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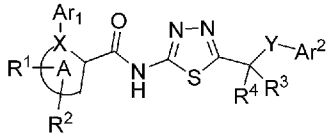
(54) **Title:** NOVEL THIADIAZOLYL DERIVATIVES OF DNA POLYMERASE THETA INHIBITORS



(I)

(57) **Abstract:** Poly theta inhibitor (I), X is -N-or -C-; ring A is phenyl or a five to ten membered heteroaryl ring containing, inclusive of X, one to four heteroatoms independently selected from nitrogen, oxygen, or sulfur, Ar1 is phenyl, heteroaryl, heterocyclyl, bicyclic heterocyclyl, bridged heterocyclyl, or spiroheterocyclyl, wherein each of the aforementioned ring is substituted with Ra, Rb, and/or Rc,wherein Ra and Rb are independently selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, cycloalkyloxy, acyl, acylamino, monoalkylamino, dialkylamino, alkylsulfonyl,cyano, and hydroxy; or Ra and Rb, when on adjacent ring vertices, combine to form a C3-6 cycloalkyl, or Ra and Rb, when on the same ring vertex, combine to form oxo, and Rc is selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclylalkyl, heterocyclyloxy, aminocarbonyl; Ar2 is phenyl, heteroaryl, or cycloalkyl, wherein said phenyl and heteroaryl are substituted with Rd, Re and/or Rf, wherein Rd and Re are independently selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, and cyano and Rf is selected from hydrogen, alkyl, cycloalkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, cyanomethyl, aminocarbonylmethyl, heteroaryl, and heterocyclyl, wherein said heteroaryl and heterocyclyl of Rf are unsubstituted or substituted with one, two, or three substituents independently selected from alkyl, halo, haloalkyl, and hydroxy; R1 is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, hydroxy, cyano, cyanoalkyl,carboxy, alkoxycarbonyl, acylamino, aminocarbonyl optionally substituted heteroaryl, hydroxyalkyl, cycloalkyl, hydroxyalkynyl, alkoxyalkyl, aminoalkyl, aminocarbonylalkyl,sulfonylalkyl, aminosulfonylalkyl, optionally substituted heteroaralkyl, or optionally substituted heterocyclylalkyl; and R2 is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, or cyano; Y is O or S or NH or NRg, Rg is a C1 to C3 aliphatic group; R3 and R4 are H, C1-6 aliphatic group.

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Novel Thiadiazolyl derivatives of DNA polymerase theta inhibitors

FIELD OF THE INVENTION

This application relates to DNA polymerase theta inhibitors, which could be applied in novel synthetic lethal therapy in cancers containing DNA repair defects.

BACKGROUND OF THE INVENTION

DNA damage repair processes are critical for genome maintenance and cell viability. Double strand breaks (DSBs) can be repaired by one of three main pathways: homologous recombination (HR), non-homologous end-joining (NHEJ) and alternative NHEJ (alt-NHEJ). An alternative end joining (alt-NHEJ), also known as microhomology- mediated end-joining (MMEJ) pathway, is commonly considered as a "backup" DSB repair pathway when NHEJ or HR are compromised (Truong *et al.* PNAS 2013, 110 (19), 7720-7725).

An aberrant DNA damage response (DDR) often can sensitize cancer cells to specific types of DNA damage, thus, defective DDR can be developed into targeted cancer therapies. Targeting DNA repair deficiencies has become a proven and effective strategy in cancer treatment. For example, the success of poly (ADP-ribose) polymerase (PARP) inhibitors in treating BRCA-deficient breast, ovarian, prostate and pancreatic cancers (Audeh M. W., et al., Lancet (2010); 376 (9737): 245-51).

Numerous genetic, cell biological and biochemical studies have demonstrated that DNA polymerase theta (UniProtKB - 075417 (DPOLQ_HUMAN) is a the key protein involved in MMEJ (Kent *et al.* Nature Structural & Molecular Biology (2015), 22(3), 230-237, Mateos-Gomez *et al.* Nature (2015), 518(7538), 254-257).

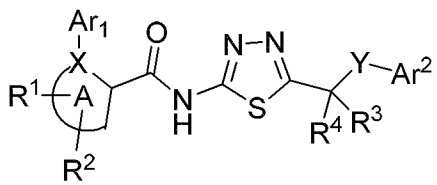
PolQ is distinct among human DNA polymerases, comprising an N-terminal helicase domain (SF2 HEL308-type) and a C-terminal low-fidelity DNA polymerase domain (A-type) (Wood & Doublie DNA Repair (2016), 44, 22-32). In homologous recombination deficient (HRD) cells, PolQ can carry out error-prone DNA synthesis at DNA damage sites through alt-NHEJ pathway. It has been shown that the helicase

domain of PolQ mediates the removal of RPA protein from ssDNA ends and stimulates annealing. This anti-recombinase activity of PolQ promotes the alt-NHEJ pathway. In addition, the helicase domain of Pol0 contributes to microhomology-mediated strand annealing (Chan SH et al., PLoS Genet. (2010);6: el001005; and Kawamura K et al., Int. J. Cancer (2004); 109: 9-16). PolQ can promote end joining in alt-NHEJ pathway by employing this annealing activity when ssDNA overhangs contain >2 bp of microhomology (Kent T., et al., Elife (2016); 5: el3740), and Kent T., et al., Nat. Struct. Mol. Biol. (2015); 22: 230-237). This reannealing activity is obtained through coupled actions of Rad51 interaction followed by ATPase-mediated displacement of Rad51 from DSB damage sites. Once annealed, the polymerase domain extends the ssDNA ends and fills the remaining gaps.

The expression of PolQ is low in normal cells but significantly overexpressed in subsets of HRD ovarian, uterine and breast cancers with associated poor prognosis (Higgins *et al.* Oncotarget (2010), 1, 175-184, Lemee *et al.* PNAS (2010), 107(30), 13390-13395, Ceccaldi *et al.* (2015), *supra).* Secondly, recent studies suggests that cancer cells with deficiency in HR, NHEJ or ATM are highly dependent on PolQ expression (Ceccaldi R., et al., Nature (2015); 518: 258-62, Mateos-Gomez PA et al., Nature (2015); 518: 254-57, and Wyatt D.W., et al., Mol. Cell (2016); 63: 662-73). Finally, PolQ inhibition could conceivably prevent the MMEJ-dependent functional reversion of BRCA1- or BRCA2- mutations that underlies the emergence of cisplatin and PARPi resistance in tumors (Zatreanu D., et al., Nature Communications (2021)12: 3636). Therefore, PolQ is an attractive target for novel synthetic lethal therapy in cancers containing DNA repair defects.

SUMMARY OF THE INVENTION

Poly theta inhibitor



Wherein:

X is -N- or -C-;

ring A is phenyl or a five to ten membered heteroaryl ring containing, inclusive of X, one to four heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ar1 is phenyl, heteroaryl, heterocyclyl, bicyclic heterocyclyl, bridged heterocyclyl, or spiroheterocyclyl, wherein each of the aforementioned ring is substituted with Ra, Rb, and/or Rc,

wherein Ra and Rb are independently selected from hydrogen, alkyl, halo, haloalkyl, alkoxy,

haloalkoxy, cycloalkyloxy, acyl, acylamino, monoalkylamino, dialkylamino, alkylsulfonyl,

cyano, and hydroxy; or Ra and Rb, when on adjacent ring vertices, combine to form a C3-6

cycloalkyl, or Ra and Rb, when on the same ring vertex, combine to form oxo, and Rc is selected

from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl,

aminoalkyl, heterocyclylalkyl, heterocyclyloxy, aminocarbonyl;

Ar2 is phenyl, heteroaryl, or cycloalkyl, wherein said phenyl and heteroaryl are substituted with Rd, Re and/or Rf, wherein Rd and Re are independently selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, and cyano and Rf is selected from hydrogen, alkyl, cycloalkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, cyanomethyl, aminocarbonylmethyl, heteroaryl, and heterocyclyl, wherein said heteroaryl and heterocyclyl of

Rf are unsubstituted or substituted with one, two, or three substituents independently selected

from alkyl, halo, haloalkyl, and hydroxy;

R1 is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, hydroxy, cyano, cyanoalkyl,

carboxy, alkoxycarbonyl, acylamino, aminocarbonyl · optionally substituted heteroaryl, hydroxyalkyl, cycloalkyl, hydroxyalkynyl, alkoxyalkyl, aminoalkyl, aminocarbonylalkyl,

sulfonylalkyl, aminosulfonylalkyl, optionally substituted heteroaralkyl, or optionally substituted

heterocyclylalkyl; and

R2 is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, or cyano;

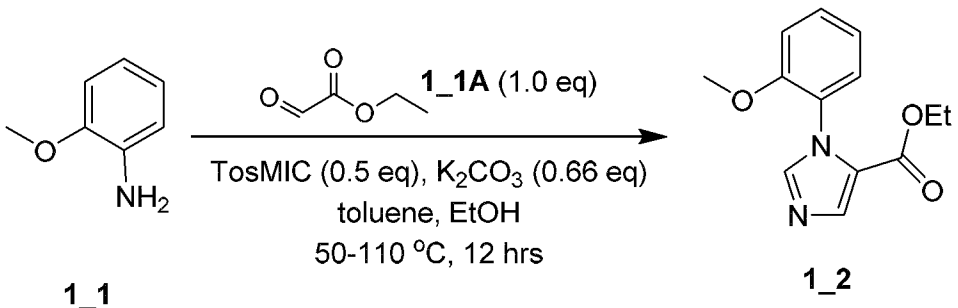
Y is O or S or NH or NR^g, R^g is a C1 to C3 aliphatic group;

R3 and R4 are H, C1-6 aliphatic group.

DETAILED DESCRIPTION OF THE INVENTION

Example 1: N-(5-((4-chlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)-1-(2-methoxyphenyl)-1H-imidazole-5-carboxamide

Step 1: Preparation of ethyl 1-(2-methoxyphenyl)-1H-imidazole-5-carboxylate



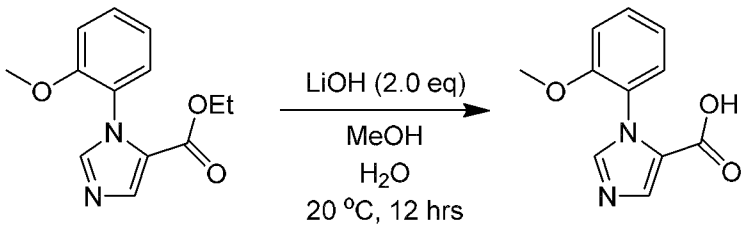
1_1 1_2

(1_2)

A mixture of compound **1_1A** (3.32 g, 16.2 mmol, 50% purity in toluene, 1.00 *eq*), compound **1_1** (2.00 g, 16.24 mmol, 1.83 mL, 1 *eq*), Na_2SO_4 (13.8 g, 97.4 mmol, 9.89 mL, 6.00 *eq*) in toluene (20 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 110 °C for 1 hr under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue as "A". A mixture of "A", K_2CO_3 (1.48 g, 10.7 mmol, 0.66 *eq*),

TosMIC (1.59 g, 8.12 mmol, 0.50 *eq*) in EtOH (20 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 50 °C for 12 hrs under N_2 atmosphere. LCMS showed compound **1_1** was consumed completely and one main peak with desired MS was detected. The reaction mixture was quenched by with H_2O (30 mL) at 25°C, and then extracted with EtOAc (50 mL, 30 mL, 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100/1 to 0/1). Compound **1_2** (1.10 g, 4.47 mmol, 27.50% yield) was obtained as a brown solid.

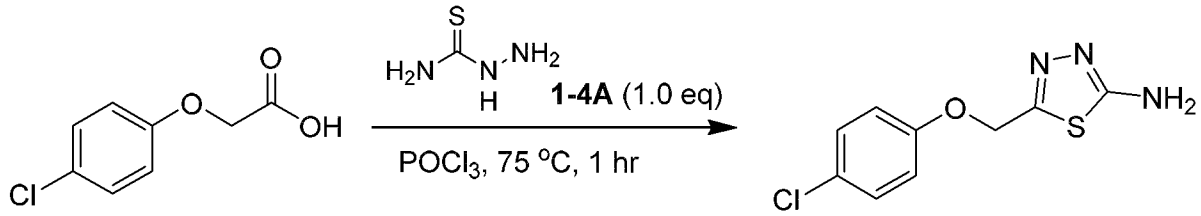
Step 2: preparation of compound 1-(2-methoxyphenyl)-1H-imidazole-5-carboxylic acid (1_3)



1_2 **1_3**

A mixture of compound **1_2** (500 mg, 2.03 mmol, 1.00 *eq*), $LiOH{\cdot}H_2O$ (170 mg, 4.06 mmol, 2.00 *eq*) in MeOH (5 mL) and H_2O (4 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20 °C for 12 hrs under N_2 atmosphere. LCMS showed compound **1_2** was consumed completely and one main peak with desired MS was detected. Diluted with H_2O 15 mL and extracted with EtOAc (20 mL, 15 mL, 10 mL). And then the PH of the aqueous phase was adjusted to the 4-5 with HCl (2 M) at 20 °C, extracted with EtOAc (30 mL, 20 mL, 20 mL, 10 mL). The combined organic layers were washed with brine 15 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product (200 mg, 917 umol) was used into the next step without further purification as a yellow solid.

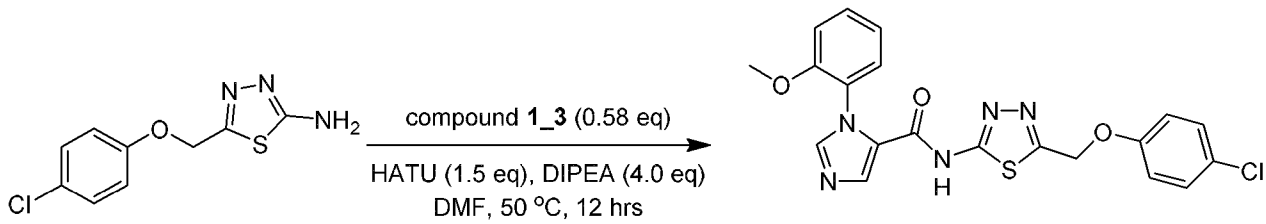
Step 3: Preparation of compound 5-((4-chlorophenoxy)methyl)-1,3,4-thiadiazol-2-amine (1_5)



1_4 1_5

Add compound **1_4** (2.00 g, 10.7 mmol, 1.00 *eq*) and compound **1_4A** (977 mg, 10.7 mmol, 1.00 *eq*) in the 250ml three-neck flask. And then $POCl_3$ (8 mL) was slowly poured into the mixture. The mixture was stirred at 75 °C for 1 hr. LCMS showed compound **1_4** was consumed completely and one main peak with desired MS was detected. The reaction mixture was poured into the ice water 30 mL at 0 °C and stirred at 0 °C for 2 hrs. And then filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with EtOAc 10 mL at 25 °C for 1 hr. The product was dried for 2 hrs at 80-100 °C in the drying oven. Compound **1_5** (2.10 g, 8.69 mmol, 81.1% yield) was obtained as a white solid.

Step 4 preparation of N-(5-((4-chlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)-1-(2-methoxyphenyl)-1H-imidazole-5-carboxamide (1*)*



1_5 1

A mixture of compound **1_3** (200 mg, 917 umol, 1.00 *eq*), DIPEA (474 mg, 3.67 mmol, 639 uL, 4.00 *eq*), compound **1_5** (377 mg, 1.56 mmol, 1.70 *eq*), HATU (523 mg, 1.37 mmol, 1.50 *eq*) in DMF (4 mL) was degassed and purged with N_2

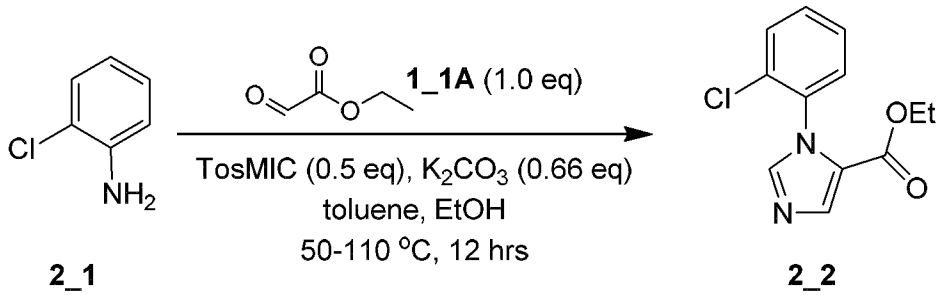
for 3 times, and then the mixture was stirred at 50 °C for 12 hrs under N_2 atmosphere. LCMS showed **compound 1_3** was consumed completely and one main peak with desired MS was detected. The reaction mixture was diluted with H_2O 20 mL and extracted with EtOAc (30 mL, 20 mL, 10 mL). The combined organic layers were washed with brine 20 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex C18 (80*40mm*3um); mobile phase:[water(NH_4HCO_3)-ACN]; B%: 40%-60%,8 min). **1** (95 mg, 215 umol, 23.5% yield) was obtained as a yellow solid.

^{1}H NMR : (400 MHz, $CDCl_3$)

δ 11.3 (s, 1H), 8.27 (s, 1H), 7.77 (s, 1H), 7.50-7.73 (m, 1H), 7.33 (d, *J* = 6.4 Hz, 1H), 7.24-7.25 (m, 1H), 7.06-7.12 (m, 2H), 6.92 (d, *J* = 9.2 Hz, 2H), 5.41 (s, 2H), 3.76(s, 3H).

Example 2: N-(5-((4-chlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)-1-(2-chlorophenyl)-1H-imidazole-5-carboxamide (2)

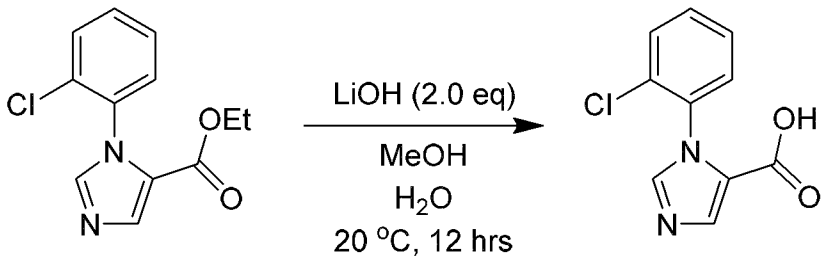
Step 1: Preparation of ethyl 1-(2-chlorophenyl)-1H-imidazole-5-carboxylate (2_2)



A mixture of compound **1_1A** (3.20 g, 15.7 mmol, 50% purity in toluene, 1.00 *eq*), compound **2_1** (2.00 g, 15.7 mmol, 1.65 mL, 1.00 *eq*), Na_2SO_4 (13.4 g, 94.1 mmol, 6.00 *eq*) in toluene (20 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 110 °C for 1 hr under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a

residue as "A". A mixture of "A", K_2CO_3 (1.43 g, 10.4 mmol, 0.66 *eq*), TosMIC (1.53 g, 7.84 mmol, 0.50 *eq*) in EtOH (20 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 50 °C for 12 hrs under N_2 atmosphere. LCMS showed compound **2_1** was consumed completely and one main peak with desired MS was detected. The reaction mixture was quenched by with H_2O (30 mL) at 25°C, and then extracted with EtOAc (50 mL, 30 mL, 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100/1 to 0/1). Compound **2_2** (1.20 g, 4.79 mmol, 30.5% yield) was obtained as a yellow oil.

Step 2: Preparation of 1-(2-chlorophenyl)-1H-imidazole-5-carboxylic acid (2_3)



2_2 **2_3**

A mixture of compound **2_2** (600 mg, 2.39 mmol, 1.00 *eq*), $LiOH{\cdot}H_2O$ (201 mg, 4.79 mmol, 2.00 *eq*) in MeOH (3 mL) and H_2O (2.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 12 hrs under N_2 atmosphere. LCMS showed compound **2_2** was consumed completely and one main peak with desired MS was detected. Diluted with H_2O 15 mL and extracted with EtOAc (20 mL, 15 mL, 10 mL). And then the PH of the aqueous phase was adjusted to the 5-6 with HCl (2 M) at 20 °C, extracted with EtOAc (30 mL, 20 mL, 20 mL, 10 mL). The combined organic layers were washed with brine 15 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product (400 mg, 1.80 mmol) was used into the next

step without further purification as a yellow solid.

^{1}H NMR : ET51185-16-P1D3 (400 MHz, DMSO)

δ 12.8 (s, 1H), 8.00 (s, 1H), 7.75 (s, 1H), 7.64 (d, *J* = 1.2 Hz, 1H), 7.50-7.55 (m, 3H).

Step 3: Preparation of N-(5-((4-chlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)-1-(2-chlorophenyl)-1H-imidazole-5-carboxamide (2)

1_5 **2**

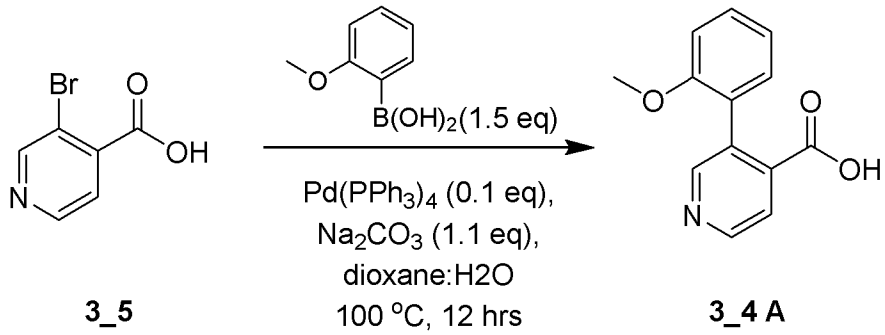
A mixture of compound **2_3** (200 mg, 898 umol, 1.00 *eq*), DIPEA (464 mg, 3.59 mmol, 626 uL, 4.00 *eq*), compound **1_5** (304 mg, 1.26 umol, 1.40 *eq*), HATU (512 mg, 1.35 mmol, 1.50 *eq*) in DMF (4 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 50 °C for 12 hrs under N_2 atmosphere. LCMS showed **compound 2_3** was consumed completely and one main peak with desired MS was detected. The reaction mixture was diluted with H_2O 20 mL and extracted with EtOAc (30 mL, 20 mL, 10 mL). The combined organic layers were washed with brine 20 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex C18 (80*40mm*3um); mobile phase:[water(NH_4HCO_3)-ACN]; B%: 30%-60%,8 min). **2** (95 mg, 213 umol, 23.7% yield) was obtained as a yellow solid.

^{1}H NMR : ET51185-17-P1B3 (400 MHz, MeOD)

δ 12.4 (s, 1H), 8.54 (s, 1H), 7.79 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.44-7.51 (m, 3H), 7.25-7.44 (m, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.42 (s, 2H).

Example 3: 5-(((4-chlorophenyl)amino)methyl)-1,3,4-thiadiazol-2-amine (3)

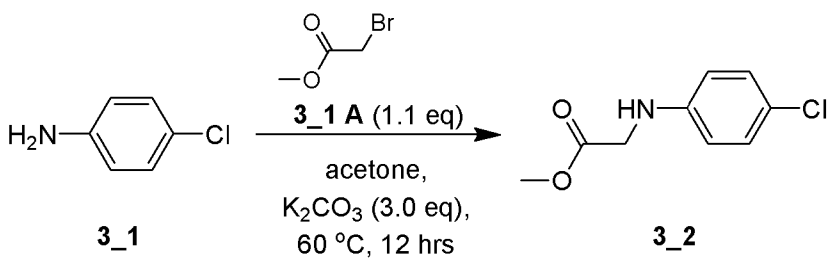
Step 1: preparation of 3-(2-methoxyphenyl)isonicotinic acid (3_4)



3_5 3_4 A

To a solution of compound **3_5** (2.00 g, 9.90 mmol, 1.00 *eq*) and (2-methoxyphenyl) boronic acid (2.26 g, 14.9 mmol, 1.50 *eq*) in 1,4-dioxane (10.0 mL) and H_2O (10.0 mL) was added Na_2CO_3 (1.15 g, 10.9 mmol, 1.10 *eq*) and $Pd(PPh_3)_4$ (1.14 g, 990 umol, 0.10 *eq*). The mixture was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100°C for 12 hrs under N_2 atmosphere. LC-MS (ET51179-2-P1A, compound **3_5**: RT = 0.161 min, compound **3_4A**: RT = 0.509 min) showed ~16.9% of compound **3_5** remained. Several new peaks were shown on LC-MS and ~13.9% of desired compound was detected. The mixture was cooled to room temperature and diluted with water 20.0 mL. The mixture was extracted with EtOAc (2 x 20.0 mL). The aqueous layer was acidified to pH 6 with HC1 (1.00 M), and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. Compound **3_4A** (0.50 g, crude, ~68% purity) was obtained as a yellow solid. LCMS (compound **3_4A**: RT = 0.474 min).

Step 2: Preparation of methyl (4-chlorophenyl)glycinate (3_3)



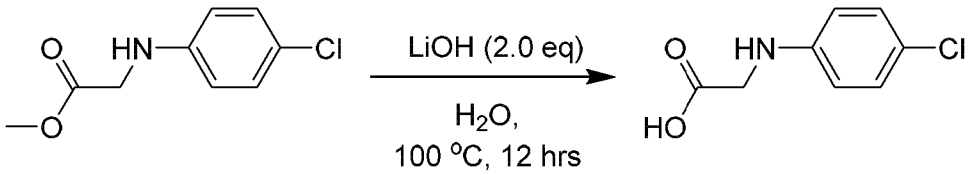
3_1 3_2

To a solution of compound **3_1** (5.00 g, 39.2 mmol, 1.00 *eq*) in acetone (35.0 mL) was added K_2CO_3 (16.3 g, 118 mmol, 3.00 *eq*) and compound **3_1A** (6.60 g, 43.1 mmol, 1.10 *eq*). The mixture was stirred at 60°C for 12 hrs under N_2 atmosphere. LC-MS (compound **3_2**: RT = 0.634 min) showed ~69.7% of desired compound was detected. The reaction mixture was quenched by addition H_2O 50.0 mL, and then extracted with EtOAc (15.0 mL x 3). The combined organic layers were washed with brine 15.0 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. Compound **3_2** (7.25 g, 29.1 mmol, 74.2% yield, 80.1% purity) was obtained as a yellow solid.

^{1}HNMR: ET51179-1-P1A (400 MHz, $CDCl_3$)

δ 7.15 (d, *J* = 8.8 Hz, 2H), 6.54 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 2H), 3.79 (s, 3H).

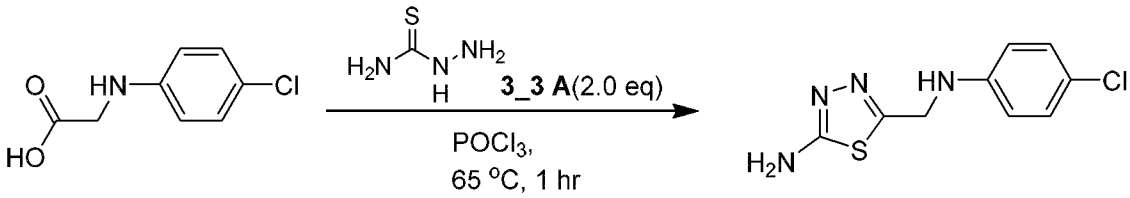
Step 3: Preparation of (4-chlorophenyl)glycine (3_3)



3_2 **3_3**

To a solution of compound **3_2** (7.25 g, 36.3 mmol, 1.00 *eq*) in H_2O (50.8 mL) was added $LiOH.H_2O$ (3.05 g, 72.6 mmol, 2.00 *eq*). The mixture was stirred at 100°C for 12 hrs. LC-MS (ET51179-3-P1A, compound **3_3**: RT = 0.548 min) showed compound **3_2** was consumed completely and one main peak with desired mass was detected. The reaction mixture was extracted with EtOAc (20.0 mL) and discarded the EtOAc phase. The aqueous layer was acidified to pH 6 with HC1 (1.00 M), and extracted with EtOAc (50.0 mL x 3). The combined organic layers were washed with brine 20.0 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. Compound **3_3** (5.10 g, 27.5 mmol, 75.7% yield) was obtained as a yellow solid.

Step 4: Preparation of 5-(((4-chlorophenyl)amino)methyl)-1,3,4-thiadiazol-2-amine (3_4)



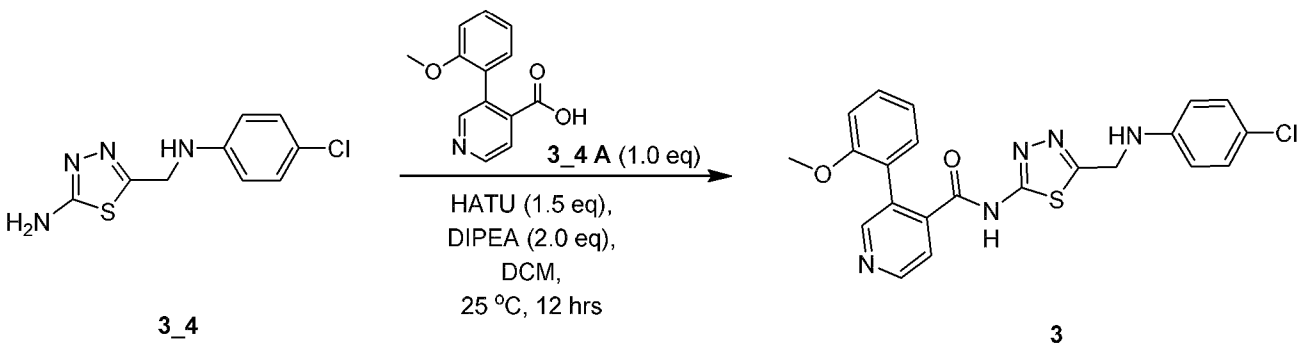
3_3 3_4

$POCl_3$ (33.0 g, 215 mmol, 20.0 mL, 7.99 *eq*) was added to a mixture of compound **3_3** (5.00 g, 26.9 mmol, 1.00 *eq*) and compound **3_3A** (2.46 g, 26.9 mmol, 1.00 *eq*). The reaction mixture was stirred at 65°C under N_2 atmosphere for 1 hr. TLC (Petroleum ether/Ethyl acetate = 0:1, compound **3_3**: RT = 0.07, compound **3_4**: RT = 0.43) indicated compound **3_3** was consumed completely and one main new spot formed. The reaction was messy according to TLC. The mixture was poured into ice-water 100 mL and stirred at 0 °C for 20 min, and extracted with EtOAc (10.0 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (0.1% NH_4HCO_3 condition). Compound **3_4** (3.00 g, 12.5 mmol, 46.3% yield) was obtained as a yellow solid.

^{1}HNMR: (400 MHz, DMSO)

δ 7.10 (d, *J* = 8.8 Hz, 2H), 7.03 (s, 2H), 6.63 (d, *J* = 8.8 Hz, 2H), 6.53 (t, *J* = 6.4 Hz, 1H), 4.39 (d, *J* = 6.4 Hz, 2H).

Step 5: Preparation of 5-(((4-chlorophenyl)amino)methyl)-1,3,4-thiadiazol-2-amine (3)



3_4 3

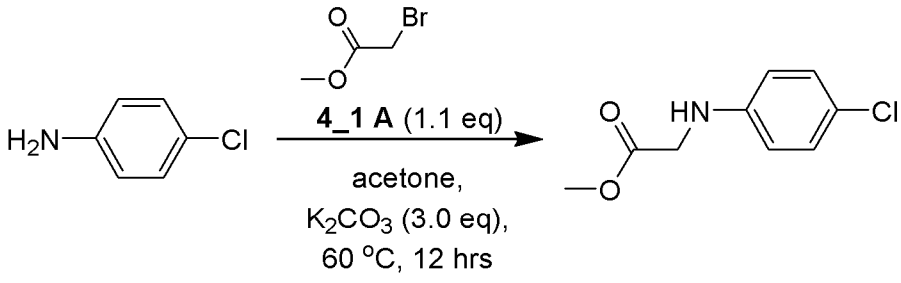
To a solution of compound **3_4** (150 mg, 623 umol, 1.00 *eq*) and compound **3_4A** (143 mg, 623 umol, 1.00 *eq*) in DCM (1.5 mL) was added DIPEA (161 mg, 1.25 mmol, 2.00 *eq*) and HATU (355 mg, 935 umol, 1.50 *eq*). The mixture was stirred for 12 hrs at 25°C under nitrogen. LC-MS (ET51179-18-P1A, **3**: RT = 0.608 min) showed compound **3_4** was consumed completely and one main peak with desired mass was detected. The reaction mixture was diluted with H_2O 20.0 mL and extracted with EtOAc (10.0 mL x 3). The combined organic layers were washed with brine 10.0 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate = 1/5). TLC (Petroleum ether/Ethyl acetate = 1/5, **3**: R_f = 0.39 min). Then purified by prep-HPLC (column: Phenomenex Luna 80*30mm*3um; mobile phase: [water (HCl)-ACN]; B%: 35%-65%, 8min). Finally, 18 mg (99.2% purity) of product as yellow solid.

^{1}HNMR: (400 MHz, DMSO)

δ 13.03 (brs, 1H), 8.78 (d, *J* = 5.2 Hz, 1H), 8.69 (s, 1H), 7.76 (br d, *J* = 4.8 Hz, 1H), 7.30-7.44 (m, 2H), 7.01 - 7.19 (m, 3H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 8.8 Hz, 2H), 4.62 (s, 2H), 3.41 (s, 3H).

Example 4:

Step 1: Preparation of methyl (4-chlorophenyl)glycinate (4_2)



4_1 **4_2**

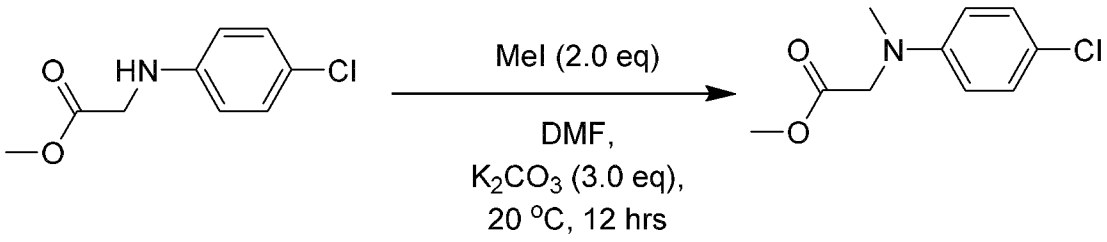
To a solution of compound **4_1** (5.00 g, 39.2 mmol, 1.00 *eq*) in acetone (35.0 mL) was added K_2CO_3 (16.3 g, 118 mmol, 3.00 *eq*) and compound **4_1A** (6.60 g, 43.1 mmol, 1.10 *eq*). The mixture was stirred at 60°C for 12 hrs under N_2

atmosphere. LCMS (**4_2**: RT = 0.634 min) showed ~69.7% of desired compound was detected. The reaction mixture was quenched by addition H_2O 50.0 mL, and then extracted with EtOAc (15.0 mL x 3). The combined organic layers were washed with brine 15.0 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. Compound **4_2** (7.25 g, 29.1 mmol, 74.2% yield, 80.1% purity) was obtained as a yellow solid.

^{1}HNMR: ET51179-1-P1A (400 MHz, $CDCl_3$)

δ 7.15 (d, *J* = 8.8 Hz, 2H), 6.54 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 2H), 3.79 (s, 3H).

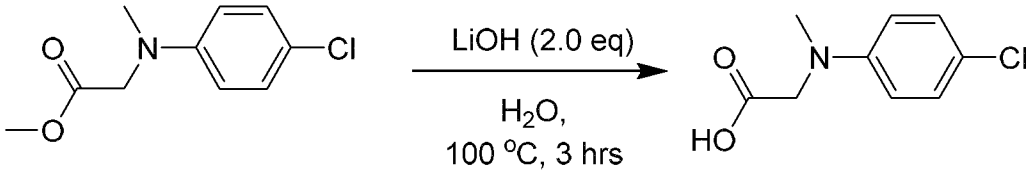
Step 2: preparation of methyl N-(4-chlorophenyl)-N-methylglycinate (4_3)



4_2 **4_3**

To a solution of compound **4_2** (3.50 g, 17.5 mmol, 1.00 *eq*) in DMF (24.5 mL) were added K_2CO_3 (7.27 g, 52.6 mmol, 3.00 *eq*) and MeI (4.98 g, 35.1 mmol, 2.00 *eq*), and the mixture was stirred for 12 hrs at 20°C. LCMS (**4_2**: RT = 0.955 min, compound **4_3**: RT = 1.004 min) showed ~1.63% of compound **4_3** remained. One of new peaks was shown on LC-MS with desired compound was detected. The reaction mixture was poured into water 30.0 mL and extracted with ethyl acetate (15.0 mL x 3). The extract was washed with brine 10.0 mL and dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. Compound **4_3** (2.50 g, 11.7 mmol, 66.7% yield) was obtained as a yellow solid.

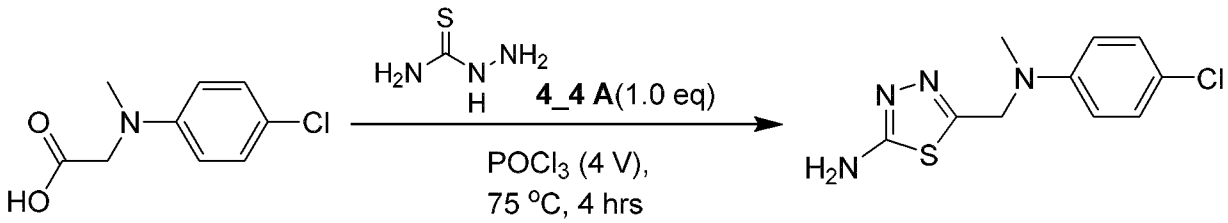
Step 3: Preparation of N-(4-chlorophenyl)-N-methylglycine (4_4)



4_3 **4_4**

To a solution of compound **4_3** (1.50 g, 7.02 mmol, 1.00 *eq*) in H_2O (10.5 mL) was added $LiOH.H_2O$ (589 mg, 14.04 mmol, 2.00 *eq*). The mixture was stirred at 100°C for 12 hrs. TLC (Petroleum ether/Ethyl acetate = 0:1, product: R_f = 0.1) indicated compound **4_3** was consumed completely and one new spot formed. The reaction mixture was extracted with EtOAc (10.0 mL) and discarded the EtOAc phase. The aqueous layer was acidified to pH 6 with HC1 (1.00 M), and extracted with EtOAc (10.0 mL x 3). The combined organic layers were washed with brine 10.0 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. Compound **4_4** (1.30 g, 6.51 mmol, 92.8% yield) was obtained as a yellow solid.

Step 4: Preparation of 5-(((4-chlorophenyl)(methyl)amino)methyl)-1,3,4-thiadiazol-2-amine (4_5)

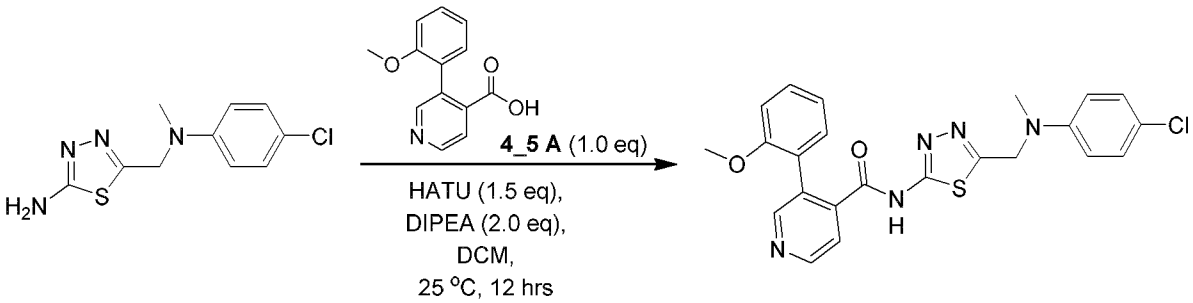


4_4 **4_5**

$POCl_3$ (6.60 g, 43.0 mmol, 4.00 mL) was added to a mixture of compound **4_4** (1.00 g, 5.01 mmol, 1.00 *eq*) and compound **4_4A** (457 mg, 5.01 mmol, 1.00 *eq*). The reaction mixture was stirred at 75°C under N_2 atmosphere for 4 hrs. LCMS (compound **4_5**: RT = 0.568 min) showed compound **4_4** was consumed

completely and one of main peaks with desired MS was detected. The mixture was poured into ice-water 20.0 mL and stirred at 0°C for 20 min, and extracted with EtOAc (15.0 mL x 3). The combined organic layers were washed with brine 10.0 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate = 0/1). TLC (Petroleum ether/Ethyl acetate=0/1). Compound **4_5** (0.20 g, 785 umol, 15.7% yield) was obtained as a yellow solid.

Step 5: preparation of N-(5-(((4-chlorophenyl)(methyl)amino)methyl)-1,3,4-thiadiazol-2-yl)-3-(2-methoxyphenyl)isonicotinamide (4)



4_5 **4**

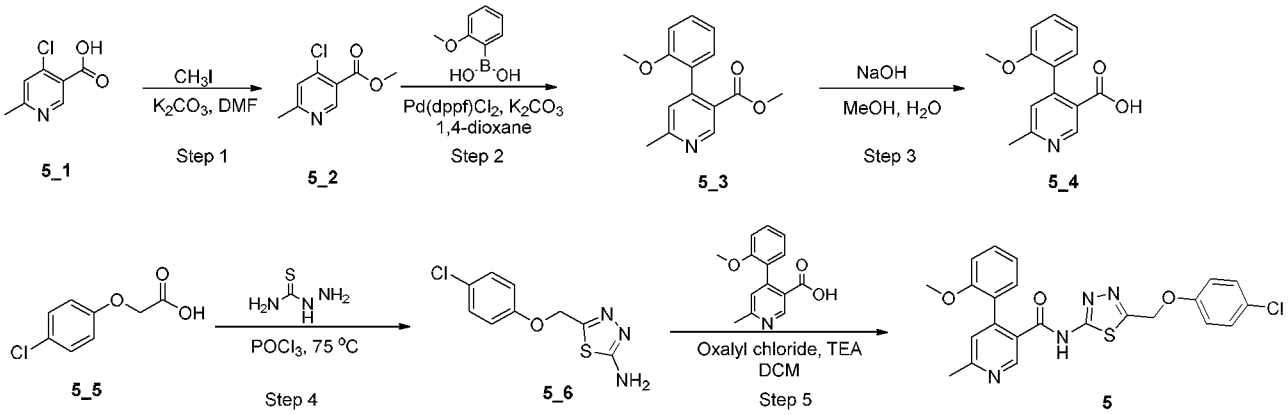
To a solution of compound **4_5** (0.20 g, 785 umol, 1.00 *eq*) and compound **4_5A** (180 mg, 785 umol, 1.00 *eq*) in DCM (2.00 mL) was added DIPEA (203 mg, 1.57 mmol, 2.00 *eq*) and HATU (448 mg, 1.18 mmol, 1.50 *eq*). The mixture was stirred for 12 hrs at 25°C under nitrogen. LCMS (**4**: RT = 0.635 min) showed compound **4_5** was consumed completely and one of peaks with desired MS was detected. The reaction mixture was diluted with H_2O 20.0 mL and extracted with EtOAc (10.0 mL x 3). The combined organic layers were washed with brine 10.0 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate = 1**:5**, **4**: R_f = 0.39). Then purified by prep-HPLC (column: Phenomenex Luna 80 x 30mm x 3um; mobile phase: [water (HCl)-ACN]; B%: 35%-65%, 8min). **4** (3.00 mg, 5.97 umol, 0.76% yield, 100% purity,

HCl) was obtained as a yellow solid.

^{1}HNMR:ET51179-19-P1A (400 MHz, DMSO)

δ 13.05 (br s, 1H), 8.73 (d, *J* = 5.2 Hz, 1H), 8.64 (s, 1H), 7.68 (br d, *J* = 4.8 Hz, 1H), 7.30 - 7.43 (m, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 9.2 Hz, 2H), 4.90 (s, 2H), 4.34 - 4.44 (m, 2H), 3.40 (s, 3H), 2.97 (s, 3H).

Example 5: N-(5-((4-chlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide (5)



Step 1: methyl 4-chloro-6-methylnicotinate

To a solution of 4-chloro-6-methylnicotinic acid (4.0 g, 23 mmol) in DMF (40 mL) was added K_2CO_3 (4.8 g, 35 mmol) and MeI (4.3 g, 30 mmol) and the reaction mixture was stirred at room temperature for 6 hours. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give the title compound (3.5 g, 82% yield) as light yellow solid. LC/MS (ESI) (m/z): 186 $(M+H)^+$.

Step 2: methyl 4-(2-methoxyphenyl)-6-methylnicotinate

To a mixture of methyl 4-chloro-6-methylnicotinate (3.0 g, 16 mmol) and (2-methoxyphenyl)boronic acid (5.0 g, 32 mmol) in 1,4-dioxane (24 mL) and H_2O (3 mL) was added K_2CO_3 (4.4 g, 32 mmol) followed by $Pd(dppf)Cl_2$ (1.1 g,1.6 mmol) under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for

three times and stirred at 80 °C for 16 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% of EtOAc in PE) to give the title compound (4.0 g, 82% yield) as yellow solid. LC/MS (ESI) (m/z): 258 $(M+H)^+$.

Step 3: 4-(2-methoxyphenyl)-6-methylnicotinic acid

To a solution of methyl 4-(2-methoxyphenyl)-6-methylnicotinate (4 g, 15.6 mmol) in MeOH (20 mL) and H_2O (20 mL) was added NaOH (1 g, 23.4 mmol) and the mixture was stirred at room temperature for 8 hours. The mixture was acidified with 1N aq.HCl to pH~3 and extracted with DCM (2 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give the title compound (3.6 g, 94.5% yield) as yellow solid. LC/MS (ESI) (m/z): 244 $(M+H)^+$.

Step 4: 5-((4-chlorophenoxy)methyl)-1,3,4-thiadiazol-2-amine

A mixture of 2-(4-chlorophenoxy)acetic acid (5 g, 26.8 mmol) and hydrazinecarbothioamide (2.4 g, 26.8 mmol) in $POCl_3$ (20 mL) was stirred at 75 °C under N_2 atmosphere for 1 hour. The mixture was poured into ice-water and stirred at 0 °C for 20 min. The slurry was filtered and the filter cake was dried under vacuum to give the title compound (4.2 g, 65.0% yield) as yellow solid. LC/MS (ESI) (m/z): 242 $(M+H)^+$

Step 5: N-(5-((4-chlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide (5)

To a solution of 4-(2-methoxyphenyl)-6-methylnicotinic acid (500 mg, 2.05 mmol) in DCM (5 mL) was added Oxalyl chloride (0.2 mL, 2.36 mmol) at 0 °C and the mixture was stirred at room temperature for 1 hour. Then a mixture of 5-((4-chlorophenoxy)methyl)-1,3,4-thiadiazol-2-amine (496 mg, 2.05 mmol) and TEA (0.6 mL, 4.1 mmol) in DCM (5 mL) was added drop-wisely to the mixture at 0 °C and the resulting mixture was stirred at room temperature for 1 hour. The mixture was concentrated to dryness and the residue was purified by prep-HPLC to

give the title compound (65 mg, 6.8% yield) as white solid. ^{1}H NMR (400 MHz, DMSO) δ 13.03 (s, 1H), 8.69 (s, 1H), 7.41 - 7.34 (m, 4H), 7.31 (s, 1H), 7.11 - 7.05 (m, 3H), 6.95 (d, *J* = 8.2 Hz, 1H), 5.50 (s, 2H), 3.43 (s, 3H), 2.57 (s, 3H). LC/MS (ESI) (m/z): 467 $(M+H)^+$.

Example 6: Biological evaluation

The ability of the compounds to inhibit ATPase activity of PolQ (1- 899) was determined using the assay described below.

PolQ ATPase activity was determined by ADP-Glo assay. 10-point dilution series of compounds were used in a 384 well format for the inhibition assays. Pol theta (1-899) (1 nM) in assay buffer (20 mM Tris HC1 (pH 8.0), 80 mM KC1, 10 mM MgCl2, 1 mM DTT, 0.01% BSA, 0.01% Tween, 5% glycerol) was transferred to the test wells (20 uL), except the low control wells (20 uL of assay buffer was added to the low control wells). The plate was then incubated at room temperature for 30 min. An equal volume (20 uL) of 100 uM ATP, 150 nM ssDNA containing 50 thymine bases in assay buffer was added to all the test wells. The plates were covered and left to incubate for 1 hour at room temperature before the addition of the ADP Glo detection reagents. After 60 min incubation, transfer 5 ul reaction mix to another 384-well plate and add 5 μL ADP Glo and plates incubated for 60 minutes before addition of 10 μL kinase detection reagent. After the addition of the kinase detection reagent, the plates were covered and incubated for 60 minutes and read luminescence on Envision

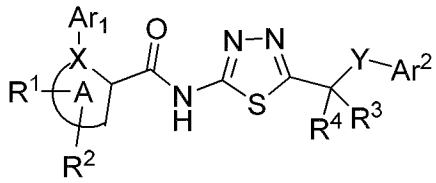
Percent inhibition was calculated as follows: 100-((Compound-Min) / (Max-Min) *100) where “Max” is the high control (DMSO) and “Min” is the no enzyme control. IC50 values were calculated using a four-parameter logistic curve fit using the following formula: LowerBound+((UpperBound- LowerBound)/(1+((IC50/x)^Hill)))

Compound	IC50 (nM)

1	193
2	694
3	843
4	1412
5	36

CLAIMS

1. Poly theta inhibitor



Wherein:

X is -N- or -C-;

ring A is phenyl or a five to ten membered heteroaryl ring containing, inclusive of X, one to four heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ar1 is phenyl, heteroaryl, heterocyclyl, bicyclic heterocyclyl, bridged heterocyclyl, or spiroheterocyclyl, wherein each of the aforementioned ring is substituted with Ra, Rb, and/or Rc,

wherein Ra and Rb are independently selected from hydrogen, alkyl, halo, haloalkyl, alkoxy,

haloalkoxy, cycloalkyloxy, acyl, acylamino, monoalkylamino, dialkylamino, alkylsulfonyl,

cyano, and hydroxy; or Ra and Rb, when on adjacent ring vertices, combine to form a C3-6

cycloalkyl, or Ra and Rb, when on the same ring vertex, combine to form oxo, and Rc is selected

from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl,

aminoalkyl, heterocyclylalkyl, heterocyclyloxy, aminocarbonyl;

Ar2 is phenyl, heteroaryl, or cycloalkyl, wherein said phenyl and heteroaryl are substituted with Rd, Re and/or Rf, wherein Rd and Re are independently selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, and cyano and Rf is selected from hydrogen, alkyl, cycloalkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, cyanomethyl, aminocarbonylmethyl, heteroaryl, and heterocyclyl,

wherein said heteroaryl and heterocyclyl of

Rf are unsubstituted or substituted with one, two, or three substituents independently selected

from alkyl, halo, haloalkyl, and hydroxy;

R1 is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, hydroxy, cyano, cyanoalkyl,

carboxy, alkoxycarbonyl, acylamino, aminocarbonyl · optionally substituted heteroaryl, hydroxyalkyl, cycloalkyl, hydroxyalkynyl, alkoxyalkyl, aminoalkyl, aminocarbonylalkyl,

sulfonylalkyl, aminosulfonylalkyl, optionally substituted heteroaralkyl, or optionally substituted

heterocyclylalkyl; and

R2 is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, or cyano;

Y is O or S or NH or NR^g, R^g is a C1 to C3 aliphatic group;

R3 and R4 are H, C1-6 aliphatic group.

2. The compound of claim 1, wherein:

X is -N- or -C-;

alk is alkylene;

ring A is phenyl or a five or six membered heteroaryl ring containing, inclusive of X, one to three heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ar^1 is phenyl, heteroaryl, heterocyclyl, bicyclic heterocyclyl, bridged heterocyclyl, or spiroheterocyclyl, wherein each of the aforementioned ring is substituted with R^a, R^b, and/or R^c, wherein R^a and R^b are independently selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, cycloalkyloxy, acyl, acylamino, monoalkylamino, dialkylamino, alkylsulfonyl, cyano, and hydroxy, and R^c is selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclylalkyl, and

aminocarbonyl;

Ar^2 is phenyl, heteroaryl, or cycloalkyl, wherein said phenyl and heteroaryl are substituted with R^d, R^e and/or R^f, wherein R^d and R^e are independently selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, and cyano and R^f is selected from hydrogen, alkyl, cycloalkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, cyanomethyl, aminocarbonylmethyl, heteroaryl, and heterocyclyl, wherein said heteroaryl and heterocyclyl of R^f are unsubstituted or substituted with one, two, or three substituents independently selected from alkyl, halo, haloalkyl, and hydroxy;

R^1 is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, hydroxy, cyano, cyanoalkyl, carboxy, alkoxycarbonyl, acylamino, aminocarbonyl· optionally substituted heteroaryl, hydroxyalkyl, hydroxyalkynyl, alkoxyalkyl, aminoalkyl, aminocarbonylalkyl, sulfonylalkyl, aminosulfonylalkyl, optionally substituted heteroaralkyl, or optionally substituted

heterocyclylalkyl; and

R^2 is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, or cyano; or

a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein:

X is -N- or -C-;

alk is alkylene;

ring A is phenyl or a five or six membered heteroaryl ring containing, inclusive of X, one to three heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ar^1 is phenyl, heteroaryl, heterocyclyl, bicyclic heterocyclyl, bridged heterocyclyl, or spiroheterocyclyl, wherein each of the aforementioned ring is substituted with R^a, R^b, and/or R^c, wherein R^a and R^b are independently selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, cycloalkyloxy, acyl, acylamino, monoalkylamino, dialkylamino, alkylsulfonyl, cyano, and hydroxy, and R^c is selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl,

alkoxyalkyl, aminoalkyl, heterocyclylalkyl, and

aminocarbonyl;

Ar^2 is phenyl, heteroaryl, or cycloalkyl, wherein said phenyl and heteroaryl are substituted with R^d, R^e and/or R^f, wherein R^d and R^e are independently selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, and cyano and R^f is selected from hydrogen, alkyl, cycloalkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, cyanomethyl, aminocarbonylmethyl, heteroaryl, and heterocyclyl, wherein said heteroaryl and heterocyclyl of R^f are unsubstituted or substituted with one, two, or three substituents independently selected from alkyl, halo, haloalkyl, and hydroxy;

R^1 is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, hydroxy, cyano, carboxy, alkoxycarbonyl, acylamino, aminocarbonyl· optionally substituted heteroaryl, hydroxyalkyl, hydroxyalkynyl, alkoxyalkyl, aminoalkyl, aminocarbonylalkyl, sulfonylalkyl,

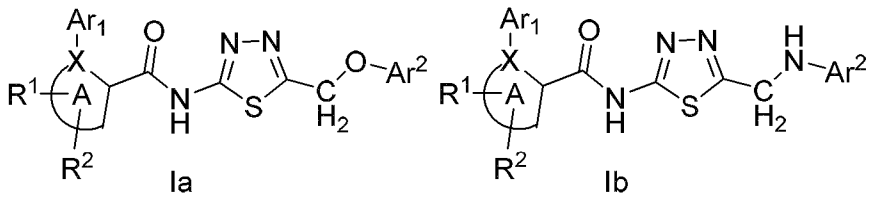
aminosulfonylalkyl, optionally substituted heteroaralkyl, or optionally substituted

heterocyclylalkyl; and

R^2 is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, or cyano; or

a pharmaceutically acceptable salt thereof.

4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof wherein the compound has a structure of formula (Ia or Ib):



5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof wherein ring A is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, imidazolyl, pyrazolyl, triazolyl, imidazo[1,2-a]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl,

imidazo[l,5-a]pyridinyl, pyrrolo[2, 3 -bjpyridinyl, pyrrolo[3 ,2-b]pyridinyl, pyrazolo[1 ,5-a]pyridinyl, [1 ,2,4]triazolo[1,5- a] pyridinyl, 1,6-naphthyridinyl, or 1,7-naphthyridinyl.

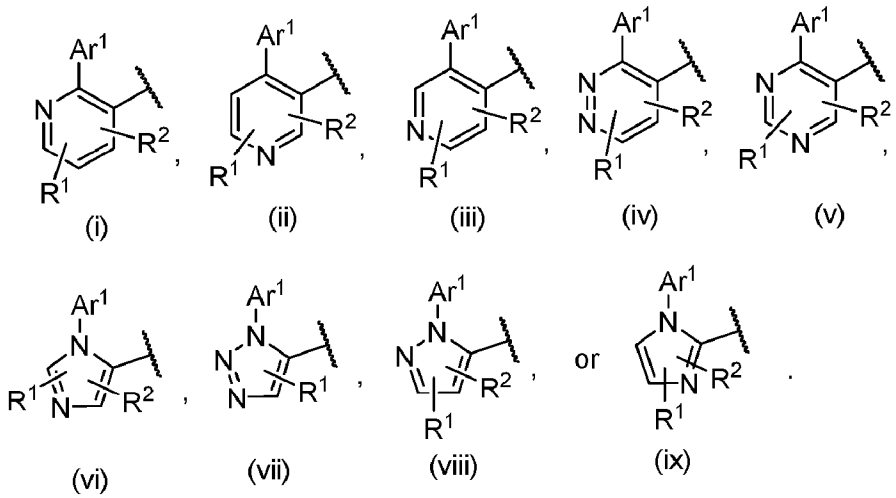
6. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof wherein ring A is a nine or ten membered heteroaryl ring.

7. The compound of claim 6, or a pharmaceutically acceptable salt thereof wherein ring A is imidazo[l,2-a]pyridinyl, [l,2,3]triazolo[l,5-a]pyridinyl, imidazo[l,5-a]pyridinyl, pyrrolo[2, 3 -bjpyridinyl, pyrrolo[3 ,2-b]pyridinyl, pyrazolo[1 ,5-a]pyridinyl, [1 ,2,4]triazolo[1,5- ajpyridinyl, 1,6-naphthyridinyl, or 1,7-naphthyridinyl.

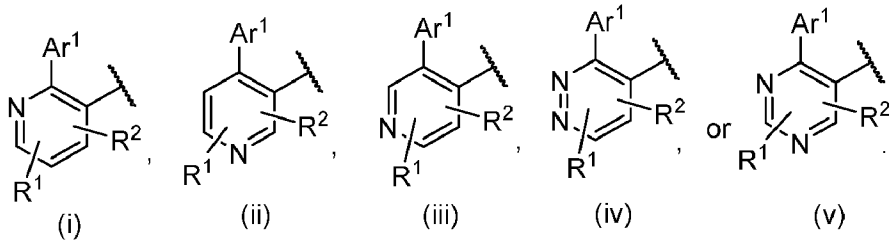
8. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof wherein ring A is a five or six membered heteroaryl ring.

9. The compound of claim 8, or a pharmaceutically acceptable salt thereof wherein ring A is pyridinyl, pyridazinyl, pyrimidinyl, imidazolyl, pyrazolyl, or triazolyl.

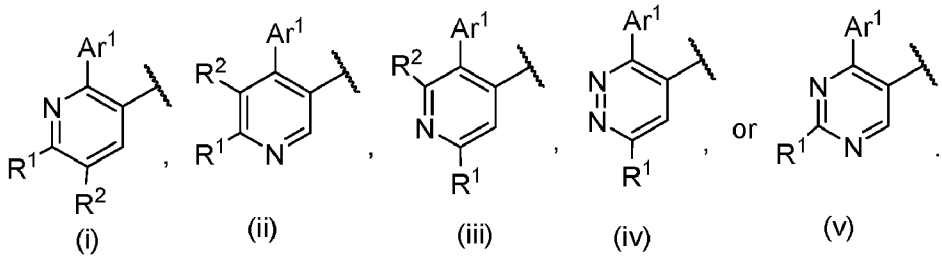
10. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is:



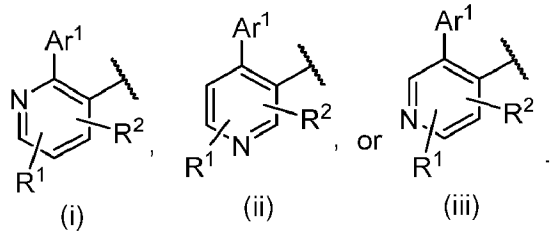
11. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is:



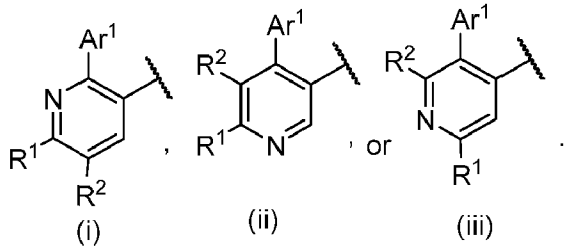
12. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is:



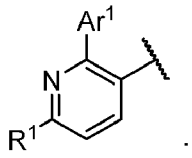
13. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is:



14. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is:

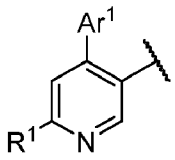


15. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is:



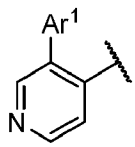
(i)

16. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is:



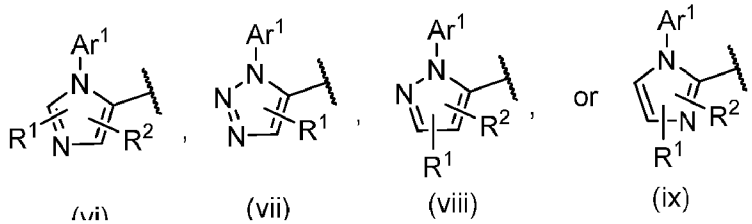
(ii)

17. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is:



(iii)

18. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is:



(vi) (vii) (viii) (ix)

19. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is phenyl.

20. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof wherein Ar^1 is heterocyclyl substituted with R^a, R^b, and/or R^c.

21. The compound of claim 20, or a pharmaceutically acceptable salt thereof wherein Ar^1 is piperidinyl, piperazinyl, morpholinyl, homomorpholinyl, 2-oxopiperazinyl, 2- oxohomopiperazinyl, tetrahydropyranyl, 3,6-dihydro-2H-pyranyl, 2-oxo-l,2-dihydropyridinyl, thiomorpholinyl, or 1, 1-dioxothiomorpholinyl substituted with R^a, R^b, and/or R^c.

22. The compound of claim 20, or a pharmaceutically acceptable salt thereof wherein Ar^1 is piperidin-l-yl, piperazin-l-yl, morpholin-4-yl, homomorpholin-4-yl, 3-oxopiperazin-l-yl, 3-oxohomopiperazin-l-yl, 5-oxohomopiperazin-l-yl, tetrahydropyran-4-yl, 3,6-dihydro-2H- pyran-4-yl, 6-oxo-l,6-dihydropyridin-3-yl, 6-oxo-l,6-dihydropyridin-4-yl, thiomorpholin-4-yl, or l, l-dioxothiomorpholin-4-yl substituted with R^a, R^b, and/or R^c.

23. The compound of claim 20, or a pharmaceutically acceptable salt thereof wherein Ar^1 is morpholin-4-yl substituted with R^a, R^b, and/or R^c.

24. The compound of any one of claims 20 to 23, or a pharmaceutically acceptable salt thereof wherein R^a is hydrogen or alkyl, R^b is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, acyl, alkylsulfonyl, cyano, or hydroxy, and R^c is selected from alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclylalkyl, and aminocarbonyl.

25. The compound of any one of claims 20 to 23, or a pharmaceutically acceptable salt thereof wherein R^a and R^b, when on adjacent ring vertices, combine to form a cyclopropyl or cyclobutyl ring, and R^c is hydrogen.

26. The compound of any one of claims 20 to 23, or a pharmaceutically acceptable salt thereof wherein Ar^1 is substituted with R^b and/or R^c wherein R^b is hydrogen, methyl, fluoro, cyano, methylsulfonyl, or methylcarbonyl and R^c is hydrogen, methyl, ethyl, fluoro,

difluoromethyl, trifluoromethyl, trifluoroethyl, methoxy, ethoxy, difluoromethoxy,

trifluoromethoxy, trifluoroethoxy, hydroxy, 2-hydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2- morpholin-l-yl ethyl, -CONH2, methylaminocarbonyl, or dimethylaminocarbonyl.

27. The compound of claim 20, or a pharmaceutically acceptable salt thereof wherein Ar^1 is morpholin-4-yl, homomorpholin-4-yl, 2-methylmorpholin-4-yl, 3-methylmorpholin-4-yl, 3R-methylmorpholin-4-yl, 3S-methylmorpholin-4-yl, 3-oxopiperazin-l-yl, 4-methyl-3-oxo- piperazin-l-yl, 2-methyl-3-oxopiperazin-l-yl, 6-methyl-3-oxopiperazin-l-yl, 5-methyl-3- oxopiperazin-l-yl, 3-oxohomopiperazin-l-yl, 5-oxohomopiperazin-l-yl, 4-dimethylaminocarbonylpiperazin-l-yl, tetrahydropyran-4-yl, 3,6-dihydro-2H-pyran-4-yl, 4-(2- hydroxyethyl)-3-oxopiperazin-l-yl, 6-oxo-l,6-dihydropyridin-4-yl, 6-oxo-l,6-dihydropyridin-3- yl, l-methyl-6-oxo-l,6-dihydropyri din-3 -yl, 4-(2-morpholin-4-ylethyl)-3-oxopiperazin-l-yl, 4- methylcarbonylpiperazin-l-yl, 4-methylsulfonylpiperazin-l-yl, l,l-dioxothiomorpholin-4-yl, or 4,4-difluoropiperidin-1 -yl .

28. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof wherein wherein Ar^1 is bicyclic heterocyclyl substituted with R^a, R^b, and/or R^c.

29. The compound of claim 28, or a pharmaceutically acceptable salt thereof wherein Ar^1 is 6-oxohexahydropyrrolo[l,2-a]pyrazin-2(lH)-yl or

2,3-dihydro-4H-benzo[b][l,4]oxazin-4- yl, each ring substituted with R^a, R^b, and/or R^c.

30. The compound of claim 28, or a pharmaceutically acceptable salt thereof wherein Ar^1 is selected from the group consisting of 6-oxohexahydropyrrolo[l,2-a]pyrazin-2(lH)-yl 3- oxo-3, 4-dihydro-2H-benzo[b][l,4]oxazin-8-yl, benzo[d][l,3]dioxol-4-yl, (3,4-dihydro-2H-l,4- benzoxazin-8-yl), [5H,6H,7H-pyrazolo[l,5-a]pyrimidin-4-yl] and 2,3-dihydro-4H- benzo[b][l,4]oxazin-4-yl, each ring substituted with R^a, R^b, and/or R^c.

31. The compound of any one of claims 28 to 30, or a pharmaceutically acceptable salt thereof wherein R^a is hydrogen, R^b is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, acyl, alkylsulfonyl, cyano, or hydroxy, and R^c is selected from alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclylalkyl, and

aminocarbonyl.

32. The compound of any one of claims 28 to 30, or a pharmaceutically acceptable salt thereof wherein Ar^1 is substituted with R^b and/or R^c wherein R^b is hydrogen, methyl, fluoro, cyano, methylsulfonyl, or methylcarbonyl and R^c is hydrogen, methyl, ethyl, fluoro,

difluoromethyl, trifluoromethyl, trifluoroethyl, methoxy, ethoxy, difluoromethoxy,

trifluoromethoxy, trifluoroethoxy, hydroxy, 2-hydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2- morpholin-l-yl ethyl, -CONH2, methylaminocarbonyl, or dimethylaminocarbonyl.

33. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof wherein Ar^1 is spiroheterocyclyl substituted with R^a, R^b,

and/or R^c.

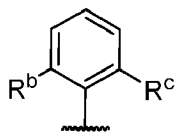
34. The compound of claim 33, or a pharmaceutically acceptable salt thereof wherein Ar^1 is 4-oxa-7-azaspiro[2.5]octan-7-yl substituted with R^a, R^b, and/or R^c.

35. The compound of claim 33 or 34, or a pharmaceutically acceptable salt thereof wherein Ar^1 is substituted with R^b and/or R^c wherein R^b is hydrogen, methyl, fluoro, cyano, methylsulfonyl, or methylcarbonyl and R^c is hydrogen, methyl, ethyl, fluoro, difluoromethyl, trifluoromethyl, trifluoroethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, hydroxy, 2-hydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2-morpholin-l-yl ethyl, -CONH2, methylaminocarbonyl, or dimethylaminocarbonyl.

36. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof wherein Ar^1 is phenyl substituted with R^a, R^b, and/or R^c.

37. The compound of claim 36, or a pharmaceutically acceptable salt thereof, wherein

Ar^1 is



38. The compound of claim 36 or claim 37, or a pharmaceutically acceptable salt thereof wherein R^a is hydrogen or alkyl, R^b is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, acyl, alkylsulfonyl, cyano, or hydroxy, and R^c is selected from alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclylalkyl, and aminocarbonyl.

39. The compound of any one of claims 36 to 38, or a pharmaceutically

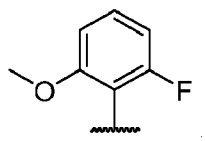
acceptable salt thereof wherein Ar^1 is substituted with R^b and/or R^c wherein R^b is hydrogen, methyl, fluoro, cyano, methylsulfonyl, or methylcarbonyl and R^c is hydrogen, methyl, ethyl, fluoro,

difluoromethyl, trifluoromethyl, trifluoroethyl, methoxy, ethoxy, difluoromethoxy,

trifluoromethoxy, trifluoroethoxy, hydroxy, 2-hydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2- morpholin-l-yl ethyl, -CONH2, methylaminocarbonyl, or dimethylaminocarbonyl.

40. The compound of claim 36, or a pharmaceutically acceptable salt thereof, wherein

Ar^1 is



41. The compound of claim 36, or a pharmaceutically acceptable salt thereof wherein Ar^1 is phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,4-dimethoxyphenyl, 2- chlorophenyl, 2-cyanophenyl, or 2-cyclopropyl -oxyphenyl.

42. The compound of claim 36, or a pharmaceutically acceptable salt thereof wherein Ar^1 is 2-methoxyphenyl.

43. The compound of claim 36, or a pharmaceutically acceptable salt thereof wherein Ar^1 is 3-methoxyphenyl.

44. The compound of claim 36, or a pharmaceutically acceptable salt thereof wherein Ar^1 is 2,4-dimethoxyphenyl.

45. The compound of any one of claims 1 to 19, or a pharmaceutically

acceptable salt thereof wherein Ar^1 is heteroaryl substituted with R^a, R^b, and/or R^c.

46. The compound of claim 45, or a pharmaceutically acceptable salt thereof wherein Ar^1 is benzo[c][l,2,5]thiadiazolyl, benzo[d]oxazolyl, liT-indazolyl, substituted with R^a, R^b, and/or R^c where R^a is hydrogen or alkyl, R^b is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, acyl, alkylsulfonyl, cyano, or hydroxy, and R^c is selected from hydrogen alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclylalkyl, and aminocarbonyl.

47. The compound of claim 45, or a pharmaceutically acceptable salt thereof wherein Ar^1 is pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, imidazolyl, or triazolyl substituted with R^a, R^b, and/or R^c where R^a is hydrogen or alkyl, R^b is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, acyl, alkylsulfonyl, cyano, or hydroxy, and R^c is selected from alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclylalkyl, and aminocarbonyl.

48. The compound of any one of claims 45 to 47, or a pharmaceutically acceptable salt thereof wherein Ar^1 is substituted with R^b and/or R^c wherein R^b is hydrogen, methyl, fluoro, cyano, methylsulfonyl, or methylcarbonyl and R^c is hydrogen, methyl, ethyl, fluoro,

difluoromethyl, trifluoromethyl, trifluoroethyl, methoxy, ethoxy, difluoromethoxy,

trifluoromethoxy, trifluoroethoxy, hydroxy, 2-hydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2- morpholin-l-yl ethyl, -CONH2, methylaminocarbonyl, or dimethylaminocarbonyl.

49. The compound of any one of claims 1 to 48, or a pharmaceutically acceptable salt thereof wherein Ar^2 is phenyl substituted with R^d, R^e and/or R^f.

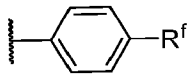
50. The compound of claim 49, or a pharmaceutically acceptable salt thereof

wherein R^d is hydrogen, R^e is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, or cyano and R^f is selected from hydrogen, alkyl, cycloalkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, cyanomethyl, aminocarbonylmethyl, heteroaryl, and heterocyclyl, wherein said heteroaryl and heterocyclyl of R^f are unsubstituted or substituted with one, two, or three substituents independently selected from alkyl, halo, haloalkyl, and hydroxy.

51. The compound of claim 49, or a pharmaceutically acceptable salt thereof wherein R^f is cycloalkyl optionally substituted with cyano.

52. The compound of claim 49, or a pharmaceutically acceptable salt thereof wherein Ar^2 is phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 2-chloro-4-fluorophenyl, 4- cyanophenyl, 4-bromophenyl, 4-oxetan— 3-ylphenyl, 4-chloro-3-methoxyphenyl, 4- cyclopropylphenyl, or 4-oxazol-2-ylphenyl.

53. The compound of any one of claims 49 to 51, or a pharmaceutically acceptable salt thereof wherein Ar^2 is



54. The compound of claim 49, or a pharmaceutically acceptable salt thereof wherein Ar^2 is 4-fluorophenyl.

55. The compound of claim 49, or a pharmaceutically acceptable salt thereof wherein Ar^2 is 4-chlorophenyl.

56. The compound of any one of claims 1 to 48, or a pharmaceutically acceptable salt thereof wherein Ar^2 is heteroaryl substituted with R^d, R^e and/or R^f.

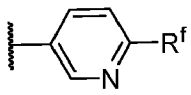
57. The compound of claim 56, or a pharmaceutically acceptable salt thereof

wherein R^d is hydrogen, R^e is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, or cyano and R^f is selected from hydrogen, alkyl, cycloalkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, cyanomethyl, aminocarbonylmethyl, heteroaryl, and heterocyclyl, wherein said heteroaryl and heterocyclyl of R^f are unsubstituted or substituted with one, two, or three substituents independently selected from alkyl, halo, haloalkyl, and hydroxy.

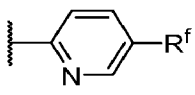
58. The compound of claim 56, or a pharmaceutically acceptable salt thereof wherein R^f is cycloalkyl optionally substituted with cyano.

59. The compound of any one of claims 56 to 58, or a pharmaceutically acceptable salt thereof wherein Ar^2 is heteroaryl selected from pyridinyl or pyrimidinyl.

60. The compound of any one of claims 56 to 58, or a pharmaceutically acceptable salt thereof wherein Ar^2 is



61. The compound of any oen of claims 56 to 58, or a pharmaceutically acceptable salt thereof wherein Ar^2 is



62. The compound of any one of claims 1 to 48, or a pharmaceutically acceptable salt thereof wherein Ar^2 is cycloalkyl.

63. The compound of any one of claims 1 to 62, or a pharmaceutically acceptable salt thereof wherein R^1 is hydrogen, cyano, -CONH2, methylaminocarbonyl, dimethylaminocarbonyl, imidazol-2-yl, methoxy, hydroxy,

bromo, carboxy, or fluoro.

64. The compound of any one of claims 1 to 62, or a pharmaceutically acceptable salt thereof wherein R^1 is hydroxyalkyl, alkoxyalkyl, aminoalkyl, aminocarbonylalkyl, sulfonylalkyl, aminosulfonylalkyl, optionally substituted heteroaralkyl, or optionally substituted

heterocyclyl alkyl.

65. The compound of any one of claims 1 to 64, or a pharmaceutically acceptable salt thereof wherein R^2 is hydrogen, cyano, or fluoro.

66. A pharmaceutical composition comprising a compound of any one of claims 1 to 64 and at least one pharmaceutically acceptable excipient.

67. A method for treating a disease characterized by overexpression of Roťq in a patient comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1 to 64 or a pharmaceutical composition of claim 66.

68. The method of claim 67, wherein the patient is in recognized need of such treatment and the disease is a cancer.

69. A method of treating a homologous recombinant (HR) deficient cancer in a patient comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1 to 64 or a pharmaceutical composition of claim 66.

70. The method of claim 69, wherein the patient is in recognized need of such treatment.

71. A method for treating a cancer in a patient, wherein the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the

BRAC gene, or reduced function of BRCA protein, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 64 or a pharmaceutical composition of claim 44.

72. The method of any one of claims 67 to 71, wherein the cancer is lymphoma, soft tissue, rhabdoid, multiple myeloma, uterus, gastric, peripheral nervous system,

rhabdomyosarcoma, bone, colorectal, mesothelioma, breast, ovarian, lung, fibroblast, central nervous system, urinary tract, upper aerodigestive, leukemia, kidney, skin, esophagus, and pancreas.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2021/124155

A. CLASSIFICATION OF SUBJECT MATTER

C07D 285/02(2006.01)i; C07D 285/04(2006.01)i; C07D 417/12(2006.01)i; A61K 31/433(2006.01)i; A61P 35/00(2006.01)i

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)

C07D; A61K; A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DWPI, SIPOABS, WOTXT, EPTXT, USTXT, CNTXT, CATXT, GBTXT, JPTXT, KRABS, CNABS, CNKI,STNext,ISI Web of Science: thiadiazole, polymerase, inhibitor, DNA, BEIJING DANATLAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008104524 A1 (SMITHKLINE BEECHAM CORPORATION) 04 September 2008 (2008-09-04) the abstract; claims 1, 17; example 74	1-72
X	WO 2013074059 A2 (REGENTS OF THE UNIVERSITY OF MINNESOTA) 23 May 2013 (2013-05-23) the abstract; claim 20	1-66
X	WO 2010086551 A1 (SANOFI-AVENTIS) 05 August 2010 (2010-08-05) claims 1-18	1-66
X	AN,Yue et al. "Synthesis and auxin activities of amides with substituted-1H-pyrazole-5-formic acid and substituted thiadiazole-2-ammonia." *Yingyong Huaxue*, Vol. 27, No. 6, 31 December 2010 (2010-12-31), pages 646-650	1-66
X	AN, Yue et al. "Synthesis and biological activity of N-(5-substituted - 1, 3, 4-thiadiazol-2-yl)-1, 4-disubstituted- 3-phenyl- 1H-pyrazole amides." *Youji Huaxue*, Vol. 30, No. 11, 31 December 2010 (2010-12-31), pages 1726-1731	1-66

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" 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)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" 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
"X" 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
"Y" 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	Date of mailing of the international search report
28 June 2022	**19 July 2022**
Name and mailing address of the ISA/CN **National Intellectual Property Administration, PRC** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing** **100088, China** Facsimile No. **(86-10)62019451**	Authorized officer **CUI,Yiwen** Telephone No. **(86-10)53961855**

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MOUGENOT, Patrick et al. "Thiadiazoles as new inhibitors of diacylglycerol acyltransferase type 1." *Bioorganic & medicinal chemistry letters.,* Vol. 22, No. 7, 14 February 2012 (2012-02-14), pages 2497-2502	1-66
X	WANG, Xicun et al. "A new route to 2-(5-aryl-2-furoylamido)-5 -aryloxymethyl-1, 3, 4-thiadiazoles." *Synthetic communications,* Vol. 32, No. 7, 21 August 2006 (2006-08-21), pages 1105-1111	1-66

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2021/124155

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **67-72**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 67-72 relate to methods of treating cancer. They do not meet the criteria set out in PCT Rules 39.1 (iv). The search has been made and based on the use of the compound or composition for the manufacturing of medicament for the treatment of diseases.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2021/124155

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