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(54) Title: PHARMACEUTICAL COMBINATIONS COMPRISING A SUBSTITUTED THIOPHENE FUSED CYCLOHEXANONE DERIVATIVE AND A CYCLOOXYGENASE (COX) INHIBITOR, AND THEIR USE FOR THE TREATMENT OF PAIN

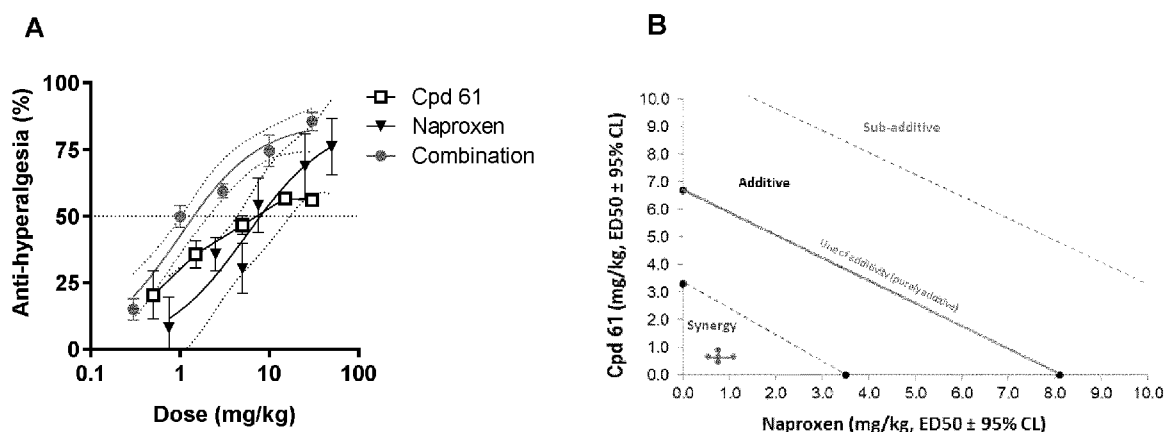
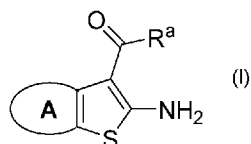


Figure 1

(57) Abstract: There is provided a pharmaceutical combination comprising a cyclooxygenase (COX) inhibitor and a compound having the Formula (I) or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the COX inhibitor can comprise a Non-Steroidal Anti-Inflammatory Drug (NSAID). The pharmaceutical combination can be used in the treatment of pain in a subject in need thereof, such inflammatory pain. There is also provided a kit comprising a first single dose form of a cyclooxygenase (COX) inhibitor and a second single dose form of a compound having the Formula (I) or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and instructions for use. (I)



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**PHARMACEUTICAL COMBINATIONS COMPRISING A SUBSTITUTED THIOPHENE FUSED
CYCLOHEXANONE DERIVATIVE AND A CYCLOOXYGENASE (COX) INHIBITOR, AND
THEIR USE FOR THE TREATMENT OF PAIN**

PRIORITY APPLICATION

- 5 The present application claims priority from U.S. provisional application No. 63/519.108, filed August 11, 2023, which is incorporated herein by reference.

TECHNICAL FIELD

- The technical field generally relates to pharmaceutical combinations and their uses in the treatment of pain. The pharmaceutical combinations comprise thiophene fused cyclohexanone derivatives and cyclooxygenase (COX) inhibitors. Particularly, the thiophene fused
10 cyclohexanone derivatives are acid-sensing ion channels (ASICs) inhibitors.

BACKGROUND

- Since the discovery of acid-sensing ion channels (ASICs) in 1997, their importance in the health of neurons and other non-neuronal cells has gained significant importance. ASICs play important
15 roles in mediating pain sensation and their activity contributes to diseases such as stroke, inflammation, arthritis, cancer, and migraine.

- ASICs are permeable to Na⁺ ions (and other cations), they are activated by low extracellular pH and widely expressed in the central nervous system (CNS) and the peripheral nervous system (PNS). ASICs are formed by homo- and heterotrimeric assemblies of subunits including ASIC1a,
20 ASIC1b, ASIC2a, ASIC2b and ASIC3. ASIC1a are expressed in the PNS and CNS, ASIC1b in the PNS.

- Tissue injury and inflammation cause acidosis and acidification is considered a significant contributor to associated pain. The literature indicates that ASIC inhibitors might relieve pain in a variety of clinical conditions. In addition, because their mechanism of action is distinct, ASIC
25 antagonists may provide new treatment options for patients who do not benefit from or do not tolerate the adverse side effects of certain current pain medications.

Developing new pharmaceutical combinations comprising small molecule inhibitors that are specific for ASICs is therefore important to provide alternative therapeutic treatments against ASICs-related disorders or conditions, such as pain.

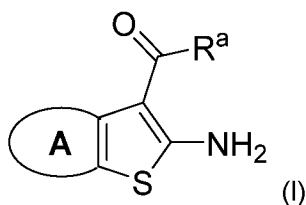
30 **SUMMARY**

The present application relates to a pharmaceutical combination comprising a cyclooxygenase (COX) inhibitor and a compound which is a thiophene fused cyclohexanone derivative of Formula

(I) or a pharmaceutically acceptable salt, solvate, or prodrug thereof. The pharmaceutical combination can be useful for the treatment of pain.

According to one aspect, the present application relates to a pharmaceutical combination comprising:

- 5 (a) a cyclooxygenase (COX) inhibitor; and
 (b) a compound having the Formula (I)



or a pharmaceutically acceptable salt, solvate, or prodrug thereof,

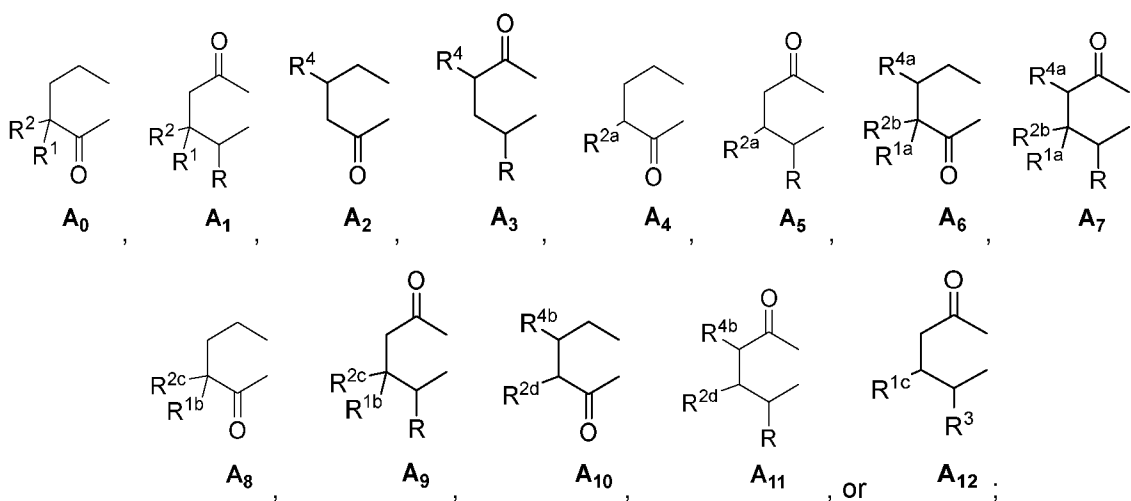
wherein:

- 10 R^a is $-NH_2$, $-NH-OH$, $-OH$, $-NHR^b$ or $-NHR^cR^d$;

R^b is C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, or 3- to 6-membered heterocycloalkyl, wherein C_1 - C_6 alkyl is optionally substituted with 1 to 3 halogens, 1 to 3 $-OH$, $-OC_1$ - C_3 alkyl, $-COOH$, or cyclopropyl optionally substituted with $-OH$, and wherein C_3 - C_6 cycloalkyl is optionally substituted with $-CN$;

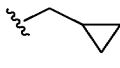
- R^c and R^d form with the nitrogen to which they are attached a 4-membered heterocycloalkyl,
 15 wherein the 4-membered heterocycloalkyl is optionally substituted with at least one of $-OH$ and C_1 - C_3 alkyl;

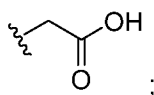
A represents one of the following residues **A**₀ to **A**₁₂



- 20 wherein:

R is H , C_1 - C_6 alkyl or phenyl;

R^1 and R^2 are independently -CN, C₆-C₁₀aryl, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, 4- to 14-membered heterocycloalkyl, 5- to 10-membered heteroaryl, -C(O)NH₂, -C(O)NHR⁵, -C(O)R⁶, or -C(O)OR⁵, wherein each C₁-C₆alkyl is optionally substituted with 1 to 3 R⁷ substituents, each C₆-C₁₀aryl is optionally substituted with 1 to 3 R⁸ substituents, and each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R²² substituents, with the proviso that when R^a is -OH,  represents A₀, and R¹ is , then R² in residue A₀ is different than



each R⁵ is independently C₁-C₆alkyl, wherein each C₁-C₆alkyl is optionally substituted with 1 to 3 R⁹ substituents;

- 10 each R⁶ is independently C₃-C₆cycloalkyl, 4- to 6-membered heterocycloalkyl, or C₆-C₁₀aryl;
- each R⁷ is independently -OH, -C(O)R¹¹, C₃-C₆cycloalkyl, -CN, C₆-C₁₀aryl, halogen, -C(O)OH, 5- to 10-membered heteroaryl, -NH(C(O)OC₁-C₆alkyl), -N(C₁-C₄alkyl)(C(O)OC₁-C₆alkyl), 4- to 6-membered heterocycloalkyl, -NH(C(O)C₁-C₆alkyl), -OR²⁰, -SC₁-C₆alkyl, -NH₂, -NH(C₁-C₄alkyl), or -N(C₁-C₄alkyl)₂, wherein each C₃-C₆cycloalkyl is optionally substituted with 1 to 3 R¹² substituents,
- 15 each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R¹³ substituents, and each 4- to 6-membered heterocycloalkyl is optionally substituted with C₁-C₄alkyl or oxo;

each R⁸ is independently halogen, C₁-C₆alkyl, -OC₁-C₆alkyl, C₃-C₆cycloalkyl, or 5- to 10-membered heteroaryl, wherein each -OC₁-C₆alkyl is optionally substituted with -OC₁-C₄alkyl, and each 5- to 10-membered heteroaryl is optionally substituted with C₁-C₄alkyl;

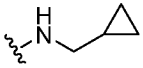
- 20 each R²² is independently C₁-C₆alkyl optionally substituted with phenyl;
- each R⁹ is independently -OH, -C(O)R¹⁵, C₃-C₆cycloalkyl, -CN, C₆-C₁₀aryl, halogen, -C(O)OH, 4- to 6-membered heterocycloalkyl, -NH(C(O)C₁-C₆alkyl), -OC₁-C₆alkyl, -SC₁-C₆alkyl, -NH₂, -NH(C₁-C₄alkyl), or -N(C₁-C₄alkyl)₂, wherein each 4- to 6-membered heterocycloalkyl is optionally substituted with C₁-C₄alkyl, and each -OC₁-C₆alkyl is optionally substituted with -OC₁-C₄alkyl;
- 25 each R¹¹ is independently -NH₂, -NH(C₁-C₄alkyl), -N(C₁-C₄alkyl)₂, or 4- to 6-membered heterocycloalkyl;
- each R²⁰ is independently C₁-C₆alkyl or 5- to 10-membered heteroaryl, wherein each C₁-C₆alkyl is optionally substituted with 1 to 3 R¹⁴ substituents and each 5- to 10-membered heteroaryl is optionally substituted with -OH or -NH(cyclopropyl);
- 30 each R¹² is independently C₁-C₄alkyl, -SC₁-C₄alkyl, -Ph, -OC₁-C₄alkyl, or -SPh, wherein each C₁-C₄alkyl is optionally substituted with -OH;

each R^{13} is independently halogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, -OH, - OC_1 - C_6 alkyl, - SC_1 - C_6 alkyl, - $S(O)_2C_1$ - C_6 alkyl, - NH_2 , - $NH(C_1$ - C_4 alkyl), or - $N(C_1$ - C_4 alkyl) $_2$, wherein each - OC_1 - C_6 alkyl, - SC_1 - C_6 alkyl, - $S(O)_2C_1$ - C_6 alkyl, - $NH(C_1$ - C_4 alkyl), and - $N(C_1$ - C_4 alkyl) $_2$ is optionally substituted with 1 to 3 R^9 substituents;

5 each R^{14} is independently halogen, - OC_1 - C_4 alkyl, or C_3 - C_6 cycloalkyl;

each R^{15} is independently - NH_2 , - $NH(C_1$ - C_4 alkyl), - $N(C_1$ - C_4 alkyl) $_2$, or 4- to 6-membered heterocycloalkyl;

R^4 is C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{10} aryl, 7- to 10-membered partially unsaturated heterocyclic group, or 5- to 10-membered heteroaryl, wherein C_1 - C_6 alkyl and C_3 - C_8 cycloalkyl are optionally substituted with 1 to 3 R^9 substituents, and C_6 - C_{10} aryl and 5- to 10-membered heteroaryl are
10 optionally substituted with 1 to 3 R^{10} substituents, with the proviso that: (i) when R^a is -OH, - NH_2 ,

or , and  represents A_2 , then R^4 in residue A_2 is different than - CH_3 ; and (ii)

when R^a is - NH_2 and  represents A_3 , then R^4 in residue A_3 is different than - $C(CH_3)_3$;

each R^{10} is independently C_1 - C_4 alkyl, halogen, - OC_1 - C_6 alkyl, - NH_2 , - $NH(C_1$ - C_4 alkyl), or - $N(C_1$ -
15 C_4 alkyl) $_2$, wherein each C_1 - C_4 alkyl is optionally substituted with 1 to 3 halogens;

R^{2a} is C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, or C_6 - C_{10} aryl, wherein C_1 - C_6 alkyl and C_3 - C_8 cycloalkyl are optionally substituted with 1 to 3 R^9 substituents, and C_6 - C_{10} aryl is optionally substituted with 1 to 3 R^{10} substituents;

R^{1a} and R^{2b} are independently -CN, C_6 - C_{10} aryl, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, - $C(O)NH_2$, -
20 $C(O)NHR^5$, or - $C(O)OC_1$ - C_6 alkyl, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 3 R^{16} substituents and each C_6 - C_{10} aryl is optionally substituted with 1 to 3 R^{17} substituents;

each R^{16} is independently -OH, - $C(O)NH_2$, - $C(O)NH(C_1$ - C_4 alkyl), C_3 - C_6 cycloalkyl, -CN, C_6 - C_{10} aryl, halogen, - $C(O)OH$, 5- to 10-membered heteroaryl, - $NH(C(O)OC_1$ - C_6 alkyl), 4- to 6-membered heterocycloalkyl, - $NH(C(O)C_1$ - C_6 alkyl), or - OC_1 - C_4 alkyl(OC_1 - C_4 alkyl), wherein each C_3 -
25 C_6 cycloalkyl is optionally substituted with 1 to 3 R^{18} substituents, each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R^{21} substituents, and each 4- to 6-membered heterocycloalkyl is optionally substituted with C_1 - C_4 alkyl;

each R^{17} is independently halogen, C_1 - C_6 alkyl, - OC_1 - C_6 alkyl, or 5- to 10-membered heteroaryl, wherein each 5- to 10-membered heteroaryl is optionally substituted with C_1 - C_4 alkyl;

30 each R^{18} is independently C_1 - C_4 alkyl, - SC_1 - C_4 alkyl, -Ph, or - OC_1 - C_4 alkyl;

each R^{21} is independently halogen or C_1 - C_4 alkyl;

R^{4a} is C₁-C₆alkyl or C₃-C₈cycloalkyl, wherein each C₁-C₆alkyl and C₃-C₈cycloalkyl are optionally substituted with 1 to 3 R¹⁹ substituents;

each R¹⁹ is independently halogen, -OH, -OC₁-C₄alkyl, -SC₁-C₄alkyl, -NH₂, -NH(C₁-C₄alkyl), or -N(C₁-C₄alkyl)₂;

- 5 R^{1b} and R^{2c} form together with the carbon atom to which they are attached a C₃-C₈cycloalkyl, 4- to 14-membered heterocycloalkyl, 8- to 14-membered partially unsaturated heterocyclic group, or 8- to 14-membered partially unsaturated carbocyclic group, wherein C₃-C₈cycloalkyl is optionally substituted with 1 to 3 R⁹ substituents, and wherein 4- to 14-membered heterocycloalkyl, 8- to 14-membered partially unsaturated heterocyclic group, or 8- to 14-membered partially unsaturated carbocyclic group is optionally substituted with oxo (=O), oxime (=N-OH), C₁-C₃alkoxyoxime (=N-OC₁-C₃alkyl), or 1 to 3 substituents independently selected from -OH and -CF₃;

R^{2d} and R^{4b} form together with the carbon atoms to which they are attached a C₃-C₈cycloalkyl or 4- to 14-membered heterocycloalkyl, wherein C₃-C₈cycloalkyl is optionally substituted with 1 to 3 R¹⁹ substituents; and

- 15 R^{1c} and R³ form together with the carbon atoms to which they are attached a C₃-C₈cycloalkyl or 4- to 14-membered heterocycloalkyl, wherein C₃-C₈cycloalkyl is optionally substituted with 1 to 3 R¹⁹ substituents.

In some embodiments, the pharmaceutical combination can comprise a compound of Formula (I) which is a compound of Formula (Ia), of Formula (Ia'), of Formula (Ib), of Formula (Ib'), of Formula (Ic), of Formula (Ic'), of Formula (Id), of Formula (Id'), of Formula (Ie), of Formula (Ie'), of Formula (If), of Formula (If'), or of Formula (Ig), as described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments, the pharmaceutical combination can comprise a compound of Formula (I) which is a compound of Table 1 of the present description, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments, the pharmaceutical combination is such that the COX inhibitor can comprise a Non-Steroidal Anti-Inflammatory Drug (NSAID). In some embodiments, the pharmaceutical combination is such that the COX inhibitor is acetaminophen.

In some embodiments, the pharmaceutical combination can be a synergistic pharmaceutical combination.

Another aspect relates to a pharmaceutical combination as defined herein, for use in the treatment of pain in a subject in need thereof. Similarly, this aspect relates to the use of a pharmaceutical combination as defined herein, for the treatment of pain in a subject in need thereof. Furthermore, this aspect relates to a method for the treatment of pain, comprising administering to a subject in

need thereof a pharmaceutical combination as defined herein. In some embodiments, the pain is inflammatory pain, neuropathic pain or cancer pain. In some embodiments, the pain is inflammatory pain. In another embodiment, the pain is neuropathic pain. In yet another embodiment, the pain is cancer pain. In some embodiments, the treatment is an oral treatment.

- 5 Another aspect relates to a method for the treatment of pain, comprising administering to a subject in need thereof a cyclooxygenase (COX) inhibitor and a compound having the Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein. In some embodiments, the COX inhibitor can comprise a Non-Steroidal Anti-Inflammatory Drug (NSAID). In some embodiments, the COX inhibitor is acetaminophen. In some embodiments, the pain is
- 10 inflammatory pain, neuropathic pain or cancer pain. In some embodiments, the pain is inflammatory pain. In another embodiment, the pain is neuropathic pain. In yet another embodiment, the pain is cancer pain. In some embodiments, the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof are administered orally.
- 15 Another aspect relates to a kit comprising a first single dose form of a cyclooxygenase (COX) inhibitor and a second single dose form of a compound having the Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and instructions for use. In some embodiments, the kit can comprise a COX inhibitor which is a Non-Steroidal Anti-Inflammatory Drug (NSAID). In some embodiments, the COX inhibitor can be
- 20 acetaminophen. In some embodiments, the kit is for use in the treatment of pain. In some embodiments, the pain is inflammatory pain, neuropathic pain or cancer pain. In some embodiments, the pain is inflammatory pain. In another embodiment, the pain is neuropathic pain. In yet another embodiment, the pain is cancer pain. In some embodiments, the treatment is an oral treatment.

25 BRIEF DESCRIPTION OF THE FIGURES

- Figure 1** shows: **(A)** the dose response curve of compound 61, naproxen, and compound 61:naproxen combination in the carrageenan-induced inflammation model. Analysis of carrageenan-treated rats using linear regression analysis reveals that the ED₅₀ of the combination is 1.4 mg/kg, with 95% confidence limits (CL) of 1.0 and 2.0 mg/kg as compared to
- 30 compound 61 or naproxen alone, which produces an ED₅₀ of 6.7 and 8.1 mg/kg, respectively. All compounds administered orally and tested 30 minutes later. Dose ratio of combination was 1:0.83 (naproxen: compound 61). Non-linear regression analysis using the variable slope sigmoidal equation model. % anti-hyperalgesia = $(PWL_{(dose)} - PWL_{(vehicle)}) / (PWL_{(naive)} - PWL_{(vehicle)}) \times 100$. Dotted lines represent 95% CL. **(B)** the isobologram of compound 61 to naproxen. The
- 35 isobolographic analysis was performed using normalized data. The data point representing the

ED50 value of the combination therapy lies below the line of additivity (line connecting compound 61 and naproxen ED50 values) with its 95% CL never crossing the dotted line.

Figure 2 shows: **(A)** the dose response curve of compound 61, naproxen, and compound 61:naproxen combination in the carrageenan-induced inflammation model. Analysis of carrageenan-treated rats using linear regression analysis reveals that the ED50 of the combination is 1.8 mg/kg, with 95% confidence limits (CL) of 1.4 and 2.3 mg/kg as compared to compound 61 or naproxen alone, which produces an ED50 of 6.7 and 8.1 mg/kg, respectively. All compounds administered orally and tested 30 minutes later. Dose ratio of combination was 1:0.83 (naproxen: compound 61). Non-linear regression analysis using the variable slope sigmoidal equation model. % anti-hyperalgesia = $(PWL_{(dose)} - PWL_{(vehicle)}) / (PWL_{(naive)} - PWL_{(vehicle)}) \times 100$. Dotted lines represent 95% CL. **(B)** the isobologram of compound 61 to naproxen. The isobolographic analysis was performed using normalized data. The data point representing the ED50 value of the combination therapy lies below the line of additivity (line connecting compound 61 and naproxen ED50 values) with its 95% CL never crossing the dotted line.

Figure 3 shows: **(A)** the dose response curve of compound 61, celecoxib, and compound 61:celecoxib combination in the carrageenan-induced inflammation model. Analysis of carrageenan-treated rats using linear regression analysis reveals that the ED50 of the combination is 2.3 mg/kg, with 95% confidence limits (CL) of 1.5 and 2.9 mg/kg as compared to compound 61 or celecoxib alone, which produces an ED50 of 6.7 and 12.9 mg/kg, respectively. All compounds administered orally and tested 30 minutes later. Dose ratio of combination was 1:0.52 (celecoxib: compound 61). Non-linear regression analysis using the variable slope sigmoidal equation model. % anti-hyperalgesia = $(PWL_{(dose)} - PWL_{(vehicle)}) / (PWL_{(naive)} - PWL_{(vehicle)}) \times 100$. Dotted lines represent 95% CL. **(B)** the isobologram of compound 61 to celecoxib. The isobolographic analysis was performed using normalized data. The data point representing the ED50 value of the combination therapy lies below the line of additivity (line connecting compound 61 and celecoxib ED50 values) with its 95% CL never crossing the dotted line.

Figure 4 shows: **(A)** the dose response curve of compound 61, ibuprofen, and compound 61:ibuprofen combination in the carrageenan-induced inflammation model. Analysis of carrageenan-treated rats using linear regression analysis reveals that the ED50 of the combination is 2.1 mg/kg, with 95% confidence limits (CL) of 1.1 and 4.6 mg/kg as compared to compound 61 or ibuprofen alone, which produces an ED50 of 6.7 and 12.6 mg/kg, respectively. All compounds administered orally and tested 30 minutes later. Dose ratio of combination was 1:0.53 (ibuprofen: compound 61). Non-linear regression analysis using the variable slope sigmoidal equation model. % anti-hyperalgesia = $(PWL_{(dose)} - PWL_{(vehicle)}) / (PWL_{(naive)} - PWL_{(vehicle)}) \times 100$. Dotted lines represent 95% CL. **(B)** the isobologram of compound 61 to ibuprofen. The isobolographic analysis was performed using normalized data. The data point representing the ED50 value of the

combination therapy lies below the line of additivity (line connecting compound 61 and ibuprofen ED50 values) with its 95% CL never crossing the dotted line.

Figure 5 shows: **(A)** the dose response curve of compound 61, diclofenac, and compound 61: diclofenac combination in the carrageenan-induced inflammation model. Analysis of carrageenan-treated rats using linear regression analysis reveals that the ED50 of the combination is 1.6 mg/kg, with 95% confidence limits (CL) of 0.9 and 2.8 mg/kg as compared to compound 61 or diclofenac alone, which produces an ED50 of 6.7 and 11.7 mg/kg, respectively. All compounds administered orally and tested 30 minutes later. Dose ratio of combination was 1:0.57 (diclofenac: compound 61). Non-linear regression analysis using the variable slope sigmoidal equation model. $\% \text{ anti-hyperalgesia} = (\text{PWL}_{(\text{dose})} - \text{PWL}_{(\text{vehicle})}) / (\text{PWL}_{(\text{naïve})} - \text{PWL}_{(\text{vehicle})}) \times 100$. Dotted lines represent 95% CL. **(B)** the isobologram of compound 61 to diclofenac. The isobolographic analysis was performed using normalized data. The data point representing the ED50 value of the combination therapy lies below the line of additivity (line connecting compound 61 and diclofenac ED50 values) with its 95% CL never crossing the dotted line.

Figure 6 shows: **(A)** the dose response curve of compound 63, naproxen, and compound 63:naproxen combination in the carrageenan-induced inflammation model. Analysis of carrageenan-treated rats using linear regression analysis reveals that the ED50 of the combination is 0.87 mg/kg, with 95% confidence limits (CL) of 0.4 and 2.0 mg/kg as compared to compound 63 or naproxen alone, which produces an ED50 of 1.4 and 8.1 mg/kg, respectively. All compounds administered orally and tested 30 minutes later. Dose ratio of combination was 1:0.178 (naproxen: compound 63). Non-linear regression analysis using the variable slope sigmoidal equation model. $\% \text{ anti-hyperalgesia} = (\text{PWL}_{(\text{dose})} - \text{PWL}_{(\text{vehicle})}) / (\text{PWL}_{(\text{naïve})} - \text{PWL}_{(\text{vehicle})}) \times 100$. Dotted lines represent 95% CL. **(B)** the isobologram of compound 63 to naproxen. The isobolographic analysis was performed using normalized data. The data point representing the ED50 value of the combination therapy lies below the line of additivity (line connecting compound 63 and naproxen ED50 values) with its 95% CL never crossing the dotted line.

DETAILED DESCRIPTION

General Definitions

All technical and scientific terms used herein have the same meaning as commonly understood by one ordinary skilled in the art to which the present technology pertains. For convenience, the meaning of certain terms and phrases used herein are provided below.

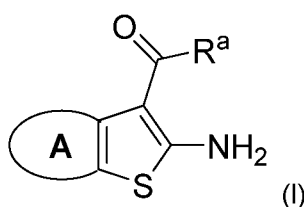
To the extent the definitions of terms in the publications, patents, and patent applications incorporated herein by reference are contrary to the definitions set forth in this specification, the definitions in this specification control. The section headings used herein are for organizational purposes only, and are not to be construed as limiting the subject matter disclosed.

The terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting. It should be noted that, the singular forms "a", "an", and "the" include plural forms as well, unless the content clearly dictates otherwise. Thus, for example, reference to a composition containing "a compound" also contemplates a mixture of two or more compounds. It should also be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise. Furthermore, to the extent that the terms "including", "includes", "having", "has", "with", or variants thereof are used in either the detailed description and/or the claims, such terms are intended to be inclusive in a manner similar to the term "comprising".

The term "about" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, "about" can mean within 1 or more than 1 standard deviation, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, preferably up to 10%, more preferably up to 5%, and more preferably still up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value. Where particular values are described in the application and claims, unless otherwise stated the term "about" meaning within an acceptable error range for the particular value should be assumed.

Thiophene fused cyclohexanone derivative ASIC inhibitors

The present application relates to pharmaceutical combinations comprising thiophene fused cyclohexanone derivatives having ASIC inhibition properties, which are compounds of general Formula (I)



or pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein R^a and **A** will be defined in further detail below.

The compounds described in the present application thus encompass those represented by the chemical structure of Formula I, with reference to any of the applicable embodiments described below, and exemplary compounds, such as Compounds 4, 8, 9, 14-39, 47-54, 59, 60a, 60b, 61-72, 75, 81-84, 89, 91, 97, 101, 108, 109, 119-136, 138-150, 154, 155, 163, 168-170, 173-175, 178-181, 183, 189-195, 197-202, 211-216, 219, 221, 227-232, 237, 238, 239, 245-251, 253, 254,

255, 257, 258, 263, 264, 271, 272, 273, 278-281, 287, 288, 290, 291, 297, 298, 305, 306, 313, 314, 321, 322, 330, 331, 337-349, 352-358, 360, 362, 371, 378, 391-393, 394a, 394b, 395a, 395b, 396, 397, 401-403, 406-408, 412-414, 416, 418, 422, 427-431, 433, 434, 445-454, 462-466, 468-476, 478-483, 486, 488, 489, 492, 495-498, 511-515, 520, 523, 524, or 534 of Table 1, as well as their pharmaceutically acceptable salts, solvates, and prodrugs when applicable.

Compounds may be identified either by their chemical structure or their chemical name. In a case where the chemical structure and chemical name would conflict, the chemical structure will prevail.

Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure, for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the present description. Unless otherwise stated, all tautomeric forms of the compounds are within the scope of the present description. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of the present description. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present description.

Definitions of specific functional groups and chemical terms are provided below.

The chemical structures herein are drawn according to the conventional standards known in the art. Thus, where an atom, such as a carbon atom, as drawn appears to have an unsatisfied valency, then that valency is assumed to be satisfied by a hydrogen atom even though that hydrogen atom is not necessarily explicitly drawn. Hydrogen atoms should be inferred to be part of the compound.

The number of carbon atoms in a hydrocarbyl substituent can be indicated by the prefix " $\text{C}_x\text{-C}_y$," where x is the minimum and y is the maximum number of carbon atoms in the substituent. When reference is made to "x to y membered" heterocyclic group (e.g., heterocycloalkyl, partially unsaturated heterocyclic group, or heteroaryl), then x and y define respectively, the minimum and maximum number of atoms in the cyclic group, including carbons as well as heteroatom(s).

The term "halogen" as used herein refers to an atom selected from fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), and iodine (iodo, -I).

The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon, more particularly oxygen, sulfur, or nitrogen.

The term "alkyl" as used herein, refers to a saturated, straight- (linear) or branched-chain hydrocarbon radical. In some embodiments, the alkyl group can contain from 1 to 6 carbon atoms, although alkyl groups with more than 6 carbon atoms can be contemplated. For example, "C₁-C₆alkyl" contains from one to six carbon atoms. Examples of alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl, *tert*-butyl, neopentyl, n-hexyl, heptyl, octyl radicals and the like.

The term "alkenyl" as used herein, denotes a straight- or branched-chain hydrocarbon radical containing one or more double bonds. In some embodiments, the alkenyl groups can contain from 2 to 6 carbon atoms, although alkenyl groups with more than 6 carbon atoms can be contemplated. For example, "C₂-C₆alkenyl" contains from two to six carbon atoms. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, pentenyl, 1-methyl-2-buten-1-yl, hexenyl, and the like.

The term "alkynyl" as used herein, denotes a straight- or branched-chain hydrocarbon radical containing one or more triple bonds. In some embodiments, the alkynyl groups can contain from 2 to 6 carbon atoms, although alkynyl groups with more than 6 carbon atoms can be contemplated. For example, "C₂-C₆alkynyl" contains from two to six carbon atoms. Alkynyl groups include, but are not limited to, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like.

The term "cycloalkyl", used alone or as part of a larger moiety, refers to a group comprising a saturated carbocyclic ring in a monocyclic or polycyclic ring system, including spiro (sharing one atom), fused (sharing at least one bond) or bridged (sharing two or more bonds) carbocyclic ring systems, having from three to fifteen ring members. In some embodiments, the cycloalkyl groups can contain from 3 to 8 carbon atoms. For example, "C₃-C₈cycloalkyl" contains from three to eight carbon atoms in the cyclic ring. Examples of cycloalkyl groups can include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[4.2.0]octyl, norbornyl, and the like.

The term "aryl" used herein refers to a monocyclic moiety or to a bicyclic or tricyclic fused ring system wherein the ring system is carbocyclic and fully aromatic. In some embodiments, the aryl groups can contain from 6 to 14 carbon atoms, such as 6 to 10 carbon atoms for instance. For example, a "C₆-C₁₀aryl" group contains from six to ten carbon atoms in the aromatic system. In certain embodiments, "aryl" refers to an aromatic ring system which includes, without being limited to, phenyl, naphthyl, azulenyl, anthracyl, and the like.

As used herein, the term "heterocyclic group" refers to a chemically stable, saturated, partially unsaturated, or fully aromatic monocyclic or polycyclic ring system, including spiro (sharing one atom), fused (sharing at least one bond) or bridged (sharing two or more bonds) carbocyclic ring system, including at least one heteroatom as defined above. A heterocyclic group can be a

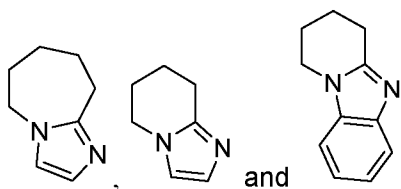
heterocycloalkyl group, a heteroaryl group, or a partially unsaturated heterocyclic group, as defined herein.

The term "heterocycloalkyl" used alone or as part of a larger moiety, refers to a saturated cyclic group containing at least one heteroatom as defined herein, which can include a single ring, or two or more rings. In some embodiments, the heterocycloalkyl groups can include 3 to 14 ring atoms although heterocycloalkyl groups with more than 14 ring atoms can be contemplated. In some embodiments, the heterocycloalkyl groups can contain 4 to 14 ring atoms, or 4 to 6 ring atoms or 3 to 6 ring atoms for instance. For example, a "3- to 14-membered heterocycloalkyl group" contains from three to fourteen atoms, by counting the total number of carbon atoms and heteroatoms, in the saturated heterocyclic moiety. In some embodiments, the heterocycloalkyl group can contain from one to four heteroatoms. Heterocycloalkyl groups can include, without limitation, oxiranyl, aziridinyl, oxetanyl, tetrahydropyranyl (oxanyl), tetrahydrofuranyl (oxolanyl), pyrrolidinyl (azolidinyl), piperidinyl, dioxanyl, morpholinyl, thietanyl, azetidyl, diazetidinyl, oxathiolanyl, oxepanyl, azocanyl (octahydroazocinyl), thiocanyl, azonanyl (octahydroazoninyl), 1,3-dioxolanyl, pyrazolidinyl, imidazolidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothienyl, tetrahydrodithienyl, thiomorpholinyl, thioxanyl, homopiperidinyl, thiepanyl, dithianyl, dithiolanyl, 3-azabicyclo[3,1,0]hexanyl, 3-azabicyclo[4,1,0]heptanyl, quinuclidinyl, decahydroquinolanyl, octahydroindolyl, and the like. A heterocycloalkyl can be attached to its pendant group at any heteroatom or carbon atom that results in a chemically stable structure.

The term "heteroaryl" used alone or as part of a larger moiety, refers to a fully aromatic cyclic group containing at least one heteroatom as defined herein, which can include a single ring, or two or more fused rings. In some embodiments, the heteroaryl groups can include from 5 to 10 ring atoms although heteroaryl groups with more than 10 ring atoms can be contemplated. In some embodiments, the heteroaryl group can contain from one to four heteroatoms. Heteroaryl groups can include, without limitation, thienyl, furanyl (furyl), pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, benzofuranyl, dibenzofuranyl, benzimidazolyl, benzothiazolyl, benzothienyl (benzothiophenyl), benzoxazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, furopyridinyl, indolyl, indazolyl, isoindolyl, indoliziny, purinyl, quinolyl (quinolinyl), isoquinolyl (isoquinolinyl), acridinyl, cinnolyl, quinazolinyl, naphthyridinyl, carbazolyl, phenanthridinyl, phenazinyl, phenothiazinyl, phenoxazinyl and pteridinyl. A heteroaryl group can be attached to its pendant group at any heteroatom or carbon atom that results in a chemically stable structure.

As used herein, the term "partially unsaturated heterocyclic group" refers to a carbocyclic ring system including at least one double bond between ring atoms but is not fully aromatic and comprises at least one heteroatom. The "partially unsaturated heterocyclic group" is intended to

encompass ring systems, which can be mono, bi or tricyclic and having one or multiple sites of unsaturation. In some embodiments, the partially unsaturated heterocyclic group can include a multicyclic ring system where at least one ring is aromatic while at least another ring is not aromatic. For instance, the partially unsaturated heterocyclic group can include an aryl fused with a heterocycloalkyl, a heteroaryl fused with a cycloalkyl, or a heteroaryl fused with a heterocycloalkyl, where each of the aryl, heteroaryl, cycloalkyl and heterocycloalkyl can itself be monocyclic or bicyclic. In some embodiments, the partially unsaturated heterocyclic groups can contain from 7 to 14 carbon atoms, such as 7 to 10 carbon atoms or 8 to 14 carbon atoms for instance. For example, a "7- to 10-membered partially unsaturated heterocyclic group" contains from seven to ten atoms, by counting the total number of carbon atoms and heteroatoms, in the heterocyclic moiety. The partially unsaturated heterocyclic group can contain, in some embodiments, from one to four heteroatoms. The partially unsaturated heterocyclic group can be attached to its pendant group at any heteroatom or carbon atom that results in a chemically stable structure. Non-limiting examples of partially unsaturated heterocyclic group include pyrazolinyl, imidazolinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2H-pyranyl, 4H-pyranyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, quinolizinyl, tetrahydroquinolynyl, tetrahydroisoquinolynyl, 1,3-benzodioxolyl, chromanyl, chromenyl, indolinyl, quinolonyl, isoquinolonyl, oxazepinyl, diazepinyl, thiazepinyl, phthalazinyl, quinoxalinyl, pyrido[2,3-b]-1,4-oxazin-3(4H)-one,

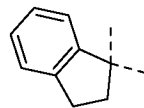


. When used in reference to a ring atom of a heterocyclic group, the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen, the nitrogen may be N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl), or NR₀ (as in N-substituted pyrrolidinyl).

As used herein, the term "partially unsaturated carbocyclic group" refers to a carbocyclic ring system including at least one double bond between ring atoms but is not fully aromatic. The "partially unsaturated carbocyclic group" is intended to encompass ring systems, which comprise only carbon atoms within the ring, said ring being mono, bi or tricyclic and having one or multiple sites of unsaturation. In some embodiments, the partially unsaturated carbocyclic group can include a multicyclic ring system where at least one ring is aromatic while at least another ring is not aromatic. For instance, the partially unsaturated heterocyclic group can include an aryl fused with a cycloalkyl, where each of the aryl and cycloalkyl can itself be monocyclic or bicyclic. In some embodiments, the partially unsaturated carbocyclic groups can contain from 7 to 14 carbon atoms, such as 7 to 10 carbon atoms or 8 to 14 carbon atoms for instance. For example, a "8- to

14-membered partially unsaturated carbocyclic group" contains from eight to fourteen carbon atoms in the cyclic moiety. The partially unsaturated carbocyclic group can be attached to its pendant group at any carbon atom that results in a chemically stable structure. A non-limiting

example of partially unsaturated carbocyclic group includes

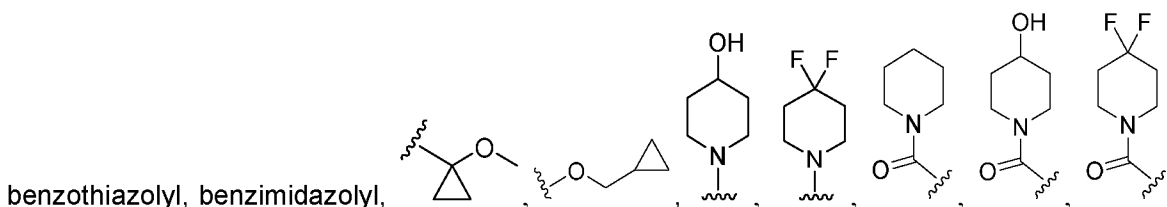


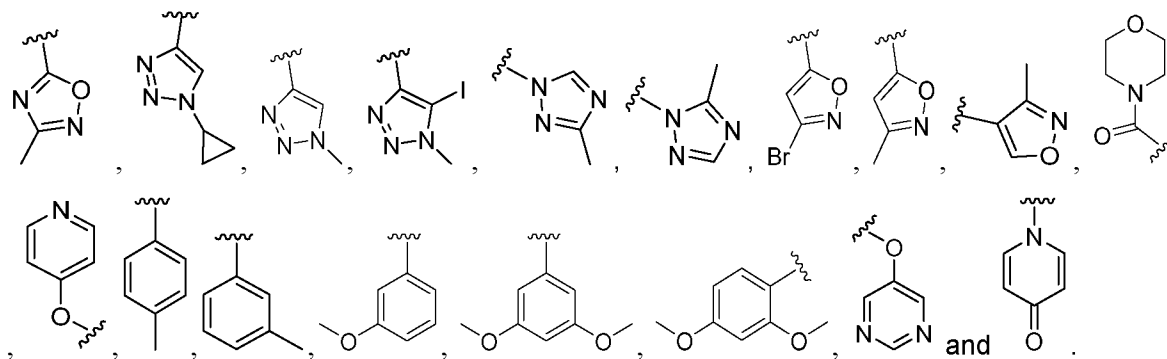
- 5 As described herein, various chemical groups present in the compounds of the present description, such as any of the above-defined groups, can be optionally substituted. In general, the term "substituted" means that one or more hydrogen atoms of the designated moiety is replaced with a suitable substituent. Unless otherwise indicated, a substituted chemical group may have a suitable substituent at each substitutable position of the group, and when more than
- 10 one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at each position. Combinations of substituents envisioned under the present description are preferably those that result in the formation of chemically stable or chemically feasible compounds. The term "chemically stable", as used herein, refers to compounds that are not substantially altered when
- 15 subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

In some particular embodiments, when any chemical group is substituted, it can be substituted by independent replacement of one, two, or three or more of the hydrogen atoms with substituents including, but not limited to halogen (i.e., -F, -Cl, -Br, -I), -OH, -CO₂H, alkoxy such as methoxy,

20 ethoxy, or propyloxy, -OCHF₂, -OCH₂CHF₂, -OCH₂CF₃, -OCH₂CH₂OCH₃, protected alkoxy, alkyl groups as defined above such as methyl, ethyl, propyl, or -C(CH₃)₃, aryl groups as defined above such as phenyl, cycloalkyl groups as defined above such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, oxo (=O), thioxo (=S), oxime (=N-OH), C₁-C₃alkoxyoxime (=N-OC₁-C₃alkyl), -NO₂, -CN, -NH₂, -NHMe, -NH₂Et, -N(Me)₂, -NHCOMe, -NH(COO^tBu), -N(Et)(COO^tBu), protected amino,

25 -CH₂OH, -COOH, -COOMe, -COOEt, -CONH₂, -CONHMe, -CONHEt, -CF₃, -CHF₂, -CH₂F, -Si(Me), -OSi(Me)₂(^tBu), -SMe, -SO₂NH(CH₂)₃OH, -SO₂Me, -SO₂Ph, -SPh, pyrazolyl, pyrrolyl, pyridyl, piperidyl, triazolyl, tetrazolyl, morpholinyl, isoxazolyl, oxazolyl, thiazolyl, imidazolyl,





The expression "pharmaceutically acceptable salt" refers to those salts of the compounds of the present description which are suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. The salts can be prepared *in situ* during the final isolation and purification of the compounds of the present description, or separately by reacting a free base function of the compound with a suitable organic or inorganic acid (acid addition salts) or by reacting an acidic function of the compound with a suitable organic or inorganic base (base-addition salts). Examples of pharmaceutically acceptable salts include, but are not limited to, nontoxic acid addition salts, or salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Representative base addition alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, or magnesium salts, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, sulfonate and aryl sulfonate.

The term “solvate” refers to a physical association of one of the present compounds with one or more solvent molecules. This physical association includes hydrogen bonding. In certain instances, the solvate will be capable of isolation, for example when one or more solvent

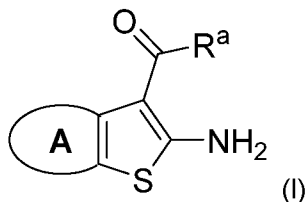
molecules are incorporated in the crystal lattice of a crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include, without limitation, hydrates, hemihydrates, ethanolates, hemiethanolates, n-propanolates, iso-propanolates, 1-butanolates, 2-butanolate, and solvates of other physiologically acceptable solvents. The compounds as herein
5 described also include each of their solvates and mixtures thereof.

The term " prodrug" as used herein refers to those prodrugs of the compounds of the present description which are suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use. "Prodrug", as used herein means a
10 compound which is convertible in vivo by metabolic means (e.g., by hydrolysis) to afford any compound delineated by the formulae of the instant description. Various forms of prodrugs are known in the art.

The compounds of the present application may be prepared by conventional chemical synthesis, such as exemplified in the general schemes provided hereafter and in Examples 1 to 260 for
15 instance. As can be appreciated by the skilled artisan, further methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. In addition, the solvents, temperatures, reaction duration, etc. delineated herein are for purposes of illustration only and one of ordinary skill in the art will recognize that
20 variation of the reaction conditions can produce the desired products of the present description. Synthetic chemistry transformations and/or protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art. The synthesized compounds can be separated from a reaction mixture and further purified by standard methods such as column chromatography, high pressure liquid chromatography, or
25 recrystallization.

The thiophene fused cyclohexanone derivatives such as the compounds of Formula (I) may be modified by appending various functionalities via any synthetic means delineated herein to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic
30 system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

In some embodiments, the thiophene fused cyclohexanone derivative can thus be a compound having the Formula (I),



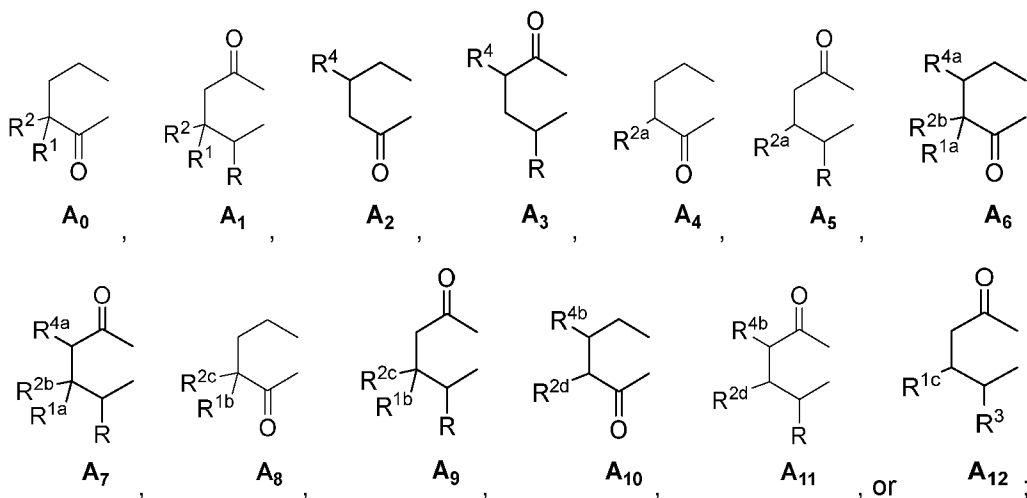
or a pharmaceutically acceptable salt, solvate, or prodrug thereof,

wherein:

R^a is $-NH_2$, $-NH-OH$, $-OH$, $-NHR^b$, or $-NHR^cR^d$;

- 5 R^b is C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, or 3- to 6-membered heterocycloalkyl, wherein C_1 - C_6 alkyl is optionally substituted with 1 to 3 halogens, 1 to 3 $-OH$, $-OC_1$ - C_3 alkyl, $-COOH$, or cyclopropyl optionally substituted with $-OH$, and wherein C_3 - C_6 cycloalkyl is optionally substituted with $-CN$;
 R^c and R^d form with the nitrogen to which they are attached a 4-membered heterocycloalkyl, wherein the 4-membered heterocycloalkyl is optionally substituted with at least one of $-OH$ and
 10 C_1 - C_3 alkyl;

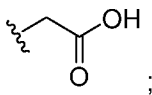
A represents one of the following residues **A**₀ to **A**₁₂



and wherein:

- 15 R is H , C_1 - C_6 alkyl or phenyl;
 R^1 and R^2 are independently $-CN$, C_6 - C_{10} aryl, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, 4- to 14-membered heterocycloalkyl, 5- to 10-membered heteroaryl, $-C(O)NH_2$, $-C(O)NHR^5$, $-C(O)R^6$, or $-C(O)OR^5$, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 3 R^7 substituents, each C_6 - C_{10} aryl is optionally substituted with 1 to 3 R^8 substituents, and each 5- to
 20 10-membered heteroaryl is optionally substituted with 1 to 3 R^{22} substituents, with the proviso that

when R^a is $-OH$, **A** represents **A**₀, and R^1 is , then R^2 in residue **A**₀ is different than



each R^5 is independently C_1 - C_6 alkyl, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 3 R^9 substituents;

each R^6 is independently C_3 - C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, or C_6 - C_{10} aryl;

- 5 each R^7 is independently -OH, $-C(O)R^{11}$, C_3 - C_6 cycloalkyl, -CN, C_6 - C_{10} aryl, halogen, $-C(O)OH$, 5- to 10-membered heteroaryl, $-NH(C(O)OC_1-C_6alkyl)$, $-N(C_1-C_4alkyl)(C(O)OC_1-C_6alkyl)$, 4- to 6-membered heterocycloalkyl, $-NH(C(O)C_1-C_6alkyl)$, $-OR^{20}$, $-SC_1-C_6alkyl$, $-NH_2$, $-NH(C_1-C_4alkyl)$, or $-N(C_1-C_4alkyl)_2$, wherein each C_3 - C_6 cycloalkyl is optionally substituted with 1 to 3 R^{12} substituents, each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R^{13} substituents, and each
- 10 4- to 6-membered heterocycloalkyl is optionally substituted with C_1 - C_4 alkyl or oxo;

each R^8 is independently halogen, C_1 - C_6 alkyl, $-OC_1-C_6alkyl$, C_3 - C_6 cycloalkyl, or 5- to 10-membered heteroaryl, wherein each $-OC_1-C_6alkyl$ is optionally substituted with $-OC_1-C_4alkyl$, and each 5- to 10-membered heteroaryl is optionally substituted with C_1 - C_4 alkyl;

each R^{22} is independently C_1 - C_6 alkyl optionally substituted with phenyl;

- 15 each R^9 is independently -OH, $-C(O)R^{15}$, C_3 - C_6 cycloalkyl, -CN, C_6 - C_{10} aryl, halogen, $-C(O)OH$, 4- to 6-membered heterocycloalkyl, $-NH(C(O)C_1-C_6alkyl)$, $-OC_1-C_6alkyl$, $-SC_1-C_6alkyl$, $-NH_2$, $-NH(C_1-C_4alkyl)$, or $-N(C_1-C_4alkyl)_2$, wherein each 4- to 6-membered heterocycloalkyl is optionally substituted with C_1 - C_4 alkyl, and each $-OC_1-C_6alkyl$ is optionally substituted with $-OC_1-C_4alkyl$;

- each R^{11} is independently $-NH_2$, $-NH(C_1-C_4alkyl)$, $-N(C_1-C_4alkyl)_2$, or 4- to 6-membered
- 20 heterocycloalkyl;

each R^{20} is independently C_1 - C_6 alkyl or 5- to 10-membered heteroaryl, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 3 R^{14} substituents and each 5- to 10-membered heteroaryl is optionally substituted with -OH or $-NH(cyclopropyl)$;

- each R^{12} is independently C_1 - C_4 alkyl, $-SC_1-C_4alkyl$, -Ph, $-OC_1-C_4alkyl$, or -SPh, wherein each C_1 -
- 25 C_4alkyl is optionally substituted with -OH;

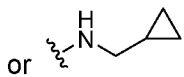
each R^{13} is independently halogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, -OH, $-OC_1-C_6alkyl$, $-SC_1-C_6alkyl$, $-S(O)_2C_1-C_6alkyl$, $-NH_2$, $-NH(C_1-C_4alkyl)$, or $-N(C_1-C_4alkyl)_2$, wherein each $-OC_1-C_6alkyl$, $-SC_1-C_6alkyl$, $-S(O)_2C_1-C_6alkyl$, $-NH(C_1-C_4alkyl)$, and $-N(C_1-C_4alkyl)_2$ is optionally substituted with 1 to 3 R^9 substituents;

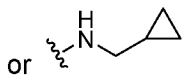
- 30 each R^{14} is independently halogen, $-OC_1-C_4alkyl$, or C_3 - C_6 cycloalkyl;

each R^{15} is independently $-NH_2$, $-NH(C_1-C_4alkyl)$, $-N(C_1-C_4alkyl)_2$, or 4- to 6-membered heterocycloalkyl;

R^4 is C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{10} aryl, 7- to 10-membered partially unsaturated heterocyclic

group, or 5- to 10-membered heteroaryl, wherein C₁-C₆alkyl and C₃-C₈cycloalkyl are optionally substituted with 1 to 3 R⁹ substituents, and C₆-C₁₀aryl and 5- to 10-membered heteroaryl are optionally substituted with 1 to 3 R¹⁰ substituents, with the proviso that: (i) when R^a is -OH, -NH₂,



or , and  represents A₂, then R⁴ in residue A₂ is different than -CH₃; and (ii)

5 when R^a is -NH₂ and  represents A₃, then R⁴ in residue A₃ is different than -C(CH₃)₃;

each R¹⁰ is independently C₁-C₄alkyl, halogen, -OC₁-C₆alkyl, -NH₂, -NH(C₁-C₄alkyl), or -N(C₁-C₄alkyl)₂, wherein each C₁-C₄alkyl is optionally substituted with 1 to 3 halogens;

R^{2a} is C₁-C₆alkyl, C₃-C₈cycloalkyl, or C₆-C₁₀aryl, wherein C₁-C₆alkyl and C₃-C₈cycloalkyl are optionally substituted with 1 to 3 R⁹ substituents, and C₆-C₁₀aryl is optionally substituted with 1 to
10 3 R¹⁰ substituents;

R^{1a} and R^{2b} are independently -CN, C₆-C₁₀aryl, C₁-C₆alkyl, C₃-C₈cycloalkyl, -C(O)NH₂, -C(O)NHR⁵, or -C(O)OC₁-C₆alkyl, wherein each C₁-C₆alkyl is optionally substituted with 1 to 3 R¹⁶ substituents and each C₆-C₁₀aryl is optionally substituted with 1 to 3 R¹⁷ substituents;

each R¹⁶ is independently -OH, -C(O)NH₂, -C(O)NH(C₁-C₄alkyl), C₃-C₆cycloalkyl, -CN, C₆-C₁₀aryl,
15 halogen, -C(O)OH, 5- to 10-membered heteroaryl, -NH(C(O)OC₁-C₆alkyl), 4- to 6-membered heterocycloalkyl, -NH(C(O)C₁-C₆alkyl), or -OC₁-C₄alkyl(OC₁-C₄alkyl), wherein each C₃-C₆cycloalkyl is optionally substituted with 1 to 3 R¹⁸ substituents, each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R²¹ substituents, and each 4- to 6-membered heterocycloalkyl is optionally substituted with C₁-C₄alkyl;

20 each R¹⁷ is independently halogen, C₁-C₆alkyl, -OC₁-C₆alkyl, or 5- to 10-membered heteroaryl, wherein each 5- to 10-membered heteroaryl is optionally substituted with C₁-C₄alkyl;

each R¹⁸ is independently C₁-C₄alkyl, -SC₁-C₄alkyl, -Ph, or -OC₁-C₄alkyl;

each R²¹ is independently halogen or C₁-C₄alkyl;

R^{4a} is C₁-C₆alkyl or C₃-C₈cycloalkyl, wherein each C₁-C₆alkyl and C₃-C₈cycloalkyl are optionally
25 substituted with 1 to 3 R¹⁹ substituents;

each R¹⁹ is independently halogen, -OH, -OC₁-C₄alkyl, -SC₁-C₄alkyl, -NH₂, -NH(C₁-C₄alkyl), or -N(C₁-C₄alkyl)₂;

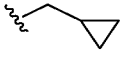
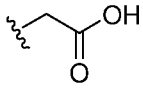
R^{1b} and R^{2c} form together with the carbon atom to which they are attached a C₃-C₈cycloalkyl, 4- to 14-membered heterocycloalkyl, 8- to 14-membered partially unsaturated heterocyclic group, or
30 8- to 14-membered partially unsaturated carbocyclic group, wherein C₃-C₈cycloalkyl is optionally substituted with 1 to 3 R⁹ substituents, and wherein 4- to 14-membered heterocycloalkyl, 8- to 14-membered partially unsaturated heterocyclic group, or 8- to 14-membered partially unsaturated carbocyclic group is optionally substituted with oxo (=O), oxime (=N-OH), C₁-C₃alkoxyoxime (=N-

OC₁-C₃alkyl), or 1 to 3 substituents independently selected from -OH and -CF₃;

R^{2d} and R^{4b} form together with the carbon atoms to which they are attached a C₃-C₈cycloalkyl or 4- to 14-membered heterocycloalkyl, wherein C₃-C₈cycloalkyl is optionally substituted with 1 to 3 R¹⁹ substituents; and

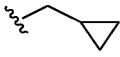
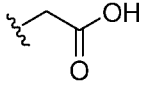
- 5 R^{1c} and R³ form together with the carbon atoms to which they are attached a C₃-C₈cycloalkyl or 4- to 14-membered heterocycloalkyl, wherein C₃-C₈cycloalkyl is optionally substituted with 1 to 3 R¹⁹ substituents.

In some embodiments, the compound of Formula (I) is such that: (i) when R^a is -OH, ,

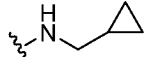
represents A₀, and R¹ is , then R² in residue A₀ is different than ; (ii) when

- 10 R^a is -OH and  represents A₂, then R⁴ in residue A₂ is different than -CH₃ and -CH₂CH₃; (iii) when R^a is -NH₂, and  represents A₂, then R⁴ in residue A₂ is different than -CH₃; and (iv) when R^a is -NH₂ and  represents A₃, then R⁴ in residue A₃ is different than -C(CH₃)₃.

In some embodiments, the compound of Formula (I) is such that: (i) when R^a is -OH, ,

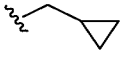
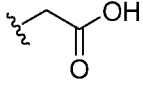
represents A₀, and R¹ is , then R² in residue A₀ is different than ; (ii) when

- 15 R^a is -OH and  represents A₂, then R⁴ in residue A₂ is different than -CH₃ and -CH₂CH₃; (iii) when R^a is -NH₂, and  represents A₂, then R⁴ in residue A₂ is different than -CH₃;

(iv) when R^a is , and , then R⁴ in residue A₂ is different than -CH₃;

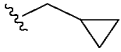
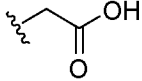
and (v) when R^a is -NH₂ and , then R⁴ in residue A₃ is different than -C(CH₃)₃.

In other embodiments, the compound of Formula (I) is such that: (i) when R^a is -OH, ,

- 20 represents A₀, and R¹ is , then R² in residue A₀ is different than ; (ii) when

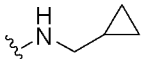
R^a is -OH and  represents A₂, then R⁴ in residue A₂ is different than alkyl; (iii) when R^a is -NH₂, and  represents A₂, then R⁴ in residue A₂ is different than -CH₃; and (iv) when R^a is -NH₂ and  represents A₃, then R⁴ in residue A₃ is different than -C(CH₃)₃.

In other embodiments, the compound of Formula (I) is such that: (i) when R^a is -OH, ,

represents A_0 , and R^1 is , then R^2 in residue A_0 is different than ; (ii) when

R^a is -OH and , represents A_2 , then R^4 in residue A_2 is different than alkyl; (iii) when R^a is -

NH_2 , and , represents A_2 , then R^4 in residue A_2 is different than -CH₃; (iv) when R^a is

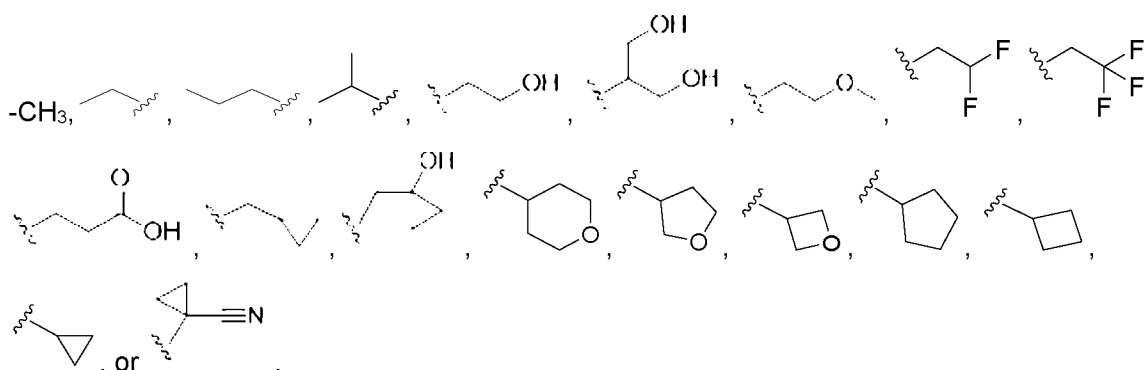
5  and , represents A_2 , then R^4 in residue A_2 is different than -CH₃; and (v) when

R^a is -NH₂ and , represents A_3 , then R^4 in residue A_3 is different than -C(CH₃)₃.

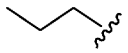
In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, or prodrug thereof, is such that R is H.

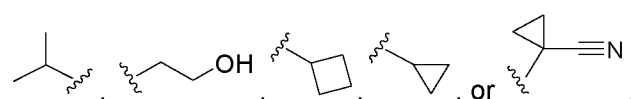
10 In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, or prodrug thereof, is such that R^a is -NHR^b and R^b represents C₁-C₆ alkyl, C₃-C₆ cycloalkyl, or 3- to 6-membered heterocycloalkyl, wherein C₁-C₆ alkyl is optionally substituted with 1 to 3 halogens, 1 to 3 -OH, -OC₁-C₃alkyl, -COOH, or cyclopropyl optionally substituted with -OH, and wherein C₃-C₆cycloalkyl is optionally substituted with -CN.

15 In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, or prodrug thereof, is such that R^a is -NHR^b and R^b represents:



In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt,

20 solvate, or prodrug thereof, is such that R^a is -NHR^b and R^b represents -CH₃, , ,



In some embodiments, R^a is -NHR^b and R^b represents .

In other embodiments, R^a is $-NR^cR^d$ and R^c and R^d form with the nitrogen to which they are attached a 4-membered heterocycloalkyl, wherein the 4-membered heterocycloalkyl is optionally substituted with at least one of $-OH$ and C_1 - C_3 alkyl.

In other embodiments, R^a is , , or .

5 In other embodiments, R^a is  or .

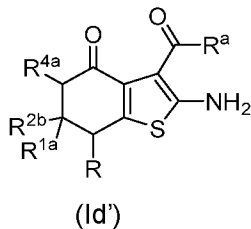
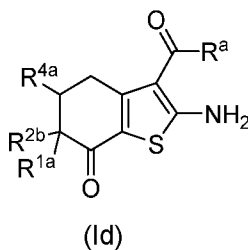
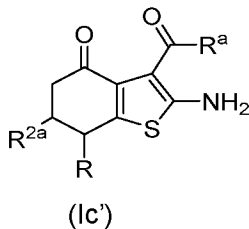
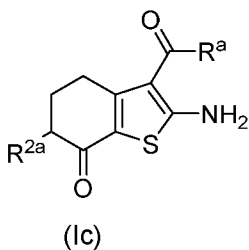
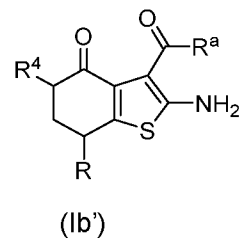
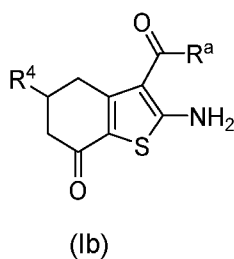
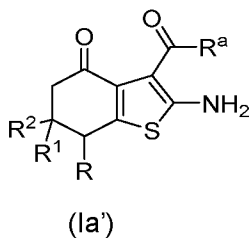
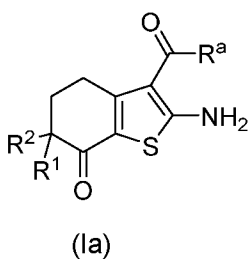
In other embodiments, R^a is $-OH$.

In other embodiments, R^a is $-NH_2$.

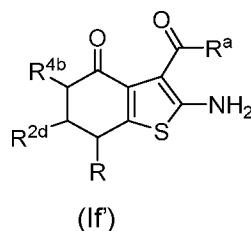
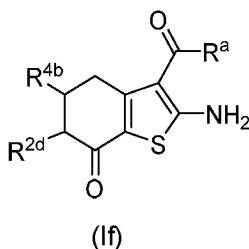
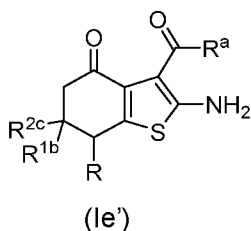
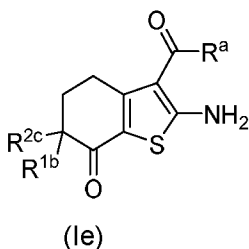
In other embodiments, R^a is $-NH-OH$.

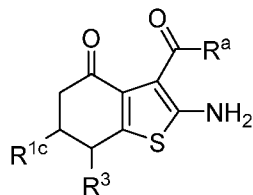
10 In some embodiments, the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, can be in the form of a racemate or any enantiomer thereof.

In some embodiments, the compound of Formula (I) can have the following structures (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), or (Ig):



15



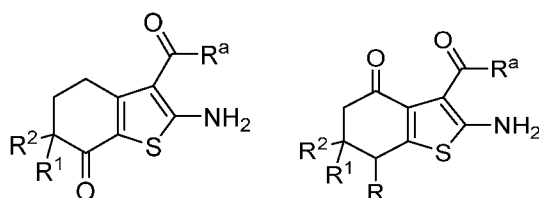


(Ig)

where R^1 , R^2 , R^3 , R^4 , R^{1a} , R^{1b} , R^{1c} , R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^{4a} , R^{4b} , R and R^a are as defined herein.

Compounds of Formula (Ia) and (Ia')

- 5 In some embodiments, the compound is of Formula (Ia) or (Ia'), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

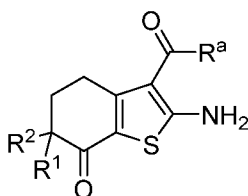


(Ia)

(Ia')

The groups R , R^a , R^1 and R^2 can be as defined for the general Formula (I) above.

- 10 In some embodiments, the compound is of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.



(Ia)

The groups R^a , R^1 and R^2 can be as defined for the general Formula (I) above.

- 15 In some embodiments, R^1 and R^2 can independently represent $-\text{CN}$, $\text{C}_6\text{-C}_{10}\text{aryl}$, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_2\text{-C}_6\text{alkynyl}$, $\text{C}_3\text{-C}_8\text{cycloalkyl}$, 5- to 10-membered heteroaryl, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHR}^5$, $-\text{C}(\text{O})\text{R}^6$, or $-\text{C}(\text{O})\text{OR}^5$, wherein each $\text{C}_1\text{-C}_6\text{alkyl}$ is optionally substituted with 1 to 3 R^7 substituents, each $\text{C}_6\text{-C}_{10}\text{aryl}$ is optionally substituted with 1 to 3 R^8 substituents, and each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R^{22} substituents, and R^5 , R^6 , R^7 , R^8 and R^{22} are as defined herein.
- 20

In some embodiments, R^1 and R^2 are independently $-\text{CN}$, $\text{C}_6\text{-C}_{10}\text{aryl}$, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_2\text{-C}_6\text{alkynyl}$, $\text{C}_3\text{-C}_8\text{cycloalkyl}$, 5- to 10-membered heteroaryl, or $-\text{C}(\text{O})\text{NH}_2$, wherein each $\text{C}_1\text{-C}_6\text{alkyl}$ is optionally substituted with 1 to 3 R^7 substituents, each $\text{C}_6\text{-C}_{10}\text{aryl}$ is optionally substituted with 1 to 3 R^8

substituents, and each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R²² substituents, and R⁷, R⁸ and R²² are as defined herein.

In further embodiments, R¹ and R² can independently represent -CN, phenyl, C₁-C₄alkyl, C₂-C₄alkynyl, C₃-C₆cycloalkyl, 5-membered heteroaryl, or -C(O)NH₂, wherein each C₁-C₄alkyl is optionally substituted with 1 or 2 R⁷ substituents, each phenyl is optionally substituted with 1 or 2 halogens, and each 5-membered heteroaryl is optionally substituted with 1 or 2 -CH₃.

According to some embodiments, R¹ and R² independently represent -CN, C₆-C₁₀aryl, C₁-C₆alkyl, C₃-C₆cycloalkyl, or -C(O)NH₂, wherein each C₁-C₆alkyl is optionally substituted with 1 to 2 R⁷ substituents as defined herein.

In some embodiments, when R¹ and/or R² represent -C(O)NHR⁵ or -C(O)OR⁵, each R⁵ can be C₁-C₆alkyl. In other embodiments, when R¹ and/or R² represent -C(O)R⁶ each R⁶ can be a 4- to 6-membered heterocycloalkyl.

In some embodiments, when R¹ and/or R² represent C₁-C₆alkyl substituted with 1 to 3 R⁷ substituents, then each R⁷ can independently represent -OH, -C(O)R¹¹, C₃-C₆cycloalkyl, -CN, C₆-C₁₀aryl, halogen, -C(O)OH, 5- to 10-membered heteroaryl, -NH(C(O)OC₁-C₆alkyl), -N(C₁-C₄alkyl)(C(O)OC₁-C₆alkyl), -NH(C(O)C₁-C₆alkyl), 4- to 6-membered heterocycloalkyl, -OR²⁰, -SC₁-C₆alkyl, -NH₂, or -N(C₁-C₄alkyl)₂, wherein each C₃-C₆cycloalkyl is optionally substituted with 1 to 3 R¹² substituents, each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R¹³ substituents and each 4- to 6-membered heterocycloalkyl is optionally substituted with C₁-C₄alkyl or oxo.

In some embodiments, R⁷ can independently represent -OH, -C(O)R¹¹, -OR²⁰, C₃-C₆cycloalkyl, -CN, C₆-C₁₀aryl, halogen, -C(O)OH, or 5- to 10-membered heteroaryl, wherein each C₃-C₆cycloalkyl is optionally substituted with 1 to 3 R¹² substituents and each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R¹³ substituents.

In further embodiments, R⁷ can independently represent -OH, -C(O)NH₂, -OR²⁰, C₃-C₆cycloalkyl, -CN, phenyl, halogen, -C(O)OH, or 5-membered heteroaryl, wherein each C₃-C₆cycloalkyl is optionally substituted with -CH₃.

In another embodiment, R⁷ can independently represent -OH, -C(O)NH₂, C₃-C₆cycloalkyl, -CN, C₆-C₁₀aryl, halogen, or 5- to 8-membered heteroaryl, wherein each C₃-C₆cycloalkyl is optionally substituted with 1 to 2 C₁-C₄alkyl, and each 5- to 8-membered heteroaryl is optionally substituted with 1 to 2 R¹³ substituents.

In some embodiments, the R¹¹ substituents mentioned above can independently represent -NH₂, -NH(C₁-C₄alkyl), or 4- to 6-membered heterocycloalkyl. In some particular embodiments, R¹¹ can represent -NH₂.

In some embodiments, the R^{12} substituents mentioned above can independently represent C_1 - C_4 alkyl, $-SC_1$ - C_4 alkyl, $-Ph$, $-OC_1$ - C_4 alkyl, or $-SPh$, wherein each C_1 - C_4 alkyl is optionally substituted with $-OH$. In some particular embodiments, R^{12} is C_1 - C_4 alkyl.

5 In some embodiments, the R^{13} substituents mentioned above can independently represent halogen, C_1 - C_4 alkyl, or C_3 - C_6 cycloalkyl. In some particular embodiments, R^{13} is independently halogen or C_1 - C_4 alkyl.

In some embodiments, the R^{14} substituents mentioned above can independently represent halogen, $-OC_1$ - C_4 alkyl, or C_3 - C_6 cycloalkyl. In some particular embodiments, R^{14} is halogen.

10 In some embodiments, the R^{20} substituents mentioned above can independently represent C_1 - C_6 alkyl or 5- to 10-membered heteroaryl, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 3 R^{14} substituents as defined herein, and each 5- to 10-membered heteroaryl is optionally substituted with $-OH$ or $-NH$ (cyclopropyl). In some particular embodiments, R^{20} is C_1 - C_6 alkyl, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 3 R^{14} substituents as defined herein. In further embodiments, R^{20} is C_1 - C_6 alkyl, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 3 halogens. In some embodiments, R^{20} is 5- to 10-membered heteroaryl substituted with $-OH$ or $-NH$ (cyclopropyl). In certain embodiments, R^{20} is 5- to 10-membered heteroaryl substituted with $-OH$. In other embodiments, R^{20} is 5- or 6-membered heteroaryl substituted with $-OH$.

In some embodiments, the R^{22} substituents mentioned above can independently represent C_1 - C_4 alkyl.

20 In some embodiments, when R^1 and/or R^2 represent C_6 - C_{10} aryl substituted with 1 to 3 R^8 substituents, then each R^8 can independently represent halogen, C_1 - C_6 alkyl, or $-OC_1$ - C_6 alkyl, wherein each $-OC_1$ - C_6 alkyl is optionally substituted with $-OC_1$ - C_4 alkyl. In some particular embodiments, R^8 is a halogen. In some embodiments, when R^1 and/or R^2 represent 5- to 10-membered heteroaryl substituted with 1 to 3 R^{22} substituents, then each R^{22} can independently represent C_1 - C_6 alkyl optionally substituted with phenyl. In some embodiments, R^{22} is C_1 - C_2 alkyl substituted with phenyl.

30 In some embodiments, R^1 and R^2 are independently $-CN$, C_6 - C_{10} aryl, C_1 - C_6 alkyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, 5- to 10-membered heteroaryl, $-C(O)NH_2$, $-C(O)NHR^5$, $-C(O)R^6$, or $-C(O)OR^5$, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 3 R^7 substituents, each C_6 - C_{10} aryl is optionally substituted with 1 to 3 R^8 substituents, and each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R^{22} substituents, and

each R^5 is independently C_1 - C_6 alkyl;

each R^6 is independently a 4- to 6-membered heterocycloalkyl;

35 each R^7 is independently $-OH$, $-C(O)R^{11}$, C_3 - C_6 cycloalkyl, $-CN$, C_6 - C_{10} aryl, halogen, $-C(O)OH$, 5- to 10-membered heteroaryl, $-NH(C(O)OC_1$ - C_6 alkyl), $-N(C_1$ - C_4 alkyl)($C(O)OC_1$ - C_6 alkyl), 4-

to 6-membered heterocycloalkyl, -NH(C(O)C₁-C₆alkyl), -OR²⁰, -SC₁-C₆alkyl, -NH₂, or -N(C₁-C₄alkyl)₂, wherein each C₃-C₆cycloalkyl is optionally substituted with 1 to 3 R¹² substituents, each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R¹³ substituents, and each 4- to 6-membered heterocycloalkyl is optionally substituted with C₁-C₄alkyl or oxo;

5 each R⁸ is independently halogen, C₁-C₆alkyl, or -OC₁-C₆alkyl, wherein each -OC₁-C₆alkyl is optionally substituted with -OC₁-C₄alkyl;

each R²² is independently C₁-C₆alkyl optionally substituted with phenyl;

each R¹¹ is independently -NH₂, -NH(C₁-C₄alkyl), or 4- to 6-membered heterocycloalkyl;

each R²⁰ is independently C₁-C₆alkyl or 5- to 10-membered heteroaryl, wherein each C₁-C₆alkyl is optionally substituted with 1 to 3 R¹⁴ substituents and each 5- to 10-membered heteroaryl is optionally substituted with -OH or -NH(cyclopropyl);

10 each R¹² is independently C₁-C₄alkyl, -SC₁-C₄alkyl, -Ph, -OC₁-C₄alkyl, or -SPh, wherein each C₁-C₄alkyl is optionally substituted with -OH;

each R¹³ is independently halogen, C₁-C₄alkyl, or C₃-C₆cycloalkyl; and

15 each R¹⁴ is independently halogen, -OC₁-C₄alkyl, or C₃-C₆cycloalkyl.

In some embodiments, R¹ and R² are independently -CN, C₆-C₁₀aryl, C₁-C₆alkyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, 5- to 10-membered heteroaryl, or -C(O)NH₂, wherein each C₁-C₆alkyl is optionally substituted with 1 to 3 R⁷ substituents, each C₆-C₁₀aryl is optionally substituted with 1 to 3 R⁸ substituents, and each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R²² substituents, and

20

each R⁷ is independently -OH, -C(O)R¹¹, C₃-C₆cycloalkyl, -CN, C₆-C₁₀aryl, halogen, -C(O)OH, 5- to 10-membered heteroaryl, -NH(C(O)OC₁-C₆alkyl), -N(C₁-C₄alkyl)(C(O)OC₁-C₆alkyl), -NH(C(O)C₁-C₆alkyl), 4- to 6-membered heterocycloalkyl, -OR²⁰, -SC₁-C₆alkyl, -NH₂, or -N(C₁-C₄alkyl)₂, wherein each C₃-C₆cycloalkyl is optionally substituted with 1 to 3 R¹² substituents, each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R¹³ substituents, and each 4- to 6-membered heterocycloalkyl is optionally substituted with C₁-C₄alkyl or oxo;

25 each R⁸ is independently halogen, C₁-C₆alkyl, or -OC₁-C₆alkyl, wherein each -OC₁-C₆alkyl is optionally substituted with -OC₁-C₄alkyl;

each R¹¹ is independently -NH₂, -NH(C₁-C₄alkyl), or 4- to 6-membered heterocycloalkyl;

30 each R²⁰ is independently C₁-C₆alkyl or 5- to 10-membered heteroaryl, wherein each C₁-C₆alkyl is optionally substituted with 1 to 3 R¹⁴ substituents and each 5- to 10-membered heteroaryl is optionally substituted with -OH or -NH(cyclopropyl);

each R¹² is independently C₁-C₄alkyl, -SC₁-C₄alkyl, -Ph, -OC₁-C₄alkyl, or -SPh, wherein each C₁-C₄alkyl is optionally substituted with -OH;

35 each R¹³ is independently halogen, C₁-C₄alkyl, or C₃-C₆cycloalkyl;

each R¹⁴ is independently halogen, -OC₁-C₄alkyl, or C₃-C₆cycloalkyl; and

each R²² is independently C₁-C₄alkyl.

In some embodiments, R^1 and R^2 are independently -CN, C_6 - C_{10} aryl, C_1 - C_6 alkyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, 5- to 10-membered heteroaryl, or -C(O)NH₂, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 3 R^7 substituents, each C_6 - C_{10} aryl is optionally substituted with 1 to 3 R^8 substituents, and each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R^{22} substituents, and

each R^7 is independently -OH, -C(O) R^{11} , -OR²⁰, C_3 - C_6 cycloalkyl, -CN, C_6 - C_{10} aryl, halogen, -C(O)OH, or 5- to 10-membered heteroaryl, wherein each C_3 - C_6 cycloalkyl is optionally substituted with 1 to 3 R^{12} substituents and each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R^{13} substituents;

each R^8 is a halogen;

each R^{11} is -NH₂;

each R^{20} is C_1 - C_6 alkyl or 5- or 6-membered heteroaryl, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 3 R^{14} substituents and each 5- or 6-membered heteroaryl is optionally substituted with -OH or -NH(cyclopropyl);

each R^{12} is C_1 - C_4 alkyl;

each R^{13} is independently halogen or C_1 - C_4 alkyl;

each R^{14} is halogen; and

each R^{22} is independently C_1 - C_4 alkyl.

In some embodiments, R^1 and R^2 independently represent -CN, phenyl, C_1 - C_4 alkyl, C_2 - C_4 alkynyl, C_3 - C_6 cycloalkyl, 5-membered heteroaryl, or -C(O)NH₂, wherein each C_1 - C_4 alkyl is optionally substituted with 1 or 2 R^7 substituents, each phenyl is optionally substituted with 1 or 2 halogens, and each 5-membered heteroaryl is optionally substituted with 1 or 2 -CH₃, and

each R^7 is independently -OH, -C(O)NH₂, -OR²⁰, C_3 - C_6 cycloalkyl, -CN, phenyl, halogen, -C(O)OH, or 5-membered heteroaryl, wherein each C_3 - C_6 cycloalkyl is optionally substituted with -CH₃; and

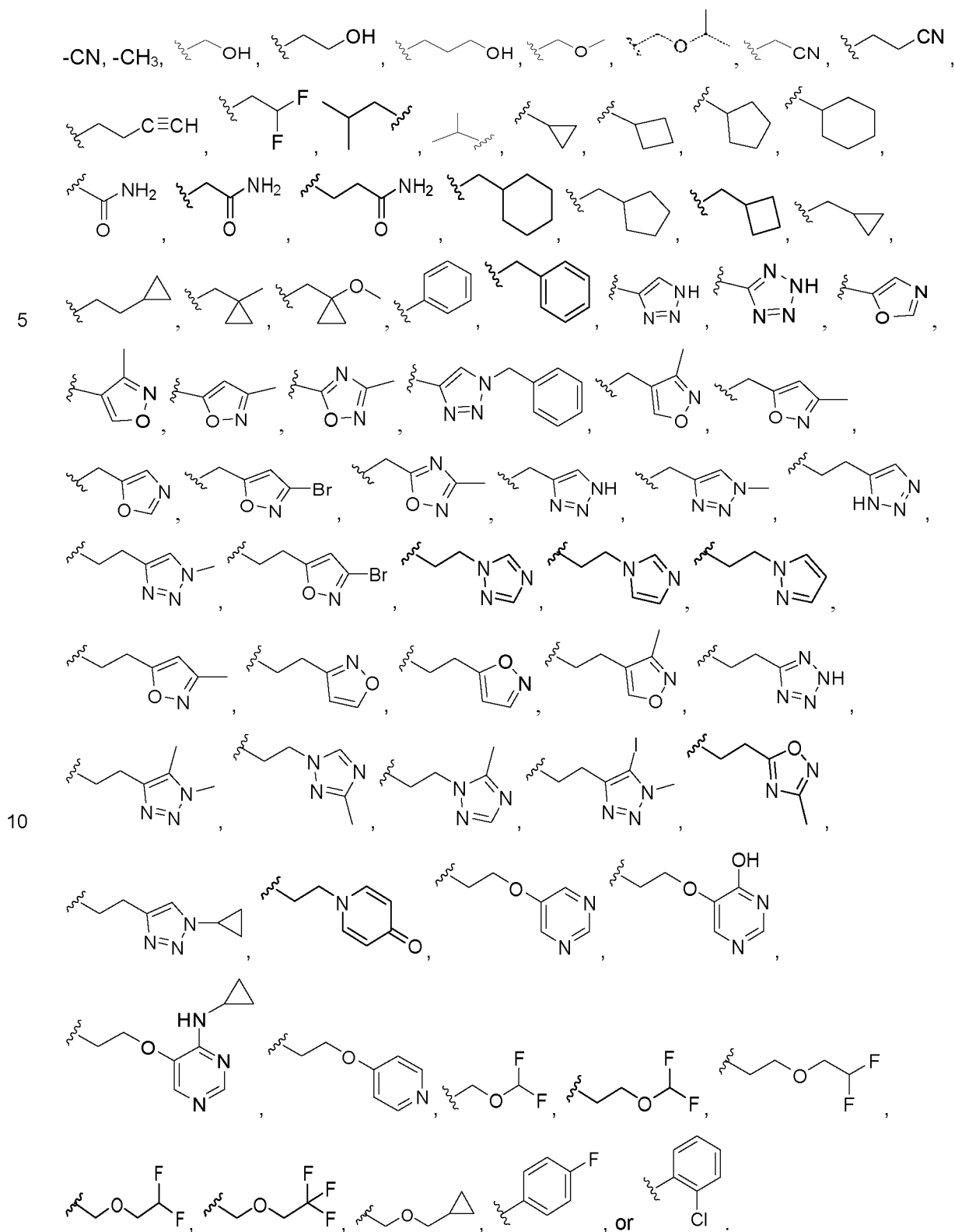
each R^{20} is C_1 - C_6 alkyl or 5- or 6-membered heteroaryl, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 3 halogen and each 5- or 6-membered heteroaryl is optionally substituted with -OH.

In some embodiments, R^1 and R^2 independently represent -CN, C_6 - C_{10} aryl, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, 5-membered heteroaryl, or -C(O)NH₂, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 2 R^7 substituents;

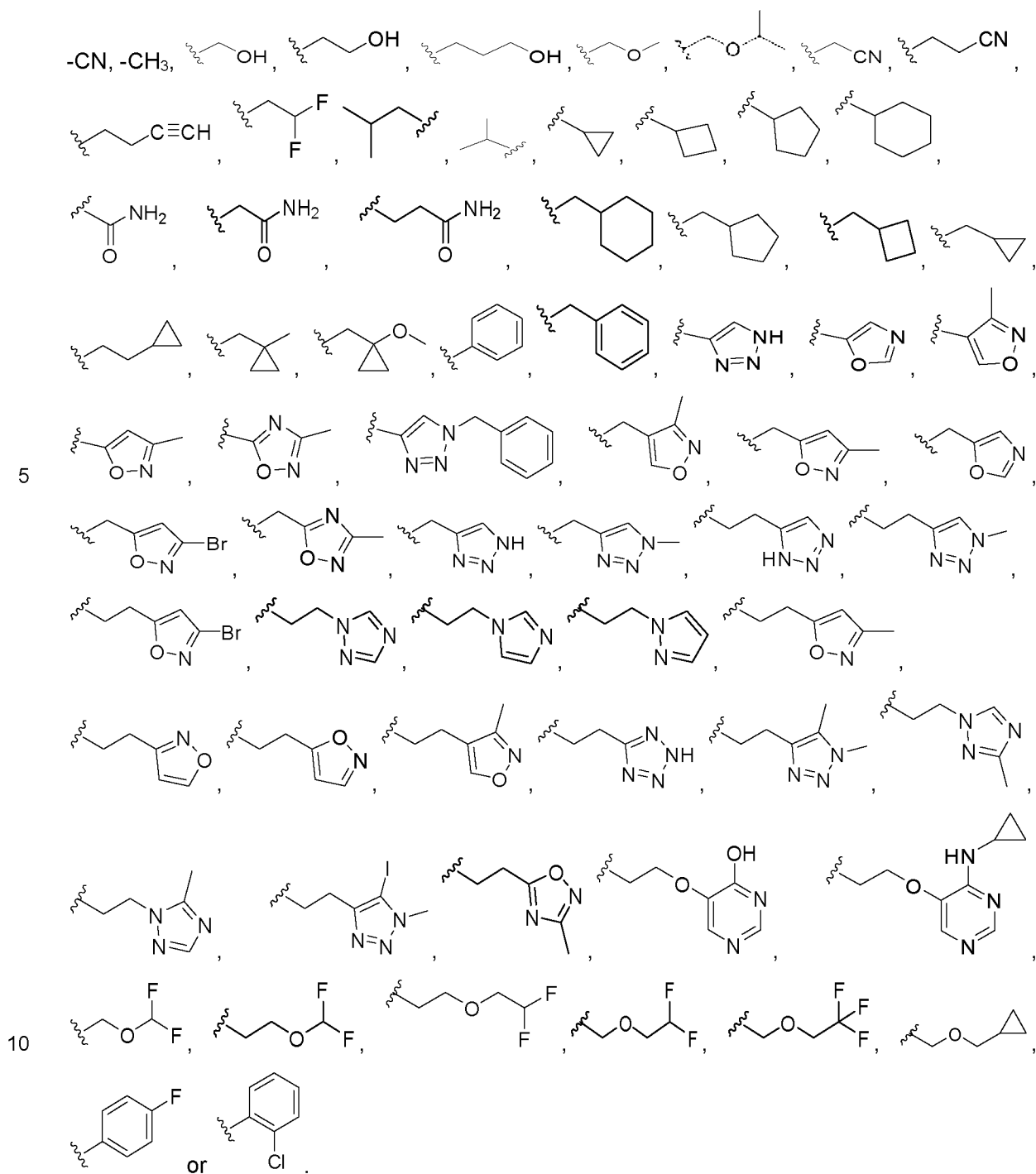
each R^7 is independently -OH, -C(O)NH₂, C_3 - C_6 cycloalkyl, -CN, C_6 - C_{10} aryl, halogen, or 5- to 8-membered heteroaryl, wherein each C_3 - C_6 cycloalkyl is optionally substituted with 1 to 2 C_1 - C_4 alkyl, and each 5- to 8-membered heteroaryl is optionally substituted with 1 to 2 R^{13} substituents; and

each R^{13} is independently halogen or C_1 - C_4 alkyl.

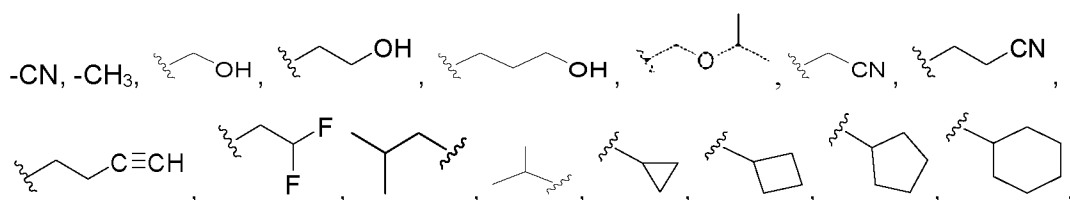
In some embodiments, R^1 and R^2 , which can be identical or different, can represent:



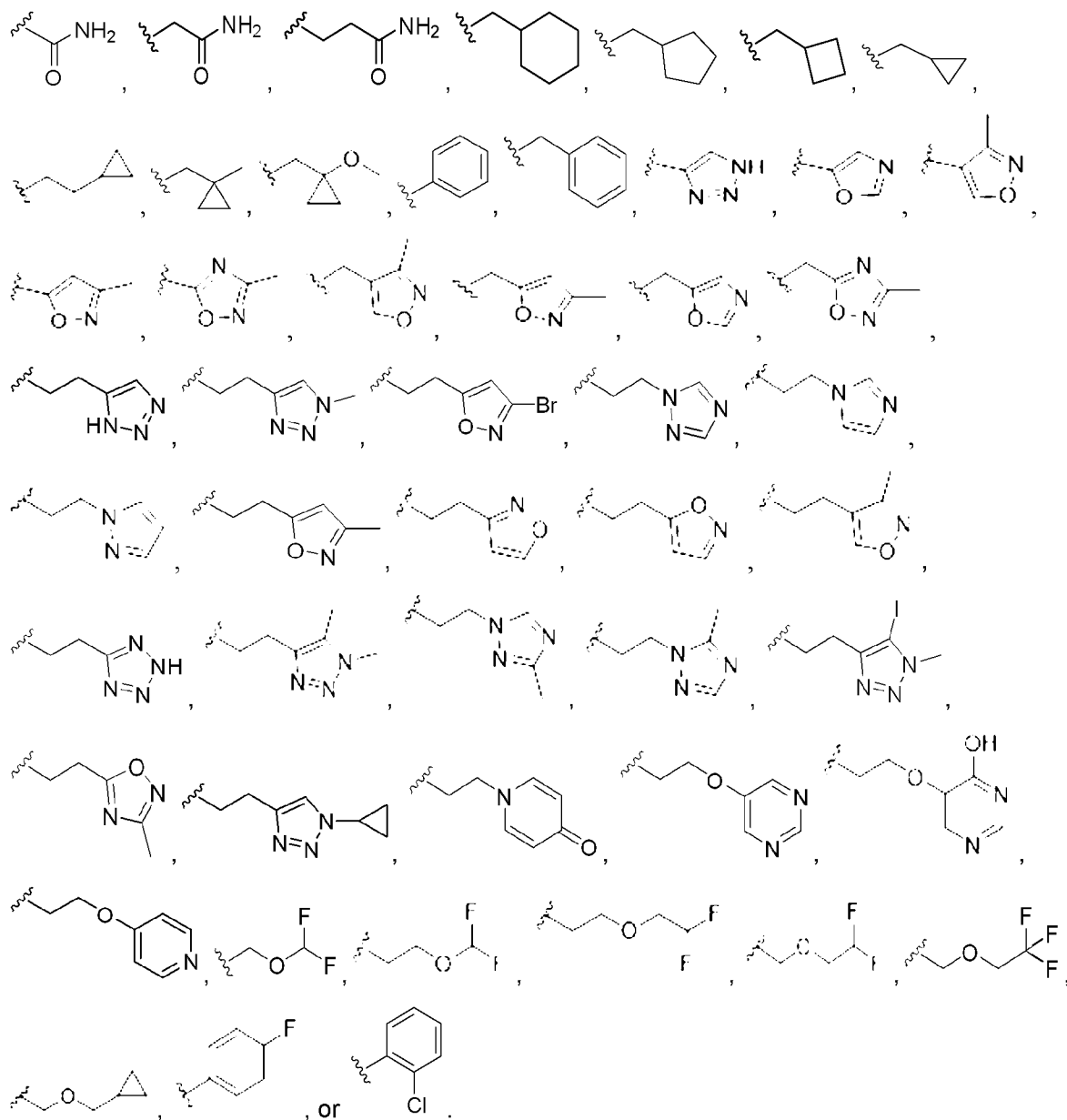
In some embodiments, R^1 and R^2 , which can be identical or different, can represent:



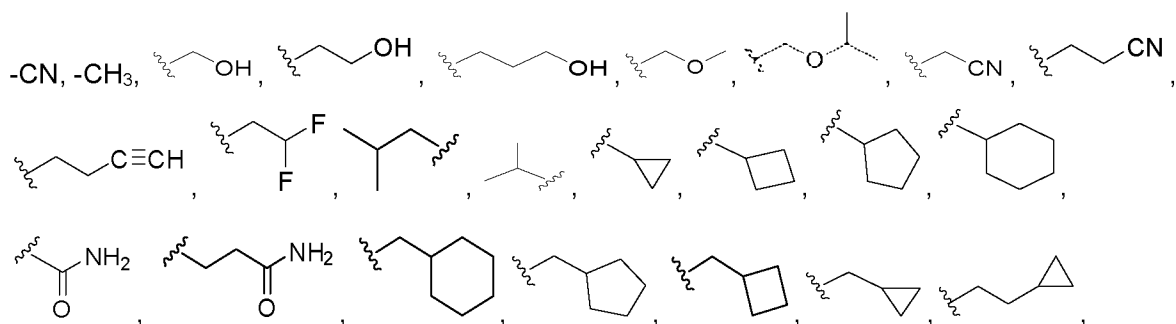
In some embodiments, R^1 and R^2 , which can be identical or different, can represent:



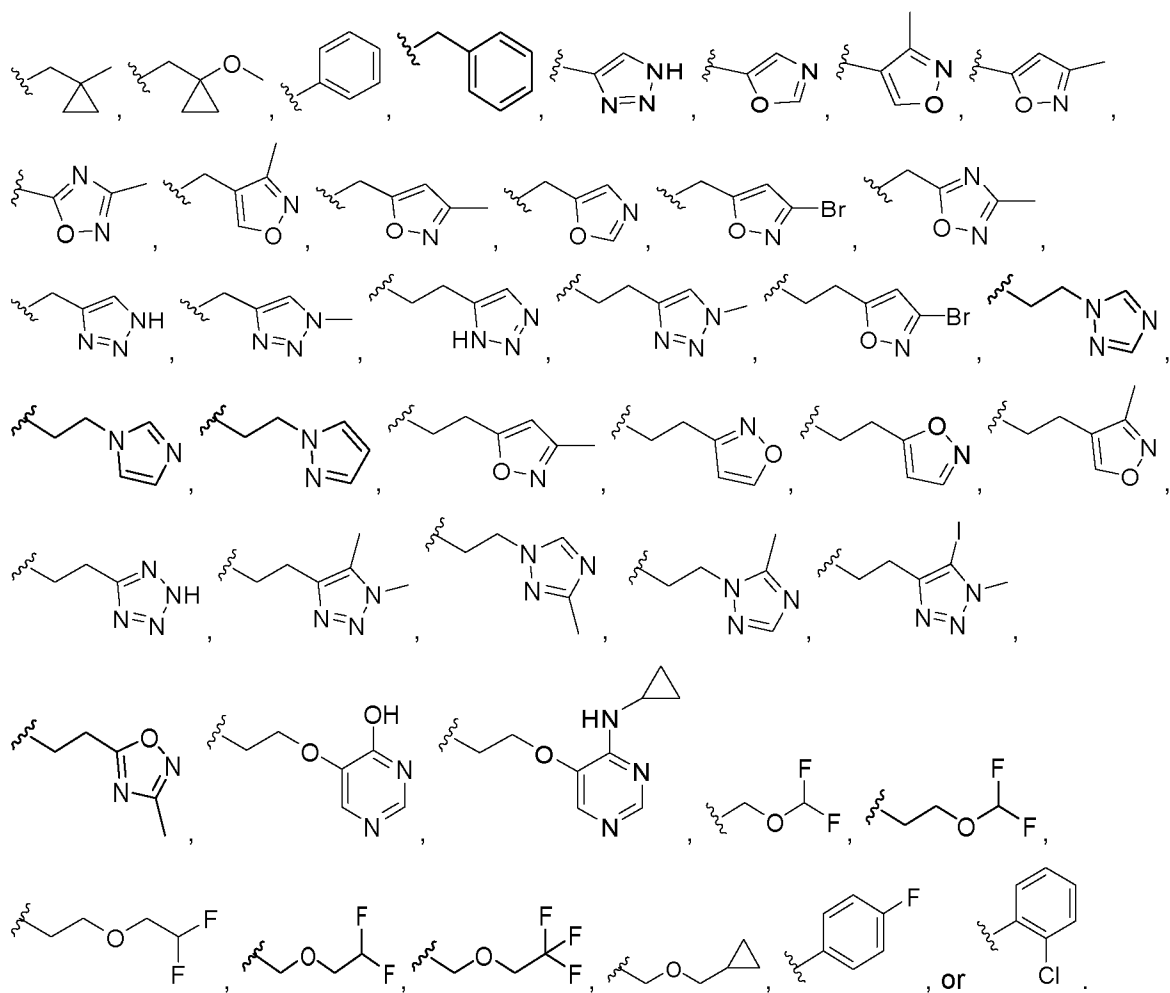
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10 In some embodiments, R^1 and R^2 , which can be identical or different, can represent:

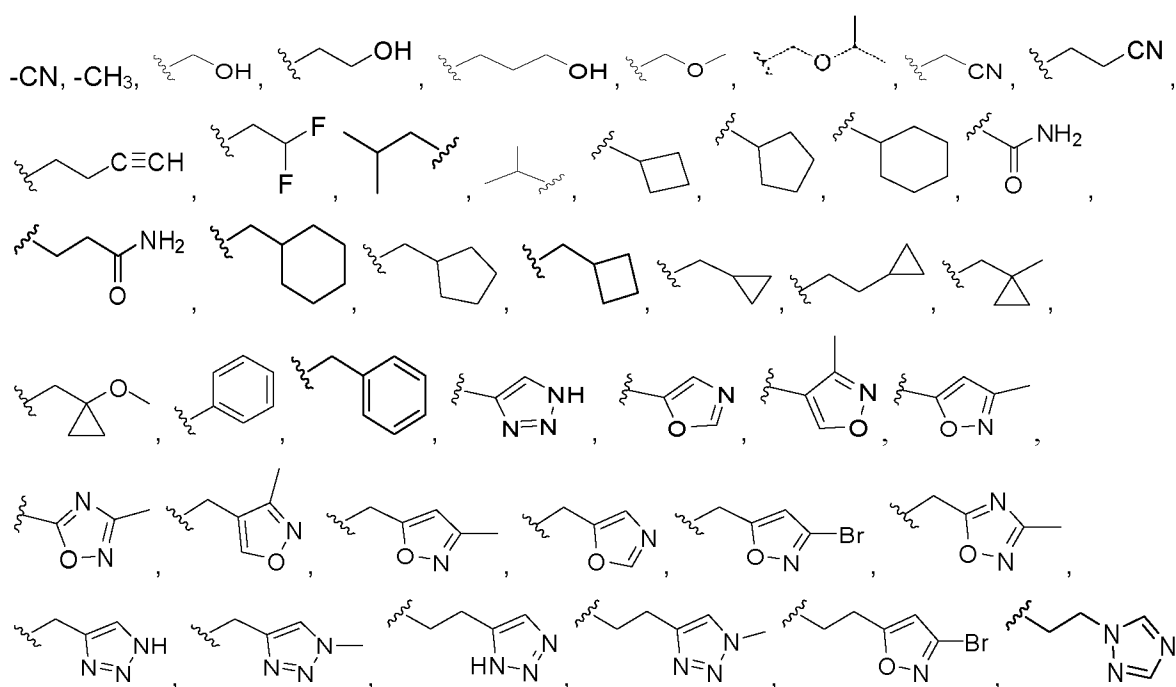


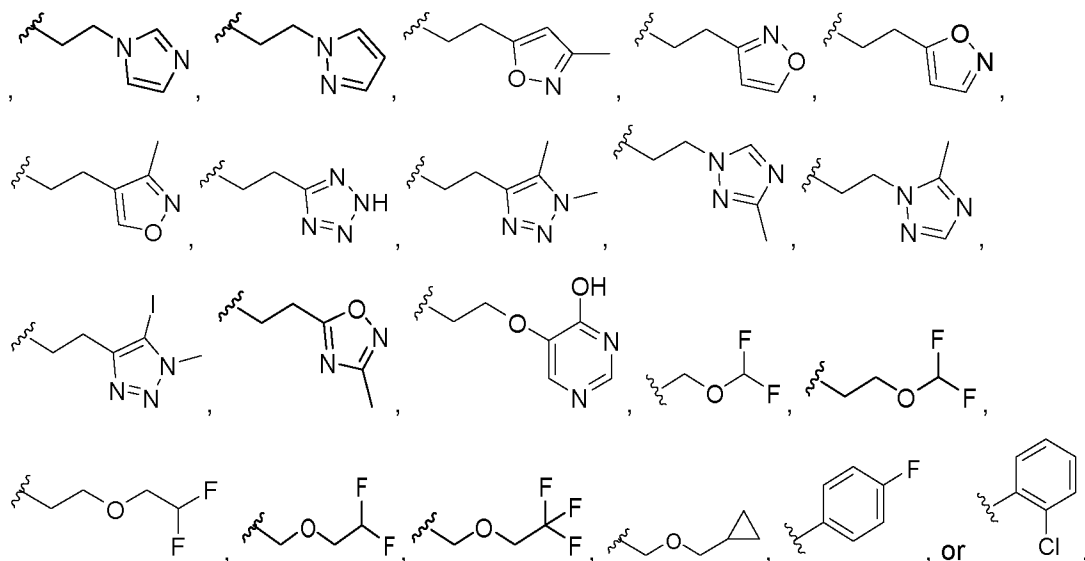
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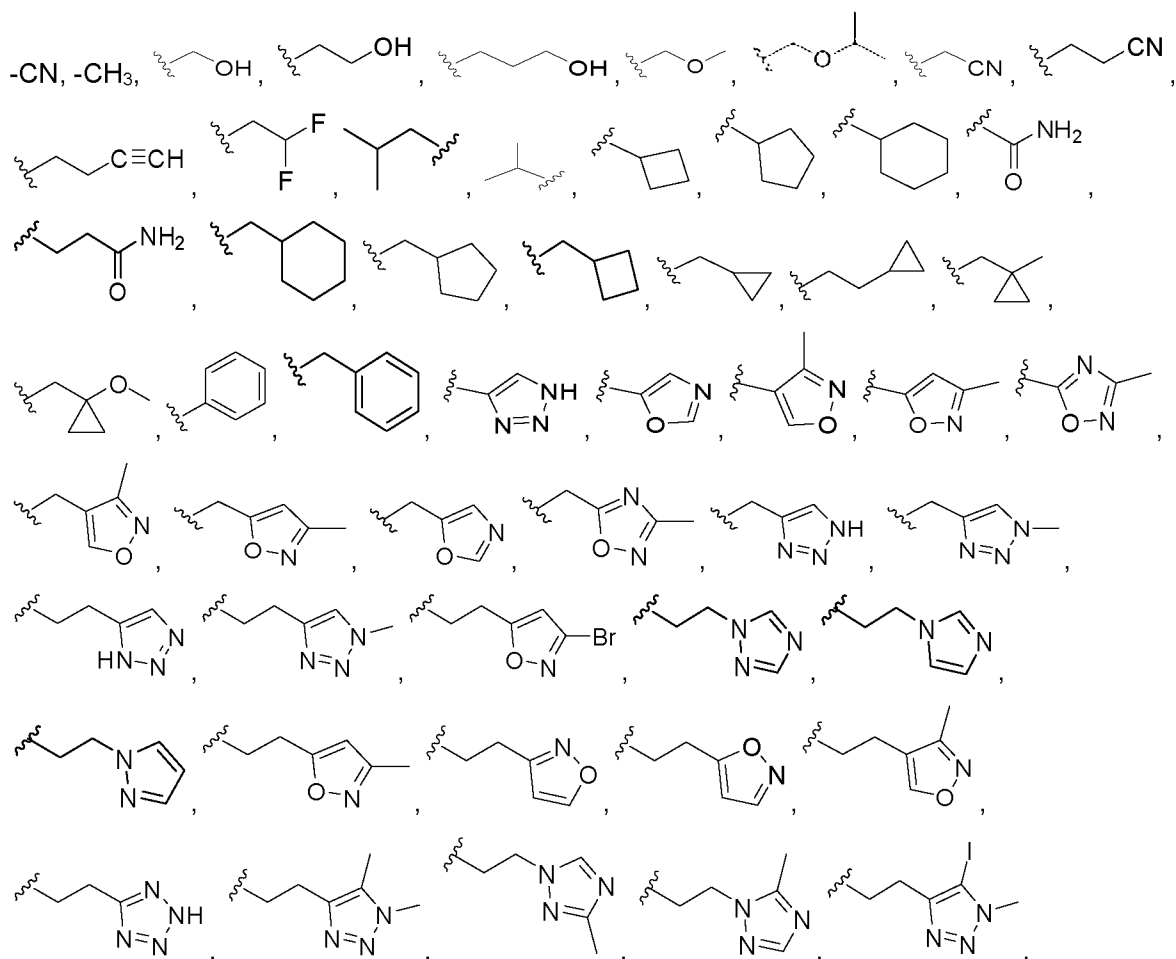
In some embodiments, R¹ and R², which can be identical or different, can represent:

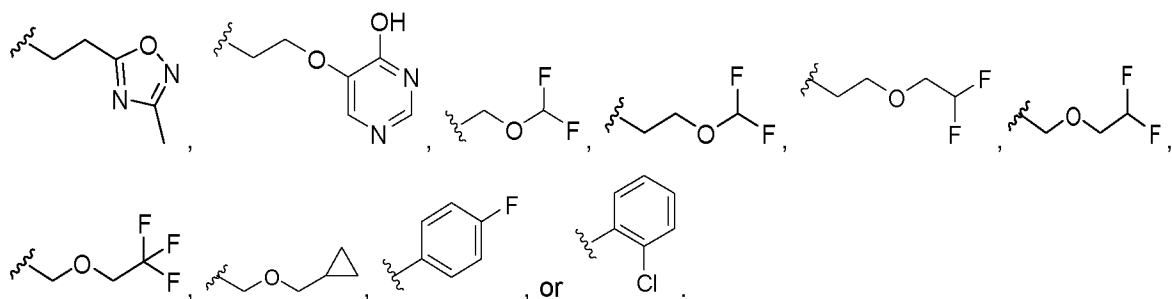
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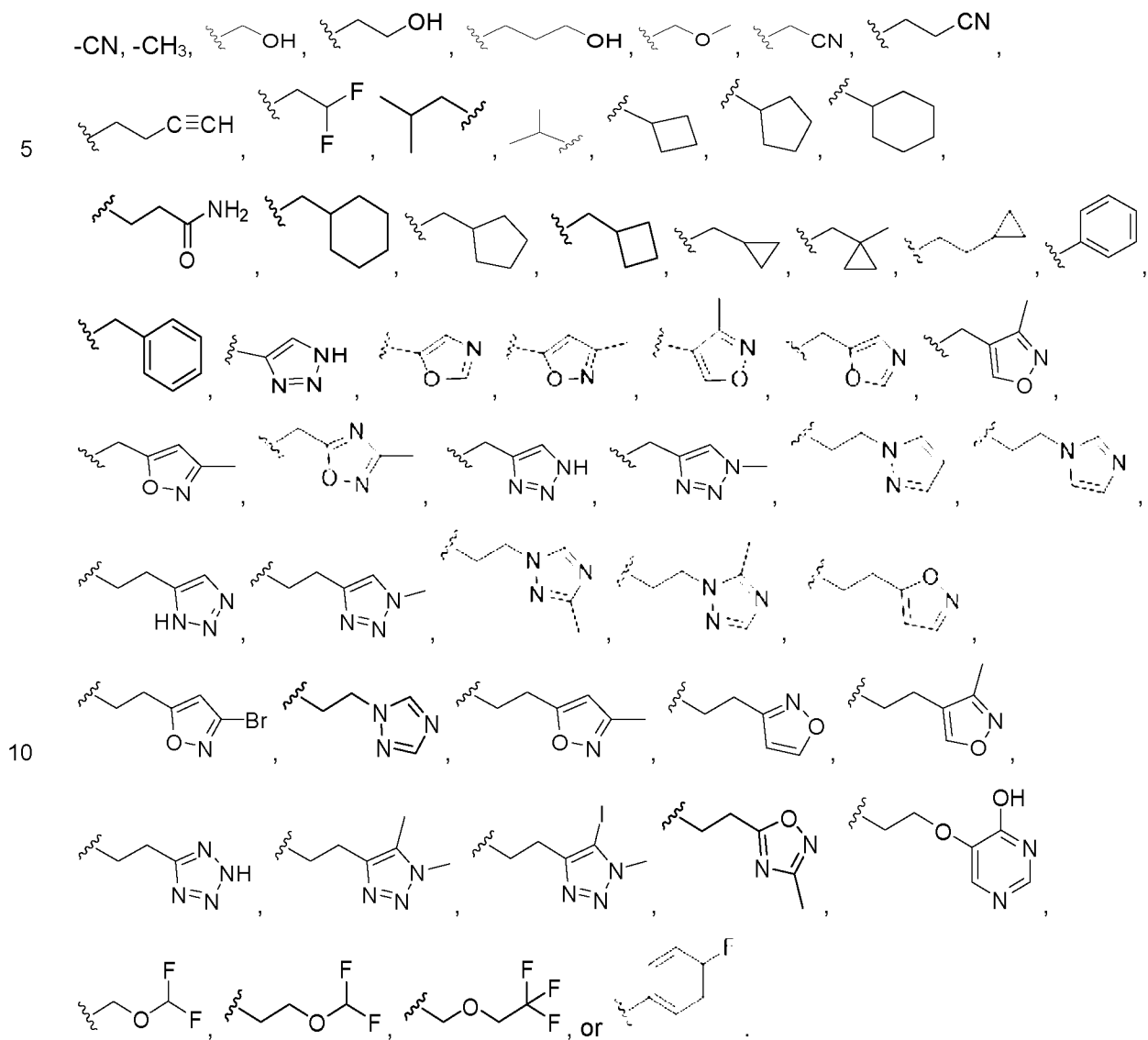


5 In some embodiments, R^1 and R^2 , which can be identical or different, can represent:

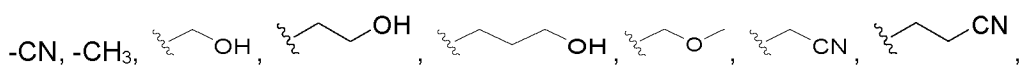


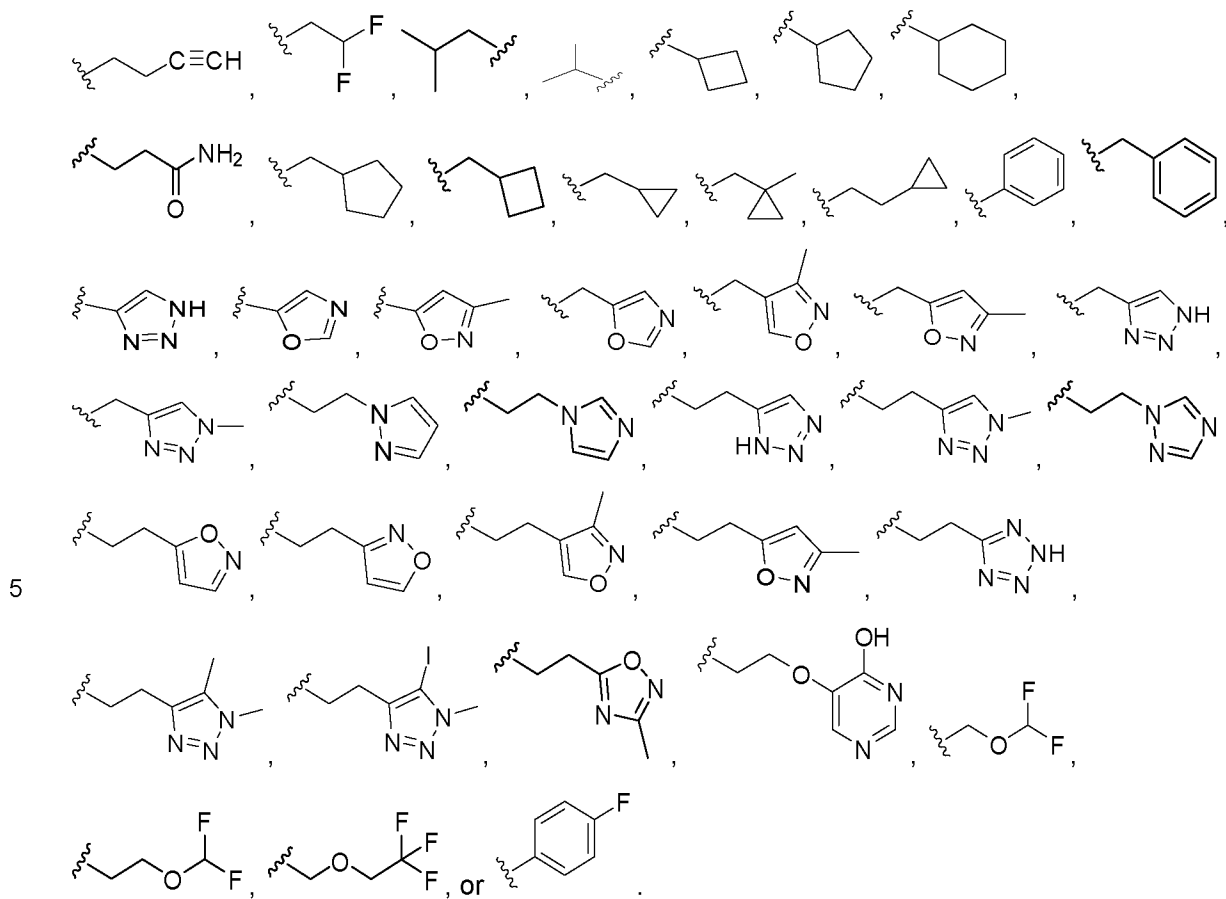


In some embodiments, R^1 and R^2 , which can be identical or different, can represent:

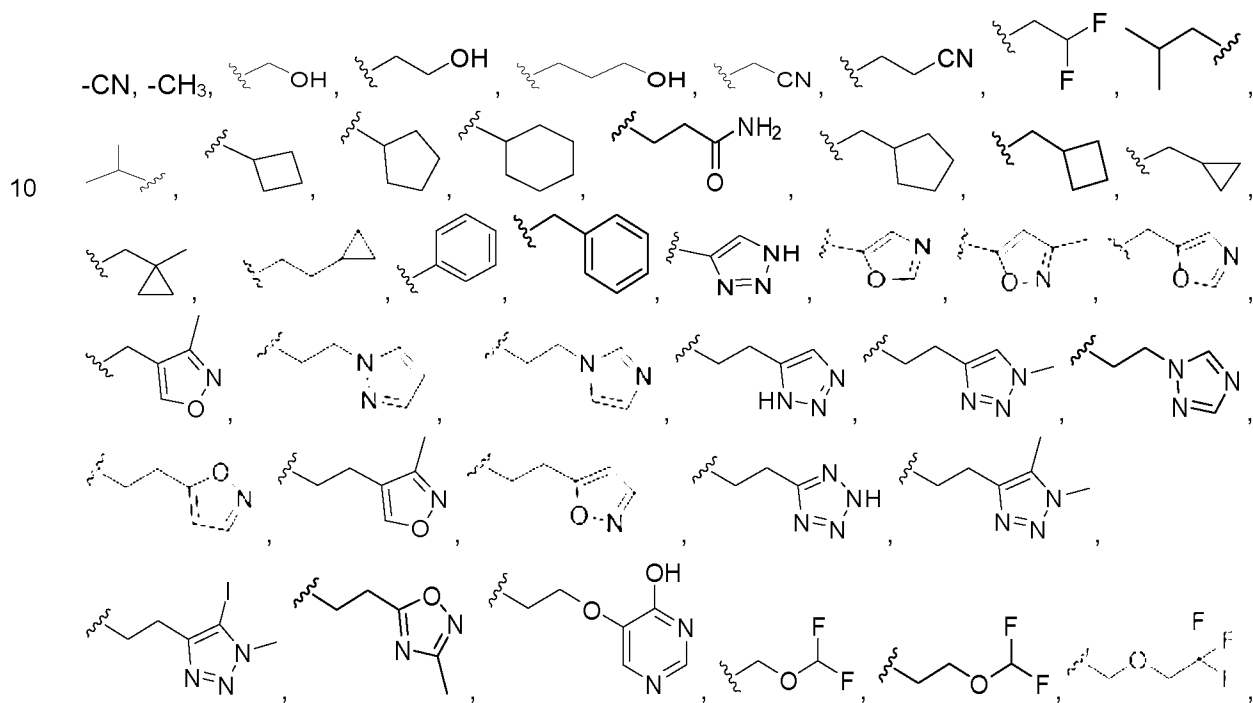


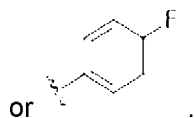
In some embodiments, R^1 and R^2 , which can be identical or different, can represent:



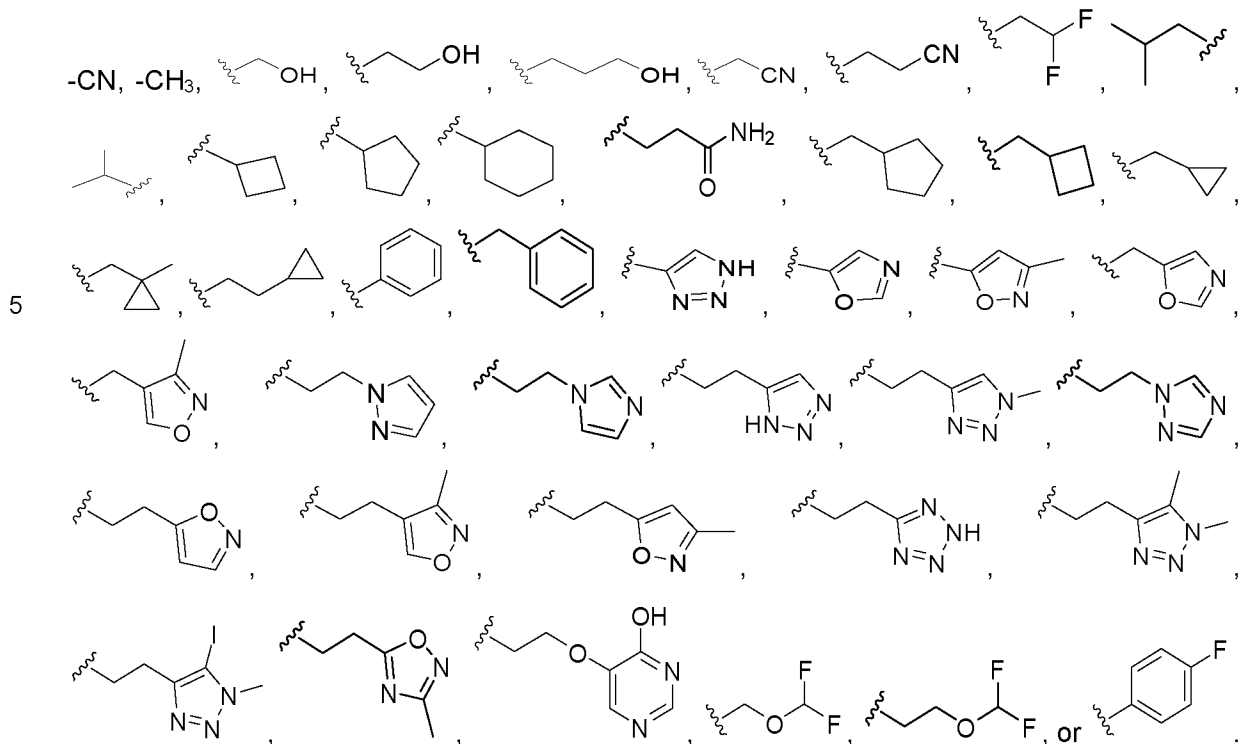


In some embodiments, R^1 and R^2 , which can be identical or different, can represent:

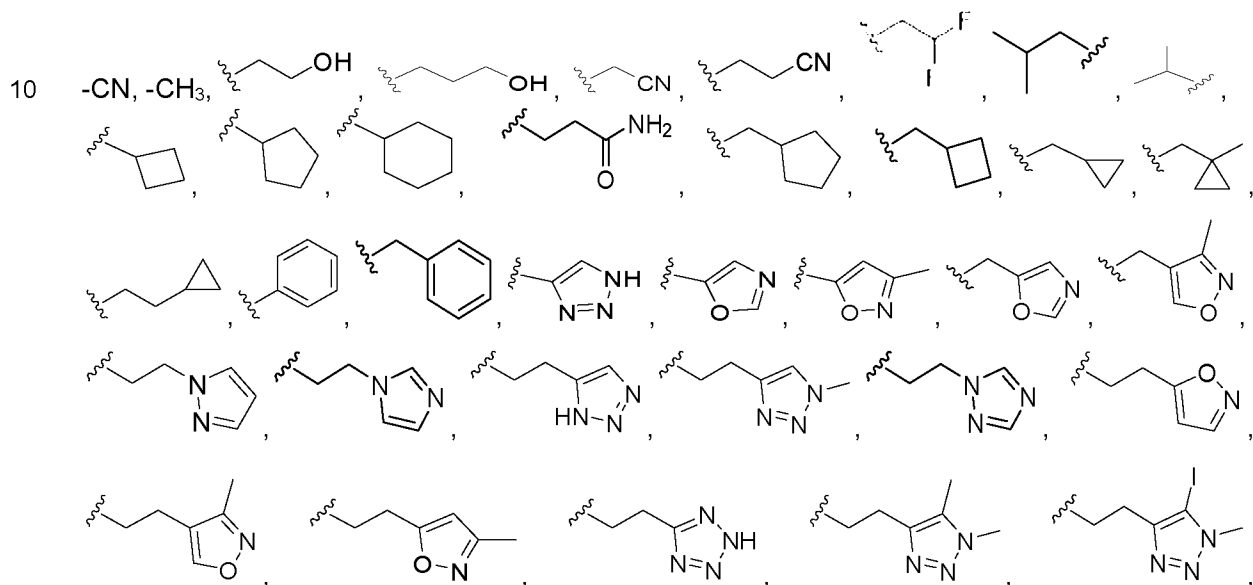


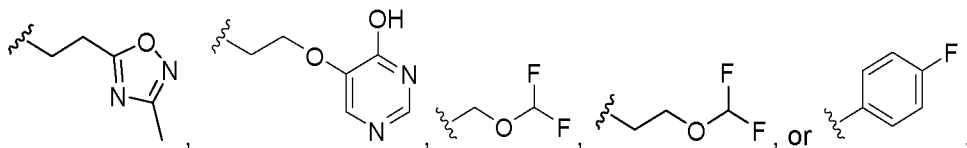


In some embodiments, R^1 and R^2 , which can be identical or different, can represent:

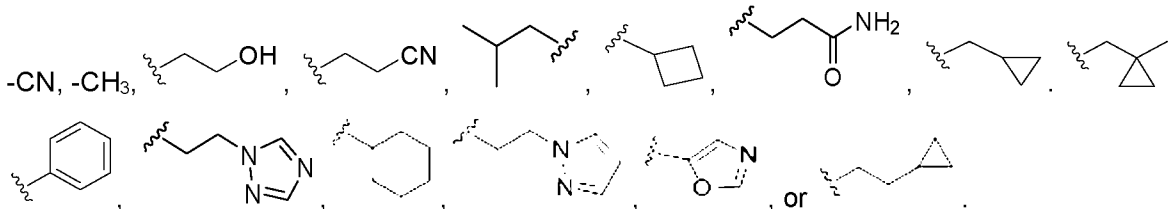


In some embodiments, R^1 and R^2 , which can be identical or different, can represent:





In some embodiments, R^1 and R^2 , which can be identical or different, can represent:



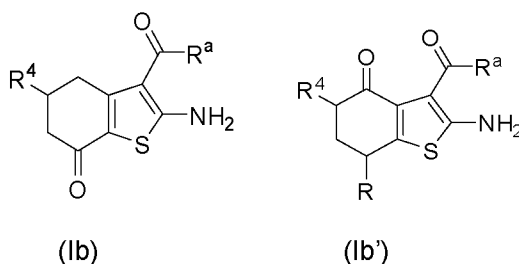
- 5 In some particular embodiments, R^1 and R^2 are different. In another particular embodiment, one of R^1 and R^2 is -CN. Other embodiments include compounds of Formula (Ia) or (Ia'), or a

pharmaceutically acceptable salt, solvate, or prodrug thereof, where one of R^1 and R^2 is

Compounds of Formula (Ib) and (Ib')

In some embodiments, the compound is of Formula (Ib) or (Ib'), or a pharmaceutically acceptable

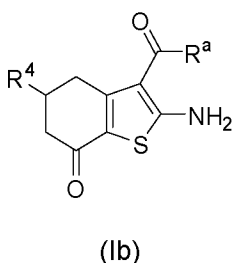
10 salt, solvate, or prodrug thereof.



The groups R , R^a , and R^4 can be as defined for the general Formula (I) above.

In some embodiments, the compound is of Formula (Ib), or a pharmaceutically acceptable salt,

15 solvate, or prodrug thereof.



The groups R^a and R^4 can be as defined for the general Formula (I) above.

In some embodiments, R^4 can represent C_1 - C_6 alkyl, C_6 - C_{10} aryl, 7- to 10-membered partially

20 unsaturated heterocyclic group, or 5- to 10-membered heteroaryl, wherein C_1 - C_6 alkyl is optionally

substituted with 1 to 3 R^9 substituents, and C_6 - C_{10} aryl and 5- to 10-membered heteroaryl are optionally substituted with 1 to 3 R^{10} substituents, and wherein R^9 and R^{10} are as defined herein.

In some embodiments, R^4 can represent C_1 - C_6 alkyl, C_6 - C_{10} aryl, 7- to 10-membered partially unsaturated heterocyclic group, or 5- to 10-membered heteroaryl, wherein C_6 - C_{10} aryl and 5- to 10-membered heteroaryl are optionally substituted with 1 to 3 R^{10} substituents, and wherein the R^{10} substituents are as defined herein.

In some embodiments, R^4 can represent C_1 - C_4 alkyl, phenyl, 9-membered partially unsaturated heterocyclic group, or 5- to 6-membered heteroaryl, wherein phenyl and 5- to 6-membered heteroaryl are optionally substituted with 1 or 2 R^{10} substituents, and wherein the R^{10} substituents are as defined herein.

In some embodiments, the R^{10} substituents can independently represent C_1 - C_4 alkyl, halogen, - OC_1 - C_6 alkyl, - NH_2 , - $NH(C_1$ - C_4 alkyl), or - $N(C_1$ - C_4 alkyl) $_2$, wherein each C_1 - C_4 alkyl is optionally substituted with 1 to 3 halogens.

In other embodiments, the R^{10} substituents can independently represent C_1 - C_4 alkyl, halogen, - OC_1 - C_6 alkyl, or - $N(C_1$ - C_4 alkyl) $_2$, wherein each C_1 - C_4 alkyl is optionally substituted with 1 to 3 halogens.

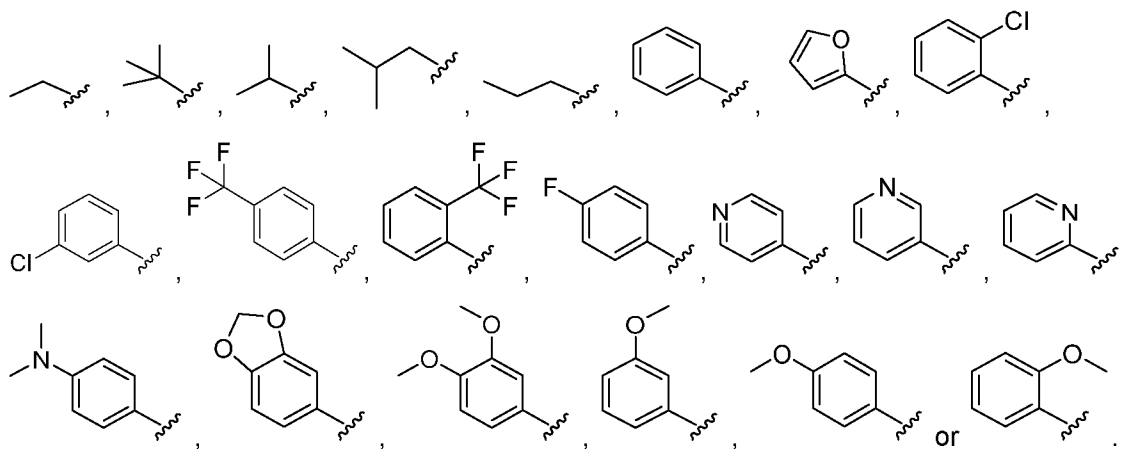
In further embodiments, the R^{10} substituents can independently represent - CF_3 , halogen, - OCH_3 , or - $N(CH_3)_2$.

In some embodiments, R^4 is C_1 - C_6 alkyl, C_6 - C_{10} aryl, 7- to 10-membered partially unsaturated heterocyclic group, or 5- to 10-membered heteroaryl, wherein C_6 - C_{10} aryl and 5- to 10-membered heteroaryl are optionally substituted with 1 to 3 R^{10} substituents, and each R^{10} is independently C_1 - C_4 alkyl, halogen, - OC_1 - C_6 alkyl, - NH_2 , - $NH(C_1$ - C_4 alkyl), or - $N(C_1$ - C_4 alkyl) $_2$, wherein each C_1 - C_4 alkyl is optionally substituted with 1 to 3 halogens.

In some embodiments, R^4 is C_1 - C_6 alkyl, C_6 - C_{10} aryl, 7- to 10-membered partially unsaturated heterocyclic group, or 5- to 10-membered heteroaryl, wherein C_6 - C_{10} aryl and 5- to 10-membered heteroaryl are optionally substituted with 1 to 3 R^{10} substituents, and each R^{10} is independently C_1 - C_4 alkyl, halogen, - OC_1 - C_6 alkyl, or - $N(C_1$ - C_4 alkyl) $_2$, wherein each C_1 - C_4 alkyl is optionally substituted with 1 to 3 halogens.

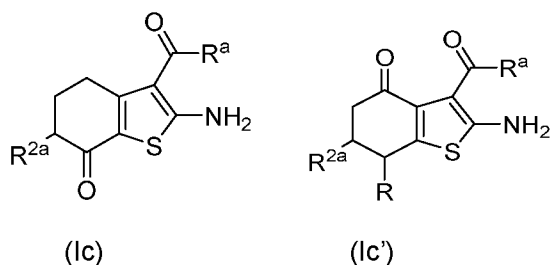
In some embodiments, R^4 is C_1 - C_4 alkyl, phenyl, 9-membered partially unsaturated heterocyclic group, or 5- to 6-membered heteroaryl, wherein phenyl and 5- to 6-membered heteroaryl are optionally substituted with 1 or 2 R^{10} substituents, and each R^{10} is independently - CF_3 , halogen, - OCH_3 , or - $N(CH_3)_2$.

Examples of particular R^4 groups can include:



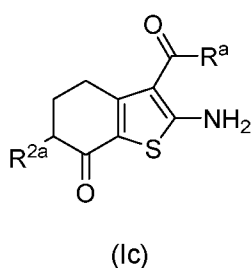
Compounds of Formula (Ic) and (Ic')

- 5 In some embodiments, the compound is of Formula (Ic) or (Ic'), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.



The groups R, R^a and R^{2a} can be as defined for the general Formula (I) above.

- 10 In some embodiments, the compound is of Formula (Ic), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.



The groups R^a and R^{2a} can be as defined for the general Formula (I) above.

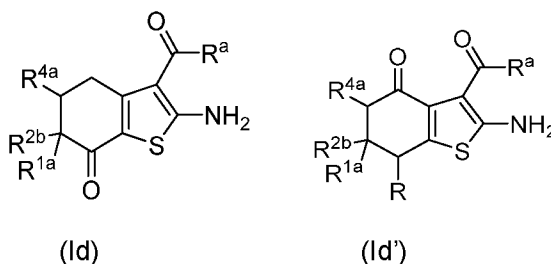
- 15 In some embodiments, R^{2a} can represent C₁-C₆alkyl or C₆-C₁₀aryl, wherein C₁-C₆alkyl is optionally substituted with 1 to 3 R⁹ substituents and C₆-C₁₀aryl is optionally substituted with 1 to 3 R¹⁰ substituents, and R⁹ and R¹⁰ are as defined herein.

In some embodiments, R^{2a} can represent C₁-C₆alkyl or C₆-C₁₀aryl, wherein C₁-C₆alkyl is optionally substituted with 1 to 3 halogens.

In some embodiments, R^{2a} is C_1 - C_6 alkyl, such as C_1 - C_4 alkyl or preferably ethyl.

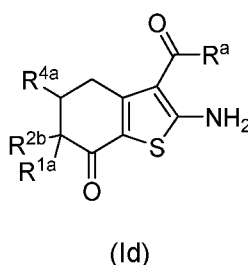
Compounds of Formula (Id) and (Id')

In some embodiments, the compound is of Formula (Id) or (Id'), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.



The groups R , R^a , R^{1a} , R^{2b} , and R^{4a} can be as defined for the general Formula (I) above.

In some embodiments, the compound is of Formula (Id), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.



The groups R^a , R^{1a} , R^{2b} , and R^{4a} can be as defined for the general Formula (I) above.

In some embodiments, R^{1a} and R^{2b} can independently represent $-CN$, C_6 - C_{10} aryl, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, or $-C(O)NH_2$, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 2 R^{16} substituents as defined herein.

In some embodiments, R^{1a} and R^{2b} can independently represent $-CN$ or C_6 - C_{10} aryl.

In some embodiments, R^{4a} can represent C_1 - C_6 alkyl.

In some embodiments, the substituents R^{16} can independently represent $-OH$, $-C(O)NH_2$, C_3 - C_6 cycloalkyl, $-CN$, C_6 - C_{10} aryl, halogen, or 5- to 8-membered heteroaryl, wherein each C_3 - C_6 cycloalkyl is optionally substituted with 1 to 2 C_1 - C_4 alkyl, and each 5- to 10-membered heteroaryl is optionally substituted with 1 to 2 R^{21} substituents as defined herein.

In some embodiments, each R^{21} can represent independently halogen or C_1 - C_4 alkyl.

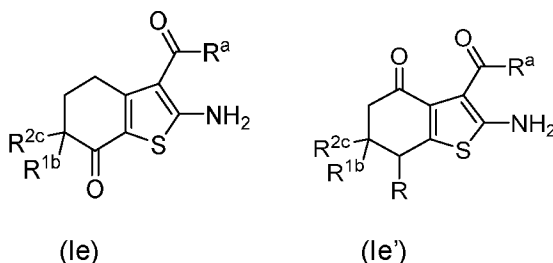
In some embodiments, R^{1a} and R^{2b} are independently $-CN$, C_6 - C_{10} aryl, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, or $-C(O)NH_2$, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 2 R^{16} substituents;

each R¹⁶ is independently -OH, -C(O)NH₂, C₃-C₆cycloalkyl, -CN, C₆-C₁₀aryl, halogen, or 5- to 8-membered heteroaryl, wherein each C₃-C₆cycloalkyl is optionally substituted with 1 to 2 C₁-C₄alkyl, and each 5- to 10-membered heteroaryl is optionally substituted with 1 to 2 R²¹ substituents; and

5 each R²¹ is independently halogen or C₁-C₄alkyl.

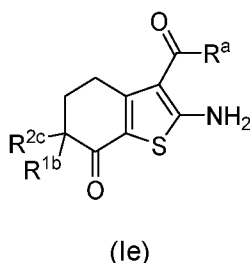
Compounds of Formula (Ie) and (Ie')

In some embodiments, the compound is of Formula (Ie) or (Ie'), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.



The groups R, R^a, R^{1b}, and R^{2c} can be as defined for the general Formula (I) above.

In some embodiments, the compound is of Formula (Ie), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.



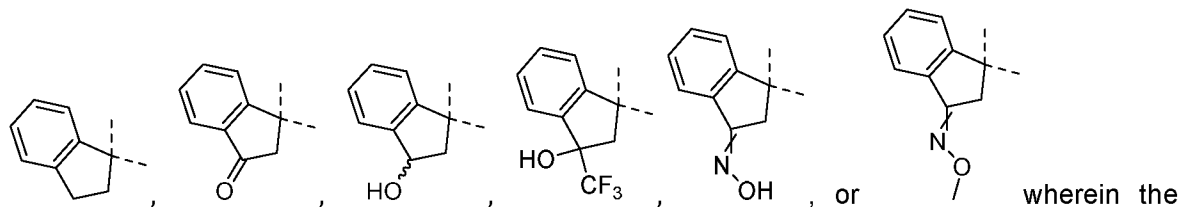
The groups R^a , R^{1b} , and R^{2c} can be as defined for the general Formula (I) above.

In some embodiments, R^{1b} and R^{2c} can form together with the carbon atom to which they are attached a C₃-C₈cycloalkyl, 4- to 14-membered heterocycloalkyl, 8- to 14-membered partially unsaturated heterocyclic group, or 8- to 14-membered partially unsaturated carbocyclic group, wherein each 4- to 14-membered heterocycloalkyl, 8- to 14-membered partially unsaturated heterocyclic group, or 8- to 14-membered partially unsaturated carbocyclic group is optionally substituted with oxo (=O), oxime (=N-OH), C₁-C₃alkoxyoxime (=N-OC₁-C₃alkyl), or 1 to 3 substituents independently selected from -OH and -CF₃.

In some embodiments, R^{1b} and R^{2c} can form together with the carbon atom to which they are attached a C₃-C₈cycloalkyl or a 8- to 10-membered partially unsaturated carbocyclic group, wherein 8- to 10-membered partially unsaturated carbocyclic group is optionally substituted with oxo (=O), oxime (=N-OH), methoxyoxime (=N-OCH₃), or 1 to 2 substituents independently

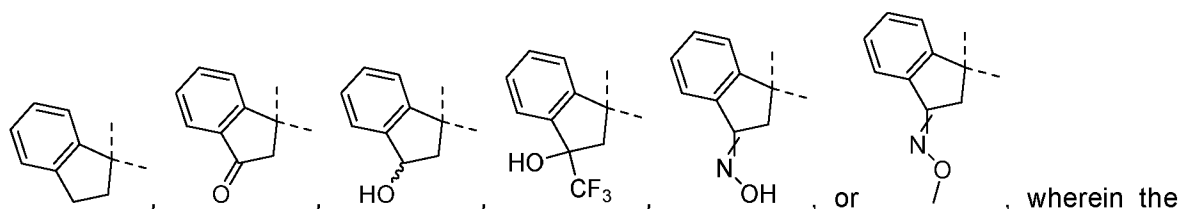
selected from -OH and -CF₃.

In some embodiments, R^{1b} and R^{2c} can form together with the carbon atom to which they are attached a C₄-C₆cycloalkyl, or a group selected from



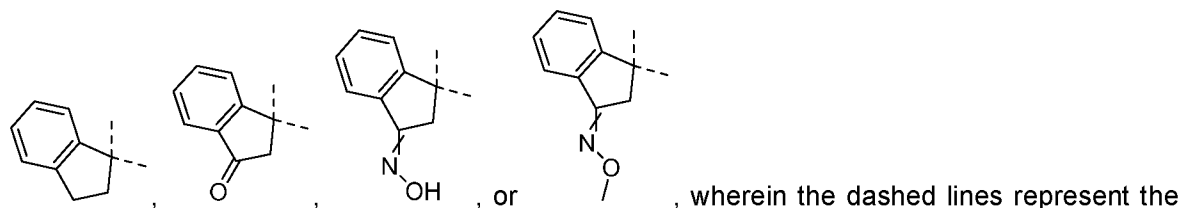
5 dashed lines represent the portion of the cyclohexanone moiety of the compound of formula (Ie) or (Ie') bearing R^{1b} and R^{2c}.

In some embodiments, R^{1b} and R^{2c} form together with the carbon atom to which they are attached a cyclopentyl, or a group selected from



10 dashed lines represent the portion of the cyclohexanone moiety of the compound of formula (Ie) or (Ie') bearing R^{1b} and R^{2c}.

In some embodiments, R^{1b} and R^{2c} can form together with the carbon atom to which they are attached a group selected from



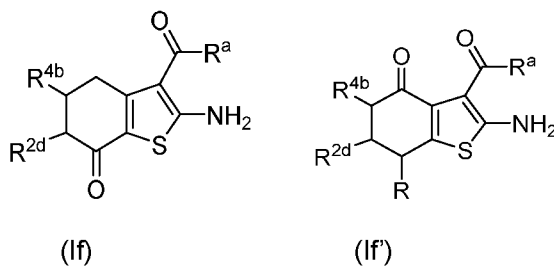
15 portion of the cyclohexanone moiety of the compound of formula (Ie) or (Ie') bearing R^{1b} and R^{2c}.

In some embodiments, R^{1b} and R^{2c} can form together with the carbon atom to which they are attached a cyclopentyl.

Compounds of Formula (If) and (If')

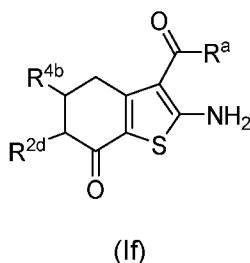
In some embodiments, the compound is of Formula (If) or (If'), or a pharmaceutically acceptable

20 salt, solvate, or prodrug thereof.



The groups R, R^a, R^{2d}, and R^{4b} can be as defined for the general Formula (I) above.

In some embodiments, the compound is of Formula (If), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.



The groups R^a, R^{2d}, and R^{4b} can be as defined for the general Formula (I) above.

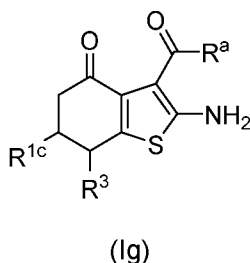
In some embodiments, R^{2d} and R^{4b} can form together with the carbon atoms to which they are attached a C₃-C₈cycloalkyl, wherein each C₃-C₈cycloalkyl is optionally substituted with 1 to 3 R¹⁹ substituents as defined herein.

In some embodiments, R^{2d} and R^{4b} can form together with the carbon atoms to which they are attached a C₃-C₈cycloalkyl.

In some embodiments, R^{2d} and R^{4b} can form together with the carbon atoms to which they are attached a cyclohexyl.

Compound of Formula (Ig)

In some embodiments, the compound is of Formula (Ig), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.



The groups R^a, R^{1c} and R³ can be as defined for the general Formula (I) above.

In some embodiments, R^{1c} and R³ can form together with the carbon atoms to which they are

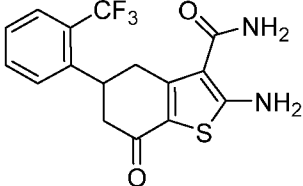
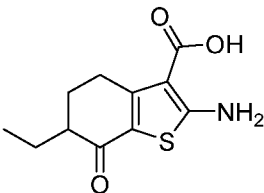
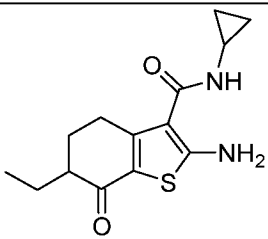
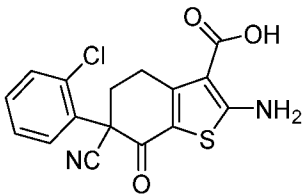
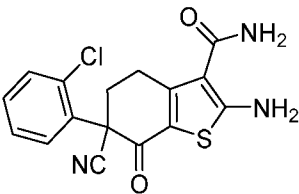
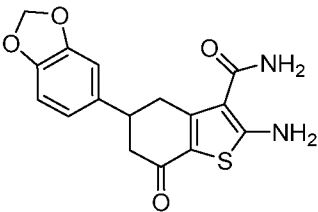
attached a C₃-C₈cycloalkyl, wherein each C₃-C₈cycloalkyl is optionally substituted with 1 to 3 R¹⁹ substituents as defined herein.

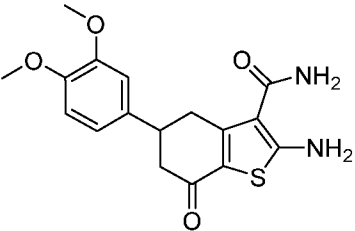
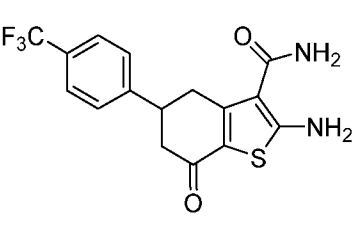
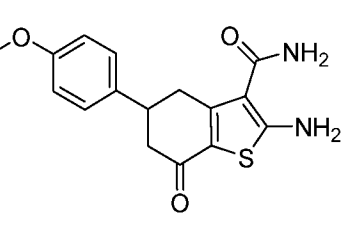
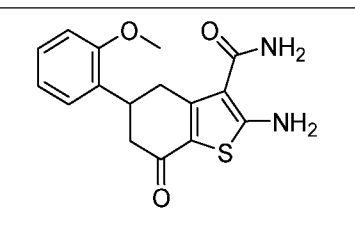
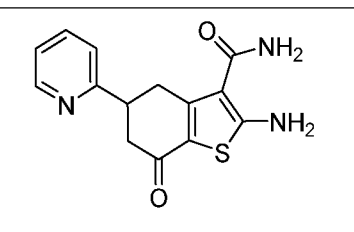
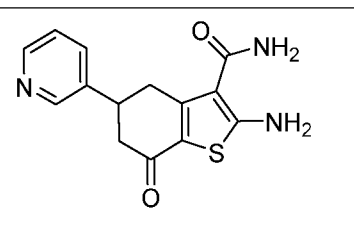
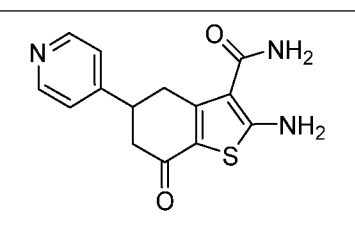
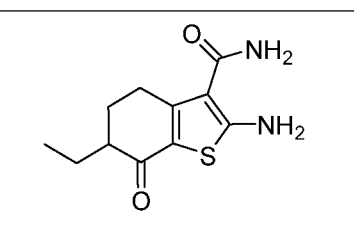
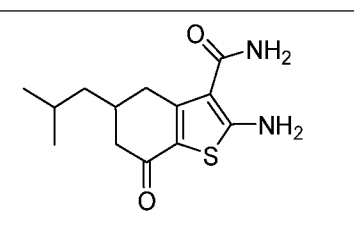
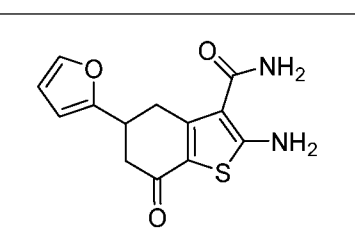
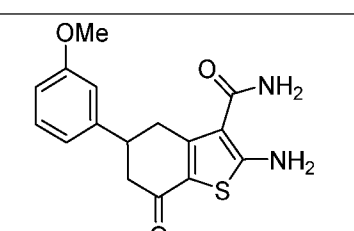
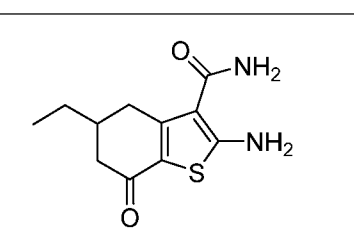
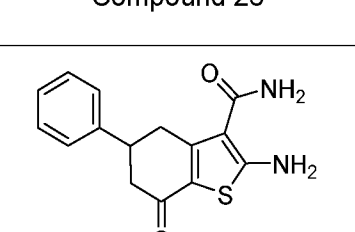
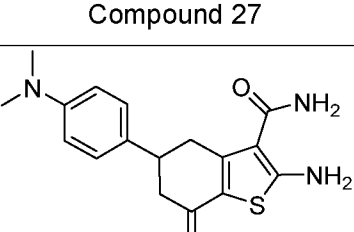
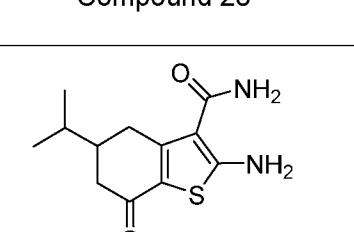
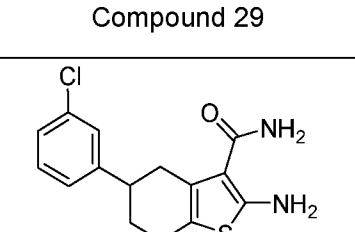
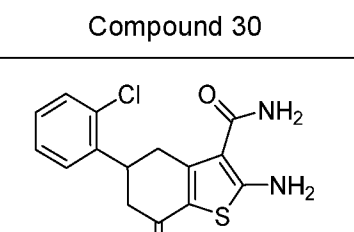
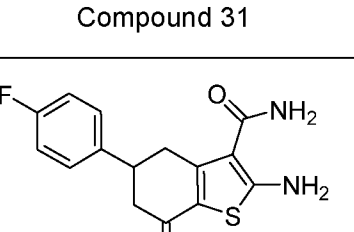
In some embodiments, R^{1c} and R³ can form together with the carbon atoms to which they are attached a C₃-C₈cycloalkyl.

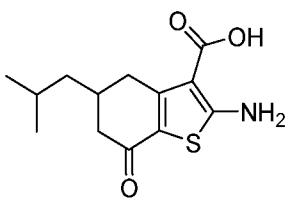
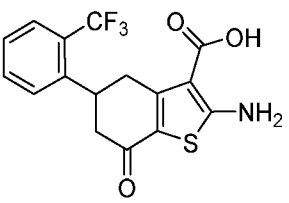
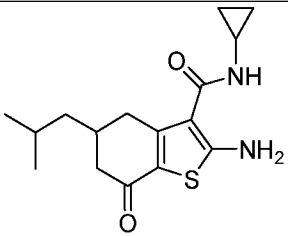
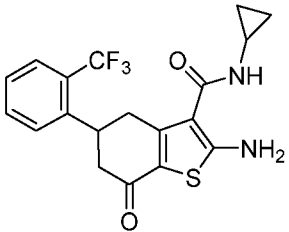
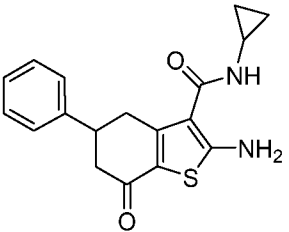
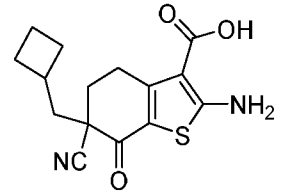
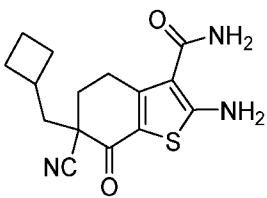
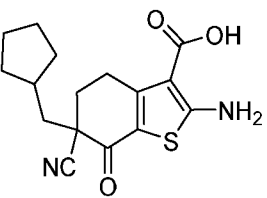
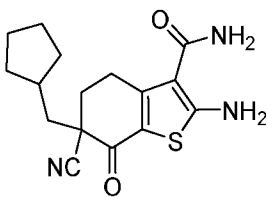
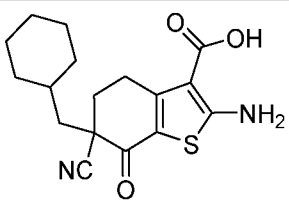
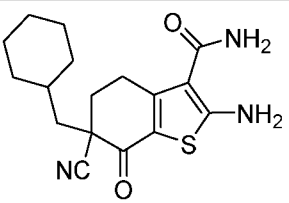
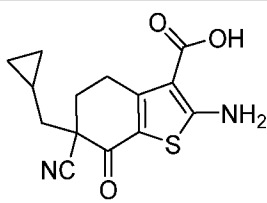
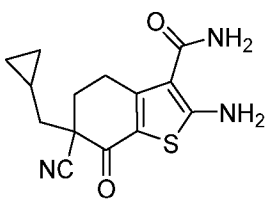
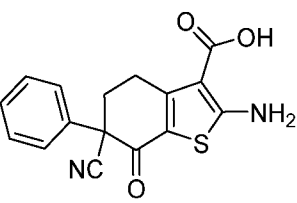
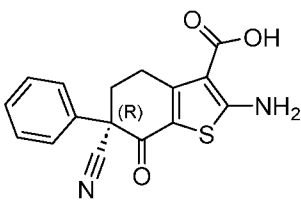
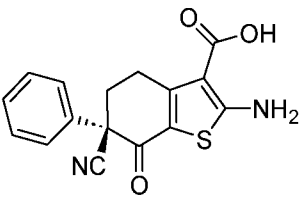
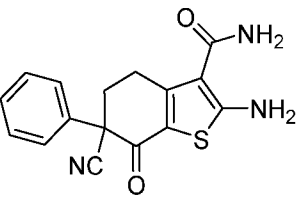
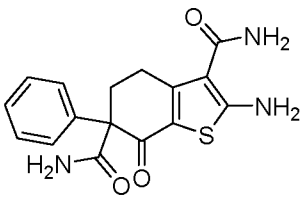
- 5 In some embodiments, R^{1c} and R³ can form together with the carbon atoms to which they are attached a cyclohexyl.

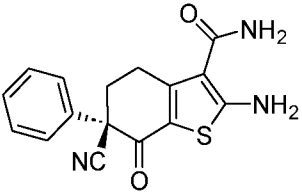
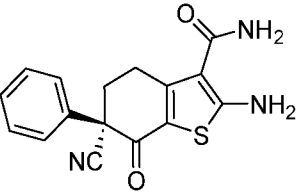
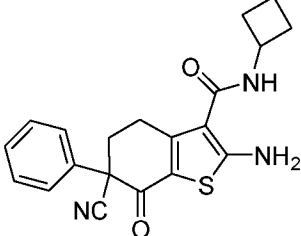
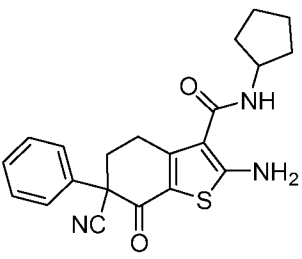
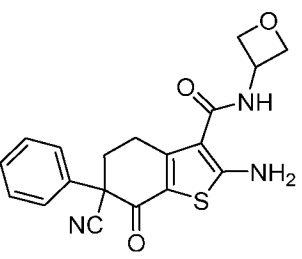
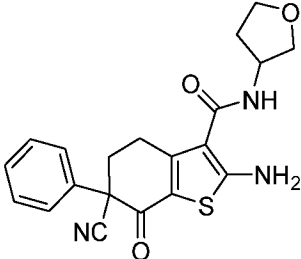
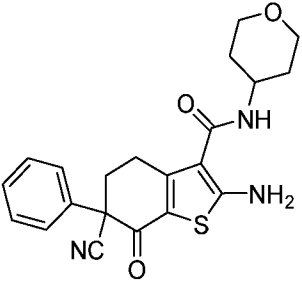
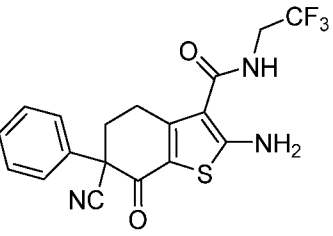
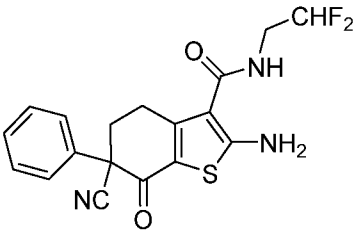
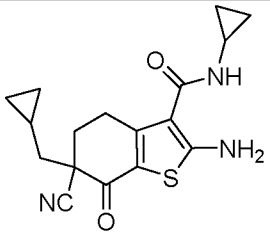
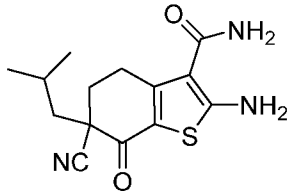
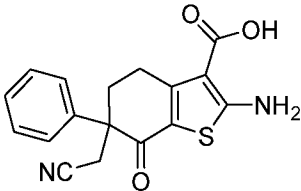
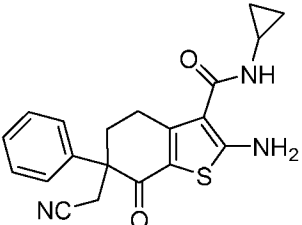
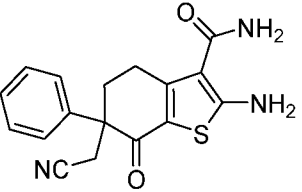
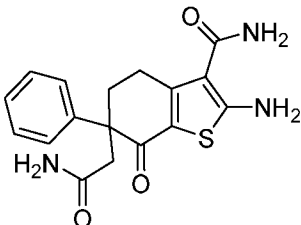
In some embodiments, the compound of Formula (I) as described herein can be selected from Compound 4, 8, 9, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 47, 48, 49, 50, 51, 52, 53, 54, 59, 60a, 60b, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 75, 81, 82, 83, 84, 89, 91, 97, 101, 108, 109, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 154, 155, 163, 168, 169, 170, 173, 174, 175, 178, 179, 180, 181, 183, 189, 190, 191, 192, 193, 194, 195, 197, 198, 199, 200, 201, 202, 211, 212, 213, 214, 215, 216, 219, 221, 227, 228, 229, 230, 231, 232, 237, 238, 239, 245, 246, 247, 248, 249, 250, 251, 253, 254, 255, 257, 258, 263, 264, 271, 272, 273, 278, 279, 280, 281, 287, 288, 290, 291, 297, 298, 305, 306, 313, 314, 321, 322, 330, 331, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 352, 353, 354, 355, 356, 357, 358, 360, 362, 371, 378, 391, 392, 393, 394a, 394b, 395a, 395b, 396, 397, 401, 402, 403, 406, 407, 408, 412, 413, 414, 416, 418, 422, 427, 428, 429, 430, 431, 433, 434, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 462, 463, 464, 465, 466, 468, 469, 470, 471, 472, 473, 474, 475, 476, 478, 479, 480, 481, 482, 483, 486, 488, 489, 492, 495, 496, 497, 498, 511, 512, 513, 514, 515, 520, 523, 524, and 534 of Table 1 below, or can be any pharmaceutically acceptable salt, solvate, or prodrug thereof.

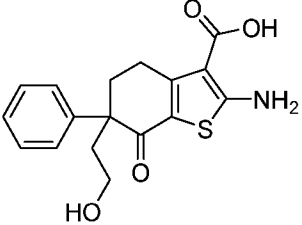
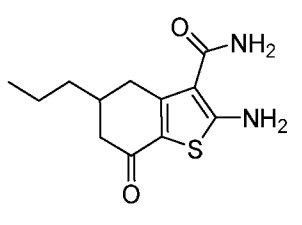
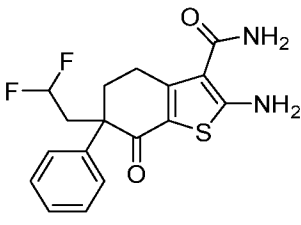
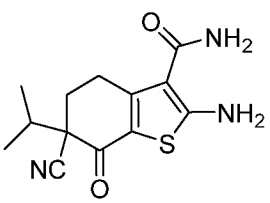
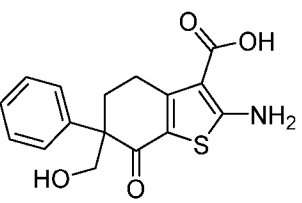
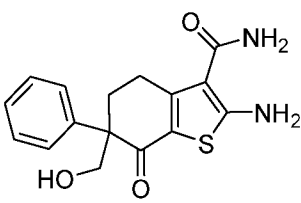
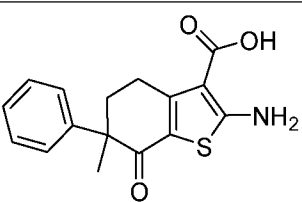
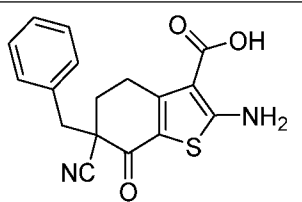
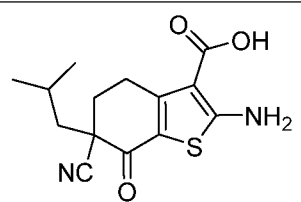
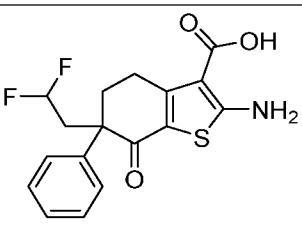
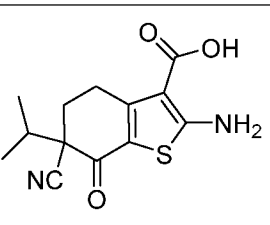
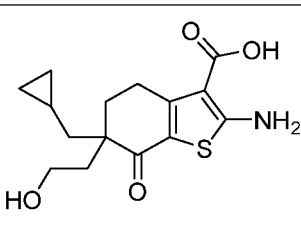
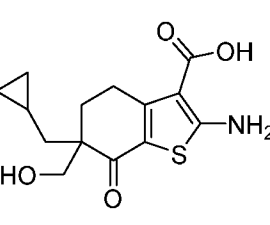
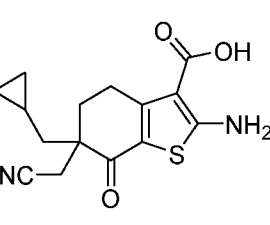
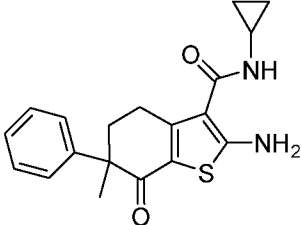
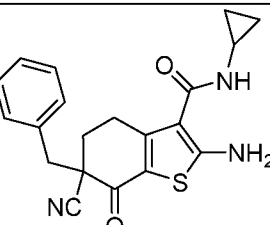
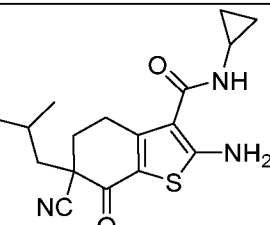
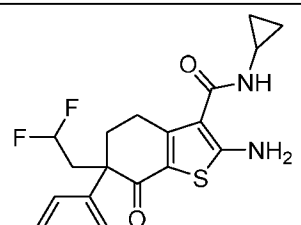
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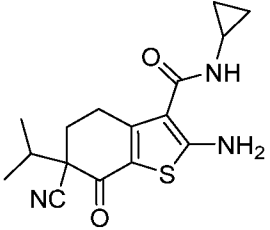
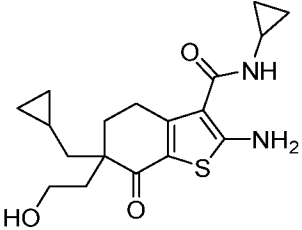
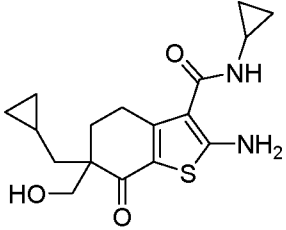
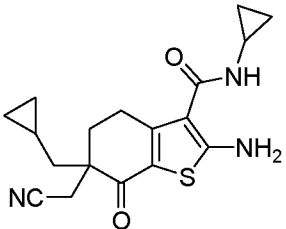
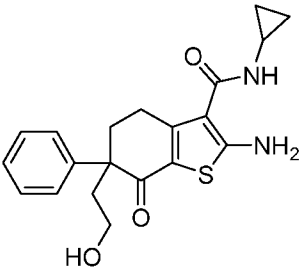
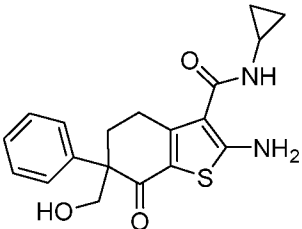
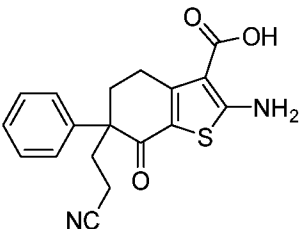
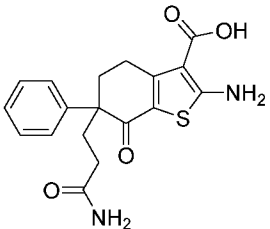
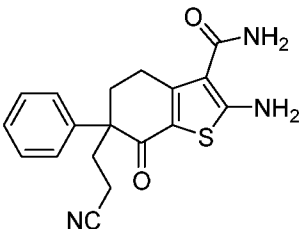
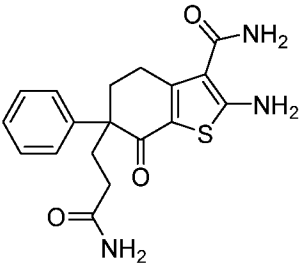
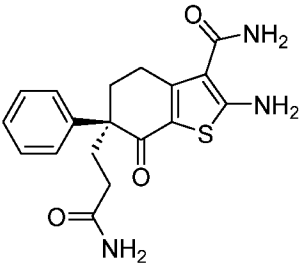
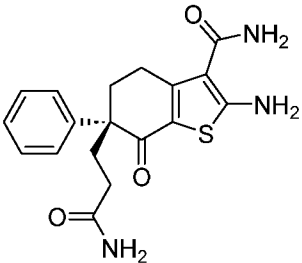
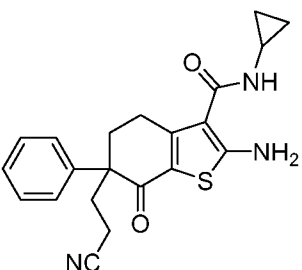
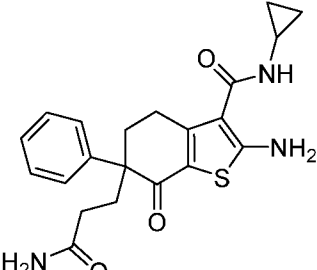
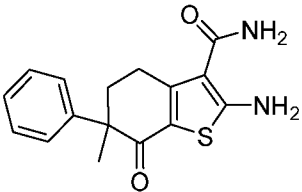
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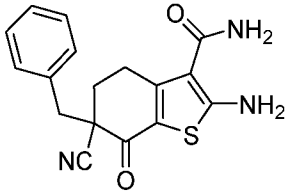
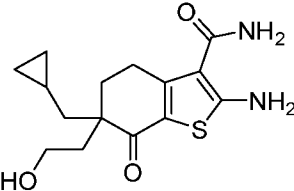
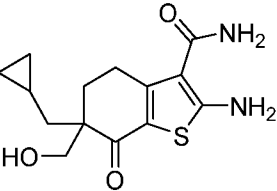
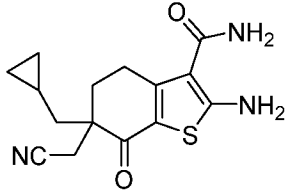
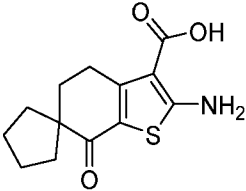
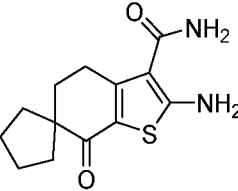
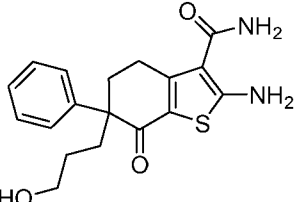
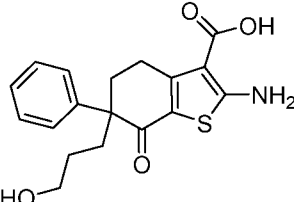
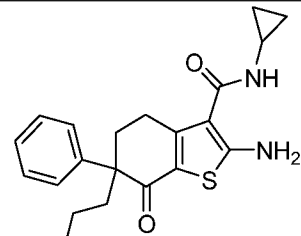
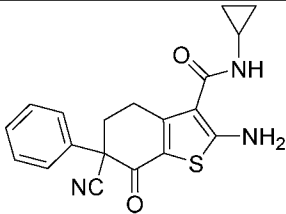
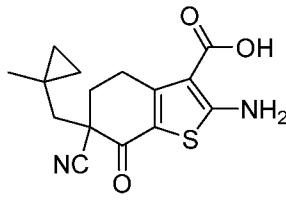
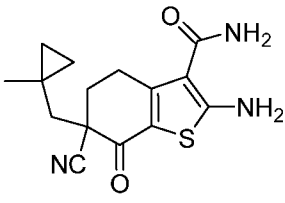
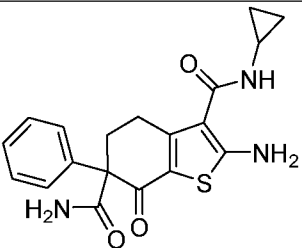
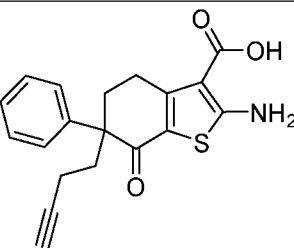
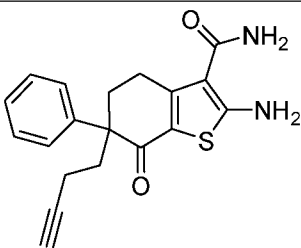
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 Compound 20	 Compound 21	 Compound 22
 Compound 23	 Compound 24	 Compound 25
 Compound 26	 Compound 27	 Compound 28
 Compound 29	 Compound 30	 Compound 31
 Compound 32	 Compound 33	 Compound 34

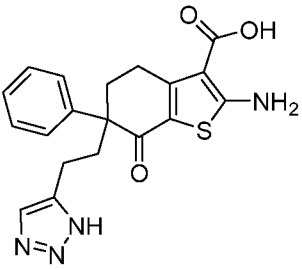
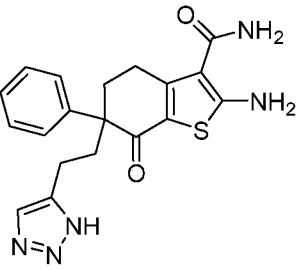
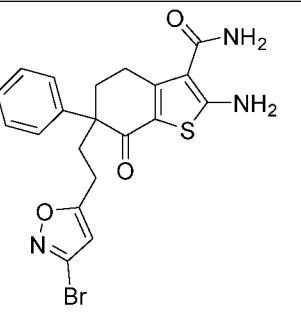
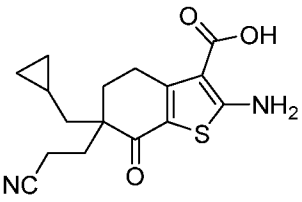
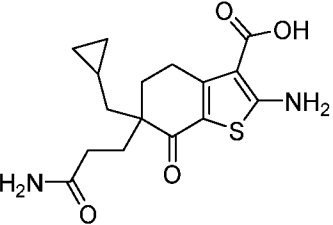
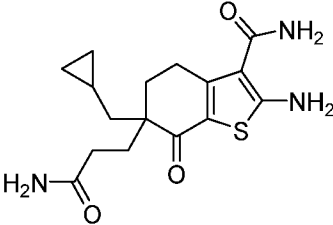
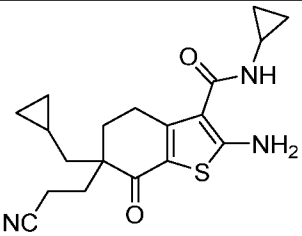
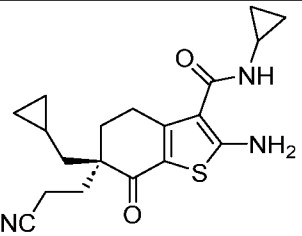
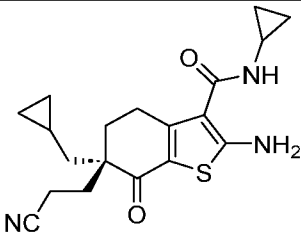
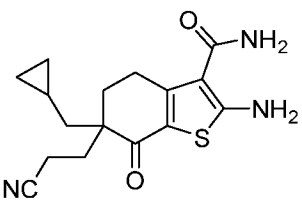
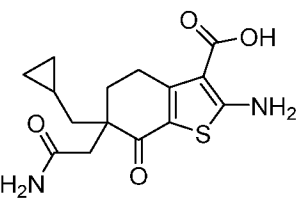
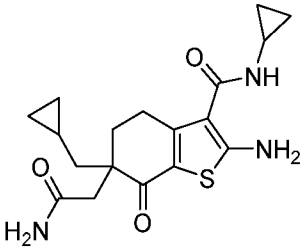
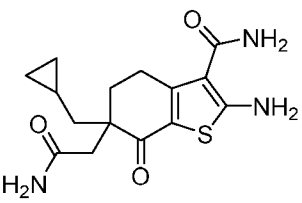
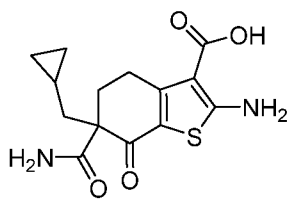
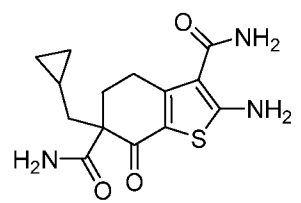
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 Compound 51	 Compound 52	 Compound 53
 Compound 54	 Compound 59	 Compound 60a
 Compound 60b	 Compound 61	 Compound 62

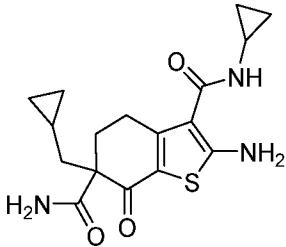
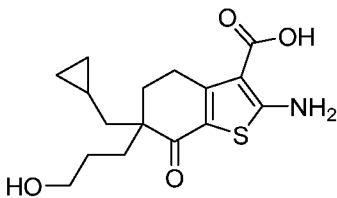
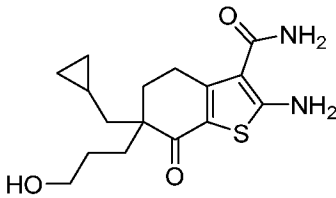
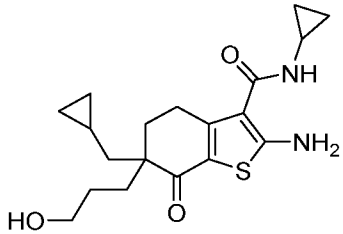
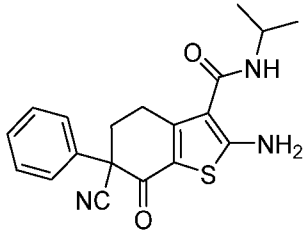
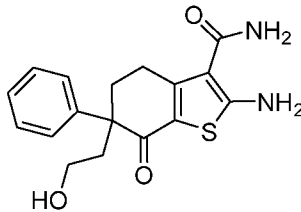
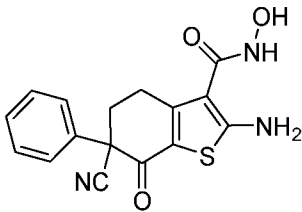
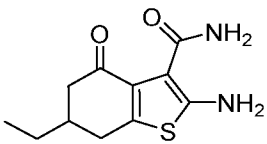
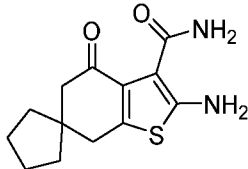
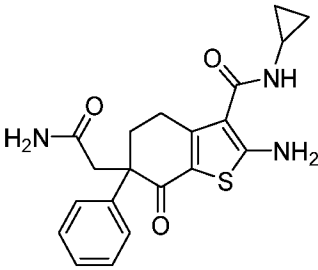
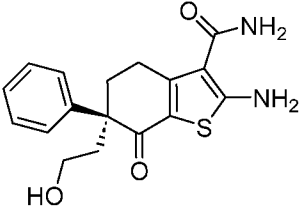
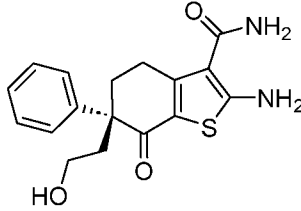
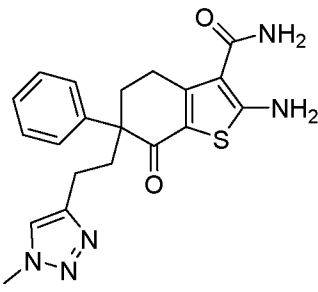
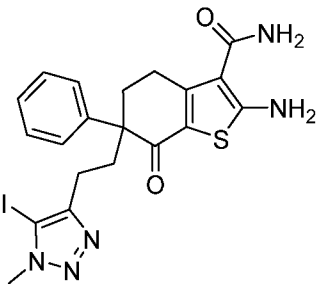
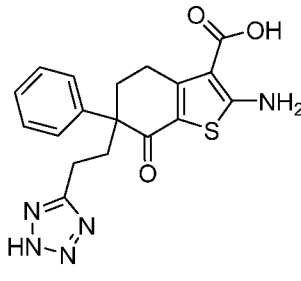
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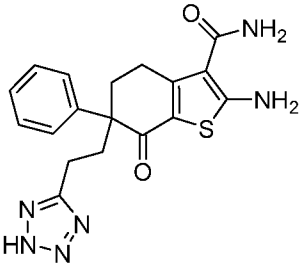
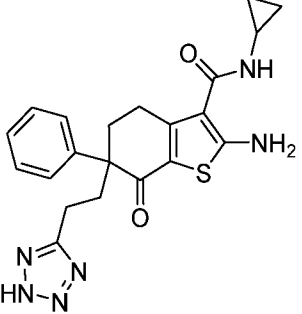
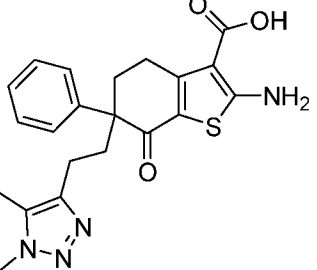
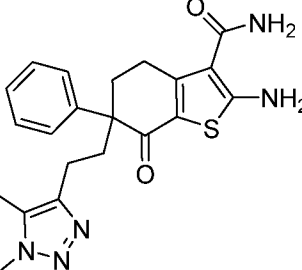
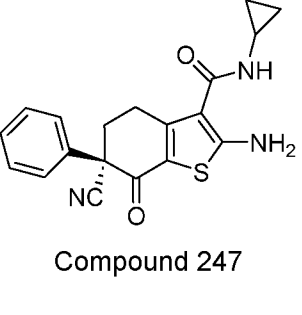
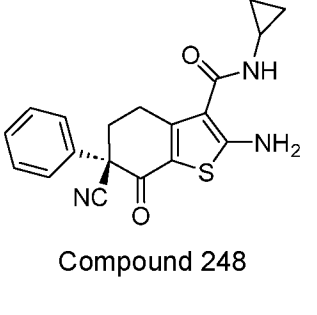
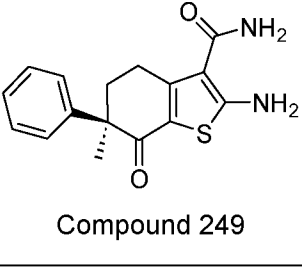
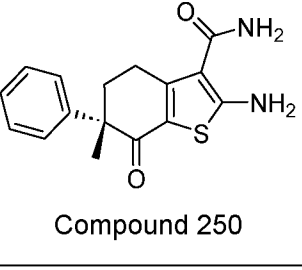
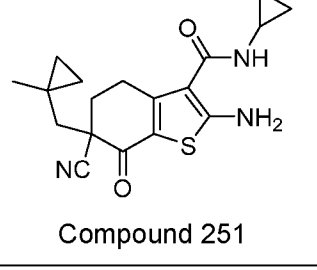
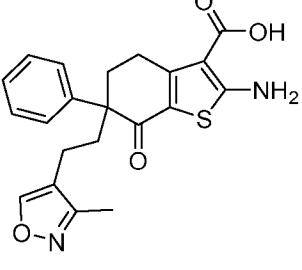
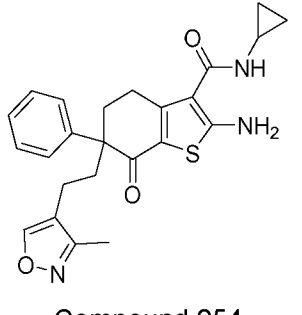
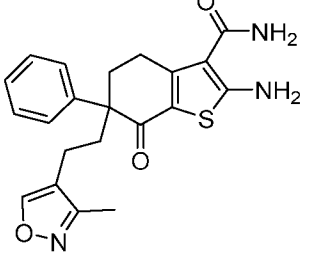
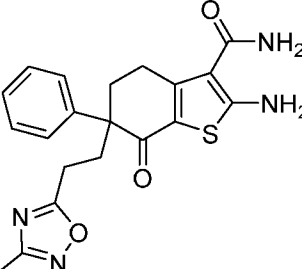
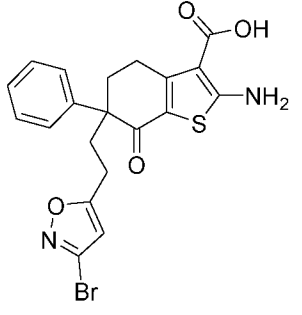
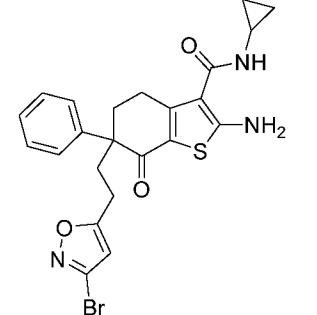
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 Compound 128	 Compound 129	 Compound 130

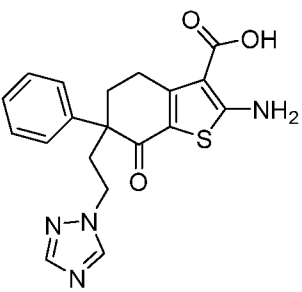
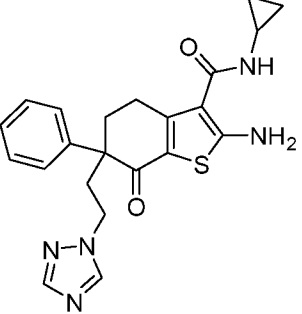
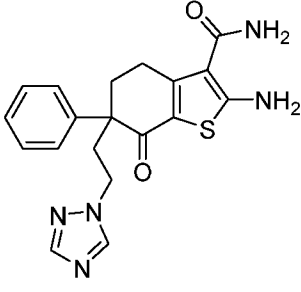
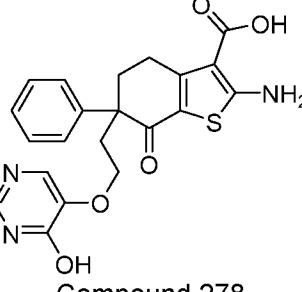
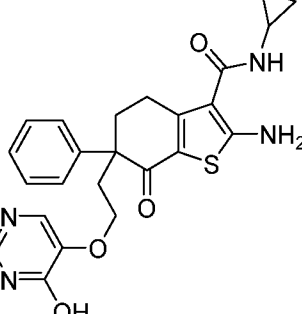
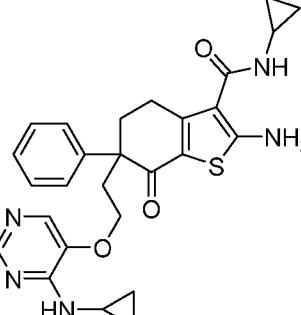
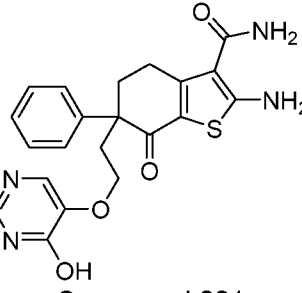
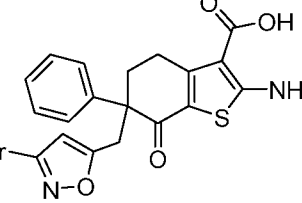
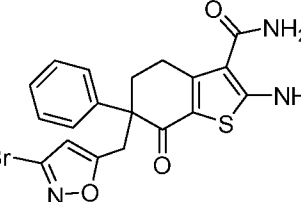
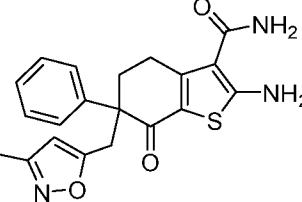
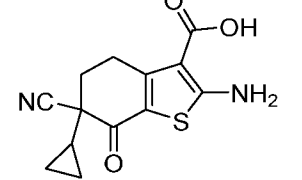
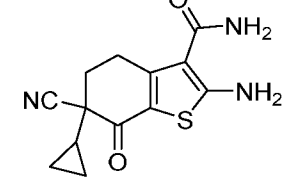
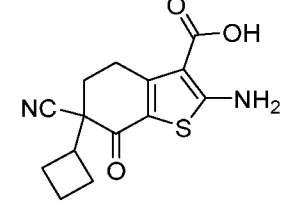
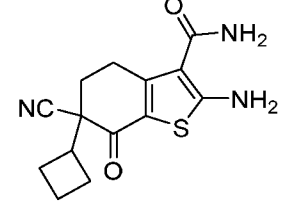
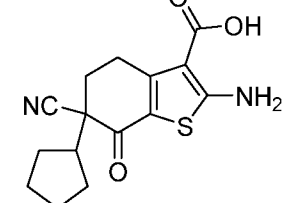
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 Compound 138	 Compound 139	 Compound 140
 Compound 141	 Compound 142	 Compound 143
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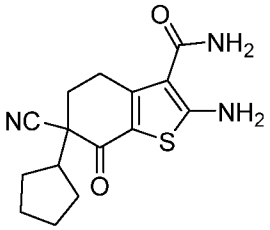
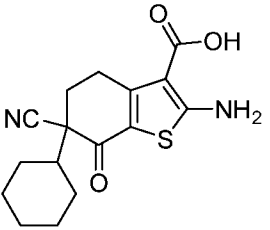
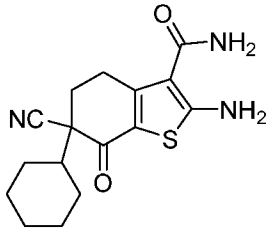
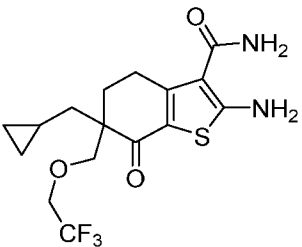
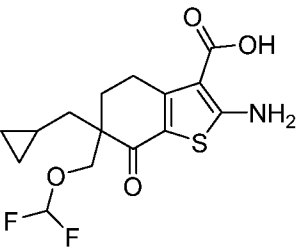
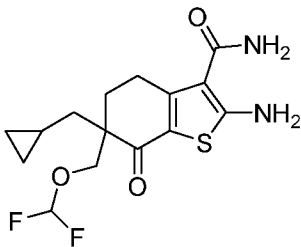
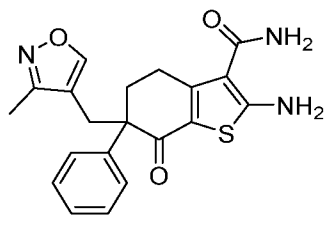
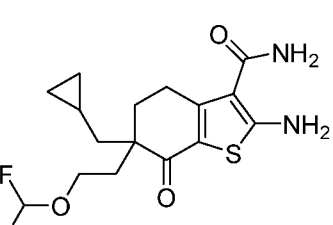
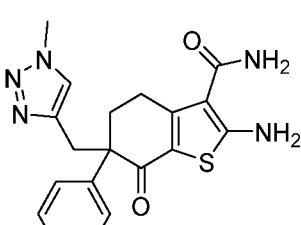
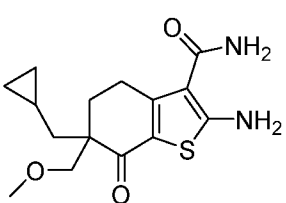
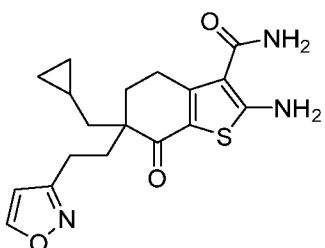
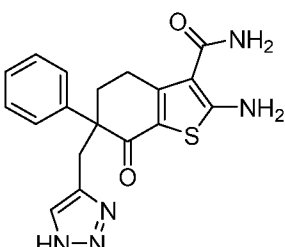
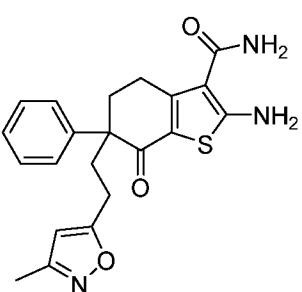
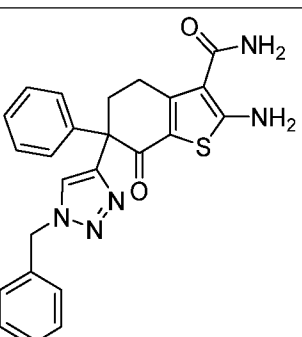
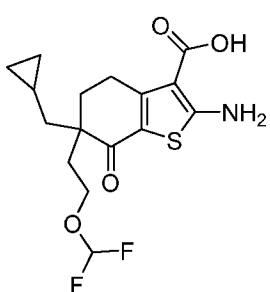
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 Compound 150	 Compound 154	 Compound 155
 Compound 163	 Compound 168	 Compound 169
 Compound 170	 Compound 173	 Compound 174
 Compound 175	 Compound 178	 Compound 179

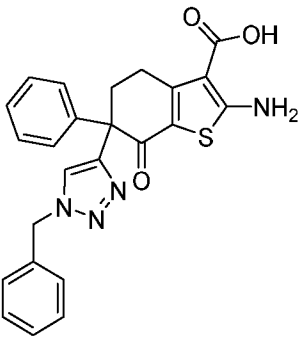
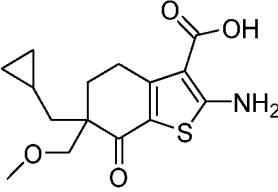
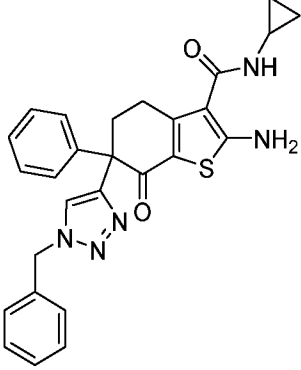
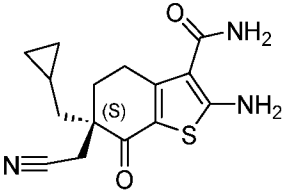
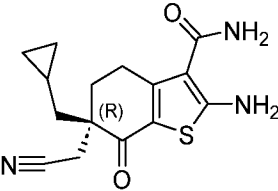
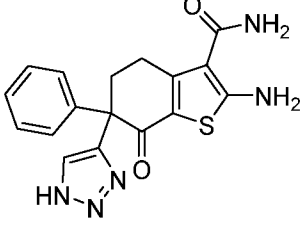
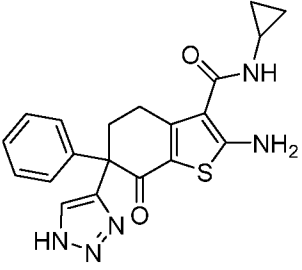
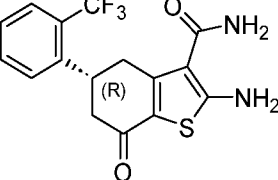
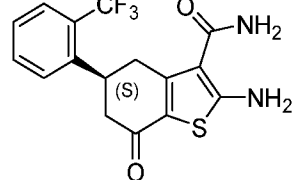
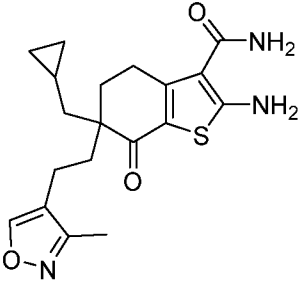
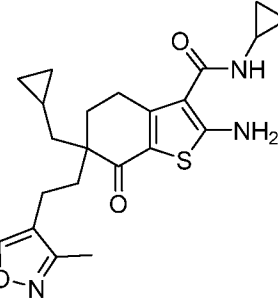
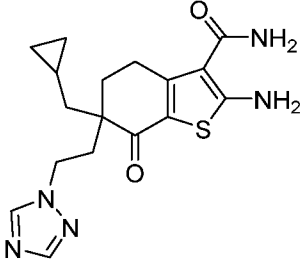
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 Compound 189	 Compound 190	 Compound 191
 Compound 192	 Compound 193	 Compound 194
 Compound 195	 Compound 197	 Compound 198
 Compound 199	 Compound 200	 Compound 201

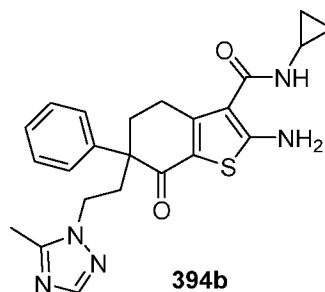
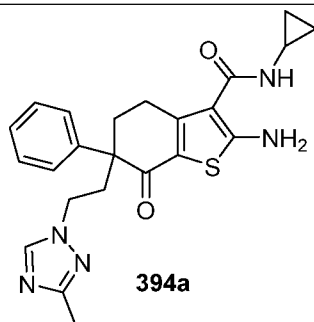
 Compound 202	 Compound 211	 Compound 212
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 Compound 228	 Compound 229	 Compound 230
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 Compound 238	 Compound 239	 Compound 245
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 Compound 249	 Compound 250	 Compound 251
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 Compound 258	 Compound 263	 Compound 264

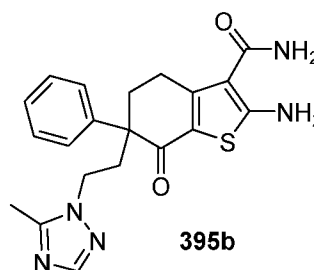
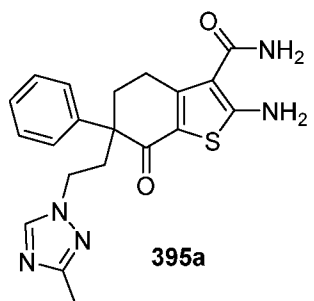
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 Compound 278	 Compound 279	 Compound 280
 Compound 281	 Compound 287	 Compound 288
 Compound 291	 Compound 297	 Compound 298
 Compound 305	 Compound 306	 Compound 313

 Compound 314	 Compound 321	 Compound 322
 Compound 331	 Compound 337	 Compound 338
 Compound 339	 Compound 340	 Compound 341
 Compound 342	 Compound 343	 Compound 344
 Compound 345	 Compound 346	 Compound 347

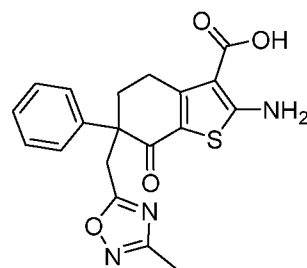
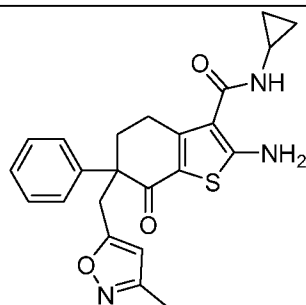
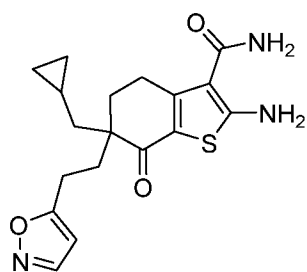
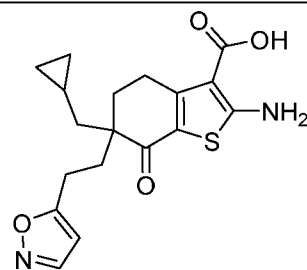
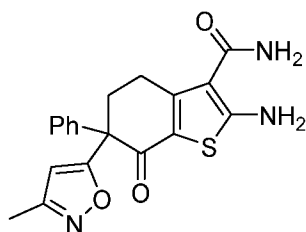
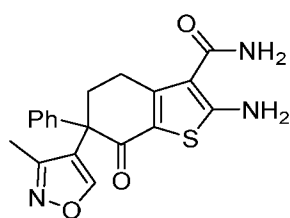
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 Compound 356	 Compound 357	 Compound 358
 Compound 391	 Compound 392	 Compound 393

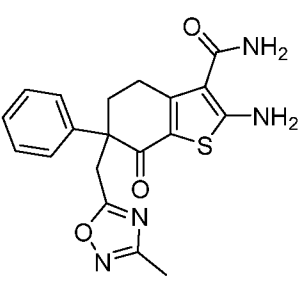
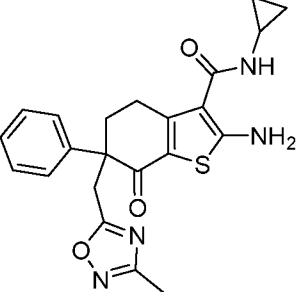
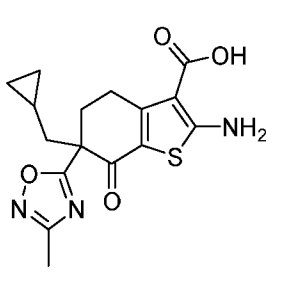
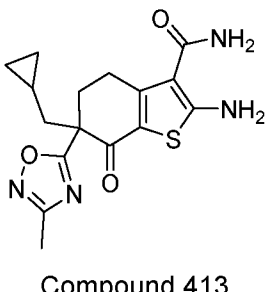
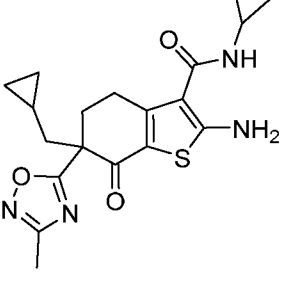
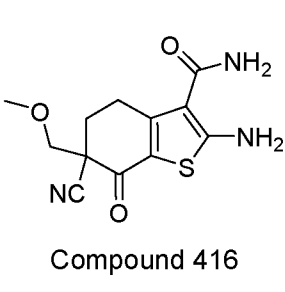
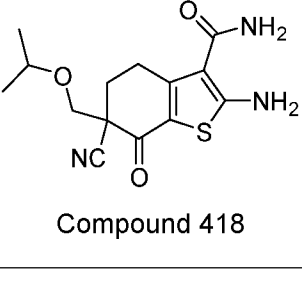
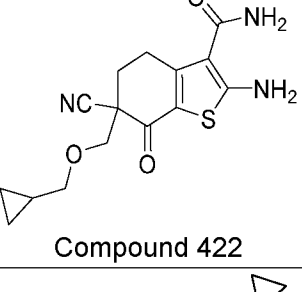
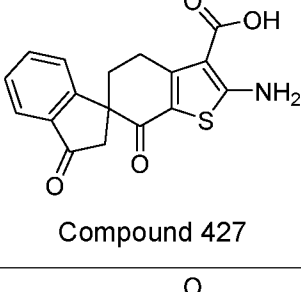
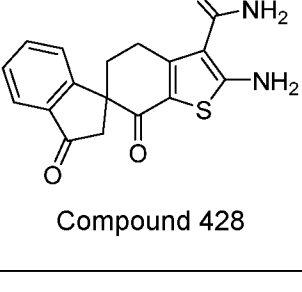
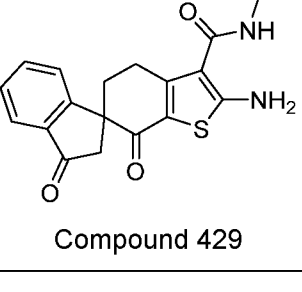
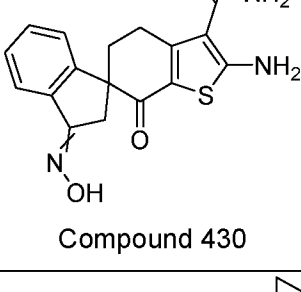
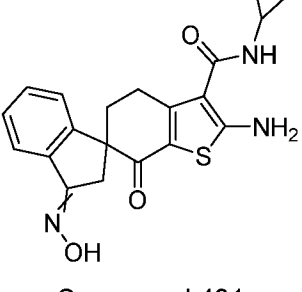
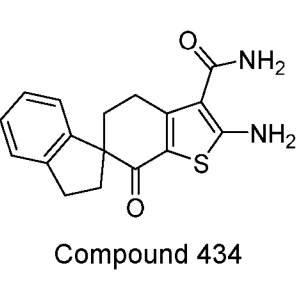
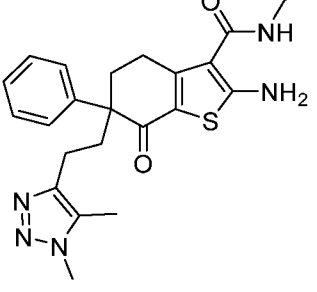


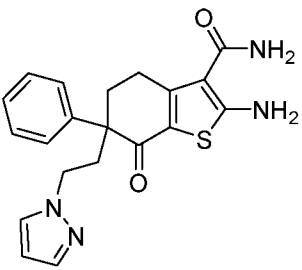
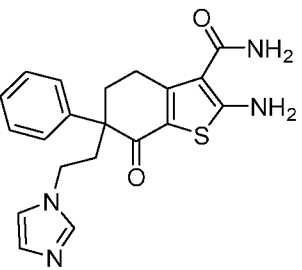
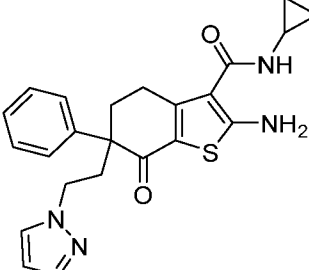
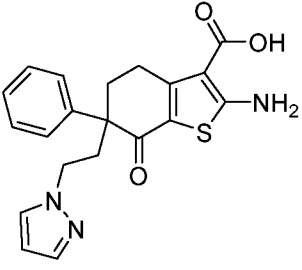
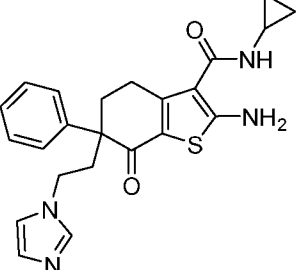
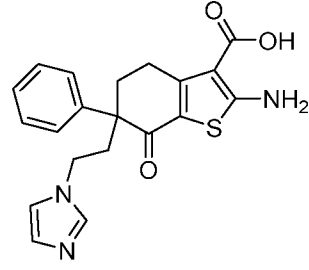
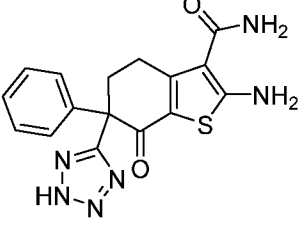
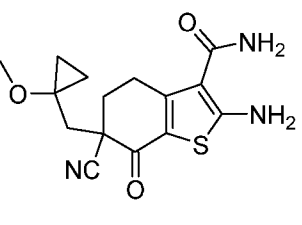
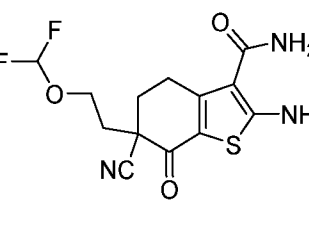
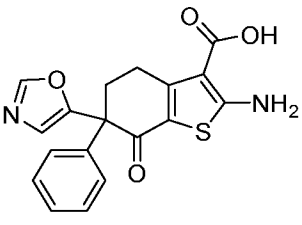
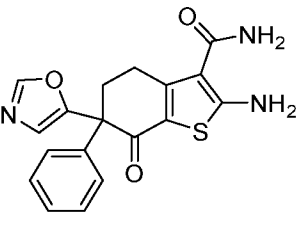
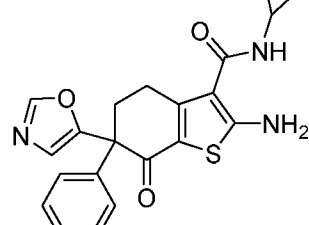
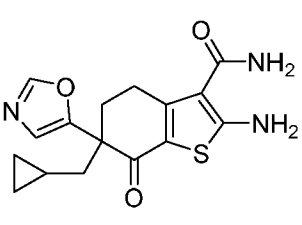
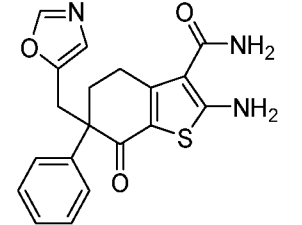
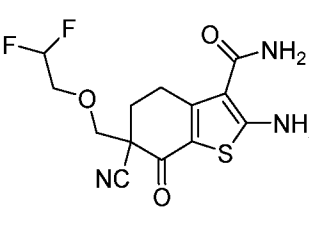
Compound 394 (mixture of regioisomers 394a and 394b)

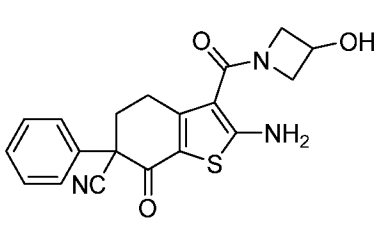
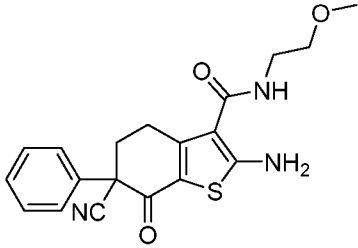
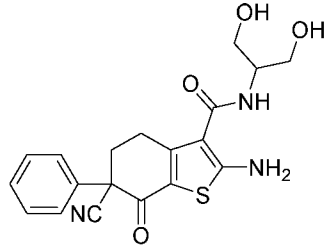
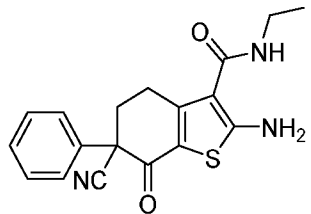
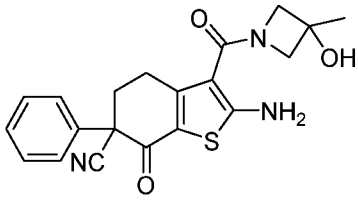
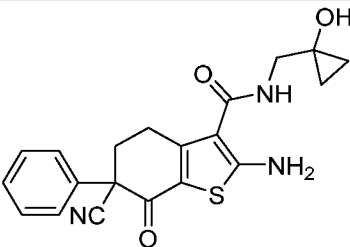
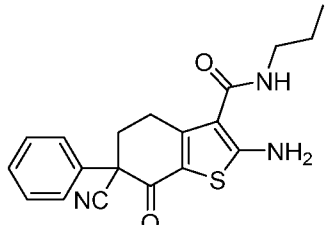
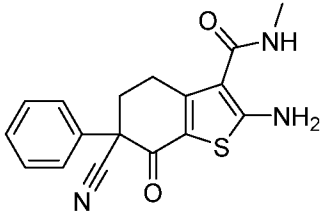
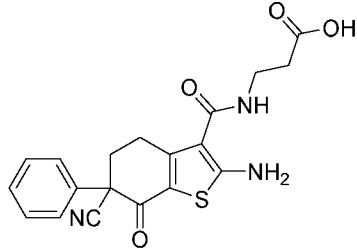
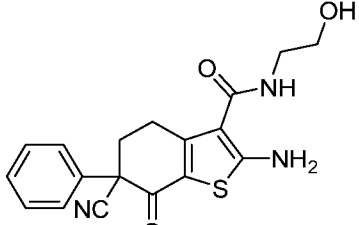
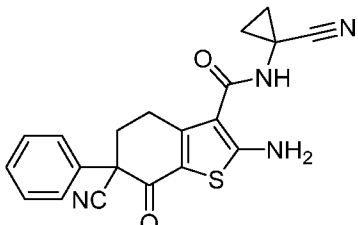
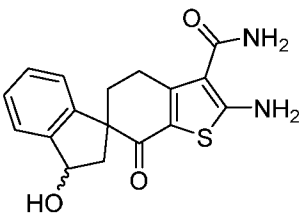
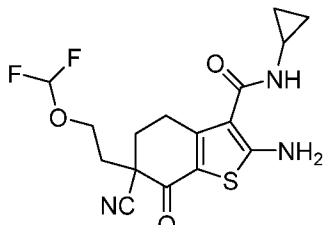
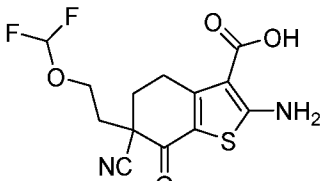
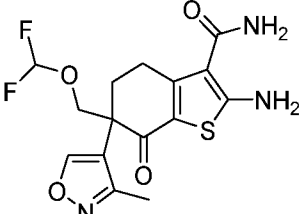


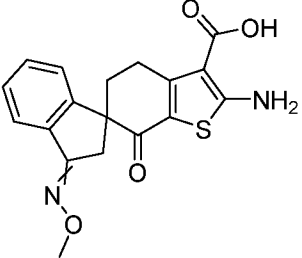
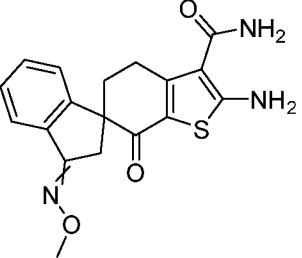
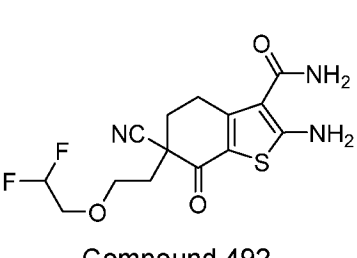
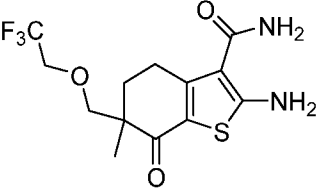
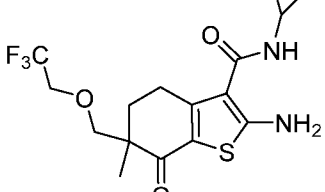
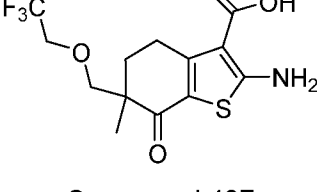
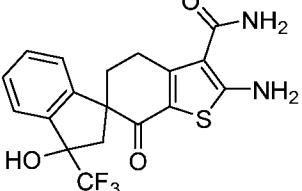
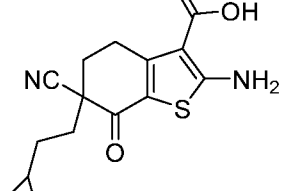
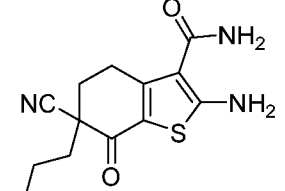
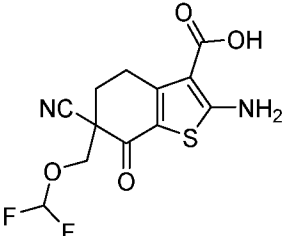
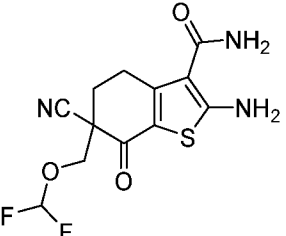
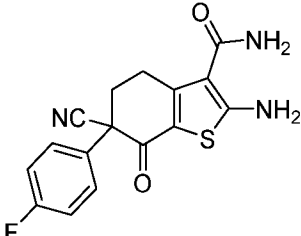
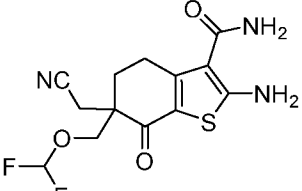
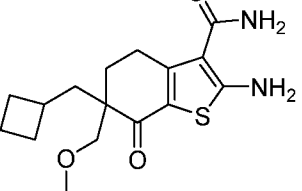
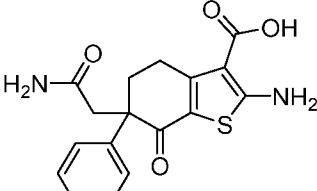
Compound 395 (mixture of regioisomers 395a and 395b)

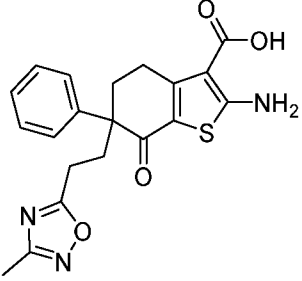
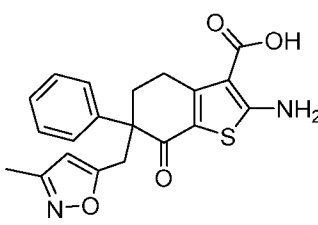
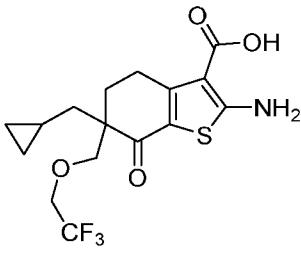
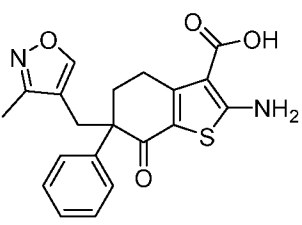
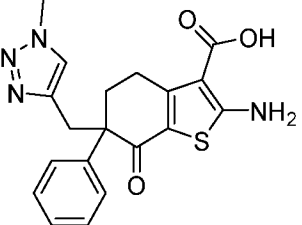
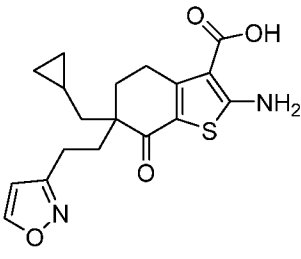
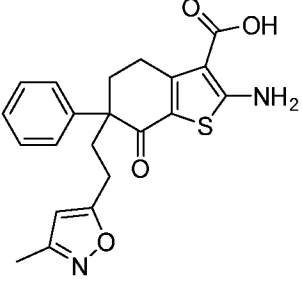
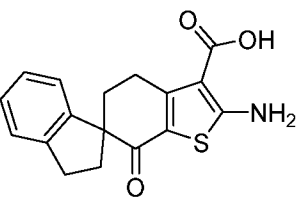
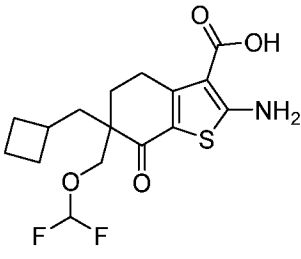
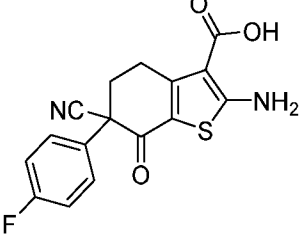


 Compound 407	 Compound 408	 Compound 412
 Compound 413	 Compound 414	 Compound 416
 Compound 418	 Compound 422	 Compound 427
 Compound 428	 Compound 429	 Compound 430
 Compound 431	 Compound 434	 Compound 445

 Compound 446	 Compound 447	 Compound 448
 Compound 449	 Compound 450	 Compound 451
 Compound 452	 Compound 453	 Compound 454
 Compound 462	 Compound 463	 Compound 464
 Compound 465	 Compound 466	 Compound 468

 Compound 469	 Compound 470	 Compound 471
 Compound 472	 Compound 473	 Compound 474
 Compound 475	 Compound 476	 Compound 478
 Compound 479	 Compound 480	 Compound 481
 Compound 482	 Compound 483	 Compound 486

 Compound 488	 Compound 489	 Compound 492
 Compound 495	 Compound 496	 Compound 497
 Compound 498	 Compound 511	 Compound 512
 Compound 513	 Compound 514	 Compound 515
 Compound 520	 Compound 524	 Compound 227

 Compound 257	 Compound 290	 Compound 330
 Compound 360	 Compound 362	 Compound 371
 Compound 378	 Compound 433	 Compound 523
 Compound 534		

In some embodiments, the compound of Formula (I) as described herein is Compound 4, 9, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 47, 48, 49, 50, 51, 52, 53, 54, 59, 60a, 60b, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 75, 81, 82, 83, 84, 89, 91, 97, 101, 109, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 155, 163, 168, 169, 170, 173, 174, 175, 179, 180, 181, 183, 189, 191, 192, 193, 194, 195, 197, 198, 199, 200, 201, 202, 211, 212, 213, 214, 215, 216, 219, 221, 228, 229, 230, 231, 232, 237, 238, 239, 246, 247, 248, 249, 250, 251, 253, 254, 255, 258, 263, 264, 271, 272, 273, 278, 279, 280, 281,

287, 288, 291, 297, 298, 305, 306, 313, 314, 321, 322, 331, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 352, 353, 354, 355, 356, 357, or 358 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments, the compound of Formula (I) as described herein is Compound 4, 9, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 47, 48, 49, 50, 51, 52, 53, 54, 59, 60b, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 75, 81, 82, 83, 84, 89, 91, 97, 101, 109, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 138, 139, 140, 141, 143, 144, 145, 146, 147, 148, 149, 150, 155, 163, 168, 169, 170, 173, 174, 175, 179, 180, 181, 183, 189, 191, 192, 193, 194, 195, 198, 199, 200, 201, 202, 211, 212, 213, 214, 215, 216, 219, 228, 230, 231, 232, 237, 238, 239, 246, 247, 248, 249, 250, 251, 253, 254, 255, 258, 263, 264, 271, 272, 273, 278, 279, 280, 281, 287, 288, 291, 297, 298, 305, 306, 313, 314, 321, 322, 331, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 352, 353, 354, 355, 356, 357 or 358 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments, the compound of Formula (I) as described herein is Compound 4, 9, 15, 16, 17, 18, 19, 20, 21, 22, 24, 25, 26, 27, 29, 30, 31, 32, 33, 34, 36, 37, 38, 39, 47, 48, 49, 50, 51, 52, 53, 54, 59, 60b, 61, 62, 63, 64, 65, 66, 67, 68, 71, 72, 75, 81, 82, 83, 84, 89, 91, 97, 101, 109, 119, 120, 121, 122, 123, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 138, 139, 140, 141, 143, 144, 145, 146, 147, 148, 149, 150, 155, 163, 168, 169, 170, 173, 174, 175, 179, 180, 181, 183, 189, 191, 192, 194, 195, 198, 199, 201, 202, 212, 213, 214, 215, 216, 228, 230, 231, 232, 237, 238, 239, 246, 248, 249, 250, 251, 253, 254, 255, 258, 263, 264, 271, 272, 273, 278, 279, 280, 281, 287, 288, 291, 297, 298, 305, 306, 313, 314, 321, 322, 331, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 352, 353, 354, 355, 356, 357, or 358 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments, the compound of Formula (I) as described herein is Compound 4, 9, 15, 16, 17, 18, 19, 20, 21, 22, 24, 25, 26, 27, 29, 30, 31, 32, 33, 34, 36, 37, 38, 39, 47, 48, 49, 50, 51, 52, 53, 54, 59, 60b, 61, 62, 63, 64, 65, 66, 67, 68, 71, 72, 75, 81, 82, 83, 84, 89, 91, 97, 101, 109, 119, 120, 121, 122, 123, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 138, 139, 140, 141, 143, 144, 145, 146, 147, 148, 149, 150, 155, 163, 168, 169, 170, 173, 174, 175, 179, 180, 181, 183, 189, 191, 192, 194, 195, 198, 199, 201, 202, 212, 213, 214, 215, 216, 228, 230, 231, 232, 237, 238, 239, 245, 246, 248, 249, 250, 251, 253, 254, 255, 258, 263, 264, 271, 272, 273, 278, 279, 280, 281, 287, 288, 291, 297, 298, 305, 306, 313, 314, 321, 322, 331, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 352, 353, 354, 355, 356, 357, 358, 391, 392, 393, 394a, 394b, 395a, 395b, 396, 397, 401, 402, 403, 406, 407, 408, 413, 414, 416, 418, 422, 427, 428, 429, 430, 431, 434, 445, 446, 447, 448, 449, 450, 451, 453, 454, 462, 463, 464, 465, 466, 468, 470, 472, 474, 475, 476, 478, 479, 480, 481, 482, 486, 489, 492, 495, 496, 498, 511, 512, 513, 514, 515,

520, or 524 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments, the compound of Formula (I) as described herein is Compound 4, 15, 16, 17, 20, 24, 25, 26, 27, 29, 30, 31, 32, 33, 34, 36, 37, 47, 48, 49, 50, 51, 52, 53, 54, 59, 60b, 61, 62, 63, 64, 65, 66, 67, 71, 72, 75, 81, 82, 83, 84, 89, 91, 97, 101, 109, 119, 120, 121, 122, 123, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 138, 139, 140, 141, 143, 144, 145, 146, 147, 148, 149, 150, 155, 163, 168, 169, 170, 173, 174, 175, 179, 180, 181, 183, 191, 192, 194, 195, 198, 199, 201, 202, 212, 213, 214, 215, 216, 228, 230, 231, 232, 237, 238, 239, 246, 248, 250, 251, 253, 254, 255, 258, 263, 264, 271, 272, 273, 278, 279, 280, 281, 287, 288, 291, 298, 305, 306, 313, 314, 321, 322, 331, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 352, 353, 354, 355, 356, 357, 358, 391, 392, 393, 394a, 394b, 395a, 395b, 396, 397, 401, 402, 403, 406, 407, 408, 413, 414, 416, 418, 422, 428, 429, 430, 431, 434, 445, 446, 447, 448, 449, 450, 451, 453, 454, 462, 463, 464, 465, 466, 468, 470, 472, 474, 475, 476, 479, 480, 481, 482, 486, 489, 495, 496, 498, 511, 512, 513, 514, 515, 520, or 524 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments, the compound of Formula (I) as described herein is Compound 4, 15, 16, 20, 25, 26, 29, 30, 31, 32, 33, 34, 37, 47, 48, 49, 50, 51, 52, 54, 59, 60b, 61, 62, 63, 64, 65, 72, 75, 82, 83, 84, 89, 91, 97, 101, 109, 119, 121, 123, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 138, 139, 140, 141, 143, 144, 145, 146, 147, 148, 149, 150, 155, 163, 168, 169, 170, 173, 174, 175, 179, 180, 181, 183, 191, 192, 194, 195, 201, 212, 213, 214, 215, 216, 230, 231, 232, 238, 239, 246, 248, 250, 251, 253, 254, 255, 258, 263, 264, 271, 272, 273, 278, 279, 280, 281, 288, 291, 298, 305, 306, 313, 314, 321, 322, 331, 338, 339, 340, 341, 342, 343, 344, 345, 346, 352, 353, 354, 355, 356, 358, 391, 392, 393, 394a, 394b, 395a, 395b, 396, 397, 401, 402, 403, 406, 407, 408, 413, 414, 416, 418, 422, 428, 429, 430, 431, 434, 445, 446, 447, 448, 449, 450, 451, 453, 454, 462, 463, 464, 465, 466, 468, 470, 472, 474, 475, 476, 479, 480, 481, 482, 486, 489, 495, 496, 498, 511, 512, 513, 514, 515, 520, or 524 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments, the compound of Formula (I) as described herein is Compound 4, 15, 16, 20, 25, 26, 29, 30, 31, 32, 33, 34, 37, 47, 48, 49, 50, 51, 52, 54, 59, 60b, 61, 62, 63, 64, 65, 72, 75, 82, 83, 84, 89, 91, 97, 101, 109, 119, 121, 123, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 138, 139, 140, 141, 143, 144, 145, 146, 147, 148, 149, 150, 155, 163, 168, 169, 170, 173, 174, 175, 179, 180, 181, 183, 191, 192, 194, 195, 201, 212, 213, 214, 215, 216, 230, 231, 232, 238, 239, 245, 246, 248, 250, 251, 253, 254, 255, 258, 263, 264, 271, 272, 273, 278, 279, 280, 281, 288, 291, 298, 305, 306, 313, 314, 321, 322, 331, 338, 339, 340, 341, 342, 343, 344, 345, 346, 352, 353, 354, 355, 356, 358, 391, 392, 393, 394a, 394b, 395a, 395b, 396, 397, 402, 403, 407, 408, 413, 414, 416, 418, 422, 428, 429, 430, 431, 434, 445, 446, 447, 448, 449, 450, 451,

453, 454, 462, 463, 464, 465, 466, 468, 472, 475, 476, 479, 480, 481, 482, 486, 489, 495, 496, 498, 511, 512, 514, 515, 520, or 524 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments, the compound of Formula (I) as described herein is Compound 4, 15, 25, 32, 33, 47, 48, 49, 50, 52, 54, 59, 60b, 61, 62, 63, 72, 75, 82, 83, 89, 97, 101, 109, 119, 121, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 138, 139, 140, 141, 143, 144, 145, 146, 147, 148, 149, 150, 163, 169, 170, 174, 179, 181, 183, 191, 192, 194, 195, 212, 213, 214, 215, 230, 231, 232, 238, 239, 246, 248, 250, 251, 253, 254, 255, 258, 263, 264, 272, 273, 278, 279, 280, 281, 288, 291, 298, 305, 306, 313, 314, 321, 322, 331, 338, 339, 340, 341, 342, 343, 344, 345, 353, 355, 356, 358, 391, 392, 393, 394a, 394b, 395a, 395b, 396, 397, 402, 403, 407, 408, 413, 418, 422, 428, 429, 430, 431, 434, 445, 446, 447, 448, 449, 450, 451, 454, 463, 464, 465, 466, 472, 475, 476, 479, 481, 486, 489, 495, 498, 512, 514, 515, 520, or 524 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments, the compound of Formula (I) as described herein is Compound 15, 25, 32, 48, 49, 50, 52, 54, 59, 60b, 61, 62, 63, 72, 75, 82, 83, 97, 101, 109, 119, 127, 128, 129, 130, 135, 136, 140, 141, 143, 144, 145, 146, 147, 148, 149, 150, 163, 169, 170, 174, 179, 181, 183, 191, 192, 194, 195, 212, 213, 215, 230, 231, 232, 238, 239, 246, 248, 250, 251, 254, 255, 258, 263, 272, 273, 279, 281, 288, 291, 306, 313, 314, 321, 322, 331, 338, 339, 340, 341, 342, 343, 344, 345, 353, 355, 356, 358, 391, 392, 393, 394a, 394b, 395a, 395b, 396, 397, 402, 403, 407, 408, 413, 418, 422, 428, 429, 430, 431, 434, 445, 446, 447, 448, 449, 450, 451, 454, 463, 464, 465, 466, 472, 475, 476, 479, 481, 486, 489, 495, 498, 512, 514, 515, 520, or 524 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments, the compound of Formula (I) as described herein is Compound 15, 25, 32, 48, 49, 50, 52, 54, 59, 60b, 61, 62, 63, 72, 75, 82, 83, 97, 101, 109, 119, 127, 128, 129, 130, 135, 136, 140, 141, 143, 144, 145, 146, 147, 148, 149, 150, 163, 169, 170, 174, 179, 181, 183, 191, 192, 194, 195, 212, 213, 215, 230, 231, 232, 238, 239, 246, 248, 250, 251, 254, 255, 258, 263, 272, 273, 279, 281, 288, 291, 306, 313, 314, 321, 322, 331, 338, 339, 340, 341, 342, 343, 344, 345, 353, 355, 356, 358, 391, 392, 393, 394a, 394b, 395a, 395b, 396, 397, 402, 403, 407, 418, 428, 430, 431, 434, 445, 446, 447, 448, 449, 450, 454, 463, 464, 465, 466, 476, 489, 512, 514, 515, or 524 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments, the compound of Formula (I) as described herein is Compound 48, 50, 54, 60b, 61, 63, 72, 75, 83, 97, 101, 109, 127, 135, 140, 141, 143, 144, 145, 146, 147, 149, 163, 169, 170, 174, 179, 181, 191, 194, 195, 212, 215, 230, 231, 232, 238, 246, 248, 250, 251, 255, 258, 272, 273, 279, 281, 291, 306, 314, 321, 322, 331, 338, 339, 340, 341, 342, 345, 353, 355, 356, 391, 393, 395a, 395b, 397, 402, 428, 430, 431, 434, 446, 447, 448, 450, 463, 464, 465, 466,

489, 512, 514, 515, or 524 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments, the compound of Formula (I) as described herein is Compound 48, 50, 54, 60b, 61, 63, 75, 83, 97, 101, 127, 135, 140, 141, 143, 144, 146, 147, 149, 163, 170, 174, 181, 191, 195, 215, 230, 231, 232, 238, 246, 248, 250, 251, 255, 258, 272, 273, 279, 281, 306, 314, 322, 338, 339, 340, 345, 353, 355, 356, 391, 393, 397, 402, 428, 430, 431, 434, 446, 447, 450, 463, 465, 466, 489, 512, 514, 515, or 524 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments, the compound of Formula (I) as described herein is Compound 54, 61, 63, 75, 140, 143, 146, 174, 215, 230, 250, 251, 273, 306, 322, 430, 446, 463, or 512 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 61, 63, 75, 143, 146, 174, 230, 250, 273, or 306 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments, the compound of Formula (I) as described herein is Compound 4 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 33 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 47 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 89 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 121 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 131 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 132 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 133 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 134 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 138 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 139 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some

embodiments, the compound of Formula (I) as described herein is Compound 214 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 253 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
5 embodiments, the compound of Formula (I) as described herein is Compound 264 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 278 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
10 embodiments, the compound of Formula (I) as described herein is Compound 280 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 298 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
15 embodiments, the compound of Formula (I) as described herein is Compound 305 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 408 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
20 embodiments, the compound of Formula (I) as described herein is Compound 413 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 422 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
25 embodiments, the compound of Formula (I) as described herein is Compound 429 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 451 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
30 embodiments, the compound of Formula (I) as described herein is Compound 472 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 475 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
35 embodiments, the compound of Formula (I) as described herein is Compound 479 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 481 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
embodiments, the compound of Formula (I) as described herein is Compound 486 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
embodiments, the compound of Formula (I) as described herein is Compound 495 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
embodiments, the compound of Formula (I) as described herein is Compound 498 of Table 1

embodiments, the compound of Formula (I) as described herein is Compound 150 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 169 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
5 embodiments, the compound of Formula (I) as described herein is Compound 179 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 183 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
10 embodiments, the compound of Formula (I) as described herein is Compound 192 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 194 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
15 embodiments, the compound of Formula (I) as described herein is Compound 212 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 213 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
20 embodiments, the compound of Formula (I) as described herein is Compound 239 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 254 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
25 embodiments, the compound of Formula (I) as described herein is Compound 263 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 288 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
30 embodiments, the compound of Formula (I) as described herein is Compound 291 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 313 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
35 embodiments, the compound of Formula (I) as described herein is Compound 321 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 331 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
embodiments, the compound of Formula (I) as described herein is Compound 341 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
embodiments, the compound of Formula (I) as described herein is Compound 342 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
embodiments, the compound of Formula (I) as described herein is Compound 343 of Table 1

[illegible]

In some embodiments, the compound of Formula (I) as described herein is Compound 48 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some

embodiments, the compound of Formula (I) as described herein is Compound 50 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 54 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
5 embodiments, the compound of Formula (I) as described herein is Compound 60b of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 61 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
10 embodiments, the compound of Formula (I) as described herein is Compound 63 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 75 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
15 embodiments, the compound of Formula (I) as described herein is Compound 83 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 97 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
20 embodiments, the compound of Formula (I) as described herein is Compound 101 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 127 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
25 embodiments, the compound of Formula (I) as described herein is Compound 135 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 140 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
30 embodiments, the compound of Formula (I) as described herein is Compound 141 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 143 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
embodiments, the compound of Formula (I) as described herein is Compound 144 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
35 embodiments, the compound of Formula (I) as described herein is Compound 146 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 147 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
embodiments, the compound of Formula (I) as described herein is Compound 149 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
embodiments, the compound of Formula (I) as described herein is Compound 163 of Table 1

[illegible]

embodiments, the compound of Formula (I) as described herein is Compound 279 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 281 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
5 embodiments, the compound of Formula (I) as described herein is Compound 306 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 314 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
10 embodiments, the compound of Formula (I) as described herein is Compound 322 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 338 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
15 embodiments, the compound of Formula (I) as described herein is Compound 339 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 340 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
20 embodiments, the compound of Formula (I) as described herein is Compound 345 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 353 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
25 embodiments, the compound of Formula (I) as described herein is Compound 391 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 393 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
30 embodiments, the compound of Formula (I) as described herein is Compound 397 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 402 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
35 embodiments, the compound of Formula (I) as described herein is Compound 428 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 430 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some
embodiments, the compound of Formula (I) as described herein is Compound 431 of Table 1

above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 434 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 446 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 447 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 450 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 463 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 465 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 466 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 489 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 512 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 514 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 515 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof. In some embodiments, the compound of Formula (I) as described herein is Compound 524 of Table 1 above, or is any pharmaceutically acceptable salt, solvate, or prodrug thereof.

Pharmaceutical combinations

The present application relates to pharmaceutical combinations comprising a thiophene fused cyclohexanone derivative ASIC inhibitor, which is a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a cyclooxygenase (COX) inhibitor. In some embodiments, the pharmaceutical combinations can further include pharmaceutically acceptable carriers, diluents, or excipients, as will be detailed below.

The term "ASICs inhibitor" as used herein means a compound that can inhibit acid-sensing ion channels, such as the acid-sensing ion channel 1a (ASIC1a) or the acid-sensing ion channel 1b (ASIC1b).

A "cyclooxygenase (COX) inhibitor" as used in the pharmaceutical combinations of the present application, refers to a drug enabling inhibition of COX enzymes, such as COX-1 and COX-2 enzymes, for instance. In some embodiments, the COX inhibitor can affect both COX-1 and COX-2 enzymes. However, in some embodiments, the COX inhibitor can primarily affect the COX-2 enzyme or the COX-1 enzyme. In some embodiments, the COX inhibitor can comprise an NSAID, which can be highly selective for the COX-2 enzyme, such as coxibs or can be non-selective and affect both COX-1 and COX-2 enzymes, such as ibuprofen. In other embodiments, the COX inhibitor can be acetaminophen.

In some embodiments, the pharmaceutical combinations of the present disclosure can include an NSAID which can be Bromfenac, Celecoxib, Diclofenac, Etodolac, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Mefenamic acid, Meloxicam, Nabumetone, Naproxen, Nepafenac, Piroxicam, Sulindac, Tenoxicam, Tiaprofenic acid, Diflunisal, Etoricoxib, Fenoprofen, Floctafenine, Lumiracoxib, Oxaprozin, Parecoxib, Rofecoxib, Tolmetin, Valdecoxib, Meclofenamic acid, Dexketoprofen, Licoferone, Lornoxicam, Loxoprofen, Nimesulide, Tolfenamic acid, Phenylbutazone, Firocoxib, Salsalate, Choline Magnesium Trisalicylate, Acetylsalicylic acid, any pharmaceutically acceptable salt thereof, or any combination thereof.

Due to their COX-1 inhibition effect, certain NSAIDs can cause side effects such as bleeding and gastrointestinal irritation for instance. Side effects tend to be more common at high doses for a long time. Accordingly, NSAIDs are often co-administered with proton-pump inhibitors (PPIs) to reduce NSAID-induced gastrointestinal (GI) adverse events. Hence, in some embodiments, the pharmaceutical combinations of the present disclosure can further include a proton-pump inhibitor (PPI). However, in other embodiments, one can achieve pain reduction using a combination of the ASIC inhibitor of Formula (I) and the NSAID, in which the dosage of NSAID can be reduced, thanks to the pain reduction potency of the ASIC inhibitor. Then, the use of a PPI can be avoided or at least the PPI can be used in more limited dosage, thus eliminating or at least reducing side effects associated with NSAIDs.

In some embodiments, the pharmaceutical combinations of the present disclosure can include preferably, an NSAID selected from Naproxen, Celecoxib, Diclofenac, Ibuprofen, a pharmaceutically acceptable salt thereof, or any combination thereof.

In some embodiments, the pharmaceutical combinations of the present disclosure can be synergistic. In other words, the therapeutically active compounds, namely the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, can produce a therapeutic effect that is more than the sum of their individual therapeutic effects. In some embodiments, thanks to the synergy that can be observed between the two therapeutically active compounds, lower doses of at least one of the therapeutically active ingredients, preferably both, can be used. In some embodiments, this can provide

combination therapies that are much safer than the corresponding monotherapies.

In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is an NSAID.

- 5 In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is an NSAID selected from Bromfenac, Celecoxib, Diclofenac, Etodolac, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Mefenamic acid, Meloxicam, Nabumetone, Naproxen, Nepafenac, Piroxicam, Sulindac, Tenoxicam, Tiaprofenic
10 acid, Diflunisal, Etoricoxib, Fenoprofen, Floctafenine, Lumiracoxib, Oxaprozin, Parecoxib, Rofecoxib, Tolmetin, Valdecoxib, Meclofenamic acid, Dexketoprofen, Licofelone, Lornoxicam, Loxoprofen, Nimesulide, Tolfenamic acid, Phenylbutazone, Firocoxib, Salsalate, Choline Magnesium Trisalicylate, Acetylsalicylic acid, any pharmaceutically acceptable salt thereof, and any combination thereof.
- 15 In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is an NSAID selected from Naproxen, Celecoxib, Diclofenac, Ibuprofen, a pharmaceutically acceptable salt thereof, or any combination thereof.

- In some embodiments, a synergistic pharmaceutical combination can comprise a compound of
20 Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Bromfenac or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Etodolac or a pharmaceutically acceptable salt thereof. In some embodiments, a
25 synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Flurbiprofen or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor
30 which is Indomethacin or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Ketoprofen or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the
35 pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Ketorolac or a pharmaceutically acceptable salt thereof. In some embodiments, a

synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Mefenamic acid or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Meloxicam or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Nabumetone or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Nepafenac or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Piroxicam or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Sulindac or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Tenoxicam or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Tiaprofenic acid or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Diflunisal or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Etoricoxib or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Fenoprofen or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Floctafenine or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the

pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Lumiracoxib or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor

5 which is Oxaprozin or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Parecoxib or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the

10 pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Rofecoxib or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Tolmetin or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the

15 pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Valdecoxib or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Meclofenamic acid or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the

20 pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Dexketoprofen or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Licofelone or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the

25 pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Lornoxicam or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Loxoprofen or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the

30 pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Nimesulide or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor

35

which is Tolfenamic acid or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Phenylbutazone or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Firocoxib or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Salsalate or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Choline Magnesium Trisalicylate or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Acetylsalicylic acid or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Naproxen or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Celecoxib or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Diclofenac or a pharmaceutically acceptable salt thereof. In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is Ibuprofen or a pharmaceutically acceptable salt thereof.

In some embodiments, a synergistic pharmaceutical combination can comprise a compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, and a COX inhibitor which is acetaminophen.

In some embodiments, the pharmaceutical combination of the present disclosure can comprise the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, in a single dosage form. Single dosage form refers to a mixture of the therapeutically active ingredients, namely the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, that are packaged in a single dosage

form. For example, and without being limiting to, a dosage form can include a pill, a tablet, a capsule, a drink or a syrup.

In other embodiments, the pharmaceutical combination of the present disclosure can comprise the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, each being in an individual dosage form.

In some embodiments, the pharmaceutical combination can comprise the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, each in an amount ranging from about 1 mg to about 1000 mg. In other words, the pharmaceutical combination can comprise from about 1 mg to about 1000 mg of the COX inhibitor and from about 1 mg to about 1000 mg of the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments, the pharmaceutical combination can comprise the COX inhibitor in an amount of from about 1 mg to about 900 mg, or from about 1 mg to about 800 mg, or from about 1 mg to about 700 mg, or from about 1 mg to about 600 mg, or from about 1 mg to about 500 mg, or from about 1 mg to about 400 mg, or from about 1 mg to about 300 mg, or from about 1 mg to about 200 mg, or from about 1 mg to about 100 mg, or from about 1 mg to about 50 mg, or any range value in between these ranges. In some embodiments, the pharmaceutical combination can comprise the COX inhibitor in an amount of about 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 3.5 mg, 4 mg, 4.5 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 9.5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 125 mg, 150 mg, 200 mg, 250 mg, 275 mg, 300 mg, 350 mg, 375 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, or any value in between these values.

In some embodiments, the pharmaceutical combination can comprise the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, in an amount of from about 1 mg to about 900 mg, or from about 1 mg to about 800 mg, or from about 1 mg to about 700 mg, or from about 1 mg to about 600 mg, or from about 1 mg to about 500 mg, or from about 1 mg to about 400 mg, or from about 1 mg to about 300 mg, or from about 1 mg to about 200 mg, or from about 1 mg to about 100 mg, or from about 1 mg to about 50 mg, or any range value in between these ranges. In some embodiments, the pharmaceutical combination can comprise the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, in an amount of about 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 3.5 mg, 4 mg, 4.5 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 9.5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 125 mg, 150 mg, 200 mg, 250 mg, 275 mg, 300 mg, 350 mg, 375 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, or any value in between

these values.

In some embodiments, the pharmaceutical combination can comprise the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, in a ratio COX inhibitor to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, of from 1:0.1 to 1:10 by weight. In some embodiments, the ratio COX inhibitor to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, can be from 1:0.1 to 1:9 by weight, or from 1:0.1 to 1:8 by weight, or from 1:0.1 to 1:7 by weight, or from 1:0.1 to 1:6 by weight, or from 1:0.1 to 1:5 by weight, or from 1:0.1 to 1:4 by weight, or from 1:0.1 to 1:3 by weight, or from 1:0.1 to 1:2 by weight, or from 1:0.1 to 1:1 by weight. In some embodiments, the ratio COX inhibitor to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, can be from 1:0.1 to 1:1 by weight, or from 1:0.1 to 1:0.9 by weight, or from 1:0.1 to 1:0.8 by weight, or from 1:0.1 to 1:0.7 by weight, or from 1:0.1 to 1:0.6 by weight, or from 1:0.1 to 1:0.5 by weight, or from 1:0.1 to 1:0.4 by weight, or from 1:0.1 to 1:0.3 by weight, or from 1:0.1 to 1:0.2 by weight. In some embodiments, the ratio COX inhibitor to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, can be from 1:0.1 to 1:1 by weight, or from 1:0.2 to 1:1 by weight, or from 1:0.3 to 1:1 by weight, or from 1:0.4 to 1:1 by weight, or from 1:0.5 to 1:1 by weight, or from 1:0.6 to 1:1 by weight, or from 1:0.7 to 1:1 by weight, or from 1:0.8 to 1:1 by weight, or from 1:0.9 to 1:1 by weight. In some embodiments, the ratio COX inhibitor to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, can be from 1:1 to 1:2 by weight, or from 1:1 to 1:1.9 by weight, or from 1:1 to 1:1.8 by weight, or from 1:1 to 1:1.7 by weight, or from 1:1 to 1:1.6 by weight, or from 1:1 to 1:1.5 by weight, or from 1:1 to 1:1.4 by weight, or from 1:1 to 1:1.3 by weight, or from 1:1 to 1:1.2 by weight, or from 1:1 to 1:1.1 by weight.

In some embodiments, the pharmaceutical combination can comprise the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, in a ratio COX inhibitor to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, of from 1:0.1 to 1:2 by weight. In some embodiments, the pharmaceutical combination can comprise the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, in a ratio COX inhibitor to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, of from 1:0.1 to 1:1 by weight.

In some embodiments, the pharmaceutical combination can comprise the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, in a ratio COX inhibitor to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, of from about 1:0.2 to about 1:1 by weight, or from about 1:0.18 to about 1:1 by weight, or from about 1:0.2 to about 1:0.83 by weight, or from about 1:0.18 to about 1:0.83 by weight.

weight.

In some embodiments, the pharmaceutical combination can comprise the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof in a ratio by weight of COX inhibitor to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof that results in a synergistic pharmaceutical combination. In some
5 embodiments, the pharmaceutical combination can be synergistic and can comprise the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, in a ratio COX inhibitor to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, of from 1:0.1 to 1:10 by weight. In some embodiments, the
10 synergistic pharmaceutical combination can have a ratio COX inhibitor to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, ranging from 1:0.1 to 1:9 by weight, or from 1:0.1 to 1:8 by weight, or from 1:0.1 to 1:7 by weight, or from 1:0.1 to 1:6 by weight, or from 1:0.1 to 1:5 by weight, or from 1:0.1 to 1:4 by weight, or from 1:0.1 to 1:3 by weight, or from 1:0.1 to 1:2 by weight, or from 1:0.1 to 1:1 by weight. In some embodiments, the synergistic
15 pharmaceutical combination can have a ratio COX inhibitor to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, ranging from 1:0.1 to 1:1 by weight, or from 1:0.1 to 1:0.9 by weight, or from 1:0.1 to 1:0.8 by weight, or from 1:0.1 to 1:0.7 by weight, or from 1:0.1 to 1:0.6 by weight, or from 1:0.1 to 1:0.5 by weight, or from 1:0.1 to 1:0.4 by weight, or from 1:0.1 to 1:0.3 by weight, or from 1:0.1 to 1:0.2 by weight. In some embodiments, the synergistic
20 pharmaceutical combination can have a ratio COX inhibitor to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, ranging from 1:0.1 to 1:1 by weight, or from 1:0.2 to 1:1 by weight, or from 1:0.3 to 1:1 by weight, or from 1:0.4 to 1:1 by weight, or from 1:0.5 to 1:1 by weight, or from 1:0.6 to 1:1 by weight, or from 1:0.7 to 1:1 by weight, or from 1:0.8 to 1:1 by weight, or from 1:0.9 to 1:1 by weight. In some embodiments, the synergistic
25 pharmaceutical combination can have a ratio COX inhibitor to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, ranging from 1:1 to 1:2 by weight, or from 1:1 to 1:1.9 by weight, or from 1:1 to 1:1.8 by weight, or from 1:1 to 1:1.7 by weight, or from 1:1 to 1:1.6 by weight, or from 1:1 to 1:1.5 by weight, or from 1:1 to 1:1.4 by weight, or from 1:1 to 1:1.3 by weight, or from 1:1 to 1:1.2 by weight, or from 1:1 to 1:1.1 by weight.

In some embodiments, the pharmaceutical combination can be synergistic and can comprise the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, in a ratio COX inhibitor to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, of from 1:0.1 to 1:2 by weight. In some embodiments, the
30 pharmaceutical combination can be synergistic and can comprise the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, in a
35 ratio COX inhibitor to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or

prodrug thereof, of from 1:0.1 to 1:1 by weight.

In some embodiments, the pharmaceutical combination can be synergistic and can comprise the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, in a ratio COX inhibitor to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, of from about 1:0.2 to about 1:1 by weight, or from about 1:0.18 to about 1:1 by weight, or from about 1:0.2 to about 1:0.83 by weight, or from about 1:0.18 to about 1:0.83 by weight.

In some embodiments, the pharmaceutical combination can comprise an NSAID as the COX inhibitor, and a ratio of the NSAID to the compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, can be of from 1:0.1 to 1:10 by weight. In some embodiments, the ratio NSAID to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, can be from 1:0.1 to 1:9 by weight, or from 1:0.1 to 1:8 by weight, or from 1:0.1 to 1:7 by weight, or from 1:0.1 to 1:6 by weight, or from 1:0.1 to 1:5 by weight, or from 1:0.1 to 1:4 by weight, or from 1:0.1 to 1:3 by weight, or from 1:0.1 to 1:2 by weight, or from 1:0.1 to 1:1 by weight. In some embodiments, the ratio NSAID to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, can be from 1:0.1 to 1:1 by weight, or from 1:0.1 to 1:0.9 by weight, or from 1:0.1 to 1:0.8 by weight, or from 1:0.1 to 1:0.7 by weight, or from 1:0.1 to 1:0.6 by weight, or from 1:0.1 to 1:0.5 by weight, or from 1:0.1 to 1:0.4 by weight, or from 1:0.1 to 1:0.3 by weight, or from 1:0.1 to 1:0.2 by weight. In some embodiments, the ratio NSAID to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, can be from 1:0.1 to 1:1 by weight, or from 1:0.2 to 1:1 by weight, or from 1:0.3 to 1:1 by weight, or from 1:0.4 to 1:1 by weight, or from 1:0.5 to 1:1 by weight, or from 1:0.6 to 1:1 by weight, or from 1:0.7 to 1:1 by weight, or from 1:0.8 to 1:1 by weight, or from 1:0.9 to 1:1 by weight. In some embodiments, the ratio NSAID to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, can be from 1:1 to 1:2 by weight, or from 1:1 to 1:1.9 by weight, or from 1:1 to 1:1.8 by weight, or from 1:1 to 1:1.7 by weight, or from 1:1 to 1:1.6 by weight, or from 1:1 to 1:1.5 by weight, or from 1:1 to 1:1.4 by weight, or from 1:1 to 1:1.3 by weight, or from 1:1 to 1:1.2 by weight, or from 1:1 to 1:1.1 by weight.

In some embodiments, the pharmaceutical combination can comprise an NSAID as the COX inhibitor, and a ratio of the NSAID to the compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, can be of from 1:0.1 to 1:2 by weight. In some embodiments, the pharmaceutical combination can comprise an NSAID as the COX inhibitor, and a ratio of the NSAID to the compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, can be of from 1:0.1 to 1:1 by weight.

In some embodiments, the pharmaceutical combination can comprise an NSAID as the COX inhibitor, and a ratio of the NSAID to the compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, can be of from about 1:0.2 to about 1:1 by weight, or from about

1:0.18 to about 1:1 by weight, or from about 1:0.2 to about 1:0.83 by weight, or from about 1:0.18 to about 1:0.83 by weight.

In some embodiments, the pharmaceutical combination can comprise an NSAID as the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof are provided in a ratio by weight of NSAID to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof that results in a synergistic pharmaceutical combination. In some embodiments, the pharmaceutical combination can be synergistic and comprise an NSAID as the COX inhibitor, and a ratio of the NSAID to the compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, can be of from 1:0.1 to 1:10 by weight. In some embodiments, the synergistic pharmaceutical combination can have a ratio NSAID to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, ranging from 1:0.1 to 1:9 by weight, or from 1:0.1 to 1:8 by weight, or from 1:0.1 to 1:7 by weight, or from 1:0.1 to 1:6 by weight, or from 1:0.1 to 1:5 by weight, or from 1:0.1 to 1:4 by weight, or from 1:0.1 to 1:3 by weight, or from 1:0.1 to 1:2 by weight, or from 1:0.1 to 1:1 by weight. In some embodiments, the synergistic pharmaceutical combination can have a ratio NSAID to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, ranging from 1:0.1 to 1:1 by weight, or from 1:0.1 to 1:0.9 by weight, or from 1:0.1 to 1:0.8 by weight, or from 1:0.1 to 1:0.7 by weight, or from 1:0.1 to 1:0.6 by weight, or from 1:0.1 to 1:0.5 by weight, or from 1:0.1 to 1:0.4 by weight, or from 1:0.1 to 1:0.3 by weight, or from 1:0.1 to 1:0.2 by weight. In some embodiments, the synergistic pharmaceutical combination can have a ratio NSAID to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, ranging from 1:0.1 to 1:1 by weight, or from 1:0.2 to 1:1 by weight, or from 1:0.3 to 1:1 by weight, or from 1:0.4 to 1:1 by weight, or from 1:0.5 to 1:1 by weight, or from 1:0.6 to 1:1 by weight, or from 1:0.7 to 1:1 by weight, or from 1:0.8 to 1:1 by weight, or from 1:0.9 to 1:1 by weight. In some embodiments, the synergistic pharmaceutical combination can have a ratio NSAID to compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, ranging from 1:1 to 1:2 by weight, or from 1:1 to 1:1.9 by weight, or from 1:1 to 1:1.8 by weight, or from 1:1 to 1:1.7 by weight, or from 1:1 to 1:1.6 by weight, or from 1:1 to 1:1.5 by weight, or from 1:1 to 1:1.4 by weight, or from 1:1 to 1:1.3 by weight, or from 1:1 to 1:1.2 by weight, or from 1:1 to 1:1.1 by weight.

In some embodiments, the pharmaceutical combination can be synergistic and comprise an NSAID as the COX inhibitor, and a ratio of the NSAID to the compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, can be of from 1:0.1 to 1:2 by weight. In some embodiments, the pharmaceutical combination can be synergistic and comprise an NSAID as the COX inhibitor, and a ratio of the NSAID to the compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, can be of from 1:0.1 to 1:1 by weight.

In some embodiments, the pharmaceutical combination can be synergistic and comprise an NSAID

as the COX inhibitor, and a ratio of the NSAID to the compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, can be of from about 1:0.2 to about 1:1 by weight, or from about 1:0.18 to about 1:1 by weight, or from about 1:0.2 to about 1:0.83 by weight, or from about 1:0.18 to about 1:0.83 by weight.

- 5 The above-mentioned dosages and ratios are provided as examples, and one could adapt the dosages and/or ratios of the COX inhibitor and compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, for achieving a suitable treatment such as proper pain relief.

Methods, uses, formulations, kits and administration

- 10 The pharmaceutical combinations of the present disclosure, comprising a COX inhibitor and a thiophene fused cyclohexanone derivative, i.e., a compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, can be useful for the treatment of disorders or conditions including pain. In some embodiments, the treatment can involve using, or can be potentiated by using, a pharmaceutical combination of the present disclosure which can be
15 synergistic.

In certain embodiments, the present description thus provides a method for treating pain, comprising administering to a patient or subject identified as in need thereof, a COX inhibitor and a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, as disclosed herein. In some embodiments, the method for treating pain can comprise administering
20 to a patient or subject identified as in need thereof, an effective amount of the COX inhibitor and of the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein the administration results in a synergistic effect thereof.

The identification of those patients who are in need of treatment for the disorders described herein is well within the ability and knowledge of one skilled in the art. Certain of the methods for
25 identification of patients which are at risk of developing the above disorders which can be treated by the subject method are appreciated in the medical arts, such as family history, and the presence of risk factors associated with the development of that disorder state in the subject patient. A clinician skilled in the art can readily identify such candidate patients, by the use of, for example, clinical tests, physical examination and medical/family history.

- 30 As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, one can also refer to "therapeutically effective amount" which means any amount which, as compared to a corresponding subject who has not received such amount, results in treatment, healing, prevention, or amelioration of a
35 disorder, disorder, or side effect, or a decrease in the rate of advancement of a disorder or disorder.

The term also includes within its scope amounts that are effective to enhance normal physiological function.

As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disorder or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

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

The expression "pharmaceutically acceptable carrier, diluent, or excipient" and equivalent expressions, refer to a non-toxic carrier, diluent, or excipient that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, diluents or excipients that may be used in the compositions of this disclosure include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

In certain embodiments, as mentioned above, the disorders or conditions that can be treated using the pharmaceutical combination comprising the COX inhibitor and the thiophene fused cyclohexanone derivative, i.e., the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein, can include pain.

In some embodiments, the pain can include acute pain or chronic pain. In some embodiments, the pain can include inflammatory pain, neuropathic pain or cancer pain. In some embodiments, the pain can include nociceptive pain, inflammatory pain, neuropathic pain, cancer pain, idiopathic pain, musculoskeletal pain, visceral pain, or abdominal pain. In some embodiments, the pain can include inflammatory pain. In another embodiment, the pain can include neuropathic pain. In yet another embodiment, the pain can include cancer pain.

In some embodiments, the pain can include arthritis pain, pain associated with musculoskeletal trauma or soft tissue trauma, post-operative pain, dental pain, dysmenorrhea pain, episiotomy pain, endometriosis pain, post-partum pain, headache pain, ocular pain, bursitis pain, tendinitis pain, tenosynovitis pain, or polymyalgia rheumatica pain. In some embodiments, the pain can include

5 arthritis pain, pain associated with musculoskeletal trauma or soft tissue trauma, post-operative pain, dental pain, dysmenorrhea pain, episiotomy pain, endometriosis pain, post-partum pain, headache pain, ocular pain, bursitis pain, or tendinitis pain.

In some embodiments, the pain can include a rheumatic disorder-related pain.

In certain embodiments, the pain can include arthritis pain. In some embodiments, the pain can

10 include adult arthritis pain or juvenile arthritis pain. In certain embodiments, the pain can include adult arthritis pain. In some embodiments, the pain can include juvenile arthritis pain.

In some embodiments, the pain can include osteoarthritis pain, rheumatoid arthritis pain, ankylosing spondylitis pain, gout pain, psoriatic arthritis pain, or peri-arthritis pain. In certain embodiments, the pain can include osteoarthritis pain, rheumatoid arthritis pain, ankylosing spondylitis pain, gout pain,

15 or peri-arthritis pain.

In some embodiments, the pain can include osteoarthritis pain. In certain embodiments, the pain can include osteoarthritis inflammatory pain. In some embodiments, the pain can include osteoarthritis pain of the hip, osteoarthritis pain of the knee, osteoarthritis pain of the spine, osteoarthritis pain of the shoulder, osteoarthritis pain of the hand, osteoarthritis pain of the finger,

20 osteoarthritis pain of the thumb, osteoarthritis pain of the foot, or osteoarthritis pain of the toe.

In some embodiments, the pain can include rheumatoid arthritis pain. In certain embodiments, the pain can include adult rheumatoid arthritis pain or juvenile rheumatoid arthritis pain. In some embodiments, the pain can include adult rheumatoid arthritis pain. In certain embodiments, the pain can include juvenile rheumatoid arthritis pain. In certain embodiments, the pain can include

25 rheumatoid arthritis inflammatory pain. In some embodiments, the pain can include rheumatoid arthritis pain of the hand, rheumatoid arthritis pain of the finger, rheumatoid arthritis pain of the thumb, rheumatoid arthritis pain of the foot, rheumatoid arthritis pain of the toe, rheumatoid arthritis pain of the wrist, rheumatoid arthritis pain of the knee, rheumatoid arthritis pain of the ankle, rheumatoid arthritis pain of the elbow, rheumatoid arthritis pain of the hip, or rheumatoid arthritis

30 pain of the shoulder.

In certain embodiments, the pain can include ankylosing spondylitis pain.

In some embodiments, the pain can include gout pain. In some embodiments, the pain can include gout pain of the foot, gout pain of the toe, gout pain of the ankle, gout pain of the knee, or gout pain of the elbow. In certain embodiments, the pain can include gouty arthritis pain.

In certain embodiments, the pain can include psoriatic arthritis pain.

In certain embodiments, the pain can include bursitis pain. In some embodiments, the pain can include bursitis pain of the shoulder or bursitis pain of the hip.

5 In certain embodiment, the pain can include tendinitis pain. In some embodiments, the pain can include tendinitis pain of the shoulder, tendinitis pain of the elbow, tendinitis pain of the hip, tendinitis pain of the wrist, tendinitis pain of the knee, or tendinitis pain of the heel.

In some embodiments, the pain can include peri arthritis pain. In certain embodiments, the pain can include peri arthritis pain of the shoulder or peri arthritis pain of the hip.

10 In some embodiments, the pain can include pain associated with musculoskeletal trauma or soft tissue trauma including pain associated with a sprain, a strain, swelling or stiffness. In certain embodiments, the pain can include pain associated with musculoskeletal trauma or soft tissue trauma including pain associated with a sprain or a strain. In certain embodiments, the pain can include pain associated with musculoskeletal trauma or soft tissue trauma of the back, shoulder, or ankle. In certain embodiments, the pain can include myofascial pain syndrome. In other
15 embodiments, the pain can include exercise-induced pain, repetitive motion injury pain, or pain due to a bone fracture. In other embodiments, the pain can include temporomandibular joint disorder pain.

In certain embodiments, the pain can include ocular pain. In certain embodiments, the ocular pain can include post-operative pain after cataract surgery, post-operative pain after refractive surgery,
20 ocular pain from a non-penetrating wound, foreign body sensation ocular pain, burning or stinging of the eye, uveitis pain, iritis pain, retinopathy pain or optic neuritis pain.

In some embodiments, the pain can include dental pain. In certain embodiments, the dental pain can include toothache or post-operative pain after dental surgery. In some embodiments, the dental pain can include pain after dental extraction.

25 In certain embodiments, the pain can include post-operative pain. In some embodiments, the pain can include post-operative pain following minor surgery, post-operative pain following general surgery, post-operative pain following orthopaedic surgery, post-operative pain following bunionectomy, post-operative pain following hernioplasty, post-operative pain following herniorrhaphy, post-operative pain following arthroplasty including pain following knee arthroplasty
30 or pain following hip arthroplasty, post-operative pain following gynecological surgery, post-operative pain following caesarean section, post-mastectomy pain syndrome (PMPS), post-operative pain following abdominoplasty, post-operative pain following laminectomy, post-operative pain following hemorrhoid removal, or post-operative pain following thoracotomy.

In certain embodiments, the pain can include dysmenorrhea pain, episiotomy pain, endometriosis

pain, or post-partum pain. In certain embodiments, the pain can include dysmenorrhea pain, episiotomy pain, endometriosis pain, or post-partum cramping pain.

In some embodiments, the pain can include headache pain. In certain embodiments, the pain can include migraine pain, tension headache pain, or cluster headache pain. In some embodiments, the pain can include migraine pain including migraine with aura pain or migraine without aura pain.

In certain embodiments, the pain can include pain due to the common cold, pain due to the flu, sore throat pain, sinus pain including sinusitis pain, pain due to immunization, earache pain, fever pain, body pain, muscle pain, bone pain, joint pain, back pain, neck pain, or nighttime pain.

In some embodiments, the pain can include mucositis pain or stomatitis pain. In certain embodiments, the pain can include pain associated with lupus including lupus-related inflammatory pain.

In certain embodiments, the pain can include osteoarthritis neuropathic pain. In certain embodiments, the pain can include rheumatoid arthritis neuropathic pain.

In certain embodiments, the pain can include neuralgia. In some embodiments, that pain can include trigeminal neuralgia, postherpetic neuralgia, occipital neuralgia, post-surgical neuralgia, pudendal neuralgia, diabetic neuralgia, glossopharyngeal neuralgia, intercostal neuralgia, or drug therapy-induced neuralgia including cancer chemotherapy-induced neuralgia or anti-retroviral therapy-induced neuralgia.

In certain embodiments, the pain can include nerve injury pain, peripheral nerve injury pain, nerve compression pain, nerve avulsion injury pain, nerve entrapment injury pain, radiculopathy pain, brachial plexus injury pain, burning mouth syndrome pain, complex regional pain syndrome type 1, complex regional pain syndrome type 2, neuroma pain, Morton's neuroma pain, spinal cord injury pain, spinal cord compression pain, radicular pain, sciatica pain, spinal stenosis pain, cervical spine injury pain, brain injury pain, or post-stroke pain.

In some embodiments, the pain can include neuropathy pain. In certain embodiments, the pain can include peripheral neuropathy pain, polyneuropathy pain, mononeuropathy pain, multiple mononeuropathy pain, proximal neuropathy pain, sensory neuropathy pain, small fiber sensory neuropathy pain, idiopathic neuropathy pain, or distal sensory polyneuropathy pain. In certain embodiments, the pain can include diabetic neuropathy pain. In some embodiments, the pain can include diabetic peripheral neuropathy pain, diabetic polyneuropathy pain, diabetic proximal neuropathy pain, or diabetic mononeuropathy pain. In certain embodiments, the pain can include autoimmune disease neuropathy pain. In some embodiments, the pain can include Sjogren's syndrome neuropathy pain, Guillain-Barre syndrome neuropathy pain, chronic inflammatory demyelinating polyneuropathy pain, or vasculitis neuropathy pain. In some embodiments, the pain can include multiple sclerosis neuropathic pain. In certain embodiments, the pain can include

carpal tunnel syndrome pain. In certain embodiments, the pain can include neuropathy pain associated with a bacterial infection or neuropathy pain associated with a viral infection. In some embodiments, the pain can include Lyme disease neuropathy pain, Epstein-Barr virus neuropathy pain, hepatitis B virus neuropathy pain, hepatitis C virus neuropathy pain, leprosy neuropathy pain, diphtheria neuropathy pain, or human immunodeficiency virus (HIV) neuropathy pain including HIV distal symmetric polyneuropathy pain. In certain embodiments, the pain can include hereditary neuropathy pain. In some embodiments, the pain can include Charcot-Marie-Tooth disease neuropathy pain or hereditary neuropathy with pressure palsies (HNPP) pain. In certain embodiments, the pain can include neuropathy pain caused by a malignant tumor, neuropathy pain caused by a benign tumor, or paraneoplastic neuropathy pain. In some embodiments, the pain can include myeloma neuropathy pain, lymphoma neuropathy pain, or amyloid neuropathy pain. In certain embodiments, the pain can include liver disease neuropathy pain, uremic neuropathy pain, connective tissue disorder neuropathic pain, hypothyroidism neuropathy pain, alcohol use neuropathy pain, or vitamin deficiency neuropathy pain. In some embodiments, the pain can include vitamin B deficiency neuropathy pain including vitamin B1, niacin, vitamin B6, or vitamin B12 deficiency neuropathy pain, or vitamin E deficiency neuropathy pain. In certain embodiments, the pain can include toxic substance exposure neuropathy pain including neuropathy pain following lead exposure or neuropathy pain following mercury exposure. In certain embodiments, the pain can include anti-retroviral therapy-induced neuropathy pain or neurotoxic drug-induced neuropathic pain. In certain embodiments, the pain can include chemotherapy-induced neuropathy pain including platinum-based antineoplastic drug-induced neuropathic pain or chemotherapy-induced peripheral neuropathy (CIPN) pain, radiation therapy-induced pain including radiation therapy-induced neuropathy pain, cancer targeted therapy-induced neuropathy pain, or immunotherapy-induced neuropathy pain. In some embodiments, that pain can include central neuropathic pain. In certain embodiments, the pain can include central post-stroke pain, spinal cord injury-related central neuropathic pain, brain injury-related central neuropathic pain, or multiple sclerosis-related central neuropathic pain.

In certain embodiments, the pain can include cancer pain. In some embodiments, the pain can include bone cancer pain, breakthrough pain, cancer nociceptive pain, cancer neuropathy pain including neuropathy caused by a tumor pressing on a nerve.

In certain embodiments, the pain can include post-amputation pain. In some embodiments, the pain can include phantom pain, phantom limb pain, or residual limb pain.

In certain embodiments, the pain can include Paget's disease pain. In other embodiments, the pain can include pain associated with fibromyalgia. In certain embodiments, the pain can include pain associated with lupus including lupus-related inflammatory pain and lupus-related neuropathy pain. In some embodiments, the pain can include gastrointestinal motility disorder

pain, irritable bowel syndrome pain, Crohn's disease pain, ulcer-related pain, or ulcerative colitis pain. In other embodiments, the pain can include incontinence pain or interstitial cystitis pain. In certain embodiments, the pain can include herpes zoster pain. In certain embodiments, the pain can include angina-induced pain. In certain embodiments, the pain can include animal bite or
5 sting pain, or pain caused by a burn including pain caused by a first-degree, second-degree or third-degree burn.

In some embodiments, the pharmaceutical combination disclosed herein which comprises a therapeutically effective amount of at least one COX inhibitor and a therapeutically effective amount of at least one compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug
10 thereof, as defined herein, can be administered to a patient or subject, alone, or admixed with a pharmaceutically acceptable carrier, diluent, or excipient.

In some embodiments, the pharmaceutical combinations described herein are such that the COX inhibitor and the compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, are administered each in an individual dosage form. In other embodiments, the
15 pharmaceutical combinations described herein are such that the COX inhibitor and the compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, are administered together in a single dosage form.

In some embodiments, when the pharmaceutical combinations comprise separate individual dosage forms (or "single dosage form" or "single dose form" or "unit dose") of the COX inhibitor and
20 of the compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, each separate individual dosage form can be administered either simultaneously or sequentially. When administered sequentially, the individual dosage forms can be administered in any order.

Pharmaceutical combinations described herein may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, ophthalmically, intravaginally, or via an
25 implanted reservoir. Hence, in the present disclosure, the term "oral treatment" means a treatment that occurs by oral administration. In other words, an "oral treatment" refers to a treatment where the pharmaceutical combinations of the present disclosure are administered orally for the indicated treatment. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intraarticular, intrasynovial, intrasternal, intrathecal, intrahepatic, intralesional and
30 intracranial injection or infusion techniques. Other modes of administration also include intradermal or transdermal administration.

In some embodiments, the pharmaceutical combinations described herein are administered orally, i.e., via the oral cavity, including buccally.

Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically
35 acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the

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

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

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

In order to prolong the effect of a provided compound, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil carrier. Injectable depot forms are made by forming matrices of the compound microencapsulated in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled.

Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the therapeutically active compound in liposomes or microemulsions that are compatible with body tissues.

Formulations for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the therapeutically active compounds of the present description with suitable non-irritating

excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules.

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

Solid formulations of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The therapeutically active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets,
20 dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting
25 aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

30 Dosage forms for topical or transdermal administration of a compound of the present description include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of the present description. Additionally, the
35 description contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by

dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Pharmaceutical combinations provided herein may also be formulated for administration by nasal aerosol or inhalation using inhalants. Such formulations are prepared according to techniques well known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

Pharmaceutical combinations provided herein may be formulated for oral administration. Such formulations may be administered with or without food. In some embodiments, pharmaceutical combinations of this disclosure can be administered without food. In other embodiments, pharmaceutical combinations of this disclosure can be administered with food.

The amount of therapeutically active compounds that may be combined with carrier materials to produce a formulation in a single dosage form can vary depending upon the patient to be treated and the particular mode of administration. The amount of individual therapeutically active compound that may be combined with carrier materials to produce individual dosage forms can vary depending upon the patient to be treated and the particular mode of administration.

It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, the judgment of the treating physician, and the severity of the particular disorder being treated.

The pharmaceutical combinations described herein may be administered using any amount and any route of administration effective for treating or lessening the severity of the disorders or disorders as contemplated herein. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disorder or condition, the particular agent, its mode of administration, and the like. In some embodiments, the COX inhibitor and the compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof, can be formulated in unit dose for ease of administration and uniformity of dosage. The expression "unit dose" or "single dose form" as used herein refers to a physically discrete unit of therapeutically active agent(s) in an amount appropriate for the patient to be treated. In some embodiments, each unit dose form can include both the required amount of COX inhibitor and of the compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof. In other embodiments, separate unit doses can be prepared, a first unit dose including the required amount of COX inhibitor and a second unit dose including the required amount of the compound of Formula (I) or pharmaceutically acceptable salt, solvate, or prodrug thereof. It will be understood, however, that the total daily dosage of the therapeutically active compounds and/or combination

thereof will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts.

In certain embodiments, each one of the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, can be administered at dosage levels of from about 0.01 mg/kg to about 50 mg/kg, or from about 0.01 mg/kg to about 40 mg/kg, or from about 0.01 mg/kg to about 30 mg/kg, or from about 0.1 mg/kg to about 50 mg/kg, or from about 0.1 mg/kg to about 40 mg/kg, or from about 0.1 mg/kg to about 30 mg/kg, or from about 0.1 mg/kg to about 20 mg/kg, or from about 0.1 mg/kg to about 10 mg/kg of subject body weight, one or more times a day, to obtain the desired therapeutic effect.

In certain embodiments, the COX inhibitor can be administered at dosage levels of from about 0.1 mg/kg to about 50 mg/kg, or from about 0.1 mg/kg to about 40 mg/kg, or from about 0.1 mg/kg to about 30 mg/kg, or from about 0.1 mg/kg to about 20 mg/kg, or from about 0.1 mg/kg to about 10 mg/kg of subject body weight, one or more times a day. In some preferred embodiments, the COX inhibitor can be administered at dosage levels of from about 0.1 to about 20 mg/kg.

In certain embodiments, the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, can be administered at dosage levels of from about 0.1 mg/kg to about 50 mg/kg, or from about 0.1 mg/kg to about 40 mg/kg, or from about 0.1 mg/kg to about 30 mg/kg, or from about 0.1 mg/kg to about 20 mg/kg, or from about 0.1 mg/kg to about 10 mg/kg of subject body weight, one or more times a day. In some preferred embodiments, the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, can be administered at dosage levels of from about 0.1 to about 30 mg/kg, or from about 0.1 mg/kg to about 20 mg/kg, or from about 0.1 mg/kg to about 15 mg/kg.

In certain embodiments, the COX inhibitor can be administered at dosage levels of from about 0.1 to about 20 mg/kg and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, can be administered at dosage levels of from about 0.1 to about 30 mg/kg.

In certain embodiments, the COX inhibitor can be administered at dosage levels of from about 0.1 to about 20 mg/kg and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, can be administered at dosage levels of from about 0.1 mg/kg to about 20 mg/kg.

In certain embodiments, the COX inhibitor can be administered at dosage levels of from about 0.1 to about 20 mg/kg and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate,

or prodrug thereof, can be administered at dosage levels of from about 0.1 mg/kg to about 15 mg/kg.

In some embodiments, the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, are administered in a single dosage form. In other embodiments, the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, are administered each in an individual dosage form. In some embodiments, the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, are administered simultaneously or sequentially. In some embodiments, the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, are administered simultaneously. In some embodiments, the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, are administered sequentially. It is to be noted that when the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, are administered sequentially, they can be administered in any order. Hence, the COX inhibitor can be administered first and then the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof can be administered. Alternatively, the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof can be administered first and the COX inhibitor in second.

Upon improvement of a subject's condition, a maintenance dose of the pharmaceutical combination of the present description may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. The subject may, however, require intermittent treatment on a long-term basis upon any recurrence of disorder symptoms.

The total daily inhibitory dose of the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof as defined herein, administered to a subject in single or in divided doses, can be in amounts, for example, from 0.01 to 50 mg/kg body weight, or more usually from 0.1 to 30 mg/kg body weight. Single dose formulations may contain such amounts or submultiples thereof to make up the daily dose. In some embodiments, treatment regimens according to the present description can comprise administration to a patient in need of such treatment of from about 1 mg to about 1000 mg per day in single or multiple doses, of the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof.

The pharmaceutical combinations described herein may be commercialized in the form of a kit. The kit can comprise at least one single dose form of the COX inhibitor (also referred to as "first single dose form of the COX inhibitor") and at least one single dose form of the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined herein (also referred

to as “second single dose form of the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof”). It should be noted that the terms “first” and “second” with reference to the single dose forms of each active ingredient, are used to differentiate the single dose forms and do not relate to any order for using/administering these dose forms. In fact, each of
5 the first and second single dose forms can be administered in any order or even simultaneously.

The kit can thus comprise separate dose forms (dose units) of the COX inhibitor and of the compound having the Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof. Each separate dose can include the same amount of the therapeutically active ingredients or different amounts thereof. In some embodiments, the kit can be tailored for a specific patient by
10 selecting suitable amounts of each therapeutically active ingredient. The kit generally also includes instructions for its proper use by a patient.

In some embodiments, the kit is such that the first single dose form can include the COX inhibitor in any amount as described above with respect to the pharmaceutical combinations. In some embodiments, the kit is such that the second single dose form can include the compound of Formula
15 (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof in any amount as described above with respect to the pharmaceutical combinations.

In some embodiments, the kit is such that the amount of the COX inhibitor in the first single dose form and the amount of the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof in the second single dose form, provide a ratio of the COX inhibitor to
20 the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as described above with respect to the pharmaceutical combinations.

In some embodiments, the kit can include a first single dose form of the COX inhibitor and a second single dose form of the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, and is useful for the treatment of a patient suffering from pain, such as any of
25 the pain disclosed in the present disclosure. In some embodiments, the use of the kit, can result in a synergistic effect of the COX inhibitor and of the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, in alleviating pain.

EXAMPLES

General Methods

Preparation of the thiophene fused cyclohexanone derivative compounds

Reagent grade chemicals and anhydrous solvents were purchased from commercial sources and, unless otherwise mentioned, were used without further purification. The names of the products were determined using the naming software included in ChemDraw (PerkinElmer). Where it is stated that compounds were prepared analogously to earlier examples or intermediates, reaction time, number of equivalents of reagents, temperature, work-up and purification techniques may differ slightly from the described example.

Purifications

Chromatographic separations were performed on:

- Teledyne ISCO CombiFlash flash chromatography systems, using pre-packaged SiO₂ or C₁₈ columns.
- Teledyne ISCO ACCQPrep high pressure preparative liquid chromatography system; Column: Gemini 5 μ m C18 110 Å, 150 x 30 mm.
- Biotage Isolera flash chromatography systems, using pre-packaged SiO₂ or C₁₈ columns.
- Waters Mass Trigger Semi-Prep HPLC; Column: Gemini 5 μ m NX-C18 110 Å, 100 x 30 mm.

Chiral separations were performed on:

- Mettler Toledo Berger Minigram supercritical fluid chromatography; Column: ChiralPak IG, 20 x 250 mm or ChiralPak IG, 10 x 250 mm.
- Waters ACQUITY UPC2 supercritical fluid chromatography; Column: ChiralPak IG, 10 x 250 mm.

Analytical Methods

LC-MS were performed on:

- Waters UPLC-MS; Column: Acquity UPLC, CSH C18, 1.7 μ m, 2.1 x 30 mm; Methods: from 5% to 95% of CH₃CN in H₂O with 0.1% (v/v) formic acid in 2 min or from 5% to 95% of CH₃CN in 10 mM ammonium bicarbonate in 2 min.
- Agilent HPLC-MS; Column: Kinetex EVO C18 100 Å 2.6 μ m, 50 x 3 mm; Method: from 10% to 95% of CH₃CN with 0.1% (v/v) formic acid in H₂O with 0.1% (v/v) formic acid in 4.5 min.
- Agilent UPLC-MS; Column: Kinetex EVO C18 100 Å 1.7 μ m, 50 x 3 mm; Method: from 5% to 95% of CH₃CN with 0.1% (v/v) formic acid in H₂O with 0.1% (v/v) formic acid in 3 min.

Analytical SFC were performed on Waters ACQUITY UPC2; Column: ChiralPak IG 4.6 x 250 mm or ChiralPak IC 4.6 x 150 mm.

NMR spectroscopy was carried out using a Varian NMR (AS 400) 400 MHz Spectrometer with Inova interface. In all cases, NMR data were consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million using conventional abbreviations for designation of peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; etc.

Abbreviations

	9-BBN	9-Borabicyclo[3.3.1]nonane
	δ	Chemical shift
	Å	Angström
10	Ac	Acetyl
	Bn	Benzyl
	Boc	<i>tert</i> -Butoxycarbonyl
	bs	"Broad singlet"
	Bu	Butyl
15	Calcd	Calculated
	d	Doublet
	DAST	Diethylaminosulfur trifluoride
	dd	Doublet of doublets
	dt	Doublet of triplets
20	DCM	Dichloromethane
	DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
	DIBALH	Diisobutylaluminium hydride
	DIPEA	<i>N,N</i> -Diisopropylethylamine
	DMAP	4-Dimethylaminopyridine
25	DMF	<i>N,N</i> -Dimethylformamide
	DMP	Dess-Martin periodinane
	DMPU	<i>N,N'</i> -Dimethylpropyleneurea
	DMSO	Dimethylsulfoxide
	Dppf	1,1'-Bis(diphenylphosphino)ferrocene
30	EA	Ethyl acetate
	ee	Enantiomeric excess
	Et	Ethyl
	EtOH	Ethanol
	eq	Equivalents
35	g	Gram
	HATU	Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium
	Hz	Hertz

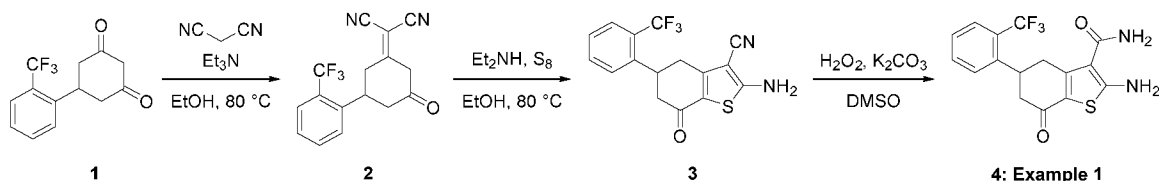
	HPLC	High performance liquid chromatography
	<i>i</i> -Pr	Isopropyl
	<i>J</i>	Coupling constant
	L	Liter
5	LC-MS	Liquid chromatography-mass spectrometry
	LDA	Lithium diisopropylamide
	LHMDS	Lithium bis(trimethylsilyl)amide
	M	Molar
	m	Multiplet
10	mCPBA	<i>meta</i> -chloroperoxybenzoic acid
	Me	Methyl
	MeOH	Methanol
	mg	Milligram
	MHz	Megahertz
15	min	Minutes
	mL	Milliliter
	mm	Millimeter
	mmol	Millimole
	mol	Mole
20	MS	Mass spectrometry
	N	Normal
	NBS	<i>N</i> -bromosuccinimide
	PCC	Pyridinium chlorochromate
	pH	Potential of hydrogen
25	Ph	Phenyl
	PPh ₃	Triphenylphosphine
	ppm	Parts per million
	PyBOP	Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
	q	Quadruplet
30	RT	Room temperature
	rt	Retention time
	NMR	Nuclear magnetic resonance
	s	Singulet
	sat	Saturated
35	SFC	Supercritical fluid chromatography
	sxt	sextuplet
	<i>t</i>	<i>tert</i>

	t	Triplet
	tt	Triplet of triplet
	<i>t</i> -Bu	<i>tert</i> -Butyl
	TMS	Trimethylsilyl
5	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran
	Ts	Tosyl
	uL	Microliter
	umol	Micromole
10	v/v	Volume/volume
	°	Degree
	%	Percentage

Example 1

2-Amino-7-oxo-5-(2-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (4)

Scheme 1



Step 1. 2-(3-Oxo-5-(2-(trifluoromethyl)phenyl)cyclohexylidene)malononitrile (2)

A solution of malononitrile (100 mg, 1.51 mmol, recrystallized from EtOH), triethylamine (253 uL, 1.82 mmol) and 5-(2-(trifluoromethyl)phenyl)cyclohexane-1,3-dione (**1**, 396 mg, 1.51 mmol) in EtOH (1.30 mL) was stirred at 80 °C for 2 hours. Then, another 62 mg of malononitrile (0.94 mmol) and 250 uL of triethylamine (1.82 mmol) were added and the mixture was stirred at 80 °C for 16 hours. The mixture was then allowed to cool to RT, concentrated to dryness, and the crude product **2** was used in Step 2 without purification. LC-MS: *rt* = 1.94 min, MS: 304.1 (calcd), 305.1 (*M*+*H*⁺, found).

Step 2. 2-Amino-7-oxo-5-(2-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (3)

A mixture of sulfur (50.9 mg, 198 umol), diethylamine (157 uL, 1.52 mmol) and **2** (461 mg, 1.52 mmol, assuming the quantitative yield in Step 1) in EtOH (2.00 mL) was stirred at 80 °C for 16 hours. The mixture was then allowed to cool to RT and concentrated by rotary evaporation and the residue was purified by flash column chromatography (eluent gradient from 40% to 100% of EA in hexane) to afford title compound **3** as a light-brown solid (220 mg, 43% yield over two steps). LC-MS: *rt* = 1.73 min, MS: 336.1 (calcd), 337.0 (*M*+*H*⁺, found).

Step 3. 2-Amino-7-oxo-5-(2-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (4)

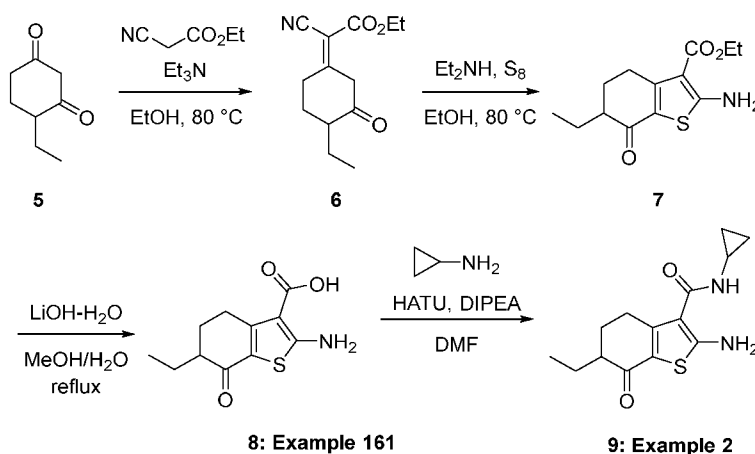
30% Aqueous hydrogen peroxide solution (0.33 mL) was added to a suspension of **3** (41.1 mg, 122 μ mol) and potassium carbonate (33.8 mg, 244 μ mol) in DMSO (1.64 mL). The mixture was stirred at RT for 2 hours, then partitioned between EA and water (20 mL each). The layers were separated and the aqueous phase was extracted with another 20 mL of EA. The combined organics were washed with brine (20 mL), dried over Na₂SO₄, filtered, concentrated and dried in vacuo to afford title compound **4** as a light-yellow solid (36.7 mg, 85% yield).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.06 (s, 2H), 7.90 (d, J = 8.0 Hz, 1H), 7.76-7.68 (m, 2H), 7.49 (t, J = 7.7 Hz, 1H), 6.96 (bs, 2H), 3.73-3.58 (m, 1H), 3.40-3.29 (m, 1H), 3.07-2.90 (m, 2H), 2.36 (dd, J = 16.3, 3.8 Hz, 1H). ¹⁹F NMR: 376 MHz, DMSO-d₆, δ (ppm): -57.5 (s). LC-MS: rt = 1.40 min, MS: 354.1 (calcd), 355.1 (M+H⁺, found).

Example 2

2-Amino-N-cyclopropyl-6-ethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (9)

Scheme 2



Step 1. Ethyl 2-cyano-2-(4-ethyl-3-oxocyclohexylidene)acetate (6)

A mixture of 4-ethylcyclohexane-1,3-dione (**5**, 150 mg, 910 μ mol) (*Synlett*. **2012**, 1199-1204), triethylamine (380 μ L, 2.73 mmol) and ethyl 2-cyanoacetate (145 μ L, 1.36 mmol) in EtOH (784 μ L) was stirred at 80 °C for 16 hours. Then, another 100 μ L of ethyl 2-cyanoacetate (0.94 mmol) and 130 μ L of triethylamine (0.93 mmol) were added and the resulting mixture was stirred at 80 °C for another 24 hours. The mixture was then allowed to cool to RT, concentrated to dryness, and the crude product **6** was used in Step 2 without purification. LC-MS: rt = 1.73 min, MS: 235.1 (calcd), 236.1 (M+H⁺, found).

Step 2. Ethyl 2-amino-6-ethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (7)

A mixture of crude **6** (214 mg, 910 μ mol; assuming the quantitative yield in Step 1), sulfur (30.6 mg, 119 μ mol) and diethylamine (94.1 μ L, 910 μ mol) in EtOH (910 μ L) was stirred at 80 °C

for 2 hours. The mixture was then allowed to cool to RT, concentrated to dryness, and the residue was purified by flash column chromatography (eluent gradient from 5% to 50% of EA in hexane) to afford title compound **7** as a yellow solid (135.2 mg, 52% yield over two steps). LC-MS: rt = 1.77 min, MS: 267.1 (calcd), 268.1 (M+H⁺, found).

5 Step 3. 2-Amino-6-ethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**8**)

Lithium hydroxide monohydrate (68.0 mg, 1.62 mmol) was added to **7** (86.6 mg, 324 μmol) suspended in a mixture of MeOH (4.86 mL) and H₂O (1.62 mL). The resulting mixture was stirred under reflux for 2 hours, then allowed to cool to RT, diluted with water (20 mL) and washed with EA (20 mL). The organic phase was discarded and the aqueous phase was then acidified to pH
10 2-3 using 3 N HCl and extracted using EA (3 x 20 mL). The combined organics were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated to afford title compound **8** as an off-white solid (60.5 mg, 78% yield). The crude product was used in Step 4 with no additional purification. (See table 6 for characterization)

15 Step 4. 2-Amino-N-cyclopropyl-6-ethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**9**)

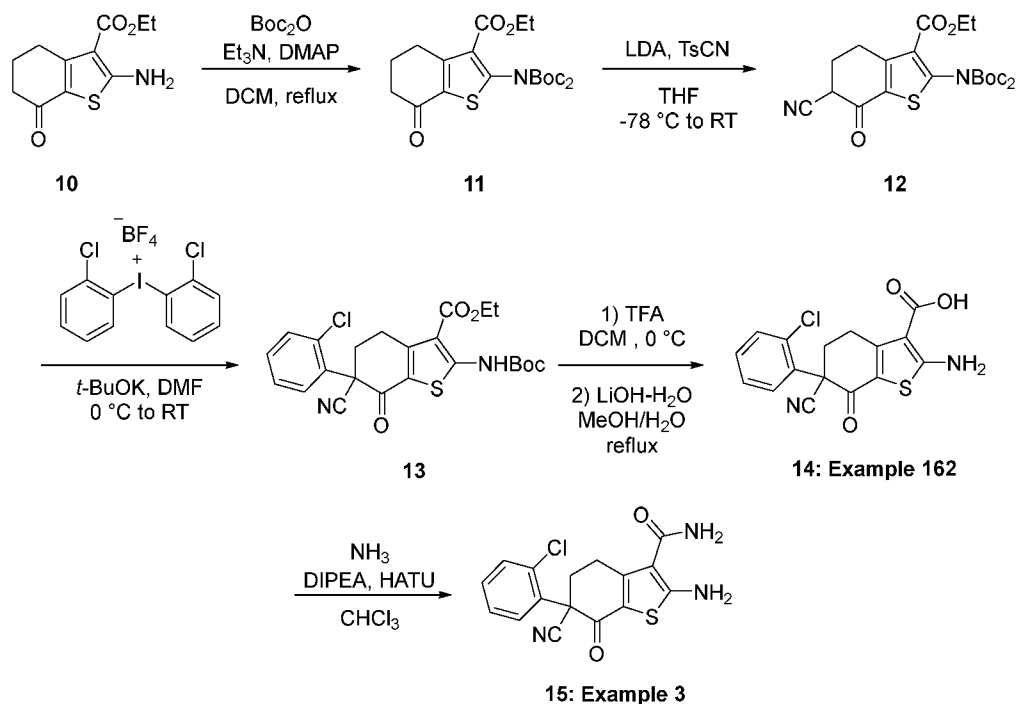
To a solution of **8** (60.5 mg, 253 μmol) in DMF (3.16 mL) were added *N,N*-diisopropylethylamine (132 μL, 758 μmol), cyclopropylamine (19.3 μL, 278 μmol) and HATU (115 mg, 303 μmol). The resulting mixture was stirred at RT for 16 hours. The mixture was then diluted with saturated aqueous NH₄Cl (30 mL) and extracted with EA (3 x 20 mL). The combined organics
20 were washed with ice-cold brine (40 mL), dried over Na₂SO₄, filtered and concentrated to dryness. The residue was first purified by flash column chromatography (eluent gradient from 1% to 10% of MeOH in DCM) and then recrystallized from hot EA to afford title compound **9** as a white solid (16.4 mg, 23% yield).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 7.68 (d, *J* = 5.7 Hz, 2H), 7.34 (d, *J* = 3.8 Hz, 1H),
25 2.86 (dt, *J* = 17.3, 5.2 Hz, 1H), 2.76 (ddt, *J* = 19.0, 7.1, 4.2 Hz, 2H), 2.20 (ddt, *J* = 9.4, 7.8, 4.7 Hz, 1H), 2.06 (dq, *J* = 13.2, 5.0 Hz, 1H), 1.82-1.67 (m, 2H), 1.50-1.33 (m, 1H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.66 (td, *J* = 7.0, 4.6 Hz, 2H), 0.57-0.47 (m, 2H). LC-MS: rt = 1.26 min, MS: 278.1 (calcd), 279.1 (M+H⁺, found).

Example 3

30 **2-Amino-6-(2-chlorophenyl)-6-cyano-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**15**)**

Scheme 3



Step 1. Ethyl 2-((di-*tert*-butoxycarbonyl)amino)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (11)

To a suspension of ethyl 2-amino-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**10**, 2.26 g, 9.25 mmol) in DCM (58.2 mL) were added triethylamine (2.85 mL, 20.4 mmol), 4-dimethylaminopyridine (228 mg, 1.85 mmol) and di-*tert*-butyldicarbonate (4.44 g, 20.4 mmol). The resulting solution was stirred under reflux for 4 hours. The mixture was then allowed to cool to RT, diluted with DCM (50 mL) and washed successively with 1 N HCl, water and brine (70 mL each). The organic phase was dried over Na_2SO_4 , filtered and concentrated and the residue was purified by flash column chromatography (eluent gradient from 10% to 60% of EA in hexane) to afford title compound **11** as a light-orange solid (3.42 g, 84% yield). LC-MS: $t_r = 1.78$ min, MS: 439.2 (calcd), 462.2 ($\text{M}+\text{Na}^+$, found).

Step 2. Ethyl 2-((di-*tert*-butoxycarbonyl)amino)-6-cyano-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (12)

To a solution of LDA (10.4 mL, 1 M in THF/hexane, 10.4 mmol) cooled to -78°C under Ar was added a solution of **11** (2.29 g, 5.22 mmol) in anhydrous THF (16 mL). The resulting mixture was stirred at -78°C for 15 min, then a solution of TsCN (975 mg, 5.22 mmol) in anhydrous THF (16 mL) was added dropwise. The mixture was stirred at -78°C for 20 min, then from -78°C to RT for 4 hours. Subsequently, the mixture was quenched with saturated aqueous NH_4Cl (200 mL) and extracted with DCM (2 x 200 mL). The combined organics were dried over Na_2SO_4 , filtered and concentrated, and the residue was purified by flash column chromatography (eluent gradient

from 5% to 50% of EA in hexane) to afford title compound **12** as a light-yellow solid (1.13 g, 46% yield). LC-MS: rt = 1.73 min, MS: 464.2 (calcd), 487.2 (M+Na⁺, found).

Step 3. Ethyl 2-((*tert*-butoxycarbonyl)amino)-6-(2-chlorophenyl)-6-cyano-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**13**)

To a flame-dried microwave vial charged with *t*-BuOK (57.5 mg, 512 μ mol) and anhydrous DMF (860 μ L) under Ar was added **12** (200 mg, 431 μ mol) in anhydrous DMF (1.3 mL). The resulting mixture was stirred at 0 °C for 35 min, then bis(2-chlorophenyl)iodonium tetrafluoroborate (188 mg, 431 μ mol) (*J. Am. Chem. Soc.* **2016**, 13183-13186.) in anhydrous DMF (430 μ L) was added dropwise and the mixture was stirred at RT for 2.5 hours. Then, more bis(2-chlorophenyl)iodonium tetrafluoroborate (40 mg, 92 μ mol dissolved in 500 μ L of anhydrous DMF) was added and the mixture was stirred at RT for 16 hours. The mixture was then diluted with water (2 mL) and acidified with 1 N HCl to pH 6-7. Another 10 mL of water was added and the product was extracted with EA (3 x 20 mL). The combined organics were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated. The residue was taken up in heptanes and concentrated by rotary evaporation several times to get rid of residual DMF. The resulting solid was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane) to afford title compound **13** as a light-yellow solid (40 mg, 20% yield). LC-MS: rt = 2.06 min, MS: 474.1 (calcd), 475.1 (M+H⁺, found).

Step 4. 2-Amino-6-(2-chlorophenyl)-6-cyano-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (**14**)

TFA (2.26 mL, 29.6 mmol) was added dropwise to a solution of **13** (40.0 mg, 84.2 μ mol) in DCM (4.6 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 hour, then concentrated to dryness to afford a crude intermediate as a brown solid (33 mg), which was dissolved in MeOH (10 mL). A solution of lithium hydroxide monohydrate (17.4 mg, 414 μ mol) in water (10 mL) was added to the solution, which was stirred under reflux for 1 hour. The mixture was then allowed to cool to RT and concentrated to dryness. The residue was washed with EA (10 mL), then acidified to pH 1-2 using 1 N HCl and extracted with EA (3 x 10 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated to afford title compound **14** as a brown solid (26.9 mg, 94% yield). The crude product was used in Step 5 with no additional purification. (See table 6 for characterization)

Step 5. 2-Amino-6-(2-chlorophenyl)-6-cyano-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**15**)

To a suspension of **14** (19.9 mg, 57.4 μ mol) in CHCl₃ (398 μ L) were added *N,N*-diisopropylethylamine (30.0 μ L, 172 μ mol), saturated NH₃ solution in CHCl₃ (0.3 mL) (prepared in-house) and HATU (24.0 mg, 63.1 μ mol). The mixture was stirred at RT. After stirring for 5 hours, another 24 mg of HATU (63.1 μ mol) and 0.5 mL of saturated NH₃ solution in CHCl₃ were added. The mixture was stirred for 16 hours, then another 25 mg of HATU (65.7 μ mol) and 0.6 mL of

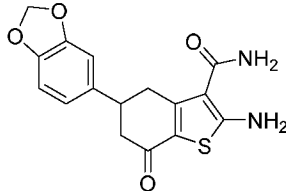
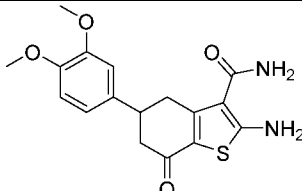
saturated NH_3 solution in CHCl_3 were added and stirring continued for another 4.5 hours. The mixture was then diluted with 5 mL of water and 5 mL CHCl_3 . The layers were separated and the aqueous phase was extracted with CHCl_3 (2 x 5 mL). The combined organics were dried over Na_2SO_4 , filtered and concentrated, and the residue was purified by reverse-phase flash column chromatography (eluent gradient from 0% to 100% of CH_3CN in H_2O with 0.1% (v/v) formic acid) to afford title compound **15** as a white solid (6.2 mg, 31% yield).

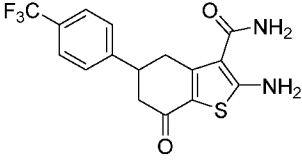
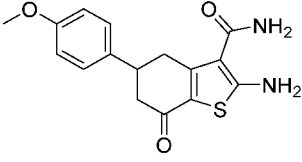
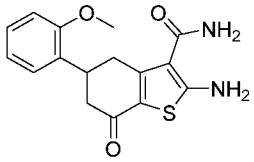
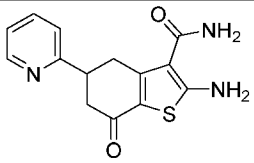
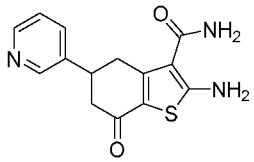
^1H NMR: 400 MHz, CD_3OD , δ (ppm): 7.73-7.68 (m, 1H), 7.50-7.45 (m, 1H), 7.45-7.40 (m, 2H), 3.29-3.11 (m, 3H), 2.48-2.41 (m, 1H). LC-MS: t_r = 1.15 min, MS: 345.0 (calcd), 346.0 ($\text{M}+\text{H}^+$, found).

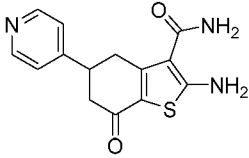
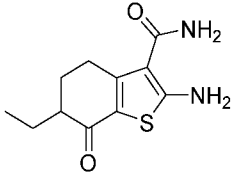
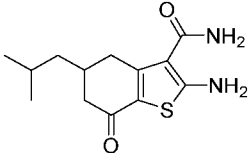
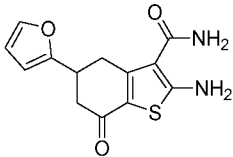
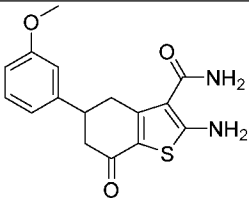
Examples 4-27

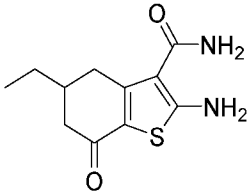
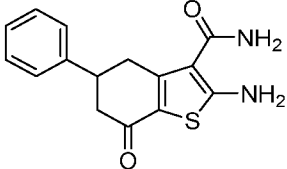
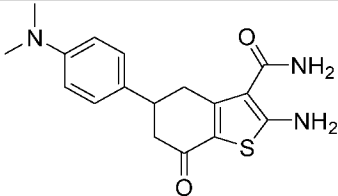
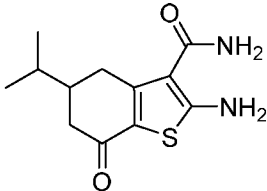
Compounds **16-34** (examples 4-22) were synthesized starting from appropriately substituted diketones by following the procedures described above for the synthesis of compound **4** (example 1, scheme 1). Compounds **35** and **36** (examples 23 and 24) were synthesized in a similar fashion by following the procedures described above for the synthesis of compound **8** (scheme 2). Compounds **37-39** (examples 25-27) were synthesized in a similar fashion by following the procedures described above for the synthesis of compound **9** (scheme 2). Characterization of compounds **16-39** (examples 4-27) is provided in the table 2.

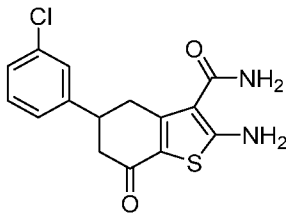
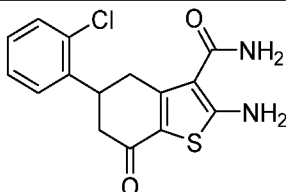
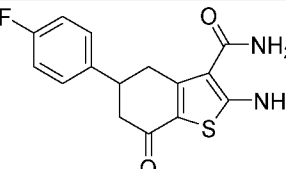
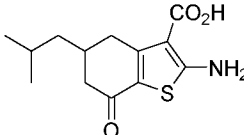
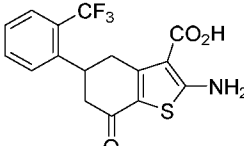
Table 2. Characterization of compounds **16-39** (examples 4-27).

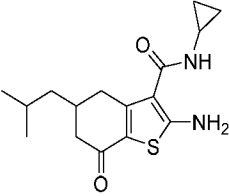
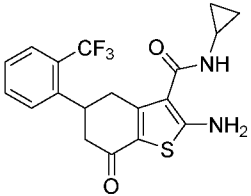
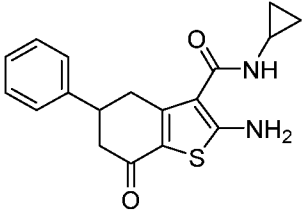
Ex. No.	Compound No.	Structure	Characterization
4	16	 2-Amino-5-(benzo[d][1,3]dioxol-5-yl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	^1H NMR: 400 MHz, $\text{DMSO}-d_6$, δ (ppm): 8.01 (s, 2H), 7.01 (d, J = 1.6 Hz, 1H), 6.96 (bs, 1H), 6.86 (d, J = 7.9 Hz, 1H), 6.82 (dd, J = 8.0, 1.6 Hz, 1H), 5.98 (s, 2H), 3.40-3.35 (m, 1H), 3.10-3.04 (m, 2H), 2.74 (dd, J = 16.2, 12.9 Hz, 1H), 2.42 (dd, J = 16.2, 3.9 Hz, 1H). LC-MS: t_r = 1.14 min, MS: 330.1 (calcd), 331.0 ($\text{M}+\text{H}^+$, found).
5	17	 2-Amino-5-(3,4-dimethoxyphenyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	^1H NMR: 400 MHz, $\text{DMSO}-d_6$, δ (ppm): 8.00 (s, 2H), 7.06-6.82 (m, 5H), 3.76 (s, 3H), 3.73 (s, 3H), 3.40-3.30 (m, 1H), 3.14-3.06 (m, 2H), 2.77 (dd, J = 16.2, 12.9 Hz, 1H), 2.45 (dd, J = 16.6, 4.5 Hz, 1H). LC-MS: t_r = 1.03 min, MS: 346.1 (calcd), 347.0 ($\text{M}+\text{H}^+$, found).

6	18	 2-Amino-7-oxo-5-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.04 (s, 2H), 7.71 (d, <i>J</i> = 8.2 Hz, 2H), 7.63 (d, <i>J</i> = 8.1 Hz, 2H), 6.98 (bs, 2H), 3.62-3.51 (m, 1H), 3.20-3.13 (m, 2H), 2.82 (dd, <i>J</i> = 16.1, 12.8 Hz, 1H), 2.53 (d, <i>J</i> = 4.4 Hz, 1H). ¹⁹F NMR: 376 MHz, DMSO-d₆, δ (ppm): -60.8 (s). LC-MS: rt = 1.48 min, MS: 354.1 (calcd), 355.0 (M+H⁺, found).
7	19	 2-Amino-5-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.02 (s, 2H), 7.29 (d, <i>J</i> = 8.3 Hz, 2H), 6.97 (bs, 2H), 6.89 (d, <i>J</i> = 8.3 Hz, 2H), 3.73 (s, 3H), 3.40-3.33 (m, 1H), 3.12-3.05 (m, 2H), 2.72 (dd, <i>J</i> = 16.2, 12.8 Hz, 1H), 2.44 (dd, <i>J</i> = 16.3, 4.0 Hz, 1H). LC-MS: rt = 1.15 min, MS: 316.1 (calcd), 317.0 (M+H⁺, found).
8	20	 2-Amino-5-(2-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.01 (s, 2H), 7.33 (d, <i>J</i> = 7.3 Hz, 1H), 7.24 (t, <i>J</i> = 7.7 Hz, 1H), 7.04-6.91 (m, 4H), 3.80 (s, 3H), 3.74-3.63 (m, 1H), 3.21-2.97 (m, 2H), 2.76 (dd, <i>J</i> = 16.1, 12.9 Hz, 1H), 2.43 (dd, <i>J</i> = 16.0, 3.8 Hz, 1H). LC-MS: rt = 1.23 min, MS: 316.1 (calcd), 317.1 (M+H⁺, found).
9	21	 2-Amino-7-oxo-5-(pyridin-2-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.54 (dd, <i>J</i> = 5.0, 1.7 Hz, 1H), 7.98 (s, 2H), 7.77 (td, <i>J</i> = 7.7, 1.9 Hz, 1H), 7.41 (d, <i>J</i> = 7.9 Hz, 1H), 7.27 (ddd, <i>J</i> = 7.6, 4.8, 1.1 Hz, 1H), 7.00 (bs, 2H), 3.66-3.52 (m, 1H), 3.28-3.14 (m, 2H), 2.85 (dd, <i>J</i> = 16.4, 12.1 Hz, 1H), 2.60-2.53 (m, 1H). LC-MS: rt = 0.31 min, MS: 287.1 (calcd), 288.1 (M+H⁺, found).
10	22	 2-Amino-7-oxo-5-(pyridin-3-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.62 (d, <i>J</i> = 2.3 Hz, 1H), 8.47 (dd, <i>J</i> = 4.8, 1.6 Hz, 1H), 8.07 (s, 2H), 7.82 (dt, <i>J</i> = 8.0, 2.0 Hz, 1H), 7.38 (dd, <i>J</i> = 7.9, 4.7 Hz, 1H), 7.02 (bs, 2H), 3.55-3.44 (m, 1H), 3.23-3.10 (m, 2H), 2.83 (dd, <i>J</i> = 16.2, 12.9 Hz, 1H), 2.55-2.45 (m, 1H, partially overlapping with the solvent signal).

			LC-MS: rt = 0.80 min, MS: 287.1 (calcd), 288.0 (M+H ⁺ , found).
11	23	 2-Amino-7-oxo-5-(pyridin-4-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.53 (d, <i>J</i> = 5.3 Hz, 2H), 8.06 (s, 2H), 7.42 (d, <i>J</i> = 5.8 Hz, 2H), 7.02 (bs, 2H), 3.48 (dtd, <i>J</i> = 11.9, 7.5, 3.8 Hz, 1H), 3.14 (d, <i>J</i> = 7.7 Hz, 2H), 2.79 (dd, <i>J</i> = 16.2, 12.7 Hz, 1H), 2.53 (d, <i>J</i> = 4.2 Hz, 1H, partially overlapping with the solvent signal). LC-MS: rt = 0.71 min, MS: 287.1 (calcd), 288.1 (M+H⁺, found).
12	24	 2-Amino-6-ethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 7.97 (s, 2H), 6.94 (bs, 2H), 2.98 (dt, <i>J</i> = 17.3, 5.1 Hz, 1H), 2.86 (ddd, <i>J</i> = 17.2, 9.0, 4.7 Hz, 1H), 2.23 (ddt, <i>J</i> = 12.2, 9.2, 4.7 Hz, 1H), 2.10 (dq, <i>J</i> = 14.1, 4.6 Hz, 1H), 1.84-1.71 (m, 2H), 1.48-1.35 (m, 1H), 0.90 (t, <i>J</i> = 7.4 Hz, 3H). LC-MS: rt = 0.92 min, MS: 238.1 (calcd), 239.1 (M+H⁺, found).
13	25	 2-Amino-5-isobutyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, CD₃OD, δ (ppm): 3.08 (dd, <i>J</i> = 16.86, 4.03 Hz, 1H), 2.62-2.49 (m, 2H), 2.26-2.19 (m, 2H), 1.78-1.71 (m, 1H), 1.39-1.31 (m, 2H), 0.92 (d, <i>J</i> = 6.56 Hz, 6H). LC-MS: rt = 1.30 min, MS: 266.1 (calcd), 267.1 (M+H⁺, found).
14	26	 2-Amino-5-(furan-2-yl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.41 (s, 1H), 6.33 (s, 1H), 6.16 (s, 1H), 3.65-3.55 (m, 1H), 3.37 (dd, <i>J</i> = 16.83, 4.48 Hz, 1H), 3.15 (dd, <i>J</i> = 16.83, 9.56 Hz, 1H), 2.83-2.70 (m, 2H). LC-MS: rt = 0.99 min, MS: 276.1 (calcd), 277.1 (M+H⁺, found).
15	27	 2-Amino-5-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 7.99 (s, 2H), 7.24 (t, <i>J</i> = 7.85 Hz, 1H), 6.94-6.92 (m, 4H), 6.80 (d, <i>J</i> = 8.15 Hz, 1H), 3.73 (s, 3H), 3.17-3.04 (m, 3H), 2.75 (t, <i>J</i> = 14.49 Hz, 1H), 2.45-2.40 (m, 1H). LC-MS: rt = 1.22 min, MS: 316.1 (calcd), 317.1 (M+H⁺, found).

		tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	
16	28	 2-Amino-5-ethyl-7-oxo-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹ H NMR: 400 MHz, DMSO- <i>d</i> ₆ , δ (ppm): 7.95 (s, 2H), 6.95 (bs, 2H), 2.95 (d, <i>J</i> = 16.99 Hz, 1H), 2.60 (dd, <i>J</i> = 16.97, 10.34 Hz, 1H), 2.36 (d, <i>J</i> = 16.35 Hz, 1H), 2.14 (t, <i>J</i> = 14.16 Hz, 1H), 2.10-1.94 (m, 1H), 1.48-1.33 (m, 2H), 0.90 (t, <i>J</i> = 7.36 Hz, 3H). LC-MS: rt = 0.94 min, MS: 238.1 (calcd), 239.1 (M+H ⁺ , found).
17	29	 2-Amino-7-oxo-5-phenyl-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹ H NMR: 400 MHz, DMSO- <i>d</i> ₆ , δ (ppm): 8.01 (s, 2H), 7.40-7.32 (m, 4H), 7.26-7.23 (m, 1H), 6.97 (bs, 2H), 3.47-3.39 (m, 1H), 3.18-3.09 (m, 2H), 2.78 (dd, <i>J</i> = 8.0, 2.1 Hz, 1H), 2.54-2.45 (m, 1H). LC-MS: rt = 1.05 min, MS: 286.1 (calcd), 287.1 (M+H ⁺ , found).
18	30	 2-Amino-5-(4-(dimethylamino)phenyl)-7-oxo-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹ H NMR: 400 MHz, DMSO- <i>d</i> ₆ , δ (ppm): 7.98 (s, 2H), 7.17 (d, <i>J</i> = 8.3 Hz, 2H), 6.95 (bs, 2H), 6.70 (d, <i>J</i> = 8.3 Hz, 2H), 3.31-3.25 (m, 1H), 3.06 (d, <i>J</i> = 7.6 Hz, 2H), 2.86 (s, 6H), 2.70 (dd, <i>J</i> = 16.2, 12.4 Hz, 1H), 2.43 (dd, <i>J</i> = 16.2, 3.9 Hz, 1H). LC-MS: rt = 2.48 min, MS: 329.1 (calcd), 330.1 (M+H ⁺ , found).
19	31	 2-Amino-5-isopropyl-7-oxo-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹ H NMR: 400 MHz, DMSO- <i>d</i> ₆ , δ (ppm): 7.98 (s, 2H), 7.00 (bs, 2H), 2.87 (dd, <i>J</i> = 16.9, 4.2 Hz, 1H), 2.70 (dd, <i>J</i> = 16.9, 11.0 Hz, 1H), 2.31 (dd, <i>J</i> = 16.0, 4.0 Hz, 1H), 2.20 (dd, <i>J</i> = 16.0, 12.6 Hz, 1H), 1.97-1.88 (m, 1H), 1.69-1.61 (m, 1H), 0.94-0.91 (m, 6H). LC-MS: rt = 3.15 min, MS: 252.1 (calcd), 253.1 (M+H ⁺ , found).

20	32	 2-Amino-5-(3-chlorophenyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.04 (s, 2H), 7.50 (s, 1H), 7.40-7.35 (m, 2H), 7.34-7.30 (m, 1H), 6.99 (bs, 2H), 3.50-3.42 (m, 1H), 3.18-3.08 (m, 2H), 2.79 (dd, <i>J</i> = 16.1, 13.0 Hz, 1H), 2.50-2.45 (m, 1H). LC-MS: rt = 2.74 min, MS: 320.0 (calcd), 321.1 (M+H⁺, found).
21	33	 2-Amino-5-(2-chlorophenyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.04 (s, 2H), 7.58 (d, <i>J</i> = 7.7, 1H), 7.47 (d, <i>J</i> = 7.9, 1H), 7.38 (t, <i>J</i> = 7.4, 1H), 7.30 (t, <i>J</i> = 7.6, 1H), 7.00 (bs, 2H), 3.80-3.73 (m, 1H), 3.20-3.09 (m, 2H), 2.82-2.75 (m, 1H), 2.50-2.44 (m, 1H). LC-MS: rt = 2.65 min, MS: 320.0 (calcd), 321.0 (M+H⁺, found).
22	34	 2-Amino-5-(4-fluorophenyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.03 (s, 2H), 7.45-7.41 (m, 2H), 7.19-7.15 (m, 2H), 7.00 (bs, 2H), 3.49-3.40 (m, 1H), 3.10 (d, <i>J</i> = 7.8 Hz, 2H), 2.77 (dd, <i>J</i> = 16.1, 12.9 Hz, 1H), 2.46 (dd, <i>J</i> = 15.9, 3.6 Hz, 1H). ¹⁹F NMR: 376 MHz, DMSO-d₆, δ (ppm): -116.5 (m). LC-MS: rt = 1.08 min, MS: 304.1 (calcd), 305.0 (M+H⁺, found).
23	35	 2-Amino-5-isobutyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 12.49 (bs, 1H), 8.22 (bs, 2H), 3.26 (dd, <i>J</i> = 17.5, 3.4 Hz, 1H), 2.45-2.30 (m, 2H), 2.22-2.10 (m, 2H), 1.65 (hept, <i>J</i> = 6.7 Hz, 1H), 1.31-1.21 (m, 2H), 0.86 (d, <i>J</i> = 6.5 Hz, 6H). LC-MS: rt = 1.27 min, MS: 267.1 (calcd), 268.1 (M+H⁺, found).
24	36	 2-Amino-7-oxo-5-(2-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.82 (d, <i>J</i> = 7.9 Hz, 1H), 7.71 (d, <i>J</i> = 7.9 Hz, 1H), 7.66 (t, <i>J</i> = 7.8 Hz, 1H), 7.44 (t, <i>J</i> = 7.7 Hz, 1H), 3.88-3.75 (m, 1H), 3.58 (ddd, <i>J</i> = 18.0, 4.1, 1.1 Hz, 1H), 3.05 (dd, <i>J</i> = 17.9, 11.7 Hz, 1H), 2.96 (dd, <i>J</i> = 16.4, 13.2 Hz, 1H), 2.53 (ddd, <i>J</i> = 16.3, 4.0, 1.3 Hz, 1H). ¹⁹F

		tetrahydrobenzo[<i>b</i>]thiophene-3-carboxylic acid	NMR: 376 MHz, CD ₃ OD, δ (ppm): – 60.1 (s). LC-MS: rt = 1.34 min, MS: 355.1 (calcd), 356.1 (M+H ⁺ , found).
25	37	 2-Amino-<i>N</i>-cyclopropyl-5-isobutyl-7-oxo-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹ H NMR: 400 MHz, CDCl ₃ , δ (ppm): 6.88 (bs, 2H), 5.68 (bs, 1H), 2.98-2.87 (m, 1H), 2.86-2.78 (m, 1H), 2.60 (dd, <i>J</i> = 15.8, 2.8 Hz, 1H), 2.43-2.31 (m, 2H), 2.27-2.14 (m, 1H), 1.76-1.63 (m, 1H), 1.45-1.22 (m, 3H), 0.95-0.83 (m, 7H), 0.62-0.56 (m, 2H). LC-MS: rt = 1.31 min, MS: 306.1 (calcd), 307.2 (M+H ⁺ , found).
26	38	 2-Amino-<i>N</i>-cyclopropyl-7-oxo-5-(2-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹ H NMR: 400 MHz, CDCl ₃ , δ (ppm): 7.71 (d, <i>J</i> = 7.9 Hz, 1H), 7.64-7.56 (m, 2H), 7.42 (t, <i>J</i> = 7.4 Hz, 1H), 6.97 (bs, 2H), 5.59 (bs, 1H), 4.01-3.89 (m, 1H), 3.10 (dd, <i>J</i> = 15.8, 4.5 Hz, 1H), 2.93-2.78 (m, 2H), 2.79-2.66 (m, 2H), 0.84-0.77 (m, 2H), 0.55-0.47 (m, 2H). ¹⁹ F NMR: 376 MHz, CDCl ₃ , δ (ppm): –58.7 (s). LC-MS: rt = 1.36 min, MS: 394.1 (calcd), 395.1 (M+H ⁺ , found).
27	39	 2-Amino-<i>N</i>-cyclopropyl-7-oxo-5-phenyl-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹ H NMR: 400 MHz, DMSO- <i>d</i> ₆ , δ (ppm): 7.72 (s, 2H), 7.49-7.48 (m, 1H), 7.37-7.32 (m, 4H), 7.27-7.23 (m, 1H), 3.45-3.37 (m, 1H), 3.11-2.95 (m, 2H), 2.78-2.67 (m, 2H), 2.50-2.46 (m, 1H), 0.66-0.59 (m, 2H), 0.50-0.42 (m, 2H). LC-MS: rt = 2.81 min, MS: 326.1 (calcd), 327.1 (M+H ⁺ , found).

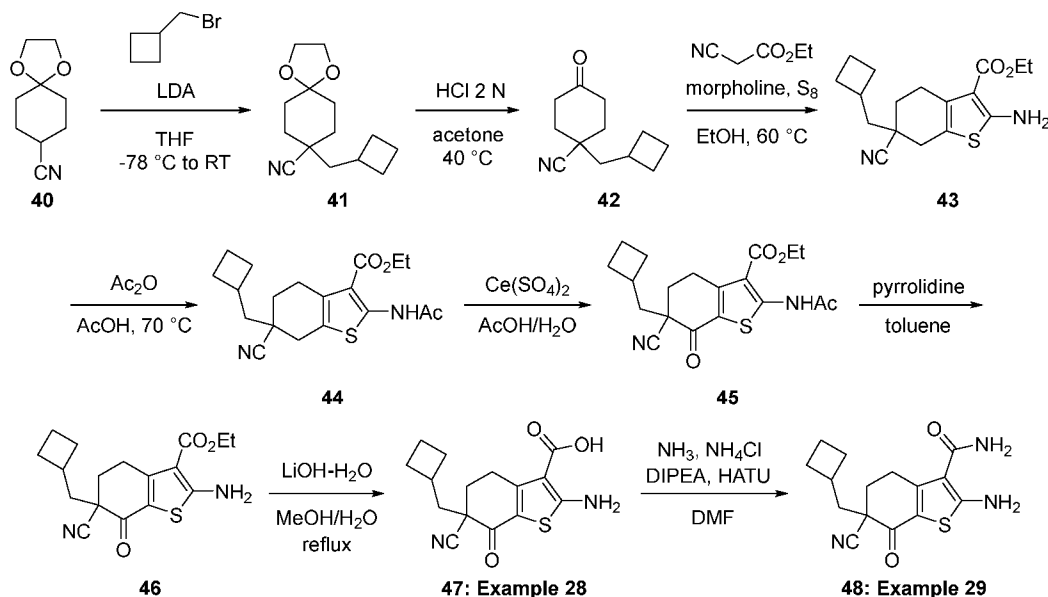
Example 28

2-Amino-6-cyano-6-(cyclobutylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (47) and

Example 29

2-Amino-6-cyano-6-(cyclobutylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (48)

Scheme 4



Step 1. 8-(Cyclobutylmethyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (**41**)

A flame-dried round bottom flask was charged with a solution of LDA (2.69 mL, 1 M in THF/hexane, 2.69 mmol) in anhydrous THF (3.60 mL) under Ar. The solution was cooled to -78 °C and 1,4-dioxaspiro[4.5]decane-8-carbonitrile (**40**, 265 uL, 1.79 mmol) was added. The mixture was stirred at -78 °C for 30 min, then (bromomethyl)cyclobutane (202 uL, 1.79 mmol) was added. The reaction vessel was removed from the acetone/dry ice bath and the solution was stirred at RT for 64 hours. The mixture was then partitioned between EA and water (15 mL each), the layers were separated and the aqueous phase was extracted with EA (2 x 15 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated to afford the crude title compound **41** as an orange oil, which was used in Step 2 without purification and without characterization.

Step 2. 1-(Cyclobutylmethyl)-4-oxocyclohexane-1-carbonitrile (**42**)

A solution of **41** (422 mg, 1.79 mmol, assuming the quantitative yield in Step 1) in acetone (25.3 mL) was treated with 2 N HCl (4.59 mL, 9.19 mmol) and the resulting mixture was stirred at 40 °C for 64 hours. The mixture was then allowed to cool to RT, concentrated by rotary evaporation to remove acetone, and the aqueous residue was extracted with EA (3 x 30 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated to afford the crude title compound **42** as a brown solid, which was used in Step 3 without purification and without characterization.

Step 3. Ethyl 2-amino-6-cyano-6-(cyclobutylmethyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**43**)

A suspension of ethyl 2-cyanoacetate (210 uL, 1.97 mmol), morpholine (172 uL, 1.97 mmol), sulfur (63 mg, 247 umol) and **42** (342 mg, 1.79 mmol, assuming the quantitative yield in Step 2) in EtOH (1.8 mL) was stirred at 60 °C for 16 hours. The mixture was allowed to cool to RT, then concentrated by rotary evaporation and the residue was partitioned between EA and

water (20 mL each). The organic phase was dried over Na₂SO₄, filtered and concentrated and the residue was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane) to afford title compound **43** as a light-yellow solid (353 mg, 62% yield over three steps). LC-MS: rt = 1.74 min, MS: 318.1 (calcd), 319.1 (M+H⁺, found).

5 Step 4. Ethyl 2-acetamido-6-cyano-6-(cyclobutylmethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**44**)

A suspension of **43** (227 mg, 713 umol) in acetic acid (4.09 mL) was treated with acetic anhydride (80.9 uL, 856 umol) and the resulting mixture was stirred at 70 °C for 3 hours. The mixture was then allowed to cool to RT and concentrated to dryness. The residue was diluted
10 with DCM (10 mL) and washed successively with saturated aqueous NaHCO₃, water and brine (10 mL each), then dried over Na₂SO₄, filtered and concentrated to afford title compound **44** as a yellow solid (227 mg, 88% yield). LC-MS: rt = 1.79 min, MS: 360.2 (calcd), 361.1 (M+H⁺, found).

Step 5. Ethyl 2-acetamido-6-cyano-6-(cyclobutylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**45**)

15 To a suspension of **44** (227 mg, 630 umol) in acetic acid (2.1 mL) and water (6.3 mL) was added ceric sulfate (1.81 g, 5.44 mmol). The mixture was sonicated for 1 min, then stirred at RT for 88 hours. Subsequently, the mixture was diluted with water and EA (30 mL each), sonicated for 3 minutes and transferred into a separatory funnel. The layers were separated and the organic phase was washed successively with 1 N NaOH and brine (30 mL each), then dried over Na₂SO₄,
20 filtered and concentrated to afford title compound **45** as a yellow gum (175.1 mg, 74% yield), which was used in Step 6 without purification. LC-MS: rt = 1.71 min, MS: 374.1 (calcd), 375.2 (M+H⁺, found).

Step 6. Ethyl 2-amino-6-cyano-6-(cyclobutylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**46**)

25 A solution of **45** (170 mg, 454 umol) in toluene (744 uL) was treated with pyrrolidine (559 uL, 6.81 mmol) and stirred at RT for 1 hour. The mixture was then concentrated by rotary evaporation and the residue was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane) to afford title compound **46** as an off-white solid (118.1 mg, 78% yield). LC-MS: rt = 1.63 min, MS: 332.1 (calcd), 333.1 (M+H⁺, found).

30 Step 7. 2-Amino-6-cyano-6-(cyclobutylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**47**)

A solution of lithium hydroxide monohydrate (66.9 mg, 1.59 mmol) in water (38.4 mL) was added to a solution of **46** (100 mg, 261 umol) in MeOH (38.4 mL). The mixture was stirred under reflux for 16 hours, then allowed to cool to RT and concentrated by rotary evaporation to remove
35 most of MeOH. The aqueous residue was washed with EA (2 x 25 mL), then acidified to pH 1-2 using 3 N HCl and extracted with EA (3 x 25 mL). The organics were dried over Na₂SO₄, filtered and concentrated to afford title compound **47** as an off-white solid (78.2 mg, 81% yield).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 12.75 (bs, 1H), 8.48 (bs, 2H), 3.08-3.02 (m, 2H), 2.55-2.42 (m, 1H), 2.43-2.29 (m, 1H), 2.27-2.16 (m, 1H), 2.13-1.96 (m, 3H), 1.93-1.61 (m, 5H). LC-MS: rt = 1.32 min, MS: 304.1 (calcd), 305.1 (M+H⁺, found).

Step 8. 2-Amino-6-cyano-6-(cyclobutylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (48)

To a suspension of **47** (38.3 mg, 126 μmol), saturated NH₃ solution in chloroform (780 μL) (prepared in-house), ammonium chloride (135 mg, 2.52 mmol) and *N,N*-diisopropylethylamine (43.8 μL, 252 μmol) in DMF (1.39 mL) was added HATU (73.2 mg, 189 μmol). The resulting mixture was stirred at RT for 16 hours, then diluted with saturated aqueous NH₄Cl (20 mL) and extracted with EA (3 x 10 mL). The combined organics were washed with ice-cold brine (2 x 15 mL), dried over Na₂SO₄, filtered and concentrated. The residue was first purified by reverse-phase flash column chromatography (eluent gradient from 0% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) and then Semi-Prep HPLC-MS (eluent gradient from 25% to 100% of CH₃CN in 10 mM ammonium bicarbonate) to afford title compound **48** as a white solid (14.5 mg, 38%).

¹H NMR (400 MHz, CD₃OD): δ 3.16-3.08 (m, 2H), 2.65-2.57 (m, 1H), 2.47 (ddd, *J* = 13.3, 7.7, 5.4 Hz, 1H), 2.30 (ddd, *J* = 13.7, 6.0, 5.0 Hz, 1H), 2.20-2.10 (m, 3H), 2.00-1.90 (m, 2H), 1.87-1.74 (m, 3H). LC-MS: rt = 1.15 min, MS: 303.1 (calcd), 304.1 (M+H⁺, found).

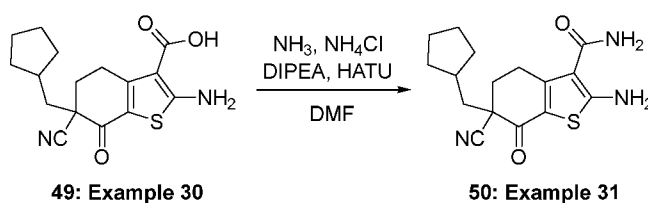
Example 30

2-Amino-6-cyano-6-(cyclopentylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (49) and

Example 31

2-Amino-6-cyano-6-(cyclopentylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (50)

Scheme 5



2-Amino-6-cyano-6-(cyclopentylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (49)

Compound **49** (example 30) was synthesized similarly to compound **47** (example 28, scheme 4) starting from 1,4-dioxaspiro[4.5]decane-8-carbonitrile (**40**) and using in the first step (bromomethyl)cyclopentane instead of (bromomethyl)cyclobutane.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 12.75 (bs, 1H), 8.48 (bs, 2H), 3.13-3.00 (m, 2H), 2.48-2.38 (m, 1H), 2.29 (dt, *J* = 13.5, 5.2 Hz, 1H), 2.04-1.76 (m, 5H), 1.63-1.37 (m, 4H), 1.25-1.05 (m, 2H). LC-MS: rt = 1.41 min, MS: 318.1 (calcd), 319.1 (M+H⁺, found).

2-Amino-6-cyano-6-(cyclopentylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (50)

To a suspension of **49** (40.0 mg, 126 μ mol), saturated NH_3 solution in chloroform (741 μ L) (prepared in-house), ammonium chloride (134 mg, 2.51 mmol) and *N,N*-diisopropylethylamine (43.8 μ L, 252 μ mol) in DMF (1.39 mL) was added HATU (73.1 mg, 188 μ mol). The resulting mixture was stirred at RT for 16 hours, then another 40 μ L of *N,N*-diisopropylethylamine (230 μ mol), 550 μ L of saturated NH_3 solution in chloroform and 65 mg of HATU (167 μ mol) were added and the mixture was stirred at 40 $^\circ\text{C}$ for 24 hours. Subsequently, the mixture was partitioned between saturated aqueous NH_4Cl and EA (20 mL each), the layers were separated and the organic phase was washed with ice-cold brine (2 x 15 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by reverse-phase flash column chromatography (eluent gradient from 0% to 100% of CH_3CN in H_2O with 0.1% (v/v) formic acid) to afford title compound **50** as an off-white solid (14.5 mg, 36%).

^1H NMR: 400 MHz, CD_3OD , δ (ppm): 3.25-3.05 (m, 2H), 2.54 (ddd, $J = 13.4, 7.9, 5.4$ Hz, 1H), 2.38 (ddd, $J = 13.7, 5.9, 5.0$ Hz, 1H), 2.12 (dd, $J = 13.5, 6.7$ Hz, 1H), 2.07-1.85 (m, 4H), 1.73-1.51 (m, 4H), 1.26-1.18 (m, 2H). LC-MS: $t_r = 1.25$ min, MS: 317.1 (calcd), 318.0 ($\text{M}+\text{H}^+$, found).

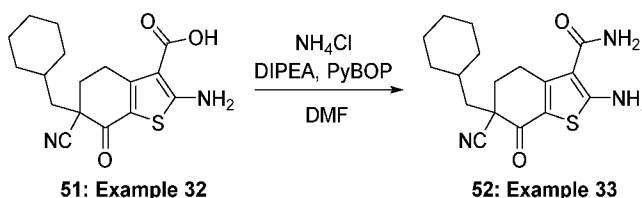
Example 32

2-Amino-6-cyano-6-(cyclohexylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (51) and

Example 33

2-Amino-6-cyano-6-(cyclohexylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (52)

Scheme 6



2-Amino-6-cyano-6-(cyclohexylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (51)

Compound **51** (example 32) was synthesized similarly to compound **47** (example 28, scheme 4) starting from 1,4-dioxaspiro[4.5]decane-8-carbonitrile (**40**) and using in the first step (bromomethyl)cyclohexane instead of (bromomethyl)cyclobutane.

^1H NMR: 400 MHz, $\text{DMSO}-d_6$, δ (ppm): 12.69 (bs, 1H), 8.48 (bs, 2H), 3.12-2.97 (m, 2H), 2.47-2.36 (m, 1H), 2.27 (dt, $J = 13.7, 5.5$ Hz, 1H), 1.84-1.54 (m, 6H), 1.53-1.46 (m, 1H), 1.28-1.07 (m, 4H), 1.03-0.90 (m, 2H). LC-MS: $t_r = 1.49$ min, MS: 332.1 (calcd), 333.0 ($\text{M}+\text{H}^+$, found).

2-Amino-6-cyano-6-(cyclohexylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (52)

To a solution of **51** (24.0 mg, 72.2 μmol) in DMF (798 μL) were added PyBOP (56.5 mg, 108 μmol), *N,N*-diisopropylethylamine (40.0 μL , 230 μmol) and ammonium chloride (38.6 mg, 722 μmol). The resulting mixture was stirred at RT for 80 minutes, then diluted with saturated aqueous NH_4Cl (5 mL) and extracted with EA (3 x 5 mL). The combined organics were washed with ice-cold brine (2 x 10 mL), dried over Na_2SO_4 , filtered and concentrated and the residue was purified by flash column chromatography (eluent gradient from 10% to 100% of EA in hexane) to afford title compound **52** as an orange solid (13.6 mg, 57% yield).

^1H NMR: 400 MHz, CD_3OD , δ (ppm): 3.18-3.09 (m, 2H), 2.51 (ddd, $J = 13.3, 7.5, 5.6$ Hz, 1H), 2.36 (dt, $J = 13.6, 5.5$ Hz, 1H), 1.98-1.80 (m, 3H), 1.79-1.59 (m, 5H), 1.38-1.16 (m, 4H), 1.13-0.97 (m, 2H). LC-MS: $t_r = 1.34$ min, MS: 331.1 (calcd), 332.2 ($\text{M}+\text{H}^+$, found).

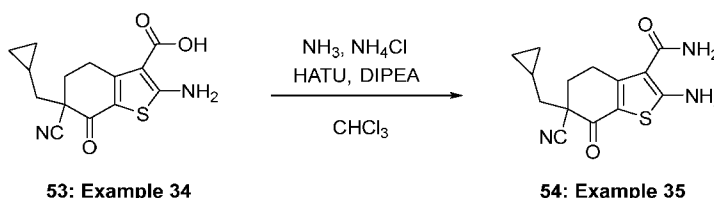
Example 34

2-Amino-6-cyano-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (53) and

Example 35

2-Amino-6-cyano-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (54)

Scheme 7



2-Amino-6-cyano-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (53).

Compound **53** (example 34) was synthesized similarly to compound **47** (example 28, scheme 4) starting from 1,4-dioxaspiro[4.5]decane-8-carbonitrile (**40**) and using in the first step (bromomethyl)cyclopropane instead of (bromomethyl)cyclobutane.

^1H NMR: 400 MHz, CD_3OD , δ (ppm): 3.23-3.19 (m, 2H), 2.54-2.50 (m, 1H), 2.42-2.39 (m, 1H), 1.89 (dd, $J = 14.27, 7.15$ Hz, 1H), 1.78 (dd, $J = 14.26, 6.72$ Hz, 1H), 0.91-0.87 (m, 1H), 0.57-0.53 (m, 2H), 0.22-0.19 (m, 2H). LC-MS: $t_r = 1.18$ min, MS: 290.1 (calcd), 291.0 ($\text{M}+\text{H}^+$, found).

2-Amino-6-cyano-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (54).

To a suspension of **53** (36.4 mg, 0.125 mmol) in CHCl_3 (871 μL) was added HATU (52.4 mg, 0.138 mmol) and *N,N*-diisopropylethylamine (65.5 μL , 0.376 mmol). The mixture was stirred

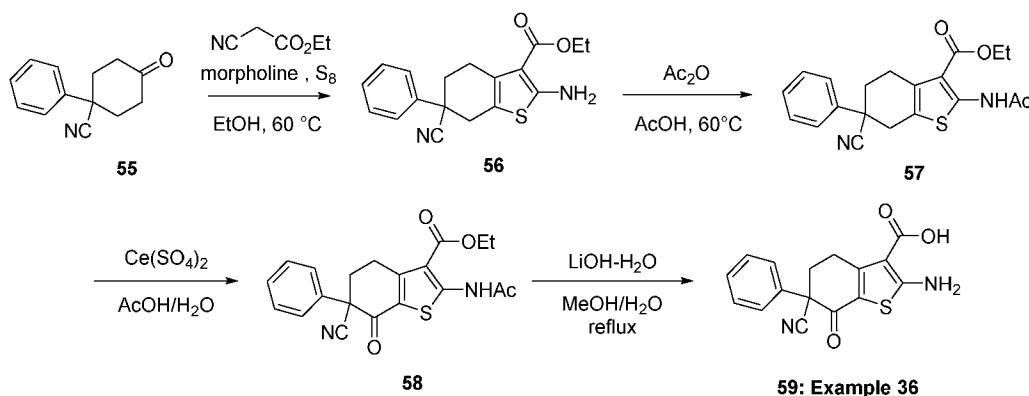
20 min at RT and to it was added saturated NH_3 solution in CHCl_3 (0.8 mL) (prepared in-house) and NH_4Cl (6.71 mg, 0.125 mmol). The reaction mixture was stirred for 16 hours and partitioned between EA and a saturated aqueous solution of NaHCO_3 . The layers were separated and the organic phase was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 20% to 100% of EA in hexane) to afford title compound **54** as a white solid (20.0 mg, 55% yield).

^1H NMR: 400 MHz, CD_3OD , δ (ppm): 3.13 (t, J = 6.03 Hz, 2H), 2.60-2.53 (m, 1H), 2.48-2.42 (m, 1H), 1.93 (dd, J = 14.28, 7.11 Hz, 1H), 1.80 (dd, J = 14.28, 6.79 Hz, 1H), 0.94-0.84 (m, 1H), 0.58-0.55 (m, 2H), 0.24-0.20 (m, 2H). LC-MS: rt = 1.02 min, MS: 289.1 (calcd), 290.1 ($\text{M}+\text{H}^+$, found).

Example 36

2-Amino-6-cyano-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**59**)

Scheme 8



Step 1. Ethyl 2-amino-6-cyano-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**56**).

To a solution of 4-oxo-1-phenylcyclohexane-1-carbonitrile (**55**) (6.00 g, 30.1 mmol) and ethyl 2-cyanoacetate (2.91 mL, 27.4 mmol) in EtOH (48.0 mL) were added morpholine (2.60 mL, 30.1 mmol) and sulfur (969 mg, 3.78 mmol). The reaction mixture was stirred at 60 °C for 16 hours. The mixture was allowed to cool to RT and a white precipitate appeared. This solid was collected by filtration, washed with EtOH and dried in vacuo to afford title compound **56** as a white solid (8.15 g, 91% yield). LC-MS: rt = 1.55 min, MS: 326.1 (calcd), 327.0 ($\text{M}+\text{H}^+$, found).

Step 2. Ethyl 2-acetamido-6-cyano-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**57**).

To a solution of **56** (8.15 g, 25.0 mmol) in acetic acid (143 mL) was added acetic anhydride (2.83 mL, 30.0 mmol). The mixture was stirred at 60 °C for 1 day, then allowed to cool to RT and concentrated to dryness. The residue was partitioned between DCM and water. The layers were separated and the organic phase was washed with a saturated aqueous solution of NaHCO_3 ,

water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated to afford title compound **57** as a white solid (9.0 g, 98% yield). LC-MS: rt = 1.61 min, MS: 368.1 (calcd), 369.1 (M+H⁺, found).

Step 3. Ethyl 2-acetamido-6-cyano-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**58**).

To a solution of **57** (9.00 g, 24.4 mmol) in acetic acid (66 mL) and water (66 mL) was added ceric sulfate (70.1 g, 211 mmol). The mixture was sonicated until it became homogenous, and stirred at RT for 24 hours. The suspension was partitioned between EA and water. The layers were separated and the organic phase was washed with NaOH 1 N, water and brine. The organic layer was then dried over Na₂SO₄, filtered and concentrated to afford title compound **58** as an off-white solid (9.10 g, 97% yield). LC-MS: rt = 1.56 min, MS: 382.1 (calcd), 383.1 (M+H⁺, found).

Step 4. 2-Amino-6-cyano-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**59**).

To a suspension of **58** (4.00 g, 10.44 mmol) in MeOH (1.26 L) was added a solution of lithium hydroxide monohydrate (2.20 g, 52.4 mmol) in water (1.26 L). The reaction mixture was stirred under reflux for 2 hours, then allowed to cool to RT. The mixture was diluted with water and concentrated to remove most of the organic solvent, then washed with EA. The aqueous layer was acidified by slow addition of HCl 3 N and extracted with EA. This organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by trituration with a DCM/pentane mixture to afford title compound **59** as a greyish solid (2.54 g, 78% yield).

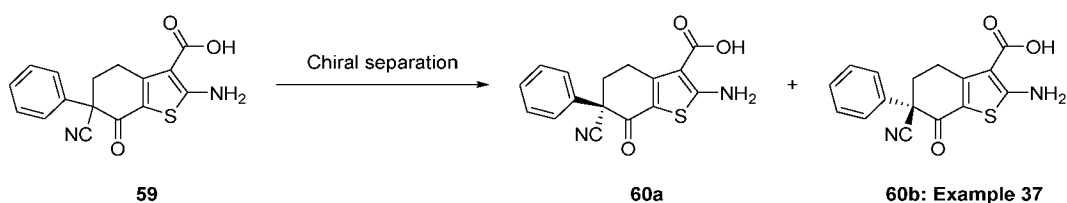
¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.43-7.31 (m, 5H), 3.27-3.23 (m, 1H), 2.88-2.73 (m, 2H), 2.71-2.61 (m, 1H). LC-MS: rt = 1.23 min, MS: 312.1 (calcd), 313.1 (M+H⁺, found).

Example 37

(R)-2-Amino-6-cyano-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (60a**)**

(S)-2-Amino-6-cyano-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (60b**)**

Scheme 9



Racemic compound **59** (86.0 mg) was submitted to SFC chiral separation (isocratic 35% MeOH in CO₂) to afford enantioenriched compound **60a** as a light-pink solid (33.1 mg, 38% separation yield) and **60b** as a white solid (35.4 mg, 41% separation yield) (the absolute configurations were assigned based on resolved crystal structure of enantiomer **60a**).

60a: ^1H NMR: same as racemic mixture (**59**). LC-MS: $r_t = 1.23$ min, MS: 312.1 (calcd), 313.1 ($\text{M}+\text{H}^+$, found). Analytical SFC (IG column with 5-60% MeOH in water (95-40% CO_2) gradient): $r_t = 3.84$ min, ee. = 99.9%.

60b: ^1H NMR: same as racemic mixture (**59**). LC-MS: $r_t = 1.23$ min, MS: 312.1 (calcd), 313.1 ($\text{M}+\text{H}^+$, found). Analytical SFC (IG column with 5-60% MeOH in water (95-40% CO_2) gradient): $r_t = 4.76$ min, ee. = 97.6%.

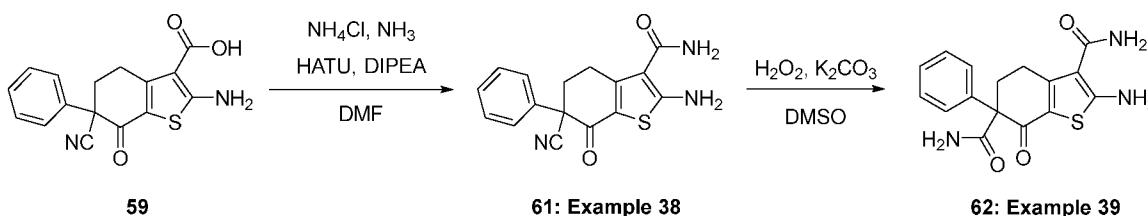
Example 38

2-Amino-6-cyano-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**61**) and

Example 39

2-Amino-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3,6-dicarboxamide (**62**)

Scheme 10



Step 1. 2-Amino-6-cyano-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**61**).

To a solution of **59** (2.54 g, 8.13 mmol) in DMF (90.0 mL) were added HATU (4.73 g, 12.2 mmol) and *N,N*-diisopropylethylamine (2.83 mL, 16.4 mmol) and the mixture was stirred at RT for 20 min. Then, ammonium chloride (8.74 g, 163 mmol), NH_3 solution in THF (45.0 mL, 18.0 mmol, 0.4 M) and saturated NH_3 solution in chloroform (45.0 mL) (prepared in-house) were added to the mixture. The reaction mixture was stirred at RT for 16 hours and partitioned between EA and a saturated aqueous solution of NaHCO_3 . The layers were separated, and the organic phase was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 20% to 100% of EA in hexane) and then by reverse-phase flash column chromatography (eluent gradient from 0% to 100% CH_3CN in H_2O with 0.1% (v/v) formic acid) to afford title compound **61** as a white solid (1.20 g, 47% yield).

^1H NMR: 400 MHz, CD_3OD , δ (ppm): 7.41-7.36 (m, 5H), 3.17-3.11 (m, 1H), 2.87-2.77 (m, 2H), 2.74-2.66 (m, 1H). LC-MS: $r_t = 1.04$ min, MS: 311.1 (calcd), 312.0 ($\text{M}+\text{H}^+$, found).

Step 2. 2-Amino-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3,6-dicarboxamide (**62**)

30% Aqueous hydrogen peroxide solution (170 μL) was added to a suspension of **61** (13.2 mg, 42.4 μmol) and potassium carbonate (11.7 mg, 84.8 μmol) in DMSO (569 μL). The mixture was stirred at RT for 3 hours, then partitioned between EA and water (5 mL each). The layers were separated, the organic phase was washed with 5 mL of water and the combined aqueous

phase was extracted with EA (2 x 3 mL). The combined organics were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by reverse-phase flash column chromatography (eluent gradient from 0% to 70% of CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **62** as a white solid (3.6 mg, 28% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.41-7.25 (m, 5H), 3.05 (dt, *J* = 16.8, 4.2 Hz, 1H), 2.78-2.59 (m, 3H). LC-MS: rt = 0.86 min, MS: 329.1 (calcd), 329.9 (M+H⁺, found).

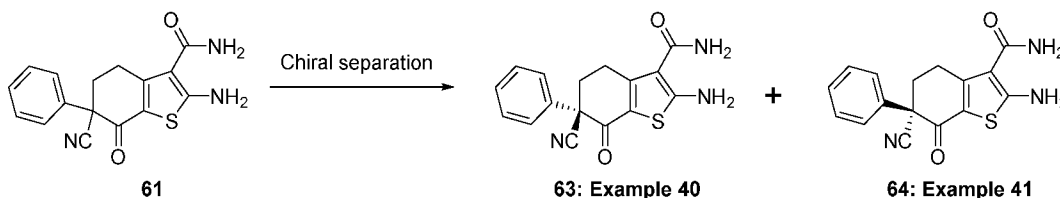
Example 40

(S)-2-Amino-6-cyano-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (63) and

Example 41

(R)-2-Amino-6-cyano-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (64)

Scheme 11



Racemic compound **61** (96.5 mg) was submitted to SFC chiral separation (isocratic: 45% of CH₃CN/EtOH 1:1 in CO₂) to yield enantioenriched compound **63** as a white solid (29.0 mg, 30% separation yield) and enantioenriched compound **64** as a white solid (29.0 mg, 30% separation yield) (the absolute configurations were assigned based on resolved crystal structure of enantiomer **64**).

63: ¹H NMR: same as racemic mixture (**61**). LC-MS: rt = 1.04 min, MS: 311.1 (calcd), 312.0 (M+H⁺, found). Analytical SFC (IG column with 5-60% ACN/EtOH (95-40% CO₂) gradient): rt = 4.71 min, ee. = >99.9%.

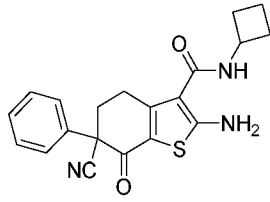
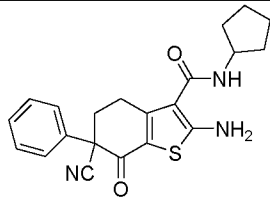
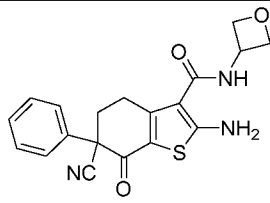
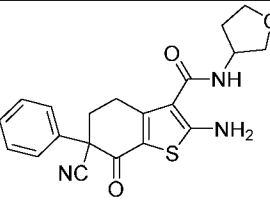
64: ¹H NMR: same as racemic mixture (**61**). LC-MS: rt = 1.04 min, MS: 311.1 (calcd), 312.0 (M+H⁺, found). Analytical SCF (IG column with 5-60% ACN/EtOH (95-40% CO₂) gradient): rt = 4.09 min, ee. = >99.9%.

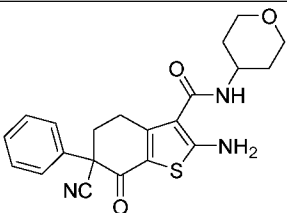
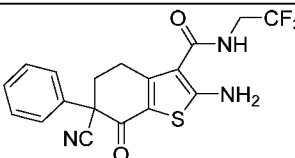
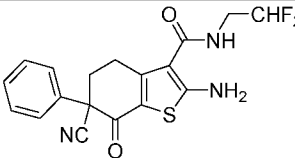
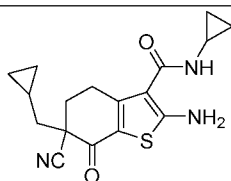
Examples 42-49

Compounds **65-71** (examples 42-48) were synthesized by following a procedure similar to the one described above for the synthesis of compound **9** (example 2, scheme 2), starting from compound **59** (example 36, scheme 8) instead of compound **8**, and using cyclobutylamine, cyclopentylamine, 3-aminoxetane, 3-aminotetrahydrofuran, 4-aminotetrahydropyran, 2,2,2-trifluoroethylamine and 2,2-difluoroethan-1-amine respectively, instead of cyclopropylamine. Compound **72** (example 49) was obtained in the same fashion starting from compound **53**

(example 34, scheme 7). Characterization of compounds **65-72** (examples 42-49) is provided in the table 3.

Table 3. Characterization of compounds **65-72** (examples 42-49).

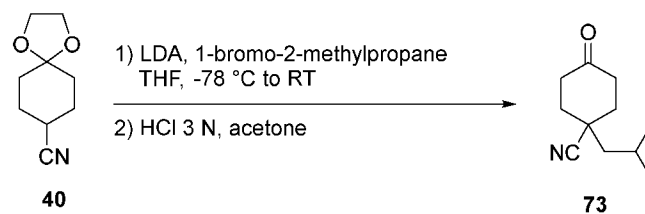
Ex. #	Cpd #	Structure	Characterization
42	65	 2-Amino-6-cyano-<i>N</i>-cyclobutyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 7.42-7.40 (m, 4H), 7.39-7.35 (m, 1H), 4.37 (t, <i>J</i> = 8.33 Hz, 1H), 3.12-3.06 (m, 1H), 2.85-2.74 (m, 2H), 2.71-2.66 (m, 1H), 2.31-2.25 (m, 2H), 2.04-1.97 (m, 2H), 1.75-1.69 (m, 2H). LC-MS: rt = 1.39 min, MS: 365.1 (calcd), 366.1 (M+H ⁺ , found).
43	66	 2-Amino-6-cyano-<i>N</i>-cyclopentyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹ H NMR: 400 MHz CD ₃ OD, δ (ppm): 7.40-7.35 (m, 5H), 4.20 (t, <i>J</i> = 6.96 Hz, 1H), 3.10-3.03 (m, 1H), 2.82-2.74 (m, 2H), 2.70-2.65 (m, 1H), 1.98-1.92 (m, 2H), 1.73-1.67 (m, 2H), 1.60-1.55 (m, 2H), 1.52-1.45 (m, 2H). LC-MS: rt = 1.46 min, MS: 379.1 (calcd), 380.1 (M+H ⁺ , found).
44	67	 2-Amino-6-cyano-<i>N</i>-(oxetan-3-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 7.41-7.36 (m, 5H), 5.00-4.95 (m, 1H), 4.87-4.85 (m, 2H), 4.61 (t, <i>J</i> = 6.76 Hz, 2H), 3.15 (ddd, <i>J</i> = 17.50, 6.18, 4.45 Hz, 1H), 2.90-2.76 (m, 2H), 2.71-2.67 (m, 1H). LC-MS: rt = 1.13 min, MS: 367.1 (calcd), 368.2 (M+H ⁺ , found).
45	68	 2-Amino-6-cyano-7-oxo-6-phenyl-<i>N</i>-(tetrahydrofuran-3-yl)-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 7.41-7.36 (m, 5H), 4.47-4.44 (m, 1H), 3.92-3.85 (m, 2H), 3.80-3.74 (m, 1H), 3.69-3.62 (m, 1H), 3.13-3.05 (m, 1H), 2.84-2.75 (m, 2H), 2.71-2.66 (m, 1H), 2.26-2.20 (m, 1H), 1.93-1.87 (m, 1H). LC-MS: rt = 1.15 min, MS: 381.1 (calcd), 382.1 (M+H ⁺ , found).

46	69	 2-Amino-6-cyano-7-oxo-6-phenyl-<i>N</i>-(tetrahydro-2H-pyran-4-yl)-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.41-7.36 (m, 5H), 4.02-3.96 (m, 1H), 3.93-3.89 (m, 2H), 3.50-3.43 (m, 2H), 3.12-3.05 (m, 1H), 2.87-2.74 (m, 2H), 2.72-2.64 (m, 1H), 1.90-1.81 (m, 2H), 1.65-1.51 (m, 2H). LC-MS: rt = 1.21 min, MS: 395.1 (calcd), 396.1 (M+H⁺, found).
47	70	 2-Amino-6-cyano-7-oxo-6-phenyl-<i>N</i>-(2,2,2-trifluoroethyl)-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.41-7.36 (m, 5H), 4.10-3.86 (m, 2H), 3.14-3.05 (m, 1H), 2.87-2.77 (m, 2H), 2.75-2.66 (m, 1H). ¹⁹F NMR: 376 MHz, CD₃OD, δ (ppm): -73.7 (t, <i>J</i> = 9.2 Hz). LC-MS: rt = 1.37 min, MS: 393.1 (calcd), 394.1 (M+H⁺, found).
48	71	 2-Amino-6-cyano-<i>N</i>-(2,2-difluoroethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.42-7.37 (m, 5H), 5.95 (tt, <i>J</i> = 56.4, 4.07 Hz, 1H), 3.69-3.57 (m, 2H), 3.13-3.07 (m, 1H), 2.85-2.76 (m, 2H), 2.73-2.63 (m, 1H). ¹⁹F NMR: 376 MHz, CD₃OD, δ (ppm): -124.4 (dt). LC-MS: rt = 1.27 min, MS: 375.1 (calcd), 376.1 (M+H⁺, found).
49	72	 2-Amino-6-cyano-<i>N</i>-cyclopropyl-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹H NMR: 400 MHz, CD₃OD, δ (ppm): 3.01 (t, <i>J</i> = 6.04 Hz, 2H), 2.78-2.72 (m, 1H), 2.57-2.48 (m, 1H), 2.45-2.36 (m, 1H), 1.91 (dd, <i>J</i> = 14.26, 7.18 Hz, 1H), 1.80 (dd, <i>J</i> = 14.24, 6.72 Hz, 1H), 0.90-0.86 (m, 1H), 0.79-0.74 (m, 2H), 0.60-0.53 (m, 4H), 0.23-0.19 (m, 2H). LC-MS: rt = 1.23 min, MS: 329.1 (calcd), 330.1 (M+H⁺, found).

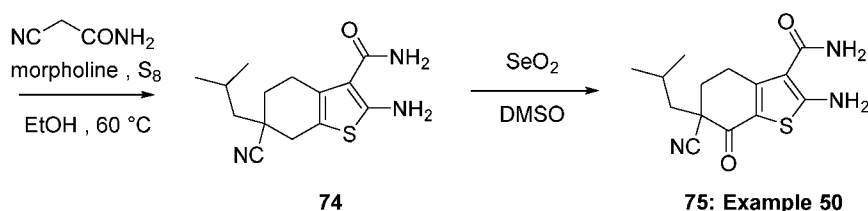
Example 50

2-Amino-6-cyano-6-isobutyl-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (75)

Scheme 12



Scheme 4

Step 1. 1-Isobutyl-4-oxocyclohexane-1-carbonitrile (73).

To a solution of 1,4-dioxaspiro[4.5]decane-8-carbonitrile (**40**, 221 μ L, 1.50 mmol, scheme 4) in THF (3.0 mL) at -78 °C was added dropwise LDA (2.39 mL, 1 M in THF/hexane, 2.39 mmol). After 30 min, 1-bromo-2-methylpropane (164 μ L, 1.50 mmol) was added dropwise and the reaction mixture was stirred at RT for 72 hours. The reaction mixture was then partitioned between hexane and water. The layers were separated and the aqueous phase was extracted with EA. The combined organic layers were combined, dried over Na₂SO₄, filtered and concentrated. The dry residue was dissolved in acetone (19.7 mL) and HCl 3 N (4.98 mL, 15.0 mmol) was added slowly. The mixture was stirred for 16 hours, then neutralized by slowly adding saturated NaHCO₃ solution and concentrated to remove the organic solvent. The remaining aqueous solution was extracted with EA and the organic layer was dried over Na₂SO₄, filtered and concentrated to dryness to afford title compound **73** (141 mg, 52% yield over two steps). LC-MS: *rt* = 1.45 min, MS: 179.1 (calcd), 180.0 (M+H⁺, found).

Step 2. 2-Amino-6-cyano-6-isobutyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (74).

To a solution of **73** (141 mg, 0.784 mmol) and cyanoacetamide (59.9 mg, 0.713 mmol) in EtOH (713 μ L) were added morpholine (67.6 μ L, 0.784 mmol) and sulfur (25.2 mg, 98.3 μ mol). The reaction mixture was stirred at 60 °C for 19 hours, allowed to cool to RT and concentrated to dryness. The residue was partitioned between EA and water. The layers were separated and the organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 100% of EA in hexane) to afford title compound **74** as a beige solid (115 mg, 58% yield). LC-MS: *rt* = 1.49 min, MS: 277.1 (calcd), 277.9 (M+H⁺, found).

Step 3. 2-Amino-6-cyano-6-isobutyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (75).

To a solution of **74** (30 mg, 0.108 mmol) in DMSO (643 μ L) was added selenium dioxide (12.0 mg, 0.108 mmol). The reaction mixture was stirred at RT for 12 hours, then partitioned between brine and EA. The layers were separated and the organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 10% of MeOH in DCM) then by Semi-Prep HPLC-MS (35% to 100% MeOH in 10 mM ammonium formate pH = 3.8) to afford title compound **75** as a white solid (3.20 mg, 10% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 3.19-3.09 (m, 2H), 2.51 (ddd, J = 13.71, 7.59, 5.42 Hz, 1H), 2.36 (dt, J = 13.65, 5.45 Hz, 1H), 1.97-1.85 (m, 2H), 1.80-1.75 (m, 1H), 1.03 (d, J = 6.05 Hz, 6 H). LC-MS: t_r = 1.11 min, MS: 291.1 (calcd), 292.1 (M+H⁺, found).

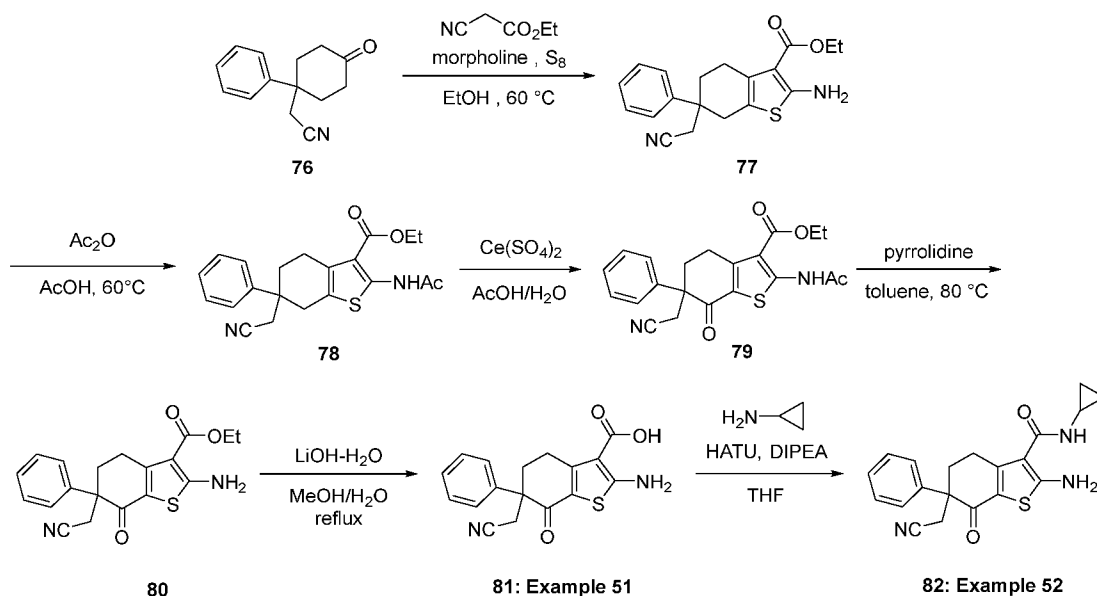
Example 51

2-Amino-6-(cyanomethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (81) and

Example 52

2-Amino-6-(cyanomethyl)- N-cyclopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (82)

Scheme 13



Step 1. Ethyl 2-amino-6-(cyanomethyl)-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (77).

To a solution of 2-(4-oxo-1-phenylcyclohexyl)acetonitrile (**76**) (*Bioorg. Med. Chem. Lett.*, 21, p. 405, 2011) (705 mg, 3.31 mmol) and ethyl 2-cyanoacetate (351 μ L, 3.01 mmol) in EtOH

(3.01 mL) were added morpholine (285 μ L, 3.31 mmol) and sulfur (106 mg, 0.415 mmol). The mixture was stirred at 60 °C for 16 hours, then allowed to cool to RT and a white precipitate formed. This solid was collected by filtration, washed with EtOH and dried in vacuo to afford title compound **77** as a white solid (682 mg, 67% yield). LC-MS: rt = 1.55 min, MS: 340.1 (calcd), 341.1 ($M+H^+$, found).

Step 2. Ethyl 2-acetamido-6-(cyanomethyl)-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**78**).

To a solution of **77** (682 mg, 2.00 mmol) in acetic acid (11.5 mL) was added acetic anhydride (227 μ L, 2.40 mmol). The mixture was stirred at 60 °C for 24 hours, then allowed to cool to RT and concentrated to dryness. The residue was partitioned between DCM and water. The layers were separated and the organic phase was washed with a saturated aqueous solution of $NaHCO_3$, water and brine. The organic layer was dried over Na_2SO_4 , filtered and concentrated to afford title compound **78** as a white solid (766 mg, >99% yield). LC-MS: rt = 1.61 min, MS: 382.1 (calcd), 383.1 ($M+H^+$, found).

Step 3. Ethyl 2-acetamido-6-(cyanomethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**79**).

To a solution of **78** (766 mg, 2.00 mmol) in acetic acid (6.73 mL) and water (6.73 mL) was added ceric sulfate (5.75 g, 17.3 mmol). The suspension was sonicated until it became homogenous, and stirred at RT for 1 day, then it was partitioned between EA and water. The layers were separated and the organic phase was washed with NaOH 1 N, water and brine. The organic layer was dried over Na_2SO_4 , filtered and concentrated to afford title compound **79** as an off-white solid (794 mg, >99% yield). LC-MS: rt = 1.47 min, MS: 396.1 (calcd), 397.1 ($M+H^+$, found).

Step 4. Ethyl 2-amino-6-(cyanomethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**80**).

To a suspension of **79** (793 mg, 2.00 mmol) in toluene (3.28 mL) was added pyrrolidine (2.46 mL, 30.0 mmol). The suspension turned into a solution after a few minutes of stirring and the reaction mixture was stirred at 80 °C for 1 hour, then allowed to cool to RT and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 100% of EA in hexane) to afford title compound **80** as a white solid (408 mg, 57% yield). LC-MS: rt = 1.43 min, MS: 354.1 (calcd), 355.0 ($M+H^+$, found).

Step 5. 2-Amino-6-(cyanomethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**81**).

To a suspension of **80** (408 mg, 1.15 mmol) in MeOH (139 mL) was added a solution of lithium hydroxide monohydrate (242 mg, 5.76 mmol) in water (139 mL). The reaction mixture was stirred under reflux for 16 hours, then allowed to cool to RT. The mixture was diluted with water and concentrated to remove most of the organic solvent, then washed with EA. The aqueous

layer was collected, acidified by slow addition of HCl 2N and extracted with EA. This organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 10% of MeOH in DCM) to afford title compound **81** as a white solid (376 mg, >99% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.34-7.27 (m, 5H), 3.35-3.30 (m, 1H), 3.01 (d, *J* = 16.71 Hz, 1H), 2.89 (d, *J* = 16.71 Hz, 1H), 2.77-2.74 (m, 1H), 2.49-2.45 (m, 2H). LC-MS: *rt* = 1.16 min, MS: 326.1 (calcd), 327.0 (M+H⁺, found).

Step 6. 2-Amino-6-(cyanomethyl)- *N*-cyclopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**82**).

To a suspension of **81** (154 mg, 0.472 mmol) in THF (5.90 mL) were added HATU (359 mg, 0.944 mmol) and *N,N*-diisopropylethylamine (164 μL, 0.944 mmol). The mixture was stirred at RT for 20 min and then cyclopropylamine (327 μL, 4.72 mmol) was added. The reaction mixture was stirred for an additional 16 hours, then partitioned between EA and a saturated aqueous solution of NH₄Cl. The layers were separated and the organic phase was collected, washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 20% to 100% of EA in hexane) and then by reverse-phase flash column chromatography (eluent gradient from 0% to 100% CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **82** as a white solid (46.5 mg, 27% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.35-7.27 (m, 5H), 3.00 (d, *J* = 16.70 Hz, 1H), 2.89 (d, *J* = 16.71 Hz, 1H), 2.82-2.78 (m, 1H), 2.77-2.74 (m, 1H), 2.69-2.64 (m, 2H), 2.49-2.42 (m, 1H), 0.72-0.67 (m, 2H), 0.54-0.48 (m, 2H). LC-MS: *rt* = 1.20 min, MS: 365.1 (calcd), 366.1 (M+H⁺, found).

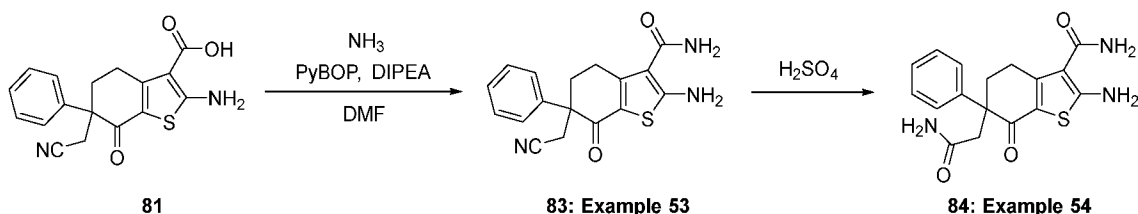
Example 53

2-Amino-6-(cyanomethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (83**) and**

Example 54

2-Amino-6-(2-amino-2-oxoethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (84**)**

Scheme 14



Step 1. 2-Amino-6-(cyanomethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**83**).

A suspension of **81** (50.0 mg, 0.153 mmol) in anhydrous DMF (1.69 mL) was saturated with gaseous NH₃. Then, PyBOP (120 mg, 0.230 mmol) and *N,N*-diisopropylethylamine (53.4 μ L, 0.306 mmol) were added and the reaction mixture was stirred at RT for 16 hours. Afterwards, the mixture was partitioned between EA and a saturated aqueous solution of NH₄Cl. The layers were separated and the aqueous phase was extracted with EA. The combined organics were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 20% to 100% of EA in hexane) then by reverse-phase flash column chromatography (eluent gradient from 0% to 100% CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **83** as a white solid (47.0 mg, 94% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.39-7.29 (m, 5H), 3.02-2.95 (m, 2H), 2.90 (d, *J* = 16.72 Hz, 1H), 2.80 (ddd, *J* = 13.55, 4.09, 2.50 Hz, 1H), 2.67 (ddd, *J* = 17.32, 11.78, 4.10 Hz, 1H), 2.49 (ddd, *J* = 13.53, 11.79, 4.45 Hz, 1H). LC-MS: *rt* = 1.01 min, MS: 325.1 (calcd), 326.0 (M+H⁺, found).

Step 2. 2-Amino-6-(2-amino-2-oxoethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**84**).

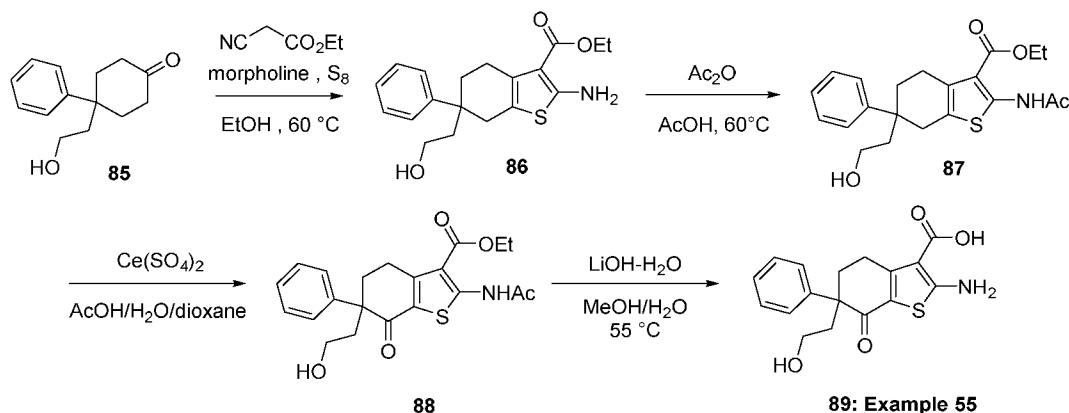
A suspension of **83** (47.0 mg, 0.144 mmol) in concentrated sulfuric acid (470 μ L) was stirred at RT for 72 hours, then poured on crushed ice and the resulting mixture was basified using a 4 N NaOH solution. The solution was extracted with DCM. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 10% of MeOH in DCM, then 100% isopropanol) to afford title compound **84** as a white solid (17.5 mg, 35% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.32-7.27 (m, 4H), 7.23-7.19 (m, 1H), 2.99 (d, *J* = 14.78 Hz, 1H), 2.92-2.87 (m, 1H), 2.78-2.71 (m, 1H), 2.65 (d, *J* = 14.76 Hz, 2H), 2.60-5.50 (m, 1H). LC-MS: *rt* = 0.84 min, MS: 343.1 (calcd), 344.1 (M+H⁺, found).

Example 55

2-Amino-6-(2-hydroxyethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (89**).**

Scheme 15



Step 1. Ethyl 2-amino-6-(2-hydroxyethyl)-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (86).

To a solution of 4-(2-hydroxyethyl)-4-phenylcyclohexan-1-one (**85**) (*Bioorg. Med. Chem. Lett.*, 21, p. 405, 2011) (7.95 g, 36.4 mmol) and ethyl 2-cyanoacetate (4.26 mL, 40.1 mmol) in EtOH (36.4 mL) were added morpholine (3.50 mL, 40.1 mmol) and sulfur (1.29 g, 5.03 mmol). The reaction mixture was stirred at 60 °C for 16 hours, then allowed to cool to RT and a white precipitate formed. This solid was collected by filtration, washed with EtOH and dried in vacuo to afford title compound **86** as a white solid (9.40 g, 72% yield). LC-MS: rt = 1.41 min, MS: 345.1 (calcd), 346.1 (M+H⁺, found).

Step 2. Ethyl 2-acetamido-6-(2-hydroxyethyl)-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (87).

To a solution of **86** (8.30 g, 24.0 mmol) in acetic acid (138 mL) was added acetic anhydride (2.73 mL, 28.8 mmol). The mixture was stirred at 60 °C for 2 hours, then allowed to cool to RT and concentrated to dryness to afford title compound **87** as a brown oil which was used directly for the next step. LC-MS: rt = 1.78 min, MS: 387.2 (calcd), 388.2 (M+H⁺, found).

Step 3. Ethyl 2-acetamido-6-(2-hydroxyethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (88).

To a solution of **87** (24.0 mmol) in acetic acid (160 mL), water (160 mL) and dioxane (160 mL) was added ceric sulfate (69.0 g, 208 mmol). The mixture was sonicated until it became homogenous, stirred at RT for 24 hours and partitioned between EA and water. The layers were separated and the organic phase was washed with NaOH 1 N, water and brine. The organic layer was then dried over Na₂SO₄, filtered and concentrated to afford title compound **88** as an orange solid (9.60 g, 91% yield). LC-MS: rt = 1.56 min, MS: 401.1 (calcd), 402.1 (M+H⁺, found).

Step 4. 2-Amino-6-(2-hydroxyethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (89).

To a suspension of **88** (9.60 g, 24.1 mmol) in MeOH (1.11 L) was added a solution of lithium hydroxide monohydrate (6.86 g, 163.4 mmol) in water (1.11 L). The reaction mixture was stirred at 55 °C for 24 hours, then allowed to cool to RT. The cooled mixture was diluted with

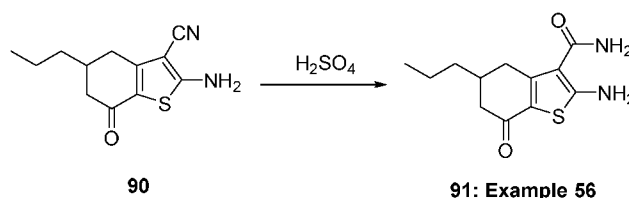
water and concentrated to remove most of the organic solvent, then washed with EA. The aqueous layer was collected, acidified by slow addition of HCl 2 N and extracted with EA. This organic extract was dried over Na₂SO₄, filtered and concentrated to afford title compound **89** as an orange solid (7.0 g, 88% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.29-7.16 (m, 5H), 3.53-3.38 (m, 2H), 3.20-3.12 (m, 1H), 2.61-2.53 (dt, *J* = 13.63, 3.48 Hz, 1H), 2.44 (ddd, *J* = 18.55, 11.61, 4.01 Hz, 1H), 2.34-2.23 (m, 1H), 2.15-2.03 (m, 2H). LC-MS: rt = 1.04 min, MS: 331.1 (calcd), 332.0 (M+H⁺, found).

Example 56

2-Amino-7-oxo-5-propyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (91)

Scheme 16



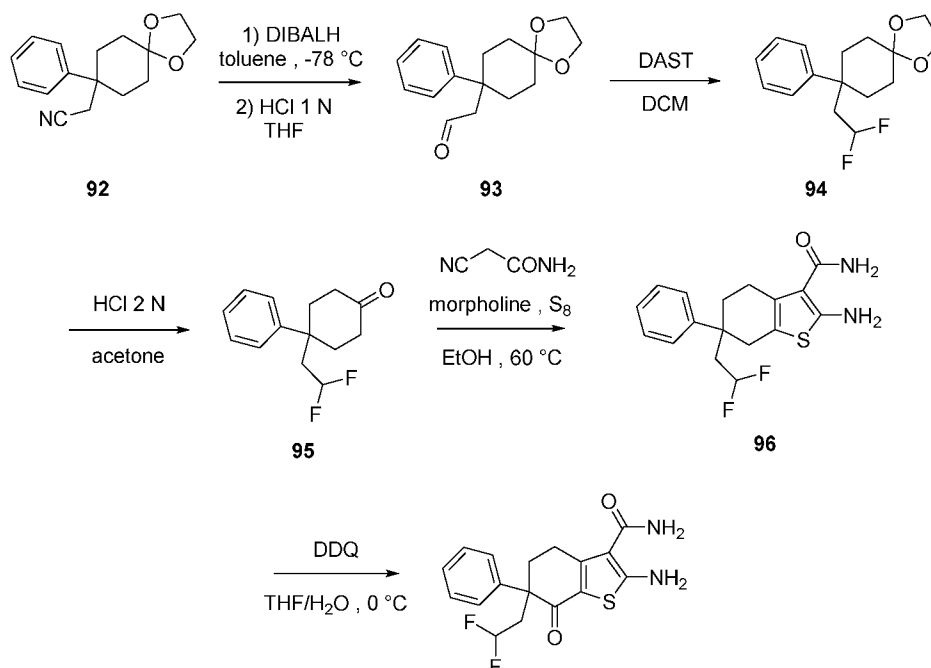
Compound **90** (277 mg, 1.18 mmol, synthesized similarly to compound **3** in scheme 1 starting from 5-propyl-1,3-cyclohexanedione instead of 5-(2-(trifluoromethyl)phenyl)cyclohexane-1,3-dione) was dissolved in H₂SO₄ 98% (2.5 mL) and the mixture was stirred at RT for 24 hours. Then, the reaction mixture was slowly poured into ice-cold aqueous K₂CO₃, diluted with water and extracted with EA (Part of the product precipitated. It was collected by filtration and combined with the rest of the crude). The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 50% to 100% of EA in hexane) to afford title compound **91** as an off-white solid (144 mg, 48% yield).

¹H NMR: 400 MHz, DMSO-*d*₆, δ (ppm): 7.97 (s, 2H), 6.96 (bs, 2H), 2.99-2.95 (m, 1H), 2.67-2.57 (m, 1H), 2.38-2.32 (m, 1H), 2.19-2.07 (2H, m), 1.36 (bs, 4H), 0.88 (bs, 3H). LC-MS: rt = 2.30 min, MS: 252.1 (calcd), 253.1 (M+H⁺, found).

Example 57

2-Amino-6-(2,2-difluoroethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (97)

Scheme 17



97: Example 57

Step 1. 2-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)acetaldehyde (93)

To a solution of 2-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)acetonitrile (**92**) (1.0 g, 3.89 mmol) (*Bioorg Med. Chem Lett.* 21, p. 405, 2011) in anhydrous toluene (24.5 mL) at -78 °C was added dropwise DIBALH (3.92 mL, 25% in toluene, 5.83 mmol). The reaction mixture was stirred at -78 °C for 2 hours, before being carefully quenched with MeOH and saturated NH₄Cl solution. Afterwards, the mixture was allowed to reach RT and diluted with Et₂O, then filtered through a celite pad. The layers were separated and the organic phase was concentrated. The residue was dissolved in THF (15.0 mL) and HCl 1 N (3.89 mL 3.89 mmol) was added. The mixture was stirred at RT for 15 min, before being quenched with saturated NaHCO₃ solution and extracted with Et₂O. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 5% to 100% of EA in hexane) to afford title compound **93** (605 mg, 60% yield) as a colorless oil, which was not characterized and used directly for the next step.

Step 2. 8-(2,2-Difluoroethyl)-8-phenyl-1,4-dioxaspiro[4.5]decane (94)

To a solution of **93** (200 mg, 0.77 mmol) in anhydrous DCM (9.5 mL) at 0 °C was added DAST (0.19 mL, 1.54 mmol). The reaction mixture was stirred at RT for 1 hour, then it was quenched with saturated NaHCO₃ solution and extracted with DCM. The organic layer was dried over Na₂SO₄, filtered and concentrated to afford title compound **94** (213 mg, 98% yield) as a colorless oil, which was not characterized and used directly for the next step.

Step 3. 4-(2,2-Difluoroethyl)-4-phenylcyclohexan-1-one (95)

To a solution of **94** (213 mg, 0.75 mmol) in acetone (10.5 mL) was added HCl 2 N (1.89 mL, 3.77 mmol) and the reaction mixture was stirred at RT for 16 hours. Then, the mixture was neutralized by slowly adding saturated NaHCO₃ solution and concentrated to remove the organic solvent. The residue was extracted with EA and the organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness to afford title compound **95** (169 mg, 94% yield) as a colorless oil, which was not characterized and used directly for the next step.

Step 4. 2-Amino-6-(2,2-difluoroethyl)-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**96**)

To a solution of **95** (169 mg, 0.709 mmol) and cyanoacetamide (66 mg, 0.78 mmol) in EtOH (0.7 mL) were added morpholine (0.068 mL, 0.78 mmol) and sulfur (25 mg, 0.098 mmol). The reaction mixture was stirred at 60 °C for 16 hours, then allowed to cool to RT and concentrated to dryness. The residue was partitioned between water and EA. The layers were separated and the organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 50% to 100% of EA in hexane) to afford title compound **96** (93 mg, 39% yield). LC-MS: rt = 1.39 min, MS: 336.1 (calcd), 337.1 (M+H⁺, found).

Step 5. 2-Amino-6-(2,2-difluoroethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**97**)

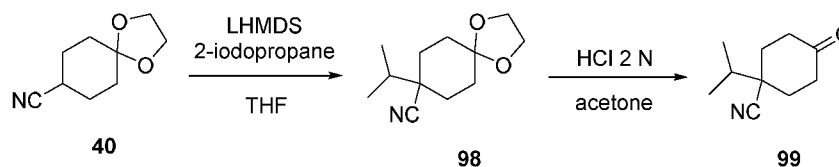
To a mixture of **96** (40 mg, 0.119 mmol) in THF (0.4 mL) and water (0.08 mL) at 0 °C was added dropwise a solution of DDQ (82 mg, 0.36 mmol) in THF (0.4 mL). The reaction mixture was stirred at 0 °C for 30 min, then the mixture was quenched with saturated NaHCO₃ solution and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 50% to 100% of EA in hexane) to afford title compound **97** as a pale-yellow solid (3 mg, 7% yield).

¹H NMR: 400 MHz, CDCl₃, δ (ppm): 7.37-7.27 (m, 5H), 7.04 (s, 2H), 5.80 (tt, *J* = 56.4, 4.6, 1H), 5.32 (s, 2H), 2.97-2.92 (m, 1H), 2.83-2.78 (m, 1H), 2.65-2.57 (m, 1H), 2.53-2.42 (m, 3H). ¹⁹F NMR: 376 MHz, CDCl₃, δ (ppm): -110.4 (ddt, *J* = 287.8, 56.1, 18.0 Hz, 1F), -111.5 (ddt, *J* = 287.8, 56.5, 16.3 Hz, 1F). LC-MS: rt = 1.25 min, MS: 350.1 (calcd), 351.0 (M+H⁺, found).

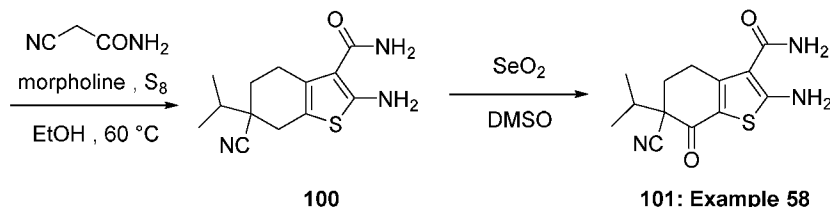
Example 58

2-Amino-6-cyano-6-isopropyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (101**)**

Scheme 18



Scheme 4



Step 1. 8-Isopropyl-1,4-dioxaspiro[4.5]decane-8-carbonitrile (**98**)

To a solution of 1,4-dioxaspiro[4.5]decane-8-carbonitrile (**40**, scheme 4) (1.0 g, 5.98 mmol) in anhydrous THF (12.0 mL) at 0 °C was added dropwise LHMDS (6.88 mL, 1 M in THF, 6.88 mmol). The reaction mixture was stirred at 0 °C for 1 hour, before adding dropwise 2-iodopropane (0.597 mL, 5.98 mmol). Then, the reaction mixture was allowed to slowly reach RT and stirred for 16 hours. Afterwards, the reaction mixture was quenched with water and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated to dryness to afford title compound **98** as a brown solid, which was used directly for the next step. LC-MS: *rt* = 3.05 min, MS: 209.1 (calcd), 210.1 (M+H⁺, found).

Step 2. 1-Isopropyl-4-oxocyclohexane-1-carbonitrile (**99**)

To a solution of **98** (5.98 mmol) in acetone (80 mL) was added HCl 2 N (23.9 mL, 47.8 mmol) and the reaction mixture was stirred at RT for 2 days. Then, the mixture was neutralized by slowly adding saturated NaHCO₃ solution and concentrated to remove the organic solvent. The residue was extracted with EA and the organic layer was dried over Na₂SO₄, filtered and concentrated to dryness to afford title compound **99** (445 mg, 45% yield over two steps). LC-MS: *rt* = 2.35 min, MS: 165.2 (calcd), 166.1 (M+H⁺, found).

Step 3. 2-Amino-6-cyano-6-isopropyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**100**)

To a solution of **99** (445 mg, 2.69 mmol) and cyanoacetamide (206 mg, 2.45 mmol) in EtOH (4.9 mL) were added morpholine (0.24 mL, 2.69 mmol) and sulfur (87 mg, 0.338 mmol). The reaction mixture was stirred at 60 °C for 16 hours and an abundant precipitate appeared. This solid was collected by filtration to afford title compound **100** (477 mg, 74% yield) as a white solid. LC-MS: *rt* = 2.60 min, MS: 263.1 (calcd), 264.1 (M+H⁺, found).

Step 4. 2-Amino-6-cyano-6-isopropyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**101**)

To a solution of **100** (100 mg, 0.38 mmol) in DMSO (2.25 mL) was added selenium dioxide (42 mg, 0.38 mmol). The reaction mixture was stirred at RT for 16 hours, then it was partitioned

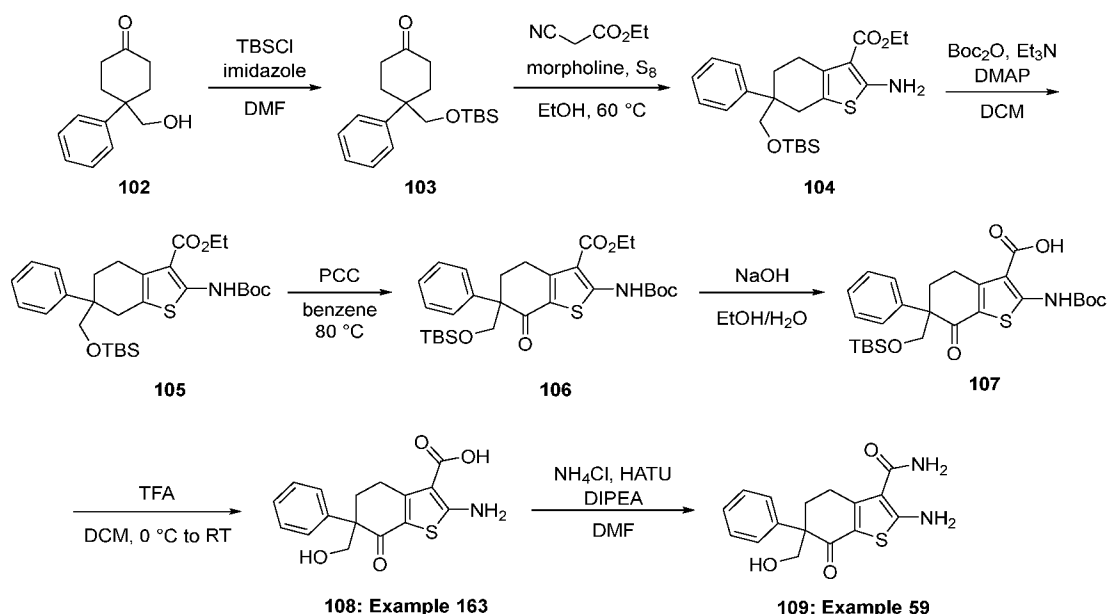
between brine and EA and the organic layer was concentrated. The residue was purified by flash column chromatography (eluent gradient from 0.5% to 10% of MeOH in DCM), then it was purified again by Semi-Prep HPLC-MS (eluent gradient from 30% to 100% of MeOH in 10 mM ammonium bicarbonate) to afford title compound **101** as a white solid (5.0 mg, 5% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 3.18 (ddd, *J* = 17.9, 8.2, 5.1 Hz, 1H), 3.06 (dt, *J* = 17.9, 5.4 Hz, 1H), 2.50-2.39 (m, 3H), 1.12-1.08 (m, 6H). LC-MS: rt = 0.97 min, MS: 277.1 (calcd), 278.1 (M+H⁺, found).

Example 59

2-Amino-6-((hydroxymethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**109**)

Scheme 19



Step 1. 4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-phenylcyclohexan-1-one (**103**)

To a solution of 4-(hydroxymethyl)-4-phenylcyclohexan-1-one (**102**) (*Bioorg. Med. Chem. Lett.*, 21, p. 405, 2011) (890 mg, 4.36 mmol) in anhydrous DMF (40 mL) were added *tert*-butyldimethylsilyl chloride (737 mg, 4.79 mmol) and imidazole (653 mg, 9.59 mmol). The resulting mixture was stirred at RT for 16 hours, then diluted with water (30 mL) and extracted with EA (70 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated, and the residue was purified by flash column chromatography (eluent gradient from 0% to 20% of EA in hexane) to afford title compound **103** as a white solid (1.20 g, 86% yield), which was not characterized and used directly for the next step.

Step 2. Ethyl 2-amino-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**104**)

A suspension of **103** (1.20 g, 3.77 mmol), morpholine (330 μ L, 3.77 mmol), sulfur (121 mg, 473 μ mol) and ethyl 2-cyanoacetate (364 μ L, 3.42 mmol) in EtOH (6.01 mL) was stirred at 60 °C for 16 hours. The mixture was then allowed to cool to RT and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 100% of EA in hexane) to afford title compound **104** as an off-white solid (1.49 g, 97% yield). LC-MS: rt = 2.34 min, MS: 445.2 (calcd), 446.2 (M+H⁺, found).

Step 3. Ethyl 2-((*tert*-butoxycarbonyl)amino)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**105**)

To a solution of **104** (1.49 g, 3.34 mmol), DMAP (41.7 mg, 334 μ mol) and triethylamine (699 μ L, 5.01 mmol) in DCM (66.8 mL) at 0 °C was added dropwise a solution of di-*tert*-butyldicarbonate (802 mg, 3.68 mmol) in DCM. The resulting mixture was stirred at RT for 16 hours, then quenched with saturated aqueous NH₄Cl solution. The layers were separated and the aqueous phase was extracted with DCM. The combined organics were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 100% of EA in hexane) to afford title compound **105** as an off-white solid (1.66 g, 91% yield). LC-MS: rt = 2.63 min, MS: 545.3 (calcd), 546.0 (M+H⁺, found).

Step 4. Ethyl 2-((*tert*-butoxycarbonyl)amino)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**106**)

A suspension of pyridinium chlorochromate (4.50 g, 20.9 mmol), celite (1.50 g) and **105** (1.50 g, 2.75 mmol) in anhydrous benzene (40.7 mL) was stirred at 80 °C for 4 hours. The mixture was then allowed to cool to RT, filtered through a pad of celite and the solid residue was washed with CHCl₃. The filtrate was concentrated, and the residue was purified by flash column chromatography (eluent gradient from 0% to 30% of EA in hexane) to afford title compound **106** as a white solid (395 mg, 26% yield). LC-MS: rt = 2.52 min, MS: 559.2 (calcd), 560.2 (M+H⁺, found).

Step 5. 2-((*tert*-Butoxycarbonyl)amino)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (**107**)

To a solution of **106** (380 mg, 679 μ mol) in EtOH (20.0 mL) was added a solution of NaOH (136 mg, 3.39 mmol) in water (20.0 mL). The resulting mixture was sonicated for 1 min and then vigorously stirred at RT for 68 hours. Subsequently, the mixture was diluted with water (15 mL) and extracted with EA (3 x 30 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane, then from 0% to 30% of MeOH in DCM) to afford title compound **107** as a white solid (264 mg, 73% yield). LC-MS: rt = 1.60 min, MS: 531.2 (calcd), 532.1 (M+H⁺, found).

Step 6. 2-Amino-6-(hydroxymethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (**108**)

Trifluoroacetic acid (5.99 mL, 78.2 mmol) was added dropwise to a solution of **107** (260 mg, 489 μmol) in DCM (30.0 mL) at 0 °C. The mixture was stirred at 0 °C for 2 hours, then the reaction vessel was removed from the ice bath and stirring continued at RT for another 2 hours. The mixture was then concentrated, the residue was taken up in DCM and concentrated 3 times, then purified by flash column chromatography (eluent gradient from 0% to 13% of MeOH in DCM) to afford title compound **108** as a light-yellow solid (80 mg, 52% yield). (See table 6 for characterization)

Step 7. 2-Amino-6-(hydroxymethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (109**)**

To a suspension of **108** (54.0 mg, 170 μmol), ammonium chloride (182 mg, 3.40 mmol) and HATU (97.0 mg, 255 μmol) in DMF (4.00 mL) was added dropwise *N,N*-diisopropylethylamine (59.3 μL , 340 μmol). The mixture was stirred at RT for 16 hours, then another 97 mg of HATU (255 μmol) were added and stirring continued for 1 hour. The mixture was diluted with saturated aqueous NH_4Cl solution and extracted with EA (3 x 20 mL). The combined organics were washed successively with brine (3 x 20 mL) and 0.05 N aqueous HCl, then concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 15% of MeOH in DCM), then it was purified again by reverse-phase flash column chromatography (eluent gradient from 10% to 100% of CH_3CN in H_2O with 0.1% (v/v) formic acid) to afford title compound **109** as an off-white solid (17.2 mg, 32% yield).

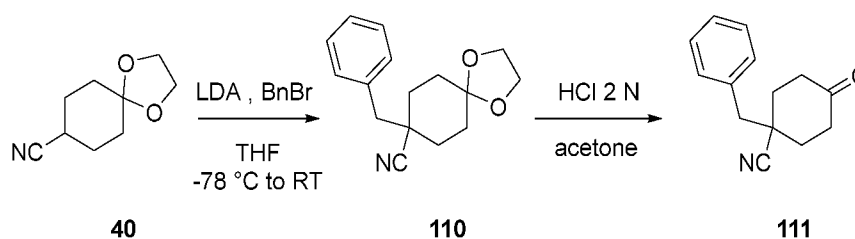
^1H NMR: 400 MHz, $\text{DMSO}-d_6$, δ (ppm): 8.06 (s, 2H), 7.32-7.27 (m, 4H), 7.23-7.20 (m, 1H), 6.88 (bs, 2H), 4.77 (t, J = 5.5 Hz, 1H), 3.92 (dd, J = 10.4, 5.6 Hz, 1H), 3.35-3.32 (m, 1H), 2.89-2.84 (m, 1H), 2.73-2.67 (m, 1H), 2.50-2.48 (m, 1H, partially overlapping with the solvent signal). LC-MS: t_r = 0.88 min, MS: 316.1 (calcd), 317.0 ($\text{M}+\text{H}^+$, found).

Examples 60-67

Intermediate compound 111

1-Benzyl-4-oxocyclohexane-1-carbonitrile (111**)**

Scheme 20



Scheme 4

Step 1. 8-Benzyl-1,4-dioxaspiro[4.5]decane-8-carbonitrile (110**).**

To a solution of **40** (scheme 4) (1.0 g, 5.98 mmol) in anhydrous THF (24.0 mL) at -78 °C was added dropwise LDA (6.58 mL, 1 M in THF/hexane, 6.58 mmol). The reaction mixture was stirred at -78 °C for 45 min then benzyl bromide (0.870 mL, 7.18 mmol) was added dropwise. The reaction mixture was allowed to reach RT and stirred for 2.5 hours. Afterwards, the reaction mixture was quenched with water and extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 30% of EA in hexane) to afford title compound **110** (1.22 g, 79% yield) as a white solid, which was not characterized and used directly for the next step.

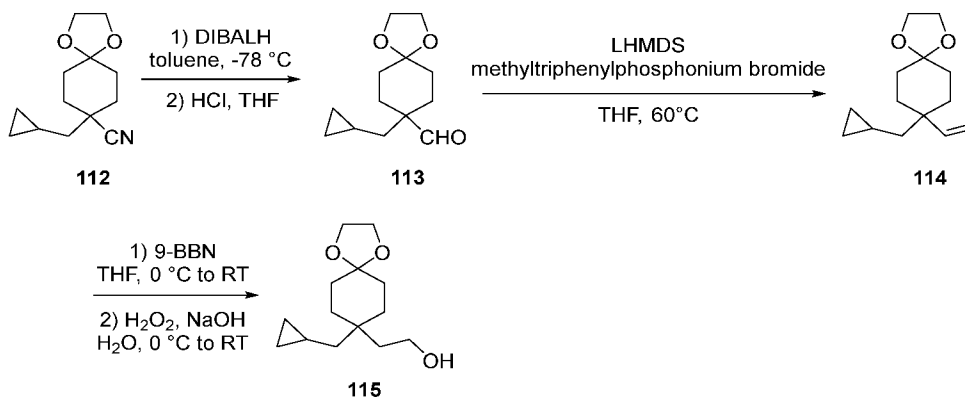
Step 2. 1-Benzyl-4-oxocyclohexane-1-carbonitrile (**111**).

To a solution of **110** (1.21 g, 4.70 mmol) in acetone (63 mL) was added HCl 2 N (11.8 mL, 23.5 mmol) and the reaction mixture was stirred at RT for 16 hours. Then, the mixture was neutralized by slowly adding saturated NaHCO₃ solution and concentrated to remove the organic solvent. The residue was extracted with EA and the organic layer was dried over Na₂SO₄, filtered and concentrated to dryness to afford title compound **111** (1.00 g, >99% yield). LC-MS: rt = 2.93 min, MS: 213.1 (calcd), 214.1 (M+H⁺, found).

Intermediate compound 115

2-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)ethan-1-ol (**115**)

Scheme 21



Step 1. 8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-carbaldehyde (**113**)

Diisobutylaluminum hydride (25% solution in toluene; 121 mL, 180.0 mmol) was added dropwise to a solution of 8-(cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-carbonitrile (**112**) (24.3 g, 110 mmol) (*ACS Med. Chem. Lett.* **2010**, 350-354) in anhydrous toluene (600 mL) at -78 °C and the resulting mixture was stirred at -78 °C for 2 hours. The reaction mixture was then quenched with methanol (15 mL) at -78 °C and partitioned between saturated aqueous NH₄Cl solution (200 mL) and diethyl ether (300 mL). The mixture was allowed to slowly reach RT and a saturated aqueous solution of Rochelle's salt (1 L) was added. The layers were separated and the organic phase was washed with brine (2 x 200 mL), dried over Na₂SO₄, filtered and

concentrated. The residue was dissolved in THF (400 mL) and treated with 2 N aqueous HCl (27.5 mL, 54.9 mmol). The mixture was stirred at RT for 1 hour, then quenched with saturated aqueous NaHCO₃ and concentrated to remove the organic solvent. The aqueous residue was extracted with diethyl ether and the organics were dried over Na₂SO₄, filtered and concentrated to afford title compound **113** as a colorless oil (24.6 g, >99% yield), which was not characterized and used directly for the next step.

Step 2. 8-(Cyclopropylmethyl)-8-vinyl-1,4-dioxaspiro[4.5]decane (114**)**

To a 1 M solution of LHMDS in THF (10 mL, 10.0 mmol) diluted with anhydrous THF (55.0 mL) at 60 °C was added methyltriphenylphosphonium bromide (2.23 g, 6.24 mmol) in 4 portions over 30 minutes. The reaction mixture was stirred at 60 °C for 1 hour after the last addition. Then, **113** (700 mg, 3.12 mmol) in anhydrous THF (10.0 mL) was added dropwise and the reaction mixture was stirred at 60 °C for another 30 minutes. The mixture was then allowed to cool to RT, quenched with a saturated solution of NH₄Cl (40 mL) and extracted 2 times with EA (2 x 50 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated and the residue was purified by flash column chromatography (eluent gradient from 0% to 30% of Et₂O in hexane) to afford title compound **114** as a colorless oil (527 mg, 76% yield), which was not characterized and used directly for the next step.

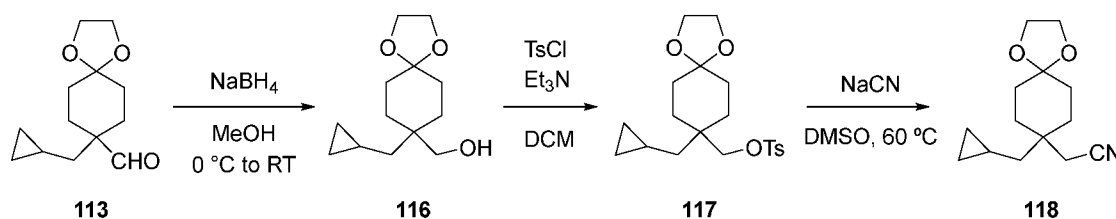
Step 3. 2-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)ethan-1-ol (115**)**

To a solution of **114** (520 mg, 2.34 mmol) in anhydrous THF (12 mL) at 0 °C was added dropwise 9-BBN (9.35 mL, 0.5 M in THF, 4.68 mmol). The reaction mixture was stirred at RT for 2.5 hours, then it was cooled to 0 °C again and water (42 uL, 2.34 mmol), NaOH 1 N (7.0 mL, 7.0 mmol) and H₂O₂ 30% (12 mL) were added. The reaction mixture was stirred at 0 °C for 10 min, then it was stirred at RT for 16 hours. Afterwards, the mixture was diluted with EA and water. The layers were separated, and the organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 30% to 100% of EA in hexane) to afford title compound **115** as a colorless oil (479 mg, 85% yield), which was not characterized and used directly for the synthesis of relevant examples.

Intermediate compound 118

2-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)acetonitrile (118**)**

Scheme 22



Scheme 21

Step 1. (8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)methanol (116)

Sodium borohydride (816 mg, 21.1 mmol) was added to a solution of **113** (scheme 21) (3.16 g, 14.1 mmol) in MeOH (86.8 mL) at 0 °C. The resulting solution was stirred at RT for 1 hour, then the reaction mixture was quenched with saturated aqueous NH₄Cl solution (30 mL).
5 The mixture was diluted with EA (30 mL), the layers were separated, and the aqueous layer was extracted with EA (30 mL). The combined organics were washed with 0.2 N HCl (50 mL) and brine, then dried over Na₂SO₄, filtered and concentrated to afford title compound **116** (2.95 g, 93% yield) as a colorless oil, which was not characterized and used directly for the next step.

Step 2. (8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)methyl 4-

methylbenzenesulfonate (117)

To a solution of **116** (2.70 g, 11.9 mmol) in pyridine (51.9 mL) was added *p*-toluenesulfonyl chloride (7.96 g, 41.8 mmol) and the resulting mixture was stirred at RT for 16 hours. The mixture was then diluted with EA and water (30 mL each) and the layers were separated. The aqueous phase was extracted with EA (30 mL) and the combined organics were
15 washed with water (30 mL) and brine (2 x 30 mL), then dried over Na₂SO₄, filtered and concentrated. The residue was diluted with heptanes and concentrated to dryness, then purified by flash column chromatography (eluent gradient from 0% to 40% of EA in hexane) to afford title compound **117** (3.65 g, 80% yield) as a colorless oil. LC-MS: rt = 1.78 min. MS: 380.2 (calcd), 381.3 (M+H⁺, found).

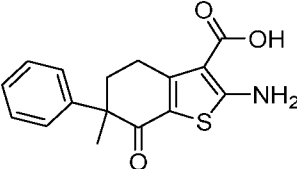
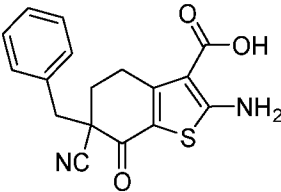
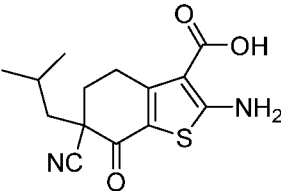
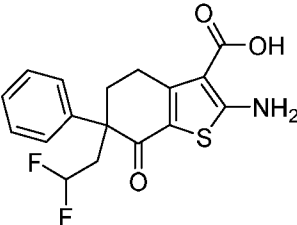
Step 3. 2-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)acetonitrile (118)

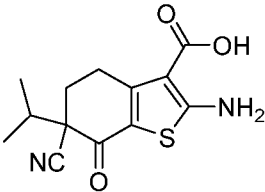
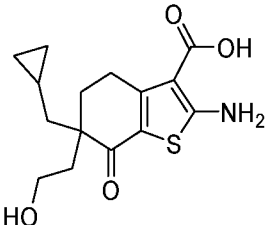
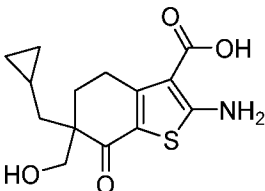
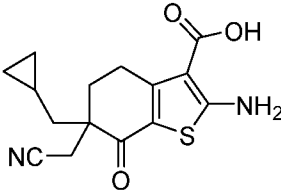
To a solution of **117** (3.65 g, 9.59 mmol) in DMSO (57.1 mL) was added sodium cyanide (1.41 g, 28.8 mmol) and the resulting mixture was stirred at 60 °C for 96 hours. The mixture was allowed to cool to RT and diluted with saturated aqueous NaHCO₃ solution (50 mL). The mixture was then diluted with EA (50 mL) and water (40 mL), the layers were separated and the aqueous
25 phase was extracted with EA (2 x 50 mL). The combined organics were washed with water (2 x 30 mL) and brine (30 mL), dried over Na₂SO₄, filtered and concentrated to afford title compound **118** (2.5 g, 72% yield) as a yellow oil, which was not characterized and used directly for the synthesis of relevant examples.

Compounds 119-126

Compounds **119-123** (examples 60-64) were synthesized similarly to compound **81** (example 51, scheme 13) starting from 4-methyl-4-phenylcyclohexan-1-one, compound **111** (scheme 20), compound **73** (scheme 12), compound **95** (scheme 17), and compound **99** (scheme 18), respectively, instead of 2-(4-oxo-1-phenylcyclohexyl)acetonitrile (**76**). Compounds **124-126** (examples 65-67) were synthesized similarly to compound **47** (example 28, scheme 4) starting
35 from compound **115** (scheme 21), compound **116** (scheme 22), and compound **118** (scheme 22), respectively, instead of compound **41**. Characterization of compounds **119-126** (examples 60-67) is provided in the table 4.

Table 4. Characterization of compounds **119-126** (examples 60-67).

Ex. No.	Compound No.	Structure	Characterization
60	119	 2-Amino-6-methyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	¹ H NMR: 400 MHz, DMSO-d ₆ , δ (ppm): 12.47 (s, 1H), 8.24 (s, 2H), 7.32-7.19 (m, 5H), 3.05 (dt, J = 18.5, 3.9 Hz, 1H), 2.56-2.51 (m, 1H), 2.43-2.33 (m, 1H), 2.15-2.08 (m, 1H), 1.35 (s, 3H). LC-MS: rt = 1.30 min, MS: 301.1 (calcd), 302.1 (M+H ⁺ , found).
61	120	 2-Amino-6-benzyl-6-cyano-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	¹ H NMR: 400 MHz, DMSO-d ₆ , δ (ppm): 8.71 (bs, 2H), 7.37-7.28 (m, 5H), 3.26-3.22 (m, 2H), 3.09-2.97 (m, 2H), 2.20-2.14 (m, 1H), 2.11-2.04 (m, 1H). LC-MS: rt = 1.30 min, MS: 326.1 (calcd), 327.1 (M+H ⁺ , found).
62	121	 2-Amino-6-cyano-6-isobutyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	¹ H NMR: 400 MHz, DMSO-d ₆ , δ (ppm): 12.76 (s, 1H), 8.48 (s, 2H), 3.13-2.99 (m, 2H), 2.47-2.40 (m, 1H), 2.31-2.25 (m, 1H), 1.87-1.74 (m, 2H), 1.71-1.65 (m, 1H), 0.98-0.94 (m, 6H). LC-MS: rt = 1.28 min, MS: 292.1 (calcd), 293.1 (M+H ⁺ , found).
63	122	 2-Amino-6-(2,2-difluoroethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 7.34-7.28 (m, 4H), 7.26-7.21 (m, 1H), 5.86 (tt, J = 56.6, 4.5 Hz, 1H), 3.27-3.21 (m, 1H), 2.73-2.69 (m, 1H), 2.51-2.34 (m, 4H). LC-MS: rt = 1.40 min, MS: 351.1 (calcd), 352.1 (M+H ⁺ , found).

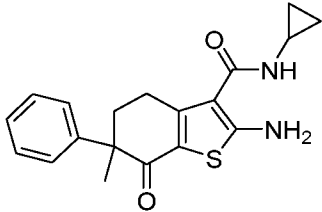
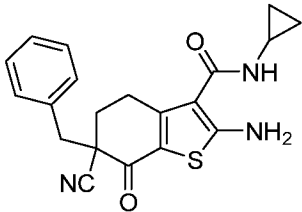
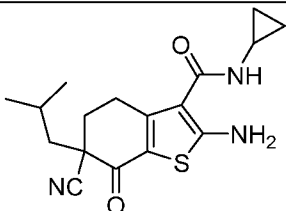
64	123	 2-Amino-6-cyano-6-isopropyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	¹ H NMR: 400 MHz, DMSO-d ₆ , δ (ppm): 12.74 (s, 1H), 8.47 (s, 2H), 3.10-2.97 (m, 2H), 2.37-2.27 (m, 3H), 1.01 (d, <i>J</i> = 6.7 Hz, 3H), 0.96 (d, <i>J</i> = 6.8 Hz, 3H). LC-MS: rt = 1.15 min, MS: 278.1 (calcd), 279.1 (M+H ⁺ , found).
65	124	 2-Amino-6-(cyclopropylmethyl)-6-(2-hydroxyethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 3.66-3.55 (m, 2H), 3.19-3.04 (m, 2H), 2.25-2.19 (m, 1H), 2.11-2.00 (m, 2H), 1.86-1.79 (m, 1H), 1.71 (dd, <i>J</i> = 14.1, 6.1 Hz, 1H), 1.38 (dd, <i>J</i> = 14.2, 7.2 Hz, 1H), 0.71-0.65 (m, 1H), 0.49-0.41 (m, 2H), 0.11-0.00 (m, 2H). LC-MS: rt = 1.05 min, MS: 309.1 (calcd), 310.2 (M+H ⁺ , found).
66	125	 2-Amino-6-(cyclopropylmethyl)-6-(hydroxymethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	¹ H NMR: 400 MHz, DMSO-d ₆ , δ (ppm): 12.38 (bs, 1H), 8.19 (s, 2H), 4.57 (bs, 1H), 3.68 (d, <i>J</i> = 10.5 Hz, 1H), 3.36-3.33 (m, 1H), 3.07-2.99 (m, 1H), 2.95-2.88 (m, 1H), 2.16-2.09 (m, 1H), 2.07-2.00 (m, 1H), 1.57 (dd, <i>J</i> = 14.1, 6.2 Hz, 1H), 1.27 (dd, <i>J</i> = 14.1, 7.3 Hz, 1H), 0.61-0.53 (m, 1H), 0.39-0.30 (m, 2H), 0.01 - -0.10 (m, 2H). LC-MS: rt = 1.01 min, MS: 295.1 (calcd), 296.1 (M+H ⁺ , found).
67	126	 2-Amino-6-(cyanomethyl)-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	¹ H NMR: 400 MHz, DMSO-d ₆ , δ (ppm): 12.58 (s, 1H), 8.30 (s, 2H), 3.18-3.11 (m, 1H), 2.92-2.78 (m, 3H), 2.12-2.05 (m, 2H), 1.50 (d, <i>J</i> = 6.74 Hz, 2H), 0.62-0.57 (m, 1H), 0.43-0.35 (m, 2H), 0.07-0.02 (m, 1H), -0.05 - -0.09 (m, 1H). LC-MS: rt = 1.10 min. MS: 304.1 (calcd), 305.0 (M+H ⁺ , found).

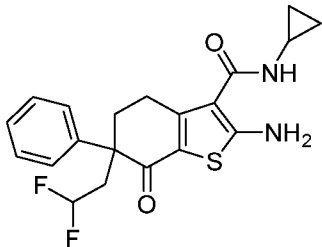
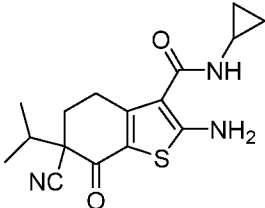
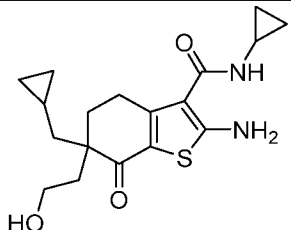
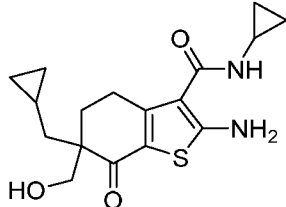
Examples 68-77

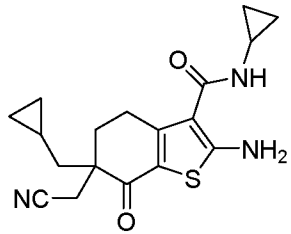
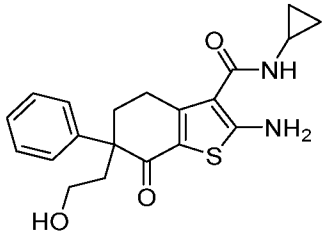
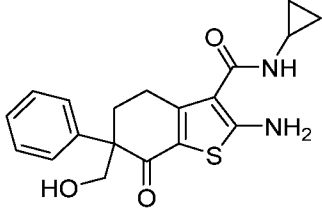
Compounds **127-133** (examples 68-74) were synthesized similarly to compound **82** (example 52, scheme 13) starting from compounds **119-125** (examples 60-66, table 4),

respectively, instead of compound **81**. Compounds **134-135** (examples 75-76) were synthesized similarly to compound **9** (example 2, scheme 2) starting from compound **126** (example 67, table 4) and compound **89** (example 55, scheme 15), respectively, instead of compound **8**. Compound **136** (example 77) was synthesized similarly to compound **82** (example 52, scheme 13) starting from compound **108** (scheme 19) instead of compound **81**. Characterization of compounds **127-136** (examples 68-77) is provided in the table 5.

Table 5. Characterization of compounds **127-136** (examples 68-77).

Ex. No.	Compound No.	Structure	Characterization
68	127	 2-Amino-N-cyclopropyl-6-methyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 7.32-7.27 (m, 4H), 7.24-7.18 (m, 1H), 2.81-2.74 (m, 1H), 2.72-2.66 (m, 1H), 2.63-2.55 (m, 2H), 2.24-2.17 (m, 1H), 1.47 (s, 3H), 0.77-0.69 (m, 2H), 0.56-0.49 (m, 2H). LC-MS: rt = 1.35 min, MS: 340.1 (calcd), 341.2 (M+H ⁺ , found).
69	128	 2-Amino-6-benzyl-6-cyano-N-cyclopropyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹ H NMR: 400 MHz, DMSO-d ₆ , δ (ppm): 8.08 (bs, 2H), 7.61 (bs, 1H), 7.38-7.29 (m, 5H), 3.24 (d, J = 13.6 Hz, 1H), 3.10-3.02 (m, 2H), 2.97-2.89 (m, 1H), 2.77-2.72 (m, 1H), 2.19-2.13 (m, 1H), 2.09-2.02 (m, 1H), 0.70-0.65 (m, 2H), 0.55-0.51 (m, 2H). LC-MS: rt = 1.33 min, MS: 365.1 (calcd), 366.2 (M+H ⁺ , found).
70	129	 2-Amino-6-cyano-N-cyclopropyl-6-isobutyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹ H NMR: 400 MHz, DMSO-d ₆ , δ (ppm): 8.02 (s, 2H), 7.55 (s, 1H), 3.04-2.87 (m, 2H), 2.78-2.72 (m, 1H), 2.38 (ddd, J = 13.6, 7.9, 4.9 Hz, 1H), 2.24 (dt, J = 13.7, 5.4 Hz, 1H), 1.86-1.78 (m, 2H), 1.73-1.66 (m, 1H), 0.97 (d, J = 4.2 Hz, 3H), 0.95 (d, J = 3.9 Hz, 3H), 0.70-0.66 (m, 2H), 0.55-0.51 (m, 2H). LC-MS: rt = 1.30 min, MS: 331.1 (calcd), 332.2 (M+H ⁺ , found).

71	130	 2-Amino-<i>N</i>-cyclopropyl-6-(2,2-difluoroethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹H NMR: 400 MHz, CDCl₃, δ (ppm): 7.37-7.28 (m, 5H), 6.98 (s, 2H), 5.80 (tt, <i>J</i> = 56.4, 4.6 Hz, 1H), 5.50 (s, 1H), 2.83-2.70 (m, 3H), 2.54-2.40 (m, 4H), 0.88-0.76 (m, 2H), 0.57-0.49 (m, 2H). LC-MS: rt = 1.43 min, MS: 390.1 (calcd), 391.2 (M+H⁺, found).
72	131	 2-Amino-6-cyano-<i>N</i>-cyclopropyl-6-isopropyl-7-oxo-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹H NMR: 400 MHz, DMSO-<i>d</i>₆, δ (ppm): 8.00 (s, 2H), 7.52 (d, <i>J</i> = 3.8 Hz, 1H), 3.04 (ddd, <i>J</i> = 18.0, 7.8, 5.4 Hz, 1H), 2.84 (dt, <i>J</i> = 18.0, 5.2 Hz, 1H), 2.78-2.72 (m, 1H), 2.37-2.28 (m, 3H), 1.00 (d, <i>J</i> = 6.7, 3H), 0.97 (d, <i>J</i> = 6.8 Hz, 3H), 0.70-0.65 (m, 2H), 0.54-0.51 (m, 2H). LC-MS: rt = 1.18 min, MS: 317.1 (calcd), 318.1 (M+H⁺, found).
73	132	 2-Amino-<i>N</i>-cyclopropyl-6-(cyclopropylmethyl)-6-(2-hydroxyethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹H NMR: 400 MHz, CD₃OD, δ (ppm): 3.66-3.55 (m, 2H), 2.99-2.85 (m, 2H), 2.79-2.73 (m, 1H), 2.23 (dt, <i>J</i> = 13.8, 5.9 Hz, 1H), 2.12-2.01 (m, 2H), 1.84 (ddd, <i>J</i> = 13.7, 8.9, 6.2 Hz, 1H), 1.74 (dd, <i>J</i> = 14.1, 6.1 Hz, 1H), 1.40 (dd, <i>J</i> = 14.1, 7.3 Hz, 1H), 0.82-0.77 (m, 2H), 0.72-0.65 (m, 1H), 0.63-0.59 (m, 2H), 0.50-0.41 (m, 2H), 0.10-0.00 (m, 2H). LC-MS: rt = 1.10 min, MS: 348.2 (calcd), 349.2 (M+H⁺, found).
74	133	 2-Amino-<i>N</i>-cyclopropyl-6-(cyclopropylmethyl)-6-(hydroxymethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹H NMR: 400 MHz, DMSO-<i>d</i>₆, δ (ppm): 7.70 (s, 2H), 7.33 (d, <i>J</i> = 3.8 Hz, 1H), 4.53 (t, <i>J</i> = 5.4 Hz, 1H), 3.70 (dd, <i>J</i> = 10.5, 5.5 Hz, 1H), 3.37 (dd, <i>J</i> = 10.5, 5.2 Hz, 1H), 2.93-2.79 (m, 2H), 2.78-2.71 (m, 1H), 2.13-2.06 (m, 1H), 2.03-1.97 (m, 1H), 1.56 (dd, <i>J</i> = 14.0, 6.3 Hz, 1H), 1.31 (dd, <i>J</i> = 14.0, 7.2 Hz, 1H), 0.69-0.64 (m, 2H), 0.62-0.56 (m, 1H), 0.54-0.50 (m, 2H), 0.40-0.32 (m, 2H), 0.04-0.00 (m, 1H), -0.05 - -0.10 (m, 1H). LC-MS: rt = 1.07 min, MS: 334.1 (calcd), 335.1 (M+H⁺, found).

75	134	 2-Amino-6-(cyanomethyl)-<i>N</i>-cyclopropyl-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹ H NMR: 400 MHz, DMSO- <i>d</i> ₆ , δ (ppm): 7.82 (s, 2H), 7.38 (d, <i>J</i> = 3.83 Hz, 1H), 3.08-2.98 (m, 1H), 2.90 (d, <i>J</i> = 16.76 Hz, 1H), 2.78-2.71 (m, 3H), 2.12-2.04 (m, 2H), 1.57-1.46 (m, 2H), 0.68-0.56 (m, 3H), 0.54-0.50 (m, 2H), 0.47-0.35 (m, 2H), 0.10-0.06 (m, 1H), 0.00 - -0.09 (m, 1 H). LC-MS: <i>rt</i> = 1.13 min. MS: 343.1 (calcd), 344.1 (M+H ⁺ , found).
76	135	 2-Amino-<i>N</i>-cyclopropyl-6-(2-hydroxyethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 7.34-7.29 (m, 4H), 7.25-7.21 (m, 1H), 3.54-3.41 (m, 2H), 2.82-2.74 (m, 1H), 2.71-2.55 (m, 3H), 2.37-2.30 (m, 1H), 2.17-2.04 (m, 2H), 0.76-0.65 (m, 2H), 0.56-0.48 (m, 2H). LC-MS: <i>rt</i> = 1.11 min, MS: 370.1 (calcd), 371.2 (M+H ⁺ , found).
77	136	 2-Amino-<i>N</i>-cyclopropyl-6-(hydroxymethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 7.35-7.29 (m, 4H), 7.26-7.22 (m, 1H), 4.09 (d, <i>J</i> = 11.0 Hz, 1H), 3.56 (d, <i>J</i> = 11.0 Hz, 1H), 2.84-2.78 (m, 1H), 2.70-2.65 (m, 2H), 2.60-2.53 (m, 2H), 0.74-0.70 (m, 2H), 0.54-0.52 (m, 2H). LC-MS: <i>rt</i> = 1.09 min, MS: 356.1 (calcd), 357.2 (M+H ⁺ , found).

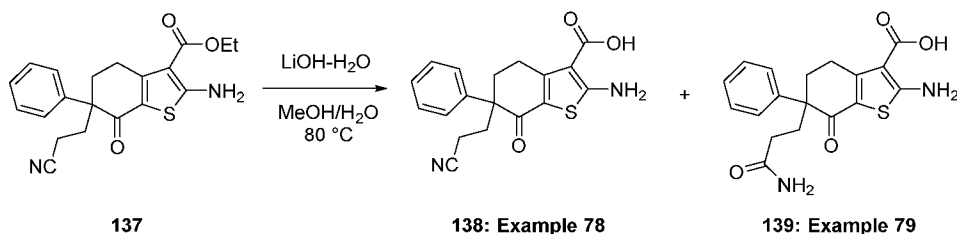
Example 78

2-Amino-6-(2-cyanoethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (138) and

Example 79

5 **2-Amino-6-(3-amino-3-oxopropyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (139)**

Scheme 23



To a solution of **137** (1.0 g, 2.71 mmol, synthesized similarly to compound **80** in scheme 13 starting from 3-(4-oxo-1-phenylcyclohexyl)propanenitrile (*Bioorg Med. Chem Lett.* 21, p. 405, 2011) instead of 2-(4-oxo-1-phenylcyclohexyl)acetonitrile (**76**)) in MeOH (330 mL) was added a solution of lithium hydroxide monohydrate (569 mg, 13.6 mmol) in water (330 mL). The reaction mixture was stirred at 80 °C for 16 hours, then allowed to cool to RT. The mixture was concentrated to remove most of the organic solvent. The aqueous layer was acidified by slowly adding HCl 1 N and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 30% of MeOH in DCM) to afford title compound **138** as a yellow solid (648 mg, 70% yield) and title compound **139**. The latter was purified again by Semi-Prep HPLC-MS (eluent gradient from 15% to 100% of MeOH in 10 mM ammonium bicarbonate) to afford a white solid (142 mg, 15% yield).

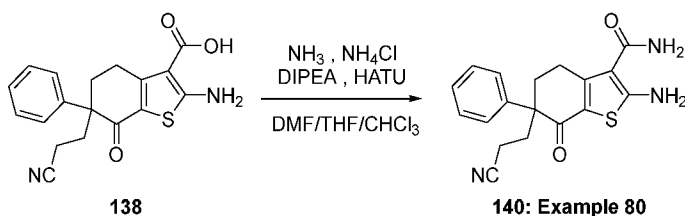
138: ¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 12.51 (bs, 1H), 8.28 (s, 2H), 7.36-7.32 (m, 2H), 7.27-7.24 (m, 3H), 3.15-3.09 (m, 1H), 2.60-2.55 (m, 1H), 2.48-2.42 (m, 1H), 2.38-2.30 (m, 1H), 2.26-2.18 (m, 2H), 2.12-2.07 (m, 2H). LC-MS: rt = 1.23 min, MS: 340.1 (calcd), 341.1 (M+H⁺, found).

139: ¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.30 (bs, 2H), 7.33-7.26 (m, 4H), 7.23-7.19 (m, 1H), 7.18 (s, 1H), 6.62 (s, 1H), 3.20-3.15 (m, 2H), 2.45-2.37 (m, 1H), 2.16-2.07 (m, 1H), 2.00-1.91 (m, 4H). LC-MS: rt = 0.98 min, MS: 358.1 (calcd), 359.1 (M+H⁺, found).

Example 80

2-Amino-6-(2-cyanoethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**140**)

Scheme 24



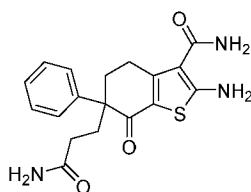
To a suspension of **138** (500 mg, 1.47 mmol) and ammonium chloride (1.57 g, 29.4 mmol) in anhydrous DMF (16.2 mL) were added HATU (855 mg, 2.20 mmol) and *N,N*-diisopropylethylamine (0.512 mL, 2.94 mmol). Then, saturated NH₃ solution in CHCl₃ (8.7 mL)

(prepared in-house) and NH_3 0.4 M solution in THF (9.2 mL) were added dropwise and the reaction mixture was stirred at RT for 16 hours. Afterwards, the reaction mixture was quenched with a saturated NH_4Cl solution and extracted with EA. The organic layer was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by reverse-phase flash column chromatography (eluent gradient from 0% to 100% of CH_3CN in H_2O with 0.1% (v/v) formic acid) to afford title compound **140** as a white solid (419 mg, 84% yield).

^1H NMR: 400 MHz, DMSO-d_6 , δ (ppm): 8.13 (s, 2H), 7.37-7.24 (m, 5H), 6.88 (bs, 2H), 2.91-2.84 (m, 1H), 2.68-2.56 (m, 2H), 2.46-2.42 (m, 1H), 2.25-2.17 (m, 2H), 2.13-2.07 (m, 2H). LC-MS: rt = 1.10 min, MS: 339.1 (calcd), 340.1 ($\text{M}+\text{H}^+$, found).

Example 81

2-Amino-6-(2-cyanoethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**141**)



141: Example 81

Compound **141** (example 81) was synthesized similarly to compound **62** (example 39, scheme 10) starting from compound **140** (example 80, scheme 24) instead of compound **61**.

^1H NMR: 400 MHz, DMSO-d_6 , δ (ppm): 8.08 (s, 2H), 7.35-7.21 (m, 5H), 7.17 (s, 1H), 6.87 (bs, 2H), 6.63 (s, 1H), 2.91-2.84 (m, 1H), 2.73-2.65 (m, 1H), 2.55-2.53 (m, 1H), 2.20-2.12 (m, 1H), 2.02-1.90 (m, 4H). LC-MS: rt = 0.88 min, MS: 357.1 (calcd), 358.2 ($\text{M}+\text{H}^+$, found).

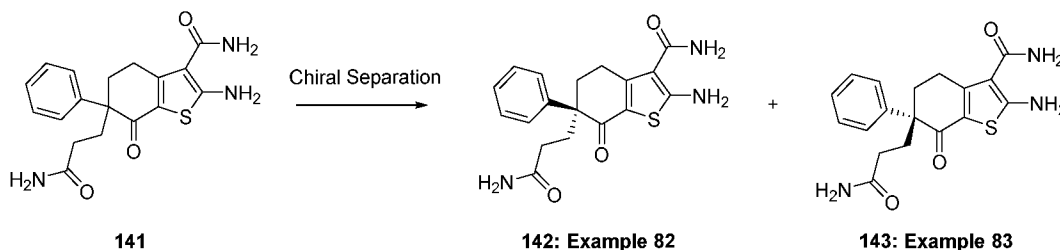
Example 82

(S)-2-Amino-6-(3-amino-3-oxopropyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**142**) and

Example 83

(R)-2-Amino-6-(3-amino-3-oxopropyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**143**)

Scheme 25



100.3 mg of racemic compound **141** were submitted to SFC Chiral Separation to afford enantioenriched title compound **142** as a white solid (29.9 mg, 30% separation yield) and

enantioenriched title compound **143** as a white solid (26.2 mg, 26% separation yield). Absolute configurations of compounds **142** and **143** were assigned based on analogy with the assignment of the absolute configuration of a crystallized compound within the same or similar series.

142: ^1H NMR: same as racemic mixture (**141**). LC-MS: rt = 0.88 min, MS: 357.1 (calcd), 358.2 ($\text{M}+\text{H}^+$, found). Analytical SFC (IC column with 5-60% MeOH + 10mM AmFor (95-40% CO_2) gradient): rt = 5.80 min, ee. = 99.76%.

143: ^1H NMR: same as racemic mixture (**141**). LC-MS: rt = 0.88 min, MS: 357.1 (calcd), 358.2 ($\text{M}+\text{H}^+$, found). Analytical SFC (IC column with 5-60% MeOH + 10mM AmFor (95-40% CO_2) gradient): rt = 6.45 min, ee. = 97.82%.

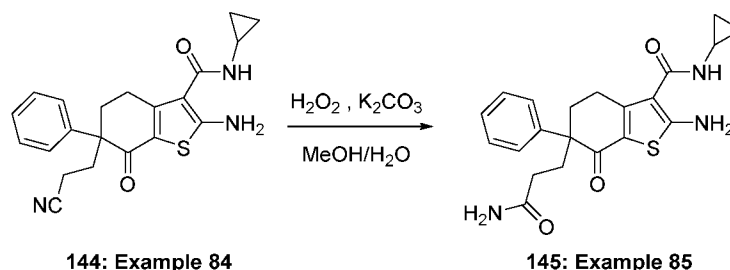
Example 84

2-Amino-6-(2-cyanoethyl)-N-cyclopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (144) and

Example 85

2-Amino-6-(3-amino-3-oxopropyl)-N-cyclopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (145)

Scheme 26



Compound **144** (example 84) was synthesized similarly to compound **82** (example 52, scheme 13) starting from compound **138** (example 78, scheme 23) instead of compound **81**.

^1H NMR: 400 MHz, DMSO- d_6 , δ (ppm): 7.87 (s, 2H), 7.37-7.25 (m, 6H), 2.74-2.52 (m, 4H), 2.48-2.41 (m, 1H), 2.24-2.07 (m, 4H), 0.64-0.57 (m, 2H), 0.50-0.43 (m, 2H). LC-MS: rt = 1.27 min, MS: 379.1 (calcd), 380.2 ($\text{M}+\text{H}^+$, found).

To a suspension of **144** (35 mg, 0.092 mmol) and K_2CO_3 (26 mg, 0.18 mmol) in MeOH (1.8 mL) and water (0.6 mL) was added H_2O_2 30% (0.09 mL). The reaction mixture was vigorously stirred at RT for 2 days. Then, more H_2O_2 30% (0.19 mL) was added and the reaction mixture was vigorously stirred at RT for another 24 hours. Afterwards, the mixture was concentrated to remove the organic solvent and the residue was extracted with EA. The organic layer was dried over Na_2SO_4 , filtered and concentrated to afford title compound **145** as an off-white solid (17 mg, 46% yield).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 7.81 (s, 2H), 7.35-7.21 (m, 6H), 7.17 (bs, 1H), 6.63 (bs, 1H), 2.77-2.59 (m, 3H), 2.50-2.48 (m, 1H), 2.16-2.08 (m, 1H), 2.01-1.90 (m, 4H), 0.64-0.58 (m, 2H), 0.50-0.45 (m, 2H). LC-MS: rt = 1.05 min, MS: 397.2 (calcd), 398.3 (M+H⁺, found).

Example 86

5 2-Amino-6-methyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (146)

Scheme 27

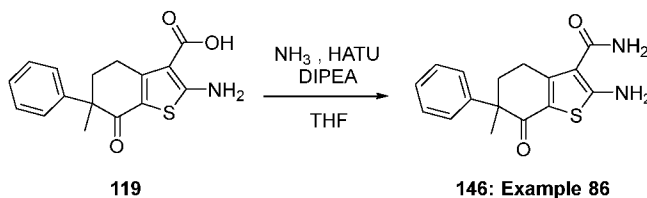


Table 4

Compound **119** (table 4) (50 mg, 0.17 mmol) was dissolved in a NH₃ 0.4 M solution in THF
 10 (17 mL) and HATU (126 mg, 0.33 mmol) and *N,N*-diisopropylethylamine (0.058 mL, 0.33 mmol) were added to the mixture. Then, the reaction mixture was stirred at RT for 16 hours. Afterwards, the reaction mixture was quenched with a saturated NH₄Cl solution and extracted with EA. The organic layer was washed with water and brine, then dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from
 15 40% to 100% of EA in hexane), then it was purified again by Semi-Prep HPLC-MS (eluent gradient from 35% to 100% of CH₃CN in 10 mM ammonium bicarbonate) to afford title compound **146** as a white solid (22 mg, 44% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.32-7.28 (m, 4H), 7.24-7.19 (m, 1H), 2.95-2.89 (m, 1H), 2.68-2.58 (m, 2H), 2.28-2.21 (m, 1H), 1.48 (s, 3H). LC-MS: rt = 1.13, MS: 300.1 (calcd),
 20 301.1 (M+H⁺, found).

Example 87

25 2-Amino-6-benzyl-6-cyano-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (147)

Scheme 28

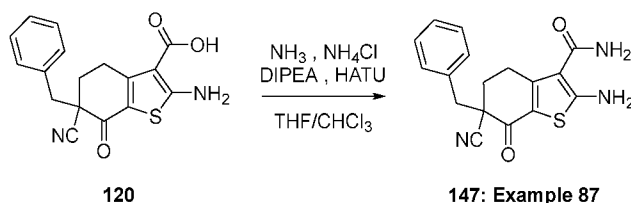


Table 4

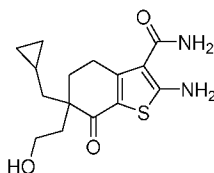
To a suspension of **120** (table 4) (50 mg, 0.153 mmol) and ammonium chloride (164 mg, 3.06 mmol) in anhydrous THF (2.0 mL) were added HATU (87 mg, 0.230 mmol) and *N,N*-diisopropylethylamine (0.053 mL, 0.306 mmol). Then, saturated NH₃ solution in CHCl₃ (0.25 mL) (prepared in-house) was added dropwise and the reaction mixture was stirred at RT for 16 hours.

Afterwards, the reaction mixture was quenched with a saturated NH₄Cl solution and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by reverse-phase flash column chromatography (eluent gradient from 0% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **147** as a white solid (35 mg, 70% yield).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.34 (bs, 2H), 7.40-7.30 (m, 5H), 7.13 (bs, 2H), 3.25-3.16 (m, 2H), 3.10-2.98 (m, 2H), 2.23-2.16 (m, 1H), 2.11-2.04 (m, 1H). LC-MS: rt = 1.15 min, MS: 325.1 (calcd), 326.1 (M+H⁺, found).

Example 88

2-Amino-6-(cyclopropylmethyl)-6-(2-hydroxyethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**148**)



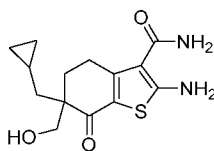
148: Example 88

Compound **148** (example 88) was synthesized similarly to compound **140** (example 80, scheme 24) starting from compound **124** (table 4) instead of compound **138**.

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 3.67-3.56 (m, 2H), 3.03 (t, *J* = 6.1 Hz, 2H), 2.28 (dt, *J* = 13.8, 5.9 Hz, 1H), 2.17-2.10 (m, 1H), 2.05 (ddd, *J* = 13.7, 8.9, 6.1 Hz, 1H), 1.85 (ddd, *J* = 13.7, 8.9, 6.2 Hz, 1H), 1.74 (dd, *J* = 14.1, 6.1 Hz, 1H), 1.41 (dd, *J* = 14.2, 7.2 Hz, 1H), 0.74-0.64 (m, 1H), 0.50-0.42 (m, 2H), 0.11-0.00 (m, 2H). LC-MS: rt = 0.92 min, MS: 308.1 (calcd), 309.2 (M+H⁺, found).

Example 89

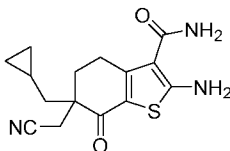
2-Amino-6-(cyclopropylmethyl)-6-(hydroxymethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**149**)



149: Example 89

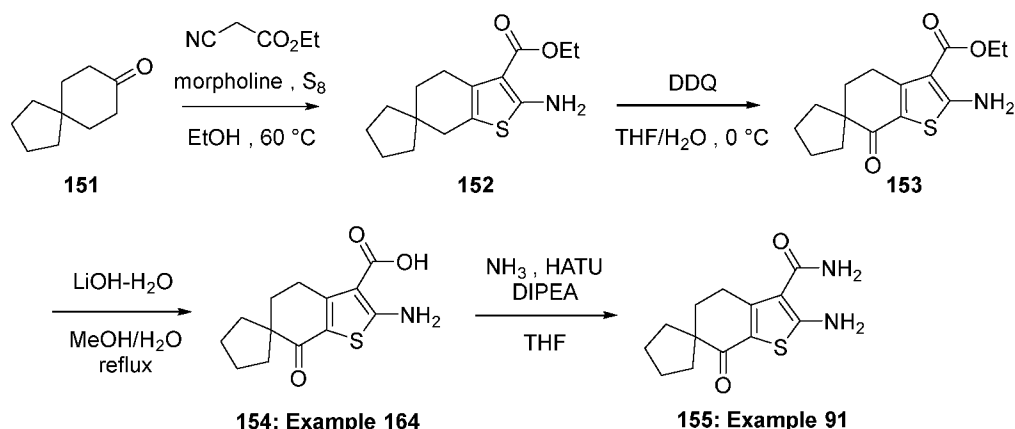
Compound **149** (example 89) was synthesized similarly to compound **140** (example 80, scheme 24) starting from compound **125** (table 4) instead of compound **138**.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 7.97 (s, 2H), 6.92 (bs, 2H), 4.54 (t, *J* = 5.4 Hz, 1H), 3.71 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.39 (dd, *J* = 10.5, 5.3 Hz, 1H), 3.03-2.87 (m, 2H), 2.17-2.10 (m, 1H), 2.07-2.01 (m, 1H), 1.54 (dd, *J* = 14.0, 6.5 Hz, 1H), 1.32 (dd, *J* = 14.0, 7.0 Hz, 1H), 0.64-0.55 (m, 1H), 0.40-0.32 (m, 2H), 0.07-0.01 (m, 1H), -0.05 - -0.09 (m, 1H). LC-MS: rt = 0.88 min, MS: 294.1 (calcd), 295.0 (M+H⁺, found).

Example 90**2-Amino-6-(cyanomethyl)-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (150)****150: Example 90**

Compound **150** (example 90) was synthesized similarly to compound **109** (example 59, scheme 19) starting from compound **126** (table 4) instead of compound **108**.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.06 (s, 2H), 6.97 (bs, 2H), 3.16-3.03 (m, 1H), 2.99-2.81 (m, 3H), 2.16-2.02 (m, 2H), 1.60-1.44 (m, 2H), 0.66-0.57 (m, 1H), 0.47-0.35 (m, 2H), 0.13-0.07 (m, 1H), -0.01 - -0.07 (m, 1H). LC-MS: rt = 0.94 min. MS: 303.1 (calcd), 304.0 (M+H⁺, found).

Example 91**2-Amino-7-oxo-4,7-dihydro-5H-spiro[benzo[*b*]thiophene-6,1'-cyclopentane]-3-carboxamide (155)****Scheme 29****154: Example 164****155: Example 91****Step 1. Ethyl 2-amino-4,7-dihydro-5H-spiro[benzo[*b*]thiophene-6,1'-cyclopentane]-3-carboxylate (152)**

To a solution of spiro[4.5]decan-8-one (**151**) (199 mg, 1.31 mmol) and ethyl 2-cyanoacetate (0.139 mL, 1.31 mmol) in EtOH (1.3 mL) were added morpholine (0.126 mL, 1.44

mmol) and sulfur (46 mg, 0.18 mmol). The reaction mixture was stirred at 60 °C for 16 hours, then allowed to cool to RT and concentrated to dryness. The residue was purified by flash column chromatography to afford title compound **152** (270 mg, 74% yield). LC-MS: rt = 1.98 min, MS: 279.1 (calcd), 280.1 (M+H⁺, found).

5 Step 2. Ethyl 2-amino-7-oxo-4,7-dihydro-5H-spiro[benzo[*b*]thiophene-6,1'-cyclopentane]-3-carboxylate (**153**)

To a mixture of **152** (100 mg, 0.358 mmol) in THF (1.2 mL) and water (0.2 mL) at 0 °C was added dropwise a solution of DDQ (81 mg, 0.358 mmol) in THF (1.0 mL) and the reaction mixture was stirred at 0 °C for 30 min. Then, the reaction mixture was quenched with saturated
10 NaHCO₃ solution and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography to afford title compound **153** (15 mg, 14% yield). LC-MS: rt = 1.63 min, MS: 293.1 (calcd), 294.1 (M+H⁺, found).

Step 3. 2-Amino-7-oxo-4,7-dihydro-5H-spiro[benzo[*b*]thiophene-6,1'-cyclopentane]-3-carboxylic acid (**154**)

15 To a solution of **153** (15 mg, 0.051 mmol) in MeOH (1.1 mL) was added a solution of lithium hydroxide monohydrate (7 mg, 0.283 mmol) in water (1.1 mL). The reaction mixture was stirred under reflux for 16 hours, then allowed to cool to RT. The mixture was diluted with water and concentrated to remove most of the organic solvent. The aqueous layer was acidified by slowly adding HCl 1 N and extracted with EA. The organic layer was dried over Na₂SO₄, filtered
20 and concentrated to afford title compound **154** as a white solid (6 mg, 44% yield). (See table 6 for characterization)

Step 4. 2-Amino-7-oxo-4,7-dihydro-5H-spiro[benzo[*b*]thiophene-6,1'-cyclopentane]-3-carboxamide (**155**)

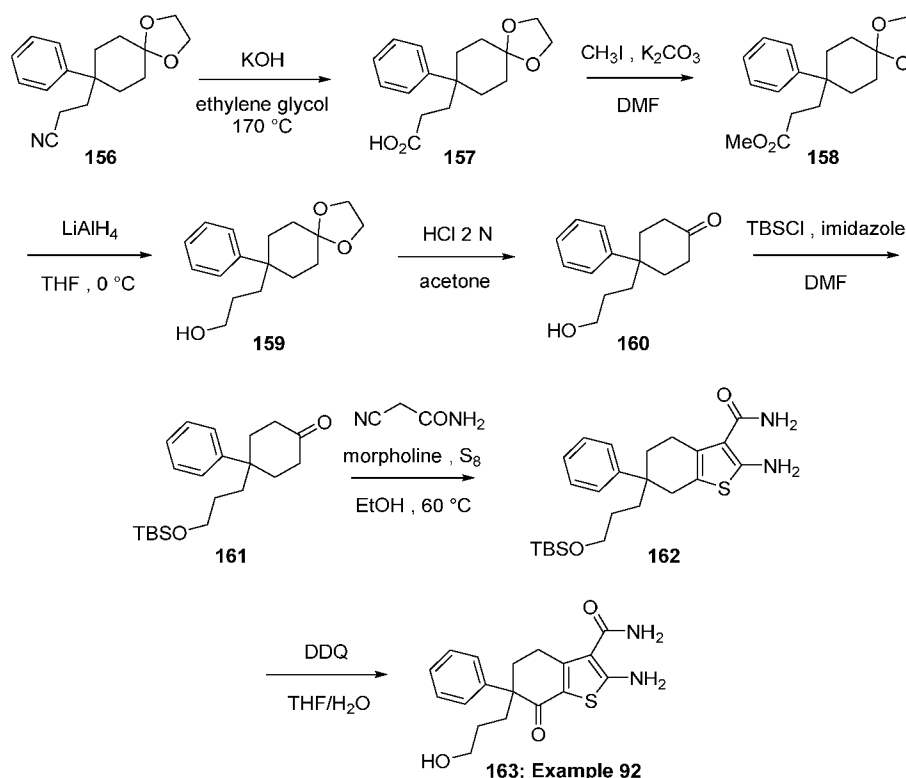
Compound **154** (6 mg, 0.023 mmol) was dissolved in a NH₃ 0.4 M solution in THF (1.5
25 mL) and HATU (17 mg, 0.045 mmol) and *N,N*-diisopropylethylamine (0.008 mL, 0.045 mmol) were added to the mixture. Then, the reaction mixture was stirred at RT for 16 hours. Afterwards, the reaction mixture was quenched with a saturated NH₄Cl solution and extracted with EA. The organic layer was washed with water and brine, then dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography to afford title compound
30 **155** as a white solid (3.7 mg, 62% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 2.99 (t, *J* = 6.0 Hz, 2H), 2.06 (t, *J* = 6.0 Hz, 2H), 2.03-1.97 (m, 2H), 1.79-1.68 (m, 4H), 1.62-1.56 (m, 2H). LC-MS: rt = 1.07 min, MS: 264.1 (calcd), 265.1 (M-H⁺, found).

Example 92

35 **2-Amino-6-(3-hydroxypropyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**163**)**

Scheme 30



Step 1. 3-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)propanoic acid (**157**)

To a solution of 3-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)propanenitrile (**156**) (2.30 g, 8.48 mmol) (*Bioorg Med. Chem Lett.* 21, p. 405, 2011) in ethylene glycol (40.0 mL) were added potassium hydroxide (3.80 g, 67.8 mmol) and water (0.030 mL, 1.70 mmol). The reaction mixture was stirred at $170\text{ }^{\circ}\text{C}$ for 16 hours, then allowed to cool to RT and diluted with water and DCM. The layers were separated and the aqueous phase was acidified by slowly adding HCl 2 N and extracted with DCM. This organic layer was dried over MgSO_4 , filtered and concentrated to afford title compound **157** (2.03 g, 82% yield) as a brown solid. LC-MS: $r_t = 0.84\text{ min}$, MS: 290.2 (calcd), 289.2 ($[\text{M}-\text{H}]^-$, found).

Step 2. Methyl 3-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)propanoate (**158**)

To a solution of **157** (1.30 g, 4.48 mmol) in anhydrous DMF (10.0 mL) at $0\text{ }^{\circ}\text{C}$ were added potassium carbonate (1.86 g, 13.4 mmol) and iodomethane (0.418 mL, 6.72 mmol). The reaction mixture was stirred at RT for 16 hours, then diluted with water and extracted with Et_2O . This organic layer was washed with brine and dried over MgSO_4 , filtered and concentrated to afford title compound **158** (1.35 g, 99% yield) as an oil. LC-MS: $r_t = 1.53\text{ min}$, MS: 304.2 (calcd), 305.2 ($[\text{M}+\text{H}]^+$, found).

Step 3. 3-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)propan-1-ol (**159**)

To a solution of lithium aluminum hydride (6.25 mL, 1 M in THF, 6.25 mmol) in anhydrous THF (7.0 mL) at $0\text{ }^{\circ}\text{C}$ was added dropwise a solution of **158** (865 mg, 2.84 mmol) in anhydrous THF (10.0 mL). The reaction mixture was stirred at $0\text{ }^{\circ}\text{C}$ for 1 hour, before being carefully

quenched with MeOH and water at 0 °C. Then, the mixture was diluted with EA and saturated Rochelle's salt solution and stirred at RT for 30 min. The layers were separated and the aqueous phase was extracted with EA. The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 70% of EA in hexane) to afford title compound **159** (760 mg, 97% yield) as a yellow oil. LC-MS: rt = 1.28 min, MS: 276.2 (calcd), 277.2 (M+H⁺, found).

Step 4. 4-(3-Hydroxypropyl)-4-phenylcyclohexan-1-one (**160**)

To a solution of **159** (368 mg, 1.33 mmol) in acetone (18.0 mL) was added HCl 2 N (3.33 mL, 6.66 mmol) and the reaction mixture was stirred at RT for 16 hours. Then, the mixture was neutralized by slowly adding saturated aqueous NaHCO₃ solution and concentrated to remove the organic solvent. The residue was extracted with EA and the organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness to afford title compound **160** (289 mg, 94% yield) as a yellow oil, which was not characterized and used directly for the next step.

Step 5. 4-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-4-phenylcyclohexan-1-one (**161**)

To a solution of **160** (196 mg, 0.84 mmol) in anhydrous DMF (4.2 mL) were added *tert*-butyldimethylsilyl chloride (162 mg, 1.08 mmol) and imidazole (144 mg, 2.11 mmol). The reaction mixture was stirred at RT for 16 hours, then it was diluted with water and EA. The layers were separated and the organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 30% of EA in hexane) to afford title compound **161** (259 mg, 89% yield) as a pale-yellow oil which was not characterized and used directly for the next step.

Step 6. 2-Amino-6-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**162**)

To a solution of **161** (259 mg, 0.747 mmol) and cyanoacetamide (57 mg, 0.679 mmol) in EtOH (1.4 mL) were added morpholine (0.065 mL, 0.747 mmol) and sulfur (24 mg, 0.093 mmol). The reaction mixture was stirred at 60 °C for 16 hours, allowed to cool to RT and concentrated to dryness. The residue was purified by flash column chromatography (eluent gradient from 0% to 10% of MeOH in DCM) to afford title compound **162** (200 mg, 60% yield). LC-MS: rt = 2.07 min, MS: 444.2 (calcd), 445.3 (M+H⁺, found).

Step 7. 2-Amino-6-(3-hydroxypropyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**163**)

To a mixture of **162** (200 mg, 0.450 mmol) in THF (1.5 mL) and water (0.25 mL) at 0 °C was added dropwise a solution of DDQ (306 mg, 1.35 mmol) in THF (1.25 mL). The reaction mixture was allowed to slowly reach RT and stirred for 16 hours. Then, the mixture was quenched with saturated NaHCO₃ solution and extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 2% to 10% of MeOH in DCM), then it was purified again

by Semi-Prep HPLC-MS (eluent gradient from 30% to 100% of MeOH in 10 mM ammonium bicarbonate) to afford title compound **163** as a white solid (10 mg, 6% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.34-7.28 (m, 4H), 7.23-7.19 (m, 1H), 3.54-3.43 (m, 2H), 2.96 (ddd, *J* = 17.1, 4.4, 3.1 Hz, 1H), 2.75-2.69 (m, 1H), 2.67-2.60 (m, 1H), 2.41-2.33 (m, 1H),
 5 2.00-1.83 (m, 2H), 1.58-1.44 (m, 2H). LC-MS: rt = 0.96 min, MS: 344.1 (calcd), 345.1 (M+H⁺, found).

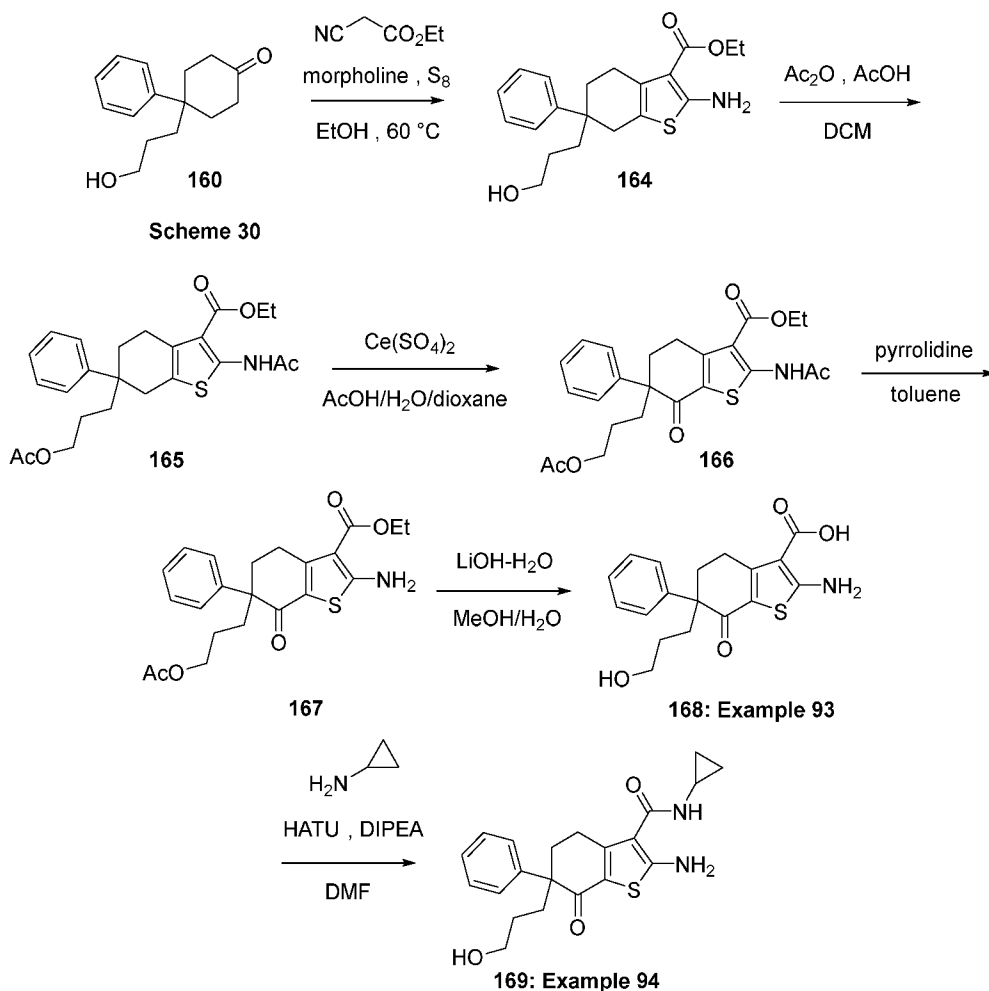
Example 93

2-Amino-6-(3-hydroxypropyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (**168**) and

Example 94

2-Amino-*N*-cyclopropyl-6-(3-hydroxypropyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**169**)

Scheme 31



Step 1. Ethyl 2-amino-6-(3-hydroxypropyl)-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**164**)

To a solution of **160** (scheme 30) (289 mg, 1.24 mmol) and ethyl 2-cyanoacetate (0.149 mL, 1.37 mmol) in EtOH (10.0 mL) were added morpholine (0.120 mL, 1.37 mmol) and sulfur (44 mg, 0.172 mmol). The reaction mixture was stirred at 60 °C for 24 hours, then allowed to cool to RT and concentrated to dryness. The residue was partitioned between EA and water. The layers were separated and the aqueous phase was extracted with EA. The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane) to afford title compound **164** as a white solid (336 mg, 75% yield). LC-MS: rt = 1.53 min, MS: 359.2 (calcd), 360.2 (M+H⁺, found).

Step 2. Ethyl 2-acetamido-6-(3-acetoxypropyl)-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**165**)

To a suspension of **164** (336 mg, 0.935 mmol) in anhydrous DCM (3.0 mL) were added acetic anhydride (0.265 mL, 2.80 mmol) and acetic acid (0.054 mL, 0.935 mmol). The reaction mixture was stirred at RT for 4 days, then it was diluted with DCM and washed with saturated NaHCO₃ solution, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane) to afford title compound **165** as a white solid (208 mg, 50% yield). LC-MS: rt = 1.86 min, MS: 443.2 (calcd), 444.3 (M+H⁺, found).

Step 3. Ethyl 2-acetamido-6-(3-acetoxypropyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**166**)

Intermediate **165** (208 mg, 0.469 mmol) and ceric sulfate (1.35 g, 4.05 mmol) were added to a 1:1:1 acetic acid/water/dioxane mixture (15 mL). The flask was sonicated to make the suspension homogeneous and the reaction mixture was vigorously stirred at RT for 16 hours. Afterwards, the mixture was diluted with water and extracted with EA. The organic layer was washed with NaOH 1 N, water and brine, then dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 45% of EA in hexane) to afford title compound **166** as a white solid (122 mg, 57% yield). LC-MS: rt = 1.73 min, MS: 457.2 (calcd), 458.3 (M+H⁺, found).

Step 4. Ethyl 6-(3-acetoxypropyl)-2-amino-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**167**)

To a solution of **166** (122 mg, 0.267 mmol) in toluene (0.5 mL) was added pyrrolidine (0.35 mL, 4.26 mmol) and the reaction mixture was stirred at RT for 1 hour. Afterwards, the mixture was diluted with brine and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated to afford title compound **167** as a dark orange oil, which was used directly for the next step. LC-MS: rt = 1.64 min, MS: 415.2 (calcd), 416.3 (M+H⁺, found).

Step 5. 2-Amino-6-(3-hydroxypropyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**168**)

To a solution of **167** (0.267 mmol) in MeOH (4.0 mL) was added a solution of lithium hydroxide monohydrate (162 mg, 3.86 mmol) in water (2.0 mL). The reaction mixture was stirred at 60 °C for 3 days, then allowed to cool to RT. The mixture was concentrated to remove most of the organic solvent. The aqueous layer was acidified by slowly adding HCl 1 N and extracted with

5 EA. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 50% to 100% of EA in hexane) to afford title compound **168** as a yellow solid (70 mg, 76% yield over two steps).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.32-7.28 (m, 4H), 7.23-7.18 (m, 1H), 3.53-3.43 (m, 2H), 3.26-3.19 (m, 1H), 2.60-2.51 (m, 2H), 2.35-2.27 (m, 1H), 1.98-1.83 (m, 2H), 1.55-1.44 (m,

10 2H). LC-MS: rt = 1.09 min, MS: 345.1 (calcd), 346.0 (M+H⁺, found).

Step 6. 2-Amino-N-cyclopropyl-6-(3-hydroxypropyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**169**)

To a solution of **168** (54 mg, 0.156 mmol) in anhydrous DMF (1.95 mL) were added HATU (119 mg, 0.313 mmol), *N,N*-diisopropylethylamine (0.082 mL, 0.469 mmol) and cyclopropylamine

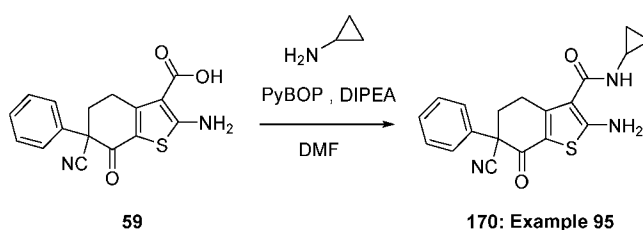
15 (0.012 mL, 0.172 mmol). Then, the reaction mixture was stirred at RT for 16 hours. Afterwards, the reaction mixture was diluted with EA and washed with saturated NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 30% to 100% of EA in hexane) to afford title compound **169** as an off-white solid (46 mg, 77% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.33-7.26 (m, 4H), 7.21-7.17 (m, 1H), 3.52-3.42 (m, 2H), 2.81 (ddd, *J* = 17.3, 4.4, 3.3 Hz, 1H), 2.70-2.62 (m, 2H), 2.58 (dt, *J* = 13.9, 3.7 Hz, 1H), 2.31 (ddd, *J* = 13.8, 11.2, 4.6 Hz, 1H), 1.98-1.81 (m, 2H), 1.56-1.41 (m, 2H), 0.76-0.68 (m, 2H), 0.57-0.50 (m, 2H). LC-MS: rt = 1.13 min, MS: 384.1 (calcd), 385.1 (M+H⁺, found).

Example 95

2-Amino-6-cyano-N-cyclopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (170**)**

Scheme 32



Scheme 8

To a solution of **59** (example 36, scheme 8) (2.03 g, 6.50 mmol) in anhydrous DMF (72 mL) at 0 °C were added PyBOP (3.73 g, 7.15 mmol), *N,N*-diisopropylethylamine (2.26 mL, 13.0 mmol) and cyclopropylamine (2.25 mL, 32.5 mmol). Then, the reaction mixture was stirred at RT

30

for 16 hours. Afterwards, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EA. The organic layer was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 40% to 100% of EA in hexane), then it was purified again by reverse-phase flash column chromatography (eluent gradient from 10% to 100% of CH_3CN in H_2O with 0.1% (v/v) formic acid) to afford title compound **170** as an off-white solid (1.48 g, 65% yield).

^1H NMR: 400 MHz, $\text{DMSO}-d_6$, δ (ppm): 8.16 (s, 2H), 7.61-7.59 (m, 1H), 7.47-7.38 (m, 5H), 3.04-2.97 (m, 1H), 2.80-2.70 (m, 3H), 2.64-2.57 (m, 1H), 0.68-0.60 (m, 2H), 0.54-0.48 (m, 2H). LC-MS: rt = 1.25 min, MS: 351.1 (calcd), 352.2 ($\text{M}+\text{H}^+$, found).

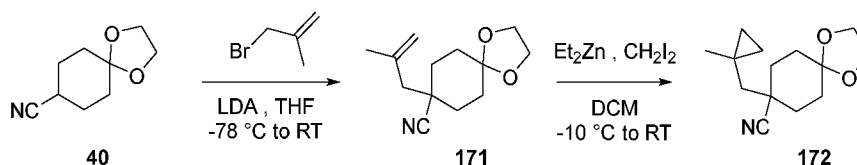
Example 96

2-Amino-6-cyano-6-((1-methylcyclopropyl)methyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**174**)

Intermediate compound **172**

8-((1-Methylcyclopropyl)methyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (**172**)

Scheme 33



Scheme 4

Step 1. 8-(2-Methylallyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (**171**)

To a solution of 1,4-dioxaspiro[4.5]decane-8-carbonitrile (**40**, scheme 4) (0.696 mL, 4.44 mmol) in anhydrous THF (10 mL) at $-78\text{ }^\circ\text{C}$ was added dropwise LDA (6.67 mL, 1 M in THF/hexane, 6.67 mmol). The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 30 min, before adding dropwise a solution of 3-bromo-2-methylpropene (0.448 mL, 4.44 mmol) in anhydrous THF (10 mL). Then, the reaction mixture was allowed to reach RT and stirred for 3 days. Afterwards, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EA. The organic layer was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane) to afford title compound **171** (753 mg, 77% yield) as a colorless oil, which was not characterized and used directly for the next step.

Step 2. 8-((1-Methylcyclopropyl)methyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (**172**)

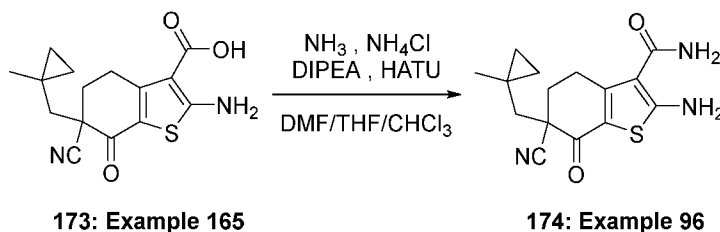
To a solution of **171** (650 mg, 2.94 mmol) in anhydrous DCM (29 mL) at $-10\text{ }^\circ\text{C}$ were added diethylzinc (5.87 mL, 1 M in hexane, 5.87 mmol) and diiodomethane (0.946 mL, 11.7 mmol). The reaction mixture was stirred at $-10\text{ }^\circ\text{C}$ for 30 min, then it was allowed to reach RT and stirred for 3 days. Afterwards, the reaction mixture was quenched with saturated NH_4Cl solution and the

layers were separated. The organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane) to afford title compound **172** (233 mg, 34% yield) as a colorless oil, which was not characterized and used directly for the synthesis of relevant examples.

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2-Amino-6-cyano-6-((1-methylcyclopropyl)methyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (174)

Scheme 34

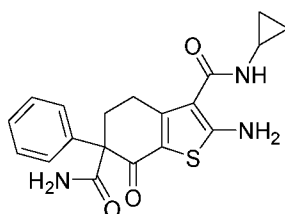


To a suspension of **173** (See table 6 for characterization) (synthesized similarly to compound **47** (scheme 4) starting from compound **172** (scheme 33) instead of compound **41**) (46 mg, 0.151 mmol) and ammonium chloride (162 mg, 3.02 mmol) in anhydrous DMF (2.0 mL) were added HATU (88 mg, 0.227 mmol) and *N,N*-diisopropylethylamine (0.053 mL, 0.302 mmol). Then, saturated NH₃ solution in CHCl₃ (0.9 mL) (prepared in-house) and NH₃ 0.4 M in THF (0.9 mL) were added dropwise and the reaction mixture was stirred at RT for 16 hours. Afterwards, the reaction mixture was quenched with a saturated NH₄Cl solution and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by reverse-phase flash column chromatography (eluent gradient from 0% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **174** as a white solid (26 mg, 57% yield).

¹H NMR: 400 MHz, DMSO-*d*₆, δ (ppm): 8.24 (s, 2H), 7.09 (bs, 2H), 3.15-3.01 (m, 2H), 2.46-2.43 (m, 1H), 2.39-2.32 (m, 1H), 1.88 (s, 2H), 1.12 (s, 3H), 0.46-0.38 (m, 1H), 0.32-0.24 (m, 3H). LC-MS: rt = 1.12 min, MS: 303.1 (calcd), 304.1 (M+H⁺, found).

Example 97

2-Amino-*N*³-cyclopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3,6-dicarboxamide (175)



175: Example 97

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Compound **175** (example 97) was synthesized similarly to compound **145** (example 85, scheme 26) starting from compound **170** (example 95, scheme 32) instead of compound **144**.

^1H NMR: 400 MHz, CD_3OD , δ (ppm): 7.35-7.33 (m, 4H), 7.32-7.28 (m, 1H), 2.92 (dt, J = 17.1, 4.8 Hz, 1H), 2.73-2.68 (m, 3H), 2.58 (ddd, J = 17.1, 7.9, 5.5 Hz, 1H), 0.76-0.71 (m, 2H), 0.57-0.53 (m, 2H). LC-MS: rt = 1.02 min, MS: 369.1 (calcd), 370.2 ($\text{M}+\text{H}^+$, found).

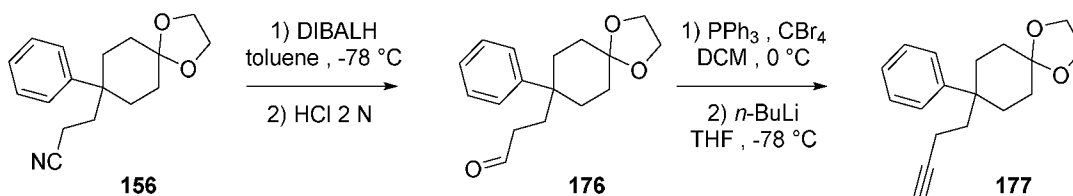
Example 98

2-Amino-6-(but-3-yn-1-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (179)

Intermediate compound 177

8-(But-3-yn-1-yl)-8-phenyl-1,4-dioxaspiro[4.5]decane (177)

Scheme 35



Scheme 30

Step 1. 3-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)propanal (176)

To a solution of 3-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)propanenitrile (**156**, scheme 30) (1.40 g, 5.16 mmol) (*Bioorg Med. Chem Lett.* 21, p. 405, 2011) in anhydrous toluene (33 mL) at $-78\text{ }^{\circ}\text{C}$ was added dropwise DIBALH (4.16 mL, 25% in toluene, 6.19 mmol). The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 5 min, then it was quenched with saturated NH_4Cl solution. Afterwards, the mixture was allowed to reach RT and HCl 2 N (2.58 mL, 5.16 mmol) was added. The mixture was extracted with Et_2O and this organic layer was washed with saturated NaHCO_3 solution and brine, dried over Na_2SO_4 , filtered and concentrated to afford title compound **176** as a colorless oil, which was used directly for the next step without characterization.

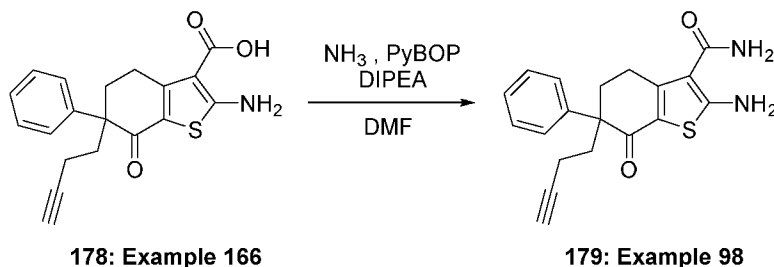
Step 2. 8-(But-3-yn-1-yl)-8-phenyl-1,4-dioxaspiro[4.5]decane (177)

To a solution of triphenylphosphine (3.59 g, 13.4 mmol) in anhydrous DCM (32 mL) at $0\text{ }^{\circ}\text{C}$ was added carbon tetrabromide (2.22 g, 6.71 mmol). The reaction mixture was stirred at RT for 30 min, then it was cooled to $0\text{ }^{\circ}\text{C}$ again and a solution of **176** (5.16 mmol) in anhydrous DCM (8 mL) was added and the reaction mixture was stirred at $0\text{ }^{\circ}\text{C}$ for 30 min. Afterwards, the reaction mixture was diluted with hexane, filtered through a celite pad and concentrated. The residue was diluted with hexane, filtered through a celite pad and concentrated again. This residue was dissolved in anhydrous THF (23 mL) and the solution was cooled to $-78\text{ }^{\circ}\text{C}$. Then, *n*-butyl lithium (4.13 mL, 2.5 M in hexane, 10.3 mmol) was added dropwise and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 hour. Afterwards, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from

0% to 50% of EA in hexane) to afford title compound **177** as a white solid (734 mg, 53% yield over two steps), which was not characterized and used directly for the synthesis of relevant examples.

2-Amino-6-(but-3-yn-1-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (179)

Scheme 36



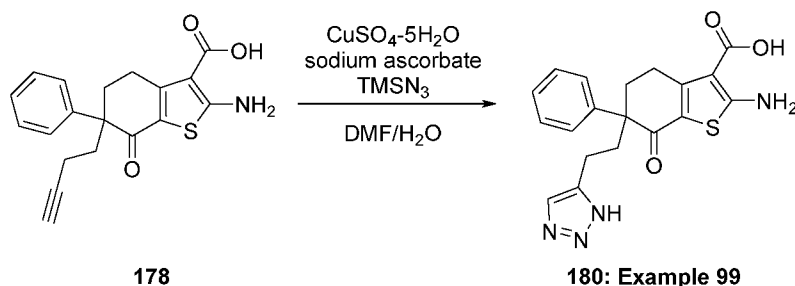
A solution of **178** (See table 6 for characterization) (synthesized similarly to compound **47** (scheme 4) starting from compound **177** (scheme 35) instead of compound **41**) (83 mg, 0.25 mmol) in anhydrous DMF (2.7 mL) was saturated with bubbling NH₃ from a balloon. Then PyBOP (191 mg, 0.37 mmol) and *N,N*-diisopropylethylamine (0.085 mL, 0.49 mmol) were added and the reaction mixture was stirred at RT for 16 hours. Afterwards, the reaction mixture was quenched with saturated NH₄Cl solution and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 40% to 100% of EA in hexane) to afford title compound **179** as an off-white solid (50 mg, 60% yield).

¹H NMR: 400 MHz, CDCl₃, δ (ppm): 7.34-7.23 (m, 5H), 6.99 (s, 2H), 5.29 (s, 2H), 2.96-2.88 (m, 1H), 2.68-2.56 (m, 2H), 2.47-2.40 (m, 1H), 2.35-2.26 (m, 1H), 2.23-2.11 (m, 2H), 2.09-2.01 (m, 1H), 1.91 (t, *J* = 2.5 Hz, 1H). LC-MS: *rt* = 1.24 min, MS: 338.1 (calcd), 339.1 (*M*+H⁺, found).

Example 99

6-(2-(1H-1,2,3-Triazol-5-yl)ethyl)-2-amino-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (180)

Scheme 37



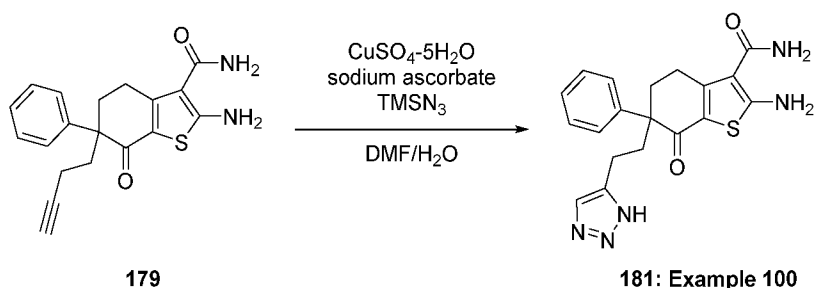
To a suspension of **178** (scheme 36) (20 mg, 0.059 mmol) in DMF (0.6 mL) and water (0.3 mL) were added copper(II) sulfate pentahydrate (30 mg, 0.12 mmol) and sodium ascorbate (24 mg, 0.12 mmol). The flask was evacuated and backfilled with nitrogen, then trimethylsilyl azide (0.06 mL, 0.47 mmol) was added and the reaction mixture was stirred at RT for 10 min. Afterwards, the mixture was purified by reverse-phase flash column chromatography (eluent gradient from 10% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **180** as a white solid (16 mg, 71% yield).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.26 (s, 2H), 7.49 (bs, 1H), 7.35-7.31 (m, 4H), 7.26-7.21 (m, 1H), 3.17-3.12 (m, 1H), 2.67-2.63 (m, 1H), 2.50-2.41 (m, 3H), 2.33-2.23 (m, 1H), 2.11-2.07 (m, 2H). LC-MS: rt = 1.11 min, MS: 382.1 (calcd), 383.2 (M+H⁺, found).

Example 100

6-(2-(1H-1,2,3-Triazol-5-yl)ethyl)-2-amino-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**181**)

Scheme 38



Scheme 36

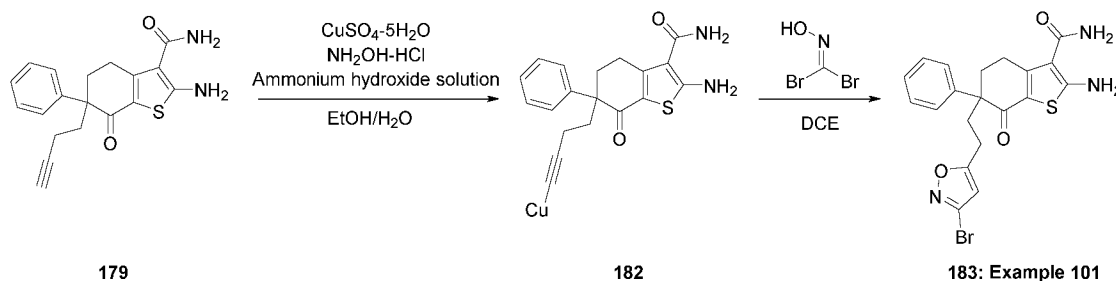
To a suspension of **179** (scheme 36) (25 mg, 0.074 mmol) in DMF (0.8 mL) and water (0.4 mL) were added copper(II) sulfate pentahydrate (37 mg, 0.148 mmol) and sodium ascorbate (29 mg, 0.148 mmol). The flask was evacuated and backfilled with nitrogen, then trimethylsilyl azide (0.078 mL, 0.591 mmol) was added and the reaction mixture was stirred at RT for 10 min. Then, the reaction mixture was quenched with saturated NH₄Cl solution and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 20% of MeOH in DCM) to afford title compound **181** as a white solid (13 mg, 46% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.52 (bs, 1H), 7.37-7.31 (m, 4H), 7.26-7.22 (m, 1H), 3.02-2.98 (m, 1H), 2.85-2.57 (m, 4H), 2.48-2.41 (m, 1H), 2.30-2.16 (m, 2H). LC-MS: rt = 0.98 min, MS: 381.1 (calcd), 382.2 (M+H⁺, found).

Example 101

2-Amino-6-(2-(3-bromoisoxazol-5-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**183**)

Scheme 39



Scheme 36

Step 1. (4-(2-Amino-3-carbamoyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophen-6-yl)but-1-yn-1-yl)copper (182)

To a solution of cupric sulfate pentahydrate (88.5 mg, 355 μmol) and aqueous ammonium hydroxide 28% (177 μL , 1.32 mmol) in water (1 mL) cooled to 0 °C was added hydroxylamine hydrochloride (24.6 mg, 355 μmol) under N_2 . The mixture was stirred for 10 minutes and then a solution of **179** (scheme 36) (30.0 mg, 88.6 μmol) in ethanol (3 mL) was added in one portion. The resulting mixture was stirred for 5 minutes, then stirring was stopped and the mixture was allowed to stand for an additional 5 minutes. The precipitate was filtered off and washed successively with water (5 x 5 mL), EtOH (5 x 5 mL) and Et₂O (5 x 5 mL). The precipitate was then dried in vacuo overnight to afford title compound **182** as a dark yellow solid (30 mg, 84% yield), which was used directly for the next step without characterization.

Step 2. 2-Amino-6-(2-(3-bromoisoxazol-5-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (183)

To a suspension of **182** (30.0 mg, 74.8 μmol) in DCE (1 mL) was added 1,1-dibromoformaldoxime (18.2 mg, 89.8 μmol) and the resulting mixture was stirred at 45 °C for 4 hours. The mixture was then allowed to cool to RT and purified by flash column chromatography (eluent gradient from 0% to 100% of EA in hexane) and then reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **183** a pale-yellow solid (2.6 mg, 7.5%).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.10 (s, 2H), 7.35-7.30 (m, 4H), 7.27-7.21 (m, 1H), 6.85 (bs, 2H); 6.53 (s, 1H), 2.91-2.81 (m, 1H), 2.78-2.63 (m, 2H), 2.63-2.54 (m, 2H), 2.33-2.19 (m, 1H), 2.16-2.09 (m, 2H). LC-MS: rt = 1.39 min, MS: 459.0 and 461.0 (calcd), 460.0 and 462.0 (M+H⁺, found).

Example 102

2-Amino-6-(2-cyanoethyl)-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (189)

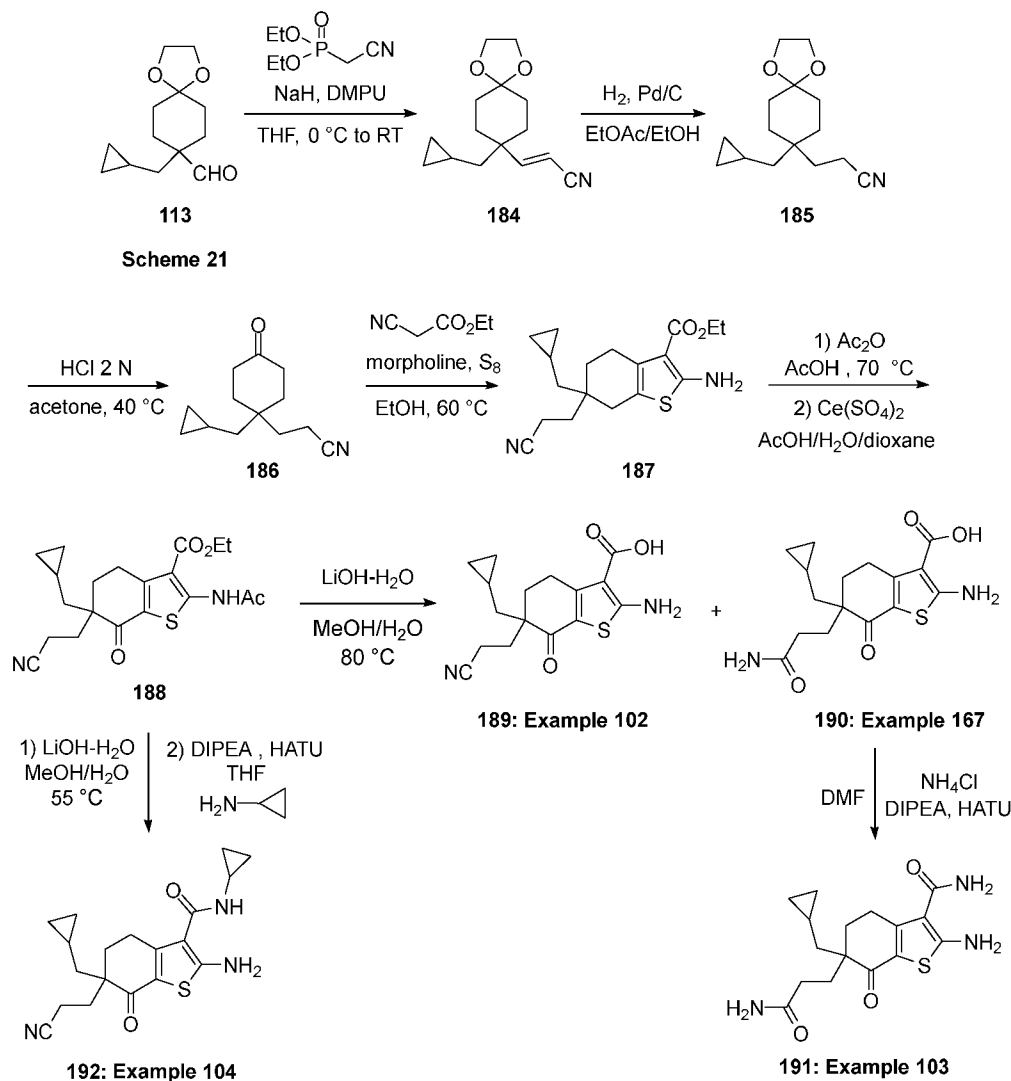
Example 103

2-Amino-6-(3-amino-3-oxopropyl)-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (191)

Example 104

2-Amino-6-(2-cyanoethyl)-N-cyclopropyl-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (192)

Scheme 40



5 Step 1. 3-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)acrylonitrile (184)

To a mixture of sodium hydride (2.14 g, 53.5 mmol) and DMPU (11.3 mL, 93.6 mmol) in anhydrous THF (40 mL) at 0 °C was slowly added diethylcyanomethylphosphonate (8.65 mL, 53.5 mmol). The mixture was stirred at 0 °C for 1 hour, then a solution of **113** (scheme 21) (10.0 g, 44.6 mmol) in anhydrous THF (65 mL) was added dropwise and the reaction mixture was stirred

10 at RT for 24 hours. The mixture was partitioned between water and EA (200 mL each). The layers were separated and the organic phase was washed with brine (150 mL), dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography (eluent mixture 50% of Et₂O in hexane) to afford title compound **184** as a colorless oil (10.0 g, 91% yield), which was not characterized and used directly for the next step.

Step 2. 3-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)propanenitrile (185)

A suspension of **184** (10.0 g, 40.4 mmol) and Pd/C 10% (215 mg) in EA (189 mL) and EtOH (246 mL) was stirred under hydrogen atmosphere (balloon) at RT for 24 hours. The mixture was then filtered and the filtrate was concentrated to afford title compound **185** as a colorless oil (9.90 g, 98% yield), which was used in Step 4 without purification and without characterization.

Step 3. 3-(1-(Cyclopropylmethyl)-4-oxocyclohexyl)propanenitrile (186)

2 N aqueous HCl (186 mL, 372 mmol) was added to a solution of **185** (9.30 g, 37.3 mmol) in acetone (460 mL) and the resulting mixture was stirred at 40 °C for 24 hours, then quenched with saturated aqueous NaHCO₃ (200 mL) and concentrated to remove the organic solvent. The residue was extracted with EA (2 x 250 mL). The combined organics were washed with brine, dried over Na₂SO₄, filtered and concentrated to afford title compound **186** as a colorless oil (6.90 g, 90% yield), which was used in Step 5 without purification and without characterization.

Step 4. Ethyl 2-amino-6-(2-cyanoethyl)-6-(cyclopropylmethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (187)

A suspension of **186** (6.10 g, 29.7 mmol), morpholine (2.82 mL, 32.7 mmol), sulfur (1.05 g, 4.10 mmol) and ethyl 2-cyanoacetate (3.16 mL, 29.7 mmol) in EtOH (52 mL) was stirred at 60 °C for 16 hours. The mixture was then allowed to cool to RT, diluted with brine (100 mL) and extracted with EA (3 x 100 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 70% of EA in hexane) to afford title compound **187** as a dark yellow oil (4.10 g, 42% yield). LC-MS: rt = 1.71 min, MS: 332.2 (calcd), 333.1 (M+H⁺, found).

Step 5. Ethyl 2-acetamido-6-(2-cyanoethyl)-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (188)

A mixture of **187** (4.10 g, 12.3 mmol) and acetic anhydride (1.40 mL, 14.8 mmol) in acetic acid (71 mL) was stirred at 70 °C for 2 hours. The mixture was allowed to cool to RT and concentrated to around 50 mL. Then, the mixture was diluted with water (50 mL) and dioxane (50 mL) and ceric sulfate (37.3 g, 107 mmol) was added. The reaction mixture was stirred at RT for 24 hours. Then, the yellow solid was filtered off, rinsed with EA (150 mL) and the filtrate was diluted with brine. The layers were separated, and the aqueous phase was extracted with EA (150 mL). The combined organics were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated to afford title compound **188** as an orange oil (4.20 g, 88% yield). LC-MS: rt = 1.63 min, MS: 388.2 (calcd), 389.3 (M+H⁺, found).

Step 6a. 2-Amino-6-(2-cyanoethyl)-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (189) and 2-Amino-6-(3-amino-3-oxopropyl)-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (190)

A solution of lithium hydroxide monohydrate (109 mg, 2.60 mmol) in water (63 mL) was added to a solution of **188** (202 mg, 0.52 mmol) in MeOH (63 mL). The mixture was stirred at 80

°C for 16 hours, then allowed to cool to RT and concentrated by rotary evaporation to remove most of the organic solvent. The aqueous residue was washed with EA and the layers were separated. The aqueous layer was acidified by slowly adding 1 N HCl and extracted with EA (3 x 40 mL). These organics were dried over Na₂SO₄, filtered and concentrated to afford a mixture of title compounds **189** and **190**. This crude was purified by flash column chromatography (eluent gradient from 0% to 35% of MeOH in DCM) to afford **189** (111 mg, 67% yield) and **190** (40.0 mg, 23% yield). 24 mg of **189** were further purified by Semi-Prep HPLC-MS (eluent gradient from 20% to 100% of MeOH in 10 mM ammonium bicarbonate) to afford 14.8 mg of highly pure material as an off-white solid.

¹H NMR of **189**: 400 MHz, DMSO-d₆, δ (ppm): 8.32 (bs, 2H), 3.09-3.03 (m, 1H), 2.94-2.87 (m, 1H), 2.43-2.31 (m, 2H), 2.07-1.93 (m, 3H), 1.84-1.74 (m, 1H), 1.54 (dd, *J* = 14.2, 6.3 Hz, 1H), 1.30 (dd, *J* = 14.2, 7.0 Hz, 1H), 0.60-0.55 (m, 1H), 0.39-0.37 (m, 2H), 0.03 - -0.01 (m, 1H), -0.04 - -0.08 (m, 1H). LC-MS of **189**: rt = 1.22 min, MS: 318.1 (calcd), 319.1 (M+H⁺, found).

(See table 6 for characterization of **190**)

Step 7. 2-Amino-6-(3-amino-3-oxopropyl)-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**191**)

To a solution of **190** (40.0 mg, 119 μmol) in anhydrous DMF (1.26 mL) were added ammonium chloride (127 mg, 2.38 mmol), HATU (69.2 mg, 178 μmol) and *N,N*-diisopropylethylamine (41.4 μL, 238 μmol). The resulting mixture was stirred at RT for 16 hours, then it was concentrated. The residue was purified by reverse-phase column chromatography (eluent gradient from 0% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **191** as an off-white solid (15.8 mg, 40% yield).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 7.97 (s, 2H), 7.20 (s, 1H), 6.92 (bs, 2H), 6.64 (s, 1H), 2.98-2.90 (m, 2H), 2.12-2.04 (m, 1H), 2.00-1.87 (m, 3H), 1.84-1.71 (m, 2H), 1.57 (dd, *J* = 14.1, 6.3 Hz, 1H), 1.27 (dd, *J* = 14.1, 6.8 Hz, 1H), 0.61-0.54 (m, 1H), 0.40-0.36 (m, 2H), 0.06-0.01 (m, 1H), -0.02 - -0.08 (m, 1H). LC-MS: rt = 0.88 min, MS: 335.1 (calcd), 336.0 (M+H⁺, found).

Step 6b. 2-Amino-6-(2-cyanoethyl)-*N*-cyclopropyl-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**192**)

A solution of lithium hydroxide monohydrate (3.10 g, 73.8 mmol) in water (500 mL) was added to a solution of **188** (4.20 g, 10.8 mmol) in MeOH (500 mL). The mixture was stirred at 55 °C for 16 hours, then allowed to cool to RT and concentrated by rotary evaporation to remove most of the organic solvent. The aqueous residue was washed with DCM and the layers were separated. The aqueous layer was acidified by slowly adding 1 N HCl and extracted with EA (3 x 100 mL). These organics were dried over Na₂SO₄, filtered and concentrated. The residue was dissolved in anhydrous THF (90 mL) and HATU (7.17 g, 18.8 mmol), *N,N*-diisopropylethylamine (3.28 mL, 18.8 mmol) and cyclopropylamine (6.53 mL, 94.2 mmol) were added. The reaction

mixture was stirred at RT for 3 hours, then it was diluted with brine (50 mL) and extracted with EA (3 x 100 mL). The combined organics were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 100% of EA in hexane) to afford title compound **192** (1.86 g, 45% yield over two steps) as a yellow solid.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 7.73 (s, 2H), 7.31 (d, *J* = 3.8 Hz, 1H), 2.93-2.82 (m, 1H), 2.81-2.77 (m, 1H), 2.77-2.67 (m, 1H), 2.38-2.32 (m, 2H), 2.02-1.98 (m, 2H), 1.94-1.86 (m, 1H), 1.84-1.76 (m, 1H), 1.54 (dd, *J* = 14.2, 6.3 Hz, 1H), 1.29 (dd, *J* = 14.1, 7.0 Hz, 1H), 0.66-0.60 (m, 2H), 0.60-0.52 (m, 1H), 0.51-0.46 (m, 2H), 0.37-0.35 (m, 2H), 0.04 - -0.01 (m, 1H), -0.04 - -0.1 (m, 1H). LC-MS: rt = 1.25 min, MS: 357.2 (calcd), 358.1 (M+H⁺, found).

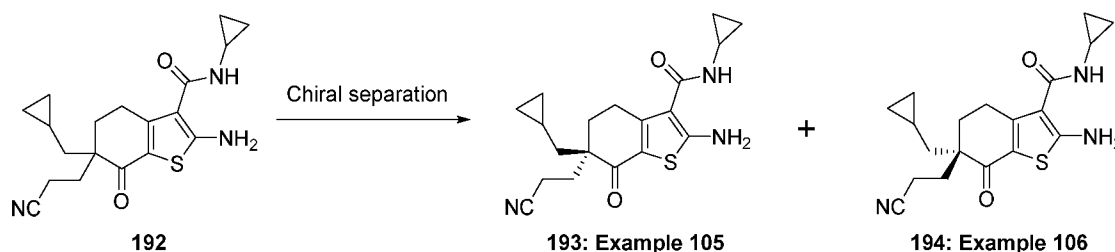
Example 105

(S)-2-Amino-6-(2-cyanoethyl)-*N*-cyclopropyl-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (193) and

Example 106

(R)-2-Amino-6-(2-cyanoethyl)-*N*-cyclopropyl-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (194)

Scheme 41



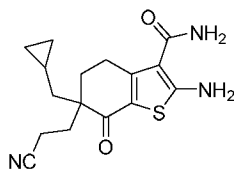
Racemic compound **192** (scheme 40) (1.14 g) was submitted to SFC chiral separation (isocratic: 50% of MeOH 1:1 in CO₂) to yield enantioenriched compound **193** as a orange solid (468.9 mg, 41% separation yield) and enantioenriched compound **194** as an off-white solid (424.5 mg, 37% separation yield) (the absolute configurations were assigned based on resolved crystal structure of enantiomer **194**).

193: ¹H NMR: same as racemic mixture (**192**). LC-MS: rt = 1.27 min, MS: 357.2 (calcd), 358.2 (M+H⁺, found). Analytical SFC (IG column with 5-60% MeOH in water (95-40% CO₂) gradient): rt = 5.44 min, ee. = >99.9%.

194: ¹H NMR: same as racemic mixture (**192**). LC-MS: rt = 1.27 min, MS: 357.2 (calcd), 358.2 (M+H⁺, found). Analytical SFC (IG column with 5-60% MeOH in water (95-40% CO₂) gradient): rt = 6.49 min, ee. = 99.4%.

Example 107

2-Amino-6-(2-cyanoethyl)-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (195)



195: Example 107

Compound **195** (example 107) was synthesized similarly to compound **109** (example 59, scheme 19) starting from compound **189** (scheme 40) instead of compound **108**.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.01 (s, 2H), 6.94 (bs, 2H), 3.05-2.89 (m, 2H), 2.44-2.32 (m, 2H), 2.08-2.02 (m, 2H), 1.99-1.92 (m, 1H), 1.86-1.79 (m, 1H), 1.55 (dd, *J* = 14.2, 6.4 Hz, 1H), 1.35 (dd, *J* = 14.2, 6.8 Hz, 1H), 0.63-0.54 (m, 1H), 0.40-0.35 (m, 2H), 0.08-0.04 (m, 1H), -0.03 - -0.07 (m, 1H). LC-MS: *rt* = 1.07 min. MS: 317.1 (calcd), 318.2 (M+H⁺, found).

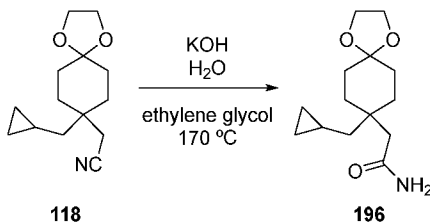
Example 108

2-Amino-6-(2-amino-2-oxoethyl)-*N*-cyclopropyl-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (198)

Intermediate compound 196

2-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)acetamide (196)

Scheme 42

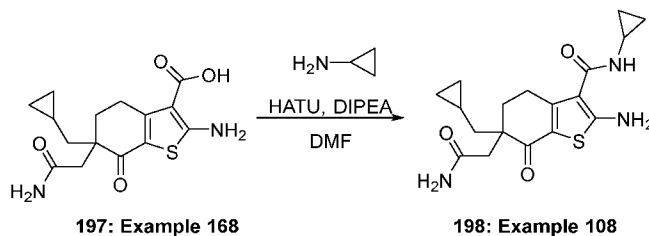


Scheme 22

To a solution of **118** (scheme 22) (814 mg, 3.46 mmol) in ethylene glycol (18.3 mL) were added potassium hydroxide (1.55 g, 27.7 mmol) and water (1 mL). The resulting mixture was stirred at 170 °C for 24 hours, then more potassium hydroxide (1.55 g, 27.7 mmol) and water (1 mL) were added and the reaction mixture was stirred at 170 °C for additional 24 hours. The mixture was allowed to cool to RT, diluted with water (50 mL) and extracted with EA (2 x 50 mL). The aqueous layer was acidified by adding HCl 2 N and extracted with EA (3 x 50 mL). The combined organics were washed with water (50 mL) and brine (50 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 100% of EA in hexane, then from 0% to 20% of MeOH in DCM) to afford title compound **196** as a white solid (320 mg, 37% yield), which was not characterized and used directly for the synthesis of relevant examples.

2-Amino-6-(2-amino-2-oxoethyl)-*N*-cyclopropyl-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (198)

Scheme 43

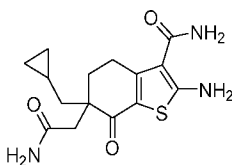


Compound **197** (See table 6 for characterization) (synthesized similarly to compound **47** (example 28, scheme 4) starting from compound **196** (scheme 42) instead of compound **41**) (70.0 mg, 217 μmol) was dissolved in DMF (1 mL). HATU (248 mg, 651 μmol), cyclopropylamine (150 μL , 2.17 mmol) and *N,N*-diisopropylethylamine (113 μL , 651 μmol) were added and the resulting mixture was stirred at RT for 1 hour. The crude mixture was directly purified by reverse-phase column chromatography (eluent gradient from 5% to 100% of CH_3CN in H_2O with 0.1% (v/v) formic acid) to afford title compound **198** (19.2 mg, 24% yield) as a pale-yellow solid.

^1H NMR: 400 MHz, $\text{DMSO}-d_6$, δ (ppm): 7.68 (s, 2H), 7.29 (s, 1H), 7.15 (s, 1H), 6.67 (s, 1H), 2.96-2.85 (m, 1H), 2.75-2.70 (m, 2H), 2.56 (d, $J = 14.81$ Hz, 1H), 2.36-2.28 (m, 1H), 2.24 (d, $J = 14.80$ Hz, 1H), 2.06-2.00 (m, 1H), 1.65 (dd, $J = 14.02, 6.34$ Hz, 1H), 1.30 (dd, $J = 14.00, 7.00$ Hz, 1H), 0.68-0.61 (m, 3H), 0.53-0.49 (m, 2H), 0.38-0.36 (m, 2H), 0.08-0.02 (m, 1H), $-0.06 - -0.13$ (m, 1H). LC-MS: $r_t = 1.00$ min. MS: 361.1 (calcd), 362.2 ($\text{M}+\text{H}^+$, found).

Example 109

2-Amino-6-(2-amino-2-oxoethyl)-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (199)



199: Example 109

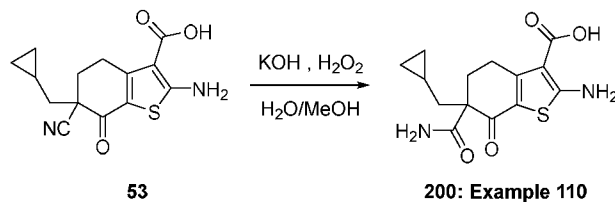
Compound **199** (example 109) was synthesized similarly to compound **109** (example 59, scheme 19) starting from compound **197** instead of compound **108**.

^1H NMR: 400 MHz, $\text{DMSO}-d_6$, δ (ppm): 7.92 (s, 2H), 7.13 (s, 1H), 6.88 (bs, 1H), 6.65 (s, 1H), 3.00-2.90 (m, 1H), 2.88-2.81 (m, 1H), 2.53 (d, $J = 14.81$ Hz, 1H), 2.35-2.27 (m, 1H), 2.24 (d, $J = 14.81$ Hz, 1H), 2.06-2.00 (m, 1H), 1.62-1.56 (m, 1H), 1.33-1.28 (m, 1H), 0.62-0.55 (m, 1H), 0.38-0.30 (m, 2H), 0.07-0.02 (m, 1H), $-0.08 - -0.14$ (m, 1H). LC-MS: $r_t = 0.83$ min. MS: 321.1 (calcd), 322.2 ($\text{M}+\text{H}^+$, found).

Example 110

2-Amino-6-carbamoyl-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (200)

Scheme 44



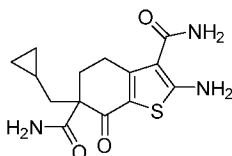
Scheme 7

To a mixture of **53** (scheme 7) (100 mg, 344 μ mol) in methanol (4.39 mL) and water (1.41 mL) were added 30% aqueous hydrogen peroxide (352 μ L, 3.44 mmol) and potassium hydroxide (199 mg, 3.55 mmol) and the reaction mixture was stirred at RT for 24 hours. The mixture was diluted with water (5 mL) and concentrated to remove the organic solvent. The aqueous residue was washed with EA (10 mL), then it was acidified to pH 1 and extracted with EA (3 x 10 mL). These organics were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 30% of MeOH in DCM), then it was purified again by reverse-phase column chromatography (eluent gradient from 5% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **200** (7 mg, 6% yield) as a yellow solid.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 2.50 (bs, 1H), 8.29 (bs, 2H), 7.05 (s, 1H), 6.77 (s, 1H), 3.08-3.01 (m, 1H), 2.92-2.83 (m, 1H), 2.47-2.44 (m, 1H), 2.14-2.06 (m, 1H), 1.76 (dd, *J* = 13.99, 6.23 Hz, 1H), 1.65 (dd, *J* = 13.99, 6.23 Hz, 1H), 0.63-0.56 (m, 1H), 0.39-0.35 (m, 2H), 0.05 - -0.01 (m, 2H). LC-MS: rt = 0.99 min. MS: 308.1 (calcd), 309.0 (M+H⁺, found).

Example 111

2-Amino-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3,6-dicarboxamide (201)



201: Example 111

Compound **201** (example 111) was synthesized similarly to compound **109** (example 59, scheme 19) starting from compound **200** instead of compound **108**.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.12 (s, 2H), 7.06 (s, 1H), 6.94 (bs, 1H), 6.77 (s, 1H), 3.07-2.97 (m, 1H), 2.90-2.83 (m, 1H), 2.49-2.44 (m, 1H), 2.16-2.08 (m, 1H), 1.79-1.66 (m,

2H), 0.64-0.57 (m, 1H), 0.38-0.34 (m, 2H), 0.08-0.03 (m, 2H). LC-MS: rt = 0.89 min. MS: 307.1 (calcd), 308.0 (M+H⁺, found).

Example 112

2-Amino-N³-cyclopropyl-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3,6-dicarboxamide (202)

Scheme 45

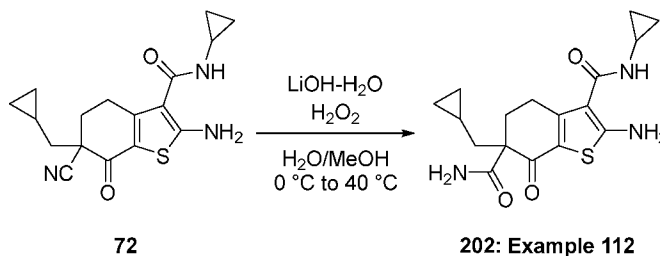


Table 3

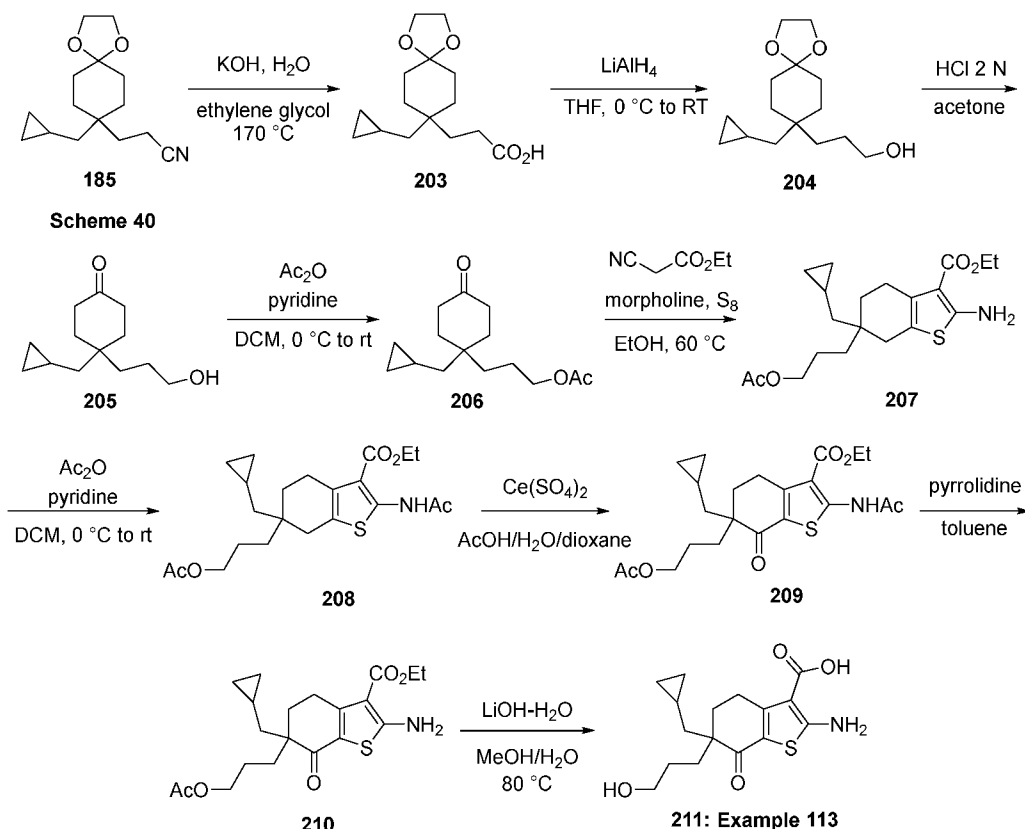
To a solution of compound **72** (Table 3) (77.0 mg, 234 μ mol) in a mixture of MeOH (10.1 mL) and water (10.1 mL) was added lithium hydroxide monohydrate (19.6 mg, 467 μ mol) at RT. The reaction mixture was cooled to 0 °C and 30% H₂O₂ (145 μ L) was added. The mixture was stirred at 0 °C for 1 hour, then more 30% H₂O₂ (145 μ L) was added, and the reaction mixture was stirred at RT for an additional 2.5 hours, then at 40 °C for 45 min. Afterwards, the mixture was cooled to 0 °C and diluted with brine (10 mL) and EA (10 mL). The layers were separated and the aqueous phase was extracted with EA (3 x 10 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 100% of EA in hexane) to afford title compound **202** (13.2 mg, 16% yield) as a white solid.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 7.84 (s, 2H), 7.40 (d, J = 3.86 Hz, 1H), 7.05 (s, 1H), 6.74 (s, 1H), 2.98-2.90 (m, 1H), 2.75-2.68 (m, 2H), 2.46-2.41 (m, 1H), 2.12-2.04 (m, 1H), 1.78-1.73 (m, 1H), 1.68-1.63 (m, 1H), 0.66-0.55 (m, 3H), 0.53-0.48 (m, 2H), 0.37-0.34 (m, 2H), 0.05-0.02 (m, 2H). LC-MS: rt = 1.05 min. MS: 347.1 (calcd), 348.1 (M+H⁺, found).

Example 113

2-Amino-6-(cyclopropylmethyl)-6-(3-hydroxypropyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (211)

Scheme 46



Step 1. 3-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)propanoic acid (203)

To a solution of **185** (scheme 40) (2.14 g, 8.58 mmol) in ethylene glycol (45.5 mL) were added potassium hydroxide (3.85 g, 68.7 mmol) and water (31.0 uL, 1.72 mmol). The resulting mixture was stirred at 170 °C for 24 hours. The mixture was allowed to cool to RT, diluted with water (50 mL) and washed with DCM (2 x 50 mL). The aqueous phase was acidified to pH 2 by adding 2 N HCl and extracted with DCM (3 x 10 mL). These organics were dried over MgSO₄, filtered and concentrated to afford title compound **203** as a red oil, which was used directly in Step 2 without purification and characterization.

Step 2. 3-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)propan-1-ol (204)

To a solution of **203** (8.58 mmol) in anhydrous THF (54 mL) at 0 °C was added dropwise lithium aluminum hydride (9.55 mL, 2 M in THF, 19.1 mmol). The resulting mixture was stirred at 0 °C for 1 hour, allowed to reach RT and it stirred for 16 hours. A saturated aqueous solution of Rochelle's salt (30 mL) was added dropwise, then the mixture was diluted with EA (50 mL), stirred at RT for 30 min and filtered through a celite pad. The layers were separated and the aqueous phase was extracted with EA (2 x 50 mL). The combined organics were dried over MgSO₄, filtered and concentrated to afford title compound **204** as a yellow oil (2.07 g, 95% yield over two steps), which was used in Step 3 without purification and characterization.

Step 3. 4-(Cyclopropylmethyl)-4-(3-hydroxypropyl)cyclohexan-1-one (205)

To a solution of **204** (2.07 g, 8.14 mmol) in acetone (125 mL) was added 2 N aqueous HCl (22.9 mL, 45.7 mmol) and the resulting mixture was stirred at RT for 70 hours. Then, the mixture was neutralized with a saturated aqueous NaHCO₃ solution (50 mL) and concentrated to remove the organic solvent. The residue was then partitioned between EA (50 mL) and water (40 mL), the layers were separated and the organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was taken up in DCM (30 mL) and the insoluble impurity was filtered off and washed with DCM (50 mL). The filtrate and washings were combined and concentrated to afford title compound **205** as a thick pale-yellow oil (1.53 g, 89% yield), which was used in Step 4 without purification and characterization.

Step 4. 3-(1-(Cyclopropylmethyl)-4-oxocyclohexyl)propyl acetate (**206**)

To a solution of **205** (1.53 g, 7.27 mmol) in anhydrous DCM (15.9 mL) at 0 °C were added acetic anhydride (1.65 mL, 17.5 mmol) and pyridine (1.77 mL, 21.8 mmol). The reaction mixture was allowed to reach RT and stirred for 19 hours. Then, the mixture was diluted with DCM (40 mL) and washed with 1 N HCl (40 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated to give title compound **206** as a yellow oil (1.80 g, 98% yield), which was used in Step 5 without purification and characterization.

Step 5. Ethyl 6-(3-acetoxypropyl)-2-amino-6-(cyclopropylmethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**207**)

A suspension of sulfur (253 mg, 984 μmol), **206** (1.80 g, 7.13 mmol), morpholine (677 μL, 7.85 mmol) and ethyl 2-cyanoacetate (759 μL, 7.13 mmol) in EtOH (12.5 mL) was stirred at 60 °C for 16 hours. The mixture was allowed to cool to RT, then diluted with brine (20 mL) and extracted with EA (3 x 20 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 35% of EA in hexane) to afford title compound **207** as a yellow oil (2.25 g, 83% yield). LC-MS: rt = 1.90 min, MS: 379.2 (calcd), 380.2 (M+H⁺, found).

Step 6. Ethyl 2-acetamido-6-(3-acetoxypropyl)-6-(cyclopropylmethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**208**)

To a solution of **207** (2.25 g, 5.93 mmol) in anhydrous DCM (12.9 mL) at 0 °C were added acetic anhydride (1.34 mL, 14.2 mmol) and pyridine (1.44 mL, 17.8 mmol). The reaction mixture was allowed to reach RT and stirred for 16 hours. Then, the mixture was diluted with DCM (20 mL) and washed with 1 N HCl (40 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated to give title compound **208** as a yellow oil (2.50 g, >99% yield), which was used in Step 7 without purification. LC-MS: rt = 1.96 min, MS: 421.2 (calcd), 422.2 (M+H⁺, found).

Step 7. Ethyl 2-acetamido-6-(3-acetoxypropyl)-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**209**)

To a solution of **208** (2.50 g, 5.93 mmol) in dioxane (27.1 mL) were added acetic acid (27.1 mL), ceric sulfate (17.0 g, 51.2 mmol) and water (12.9 mL). The resulting mixture was stirred

at RT for 16 hours, then the solid was filtered off and washed with EA (100 mL). The filtrate and washings were combined, diluted with water (50 mL), the layers were separated, and the aqueous phase was extracted with EA (2 x 50 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated to afford title compound **209** as a solid (2.50 g, 97% yield), which was used in Step 8 without purification. LC-MS: rt = 1.76 min, MS: 435.2 (calcd), 436.3 (M+H⁺, found).

Step 8. Ethyl 6-(3-acetoxypropyl)-2-amino-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**210**)

To a solution of **209** (2.50 g, 5.74 mmol) in toluene (9.71 mL) was added pyrrolidine (7.30 mL, 88.9 mmol). The resulting mixture was stirred at RT for 1 hour, then diluted with EA (40 mL) and brine (40 mL). The layers were separated and the aqueous phase was extracted with EA (2 x 40 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated to afford title compound **210** as a dark oil (2.26 g, >99% yield), which was used in Step 9 without purification. LC-MS: rt = 1.68 min, MS: 393.2 (calcd), 394.3 (M+H⁺, found).

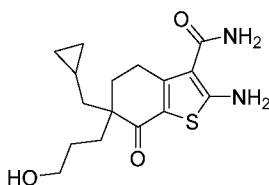
Step 9. 2-Amino-6-(cyclopropylmethyl)-6-(3-hydroxypropyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**211**)

To a solution of **210** (2.26 g, 5.74 mmol) in MeOH (100 mL) was added a solution of lithium hydroxide monohydrate (1.24 g, 29.6 mmol) in water (100 mL). The resulting mixture was stirred at 80 °C for 4 hours, then concentrated to remove most of the organic solvent. The aqueous residue was washed with EA (40 mL), then acidified to pH 4 by slowly adding 1 N aqueous HCl and extracted with EA (2 x 70 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 15% of MeOH in DCM) to afford title compound **211** as a light-brown solid (1.07 g, 58% yield).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 12.44 (s, 1H), 8.17 (s, 2H), 4.32 (t, J = 5.1 Hz, 1H), 3.34-3.29 (m, 2H, partially overlapping with the water signal), 3.01-2.83 (m, 2H), 2.14-2.04 (m, 1H), 1.98-1.88 (m, 1H), 1.65-1.52 (m, 2H), 1.52-1.41 (m, 1H), 1.38-1.27 (m, 2H), 1.22 (dd, J = 14.1, 7.4 Hz, 1H), 0.61-0.50 (m, 1H), 0.40-0.30 (m, 2H), 0.02 - -0.01 (m, 2H). LC-MS: rt = 1.11 min. MS: 323.1 (calcd), 324.1 (M+H⁺, found).

Example 114

2-Amino-6-(cyclopropylmethyl)-6-(3-hydroxypropyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (212**)**



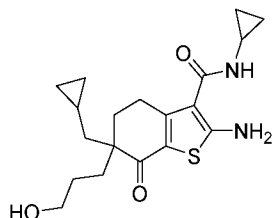
212: Example 114

Compound **212** (example 114) was synthesized similarly to compound **109** (example 59, scheme 19) starting from compound **211** (scheme 46) instead of compound **108**.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 7.96 (s, 2H), 6.90 (bs, 1H), 4.33 (t, *J* = 5.2 Hz, 1H), 3.36-3.30 (m, 2H, partially overlapping with the water signal), 2.93 (t, *J* = 6.0 Hz, 2H), 2.12-2.06 (m, 1H), 1.98-1.91 (m, 1H), 1.62-1.46 (m, 3H), 1.39-1.23 (m, 3H), 0.61-0.54 (m, 1H), 0.38-0.33 (m, 2H), 0.06-0.00 (m, 1H), -0.02 - -0.08 (m, 1H). LC-MS: *rt* = 0.97 min. MS: 322.1 (calcd), 323.2 (*M*+*H*⁺, found).

Example 115

2-Amino-*N*-cyclopropyl-6-(cyclopropylmethyl)-6-(3-hydroxypropyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**213**)



213: Example 115

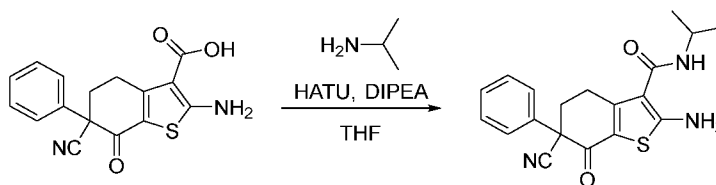
Compound **213** (example 115) was synthesized similarly to compound **82** (example 52, scheme 13) starting from compound **211** (scheme 46) instead of compound **81**.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 7.68 (bs, 2H), 7.31 (d, *J* = 3.8 Hz, 1H), 4.33 (t, *J* = 5.2 Hz, 1H), 3.35-3.27 (m, 2H, partially overlapping with the water signal), 2.83 (t, *J* = 6.0 Hz, 2H), 2.75-2.70 (m, 1H), 2.07-2.02 (m, 1H), 1.93-1.88 (m, 1H), 1.63-1.50 (m, 3H), 1.35-1.23 (m, 3H), 0.67-0.62 (m, 2H), 0.59-0.54 (m, 1H), 0.52-0.49 (m, 2H), 0.38-0.33 (m, 2H), 0.03 - -0.02 (m, 1H), -0.02 - -0.09 (m, 1H). LC-MS: *rt* = 1.15 min. MS: 362.2 (calcd), 363.2 (*M*+*H*⁺, found).

Example 116

2-Amino-6-cyano-*N*-isopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**214**)

Scheme 47



59

214: Example 116

Scheme 8

To a solution of compound **59** (example 36, scheme 8) (50.0 mg, 160 μmol) in anhydrous DMF (1.58 mL) were added isopropylamine (55.0 μL, 640 μmol), HATU (124 mg, 320 μmol) and

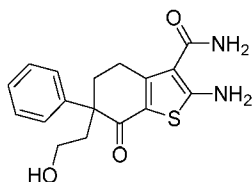
N,N-diisopropylethylamine (55.8 μ L, 320 μ mol). The resulting mixture was stirred at RT for 30 min, then it was diluted with EA (5 mL) and water (5 mL). The layers were separated, and the aqueous phase was extracted with EA (5 mL). The combined organics were washed with brine (2 x 10 mL) and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 100% of EA in hexane), then it was purified again by reverse-phase column chromatography (eluent gradient from 0% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **214** (16.2 mg, 29% yield) as an off-white solid.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.11 (bs, 1H), 7.47-7.36 (m, 6H), 4.03-3.95 (m, 1H), 3.10-3.02 (m, 1H), 2.81-2.70 (m, 2H), 2.67-2.59 (m, 1H), 1.11 (dd, *J* = 6.58, 3.79 Hz, 6H).

LC-MS: rt = 1.33 min. MS: 353.1 (calcd), 354.1 (M+H⁺, found).

Example 117

2-Amino-6-(2-hydroxyethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (215)



215: Example 117

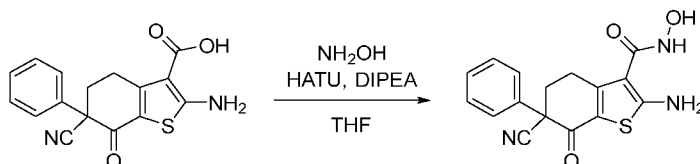
Compound **215** (example 117) was synthesized similarly to compound **61** (example 38, scheme 10) starting from compound **89** (scheme 15) instead of compound **59**.

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.30-7.25 (m, 4H), 7.21-7.17 (m, 1H), 3.51-3.38 (m, 2H), 2.95-2.87 (m, 1H), 2.63-2.60 (m, 2H), 2.38-2.29 (m, 1H), 2.15-2.06 (m, 2H). LC-MS: rt = 0.90 min, MS: 330.1 (calcd), 331.2 (M+H⁺, found).

Example 118

2-Amino-6-cyano-*N*-hydroxy-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (216)

Scheme 48



59

216: Example 118

Scheme 8

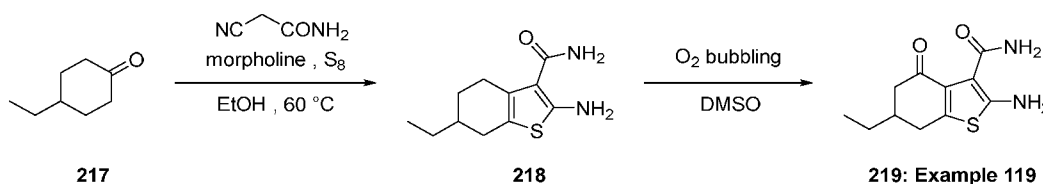
N,N-Diisopropylethylamine (26.8 uL, 154 umol) was added to a solution of 2-amino-6-cyano-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (**59**, scheme 8) (40.0 mg, 128 umol) and HATU (49.7 mg, 128 umol) in anhydrous DMF (4.20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. In a separate reaction vessel, to a solution of hydroxylamine (5.23 mg, 154 umol) in anhydrous DMF (1.00 mL) was added *N,N*-diisopropylethylamine (68.3 uL, 384 umol) and the resulting mixture was stirred for 5 minutes or until complete dissolution of hydroxylamine. The resulting solution was then added to the reaction mixture, which was stirred at RT for 2.5 hours, then diluted with brine (5 mL) and EA (5 mL). The layers were separated, and the aqueous phase was extracted with EA (2 x 10 mL). The combined organics were washed with brine (10 mL), HCl 1 N (2 x 10 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid), then it was purified a second time by reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH₃CN in 10 mM ammonium bicarbonate), then it was purified a third time by reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **216** as an off-white solid (8.1 mg, 19% yield).

¹H NMR: 400 MHz, DMSO-*d*₆, δ (ppm): 9.21 (bs, 1H), 8.29-8.05 (m, 2H), 7.48-7.31 (m, 5H), 3.05-2.94 (m, 1H), 2.80-2.71 (m, 2H), 2.68-2.56 (m, 1H). LC-MS: rt = 0.78 min. MS: 327.1 (calcd), 328.1 (M+H⁺, found).

Example 119

2-Amino-6-ethyl-4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**219**)

Scheme 49



Step 1. 2-Amino-6-ethyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**218**)

To a solution of 4-ethylcyclohexan-1-one (**217**) (0.776 mL, 5.50 mmol) and cyanoacetamide (420 mg, 5.00 mmol) in EtOH (5 mL) were added morpholine (0.474 mL, 5.50 mmol) and sulfur (177 mg, 0.69 mmol). The reaction mixture was stirred at 60 °C for 19 hours, then allowed to cool to RT and concentrated to dryness. The residue was purified by flash column chromatography (eluent gradient from 0 to 10% of MeOH in DCM) to afford title compound **218** as a light-orange solid (658 mg, 59% yield). LC-MS: rt = 1.43 min, MS: 224.1 (calcd), 225.1 (M+H⁺, found).

Step 2. 2-Amino-6-ethyl-4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**219**)

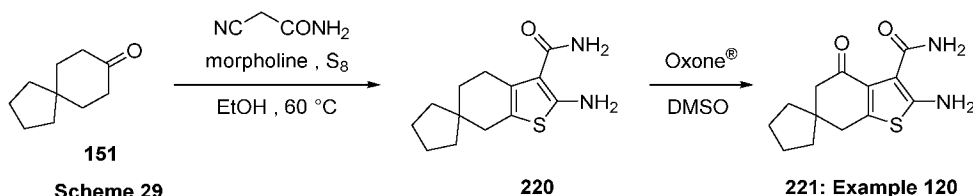
Compound **218** (50.0 mg, 0.223 mmol) was dissolved in DMSO (5 mL) and O₂ was bubbled through the mixture for 4 days. The mixture was then directly purified by flash column chromatography (eluent gradient from 0% to 100% of EA in hexane with a 90:10 DCM/MeOH wash). The fractions containing the desired compound were combined and diluted with EA and water. The aqueous layer was extracted with EA. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. A subsequent recrystallization from EA yielded title compound **219** as a yellow solid (16.0 mg, 30% yield).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 9.47 (s, 1H), 7.88 (s, 2H), 6.83 (s, 1H), 2.95 (dd, *J* = 16.85, 4.44 Hz, 1H), 2.56-2.50 (m, 2H), 2.35 (dd, *J* = 16.26, 11.90 Hz, 1H), 2.12-1.98 (m, 1H), 1.38 (p, *J* = 7.23 Hz, 2H), 0.88 (t, *J* = 7.41 Hz, 3H). LC-MS: rt = 1.31 min, MS: 238.1 (calcd), 239.1 (M+H⁺, found).

Example 120

2-Amino-4-oxo-4,7-dihydro-5H-spiro[benzo[*b*]thiophene-6,1'-cyclopentane]-3-carboxamide (**221**)

Scheme 50



Step 1. 2-Amino-4,7-dihydro-5H-spiro[benzo[*b*]thiophene-6,1'-cyclopentane]-3-carboxamide (**220**)

To a solution of spiro[4.5]decan-8-one (**151**, scheme 29) (99.6 mg, 0.654 mmol) and cyanoacetamide (50.0 mg, 0.595 mmol) in EtOH (0.595 mL) were added morpholine (0.056 mL, 0.654 mmol) and sulfur (21.1 mg, 0.082 mmol). The reaction mixture was stirred at 60 °C for 19 hours, then allowed to cool to RT and concentrated to dryness. The residue was first purified by flash column chromatography (eluent gradient from 0 to 10% of MeOH in DCM), then by reverse-phase flash column chromatography (eluent gradient from 10 to 100% CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **220** as a white solid (77.0 mg, 50% yield). LC-MS: rt = 1.73 min, MS: 250.1 (calcd), 251.1 (M+H⁺, found).

Step 2. 2-Amino-4-oxo-4,7-dihydro-5H-spiro[benzo[*b*]thiophene-6,1'-cyclopentane]-3-carboxamide (**221**)

A mixture of **220** (10.0 mg, 0.040 mmol) and Oxone® (6.72 mg, 0.040 mmol) in DMSO (0.896 mL) was stirred at RT for 72 hours. The mixture was then diluted with EA and water and the aqueous layer was extracted with EA. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was first purified by flash column

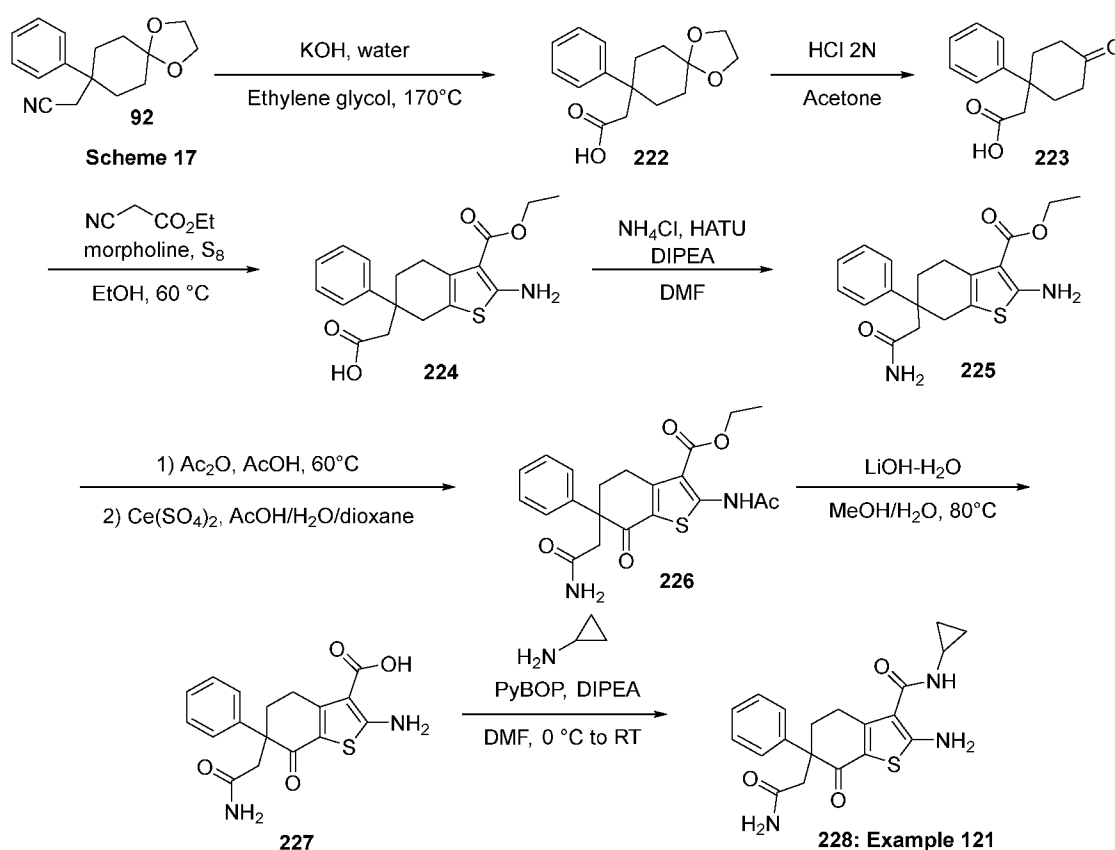
chromatography (eluent gradient from 0% to 10% of MeOH in DCM), then by Semi-Prep HPLC-MS (eluent gradient from 30% to 100% of ACN in 10 mM ammonium formate) to afford title compound **221** as a white solid (1.10 mg, 10% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 2.86 (s, 2H), 2.59 (s, 2H), 1.74-1.67 (m, 4H), 1.63-1.47 (m, 4H). LC-MS: rt = 1.55 min, MS: 264.1 (calcd), 265.1 (M+H⁺, found).

Example 121

2-Amino-6-(2-amino-2-oxoethyl)-N-cyclopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**228**)

Scheme 51



Step 1. 2-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)acetic acid (**222**)

Powdered potassium hydroxide (48.8 g, 799.0 mmol) was added to a solution of 2-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)acetonitrile (**92**, scheme 17) (25.7 g, 99.9 mmol) (*Bioorg Med. Chem Lett.* 21, p. 405, 2011) in ethylene glycol (524 mL) and water (12.9 mL). The resulting mixture was stirred at 170°C for 16 hours. The mixture was then allowed to cool to RT, diluted with water (250 mL) and washed with DCM (250 mL). This organic layer was discarded. The aqueous layer was acidified with 2 N HCl and extracted with DCM (2 x 250 mL). These organic

phases were combined and dried over Na₂SO₄, then filtered and concentrated to afford title compound **222** as a light-orange solid (24.8 g, 90% yield) which was not characterized and used directly for the next step.

Step 2. 2-(4-Oxo-1-phenylcyclohexyl)acetic acid (**223**)

To a solution of **222** (2.83 g, 10.2 mmol) in acetone (127 mL) was added 2 N HCl (51.2 mL, 102 mmol) and the reaction mixture was stirred at RT for 16 hours. Then, the mixture was neutralized by slowly adding saturated aqueous NaHCO₃ solution and concentrated to remove the organic solvent. The residue was extracted with EA and the organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness to afford title compound **223** as a yellow oil (2.38 g, 96% yield), which was not characterized and used directly for the next step.

Step 3. 2-(2-Amino-3-(ethoxycarbonyl)-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophen-6-yl)acetic acid (**224**)

To a solution of **223** (2.38 g, 10.2 mmol) and ethyl 2-cyanoacetate (1.20 mL, 11.3 mmol) in EtOH (10.2 mL) were added morpholine (1.97 mL, 22.5 mmol) and sulfur (363 mg, 1.41 mmol). The reaction mixture was stirred at 60 °C for 16 hours, then allowed to cool to RT and concentrated to dryness. The residue was partitioned between water and EA. The layers were separated and the organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was triturated in MeOH to afford title compound **224** as a beige solid (2.44 g, 66% yield). LC-MS: rt = 1.42 min, MS: 359.1 (calcd), 360.0 (M+H⁺, found).

Step 4. Ethyl 2-amino-6-(2-amino-2-oxoethyl)-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**225**)

Compound **224** (400 mg, 1.11 mmol) was dissolved in anhydrous DMF (11.0 mL). Then, ammonium chloride (1.19 g, 22.3 mmol), HATU (648 mg, 1.67 mmol) and DIPEA (0.388 mL, 2.23 mmol) were added and the reaction mixture was stirred at RT for 16 hours. The mixture was partitioned between aqueous NH₄Cl, brine and EA. The organic phase was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by reverse-phase flash column chromatography (eluent gradient from 5 to 100% CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **225** as a white powder (320 mg, 80% yield). LC-MS: rt = 1.21 min, MS: 358.1 (calcd), 359.2 (M+H⁺, found).

Step 5. Ethyl 2-acetamido-6-(2-amino-2-oxoethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**226**)

Acetic anhydride (0.101 mL, 1.07 mmol) was added to a suspension of **225** (320 mg, 893 μmol) in acetic acid (5.12 mL). The resulting mixture was stirred at 60°C for 1.5 hours, then at RT for 16 hours. After completion of the acylation, dioxane (2.59 mL), water (2.59 mL) and ceric sulfate (2.57 g, 7.72 mmol) were added to the mixture. The resulting suspension was stirred for 16 hours at RT. Afterwards, the mixture was diluted with water and extracted with EA. The organic layer was washed successively with NaOH 1 N, water and brine, then dried over Na₂SO₄, filtered

and concentrated to afford title compound **226** as a an off-white solid (189 mg, 51% yield). LC-MS: rt = 1.25 min, MS: 414.1 (calcd), 415.2 (M+H⁺, found).

Step 6. 2-Amino-6-(2-amino-2-oxoethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**227**)

To a solution of **226** (189 mg, 0.456 mmol) in MeOH (55 mL) was added a solution of lithium hydroxide monohydrate (95.7 mg, 2.28 mmol) in water (55 mL). The reaction mixture was stirred at 80 °C for 2 hours, then allowed to cool to RT. The mixture was concentrated to remove most of the organic solvent. The aqueous residue was acidified by slowly adding HCl 1 N and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated to afford title compound **227** as an orange solid (143 mg, 91% yield). LC-MS: rt = 0.92 min, MS: 344.1 (calcd), 345.1 (M+H⁺, found).

Step 7. 2-Amino-6-(2-amino-2-oxoethyl)-N-cyclopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**228**)

To a solution of **227** (143 mg, 0.415 mmol) in anhydrous DMF (4.59 mL) at 0 °C were added PyBOP (238.0 mg, 0.457 mmol), *N,N*-diisopropylethylamine (0.145 mL, 0.83 mmol) and cyclopropylamine (0.144 mL, 2.08 mmol). Then, the reaction mixture was allowed to warm up to RT and stirred for 16 hours. Subsequently, the mixture was diluted with a saturated aqueous solution of NH₄Cl and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was first purified by flash column chromatography (eluent gradient from 20% to 100% of EA in hexane), then by Semi-Prep HPLC-MS (eluent gradient from 30% to 100% of MeOH in 10 mM ammonium formate) to afford title compound **228** as a white solid (31.5 mg, 20% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.32-7.28 (m, 4H), 7.23-7.20 (m, 1H), 2.98 (d, *J* = 14.80 Hz, 1H), 2.78-2.74 (m, 1H), 2.73-2.70 (m, 1H), 2.69-2.66 (m, 1H), 2.65-2.59 (m, 2H), 2.55-2.47 (m, 1H), 0.71-0.67 (m, 2H), 0.51-0.48 (m, 2H). LC-MS: rt = 0.99 min, MS: 383.1 (calcd), 384.3 (M+H⁺, found).

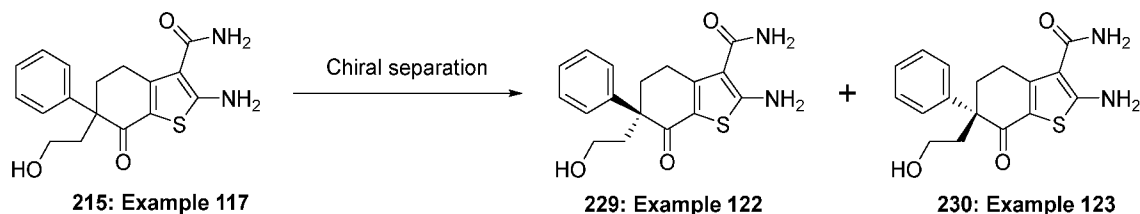
Example 122

(S)-2-Amino-6-(2-hydroxyethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (229**) and**

Example 123

(R)-2-Amino-6-(2-hydroxyethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (230**)**

Scheme 52



Racemic compound **215** (example 117) (917 mg) was submitted to SFC chiral separation (isocratic: 50% of MeOH 1:1 in CO₂) to yield enantioenriched compound **229** as a white solid (177 mg, 19% separation yield) and enantioenriched compound **230** as a white solid (176 mg, 19% separation yield). Absolute configurations of compounds **229** and **230** were assigned based on analogy with the assignment of the absolute configuration of a crystallized compound within the same or similar series.

229: ¹H NMR: same as racemic mixture (**215**). LC-MS: rt = 0.94 min, MS: 330.1 (calcd), 331.0 (M+H⁺, found). Analytical SFC (from 5% to 60% of MeOH 1:1 in water): rt = 3.55 min, ee. = 98.3%.

230: ¹H NMR: same as racemic mixture (**215**). LC-MS: rt = 0.94 min, MS: 330.1 (calcd), 331.0 (M+H⁺, found). Analytical SFC (from 5% to 60% of MeOH 1:1 in water): rt = 3.83 min, ee. = 98.6%.

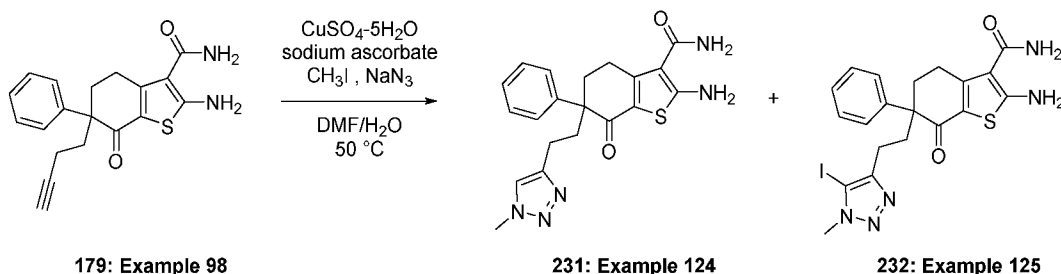
Example 124

2-Amino-6-(2-(1-methyl-1H-1,2,3-triazol-4-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (231) and

Example 125

2-Amino-6-(2-(5-iodo-1-methyl-1H-1,2,3-triazol-4-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (232)

Scheme 53



Scheme 36

Copper(II) sulfate pentahydrate (60 mg, 0.24 mmol) and sodium ascorbate (47 mg, 0.24 mmol) were added to a solution of 2-amino-6-(but-3-yn-1-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**179**, scheme 36, example 98) (40 mg, 0.12 mmol) in DMF/H₂O 1:1 (2.6 mL). The flask was evacuated and backfilled with nitrogen, then iodomethane

(0.06 mL, 0.95 mmol) and sodium azide (61 mg, 0.95 mmol) were added and the reaction mixture was stirred for 5 days at 50 °C. The mixture was then quenched with a saturated aqueous solution of NaHCO₃ and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 20% of MeOH in DCM) to afford title compound **231** as an off-white solid (10 mg, 21% yield) and title compound **232** as a pale-yellow solid (12 mg, 19% yield).

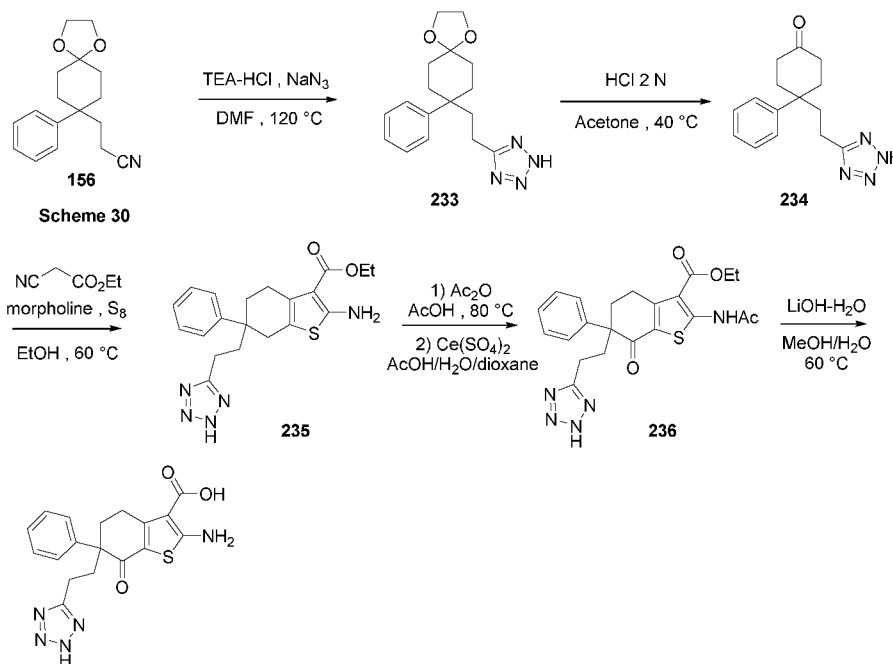
231: ¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.60 (s, 1H), 7.36-7.29 (m, 4H), 7.25-7.21 (m, 1H), 4.01 (s, 3H), 3.01-2.94 (m, 1H), 2.77-2.67 (m, 3H), 2.61-2.53 (m, 1H), 2.46-2.39 (m, 1H), 2.27-2.14 (m, 2H). LC-MS: rt = 1.00 min, MS: 395.1 (calcd), 396.3 (M+H⁺, found).

232: ¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.38-7.31 (m, 4H), 7.25-7.20 (m, 1H), 4.01 (s, 3H), 3.02-2.95 (m, 1H), 2.78-2.61 (m, 3H), 2.58-2.50 (m, 1H), 2.46-2.38 (m, 1H), 2.21-2.16 (m, 2H). LC-MS: rt = 1.17 min, MS: 521.0 (calcd), 522.1 (M+H⁺, found).

Example 126

6-(2-(2H-Tetrazol-5-yl)ethyl)-2-amino-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**237**)

Scheme 54



237: Example 126

Step 1. 5-(2-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)-2H-tetrazole (**233**)

Triethylamine hydrochloride (1.27 g, 9.21 mmol) and sodium azide (719 mg, 11.1 mmol) were added to a solution of 3-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)propanenitrile (**156**, scheme 30) (500 mg, 1.84 mmol) in DMF (15 mL). The reaction was stirred at 120 °C for 18 hours, then it was diluted with water and neutralized by slow addition of 1 N HCl. The product was

extracted with EA and the organic layer was dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by flash column chromatography (eluent gradient from 0% to 20% of MeOH in DCM). The collected fractions were concentrated, suspended in heptane and concentrated again to afford title compound **233** as a pale-yellow solid, which was used directly for the following step.

Step 2. 4-(2-(2H-Tetrazol-5-yl)ethyl)-4-phenylcyclohexan-1-one (**234**)

To a solution of **233** in acetone (15 mL) was added HCl 2 N (6.15 mL, 12.3 mmol) and the reaction was stirred at 40 °C for 16 hours. Then, the mixture was concentrated to remove the organic solvent. The residue was extracted with EA and the organic layer was dried over Na₂SO₄, filtered and concentrated to afford title compound **234** as a yellow oil (350 mg, 70% yield over two steps). LC-MS: rt = 0.98 min, MS: 270.3 (calcd), 271.2 (M+H⁺, found).

Step 3. Ethyl 6-(2-(2H-tetrazol-5-yl)ethyl)-2-amino-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**235**)

To a solution of **234** (350 mg, 1.29 mmol) and ethyl 2-cyanoacetate (0.155 mL, 1.42 mmol) in EtOH (1.3 mL) were added morpholine (0.24 mL, 2.10 mmol) and sulfur (46 mg, 0.179 mmol). The reaction mixture was stirred at 60 °C for 16 hours, then allowed to cool to RT and concentrated to dryness. The residue was partitioned between EA and water. The layers were separated and the aqueous phase was acidified by adding 1 N HCl and extracted again with EA. The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 20% to 100% of EA in hexane) to afford title compound **235** as a pale-yellow solid (119 mg, 23% yield). LC-MS: rt = 1.40 min, MS: 397.2 (calcd), 398.3 (M+H⁺, found).

Step 4. Ethyl 6-(2-(2H-tetrazol-5-yl)ethyl)-2-acetamido-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**236**)

To a solution of **235** (119 mg, 0.30 mmol) in acetic acid (1.7 mL) was added acetic anhydride (0.034 mL, 0.36 mmol). The reaction was stirred at 80 °C for 2 hours. Then, the mixture was allowed to cool to RT and diluted with acetic acid (0.3 mL), water (2.0 mL) and dioxane (2.0 mL). Ceric sulfate (798 mg, 2.40 mL) was added to the mixture and the flask was sonicated to make the suspension homogeneous. Then, the reaction was vigorously stirred at RT for 24 hours. Afterwards, the mixture was diluted with water and extracted with EA. The organic layer was washed with brine, then dried over Na₂SO₄, filtered and concentrated to afford title compound **236** as a yellow paste (91 mg, 67% yield). LC-MS: rt = 1.37 min, MS: 453.2 (calcd), 454.3 (M+H⁺, found).

Step 5. 6-(2-(2H-Tetrazol-5-yl)ethyl)-2-amino-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**237**)

To a solution of **236** (91 mg, 0.20 mmol) in MeOH (25 mL) was added a solution of lithium hydroxide monohydrate (42 mg, 1.0 mmol) in water (25 mL). The reaction was stirred at 60 °C for

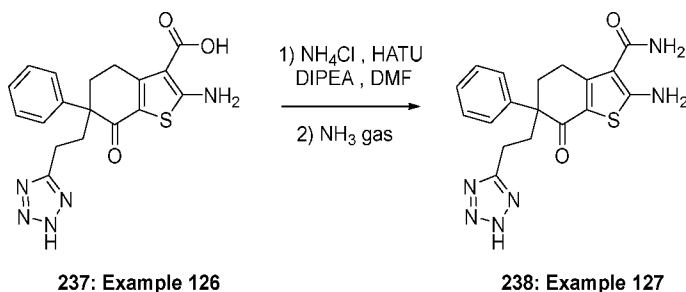
16 hours, then more lithium hydroxide monohydrate (42 mg, 1.0 mmol) was added and the reaction was stirred at 60 °C for additional 8 hours. The mixture was allowed to cool to RT and concentrated to remove most of the organic solvent. Then, it was acidified by slowly adding 1N HCl and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated to afford title compound **237** as a pale-yellow solid (77 mg, >99% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.38-7.30 (m, 4H), 7.26-7.22 (m, 1H), 3.28-3.21 (m, 1H), 3.12-3.04 (m, 1H), 2.84-2.76 (m, 1H), 2.66-2.61 (m, 1H), 2.54-2.45 (m, 1H), 2.40-2.34 (m, 1H), 2.33-2.29 (m, 2H). LC-MS: rt = 1.03 min, MS: 383.1 (calcd), 384.2 (M+H⁺, found).

Example 127

6-(2-(2H-Tetrazol-5-yl)ethyl)-2-amino-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**238**)

Scheme 55



Scheme 54

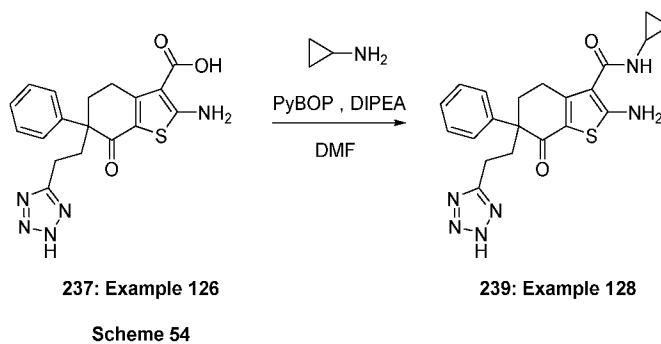
To a mixture of **237** (scheme 54, example 126) (40 mg, 0.10 mmol) and ammonium chloride (56 mg, 1.04 mmol) in anhydrous DMF (1.3 mL) were added HATU (79 mg, 0.21 mmol) and *N,N*-diisopropylethylamine (0.073 mL, 0.417 mmol). The reaction was stirred for 10 minutes, before bubbling gaseous NH₃ through the mixture for additional 30 minutes. Afterwards, the reaction was quenched with a saturated aqueous solution of NH₄Cl and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by reverse phase flash column chromatography (eluent gradient from 0% to 100% of CH₃CN in 0.1% formic acid (v/v) in water) to afford title compound **238** as a pale-yellow solid (18 mg, 45% yield).

¹H NMR: 400 MHz, DMSO-*d*₆, δ (ppm): 8.11 (s, 2H), 7.36-7.31 (m, 4H), 7.27-7.23 (m, 1H), 6.89 (bs, 2H), 2.91-2.86 (m, 1H), 2.84-2.78 (m, 1H), 2.74-2.61 (m, 3H), 2.31-2.22 (m, 1H), 2.21-2.17 (m, 2H). LC-MS: rt = 0.94 min, MS: 382.1 (calcd), 383.2 (M+H⁺, found).

Example 128

6-(2-(2H-Tetrazol-5-yl)ethyl)-2-amino-*N*-cyclopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**239**)

Scheme 56



To a solution of **237** (scheme 4, example 126) (30 mg, 0.078 mmol) in anhydrous DMF (1.0 mL) were added PyBOP (82 mg, 0.156 mmol), *N,N*-diisopropylethylamine (0.041 mL, 0.235 mmol) and cyclopropylamine (0.054 mL, 0.782 mmol) and the reaction mixture was stirred at RT for 3 hours. Then, the reaction was quenched with a saturated aqueous solution of NH_4Cl , the mixture was acidified with 1 N HCl and extracted with EA. The organic layer was dried over Na_2SO_4 , filtered and concentrated. The residue was first purified by reverse-phase flash column chromatography (eluent gradient from 0% to 100% of CH_3CN in 0.1% formic acid (v/v) in water) and then Semi-Prep HPLC-MS (eluent gradient from 5% to 100% of CH_3CN in 10 mM ammonium bicarbonate) to afford title compound **239** as a white solid (8 mg, 24% yield).

^1H NMR: 400 MHz, CD_3OD , δ (ppm): 7.36-7.30 (m, 4H), 7.26-7.21 (m, 1H), 3.08-3.00 (m, 1H), 2.84-2.73 (m, 2H), 2.70-2.60 (m, 3H), 2.41-2.36 (m, 1H), 2.33-2.28 (m, 2H), 0.76-0.67 (m, 2H), 0.56-0.48 (m, 2H). LC-MS: rt = 1.11 min, MS: 422.2 (calcd), 423.4 ($\text{M}+\text{H}^+$, found).

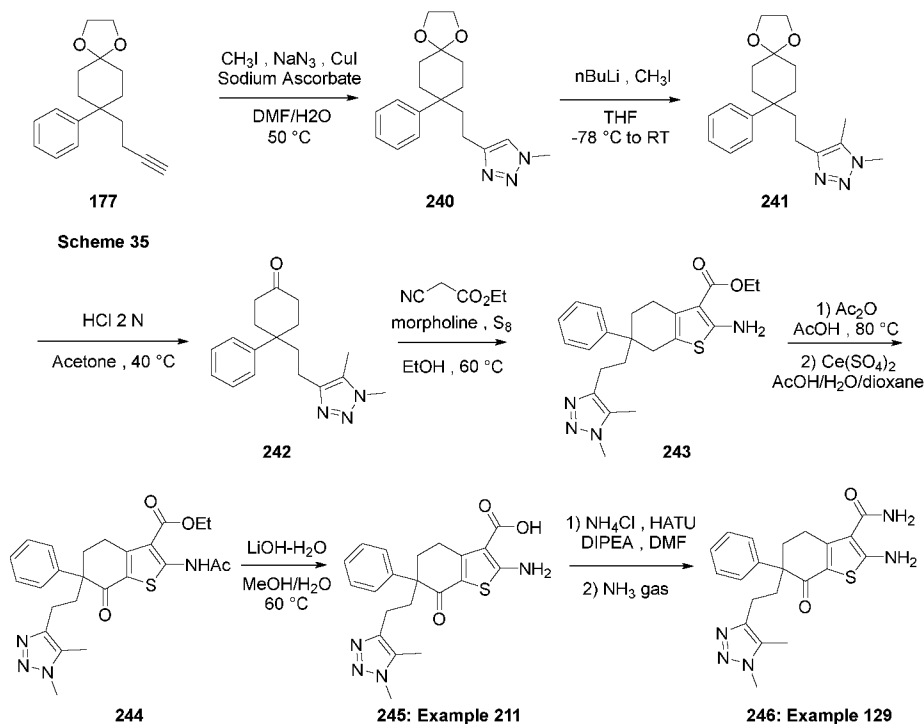
Example 211

2-Amino-6-(2-(1,5-dimethyl-1H-1,2,3-triazol-4-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (245) and

Example 129

2-Amino-6-(2-(1,5-dimethyl-1H-1,2,3-triazol-4-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (246)

Scheme 57



Step 1. 1-Methyl-4-(2-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)-1H-1,2,3-triazole (240)

Sodium ascorbate (15 mg, 0.074 mmol) and copper(I) iodide (141 mg, 0.74 mmol) were added to a solution of 8-(but-3-yn-1-yl)-8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl (**177**, scheme 35) (100 mg, 0.37 mmol) in a DMF/H₂O 1:1 mixture (8 mL). The flask was evacuated and backfilled with nitrogen. Then, iodomethane (0.186 mL, 2.96 mmol) and sodium azide (192 mg, 2.96 mmol) were added and the reaction mixture was stirred at 50 °C for 30 minutes. The mixture was then diluted with a saturated aqueous solution of NH₄Cl and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was suspended in heptane and concentrated again to afford title compound **240** as a white solid (113 mg, 93% yield). LC-MS: rt = 1.30 min, MS: 327.2 (calcd), 328.2 (M+H⁺, found).

Step 2. 1,5-Dimethyl-4-(2-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)-1H-1,2,3-triazole (241)

n-Butyl lithium (0.21 mL, 2.5 M in hexane, 0.52 mmol) was added to a solution of **240** (113 mg, 0.35 mmol) in anhydrous THF (2.6 mL) at -78 °C and the reaction mixture was stirred at the same temperature for 1 hour. Then, iodomethane (0.043 mL, 0.69 mmol) was added and the reaction mixture was allowed to slowly reach RT and stirred for 24 hours. The reaction was quenched with a saturated aqueous solution of NH₄Cl and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated to afford title compound **241** as a yellow oil (116 mg, 98% yield). LC-MS: rt = 1.26 min, MS: 341.2 (calcd), 342.2 (M+H⁺, found).

Step 3. 4-(2-(1,5-Dimethyl-1H-1,2,3-triazol-4-yl)ethyl)-4-phenylcyclohexan-1-one (242)

To a solution of **241** (116 mg, 0.34 mmol) in acetone (4 mL) was added 2 N HCl (1.70 mL, 3.40 mmol) and the reaction was stirred at 40 °C for 16 hours. Then, the mixture was neutralized with a saturated aqueous solution of NaHCO₃ and concentrated to remove the organic solvent. The residue was extracted with EA and the organic layer was dried over Na₂SO₄, filtered and concentrated to afford title compound **242** as an off-white solid (91 mg, 90% yield). LC-MS: rt = 1.18 min, MS: 297.2 (calcd), 298.2 (M+H⁺, found).

Step 4. Ethyl 2-amino-6-(2-(1,5-dimethyl-1H-1,2,3-triazol-4-yl)ethyl)-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**243**)

To a solution of **242** (91 mg, 0.306 mmol) and ethyl 2-cyanoacetate (0.036 mL, 0.337 mmol) in EtOH (0.3 mL) were added morpholine (0.029 mL, 0.337 mmol) and sulfur (11 mg, 0.042 mmol). The reaction was heated at 60 °C for 16 hours, then allowed to cool to RT and concentrated to dryness. The residue was partitioned between EA and water. The layers were separated and the organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 40% to 100% of EA in hexane) to afford title compound **243** as a pale-orange solid (89 mg, 69% yield). LC-MS: rt = 1.51 min, MS: 424.2 (calcd), 425.3 (M+H⁺, found).

Step 5. Ethyl 2-acetamido-6-(2-(1,5-dimethyl-1H-1,2,3-triazol-4-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**244**)

To a solution of **243** (89 mg, 0.21 mmol) in acetic acid (1.2 mL) was added acetic anhydride (0.024 mL, 0.25 mmol). The reaction was stirred at 80 °C for 3 hours. Then, the mixture was allowed to cool to RT and diluted with acetic acid (0.2 mL), water (1.4 mL) and dioxane (1.4 mL). Ceric sulfate (558 mg, 1.68 mL) was added to the mixture and the flask was sonicated to make the suspension homogeneous. Then, the reaction was vigorously stirred at RT for 24 hours. Afterwards, the mixture was diluted with water and extracted with EA. The organic layers were washed successively with 1 N NaOH, water and brine, then dried over Na₂SO₄, filtered and concentrated to afford title compound **244** as an off-white solid (71 mg, 70% yield). LC-MS: rt = 1.46 min, MS: 480.2 (calcd), 481.3 (M+H⁺, found).

Step 6. 2-Amino-6-(2-(1,5-dimethyl-1H-1,2,3-triazol-4-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**245**)

To a solution of **244** (71 mg, 0.148 mmol) in MeOH (19 mL) was added a solution of lithium hydroxide monohydrate (31 mg, 0.74 mmol) in water (19 mL). The reaction mixture was stirred at 60 °C for 16 hours, then more lithium hydroxide monohydrate (31 mg, 0.74 mmol) was added and the mixture was stirred at 60 °C for another 8 hours. The mixture was then allowed to cool to RT and concentrated to remove most of the organic solvent. Then, it was acidified by slowly adding 1 N HCl and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated to afford title compound **245** as a yellow solid (69 mg, >99% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.33-7.28 (m, 4H), 7.24-7.19 (m, 1H), 3.88 (s, 3H), 3.27-3.21 (m, 1H), 2.71-2.60 (m, 2H), 2.57-2.44 (m, 2H), 2.43-2.36 (m, 1H), 2.18 (s, 3H), 2.17-2.08 (m, 2H). LC-MS: rt = 1.06 min, MS: 410.1 (calcd), 411.2 (M+H⁺, found).

Step 7. 2-Amino-6-(2-(1,5-dimethyl-1H-1,2,3-triazol-4-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (246)

To a mixture of **245** (59 mg, 0.144 mmol) and ammonium chloride (77 mg, 1.44 mmol) in anhydrous DMF (1.8 mL) were added HATU (109 mg, 0.287 mmol) and *N,N*-diisopropylethylamine (0.075 mL, 0.431 mmol). The resulting mixture was stirred for 10 minutes, before bubbling gaseous NH₃ through the mixture for additional 30 minutes. Afterwards, the reaction was quenched with a saturated aqueous solution of NH₄Cl and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was first purified by reverse-phase flash column chromatography (eluent gradient from 0% to 100% of CH₃CN in 0.1% formic acid (v/v) in water) and then Semi-Prep HPLC-MS (eluent gradient from 20% to 100% of CH₃CN in 10 mM ammonium bicarbonate) to afford title compound **246** as a white solid (3.7 mg, 6% yield over two steps).

¹H NMR: 400 MHz, DMSO-*d*₆, δ (ppm): 8.08 (s, 2H), 7.33-7.30 (m, 4H), 7.26-7.20 (m, 1H), 6.84 (bs, 2H), 3.81 (s, 3H), 2.92-2.86 (m, 1H), 2.76-2.61 (m, 2H), 2.46-2.41 (m, 1H), 2.37-2.26 (m, 2H), 2.10 (s, 3H), 2.05-1.93 (m, 2H). LC-MS: rt = 1.00 min, MS: 409.2 (calcd), 410.2 (M+H⁺, found).

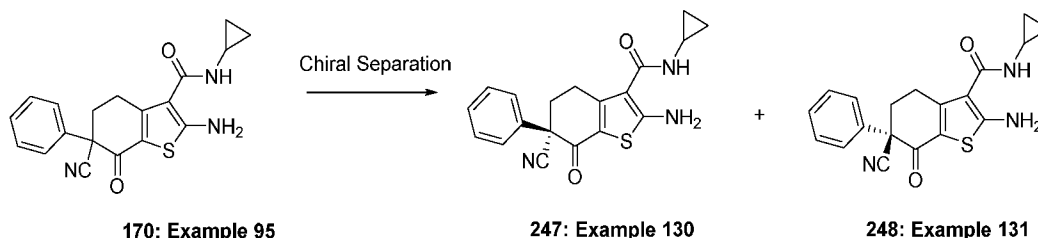
Example 130

(*R*)-2-Amino-6-cyano-N-cyclopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (247) and

Example 131

(*S*)-2-Amino-6-cyano-N-cyclopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (248)

Scheme 58



Scheme 32

1.05 g of racemic compound **170** (scheme 32, example 95) were submitted to SFC Chiral Separation to afford enantioenriched title compound **247** as a white solid (302 mg, 29% separation yield) and enantioenriched title compound **248** as a white solid (258 mg, 25% separation yield).

Absolute configurations of compounds **247** and **248** were assigned based on analogy with the assignment of the absolute configuration of a crystallized compound within the same or similar series.

247: ¹H NMR: same as racemic mixture (**170**). LC-MS: rt = 1.25 min, MS: 351.1 (calcd), 352.2 (M+H⁺, found). Analytical SFC (IG column with 5-60% MeOH in water (95-40% CO₂) gradient): rt = 4.50 min, ee. = 99.98%.

248: ¹H NMR: same as racemic mixture (**170**). LC-MS: rt = 1.25 min, MS: 351.1 (calcd), 352.2 (M+H⁺, found). Analytical SFC (IG column with 5-60% MeOH in water (95-40% CO₂) gradient): rt = 5.93 min, ee. = 98.88%.

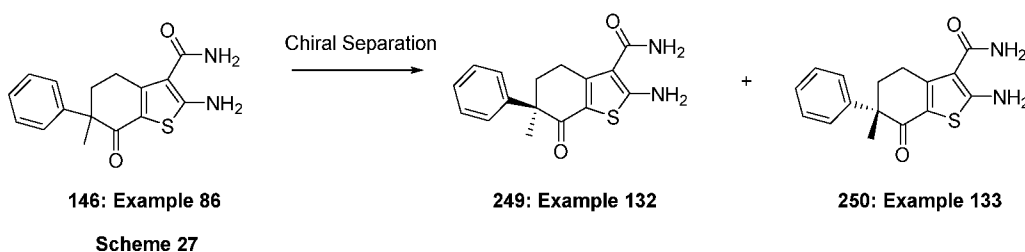
Example 132

(R)-2-Amino-6-cyano-N-cyclopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (249) and

Example 133

(S)-2-Amino-6-cyano-N-cyclopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (250)

Scheme 59



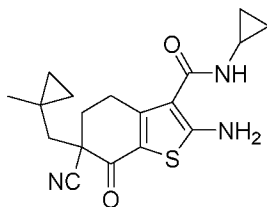
2.18 g of racemic compound **146** (scheme 27, example 86) were submitted to SFC Chiral Separation to afford enantioenriched title compound **249** as an off-white solid (932 mg, 43% separation yield) and enantioenriched title compound **250** as an off-white solid (903 mg, 41% separation yield). Absolute configurations of compounds **249** and **250** were assigned based on analogy with the assignment of the absolute configuration of a crystallized compound within the same or similar series.

249: ¹H NMR: same as racemic mixture (**146**). LC-MS: rt = 1.09 min, MS: 300.1 (calcd), 301.1 (M+H⁺, found). Analytical SFC (IG column with 5-60% MeOH in water (95-40% CO₂) gradient): rt = 4.67 min, ee. = 99.94%.

250: ¹H NMR: same as racemic mixture (**146**). LC-MS: rt = 1.09 min, MS: 300.1 (calcd), 301.1 (M+H⁺, found). Analytical SFC (IG column with 5-60% MeOH in water (95-40% CO₂) gradient): rt = 6.17 min, ee. = 97.60%.

Example 134

2-Amino-6-cyano-N-cyclopropyl-6-((1-methylcyclopropyl)methyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (251)

**251: Example 134**

Compound **251** (example 134) was synthesized similarly to compound **82** (scheme 13) starting from compound **173** (scheme 34) instead of compound **81**.

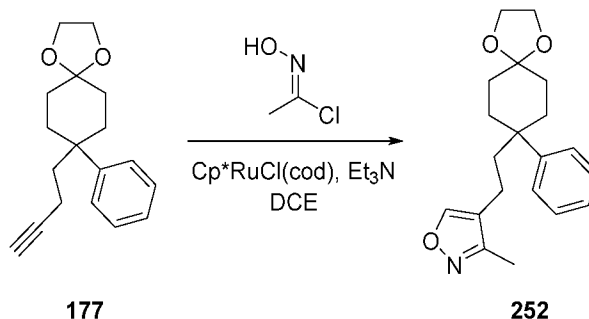
¹H NMR (400 MHz, CDCl₃) δ 7.06 (bs, 2H), 5.69 (bs, 1H), 3.16-2.95 (m, 2H), 2.87-2.78 (m, 1H), 2.66 (dt, *J* = 13.6, 4.3 Hz, 1H), 2.34 (ddd, *J* = 14.0, 9.6, 4.7 Hz, 1H), 2.13 (d, *J* = 14.7 Hz, 1H), 1.91 (d, *J* = 14.7 Hz, 1H), 1.17 (s, 3H), 0.93-0.87 (m, 2H), 0.65-0.57 (m, 2H), 0.42-0.35 (m, 4H). LC-MS: *rt* = 1.28 min, MS: 343.1 (calcd), 344.2 (*M*+H⁺, found).

Example 135

2-Amino-6-(2-(3-methylisoxazol-4-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (253)

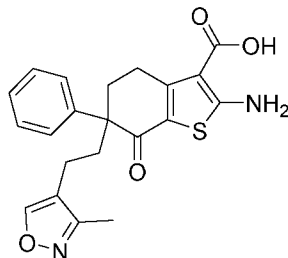
Intermediate compound 252

3-Methyl-4-(2-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)isoxazole (252)

Scheme 60**Scheme 35**

A solution of *N*-hydroxyacetimidoyl chloride (*Angew. Chem. Int. Ed.* **2017**, 12586-12589.) (174 mg, 1.86 mmol) in DCE (9.86 mL) was purged with argon for 2 min, then 8-(but-3-yn-1-yl)-8-phenyl-1,4-dioxaspiro[4.5]decane (**177**, scheme 35) (504 mg, 1.86 mmol), chloro(pentamethylcyclopentadienyl)(cyclooctadiene)ruthenium(II) (36.1 mg, 93.2 μmol) and triethylamine (0.326 mL, 2.33 mmol) were added and the resulting mixture was stirred at RT for 16 hours. The mixture was then filtered, the filtrate was concentrated to dryness, and the residue was purified by flash column chromatography (eluent gradient from 5% to 80% of EA in hexane) to afford title compound **252** as a light-yellow gum (442 mg, 72% yield). LC-MS: *rt* = 1.61 min, MS: 327.2 (calcd), 328.2 (*M*+H⁺, found).

2-Amino-6-(2-(3-methylisoxazol-4-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (253)



253: Example 135

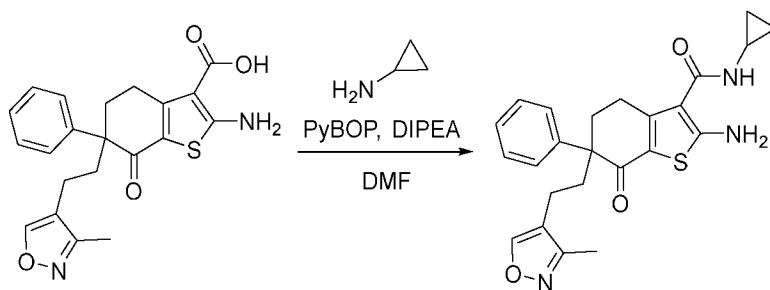
Compound **253** was synthesized similarly to compound **189** (scheme 40) starting from compound **252** instead of compound **185**.

¹H NMR (400 MHz, CDCl₃) δ 8.02 (s, 1H), 7.36-7.29 (m, 4H), 7.29-7.21 (m, 1H, partially overlapping with the solvent signal), 6.65 (bs, 2H), 3.28-3.19 (m, 1H), 2.78-2.54 (m, 2H), 2.49-2.33 (m, 2H), 2.26-2.20 (m, 1H), 2.19 (s, 3H), 2.12 (dd, *J* = 12.9, 4.0 Hz, 1H), 2.08-1.99 (m, 1H). LC-MS: rt = 1.36 min, MS: 396.1 (calcd), 397.3 (M+H⁺, found).

Example 136

2-Amino-*N*-cyclopropyl-6-(2-(3-methylisoxazol-4-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (254)

Scheme 61



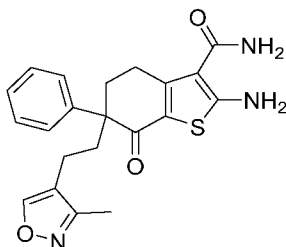
253

254: Example 136

To a solution of **253** (34.8 mg, 87.8 μmol) in DMF (0.97 mL) were added *N,N*-diisopropylethylamine (49 μL, 281 μmol), PyBOP (68.7 mg, 132 μmol) and cyclopropylamine (62.7 μL). The resulting mixture was stirred at RT for 2.5 hours. The mixture was then diluted with saturated aqueous NH₄Cl (5 mL) and extracted with EA (3 x 5 mL). The combined organics were washed with ice-cold brine (10 mL), dried over Na₂SO₄, filtered and concentrated to dryness. The residue was first purified by reverse-phase flash column chromatography (eluent gradient from 0% to 100% CH₃CN in 10 mM aqueous ammonium bicarbonate) and then by flash column chromatography (eluent gradient from 0% to 100% of EA in hexane) to afford title compound **254** as an off-white solid (15.5 mg, 41% yield).

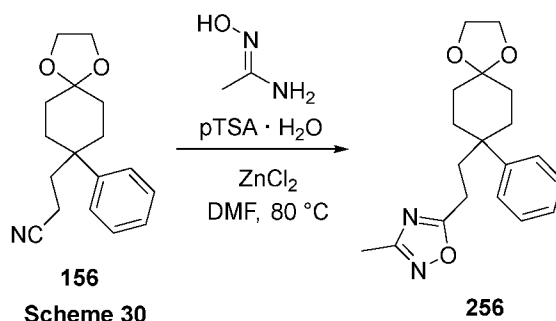
^1H NMR (400 MHz, CDCl_3) δ 8.01 (s, 1H), 7.38-7.26 (m, 5H), 7.01 (bs, 2H), 5.53 (bs, 1H), 2.89-2.78 (m, 1H), 2.76-2.68 (m, 1H), 2.65-2.57 (m, 1H), 2.56-2.40 (m, 3H), 2.29-2.09 (m, 5H), 2.03-1.94 (m, 1H), 0.91-0.74 (m, 2H), 0.58-0.47 (m, 2H). LC-MS: r_t = 1.33 min, MS: 435.2 (calcd), 436.3 ($\text{M}+\text{H}^+$, found).

5

Example 137**2-Amino-6-(2-(3-methylisoxazol-4-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (255)****255: Example 137**

Compound **255** was synthesized similarly to compound **52** (scheme 6) starting from compound **253** instead of compound **51**.

^1H NMR (400 MHz, CDCl_3) δ 8.02 (s, 1H), 7.40-7.22 (m, 5H), 7.06 (bs, 2H), 5.36 (bs, 2H), 2.96 (d, J = 15.6 Hz, 1H), 2.71-2.56 (m, 2H), 2.53-2.42 (m, 2H), 2.27-2.10 (m, 5H), 2.07-1.96 (m, 1H). LC-MS: r_t = 1.16 min, MS: 395.1 (calcd), 396.2 ($\text{M}+\text{H}^+$, found).

Example 138**2-Amino-6-(2-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (258)****Intermediate compound 256****3-Methyl-5-(2-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)-1,2,4-oxadiazole (256)**Scheme 62

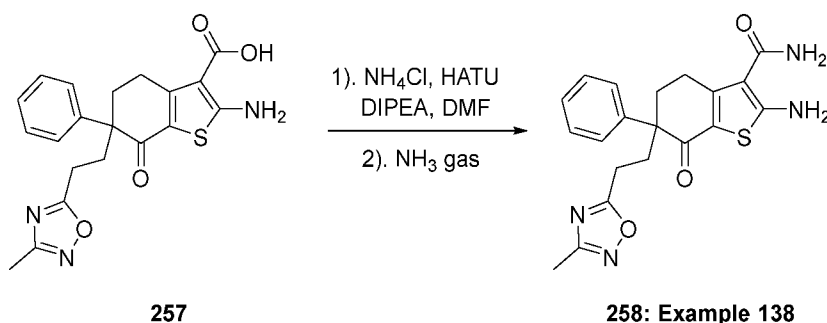
20

To a mixture of 3-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)propanenitrile (**156**, scheme 30) (300 mg, 1.11 mmol) (*Bioorg Med. Chem Lett.* 21, p. 405, 2011) and *N'*-hydroxyacetimidamide (93.8 mg, 1.22 mmol) in DMF (0.91 mL) were added 4-toluenesulfonic acid monohydrate (63.1

mg, 332 μmol) and zinc chloride (45.2 mg, 332 μmol). The resulting mixture was stirred under nitrogen at 80 °C for 8 days, then allowed to cool to RT, diluted with EA (10 mL), washed with saturated aqueous sodium bicarbonate (3 x 10 mL) and ice-cold brine (2 x 15 mL), then dried over Na_2SO_4 , filtered and concentrated to dryness. The residue was purified by flash column chromatography (eluent gradient from 0% to 60% of EA in hexane) to afford title compound **256** as a colorless oil (39.8 mg, 11% yield). LC-MS: t_r = 1.42 min, MS: 328.2 (calcd), 329.2 ($\text{M}+\text{H}^+$, found).

2-Amino-6-(2-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (258)

Scheme 63



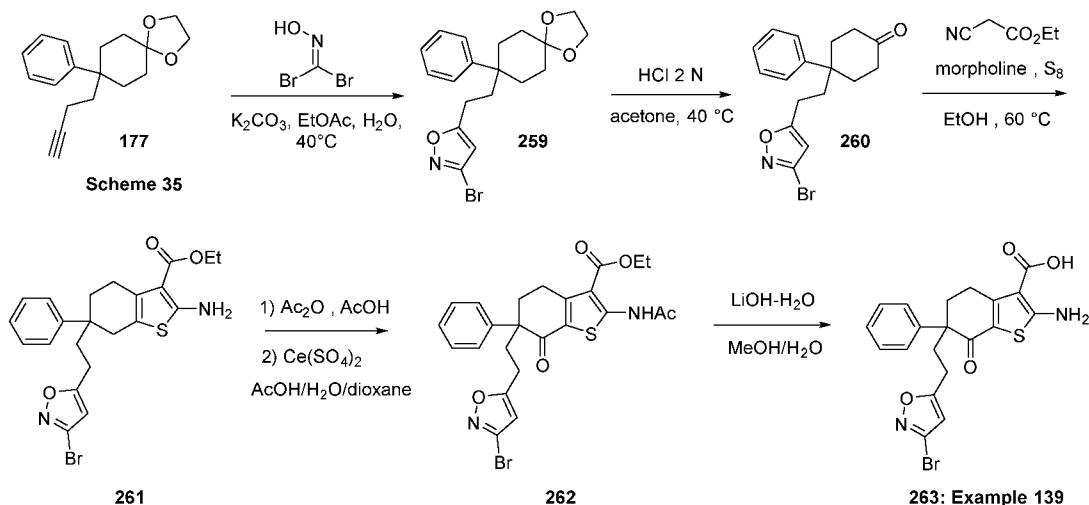
To a solution of **257** (synthesized similarly to compound **189** (scheme 40) starting from compound **256** instead of compound **185**) (22 mg, 55.4 μmol) in DMF (0.7 mL) were added ammonium chloride (29.6 mg, 554 μmol), HATU (42.1 mg, 111 μmol) and *N,N*-diisopropylethylamine (40 μL , 230 μmol). The resulting solution was stirred at RT for 10 minutes, then excess of gaseous NH_3 was bubbled through the mixture from a balloon. Stirring continued at RT for 30 minutes, then the mixture was diluted with saturated aqueous NH_4Cl (10 mL) and extracted with EA (3 x 10 mL). The combined organics were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by reverse-phase flash column chromatography (eluent gradient from 0% to 100% of CH_3CN in H_2O with 0.1% (v/v) formic acid) to afford title compound **258** as a light-yellow solid (7 mg, 32% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.36-7.26 (m, 5H), 7.03 (bs, 2H), 5.34 (bs, 2H), 3.11 (ddd, J = 16.3, 10.9, 5.8 Hz, 1H), 3.00-2.90 (m, 1H), 2.74-2.62 (m, 1H), 2.62-2.53 (m, 2H), 2.47-2.34 (m, 3H), 2.33 (s, 3H). LC-MS: t_r = 1.11 min, MS: 396.1 (calcd), 397.2 ($\text{M}+\text{H}^+$, found).

Example 139

2-Amino-6-(2-(3-bromoisoxazol-5-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (263)

Scheme 64



Step 1. 3-Bromo-5-(2-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)isoxazole (259)

A solution of dibromoformaldoxime (2.21 g, 10.9 mmol) in 13 mL of EA was added dropwise to a solution of **177** (scheme 35) (737 mg, 2.73 mmol) and potassium carbonate (755 mg, 5.5 mmol) in EA (60 mL) and water (7.3 mL). The reaction mixture was heated at 40 °C for 20 hours. The mixture was then allowed to cool to RT, additional potassium carbonate (755 mg, 5.5 mmol) and dibromoformaldoxime (1.1 g, 5.5 mmol) were added and stirring at 40 °C was continued for another 72 hours. EA (20 mL) and water (20 mL) were then added, the organic layer was separated and the desired product was extracted with an additional 40 mL of EA. The organic layers were combined, washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (eluent gradient from 0% to 25% of EA in hexane) to afford title compound **259** as a pale-yellow sticky solid (885 mg, 83% yield).

Step 2. 4-(2-(3-Bromoisoxazol-5-yl)ethyl)-4-phenylcyclohexan-1-one (**260**)

To a solution of **259** (680 mg, 1.73 mmol) in acetone (24 mL) was added 2 N HCl (8.7 mL, 17.3 mmol) and the reaction mixture was stirred at 40 °C for 16 hours. Then, the mixture was neutralized by slowly adding a saturated aqueous solution of NaHCO₃ and concentrated to remove the organic solvent. The residue was extracted with EA and the organic layer was dried over Na₂SO₄, filtered and concentrated to dryness to afford title compound **260** as a white solid (589 mg, 98% yield). LC-MS: rt = 1.60 min, MS: 347.1 and 349.1 (calcd), 348.1 and 350.2 (M+H⁺, found).

Step 3. Ethyl 2-amino-6-(2-(3-bromoisoxazol-5-yl)ethyl)-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**261**)

To a solution of **260** (604 mg, 1.73 mmol) and ethyl 2-cyanoacetate (0.185 mL, 1.73 mmol) in EtOH (3 mL) were added morpholine (0.165 mL, 1.91 mmol) and sulfur (61.4 mg, 0.239 mmol). The reaction mixture was stirred at 60 °C for 16 hours, then allowed to cool to RT and concentrated to dryness. The residue was purified by flash column chromatography (eluant

gradient from 0% to 60% of EA in hexane) to afford title compound **261** as a yellow oil (547 mg, 66% yield). LC-MS: rt = 1.94 min, MS: 474.1 and 476.1 (calcd), 475.2 and 477.2 (M+H⁺, found).

Step 4. Ethyl 2-acetamido-6-(2-(3-bromoisoxazol-5-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**262**)

5 A mixture of **261** (545 mg, 1.15 mmol) and acetic anhydride (0.130 mL, 1.38 mmol) in acetic acid (6.6 mL) was stirred at 70 °C for 1.5 hours. The mixture was then allowed to cool to RT, diluted with water (5 mL) and dioxane (5 mL) and ceric sulfate (3.5 g, 9.9 mmol) was added. The reaction mixture was stirred at RT for 3.5 hours. Then, the solid was filtered off, rinsed with EA (150 mL) and the filtrate was diluted with brine. The layers were separated, and the aqueous
10 phase was extracted with EA (150 mL). The combined organics were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated to afford title compound **262** as a yellow solid (400 mg, 66% yield). LC-MS: rt = 1.89 min, MS: 530.1 and 532.1 (calcd), 531.1 and 533.1 (M+H⁺, found).

Step 5. 2-Amino-6-(2-(3-bromoisoxazol-5-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**263**)

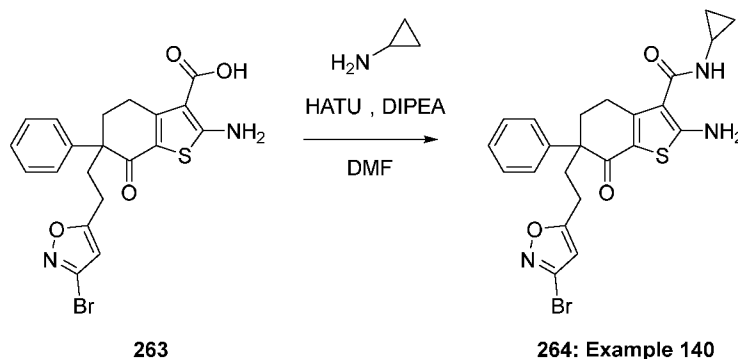
15 To a suspension of **262** (400 mg, 0.753 mmol) in MeOH (35 mL) was added a solution of lithium hydroxide monohydrate (537 mg, 12.8 mmol) in water (35 mL). The reaction mixture was stirred at 55 °C for 20 hours at which point additional lithium hydroxide monohydrate (316 mg, 7.5 mmol) was added. The mixture was stirred for another 20 hours at 55 °C, then allowed to cool to
20 RT. The mixture was diluted with water and concentrated to remove most of the organic solvent and the aqueous residue was extracted with EA. This organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by reverse-phase flash column chromatography (eluent gradient from 0% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **263** as a pale-yellow solid (342 mg, 98% yield).

25 ¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 12.50 (s, 1H), 8.26 (s, 2H), 7.33-7.27 (m, 4H), 7.25-7.21 (m, 1H), 6.55 (s, 1H), 3.14-3.09 (m, 1H), 2.78-2.70 (m, 1H), 2.63-2.53 (m, 2H), 2.43-2.35 (m, 1H), 2.28-2.21 (m, 1H), 2.15-2.02 (m, 2H). LC-MS: rt = 1.54 min, MS: 460.0 and 462.0 (calcd), 461.1 and 463.1 (M+H⁺, found).

Example 140

30 **2-Amino-6-(2-(3-bromoisoxazol-5-yl)ethyl)-N-cyclopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**264**)**

Scheme 65



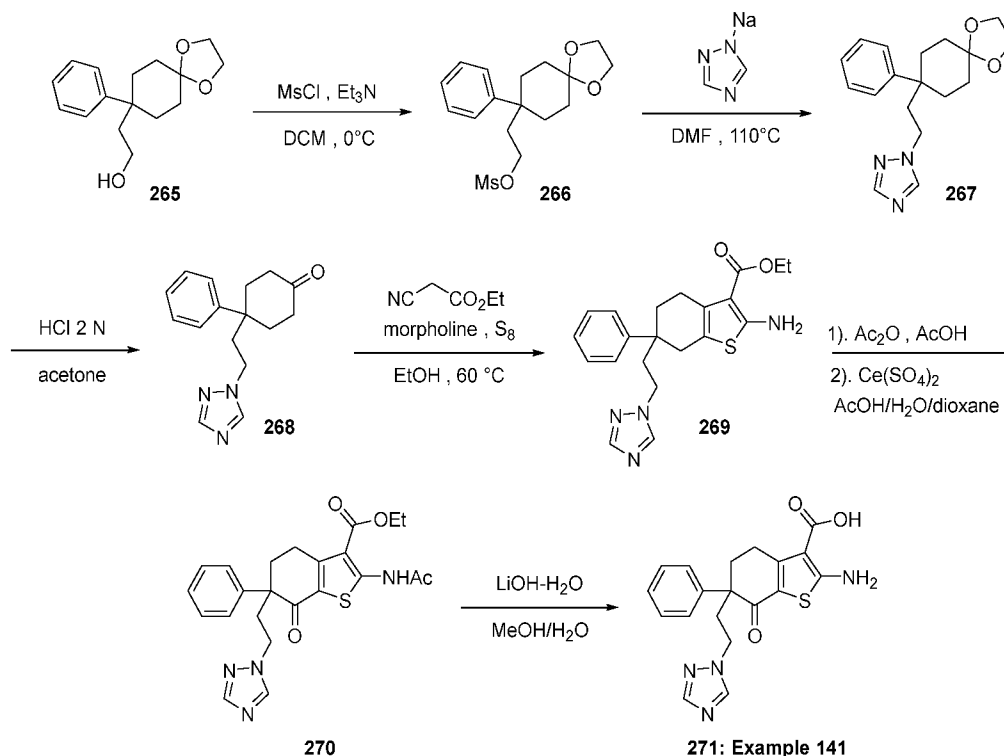
To a suspension of **263** (100 mg, 0.217 mmol) in DMF (2 mL) were added HATU (165 mg, 0.434 mmol) and *N,N*-diisopropylethylamine (75.5 μ L, 0.434 mmol). The mixture was stirred at RT for 20 minutes and then cyclopropylamine (150 μ L, 2.17 mmol) was added. The reaction mixture was then stirred at RT for 72 hours at which point additional HATU (165 mg, 0.434 mmol) and *N,N*-diisopropylethylamine (75.5 μ L, 0.434 mmol) were added and stirring continued at RT for another 2 hours. The mixture was then partitioned between EA and a saturated aqueous solution of NH_4Cl . The layers were separated and the organic phase was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 15% to 100% of EA in hexane) to afford title compound **264** as a pale-yellow solid (46.0 mg, 42% yield).

^1H NMR: 400 MHz, $\text{DMSO}-d_6$, δ (ppm): 7.83 (s, 2H), 7.30-7.27 (m, 5H), 7.24-7.20 (m, 1H), 6.52 (s, 1H), 2.75-2.51 (m, 6H), 2.22-2.12 (m, 1H), 2.12-2.05 (m, 2H), 0.61-0.53 (m, 2H), 0.49-0.38 (m, 2H). LC-MS: *rt* = 1.58 min, MS: 499.1 and 501.1 (calcd), 500.3 and 502.2 ($\text{M}+\text{H}^+$, found).

Example 141

6-(2-(1H-1,2,4-Triazol-1-yl)ethyl)-2-amino-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (271)

Scheme 66



Step 1. 2-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethyl methanesulfonate (**266**)

To a solution of 2-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethan-1-ol (**265**) (*Bioorg. Med. Chem. Lett.*, 21, p. 405, 2011) (5.64 g, 21.5 mmol) in anhydrous DCM (160 mL) at 0 °C were added methanesulfonyl chloride (1.83 mL, 23.6 mmol) and triethylamine (5.99 mL, 43.0 mmol). The reaction mixture was stirred at RT for 1 hour, then diluted with water and extracted with DCM. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 70% of EA in hexane) to afford title compound **266** as a white solid (5.10 g, 70% yield).

Step 2. 1-(2-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)-1H-1,2,4-triazole (**267**)

To a solution of **266** (1.20 g, 3.52 mmol) in anhydrous DMF (35 mL) was added 1,2,4-triazole sodium salt (1.60 g, 17.6 mmol). The reaction mixture was stirred at 110 °C for 20 hours, then allowed to cool to RT and quenched with saturated aqueous NH₄Cl solution (30 mL) diluted with water (15 mL). Then, the desired product was extracted with EA (2 x 40 mL). The organic layers were combined, washed with brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 15% to 100% of EA in hexane) to afford title compound **267** as a colorless oil (970 mg, 88% yield). LC-MS: rt = 1.19 min, MS: 313.2 (calcd), 314.2 (M+H⁺, found).

Step 3. 4-(2-(1H-1,2,4-Triazol-1-yl)ethyl)-4-phenylcyclohexan-1-one (**268**)

To a solution of **267** (965 mg, 3.08 mmol) in acetone (42 mL) was added 2 N HCl (15.4 mL, 30.8 mmol) and the reaction mixture was stirred at 40 °C for 16 hours. Then, the mixture was

neutralized by slowly adding a saturated aqueous solution of NaHCO_3 (20 mL). The residue was extracted with EA (3 x 20 mL) and the organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated to dryness to afford title compound **268** as a colorless oil (803 mg, 73% yield). LC-MS: rt = 1.04 min, MS: 269.2 (calcd), 270.3 ($\text{M}+\text{H}^+$, found).

5 Step 4. Ethyl 6-(2-(1H-1,2,4-Triazol-1-yl)ethyl)-2-amino-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**269**)

To a solution of **268** (603 mg, 2.24 mmol) and ethyl 2-cyanoacetate (0.238 mL, 2.24 mmol) in EtOH (4 mL) were added morpholine (0.212 mL, 2.46 mmol) and sulfur (79 mg, 0.309 mmol). The reaction mixture was stirred at 60 °C for 16 hours, then allowed to cool to RT and concentrated to dryness. The residue was purified by flash column chromatography (eluant gradient from 0% to 100% of EA in hexane) to afford title compound **269** as a yellow oil (701 mg, 79% yield). LC-MS: rt = 1.46 min, MS: 396.2 (calcd), 397.3 ($\text{M}+\text{H}^+$, found).

10 Step 5. Ethyl 6-(2-(1H-1,2,4-Triazol-1-yl)ethyl)-2-acetamido-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**270**)

15 A mixture of **269** (701 mg, 1.77 mmol) and acetic anhydride (0.334 mL, 3.54 mmol) in acetic acid (10 mL) was stirred at 60 °C for 1 hour. The mixture was allowed to cool to RT, then diluted with water (25 mL) and acetic acid (15 mL) and ceric sulfate (4.95 g, 14.1 mmol) was added. The reaction mixture was stirred at RT for 72 hours. EA (150 mL) and brine (100 mL) were then added and the organic layer was separated, washed successively with brine (100 mL) and saturated NaHCO_3 solution (3 x 100 mL), dried over Na_2SO_4 , filtered and concentrated to afford title compound **270** as an orange solid (560 mg, 70% yield). LC-MS: rt = 1.41 min, MS: 452.2 (calcd), 453.2 ($\text{M}+\text{H}^+$, found).

20 Step 6. 6-(2-(1H-1,2,4-Triazol-1-yl)ethyl)-2-amino-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**271**)

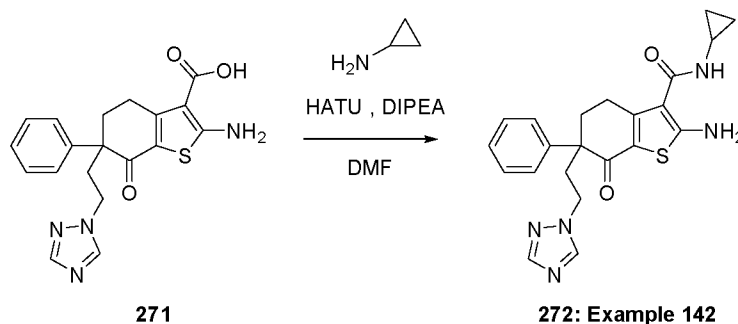
25 To a suspension of **270** (560 mg, 1.24 mmol) in MeOH (57 mL) was added a solution of lithium hydroxide monohydrate (883 mg, 21.0 mmol) in water (57 mL). The reaction mixture was stirred at 50 °C for 16 hours, then allowed to cool to RT. The mixture was concentrated to remove most of the organic solvent. The aqueous layer was washed with EA. Then, the aqueous layer was acidified by slowly adding 1 N HCl and extracted with EA. The organic layer was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH_3CN in H_2O with 0.1% (v/v) formic acid) to afford the title compound **271** as a pale-yellow solid (260 mg, 55% yield).

30 ^1H NMR: 400 MHz, $\text{DMSO}-d_6$, δ (ppm): 8.58 (bs, 1H), 8.48 (s, 2H), 8.37 (s, 1H), 7.85 (s, 1H), 7.30-7.25 (m, 4H), 7.21-7.16 (m, 1H), 4.24-4.17 (m, 1H), 3.97-3.90 (m, 1H), 3.42-3.35 (m, 2H), 2.27-2.21 (m, 3H), 2.16-2.09 (m, 1H). LC-MS: rt = 1.03 min, MS: 382.1 (calcd), 383.2 ($\text{M}+\text{H}^+$, found).

Example 142

6-(2-(1H-1,2,4-Triazol-1-yl)ethyl)-2-amino-*N*-cyclopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (272)

Scheme 67



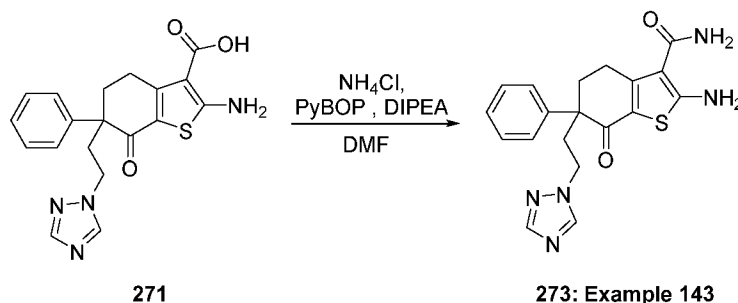
To a suspension of **271** (80 mg, 0.209 mmol) in DMF (2 mL) were added HATU (159 mg, 0.418 mmol) and *N,N*-diisopropylethylamine (72.9 μ L, 0.418 mmol). The mixture was stirred at RT for 20 minutes and then cyclopropylamine (145 μ L, 2.09 mmol) was added and stirring continued for another 20 hours. The crude mixture was then directly purified first by reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) and then by Semi-Prep HPLC-MS (eluent gradient from 40% to 100% of MeOH in 10 mM ammonium bicarbonate) to afford title compound **272** as an off-white solid (18.5 mg, 21% yield).

¹H NMR: 400 MHz, DMSO-*d*₆, δ (ppm): 8.37 (s, 1H), 7.86-7.81 (m, 3H), 7.34-7.28 (m, 4H), 7.25-7.21 (m, 1H), 4.20-4.13 (m, 1H), 3.94-3.87 (m, 1H), 2.71-2.61 (m, 2H), 2.61-2.51 (m, 2H), 2.28-2.10 (m, 3H), 0.60-0.52 (m, 2H), 0.45-0.41 (m, 2H). LC-MS: *rt* = 1.08 min, MS: 421.2 (calcd), 422.3 (*M*+H⁺, found).

Example 143

6-(2-(1H-1,2,4-Triazol-1-yl)ethyl)-2-amino-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (273)

Scheme 68



To a solution of **271** (70.0 mg, 183.0 μ mol) in DMF (2.3 mL) were added PyBOP (143 mg, 275 μ mol), *N,N*-diisopropylethylamine (128 μ L, 732 μ mol) and ammonium chloride (97.9 mg, 1.83 mmol). The resulting mixture was stirred at RT for 20 hours. The crude mixture was directly

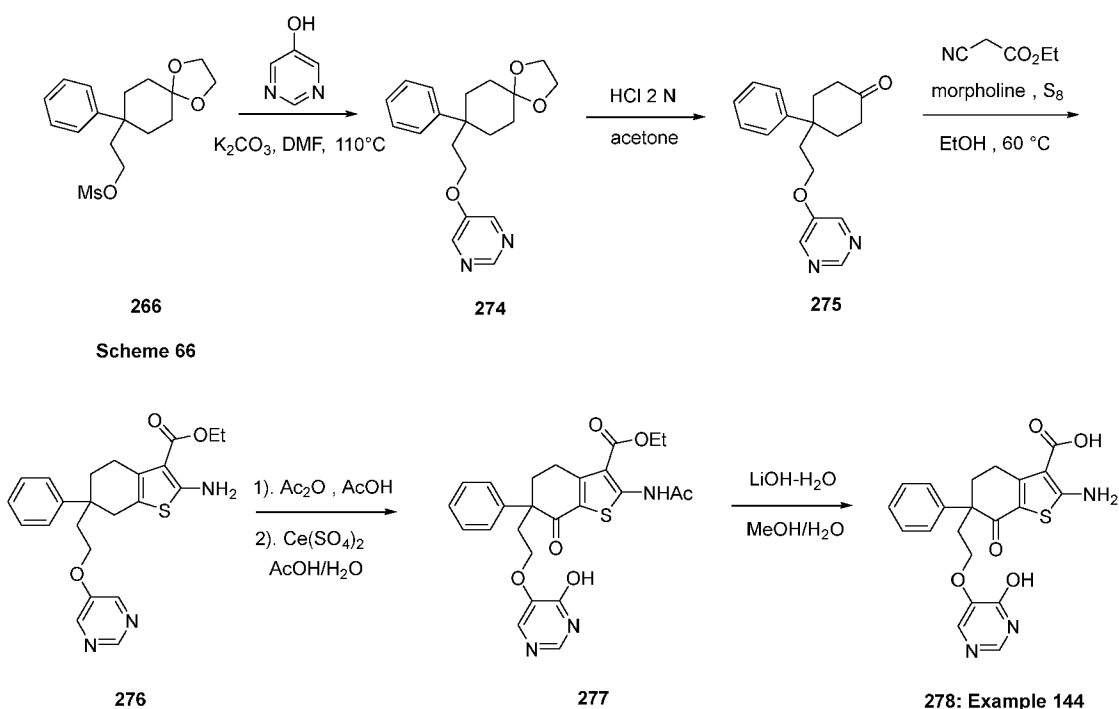
purified by reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **273** as a yellow solid (26.5 mg, 38% yield).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.37 (s, 1H), 8.10 (s, 2H), 7.86 (s, 1H), 7.34-7.30 (m, 4H), 7.26-7.20 (m, 1H), 6.85 (bs, 1H), 4.21-4.13 (m, 1H), 3.95-3.88 (m, 1H), 2.87-2.79 (m, 1H), 2.68-2.55 (m, 2H), 2.29-2.19 (m, 3H). LC-MS: rt = 0.95 min, MS: 381.1 (calcd), 382.2 (M+H⁺, found).

Example 144

2-Amino-6-(2-((4-hydroxypyrimidin-5-yl)oxy)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (**278**)

Scheme 69



Step 1. 5-(2-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethoxy)pyrimidine (**274**)

To a solution of **266** (scheme 66) (1.20 g, 3.52 mmol) in anhydrous DMF (24 mL) was added potassium carbonate (1.46 g, 10.6 mmol) and pyrimidin-5-ol (406 mg, 4.23 mmol). The reaction mixture was stirred at 110 °C for 20 hours. The reaction mixture was then quenched with a saturated aqueous solution of NH₄Cl (30 mL) and diluted with water (15 mL). Then, the desired product was extracted with EA (2 x 40 mL). The organic layers were combined, washed with brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 15% to 100% of EA in hexane) to afford title compound **274** as a yellow oil (927 mg, 77% yield). LC-MS: rt = 1.37 min, MS: 340.2 (calcd), 341.2 (M+H⁺, found).

Step 2. 4-Phenyl-4-(2-(pyrimidin-5-yloxy)ethyl)cyclohexan-1-one (**275**)

To a solution of **274** (925 mg, 2.72 mmol) in acetone (37 mL) was added 2 N HCl (13.6 mL, 27.2 mmol) and the reaction mixture was stirred at 40 °C for 16 hours. Then, the mixture was neutralized by slowly adding a saturated aqueous solution of NaHCO₃ (20 mL). The residue was extracted with EA (3 x 20 mL) and the organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness to afford title compound **275** as a yellow oil (805 mg, 99% yield). LC-MS: rt = 1.22 min, MS: 296.2 (calcd), 297.3 (M+H⁺, found).

Step 3. Ethyl 2-amino-6-phenyl-6-(2-(pyrimidin-5-yloxy)ethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**276**)

To a solution of **275** (805 mg, 2.72 mmol) and ethyl 2-cyanoacetate (0.289 mL, 2.72 mmol) in EtOH (4.8 mL) were added morpholine (0.258 mL, 2.99 mmol) and sulfur (96.2 mg, 0.375 mmol). The reaction mixture was stirred at 60 °C for 16 hours, then allowed to cool to RT and concentrated to dryness. The residue was purified by flash column chromatography (eluent gradient from 0% to 55% of EA in hexane) to afford title compound **276** as a yellow oil (1.0 g, 87% yield). LC-MS: rt = 1.64 min, MS: 423.2 (calcd), 424.3 (M+H⁺, found).

Step 4. Ethyl 2-acetamido-7-oxo-6-phenyl-6-(2-(pyrimidin-5-yloxy)ethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**277**)

A mixture of **276** (1.0 g, 2.36 mmol) and acetic anhydride (0.446 mL, 4.72 mmol) in acetic acid (14 mL) was stirred at 60 °C for 1 hour. The mixture was then allowed to cool to RT and diluted with water (33 mL) and acetic acid (20 mL) and ceric sulfate (6.61 g, 18.9 mmol) was added. The reaction mixture was stirred at RT for 72 hours. EA (150 mL) and brine (100 mL) were then added and the organic layer was separated, washed successively with brine (100 mL) and a saturated aqueous solution of NaHCO₃ (3 x 100 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 10% to 100% of EA in hexane, then 15% MeOH in DCM) to afford title compound **277** as an orange solid (510 mg, 44% yield). LC-MS: rt = 1.33 min, MS: 495.2 (calcd), 496.3 (M+H⁺, found).

Step 5. 2-Amino-6-(2-((4-hydroxypyrimidin-5-yl)oxy)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**278**)

To a suspension of **277** (510 mg, 1.03 mmol) in MeOH (48 mL) was added a solution of lithium hydroxide monohydrate (650 mg, 15.5 mmol) in water (48 mL). The reaction mixture was stirred at 50 °C for 16 hours, then allowed to cool to RT. The mixture was concentrated to remove most of the organic solvent. The aqueous layer was washed with EA. Then, the aqueous layer was acidified by slowly adding 1 N HCl and extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford the title compound **278** as a yellow solid (105 mg, 24% yield).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 12.48 (bs, 1H), 8.23 (bs, 2H), 7.75 (s, 1H), 7.38 (s, 1H), 7.33-7.25 (m, 4H), 7.23-7.16 (m, 2H), 3.96-3.89 (m, 1H), 3.71-3.64 (m, 1H), 3.10-3.03 (m,

1H), 2.72-2.66 (m, 1H), 2.36-2.12 (m, 4H). LC-MS: rt = 0.96 min, MS: 425.1 (calcd), 426.2 (M+H⁺, found).

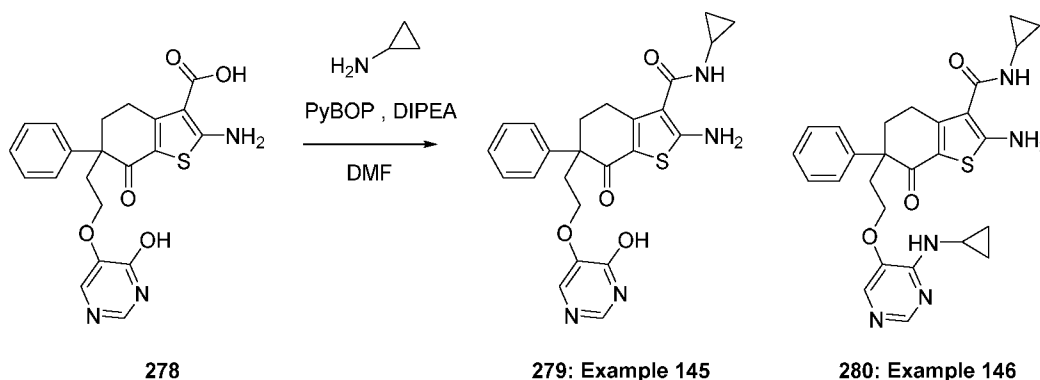
Example 145

2-Amino-N-cyclopropyl-6-(2-((4-hydroxypyrimidin-5-yl)oxy)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (279) and

Example 146

2-Amino-N-cyclopropyl-6-(2-((4-(cyclopropylamino)pyrimidin-5-yl)oxy)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (280)

Scheme 70



To a suspension of **278** (60 mg, 0.188 mmol) in DMF (1.35 mL) were added PyBOP (112 mg, 0.212 mmol) and *N,N*-diisopropylethylamine (98.3 μ L, 0.564 mmol). The mixture was stirred at RT for 1.5 hours. The crude mixture was directly purified first by reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid), then by flash column chromatography (eluent gradient from 0% to 15% of MeOH in DCM) and finally by Semi-Prep HPLC-MS (eluent gradient from 40% to 100% of MeOH in 10 mM ammonium formate) to afford title compound **279** as an off-white solid (13.4 mg, 20% yield) and **280** as an off-white solid (12.2 mg, 21% yield).

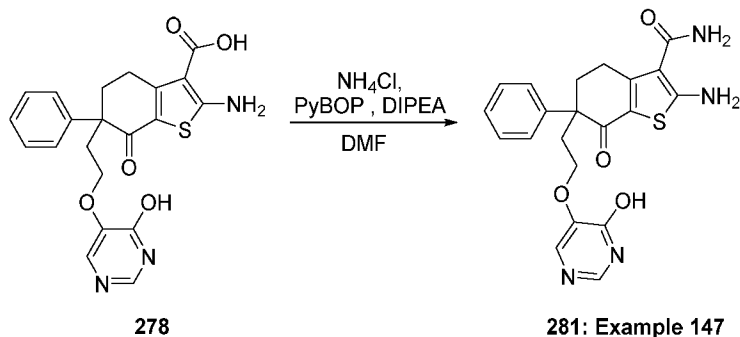
279: ¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 7.83 (s, 2H), 7.75 (s, 1H), 7.37 (s, 1H), 7.30-7.29 (m, 5H), 7.22-7.19 (m, 1H), 3.92-3.89 (m, 1H), 3.68-3.63 (m, 1H), 2.70-2.58 (m, 4H), 2.25-2.09 (m, 4H), 0.59-0.54 (m, 2H), 0.46-0.42 (m, 2H). LC-MS: rt = 1.05 min, MS: 464.2 (calcd), 465.3 (M+H⁺, found).

280: ¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.23 (s, 1H), 8.08 (s, 1H), 7.85 (s, 2H), 7.65 (s, 1H), 7.37-7.34 (m, 4H), 7.26-7.21 (m, 1H), 6.66-6.65 (m, 1H), 4.01-3.95 (m, 1H), 3.94-3.88 (m, 1H), 2.78-2.71 (m, 1H), 2.69-2.59 (m, 4H), 2.41-2.31 (m, 1H), 2.27-2.21 (m, 1H), 2.17-2.10 (m, 1H), 0.71-0.67 (m, 2H), 0.63-0.57 (m, 2H), 0.55-0.51 (m, 2H), 0.47-0.43 (m, 2H). LC-MS: rt = 0.98 min, MS: 503.2 (calcd), 504.3 (M+H⁺, found).

Example 147

2-Amino-6-(2-((4-hydroxypyrimidin-5-yl)oxy)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (281)

Scheme 71



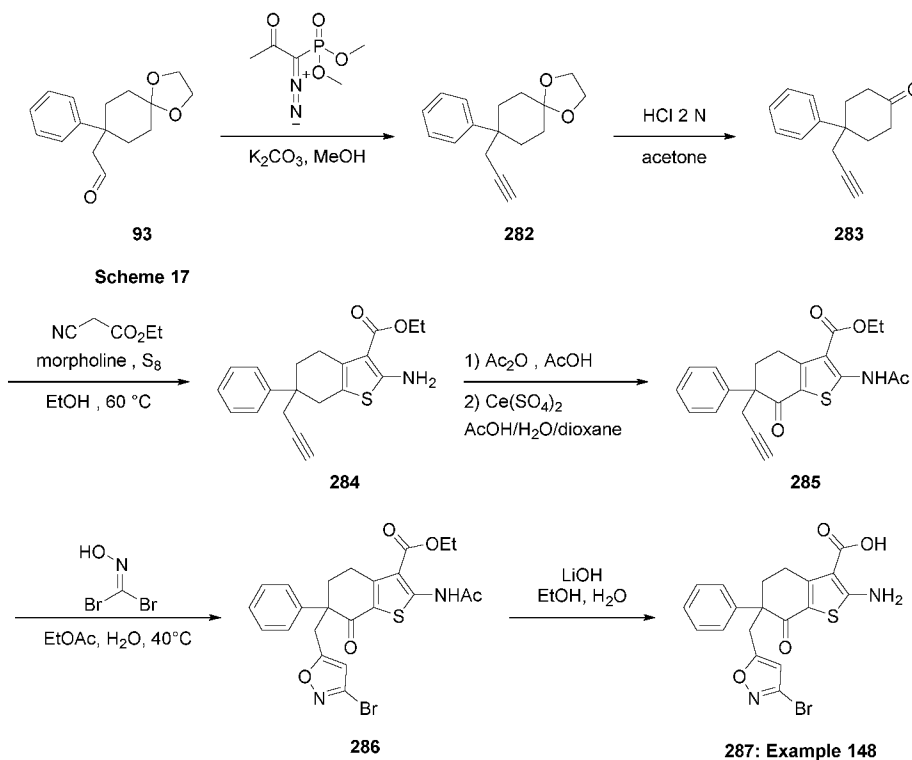
To a solution of **278** (80.0 mg, 188.0 μmol) in DMF (2.35 mL) were added PyBOP (147 mg, 282 μmol), *N,N*-diisopropylethylamine (131 μL , 752 μmol) and ammonium chloride (101 mg, 1.88 mmol). The resulting mixture was stirred at RT for 20 hours. The crude mixture was directly purified first by reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH_3CN in H_2O with 0.1% (v/v) formic acid), then by Semi-Prep HPLC-MS (eluent gradient from 5% to 100% of MeOH in 10 mM ammonium formate) to afford title compound **281** as a white solid (6.9 mg, 9% yield).

^1H NMR: 400 MHz, $\text{DMSO}-d_6$, δ (ppm): 8.09 (bs, 2H), 7.73 (s, 1H), 7.36 (s, 1H), 7.31-7.26 (m, 4H), 7.25-7.18 (m, 1H), 6.83 (bs, 2H), 3.93-3.86 (m, 1H), 3.69-3.62 (m, 1H), 2.86-2.78 (m, 1H), 2.73-2.61 (m, 2H), 2.30-2.14 (m, 3H). LC-MS: rt = 0.87 min, MS: 424.1 (calcd), 425.2 ($\text{M}+\text{H}^+$, found).

Example 148

2-Amino-6-((3-bromoisoxazol-5-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (287)

Scheme 72



Step 1. 8-Phenyl-8-(prop-2-yn-1-yl)-1,4-dioxaspiro[4.5]decane (282)

To a solution of **93** (scheme 17) (4.96 g, 19.1 mmol) in MeOH (235 mL) were added K₂CO₃ (6.58 g, 47.6 mmol) and dimethyl (1-diazo-2-oxopropyl)phosphonate (4.71 mL, 28.6 mmol). The mixture was stirred at RT for 1 hour, then water (200 mL) and EA (200 mL) were added. The organic layer was separated, washed with brine (3 x 100 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 40% of EA in hexane) to afford title compound **282** as a white solid (2.65 g, 54% yield).

Step 2. 4-Phenyl-4-(prop-2-yn-1-yl)cyclohexan-1-one (283)

To a solution of **282** (800 mg, 3.12 mmol) in acetone (47 mL) was added 2 N HCl (15.6 mL, 31.2 mmol) and the reaction mixture was stirred at 40 °C for 16 hours. Then, the mixture was neutralized by slowly adding a saturated aqueous solution of NaHCO₃ (25 mL). The residue was extracted with EA (3 x 20 mL) and the organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness to afford title compound **283** as a white solid (640 mg, 97% yield).

Step 3. Ethyl 2-amino-6-phenyl-6-(prop-2-yn-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (284)

To a solution of **283** (640 mg, 3.01 mmol) and ethyl 2-cyanoacetate (0.292 mL, 2.74 mmol) in EtOH (4.81 mL) were added morpholine (0.26 mL, 3.01 mmol) and sulfur (97.0 mg, 0.378 mmol). The reaction mixture was stirred at 60 °C for 16 hours, then allowed to cool to RT and concentrated to dryness. The residue was purified by flash column chromatography (eluent

gradient from 0% to 55% of EA in hexane) to afford title compound **284** as a white solid (890 mg, 96% yield). LC-MS: rt = 1.67 min, MS: 339.1 (calcd), 340.1 (M+H⁺, found).

Step 4. Ethyl 2-acetamido-7-oxo-6-phenyl-6-(prop-2-yn-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**285**)

Acetic anhydride (0.297 mL, 3.15 mmol) was added to a suspension of **284** (890 mg, 2.62 mmol) in acetic acid (15 mL). The resulting mixture was heated up to 60 °C for 2 hours. After completion of the acylation step, dioxane (18.4 mL), water (18.4 mL) and ceric sulfate (5.35 g, 13.1 mmol) were added to the mixture. The resulting suspension was stirred at RT for 16 hours. The mixture was then diluted with water and extracted with EA. The organic layer was washed successively with NaOH 1 N, water and brine, then dried over Na₂SO₄, filtered and concentrated to afford title compound **285** as a an off-white solid (1.02 g, 98% yield over two steps). LC-MS: rt = 1.59 min, MS: 395.1 (calcd), 396.2 (M+H⁺, found).

Step 5. Ethyl 2-acetamido-6-((3-bromoisoxazol-5-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**286**)

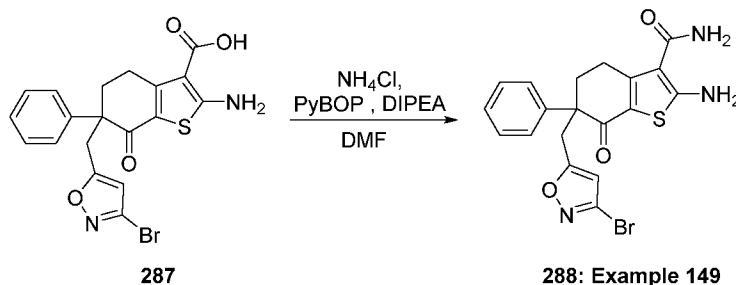
To a solution of **285** (50 mg, 0.126 mmol) in EA (3.4 mL) and water (0.34 mL) was added K₂CO₃ (70 mg, 0.506 mmol). Then, 1,1-dibromoformaldoxime (154 mg, 0.759 mmol) in EA (2 mL) was added dropwise and the reaction mixture was stirred at 40 °C for 16 hours. The mixture was then allowed to cool to RT and additional 1,1-dibromoformaldoxime (308 mg, 1.52 mmol) and K₂CO₃ (192 mg, 1.39 mmol) were added. Stirring continued at 40 °C for another 1 hour. Brine (10 mL) and EA (10 mL) were then added, the organic layer was separated, washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane) to afford title compound **286** as a white solid (49 mg, 75% yield). LC-MS: rt = 1.75 min, MS: 516.0 and 518.0 (calcd), 517.1 and 519.0 (M+H⁺, found).

Step 6. 2-Amino-6-((3-bromoisoxazol-5-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**287**)

To a suspension of **286** (58 mg, 0.112 mmol) in EtOH (5 mL) was added a solution of lithium hydroxide monohydrate (80 mg, 1.91 mmol) in water (5 mL). The reaction mixture was stirred at 55 °C for 16 hours, then allowed to cool to RT. The mixture was concentrated to remove most of the organic solvent. The residue was purified by reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford the title compound **287** as an off-white solid (21 mg, 42% yield).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 12.49 (bs, 1H), 8.27 (bs, 2H), 7.31-7.20 (m, 5H), 6.16 (s, 1H), 3.35-3.30 (m, 1H), 3.26-3.22 (m, 1H), 3.13-3.06 (m, 1H), 2.65-2.59 (m, 1H), 2.36-2.27 (m, 1H), 2.13-2.05 (m, 1H). LC-MS: rt = 1.48 min, MS: 446.0 and 448.0 (calcd), 447.1 and 449.1 (M+H⁺, found).

Example 149

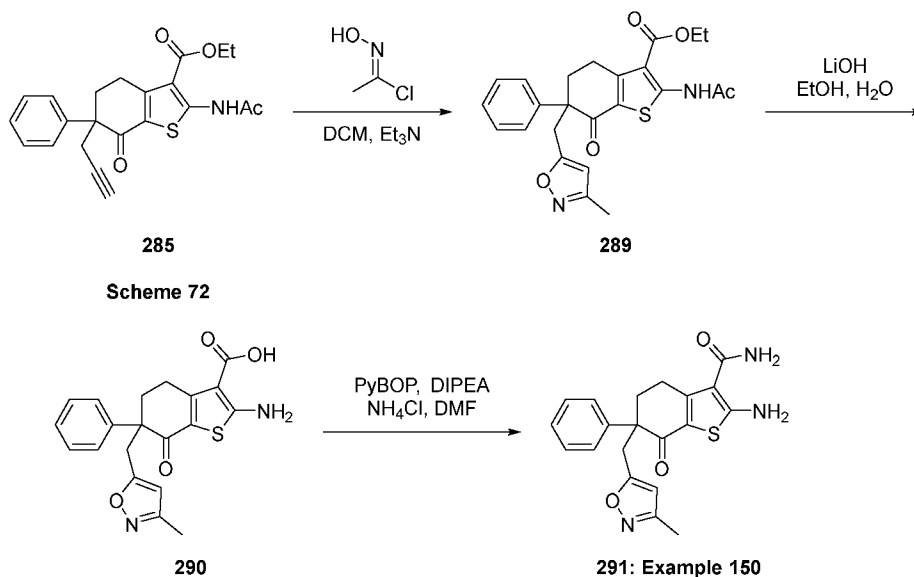
2-Amino-6-((3-bromoisoxazol-5-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (288)Scheme 73

To a solution of **287** (20 mg, 44.7 μmol) in DMF (0.6 mL) were added PyBOP (35 mg, 67.1 μmol), *N,N*-diisopropylethylamine (31.2 μL , 179 μmol) and ammonium chloride (23.9 mg, 0.447 mmol). The resulting mixture was stirred at RT for 30 minutes. The crude mixture was directly purified first by reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH_3CN in H_2O with 0.1% (v/v) formic acid), then by Semi-Prep HPLC-MS (eluent gradient from 30% to 100% of MeOH in 10 mM ammonium bicarbonate) to afford title compound **288** as a white solid (11.5 mg, 58% yield).

^1H NMR: 400 MHz, $\text{DMSO}-d_6$, δ (ppm): 8.09 (s, 2H), 7.32-7.21 (m, 5H), 6.86 (bs, 2H), 6.15 (s, 1H), 3.36 (d, $J = 14.77$ Hz, 1H), 3.23 (d, $J = 14.77$ Hz, 1H), 2.85-2.78 (m, 1H), 2.66-2.56 (m, 2H), 2.13-2.05 (m, 1H). LC-MS: $t_r = 1.34$ min, MS: 445.0 and 447.0 (calcd), 446.2 and 448.1 ($\text{M}+\text{H}^+$, found).

Example 150

2-Amino-6-((3-methylisoxazol-5-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (291)Scheme 74



Step 1. Ethyl 2-acetamido-6-((3-methylisoxazol-5-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (289**)**

To a solution of **285** (scheme 72) (50 mg, 0.126 mmol) in DCM (1 mL) were added triethylamine (53 μ L, 0.379 mmol) and *N*-hydroxyacetimidoyl chloride (*Angew. Chem. Int. Ed.*, 56(41), p. 12589, 2017) (35 mg, 0.379 mmol). The reaction mixture was stirred at RT for 16 hours. Then, additional triethylamine (0.106 mL, 0.758 mmol) and *N*-hydroxyacetimidoyl chloride (70 mg, 0.758 mmol) were added and stirring continued at RT for another 16 hours. The mixture was then diluted with brine (15 mL) and DCM (10 mL). The organic layer was separated, washed with brine (15 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 45% of EA in hexane) to afford title compound **289** as a pale-yellow solid (27.5 mg, 48% yield). LC-MS: t_r = 1.61 min, MS: 452.1 (calcd), 453.2 ($\text{M}+\text{H}^+$, found).

Step 2. 2-Amino-6-((3-methylisoxazol-5-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (290**)**

To a suspension of **289** (40 mg, 88.4 μ mol) in EtOH (4 mL) was added a solution of lithium hydroxide monohydrate (63 mg, 1.50 mmol) in water (4 mL). The reaction mixture was stirred at 55 $^\circ\text{C}$ for 16 hours, then allowed to cool to RT. The mixture was concentrated to remove most of the organic solvent. The aqueous layer was washed with EA. Then, the aqueous layer was acidified by slowly adding HCl 1 N and extracted with EA. The organic layer was dried over Na_2SO_4 , filtered and concentrated to afford title compound **290** as a red solid (36 mg, >99% yield), which was used directly for the next step without purification. LC-MS: t_r = 1.32 min, MS: 382.1 (calcd), 383.2 ($\text{M}+\text{H}^+$, found).

Step 3. 2-Amino-6-((3-methylisoxazol-5-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (291**)**

To a solution of **290** (33 mg, 86.3 μmol) in DMF (1.1 mL) were added PyBOP (68 mg, 129 μmol), *N,N*-diisopropylethylamine (60 μL , 345 μmol) and ammonium chloride (46 mg, 0.863 mmol). The resulting mixture was stirred at RT for 30 minutes. The crude mixture was directly purified first by reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH_3CN in H_2O with 0.1% (v/v) formic acid) and then by Semi-Prep HPLC-MS (eluent gradient from 35% to 100% of MeOH in 10 mM ammonium bicarbonate) to afford title compound **291** as a white solid (11.9 mg, 36% yield).

^1H NMR: 400 MHz, $\text{DMSO}-d_6$, δ (ppm): 8.09 (bs, 2H), 7.31-7.28 (m, 4H), 7.27-7.22 (m, 1H), 6.86 (bs, 1H), 5.80 (s, 1H), 3.35 (d, $J = 14.65$ Hz, 1H), 3.09 (d, $J = 14.65$ Hz, 1H), 2.87-2.81 (m, 1H), 2.67-2.57 (m, 2H), 2.11 (s, 3H), 2.08-2.02 (m, 1H). LC-MS: $t_r = 1.18$ min, MS: 381.1 (calcd), 382.2 ($\text{M}+\text{H}^+$, found).

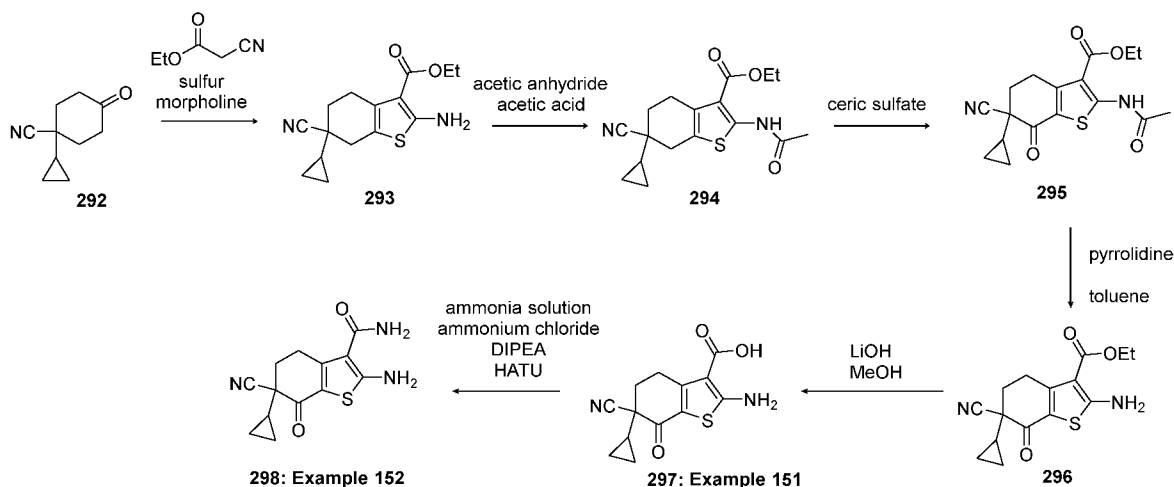
Example 151

2-amino-6-cyano-6-cyclopropyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (297) and

Example 152

2-amino-6-cyano-6-cyclopropyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (298)

Scheme 75



Step 1 Ethyl 2-amino-6-cyano-6-cyclopropyl-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (293).

A 20 mL vial equipped with a stir bar was charged with 1-cyclopropyl-4-oxocyclohexane-1-carbonitrile (**292**) (700 mg, 4.29 mmol, 1 equiv.), ethyl 2-cyanoacetate (485 mg, 4.29 mmol, 1 equiv.), elemental sulfur (152 mg, 592 μmol , 0.138 equiv.), morpholine (411 mg, 4.72 mmol, 1.1 equiv.) and ethanol (6.84 mL, 0.627 M). The vial was sealed with a lid with a pressure relief septum and the reaction was stirred at 60 $^{\circ}\text{C}$ for 18 hours. The reaction was cooled to room temperature

and vacuum filtered. The solids were washed with diethyl ether (2 x 5 ml) to yield the title compound as a pale-yellow solid (658 mg, 2.27 mmol, 53% yield). LC-MS: calc. 290.4, found (M+H) 291.3, retention time 0.44 min.

Step 2 Ethyl 6-cyano-6-cyclopropyl-2-acetamido-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (294).

A 20 ml vial equipped with a stir bar was charged with ethyl 2-amino-6-cyano-6-cyclopropyl-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**293**) (658 mg, 2.27 mmol, 1 equiv.) and suspended in acetic acid (13 ml, 0.174 M). Acetic anhydride (257 μ l, 2.72 mmol, 1.2 equiv.) was added in a single portion. The vial was sealed with a lid with a pressure relief septum and the reaction was stirred at 60 °C for 18 hours. The reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The residue was dissolved in DCM (20 ml), consecutively washed with sat. sodium bicarbonate, water and brine. The organic fraction was dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound (618 mg, 1.86 mmol, 82% yield). ¹H NMR (400 MHz, CDCl₃): δ 11.27 (s, 1H), 4.34 (q, J = 7.1 Hz, 2H), 3.16 – 2.78 (m, 3H), 2.26 (s, 3H), 2.26 – 2.20 (m, 1H), 1.85 (ddd, J = 13.3, 10.1, 5.9 Hz, 1H), 1.40 (t, J = 7.1 Hz, 3H), 1.07 – 0.92 (m, 1H), 0.66 – 0.60 (m, 4H).

Step 3 Ethyl 6-cyano-6-cyclopropyl-2-acetamido-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (295).

A 20 ml vial equipped with an egg shaped stir bar was charged with ethyl 6-cyano-6-cyclopropyl-2-acetamido-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**294**) (618 mg, 1.86 mmol, 1 equiv.), ceric sulfate (5.33 g, 16.1 mmol, 8.64 equiv.), glacial acetic acid (6.14 ml, 0.303 M) and water (6.14 ml, 0.303 M). The vial was sealed with a lid with a pressure relief septum and sonicated for 15 minutes to form a fine yellow suspension. The reaction was stirred vigorously at room temperature for 18 hours. The reaction mixture was diluted with water (10 ml) and ethyl acetate (10 ml). The aqueous phase was extracted with ethyl acetate (3x10 ml) and the organic fractions were combined and consecutively washed with 1N NaOH (10 ml), water (10ml) and brine (10 ml). The organic phase was dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound (587 mg, 1.69 mmol, 91% yield). LC-MS: calc. 346.4, found (M+H) 347.2, retention time 0.2 min.

Step 4 Ethyl 2-amino-6-cyano-6-cyclopropyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (296).

A 20 ml vial equipped with a stir bar was charged with ethyl 6-cyano-6-cyclopropyl-2-acetamido-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**295**) (587 mg, 1.69 mmol, 1 equiv.) and toluene (2.78 ml, 0.61 M). Pyrrolidine (2.09 ml, 25.4 mmol, 15 equiv.) was added in a single portion with a syringe. The vial was sealed with a lid with a pressure relief septum and the reaction was stirred at 80 °C for 2 hours. The reaction was cooled to room temperature, diluted with ethyl acetate (20 ml) and washed with brine. The organic fraction was dried over

sodium sulfate, filtered and the volatiles were removed *in vacuo*. The crude material was purified by automated column chromatography using silica gel and a gradient of 0 – 100% ethyl acetate in hexane as eluent to obtain the title compound as a yellow solid (420 mg, 1.38 mmol, 81% yield). LC-MS: calc. 304.4, found (M+H) 305.4, retention time 3.357 min.

5 Step 5 2-amino-6-cyano-6-cyclopropyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (297).

A 500 ml round bottom flask equipped with a stir bar was charged with ethyl 2-amino-6-cyano-6-cyclopropyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (296) (420 mg, 1.38 mmol, 1 equiv.), lithium hydroxide monohydrate (290 mg, 6.9 mmol, 5 equiv.), water (167
10 ml, 8.27 mM) and methanol (167 ml, 8.27 mM). A reflux condenser was affixed to the flask and the reaction was stirred at 80 °C for 18 hours. The reaction was cooled to room temperature, acidified by addition of 6 M HCl solution and extracted to ethyl acetate. The organic fractions were combined, dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound (312 mg, 1.13 mmol, 82% yield). The title compound was purified by
15 reverse phase chromatography using a C18 column and a gradient of 0 – 100% ACN in water and dried by lyophilization. ¹H NMR (400 MHz, CDCl₃): δ 12.74 (s, 1H), 8.49 (s, 2H), 3.25 – 2.99 (m, 2H), 2.44 (td, *J* = 8.7, 4.4 Hz, 1H), 2.38 – 2.29 (m, 1H), 1.40 (tt, *J* = 8.2, 5.1 Hz, 1H), 0.69 – 0.30 (m, 5H). LC-MS: calc. 276.3, found (M+H) 277.2, retention time 0.26 min.

20 Step 6 2-amino-6-cyano-6-cyclopropyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (298).

A 20 ml vial equipped with a stir bar was charged with 2-amino-6-cyano-6-cyclopropyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (297) (200 mg, 0.724 mmol, 1 equiv.), DIPEA (252 µl, 1.45 mmol, 2 equiv.), ammonium chloride (774 mg, 14.5 mmol, 20 equiv.), HATU (413 mg, 1.09 mmol, 1.5 equiv.) and DMF (8 ml, 90.5 mM). The vial was sealed with a pressure
25 relief septum and the reaction was sparged with argon for 5 min. Ammonia 0.4 M in THF solution (18.1 ml, 7.24 mmol, 10 equiv.) was added dropwise via syringe while stirring resulting in the formation of a beige precipitate and the reaction was subsequently stirred at room temperature overnight. The reaction was quenched by addition of 10 ml of saturated ammonium chloride solution and extracted into ethyl acetate. The organic layers were combined, dried over sodium
30 sulfate, filtered and the volatiles were removed *in vacuo*. The product was purified by preparative HPLC and subsequently dried by lyophilization to yield the title compound as a white solid (32 mg, 0.116 mmol, 16% yield). ¹H NMR (400 MHz, DMSO-d₆): δ 8.25 (s, 2H), 7.09 (br s, 2H), 3.20 (ddd, *J* = 17.9, 8.9, 4.8 Hz, 1H), 3.03 (dt, *J* = 17.8, 5.1 Hz, 1H), 2.43 (ddd, *J* = 13.5, 8.9, 4.9 Hz, 1H), 2.32 (dt, *J* = 13.3, 5.0 Hz, 1H), 1.39 (tt, *J* = 8.2, 5.1 Hz, 1H), 0.69 – 0.37 (m, 4H). LC-MS:
35 calc. 275.3, found (M+H) 276.3 m/z, retention time 0.26 min.

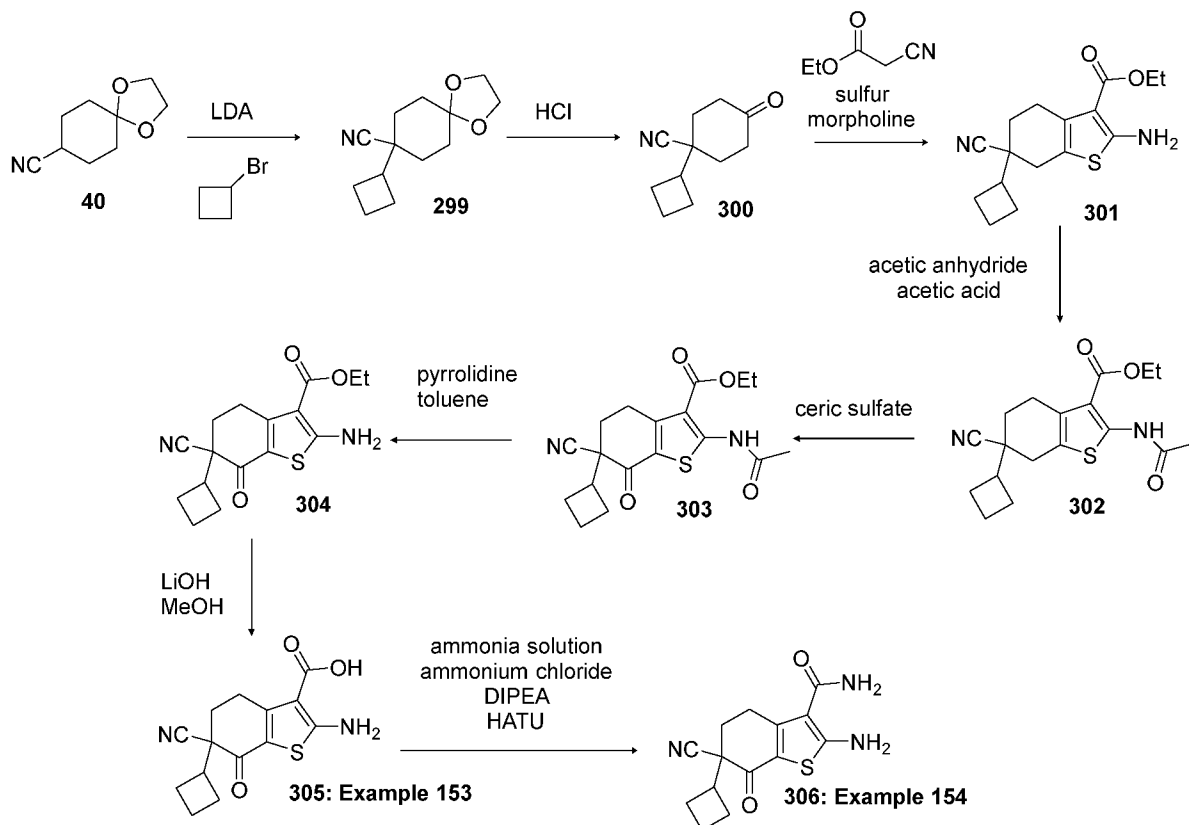
Example 153

2-amino-6-cyano-6-cyclobutyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (305) and

Example 154

2-amino-6-cyano-6-cyclobutyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (306)

Scheme 76



Step 1 8-cyclobutyl-1,4-dioxaspiro[4.5]decane-8-carbonitrile (299).

A dry 100 ml round bottom flask equipped with a stir bar was charged with 1,4-dioxaspiro[4.5]decane-8-carbonitrile (**40**) (500 mg, 2.99 mmol, 1 equiv.) and 15 ml of dry THF. The solution was sparged with argon for 10 minutes with an argon balloon and cooled to -78 °C with a dry ice acetone bath under positive argon atmosphere. Lithium diisopropylamide 1 M solution in THF/heptanes (3.29 ml, 3.29 mmol, 1.1 equiv.) was added dropwise to the flask and the reaction was stirred at -78 °C for 1.5 hours. A degassed solution of cyclobutylbromide (444 mg, 3.29 mmol, 1.1 equiv.) in 5 ml dry THF was added to the flask by syringe and the reaction was stirred at room temperature overnight. The reaction was quenched with 15 ml saturated ammonium chloride solution and extracted to diethyl ether. The organic fractions were combined, dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound as a pale-yellow oil (622 mg, 2.81 mmol, 94% yield). ¹H NMR (400 MHz, CDCl₃): δ 4.05 – 3.75 (m, 4H), 2.30 (p, *J* = 8.6 Hz, 1H), 2.08 – 1.69 (m, 12H), 1.55 – 1.38 (m, 2H).

Step 2 1-cyclobutyl-4-oxocyclohexane-1-carbonitrile (300).

A 20 ml vial equipped with a stir bar was charged with 8-cyclobutyl-1,4-dioxaspiro[4.5]decane-8-carbonitrile (**299**) (622 mg, 2.81 mmol, 1 equiv.) and acetone (5.62 ml, 0.5 M). 12 M HCl (4.68 ml, 56.2 mmol, 20 equiv.) was added to the flask slowly while stirring. The reaction was stirred at room temperature for 48 hours, quenched with saturated sodium bicarbonate solution and extracted to diethyl ether. The organic layers were combined, dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound (538 mg, 3.04 mmol, quant. yield). ¹H NMR (400 MHz, CDCl₃): δ 2.75 – 2.57 (m, 1H), 2.44 – 1.80 (m, 10H), 1.68 (s, 2H), 1.55 (td, *J* = 13.8, 4.4 Hz, 1H), 1.23 (s, 1H).

Step 3 Ethyl 2-amino-6-cyano-6-cyclobutyl-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (301).

A 20 ml vial equipped with a stir bar was charged with 1-cyclobutyl-4-oxocyclohexane-1-carbonitrile (**300**) (538 mg, 3.04 mmol, 1 equiv.), ethyl 2-cyanoacetate (343 mg, 3.04 mmol, 1 equiv.), elemental sulfur (107 mg, 419 μmol, 0.138 equiv.), morpholine (291 mg, 3.34 mmol, 1.1 equiv.) and ethanol (4.82 ml, 0.63 M). The vial was sealed with a lid with a pressure relief septum and the reaction was stirred at 60 °C for 18 hours. The reaction was cooled to room temperature and cooled to 5 °C for 1 hour to induce precipitation of product. The product was isolated by vacuum filtration and the solids were washed diethyl ether (2 x 5 ml) to yield the title compound as a pale-yellow solid (337 mg, 1.11 mmol, 37% yield). ¹H NMR (400 MHz, CDCl₃): δ 4.25 (q, *J* = 7.1 Hz, 2H), 2.98 – 2.82 (m, 2H), 2.46 – 2.38 (m, 2H), 2.11 – 1.96 (m, 6H), 1.94 – 1.81 (m, 2H), 1.53 (ddd, *J* = 13.4, 9.6, 6.2 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H).

Step 4 Ethyl 6-cyano-6-cyclobutyl-2-acetamido-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (302).

A 20 ml vial equipped with a stir bar was charged with ethyl 2-amino-6-cyano-6-cyclobutyl-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**301**) (337 mg, 1.11 mmol, 1 equiv.) and acetic acid (6.36 ml, 174 mM). The reaction was stirred to form an even suspension and acetic anhydride (126 μl, 1.33 mmol, 1.2 equiv.) was added in a single portion. The vial was sealed with a lid with a pressure relief septum and the reaction was stirred at 60 °C for 18 hours. The reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The residue was dissolved in DCM (10 ml), consecutively washed with sat. sodium bicarbonate, water and brine. The organic fraction was dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound (360 mg, 1.04 mmol, 94% yield). ¹H NMR (400 MHz, CDCl₃): δ 11.27 (s, 1H), 4.33 (q, *J* = 7.1 Hz, 3H), 3.03 – 2.92 (m, 2H), 2.63 – 2.36 (m, 2H), 2.26 (s, 3H), 2.15 – 2.03 (m, 6H), 1.97 – 1.84 (m, 2H), 1.65 – 1.52 (m, 1H), 1.39 (t, *J* = 7.1 Hz, 3H).

Step 5 Ethyl 6-cyano-6-cyclobutyl-2-acetamido-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (303).

A 20 ml vial equipped with an egg shaped stir bar was charged with ethyl 6-cyano-6-cyclobutyl-2-acetamido-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**302**) (360 mg, 1.04 mmol, 1 equiv.), ceric sulfate (2.98 g, 8.64 mmol, 8.64 equiv.), glacial acetic acid (460 μ l, 2.26 M) and water (460 μ l, 2.26 M). The vial was sealed with a lid with a pressure relief septum and sonicated for 15 minutes to form a fine yellow suspension. The reaction was stirred vigorously at room temperature for 18 hours. The reaction mixture was diluted with water (10 ml) and ethyl acetate (10 ml). The aqueous phase was extracted with ethyl acetate (3x10 ml) and the organic fractions were combined and consecutively washed with 1N NaOH (10 ml), water (10ml) and brine (10 ml). The organic phase was dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound (84.9 mg, 0.236 mmol, 23% yield). LC-MS: calc. 360.4, found 361.1 (M+H), retention time 0.28 min.

Step 6 Ethyl 2-amino-6-cyano-6-cyclobutyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**304**).

A 20 ml vial equipped with a stir bar was charged with ethyl 6-cyano-6-cyclobutyl-2-acetamido-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**303**) (85 mg, 236 μ mol, 1 equiv.) and toluene (387 μ l, 0.61 M). Pyrrolidine (252 mg, 3.54 mmol, 15 equiv.) was added in a single portion with a syringe. The vial was sealed with a lid with a pressure relief septum and the reaction was stirred at 80 °C for 2 hours. The reaction was cooled to room temperature, diluted with ethyl acetate (10 ml) and washed with brine. The organic fraction was dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound as an orange oil (76.4 mg, 240 μ mol, quant yield). LC-MS: calc. 318.4, found (M+H), retention time 0.21 min.

Step 7 2-amino-6-cyano-6-cyclobutyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (**305**).

A 100 ml round bottom flask equipped with a stir bar was charged with ethyl 2-amino-6-cyano-6-cyclobutyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**304**) (76.4 mg, 240 μ mol, 1 equiv.), lithium hydroxide monohydrate (50.3 mg, 1.2 mmol, 5 equiv.), water (29 ml, 8.27 mM) and methanol (29 ml, 8.27 mM). A reflux condenser was affixed to the flask and the reaction was stirred at 80 °C for 18 hours. The reaction was cooled to room temperature, acidified by addition of 6 M HCl solution and extracted to ethyl acetate. The organic fractions were combined, dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound (57 mg, 196 μ mol, 82% yield). The title compound was purified by reverse phase chromatography using a C18 column and a gradient of 0 – 100% ACN in water and dried by lyophilization. LC-MS: calc. 290.3, found (M+H) 291.3, retention time 3.169 min. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.68 (br. s, 1H), 8.42 (br. s, 2H), 3.10 – 3.00 (m, 1H), 2.96 – 2.86 (m, 1H), 2.81 (t, *J* = 8.3 Hz, 1H), 2.34 – 2.25 (m, 1H), 2.14 – 2.07 (m, 1H), 2.03 – 1.97 (m, 2H), 1.92 – 1.77 (m, 3H), 1.75 – 1.68 (m, 1H).

Step 8 2-amino-6-cyano-6-cyclobutyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (306).

A 5 ml vial equipped with a stir bar was charged with 2-amino-6-cyano-6-cyclobutyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (**305**) (40 mg, 0.138 mmol, 1 equiv.), DIPEA (48 μ l, 0.276 mmol, 2 equiv.), ammonium chloride (147 mg, 2.76 mmol, 20 equiv.), HATU (78.6 mg, 0.207 mmol, 1.5 equiv.) and DMF (1.52 ml, 90.5 mM). The vial was sealed with a pressure relief septum and the reaction was sparged with argon for 5 min. Ammonia 0.4 M in THF solution (6.89 ml, 2.76 mmol, 20 equiv.) was added dropwise via syringe while stirring resulting in the formation of a beige precipitate and the reaction was subsequently stirred at room temperature overnight. The reaction was quenched by addition of 10 ml of saturated ammonium chloride solution and extracted into ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered and the volatiles were removed *in vacuo*. The product was purified by preparative HPLC and subsequently dried by lyophilization to yield the title compound as a white solid (8.2 mg, 0.0283 mmol, 21% yield). ^1H NMR (400 MHz, CDCl_3): δ 5.50 (br. s, 2H), 3.52 (s, 2H), 3.15 – 2.98 (m, 2H), 2.85 (t, J = 8.0, 1H), 2.53 – 2.45 (m, 1H), 2.37 (t, J = 12.0 1H), 2.26 – 2.07 (m, 6H), 2.01 – 1.89 (m, 2H). LC-MS: calc. 289.4, found (M+H) 290.2, retention time 0.26 min.

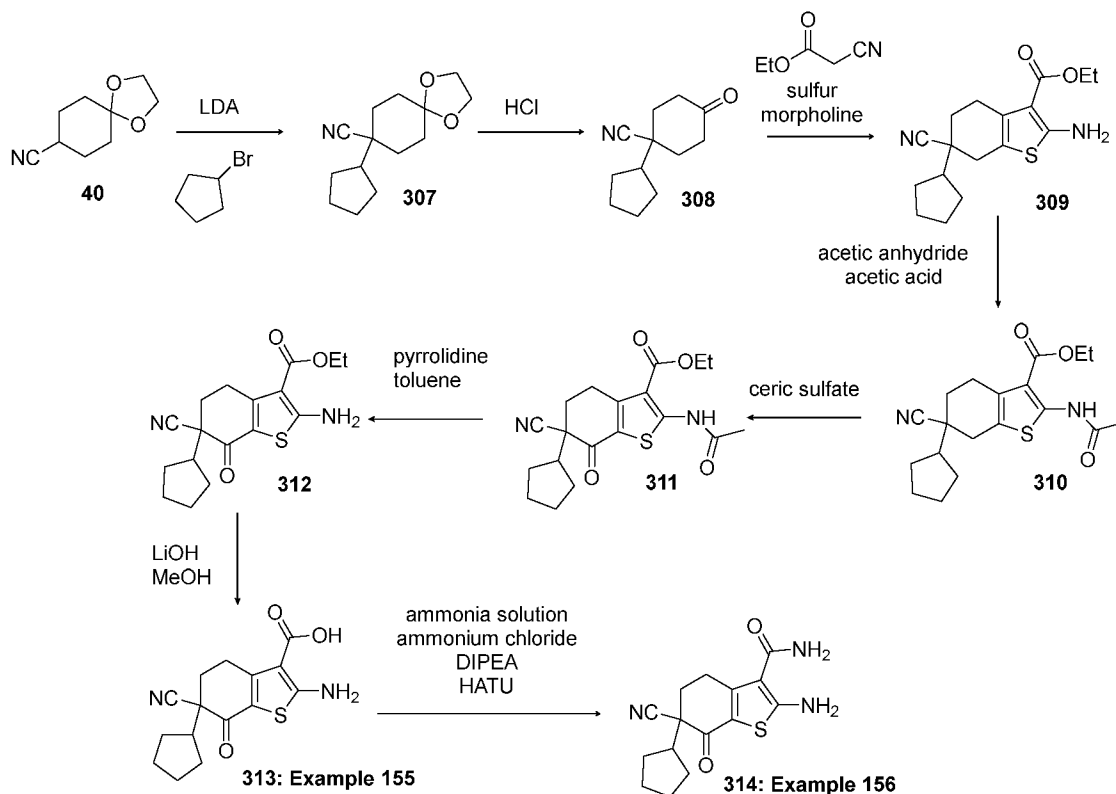
Example 155

2-amino-6-cyano-6-cyclopentyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (313) and

Example 156

2-amino-6-cyano-6-cyclopentyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (314)

Scheme 77



Step 1 8-cyclopentyl-1,4-dioxaspiro[4.5]decane-8-carbonitrile (**307**).

A dry 250 ml round bottom flask equipped with a stir bar was charged with 1,4-dioxaspiro[4.5]decane-8-carbonitrile (**40**) (2 g, 12 mmol, 1 equiv.) and 40 ml of dry THF. The solution was sparged with argon for 10 minutes with an argon balloon and cooled to -78 °C with a dry ice acetone bath under positive argon atmosphere. Lithium diisopropylamide 1 M solution in THF/heptanes (13.2 ml, 13.2 mmol, 1.1 equiv.) was added dropwise to the flask and the reaction was stirred at -78 °C for 1.5 hours. A degassed solution of cyclopentylbromide (1.96 mg, 13.2 mmol, 1.1 equiv.) in 10 ml dry THF was added to the flask by syringe and the reaction was stirred at room temperature overnight. The reaction was quenched with 50 ml saturated ammonium chloride solution and extracted to diethyl ether. The organic fractions were combined, dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound as a pale-yellow oil (2.87 g, 12.2 mmol, quant. yield). ¹H NMR (400 MHz, CDCl₃): δ 3.99 – 3.89 (m, 4H), 2.04 – 1.97 (m, 2H), 1.94 – 1.85 (m, 3H), 1.85 – 1.69 (m, 8H), 1.66 – 1.54 (m, 4H).

Step 2 1-cyclopentyl-4-oxocyclohexane-1-carbonitrile (**308**).

A 20 ml vial equipped with a stir bar was charged with 8-cyclopentyl-1,4-dioxaspiro[4.5]decane-8-carbonitrile (**307**) (937 mg, 3.98 mmol, 1 equiv.) and acetone (2 ml, 2.0 M). 12 M HCl (6.64 ml, 79.6 mmol, 20 equiv.) was added to the vial slowly while stirring. The reaction was stirred at room temperature for 48 hours, quenched with saturated sodium

bicarbonate solution and extracted to diethyl ether. The organic layers were combined, dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound (638 mg, 3.33 mmol, 84%). ¹H NMR (400 MHz, CDCl₃): δ 2.70 (td, *J* = 12, 6 Hz, 2H), 2.45 (p, *J* = 2.4 Hz, 1H), 2.41 (p, *J* = 2.4 Hz, 1H), 2.38 – 2.31 (m, 2H), 1.90 – 1.83 (m, 3H), 1.80 – 1.68 (m, 4H), 1.65 – 1.49 (m, 4H).

Step 3 Ethyl 2-amino-6-cyano-6-cyclopentyl-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (309).

A 20 ml vial equipped with a stir bar was charged with 1-cyclopentyl-4-oxocyclohexane-1-carbonitrile (**308**) (638 mg, 3.34 mmol, 1 equiv.), ethyl 2-cyanoacetate (377 mg, 3.34 mmol, 1 equiv.), elemental sulfur (118 mg, 460 μmol, 0.138 equiv.), morpholine (320 mg, 3.67 mmol, 1.1 equiv.) and ethanol (5.32 ml, 0.63 M). The vial was sealed with a lid with a pressure relief septum and the reaction was stirred at 60 °C for 18 hours. The reaction was cooled to room temperature the product was isolated by vacuum filtration. The solids were washed diethyl ether (2 x 5 ml) to yield the title compound as a pale-yellow solid (522 mg, 1.64 mmol, 49% yield). ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.00 (s, 2H), 6.61 (s, 2H), 2.89 – 2.73 (m, 3H), 2.71 – 2.57 (m, 1H), 2.14 – 1.97 (m, 2H), 1.93 – 1.79 (m, 2H), 1.73 – 1.62 (m, 3H), 1.60 – 1.50 (m, 2H), 1.44 – 1.34 (m, 2H).

Step 4 Ethyl 6-cyano-6-cyclopentyl-2-acetamido-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (310).

A 20 ml vial equipped with a stir bar was charged with ethyl 2-amino-6-cyano-6-cyclopentyl-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**309**) (522 mg, 1 mmol, 1 equiv.) and acetic acid (9.41 ml, 174 mM). The reaction was stirred to form an even suspension and acetic anhydride (201 mg, 1.97 mmol, 1.2 equiv.) was added in a single portion. The vial was sealed with a lid with a pressure relief septum and the reaction was stirred at 60 °C for 18 hours. The reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The residue was dissolved in DCM (10 ml), consecutively washed with sat. sodium bicarbonate, water and brine. The organic fraction was dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound (497 mg, 1.38 mmol, 84% yield). LC-MS: calc. 360.5, found (M+H) 361, retention time 0.63 min.

Step 5 Ethyl 6-cyano-6-cyclopentyl-2-acetamido-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (311).

A 20 ml vial equipped with an egg shaped stir bar was charged with ethyl 6-cyano-6-cyclopentyl-2-acetamido-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**310**) (200 mg, 555 μmol, 1 equiv.), ceric sulfate (1.59 g, 4.79 mmol, 8.64 equiv.), glacial acetic acid (1.83 ml, 0.303 M) and water (1.83 ml, 0.303 M). The vial was sealed with a lid with a pressure relief septum and sonicated for 15 minutes to form a fine yellow suspension. The reaction was stirred vigorously at room temperature for 18 hours. The reaction mixture was diluted with water (10 ml) and ethyl acetate (10 ml). The aqueous phase was extracted with ethyl acetate (3x10 ml) and the organic

fractions were combined and consecutively washed with 1N NaOH (10 ml), water (10ml) and brine (10 ml). The organic phase was dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound (191 mg, 0.51 mmol, 92% yield). LC-MS: calc. 374.5, found (M+H) 375, retention time 0.20 min.

5 Step 6 Ethyl 2-amino-6-cyano-6-cyclopentyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (312).

A 5 ml vial equipped with a stir bar was charged with ethyl 6-cyano-6-cyclopentyl-2-acetamido-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**311**) (191 mg, 510 μ mol, 1 equiv.) and toluene (836 μ l, 0.61 M). Pyrrolidine (544 mg, 7.65 mmol, 15 equiv.) was added in a
10 single portion with a syringe. The vial was sealed with a lid with a pressure relief septum and the reaction was stirred at 80 °C for 2 hours. The reaction was cooled to room temperature, diluted with ethyl acetate (30 ml) and washed with 30 ml brine. The organic fraction was dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound (176 mg, 530 μ mol, quant yield). LC-MS: calc. 332.4, found (M+H) 333.4, retention time 3.008 min.

15 Step 7 2-amino-6-cyano-6-cyclopentyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (313).

A 250 ml round bottom flask equipped with a stir bar was charged with ethyl 2-amino-6-cyano-6-cyclopentyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**312**) (176 mg, 529 μ mol, 1 equiv.), lithium hydroxide monohydrate (111 mg, 2.65 mmol, 5 equiv.), water (64 ml, 8.27 mM) and methanol (64 ml, 8.27 mM). A reflux condenser was affixed to the flask and the
20 reaction was stirred at 80 °C for 18 hours. The reaction was cooled to room temperature, acidified by addition of 6 M HCl solution and extracted to ethyl acetate. The organic fractions were combined, dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound (69.9 mg, 230 μ mol, 43% yield). The title compound was purified by reverse phase
25 chromatography using a C18 column and a gradient of 0 – 100% ACN in water and dried by lyophilization. LC-MS: calc. 304.4, found (M+H) 305.2, retention time 0.28 min. ¹H NMR (400 MHz, DMSO-*d*6): δ 12.69 (br. s, 1H), 8.43 (s, 2H), 3.18 – 3.09 (m, 1H), 3.01 – 2.88 (m, 1H), 2.42 – 2.28 (m, 4H), 1.94 – 1.84 (m, 1H), 1.63 – 1.58 (m, 1H), 1.53 – 1.46 (m, 3H), 1.40 – 1.31 (m 1H).

Step 8 2-amino-6-cyano-6-cyclopentyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (314).

A 20 ml vial equipped with a stir bar was charged with 2-amino-6-cyano-6-cyclopentyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (**313**) (30 mg, 0.138 mmol, 1 equiv.), DIPEA (25.5 mg, 0.197 mmol, 2 equiv.), ammonium chloride (105 mg, 1.97 mmol, 20 equiv.), HATU (56.2 mg, 0.148 mmol, 1.5 equiv.) and DMF (1.09 ml, 90.5 mM). The vial was sealed with
35 a pressure relief septum and the reaction was sparged with argon for 5 min. Ammonia 0.4 M in THF solution (4.93 ml, 1.97 mmol, 20 equiv.) was added dropwise via syringe while stirring resulting in the formation of an orange precipitate and the reaction was subsequently stirred at

room temperature overnight. The reaction was quenched by addition of 10 ml of saturated ammonium chloride solution and extracted into ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered and the volatiles were removed *in vacuo*. The product was purified by preparative HPLC and subsequently dried by lyophilization to yield the title compound as a white solid (4.8 mg, 0.0158 mmol, 16% yield). ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.19 (s, 2H), 7.04 (br. s, 2H), 3.19 (ddd, *J* = 18.0, 10.1, 4.8 Hz, 1H), 2.93 (dt, *J* = 18.0, 4.5 Hz, 1H), 2.47 – 2.23 (m, 3H), 1.95 – 1.81 (m, 1H), 1.70 – 1.59 (m, 1H), 1.58 – 1.47 (m, 6H), 1.38 (dt, *J* = 17.9, 8.1 Hz, 1H). LC-MS: calc. 303.4, found (*M*+*H*) 304.3, retention time 1.14 min.

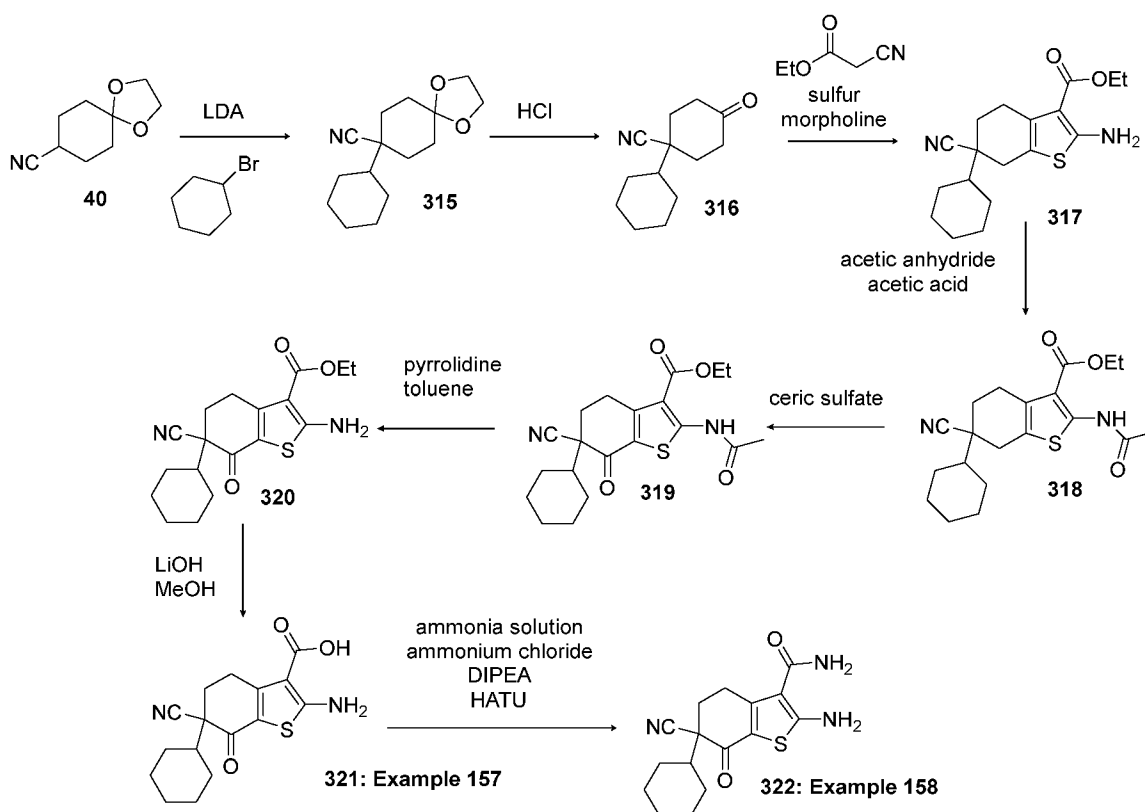
Example 157

2-amino-6-cyano-6-cyclohexyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (321) and

Example 158

2-amino-6-cyano-6-cyclohexyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (322)

Scheme 78



Step 1 8-cyclohexyl-1,4-dioxaspiro[4.5]decane-8-carbonitrile (315).

A dry 250 ml round bottom flask equipped with a stir bar was charged with 1,4-dioxaspiro[4.5]decane-8-carbonitrile (**40**) (3 g, 17.9 mmol, 1 equiv.) and 70 ml of dry THF. The solution was sparged with argon for 10 minutes with an argon balloon and cooled to -78 °C with a dry ice acetone bath under positive argon atmosphere. Lithium diisopropylamide 1 M solution in THF/heptanes (19.7 ml, 19.7 mmol, 1.1 equiv.) was added dropwise to the flask and the reaction was stirred at -78 °C for 1 hour. A degassed solution of cyclohexylbromide (4.39 g, 26.9 mmol, 1.5 equiv.) in 20 ml dry THF was added to the flask by syringe and the reaction was heated to 60 °C while stirring for 36 hours. Note: Reaction does not exceed 50% completion. The reaction cooled to room temperature, quenched with 50 ml saturated ammonium chloride solution and extracted to diethyl ether (2x50 ml). The organic fractions were combined, dried over sodium sulfate, filtered and the volatiles were removed *in vacuo*. The crude material was purified by automated column chromatography using silica gel and a gradient of 0 – 100% ethyl acetate in hexane as eluent to yield the title compound as a pale-yellow oil (783 mg, 3.14 mmol, 18% yield). ¹H NMR (400 MHz, CDCl₃): δ 4.11 – 3.67 (m, 4H), 2.16 – 1.47 (m, 15H), 1.30 – 1.09 (m, 5H).

Step 2 1-cyclohexyl-4-oxocyclohexane-1-carbonitrile (**316**).

A 20 ml vial equipped with a stir bar was charged with 8-cyclohexyl-1,4-dioxaspiro[4.5]decane-8-carbonitrile (**315**) (787 mg, 3.16 mmol, 1 equiv.) and acetone (5.3 ml, 0.6 M). 12 M HCl (5.26 ml, 63.1 mmol, 20 equiv.) was added to the vial slowly while stirring. The reaction was stirred at room temperature for 18 hours, quenched with saturated sodium bicarbonate solution and extracted to diethyl ether. The organic layers were combined, dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound (728 mg, 3.55 mmol, quant. yield). ¹H NMR (400 MHz, CDCl₃): δ 2.70 (td, *J* = 15.4 Hz, 5.9 Hz, 1H), 2.44 (d, *J* = 20.0 Hz, 1H) 2.25 – 2.11 (m, 2H), 2.00 – 1.80 (m, 4H), 1.78 – 1.65 (m, 4H), 1.34 – 1.14 (m, 5H).

Step 3 Ethyl 2-amino-6-cyano-6-cyclohexyl-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**317**).

A 20 ml vial equipped with a stir bar was charged with 1-cyclohexyl-4-oxocyclohexane-1-carbonitrile (**316**) (900 mg, 4.38 mmol, 1 equiv.), ethyl 2-cyanoacetate (4.96 mg, 4.38 mmol, 1 equiv.), elemental sulfur (155 mg, 605 μmol, 0.138 equiv.), morpholine (420 mg, 4.82 mmol, 1.1 equiv.) and ethanol (7.0 ml, 0.63 M). The vial was sealed with a lid with a pressure relief septum and the reaction was stirred at 60 °C for 18 hours. The reaction was cooled to room temperature the product was isolated by vacuum filtration. The solids were washed diethyl ether (2 x 5 ml) to yield the title compound as a pale-yellow solid (869 mg, 2.61 mmol, 60% yield). LC-MS: calculated 332.5, found (M+H) 333.5, retention time 3.895 min.

Step 4 Ethyl 6-cyano-6-cyclohexyl-2-acetamido-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**318**).

A 20 ml vial equipped with a stir bar was charged with ethyl 2-amino-6-cyano-6-cyclohexyl-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**317**) (869 mg, 2.61 mmol, 1 equiv.) and acetic acid (15 ml, 174 mM). The reaction was stirred to form an even suspension and acetic anhydride (320 mg, 3.14 mmol, 1.2 equiv.) was added in a single portion. The vial was sealed with a lid with a pressure relief septum and the reaction was stirred at 60 °C for 18 hours. The reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The residue was dissolved in DCM (10 ml), consecutively washed with sat. sodium bicarbonate, water and brine. The organic fraction was dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound (409 mg, 1.09 mmol, 42% yield). LC-MS: Calculated 374.5, found (M+H) 375.5, retention time 3.971 min.

Step 5 Ethyl 6-cyano-6-cyclopentyl-2-acetamido-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**319**).

A 20 ml vial equipped with an egg shaped stir bar was charged with ethyl 6-cyano-6-cyclohexyl-2-acetamido-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**318**) (409 mg, 1.09 mmol, 1 equiv.), ceric sulfate (3.14 g, 9.46 mmol, 8.64 equiv.), glacial acetic acid (3.61 ml, 0.303 M) and water (3.61 ml, 0.303 M). The vial was sealed with a lid with a pressure relief septum and sonicated for 15 minutes to form a fine yellow suspension. The reaction was stirred vigorously at room temperature for 18 hours. The reaction mixture was diluted with water (10 ml) and ethyl acetate (10 ml). The aqueous phase was extracted with ethyl acetate (3x10 ml) and the organic fractions were combined and consecutively washed with 1N NaOH (10 ml), water (10ml) and brine (10 ml). The organic phase was dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound (352 mg, 0.91 mmol, 83% yield). LC-MS: Calculated 388.5, found (M+H) 389.1, retention time 0.44 min.

Step 6 Ethyl 2-amino-6-cyano-6-cyclohexyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**320**).

A 20 ml vial equipped with a stir bar was charged with ethyl 6-cyano-6-cyclohexyl-2-acetamido-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**319**) (352 mg, 510 µmol, 1 equiv.) and toluene (1.48, 0.61 M). Pyrrolidine (965 mg, 13.6 mmol, 15 equiv.) was added in a single portion with a syringe. The vial was sealed with a lid with a pressure relief septum and the reaction was stirred at 80 °C for 2 hours. The reaction was cooled to room temperature, diluted with ethyl acetate (30 ml) and washed with 30 ml brine. The organic fraction was dried over sodium sulfate, filtered and the volatiles were removed *in vacuo*. The crude material was purified by automated column chromatography using silica gel and a gradient of 0 – 100% ethyl acetate in hexane to yield the title compound (194 mg, 559 µmol, 62% yield). ¹H NMR (400 MHz, CDCl₃): δ 4.31 (qq, *J* = 7.2, 3.7 Hz, 2H), 3.25 – 2.94 (m, 2H), 2.46 – 2.27 (m, 2H), 2.11 – 1.98 (m, 1H), 1.88 – 1.58 (m, 4H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.33 – 1.04 (m, 5H).

Step 7 2-amino-6-cyano-6-cyclohexyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (321).

A 250 ml round bottom flask equipped with a stir bar was charged with ethyl 2-amino-6-cyano-6-cyclohexyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**320**) (194 mg, 560 μ mol, 1 equiv.), lithium hydroxide monohydrate (117 mg, 2.8 mmol, 5 equiv.), water (68 ml, 8.27 mM) and methanol (68 ml, 8.27 mM). A reflux condenser was affixed to the flask and the reaction was stirred at 80 °C for 18 hours. The reaction was cooled to room temperature, acidified by addition of 6 M HCl solution and extracted to ethyl acetate. The organic fractions were combined, dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound (150 mg, 471 μ mol, 84% yield). ^1H NMR (400 MHz, DMSO-*d*6): δ 12.8 (br. s, 1H), 8.46 (s, 2H), 3.10 – 2.94 (m, 2H), 2.46 – 2.27 (m, 2H), 1.99 – 1.90 (m, 1H), 1.83 – 1.55 (m, 6H), 1.34 – 1.03 (m, 6H). LC-MS: Calculated 318.4, found (M+H) 319.3, retention time 0.26 min.

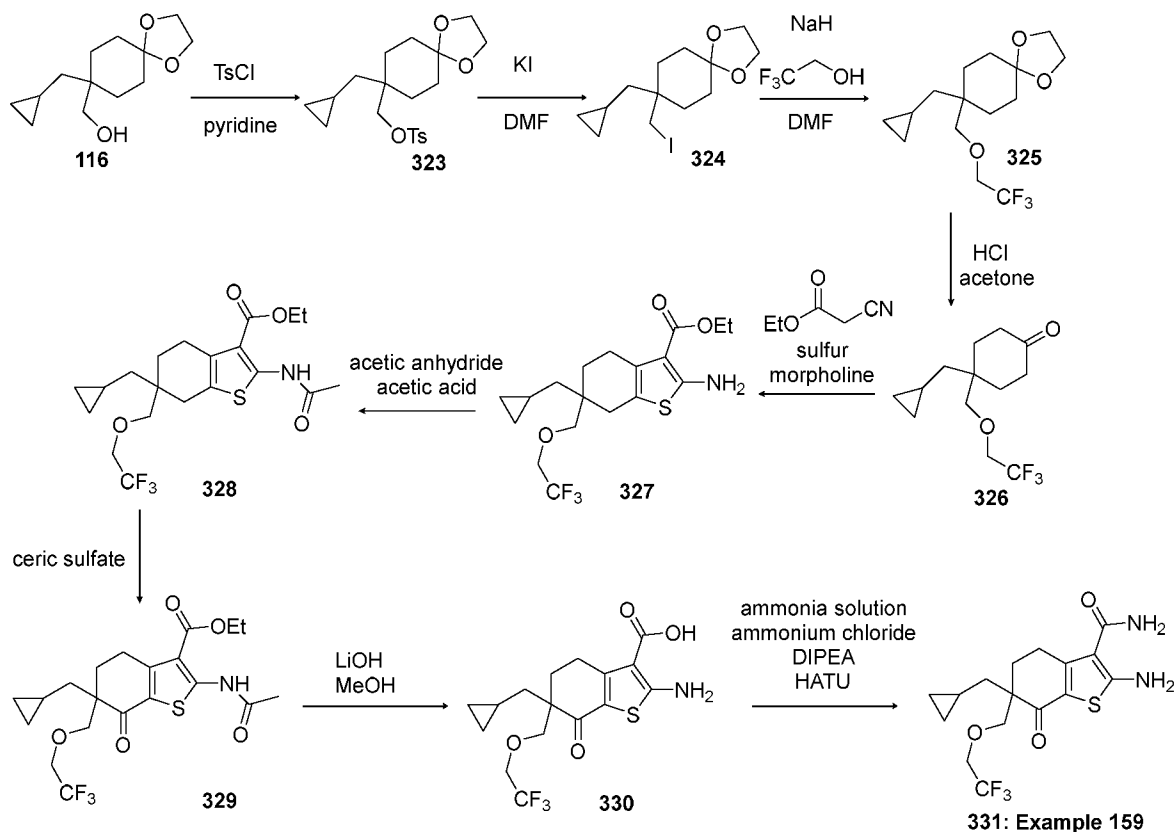
Step 8 2-amino-6-cyano-6-cyclohexyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (322).

A 20 ml vial equipped with a stir bar was charged with 2-amino-6-cyano-6-cyclohexyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (**321**) (150 mg, 0.47 mmol, 1 equiv.), DIPEA (122 mg, 0.94 mmol, 2 equiv.), ammonium chloride (503 mg, 9.41 mmol, 20 equiv.), HATU (166 mg, 0.706 mmol, 1.5 equiv.) and DMF (5.2 ml, 90.5 mM). The vial was sealed with a pressure relief septum and the reaction was sparged with argon for 5 min. Ammonia 0.4 M in THF solution (23.5 ml, 9.41 mmol, 20 equiv.) was added dropwise via syringe while stirring resulting in the formation of an orange precipitate and the reaction was subsequently stirred at room temperature overnight. The reaction was quenched by addition of 10 ml of saturated ammonium chloride solution and extracted into ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered and the volatiles were removed *in vacuo*. The product was purified by preparative HPLC and subsequently dried by lyophilization to yield the title compound as a white solid (84 mg, 0.265 mmol, 56% yield). ^1H NMR (500 MHz, DMSO-*d*6): δ 8.22 (s, 2H), 7.07 (s, 2H), 3.14 (ddd, J = 18.0, 9.1, 4.6 Hz, 1H), 2.92 (dt, J = 18.0, 5.0 Hz, 1H), 2.40 (dt, J = 13.7, 4.8 Hz, 1H), 2.30 (ddd, J = 13.8, 9.1, 4.8 Hz, 1H), 1.96 (d, J = 11.8 Hz, 1H), 1.77 (d, J = 14.2 Hz, 3H), 1.64 (d, J = 12.3 Hz, 2H), 1.36 – 1.01 (m, 5H). LC-MS: Calculated 317.4, found (M+H) 318.2 m/z, retention time 0.28 min.

Example 159

2-amino-6-(cyclopropylmethyl)-7-oxo-6-[(2,2,2-trifluoroethoxy)methyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (331)

Scheme 79



Compound **331** (example 159) was synthesized starting from intermediate **116** which was prepared according to scheme 22.

Step 1 [8-(cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl]methyl 4-methylbenzene-1-sulfonate (323).

A 50 ml round bottom flask equipped with a stirbar was charged with [8-(cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl]methanol (**116**) (600 mg, 2.65 mmol, 1 equiv.) and pyridine (11.5 ml). 4-methylbenzene-1-sulfonyl chloride was added and the reaction was stirred at room temperature for 22 hours. Water (10 mL) and the product was extracted to ethyl acetate (2x 10 mL). The organic layers were combined, washed with water and brine. The organic layer was dried over sodium sulfate, filtered and the volatiles were removed *in vacuo*. The material was purified by silica gel column chromatography (0-40% EtOAc in hexane) to yield the title compound as a colourless oil (617 mg, 1.62 mmol, 61% yield). ¹H NMR (CDCl₃, 400 MHz): δ 7.82 – 7.68 (m, 2H), 7.37 – 7.26 (m, 2H), 3.91 (s, 2H), 3.87 (s, 4H), 2.42 (s, 3H), 1.54 – 1.42 (m, 8H), 1.27 (d, *J* = 6.8 Hz, 2H), 0.48 – 0.40 (m, 1H), 0.35 – 0.30 (m, 2H), -0.02 – -0.06 (m, 2H).

Step 2 8-(cyclopropylmethyl)-8-(iodomethyl)-1,4-dioxaspiro[4.5]decane (324).

A 50 ml pear shaped flask equipped with a stirbar was charged with [8-(cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl]methyl 4-methylbenzene-1-sulfonate (**323**) (424 mg, 1.11 mmol, 1 equiv.) DMF (2.78 ml) and potassium iodide (924 mg, 5.57 mmol, 5 equiv.). A reflux condenser was affixed to the flask and the reaction was stirred at 100 °C for 18 hours.

The reaction was cooled to room temperature, filtered and the filtrate was diluted with ethyl acetate. The organic layer was washed with brine (5x10 ml), dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound (289 mg, 0.861 mmol, 77.3% yield). LC-MS: Calculated 336.2, found (M+H) 337.3 m/z, retention time 0.75 min.

5 Step 3 8-(cyclopropylmethyl)-8-[(2,2,2-trifluoroethoxy)methyl]-1,4-dioxaspiro[4.5]decane (325).

A dry 2 necked round bottom flask equipped with a stirbar was charged with sodium hydride 60 wt% (71.4 mg, 1.78 mmol, 3 equiv.) and evacuated and refilled with dinitrogen gas. Anhydrous DMF (1.13 ml, 0.526 M) was added and the flask was cooled to 0 °C with an icebath. Degassed trifluoroethanol (179 mg, 1.78 mmol, 3 equiv.) was added dropwise via syringe. The reaction was stirred at room temperature for 30 min. A degassed solution of 8-(cyclopropylmethyl)-8-(iodomethyl)-1,4-dioxaspiro[4.5]decane (324) (200 mg, 0.595 mmol, 1 equiv.) in degassed DMF (0.2 ml) was added dropwise via syringe. A reflux condenser was affixed to the flask and the reaction was heated to 100 °C for 18 hours under positive dinitrogen atmosphere. The reaction was cooled to 0 °C with an icebath and water (5 ml) was slowly added via syringe. The product was extracted to ethyl acetate (3x10 ml), washed with brine, dried with sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound (173 mg, 0.561 mmol, 94% yield). ¹H NMR (CDCl₃, 400 MHz): δ 3.94 (s, 4H), 3.79 (q, *J* = 8.8 Hz, 2H), 3.52 (s, 2H), 1.70 – 1.52 (m, 8H), 1.32 (d, *J* = 6.8 Hz, 2H), 0.64 – 0.56 (m, 1H), 0.49 – 0.35 (m, 2H), 0.11 – -0.04 (m, 2H).

20 Step 4 4-(cyclopropylmethyl)-4-[(2,2,2-trifluoroethoxy)methyl]cyclohexan-1-one (326).

A 50 ml round bottom flask equipped with a stirbar was charged with 8-(cyclopropylmethyl)-8-[(2,2,2-trifluoroethoxy)methyl]-1,4-dioxaspiro[4.5]decane (325) (248 mg, 0.804 mmol, 1 equiv.) and acetone (4.02 ml, 0.2 M). Aqueous HCl (12 M, 670 ul, 10 equiv.) was added via syringe and the reaction was stirred at room temperature for 7.5 hours. Saturated sodium bicarbonate solution was added until pH 7 was recorded. The product was extracted with ethyl acetate (3x10 ml), washed with brine, dried over sodium sulfate and the volatiles were removed *in vacuo* to yield the title compound (192 mg, 0.726 mmol, 90% yield). ¹H NMR (500 MHz, CDCl₃) δ 3.84 (q, *J* = 8.7 Hz, 2H), 3.63 (s, 2H), 2.35 (t, *J* = 6.9 Hz, 4H), 1.91 – 1.74 (m, 4H), 1.45 (d, *J* = 6.8 Hz, 2H), 0.68 – 0.60 (m, 1H), 0.52 – 0.46 (m, 2H), 0.10 – 0.06 (m, 2H).

30 Step 5 ethyl 2-amino-6-(cyclopropylmethyl)-6-[(2,2,2-trifluoroethoxy)methyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (327).

To a 2 dram vial equipped with a stirbar was added 4-(cyclopropylmethyl)-4-[(2,2,2-trifluoroethoxy)methyl]cyclohexan-1-one (326) (182 mg, 0.689 mmol, 1 equiv.), ethyl 2-cyanoacetate (73.3 ul, 0.689 mmol, 1 equiv.), elemental sulfur (24.4 mg, 0.689 mmol, 1 equiv.), morpholine (65.3 ul, 0.758 mmol, 1.1 equiv.) and ethanol (1.1 ml, 0.627 M). The vial was sealed with a pressure relief cap and heated to 60 °C while stirring for 18 hours. The vial was cooled to room temperature and the mixture was filtered. The filtrate was collected and the solvent was

removed *in vacuo* to yield the title compound as an orange oil (231 mg, 0.591 mmol, 86% yield). LC-MS: Calculated 391.4, found (M+H) 392 m/z, retention time 1.19 min.

Step 6 ethyl 6-(cyclopropylmethyl)-2-acetamido-6-[(2,2,2-trifluoroethoxy)methyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (328).

5 A 2 dram vial equipped with a stir bar was charged with ethyl 2-amino-6-(cyclopropylmethyl)-6-[(2,2,2-trifluoroethoxy)methyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**327**) (231 mg, 0.59 mmol, 1 equiv.) and acetic acid (3.39 ml, 174 mM). The vial was stirred at room temperature and acetic anhydride (68.9 μ l, 0.708 mmol, 1.2 equiv.) was added in a single portion. The reaction was stirred at 60 °C for 2 hours and cooled to room temperature.

10 Acetic acid was removed by rotary evaporation and the residue was dissolved in 5 ml DCM, washed with saturated sodium bicarbonate solution (5 ml), water (5 ml) and brine (5 ml). The organic fraction was dried with sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound as an orange residue (209 mg, 0.483 mmol, 82% yield). LC-MS: Calculated 433.5, found (M+H) 434.3, retention time 1.42.

15 Step 7 ethyl 6-(cyclopropylmethyl)-2-acetamido-7-oxo-6-[(2,2,2-trifluoroethoxy)methyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (329).

 A 2 dram vial equipped with an egg shaped stir bar was charged with ethyl 6-(cyclopropylmethyl)-2-acetamido-6-[(2,2,2-trifluoroethoxy)methyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**328**) (209 mg, 0.483 mmol, 1 equiv.), ceric sulfate (1.38 g, 4.17 mmol, 8.64 equiv.), acetic acid (1.59 ml, 0.303 M) and deionized water (1.59 ml, 0.303 M). The mixture was sonicated to form a yellow slurry. The reaction was stirred vigorously at room temperature for 18 hours. The mixture was diluted with deionized water (2 ml) and ethyl acetate (2 ml). The aqueous phase was extracted with ethyl acetate (3x 5 ml). The organic fractions were combined and washed consecutively with 1N NaOH (5 ml), water (5 ml) and brine (5 ml). The

20 organic fraction was dried with sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound as a pale yellow oil (176 mg, 0.394 mmol, 82% yield). LC-MS: Calculated 447.5, found (M+H) 448.2, retention time 0.80.

Step 8 2-amino-6-(cyclopropylmethyl)-7-oxo-6-[(2,2,2-trifluoroethoxy)methyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (330).

30 A 250 ml round bottom flask equipped with a stir bar was charged with ethyl 6-(cyclopropylmethyl)-2-acetamido-7-oxo-6-[(2,2,2-trifluoroethoxy)methyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**329**) (166 mg, 0.371 mmol, 1 equiv.), deionized water (44.9 ml, 8.27 mM), and methanol (44.9 ml, 8.27 mM). Lithium hydroxide monohydrate (77.8 mg, 1.85 mmol, 5 equiv.) was added in a single portion. A reflux condenser was affixed to the flask and the

35 reaction was heated at 80 °C for 18 hours. The reaction was cooled to room temperature and methanol was removed *in vacuo*. The mixture was acidified by addition of 1 M HCl solution and extracted to ethyl acetate (3 x 50 ml). The organic fractions were combined, dried with sodium

sulfate and filtered. The volatiles were removed from the filtrate *in vacuo* to yield the title compound as a yellow oil (114 mg, 0.302 mmol, 82% yield). LC-MS: Calculated 377.4, found 378.2 (M+H), retention time 0.28.

Step 9 2-amino-6-(cyclopropylmethyl)-7-oxo-6-[(2,2,2-trifluoroethoxy)methyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (331).

To a 25 ml pear shaped round bottom flask equipped with a stir bar was added 2-amino-6-(cyclopropylmethyl)-7-oxo-6-[(2,2,2-trifluoroethoxy)methyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (**330**) (60 mg, 0.159 mmol, 1 equiv.), DMF (1.76 ml, 90.5 mM), HATU (90.7 mg, 0.238 mmol, 1.5 equiv.), DIPEA (55 μ l, 0.318 mmol, 2 equiv.) and ammonium chloride (170 mg, 3.17 mmol, 20 equiv.). The flask was sealed with a septum and sparged with a balloon of argon for 10 mins. Ammonium in THF (0.4 M solution, 8 ml, 3.18 mmol, 20 equiv.) was added to the reaction by syringe resulting the formation of a beige precipitate. The reaction was stirred at room temperature for 18 hours under argon atmosphere. The reaction was quenched by addition of 10 ml of saturated ammonium chloride solution and extracted to ethyl acetate (3x10 ml). The ethyl acetate fractions were combined and washed with brine (7 x 10 ml) to remove DMF, dried with sodium sulfate, filtered and the volatiles were removed *in vacuo*. The crude material was dissolved in 1 ml DMSO and purified with a Prep C18 column 20 x 150 mm 100 Å 5 μ m (gradient 0 – 100% acetonitrile in water) and dried by lyophilization to yield the title compound as a white solid (3.4 mg, 9.03 μ mol, 6% yield). ^1H NMR (CDCl_3): δ 7.03 (br s, 2H), 5.48 (s, 2H), 3.99 - 3.95 (m, 1H), 3.89 - 3.77 (m, 3H), 3.05 - 2.90 (m, 2H), 2.46 - 2.39 (m, 1H), 2.29 - 2.22 (m, 1H), 1.65 - 1.59 (m, 1H), 1.53 - 1.47 (1H), 0.70 - 0.63 (m, 1H), 0.50 - 0.42 (m, 2H), 0.08 - -0.06 (m, 2H). ^{19}F $\{^1\text{H}\}$ NMR (CDCl_3): δ -74.1 (s). LC-MS: Calculated 376.4, found m/z 377.2 (M+H), retention time 0.86 min.

Examples 160-169

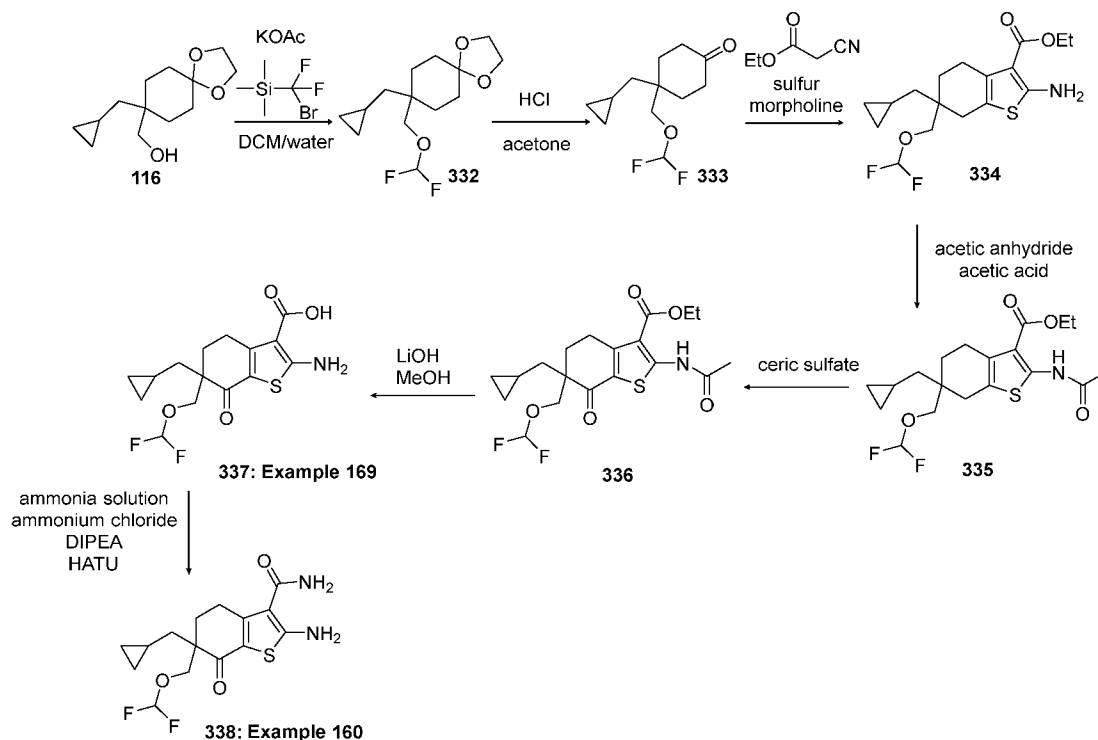
Example 160

2-amino-6-(cyclopropylmethyl)-6-[(difluoromethoxy)methyl]-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (338)

Example 169

2-amino-6-(cyclopropylmethyl)-6-[(difluoromethoxy)methyl]-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (337)

Scheme 80



Compound **338** (example 160) was synthesized starting from intermediate **116** which was prepared according to scheme 22.

Step 1 8-(cyclopropylmethyl)-8-[(difluoromethoxy)methyl]-1,4-dioxaspiro[4.5]decane (**332**).

- 5 To a 10 ml vial was added [8-(cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl]methanol (**116**) (602 mg, 2.66 mmol, 1 equiv.), KOAc (1.57 g, 16 mmol, 6 equiv.), DCM (1.6 ml, 1.67 M) and water (1.6 ml, 1.67 M). The reaction was stirred at room temperature and (bromodifluoromethyl)trimethylsilane (1.24 ml, 7.98 mmol, 3 equiv.) was added in a single portion by syringe. The reaction was stirred at room temperature for 18 hours. The reaction was diluted
- 10 with DCM (10 ml), washed with brine, dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound as a clear oil (624 mg, 2.26 mmol, 85% yield). ¹H NMR (400 MHz, CDCl₃): δ 6.20 (t, *J* = 76 Hz, 1H), 3.93 (s, 4H), 3.78 (s, 2H), 1.64 - 1.57 (m, 8H), 1.32 (d, *J* = 6.8 Hz, 2H), 0.65 - 0.56 (m, 1H), 0.46 - 0.40 (m, 2H), 0.09 - -0.01 (m, 2H).

Step 2 4-(cyclopropylmethyl)-4-[(difluoromethoxy)methyl]cyclohexan-1-one (**333**).

- 15 A 50 ml pear shaped flask equipped with a stir bar was charged with 8-(cyclopropylmethyl)-8-[(difluoromethoxy)methyl]-1,4-dioxaspiro[4.5]decane (**332**) (624 mg, 2.26 mmol, 1 equiv.) and acetone (11.3 ml, 0.2 M). HCl (12 M, 1.88 ml, 10 equiv.) was added in a single portion with a syringe. The reaction was stirred at room temperature for 5 hours, then quenched with sat. sodium bicarb solution until pH 7 and extracted to ethyl acetate (3 x 15 ml).
- 20 The organic fractions were combined, washed with brine, dried over sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound as a yellow oil (476 mg, 66% yield). ¹H NMR (400 MHz, CDCl₃): δ 6.24 (t, *J* = 72 Hz, 1H), 3.93 (s, 2H), 2.36 (t, *J* = 12 Hz, 4H),

1.84 (t, $J = 7$ Hz, 4H), 1.46 (d, $J = 8$ Hz, 2H), 0.70 - 0.59 (m, 1H), 0.53 - 0.48 (m, 2H), 0.13 - 0.068 (m, 2H).

Step 3 ethyl 2-amino-6-(cyclopropylmethyl)-6-[(difluoromethoxy)methyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (334).

A 1 dram vial equipped with a stir bar was charged with 4-(cyclopropylmethyl)-4-[(difluoromethoxy)methyl]cyclohexan-1-one (**333**) (476 mg, 1.44 mmol, 1 equiv.), ethyl 2-cyanoacetate (218 μ l, 2.05 mmol, 1 equiv.), morpholine (194 μ l, 2.25 mmol, 1.1 equiv.), sulfur (72.4 mg, 2.05 mmol, 1 equiv.) and ethanol (3.27 ml, 0.627 M). The vial was sealed with a pressure relief cap and heated at 60 °C for 18 hours, resulting in the formation of an orange solution. The volatiles were removed *in vacuo* and the crude material was purified by automated column chromatography with silica gel and 0 - 40% EA in hexane as the eluent to yield the title compound an orange oil (150.7 mg, 0.42 mmol, 21% yield). ^1H NMR (400 MHz, CDCl_3): δ 6.17 (t, $J = 75.3$ Hz, 1H), 4.24 (q, $J = 7.1$ Hz, 2H), 3.78 (t, $J = 8.0$ Hz, 2H), 2.76 - 2.61 (m, 2H), 2.45 - 2.41 (m, 2H), 1.74 - 1.59 (m, 2H), 1.47 - 1.41 (1H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.24 - 1.17 (m, 1H), 0.67 - 0.57 (m, 1H), 0.45 - 0.39 (m, 2H), 0.03 - -0.01 (m, 2H).

Step 4 ethyl 6-(cyclopropylmethyl)-6-[(difluoromethoxy)methyl]-2-acetamido-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (335).

A 2 dram vial equipped with a stir bar was charged with ethyl 2-amino-6-(cyclopropylmethyl)-6-[(difluoromethoxy)methyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**334**) (151 mg, 0.42 mmol, 1 equiv.) and acetic acid (2.4 ml, 174 mM). The vial was stirred at room temperature and acetic anhydride (48.7 μ l, 0.501 mmol, 1.2 equiv.) was added in a single portion. The reaction was stirred at 60 °C for 1.5 hours and cooled to room temperature resulting in a pink solution. Acetic acid was removed *in vacuo* and the residue was dissolved in 5 ml DCM, washed with saturated sodium bicarbonate solution (5 ml), water (5 ml) and brine (5 ml). The organic fraction was dried with sodium sulfate, filtered and the volatiles were removed *in vacuo* to yield the title compound as a dark red oil (138 mg, 0.344 mmol, 82% yield). ^1H NMR (400 MHz, CDCl_3): δ 11.25 (s, 1H), 6.21 (t, $J = 75.2$ Hz, 1H), 4.33 (q, $J = 8$ Hz, 2H), 3.84 - 3.77 (m, 2H), 2.81 - 2.72 (m, 2H), 2.67 - 2.52 (m, 2H), 2.25 (s, 3H), 1.84 - 1.65 (m, 2H), 1.52 - 1.44 (m, 1H), 1.39 (t, $J = 8$ Hz, 3H), 1.31 - 1.19 (m, 2H), 0.73 - 0.61 (m, 1H), 0.52 - 0.41 (m, 2H), 0.07 - 0.00 (m, 2H).

Step 5 ethyl 6-(cyclopropylmethyl)-6-[(difluoromethoxy)methyl]-2-acetamido-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (336).

A 2 dram vial equipped with an egg shaped stir bar was charged with ethyl 6-(cyclopropylmethyl)-2-acetamido-6-[(2,2,2-trifluoroethoxy)methyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**335**) (69 mg, 0.172 mmol, 1 equiv.), ceric sulfate (493 mg, 1.48 mmol, 8.64 equiv.), acetic acid (567 μ l, 0.303 M) and deionized water (567 ml, 0.303 M). The mixture was sonicated to form a yellow slurry. The reaction was stirred vigorously at room

temperature for 18 hours. The mixture was diluted with deionized water (2 ml) and ethyl acetate (2 ml). The aqueous phase was extracted with ethyl acetate (3x 5 ml). The organic fractions were combined and washed consecutively with 1N NaOH (5 ml), water (5 ml) and brine (5 ml). The organic fraction was dried with sodium sulfate, filtered and the volatiles were removed in vacuo to yield the title compound as a pale yellow oil (60 mg, 0.144 mmol, 84% yield). LC-MS: retention time 0.28, 416.2 m/z (M+H).

Step 6 2-amino-6-(cyclopropylmethyl)-6-[(difluoromethoxy)methyl]-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (337).

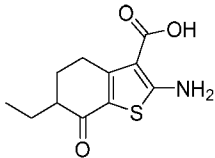
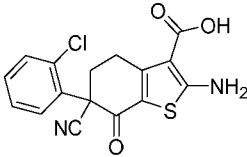
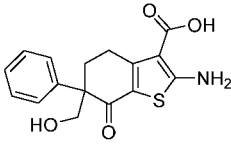
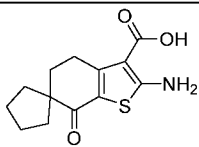
A 20 ml vial equipped with a stir bar was charged with ethyl 6-(cyclopropylmethyl)-6-[(difluoromethoxy)methyl]-2-acetamido-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (336) (60 mg, 0.144 mmol, 1 equiv.), deionized water (17.5 ml, 8.27 mM), and methanol (17.5 ml, 8.27 mM). Lithium hydroxide monohydrate (30.3 mg, 0.722 mmol, 5 equiv.) was added in a single portion. The vial was sealed with a pressure relief cap and the reaction was heated at 80 °C for 18 hours. The reaction was cooled to room temperature and methanol was removed by rotary evaporation. The mixture was acidified by addition of 1 M HCl solution and extracted to ethyl acetate (3 x 50 ml). The organic fractions were combined, dried with sodium sulfate and filtered. The volatiles were removed from the filtrate *in vacuo* to yield the title compound as a yellow oil (56 mg, 0.162 mmol). The crude material was dissolved in 1 ml DMSO and purified with a Prep C18 column 20 x 150 mm 100 Å 5 µm (gradient 0 – 100% acetonitrile in water) and dried by lyophilization to yield the title compound as a white solid. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 12.54 (br. s, 1H), 8.27 (s, 2H), 6.64 (t, *J* = 76.4 Hz, 1H), 4.19 (d, *J* = 9.4 Hz, 1H), 3.88 (d, *J* = 9.4 Hz, 1H), 3.19 – 3.08 (m, 1H), 2.95 – 2.79 (m, 1H), 2.23 – 2.00 (m, 2H), 1.55 – 1.38 (m, 2H), 0.68 – 0.56 (m, 1H), 0.45 – 0.31 (m, 2H), 0.07 - -0.11 (m, 2H). LC-MS: Calculated 345.36, found 346.1 (M+H), retention time 0.27.

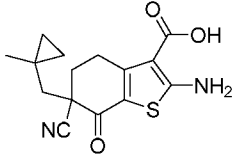
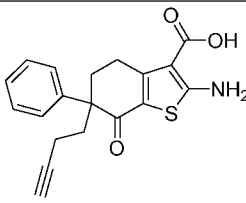
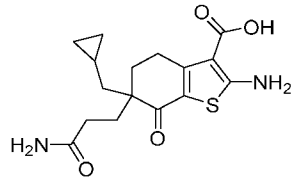
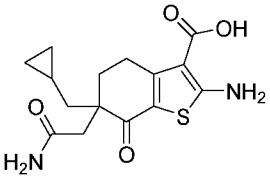
Step 7 2-amino-6-(cyclopropylmethyl)-6-[(difluoromethoxy)methyl]-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (338).

To a 25 ml pear shaped round bottom flask equipped with a stir bar was added 2-amino-6-(cyclopropylmethyl)-6-[(difluoromethoxy)methyl]-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (337) (30 mg, 0.0869 mmol, 1 equiv.), DMF (960 µl, 90.5 mM), HATU (49.5 mg, 0.130 mmol, 1.5 equiv.), DIPEA (22.5 mg, 0.174 mmol, 2 equiv.) and ammonium chloride (92.9 mg, 1.74 mmol, 20 equiv.). The flask was sealed with a septum and sparged with a balloon of argon for 10 mins. Ammonium in THF (0.4 M solution, 4.34 ml, 1.74 mmol, 20 equiv.) was added to the reaction by syringe resulting the formation of a beige precipitate. The reaction was stirred at room temperature for 18 hours with an argon balloon. The reaction was quenched by addition of 10 ml of saturated NH₄Cl solution and extracted to ethyl acetate (3x10 ml). The ethyl acetate fractions were combined and washed with brine (7 x 10 ml) to remove DMF, dried with sodium sulfate, filtered and rotovapped to yield the crude material as a brown residue. The crude material

was dissolved in 1 ml DMSO and purified with a Prep C18 column 20 x 150 mm 100 Å 5 µm (gradient 0 – 100% acetonitrile in water) and dried by lyophilization to yield the title compound as a pale yellow solid (2.6 mg, 7.55 µmol, 9% yield). ¹H NMR (DMSO-*d*₆, 400 MHz): δ 8.03 (s, 2H), 6.64 (t, *J* = 80 Hz, 1H), 4.20 (d, *J* = 10 Hz, 1H), 3.88 (d, *J* = 10 Hz, 1H), 3.29 (s, 2H), 3.12 - 2.86 (m, 2H), 2.22 - 2.00 (m, 2H), 1.53 - 1.39 (m, 2H), 0.69 - 0.57 (m, 1H), 0.47 - 0.33 (m, 2H), 0.11 - -0.12 (m, 2H). ¹⁹F NMR (CDCl₃, 400 MHz): δ -84.06 (dd, *J* = 81.2 Hz, *J* = 24.0 Hz, 2F). LC-MS: Calculate 344.4, found 345.2 (M+H), retention time 0.28 min.

Table 6. Characterization of compounds **8**, **14**, **108**, **154**, **173**, **178**, **190**, **197** (examples 161-168).

Ex. No.	Compound No.	Scheme #, Step #	Structure	Characterization
161	8	Scheme 2, Step 8	 2-Amino-6-ethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	LC-MS: rt = 1.23 min, MS: 239.1 (calcd), 240.1 (M+H ⁺ , found).
162	14	Scheme 3, Step 4	 2-Amino-6-(2-chlorophenyl)-6-cyano-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): ¹ H-NMR (CD ₃ OD) δ: (ppm)) 7.70-7.65 (m, 1H), 7.48-7.44 (m, 1H), 7.41-7.38 (m, 2H), 3.51-3.43 (m, 1H), 3.24-3.11 (m, 2H), 2.44-2.33 (m, 1H). LC-MS: rt = 1.33 min, MS: 346.0 (calcd), 347.0 (M+H ⁺ , found).
163	108	Scheme 19, Step 6	 2-Amino-6-(hydroxymethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 7.34-7.28 (m, 4H), 7.26-7.20 (m, 1H), 4.10 (d, <i>J</i> = 11.01 Hz, 1H), 3.54 (d, <i>J</i> = 11.03 Hz, 1H), 3.26-3.23 (m, 1H), 2.64-2.42 (m, 3H). LC-MS: rt = 1.03 min, MS: 317.1 (calcd), 318.0 (M+H ⁺ , found).
164	154	Scheme 29, Step 3	 2-Amino-7-oxo-4,7-dihydro-5H-spiro[benzo[b]thiophene-6,1'-cyclopentane]-3-carboxylic acid	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 3.07 (t, <i>J</i> = 6.06 Hz, 2H), 2.02-1.93 (m, 4H), 1.79-1.64 (m, 4H), 1.61-1.52 (m, 2H).

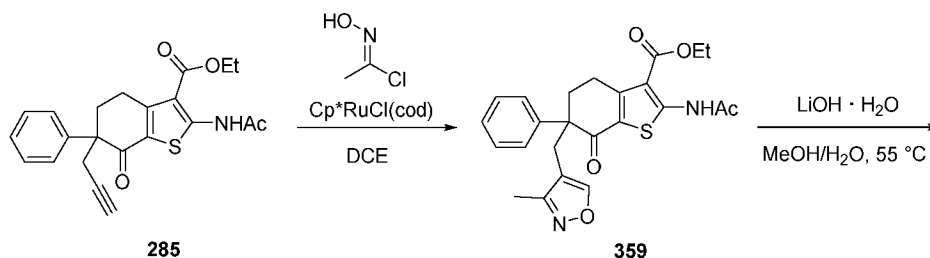
			cyclopentane]-3-carboxylic acid	LC-MS: rt = 1.38 min, MS: 265.1 (calcd), 266.1 (M+H ⁺ , found).
165	173	Scheme 34	 2-Amino-6-cyano-6-((1-methylcyclopropyl)methyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 3.21 (ddd, <i>J</i> = 9.22, 6.95, 5.18 Hz, 2H), 2.59-2.51 (m, 1H), 2.45-2.36 (m, 1H), 1.95 (s, 1H), 1.95 (s, 1H), 1.18 (s, 3H), 0.45-0.38 (m, 1H), 0.37-0.30 (m, 3H). LC-MS: rt = 1.26 min, MS: 304.1 (calcd), 305.0 (M+H ⁺ , found).
166	178	Scheme 36	 2-Amino-6-(but-3-yn-1-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 7.34-7.18 (m, 5H), 3.25-3.16 (m, 1H), 2.61-2.54 (m, 1H), 2.53-2.43 (m, 1H), 2.34-2.00 (m, 6H). LC-MS: rt = 1.39 min, MS: 339.1 (calcd), 340.0 (M+H ⁺ , found).
167	190	Scheme 40, Step 6a	 2-Amino-6-(3-amino-3-oxopropyl)-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	¹ H NMR: 400 MHz, DMSO-d ₆ , δ (ppm): 8.29 (s, 2H), 3.09-3.00 (m, 1H), 2.94-2.82 (m, 1H), 2.42-2.23 (m, 2H), 2.05-1.87 (m, 3H), 1.82-1.71 (m, 1H), 1.51 (dd, <i>J</i> = 14.19, 6.28 Hz, 1H), 1.27 (dd, <i>J</i> = 14.18, 7.00 Hz, 1H), 0.60-0.51 (m, 1H), 0.38-0.32 (m, 2H), -0.00- -0.11 (m, 2H). LC-MS: rt = 0.99 min, MS: 336.1 (calcd), 337.1 (M+H ⁺ , found).
168	197	Scheme 43	 2-Amino-6-(2-amino-2-oxoethyl)-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	¹ H NMR: 400 MHz, DMSO-d ₆ , δ (ppm): 8.27-8.14 (m, 2H), 7.14 (s, 1H), 6.65 (s, 1H), 3.11-3.01 (m, 1H), 2.86-2.75 (m, 1H), 2.51 (d, <i>J</i> = 14.77 Hz, 1H), 2.30-2.24 (m, 1H), 2.21 (d, <i>J</i> = 14.84 Hz, 1H), 2.02-1.97 (m, 1H), 1.62 (dd, <i>J</i> = 14.07, 6.23 Hz, 1H), 1.27 (dd, <i>J</i> = 14.05, 7.10 Hz, 1H), 0.62-0.52 (m, 1H), 0.38-0.28 (m, 2H), 0.02- -

				0.06 (m, 1H), -0.08- -0.15 (m, 1H). LC-MS: rt = 0.95 min, MS: 322.1 (calcd), 323.2 (M+H ⁺ , found).

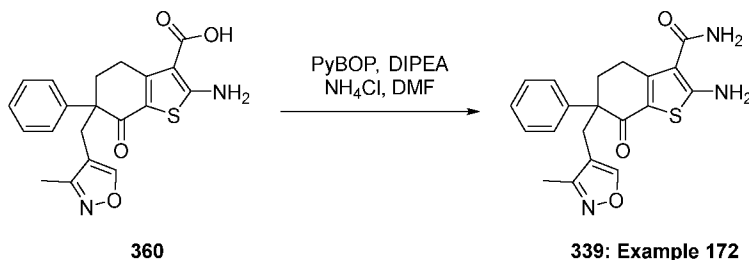
Example 172

2-Amino-6-((3-methylisoxazol-4-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (339)

Scheme 81



Scheme 72



Step 1. Ethyl 2-acetamido-6-((3-methylisoxazol-4-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (359)

A solution of *N*-hydroxyacetimidoyl chloride (236 mg, 379 μ mol) (*Angew. Chem. Int. Ed.* **2017**, 12586-12589.) in DCE (2.01 mL) was purged with argon for 2 minutes, then **285** (scheme 72) (150 mg, 379 μ mol) and chloro(1,5-cyclooctadiene) $\text{Cp}^*\text{Ru}(\text{II})$ (7.35 mg, 19.0 μ mol) were added, followed by triethylamine (66.4 μ L, 474 μ mol). The mixture was stirred at RT under argon for 16 hours. The mixture was then filtered, the solvent removed under reduced pressure and the residue was purified by flash column chromatography (eluent gradient from 5% to 80% of EA in hexane) to afford title compound **359** as a clear oil (102 mg, 59% yield). LC-MS: rt = 1.60 min, MS: 452.1 (calcd), 453.2 (M+H⁺, found).

Step 2. 2-Amino-6-((3-methylisoxazol-4-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (360)

To a suspension of **359** (102 mg, 225 μ mol) in MeOH (13.8 mL) was added a solution of lithium hydroxide monohydrate (64.6 mg, 1.54 mmol) in water (13.8 mL). The reaction mixture was

stirred at 55 °C for 48 hours, then allowed to cool to RT. The mixture was concentrated to remove most of the organic solvent. Then, the aqueous layer was acidified by slowly adding a 2 N aqueous solution of HCl and the product was extracted with EA. The organic layers were combined then washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 15% of MeOH in DCM) to afford title compound **360** (68.8 mg, 80% yield). LC-MS: rt = 1.33 min, MS: 382.1 (calcd), 383.2 (M+H⁺, found).

Step 3. 2-Amino-6-((3-methylisoxazol-4-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**339**)

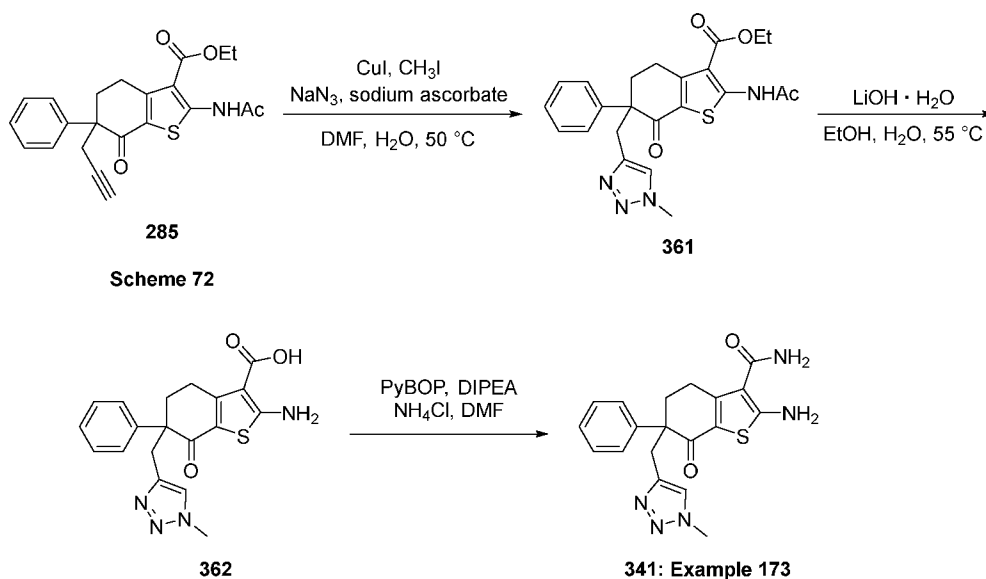
To a solution of **360** (68.8 mg, 183.0 μmol) in DMF (2.3 mL) were added PyBOP (141 mg, 270 μmol), *N,N*-diisopropylethylamine (125 μL, 720 μmol) and ammonium chloride (96.2 mg, 1.80 mmol). The resulting mixture was stirred at RT for 45 minutes. The crude mixture was directly purified by reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid), then by Semi-Prep HPLC-MS (eluent gradient from 40% to 100% of MeOH in 10 mM ammonium formate) to afford title compound **339** as an off-white solid (29.6 mg, 43% yield).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.18 (s, 1H), 8.06 (bs, 2H), 7.31-7.27 (m, 2H), 7.24-7.21 (m, 3H), 6.82 (bs, 2H), 2.89-2.75 (m, 3H), 2.69-2.61 (m, 1H), 2.57-2.50 (m, 1H), 2.12-2.03 (m, 1H), 1.76 (s, 3H). LC-MS: rt = 1.19 min, MS: 381.1 (calcd), 382.2 (M+H⁺, found).

Example 173

2-Amino-6-((1-methyl-1H-1,2,3-triazol-4-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (341**)**

Scheme 82



Step 1. Ethyl 2-acetamido-6-((1-methyl-1H-1,2,3-triazol-4-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**361**)

Sodium ascorbate (10.1 mg, 50.6 μ mol) and copper iodide (96.3 mg, 0.506 mmol) were added to a solution of **285** (scheme 72) (100 mg, 0.253 mmol) in DMF (2.8 mL) and water (2.8 mL). The flask was evacuated and backfilled with nitrogen. Then, iodomethane (127 μ L, 2.02 mmol) and sodium azide (132 mg, 2.02 mmol) were added and the reaction mixture was stirred at 50 °C for 20 hours. The mixture was then diluted with brine (10 mL) and extracted with EA (2 x 15 mL). Saturated sodium bicarbonate solution was added to the aqueous layer and the product was extracted with EA (3 x 15 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 15% to 100% of EA in hexane) to afford title compound **361** as a black oil (65.0 mg, 57% yield). LC-MS: rt = 1.36 min, MS: 452.2 (calcd), 453.4 (M+H⁺, found).

Step 2. 2-Amino-6-((1-methyl-1H-1,2,3-triazol-4-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**362**)

To a suspension of **361** (65.0 mg, 144 μ mol) in EtOH (8.8 mL) was added a solution of lithium hydroxide monohydrate (90.4 mg, 2.15 mmol) in water (8.8 mL). The reaction mixture was stirred at 55 °C for 20 hours, then allowed to cool to RT. The mixture was concentrated to remove most of the organic solvent. The aqueous layer was purified by reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **362** (31.0 mg, 56% yield). LC-MS: rt = 0.97 min, MS: 382.1 (calcd), 383.1 (M+H⁺, found).

Step 3. 2-Amino-6-((1-methyl-1H-1,2,3-triazol-4-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**341**)

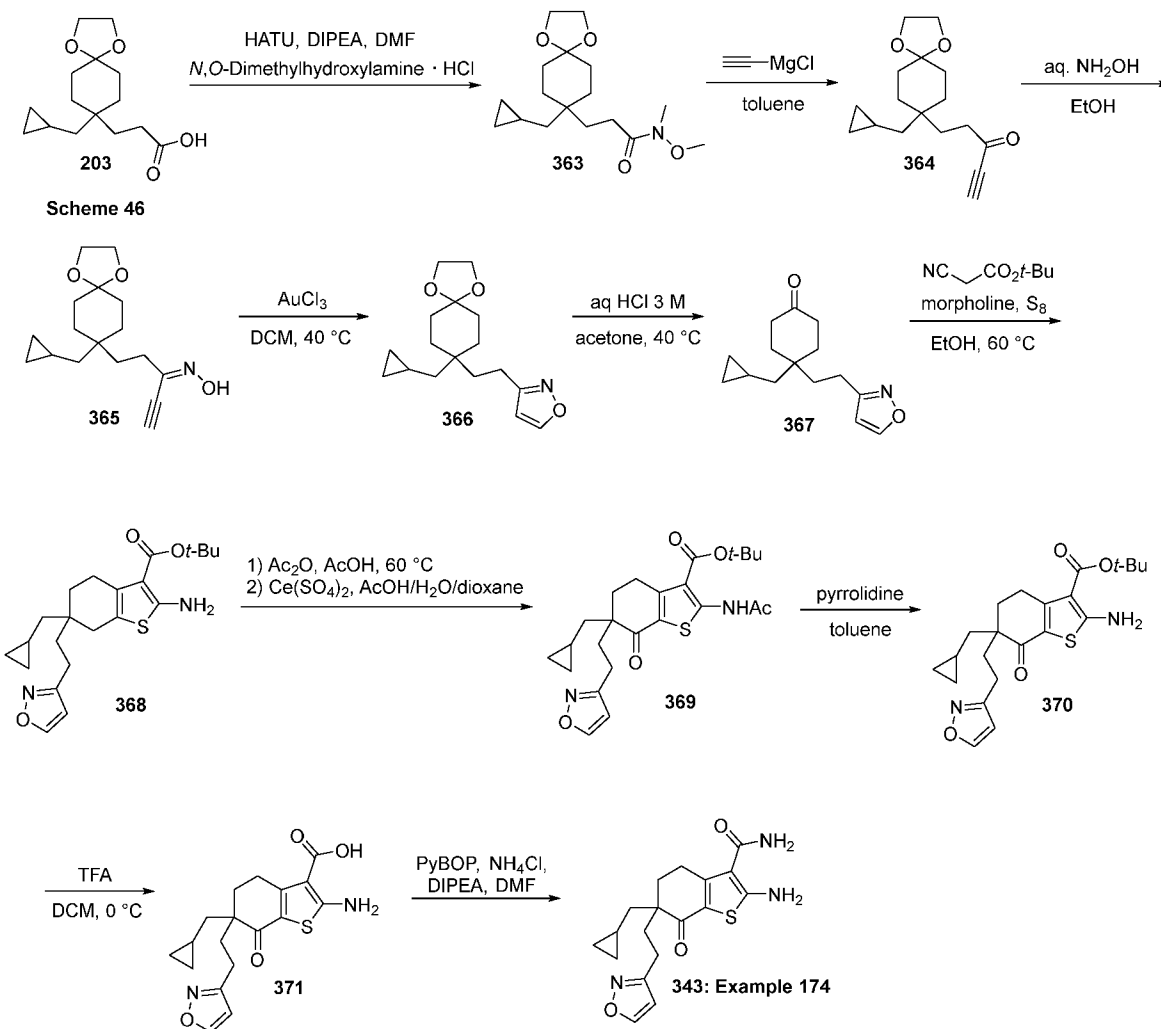
To a solution of **362** (31 mg, 81.1 μ mol) in DMF (0.7 mL) were added PyBOP (63.4 mg, 122 μ mol), *N,N*-diisopropylethylamine (56.5 μ L, 324 μ mol) and ammonium chloride (43.4 mg, 0.811 mmol). The resulting mixture was stirred at RT for 1 hour. The crude mixture was directly purified by reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH₃CN in H₂O with 10 mM ammonium bicarbonate aqueous solution) to afford title compound **341** as a beige solid (14.6 mg, 47% yield).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.04 (s, 2H), 7.36 (s, 1H), 7.29-7.26 (m, 4H), 7.23-7.18 (m, 1H), 6.81 (m, 1H), 3.89 (s, 3H), 3.24 (d, 1H, *J* = 14.2 Hz), 2.93 (d, 1H, *J* = 14.2 Hz), 2.82-2.76 (m, 1H), 2.65-2.49 (m, 2H), 2.13-2.05 (m, 1H). LC-MS: rt = 0.97 min, MS: 381.1 (calcd), 382.2 (M+H⁺, found).

Example 174

2-Amino-6-(cyclopropylmethyl)-6-(2-(isoxazol-3-yl)ethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (343**)**

Scheme 83



Step 1. 3-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)-N-methoxy-N-methylpropanamide (363)

Compound **203** (scheme 46) (1.19 g, 4.43 mmol) was dissolved in dry DMF (28 mL). *N,O*-Dimethylhydroxylamine hydrochloride (865 mg, 8.87 mmol), HATU (2.58 g, 6.65 mmol) and DIPEA (3.1 mL, 17.7 mmol) were added and the reaction mixture was stirred at RT for 20 hours. EA (40 mL) and brine (40 mL) were then added and the layers were separated. The aqueous phase was extracted with EA (2 x 40 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 30% to 100% of EA in hexane) to afford title compound **363** as a colorless oil (1.2 g, 86% yield), which was not characterized and used directly for the next step.

Step 2. 5-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)pent-1-yn-3-one (364)

To a solution of **363** (1 g, 3.21 mmol) in dry toluene (30 mL) was added dropwise ethynylmagnesium chloride (9.6 mL, 0.5 M in THF, 4.82 mmol) and the resulting mixture was stirred at RT for 45 minutes. A saturated solution of ammonium chloride (30 mL) and EA (40 mL)

were then added. The layers were separated and the aqueous phase was extracted with EA (2 x 40 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane) to afford title compound **364** as a colorless oil (366 mg, 41% yield), which was not characterized and used directly for the next step.

Step 3. 5-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)pent-1-yn-3-one oxime (365)

To a solution of **364** (575 mg, 2.08 mmol) in ethanol (30 mL) was added a 50% aqueous solution of hydroxylamine (1.27 mL, 20.8 mmol). The reaction mixture was stirred at RT for 1 hour. Brine (50 mL) and EA (30 mL) were then added and the layers were separated. The aqueous phase was extracted with EA (2 x 40 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated to afford title compound **365** as a white gum (606 mg, 100% yield), which was not characterized and used directly for the next step.

Step 4. 3-(2-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)isoxazole (366)

To a solution of **365** (380 mg, 1.30 mmol) in DCM (20 mL) was added gold (III) chloride (4.0 mg, 13 μ mol). The reaction mixture was stirred at 40 °C for 20 hours, then concentrated to afford title compound **366** as a brown oil (328 mg, 86% yield), which was not characterized and used directly for the next step.

Step 5. 4-(Cyclopropylmethyl)-4-(2-(isoxazol-3-yl)ethyl)cyclohexan-1-one (367)

To a solution of **366** (328 mg, 1.13 mmol) in acetone (16.8 mL) was added HCl 3 N (3.75 mL, 11.3 mmol) and the reaction mixture was stirred at 40 °C for 20 hours. EA (15 mL) and brine (10 mL) were then added, the layers were separated and the organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 55% of EA in hexane) to afford title compound **367** as a colorless oil (226 mg, 81% yield), which was not characterized and used directly for the next step.

Step 6. *tert*-Butyl 2-amino-6-(cyclopropylmethyl)-6-(2-(isoxazol-3-yl)ethyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (368)

A suspension of sulfur (32.2 mg, 126 μ mol), **367** (225 mg, 0.910 mmol), morpholine (86.3 μ L, 1.00 mmol) and *tert*-butyl cyanoacetate (133 μ L, 0.910 mmol) in EtOH (5 mL) was stirred at 60 °C for 72 hours. The mixture was allowed to cool to RT, then diluted with brine (20 mL) and extracted with EA (3 x 20 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane) to afford title compound **368** as a yellow oil (288 mg, 79% yield). LC-MS: *rt* = 2.01 min, MS: 402.2 (calcd), 403.4 (M+H⁺, found).

Step 7. *tert*-Butyl 2-acetamido-6-(cyclopropylmethyl)-6-(2-(isoxazol-3-yl)ethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (369)

To a solution of **368** (288 mg, 0.715 mmol) in acetic acid (4.1 mL) was added acetic anhydride (135 μ L, 1.43 mmol). The reaction mixture was stirred at 60 °C for 1 hour, then allowed to cool to RT and diluted with acetic acid (5.9 mL), water (10.1 mL) and dioxane (8.5 mL). Ceric sulfate (1.25 g, 3.58 mmol) was added to the mixture and the flask was sonicated to make the suspension homogeneous. Then, the reaction was vigorously stirred at RT for 20 hours. Afterwards, the mixture was diluted with water (50 mL) and extracted with EA (70 mL). The organic layer was washed with saturated solution of ammonium bicarbonate (3 x 100 mL), then dried over Na₂SO₄, filtered and concentrated to afford title compound **369** as a yellow oil (349 mg, >99% yield). LC-MS: rt = 1.76 min, MS: 458.2 (calcd), 459.3 (M+H⁺, found).

Step 8. *tert*-Butyl 2-amino-6-(cyclopropylmethyl)-6-(2-(isoxazol-3-yl)ethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**370**)

A solution of **369** (259 mg, 565 μ mol) in toluene (6.9 mL) was treated with pyrrolidine (696 μ L, 8.47 mmol) and stirred at RT for 2 hours. Water (15 mL) and EA (10 mL) were then added, the layers were separated and the aqueous phase was extracted with another 10 mL of EA. The combined organics were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated to afford title compound **370** as a brown oil (188 mg, 80% yield). LC-MS: rt = 1.70 min, MS: 416.2 (calcd), 417.3 (M+H⁺, found).

Step 9. 2-Amino-6-(cyclopropylmethyl)-6-(2-(isoxazol-3-yl)ethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**371**)

To a solution of **370** (188 mg, 451 μ mol) in DCM (4.3 mL) cooled to 0 °C was added TFA (1.9 mL) and the resulting mixture was stirred at 0 °C for 3 hours. The solvent was then removed under reduced pressure and the residue was purified by reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **371** as a yellow solid (92 mg, 45% yield). LC-MS: rt = 1.34 min, MS: 360.1 (calcd), 361.2 (M+H⁺, found).

Step 10. 2-Amino-6-(cyclopropylmethyl)-6-(2-(isoxazol-3-yl)ethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**343**)

To a solution of **371** (90 mg, 250 μ mol) in DMF (1.2 mL) were added PyBOP (195 mg, 375 μ mol), *N,N*-diisopropylethylamine (174 μ L, 999 μ mol) and ammonium chloride (134 mg, 2.50 mmol). The resulting mixture was stirred at RT for 45 minutes. The crude mixture was directly purified first by reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid), then by Semi-Prep HPLC-MS (eluent gradient from 40% to 100% of MeOH in 10 mM ammonium formate) to afford title compound **343** as a pale-yellow solid (40.5 mg, 45% yield).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.40 (s, 1H), 7.99 (s, 2H), 6.91 (bs, 2H), 6.24 (s, 1H), 3.01-2.91 (m, 2H), 2.72-2.62 (m, 2H), 2.15-2.09 (m, 1H), 2.05-1.98 (m, 2H), 1.89-1.81 (m, 1H), 1.62 (dd, 1H, *J* = 14.1, 6.3 Hz), 1.38 (dd, 1H, *J* = 14.1, 6.9 Hz), 0.66-0.57 (m, 1H), 0.43-0.35

(m, 2H), 0.07-0.04 (m, 1H), 0.01- -0.06 (m, 1H). LC-MS: rt = 1.18 min, MS: 359.1 (calcd), 360.2 (M+H⁺, found).

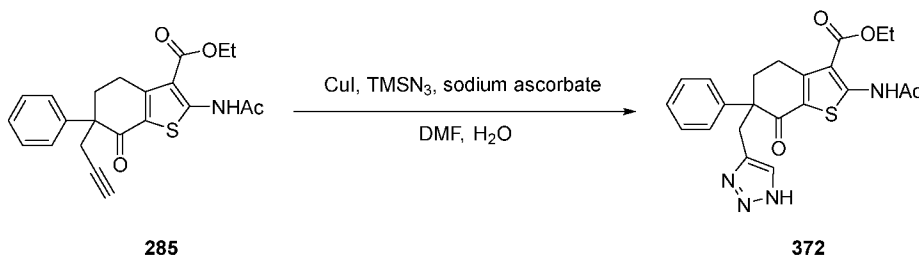
Example 175

6-((1H-1,2,3-Triazol-4-yl)methyl)-2-amino-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (344)

Intermediate compound 372

Ethyl 6-((1H-1,2,3-triazol-4-yl)methyl)-2-acetamido-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (372)

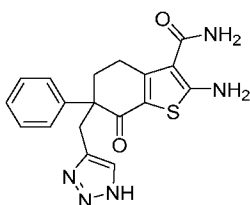
Scheme 84



Scheme 72

Sodium ascorbate (201 mg, 1.01 mmol) and copper iodide (193 mg, 1.01 mmol) were added to a solution of ethyl 2-acetamido-7-oxo-6-phenyl-6-(prop-2-yn-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**285**, scheme 72) (200 mg, 506 μmol) in DMF (5.47 mL) and water (2.73 mL). The flask was evacuated and backfilled with nitrogen. Then, azidotrimethylsilane (537 μL , 4.05 mmol) was added and the reaction mixture was stirred at RT for 16 hours. The mixture was then diluted with EA, a saturated solution of NH₄Cl and brine and then extracted twice with EA. Saturated aqueous sodium bicarbonate solution was added to the aqueous layer and the product was extracted three times with EA. The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by reverse-phase flash column chromatography (eluent gradient from 10% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **372** as a white solid (120 mg, 54% yield). LC-MS: rt = 1.32 min, MS: 438.1 (calcd), 439.2 (M+H⁺, found).

6-((1H-1,2,3-Triazol-4-yl)methyl)-2-amino-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (344)



344: Example 175

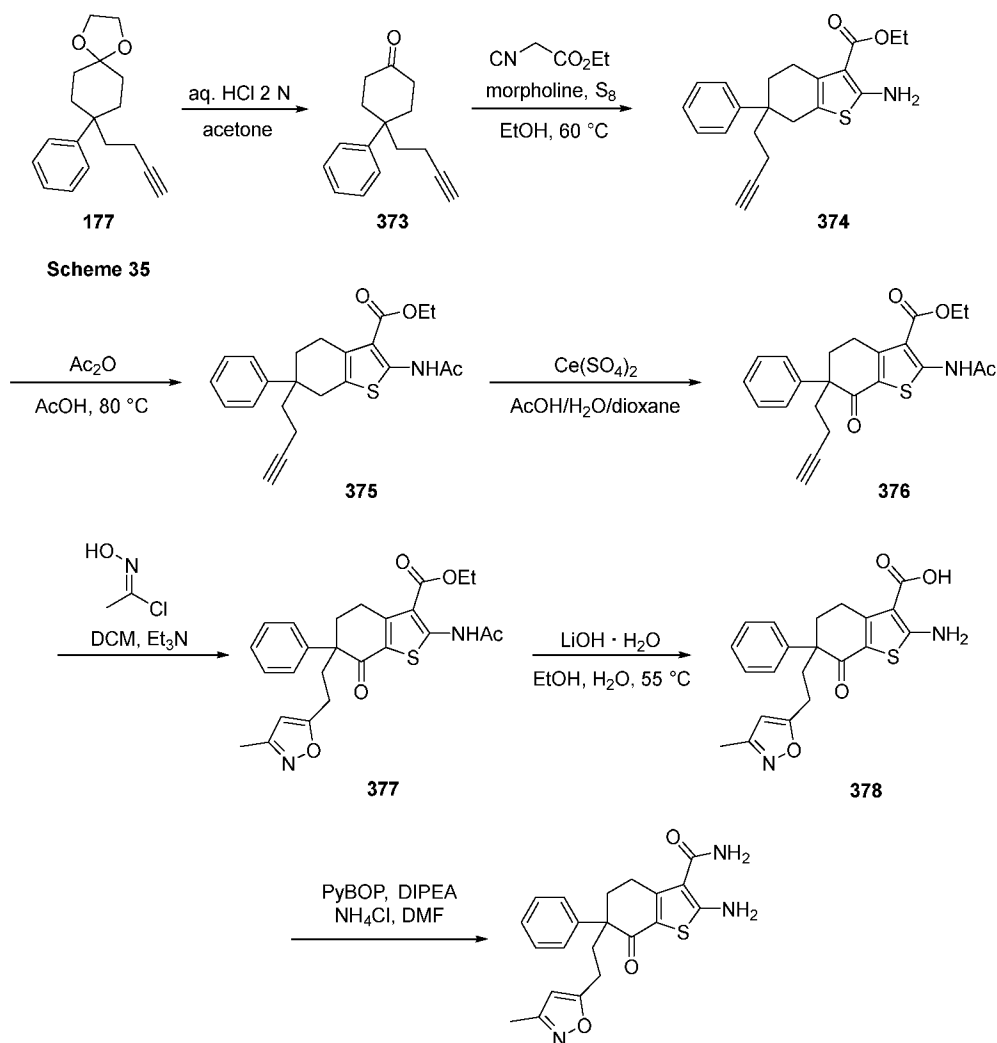
Compound **344** (example 175) was synthesized similarly to compound **341** (example 173, scheme 82) starting from compound **372** (scheme 84) instead of compound **361**.

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.33-7.27 (m, 4H), 7.25-7.23 (m, 1H), 7.21 (s, 1H), 3.40 (d, *J* = 14.4 Hz, 1H), 3.17 (d, *J* = 14.4 Hz, 1H), 2.91-2.87 (m, 1H), 2.66-2.60 (m, 2H), 2.21-2.14 (m, 1H). LC-MS: rt = 0.85 min, MS: 367.1 (calcd), 368.1 (M+H⁺, found).

Example 176

2-Amino-6-(2-(3-methylisoxazol-5-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**345**)

Scheme 85



Step 1. 4-(But-3-yn-1-yl)-4-phenylcyclohexan-1-one (**373**)

To a solution of compound **177** (scheme 35) (734 mg, 2.71 mmol) in acetone (33.6 mL) was added HCl 2 N (13.6 mL, 27.1 mmol) and the reaction mixture was stirred at RT for 20 hours. The mixture was neutralized with saturated solution of ammonium bicarbonate and concentrated

to remove the organic solvent. The product was extracted with EA and the organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated to afford title compound **373** as a white solid (599 mg, 97% yield), which was not characterized and used directly for the next step.

Step 2. Ethyl 2-amino-6-(but-3-yn-1-yl)-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**374**)

A suspension of sulfur (94 mg, 365 μ mol), **373** (599 mg, 2.65 mmol), morpholine (255 μ L, 2.91 mmol) and ethyl 2-cyanoacetate (310 μ L, 2.91 mmol) in EtOH (2.7 mL) was stirred at 60 °C for 20 hours. The mixture was concentrated and the residue was partitioned between water and EA. The layers were separated and the organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane) to afford title compound **374** as a white solid (870 mg, 93% yield). LC-MS: rt = 1.84 min, MS: 353.1 (calcd), 354.1 (M+H⁺, found).

Step 3. Ethyl 2-acetamido-6-(but-3-yn-1-yl)-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**375**)

To a solution of **374** (841 mg, 2.38 mmol) in acetic acid (13.6 mL) was added acetic anhydride (0.41 mL, 4.28 mmol). The mixture was stirred at 80 °C for 24 hours. The mixture was then concentrated, the residue was dissolved in DCM and washed with saturated aqueous solution of sodium bicarbonate, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated to afford title compound **375** as a light-orange powder (1.01 g, >99% yield). LC-MS: rt = 1.93 min, MS: 395.2 (calcd), 396.3 (M+H⁺, found).

Step 4. Ethyl 2-acetamido-6-(but-3-yn-1-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**376**)

To a solution of **375** (941 mg, 2.38 mmol) in acetic acid (16 mL), water (16 mL) and dioxane (16 mL) was added ceric sulfate (6.83 g, 20.6 mmol). The mixture was sonicated until it became homogenous, and then stirred at RT for 72 hours. The suspension was partitioned between EA and water, the layers were separated and the organic phase was washed with NaOH 1 N, water and brine, then dried over Na₂SO₄, filtered and concentrated to afford title compound **376** as a light-orange solid (713 mg, 73% yield). LC-MS: rt = 1.76 min, MS: 409.1 (calcd), 410.2 (M+H⁺, found).

Step 5. Ethyl 2-acetamido-6-(2-(3-methylisoxazol-5-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**377**)

To a solution of **376** (150 mg, 366 μ mol) in DCM (3.0 mL) was added *N*-hydroxyacetimidoyl chloride (103 mg, 1.10 mmol) (*Angew. Chem. Int. Ed.* **2017**, 12586-12589.) and triethylamine (154 μ L, 1.10 mmol). The reaction mixture was stirred at RT for 4 days. Brine (15 mL) and DCM (10 mL) were then added, the layers were separated and the aqueous phase was extracted with another 15 mL of EA. Organic layers were combined and washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column

chromatography (eluent gradient from 0% to 45% of EA in hexane) to afford title compound **377** as a light-yellow solid (99 mg, 58% yield). LC-MS: *rt* = 1.64 min, MS: 466.2 (calcd), 467.2 ($M+H^+$, found).

Step 6. 2-Amino-6-(2-(3-methylisoxazol-5-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (378**)**

To a suspension of **377** (99.0 mg, 212 μ mol) in EtOH (13 mL) was added a solution of lithium hydroxide monohydrate (89 mg, 2.12 mmol) in water (13 mL). The reaction mixture was stirred at 55 °C for 24 hours, then allowed to cool to RT. The mixture was concentrated to remove most of the organic solvent. The aqueous layer was acidified with 1 M HCl to pH 4, which induced precipitation of a light-yellow solid. This solid was filtered, rinsed with water (25 mL) and dried to afford title compound **378** (75 mg, 89% yield). LC-MS: *rt* = 1.29 min, MS: 396.1 (calcd), 397.2 ($M+H^+$, found).

Step 7. 2-Amino-6-(2-(3-methylisoxazol-5-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (345**)**

To a solution of **378** (70 mg, 177 μ mol) in DMF (3.8 mL) were added PyBOP (138 mg, 265 μ mol), *N,N*-diisopropylethylamine (123 μ L, 706 μ mol) and ammonium chloride (94.4 mg, 1.77 mmol). The resulting mixture was stirred at RT for 45 minutes. The crude mixture was directly purified by reverse-phase flash column chromatography (eluent gradient from 5% to 100% of CH_3CN in H_2O with 0.1% (v/v) formic acid), then by Semi-Prep HPLC-MS (eluent gradient from 30% to 100% of acetonitrile in 10 mM ammonium formate) to afford title compound **345** as a light-yellow solid (32.8 mg, 47% yield).

^1H NMR: 400 MHz, $DMSO-d_6$, δ (ppm): 8.08 (bs, 2H), 7.31-7.26 (m, 4H), 7.24-7.20 (m, 1H), 6.84 (bs, 2H), 6.01 (s, 1H), 2.89-2.81 (m, 1H), 2.71-2.53 (m, 2H), 2.43-2.35 (m, 1H), 2.32-2.15 (m, 2H), 2.09 (s, 3H), 2.09-2.02 (m, 2H). LC-MS: *rt* = 1.15 min, MS: 395.1 (calcd), 396.2 ($M+H^+$, found).

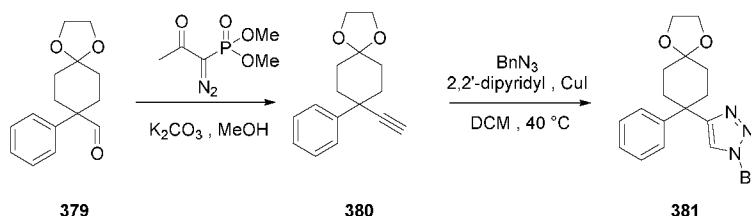
Example 177

2-Amino-6-(1-benzyl-1H-1,2,3-triazol-4-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (348**)**

Intermediate compound 381

1-Benzyl-4-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)-1H-1,2,3-triazole (381**)**

Scheme 86



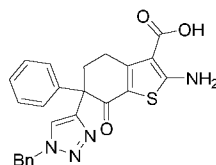
Step 1. 8-Ethynyl-8-phenyl-1,4-dioxaspiro[4.5]decane (380**)**

To a solution of 8-phenyl-1,4-dioxaspiro[4.5]decane-8-carbaldehyde (**379**) (*Bioorg Med. Chem Lett.* 21, p. 405, 2011) (500 mg, 2.03 mmol) in MeOH (25 mL) were added K₂CO₃ (700 mg, 5.08 mmol) and dimethyl (1-diazo-2-oxopropyl)phosphonate (0.50 mL, 3.05 mmol). The mixture was stirred at RT for 1 hour, then it was diluted with water (25 mL) and concentrated to remove most of the organic solvent. The residue was extracted with EA (50 mL) and the organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane) to afford title compound **380** as a white solid (395 mg, 80% yield), which was used directly for the next step without characterization.

Step 2. 1-Benzyl-4-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)-1H-1,2,3-triazole (381**)**

A solution of **380** (370 mg, 1.53 mmol) and benzyl azide (3.7 mL, 0.5 M in DCM, 1.85 mmol) in DCM (10 mL) was added to a solution of CuI (29 mg, 0.15 mmol) and 2,2'-dipyridyl (24 mg, 0.15 mmol) in DCM (10 mL). The reaction mixture was stirred at 40 °C for 24 hours. Then, the mixture was filtered through a celite pad and the filtrate was concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 100% of EA in hexane) to afford title compound **381** as a white solid (490 mg, 85% yield), which was not characterized and used directly for the synthesis of relevant examples.

2-Amino-6-(1-benzyl-1H-1,2,3-triazol-4-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (348**)**



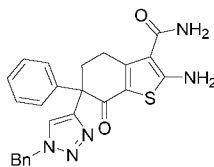
348: Example 177

Compound **348** (example 177) was synthesized similarly to compound **189** (example 102, scheme 40) starting from compound **381** (scheme 86) instead of compound **185**.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 12.51 (bs, 1H), 8.31 (s, 2H), 7.69 (s, 1H), 7.36-7.20 (m, 8H), 7.15-7.12 (m, 2H), 5.52 (s, 2H), 2.99 (dt, *J* = 18.5, 4.9 Hz, 1H), 2.91-2.78 (m, 2H), 2.61 (ddd, *J* = 18.5, 8.6, 4.6 Hz, 1H). LC-MS: rt = 1.25 min, MS: 444.1 (calcd), 445.2 (M+H⁺, found).

Example 178

2-Amino-6-(1-benzyl-1H-1,2,3-triazol-4-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (346**)**



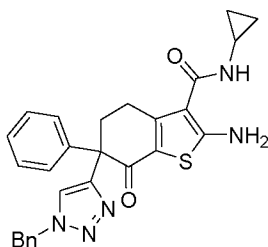
346: Example 178

Compound **346** (example 178) was synthesized similarly to compound **258** (example 138, scheme 63) starting from compound **348** (example 177) instead of compound **257**.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.15 (s, 2H), 7.68 (s, 1H), 7.36-7.20 (m, 8H), 7.15-7.12 (m, 2H), 6.90 (bs, 2H), 5.52 (s, 2H), 2.94-2.86 (m, 2H), 2.82-2.69 (m, 2H). LC-MS: rt = 1.25 min, MS: 443.1 (calcd), 444.3 (M+H⁺, found).

Example 179

2-Amino-6-(1-benzyl-1H-1,2,3-triazol-4-yl)-N-cyclopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (352)



352: Example 179

Compound **352** (example 179) was synthesized similarly to compound **170** (example 95, scheme 32) starting from compound **348** (example 177) instead of compound **59**.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 7.90 (s, 2H), 7.66 (s, 1H), 7.38-7.20 (m, 9H), 7.14-7.11 (m, 2H), 5.52 (s, 2H), 2.93-2.85 (m, 1H), 2.82-2.73 (m, 2H), 2.71-2.62 (m, 2H), 0.63-0.58 (m, 2H), 0.50-0.46 (m, 2H). LC-MS: rt = 1.32 min, MS: 483.2 (calcd), 484.2 (M+H⁺, found).

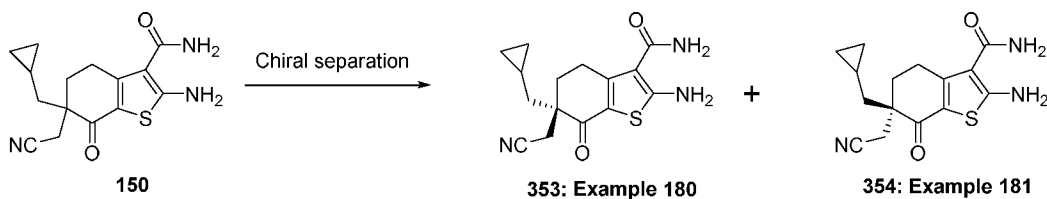
Example 180

(S)-2-Amino-6-cyano-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (353) and

Example 181

(R)-2-Amino-6-cyano-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (354)

Scheme 87



Racemic compound **150** (1.71 g) was submitted to SFC chiral separation (isocratic: 40% of MeOH in CO₂) to yield enantioenriched compound **353** as an off-white solid (493 mg, 29% separation yield) and enantioenriched compound **354** as a pale-yellow solid (534 mg, 31% separation yield). Absolute configurations of compounds **353** and **354** were assigned based on analogy with the assignment of the absolute configuration of a crystallized compound within the same or similar series.

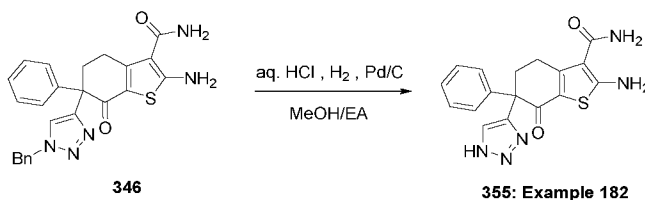
353: ¹H NMR: same as racemic mixture (**150**). LC-MS: rt = 1.03 min, MS: 303.1 (calcd), 304.1 (M+H⁺, found). Analytical SFC (isocratic 30% iPrOH in CO₂): rt = 3.56 min, ee. = 92.5%.

354: ¹H NMR: same as racemic mixture (**150**). LC-MS: rt = 1.03 min, MS: 303.1 (calcd), 304.1 (M+H⁺, found). Analytical SFC (isocratic 30% iPrOH in CO₂): rt = 2.71 min, ee. = 98.2%.

Example 182

2-Amino-7-oxo-6-phenyl-6-(1H-1,2,3-triazol-4-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**355**)

Scheme 88

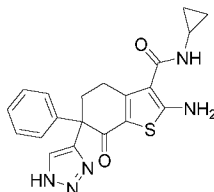


1 N aqueous HCl (0.8 mL, 0.8 mmol) was added to a suspension of **346** (72 mg, 0.16 mmol) and Pd/C 10% (wet) (60 mg) in a 5:1 MeOH/EA mixture (24 mL). Then, the reaction mixture was vigorously stirred under a hydrogen atmosphere (balloon) at RT for 16 hours. The mixture was filtered through a celite pad and the filtrate was concentrated. The residue was purified by reverse-phase flash column chromatography (eluent gradient from 0% to 100% CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **355** as a white solid (24 mg, 42% yield).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.15 (s, 2H), 7.39 (bs, 1H), 7.31-7.28 (m, 2H), 7.25-7.21 (m, 1H), 7.11-7.09 (m, 2H), 6.90 (bs, 2H), 2.92-2.82 (m, 2H), 2.80-2.71 (m, 2H). LC-MS: rt = 0.93 min, MS: 353.1 (calcd), 354.2 (M+H⁺, found).

Example 183

2-Amino-N-cyclopropyl-7-oxo-6-phenyl-6-(1H-1,2,3-triazol-4-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**356**)



356: Example 183

Compound **356** (example 183) was synthesized similarly to compound **355** (example 182, scheme 88) starting from compound **352** (example 179) instead of compound **346**.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 7.89 (s, 2H), 7.39-7.36 (m, 2H), 7.31-7.27 (m, 2H), 7.25-7.21 (m, 1H), 7.10-7.08 (m, 2H), 2.85-2.63 (m, 5H), 0.63-0.58 (m, 2H), 0.49-0.46 (m, 2H). LC-MS: rt = 1.09 min, MS: 393.1 (calcd), 394.3 (M+H⁺, found).

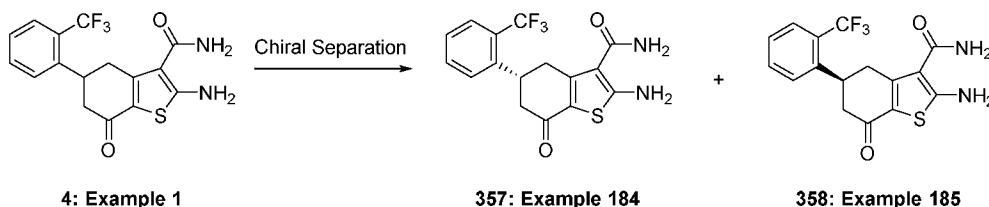
Example 184

(R)-2-Amino-7-oxo-5-(2-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (357) and

Example 185

(S)-2-Amino-7-oxo-5-(2-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (358)

Scheme 89



4: Example 1

357: Example 184

358: Example 185

Scheme 1

718 mg of racemic compound **4** (scheme 1, example 1) were submitted to SFC chiral separation (isocratic 30% *i*-PrOH in CO₂) to afford enantioenriched title compound **357** as a brown solid (234 mg, 33% separation yield) and enantioenriched title compound **358** as a brown solid (287 mg, 40% separation yield) (the absolute configurations were assigned based on resolved crystal structure of enantiomer **357**).

357: ¹H NMR: same as racemic mixture (**4**). LC-MS: rt = 1.13 min, MS: 354.1 (calcd), 355.1 (M+H⁺, found). Analytical chiral SFC (30% of *i*-PrOH in CO₂): rt = 3.20 min, ee. = 99.29%.

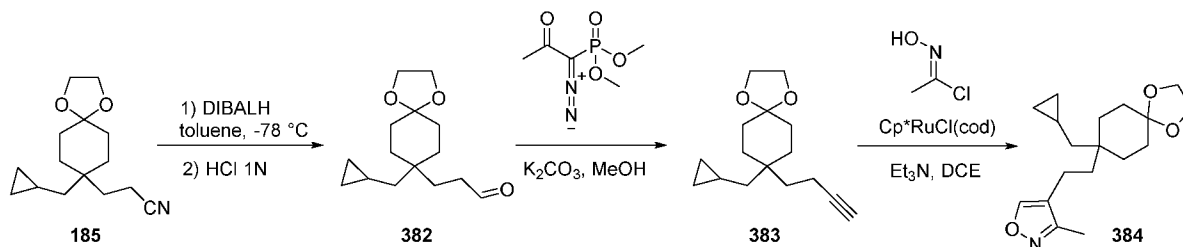
358: ¹H NMR: same as racemic mixture (**4**). LC-MS: rt = 1.13 min, MS: 354.1 (calcd), 355.1 (M+H⁺, found). Analytical chiral SFC (30% of *i*-PrOH in CO₂): rt = 2.35 min, ee. = 99.85%.

Examples 186-192

Intermediate compound 384

4-(2-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)-3-methylisoxazole (384)

Scheme 90



Scheme 40

Step 1. 3-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)propanal (**382**)

To a solution of compound **185** (scheme 40) (2.50 g, 10 mmol) in anhydrous toluene (63 mL) at -78 °C was added dropwise DIBALH (8.09 mL, 25% in toluene, 12 mmol). The reaction mixture was stirred at -78 °C for 2 hours, before being carefully quenched with MeOH and saturated NH₄Cl solution. Afterwards, the mixture was allowed to reach RT and diluted with Et₂O, then filtered through a celite pad. The layers were separated, and the organic phase was concentrated. The residue was dissolved in THF (134 mL) and HCl 1 N (10 mL, 10 mmol) was added. The mixture was stirred at RT for 15 min, before being quenched with saturated NaHCO₃ solution and extracted with Et₂O. The organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography (eluent gradient from 5% to 100% of EA in hexane) to afford title compound **382** (2.4 g, 95% yield) as a colorless oil, which was not characterized and used directly for the next step.

Step 2. 8-(But-3-yn-1-yl)-8-(cyclopropylmethyl)-1,4-dioxaspiro[4.5]decane (**383**)

To a solution of compound **382** (2.40 g, 9.51 mmol) in MeOH (117 mL) were added K₂CO₃ (3.29 g, 23.8 mmol) and dimethyl (1-diazo-2-oxopropyl)phosphonate (2.35 mL, 14.3 mmol). The mixture was stirred at RT for 1 hour, then it was diluted with water (25 mL) and concentrated to remove most of the organic solvent. The residue was extracted with EA (50 mL) and the organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane) to afford title compound **383** as a white solid (1.55 g, 66% yield), which was used directly for the next step without characterization.

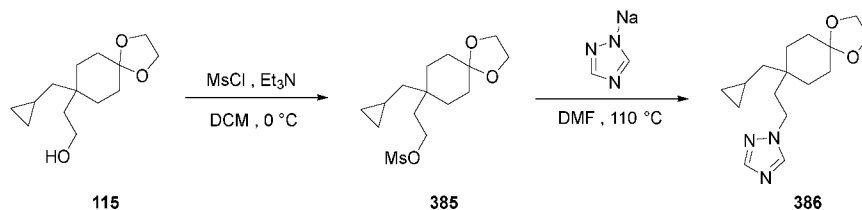
Step 3. 4-(2-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)-3-methylisoxazole (**384**)

A solution of *N*-hydroxyacetimidoyl chloride (*Angew. Chem. Int. Ed.* **2017**, 12586-12589.) (56.5 mg, 604 μmol) in DCE (3.20 mL) was purged with argon for 2 min, then compound **383** (150 mg, 604 μmol) and chloro(pentamethylcyclopentadienyl)(cyclooctadiene)ruthenium(II) (11.7 mg, 30.2 μmol) were added followed by triethylamine (106 μL, 755 μmol). The mixture was stirred under Ar at RT for 48 hours. The reaction mixture was then directly purified by flash column chromatography (eluent gradient from 5% to 80% of EA in hexane) to afford a colorless oil (93.0 mg, 50% yield) which was not characterized and used directly for the next step.

Intermediate compound 386

1-(2-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)-1H-1,2,4-triazole (386)

Scheme 91



Scheme 21

Step 1. 2-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)ethyl methanesulfonate (385)

To a solution of compound **115** (scheme 21) (5.0 g, 19.1 mmol) in anhydrous DCM (95 mL) at 0 °C were added methanesulfonyl chloride (2.4 g, 21.0 mmol) and triethylamine (5.31 mL, 38.1 mmol). The reaction mixture was stirred at RT for 1 hour, then diluted with water and extracted with DCM. The organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 40% of EA in hexane) to afford title compound **385** as a white solid (5.2 g, 80% yield) which was not characterized and used directly for the next step.

Step 2. 1-(2-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)-1H-1,2,4-triazole (386)

To a solution of **385** (50 mg, 157 μmol) in anhydrous DMF (1.57 mL) was added 1,2,4-triazole sodium salt (71.5 mg, 785 μmol). The reaction mixture was stirred at 110 °C for 20 hours, then allowed to cool to RT and quenched with saturated aqueous NH₄Cl solution (10 mL) diluted with water (10 mL). Then, the desired product was extracted with EA (2 x 20 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography (eluent gradient from 15% to 100% of EA in hexane) to afford title compound **386** as a colorless oil (45 mg, 99%). which was not characterized and used directly for the next step.

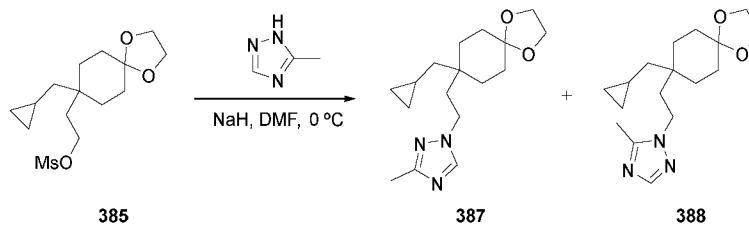
Intermediate compound 387

1-(2-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)-3-methyl-1H-1,2,4-triazole (387) and

Intermediate compound 388

1-(2-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)-5-methyl-1H-1,2,4-triazole (388)

Scheme 92

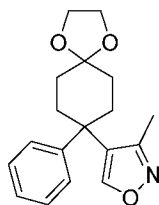


Scheme 91

To a suspension of sodium hydride (117 mg, 2.94 mmol) in DMF (7 mL) at 0 °C was added 3-methyl-1H-1,2,4-triazole (125 mg, 1.47 mmol). The resulting mixture was stirred at 0 °C for 15 minutes and then compound **385** (scheme 91) (500 mg, 1.47 mmol) was added dropwise as a solution in DMF (7 mL). The reaction mixture was stirred at RT for 18 hours, then quenched with saturated aqueous NH₄Cl solution (30 mL) and diluted with water (15 mL). Then, the desired product was extracted with EA (2 x 40 mL) and purified by flash column chromatography (eluent gradient from 15% to 100% of EA in hexane) to afford a 1 :1 regioisomeric mixture of title compounds **387** and **388** as a colorless oil (274 mg, 57%), which was not characterized and used directly for the next step.

Intermediate compound 389

3-Methyl-4-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)isoxazole (389)



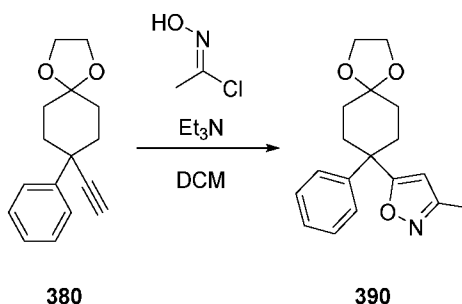
389

Intermediate **389** was synthesized similarly to compound **384** (scheme 90) starting from compound **380** (scheme 86) instead of compound **383**. The product was not characterized and used directly for the next step.

Intermediate compound 390

3-Methyl-5-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)isoxazole (390)

Scheme 93



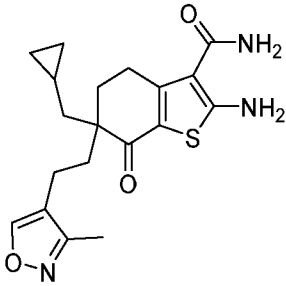
Scheme 86

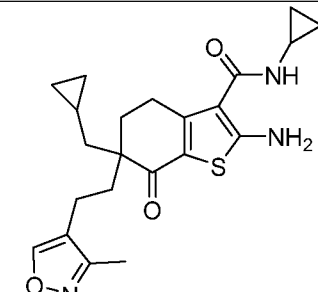
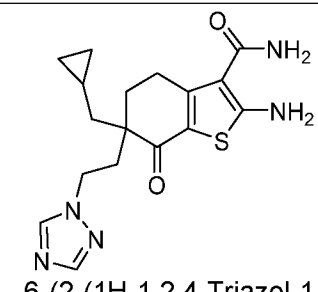
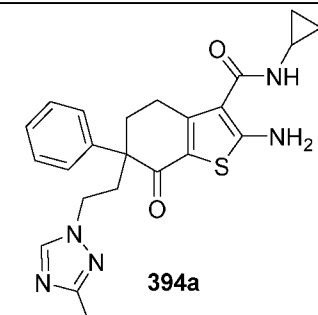
To a solution of compound **380** (scheme 86) (700 mg, 2.89 mmol) in DCM (23 mL) was added *N*-hydroxyacetimidoyl chloride (810 mg, 8.66 mmol) (*Angew. Chem. Int. Ed.* **2017**, 12586-12589.) and triethylamine (1.2 mL, 8.66 mmol). The reaction mixture was stirred at RT for 4 days. Subsequently, brine (15 mL) and DCM (10 mL) were added, the layers were separated, and the aqueous phase was extracted with another 15 mL of EA. The organic layers were combined, washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography (eluent gradient from 10% to 50% of EA in hexane) to afford title compound **390** as a colorless oil (174 mg, 20% yield), which was not characterized and used directly for the next step.

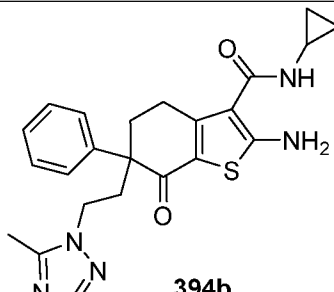
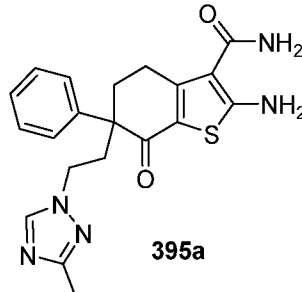
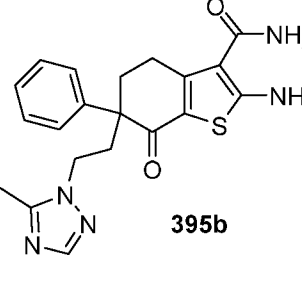
Compounds 391-397

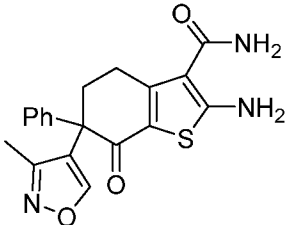
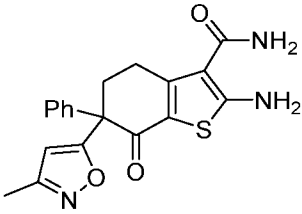
Compounds **391**, **393** and **396-397** (examples 186, 188 and 191-192) were synthesized similarly to compound **246** (example 129, scheme 57) starting from compounds **384** (scheme 90), **386** (scheme 91), **389** and **390** (scheme 93), respectively, instead of compound **241**. Compound **392** (example 187) was synthesized similarly to compound **192** (example 104, scheme 40) starting from compound **384** (scheme 90) instead of compound **185**. **394** (example 189) refers to a 1:1 mixture of regioisomers **394a** and **394b** that were synthesized similarly to compound **192** (example 104, scheme 40) starting from the 1:1 mixture of regioisomers **387** and **388** instead of compound **185**. **395** (example 190) refers to a 1:1 mixture of regioisomers **395a** and **395b** that were synthesized similarly to compound **246** (example 129, scheme 57) starting from the 1:1 mixture of regioisomers **387** and **388** instead of compound **241**. Characterization of compounds **391-397** (examples 186-192) is provided in the table 7.

Table 7. Characterization of compounds **391-397** (examples 186-192).

Ex. #	Cpd. #	Structure	Characterization
186	391	 2-Amino-6-(cyclopropylmethyl)-6-(2-(3-methylisoxazol-4-yl)ethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, CDCl₃, δ (ppm): 8.07 (s, 1H), 7.03 (s, 2H), 5.46 (s, 2H), 2.97 (t, <i>J</i> = 6.0 Hz, 2H), 2.36-2.25 (m, 4H), 2.13-2.07 (m, 1H), 1.83-1.72 (m, 2H), 1.53-1.45 (m, 2H), 0.67 (s, 1H), 0.48 (d, <i>J</i> = 8.0 Hz, 2H), 0.04 (d, <i>J</i> = 7.6 Hz, 2H). LC-MS: rt = 1.23 min, MS: 373.2 (calcd), 374.3 (M+H⁺, found).

187	392	 2-Amino-N-cyclopropyl-6-(cyclopropylmethyl)-6-(2-(3-methylisoxazol-4-yl)ethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, CDCl₃, δ (ppm): 8.06 (s, 1H), 6.99 (s, 2H), 5.75 (s, 1H), 2.88-2.78 (m, 3H), 2.36-2.22 (m, 6H), 2.11-2.03 (m, 1H), 1.83-1.72 (m, 2H), 1.46 (dd, <i>J</i> = 14.2, 7.2 Hz, 1H), 0.90-0.83 (m, 3H), 0.67-0.62 (m, 1H), 0.61-0.57 (m, 2H), 0.48 (d, <i>J</i> = 8.0 Hz, 2H), 0.04 (m, 2H). LC-MS: rt = 1.46 min, MS: 413.2 (calcd), 414.3 (M+H⁺, found).
188	393	 6-(2-(1H-1,2,4-Triazol-1-yl)ethyl)-2-amino-6-(cyclopropylmethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, CDCl₃, δ (ppm): 8.07 (s, 1H), 7.91 (s, 1H), 7.11 (s, 2H), 5.48 (s, 2H), 4.26 (dt, <i>J</i> = 10.2, 5.3 Hz, 2H), 2.97 (t, <i>J</i> = 5.8 Hz, 2H), 2.43-2.30 (m, 2H), 2.19 (td, <i>J</i> = 13.2, 6.6 Hz, 2H), 1.72 (dd, <i>J</i> = 14.3, 6.4 Hz, 1H), 1.53 (dd, <i>J</i> = 14.4, 7.0 Hz, 1H), 0.67 (s, 1H), 0.51 (d, <i>J</i> = 8.0 Hz, 2H), 0.07-0.05 (m, 2H). LC-MS: rt = 0.84 min, MS: 359.1 (calcd), 360.1 (M+H⁺, found).
189	394	 394a	¹H NMR: 400 MHz, CD₃OD, δ (ppm): 8.06 (s, 1H), 7.72 (s, 1H), 7.31 (t, <i>J</i> = 4.9 Hz, 10H), 7.23 (t, <i>J</i> = 4.6 Hz, 2H), 4.35-4.26 (m, 2H), 4.01-3.96 (m, 1H), 3.91-3.89 (m, 1H), 2.79-2.73 (m, 3H), 2.69-2.53 (m, 6H), 2.37-2.31 (m, 5H), 2.30 (s, 3H), 2.26 (s, 3H), 0.89-0.86 (m, 2H), 0.71-0.67 (m, 4H), 0.51-0.48 (m, 5H). LC-MS: rt = 1.11 min, MS: 435.2 (calcd), 436.3 (M+H⁺, found). 1:1 mixture of regioisomers

		 394b 2-Amino-N-cyclopropyl-6-(2-(3-methyl-1H-1,2,4-triazol-1-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (394a) and 2-Amino-N-cyclopropyl-6-(2-(5-methyl-1H-1,2,4-triazol-1-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (394b)	
190	395	 395a  395b 2-Amino-6-(2-(3-methyl-1H-1,2,4-triazol-1-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (395a) and 2-Amino-6-(2-(5-methyl-1H-1,2,4-triazol-1-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (395b)	¹H NMR: 400 MHz, CD₃OD, δ (ppm): 8.10 (s, 1H), 7.75 (s, 1H), 7.37-7.28 (m, 10H), 4.37 (dd, <i>J</i> = 20.4, 12.0 Hz, 2H), 4.04-3.95 (m, 1H), 2.98-2.92 (m, 4H), 2.66-2.63 (m, 4H), 2.40 (t, <i>J</i> = 8.0 Hz, 4H), 2.34 (s, 3H), 2.29 (s, 3H). LC-MS: rt = 0.90 min, MS: 395.1 (calcd), 396.2 (M+H⁺, found). 1:1 mixture of regioisomers

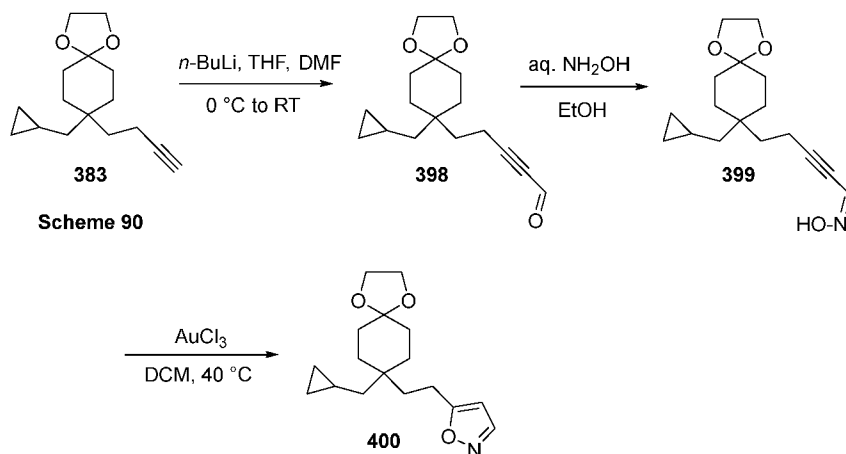
191	396	 2-Amino-6-(3-methylisoxazol-4-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 8.30 (s, 1H), 7.36-7.27 (m, 3H), 7.22 (d, <i>J</i> = 7.5 Hz, 2H), 3.01-2.94 (m, 1H), 2.89-2.82 (m, 1H), 2.74 (dt, <i>J</i> = 13.3, 3.7 Hz, 1H), 2.62-2.54 (m, 1H), 1.80 (s, 3H). LC-MS: rt = 1.03 min, MS: 367.1 (calcd), 368.1 (M+H ⁺ , found).
192	397	 2-Amino-6-(3-methylisoxazol-5-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹ H NMR: 400 MHz, DMSO-d ₆ , δ (ppm): 8.19 (s, 2H), 7.39-7.31 (m, 3H), 7.22-7.20 (m, 2H), 7.07-6.83 (m, 2H), 5.92 (s, 1H), 2.94-2.85 (m, 1H), 2.83-2.74 (m, 3H), 2.17 (s, 3H). LC-MS: rt = 1.07 min, MS: 367.1 (calcd), 368.1 (M+H ⁺ , found).

Example 193

2-Amino-6-(cyclopropylmethyl)-6-(2-(isoxazol-5-yl)ethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (401)

Intermediate compound 400

5 **5-(2-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)isoxazole (400)**

Scheme 94Step 1. 5-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)pent-2-ynal (398)

To a solution of **383** (scheme 90) in dry THF (8.2 mL) cooled to 0 °C was added dropwise *n*-butyl lithium (676 μL, 2.5 M in hexane, 1.69 mmol). The reaction mixture was stirred at 0 °C for 15 minutes, then dry DMF (103 μL, 1.33 mmol) was added. The resulting mixture was allowed to warm to RT over 2 hours. In another flask, sodium dihydrogenphosphate (580 mg, 4.83 mmol)

was dissolved in deionized water (6 mL). Diethyl ether (30 mL) was added and the mixture was stirred vigorously. The contents of the first flask were then added dropwise at 0 °C and the mixture was allowed to stir for 30 minutes at RT. The layers were separated and the ether layer was washed with water (2 x 30 mL), brine (2 x 20 mL), dried over Na₂SO₄, filtered and concentrated.

- 5 The residue was purified by flash column chromatography (eluent gradient from 0% to 35% of EA in hexane) to afford title compound **398** as a colorless oil (226 mg, 68% yield), which was not characterized and used directly for the next step.

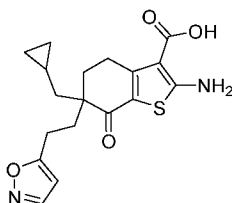
Step 2. 5-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)pent-2-ynal oxime (**399**)

- 10 To a solution of **398** (358 mg, 1.30 mmol) in ethanol (21.1 mL) was added a 50% aqueous solution of hydroxylamine (794 uL, 13.0 mmol). The reaction mixture was stirred at RT for 2 hours. Brine (50 mL) and EA (30 mL) were then added and the layers were separated. The aqueous phase was extracted with EA (2 x 40 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated to afford title compound **399** as a yellow oil (362 mg, 96% yield), which was not characterized and used directly for the next step.

- 15 Step 3. 5-(2-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)isoxazole (**400**)

To a solution of **399** (377 mg, 1.29 mmol) in DCM (20 mL) was added gold (III) chloride (4.0 mg, 13 umol). The reaction mixture was stirred at 40 °C for 20 hours, then concentrated to afford a colorless oil (275 mg, 73% yield), which was not characterized and used directly for the next step.

- 20 **2-Amino-6-(cyclopropylmethyl)-6-(2-(isoxazol-5-yl)ethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**401**)**



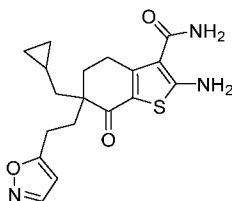
401: Example 193

Compound **401** (example 193) was synthesized similarly to compound **189** (example 102, scheme 40) starting from compound **400** (scheme 94) instead of compound **185**.

- 25 ¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 12.52 (s, 1H), 8.43 (s, 1H), 8.25 (s, 2H), 6.28 (s, 1H), 3.04-2.99 (m, 2H), 2.73-2.67 (m, 2H), 2.15-2.08 (m, 3H), 1.91-1.82 (m, 1H), 1.68-1.61 (m, 1H), 1.41-1.34 (m, 1H), 0.66-0.60 (m, 1H), 0.43-0.36 (m, 2H), 0.07- -0.01 (m, 2H). LC-MS: rt = 1.34 min, MS: 360.1 (calcd), 361.2 (M+H⁺, found).

Example 194

- 30 **2-Amino-6-(cyclopropylmethyl)-6-(2-(isoxazol-5-yl)ethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**402**)**



402: Example 194

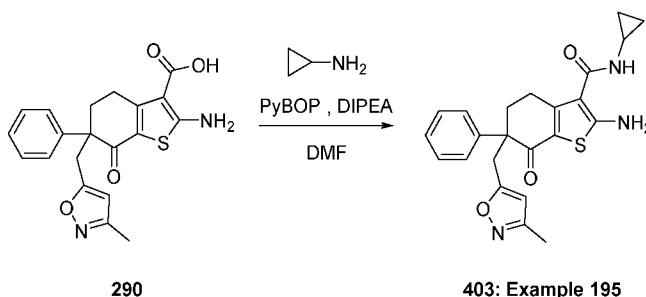
Compound **402** (example 194) was synthesized similarly to compound **52** (example 33, scheme 6) starting from compound **401** (example 193) instead of compound **51**.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.38 (s, 1H), 7.97 (s, 2H), 6.91 (bs, 1H), 6.22 (s, 1H), 2.98-2.93 (m, 2H), 2.69-2.63 (m, 2H), 2.13-2.06 (m, 1H), 2.03-1.96 (m, 2H), 1.88-1.80 (m, 1H), 1.57-1.63 (m, 1H), 1.33-1.39 (m, 1H), 0.56-0.62 (m, 1H), 0.35-0.39 (m, 2H), 0.01-0.06 (m, 1H), -0.01- -0.06. LC-MS: rt = 1.17 min, MS: 359.1 (calcd), 360.1 (M+H⁺, found).

Example 195

2-Amino-*N*-cyclopropyl-6-((3-methylisoxazol-5-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**403**)

Scheme 95



Scheme 74

403: Example 195

To a solution of **290** (scheme 74) (65.0 mg, 0.170 mmol) in anhydrous DMF (1.6 mL) were added PyBOP (133 mg, 0.255 mmol), *N,N*-diisopropylethylamine (118 μL, 0.680 mmol) and cyclopropylamine (121 μL, 1.70 mmol) and the reaction mixture was stirred at RT for 20 hours. The crude was purified by reverse-phase flash column chromatography (eluent gradient from 0% to 100% of CH₃CN in 0.1% formic acid (v/v) in water) and then Semi-Prep HPLC-MS (eluent gradient from 30% to 50% of CH₃CN in 10 mM ammonium formate) to afford title compound **403** as an off-white solid (19.6 mg, 27% yield).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 7.80 (s, 2H), 7.32-7.27 (m, 5H), 7.24-7.21 (m, 1H), 5.78 (s, 1H), 3.34 (d, *J* = 14.7 Hz, 1H), 3.04 (d, *J* = 14.6 Hz, 1H), 2.65-2.60 (m, 2H), 2.58-2.50 (m, 2H), 2.09 (s, 3H), 2.05-1.95 (m, 1H), 0.60-0.51 (m, 2H), 0.43-0.40 (m, 2H). LC-MS: rt = 1.35 min, MS: 421.2 (calcd), 422.3 (M+H⁺, found).

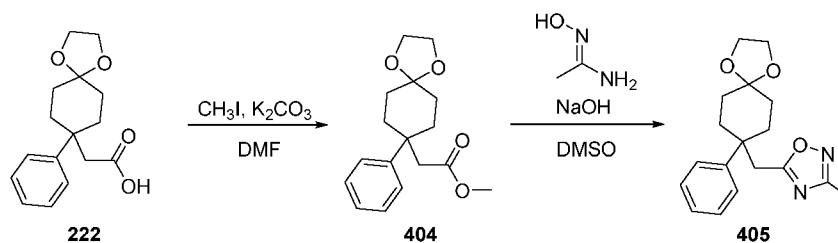
Example 196

2-Amino-6-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (**406**)

Intermediate compound 405

3-Methyl-5-((8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)methyl)-1,2,4-oxadiazole (405)

Scheme 96



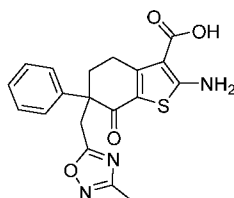
Scheme 51

Step 1. Methyl 2-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)acetate (404)

To a solution of compound **222** (scheme 51) (936 mg, 3.39 mmol) in DMF (18.7 mL) were added potassium carbonate (936 mg, 6.77 mmol) and iodomethane (426 μ L, 6.77 mmol). The resulting solution was stirred at RT for 20 hours, then the reaction mixture was quenched with water (20 mL). The mixture was diluted with EA (15 mL), the layers were separated, and the aqueous layer was extracted with EA (30 mL). The combined organics were washed with brine (2 x 50 mL), then dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 60% of EA in hexane) to afford title compound **404** (718 mg, 73% yield) as a yellow oil, which was not characterized and used directly for the next step.

Step 2. 3-Methyl-5-((8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)methyl)-1,2,4-oxadiazole (405)

To a solution of **404** (100 mg, 0.373 mmol) and *N*'-hydroxyacetimidamide (31.6 mg, 0.410 mmol) in DMSO (3.0 mL) was added ground sodium hydroxide (22.4 mg, 0.559 mmol). The reaction mixture was stirred at RT for 5 days, then quenched with brine (30 mL) and extracted with EA (40 mL). The organic layer was separated and the aqueous phase was extracted with EA (3 x 30 mL). All the organic phases were combined, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 70% of EA in hexane) to afford title compound **405** as a colorless oil (26.0 mg, 25% yield), which was not characterized and used directly for the next step.

2-Amino-6-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (406)

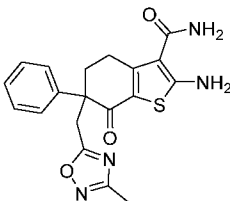
406: Example 196

Compound **406** (example 196) was synthesized similarly to compound **189** (example 102, scheme 40) starting from compound **405** (scheme 96) instead of compound **185**.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 12.52 (s, 1H), 8.29 (s, 2H), 7.32-7.22 (m, 5H), 3.37 (s, 2H), 3.15 (d, *J* = 18.5 Hz, 1H), 2.74 (d, *J* = 13.9 Hz, 1H), 2.55-2.48 (m, 1H), 2.37-2.28 (m, 1H),
 5 2.23 (s, 3H). LC-MS: rt = 1.17 min, MS: 383.1 (calcd), 384.1 (M+H⁺, found).

Example 197

2-Amino-6-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (407)



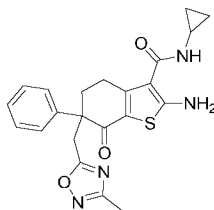
407: Example 197

Compound **407** (example 197) was synthesized similarly to compound **52** (example 33, scheme 6) starting from compound **406** (example 196) instead of compound **51**.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.11 (s, 2H), 7.33-7.22 (m, 5H), 6.90 (bs, 2H), 3.38 (s, 2H), 2.90-2.85 (m, 1H), 2.76-2.69 (m, 1H), 2.68-2.63 (m, 1H), 2.60-2.52 (m, 1H), 2.23 (s, 3H).
 LC-MS: rt = 1.10 min, MS: 382.1 (calcd), 383.2 (M+H⁺, found).

Example 198

2-Amino-N-cyclopropyl-6-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (408)



408: Example 198

Compound **408** (example 198) was synthesized similarly to compound **170** (example 95, scheme 32) starting from compound **406** (example 196) instead of compound **59**.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 7.33-7.30 (m, 4H), 7.28-7.23 (m, 1H), 3.50-3.40 (m, 2H), 2.83-2.78 (m, 2H), 2.70-2.66 (m, 1H), 2.64-2.55 (m, 2H), 2.28 (s, 3H), 0.73-0.66 (m, 2H), 0.56-0.47 (m, 2H). LC-MS: rt = 1.21 min, MS: 422.1 (calcd), 423.2 (M+H⁺, found).

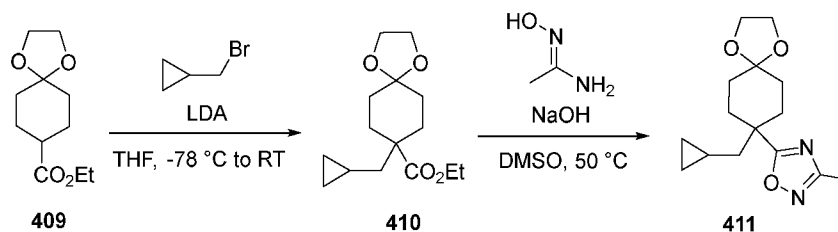
Example 199

2-Amino-6-(cyclopropylmethyl)-6-(3-methyl-1,2,4-oxadiazol-5-yl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (412)

Intermediate compound 411

5-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)-3-methyl-1,2,4-oxadiazole (411)

Scheme 97



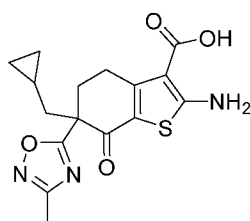
Step 1. Ethyl 8-(cyclopropylmethyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate (410)

A flame-dried round bottom flask was charged with a solution of LDA (33.6 mL, 1 M in THF/hexane, 2.69 mmol) in anhydrous THF (4.02 mL) under argon. The solution was cooled to -78 °C and ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (**409**, 6 g, 26.9 mmol) was added. The mixture was stirred at -78 °C for 35 min, then (bromomethyl)cyclopropane (2.96 mL, 29.6 mmol) was added. The reaction vessel was removed from the acetone/dry ice bath and the solution was stirred at RT for 20 hours. The mixture was then partitioned between EA and water, the layers were separated and the aqueous phase was extracted with EA. The combined organics were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 5% to 50% of EA in hexane) to afford title compound **410** (5.33 g, 74% yield) as a yellow oil, which was not characterized and used directly for the next step.

Step 2. 5-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)-3-methyl-1,2,4-oxadiazole (411)

To a solution of **410** (1 g, 3.73 mmol) and *N'*-hydroxyacetimidamide (316 mg, 4.10 mmol) in DMSO (30 mL) was added ground sodium hydroxide (224 mg, 5.59 mmol). The reaction mixture was stirred at 50 °C for 5 days, then quenched with brine (30 mL) and extracted with EA (40 mL). The organic layer was separated and the aqueous phase was extracted with EA (3 x 30 mL). All the organic layers were combined, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane) to afford title compound **411** as a colorless oil (454 mg, 44% yield), which was not characterized and used directly for the next step.

2-Amino-6-(cyclopropylmethyl)-6-(3-methyl-1,2,4-oxadiazol-5-yl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (412)



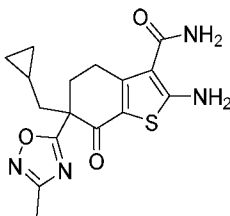
412: Example 199

Compound **412** (example 199) was synthesized similarly to compound **189** (example 102, scheme 40) starting from compound **411** (scheme 97) instead of compound **185**.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 12.62 (bs, 1H), 8.38 (s, 2H), 3.17-3.08 (m, 1H), 3.05-2.97 (m, 1H), 2.72-2.66 (m, 1H), 2.47-2.38 (m, 1H), 2.30 (s, 3H), 1.98-1.87 (m, 2H), 0.70-0.59 (m, 1H), 0.42-0.33 (m, 1H), 0.33-0.26 (m, 1H), 0.10-0.04 (m, 1H), -0.10- -0.19 (m, 1H). LC-MS: rt = 1.25 min, MS: 347.1 (calcd), 348.2 (M+H⁺, found).

Example 200

2-Amino-6-(cyclopropylmethyl)-6-(3-methyl-1,2,4-oxadiazol-5-yl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (413)



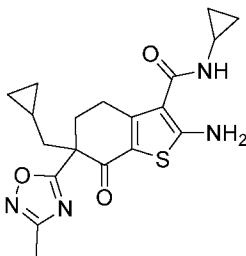
413: Example 200

Compound **413** (example 200) was synthesized similarly to compound **52** (example 33, scheme 6) starting from compound **412** (example 199) instead of compound **51**.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.15 (s, 2H), 7.01 (bs, 2H), 3.03-3.00 (m, 2H), 2.72-2.66 (m, 1H), 2.45-2.40 (m, 1H), 2.31 (s, 3H), 2.00 (dd, J = 14.2, 6.9 Hz, 1H), 1.86 (dd, J = 14.2, 6.7 Hz, 1H), 0.70-0.60 (m, 1H), 0.42-0.26 (m, 2H), 0.18-0.09 (m, 1H), -0.08- -0.17 (m, 1H). LC-MS: rt = 1.10 min, MS: 346.1 (calcd), 347.1 (M+H⁺, found).

Example 201

2-Amino-N-cyclopropyl-6-(cyclopropylmethyl)-6-(3-methyl-1,2,4-oxadiazol-5-yl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (414)



414: Example 201

Compound **414** (example 201) was synthesized similarly to compound **170** (example 95, scheme 32) starting from compound **412** (example 199) instead of compound **59**.

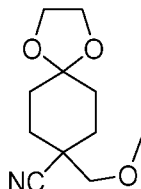
¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 7.91 (s, 2H), 7.46 (d, J = 3.71 Hz, 1H), 2.95-2.88 (m, 2H), 2.74-2.63 (m, 2H), 2.45-2.35 (m, 1H), 2.31 (s, 3H), 1.98-1.85 (m, 2H), 0.67-0.63 (m, 3H), 0.53-0.49 (m, 2H), 0.39-0.29 (m, 2H), 0.15-0.08 (m, 1H), -0.09- -0.19 (m, 1H). LC-MS: rt = 1.30 min, MS: 386.1 (calcd), 387.3 (M+H⁺, found).

Example 202

2-Amino-6-cyano-6-(methoxymethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (416)

Intermediate compound 415

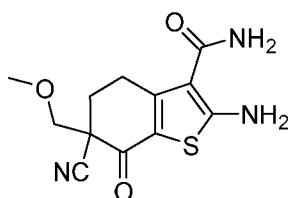
8-(Methoxymethyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (415)



415

Intermediate **415** was synthesized similarly to compound **41** (scheme 4) starting from 1,4-dioxaspiro[4.5]decane-8-carbonitrile (**40**) and using chloromethyl methyl ether instead of (bromomethyl)cyclobutane.

2-Amino-6-cyano-6-(methoxymethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (416)



416: Example 202

Compound **416** (example 202) was synthesized similarly to compound **246** (example 129, scheme 57) starting from compound **415** instead of compound **241**.

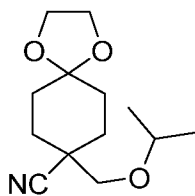
¹H NMR: 400 MHz, DMSO-*d*₆, δ (ppm): 7.11 (bs, 2H), 3.73 (d, *J* = 9.5 Hz, 1H), 3.67 (d, *J* = 9.5 Hz, 1H), 3.33 (s, 3H), 3.06 (t, *J* = 6.0 Hz, 2H), 2.41-2.35 (m, 1H), 2.32-2.25 (m, 1H). LC-MS: rt = 0.88 min, MS: 279.1 (calcd), 280.1 (M+H⁺, found).

Example 203

2-Amino-6-cyano-6-(isopropoxymethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (418)

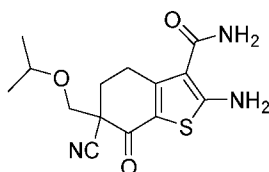
Intermediate compound 417

8-(Isopropoxymethyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (417)

**417**

Intermediate **417** was synthesized similarly to compound **41** (scheme 4) starting from 1,4-dioxaspiro[4.5]decane-8-carbonitrile (**40**) and using 2-(chloromethoxy)propane instead of (bromomethyl)cyclobutane.

2-Amino-6-cyano-6-(isopropoxymethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (418)

**418: Example 203**

Compound **418** (example 203) was synthesized similarly to compound **246** (example 129, scheme 57) starting from compound **417** instead of compound **241**.

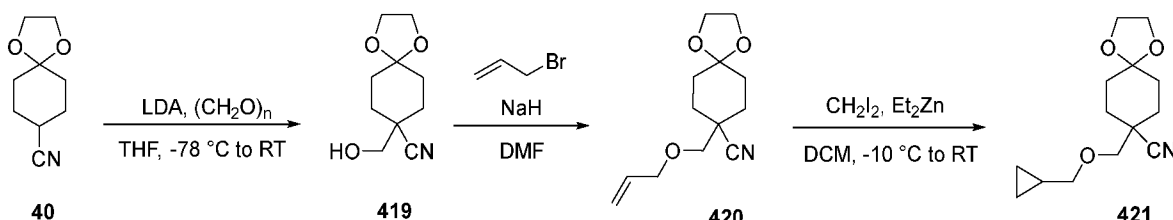
¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.26 (s, 2H), 7.08 (s, 2H), 3.74-3.66 (m, 2H), 3.64-3.59 (m, 1H), 3.04 (t, *J* = 6.0 Hz, 2H), 2.37-2.24 (m, 2H), 1.10-1.06 (m, 6H). LC-MS: rt = 1.04 min, MS: 307.1 (calcd), 308.2 (M+H⁺, found).

Example 204

2-Amino-6-cyano-6-((cyclopropylmethoxy)methyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (422)

Intermediate compound 421

8-((Cyclopropylmethoxy)methyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile

Scheme 98**Scheme 4**

Step 1. 8-(Hydroxymethyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (419)

A flame-dried round-bottom flask was evacuated, filled with Ar and charged with LDA (2.63 mL, 1 M in THF/hexane, 2.63 mmol) and dry THF (2 mL). The resulting solution was cooled to -

78 °C and 1,4-dioxaspiro[4.5]decane-8-carbonitrile (**40**, scheme 4) (412 mg, 2.39 mmol) dissolved in 1 mL THF was added. The mixture was stirred at -78 °C for 1 hour and then paraformaldehyde (108 mg, 3.59 mmol) suspended in 2.78 mL THF was slowly added. The reaction vessel was taken out of the acetone/dry ice bath and the mixture was allowed to warm to RT overnight. The mixture was then quenched with saturated aqueous NH₄Cl solution (30 mL) and extracted with EA (3 x 30 mL). The combined organics were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated to afford title compound **419** as a yellow solid (480.3 mg, >99% yield), which was not characterized and used directly for the next step.

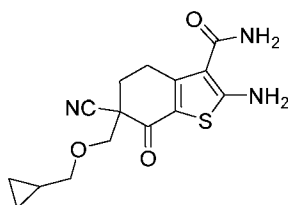
Step 2. 8-((Allyloxy)methyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (**420**)

To a solution of **419** (150 mg, 0.761 mmol) in DMF (6 mL) was added sodium hydride (36.5 mg, 0.913 mmol). The reaction mixture was stirred at RT for 30 minutes, then allyl bromide (78.9 µL, 0.913 mmol) was added. The resulting mixture was stirred at RT for 4 hours, then diluted with water (10 mL) and EA (15 mL). The layers were separated and the aqueous phase was extracted with another 10 mL of EA. The combined organics were washed with water (2 x 15 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 70% of EA in hexane) to afford title compound **420** as a colorless oil (72 mg, 40% yield), which was not characterized and used directly for the next step.

Step 3. 8-((Cyclopropylmethoxy)methyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (**421**)

Diethylzinc (0.61 mL, 1 M in hexane, 0.61 mmol) and diiodomethane (97.8 µL, 1.21 mmol) were added to a solution of **420** (72 mg, 0.303 mmol) in dry DCM (3 mL) under argon at -10 °C. The resulting solution was stirred at -10 °C for 15 minutes, then allowed to reach room temperature and stirred at RT for 20 hours. The reaction mixture was quenched with saturated aqueous NH₄Cl solution (10 mL) and the layers were separated. The organic phase was dried over Na₂SO₄, filtered and concentrated to afford title compound **421** as a colorless oil (98 mg, >99% yield), which was not characterized and used directly for the next step.

2-Amino-6-cyano-6-((cyclopropylmethoxy)methyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (422**)**



422: Example 204

Compound **422** (example 204) was synthesized similarly to compound **246** (example 129, scheme 57) starting from compound **421** (scheme 98) instead of compound **241**.

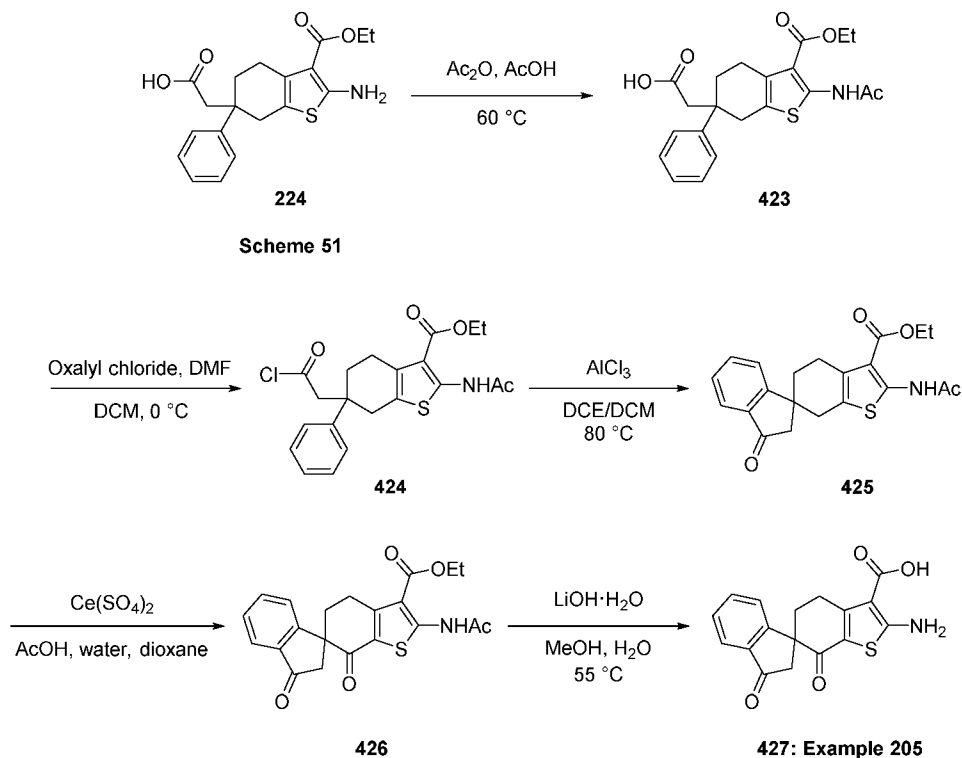
¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.27 (s, 2H), 7.10 (bs, 2H), 3.80-3.77 (m, 1H), 3.74-3.70 (m, 1H), 3.37-3.32 (m, 2H), 3.07-3.02 (m, 2H), 2.41-2.27 (m, 2H), 1.02-0.95 (m, 1H),

0.49-0.41 (m, 2H), 0.20-0.13 (m, 2H). LC-MS: rt = 0.99 min, MS: 319.1 (calcd), 320.1 (M+H⁺, found).

Example 205

2-Amino-3',7-dioxo-2',3',4,7-tetrahydro-5H-spiro[benzo[b]thiophene-6,1'-indene]-3-carboxylic acid (**427**)

Scheme 99



Step 1. 2-(2-Acetamido-3-(ethoxycarbonyl)-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophen-6-yl)acetic acid (**423**)

A suspension of **224** (scheme 51) (1.0 g, 2.78 mmol) in acetic acid (15.9 mL) was treated with acetic anhydride (526 μ L, 5.56 mmol) and the resulting mixture was stirred at 60 °C for 45 minutes. The mixture was then allowed to cool to RT, diluted with EA and washed successively with saturated aqueous NaHCO₃, water and brine (10 mL each), then dried over Na₂SO₄, filtered and concentrated to afford title compound **423** as an off-white solid (1.04 g, 93% yield). LC-MS: rt = 1.45 min, MS: 401.1 (calcd), 402.3 (M+H⁺, found).

Step 2. Ethyl 2-acetamido-6-(2-chloro-2-oxoethyl)-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**424**)

To a suspension of **423** (1.04 g, 2.59 mmol) in DCM (20.8 mL) at 0 °C was added dropwise oxalyl chloride (438 μ L, 5.18 mmol) and 1 drop of DMF. The mixture was stirred at RT for 3 hours. The reaction progress was followed by LCMS by quenching an aliquot with MeOH. The solvent was removed in vacuo to afford title compound **424** as an orange solid that was used for the next

step without further purification or characterization. LC-MS: *rt* = 1.64 min, MS: 415.1 (calcd for M-Cl+OMe), 416.2 (M-Cl+OMe+H⁺, found).

Step 3. Ethyl 2-acetamido-3'-oxo-2',3',4,7-tetrahydro-5H-spiro[benzo[*b*]thiophene-6,1'-indene]-3-carboxylate (**425**)

5 A suspension of aluminium chloride (839 mg, 6.23 mmol) in DCM (2.18 mL) was cooled to 0 °C and a solution of **424** (1.09 g, 2.60 mmol) in DCE (3.27 mL) was added dropwise. The reaction was heated at reflux for 1.5 hours, then poured onto ice-water. The layers were separated, the aqueous layer was extracted with DCM and the combined organics were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to afford title
10 compound **425** as an off-white solid (924 mg, 93% yield). LC-MS: *rt* = 1.55 min, MS: 383.1 (calcd), 384.2 (M+H⁺, found).

Step 4. Ethyl 2-acetamido-3',7-dioxo-2',3',4,7-tetrahydro-5H-spiro[benzo[*b*]thiophene-6,1'-indene]-3-carboxylate (**426**)

To a suspension of **425** (600 mg, 1.56 mmol) in acetic acid (11.0 mL), dioxane (11.0 mL)
15 and water (11.0 mL) was added ceric sulfate (3.19 g, 7.82 mmol). The mixture was sonicated for 1 min, then stirred at RT for 16 hours. Subsequently, the mixture was diluted with water and EA, sonicated for 3 minutes, filtered, and the filtrate was transferred into a separatory funnel. The layers were separated and the organic phase was washed successively with a 1 N aqueous solution of NaOH and brine, then dried over Na₂SO₄, filtered and concentrated to afford title
20 compound **426** as an off-white powder (554 mg, 89% yield). LC-MS: *rt* = 1.40 min, MS: 397.1 (calcd), 398.1 (M+H⁺, found).

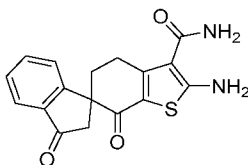
Step 5. 2-Amino-3',7-dioxo-2',3',4,7-tetrahydro-5H-spiro[benzo[*b*]thiophene-6,1'-indene]-3-carboxylic acid (**427**)

To a suspension of **426** (377 mg, 949 μmol) in MeOH (58.1 mL) was added a solution of
25 lithium hydroxide monohydrate (272 mg, 6.48 mmol) in water (58.1 mL). The reaction mixture was stirred at 55 °C for 24 hours, then allowed to cool to RT. The mixture was concentrated to remove most of the organic solvent. Then, the aqueous layer was acidified by slowly adding a 2 N aqueous solution of HCl and the product was extracted with EA. The organic layers were combined then washed with brine, dried over Na₂SO₄, filtered and concentrated to afford title compound **427** (326
30 mg, >99% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.74 (d, *J* = 7.7 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.80 Hz, 1H), 3.37-3.34 (m, 1H), 3.28-3.20 (m, 1H), 3.13 (d, *J* = 18.67 Hz, 1H), 2.70 (d, *J* = 18.70 Hz, 1H), 2.49-2.34 (m, 2H). LC-MS: *rt* = 1.01 min, MS: 327.1 (calcd), 328.0 (M+H⁺, found).

Example 206

2-Amino-3',7-dioxo-2',3',4,7-tetrahydro-5H-spiro[benzo[*b*]thiophene-6,1'-indene]-3-carboxamide (428**)**



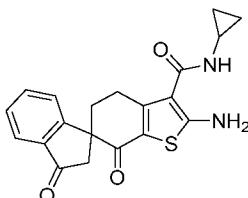
428: Example 206

Compound **428** (example 206) was synthesized similarly to compound **238** (example 127, scheme 55) starting from compound **427** (scheme 99) instead of compound **237**.

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.75 (d, *J* = 7.7 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 3.26 (t, *J* = 6.4 Hz, 1H), 3.20-3.11 (m, 2H), 2.72 (d, *J* = 18.7 Hz, 1H), 2.53-2.47 (m, 1H), 2.43-2.36 (m, 1H). LC-MS: *rt* = 0.93 min, MS: 326.1 (calcd), 327.1 (*M*+*H*⁺, found).

Example 207

2-Amino-*N*-cyclopropyl-3',7-dioxo-2',3',4,7-tetrahydro-5H-spiro[benzo[*b*]thiophene-6,1'-indene]-3-carboxamide (**429**)



429: Example 207

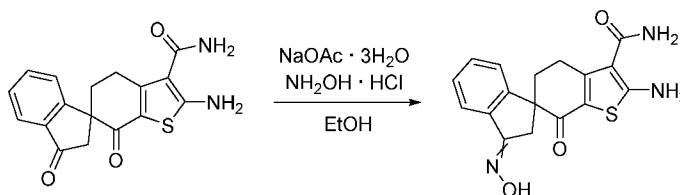
Compound **429** (example 207) was synthesized similarly to compound **170** (example 95, scheme 32) starting from compound **427** (scheme 99) instead of compound **59**.

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.74 (d, *J* = 7.7 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.52-7.47 (m, 2H), 3.21-3.03 (m, 3H), 2.82-2.78 (m, 1H), 2.74-2.66 (m, 1H), 2.47-2.42 (m, 1H), 2.38-2.33 (m, 1H), 0.84-0.76 (m, 2H), 0.65-0.59 (m, 2H). LC-MS: *rt* = 1.03 min, MS: 366.1 (calcd), 367.2 (*M*+*H*⁺, found).

Example 208

2-Amino-3'-(hydroxyimino)-7-oxo-2',3',4,7-tetrahydro-5H-spiro[benzo[*b*]thiophene-6,1'-indene]-3-carboxamide (**430**)

Scheme 100



428

430: Example 208

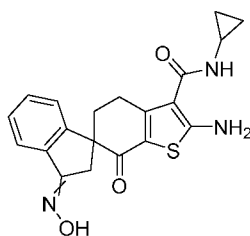
To a solution of **428** (70.0 mg, 214 μmol) in EtOH (2.47 mL) was added hydroxylamine hydrochloride (44.7 mg, 643 μmol) and sodium acetate trihydrate (135 mg, 991 μmol). The mixture

was stirred at RT for 16 hours. The reaction mixture was then diluted with water and EA, the layers were separated and the organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by Semi-Prep HPLC-MS (eluent gradient from 25% to 100% of MeOH in 10 mM ammonium bicarbonate) to afford title compound **430** as a white solid (50.9 mg, 70 % yield; single product, *E/Z* stereochemistry not established).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 10.98 (s, 1H), 8.12 (s, 2H), 7.56-7.53 (m, 1H), 7.32-7.28 (m, 2H), 7.09-6.94 (m, 1H), 3.17-3.12 (m, 1H), 3.10-3.00 (m, 2H), 2.72 (d, *J* = 18.41 Hz, 1H), 2.27-2.15 (m, 2H). LC-MS: rt = 0.92 min, MS: 341.1 (calcd), 342.1 (M+H⁺, found).

Example 209

2-Amino-*N*-cyclopropyl-3'-(hydroxyimino)-7-oxo-2',3',4,7-tetrahydro-5H-spiro[benzo[*b*]thiophene-6,1'-indene]-3-carboxamide (**431**)



431: Example 209

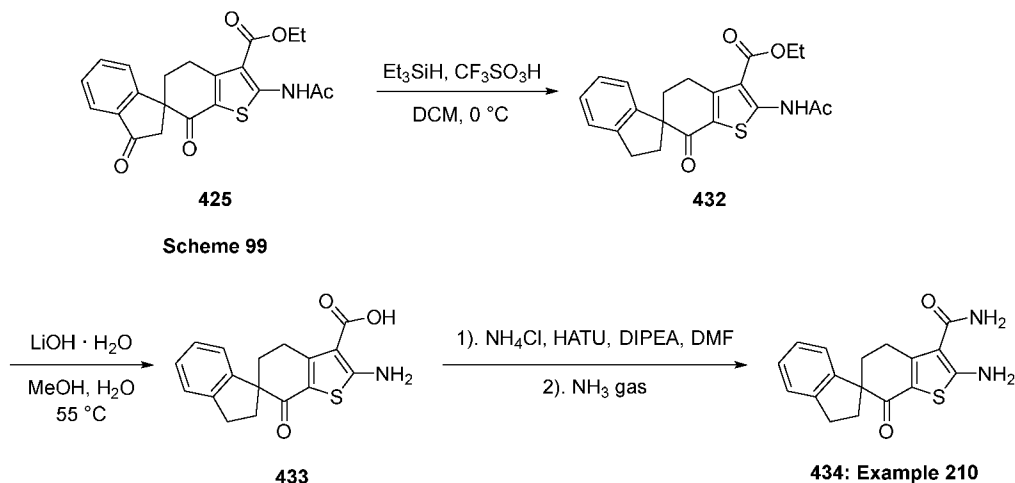
Compound **431** (example 209; single product, *E/Z* stereochemistry not established) was synthesized similarly to compound **430** (example 208, scheme 100) starting from compound **429** (example 207) instead of compound **428**.

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.69-7.67 (m, 1H), 7.34-7.31 (m, 2H), 7.26-7.24 (m, 1H), 3.33 (d, *J* = 12.9 Hz, 1H), 3.06-3.03 (m, 2H), 2.95 (d, *J* = 18.5 Hz, 1H), 2.82-2.73 (m, 1H), 2.35-2.20 (m, 2H), 0.81-0.76 (m, 2H), 0.64-0.60 (m, 2H). LC-MS: rt = 1.10 min, MS: 381.1 (calcd), 382.3 (M+H⁺, found).

Example 210

2-Amino-7-oxo-2',3',4,7-tetrahydro-5H-spiro[benzo[*b*]thiophene-6,1'-indene]-3-carboxamide (**434**)

Scheme 101



Step 1. Ethyl 2-acetamido-7-oxo-2',3',4,7-tetrahydro-5H-spiro[benzo[*b*]thiophene-6,1'-indene]-3-carboxylate (432**)**

A solution of trifluoromethanesulfonic acid (71.2 uL, 788 umol) in dry DCM (300 uL) was added dropwise to a stirred solution of **425** (scheme 99) (78.3 mg, 197 umol) in dry DCM (300 uL) at 0 °C under nitrogen. Then, a solution of triethylsilane (95.4 uL, 591 umol) in dry DCM (300 uL) was added dropwise. After 5 minutes of stirring, additional trifluoromethanesulfonic acid (71.2 uL, 788 umol) was added, followed by the addition of triethylsilane (95.4 uL, 591 umol). The mixture was stirred at RT for 1 hour, then poured into cold saturated aqueous NaHCO₃ solution and extracted with DCM. The organic layer was dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 100% of EA in hexane) to afford title compound **432** as a brown solid (44.8 mg, 59 % yield). LC-MS: rt = 1.77 min, MS: 383.1 (calcd), 384.2 (M+H⁺, found).

Step 2. 2-Amino-7-oxo-2',3',4,7-tetrahydro-5H-spiro[benzo[*b*]thiophene-6,1'-indene]-3-carboxylic acid (433**)**

To a suspension of **432** (44.8 mg, 117 umol) in MeOH (7.15 mL) was added a solution of lithium hydroxide monohydrate (33.5 mg, 798 umol) in water (7.15 mL). The reaction mixture was stirred at 55 °C for 48 hours, then allowed to cool to RT and concentrated to remove most of the organic solvent. The aqueous residue was acidified by slowly adding a 2 N aqueous solution of HCl and the product was extracted with EA. The combined organics were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by reverse-phase flash column chromatography (eluent gradient from 10% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **433** as a white solid (20.0 mg, 55% yield). LC-MS: rt = 1.37 min, MS: 313.1 (calcd), 314.1 (M+H⁺, found).

Step 3. 2-Amino-7-oxo-2',3',4,7-tetrahydro-5H-spiro[benzo[*b*]thiophene-6,1'-indene]-3-carboxamide (434**)**

To a mixture of **433** (20.0 mg, 63.8 μmol) and ammonium chloride (34.3 mg, 638 μmol) in anhydrous DMF (798 μL) were added HATU (49.5 mg, 128 μmol) and *N,N*-diisopropylethylamine (33.3 μL , 191 μmol). The reaction mixture was stirred at RT for 10 minutes, then gaseous NH_3 was bubbled through the mixture for additional 40 minutes. Afterwards, the reaction was quenched with a saturated aqueous NH_4Cl solution and extracted with EA. The organic layer was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by reverse phase flash column chromatography (eluent gradient from 10% to 100% of CH_3CN in 0.1% formic acid (v/v) in water) to afford title compound **434** as an off-white solid (14.7 mg, 74% yield).

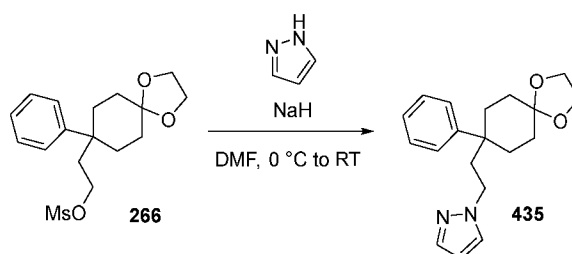
^1H NMR: 400 MHz, CD_3OD , δ (ppm): 7.25 (d, $J = 7.5$ Hz, 1H), 7.20-7.16 (m, 1H), 7.12 (t, $J = 7.4$ Hz, 1H), 7.03 (d, $J = 7.5$ Hz, 1H), 3.09-3.04 (m, 2H), 3.04-2.98 (m, 2H), 2.63-2.58 (m, 1H), 2.36-2.31 (m, 1H), 2.21-2.16 (m, 1H), 2.14-2.06 (m, 1H). LC-MS: $t_{\text{r}} = 1.16$ min, MS: 312.1 (calcd), 313.2 ($\text{M}+\text{H}^+$, found).

Examples 212-221

Intermediate compound 435

1-(2-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)-1H-pyrazole (435)

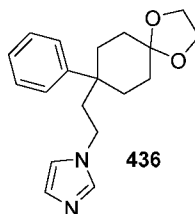
Scheme 102



To a solution of pyrazole (40 mg, 0.59 mmol) in anhydrous DMF (2 mL) at 0 °C was added sodium hydride (24 mg, 60% in mineral oil, 0.59 mmol) and the mixture was stirred for 15 minutes at the same temperature. Then, a solution of **266** (scheme 66) (100 mg, 0.294 mmol) in anhydrous DMF (1 mL) was added and the reaction mixture was allowed to reach RT and stirred for 16 hours. Then, the mixture was quenched with saturated aqueous NH_4Cl solution, diluted with water and extracted with EA. The organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 40% to 100% of EA in hexane) to afford title compound **435** as a colorless oil (78 mg, 85% yield). LC-MS: $t_{\text{r}} = 1.37$ min, MS: 312.2 (calcd), 313.2 ($\text{M}+\text{H}^+$, found).

Intermediate compound 436

1-(2-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)-1H-imidazole (436)

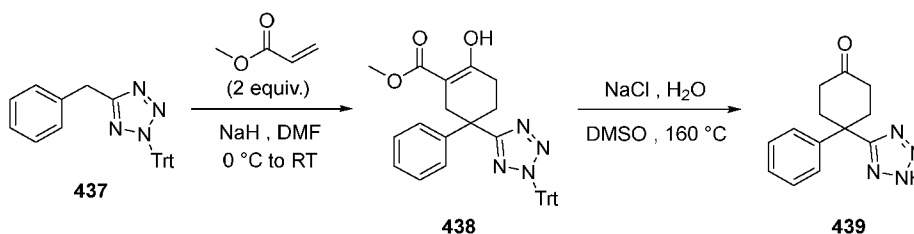


Intermediate **436** was synthesized similarly to intermediate **435** (scheme 102), but using imidazole instead of pyrazole. LC-MS: rt = 0.77 min, MS: 312.2 (calcd), 313.2 (M+H⁺, found).

Intermediate compound 439

4-Phenyl-4-(2H-tetrazol-5-yl)cyclohexan-1-one (**439**)

Scheme 103



Step 1. Methyl 4-hydroxy-1-(2-trityl-2H-tetrazol-5-yl)-1,2,5,6-tetrahydro-[1,1'-biphenyl]-3-carboxylate (**438**)

To a stirred suspension of 5-benzyl-2-trityl-2H-tetrazole **437** (N. Choi *et al.* WO2007124544) (1.06 g, 2.63 mmol) and methyl acrylate (0.48 mL, 5.26 mmol) in anhydrous DMF (10 mL) at 0 °C was added sodium hydride (211 mg, 60% in mineral oil, 5.26 mmol) and the resulting mixture was vigorously stirred at RT for 2.5 hours. Afterwards, the mixture was cooled down to 0 °C, acidified with 1 N aqueous HCl and extracted with DCM. The combined organics were washed with brine and dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane) to afford title compound **438** as a colorless oil (350 mg, 24% yield). LC-MS: rt = 2.15 min, MS: 542.2 (calcd), 559.3 ([M+H₂O-H]⁺, found).

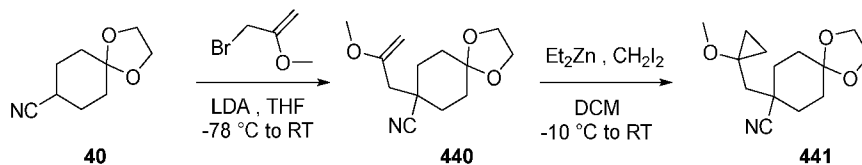
Step 2. 4-Phenyl-4-(2H-tetrazol-5-yl)cyclohexan-1-one (**439**)

To a solution of **438** (350 mg, 0.645 mmol) in DMSO (1.3 mL) were added H₂O (0.013 mL) and NaCl (11 mg, 0.19 mmol) and the resulting mixture was stirred at 160 °C for 1 hour. Then, the mixture was diluted with H₂O and extracted with EA. The combined organics were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 20% of MeOH in DCM) to afford title compound **439** as a light-orange oil (69 mg, 44% yield). LC-MS: rt = 1.71 min, MS: 242.1 (calcd), 243.3 (M+H⁺, found).

Intermediate compound 441

8-((1-Methoxycyclopropyl)methyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (**441**)

Scheme 104



Scheme 4

Step 1. 8-(2-Methoxyallyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (440**)**

To a solution of 1,4-dioxaspiro[4.5]decane-8-carbonitrile (**40**, scheme 4) (959 mg, 5.56 mmol) in anhydrous THF (13 mL) at -78 °C was added dropwise LDA (8.34 mL, 1 M in THF/hexane, 8.34 mmol). The reaction mixture was stirred at -78 °C for 30 min, then a solution of 3-bromo-2-methoxyprop-1-ene (*J. Org. Chem.* 42, 15, p. 2545, 1977) (840 mg, 5.56 mmol) in anhydrous THF (13 mL) was added dropwise. The reaction mixture was allowed to reach RT and stirred for 16 hours. Afterwards, the reaction mixture was quenched with saturated NH₄Cl solution and extracted with EA. The organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane) to afford title compound **440** as a colorless oil (756 mg, 57% yield), which was not characterized and used directly for the next step.

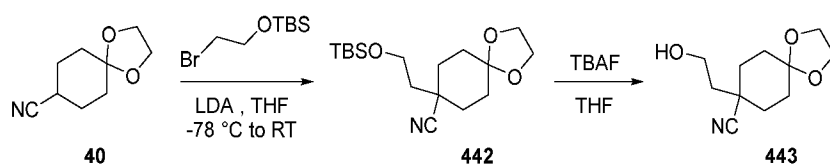
Step 2. 8-((1-Methoxycyclopropyl)methyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (441**)**

To a solution of **440** (688 mg, 2.90 mmol) in anhydrous DCM (29 mL) at -10 °C were added diethylzinc (5.80 mL, 1 M in hexane, 5.80 mmol) and diiodomethane (0.934 mL, 11.6 mmol). The reaction mixture was stirred at -10 °C for 30 min, then it was allowed to reach RT and stirred for 16 hours. Afterwards, the reaction mixture was quenched with saturated NH₄Cl solution and the layers were separated. The organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane) to afford title compound **441** as a colorless oil (340 mg, 47% yield) as a colorless oil, which was not characterized and used directly for the synthesis of relevant examples.

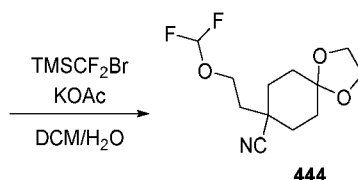
Intermediate compound 444

8-(2-(Difluoromethoxy)ethyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (444**)**

Scheme 105



Scheme 4



Step 1. 8-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (442)

To a solution of 1,4-dioxaspiro[4.5]decane-8-carbonitrile (**40**, scheme 4) (1.0 g, 5.80 mmol) in anhydrous THF (12 mL) at -78 °C was added dropwise LDA (6.38 mL, 1 M in THF/hexane, 6.38 mmol). The reaction mixture was stirred at -78 °C for 1 hour, then (2-bromoethoxy)(*tert*-butyl)dimethylsilane (1.56 g, 6.38 mmol) was added. The reaction mixture was allowed to reach RT and stirred for 16 hours. Afterwards, the reaction mixture was quenched with saturated NH₄Cl solution and extracted with EA. The organic phase was dried over Na₂SO₄, filtered and concentrated to afford title compound **442** (1.89 g, >99% yield) as a light-yellow oil, which was not characterized and used directly for the next step without further purification.

Step 2. 8-(2-Hydroxyethyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (443)

To a solution of **442** (1.79 g, 5.50 mmol) in anhydrous THF (55 mL) at 0 °C was added TBAF (8.25 mL, 1 M in THF, 8.25 mmol). The reaction mixture was stirred at RT for 30 minutes, then it was quenched with saturated NH₄Cl solution and extracted with EA. The organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 100% of EA in hexane) to afford title compound **443** as a colorless oil (1.09 g, 94% yield), which was not characterized and used directly for the next step.

Step 3. 8-(2-(Difluoromethoxy)ethyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (444)

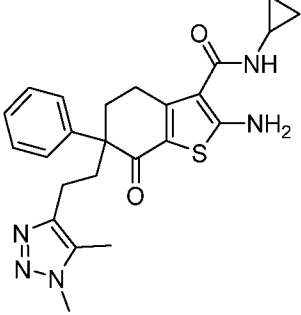
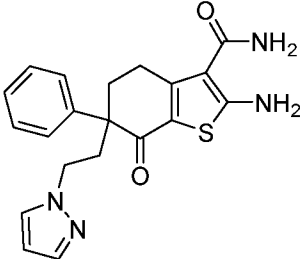
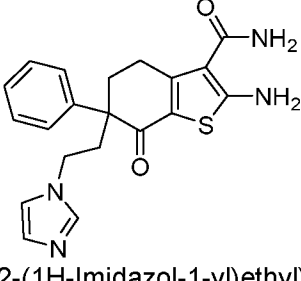
A plastic vial was charged with **443** (54 mg, 0.256 mmol) and potassium acetate (101 mg, 1.02 mmol), then, DCM (0.16 mL) and water (0.16 mL) were added. The mixture was stirred at RT and (bromodifluoromethyl)trimethylsilane (0.081 mL, 0.511 mmol) was added. The resulting mixture was stirred for 48 hours. Afterwards, the mixture was diluted with water and extracted with DCM. The combined organics were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 50% of EA in hexane) to afford title compound **444** as a colorless oil (19 mg, 28% yield), which was not characterized and used directly for the synthesis of relevant examples.

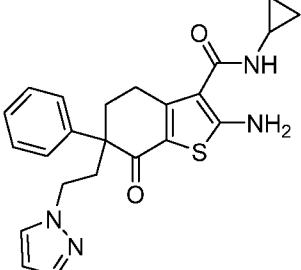
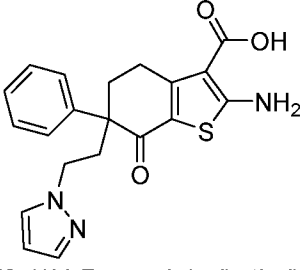
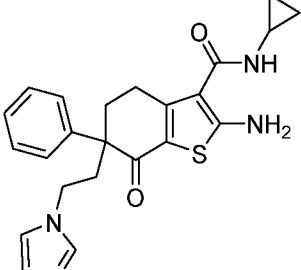
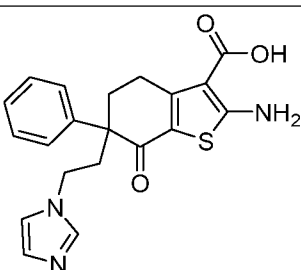
Compounds 445-454

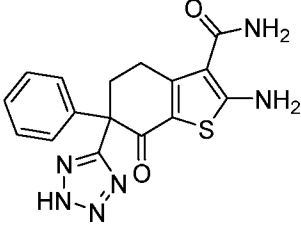
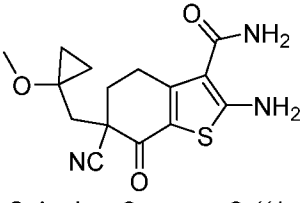
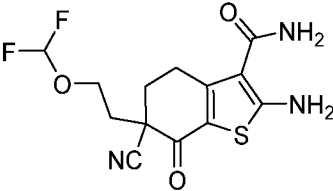
Compound **445** (example 212) was synthesized similarly to compound **170** (example 95, scheme 32) starting from compound **245** (example 211, scheme 57) instead of compound **59**. Compounds **446-447** and **453-454** (examples 213-214 and 220-221) were synthesized starting from intermediates **435** (scheme 102), **436**, **441** (scheme 104) and **444** (scheme 105), respectively, following the procedure reported for the synthesis of compound **246** (example 129, scheme 57) from intermediate **241**. Compound **452** (example 219) was synthesized similarly to compound **246** (example 129, scheme 57) starting from intermediate **439** (scheme 103) instead of intermediate **242**. Compounds **448** (example 215) and **450** (example 217) were synthesized starting from intermediates **435** (scheme 102) and **436**, respectively, following the procedure

reported for the synthesis of compound **192** (example 104, scheme 40) from intermediate **185**. Compounds **449** (example 216) and **451** (example 218) were synthesized starting from intermediates **435** (scheme 102) and **436**, respectively, following the procedure reported for the synthesis of compound **189** (example 102, scheme 40) from intermediate **185**. Characterization of compounds **445-454** (examples 212-221) is provided in table 8.

Table 8. Characterization of compounds **445-454** (examples 212-221).

Ex. #	Cpd. #	Structure	Characterization
212	445	 2-Amino-N-cyclopropyl-6-(2-(1,5-dimethyl-1H-1,2,3-triazol-4-yl)ethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹ H NMR: 400 MHz, DMSO-d ₆ , δ (ppm): 7.82 (bs, 2H), 7.34-7.30 (m, 5H), 7.25-7.21 (m, 1H), 3.81 (s, 3H), 2.79-2.58 (m, 4H), 2.46-2.40 (m, 1H), 2.35-2.22 (m, 2H), 2.09 (s, 3H), 2.05-1.92 (m, 2H), 0.63-0.58 (m, 2H), 0.49-0.45 (m, 2H). LC-MS: rt = 1.15 min, MS: 449.2 (calcd), 450.3 (M+H ⁺ , found).
213	446	 6-(2-(1H-Pyrazol-1-yl)ethyl)-2-amino-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹ H NMR: 400 MHz, DMSO-d ₆ , δ (ppm): 8.11 (s, 2H), 7.60 (dd, J = 2.3, 0.7 Hz, 1H), 7.37-7.31 (m, 5H), 7.27-7.23 (m, 1H), 6.85 (bs, 2H), 6.16-6.15 (m, 1H), 4.13-4.06 (m, 1H), 3.92-3.84 (m, 1H), 2.88-2.82 (m, 1H), 2.71-2.65 (m, 1H), 2.64-2.57 (m, 1H), 2.33-2.19 (m, 3H). LC-MS: rt = 1.08 min, MS: 380.1 (calcd), 381.1 (M+H ⁺ , found).
214	447	 6-(2-(1H-Imidazol-1-yl)ethyl)-2-amino-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 8.19 (s, 1H), 7.36-7.31 (m, 5H), 7.29-7.23 (m, 1H), 7.21 (s, 1H), 4.39-4.32 (m, 1H), 4.03-3.95 (m, 1H), 2.97-2.91 (m, 1H), 2.69-2.57 (m, 2H), 2.42-2.34 (m, 3H). LC-MS: rt = 0.61 min, MS: 380.1 (calcd), 381.2 (M+H ⁺ , found).

215	448	 6-(2-(1H-Pyrazol-1-yl)ethyl)-2-amino-N-cyclopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.46 (dd, <i>J</i> = 2.3, 0.7 Hz, 1H), 7.40 (dd, <i>J</i> = 2.0, 0.7 Hz, 1H), 7.35-7.30 (m, 4H), 7.26-7.21 (m, 1H), 6.20 (t, <i>J</i> = 2.1 Hz, 1H), 4.34-4.26 (m, 1H), 3.99-3.92 (m, 1H), 2.80-2.74 (m, 1H), 2.70-2.56 (m, 3H), 2.37-2.27 (m, 3H), 0.75-0.66 (m, 2H), 0.55-0.47 (m, 2H). LC-MS: rt = 1.18 min, MS: 420.2 (calcd), 421.2 (M+H⁺, found).
216	449	 6-(2-(1H-Pyrazol-1-yl)ethyl)-2-amino-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.48 (s, 1H), 7.41 (s, 1H), 7.35-7.30 (m, 4H), 7.26-7.22 (m, 1H), 6.21 (s, 1H), 4.34-4.27 (m, 1H), 4.01-3.93 (m, 1H), 3.23-3.17 (m, 1H), 2.61-2.56 (m, 1H), 2.50-2.41 (m, 1H), 2.40-2.27 (m, 3H). LC-MS: rt = 1.28 min, MS: 381.1 (calcd), 382.2 (M+H⁺, found).
217	450	 6-(2-(1H-Imidazol-1-yl)ethyl)-2-amino-N-cyclopropyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.51 (s, 1H), 7.35-7.33 (m, 4H), 7.28-7.23 (m, 1H), 7.03 (s, 1H), 6.89 (s, 1H), 4.24-4.16 (m, 1H), 3.83-3.75 (m, 1H), 2.81-2.75 (m, 1H), 2.70-2.56 (m, 3H), 2.36-2.28 (m, 3H), 0.75-0.67 (m, 2H), 0.55-0.48 (m, 2H). LC-MS: rt = 0.79 min, MS: 420.2 (calcd), 421.2 (M+H⁺, found).
218	451	 6-(2-(1H-Imidazol-1-yl)ethyl)-2-amino-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid	¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.63 (s, 1H), 7.35-7.30 (m, 4H), 7.26-7.22 (m, 1H), 7.08 (s, 1H), 6.95 (s, 1H), 4.27-4.19 (m, 1H), 3.90-3.81 (m, 1H), 3.29-3.24 (m, 1H), 2.62-2.57 (m, 1H), 2.49-2.41 (m, 1H), 2.36-2.29 (m, 3H). LC-MS: rt = 0.79 min, MS: 381.1 (calcd), 382.2 (M+H⁺, found).

219	452	 2-Amino-7-oxo-6-phenyl-6-(2H-tetrazol-5-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.34-7.25 (m, 3H), 7.15-7.13 (m, 2H), 3.17-3.10 (m, 1H), 3.03-2.96 (m, 2H), 2.76-2.67 (m, 1H). LC-MS: rt = 0.81 min, MS: 354.1 (calcd), 355.1 (M+H⁺, found).
220	453	 2-Amino-6-cyano-6-((1-methoxycyclopropyl)methyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.26 (s, 2H), 7.11 (bs, 2H), 3.15 (s, 3H), 3.11-3.07 (m, 2H), 2.59-2.53 (m, 1H), 2.45-2.38 (m, 1H), 2.26 (d, J = 15.1 Hz, 1H), 2.07 (d, J = 15.1 Hz, 1H), 0.77-0.71 (m, 2H), 0.62-0.50 (m, 2H). LC-MS: rt = 0.95 min, MS: 319.1 (calcd), 320.1 (M+H⁺, found).
221	454	 2-Amino-6-cyano-6-(2-(difluoromethoxy)ethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹H NMR: 400 MHz, CD₃OD, δ (ppm): 6.38 (t, J = 75.1 Hz, 1H), 4.12 (t, J = 6.6 Hz, 2H), 3.16 (t, J = 6.0 Hz, 2H), 2.55 (dt, J = 13.7, 5.6 Hz, 1H), 2.45-2.33 (m, 2H), 2.22-2.15 (m, 1H). ¹⁹F NMR: 376 MHz, CD₃OD, δ (ppm): -86.2 (dd, J = 75.1, 7.5 Hz). LC-MS: rt = 0.90 min, MS: 329.1 (calcd), 330.1 (M+H⁺, found).

Example 222

2-Amino-6-(oxazol-5-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (462) and

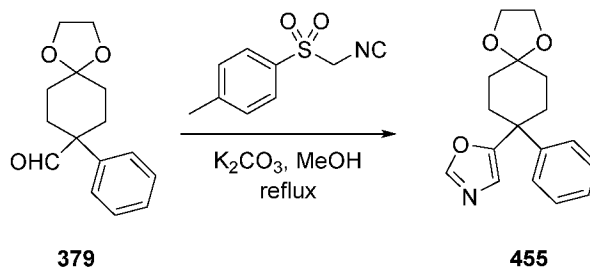
Example 223

2-Amino-6-(oxazol-5-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (463)

Intermediate compound 455

5-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)oxazole (455)

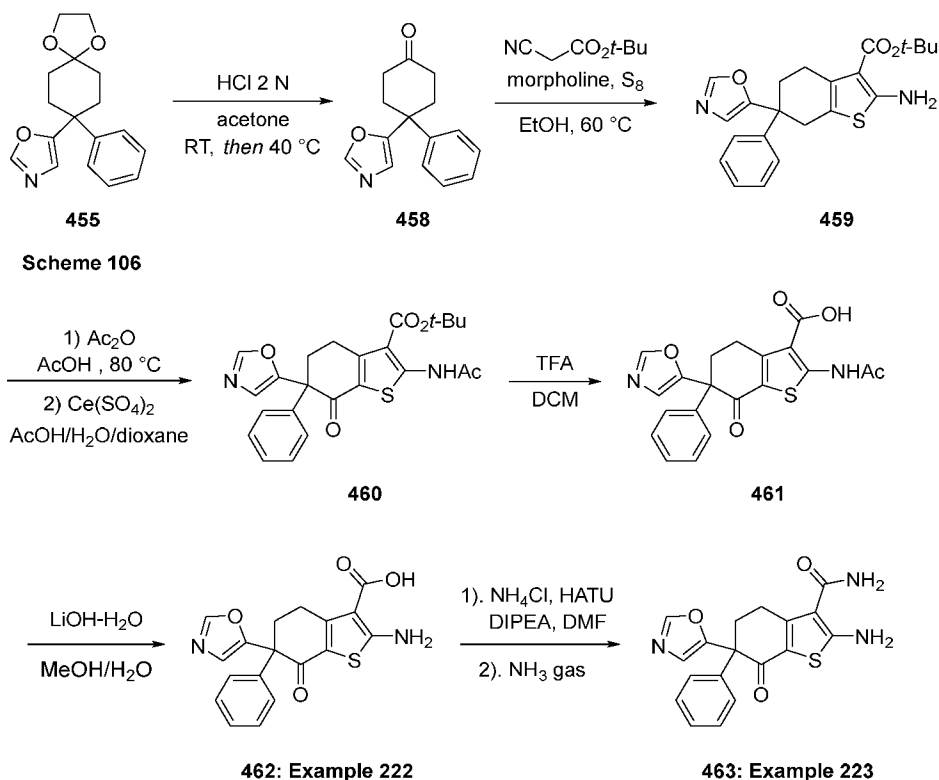
Scheme 106



To a solution of 8-phenyl-1,4-dioxaspiro[4.5]decane-8-carbaldehyde (**379**) (*Bioorg Med. Chem Lett.* 21, p. 405, 2011) (2.99 g, 12.2 mmol) in MeOH (101 mL) were added K₂CO₃ (5.04 g, 36.5 mmol) and toluenesulfonylmethyl isocyanide (3.56 g, 18.2 mmol). The resulting mixture was stirred under reflux for 16 hours, then allowed to cool to RT and partitioned between EA and water (100 mL each). The layers were separated and the aqueous phase was extracted with another 3 x 50 mL EA. The combined organics were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified twice by flash column chromatography (first eluent gradient from 30% to 100% of EA in hexane; second eluent gradient from 25% to 100% of EA in hexane) to afford the title compound **455** as a yellow solid (592 mg, 17% yield), which was not characterized and used directly for the next step.

2-Amino-6-(oxazol-5-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (462) and
2-Amino-6-(oxazol-5-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (463)

Scheme 107



Step 1. 4-(Oxazol-5-yl)-4-phenylcyclohexan-1-one (**458**)

2 N aqueous HCl (10.3 mL, 20.6 mmol) was added to a solution of **455** (590 mg, 2.07 mmol) in acetone (25.6 mL) and the resulting mixture was stirred at RT for 16 hours. Then, another 5 mL of 2 N aqueous HCl (10 mmol) was added and the mixture was stirred at 40 °C for 5 hours. Subsequently, the mixture was quenched with saturated aqueous NaHCO₃ and concentrated to remove the organic solvent. The residue was extracted with EA (3 x 25 mL). The combined organics were washed with brine (25 mL), dried over Na₂SO₄, filtered and concentrated to afford title compound **458** as a yellow solid (455 mg, 91% yield), which was not characterized and used directly for the next step.

Step 2. *tert*-Butyl 2-amino-6-(oxazol-5-yl)-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**459**)

A suspension of **458** (448 mg, 1.86 mmol), morpholine (178 uL, 2.04 mmol), sulfur (65.7 mg, 256 umol) and *tert*-butyl 2-cyanoacetate (298 uL, 2.04 mmol) in EtOH (1.86 mL) was stirred at 60 °C for 4.5 hours. The mixture was then allowed to cool to RT and concentrated. The residue was purified by flash column chromatography (eluent gradient from 10% to 100% of EA in hexane) to afford title compound **459** as a light-yellow solid (538 mg, 64% yield). LC-MS: rt = 1.64 min, MS: 396.2 (calcd), 397.2 (M+H⁺, found).

Step 3. *tert*-Butyl 2-acetamido-6-(oxazol-5-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**460**)

A mixture of **459** (532 mg, 1.34 mmol) and acetic anhydride (152 μ L, 1.61 mmol) in acetic acid (7.7 mL) was stirred at 80 °C for 1 hour. The mixture was then allowed to cool to RT, diluted with water (8.95 mL), dioxane (8.95 mL) and acetic acid (1.23 mL) and treated with ceric sulfate (3.86 g, 11.6 mmol). The resulting mixture was sonicated for 1 minute, stirred at RT for 2.5 hours, then diluted with water (30 mL) and extracted with EA (3 x 30 mL). The combined organics were successively washed with 1 M aqueous NaOH (30 mL), water (30 mL) and brine (30 mL), dried over Na₂SO₄, filtered and concentrated to afford title compound **460** as a yellow gum (623.3 mg, >99% yield). LC-MS: rt = 1.69 min, MS: 452.1 (calcd), 453.3 (M+H⁺, found).

Step 4. 2-Acetamido-6-(oxazol-5-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**461**)

To a solution of **460** (622 mg, 1.37 mmol) in DCM (12.1 mL) was added TFA (5.79 mL, 75.6 mmol) and the mixture was stirred at RT for 16 hours. Then, the mixture was concentrated to afford title compound **461** as a brown gum (938 mg, >99% yield). LC-MS: rt = 1.30 min, MS: 396.1 (calcd), 397.2 (M+H⁺, found).

Step 5. 2-Amino-6-(oxazol-5-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**462**)

To a solution of **461** (938 mg) in MeOH (3.5 mL) and water (3.5 mL) was added lithium hydroxide monohydrate (406 mg, 9.68 mmol) and the resulting mixture was stirred at RT for 1.5 hours. The mixture was then concentrated to remove most of the organic solvent and the residue was diluted with water (15 mL) and EA (15 mL). The layers were separated and the aqueous phase was acidified by slowly adding 1 N HCl and then extracted with EA (3 x 15 mL). These organics were combined, dried over Na₂SO₄, filtered and concentrated and the residue was purified by reverse-phase column chromatography (eluent gradient from 0% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **462** as a beige solid (279 mg, 57% yield).

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 12.61 (bs, 1H), 8.37 (bs, 2H), 8.30 (s, 1H), 7.42-7.28 (m, 3H), 7.21 (d, *J* = 7.3 Hz, 2H), 6.72 (s, 1H), 3.06 (dt, *J* = 18.5, 4.5 Hz, 1H), 2.89-2.68 (m, 2H), 2.65-2.55 (m, 1H). LC-MS: rt = 1.19 min, MS: 354.1 (calcd), 355.1 (M+H⁺, found).

Step 6. 2-Amino-6-(oxazol-5-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**463**)

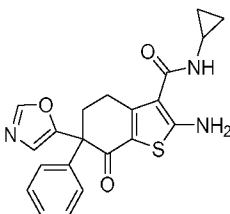
To a solution of **462** (21.5 mg, 60.7 μ mol) in DMF (0.76 mL) were added ammonium chloride (32.5 mg, 607 μ mol), HATU (46.1 mg, 121 μ mol) and *N,N*-diisopropylethylamine (44 μ L, 252 μ mol). The resulting solution was stirred at RT for 10 minutes, then excess of gaseous NH₃ was bubbled through the mixture from a balloon. Stirring continued at RT for 30 minutes, then the mixture was diluted with saturated aqueous NH₄Cl (3 mL) and extracted with EA (3 x 3 mL). The combined organics were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reverse-phase flash column

chromatography (eluent gradient from 0% to 100% of CH₃CN in H₂O with 0.1% (v/v) formic acid), then by Semi-Prep HPLC-MS (eluent gradient from 30% to 100% of MeOH in 10 mM ammonium formate) and then by flash column chromatography (eluent gradient from 0% to 20% of MeOH in DCM) to afford title compound **463** as a white solid (2.7 mg, 13% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 8.16 (s, 1H), 7.41-7.27 (m, 5H), 6.67 (s, 1H), 3.01 (dt, *J* = 16.7, 4.3 Hz, 1H), 2.94-2.84 (m, 2H), 2.82-2.73 (m, 1H). LC-MS: rt = 0.88 min, MS: 353.1 (calcd), 354.1 (M+H⁺, found).

Example 224

2-Amino-*N*-cyclopropyl-6-(oxazol-5-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**464**)



464: Example 224

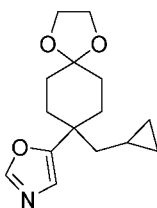
Compound **464** (example 224) was synthesized similarly to compound **170** (example 95, scheme 32) starting from compound **462** (scheme 107) instead of compound **59**.

¹H NMR: 400 MHz, CDCl₃, δ (ppm): 7.85 (s, 1H), 7.40-7.32 (m, 3H), 7.30-7.26 (m, 2H), 7.04 (bs, 2H), 6.69 (s, 1H), 5.53 (s, 1H), 3.00-2.88 (m, 1H), 2.87-2.83 (m, 1H), 2.82-2.79 (m, 1H), 2.78-2.71 (m, 1H), 2.65-2.55 (m, 1H), 0.94-0.75 (m, 2H), 0.62-0.46 (m, 2H). LC-MS: rt = 1.19 min, MS: 393.1 (calcd), 394.2 (M+H⁺, found).

Example 225

Intermediate compound **456**

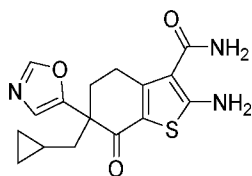
5-(8-(Cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)oxazole (**456**)



456

Intermediate **456** was synthesized similarly to intermediate **455** (scheme 106), starting from compound **113** (scheme 21) instead of compound **379**.

2-Amino-6-(cyclopropylmethyl)-6-(oxazol-5-yl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**465**)



465: Example 225

Compound **465** (example 225) was synthesized similarly to compound **463** (example 223, scheme 107) starting from intermediate **456** instead of intermediate **455**.

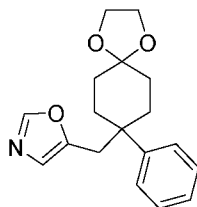
¹H NMR: 400 MHz, CD₃OD, δ (ppm): 8.15 (s, 1H), 6.98 (s, 1H), 3.12 (dt, *J* = 17.6, 5.4 Hz, 1H), 2.97 (ddd, *J* = 17.6, 8.5, 4.9 Hz, 1H), 2.64 (ddd, *J* = 13.8, 5.8, 4.9 Hz, 1H), 2.55 (ddd, *J* = 13.7, 8.5, 5.0 Hz, 1H), 1.98 (dd, *J* = 14.2, 6.3 Hz, 1H), 1.89 (dd, *J* = 14.1, 7.2 Hz, 1H), 0.74-0.60 (m, 1H), 0.50-0.35 (m, 2H), 0.16-0.05 (m, 1H), -0.00 – -0.12 (m, 1H). LC-MS: *rt* = 1.02 min, MS: 331.1 (calcd), 332.2 (M+H⁺, found).

Example 226

2-Amino-6-(oxazol-5-ylmethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (466)

Intermediate compound 457

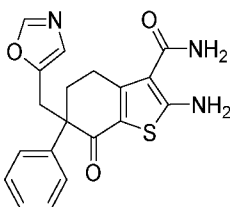
5-((8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)methyl)oxazole (457)



457

Intermediate **457** was synthesized similarly to intermediate **455** (scheme 106), starting from compound **93** (scheme 17) instead of compound **379**.

2-Amino-6-(oxazol-5-ylmethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (466)



466: Example 226

Compound **466** (example 226) was synthesized similarly to compound **463** (example 223, scheme 107) starting from intermediate **457** instead of intermediate **455**.

^1H NMR: 400 MHz, CD_3OD , δ (ppm): 8.03 (s, 1H), 7.40-7.19 (m, 5H), 6.68 (s, 1H), 3.42 (d, $J = 15.1$ Hz, 1H), 3.21 (d, $J = 15.1$ Hz, 1H), 3.01-2.89 (m, 1H), 2.81-2.61 (m, 3H). LC-MS: rt = 1.02 min, MS: 367.1 (calcd), 368.1 ($\text{M}+\text{H}^+$, found).

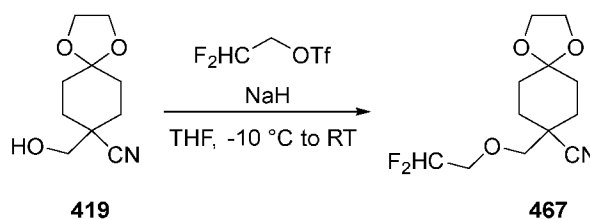
Example 227

2-Amino-6-cyano-6-((2,2-difluoroethoxy)methyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (468)

Intermediate compound 467

8-((2,2-Difluoroethoxy)methyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (467)

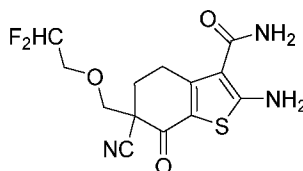
Scheme 108



Scheme 98

Compound **419** (scheme 98) (119 mg, 602 μmol) was dissolved in dry THF (2 mL) under argon and the resulting solution was cooled down to $-10\text{ }^\circ\text{C}$. Then, 2,2-difluoroethyl trifluoromethanesulfonate (155 mg, 722 μmol) was added followed by sodium hydride (28.9 mg, 60% in mineral oil, 722 μmol) suspended in dry THF (3.14 mL). The reaction vessel was taken out of the ice bath and the mixture was allowed to reach RT and stir for 2 hours. The mixture was then diluted with 10 mL saturated aqueous NaHCO_3 and extracted with 3 x 10 mL EA. The combined organics were washed with brine (15 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 0% to 70% of EA in hexane) to afford the title compound **467** as a light-yellow oil (108 mg, 69% yield), which was not characterized and used directly for the next step.

2-Amino-6-cyano-6-((2,2-difluoroethoxy)methyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (468)



468: Example 227

Compound **468** (example 227) was synthesized similarly to compound **246** (example 129, scheme 57) starting from intermediate **467** instead of intermediate **241**.

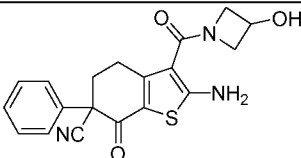
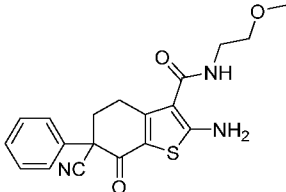
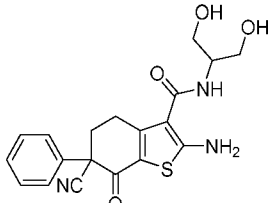
^1H NMR: 400 MHz, CD_3OD , δ (ppm): 5.97 (tt, $J = 55.2, 3.9$ Hz, 1H), 4.02 (d, $J = 9.6$ Hz, 1H), 3.98 (d, $J = 9.6$ Hz, 1H), 3.80 (tdd, $J = 14.3, 6.0, 3.9$ Hz, 2H), 3.18 (dd, $J = 6.8, 5.3$ Hz, 2H),

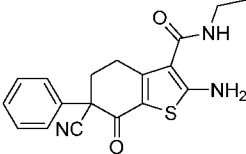
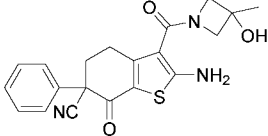
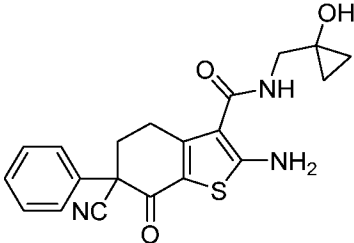
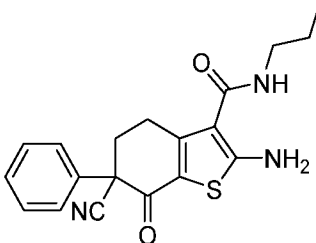
2.63-2.38 (m, 2H). ^{19}F NMR: 376 MHz, CD_3OD , δ (ppm): -127.4 (dt, $J = 55.3, 14.4$ Hz). LC-MS: rt = 0.92 min, MS: 329.1 (calcd), 330.1 ($\text{M}+\text{H}^+$, found).

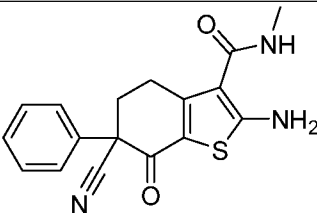
Examples 228-235

Compounds **469-476** (examples 228-235) were synthesized by following a procedure similar to the one described above for the synthesis of compound **170** (example 95, scheme 32), starting from compound **59** (example 36, scheme 8) and using azetidin-3-ol, 2-methoxyethylamine, 2-amino-1,3-propanediol, ethylamine, 3-methylazetidin-3-ol hydrochloride, 1-(aminomethyl)cyclopropanol, propylamine, and methylamine hydrochloride, respectively, instead of cyclopropylamine. Characterization of compounds **469-476** (examples 228-235) is provided in table 9.

Table 9. Characterization of compounds **469-476** (examples 228-235).

Ex. #	Cpd. #	Structure	Characterization
228	469	 2-Amino-3-(3-hydroxyazetidine-1-carbonyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-6-carbonitrile	^1H NMR: 400 MHz, CD_3OD , δ (ppm): 7.42-7.37 (m, 5H), 4.59-4.55 (m, 1H), 4.32-4.25 (m, 2H), 3.87 (dd, $J = 10.3, 4.4$ Hz, 2H), 2.99-2.93 (m, 1H), 2.80-2.64 (m, 3H). LC-MS: rt = 0.93 min, MS: 367.1 (calcd), 368.1 ($\text{M}+\text{H}^+$, found).
229	470	 2-Amino-6-cyano-N-(2-methoxyethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	^1H NMR: 400 MHz, CD_3OD , δ (ppm): 7.41-7.36 (m, 5H), 3.52-3.44 (m, 4H), 3.34 (s, 3H), 3.13-3.06 (m, 1H), 2.84-2.66 (m, 3H). LC-MS: rt = 1.10 min, MS: 369.1 (calcd), 370.1 ($\text{M}+\text{H}^+$, found).
230	471	 2-Amino-6-cyano-N-(1,3-dihydroxypropan-2-yl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	^1H NMR: 400 MHz, CD_3OD , δ (ppm): 7.41-7.36 (m, 5H), 4.10-4.06 (m, 1H), 3.70-3.64 (m, 4H), 3.18-3.11 (m, 1H), 2.87-2.68 (m, 3H). LC-MS: rt = 0.90 min, MS: 385.1 (calcd), 386.2 ($\text{M}+\text{H}^+$, found).

231	472	 2-Amino-6-cyano-N-ethyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 7.42-7.37 (m, 5H), 3.34 (m, 2H), 3.14-3.07 (m, 1H), 2.86-2.77 (m, 2H), 2.73-2.66 (m, 1H), 1.16 (t, <i>J</i> = 7.2 Hz, 3H). LC-MS: <i>rt</i> = 1.15 min, MS: 339.1 (calcd), 340.1 (M+H ⁺ , found).
232	473	 2-Amino-3-(3-hydroxy-3-methylazetidine-1-carbonyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-6-carbonitrile	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 7.45-7.40 (m, 5H), 4.03-3.94 (m, 4H), 2.99 (m, 1H), 2.81-2.65 (m, 3H), 1.49 (3H, s). LC-MS: <i>rt</i> = 0.99 min, MS: 381.1 (calcd), 382.2 (M+H ⁺ , found).
233	474	 2-Amino-6-cyano-N-((1-hydroxycyclopropyl)methyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 7.43-7.38 (m, 5H), 3.50-3.40 (m, 2H), 3.21-3.14 (m, 1H), 2.91-2.71 (m, 3H), 0.71-0.60 (m, 4H). LC-MS: <i>rt</i> = 1.06 min, MS: 381.1 (calcd), 382.2 (M+H ⁺ , found).
234	475	 2-Amino-6-cyano-7-oxo-6-phenyl-N-propyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 7.42-7.38 (m, 5H), 3.24 (m, 3H), 3.10 (m, 1H), 2.85-2.79 (m, 3H), 2.73-2.69 (m, 1H), 1.59-1.54 (m, 2H), 0.93 (t, <i>J</i> = 7.4 Hz, 3H). LC-MS: <i>rt</i> = 1.25 min, MS: 353.1 (calcd), 354.2 (M+H ⁺ , found).

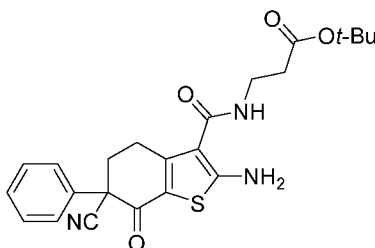
235	476	 2-Amino-6-cyano-<i>N</i>-methyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophene-3-carboxamide	¹ H NMR: 400 MHz, CD ₃ OD, δ (ppm): 7.42-7.38 (m, 5H), 3.13-3.05 (m, 1H), 2.86-2.65 (m, 3H), 2.86 (s, 3H). LC-MS: rt = 1.11 min, MS: 325.1 (calcd), 326.1 (M+H ⁺ , found).

Example 236

3-(2-Amino-6-cyano-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamido)propanoic acid (478)

Intermediate compound 477

tert-Butyl 3-(2-amino-6-cyano-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamido)propanoate (477)



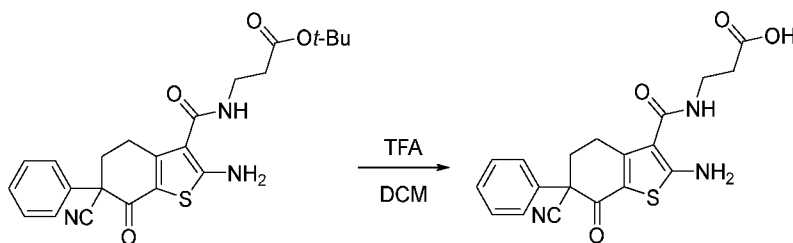
477

Intermediate **477** was synthesized similarly to compound **170** (example 95, scheme 32), starting from compound **59** (example 36, scheme 8) and using β-alanine *tert*-butyl ester hydrochloride instead of cyclopropylamine.

LC-MS: rt = 1.38 min, MS: 439.2 (calcd), 440.3 (M+H⁺, found).

3-(2-Amino-6-cyano-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamido)propanoic acid (478)

Scheme 109



477

478: Example 236

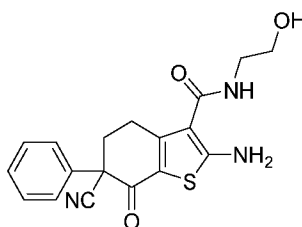
To a stirred solution of **477** (46.9 mg, 0.107 mmol) in DCM (1.07 mL) was added TFA (449 μL, 5.87 mmol). The reaction mixture was stirred at RT for 3 hours, then concentrated under

reduced pressure. The residue was purified by reverse-phase flash column chromatography (eluent gradient from 0% to 100% CH₃CN in H₂O with 0.1% (v/v) formic acid) to afford title compound **478** as a white solid (30 mg, 74% yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.43-7.38 (m, 5H), 3.59-3.51 (m, 2H), 3.14-3.08 (m, 1H), 2.85-2.67 (m, 4H), 2.59 (t, *J* = 6.6 Hz, 2H). LC-MS: rt = 1.00 min, MS: 383.2 (calcd), 384.1 (M+H⁺, found).

Example 237

2-Amino-6-cyano-*N*-(2-hydroxyethyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (479)



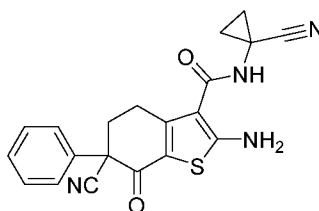
479: Example 237

Compound **479** (example 237) was synthesized similarly to compound **170** (example 95, scheme 32), starting from compound **59** (example 36, scheme 8) and using ethanolamine instead of cyclopropylamine.

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.42-7.37 (m, 5H), 3.65 (t, *J* = 5.6 Hz, 2H), 3.44-3.40 (m, 2H), 3.17-3.11 (m, 1H), 2.86-2.77 (m, 2H), 2.73-2.68 (m, 1H). LC-MS: rt = 1.03 min, MS: 355.1 (calcd), 356.2 (M+H⁺, found).

Example 238

2-Amino-6-cyano-*N*-(1-cyanocyclopropyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (480)

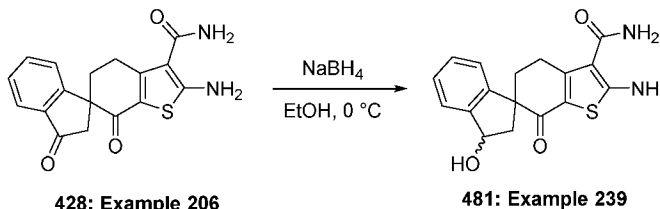


480: Example 238

Compound **480** (example 238) was synthesized similarly to compound **170** (example 95, scheme 32), starting from compound **59** (example 36, scheme 8) and using 1-amino-cyclopropanecarbonitrile instead of cyclopropylamine.

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.42-7.37 (m, 5H), 3.06-3.01 (m, 1H), 2.80-2.65 (m, 3H), 1.51-1.44 (m, 2H), 1.32-1.27 (m, 2H). LC-MS: rt = 1.26 min, MS: 376.1 (calcd), 377.2 (M+H⁺, found).

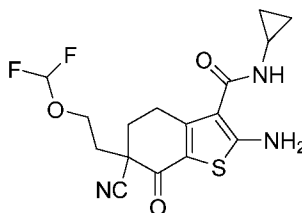
Example 239

2-Amino-3'-hydroxy-7-oxo-2',3',4,7-tetrahydro-5H-spiro[benzo[*b*]thiophene-6,1'-indene]-3-carboxamide (481)Scheme 110

Sodium borohydride (1.17 mg, 36.6 μ mol) was added to a solution of 2-amino-3',7-dioxo-2',3',4,7-tetrahydro-5H-spiro[benzo[*b*]thiophene-6,1'-indene]-3-carboxamide (**428**, example 206) (20.0 mg, 61.3 μ mol) in EtOH (0.096 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hour, then diluted with water and EA. The layers were separated and the organic phase was washed with
 10 brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by Semi-Prep HPLC-MS (eluent gradient from 15% to 100% of ACN in 10 mM ammonium formate) to afford title compound **481** as a white solid (2.5 mg, 12 % yield).

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 7.42 (d, *J* = 7.5 Hz, 1H), 7.31-7.26 (m, 1H), 7.24-7.19 (m, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 5.24 (t, *J* = 6.8 Hz, 1H), 3.10-3.07 (m, 2H), 2.49 (dd, *J* =
 15 13.0, 6.7 Hz, 1H), 2.40 (dd, *J* = 13.0, 6.9 Hz, 1H), 2.26-2.17 (m, 2H). LC-MS: *rt* = 0.89 min, MS: 328.1 (calcd), 327.1 (M-H⁺, found).

Example 240

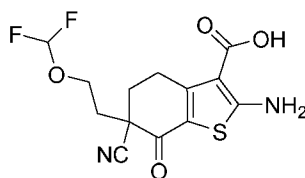
2-Amino-6-cyano-*N*-cyclopropyl-6-(2-(difluoromethoxy)ethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (482)**482: Example 240**

Compound **482** (example 240) was synthesized similarly to compound **192** (example 104, scheme 40), starting from compound **444** (scheme 105) instead of compound **185**.

¹H NMR: 400 MHz, DMSO-*d*₆, δ (ppm): 8.04 (s, 2H), 7.57 (d, *J* = 3.9 Hz, 1H), 6.67 (t, *J* = 77.2 Hz, 1H), 4.01 (t, *J* = 6.8 Hz, 2H), 2.99-2.92 (m, 2H), 2.75-2.70 (m, 1H), 2.43-2.35 (m, 1H),
 25 2.34-2.27 (m, 1H), 2.27-2.18 (m, 1H), 2.15-2.01 (m, 1H), 0.66-0.61 (m, 2H), 0.53-0.48 (m, 2H).
¹⁹F NMR: 376 MHz, DMSO-*d*₆, δ (ppm): -83.4 (d, *J* = 75.2 Hz). LC-MS: *rt* = 1.09 min, MS: 369.1 (calcd), 370.1 (M+H⁺, found).

Example 241

2-Amino-6-cyano-6-(2-(difluoromethoxy)ethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (483)



483: Example 241

Compound **483** (example 241) was synthesized similarly to compound **189** (example 102, scheme 40), starting from compound **444** (scheme 105) instead of compound **185**.

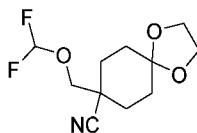
¹H NMR: 400 MHz, DMSO-*d*₆, δ (ppm): 12.79 (bs, 1H), 8.52 (bs, 2H), 6.69 (t, *J* = 75.7 Hz, 1H), 4.02 (t, *J* = 6.7 Hz, 2H), 3.15 (dt, *J* = 19.3, 5.8 Hz, 1H), 3.02 (ddd, *J* = 19.3, 7.5, 4.9 Hz, 1H), 2.47-2.42 (m, 1H), 2.32-2.26 (m, 2H), 2.15-2.08 (m, 1H). ¹⁹F NMR: 376 MHz, CD₃OD, δ (ppm): –83.4 (d, *J* = 75.2 Hz). LC-MS: *rt* = 1.16 min, MS: 330.1 (calcd), 331.1 (*M*+*H*⁺, found).

Example 242

2-Amino-6-((difluoromethoxy)methyl)-6-(3-methylisoxazol-4-yl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (486)

Intermediate compound 484

8-((Difluoromethoxy)methyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (484)

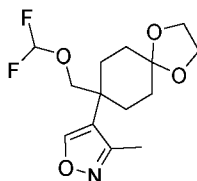


484

Intermediate compound **484** was synthesized similarly to intermediate compound **444** (scheme 105), starting from 8-(hydroxymethyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (**419**, scheme 98) instead of 8-(2-hydroxyethyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (**443**, scheme 105). The product was not characterized and used directly for the synthesis of relevant examples.

Intermediate compound 485

4-(8-((Difluoromethoxy)methyl)-1,4-dioxaspiro[4.5]decan-8-yl)-3-methylisoxazole (485)

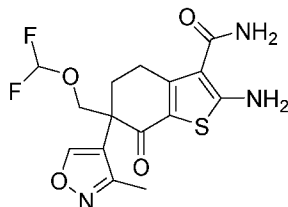


485

Intermediate compound **485** was synthesized similarly to intermediate compound **384** (scheme 90), starting from 8-((difluoromethoxy)methyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (intermediate compound **484**) instead of 3-(8-(cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-

yl)propanenitrile (**185**). The product was not characterized and used directly for the synthesis of relevant examples.

2-Amino-6-((difluoromethoxy)methyl)-6-(3-methylisoxazol-4-yl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (486**)**



486: Example 242

Compound **486** (example 242) was synthesized similarly to compound **246** (example 129, scheme 57) starting from intermediate **485** instead of intermediate **241**.

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 8.46 (s, 1H), 6.40 (t, *J* = 75.3 Hz, 1H), 4.29 (d, *J* = 9.8 Hz, 1H), 4.09 (d, *J* = 9.8 Hz, 1H), 3.09 (dt, *J* = 17.7, 4.8 Hz, 1H), 2.89 (ddd, *J* = 17.7, 9.6, 4.8 Hz, 1H), 2.57 (dt, *J* = 14.0, 4.8 Hz, 1H), 2.46 (ddd, *J* = 14.0, 9.6, 4.8 Hz, 1H), 2.26 (s, 3H). ¹⁹F NMR: 376 MHz, CD₃OD, δ (ppm): -85.5 (dd, *J* = 162.8, 75.3 Hz, 1F), -86.1 (dd, *J* = 162.8, 75.3 Hz, 1F). LC-MS: rt = 0.98 min, MS: 371.1 (calcd), 372.1 (M+H⁺, found).

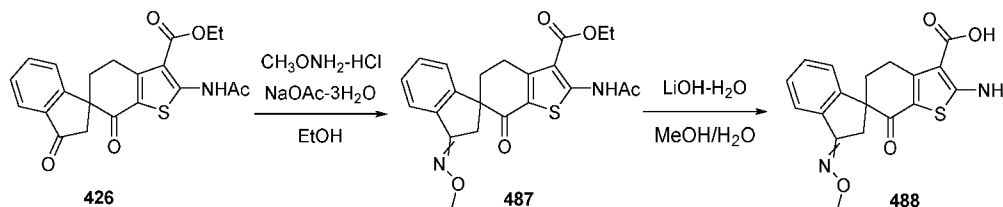
Example 243

2-Amino-3'-(methoxyimino)-7-oxo-2',3',4,7-tetrahydro-5H-spiro[benzo[*b*]thiophene-6,1'-indene]-3-carboxamide (489**)**

Intermediate compound 488

2-Amino-3'-(methoxyimino)-7-oxo-2',3',4,7-tetrahydro-5H-spiro[benzo[*b*]thiophene-6,1'-indene]-3-carboxylic acid (488**)**

Scheme 111



Scheme 99

Step 1. Ethyl 2-acetamido-3'-(methoxyimino)-7-oxo-2',3',4,7-tetrahydro-5H-spiro[benzo[*b*]thiophene-6,1'-indene]-3-carboxylate (487**)**

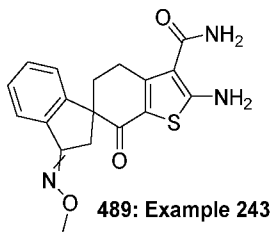
To a solution of ethyl 2-acetamido-3',7-dioxo-2',3',4,7-tetrahydro-5H-spiro[benzo[*b*]thiophene-6,1'-indene]-3-carboxylate (**426**, scheme 99) (60 mg, 0.151 mmol) in EtOH (1.7 mL) were added sodium acetate trihydrate (95 mg, 0.697 mmol) and methoxyamine hydrochloride (38 mg, 0.453 mmol). The reaction mixture was stirred at RT for 72 hours. Then, it was diluted with EA and water. The layers were separated and the organic layer was dried over

Na₂SO₄, filtered and concentrated to give title compound **487** (64 mg, 99% yield) as a white solid. LC-MS: rt = 1.70 min, MS: 426.1 (calcd), 427.3 (M+H⁺, found).

Step 2. 2-Amino-3'-(methoxyimino)-7-oxo-2',3',4,7-tetrahydro-5H-spiro[benzo[b]thiophene-6,1'-indene]-3-carboxylic acid (**488**)

To a solution of **487** (64 mg, 0.150 mmol) in MeOH (1.9 mL) was added a solution of lithium hydroxide monohydrate (18 mg, 0.75 mmol) in water (1.9 mL). The reaction mixture was stirred for 16 hours at 55 °C. The mixture was then concentrated to remove most of the organic solvent and the residue was diluted with water (15 mL) and EA (15 mL). The layers were separated and the aqueous phase was acidified by slowly adding 1 N HCl and then extracted with EA (3 x 15 mL). These organics were combined, dried over Na₂SO₄, filtered and concentrated to give title compound **488** (53 mg, 99% yield) as a yellow solid. LC-MS: rt = 0.88 min, MS: 356.1 (calcd), 357.1 (M+H⁺, found).

2-Amino-3'-(methoxyimino)-7-oxo-2',3',4,7-tetrahydro-5H-spiro[benzo[b]thiophene-6,1'-indene]-3-carboxamide (489**)**



Compound **489** (example 243; single product, *E/Z* stereochemistry not established) was synthesized similarly to compound **238** (example 127, scheme 55) starting from intermediate compound **488** (scheme 111) instead of compound **237**.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.21-8.09 (bs, 2H), 7.60-7.58 (m, 1H), 7.38-7.31 (m, 2H), 7.28-7.23 (m, 1H), 7.13-6.97 (bs, 2H), 3.90 (s, 3H), 3.22-3.01 (m, 3H), 2.78-2.72 (m, 1H), 2.27-2.19 (m, 2H). LC-MS: rt = 1.04 min, MS: 355.4 (calcd), 356.1 (M+H⁺, found).

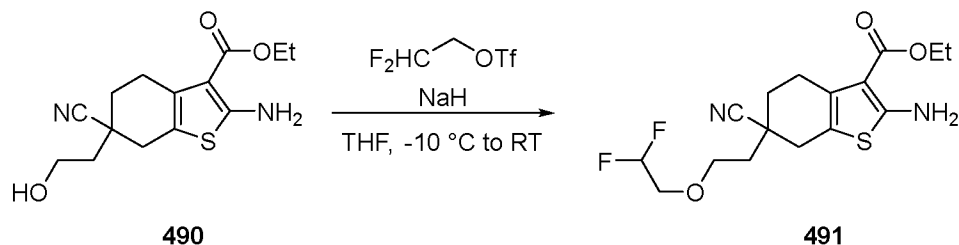
Example 244

2-Amino-6-cyano-6-(2-(2,2-difluoroethoxy)ethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (492**)**

Intermediate compound 491

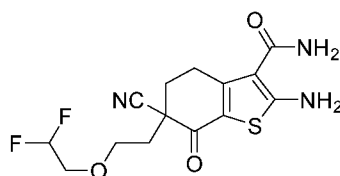
Ethyl 2-amino-6-cyano-6-(2-(2,2-difluoroethoxy)ethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (491**)**

Scheme 112



To a suspension of sodium hydride (24.1 mg, 604 μmol) in anhydrous THF (0.5 mL) cooled down to $-10\text{ }^{\circ}\text{C}$ was added ethyl 2-amino-6-cyano-6-(2-hydroxyethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**490**, synthesized similarly to compound **43**, scheme 4, starting from compound **443**, scheme 105, instead of **41**) (148 mg, 503 μmol) dissolved in anhydrous THF (6 mL). The mixture was allowed to stir at $-10\text{ }^{\circ}\text{C}$ for 1 minute, then 2,2-difluoroethyl trifluoromethanesulfonate (79.8 μL , 604 μmol) was added dropwise. The reaction vessel was removed from the cold bath and the mixture was allowed to stir for 2 hours at RT, then diluted with saturated aqueous NaHCO_3 (10 mL) and EA (10 mL). The layers were separated and the aqueous layer was extracted with additional EA (2 x 20 mL). The combined organics were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (eluent gradient from 10% to 100% of EA in hexane) to afford the title compound **491** as a yellow gum (33 mg, 18% yield). LC-MS: $r_t = 1.38\text{ min}$, MS: 358.1 (calcd), 359.1 ($\text{M}+\text{H}^+$, found).

2-Amino-6-cyano-6-(2-(2,2-difluoroethoxy)ethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (492)



492: Example 244

Compound **492** (example 244) was synthesized similarly to compound **246** (example 129, scheme 57), starting from compound **491** (scheme 112) instead of compound **243**.

^1H NMR: 400 MHz, $\text{DMSO}-d_6$, δ (ppm): 8.24 (bs, 2H), 7.08 (bs, 2H), 6.09 (tt, $J = 55.0, 3.7\text{ Hz}$, 1H), 3.73-3.63 (m, 4H), 3.08-3.01 (m, 2H), 2.44-2.36 (m, 1H), 2.25-2.17 (m, 2H), 2.07-1.99 (m, 1H). ^{19}F NMR: 376 MHz, $\text{DMSO}-d_6$, δ (ppm): -125.2 (dt, $J = 55.0, 15.1\text{ Hz}$, 2F). LC-MS: $r_t = 0.91\text{ min}$, MS: 343.1 (calcd), 344.1 ($\text{M}+\text{H}^+$, found).

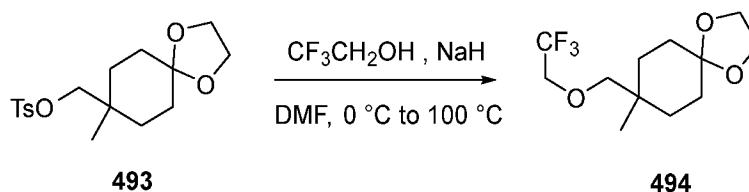
Example 245

2-Amino-6-methyl-7-oxo-6-((2,2,2-trifluoroethoxy)methyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (495)

Intermediate compound 494

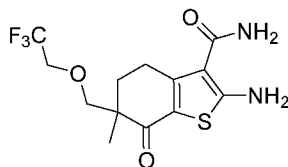
8-Methyl-8-((2,2,2-trifluoroethoxy)methyl)-1,4-dioxaspiro[4.5]decane (494)

Scheme 113



To a suspension of sodium hydride (176 mg, 4.41 mmol) in anhydrous DMF (1.5 mL) at 0 °C was added trifluoroethanol (0.317 mL, 4.41 mmol, previously degassed) and the mixture was stirred at RT for 1 hour. Then, a degassed solution of (8-methyl-1,4-dioxaspiro[4.5]decan-8-yl)methyl 4-methylbenzenesulfonate (**493**, WO 2014/053666) (500 mg, 1.47 mmol) in anhydrous DMF (0.79 mL) was added dropwise. The reaction was stirred at 100 °C for 18 hours. Then, it was allowed to reach RT, cooled down to 0 °C and carefully quenched by adding MeOH (0.5 mL) and water (1 mL). The mixture was diluted with EA (25 mL) and washed with brine (5 x 20 mL). The organic layer was dried over MgSO₄, filtered and concentrated to give title compound **494** (411 mg, >99% yield) as an orange oil, which was not characterized and used directly for the synthesis of relevant examples.

2-Amino-6-methyl-7-oxo-6-((2,2,2-trifluoroethoxy)methyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (495**)**



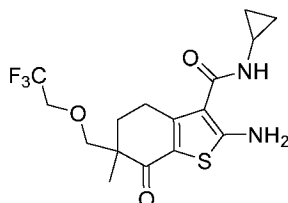
495: Example 245

Compound **495** (example 245) was synthesized similarly to compound **246** (example 129, scheme 57) starting from intermediate compound **494** (scheme 113) instead of intermediate **241**.

¹H NMR: 400 MHz, DMSO-d₆, δ (ppm): 8.02 (s, 2H), 6.96 (bs, 2H), 4.03 (q, *J* = 9.4 Hz, 2H), 3.83 (d, *J* = 9.2 Hz, 1H), 3.43 (d, *J* = 9.2 Hz, 1H), 3.03-2.88 (m, 2H), 2.20-2.13 (m, 1H), 1.79 (dt, *J* = 13.5, 4.8 Hz, 1H), 1.02 (s, 3H). ¹⁹F NMR: 376 MHz, DMSO-d₆, δ (ppm): -72.8 (t, *J* = 9.4 Hz, 3F). LC-MS: rt = 1.12 min, MS: 336.1 (calcd), 337.2 (M+H⁺, found).

Example 246

2-Amino-N-cyclopropyl-6-methyl-7-oxo-6-((2,2,2-trifluoroethoxy)methyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (496**)**



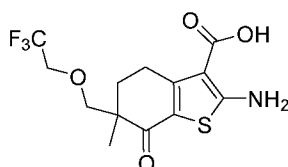
496: Example 246

Compound **496** (example 246) was synthesized similarly to compound **192** (example 104, scheme 40), starting from intermediate compound **494** (scheme 113) instead of compound **185**.

¹H NMR: 400 MHz, CD₃OD, δ (ppm): 3.93-3.85 (m, 3H), 3.48 (d, *J* = 9.1 Hz, 1H), 2.94-2.85 (m, 2H), 2.78-2.71 (m, 1H), 2.35-2.28 (m, 1H), 1.86 (dt, *J* = 13.6, 4.9 Hz, 1H), 1.12 (s, 3H),
 5 0.79-0.74 (m, 2H), 0.61-0.57 (m, 2H). ¹⁹F NMR: 376 MHz, CD₃OD, δ (ppm): -75.96 (t), LC-MS: rt = 1.33 min, MS: 376.1 (calcd), 377.1 (M+H⁺, found).

Example 247

2-Amino-6-methyl-7-oxo-6-((2,2,2-trifluoroethoxy)methyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (**497**)



497: Example 247

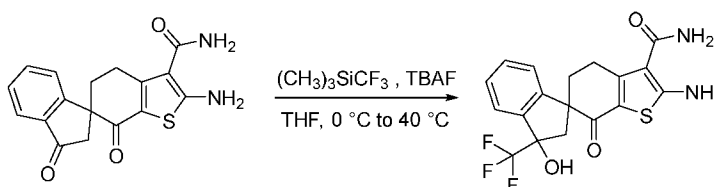
Compound **497** (example 247) was synthesized similarly to compound **189** (example 102, scheme 40), starting from intermediate compound **494** (scheme 113) instead of compound **185**.

¹H NMR: 400 MHz, DMSO-*d*₆, δ (ppm): 8.23-8.22 (m, 2H), 4.01 (q, *J* = 9.4 Hz, 2H), 3.80 (d, *J* = 9.1 Hz, 1H), 3.40 (d, *J* = 6.9 Hz, 1H), 3.13-3.02 (m, 1H), 2.89-2.77 (m, 1H), 2.16-2.09 (m, 1H), 1.80-1.75 (m, 1H), 0.99 (s, 3H). ¹⁹F NMR: 376 MHz, CD₃OD, δ (ppm): -76.0 (t). LC-MS: rt =
 15 1.29 min, MS: 337.1 (calcd), 338.1 (M+H⁺, found).

Example 248

2-Amino-3'-hydroxy-7-oxo-3'-(trifluoromethyl)-2',3',4,7-tetrahydro-5H-spiro[benzo[*b*]thiophene-6,1'-indene]-3-carboxamide (**498**)

Scheme 114



428: Example 206

498: Example 248

To a mixture of **428** (example 206) (50.0 mg, 153 μmol) and trifluoromethyltrimethylsilane (116 μL, 766 μmol) in anhydrous THF (198 μL) under an argon atmosphere was added tetrabutylammonium fluoride (230 μL, 230 μmol) at 0 °C. Then, the reaction was stirred at RT for
 25 16 hours. More trifluoromethyltrimethylsilane (116 μL, 766 μmol) and tetrabutylammonium fluoride (230 μL, 230 μmol) were added and the mixture was stirred at 40 °C for 24 hours. Afterwards, the mixture was diluted with water and extracted with EA twice. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude was first purified by flash column chromatography (eluent gradient from 5% to 100% of EA in hexane),

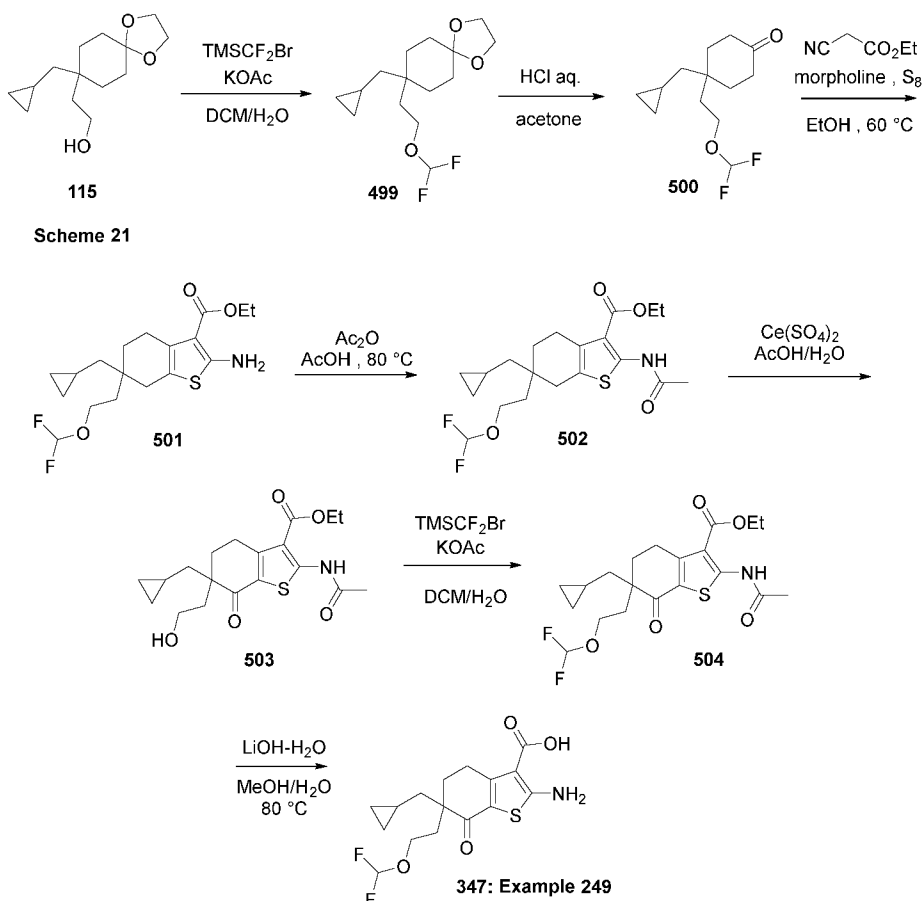
then by Semi-Prep HPLC-MS (eluent gradient from 40% to 100% of MeOH in 10 mM ammonium formate) to afford title compound **498** as a white solid (4.8 mg, 8% yield).

^1H NMR: 400 MHz, CD_3OD , δ (ppm): 7.53 (s, 1H), 7.38-7.35 (m, 2H), 7.24-7.22 (m, 1H), 3.26-3.24 (m, 1H), 3.15-3.11 (m, 1H), 2.75 (d, $J = 14.9$ Hz, 1H), 2.57 (d, $J = 14.8$ Hz, 1H), 2.41-2.33 (m, 2H). ^{19}F NMR: 376 MHz, CD_3OD , δ (ppm): -81.0 (s). LC-MS: $\text{rt} = 1.20$ min, MS: 396.1 (calcd), 397.1 ($\text{M} + \text{H}^+$, found).

Example 249

2-Amino-6-(cyclopropylmethyl)-6-(2-(difluoromethoxy)ethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (**347**)

Scheme 115



Step 1. 8-(Cyclopropylmethyl)-8-[2-(difluoromethoxy)ethyl]-1,4-dioxaspiro[4.5]decane (**499**)

To a 20 mL vial equipped with a stir bar were added 2-[8-(cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl]ethan-1-ol (**115**, scheme 21) (690 mg, 2.87 mmol), potassium acetate (1.69 g, 17.2 mmol), DCM (1.72 mL), water (1.72 mL) and (bromodifluoromethyl)trimethylsilane (1.34 mL, 8.61 mmol). The reaction mixture was stirred at RT for 18 hours, then diluted with 50 mL DCM, dried over Na_2SO_4 , filtered and concentrated to yield title compound **499** as a clear oil (700 mg, 84% yield). ^1H NMR: 400 MHz, CDCl_3 , δ (ppm): 6.18 (t, $J = 75.1$ Hz, 1H), 3.93 (s, 4H),

3.90 (t, $J = 7.6$ Hz, 2H), 1.81 (t, $J = 7.6$ Hz, 2H), 1.66-1.48 (m, 8H), 1.25 (d, $J = 6.6$ Hz, 2H), 0.66-0.57 (m, 1H), 0.51-0.39 (m, 2H), 0.15-0.04 (m, 2H).

Step 2. 4-(Cyclopropylmethyl)-4-[2-(difluoromethoxy)ethyl]cyclohexan-1-one (500)

To a 20 mL vial equipped with a stir bar were added **499** (690 mg, 2.38 mmol) and acetone (11.9 mL). 12 N aqueous HCl (1.98 mL, 23.8 mmol) was then added and the reaction mixture was stirred at RT for 6 hours. The reaction mixture was neutralized by addition of saturated NaHCO₃ aqueous solution and extracted with EA (3 x 50 mL). The organic fractions were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated to yield title compound **500** as a clear oil (592 mg, >99% yield). ¹H NMR: 400 MHz, CDCl₃, δ (ppm): 6.20 (t, $J = 74.6$ Hz, 1H), 3.96 (t, $J = 7.3$ Hz, 2H), 2.35 (q, $J = 6.8$ Hz, 4H), 1.95 (t, $J = 7.3$ Hz, 2H), 1.87-1.75 (m, 4H), 1.38 (dd, $J = 6.6, 4.9$ Hz, 2H), 0.74-0.56 (m, 1H), 0.55-0.48 (m, 2H), 0.11-0.05 (m, 2H).

Step 3. Ethyl 2-amino-6-(cyclopropylmethyl)-6-[2-(difluoromethoxy)ethyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (501)

A 20 mL vial equipped with a stir bar was charged with **500** (680 mg, 2.76 mmol), ethyl 2-cyanoacetate (294 μ L, 2.76 mmol), morpholine (262 μ L, 3.04 mmol), sulfur (97.5 mg, 2.76 mmol) and EtOH (4.4 mL). The vial was sealed with a pressure relief cap and heated at 60 °C overnight, resulting in the formation of a dark red solution. The reaction was cooled to room temperature and concentrated to yield title compound **501** as a red oil (1.03 g, >99% yield), which was not characterized and used directly for the next step.

Step 4. Ethyl 6-(cyclopropylmethyl)-6-[2-(difluoromethoxy)ethyl]-2-acetamido-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (502)

A 1 dram vial equipped with a stir bar was charged with **501** (1.02 g, 2.73 mmol) and acetic acid (15.7 mL). Acetic anhydride (319 μ L, 3.28 mmol) was then added in a single portion and the reaction mixture was stirred at 60 °C for 2.5 hours, then cooled to room temperature and concentrated. The residue was dissolved in DCM (50 mL), washed with saturated NaHCO₃ aqueous solution, then brine, dried over Na₂SO₄ and concentrated to yield title compound **502** as a red oil (880 mg, 76% yield). MS: 416.1 (calcd), 417.1 (M+H⁺, found).

Step 5. Ethyl 6-(cyclopropylmethyl)-2-acetamido-6-(2-hydroxyethyl)-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (503)

To a 20 mL vial equipped with a stir bar was added **502** (820 mg, 1.97 mmol), acetic acid (6.51 mL), water (6.51 mL) and ceric sulfate (5.66 g, 17.1 mmol). The resulting slurry was stirred vigorously at RT for 18 hours. The mixture was then diluted with deionized water (6 mL) and EA (6 mL). The aqueous phase was extracted with EA (3 x 10 mL). The organic fractions were combined and washed consecutively with 1N NaOH (10 mL), water (10 mL) and brine (10 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel chromatography (eluent 0-100% EtOAc in heptane) to yield title compound **503** as an orange oil (324 mg, 43% yield). ¹H NMR: 400 MHz, CDCl₃, δ (ppm): 11.52 (bs, 1H), 4.38 (q, J

= 7.1 Hz, 2H), 4.19-4.12 (m, 2H), 3.18-3.00 (m, 2H), 2.31 (s, 3H), 2.27-2.11 (m, 4H), 1.97-1.90 (m, 1H), 1.75-1.68 (m, 1H), 1.43 (t, $J = 7.0$ Hz, 3H), 0.72-0.62 (m, 1H), 0.49-0.43 (m, 2H), 0.08-0.05 (m, 2H). MS: 379.1 (calcd), 380.1 ($M+H^+$, found).

Step 6. Ethyl 6-(cyclopropylmethyl)-6-[2-(difluoromethoxy)ethyl]-2-acetamido-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (504)

To a 1 dram vial equipped with a stir bar was added **503** (83.6 mg, 229 μ mol), potassium acetate (135 mg, 1.37 mmol), DCM (137 μ L), water (137 μ L) and (bromodifluoromethyl)trimethylsilane (139 mg, 686 μ mol). The reaction mixture was stirred at RT for 18 hours, then diluted with 10 mL EA, dried over Na_2SO_4 , filtered and concentrated to yield title compound **504** as an orange oil (66 mg, 67% yield). ^1H NMR: 400 MHz, $CDCl_3$, δ (ppm): 11.52 (bs, 1H), 4.38 (q, $J = 7.1$ Hz, 2H), 4.19-4.12 (m, 2H), 3.18-3.00 (m, 2H), 2.31 (s, 3H), 2.27-2.11 (m, 4H), 1.97-1.90 (m, 1H), 1.75-1.68 (m, 1H), 1.43 (t, $J = 7.0$ Hz, 3H), 0.72-0.62 (m, 1H), 0.49-0.43 (m, 2H), 0.08-0.05 (m, 2H). MS: 429.1 (calcd), 430.1 ($M+H^+$, found).

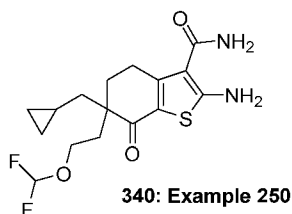
Step 7. 2-Amino-6-(cyclopropylmethyl)-6-(2-(difluoromethoxy)ethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (347)

A 50 mL round bottom flask equipped with a stir bar was charged with **504** (66.0 mg, 0.154 mmol), water (18.6 mL), and MeOH (18.6 mL). Lithium hydroxide monohydrate (32.2 mg, 0.768 mmol) was added in a single portion. A reflux condenser was attached to the flask and the reaction mixture was stirred at 80 $^{\circ}C$ for 18 hours. The mixture was then cooled to room temperature and MeOH was removed by rotary evaporation. The aqueous residue was acidified by addition of 1 N HCl solution and extracted with EA (3 x 50 mL). The organic fractions were combined, dried over Na_2SO_4 , filtered and concentrated. The residue was purified with RediSep Prep C18 column 20 x 150 mm 100 $\text{\AA}$ 5 μ m; gradient 10% ACN in water 0-1.0 min, 10-100% ACN in water 1.0-12.0 min, 100% ACN 12.0-14.0 min to yield title compound **347** as a white solid (2.11 mg, 3.7% yield).

^1H NMR: 500 MHz, $DMSO-d_6$, δ (ppm): 8.27 (bs., 1H), 6.61 (t, $J = 76.4$ Hz, 1H), 3.85-3.80 (m, 2H), 3.06-2.90 (m, 2H), 2.53-2.51 (m, 2H), 2.13-1.94 (m, 3H), 1.87-1.79 (m, 1H), 1.59 (dd, $J = 14.2, 6.2$ Hz, 1H), 1.32 (dd, $J = 14.2, 7.1$ Hz, 1H), 0.64-0.57 (m, 1H), 0.39 (dd, $J = 8.0, 2.4$ Hz, 2H), 0.08-0.10 (m, 2H). MS: 359.1 (calcd), 360.1 ($M+H^+$, found).

Example 250

2-Amino-6-(cyclopropylmethyl)-6-(2-(difluoromethoxy)ethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (340)



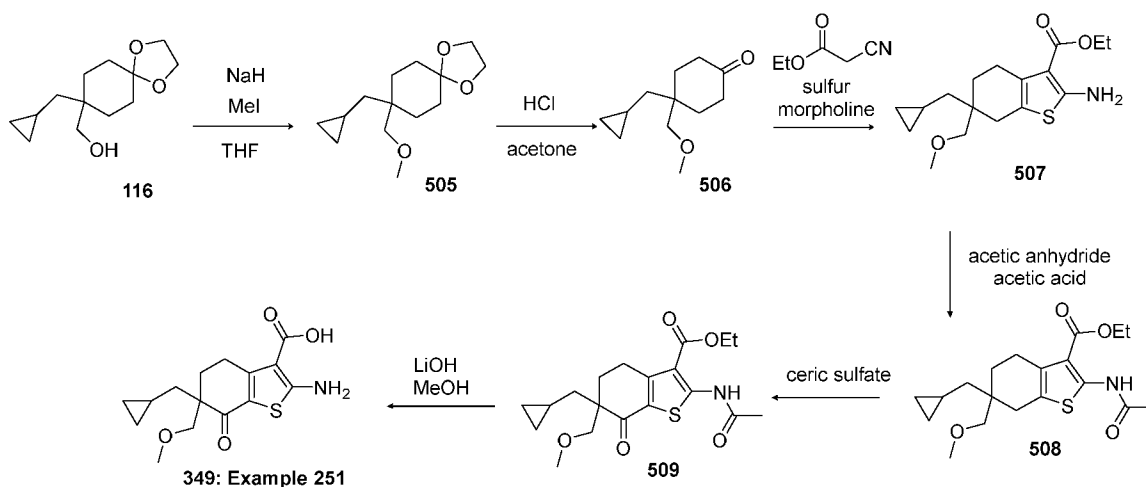
To a 50 mL round bottom flask equipped with a stir bar was added **347** (25.5 mg, 71 μ mol), DMF (784 μ L), HATU (40.5 mg, 0.106 mmol), DIPEA (24.7 μ L, 0.142 mmol) and ammonium chloride (75.9 mg, 1.42 mmol). The flask was sealed with a septum and sparged with a balloon of argon for 10 mins. Ammonia in THF (0.4 M solution, 3.55 mL, 1.42 mmol) was added to the reaction by syringe. The reaction mixture was stirred at r t for 18 hours under an atmosphere of argon. The reaction was quenched by addition of 50 mL of saturated NH_4Cl solution and extracted with EA (3 x 50 mL). The EA fractions were combined and washed with brine (10 mL), dried with Na_2SO_4 , filtered and concentrated. The crude material was purified using a RediSep Prep C18 column 20 x 150 mm 100 $\text{\AA}$ 5 μ m (gradient 10% ACN in water 0-1.0 min, 10-100% ACN in water 1.0-12.0 min, 100% ACN 12.0-14.0 min) and dried by lyophilization to yield the title compound as a white solid (4.99 mg, 19% yield).

^1H NMR: 500 MHz, $\text{DMSO}-d_6$, δ (ppm): 8.00 (s, 2H), 6.60 (t, J = 76.4 Hz, 1H), 3.85-3.79 (m, 2H), 3.28 (s, 2H), 3.03-2.88 (m, 2H), 2.14-1.93 (m, 3H), 1.88-1.81 (m, 1H), 1.57 (dd, J = 14.1, 6.4 Hz, 1H), 1.35 (dd, J = 14.1, 6.9 Hz, 1H), 0.65-0.57 (m, 1H), 0.42-0.37 (m, 2H), 1.91 (m, 2H). MS: 358.1 (calcd), 359.1 ($\text{M}+\text{H}^+$, found).

Example 251

2-Amino-6-(cyclopropylmethyl)-6-(methoxymethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (**349**)

Scheme 116



Step 1: 8-(Cyclopropylmethyl)-8-(methoxymethyl)-1,4-dioxaspiro[4.5]decane (**505**)

A dry 100 mL Schlenk flask equipped with a stir bar under nitrogen was charged with NaH (302 mg, 12.6 mmol). Anhydrous THF (5.4 mL) was added via syringe and the flask was stirred at 0 °C for 15 mins. A degassed solution of [8-(cyclopropylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl]methanol (**116**, scheme 22) (950 mg, 4.2 mmol) in anhydrous THF (3 mL) was added via syringe and the reaction was stirred at RT for 1 hour. The flask was then cooled to 0 °C and degassed methyl iodide (784 μ L, 12.6 mmol) was added via syringe in a single portion. The

resulting mixture was stirred at 50 °C for 18 hours, then cooled to room temperature and then to 0 °C. The mixture was quenched by dropwise addition of MeOH by syringe (~0.5 mL). 50 mL brine was then added and the product was extracted with EA (3 x 50 mL). The organic fractions were combined, dried over Na₂SO₄, filtered, and concentrated to yield title compound **505** as a yellow oil (930 mg, 92% yield).

¹H NMR: 400 MHz, CDCl₃, δ (ppm): 3.93 (s, 4H), 3.32 (s, 3H), 3.29 (s, 2H), 1.67-1.50 (m, 8H), 1.29 (d, *J* = 6.8 Hz, 2H), 0.67-0.54 (m, 2H), 0.44-0.38 (m, 2H), 0.05-0.00 (m, 2H).

Step 2. 4-(cyclopropylmethyl)-4-(methoxymethyl)cyclohexan-1-one (**506**)

A 50 mL round bottom flask equipped with a stir bar was charged with **505** (930 mg, 3.87 mmol) and acetone (19.3 mL). HCl (12 M, 3.22 mL) was added in a single portion with a syringe. The reaction was stirred at RT for 5 h. The reaction was quenched with sat. NaHCO₃ until pH 7 and extracted with EA (3 x 15 mL). The organic fractions were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated to yield title compound **506** as a yellow oil. (638 mg, 84% yield).

¹H NMR: 400 MHz, CDCl₃, δ (ppm): 3.36 (s, 2H), 3.32 (s, 3H), 2.31 (t, *J* = 6.9 Hz, 5H), 1.77 (q, *J* = 6.6 Hz, 5H), 1.38 (d, *J* = 7.4 Hz, 2H), 0.73-0.54 (m, 1H), 0.49-0.42 (m, 2H), 0.17-0.15 (m, 2H).

Step 3. ethyl 2-amino-6-(cyclopropylmethyl)-6-(methoxymethyl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**507**)

A 20 mL vial equipped with a stir bar was charged with **506** (638 mg, 3.25 mmol), ethyl 2-cyanoacetate (346 uL, 3.25 mmol), morpholine (308 uL, 3.58 mmol), sulfur (115 mg, 0.449 mmol) and ethanol (5.18 mL). The vial was sealed and heated at 60 °C overnight. The reaction was cooled to RT and concentrated to yield the crude product **507** as a red oil (1.21 g, quant yield). MS: 323.3 (calcd), 324.3 (M+H⁺, found).

Step 4. ethyl 6-(cyclopropylmethyl)-2-acetamido-6-(methoxymethyl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**508**)

A 40 mL vial equipped with a stir bar was charged with **507** (1.2 mg, 3.71 mmol) and acetic acid (21.3 mL). The vial was stirred at room temperature and acetic anhydride (433 uL, 4.45 mmol) was added in a single portion. The reaction was stirred at 60 °C for 2 hours and cooled to RT. The reaction mixture was concentrated, and the residue was dissolved in 50 mL DCM, washed with saturated NaHCO₃ solution (25 mL), water (25 mL) and brine (25 mL). The organic fraction was dried with Na₂SO₄, filtered, and concentrated to yield the title compound **508** as a red oil (1.17 g, 86% yield). MS: 365.2 (calcd), 366.2 (M+H⁺, found).

Step 5. ethyl 6-(cyclopropylmethyl)-2-acetamido-6-(methoxymethyl)-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**509**)

A 20 mL vial equipped with a stir bar was charged with **508** (500 mg, 1.37 mmol), ceric sulfate (3.92 g, 11.8 mmol), acetic acid (4.51 mL) and deionized water (4.51 mL). The mixture

was sonicated then stirred vigorously at RT for 18 hours. The mixture was diluted with deionized water (5 mL) and EA (5 mL). The aqueous phase was extracted with EA (3 x 10 mL). The organic fractions were combined and washed with 1N NaOH (10 mL), water (10 mL) and brine (10 mL). The organic fraction was dried with Na₂SO₄, filtered, and concentrated to yield the title compound **509** as a yellow oil (320 mg, 62% yield). MS: 379.1 (calcd), 380.2 (M+H⁺, found).

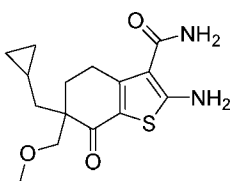
Step 6. 2-amino-6-(cyclopropylmethyl)-6-(methoxymethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**349**)

A 500 mL round bottom equipped with a stir bar was charged with **509** (320 mg, 0.843 mmol), deionized water (102 mL), and methanol (102 mL). Lithium hydroxide monohydrate (177 mg, 4.22 mmol) was added in a single portion. A reflux condenser was affixed to the flask and the reaction was heated at 80 °C for 18 hours. The reaction was cooled to RT and methanol was removed by rotary evaporation. The mixture was acidified by addition of 1 M HCl solution and extracted with EA (3 x 50 mL). The organic fractions were combined, dried with Na₂SO₄, filtered, and concentrated to yield the title compound **349** as a yellow oil. The crude material was purified by Waters Prep HPLC-MS. XSELECT CSH C18 5 µm 30 x 75 mm Column (Eluent A: Acetonitrile, Eluent B: H₂O + 0.1% Formic Acid) to yield the title compound as a white solid (3.94 mg, 1% yield).

¹H NMR: 500 MHz, DMSO-d₆, δ (ppm): 8.24 (s, 2H), 3.61 (d, J = 8.9 Hz, 1H), 3.36 (d, J = 8.9 Hz, 2H), 3.22 (s, 3H), 3.06 (dt, J = 18.7, 5.3 Hz, 2H), 2.9-2.86 (m, 2H), 2.19-2.00 (m, 2H), 1.50 (dd, J = 14.2, 6.6 Hz, 1H), 1.44-1.42 (m, 1H), 1.36 (dd, J = 14.2, 6.9 Hz, 1H), 0.65-0.57 (m, 1H), 0.41-0.35 (m, 2H), 0.04-0.10 (m, 2H). MS: 309.1 (calcd), 310.1 (M+H⁺, found).

Example 252

2-Amino-6-(cyclopropylmethyl)-6-(methoxymethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (342**)**



342: Example 252

To a 50 mL round bottom flask equipped with a stir bar was added **349** (124 mg, 0.401 mmol), DMF (4.43 mL), HATU (229 mg, 0.601 mmol), DIPEA (140 µL, 0.802 mmol) and NH₄Cl (429 mg, 8.02 mmol). The flask was sealed with a septum and sparged with a balloon of argon for 10 mins. Ammonia in THF (0.4 M solution, 20.0 mL, 8.02 mmol) was added to the reaction by syringe. The reaction was stirred at RT for 18 hours with an argon balloon. The reaction was quenched by addition of 50 mL of saturated NH₄Cl solution and extracted with EA (3 X 50 mL). The EA fractions were combined and washed with brine (7 x 10 mL), dried with Na₂SO₄, filtered, and concentrated to yield title compound as a brown residue. The crude material was purified by

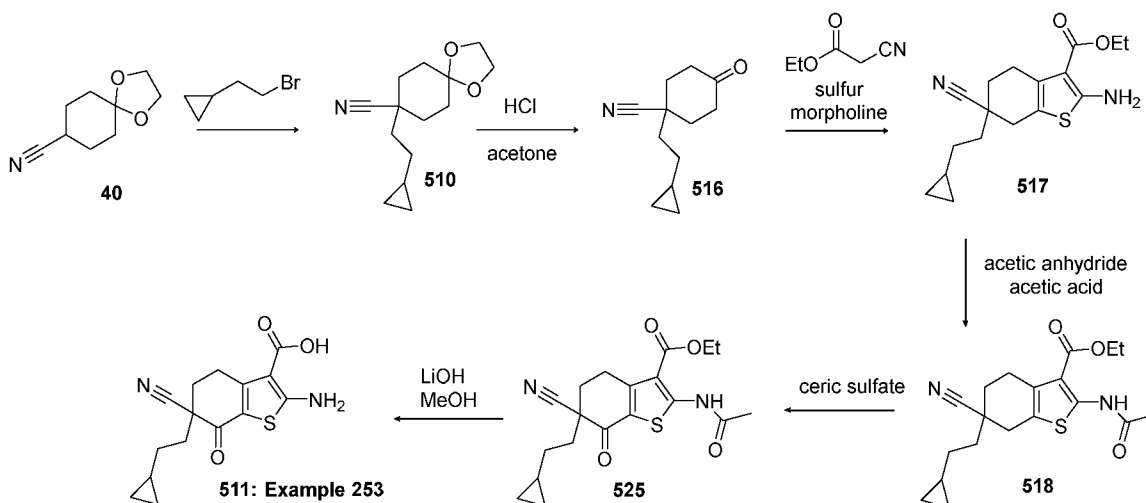
Waters Prep HPLC-MS. XSELECT CSH C18 5 μ m 30 x 75 mm Column (Eluent A: Acetonitrile, Eluent B: H₂O + 0.1% Formic Acid) to yield the title compound **342** as a white solid (2.09 mg, 1% yield).

¹H NMR: 500 MHz, DMSO-d₆, δ (ppm): 7.99 (s, 2H), 3.61 (d, J = 8.9 Hz, 1H), 3.36 (d, J = 8.9 Hz, 1H), 3.22 (s, 3H), 3.12-2.80 (m, 2H), 2.25-1.96 (m, 2H), 1.52-1.35 (m, 2H), 0.64-0.54 (m, 1H), 0.41-0.34 (m, 2H), 0.07-0.11 (m, 2H). MS: 308.1 (calcd), 309.1 (M+H⁺, found).

Example 253

2-Amino-6-cyano-6-(2-cyclopropylethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (**511**)

Scheme 117



Step 1. 8-(2-cyclopropylethyl)-1,4-dioxaspiro[4.5]decanecarbonitrile (**510**)

A dry 100 mL round bottom flask equipped with a stir bar was charged with 1,4-dioxaspiro[4.5]decanecarbonitrile (1.80 g, 10.8 mmol) and 50 mL of dry THF. The solution was sparged with argon for 10 minutes with an argon balloon and cooled to -78 °C. Lithium diisopropylamide 1 M solution in THF/heptanes (12.0 mL, 12.0 mmol) was added dropwise to the flask and the reaction was stirred at -78 °C for 1 hour. A degassed solution of 1-(2-bromoethyl)cyclopropane (1.79 g, 12.0 mmol) in 10 mL anhydrous THF was added to the flask by syringe and the reaction was stirred at RT overnight. The reaction was quenched with 20 mL saturated NH₄Cl solution and extracted with EA (3 x 20 mL). The organic fractions were combined, dried over Na₂SO₄, filtered and concentrated to yield the title compound **510** as a yellow solid (2.34 g, 83% yield).

¹H NMR: 400 MHz, CDCl₃, δ (ppm): 4.00-3.88 (m, 4H), 2.02-1.83 (m, 4H), 1.77-1.62 (m, 4H), 1.58 (t, J = 13.3, 2H), 1.42-1.34 (m, 2H), 0.72-0.61 (m, 1H), 0.48-0.41 (m, 2H), 0.08-0.02 (m, 2H).

Step 2. 1-(2-cyclopropylethyl)-4-oxocyclohexanecarbonitrile (**516**)

A 250 mL round bottom flask equipped with a stir bar was charged with **510** (2.34 g, 9.94 mmol) and acetone (49.7 mL). Aqueous HCl (16.6 mL, 199 mmol, 12 M) was added in a single portion. The reaction was stirred at RT for 18 hours. Saturated aqueous NaHCO₃ (400 mL) was added. The product was extracted with EA (3 x 200 mL), washed with brine, dried with Na₂SO₄,
5 filtered and concentrated. The crude material was purified by silica gel chromatography (eluent 0-50% ethyl acetate in heptanes) to yield the title compound **516** as a white solid (746 mg, 39% yield).

¹H NMR: 400 MHz, CDCl₃, δ (ppm): 2.69 (ddd, *J* = 20.1, 10.2, 5.5 Hz, 2H), 2.43 (d, *J* = 15.8 Hz, 2H), 2.38-2.23 (m, 2H), 1.86-1.61 (m, 4H), 1.52-1.38 (m, 2H), 0.78-0.62 (m, 1H), 0.55-
10 0.40 (m, 2H), 0.17-0.01 (m, 2H).

Step 3. ethyl 2-amino-6-cyano-6-(2-cyclopropylethyl)-4,5,6,7-tetrahydro-1-thia-3-indenecarboxylate (**517**)

A 20 mL vial equipped with a stir bar was charged with **516** (746 mg, 3.9 mmol), ethyl 2-cyanoacetate (415 uL, 3.9 mmol), morpholine (370 uL, 4.29 mmol), sulfur (138 mg, 538 umol)
15 and ethanol (6.22 mL). The vial was sealed and heated at 60 °C for 18 hours. The reaction was cooled to RT and concentrated. The crude material was purified by silica gel chromatography (eluent 0-60% ethyl acetate in heptanes) to yield the title compound **517** as a yellow solid (924 mg, 74% yield).

¹H NMR: 400 MHz, CDCl₃, δ (ppm): 4.26 (q, *J* = 7.1, 2H), 2.99-2.82 (m, 2H), 2.54 (d, *J* = 16.0 Hz, 1H), 2.2-2.07 (m, 1H), 1.92-1.62 (m, 4H), 1.88-1.64 (m, 4H), 1.53-1.40 (m, 3H), 1.34 (t, *J* = 7.1, 3H), 0.79-0.60 (m, 1H), 0.58-0.33 (m, 2H), 0.08 (d, *J* = 4.6 Hz, 2H).
20

Step 4. ethyl 2-acetylamino-6-cyano-6-(2-cyclopropylethyl)-4,5,6,7-tetrahydro-1-thia-3-indenecarboxylate (**518**)

A 40 mL vial equipped with a stir bar was charged with **517** (924 mg, 2.90 mmol) and
25 acetic acid (16.7 mL). Acetic anhydride (329 uL, 3.48 mmol) was added in a single portion by syringe and the reaction was stirred at 60 °C for 1 hour. The reaction was cooled to RT and concentrated. The crude residue was dissolved in DCM (50 mL), washed with aq. sat. NaHCO₃ (10 mL), water (10 mL) and brine (10 mL). The organic fraction was dried over Na₂SO₄, filtered and concentrated to yield the title compound as an orange residue (963 mg, 92% yield).

¹H NMR: 400 MHz, CDCl₃, δ (ppm): 11.27 (s, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.13-2.96 (m, 3H), 2.65 (d, *J* = 16.1 Hz, 1H), 2.26 (s, 3H), 2.21-2.12 (m, 1H), 1.87-1.67 (m, 3H), 1.51-1.43 (m, 2H), 1.39 (t, *J* = 7.1, 3H), 0.70 (d, *J* = 7.6 Hz, 1H), 0.47 (d, *J* = 7.9 Hz, 2H), 0.09 (d, *J* = 5.0 Hz, 2H). MS: 360.1 (calcd), 361.2 (M+H⁺, found).
30

Step 5. ethyl 2-acetylamino-6-cyano-6-(2-cyclopropylethyl)-7-oxo-4,5,6,7-tetrahydro-1-thia-3-indenecarboxylate (**525**)

To a 50 mL round bottom equipped with a stir bar was added **518** (963 mg, 2.67 umol), acetic acid (8.82 mL) and water (8.82 uL). Cerium (IV) sulfate (7.67 mg, 23.1 mmol) was added
35

in a single portion and the reaction was stirred vigorously at RT for 18 hours. EA (50 mL) and water (50 mL) were added and the product was extracted to EA (3 x 50 mL). The organic fractions were combined and washed with 1 M NaOH (50 mL), water (50 mL) and brine (50 mL) and dried over Na₂SO₄, filtered and concentrated to yield the title compound **525** as an orange residue (767 mg, 76% yield).

¹H NMR: 400 MHz, CDCl₃, δ (ppm): 11.58 (s, 1H), 4.40 (qd, *J* = 7.1, 1.9 Hz, 2H), 3.38-3.09 (m, 2H), 2.58-2.41 (m, 1H), 2.34 (s, 3H), 2.31-2.13 (m, 2H), 1.94-1.85 (m, 1H), 1.50-1.36 (m, 5H), 0.81-0.61 (m, 1H), 0.60-0.31 (m, 2H), 0.19-0.05 (m, 2H). MS: 374.1 (calcd), 375.1 (M+H⁺, found).

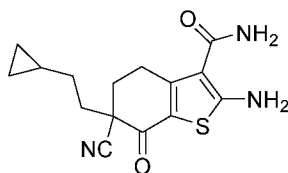
Step 6. 2-amino-6-cyano-6-(2-cyclopropylethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (511**)**

A 100 mL round bottom equipped with a stir bar was charged with **525** (100 mg, 267 μmol), deionized water (32.3 mL), and methanol (32.3 mL). Lithium hydroxide monohydrate (56 mg, 1.34 mmol) was added in a single portion. A reflux condenser was affixed to the flask and the reaction was heated at 80 °C for 18 hours. The reaction was cooled to RT and aqueous 1 M HCl was added. The product was extracted with EA (3 x 50 mL), washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated. The crude material was purified by C18 reverse phase chromatography (eluent 0-100% acetonitrile in water) to yield the title compound **511** as an off white solid (1.16 mg, 1% yield).

¹H NMR: 500 MHz, DMSO-*d*₆, δ (ppm): 8.49 (br s, 1H), 3.06 (t, *J* = 6.1 Hz, 2H), 2.45-2.35 (m, 1H), 2.30-2.20 (m, 1H), 2.04-1.95 (m, 1H), 1.89-1.81 (m, 2H), 1.90-1.81 (m, 2H), 1.44-1.24 (m, 3H), 0.77-0.66 (m, 3H), 0.40 (dd, *J* = 8.0, 1.7 Hz, 2H), 0.19-0.09 (m, 2H). MS: 304.1 (calcd), 305.1 (M+H⁺, found).

Example 254

2-Amino-6-cyano-6-(2-cyclopropylethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (512**)**



512: Example 254

To a 50 mL round bottom flask equipped with a stir bar was added **511** (96.2 mg, 316 μmol), DMF (3.49 mL), HATU (180 mg, 474 μmol), DIPEA (110 μL, 632 μmol) and ammonium chloride (338 mg, 6.32 mmol). The flask was sealed with a septum and sparged with a balloon of argon for 10 mins. Ammonia in THF (0.4 M solution, 15.8 mL, 6.32 mmol) was added to the reaction by syringe. The reaction was stirred at RT for 18 hours with an argon balloon. The reaction was quenched by addition of 50 mL of saturated NH₄Cl solution and extracted with EA

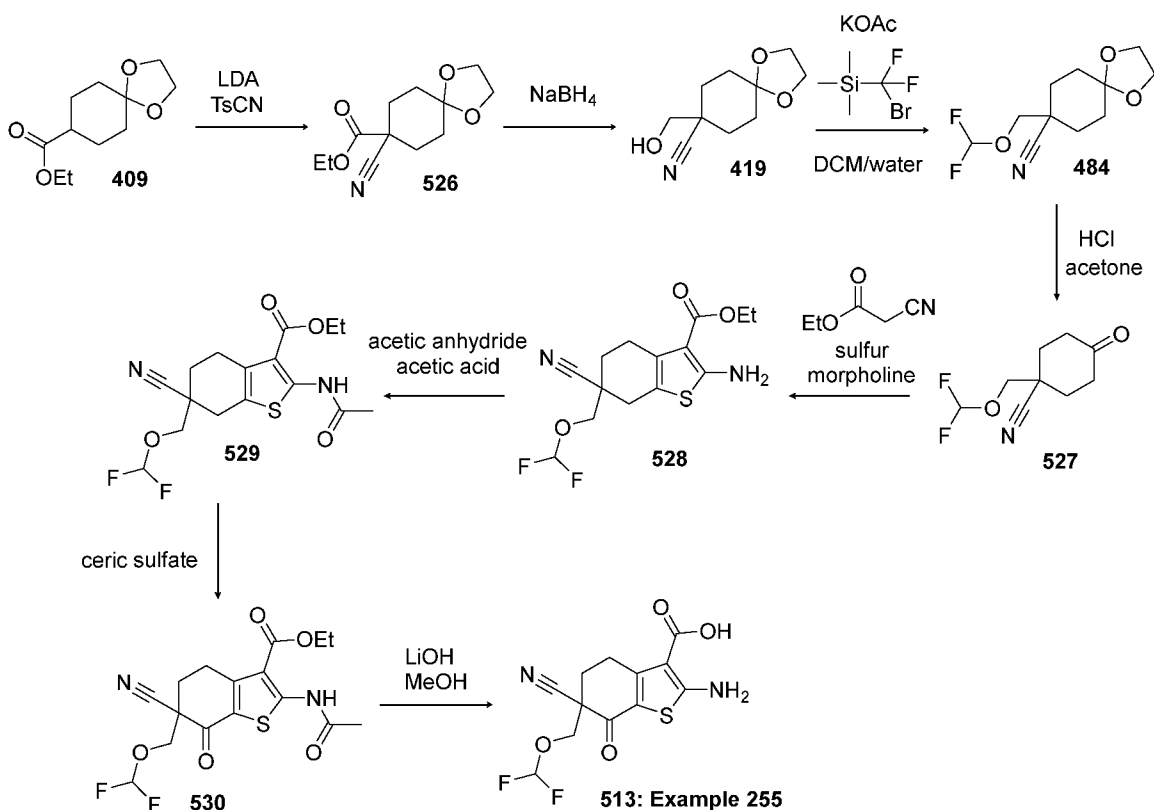
(3 x 50 mL). The EA fractions were combined, washed with brine (10 mL), dried with Na₂SO₄, filtered and concentrated. The crude material was purified with reverse phase C18 chromatography (eluent 0-100% acetonitrile in water) to yield the title compound **512** as a pale yellow solid (1.78 mg, 2% yield).

¹H NMR: 500 MHz, DMSO-d₆, δ (ppm): 8.24 (s, 2H), 3.20-2.92 (m, 2H), 2.69 (s, 1H), 2.43-2.34 (m, 2H), 2.29-2.18 (m, 1H), 2.05-1.91 (m, 1H), 1.91-1.81 (m, 1H), 1.40-1.27 (m, 2H), 0.77-0.66 (m, 1H), 0.46-0.35 (m, 2H), 0.14-0.02 (m, 2H). MS: 303.1 (calcd), 304.1 (M+H⁺, found).

Example 255

2-Amino-6-cyano-6-((difluoromethoxy)methyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**513**)

Scheme 118



Step 1. ethyl 8-cyano-1,4-dioxa-8-spiro[4.5]decanecarboxylate (**526**)

To a dry 250 mL round bottom flask equipped with a stir bar under argon was charged with ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (3.00 g, 14.0 mmol) and anhydrous THF (60 mL). The flask was cooled to -78 °C and LDA (15.4 mL, 15.4 mmol, 1 M in THF/hexanes) was added slowly. The reaction mixture was stirred for 1 hour at -78 °C and a degassed suspension of 4-methylbenzene-1-sulfonyl cyanide (2.79 g, 15.4 mmol) in anhydrous THF (10.0 mL) was added slowly by syringe. The reaction was stirred at RT for 18 hours. The reaction mixture was

quenched by addition of saturated NH_4Cl solution (50 mL) and extracted with EA (3 x 50 mL). The organic fractions were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated. The crude material was purified by silica gel chromatography with eluent 0-100% ethyl acetate in heptanes to yield the title compound **526** as a white solid (2.31 g, 69% yield).

¹H NMR: 400 MHz, CDCl_3 , δ (ppm): 4.27 (q, J = 7.1 Hz, 2H), 4.09-3.79 (m, 4H), 2.17 (dd, J = 10.8, 4.3 Hz, 4H), 1.98-1.86 (m, 2H), 1.86-1.73 (m, 2H), 1.32 (t, J = 7.2 Hz, 3H).

Step 2. 8-(hydroxymethyl)-1,4-dioxo-8-spiro[4.5]decanecarbonitrile (**419**)

To a 250 mL round bottom flask equipped with a stir bar was added **526** (2.31 g, 9.65 mmol) and methanol (48.3 mL). The flask was cooled to 0 °C and sodium borohydride (1.46 mg, 38.6 mmol) was added in a single portion. The reaction was stirred at RT for 2.5 hours then concentrated. DCM (50 mL) was added, and the solution was washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated to yield the title compound **419** as a white solid (1.61 g, 85% yield).

¹H NMR: 400 MHz, CDCl_3 , δ (ppm): 4.00-3.90 (m, 4H), 3.66 (s, 2H), 2.08-2.01 (m, 2H), 1.97-1.84 (m, 2H), 1.85-1.74 (m, 2H), 1.63 (td, J = 13.4, 3.8 Hz, 2H), 1.55 (s, 1H).

Step 3. 8-(difluoromethoxymethyl)-1,4-dioxo-8-spiro[4.5]decanecarbonitrile (**484**)

To a 25 mL round bottom flask equipped with a stir bar was added **419** (1.61 g, 8.16 mmol), potassium acetate (4.81 g, 49 mmol), DCM (4.89 mL), water (4.89 mL) and (bromodifluoromethyl)trimethylsilane (3.81 mL, 24.5 mmol). The reaction was stirred at RT for 22 hours. The reaction was diluted with 20 mL DCM, dried over Na_2SO_4 , filtered and concentrated. The crude material was purified by silica gel chromatography (eluent 0-70% ethyl acetate in heptanes) to yield the title compound **484** as a white solid (668 mg, 33% yield).

¹H NMR: 400 MHz, CDCl_3 , δ (ppm): 6.29 (t, J = 73 Hz, 1H), 4.01-3.90 (m, 4H), 3.86 (s, 2H), 2.08-2.01 (m, 2H), 1.93 (td, J = 13.7, 4.0 Hz, 3H), 1.86-1.75 (m, 2H), 1.69 (td, J = 13.3, 3.8 Hz, 2H).

Step 4. 1-(difluoromethoxymethyl)-4-oxocyclohexanecarbonitrile (**527**)

To a 1 dram vial equipped with a stir bar was charged with **484** (668 mg, 2.7 mmol) and acetone (13.5 mL). Aqueous HCl (2.25 mL, 12 M) was added in a single portion via syringe. The reaction was stirred at RT for 5 hours. Saturated NaHCO_3 (100 mL) was added, and extracted with EA (3x20 mL). The organic fractions were combined, washed with brine, dried over Na_2SO_4 , filtered, and concentrated to yield the title compound **527** (535 mg, 81% yield).

¹H NMR: 400 MHz, CDCl_3 , δ (ppm): 6.32 (t, J = 72 Hz, 1H), 3.95 (s, 2H), 2.72 (td, J = 15.0, 4.0 Hz, 2H), 2.51 (d, J = 15.0 Hz, 2H), 2.38 (d, J = 14.3, 2H), 1.83 (td, J = 13.8, 4.3 Hz, 2H).

Step 5. ethyl 2-amino-6-cyano-6-(difluoromethoxymethyl)-4,5,6,7-tetrahydro-1-thia-3-indenecarboxylate (**528**)

A 20 mL vial equipped with a stir bar was charged with **527** (170 mg, 837 μmol), ethyl 2-cyanoacetate (89 μL , 837 μmol), morpholine (79.4 μL , 920 μmol), sulfur (29.6 mg, 837 μmol) and

ethanol (1.33 mL). The vial was heated at 60 °C for 18 hours. The reaction was cooled to RT and concentrated. The crude material was purified by silica gel chromatography (eluent 0-100% ethyl acetate in heptanes) to yield the title compound **528** as a yellow oil (240 mg, 70% yield).

¹H NMR: 400 MHz, CDCl₃, δ (ppm): δ 6.31 (t, *J* = 73.0, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.07-3.90 (m, 2H), 3.04-2.91 (m, 2H), 2.71 (dt, *J* = 16.4 Hz, *J* = 2.0 Hz, 1H), 2.22-2.14 (m, 1H), 2.09-2.00 (m, 1H), 1.97-1.64 (m, 3H), 1.35 (m, *J* = 7.1 Hz, 3H). LC-MS: 331.1 m/z (M+H), retention time 1.17 min.

Step 6 ethyl 2-acetylamino-6-cyano-6-(difluoromethoxymethyl)-4,5,6,7-tetrahydro-1-thia-3-indenecarboxylate (**529**)

A 1 dram vial equipped with a stir bar was charged with ethyl 2-amino-6-cyano-6-(difluoromethoxymethyl)-4,5,6,7-tetrahydro-1-thia-3-indenecarboxylate (240 mg, 726 μmol) and acetic acid (4.18 mL). Acetic anhydride (82.4 μL, 872 μmol) was added in a single portion by syringe and the reaction was stirred at 60 °C for 2 hours. The reaction was cooled to RT and concentrated. The crude material was dissolved in DCM (5ml) and washed with sat. NaHCO₃ solution (3 mL). The organic layer was dried over Na₂SO₄ and concentrated to yield the title compound **529** as a yellow solid (109 mg, 40% yield).

¹H NMR: 400 MHz, CDCl₃, δ (ppm): 11.28 (s, 1H), 6.31 (t, *J* = 73.0 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.05-3.90 (m, 3H), 3.16-3.10 (m, 1H), 3.08-3.00 (m, 1H), 2.85-2.78 (m, 1H), 2.27 (s, 3H), 1.98-1.65 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H). MS: 372 (calcd), 373 (M+H⁺, found).

Step 7. ethyl 2-acetylamino-6-cyano-6-(difluoromethoxymethyl)-7-oxo-4,5,6,7-tetrahydro-1-thia-3-indenecarboxylate (**530**)

529 (109 mg, 1 equiv.), acetic acid (966 μL) and water (966 μL) were added to a 2 dram vial equipped with a stir bar. Cerium (IV) sulfate (840 mg, 2.53 mmol) was added in a single portion and the reaction was stirred vigorously at RT for 18 hours. EA (2 mL) and water (2 mL) were added, and the product was extracted to EA (3 x 10 mL). The organic fractions were combined and washed with 1 M NaOH (10 mL), water (10 mL) and brine (10 mL) and dried over Na₂SO₄, filtered and concentrated to yield the title compound **530** as a yellow residue (82.2 mg, 73% yield).

¹H NMR: 400 MHz, CDCl₃, δ (ppm): 11.63 (s, 1H), 6.31 (t, *J* = 73.3 Hz, 1H), 4.47-4.37 (m, 4H), 3.43 (dt, *J* = 18.9, 4.4 Hz, 1H), 3.32-3.21 (m, 1H), 2.62 (dt, *J* = 13.9, 4.3 Hz, 1H), 2.40-2.32 (m, 1H), 2.35 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 4H). MS: 386.1 (calcd), 387.0 (M+H⁺, found).

Step 8. 2-amino-6-cyano-6-((difluoromethoxy)methyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (**513**)

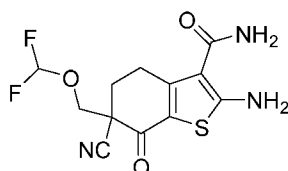
530 (82.2 mg, 1 equiv.), methanol (25.7 mL) and water (25.7 mL) were added to a 100 mL round bottom flask equipped with a stir bar. Lithium hydroxide monohydrate (44.6 mg, 1.06 mmol) was added in a single portion. A reflux condenser was affixed to the flask and the reaction was heated at 80 °C for 18 hours. The reaction was cooled to RT and concentrated. Aqueous 1 M HCl was added. The product was extracted to EA (3x 5 mL), washed with brine, dried over Na₂SO₄,

filtered, and concentrated. The crude material was purified by preparative HPLC to yield the title compound as a white solid (8.56 mg, 13% yield).

¹H NMR: 500 MHz, DMSO-d₆, δ (ppm): 8.69 (s, 1H), 6.79 (t, *J* = 74.7 Hz, 1H), 4.31 (d, *J* = 10.1 Hz, 1H), 4.22 (d, *J* = 10.2 Hz, 1H), 3.36-3.32 (m, 1H), 3.02-2.94 (m, 1H), 2.52-2.51 (m, 2H), 2.48-2.42 (m, 1H), 2.34-2.27 (m, 1H). LC-MS: retention time 3.47 min, *m/z* 317.033 (M+H). MS: 316.0 (calcd), 317.0 (M+H⁺, found).

Example 256

2-Amino-6-cyano-6-((difluoromethoxy)methyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (514)



514: Example 256

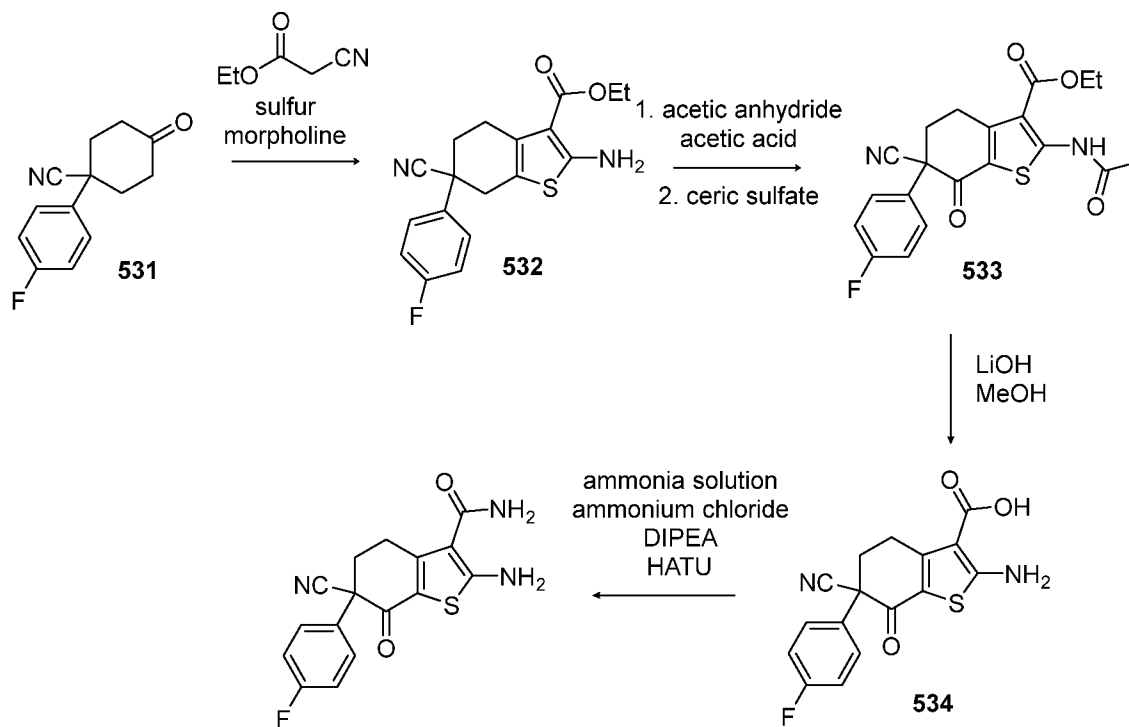
To a 50 mL round bottom flask equipped with a stir bar was added **513** (40.6 mg, 128 μmol), DMF (1.42 mL), HATU (73.3 mg, 193 μmol), DIPEA (44.7 μL, 257 μmol) and ammonium chloride (137 mg, 2.57 mmol). The flask was sealed and sparged with a balloon of argon for 10 mins. Ammonia in THF (0.4 M solution, 6.42 mL, 2.57 mmol) was added to the reaction by syringe. The reaction was stirred at RT for 18 hours under an atmosphere of argon. The reaction was quenched by addition of 50 mL of saturated NH₄Cl solution and extracted with EA (3 x 50 mL), washed with brine (10 mL), dried with Na₂SO₄, filtered and concentrated. The crude product was purified by RediSep Prep C18 column 20 x 150 mm 100 Å 5 μm; gradient 10% ACN in water 0-1.0 min, 10-100% ACN in water 1.0-12.0 min, 100% ACN 12.0-14.0 min and dried by lyophilization to yield the title compound **514** as a yellow solid (2.44 mg, 6% yield).

¹H NMR: 500 MHz, DMSO-d₆, δ (ppm): 8.35 (s, 2H), 6.80 (t, *J* = 74.6 Hz, 1H), 4.33 (d, *J* = 10.1 Hz, 1H), 4.22 (d, *J* = 10.1 Hz, 1H), 3.13 (s, 2H), 2.48-2.42 (m, 3H), 2.34-2.27 (m, 1H). MS: 315.0 (calcd), 316.0 (M+H⁺, found).

Example 257

2-Amino-6-cyano-6-(4-fluorophenyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (515)

Scheme 119



515: Example 257

Step 1. Ethyl 2-amino-6-cyano-6-(4-fluorophenyl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (532)

A 4 mL dram vial equipped with a stir bar was charged with 1-(p-fluorophenyl)-4-oxocyclohexanecarbonitrile (1 g, 4.6 mmol), ethyl cyanoacetate (0.49 mL, 4.6 mmol), elemental sulfur (163 mg, 0.428 mmol), morpholine (0.438 g, 5.07 mmol) and ethanol (7 mL). The reaction vessel was sealed and heated to 60 °C for 2 h, cooled to RT, filtered and the crystals washed with diethyl ether (2 x 4 mL), to afford the title compound **532** as a white solid (1.34 g, 85% yield).

¹H NMR: 500 MHz, CDCl₃, δ (ppm): 7.55-7.45 (m, 2H), 7.17-7.06 (m, 2H), 5.63 (s, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.22-2.94 (m, 4H), 2.43-2.31 (m, 1H), 2.31-2.13 (m, 1H), 1.40 (t, J = 7.1 Hz, 3H). MS: 344.1 (calcd), 345.1 (M+H⁺, found).

Step 2. Ethyl 6-cyano-6-(4-fluorophenyl)-2-acetamido-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (533)

A 100 mL round bottom flask with stir bar was charged with **532** (1 g, 2.9 mmol) and acetic acid (14.5 mL). Acetic anhydride (329 μL, 3.48 mmol) was added and the reaction mixture heated to 60 °C for 3h. The reaction was cooled to RT, and water (15 mL) and 1,4-dioxane (15 mL) were added, followed by Ce(IV) sulfate (8.18 g, 24.5 mmol), and the suspension was stirred at RT overnight. The reaction mixture was filtered, washed with EA, and the filtrate was diluted with water (100 mL), extracted with EA (2 x 100 mL), and the combined organic extracts were washed with 1N NaOH (70 mL), water (70 mL) and brine (70 mL), dried over Na₂SO₄, filtered, and concentrated to afford the title compound **533** as a white solid (259 mg, 22% yield).

¹H NMR: 500 MHz, CDCl₃, δ (ppm): 11.62 (s, 1H), 7.50-7.32 (m, 2H), 7.10 (t, *J* = 8.6 Hz, 2H), 4.40 (q, *J* = 7.2 Hz, 2H), 3.38 (ddd, *J* = 18.8, 7.5, 5.0 Hz, 1H), 3.21-3.01 (m, 1H), 2.75 (td, *J* = 7.2, 4.8 Hz, 2H), 2.35 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H). MS: 400.1 (calcd), 401.0 (M+H⁺, found).

Step 3. 2-amino-6-cyano-6-(4-fluorophenyl)-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-

5 3-carboxylic acid (534)

A 500 mL round bottom flask with stir bar was charged with **533** (259 mg, 0.647 mmol), lithium hydroxide monohydrate (136 mg, 3.23 mmol), methanol (80 mL), and water (80 mL). A reflux condenser was affixed to the flask and the reaction was stirred at 80 °C for 18 hours. The reaction was cooled to RT, concentrated to approximately half-volume, acidified by addition of 6 M HCl solution and extracted with EA. The organic fractions were combined, dried over Na₂SO₄,
10 filtered and concentrated. The residue was washed with Et₂O. The washings were concentrated to afford crude title compound as a white solid (30 mg, 14% yield) MS: 330.1 (calcd), 331.0 (M+H⁺, found).

Step 4. 2-amino-6-cyano-6-(4-fluorophenyl)-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-

15 3-carboxamide (515)

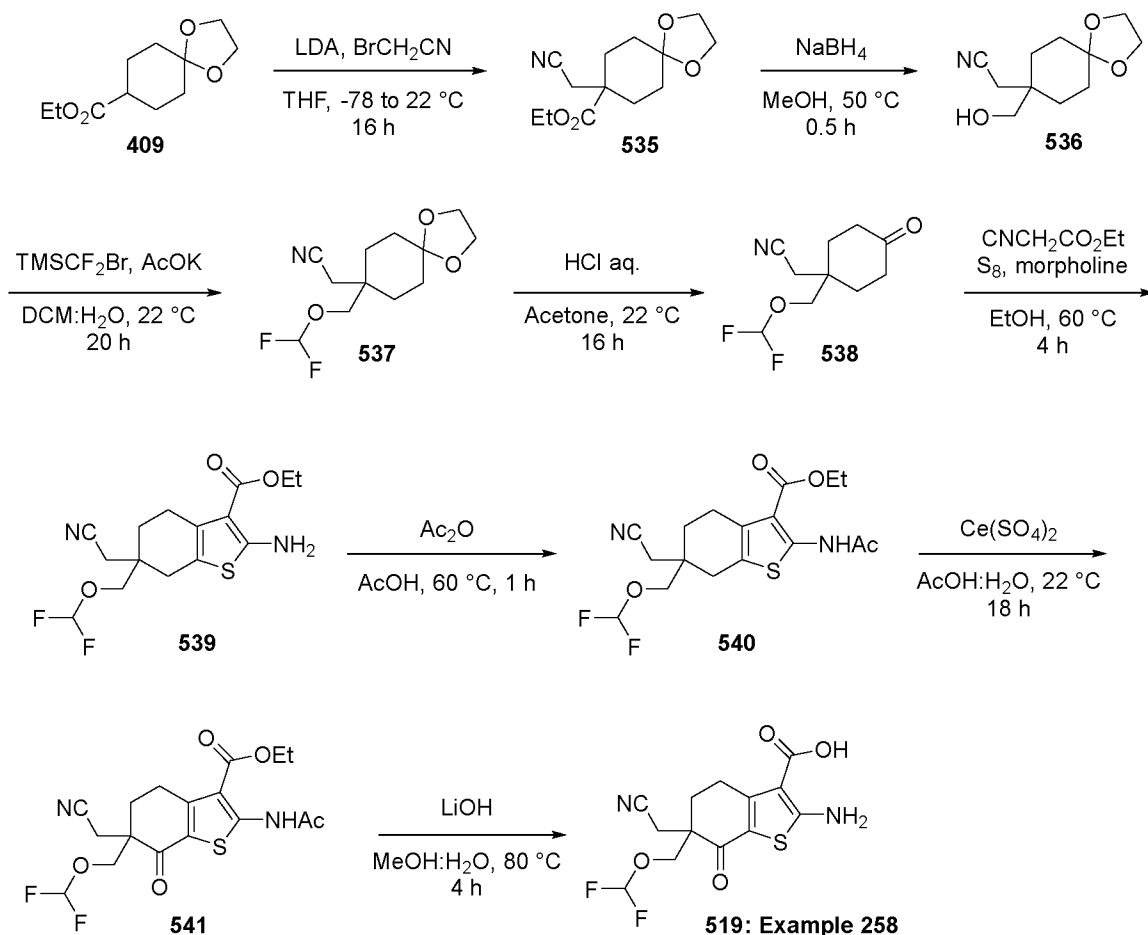
A 1-dram vial equipped with a stir bar was charged with **534** (30 mg, 90.8 μmol), ammonium chloride (146 mg, 2.72 mmol) and DMF (0.725 mL). HATU (51.8 mg, 0.136 mmol) was added, followed by *N*-ethylbis(isopropyl)amine (70.4 mg, 6 eq., 0.545 mmol), and the reaction mixture was stirred at RT for 2 h. The crude reaction was purified by preparative HPLC to yield
20 the title compound **515** as an off-white solid (2.74 mg, 9%).

¹H NMR: 500 MHz, DMSO-*d*₆, δ (ppm): 8.38 (s, 2H), 7.53-7.39 (m, 2H), 7.35-7.23 (m, 2H), 7.11 (s, 2H), 3.10 (ddd, *J* = 18.6, 6.9, 4.6 Hz, 1H), 2.92-2.75 (m, 2H), 2.71-2.59 (m, 1H). MS: 329.0 (calcd), 330.1 (M+H⁺, found).

Example 258

25 **2-Amino-6-(cyanomethyl)-6-((difluoromethoxy)methyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (519)**

Scheme 120



Step 1. ethyl 8-(cyanomethyl)-1,4-dioxaspiro[4.5]decanecarboxylate (535**)**

LDA (1 M in THF, 25.7 mL) was added to a solution of ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (5.00 g, 23.3 mmol) in THF (50.0 mL) at -78 °C, and the mixture was stirred at -78 °C for 1 h. A solution of 2-bromoacetonitrile (1.95 mL, 28.0 mmol) and DMPU (1.41 mL, 11.7 mmol) in THF (10.0 mL) was added, and the resulting mixture was slowly warmed to RT and stirred for 16 h. The mixture was diluted with sat. aq. NH_4Cl (200 mL), and the aqueous phase was extracted with EA (2 x 400 mL). The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography eluting with a gradient of heptane and EA (5-100%) to provide the title compound **535** as a yellow oil (4.21 g, 71% yield).

^1H NMR (400 MHz, CDCl_3) δ (ppm): 4.24 (q, $J = 7.1$ Hz, 2H), 4.00- 3.89 (m, 4H), 2.58 (s, 2H), 2.24 (qd, $J = 4.9, 3.6$ Hz, 2H), 1.78-1.62 (m, 6H), 1.30 (t, $J = 7.1$ Hz, 3H).

Step 2. {8-(hydroxymethyl)-1,4-dioxaspiro[4.5]decyl}acetonitrile (536**)**

NaBH_4 (3.77 g, 99.7 mmol) was added to a solution of **535** (4.21 g, 16.6 mmol) in MeOH (40.0 mL), and the mixture was stirred at 50 °C for 30 min. The mixture was diluted with water (200 mL), and the aqueous phase was extracted with EA (2 x 200 mL). The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel

chromatography eluting with a gradient of heptane and EA (5-100%) to provide the title compound **536** as a colorless solid (1.90 g, 59% yield).

¹H NMR (400 MHz, CDCl₃) δ (ppm): 3.94 (d, *J* = 1.4 Hz, 4H), 3.62 (s, 2H), 2.48 (s, 2H), 1.75-1.55 (m, 9H).

5 Step 3. 2-{8-[(difluoromethoxy)methyl]-1,4-dioxaspiro[4.5]decan-8-yl}acetonitrile (**537**)

A solution of KOAc (5.30 g, 54.0 mmol) in water (7.60 mL) was added to a solution of (bromodifluoromethyl)trimethylsilane (4.20 mL, 27.0 mmol) and **536** (1.90 g, 8.99 mmol) in DCM (7.60 mL), and the mixture was stirred at RT for 20 h. The mixture was diluted with water (200 mL), and the aqueous phase was extracted with DCM (2 x 200 mL). The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography eluting with a gradient of heptane and EA (5-100%) to provide the title compound **537** as a colorless solid (1.43 g, 61% yield).

¹H NMR (400 MHz, CDCl₃) δ (ppm): 6.24 (t, *J* = 74.1 Hz, 1H), 3.95 (s, 4H), 3.82 (s, 2H), 2.46 (s, 2H), 1.78-1.56 (m, 8H). ¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -84.77 (d, *J* = 73.9 Hz).

15 Step 4. 2-{1-[(difluoromethoxy)methyl]-4-oxocyclohexyl}acetonitrile (**538**)

Aq. HCl (37%, 1.66 mL, 54.7 mmol) was added to a solution of **537** (1.43 g, 5.47 mmol) in acetone (25.0 mL), and the mixture was stirred at RT for 16 h. The mixture was diluted with sat. aq. NaHCO₃ (200 mL), and the aqueous phase was extracted with EA (2 x 200 mL). The organic phase was washed with brine, dried over Na₂SO₄ and concentrated to provide the title compound **538** as a colorless oil (80% pure, 5.20 g, 80% yield).

¹H NMR (500 MHz, CDCl₃) δ (ppm): 6.30 (t, *J* = 73.5 Hz, 1H), 3.96 (s, 2H), 2.58 (s, 2H), 2.44-2.32 (m, 4H), 2.02-1.87 (m, 4H).

Step 5. ethyl 2-amino-6-(cyanomethyl)-6-[(difluoromethoxy)methyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**539**)

25 Ethyl 2-cyanoacetate (0.470 mL, 4.42 mmol) was added to a mixture of **538** (80% pure, 1.20 g, 4.42 mmol), sulfur (0.138 g, 0.610 mmol) and morpholine (0.419 mL, 4.86 mmol) in EtOH (8.00 mL), and the mixture was stirred at 60 °C for 4 h. The mixture was concentrated and the residue was purified by silica gel chromatography eluting with a gradient of heptane and EA (5-100%) to provide the title compound **539** as a yellow solid (810 mg, 53% yield). MS: 344.4 (calcd), 345.1 (M+H⁺, found).

30 Step 6. ethyl 6-(cyanomethyl)-6-[(difluoromethoxy)methyl]-2-acetamido-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**540**)

Acetic anhydride (275 uL, 2.82 mmol) was added to a mixture of **539** (810 mg, 2.35 mmol) in AcOH (8.50 mL), and the mixture was stirred at 60 °C for 1 h. The mixture was concentrated in vacuo and the residue was diluted with sat. aq. NaHCO₃ (50 mL). The aqueous phase was extracted with EA (2 x 50 mL), and the organic phase was dried over Na₂SO₄ and concentrated

to provide the title compound **540** as a yellow solid (751 mg, 82% yield). MS: 386.4 (calcd), 387.1 (M+H⁺, found).

Step 7. ethyl 6-(cyanomethyl)-6-[(difluoromethoxy)methyl]-2-acetamido-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (**541**)

5 Cerium(IV) sulfate (5.55 g, 16.7 mmol) was added to a mixture of ethyl 6-(cyanomethyl)-6-[(difluoromethoxy)methyl]-2-acetamido-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (0.751 g, 1.94 mmol) in water (7.00 mL) and acetic acid (7.00 mL), and the mixture was stirred at RT for 18 h. The mixture was diluted with water (100 mL), and the aqueous phase was extracted with EA (2 x 100 mL). The organic phase was washed with aq. NaOH (1 M, 100 mL), dried over
10 Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography eluting with a gradient of heptane and EA (5-100%) to provide the title compound **541** as a colorless solid (454 mg, 58%).

¹H NMR (400 MHz, CDCl₃) δ 11.58 (s, 1H), 6.24 (t, *J* = 73.3 Hz, 1H), 4.41 (qd, *J* = 7.2, 1.3 Hz, 2H), 4.04 (dd, *J* = 58.8, 10.3 Hz, 2H), 3.35 – 3.25 (m, 1H), 3.08 (ddd, *J* = 19.1, 9.9, 5.2
15 Hz, 1H), 2.87 – 2.75 (m, 2H), 2.47 – 2.24 (m, 5H), 1.44 (t, *J* = 7.1 Hz, 3H). MS: 400.4 (calcd), 401.0 (M⁺H⁺, found).

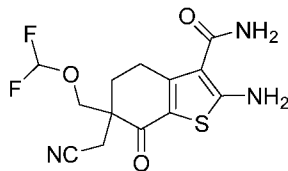
Step 8. 2-amino-6-(cyanomethyl)-6-(difluoromethoxymethyl)-7-oxo-4,5,6,7-tetrahydro-1-thia-3-indenecarboxylic acid (**519**)

20 LiOH.H₂O (21.0 mg, 0.499 mmol) was added to a mixture of ethyl 2-acetyl-amino-6-(cyanomethyl)-6-(difluoromethoxymethyl)-7-oxo-4,5,6,7-tetrahydro-1-thia-3-indenecarboxylate (40.0 mg, 0.0999 mmol) in water (10.0 mL) and methanol (10.0 mL), and the mixture was stirred in a sealed tube at 80°C for 5 h. The mixture was diluted with aq. HCl (1 M, 5 mL), and the aqueous phase was extracted with EA (2 x 10 mL), dried over Na₂SO₄ and concentrated. The
25 residue was purified by C18 chromatography eluting with a gradient of H₂O + 0.1% HCO₂H and MeCN + 0.1% HCO₂H (5-100%) followed by RediSep Prep C18 column 20 x 150 mm 100 Å 5 μm (gradient 10% ACN in water 5-100%) to provide the title compound as a colorless solid (1.35 mg, 4% yield).

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.41 (br s, 1H), 6.68 (t, *J* = 75.3 Hz, 1H), 4.16-
30 3.82 (m, 2H), 3.20- 2.96 (m, 2H), 2.95- 2.75 (m, 2H), 2.24- 2.03 (m, 2H). MS: 330.3 (calcd), 331.1 (M+H⁺, found).

Example 259

2-Amino-6-(cyanomethyl)-6-[(difluoromethoxy)methyl]-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (520**)**

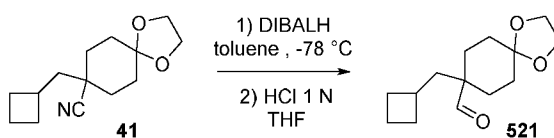
**520: Example 259**

Ammonia (0.4 M in THF, 7.57 mL, 3.03 mmol) was added to a mixture of 2-amino-6-(cyanomethyl)-6-(difluoromethoxymethyl)-7-oxo-4,5,6,7-tetrahydro-1-thia-3-indenecarboxylic acid (**519**) (50.0 mg, 0.151 mmol), HATU (86.3 mg, 0.227 mmol), DIPEA (52.7 μ L, 0.303 mmol), ammonium chloride (162 mg, 3.03 mmol) in DMF (2.00 mL), and the mixture was stirred at RT for 2 h. The mixture was diluted with sat. aq. NaHCO_3 (20 mL), and the aqueous phase was extracted with EA (2 x 30 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by C18 chromatography eluting with a gradient of MeCN in water + 0.1% formic acid (5-100%), followed by C18 chromatography eluting with a gradient of MeCN in water + 0.1% formic acid (5-50%) to provide title compound (**520**) a light yellow solid (5.12 mg, 10%).

^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.16 (s, 2H), 7.02 (bs, 2H), 6.70 (t, $J = 75.2$ Hz, 1H), 4.00 (dd, $J = 59.8, 10.0$ Hz, 2H), 3.15-2.88 (m, 2H), 2.96-2.75 (m, 2H), 2.25-2.04 (m, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ (ppm): -82.05 - -83.93 (m). MS: 329.3 (calcd), 328.0 ($\text{M}+\text{H}^+$, found).

Example 260

2-Amino-6-(cyclobutylmethyl)-6-((difluoromethoxy)methyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (524**)**

Intermediate compound 522**(8-(Cyclobutylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)methanol (**522**)**Scheme 121**Scheme 4**Step 1. 8-(Cyclobutylmethyl)-1,4-dioxaspiro[4.5]decanecarbaldehyde (**521**)

To a dry 100 mL round bottom flask equipped with a stir bar were added 8-(cyclobutylmethyl)-1,4-dioxaspiro[4.5]decanecarbonitrile (**41**, scheme 4) (558 mg, 2.37 mmol) and anhydrous toluene (13 mL). The reaction mixture was sparged with argon gas and cooled to -78 °C. DIBAL-H (3.89 mL, 3.89 mmol, 1 M in toluene) was then added dropwise and the resulting

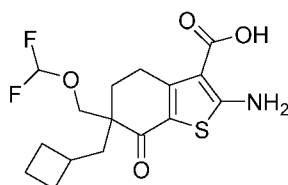
mixture was stirred at -78 °C for 2 hours. Subsequently, the reaction mixture was quenched with 1 mL of methanol at -78 °C. Saturated Rochelle's salt solution (50 mL) was added and the mixture was allowed to warm up to RT. The product was extracted with diethyl ether (3 x 50 mL). The organic fractions were combined, dried over Na₂SO₄, filtered and concentrated. The crude material was dissolved in THF (8.99 mL) and 2 N aq. HCl (593 uL, 1.19 mmol, 0.5 equiv.) was added. The mixture was stirred at RT for 20 minutes, then saturated aqueous NaHCO₃ (20 mL) was added and the product was extracted with EA (3 x 25 mL), washed with brine (10 mL), dried over Na₂SO₄ and concentrated to yield title compound **521** as a pale yellow oil (425 mg, 75% yield). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 9.43 (s, 1H), 3.92 (s, 4H), 2.28 (sept, *J* = 8.0 Hz, 1H), 2.09-1.88 (m, 4H), 1.87-1.43 (m, 12H).

Step 2. (8-(Cyclobutylmethyl)-1,4-dioxaspiro[4.5]decan-8-yl)methanol (522**)**

To a 250 mL round bottom flask equipped with a stir bar was added **521** (425 mg, 1.78 mmol) and MeOH (8.9 mL). The resulting solution was cooled to 0 °C and NaBH₄ (202 mg, 5.35 mmol) was added in a single portion. The reaction mixture was stirred at RT for 1.5 hours. The volatiles were then removed *in vacuo*, brine (20 mL) was added and the residue was extracted with EA (3 x 25 mL). The organic fractions were combined, dried over Na₂SO₄, filtered and concentrated. The crude material was purified by silica gel chromatography using eluent 0-100% EA in heptane to yield title compound **522** as a clear oil (134 mg, 31%). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 4.02-3.86 (m, 4H), 3.45 (s, 2H), 2.41 (ddq, *J* = 14.4, 9.1, 7.6 Hz, 1H), 2.12-1.96 (m, 3H), 1.99-1.56 (m, 8H), 1.56-1.40 (m, 6H).

Intermediate compound 523

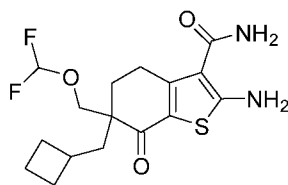
2-Amino-6-(cyclobutylmethyl)-6-((difluoromethoxy)methyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (523**)**



523

Compound **523** was synthesized similarly to compound **347** (example 249, scheme 115), starting from intermediate compound **522** (scheme 121) instead of compound **115**. MS: 359.2 (calcd), 360.2 (M+H⁺, found).

2-Amino-6-(cyclobutylmethyl)-6-((difluoromethoxy)methyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (524**)**

**524: Example 260**

Compound **524** (example 260) was synthesized similarly to compound **238** (example 127, scheme 55) starting from intermediate compound **523** instead of compound **237**.

^1H NMR (500 MHz, CD_3OD) δ (ppm): 6.35 (dd, $J = 76.5, 75.2$ Hz, 1H), 4.14 (d, $J = 9.5$ Hz, 1H), 3.79 (d, $J = 9.6$ Hz, 1H), 3.23-2.91 (m, 2H), 2.46 (dt, $J = 15.5, 8.0$ Hz, 1H), 2.29 (ddd, $J = 13.8, 10.3, 5.4$ Hz, 1H), 2.15-1.93 (m, 3H), 1.93-1.81 (m, 1H), 1.81-1.67 (m, 3H), 1.58 (p, $J = 9.6$ Hz, 1H). ^{19}F NMR (470 MHz, CD_3OD) δ (ppm): -85.07, -85.41, -85.61, -85.96 (two overlapping doublets.). MS: 358.2 (calcd), 359.2 ($\text{M}+\text{H}^+$, found).

Example 261

Protocol for the human acid-sensing channel 1a (hASIC1a) assay

A human acid-sensing channel 1a (hASIC1a) assay was developed to evaluate both the potential agonistic and antagonistic activity of compounds on human acid-sensing channel 1a (hASIC1a) in a single run. hASIC1a is generally activated in acidic conditions and leads to Ca^{2+} influx into the cell. Therefore, detection and quantification of the change in intracellular Ca^{2+} may be used as a measure of hASIC1a activity or inhibition. In this assay, cells expressing hASIC1a containing a Ca^{2+} -specific fluorescent dye are first treated with a compound of interest at a neutral pH to evaluate the agonist effect of solely the compound on hASIC1a in the absence of an acidic environment. Then the same cells, without washing, are subsequently treated with an acidic solution to determine the antagonistic effect of the compound on hASIC1a activation caused by the acidic environment.

Briefly, black 384-well plates were first coated with 0.005% Polyethylenimine (PEI) (50 μl /well for 24 hours at 37°C) to fix the cells and avoid resuspension during the measurements and washed 4 times ddH₂O before use. F9 cells (HEK293S) stably expressing hASIC1a were resuspended in extracellular fluid buffer pH 7.4 (ECF 7.4; 140 mM NaCl, 5 mM KCl, 2 mM CaCl_2 , 2 mM MgCl_2 , 10 mM HEPES, and 10 mM glucose) and labelled with Fluo-8TM AM dye (4 μM final), which is fluorescent upon binding to Ca^{2+} , according to the manufacturer's protocol. Cells were then washed and resuspended in ECF 7.4, and plated (40,000 cells/well; 15 μl /well) in the PEI pre-coated black 384-well plate, centrifuged at 400 rpm for 1 minute, and incubated for 60 minutes at room temperature in the dark before addition of the test samples. Extracellular fluid buffer pH 5.85 (ECF 5.85; 140 mM NaCl, 5 mM KCl, 2 mM CaCl_2 , 2 mM MgCl_2 , 10 mM HEPES, and 10 mM glucose) is added to some wells (50 μl /well), which is used as a positive control for the agonist mode. 200 μM Benzamil is added to other wells (50 μl /well), which is used as a positive control

for the antagonist mode. 100% DMSO is added to other wells, which is used as a baseline level of fluorescence.

Agonist mode (1st addition)

The agonist activity of the compound of interest is assessed first. Serial dilutions (e.g., 1:2.2) prepared of the compounds to be tested are prepared in ECF 7.4 in duplicates at a 4X and are subsequently added to the cells (15µl/well) (effectively diluting the compounds to 2X final concentration) and incubated for 4 minutes inside an FDSS7000™ (Functional Drug Screening System; Hamamatsu) instrument (exposure: 200 ms (normal); excitation filter: 472 nm (+/- 30); emission filter (540 nm (+/- 40)) to measure the fluorescence (i.e., Ca²⁺ influx). Addition of the compounds is made at photo 11 (at 11 seconds). Data acquisition is performed for 70 seconds (70 photos x 1 sec)

Antagonist mode (2nd addition)

The antagonist activity of the compound of interest is then assessed. 30 µl ECF 5.85 each well is then added to the cells (effectively diluting the compounds to 1X final concentration) and measurements are taken for the next minute inside the FDSS7000. After addition of ECF 5.85, the resulting final pH of the well is roughly 6.5. Addition of ECF 5.85 is made at photo 241 (at 241 seconds). Data acquisition is performed for 60 seconds (60 photos x 1 sec).

After the readings, three sets of data (outputs) are exported as text file format (.TXT) with the FDSS7000 hASIC1a assay protocol:

Output 1 (.TXT): Is the Max and Min FU counts for the agonist mode (after the addition of compounds (between 11 and 80 seconds)

Output 2 (_2.TXT): Is the Max and Min FU counts for the antagonist mode (after the addition of ECF pH 5.85 (between 241 and 300 seconds))

Output 3 (_3.TXT): Is the maximum baseline value (maximum FU value just prior the addition of ECF pH 5.85 (between intervals 235-240 seconds))

For the agonist mode, the MAX minus MIN FU values from the Output 1 text file (.TXT) are used for the curve fitting. Max-Min data in Fluorescent Unit (FU) from each well are converted in percent value relative to the pH 6.5 (final pH of the well after addition of ECF 5.85) maximum effect (maximum FU) using the following formula:

$$\frac{[(\text{well FU} - \text{mean baseline FU with DMSO}) / (\text{mean maximum FU at pH 6.5} - \text{mean baseline FU with DMSO})] * 100}$$

A 100% effect corresponds to the control wells containing a final pH of 6.5 and the 0% effect to the control wells with DMSO only (No ECF 5.85). Dose-response relationships are analyzed using the transformed Max-Min data in relative percent value and XLfit™ software (Model 205, 4 parameters logistic equation).

For the antagonist mode, the ratio MAX FU values over MAX baseline FU values are used for the curve fitting. The Max values and the Max baseline values used are respectively from the

Output 2 file (_2.TXT) and the Output 3 file (_3.TXT). The ratio MAX over MAX baseline data from each well are converted in percent value relative to the Benzamil maximum effect (maximum FU) at 50 μ M final using the formula:

$$(1 - [(well\ ratio - mean\ ratio\ Benzamil) / (mean\ ratio\ with\ DMSO - mean\ ratio\ Benzamil)]) * 100$$

- 5 A 100% effect corresponds to the control wells containing 50 μ M Benzamil and the 0% effect to the control wells with DMSO only (with ECF 5.85). Dose-response relationships are analyzed using the transformed ratio MAX over MAX baseline data in relative percent value and XLfit™ software (Model 205, 4 parameters logistic equation). Average hASIC1a antagonist IC₅₀ (nM) values of tested compounds are provided in Table 10.

10 **Table 10.** Average hASIC1a Antagonist IC₅₀ (nM) of Compounds

Compound No.	hASIC1a Antagonist Assay: Average IC ₅₀ (nM)	Compound No.	hASIC1a Antagonist Assay: Average IC ₅₀ (nM)
4	53	239	36
9	569	245	142
15	47	246	18
16	180	247	1063
17	229	248	11
18	500	249	721
19	601	250	5
20	116	251	10
21	684	253	59
22	562	254	46
23	2450	255	12
24	279	258	14
25	35	263	30
26	148	264	54
27	219	271	140
28	2263	272	14
29	137	273	9
30	159	278	96
31	149	279	13
32	48	280	68
33	65	281	13
34	196	287	258
35	1825	288	48

36	342	291	23
37	192	297	673
38	763	298	99
39	543	305	61
47	67	306	9
48	11	313	41
49	27	314	13
50	12	321	25
51	121	322	10
52	36	331	23
53	430	338	17
54	10	173	132
59	31	339	14
60a	7953	340	15
60b	16	341	22
61	9	342	24
62	48	343	27
63	5	344	27
64	189	345	16
65	141	346	117
66	218	347	395
67	228	348	949
68	694	349	1184
69	2555	337	1418
70	1070	352	114
71	237	353	11
72	25	354	155
75	8	355	11
81	461	356	20
82	40	357	360
83	19	358	29
84	106	391	17
89	88	392	36
91	162	393	19
97	19	394*	33
101	13	395**	22

109	23	396	39
119	35	397	16
120	244	401	292
121	59	402	16
122	220	403	47
123	192	406	287
124	3320	407	28
125	1152	408	54
126	2462	412	3522
127	13	413	63
128	32	414	163
129	29	416	135
130	30	418	43
131	61	422	71
132	71	427	625
133	88	428	14
134	68	429	68
135	17	430	10
136	45	431	16
138	94	434	17
139	78	445	45
140	10	446	9
141	12	447	11
142	7368	448	24
143	8	449	39
144	17	450	17
145	25	451	89
146	8	452	2477
147	17	453	115
148	37	454	30
149	20	462	160
150	35	463	10
155	187	464	24
163	11	465	19
168	134	466	18
169	22	468	128

170	17	469	5657
174	9	470	413
175	135	471	2691
179	24	472	52
180	104	473	1301
181	14	474	411
183	32	475	64
189	719	476	30
191	15	478	542
192	34	479	88
193	2667	480	191
194	22	481	54
195	18	482	143
197	10000	483	1280
198	478	486	70
199	233	489	14
200	2327	492	671
201	112	495	54
202	306	496	119
211	1429	497	3164
212	23	498	65
213	36	511	102
214	92	512	6
215	10	513	458
216	166	514	16
219	1132	515	16
221	7368	520	83
228	307	524	17
229	5093		
230	9		
231	11		
232	14		
237	455		
238	17		

*394 is mixture of regioisomers 394a and 394b

**395 is mixture of regioisomers 395a and 395b

Example 262Efficacy of combination therapy in inflammatory painMaterial and Methods*Animals*

5 Experiments were conducted in male Sprague-Dawley rats (~250g, Charles River, St. Constant, Canada). Rats were group-housed on autoclaved corncob bedding in individual HEPA ventilated cages (Innocage® IVC, Innovive, San Diego, CA, USA) in a temperature-controlled environment (22±1.5 °C, 30-80 % relative humidity, 12-hr light/dark) and had irradiated food (Harlan Teklad, Montreal, Canada) and filtered water *ad libitum*. Rats were acclimatized in the
10 animal facility (adMare BioInnovations, Montreal, Canada) for at least 5 days prior to use. Studies were conducted under a protocol that has been approved by the NEOMED Animal Care Committee and performed during the light phase of the cycle. The number of rats used was the minimum necessary to achieve an 80% statistical power to detect a 40% change.

Carrageenan-induced Inflammation Model

15 The effect of specific compounds, either alone or in combination with a cyclooxygenase (COX) inhibitor, was assessed in the carrageenan-induced inflammation model, as previously described in Ferenbacher, J. C. et al. (2012). Briefly, carrageenan is administered in the paw of rats to induce inflammation and hypersensitivity (e.g., thermal hypersensitivity), prior to administering a test drug. Rat paws are then subjected to a heat source and the withdrawal time
20 of the paw is then evaluated as a measure of heat hyperalgesia.

Carrageenan-lambda (Sigma-Aldrich) was dissolved in sterile saline 0.9% at a concentration of 1% w/v. Rats were placed in a plexiglass chamber with 2% isoflurane at a flow rate of 0.8-1l/hr with oxygen, for approximately 60-90 seconds, until a light-medium depth of anesthesia was attained. One hundred microliters of carrageenan solution were injected into the
25 subcutaneous space of the dorsal aspect of the left hind paw, in the center of the four pads.

Test compounds and COX inhibitors were dissolved in 40% polyethylene glycol (PEG) 400 (in 0.9% sterile saline) and orally administered 2 hr after carrageenan inoculation, once inflammation was established, at a volume of 5ml/kg, and heat hyperalgesia was assessed 30min later. For the combination studies, the COX inhibitor to compound dose ratio was kept fixed for
30 all dose levels.

Heat hyperalgesia was assessed using the Hargreaves Plantar test. Animals were placed on a glass surface, and a heat-source was focused onto the plantar surface of the affected paw. The time from the initiation of the heat until the animal withdraws the paw was recorded and defined as the Paw Withdrawal Latency (PWL).

Statistical significance was determined using one-way ANOVA on raw data followed by a post-hoc Holm-Sidak t-test. The level of statistical significance was set at $p < 0.05$. Raw data were normalized using the following formula: % Anti-hyperalgesia = $(PWL_{(dose)} - PWL_{(vehicle)}) / (PWL_{(naïve)} - PWL_{(vehicle)}) \times 100$. Data are expressed as mean $\pm$ SEM.

It is to be noted that the present study involved assessment of hyperalgesia based on thermal response and Paw Withdrawal Latency. Alternatively, one can assess mechanical allodynia using the Dynamic Von Frey test. In the Dynamic Von Frey test, animals are placed on a wire mesh surface, and the Von Frey filament is applied onto the plantar surface of the affected paw at an increasing force in grams. The force required for the animal to withdraw its paw is then recorded. The data can be expressed as mean $\pm$ SEM. Statistical significance can be determined using one-way ANOVA on raw data followed by a post-hoc Holm-Sidak t-test. The level of statistical significance can be set at $p < 0.05$. Raw data can be normalized using the following formula: % efficacy = $(Force_{(dose)} - Force_{(vehicle)}) / (Force_{(naïve)} - Force_{(vehicle)}) \times 100$.

Isobolographic Analysis

After generating individual dose-response curves for each compound or COX inhibitor in the carrageenan model and determining their ED50 values (with 95% CL), compound and COX inhibitor combinations were administered at selected dose-ratio derived from their ED50 values. Evaluation of the co-administration effect was performed using a graphical approach visualized by an isobologram to compare experimentally obtained ED50 values (Tallarida, R. J. et al. (1989)). The theoretical additive ED50 was estimated according to the methodology. The criterion for establishing a statistical significance was $P < 0.05$. Graphically, mean ED50 values (with 95% CL) for each compound or COX inhibitor administered either alone or as part of a combination were plotted. In this analysis, the line that connects the ED50 values for each compound or COX inhibitor alone is the theoretical line of additivity. Experimentally obtained ED50 of the combination and its 95% CLs that fall above the line of additivity are suggestive of subadditivity (antagonism), whereas points that fall below are suggestive of supra-additivity (synergism).

Results

Having available efficacy data for both compound 61 (oral ED50 = 6.7 mg/kg with 95% confidence limits (CL) of 3.3 to 19.5 mg/kg) and naproxen (oral ED50 = 8.1 mg/kg with 95% CL of 3.5 to 20 mg/kg), the first step was to determine the potency ratio, in this case the ratio of the ED50 values of naproxen to compound 61 was 1.0 to 0.83. Through isobolographic analysis, the theoretical ED50 value for the combination, assuming additivity, was calculated to be 7.4 mg/kg. Consequently, selected doses for the combination, keeping the ratio fixed, were 0.3, 1.0, 3.0, 10.0, and 30.0 mg/kg. In the carrageenan model, the combination resulted in a maximum effect of 86% at the highest dose tested. The ED50 for the combination was calculated to be 1.4 mg/kg with 95% CL of 1.0 to 2.0 mg/kg (Figure 1A). In comparison to the theoretical ED50, the effect of

the combination was 5.3-fold more than expected if the interaction was purely additive. Using the calculated ratio, 1.4 mg/kg represents an ED₅₀ for compound 61 of 0.63 mg/kg (with 95% CL of 0.45 to 0.91 mg/kg), and for naproxen of 0.77 mg/kg (with 95% CL of 0.55 to 1.1 mg/kg). Comparing the new ED₅₀ values, the combination of compound 61 and naproxen showed a 10.6-fold increase in potency as compared to when given alone. The isobolographic analysis (Figure 1B) demonstrated that the ED₅₀ of the combination lies below the line of additivity indicating a synergistic interaction. Isobolographic analysis confirms that there exists a ratio-dependent synergy of compound 61 in combination with naproxen, celecoxib, ibuprofen, or diclofenac, as well as compound 63 in combination with naproxen (Table 11, Figure 2, Figure 3, Figure 4, Figure 5, Figure 6). As noted in Table 11, the combination of compound 61 and naproxen was tested in duplicate (see Figures 1 and 2).

Table 11. Anti-hyperalgesic response of ASIC1 inhibitors in combination with COX inhibitors

Inhibition of heat hyperalgesia in the rat carrageenan-induced inflammation model					
Compound, COX inhibitor, or combination	Dose range (mg/kg)	Dose ratio (COX inhibitor:compound)	ED ₅₀ (mg/kg, 95% CL)	Fold shift in potency	Outcome
Compound 61	0.5-30	NA	6.7 (3.3-19.5)	NA	NA
Compound 63	0.15-5	NA	1.4 (0.7-5)	NA	NA
Naproxen	0.75-50	NA	8.1 (3.5-20)	NA	NA
Celecoxib	1-100	NA	12.9 (4.1-72.4)	NA	NA
Ibuprofen	3-60	NA	12.6 (8.3-30.2)	NA	NA
Diclofenac	3-100	NA	11.7 (6.3-25.1)	NA	NA
Naproxen: compound 61	0.3-30	1:0.83	1.4 (1-2)	10.6	Synergy
Naproxen: compound 61	0.3-30	1:0.83	1.8 (1.4-2.3)	8.2	Synergy
Celecoxib: compound 61	0.3-30	1:1.52	2.3 (1.5-4.9)	8.5	Synergy
Ibuprofen: compound 61	0.3-30	1:0.53	2.1 (1.1-4.6)	9.2	Synergy
Diclofenac: compound 61	0.3-30	1:0.57	1.6 (0.9-2.8)	11.5	Synergy
Naproxen: compound 63	0.15-15	1:0.178	0.87 (0.4-2)	11	Synergy

% Anti-hyperalgesia = $(PWL_{(dose)} - PWL_{(vehicle)}) / (PWL_{(naive)} - PWL_{(vehicle)}) \times 100$. ED₅₀ calculated from the non-linear regression curve using the variable slope sigmoidal equation model. "NA" = not applicable

Example 263Combination therapy in a Neuropathic Pain ModelMaterial and Methods*Animals*

Experiments were conducted in male Sprague-Dawley rats (~250g, Charles River, St. Constant, Canada). Rats were group-housed on autoclaved corn cob bedding in individual HEPA ventilated cages (Innocage® IVC, Innovive, San Diego, CA, USA) in a temperature-controlled environment (22±1.5 °C, 30-80 % relative humidity, 12-h light/dark) and had irradiated food (Harlan Teklad, Montreal, Canada) and filtered water ad libitum. Rats were acclimatized in the animal facility (adMare BioInnovations, Montreal, Canada) for at least 5 days prior to use. Studies were conducted under a protocol that has been approved by the Animal Care Committee and performed during the light phase of the cycle. The number of rats used was the minimum necessary to achieve an 80% statistical power

Chronic Constriction Injury (CCI) model of neuropathic pain and testing

CCI was performed under anesthesia. About a 3-cm long blunt dissection was made into the skin overlying the area between the gluteus and biceps femoris muscles, and the common sciatic nerve of the hind paw was exposed at the mid-thigh level. Approximately 7 mm of the nerve was freed, proximal to the sciatic trifurcation, and four or three loose ligatures (about 1 mm spacing) of 4-0 chromic guts (or 4-0 silk) were placed around the sciatic nerve until a brief twitch was observed. The wound was closed with sutures in the muscle and staples in the skin. The animal was then allowed to recover from surgery for 24 h before pain hypersensitivity testing began.

Compound 61 alone or in combination with naproxen or diclofenac was dissolved in 40% polyethylene glycol (PEG) 400 (in 0.9% sterile saline) and orally administered at a volume of 5mL/kg and tested 30min later. The ratio Compound 61 to naproxen in the tested combination was 0.83:1 and the ratio Compound 61 to diclofenac in the tested combination was 0.57:1.

Heat hyperalgesia was assessed using the Hargreaves Plantar test. Animals were placed on a glass surface, and a heat-source was focused onto the plantar surface of the affected paw. The time from the initiation of the heat until the animal withdraws the paw was recorded and defined as the Paw Withdrawal Latency (PWL).

Statistical significance was determined using one-way ANOVA on raw data followed by a post-hoc Holm-Sidak t-test. The level of statistical significance was set at $p < 0.05$. Raw data were normalized using the following formula: $\% \text{ Anti-hyperalgesia} = (\text{Response}_{(\text{dose})} - \text{Response}_{(\text{vehicle})}) / (\text{Response}_{(\text{naive})} - \text{Response}_{(\text{vehicle})}) \times 100$. Data are expressed as mean ± SEM.

PWL and % efficacy values of the naproxen:Compound 61 and diclofenac:Compound 61 combinations are provided in Table 12.

Isobolographic analysis: After generating a dose-response curve for compound 61 in the CCI model its ED30 value (with 95% CI) was determined. Evaluation of the co-administration effect was performed using a graphical approach visualized by an isobologram to compare experimentally obtained ED30. For the CCI model, modified type II isobolographic analysis was used (modified analytical method as described in Matsumura, N. et al. (2014)), with selected dose ratio derived from studies conducted in inflammatory models. Additionally, the theoretical additive ED30 was estimated according to the methodology. The criterion for establishing a statistical significance was $P < 0.05$. Graphically, mean ED30 values (with 95% CI) for compound 61 administered either alone or as part of a combination were plotted. In this analysis, the line that connects the ED30 values is the theoretical line of additivity. Experimentally obtained ED30 of the combination and its 95% CIs that fall above the area of additivity are suggestive of subadditivity (antagonism), whereas points that fall below are suggestive of supra-additivity (synergism).

Results

Having available efficacy data for each of Compound 61 (oral ED30 = 7.9 mg/kg with 95% confidence limits (CL) of 4.6 to 14.5 mg/kg), naproxen (maximum efficacy of 19%) and diclofenac (maximum efficacy of 21%) in the CCI model, combination studies were performed using selected dose ratios of 1:0.83 (naproxen:Compound 61) and 1:0.57 (diclofenac: Compound 61), which were derived from studies conducted in inflammatory pain models. Through isobolographic analysis, the theoretical combination ED30 assuming additivity was calculated to be 17.5 mg/kg for naproxen:Compound 61 and 21.7 mg/kg for diclofenac:Compound 61. Consequently, selected doses for the combination, keeping the ratio fixed, were 2, 5, 10, 20 and 50.0 mg/kg for naproxen:Compound 61 and 3, 6, 15, 30 and 60.0 mg/kg for diclofenac:Compound 61.

In the CCI model, the naproxen:Compound 61 combination dose-dependently increased the withdrawal latency to a heat stimulus, indicating a reduction in heat hyperalgesia with a maximum efficacy of 35 % at the highest dose tested (Table 12). The ED30 for the combination was calculated to be 22.4 mg/kg with 95% CL of 11 to 35 mg/kg. Using the dose ratio, the new ED30 for Compound 61 was calculated to be 10.1 mg/kg (with 95% CL of 5 to 15.8 mg/kg). The isobolographic analysis demonstrated that the ED30 of the naproxen:Compound 61 combination lies within the area of additivity indicating a ratio-dependent additive interaction of Compound 61 in combination with naproxen in the CCI model (Table 13). The diclofenac:Compound 61 combination dose-dependently increased the withdrawal latency to a heat stimulus, indicating a reduction in heat hyperalgesia with a maximum efficacy of 45 % at the highest dose tested (Table 12). The ED30 for the diclofenac:Compound 61 combination was calculated to be 18.4 mg/kg with 95% CL of 3.5 to 37.1 mg/kg, with a new ED30 for Compound 61 of 6.7 mg/kg (with 95% CL

of 1.3 to 13.5 mg/kg). The isobolographic analysis demonstrated that the ED30 of the diclofenac:Compound 61 combination lies within the area of additivity indicating a ratio-dependent additive interaction of Compound 61 in combination with diclofenac in the CCI model (Table 13).

Table 12. Anti-hyperalgesic response of ASIC1 inhibitors in combination with COX inhibitors in the CCI model of neuropathic pain

Combination	Ratio COX inhibitor: Compound 61	Dose (mg/kg)	PWL (s)	Efficacy (%)	N
Naproxen:Compound 61	1:0.83	Naive	10.53	N/A	5
		Vehicle	5.57	0.00	5
		2	5.81	4.88	5
		5	6.21	12.97	5
		10	6.63*	21.43	5
		20	7.01**	29.09	5
		50	7.28***	34.54	5
Diclofenac:Compound 61	1:0.57	Naive	10.52	N/A	5
		Vehicle	5.49	0.00	5
		3	6.33	16.59	5
		6	6.53*	20.64	5
		15	6.79**	25.82	5
		30	7.48***	39.49	5
		60	7.78***	45.41	5

NA: Not applicable

* p<0.05, ** p<0.01, *** p<0.001

% Efficacy = (Response_(dose)-Response_(vehicle)) / (Response_(naïve)-Response_(vehicle)) X 100.

Table 13. Isobolographic analysis of ASIC1 inhibitors in combination with COX inhibitors in the CCI model of neuropathic pain

Compound, COX inhibitor, or combination	Dose range (mg/kg)	Dose ratio (COX inhibitor:Compound 61)	ED30 (mg/kg, 95% CL)	Fold shift in potency	Outcome
Compound 61	3-60	NA	7.9 (4.6-14.5)	NA	NA
Naproxen	0.75-50	NA	NA	NA	NA
Diclofenac	3-200	NA	NA	NA	NA
Naproxen: Compound 61	2-50	1:0.83	22.4 (11-35)	-1.3	Additive
Diclofenac: Compound 61	3-60	1:0.57	18.4 (3.5-37.1)	1.2	Additive

Although the invention has been illustrated and described with respect to one or more implementations, equivalent alterations and modifications will occur to others skilled in the art upon the reading and understanding of this specification. In addition, while a particular feature of the invention may have been disclosed with respect to only one of several implementations, such
5 feature may be combined with one or more other features of the other implementations as may be desired and advantageous for any given or particular application.

Accordingly, it is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this
10 application and scope of the appended claims. Any publication, document, patent, patent application or publication referred to herein should be construed as incorporated by reference each in their entirety for all purposes.

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15 Complete Freund's Adjuvant-Induced Edema and Hypersensitivity in the Rat. *Curr. Protoc. Pharmacol. Chapter 5: Unit 5.4*, 2012.

Matsumura, N. and Nakaki, T.: Isobolographic analysis of the mechanisms of action of anticonvulsants from a combination effect. *European Journal of Pharmacology*, 741:237-246, 2014.

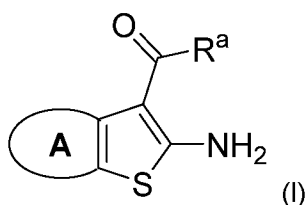
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CLAIMS

1. A pharmaceutical combination comprising:

5 (a) a cyclooxygenase (COX) inhibitor; and

(b) a compound having the Formula (I)



or a pharmaceutically acceptable salt, solvate, or prodrug thereof,

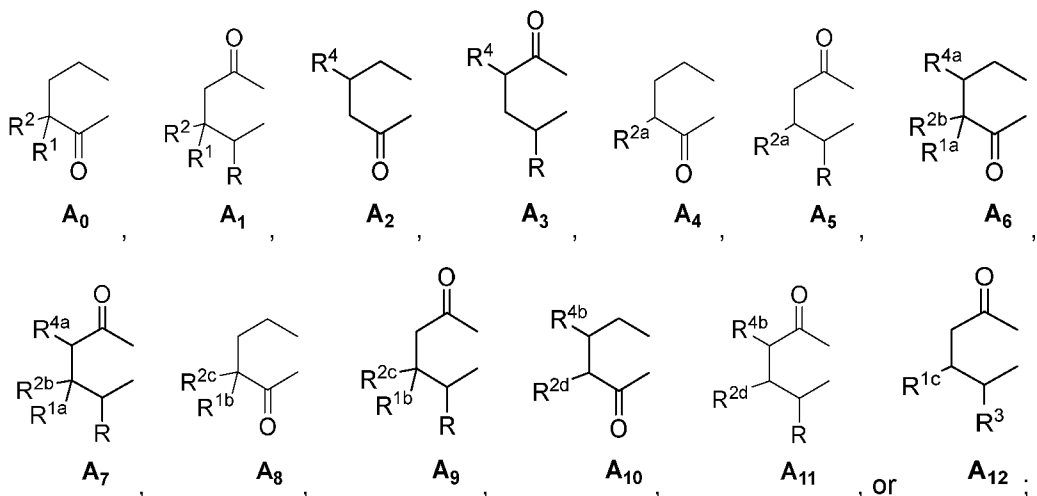
wherein:

10 R^a is $-NH_2$, $-NH-OH$, $-OH$, $-NHR^b$ or $-NR^cR^d$;

R^b is C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, or 3- to 6-membered heterocycloalkyl, wherein C_1 - C_6 alkyl is optionally substituted with 1 to 3 halogens, 1 to 3 $-OH$, $-OC_1$ - C_3 alkyl, $-COOH$, or cyclopropyl optionally substituted with $-OH$, and wherein C_3 - C_6 cycloalkyl is optionally substituted with $-CN$;

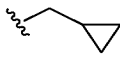
15 R^c and R^d form with the nitrogen to which they are attached a 4-membered heterocycloalkyl, wherein the 4-membered heterocycloalkyl is optionally substituted with at least one of $-OH$ and C_1 - C_3 alkyl;

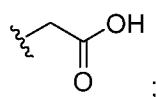
A represents one of the following residues A_0 to A_{12}



20 wherein:

R is H, C_1 - C_6 alkyl or phenyl;

R^1 and R^2 are independently -CN, C_6 - C_{10} aryl, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, 4- to 14-membered heterocycloalkyl, 5- to 10-membered heteroaryl, -C(O)NH₂, -C(O)NHR⁵, -C(O)R⁶, or -C(O)OR⁵, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 3 R^7 substituents, each C_6 - C_{10} aryl is optionally substituted with 1 to 3 R^8 substituents, and each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R^{22} substituents, with the proviso that when R^a is -OH,  represents A_0 , and R^1 is , then R^2 in residue A_0 is different than



each R^5 is independently C_1 - C_6 alkyl, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 3 R^9 substituents;

- 10 each R^6 is independently C_3 - C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, or C_6 - C_{10} aryl;
- each R^7 is independently -OH, -C(O)R¹¹, C_3 - C_6 cycloalkyl, -CN, C_6 - C_{10} aryl, halogen, -C(O)OH, 5- to 10-membered heteroaryl, -NH(C(O)OC₁- C_6 alkyl), -N(C₁- C_4 alkyl)(C(O)OC₁- C_6 alkyl), 4- to 6-membered heterocycloalkyl, -NH(C(O)C₁- C_6 alkyl), -OR²⁰, -SC₁- C_6 alkyl, -NH₂, -NH(C₁- C_4 alkyl), or -N(C₁- C_4 alkyl)₂, wherein each C_3 - C_6 cycloalkyl is optionally substituted with 1 to 3 R^{12} substituents,
- 15 each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R^{13} substituents, and each 4- to 6-membered heterocycloalkyl is optionally substituted with C_1 - C_4 alkyl or oxo;

each R^8 is independently halogen, C_1 - C_6 alkyl, -OC₁- C_6 alkyl, C_3 - C_6 cycloalkyl, or 5- to 10-membered heteroaryl, wherein each -OC₁- C_6 alkyl is optionally substituted with -OC₁- C_4 alkyl, and each 5- to 10-membered heteroaryl is optionally substituted with C_1 - C_4 alkyl;

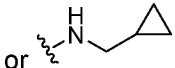
- 20 each R^{22} is independently C_1 - C_6 alkyl optionally substituted with phenyl;
- each R^9 is independently -OH, -C(O)R¹⁵, C_3 - C_6 cycloalkyl, -CN, C_6 - C_{10} aryl, halogen, -C(O)OH, 4- to 6-membered heterocycloalkyl, -NH(C(O)C₁- C_6 alkyl), -OC₁- C_6 alkyl, -SC₁- C_6 alkyl, -NH₂, -NH(C₁- C_4 alkyl), or -N(C₁- C_4 alkyl)₂, wherein each 4- to 6-membered heterocycloalkyl is optionally substituted with C_1 - C_4 alkyl, and each -OC₁- C_6 alkyl is optionally substituted with -OC₁- C_4 alkyl;
- 25 each R^{11} is independently -NH₂, -NH(C₁- C_4 alkyl), -N(C₁- C_4 alkyl)₂, or 4- to 6-membered heterocycloalkyl;
- each R^{20} is independently C_1 - C_6 alkyl or 5- to 10-membered heteroaryl, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 3 R^{14} substituents and each 5- to 10-membered heteroaryl is optionally substituted with -OH or -NH(cyclopropyl);
- 30 each R^{12} is independently C_1 - C_4 alkyl, -SC₁- C_4 alkyl, -Ph, -OC₁- C_4 alkyl, or -SPh, wherein each C_1 - C_4 alkyl is optionally substituted with -OH;

each R^{13} is independently halogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, -OH, - OC_1 - C_6 alkyl, - SC_1 - C_6 alkyl, - $S(O)_2C_1$ - C_6 alkyl, - NH_2 , - $NH(C_1$ - C_4 alkyl), or - $N(C_1$ - C_4 alkyl) $_2$, wherein each - OC_1 - C_6 alkyl, - SC_1 - C_6 alkyl, - $S(O)_2C_1$ - C_6 alkyl, - $NH(C_1$ - C_4 alkyl), and - $N(C_1$ - C_4 alkyl) $_2$ is optionally substituted with 1 to 3 R^9 substituents;

5 each R^{14} is independently halogen, - OC_1 - C_4 alkyl, or C_3 - C_6 cycloalkyl;

each R^{15} is independently - NH_2 , - $NH(C_1$ - C_4 alkyl), - $N(C_1$ - C_4 alkyl) $_2$, or 4- to 6-membered heterocycloalkyl;

R^4 is C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{10} aryl, 7- to 10-membered partially unsaturated heterocyclic group, or 5- to 10-membered heteroaryl, wherein C_1 - C_6 alkyl and C_3 - C_8 cycloalkyl are optionally substituted with 1 to 3 R^9 substituents, and C_6 - C_{10} aryl and 5- to 10-membered heteroaryl are optionally substituted with 1 to 3 R^{10} substituents, with the proviso that: (i) when R^a is -OH, - NH_2 ,

or , and  represents A_2 , then R^4 in residue A_2 is different than - CH_3 ; and (ii) when R^a is - NH_2 and  represents A_3 , then R^4 in residue A_3 is different than - $C(CH_3)_3$;

each R^{10} is independently C_1 - C_4 alkyl, halogen, - OC_1 - C_6 alkyl, - NH_2 , - $NH(C_1$ - C_4 alkyl), or - $N(C_1$ - C_4 alkyl) $_2$, wherein each C_1 - C_4 alkyl is optionally substituted with 1 to 3 halogens;

R^{2a} is C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, or C_6 - C_{10} aryl, wherein C_1 - C_6 alkyl and C_3 - C_8 cycloalkyl are optionally substituted with 1 to 3 R^9 substituents, and C_6 - C_{10} aryl is optionally substituted with 1 to 3 R^{10} substituents;

R^{1a} and R^{2b} are independently -CN, C_6 - C_{10} aryl, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, - $C(O)NH_2$, - $C(O)NHR^5$, or - $C(O)OC_1$ - C_6 alkyl, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 3 R^{16} substituents and each C_6 - C_{10} aryl is optionally substituted with 1 to 3 R^{17} substituents;

each R^{16} is independently -OH, - $C(O)NH_2$, - $C(O)NH(C_1$ - C_4 alkyl), C_3 - C_6 cycloalkyl, -CN, C_6 - C_{10} aryl, halogen, - $C(O)OH$, 5- to 10-membered heteroaryl, - $NH(C(O)OC_1$ - C_6 alkyl), 4- to 6-membered heterocycloalkyl, - $NH(C(O)C_1$ - C_6 alkyl), or - OC_1 - C_4 alkyl(OC_1 - C_4 alkyl), wherein each C_3 - C_6 cycloalkyl is optionally substituted with 1 to 3 R^{18} substituents, each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R^{21} substituents, and each 4- to 6-membered heterocycloalkyl is optionally substituted with C_1 - C_4 alkyl;

each R^{17} is independently halogen, C_1 - C_6 alkyl, - OC_1 - C_6 alkyl, or 5- to 10-membered heteroaryl, wherein each 5- to 10-membered heteroaryl is optionally substituted with C_1 - C_4 alkyl;

30 each R^{18} is independently C_1 - C_4 alkyl, - SC_1 - C_4 alkyl, -Ph, or - OC_1 - C_4 alkyl;

each R^{21} is independently halogen or C_1 - C_4 alkyl;

R^{4a} is C₁-C₆alkyl or C₃-C₈cycloalkyl, wherein each C₁-C₆alkyl and C₃-C₈cycloalkyl are optionally substituted with 1 to 3 R¹⁹ substituents;

each R¹⁹ is independently halogen, -OH, -OC₁-C₄alkyl, -SC₁-C₄alkyl, -NH₂, -NH(C₁-C₄alkyl), or -N(C₁-C₄alkyl)₂;

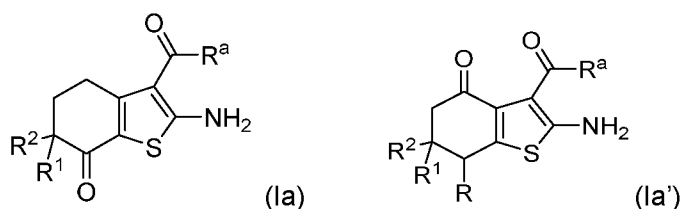
- 5 R^{1b} and R^{2c} form together with the carbon atom to which they are attached a C₃-C₈cycloalkyl, 4- to 14-membered heterocycloalkyl, 8- to 14-membered partially unsaturated heterocyclic group, or 8- to 14-membered partially unsaturated carbocyclic group, wherein C₃-C₈cycloalkyl is optionally substituted with 1 to 3 R⁹ substituents, and wherein 4- to 14-membered heterocycloalkyl, 8- to 14-membered partially unsaturated heterocyclic group, or 8- to 14-membered partially unsaturated carbocyclic group is optionally substituted with oxo (=O), oxime (=N-OH), C₁-C₃alkoxyoxime (=N-OC₁-C₃alkyl), or 1 to 3 substituents independently selected from -OH and -CF₃;

R^{2d} and R^{4b} form together with the carbon atoms to which they are attached a C₃-C₈cycloalkyl or 4- to 14-membered heterocycloalkyl, wherein C₃-C₈cycloalkyl is optionally substituted with 1 to 3 R¹⁹ substituents; and

- 15 R^{1c} and R³ form together with the carbon atoms to which they are attached a C₃-C₈cycloalkyl or 4- to 14-membered heterocycloalkyl, wherein C₃-C₈cycloalkyl is optionally substituted with 1 to 3 R¹⁹ substituents.

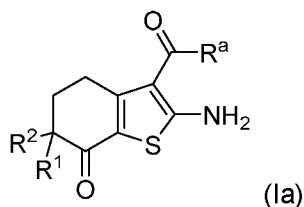
2. The pharmaceutical combination of claim 1, wherein in the compound of Formula (I) or the
20 pharmaceutically acceptable salt, solvate, or prodrug thereof, R is H.

3. The pharmaceutical combination of claim 1 or 2, wherein the compound of Formula (I) is represented by the formula (Ia) or (Ia'):



- 25 wherein R¹, R², R and R^a are as defined in claim 1 or 2,
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

4. The pharmaceutical combination of claim 3, wherein the compound of Formula (I) is represented by the formula (Ia):



wherein R^1 , R^2 and R^a are as defined in claim 1,

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

- 5 5. The pharmaceutical combination of any one of claims 1 to 4, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^1 and R^2 are independently -CN, C_6 - C_{10} aryl, C_1 - C_6 alkyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, 5- to 10-membered heteroaryl, -C(O)NH₂, -C(O)NHR⁵, -C(O)R⁶, or -C(O)OR⁵, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 3 R^7 substituents, each C_6 - C_{10} aryl is optionally substituted with 1 to 3 R^8 substituents, and each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R^{22} substituents, and R^5 , R^6 , R^7 , R^8 and R^{22} are as defined in claim 1.

6. The pharmaceutical combination of any one of claims 1 to 5, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof:

- 15 R^1 and R^2 are independently -CN, C_6 - C_{10} aryl, C_1 - C_6 alkyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, 5- to 10-membered heteroaryl, -C(O)NH₂, -C(O)NHR⁵, -C(O)R⁶, or -C(O)OR⁵, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 3 R^7 substituents, each C_6 - C_{10} aryl is optionally substituted with 1 to 3 R^8 substituents, and each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R^{22} substituents, and wherein:

20 each R^5 is independently C_1 - C_6 alkyl;

each R^6 is independently a 4- to 6-membered heterocycloalkyl;

each R^7 is independently -OH, -C(O)R¹¹, C_3 - C_6 cycloalkyl, -CN, C_6 - C_{10} aryl, halogen, -C(O)OH, 5- to 10-membered heteroaryl, -NH(C(O)OC₁- C_6 alkyl), -N(C_1 - C_4 alkyl)(C(O)OC₁- C_6 alkyl), 4- to 6-membered heterocycloalkyl, -NH(C(O)C₁- C_6 alkyl), -OR²⁰, -SC₁- C_6 alkyl, -NH₂, or -N(C_1 - C_4 alkyl)₂, wherein each C_3 - C_6 cycloalkyl is optionally substituted with 1 to 3 R^{12} substituents, each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R^{13} substituents, and each 4- to 6-membered heterocycloalkyl is optionally substituted with C_1 - C_4 alkyl or oxo;

each R^8 is independently halogen, C_1 - C_6 alkyl, or -OC₁- C_6 alkyl, wherein each -OC₁- C_6 alkyl is optionally substituted with -OC₁- C_4 alkyl;

each R^{22} is independently C_1 - C_6 alkyl optionally substituted with phenyl;

each R¹¹ is independently -NH₂, -NH(C₁-C₄alkyl), or 4- to 6-membered heterocycloalkyl;

each R²⁰ is independently C₁-C₆alkyl or 5- to 10-membered heteroaryl, wherein each C₁-C₆alkyl is optionally substituted with 1 to 3 R¹⁴ substituents and each 5- to 10-membered heteroaryl is optionally substituted with -OH or -NH(cyclopropyl);

5 each R¹² is independently C₁-C₄alkyl, -SC₁-C₄alkyl, -Ph, -OC₁-C₄alkyl, or -SPh, wherein each C₁-C₄alkyl is optionally substituted with -OH;

each R¹³ is independently halogen, C₁-C₄alkyl, or C₃-C₆cycloalkyl; and

each R¹⁴ is independently halogen, -OC₁-C₄alkyl, or C₃-C₆cycloalkyl.

10 7. The pharmaceutical combination of any one of claims 1 to 5, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R¹ and R² are independently -CN, C₆-C₁₀aryl, C₁-C₆alkyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, 5- to 10-membered heteroaryl, or -C(O)NH₂, wherein each C₁-C₆alkyl is optionally substituted with 1 to 3 R⁷ substituents, each C₆-C₁₀aryl is optionally substituted with 1 to 3 R⁸ substituents, and each 5- to
15 10-membered heteroaryl is optionally substituted with 1 to 3 R²² substituents, and R⁷, R⁸, and R²² are as defined in claim 1.

8. The pharmaceutical combination of any one of claims 1 to 5, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof:

20 R¹ and R² are independently -CN, C₆-C₁₀aryl, C₁-C₆alkyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, 5- to 10-membered heteroaryl, or -C(O)NH₂, wherein each C₁-C₆alkyl is optionally substituted with 1 to 3 R⁷ substituents, each C₆-C₁₀aryl is optionally substituted with 1 to 3 R⁸ substituents, and each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R²² substituents, and wherein:

25 each R⁷ is independently -OH, -C(O)R¹¹, C₃-C₆cycloalkyl, -CN, C₆-C₁₀aryl, halogen, -C(O)OH, 5- to 10-membered heteroaryl, -NH(C(O)OC₁-C₆alkyl), -N(C₁-C₄alkyl)(C(O)OC₁-C₆alkyl), -NH(C(O)C₁-C₆alkyl), 4- to 6-membered heterocycloalkyl, -OR²⁰, -SC₁-C₆alkyl, -NH₂, or -N(C₁-C₄alkyl)₂, wherein each C₃-C₆cycloalkyl is optionally substituted with 1 to 3 R¹² substituents, each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R¹³ substituents, and each 4- to 6-membered heterocycloalkyl is optionally substituted with
30 C₁-C₄alkyl or oxo;

each R⁸ is independently halogen, C₁-C₆alkyl, or -OC₁-C₆alkyl, wherein each -OC₁-C₆alkyl is optionally substituted with -OC₁-C₄alkyl;

each R¹¹ is independently -NH₂, -NH(C₁-C₄alkyl), or 4- to 6-membered heterocycloalkyl;

each R²⁰ is independently C₁-C₆alkyl or 5- to 10-membered heteroaryl, wherein each C₁-C₆alkyl is optionally substituted with 1 to 3 R¹⁴ substituents and each 5- to 10-membered heteroaryl is optionally substituted with -OH or -NH(cyclopropyl);

each R¹² is independently C₁-C₄alkyl, -SC₁-C₄alkyl, -Ph, -OC₁-C₄alkyl, or -SPh, wherein each C₁-C₄alkyl is optionally substituted with -OH;

each R¹³ is independently halogen, C₁-C₄alkyl, or C₃-C₆cycloalkyl;

each R¹⁴ is independently halogen, -OC₁-C₄alkyl, or C₃-C₆cycloalkyl; and

each R²² is independently C₁-C₄alkyl.

9. The pharmaceutical combination of any one of claims 1 to 5, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof:

R¹ and R² are independently -CN, C₆-C₁₀aryl, C₁-C₆alkyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, 5- to 10-membered heteroaryl, or -C(O)NH₂, wherein each C₁-C₆alkyl is optionally substituted with 1 to 3 R⁷ substituents, each C₆-C₁₀aryl is optionally substituted with 1 to 3 R⁸ substituents, and each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R²² substituents, and wherein:

each R⁷ is independently -OH, -C(O)R¹¹, -OR²⁰, C₃-C₆cycloalkyl, -CN, C₆-C₁₀aryl, halogen, -C(O)OH, or 5- to 10-membered heteroaryl, wherein each C₃-C₆cycloalkyl is optionally substituted with 1 to 3 R¹² substituents and each 5- to 10-membered heteroaryl is optionally substituted with 1 to 3 R¹³ substituents;

each R⁸ is a halogen;

each R¹¹ is -NH₂;

each R²⁰ is C₁-C₆alkyl or 5- or 6-membered heteroaryl, wherein each C₁-C₆alkyl is optionally substituted with 1 to 3 R¹⁴ substituents and each 5- or 6-membered heteroaryl is optionally substituted with -OH or -NH(cyclopropyl);

each R¹² is C₁-C₄alkyl;

each R¹³ is independently halogen or C₁-C₄alkyl;

each R¹⁴ is halogen; and

each R²² is independently C₁-C₄alkyl.

10. The pharmaceutical combination of any one of claims 1 to 5, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof:

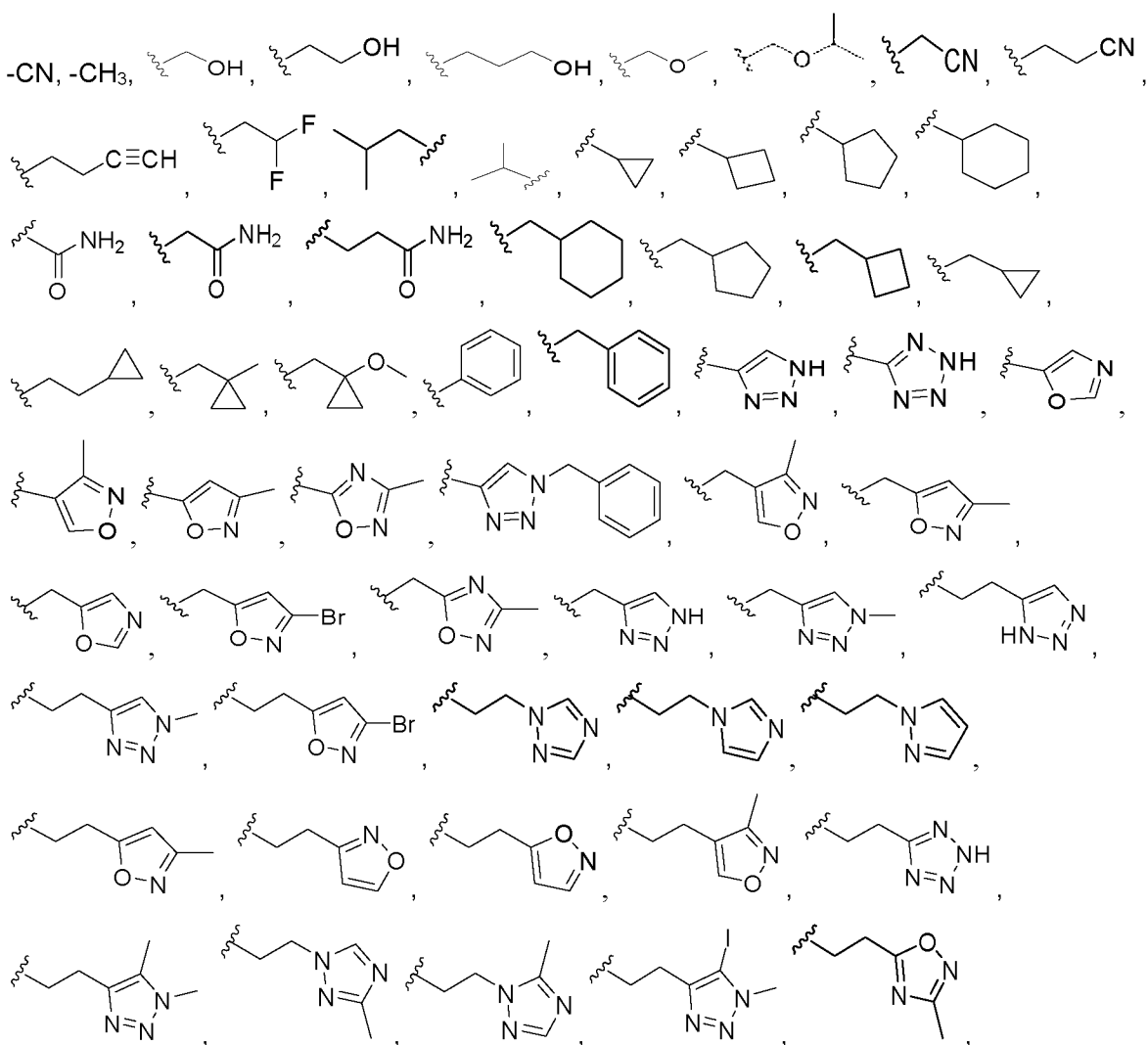
R¹ and R² are independently -CN, phenyl, C₁-C₄alkyl, C₂-C₄alkynyl, C₃-C₆cycloalkyl, 5-membered heteroaryl, or -C(O)NH₂, wherein each C₁-C₄alkyl is optionally substituted with 1 or 2 R⁷

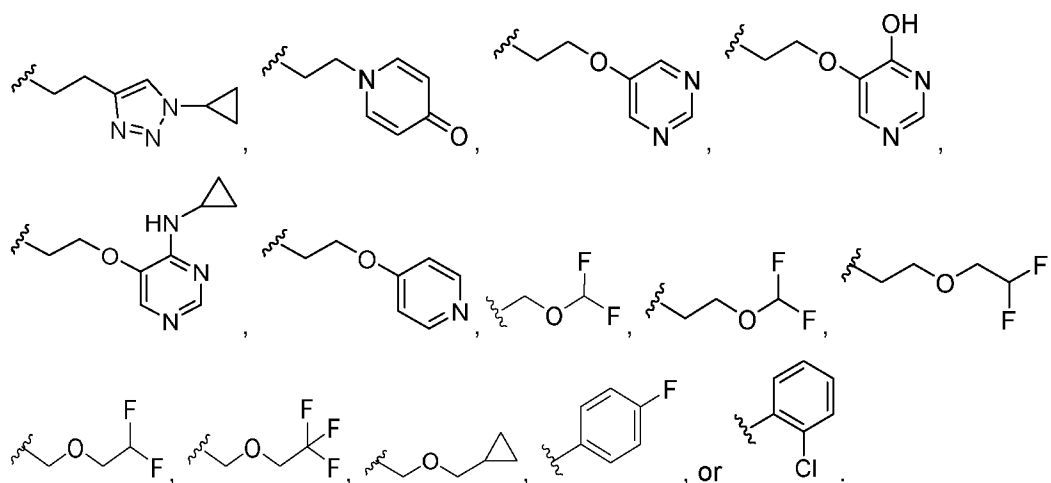
substituents, each phenyl is optionally substituted with 1 or 2 halogens, and each 5-membered heteroaryl is optionally substituted with 1 or 2 -CH₃, and wherein:

each R⁷ is independently -OH, -C(O)NH₂, -OR²⁰, C₃-C₆cycloalkyl, -CN, phenyl, halogen, -C(O)OH, or 5-membered heteroaryl, wherein each C₃-C₆cycloalkyl is optionally substituted with -CH₃; and

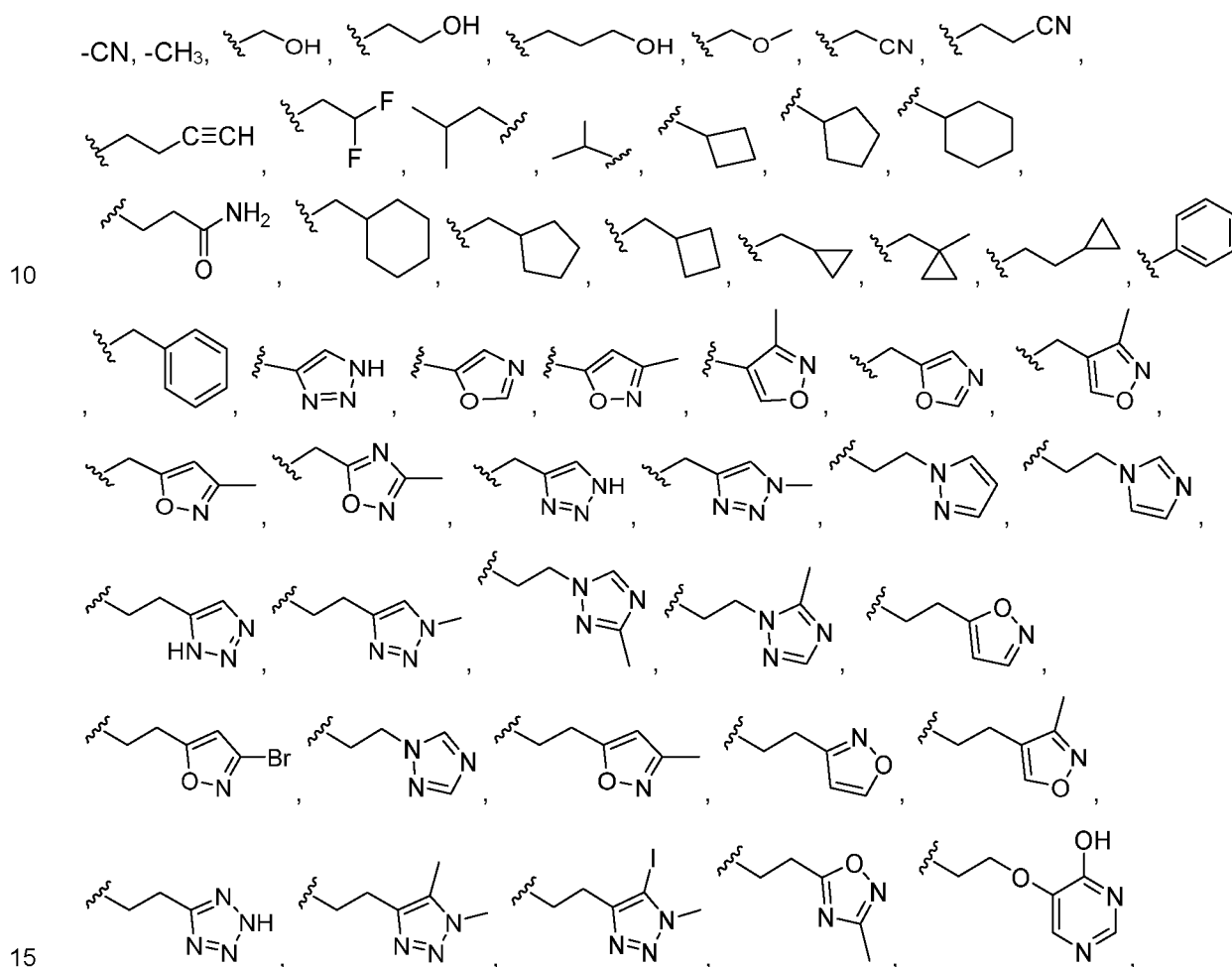
each R²⁰ is C₁-C₆alkyl or 5- or 6-membered heteroaryl, wherein each C₁-C₆alkyl is optionally substituted with 1 to 3 halogen and each 5- or 6-membered heteroaryl is optionally substituted with -OH.

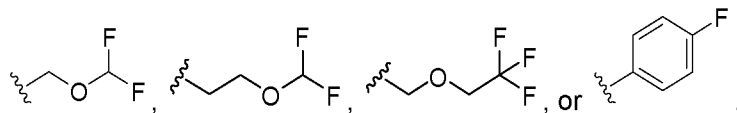
11. The pharmaceutical combination of any one of claims 1 to 5, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R¹ and R² independently represent:



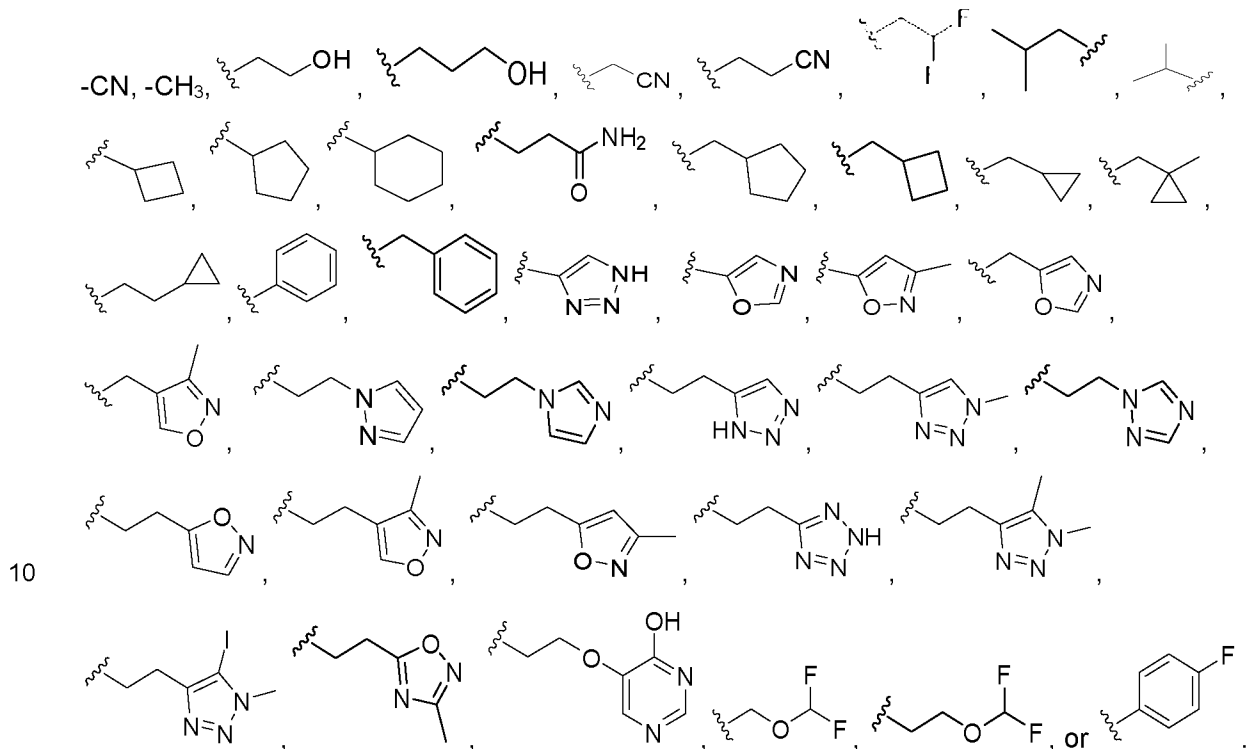


- 5 12. The pharmaceutical combination of any one of claims 1 to 5, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R¹ and R² independently represent:

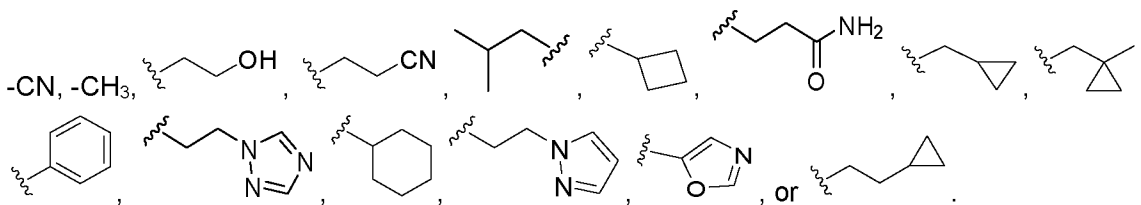




13. The pharmaceutical combination of any one of claims 1 to 5, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R¹ and R² independently represent:



14. The pharmaceutical combination of any one of claims 1 to 5, wherein in the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R¹ and R² independently represent:



15. The pharmaceutical combination of any one of claims 1 to 5, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof:

R¹ and R² are independently -CN, C₆-C₁₀aryl, C₁-C₆alkyl, C₃-C₈cycloalkyl, 5-membered heteroaryl, or -C(O)NH₂, wherein each C₁-C₆alkyl is optionally substituted with 1 to 2 R⁷ substituents;

each R^7 is independently -OH, -C(O)NH₂, C₃-C₆cycloalkyl, -CN, C₆-C₁₀aryl, halogen, or 5- to 8-membered heteroaryl, wherein each C₃-C₆cycloalkyl is optionally substituted with 1 to 2 C₁-C₄alkyl, and each 5- to 8-membered heteroaryl is optionally substituted with 1 to 2 R^{13} substituents; and wherein

5 each R^{13} is independently halogen or C₁-C₄alkyl.

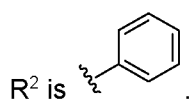
16. The pharmaceutical combination of any one of claims 1 to 15, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^1 and R^2 are different.

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17. The pharmaceutical combination of any one of claims 1 to 16, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, one of R^1 and R^2 is -CN.

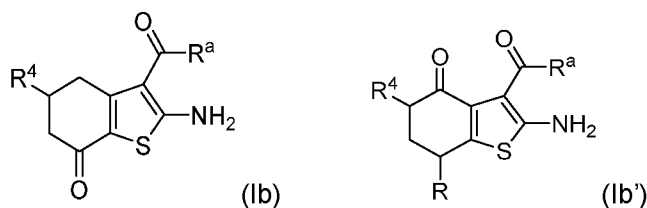
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18. The pharmaceutical combination of any one of claims 1 to 17, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, one of R^1 and



19. The pharmaceutical combination of claim 1 or 2, wherein the compound of Formula (I) is represented by the formula (Ib) or (Ib'):

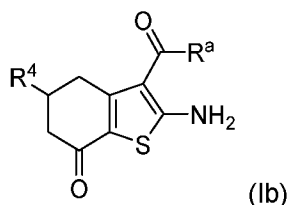
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wherein R^4 , R and R^a are as defined in claim 1 or 2,
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

25

20. The pharmaceutical combination of claim 19, wherein the compound of Formula (I) is represented by the formula (Ib):



wherein R^4 and R^a are as defined in claim 1,
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

21. The pharmaceutical combination of any one of claims 1, 2, 19 and 20, wherein in the
5 compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^4
is C_1 - C_6 alkyl, C_6 - C_{10} aryl, 7- to 10-membered partially unsaturated heterocyclic group, or 5- to 10-
membered heteroaryl, wherein C_1 - C_6 alkyl is optionally substituted with 1 to 3 R^9 substituents, and
 C_6 - C_{10} aryl and 5- to 10-membered heteroaryl are optionally substituted with 1 to 3 R^{10}
substituents, and R^9 and R^{10} are as defined in claim 1.

22. The pharmaceutical combination of any one of claims 1, 2, 19 and 20, wherein in the
compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^4
is C_1 - C_6 alkyl, C_6 - C_{10} aryl, 7- to 10-membered partially unsaturated heterocyclic group, or 5- to 10-
membered heteroaryl, wherein C_6 - C_{10} aryl and 5- to 10-membered heteroaryl are optionally
15 substituted with 1 to 3 R^{10} substituents, and wherein:

each R^{10} is independently C_1 - C_4 alkyl, halogen, $-OC_1$ - C_6 alkyl, $-NH_2$, $-NH(C_1$ - C_4 alkyl), or $-$
 $N(C_1$ - C_4 alkyl) $_2$, wherein each C_1 - C_4 alkyl is optionally substituted with 1 to 3 halogens.

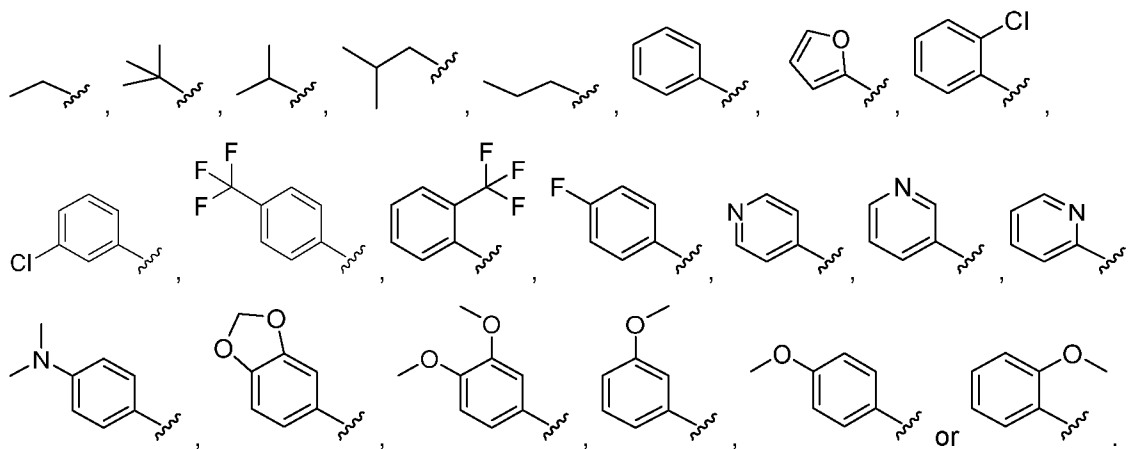
23. The pharmaceutical combination of any one of claims 1, 2, 19 and 20, wherein in the
compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^4
is C_1 - C_6 alkyl, C_6 - C_{10} aryl, 7- to 10-membered partially unsaturated heterocyclic group, or 5- to 10-
membered heteroaryl, wherein C_6 - C_{10} aryl and 5- to 10-membered heteroaryl are optionally
substituted with 1 to 3 R^{10} substituents, and wherein:

25 each R^{10} is independently C_1 - C_4 alkyl, halogen, $-OC_1$ - C_6 alkyl, or $-N(C_1$ - C_4 alkyl) $_2$, wherein
each C_1 - C_4 alkyl is optionally substituted with 1 to 3 halogens.

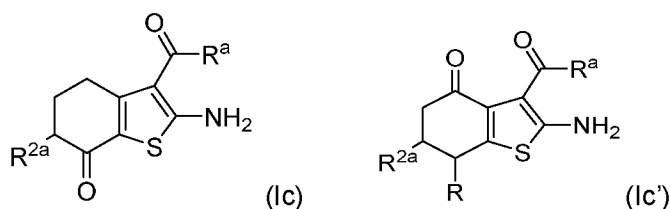
24. The pharmaceutical combination of any one of claims 1, 2, 19 and 20, wherein in the
compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^4
30 is C_1 - C_4 alkyl, phenyl, 9-membered partially unsaturated heterocyclic group, or 5- to 6-membered
heteroaryl, wherein phenyl and 5- to 6-membered heteroaryl are optionally substituted with 1 or
2 R^{10} substituents, and wherein:

each R^{10} is independently $-CF_3$, halogen, $-OCH_3$, or $-N(CH_3)_2$.

25. The pharmaceutical combination of any one of claims 1, 2, 19 and 20, wherein in the
compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^4
represents:

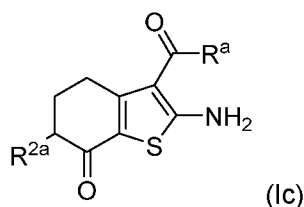


26. The pharmaceutical combination of claim 1 or 2, wherein the compound of Formula (I) is represented by the formula (Ic) or (Ic'):



wherein R^{2a} , R and R^a are as defined in claim 1 or 2,
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

27. The pharmaceutical combination of claim 26, wherein the compound of Formula (I) is represented by the formula (Ic):



wherein R^{2a} and R^a are as defined in claim 1,
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

28. The pharmaceutical combination of any one of claims 1, 2, 26 and 27, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{2a} is C_1 - C_6 alkyl or C_6 - C_{10} aryl, wherein C_1 - C_6 alkyl is optionally substituted with 1 to 3 R^9 substituents and C_6 - C_{10} aryl is optionally substituted with 1 to 3 R^{10} substituents, and R^9 and R^{10} are as defined in claim 1.

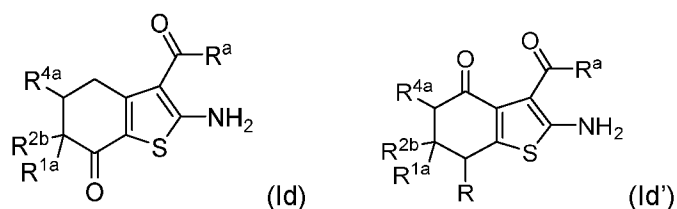
29. The pharmaceutical combination of any one of claims 1, 2, 26 and 27, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{2a} is C_1 - C_6 alkyl or C_6 - C_{10} aryl, wherein C_1 - C_6 alkyl is optionally substituted with 1 to 3 halogens.

30. The pharmaceutical combination of any one of claims 1, 2, 26 and 27, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{2a} is C_1 - C_6 alkyl.

31. The pharmaceutical combination of any one of claims 1, 2, 26 and 27, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{2a} is C_1 - C_4 alkyl.

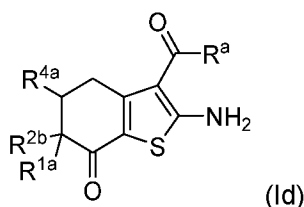
32. The pharmaceutical combination of any one of claims 1, 2, 26 and 27, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{2a} is ethyl.

33. The pharmaceutical combination of claim 1 or 2, wherein the compound of Formula (I) is represented by the formula (Id) or (Id'):



wherein R^{1a} , R^{2b} , R^{4a} , R and R^a are as defined in claim 1 or 2,
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

34. The pharmaceutical combination of claim 33, wherein the compound of Formula (I) is represented by the formula (Id):



wherein R^{1a} , R^{2b} , R^{4a} and R^a are as defined in claim 1,
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

35. The pharmaceutical combination of any one of claims 1, 2, 33 and 34, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{1a} and R^{2b} are independently -CN, C_6 - C_{10} aryl, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, or -C(O)NH₂, wherein each C_1 - C_6 alkyl is optionally substituted with 1 to 2 R^{16} substituents, and wherein:

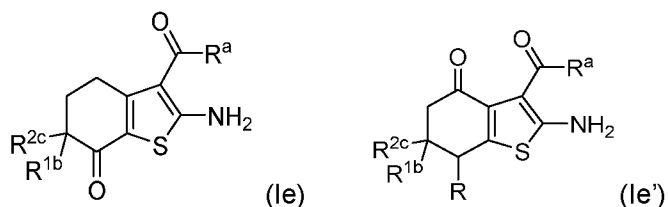
each R^{16} is independently -OH, -C(O)NH₂, C_3 - C_6 cycloalkyl, -CN, C_6 - C_{10} aryl, halogen, or 5- to 8-membered heteroaryl, wherein each C_3 - C_6 cycloalkyl is optionally substituted with 1 to 2 C_1 - C_4 alkyl, and each 5- to 10-membered heteroaryl is optionally substituted with 1 to 2 R^{21} substituents; and

each R^{21} is independently halogen or C_1 - C_4 alkyl.

36. The pharmaceutical combination of any one of claims 1, 2, 33 and 34, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{1a} and R^{2b} are independently -CN or C_6 - C_{10} aryl.

37. The pharmaceutical combination of any one of claims 1, 2, 33, 34, 35 and 36, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{4a} is C_1 - C_6 alkyl.

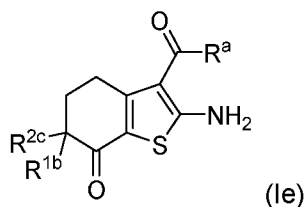
38. The pharmaceutical combination of claim 1 or 2, wherein the compound of Formula (I) is represented by the formula (Ie) or (Ie'):



wherein R, R^a , R^{1b} and R^{2c} are as defined in claim 1 or 2,

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

39. The pharmaceutical combination of claim 38, wherein the compound of Formula (I) is represented by the formula (Ie):

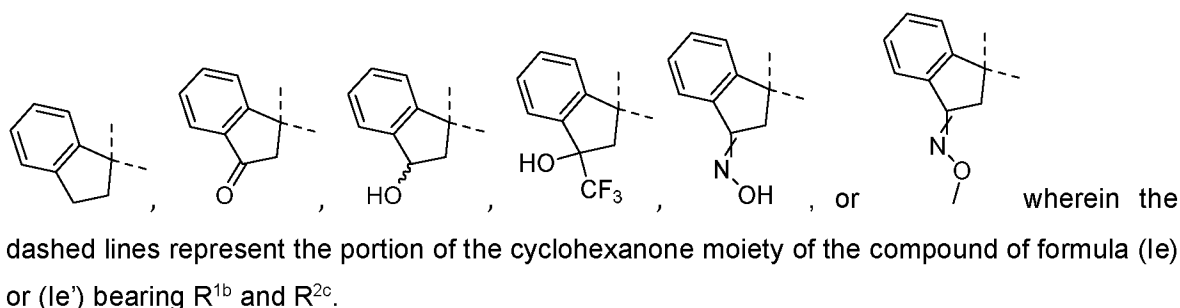


wherein R^a , R^{1b} and R^{2c} are as defined in claim 1,
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

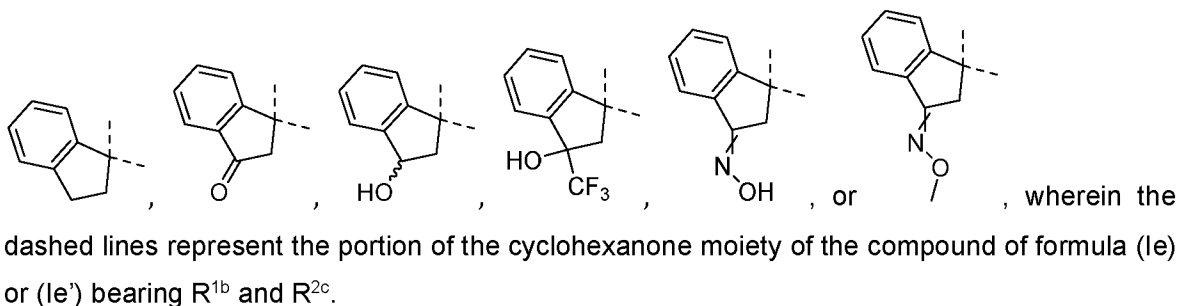
40. The pharmaceutical combination of any one of claims 1, 2, 38 and 39, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{1b} and R^{2c} form together with the carbon atom to which they are attached a C_3 - C_8 cycloalkyl, 4- to 14-membered heterocycloalkyl, 8- to 14-membered partially unsaturated heterocyclic group, or 8- to 14-membered partially unsaturated carbocyclic group, wherein each 4- to 14-membered heterocycloalkyl, 8- to 14-membered partially unsaturated heterocyclic group, or 8- to 14-membered partially unsaturated carbocyclic group is optionally substituted with oxo ($=O$), oxime ($=N-OH$), C_1 - C_3 alkoxyoxime ($=N-OC_1-C_3$ alkyl), or 1 to 3 substituents independently selected from $-OH$ and $-CF_3$.

41. The pharmaceutical combination of any one of claims 1, 2, 38 and 39, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{1b} and R^{2c} form together with the carbon atom to which they are attached a C_3 - C_8 cycloalkyl or a 8- to 10-membered partially unsaturated carbocyclic group, wherein 8- to 10-membered partially unsaturated carbocyclic group is optionally substituted with oxo ($=O$), oxime ($=N-OH$), methoxyoxime ($=N-OCH_3$), or 1 to 2 substituents independently selected from $-OH$ and $-CF_3$.

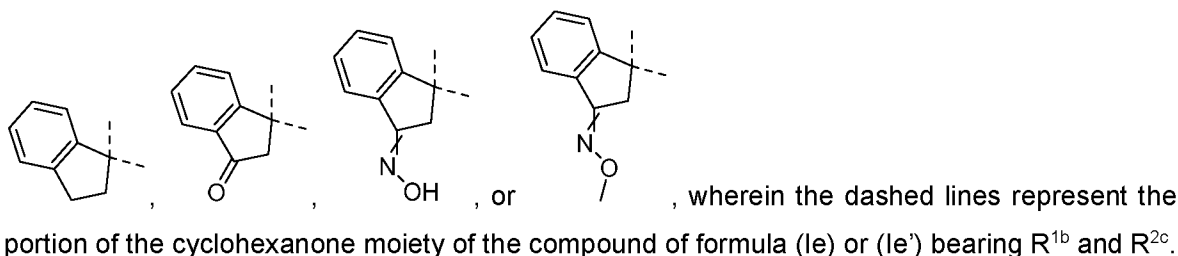
42. The pharmaceutical combination of any one of claims 1, 2, 38 and 39, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{1b} and R^{2c} form together with the carbon atom to which they are attached a C_4 - C_6 cycloalkyl, or a group selected from



43. The pharmaceutical combination of any one of claims 1, 2, 38 and 39, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{1b} and R^{2c} form together with the carbon atom to which they are attached a cyclopentyl, or a group selected from

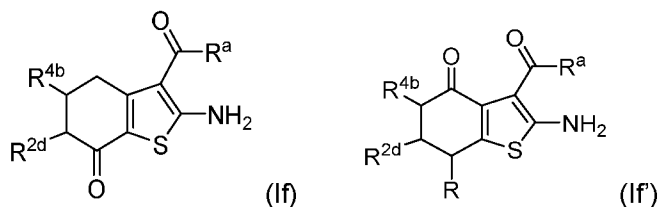


- 5 44. The pharmaceutical combination of any one of claims 1, 2, 38 and 39, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{1b} and R^{2c} form together with the carbon atom to which they are attached a group selected from



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45. The pharmaceutical combination of claim 1 or 2, wherein the compound of Formula (I) is represented by the formula (If) or (If'):

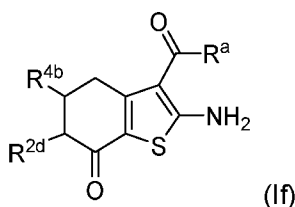


wherein R , R^a , R^{4b} and R^{2d} are as defined in claim 1 or 2,

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or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

46. The pharmaceutical combination of claim 45, wherein the compound of Formula (I) is represented by the formula (If):



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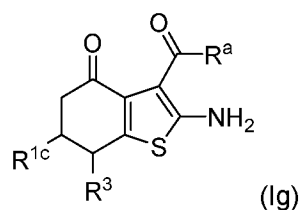
wherein R^a , R^{4b} and R^{2d} are as defined in claim 1,

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

47. The pharmaceutical combination of any one of claims 1, 2, 45 and 46, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{2d} and R^{4b} form together with the carbon atoms to which they are attached a C_3 - C_8 cycloalkyl, wherein
 5 each C_3 - C_8 cycloalkyl is optionally substituted with 1 to 3 R^{19} substituents as defined in claim 1.

48. The pharmaceutical combination of any one of claims 1, 2, 45 and 46, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{2d} and R^{4b} form together with the carbon atoms to which they are attached a C_3 - C_8 cycloalkyl.

49. The pharmaceutical combination of claim 1 or 2, wherein the compound of Formula (I) is represented by the formula (Ig):



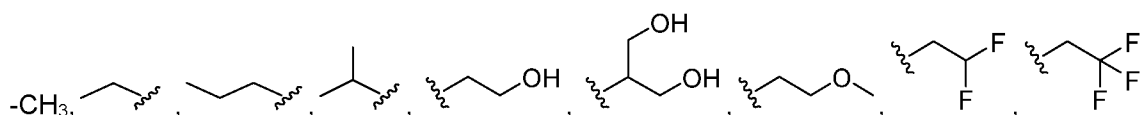
wherein R^a , R^{1c} and R^3 are as defined in claim 1,

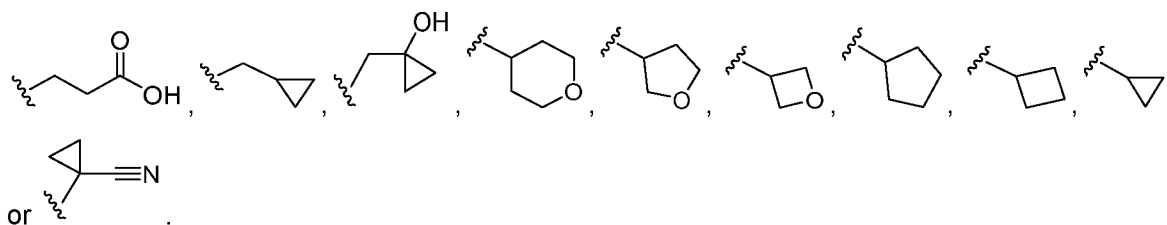
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

50. The pharmaceutical combination of any one of claims 1, 2 and 49, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{1c} and R^3 form together with the carbon atoms to which they are attached a C_3 - C_8 cycloalkyl, wherein
 20 each C_3 - C_8 cycloalkyl is optionally substituted with 1 to 3 R^{19} substituents as defined in claim 1.

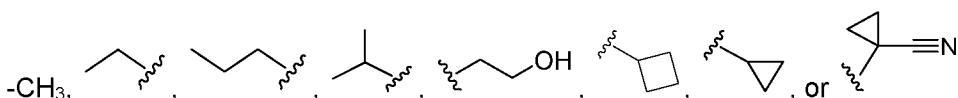
51. The pharmaceutical combination of any one of claims 1, 2 and 49, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{1c} and R^3 form together with the carbon atoms to which they are attached a C_3 - C_8 cycloalkyl.

52. The pharmaceutical combination of any one of claims 1 to 51, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^a is $-NHR^b$ and R^b represents:



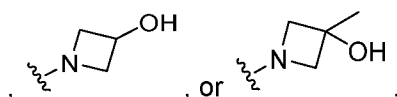


53. The pharmaceutical combination of any one of claims 1 to 52, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^a is $-NHR^b$ and R^b represents:

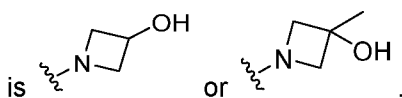


54. The pharmaceutical combination of any one of claims 1 to 53, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^a is $-NHR^b$ and R^b represents

55. The pharmaceutical combination of any one of claims 1 to 51, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^a is



56. The pharmaceutical combination of any one of claims 1 to 51 and 55, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^a



57. The pharmaceutical combination of any one of claims 1 to 51, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^a is $-OH$.

58. The pharmaceutical combination of any one of claims 1 to 51, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^a is $-NH_2$.

59. The pharmaceutical combination of any one of claims 1 to 51, wherein in the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, R^a is $-NH-OH$.

60. The pharmaceutical combination of any one of claims 1 to 59, wherein the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, or prodrug thereof, is in the form of a racemate or any enantiomer thereof.

5 61. The pharmaceutical combination of claim 1, wherein the compound is Compound 4, 8, 9, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 47, 48, 49, 50, 51, 52, 53, 54, 59, 60a, 60b, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 75, 81, 82, 83, 84, 89, 91, 97, 101, 108, 109, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 10 154, 155, 163, 168, 169, 170, 173, 174, 175, 178, 179, 180, 181, 183, 189, 190, 191, 192, 193, 194, 195, 197, 198, 199, 200, 201, 202, 211, 212, 213, 214, 215, 216, 219, 221, 227, 228, 229, 230, 231, 232, 237, 238, 239, 245, 246, 247, 248, 249, 250, 251, 253, 254, 255, 257, 258, 263, 264, 271, 272, 273, 278, 279, 280, 281, 287, 288, 290, 291, 297, 298, 305, 306, 313, 314, 321, 322, 330, 331, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 352, 353, 354, 15 355, 356, 357, 358, 360, 362, 371, 378, 391, 392, 393, 394a, 394b, 395a, 395b, 396, 397, 401, 402, 403, 406, 407, 408, 412, 413, 414, 416, 418, 422, 427, 428, 429, 430, 431, 433, 434, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 462, 463, 464, 465, 466, 468, 469, 470, 471, 472, 473, 474, 475, 476, 478, 479, 480, 481, 482, 483, 486, 488, 489, 492, 495, 496, 497, 498, 511, 512, 513, 514, 515, 520, 523, 524, or 534 of Table 1 of the description, or a pharmaceutically 20 acceptable salt, solvate, or prodrug thereof.

62. The pharmaceutical combination of claim 1, wherein the compound is Compound 4, 15, 16, 17, 20, 24, 25, 26, 27, 29, 30, 31, 32, 33, 34, 36, 37, 47, 48, 49, 50, 51, 52, 53, 54, 59, 60b, 61, 62, 63, 64, 65, 66, 67, 71, 72, 75, 81, 82, 83, 84, 89, 91, 97, 101, 109, 119, 120, 121, 122, 25 123, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 138, 139, 140, 141, 143, 144, 145, 146, 147, 148, 149, 150, 155, 163, 168, 169, 170, 173, 174, 175, 179, 180, 181, 183, 191, 192, 194, 195, 198, 199, 201, 202, 212, 213, 214, 215, 216, 228, 230, 231, 232, 237, 238, 239, 246, 248, 250, 251, 253, 254, 255, 258, 263, 264, 271, 272, 273, 278, 279, 280, 281, 287, 288, 291, 298, 305, 306, 313, 314, 321, 322, 331, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 352, 353, 30 354, 355, 356, 357, 358, 391, 392, 393, 394a, 394b, 395a, 395b, 396, 397, 401, 402, 403, 406, 407, 408, 413, 414, 416, 418, 422, 428, 429, 430, 431, 434, 445, 446, 447, 448, 449, 450, 451, 453, 454, 462, 463, 464, 465, 466, 468, 470, 472, 474, 475, 476, 479, 480, 481, 482, 486, 489, 495, 496, 498, 511, 512, 513, 514, 515, 520, or 524 of Table 1 of the description, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

35 63. The pharmaceutical combination of claim 1, wherein the compound is Compound 4, 15, 25, 32, 33, 47, 48, 49, 50, 52, 54, 59, 60b, 61, 62, 63, 72, 75, 82, 83, 89, 97, 101, 109, 119, 121, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 138, 139, 140, 141, 143, 144, 145, 146, 147,

148, 149, 150, 163, 169, 170, 174, 179, 181, 183, 191, 192, 194, 195, 212, 213, 214, 215, 230, 231, 232, 238, 239, 246, 248, 250, 251, 253, 254, 255, 258, 263, 264, 272, 273, 278, 279, 280, 281, 288, 291, 298, 305, 306, 313, 314, 321, 322, 331, 338, 339, 340, 341, 342, 343, 344, 345, 353, 355, 356, 358, 391, 392, 393, 394a, 394b, 395a, 395b, 396, 397, 402, 403, 407, 408, 413, 418, 422, 428, 429, 430, 431, 434, 445, 446, 447, 448, 449, 450, 451, 454, 463, 464, 465, 466, 472, 475, 476, 479, 481, 486, 489, 495, 498, 512, 514, 515, 520, or 524 of Table 1 of the description, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

64. The pharmaceutical combination of claim 1, wherein the compound is Compound 48, 50, 54, 60b, 61, 63, 72, 75, 83, 97, 101, 109, 127, 135, 140, 141, 143, 144, 145, 146, 147, 149, 163, 169, 170, 174, 179, 181, 191, 194, 195, 212, 215, 230, 231, 232, 238, 246, 248, 250, 251, 255, 258, 272, 273, 279, 281, 291, 306, 314, 321, 322, 331, 338, 339, 340, 341, 342, 345, 353, 355, 356, 391, 393, 395a, 395b, 397, 402, 428, 430, 431, 434, 446, 447, 448, 450, 463, 464, 465, 466, 489, 512, 514, 515, or 524 of Table 1 of the description, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

65. The pharmaceutical combination of claim 1, wherein the compound is Compound 54, 61, 63, 75, 140, 143, 146, 174, 215, 230, 250, 251, 273, 306, 322, 430, 446, 463, or 512 of Table 1 of the description, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

66. The pharmaceutical combination of any one of claims 1 to 65, wherein the COX inhibitor comprises a Non-Steroidal Anti-Inflammatory Drug (NSAID).

67. The pharmaceutical combination of claim 66, wherein the NSAID is selected from the group consisting of Bromfenac, Celecoxib, Diclofenac, Etodolac, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Mefenamic acid, Meloxicam, Nabumetone, Naproxen, Nepafenac, Piroxicam, Sulindac, Tenoxicam, Tiaprofenic acid, Diflunisal, Etoricoxib, Fenoprofen, Floctafenine, Lumiracoxib, Oxaprozin, Parecoxib, Rofecoxib, Tolmetin, Valdecoxib, Meclofenamic acid, Dexketoprofen, Licofelone, Lornoxicam, Loxoprofen, Nimesulide, Tolfenamic acid, Phenylbutazone, Firocoxib, Salsalate, Choline Magnesium Trisalicylate, Acetylsalicylic acid, any pharmaceutically acceptable salt thereof, and any combination thereof.

68. The pharmaceutical combination of claim 66, wherein the NSAID is Naproxen, Celecoxib, Diclofenac, Ibuprofen, a pharmaceutically acceptable salt thereof, or any combination thereof.

69. The pharmaceutical combination of any one of claims 1 to 65, wherein the COX inhibitor is acetaminophen.

70. The pharmaceutical combination of any one of claims 1 to 69, wherein the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof are combined in a single dosage form.

5 71. The pharmaceutical combination of any one of claims 1 to 69, wherein the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof are each in an individual dosage form.

72. The pharmaceutical combination of any one of claims 1 to 71, comprising the COX inhibitor
10 and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof each in an amount ranging from about 1 mg to about 1000 mg.

73. The pharmaceutical combination of any one of claims 1 to 72, comprising the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug
15 thereof in a ratio of 1:0.1 to 1:10 by weight.

74. The pharmaceutical combination of any one of claims 1 to 73, comprising the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof in a ratio of 1:0.1 to 1:1 by weight.
20

75. The pharmaceutical combination of any one of claims 1 to 74, wherein the pharmaceutical combination is a synergistic pharmaceutical combination.

76. The pharmaceutical combination of any one of claims 1 to 75, for use in the treatment of
25 pain in a subject in need thereof.

77. Use of a pharmaceutical combination as defined in any one of claims 1 to 75, for the treatment of pain in a subject in need thereof.

30 78. A method for the treatment of pain, comprising administering to a subject in need thereof the pharmaceutical combination as defined in any one of claims 1 to 75.

79. The pharmaceutical combination for use of claim 76, the use of claim 77, or the method of claim 78, wherein the pain is inflammatory pain, neuropathic pain or cancer pain.
35

80. The pharmaceutical combination for use of claim 76, the use of claim 77, or the method of claim 78, wherein the pain is inflammatory pain.

81. The pharmaceutical combination for use of claim 76, the use of claim 77, or the method of claim 78, wherein the pain is neuropathic pain.

82. The pharmaceutical combination for use of claim 76, the use of claim 77, or the method of claim 78, wherein the pain is cancer pain.

83. The pharmaceutical combination for use of claim 76, 79 or 80, the use of claim 77, 79 or 80, or the method of claim 78, 79 or 80, wherein the pain is arthritis pain, pain associated with musculoskeletal trauma or soft tissue trauma, post-operative pain, dental pain, dysmenorrhea pain, episiotomy pain, endometriosis pain, post-partum pain, headache pain, ocular pain, bursitis pain, or tendinitis pain.

84. The pharmaceutical combination for use of claim 83, the use of claim 83, or the method of claim 83, wherein the pain is arthritis pain, and the arthritis pain is osteoarthritis pain, rheumatoid arthritis pain, ankylosing spondylitis pain, gout pain, or periarthritis pain.

85. The pharmaceutical combination for use of claim 83, the use of claim 83, or the method of claim 83, wherein the pain is pain associated with musculoskeletal trauma or soft tissue trauma, and the pain associated with musculoskeletal trauma or soft tissue trauma is pain associated with a sprain or pain associated with a strain.

86. The pharmaceutical combination for use of claim 83, the use of claim 83, or the method of claim 83, wherein the pain is post-operative pain, and the post-operative pain is post-operative pain following minor surgery, post-operative pain following general surgery, post-operative pain following orthopaedic surgery, post-operative pain following bunionectomy, post-operative pain following hernioplasty, post-operative pain following herniorrhaphy, post-operative pain following arthroplasty including pain following knee arthroplasty or pain following hip arthroplasty, post-operative pain following gynecological surgery, post-operative pain following cesarean section, post-mastectomy pain syndrome (PMPS), post-operative pain following abdominoplasty, post-operative pain following laminectomy, post-operative pain following hemorrhoid removal, or post-operative pain following thoracotomy.

87. The pharmaceutical combination for use of claim 83, the use of claim 83, or the method of claim 83, wherein the pain is dental pain, and the dental pain is toothache or post-operative pain after dental surgery.

88. The pharmaceutical combination for use of claim 83, the use of claim 83, or the method of claim 83, wherein the pain is dental pain, and the dental pain is pain after dental extraction.

89. The pharmaceutical combination for use of claim 83, the use of claim 83, or the method of claim 83, wherein the pain is dysmenorrhea pain, episiotomy pain, endometriosis pain, or post-partum cramping pain.

90. The pharmaceutical combination for use of claim 83, the use of claim 83, or the method of claim 83, wherein the pain is headache pain, and the headache pain is migraine pain, tension headache pain, or cluster headache pain.

91. The pharmaceutical combination for use of claim 83, the use of claim 83, or the method of claim 83, wherein the pain is ocular pain, and the ocular pain is post-operative pain after cataract surgery, post-operative pain after refractive surgery, ocular pain from a non-penetrating wound, foreign body sensation ocular pain, burning or stinging of the eye, uveitis pain, iritis pain, retinopathy pain or optic neuritis pain.

92. The pharmaceutical combination for use of any one of claims 76 and 79 to 91, the use of any one of claims 77 and 79 to 91, or the method of any one of claims 78 to 91, wherein the treatment is an oral treatment.

93. The pharmaceutical combination for use of any one of claims 76 and 79 to 92, the use of any one of claims 77 and 79 to 92, or the method of any one of claims 78 to 92, wherein the subject is a mammal.

94. The pharmaceutical combination for use of any one of claims 76 and 79 to 93, the use of any one of claims 77 and 79 to 93, or the method of any one of claims 78 to 93, wherein the subject is a human.

95. A method for the treatment of pain, comprising administering to a subject in need thereof a cyclooxygenase (COX) inhibitor and a compound having the Formula (I) as defined in any one of claims 1 to 65 or the pharmaceutically acceptable salt, solvate, or prodrug thereof.

96. The method of claim 95, wherein the COX inhibitor comprises a Non-Steroidal Anti-Inflammatory Drug (NSAID).

97. The method of claim 96, wherein the NSAID is selected from the group consisting of Bromfenac, Celecoxib, Diclofenac, Etodolac, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Mefenamic acid, Meloxicam, Nabumetone, Naproxen, Nepafenac, Piroxicam, Sulindac, Tenoxicam, Tiaprofenic acid, Diflunisal, Etoricoxib, Fenoprofen, Floctafenine, Lumiracoxib, Oxaprozin, Parecoxib, Rofecoxib, Tolmetin, Valdecoxib, Meclofenamic acid, Dexketoprofen, Licofelone, Lornoxicam, Loxoprofen, Nimesulide, Tolfenamic acid, Phenylbutazone, Firocoxib, Salsalate, Choline Magnesium Trisalicylate, Acetylsalicylic acid, any pharmaceutically acceptable salt thereof, and any combination thereof.

98. The method of claim 96, wherein the NSAID is Naproxen, Celecoxib, Diclofenac, Ibuprofen, a pharmaceutically acceptable salt thereof, or any combination thereof.

99. The method of claim 95, wherein the COX inhibitor is acetaminophen.

100. The method of any one of claims 95 to 99, wherein the pain is inflammatory pain, neuropathic pain or cancer pain.

101. The method of any one of claims 95 to 100, wherein the pain is inflammatory pain.

102. The method of any one of claims 95 to 100, wherein the pain is neuropathic pain.

103. The method of any one of claims 95 to 100, wherein the pain is cancer pain.

104. The method of any one of claims 95 to 101, wherein the pain is arthritis pain, pain associated with musculoskeletal trauma or soft tissue trauma, post-operative pain, dental pain, dysmenorrhea pain, episiotomy pain, endometriosis pain, post-partum pain, headache pain, ocular pain, bursitis pain, or tendinitis pain.

105. The method of claim 104, wherein the pain is arthritis pain, and the arthritis pain is osteoarthritis pain, rheumatoid arthritis pain, ankylosing spondylitis pain, gout pain, or periarthritis pain.

106. The method of claim 104, wherein the pain is pain associated with musculoskeletal trauma or soft tissue trauma, and the pain associated with musculoskeletal trauma or soft tissue trauma is pain associated with a sprain or pain associated with a strain.

107. The method of claim 104, wherein the pain is post-operative pain, and the post-operative pain is post-operative pain following minor surgery, post-operative pain following general surgery,

post-operative pain following orthopaedic surgery, post-operative pain following bunionectomy, post-operative pain following hernioplasty, post-operative pain following herniorrhaphy, post-operative pain following arthroplasty including pain following knee arthroplasty or pain following hip arthroplasty, post-operative pain following gynecological surgery, post-operative pain following caesarean section, post-mastectomy pain syndrome (PMPS), post-operative pain following abdominoplasty, post-operative pain following laminectomy, post-operative pain following hemorrhoid removal, or post-operative pain following thoracotomy.

108. The method of claim 104, wherein the pain is dental pain, and the dental pain is toothache or post-operative pain after dental surgery.

109. The method of claim 104, wherein the pain is dental pain, and the dental pain is pain after dental extraction.

110. The method of claim 104, wherein the pain is dysmenorrhea pain, episiotomy pain, endometriosis pain, or post-partum cramping pain.

111. The method of claim 104, wherein the pain is headache pain, and the headache pain is migraine pain, tension headache pain, or cluster headache pain.

112. The method of claim 104, wherein the pain is ocular pain, and the ocular pain is post-operative pain after cataract surgery, post-operative pain after refractive surgery, ocular pain from a non-penetrating wound, foreign body sensation ocular pain, burning or stinging of the eye, uveitis pain, iritis pain, retinopathy pain or optic neuritis pain.

113. The method of any one of claims 95 to 112, wherein the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof are administered simultaneously or sequentially.

114. The method of any one of claims 95 to 112, wherein the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof are administered simultaneously.

115. The method of any one of claims 95 to 114, wherein the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof are administered each in an individual dosage form.

116. The method of any one of claims 95 to 114, wherein the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof are administered in a single dosage form.

5 117. The method of any one of claims 95 to 116, wherein the COX inhibitor and the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof are administered orally.

118. The method of any one of claims 95 to 117, wherein the COX inhibitor is administered at
10 a dose of 0.1 to 20 mg/kg.

119. The method of any one of claims 95 to 118, wherein the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof is administered at a dose of 0.1 to 30 mg/kg, preferably 0.1 to 15 mg/kg.

15 120. The method of any one of claims 95 to 119, wherein the subject is a mammal.

121. The method of any one of claims 95 to 120, wherein the subject is a human.

20 122. A kit comprising a first single dose form of a cyclooxygenase (COX) inhibitor and a second single dose form of a compound having the Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof, as defined in any one of claims 1 to 65, and instructions for use.

25 123. The kit of claim 122, wherein the COX inhibitor comprises a Non-Steroidal Anti-Inflammatory Drug (NSAID).

124. The kit of claim 123, wherein the NSAID is selected from the group consisting of Bromfenac, Celecoxib, Diclofenac, Etodolac, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Mefenamic acid, Meloxicam, Nabumetone, Naproxen, Nepafenac, Piroxicam,
30 Sulindac, Tenoxicam, Tiaprofenic acid, Diflunisal, Etoricoxib, Fenoprofen, Floctafenine, Lumiracoxib, Oxaprozin, Parecoxib, Rofecoxib, Tolmetin, Valdecoxib, Meclofenamic acid, Dexketoprofen, Licofelone, Lornoxicam, Loxoprofen, Nimesulide, Tolfenamic acid, Phenylbutazone, Firocoxib, Salsalate, Choline Magnesium Trisalicylate, Acetylsalicylic acid, any pharmaceutically acceptable salt thereof, and any combination thereof.

35 125. The kit of claim 123, wherein the NSAID is Naproxen, Celecoxib, Diclofenac, Ibuprofen, a pharmaceutically acceptable salt thereof, or any combination thereof.

126. The kit of claim 122, wherein the COX inhibitor is acetaminophen.

127. The kit of any one of claims 122 to 126, wherein the first single dose form comprises the COX inhibitor in an amount ranging from about 1 mg to about 1000 mg and the second single
5 dose form comprises the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, or prodrug thereof in an amount ranging from about 1 mg to about 1000 mg.

128. The kit of any one of claims 122 to 127, for use in the treatment of pain.

10 129. The kit for use of claim 128, wherein the pain is inflammatory pain, neuropathic pain or cancer pain.

130. The kit for use of claim 128 or 129, wherein the pain is inflammatory pain.

15 131. The kit for use of claim 128 or 129, wherein the pain is neuropathic pain.

132. The kit for use of claim 128 or 129, wherein the pain is cancer pain.

133. The kit for use of any one of claims 128 to 130, wherein the pain is arthritis pain, pain
20 associated with musculoskeletal trauma or soft tissue trauma, post-operative pain, dental pain, dysmenorrhea pain, episiotomy pain, endometriosis pain, post-partum pain, headache pain, ocular pain, bursitis pain, or tendinitis pain.

134. The kit for use of any one of claims 128 to 130, wherein the pain is arthritis pain, and the
25 arthritis pain is osteoarthritis pain, rheumatoid arthritis pain, ankylosing spondylitis pain, gout pain, or periarthritis pain.

135. The kit for use of any one of claims 128 to 130, wherein the pain is pain associated with
30 musculoskeletal trauma or soft tissue trauma, and the pain associated with musculoskeletal trauma or soft tissue trauma is pain associated with a sprain or pain associated with a strain.

136. The kit for use of any one of claims 128 to 130, wherein the pain is post-operative pain,
and the post-operative pain is post-operative pain following minor surgery, post-operative pain
following general surgery, post-operative pain following orthopaedic surgery, post-operative pain
35 following bunionectomy, post-operative pain following hernioplasty, post-operative pain following
herniorrhaphy, post-operative pain following arthroplasty including pain following knee
arthroplasty or pain following hip arthroplasty, post-operative pain following gynecological
surgery, post-operative pain following cesarean section, post-mastectomy pain syndrome

(PMPS), post-operative pain following abdominoplasty, post-operative pain following laminectomy, post-operative pain following hemorrhoid removal, or post-operative pain following thoracotomy.

5 137. The kit for use of any one of claims 128 to 130, wherein the pain is dental pain, and the dental pain is toothache or post-operative pain after dental surgery.

138. The kit for use of any one of claims 128 to 130, wherein the pain is dental pain, and the dental pain is pain after dental extraction.

10

139. The kit for use of any one of claims 128 to 130, wherein the pain is dysmenorrhea pain, episiotomy pain, endometriosis pain, or post-partum cramping pain.

15

140. The kit for use of any one of claims 128 to 130, wherein the pain is headache pain, and the headache pain is migraine pain, tension headache pain, or cluster headache pain.

20

141. The kit for use of any one of claims 128 to 130, wherein the pain is ocular pain, and the ocular pain is post-operative pain after cataract surgery, post-operative pain after refractive surgery, ocular pain from a non-penetrating wound, foreign body sensation ocular pain, burning or stinging of the eye, uveitis pain, iritis pain, retinopathy pain or optic neuritis pain.

142. The kit for use of any one of claims 128 to 141, wherein the treatment is an oral treatment.

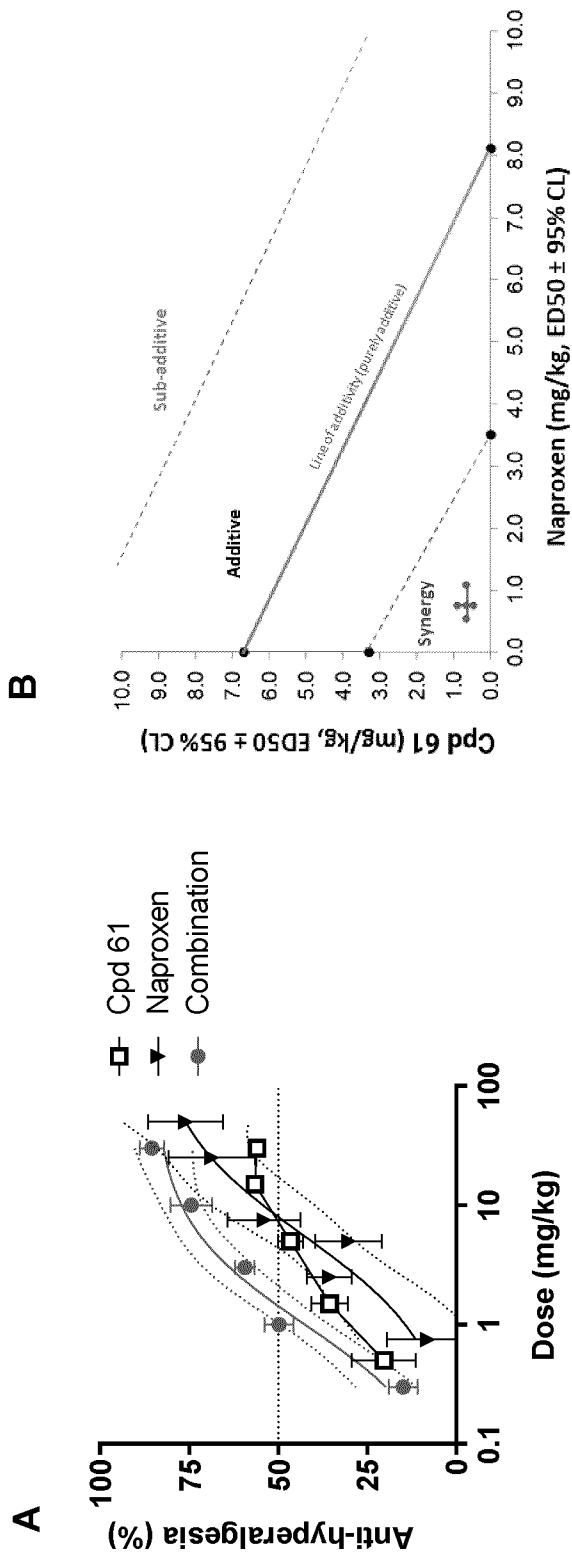


Figure 1

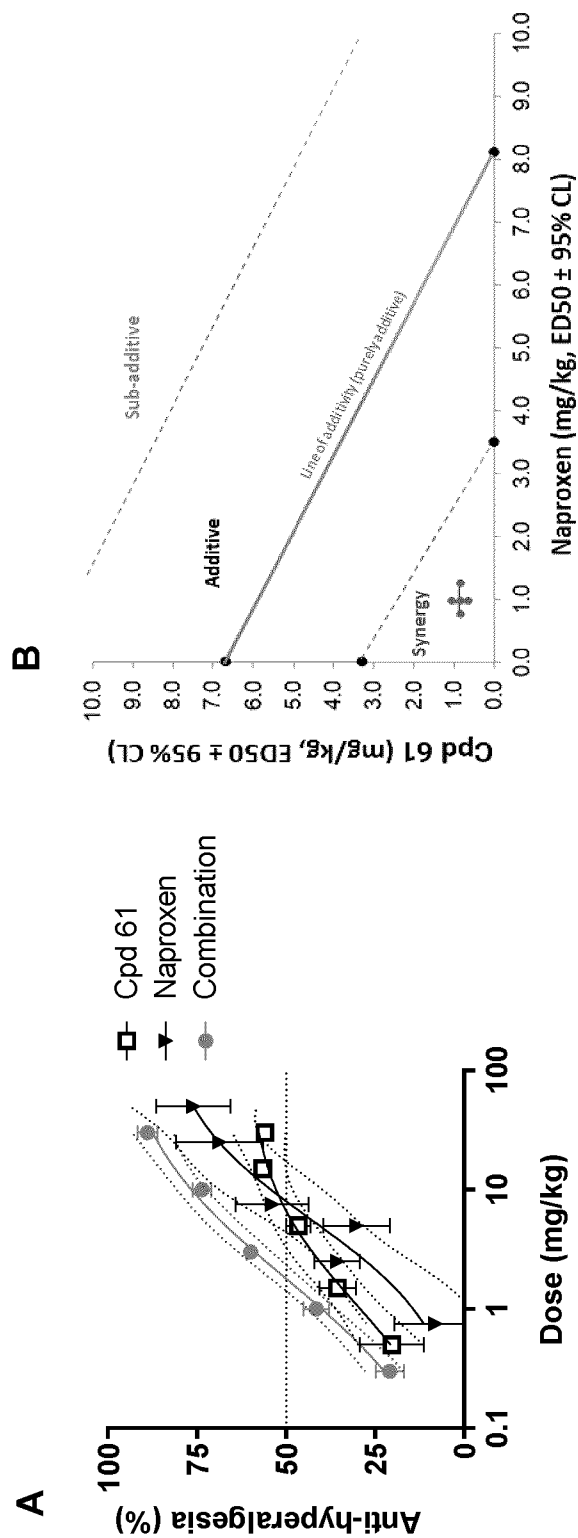


Figure 2

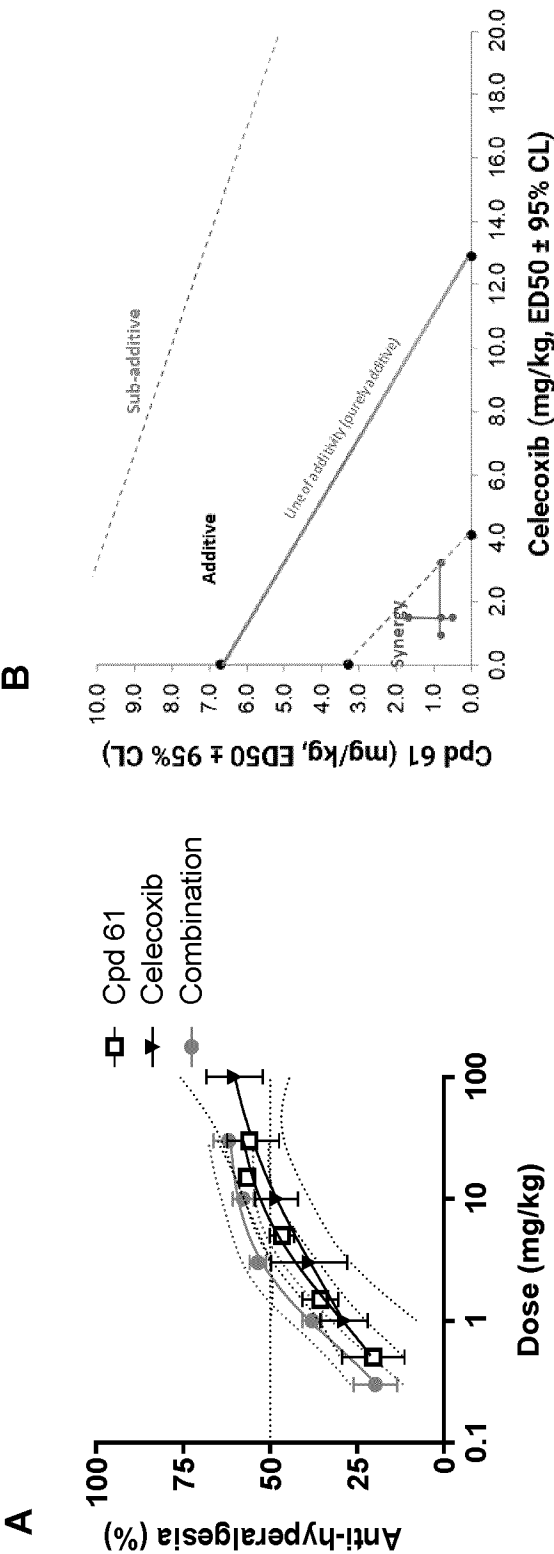


Figure 3

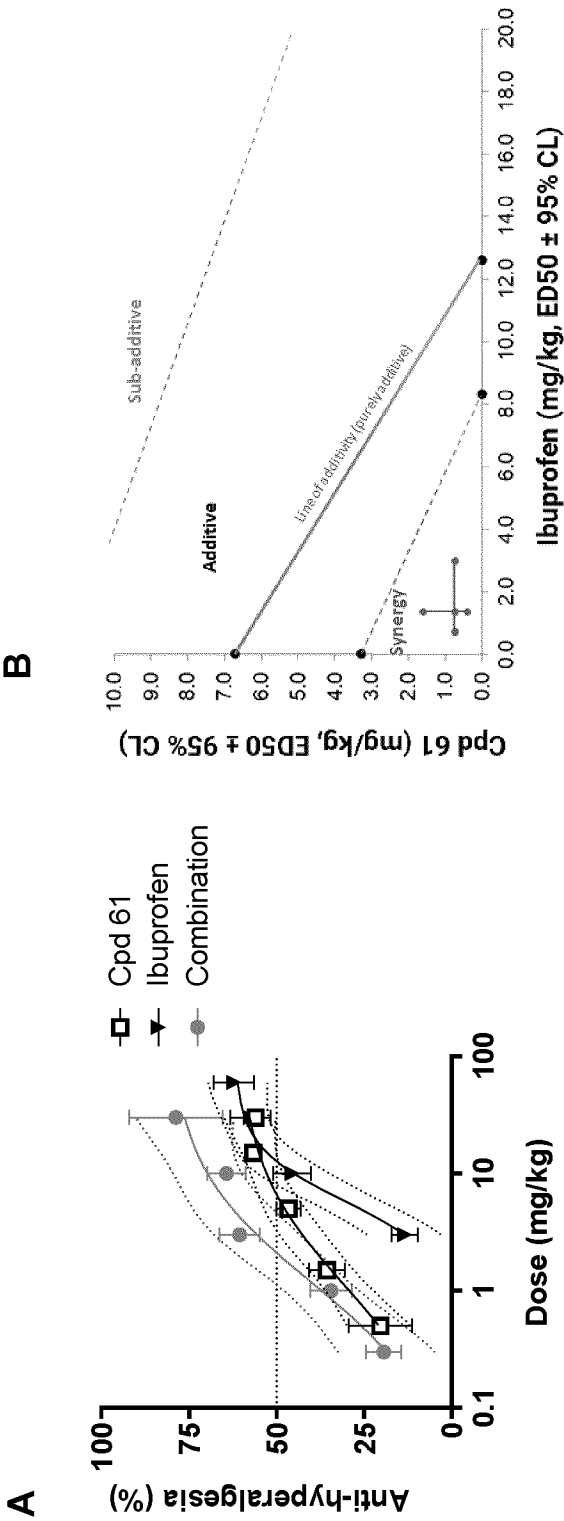


Figure 4

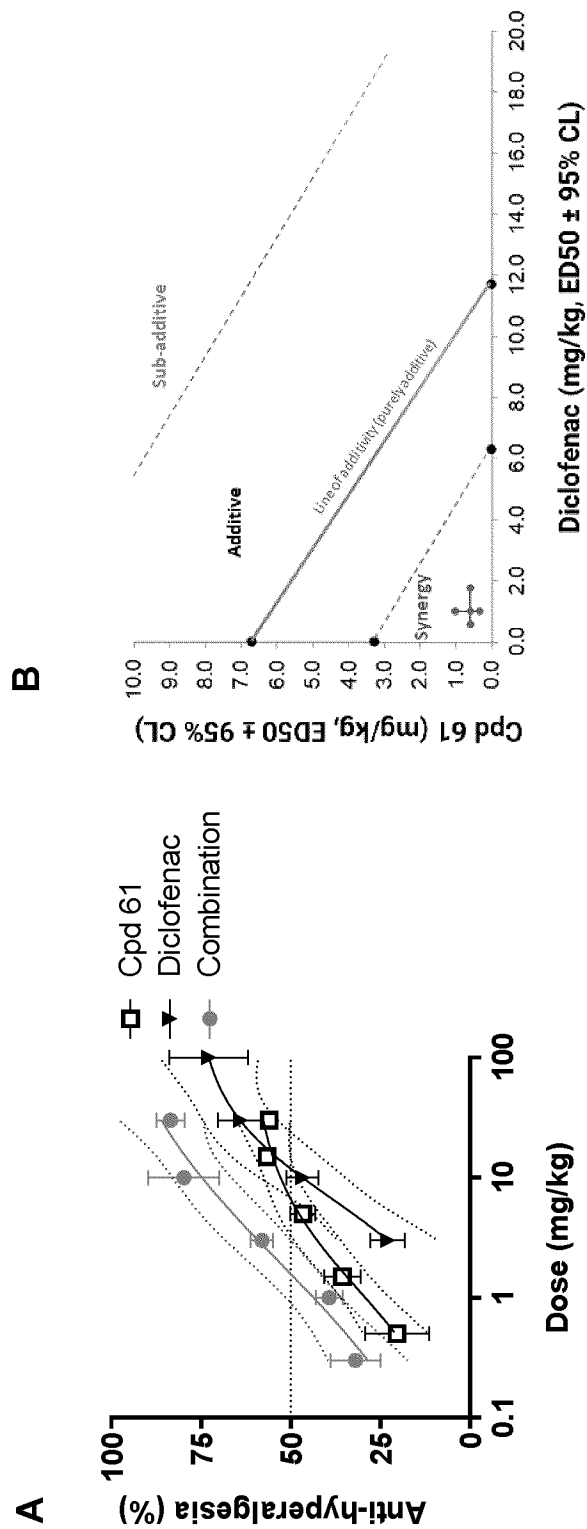


Figure 5

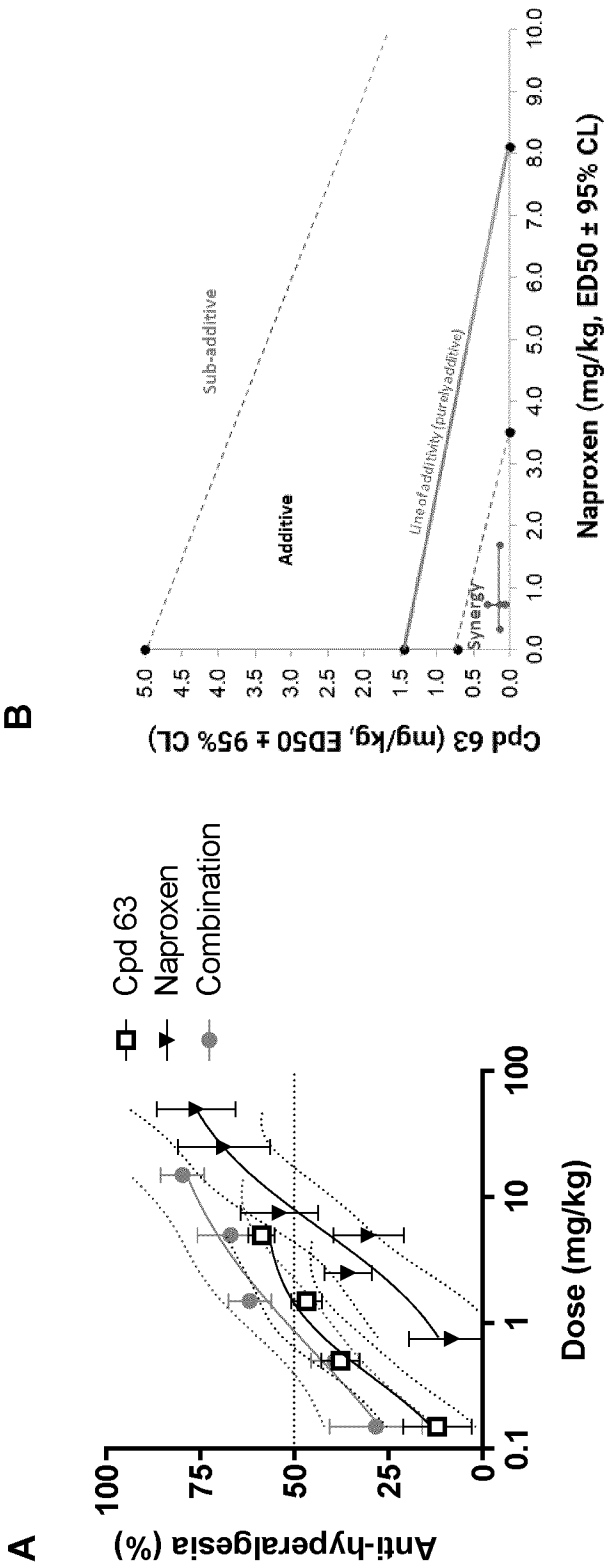


Figure 6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA2024/051045

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **A61K 31/381** (2006.01), **A61K 31/41** (2006.01), **A61K 31/167** (2006.01), **A61K 31/192** (2006.01),
A61K 31/196 (2006.01), **A61K 31/422** (2006.01) (more IPCs on the last page)

CPC: A61K 31/41 (2013.01), A61K 31/167 (2013.01), A61K 31/196 (2013.01),
A61K 31/381 (2013.01), A61K 31/422 (2013.01) (more CPCs on the last page)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Keywords and structures searched across the whole IPC

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

Databases: STN (CAPLUS, REGISTRY), Questel-Orbit

Keywords: acid-sensing ion channel, thiophene, pain, analgesia, cyclooxygenase

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E,Y	WO2024/192520 A1 (SEGUELA, PHILIPPE et al.) 26 September 2024 (26-09-2024) *entire document*	1-142
E,A	WO2024/192522 A1 (SEGUELA, PHILIPPE et al.) 26 September 2024 (26-09-2024) *entire document*	1-142
A	WO2008/124496 A1 (MICHAEL R. JOHNSON et al.) 16 October 2008 (16-10-2008) *pages 1-3*	1-142

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* "A" "D" "E" "L" "O" "P"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance document cited by the applicant in the international application earlier application or patent but published on or after the international filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed	"T" "X" "Y" "&"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art document member of the same patent family

Date of the actual completion of the international search
17 October 2024 (17-10-2024)

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25 October 2024 (25-10-2024)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
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Christopher Doyle

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA2024/051045

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GIUSTINO VARRASSI et al., " <i>The Expanding Role of the COX Inhibitor/Opioid Receptor Agonist Combination in the Management of Pain</i> ". <i>Drugs</i> , Published online: 4 August 2020 (04-08-2020), Vol. 80, pp. 1443-1453, [online] [retrieved on 16 October 2024 (16-10-2024)] ISSN 1179-1950. *Abstract, Section 4*	1-142

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA2024/051045

IPC:

A61K 31/506 (2006.01), *A61K 31/635* (2006.01), *A61K 31/4192* (2006.01), *A61K 31/4196* (2006.01),
A61K 31/4245 (2006.01), *A61K 31/4436* (2006.01), *A61P 25/04* (2006.01), *A61P 29/00* (2006.01)

CPC:

A61K 31/506 (2013.01), A61K 31/635 (2020.08), A61K 31/4192 (2013.01), A61K 31/4196 (2013.01),
A61K 31/4245 (2013.01), A61K 31/4436 (2013.01), A61P 25/04 (2018.01)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/CA2024/051045

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO2024192520A1	26 September 2024 (26-09-2024)	None	
WO2024192522A1	26 September 2024 (26-09-2024)	None	
WO2008124496A1	16 October 2008 (16-10-2008)	US2008293740A1	27 November 2008 (27-11-2008)