_2 atmosphere. The reaction was monitored by LCMS. The reaction solution was poured into aqueous HCl (1M, 20mL). An insoluble solid appeared and the mixture was filtered. The solid was washed with H_2O (20 mL*2) to give **36-3** (68 mg, crude).

Step 3: 2-(5-(2-((2-fluorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol

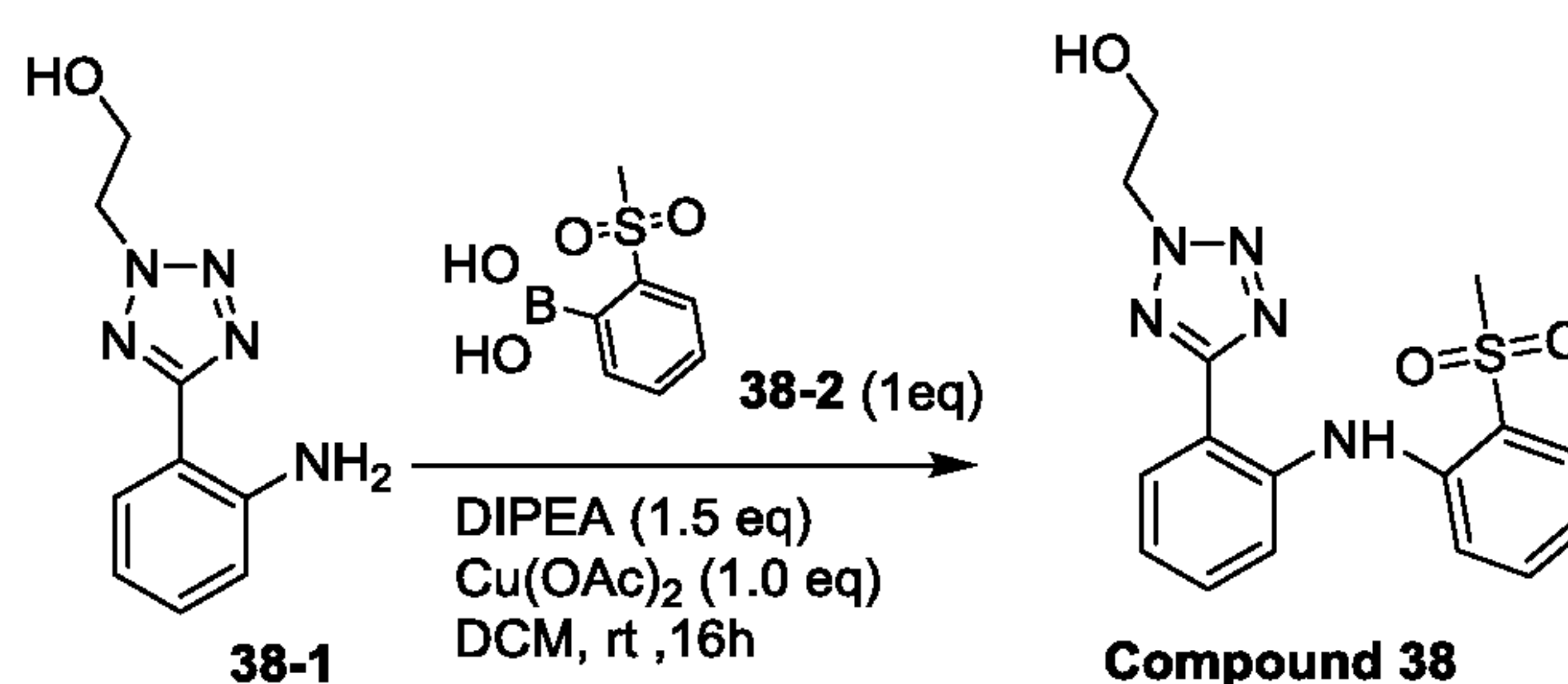
[00362] To the solution of **36-3A** (40 mg, 0.3 mmol, 23 μL , 1.2 eq) in DMF (5 mL) was added **36-3** (68 mg, 0.3 mmol, 1.0 eq) and K_2CO_3 (55 mg, 0.4 mmol, 1.5 eq). The mixture was stirred at 100 °C for 16 hr. The reaction was monitored by LCMS. The reaction solution was concentrated under reduced pressure. The residue was purified by Prep-HPLC to give **Compound 36** (29.79 mg, 97.5 μmol , 36.6% yield). LCMS (ESI): RT = 1.129 min, mass calc. for $\text{C}_{15}\text{H}_{14}\text{FN}_5\text{O}$ 299.12, m/z found 299.9 $[\text{M}+\text{H}]^+$, ^1H NMR (400MHz, $\text{CHLOROFORM-}d$) δ 8.75 (s, 1H), 8.22 - 8.17 (m, 1H), 7.46 (dt, $J=1.5, 8.2$ Hz, 1H), 7.38 - 7.26 (m, 2H), 7.18 - 6.91 (m, 4H), 4.86 - 4.79 (m, 2H), 4.28 - 4.20 (m, 2H).

Example 37: 2-[5-[2-(2,6-difluoroanilino)phenyl]tetrazol-2-yl]ethanol (Compound 37)



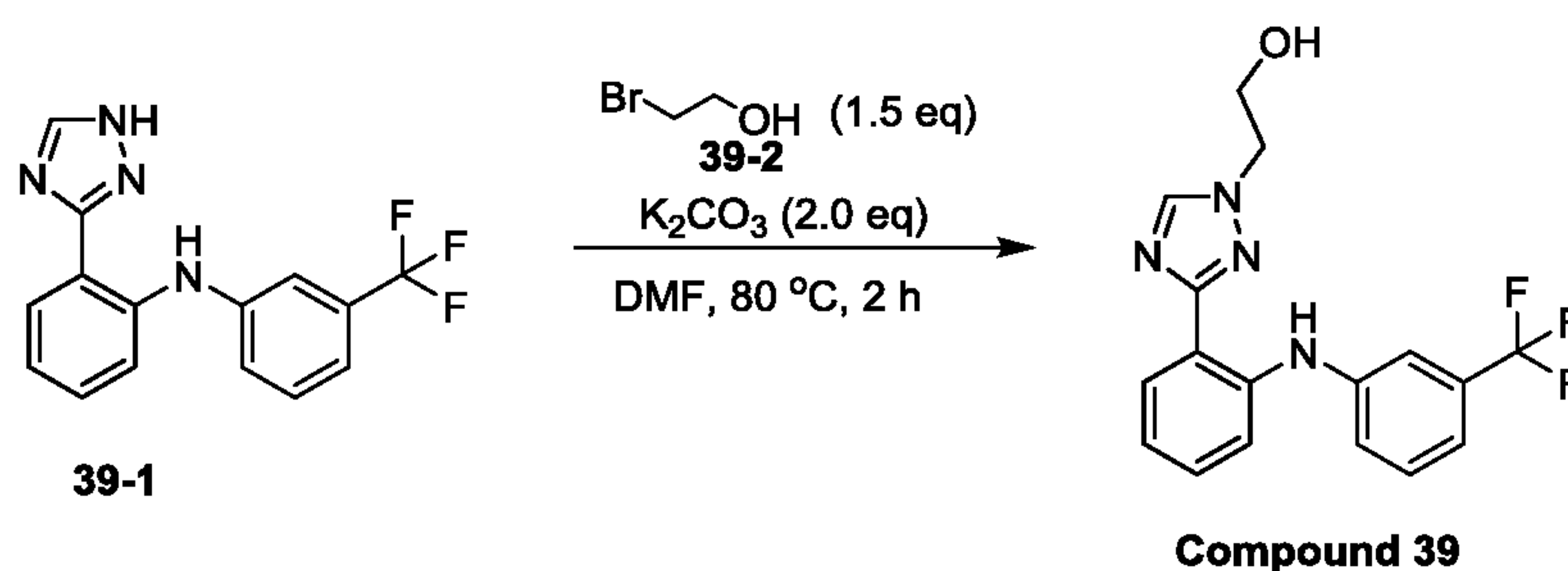
[00363] To a solution of **37-2** (100 mg, 0.633 mmol, 1.00 *eq*), DIEA (123 mg, 0.950 mmol, 0.16 mL, 1.50 *eq*), Cu(OAc)₂ (115 mg, 0.633 mmol, 1.00 *eq*) in DCM (7 mL) was added **37-1** (125 mg, 0.609 mmol, 0.96 *eq*). The mixture was stirred at 25 °C for 16 h under O₂ atmosphere. The reaction was monitored by LCMS. To the reaction mixture was added additional **37-2** (100 mg, 0.633 mmol, 1.00 *eq*) and continued stirred 4 h. LCMS indicated the amount of the desired compound was increased. The reaction mixture was continued stirred 18h. LCMS showed no obvious changed. The reaction mixture was filtered and washed with EtOAc (5 mL*6), and then concentrated under vacuum. The residue was purified by flash silica gel chromatography and then purified by prep-HPLC (basic condition) to obtain the title compound (2.27 mg, 7.15 umol, 1.1% yield). LCMS (ESI): RT = 0.784 min, mass calcd. for C₁₅H₁₃F₂N₅O, 317.11 m/z found 317.9[M+H]⁺. ¹H NMR (400MHz, CHLOROFORM-*d*) δ 8.56 (s, 1H), 8.21 (dd, *J*=1.60, 8.00 Hz, 1H), 7.35 - 7.28 (m, 1H), 7.18 - 7.11 (m, 1H), 7.05 - 6.93 (m, 3H), 6.75 - 6.71 (m, 1H), 4.90 - 4.85 (m, 2H), 4.30 - 4.25 (m, 2H), 2.36 - 2.32 (m, 1H).

Example 38: 2-[5-[2-(2-methylsulfonylanilino)phenyl]tetrazol-2-yl]ethanol (Compound 38)



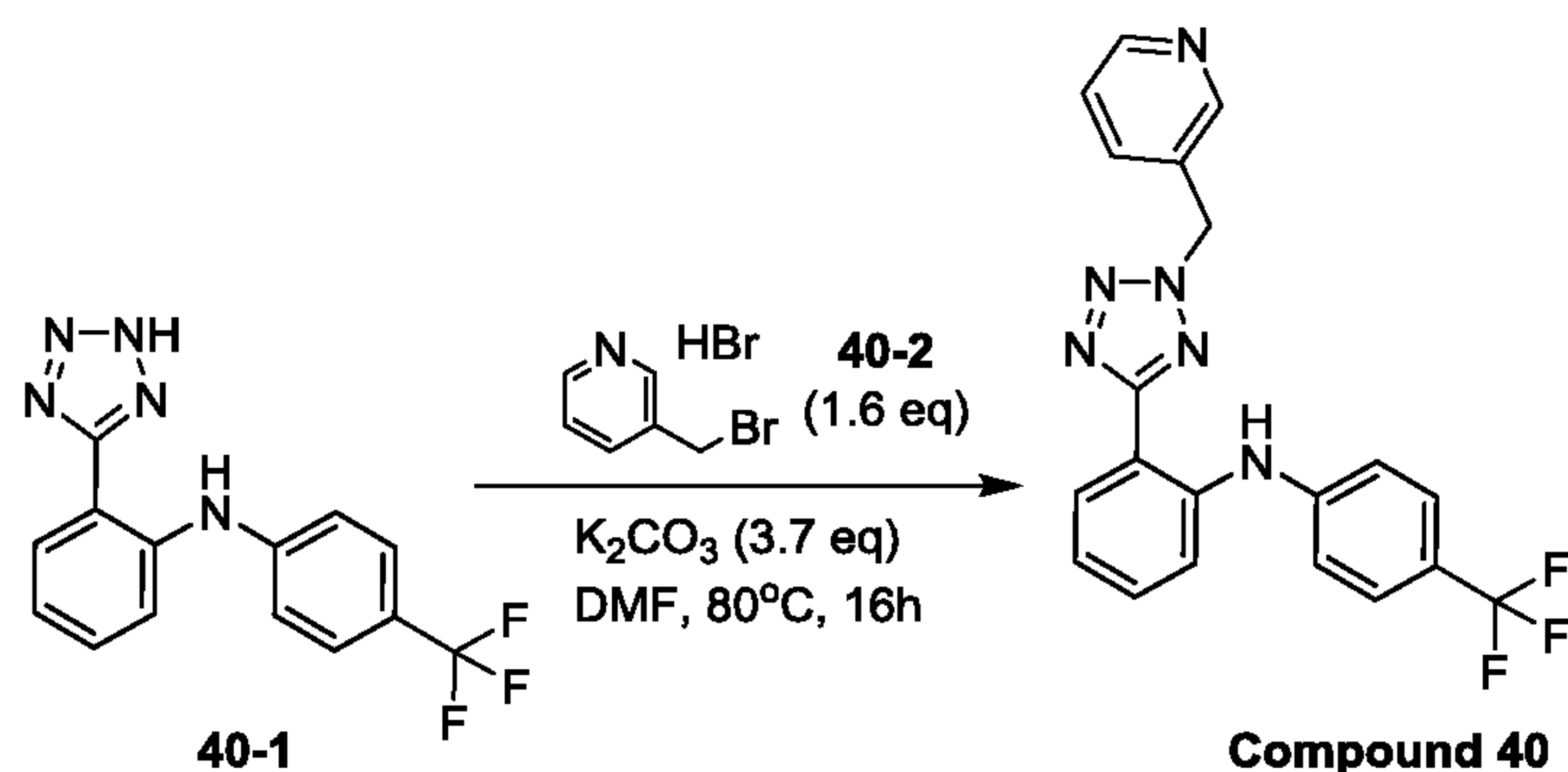
[00364] To the solution of **38-2** (91 mg, 0.455 mmol, 1.00 *eq*), DIPEA (88 mg, 682.43 umol, 0.12 mL, 1.50 *eq*), Cu(OAc)₂ (83 mg, 0.455 mmol, 1.00 *eq*) in DCM (7 mL) was added compound **38-1** (100 mg, 487.28 umol, 1.07 *eq*). The mixture was stirred at 25 °C for 16 hr under O₂ atmosphere. The reaction was monitored by LCMS and TLC. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with water (8 mL) and extracted with EtOAc (10 mL * 6). The combined organic layers were washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by flash silica gel chromatography and then purified by prep-HPLC (basic condition) to obtain the title compound (28.03 mg, 77.21 umol, 16.97% yield). LCMS (ESI): RT = 0.728 min, mass calcd. for C₁₆H₁₇N₅O₃S, 359.11 m/z found 360.0[M+H]⁺. ¹H NMR (400MHz, CHLOROFORM-*d*) δ 9.26 (s, 1H), 8.35 (dd, *J*=8.00, 1.60 Hz, 1H), 7.98 (dd, *J*=8.40, 1.20 Hz, 1H), 7.56 - 7.45 (m, 3H), 7.43 - 7.35 (m, 1H), 7.22 - 7.14 (m, 1H), 7.13 - 7.07 (m, 1H), 4.86 - 4.81 (m, 2H), 4.30 - 4.20 (m, 2H), 3.15 (s, 3H), 2.99 (t, *J*=6.40 Hz, 1H).

Example 39: 2-(3-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-1,2,4-triazol-1-yl)ethanol (Compound 39)



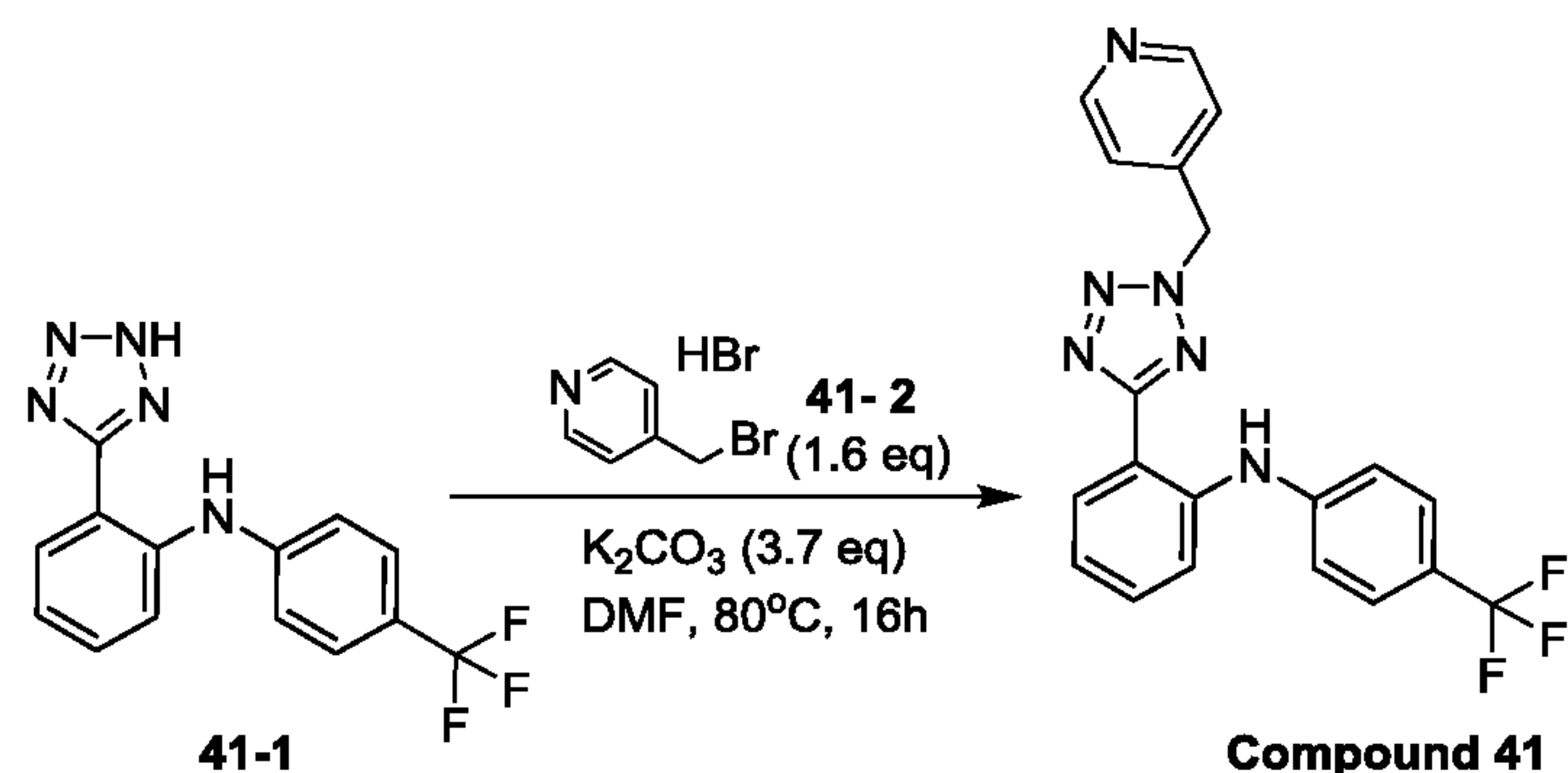
[00365] To a mixture of **39-1** (35.0 mg, 0.1 mmol, 1.00 *eq*) and K_2CO_3 (31.8 mg, 0.2 mmol, 2.00 *eq*) in DMF (3.0 mL), was added **39-2** (21.6 mg, 0.1 mmol, 1.50 *eq*). The resulting mixture was stirred at 80 °C under N_2 for 2 h. LCMS showed the reaction was complete. The mixture was filtered, and the solid was washed with DMF (1 mL). The filtrate was purified by prep-HPLC (acidic HCl condition) to provide the title compound (6.88 mg, 16.6 μ mol, 14.5% yield, HCl). LCMS (ESI): RT = 1.174 min, mass calc. for $C_{17}H_{15}F_3N_4O$ 348.12, m/z found 349.1 $[M+H]^+$. ^1H NMR (400MHz, $DMSO-d_6$) δ 8.68 (s, 1H), 8.10 (dd, J = 1.5, 7.8 Hz, 1H), 7.46 - 7.54 (m, 2H), 7.44 (s, 1H), 7.39 - 7.42 (m, 1H), 7.31 - 7.37 (m, 1H), 7.24 (d, J = 7.0 Hz, 1H), 6.97 - 7.03 (m, 1H), 4.31 (t, J = 5.3 Hz, 2H), 3.80 (t, J = 5.3 Hz, 2H).

Example 40: 2-[2-(3-pyridylmethyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 40)



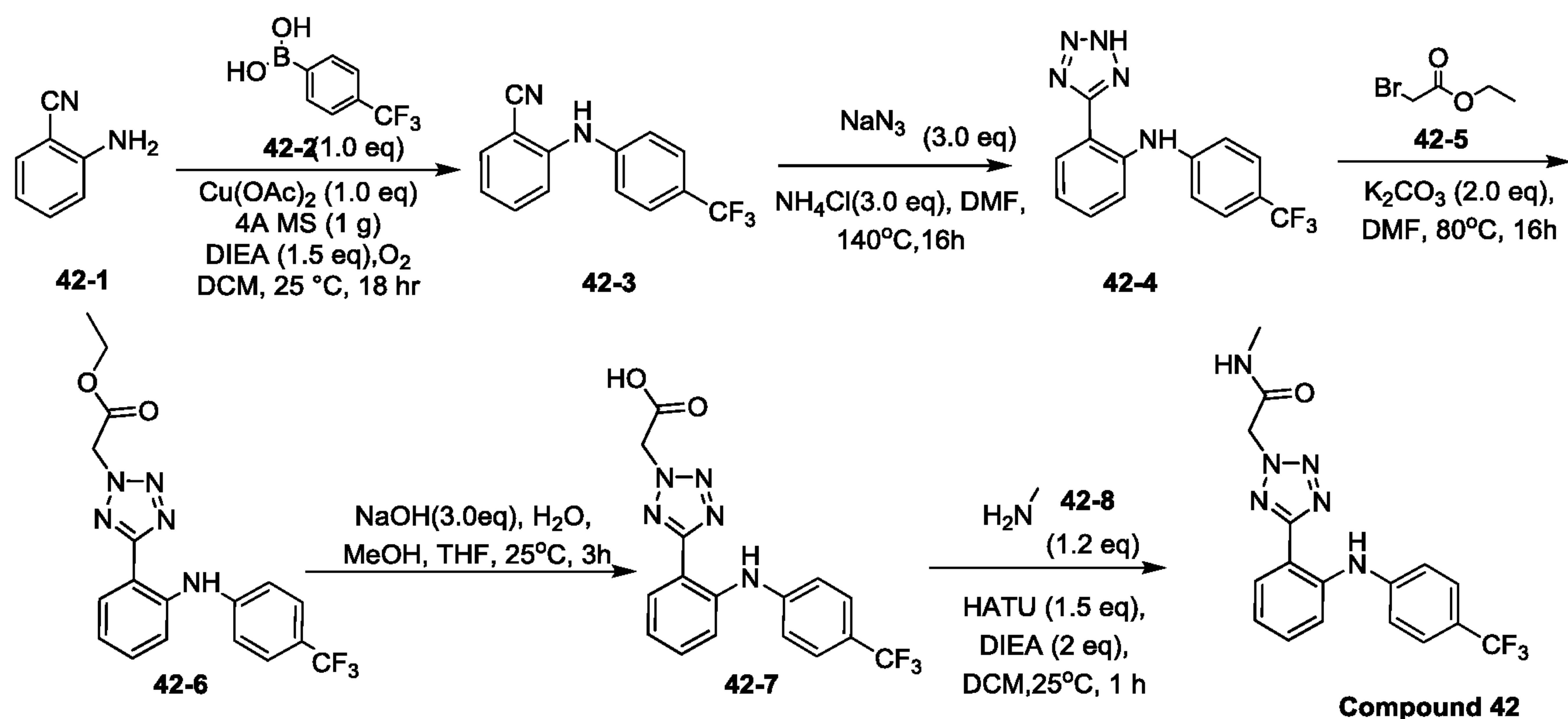
[00366] To a mixture of **40-1** (60 mg, 0.197 mmol, 1.00 *eq*) and **40-2** (80 mg, 0.316 mmol, 1.61 *eq*, HBr) in DMF (2 mL) was added K_2CO_3 (100 mg, 0.723 mmol, 3.68 *eq*) in one portion at 25 °C. The mixture was stirred at 80 °C for 16 h. LCMS showed the starting material was consumed completely. TLC showed one new spot was formed. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (20 mL * 3). The combined organic layers were dried with anhydrous Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by flash silica gel chromatography to obtain the title compound (36.35 mg, 90 μ mol, 46.2% yield). LCMS (ESI): RT = 0.797 min, mass calcd. for $C_{20}H_{15}F_3N_6$, 396.13 m/z found 377.0 $[M+H-20]^+$. ^1H NMR (400MHz, $DMSO-d_6$) δ 8.74 - 8.67 (m, 2H), 8.58 (dd, J = 4.80, 1.60 Hz, 1H), 8.04 - 7.95 (m, 1H), 7.84 - 7.77 (m, 1H), 7.54 - 7.47 (m, 4H), 7.44 - 7.39 (m, 1H), 7.23 - 7.16 (m, 1H), 7.12 (d, J = 8.80 Hz, 2H), 6.06 (s, 2H).

**Example 41: 2-[2-(4-pyridylmethyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline
(Compound 41)**



[00367] To a mixture of **41-1** (60 mg, 0.197 mmol, 1.00 *eq*) and **41-2** (80 mg, 0.316 mmol, 1.61 *eq*, HBr) in DMF (2.5 mL) was added K_2CO_3 (100 mg, 0.723 mmol, 3.68 *eq*) in one portion at 25°C. The mixture was stirred at 80 °C for 16 h. The reaction was monitored by LCMS. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (20 mL * 3). The combined organic layers were dried with anhydrous Na_2SO_4 , filtered and concentrated under vacuum. The residue was purified by flash silica gel chromatography to provide the title compound (31.32 mg, 75 μ mol, 38.2% yield). LCMS (ESI): RT = 1.126 min, mass calcd. for $C_{20}H_{15}F_3N_6$, 396.13 m/z found 397.0[M+H]⁺ and 377.0[M+H-20]⁺. ¹HNMR (400MHz, DMSO-*d*₆) δ 8.71 (s, 1H), 8.61 - 8.53 (m, 2H), 8.03 - 7.97 (m, 1H), 7.56 - 7.48 (m, 4H), 7.32 - 7.26 (m, 2H), 7.24 - 7.17 (m, 1H), 7.11 (d, *J*=8.50 Hz, 2H), 6.09 (s, 2H).

**Example 42: N-methyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetamide
(Compound 42)**



Step 1: 2-[4-(trifluoromethyl)anilino]benzonitrile

[00368] To a solution of **42-1** (1.2 g, 10.2 mmol, 1.0 *eq*) and **42-2** (2.9 g, 15.2 mmol, 1.5 *eq*) in DCM (20.0 mL) was added DIEA (1.6 g, 12.2 mmol, 2.13 mL, 1.2 *eq*) and Cu(OAc)₂ (1.9 g, 10.2 mmol, 1.0 *eq*). The mixture was stirred at 25 °C for 16 hour under O₂ atmosphere. LCMS showed the desired compound was formed. TLC (30% ethyl acetate in petroleum ether, R_f = 0.6) showed a new spot. The reaction was filtered through celite and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography over silica gel to give **42-3** (1.0 g, 3.7 mmol, 36.8% yield) as a colourless oil. LCMS (ESI): RT = 0.817 min, mass calc. for C₁₄H₉F₃N₂ 262.07 m/z found 262.8 [M+H]⁺.

Step2: 2-(2H-tetrazol-5-yl)-N-[4-(trifluoromethyl)phenyl]aniline

[00369] To a solution of **42-3** (1.0 g, 3.8 mmol, 1.0 *eq*) in DMF (10.0 mL) was added NH₄Cl (611.9 mg, 11.4 mmol, 0.4 mL, 3.0 *eq*) and NaN₃ (743.1 mg, 11.4 mmol, 3.0 *eq*). The mixture was stirred at 140 °C for 16 hour under an N₂ atmosphere. LCMS showed the desired compound was formed. The reaction mixture was poured into sat. aq. NaHCO₃ (5 mL) and extracted with EtOAc (5 mL*2). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and filtered. The solvent was removed under reduced pressure to afford the crude compound **42-4** (1.1 g, 3.6 mmol, 94.6% yield). LCMS (ESI): RT = 0.806 min, mass calc. for C₁₄H₁₀F₃N₅ 305.09, m/z found 305.9 [M+H]⁺;

Step 3: ethyl 2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetate

[00370] To a solution of **42-4** (500.0 mg, 1.6 mmol, 1.0 *eq*) in DMF (5.0 mL) was added K₂CO₃ (339.6 mg, 2.5 mmol, 1.5 *eq*) and **42-5** (273.5 mg, 1.6 mmol, 0.18 mL, 1.0 *eq*). The mixture was stirred at 80 °C for 16 hour under an N₂ atmosphere. LCMS showed the desired compound was formed. TLC (Petroleum ether : Ethyl acetate=3/1) showed the starting material was consumed completely. The reaction mixture was concentrated to give the crude product. The crude product was purified by column chromatography over silica gel to give **42-6** (480.0 mg, 1.2 mmol, 72.5% yield). LCMS (ESI): RT = 0.886 min, mass calc. for C₁₈H₁₆F₃N₅O₂, 391.13 m/z found 392.0 [M+H]⁺.

Step 4: 2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetic acid

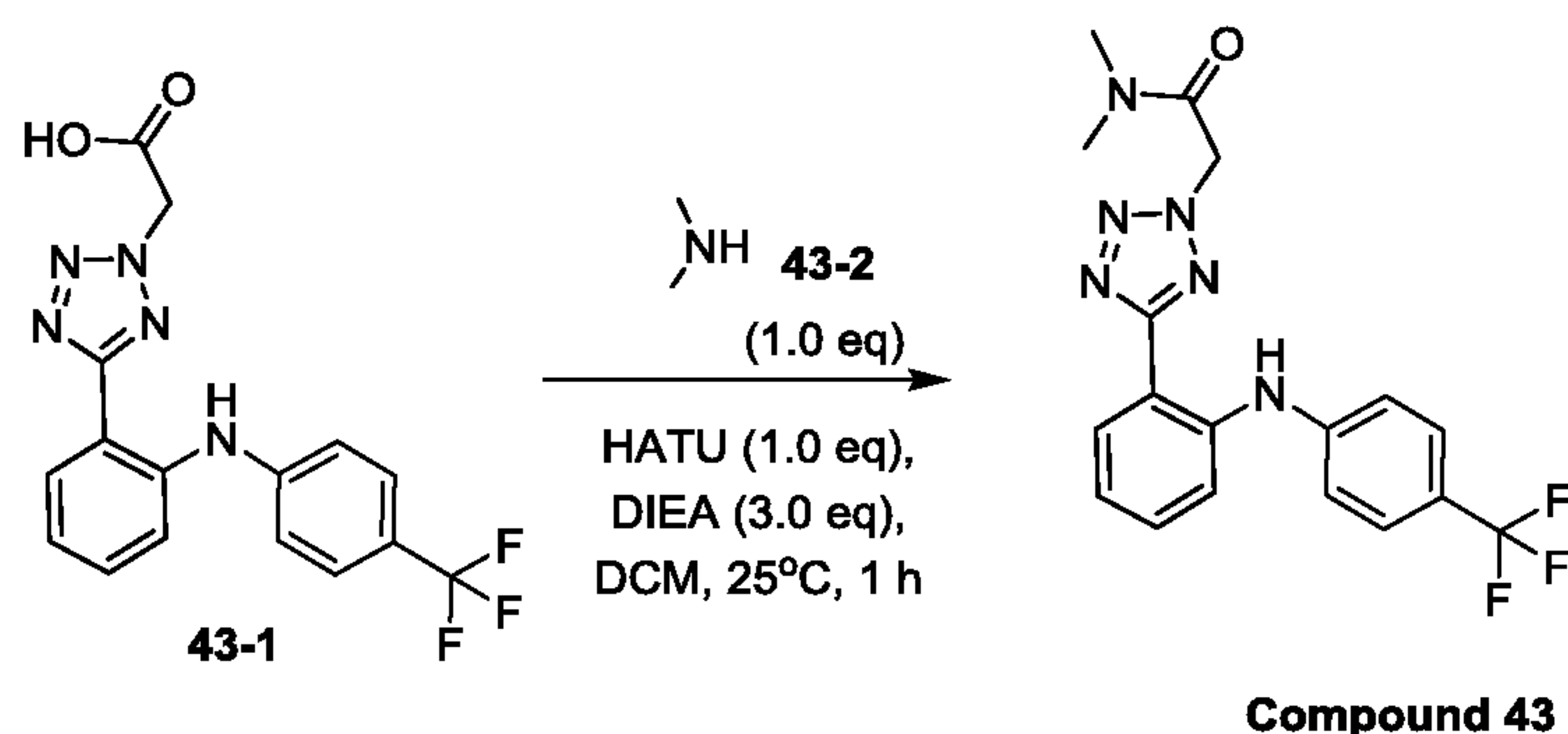
[00371] To a solution of **42-6** (480.0 mg, 1.2 mmol, 1.0 *eq*) in H₂O (2.0 mL) and MeOH (4.0 mL) was added NaOH (147.2 mg, 36.8 mmol, 29.9 *eq*). The resulting mixture was stirred at 25 °C for 4 hours. LCMS showed the desired compound was formed. TLC (Petroleum ether : Ethyl acetate=3/1) showed the starting material was consumed and a new spot appeared. The reaction solvent was removed under reduced pressure and water (5 mL) was added. The reaction was acidified by adding 1M HCl (10mL) to precipitate a solid. The mixture was washed with EtOAc (20 mL x 2). The combined organic layers were concentrated to give crude **42-7** (400.0 mg,

1.1 mmol, 89.5% yield). LCMS (ESI): RT = 0.826 min, mass calc. for C₁₆H₁₂F₃N₅O₂ 363.09m/z found 363.9 [M+H]⁺.

Step 5: N-methyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetamide

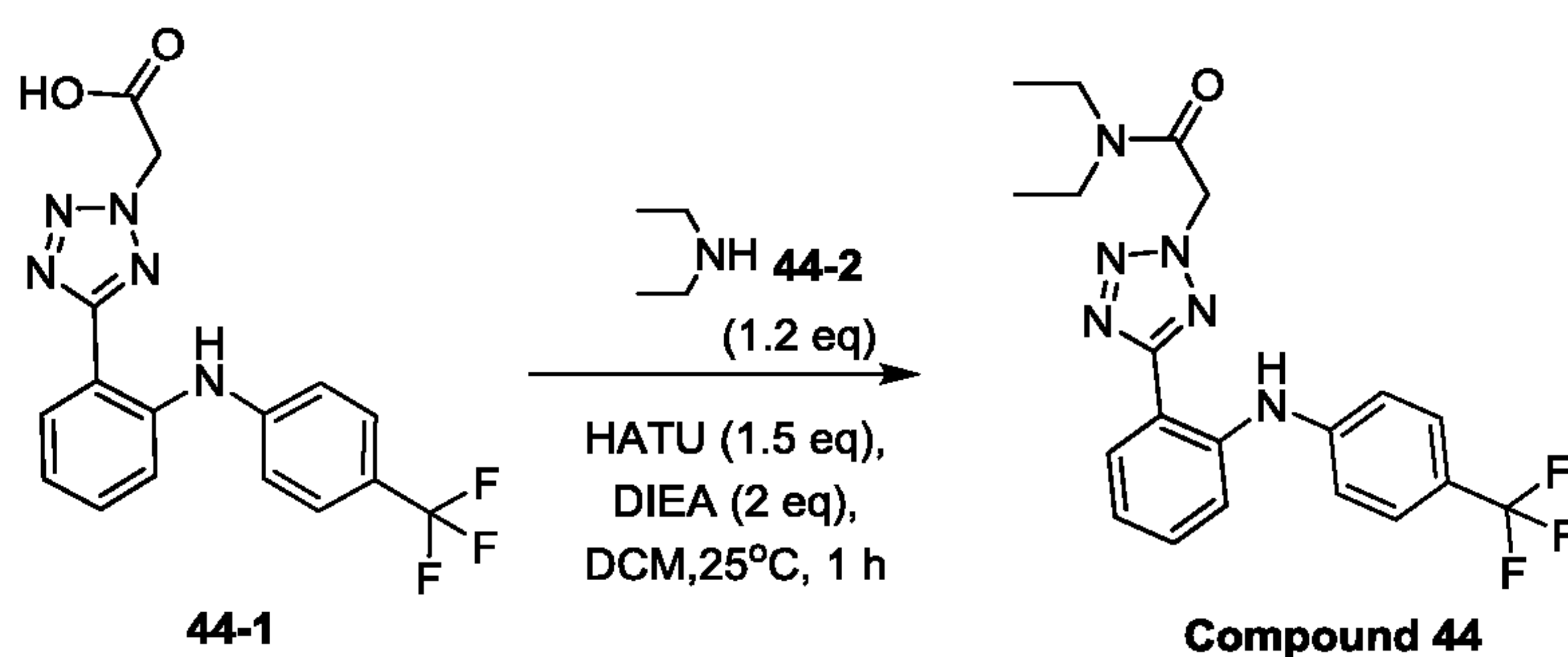
[00372] To a solution of **42-7** (50.0 mg, 0.14 mmol, 1.0 *eq*) and **42-8** (4.3 mg, 0.14 mmol, 1.0 *eq*) in DCM (5.0 mL) was added HATU (52.3 mg, 0.14 mmol, 1.0 *eq*) and DIEA (53.4 mg, 0.41 mmol, 3.0 *eq*). The resulting mixture was stirred at 20 °C for 1 hour. LCMS showed the desired compound was formed. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC to give **Compound 42** (8.24 mg, 20.36 umol, 14.80% yield). LCMS (ESI): RT = 0.814 min, mass calc. for C₁₇H₁₅F₃N₆O 376.13, m/z found 377.0 [M+H]⁺; ¹HNMR (400 MHz, DMSO-*d*₆) δ = 8.78 (s, 1H), 8.37 (br d, *J*=4.3 Hz, 1H), 8.04 (dd, *J*=1.3, 7.8 Hz, 1H), 7.56 (t, *J*=7.7 Hz, 3H), 7.52 - 7.46 (m, 1H), 7.24 (d, *J*=8.5 Hz, 2H), 7.21 - 7.15 (m, 1H), 5.51 (s, 2H), 2.66 (d, *J*=4.5 Hz, 3H).

Example 43: N,N-dimethyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetamide (Compound 43)



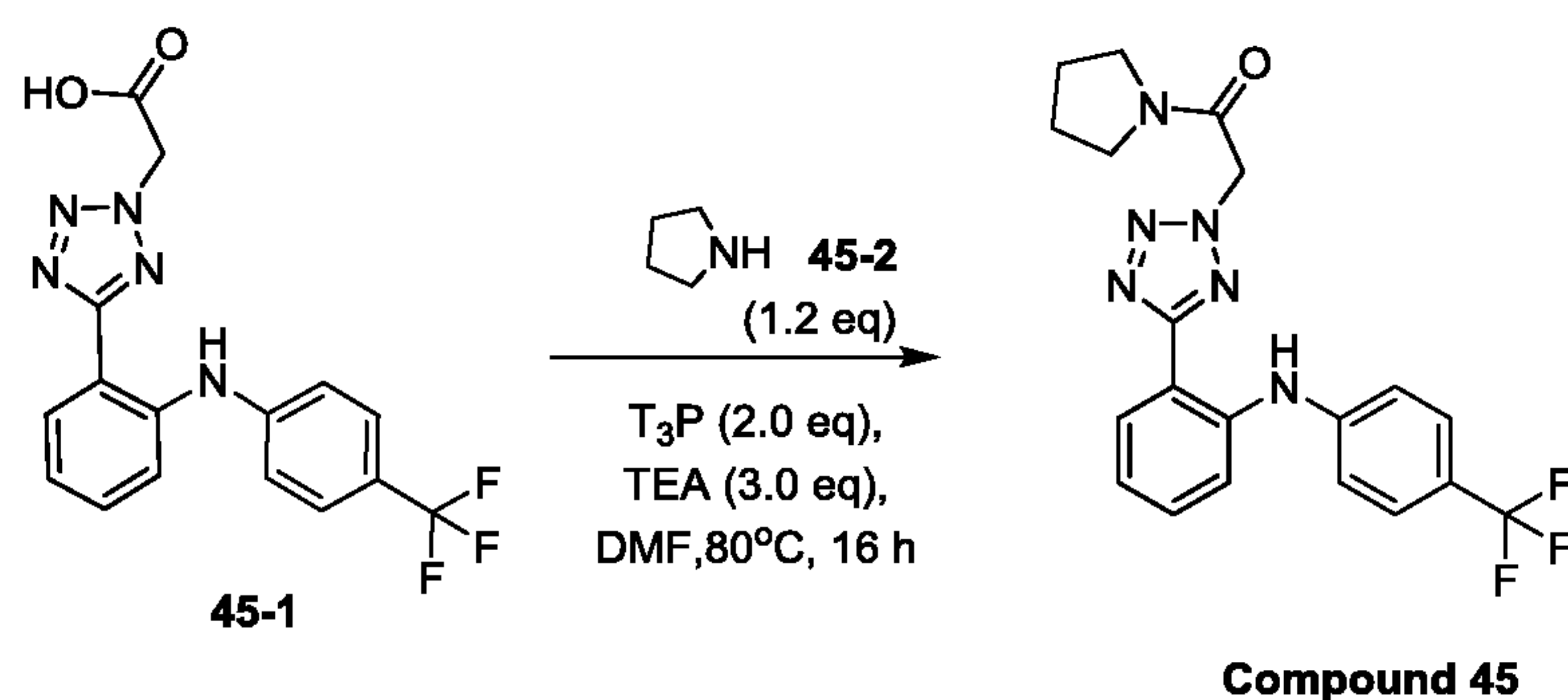
[00373] To a solution of **43-1** (50.0 mg, 0.14 mmol, 1.0 *eq*) and **43-2** (6.2 mg, 0.14 mmol, 7.0 uL, 1.0 *eq*) in DCM (5.0 mL) was added HATU (52.3 mg, 0.14 mmol, 1.0 *eq*) and DIEA (53.4 mg, 0.41 mmol, 72.1 uL, 3.0 *eq*). The resulting mixture was stirred at 20 °C for 1 hour. LCMS showed the desired compound was formed. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC to give the title compound (14.31 mg, 35.93 umol, 26.10% yield). LCMS (ESI): RT = 0.830 min, mass calc. for C₁₈H₁₇F₃N₆O 390.14, m/z found 391.0 [M+H]⁺; ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.82 (s, 1H), 8.08 - 8.03 (m, 1H), 7.56 (t, *J*=9.2 Hz, 3H), 7.51 - 7.46 (m, 1H), 7.27 (d, *J*=8.3 Hz, 2H), 7.18 (t, *J*=7.2 Hz, 1H), 5.95 (s, 2H), 3.08 (s, 3H), 2.87 (s, 3H).

Example 44: N,N-diethyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetamide (Compound 44)



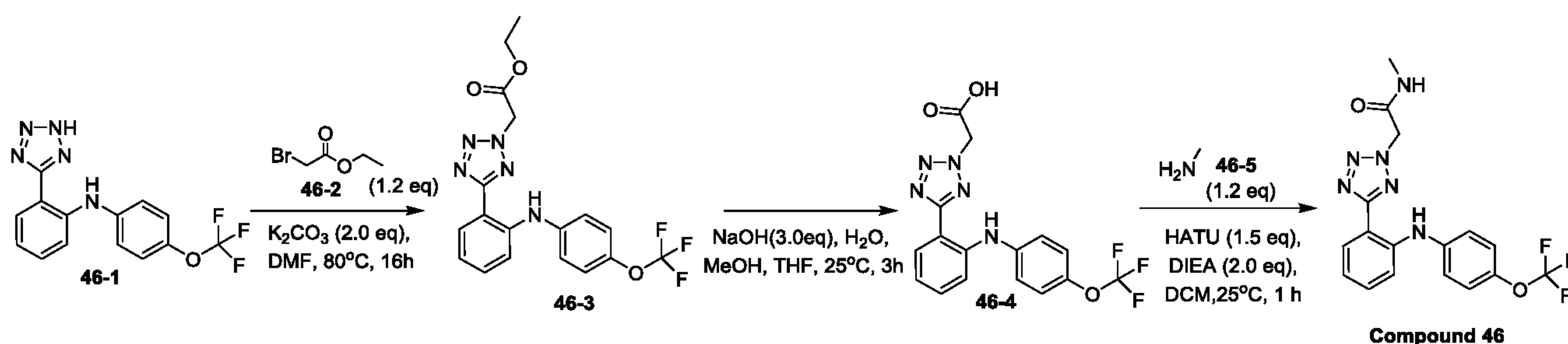
[00374] To a solution of **44-1** (50.0 mg, 0.14 mmol, 1.0 *eq*) and **44-2** (10.1 mg, 0.14 mmol, 14.2 μ L, 1.0 *eq*) in DCM (5.0 mL) was added HATU (52.3 mg, 0.14 mmol, 1.0 *eq*) and DIEA (53.4 mg, 0.41 mmol, 72.1 μ L, 3.0 *eq*). The resulting mixture was stirred at 20 °C for 1 hour. LCMS showed the desired compound was formed. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC to give the title compound (4.44 mg, 10.61 μ mol, 7.71% yield). LCMS (ESI): RT = 0.886 min, mass calc. for $C_{20}H_{21}F_3N_6O$ 418.17, m/z found 441.1 $[M+23]^+$; ^1H NMR (400 MHz, $DMSO-d_6$) δ 8.83 (s, 1H), 8.06 (dd, $J=1.0, 7.8$ Hz, 1H), 7.56 (t, $J=8.4$ Hz, 3H), 7.51 - 7.46 (m, 1H), 7.26 (m, $J=8.5$ Hz, 2H), 7.18 (t, $J=7.3$ Hz, 1H), 5.93 (s, 2H), 3.42 (q, $J=7.0$ Hz, 2H), 3.30 (q, $J=7.0$ Hz, 2H), 1.21 (t, $J=7.0$ Hz, 3H), 1.04 (t, $J=7.0$ Hz, 3H).

Example 45: 1-pyrrolidin-1-yl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanone (Compound 45)



[00375] To a solution of **45-1** (30.0 mg, 82.6 μ mol, 1.0 *eq*) and **45-2** (5.9 mg, 82.6 μ mol, 6.9 μ L, 1.0 *eq*) in DMF (2.0 mL) was added TEA (33.4 mg, 0.33 mmol, 45.8 μ L, 4.0 *eq*) and T_3P (52.6 mg, 82.6 μ mol, 49.1 μ L, 50% purity, 1.0 *eq*). The resulting mixture was stirred at 80 °C for 16 hours. LCMS showed the desired compound was formed. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC to give the title compound (8.34 mg, 19.83 μ mol, 24.01% yield). LCMS (ESI): RT = 0.855 min, mass calc. for $C_{20}H_{19}F_3N_6O$ 416.16, m/z found 439.0 $[M+23]^+$; ^1H NMR (400 MHz, $CDCl_3-d$) δ 8.97 (s, 1H), 8.22 (dd, $J=1.5, 7.8$ Hz, 1H), 7.53 (t, $J=8.0$ Hz, 3H), 7.40 - 7.34 (m, 1H), 7.30 (d, $J=8.5$ Hz, 2H), 7.03 (t, $J=7.7$ Hz, 1H), 5.50 (s, 2H), 3.57 (q, $J=6.4$ Hz, 4H), 2.13 - 2.05 (m, 2H), 1.98 - 1.90 (m, 2H).

Example 46: N-methyl-2-[5-[2-[4-(trifluoromethoxy)anilino]phenyl]tetrazol-2-yl]acetamide

(Compound 46)**Step 1: ethyl 2-[5-[2-[4-(trifluoromethoxy)anilino]phenyl]tetrazol-2-yl]acetate**

[00376] To a solution of **46-1** (600.0 mg, 1.9 mmol, 1.0 *eq*) in DMF (5.0 mL) was added K₂CO₃ (387.2 mg, 2.8 mmol, 1.5 *eq*) and **46-2** (374.8 mg, 2.2 mmol, 0.25 mL, 1.2 *eq*). The mixture was stirred at 80 °C for 16 hour under N₂ atmosphere. LCMS showed the desired compound was formed. TLC (Petroleum ether : Ethyl acetate=3/1) showed the starting material was consumed completely. The reaction was filtered to give a crude product. The crude product was purified by column chromatography over silica gel to give **46-3** (620.0 mg, 1.5 mmol, 81.4% yield). LCMS (ESI): RT = 0.897 min, mass calc. for C₁₈H₁₆F₃N₅O₃ 407.12, m/z found 408.0 [M+H]⁺.

Step 2: 2-[5-[2-[4-(trifluoromethoxy)anilino]phenyl]tetrazol-2-yl]acetic acid

[00377] To a solution of **46-3** (620.0 mg, 1.5 mmol, 1.0 *eq*) in H₂O (2.0 mL) MeOH (4.0 mL) was added NaOH (243.2 mg, 6.1 mmol, 4.0 *eq*). The resulting mixture was stirred at 20 °C for 4 hours. LCMS showed the desired compound was formed. TLC (Petroleum ether : Ethyl acetate=3/1) showed the starting material was consumed and a new spot appeared. The reaction solvent was removed under reduced pressure and water (5 mL) was added. The reaction was acidified by adding 1M HCl (10mL) and solid precipitated. The mixture was washed with EtOAc (20 mL x 2). The combined organic layers were concentrated to give crude **46-4** (250.0 mg, 0.66 mmol, 43.4% yield). LCMS (ESI): RT = 0.806 min, mass calc. for C₁₆H₁₂F₃N₅O₃ 379.09, m/z found 379.9 [M+H]⁺.

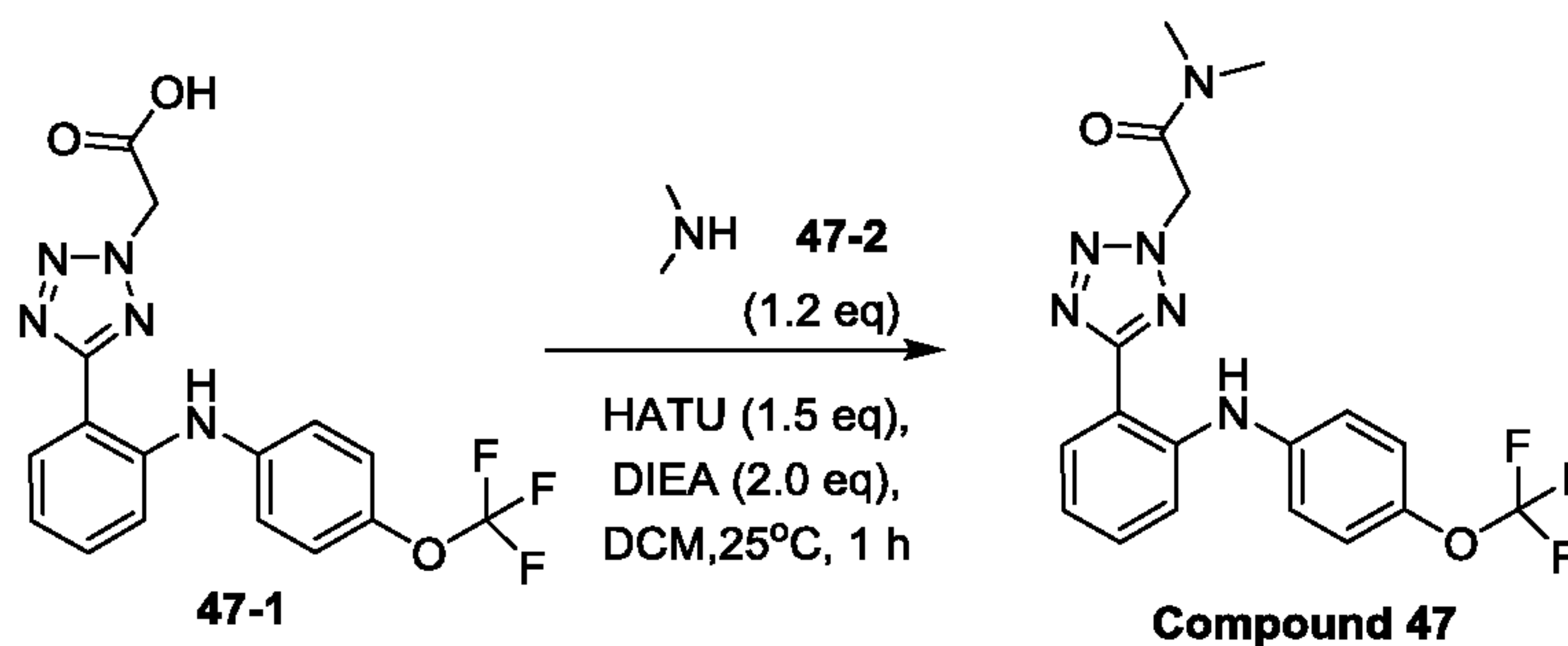
Step 3: N-methyl-2-[5-[2-[4-(trifluoromethoxy)anilino]phenyl]tetrazol-2-yl]acetamide

[00378] To a solution of **46-4** (40.0 mg, 0.11 mmol, 1.0 *eq*) and compound **5** (4.9 mg, 0.16 mmol, 1.5 *eq*) in DCM (5.0 mL) was added HATU (40.1 mg, 0.11 mmol, 1.0 *eq*) and DIEA (40.9 mg, 0.32 mmol, 55.3 uL, 3.0 *eq*). The resulting mixture was stirred at 20 °C for 1 hour. LCMS showed the desired compound was formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 46** (2.38 mg, 6.07 umol, 5.75% yield). LCMS (ESI): RT = 0.830 min, mass calc. for C₁₇H₁₅F₃N₆O₂ 392.12, m/z found 393.0 [M+H]⁺; ¹HNMR (400 MHz, CDCl₃-d) δ 8.77 (s, 1H), 8.20 (d, *J*=8.0 Hz, 1H), 7.37 (s, 2H),

7.29 (br s, 2H), 7.23 - 7.17 (m, 2H), 6.98 (br t, $J=6.7$ Hz, 1H), 5.86 (br s, 1H), 5.43 (s, 2H), 2.88 (d, $J=4.8$ Hz, 3H).

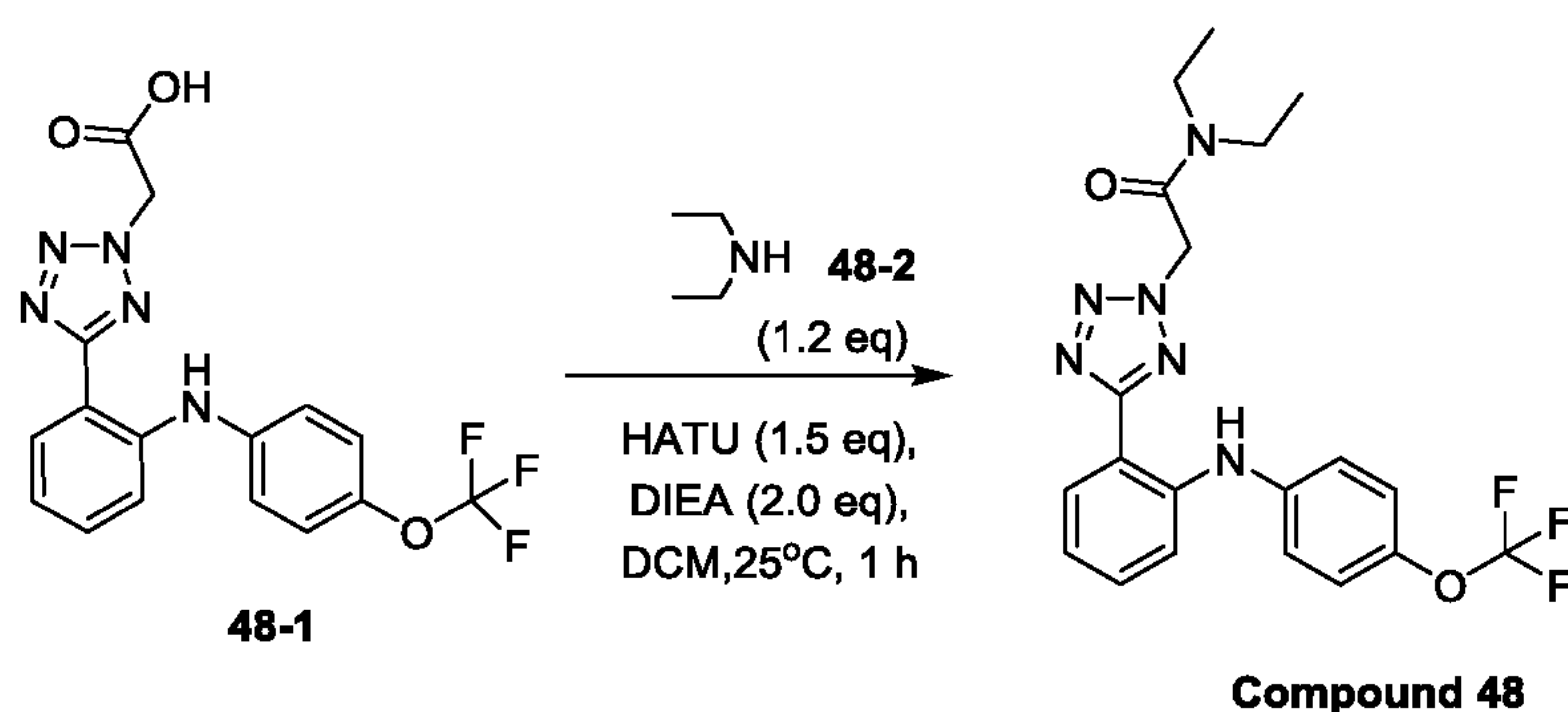
Example 47: N,N-dimethyl-2-[5-[2-[4-(trifluoromethoxy)anilino]phenyl]tetrazol-2-yl]acetamide

(Compound 47)



[00379] To a solution of **47-1** (40.0 mg, 0.11 mmol, 1.0 *eq*) and **47-2** (4.8 mg, 0.11 mmol, 5.3 μ L, 1.0 *eq*) in DCM (5.0 mL) was added HATU (40.1 mg, 0.11 mmol, 1.0 *eq*) and DIEA (40.9 mg, 0.32 mmol, 55.3 μ L, 3.0 *eq*). The resulting mixture was stirred at 20 °C for 1 hour. LCMS showed the desired compound was formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the title compound (2.49 mg, 6.13 μ mol, 5.81% yield). LCMS (ESI): RT = 0.853 min, mass calc. for $C_{18}H_{17}F_3N_6O_2$ 406.14, m/z found 407.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3-d$) δ 8.82 (s, 1H), 8.22 (d, $J=7.8$ Hz, 1H), 7.39 - 7.31 (m, 2H), 7.30 - 7.27 (m, 2H), 7.22 - 7.16 (m, 2H), 6.96 (t, $J=7.3$ Hz, 1H), 5.59 (s, 2H), 3.17 (s, 3H), 3.06 (s, 3H).

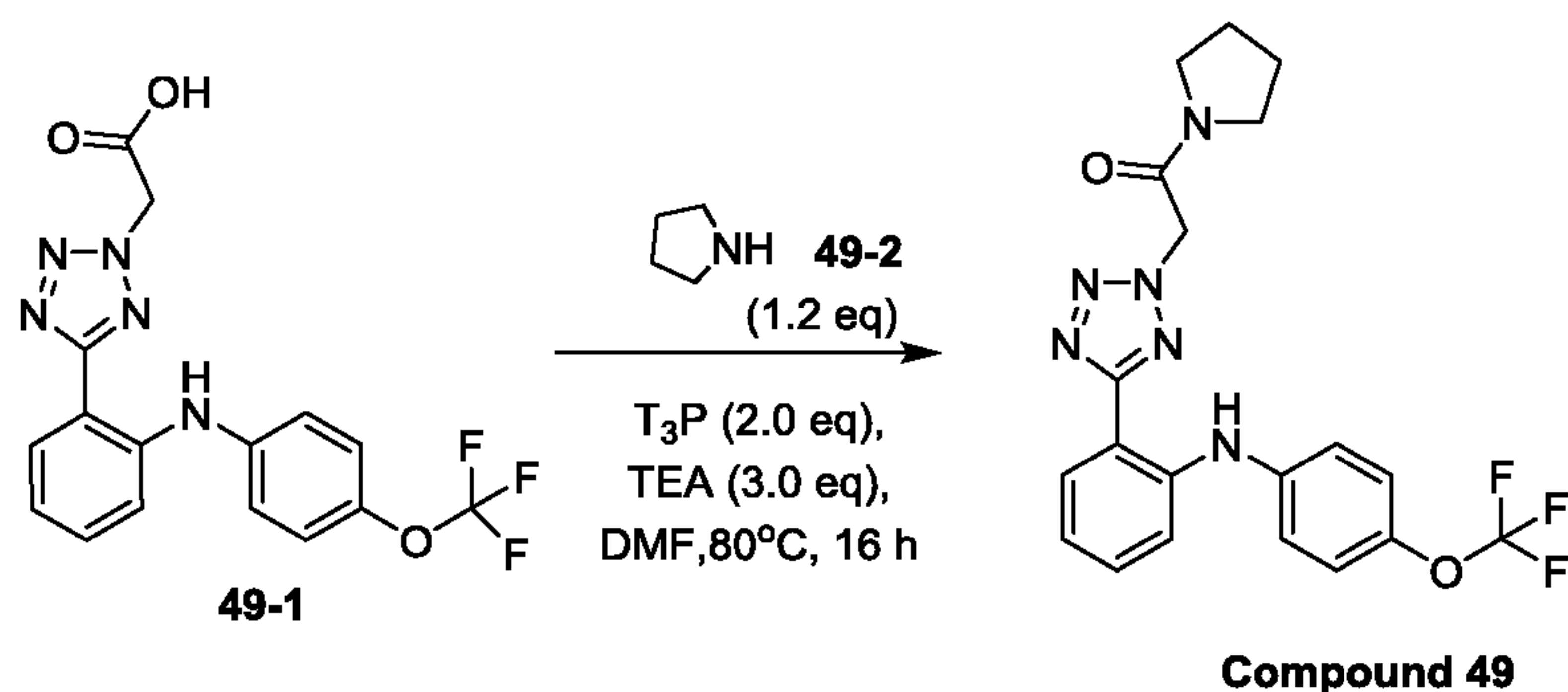
Example 48: N,N-diethyl-2-[5-[2-[4-(trifluoromethoxy)anilino]phenyl]tetrazol-2-yl]acetamide
(Compound 48)



[00380] To a solution of **48-1** (40.0 mg, 0.11 mmol, 1.0 *eq*) and **48-2** (7.7 mg, 0.11 mmol, 10.9 μ L, 1.0 *eq*) in DCM (5.0 mL) was added HATU (40.1 mg, 0.11 mmol, 1.0 *eq*) and DIEA (40.9 mg, 0.32 mmol, 55.3 μ L, 3.0 *eq*). The resulting mixture was stirred at 20 °C for 1 hour. LCMS showed the desired compound was formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the title compound (4.44 mg, 10.61 μ mol, 7.71% yield). LCMS (ESI): RT = 0.906 min, mass calc. for $C_{20}H_{21}F_3N_6O_2$ 434.17, m/z

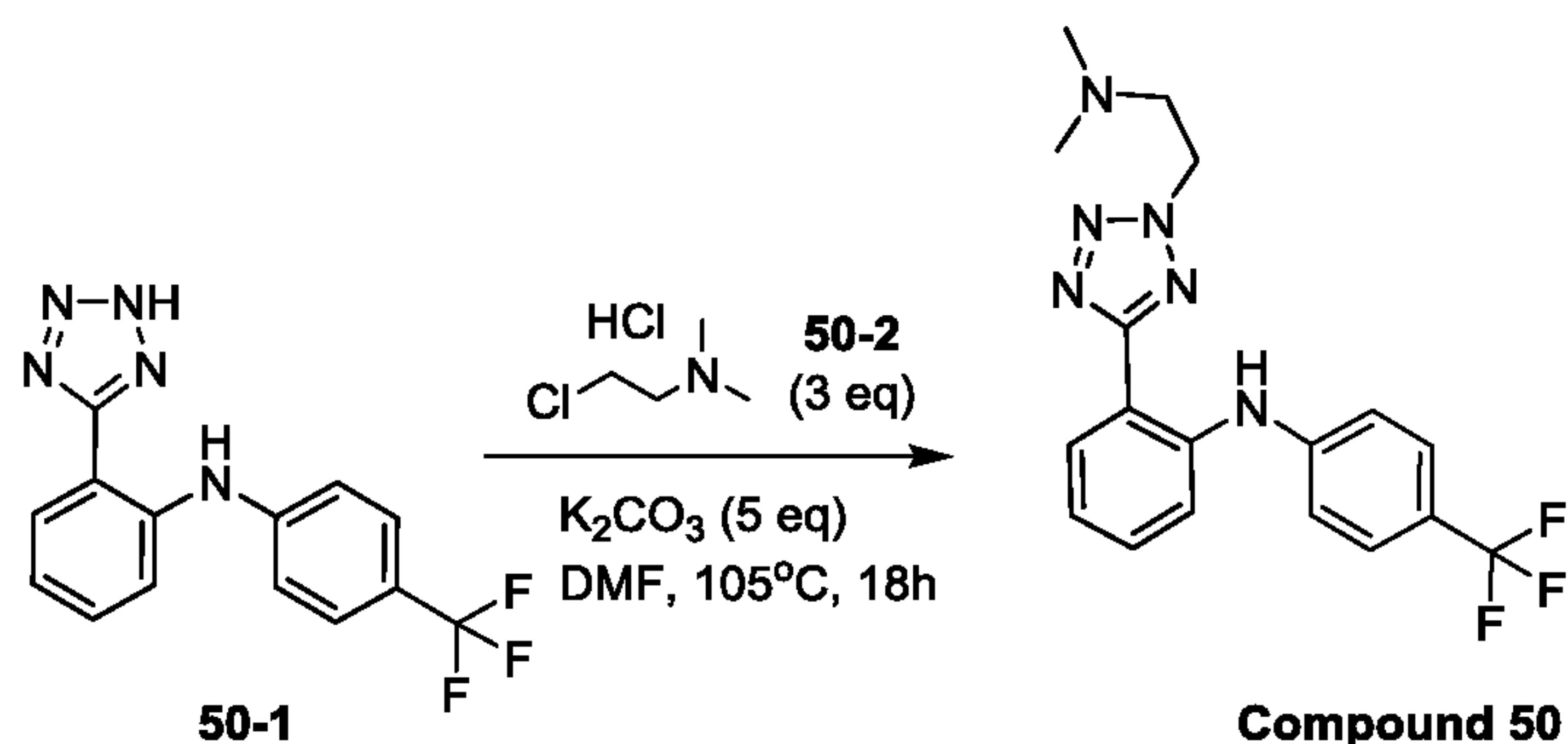
found 435.1 $[M+H]^+$; ^1H NMR (400 MHz, CDCl_3 -*d*) δ 8.83 (s, 1H), 8.22 (dd, $J=1.1, 7.9$ Hz, 1H), 7.39 - 7.31 (m, 2H), 7.31 - 7.27 (m, 2H), 7.21 - 7.17 (m, 2H), 7.01 - 6.92 (m, 1H), 5.57 (s, 2H), 3.46 (t, $J=7.2, 9.7$ Hz, 4H), 1.34 (t, $J=7.2$ Hz, 3H), 1.19 (t, $J=7.2$ Hz, 3H).

Example 49: 1-(pyrrolidin-1-yl)-2-(5-(2-((4-(trifluoromethoxy)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-one (Compound 49)



[00381] To a solution of **49-1** (50.0 mg, 0.13 mmol, 1.0 *eq*) and **49-2** (14.1 mg, 0.20 mmol, 16.5 μL , 1.5 *eq*) in DMF (2.0 mL) was added TEA (53.4 mg, 0.52 mmol, 73.1 μL , 4.0 *eq*) and T_3P (83.9 mg, 0.13 mmol, 78.4 μL , 50% purity, 1.0 *eq*). The resulting mixture was stirred at 80 °C for 16 hour. LCMS showed the desired compound was formed. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC to give the title compound (11.54 mg, 26.69 μmol , 20.24% yield). LCMS (ESI): RT = 0.873 min, mass calc. for $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_6\text{O}_2$ 432.15, m/z found 433.0 $[M+H]^+$; ^1H NMR (400 MHz, CDCl_3 -*d*) δ 8.82 (s, 1H), 8.22 (d, $J=8.0$ Hz, 1H), 7.38 - 7.30 (m, 2H), 7.30 - 7.27 (m, 2H), 7.21 - 7.15 (m, 2H), 6.95 (t, $J=7.5$ Hz, 1H), 5.49 (s, 2H), 3.56 (q, $J=6.9$ Hz, 4H), 2.08 (t, $J=6.6$ Hz, 2H), 1.94 (t, $J=6.7$ Hz, 2H).

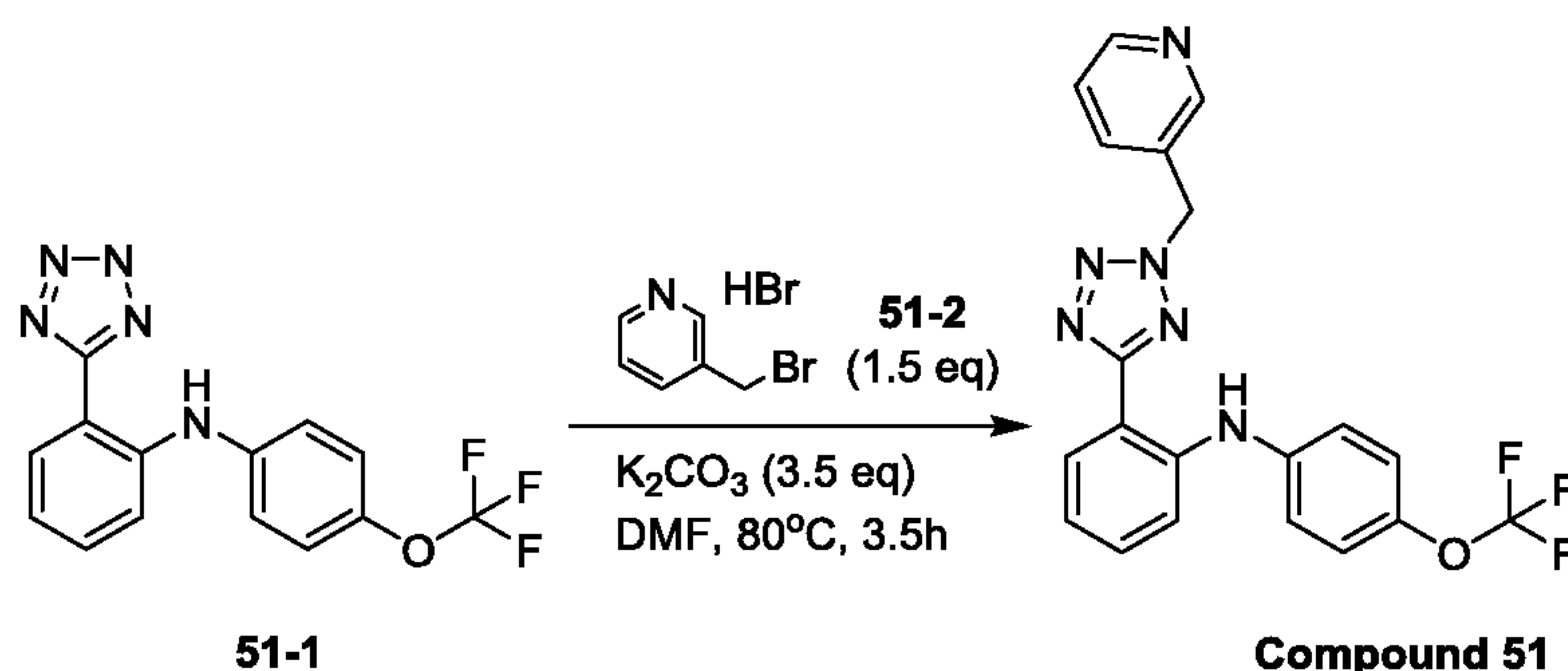
Example 50: 2-[2-[2-(dimethylamino)ethyl]tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 50)



[00382] To a mixture of **50-1** (100 mg, 0.327 mmol, 1.00 *eq*) and **50-2** (141 mg, 0.979 mmol, 2.99 *eq*, HCl) in DMF (5 mL) was added K_2CO_3 (226 mg, 1.63 mmol, 4.99 *eq*) in one portion at 25 °C. The mixture was stirred at 105 °C for 18 h. LCMS showed the starting material was consumed completely and one main peak with the desired MS was detected. TLC showed many new spots were formed. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (20

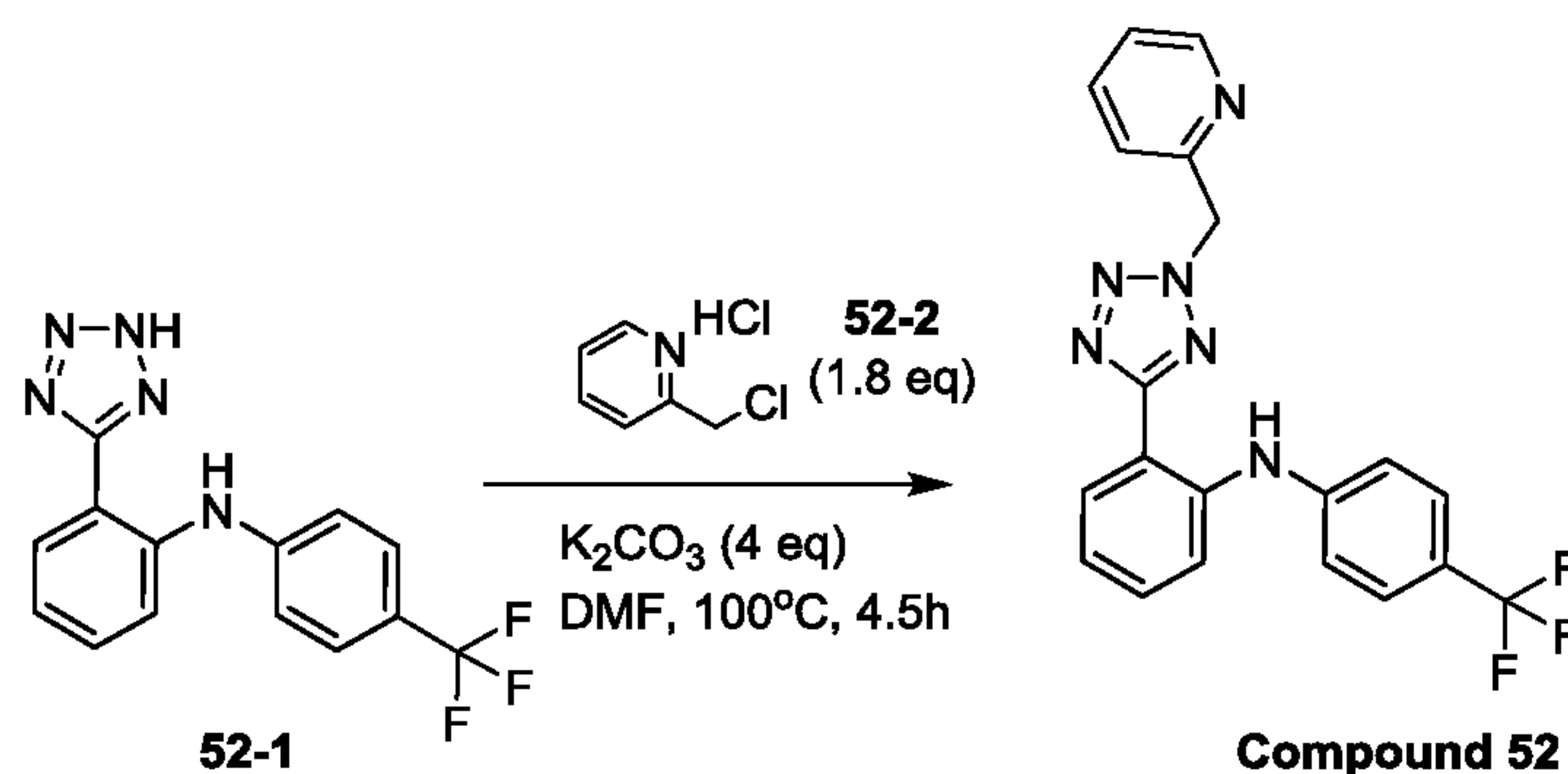
mL * 3). The combined organic layers were dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by flash silica gel chromatography to provide the title compound (40.12 mg, 106.6 μ mol, 32.5% yield). LCMS (ESI): RT = 1.023 min, mass calc. for C₁₈H₁₉F₃N₆ 376.16, m/z found 377.1[M+H]⁺ and 357.1[M+H-20]⁺. ¹HNMR (400MHz, DMSO-*d*₆) δ 8.82 (s, 1H), 8.08 - 7.99 (m, 1H), 7.57 - 7.46 (m, 4H), 7.23 - 7.13 (m, 3H), 4.82 (t, *J* = 6.00 Hz, 2H), 2.81 (t, *J* = 6.00 Hz, 2H), 2.14 (s, 6H).

Example 51: 2-[2-(3-pyridylmethyl)tetrazol-5-yl]-N-[4-(trifluoromethoxy)phenyl]aniline (Compound 51)



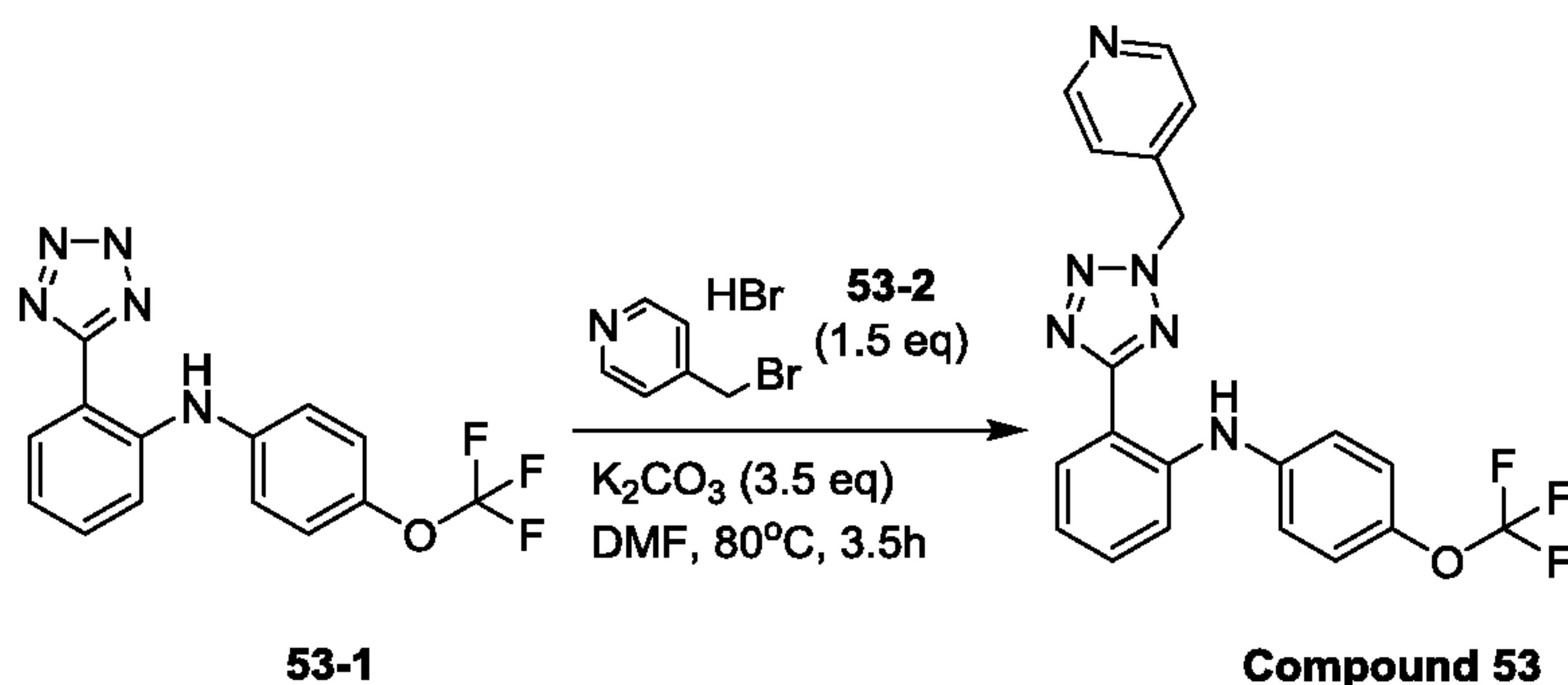
[00383] To a mixture of **51-1** (60 mg, 0.186 mmol, 1.00 *eq*) and **51-2** (85 mg, 0.336 mmol, 1.80 *eq*, HBr) in DMF (3 mL) was added K₂CO₃ (100 mg, 0.723 mmol, 3.87 *eq*) in one portion at 25°C. The mixture was stirred at 80 °C for 3.5 h. LCMS showed the starting material was consumed completely and one main peak with the desired MS was detected. TLC showed one new spot was formed. The reaction mixture was extracted with EtOAc (40 mL) and washed with brine (30 mL*4). The organic layer was dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by flash silica gel chromatography to provide the title compound (35.20 mg, 85.4 μ mol, 45.7% yield). LCMS (ESI): RT = 1.174 min, mass calc. for C₂₀H₁₅F₃N₆O 412.13, m/z found 413.1[M+H]⁺. ¹HNMR (400MHz, DMSO-*d*₆) δ 8.73 (d, *J* = 2.00 Hz, 1H), 8.63 - 8.55 (m, 2H), 8.00 (dd, *J* = 8.00, 1.20 Hz, 1H), 7.89 - 7.82 (m, 1H), 7.47 - 7.35 (m, 3H), 7.30 - 7.16 (m, 4H), 7.09 - 7.01 (m, 1H), 6.09 (s, 2H).

Example 52: 2-[2-(2-pyridylmethyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 52)



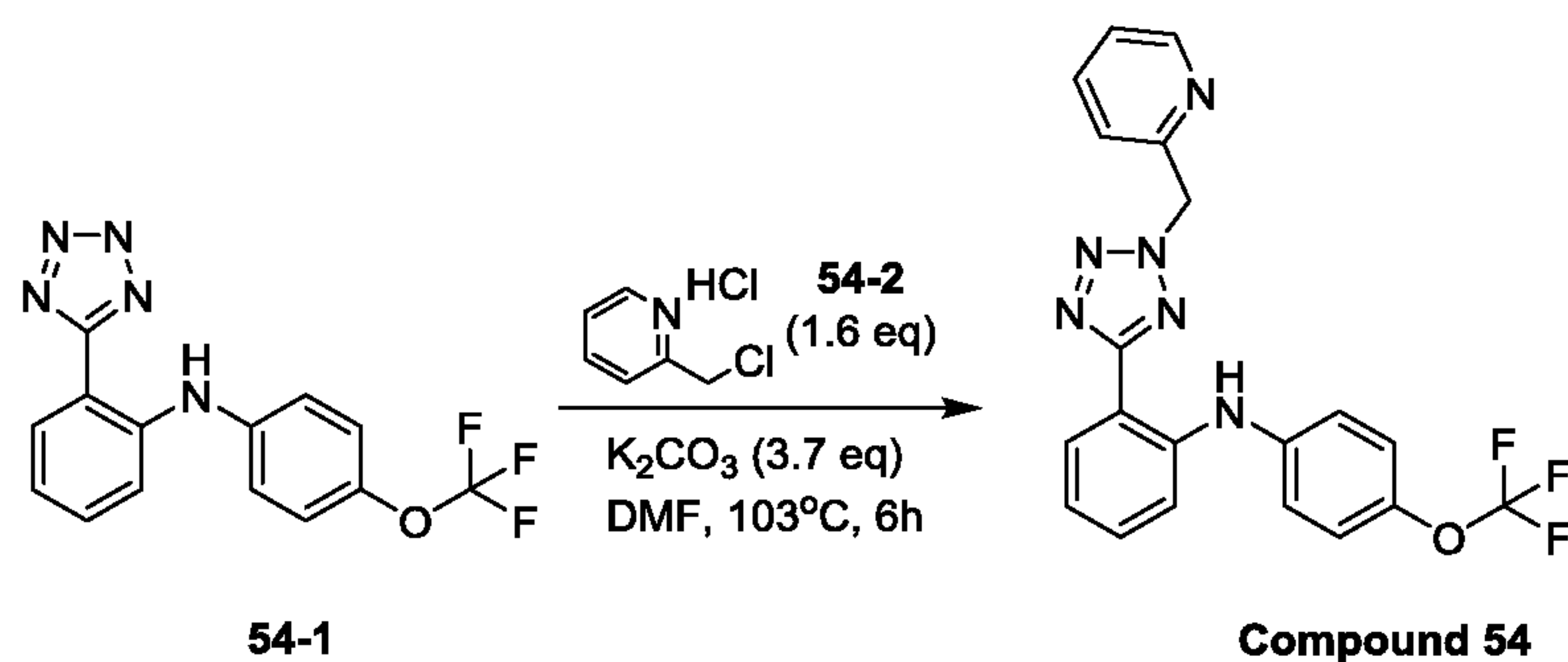
[00384] To a mixture of **52-1** (60 mg, 0.197 mmol, 1.00 *eq*) and **52-2** (60 mg, 366 mmol, 1.86 *eq*, HCl) in DMF (3 mL) was added K₂CO₃ (110 mg, 0.796 mmol, 4.05 *eq*) in one portion at 25 °C. The mixture was stirred at 100 °C for 4.5 h. The reaction was monitored by LCMS and TLC. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (20 mL * 3). The combined organic layers were dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by flash silica gel chromatography to provide the title compound (48.77 mg, 123.0 umol, 62.6% yield). LCMS (ESI): RT = 1.294 min, mass calc. for C₂₀H₁₅F₃N₆ 396.13, m/z found 397.0[M+H]⁺ and 377.0 [M+H-20]⁺. ¹HNMR (400MHz, DMSO-*d*₆) δ 8.77 (s, 1H), 8.51 (d, *J*=4.00 Hz, 1H), 8.06 - 7.97 (m, 1H), 7.88 - 7.81 (m, 1H), 7.56 - 7.36 (m, 6H), 7.21 - 7.10 (m, 3H), 6.11 (s, 2H).

Example 53: 2-[2-(4-pyridylmethyl)tetrazol-5-yl]-N-[4-(trifluoromethoxy)phenyl]aniline (Compound 53)



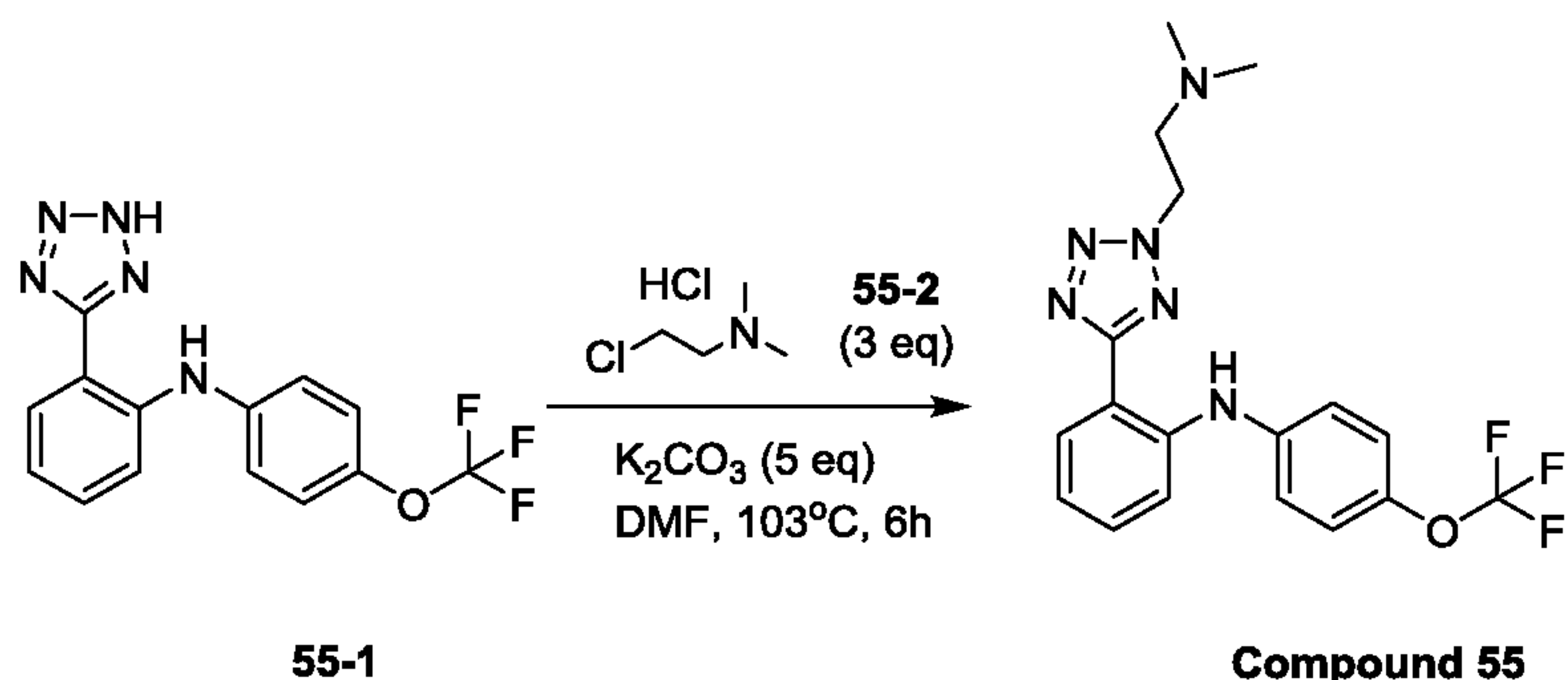
[00385] To a mixture of **53-1** (60 mg, 0.187 mmol, 1.00 *eq*) and **53-2** (85 mg, 0.336 mmol, 1.80 *eq*, HBr) in DMF (3 mL) was added K₂CO₃ (100 mg, 0.723 mmol, 3.87 *eq*) in one portion at 25°C. The mixture was stirred at 80 °C for 3.5 h. LCMS showed the starting material was consumed completely and one main peak with the desired MS was detected. TLC showed one new spot was formed. The reaction mixture was extracted with EtOAc (40 mL) and washed with brine (30 mL*4). The organic layer was dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by flash silica gel chromatography and then by prep-HPLC (basic condition) to provide the title compound (11.77 mg, 28.5 umol, 15.3% yield). LCMS (ESI): RT = 1.120 min, mass calc. for C₂₀H₁₅F₃N₆O 412.13, m/z found 413.0[M+H]⁺. ¹HNMR (400MHz, DMSO-*d*₆) δ 8.65 - 8.55 (m, 3H), 8.01 (d, *J*=8.00 Hz, 1H), 7.47 - 7.37 (m, 2H), 7.33 (br d, *J*=5.20 Hz, 2H), 7.30 - 7.24 (m, 2H), 7.23 - 7.17 (m, 2H), 7.06 (t, *J*=6.80 Hz, 1H), 6.12 (s, 2H).

Example 54: 2-(2-(pyridin-2-ylmethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethoxy)phenyl)aniline (Compound 54)



[00386] To a mixture of **54-1** (60 mg, 0.187 mmol, 1.00 *eq*) and **54-2** (60 mg, 0.366 mmol, 1.96 *eq*, HCl) in DMF (3 mL) was added K_2CO_3 (105 mg, 0.760 mmol, 4.07 *eq*) in one portion at 25 °C. The mixture was stirred at 103 °C for 6 h. LCMS showed the starting material was consumed completely and one main peak with the desired MS was detected. The reaction mixture was extracted with EtOAc (40 mL) and washed with brine (30 mL*4). The organic layer was dried with anhydrous Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by prep-HPLC (basic condition) to provide the title compound (42.39 mg, 0.102 mmol, 54.5% yield). LCMS (ESI): RT = 1.295 min, mass calc. for $C_{20}H_{15}F_3N_6O$ 412.13, m/z found 413.0[M+H]⁺. ¹HNMR (400MHz, DMSO-*d*₆) δ 8.66 (s, 1H), 8.52 (br d, J =3.60 Hz, 1H), 8.02 (d, J =8.00 Hz, 1H), 7.86 (t, J =7.60 Hz, 1H), 7.47 (d, J =7.60 Hz, 1H), 7.44 - 7.35 (m, 3H), 7.31 - 7.20 (m, 4H), 7.04 (t, J =6.80 Hz, 1H), 6.15 (s, 2H).

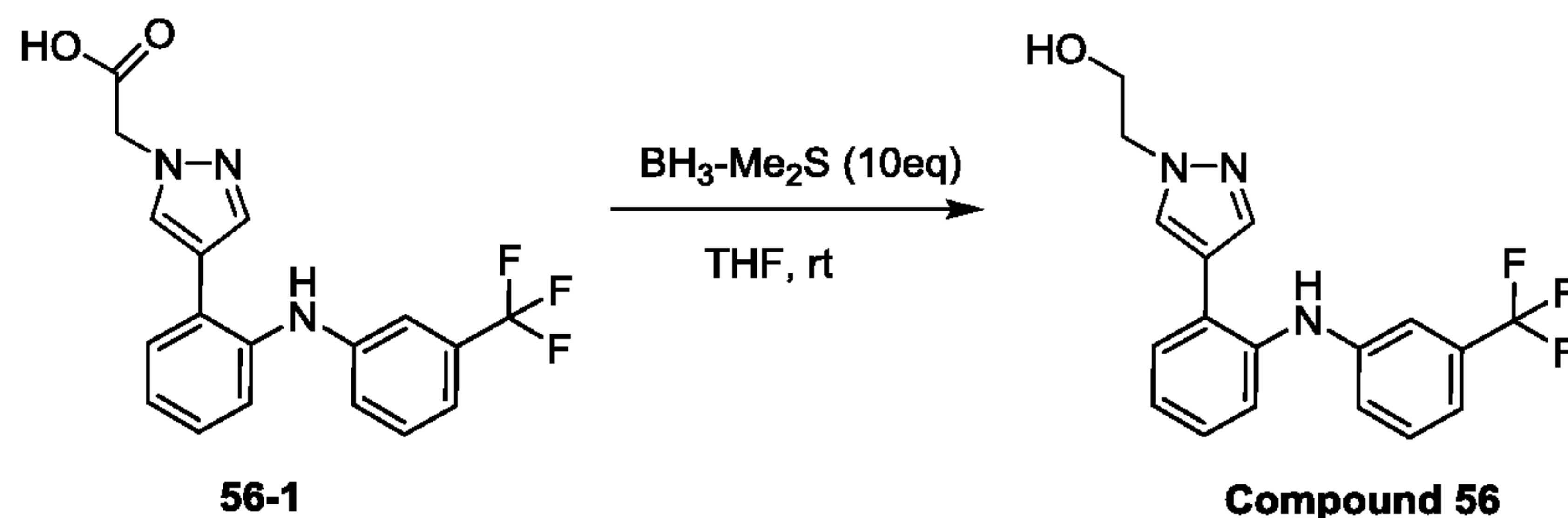
Example 55: 2-[2-[2-(dimethylamino)ethyl]tetrazol-5-yl]-N-[4-(trifluoromethoxy)phenyl]aniline (Compound 55)



[00387] To a mixture of **55-1** (100 mg, 0.311 mmol, 1.00 *eq*) and **55-2** (135 mg, 0.934 mmol, 3.00 *eq*, HCl) in DMF (5 mL) was added K_2CO_3 (215 mg, 1.56 mmol, 5.00 *eq*) in one portion at 25 °C. The mixture was stirred at 103 °C for 6 h. LCMS showed the starting material was consumed completely and one main peak with the desired MS was detected. The reaction mixture was extracted with EtOAc (40 mL) and washed with brine (30 mL*4). The organic layer was dried with anhydrous Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by prep-HPLC (basic condition) to provide the title compound (67.62 mg, 0.171 mmol, 54.8% yield). LCMS (ESI): RT = 1.038 min, mass calc. for $C_{18}H_{19}F_3N_6O$ 392.16, m/z found 393.4[M+H]⁺. ¹HNMR (400MHz, DMSO-*d*₆) δ 8.71 (s, 1H), 8.05 (d, J = 7.60 Hz, 1H), 7.45 - 7.37 (m, 2H), 7.32 -

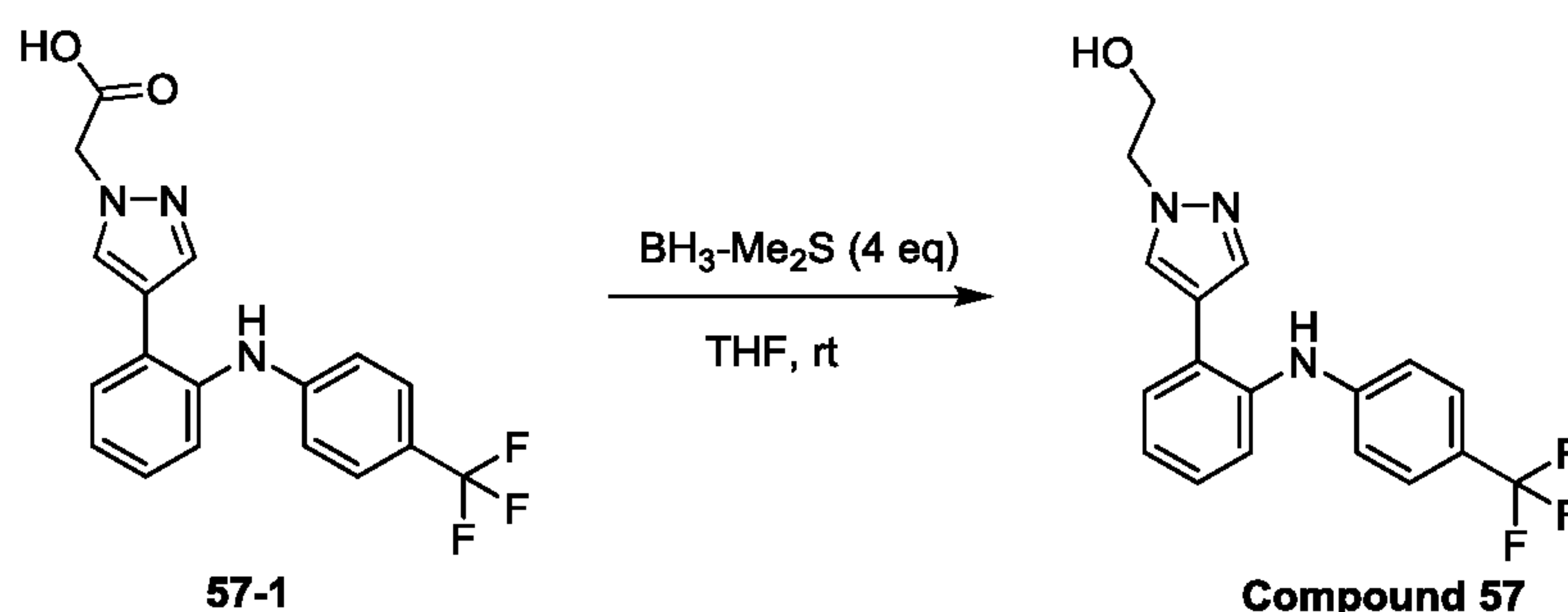
7.23 (m, 4H), 7.06 (t, $J = 6.80$ Hz, 1H), 4.85 (t, $J = 6.00$ Hz, 2H), 2.86 (t, $J = 6.00$ Hz, 2H), 2.16 (s, 6H).

Example 56: 2-[4-[2-[3-(trifluoromethyl)anilino]phenyl]pyrazol-1-yl]ethanol (Compound 56)



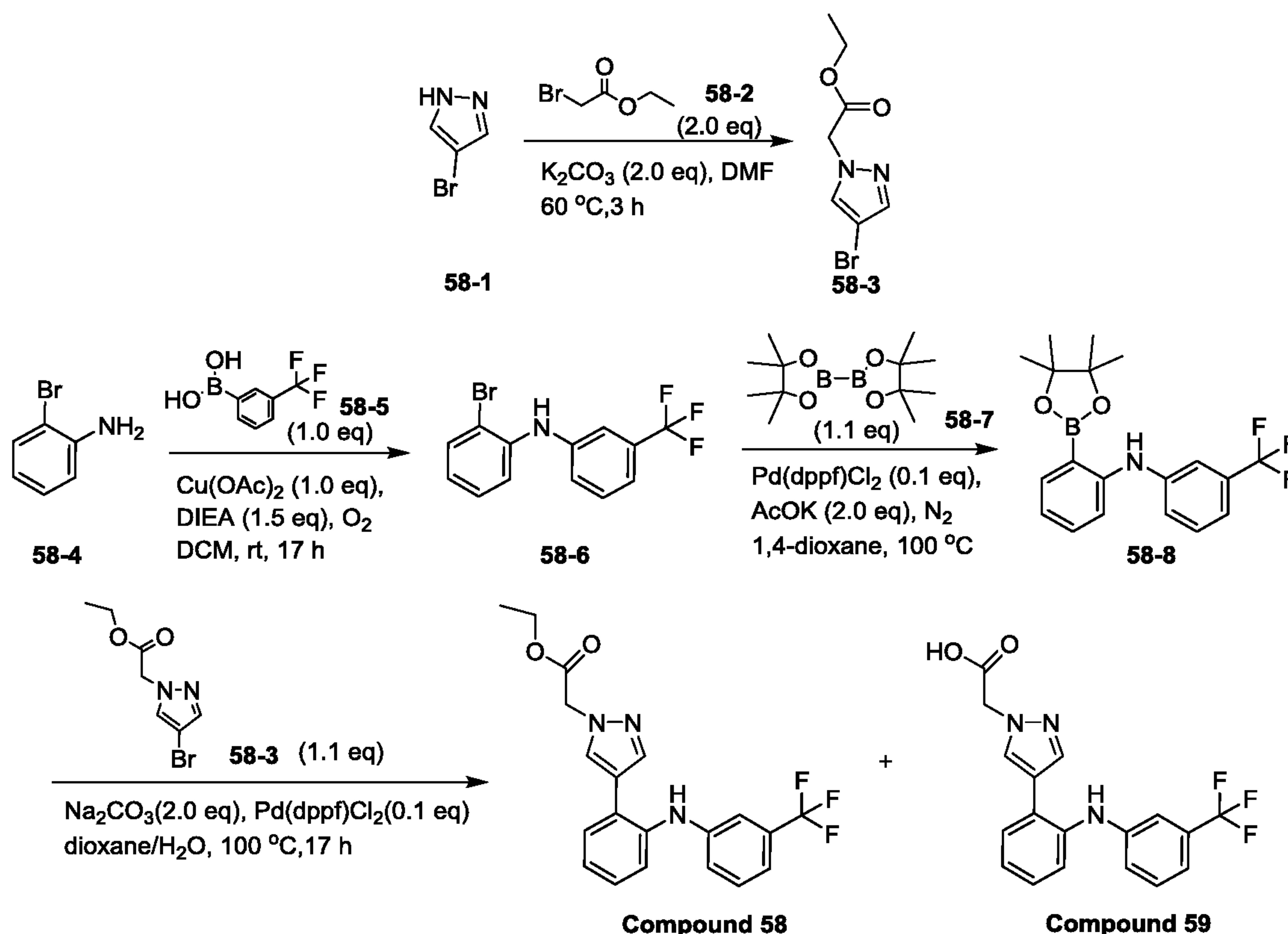
[00388] To a solution of **56-1** (50 mg, 0.14 mmol, 1.00 *eq*) in THF (3 mL) was added $\text{BH}_3\text{-Me}_2\text{S}$ (10 M, 138.38 μL , 10.00 *eq*) and the resulting mixture was stirred at 25°C for 16 hr. LCMS showed that the desired MS signal was detected. The reaction was quenched by MeOH (10 mL) slowly and concentrated. The crude product was purified by CombiFlash to give the title compound (12 mg, 28.68 μmol , 20.72% yield). LCMS (ESI): RT = 0.781 min, mass calc. for $\text{C}_{18}\text{H}_{16}\text{F}_3\text{N}_3\text{O}$ 347.12, m/z found 347.9 $[\text{M}+\text{H}]^+$. ^1H NMR (400MHz, $\text{CHLOROFORM-}d$) δ 7.71 (s, 1H), 7.62 (s, 1H), 7.40 - 7.20 (m, 1H), 7.16 (s, 1H), 7.15 - 7.00 (m, 4H), 5.71 (brs, 1H), 4.30-4.20 (m, 2H), 4.10 - 3.95 (m, 2H).

Example 57: 2-[4-[2-[3-(trifluoromethyl)anilino]phenyl]pyrazol-1-yl]ethanol (Compound 57)



[00389] To a solution of **57-1** (20 mg, 55.35 μmol , 1.00 *eq*) in THF (2 mL) was added $\text{BH}_3\text{-Me}_2\text{S}$ (10 M, 22.14 μL , 4.00 *eq*) and the resulting mixture was stirred at 30°C for 16 hr. LCMS showed that the desired MS signal was detected. The reaction was quenched by MeOH (10 mL) slowly and concentrated. The crude product was purified by CombiFlash to give the title compound (15.00 mg, 39.30 μmol , 71.00% yield). LCMS (ESI): RT = 0.786 min, mass calc. for $\text{C}_{18}\text{H}_{16}\text{F}_3\text{N}_3\text{O}$ 347.12, m/z found 347.9 $[\text{M}+\text{H}]^+$. ^1H NMR (400MHz, $\text{CHLOROFORM-}d$) δ 7.70 (s, 1H), 7.60 (s, 1H), 7.40 - 7.30 (m, 4H), 7.28 - 7.20 (m, 1H), 7.16 (s, 1H), 7.03 - 6.80 (m, 2H), 5.76 (brs, 1H), 4.30 - 4.20 (m, 2H), 4.10 - 3.95 (m, 2H).

Example 58: ethyl 2-(4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetate (Compound 58) and 2-(4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetic acid (Compound 59)



Step 1: ethyl 2-(4-bromo-1H-pyrazol-1-yl)acetate

[00390] To a mixture of **58-1** (1.0 g, 6.8 mmol, 1.00 *eq*) and K₂CO₃ (1.9 g, 13.6 mmol, 2.00 *eq*) in DMF (10.0 mL), was added **58-2** (2.3 g, 13.6 mmol, 1.5 mL, 2.00 *eq*). The resulting mixture was stirred at 26 °C for 2 h. LCMS showed the starting material remained. The mixture was stirred at 26 °C for an additional 17 h. TLC showed the starting material remained. The mixture was stirred at 60 °C for an additional 3 h. LCMS showed the reaction was complete. The mixture was diluted with EtOAc (40 mL), and washed with water (40 mL *5). The organic layer was dried over anhydrous Na₂SO₄, and concentrated under vacuum. The residue was purified by silica gel chromatography to provide **58-3** (1.8 g, 4.3 mmol, 62.5% yield) as a light yellow oil.

Step 2: 2-bromo-N-(3-(trifluoromethyl)phenyl)aniline

[00391] To a mixture of **58-4** (4.5 g, 26.3 mmol, 1.00 *eq*), **58-5** (5.0 g, 26.3 mmol, 1.00 *eq*) and Cu(OAc)₂ (4.8 g, 26.3 mmol, 1.00 *eq*) in DCM (100.0 mL), was added DIEA (5.1 g, 39.5 mmol, 6.9 mL, 1.50 *eq*). The mixture was degassed under vacuum and purged with O₂ 3 times. The resulting mixture was stirred at 26 °C under O₂ (15 Psi) for 17 h. The reaction was monitored by LCMS. The mixture was filtered, and the solid was washed with DCM (10 mL *3). The filtrate was washed with water (100 mL). The combined organic washings were dried over anhydrous Na₂SO₄,

and concentrated under vacuum. The residue was purified by silica gel chromatography to provide **58-6** (4.25 g, 11.8 mmol, 44.9% yield). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 7.58 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.44 - 7.39 (m, 1H), 7.37 (s, 1H), 7.30 (d, *J* = 1.5 Hz, 1H), 7.28 (d, *J* = 1.5 Hz, 1H), 7.27 - 7.20 (m, 2H), 6.84 (ddd, *J* = 1.6, 7.2, 8.0 Hz, 1H), 6.16 (s, 1H).

Step 3: 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(3-(trifluoromethyl)phenyl)aniline

[00392] To a mixture of **58-6** (1.0 g, 3.2 mmol, 1.00 *eq*), **58-7** (882.7 mg, 3.5 mmol, 1.10 *eq*) and Pd(dppf)Cl₂ (231.2 mg, 0.3 mmol, 0.10 *eq*) in dioxane (20.0 mL), was added AcOK (620.2 mg, 6.3 mmol, 2.00 *eq*). The mixture was degassed under vacuum and purged with N₂ 3 times. The resulting mixture was stirred at 100 °C under N₂ for 17 h. LCMS showed the reaction was complete. The mixture was concentrated under vacuum. The residue was purified by silica gel chromatography to provide **58-8** (900.0 mg, crude).

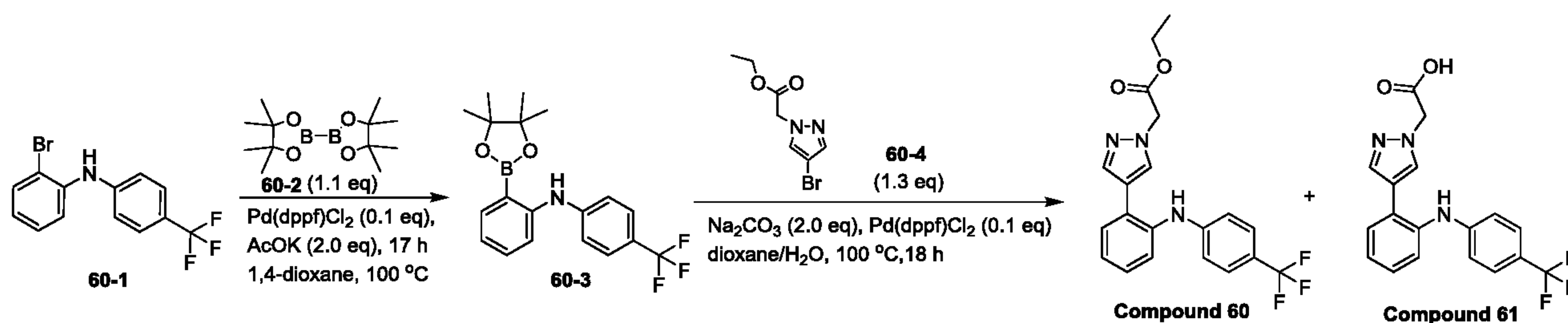
Step 4: ethyl 2-(4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetate and 2-(4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetic acid

[00393] To a mixture of **58-8** (200.0 mg, 0.6 mmol, 1.00 *eq*), **58-3** (154.0 mg, 0.7 mmol, 1.20 *eq*) and Na₂CO₃ (116.7 mg, 1.1 mmol, 2.00 *eq*) in dioxane (4.0 mL) and H₂O (0.5 mL), was added Pd(dppf)Cl₂ (40.3 mg, 55.1 μmol, 0.10 *eq*). The mixture was degassed under vacuum and purged with N₂ 3 times. The resulting mixture was stirred at 100 °C for 17 h. LCMS showed the reaction was complete. The mixture was concentrated under vacuum. The residue was purified by silica gel chromatography to afford the crude products. The crude products were purified by prep-HPLC (acidic HCl condition) to provide **Compound 58** and **Compound 59**.

[00394] Compound 58: 2.31 mg, 4.4 μmol, 0.8% yield, HCl. LCMS (ESI): RT = 0.852 min, mass calc. for C₂₀H₁₈F₃N₃O₂ 389.14, *m/z* found 390.0 [M+H]⁺. ¹H NMR (400MHz, CHLOROFORM-*d*) δ 7.74 (s, 1H), 7.66 (s, 1H), 7.41 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.38 - 7.31 (m, 2H), 7.29 - 7.24 (m, 1H), 7.20 (s, 1H), 7.15 - 7.06 (m, 3H), 5.78 (s, 1H), 4.94 (s, 2H), 4.26 (q, *J* = 7.0 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H).

[00395] Compound 59: 52.51 mg, 0.1 mmol, 24.0% yield, HCl. LCMS (ESI): RT = 0.783 min, mass calc. for C₁₈H₁₄F₃N₃O₂ 361.10, *m/z* found 361.9 [M+H]⁺. ¹H NMR (400MHz, METHANOL-*d*₄) δ 7.81 (s, 1H), 7.65 (s, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.34 - 7.27 (m, 2H), 7.26 - 7.21 (m, 1H), 7.15 - 7.10 (m, 1H), 7.09 - 7.06 (m, 2H), 6.97 (d, *J* = 7.8 Hz, 1H), 4.77 (s, 2H).

Example 59: ethyl 2-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetate (Compound 60) and 2-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetic acid (Compound 61)



Step 1: 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00396] To a mixture of **60-1** (2.0 g, 6.3 mmol, 1.00 *eq*), **60-2** (1.8 g, 7.0 mmol, 1.10 *eq*) and Pd(dppf)Cl₂ (462.9 mg, 0.6 mmol, 0.10 *eq*) in 1,4-dioxane (20.0 mL), was added AcOK (1.2 g, 12.7 mmol, 2.00 *eq*). The mixture was degassed under vacuum and purged with N₂ 3 times. The resulting mixture was stirred at 100 °C under N₂ for 17 h. LCMS showed the reaction was complete. The mixture was concentrated under vacuum. The residue was purified by silica gel chromatography to provide **60-3** (1.70 g, crude).

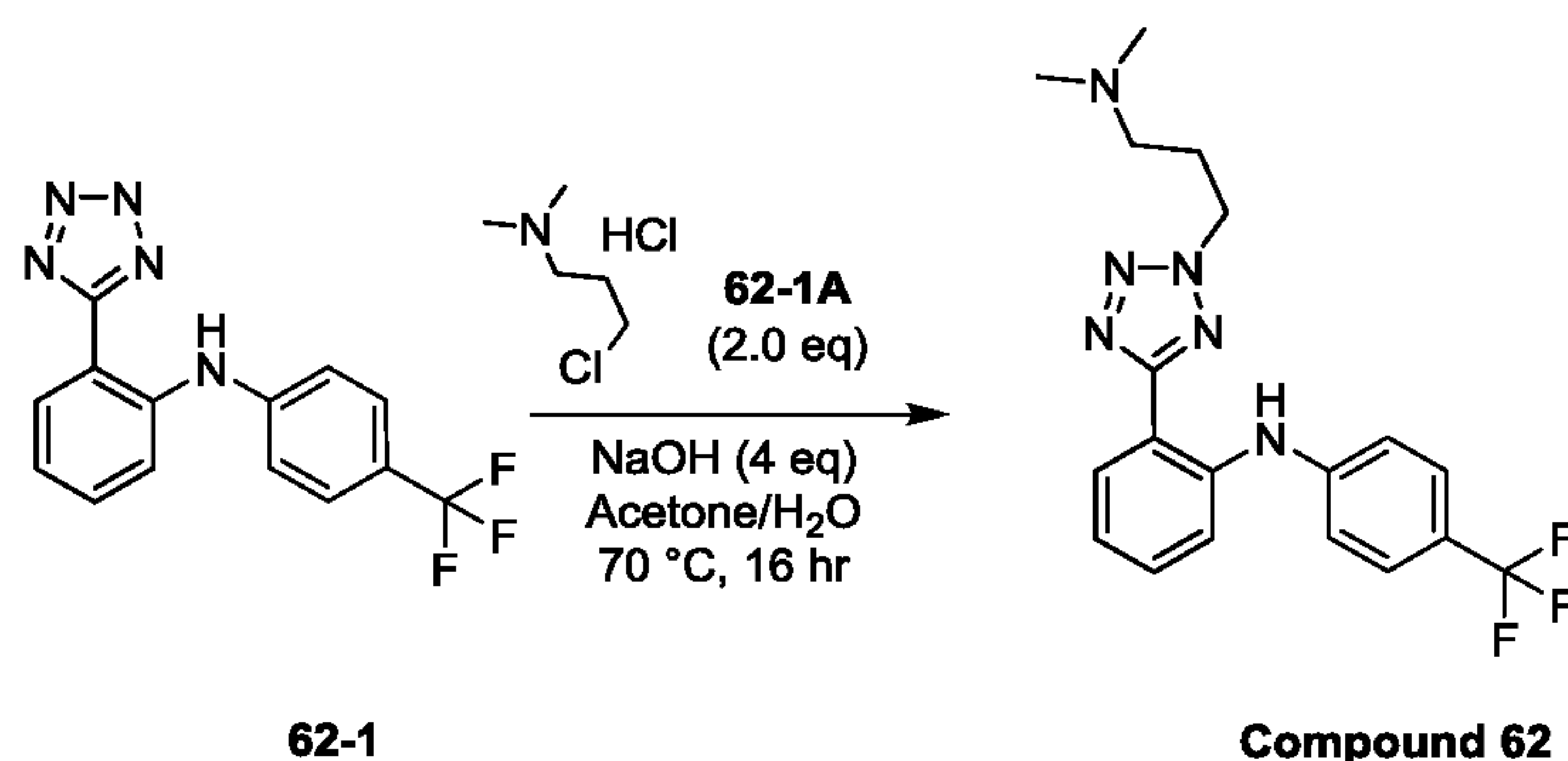
Step 2: ethyl 2-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetate and 2-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetic acid

[00397] To a mixture of **60-3** (300.0 mg, 0.8 mmol, 1.00 *eq*), **60-4** (250.3 mg, 1.1 mmol, 1.30 *eq*) and Na₂CO₃ (175.1 mg, 1.7 mmol, 2.00 *eq*) in 1,4-dioxane (4.0 mL) and H₂O (0.5 mL), was added Pd(dppf)Cl₂ (60.4 mg, 82.6 μmol, 0.10 *eq*). The mixture was degassed under vacuum and purged with N₂ 3 times. The resulting mixture was stirred at 100 °C under N₂ for 18 h. LCMS showed the reaction was complete. The mixture was diluted with water (30 mL), acidified with 2 M aqueous HCl to pH 6. The mixture was extracted with DCM (30 mL *4). The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated under vacuum. The residue was purified by prep-HPLC (acidic HCl condition) to provide **Compound 60** and **Compound 61**.

[00398] Compound 60: 37.81 mg, 88.8 μmol, 10.8% yield, HCl salt. LCMS (ESI): RT = 0.861 min, mass calc. for C₂₀H₁₈F₃N₃O₂ 389.14, m/z found 390.0 [M+H]⁺. ¹HNMR (400MHz, CHLOROFORM-*d*) δ 7.73 (s, 1H), 7.65 (s, 1H), 7.49 - 7.38 (m, 4H), 7.31 - 7.27 (m, 1H), 7.18 - 7.11 (m, 1H), 6.98 (d, *J* = 8.3 Hz, 2H), 5.78 (s, 1H), 4.93 (s, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.0 Hz, 3H).

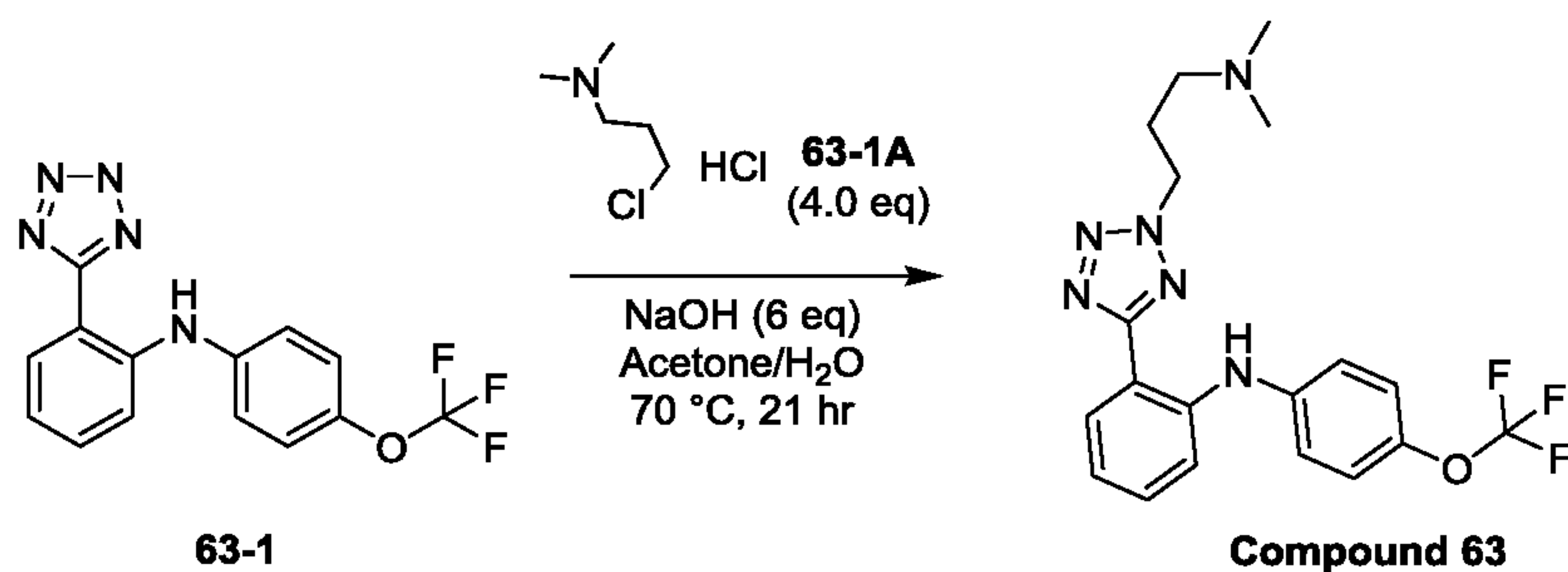
[00399] Compound 61: 22.17 mg, 55.7 μmol, 6.8% yield, HCl salt. LCMS (ESI): RT = 0.779 min, mass calc. for C₁₈H₁₄F₃N₃O₂ 361.10, m/z found 362.0 [M+H]⁺. ¹HNMR (400MHz, METHANOL-*d*₄) δ 7.88 (s, 1H), 7.73 (s, 1H), 7.55 (dd, *J* = 1.0, 7.5 Hz, 1H), 7.39 - 7.33 (m, 3H), 7.28 (dt, *J* = 1.5, 7.7 Hz, 1H), 7.23 - 7.17 (m, 1H), 6.84 (d, *J* = 8.5 Hz, 2H), 4.96 (s, 2H).

Example 60: 2-(2-(3-(dimethylamino)propyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 62)



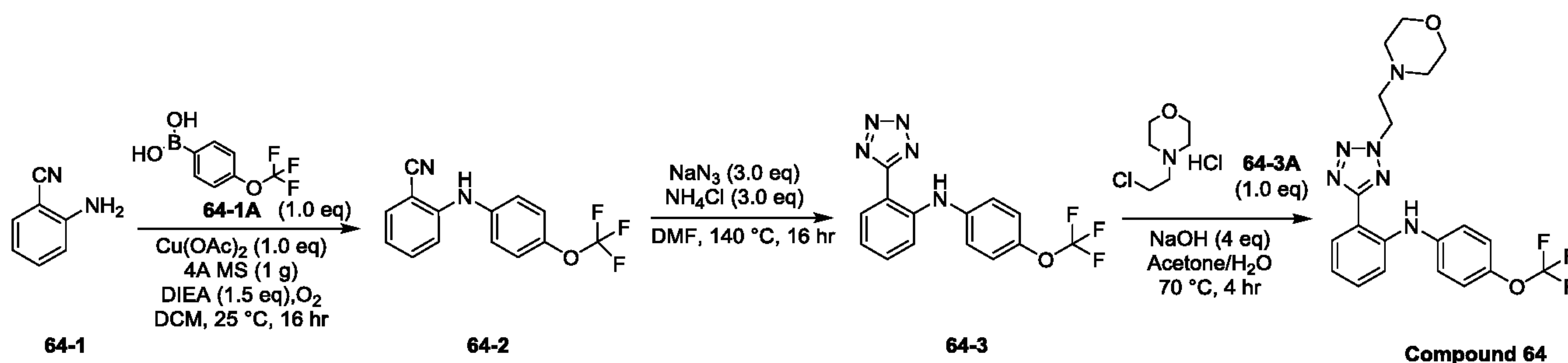
[00400] To the solution of **62-1** (100 mg, 0.3 mmol, 1.0 *eq*) in acetone (1 mL) was added **62-1A** (103 mg, 0.7 mmol, 2.0 *eq*, HCl). Then NaOH (52 mg, 1.3 mmol, 4.0 *eq*) in H₂O (1.00 mL) was added to the mixture. The solution was stirred at 70 °C for 16 hr. The reaction was monitored by LCMS. The residue was purified by Prep-HPLC to give the title compound (9.22 mg, 21.6 μ mol, 6.6% yield, HCl salt). LCMS (ESI): RT = 1.048 min, mass calc. for C₁₉H₂₁F₃N₆ 390.18, m/z found 391.1 [M+H]⁺, ¹HNMR (400MHz, CHLOROFORM-*d*) δ 8.97 (s, 1H), 8.22 - 8.15 (m 1H), 7.57 - 7.49 (m, 3H), 7.42 - 7.35 (m, 1H), 7.30 (d, *J*=8.5 Hz, 2H), 7.05 (t, *J*=7.7 Hz, 1H), 4.87 (t, *J*=6.5 Hz, 2H), 2.90 - 2.77 (m, 2H), 2.62 - 2.49 (m, 8H).

Example 61: 2-(2-(3-(dimethylamino)propyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethoxy)phenyl)aniline (Compound 63)



[00401] To the solution of **63-1** (100 mg, 0.3 mmol, 1.0 *eq*) in acetone (1 mL) was added **63-1A** (197 mg, 1.3 mmol, 4.0 *eq*, HCl salt). Then a solution of NaOH (50 mg, 1.3 mmol, 4.0 *eq*) in H₂O (1 mL) was added to the mixture. The solution was stirred at 70 °C for 21 hr. The reaction was monitored by LCMS. The residue was purified by Prep-HPLC to provide the title compound (13.83 mg, 31.2 μ mol, 10.0% yield, HCl salt). LCMS (ESI): RT = 1.062 min, mass calc. for C₁₉H₂₁F₃N₆O 406.17, m/z found 407.1 [M+H]⁺, ¹HNMR (400MHz, CHLOROFORM-*d*) δ 12.70 (s, 1H), 8.14 (d, *J*=7.3 Hz, 1H), 7.39 - 7.25 (m, 4H), 7.18 (d, *J*=7.8 Hz, 2H), 6.96 (t, *J*=6.7 Hz, 1H), 4.93 (s, 2H), 3.38 - 2.36 (m, 10H).

Example 62: 2-(2-(2-morpholinoethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethoxy)phenyl)aniline (Compound 64)



Step 1: 2-((4-(trifluoromethoxy)phenyl)amino)benzonitrile

[00402] To the solution of **64-1** (2.0 g, 17.0 mmol, 1.0 *eq*) in DCM (70 mL) was added **64-1A** (3.5 g, 17.0 mmol, 1.0 *eq*), Cu(OAc)₂ (3.1 g, 17.0 mmol, 1.0 *eq*) and DIEA (3.3 g, 25.5 mmol, 4.5 mL, 1.5 *eq*). The mixture was stirred at 25 °C for 16 hr under O₂ atmosphere. The reaction was monitored by TLC. The reaction was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂) to give **64-2** (1.4 g, 5.0 mmol, 29.6% yield).

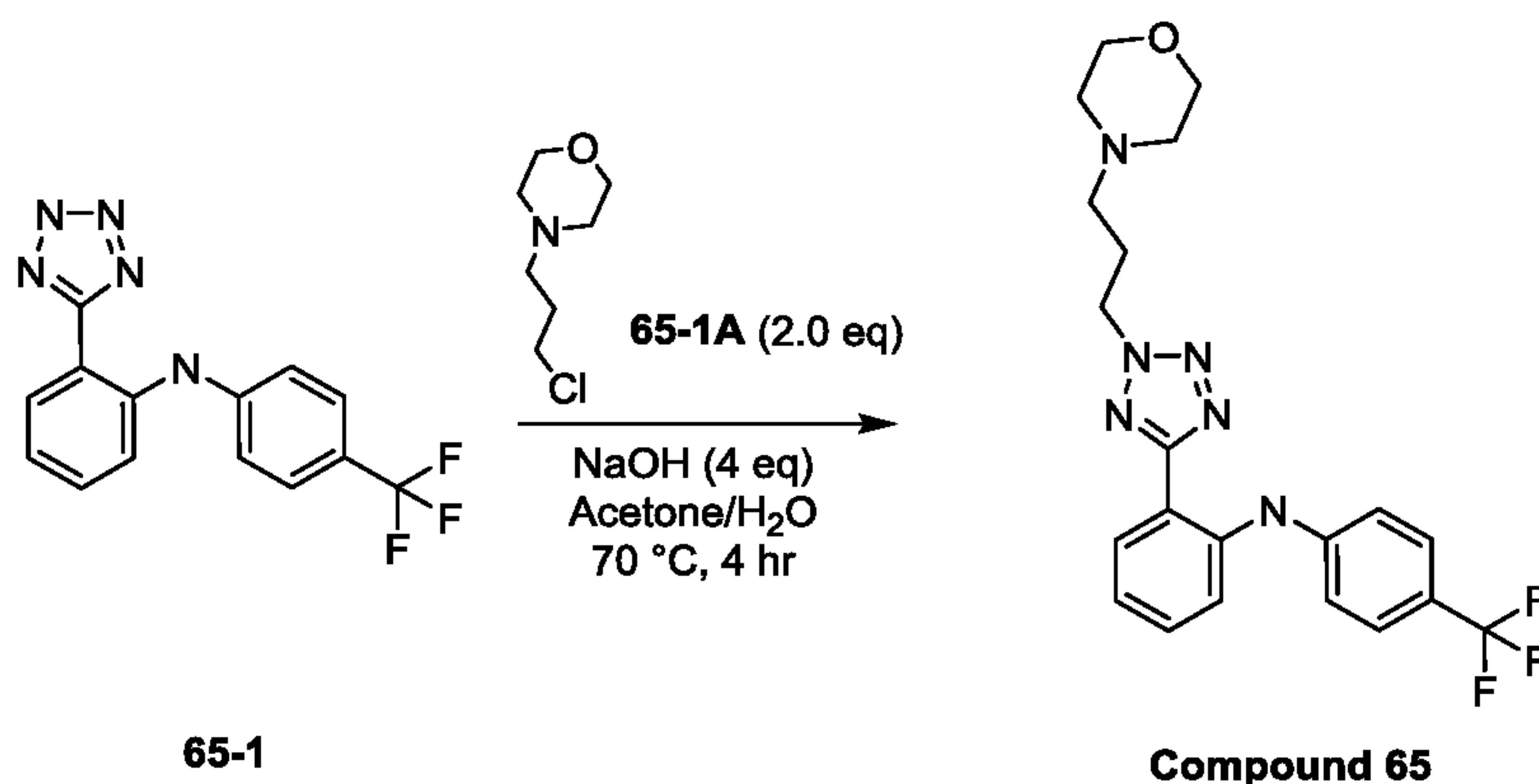
Step 2: 2-(2H-tetrazol-5-yl)-N-(4-(trifluoromethoxy)phenyl)aniline

[00403] To the solution of **64-2** (1.4 g, 5.0 mmol, 1.0 *eq*) in DMF (10 mL) was added NH₄Cl (807 mg, 15.1 mmol, 3.0 *eq*) and NaN₃ (1.0 g, 15.7 mmol, 3.0 *eq*). The mixture was stirred at 140 °C for 16 hr. The reaction was monitored by LCMS. The reaction solution was poured into aqueous HCl (1M, 50 mL). An insoluble solid appeared. The mixture was filtered and the solid was washed with H₂O (30 mL) to give compound **64-3** (1.6 g, 5.0 mmol, 99.0% yield).

Step 3: 2-(2-(2-morpholinoethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethoxy)phenyl)aniline

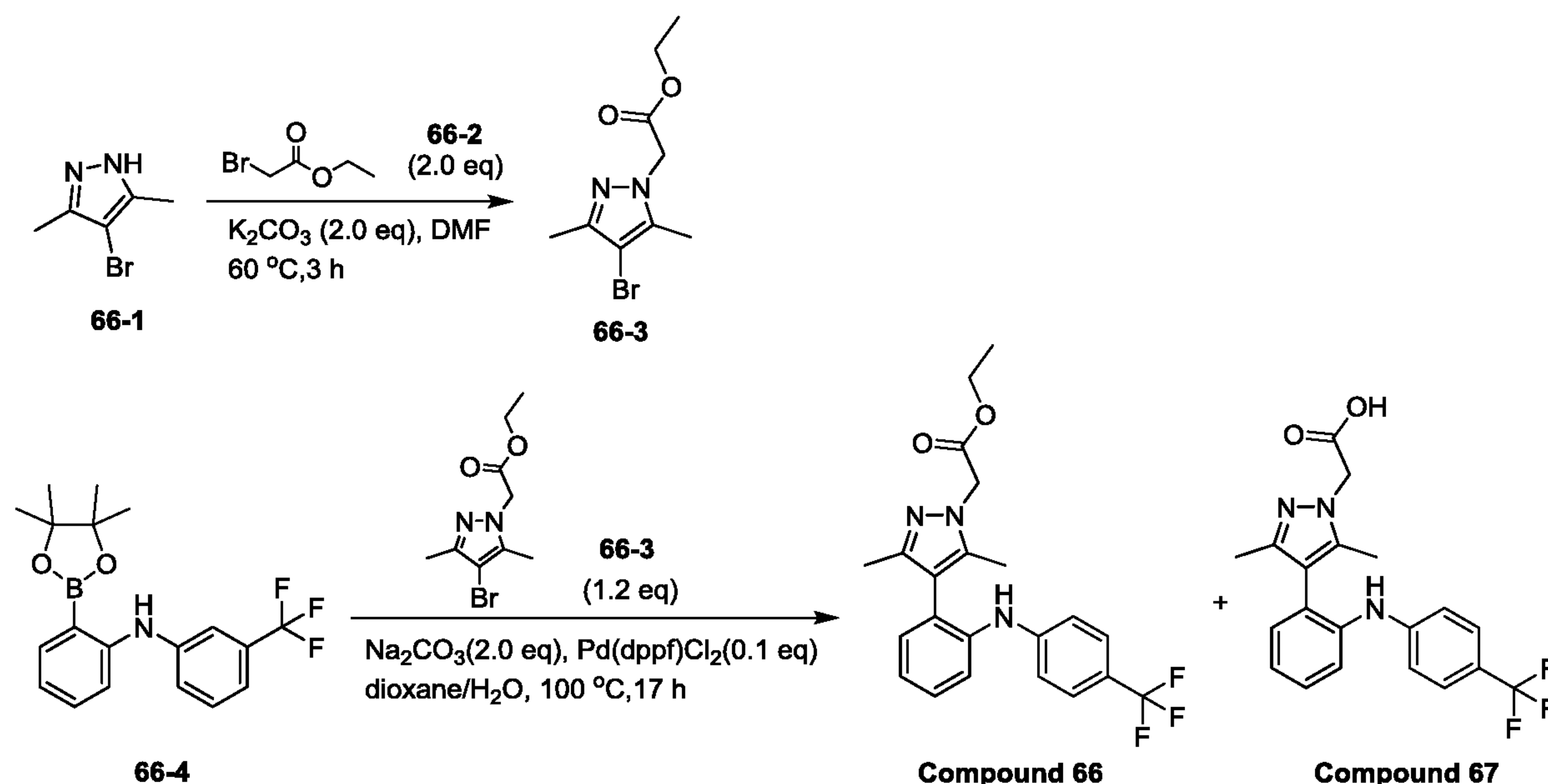
[00404] To the solution of **64-3** (100 mg, 0.3 mmol, 1.0 *eq*) in acetone (1 mL) was added **64-3A** (58 mg, 0.3 mmol, 1.0 *eq*, HCl). Then NaOH (50 mg, 1.3 mmol, 4.0 *eq*) in H₂O (1 mL) was added to the mixture. The solution was stirred at 70 °C for 4 hr. The reaction was monitored by LCMS. The reaction solution was concentrated under reduced pressure. The residue was purified by Prep-HPLC to give **Compound 64** (19.13 mg, 40.22 μmol, 12.92% yield, HCl salt). LCMS (ESI): RT = 1.062 min, mass calc. for C₂₀H₂₁F₃N₆O₂ 434.17, m/z found 435.1 [M+H]⁺, ¹HNMR (400MHz, CHLOROFORM-*d*) δ 8.92 (s, 1H), 8.25 - 8.18 (m, 1H), 7.40 - 7.23 (m, 4H), 7.23 - 7.17 (m, 2H), 6.97 (t, *J*=7.1 Hz, 1H), 4.82 (t, *J*=6.5 Hz, 2H), 3.71 - 3.61 (m, 4H), 3.06 (t, *J*=6.5 Hz, 2H), 2.59 - 2.50 (m, 4H).

Example 63: 2-(2-(3-morpholinopropyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 65)



[00405] To the solution of **65-1** (100 mg, 0.3 mmol, 1.0 *eq*) in acetone (1 mL) was added **65-1A** (107 mg, 0.7 mmol, 2.0 *eq*). Then NaOH (52 mg, 1.3 mmol, 4.0 *eq*) in H₂O (1 mL) was added to the mixture. The solution was stirred at 70 °C for 4 hr. The residue was purified by Prep-HPLC to give the title compound (34.91 mg, 74.5 μmol, 22.7% yield, HCl salt). LCMS (ESI): RT = 1.050 min, mass calc. for C₂₁H₂₃F₃N₆O 432.19, m/z found 433.1 [M+H]⁺, ¹HNMR (400MHz, CHLOROFORM-*d*) δ 9.02 (s, 1H), 8.23 - 8.15 (m, 1H), 7.60 - 7.44 (m, 3H), 7.38 (t, *J*=7.1 Hz, 1H), 7.33 - 7.25 (m, 2H), 7.04 (t, *J*=7.4 Hz, 1H), 4.92 - 4.68 (m, 2H), 3.85 - 3.65 (m, 4H), 2.80 - 2.22 (m, 8H).

Example 64: ethyl 2-(3,5-dimethyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetate (Compound 66) and 2-(3,5-dimethyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetic acid (Compound 67)



Step 1: ethyl 2-(4-bromo-3,5-dimethyl-1H-pyrazol-1-yl)acetate

[00406] To a mixture of **66-1** (1.0 g, 5.7 mmol, 1.00 *eq*) and K₂CO₃ (1.6 g, 11.4 mmol, 2.00 *eq*) in DMF (10.0 mL), was added **66-2** (1.9 g, 11.4 mmol, 1.3 mL, 2.00 *eq*). The resulting mixture was stirred at 60 °C for 3 h. LCMS showed the reaction was complete. The mixture was diluted with

EtOAc (40 mL), washed with water (40 mL *5). The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated under vacuum. **66-3** (1.5 g, crude) was obtained.

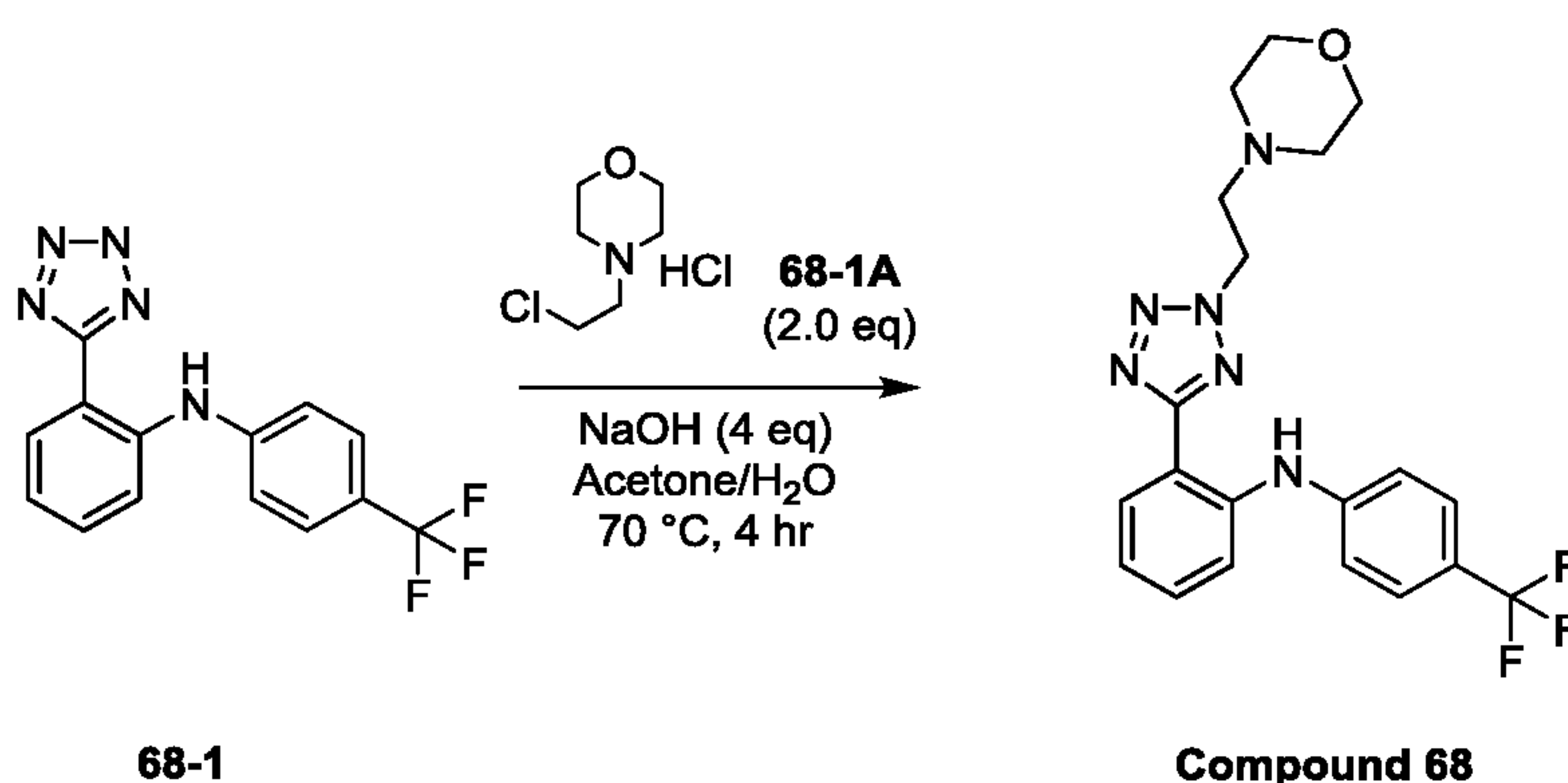
Step 2: 2-(3,5-dimethyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetate

[00407] To a mixture of **66-3** (258.8 mg, 1.0 mmol, 1.20 *eq*), **66-4** (300.0 mg, 0.8 mmol, 1.00 *eq*) and Na₂CO₃ (175.1 mg, 1.7 mmol, 2.00 *eq*) in 1,4-dioxane (4.0 mL) and H₂O (0.5 mL), was added Pd(dppf)Cl₂ (60.4 mg, 82.6 μmol, 0.10 *eq*). The mixture was degassed under vacuum and purged with N₂ 3 times. The resulting mixture was stirred at 100 °C under N₂ for 17 h. LCMS showed the reaction was complete. The mixture was concentrated under vacuum. The residue was purified by silica gel chromatography to afford **Compound 66** (0.3 g) and **Compound 67** (0.4 g).

[00408] Crude **Compound 66** was purified by prep-HPLC (acidic_HCl condition): 87.22 mg, 177.87 μmol, 21.53% yield, 2HCl salt. LCMS (ESI): RT = 1.277 min, mass calc. for C₂₂H₂₂F₃N₃O₂ 417.17, m/z found 418.1 [M+H]⁺. ¹HNMR (400MHz, CHLOROFORM-*d*) δ 7.66 (s, 3H), 7.53 (t, *J* = 6.5 Hz, 1H), 7.46 (s, 1H), 7.43 - 7.23 (m, 3H), 5.94 (s, 1H), 5.18 (s, 2H), 4.46 (d, *J* = 5.8 Hz, 2H), 2.37 (s, 3H), 2.28 (s, 3H), 1.55 - 1.44 (m, 3H).

[00409] Crude **Compound 67** was purified by prep-HPLC (acidic_TFA condition): 52.68 mg, 104.7 μmol, 12.7% yield, TFA salt. LCMS (ESI): RT = 1.172 min, mass calc. for C₂₀H₁₈F₃N₃O₂ 389.14, m/z found 390.0 [M+H]⁺. ¹HNMR (400MHz, METHANOL-*d*₄) δ 7.48 - 7.42 (m, 1H), 7.39 (d, *J* = 6.8 Hz, 2H), 7.36 - 7.29 (m, 1H), 7.23 - 7.17 (m, 1H), 7.12 (dd, *J* = 3.3, 6.0 Hz, 1H), 7.07 - 7.00 (m, 2H), 4.82 (s, 2H), 2.06 (s, 6H).

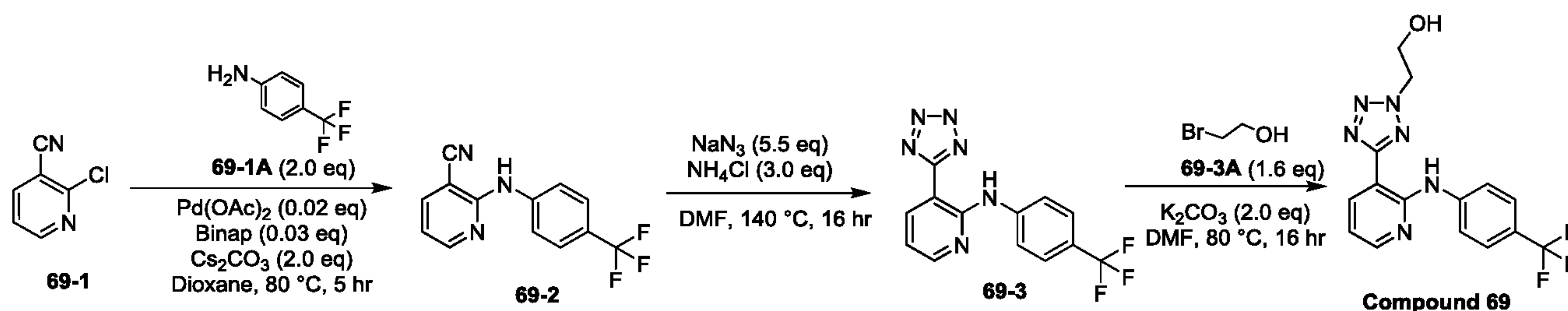
Example 65: 2-(2-(2-morpholinoethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 68)



[00410] To the solution of **68-1** (100 mg, 0.3 mmol, 1.0 *eq*) in acetone (1 mL) was added **68-1A** (122 mg, 0.7 mmol, 2.00 *eq*, HCl salt). Then NaOH (52 mg, 1.3 mmol, 4.0 *eq*) in H₂O (1 mL) was added to the mixture. The solution was stirred at 70 °C for 4 hr. The reaction was monitored by LCMS. The residue was purified by Prep-HPLC to give the title compound (33.76 mg, 72.0 μmol, 22.0% yield, HCl salt). LCMS (ESI): RT = 1.041 min, mass calc. for C₂₀H₂₁F₃N₆O 418.17, m/z

found 419.1 $[M+H]^+$, $^1\text{HNMR}$ (400MHz, $\text{CHLOROFORM-}d$) δ 9.08 (s, 1H), 8.21 (d, $J=7.8$ Hz, 1H), 7.59 - 7.50 (m, 3H), 7.41 - 7.26 (m, 3H), 7.05 (t, $J=7.4$ Hz, 1H), 4.82 (t, $J=6.3$ Hz, 2H), 3.71 - 3.60 (m, 4H), 3.05 (t, $J=6.4$ Hz, 2H), 2.59 - 2.49 (m, 4H).

Example 66: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)pyridin-3-yl)-2H-tetrazol-2-yl)ethanol (Compound 69)



Step 1: 2-((4-(trifluoromethyl)phenyl)amino)nicotinonitrile

[00411] To the solution of **69-1** (500 mg, 3.6 mmol, 1.0 *eq*) in dioxane (15 mL) was added **69-1A** (1.2 g, 7.2 mmol, 0.9 mL, 2.0 *eq*), $\text{Pd}(\text{OAc})_2$ (16 mg, 72 μmol , 0.02 *eq*), BINAP (67 mg, 0.1 mmol, 0.03 *eq*), Cs_2CO_3 (2.4 g, 7.2 mmol, 2.0 *eq*). The mixture was stirred at 80 °C for 5 hr under N_2 atmosphere. The reaction was monitored by LCMS. The reaction solution was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2) to give the yellow solid. The solid was dissolved in MeOH (4 mL). The solution was poured into H_2O (10 mL). The insoluble solid disappeared. The mixture was filtered. The solid was dried under reduced pressure to give **69-2** (960 mg, crude) as a yellow solid.

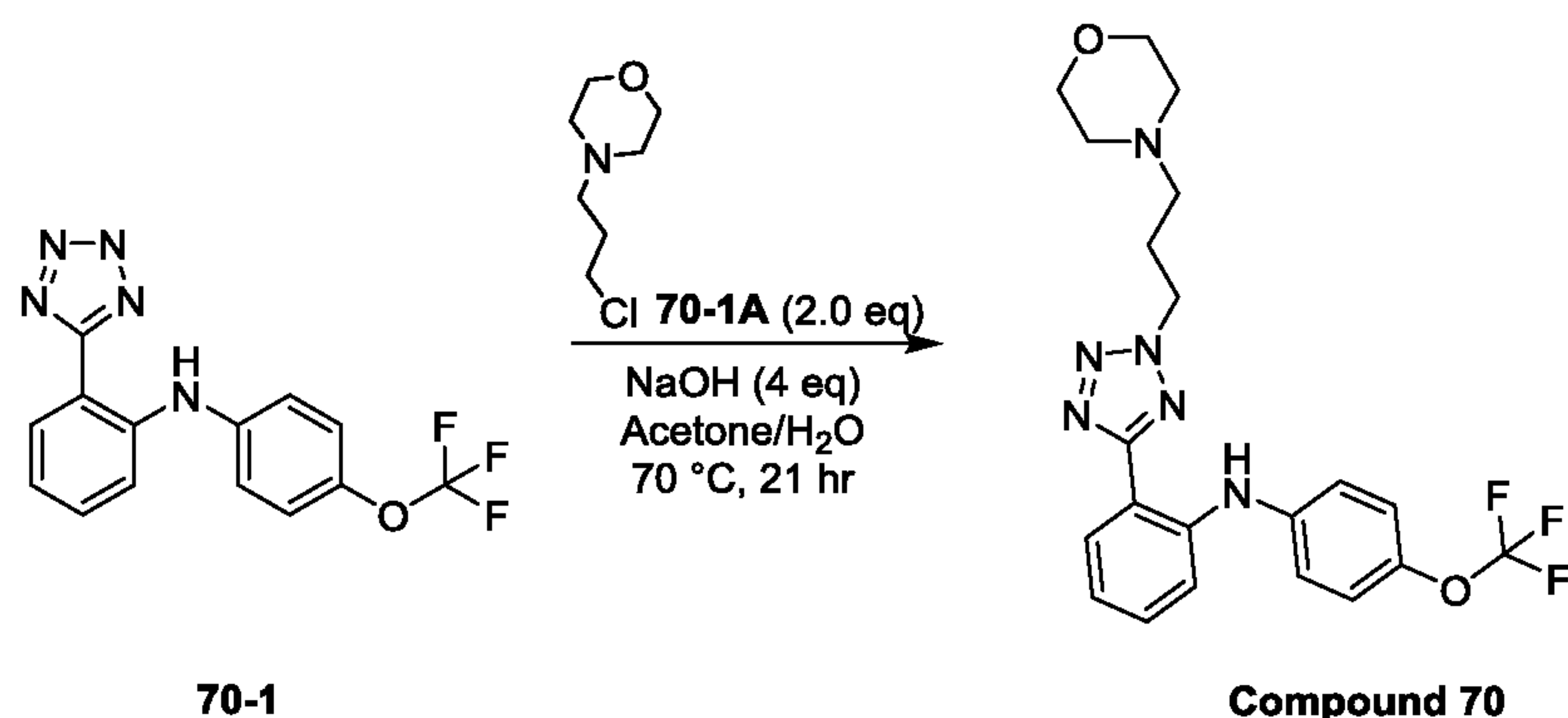
Step 2: 3-(2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-2-amine

[00412] To the solution of **69-2** (200 mg, 0.8 mmol, 1.0 *eq*) in DMF (2 mL) was added NaN_3 (270 mg, 4.2 mmol, 5.5 *eq*) and NH_4Cl (122 mg, 2.3 mmol, 3.0 *eq*). The mixture was stirred at 140 °C for 16 hr. The reaction was monitored with LCMS. The reaction solution was poured into HCl aqueous (1M, 15mL). The insoluble solid appeared. The mixture was filtered. The solid was washed with H_2O (20 mL) to give **69-3** (130 mg, 0.4 mmol, 56% yield).

Step 3: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)pyridin-3-yl)-2H-tetrazol-2-yl)ethanol

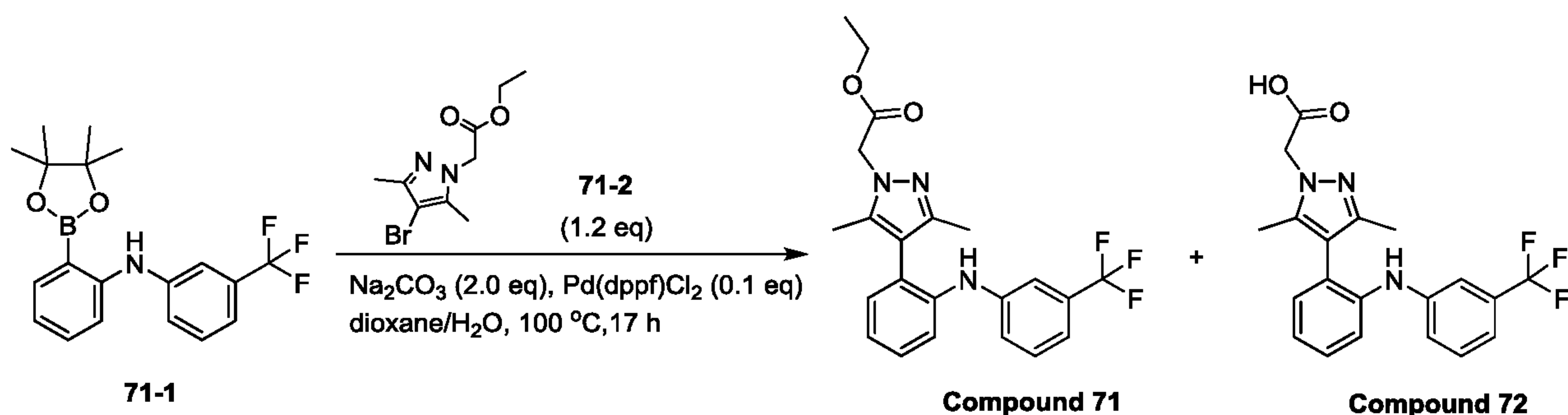
[00413] To the solution of **69-3** (130 mg, 0.4 mmol, 1.0 *eq*) in DMF (2 mL) was added **69-3A** (85 mg, 0.7 mmol, 48 μL , 1.6 *eq*) and K_2CO_3 (117 mg, 0.8 mmol, 2.0 *eq*). The mixture was stirred at 80 °C for 16 hr. The reaction was monitored by LCMS. The residue was purified by Prep-HPLC to give **Compound 69** (15.50 mg, 44.3 μmol , 10.4% yield). LCMS (ESI): RT = 3.142 min, mass calcd. for $\text{C}_{15}\text{H}_{13}\text{F}_3\text{N}_6\text{O}$ 350.11, m/z found 350.9 $[M+H]^+$, $^1\text{HNMR}$ (400MHz, $\text{DMSO-}d_6$) δ 9.95 (s, 1H), 8.48 - 8.40 (m, 2H), 7.99 (d, $J=8.5$ Hz, 2H), 7.67 (d, $J=8.5$ Hz, 2H), 7.15 - 7.07 (m, 1H), 4.86 (t, $J=5.1$ Hz, 2H), 4.01 (t, $J=5.1$ Hz, 2H).

Example 67: 2-(2-(3-morpholinopropyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethoxy)phenyl)aniline (Compound 70)



[00414] To the solution of **70-1** (100 mg, 0.3 mmol, 1.0 *eq*) in acetone (1 mL) was added **70-1A** (102 mg, 0.6 mmol, 2.0 *eq*). Then the solution of NaOH (50 mg, 1.3 mmol, 4.0 *eq*) in H₂O (1 mL) was added to the mixture. The solution was stirred at 70 °C for 21 hr. The reaction was monitored by LCMS. The residue was purified by Prep-HPLC to give the title compound (31.14 mg, 61.7 umol, 19.8% yield, HCl). LCMS (ESI): RT = 1.070 min, mass calcd. for C₂₁H₂₃F₃N₆O₂ 418.17, m/z found 448.18 [M+H]⁺, ¹HNMR (400MHz, CHLOROFORM-*d*) δ 13.20 (s, 1H), 8.13 (d, *J*=7.0 Hz, 1H), 7.39 - 7.14 (m, 6H), 7.00 - 6.91 (m, 1H), 5.06 - 4.75 (m, 2H), 4.37 - 3.81 (m, 4H), 3.62 - 2.60 (m, 8H).

Example 68: ethyl 2-(3,5-dimethyl-4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetate (Compound 71) and 2-(3,5-dimethyl-4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetic acid (Compound 72)



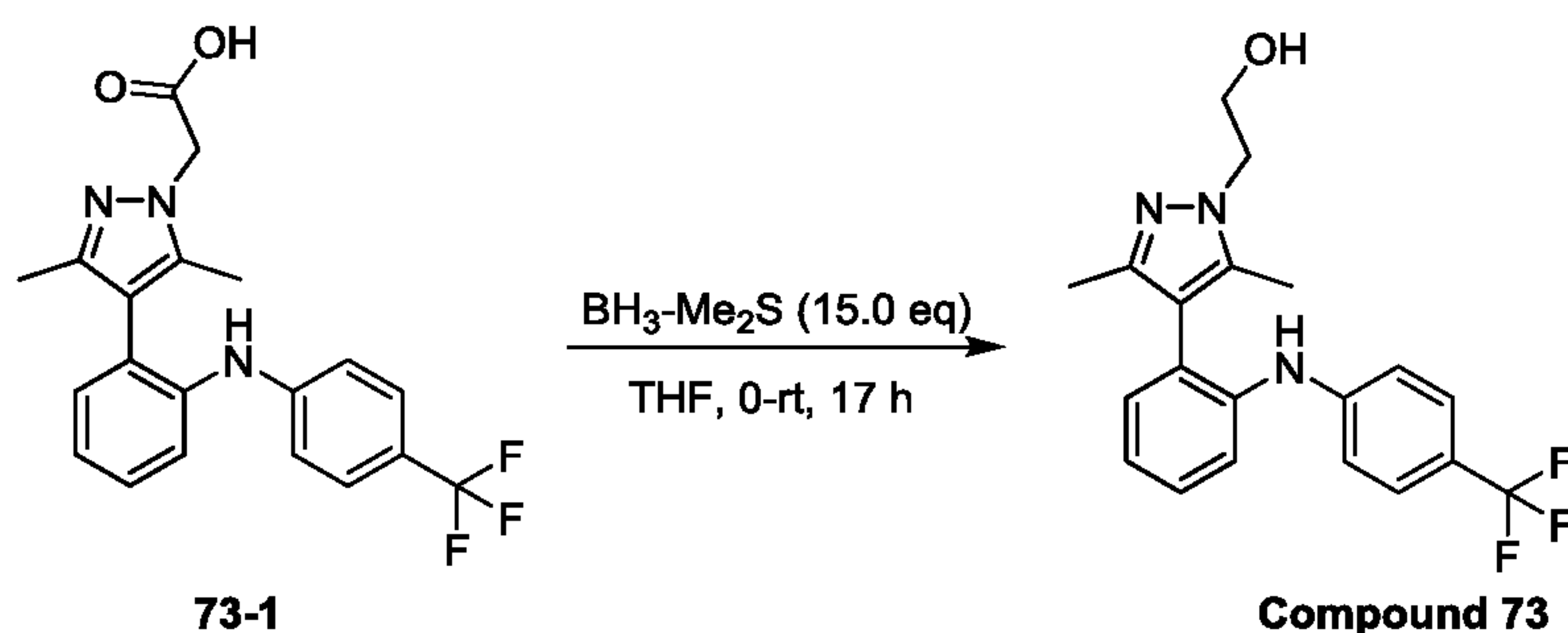
[00415] To a mixture of **71-1** (200.0 mg, 0.6 mmol, 1.00 *eq*), **72-2** (172.6 mg, 0.7 mmol, 1.20 *eq*) and Na₂CO₃ (116.7 mg, 1.1 mmol, 2.00 *eq*) in dioxane (4.0 mL) and H₂O (0.5 mL), was added Pd(dppf)Cl₂ (40.3 mg, 55.1 umol, 0.10 *eq*). The mixture was degassed under vacuum and purged with N₂ 3 times. The resulting mixture was stirred at 100 °C under N₂ for 17 h. LCMS showed the reaction was complete. The mixture was concentrated under vacuum. The residue was purified by silica gel chromatography to give **Compound 71** and **Compound 72**.

[00416] **Compound 71**: 8.63 mg, 18.8 umol, 3.4% yield, HCl salt. LCMS (ESI): RT = 1.267 min, mass calc. for C₂₂H₂₂F₃N₃O₂ 417.17, m/z found 418.5 [M+H]⁺. ¹HNMR (400MHz,

CHLOROFORM-*d*) δ 7.45 - 7.24 (m, 5H), 7.22 - 7.01 (m, 3H), 5.81 (s, 1H), 5.08 (s, 2H), 4.26 (d, J = 6.5 Hz, 2H), 2.21 (s, 3H), 2.12 (s, 3H), 1.31 (t, J = 6.0 Hz, 3H).

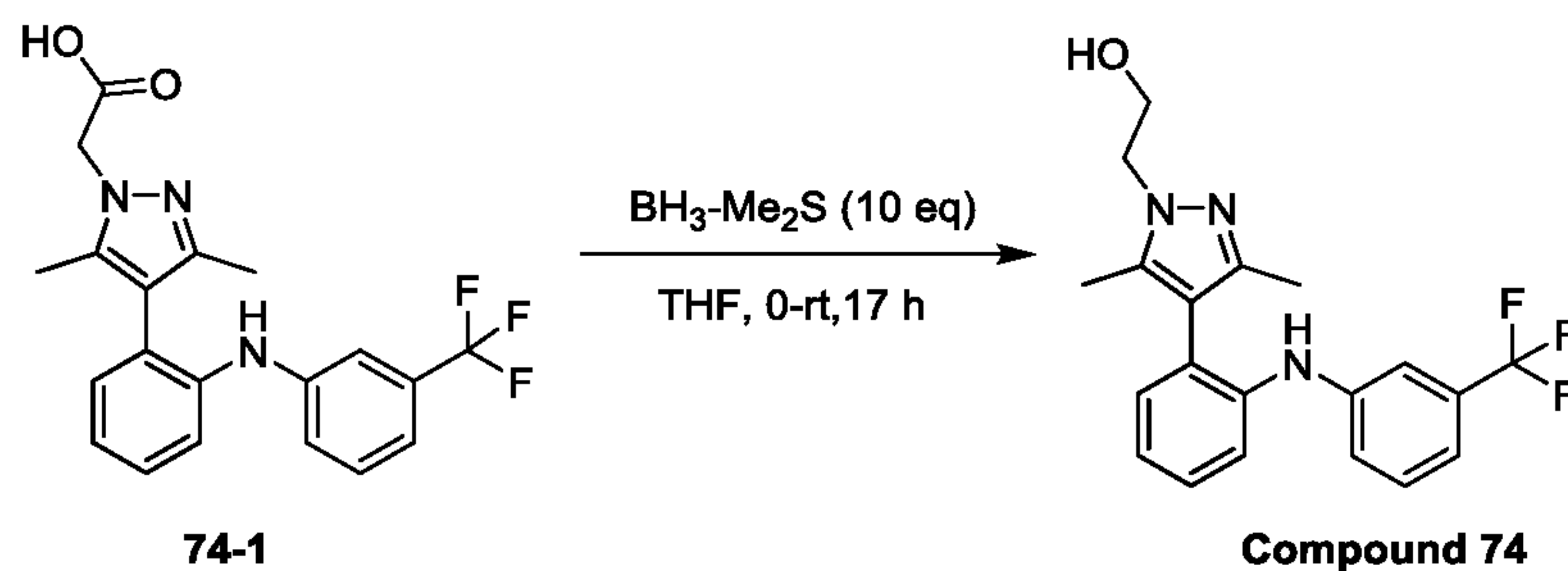
[00417] **Compound 72:** 46.98 mg, 110.3 μ mol, 20.0% yield, HCl salt. LCMS (ESI): RT = 1.166 min, mass calc. for $C_{20}H_{18}F_3N_3O_2$ 389.14, m/z found 390.0 $[M+H]^+$. ^1H NMR (400MHz, METHANOL-*d*₄) δ 7.46 - 7.39 (m, 2H), 7.35 - 7.29 (m, 1H), 7.28 - 7.25 (m, 1H), 7.21 - 7.12 (m, 2H), 7.08 - 7.01 (m, 2H), 5.13 (d, J = 3.3 Hz, 2H), 2.25 (s, 3H), 2.22 (s, 3H).

Example 69: 2-(3,5-dimethyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)ethanol (Compound 73)



[00418] To a mixture of **73-1** (40.0 mg, 0.1 mmol, 1.00 *eq*) in THF (5.0 mL), was added BH_3-Me_2S (10 M, 0.2 mL, 15.00 *eq*) at 0 °C. The resulting mixture was stirred at 26 °C for 17 h. LCMS showed the reaction was complete. The mixture was quenched with MeOH (5 mL). The mixture was concentrated under vacuum. The residue was diluted with water (10 mL), extracted with DCM (10 mL *3). The combined organic layers were dried over anhydrous Na_2SO_4 , and concentrated under vacuum. The residue was purified by prep-HPLC (acidic_HCl condition). The desired compound was combined with the previous batch and lyophilized to provide the title compound (25.59 mg, 68.17 μ mol, 66.36% yield). LCMS (ESI): RT = 1.147 min, mass calc. for $C_{20}H_{20}F_3N_3O$ 375.16, m/z found 376.1 $[M+H]^+$. ^1H NMR (400MHz, DMSO-*d*₆) δ 7.92 (s, 1H), 7.42 (d, J = 8.8 Hz, 2H), 7.40 - 7.30 (m, 2H), 7.23 - 7.18 (m, 1H), 7.16 - 7.08 (m, 1H), 6.98 (d, J = 8.5 Hz, 2H), 4.09 (q, J = 4.5 Hz, 2H), 3.66 (t, J = 5.6 Hz, 3H), 2.05 (s, 3H), 2.03 (s, 3H).

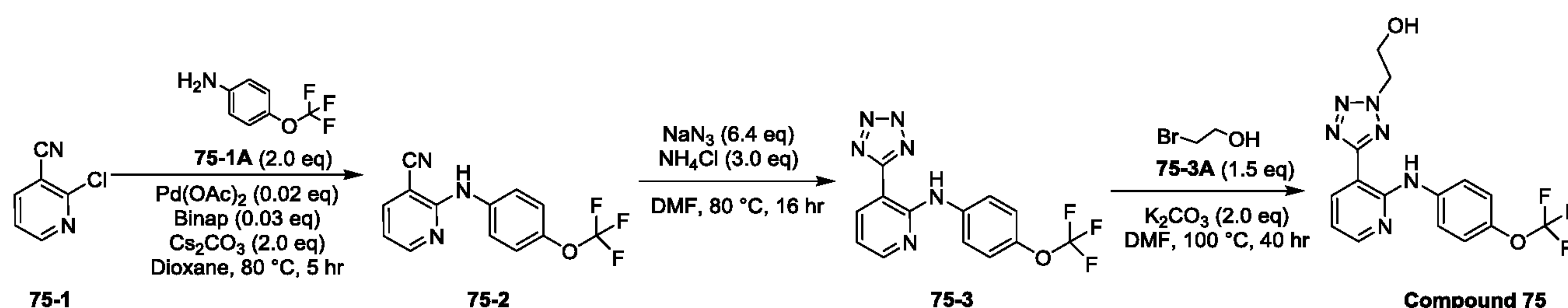
Example 70: 2-(3,5-dimethyl-4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)ethanol (Compound 74)



[00419] To a mixture of **74-1** (40.0 mg, 0.1 mmol, 1.00 *eq*) in THF (5.0 mL), was added BH_3-Me_2S (10 M, 102.7 μ L, 10.00 *eq*) at 0 °C. The resulting mixture was stirred at 22 °C for 17 h.

LCMS showed the reaction was complete. The mixture was quenched with MeOH (5 mL), and concentrated under vacuum. The residue was diluted with water (15 mL), and extracted with DCM (15 mL *3). The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated under vacuum. The residue was purified by prep-HPLC (acidic_HCl condition) to provide the title compound (15.22 mg, 37.0 μ mol, 36.0% yield, HCl salt). LCMS (ESI): RT = 0.777 min, mass calc. for C₂₀H₂₀F₃N₃O 375.16, m/z found 376.1 [M+H]⁺. ¹HNMR (400MHz, DMSO-*d*₆) δ 7.86 (s, 1H), 7.37 - 7.31 (m, 3H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.14 (s, 1H), 7.12 - 7.07 (m, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 4.16 (d, *J* = 2.3 Hz, 2H), 3.69 (t, *J* = 5.4 Hz, 2H), 2.10 (s, 3H), 2.08 (s, 3H).

Example 71: 2-(5-(2-((4-(trifluoromethoxy)phenyl)amino)pyridin-3-yl)-2H-tetrazol-2-yl)ethanol (Compound 75)



Step 1: 2-((4-(trifluoromethoxy)phenyl)amino)nicotinonitrile

[00420] To the solution of **75-1** (500 mg, 3.6 mmol, 1.0 *eq*) in dioxane (15 mL) was added **75-1A** (1.28 g, 7.2 mmol, 976 μ L, 2.0 *eq*), Pd(OAc)₂ (16 mg, 72 μ mol, 0.02 *eq*), BINAP (67 mg, 0.1 mmol, 0.03 *eq*), Cs₂CO₃ (2.35 g, 7.2 mmol, 2.0 *eq*). The mixture was stirred at 80 °C for 5 hr under N₂ atmosphere. The reaction was monitored by LCMS. The reaction solution was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂) to give a yellow solid. The solid was dissolved in MeOH (4 mL). The solution was poured into H₂O (10 mL). The insoluble solid disappeared. The mixture was filtered. The solid was dried under reduced pressure to give **75-2** (560 mg, 2.0 mmol, 56% yield).

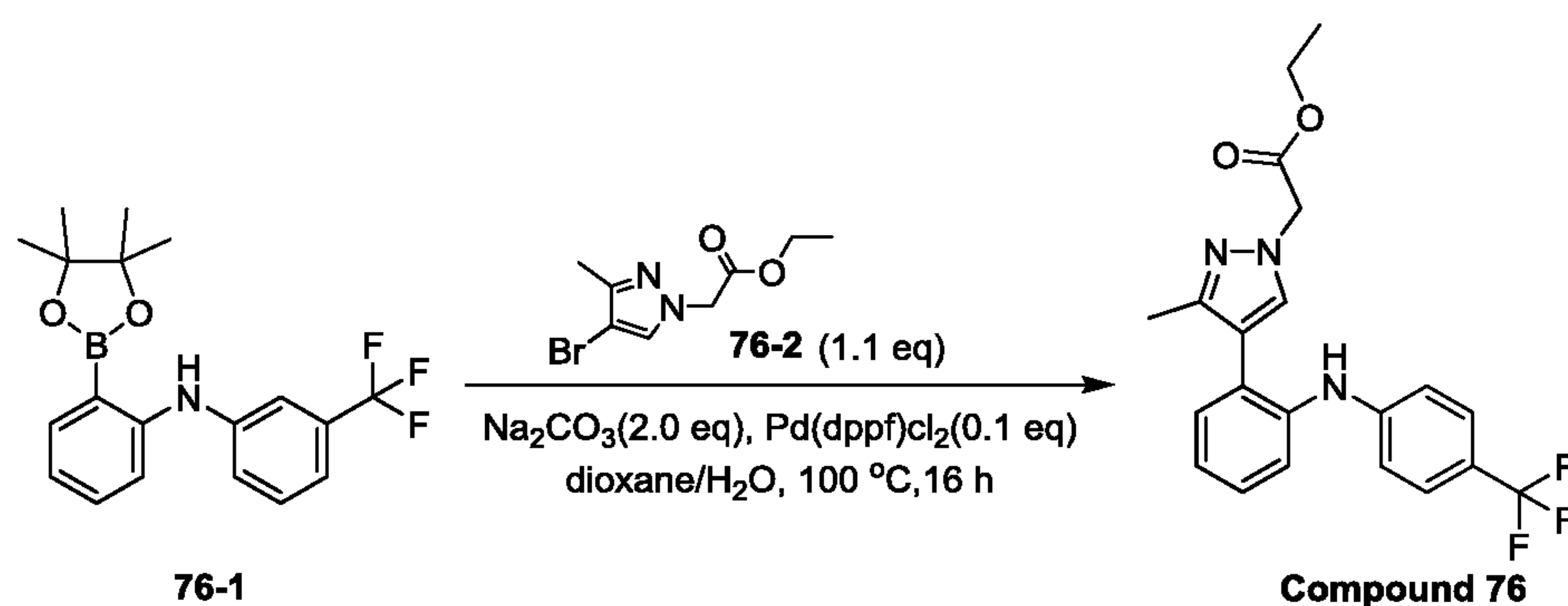
Step 2: 3-(2H-tetrazol-5-yl)-N-(4-(trifluoromethoxy)phenyl)pyridin-2-amine

[00421] To the solution of **75-2** (200 mg, 0.7 mmol, 1.0 *eq*) in DMF (2 mL) was added NaN₃ (300 mg, 4.6 mmol, 6.4 *eq*) and NH₄Cl (115 mg, 2.2 mmol, 75 μ L, 3.0 *eq*). The mixture was stirred at 140 °C for 16 hr. The reaction was monitored by LCMS. The reaction solution was poured into aqueous HCl (1M, 15 mL). The mixture was extracted with EtOAc (15 mL*4). The combined organic layers were dried with Na₂SO₄, and concentrated under reduced pressure to give **75-3** (231 mg, 0.7 mmol, 100.00% yield) in DMF as a yellow solution.

Step 3: 2-(5-(2-((4-(trifluoromethoxy)phenyl)amino)pyridin-3-yl)-2H-tetrazol-2-yl)ethanol

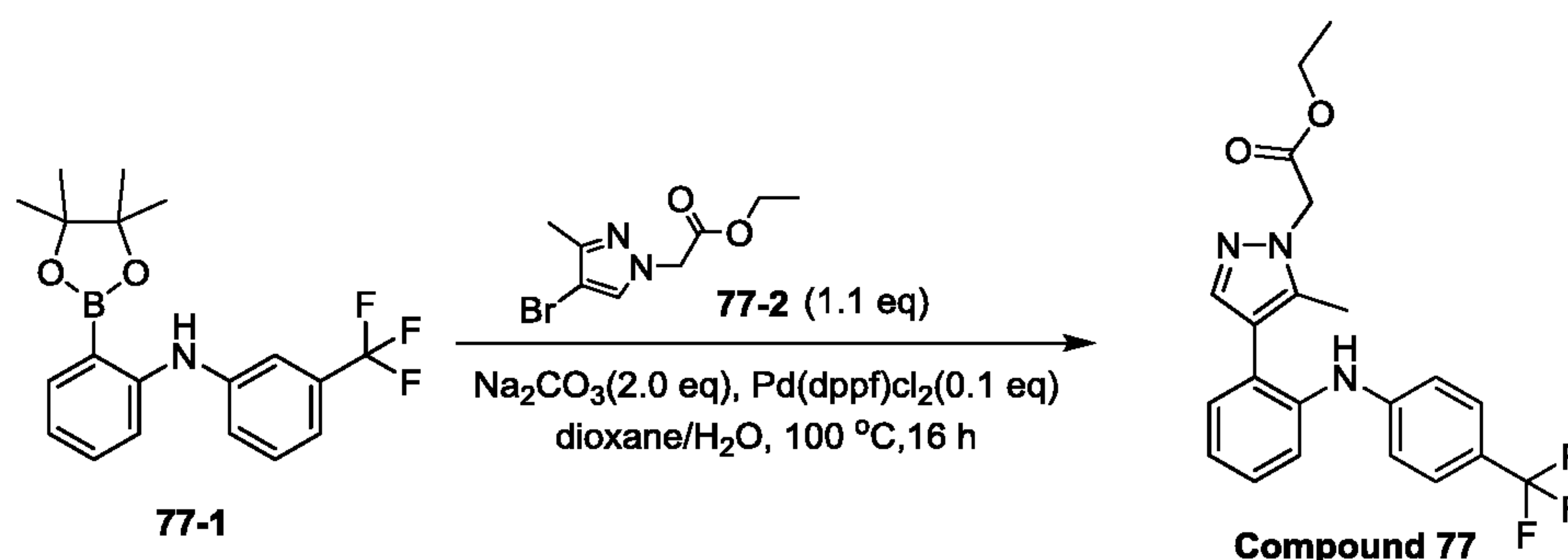
[00422] To the solution of **75-3** (230 mg, 0.7 mmol, 1.0 *eq*) in DMF (2 mL) was added **75-3A** (134 mg, 1.1 mmol, 76 μ L, 1.5 *eq*) and K_2CO_3 (197 mg, 1.4 mmol, 2.0 *eq*). The mixture was stirred at 100 °C for 40 hr. The reaction was monitored by LCMS. LCMS showed that most of the starting material was remaining, and only a small amount of the desired MS was observed. The reaction time was prolonged. LCMS showed that the starting material was consumed and the main peak was the desired MS. The residue was purified by Prep-HPLC to give **Compound 75** (63.60 mg, 173.63 μ mol, 24.33% yield). LCMS (ESI): RT = 1.118 min, mass calc. for $C_{15}H_{13}F_3N_6O_2$ 366.11, m/z found 367.0 $[M+H]^+$, ^1H NMR (400MHz, $DMSO-d_6$) δ 9.76 (s, 1H), 8.49 - 8.43 (m, 1H), 8.39 - 8.35 (m, 1H), 7.87 (d, $J=9.0$ Hz, 2H), 7.35 (d, $J=8.5$ Hz, 2H), 7.09 - 7.01 (m, 1H), 4.86 (t, $J=5.1$ Hz, 2H), 4.02 - 3.99 (m, 2H).

Example 72: ethyl 2-[3-methyl-4-[2-[4-(trifluoromethyl)anilino]phenyl]pyrazol-1-yl]acetate (Compound 76)



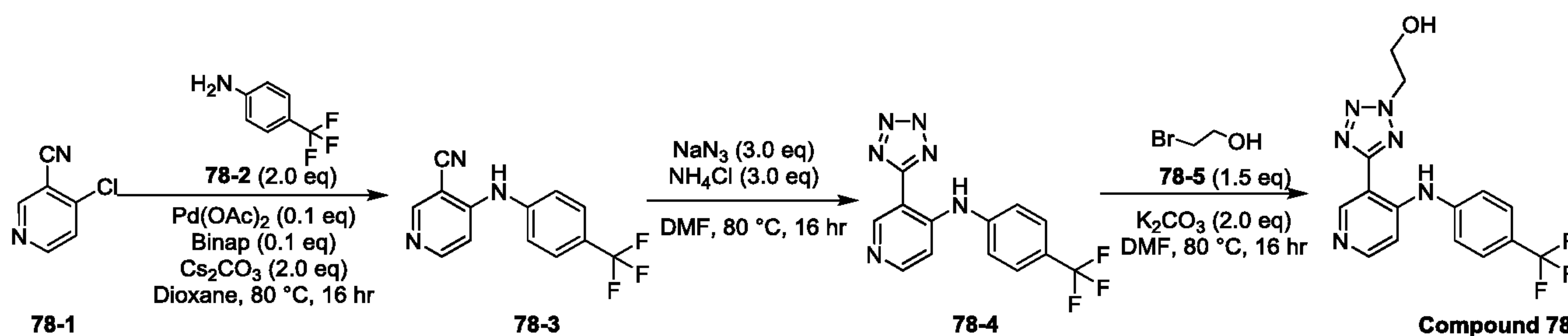
[00423] To a solution of **76-1** (400.0 mg, 1.1 mmol, 1.0 *eq*) and **76-2** (326.2 mg, 1.3 mmol, 1.2 *eq*) in dioxane (5.0 mL) was added H_2O (500.00 μ L) $Pd(dppf)Cl_2$ (80.49 mg, 0.11 mmol, 0.1 *eq*) and Na_2CO_3 (233.2 mg, 2.2 mmol, 2.0 *eq*). The mixture was stirred at 100 °C for 16 hour under N_2 atmosphere. LCMS showed the desired compound was formed. TLC (5% ethyl acetate in petroleum ether) showed the starting material remained and new spots appeared. The reaction was filtered through celite and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography over silica gel and further purified by prep-HPLC to obtain the title compound (7.08 mg, 17.20 μ mol, 1.56% yield). LCMS (ESI): RT = 0.874 min, mass calc. for $C_{21}H_{20}F_3N_3O_2$ 403.15, m/z found 404.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3-d$) δ 7.49 - 7.42 (m, 4H), 7.33 - 7.27 (m, 2H), 7.09 - 7.03 (m, 3H), 5.80 (s, 1H), 4.86 (s, 2H), 4.26 (q, $J=7.0$ Hz, 2H), 2.17 (s, 3H), 1.30 (t, $J=7.0$ Hz, 3H).

Example 73: ethyl 2-[5-methyl-4-[2-[4-(trifluoromethyl)anilino]phenyl]pyrazol-1-yl]acetate (Compound 77)



[00424] To a solution of 77-1 (400.0 mg, 1.1 mmol, 1.0 *eq*) and 77-2 (326.2 mg, 1.3 mmol, 1.2 *eq*) in dioxane (5.0 mL) was added H_2O (500.00 μL) Pd(dppf)Cl_2 (80.49 mg, 0.11 mmol, 0.1 *eq*) and Na_2CO_3 (233.2 mg, 2.2 mmol, 2.0 *eq*). The mixture was stirred at 100 °C for 16 hour under N_2 atmosphere. LCMS showed the desired compound was formed and TLC was used to monitor the reaction. The reaction was filtered through celite and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography over silica gel and further purified by prep-HPLC and then prep-SFC to obtain the title compound (2.93 mg, 7.26 μmol , 0.66% yield). LCMS (ESI): RT = 0.876 min, mass calc. for $\text{C}_{21}\text{H}_{20}\text{F}_3\text{N}_3\text{O}_2$ 403.15, m/z found 404.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3 -*d*) δ 7.52 (s, 1H), 7.46 (dd, $J=3.1, 8.4$ Hz, 3H), 7.33 - 7.27 (m, 1H), 7.24 (d, $J=1.5$ Hz, 1H), 7.10 - 7.03 (m, 3H), 5.80 (s, 1H), 4.90 (s, 2H), 4.26 (q, $J=7.3$ Hz, 2H), 2.11 (s, 3H), 1.30 (t, $J=7.2$ Hz, 3H).

Example 74: 2-[5-[4-[4-(trifluoromethyl)anilino]-3-pyridyl]tetrazol-2-yl]ethanol (Compound 78)



Step 1: 4-[4-(trifluoromethyl)anilino]pyridine-3-carbonitrile

[00425] To a solution of 78-1 (500.0 mg, 3.6 mmol, 1.0 *eq*), 78-2 (581.5 mg, 3.6 mmol, 0.45 mL, 1.0 *eq*) and Cs_2CO_3 (1.2 g, 3.6 mmol, 1.0 *eq*) in dioxane (10.0 mL) was added BINAP (224.7 mg, 0.36 mmol, 0.1 *eq*) and palladium acetate (81.0 mg, 0.36 mmol, 0.1 *eq*). The resulting mixture was stirred at 100 °C under N_2 for 15 hour. LCMS showed the desired compound was formed and the starting material was consumed completely. TLC (30% ethyl acetate in petroleum ether, $R_f = 0.4$) showed the starting material was consumed and a new spot appeared. The reaction mixture was concentrated. The crude residue was dissolved in CH_2Cl_2 (25 mL) and washed with water (2×15 mL). After drying over anhydrous Na_2SO_4 , the solvent was removed under reduced pressure to

afford the crude product. The crude product was purified by column chromatography over silica gel to provide **78-3** (620.0 mg, 2.4 mmol, 65.3% yield). LCMS (ESI): RT = 0.575 min, mass calc. for $C_{13}H_8F_3N_3$ 263.07, m/z found 263.8 $[M+H]^+$.

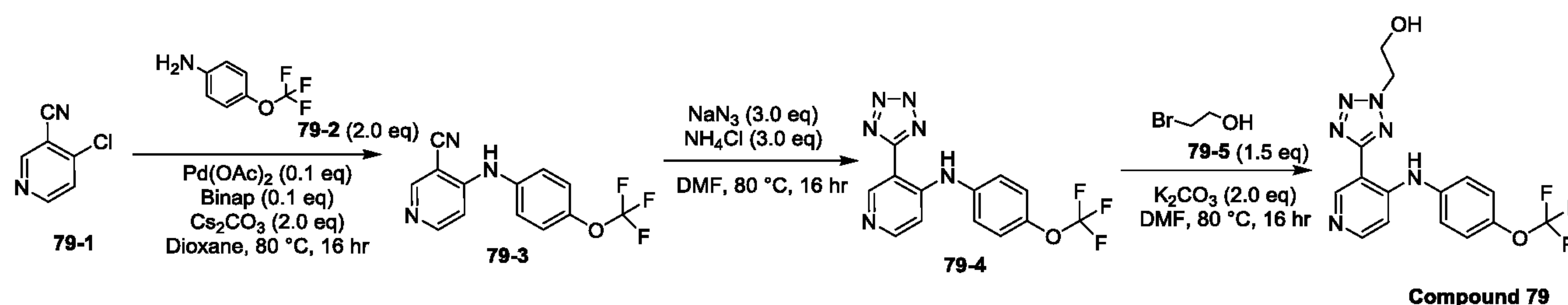
Step 2: 3-(2H-tetrazol-5-yl)-N-[4-(trifluoromethyl)phenyl]pyridin-4-amine

[00426] To a solution of **78-3** (620.0 mg, 2.4 mmol, 1.0 eq) in DMF (15.0 mL) was added NH_4Cl (378.7 mg, 7.1 mmol, 0.25 mL, 3.0 eq) and NaN_3 (460.3 mg, 7.1 mmol, 3.0 eq). The mixture was stirred at 140 °C for 16 hour under an N_2 atmosphere. LCMS showed the desired compound was formed. The reaction mixture was poured into sat. aq. $NaHCO_3$ (5 mL) and extracted with EtOAc (5 mL*2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 , and filtered. The solvent was removed under reduced pressure to afford crude **78-4** (500.0 mg, 1.6 mmol, 69.1% yield). LCMS (ESI): RT = 0.647 min, mass calc. for $C_{13}H_9F_3N_6$ 306.08, m/z found 306.8 $[M+H]^+$;

Step 3: 2-[5-[4-[4-(trifluoromethyl)anilino]-3-pyridyl]tetrazol-2-yl]ethanol

[00427] To a solution of **78-4** (100.0 mg, 0.33 mmol, 1.0 eq) in DMF (5.0 mL) was added K_2CO_3 (90.3 mg, 0.65 mmol, 2.0 eq) and **78-5** (48.9 mg, 0.39 mmol, 27.8 μL , 1.2 eq). The mixture was stirred at 100 °C for 3 hour under an N_2 atmosphere. LCMS showed the desired compound was formed. The reaction was filtered to give a crude product. The crude product was purified by prep-HPLC to give **Compound 78** (16.50 mg, 47.10 μmol , 14.43% yield). LCMS (ESI): RT = 0.631 min, mass calc. for $C_{15}H_{13}F_3N_6O$ 350.10, m/z found 350.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3-d$) δ 9.61 (s, 1H), 9.03 (s, 1H), 8.08 (d, $J=6.0$ Hz, 1H), 7.58 (d, $J=8.5$ Hz, 2H), 7.29 (d, $J=8.3$ Hz, 2H), 7.12 (d, $J=6.0$ Hz, 1H), 4.91 - 4.86 (m, 2H), 4.38 - 4.33 (m, 2H).

Example 75: 2-[5-[4-[4-(trifluoromethoxy)anilino]-3-pyridyl]tetrazol-2-yl]ethanol (Compound 79)



Step 1: 4-[4-(trifluoromethoxy)anilino]pyridine-3-carbonitrile

[00428] To a solution of **79-1** (300.0 mg, 2.2 mmol, 1.0 eq), **79-2** (384.4 mg, 2.2 mmol, 0.29 mL, 1.0 eq) and palladium acetate (48.7 mg, 0.22 mmol, 0.1 eq) in dioxane (8.0 mL) was added BINAP (135.1 mg, 0.22 mmol, 0.1 eq) and Cs_2CO_3 (707.0 mg, 2.2 mmol, 1.0 eq). The resulting mixture was stirred at 100 °C under N_2 for 15 hour. LCMS showed the desired compound was formed and

the starting material was consumed completely. TLC (30% ethyl acetate in petroleum ether, $R_f = 0.4$) showed the starting material was consumed and a new spot appeared. The reaction mixture was concentrated. The crude product residue was dissolved in CH_2Cl_2 (25 mL) and washed with water (2×15 mL). After drying over anhydrous Na_2SO_4 , the solvent was removed under reduced pressure to afford the crude product. The crude product was purified by column chromatography over silica gel to give **79-3** (400.0 mg, 1.4 mmol, 65.9% yield). LCMS (ESI): RT = 0.573 min, mass calc. for $\text{C}_{13}\text{H}_8\text{F}_3\text{N}_3\text{O}$ 279.06, m/z found 279.9 $[\text{M}+\text{H}]^+$.

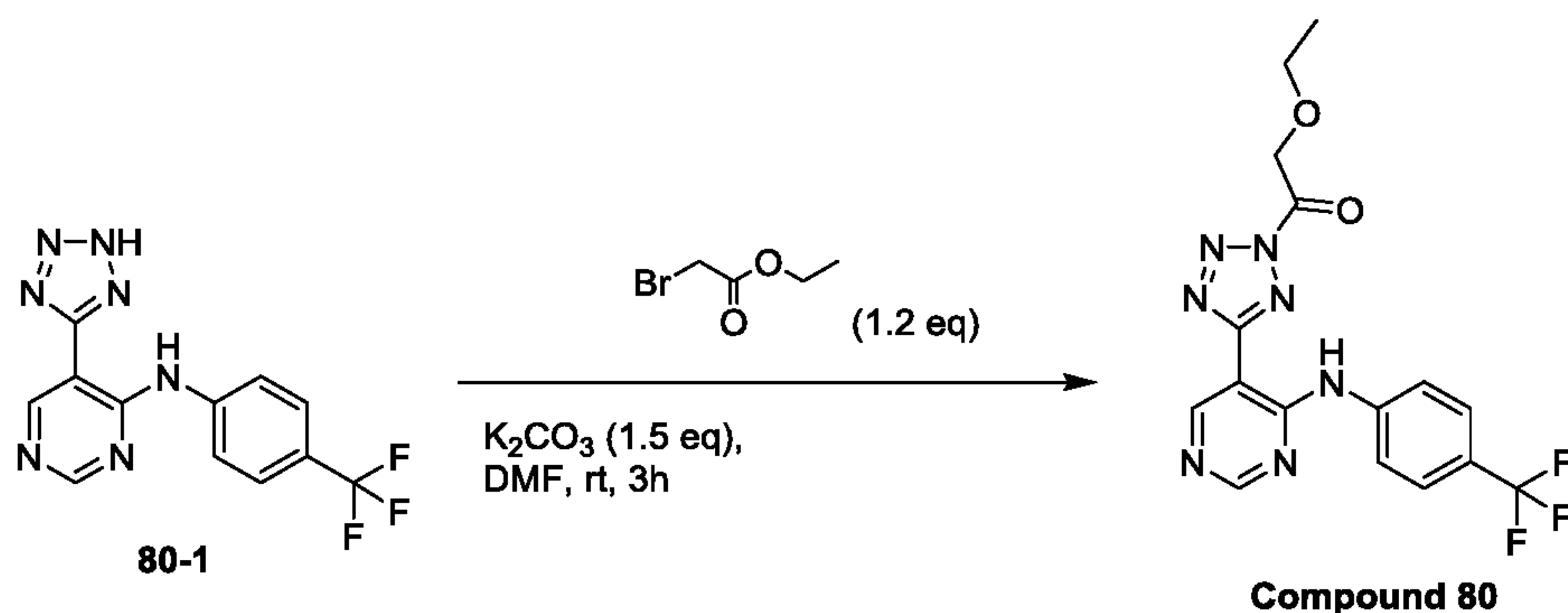
Step 2: 3-(2H-tetrazol-5-yl)-N-[4-(trifluoromethoxy)phenyl]pyridin-4-amine

[00429] To a solution of **79-3** (400.0 mg, 1.4 mmol, 1.0 *eq*) in DMF (10.0 mL) was added NH_4Cl (229.9 mg, 4.3 mmol, 0.15 mL, 3.0 *eq*) and NaN_3 (464.8 mg, 7.2 mmol, 5.0 *eq*). The mixture was stirred at 140 °C for 16 hour under an N_2 atmosphere. LCMS showed the desired compound was formed. The reaction mixture was poured into sat. aq. NaHCO_3 (5 mL) and extracted with EtOAc (5 mL*2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 , and filtered. The solvent was removed under reduced pressure to afford the crude **79-4** (300.0 mg, 0.93 mmol, 65.1% yield). LCMS (ESI): RT = 0.661 min, mass calc. for $\text{C}_{13}\text{H}_9\text{F}_3\text{N}_6\text{O}$ 322.08, m/z found 322.9 $[\text{M}+\text{H}]^+$.

Step 3: 2-[5-[4-[4-(trifluoromethoxy)anilino]-3-pyridyl]tetrazol-2-yl]ethanol

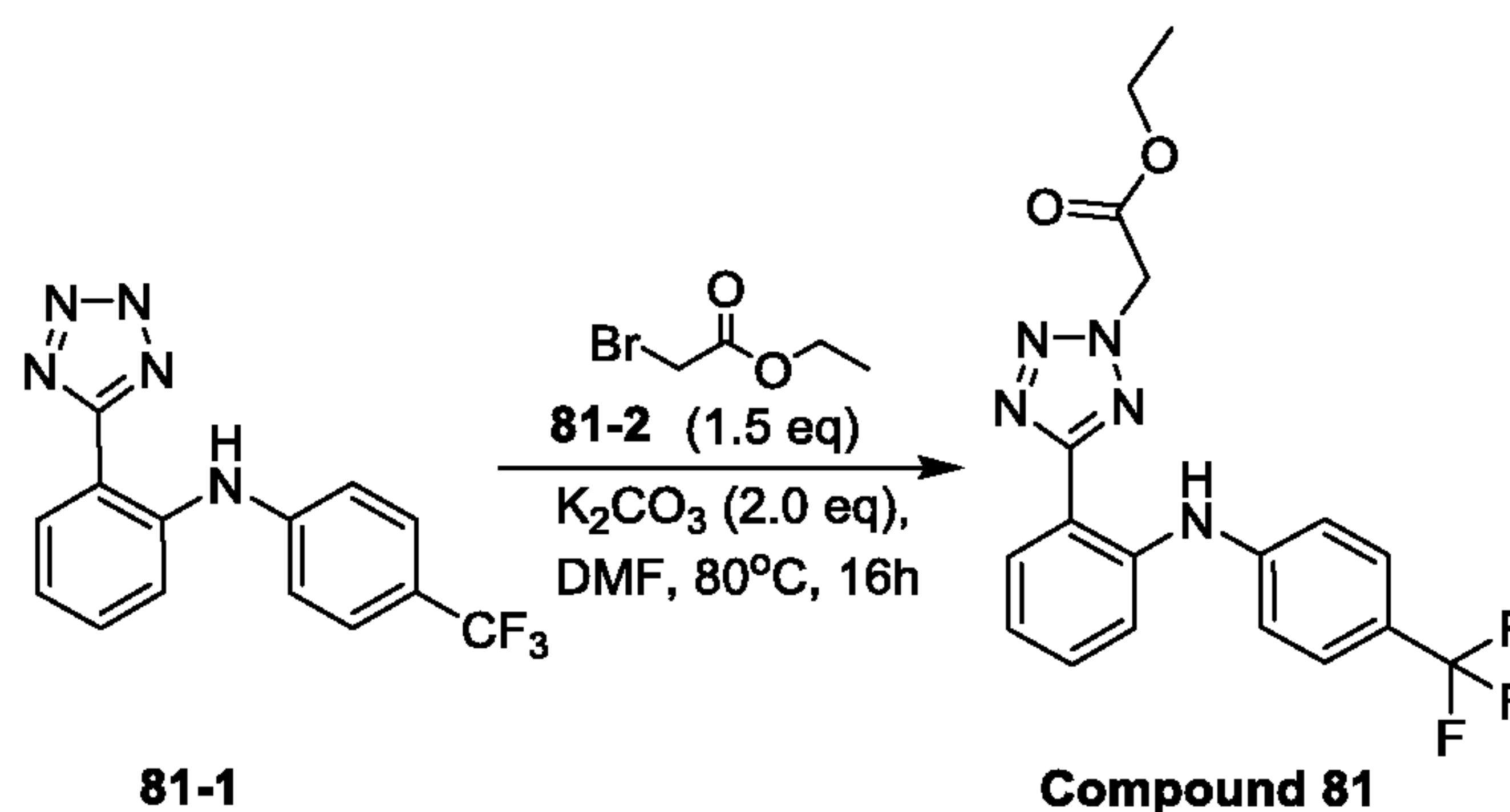
[00430] To a solution of **79-4** (100.0 mg, 0.31 mmol, 1.0 *eq*) in DMF (5.0 mL) was added K_2CO_3 (85.8 mg, 0.62 mmol, 2.0 *eq*) and **79-5** (46.5 mg, 0.37 mmol, 26.4 μL , 1.2 *eq*). The mixture was stirred at 100 °C for 3 hour under an N_2 atmosphere. LCMS showed the desired compound was formed. The reaction was filtered to give a crude product. The crude product was purified by prep-HPLC to give **Compound 79** (6.03 mg, 16.46 μmol , 5.30% yield). LCMS (ESI): RT = 0.644 min, mass calc. for $\text{C}_{15}\text{H}_{13}\text{F}_3\text{N}_6\text{O}_2$ 366.11, m/z found 367.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3 -*d*) δ 9.40 (s, 1H), 9.05 (s, 1H), 8.08 (d, $J=6.0$ Hz, 1H), 7.25 (d, $J=3.5$ Hz, 4H), 6.97 (d, $J=6.0$ Hz, 1H), 4.91 - 4.86 (m, 2H), 4.36 - 4.32 (m, 2H).

Example 76: ethyl 2-[5-[4-[4-(trifluoromethyl)anilino]pyrimidin-5-yl]tetrazol-2-yl]acetate (Compound 80)



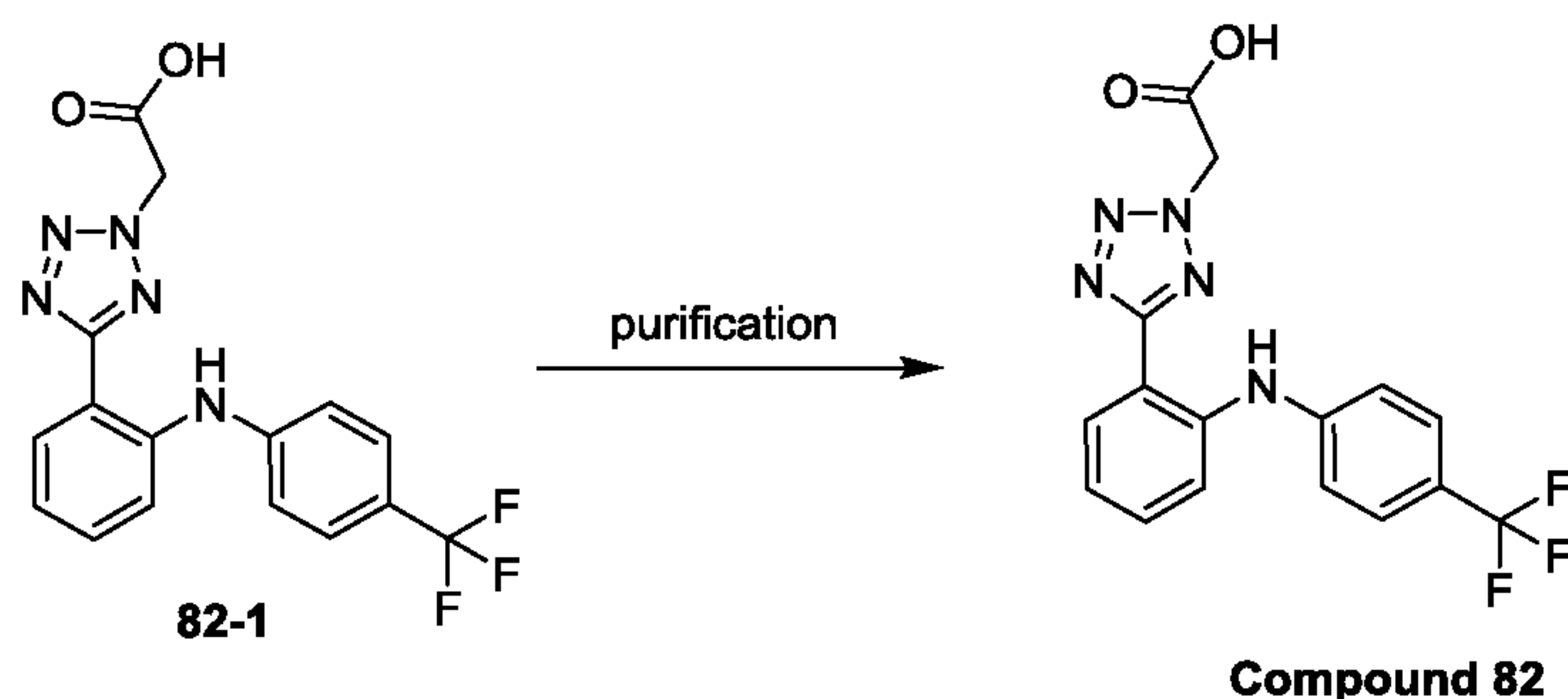
[00431] To a solution of **80-1** (50 mg, 0.16 mmol, 1.00 *eq*) and K₂CO₃ (33.7 mg, 0.24 mmol, 1.50 *eq*) in DMF (2 mL) was added ethyl 2-bromoacetate (32.6 mg, 0.20 mmol, 21.60 uL, 1.20 *eq*). The resulting mixture was stirred at 25°C for 1 hr. LCMS showed that ~40% of the desired MS signal was detected. To the reaction was added water (5 mL), and the mixture was extracted with EtOAc (2*10 mL). The combined organic extracts were washed with brine (2*10 mL), dried over Na₂SO₄, and concentrated. The residue was purified by CombiFlash to give the title compound (23 mg, 52.04 umol, 31.98% yield). LCMS (ESI): RT = 2.074 min, mass calc. for C₁₆H₁₄N₇O₂F₃ 393.12, m/z found 394.0 [M+H]⁺; ¹HNMR (400 MHz, DMSO) δ9.93 (s, 1 H), 9.17 (s, 1 H), 8.88 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 1 H), 7.78 (d, *J* = 8.4 Hz, 1 H), 6.06 (s, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.26 (t. *J* = 6.8 Hz, 3H).

Example 77: ethyl 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)acetate (Compound 81)



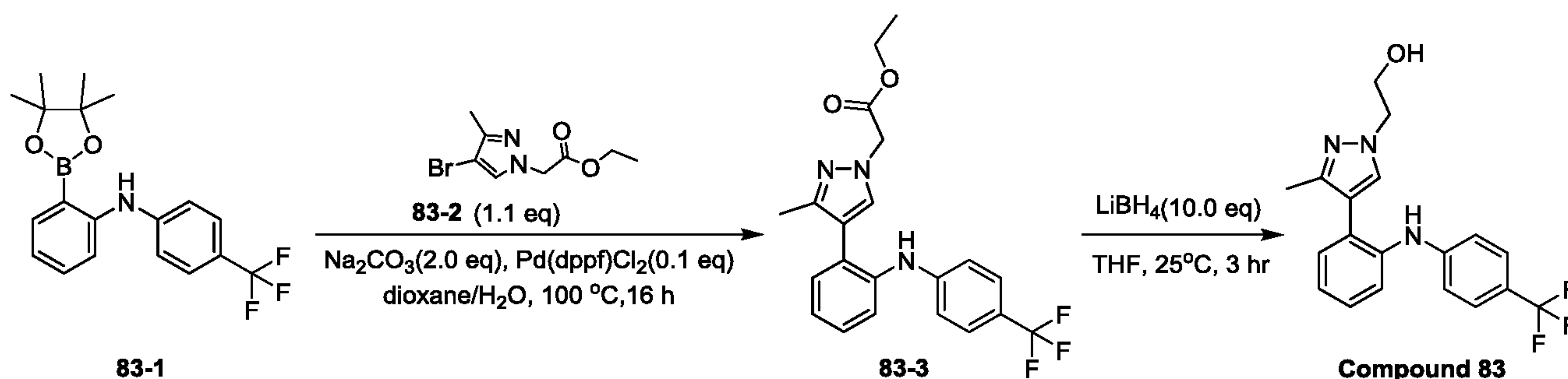
[00432] To a solution of **81-1** (50.0 mg, 0.16 mmol, 1.0 *eq*) in DMF (5.0 mL) was added K₂CO₃ (34.0 mg, 0.25 mmol, 1.5 *eq*) and **81-2** (32.8 mg, 0.20 mmol, 21.7 uL, 1.2 *eq*). The mixture was stirred at 80 °C for 16 hour under an N₂ atmosphere. LCMS showed the desired compound was formed. The reaction was filtered to give a crude product. The crude product was purified by prep-HPLC to give the title compound (8.03 mg, 19.90 umol, 12.15% yield). LCMS (ESI): RT = 0.926 min, mass calc. for C₁₈H₁₆F₃N₅O₂ 391.13, m/z found 392.1 [M+H]⁺; ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.75 (s, 1H), 8.05 (dd, *J*=1.1, 7.7 Hz, 1H), 7.59 - 7.47 (m, 4H), 7.26 - 7.17 (m, 3H), 5.90 (s, 2H), 4.20 (q, *J*=7.2 Hz, 2H), 1.21 (t, *J*=7.2 Hz, 3H).

Example 78: 2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetic acid (Compound 82)



[00433] A solution of **82-1** (10.0 mg, 27.5 μmol , 1.0 *eq*) in DMF (2.0 mL). LCMS showed the desired compound was formed. The reaction was filtered to give a crude product. The crude product was purified by prep-HPLC to give the title compound (2.78 mg, 7.65 μmol , 27.79% yield). LCMS (ESI): RT = 0.836 min, mass calc. for $\text{C}_{16}\text{H}_{12}\text{F}_3\text{N}_5\text{O}_2$ 363.09, m/z found 364.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.79 (s, 1H), 8.06 (dd, $J=1.3, 7.8$ Hz, 1H), 7.59 - 7.53 (m, 3H), 7.52 - 7.47 (m, 1H), 7.25 (d, $J=8.5$ Hz, 2H), 7.21 - 7.16 (m, 1H), 5.77 (s, 2H).

Example 79: 2-[3-methyl-4-[2-[4-(trifluoromethyl)anilino]phenyl]pyrazol-1-yl]ethanol (Compound 83)



Step 1: ethyl 2-[3-methyl-4-[2-[4-(trifluoromethyl)anilino]phenyl]pyrazol-1-yl]acetate

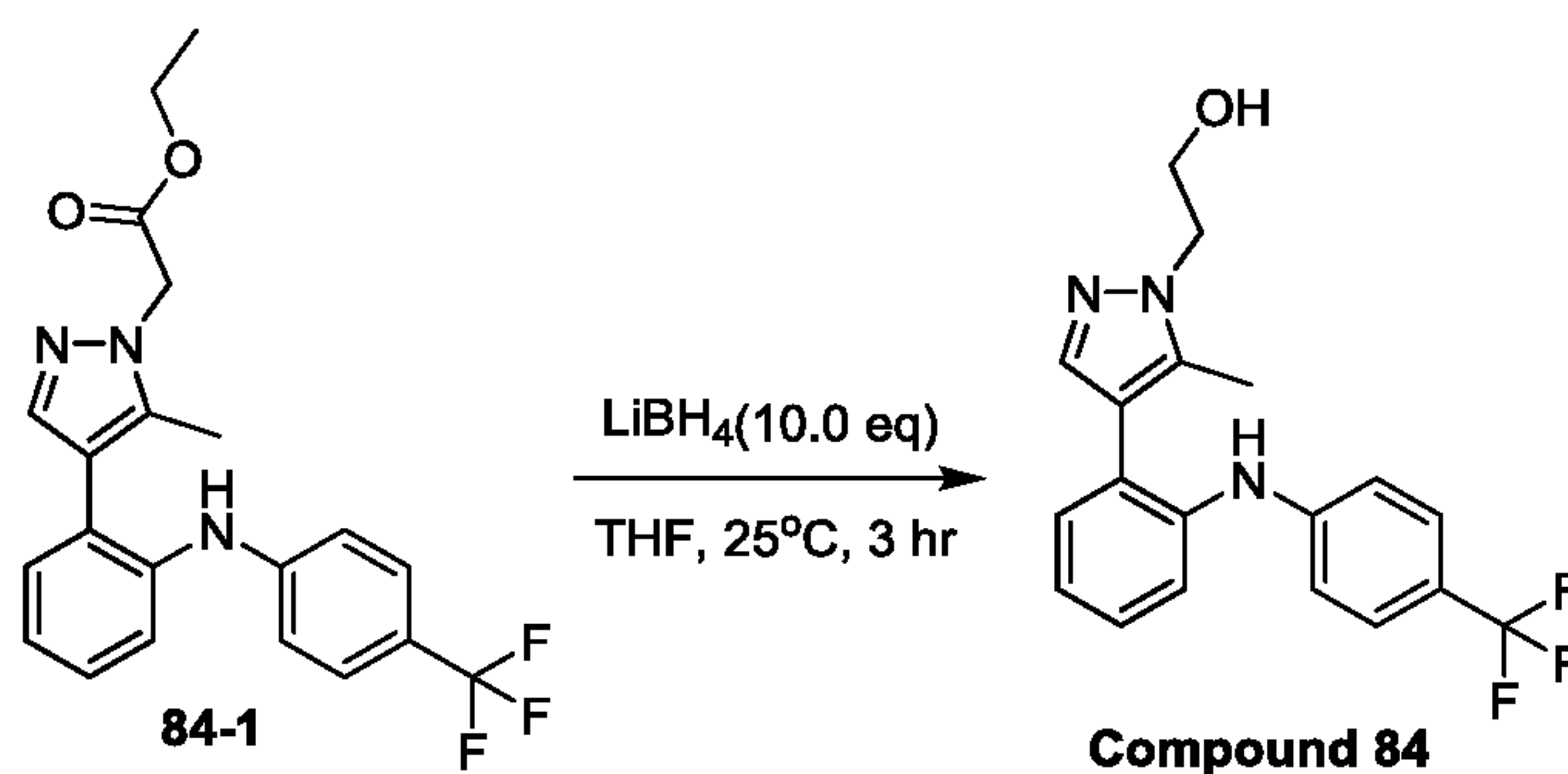
[00434] To a solution of **83-1** (400.0 mg, 1.1 mmol, 1.0 *eq*) and **83-2** (326.6 mg, 1.3 mmol, 1.2 *eq*) in dioxane (5.0 mL) was added H_2O (0.5 mL), $\text{Pd}(\text{dppf})\text{Cl}_2$ (80.6 mg, 0.11 mmol, 0.1 *eq*) and Na_2CO_3 (233.5 mg, 2.2 mmol, 2.0 *eq*). The mixture was stirred at 100 °C for 16 hour under N_2 atmosphere. LCMS showed the desired compound was formed. TLC (5% ethyl acetate in petroleum ether) showed the starting material remained and new spots appeared. The reaction was filtered through celite and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography over silica gel to give **83-3** (150.0 mg, 0.37 mmol, 33.8% yield). LCMS (ESI): RT = 0.843 min, mass calc. for $\text{C}_{21}\text{H}_{20}\text{F}_3\text{N}_3\text{O}_2$ 403.15, m/z found 404.0 $[\text{M}+\text{H}]^+$.

Step 2: 2-[3-methyl-4-[2-[4-(trifluoromethyl)anilino]phenyl]pyrazol-1-yl]ethanol

[00435] To a solution of **83-3** (150.0 mg, 0.37 mmol, 1.0 *eq*) in THF (4.0 mL) was added LiBH_4 (81.0 mg, 3.7 mmol, 10.0 *eq*). The resulting mixture was stirred at 20 °C for 3 hours. LCMS

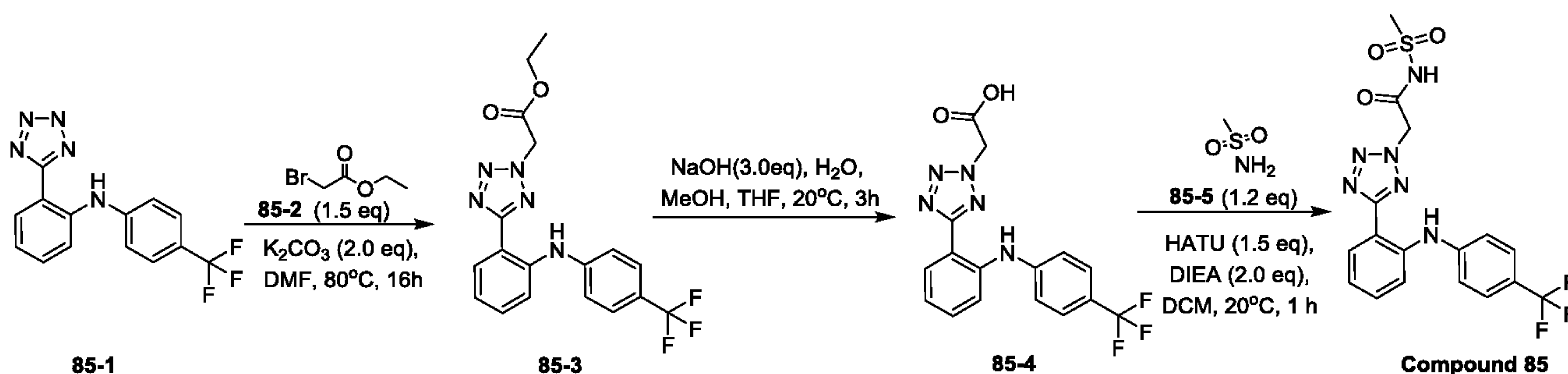
showed the desired compound was found and the starting material was consumed completely. The reaction mixture was treated dropwise with aq. NH_4Cl (5 mL) and extracted with EtOAc (5 mL*2). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , and filtered. The solvent was removed under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC and then purified by prep-SFC to give **Compound 83** (8.89 mg, 24.60 μmol , 6.62% yield). LCMS (ESI): RT = 0.795 min, mass calc. for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{N}_3\text{O}$ 361.14, m/z found 362.1 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.86 (s, 1H), 7.62 (s, 1H), 7.41 (d, $J=8.5$ Hz, 2H), 7.36 - 7.32 (m, 1H), 7.30 - 7.24 (m, 2H), 7.16 - 7.10 (m, 1H), 6.93 (d, $J=8.5$ Hz, 2H), 4.80 (t, $J=5.5$ Hz, 1H), 4.01 (t, $J=5.8$ Hz, 2H), 3.67 (q, $J=5.7$ Hz, 2H), 2.04 (s, 3H).

Example 80: 2-[5-methyl-4-[2-[4-(trifluoromethyl)anilino]phenyl]pyrazol-1-yl]ethanol (Compound 84)



[00436] To a solution of **84-1** (150.0 mg, 0.37 mmol, 1.0 *eq*) in THF (4.0 mL) was added LiBH_4 (81.0 mg, 3.7 mmol, 10.0 *eq*). The resulting mixture was stirred at 20 °C for 3 hours. LCMS showed the desired compound was found and the starting material was consumed completely. The reaction mixture was treated dropwise with aq. NH_4Cl (5 mL) and extracted with EtOAc (5 mL*2). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , and filtered. The solvent was removed under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC and then purified by prep-SFC to give the title compound (7.51 mg, 20.78 μmol , 5.59% yield). LCMS (ESI): RT = 0.799 min, mass calc. for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{N}_3\text{O}$ 361.14, m/z found 362.1 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.88 (s, 1H), 7.41 (d, $J=8.5$ Hz, 2H), 7.38 - 7.33 (m, 2H), 7.32 - 7.28 (m, 1H), 7.26 (d, $J=7.8$ Hz, 1H), 7.19 - 7.13 (m, 1H), 6.92 (d, $J=8.5$ Hz, 2H), 4.84 (t, $J=5.6$ Hz, 1H), 4.05 (t, $J=5.9$ Hz, 2H), 3.66 (q, $J=5.8$ Hz, 2H), 2.11 (s, 3H).

Example 81: N-methylsulfonyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetamide (Compound 85)



Step 1: ethyl 2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetate

[00437] To a solution of **85-1** (400.0 mg, 1.3 mmol, 1.0 eq) in DMF (5.0 mL) was added K_2CO_3 (362.1 mg, 2.6 mmol, 2.0 eq) and **85-2** (437.5 mg, 2.6 mmol, 0.29 mL, 2.0 eq). The mixture was stirred at 80 °C for 16 hours under an N_2 atmosphere. LCMS showed the desired compound was formed. TLC (Petroleum ether : Ethyl acetate=3/1) showed a new spot, and the starting material was consumed completely. The reaction mixture was concentrated to give the crude product. The crude product was purified by column chromatography over silica gel to give **85-3** (350.00 mg, 894.34 μ mol, 68.27% yield). LCMS (ESI): RT = 0.914 min, mass calc. for $C_{18}H_{16}F_3N_5O_2$ 391.13, m/z found 392.1 $[M+H]^+$.

Step 2: 2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetic acid

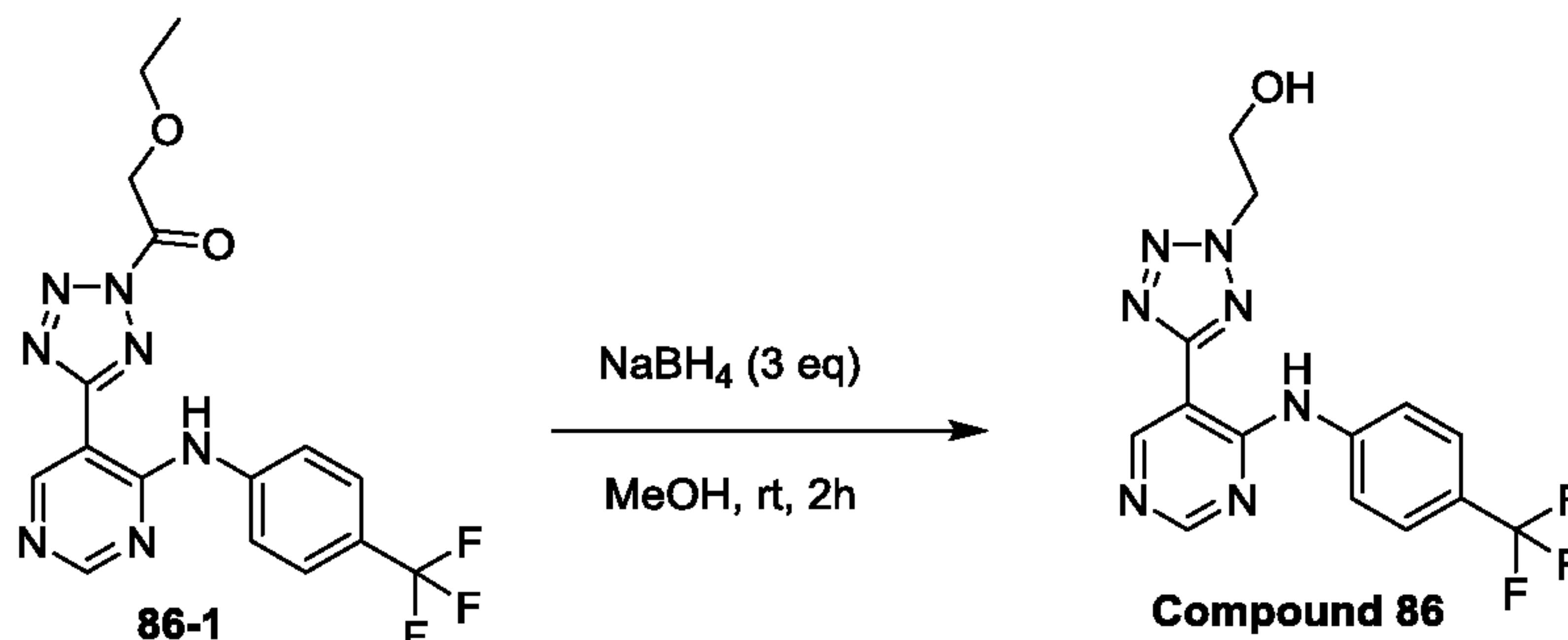
[00438] To a solution of **85-3** (350.0 mg, 0.89 mmol, 1.0 eq) in H_2O (2.0 mL) and MeOH (4.0 mL) was added NaOH (107.0 mg, 26.8 mmol, 29.9 eq). The resulting mixture was stirred at 25 °C for 4 hr. LCMS showed the desired compound was formed. TLC (Petroleum ether : Ethyl acetate=3/1) showed the starting material was consumed and a new spot appeared. The reaction solvent was removed under reduced pressure and water (5 mL) was added. The reaction was acidified by adding 1M HCl (10mL) to precipitate a solid. The solid was washed with EtOAc (20mL x 2). The combined organic layers were concentrated to give **85-4** (200.0 mg, 0.55 mmol, 61.6% yield). LCMS (ESI): RT = 0.831 min, mass calc. for $C_{16}H_{12}F_3N_5O_2$ 363.09, m/z found 363.9 $[M+H]^+$.

Step 3: N-methylsulfonyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetamide

[00439] To a solution of **85-4** (30.0 mg, 82.6 μ mol, 1.0 eq) and **85-5** (11.8 mg, 0.12 mmol, 1.5 eq) in DCM (5.0 mL) was added HATU (31.4 mg, 82.6 μ mol, 1.0 eq) and DIEA (32.0 mg, 0.25 mmol, 43.3 μ L, 3.0 eq). The resulting mixture was stirred at 20 °C for 1 hour. LCMS showed the desired compound was formed. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC to give **Compound 85** (5.07 mg, 11.51 μ mol, 13.94% yield). LCMS (ESI): RT = 0.826 min, mass calc. for $C_{17}H_{15}F_3N_6O_3S$ 440.09, m/z found 441.0 $[M+H]^+$; ^1H NMR (400 MHz, $DMSO-d_6$) δ 8.89 (s, 1H), 8.08 (dd, $J=1.3, 7.7$ Hz, 1H),

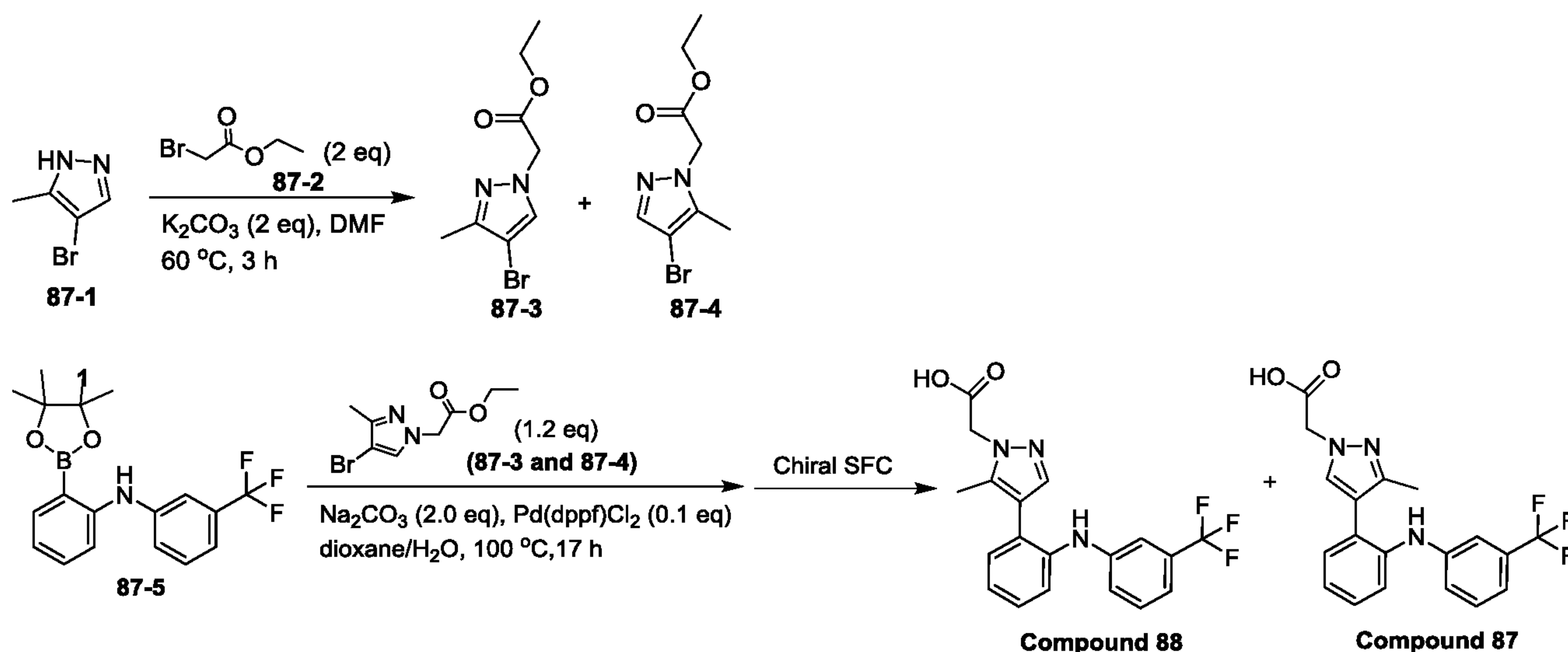
7.56 (t, $J=8.0$ Hz, 3H), 7.50 - 7.44 (m, 1H), 7.29 (d, $J=8.4$ Hz, 2H), 7.18 - 7.14 (m, 1H), 7.05 (d, $J=18.7$ Hz, 1H), 5.29 (s, 2H), 2.80 (s, 3H).

Example 82: 2-(5-(4-((4-(trifluoromethyl)phenyl)amino)pyrimidin-5-yl)-2H-tetrazol-2-yl)ethan-1-ol (Compound 86)



[00440] To a solution of **86-1** (20 mg, 50.85 μ mol, 1.00 *eq*) in MeOH (1 mL) was added NaBH₄ (5.77 mg, 0.15 mmol, 3.00 *eq*). The resulting mixture was stirred at 25°C for 2hr. LCMS showed that desired MS signal was detected. The reaction was diluted with EtOAc (10 mL) and washed with water (2*5 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by Prep-HPLC (HCl condition) to give **Compound 86** (4.84 mg, 13.78 μ mol, 27.09% yield). LCMS (ESI): RT = 1.874 min, mass calc. for C₁₄H₁₂N₇OF₃ 351.12, m/z found 351.9 [M+H]⁺; ¹HNMR (400 MHz, DMSO) δ 10.20 (s, 1 H), 9.17 (s, 1 H), 8.93 (s, 1H), 8.00 (d, $J = 8.4$ Hz, 1 H), 7.79 (d, $J = 8.4$ Hz, 1 H), 4.89 (t, $J = 5.2$ Hz, 2H), 4.02 (t, $J = 5.2$ Hz, 2H).

Example 83: 2-(3-methyl-4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetic acid (Compound 87) and 2-(5-methyl-4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetic acid (Compound 88)



Step 1: ethyl 2-(4-bromo-3-methyl-1H-pyrazol-1-yl)acetate and ethyl 2-(4-bromo-5-methyl-1H-pyrazol-1-yl)acetate

[00441] To a mixture **87-1** (1.0 g, 6.2 mmol, 1.00 *eq*) and K₂CO₃ (1.7 g, 12.4 mmol, 2.00 *eq*) in DMF (10.0 mL), was added **87-2** (2.1 g, 12.4 mmol, 1.4 mL, 2.00 *eq*). The resulting mixture was stirred at 60 °C for 3 h. LCMS showed the reaction was complete. The mixture was diluted with EtOAc (40 mL), washed with water (40 mL *5). The organic layer was dried over anhydrous Na₂SO₄, and concentrated under vacuum. A mixture of **87-3** and **87-4** (1.6 g, crude) was obtained.

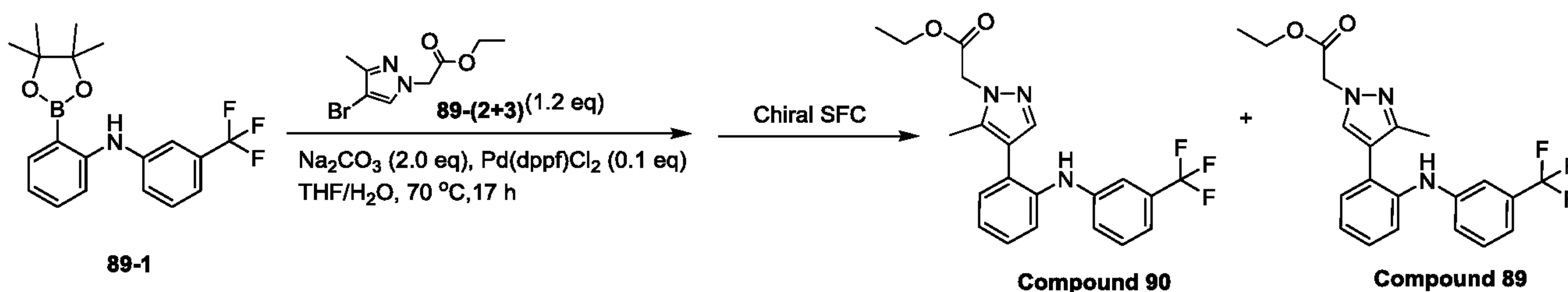
Step 2: 2-(5-methyl-4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetic acid and 2-(3-methyl-4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetic acid

[00442] To a mixture of **87-3** and **87-4** (409.2 mg, 1.7 mmol, 1.20 *eq*), **5** (500.0 mg, 1.4 mmol, 1.00 *eq*), and Na₂CO₃ (292.5 mg, 2.8 mmol, 2.00 *eq*) in dioxane (8.0 mL) and H₂O (1.0 mL), was added Pd(dppf)Cl₂ (101.0 mg, 0.1 mmol, 0.10 *eq*). The mixture was degassed under vacuum and purged with N₂ 3 times. The resulting mixture was stirred at 100 °C under N₂ for 17 h. LCMS showed the reaction was complete. The mixture was concentrated under vacuum. The residue was purified by silica gel chromatography to afford the crude product, which was then purified by prep-HPLC (acidic_HCl condition). The mixture of **Compound 87** and **Compound 88** was separated by chiral SFC.

[00443] **Compound 87**: 27.43 mg, 66.50 μmol, 41.6% yield. LCMS (ESI): RT = 0.794 min, mass calc. for C₁₉H₁₆F₃N₃O₂ 375.12, m/z found 376.0 [M+H]⁺. ¹H NMR (400MHz, DMSO-*d*₆) δ 7.67 (d, *J*=2.3 Hz, 2H), 7.34 - 7.22 (m, 4H), 7.15 - 7.07 (m, 3H), 6.96 (br d, *J*=7.3 Hz, 1H), 4.70 (s, 2H), 2.03 (s, 3H).

[00444] **Compound 88**: 12.33 mg, 29.57 μmol, 18.5% yield. LCMS (ESI): RT = 0.803 min, mass calc. for C₁₉H₁₆F₃N₃O₂ 375.12, m/z found 376.0 [M+H]⁺. ¹H NMR (400MHz, DMSO-*d*₆) δ 7.68 (s, 1H), 7.36 - 7.31 (m, 1H), 7.31 - 7.26 (m, 2H), 7.24 (d, *J* = 6.8 Hz, 1H), 7.15 - 7.08 (m, 2H), 7.06 (s, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 4.72 (s, 2H), 2.07 (s, 3H).

Example 84: ethyl 2-(3-methyl-4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetate (Compound 89) and ethyl 2-(5-methyl-4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)acetate (Compound 90)



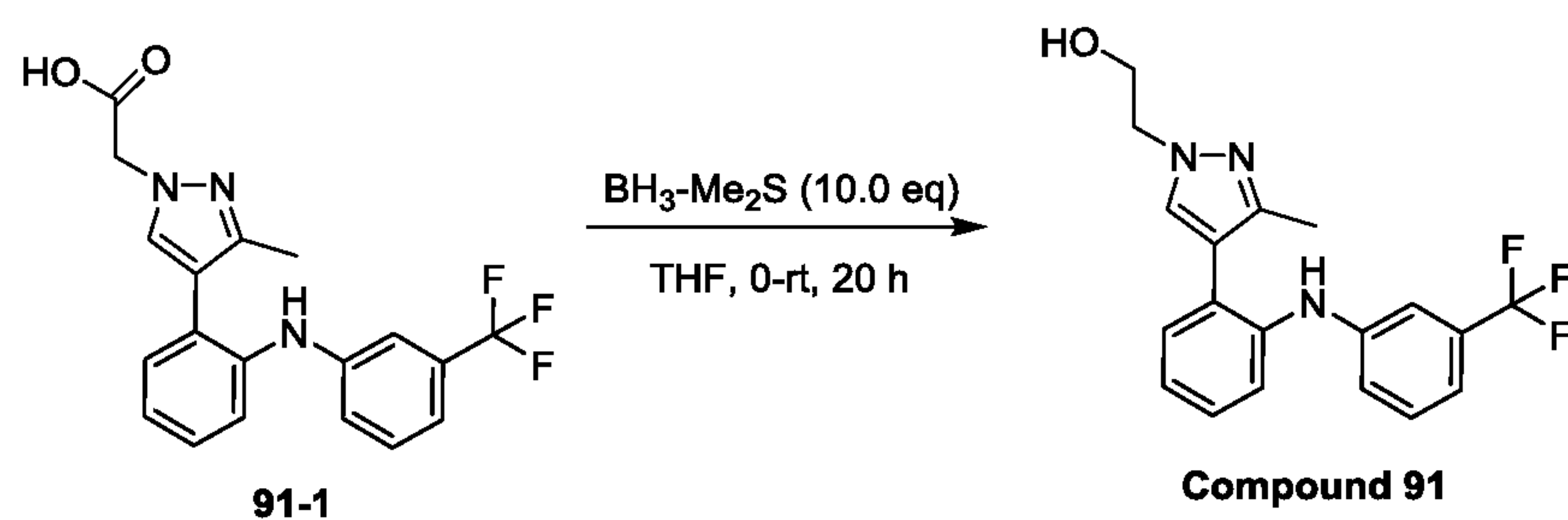
[00445] To a mixture of **89-1** (400.0 mg, 1.1 mmol, 1.00 *eq*), Pd(dppf)Cl₂ (80.5 mg, 0.1 mmol, 0.10 *eq*) and Na₂CO₃ (233.2 mg, 2.2 mmol, 2.00 *eq*) in H₂O (1.0 mL) and THF (8.0 mL), was

added the mixture of **89-2** and **89-3** (326.2 mg, 1.3 mmol, 1.20 *eq*). The mixture was degassed under vacuum and purged with N₂ 3 times. The resulting mixture was stirred at 70 °C under N₂ for 17 h. LCMS showed the reaction was complete. The mixture was concentrated under vacuum. The residue was purified by prep-HPLC (acidic_HCl condition). The mixture of **Compound 89** and **Compound 90** (100 mg) was obtained, which was separated by chiral SFC.

[00446] Compound 89: 33.39 mg, 78.6 μ mol, 31.7% yield. LCMS (ESI): RT = 0.878 min, mass calc. for C₂₁H₂₀F₃N₃O₂ 403.15, m/z found 404.1 [M+H]⁺. ¹HNMR (400MHz, CHLOROFORM-*d*) δ 7.47 (s, 1H), 7.42 - 7.38 (m, 1H), 7.38 - 7.33 (m, 1H), 7.33 - 7.26 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.05 (dt, *J* = 1.0, 7.4 Hz, 1H), 5.79 (s, 1H), 4.89 (s, 2H), 4.28 (q, *J* = 7.3 Hz, 2H), 2.21 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H).

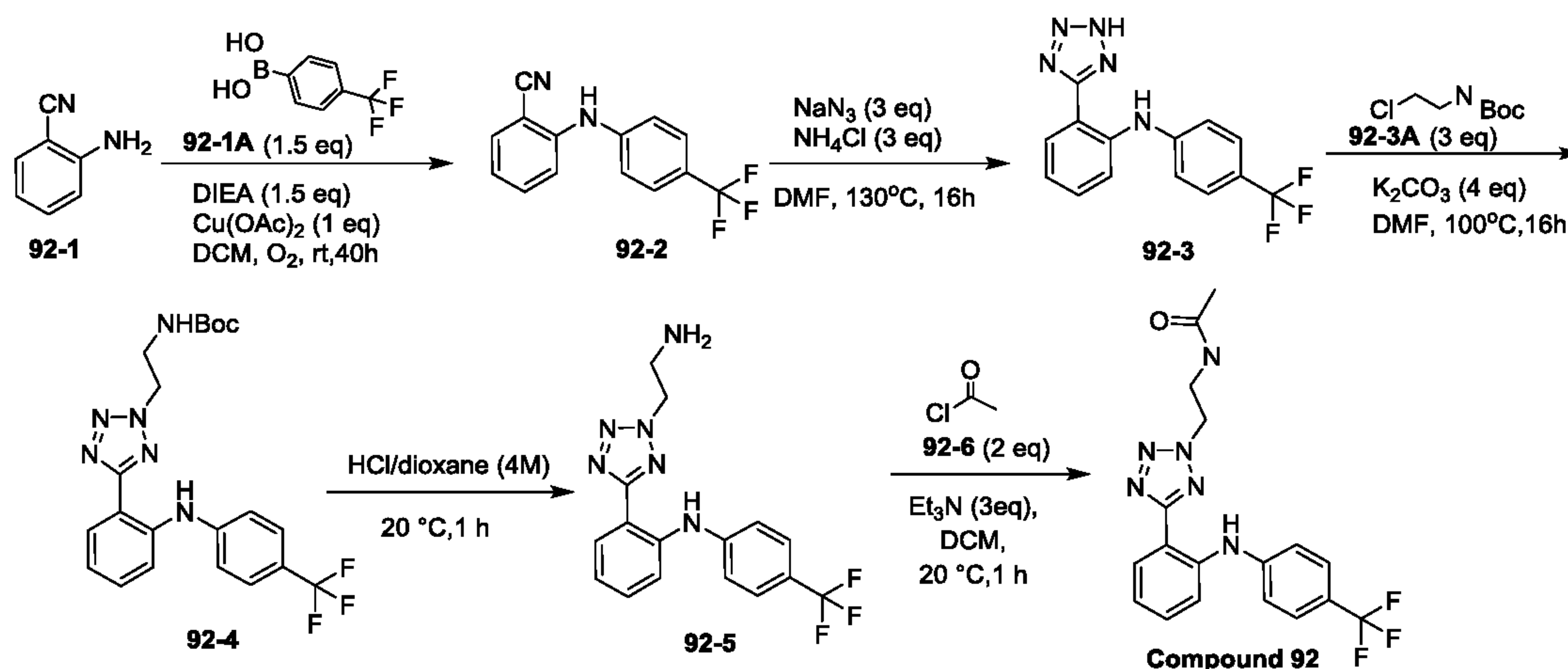
[00447] Compound 90: 17.10 mg, 39.0 μ mol, 15.7% yield. LCMS (ESI): RT = 1.375 min, mass calc. for C₂₁H₂₀F₃N₃O₂ 403.15, m/z found 404.5 [M+H]⁺. ¹HNMR (400MHz, CHLOROFORM-*d*) δ 7.54 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.36 - 7.27 (m, 3H), 7.26 - 7.18 (m, 2H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.04 (dt, *J* = 1.1, 7.5 Hz, 1H), 5.77 (s, 1H), 4.91 (s, 2H), 4.26 (q, *J* = 7.3 Hz, 2H), 2.14 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H).

Example 85: 2-(3-methyl-4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)ethanol (Compound 91)



[00448] To a mixture of **91-1** (22.0 mg, 58.6 μ mol, 1.00 *eq*) in THF (3.0 mL), was added BH₃-Me₂S (10 M, 58.6 μ L, 10.00 *eq*) at 0 °C. The resulting mixture was stirred at 20 °C for 20 h. LCMS showed the reaction was complete. The mixture was quenched with MeOH (5 mL), and concentrated under vacuum. The residue was diluted with saturated aqueous NH₄Cl (15 mL), and extracted with DCM (15 mL *3). The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated under vacuum. The residue was purified by prep-HPLC (acidic_HCl condition) to provide the title compound (12.72 mg, 31.0 μ mol, 52.9% yield, HCl salt). LCMS (ESI): RT = 1.229 min, mass calc. for C₁₉H₁₈F₃N₃O 361.14, m/z found 362.1 [M+H]⁺. ¹HNMR (400MHz, DMSO-*d*₆) δ 7.70 (s, 1H), 7.66 (s, 1H), 7.35 - 7.23 (m, 4H), 7.13 - 7.07 (m, 2H), 7.05 (s, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 4.02 (t, *J* = 5.8 Hz, 2H), 3.66 (t, *J* = 5.8 Hz, 2H), 2.05 (s, 3H).

Example 86: N-[2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl]acetamide (Compound 92)



Step 1: 2-[4-(trifluoromethyl)anilino]benzonitrile

[00449] To the solution of **92-1** (3.20 g, 27.09 mmol, 1.00 *eq*), DIEA (5.18 g, 40.08 mmol, 7 mL, 1.48 *eq*), Cu(OAc)₂ (5.07 g, 27.91 mmol, 1.03 *eq*) in DCM (50 mL) was added **92-1A** (6.00 g, 31.59 mmol, 1.17 *eq*). The mixture was stirred at 20 °C for 20 hour under an O₂ atmosphere. LCMS showed 52% of reactant **92-1** remained. Several new peaks were detected with LCMS and 27% of the desired compound was detected. The reaction mixture was continued with stirring for 2.5 h. LCMS showed no obvious changes. To the reaction mixture was added additional **92-1A** (2.00 g, 10.53 mmol, 0.39 *eq*) and stirring continued for 1 h. LCMS indicated one small new peak was found. The reaction mixture was stirred an additional 16 h. LCMS showed no obvious changes. The reaction mixture was filtered and concentrated under vacuum. TLC indicated reactant **92-1** remained, and many new spots were formed. The residue was purified by flash silica gel chromatography to provide **92-2** (1.10 g, 3.82 mmol, 14.09% yield). LCMS (ESI): RT = 0.843 min, mass calc. for C₁₄H₉F₃N₂ 262.07, m/z found 262.8[M+H]⁺.

Step 2: 2-(2H-tetrazol-5-yl)-N-[4-(trifluoromethyl)phenyl]aniline

[00450] To a mixture of **92-2** (370 mg, 1.41 mmol, 1.00 *eq*) and NaN₃ (275 mg, 4.23 mmol, 3.00 *eq*) in DMF (10 mL) was added NH₄Cl (226 mg, 4.23 mmol, 3.00 *eq*) in one portion at 25 °C under N₂. The mixture was heated to 130 °C for 16 h. TLC indicated **92-2** was consumed completely and one major new spot with high polarity was detected. The reaction mixture was treated dropwise with aq. HCl (0.8 M) to give a suspension, filtered, and the solid was dried under reduced pressure to provide **92-3** (1.20 g, 3.85 mmol, 90.9% yield). LCMS (ESI): RT = 0.810 min, mass calc. for C₁₄H₁₀F₃N₅ 305.09, m/z found 305.9[M+H]⁺.

Step 3: tert-butyl N-[2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl]carbamate

[00451] To a mixture of **92-3** (200 mg, 0.586 mmol, 1.00 *eq*, HCl) and K₂CO₃ (324 mg, 2.34 mmol, 4.00 *eq*) in DMF (6 mL) was stirred at 20 °C for 5 min. The mixture was added **92-3A** (315 mg, 1.76 mmol, 3.00 *eq*), then heated to 105 °C and stirred for 16 hours. LCMS showed **92-3**

remained and one peak with the desired MS was detected. TLC (Petroleum ether : Ethyl acetate = 3:1) indicated one new spot was formed. The reaction mixture was diluted with EtOAc (35 mL) and washed with brine (20 mL*4). The combined organic layers were dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by flash silica gel chromatography to provide **92-4** (190 mg, 0.424 mmol, 72.4% yield). LCMS (ESI): RT = 0.923 min, mass calcd. for C₂₁H₂₃F₃N₆O₂ 448.18, m/z found 449.3[M+H]⁺ and 471.1[M+23]⁺.

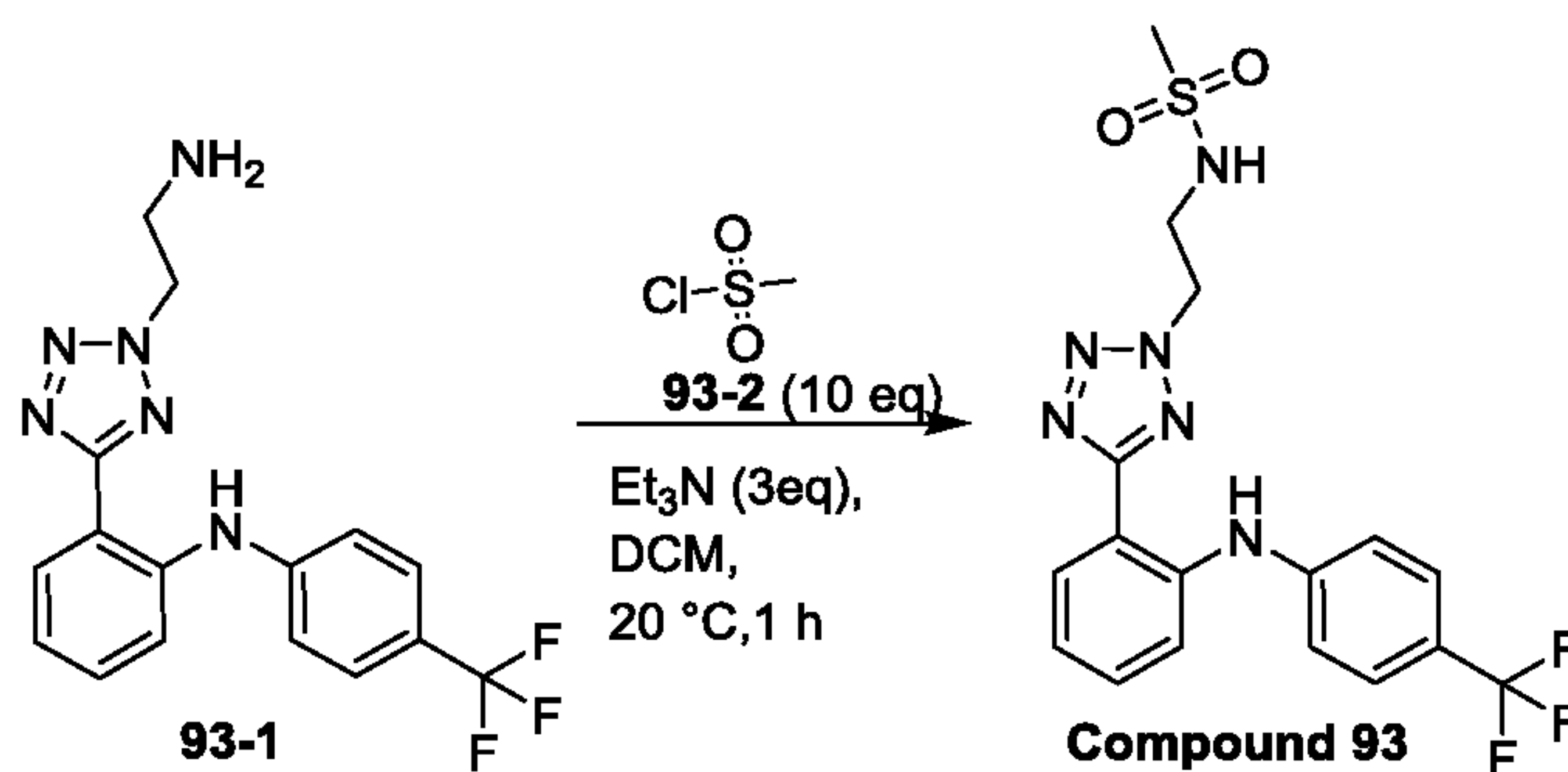
Step 4: 2-[2-(2-aminoethyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline

[00452] To a mixture of **92-4** (190 mg, 0.423 mmol, 1.00 *eq*) was added HCl/dioxane (4 M, 5.00 mL, 47.20 *eq*) in one portion at 20°C under N₂. The mixture was stirred at 20 °C for 1 h. LCMS showed the starting material was consumed completely and one main peak with MS was detected. The reaction mixture was concentrated under reduced pressure to remove solvent to provide **92-5** (160.00 mg, crude, HCl salt) which was used in the next step without further purification.

Step 5: N-[2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl]acetamide

[00453] To a mixture of **92-5** (50 mg, 0.144 mmol, 1.00 *eq*) and Et₃N (44 mg, 0.431 mmol, 60 uL, 3.00 *eq*) in DCM (2 mL) was added **92-6** (23 mg, 0.287 mmol, 21 uL, 2.00 *eq*) in one portion at 20°C under N₂. The mixture was stirred at 20 °C for 1 h. LCMS showed the compound **92-5** was consumed completely and one main peak with the desired MS was detected. The reaction mixture was concentrated under reduced pressure to remove solvent and the resulting residue was purified by prep-HPLC (basic condition) to provide **Compound 92** (19.23 mg, 48.8 umol, 34% yield). LCMS (ESI): RT = 1.265 min, mass calcd. for C₁₈H₁₇F₃N₆O 390.14, m/z found 371.1[M+H-20]⁺ and 413.1[M+23]⁺. ¹HNMR (400MHz, CHLOROFORM-*d*) δ8.98 (s, 1H), 8.19 (dd, *J*=7.60, 1.60 Hz, 1H), 7.58 - 7.51 (m, 3H), 7.43 - 7.36 (m, 1H), 7.31 (d, *J*=8.40 Hz, 2H), 7.10 - 7.03 (m, 1H), 5.82 (br s, 1H), 4.89 - 4.82 (m, 2H), 3.99 - 3.87 (m, 2H), 1.98 (s, 3H).

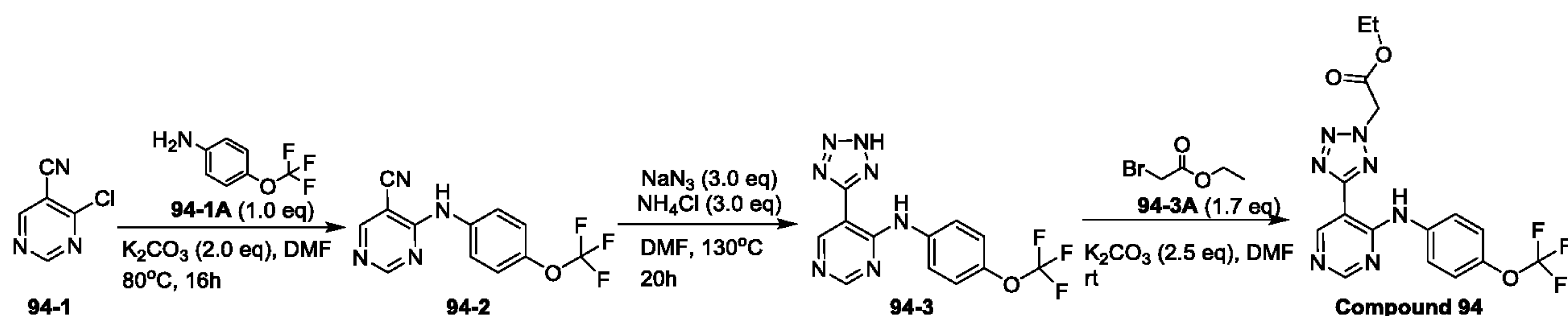
Example 87: N-[2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl]methane sulfonamide (Compound 93)



[00454] To a mixture of **93-1** (50 mg, 0.143 mmol, 1.00 *eq*) and Et₃N (44 mg, 0.431 mmol, 60 uL, 3.00 *eq*) in DCM (4 mL) was added **93-2** (170 mg, 1.48 mmol, 114 uL, 10 *eq*) in one portion at 20°C under N₂. The mixture was stirred at 20°C for 1 h. LCMS showed reactant **93-1** was

consumed completely and one main peak with the desired MS was detected. The reaction mixture was concentrated under reduced pressure to remove solvent and the resulting residue was purified by prep-HPLC (basic condition) to provide the title compound (9.83 mg, 23 μ mol, 16.1% yield). LCMS (ESI): RT = 1.290 min, mass calcd. for $C_{17}H_{17}F_3N_6O_2S$ 426.11, m/z found 427.1[M+H]⁺ and 449.1[M+23]⁺. ¹HNMR (400MHz, CHLOROFORM-*d*) δ 8.93 (s, 1H), 8.18 (dd, *J*=7.60, 1.20 Hz, 1H), 7.59 - 7.49 (m, 3H), 7.44 - 7.35 (m, 1H), 7.31 (d, *J*=8.40 Hz, 2H), 7.06 (t, *J*=7.20 Hz, 1H), 4.98 - 4.80 (m, 3H), 3.93 - 3.82 (m, 2H), 2.98 (s, 3H).

Example 88: ethyl 2-[5-[4-[4-(trifluoromethoxy)anilino]pyrimidin-5-yl]tetrazol-2-yl]acetate (Compound 94)



Step 1: 4-[4-(trifluoromethoxy)anilino]pyrimidine-5-carbonitrile

[00455] To a mixture of **94-1A** (253 mg, 1.43 mmol, 193 μ L, 1.00 *eq*) and **94-1** (200 mg, 1.43 mmol, 1.00 *eq*) in DMF (4 mL) was added K_2CO_3 (395 mg, 2.86 mmol, 2.00 *eq*) in one portion at 25°C. The mixture was stirred at 80 °C for 6 h. LCMS showed **94-1** was consumed completely. Several new peaks were detected on LCMS and 57 % of the desired compound was detected. The reaction mixture was extracted with EtOAc (40 mL) and washed with brine (30 mL*4). The combined organic layers were dried with anhydrous Na_2SO_4 , filtered, and concentrated under vacuum. TLC showed many new spots were formed. The residue was purified by flash silica gel chromatography to provide **94-2** (150 mg, 0.524 mmol, 36.7% yield). LCMS (ESI): RT = 1.154 min, mass calcd. for $C_{12}H_7F_3N_4O$ 280.06, m/z found 280.9[M+H]⁺.

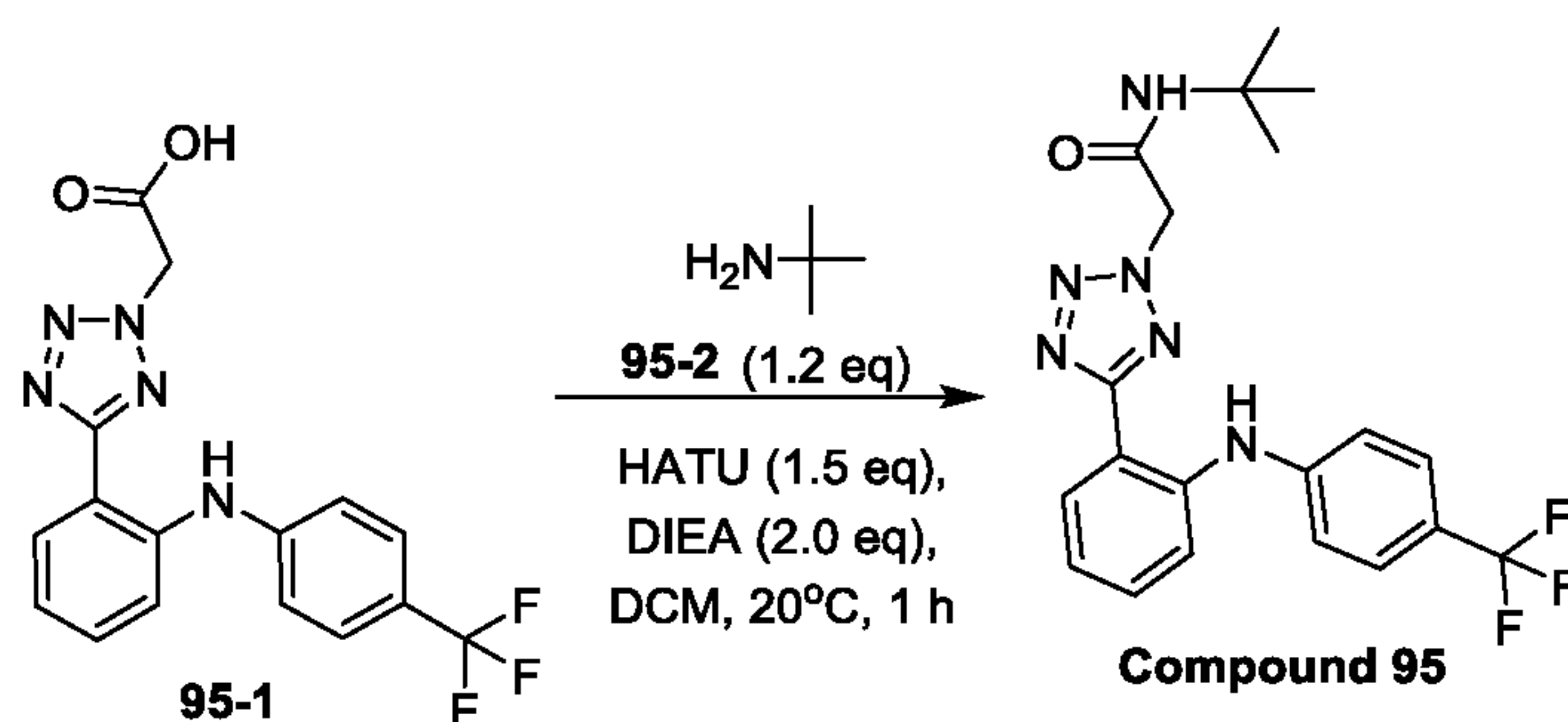
Step 2: 5-(2H-tetrazol-5-yl)-N-[4-(trifluoromethoxy)phenyl]pyrimidin-4-amine

[00456] To a mixture of **94-2** (150 mg, 0.512 mmol, 1.00 *eq*) and NaN_3 (50 mg, 0.769 mmol, 1.50 *eq*) in DMF (4.5 mL) was added NH_4Cl (41 mg, 0.768 mmol, 1.50 *eq*) in one portion at 20°C under N_2 . The mixture was heated to 130 °C for 16 h. LCMS showed the starting material was consumed completely and one main peak with the desired MS was detected. The reaction mixture was diluted with EtOAc (60 mL) and washed with brine (50 mL*5). The organic phase was dried with anhydrous Na_2SO_4 , filtered and concentrated under vacuum to provide **94-3** (160 mg, 0.480 mmol, 93.8% yield), which was used next step without further purification.

Step 3: ethyl 2-[5-[4-[4-(trifluoromethoxy)anilino]pyrimidin-5-yl]tetrazol-2-yl]acetate

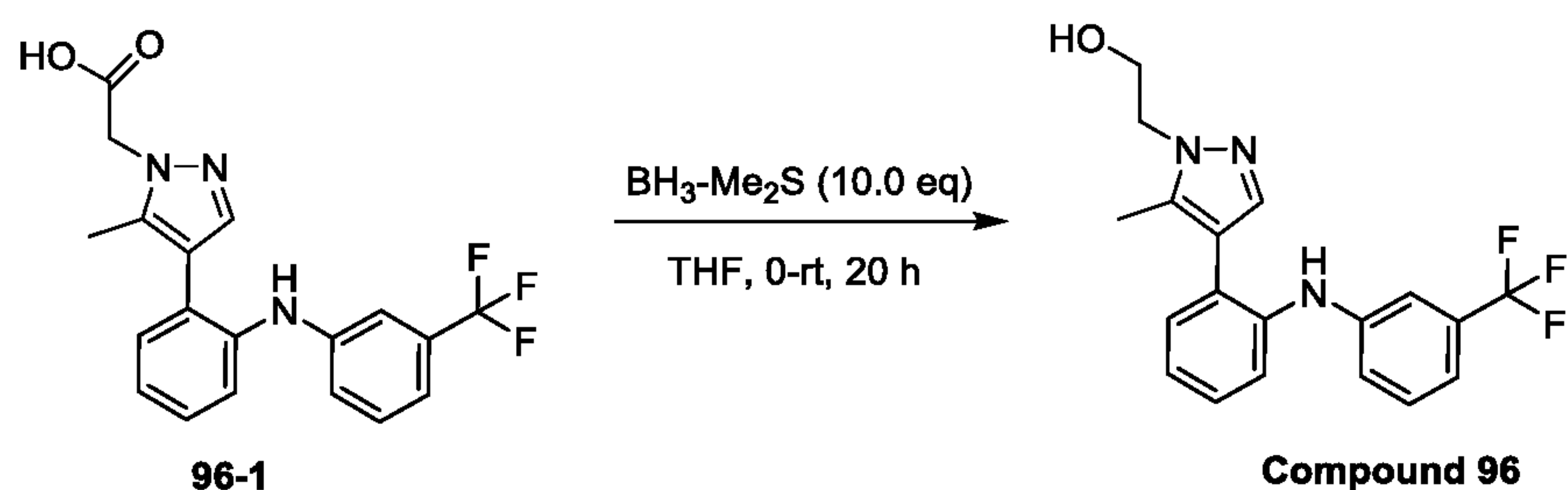
[00457] To a mixture of **94-3** (80 mg, 0.248 mmol, 1.00 *eq*) and K₂CO₃ (86 mg, 0.619 mmol, 2.50 *eq*) in DMF (2 mL) was added **94-3A** (73 mg, 0.438 mmol, 49 uL, 1.77 *eq*) in one portion at 20°C under N₂. The mixture was stirred at 20 °C for 2 h. LCMS showed the starting material was remained and one peak with the desired MS was detected. The reaction mixture was diluted with EtOAc (60 mL) and washed with brine (50 mL*5). The organic phase was dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum. HPLC showed 42% of desired product was found. The residue was purified by prep-HPLC (HCl condition) to provide **Compound 94** (26.00 mg, 59 umol, 23.9% yield). LCMS (ESI): RT = 1.198 min, mass calcd. for C₁₆H₁₄F₃N₇O₃ 409.11, m/z found 410.1[M+H]⁺. ¹HNMR (400MHz, CHLOROFORM-*d*) δ 11.10 (br s, 1H), 9.24 (br s, 1H), 8.86 (br s, 1H), 7.77 (br d, *J*=8.40 Hz, 2H), 7.37 (br d, *J*=7.60 Hz, 2H), 5.60 (br s, 2H), 4.42 - 4.32 (m, 2H), 1.37 (t, *J*=7.20 Hz, 3H).

Example 89: N-tert-butyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetamide (Compound 95)



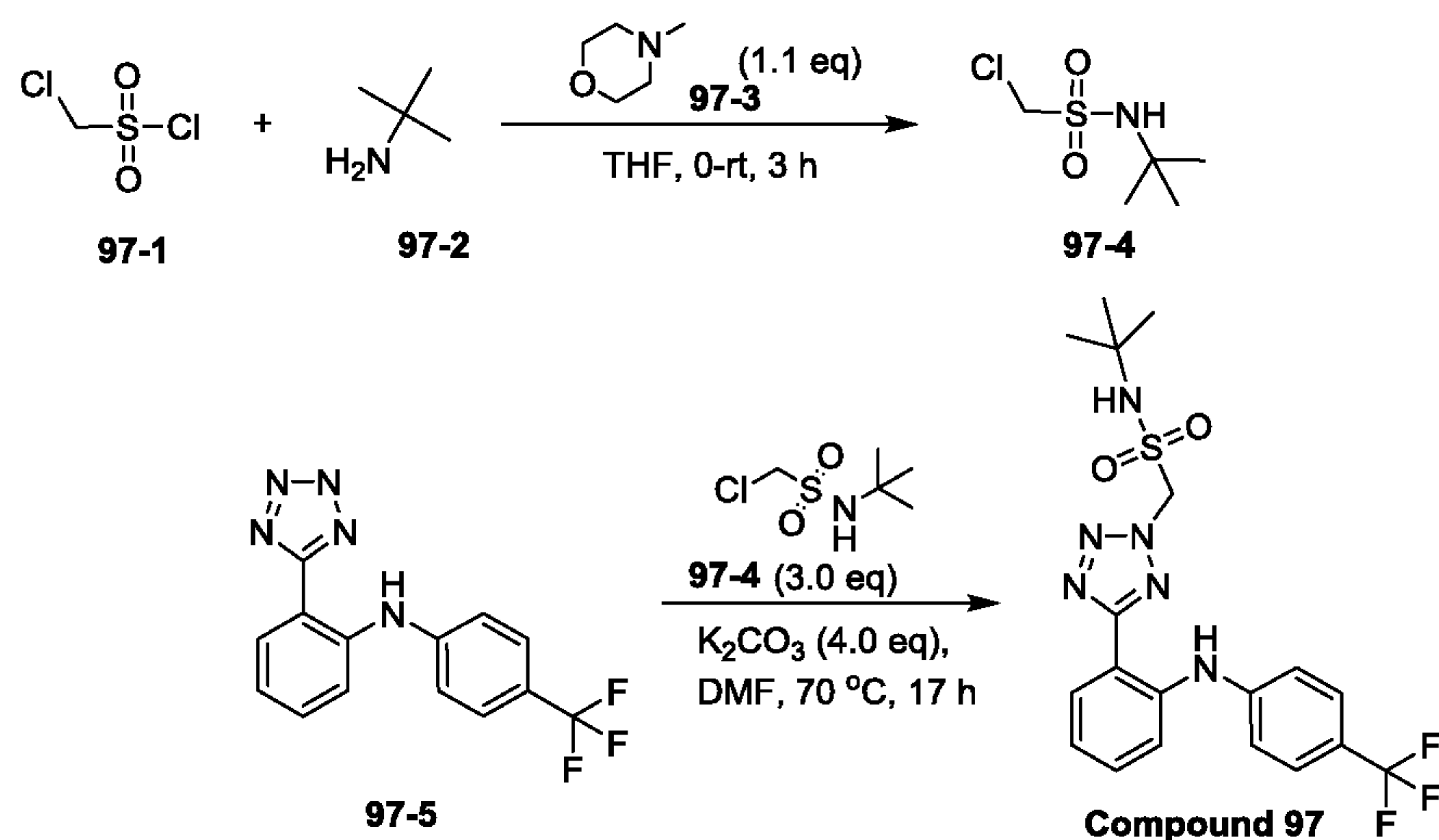
[00458] To a solution of **95-1** (30.0 mg, 82.6 umol, 1.0 *eq*) and **95-2** (9.1 mg, 0.12 mmol, 12.9 uL, 1.5 *eq*) in DCM (5.0 mL) was added HATU (31.4 mg, 82.6 umol, 1.0 *eq*) and DIEA (32.0 mg, 0.25 mmol, 43.3 uL, 3.0 *eq*). The resulting mixture was stirred at 20 °C for 1 hour. LCMS showed the desired compound was formed. TLC (Petroleum ether : Ethyl acetate=3/1) showed new spot appeared and the starting material was consumed completely. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography over silica gel and then further purified by prep-HPLC to give **Compound 95** (20.27 mg, 48.45 umol, 58.66% yield). LCMS (ESI): RT = 0.902 min, mass calc. for C₂₀H₂₁F₃N₆O 418.17, m/z found 419.2 [M+H]⁺; ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.79 (s, 1H), 8.17 (s, 1H), 8.04 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.59 - 7.53 (m, 3H), 7.52 - 7.46 (m, 1H), 7.24 (d, *J* = 8.5 Hz, 2H), 7.21 - 7.15 (m, 1H), 5.45 (s, 2H), 1.28 (s, 9H).

Example 90: 2-(5-methyl-4-(2-((3-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-1-yl)ethanol (Compound 96)



[00459] To a mixture of **96-1** (10.0 mg, 26.6 μmol , 1.00 *eq*) in THF (3.0 mL), was added $\text{BH}_3\text{-Me}_2\text{S}$ (10 M, 26.6 μL , 10.00 *eq*) at 0 °C. The resulting mixture was stirred at 20 °C for 20 h. LCMS showed the reaction was complete. The mixture was quenched with MeOH (5 mL), and concentrated under vacuum. The residue was diluted with saturated NH_4Cl aqueous (15 mL), and extracted with DCM (15 mL *3). The combined organic layers were dried over anhydrous Na_2SO_4 , and concentrated under vacuum. The residue was purified by prep-HPLC (acidic_HCl condition) to provide the title compound (3.90 mg, 9.6 μmol , 36.1% yield, HCl salt). LCMS (ESI): RT = 1.239 min, mass calc. for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{N}_3\text{O}$ 361.14, m/z found 362.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ 7.70 (s, 1H), 7.46 (s, 1H), 7.34 - 7.25 (m, 3H), 7.23 (d, $J = 7.0$ Hz, 1H), 7.13 - 7.08 (m, 2H), 7.04 (s, 1H), 6.96 (d, $J = 7.5$ Hz, 1H), 4.06 (t, $J = 5.9$ Hz, 2H), 3.68 - 3.63 (m, 2H), 2.12 (s, 3H).

Example 91: N-tert-butyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methanesulfonamide (Compound 97)



Step 1: N-tert-butyl-1-chloromethanesulfonamide

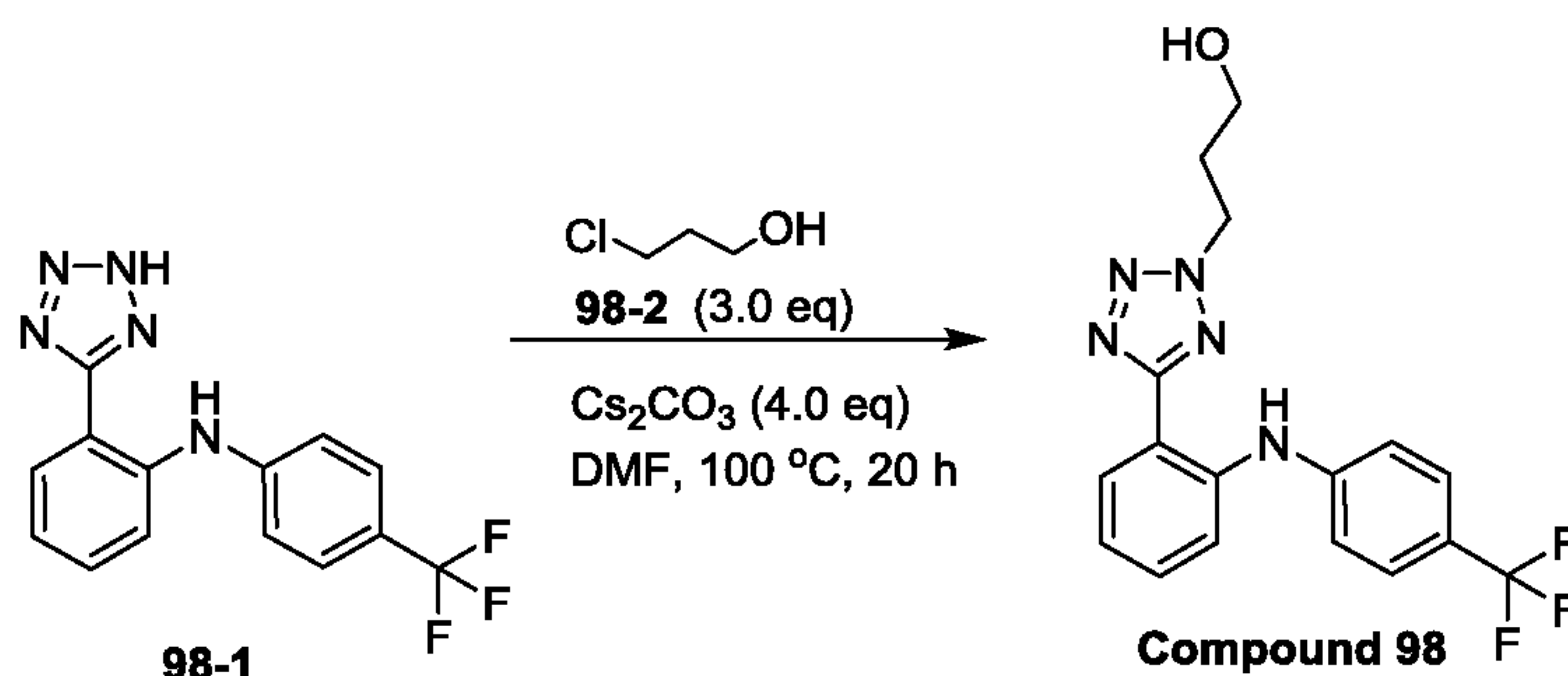
[00460] **97-2** (258.0 mg, 3.5 mmol, 1.05 *eq*) and **97-3** (373.9 mg, 3.7 mmol, 1.10 *eq*) were dissolved in THF (7 mL), and a solution of **97-1** (500.0 mg, 3.4 mmol, 1.00 *eq*) in THF (3 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 h, then 20 °C for 2.5 h. TLC detected a new spot. The mixture was diluted with EtOAc (30 mL), washed with 1 M aqueous HCl (20 mL), water (30 mL), and brine (30 mL). The organic layer was dried over anhydrous

Na₂SO₄, and concentrated under vacuum. **97-4** (460.0 mg, 2.5 mmol, 73.7% yield) was obtained as light yellow oil. ¹HNMR (400MHz, CHLOROFORM-*d*) δ 4.57 (s, 1H), 4.48 (s, 2H), 1.41 (s, 9H).

Step 2: N-tert-butyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methanesulfonamide

[00461] To a mixture of **97-5** (50.0 mg, 0.2 mmol, 1.00 *eq*) and K₂CO₃ (90.6 mg, 0.7 mmol, 4.00 *eq*) in DMF (3.0 mL), was added **97-4** (91.2 mg, 0.5 mmol, 3.00 *eq*). The resulting mixture was stirred at 70 °C for 17 h. The reaction was monitored by LCMS. The mixture was filtered, and the solid was washed with DMF (1 mL). The filtrate was checked by HPLC and purified by prep-HPLC (basic condition) to provide **Compound 97** (16.04 mg, 35.3 μmol, 21.6% yield). LCMS (ESI): RT = 1.403 min, mass calc. for C₁₉H₂₁F₃N₆O₂S 454.14, m/z found 455.1 [M+H]⁺. ¹HNMR (400MHz, DMSO-*d*₆) δ 8.70 (s, 1H), 8.09 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.61 - 7.55 (m, 3H), 7.54 - 7.46 (m, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.23 - 7.17 (m, 1H), 6.20 (s, 2H), 1.26 (s, 9H).

Example 92: 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propan-1-ol (Compound 98)

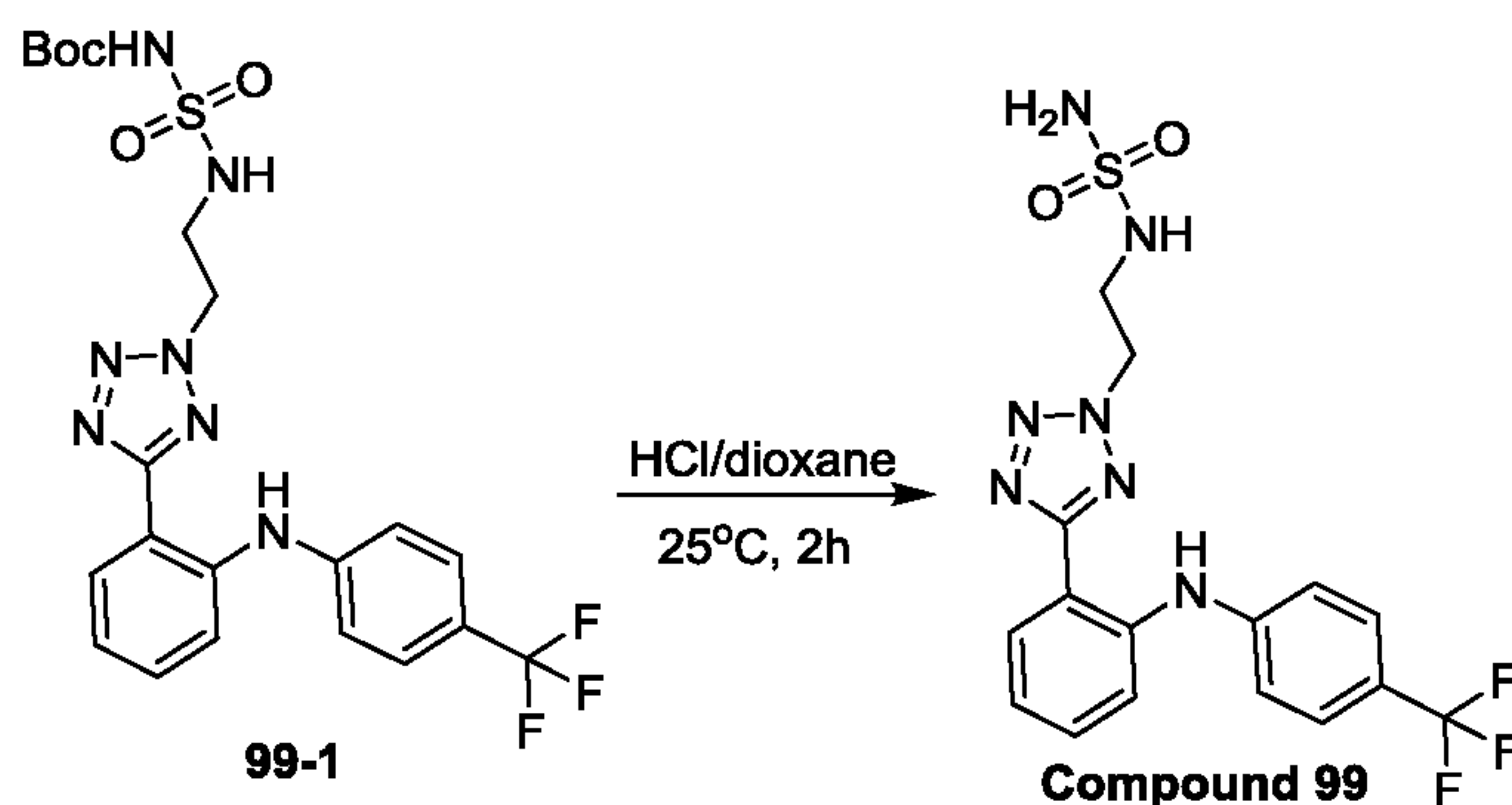


[00462] To a mixture of **98-1** (50.0 mg, 0.2 mmol, 1.00 *eq*) and Cs₂CO₃ (213.5 mg, 0.7 mmol, 4.00 *eq*) in DMF (3.0 mL), was added **98-2** (46.5 mg, 0.5 mmol, 3.00 *eq*). The resulting mixture was stirred at 100 °C for 20 h. The reaction was monitored by LCMS. The mixture was filtered, and the solid was washed with DMF (1 mL). The filtrate was checked by HPLC and purified by prep-HPLC (basic condition) to provide the title compound (6.70 mg, 18.4 μmol, 11.3% yield).

LCMS (ESI): RT = 1.329 min, mass calc. for C₁₇H₁₆F₃N₅O 363.13, m/z found 364.1 [M+H]⁺.

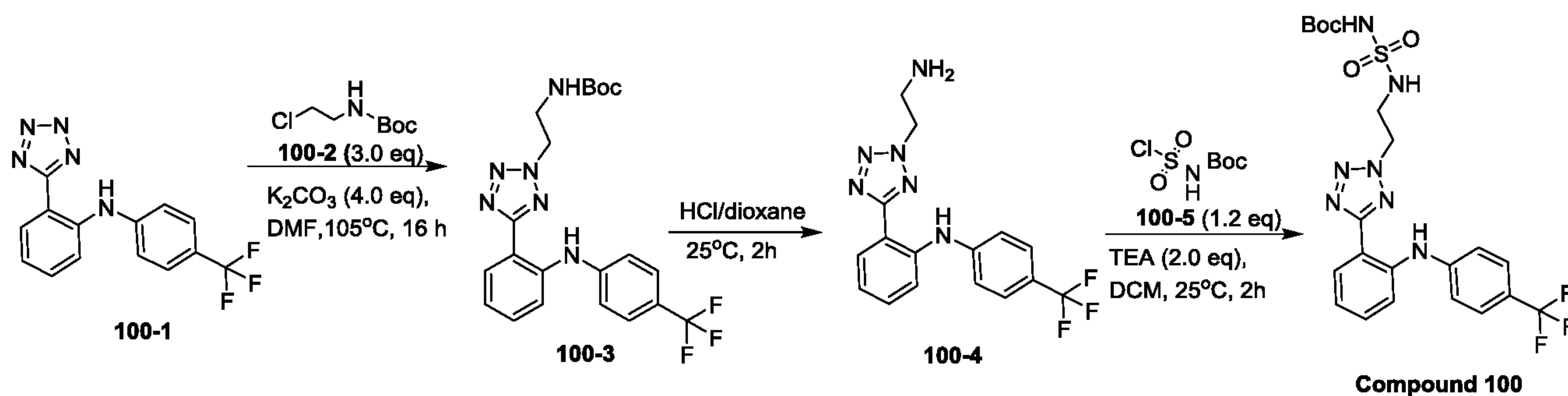
¹HNMR (400MHz, CHLOROFORM-*d*) δ 9.06 (s, 1H), 8.20 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.54 (dd, *J* = 2.8, 8.5 Hz, 3H), 7.42 - 7.35 (m, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.08 - 7.00 (m, 1H), 4.88 (t, *J* = 6.8 Hz, 2H), 3.76 (t, *J* = 5.9 Hz, 2H), 2.35 - 2.29 (m, 2H).

Example 93: 2-[2-(sulfamoylamino)ethyl]-5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazole (Compound 99)



[00463] A solution of **99-1** (100 mg, 0.190 mmol, 1.0 *eq*) in HCl/dioxane (3 mL) was stirred at 25°C for 1 hour. LCMS showed 85% of the desired compound was formed and the starting material was consumed completely. The reaction mixture was concentrated under reduced pressure to give a residue. The residue product was purified by HPLC to give the title compound (20 mg, 0.044 mmol, 23% yield). LCMS (ESI): RT = 2.299 min, mass calc. for C₁₆H₁₆F₃N₇O₂S 427.10, *m/z* found 450.0 [M+23]⁺; ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.74 (s, 1H), 8.06 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 3H), 7.53 - 7.45 (m, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 6.89 (s, 1H), 6.72 (s, 2H), 4.86 (s, 2H), 3.53 (d, *J* = 5.3 Hz, 2H).

Example 94: tert-butyl (N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethyl)sulfamoyl)carbamate (Compound 100)



Step 1: tert-butyl N-[2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl]carbamate

[00464] To a stirred mixture of **100-1** (100 mg, 0.293 mmol, 1.0 *eq*, HCl) and **100-2** (158 mg, 0.878 mmol, 3.0 *eq*) in DMF (3 mL) was added K₂CO₃ (162 mg, 1.17 mmol, 4.0 *eq*). The mixture was heated to 105°C for 16 hr. LCMS showed 87% desired compound was formed and the starting material was consumed completely. The mixture was cooled. Water (10 mL) was added and the mixture extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over magnesium sulfate, filtered, and concentrated to give a residue. The residue was purified by flash column chromatography to afford **100-3** (120 mg, 0.268 mmol, 91% yield). LCMS (ESI): RT = 0.934 min, mass calc. for C₂₁H₂₃F₃N₆O₂ 448.18, *m/z* found 393.1 [M+H-56]⁺; ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.73 (s, 1H), 8.04 (d, *J* = 7.5 Hz, 1H), 7.61 - 7.53 (m, 4H), 7.51 - 7.46 (m, 1H), 7.26

(d, $J = 8.5$ Hz, 2H), 7.18 (t, $J = 7.4$ Hz, 1H), 7.03 (t, $J = 6.0$ Hz, 1H), 4.76 (t, $J = 5.5$ Hz, 2H), 3.56 - 3.47 (m, 2H), 1.27 (s, 9H).

Step 2: 2-[2-(2-aminoethyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline

[00465] A solution of **100-3** (120 mg, 0.268 mmol, 1.0 *eq*) in HCl/dioxane (4.0 mL) was stirred at 25°C for 2 hour. LCMS showed 94% of the desired compound was formed and the starting material was consumed completely. The mixture was concentrated to give **100-4** (100 mg, 0.244 mmol, 91 % yield, HCl) as a light yellow oil. The residue was directly used without further purification.

LCMS (ESI): RT = 0.713 min, mass calc. for $C_{16}H_{15}F_3N_6$ 348.13, m/z found 328.9 $[M+H-20]^+$;

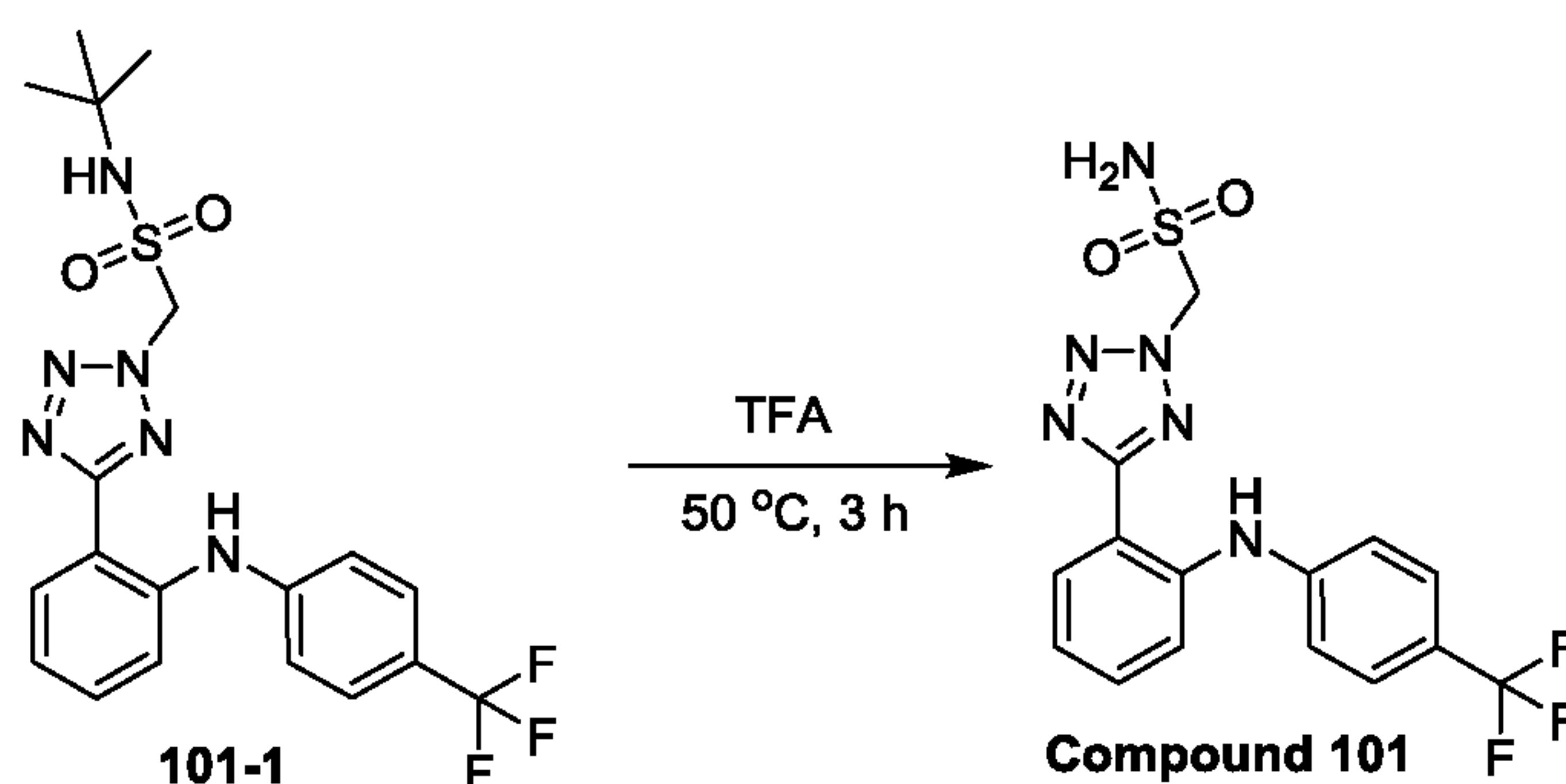
^1H NMR (400 MHz, DMSO- d_6) δ 8.76 (s, 1H), 8.16 (s, 2H), 8.07 (d, $J = 7.8$ Hz, 1H), 7.58 (d, $J = 8.3$ Hz, 3H), 7.54 - 7.48 (m, 1H), 7.27 (d, $J = 8.5$ Hz, 2H), 7.21 (t, $J = 8.0$ Hz, 1H), 5.02 (t, $J = 5.6$ Hz, 2H), 3.50 (s, 2H).

Step 3: tert-butylN-[2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethylsulfamoyl] carbamate

[00466] To a solution of **100-4** (40 mg, 0.115 mmol, 1.0 *eq*) and TEA (23 mg, 0.230 mmol, 32 μ L, 2.0 *eq*) in DCM (2 mL) was added **100-5** (30 mg, 0.138 mmol, 1.2 *eq*). The resulting mixture was stirred at 25°C for 1 hour. LCMS showed 90% desired compound was formed and the starting material was consumed completely. Water (2 ml) was added and the mixture extracted with DCM (3 $\times$ 3mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue was purified by HPLC to give **Compound 100** (18 mg, 0.034 mmol, 30% yield). LCMS (ESI): RT = 2.613 min, mass calc. for $C_{21}H_{24}F_3N_7O_4S$ 527.16, m/z found 472.1 $[M+H-56]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ 8.74 (s, 1H), 8.06 (d, $J = 6.8$ Hz, 1H), 7.64 - 7.42 (m, 4H), 7.35 - 7.04 (m, 5H), 4.83 (s, 2H), 3.49 - 3.43 (m, 2H), 1.28 (s, 9H).

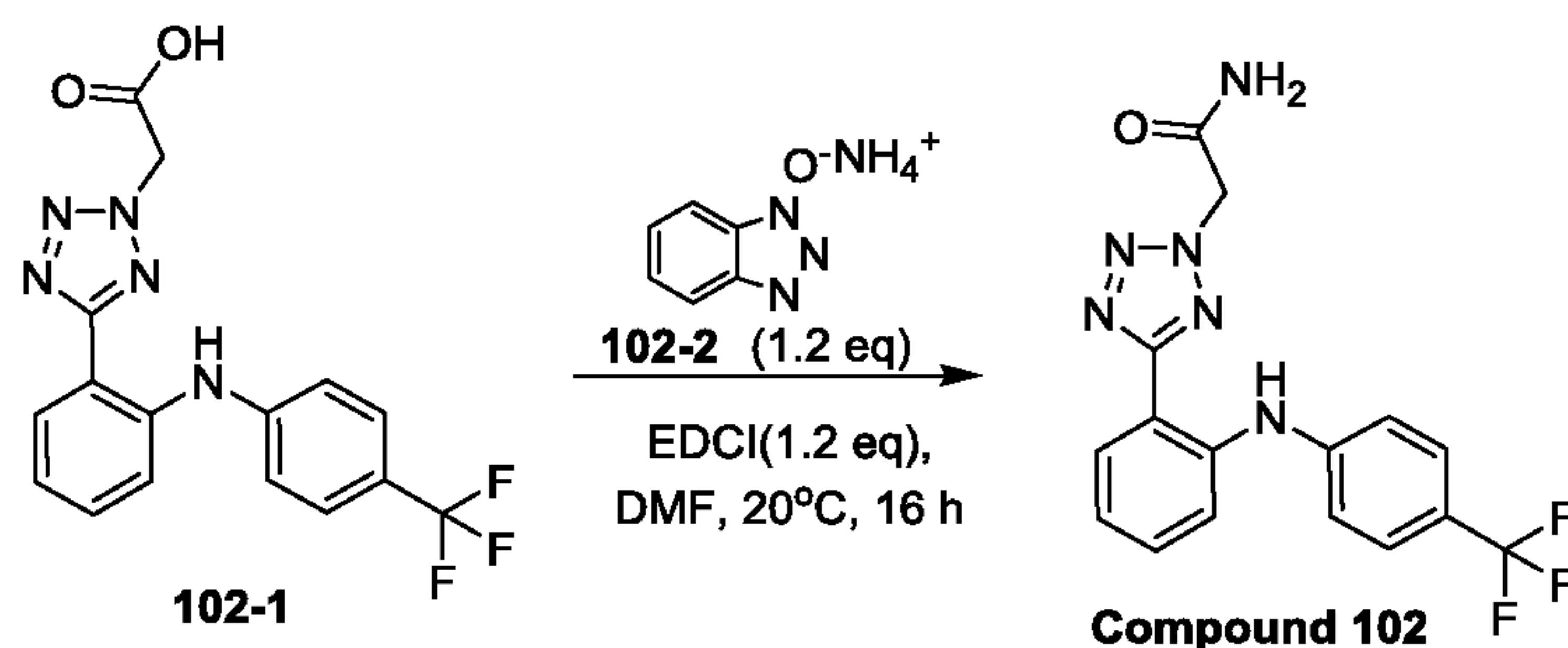
^1H NMR (400MHz, CHLOROFORM- d) δ 8.92 (s, 1H), 8.20 (d, $J = 7.8$ Hz, 1H), 7.59 - 7.49 (m, 3H), 7.39 (t, $J = 7.4$ Hz, 1H), 7.30 (d, $J = 8.5$ Hz, 2H), 7.05 (t, $J = 7.4$ Hz, 1H), 4.92 (t, $J = 5.5$ Hz, 2H), 3.84 (t, $J = 5.6$ Hz, 2H), 1.44 (s, 9H).

Example 95: (5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methane sulfonamide (Compound 101)



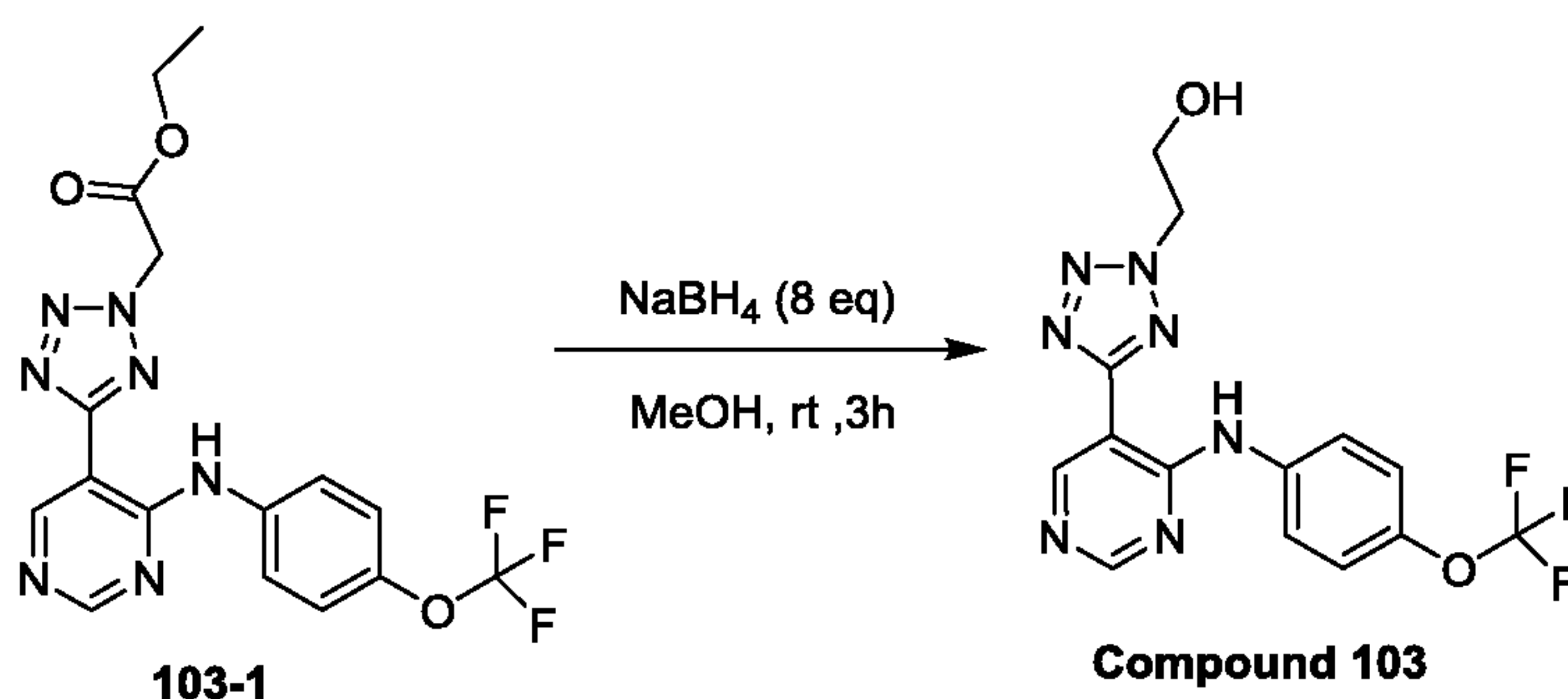
[00467] A mixture of **101-1** (30.0 mg, 66.0 μmol , 1.00 *eq*) in TFA (4.6 g, 40.5 mmol, 3.0 mL, 613.8 *eq*) was stirred at 50 °C for 3 h. LCMS showed the reaction was complete. The mixture was concentrated under vacuum. The residue was checked by HPLC and purified by prep-HPLC (acidic_HCl condition) to provide the title compound (1.91 mg, 4.2 μmol , 6.3% yield, HCl). LCMS (ESI): RT = 1.253 min, mass calc. for $\text{C}_{15}\text{H}_{13}\text{F}_3\text{N}_6\text{O}_2\text{S}$ 398.08, m/z found 399.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ 8.68 (s, 1H), 8.10 (dd, $J = 1.5, 7.8$ Hz, 1H), 7.61 - 7.48 (m, 6H), 7.25 (d, $J = 8.5$ Hz, 2H), 7.20 (dt, $J = 1.1, 7.5$ Hz, 1H), 6.18 (s, 2H).

Example 96: 2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]acetamide (Compound 102)



[00468] To a solution of **102-1** (30.0 mg, 82.6 μmol , 1.0 *eq*) and **102-2** (12.6 mg, 82.6 μmol , 1.0 *eq*) in DCM (5.0 mL) was added EDCI (17.4 mg, 90.8 μmol , 1.1 *eq*). The resulting mixture was stirred at 20 °C for 16 hours. LCMS showed the desired compound was formed. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC to give the title compound (7.81 mg, 21.56 μmol , 26.10% yield). LCMS (ESI): RT = 0.800 min, mass calc. for $\text{C}_{16}\text{H}_{13}\text{F}_3\text{N}_6\text{O}$ 362.11, m/z found 363.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.79 (s, 1H), 8.05 (d, $J = 7.8$ Hz, 1H), 7.85 (s, 1H), 7.56 (t, $J = 7.9$ Hz, 4H), 7.51 - 7.46 (m, 1H), 7.25 (d, $J = 8.5$ Hz, 2H), 7.18 (t, $J = 7.4$ Hz, 1H), 5.51 (s, 2H).

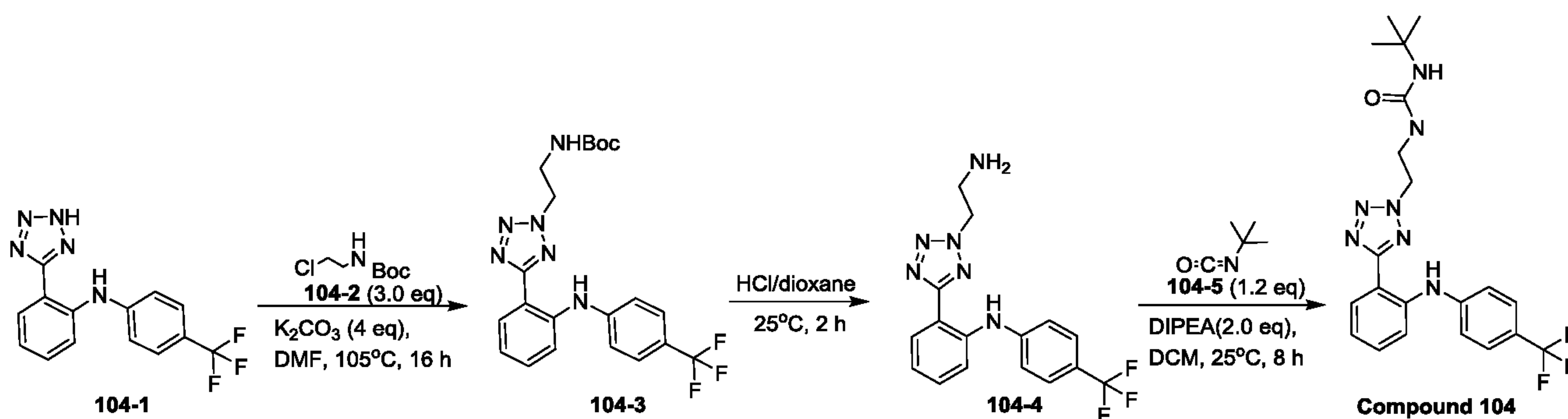
Example 97: 2-[5-[4-[4-(trifluoromethoxy)anilino]pyrimidin-5-yl]tetrazol-2-yl]ethanol (Compound 103)



[00469] To a mixture of **103-1** (20 mg, 35 μmol , 1.00 *eq*) in MeOH (2 mL) was stirred at 0 °C for 5 min. To the reaction mixture was added NaBH_4 (5.3 mg, 0.141 mmol, 4.00 *eq*) and the mixture stirred at 20 °C for 2 h. LCMS showed the starting material remained and no desired

product MS was detected. To the reaction mixture was added additional NaBH₄ (5.3 mg, 0.141 mmol, 4.00 *eq*) and stirring continued for 1 h. LCMS showed 48% of starting material was remaining and 47% of desired product was detected. The reaction mixture was quenched by addition water (5 mL), and then concentrated under reduced pressure to remove MeOH and extracted with EtOAc(5 mL * 3). The combined organic layers were dried with anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (HCl condition) to obtain the title compound (2.09 mg, 5.7 umol, 16.2% yield). LCMS (ESI): RT = 2.571 min, mass calcd. for C₁₄H₁₂F₃N₇O₂ 367.10, m/z found 368.0[M+H]⁺. ¹H NMR (400MHz, DMSO-*d*₆) δ10.10 (s, 1H), 9.02 (br s, 1H), 10.04 - 8.67 (m, 1H), 7.84 (d, *J*=8.80 Hz, 2H), 7.44 (br d, *J*=8.80 Hz, 2H), 4.88 (t, *J*=5.20 Hz, 2H), 4.02 (t, *J*=5.20 Hz, 2H).

Example 98: 1-tert-butyl-3-[2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl]urea (Compound 104)



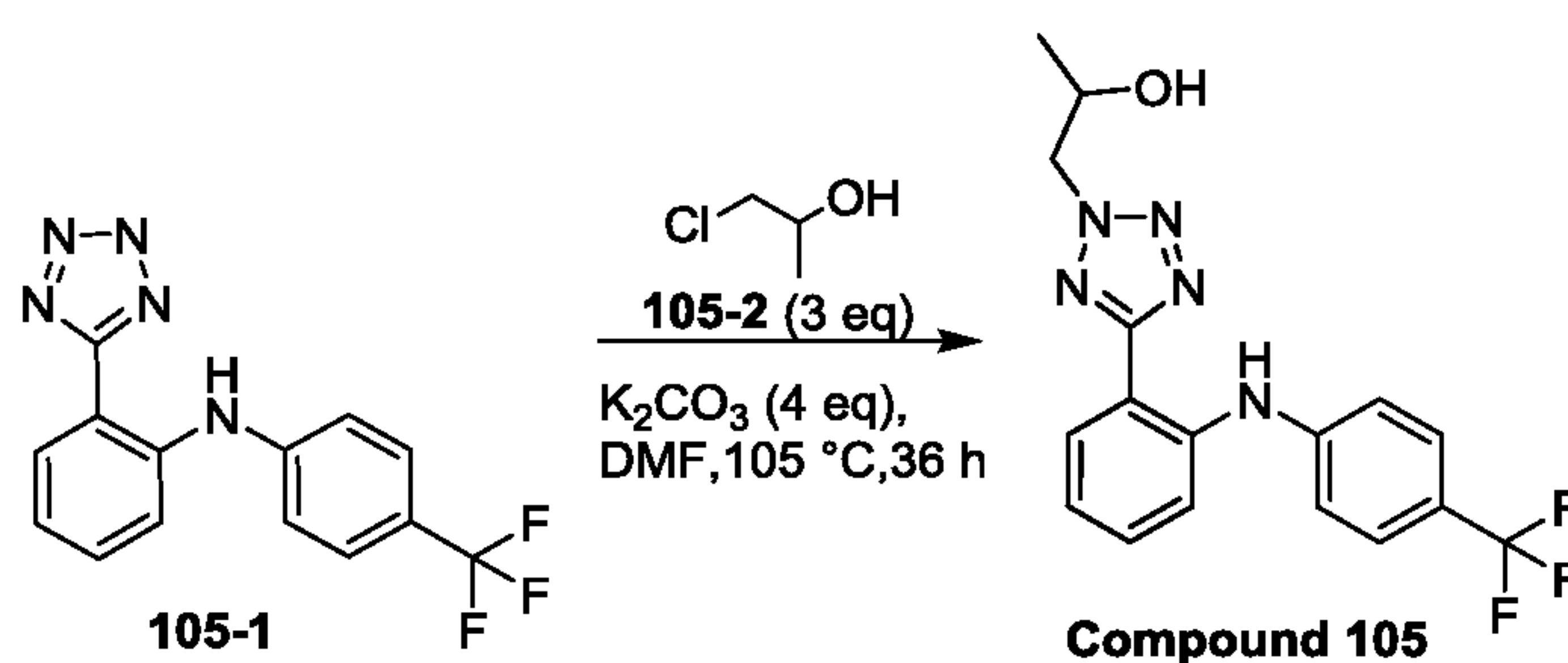
Step 1: tert-butyl N-[2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl]carbamate [00470] To a stirred mixture of **104-1** (300 mg, 0.878 mmol, 1.0 *eq*, HCl) and **104-2** (473 mg, 2.63 mmol, 3.0 *eq*) in DMF (6mL) was added K₂CO₃ (485 mg, 3.51 mmol, 4.0 *eq*). The mixture was heated to 105°C for 16 hr. LCMS showed 75% of the desired compound was formed and the starting material was consumed completely. The mixture was cooled. Water (15 mL) was added and the mixture extracted with ethyl acetate (3 x 15 mL). The combined organics were dried over magnesium sulfate, filtered, and concentrated to give a residue. The residue was purified by flash column chromatography to afford **104-3** (350 mg, 0.741 mmol, 84 % yield). LCMS (ESI): RT = 1.438 min, mass calc. for C₂₁H₂₃F₃N₆O₂ 448.18, m/z found 390.0 [M+H-56]⁺.

Step 2: 2-[2-(2-aminoethyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline [00471]

A solution of **104-3** (350 mg, 0.780 mmol, 1.0 *eq*) in HCl/dioxane (7 mL) was stirred at 25°C for 2 hour. LCMS showed 94% of the desired compound was found and the starting material was consumed completely. The mixture was concentrated to give compound **104-4** (280 mg, 0.756 mmol, 97% yield) as a light yellow oil. The oil was directly used without further purification. LCMS (ESI): RT = 0.702 min, mass calc. for C₁₆H₁₅F₃N₆ 348.13, m/z found 328.9 [M+H-20]⁺.

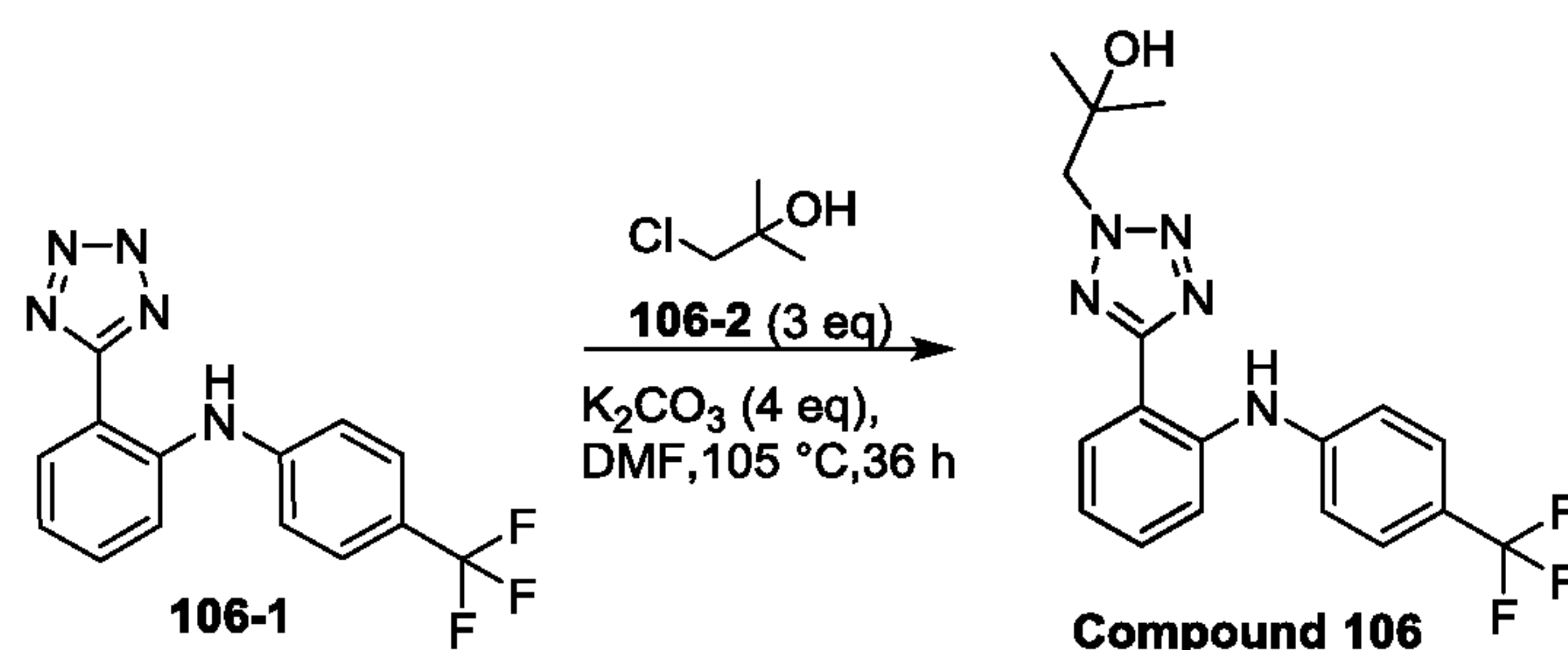
Step 3: 1-tert-butyl-3-[2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl]urea

[00472] To a solution of **104-4** (80 mg, 0.208 mmol, 1.0 *eq*, HCl) and DIPEA (54 mg, 0.416 mmol, 73 μ L, 2.0 *eq*) in DCM (6 mL) was added compound **5** (25 mg, 0.249 mmol, 29 μ L, 1.2 *eq*). The resulting mixture was stirred at 25°C for 8 hour. LCMS showed 92% of the desired compound was found and the starting material was consumed completely. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography to give **Compound 104** (50 mg, 0.112 mmol, 54% yield). LCMS (ESI): RT = 2.605 min, mass calc. for C₂₁H₂₄F₃N₇O 447.20, m/z found 470.2 [M+23]⁺; ¹HNMR (400 MHz, CHLOROFORM-*d*) δ 8.96 (s, 1H), 8.17 (dd, *J* = 1.5, 7.9 Hz, 1H), 7.55 - 7.46 (m, 3H), 7.40 - 7.33 (m, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.07 - 6.98 (m, 1H), 4.84 - 4.76 (m, 2H), 4.49 - 4.31 (m, 1H), 4.11 (s, 1H), 3.88 - 3.79 (m, 2H), 1.27 (s, 9H).

Example 99: 1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propan-2-ol (Compound 105)

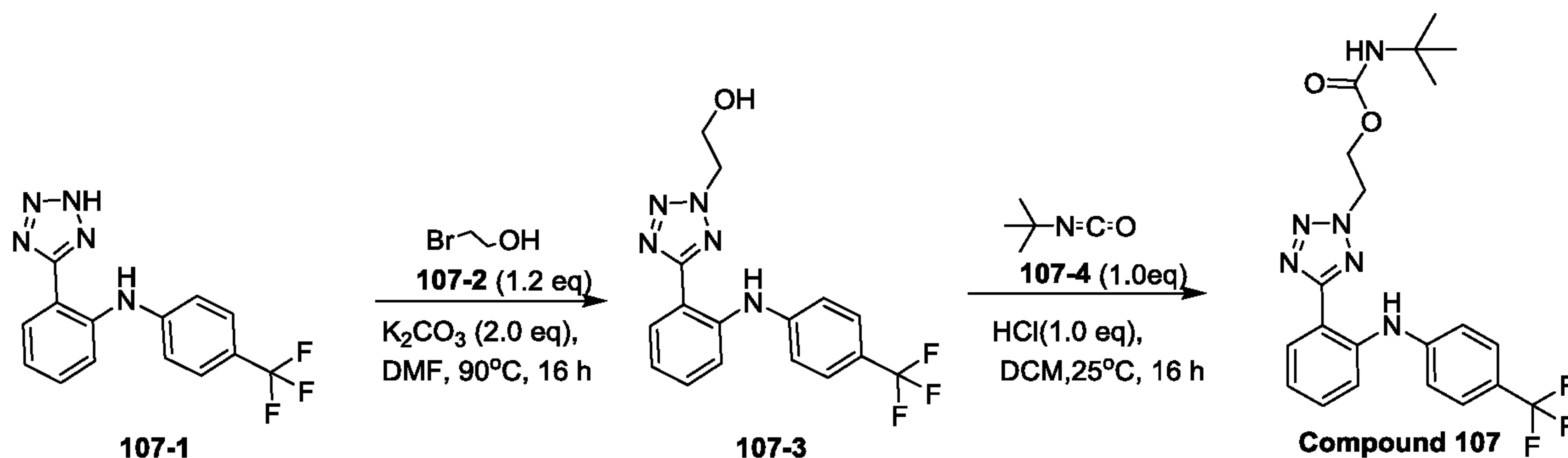
[00473] To a stirred solution of **105-1** (100 mg, 0.293 mmol, 1.0 *eq*, HCl) and K₂CO₃ (162mg, 1.17 mmol, 4.0 *eq*) in DMF (3 mL) was **105-2** (83 mg, 0.878 mmol, 3.0 *eq*). The resulting mixture was heated to 105°C for 36 hours. LCMS showed 56% of the desired compound was found and 39% of the starting material remained. The mixture was cooled. Water (10 mL) was added and the mixture extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated to give a residue. The residue was purified by HPLC to give the title compound (40 mg, 0.107 mmol, 36 % yield). LCMS (ESI): RT = 2.485 min, mass calc. for C₁₇H₁₆F₃N₅O 363.13, m/z found 364.2 [M+H]⁺; ¹HNMR (400 MHz, CHLOROFORM-*d*) δ 9.03 (s, 1H), 8.23 - 8.14 (m, 1H), 7.53 (dd, *J* = 3.5, 8.3 Hz, 3H), 7.42 - 7.34 (m, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.04 (t, *J* = 7.5 Hz, 1H), 4.78 - 4.70 (m, 1H), 4.70 - 4.62 (m, 1H), 4.54 - 4.42 (m, 1H), 2.50 (d, *J* = 4.8 Hz, 1H), 1.37 (d, *J* = 6.3 Hz, 3H).

Example 100: 1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propan-2-ol (Compound 106)



[00474] To a stirred solution of **106-1** (100 mg, 0.293 mmol, 1.0 *eq*, HCl) and K_2CO_3 (162 mg, 1.17 mmol, 4.0 *eq*) in DMF (3 mL) was added **106-2** (95 mg, 0.878 mmol, 90 μL , 3.0 *eq*). The resulting mixture was heated to 105°C for 36 hours. LCMS showed 55% of the desired compound was found and 44% of the starting material remained. The mixture was cooled. Water (10 mL) was added and the mixture extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over Na_2SO_4 , filtered, and concentrated to give a residue. The residue was purified by purified by HPLC to give the title compound (25.00 mg, 66.25 μmol , 22.64% yield). LCMS (ESI): RT = 2.536 min, mass calc. for $\text{C}_{18}\text{H}_{18}\text{F}_3\text{N}_5\text{O}$ 377.15, m/z found 378.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) δ 9.06 (s, 1H), 8.20 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.54 (d, $J = 8.5$ Hz, 3H), 7.42 - 7.35 (m, 1H), 7.29 (d, $J = 8.3$ Hz, 2H), 7.08 - 7.00 (m, 1H), 4.71 (s, 2H), 2.64 (s, 1H), 1.32 (s, 6H).

Example 101: 2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl N-tert-butylcarbamate (Compound 107)

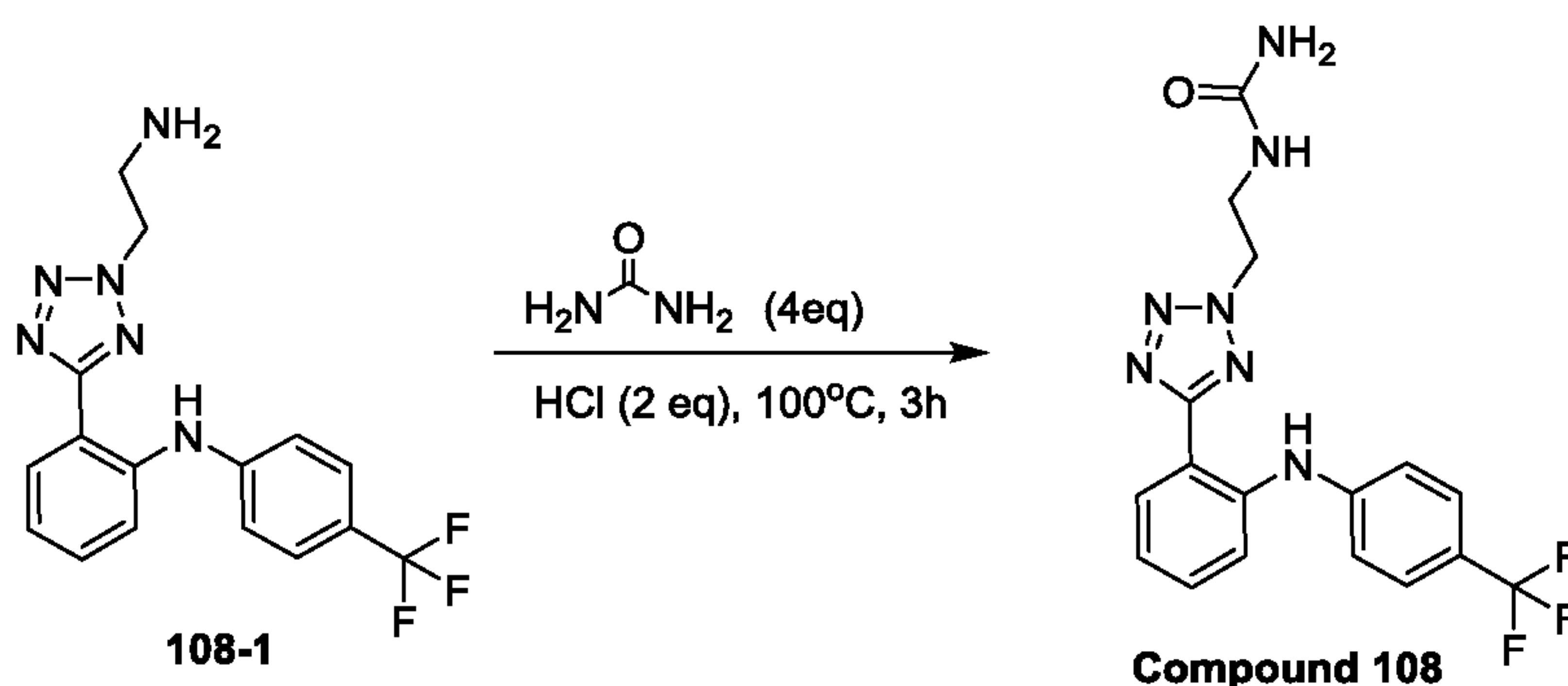


Step 1: 2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol

[00475] To a stirred solution of **107-1** (300 mg, 0.878 mmol, 1.0 *eq*, HCl salt) and K_2CO_3 (121 mg, 0.878 mmol, 1.0 *eq*) in DMF (6 mL) was added **107-2** (165 mg, 1.32 mmol, 94 μL , 1.5 *eq*). The resulting mixture was heated to 80°C for 16 hour. LCMS showed 86% of the desired compound was found and the starting material was consumed completely. The mixture was cooled. Water (15 mL) was added and the mixture extracted with ethyl acetate (3 x 15 mL). The combined organics were dried over magnesium sulfate, filtered and concentrated to give a residue. The residue was purified by flash column chromatography to afford **107-3** (300 mg, 0.764 mmol, 87 % yield) as a light yellow oil. LCMS (ESI): RT = 1.288 min, mass calc. for $\text{C}_{16}\text{H}_{14}\text{F}_3\text{N}_5\text{O}$ 349.12, m/z found 349.9 $[\text{M}+\text{H}]^+$.

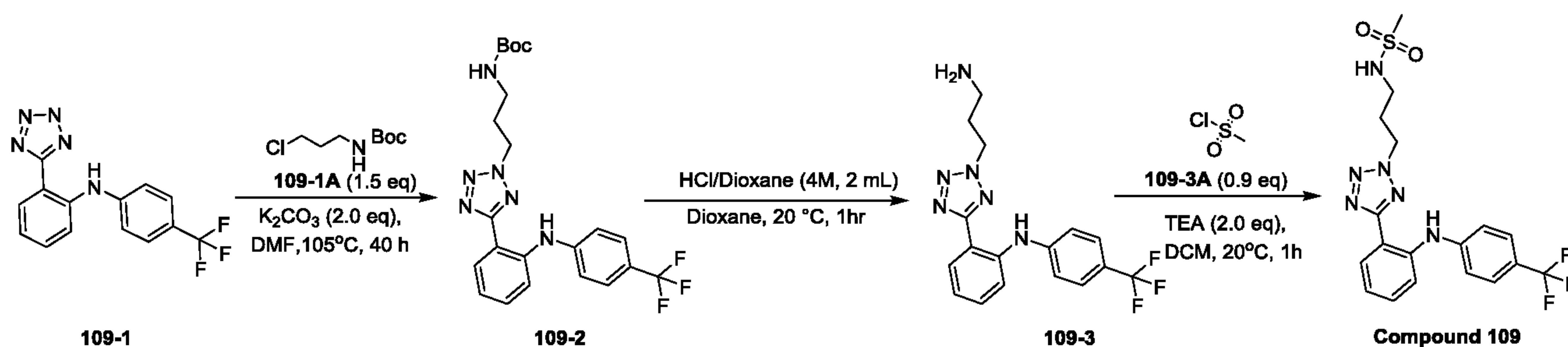
Step 2: 2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl N-tert-butylcarbamate [00476] To a solution of **107-3** (100 mg, 0.258 mmol, 1.0 *eq*) and **107-4** (31 mg, 0.309 mmol, 36 μ L, 1.2 *eq*) in DCM (4 mL) was added HCl (0.3 M, 9 μ L, 1.0 *eq*). The mixture was stirred at 30°C for 16 hours. LCMS showed 33% of the desired compound was found and 60% of the starting material remained. Water (8 mL) was added and the mixture extracted by DCM (3 $\times$ 10mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography to give **Compound 107** (30 mg, 67 μ mol, 26% yield). LCMS (ESI): RT = 2.286 min, mass calc. for C₂₁H₂₃F₃N₆O₂ 448.18, m/z found 449.0 [M+H]⁺; ¹HNMR (400 MHz, CHLOROFORM-*d*) δ 9.00 (s, 1H), 8.19 (d, *J* = 7.9 Hz, 1H), 7.52 (dd, *J* = 3.2, 8.5 Hz, 3H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.03 (t, *J* = 7.5 Hz, 1H), 4.90 (s, 2H), 4.59 (s, 3H), 1.24 (s, 9H).

Example 102: 2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethylurea (Compound 108)



[00477] To a stirred solution of **108-1** (50 mg, 0.130 mmol, 1.0 *eq*, HCl) and urea (31 mg, 0.520 mmol, 28 μ L, 4.0 *eq*) in H₂O (1.0 mL) was added HCl (9 mg, 0.260 mmol, 9 μ L, 2.0 *eq*). The mixture was heated to 100°C for 3 hour. LCMS showed 47% of the desired compound was found and the starting material was consumed completely. The mixture was cooled and extracted with DCM (3 x 4 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated to give a residue. The residue was purified by HPLC to give the title compound (23 mg, 59 μ mol, 45 % yield). LCMS (ESI): RT = 2.222 min, mass calc. for C₁₇H₁₆F₃N₇O 391.14, m/z found 414.0[M+23]⁺; ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.70 (s, 1H), 8.01 (dd, *J* = 1.3, 7.7 Hz, 1H), 7.57 - 7.49 (m, 3H), 7.48 - 7.41 (m, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.14 (t, *J* = 7.1 Hz, 1H), 6.09 (t, *J* = 6.0 Hz, 1H), 5.53 (s, 2H), 4.70 (t, *J* = 5.6 Hz, 2H), 3.54 (q, *J* = 6.0 Hz, 2H).

Example 103: N-(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propyl)methanesulfonamide (Compound 109)



Step 1: tert-butyl (3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propyl)carbamate

[00478] To the solution of **109-1** (50 mg, 0.2 mmol, 1.0 *eq*) in DMF (5 mL) was added **109-1A** (48 mg, 0.2 mmol, 1.5 *eq*) and K₂CO₃ (45. mg, 0.3 mmol, 2.0 *eq*). The mixture was stirred at 105 °C for 40 hr. The reaction was monitored by LCMS. The reaction solution was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂) to give **109-2** (99mg, 0.2 mmol, 92.80% yield).

Step 2: 2-(2-(3-aminopropyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

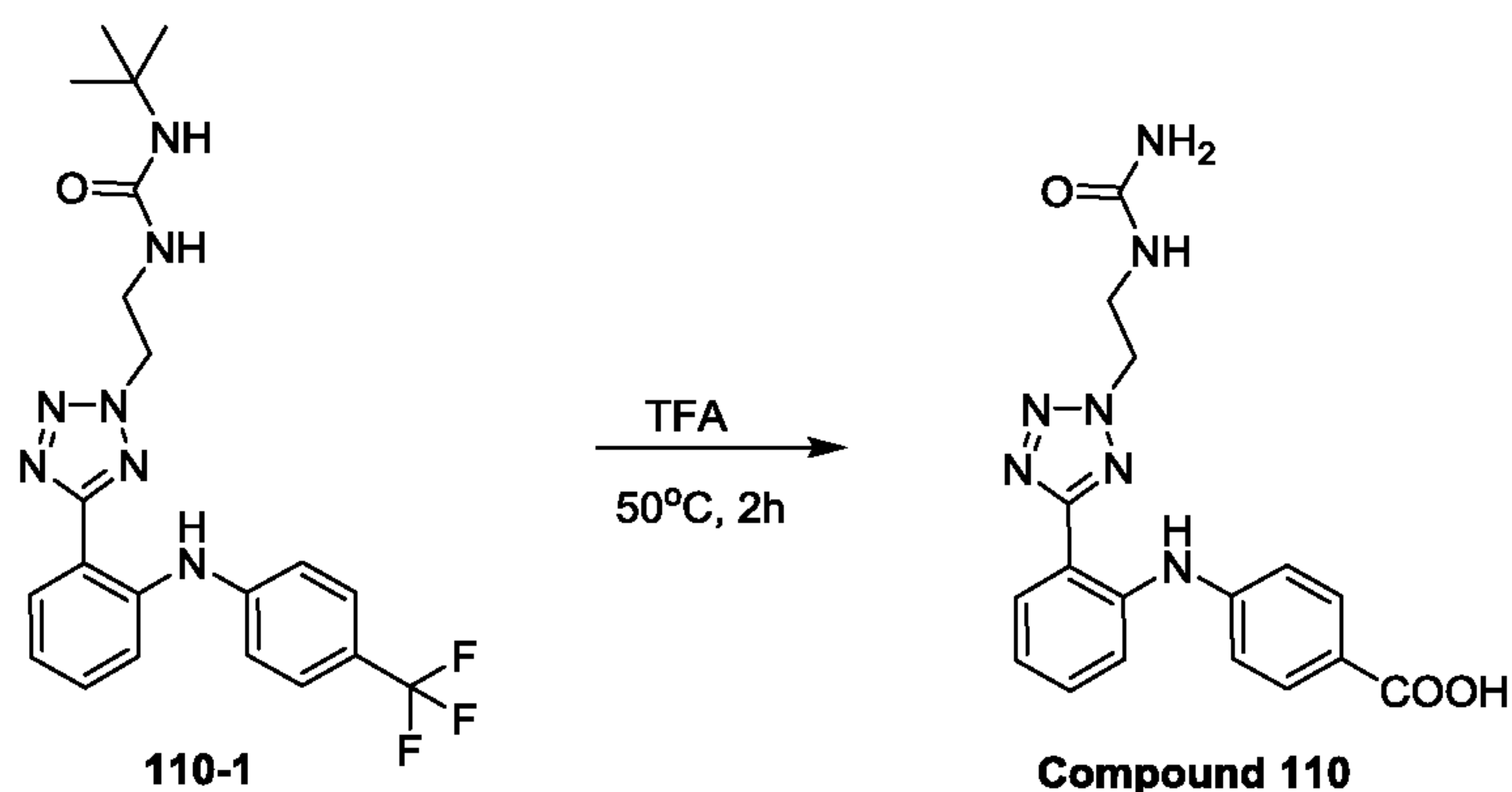
[00479] To a solution of **109-2** (99 mg, 0.2 mmol, 1.0 *eq*) in dioxane (3 mL) was added HCl/dioxane (4 M, 2.00 mL, 37 *eq*). The mixture was stirred at 20 °C for 1 hr. The reaction was monitored by LCMS. The reaction solution was concentrated under reduced pressure to give **109-3** (121 mg, crude, HCl) as yellow oil.

Step 3: N-(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propyl)methane Sulfonamide

Sulfonamide

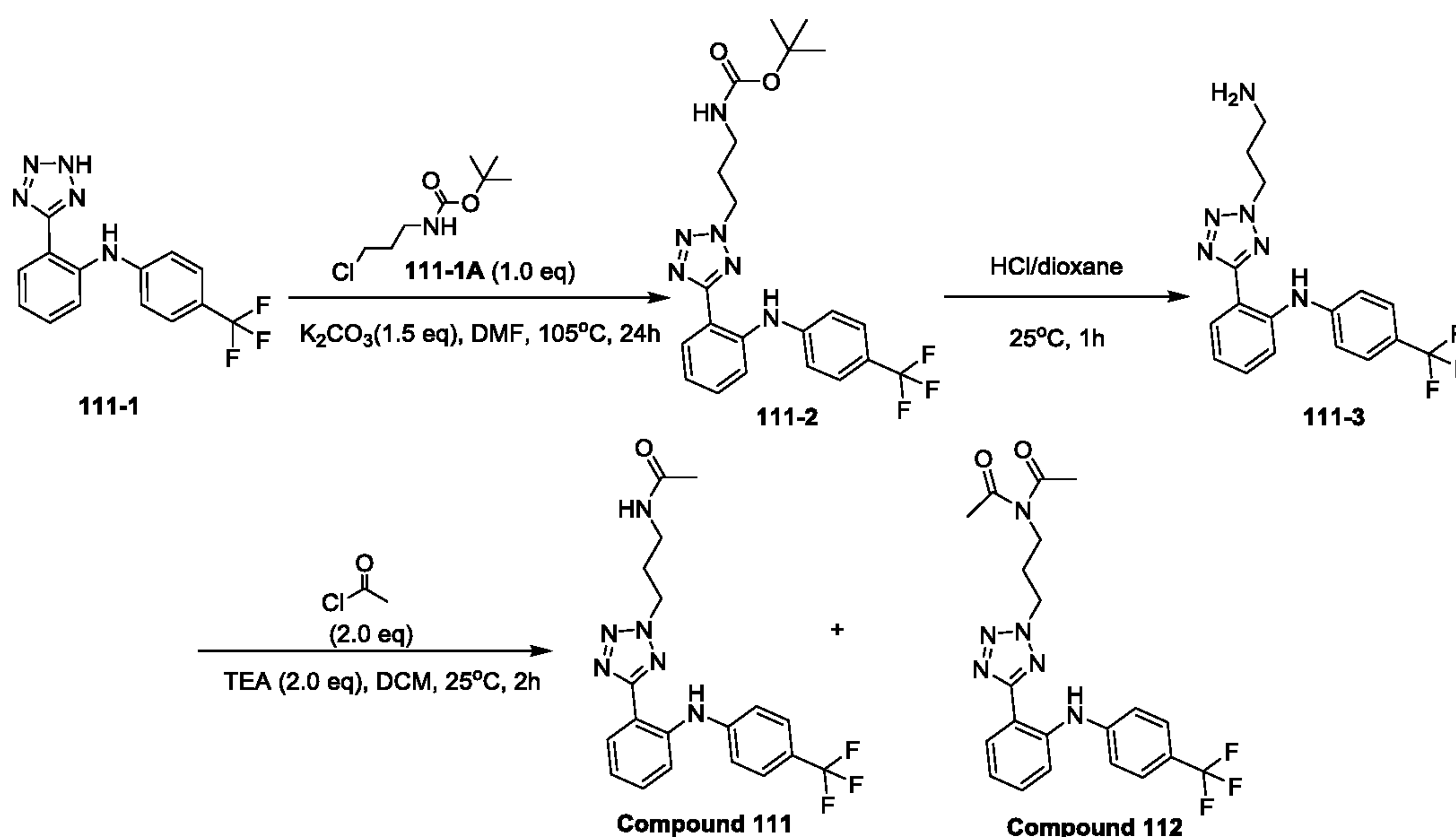
[00480] To a solution of **109-3** (121 mg, 0.3 mmol, 1.0 *eq*, HCl salt) in DCM (5 mL) was added TEA (610 mg, 0.6 mmol, 84 uL, 2.0 *eq*). The mixture was stirred for 5 min at 20 °C, then MsCl (30 mg, 0.3 mmol, 20 uL, 0.9 *eq*) was added to the solution and followed by stirring for 1 hr at 20 °C. The reaction was monitored by LCMS. The reaction solution was added dropwise into H₂O (15 mL). The mixture was extracted with DCM (10 mL*3). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-HPLC to give **Compound 109** (15.39 mg, 35.0 umol, 11.5% yield). LCMS (ESI): RT = 1.308 min, mass calc. for C₁₈H₁₉F₃N₆O₂S 440.12, m/z found 463.0 [M+Na]⁺, ¹HNMR (400MHz, DMSO-*d*₆) δ 8.76 (s, 1H), 8.07 - 8.01 (m, 1H), 7.57 - 7.47 (m, 4H), 7.25 - 7.13 (m, 4H), 4.80 (t, *J*=7.0 Hz, 2H), 3.08 - 3.00 (m, 2H), 2.90 (s, 3H), 2.20 - 2.10 (m, 2H).

Example 104: 4-[2-[2-(2-ureidoethyl)tetrazol-5-yl]anilino]benzoic acid (Compound 110)



[00481] A solution of compound **110-1** (26 mg, 0.058 mmol, 1.0 *eq*) in TFA (1 mL) was stirred at 50°C for 2 hour. The reaction was monitored by LCMS. The reaction mixture was concentrated under reduced pressure to give a residue. The residue product was purified by HPLC to give the title compound (4 mg, 0.011 mmol, 19% yield). LCMS (ESI): RT = 1.692 min, mass calc. for $C_{17}H_{17}N_7O_3$ 367.14, m/z found 389.9 $[M+23]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ 12.82 - 12.01 (m, 1H), 8.80 (s, 1H), 8.06 (d, $J = 6.8$ Hz, 1H), 7.83 (d, $J = 8.8$ Hz, 2H), 7.61 - 7.54 (m, 1H), 7.53 - 7.44 (m, 1H), 7.25 - 7.13 (m, 3H), 6.19 - 6.07 (m, 1H), 5.57 (s, 2H), 4.75 (t, $J = 5.5$ Hz, 2H), 3.68 - 3.52 (m, 2H).

Example 105: N-[3-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propyl]acetamide (Compound 111) and N-acetyl-N-[3-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propyl]acetamide (Compound 112)



Step 1: tert-butyl N-[3-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propyl]carbamate

[00482] To a solution of **111-1** (50.0 mg, 0.3 mmol, 1.0 *eq*) in DMF (2.0 mL) was added K_2CO_3 (53.5 mg, 0.4 mmol, 1.5 *eq*) and **111-1A** (94.5 mg, 0.3 mmol, 1.2 *eq*). The mixture was stirred at 105 °C for 24 h. LC-MS showed 40% of **111-1** remained. Several new peaks were detected on LC-

MS and 54% of the desired compound was detected. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (10 mL * 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to provide **111-2** (110.0 mg, 237.85 μ mol, 92 % yield). LCMS (ESI): RT = 0.940 min, mass calc. for C₂₂H₂₅F₃N₆O 462.20, m/z found 407.1 [M-tBu+H]⁺.

Step 2: 2-[2-(3-aminopropyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline

[00483] To a solution of **111-2** (110.0 mg, 0.2 mmol, 1.0 eq) in dioxane (1.0 mL) was added HCl/dioxane (3.0 mL). The mixture was stirred at 25 °C for 1 h. LC-MS showed **111-2** was consumed completely and 97% of the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give **111-3** (100.0 mg, crude). LCMS (ESI): RT = 0.713 min, mass calc. for C₁₇H₁₇F₃N₆ 362.15, m/z found 342.9 [M-F+H]⁺.

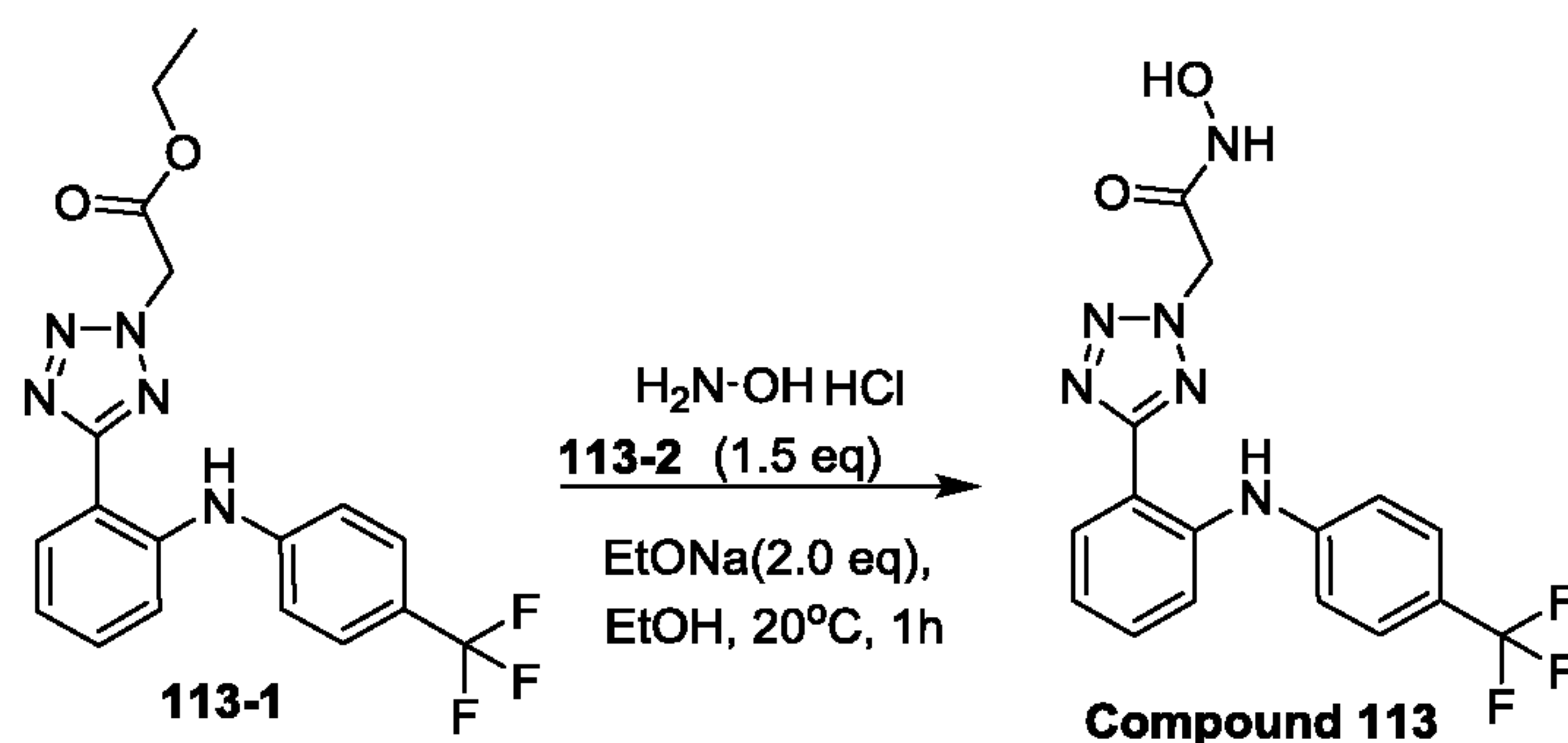
Step 3: N-[3-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propyl]acetamide and N-acetyl-N-[3-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propyl]acetamide

[00484] To a solution of **111-3** (90.0 mg, 0.2 mmol, 1.0 eq) in DCM (5.0 mL) was added TEA (50.2 mg, 0.5 mmol, 68.8 μ L, 2.0 eq) and acetyl chloride (29.2 mg, 0.4 mmol, 26.6 μ L, 1.5 eq). The mixture was stirred at 25 °C for 3 h. LC-MS showed **111-3** was consumed completely. Several new peaks were shown on LC-MS, and 51% of **Compound 111** and 36% of **Compound 112** was detected. The residue was purified by prep-HPLC to give **Compound 111** (18.68 mg, 46.19 μ mol, 18% yield) and **Compound 112** (6.81 mg, 15.10 μ mol, 6% yield).

[00485] Compound 111: LCMS (ESI): RT = 1.772 min, mass calc. for C₁₉H₁₉F₃N₆O 404.16, m/z found 427.0 [M+Na]⁺; ¹HNMR (400MHz, DCCl₃) δ (ppm) 9.00 (s, 1H), 8.19-8.17 (m, *J*=1.4, 7.9 Hz, 1H), 7.55-7.51 (m, *J*=5.0, 8.0 Hz, 3H), 7.41-7.35 (m, 1H), 7.30 (d, *J*=8.3 Hz, 2H), 7.05 (t, *J*=7.5 Hz, 1H), 5.76 (s, 1H), 4.77 (t, *J*=6.8 Hz, 2H), 3.35 (q, *J*=6.5 Hz, 2H), 2.31 (quin, *J*=6.7 Hz, 2H), 1.99 (s, 3H).

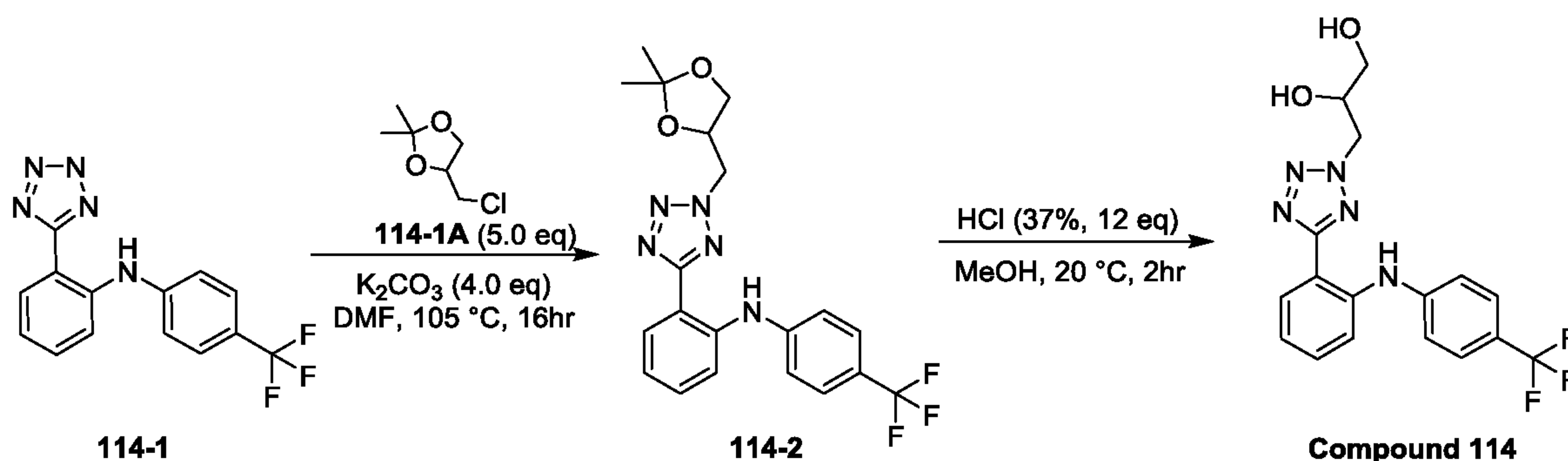
[00486] Compound 112: LCMS (ESI): RT = 1.363 min, mass calc. for C₂₁H₂₁F₃N₆O₂ 446.42, m/z found 469.0 [M+Na]⁺; ¹HNMR (400MHz, DCCl₃) δ (ppm) 8.43 (s, 1H), 7.63 (s, 2H), 7.54-7.44 (m, 2H), 7.40 (s, 1H), 7.31 (s, 2H), 6.32 (s, 1H), 4.76-4.60 (m, 2H), 3.01 (s, 1H), 2.75 (s, 1H), 2.27-2.06 (m, 2H), 1.97 (s, 6H).

Example 106: 2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanehydroxamic acid (Compound 113)



[00487] To a solution of **113-1** (50.0 mg, 0.13 mmol, 1.0 *eq*) and **113-2** (13.3 mg, 0.19 mmol, 1.5 *eq*, HCl) in EtOH (3.0 mL) was added EtONa (17.4 mg, 0.26 mmol, 2.0 *eq*). The resulting mixture was stirred at 20 °C for 1 hour. LCMS showed the desired compound was formed. The reaction was acidified by adding 1M HCl (3 mL) and filtered to give a crude product. The crude product was purified by prep-HPLC to give the title compound (15.66 mg, 41.39 μmol , 32.40% yield). LCMS (ESI): RT = 0.787 min, mass calc. for $\text{C}_{16}\text{H}_{13}\text{F}_3\text{N}_6\text{O}_2$ 378.11, m/z found 379.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.13 (s, 1H), 9.31 (s, 1H), 8.79 (s, 1H), 8.04 (dd, $J = 1.3, 8.0$ Hz, 1H), 7.59 - 7.54 (m, 3H), 7.52 - 7.47 (m, 1H), 7.26 (d, $J = 8.3$ Hz, 2H), 7.18 (t, $J = 7.4$ Hz, 1H), 5.44 (s, 2H).

Example 107: 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propane-1,2-diol (Compound 114)



Step 1: 2-(2-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

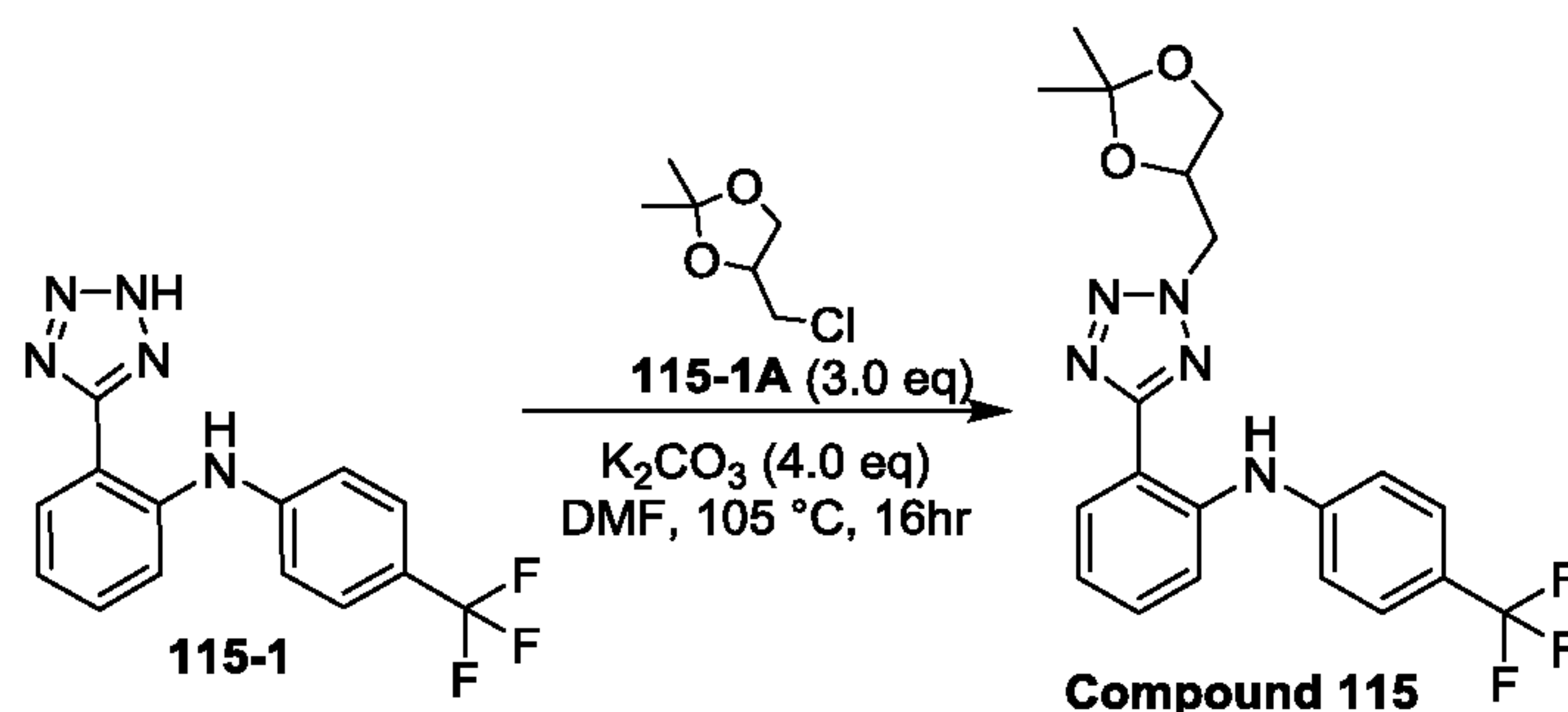
[00488] To the solution of **114-1** (300 mg, 1.0 mmol, 1.0 *eq*) in DMF (5 mL) was added **114-1A** (740 mg, 5.0 mmol, 698 μL , 5.0 *eq*) and K_2CO_3 (543 mg, 3.9 mmol, 4.0 *eq*). The solution was stirred for 16 hr at 105 °C. The reaction was monitored by LCMS. The reaction solution was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2) to give **114-2** (41 mg, 98 μmol , 10% yield).

Step 2: 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propane-1,2-diol

[00489] To the solution of **114-2** (20 mg, 48 μmol , 1.0 *eq*) in MeOH (4 mL) was added HCl (20 mg, 0.6 mmol, 20 μL , 12 *eq*). The mixture was stirred at 20 °C for 2 hr. The reaction was monitored

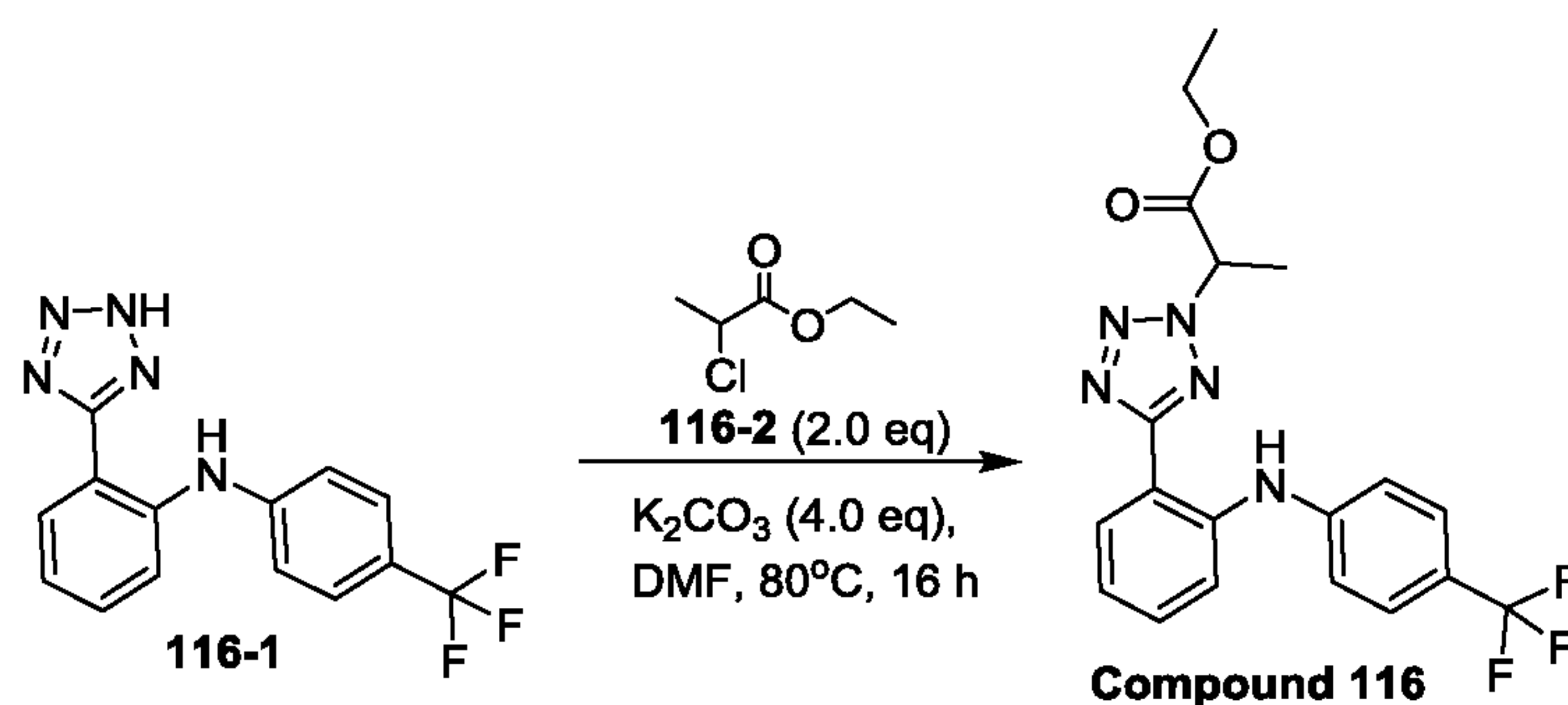
by LCMS. The reaction solution was concentrated under reduced pressure. The residue was purified by Prep-HPLC to give **Compound 114** (7.86 mg, 20.7 μ mol, 43.45% yield). LCMS (ESI): RT = 0.803 min, mass calc. for $C_{17}H_{16}F_3N_5O_2$ 379.13, m/z found 380.0 $[M+H]^+$, ^1H NMR (400MHz, CHLOROFORM-*d*) δ 8.18 (d, $J=7.5$ Hz, 1H), 7.59 - 7.50 (m, 3H), 7.39 (t, $J=7.3$ Hz, 1H), 7.32 - 7.28 (m, 2H), 7.05 (t, $J=7.4$ Hz, 1H), 4.93 - 4.77 (m, 2H), 4.47 - 4.35 (m, 1H), 3.92 - 3.65 (m, 2H).

Example 108: 2-(2-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 115)



[00490] To the solution of **115-1** (100 mg, 0.3 mmol, 1.0 *eq*) in DMF (5 mL) was added **115-1A** (148 mg, 1.0 mmol, 140 μ L, 3.0 *eq*) and K_2CO_3 (181 mg, 1.3 mmol, 4.0 *eq*). The solution was stirred for 16 hr at 105 °C. The reaction was monitored by LCMS. The reaction solution was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2) and then purified by Prep-HPLC to give the title compound (8.51 mg, 20.3 μ mol, 6.2% yield). LCMS (ESI): RT = 0.939 min, mass calc. for $C_{20}H_{20}F_3N_5O_2$ 419.16, m/z found 420.0 $[M+H]^+$, ^1H NMR (400MHz, CHLOROFORM-*d*) δ 9.01 (s, 1H), 8.22 - 8.17 (m, 1H), 7.57 - 7.50 (m, 3H), 7.38 (t, $J=7.8$ Hz, 1H), 7.32 - 7.26 (m, 2H), 7.04 (t, $J=7.2$ Hz, 1H), 4.89 - 4.77 (m, 1H), 4.77 - 4.66 (m, 2H), 4.20 - 4.14 (m, 1H), 4.07 - 4.00 (m, 1H), 1.43 (s, 3H), 1.35 (s, 3H).

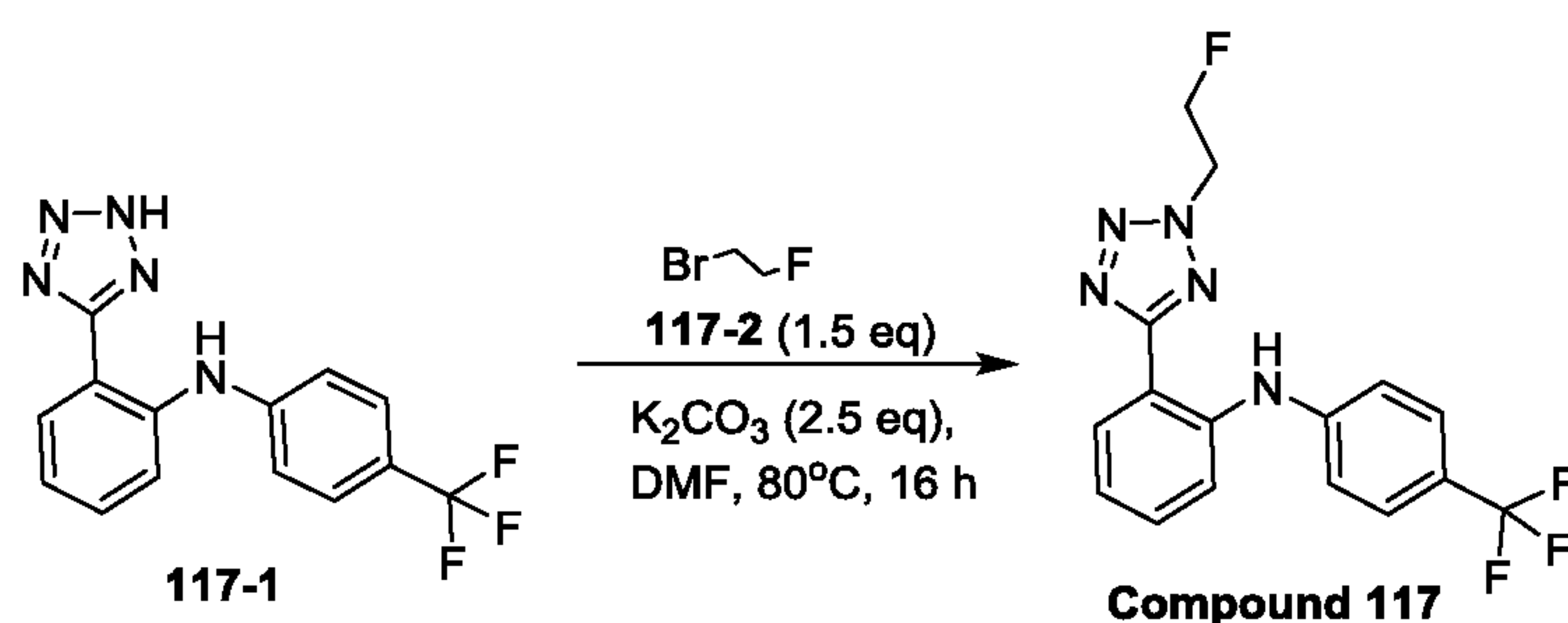
Example 109: ethyl 2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propanoate (Compound 116)



[00491] To a solution of **116-1** (150 mg, 0.491 mmol, 1.0 *eq*) and K_2CO_3 (272 mg, 1.97 mmol, 4.0 *eq*) in DMF (4 mL) was **116-2** (120 mg, 0.983 mmol, 106 μ L, 2.0 *eq*). The resulting mixture was stirred at 100 °C for 16 hours. LCMS showed 79% desired compound was found and the starting

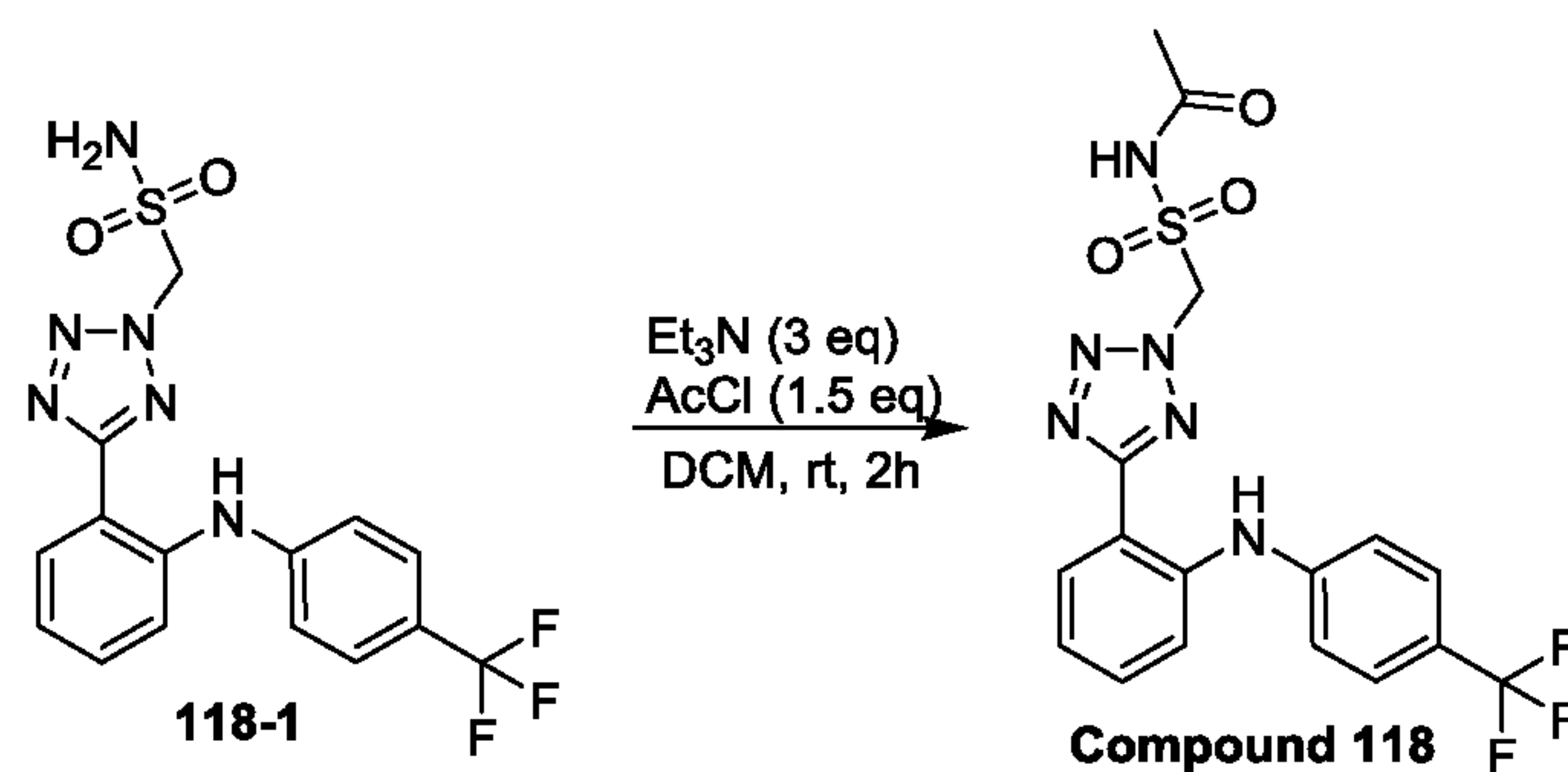
material was consumed completely. Water (10 mL) was added and the mixture extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated to give a residue. The residue was purified by flash column chromatography to afford the product (180 mg, 0.404 mmol, 82 % yield). 80 mg of the product was purified by HPLC to give the title compound (28.39 mg). LCMS (ESI): RT = 0.956 min, mass calc. for C₁₉H₁₈F₃N₅O₂ 405.14, m/z found 406.1 [M+H]⁺; ¹HNMR (400 MHz, CHLOROFORM-*d*) δ 9.02 (s, 1H), 8.23 (dd, *J* = 1.3, 7.8 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 3H), 7.44 - 7.35 (m, 1H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 5.70 (q, *J* = 7.4 Hz, 1H), 4.25 (q, *J* = 7.3 Hz, 2H), 2.05 (d, *J* = 7.3 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H).

Example 110: 2-[2-(2-fluoroethyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 117)



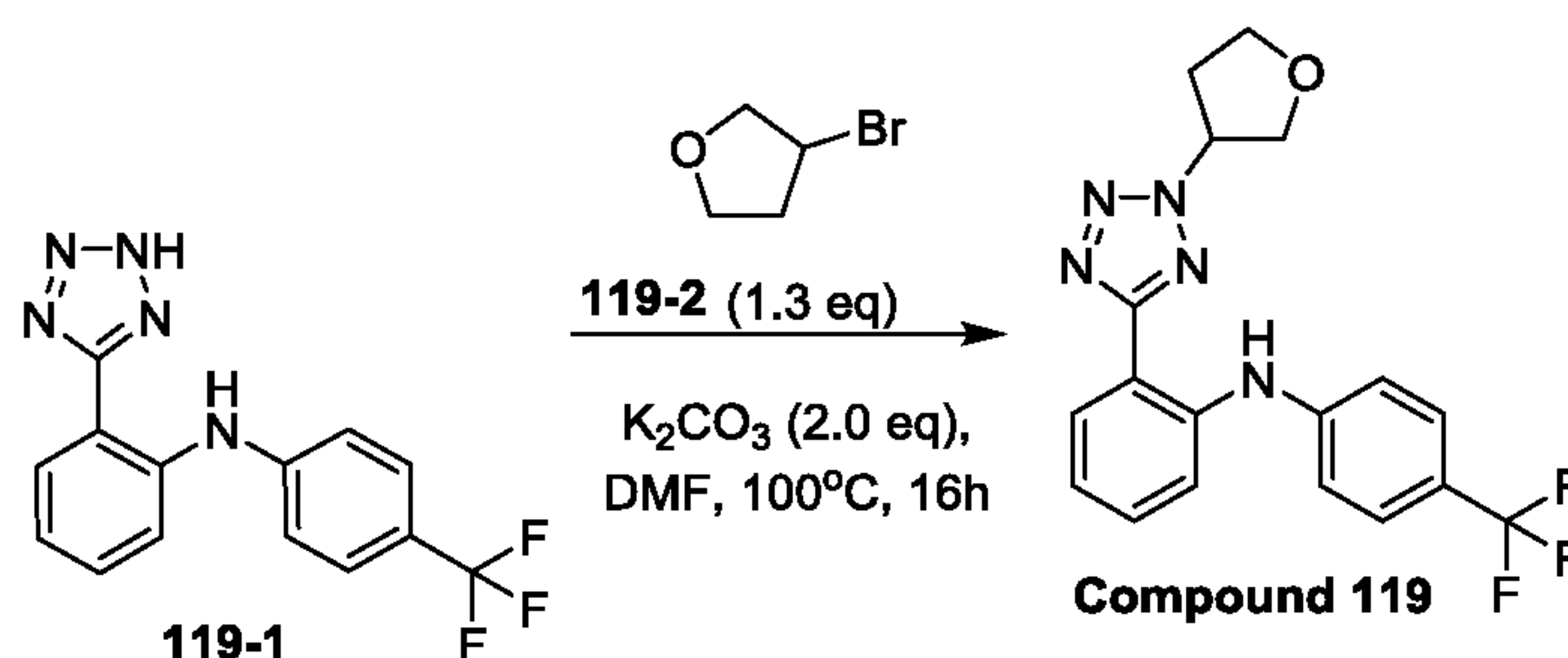
[00492] To a stirred solution of **117-1** (50 mg, 0.146 mmol, 1.0 *eq*, HCl) and K₂CO₃ (51 mg, 0.366 mmol, 2.5 *eq*) in DMF (2 mL) was added **117-2** (19 mg, 0.146 mmol, 1.0 *eq*). The resulting mixture was heated to 80°C for 16 hours. LCMS showed 39% desired compound was formed and the starting material was consumed completely. The mixture was cooled. Water (10 mL) was added and the mixture extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by purified by HPLC to give the title compound (15 mg, 42.7 umol, 29% yield). LCMS (ESI): RT = 2.716 min, mass calc. for C₁₆H₁₃F₄N₅ 351.11, m/z found 352.0 [M+H]⁺; ¹HNMR (400 MHz, CHLOROFORM-*d*) δ 9.01 (s, 1H), 8.21 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.54 (dd, *J* = 2.5, 8.5 Hz, 3H), 7.43 - 7.34 (m, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.09 - 7.00 (m, 1H), 5.11 - 5.01 (m, 2H), 5.01 - 4.93 (m, 2H).

Example 111: N-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methylsulfonyl]acetamide (Compound 118)



[00493] To a solution of **118-1** (100 mg, 0.25 mmol, 1.00 *eq*) and Et₃N (76 mg, 0.75 mmol, 0.1 mL, 3.00 *eq*) in DCM (5 mL) was added acetyl chloride (29.6 mg, 0.38 mmol, 26.87 μ L, 1.50 *eq*). The reaction was stirred at 25°C for 16 hr. LCMS showed that the desired MS signal was detected. The reaction was then concentrated. The reaction was purified by Prep.HPLC (HCl condition) to give the initial title compound (10 mg) and was then further re-purified by Prep.HPLC (basic conditions) to give the title compound (2.30 mg, 5.22 μ mol, 2.08% yield). ¹HNMR and LCMS confirmed that desired product was obtained. LCMS (ESI): RT = 0.843 min, mass calcd. for C₁₇H₁₅F₃N₆O₃S, 440.09 m/z found 441.0[M+H]⁺. ¹HNMR (400MHz, DMSO-*d*₆) δ 8.87 (s, 1H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.70 - 7.60 (m, 3H), 7.55 - 7.45 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.15 (br, 1H), 5.99 (s, 2H), 1.71 (s, 3H).

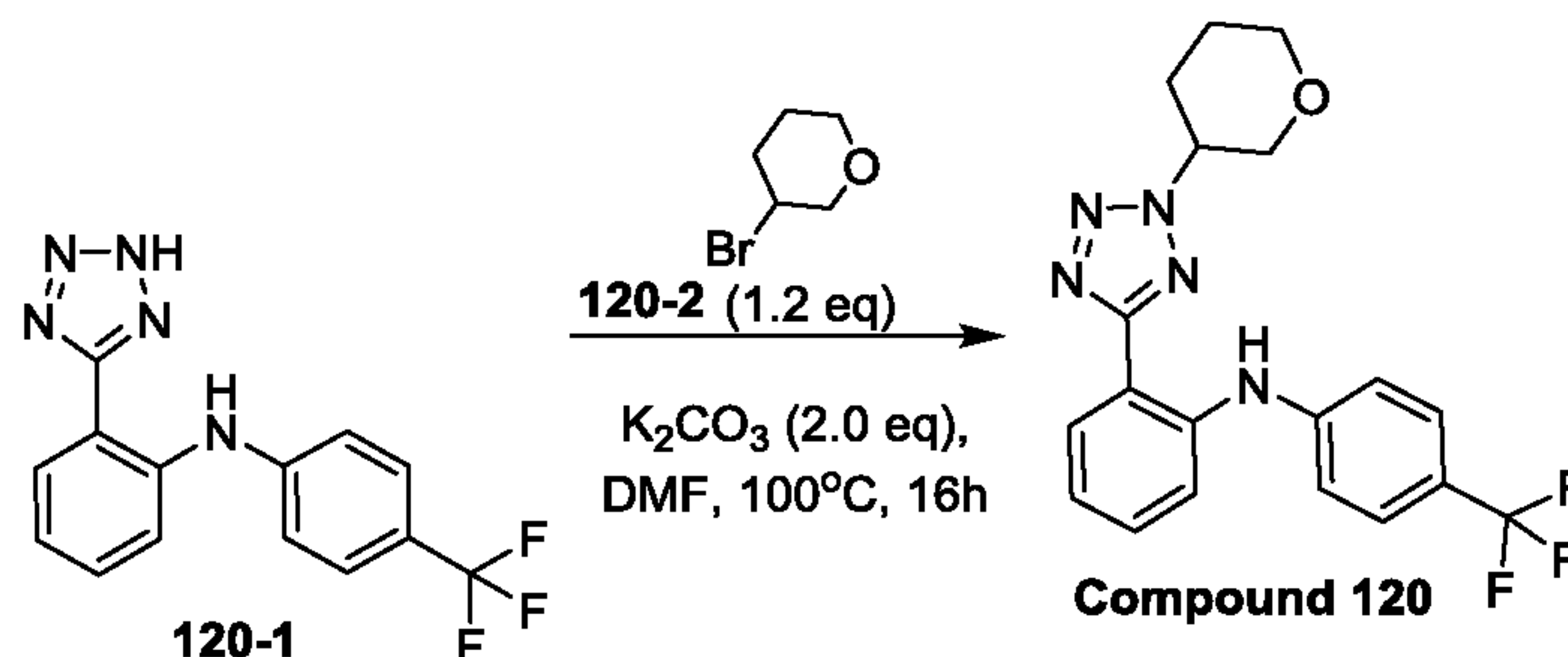
Example 112: 2-(2-(tetrahydrofuran-3-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 119)



[00494] To a solution of **119-1** (50 mg, 0.16 mmol, 1.00 *eq*) and **119-2** (32.2 mg, 0.21 mmol, 1.30 *eq*) in DMF (3 mL) was added K₂CO₃ (45.3 mg, 0.33 mmol, 2.00 *eq*). The reaction was heated to 100°C for 16 hr. LCMS showed that ~80% of desired MS signal was detected. The reaction was diluted with EtOAc (20 mL) and washed with brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by Prep.HPLC (acidic conditions) to give the title compound (17.36 mg, 46.25 μ mol, 28.24% yield). ¹HNMR and LCMS confirmed that the desired product was obtained. LCMS (ESI): RT = 0.910 min, mass calc. for C₁₈H₁₆F₃N₅O 375.13, m/z found 376.0[M+H]⁺; ¹HNMR (400 MHz, CDCl₃) δ 9.05 (s, 1H), 8.21 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.60 - 7.50 (m, 3H), 7.40 - 7.35 (m, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.05 (t, *J* = 8.0 Hz, 1H),

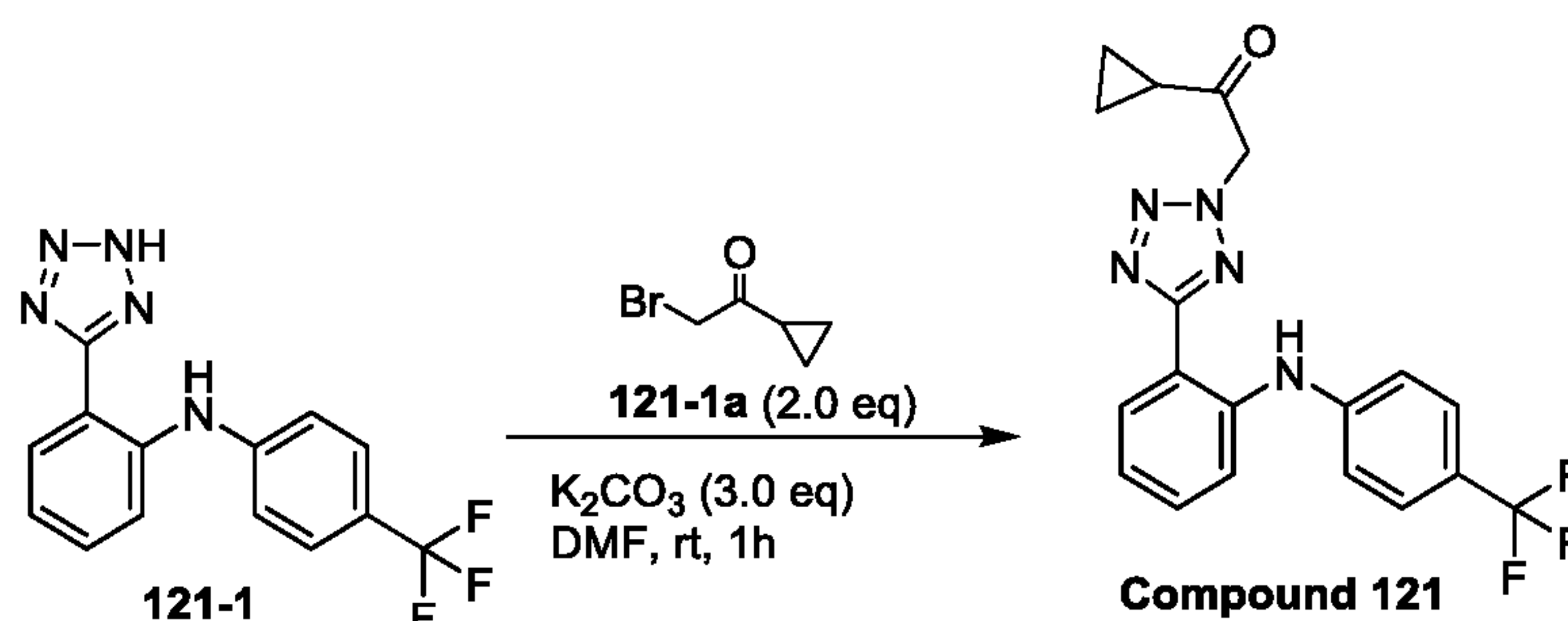
5.65 - 5.50 (m, 1H), 4.40 - 4.25 (m, 3H), 4.15 - 4.00 (m, 1H), 2.80 - 2.65 (m, 1H), 2.65 - 2.50 (m, 1H).

Example 113: 2-(2-tetrahydropyran-3-yltetrazol-5-yl)-N-[4-(trifluoromethyl)phenyl]aniline (Compound 120)



[00495] To a solution of **120-1** (50 mg, 0.16 mmol, 1.00 *eq*) and **120-2** (35 mg, 0.21 mmol, 1.30 *eq*) in DMF (3 mL) was added K₂CO₃ (45.37 mg, 0.33 mmol, 2.00 *eq*). The reaction was heated at 100°C for 16 hr. LCMS showed that only starting material was present. The reaction was heated to 150°C for 1 hr under microwave conditions. LCMS showed that about 20% of the desired MS signal was detected. The reaction was continued with stirring at 150°C for 3 hr. LCMS showed that 30% of the desired MS signal was detected. The reaction was diluted with EtOAc (20 mL) and washed with brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by Prep.HPLC (base) to give the title compound (8.72 mg, 22.40 μ mol, 13.67% yield). LCMS (ESI): RT = 0.946 min, mass calc. for C₁₉H₁₈F₃N₅O 389.15, m/z found 390.1[M+H]⁺; ¹HNMR (400 MHz, CDCl₃-*d*) δ 9.08 (s, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.65 - 7.50 (m, 3H), 7.40 - 7.35 (m, 1H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.05 (t, *J* = 8.0 Hz, 1H), 5.00 - 4.85 (m, 1H), 4.35 - 4.25 (m, 1H), 4.05 - 3.90 (m, 2H), 3.70 - 3.55 (m, 1H), 2.50 - 2.35 (m, 2H), 2.05 - 1.90 (m, 2H).

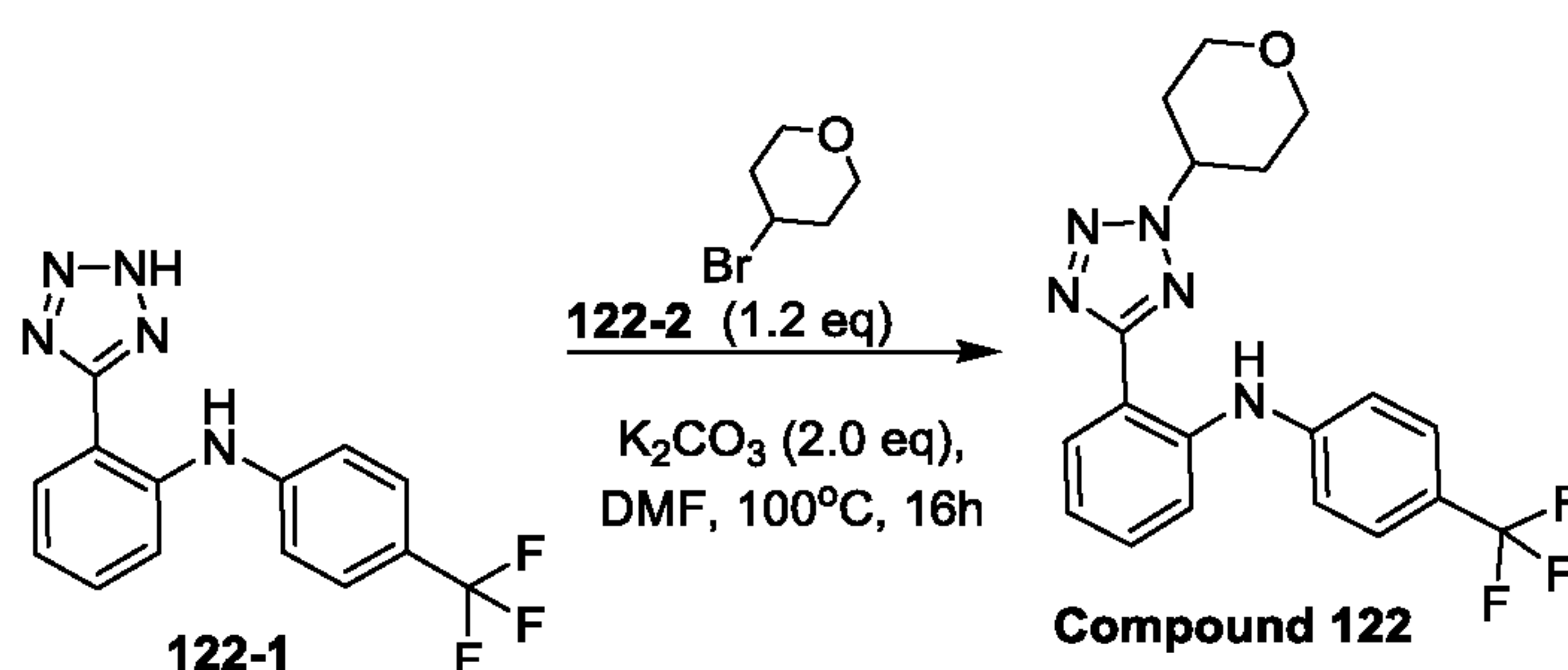
Example 114: 1-cyclopropyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanone (Compound 121)



[00496] To a mixture of **121-1** (60 mg, 0.197 mmol, 1.00 *eq*) and **121-1a** (64 mg, 0.393 mmol, 2.00 *eq*) in DMF (2 mL) was added K₂CO₃ (82 mg, 0.590 mmol, 3.00 *eq*) in one portion at 10 °C under N₂. The mixture was stirred at 10 °C for 1 hour. TLC showed the starting material was consumed completely and many new spot were formed. LCMS showed one main peak with the

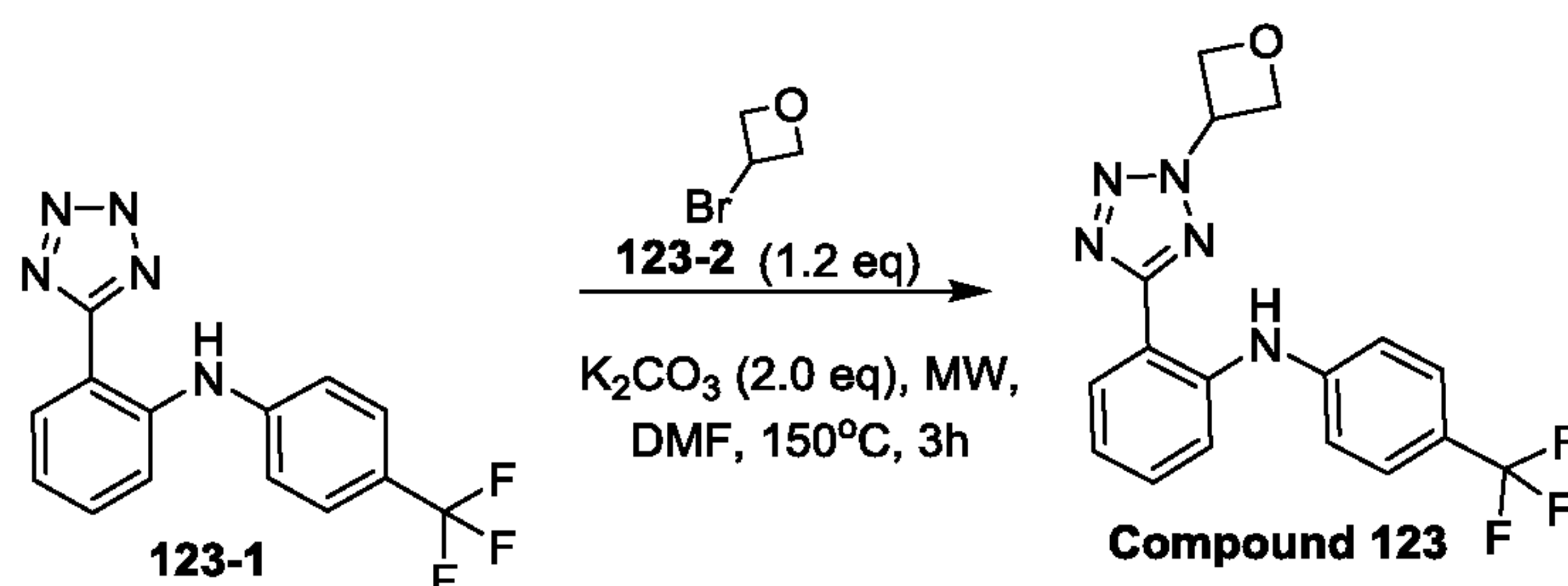
desired MS was detected. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (40 mL * 3), dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by prep-HPLC (basic condition) to provide the title compound (36.66 mg, 94 μ mol, 48.2% yield). LCMS (ESI): RT = 0.920 min, mass calcd. for C₁₉H₁₆F₃N₅O 387.13, m/z found 388.0[M+H]⁺. ¹HNMR (400MHz, CHLOROFORM-*d*) δ 8.97 (s, 1H), 8.21 (dd, *J*=7.60, 1.20 Hz, 1H), 7.57 - 7.51 (m, 3H), 7.42 - 7.35 (m, 1H), 7.30 (d, *J*=8.80 Hz, 2H), 7.04 (t, *J*=7.60 Hz, 1H), 5.69 (s, 2H), 1.97 - 1.88 (m, 1H), 1.26 (t, *J*=4.00 Hz, 2H), 1.1 - 1.07 (m, 2H).

Example 115: 2-(2-tetrahydropyran-4-yltetrazol-5-yl)-N-[4-(trifluoromethyl)phenyl]aniline (Compound 122)



[00497] To a solution of **122-1** (50.0 mg, 0.16 mmol, 1.0 *eq*) in DMF (5.0 mL) was added K₂CO₃ (45.23 mg, 0.33 mmol, 2.0 *eq*) and **122-2** (32.4 mg, 0.120 mmol, 1.2 *eq*). The mixture was stirred at 100 °C for 24 hours under an N₂ atmosphere. LCMS showed the desired compound was formed. The reaction was filtered to give a crude product. The crude product was purified by prep-HPLC to give the title compound (27.33 mg, 70.19 μ mol, 42.85% yield). LCMS (ESI): RT = 0.932 min, mass calc. for C₁₉H₁₈F₃N₅O 389.15, m/z found 390.0[M+H]⁺; ¹HNMR (400 MHz, CDCl₃-*d*) δ 9.08 (s, 1H), 8.21 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 3H), 7.41 - 7.35 (m, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.05 (t, *J* = 7.3 Hz, 1H), 5.07 - 4.95 (m, 1H), 4.16 (td, *J* = 3.3, 12.0 Hz, 2H), 3.64 (dt, *J* = 2.3, 11.5 Hz, 2H), 2.46 - 2.24 (m, 4H).

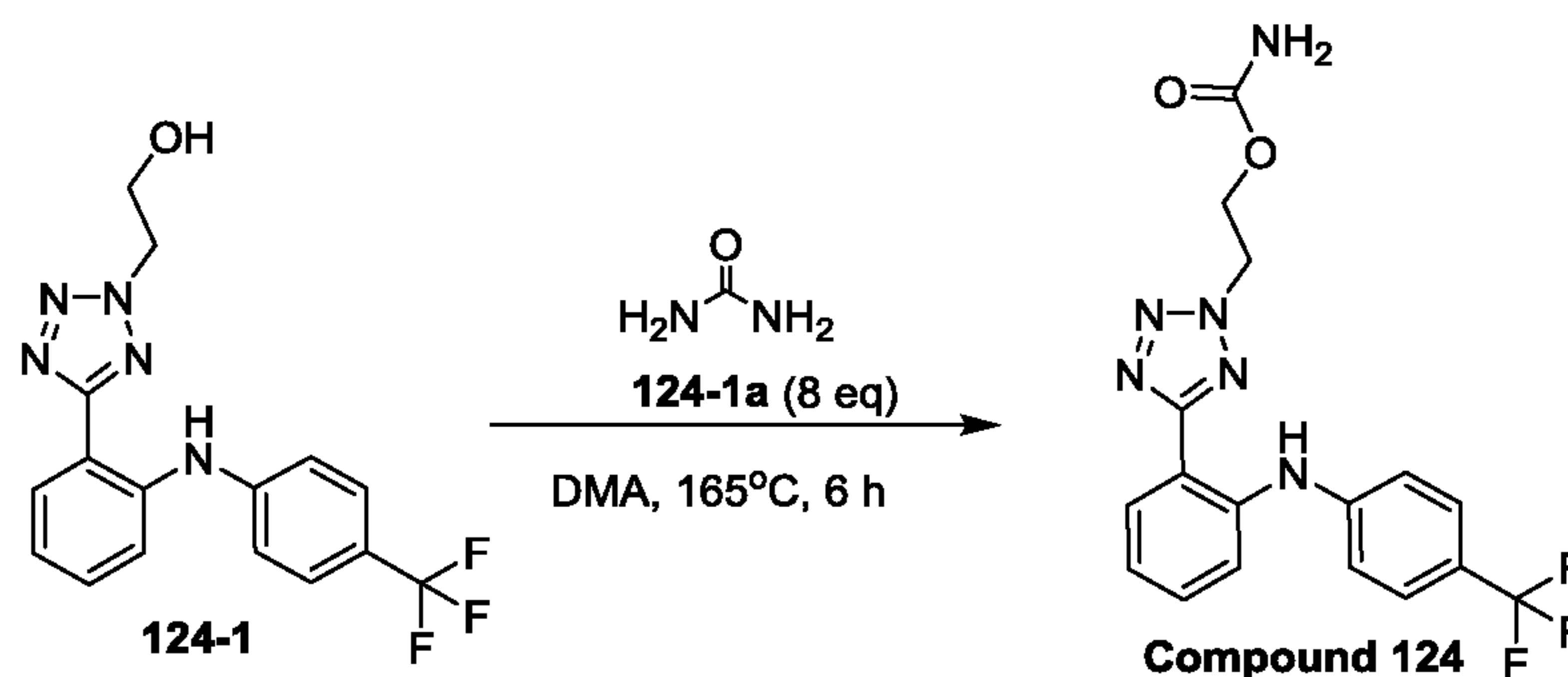
Example 116: 2-[2-(oxetan-3-yl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 123)



[00498] **123-1** (50.0 mg, 0.16 mmol, 1.0 *eq*), **123-2** (26.9 mg, 0.20 mmol, 1.2 *eq*) and K₂CO₃ (45.3 mg, 0.33 mmol, 2.0 *eq*) were taken up into a microwave tube in DMF (2.0 mL). The sealed tube

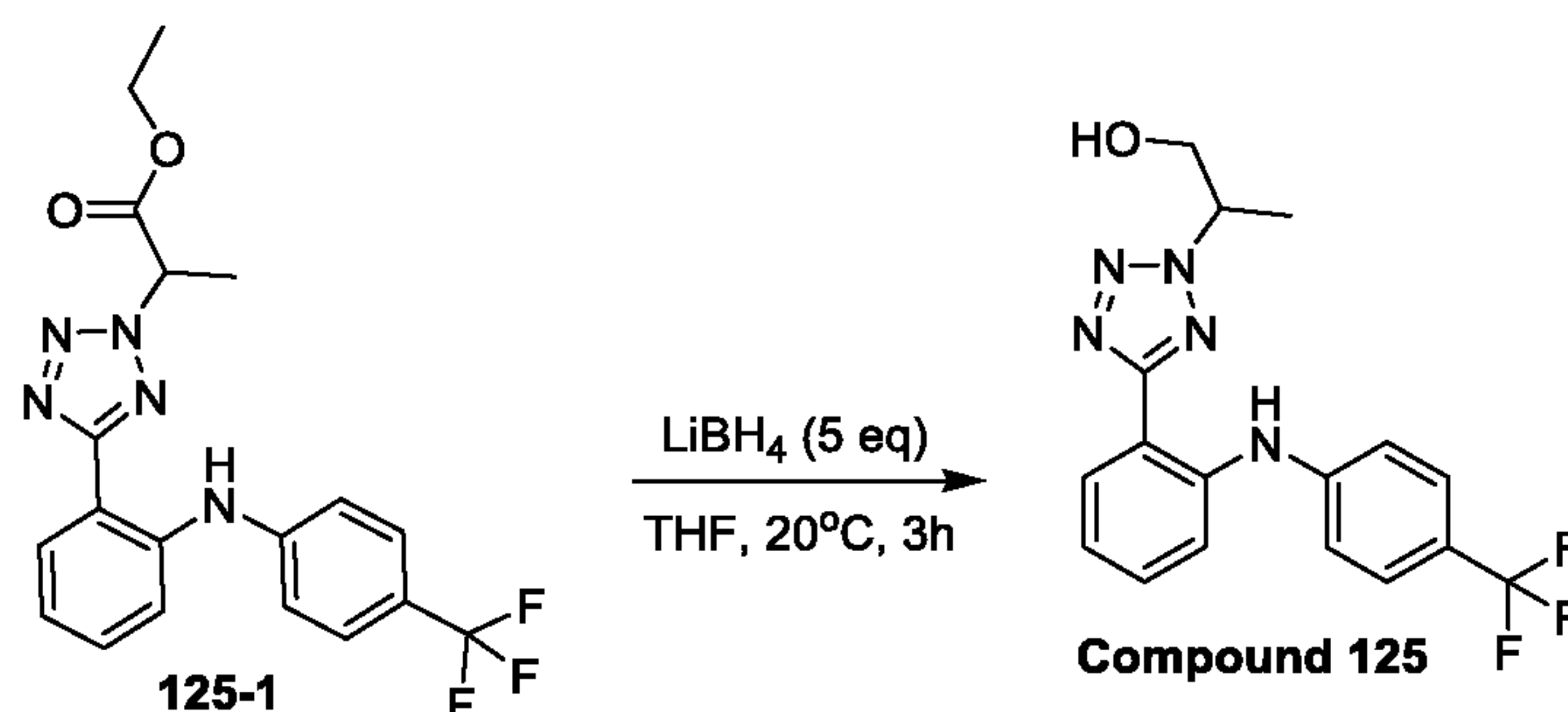
was heated at 150 °C for 3 hours under microwave conditions. LCMS showed the desired compound was formed. The reaction was filtered to give a crude product. The crude product was purified by prep-HPLC to give the title compound (2.57 mg, 6.46 μ mol, 3.94% yield, HCl). LCMS (ESI): RT = 0.890 min, mass calc. for $C_{17}H_{14}F_3N_5O$ 361.12, m/z found 362.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3-d$) δ 9.01 (s, 1H), 8.25 (dd, J = 1.5, 7.9 Hz, 1H), 7.55 (d, J = 8.4 Hz, 3H), 7.41 (dt, J = 1.5, 7.8 Hz, 1H), 7.31 (d, J = 8.6 Hz, 2H), 7.10 - 7.05 (m, 1H), 6.15 - 6.07 (m, 1H), 5.31 - 5.25 (m, 2H), 5.24 - 5.19 (m, 2H).

Example 117: 2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethyl carbamate (Compound 124)



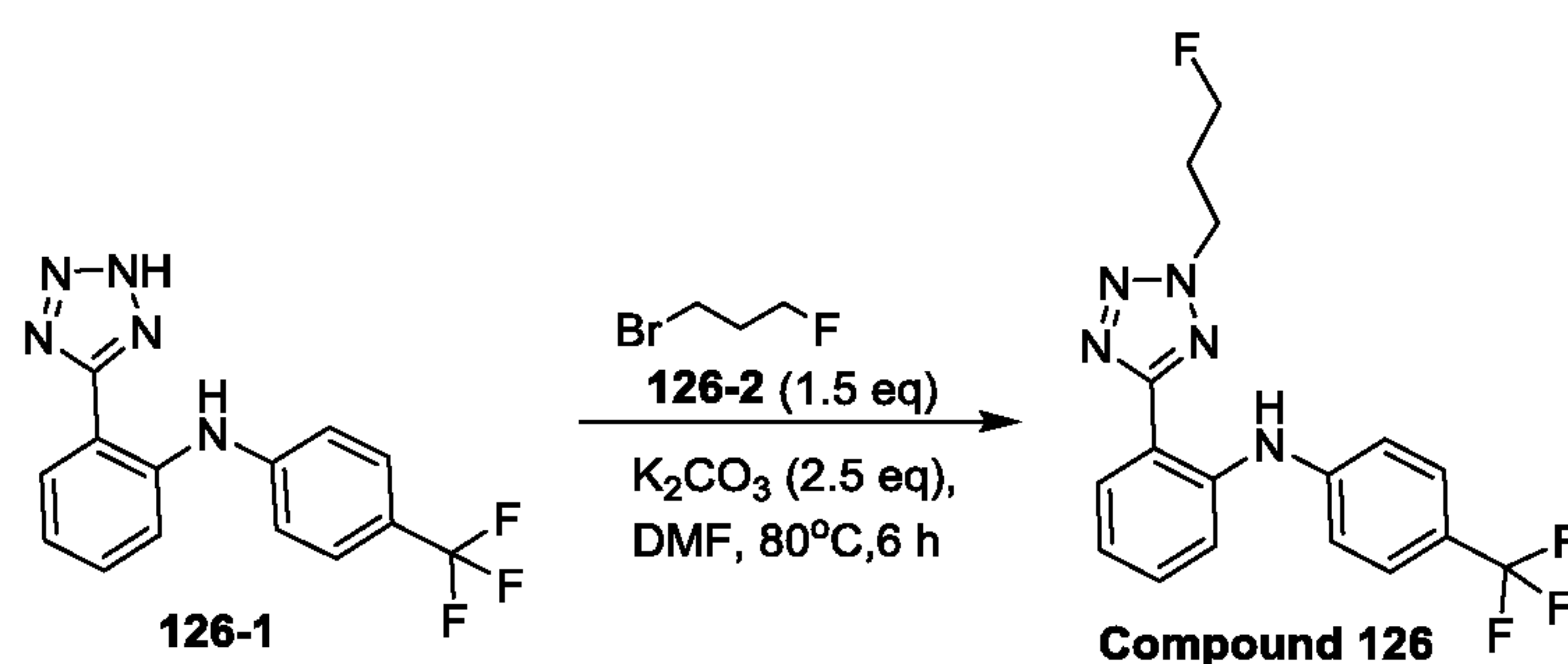
[00499] To a stirred solution of **124-1** (50 mg, 0.143 mmol, 1.0 *eq*) in DMA (100 μ L) was added **124-1a** (69 mg, 1.15 mmol, 8.0 *eq*). The resulting mixture was heated to 165°C for 5 hour. LCMS and TLC (Petroleum ether: Ethyl acetate =3/1) showed the desired compound was formed and the starting material remained. The mixture was cooled. Water (15 mL) was added and the mixture extracted with ethyl acetate (3 x 15 mL). The combined organics were dried over magnesium sulfate, filtered and concentrated to give a residue. The residue was purified by HPLC to give the title compound (10 mg, 25.49 μ mol, 18% yield). LCMS (ESI): RT = 0.834 min, mass calc. for $C_{17}H_{15}F_3N_6O_2$ 392.12, m/z found 393.1 $[M+H]^+$; ^1H NMR (400 MHz, $CHLOROFORM-d$) δ 9.00 (s, 1H), 8.21 (dd, J = 1.4, 7.9 Hz, 1H), 7.53 (dd, J = 3.5, 8.3 Hz, 3H), 7.38 (t, J = 7.2 Hz, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.05 (t, J = 7.2 Hz, 1H), 4.96 (t, J = 5.1 Hz, 2H), 4.76 - 4.51 (m, 4H).

Example 118: 2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propan-1-ol (Compound 125)



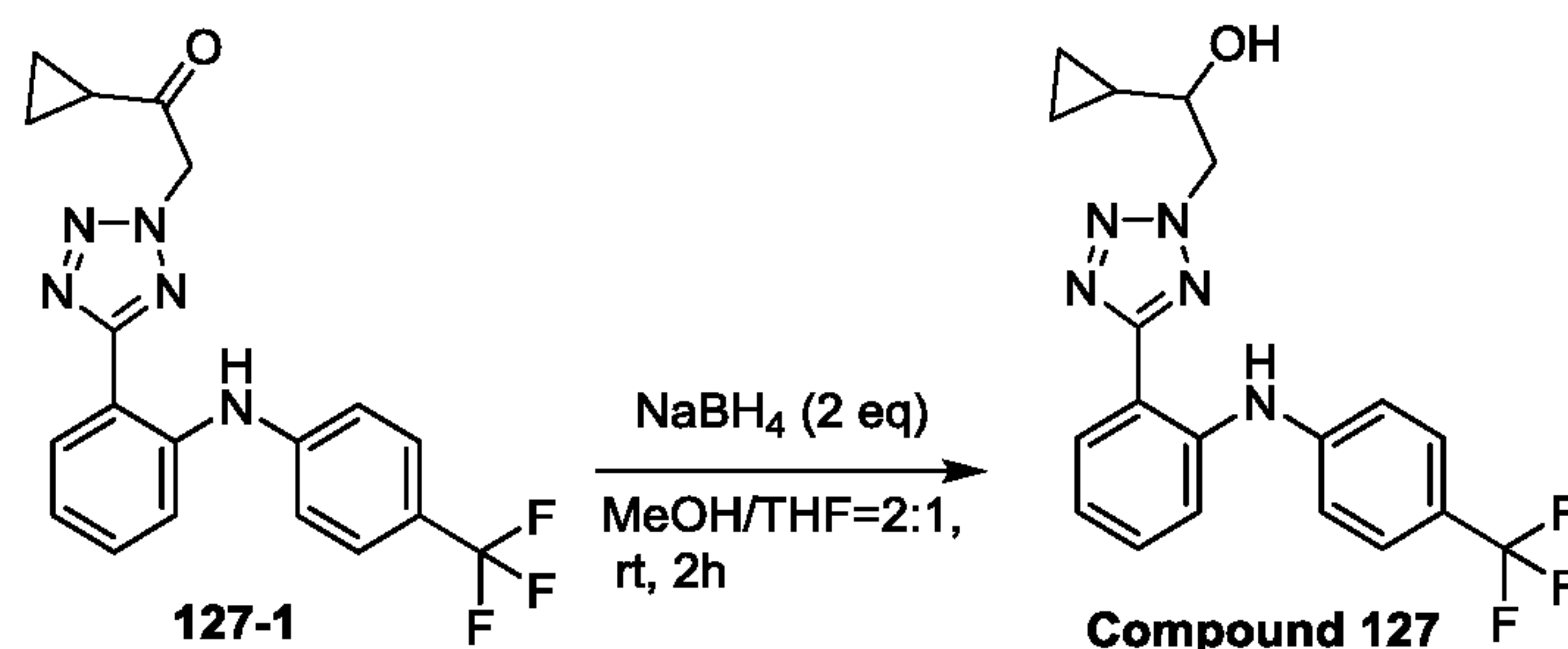
[00500] To a solution of **125-1** (100 mg, 0.247 mmol, 1.0 *eq*) in THF (3 mL) was added LiBH₄ (27 mg, 1.23 mmol, 5.0 *eq*) at 0°C under N₂. The resulting mixture was stirred at 20°C for 3 hours. LCMS showed the desired compound was found and the starting material was consumed completely. The reaction mixture was treated dropwise with aq. NH₄Cl (5 mL) and extracted with EtOAc (5 mL*2). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, and filtered. The solvent was removed under reduced pressure to afford the crude product. The crude product was purified by HPLC to give the title compound (73 mg, 0.201 mmol, 81 % yield). LCMS (ESI): RT = 0.876min, mass calc. for C₁₇H₁₆F₃N₅O 363.13, m/z found 364.0 [M+H]⁺; ¹HNMR (400 MHz, CHLOROFORM-*d*) δ 9.11 (s, 1H), 8.21 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 3H), 7.44 - 7.36 (m, 1H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 5.20 - 5.08 (m, 1H), 4.24 - 4.09 (m, 2H), 2.24 (t, *J* = 6.7 Hz, 1H), 1.75 (d, *J* = 7.0 Hz, 3H).

Example 119: 2-[2-(3-fluoropropyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 126)



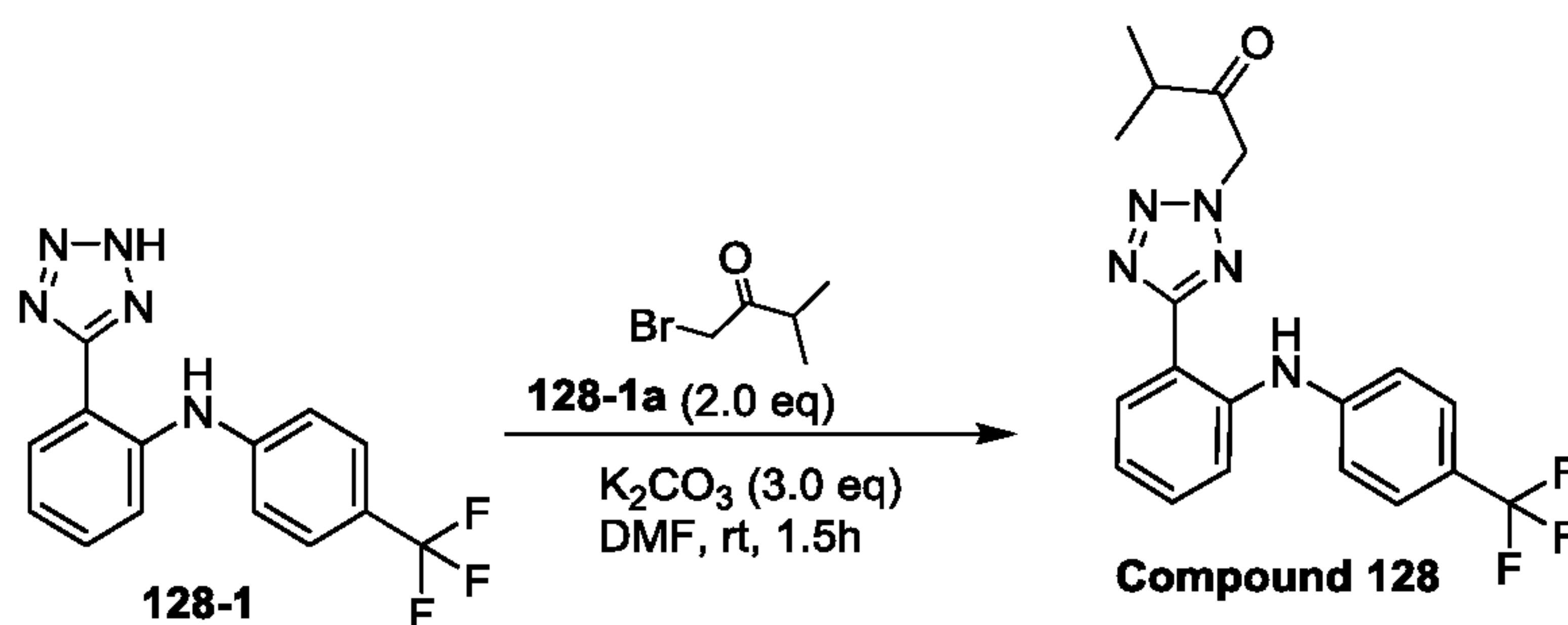
[00501] To a stirred solution of **126-1** (60 mg, 0.176 mmol, 1.0 *eq*, HCl salt) and K₂CO₃ (61 mg, 0.439 mmol, 2.5 *eq*) in DMF (2 mL) was added **126-2** (37 mg, 0.263 mmol, 1.5 *eq*). The resulting mixture was heated to 80°C for 6 hours. LCMS showed 93% of the desired compound was formed and the starting material was consumed completely. The mixture was cooled. Water (10 mL) was added and the mixture extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by purified by HPLC to give the title compound (55 mg, 0.151 mmol, 86% yield). LCMS (ESI): RT = 0.927 min, mass calc. for C₁₇H₁₅F₄N₅ 365.13, m/z found 366.0 [M+H]⁺; ¹HNMR (400 MHz, CHLOROFORM-*d*) δ 9.03 (s, 1H), 8.20 (d, *J* = 7.5 Hz, 1H), 7.60 - 7.48 (m, 3H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 4.88 (t, *J* = 6.9 Hz, 2H), 4.64 (t, *J* = 5.4 Hz, 1H), 4.52 (t, *J* = 5.5 Hz, 1H), 2.58 - 2.40 (m, 2H).

Example 120: 1-cyclopropyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol (Compound 127)



[00502] To a mixture of **127-1** (32 mg, 83 μmol , 1.00 *eq*) in MeOH (2 mL) and THF (1 mL) was added NaBH₄ (6.3 mg, 0.165 mmol, 2.00 *eq*) in one portion at 15°C under N₂. The mixture was stirred at 15 °C for 2 h. LCMS showed the compound **127-1** was consumed completely and one main peak with the desired MS was detected. The reaction mixture was quenched by addition water (5 mL) at 15°C, and then extracted with DCM (10 mL * 3). The combined organic layers were dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum to provide the title compound (22.92 mg, 58.86 μmol , 71.3% yield). LCMS (ESI): RT = 0.897 min, mass calcd. for C₁₉H₁₈F₃N₅O 389.15, *m/z* found 390.0[M+H]⁺. ¹HNMR (400MHz, DMSO-*d*₆) δ 8.81 (s, 1H), 8.04 (dd, *J*=8.00 Hz, *J*=1.20 Hz, 1H), 7.59 - 7.52 (m, 3H), 7.52 - 7.46 (m, 1H), 7.26 - 7.16 (m, 3H), 5.16 (d, *J*=5.60 Hz, 1H), 4.82 - 4.69 (m, 2H), 3.57 - 3.45 (m, 1H), 0.98 - 0.84 (m, 1H), 0.45 - 0.34 (m, 2H), 0.34 - 0.26 (m, 1H), 0.19 - 0.10 (m, 1H).

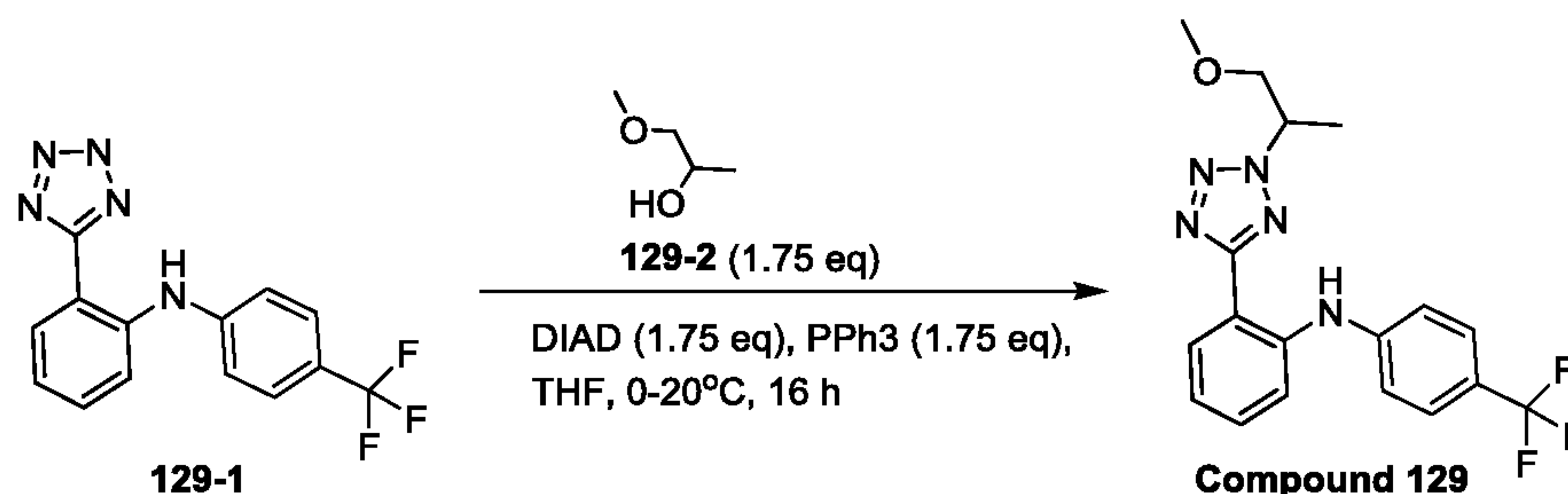
Example 121: 3-methyl-1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]butan-2-one (Compound 128)



[00503] To a mixture of **128-1** (60 mg, 0.197 mmol, 1.00 *eq*) and **128-1a** (65 mg, 0.393 mmol, 2.00 *eq*) in DMF (2 mL) was added K₂CO₃ (82 mg, 0.590 mmol, 3.00 *eq*) in one portion at 15 °C under N₂. The mixture was stirred at 15 °C for 1 hour. TLC showed the starting material was consumed completely and many new spots were formed. The reaction mixture was diluted with EtOAc (40 mL) and washed with brine (40 mL * 3), dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum. LCMS showed 69% of desired product was formed. The residue was purified by prep-HPLC (basic condition) to provide the title compound (22.00 mg, 56.5 μmol , 28.8% yield). LCMS (ESI): RT = 0.910 min, mass calcd. for C₁₉H₁₈F₃N₅O 389.15, *m/z* found 390.0[M+H]⁺. ¹HNMR (400MHz, CHLOROFORM-*d*) δ 8.96 (s, 1H), 8.24 - 8.15 (m, 1H), 7.53 (br t,

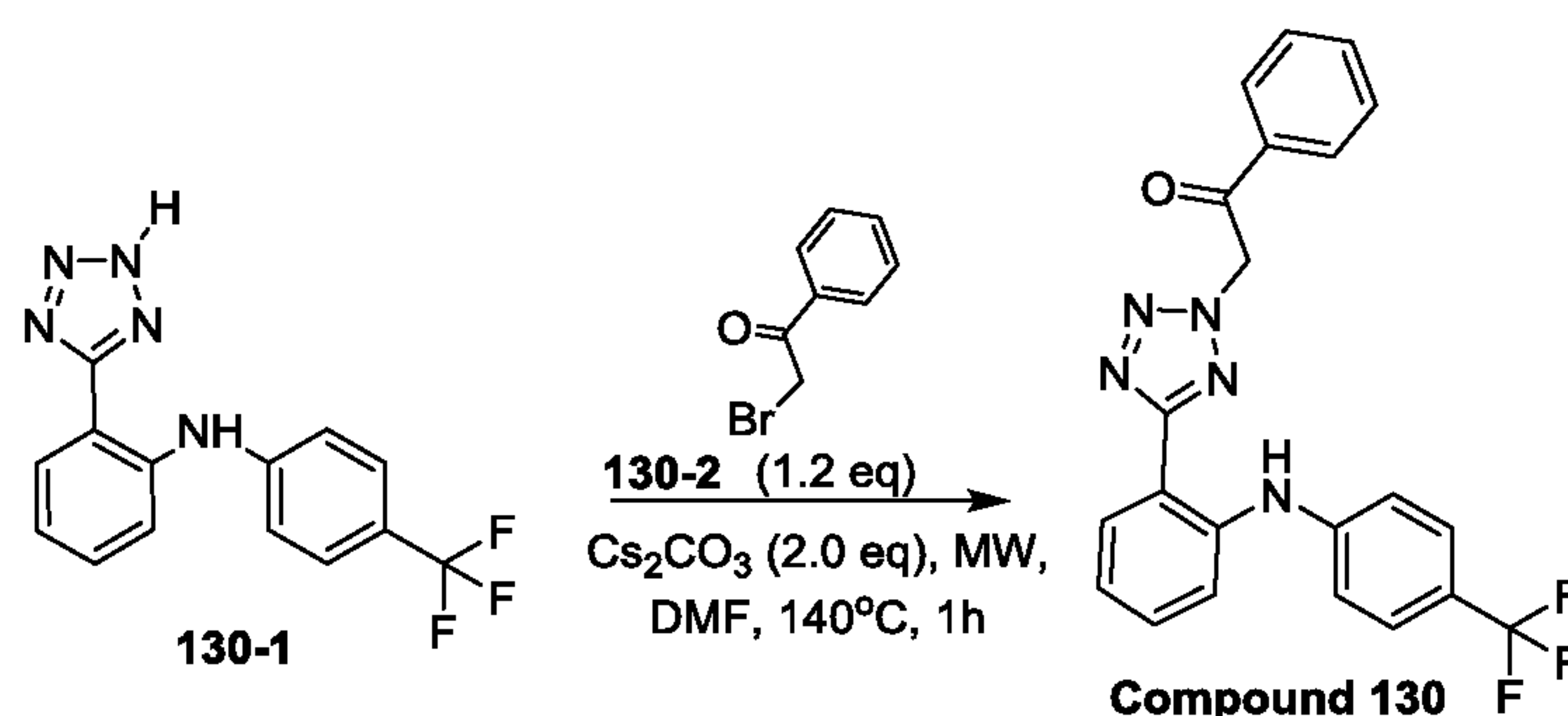
$J=6.40$ Hz, 3H), 7.42 - 7.37 (m, 1H), 7.30 (br d, $J=8.40$ Hz, 2H), 7.03 (t, $J=7.60$ Hz, 1H), 5.61 (s, 2H), 2.85 - 2.72 (m, 1H), 1.26 (d, $J=6.80$ Hz, 7H).

Example 122: 2-(2-(1-methoxypropan-2-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 129)



[00504] A solution of **129-1** (100 mg, 0.292 mmol, 1.0 *eq*, HCl) in anhydrous THF (3 mL) and DCM (1.5 mL) was cooled at 0°C under N₂. To this mixture were added **129-2** (46 mg, 0.512 mmol, 50 uL, 1.75 *eq*), PPh₃ (134 mg, 0.512 mmol, 1.75 *eq*), and DIAD (103 mg, 0.512 mmol, 100 uL, 1.75 *eq*) and the mixture was stirred for 5 min and then warmed to 20°C and stirred 16 h. LCMS showed 44% of the desired compound was formed and 17% of the starting material was remaining. The solution was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the title compound (45 mg, 0.109 mmol, 37% yield, HCl salt). LCMS (ESI): RT = 0.908 min, mass calc. for C₁₈H₁₈F₃N₅O 377.15, *m/z* found 378.0 [M+H]⁺; ¹HNMR (400 MHz, CHLOROFORM-*d*) δ 9.14 (s, 1H), 8.22 (d, $J = 7.8$ Hz, 1H), 7.53 (d, $J = 8.5$ Hz, 3H), 7.41 - 7.34 (m, 1H), 7.29 (d, $J = 8.5$ Hz, 2H), 7.04 (t, $J = 7.4$ Hz, 1H), 5.22 (dd, $J = 7.2$, 12.2 Hz, 1H), 3.95 (dd, $J = 8.0$, 10.0 Hz, 1H), 3.80 (dd, $J = 4.8$, 10.3 Hz, 1H), 3.34 (s, 3H), 1.70 (d, $J = 7.0$ Hz, 3H).

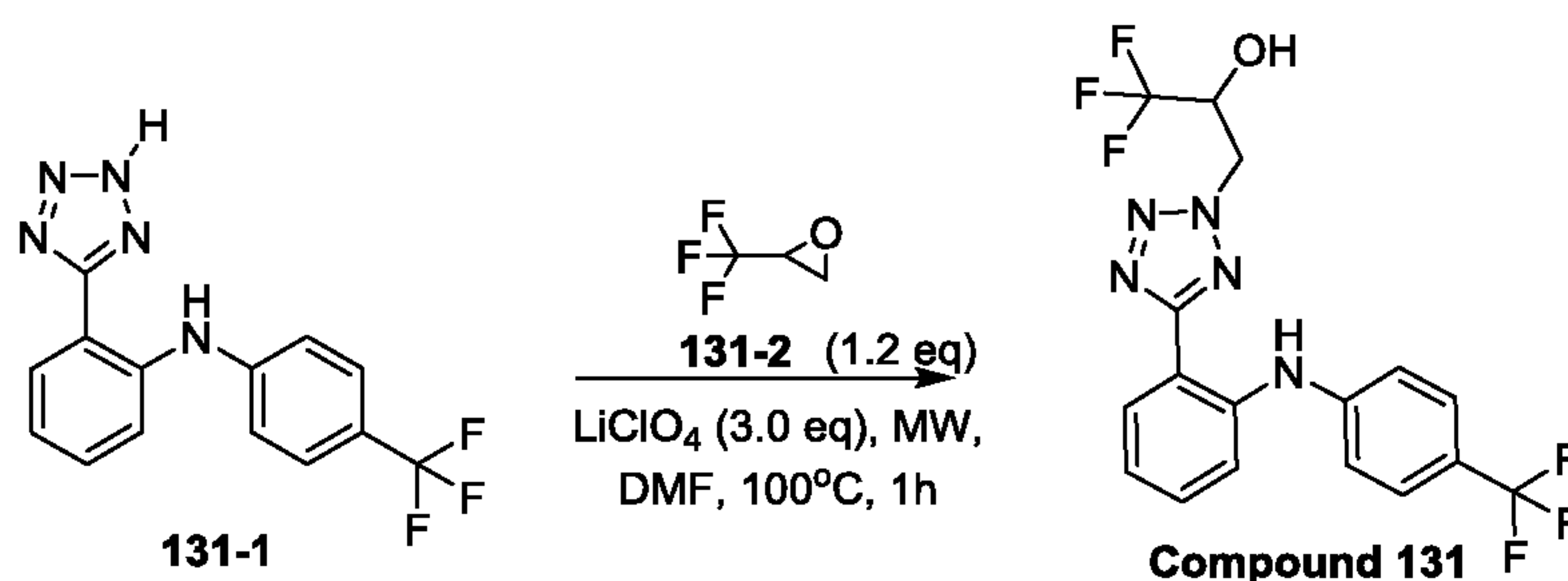
Example 123: 1-phenyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanone (Compound 130)



[00505] **130-1** (30.0 mg, 98.3 umol, 1.0 *eq*), **130-2** (46.9 mg, 0.12 mmol, 1.2 *eq*) and Cs₂CO₃ (64.0 mg, 0.20 mmol, 2.0 *eq*) were taken up into a microwave tube in DMF (3.0 mL). The sealed tube was heated at 150 °C for 1 hour under microwave conditions. LCMS showed the desired compound was formed. The reaction was filtered to give a crude product. The crude product was purified by

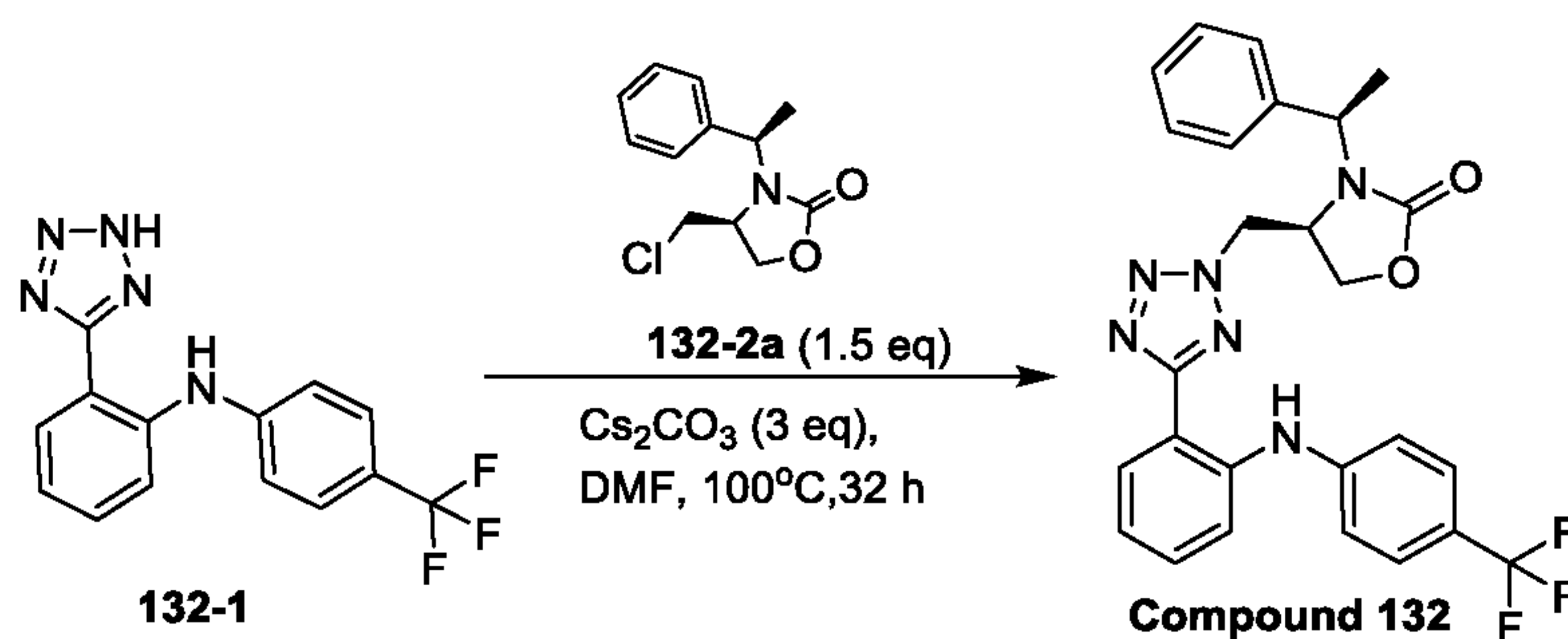
column chromatography over silica gel and then further purified by prep-HPLC to give the title compound (2.21 mg, 5.22 μmol , 5.31% yield). LCMS (ESI): RT = 0.929 min, mass calc. for $\text{C}_{22}\text{H}_{16}\text{F}_3\text{N}_5\text{O}$ 423.13, m/z found 424.1 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3-d) δ 8.98 (s, 1H), 8.24 (dd, J = 1.4, 7.9 Hz, 1H), 8.06 - 8.00 (m, 2H), 7.75 - 7.69 (m, 1H), 7.62 - 7.56 (m, 2H), 7.54 (d, J = 8.5 Hz, 3H), 7.38 (t, J = 7.8 Hz, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.05 (t, J = 7.5 Hz, 1H), 6.20 (s, 2H).

Example 124: 1,1,1-trifluoro-3-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]propan-2-ol (Compound 131)



[00506] **131-1** (30.0 mg, 98.3 μmol , 1.0 *eq*), **131-2** (33.0 mg, 0.29 mmol, 3.0 *eq*) and LiClO_4 (31.4 mg, 0.29 mmol, 12.9 μL , 3.0 *eq*) were taken up into a microwave tube in DMF (5.0 mL). The sealed tube was heated at 100 °C for 1 hour under microwave conditions. LCMS showed the desired compound was formed. The reaction was filtered to give a crude product. The product was purified by prep-HPLC to give the title compound (21.07 mg, 50.49 μmol , 51.37% yield). LCMS (ESI): RT = 0.884 min, mass calc. for $\text{C}_{17}\text{H}_{13}\text{F}_6\text{N}_5\text{O}$ 417.10, m/z found 418.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.77 (s, 1H), 8.08 (dd, J = 1.1, 7.9 Hz, 1H), 7.60 - 7.53 (m, 3H), 7.53 - 7.47 (m, 1H), 7.25 (d, J = 8.5 Hz, 2H), 7.19 (t, J = 7.0 Hz, 1H), 6.94 (d, J = 6.3 Hz, 1H), 5.10 - 5.02 (m, 1H), 4.97 - 4.89 (m, 1H), 4.76 (s, 1H).

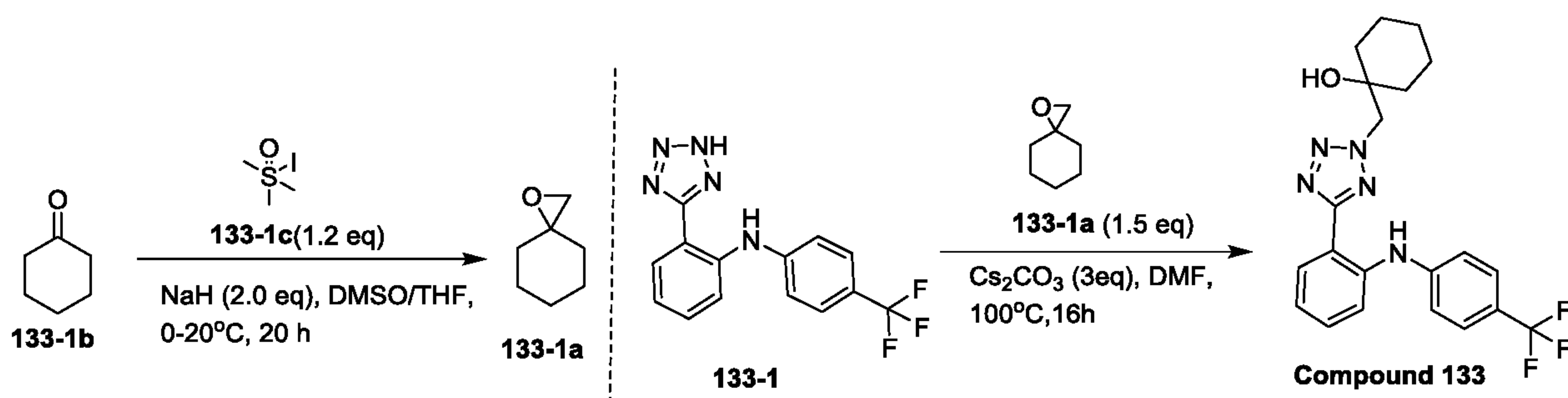
Example 125: (4R)-3-[(1R)-1-phenylethyl]-4-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]oxazolidin-2-one (Compound 132)



[00507] To a solution of **132-2a** (53 mg, 0.219 mmol, 1.5 *eq*) and Cs_2CO_3 (143 mg, 0.439 mmol, 3.0 *eq*) in DMF (2.0 mL) was added **132-1** (50 mg, 0.146 mmol, 1.0 *eq*, HCl). The resulting mixture was stirred at 100°C for 32 hours. LCMS showed 14% desired compound was formed and the starting material remained. The reaction mixture was poured into water (5 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (5 mL*3). The combined organic layers

were washed with brine (5 mL*2), dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum to give a residue. The residue was purified by HPLC to give the title compound (11.0 mg, 21.63 μ mol, 15% yield). LCMS (ESI): RT = 0.932 min, mass calc. for C₂₆H₂₃F₃N₆O₂ 508.18, m/z found 531.1 [M+23]⁺; ¹HNMR (400 MHz, CHLOROFORM -*d*) δ 8.82 (d, *J* = 16.1 Hz, 1H), 8.12 (t, *J* = 7.2 Hz, 1H), 7.52 (dd, *J* = 8.2, 13.2 Hz, 4H), 7.59 - 7.47 (m, 1H), 7.46 - 7.32 (m, 5H), 7.29 (s, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 5.29 (m, *J* = 6.8 Hz, 1H), 4.88 - 4.70 (m, 1H), 4.44 - 4.35 (m, 1H), 4.34 - 4.30 (m, 1H), 4.27 - 4.18 (m, 1H), 4.16 - 4.08 (m, 0.5H), 4.05 - 3.95 (m, 0.5H), 1.79 (t, *J* = 8.0 Hz, 3H).

Example 126: 1-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]cyclohexanol (Compound 133)



Step 1: 1-oxaspiro[2.5]octane

[00508] To a solution of **133-1b** (500 mg, 5.09 mmol, 526 μ L, 1.0 eq) in DME (15 mL) was added *t*-BuOK (571 mg, 5.09 mmol, 1.0 eq) and **133-1c** (1.12 g, 5.09 mmol, 1.0 eq). Then the mixture was stirred at 80°C for 16 hr. TLC (Petroleum ether: Ethyl acetate = 10/1, R_f = 0.6) showed the starting material was consumed completely. The mixture was quenched with H₂O (20 mL) and extracted with DCM (40 mL*3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give **133-1a** (220 mg, 1.96 mmol, 39 % yield) as an oil. The oil was directly used without further purification.

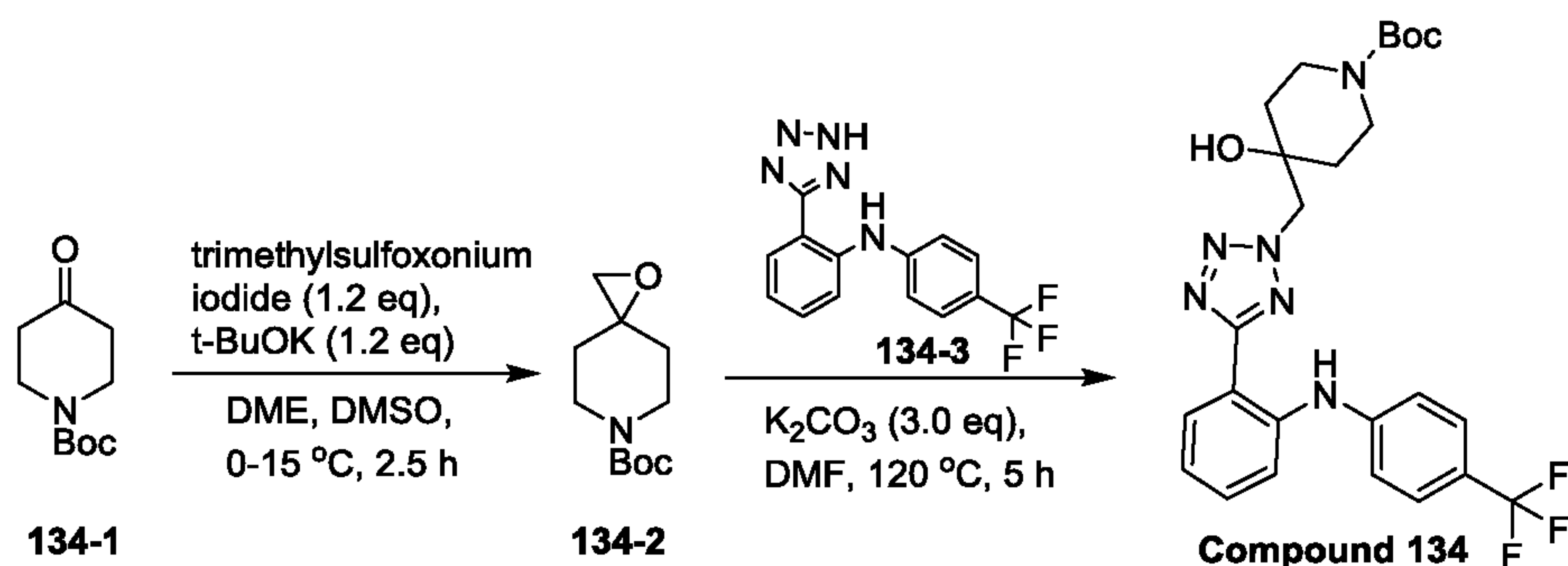
Step 2: 1-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]cyclohexanol

[00509] To a stirred solution of **133-1** (100 mg, 0.293 mmol, 1.0 eq, HCl) and Cs₂CO₃ (286 mg, 0.878 mmol, 3.0 eq) in DMF (2 mL) was added **133-1a** (66 mg, 0.585 mmol, 2.0 eq). The resulting mixture was stirred at 100°C for 16 hours. LCMS showed 19% of the desired compound was formed and 75% the starting material remained. The mixture was cooled. The reaction mixture was poured into water (10 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (10 mL*3). The combined organic phases were dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum to give a residue. The residue was purified by HPLC to give

Compound 133 (17 mg, 41 μ mol, 14% yield). LCMS (ESI): RT = 0.922 min, mass calc. for C₂₁H₂₂F₃N₅O 417.18, m/z found 418.1[M+H]⁺; ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.78 (s, 1H), 8.02

(d, $J = 8.2$ Hz, 1H), 7.52 (d, $J = 8.4$ Hz, 3H), 7.49 - 7.43 (m, 1H), 7.21 - 7.10 (m, 3H), 4.67 - 4.55 (m, 3H), 1.56 - 1.30 (m, 10H).

Example 127: tert-butyl 4-hydroxy-4-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]piperidine-1-carboxylate (Compound 134)



Step 1: tert-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate

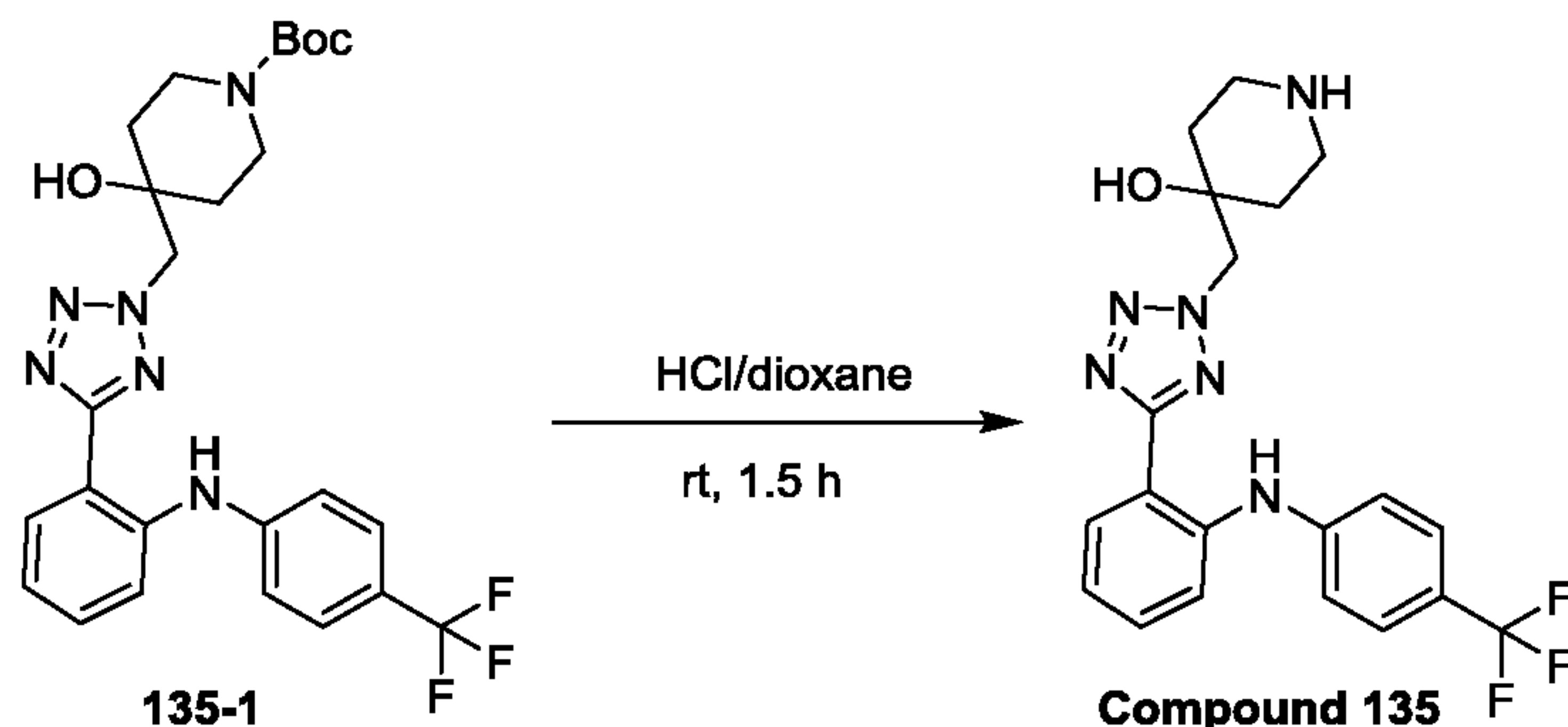
[00510] *t*-BuOK (1.35 g, 12.05 mmol, 1.20 *eq*) and DMSO (11 mL) were charged to a reaction vessel and the mixture cooled to around 20 °C with stirring. Trimethylsulfoxonium iodide (2.43 g, 11.04 mmol, 1.10 *eq*) was added in portions over a period of 10 min, maintaining the reaction temperature between 20~25°C. On completion of the addition, the mixture was maintained at this temperature for 1 hr. DME (3 mL) was added to the reaction flask and the solution cooled to 0~5°C. A pre-cooled solution of **134-1** (2 g, 10.04 mmol, 1.00 *eq*) in a mixture of DME (3 mL) and DMSO (1 mL) was transferred into the reaction mixture over a period of 15 min, maintaining the reaction temperature between 0~5°C. On completion of the addition, the reaction mixture was held at this temperature for a further 1.5 hr. TLC (EtOAc: PE=1:10) showed that starting material was consumed completely. The reaction was diluted with EtOAc (80 mL) and washed with brine (3*30 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to give **134-2** (1.80 g, 8.44 mmol, 84.06% yield). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 3.82 - 3.55 (m, 2H), 3.50 - 3.30 (m, 2H), 2.69 (s, 2H), 1.80 - 1.70 (m, 2H), 1.55 - 1.40 (m, 11H).

Step 2: tert-butyl 4-hydroxy-4-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]piperidine-1-carboxylate

[00511] To a solution of **134-3** (50 mg, 0.16 mmol, 1.00 *eq*) and K₂CO₃ (90.6 mg, 0.66 mmol, 4.00 *eq*) in DMF (4.00 mL) was added **134-2** (52.4 mg, 0.25 mmol, 1.50 *eq*). The reaction was heated to 120°C for 16 hr. LCMS showed that the desired MS signal was detected. The reaction was diluted with EtOAc (30 mL) and washed with brine (2*20 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by CombiFlash to give **Compound 134** (40 mg, 76.37 μmol, 46.63% yield). LCMS (ESI): RT = 0.933 min, mass calc. for C₂₅H₂₉F₃N₆O₃ 518.23, *m/z* found 541.1 [M+Na]⁺. ¹H NMR (400MHz, CHLOROFORM-*d*) δ 8.78 (s, 1H), 8.06 (d, $J = 7.6$ Hz, 1H), 7.58 - 7.51 (m, 4H), 7.40 (t, $J = 7.5$ Hz, 1H), 7.31 - 7.15 (m, 3H),

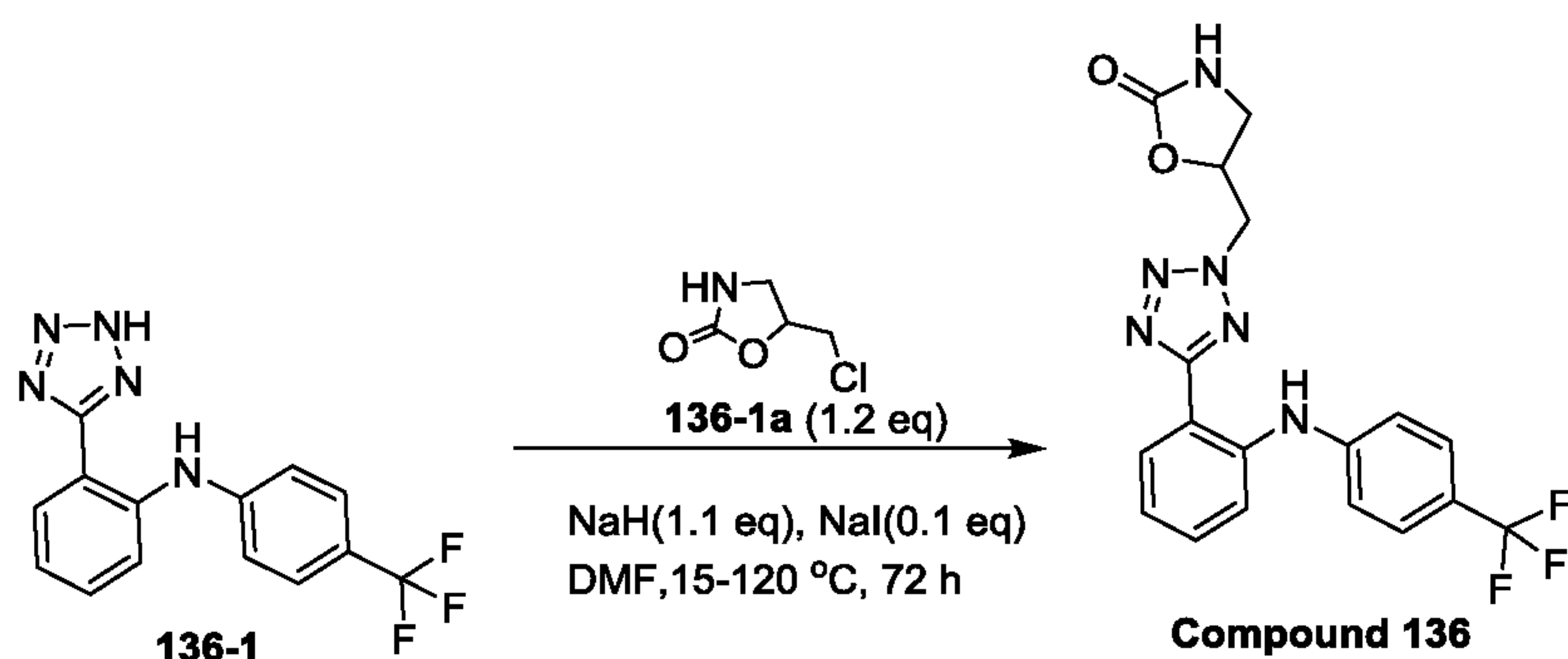
4.97 (s, 1H), 4.71 (s, 2H), 3.75 - 3.60 (m, 2H), 3.15 - 2.80 (m, 2H), 1.60 - 1.50 (m, 4H), 1.39 (s, 9H).

Example 128: 4-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]piperidin-4-ol (Compound 135)



[00512] To a solution of **135-1** (37 mg, 71.36 μmol , 1.00 *eq*) in dioxane (3 mL) was added HCl/dioxane (4 M, 462.59 μL , 25.93 *eq*) at 15°C. The reaction was stirred at 15°C for 1 hr. LCMS showed that only the desired product was detected. The reaction was concentrated to afford the title compound (27.97 mg, 56.36 μmol , 78.98% yield, 2HCl salt). LCMS (ESI): RT = 0.727 min, mass calc. for $\text{C}_{20}\text{H}_{21}\text{F}_3\text{N}_6\text{O}$ 418.16, m/z found 419.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ 8.80 (s, 1H), 8.73 (br, 1H), 8.55 (br, 1H), 8.05 (d, $J = 7.2$ Hz, 1H), 7.59 - 7.50 (m, 4H), 7.31 - 7.18 (m, 3H), 5.39 (s, 1H), 4.78 (s, 2H), 4.49 (s, 1H), 3.20 - 3.10 (m, 2H), 3.11 - 2.95 (m, 2H), 1.90 - 1.75 (m, 2H), 1.75 - 1.65 (m, 2H).

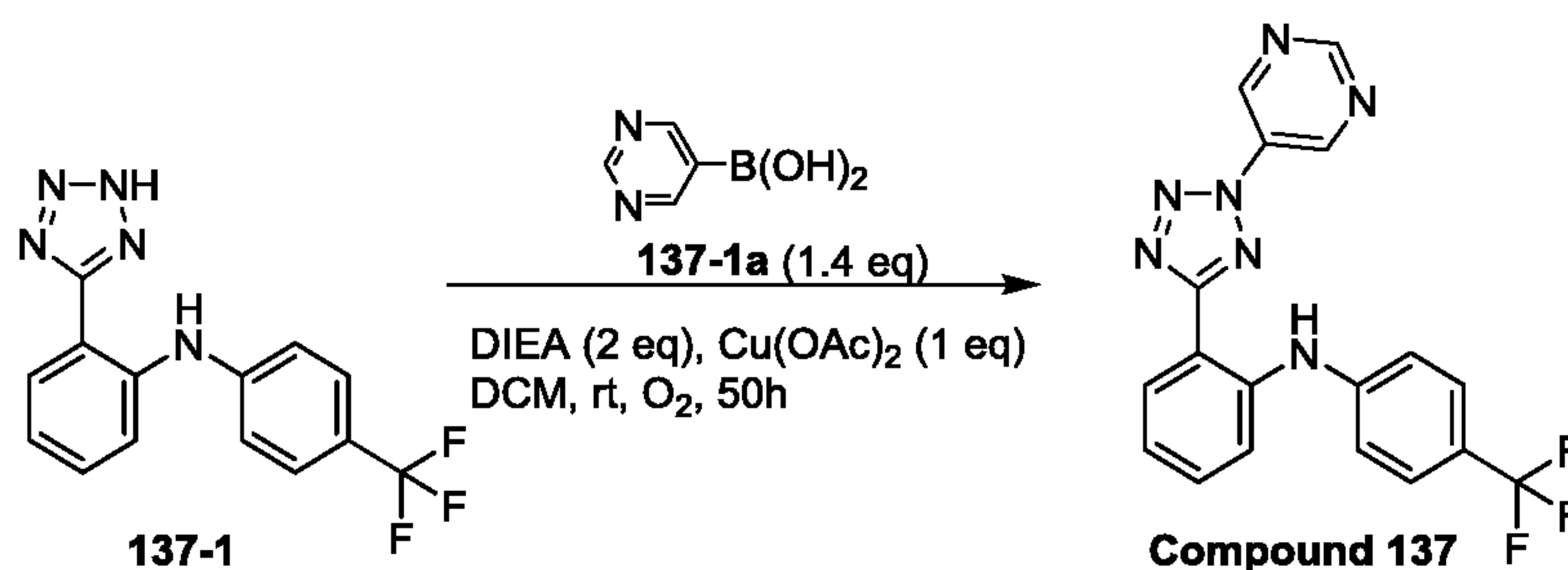
Example 129: 5-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)oxazolidin-2-one (Compound 136)



[00513] To a solution of **136-1** (30.00 mg, 98.28 μmol , 1.00 *eq*) and NaI (1.47 mg, 9.83 μmol , 0.10 *eq*) in DMF (500.00 μL) was added NaH (4.32 mg, 108.10 μmol , 60% purity, 1.10 *eq*) at 0 °C. After stirring for 10 min, **136-1a** (15.99 mg, 117.93 μmol , 1.20 *eq*) was added and then the resulting mixture was stirred at 15 °C for 16 h. TLC showed most of starting material remained. Then the mixture was stirred at 80 °C for 20 h. LCMS showed most of starting material remained, and one peak with the desired mass was detected. Then the mixture was stirred at 120 °C for 16 h. LCMS still showed around 23 % of the starting material remained and around 68% of desired

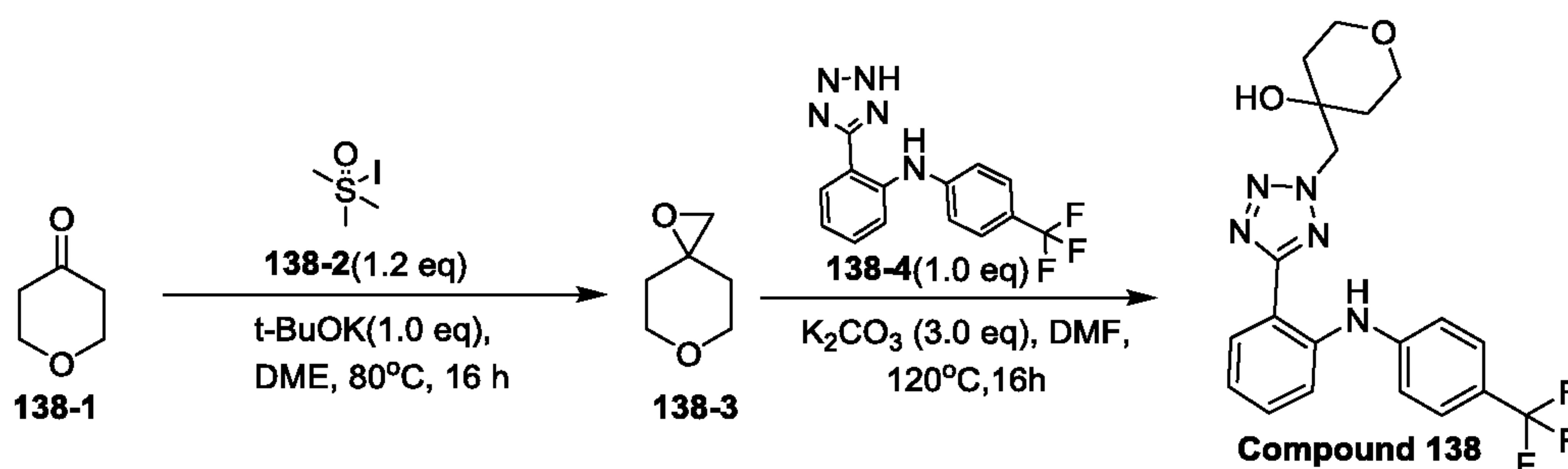
product was formed. Then the mixture was continuously stirred at 120 °C for another 20 h. LCMS showed the reaction had no further improvement. TLC showed most of material was consumed and mainly one new spot was formed. The mixture was purified by prep-HPLC to give the title compound (20.00 mg, 49.46 μ mol, 25.16% yield of two batches). LCMS (ESI): RT = 1.674 min, mass calc. for $C_{18}H_{15}F_3N_6O_2$ 404.12, m/z found 404.90 $[M+1]^+$; ^1H NMR (400MHz, DMSO- d_6) δ 8.74 (s, 1H), 8.11 - 8.03 (m, 1H), 7.66 - 7.47 (m, 5H), 7.29 - 7.15 (m, 3H), 5.18 - 5.02 (m, 3H), 3.72 - 3.63 (m, 1H), 3.38 (m, J = 5.0 Hz, 1H).

Example 130: 2-(2-pyrimidin-5-yltetrazol-5-yl)-N-[4-(trifluoromethyl)phenyl]aniline (Compound 137)



[00514] To a mixture of **137-1** (50 mg, 0.164 mmol, 1.00 *eq*) and **137-1a** (28 mg, 0.229 mmol, 1.40 *eq*) in DCM (2 mL) was added $Cu(OAc)_2$ (30 mg, 0.164 mmol, 1.00 *eq*) and DIPEA (42 mg, 0.327 mmol, 60 μ L, 2.00 *eq*) in one portion at 15 °C under O_2 . The mixture was stirred at 15 °C for 50 h. LCMS showed the starting material was consumed completely and one peak with the desired MS was detected. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by prep-HPLC (basic condition) to provide the title compound (2.03 mg, 5.3 μ mol, 3.2% yield). LCMS (ESI): RT = 0.740 min, mass calcd. for $C_{18}H_{12}F_3N_7$ 383.11, m/z found 384.0 $[M+H]^+$. ^1H NMR (400MHz, CHLOROFORM- d) δ 8.60 - 8.17 (m, 1H), 8.00 (br s, 1H), 7.62 - 7.54 (m, 1H), 7.51 - 7.39 (m, 3H), 7.39 - 7.33 (m, 1H), 7.15 - 7.00 (m, 2H).

Example 131: 4-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]tetrahydropyran-4-ol (Compound 138)



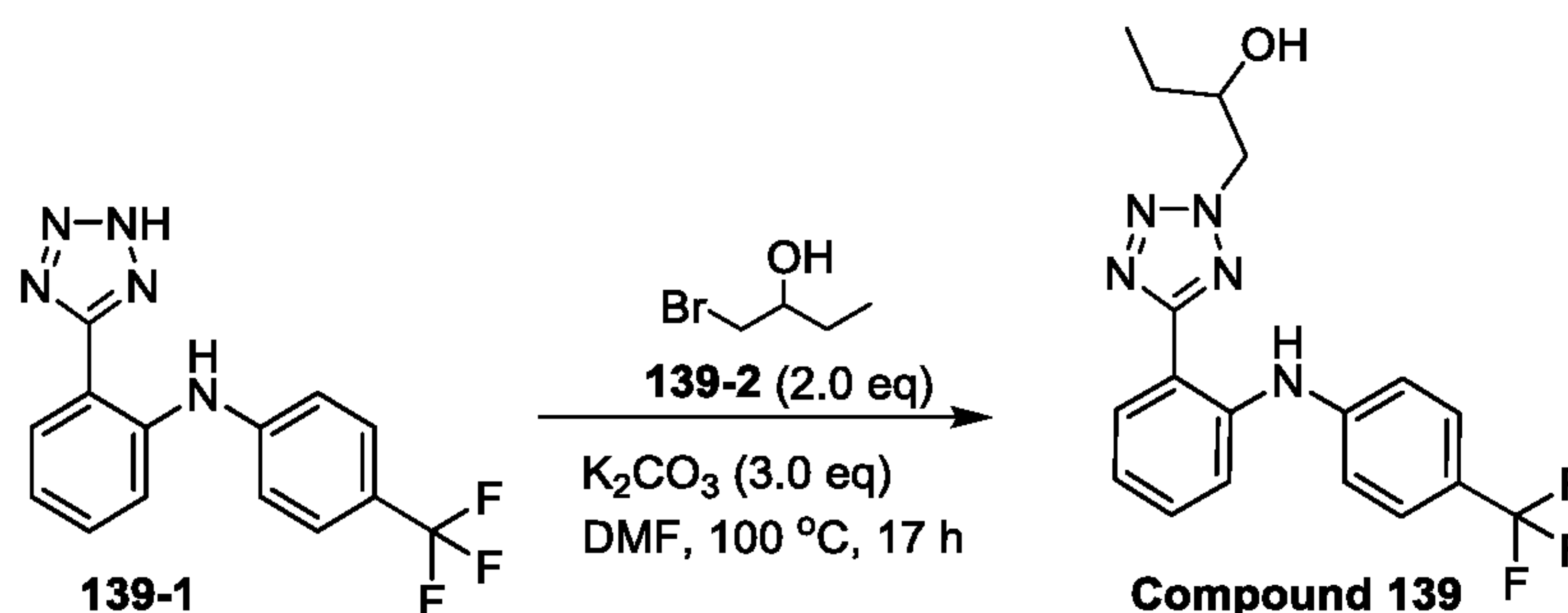
Step 1: 1,6-dioxaspiro[2.5]octane

[00515] To a solution of **138-1** (300.0 mg, 3.0 mmol, 0.28 mL, 1.0 *eq*) in DME (4.0 mL) was added *t*-BuOK (370.3 mg, 3.3 mmol, 1.1 *eq*) and **138-2** (726.2 mg, 3.3 mmol, 1.1 *eq*). The mixture

was stirred at 80 °C for 16 hour under N₂ atmosphere. TLC (Petroleum ether : Ethyl acetate=10/1) showed a new spot appeared. The reaction was filtered and concentrated under reduced pressure to give a crude product. The crude product was diluted with water (5 mL) and washed with EtOAc (10 mL x 2). The combined organic layers were concentrated to give crude **138-3** (300.0 mg, 1.8 mmol, 61.3% yield) as a yellow oil. ¹HNMR (400 MHz, CDCl₃-*d*) δ 3.89 - 3.79 (m, 4H), 2.70 (s, 2H), 1.88 (ddd, *J* = 4.6, 8.4, 13.3 Hz, 2H), 1.54 (td, *J* = 4.5, 13.4 Hz, 2H).

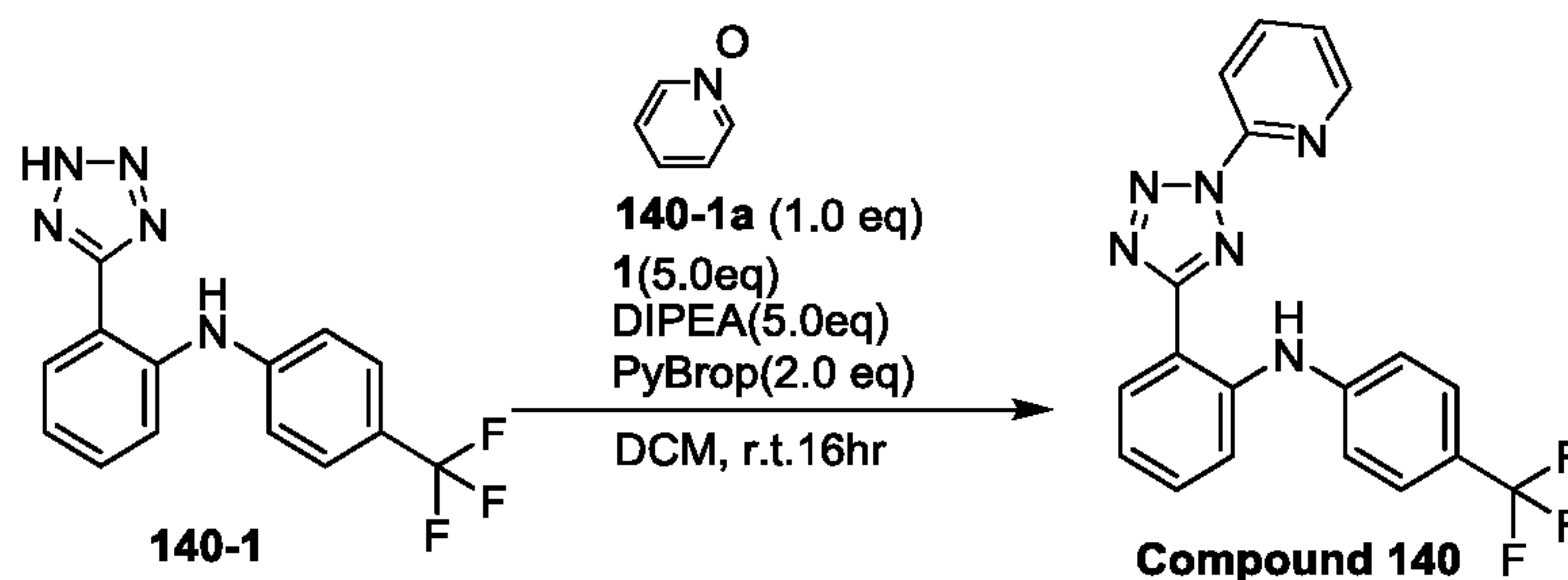
Step 2: 4-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]tetrahydropyran-4-ol [00516] To a solution of **138-4** (30.0 mg, 98.3 μmol, 1.0 *eq*) in DMF (5.0 mL) was added K₂CO₃ (27.2 mg, 0.20 mmol, 2.0 *eq*) and **138-3** (13.5 mg, 0.12 mmol, 1.2 *eq*). The mixture was stirred at 120 °C for 16 hour under an N₂ atmosphere. LCMS showed the desired compound was formed. The reaction was filtered to give a crude product. The crude product was purified by prep-HPLC to give **Compound 138** (5.80 mg, 13.83 μmol, 14.07% yield). LCMS (ESI): RT = 0.697 min, mass calc. for C₂₀H₂₀F₃N₅O₂ 419.16, *m/z* found 420.1 [M+H]⁺; ¹HNMR (400 MHz, CDCl₃-*d*) δ 9.03 (s, 1H), 8.18 (dd, *J* = 1.1, 7.9 Hz, 1H), 7.58 - 7.51 (m, 3H), 7.44 - 7.36 (m, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 4.75 (s, 2H), 3.84 - 3.76 (m, 4H), 2.70 (s, 1H), 1.82 (ddd, *J* = 6.5, 9.9, 13.7 Hz, 2H), 1.45 (d, *J* = 12.0 Hz, 2H).

Example 132: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)butan-2-ol (Compound 139)



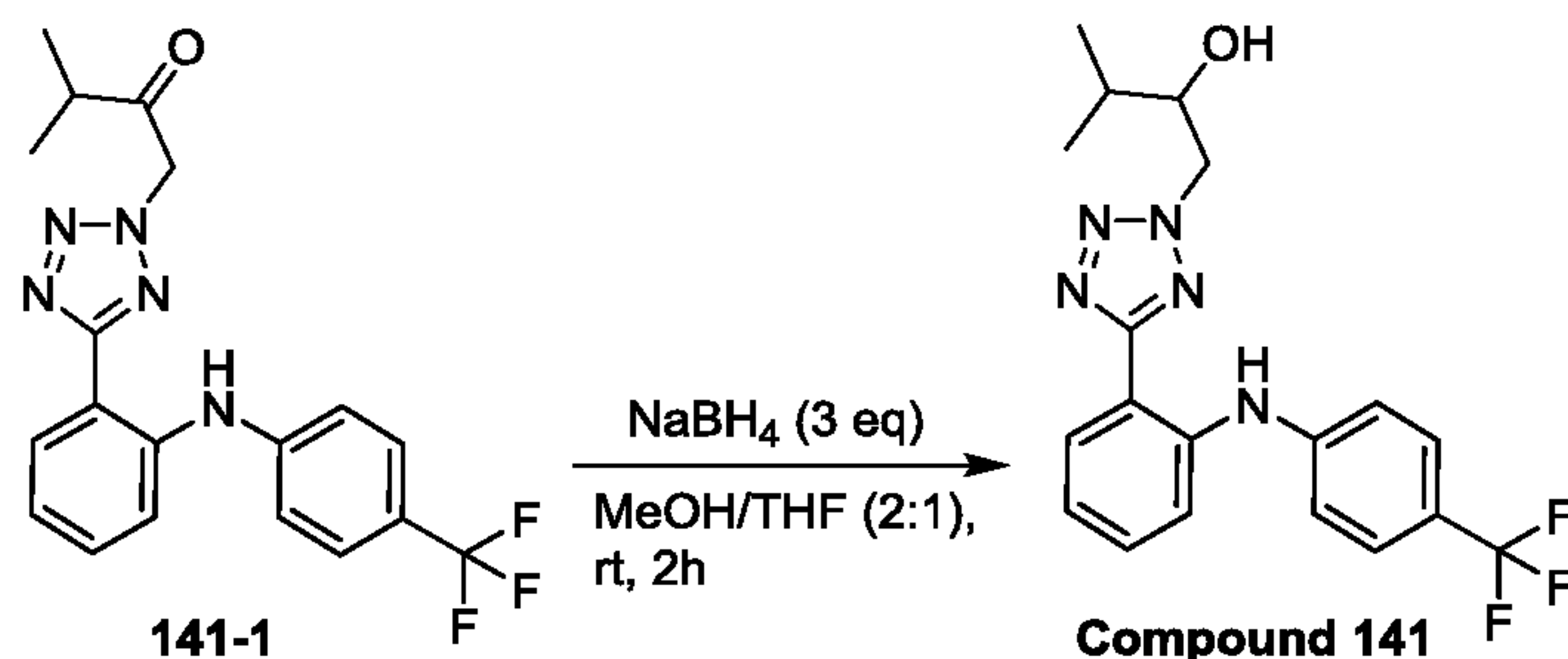
[00517] To a mixture of **139-1** (50.0 mg, 0.2 mmol, 1.00 *eq*) and K₂CO₃ (67.9 mg, 0.5 mmol, 3.00 *eq*) in DMF (3.0 mL), was added **139-2** (50.1 mg, 0.3 mmol, 2.00 *eq*). The resulting mixture was stirred at 100 °C under N₂ for 17 h. LCMS showed the reaction was complete. The mixture was filtered, and the solid was washed with 1 mL DMF. The filtrate was purified by prep-HPLC (basic condition) to obtain the title compound (15.88 mg, 41.7 μmol, 25.4% yield). LCMS (ESI): RT = 0.885 min, mass calc. for C₁₈H₁₈F₃N₅O 377.15, *m/z* found 378.0 [M+H]⁺. ¹HNMR (400MHz, DMSO-*d*₆) δ 8.87 - 8.79 (m, 1H), 8.09 - 8.02 (m, 1H), 7.59 - 7.45 (m, 4H), 7.25 - 7.12 (m, 3H), 5.17 - 4.79 (m, 1H), 4.75 - 4.56 (m, 2H), 4.00 - 3.78 (m, 1H), 1.99 - 1.32 (m, 2H), 1.00 - 0.61 (m, 3H).

Example 133: 2-[2-(2-pyridyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 140)



[00518] To a solution of **140-1a** (15.0 mg, 0.16 mmol, 1.0 eq), **140-1** (240.7 mg, 0.79 mmol, 5.0 eq) and DIEA (101.9 mg, 0.79 mmol, 137.7 μ L, 5.0 eq) in DCM (5.0 mL) was added PyBrop (147.1 mg, 0.32 mmol, 2.0 eq). The mixture was stirred at 10-15 °C for 16 hour. LC-MS showed most of **140-1** and one peak with an MS of 354.9 and 404.9. The combined reaction mixture was concentrated to give a residue. The residue was pre-purified by flash column chromatography to give crude product (150 mg), which was re-purified by prep-HPLC to give the title compound (102.06 mg, 0.24 mmol, HCl salt). LCMS (ESI): RT = 1.381 min, mass calc. for $C_{19}H_{13}F_3N_6$ 382.12, m/z found 404.9 $[M+Na]^+$; ^1H NMR (400MHz, DMSO- d_6) δ 8.76 - 8.63 (m, 2H), 8.22 - 8.14 (m, 1H), 8.14 - 8.06 (m, 2H), 7.67 (dd, J=5.0, 6.5 Hz, 1H), 7.59 - 7.44 (m, 4H), 7.26 - 7.13 (m, 3H).

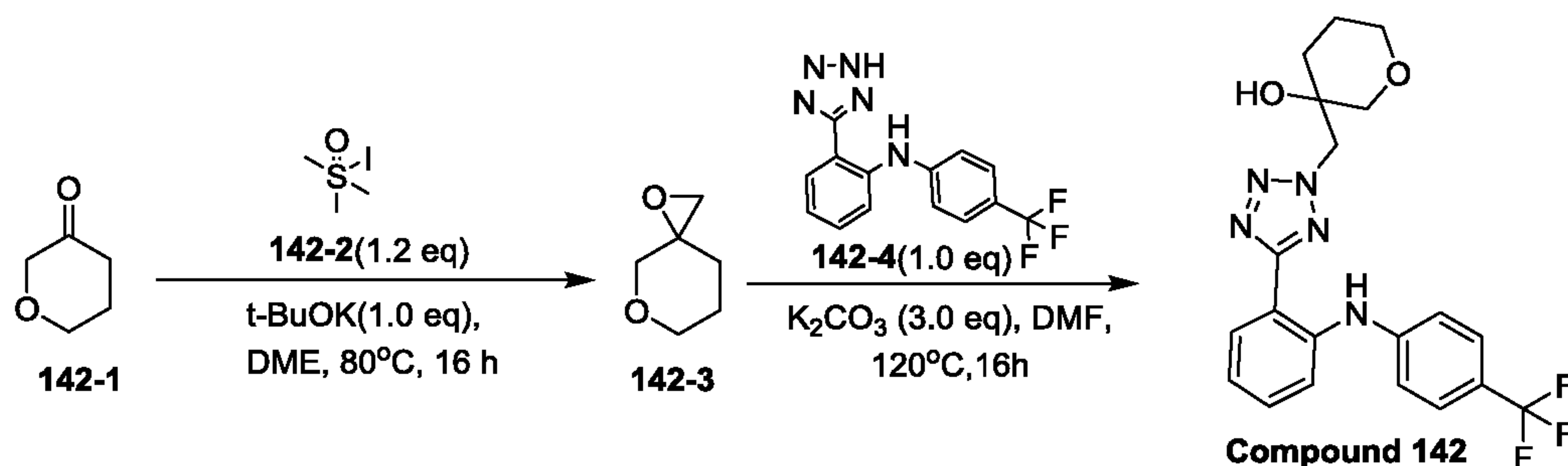
Example 134: 3-methyl-1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]butan-2-ol (Compound 141)



[00519] To a mixture of **141-1** (20 mg, 51 μ mol, 1.00 eq) in MeOH (2 mL) and THF (1 mL) was added NaBH₄ (6 mg, 0.154 mmol, 3.00 eq) in one portion at 15 °C under N₂. The mixture was stirred at 15 °C for 2 h. LCMS showed the **141-1** was consumed completely and one main peak with the desired MS was detected. The reaction mixture was quenched by addition of water (5 mL) at 15°C and concentrated under reduced pressure to remove MeOH and THF. The residue was extracted with DCM (10 mL * 3). The combined organic layers were dried with anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by prep-HPLC (basic condition) to provide the title compound (5.07 mg, 13 μ mol, 25.2% yield). LCMS (ESI): RT = 0.916 min, mass calc. for $C_{19}H_{20}F_3N_5O$ 391.16, m/z found 392.1 $[M+H]^+$. ^1H NMR (400MHz,

CHLOROFORM-*d*) δ 9.07 (s, 1H), 8.19 (d, $J=7.60$ Hz, 1H), 7.60 - 7.50 (m, 3H), 7.39 (t, $J=7.80$ Hz, 1H), 7.30 (br d, $J=8.40$ Hz, 2H), 7.05 (t, $J=7.60$ Hz, 1H), 4.84 - 4.69 (m, 2H), 4.09 - 4.01 (m, 1H), 2.39 (d, $J=4.80$ Hz, 1H), 1.89 - 1.78 (m, 1H).

Example 135: 3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]tetrahydropyran-3-ol (Compound 142)



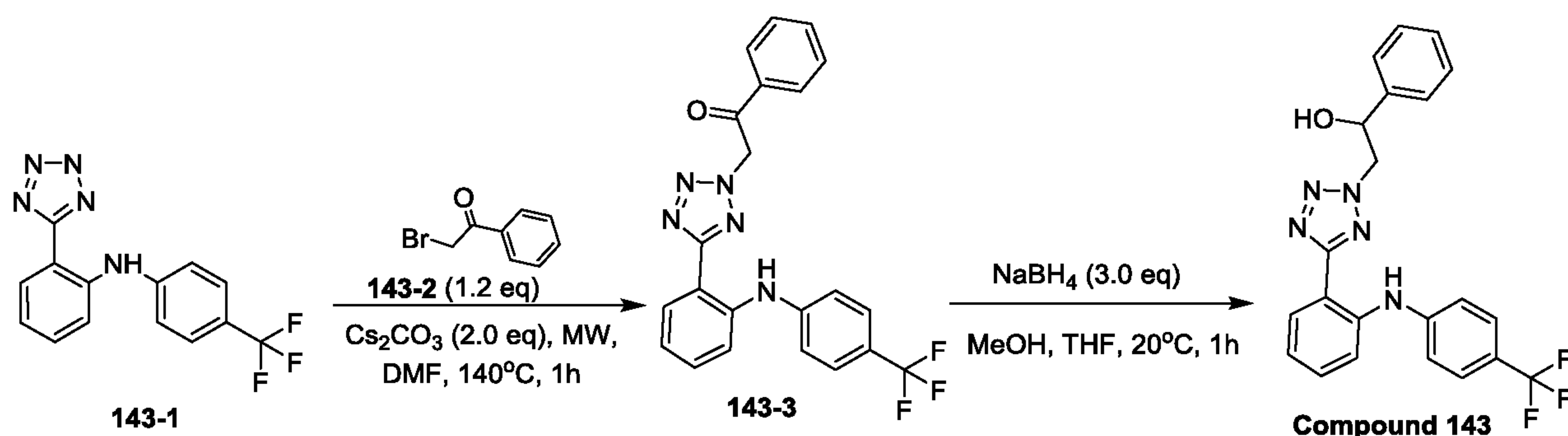
Step 1: 1,7-dioxaspiro[2.5]octane

[00520] To a solution of **142-1** (200.0 mg, 2.0 mmol, 1.0 *eq*) in DME (4.0 mL) was added *t*-BuOK (224.4 mg, 2.0 mmol, 1.0 *eq*) and **142-2** (484.2 mg, 2.2 mmol, 1.1 *eq*). The mixture was stirred at 80 °C for 16 hour under an N₂ atmosphere. TLC (Petroleum ether : Ethyl acetate=3/1) showed a new spot appeared. The reaction was filtered and concentrated under reduced pressure to give a crude product. The crude product was diluted with water (5 mL) and washed with EtOAc (10mL x 2). The combined organic layers were concentrated to give crude **142-3** (60. 0 mg, 0.53 mmol, 26.3% yield) as a yellow oil.

Step 2: 3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]tetrahydropyran-3-ol

[00521] To a solution of **142-4** (30.0 mg, 98.3 μ mol, 1.0 *eq*) in DMF (5.0 mL) was added K₂CO₃ (27.2 mg, 0.20 mmol, 2.0 *eq*) and **142-3** (11.2 mg, 98.3 μ mol, 1.0 *eq*). The mixture was stirred at 120 °C for 16 hours under an N₂ atmosphere. LCMS showed the desired compound was formed. The reaction was filtered to give a crude product. The crude product was purified by prep-HPLC to give **Compound 142** (6.22 mg, 14.83 μ mol, 15.09% yield). LCMS (ESI): RT = 0.843 min, mass calc. for C₂₀H₂₀F₃N₅O₂ 419.16, m/z found 420.0 [M+H]⁺; ¹HNMR (400 MHz, CDCl₃-*d*) δ 9.05 (s, 1H), 8.20 (dd, $J=1.4, 7.9$ Hz, 1H), 7.54 (d, $J=8.3$ Hz, 3H), 7.42 - 7.36 (m, 1H), 7.30 (d, $J=8.5$ Hz, 2H), 7.05 (t, $J=7.2$ Hz, 1H), 4.94 (d, $J=14.1$ Hz, 1H), 4.77 (d, $J=14.1$ Hz, 1H), 3.70 (d, $J=2.8$ Hz, 2H), 3.65 - 3.60 (m, 1H), 3.55 - 3.50 (m, 1H), 2.93 (s, 1H), 1.87 - 1.62 (m, 4H).

Example 136: 1-phenyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol (Compound 143)



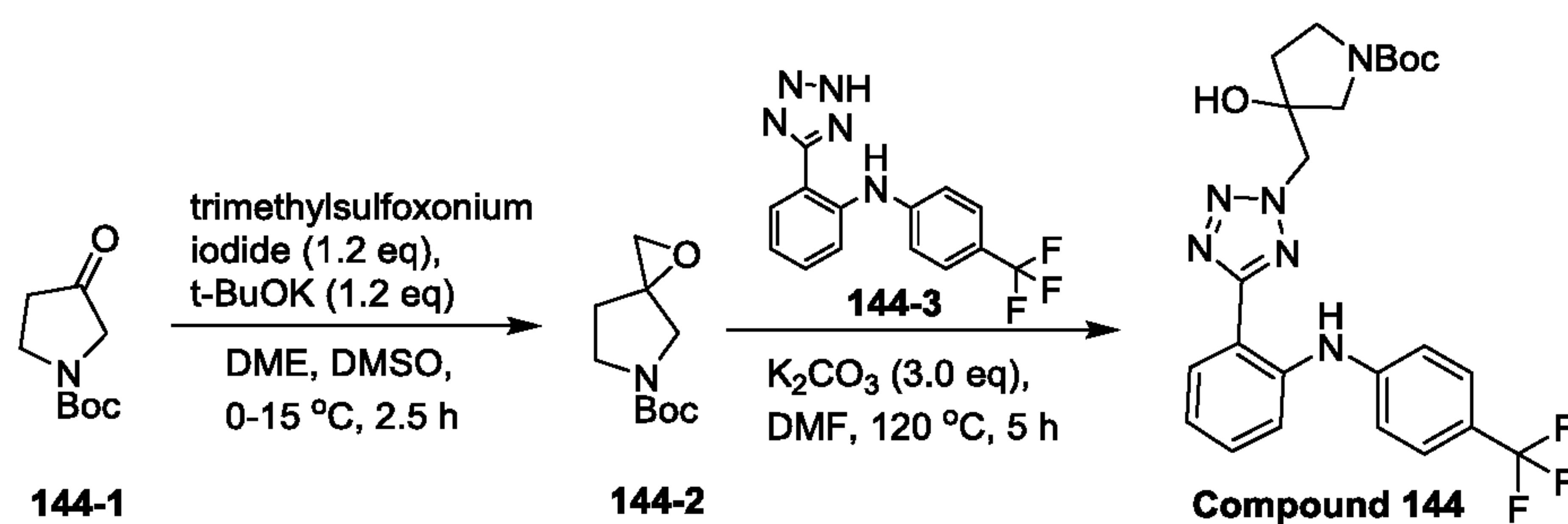
Step 1: 1-phenyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanone

[00522] **143-1** (200.0 mg, 0.66 mmol, 1.0 *eq*), **143-2** (391.2 mg, 0.98 mmol, 1.5 *eq*) and Cs₂CO₃ (426.9 mg, 1.3 mmol, 2.0 *eq*) were taken up into a microwave tube in DMF (3.0 mL). The sealed tube was heated at 150 °C for 1 hour under microwave conditions. LCMS showed the desired compound was formed. TLC (Petroleum ether : Ethyl acetate=3/1) showed new spots had appeared. The reaction was filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by column chromatography over silica gel to give **143-3** (150.0 mg, 0.26 mmol, 39.5% yield). LCMS (ESI): RT = 0.912 min, mass calc. for C₂₂H₁₆F₃N₅O 423.13, m/z found 424.0 [M+H]⁺;

Step 2: 1-phenyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol

[00523] To a solution of **143-3** (150.0 mg, 0.26 mmol, 1.0 *eq*) in THF (3.0 mL) and MeOH (3.0 mL) was added NaBH₄ (29.4 mg, 0.78 mmol, 3.0 *eq*). The resulting mixture was stirred at 20 °C for 1 hour. LCMS showed the desired compound was formed and the starting material was consumed completely. The reaction mixture was treated dropwise with aq. NH₄Cl (5 mL) and extracted with EtOAc (5 mL*2). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, and filtered. The solvent was removed under reduced pressure to afford the crude product. The product was purified by prep-HPLC to give **Compound 143** (73.20 mg, 172.07 umol, 66.53% yield). LCMS (ESI): RT = 0.897 min, mass calc. for C₂₂H₁₈F₃N₅O 425.15, m/z found 426.0 [M+H]⁺; ¹HNMR (400 MHz, CDCl₃-*d*) δ 9.00 (s, 1H), 8.20 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.57 - 7.51 (m, 3H), 7.49 - 7.45 (m, 2H), 7.44 - 7.35 (m, 4H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.08 - 7.03 (m, 1H), 5.40 (d, *J* = 7.5 Hz, 1H), 4.98 - 4.83 (m, 2H), 2.84 (s, 1H).

Example 137: tert-butyl 3-hydroxy-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)pyrrolidine-1-carboxylate (Compound 144)



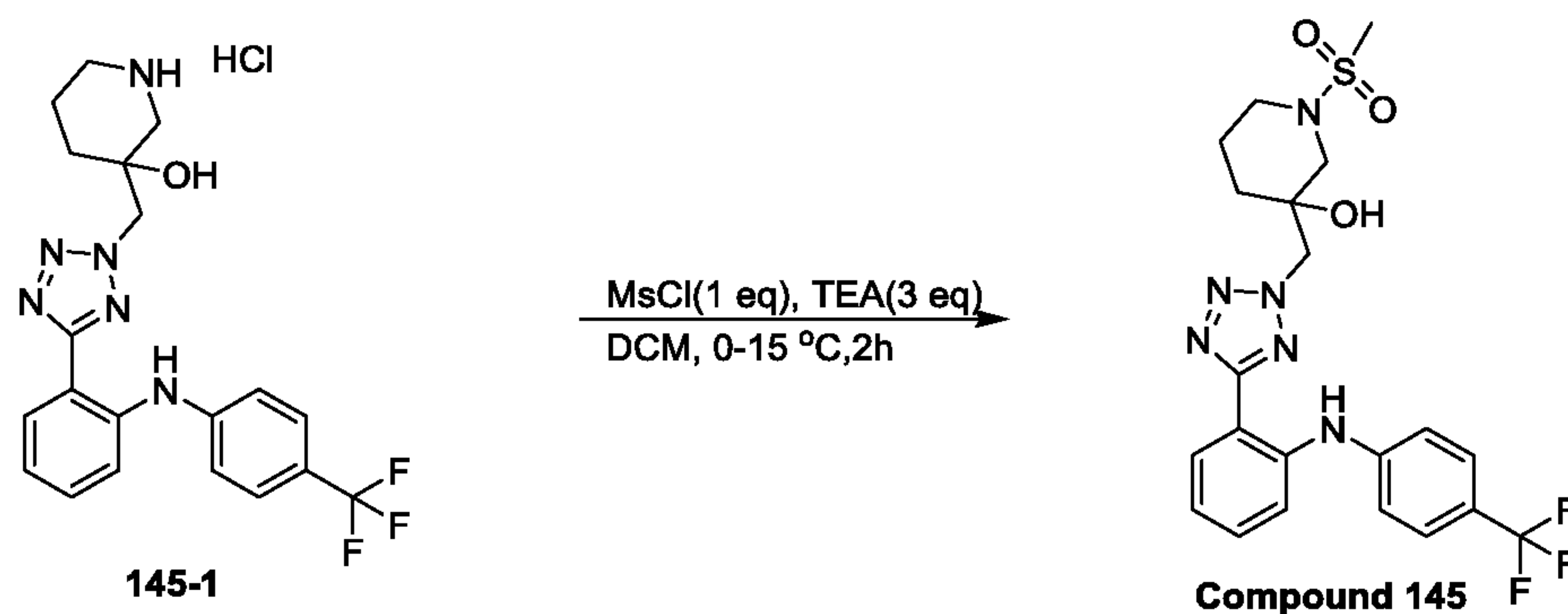
Step 1: tert-butyl 1-oxa-5-azaspiro[2.4]heptane-5-carboxylate

[00524] To a mixture of *t*-BuOK (727.1 mg, 6.5 mmol, 1.20 *eq*) in DMSO (10 mL), was added trimethylsulfoxonium iodine (1.4 g, 6.5 mmol, 1.20 *eq*) by portions. The mixture was stirred at 15 °C for 0.5 h. DME (5 mL) was added, and the mixture was cooled to 0 °C. A solution of **144-1** (1.0 g, 5.4 mmol, 1.00 *eq*) in DMSO (2 mL) and DME (4 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 2 h. TLC showed the reaction was complete. The mixture was diluted with water (20 mL), and extracted with DCM (20 mL*3). The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated under vacuum. The residue was purified by silica gel chromatography to provide **144-2** (200.0 mg, 1.0 mmol, 18.6% yield). ¹HNMR (400MHz, CHLOROFORM-*d*) δ 3.72 - 3.49 (m, 3H), 3.26 (t, *J* = 11.4 Hz, 1H), 2.93 (s, 2H), 2.26 – 2.24 (m, 1H), 1.88 - 1.78 (m, 1H), 1.46 (s, 9H).

Step 2: tert-butyl 3-hydroxy-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)pyrrolidine-1-carboxylate

[00525] To a mixture of **144-3** (70.0 mg, 0.2 mmol, 1.00 *eq*) and K₂CO₃ (95.1 mg, 0.7 mmol, 3.00 *eq*) in DMF (3.0 mL), was added **144-2** (45.7 mg, 0.2 mmol, 1.00 *eq*). The resulting mixture was stirred at 120 °C under N₂ for 5 h. LCMS showed about 67% of the desired compound, and 28% starting material remained. The mixture was combined with a previous batch, and filtered. The filtrate was checked by HPLC. The filtrate was purified by prep-HPLC (basic condition) to obtain **Compound 144** (37.19 mg, 73.7 μmol, 32.2% yield). LCMS (ESI): RT = 0.906 min, mass calc. for C₂₄H₂₇F₃N₆O₃ 504.21, *m/z* found 527.1 [M+Na]⁺. ¹HNMR (400MHz, CHLOROFORM-*d*) δ 9.00 (s, 1H), 8.24 - 8.11 (m, 1H), 7.58 - 7.51 (m, 3H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 4.90 (s, 2H), 3.66 - 3.42 (m, 4H), 2.87 (s, 1H), 2.08 - 1.93 (m, 2H), 1.46 (s, 9H).

Example 138: 1-(methylsulfonyl)-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)piperidin-3-ol (Compound 145)



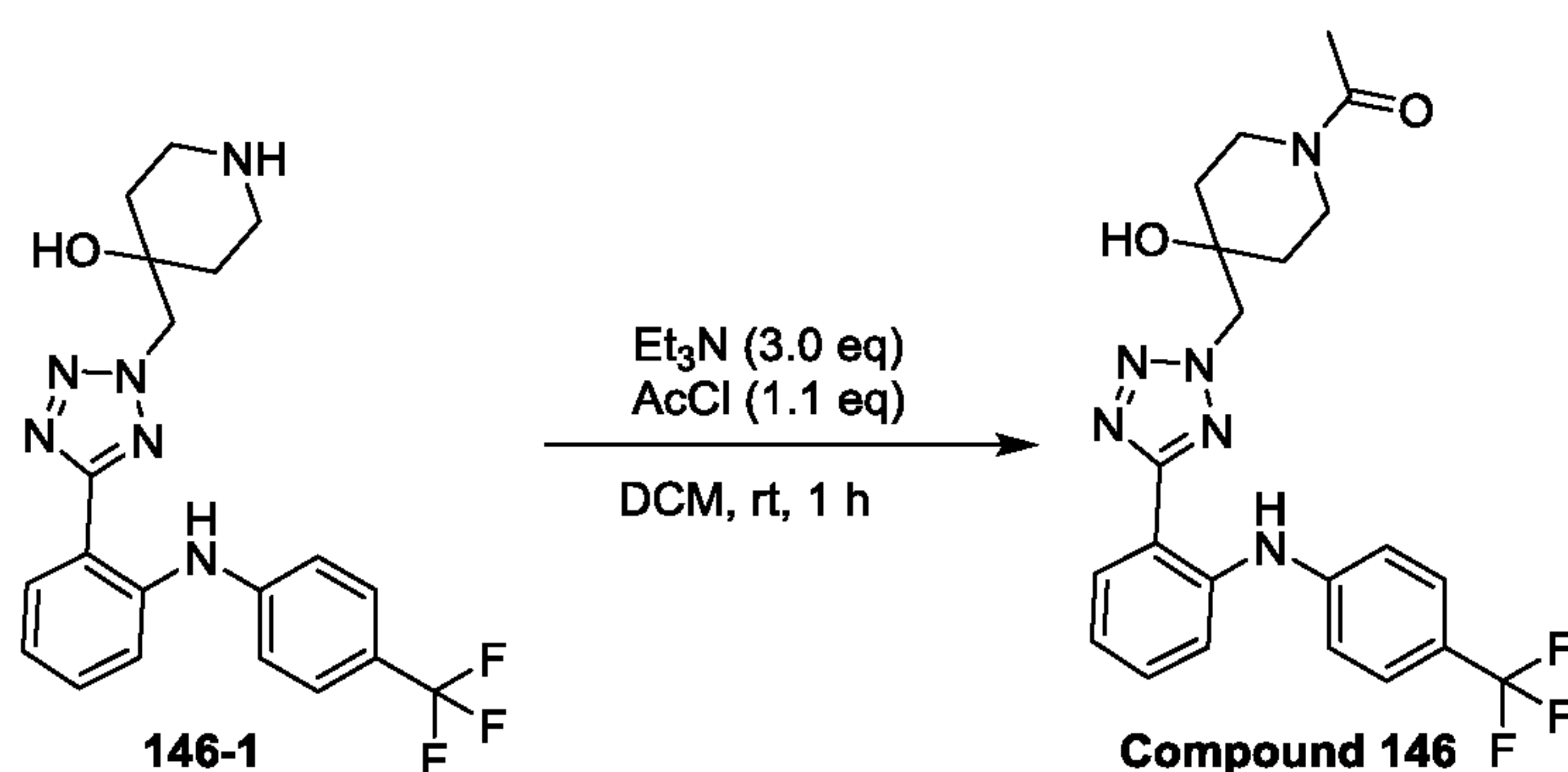
Step 1: 1-(methylsulfonyl)-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)piperidin-3-ol

[00526] To a mixture of **145-1** (30.00 mg, 65.95 μmol , 1.00 *eq*, HCl salt) in DCM (1.00 mL) was added Et₃N (20.02 mg, 197.85 μmol , 27.42 μL , 3.00 *eq*) in one portion at 0°C. The mixture was stirred at 0°C for 10 min, and MsCl (7.55 mg, 65.95 μmol , 5.10 μL , 1.00 *eq*) was added and the reaction stirred for 1 hour at 15°C. The mixture became a yellow solution. LCMS showed 23% of the starting material remained and 71% of desired product was formed. Then, another batch of MsCl (4 mg) was added and the resulting solution was continuously stirred at 15 °C for another 16 h. LCMS showed only a trace of starting material remained and 93% of the desired product was formed. The solution was quenched with 2 drops of water and concentrated to give a residue, which was purified by prep HPLC to give the title compound (14.00 mg, 28.20 μmol , 42.75% yield).

LCMS (ESI): RT = 1.8 min, mass calc. for C₂₁H₂₃F₃N₆O₃S 496.15, m/z found 497.00 [M+1]⁺;

¹HNMR (400MHz, DMSO-*d*₆) δ 8.78 (s, 1H), 8.09 (d, *J* = 7.5 Hz, 1H), 7.63 - 7.46 (m, 4H), 7.31 - 7.15 (m, 3H), 5.32 (s, 1H), 4.86 - 4.73 (m, 2H), 3.25 (d, *J* = 12.0 Hz, 1H), 3.20 - 3.03 (m, 3H), 2.90 (s, 3H), 1.76 (m, 1H), 1.70 - 1.45 (m, 3H).

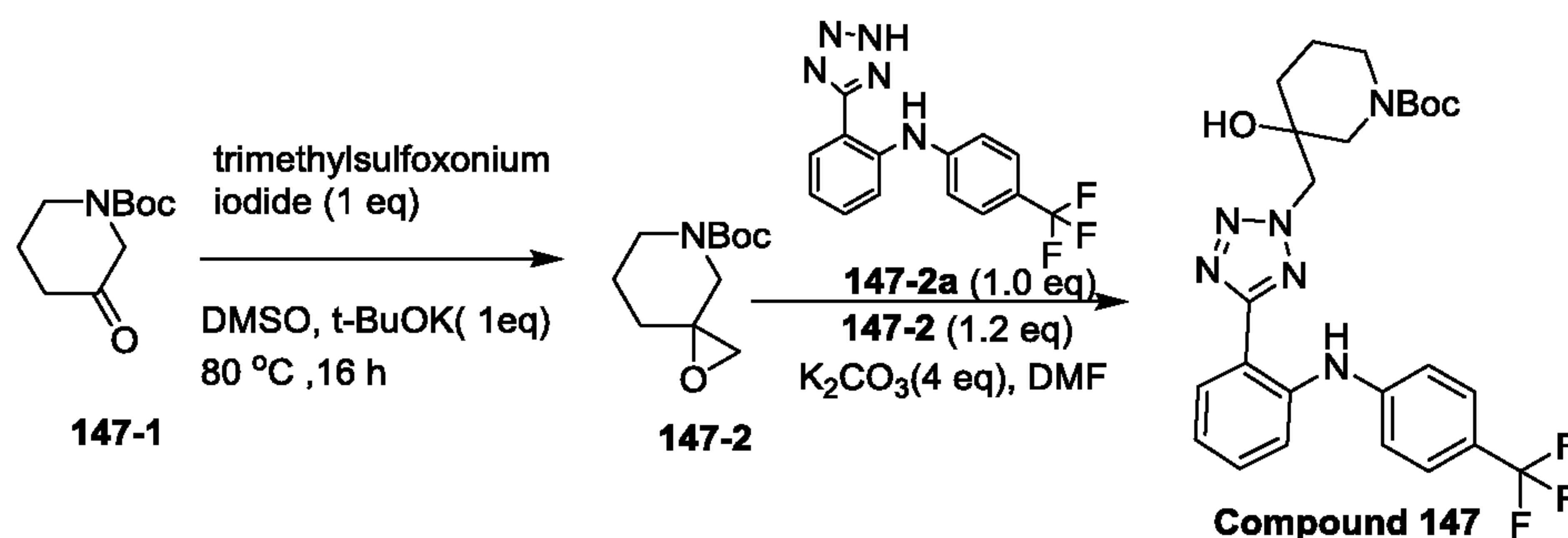
Example 139: 1-[4-hydroxy-4-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]-1-piperidyl]ethanone (Compound 146)



[00527] To a solution of **146-1** (40 mg, 95.60 μmol , 1.00 *eq*) and Et₃N (29 mg, 0.29 mmol, 39.75 μL , 3.00 *eq*) in DCM (2 mL) was added AcCl (4.73 mg, 95.60 μmol , 1.00 *eq*). The reaction was stirred at 25°C for 1 hr. LCMS showed that the desired MS signal was detected. The reaction was concentrated. The crude product was purified by Prep-HPLC (acidic conditions) to give the title

compound (11.22 mg, 23.39 μmol , 24.47% yield). LCMS (ESI): RT = 0.808 min, mass calc. for $\text{C}_{22}\text{H}_{23}\text{F}_3\text{N}_6\text{O}_2$ 460.17, m/z found 483.2 $[\text{M}+\text{Na}]^+$. ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ 8.80 (s, 1H), 8.05 (d, $J = 7.2$ Hz, 1H), 7.59 - 7.47 (m, 4H), 7.25 - 7.15 (m, 3H), 5.06 (br, 1H), 4.71 (s, 2H), 4.20 - 4.05 (m, 1H), 3.65 - 3.55 (m, 1H), 3.33 - 3.23 (m, 1H), 2.90 - 2.75 (m, 1H), 1.97 (s, 3H), 1.75 - 1.55 (m, 1H), 1.55 - 1.45 (m, 3H).

Example 140: tert-butyl 3-hydroxy-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)piperidine-1-carboxylate (Compound 147)



Step 1: tert-butyl 1-oxa-5-azaspiro[2.5]octane-5-carboxylate

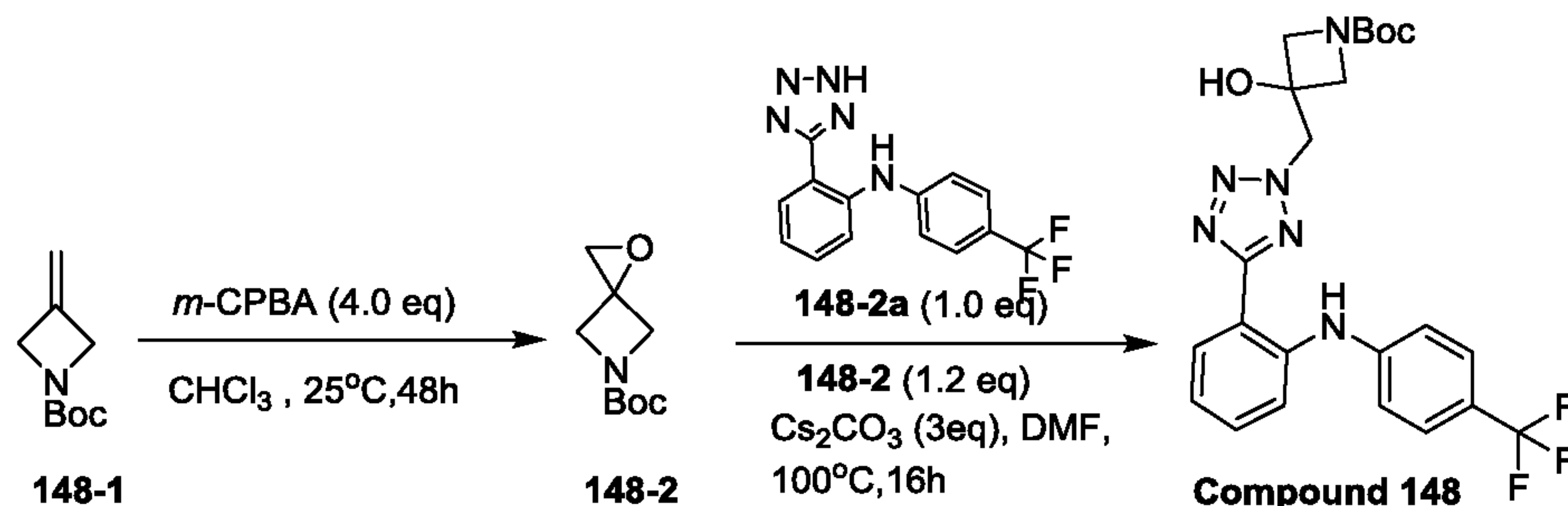
[00528] To the solution of **147-1** (2.00 g, 10.04 mmol, 1.00 *eq*) in DME (40.00 mL) was added *t*-BuOK (1.13 g, 10.04 mmol, 1.00 *eq*) and trimethylsulfoxonium iodide (2.21 g, 10.04 mmol, 1.00 *eq*). Then the mixture was stirred at 80 °C for 16 hr. TLC showed some material remained and new spots were formed. The mixture was quenched with H₂O (20 mL) and extracted with EtOAc (40 mL x3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give **147-2** (770.00 mg, 3.61 mmol, 35.96% yield) as a colorless oil. ^1H NMR (400MHz, $\text{CHLOROFORM}-d$) δ 3.50 - 3.40 (m, 3H), 3.39 - 3.31 (m, 1H), 2.76 (br s, 1H), 2.66 (d, $J = 4.5$ Hz, 1H), 1.89 - 1.78 (m, 1H), 1.77 - 1.62 (m, 3H), 1.45 (s, 9H).

Step 2: tert-butyl 3-hydroxy-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)piperidine-1-carboxylate

[00529] **147-2a** (50.00 mg, 163.79 μmol , 1.00 *eq*), **147-2** (61.92 mg, 290.34 μmol , 1.77 *eq*) and K₂CO₃ (90.55 mg, 655.16 μmol , 4.00 *eq*) were taken up into a microwave tube in DMF (2.00 mL). The sealed tube was heated at 100°C for 30 min under microwave conditions. Then the sealed tube was heated at 150°C for 2.5 h under microwave conditions. The crude LCMS showed the desired product MS value was detected. The reaction mixture was combined with another batch, and the mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give compound **Compound 147** (19.00 mg, 36.64 μmol , 11.19% yield). LCMS (ESI): RT = 2.132 min, mass calc. for $\text{C}_{25}\text{H}_{29}\text{F}_3\text{N}_6\text{O}_3$ 518.53, m/z found 541.00 $[\text{M}+23]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.17 - 1.71 (m, 13 H), 3.12 (br s, 1 H), 3.20 - 3.31 (m, 1

H), 3.39 - 3.54 (m, 2 H), 4.70 (s, 2 H), 5.06 (s, 1 H), 7.13 - 7.31 (m, 3 H), 7.44 - 7.67 (m, 4 H), 8.07 (d, $J = 7.28$ Hz, 1 H), 8.81 (br s, 1 H).

Example 141: tert-butyl 3-hydroxy-3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]azetidine-1-carboxylate (Compound 148)



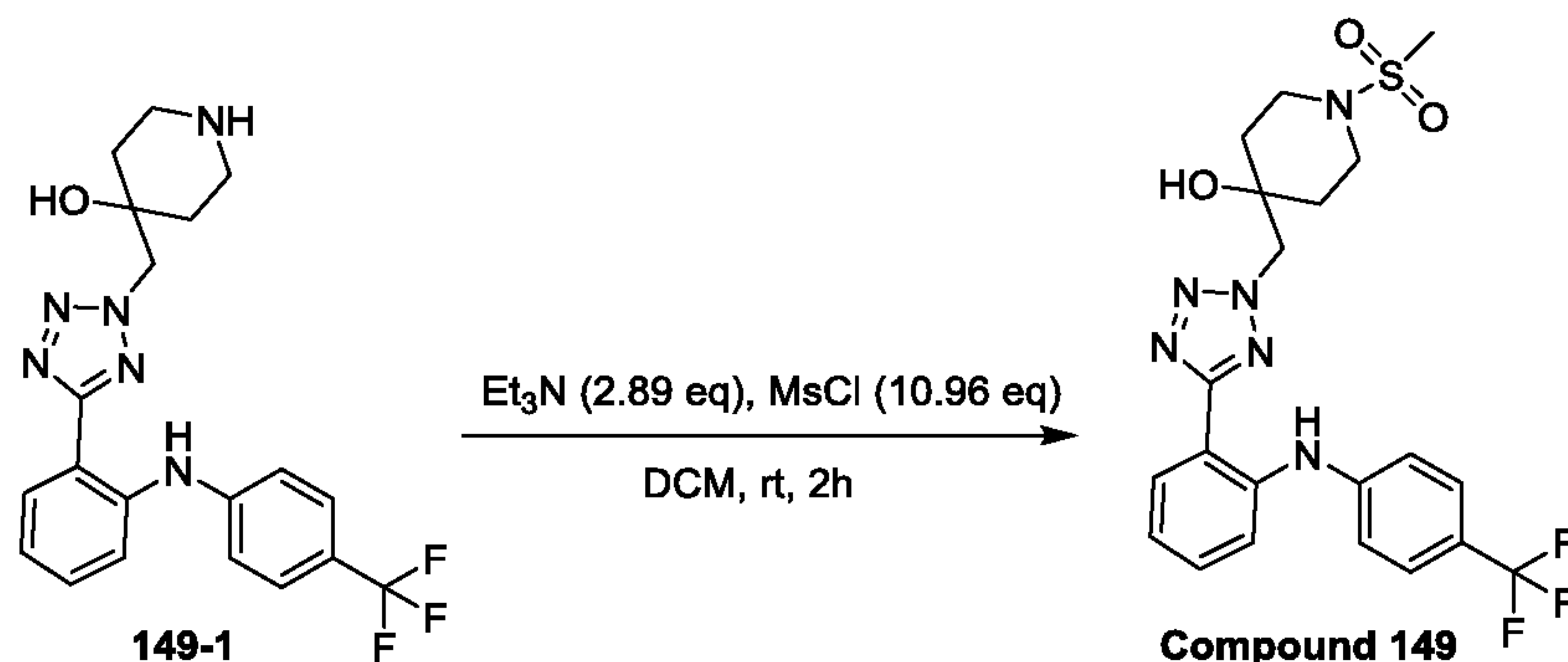
Step 1: tert-butyl 1-oxa-5-azaspiro[2.3]hexane-5-carboxylate

[00530] To a solution of **148-1** (1.0 g, 5.9 mmol, 1.0 eq) in CHCl_3 (20.0 mL) was added *m*-CPBA (4.1 g, 23.6 mmol, 4.0 eq). The mixture was stirred at 25 °C for 48 hours. TLC indicated **148-1** was consumed completely and one new spot formed. The reaction mixture was quenched by addition aq. Na_2SO_3 and aq. NaHCO_3 (50 mL, 1:1), then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (20 mL * 3), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give **148-2** (500.0 mg, 2.7 mmol, 45% yield) as a colorless oil. ^1H NMR (400 MHz, DCCl_3) δ (ppm) 4.29-4.23 (m, 2H), 4.23-4.17 (m, 2H), 2.86 (s, 2H), 1.46 (s, 9H).

Step 2: tert-butyl 3-hydroxy-3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]azetidine-1-carboxylate

[00531] To a solution of **148-2a** (100.0 mg, 0.3 mmol, 1.0 eq) in DMF (3.0 mL) was added K_2CO_3 (181.1 mg, 1.3 mmol, 4.0 eq) and **148-2** (72.8 mg, 0.4 mmol, 1.2 eq). The mixture was stirred at 150 °C under microwave conditions for 1 hour. LC-MS showed 36% of **148-2** remained. Several new peaks were shown on LC-MS and 36% of the desired compound was detected. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give **Compound 148** (60.0 mg, 122.33 μmol , 37% yield). LCMS (ESI): RT = 0.910 min, mass calc. for $\text{C}_{23}\text{H}_{25}\text{F}_3\text{N}_6\text{O}_3$ 490.19, m/z found 513.1 $[\text{M}+\text{Na}]^+$; ^1H NMR (400 MHz, DCCl_3) δ (ppm) 8.98 (s, 1H), 8.17-8.15 (m, $J=1.3$, 8.0 Hz, 1H), 7.56-7.52 (m, $J=4.4$, 8.2 Hz, 3H), 7.40 (t, $J=7.8$ Hz, 1H), 7.30 (d, $J=8.3$ Hz, 2H), 7.27 (s, 1H), 7.06 (t, $J=7.5$ Hz, 1H), 5.00 (s, 2H), 4.09 (d, $J=9.8$ Hz, 2H), 3.97 (d, $J=9.8$ Hz, 2H), 3.46 (s, 1H), 1.45 (s, 9H).

Example 142: 1-methylsulfonyl-4-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]piperidin-4-ol (Compound 149)

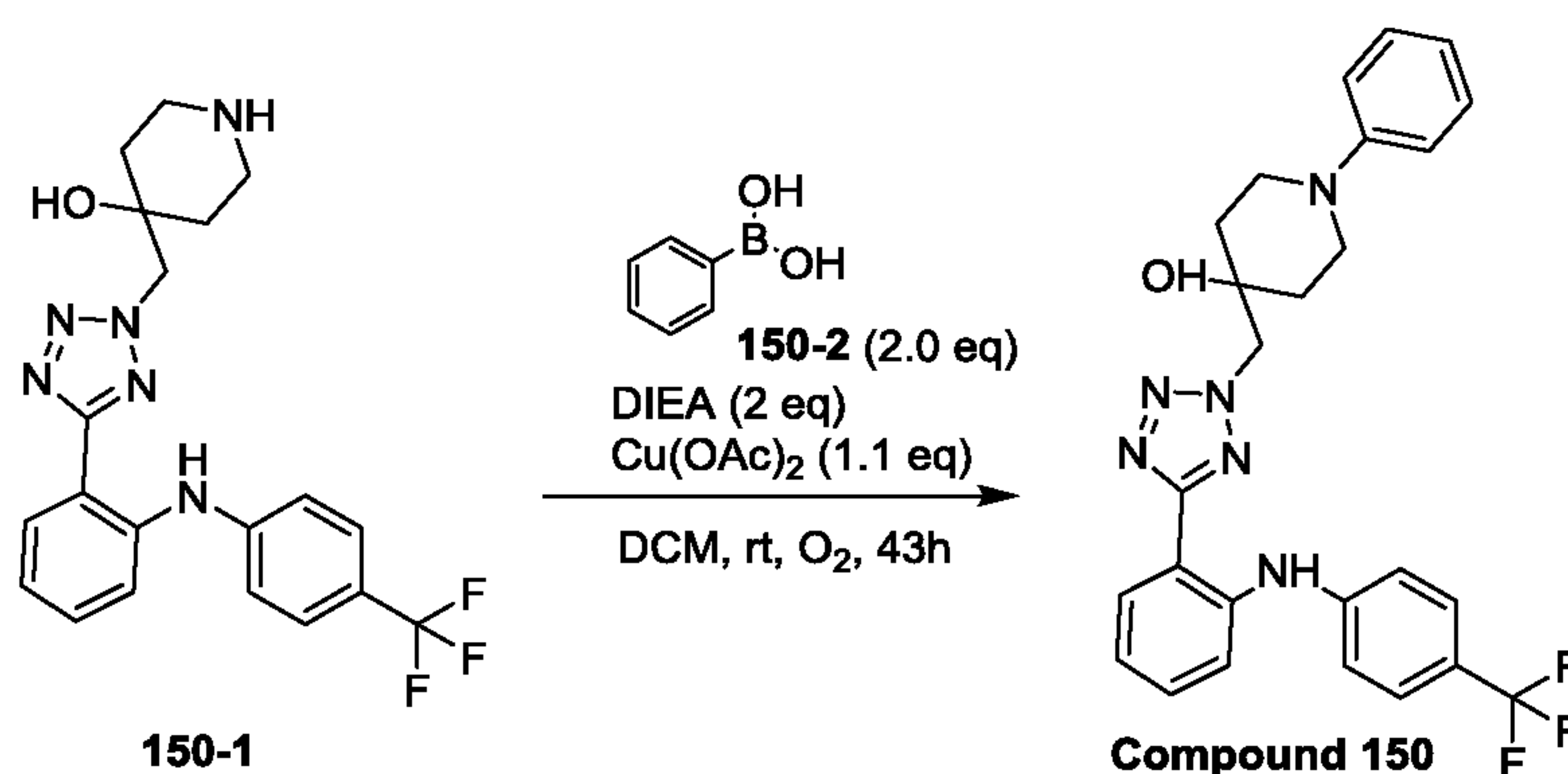


[00532] To a mixture of **149-1** (40 mg, 95.6 μmol , 1.00 *eq*) and Et_3N (28 mg, 0.277 mmol, 38 μL , 2.89 *eq*) in DCM (3 mL) was added MsCl (120 mg, 1.05 mmol, 81 μL , 10.96 *eq*) in one portion at 15 °C under N_2 . The mixture was stirred at 15 °C for 1 h. LCMS showed the starting material was nearly consumed, and one main peak with the desired MS was detected. The reaction mixture was concentrated under reduced pressure to remove the solvent. The residue was purified by prep-HPLC (basic condition) to provide the title compound (15.90 mg, 31.38 μmol , 32.8% yield).

LCMS (ESI): RT = 0.844 min, mass calcd. for $\text{C}_{21}\text{H}_{23}\text{F}_3\text{N}_6\text{O}_3\text{S}$ 496.15, m/z found

519.1 $[\text{M}+23]^+$. ^1H NMR (400MHz, $\text{CHLOROFORM-}d$) δ 9.00 (s, 1H), 8.17 (d, $J=6.80$ Hz, 1H), 7.59 - 7.52 (m, 3H), 7.41 (t, $J=8.00$ Hz, 1H), 7.30 (d, $J=8.80$ Hz, 2H), 7.06 (t, $J=7.20$ Hz, 1H), 4.76 (s, 2H), 3.68 (br d, $J=11.20$ Hz, 2H), 3.11 - 3.01 (m, 2H), 2.81 (s, 4H), 1.92 - 1.82 (m, 2H), 1.62 (br s, 1H).

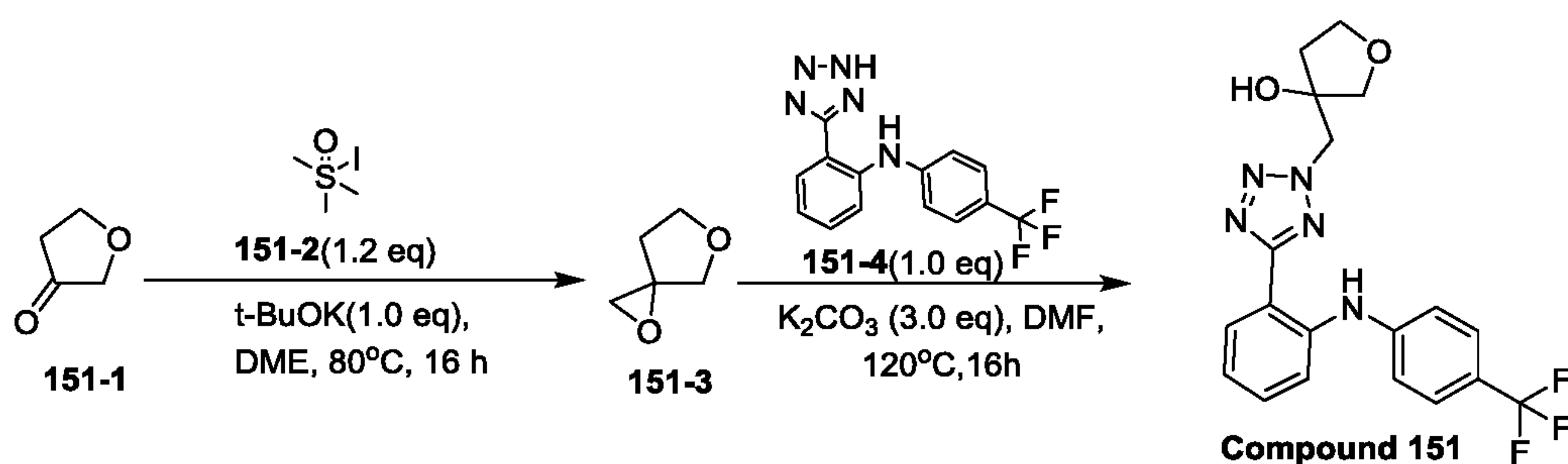
Example 143: 1-phenyl-4-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]piperidin-4-ol (Compound 150)



[00533] To a mixture of **150-1** (100 mg, 0.204 mmol, 1.00 *eq*, 2HCl) and **150-2** (50 mg, 0.407 mmol, 2.00 *eq*) in DCM (2 mL) was added $\text{Cu}(\text{OAc})_2$ (37 mg, 0.204 mmol, 1.00 *eq*) in one portion at 15 °C under O_2 . The mixture was stirred at 15 °C for 27 h. LCMS showed 38% of **150-1** remained. Several new peaks were detected on LCMS and 30% of the desired compound was detected. The reaction mixture was stirred an additional 16 h. The reaction mixture was filtered and

concentrated under reduced pressure to give a residue. LCMS showed 41% of **150-1** remained. Several new peaks were detected on LCMS and 47% of the desired compound was detected. HPLC indicated 52% of the desired compound was detected. The residue was purified by prep-HPLC to provide the title compound (10.24 mg, 20.3 μ mol, 10.0% yield). LCMS (ESI): RT = 0.806 min, mass calcd. for $C_{26}H_{25}F_3N_6O$ 494.20, m/z found 495.2[M+23]⁺. ¹HNMR (400MHz, DMSO-d₆) δ 8.80 (s, 1H), 8.07 (d, *J*=8.00 Hz, 1H), 7.61 - 7.47 (m, 4H), 7.26 - 7.14 (m, 5H), 6.92 (d, *J*=8.00 Hz, 2H), 6.74 (t, *J*=7.40 Hz, 1H), 4.93 (s, 1H), 4.74 (s, 2H), 3.44 (br d, *J*=12.00 Hz, 2H), 2.98 (br t, *J*=11.20 Hz, 2H), 1.82 - 1.69 (m, 2H), 1.59 (br d, *J*=12.40 Hz, 2H).

Example 144: 3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]tetrahydrofuran-3-ol (Compound 151)



Step 1: 1,6-dioxaspiro[2.4]heptane

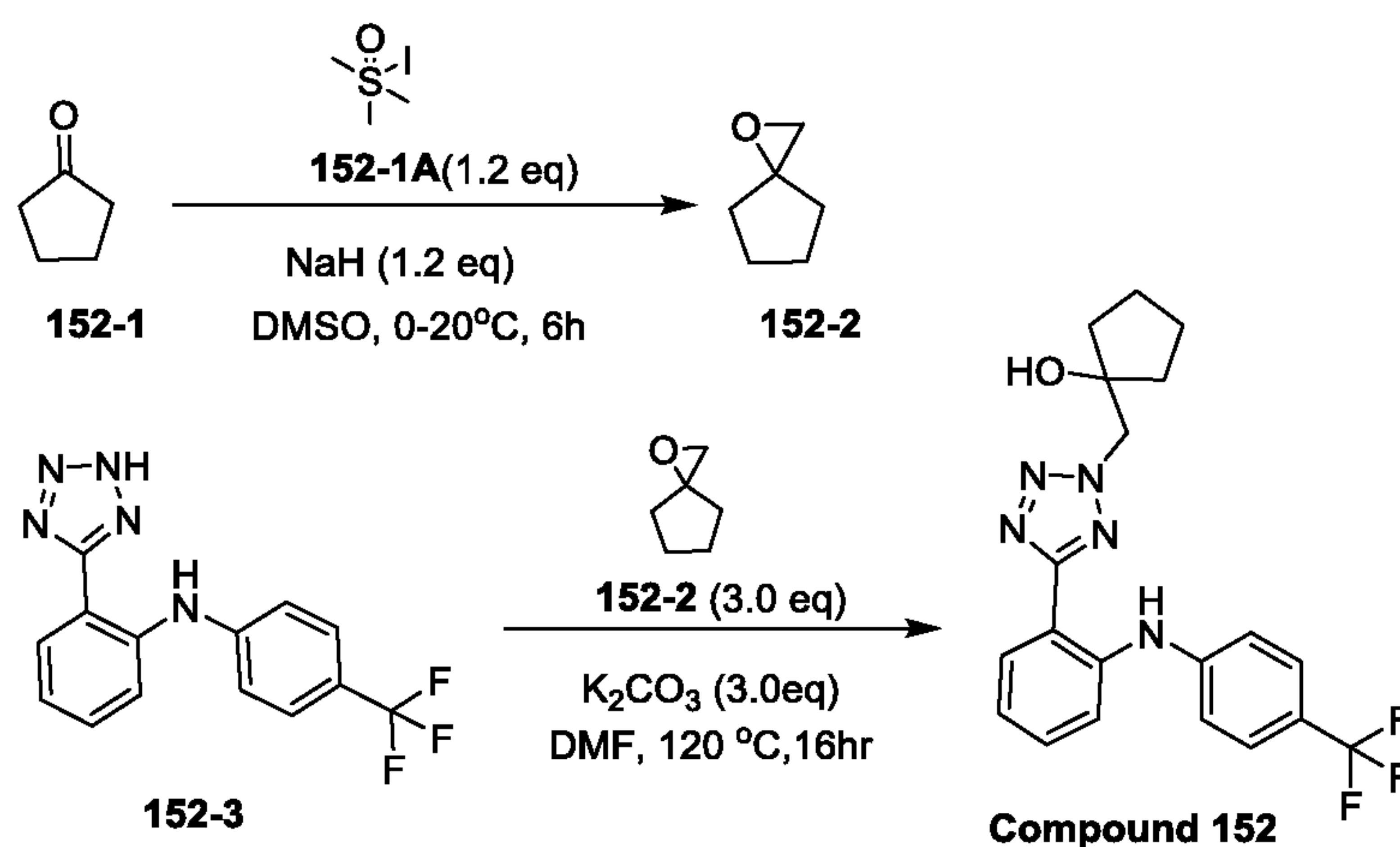
[00534] Compound *t*-BuOK (782.0 mg, 6.9 mmol, 1.2 *eq*) were added in DMSO (10.0 mL) and the mixture cooled to around 20 °C with stirring. **151-2** (1.3 g, 5.8 mmol, 1.0 *eq*) was added in portions over a period of 15 min, maintaining the reaction temperature between 20 - 25 °C. On completion of the addition, the mixture was maintained at this temperature until a yellow solution was obtained (1 h). DME (2.0 mL) was added to the reaction flask and the solution cooled to 0 - 5 °C. A pre-cooled solution of **151-1** (500.0 mg, 5.8 mmol, 1.0 *eq*) in a mixture of DME (2.0 mL) and DMSO (1.0 mL) was transferred into the reaction mixture over a period of around 45 min, maintaining the reaction temperature between 0 - 5 °C. On completion of the addition, the reaction mixture was held at this temperature for a further 1 h. TLC (Petroleum ether : Ethyl acetate=10/1) showed no new spots. The product was directly used as a solution in DMSO without further purification. **151-3** (500.0 mg, 5.0 mmol, 85.9% yield) was obtained in DMSO (11.0 mL).

Step 2: 3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]tetrahydrofuran-3-ol

[00535] To a solution of **151-4** (30.0 mg, 98.3 μ mol, 1.0 *eq*) in DMF (5.0 mL) was added K₂CO₃ (27.2 mg, 0.20 mmol, 2.0 *eq*) and **151-3** (9.8 mg, 98.3 μ mol, 1.0 *eq*). The mixture was stirred at 120 °C for 16 hours under an N₂ atmosphere. LCMS showed the desired compound was formed. The reaction was filtered to give a crude product. The crude product was purified by prep-HPLC to give **Compound 151** (6.93 mg, 17.10 μ mol, 17.39% yield). LCMS (ESI): RT = 0.849 min, mass calc.

for $C_{19}H_{18}F_3N_5O_2$ 405.14, m/z found 406.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3-d$) δ 9.02 (s, 1H), 8.18 (d, $J = 6.8$ Hz, 1H), 7.55 (dd, $J = 2.3, 8.5$ Hz, 3H), 7.40 (t, $J = 7.8$ Hz, 1H), 7.30 (d, $J = 8.5$ Hz, 2H), 7.06 (t, $J = 7.7$ Hz, 1H), 5.02 - 4.84 (m, 2H), 4.11 - 3.98 (m, 2H), 3.93 (d, $J = 9.8$ Hz, 1H), 3.79 (d, $J = 9.8$ Hz, 1H), 2.95 (s, 1H), 2.18 - 2.09 (m, 1H), 2.07 - 2.00 (m, 1H).

Example 145: 1-((5-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)cyclopentanol (Compound 152)



Step 1: 1-Oxaspiro[2.4]heptane

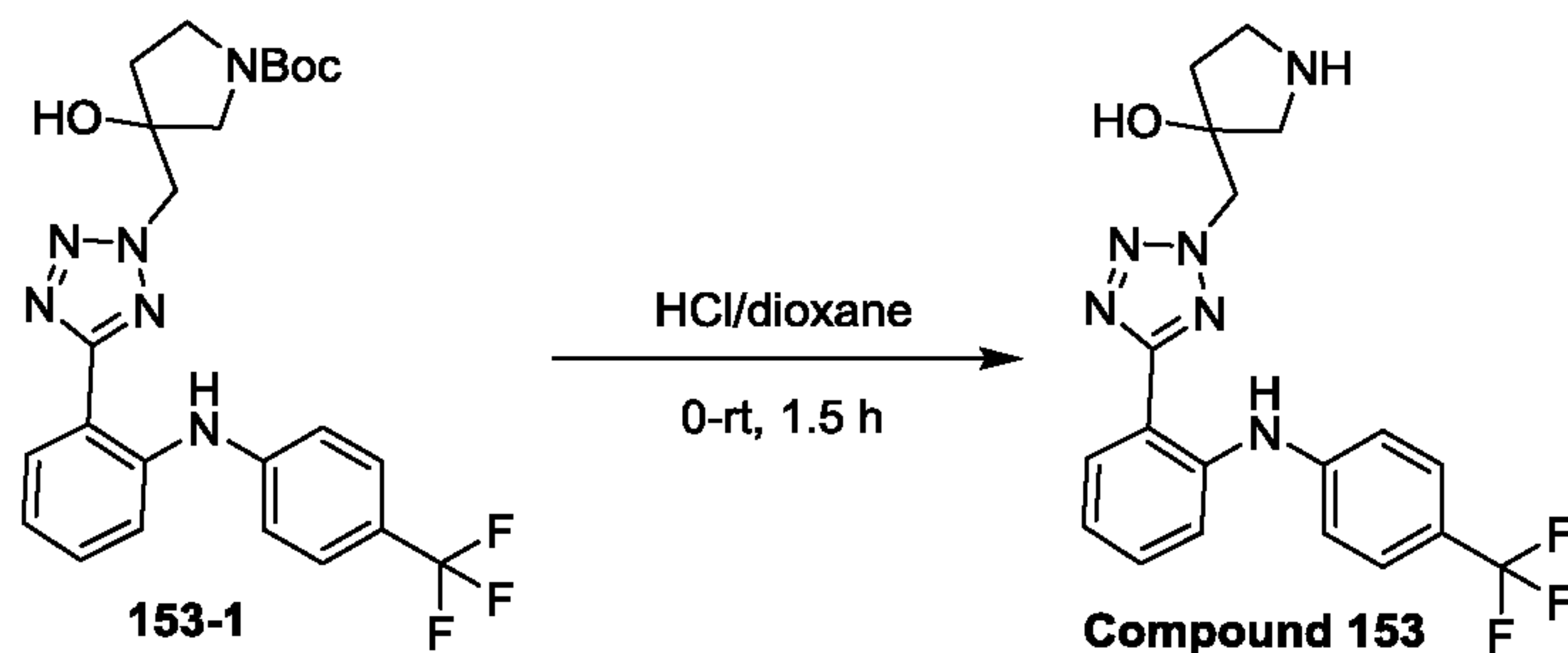
[00536] NaH (571 mg, 14.3 mmol, 60% purity, 1.2 *eq*) was added to a solution of compound **152-1A** (3.1 g, 14 mmol, 1.2 *eq*) in DMSO (20 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 1 hour. **152-1** (1.0 g, 12 mmol, 1.0 *eq*) in DMSO (4 mL) was added dropwise. The reaction mixture was stirred at 20 °C for 5 hours. The reaction was quenched by addition of water (30 mL) and then extracted with Et_2O (80 mL). The organic extract was washed with water (2 * 30 mL), dried over Na_2SO_4 , filtered, and concentrated to dryness under reduced pressure to obtain the title compound (700 mg, crude) as yellow oil. ^1H NMR (400MHz, $CDCl_3-d$) δ 2.84 (s, 2H), 1.91 - 1.82 (m, 4H), 1.74 - 1.62 (m, 4H).

Step 2: 1-((5-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)cyclopentanol

[00537] To a solution of **152-3** (100 mg, 0.328 mmol, 1.0 *eq*) and **152-2** (96 mg, 0.98 mmol, 3.0 *eq*) in DMF (4 mL) was added K_2CO_3 (136 mg, 0.983 mmol, 3.0 *eq*). The reaction mixture was stirred at 120 °C for 16 hours. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (10 mL) and the resultant mixture was extracted with DCM (30 mL * 3). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated to dryness under reduced pressure. The residue was purified by preparative high performance liquid chromatography. The pure fractions were collected and the volatiles were removed under vacuum. The residue was re-suspended in water (10 mL) and the resulting mixture was lyophilized to

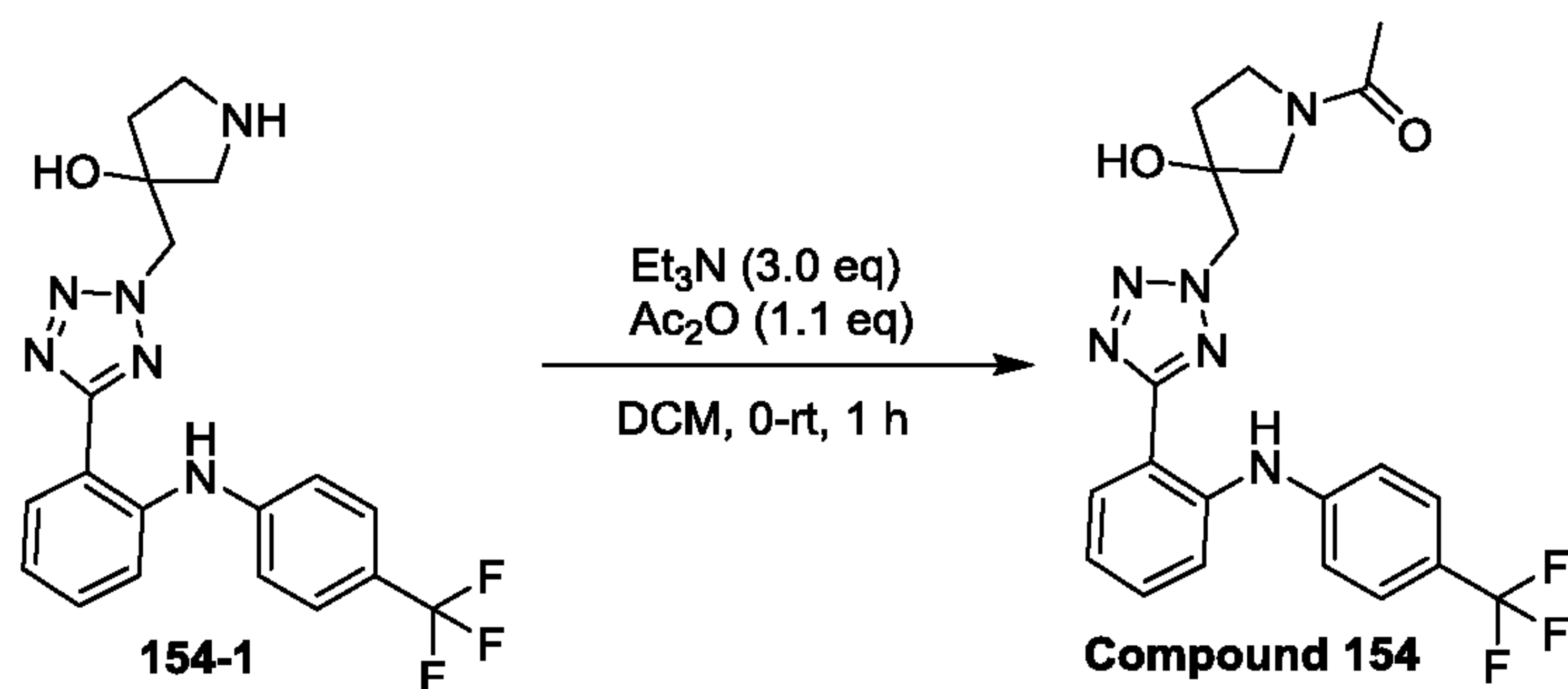
dryness to remove the solvent residue completely to obtain **Compound 152** (18.81 mg, 14% yield). LCMS (ESI): RT = 0.727 min, mass calc. for $C_{20}H_{20}F_3N_5O$ 403.16, m/z found 404.1 $[M+H]^+$, ^1H NMR (400MHz, DMSO- d_6) δ 8.83 (s, 1H), 8.07 (d, J = 7.3 Hz, 1H), 7.56 (d, J = 8.5 Hz, 3H), 7.53 - 7.46 (m, 1H), 7.25 - 7.17 (m, 3H), 4.82 - 4.72 (m, 3H), 1.79 - 1.64 (m, 4H), 1.63 - 1.50 (m, 4H).

Example 146: 3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)pyrrolidin-3-ol (Compound 153)



[00538] To a mixture of **153-1** (35.0 mg, 69.4 μ mol, 1.00 *eq*) in dioxane (2.0 mL), was added HCl/dioxane (4 M, 3.0 mL, 172.96 *eq*) at 0 °C. The mixture was stirred at 15 °C for 1.5 h. LCMS showed the reaction was complete. The mixture was concentrated under vacuum to provide the title compound (27.78 mg, 55.3 μ mol, 79.7% yield, 2HCl salt). LCMS (ESI): RT = 0.722 min, mass calc. for $C_{19}H_{19}F_3N_6O$ 404.16, m/z found 405.0 $[M+H]^+$. ^1H NMR (400MHz, DMSO- d_6) δ 9.22 (s, 2H), 8.77 (s, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.59 - 7.54 (m, 3H), 7.54 - 7.48 (m, 1H), 7.25 - 7.18 (m, 3H), 5.74 (s, 1H), 5.02 (s, 2H), 4.47 (s, 1H), 3.44 - 3.41 (m, 1H), 3.31 - 3.21 (m, 2H), 3.19 (d, J = 12.0 Hz, 1H), 2.19 - 2.08 (m, 1H), 2.01 - 1.95 (m, 1H).

Example 147: 1-(3-hydroxy-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)pyrrolidin-1-yl)ethanone (Compound 154)



[00539] To a mixture of **154-1** (25.0 mg, 52.4 μ mol, 1.00 *eq*, 2HCl salt) and TEA (15.9 mg, 157.1 μ mol, 3.00 *eq*) in DCM (5.0 mL), was added Ac_2O (5.9 mg, 57.6 μ mol, 5.4 μ L, 1.10 *eq*) at 0 °C. The resulting mixture was stirred at 15 °C for 1 h. LCMS showed the reaction was complete. The mixture was diluted with water (10 mL), and extracted with DCM (10 mL *3). The organic layer was dried over anhydrous Na_2SO_4 , concentrated under vacuum. The residue was purified by prep-

HPLC (acidic conditions) to provide the title compound (10.78 mg, 22.9 μ mol, 43.8% yield).

LCMS (ESI): RT = 0.804 min, mass calc. for $C_{21}H_{21}F_3N_6O_2$ 446.17, m/z found 469.1 $[M+Na]^+$.

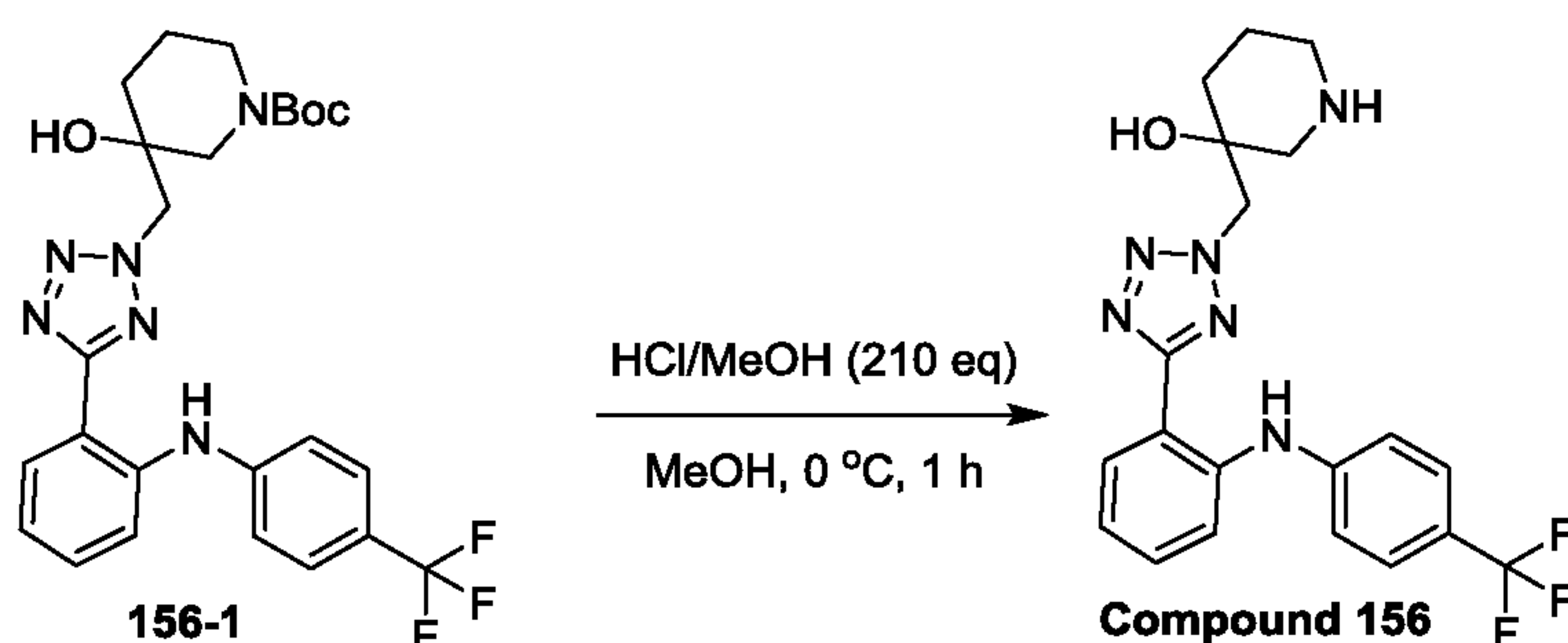
^1H NMR (400MHz, DMSO- d_6) δ 8.77 (d, J = 11.3 Hz, 1H), 8.07 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 8.3 Hz, 3H), 7.53 - 7.47 (m, 1H), 7.28 - 7.17 (m, 3H), 4.92 (d, J = 3.5 Hz, 2H), 3.70 (d, J = 10.8 Hz, 1H), 3.39 (d, J = 11.0 Hz, 2H), 3.33 - 3.23 (m, 1H), 2.16 - 1.97 (m, 1H), 1.95 - 1.80 (m, 4H).

Example 148: 1-(3-hydroxy-3-((5-(2-((4-(trifluoromethyl) phenyl) amino) phenyl) -2H-tetrazol-2-yl) methyl) piperidin-1-yl) ethanone (Compound 155)



[00540] To a mixture of compound **155-1** (30.00 mg, 65.95 μ mol, 1.00 *eq*, HCl) and TEA (20.02 mg, 197.85 μ mol, 27.42 μ L, 3.00 *eq*) in DCM (1.00 mL) was added Ac_2O (6.73 mg, 65.95 μ mol, 6.18 μ L, 1.00 *eq*) in one portion stirred at 0 °C for 15 min. The mixture was stirred at 15 °C for 70 h. The crude LCMS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the title compound (7.14 mg, 15.51 μ mol, 23.51% yield). LCMS (ESI): RT = 0.818 min, mass calc. for $C_{22}H_{23}F_3N_6O_2$ 460.45, m/z found 483.1 $[M+23]^+$; ^1H NMR (400 MHz, CHLOROFORM- d) δ 1.66 (s, 1 H), 1.72 - 2.03 (m, 4 H), 2.15 (s, 4 H), 3.28 (s, 2 H), 3.61 (s, 1 H), 3.89 - 4.19 (m, 1 H), 4.78 (s, 2 H), 7.04 (t, J = 7.28 Hz, 1 H), 7.30 (d, J = 8.28 Hz, 2 H), 7.38 (t, J = 7.65 Hz, 1 H), 7.53 (d, J = 8.28 Hz, 3 H), 8.19 (d, J = 7.78 Hz, 1 H).

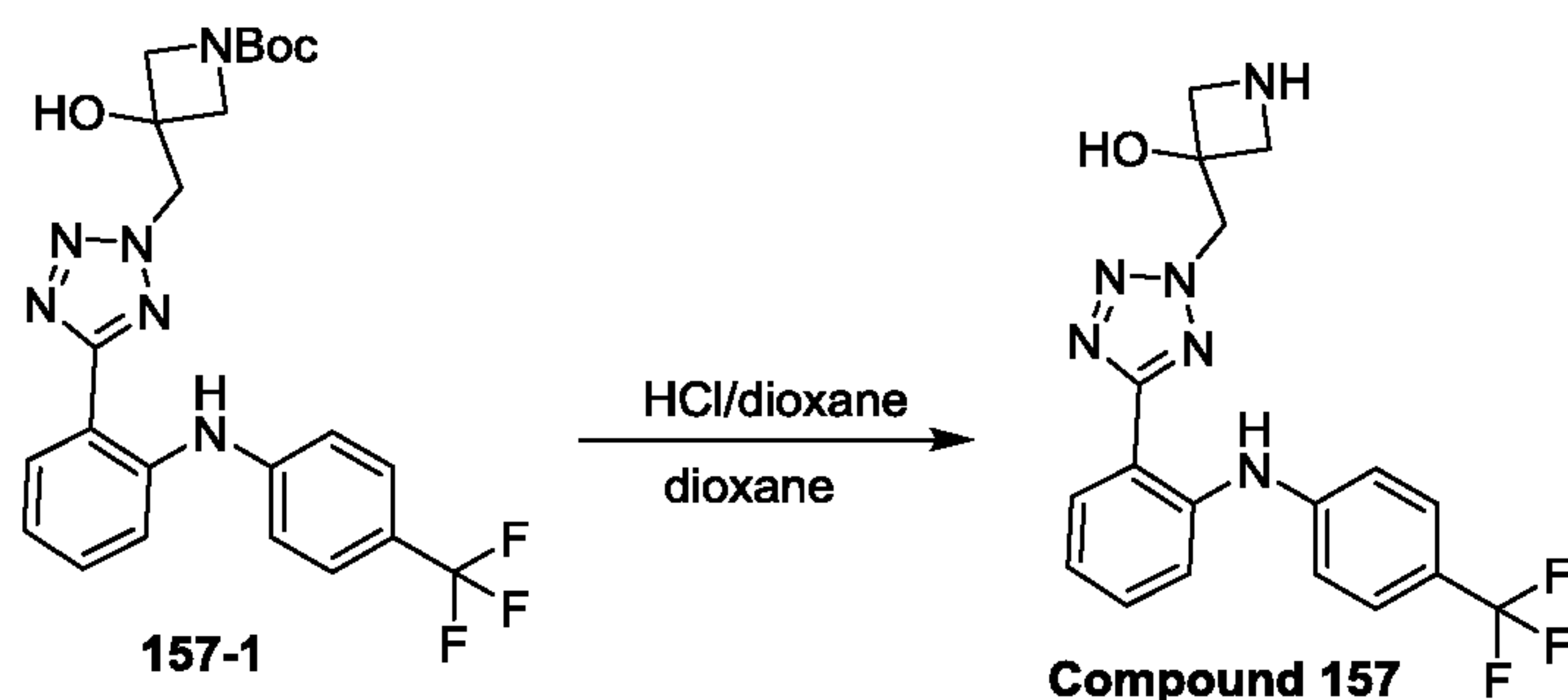
Example 149: 3-((5-(2-((4-(trifluoromethyl) phenyl) amino) phenyl)-2H-tetrazol-2-yl) methyl) piperidin-3-ol (Compound 156)



[00541] To a mixture of compound **156-1** (16.00 mg, 30.86 μ mol, 1.00 *eq*) in MeOH (2.00 mL) was added HCl/MeOH (4 M, 1.62 mL, 210.00 *eq*) at 0 °C. The mixture was stirred at 15 °C for 23 hr. The crude LCMS showed the desired product was detected. The reaction mixture was

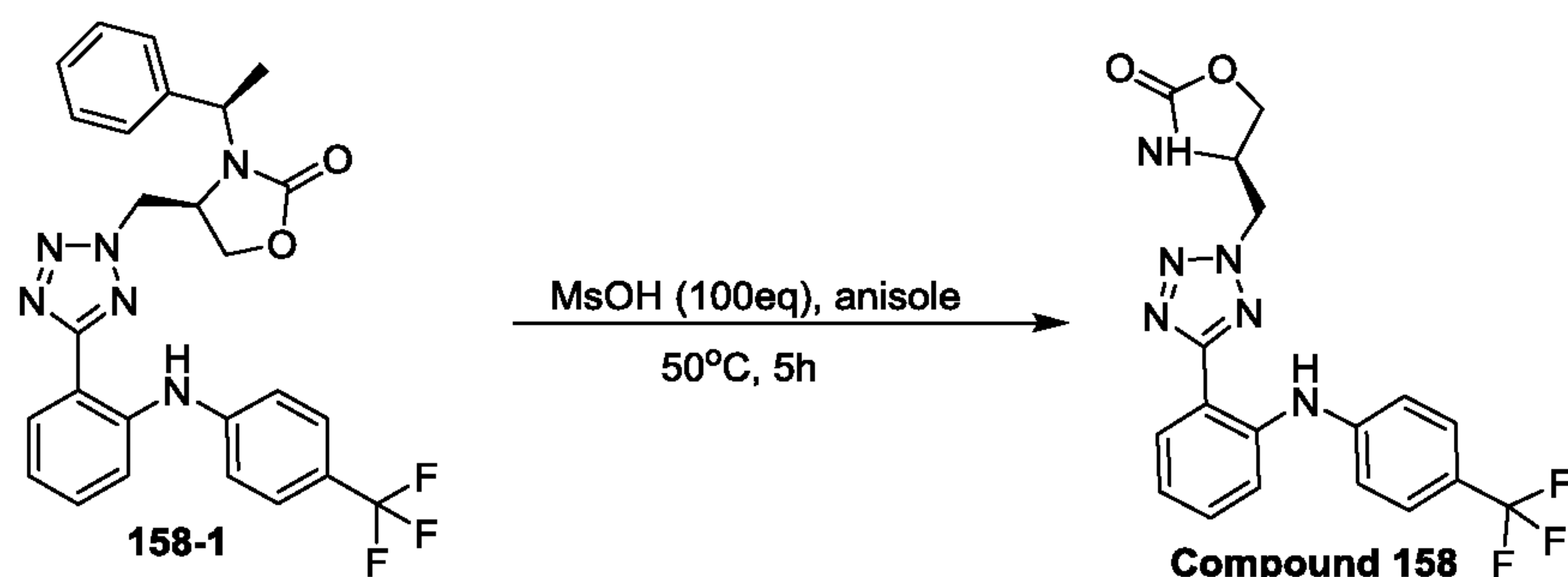
concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the title compound (2.17 mg, 5.03 μ mol, 16.30% yield). LCMS (ESI): RT = 0.743 min, mass calc. for $C_{20}H_{21}F_3N_6O$ 418.42, m/z found 419.2 $[M+1]^+$; ^1H NMR (400 MHz, $DMSO-d_6$) δ 1.38 - 1.63 (m, 4 H), 2.57-2.67 (m, 4 H), 2.76 (d, J = 12.05 Hz, 1 H), 4.67 - 4.96 (m, 3 H), 7.12-7.28 (m, 3 H), 7.43 - 7.67 (m, 4 H), 8.06 (d, J = 6.78 Hz, 1 H), 8.82 (br s, 1 H).

Example 150: 3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]azetidin-3-ol (Compound 157)



[00542] To a solution of **157-1** (20.0 mg, 40.78 μ mol, 1.0 eq) in dioxane (0.5 mL) was added HCl/dioxane (1.0 mL). The mixture was stirred at 25 °C for 0.1h. LC-MS showed **157-1** was consumed completely. Several new peaks were detected on LC-MS and 81% of the desired compound was detected. The pH of the reaction mixture was adjusted with aq. $NaHCO_3$ to 7-8, and then extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the title compound (2.70 mg, 6.92 μ mol, 17% yield). LCMS (ESI): RT = 0.738 min, mass calc. for $C_{18}H_{17}F_3N_6O_3$ 390.14, m/z found 371.2 $[M-F]^+$; ^1H NMR (400MHz, $DCCl_3$) δ (ppm) 8.80 (s, 1H), 8.06 (d, J =7.5 Hz, 1H), 7.60-7.52 (m, 3H), 7.52-7.45 (m, 1H), 7.26-7.15 (m, 3H), 5.85 (s, 1H), 4.96 (s, 2H), 3.51 (d, J =7.5 Hz, 2H), 3.43 (d, J =7.8 Hz, 2H).

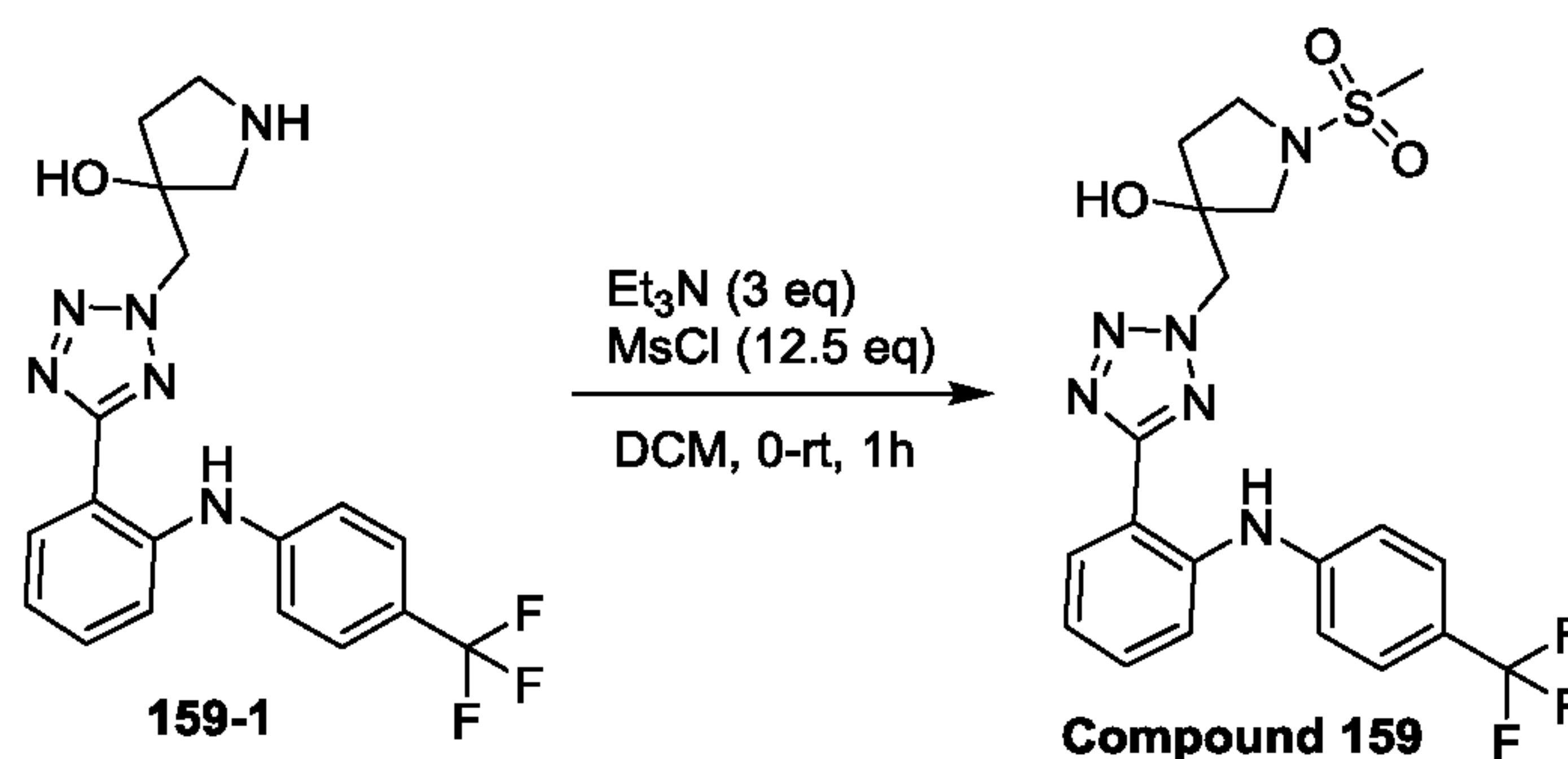
Example 151: (R)-4-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)oxazolidin-2-one (Compound 158)



[00543] A mixture of **158-1** (13 mg, 26 μ mol, 1.0 eq) and MsOH (246 mg, 2.56 mmol, 182 μ L, 100.0 eq) in anisole (260 mg, 2.4 mmol, 260 μ L, 94 eq) was stirred at 50°C for 16 hours. LCMS

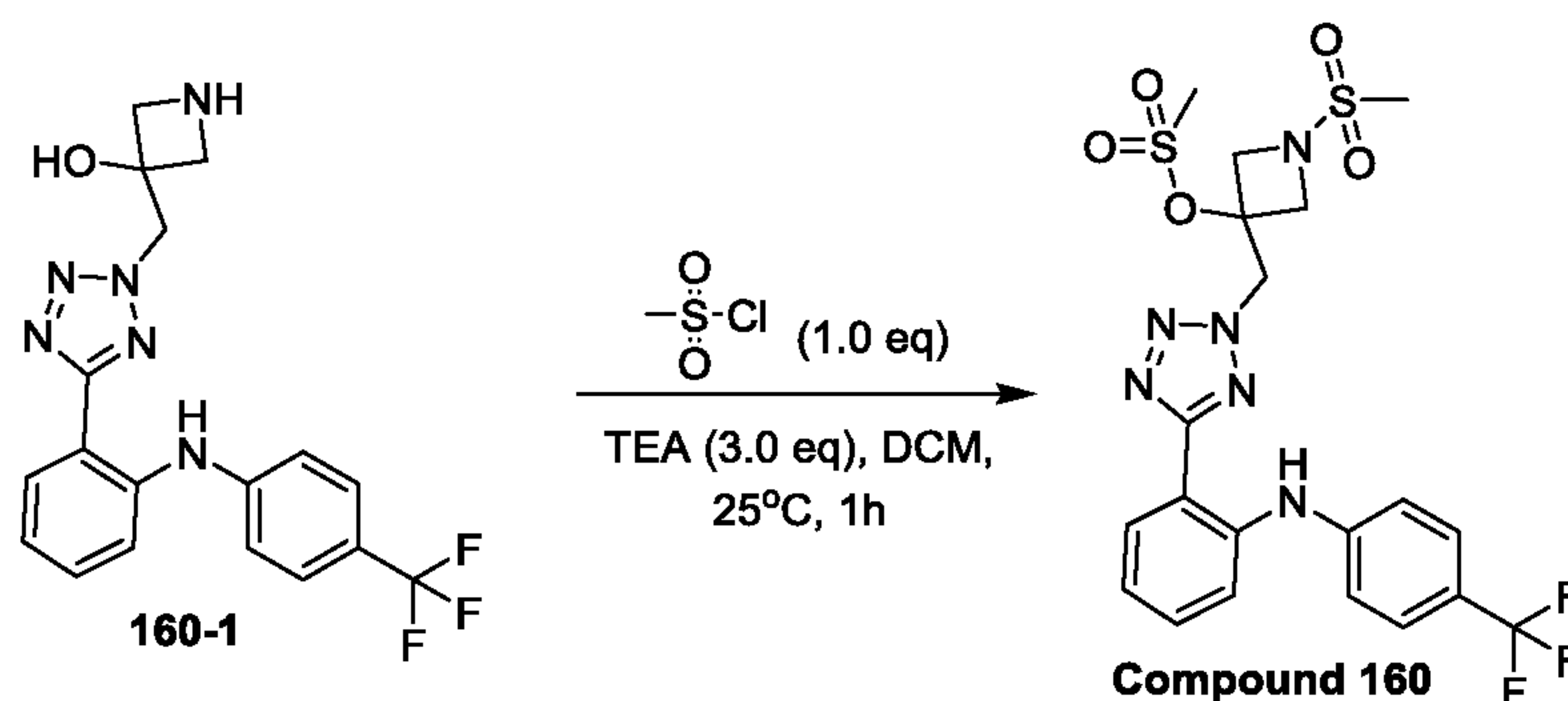
showed 12% of the desired compound was formed and the starting material was consumed completely. The mixture was combined with another batch and concentrated under vacuum to give a residue. The residue was purified by prep-HPLC to give the title compound (9 mg, 20 μ mol, 78 % yield, HCl salt). LCMS (ESI): RT = 0.838 min, mass calc. for $C_{18}H_{15}F_3N_6O_2$ 404.12, m/z found 427.0 $[M+23]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ 8.69 (s, 1H), 8.07 (d, J = 7.5 Hz, 1H), 7.97 (s, 1H), 7.57 (d, J = 8.5 Hz, 3H), 7.54 - 7.47 (m, 1H), 7.28 - 7.16 (m, 3H), 4.89 (d, J = 5.0 Hz, 2H), 4.50 - 4.36 (m, 2H), 4.25 (dd, J = 3.6, 8.2 Hz, 1H).

Example 152: 1-(methanesulfonyl)-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)tetrazol-2-yl)methyl)pyrrolidin-3-ol (Compound 159)



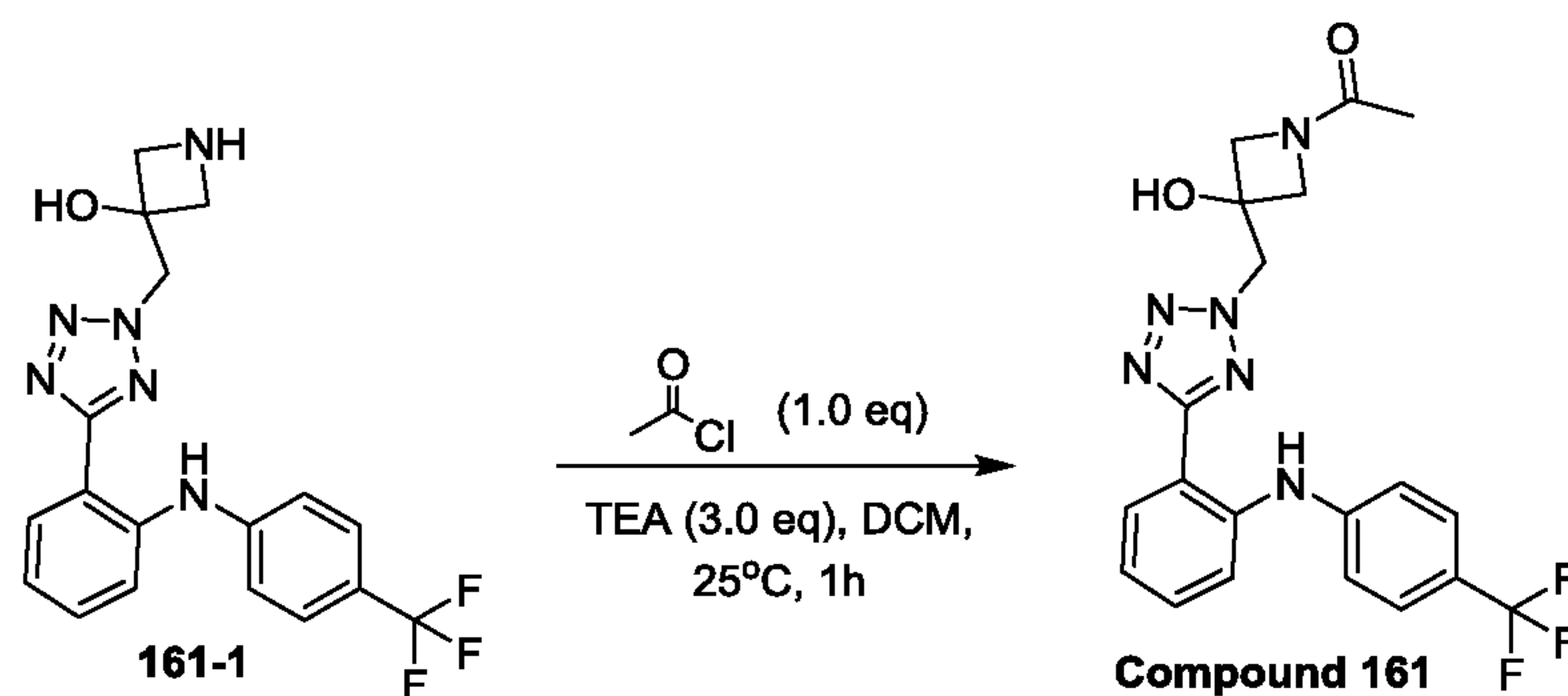
[00544] To a mixture of **159-1** (30.0 mg, 62.9 μ mol, 1.00 *eq*, 2HCl) and TEA (19.1 mg, 0.2 mmol, 3.00 *eq*) in DCM (5.0 mL), was added MsCl (90.0 mg, 0.8 mmol, 60.8 μ L, 12.50 *eq*) at 0 °C. The resulting mixture was stirred at 15 °C for 1 h. LCMS and HPLC showed the reaction was completed. The mixture was diluted with water (10 mL), and extracted with DCM (10 mL *3). The organic layer was dried over anhydrous Na_2SO_4 , and concentrated under vacuum. The residue was purified by prep-HPLC (acidic_HCl condition) to provide the title compound (7.32 mg, 15.2 μ mol, 24.1% yield). LCMS (ESI): RT = 0.837 min, mass calc. for $C_{20}H_{21}F_3N_6O_3S$ 482.13, m/z found 483.1 $[M+H]^+$. ^1H NMR (400MHz, DMSO- d_6) δ 8.76 (s, 1H), 8.07 (dd, J = 1.3, 7.8 Hz, 1H), 7.59 - 7.54 (m, 3H), 7.53 - 7.47 (m, 1H), 7.25 - 7.17 (m, 3H), 5.40 (s, 1H), 4.95 (s, 2H), 3.57 (d, J = 11.0 Hz, 1H), 3.44 - 3.40 (m, 1H), 3.33 - 3.28 (m, 2H), 2.86 (s, 3H), 2.16 - 2.08 (m, 1H), 1.90 (dd, J = 6.4, 12.7 Hz, 1H).

Example 153: [1-methanesulfonyl-3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]azetidin-3-yl] methanesulfonate (Compound 160)



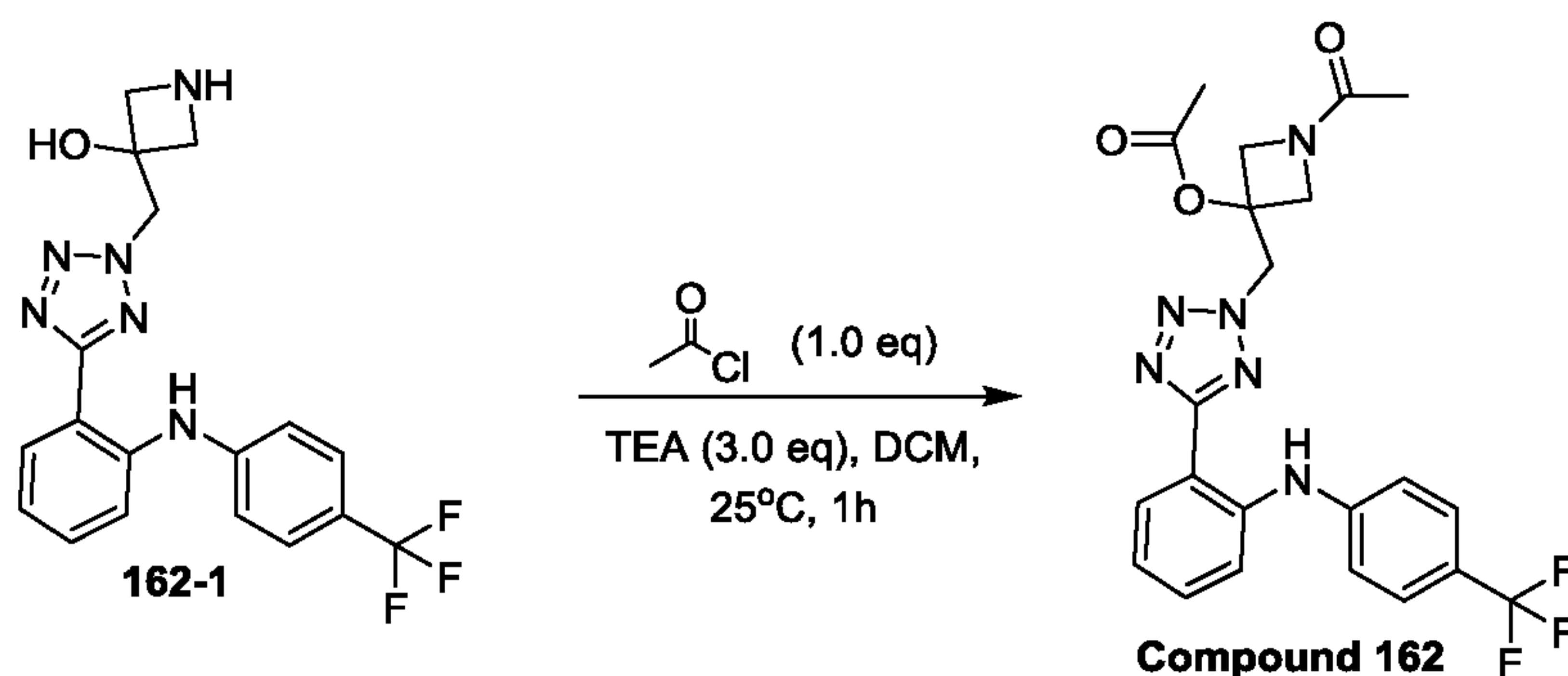
[00545] To a solution of **160-1** (70.0 mg, 0.2 mmol, 1.00 eq) in DCM (3.0 mL) was added TEA (54.4 mg, 0.5 mmol, 74.5 uL, 3.0 eq) and methanesulfonyl chloride (120.0 mg, 1.0 mmol, 81.0 uL, 5.8 eq). The mixture was stirred at 25 °C for 1 hour. LC-MS showed **160-1** was consumed completely and one main peak with the desired MS was detected. The residue was purified by prep-HPLC to give the title compound (5.59 mg, 10.3 umol, 5.7% yield). LCMS (ESI): RT = 0.836 min, mass calc. for C₂₀H₂₁F₃N₆O₅S₂ 546.10, m/z found 569.1 [M+Na]⁺; ¹HNMR (400MHz, DMSO-*d*₆) δ (ppm) 8.68 (s, 1H), 8.08 (d, *J*=7.5 Hz, 1H), 7.60-7.48 (m, 4H), 7.28-7.13 (m, 3H), 5.49 (s, 2H), 4.32 (s, 4H), 3.33 (s, 3H), 3.14 (s, 3H).

Example 154: 1-[3-hydroxy-3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]azetidin-1-yl]ethanone (Compound 161)



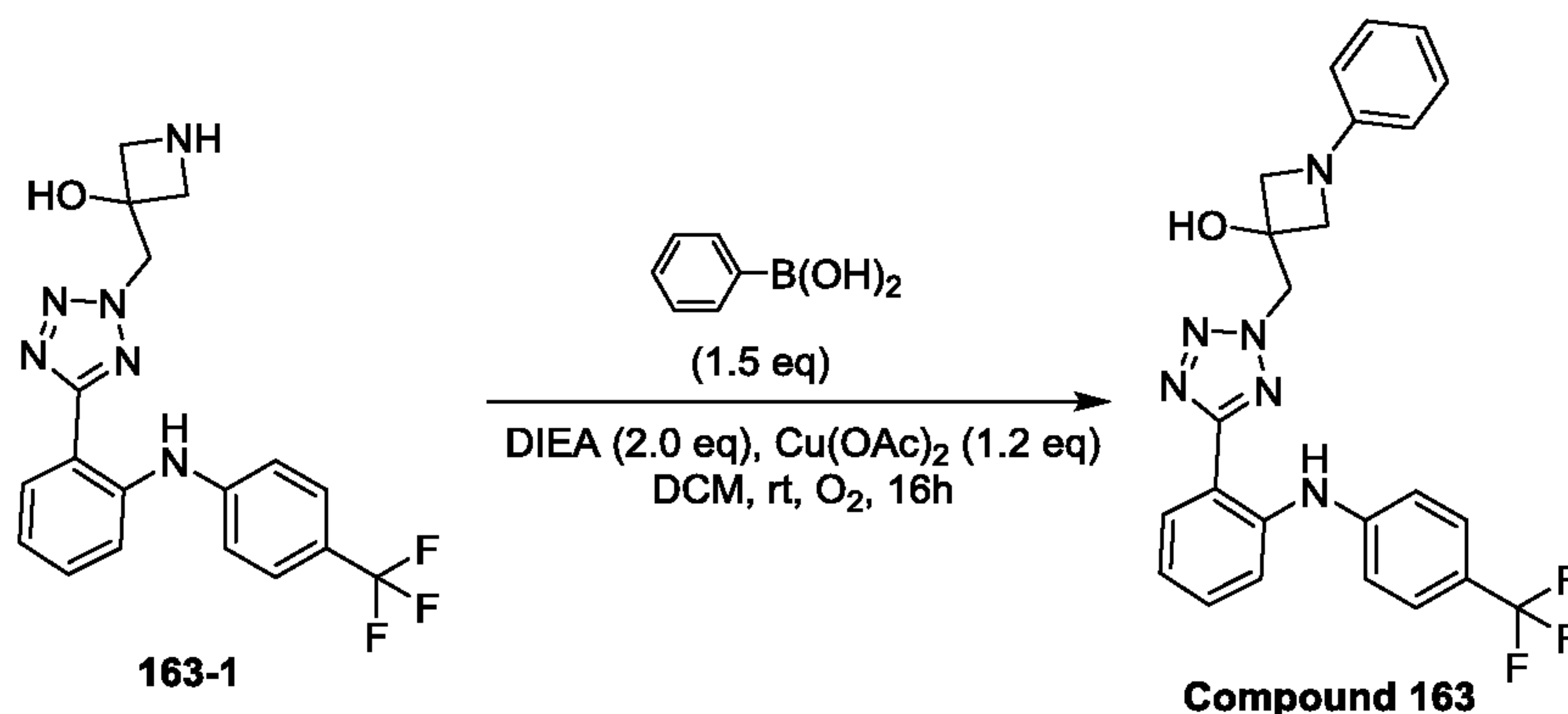
[00546] To a solution of **161-1** (60.0 mg, 0.2 mmol, 1.0 eq) in DCM (2.0 mL) was added TEA (46.6 mg, 0.5 mmol, 63.9 uL, 3.0 eq) and acetyl chloride (12.0 mg, 0.2 mmol, 10.9 uL, 1.0 eq) at 0°C. The mixture was stirred at 25 °C for 1 hour. LC-MS showed 22% of **161-1** remained. Several new peaks were detected on LC-MS and 34% of the desired compound was detected. The residue was purified by prep-HPLC to give the title compound (7.73 mg, 17.88 umol, 11% yield). LCMS (ESI): RT = 0.821 min, mass calc. for C₂₀H₁₉F₃N₆O₂ 432.15, m/z found 455.1 [M+Na]⁺; ¹HNMR (400MHz, DMSO-*d*₆) δ (ppm) 8.75 (s, 1H), 8.07 (d, *J*=7.8 Hz, 1H), 7.56 (d, *J*=8.3 Hz, 3H), 7.53-7.46 (m, 1H), 7.26-7.18 (m, 3H), 6.25 (s, 1H), 5.03 (s, 2H), 4.42 (d, *J*=9.0 Hz, 1H), 4.14 (d, *J*=10.3 Hz, 1H), 3.95 (d, *J*=9.3 Hz, 1H), 3.68 (d, *J*=10.0 Hz, 1H), 1.77 (s, 3H).

Example 155: [1-acetyl-3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]azetidin-3-yl] acetate (Compound 162)



[00547] To a solution of **162-1** (60.0 mg, 0.2 Mmol, 1.0 eq) in DCM (2.0 mL) was added TEA (46.6 mg, 0.5 mmol, 63.9 uL, 3.0 eq) and acetyl chloride (12.0 mg, 0.2 mmol, 10.9 uL, 1.0 eq) at 0° C. The mixture was stirred at 25 °C for 1 hour. LC-MS showed 22% of **162-1** remained. Several new peaks were detected on LC-MS and 34% of the desired compound was detected. The reaction mixture was purified by prep-HPLC to give the title compound (3.52 mg, 7.42 umol, 5% yield). LCMS (ESI): RT = 0.872 min, mass calc. for C₂₂H₂₁F₃N₆O₃ 474.16, m/z found 497.1 [M+Na]⁺; ¹HNMR (400MHz, DMSO-*d*₆) δ (ppm) 8.70 (s, 1H), 8.05 (d, *J*=7.5 Hz, 1H), 7.58-7.51 (m, 4H), 7.23 (t, *J*=7.7 Hz, 1H), 7.17 (d, *J*=8.5 Hz, 2H), 5.47-5.35 (m, 2H), 4.50 (d, *J*=10.3 Hz, 1H), 4.26-4.22 (m, *J*=5.4, 10.2 Hz, 2H), 3.90 (d, *J*=11.0 Hz, 1H), 1.93 (s, 3H), 1.79 (s, 3H).

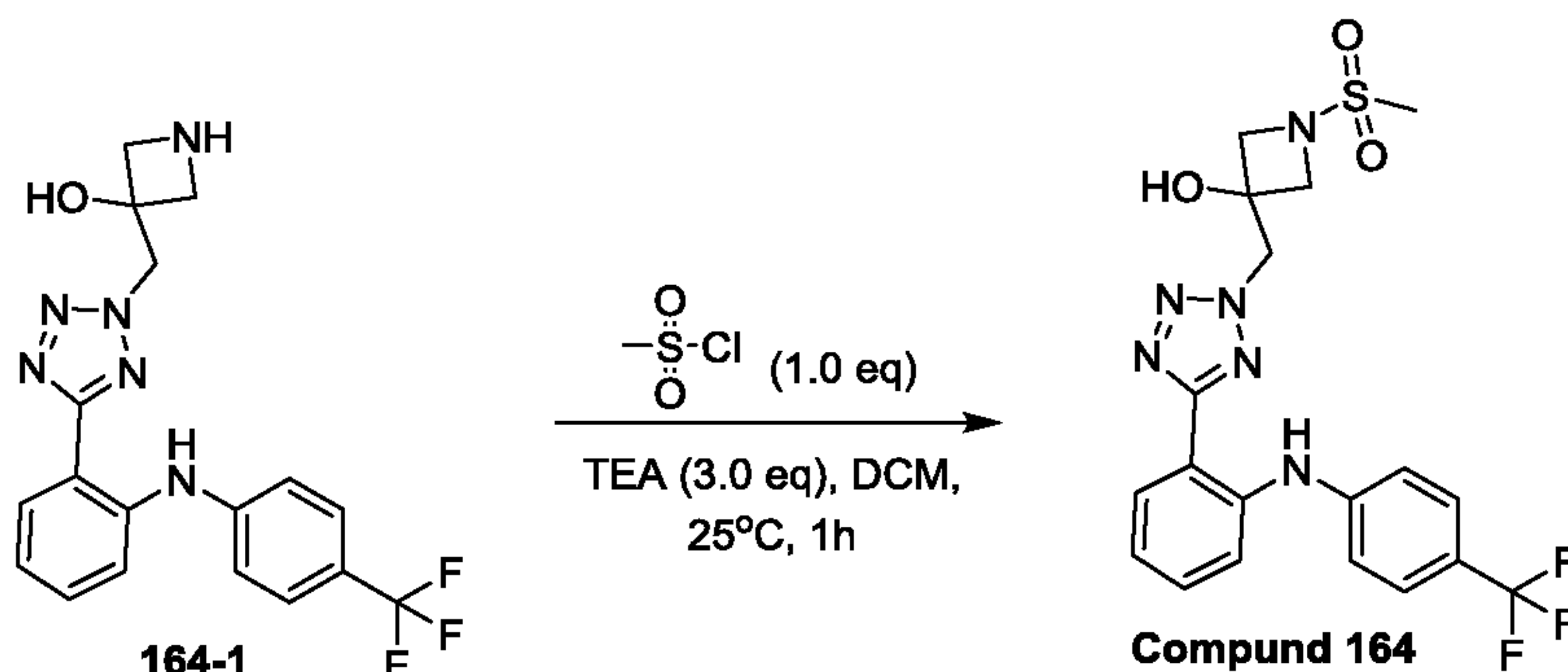
Example 156: 1-phenyl-3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]azetidin-3-ol (Compound 163)



[00548] A mixture of phenylboronic acid (12.4 mg, 0.1 mmol, 1.0 eq), **163-1** (40.0 mg, 0.1 mmol, 1.00 eq), Cu(OAc)₂ (22.3 mg, 0.1 mmol, 1.20 eq), DIPEA (52.9 mg, 0.4 mmol, 71.5 uL, 4.0 eq) in DCM (2.0 mL) was degassed and purged with O₂ 3 times, and then the mixture was stirred at 40 °C for 16 hr under an O₂ (15psi) atmosphere. LC-MS showed **163-1** was consumed completely and 24% of the desired compound was detected. The reaction mixture was washed with brine (10mL * 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC to give the title compound (6.86 mg, 14.41 umol, 14% yield). LCMS (ESI): RT = 0.907 min, mass calc. for C₂₄H₂₁F₃N₆O₃ 466.17, m/z found 467.0 [M+H]⁺; ¹HNMR (400MHz, DMSO-*d*₆) δ (ppm) 8.77 (s, 1H), 8.09 (d, *J*=6.8 Hz, 1H), 7.63-7.54 (m, 3H),

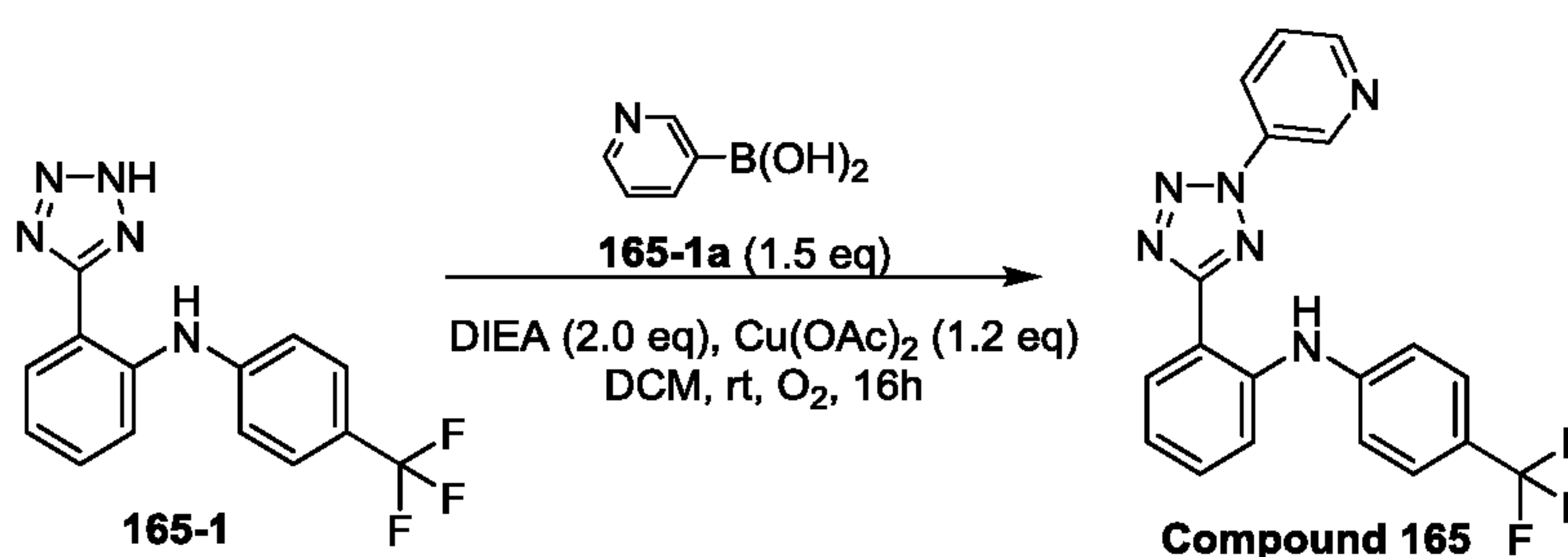
7.53-7.48 (m, 1H), 7.26-7.20 (m, 3H), 7.17 (t, $J=7.8$ Hz, 2H), 6.70 (t, $J=7.2$ Hz, 1H), 6.44 (d, $J=7.8$ Hz, 2H), 6.16 (s, 1H), 5.07 (s, 2H), 4.16 (d, $J=8.0$ Hz, 2H), 3.61 (d, $J=8.0$ Hz, 2H).

Example 157: 1-methylsulfonyl-3-[[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]methyl]azetidin-3-ol (Compound 164)



[00549] To a solution of **164-1** (40.0 mg, 0.1 mmol, 1.00 eq) in DCM (2.0 mL) was added TEA (25.9 mg, 0.3 mmol, 35.5 uL, 2.5 eq) and methanesulfonyl chloride (11.7 mg, 0.1 mmol, 7.9 uL, 1.0 eq) at 0 °C. The mixture was stirred at 25 °C for 0.5 hour. LC-MS showed **164-1** was consumed completely. Several new peaks were shown on LC-MS and 44% of the desired compound was detected. The residue was purified by prep-HPLC to provide the title compound (2.2 mg, 4.62 umol, 4% yield). LCMS (ESI): RT = 0.796 min, mass calc. for $C_{19}H_{19}F_3N_6O_3S$ 468.12, m/z found 491.1 $[M+Na]^+$; ^1H NMR (400MHz, DMSO- d_6) 8.76 (s, 1H), 8.08 (d, $J=7.0$ Hz, 1H), 7.60-7.46 (m, 4H), 7.26-7.17 (m, 3H), 6.40 (s, 1H), 5.04 (s, 2H), 4.11 (d, $J=8.8$ Hz, 2H), 3.81 (d, $J=8.8$ Hz, 2H), 3.03 (s, 3H).

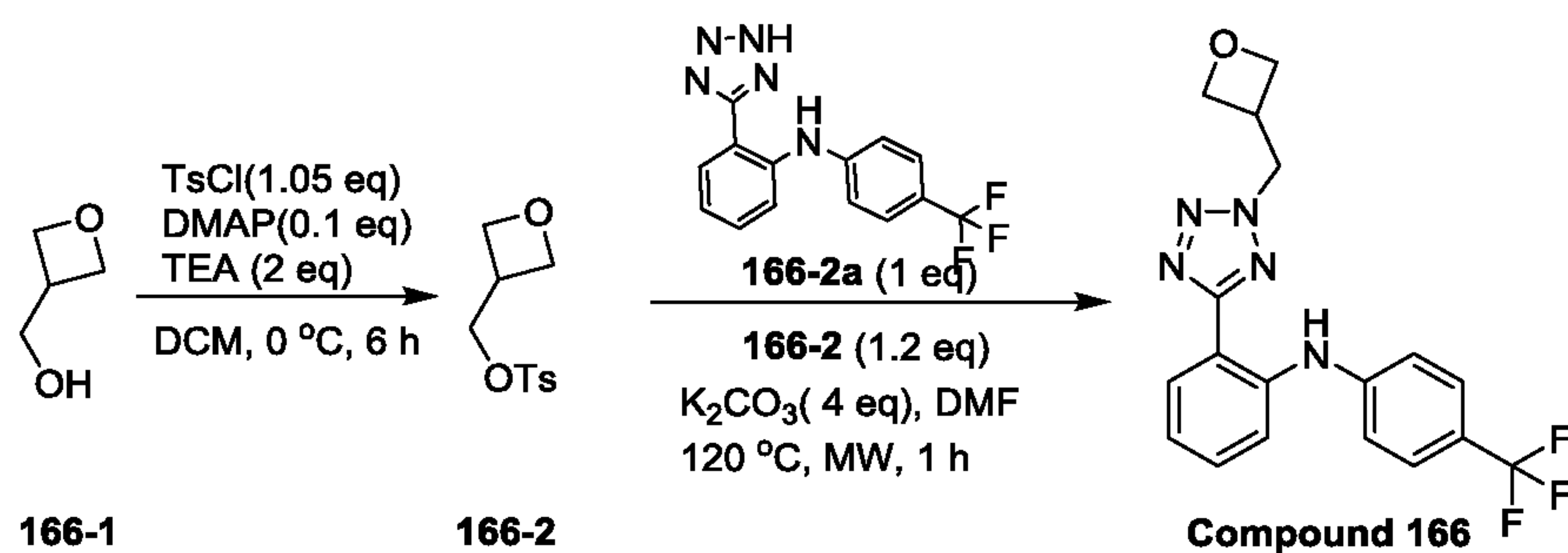
Example 158: 2-[2-(3-pyridyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 165)



[00550] A mixture of **165-1** (100.0 mg, 0.3 mmol, 1.0 eq), 3-pyridylboronic acid **165-1a** (60.4 mg, 0.5 mmol, 1.5 eq), DIPEA (84.6 mg, 0.6 mmol, 0.1 mL, 2.0 eq) and $Cu(OAc)_2$ (89.2 mg, 0.5 mmol, 1.5 eq) in DCM (2.0 mL) was degassed and purged with O_2 3 times, and then the mixture was stirred at 40 °C for 72 hour under an O_2 (15psi) atmosphere. LC-MS showed **165-1** was consumed completely. Several new peaks were detected on LC-MS and 30% of the desired compound was detected. The reaction mixture was purified by prep-HPLC to give the title compound (3.99 mg, 10.44 umol, 3.19% yield). LCMS (ESI): RT = 0.931 min, mass calc. for $C_{19}H_{13}F_3N_6O$ 382.12, m/z

found 381.1 [M-H]⁻; ¹HNMR (400MHz, DMSO-*d*₆) δ (ppm) 9.34 (s, 1H), 8.82 (d, *J*=4.3 Hz, 1H), 8.72 (s, 1H), 8.54 (d, *J*=8.3 Hz, 1H), 8.16 (d, *J*=7.8 Hz, 1H), 7.79-7.54 (m, *J*=4.8, 8.3 Hz, 1H), 7.62-7.49 (m, 4H), 7.29-7.19 (m, 3H).

Example 159: 2-(2-(oxetan-3-ylmethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl) phenyl) aniline (Compound 166)



Step 1: oxetan-3-ylmethyl 4-methylbenzenesulfonate

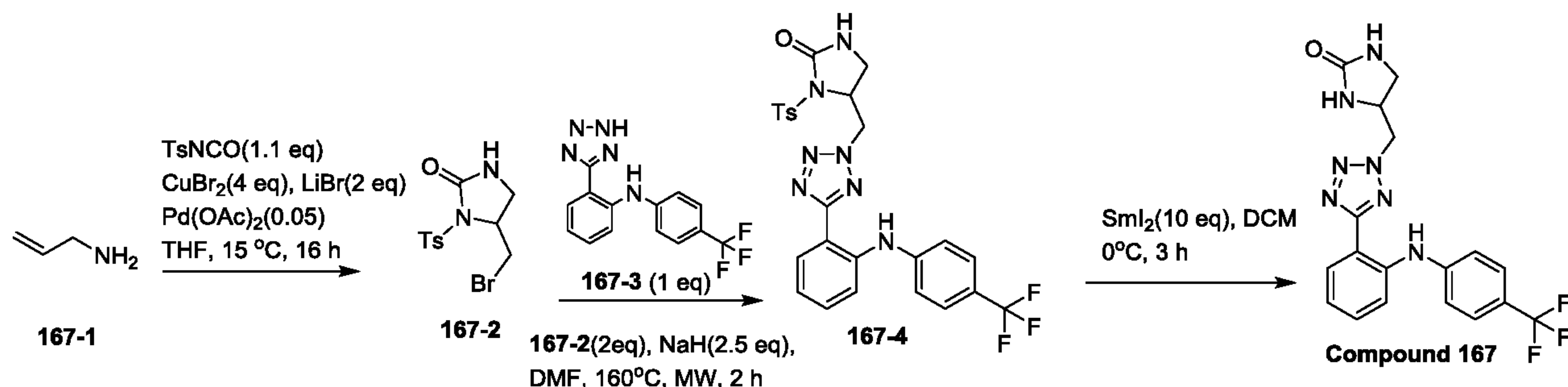
[00551] A mixture of **166-1** (200.00 mg, 2.27 mmol, 1.00 *eq*), TEA (459.38 mg, 4.54 mmol, 629.29 uL, 2.00 *eq*) and DMAP (27.73 mg, 227.00 umol, 0.10 *eq*) in DCM (10.00 mL) was stirred at 0 °C for 5 min under N₂. Then 4-methylbenzenesulfonyl chloride (454.39 mg, 2.38 mmol, 1.05 *eq*) was added, and the mixture was stirred at 0 °C for 1 h. The crude LCMS showed no desired product MS value was detected, and the mixture was stirred at 0 °C for an additional 5 h. TLC(PE:EtOAc=2:1 UV) indicated **166-1** was consumed completely and one new spot formed. The reaction mixture was diluted with DCM (20 mL), washed with brine (20 mL), and then extracted with DCM (25 mL*3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **166-2** (0.25 g, 1.02 mmol, 45.00% yield).

Step 2: 2-(2-(oxetan-3-ylmethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl) phenyl) aniline

[00552] **166-2** (100.00 mg, 412.73 umol, 1.20 *eq*), **166-2a** (104.99 mg, 343.94 umol, 1.00 *eq*) and K₂CO₃ (190.14 mg, 1.38 mmol, 4.00 *eq*) were taken up into a microwave tube in DMF (4.00 mL). The sealed tube was heated at 120 °C for 1 h under microwave conditions. The crude LCMS showed the desired product MS value was detected. The reaction mixture was combined with another batch, and the reaction mixture was quenched by addition of water (30 mL) and extracted with EtOAc (25 mL *3). The combined organic layers were washed with brine (20 mL *2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give the product, which was diluted with MeOH (5 mL) and water (5 mL). Most of MeOH was removed under reduced pressure, and the remaining aqueous layer was lyophilized to give provide **Compound 166** (0.13253 g, 353.09 umol, 68.44% yield). LCMS (ESI): RT = 0.847 min, mass calc. for C₁₈H₁₆F₃N₅O 375.35, m/z found 376.1

$[M+1]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.49 - 3.62 (m, 1 H), 4.47 (t, $J = 6.15$ Hz, 2 H), 4.67 (dd, $J = 7.65, 6.40$ Hz, 2 H), 5.06 (d, $J = 7.28$ Hz, 2 H), 7.13 - 7.24 (m, 3 H), 7.46 - 7.58 (m, 4 H), 8.03 (d, $J = 7.53$ Hz, 1 H), 8.72 (br, s, 1 H).

Example 160: 4-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)imidazolidin-2-one (Compound 167)



Step 1: 5-(bromomethyl)-1-tosylimidazolidin-2-one

[00553] Prop-2-en-1-amine **167-1** (1.30 g, 22.77 mmol, 1.71 mL, 1.00 *eq*) was reacted with 4-methyl-N-(oxomethylene)benzenesulfonamide (4.94 g, 25.05 mmol, 3.80 mL, 1.10 *eq*) in THF (110.00 mL) for 10 min at 5 °C under N_2 ; then, LiBr (3.96 g, 45.54 mmol, 1.14 mL, 2.00 *eq*), CuBr_2 (20.34 g, 91.08 mmol, 4.26 mL, 4.00 *eq*) and $\text{Pd}(\text{OAc})_2$ (255.60 mg, 1.14 mmol, 0.05 *eq*) were added and the reaction was stirred at 15 °C for 16 hr. TLC showed new spots were formed. The dark colored mixture was filtered via a pad of celite and washed with EtOAc (150 mL). The filtrate was washed with brine (50 mL) four times, dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was dissolved in 5 mL of methanol and then diluted with a mix solution of PE: EtOAc=1:1(80 mL), forming solids. The resulting mixture was filtered and the solids washed with DCM (50 mL). The filter cake was collected to give an isomeric byproduct (2.8 g) as a light yellow solid, as confirmed by ^1H NMR. The filtrate was concentrated to give crude **167-2**, which was purified by prep-HPLC to give **167-2** (750.00 mg, 2.25 mmol, 9.89% yield). ^1H NMR (400MHz, $\text{CHLOROFORM}-d$) δ 7.94 (d, $J = 8.5$ Hz, 2H), 7.34 (d, $J = 8.5$ Hz, 2H), 5.10 (br s, 1H), 4.66 - 4.54 (m, 1H), 3.83 (dd, $J = 3.0, 10.5$ Hz, 1H), 3.70 - 3.58 (m, 2H), 3.42 (dd, $J = 4.0, 9.0$ Hz, 1H), 2.45 (s, 3H).

Step 2: 1-tosyl-5-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)imidazolidin-2-one

[00554] To a solution of **167-3** in DMF (4.00 mL) was added NaH (29.26 mg, 731.60 μmol , 60% purity, 2.50 *eq*) at 0°C. After stirring for 10 min, **167-2** (117.01 mg, 351.17 μmol , 1.20 *eq*) was added and then the resulting mixture was stirred at 160 °C for 1 h under microwave conditions. The yellow mixture became a dark colored mixture. LCMS detected 47% of **167-3** remained and 5% of the desired product was detected. Another 100 mg of **167-2** (117.01 mg, 351.17 μmol , 1.20 *eq*) was

added and then the resulting mixture was stirred at 160 ° C for another 1 h under microwave conditions. LCMS detected 65% of the desired product. The resulting dark mixture was combined with another batch and concentrated to give a dark residue. The residue was purified by column chromatography (SiO₂) to give **167-4** (190.00 mg, crude) as a yellow gum. LCMS (ESI): RT = 0.904 min, mass calc. for C₂₅H₂₂F₃N₇O₃ S 557.15, m/z found 580.10 [M+23]⁺; ¹HNMR (400MHz, CHLOROFORM-*d*) δ 8.87 (s, 1H), 8.11 (d, *J* = 6.5 Hz, 1H), 8.03 - 7.97 (m, 4H), 7.58 - 7.48 (m, 3H), 7.37 - 7.29 (m, 5H), 7.02 (t, *J* = 7.5 Hz, 1H), 5.25 - 5.08 (m, 2H), 5.00 - 4.87 (m, 1H), 4.81 - 4.75 (m, 1H), 3.64 - 3.54 (m, 1H), 3.51 - 3.42 (m, 1H), 2.44 (s, 3H).

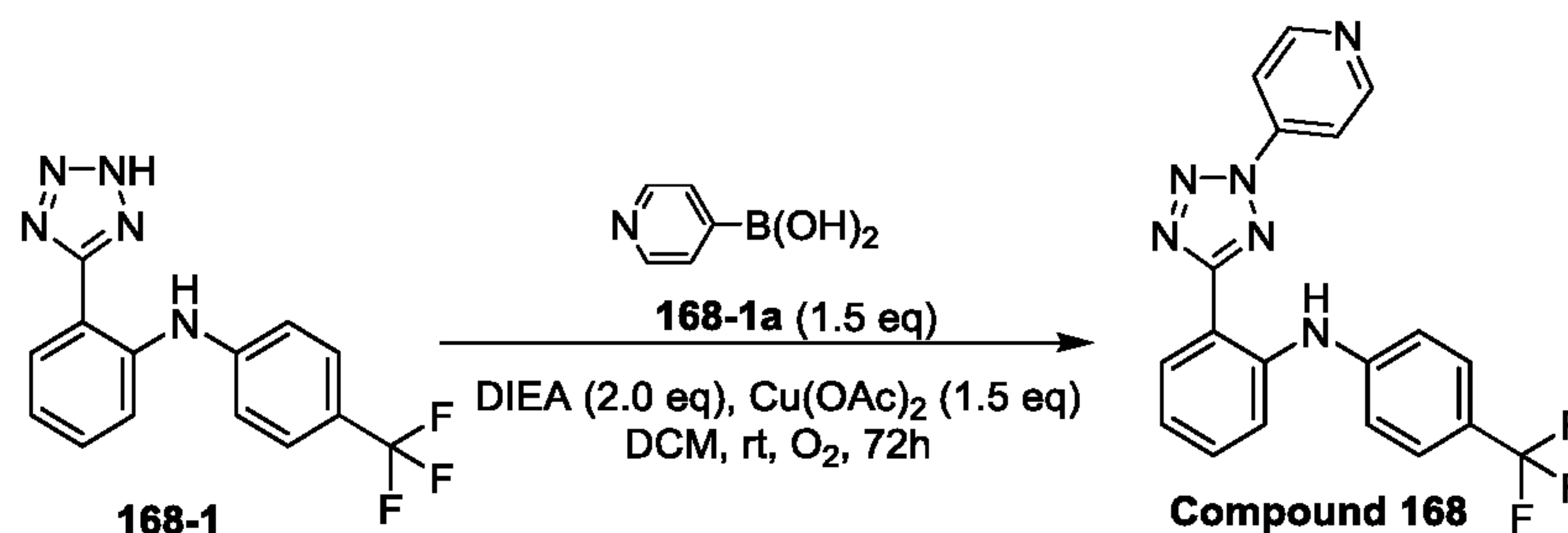
Step 3: 4-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)imidazolidin-2-one

[00555] To a colorless solution of **167-4** (135.00 mg, 242.13 μmol, 1.00 *eq*) in THF (10.00 mL) was added diiodosamarium (0.1 M, 24.21 mL, 10.00 *eq*) at 0 °C and the resulting blue solution was stirred at 0°C for 1 hr. LCMS showed 56% of the desired product was formed and 8% of the starting material remained. Then the solution was stirred at 0°C for another 2 h. LCMS showed the starting material was consumed completely and 87% of the desired product was formed. The solution was combined with another batch for workup and quenched with saturated aq. K₂CO₃ (15 mL) and separated. The separated aqueous layer was extracted with DCM (15 mL*3). The combined organic layers were dried by anhydrous Na₂SO₄, filtered, and concentrated a residue which was purified by prep-HPLC to give **Compound 167** (0.01025 g, 24.88 μmol, 10.27% yield). LCMS (ESI): RT = 0.766 min, mass calc. for C₁₈H₁₆F₃N₇O 403.14, m/z found 426.0 [M+23]⁺.

[00556] ¹HNMR (400MHz, DMSO-*d*₆) δ 8.67 (br s, 1H), 8.02 (d, *J* = 7.1 Hz, 1H), 7.64 - 7.41 (m, 4H), 7.37 - 7.07 (m, 3H), 6.53 (br s, 1H), 4.74 (br s, 2H), 4.14 (br s, 1H), 3.40 - 3.37 (m, 1H), 3.39 - 3.31 (m, 1H), 3.40 - 3.31 (m, 1H), 3.26 - 3.11 (m, 1H), 3.24 - 3.10 (m, 1H), 3.24 - 3.10 (m, 1H), 3.18 (br s, 1H).

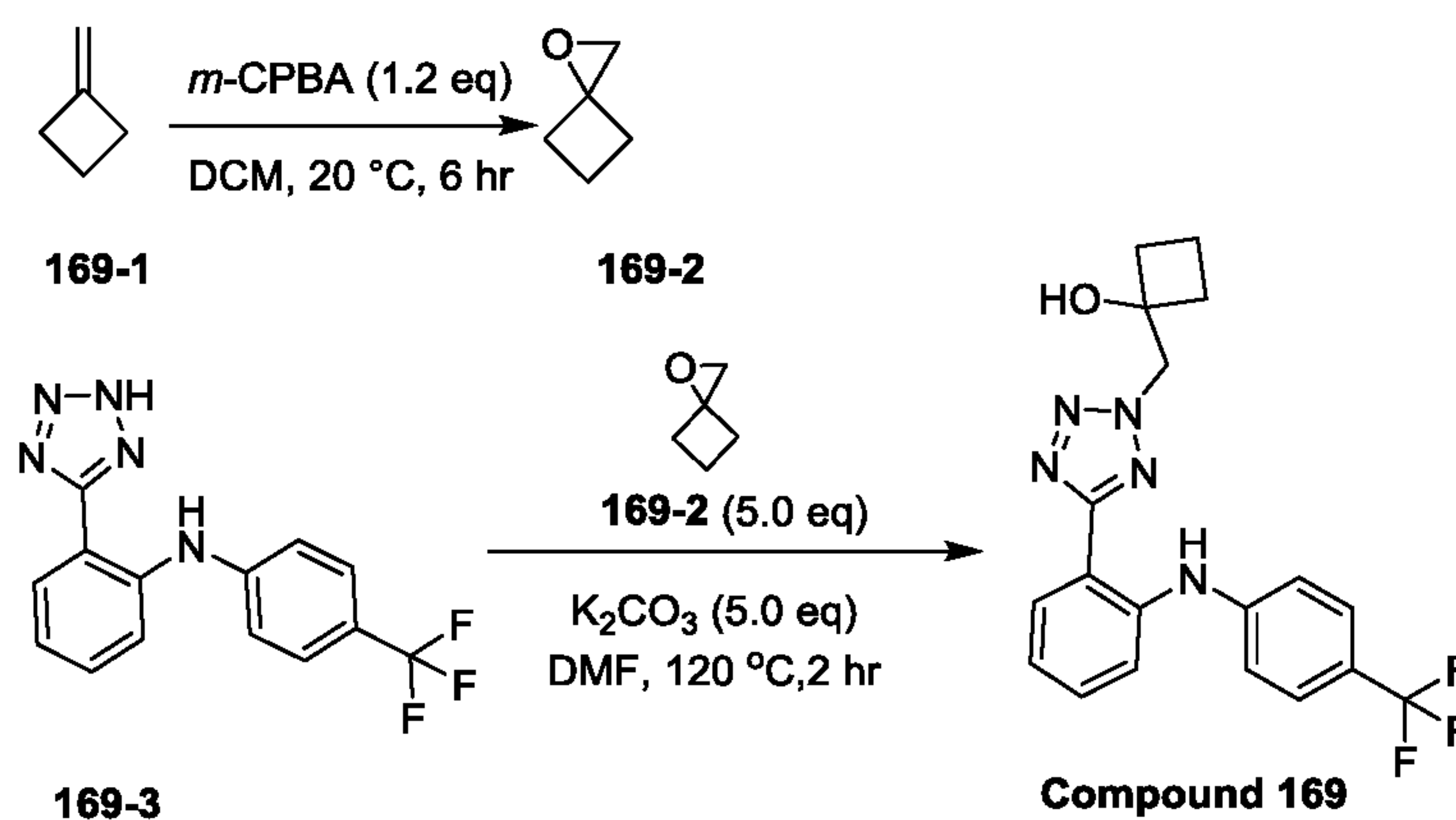
[00557] ¹HNMR (400MHz, CHLOROFORM-*d*) δ 8.15 (d, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 3H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 8.3 Hz, 1H), 7.32 - 7.27 (m, 1H), 7.04 (t, *J* = 7.3 Hz, 1H), 6.02 - 5.32 (m, 1H), 5.30 (s, 1H), 5.83 - 5.22 (m, 1H), 4.81 (br s, 2H), 4.44 (br s, 1H), 3.77 (br s, 1H), 3.49 (s, 1H), 2.17 (s, 1H).

Example 161: 2-[2-(4-pyridyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 168)



[00558] A mixture of **168-1** (200.0 mg, 0.6 mmol, 1.0 eq), **168-1a** (120.80 mg, 0.9 mmol, 1.5 eq), Cu(OAc)₂ (178.5 mg, 0.9 mmol, 1.5 eq) and DIPEA (169.3 mg, 1.3 mmol, 0.2 mL, 2.0 eq) in DCM (5.0 mL) was degassed and purged with O₂ 3 times, and the mixture was stirred at 40°C for 72 hours under an O₂ (15 psi) atmosphere. LC-MS detected 62% of **168-1** remained. Several new peaks were detected on LC-MS and 17% of the desired compound was detected. The reaction mixture was washed with brine (10mL * 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC to give the title compound (3.14 mg, 8.21 umol, 1% yield). LCMS (ESI): RT = 0.870 min, mass calc. for C₁₉H₁₃F₃N₆ 382.12, m/z found 381.1298 [M-H]⁻; ¹H NMR (400MHz, DCCl₃) δ (ppm) 8.95 (s, 2H), 8.35-8.33 (m, *J*=1.4, 7.9 Hz, 1H), 8.15 (s, 2H), 7.62-7.55 (m, 3H), 7.45 (t, *J*=7.2 Hz, 1H), 7.34 (d, *J*=8.3 Hz, 2H), 7.11 (t, *J*=7.7 Hz, 1H).

Example 162: 1-((5-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)cyclobutanol (Compound 169)



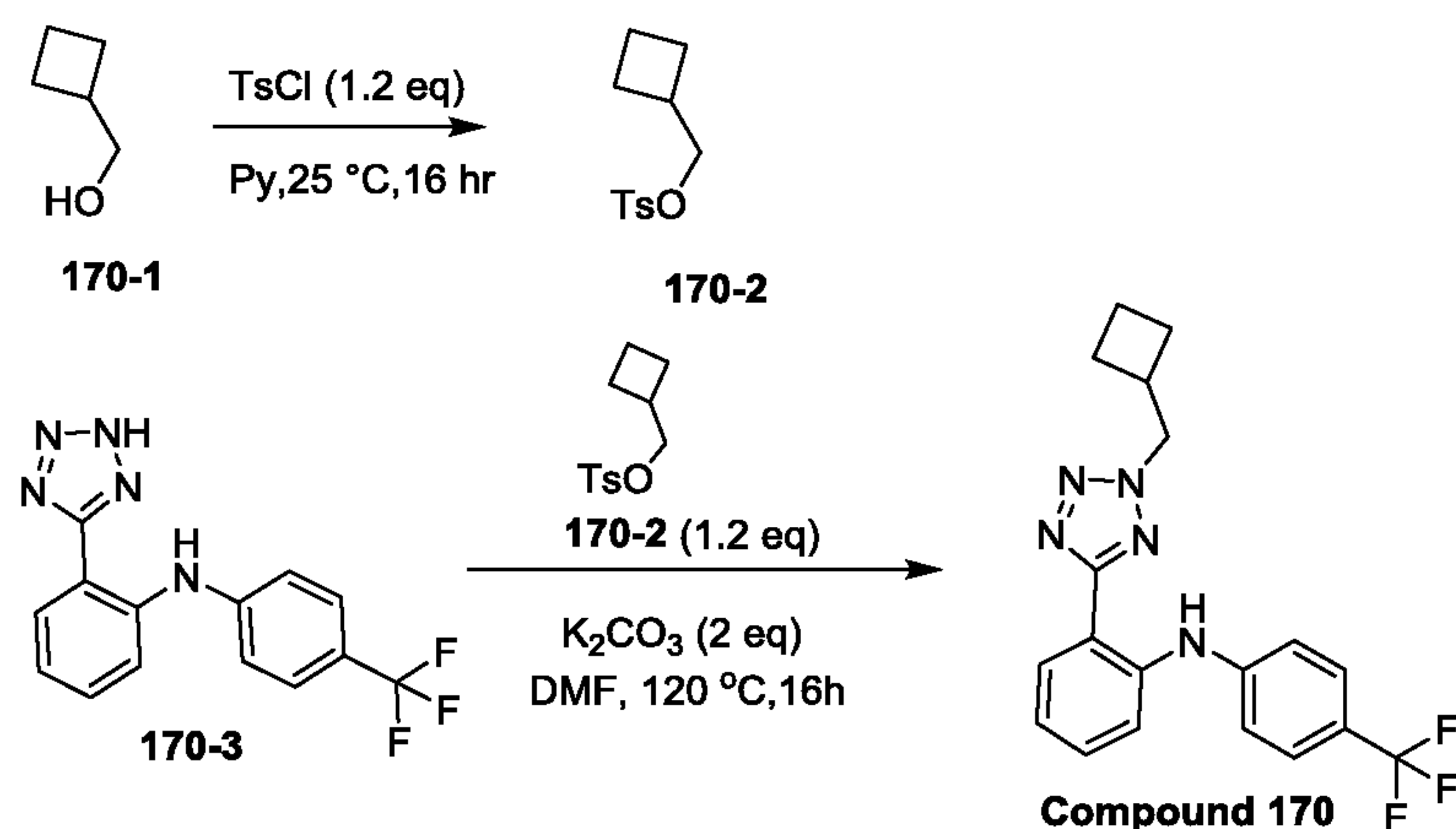
Step 1: 1-Oxaspiro[2.3]hexane

[00559] To a solution of **169-1** (980 mg, 14.4 mmol, 1.0 eq) in DCM (20 mL) was added *m*-CPBA (3.5 g, 17 mmol, 85% purity, 1.2 eq). The reaction mixture was stirred at 20 °C for 6 hours. The reaction mixture was filtered and the filtrate was washed with NaOH (0.25 M, 10 mL), and water (10 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated to dryness under reduced pressure at 10 °C to obtain **169-2** (600 mg, crude). ¹H NMR (400MHz, CDCl₃-*d*) δ 2.72 (s, 2H), 2.60 - 2.47 (m, 2H), 2.34 - 2.24 (m, 2H), 1.93 - 1.76 (m, 2H).

Step 2: 1-((5-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)cyclobutanol

[00560] To a solution of **169-3** (50 mg, 0.16 mmol, 1.0 *eq*) and **169-2** (69 mg, 0.82 mmol, 5.0 *eq*) in DMF (2 mL) was added K₂CO₃ (113 mg, 0.819 mmol, 5.0 *eq*). The reaction mixture was stirred at 120 °C for 2 hours. The mixture was diluted with water (10 mL) and the resultant mixture was extracted with EtOAc (30 mL * 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to dryness under reduced pressure. The residue was purified by preparative high performance liquid chromatography. The pure fractions were collected and the volatiles were removed under vacuum. The residue was re-suspended in water (10 mL) and the resulting mixture was lyophilized to dryness to remove the solvent residue completely to obtain **Compound 169** (28.70 mg, 45% yield). LCMS (ESI): RT = 0.864 min, mass calc. for C₁₉H₁₈F₃N₅O 389.15, m/z found 390.0 [M+H]⁺, ¹HNMR (400MHz, CDCl₃-*d*) δ 9.07 (s, 1H), 8.18 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 3H), 7.42 - 7.36 (m, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.08 - 7.02 (m, 1H), 4.86 (s, 2H), 3.01 (s, 1H), 2.29 - 2.14 (m, 4H), 1.99 - 1.87 (m, 1H), 1.80 - 1.67 (m, 1H).

Example 163: 2-(2-(Cyclobutylmethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 170)

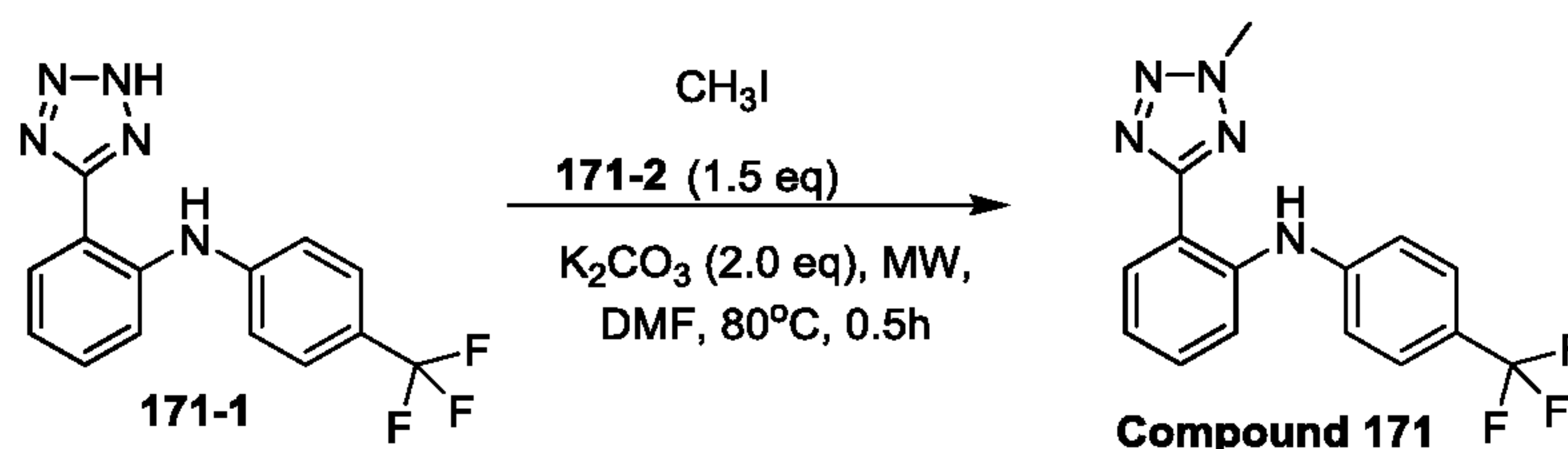


Step 1: Cyclobutylmethyl 4-methylbenzenesulfonate

[00561] To a solution of **170-1** (500 mg, 5.81 mmol, 1.0 *eq*) in pyridine (5 mL) was added TsCl (1.3 g, 7.0 mmol, 1.2 *eq*). The reaction mixture was stirred at 25 °C for 16 hours. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (10 mL) and the resultant mixture was extracted with DCM (3 mL * 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to dryness under reduced pressure to obtain the **170-2** (1.2 g, 86% yield) as a white solid. ¹HNMR (400MHz, CDCl₃-*d*) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 3.98 (d, *J* = 6.8 Hz, 2H), 2.67 - 2.55 (m, 1H), 2.45 (s, 3H), 2.06 - 1.96 (m, 2H), 1.95 - 1.77 (m, 2H), 1.76 - 1.65 (m, 2H).

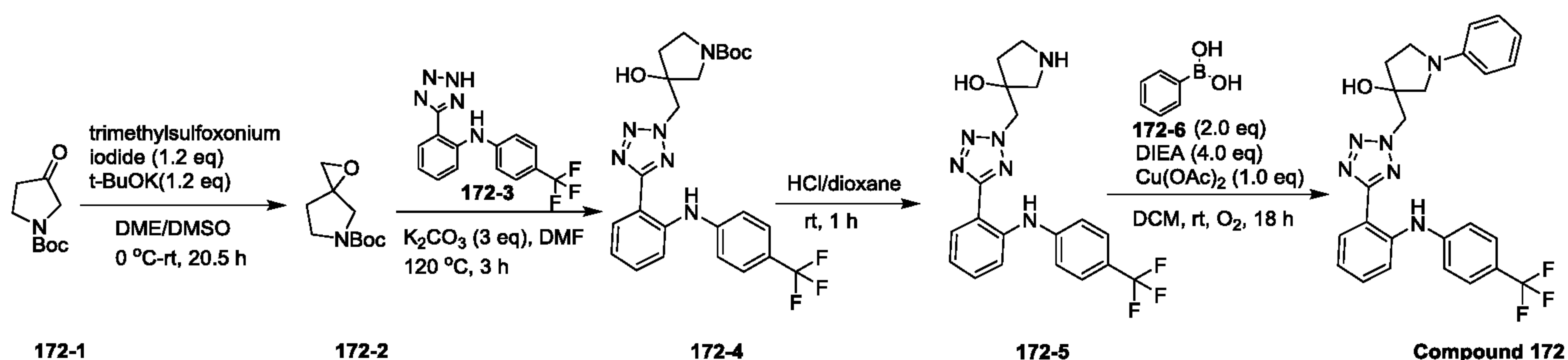
Step 2: 2-(2-(Cyclobutylmethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00562] To a solution of **170-3** (50 mg, 0.16 mmol, 1.0 *eq*) and **170-2** (47 mg, 0.20 mmol, 1.2 *eq*) in DMF (2 mL) was added K₂CO₃ (45 mg, 0.33 mmol, 2.0 *eq*). The reaction mixture was stirred at 120 °C for 16 hours. The mixture was diluted with water (10 mL) and the resultant mixture was extracted with EtOAc (30 mL * 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to dryness under reduced pressure. The residue was purified by preparative high performance liquid chromatography. The pure fractions were collected and the volatiles were removed under vacuum. The residue was re-suspended in water (10 mL) and the resulting mixture was lyophilized to dryness to remove the solvent residue completely to provide **Compound 170** (21.72 mg, 36% yield). LCMS (ESI): RT = 0.976 min, mass calc. for C₁₉H₁₈F₃N₅ 373.15, m/z found 374.0 [M+H]⁺, ¹HNMR (400MHz, CDCl₃-*d*) δ 9.08 (s, 1H), 8.21 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.53 (dd, *J* = 2.4, 8.4 Hz, 3H), 7.40 - 7.34 (m, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.08 - 7.01 (m, 1H), 4.70 (d, *J* = 7.5 Hz, 2H), 3.10 - 2.95 (m, 1H), 2.20 - 2.12 (m, 2H), 2.04 - 1.88 (m, 4H).

Example 164: 2-(2-methyltetrazol-5-yl)-N-[4-(trifluoromethyl)phenyl]aniline (Compound 171)

[00563] **171-1** (50.0 mg, 0.16 mmol, 1.0 *eq*), methyl iodide **171-2** (34.9 mg, 0.25 mmol, 15.3 uL, 1.5 *eq*) and K₂CO₃ (45.3 mg, 0.33 mmol, 2.0 *eq*) were taken up into a microwave tube in DMF (2.0 mL). The sealed tube was heated at 100 °C for 0.5 hr under microwave conditions. LCMS showed the desired compound was formed. The reaction was filtered to give a crude product. The crude product was purified by prep-HPLC to give the title compound (4.90 mg, 15.35 umol, 9.37% yield). LCMS (ESI): RT = 0.859 min, mass calc. for C₁₅H₁₂F₃N₅ 319.10, m/z found 319.9 [M+H]⁺; ¹HNMR (400 MHz, CDCl₃-*d*) δ 9.02 (s, 1H), 8.20 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.54 (t, *J* = 7.4 Hz, 3H), 7.41 - 7.35 (m, 1H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.08 - 7.02 (m, 1H), 4.45 (s, 3H).

Example 165: 1-phenyl-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)pyrrolidin-3-ol (Compound 172)



Step 1: tert-butyl 1-oxa-5-azaspiro[2.4]heptane-5-carboxylate

[00564] To a mixture of *t*-BuOK (727.0 mg, 6.5 mmol, 1.20 *eq*) in DMSO (10 mL), was added trimethylsulfoxonium iodide (1.43 g, 6.5 mmol, 1.20 *eq*) by portions at 0 °C. The mixture was stirred at 15 °C for 0.5 h. DME (5 mL) was added, and the mixture was cooled to 0 °C. A solution of **172-1** (1.0 g, 5.4 mmol, 1.00 *eq*) in DMSO (2 mL) and DME (4 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 3 h, 15 °C for 17 h. TLC showed two new spots with lower polarity, and the starting material remained. The mixture was diluted with water (20 mL), and extracted with DCM (20 mL*3). The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated under vacuum. The residue was purified by silica gel chromatography to provide **172-2** (0.22 g, 1.1 mmol, 20.5% yield). ¹HNMR (400MHz, CHLOROFORM-*d*) δ 3.73 - 3.52 (m, 3H), 3.28 (t, *J* = 11.3 Hz, 1H), 2.94 (s, 2H), 2.34 - 2.21 (m, 1H), 1.85 (ddd, *J* = 3.9, 7.5, 13.5 Hz, 1H), 1.47 (s, 9H).

Step 2: tert-butyl 3-hydroxy-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)pyrrolidine-1-carboxylate

[00565] To a mixture of **172-3** (0.3 g, 1.0 mmol, 1 *eq*) and K₂CO₃ (407.5 mg, 3.0 mmol, 3.00 *eq*) in DMF (15 mL), was added **172-2** (0.22 g, 1.1 mmol, 1.12 *eq*). The resulting mixture was stirred at 120 °C under N₂ for 3 h. LCMS detected about 74% of the desired compound. The mixture was diluted with EtOAc (30 mL), and washed with water (20 mL *3). The organic layer was dried over anhydrous Na₂SO₄, concentrated under vacuum. The residue was purified by silica gel chromatography to provide **172-4** (0.31 g, 0.6 mmol, 61.9% yield).

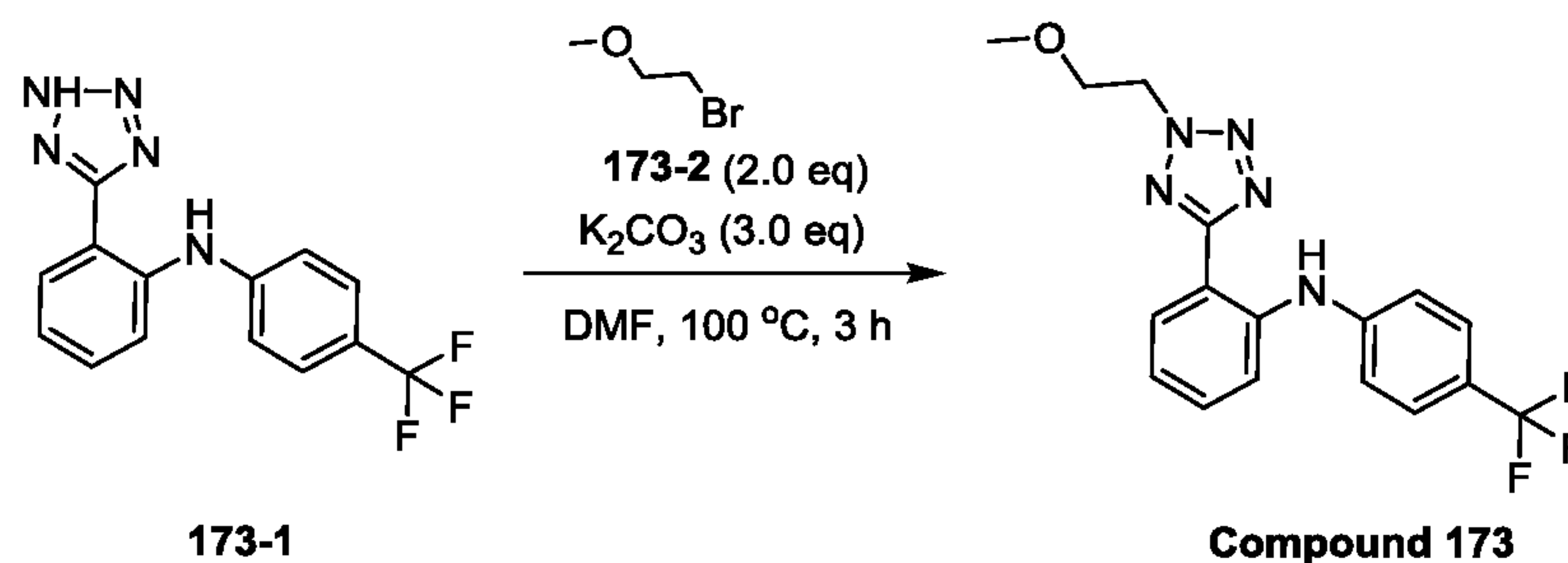
Step 3: 3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)pyrrolidin-3-ol

[00566] A mixture of **172-4** (0.2 g, 0.4 mmol, 1 *eq*) in HCl/dioxane (4 M, 4.0 mL, 1 *eq*) was stirred at 15 °C for 1 h. LCMS showed the reaction was complete. The mixture was concentrated under vacuum to obtain **172-5** (0.18 g, crude, HCl salt).

Step 4: 1-phenyl-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)pyrrolidin-3-ol

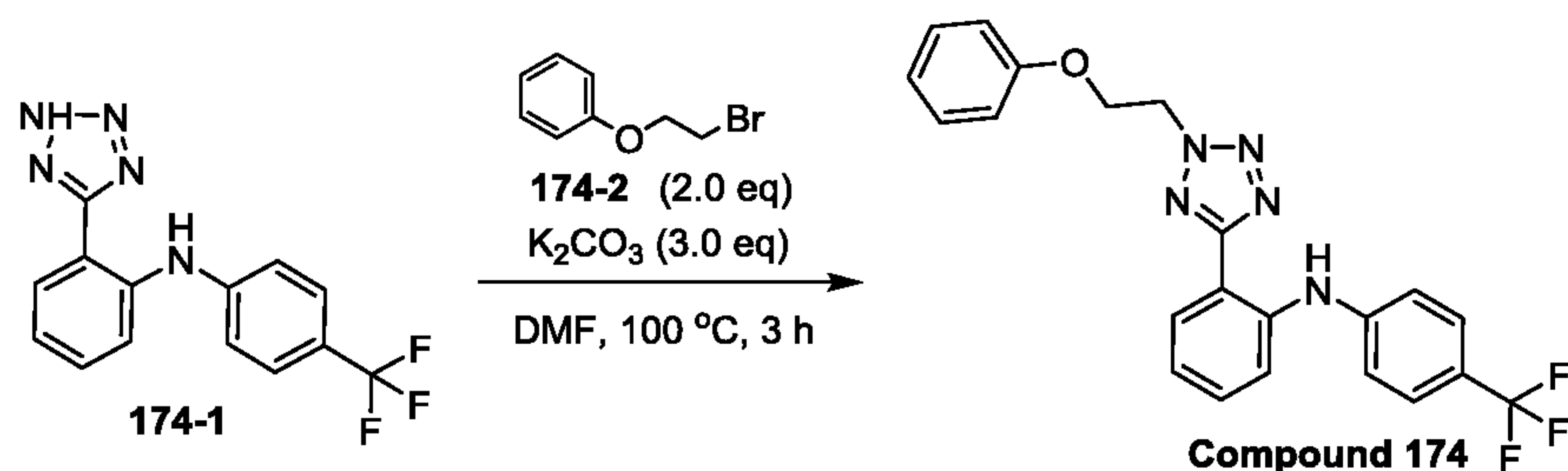
[00567] To a mixture of **172-5** (0.1 g, 0.2 mmol, 1.00 *eq*, HCl), **172-6** (55.3 mg, 0.5 mmol, 2.00 *eq*) and DIEA (117.3 mg, 1.0 mmol, 0.2 mL, 4.00 *eq*) in DCM (3 mL), was added Cu(OAc)₂ (41.2 mg, 0.2 mmol, 1.00 *eq*). The mixture was degassed under vacuum and purged with O₂ 3 times. The resulting mixture was stirred at 15 °C under O₂ (15 Psi) for 18 h. LCMS and HPLC showed about 20% of the desired compound, and 47% starting material remaining. The mixture was diluted with water (15 mL), and extracted with DCM (15 mL *2). The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated under vacuum. The residue was purified by prep-HPLC (basic conditions) to provide **Compound 172** (8.81 mg, 18.0 μmol, 7.9% yield). LCMS (ESI): RT = 0.922 min, mass calc. for C₂₅H₂₃F₃N₆O 480.19, m/z found 481.1 [M+H]⁺. ¹H NMR (400MHz, CHLOROFORM-*d*) δ 9.04 (s, 1H), 8.21 (dd, *J* = 1.3, 7.8 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 3H), 7.44 - 7.38 (m, 1H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.24 (dd, *J* = 7.7, 8.4 Hz, 2H), 7.10 - 7.04 (m, 1H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 2H), 5.03 - 4.93 (m, 2H), 3.63 - 3.48 (m, 3H), 3.39 (d, *J* = 10.3 Hz, 1H), 2.91 (s, 1H), 2.24 - 2.12 (m, 2H).

Example 166: 2-(2-(2-methoxyethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 173)



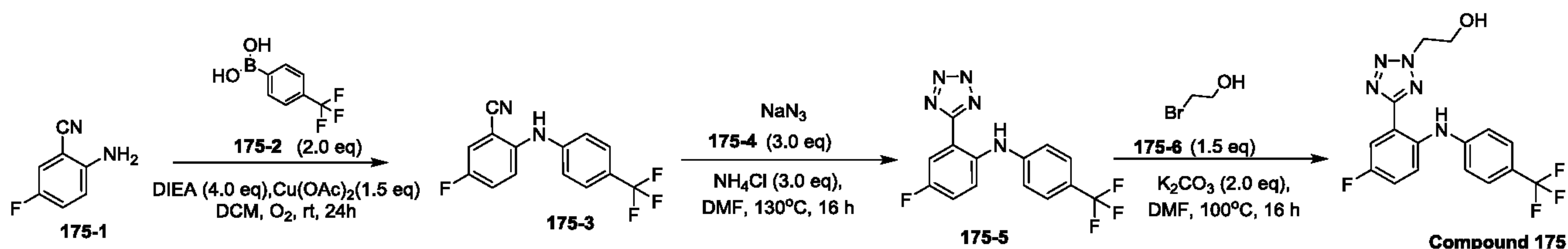
[00568] To a mixture of **173-1** (50 mg, 0.2 mmol, 1 *eq*) and K₂CO₃ (67.9 mg, 0.5 mmol, 3 *eq*) in DMF (2 mL), was added **173-2** (45.5 mg, 0.3 mmol, 2 *eq*). The resulting mixture was stirred at 100 °C for 3 h. LCMS and HPLC showed the reaction was completed. The mixture was filtered, and the solid was washed with DMF (1 mL). The filtrate was purified by prep-HPLC (basic condition) to obtain the title compound (7.03 mg, 19.4 μmol, 11.8% yield). LCMS (ESI): RT = 0.871 min, mass calc. for C₁₇H₁₆F₃N₅O 363.13, m/z found 364.0 [M+H]⁺. ¹H NMR (400MHz, CHLOROFORM-*d*) δ 9.09 (s, 1H), 8.22 (dd, *J* = 1.5, 7.8 Hz, 1H), 7.57 - 7.51 (m, 3H), 7.41 - 7.35 (m, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.08 - 7.02 (m, 1H), 4.88 (t, *J* = 5.4 Hz, 2H), 4.00 (t, *J* = 5.4 Hz, 2H), 3.38 (s, 3H).

Example 167: 2-(2-(2-phenoxyethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 174)



[00569] To a mixture of **174-1** (50 mg, 0.2 mmol, 1 *eq*) and K₂CO₃ (67.9 mg, 0.5 mmol, 3 *eq*) in DMF (2 mL), was added **174-2** (65.9 mg, 0.3 mmol, 2 *eq*). The resulting mixture was stirred at 100 °C for 3 h. LCMS showed the reaction was complete. The mixture was filtered, and the solid was washed with DMF (1 mL). The filtrate was purified by prep-HPLC (basic condition) to obtain the title compound (11.32 mg, 26.6 μmol, 16.3% yield). LCMS (ESI): RT = 0.950 min, mass calc. for C₂₂H₁₈F₃N₅O 425.15, m/z found 426.0 [M+H]⁺. ¹HNMR (400MHz, CHLOROFORM-*d*) δ 9.02 (s, 1H), 8.22 (dd, *J* = 1.5, 7.8 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 3H), 7.41 - 7.35 (m, 1H), 7.30 - 7.24 (m, 4H), 7.08 - 7.02 (m, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.91 - 6.84 (m, 2H), 5.08 (t, *J* = 5.4 Hz, 2H), 4.60 (t, *J* = 5.4 Hz, 2H).

Example 168: 2-[5-[5-fluoro-2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol (Compound 175)



Step 1: 5-fluoro-2-[4-(trifluoromethyl)anilino]benzonitrile

[00570] To a solution of **175-1** (200.0 mg, 1.5 mmol, 1.0 *eq*) and **175-2** (418.8 mg, 2.2 mmol, 1.5 *eq*) in DCM (5.0 mL) was added DIEA (759.5 mg, 5.9 mmol, 1.0 mL, 4.0 *eq*) and Cu(OAc)₂ (400.3 mg, 2.2 mmol, 1.5 *eq*). The mixture was stirred at 20 °C for 16 hr under an O₂ atmosphere. LCMS showed the desired compound was formed. TLC (Petroleum ether : Ethyl acetate=3/1) showed a new spot appeared. The reaction was filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by column chromatography over silica gel to give **175-3** (50.0 mg, 0.18 mmol, 12.1% yield). LCMS (ESI): RT = 0.773 min, mass calc. for C₁₄H₈F₄N₂ 280.06 m/z found 280.5 [M+H]⁺.

Step 2: 4-fluoro-2-(2H-tetrazol-5-yl)-N-[4-(trifluoromethyl)phenyl]aniline

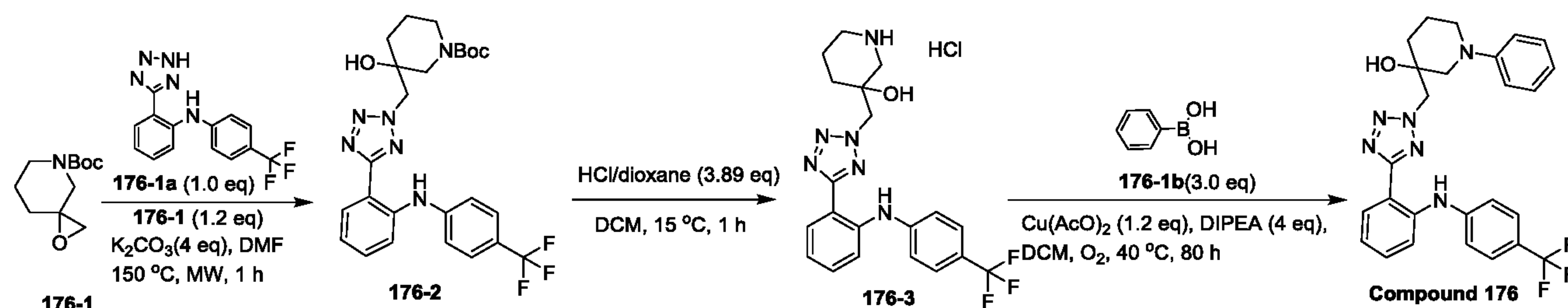
[00571] To a solution of **175-3** (50.0 mg, 0.18 mmol, 1.00 *eq*) in DMF (15.0 mL) was added NH₄Cl (28.6 mg, 0.53 mmol, 18.7 μL, 3.0 *eq*) and **175-4** (34.8 mg, 0.54 mmol, 3.0 *eq*). The mixture was stirred at 130 °C for 16 hour under an N₂ atmosphere. LCMS showed the desired compound

was formed. The reaction mixture was poured into HCl (1M, 4 mL) and extracted with EtOAc(10 mL*2). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, and filtered. The solvent was removed under reduced pressure to afford the crude **175-5** (0.06 g, 0.17 mmol, 93.48% yield, HCl). The residue was directly used without further purification.

Step 3: 2-[5-[5-fluoro-2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol

[00572] To a solution of **175-5** (30.0 mg, 83.4 μ mol, 1.0 *eq*, HCl) in DMF (2.0 mL) was added K₂CO₃ (23.1 mg, 0.17 mmol, 2.0 *eq*) and **175-6** (15.6 mg, 0.13 mmol, 8.9 μ L, 1.5 *eq*). The mixture was stirred at 100 °C for 16 hour under an N₂ atmosphere. LCMS detected the desired compound was formed. The reaction was filtered to give a crude product. The crude product was purified by prep-HPLC to give **Compound 175** (6.08 mg, 16.6 μ mol, 19.8% yield). LCMS (ESI): RT = 0.802 min, mass calc. for C₁₆H₁₃F₄N₅O 367.11, m/z found 368.0 [M+H]⁺; ¹HNMR (400 MHz, CDCl₃-*d*) δ 8.80 (s, 1H), 7.89 (dd, *J* = 3.1, 9.2 Hz, 1H), 7.55 - 7.47 (m, 3H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.13 (ddd, *J* = 3.0, 7.7, 9.1 Hz, 1H), 4.90 - 4.83 (m, 2H), 4.32 - 4.24 (m, 2H), 2.18 (s, 1H).

Example 169: 1-phenyl-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)piperidin-3-ol (Compound 176)



Step 1: tert-butyl 3-hydroxy-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)piperidine-1-carboxylate

[00573] **176-1a** (150.00 mg, 438.96 μ mol, 1.00 *eq*, HCl), **176-1** (112.34 mg, 526.75 μ mol, 1.20 *eq*) and K₂CO₃ (242.67 mg, 1.76 mmol, 4.00 *eq*) were taken up into a microwave tube in DMF (4.00 mL). The sealed tube was heated at 150 °C for 1 h under microwave conditions. The crude LCMS detected the desired product MS value. The reaction mixture was quenched by water (20 mL) and then extracted with DCM (15 mL * 4). The combined organic layers were washed with brine (15 mL * 2), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give provide **176-2** (0.2 g, 385.71 μ mol, 87.87% yield). ¹HNMR (400 MHz, DMSO-*d*₆) δ 1.30 - 1.40 (m, 13 H), 3.07 - 3.33 (m, 2 H), 3.40 (br s, 2 H), 4.66 - 4.76 (m, 2 H), 5.06 (s, 1 H), 7.15 - 7.25 (m, 3 H), 7.46 - 7.57 (m, 4 H), 8.07 (br d, *J* = 7.50 Hz, 1 H), 8.82 (s, 1 H).

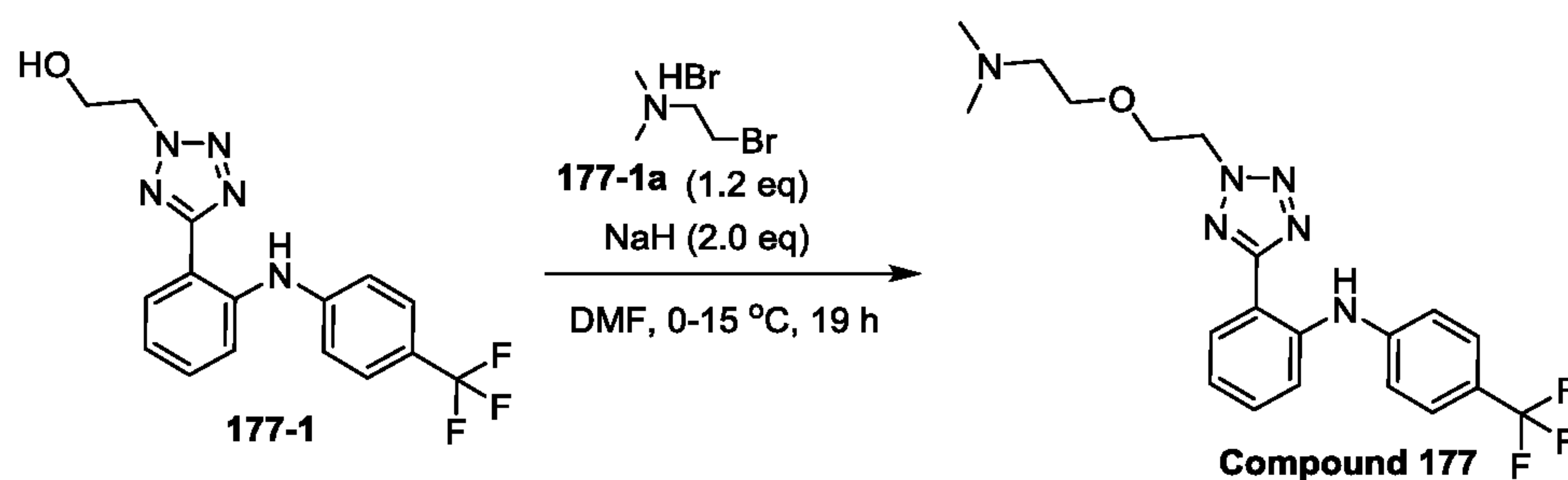
Step 2: 3-((5-(2-((4-(trifluoromethyl) phenyl) amino) phenyl)-2H-tetrazol-2-yl) methyl) piperidin-3-ol

[00574] To a mixture of **176-2** (0.2 g, 385.71 μmol , 1.00 *eq*) in DCM (1.5 mL) was added HCl/dioxane (1 M, 1.5 mL, 3.89 *eq*) at 15°C. The mixture was stirred at 15°C for 1 hr. The crude LCMS detected the desired product MS value. The reaction mixture was concentrated to give a crude compound **176-3** (0.15 g, crude, HCl salt), which was used into the next step without further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.53 - 1.97 (m, 6 H), 2.64 - 3.20 (m, 10 H), 4.82 (s, 2 H), 5.30 - 5.99 (m, 1 H), 7.23 (s, 3 H), 7.56 (s, 5 H), 7.85 - 8.12 (m, 2 H), 8.32 (br s, 1 H), 8.81 (br s, 1 H), 9.34 - 9.65 (m, 1 H).

Step 3: 1-phenyl-3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)piperidin-3-ol

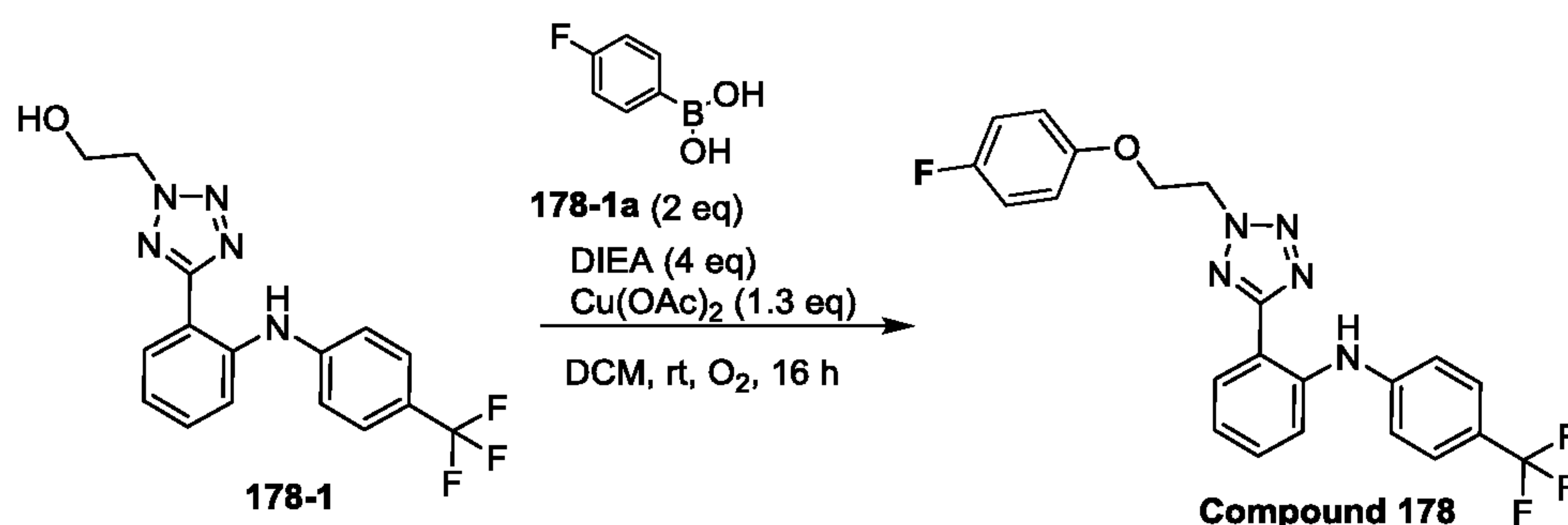
[00575] To a mixture of **176-3** (60 mg, 131.90 μmol , 1 *eq*, HCl) and compound **176-1b** (48.25 mg, 395.71 μmol , 8.82 μL , 3 *eq*) in DCM (2 mL) was added DIPEA (68.19 mg, 527.62 μmol , 91.90 μL , 4 *eq*) and $\text{Cu}(\text{OAc})_2$ (28.75 mg, 158.28 μmol , 1.2 *eq*) in one portion at 15 °C under O_2 . The mixture was heated to 40°C and stirred for 40 hours. The crude LCMS showed 25% of **176-3** remained and 30% of the desired product was detected. An additional **176-1b** (48.25 mg, 395.71 μmol , 8.82 μL , 3 *eq*) was added to the reaction mixture, and the mixture was stirred at 40 °C for 40 hours. The crude LCMS showed 10% of **176-3** remained and 27% of the desired product was detected. The reaction mixture was diluted with DCM (20 mL). The reaction mixture was purified by flash silica gel chromatography to give a residue (77 mg), which was purified by prep-HPLC to give **Compound 176** (4.72 mg, 9.54 μmol , 7.24% yield). LCMS (ESI): RT = 2.682 min, mass calc. for $\text{C}_{26}\text{H}_{25}\text{F}_3\text{N}_6\text{O}$ 494.51, m/z found 495.00 $[\text{M}+1]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.43 - 1.57 (m, 1 H), 1.63 - 1.88 (m, 3 H), 2.85 - 3.00 (m, 2 H), 3.14 - 3.28 (m, 2 H), 4.78 - 5.00 (m, 2 H), 5.10 (s, 1 H), 6.77 (t, $J = 7.15$ Hz, 1 H), 6.99 (d, $J = 7.78$ Hz, 2 H), 7.13 - 7.25 (m, 5 H), 7.44 - 7.62 (m, 4 H), 8.07 (dd, $J = 7.78, 1.26$ Hz, 1 H), 8.81 (s, 1 H).

Example 170: 2-(2-(2-(2-(dimethylamino)ethoxy)ethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 177)



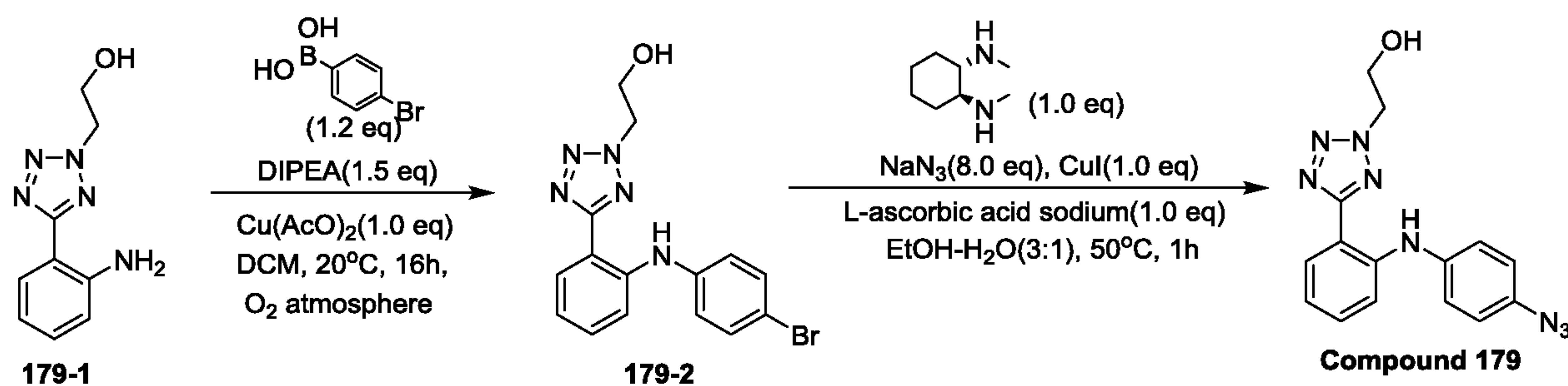
[00576] To a solution of **177-1** (30 mg, 85.9 μmol , 1 *eq*) in DMF (2 mL), was added NaH (6.9 mg, 0.2 mmol, 60% purity, 2 *eq*) at 0 °C. The mixture was stirred at 0 °C for 0.5 h. Then **177-1a** (24.0 mg, 0.1 mmol, 1.2 *eq*, HBr) was added at 0 °C. The resulting mixture was stirred at 15 °C for 2 h. LCMS detected about 17% of the desired compound, and 34% starting material remaining. The mixture was stirred at 15 °C for 17 h. LCMS detected no obvious change. The mixture was diluted with water (15 mL), and extracted with DCM (15 mL *2). The organic layer was dried over anhydrous Na_2SO_4 , and concentrated under vacuum. The residue was checked by HPLC. The residue was purified by prep-HPLC (basic condition) to provide the title compound (4.03 mg, 9.6 μmol , 11.2% yield). LCMS (ESI): RT = 0.650 min, mass calc. for $\text{C}_{20}\text{H}_{23}\text{F}_3\text{N}_6\text{O}$ 420.19, m/z found 421.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400MHz, $\text{CHLOROFORM-}d$) δ 8.36 (dd, $J = 1.9, 7.4$ Hz, 1H), 7.64 - 7.55 (m, 2H), 7.42 (d, $J = 8.8$ Hz, 2H), 7.32 (dd, $J = 1.6, 7.4$ Hz, 1H), 6.76 (d, $J = 8.8$ Hz, 2H), 4.73 - 4.66 (m, 2H), 4.20 - 4.07 (m, 4H), 3.84 (s, 1H), 3.26 (t, $J = 8.0$ Hz, 2H), 2.78 (s, 6H).

Example 171: 2-[2-[2-(4-fluorophenoxy)ethyl]tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 178)



[00577] To a solution of **178-1** (40 mg, 0.114 mmol, 1 *eq*), (4-fluorophenyl)boronic acid **178-1a** (32 mg, 0.23 mmol, 2 *eq*) and DIEA (59.2 mg, 0.16 mmol, 79.78 μL , 4 *eq*) in DCM (3 mL) was added $\text{Cu}(\text{OAc})_2$ (27 mg, 0.15 mmol, 1.3 *eq*). The reaction mixture was degassed with O_2 three times and stirred at 20 °C for 16 hr. LCMS detected that the starting material remained and ~40% of the desired product was present. The reaction was diluted with DCM (6 mL) and washed with water (10 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by Prep.HPLC (basic: column) to give the title compound (4.99 mg, 11.25 μmol , 9.83% yield). LCMS (ESI): RT = 0.935 min, mass calc. for $\text{C}_{22}\text{H}_{17}\text{F}_4\text{N}_5\text{O}$ 443.14, m/z found 444.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400MHz, $\text{CHLOROFORM-}d$) δ 9.01 (s, 1H), 8.21 (d, $J = 8.0$ Hz, 1H), 7.60 - 7.50 (m, 3H), 7.28 (d, $J = 8.4$ Hz, 1H), 7.35 - 7.25 (m, 2H), 7.10 - 7.00 (m, 1H), 7.00 - 6.85 (m, 2H), 6.85 - 6.65 (m, 2H), 5.07 (t, $J = 4.8$ Hz, 2H), 4.57 (t, $J = 5.2$ Hz, 2H).

Example 172: 2-[5-[2-(4-azidoanilino)phenyl]tetrazol-2-yl]ethanol (Compound 179)



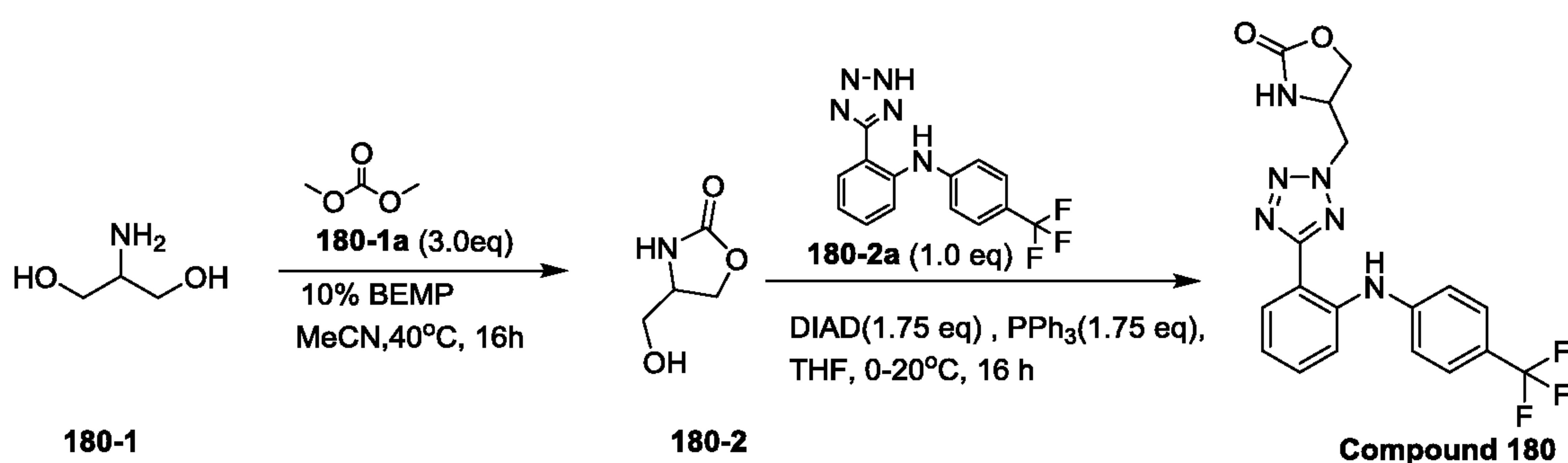
Step 1: 2-[5-[2-(4-bromoanilino)phenyl]tetrazol-2-yl]ethanol

[00578] To a solution of (4-bromophenyl)boronic acid (587.2 mg, 2.9 mmol, 1.2 eq) and **179-1** (500 mg, 2.4 mmol, 1.0 eq) in DCM (20.0 mL) was added Cu(OAc)₂ (486.8 mg, 2.7 mmol, 1.1 eq) and DIPEA (472.3 mg, 3.7 mmol, 636.6 μ L, 1.5 eq). The mixture was stirred at 20 °C for 16 hr under O₂ atmosphere. LC-MS showed **179-1** was consumed completely and one main peak with the desired MS was detected. The reaction mixture was filtered through a Celite pad and washed with DCM(30 mL). The filtrate was concentrated to give a residue. The residue was purified by flash silica gel chromatography to give **179-2** (620 mg, 1.6 mmol, 67.1% yield). LCMS (ESI): RT = 0.802 min, mass calc. for C₁₅H₁₄BrN₅O 359.04, m/z found 360.0 [M+H]⁺; ¹HNMR (400MHz, CDCl₃) δ 8.85 (s, 1H), 8.16 (dd, J=1.5, 7.8 Hz, 1H), 7.45 - 7.40 (m, 2H), 7.39 - 7.29 (m, 2H), 7.18 - 7.11 (m, 2H), 6.99 - 6.92 (m, 1H), 4.92 - 4.80 (m, 2H), 4.33 - 4.21 (m, 2H), 2.29 (t, J=6.3 Hz, 1H).

Step 2: 2-[5-[2-(4-azidoanilino)phenyl]tetrazol-2-yl]ethanol

[00579] To a solution of **179-2** (50 mg, 0.14 mmol, 1.0 eq) and NaN₃ (72.2 mg, 1.1 mmol, 8.0 eq) in EtOH (6 mL) and Water (2 mL) was added (1R, 2R)-N1,N2-dimethylcyclohexane-1,2-diamine (19.7 mg, 0.14 mmol, 1.0 eq), CuI (26.4 mg, 0.14 mmol, 1 eq) and L-sacorbic acid sodium (27.5 mg, 0.14 mmol, 1 eq). The mixture was stirred at 50 °C for 1 hr. LC-MS showed **179-2** was consumed completely and one main peak with the desired MS was detected. The reaction mixutre was poured into water (30 mL) and extracted with EtOAc (10 mL*3). The combined organic layer was washed with brine (10 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated to give a residue. The residue was purified by prep-HPLC. The resulting eluent was concentrated to give a residue and the residue was lyophilized to give **Compound 179** (19.70 mg, 61.12 μ mol, 44.03% yield). LCMS (ESI): RT = 1.198 min, mass calc. for C₁₅H₁₄N₈O 322.13, m/z found 323.0 [M+H]⁺; ¹HNMR (400MHz, DMSO-d₆) δ 8.71 (s, 1H), 8.07 (dd, J=1.4, 7.9 Hz, 1H), 7.42 - 7.35 (m, 1H), 7.34 - 7.25 (m, 3H), 7.13 - 7.07 (m, 2H), 7.04 - 6.93 (m, 1H), 5.10 (t, J=5.8 Hz, 1H), 4.80 (t, J=5.3 Hz, 2H), 3.97 (q, J=5.5 Hz, 2H).

Example 173: 4-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)oxazolidin-2-one (Compound 180)



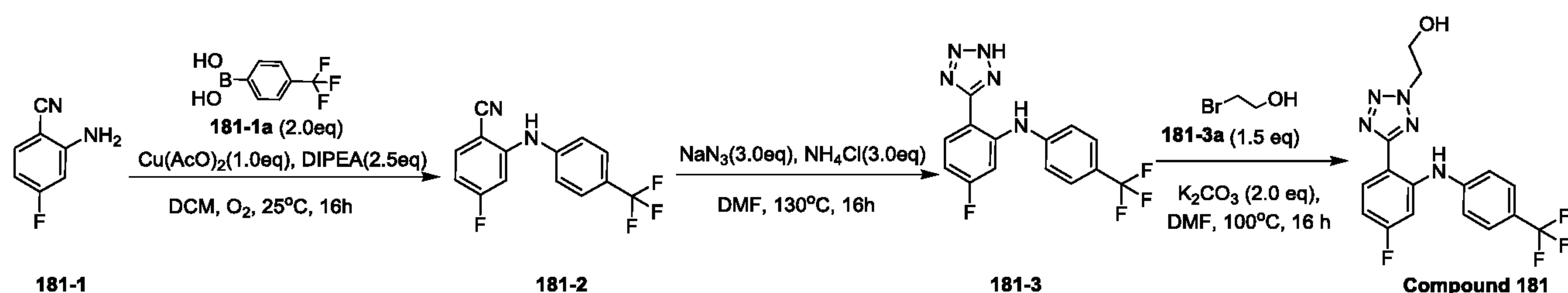
Step 1: 4-(hydroxymethyl)oxazolidin-2-one

[00580] To a mixture of the BEMP (301 mg, 1.10 mmol, 0.1 *eq*) in CH₃CN (10 mL) was added **180-1** (1.0 g, 10.98 mmol, 1.0 *eq*) and **180-1a** (2.97 g, 32.93 mmol, 2.77 mL, 3.0 *eq*). The reaction mixture was stirred at 40 °C for 16 hour. TLC (Ethyl acetate, R_f = 0.1) showed new spot was found. The reaction mixture was concentrated under vacuum to give a residue. The residue was purified by flash silica gel chromatography to give **180-2** (0.3 g, 2.56 mmol, 23% yield). ¹HNMR ((400MHz, DMSO-*d*₆) δ 7.61 (s, 1H), 4.98 (t, *J* = 5.5 Hz, 1H), 4.36 - 4.25 (m, 1H), 4.05 (dd, *J* = 5.0, 8.5 Hz, 1H), 3.80 - 3.70 (m, 1H), 3.37 (s, 1H), 3.34 (s, 1H).

Step 2: 4-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)oxazolidin-2-one

[00581] To a solution of **180-2** (34 mg, 0.293 mmol, 2.0 *eq*) and **180-2a** (50 mg, 0.146 μmol, 1.0 *eq*, HCl) in anhydrous THF (2 mL) was added PPh₃ (67 mg, 0.256 mmol, 1.75 *eq*) and the mixture was cooled to 0°C under N₂. DIAD (51.78 mg, 256.06 μmol, 49.79 μL, 1.75 *eq*) was added. The reaction mixture was stirred at 0°C for 5 min and stirred at 20°C for 16 h. LCMS showed 49% of the desired compound was found and the starting material was consumed completely. The solution was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 180** (13 mg, 32 μmol, 22% yield). LCMS (ESI): RT = 0.795 min, mass calc. for C₁₈H₁₅F₃N₆O₂ 404.12, *m/z* found 427.0 [M+23]⁺; ¹HNMR (400MHz, DMSO-*d*₆) δ 8.69 (s, 1H), 8.07 (dd, *J* = 1.3, 7.8 Hz, 1H), 7.97 (s, 1H), 7.60 - 7.54 (m, 3H), 7.54 - 7.48 (m, 1H), 7.27 - 7.17 (m, 3H), 4.89 (d, *J* = 5.3 Hz, 2H), 4.50 - 4.36 (m, 2H), 4.25 (dd, *J* = 3.9, 8.2 Hz, 1H).

Example 174: 2-[5-[4-fluoro-2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol; (Compound 181)



Step 1: 4-fluoro-2-[4-(trifluoromethyl)anilino]benzonitrile

[00582] To a mixture of **181-1** (500 mg, 3.67 mmol, 1 *eq*) and **181-1a** (1.40 g, 7.35 mmol, 2 *eq*) in DCM (7 mL) was added Cu(OAc)₂ (667 mg, 3.67 mmol, 1 *eq*) and DIPEA (1.19 g, 9.18 mmol, 1.6 mL, 2.5 *eq*) in one portion under O₂ (15 Psi). The mixture was stirred at 25 °C for 18 h. LCMS showed no desired MS was detected. TLC indicated the starting material was remained. The reaction mixture was added **181-1a** (400 mg) and continued stirred 24 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to provide **181-2** (150 mg, 0.428 mmol, 11.7% yield). The product was used next step. ¹H NMR (400MHz, CHLOROFORM-*d*) δ7.65 (d, *J* = 8.40 Hz, 2H), 7.59 - 7.54 (m, 1H), 7.32 - 7.27 (m, 2H), 7.02 - 6.96(m, 1H), 6.72 - 6.63 (m, 1H), 6.55 (br s, 1H).

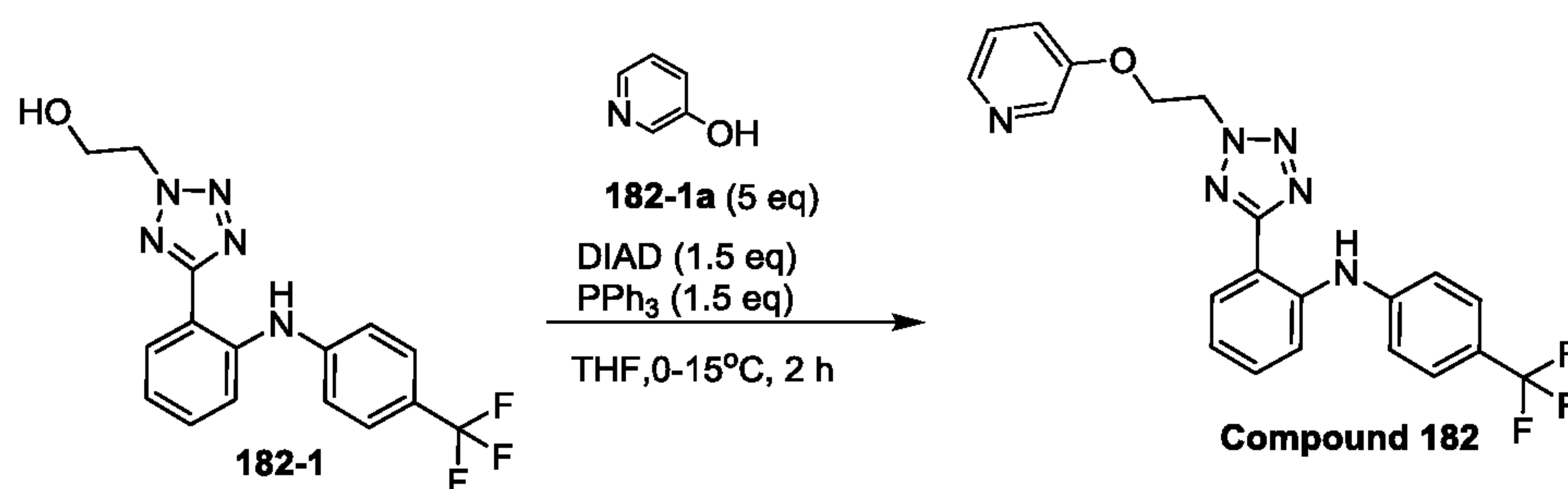
Step 2: 5-fluoro-2-(2H-tetrazol-5-yl)-N-[4-(trifluoromethyl)phenyl]aniline

[00583] To a mixture of **181-2** (150 mg, 0.535 umol, 1 *eq*) and NaN₃ (130 mg, 2.00 mmol, 3.74 *eq*) in DMF (2.5 mL) was added NH₄Cl (86 mg, 1.61 mmol, 3 *eq*) in one portion at 15°C under N₂. The mixture was stirred at 130°C for 16 h. LCMS showed no desired MS was detected. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL * 3). The combined organic layers were dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum. LCMS showed one main peak and **181-3** (150 mg, 408.36 umol, 76.29% yield) was used in the next step. ¹HNMR (400MHz, DMSO-*d*₆) δ9.42 (s, 1H), 7.95 - 7.90 (m, 1H), 7.64 (d, *J* = 8.80 Hz, 2H), 7.36 (d, *J* = 8.80 Hz, 2H), 7.32 - 7.27 (m, 1H), 7.05 - 6.99 (m, 1H).

Step 3: 2-[5-[4-fluoro-2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]ethanol

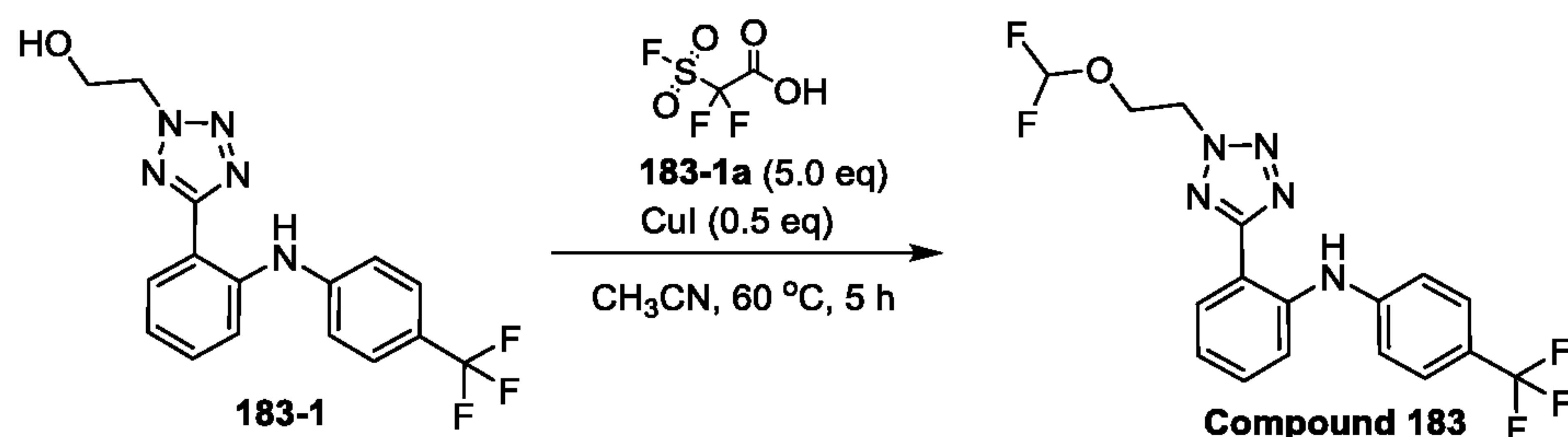
[00584] To a mixture of **181-3** (50 mg, 0.155 mmol, 1 *eq*) and **181-3a** (29 mg, 0.232 mmol, 1.5 *eq*) in DMF (1 mL) was added K₂CO₃ (43 mg, 0.309 mmol, 2 *eq*) in one portion at 15°C under N₂. The mixture was stirred at 100 °C for 16 h. LCMS showed the starting material was consumed completely but no desired MS was detected. The reaction mixture was diluted with water (4 mL) and extracted with EtOAc (4 mL * 3). The combined organic layers were dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by prep-HPLC (basic condition) to obtain **Compound 181** (7.23 mg, 19.5 umol, 12.6% yield). LCMS (ESI): RT = 1.247 min, mass calcd. for C₁₆H₁₃F₄N₅O, 367.11 m/z found 368.0[M+H]⁺. ¹HNMR (400MHz, DMSO-*d*₆) δ9.04 (s, 1H), 8.14 - 8.16 m, 1H), 7.63 (d, *J* = 8.40 Hz, 2H), 7.36 (d, *J* = 8.40 Hz, 2H), 7.32 - 7.27 (m, 1H), 7.02 - 6.94 (m, 1H), 5.06 (t, *J* = 5.60 Hz, 1H), 4.78 (t, *J* = 5.20 Hz, 2H), 3.98 - 3.91 (m, 2H).

Example 175: 2-[2-[2-(3-pyridyloxy)ethyl]tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 182)



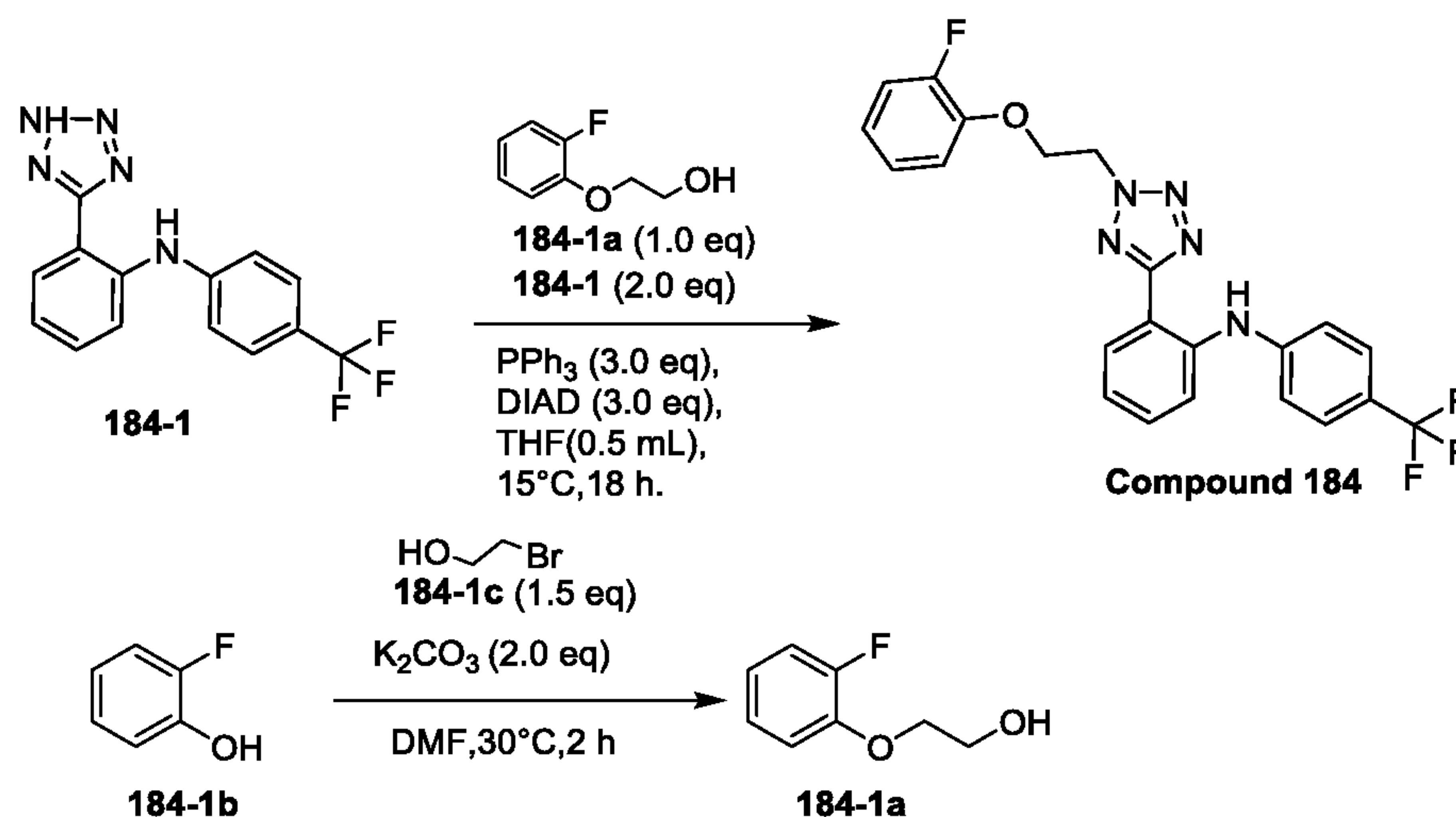
[00585] To a solution of **182-1** (50 mg, 0.14 mmol, 1 *eq*), pyridin-3-ol (68.1 mg, 0.72 mmol, 16.55 μ L, 5 *eq*) and PPh_3 (56.3 mg, 0.21 mmol, 1.5 *eq*) in THF (1.2 mL) was added DIAD (43.4 mg, 0.21 mmol, 41.75 μ L, 1.5 *eq*) at 0°C. The reaction mixture was stirred at 15°C for 2hr. LCMS showed that starting material was remained and 18% of desired product was detected. The reaction was concentrated. The crude product was purified by Prep.HPLC to give the title compound (2.51 mg, 5.57 μ mol, 3.89% yield). LCMS (ESI): RT = 0.717 min, mass calc. for $\text{C}_{21}\text{H}_{17}\text{F}_3\text{N}_6\text{O}$ 426.14, m/z found 427.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400MHz, DMSO) δ 8.66 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.70 - 7.60 (m, 1H), 7.60 - 7.50 (m, 3H), 7.50 - 7.40 (m, 1H), 7.37 (s, 1H), 7.25 - 7.18 (m, 2H), 7.18 - 7.10 (m, 2H), 6.85 (d, J = 8.4 Hz, 1H), 5.35 (t, J = 5.2 Hz, 2H), 4.80 (t, J = 5.6 Hz, 2H).

Example 176: 2-(2-(2-(difluoromethoxy)ethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 183)



[00586] To a mixture of **183-1** (30 mg, 85.9 μ mol, 1 *eq*) in CH_3CN (4 mL), was added CuI (8.2 mg, 42.9 μ mol, 0.5 *eq*). The mixture was heated to 60 °C. **183-1a** (76.5 mg, 429.4 μ mol, 44.5 μ L, 5 *eq*) was added dropwise. The resulting mixture was stirred at 60 °C for 5 h. LCMS and HPLC showed there's about 28% desired compound, and 23% starting material was remained. The mixture was diluted with water (10 mL), extracted with EtOAc (10 mL*3). The organic layer was dried over anhydrous Na_2SO_4 , concentrated under vacuum. The residue was purified by prep-HPLC to provide the title compound (6.19 mg, 15.50 μ mol, 18.05% yield). LCMS (ESI): RT = 0.885 min, mass calc. for $\text{C}_{17}\text{H}_{14}\text{F}_5\text{N}_5\text{O}$ 399.11, m/z found 400.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400MHz, CH_2Cl_2) δ 9.01 (s, 1H), 8.21 (dd, J = 1.5, 7.8 Hz, 1H), 7.57 - 7.52 (m, 3H), 7.42 - 7.36 (m, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.08 - 7.02 (m, 1H), 6.42 - 6.01 (m, 1H), 4.96 (t, J = 5.5 Hz, 2H), 4.50 (t, J = 5.4 Hz, 2H).

Example 177: 2-[2-[2-(2-fluorophenoxy)ethyl]tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 184)



Step 1: 2-(2-fluorophenoxy)ethan-1-ol

[00587] To a suspension and mixture of **184-1b** (100 mg, 0.892 mmol, 1 *eq*) and **184-1c** (223 mg, 1.78 mmol, 2 *eq*) in DMF (2 mL) was added K_2CO_3 (432 mg, 3.12 mmol, 3.5 *eq*) in one portion. The mixture was stirred at 30 °C for 2 h. TLC showed the starting material was consumed completely and one new spot was formed. The reaction mixture was diluted with EtOAc (30 mL) and washed with water (30 mL * 2), The organic phase was dried with anhydrous Na_2SO_4 , filtered and concentrated under vacuum. The residue was purified by flash silica gel chromatography to provide **184-1a** (45 mg, 0.242 mmol, 27.1% yield). ^1H NMR (400MHz, $CHCl_3$ -*d*) δ 7.14 - 6.90 (m, 4H), 4.18 - 4.15 (m, 2H), 4.02 - 3.96 (m, 2H), 2.12 (t, J = 6.40 Hz, 1H).

Step 2: 2-[2-[2-(2-fluorophenoxy)ethyl]tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline

[00588] To a solution of the **184-1a** (15 mg, 81 μ mol, 1 *eq*), PPh_3 (63 mg, 0.242 μ mol, 3 *eq*) and the **184-1** (49 mg, 0.161 mmol, 2 *eq*) in THF (0.5 mL) was added DIAD (49 mg, 0.242 mmol, 3 *eq*) in one portion at 0°C under N_2 . The mixture was stirred at 0 °C for 3 min, and then warmed to 15 °C for 2 h. LCMS showed only starting material was consumed completely and 23% of desired product was formed. The reaction mixture was continued stirred 16 h. The reaction mixture was concentrated under reduced pressure to remove solvent. HPLC indicated 16 % of desired product was detected. The residue was purified by prep-HPLC to provide **Compound 184** (6.93 mg, 15.47 μ mol, 19.18% yield). LCMS (ESI): RT = 0.932 min, mass calcd. for $C_{22}H_{17}F_4N_5O$, 443.14 m/z found 444.1 $[M+H]^+$. ^1H NMR (400MHz, $CHCl_3$ -*d*) δ 9.00 (s, 1H), 8.25 - 8.19 (m, 1H), 7.53 (d, J = 8.40 Hz, 3H), 7.43 - 7.35 (m, 1H), 7.30 (s, 2H), 7.09 - 6.99 (m, 3H), 6.98 - 6.90 (m, 2H), 5.11 (t, J = 5.40 Hz, 2H), 4.68 (t, J = 5.40 Hz, 2H).

Example 178: 2-(2-(2-(trifluoromethoxy)ethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

(75 mL). This solution was washed sequentially with saturated NaHCO_3 (15 mL*2), and water (15 mL*2). The organic phase was dried over anhydrous Na_2SO_4 , and gently evaporated, but not to complete dryness to give crude product dimethyl 2-diazopropanedioate **186-2** (3.4 g, crude), which was used for next step without further purification. ^1H NMR (400MHz, $\text{CHLOROFORM-}d$) δ 3.83 (s, 6H).

Step 2: dimethyl 2-(benzyloxy)malonate

[00591] To a solution of dimethyl 2-diazopropanedioate **186-2** (3.4 g, 10.75 mmol, 1 *eq*) in DCM (7 mL) was added phenylmethanol (1.16 g, 10.75 mmol, 1.1 mL, 1 *eq*) at 0°C under nitrogen. Diacetoxyrhodium (118.8 mg, 0.54 mmol, 0.05 *eq*) was then added. The resulting solution was stirred at 22°C for 16 h, over which time lots of precipitation was formed. TLC (PE:EtOAc=1:1 UV) showed new spots were formed. LCMS showed two main peaks were present but no desired mass was present. The reaction mixture was diluted with DCM (50 mL) and washed with brine (15 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give a residue. The residue was purified by column chromatography to give dimethyl 2-benzyloxypropanedioate **186-3** (1.9 g, 7.98 mmol, 74.18% yield). ^1H NMR (400MHz, $\text{CHLOROFORM-}d$) δ 7.43 - 7.33 (m, 5H), 4.73 - 4.68 (m, 2H), 4.57 (s, 1H), 3.83 - 3.78 (m, 6H).

Step 3: dimethyl 2-(benzyloxy)-2-(hydroxymethyl)malonate

[00592] To a solution of dimethyl 2-benzyloxypropanedioate **186-3** (1.9 g, 7.98 mmol, 1 *eq*) and NaHCO_3 (67.0 mg, 0.8 mmol, 31.02 μL , 0.1 *eq*) in EtOH (8 mL) was drop-wise added formaldehyde (711.9 mg, 8.77 mmol, 0.65 mL, 1.1 *eq*) at 0°C. The resulting mixture was stirred at 10°C for 16 h. TLC (PE:EtOAc = 2:1 UV) showed new spots were formed and material was consumed completely. LCMS showed 82% of desired product was present. The reaction mixture was concentrated and then diluted with DCM (50 mL) and washed with brine (15 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give crude product dimethyl 2-benzyloxy-2-(hydroxymethyl)propanedioate **186-4** (2.1 g, 7.83 mmol, 98.16% yield). LCMS (ESI): RT = 0.647 min, mass calc. for $\text{C}_{13}\text{H}_{16}\text{O}_6$ 268.09, m/z found 290.9 $[\text{M}+23]^+$.

Step 4: dimethyl 2-(benzyloxy)-2-(((tert-butyldiphenylsilyl)oxy)methyl)malonate

[00593] To a solution of dimethyl 2-benzyloxy-2-(hydroxymethyl)propanedioate **186-4** (2.1 g, 7.83 mmol, 1 *eq*), DMAP (95.6 mg, 0.78 mmol, 0.1 *eq*) and imidazole (1.60 g, 23.48 mmol, 3 *eq*) in DMF (15 mL) was portion-wise added TBDPSCl (3.23 g, 11.74 mmol, 3.02 mL, 1.5 *eq*) at 10°C. The resulting solution was stirred at 10°C under nitrogen for 24 h. TLC (PE:EtOAc = 10:1 UV) showed new spots were formed and material was consumed completely. LCMS showed 56% of desired product was present. The reaction mixture was diluted with EtOAc (80 mL) and washed with brine (15 mL*4). The organic phase was dried over anhydrous Na_2SO_4 and

concentrated to give a residue. The residue was purified by flash silica gel chromatography to give dimethyl 2-benzyloxy-2-[[tert-butyl(diphenyl)silyl]oxymethyl]propanedioate **186-5** (4.5, crude). LCMS (ESI): RT =1.005 min, mass calc. for C₂₉H₃₄O₆Si 506.21, m/z found 529.1 [M+23]⁺.

Step 5: 2-(benzyloxy)-2-(((tert-butyldiphenylsilyl)oxy)methyl)propane-1,3-diol

[00594] To a solution of **186-5** (4.5 g, 8.88 mmol, 1 *eq*) in THF (50 mL) was portionwise added lithiumboranuide (406.3 mg, 18.65 mmol, 2.1 *eq*) at 0 °C under nitrogen (gas evolved). The reaction was allowed to warm to 25°C and stirred at this temperature for 16 h. TLC (PE:EtOAc = 1:1 UV) showed new spot was formed and material was consumed completely. LCMS showed 52% of desired product was present. The reaction mixture was quenched with water (15 mL) at 0°C and filtered. The filtrate was diluted with EtOAc (80 mL) and washed with brine (15 mL*2). The organic phase was dried over anhydrous Na₂SO₄ and concentrated to give a residue. The residue was purified by flash silica gel chromatography to give **186-6** (2.9 g, 5.98 mmol, 67.38% yield). LCMS (ESI): RT =0.912 min, mass calc. for C₂₇H₃₄O₄Si 450.22, m/z found 473.1 [M+23]⁺.

Step 6: ((3-(benzyloxy)oxetan-3-yl)methoxy)(tert-butyl)diphenylsilane

[00595] To a solution of **186-6** (2.9 g, 6.44 mmol, 1 *eq*) in THF (30 mL) was drop-wise added n-BuLi (2.5 M, 2.7 mL, 1.05 *eq*) at 0 °C. After stirring for 20 min, a solution of 4-methylbenzenesulfonyl chloride (1.29 g, 6.76 mmol, 1.05 *eq*) in THF (5 mL) was added drop-wise. The reaction was stirred for 60 minutes at 0°C and n-BuLi (2.5 M, 2.7 mL, 1.05 *eq*) was added. After stirring at 0°C for 40 min, the reaction mixture was then heated to 60 °C and stirred at this temperature for 3.5 h. TLC (PE:EtOAc = 2:1 UV) showed new spots were formed and material was consumed completely. LCMS showed 41% of desired product was present and material was consumed completely. The reaction mixture was quenched with water (15 mL) at 0°C. The mixture was diluted with EtOAc (80 mL) and washed with brine (15 mL*2). The organic phase was dried over anhydrous Na₂SO₄ and concentrated to give a residue. The residue was purified by flash silica gel chromatography to give compound **186-7** (1.6 g, 3.7 mmol, 57.47% yield) as colorless oil. ¹HNMR (400MHz, CHLOROFORM-*d*) δ 7.69 (d, *J* = 6.5 Hz, 4H), 7.47 - 7.28 (m, 10H), 4.73 (d, *J* = 7.0 Hz, 2H), 4.61 - 4.52 (m, 4H), 4.00 (s, 2H), 1.10 (s, 8H).

Step 7: (3-(benzyloxy)oxetan-3-yl)methanol

[00596] To a solution of **186-7** (1.6 g, 3.7 mmol, 1 *eq*) in THF (15 mL) was added TBAF (1 M, 3.7 mL, 1 *eq*) at 10°C. The resulting solution was stirred at 10°C for 2 h. LCMS showed no desired mass signal was present and 27% of material was remained. Then another batch of TBAF (1 M, 3.70 mL, 1 *eq*) was added and the solution was stirred at 25 °C for 1 h. TLC (PE:EtOAc = 1:1 UV and stained by iodine) showed new spots were formed and some of material was remained. The

reaction mixture was evaporated to dryness to give a crude product. The residue was purified by flash silica gel chromatography to give **186-8** (0.4 g, 2.06 mmol, 55.69% yield) as colorless oil.

¹HNMR (400MHz, CHLOROFORM-*d*) δ 7.43 - 7.29 (m, 4H), 4.82 (d, *J* = 7.5 Hz, 2H), 4.65 (s, 2H), 4.48 (d, *J* = 7.5 Hz, 2H), 4.00 (d, *J* = 6.0 Hz, 2H), 1.87 (t, *J* = 6.3 Hz, 1H).

Step 8: 2-((2-((3-(benzyloxy)oxetan-3-yl)methyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00597] To a solution of **186-8** (0.25 g, 0.82 mmol, 1 *eq*), **186-8a** (190.8 mg, 0.98 mmol, 1.2 *eq*) and PPh₃ (257.8 mg, 0.98 mmol, 1.2 *eq*) in THF (1.7 mL) was added DIAD (198.7 mg, 0.98 mmol, 0.19 mL, 1.2 *eq*) at 10°C. The resulting lightly yellow solution was stirred at 10°C for 2 h. LCMS showed 17% of desired product was formed and 29% of material was remained. Then the solution was continuously stirred at 10°C for another 3 h. LCMS showed 34% of desired product was formed and 23% of material was remained. Then the solution was stirred at 65°C for another 6 h. LCMS showed 23% of desired product was formed and 33% of material was remained. The solution was combined with the another batch and concentrated to give a residue. The residue was purified by flash silica gel chromatography to give compound **186-9** (0.5 g, crude). LCMS (ESI): RT = 0.926 min, mass calc. for C₂₅H₂₂F₃N₅O₂ 481.17, *m/z* found 482.1 [M+1]⁺.

Step 9: 3-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)oxetan-3-ol

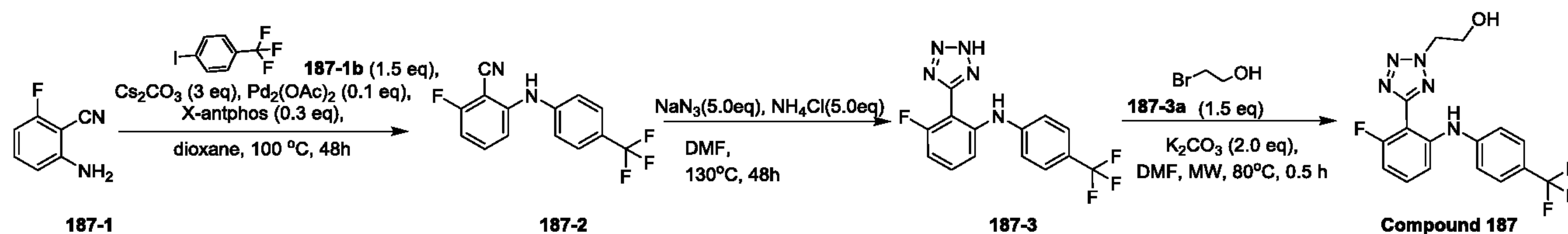
[00598] To a solution of **186-9** (0.4 g, 0.83 mmol, 1 *eq*) in MeOH (10 mL) was added Pd/C (0.35 g, 0.33 mmol, 10% purity, 0.5 *eq*) at 15°C. The resulting dark mixture was degassed and refilled with H₂ balloon for three times and then stirred at 15°C for 5 h under 1 atm H₂. LCMS showed 22% desired product was formed and 11% of material was remained. TLC (PE:EtOAc = 2:1 UV) showed a new spot was formed and a little of material was remained. The mixture was combined with the batch of page ES6650-78 and filtered via a pad of celite. The filter cake was washed with MeOH (20 mL). The filtrate was concentrated to give a residue. The residue was purified by prep_HPLC to give **Compound 186** (41.67 mg, 0.11 mmol, 12.82% yield) and recover material **186-9** (10.8 mg, 22.4 μmol, 2.70% yield).

[00599] **Compound 186**: LCMS (ESI): RT = 1.711 min, mass calc. for C₁₈H₁₆F₃N₅O₂ 391.13, *m/z* found 392.0 [M+1]⁺. ¹HNMR (400MHz, DMSO-*d*₆) δ 8.75 (s, 1H), 8.08 (br d, *J* = 7.5 Hz, 1H), 7.63 - 7.45 (m, 4H), 7.27 - 7.15 (m, 3H), 6.26 (s, 1H), 5.08 (s, 2H), 4.73 (d, *J* = 7.0 Hz, 2H), 4.48 (d, *J* = 7.0 Hz, 2H).

[00600] **186-9**: LCMS (ESI): RT = 0.921 min, mass calc. for C₂₅H₂₂F₃N₅O₂ 481.17, *m/z* found 482.1 [M+1]⁺. ¹HNMR (400MHz, CHLOROFORM-*d*) δ 8.95 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H),

7.52 (br d, $J = 8.5$ Hz, 3H), 7.38 (t, $J = 7.8$ Hz, 1H), 7.29 - 7.21 (m, 7H), 7.04 (t, $J = 7.5$ Hz, 1H), 5.27 (s, 2H), 4.90 - 4.84 (m, 2H), 4.83 - 4.78 (m, 2H), 4.68 (s, 2H), 2.18 (s, 1H).

Example 180: 2-(5-(2-fluoro-6-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-ol (Compound 187)



Step 1: 2-fluoro-6-[4-(trifluoromethyl)anilino]benzonitrile

[00601] To a mixture of **187-1** (0.2 g, 1.4 mmol, 1.0 eq), **187-1b** (599.4 mg, 2.2 mmol, 0.3 uL, 1.5 eq) and Cs_2CO_3 (1.4 g, 4.4 mmol, 3.0 eq) in dioxane (10.0 mL) was added xantphos (255.0 mg, 0.4 umol, 0.3 eq) and $\text{Pd}(\text{OAc})_2$ (32.9 mg, 0.1 umol, 0.1 eq) in one portion under N_2 . The mixture was stirred at 100 °C for 16 h. TLC indicated **187-1** was consumed completely and two new spots formed. The reaction was clean according to TLC. The reaction mixture concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2) to give **187-2** (200 mg, 0.7 mmol, 48 % yield).

Step 2: 3-fluoro-2-(2H-tetrazol-5-yl)-N-[4-(trifluoromethyl)phenyl]aniline

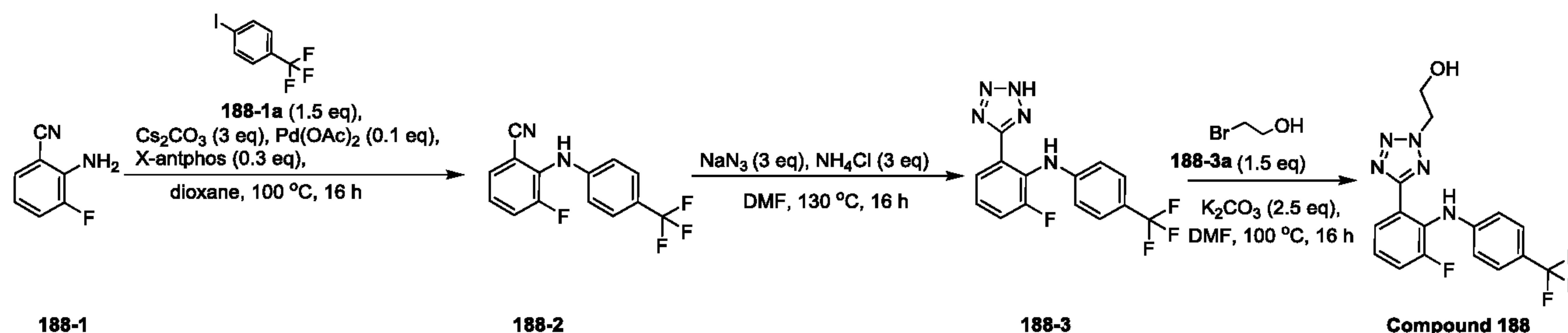
[00602] To a mixture of **187-2** (250.0 mg, 0.9 mmol, 1.0 eq) and azidosodium (289.9 mg, 4.46 mmol, 5.0 eq) in DMF (2.0 mL) was added NH_4Cl (238.61 mg, 4.46 mmol, 0.16 mL, 5.0 eq) in one portion under N_2 . The mixture was heated to 130 °C for 16 h. Several new peaks were shown on LC-MS and 35% of the desired compound was detected. The reaction mixture was added into aq.HCl (1.0 M) to give a suspension and extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2) to give **187-3** (50 mg, crude). LCMS (ESI): RT = 1.444 min, mass calc. for $\text{C}_{14}\text{H}_9\text{F}_4\text{N}_5$ 323.08, m/z found 323.9 $[\text{M}+\text{H}]^+$;

Step 3: 2-(5-(2-fluoro-6-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-ol

[00603] To a solution of **187-3** (20.0 mg, 61.8 umol, 1.0 eq) in DMF (2.0 mL) was added K_2CO_3 (17.1 mg, 0.1mmol, 2.0 eq) and **187-3a** (11.6 mg, 92.8 mmol, 6.5 uL, 1.5 eq). The mixture was stirred at 80 °C for 0.5 hr under microwave. Several new peaks were shown on LC-MS and 11% of the desired compound was detected. The mixture was purified by prep-HPLC to give **Compound 187** (2.07 mg, 5.64 umol, 9% yield). LCMS (ESI): RT = 0.781min, mass calc. for $\text{C}_{16}\text{H}_{13}\text{F}_4\text{N}_5\text{O}$

367.11, m/z found 367.8 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ (ppm) 9.04 (s, 1H), 7.54 (d, $J=8.5$ Hz, 2H), 7.37-7.29 (m, 2H), 7.25 (s, 1H), 6.84-6.77 (m, 1H), 4.94-4.85 (m, 2H), 4.33-4.19 (m, 2H), 2.40 (t, $J=6.3$ Hz, 1H).

Example 181: 2-(5-(3-fluoro-2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol (Compound 188)



Step 1: 3-fluoro-2-((4-(trifluoromethyl)phenyl)amino)benzonitrile

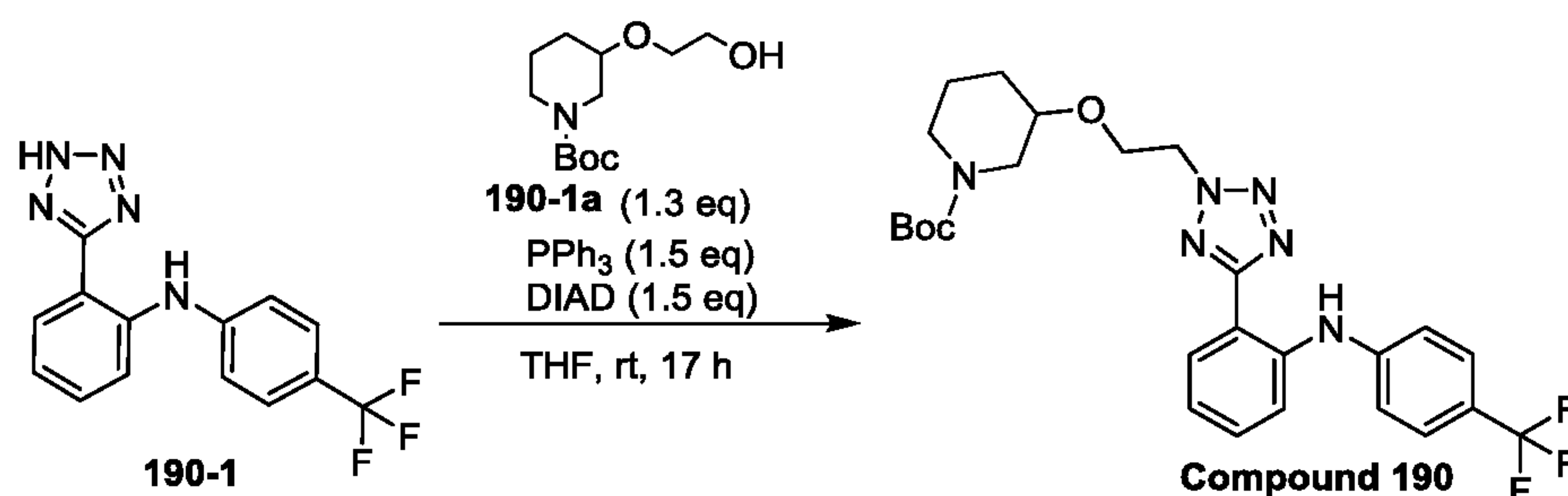
[00604] To a mixture of **188-1** (400 mg, 2.94 mmol, 1 *eq*), **188-1a** (1.20 g, 4.41 mmol, 0.648 mL, 1.5 *eq*) and Cs_2CO_3 (2.87 g, 8.82 mmol, 3 *eq*) in dioxane (10 mL) were added Xantphos (510.1 mg, 0.882 mmol, 0.3 *eq*) and $Pd(OAc)_2$ (66 mg, 0.294 mmol, 0.1 *eq*) in one portion under N_2 . The mixture was stirred at 100 °C for 16 hours. The crude LCMS showed no desired product was detected but TLC (Petroleum ether: Ethyl acetate = 10:1, R_f = 0.15, UV 254 nm) indicated compound **188-1** remained and one major new spot had formed. The reaction mixture was quenched with water (35 mL), and extracted with EtOAc (30 mL*3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give the **188-2** (239 mg, 0.853 mmol, 29.0% yield). ^1H NMR (400 MHz, $DMSO-d_6$) δ 9.01 (s, 1H), 7.69 - 7.76 (m, 2H), 7.53 (d, J = 8.53 Hz, 2H), 7.40 (td, J = 8.09, 4.89 Hz, 1H), 6.87 (d, J = 8.03 Hz, 2H).

Step 2: 2-fluoro-6-(2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00605] To a solution of **188-2** (139 mg, 0.496 mmol, 1 *eq*) in DMF (1 mL) was added NaN_3 (96.7 mg, 1.49 mmol, 3 *eq*) and NH_4Cl (79.6 mg, 1.49 mmol, 3 *eq*). The mixture was stirred at 130 °C for 16 hr. TLC (Petroleum ether: Ethyl acetate = 1:1, R_f = 0, UV 254 nm) indicated the compound **188-2** remained and one new spot had formed. The reaction mixture was combined with another batch, and the resulting reaction mixture was quenched with water (30 mL) and extracted with EtOAc (15 mL*3). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (Petroleum ether: Ethyl acetate = 1:1) to give **188-3** (118 mg, 0.365 mmol, 42.8% yield). ^1H NMR (400 MHz, $DMSO-d_6$) δ 10.22 (br s, 1H), 7.93 - 8.02 (m, 1H), 7.51 (s, 3H), 7.14 - 7.24 (m, 2H), 6.94 (s, 2H), 4.14 (br s, 1 H).

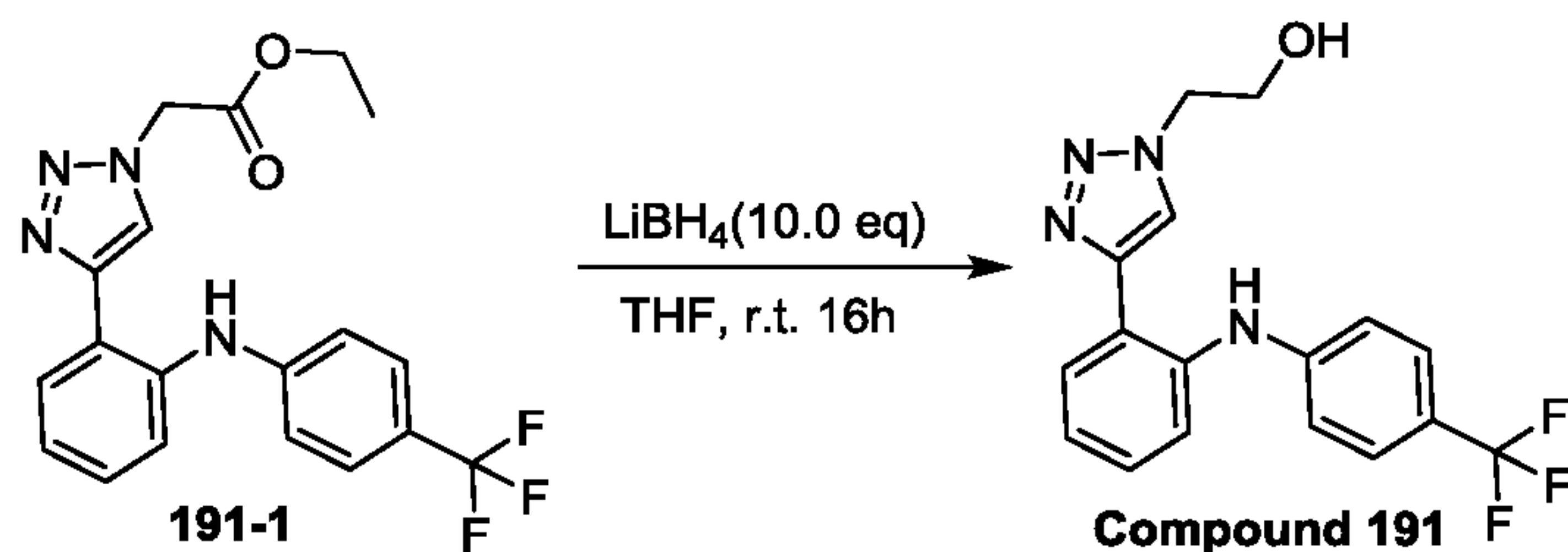
Step 3: 2-(5-(3-fluoro-2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol

[00606] To a solution of **188-3** (118 mg, 0.365 mmol, 1 *eq*) and **188-3a** (68.4 mg, 0.548 mmol, 38.9 μ L, 1.5 *eq*) in DMF (1 mL) was added K_2CO_3 (126.1 mg, 0.913 mmol, 2.5 *eq*). The mixture was stirred at 100 °C for 16 hr. The crude LCMS showed **188-3** was consumed completely and 45% of the desired product was detected. TLC (Petroleum ether: Ethyl acetate = 1:1, R_f = 0.46, UV 254 nm) indicated **188-3** remained and three new spots had formed. The reaction mixture was quenched with water (5 mL) and brine (5 mL) and extracted with EtOAc (10 mL*3). The combined organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give the crude product (around 100 mg), which was diluted with MeOH (1 mL) and water (5 mL). Most of the solvent was removed by reduced pressure and the remaining aqueous fraction was lyophilized to give the **Compound 188** (24.2 mg, 65.9 μ mol, 18.1% yield). LCMS (ESI): RT = 2.134 min, mass calc. for $C_{16}H_{13}F_4N_5O$ 367.11, m/z found 368.0 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.93 - 8.01 (m, 1H), 7.42 (d, J = 8.53 Hz, 2H), 7.28 - 7.39 (m, 2H), 6.84 (dd, J = 8.78, 2.01 Hz, 2H), 4.74 - 4.81 (m, 2H), 4.03 - 4.10 (m, 2H).

Example 182: tert-butyl 3-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethoxy)piperidine-1-carboxylate (Compound 190)

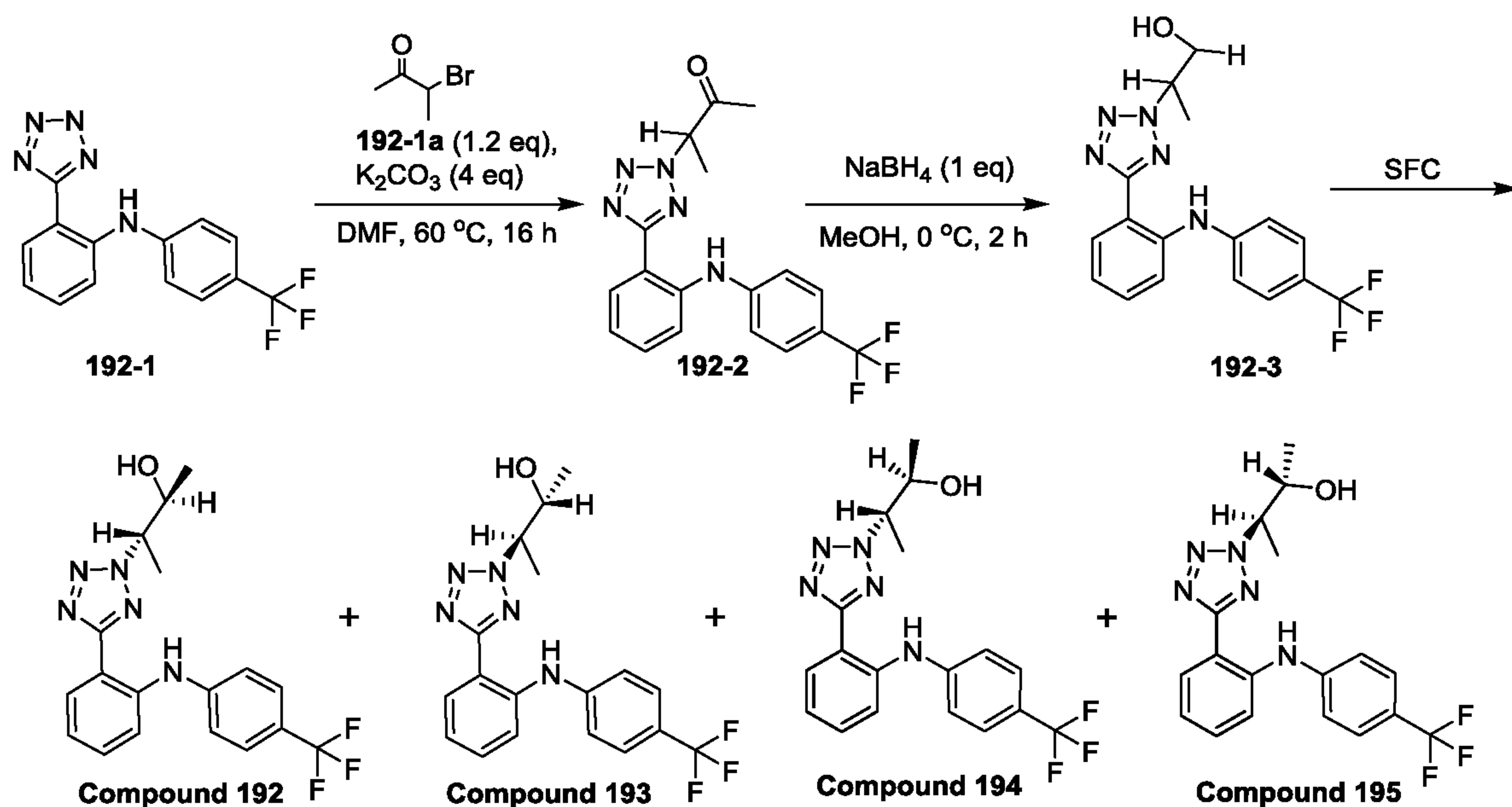
[00607] To a mixture of **190-1** (50 mg, 0.16 mmol, 1 *eq*), **190-1a** (52.2 mg, 0.21 mmol, 1.3 *eq*) and PPh_3 (64.4 mg, 0.25 mmol, 1.5 *eq*) in THF (0.5 mL) was added DIAD (49.7 mg, 0.25 mmol, 48 μ L, 1.5 *eq*). The mixture was degassed under vacuum and purged with N_2 for 3 times. The resulting mixture was stirred at 15 °C for 17 h. LCMS showed the reaction was completed. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC to provide **Compound 190** (3.49 mg, 6.6 μ mol, 4.0% yield), which was confirmed by LCMS and ^1H NMR. LCMS (ESI): RT = 0.964 min, mass calcd. For $C_{26}H_{31}F_3N_6O_3$ 532.24, m/z found 555.1 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 8.21 (dd, J = 1.4, 7.9 Hz, 1H), 7.54 (dd, J = 4.5, 8.0 Hz, 3H), 7.41 - 7.36 (m, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.07 - 7.02 (m, 1H), 4.87 (t, J = 5.4 Hz, 2H), 4.09 (t, J = 5.5 Hz, 2H), 3.59 (dd, J = 6.7, 10.2 Hz, 2H), 3.47 (tt, J = 3.7, 7.7 Hz, 1H), 3.06 (ddd, J = 3.5, 9.2, 13.2 Hz, 2H), 1.78 - 1.67 (m, 2H), 1.50 - 1.45 (m, 2H), 1.43 (s, 9H).

Example 183: 2-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-1,2,3-triazol-1-yl)ethan-1-ol (Compound 191)



[00608] To a solution of **191-1** (180 mg, 0.46 mmol, 1 eq) in THF (10 mL) was added LiBH_4 (100.5 mg, 4.6 mmol, 10 eq). The mixture was stirred at 10-15 °C for 16 hr. LC-MS showed reactant was consumed completely and one main peak with desired MS was detected. The reaction was quenched by adding sat, aq. NH_4Cl (10 mL) and stirred for 30 min. Then the mixture was extracted with EtOAc (10 mL*2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated to give a residue. The residue was purified by prep-HPLC to give compound **Compound 191** (81.6 mg, 0.21 mmol, 46.0% yield). LCMS (ESI): RT = 1.168 min, mass calc. for $\text{C}_{17}\text{H}_{15}\text{F}_3\text{N}_4\text{O}$ 348.12, m/z found 349.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.00 (s, 1H), 8.39 (s, 1H), 7.91 (dd, $J = 1.3, 7.8$ Hz, 1H), 7.50 (d, $J = 8.5$ Hz, 2H), 7.46 - 7.42 (m, 1H), 7.38 - 7.32 (m, 1H), 7.19 (t, $J = 7.0$ Hz, 1H), 7.06 (d, $J = 8.5$ Hz, 2H), 4.44 (t, $J = 5.4$ Hz, 2H), 3.78 (t, $J = 5.4$ Hz, 2H).

Example 184: (2S,3S)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)butan-2-ol (Compound 192), (2R,3R)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)butan-2-ol (Compound 193), (2R,3S)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)butan-2-ol (Compound 194), and (2S,3R)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)butan-2-ol (Compound 195)



Step 1: 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)butan-2-one

[00609] To a solution of **192-1** (300 mg, 0.98 mmol, 1 *eq*) and **192-1a** (148.4 mg, 0.98 mmol, 1 *eq*) in DMF (3 mL) was added K₂CO₃ (543.3 mg, 3.93 mmol, 4 *eq*). The mixture was stirred at 25-30 °C for 16 h. The crude LCMS showed 24% of **192-1** was remained and 53% of the desired product was detected. **192-1a** (29.7 mg, 0.20 mmol, 0.2 *eq*) was added, the mixture was stirred at 25 °C for 16 h. The crude LCMS showed 21% of **192-1** was remained and 41% of the desired product was detected. The reaction mixture was quenched by water (25 mL), and then extracted with EtOAc (20 mL * 3). The combined organic layer was washed with brine (25 mL * 2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give the **192-2** (113 mg, 0.30 mmol, 30.6% yield). ¹H NMR (400 MHz, CDCl₃) δ 9.02 (br s, 1H), 8.22 (dd, *J* = 7.94, 1.54 Hz, 1H), 7.55 (d, *J* = 7.72 Hz, 4H), 7.36 - 7.43 (m, 1H), 7.30 (d, *J* = 8.38 Hz, 2H), 7.06 (t, *J* = 7.50 Hz, 1H), 5.62 (q, *J* = 7.28 Hz, 1H), 2.13 (s, 3H), 1.97 (d, *J* = 7.28 Hz, 3H).

Step 2: (2S,3S)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)butan-2-ol, (2R,3R)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)butan-2-ol, (2R,3S)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)butan-2-ol, and (2S,3R)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)butan-2-ol

[00610] A mixture of **192-2** (181 mg, 0.48 mmol, 1 *eq*) in MeOH (2 mL) was cooled to 0 °C, then NaBH₄ (21.9 mg, 0.58 mmol, 1.2 *eq*) was added, the mixture was stirred at 0 °C for 2 h. The crude LCMS showed **192-2** was consumed completely and 45% the desired product was detected. The reaction mixture was combined with another batch, and the mixture was quenched by water (15 mL), extracted with EtOAc (15 mL * 3). The combined organic layer was dried over with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the residue as yellow oil (180 mg). The residue was purified by prep-HPLC to give an impure product (88 mg), which further purified by SFC to give **Compound 192** (9.0 mg, 22.7 μmol, 17.0% yield, 99.1% chiral purity), **Compound 194** (4.3 mg, 11.5 μmol, 8.6% yield, 99.9% chiral purity), **Compound 195** (2.3 mg, 6.2 μmol, 4.6% yield, 99.5% chiral purity), and **Compound 193** (10.6 mg, 27.0 μmol, 20.2% yield, 99.6% chiral purity).

[00611] Compound 192: LCMS (ESI): RT = 2.382 min, mass calc. for C₁₈H₁₈F₃N₅O 377.15, m/z found 378.0 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 8.16 (dd, *J* = 7.91, 1.38 Hz, 1H), 7.49 - 7.58 (m, 3H), 7.44 (td, *J* = 7.78, 1.51 Hz, 1H), 7.25 (d, *J* = 8.53 Hz, 2H), 7.08 - 7.15 (m, 1H), 4.92 - 4.99 (m, 1H), 4.20 (quin, *J* = 6.15 Hz, 1H), 1.72 (d, *J* = 7.03 Hz, 3H), 1.11 (d, *J* = 6.53 Hz, 3H).

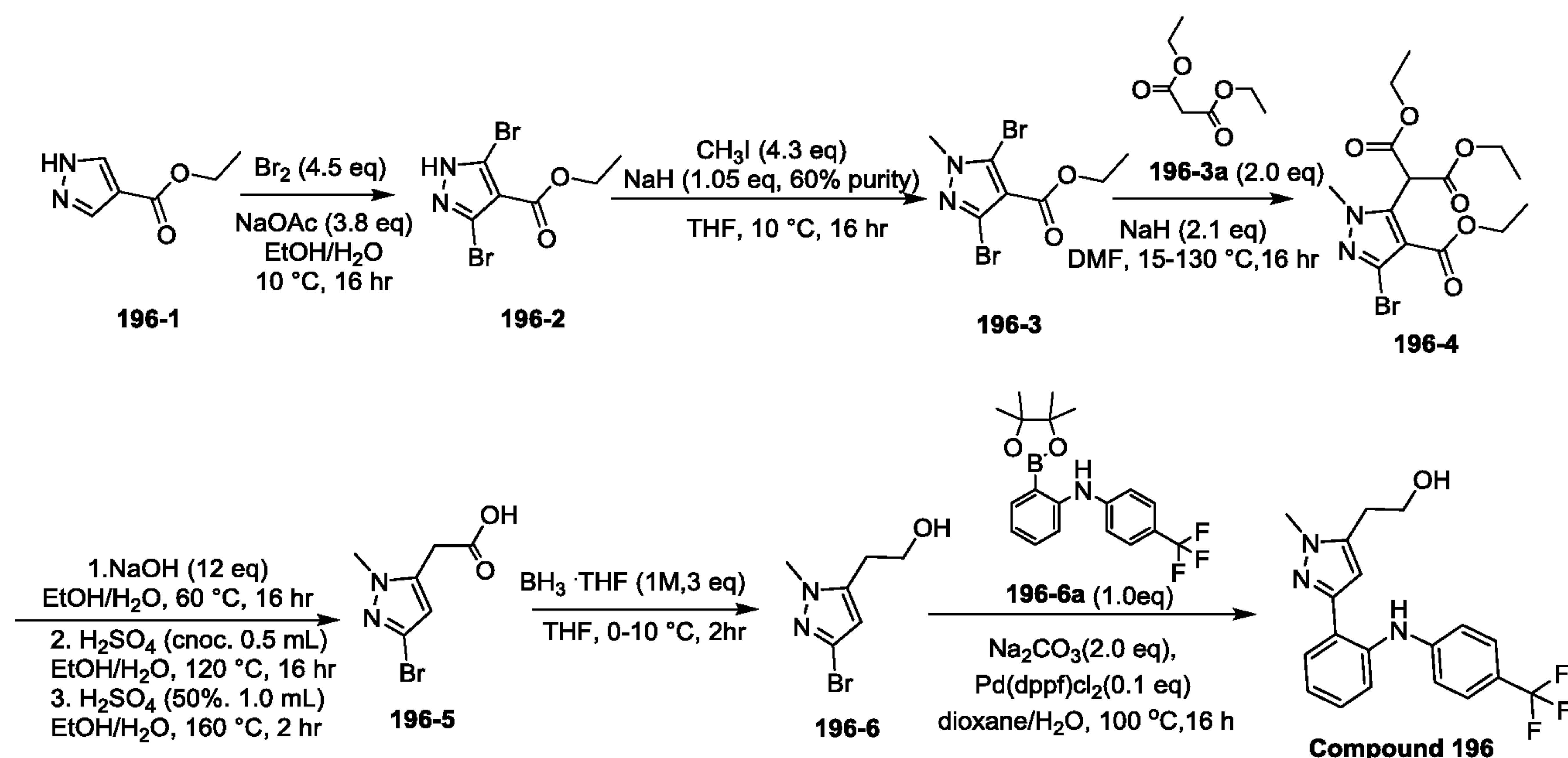
[00612] Compound 193: LCMS (ESI): RT = 2.381 min, mass calc. for C₁₈H₁₈F₃N₅O 377.15, m/z found 378.0 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 8.16 (dd, *J* = 7.91, 1.38 Hz, 1H), 7.49 - 7.59

(m, 3H), 7.44 (td, $J = 7.78, 1.51$ Hz, 1H), 7.25 (d, $J = 8.53$ Hz, 2H), 7.08 - 7.15 (m, 1H), 4.93 - 5.00 (m, 1H), 4.20 (quin, $J = 6.21$ Hz, 1H), 1.72 (d, $J = 7.03$ Hz, 3H), 1.11 (d, $J = 6.53$ Hz, 3H).

[00613] Compound 194: LCMS (ESI): RT = 2.350 min, mass calc. for $C_{18}H_{18}F_3N_5O$ 377.15, m/z found 378.0 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.16 (dd, $J = 7.78, 1.00$ Hz, 1H), 7.48 - 7.62 (m, 3H), 7.37 - 7.46 (m, 1H), 7.26 (d, $J = 8.53$ Hz, 2H), 7.09 (t, $J = 7.53$ Hz, 1H), 4.92 - 4.98 (m, 1H), 4.18 (quin, $J = 6.59$ Hz, 1H), 1.64 (d, $J = 6.78$ Hz, 3H), 1.28 (d, $J = 6.27$ Hz, 3H).

[00614] Compound 195: LCMS (ESI): RT = 2.355 min, mass calc. for $C_{18}H_{18}F_3N_5O$ 377.15, m/z found 378.0 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.16 (dd, $J = 7.78, 1.51$ Hz, 1H), 7.49 - 7.60 (m, 3H), 7.42 (td, $J = 7.78, 1.76$ Hz, 1H), 7.26 (d, $J = 8.53$ Hz, 2H), 7.06 - 7.13 (m, 1H), 4.91 - 4.98 (m, 1H), 4.18 (quin, $J = 6.59$ Hz, 1H), 1.64 (d, $J = 6.78$ Hz, 3H), 1.28 (d, $J = 6.53$ Hz, 3H).

Example 185: 2-(1-methyl-3-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-5-yl)ethan-1-ol (Compound 196)



Step 1: ethyl 3,5-dibromo-1H-pyrazole-4-carboxylate

[00615] To the solution of **196-1** (1 g, 7.1 mmol, 1 eq) in EtOH (6 mL) and H_2O (10 mL) was added NaOAc (2.2 g, 27.1 mmol, 3.8 eq) and Br_2 (5.1 g, 32.1 mmol, 1.7 mL, 4.5 eq). The mixture was stirred at 10 °C for 16 hr. The reaction was monitored by TLC. To the reaction mixture was added sodium thiosulfate (2 g), and the solvent was evaporated under reduced pressure. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over Na_2SO_4 . The solvent was evaporated under reduced pressure to give **196-2** (1.8 g, crude).

Step 2: ethyl 3,5-dibromo-1-methyl-1H-pyrazole-4-carboxylate

[00616] To the solution of **196-2** (1.8 g, 6.0 mmol, 1 *eq*) in THF (20 mL) was added NaH (254 mg, 6.4 mmol, 60% purity, 1.05 *eq*) at 0 °C. The mixture was stirred for 1 hr at 0 °C under N₂ atmosphere. Then CH₃I (3.7 g, 26 mmol, 1.6 mL, 4.30 *eq*) was added to the mixture. The solution was stirred at 10 °C for 16 hr. The reaction was monitored by LCMS. The reaction solution was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂) to give **196-3** (700 mg, 2.2 mmol, 37% yield).

Step 3: diethyl 2-(3-bromo-4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-5-yl)malonate

[00617] To the solution of **196-3a** (360 mg, 2.3 mmol, 0.3 mL, 2.0 *eq*) in DMF (2 mL) was added NaH (94 mg, 2.4 mmol, 60% purity, 2.1 *eq*) at 0 °C. The mixture was stirred for 30 min at 15 °C. Then **196-3** (350 mg, 1.1 mmol, 1 *eq*) was added to the solution. The mixture was stirred at 130 °C for 16 hr. The reaction was monitored by LCMS. The reaction solution was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂) to give **196-4** (110 mg, 0.28 mmol, 25% yield).

Step 4: 2-(3-bromo-1-methyl-1H-pyrazol-5-yl)acetic acid

[00618] To the solution of **196-4** (110 mg, 0.28 mmol, 1 *eq*) in EtOH (1 mL) and H₂O (1 mL) was added NaOH (134 mg, 3.4 mmol, 12 *eq*). The mixture was stirred at 60 °C for 16 hr. Then H₂SO₄ (920 mg, 9.4 mmol, 500 uL, 33 *eq*) was added to the mixture. The solution was stirred at 120 °C for 16 hr. Then the mixture was concentrated under reduced pressure. The residue was washed with H₂O (10 mL*5). The combined organic layer was dried with Na₂SO₄ and concentrated under reduced pressure. Then H₂SO₄ (920 mg, 4.7 mmol, 1 mL, 50% purity, 16.7 *eq*) was added to the mixture. The mixture was stirred at 160 °C for 2 hr. The reaction was monitored by LCMS. The reaction solution was dropped into ice (5g). The mixture was extracted with EtOAc (5 mL*3). The combined organic layer was dried with Na₂SO₄ and concentrated under reduced pressure to give **196-5** (70 mg, crude).

Step 5: 2-(3-bromo-1-methyl-1H-pyrazol-5-yl)ethanol

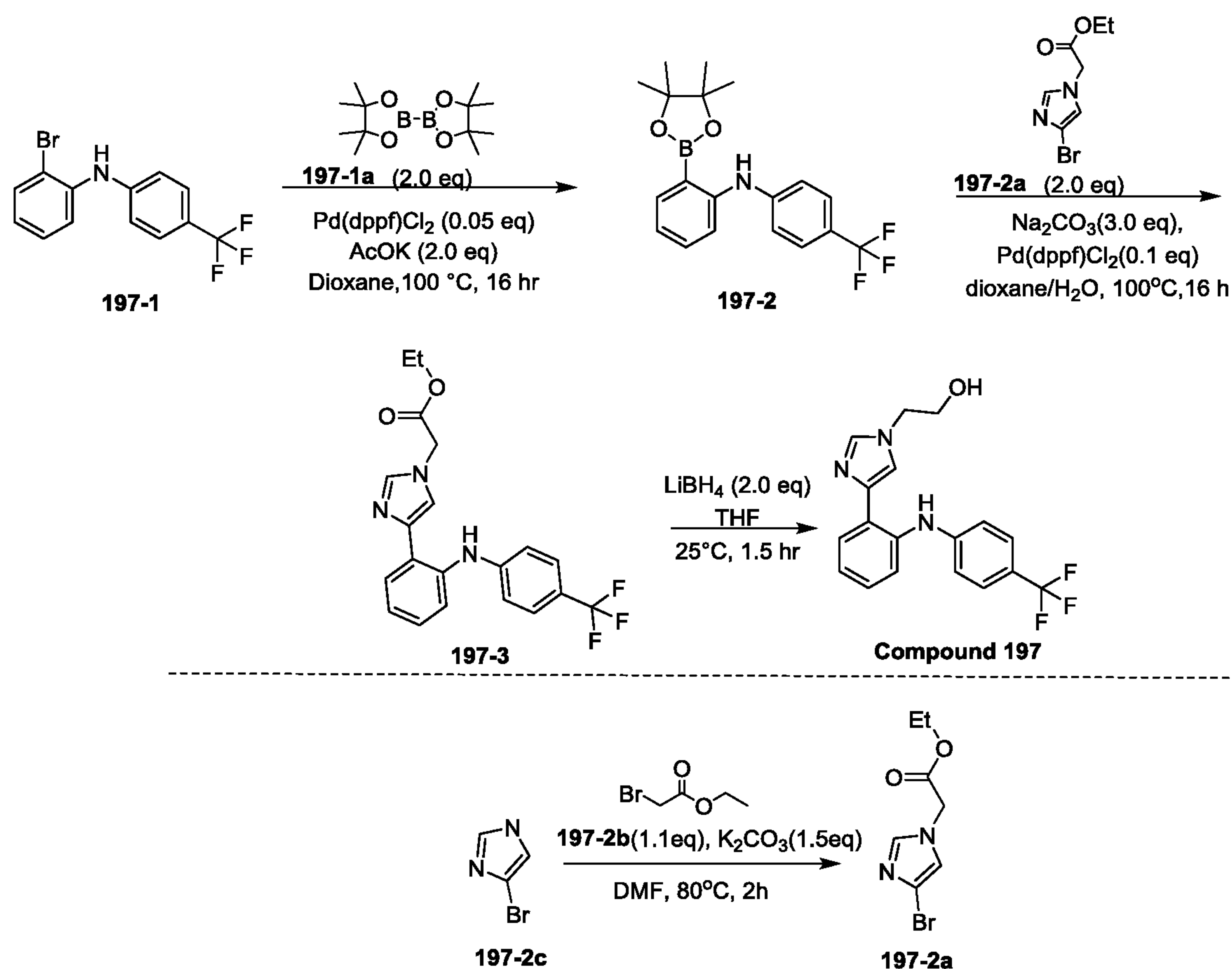
[00619] To the solution of **196-5** (70 mg, 0.31 mmol, 1 *eq*) in THF (2 mL) was added BH₃·THF (1 M, 1 mL, 3 *eq*) slowly at 0 °C. The mixture was warmed up to 10 °C and stirred for 2 hr at 10 °C. The reaction was monitored by LCMS. The reaction solution was concentrated under reduced pressure. The residue was dissolved in EtOAc (10 mL). The solution was washed with H₂O (10 mL). The organic layer was dried with Na₂SO₄ and concentrated under reduced pressure to give **196-6** (55 mg, 0.27 mmol, 84% yield).

Step 6: 2-(1-methyl-3-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-5-yl)ethanol

[00620] To the solution of **196-6** (55 mg, 0.27 mmol, 1 *eq*) in dioxane (3 mL) and H₂O (0.15 mL) was added **196-6a** (97 mg, 0.27 mmol, 1.0 *eq*) Na₂CO₃ (57 mg, 0.54 mmol, 2 *eq*) and Pd(dppf)Cl₂

(20 mg, 27 μmol , 0.1 *eq*). The mixture was stirred at 100 °C for 16 hr. The reaction was monitored by LCMS. The reaction solution was filtered. The residue was purified by Prep-HPLC to give **Compound 196** (5.3 mg, 14.4 μmol , 5.4% yield). LCMS (ESI): RT = 0.845 min, mass calcd. for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{N}_3\text{O}$ 361.14, m/z found 362.0 $[\text{M}+\text{H}]^+$, ^1H NMR (400 MHz, CDCl_3) δ 9.71 (s, 1H), 7.61 (dd, J = 1.5, 7.8 Hz, 1H), 7.53 - 7.46 (m, 3H), 7.27 - 7.20 (m, 3H), 7.01 - 6.93 (m, 1H), 6.46 (s, 1H), 3.96 (t, J = 6.4 Hz, 2H), 3.90 (s, 3H), 2.95 (t, J = 6.4 Hz, 2H).

Example 186: 2-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-imidazol-1-yl)ethan-1-ol (Compound 197)



Step 1: 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-[4-(trifluoromethyl)phenyl]aniline [00621] To a solution of **197-1** (2.0 g, 6.3 mmol, 1.0 eq) and **197-1a** (3.2 g, 12.6 mmol, 2.0 eq) in dioxane (40 mL) was added Pd(dppf)Cl_2 (462.9 mg, 0.6 mmol, 0.1 eq) and AcOK (1.2 g, 12.6 mmol, 2.0 eq). The mixture was stirred at 100 °C for 16 h under N_2 atmosphere. LC-MS showed **1** was consumed completely. Several new peaks were shown on LC-MS and 69% of desired compound was detected. The reaction mixture was filtered to give a residue. The residue was purified by column chromatography (SiO_2) to give **197-2** (2.0 g, crude). LCMS (ESI): RT = 0.998 min, mass calc. for $\text{C}_{19}\text{H}_{21}\text{BF}_3\text{NO}_2$ 363.16, m/z found 364.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 7.9 (s, 1H), 7.77 (d, J = 7.3 Hz, 1H), 7.50 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 3.3 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 6.93-6.89 (d, J = 4.0, 7.8 Hz, 1H), 1.36 (s, 12H).

Step 2: ethyl 2-(4-bromoimidazol-1-yl)acetate

[00622] To a solution of **197-2c** (1.0 g, 6.8 mmol, 1.0 eq) in DMF (10.0 mL) was added K₂CO₃ (1.4 g, 10.2 mmol, 1.5 eq) and **197-2b** (1.2 g, 7.4 mmol, 0.8 mL, 1.1 eq). The mixture was stirred at 80 °C for 2 h. TLC indicated 20% of **197-1** was remained, and one major new spot with lower polarity was detected. The reaction mixture was diluted with H₂O (20.0 mL), extracted with EtOAc (10.0 mL * 3). The combined organic layers were washed with brine (30.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂) to give **197-2a** (500.0 mg, 2.1 mmol, 31% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.38 (s, 1H), 6.94 (s, 1H), 4.69-4.61 (m, 2H), 4.30-4.20 (m, 3H), 1.35-1.26 (m, 3H).

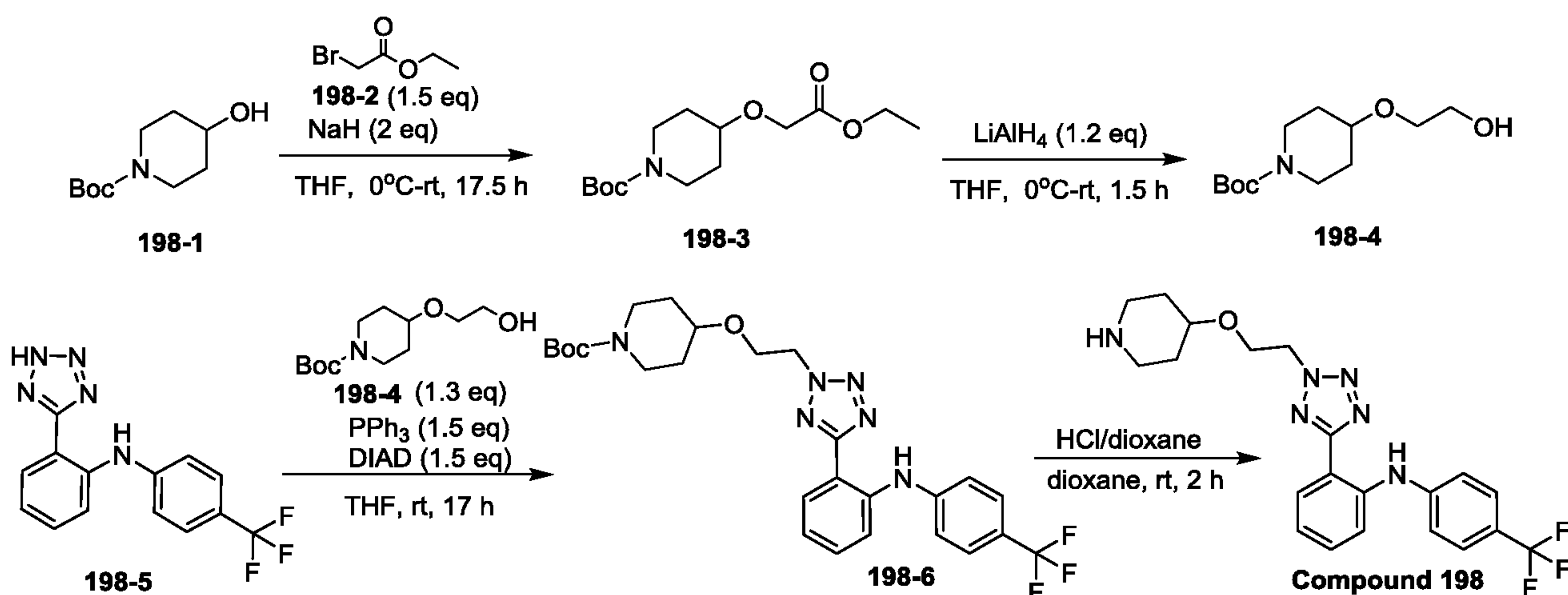
Step 3: ethyl 2-[4-[2-[4-(trifluoromethyl)anilino]phenyl]imidazol-1-yl]acetate

[00623] A mixture of **197-2** (100.0 mg, 0.3 mmol, 1.0 eq), **197-2a** (128.3 mg, 0.6 mmol, 2.0 eq), Na₂CO₃ (87.5 mg, 0.8 mmol, 3.0 eq) and Pd(dppf)Cl₂ (20.1 mg, 27.5 μmol, 0.1 eq) in dioxane (3.0 mL) and H₂O (0.5 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 19 h under N₂ atmosphere. LC-MS showed 33% of **197-2** was remained. Several new peaks were shown on LC-MS and 22% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂) to give **197-3** (40 mg, 0.1 mmol, 37% yield). LCMS (ESI): RT = 0.998 min, mass calc. for C₂₀H₁₈F₃N₃O₂ 389.14, m/z found 390.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.58 (s, 1H), 7.53-7.49 (m, 2H), 7.46 (d, *J*=9.3 Hz, 3H), 7.22 (d, *J*=10.0 Hz, 5H), 6.97-6.91 (m, 1H), 4.74 (s, 2H), 4.27 (q, *J*=7.1 Hz, 2H), 1.31 (t, *J*=7.2 Hz, 3H).

Step 4: 2-[4-[2-[4-(trifluoromethyl)anilino]phenyl]imidazol-1-yl]ethanol

[00624] To a solution of **197-3** (40.0 mg, 0.1 mmol, 1.0 eq) in THF (2.0 mL) was added LiBH₄ (4.4 mg, 0.2 mmol, 2.0 eq) at 25 °C. The mixture was stirred at 25 °C for 1.5 h. LC-MS showed **197-3** was consumed completely. Several new peaks were shown on LC-MS and 82% of desired compound was detected. The reaction mixture was quenched by addition a.q NH₄Cl (2.0 mL) and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 197** (2.52 mg, 7 μmol, 7% yield). LCMS (ESI): RT = 0.661 min, mass calc. for C₁₈H₁₆F₃N₃O 347.12, m/z found 347.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.63 (s, 1H), 7.54-7.42 (m, 4H), 7.26 (s, 1H), 7.24-7.18 (m, 3H), 6.96 (t, *J* = 7.0 Hz, 1H), 4.13 (t, *J* = 5.0 Hz, 2H), 3.97-3.91 (m, 2H).

Example 187: 2-(2-(2-(piperidin-4-yloxy)ethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 198)



Step 1: tert-butyl 4-(2-ethoxy-2-oxoethoxy)piperidine-1-carboxylate

[00625] To a mixture of **198-1** (2 g, 9.94 mmol, 1 *eq*) in THF (20 mL) was added NaH (794.9 mg, 19.87 mmol, 60% purity, 2 *eq*) at 0 °C. The mixture was stirred at 0 °C for 0.5 h. Then **198-2** (2.49 g, 14.9 mmol, 1.7 mL, 1.5 *eq*) was added at 0 °C. The resulted mixture was stirred at 15 °C for 17 h. TLC showed there's a main new spot with lower polarity, and the starting material was remained. The mixture was diluted with water (30 mL), extracted with EA (20 mL *3). The organic layer was dried over anhydrous Na₂SO₄, concentrated in vacuum. The residue was purified by silica gel chromatography. **198-3** (500 mg, crude) was obtained, which was checked by ¹H NMR. ¹H NMR (400 MHz, CDCl₃) δ 4.22 (q, *J* = 7.3 Hz, 2H), 4.12 (s, 2H), 3.85 - 3.74 (m, 2H), 3.59 - 3.53 (m, 1H), 3.08 (ddd, *J* = 3.3, 9.4, 13.2 Hz, 2H), 1.91 - 1.82 (m, 2H), 1.59 - 1.52 (m, 2H), 1.46 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H).

Step 2: tert-butyl 4-(2-hydroxyethoxy)piperidine-1-carboxylate

[00626] To a mixture of LiAlH₄ (79.2 mg, 2.09 mmol, 1.2 *eq*) in THF (4 mL) was added a solution of **198-3** (500 mg, 1.74 mmol, 1 *eq*) in THF (6 mL) drop wise at 0 °C. The resulted mixture was stirred at 0 °C for 0.5 h, 15 °C for 1 h. TLC showed the reaction was completed. Water (2.1 mL) was added to the mixture, and the mixture was stirred at 15 °C for 3 min. NaOH (25% aqueous, 2.1 mL) was added, and the mixture was stirred at 15 °C for 5 min. Then water (2.1 mL) was added, and the mixture was stirred at 15 °C for 5 min. MgSO₄ (1 g) was added, and the mixture was filtered. The solid was washed with EA (10 mL), the filtrate was concentrated in vacuum. The residue was purified by silica gel chromatography. **198-4** (320 mg, 1.3 mmol, 75.0% yield) was obtained, which was confirmed by ¹H NMR. ¹H NMR (400 MHz, CDCl₃) δ 3.90 - 3.77 (m, 2H), 3.76 - 3.72 (m, 2H), 3.61 - 3.56 (m, 2H), 3.54 - 3.49 (m, 1H), 3.08 (ddd, *J* = 3.3, 9.5, 13.2 Hz, 2H), 1.86 (dd, *J* = 3.1, 7.1 Hz, 2H), 1.57 - 1.50 (m, 2H), 1.46 (s, 9H).

Step 3: tert-butyl 4-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethoxy)piperidine-1-carboxylate

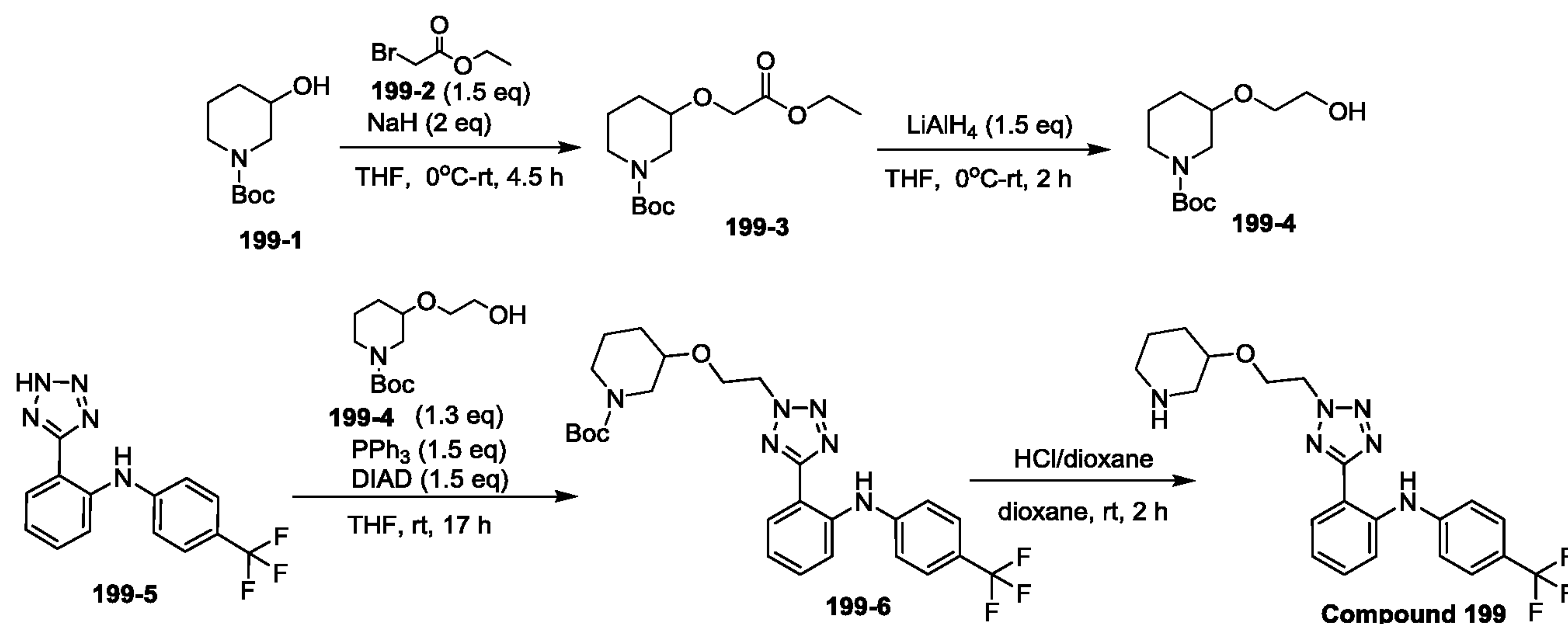
[00627] To a mixture of **198-5** (150 mg, 0.49 mmol, 1 *eq*), **198-4** (156.7 mg, 0.64 mmol, 1.3 *eq*) and PPh₃ (193.3 mg, 0.74 mmol, 1.5 *eq*) in THF (1 mL) was added DIAD (149.0 mg, 0.74 mmol, 0.14 mL, 1.5 *eq*). The mixture was degassed under vacuum and purged with N₂ for 3 times. The resulting mixture was stirred at 15 °C for 17 h. LCMS showed 26% desired compound was detected. The mixture was concentrated in vacuum. The residue was purified by silica gel chromatography. **198-6** (100 mg, 0.16 mmol, 32.5% yield) was obtained, which was checked by LCMS.

Step 4: 2-(2-(2-(piperidin-4-yloxy)ethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00628] To a mixture of **198-6** (80 mg, 0.15 mmol, 1 *eq*) in dioxane (2 mL) was added HCl/dioxane (4 M, 4.8 mL, 127.81 *eq*). The resulting mixture was stirred at 15 °C for 2 h. LCMS showed the reaction was complete. The mixture was concentrated in vacuum. The residue was purified by pre-HPLC. This compound was checked by HPLC and purified by pre-HPLC.

Compound 198 (2.69 mg, 4.9 μmol, 3.3% yield, TFA) was obtained, which was confirmed by LCMS and ¹H NMR. LCMS (ESI): RT = 0.766 min, mass calcd. for C₂₁H₂₃F₃N₆O 432.19, m/z found 433.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.80 (s, 1H), 8.43 - 8.16 (m, 2H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.59 - 7.53 (m, 3H), 7.53 - 7.47 (m, 1H), 7.25 - 7.17 (m, 3H), 4.92 (t, *J* = 4.9 Hz, 2H), 3.99 (t, *J* = 4.9 Hz, 2H), 3.58 (td, *J* = 3.5, 6.8 Hz, 1H), 3.00 - 2.91 (m, 2H), 2.87 (dt, *J* = 2.1, 3.8 Hz, 2H), 1.85 - 1.76 (m, 2H), 1.56 - 1.45 (m, 2H).

Example 188: 2-(2-(2-(piperidin-3-yloxy)ethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 199)



Step 1: tert-butyl 3-(2-ethoxy-2-oxoethoxy)piperidine-1-carboxylate

[00629] To a mixture of **199-1** (2.0 g, 9.94 mmol, 1 *eq*) in THF (20 mL) was added NaH (794.9 mg, 19.88 mmol, 60% purity, 2 *eq*) at 0 °C. The mixture was stirred at 0 °C for 0.5 h. Then **199-2**

(2.49 g, 14.91 mmol, 1.7 mL, 1.5 *eq*) was added at 0 °C. The resulted mixture was stirred at 15 °C for 17 h. TLC showed there's a new spot with lower polarity, and the start material was remained. The mixture was diluted with water (30 mL) and extracted with EA (20 mL *3). The organic layer was dried over anhydrous Na₂SO₄, concentrated in vacuum. The residue was purified by silica gel chromatography. **199-3** (500 mg, crude) was obtained, which was checked by ¹H NMR. ¹H NMR (400 MHz, CDCl₃) δ 4.22 (q, *J* = 6.9 Hz, 2H), 4.19 - 4.09 (m, 2H), 3.62 (td, *J* = 4.7, 13.4 Hz, 1H), 3.41 (dt, *J* = 4.0, 7.9 Hz, 1H), 3.16 - 2.94 (m, 2H), 2.04 - 1.94 (m, 1H), 1.82 - 1.72 (m, 1H), 1.64 - 1.54 (m, 1H), 1.46 (s, 9H), 1.43 - 1.36 (m, 1H), 1.33 - 1.23 (m, 4H).

Step 2: tert-butyl 3-(2-hydroxyethoxy)piperidine-1-carboxylate

[00630] To a mixture of LiAlH₄ (79.24 mg, 2.09 mmol, 1.2 *eq*) in THF (4 mL) was added a solution of **199-3** (500.0 mg, 1.74 mmol, 1 *eq*) in THF (6 mL) drop wise at 0 °C. The resulted mixture was stirred at 0 °C for 0.5 h, 15 °C for 1 h. TLC showed the reaction was completed. Water (2.1 mL) was added to the mixture, and the mixture was stirred at 15 °C for 3 min. NaOH (25% aqueous, 2.1 mL) was added, and the mixture was stirred at 15 °C for 5 min. Then water (2.1 mL) was added, and the mixture was stirred at 15 °C for 5 min. MgSO₄ (1 g) was added, and the mixture was filtered. The solid was washed with EA (10 mL), the filtrate was concentrated in vacuum. The residue was purified by silica gel chromatography. **199-4** (380 mg, 1.55 mmol, 89.0% yield) was obtained, which was confirmed by ¹H NMR. ¹H NMR (400 MHz, CDCl₃) δ 3.74 - 3.68 (m, 2H), 3.68 - 3.58 (m, 3H), 3.37 (td, *J* = 1.6, 3.3 Hz, 2H), 3.32 - 3.10 (m, 2H), 1.93 - 1.84 (m, 1H), 1.81 - 1.72 (m, 1H), 1.69 - 1.50 (m, 2H), 1.46 (s, 9H).

Step 3: tert-butyl 3-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethoxy)piperidine-1-carboxylate

[00631] To a mixture of **199-5** (150 mg, 0.49 mmol, 1 *eq*), **199-4** (156.7 mg, 0.64 mmol, 1.3 *eq*) and PPh₃ (193.3 mg, 0.74 mmol, 1.5 *eq*) in THF (1 mL) was added DIAD (149.1 mg, 0.74 mmol, 0.14 mL, 1.5 *eq*). The mixture was degassed under vacuum and purged with N₂ for 3 times. The resulting mixture was stirred at 15 °C for 17 h. LCMS showed 26% desired compound was detected. The mixture was concentrated in vacuum. The residue was purified by silica gel chromatography. **199-6** (60 mg, 0.11 mmol, 22.2% yield) was obtained, which was checked by LCMS.

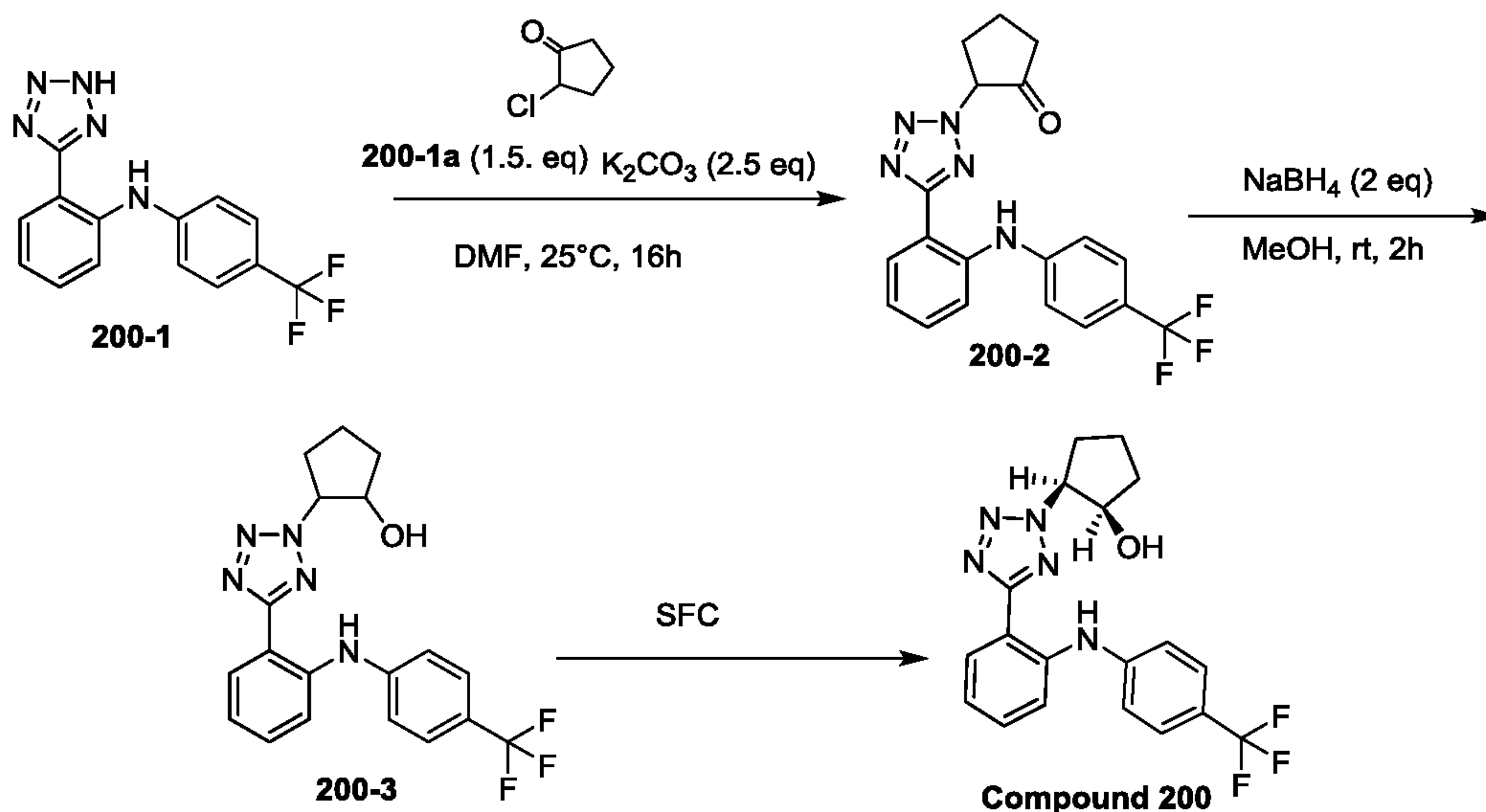
Step 4: 2-(2-(2-(piperidin-3-yloxy)ethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00632] To a mixture of **199-6** (60 mg, 0.11 mmol, 1 *eq*) in dioxane (2 mL) was added HCl/dioxane (4 M, 3 mL, 106.51 *eq*). The resulting mixture was stirred at 15 °C for 2 h. LCMS showed the reaction was complete. The mixture was concentrated in vacuum. The residue was

purified by pre-HPLC. The compound was checked by HPLC and purified by pre-HPLC.

Compound 199 (2.70 mg, 4.9 μ mol, 4.4% yield, TFA) was obtained, which was confirmed by LCMS and ^1H NMR. LCMS (ESI): RT = 0.774 min, mass calcd. for $\text{C}_{21}\text{H}_{23}\text{F}_3\text{N}_6\text{O}$ 432.19, m/z found 433.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.80 (s, 1H), 8.64 - 8.20 (m, 2H), 8.06 (dd, J = 1.1, 7.9 Hz, 1H), 7.58 - 7.53 (m, 3H), 7.53 - 7.47 (m, 1H), 7.25 - 7.17 (m, 3H), 4.93 (t, J = 4.8 Hz, 2H), 4.05 (t, J = 5.1 Hz, 2H), 3.68 - 3.63 (m, 1H), 3.08 (dd, J = 1.5, 13.1 Hz, 1H), 2.97 - 2.87 (m, 3H), 1.70 - 1.61 (m, 2H), 1.54 - 1.42 (m, 2H).

Example 189: (1R,2S)-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)cyclopentan-1-ol (Compound 200)



Step 1: 2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]cyclopentanone

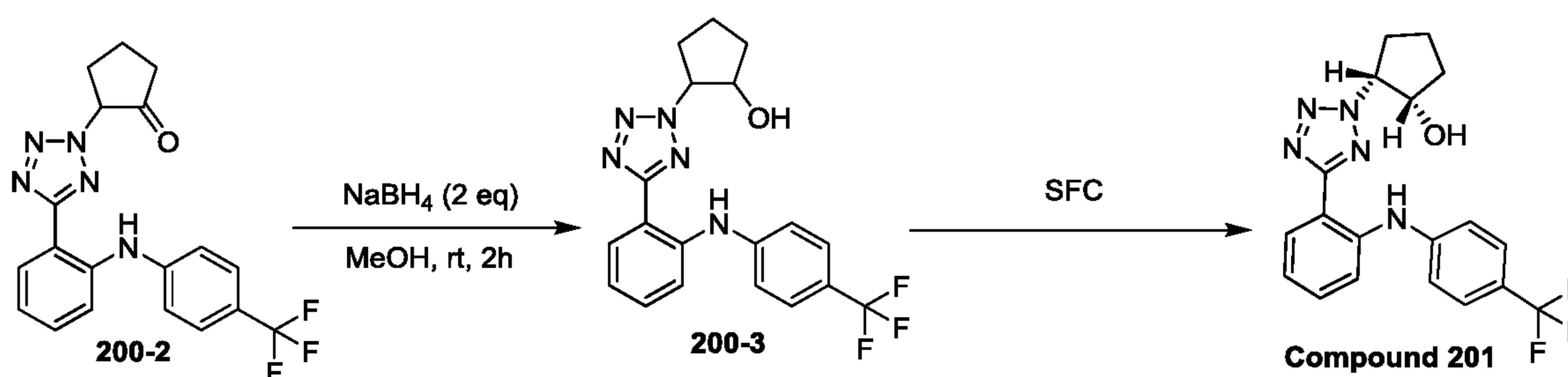
[00633] To a mixture of **200-1** (1.5 g, 4.91 mmol, 1 *eq*) and K_2CO_3 (2.72 g, 19.66 mmol, 4 *eq*) in DMF (1.5 mL) was added **200-1a** (2.04 g, 17.20 mmol, 1.71 mL, 3.5 *eq*) in one portion. The resulting mixture was stirred at 25 °C for 16 h. LCMS showed 24% of the starting material was remained and 44% of desired product was formed. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL * 5). The combined organic layers were dried with anhydrous Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2). LCMS confirmed **200-2** (260 mg, 0.577 mmol, 11.8% yield). LCMS (ESI): RT = 0.876 min, mass calcd. For $\text{C}_{19}\text{H}_{16}\text{F}_3\text{N}_5\text{O}$, 387.13 m/z found 388.1 $[\text{M}+\text{H}]^+$.

Step 2: (1R,2S)-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]cyclopentanol

[00634] To a solution of **200-2** (260 mg, 0.67 mmol, 1 *eq*) in MeOH (3 mL) was added NaBH_4 (51 mg, 1.34 mmol, 2 *eq*) in one portion at 20 °C under N_2 . The mixture was stirred at 20 °C for 2 h. LCMS showed the starting material was consumed completely and one main peak with desired MS was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with water (15 mL) and extracted with EA (15 mL * 3). The combined

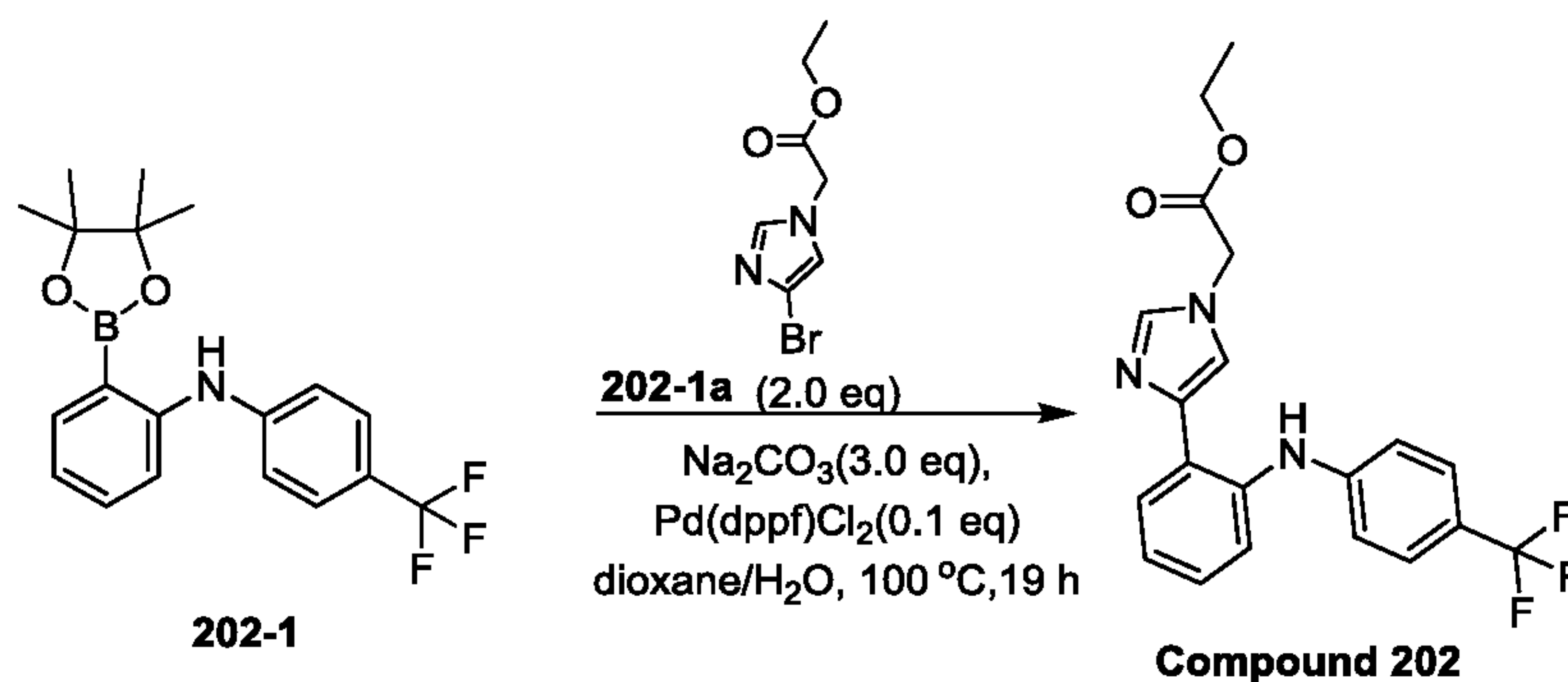
organic layers were dried with anhydrous Na_2SO_4 , filtered and concentrated in vacuum. HPLC indicated 87% of desired product was found. LCMS showed 91% of desired product (240 mg) was formed. The product was separated by SFC. ^1H NMR, LCMS and SFC and showed that **Compound 200** was obtained (95 mg, 0.24 mmol, 36.4% yield). LCMS (ESI): RT = 0.857 min, mass calcd. For $\text{C}_{19}\text{H}_{18}\text{F}_3\text{N}_5\text{O}$, 389.15 m/z found 390.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 9.10 (s, 1H), 8.20 (d, $J = 8.00$ Hz, 1H), 7.54 (d, $J = 8.30$ Hz, 3H), 7.39 (t, $J = 7.70$ Hz, 1H), 7.30 (d, $J = 8.50$ Hz, 2H), 7.05 (t, $J = 7.70$ Hz, 1H), 5.10 (dt, $J = 4.50, 8.20$ Hz, 1H), 4.69 (br s, 1H), 2.65 - 2.51 (m, 1H), 2.50 - 2.35 (m, 2H), 2.27 - 2.06 (m, 2H), 2.05 - 1.96 (m, 1H), 1.91 - 1.80 (m, 1H).

Example 190: (1S,2R)-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)cyclopentan-1-ol (Compound 201)



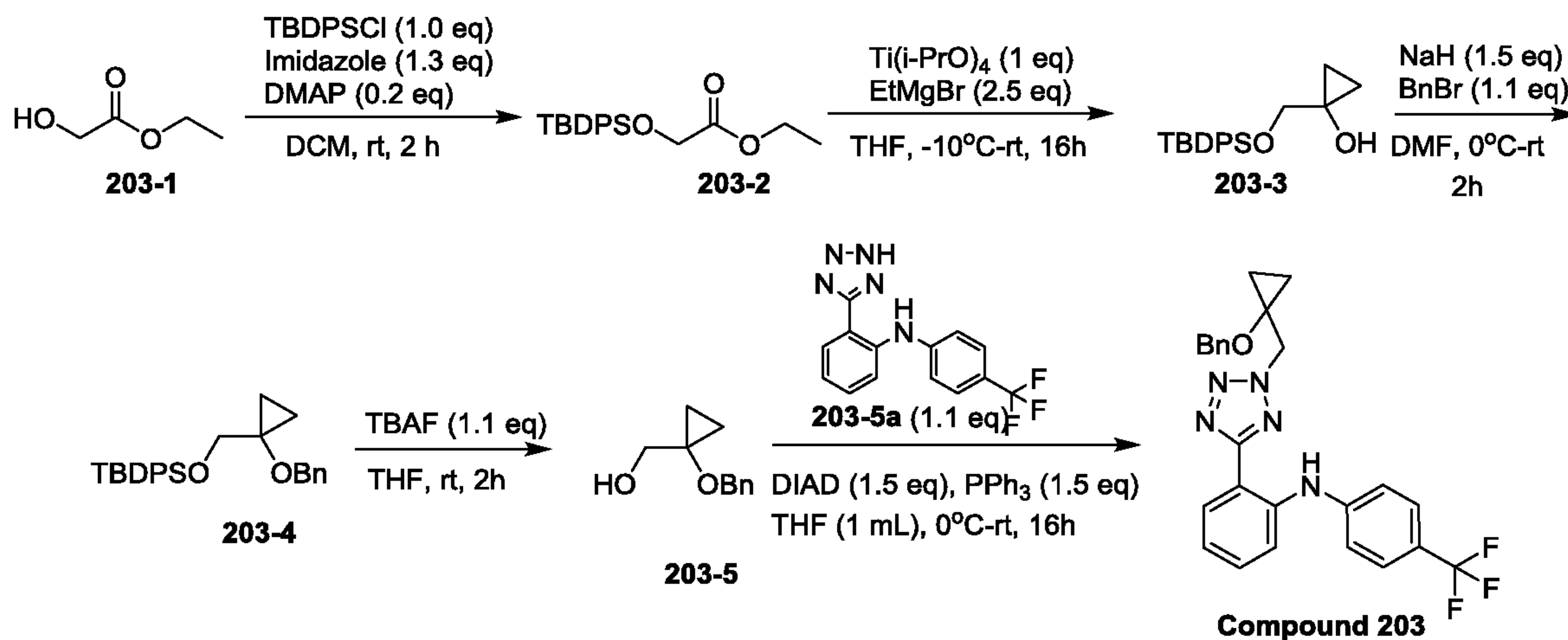
[00635] To a solution of the **200-2** (260 mg, 0.67 mmol, 1 *eq*) in MeOH (3 mL) was added NaBH_4 (51 mg, 1.34 mmol, 2 *eq*) in one portion at 20°C under N_2 . The mixture was stirred at 20 °C for 2 h. LCMS showed the starting material was consumed completely and one main peak with desired MS was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with water (15 mL) and extracted with EA (15 mL * 3). The combined organic layers were dried with anhydrous Na_2SO_4 , filtered and concentrated in vacuum. HPLC indicated 87% of desired product was found. LCMS showed 91% of desired product (240 mg) was formed. The product was separated by SFC. ^1H NMR, LCMS and SFC and showed that **Compound 201** was obtained (95 mg, 0.24 mmol, 36.4% yield). LCMS (ESI): RT = 0.858 min, mass calcd. For $\text{C}_{19}\text{H}_{18}\text{F}_3\text{N}_5\text{O}$, 389.15 m/z found 390.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 9.10 (s, 1H), 8.20 (d, $J = 7.80$ Hz, 1H), 7.54 (d, $J = 8.50$ Hz, 3H), 7.39 (t, $J = 7.70$ Hz, 1H), 7.30 (d, $J = 8.50$ Hz, 2H), 7.05 (t, $J = 7.50$ Hz, 1H), 5.10 (dt, $J = 4.60, 8.20$ Hz, 1H), 4.73 - 4.66 (m, 1H), 2.64 - 2.52 (m, 1H), 2.50 - 2.35 (m, 2H), 2.26 - 2.08 (m, 2H), 2.05 - 1.95 (m, 1H), 1.92 - 1.79 (m, 1H).

Example 191: ethyl 2-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-imidazol-1-yl)acetate (Compound 202)



[00636] A mixture of **202-1** (100.0 mg, 0.3 mmol, 1.0 eq), **202-1a** (128.3 mg, 0.6 mmol, 2.0 eq), Na_2CO_3 (87.5 mg, 0.8 mmol, 3.0 eq) and Pd(dppf)Cl_2 (20.1 mg, 27.5 μmol , 0.1 eq) in dioxane (3.0 mL) and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100°C for 19 h under N_2 atmosphere. LC-MS showed 32% of **202-1a** was remained. Several new peaks were shown on LC-MS and 23% of desired compound was detected. The mixture was purified by prep-HPLC to give **Compound 202** (5.26 mg, 13.5 μmol , 5% yield). LCMS (ESI): RT = 0.698 min, mass calc. for $\text{C}_{20}\text{H}_{18}\text{F}_3\text{N}_3\text{O}_2$ 389.14, m/z found 390.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 9.94 (s, 1H), 7.59 (s, 1H), 7.52-7.45 (m, 4H), 7.25-7.17 (m, 4H), 6.95 (t, $J=7.5$ Hz, 1H), 4.74 (s, 2H), 4.28 (q, $J=7.0$ Hz, 2H), 1.32 (t, $J=7.2$ Hz, 3H).

Example 192: 2-(2-((1-(benzyloxy)cyclopropyl)methyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 203)



Step 1: ethyl 2-((tert-butyldiphenylsilyl)oxy)acetate

[00637] To a mixture of **203-1** (2 g, 19.21 mmol, 1.9 mL, 1.06 eq), 1H-imidazole (1.61 g, 23.65 mmol, 1.3 eq) and DMAP (444.5 mg, 3.64 mmol, 0.2 eq) in DCM (15 mL), was added TBDPSCI (5 g, 18.19 mmol, 4.7 mL, 1 eq) at 0°C . The resulting mixture was stirred at 15°C for 2 h. LCMS showed the reaction was completed. The mixture was diluted with water (15 mL), extracted with DCM (15 mL * 3). The organic layer was dried over anhydrous Na_2SO_4 , concentrated in vacuum. **203-2** (5.2 g, crude) was obtained, which was checked by ^1H NMR. ^1H NMR (400 MHz, DMSO-

d_6) δ 7.63 (dd, $J = 1.4, 7.7$ Hz, 4H), 7.49 - 7.41 (m, 6H), 4.27 (s, 2H), 4.06 (q, $J = 7.0$ Hz, 2H), 1.13 (t, $J = 7.0$ Hz, 3H), 1.02 (s, 9H).

Step 2: 1-[[tert-butyl(diphenyl)silyl]oxymethyl]cyclopropanol

[00638] To a solution of **203-2** (2 g, 5.84 mmol, 1 *eq*) and $\text{Ti}(\text{i-PrO})_4$ (1.16 g, 4.09 mmol, 1.2 mL, 0.7 *eq*) in THF (20 mL) was added Ethyl magnesium bromide (3 M, 4.9 mL, 2.53 *eq*) dropwise at -10°C . The reaction was warmed to 20°C for 16 hr. TLC (EA:PE = 1:5) showed that starting material was consumed and a new spot was detected. The reaction was quenched by sat. NH_4Cl (20 mL). The THF was removed. The residue was extracted with EA (3*50 mL). The organic layer was dried over Na_2SO_4 and concentrated. **203-3** (1.7 g, 5.21 mmol, 89.17% yield) was used for next step directly. ^1H NMR showed that desired product was obtained. ^1H NMR (400 MHz, CDCl_3) δ 7.80 - 7.65 (m, 4H), 7.50 - 7.30 (m, 6H), 3.69 (s, 2H), 2.00 (s, 1H), 1.08 (s, 9H), 0.80 - 0.60 (m, 2H), 0.50 - 0.30 (m, 2H).

Step 3: (1-benzyloxycyclopropyl)methoxy-tert-butyl-diphenyl-silane

[00639] To a solution of **203-3** (1.2 g, 3.68 mmol, 1 *eq*) in DMF (10 mL) was added NaH (220.5 mg, 5.51 mmol, 60% purity, 1.5 *eq*) at 0°C , followed by BnBr (691.5 mg, 4.04 mmol, 0.5 mL, 1.1 *eq*). The reaction was stirred at 15°C for 16 hr. LCMS showed that 46% of desired MS signal was detected. The reaction was concentrated. The crude product was purified by CombiFlash to give **203-4** (0.8 g, 1.92 mmol, 52.3% yield).

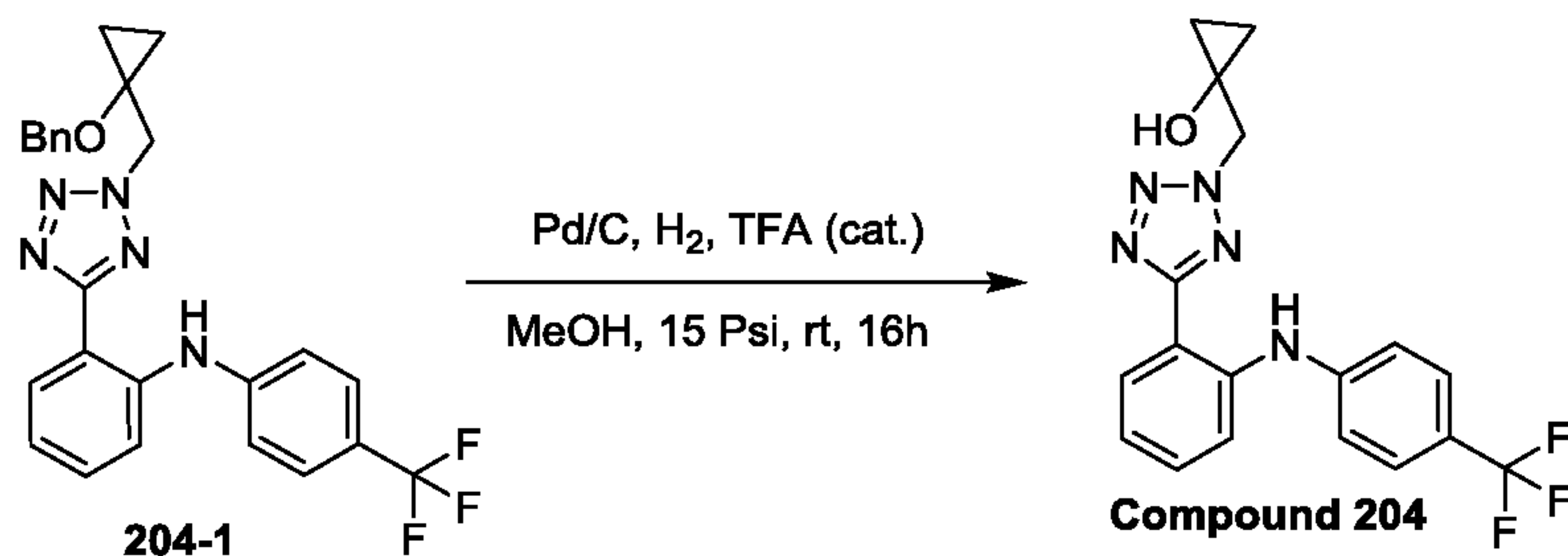
Step 4: (1-benzyloxycyclopropyl)methanol

[00640] To a solution of **203-4** (0.19 g, 4.56 mmol, 1 *eq*) in THF (4 mL) was added TBAF (1 M, 0.7 mL, 1.5 *eq*) at 0°C . The reaction was warmed to 25°C for 2 hr. TLC (EA:PE = 1:10) showed that starting material was consumed completely and two new spots were detected. LCMS showed that starting material was consumed. The reaction was concentrated. The crude product was purified by CombiFlash to give **203-5** (80 mg, 0.45 mmol, 98.4% yield).

Step 5: 2-[2-[(1-benzyloxycyclopropyl)methyl]tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl] aniline

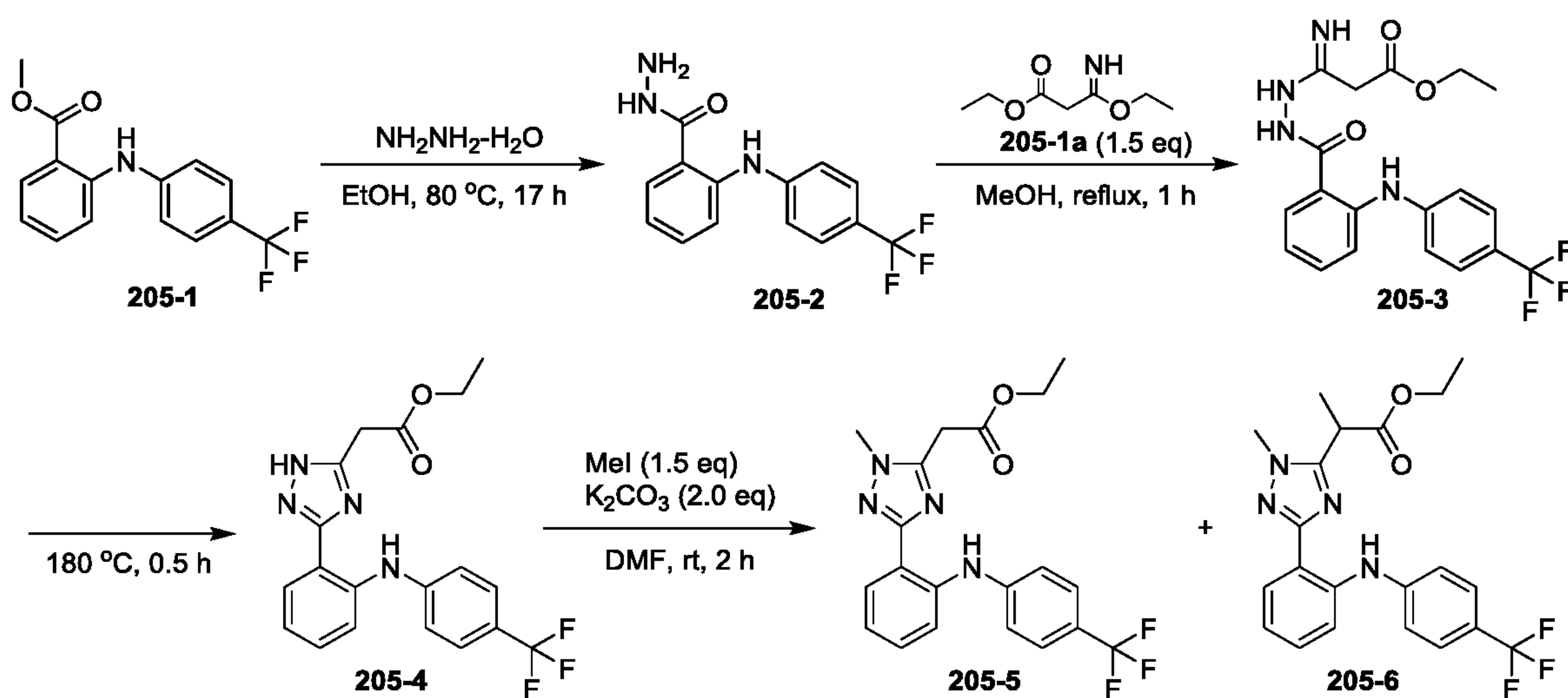
[00641] To a solution of **203-5a** (85.6 mg, 0.28 mmol, 1 *eq*), **203-5** (50 mg, 0.28 mmol, 1 *eq*) and PPh_3 (110.4 mg, 0.42 mmol, 1.5 *eq*) in THF (1 mL) was added DIAD (85.1 mg, 0.42 mmol, 82 μL , 1.5 *eq*) at 0°C . The reaction was stirred at 20°C for 12 hr. LCMS showed that 20% of desired product was detected. The reaction was concentrated. The crude product was purified by Prep.HPLC to give **Compound 203** (19 mg, 39 μmol , 13.9% yield). ^1H NMR and LCMS confirmed that desired product was obtained. LCMS (ESI): RT = 0.969 min, mass calcd. for $\text{C}_{25}\text{H}_{22}\text{F}_3\text{N}_5\text{O}$ 465.18, m/z found 466.3 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO) δ 8.64 (s, 1H), 8.10 (d, $J = 7.6$ Hz, 1H), 7.65 - 7.45 (m, 4H), 7.25 - 7.10 (m, 9H), 5.11 (s, 2H), 4.59 (s, 2H), 0.99 (m, 4H).

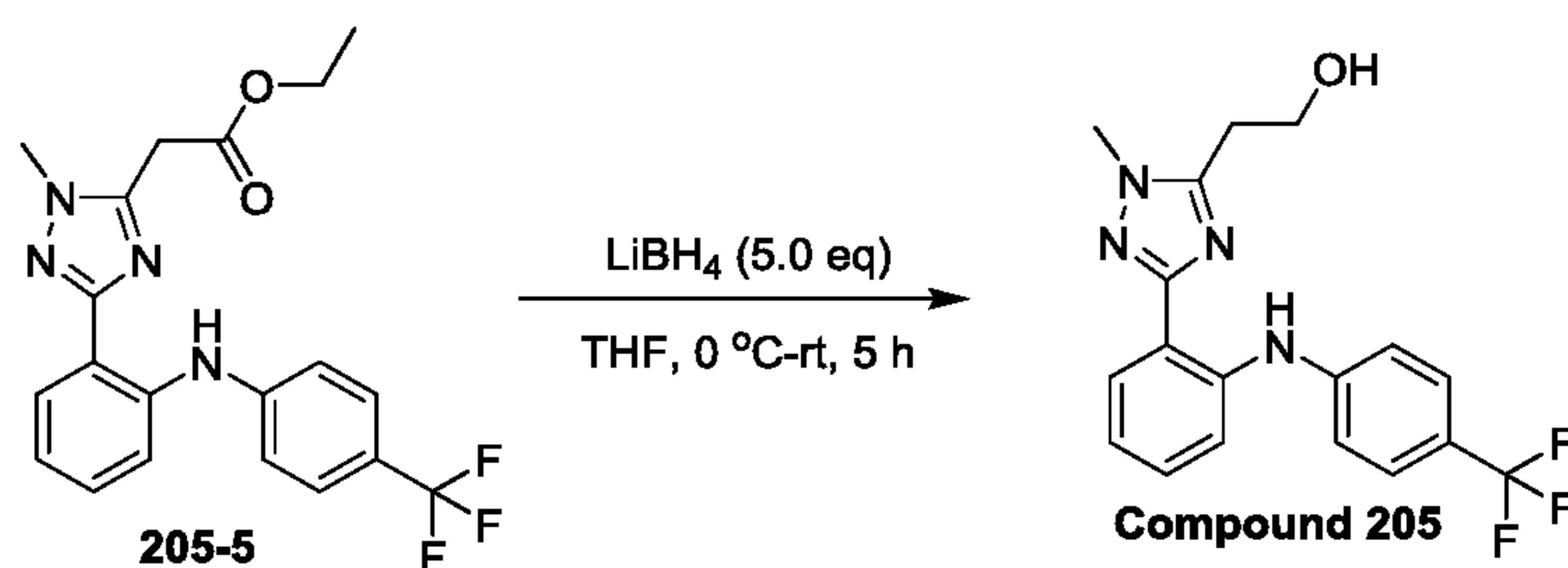
Example 193: 1-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)methyl)cyclopropan-1-ol (Compound 204)



[00642] To a solution of **204-1** (13 mg, 27.9 μmol , 1 *eq*) in MeOH (5 mL) was added dry Pd/C (3 mg, 10% purity, 1.00 *eq*) under N_2 . The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 20°C for 16 hours. LCMS showed that 95% of starting material was remained and 5% of desired MS signal was detected. To the reaction was added TFA (0.2 mL) and the reaction was stirred at 20°C for 16 hr. LCMS showed that 95% of desired product was detected. The reaction was filtered and concentrated. The crude product was purified by Prep.HPLC to give **Compound 204** (3 mg, 7.6 μmol , 27.2% yield). LCMS and HNMR confirmed that desired product was obtained. LCMS (ESI): RT = 0.833 min, mass calcd. for $\text{C}_{18}\text{H}_{16}\text{F}_3\text{N}_5\text{O}$ 375.13, m/z found 376.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 9.07 (s, 1H), 8.21 (d, $J = 8.0$ Hz, 1H), 7.65 - 7.45 (m, 3H), 7.45 - 7.35 (m, 1H), 7.35 - 7.20 (m, 2H), 7.06 (t, $J = 7.6$ Hz, 1H), 4.82 (s, 2H), 3.04 (s, 1H), 1.07 (t, $J = 6.8$ Hz, 2H), 0.92 (t, $J = 7.2$ Hz, 2H).

Example 194: 2-(1-methyl-3-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-1,2,4-triazol-5-yl)ethan-1-ol (Compound 205)





Step 1: 2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00643] To a mixture of **205-1** (1 g, 3.39 mmol, 1 *eq*) in EtOH (10 mL) was added $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (2.06 g, 34.98 mmol, 2 mL, 85% purity, 10.33 *eq*). The resulted mixture was stirred at 80 °C for 17 h. LCMS and TLC showed the reaction was complete. The mixture was concentrated in vacuum. The residue was purified by silica gel chromatography. **205-2** (600 mg, 1.77 mmol, 52.2% yield) was obtained, which was checked by LCMS.

Step 2: ethyl 3-imino-3-(2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinyl)propanoate

[00644] To a mixture of **205-2** (600 mg, 2.03 mmol, 1 *eq*) in MeOH (8 mL) was added **205-1a** (485.2 mg, 3.05 mmol, 1.5 *eq*). The resulted mixture was stirred at 70 °C for 1 h. LCMS showed the reaction was complete. The mixture was concentrated in vacuum. The residue was diluted with EA (10 mL), filtered, and the solid was dried in vacuum. **205-3** (350 mg, crude) was obtained.

Step 3: ethyl 2-(3-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-1,2,4-triazol-5-yl)acetate

[00645] **205-3** (350 mg, 0.86 mmol, 1 *eq*) was stirred at 180 °C under N_2 for 0.5 h. LCMS showed the reaction was complete. The mixture was purified by pre-TLC. **205-4** (80 mg, 0.18 mmol, 20.8% yield) was obtained, which was checked by LCMS.

Step 4: ethyl 2-(1-methyl-3-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-1,2,4-triazol-5-yl)acetate

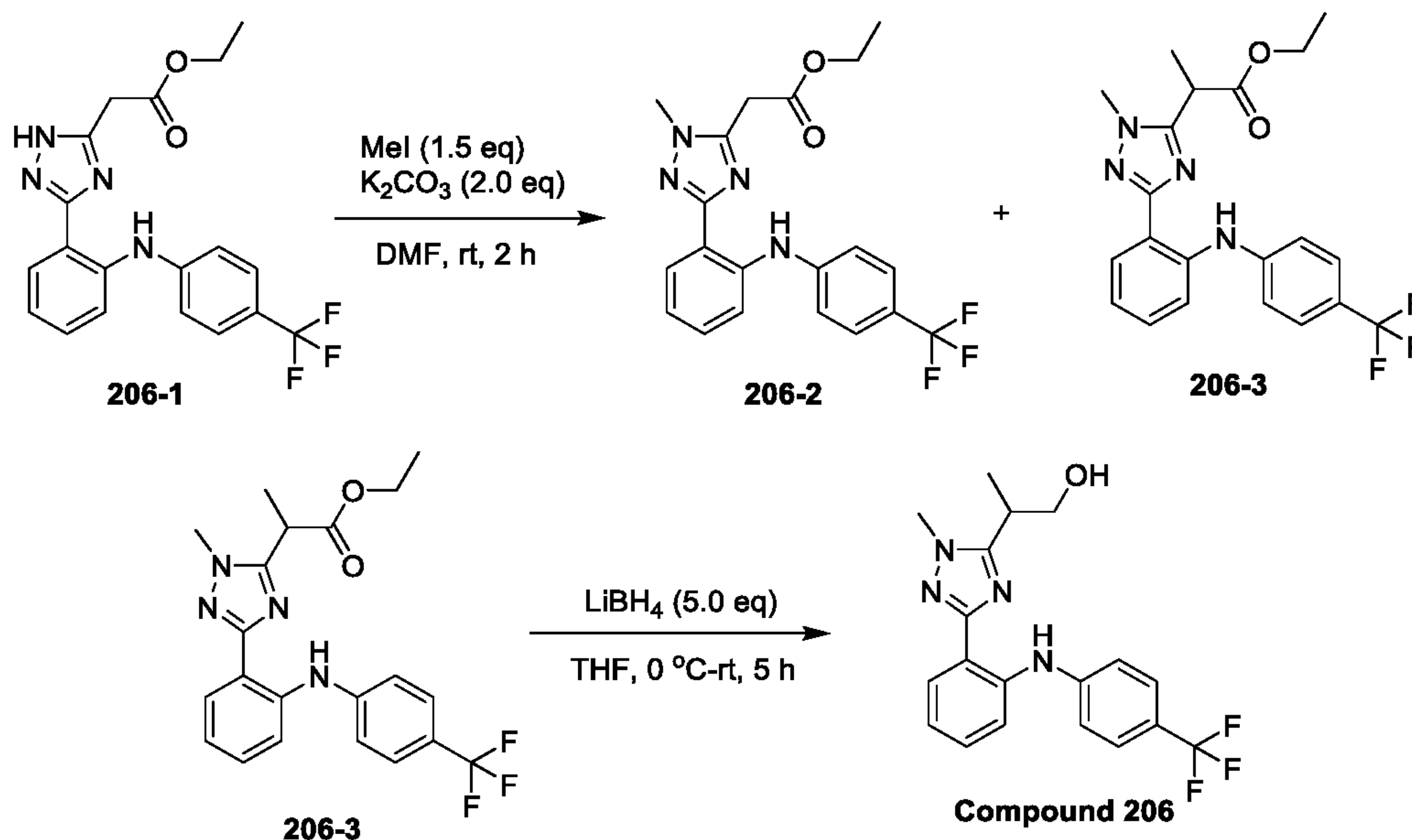
[00646] To a mixture of **205-4** (160 mg, 0.41 mmol, 1 *eq*) and K_2CO_3 (113.3 mg, 0.82 mmol, 2 *eq*) in DMF (2 mL), was added MeI (87.3 mg, 0.61 mmol, 38 μL , 1.5 *eq*). The resulting mixture was stirred at 15 °C for 2 h. LCMS showed the starting material was consumed complete. The mixture was concentrated in vacuum. The residue was diluted with water (15 mL), extracted with EA (15 mL*3). The organic layer was dried over anhydrous Na_2SO_4 , concentrated in vacuum. The residue was checked by LCMS, purified by pre-HPLC to give **205-5** (10 mg, 24.7 μmol , 6.0% yield) and **205-6** (about 10 mg), which were checked by LCMS.

Step 5: 2-(1-methyl-3-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-1,2,4-triazol-5-yl)ethanol

[00647] To a mixture of **205-5** (10 mg, 24.7 μmol , 1 *eq*) in THF (2 mL) was added LiBH_4 (2.69 mg, 0.12 mmol, 5 *eq*) at 0 °C. The resulted mixture was stirred at 15 °C for 5 h. LCMS showed the

reaction was completed. The mixture was filtered, and the filtrate was diluted with MeOH (2 mL), concentrated in vacuum. The residue was checked by HPLC, purified by pre-HPLC. **Compound 205** (2.95 mg, 8.14 μmol) was obtained, which was checked by LCMS, ^1H NMR and NOE. LCMS (ESI): RT = 0.783 min, mass calcd. For $\text{C}_{18}\text{H}_{17}\text{F}_3\text{N}_4\text{O}$ 362.14, m/z found 362.9 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.96 (s, 1H), 8.07 (d, $J = 7.6$ Hz, 1H), 7.60 (d, $J = 8.4$ Hz, 2H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.45 - 7.40 (m, 3H), 7.03 (d, $J = 7.6$ Hz, 1H), 3.91 (s, 3H), 3.82 (t, $J = 6.4$ Hz, 2H), 3.00 (t, $J = 6.8$ Hz, 2H).

Example 195: 2-(1-methyl-3-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-1,2,4-triazol-5-yl)propan-1-ol (Compound 206)



Step 1: ethyl 2-(1-methyl-3-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-1,2,4-triazol-5-yl)acetate

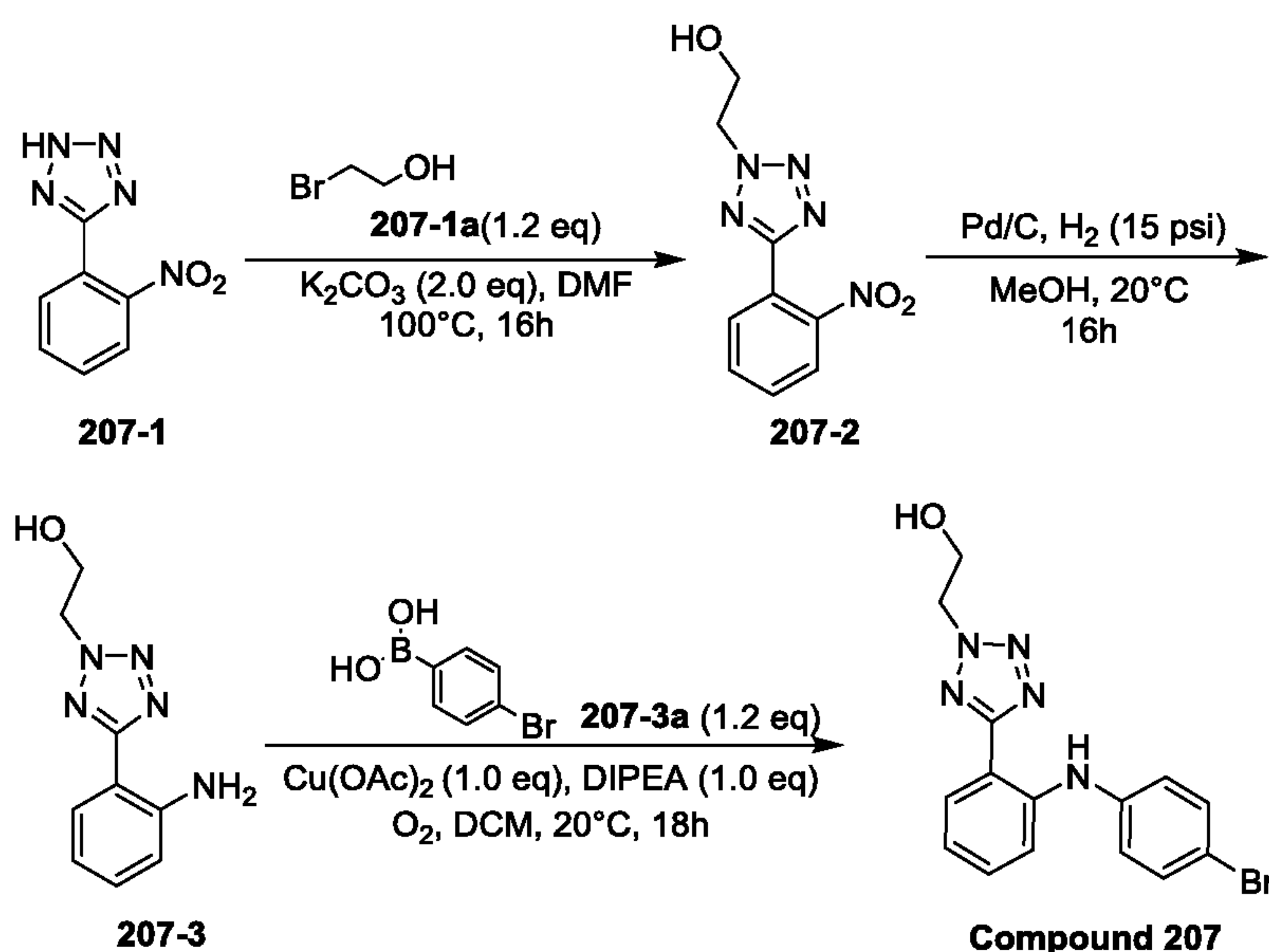
[00648] To a mixture of **206-1** (160 mg, 0.41 mmol, 1 *eq*) and K_2CO_3 (113.3 mg, 0.82 mmol, 2 *eq*) in DMF (2 mL), was added MeI (87.3 mg, 0.61 mmol, 38 μL , 1.5 *eq*). The resulting mixture was stirred at 15 $^\circ\text{C}$ for 2 h. LCMS showed the starting material was consumed complete. The mixture was concentrated in vacuum. The residue was diluted with water (15 mL), extracted with EA (15 mL*3). The organic layer was dried over anhydrous Na_2SO_4 , concentrated in vacuum. The residue was checked by LCMS, purified by pre-HPLC to give **206-2** (10 mg, 24.7 μmol , 6.0% yield) and **206-3** (about 10 mg), which were checked by LCMS.

Step 2: 2-(1-methyl-3-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-1,2,4-triazol-5-yl)propan-1-ol

[00649] To a mixture of **206-3** (10 mg, 24.7 μmol , 1 *eq*) in THF (2 mL) was added LiBH_4 (2.69 mg, 0.12 mmol, 5 *eq*) at 0 $^\circ\text{C}$. The resulted mixture was stirred at 15 $^\circ\text{C}$ for 5 h. LCMS showed the reaction was completed. The mixture was filtered, and the filtrate was diluted with MeOH (2 mL),

concentrated in vacuum. The residue was checked by HPLC, purified by pre-HPLC. **Compound 206** (5.5 mg, 14.61 μmol) was obtained, which was confirmed by LCMS, ^1H NMR and NOE. LCMS (ESI): RT = 0.818 min, mass calcd. For $\text{C}_{19}\text{H}_{19}\text{F}_3\text{N}_4\text{O}$ 376.15, m/z found 376.9 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.13 (s, 1H), 8.07 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.60 (d, $J = 8.4$ Hz, 2H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.45 - 7.40 (m, 3H), 7.03 (d, $J = 7.6$ Hz, 1H), 3.92 (s, 3H), 3.70 - 3.50 (m, 2H), 3.40 - 3.20 (m, 1H), 1.28 (d, $J = 7.2$ Hz, 3H).

Example 196: 2-(5-(2-((4-bromophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-ol
(Compound 207)



Step 1: 2-(5-(2-nitrophenyl)-2H-tetrazol-2-yl)ethanol

[00650] To a solution of **207-1** (3.0 g, 15.69 mmol, 1 *eq*) in DMF (15 mL) were added K_2CO_3 (4.34 g, 31.4 mmol, 2.0 *eq*) and **207-1a** (2.35 g, 18.83 mmol, 1.3 mL, 1.2 *eq*). The mixture was stirred at 100°C for 16 hr. TLC showed the starting material was consumed completely, and one major new spot was detected (Petroleum ether: Ethyl acetate = 1/1, $R_f = 0.35$). The mixture was cooled to 20°C and H_2O (15 mL) was added to quench the reaction. The aqueous phase was extracted with ethyl acetate (30 mL*3). The combined organic phase was washed with brine (15 mL*1), dried with anhydrous Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to give **207-2** (2.1 g, 8.21 mmol, 52% yield), which was confirmed by HNMR. ^1H NMR (400 MHz, CDCl_3) δ 7.99 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.89 (dd, $J = 7.9, 1.1$ Hz, 1H), 7.63-7.75 (m, 2H), 4.81-4.84 (m, 2H), 4.22 (t, $J = 4.6$ Hz, 2H), 2.54 (brs, 1H).

Step 2: 2-(5-(2-aminophenyl)-2H-tetrazol-2-yl)ethanol

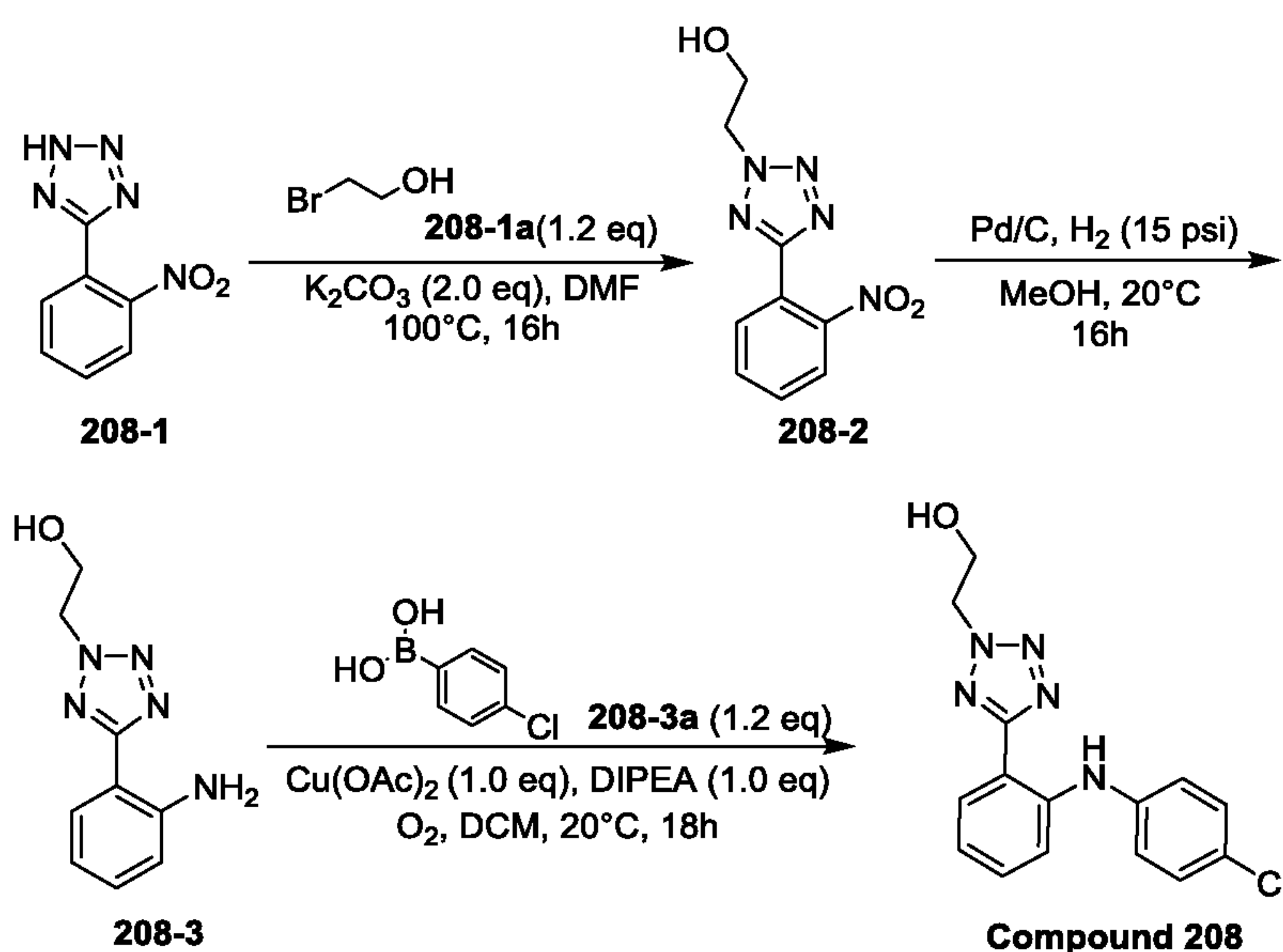
[00651] To a solution of 2-[5-(2-nitrophenyl)tetrazol-2-yl]ethanol (2.0 g, 8.50 mmol, 1 *eq*) in MeOH (20 mL) was added Pd/C (0.2 g, 8.50 mmol, 20% purity, 1 *eq*) under N_2 . The suspension was degassed under vacuum and purged with H_2 for 3 times. Then the mixture was stirred under H_2

(15 psi) at 20°C for 16 hr. LCMS showed that no starting material exist. The reaction mixture was filtered and the filter was concentrated to provide **207-3**, which was used in next step directly without further purification. ¹H NMR (400 MHz, CDCl₃) δ 8.08 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.22-7.26 (m, 1H), 6.78-6.82 (m, 2H), 5.42 (brs, 2H), 4.79-4.82 (m, 2H), 4.22 (t, *J* = 4.8 Hz, 2H), 2.62 (brs, 1H).

Step 3: 2-(5-(2-((4-bromophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol

[00652] To a solution of **207-3** (100 mg, 0.49 mmol, 1 *eq*) and **207-3a** (117.4 mg, 0.58 mmol, 1.2 *eq*) in DCM (5 mL) was added Cu(OAc)₂ (88.5 mg, 0.49 mmol, 1 *eq*) and DIPEA (63 mg, 0.49 mmol, 85 uL, 1 *eq*). The mixture was stirred at 20°C under O₂ for 18 hr. TLC(Petroleum ether: Ethyl acetate = 2/1, R_f = 0.2) showed the starting material was consumed completely, and one major new spot was detected. H₂O (5 mL) was added to quench the reaction. The aqueous phase was extracted with ethyl acetate (10 mL*3). The combined organic phase was washed with brine (10 mL*1), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to give **Compound 207** (18.1 mg, 50 umol, 10.2% yield). LCMS (ESI): RT = 1.732 min, mass calc. for C₁₅H₁₄ClN₆O 359.04, *m/z* found 359.8 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 8.83 (s, 1H), 8.16 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.41-7.44 (m, 2H), 7.30-7.37 (m, 2H), 7.13-7.16 (m, 2H), 6.94-6.98 (m, 1H), 4.83-4.86 (m, 2H), 4.24-4.28 (m, 2H), 2.40 (t, *J* = 6.3 Hz, 1H).

Example 197: 2-(5-(2-((4-chlorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethan-1-ol (Compound 208)



Step 1: 2-(5-(2-nitrophenyl)-2H-tetrazol-2-yl)ethanol

[00653] To a solution of **208-1** (3.0 g, 15.69 mmol, 1 *eq*) in DMF (15 mL) were added K₂CO₃ (4.34 g, 31.39 mmol, 2.0 *eq*) and **208-1a** (2.35 g, 18.83 mmol, 1.3 mL, 1.2 *eq*). The mixture was

stirred at 100°C for 16 hr. TLC (Petroleum ether: Ethyl acetate = 1/1, R_f = 0.35) showed the starting material was consumed completely, and one major new spot was detected. The mixture was cooled to 20°C and H₂O (15 mL) was added to quench the reaction. The aqueous phase was extracted with ethyl acetate (30 mL*3). The combined organic phase was washed with brine (15 mL*1), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to give the desired **208-2** (2.1 g, 8.21 mmol, 52% yield), which was confirmed by ¹H NMR. ¹H NMR (400 MHz, CDCl₃) δ 7.99 (dd, J = 7.8, 1.2 Hz, 1H), 7.89 (dd, J = 7.9, 1.1 Hz, 1H), 7.63-7.75 (m, 2H), 4.81-4.84 (m, 2H), 4.22 (t, J = 4.6 Hz, 2H), 2.54 (brs, 1H).

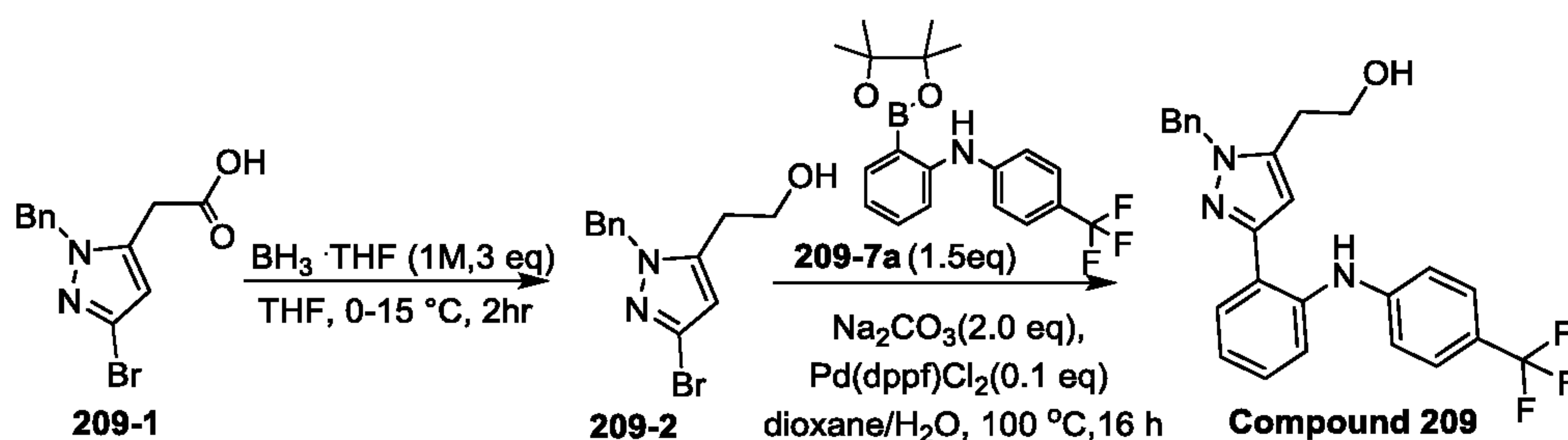
Step 2: 2-(5-(2-aminophenyl)-2H-tetrazol-2-yl)ethanol

[00654] To a solution of **208-2** (2.0 g, 8.50 mmol, 1 *eq*) in MeOH (20 mL) was added Pd/C (0.2 g, 8.50 mmol, 20% purity, 1 *eq*) under N₂. The suspension was degassed under vacuum and purged with H₂ for 3 times. Then the mixture was stirred under H₂ (15 psi) at 20°C for 16 hr. LCMS showed that no starting material existed. The reaction mixture was filtered and the filter was concentrated to get **208-3**, which was used in next step directly without further purification. ¹H NMR (400 MHz, CDCl₃) δ 8.08 (dd, J = 7.9, 1.4 Hz, 1H), 7.22-7.26 (m, 1H), 6.78-6.82 (m, 2H), 5.42 (brs, 2H), 4.79-4.82 (m, 2H), 4.22 (t, J = 4.8 Hz, 2H), 2.62 (brs, 1H).

Step 3: 2-(5-(2-((4-chlorophenyl)amino)phenyl)-2H-tetrazol-2-yl)ethanol

[00655] To a solution of **208-3** (100 mg, 0.49 mmol, 1 *eq*) and (4-chlorophenyl)boronic acid (91.4 mg, 0.58 mmol, 1.2 *eq*) in DCM (5 mL) was added Cu(OAc)₂ (88.5 mg, 0.49 mmol, 1 *eq*) and DIPEA (62.9 mg, 0.49 mmol, 85 uL, 1 *eq*). The mixture was stirred at 20°C under O₂ for 18 hr. TLC(PE/EA=2/1) showed there's no starting material. H₂O (5 mL) was added to quench the reaction. The aqueous phase was extracted with ethyl acetate (10 mL*3). The combined organic phase was washed with brine (10 mL*1), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to give **Compound 208** (13.85 mg, 42.6 umol, 8.74% yield). LCMS (ESI): RT = 1.732 min, mass calc. for C₁₅H₁₄ClN₆O 315.09, m/z found 316.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 8.84 (s, 1H), 8.16 (dd, J = 7.8, 1.0 Hz, 1H), 7.28-7.36 (m, 4H), 7.18-7.21 (m, 2H), 6.93-6.97 (m, 1H), 4.84-4.86 (m, 2H), 4.24-4.28 (m, 2H), 2.31 (t, J = 6.4 Hz, 1H).

Example 198: 2-(1-benzyl-3-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-5-yl)ethan-1-ol (Compound 209)



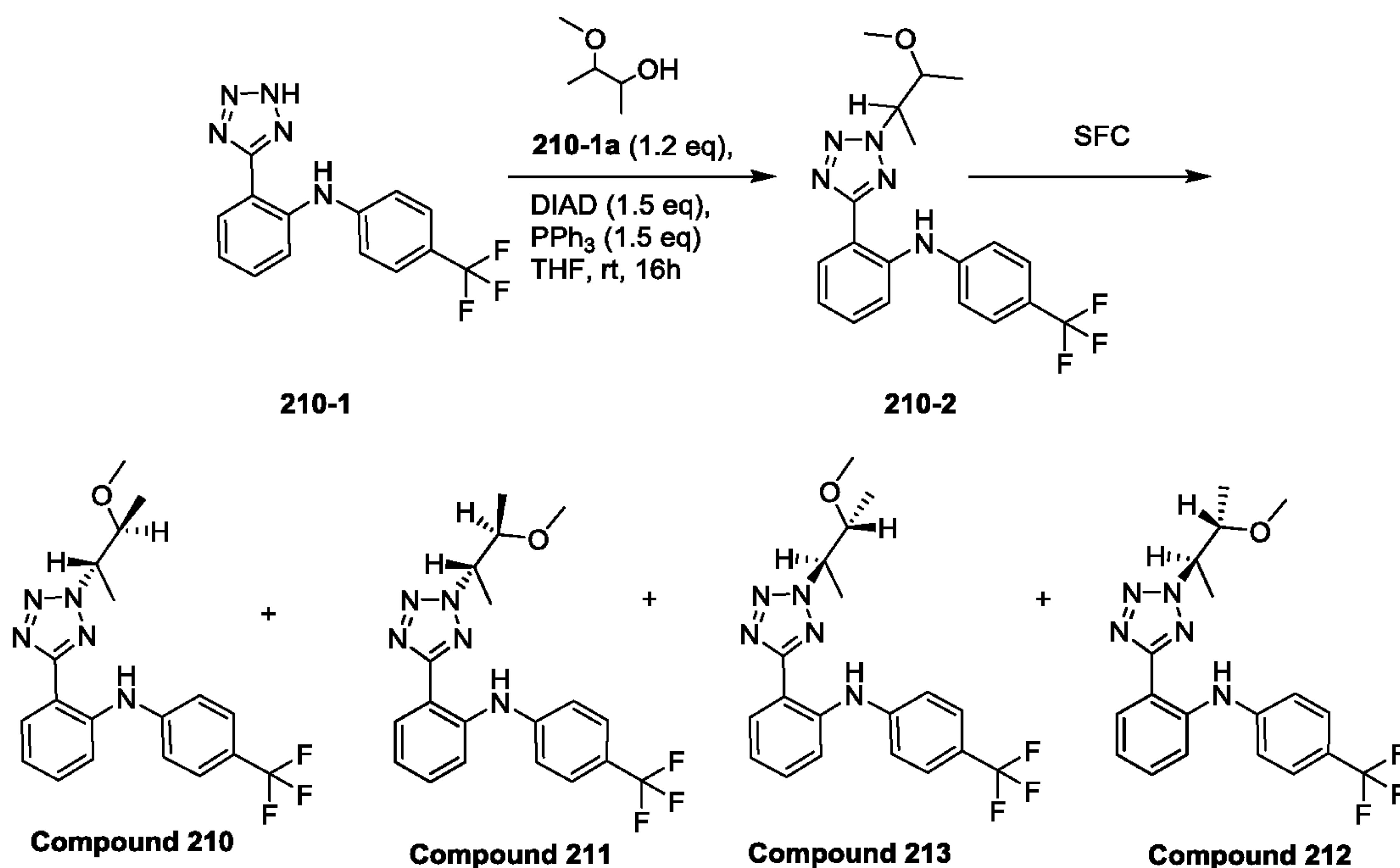
Step 1: 2-(1-benzyl-3-bromo-1H-pyrazol-5-yl)ethanol

[00656] To the solution of **209-1** (130 mg, 0.44 mmol, 1 *eq*) in THF (4 mL) was added $\text{BH}_3 \cdot \text{THF}$ (1 M, 1.3 mL, 3 *eq*) at 0 °C. The mixture was warmed up to 15 °C and stirred for 2 hr. The reaction solution was quenched with H_2O (15 mL). The mixture was extracted with EtOAc (10 mL*2). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give **209-2** (45 mg, 0.16 mmol, 36% yield).

Step 2: 2-(1-benzyl-3-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-5-yl)ethanol

[00657] To the solution of **209-2** (20 mg, 71.1 μmol , 1 *eq*) in dioxane (3 mL) and H_2O (0.15 mL) were added compound **209-7a** (25. mg, 71.1 μmol , 1 *eq*), $\text{Pd}(\text{PPh}_3)_4$ (8.2 mg, 7.1 μmol , 0.1 *eq*) and Cs_2CO_3 (34.8 mg, 0.11 mmol, 1.5 *eq*). The mixture was stirred at 100 °C for 16 hr. LCMS showed that a little of starting material was remained and one main peak with desired MS. The reaction solution was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2) to give compound **209**. 5 mg of the crude was re-purified by Prep-HPLC to give **Compound 209** (2.66 mg, 6.1 μmol , 8.6% yield). LCMS (ESI): RT = 0.890 min, mass calcd. for $\text{C}_{25}\text{H}_{22}\text{F}_3\text{N}_3\text{O}$ 437.17, m/z found 438.1 $[\text{M}+\text{H}]^+$, ^1H NMR (400 MHz, CDCl_3) δ 7.63 (dd, J = 1.3, 7.8 Hz, 1H), 7.53 - 7.47 (m, 1H), 7.43 (d, J = 8.5 Hz, 2H), 7.35 - 7.29 (m, 3H), 7.26 - 7.21 (m, 1H), 7.19 - 7.15 (m, 2H), 7.09 (d, J = 8.5 Hz, 2H), 6.98 (t, J = 7.4 Hz, 1H), 6.51 (s, 1H), 5.38 (s, 2H), 3.86 (t, J = 6.4 Hz, 2H), 2.90 (t, J = 6.4 Hz, 2H).

Example 199: 2-(2-((2S,3S)-3-methoxybutan-2-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 210), 2-(2-((2S,3R)-3-methoxybutan-2-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 211), 2-(2-((2R,3S)-3-methoxybutan-2-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 212), and 2-(2-((2R,3R)-3-methoxybutan-2-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 213)



Step 1: 2-[2-(2-methoxy-1-methyl-propyl)tetrazol-5-yl]-N-[4-(trifluoromethyl)phenyl]aniline

[00658] To a solution of **210-1** (0.5 g, 1.64 mmol, 1 *eq*), PPh₃ (644.4 mg, 2.46 mmol, 1.5 *eq*) and **210-1a** (187.6 mg, 1.80 mmol, 1.1 *eq*) in THF (10 mL) was added DIAD (496.8 mg, 2.46 mmol, 0.5 mL, 1.5 *eq*) at 0°C. The reaction was stirred at 25 °C for 16 hr. LCMS showed that 46% of desired product was detected. The reaction was concentrated. The combined crude product was purified by CombiFlash to give **210-2** (0.6 g, 1.50 mmol, 91.7% yield).

Step 2: 2-(2-((2S,3S)-3-methoxybutan-2-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline, 2-(2-((2R,3R)-3-methoxybutan-2-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline, 2-(2-((2S,3R)-3-methoxybutan-2-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline, and 2-(2-((2R,3S)-3-methoxybutan-2-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00659] **210-2** (0.6 g, 1.53 mmol, 1 *eq*) was separated by SFC. About 150 mg crude product was separated by chiral SFC again.

[00660] **Compound 210** (38.38 mg, 96.1 μmol, 6.3% yield). LCMS (ESI): RT = 0.929 min, mass calcd. For C₁₉H₂₀F₃N₅O, 391.16 m/z found 392.0[M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.14 (s, 1H), 8.22 (d, *J* = 7.6 Hz, 1H), 7.60 - 7.50 (m, 3H), 7.37 (t, *J* = 7.20 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.04 (t, *J* = 7.20 Hz, 1H), 5.10 - 5.02 (m, 1H), 3.85 - 3.66 (m, 1H), 3.37 (s, 3H), 1.77 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H).

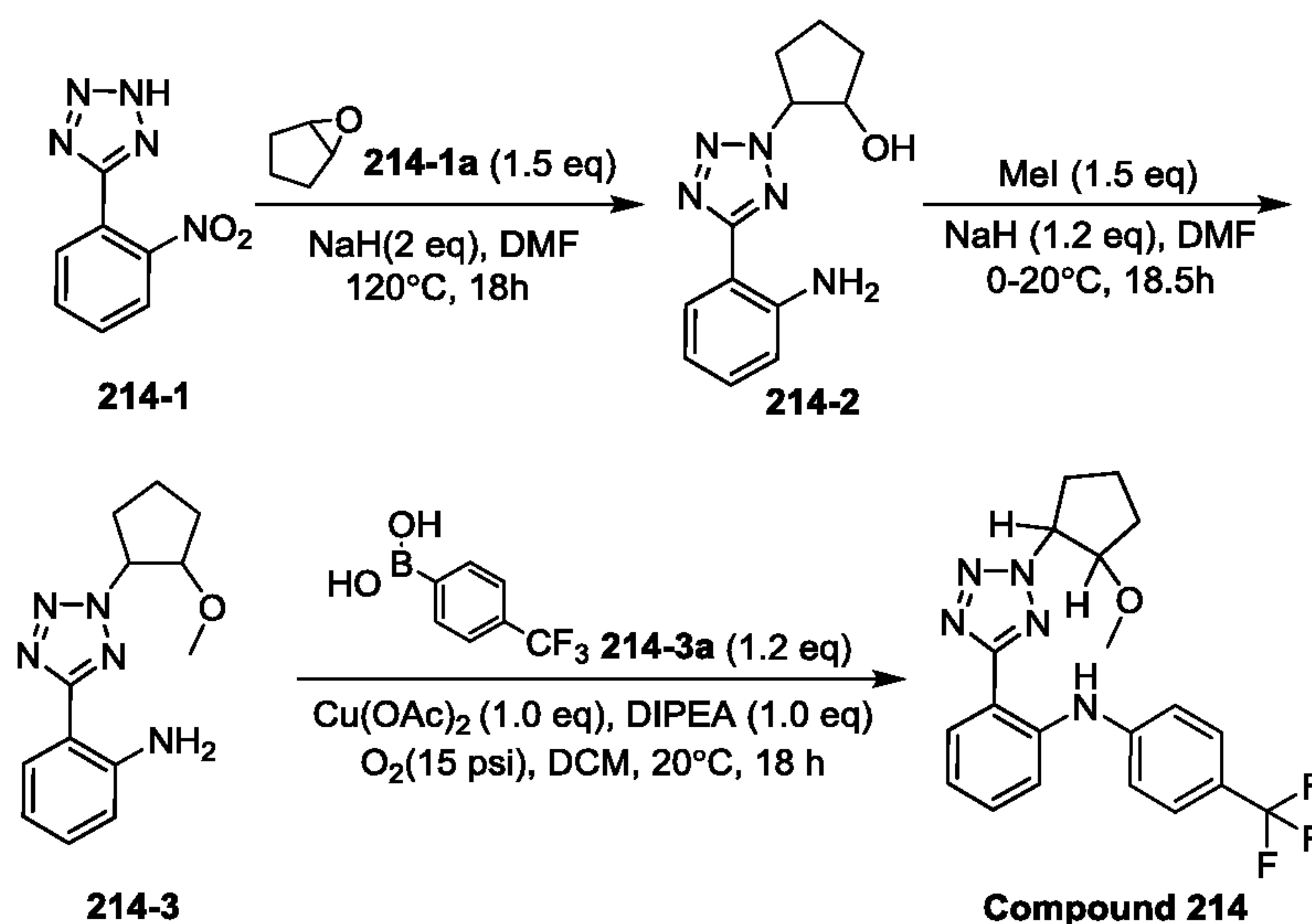
[00661] **Compound 213** (30 mg, 76.7 μmol, 5.0% yield). LCMS (ESI): RT = 0.924 min, mass calcd. For C₁₉H₂₀F₃N₅O, 391.16 m/z found 392.0[M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.14 (s, 1H), 8.22 (d, *J* = 7.6 Hz, 1H), 7.60 - 7.50 (m, 3H), 7.37 (t, *J* = 7.20 Hz, 1H), 7.30 (d, *J* = 7.6 Hz,

2H), 7.04 (t, $J = 7.20$ Hz, 1H), 5.10 - 5.02 (m, 1H), 3.85 - 3.66 (m, 1H), 3.37 (s, 3H), 1.77 (d, $J = 6.8$ Hz, 3H), 1.12 (d, $J = 6.8$ Hz, 3H).

[00662] Compound 211 (135.21 mg, 0.33 mmol, 21.4% yield). LCMS (ESI): RT = 0.935 min, mass calcd. For $C_{19}H_{20}F_3N_5O$, 391.16 m/z found 392.0[M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.17 (s, 1H), 8.23 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.54 (d, $J = 8.00$ Hz, 3H), 7.40 - 7.30 (m, 1H), 7.29 (br d, $J = 8.40$ Hz, 2H), 7.04 (t, $J = 8.0$ Hz, 1H), 5.10 - 5.02 (m, 1H), 3.90 - 3.75 (m, 1H), 3.23 (s, 3H), 1.67 (d, $J = 6.8$ Hz, 3H), 1.27 (d, $J = 6.0$ Hz, 3H).

[00663] Compound 212 (179.88 mg, 0.45 mmol, 29.4% yield). LCMS (ESI): RT = 0.927 min, mass calcd. For $C_{19}H_{20}F_3N_5O$, 391.16 m/z found 392.0[M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.17 (s, 1H), 8.23 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.54 (d, $J = 8.00$ Hz, 3H), 7.40 - 7.30 (m, 1H), 7.29 (br d, $J = 8.40$ Hz, 2H), 7.04 (t, $J = 8.0$ Hz, 1H), 5.10 - 5.02 (m, 1H), 3.90 - 3.75 (m, 1H), 3.23 (s, 3H), 1.67 (d, $J = 6.8$ Hz, 3H), 1.27 (d, $J = 6.0$ Hz, 3H).

Example 200: 2-(2-(2-methoxycyclopentyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 214)



Step 1: 2-(5-(2-aminophenyl)-2H-tetrazol-2-yl)cyclopentanol

[00664] To a mixture of **214-1** (1.0 g, 5.2 mmol, 1 eq) and **214-1a** (880.1 mg, 10.5 mmol, 0.9 mL, 2 eq) in DMF (15 mL) was added NaH (418.4 mg, 10.5 mmol, 60% purity, 2 eq). The reaction mixture was stirred at 120°C under N₂ for 18 hr. TLC and LCMS showed the desired product was generated, the starting material wasn't consumed completely. The reaction was quenched with H₂O (5 mL) and extracted with EA (10 mL * 3), the combined organic phase was washed with brine (10 mL) and dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography. **214-2** (220 mg, 0.90 mmol, 17.2% yield) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 8.08 (dd, $J = 1.3, 7.8$ Hz, 1H), 7.23 (dt, $J = 1.6, 7.7$ Hz, 1H), 6.88 - 6.71 (m, 2H), 5.42 (br s,

2H), 5.01 (dt, $J=5.8, 7.9$ Hz, 1H), 4.68 (q, $J=6.5$ Hz, 1H), 2.73 - 2.60 (m, 1H), 2.57 - 2.45 (m, 1H), 2.37 - 2.19 (m, 2H), 2.03 - 1.92 (m, 2H), 1.88 - 1.76 (m, 1H).

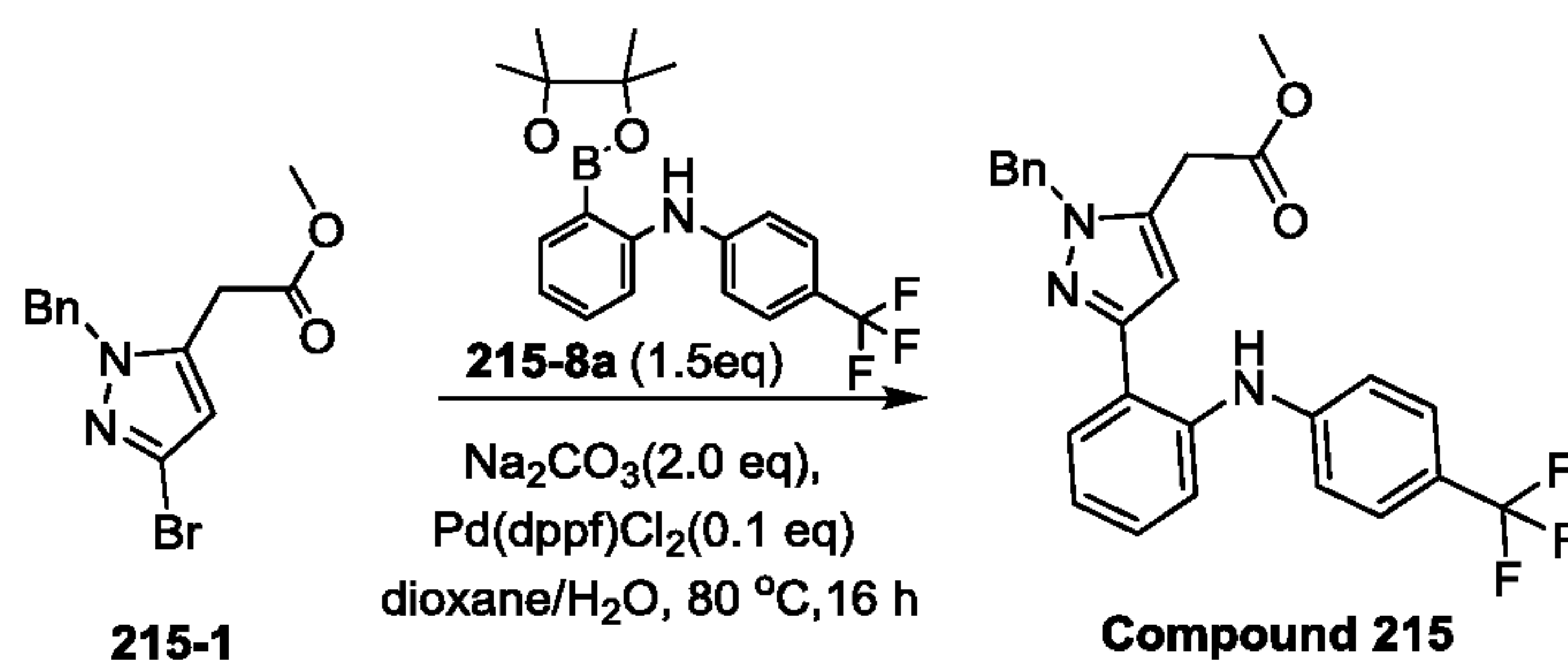
Step 2: 2-(2-(2-methoxycyclopentyl)-2H-tetrazol-5-yl)aniline

[00665] To a solution of **214-2** (210 mg, 0.86 mmol, 1 *eq*) in DMF (2 mL) was added NaH (41.1 mg, 1.0 mmol, 60% purity, 1.2 *eq*) at 0°C under N₂. The mixture was stirred at 0°C for 30 min followed by adding MeI (430 mg, 3.0 mmol, 0.19 mL, 3.5 *eq*). After that, the reaction mixture was stirred at 20°C under N₂ for 18 hr. LCMS showed the desired product was generated, no starting material existed. The reaction was quenched with H₂O (5 mL), the aqueous phase was extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (5 mL * 1), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography. **214-3** (143 mg, 0.55 mmol, 64.4% yield) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 8.12 (dd, $J=1.3, 8.0$ Hz, 1H), 7.24 (dt, $J=1.6, 7.7$ Hz, 1H), 6.87 - 6.75 (m, 2H), 5.45 (br s, 2H), 5.21 (m, 1H), 4.25 (td, $J=4.5, 6.5$ Hz, 1H), 3.35 (s, 3H), 2.52 - 2.38 (m, 1H), 2.35 - 2.15 (m, 2H), 2.09 - 1.91 (m, 2H), 1.90 - 1.79 (m, 1H).

Step 3: 2-(2-(2-methoxycyclopentyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

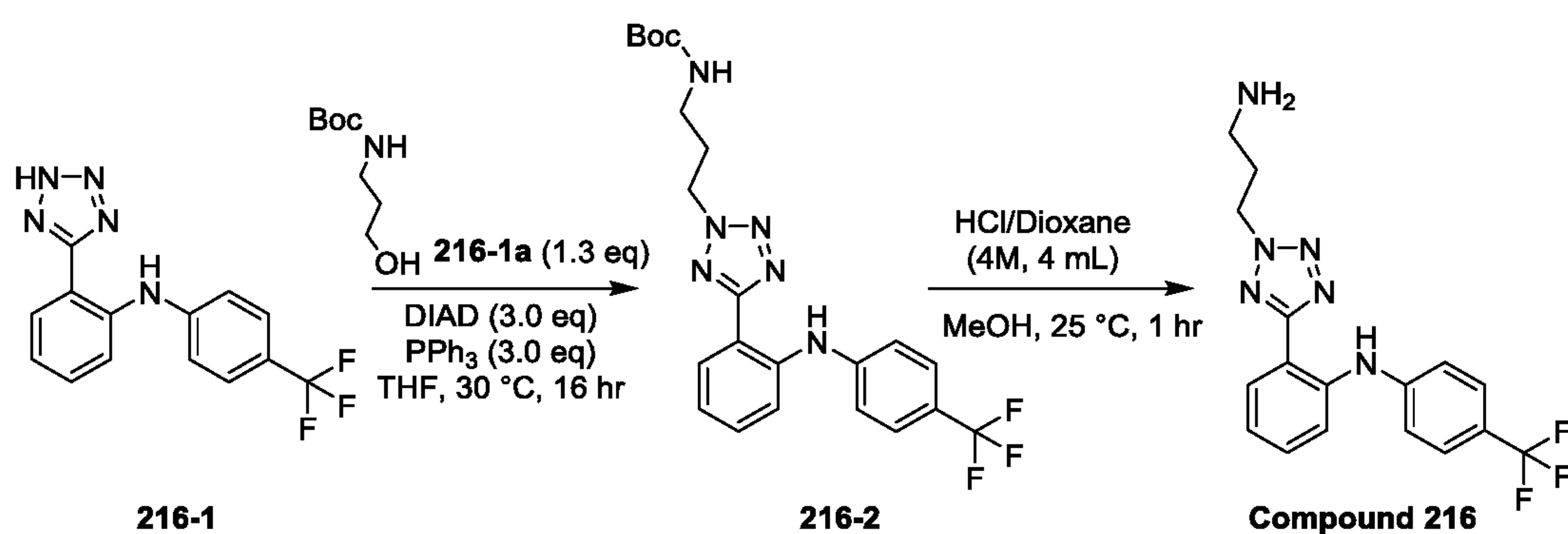
[00666] To a solution of **214-3** (71 mg, 0.27 mmol, 1 *eq*) and **214-3a** (62.4 mg, 0.33 mmol, 1.2 *eq*) in DCM (5 mL) were added Cu(OAc)₂ (49.7 mg, 0.27 mmol, 1.0 *eq*) and DIPEA (35.4 mg, 0.27 mmol, 48 uL, 1.0 *eq*). The mixture was stirred at 20°C under O₂ for 18 hr. LCMS showed the desired product was generated, starting material was consumed completely. H₂O (10 mL) was added to quench the reaction, the aqueous phase was extracted with ethyl acetate (20 mL * 3). The combined organic phase was washed with brine (20 mL * 2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC. **Compound 214** (38.6 mg, 96 umol, 35.0% yield) was obtained. LCMS (ESI): RT = 0.944 min, mass calc. for C₂₀H₂₀F₃N₅O 403.16, m/z found 403.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.10 (s, 1H), 8.21 (dd, $J=1.5, 7.8$ Hz, 1H), 7.54 (d, $J=8.3$ Hz, 3H), 7.44 - 7.35 (m, 1H), 7.29 (d, $J=8.5$ Hz, 2H), 7.11 - 7.00 (m, 1H), 5.22 (m, 1H), 4.24 (m, 1H), 3.35 (s, 3H), 2.54 - 2.40 (m, 1H), 2.36 - 2.25 (m, 1H), 2.25 - 2.17 (m, 1H), 2.04 - 1.93 (m, 2H), 1.92 - 1.79 (m, 1H).

Example 201: methyl 2-(1-benzyl-3-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-pyrazol-5-yl)acetate (Compound 215)



[00667] To the solution of **215-1** (200 mg, 0.65 mmol, 1 *eq*) in dioxane (4 mL) and H_2O (2 mL) were added **215-8a** (235 mg, 0.65 mmol, 1 *eq*), $\text{Pd(PPh}_3)_4$ (75 mg, 64.7 μmol , 0.1 *eq*) and Cs_2CO_3 (316 mg, 0.97 mmol, 1.5 *eq*). The mixture was stirred at 80°C for 16 hr. The reaction was monitored by LCMS. LCMS showed that the starting material was consumed and the peak with the desired MS was observed. The reaction solution was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2) to give **Compound 215** (100 mg, 0.20 mmol, 31% yield). 10 mg of the crude product was re-purified by Prep-HPLC to give **Compound 215** (2.50 mg, 5.3 μmol , 8.14e-1% yield). LCMS (ESI): RT = 0.951 min, mass calcd. for $\text{C}_{26}\text{H}_{22}\text{F}_3\text{N}_3\text{O}_2$ 465.17, m/z found 466.0 $[\text{M}+\text{H}]^+$, ^1H NMR (400 MHz, CDCl_3) δ 9.64 (s, 1H), 7.62 (d, $J = 7.8$ Hz, 1H), 7.53 - 7.40 (m, 3H), 7.32 (s, 3H), 7.17 (d, $J = 5.3$ Hz, 2H), 7.08 (d, $J = 8.5$ Hz, 2H), 6.97 (t, $J = 7.7$ Hz, 1H), 6.60 (s, 1H), 5.38 (s, 2H), 3.71 - 3.61 (m, 1H), 3.71 - 3.61 (m, 1H), 3.71 - 3.61 (m, 5H).

Example 202: 2-(2-(3-aminopropyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 216)



Step 1: tert-butyl (3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propyl) carbamate

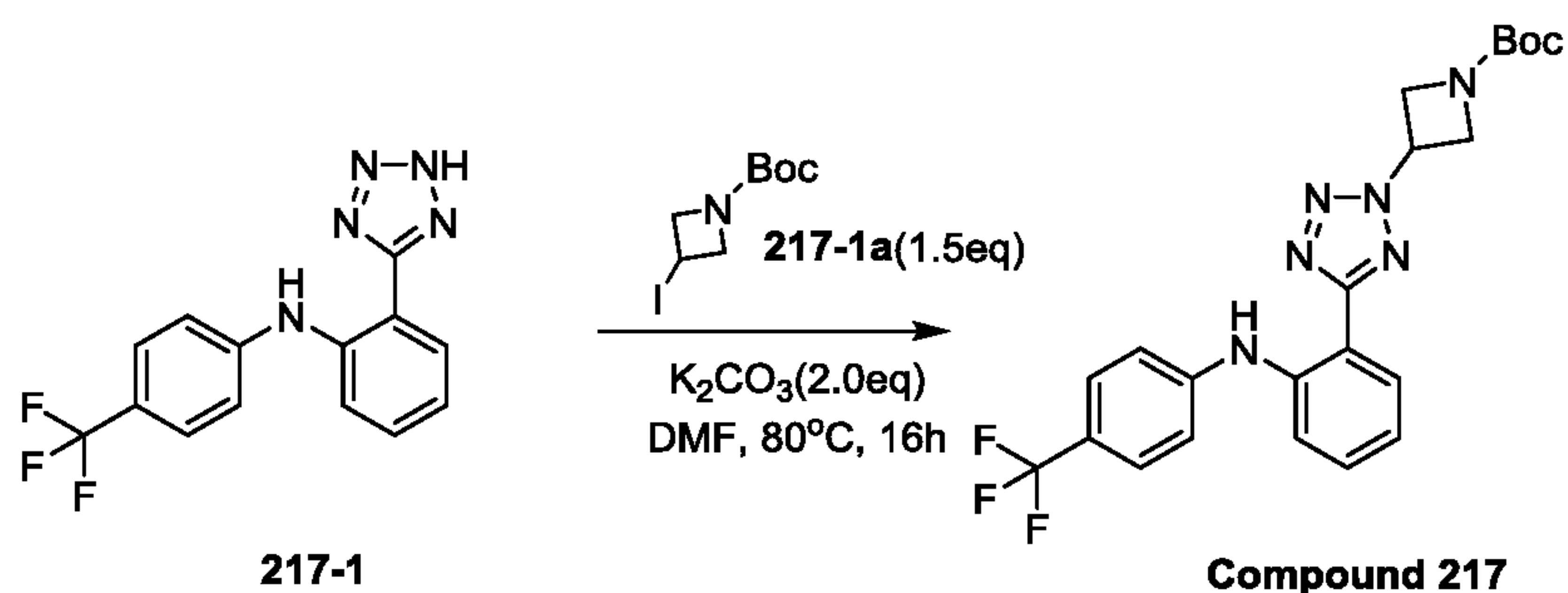
[00668] To the solution of **216-1** (50 mg, 0.16 mmol, 1 *eq*) in THF (1 mL) was added **216-1a** (37 mg, 0.2 mmol, 37 μL , 1.3 *eq*) and PPh_3 (129 mg, 0.49 mmol, 3 *eq*) at 0°C . Then DIAD (99 mg, 0.49 mmol, 96 μL , 3 *eq*) was added to the mixture. The solution was warmed up to 30°C and stirred for 16 hr. The reaction was monitored by LCMS. LCMS showed that the starting material was consumed and the main peak was the desired MS. The reaction solution was concentrated

under reduced pressure. The residue was purified by column chromatography (SiO₂) to give **216-2** (100 mg, crude).

Step 2: 2-(2-(3-aminopropyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

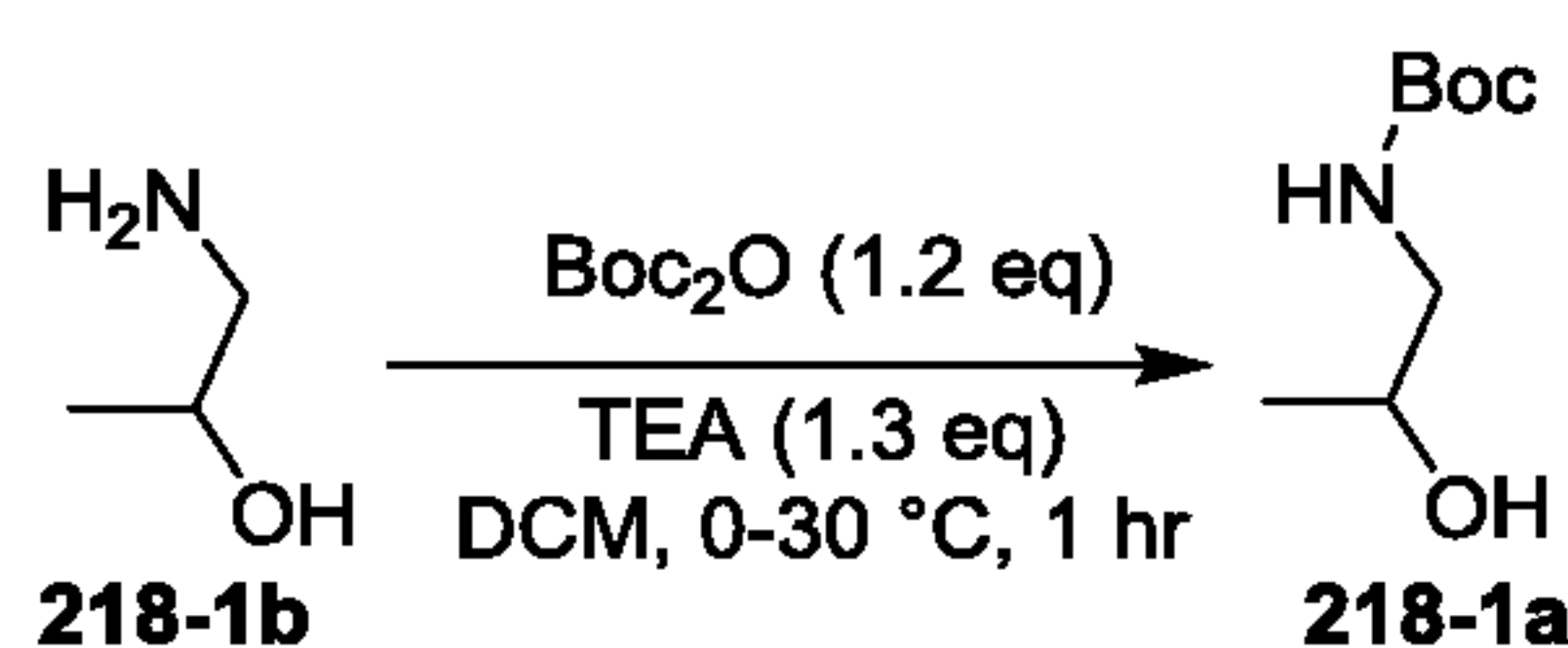
[00669] To the solution of **216-2** (100 mg, 0.22 mmol, 1 *eq*) in MeOH (4 mL) was added HCl/dioxane (4 M, 4 mL, 74 *eq*). The mixture was stirred at 25 °C for 1 hr. The reaction was monitored by LCMS. LCMS showed that the starting material remained a little and the desired MS was observed. The reaction solution was concentrated under reduced pressure. The residue was purified by Prep-HPLC to give **Compound 216** (4.16 mg, 11.5 μ mol, 5 % yield). LCMS (ESI): RT = 0.689 min, mass calcd. for C₁₇H₁₇F₃N₆ 362.15, *m/z* found 342.9 [M-F-1]⁺, ¹H NMR (400 MHz, CDCl₃) δ 9.04 (s, 1H), 8.18 (d, *J* = 6.5 Hz, 1H), 7.56 - 7.48 (m, 3H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.32 - 7.26 (m, 2H), 7.03 (t, *J* = 7.4 Hz, 1H), 4.91 - 4.72 (m, 2H), 2.91 - 2.77 (m, 2H), 2.28 - 2.19 (m, 2H).

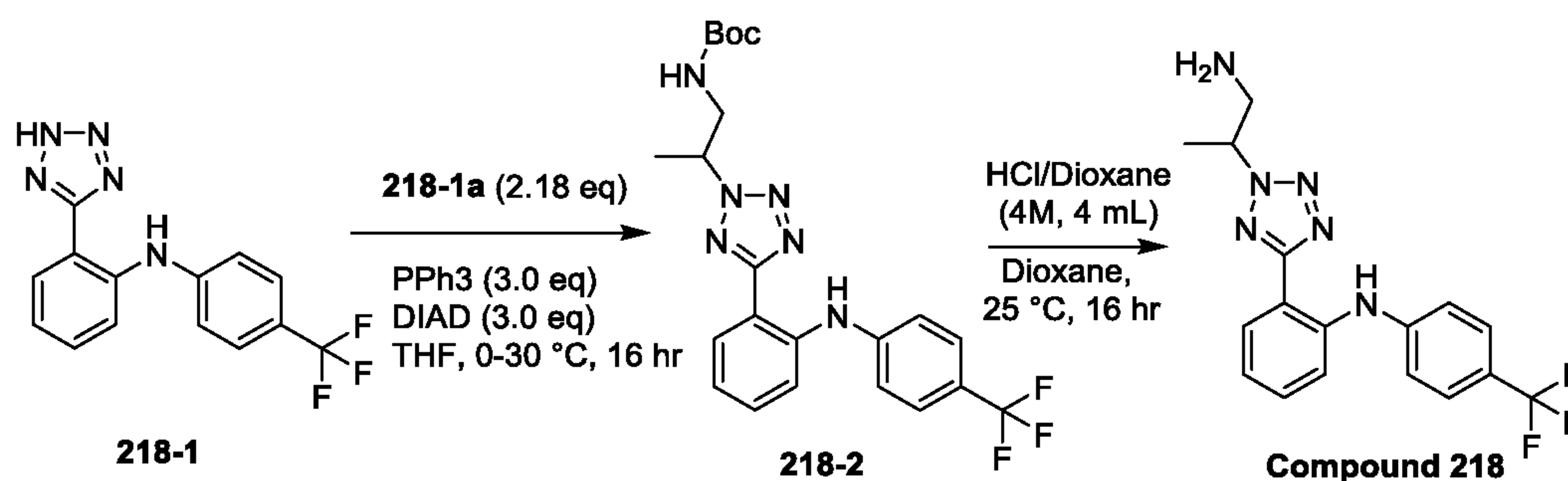
Example 203: tert-butyl 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)azetidine-1-carboxylate (Compound 217)



[00670] To a solution of **217-1** (100 mg, 0.3 mmol, 1.0 *eq*) in DMF (3.0 mL) was added K₂CO₃ (90.5 mg, 0.6 mmol, 2.0 *eq*) and **217-1a** (139.1 mg, 0.5 mmol, 1.5 *eq*). The mixture was stirred at 80 °C for 16 h. LC-MS showed 37% of **217-1** remained. Several new peaks were shown on LC-MS and 48% of desired compound was detected. The mixture was purified by prep-HPLC to give **Compound 217** (25.9 mg, 56.3 μ mol, 17% yield). LCMS (ESI): RT = 0.935 min, mass calc. for C₂₂H₂₃F₃N₆O 460.18 *m/z* found 483.17 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 8.99 (s, 1H), 8.24 - 8.21 (d, *J* = 1.5, 8.0 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 3H), 7.44 - 7.37 (m, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.10 - 7.03 (m, 1H), 5.73 - 5.66 (m, *J* = 5.5, 7.6 Hz, 1H), 4.62 - 4.48 (m, 4H), 1.53 - 1.48 (m, 9H).

Example 204: 2-(2-(1-aminopropan-2-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 218)





Step 1: tert-butyl (2-hydroxypropyl)carbamate

[00671] To the solution of **218-1b** (100 mg, 1.3 mmol, 0.1 mL, 1 *eq*) in DCM (1 mL) were added TEA (175 mg, 1.7 mmol, 0.2 mL, 1.3 *eq*) and Boc_2O (349 mg, 1.6 mmol, 0.4 mL, 1.2 *eq*) at 0 °C. The reaction solution was warmed up to 30 °C and stirred for 1 hr. The reaction was monitored by TLC. TLC (PE:EA = 3:1) showed that the starting material was consumed and several new spots with smaller polarity was observed. The reaction was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2) to give **218-1a** (250 mg, crude). ^1H NMR (400 MHz, CDCl_3) δ 3.96 - 3.85 (m, 1H), 3.34 - 3.21 (m, 1H), 3.07 - 2.95 (m, 1H), 1.45 (s, 9H), 1.18 (d, $J = 6.5$ Hz, 3H).

Step 2: tert-butyl (2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propyl)carbamate

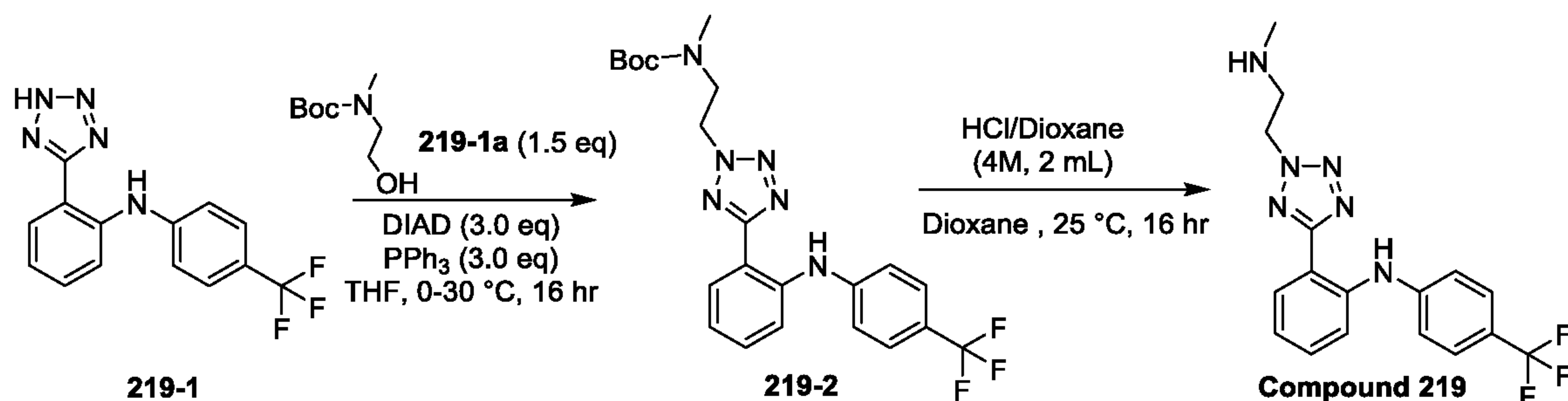
[00672] To the solution of **218-1a** (250 mg, 1.4 mmol, 2.2 *eq*) in THF (2 mL) was added PPh_3 (516 mg, 2.0 mmol, 3 *eq*) and **218-1** (200 mg, 0.66 mmol, 1 *eq*) at 0 °C. Then DIAD (397 mg, 2.0 mmol, 0.4 mL, 3 *eq*) was added to the mixture. The solution was warmed up to 30 °C and stirred for 16 hr. The reaction was monitored by LCMS. LCMS showed that the starting material was consumed and the main peak was the desired MS. The reaction was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2) to give **218-2** (180 mg, 0.35 mmol, 54% yield). ^1H NMR (400 MHz, CDCl_3) δ 9.04 (s, 1H), 8.20 (d, $J = 6.5$ Hz, 1H), 7.54 (d, $J = 8.5$ Hz, 3H), 7.41 - 7.35 (m, 1H), 7.30 (d, $J = 8.5$ Hz, 2H), 7.05 (t, $J = 7.5$ Hz, 1H), 5.24 - 5.12 (m, 1H), 4.85 - 4.75 (m, 1H), 3.84 - 3.64 (m, 2H), 1.69 (d, $J = 6.8$ Hz, 3H), 1.40 - 1.36 (m, 9H).

Step 3: 2-(2-(1-aminopropan-2-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00673] To the solution of **218-2** (50 mg, 0.11 mmol, 1 *eq*) in dioxane (2 mL) was added HCl/dioxane (4 M, 2 mL, 74 *eq*). The mixture was stirred at 25 °C for 16 hr. The reaction was monitored by LCMS. LCMS showed that the starting material was consumed and one main peak with desired MS. The reaction solution was concentrated under reduced pressure. The residue was purified by prep-HPLC to give **Compound 218** (16.08 mg, 39.5 μmol , 36.6% yield, HCl). LCMS (ESI): RT = 0.689 min, mass calcd. for $\text{C}_{17}\text{H}_{17}\text{F}_3\text{N}_6$ 362.15, m/z found 342.9 $[\text{M}-\text{F}-1]^+$, ^1H NMR

(400 MHz, DMSO-*d*₆) δ 8.79 (s, 1H), 8.17 (br, 3H), 8.06 (dd, *J* = 1.3, 7.8 Hz, 1H), 7.59 - 7.51 (m, 4H), 7.25 - 7.19 (m, 3H), 5.41 - 5.31 (m, 1H), 3.49 - 3.44 (m, 2H), 1.60 (d, *J* = 6.8 Hz, 3H).

Example 205: 2-(2-(2-(methylamino)ethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 219)



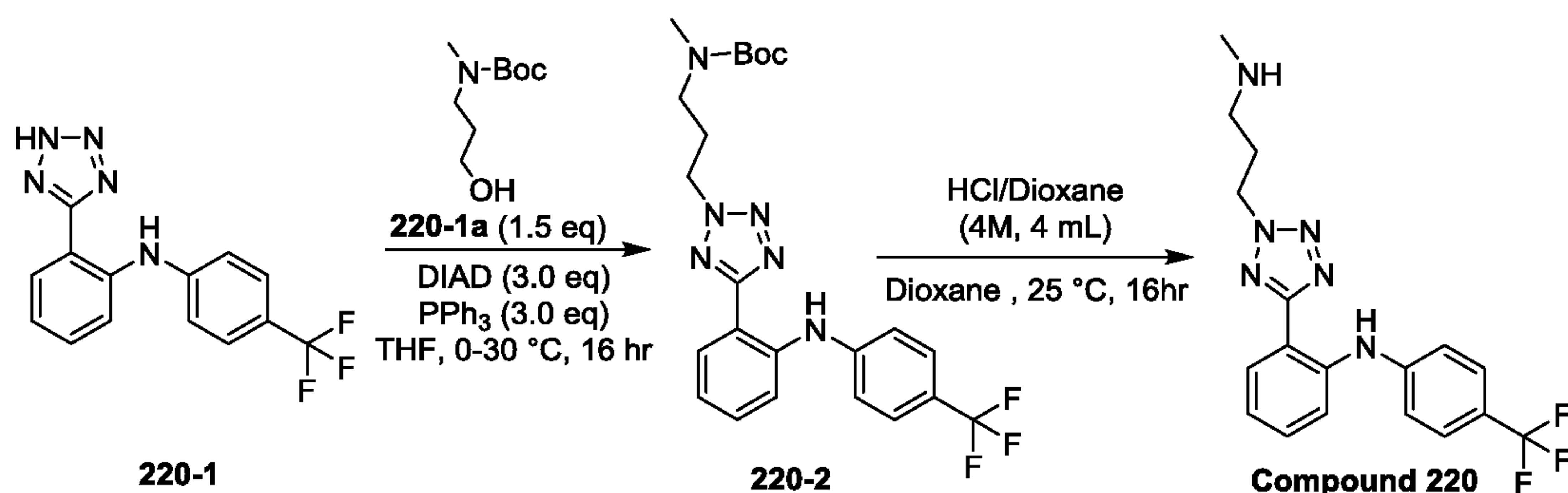
Step 1: tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethyl)carbamate

[00674] To the solution of **219-1** (200 mg, 0.66 mmol, 1 *eq*) in THF (2 mL) were added PPh₃ (516 mg, 2.0 mmol, 3 *eq*) and **219-1a** (172 mg, 0.98 mmol, 59 μ L, 1.5 *eq*) at 0 °C. Then DIAD (397 mg, 2.0 mmol, 0.4 mL, 3 *eq*) was added to the mixture. The reaction solution was warmed up to 30 °C and stirred for 16 hr. The reaction was monitored by LCMS. LCMS showed that the starting material was consumed and the desired MS was observed. The reaction was concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂) to give **219-2** (45 mg, 97 μ mol, 15% yield).

Step 2: 2-(2-(2-(methylamino)ethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00675] To the solution of **219-2** (40 mg, 86 μ mol, 1 *eq*) in dioxane (2 mL) was added HCl/dioxane (4 M, 2 mL, 92 *eq*). The mixture was stirred at 25 °C for 16 hr. The reaction was monitored by LCMS. LCMS showed that the starting material was consumed and the main peak was the desired MS. The reaction solution was concentrated under reduced pressure. The residue was purified by prep-HPLC to give **Compound 219** (2.76 mg, 6.9 μ mol, 8.0% yield, HCl). LCMS (ESI): RT = 0.693 min, mass calcd. for C₁₇H₁₇F₃N₆ 362.15, *m/z* found 342.9 [M-F-1]⁺, ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.17 (br, 2H), 8.80 (s, 1H), 8.03 (d, *J* = 6.8 Hz, 1H), 7.60 - 7.48 (m, 4H), 7.27 (d, *J* = 8.5 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 5.12 (t, *J* = 5.6 Hz, 2H), 3.63 - 3.54 (m, 2H), 2.60 (t, *J* = 5.0 Hz, 3H).

Example 206: 2-(2-(3-(methylamino)propyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 220)



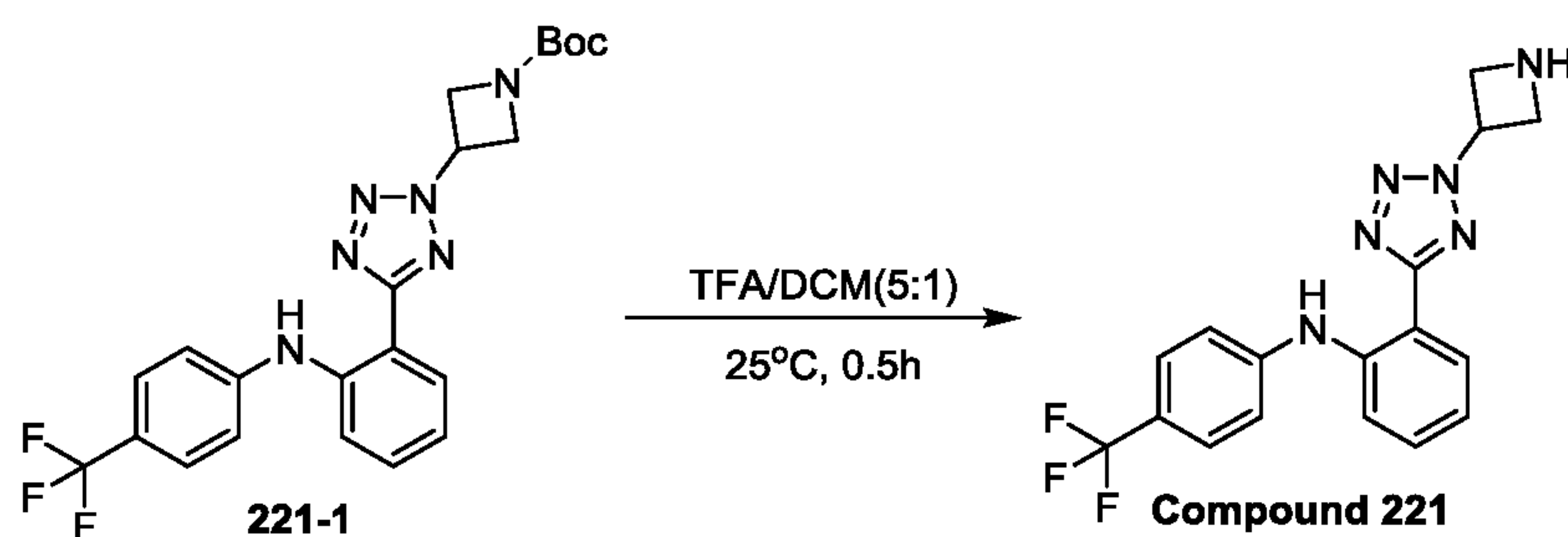
Step 1: tert-butyl methyl(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propyl)carbamate

[00676] To the solution of **220-1** (200 mg, 0.66 mmol, 1 *eq*) in THF (2 mL) was added PPh₃ (516 mg, 2.0 mmol, 3 *eq*) and **220-1a** (186 mg, 0.98 mmol, 1.5 *eq*) at 0 °C. Then DIAD (397 mg, 2.0 mmol, 0.4 mL, 3 *eq*) was added to the mixture. The reaction solution was warmed up to 30 °C and stirred for 16 hr. The reaction was monitored by LCMS. LCMS showed that the starting material was consumed and the desired MS was observed. The reaction was concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂) to give **220-2** (241 mg, 0.48 mmol, 73% yield). ¹H NMR (400 MHz, CDCl₃) δ 9.04 (s, 1H), 8.19 (d, *J* = 6.5 Hz, 1H), 7.53 (dd, *J* = 2.9, 8.7 Hz, 3H), 7.37 (t, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.04 (t, *J* = 7.5 Hz, 1H), 4.72 (t, *J* = 7.2 Hz, 2H), 3.44 - 3.35 (m, 2H), 2.89 (s, 3H), 2.39 - 2.27 (m, 2H), 1.44 (br s, 9H).

Step 2: 2-(2-(3-(methylamino)propyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

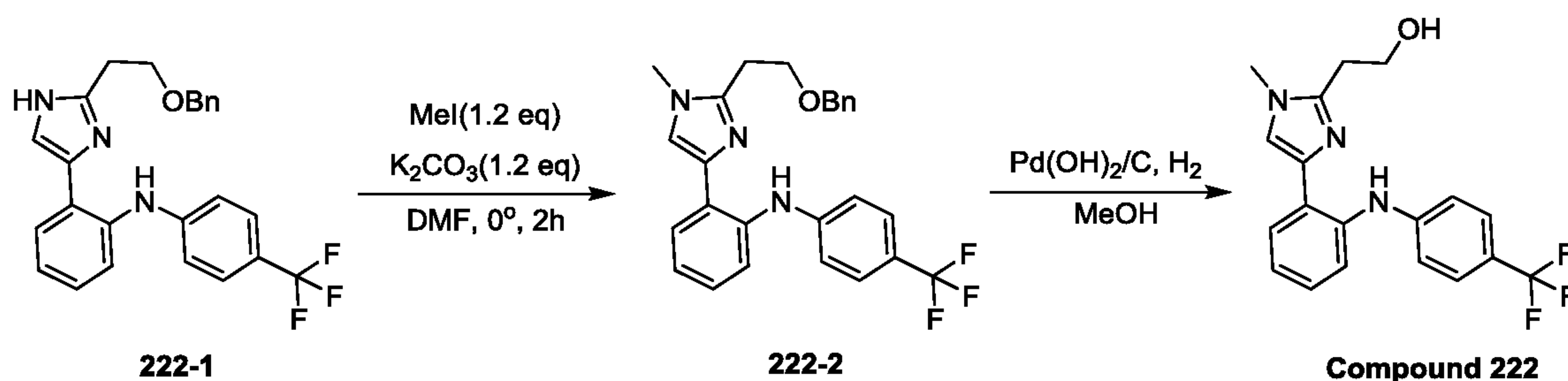
[00677] To the solution of **220-2** (50 mg, 0.1 mmol, 1 *eq*) in dioxane (2 mL) was added HCl/dioxane (4 M, 4 mL, 152 *eq*). The mixture was stirred at 25 °C for 16 hr. The reaction was monitored by LCMS. LCMS showed that the starting material was consumed and the main peak was the desired MS. The reaction solution was concentrated under reduced pressure. The residue was purified by prep-HPLC to give **Compound 220** (6.49 mg, 16.9 μmol, 16.1% yield). LCMS (ESI): RT = 0.707 min, mass calcd. for C₁₈H₁₉F₃N₆ 376.16, *m/z* found 376.9[M+1]⁺, ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (br, 2H), 8.76 (s, 1H), 8.03 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.59 - 7.47 (m, 4H), 7.25 - 7.16 (m, 3H), 4.87 (t, *J* = 6.9 Hz, 2H), 3.04 - 2.93 (m, 2H), 2.54 - 2.52 (m, 2H), 2.37 - 2.27 (m, 2H).

Example 207: 2-(2-(azetidin-3-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 221)



[00678] To a solution of **221-1** (20.0 mg, 43.4 μmol , 1.0 eq) in DCM (1.0 mL) was added TFA (770 mg, 6.7 mmol, 0.5 mL, 155.4 eq). The mixture was stirred at 25 °C for 0.5 h. LC-MS showed **221-1** was consumed completely and one main peak with desired MS was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 221** (5.52 mg, 15.3 μmol , 35% yield). LCMS (ESI): RT = 0.696 min, mass calc. for $\text{C}_{17}\text{H}_{15}\text{F}_3\text{N}_6$ 360.13 m/z found 340.9 $[\text{M}-\text{F}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.04 (s, 1H), 8.22 (d, $J = 7.5$ Hz, 1H), 7.54 (d, $J = 8.0$ Hz, 3H), 7.39 (t, $J = 7.5$ Hz, 1H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.06 (t, $J = 7.4$ Hz, 1H), 5.86 - 5.79 (m, $J = 7.2$ Hz, 1H), 4.40 (t, $J = 7.7$ Hz, 2H), 4.17 (t, $J = 8.2$ Hz, 2H).

Example 208: 2-(1-methyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1H-imidazol-2-yl)ethan-1-ol (Compound 222)



Step 1: 2-[2-(2-benzyloxyethyl)-1-methyl-imidazol-4-yl]-N-[4-(trifluoromethyl)phenyl]aniline

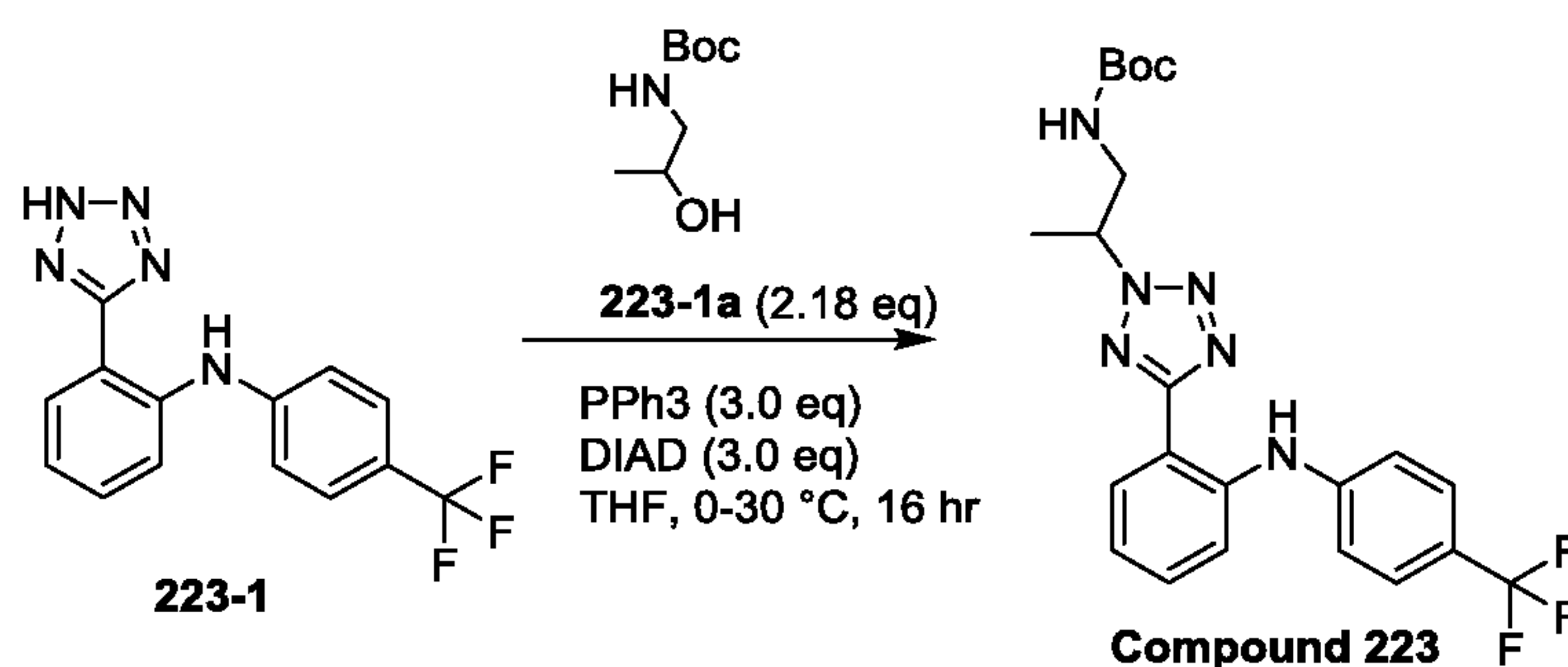
[00679] To a solution of **222-1** (80 mg, 0.18 mmol, 1 eq) and K_2CO_3 (37.9 mg, 0.27 mmol, 1.5 eq) in DMF (3 mL) was added MeI (31.2 mg, 0.22 mmol, 14 μL , 1.2 eq) at 0°C. The mixture was stirred at 0 °C for 2 hr. TLC showed reactant was consumed completely and one main spot was formed. The reaction mixture was poured into water (10 mL), extracted with EtOAc (5 mL *3). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated to give **222-2** (85 mg, crude), which was used in the next step directly without further purification.

Step 2: 2-[1-methyl-5-[2-[4-(trifluoromethyl)anilino]phenyl]imidazol-2-yl]ethanol

[00680] To a solution of **222-2** (85 mg, 0.19 mmol, 1 eq) in MeOH (2 mL) was added $\text{Pd}(\text{OH})_2/\text{C}$ (20%, 20 mg) under N_2 . The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 50°C for 16 hours. To the mixture was added

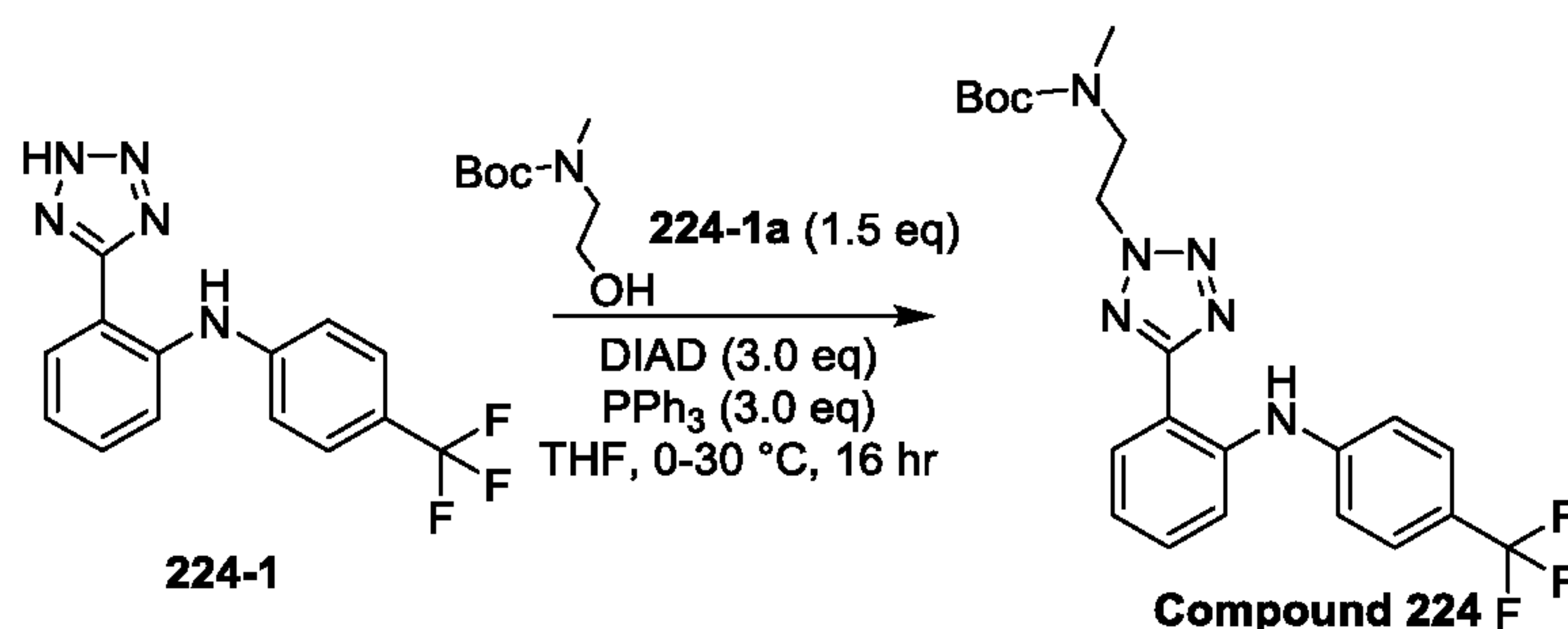
ammonium formate (237.4 mg, 3.77 mmol, 20 eq) and the mixture was stirred for 16 h at 70°C. The reaction mixture was filtered to remove Pd(OH)₂/C, and the filtrate was concentrated to give a residue. The residue was dissolved in MeOH (5mL) and Pd(OH)₂/C (10%, 20 mg) was added under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 20-30°C for 16 hours. The reaction mixture was stirred for another 6 h at 20-30°C. LC-MS showed ~30% of **222-2** was remained and ~60% of desired compound was detected. The reaction mixture was filtered and the residue was concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 222** (6.15 mg, 17.0 umol, 9.0% yield), which was confirmed by H NMR and NOE. LCMS (ESI): RT = 0.658 min, mass calc. for C₁₉H₁₈F₃N₃O 361.14, m/z found 361.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.49 (s, 1H), 7.66 (d, *J* = 7.0 Hz, 1H), 7.54 - 7.46 (m, 3H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.20 - 7.12 (m, 3H), 6.99 (t, *J* = 7.4 Hz, 1H), 4.84 (t, *J* = 5.3 Hz, 1H), 3.80 (q, *J* = 6.5 Hz, 2H), 3.62 (s, 3H), 2.86 (t, *J* = 6.7 Hz, 2H).

Example 209: tert-butyl (2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propyl)carbamate (Compound 223)



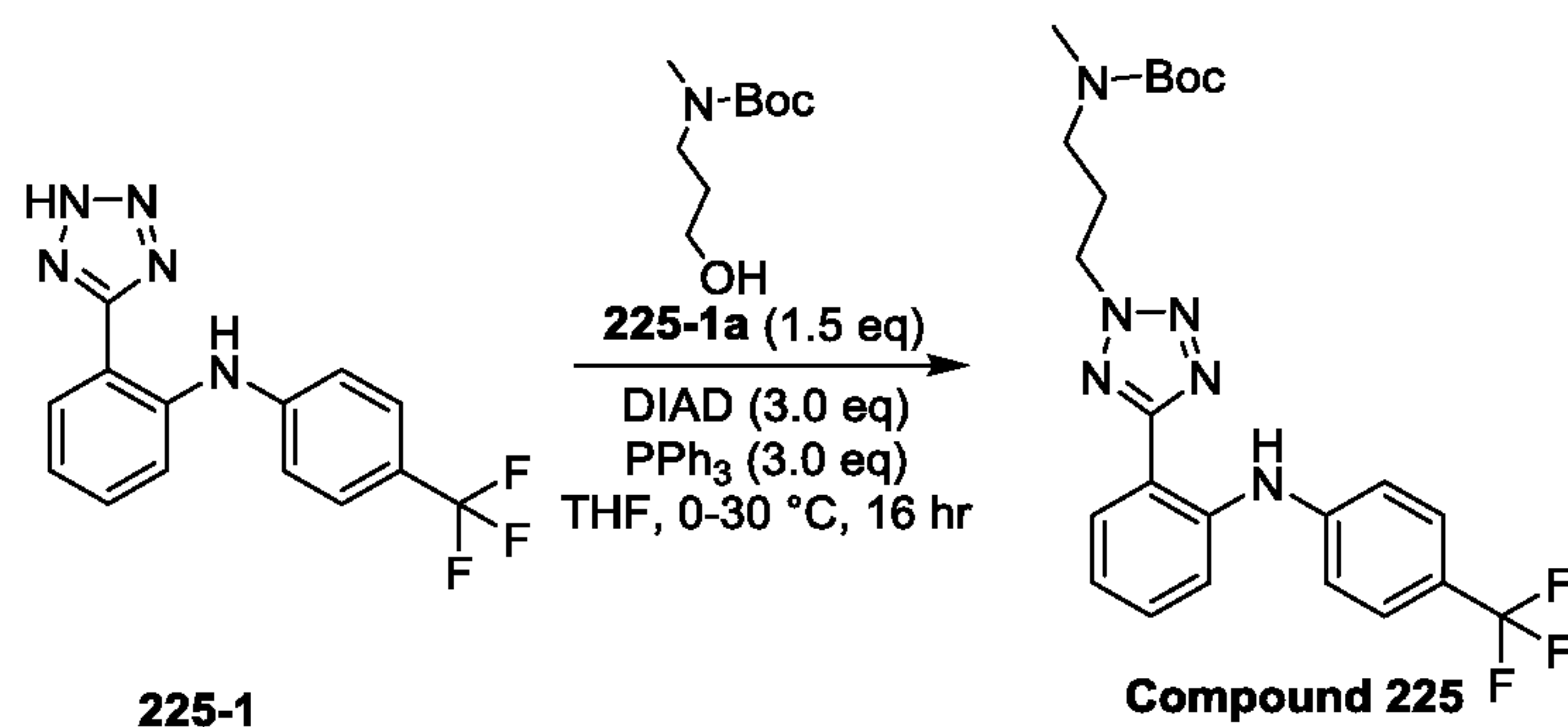
[00681] To the solution of **223-1a** (250 mg, 1.4 mmol, 2.2 eq) in THF (2 mL) was added PPh₃ (516 mg, 2.0 mmol, 3 eq) and compound **223-1** (200 mg, 0.66 mmol, 1 eq) at 0°C. Then DIAD (397 mg, 2.0 mmol, 0.4 mL, 3 eq) was added to the mixture. The solution was warmed up to 30 °C and stirred for 16 hr. The reaction was monitored by LCMS. LCMS showed that the starting material was consumed and one main peak with desired MS. The reaction was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂) to give **Compound 223** (180 mg, 0.35 mmol, 54% yield). LCMS (ESI): RT = 0.922 min, mass calcd. for C₂₂H₂₅F₃N₆O₂ 462.20, m/z found 485.0 [M+Na]⁺, ¹H NMR (400 MHz, CDCl₃) δ 9.04 (s, 1H), 8.20 (d, *J* = 6.5 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 3H), 7.41 - 7.35 (m, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 5.24 - 5.12 (m, 1H), 4.85 - 4.75 (m, 1H), 3.84 - 3.64 (m, 2H), 1.69 (d, *J* = 6.8 Hz, 3H), 1.40 - 1.36 (m, 9H).

Example 210: tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)ethyl)carbamate (Compound 224)



[00682] To the solution of **224-1** (200 mg, 0.66 mmol, 1 *eq*) in THF (2 mL) was added PPh₃ (516 mg, 2.0 mmol, 3 *eq*) and **224-1a** (172 mg, 0.98 mmol, 59 μ L, 1.5 *eq*) at 0 °C. Then DIAD (397 mg, 2.0 mmol, 0.4 mL, 3 *eq*) was added to the mixture. The reaction solution was warmed up to 30 °C and stirred for 16 hr. The reaction was monitored by LCMS. LCMS showed that the starting material was consumed and the desired MS was observed. The reaction was concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂) to give compound the crude product. 20 mg of the crude product was re-purified by prep-HPLC to give **Compound 224** (2.84 mg, 6.08 μ mol, 9.28e-1% yield). LCMS (ESI): RT = 0.908 min, mass calcd. for C₂₂H₂₅F₃N₆O₂ 462.20, m/z found 485.1 [M+Na]⁺, ¹H NMR (400 MHz, CDCl₃) δ 8.96 (s, 1H), 8.20 (dd, *J* = 1.5, 7.8 Hz, 1H), 7.56 - 7.50 (m, 3H), 7.40 - 7.34 (m, 1H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.07 - 7.00 (m, 1H), 4.92 - 4.79 (m, 2H), 3.91 - 3.81 (m, 2H), 2.93 - 2.67 (m, 3H), 1.39 - 1.30 (m, 9H).

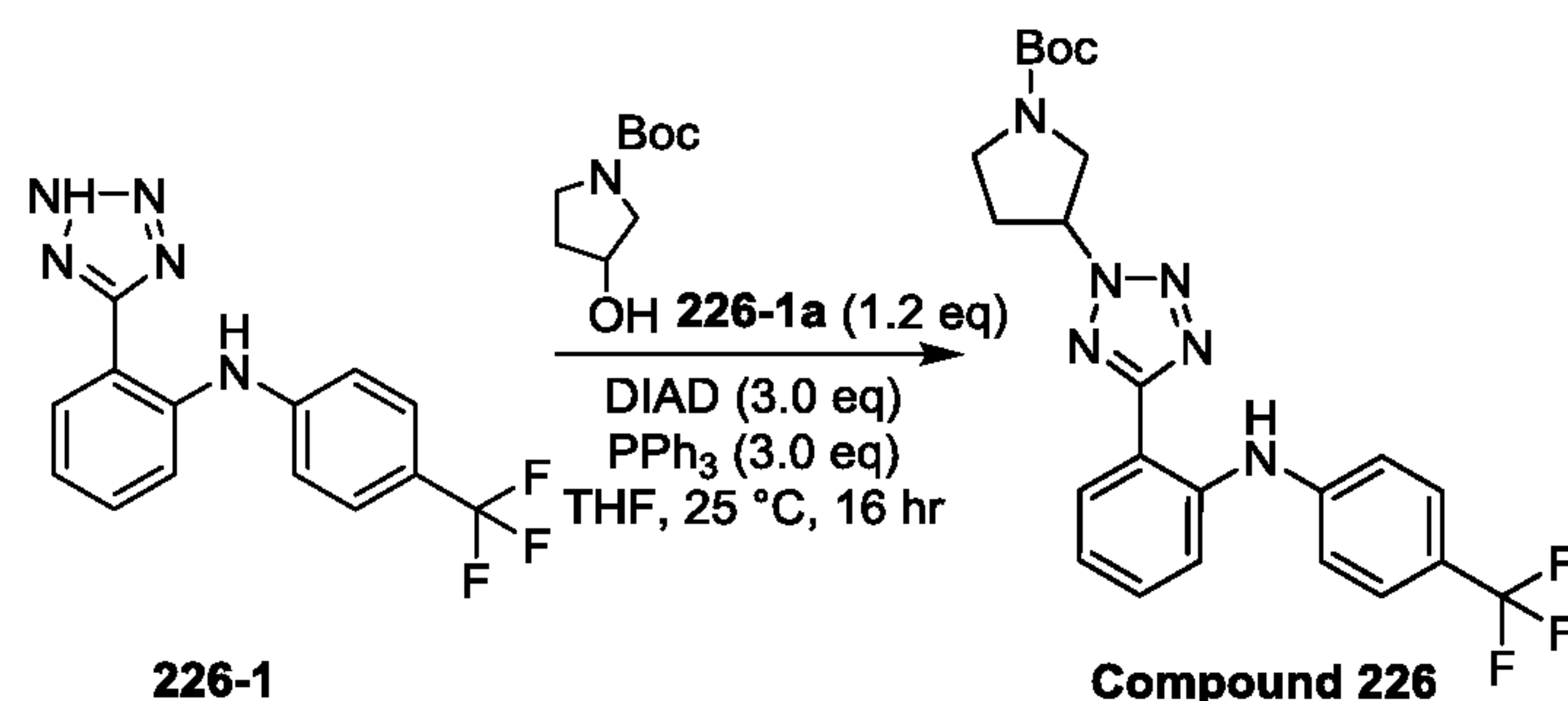
Example 211: tert-butyl methyl(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)propyl)carbamate (Compound 225)



[00683] To the solution of **225-1** (200 mg, 0.66 mmol, 1 *eq*) in THF (2 mL) was added PPh₃ (516 mg, 2.0 mmol, 3 *eq*) and **225-1a** (186 mg, 0.98 mmol, 1.5 *eq*) at 0 °C. Then DIAD (397 mg, 2.0 mmol, 0.4 mL, 3 *eq*) was added to the mixture. The reaction solution was warmed up to 30 °C and stirred for 16 hr. The reaction was monitored by LCMS. LCMS showed that the starting material was consumed and the desired MS was observed. The reaction was concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂) to give **Compound 225** (241 mg, 0.48 mmol, 73% yield). LCMS (ESI): RT = 0.944 min, mass calcd. for C₂₃H₂₇F₃N₆O₂ 476.21, m/z found 499.1[M+Na]⁺, ¹H NMR (400 MHz, CDCl₃) δ 9.04 (s, 1H), 8.19 (d, *J* = 6.5 Hz, 1H), 7.53

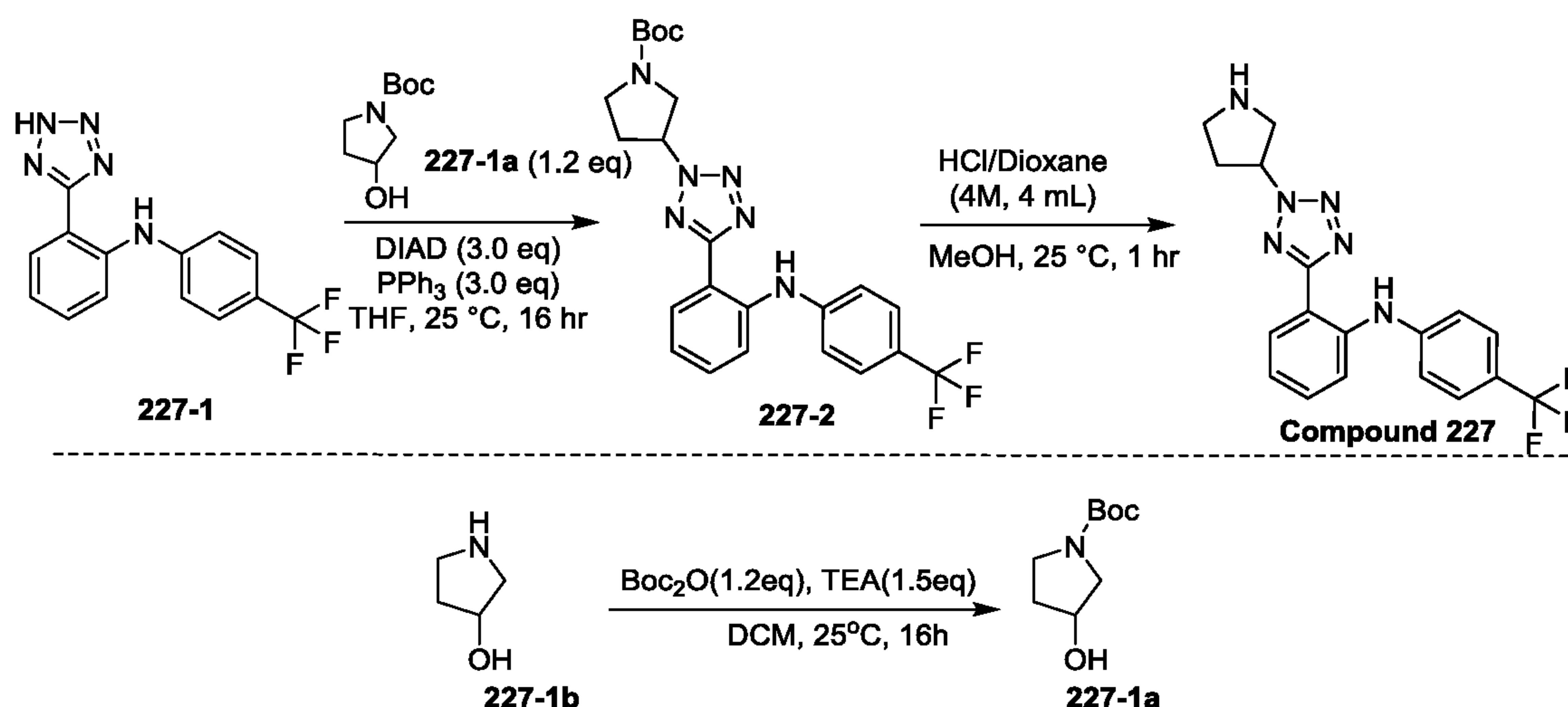
(dd, $J = 2.9, 8.7$ Hz, 3H), 7.37 (t, $J = 8.5$ Hz, 1H), 7.30 (d, $J = 8.5$ Hz, 2H), 7.04 (t, $J = 7.5$ Hz, 1H), 4.72 (t, $J = 7.2$ Hz, 2H), 3.44 - 3.35 (m, 2H), 2.89 (s, 3H), 2.39 - 2.27 (m, 2H), 1.44 (br s, 9H).

Example 212: tert-butyl 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-2H-tetrazol-2-yl)pyrrolidine-1-carboxylate (Compound 226)



[00684] To a solution of **226-1** (100.0 mg, 0.3 mmol, 1.0 eq), **226-1a** (73.6 mg, 0.4 mmol, 32 uL, 1.2 eq), PPh_3 (257.7 mg, 1.0 mmol, 3.0 eq) in THF (2.0 mL) was added dropwise DIAD (198.7 mg, 1.0 mmol, 0.2 mL, 3.0 eq) at 0 °C over 10 min. After addition, the mixture was stirred for 16 h at 25 °C. LC-MS showed 19% of **1** was remained and 40% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by column chromatography (SiO_2) to give **Compound 226** (70 mg, 0.1 mmol, 42% yield). 20 mg was repurified by prep-HPLC to give **Compound 226** (2.93 mg). LCMS (ESI): RT = 0.928 min, mass calc. for $\text{C}_{23}\text{H}_{25}\text{F}_3\text{N}_6\text{O}_2$ 474.20 m/z found 497.1 $[\text{M}+\text{Na}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 8.98 (s, 1H), 8.21 (d, $J = 7.0$ Hz, 1H), 7.54 (d, $J = 8.5$ Hz, 3H), 7.39 (t, $J = 7.7$ Hz, 1H), 7.30 (d, $J = 8.3$ Hz, 2H), 7.05 (t, $J = 7.4$ Hz, 1H), 5.50 (s, 1H), 4.19-3.92 (m, 2H), 3.85-3.56 (m, 2H), 2.81-2.46 (m, 2H), 1.47 (s, 9H).

Example 213: 2-(2-(pyrrolidin-3-yl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 227)



Step 1: tert-butyl 3-hydroxypyrrolidine-1-carboxylate

[00685] To a solution of **227-1b** (0.7 g, 8.0 mmol, 0.6 uL, 1.0 eq) in DCM (10.0 mL) were added TEA (1.2 g, 12.0 mmol, 1.6 mL, 1.5 eq) and Boc₂O (2.1 g, 9.6 mmol, 2.2 mL, 1.2 eq). The mixture was stirred at 25 °C for 16 h. TLC (Petroleum ether : Ethyl acetate = 3:1) indicated **227-1b** was consumed completely and many new spots formed. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by column chromatography (SiO₂) to give **227-1a** (1.4 g, 7.5 mmol, 93% yield).

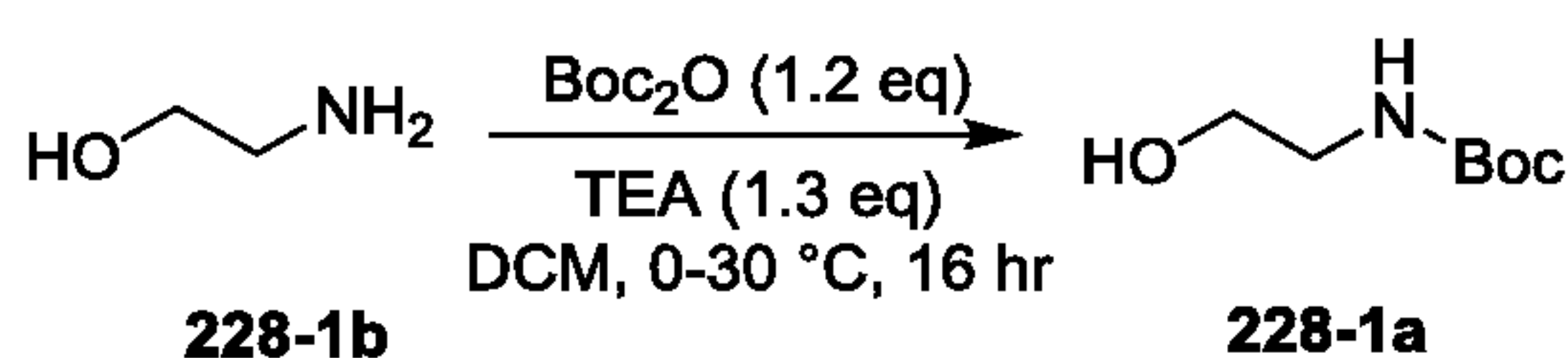
Step 2: tert-butyl 3-[5-[2-[4-(trifluoromethyl)anilino]phenyl]tetrazol-2-yl]azetidine-1-carboxylate

[00686] To a solution of **227-1** (100.0 mg, 0.3 mmol, 1.0 eq), **227-1a** (73.6 mg, 0.4 mmol, 31.7 uL, 1.2 eq), PPh₃ (257.7 mg, 1.0 mmol, 3.0 eq) in THF (2.0 mL) was added drop-wise DIAD (198.7 mg, 1.0 mmol, 0.2 mL, 3.0 eq) at 0 °C over 10 min. After addition, the mixture was stirred at this temperature for 16 h at 25 °C. LC-MS showed 19% of **227-1** was remained and 40% of desired compound was detected. The reaction mixture concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂) to give **227-2** (70 mg, 0.1 mmol, 42% yield). 20 mg was re-purified by prep-HPLC to give **227-2** (2.93 mg). LCMS (ESI): RT = 0.928 min, mass calc. for C₂₃H₂₅F₃N₆O₂ 474.20 m/z found 497.1 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 8.98 (s, 1H), 8.21 (d, *J* = 7.0 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 3H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.05 (t, *J* = 7.4 Hz, 1H), 5.50 (s, 1H), 4.19-3.92 (m, 2H), 3.85-3.56 (m, 2H), 2.81-2.46 (m, 2H), 1.47 (s, 9H).

Step 3: 2-(2-pyrrolidin-3-yltetrazol-5-yl)-N-[4-(trifluoromethyl)phenyl]aniline

[00687] To a solution of **227-2** (35.0 mg, 73.7 umol, 1.0 eq) in dioxane (1.0 mL) was added HCl/dioxane (3.0 mL). The mixture was stirred at 25 °C for 1 hr. LC-MS showed **227-2** was consumed completely and one main peak with desired MS was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 227** (11.09 mg, 29.6 umol, 40% yield). LCMS (ESI): RT = 0.692 min, mass calc. for C₁₈H₁₇N₃F₃N₆ 374.15 m/z found 374.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.03 (s, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 3H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 3.5 Hz, 2H), 7.02 (t, *J* = 7.4 Hz, 1H), 5.56-5.26 (m, 1H), 3.54-3.45 (m, 1H), 3.44-3.29 (m, 2H), 3.21-3.03 (m, 1H), 2.54-2.33 (m, 2H).

Example 214: 2-(2-(2-aminoethyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 228)



DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 317

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 317

NOTE: For additional volumes, please contact the Canadian Patent Office

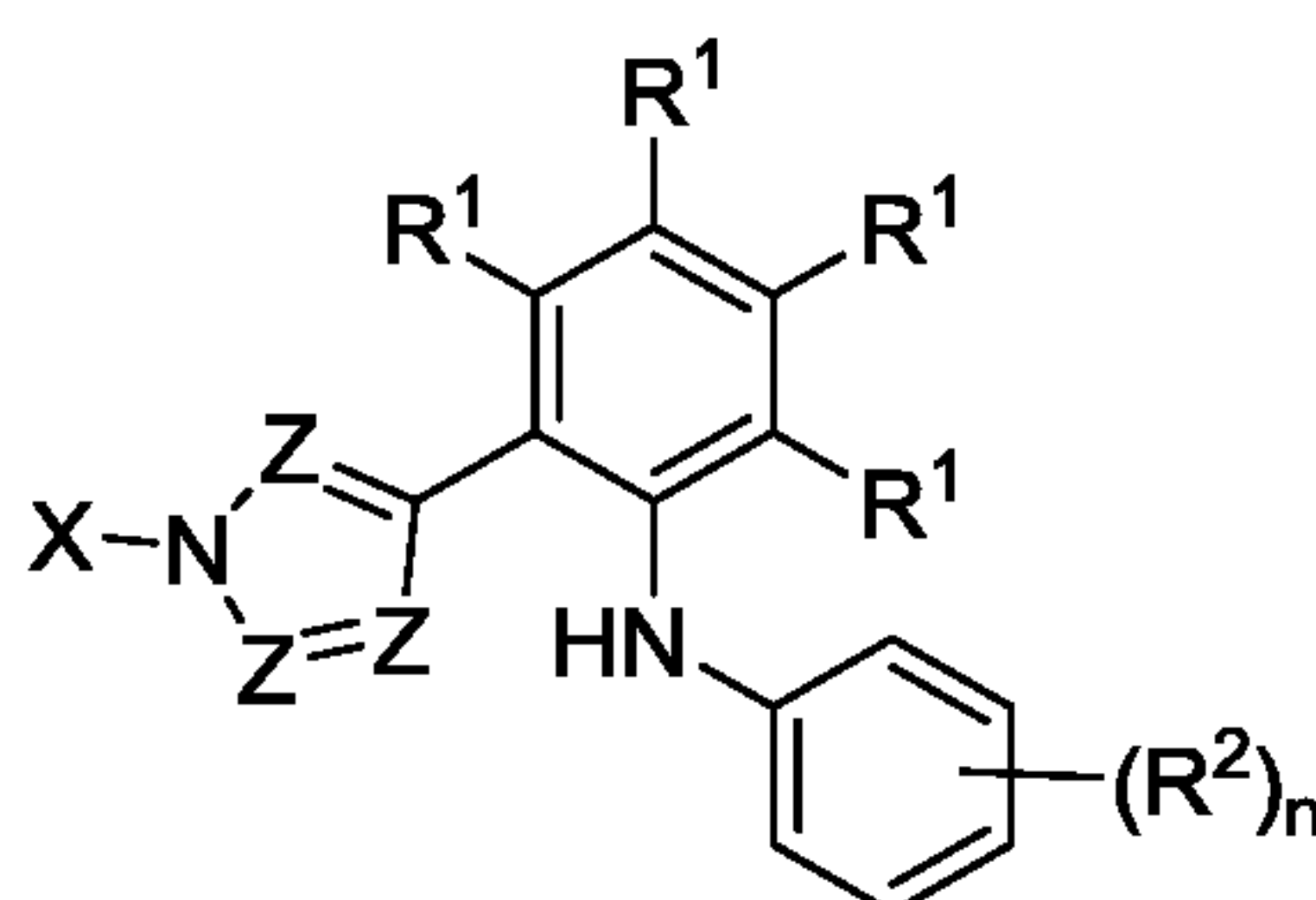
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CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein:

each Z is independently N or CR^Z;

each R^Z is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

X is substituted or unsubstituted C₂-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, unsubstituted aryl, substituted or unsubstituted heteroaryl, -L¹-Y¹, or -L²-L³-Y²;

L¹ is substituted or unsubstituted C₁-C₆alkylene;

Y¹ is substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L² is absent or substituted or unsubstituted C₁-C₆alkylene;

L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -O-NR³(C=O)-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)-, -(SO₂)NR³-(C=O)O-, -O(C=O)-NR³(SO₂)-, -NR³(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)NR³-, -O(C=O)-NR³(SO₂)-NR³-, or -NR³(SO₂)NR³-(C=O)O-;

each R³ is independently H or substituted or unsubstituted C₁-C₆alkyl;

Y² is H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl,

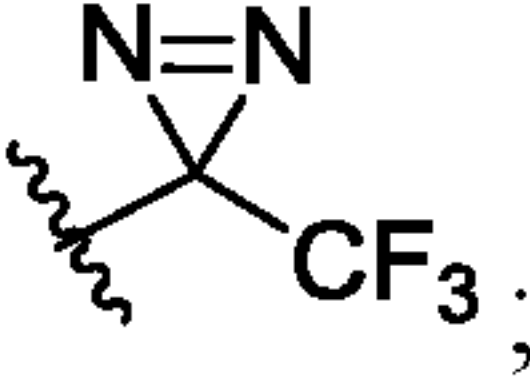
substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or R³ and Y² on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

each R¹ is independently H, halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

n is 1, 2, 3, 4, or 5;

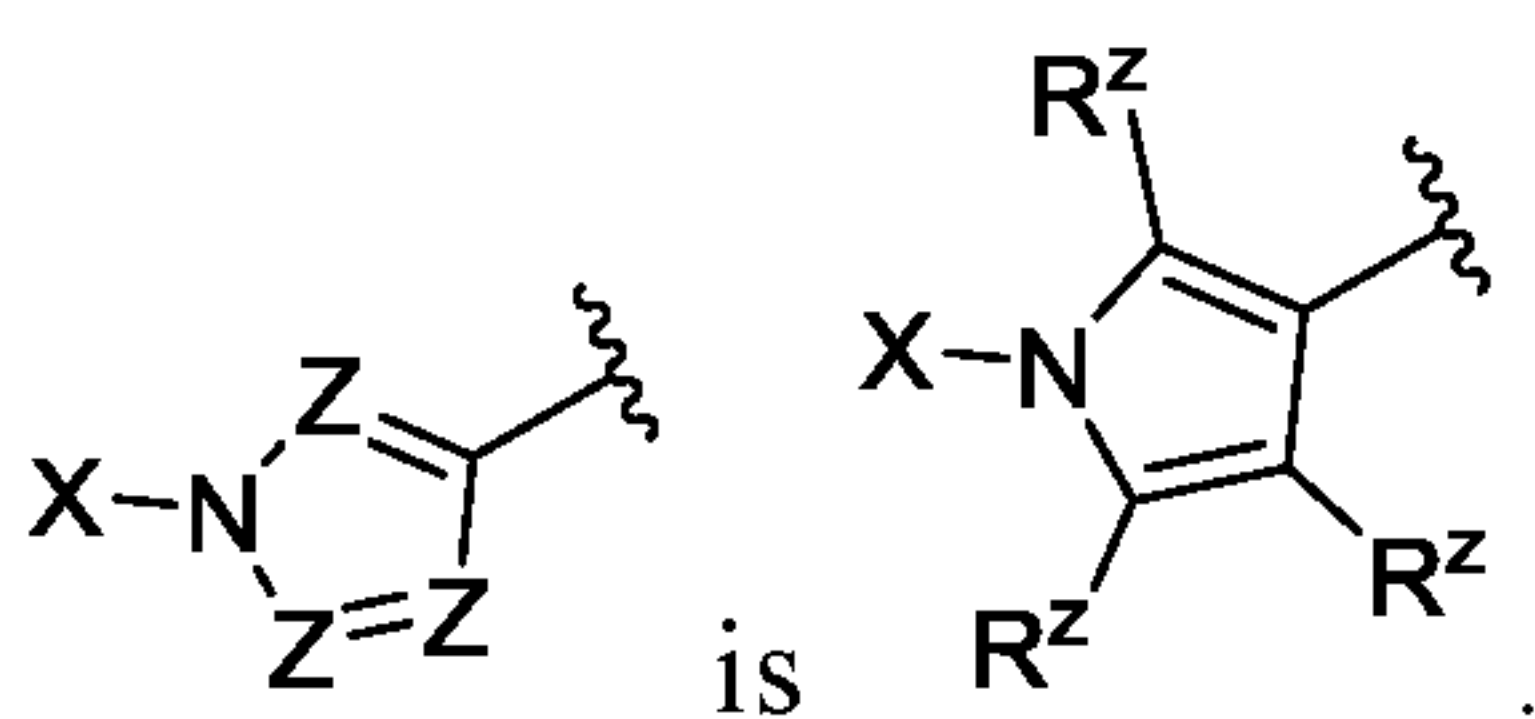
each R² is independently halogen, -N₃, -CN, -OR⁵, -SR⁵, -(SO₂)R⁵, -N(R⁵)₂, -CO₂R⁵, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or

unsubstituted aryl, substituted or unsubstituted heteroaryl, or ;

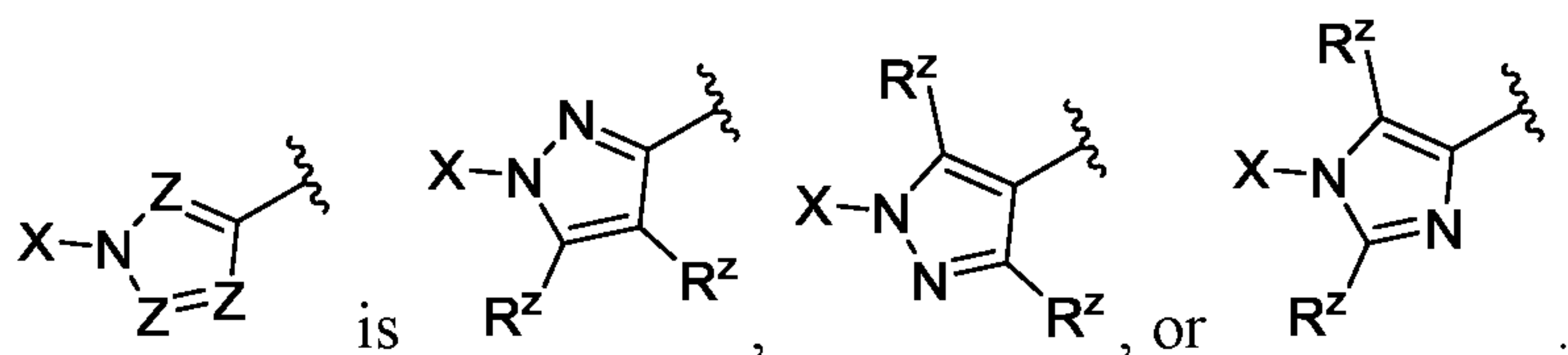
each R⁴ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

each R⁵ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

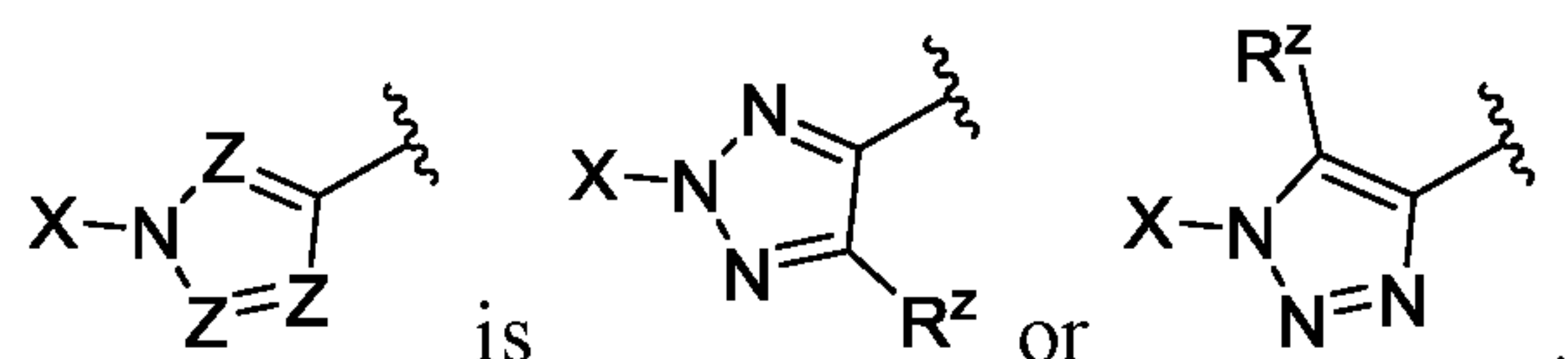
2. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein:



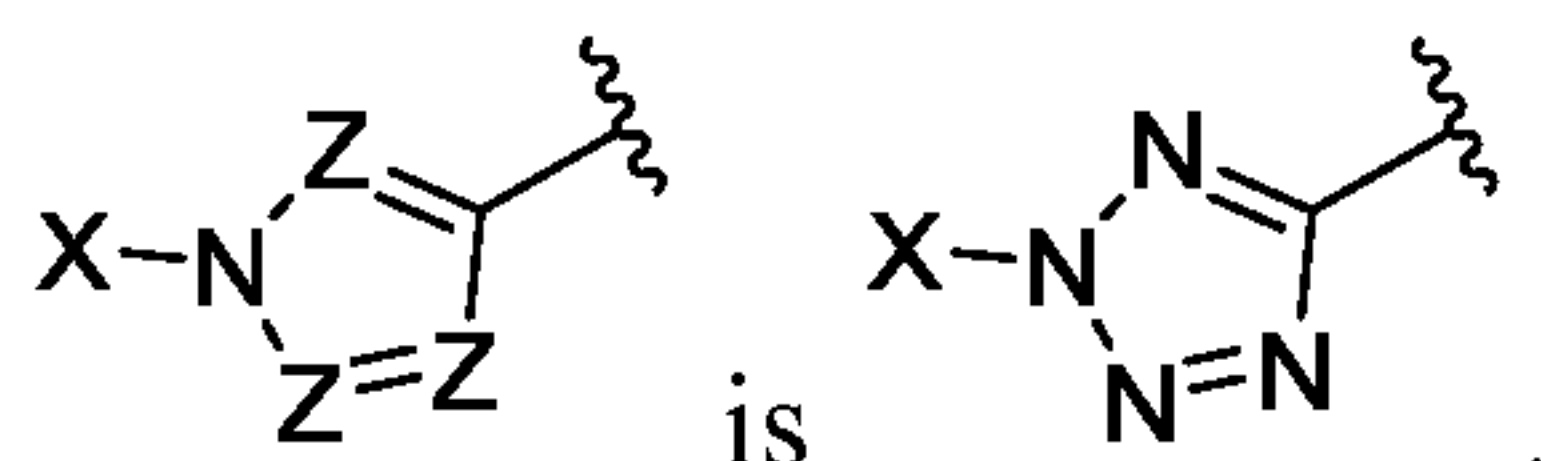
3. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein:



4. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein:



5. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein:



6. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-5, wherein:

each R^Z is independently H or substituted or unsubstituted C_1 - C_6 alkyl.

7. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-6, wherein:

X is substituted or unsubstituted C_2 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, unsubstituted aryl, or substituted or unsubstituted heteroaryl.

8. The compound, or pharmaceutically acceptable salt thereof, of claim 7, wherein:

X is substituted or unsubstituted C_2 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, or substituted or unsubstituted heteroaryl.

9. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-6, wherein:

X is $-L^1-Y^1$.

10. The compound, or pharmaceutically acceptable salt thereof, of claim 9, wherein:

L^1 is substituted or unsubstituted C_1 - C_4 alkylene; and

Y^1 is substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_6 heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl.

11. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-6, wherein:

X is $-L^2-L^3-Y^2$.

12. The compound, or pharmaceutically acceptable salt thereof, of claim 11, wherein:

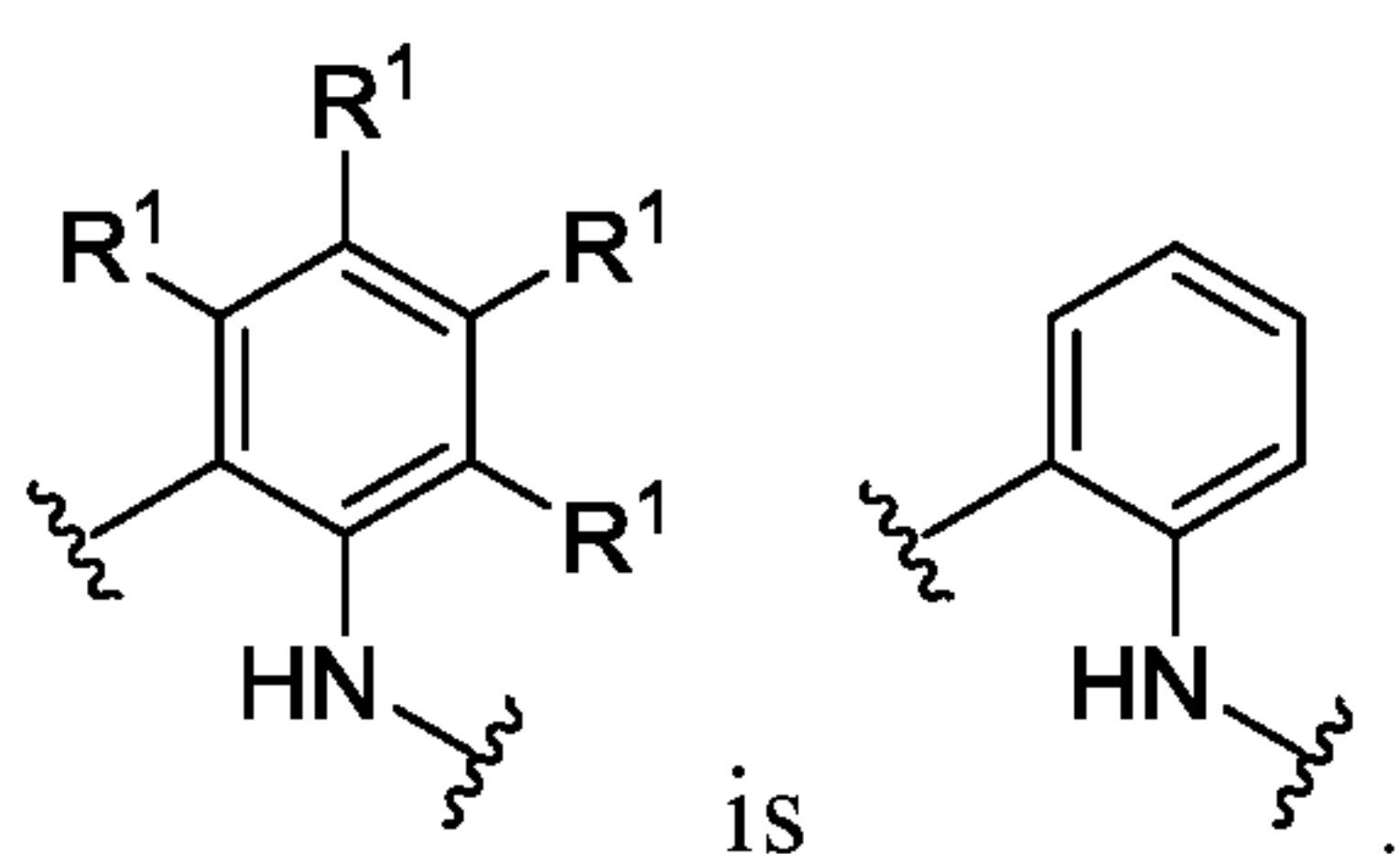
L^2 is substituted or unsubstituted C_1 - C_4 alkylene;

L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-,
 -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -
 NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -
 NR³(SO₂)NR³-(C=O)-, or -NR³(SO₂)NR³-(C=O)O-;

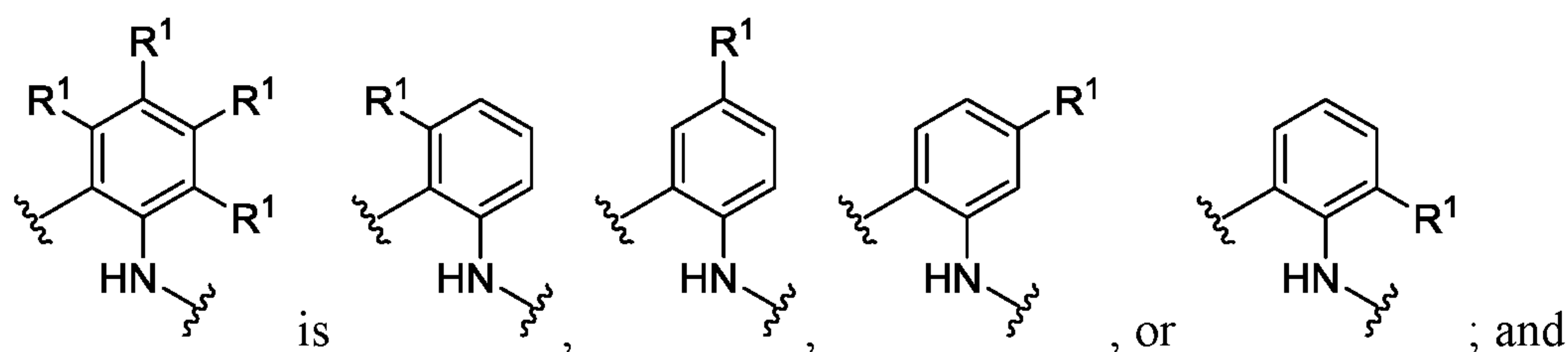
each R³ is independently H or substituted or unsubstituted C_1 - C_4 alkyl; and

Y² is H, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl,
 substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl,
 substituted or unsubstituted C_2 - C_6 heterocycloalkyl, substituted or unsubstituted phenyl, or
 substituted or unsubstituted monocyclic heteroaryl.

13. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-12,
 wherein:

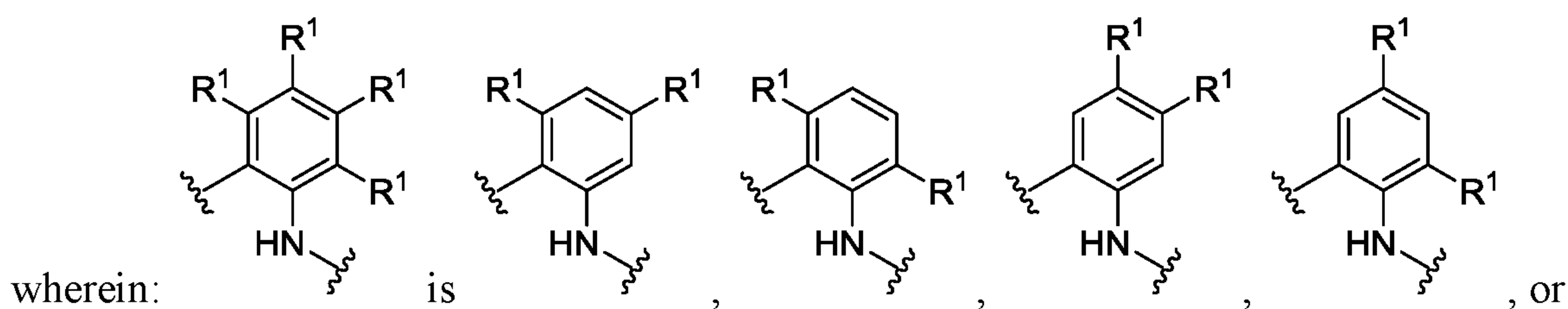


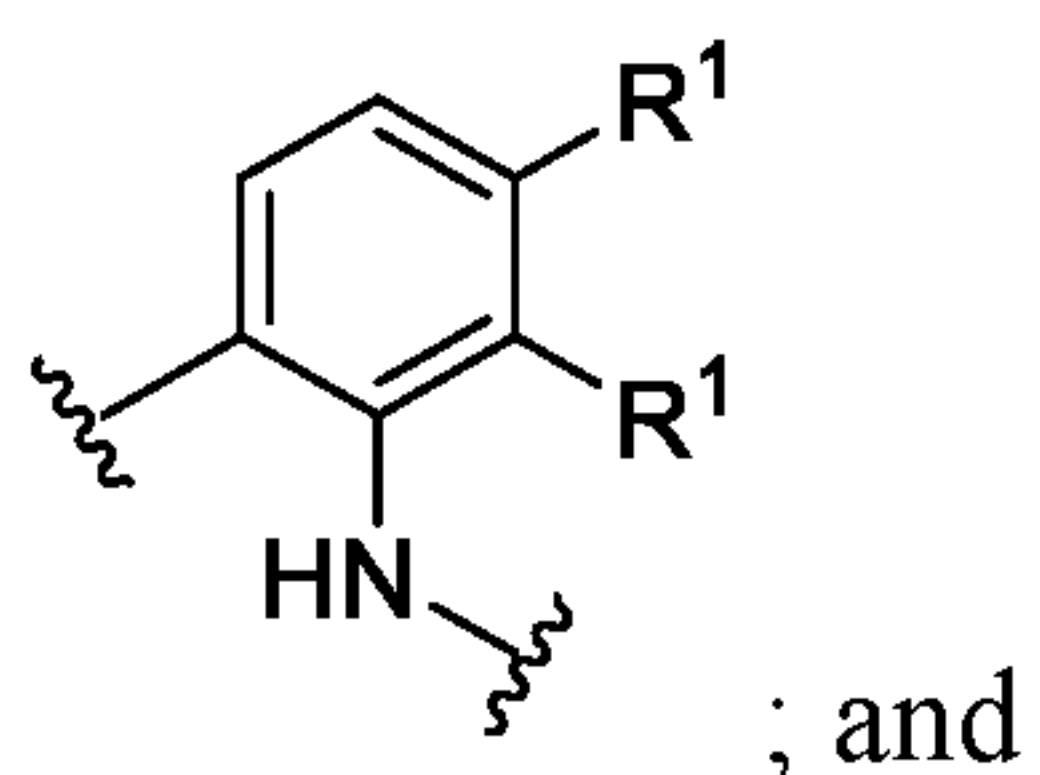
14. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-12,
 wherein:



R¹ is halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C_1 - C_6 alkyl, substituted or
 unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or
 unsubstituted aryl, or substituted or unsubstituted heteroaryl.

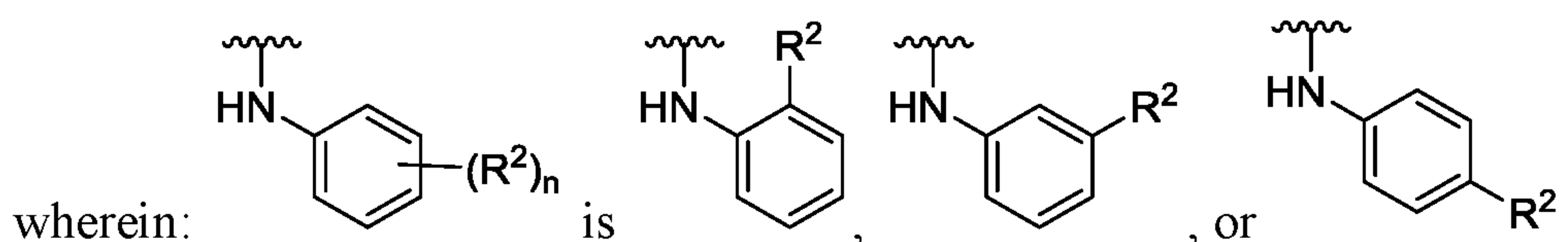
15. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-12,



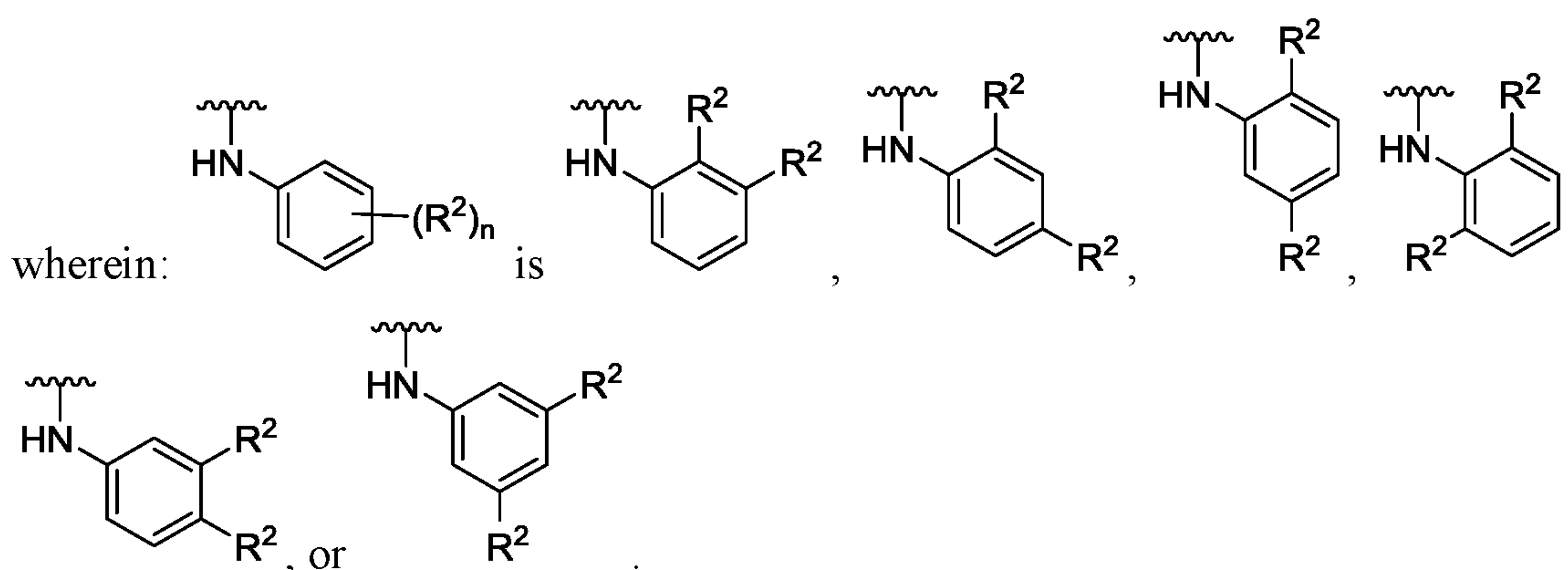


each R^1 is independently halogen, $-\text{CN}$, $-\text{OR}^4$, $-\text{SR}^4$, $-\text{N}(\text{R}^4)_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

16. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-15,



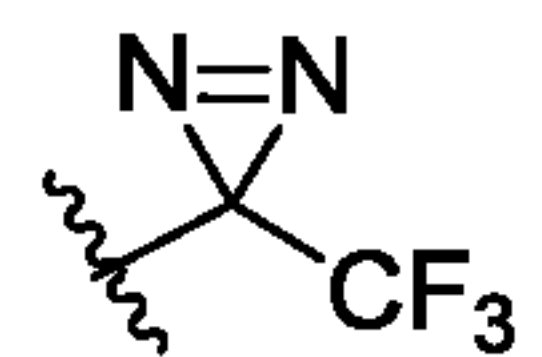
17. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-15,



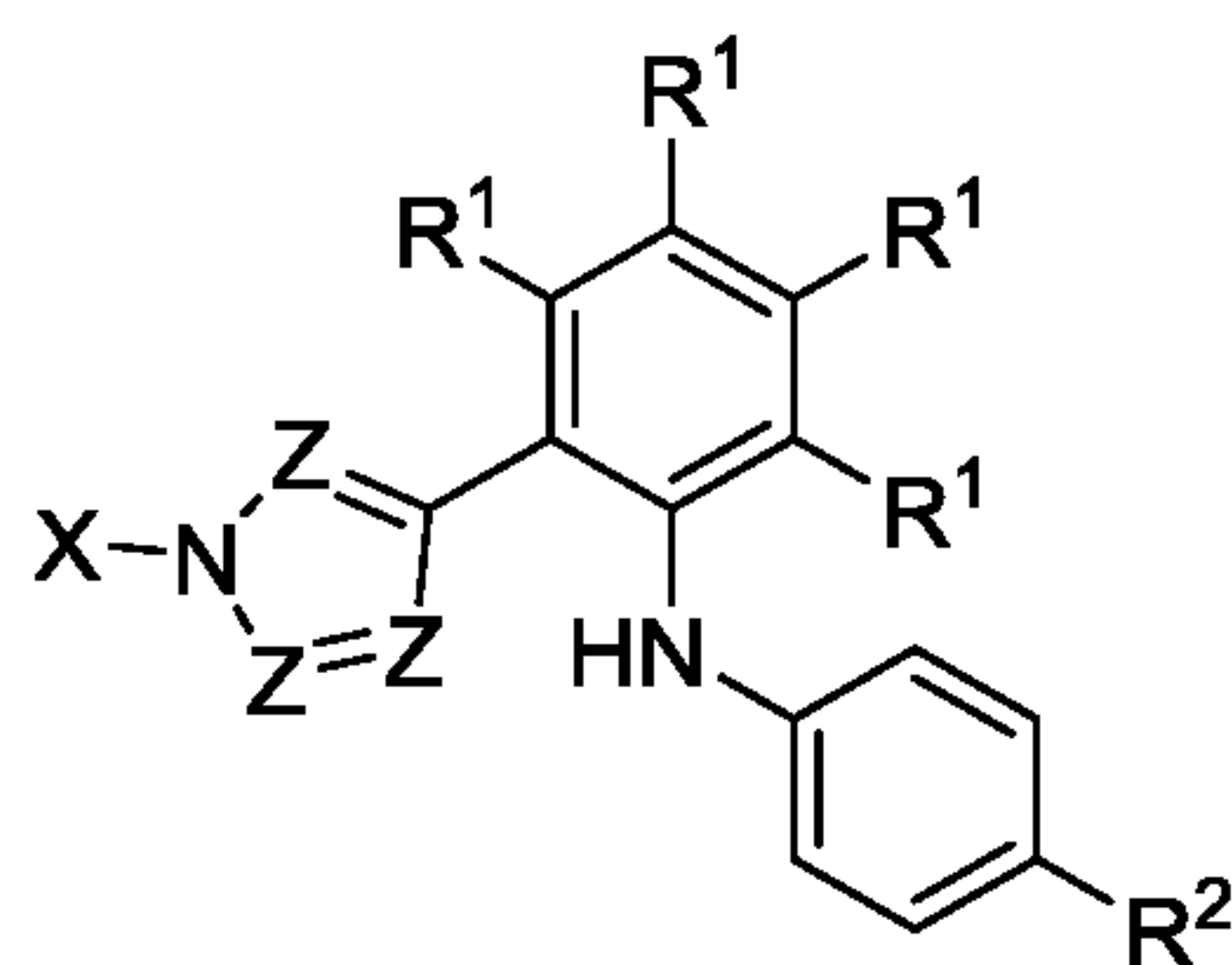
18. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-17, wherein:

each R^2 is independently halogen, $-\text{N}_3$, $-\text{OR}^5$, $-(\text{SO}_2)\text{R}^5$, $-\text{CO}_2\text{R}^5$, substituted or unsubstituted C_1 -

C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, or

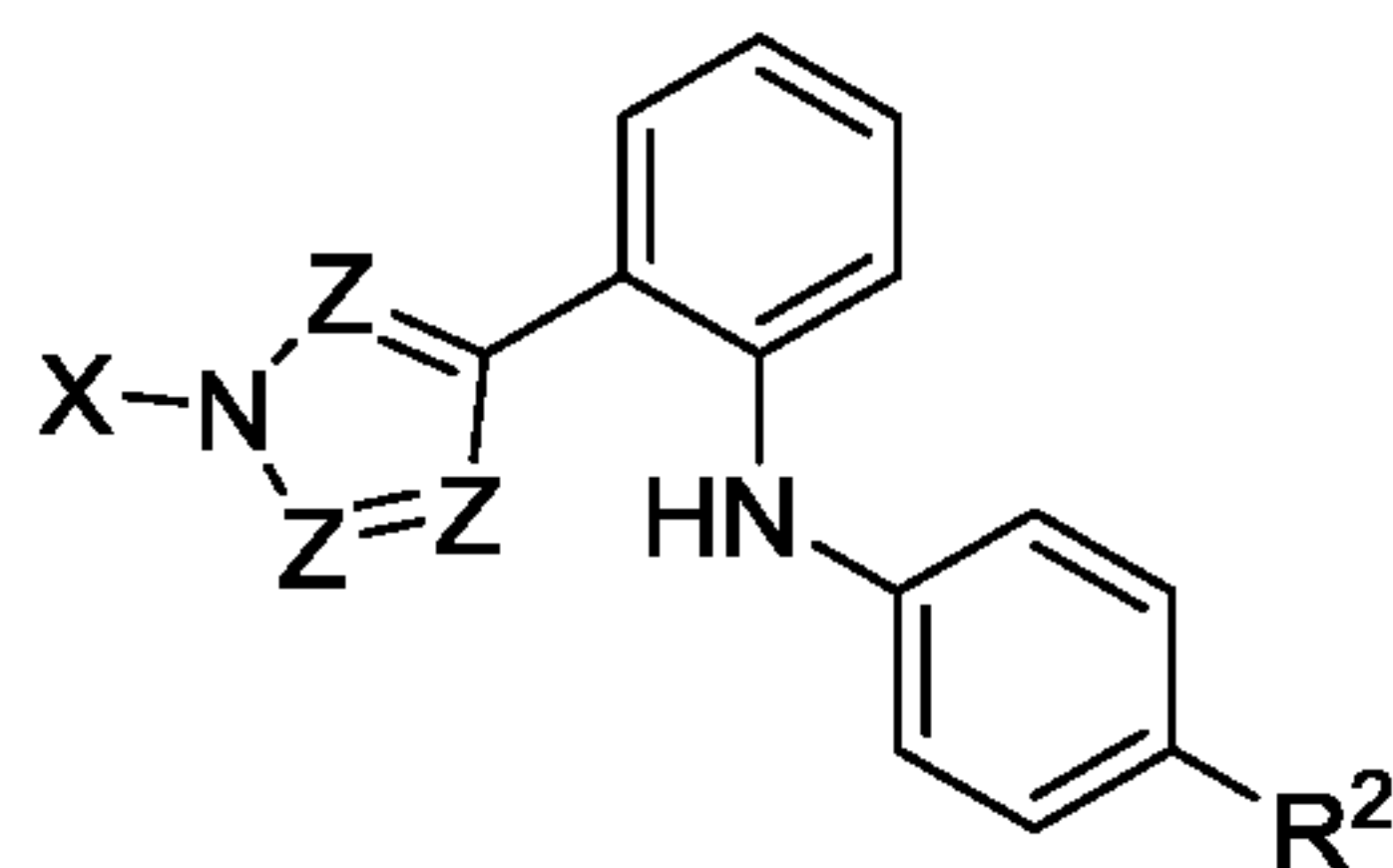


19. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein the compound has the structure of Formula (Ia), or a pharmaceutically acceptable salt thereof:



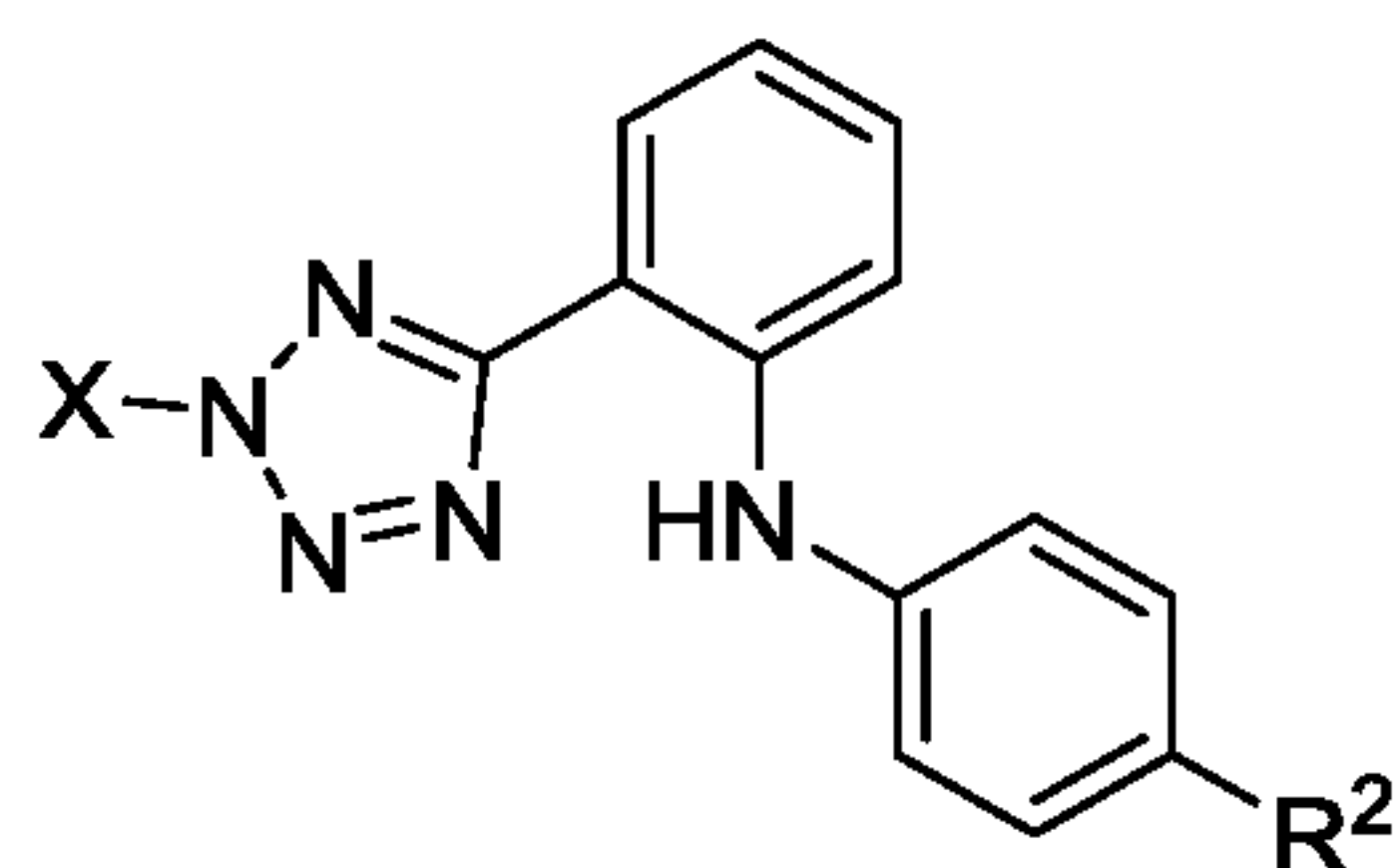
Formula (Ia).

20. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein the compound has the structure of Formula (Ib), or a pharmaceutically acceptable salt thereof:



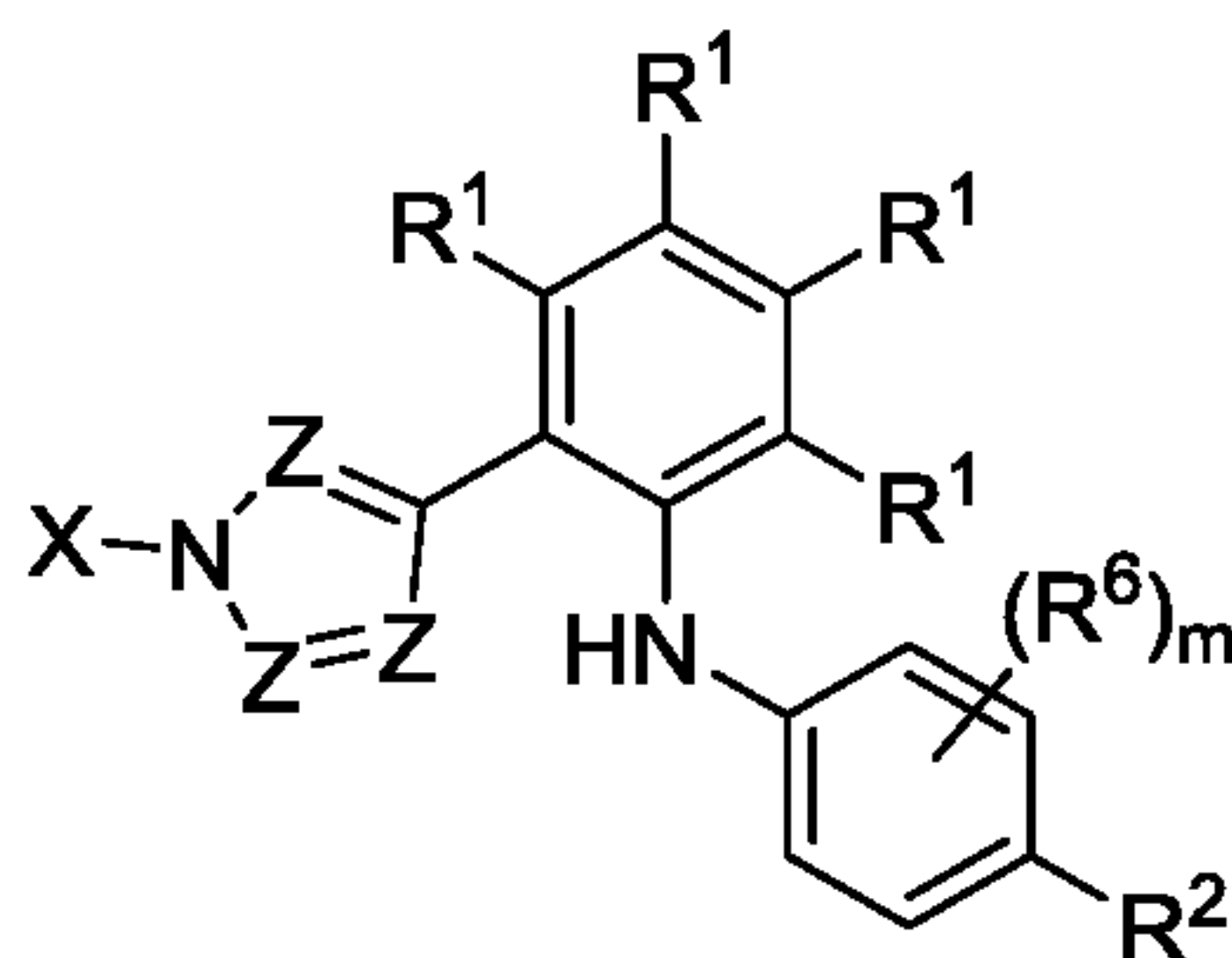
Formula (Ib).

21. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein the compound has the structure of Formula (Ic), or a pharmaceutically acceptable salt thereof:



Formula (Ic).

22. A compound of Formula (II), or a pharmaceutically acceptable salt thereof:



Formula (II)

wherein:

each Z is independently N or CR^Z;

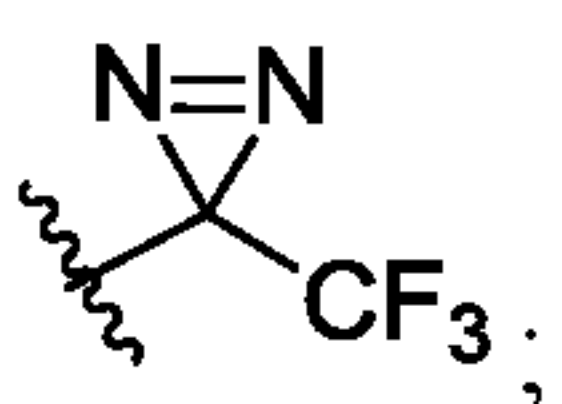
each R^Z is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

X is methyl;

each R¹ is independently H, halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-

C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R² is halogen, -N₃, -CN, -OR⁵, -SR⁵, -(SO₂)R⁵, -N(R⁵)₂, -CO₂R⁵, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted

aryl, substituted or unsubstituted heteroaryl, or ;

each R⁶ is independently H, halogen, -N₃, -CN, -OR⁷, -SR⁷, -(SO₂)R⁷, -N(R⁷)₂, -CO₂R⁷, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

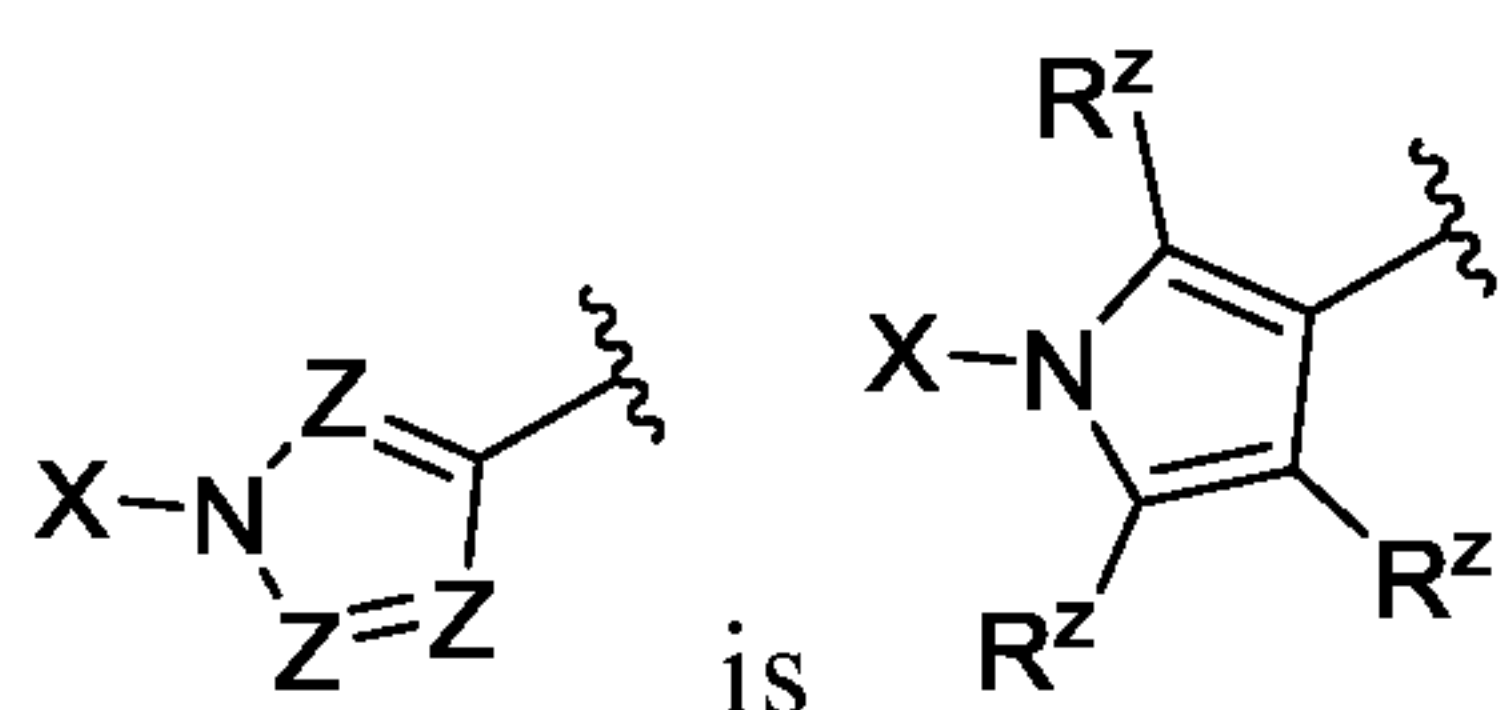
each R⁴ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R⁵ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

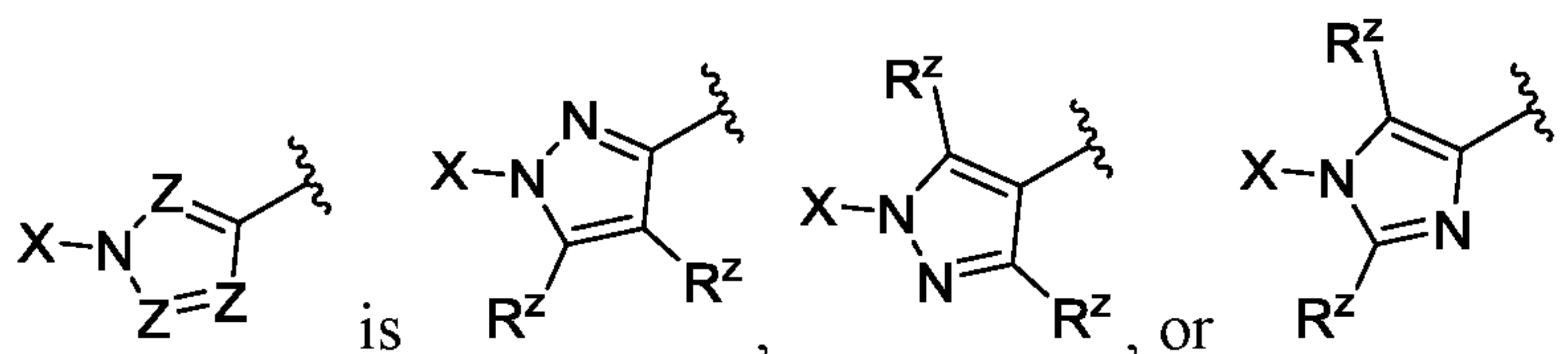
each R⁷ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

m is 0, 1, 2, 3, or 4.

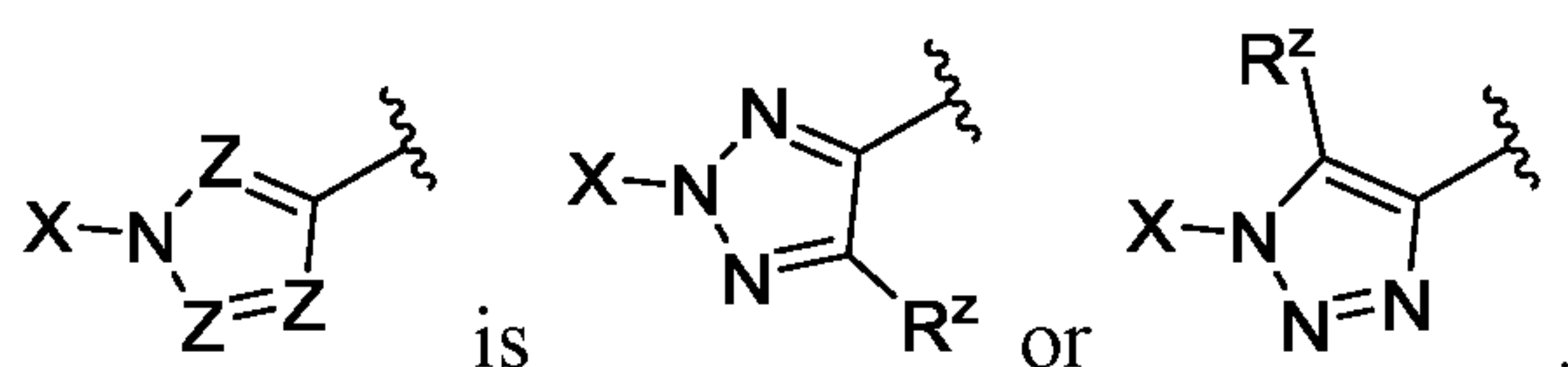
23. The compound, or pharmaceutically acceptable salt thereof, of claim 22, wherein:



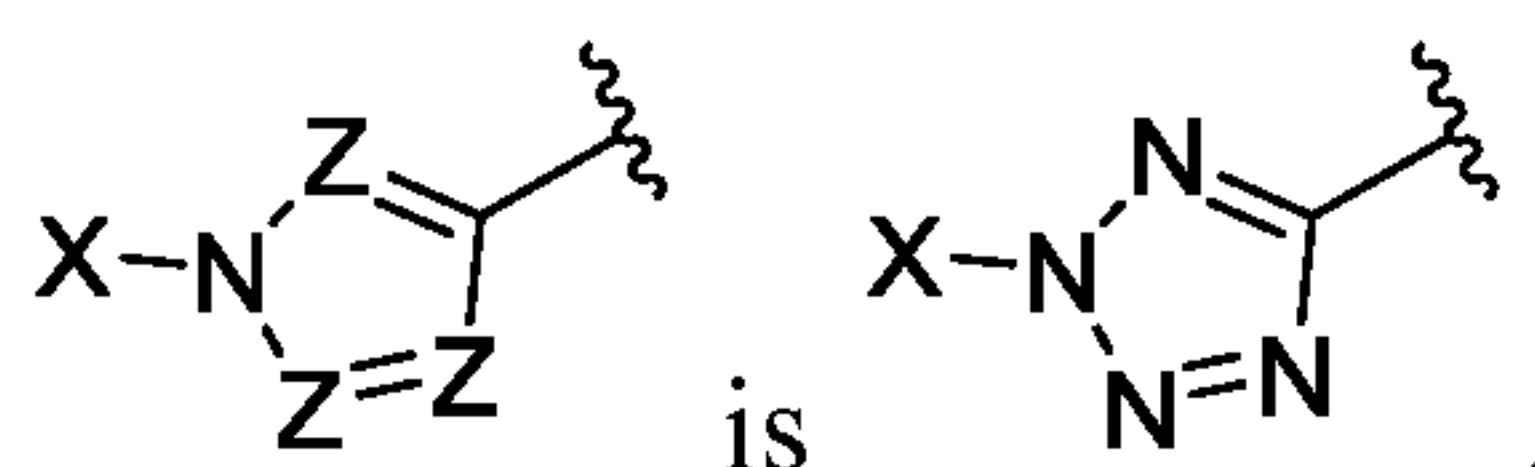
24. The compound, or pharmaceutically acceptable salt thereof, of claim 22, wherein:



25. The compound, or pharmaceutically acceptable salt thereof, of claim 22, wherein:



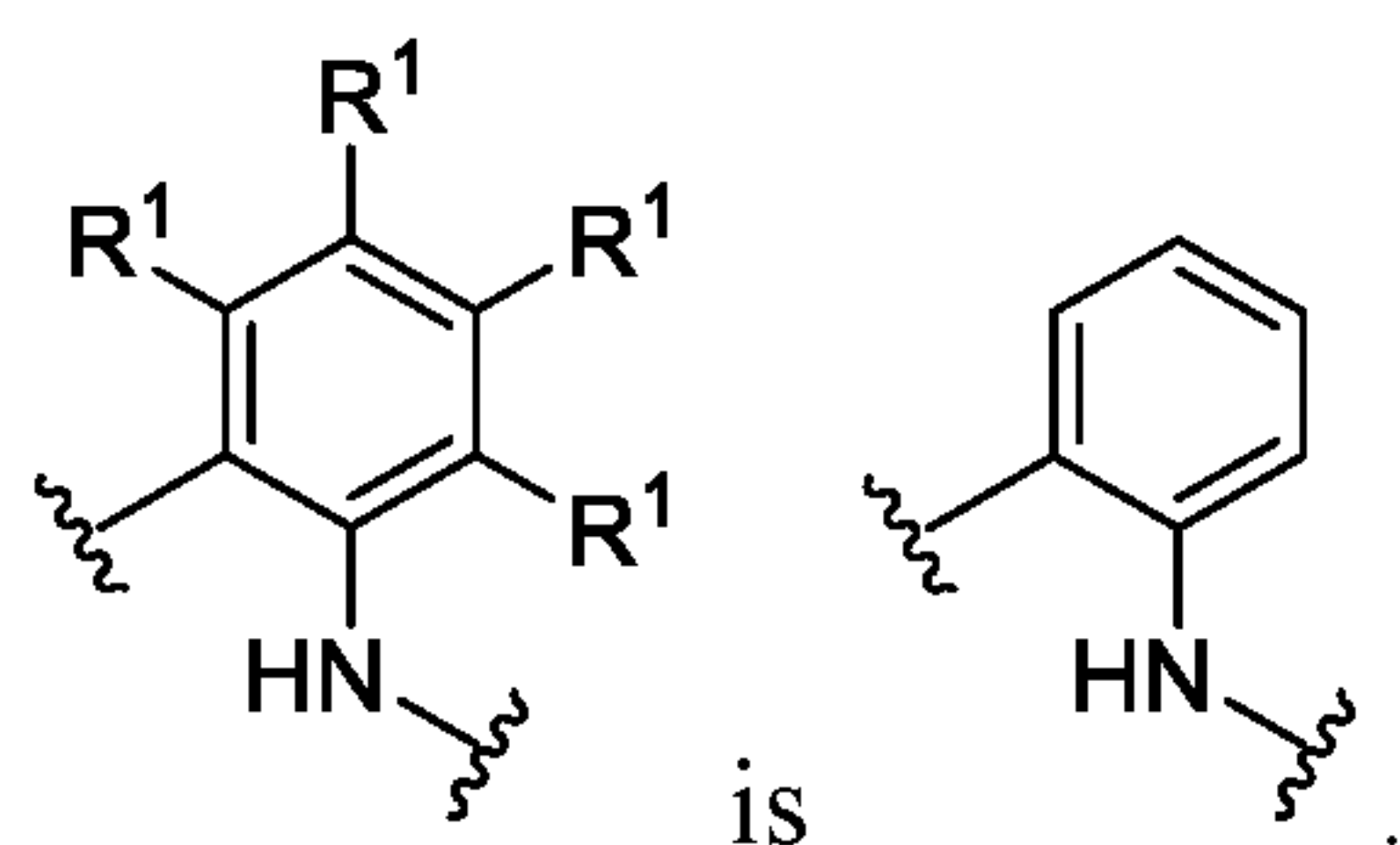
26. The compound, or pharmaceutically acceptable salt thereof, of claim 22, wherein:



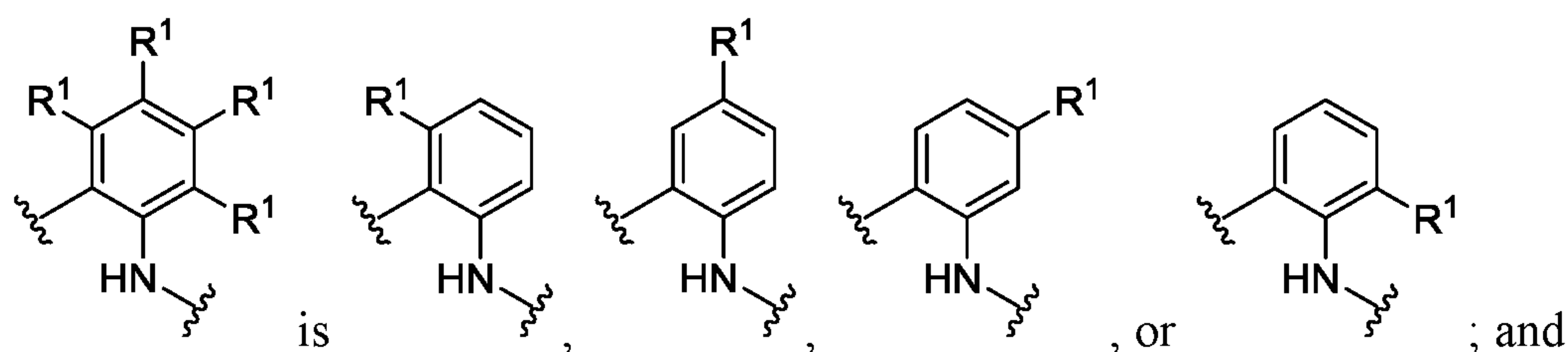
27. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 22-26, wherein:

each R^Z is independently H or substituted or unsubstituted C_1 - C_6 alkyl.

28. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 22-27, wherein:

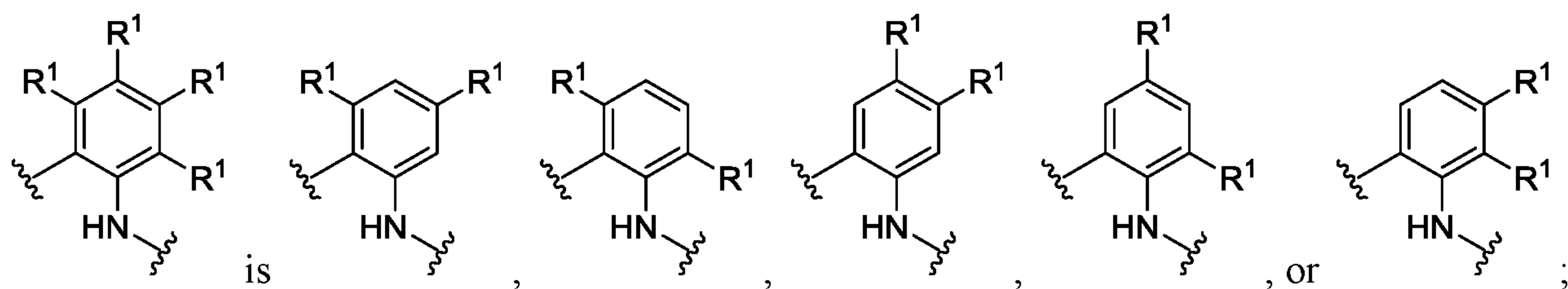


29. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 22-27, wherein:



R^1 is halogen, $-CN$, $-OR^4$, $-SR^4$, $-N(R^4)_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

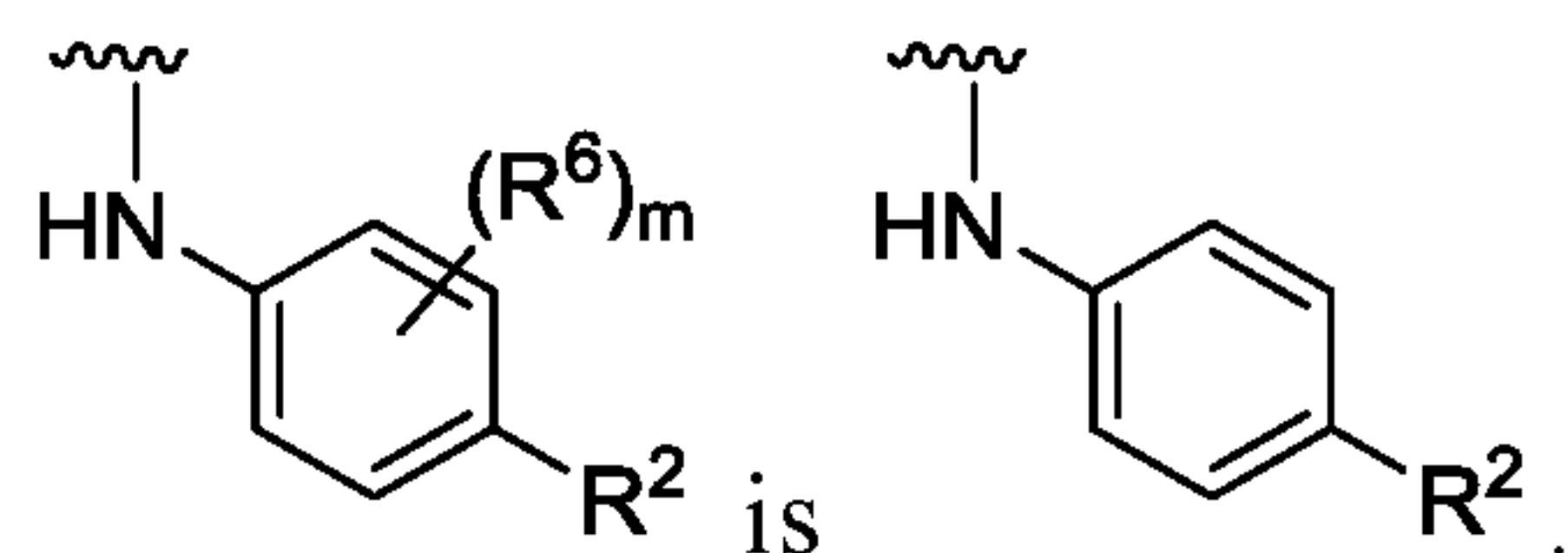
30. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 22-27, wherein:



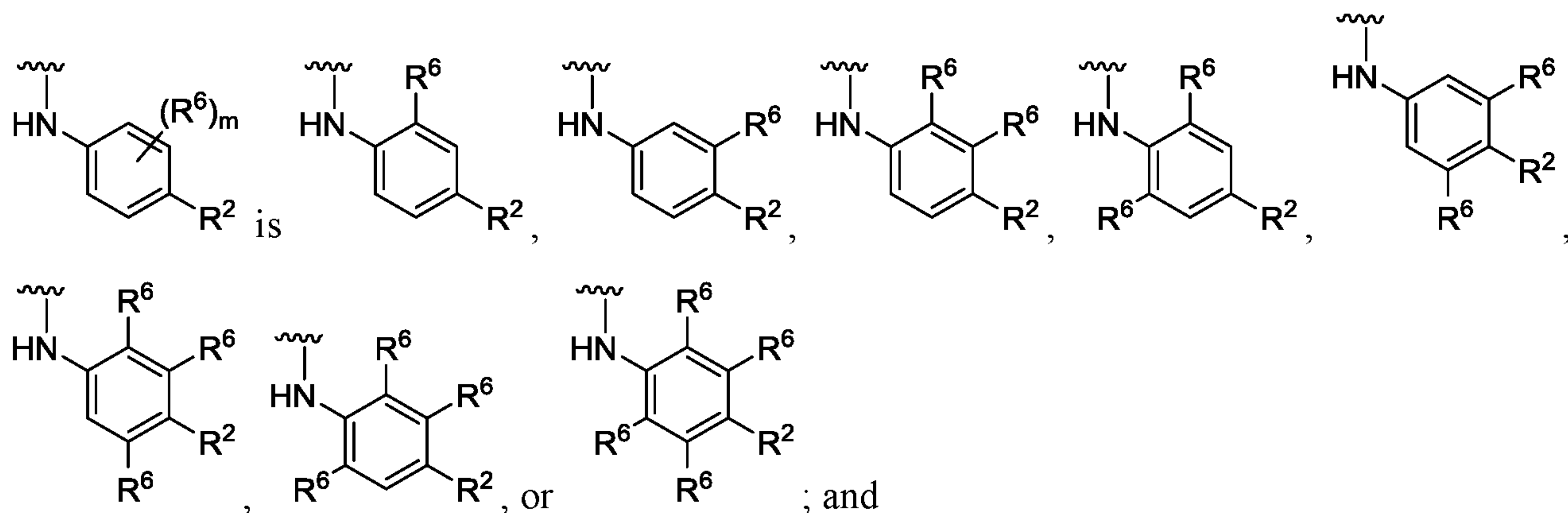
and

each R¹ is independently halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

31. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 22-30, wherein:



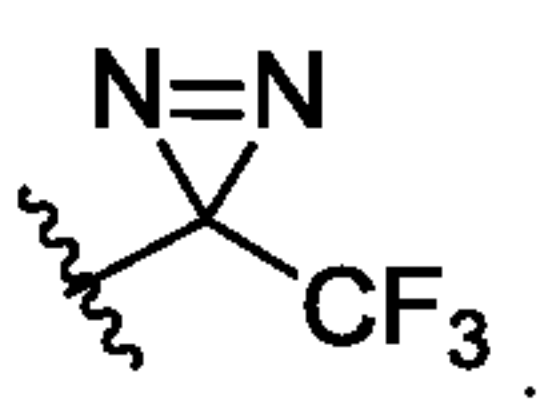
32. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 22-30, wherein:



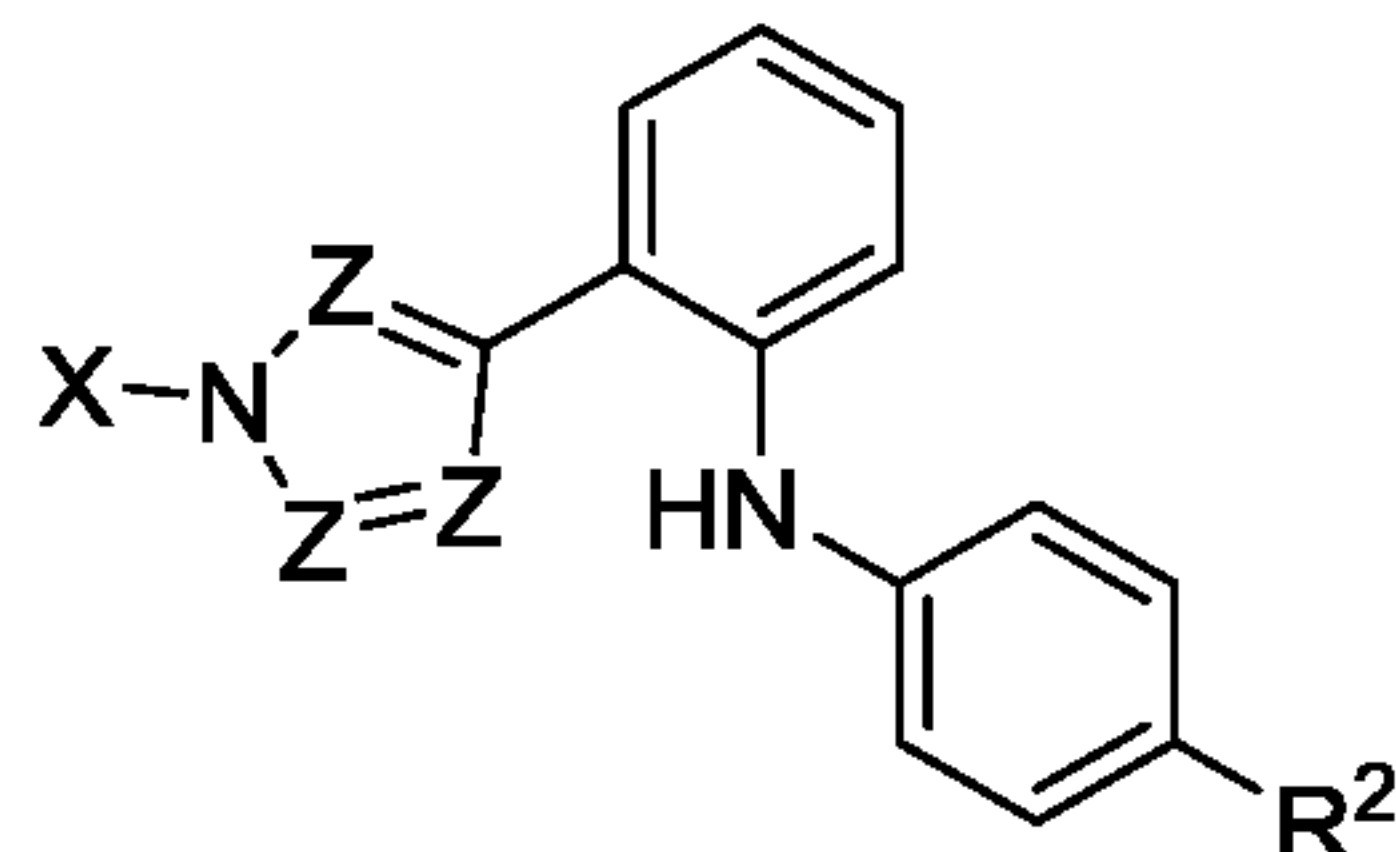
each R⁶ is independently halogen, -N₃, -CN, -OR⁷, -SR⁷, -(SO₂)R⁷, -N(R⁷)₂, -CO₂R⁷, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

33. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 22-32, wherein:

R² is halogen, -N₃, -OR⁵, -(SO₂)R⁵, -CO₂R⁵, substituted or unsubstituted C₁-C₆alkyl, substituted or

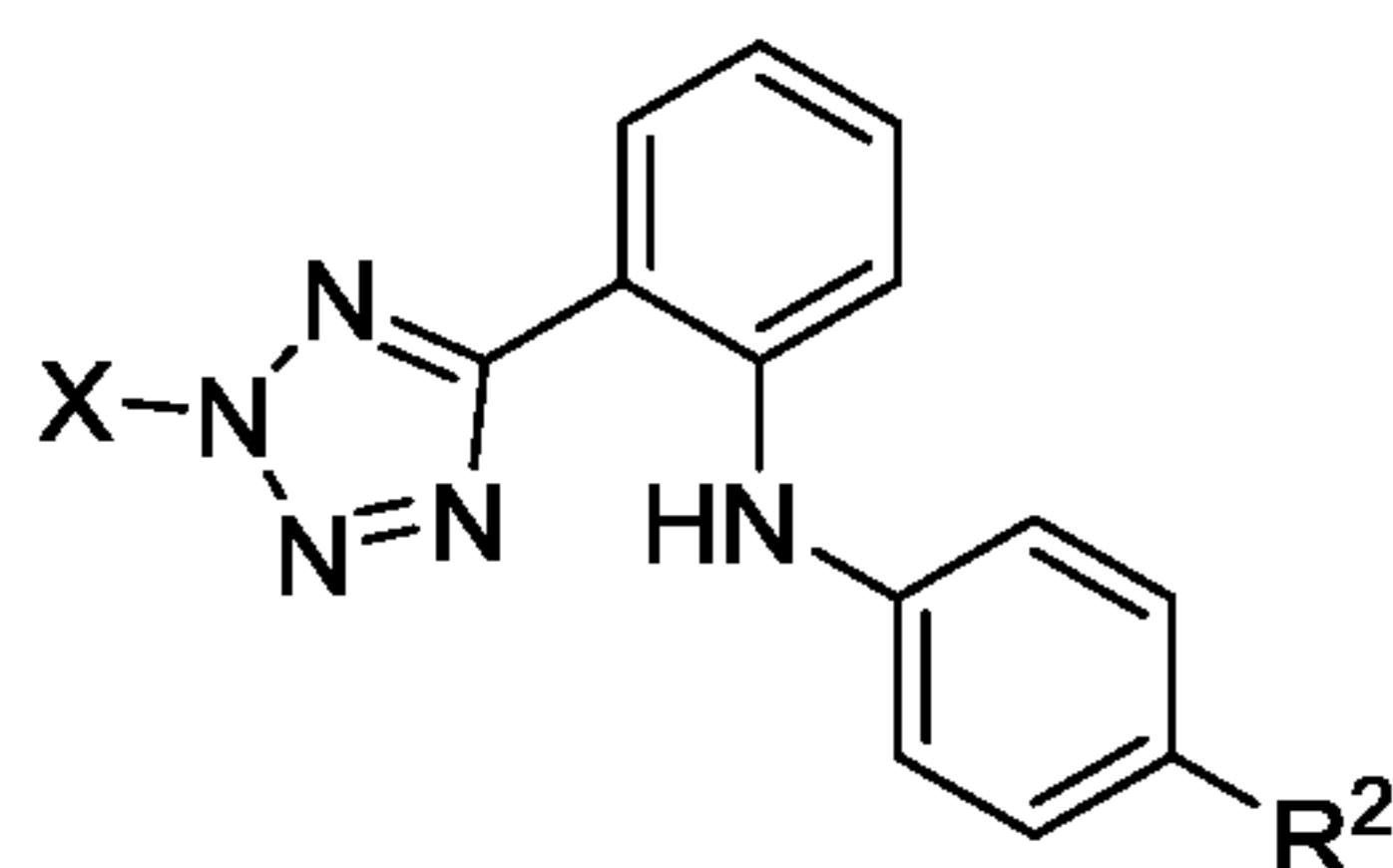
unsubstituted C₁-C₆haloalkyl, or .

34. The compound, or pharmaceutically acceptable salt thereof, of claim 22, wherein the compound has the structure of Formula (IIa), or a pharmaceutically acceptable salt thereof:



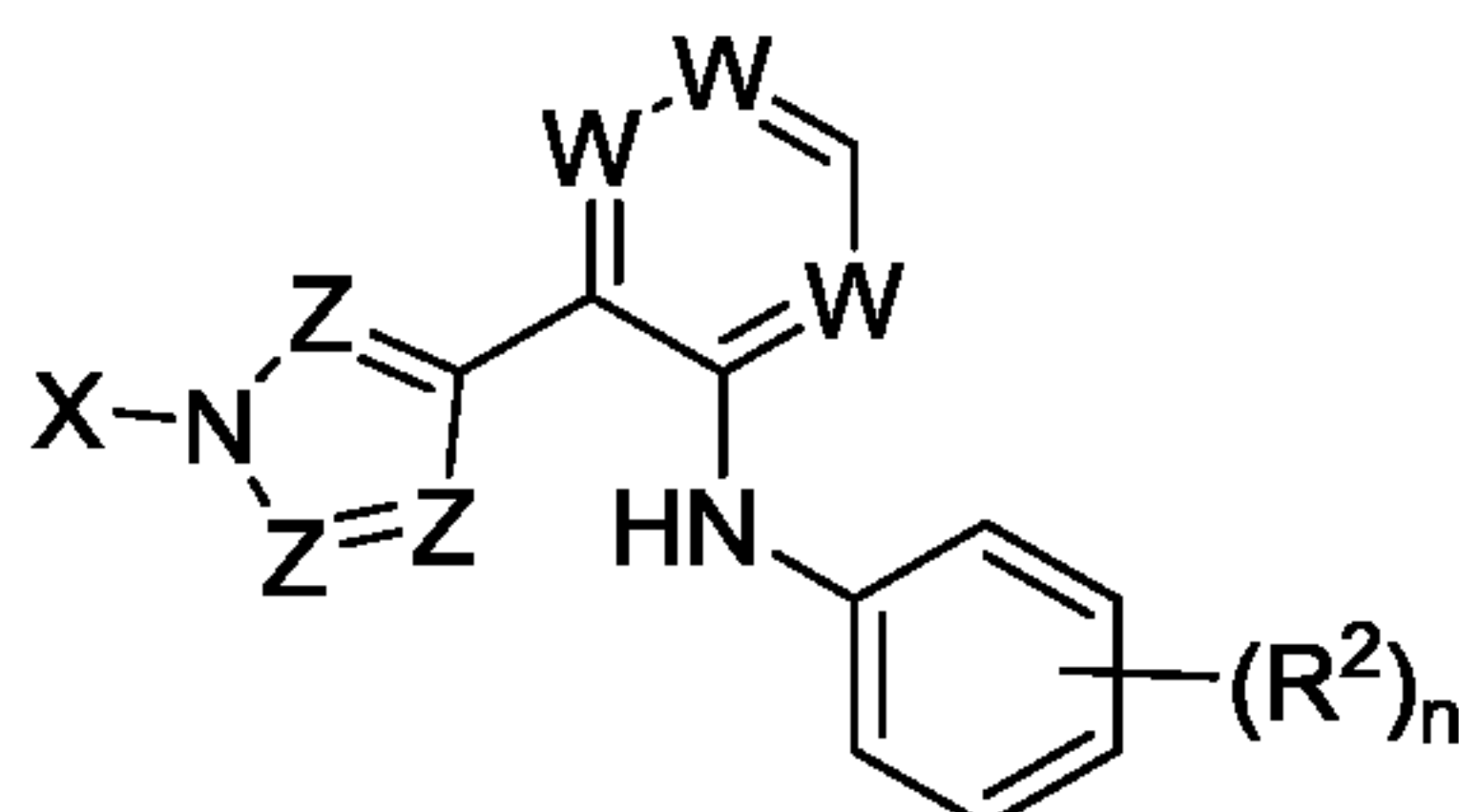
Formula (IIa).

35. The compound, or pharmaceutically acceptable salt thereof, of claim 22, wherein the compound has the structure of Formula (IIb), or a pharmaceutically acceptable salt thereof:



Formula (IIb).

36. A compound of Formula (III), or a pharmaceutically acceptable salt thereof:



Formula (III)

wherein:

each Z is independently N or CR^Z;

each R^Z is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

X is substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -L¹-Y¹, or -L²-L³-Y²;

L^1 is substituted or unsubstituted C_1 - C_6 alkylene;

Y^1 is substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^2 is absent or substituted or unsubstituted C_1 - C_6 alkylene;

L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -O-NR³(C=O)-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)-, -(SO₂)NR³-(C=O)O-, -O(C=O)-NR³(SO₂)-, -NR³(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)NR³-, -O(C=O)-NR³(SO₂)NR³-, or -NR³(SO₂)NR³-(C=O)O-;

each R³ is independently H or substituted or unsubstituted C_1 - C_6 alkyl;

Y^2 is H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

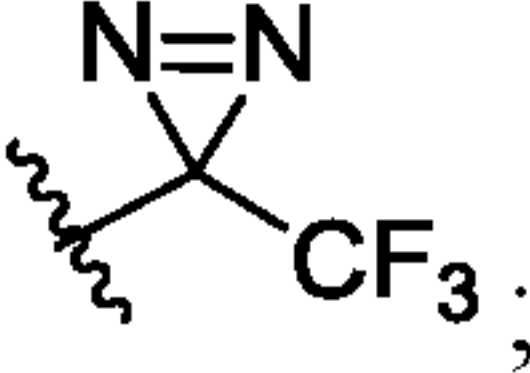
or R³ and Y^2 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

each W is CR¹ or N with the provision that at least one W is N;

each R¹ is independently H, halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

n is 0, 1, 2, 3, 4, or 5;

each R² is independently H, halogen, -N₃, -CN, -OR⁵, -SR⁵, -(SO₂)R⁵, -N(R⁵)₂, -CO₂R⁵, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or

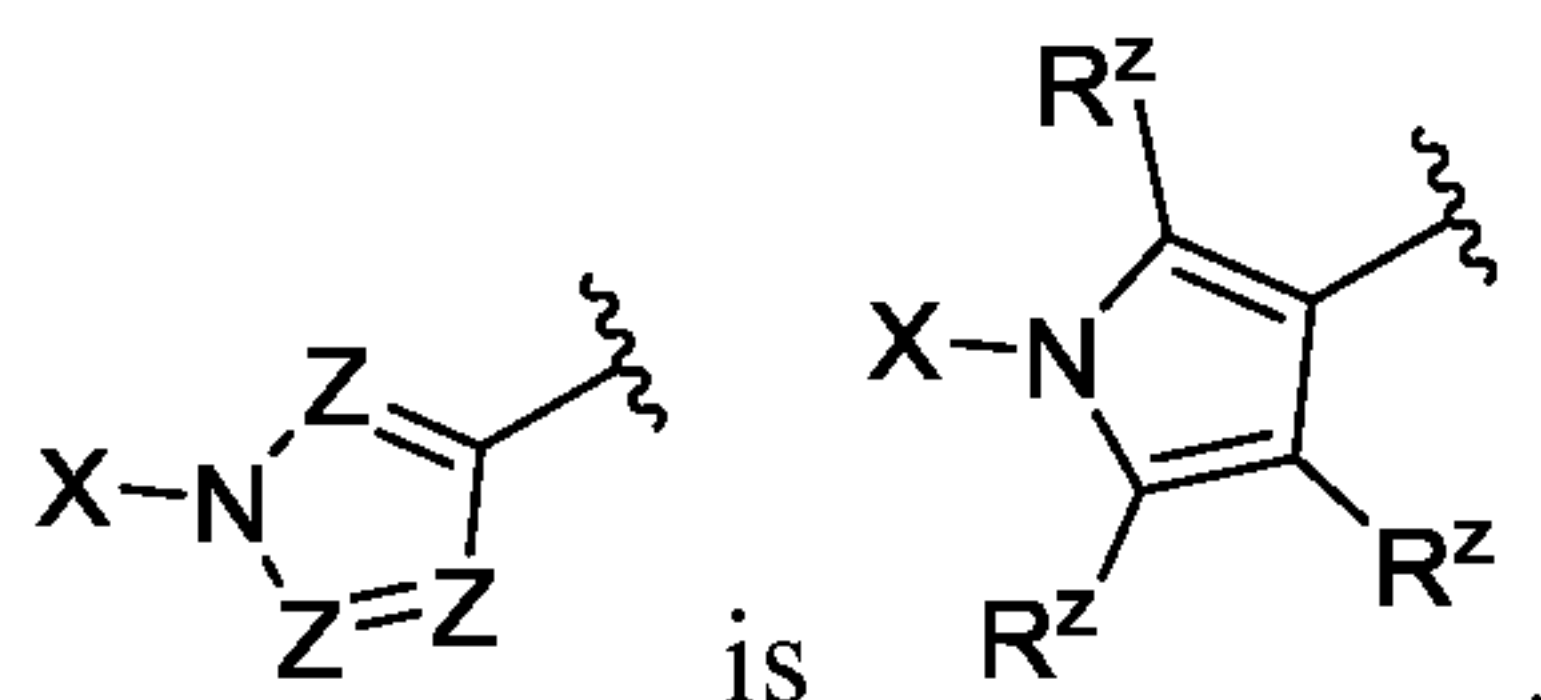
unsubstituted aryl, substituted or unsubstituted heteroaryl, or ;

each R⁴ is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or

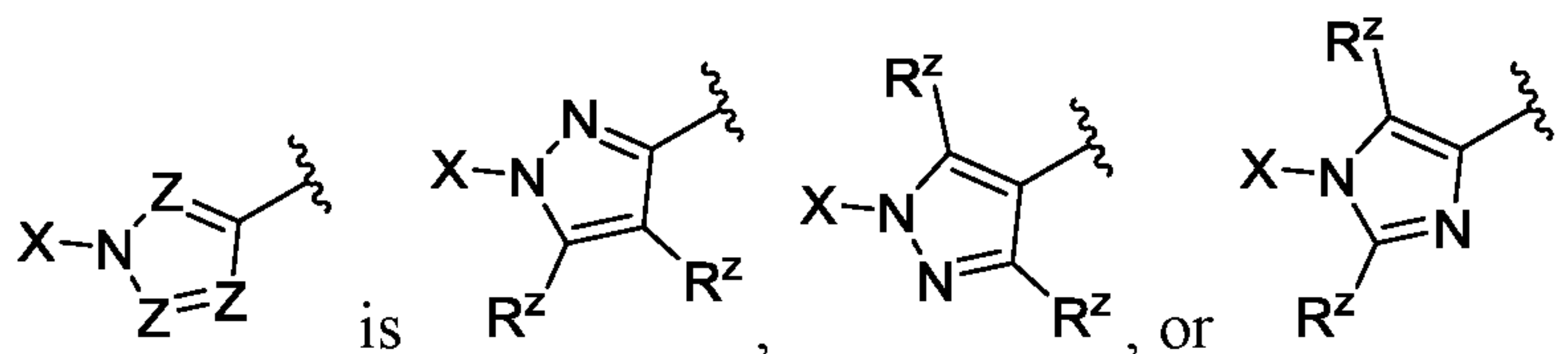
unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

each R^5 is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

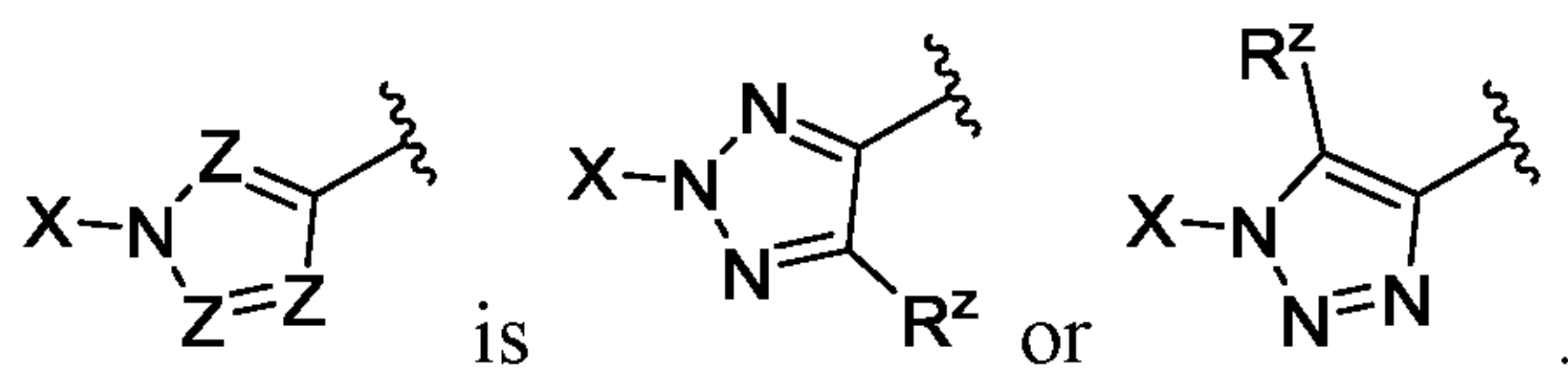
37. The compound, or pharmaceutically acceptable salt thereof, of claim 36, wherein:



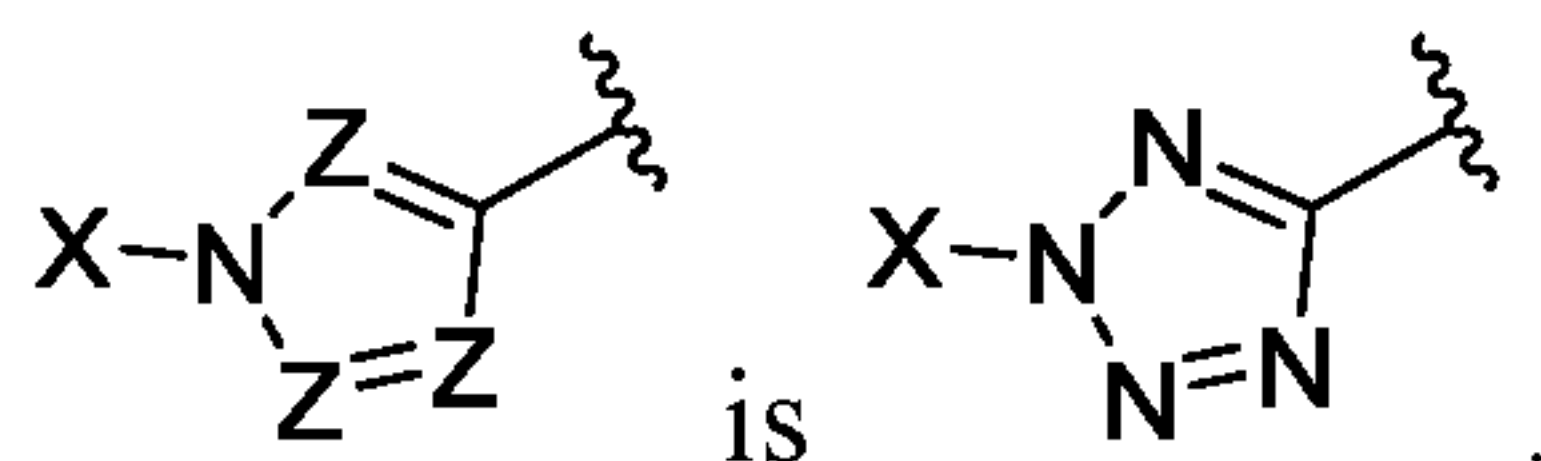
38. The compound, or pharmaceutically acceptable salt thereof, of claim 36, wherein:



39. The compound, or pharmaceutically acceptable salt thereof, of claim 36, wherein:



40. The compound, or pharmaceutically acceptable salt thereof, of claim 36, wherein:



41. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 36-40, wherein:

each R^Z is independently H or substituted or unsubstituted C_1 - C_6 alkyl.

42. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 36-41, wherein:

X is substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted

or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

43. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 36-41, wherein:

X is $-L^1-Y^1$.

44. The compound, or pharmaceutically acceptable salt thereof, of claim 43, wherein:

L^1 is substituted or unsubstituted C_1-C_4 alkylene; and

Y^1 is substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl.

45. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 36-41, wherein:

X is $-L^2-L^3-Y^2$.

46. The compound, or pharmaceutically acceptable salt thereof, of claim 45, wherein:

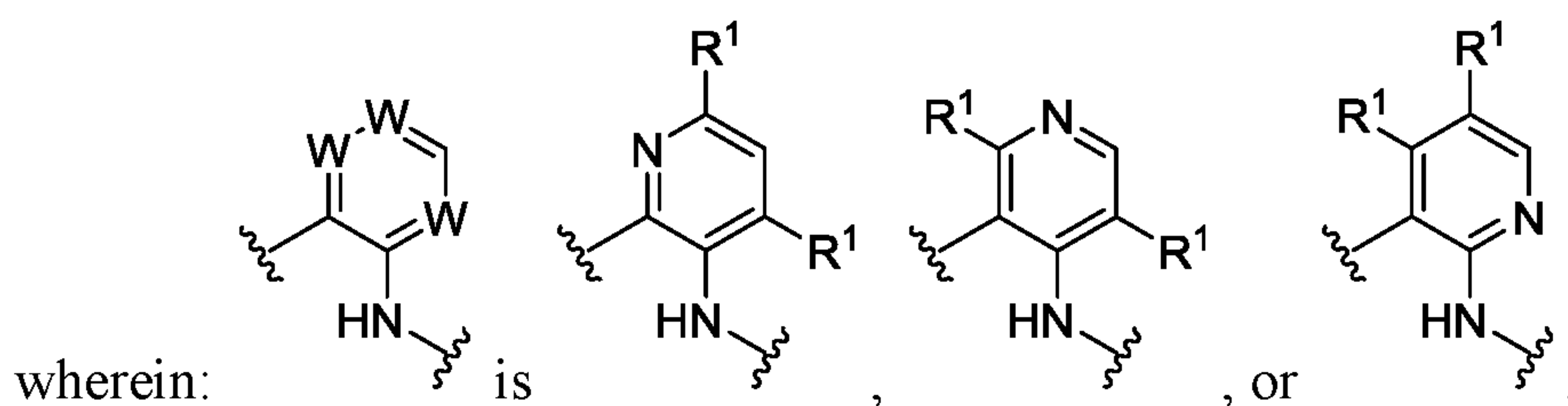
L^2 is substituted or unsubstituted C_1-C_4 alkylene;

L^3 is $-O-$, $-S-$, $-(S=O)-$, $-(SO_2)-$, $-NR^3-$, $-(C=O)-$, $-(C=O)O-$, $-O(C=O)-$, $-(C=O)NR^3-$, $-(C=O)NR^3-O-$, $-NR^3(C=O)-$, $-NR^3(C=O)NR^3-$, $-O(C=O)NR^3-$, $-NR^3(C=O)O-$, $-NR^3(SO_2)NR^3-$, $-NR^3(SO_2)-$, $-(SO_2)NR^3-$, $-(SO_2)NR^3-(C=O)-$, $-(SO_2)NR^3-(C=O)O-$, $-NR^3(SO_2)NR^3-(C=O)-$, or $-NR^3(SO_2)NR^3-(C=O)O-$;

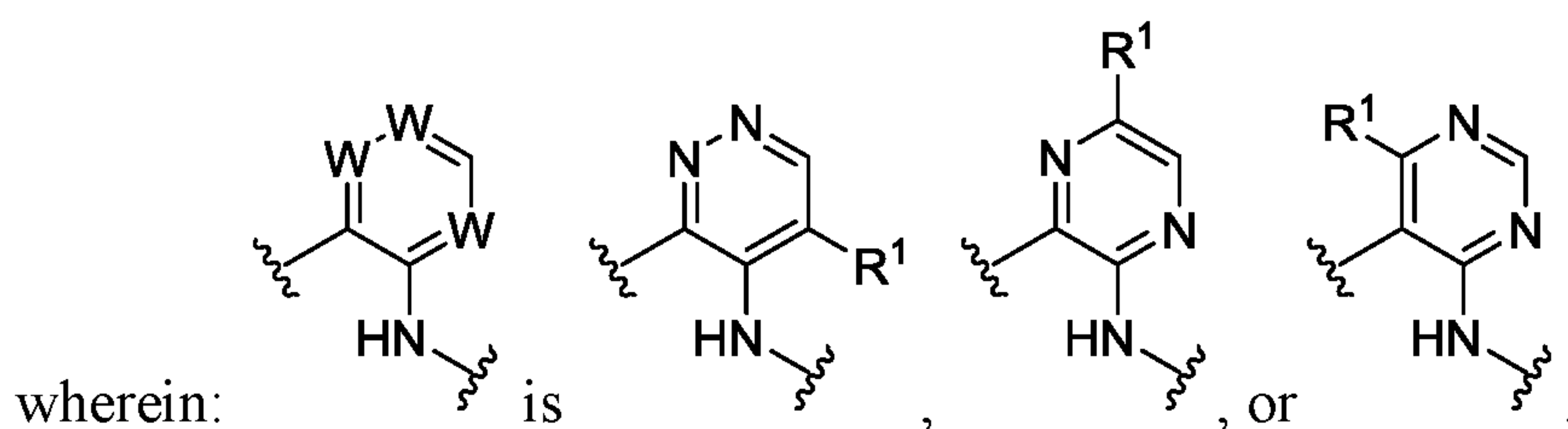
each R^3 is independently H or substituted or unsubstituted C_1-C_4 alkyl; and

Y^2 is H, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 haloalkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl.

47. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 36-46,



48. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 36-46,



The image shows two chemical structures side-by-side. The structure on the left is a pyrimidine ring, a six-membered aromatic heterocycle consisting of two nitrogen atoms at the 1 and 3 positions. It has wavy lines at the 2, 4, and 6 positions, indicating attachment points. The structure on the right is an imidazole ring, a five-membered aromatic heterocycle consisting of two nitrogen atoms at the 1 and 3 positions. It also has wavy lines at the 2, 4, and 5 positions, indicating attachment points.

is



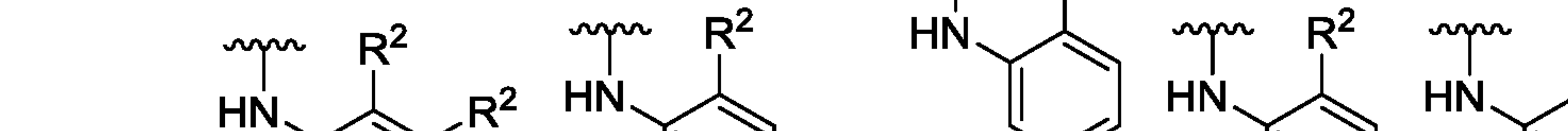

is

is

or

unsubstituted C₁-C₆haloalkyl, or 

unsubstituted C₁-C₆haloalkyl, or



is

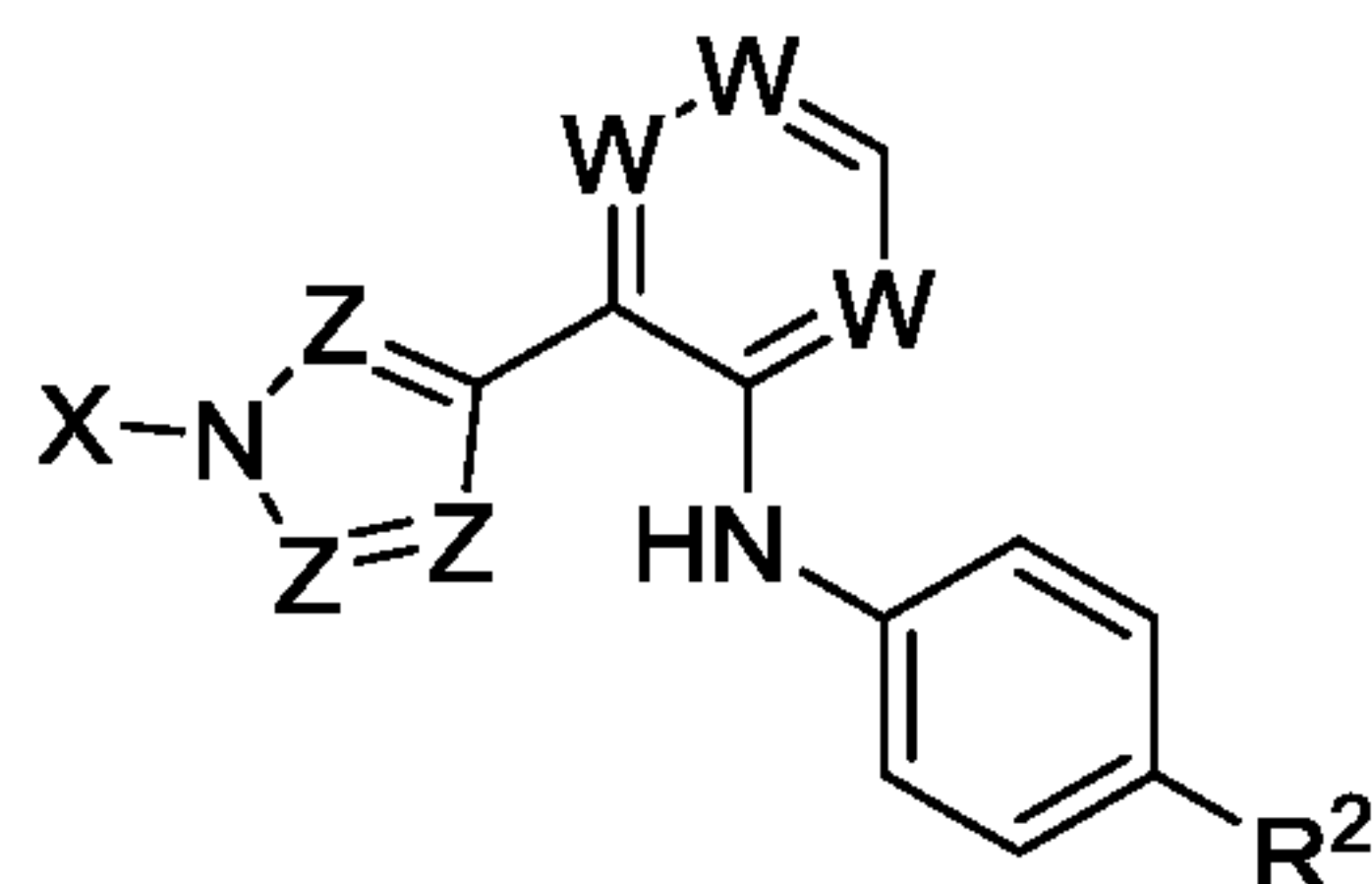
2

or

C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, or 

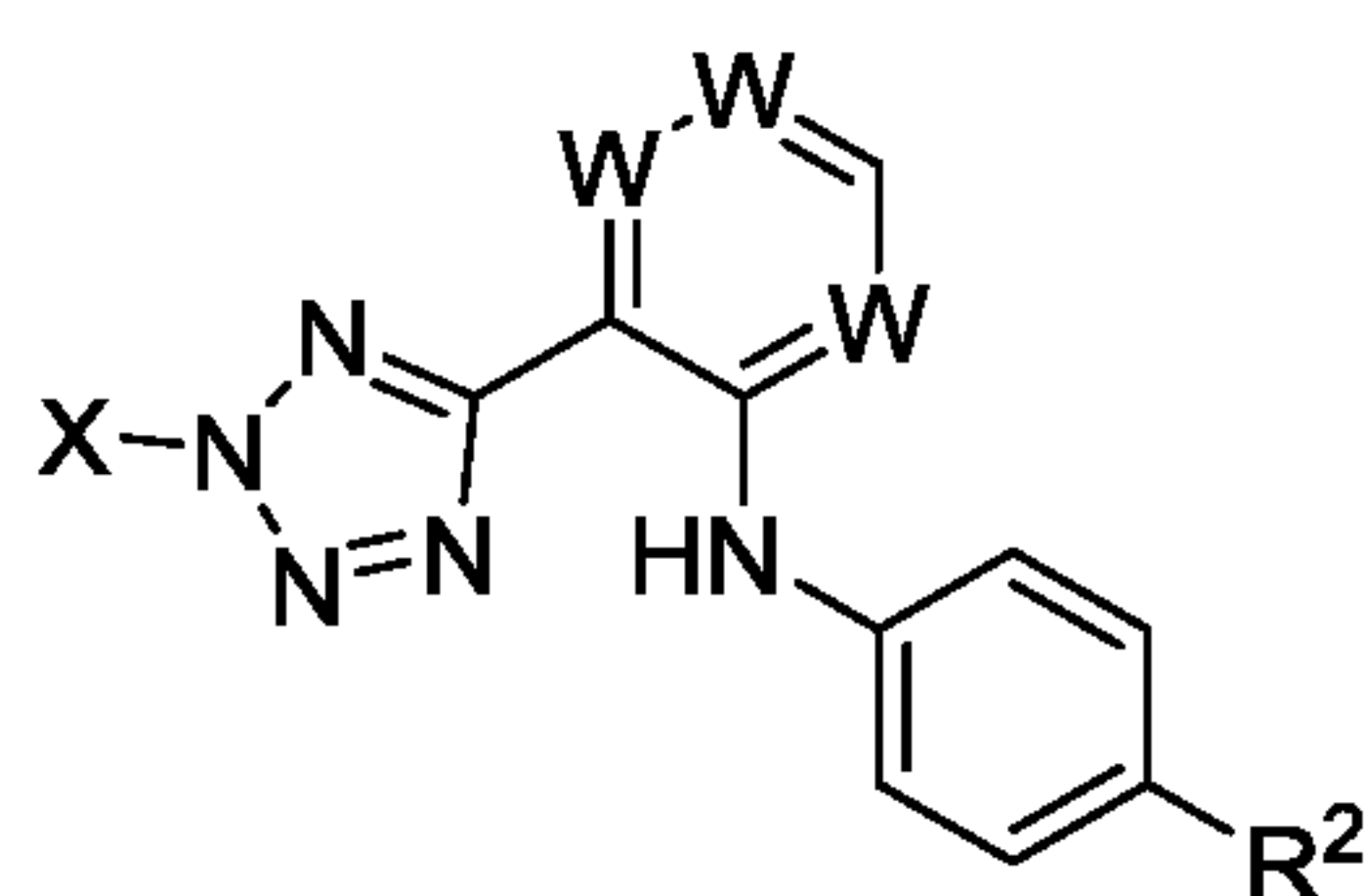
C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, or

54. The compound, or pharmaceutically acceptable salt thereof, of claim 36, wherein the compound has the structure of Formula (IIIa), or a pharmaceutically acceptable salt thereof:



Formula (IIIa).

55. The compound, or pharmaceutically acceptable salt thereof, of claim 36, wherein the compound has the structure of Formula (IIIb), or a pharmaceutically acceptable salt thereof:



Formula (IIIb).

56. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-55, wherein the compound exhibits an IC₅₀ of no more than about 5.000 μM.

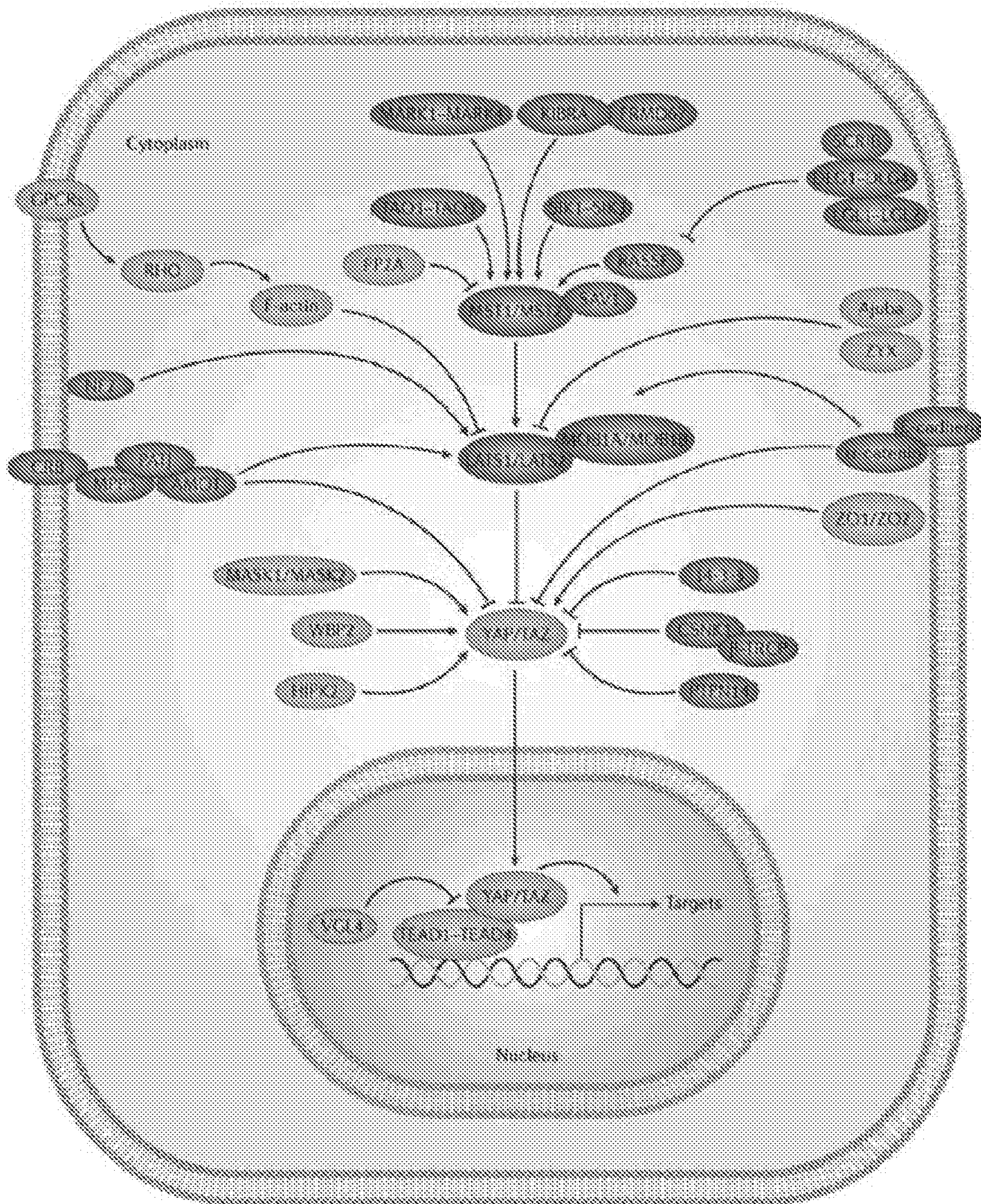
57. A compound, or pharmaceutically acceptable salt thereof, wherein the compound is a compound from Table 1 or 2, or a pharmaceutically acceptable salt thereof.

58. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of any one of claims 1-57, or a pharmaceutically acceptable salt thereof.

59. A method for treating a cancer in a subject in need thereof comprising administering a therapeutically effective amount of a compound of any one of claims 1-57, or a pharmaceutically acceptable salt thereof.

1/2

FIG.1



2/2

FIG. 2

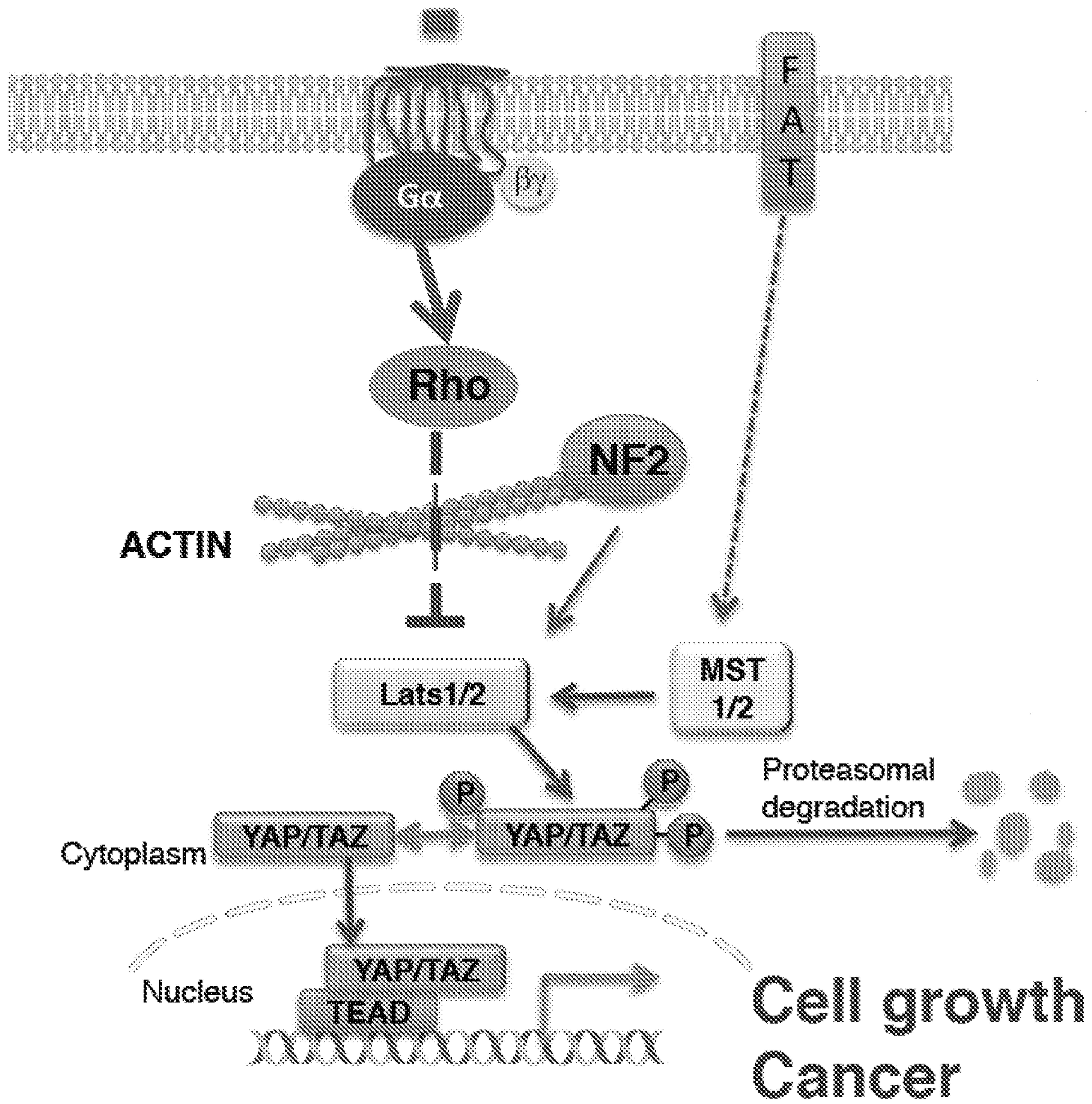


FIG.1

