# Discovery of a potent dihydrooxadiazole series of non-ATP-competitive MK2 (MAPKAPK2) inhibitors

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## Experimental Procedures

**Analytical methods:** All reactions were carried out under nitrogen atmosphere in anhydrous conditions, unless otherwise noted. Solvents were purchased from Aldrich and Acros without further purification. Reagents and chemicals were purchased from commercial sources with purity ≥ 95% without further purification. Flash chromatography was carried out with EM Science silica gel 60 (neutral, 230-400 mesh). $^{1}$H NMR and $^{13}$C NMR were recorded on a Bruker Avance 500 NMR Spectrometer. LCMS analyses were performed on Applied Biosystem API-150. HRMS analyses were recorded on a Micromass QT of Ultima API US Mass Spectrometer by FAB.

**LC/MS conditions:** Agilent 6140 Quadrupole LC/MS System; Column Zorbax SB-C18, 3.0 x 50.0 mm, 1.8 micron; Mobile phase A: $H_2O$/0.05% TFA/0.5% acetic acid; Mobile phase B: acetonitrile/0.5% acetic acid; Flow: 1.0 ml/min; Gradient: 0 min 10% B, 1.5 min 95% B, 2.7 min 95% B, 2.8 min 10% B, Stop 3.6 min; Column temperature: 50 $^{o}$C.

**All of the biologic assays and experiments with animal models performed in Merck & CO., Inc were in accordance with all national or local guidelines and regulations.**

## MK2 IMAP ASSAY:

### Assay Reagents

5X Reaction Buffer T (Molecular Device, R7364)
10 mM ATP (New England, P0756S)
Substrate: TAMRA labeled Glycogen Synthase-derived Peptide (5TAMRA-KKLNRTLSVA-COOH, Molecular Device, R7277)
5X Progressive Binding Buffer A (Molecular Device, R7279)
Progressive Binding Reagent (Molecular Device, R7281)

All the components of MK2 phosphorylation reaction made as 4X concentrated in 1X Reaction Buffer T containing 10 mM Tris, pH7.2, 10 mM $MgCl_2$, 1 mM DTT (fresh

added), 0.05% azide and 0.01% Tween 20, and the reaction is carried in 384 well black reaction plate (Fisher, 09-761-85) at room temperature in dark.

### Reaction Setup

Mix 5 µl of 4X inhibitor in 4% DMSO, 5 µl of 400 µM ATP and 5 µl of 200 pM MK2 kinase and incubate for 30 min. Reaction is started by adding 5 ml of 400 nM TAMRA labeled peptide and incubating 30 min in dark. The final concentrations are: 1X inhibitor, 1% DMSO, 100 µM ATP, 50 pM MK2 and 100 nM substrate.

### Detection

Reaction is stopped by adding 60 µl of 1:400 diluted Progressive Binding Reagent in 1X Progressive Binding Buffer A and incubating 30 min in dark. Read plate at Analyst HT 96-384 Plate Reader (LJL BioSystem) equipped with Fluorescence Polarization module (Excitation wavelength 530 nm and Emission wavelength 580 nm).

## LPS Induced Phospho-HSP27 Serine78 Assay:

Cells: THP-1 (ATCC # TIB-202)
TNFα Detection: MesoScale(Phospho-HSP27 Serine78 ) - 384 Format

### Reagents and Materials

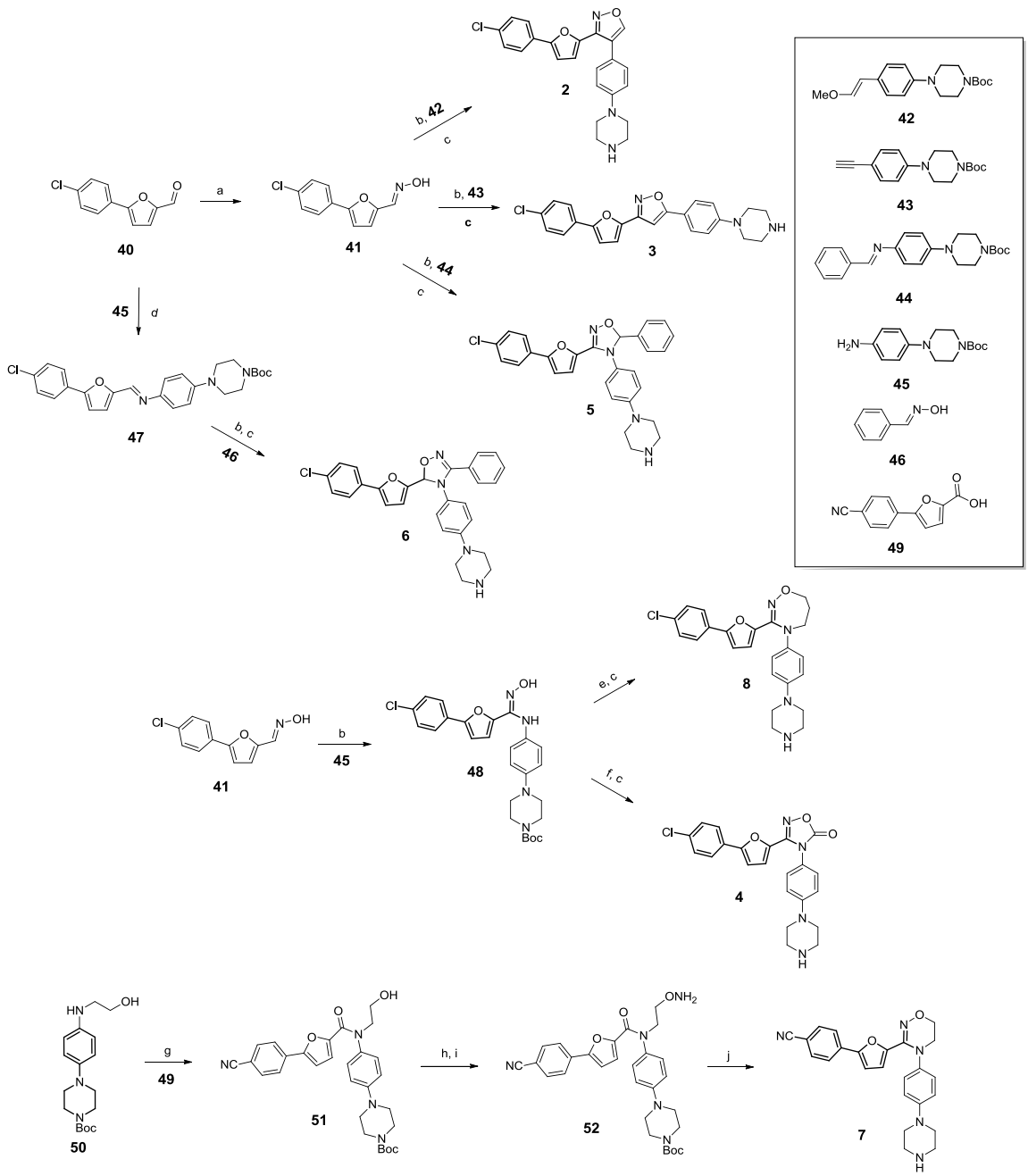
1. Complete RPMI-1640 medium
   2 mM L-glutamine
   1 mM Sodium Pyruvate
   4.5 g/L Glucose
   1.5 g/L Sodium Bicarbonate
   10 mM HEPES
   0.05 mM 2β-mercaptoethanol
   10% FBS
2. RPMI-1640 without FBS (Completed RPMI-1640 without FBS)
3. 10X Cell Lysis Buffer (Cell Signaling, Cat#9803)
4. Okadaic Acid Sigma, Cat#O7885, MW = 843, 1mg/ml = ~1.2mM
5. Halt Protease & Phosphotase Inhibitor Cocktail (100X) Thermo Scientific, Cat#1861282
6. MesoScale Phospho-HSP27 (Ser78) 384-well Plate Cat#N310FOB-1
7. Flat-bottom Microtest Tissue Culture Plate (96-well) Becton Dickinson, Cat#3075
8. Glass Fiber Filter Plate (96-well) Millipore, Cat#MSFBN6B50
9. 96-well Storage Plate BD Falcon, Cat#353263
10. LPS Sigma, Cat#L3129, 1mg/ml stored at -80 $^{o}$C

### LPS Induction and Cell Lysate Preparation

1. Bring the THP-1 cells to Log-phase by passing the cells at proper density a day previous to the assay (~ 1 x $10^5$ cells/ml)
2. Spin to collect cells and suspend in fresh complete-RPMI-1640 Medium at cell density of 2.5x$10^6$ cells/ml
3. Add equal volume of RPMI-1640 without FBS containing 40 nM Okadaic Acid (final: 100,000 cells/80 μl/well)
4. Plate 100,000 cells/80 μl into flat-bottom cell culture plate and incubate at 37 $^oC$ for 60 min
5. Add 10 μl of 10X diluted-compound in 1% DMSO in 5% FBS-RPMI medium and incubate at 37 $^oC$ for 60 min
6. Add 10 μl of 10X LPS in 5% FBS-RPMI medium and incubate at 37 $^oC$ for 60 min
7. Add 25 μl 5X Cell Lysis Buffer containing 5X Halt Inhibitors and incubate on ice for 30 min
8. Transfer cell lysate to glass fiber filter plate and stack the filter plate on top of a 96-well storage plate
9. Spin stacked filter-storage plate at 3,500 rpm for 5 min at 4 $^oC$

MesoScale pHSP27 S78 Assay: 10 ~ 20 μl cell lysate was used in this assay. Follow the manufacturer's instructions.

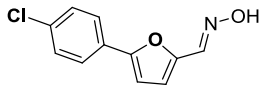
## General procedure for the preparation of analogues:




Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, Py; (b) NCS, 60 $^oC \rightarrow$rt, $Et_3N$, DMF; (c) TFA/$CH_2Cl_2$; (d) *p*-TsOH, $CH_2Cl_2$; (e) $Br(CH_2)_3Br$, $Cs_2CO_3$, DMF; (f) CDI, $Cs_2CO_3$, DMF; (g) EDC, DMAP, DMF; (h) $Bu_3P$, ADDP, *N*-hydroxyphthalimide, THF, 80 $^oC$; (i) $NH_2NH_2{\cdot}xH_2O$, $CH_2Cl_2$/MeOH; (j) $H_3PO_4$, microwave, 120 $^oC$.

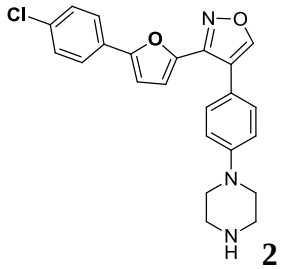
Compound **40** was converted to oxime ether **41** by condensing with $NH_2OH$ in pyridine. After **41** was treated with NCS to form imidoyl chloride, a subsequent [3+2] cycloaddition with enol ether **42**, alkyne **43** or imine **44,** followed by removal of the Boc group delivered analogues **2**, **3** or **5** respectively. In a similar fashion, a [3+2] cycloaddition between oxime ether **46** and imine **47** provided compound **6** after deprotection of the Boc group. Reaction of hydroxyamidine **48** with 1,3-dibromopropane

in the presence of base through consecutive inter- and intramolecular alkylation provided **8** after removal of protection group. Compound **4** was also prepared in a similar method to **8** using CDI. The synthesis of **7** started from coupling of **49** with **50** to give tertiary amide **51**. A subsequent two step transformation converted **51** to hydroxylamine intermediate **52**, which eventually led to the formation of dihydrooxadiazine compound **7** through a one pot cyclization and deprotection.



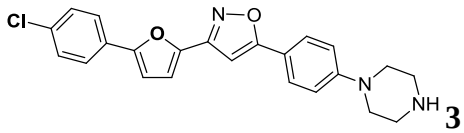

**41**

To a solution of compound **40** (15.0 g, 72.8 mmol) in pyridine (100 ml) was added $NH_2OH{\cdot}HCl$ (7.5 g, 109.2 mmol) and the mixture was stirred at room temperature overnight. It was then concentrated to remove the pyridine. The residue was dissolved in $CH_2Cl_2$, washed with $H_2O$, brine, dried with $Na_2SO_4$ and filtered. The filtrate was concentrated and the product was formed as solid during the concentration process. It was then collected by filtration and dried by vacuum to give **41** as white solid (13.0 g, 81%).




**2**

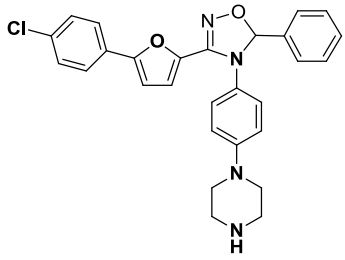
To a solution of **41** (300 mg, 1.36 mmol) in DMF (10 ml) was added NCS (200 mg, 1.5 mmol) and was heated at 60 $^oC$ for 1 h. Then **42** (319 mg, 1.0 mmol) and $Et_3N$ (227 µl, 1.63 mmol) were added to the mixture and was heated at 70 $^oC$ for 2 d. The mixture was diluted with EtOAc, washed with $H_2O$, brine, dried with $Na_2SO_4$ and filtered. The filtrate was concentrated and purified by flash chromatography (EtOAc/Hex) to provide product 70 mg, which was then dissolved in $TFA/CH_2Cl_2$ (10/10 ml) and was stirred for 2 h. The solvent was removed and the residue was purified by HPLC to give the product **2** as colorless oil (43 mg, 11% for two steps).




**3**

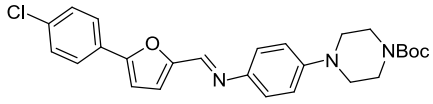
To a solution of **41** (442 mg, 2.0 mmol) in DMF (15 ml) was added NCS (295 mg, 2.2 mmol) and was heated at 60 $^oC$ for 1 h. The mixture was cooled and then compound **43** (430 mg, 1.5 mmol) and $Et_3N$ (417 µl, 3.0 mmol) were added and was stirred at room temperature overnight. It was then diluted with EtOAc, washed with $H_2O$, brine, dried with $Na_2SO_4$ and filtered. The filtrate was concentrated and purified by flash chromatography (EtOAc/Hex) to provide product 200 mg, which was dissolved in

TFA/$CH_2Cl_2$ (10/10 ml) and was stirred for 2 h. The solvent was removed and the residue was purified by flash chromatography ($CH_2Cl_2$/MeOH) to give the product **3** as colorless oil (113 mg, 14% for two steps).



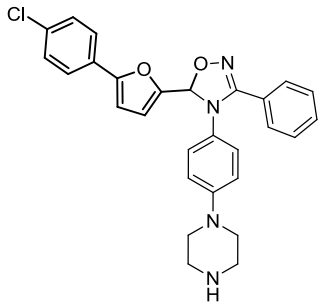
**5**

To a solution of **41** (1.50 g, 6.79 mmol) in DMF (15 ml) was added NCS (1.0 g, 7.46 mmol) and was heated at 60 $^oC$ for 1 h. The mixture was cooled and then compound **44** (2.06 g, 5.66 mmol) and $Et_3N$ (1.04 ml, 7.46 mmol) were added and was stirred at room temperature overnight. It was then diluted with EtOAc, washed with $H_2O$, brine, dried with $Na_2SO_4$ and filtered. The filtrate was concentrated and purified by flash chromatography (EtOAc/Hex) to provide 900 mg product as off-white solid, which was dissolved in TFA/$CH_2Cl_2$ (15/15 ml) and was stirred for 2 h. The solvent was removed and the residue was purified by flash chromatography ($CH_2Cl_2$/MeOH) to give the product **5** as yellowish solid (600 mg, 22% for two steps).



**47**

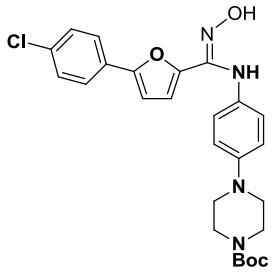
To a mixture of **40** (2.27 g, 11.0 mmol) and **45** (2.77 g, 11.0 mmol) in $CH_2Cl_2$ (20 ml) was added *p*-TsOH (300 mg) and was stirred at room temperature overnight. It was then diluted with $CH_2Cl_2$, washed with $H_2O$, brine, dried with $Na_2SO_4$ and filtered. The filtrate was concentrated and purified by flash chromatography (EtOAc/Hex, deactivated with $Et_3N$/Hex = 5/100) to provide product **47** as off-white solid (4.0 g, 86%).



**6**

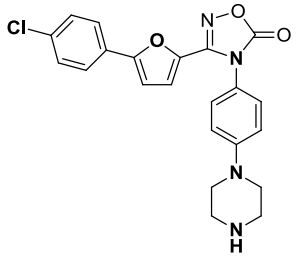
To a solution of **46** (800 mg, 6.61 mmol) in DMF (10 ml) was added NCS (974 mg, 7.27 mmol) and was heated at 60 $^oC$ for 1 h. The mixture was cooled and **47** (2.36 g, 5.08 mmol) and $Et_3N$ (1.01 ml, 7.27 mmol) were added and was stirred at room temperature overnight. It was then diluted with EtOAc, washed with $H_2O$, brine, dried with $Na_2SO_4$ and filtered. The filtrate was concentrated and purified by flash chromatography (EtOAc/Hex) to provide 260 mg product as off-white solid, which was dissolved in TFA/$CH_2Cl_2$ (5/5 ml) and was stirred for 2 h. Then the solvent was removed and the

residue was purified by flash chromatography ($CH_2Cl_2$/MeOH) to give the product **6** as off-white powder (30 mg, 1.2% for two steps).



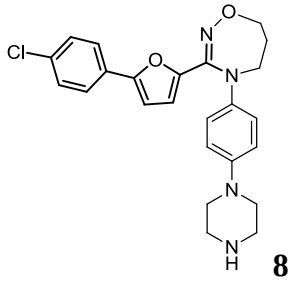

**48**

To a solution of **41** (5.0 g, 22.6 mmol) in DMF (30 ml) was added NCS (3.33 g, 24.9 mmol) and was heated at 60 $^oC$ for 1 h. The mixture was cooled and compound **45** (3.13 g, 11.3 mmol) and $Et_3N$ (3.77 ml, 27.1 mmol) were added and was stirred at room temperature overnight. It was then diluted with EtOAc, washed with $H_2O$, brine, dried with $Na_2SO_4$ and filtered. The filtrate was concentrated and purified by flash chromatography (EtOAc/Hex) to give product **48** as brownish solid (2.3 g, 41%)




**4**

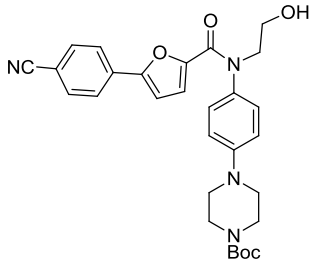
A mixture of **48** (300 mg, 0.60 mmol), CDI (107 mg, 0.66 mmol) and $Cs_2CO_3$ (430 mg, 1.32 mmol) in DMF (5 ml) was stirred at room temperature overnight. It was then diluted with EtOAc, washed with $H_2O$, brine, dried with $Na_2SO_4$ and filtered. The filtrate was concentrated and purified by flash chromatography (EtOAc/Hex) to give product 110 mg as off-white solid, which was then dissolved in TFA/$CH_2Cl_2$ (10/10 ml) and was stirred for 2 h. The solvent was removed and the residue was purified by flash chromatography ($CH_2Cl_2$/MeOH) to give the product **4** as yellowish solid (60 mg, 24% for two steps).




**8**

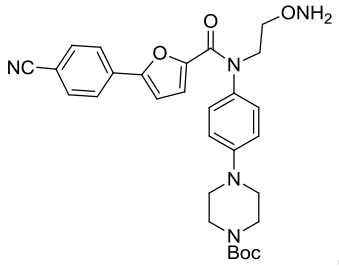
A mixture of **48** (250 mg, 0.50 mmol), $Br(CH_2)_3Br$ (110 mg, 0.55 mmol) and $Cs_2CO_3$ (359 mg, 1.10 mmol) in DMF (5 ml) was stirred at room temperature overnight. It was then diluted with EtOAc, washed with $H_2O$, brine, dried with $Na_2SO_4$ and filtered. The filtrate was concentrated and purified by flash chromatography (EtOAc/Hex) to give product 90 mg as yellowish oil, which was dissolved in TFA/$CH_2Cl_2$ (5/5 ml) and was stirred for 2 h. The solvent was removed and the residue was purified by flash

chromatography ($CH_2Cl_2$/MeOH) to give the product **8** as yellowish powder (60 mg, 28% for two steps).



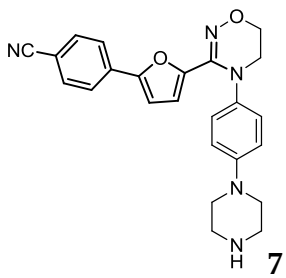

**51**

A mixture of compound **49** (0.33 g, 1.56 mmol), **50** (0.50 g, 1.56 mmol), EDC (0.60 g, 3.12 mmol) and DMAP (95.3 mg, 0.78 mmol) in DMF (8.0 ml) was stirred at room temperature overnight. It was then diluted with ethyl acetate and washed with aqueous $NH_4Cl$, water, brine and dried ($MgSO_4$). After filtration and solvent removal, the residue was purified with silica gel column (EtOAc/Hex) to give product **51** as colorless oil (155 mg, 19%).




**52**

A mixture of compound **51** (155 mg, 0.30 mmol), ADDP (109 mg, 0.45 mmol), $PBu_3$ (109 µl, 0.45 mmol) and *N*-hydroxyphthalimide (74 mg, 0.42 mmol) in THF (3.0 ml) was heated at 80 $^oC$ overnight. It was cooled and solid was filtered and washed with ether. The filtrate was diluted with ethyl acetate and washed with $NaHCO_3$, brine and dried ($MgSO_4$). After filtration and solvent removal, the residue was purified with silica gel column (EtOAc/Hex) to give product (124 mg, 78%), which was then dissolved in $CH_2Cl_2$/MeOH (1.5/1.5 ml) and $NH_2NH_2.xH_2O$ (23 µl, 0.47 mmol) was added to the solution. The mixture was stirred for 1 h at room temperature. It was diluted with ethyl acetate and washed with 0.5 N NaOH, sat. aqueous $NaHCO_3$, brine and dried ($MgSO_4$). After filtration and solvent removal, the residue was used in the next step without purification.

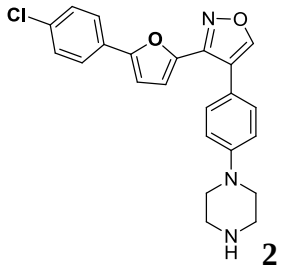



**7**

The product obtained from previous step was dissolved in EtOH (4.0 ml) followed with addition of $H_3PO_4$ (200 µl). The mixture was heated in a microwave reactor at 120 $^oC$ for 1.5 h. Then it was cooled and diluted with ethyl acetate and basified with 1 N NaOH until aqueous layer pH = 9. The aqueous layer was separated and extracted with ethyl acetate. The combined organic phases were washed with water, brine and dried ($MgSO_4$). After filtration and solvent removal, the residue was purified with preparative TLC plate (EtOAc/Hex) to give product **7** as white solid (24 mg, 19% for three steps).

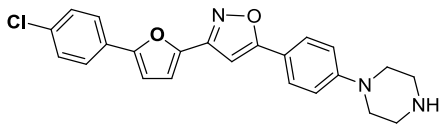
**Compound 33 was resolved to provide 38 and 39 by the following HPLC condition:** CHIRALCEL® OD preparative column, hexane : ethanol : $Et_2NH$ = 50 : 50 : 0.20 (v/v/v). Under this condition, enantiomer **38** had a shorter (92.90 minutes) retention time than enantiomer **39** (137.85 minutes). Both enantiomers have purity of >95% enantiomeric excess.

## $^1$H NMR and LCMS data:



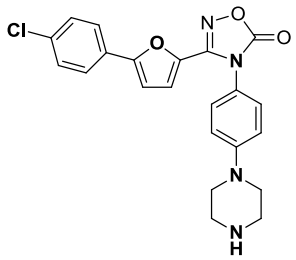
**2**

**3-(5-(4-chlorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)isoxazole:** $^1$H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1 H), 7.59 (d, J = 8.50 Hz, 2 H), 7.42-7.35 (m, 4 H), 7.04 (d, J = 9.00 Hz, 2 H), 6.74 (d, J = 3.50 Hz, 1 H), 6.71 (d, J = 3.50 Hz, 1 H), 3.34-3.28 (m, 4H), 3.19-3.14 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 406.2 (96% purity).



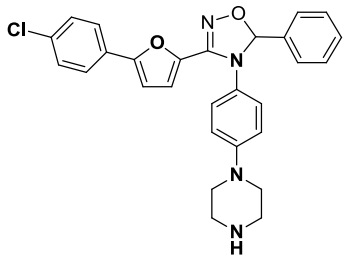
**3**

**3-(5-(4-chlorophenyl)furan-2-yl)-5-(4-(piperazin-1-yl)phenyl)isoxazole:** $^1$H NMR (500 MHz, $CDCl_3$) δ 7.83-7.73 (m, 4 H), 7.45 (d, J = 8.50 Hz, 2 H), 7.06 (d, J = 4.00 Hz, 1 H), 7.03 (d, J = 8.50 Hz, 2 H), 6.83 (d, J = 3.50 Hz, 1H), 6.74 (s, 1 H), 3.39-3.33 (m, 4H), 3.18-3.11 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 406.2 (95% purity).



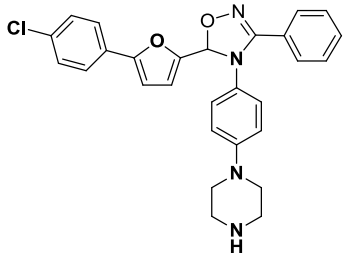
**4**

**3-(5-(4-chlorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)-1,2,4-oxadiazol-5(4H)-one:** $^1$H NMR (500 MHz, DMSO) δ 7.58 (d, J = 9.00 Hz, 2 H), 7.50 (d, J = 9.00 Hz, 2 H), 7.44 (d, J = 9.00 Hz, 2 H), 7.16 (d, J = 4.00 Hz, 1 H), 7.08 (d, J = 9.00 Hz, 2H), 6.52 (d, J = 4.00 Hz, 1 H), 3.22-3.14 (m, 4H), 2.89-2.83 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 423.2 (100% purity).



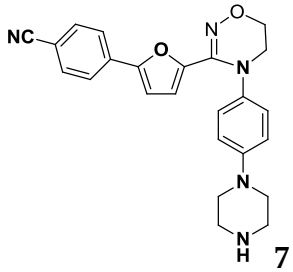
**5**

**3-(5-(4-chlorophenyl)furan-2-yl)-5-phenyl-4-(4-(piperazin-1-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CDCl_3$) δ 7.64-7.58 (m, 2 H), 7.52 (d, J = 8.50 Hz, 2 H), 7.49-7.44 (m, 3 H), 7.36 (d, J = 9.00 Hz, 2 H), 7.01 (d, J = 9.00 Hz, 2 H), 6.86 (d, J = 9.00 Hz, 2 H), 6.61 (d, J = 3.50 Hz, 1 H), 6.45 (s, 1H), 6.43 (d, J = 3.50 Hz, 1 H), 3.25-3.18 (m, 4H), 3.14-3.08 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 485.2 (95% purity).



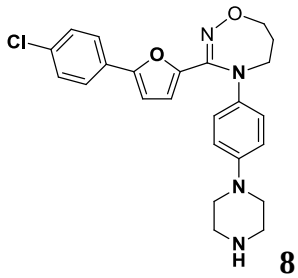
**6**

**5-(5-(4-chlorophenyl)furan-2-yl)-3-phenyl-4-(4-(piperazin-1-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CDCl_3$) δ 7.72-7.61 (m, 4 H), 7.48-7.34 (m, 5 H), 6.90 (d, J = 9.00 Hz, 2 H), 6.79 (d, J = 9.00 Hz, 2 H), 6.72 (d, J = 3.00 Hz, 1 H), 6.70 (d, J = 3.00 Hz, 1 H), 6.59 (s, 1 H), 3.21-3.15 (m, 4H), 3.12-3.05 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 485.2 (100% purity).



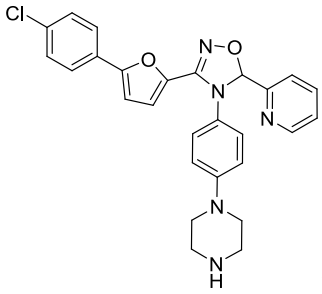
**7**

**4-(5-(4-(4-(piperazin-1-yl)phenyl)-5,6-dihydro-4H-1,2,4-oxadiazin-3-yl)furan-2-yl)benzonitrile:** $^1$H NMR (500 MHz, $CDCl_3$) 7.56 (d, J = 8.50 Hz, 2 H), 7.43 (d, J = 8.5 Hz, 2 H), 7.01 (d, J = 9.00 Hz, 2 H), 6.83 (d, J = 9.00 Hz, 2 H), 6.66 (d, J = 3.50 Hz, 1 H), 6.56 (d, J = 3.50 Hz, 1 H), 4.25 (t, J = 4.50 Hz, 2 H), 3.81 (t, J = 4.50 Hz, 2 H), 3.09-3.07 (m, 4 H), 3.04-3.02 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 414.2 (95% purity).



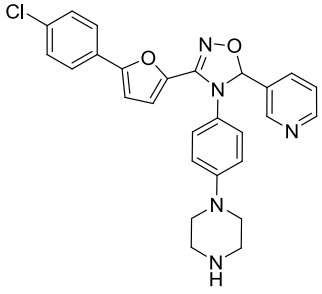
**8**

**3-(5-(4-chlorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)-4,5,6,7-tetrahydro-1,2,4-oxadiazepine:** $^1$H NMR (500 MHz, $CDCl_3$) δ 7.35-7.23 (m, 4 H), 6.88 (d, J = 9.00 Hz, 2 H), 6.75 (d, J = 9.00 Hz, 2 H), 6.66 (brs, 1 H), 6.61 (d, J = 3.50 Hz, 1 H), 4.07 (t, J = 7.00 Hz, 2 H), 3.86 (t, J = 7.50 Hz, 2 H), 3.19-3.08 (m, 8 H), 2.46-2.36 (m, 2 H) ppm; ES-LCMS $(M + H)^+$ = 437.2 (90% purity).



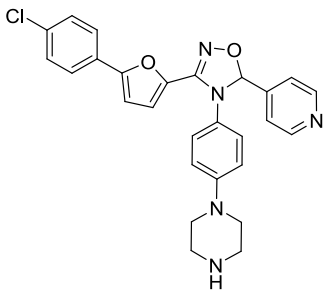
**9**

**3-(5-(4-chlorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)-5-(pyridin-2-yl)-4,5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CDCl_3$) 8.69-8.64 (m, 1 H), 7.89-7.82 (m, 2 H), 7.52 (d, J = 8.00 Hz, 2 H), 7.40-7.33 (m, 3 H), 7.10 (d, J = 8.50 Hz, 2 H), 6.87 (d, J = 9.00 Hz, 2 H), 6.62 (d, J = 3.50 Hz, 1 H), 6.58 (s, 1H), 6.48 (d, J = 4.00 Hz, 1 H), 3.32-3.23 (m, 4 H), 3.20-3.12 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 486.2 (99% purity).



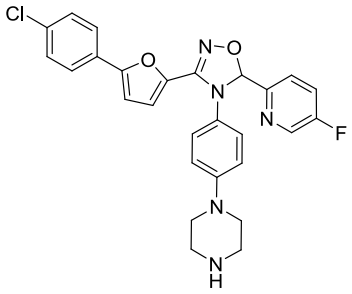
**10**

**3-(5-(4-chlorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)-5-(pyridin-3-yl)-4,5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CDCl_3$) 8.76-8.67 (m, 2 H), 8.03-7.98 (m, 1 H), 7.51 (d, J = 8.50 Hz, 2 H), 7.45-7.39 (m, 1 H), 7.35 (d, J = 8.50 Hz, 2 H), 7.03 (d, J = 9.00 Hz, 2 H), 6.87 (d, J = 9.00 Hz, 2 H), 6.62 (d, J = 3.50 Hz, 1 H), 6.49 (s, 1H), 6.43 (d, J = 3.50 Hz, 1 H), 3.34-3.27 (m, 4 H), 3.24-3.15 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 486.2 (99% purity).



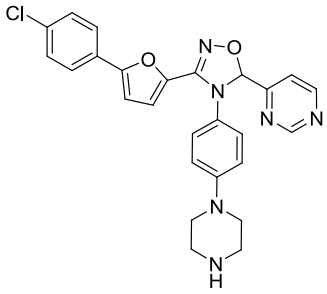
**11**

**3-(5-(4-chlorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)-5-(pyridin-4-yl)-4,5-dihydro-1,2,4-oxadiazole:** $^{1}$H NMR (500 MHz, $CDCl_3$) 9.05-8.56 (m, 2 H), 7.64-7.54 (m, 2 H), 7.51 (d, J = 8.50 Hz, 2 H), 7.35 (d, J = 8.50 Hz, 2 H), 7.06 (d, J = 8.50 Hz, 2 H), 6.89 (d, J = 8.50 Hz, 2 H), 6.63 (d, J = 4.00 Hz, 1 H), 6.48 (d, J = 3.50 Hz, 1 H), 6.43 (s, 1H), 3.49-3.41 (m, 4 H), 3.40-3.30 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 486.2 (99% purity).



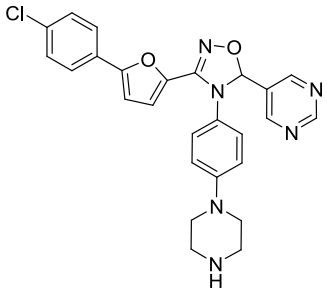
**12**

**3-(5-(4-chlorophenyl)furan-2-yl)-5-(5-fluoropyridin-2-yl)-4-(4-(piperazin-1-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** $^{1}$H NMR (500 MHz, $CDCl_3$) 8.55-8.48 (m, 1 H), 7.89-7.82 (m, 1 H), 7.61-7.54 (m, 1 H), 7.51 (d, J = 8.50 Hz, 2 H), 7.34 (d, J = 8.00 Hz, 2 H), 7.12 (d, J = 8.50 Hz, 2 H), 6.88 (d, J = 8.50 Hz, 2 H), 6.63 (d, J = 3.50 Hz, 1 H), 6.57 (s, 1H), 6.50 (d, J = 3.50 Hz, 1 H), 3.47-3.20 (m, 8 H) ppm; ES-LCMS $(M + H)^+$ = 504.2 (99% purity).



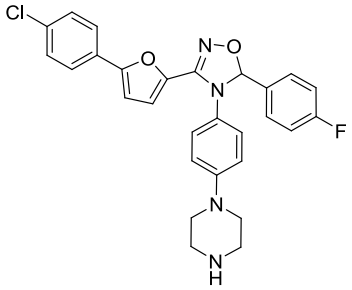
**13**

**3-(5-(4-chlorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)-5-(pyrimidin-4-yl)-4,5-dihydro-1,2,4-oxadiazole:** $^{1}$H NMR (500 MHz, $CDCl_3$) 9.50(s, 1 H), 9.12-8.76 (m, 1 H), 8.05-7.78 (m, 1 H), 7.52 (d, J = 8.00 Hz, 2 H), 7.34 (d, J = 8.00 Hz, 2 H), 7.23 (d, J = 8.00 Hz, 2 H), 6.91 (d, J = 7.50 Hz, 2 H), 6.69-6.59 (m,1 H), 6.58-6.50 (m, 1H), 6.46 (s, 1 H), 3.49-3.06 (m, 8 H) ppm; ES-LCMS $(M + H)^+$ = 487.3 (99% purity).



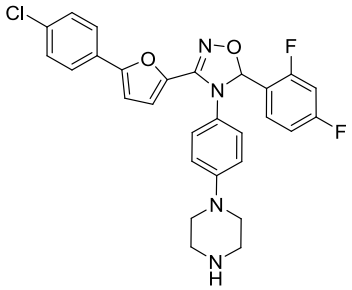
**14**

**3-(5-(4-chlorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)-5-(pyrimidin-5-yl)-4,5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CDCl_3$) 9.53 (s, 2 H), 9.05 (s, 1 H), 7.49 (d, J = 7.50 Hz, 2 H), 7.32 (d, J = 7.00 Hz, 2 H), 7.16-7.02 (m, 2 H), 6.97-6.82 (m, 2 H), 6.67-6.58 (m,1 H), 6.54 (s, 1H), 6.49-6.41 (m, 1 H), 3.72-3.08 (m, 8 H) ppm; ES-LCMS $(M + H)^+$ = 487.3 (99% purity).



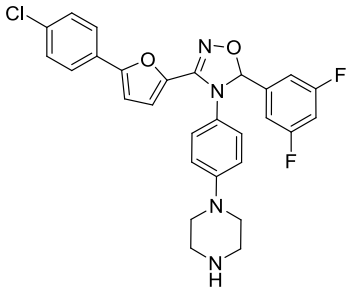
**15**

**3-(5-(4-chlorophenyl)furan-2-yl)-5-(4-fluorophenyl)-4-(4-(piperazin-1-yl)phenyl)-5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CDCl_3$) 7.63-7.53 (m, 2 H), 7.49 (d, J = 8.50 Hz, 2 H), 7.39-7.29 (m, 2 H), 7.16-7.09 (m, 2 H), 7.00 (d, J = 8.00Hz, 2 H), 6.92-6.80 (m, 2 H), 6.65-6.58 (m,1 H), 6.42 (s, 1 H), 6.41-6.39 (m, 1 H), 3.64-3.09 (m, 8 H) ppm; ES-LCMS $(M + H)^+$ = 503.2 (99% purity).



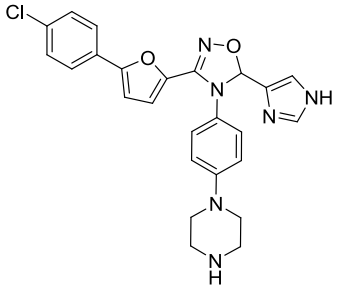
**16**

**3-(5-(4-chlorophenyl)furan-2-yl)-5-(2,4-difluorophenyl)-4-(4-(piperazin-1-l)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CDCl_3$) 7.80-7.72 (m, 1 H), 7.50 (d, J = 8.50 Hz, 2 H), 7.34 (d, J = 8.00Hz, 2 H), 7.06 (d, J = 8.50Hz, 2 H), 7.03-6.97 (m, 1 H), 6.90-6.84 (m, 3 H), 6.80 (s, 1 H), 6.63 (d, J = 3.50Hz, 1 H), 6.48 (d, J = 3.50Hz, 1 H), 3.64-3.05 (m, 8 H) ppm; ES-LCMS $(M + H)^+$ = 521.2 (99% purity).



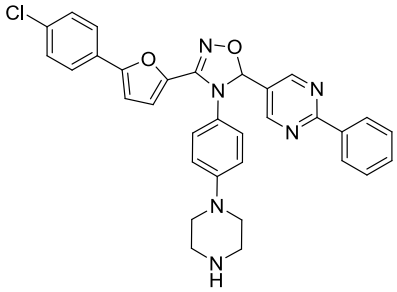
**17**

**3-(5-(4-chlorophenyl)furan-2-yl)-5-(3,5-difluorophenyl)-4-(4-(piperazin-1-l)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** $^{1}$H NMR (500 MHz, $CDCl_3$) 7.51 (d, J = 8.50 Hz, 2 H), 7.35 (d, J = 8.50Hz, 2 H), 7.18-7.11 (m, 2 H), 7.03 (d, J = 9.00 Hz, 2 H), 6.92-6.89 (m, 1 H),, 6.88 (d, J = 9.00Hz, 2 H), 6.61 (d, J = 3.50Hz, 1 H), 6.43 (d, J = 3.50Hz, 1 H), 6.39 (s, 1 H), 3.24-3.18 (m, 4 H), 3.13-3.05 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 521.2 (99% purity).



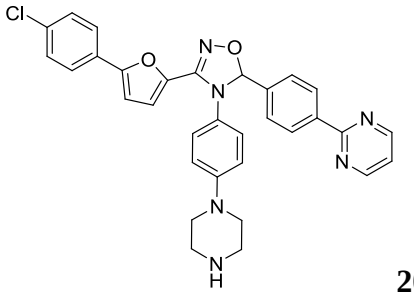
**18**

**3-(5-(4-chlorophenyl)furan-2-yl)-5-(1H-imidazol-4-yl)-4-(4-(piperazin-1-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** $^{1}$H NMR (500 MHz, $CDCl_3$) 7.79 (s, 1 H), 7.48 (d, J = 8.00 Hz, 2 H), 7.35-7.28 (m, 3 H), 7.09 (d, J = 8.50Hz, 2 H), 6.92 (d, J = 8.50 Hz, 2 H), 6.75 (d, J = 3.50Hz, 1 H), 6.56 (s, 1 H), 6.40 (d, J = 3.50Hz, 1 H), 3.28-3.07 (m, 8 H) ppm; ES-LCMS $(M + H)^+$ = 475.2 (99% purity).



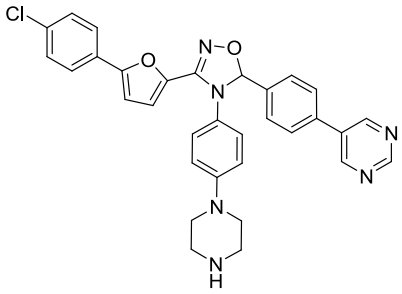
**19**

**3-(5-(4-chlorophenyl)furan-2-yl)-5-(2-phenylpyrimidin-5-yl)-4-(4-(piperazin-1-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** $^{1}$H NMR (500 MHz, $CDCl_3$) 8.97 (s, 2 H), 8.55-8.46 (m, 2 H), 7.57-7.52 (m, 3 H), 7.50 (d, J = 8.50Hz, 2H), 7.34 (d, J = 8.50 Hz, 2 H), 7.09 (d, J = 8.50 Hz, 2 H), 6.88 (d, J = 9.00Hz, 2 H), 6.62 (d, J = 3.50Hz, 1 H), 6.52 (s, 1 H), 6.45 (d, J = 3.50Hz, 1 H), 3.51-3.39 (m, 4 H), 3.38-3.25 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 563.2 (99% purity).



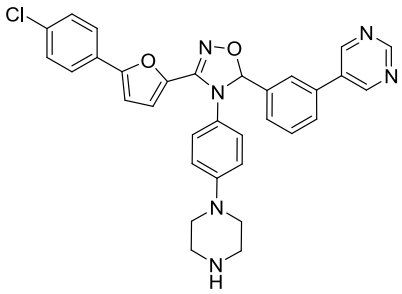
**20**

**3-(5-(4-chlorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)-5-(4-(pyrimidin-2-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** ES-LCMS $(M + H)^+$ = 563.2 (99% purity).



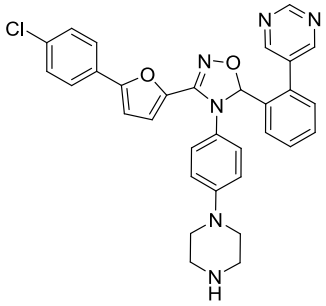
**21**

**3-(5-(4-chlorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)-5-(4-(pyrimidin-5-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CDCl_3$) 9.29 (s, 1 H), 9.06 (s, 2 H), 7.72 (d, J = 8Hz, 2H), 7.66 (d, J = 7.50 Hz, 2 H), 7.46 (d, J = 8.50 Hz, 2 H), 7.29 (d, J = 8.50Hz, 2 H), 7.04 (d, J = 8.50Hz, 2 H), 6.86 (d, J = 8.00 Hz, 2 H), 6.60 (d, J = 3.50Hz, 1 H), 6.49 (s, 1 H), 6.40 (d, J = 3.50Hz, 1 H), 3.51-3.23 (m, 8 H) ppm; ES-LCMS $(M + H)^+$ = 563.2 (99% purity).



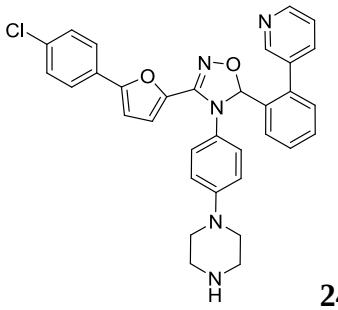
**22**

**3-(5-(4-chlorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)-5-(3-(pyrimidin-5-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CDCl_3$) 9.24 (s, 1 H), 8.98 (s, 2 H), 7.79-7.75 (m, 1 H), 7.71-7.65 (m, 2 H), 7.64-7.59 (m, 1 H), 7.49 (d, J = 8.50 Hz, 2 H), 7.33 (d, J = 8.50Hz, 2 H), 7.05 (d, J = 8.50Hz, 2 H), 6.87 (d, J = 9.00Hz, 2 H), 6.62 (d, J = 4.00 Hz, 1 H), 6.52 (s, 1 H), 6.45 (d, J = 3.50Hz, 1 H), 3.49-3.24 (m, 8 H) ppm; ES-LCMS $(M + H)^+$ = 563.3 (99% purity).



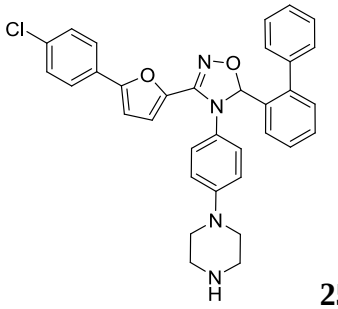
**23**

**3-(5-(4-chlorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)-5-(2-(pyrimidin-5-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CDCl_3$) 9.03 (s, 1 H), 8.59 (s, 2 H), 7.92-7.83 (m, 1 H), 7.63-7.51 (m, 2 H), 7.42 (d, J = 8.50 Hz, 2 H), 7.34-7.24 (m, 3 H), 6.84 (q, J = 7.50Hz, 4 H), 6.67 (d, J = 3.50 Hz, 1 H), 6.44 (s, 1 H), 6.29 (d, J = 4.00Hz, 1 H), 3.33 (p, J = 1.5 Hz, 1H), 3.15-3.03 (m, 4 H), 2.98-2.86 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 563.2 (99% purity).



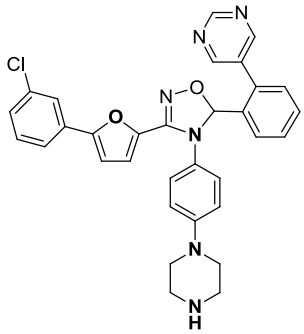
**24**

**3-(5-(4-chlorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)-5-(2-(pyridin-3-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CDCl_3$) 8.08-7.99 (m, 1 H), 7.92-7.81 (m, 1 H), 7.65-7.58 (m, 1 H), 7.57-7.51 (m, 2 H), 7.50-7.43 (m, 3 H), 7.37-7.25 (m, 4 H), 6.93-6.84 (m, 2 H), 6.83-6.74 (m, 2 H), 6.59 (s, 1 H), 6.44-6.30 (m, 2 H), 3.47-3.22 (m, 8 H) ppm; ES-LCMS $(M + H)^+$ = 562.2 (99% purity).



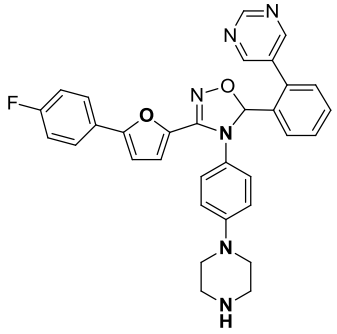
**25**

**5-(biphenyl-2-yl)-3-(5-(4-chlorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CDCl_3$) 8.12-8.00 (m, 1 H), 7.58-7.43 (m, 4 H), 7.39-7.27 (m, 6 H), 7.25-7.15 (m, 2 H), ), 6.88 (d, J = 8.50Hz, 2 H), 6.76 (d, J = 9.00Hz, 2 H), 6.59 (d, J = 3.50 Hz, 1 H), 6.50 (s, 1 H), 6.42 (d, J = 3.50Hz, 1 H), 3.49-3.12 (m, 8 H) ppm; ES-LCMS $(M + H)^+$ = 561.2 (99% purity).



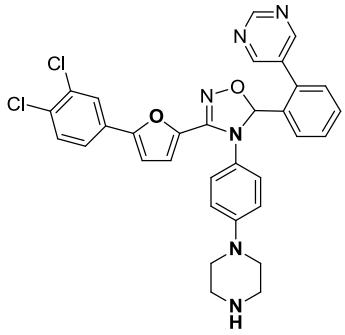
**26**

**3-(5-(3-chlorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)-5-(2-(pyrimidin-5-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CDCl_3$) δ 9.20 (s, 1 H), 8.63 (s, 2 H), 8.09 (d, J = 8.00 Hz, 1 H), 7.66 (t, J = 6.50 Hz, 1 H), 7.58 (t, J = 6.50 Hz, 1 H), 7.48-7.40 (m, 2 H), 7.34-7.25 (m, 3 H), 6.92 (d, J = 9.00 Hz, 2 H), 6.83 (d, J = 9.00 Hz, 2 H), 6.64 (d, J = 3.5 Hz, 1 H), 6.48 (d, J = 3.5 Hz, 1 H), 6.42 (s, 1 H), 3.25-3.17 (m, 4 H), 3.12-3.05 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 562.7 (95% purity).



**27**

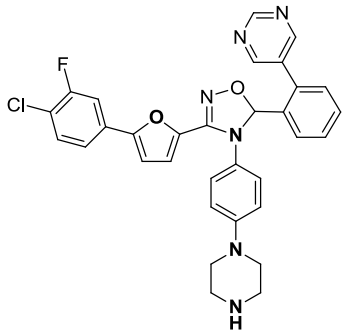
**3-(5-(4-fluorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)-5-(2-(pyrimidin-5-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CDCl_3$) δ 9.19 (s, 1 H), 8.62 (s, 2 H), 8.07 (d, J = 8.00 Hz, 1 H), 7.69-7.49 (m, 4 H), 7.29 (d, J = 6.00 Hz, 1 H), 7.07 (t, J = 9.00 Hz, 2H), 6.91 (d, J = 9.00 Hz, 2 H), 6.82 (d, J = 9.00 Hz, 2 H), 6.54 (d, J = 3.5 Hz, 1 H), 6.40 (s, 1 H), 6.38 (d, J = 3.5 Hz, 1 H), 3.29-3.18 (m, 4 H), 3.16-3.06 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 547.1 (99% purity).



**28**

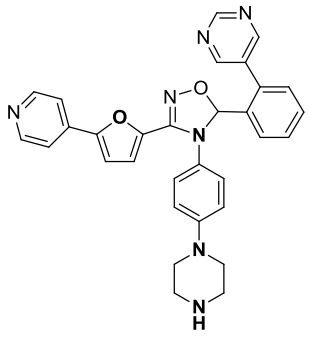
**3-(5-(3,4-dichlorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)-5-(2-(pyrimidin-5-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CDCl_3$) δ 9.18 (s, 1 H), 8.65 (s, 2 H), 7.98 (d, J = 8.00 Hz, 1 H), 7.65 (t, J = 7.00 Hz, 1 H), 7.59 (t, J = 7.00 Hz, 1 H), 7.46 (s, 1H), 7.42 (d, J = 8.50 Hz, 1 H), 7.35 (d, J = 8.50 Hz, 1 H), 7.28 (d, J = 8.50 Hz, 1 H), 6.90 (d, J = 9.00 Hz, 2 H), 6.82 (d, J = 9.00 Hz, 2 H), 6.62 (d, J = 3.50 Hz, 1 H),

6.47 (d, J = 3.50 Hz, 1 H), 6.38 (s, 1 H), 3.29-3.18 (m, 4 H), 3.16-3.06 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 596.7 (99% purity).



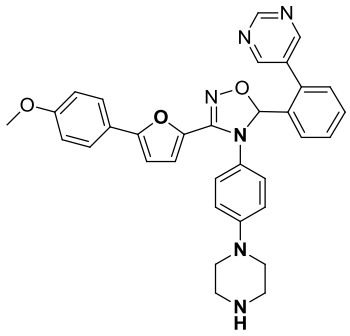
**29**

**3-(5-(4-chloro-3-fluorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)-5-(2-(pyrimidin-5-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CDCl_3$) δ 9.19 (s, 1 H), 8.68 (s, 2 H), 7.98 (d, J = 8.00 Hz, 1 H), 7.65 (t, J = 7.00 Hz, 1 H), 7.59 (t, J = 7.00 Hz, 1 H), 7.36 (t, J = 7.50 Hz, 1 H), 7.31-7.22 (m, 2 H), 7.09 (d, J = 10.00 Hz, 1 H), 6.91 (d, J = 9.00 Hz, 2 H), 6.83 (d, J = 9.00 Hz, 2 H), 6.62 (d, J = 3.50 Hz, 1 H), 6.49 (d, J = 3.50 Hz, 1 H), 6.38 (s, 1 H), 3.49-3.28 (m, 8 H) ppm; ES-LCMS $(M + H)^+$ = 580.7 (99% purity).



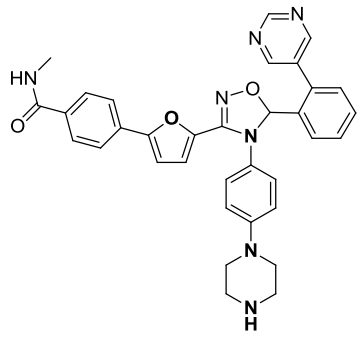
**30**

**4-(4-(piperazin-1-yl)phenyl)-3-(5-(pyridin-4-yl)furan-2-yl)-5-(2-(pyrimidin-5-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CD_3OD$) δ 9.04 (s, 1 H), 8.77 (d, J = 7.0 Hz, 2 H), 8.65 (s, 2 H), 8.08 (d, J = 6.50 Hz, 2H), 7.92-7.86 (m, 1 H), 7.71-7.61 (m, 2 H), 7.55 (d, J = 4.00 Hz, 1 H), 7.44-7.38 (m, 1 H), 6.99 (s, 4 H), 6.55 (s, 1 H), 6.53 (d, J = 4.00 Hz, 1 H), 3.47-3.40 (m, 4 H), 3.39-3.35 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 529.8 (99% purity).



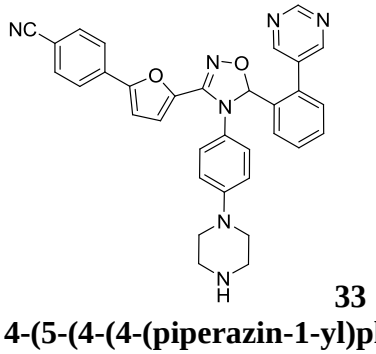
**31**

**3-(5-(4-methoxyphenyl)furan-2-yl)-4-(4-(piperazin-1-yl)phenyl)-5-(2-(pyrimidin-5-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CDCl_3$) δ 9.20 (s, 1 H), 8.63 (s, 2 H), 8.10 (d, J = 8.00 Hz, 1H), 7.65 (t, J = 7.00 Hz, 1 H), 7.58 (t, J = 7.50 Hz, 1 H), 7.51 (d, J = 9.00 Hz, 2 H), 7.28 (d, J = 9.00 Hz, 1 H), 6.95-6.88 (m, 4 H), 6.83 (d, J = 9.00 Hz, 2 H), 6.48 (d, J = 4.00 Hz, 1 H), 6.40 (s, 1 H),6.35 (d, J = 4.00 Hz, 1 H), 3.87 (s, 3 H), 3.22-3.15 (m, 4 H), 3.10-3.03 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 558.9 (99% purity).



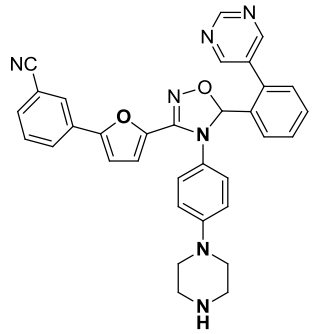
**32**

**N-methyl-4-(5-(4-(4-(piperazin-1-yl)phenyl)-5-(2-(pyrimidin-5-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazol-3-yl)furan-2-yl)benzamide:** $^1$H NMR (500 MHz, $CDCl_3$) δ 9.20 (s, 1 H), 8.63 (s, 2 H), 8.10 (d, J = 8.00 Hz, 1H), 7.78 (d, J = 8.50 Hz, 2 H), 7.66 (t, J = 7.50 Hz, 1 H), 7.62-7.54 (m, 3 H), 7.28 (d, J = 7.50 Hz, 1 H), 6.92 (d, J = 9.00 Hz, 2 H), 6.83 (d, J = 9.00 Hz, 2 H), 6.71 (d, J = 4.00 Hz, 1 H), 6.51-6.45 (m, 2 H), 6.42 (s, 1 H), 3.28-3.18 (m, 4 H), 3.13-3.08 (m, 4 H), 3.05 (d, J = 5.00 Hz, 3 H) ppm; ES-LCMS $(M + H)^+$ = 585.8 (99% purity).



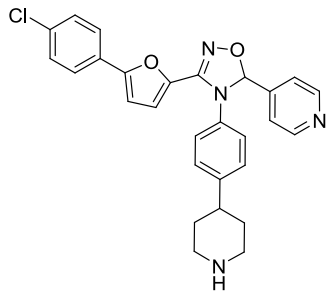
**33**

**4-(5-(4-(4-(piperazin-1-yl)phenyl)-5-(2-(pyrimidin-5-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazol-3-yl)furan-2-yl)benzonitrile:** $^1$H NMR (500 MHz, $CDCl_3$) 9.11 (s, 1 H), 8.57 (s, 2 H), 8.04-7.97 (m, 1 H), 7.60-7.53 (m, 6 H), 7.27-7.20 (m, 1 H), 6.87 (d, J = 9.00 Hz, 2 H), 6.78 (d, J = 9.00 Hz, 2 H), 6.72 (d, J = 3.50 Hz, 1 H), 6.39-6.36 (m, 2 H), 3.26-3.19 (m, 4 H), 3.12-3.05 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 554.2 (99% purity).



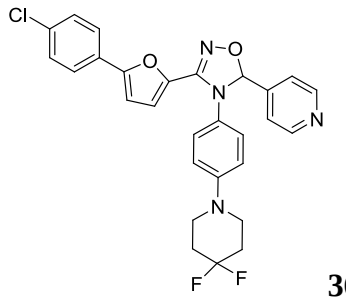
**34**

**3-(5-(4-(4-(piperazin-1-yl)phenyl)-5-(2-(pyrimidin-5-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazol-3-yl)furan-2-yl)benzonitrile:** $^1$H NMR (500 MHz, $CDCl_3$) δ 9.17 (s, 1 H), 8.63 (s, 2 H), 8.01 (d, J = 8.00 Hz, 1H), 7.71 (d, J = 8.00 Hz, 1 H), 7.65 (t, J = 8.00 Hz, 1 H), 7.58 (t, J = 8.00 Hz, 1 H), 7.52 (d, J = 8.00 Hz, 1 H), 7.49-7.41 (m, 2 H), 7.28 (d, J = 7.50 Hz, 1 H), 6.92 (d, J = 9.00 Hz, 2 H), 6.84 (d, J = 9.00 Hz, 2 H), 6.71 (d, J = 4.00 Hz, 1 H), 6.67 (d, J = 4.00 Hz, 1 H), 6.40 (s, 1 H), 3.49-3.40 (m, 4 H), 3.39-3.29 (m, 4 H), ppm; ES-LCMS $(M + H)^+$ = 553.8 (99% purity).



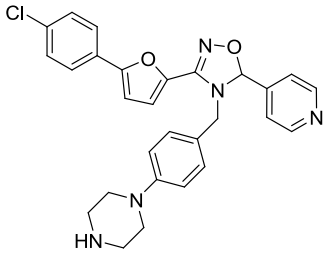
**35**

**3-(5-(4-chlorophenyl)furan-2-yl)-4-(4-(piperidin-4-yl)phenyl)-5-(pyridin-4-yl)-4,5-dihydro-1,2,4-oxadiazole:** $^1$H NMR (500 MHz, $CDCl_3$) 8.63 (d, J = 6.00 Hz, 2 H), 7.64 (d, J = 6.00 Hz, 2 H), 7.45 (d, J = 8.50 Hz, 2 H), 7.36-7.25 (m, 4 H), 7.13 (d, J = 8.50 Hz, 2 H), 6.81 (d, J = 4.00 Hz, 1 H), 6.65 (s, 1H), 6.63 (d, J = 3.50 Hz, 1 H), 3.60-3.42 (m, 2 H), 3.18-3.07 (m, 2 H), 2.96-2.87 (m, 1 H), 2.07-1.96 (m, 2 H), 1.95-1.82 (m, 2 H) ppm; ES-LCMS $(M + H)^+$ = 485.2 (99% purity).



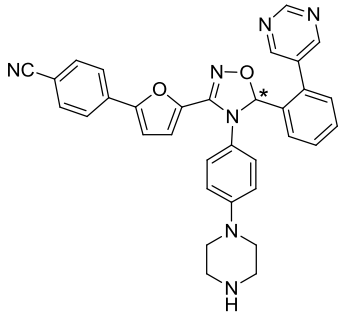
**36**

**3-(5-(4-chlorophenyl)furan-2-yl)-4-(4-(4,4-difluoropiperidin-1-yl)phenyl)-5-(pyridin-4-yl)-4,5-dihydro-1,2,4-oxadiazole: :** $^1$H NMR (500 MHz, $CDCl_3$) 8.71 (d, J = 5.50 Hz, 2 H), ), 7.53-7.46 (m, 4 H), 7.32 (d, J = 8.50 Hz, 2 H), 7.02 (d, J = 9.00 Hz, 2 H), 6.89 (d, J = 9.00 Hz, 2 H), 6.61 (d, J = 3.50 Hz, 1 H), 6.45 (d, J = 4.00 Hz, 1 H), 6.41 (s, 1H), 3.38 (t, J = 5.5Hz, 4 H), 2.15-2.05 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 521.2 (99% purity).



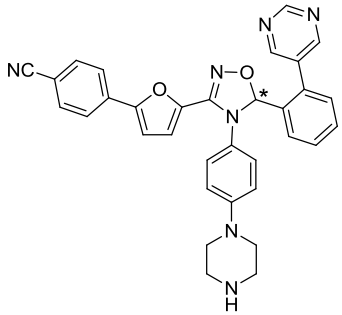
**37**

**3-(5-(4-chlorophenyl)furan-2-yl)-4-(4-(piperazin-1-yl)benzyl)-5-(pyridin-4-yl)-4,5-dihydro-1,2,4-oxadiazole:3-(5-(4-chlorophenyl)furan-2-yl)-4-(4-(piperidin-4-yl)phenyl)-5-(pyridin-4-yl)-4,5-dihydro-1,2,4-oxadiazole:** $^{1}$H NMR (500 MHz, $CDCl_3$) 8.50 (d, J = 5.00 Hz, 2 H), 7.71 (d, J = 8.00 Hz, 2 H), 7.41 (d, J = 8.50 Hz, 2 H), 7.22 (d, J = 3.50 Hz, 1 H), 7.19 (d, J = 5.50 Hz, 2 H), 7.06 (d, J = 8.50 Hz, 2 H), 6.84 (d, J = 3.00 Hz, 1 H), 6.74 (d, J = 8.00 Hz, 2 H), 6.58 (s, 1H), 4.75 (d, J = 15.00 Hz, 1 H), 4.61 (d, J = 15.00 Hz, 1 H), 3.43-3.10 (m, 8 H) ppm; ES-LCMS $(M + H)^+$ = 500.2 (99% purity).



**38**

**4-(5-(4-(4-(piperazin-1-yl)phenyl)-5-(2-(pyrimidin-5-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazol-3-yl)furan-2-yl)benzonitrile:** $^{1}$H NMR (500 MHz, $CDCl_3$) 9.11 (s, 1 H), 8.57 (s, 2 H), 8.04-7.97 (m, 1 H), 7.60-7.53 (m, 6 H), 7.27-7.20 (m, 1 H), 6.87 (d, J = 9.00 Hz, 2 H), 6.78 (d, J = 9.00 Hz, 2 H), 6.72 (d, J = 3.50 Hz, 1 H), 6.39-6.36 (m, 2 H), 3.26-3.19 (m, 4 H), 3.12-3.05 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 554.2 (>95% ee, 98% purity).



**39**

**4-(5-(4-(4-(piperazin-1-yl)phenyl)-5-(2-(pyrimidin-5-yl)phenyl)-4,5-dihydro-1,2,4-oxadiazol-3-yl)furan-2-yl)benzonitrile:** $^{1}$H NMR (500 MHz, $CDCl_3$) 9.11 (s, 1 H), 8.57 (s, 2 H), 8.04-7.97 (m, 1 H), 7.60-7.53 (m, 6 H), 7.27-7.20 (m, 1 H), 6.87 (d, J = 9.00 Hz, 2 H), 6.78 (d, J = 9.00 Hz, 2 H), 6.72 (d, J = 3.50 Hz, 1 H), 6.39-6.36 (m, 2 H), 3.26-3.19 (m, 4 H), 3.12-3.05 (m, 4 H) ppm; ES-LCMS $(M + H)^+$ = 554.2 (>95% ee, 98% purity).