

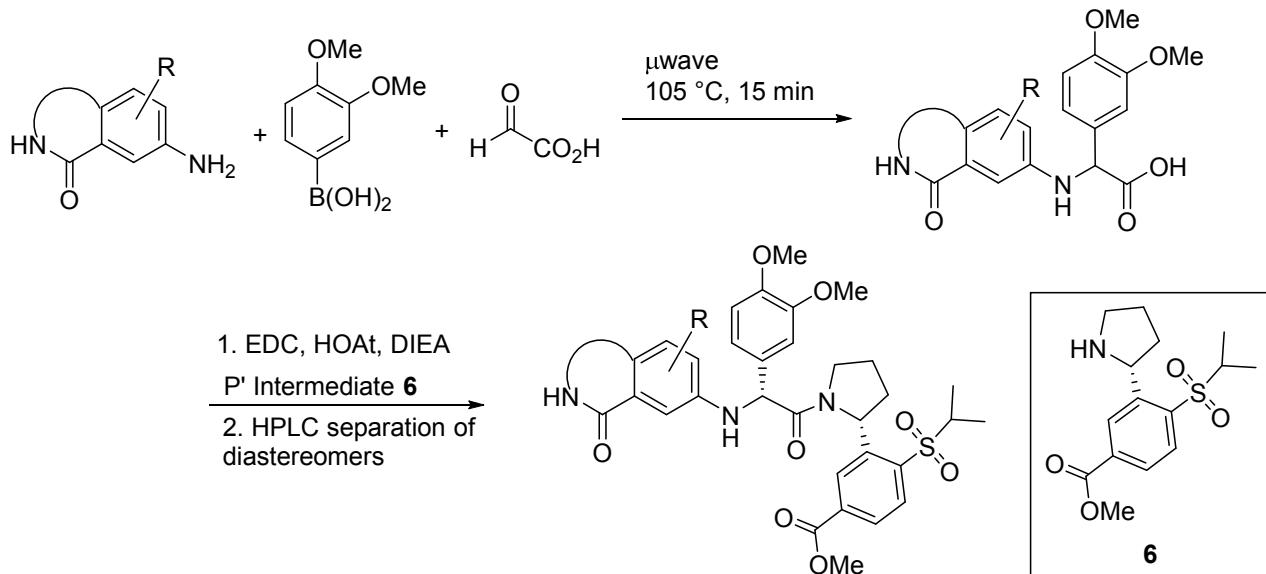
## Experimental Sections

**Biological Assays.** The FVIIa, FXa, FXIa, thrombin, trypsin, plasmin, plasma kallikrein, tissue kallikrein, TPA, urokinase and aPC enzyme assays and the FVIIa-deficient prothrombin assay were performed according to published protocols.<sup>5</sup> Ki values were averaged from two experiments. The intraassay and interassay variabilities are 5% and 20%, respectively.

**General Chemistry Methods.** Unless otherwise stated, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents were purchased from Aldrich or VWR and used directly. All reactions involving air- or moisture sensitive reagents were performed under a nitrogen or argon atmosphere. All microwave assisted reactions were conducted with a Biotage Synthesizer. Purification of intermediates and final products was carried out via either normal or reverse phase chromatography. Normal phase chromatography was carried out on an ISCO CombiFlash™ System using prepacked SiO<sub>2</sub> cartridges eluted with gradients of hexanes and ethyl acetate. All compounds for biological testing were purified by preparative HPLC, and the purity was analyzed with two orthogonal HPLC conditions: Injection 1: a linear gradient using solvent A (5% acetonitrile, 95% water, 0.05% TFA) and solvent B (95% acetonitrile, 5% water, 0.05% TFA); 10-100% of solvent B over 10 min and then 100% of solvent B over 5 min. Column: Sunfire C18 3.5  $\mu$ m (4.6 x 150 mm). Flow rate was 2 ml/min. and UV detection was set to 220 nm; Injection 2: a linear gradient using solvent A (5% acetonitrile, 95% water, 0.05% TFA) and solvent B (95% acetonitrile, 5% water, 0.05% TFA); 10-100% of solvent B over 10 min and then 100% of solvent B over 5 min. Column: Xbridge Phenyl 3.5  $\mu$ m (4.6 x 150 mm). Flow rate was 2 ml/min. and UV detection was set to 220 nm. The columns were maintained at room temperature. Reverse phase preparative HPLC was carried out using a Shimadzu Preparative HPLC system running DiscoveryVP software using with a Sunfire 5  $\mu$ m C18 30x100 mm column, a Phenomenex AXIA Luna 5  $\mu$ m C18 30 x 75 mm column, or a Phenomenex Luna 5  $\mu$ m C18 30 x 100 mm column with either methanol/water/0.1% TFA or acetonitrile/water/0.1%TFA as eluents. LCMS chromatograms were obtained on a Shimadzu HPLC system running DiscoveryVP

software, coupled with a Waters ZQ mass spectrometer running MassLynx version 3.5 software. All final compounds were purified to >95% purity, as determined by LC/MS. <sup>1</sup>H NMR spectra were determined with a Bruker or Joel 300 MHz spectrometer. Chemical shifts are reported in parts per million (ppm,  $\delta$  units).

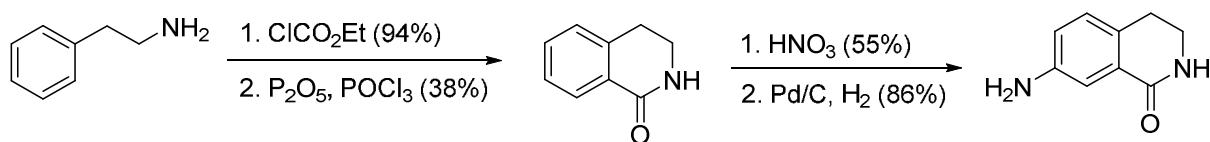
**Scheme 1.** General synthesis of phenylglycine lactams.



**General Petasis Procedure.** A solution of P1 aniline (2.0 mmol), 3,4-dimethoxyphenylboronic acid (370 mg, 2.0 mmol) and glyoxylic acid monohydrate (220 mg, 2.4 mmol) in acetonitrile/ DMF (4 mL, 4:1) was heated in a microwave reactor at 100 °C for 10 min. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (0% to 20% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to yield the desired phenylglycine.

**General Coupling Procedure.** A mixture of intermediate acid (1 eq), phenylpyrrolidine **6** (1.2- 1.8 eq), EDCI (1.5-2.5 eq), HOAt (0.4-1.0 eq), DIEA (0-5 eq) in CH<sub>2</sub>Cl<sub>2</sub> (0.1 M) or CH<sub>2</sub>Cl<sub>2</sub>/DMF (0.3 M, 10:1) was stirred at rt for 4 h to overnight. The reaction product was concentrated and purified *via* preparative HPLC (MeOH/H<sub>2</sub>O/TFA or CH<sub>3</sub>CN/H<sub>2</sub>O/TFA) to provide the desired amide. The coupling gave a mixture of two diastereoisomers which were separated by prep HPLC.

**Scheme 2.** 3,4-Dihydroisoquinolin-1(2H)-one synthesis.



**7-amino-3,4-dihydroisoquinolin-1(2H)-one.** Ethyl chloroformate (21 g, 0.19 mol) was added dropwise to a solution of phenethylamine (16 g, 0.13 mol) and triethylamine (180 mL) in diethyl ether (500 mL) while maintaining the internal temperature of the reaction below 10 °C. The reaction mixture was stirred two additional hours at ambient temperature and then filtered. The filtrate was concentrated *in vacuo* and the resulting oil was purified by flash chromatography (0-100% EtOAc in hexane) to yield ethyl phenethylcarbamate (23 g, 94%). MS (ESI) *m/z* 193.4 (M+H)<sup>+</sup>.

Ethyl phenethylcarbamate (4.0 g, 0.020 mol) was refluxed in a mixture of phosphorous pentoxide (5.0 g) and phosphorous oxychloride (25 mL) for 2 h. The reaction mixture was concentrated *in vacuo* to an oil, carefully quenched with wet ice followed by neutralization with sodium bicarbonate and extracted with diethyl ether. The combined organics were washed with water (2 x 50 mL), brine, dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-100% EtOAc in hexane) to yield 3,4-dihydroisoquinolin-1(2H)-one (1.1 g, 38%). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 2.97 (t, *J*=6.59 Hz, 2 H) 3.44 - 3.53 (t, *J*=6.52 Hz, 2 H) 7.26 - 7.30 (m, *J*=7.91 Hz, 1 H) 7.31 - 7.38 (m, 1 H) 7.43 - 7.52 (m, 1 H) 7.92 (dd, *J*=7.69, 1.10 Hz, 1 H)

3,4-Dihydroisoquinolin-1(2H)-one (1.1 g, 7.5 mmol) was added portionwise to a mixture of sulfuric acid (1 mL) and fuming nitric acid (5 mL) at 0 °C with stirring. The reaction was allowed to warm to ambient temperature and stirred for 2.5 h before pouring onto ice. The precipitate was collected by filtration and dried *in vacuo* to yield 7-nitro-3,4-dihydroisoquinolin-1(2H)-one (770 mg, 55% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 2.81 (t, *J*=6.59 Hz, 2 H) 3.42 (t *J*=6.52 Hz, 2 H) 6.84 (dd, *J*=8.13, 2.42 Hz, 1 H) 7.02 (d, *J*=7.91 Hz, 1 H) 7.26 (d, *J*=2.64 Hz, 1 H).

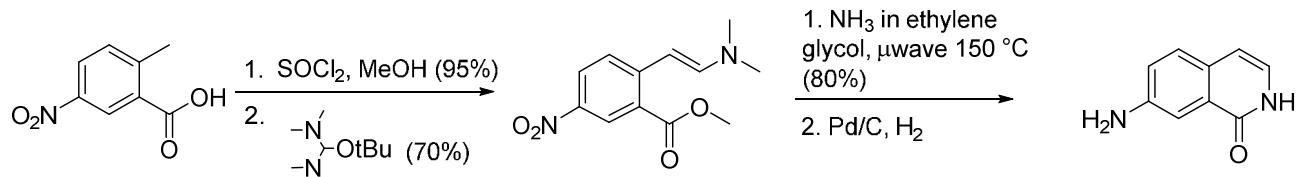
7-Nitro-3,4-dihydroisoquinolin-1(2H)-one (700 mg, 3.6 mmol) was stirred in MeOH (25 mL) with 10% Pd/C (cat.) under H<sub>2</sub> (60 psi) for 1 h. The reaction was filtered through Celite<sup>®</sup> and concentrated

in *vacuo* to give 7-amino-3,4-dihydroisoquinolin-1(2H)-one (500 mg, 86% yield). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 2.81 (t, *J*=6.59 Hz, 2 H) 3.42 (t, *J*=6.55 Hz, 2 H) 6.84 (dd, *J*=8.13, 2.42 Hz, 26 H) 7.02 (d, *J*=7.91 Hz, 1 H) 7.26 (d, *J*=2.64 Hz, 1 H).

**Methyl 3-((R)-1-((R)-2-(3,4-dimethoxyphenyl)-2-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-ylamino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (8).** The compound was synthesized using the general methods with 7-amino-3,4-dihydroisoquinolin-1(2H)-one. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 1.17 (d, *J*=6.59 Hz, 3 H) 1.42 (d, *J*=7.03 Hz, 3 H) 1.59 - 2.59 (m, 3 H) 2.87 (t, 2 H) 3.44 (t, *J*=6.59 Hz, 2 H) 3.65 (s, 3 H) 3.69 (s, 3 H) 3.83 (s, 3 H) 3.86 - 4.14 (m, 2 H) 5.40 (s, 1 H) 5.62 - 5.70 (m, *J*=8.35, 4.83 Hz, 1 H) 6.79 - 6.85 (m, 1 H) 6.88 - 6.91 (m, 2 H) 6.97 (dd, *J*=8.13, 2.42 Hz, 1 H) 7.06 - 7.11 (m, 1 H) 7.14 (d, *J*=8.35 Hz, 1 H) 7.23 (dd, *J*=8.79, 2.20 Hz, 1 H) 7.42 (d, *J*=2.64 Hz, 1 H) 7.74 (d, *J*=8.79 Hz, 1 H). MS Calcd. for [M+H]<sup>+</sup> : 665.3. Found: 665.7. HPLC Purity: 98%.

**Methyl (3-((S)-1-((S)-2-(3,4-dimethoxyphenyl)-2-((3-(methylcarbamoyl)phenyl)amino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenyl)carbamate (9).** The compound was synthesized using the general methods with 3-amino-N-methylbenzamide. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 1.17 (d, *J*=6.6 Hz, 3H), 1.42 (d, *J*=7.0 Hz, 3H), 1.78 - 1.63 (m, 1H), 2.18 - 1.98 (m, 2H), 2.56 - 2.41 (m, 1H), 2.89 (s, 3H), 3.66 (s, 3H), 3.69 - 3.67 (m, 1H), 3.70 (s, 3H), 3.83 (s, 3H), 3.96 (quin, *J*=6.8 Hz, 1H), 4.09 (dt, *J*=10.3, 6.7 Hz, 1H), 5.67 (dd, *J*=7.9, 4.8 Hz, 1H), 5.38 (s, 1H), 6.84 (d, *J*=1.8 Hz, 1H), 6.94 - 6.87 (m, 3H), 7.07 (s, 1H), 7.27 - 7.17 (m, 4H), 7.74 (d, *J*=8.8 Hz, 1H). MS Calcd. for [M+H]<sup>+</sup> : 653.3. Found: 653.3. HPLC Purity: 95%.

**Scheme 3.** Synthesis of substituted isoquinolin-1(2H)-ones.



**7-Aminoisoquinolin-1(2H)-one.** To 2-methyl-5-nitrobenzoic acid (2.7 g, 15 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) was added thionyl chloride (5.4 mL, 74 mmol) and DMF (0.5 mL). The mixture was stirred at 80 °C (oil bath) for 3.5 h. After it was cooled to rt, the solvent was removed and the residue was

azeotroped with toluene. The crude solid acyl chloride was dried *in vacuo* for 20 min. It was then dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and MeOH (10 mL) and stirred at rt for 30 min. Solvent was removed and the residue was diluted in EtOAc/hexanes, washed with sat. NaHCO<sub>3</sub>, brine, dried over Na<sub>2</sub>SO<sub>4</sub>. After evaporation of the solvent, 7-aminoisoquinolin-1(2*H*)-one (2.8 g) was obtained as a white solid and used in the next step without purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 2.70 (s, 3 H) 3.93 (s, 3 H) 7.42 (d, *J*=8.35 Hz, 1 H) 8.22 (dd, *J*=8.57, 2.42 Hz, 1 H) 8.76 (d, *J*=2.20 Hz, 1 H).

A mixture of 7-aminoisoquinolin-1(2*H*)-one (2.4 g, 12 mmol) and 1-*tert*-butoxy-*N,N,N',N'*-tetramethylmethanediamine (5.8 mL, 28 mmol) was heated at 115 °C (neat) for 3.5 h. After the mixture was cooled to rt, it was triturated with hexanes/EtOAc (6 : 1). After overnight standing at room temperature, the precipitate was collected by filtration to give solid (E)-methyl 2-(2-(dimethylamino)vinyl)-5-nitrobenzoate (2.7 g, 90% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 2.99 (s, 6 H) 3.89 (s, 3 H) 6.39 (d, *J*=13.18 Hz, 1 H) 7.17 (d, *J*=13.62 Hz, 1 H) 7.43 (d, *J*=9.23 Hz, 1 H) 8.03 (dd, *J*=9.23, 2.64 Hz, 1 H) 8.70 (d, *J*=2.64 Hz, 1 H).

To (E)-methyl 2-(2-(dimethylamino)vinyl)-5-nitrobenzoate (3.0 g, 12 mmol) in toluene (18 mL) was added (2,4-dimethoxyphenyl)methanamine (2.5 mL, 16 mmol). The mixture was stirred at 125 °C (oil bath) for 3.5 h. The color changed from deep red to yellow. After the mixture was cooled to rt, it was triturated with EtOAc/hexanes (1:2) and left standing overnight. The yellow precipitate was collected by filtration to give 2-(2,4-dimethoxybenzyl)-7-nitroisoquinolin-1(2*H*)-one (3.9 g, 96% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 3.79 (s, 3 H) 3.84 (s, 3 H) 5.13 (s, 2 H) 6.47 - 6.51 (m, 3 H) 7.39 - 7.48 (m, 2 H) 7.58 (d, *J*=8.79 Hz, 1 H) 8.37 (dd, *J*=8.79, 2.20 Hz, 1 H) 9.29 (d, *J*=2.64 Hz, 1 H).

2-(2,4-dimethoxybenzyl)-7-nitroisoquinolin-1(2*H*)-one (1.2 g, 3.5 mmol) in TFA (20.0 mL) was stirred at 85 °C for 2.5 h. After the mixture was cooled to rt, TFA was removed under vacuum. The crude was chased with methanol once and dried under high vacuum to give a deep purple solid. The solid was further triturated with EtOAc and collected by filtration to give 7-nitroisoquinolin-1(2*H*)-one (1.0 g, 100%) as TFA solvate. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 6.72 (d, *J*=7.03 Hz, 1 H) 7.42 -

7.48 (m, 1 H) 7.90 (d,  $J=8.79$  Hz, 1 H) 8.43 (dd,  $J=8.79, 2.64$  Hz, 1 H) 8.88 (d,  $J=2.20$  Hz, 1 H) 11.77 (s, 1 H).

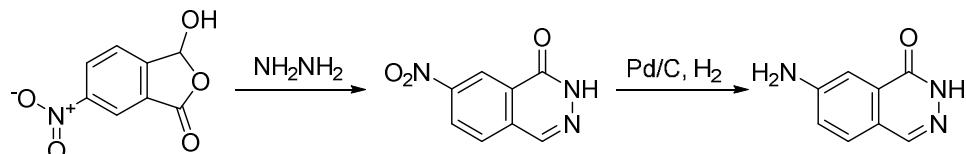
To 7-nitroisoquinolin-1(2*H*)-one (710 mg, 3.7 mmol) was added tetrahydrofuran (160 mL, stabilized with 25 ppm BHT) and water (0.95 mL). The solution was sonicated to near complete dissolution and 10% Pd/C (290 mg) was added. This solution was then hydrogenated with a hydrogen balloon for 50 min. Pd/C was removed by filtration and the filtrate was condensed to give slightly yellow solid 7-aminoisoquinolin-1(2*H*)-one (570 mg, 95% yield).  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm 5.47 (s, 2 H) 6.32 (d,  $J=7.15$  Hz, 1 H) 6.78 (d,  $J=4.95$  Hz, 1 H) 6.95 (dd,  $J=8.52, 2.47$  Hz, 1 H) 7.27 - 7.32 (m, 2 H) 10.81 (s, 1 H). Calcd. for [M+H]<sup>+</sup> : 161.1. Found: 161.0.

**Methyl 3-((R)-1-((R)-2-(3,4-dimethoxyphenyl)-2-(1-oxo-1,2-dihydroisoquinolin-7-ylamino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (10).** The compound was synthesized using the general methods with 7-aminoisoquinolin-1(2*H*)-one.  $^1\text{H}$  NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  ppm 1.13 (d,  $J=6.59$  Hz, 3 H) 1.38 (d,  $J=7.03$  Hz, 3 H) 1.63 - 1.78 (m, 1 H) 2.02 - 2.15 (m, 2 H) 2.44 - 2.58 (m, 1 H) 3.66 (s, 3 H) 3.69 (s, 3 H) 3.83 (s, 3 H) 3.85 - 4.02 (m, 2 H) 4.12 - 4.25 (m, 1 H) 5.41 (s, 1 H) 5.63 - 5.74 (m,  $J=7.91, 4.83$  Hz, 1 H) 6.56 (d,  $J=7.03$  Hz, 1 H) 6.87 - 6.92 (m, 2 H) 6.93 - 7.00 (m, 2 H) 7.02 - 7.07 (m, 1 H) 7.17 - 7.28 (m, 2 H) 7.40 - 7.47 (m, 2 H) 7.73 (d,  $J=8.35$  Hz, 1 H) 7.97 (s, 1 H) 9.37 (s, 1 H). MS Calcd. for [M+H]<sup>+</sup> : 663.2. Found: 663.3. HPLC Purity: 98%.

**Methyl 3-((R)-1-((R)-2-(3,4-dimethoxyphenyl)-2-(4-oxo-3,4-dihydroquinazolin-6-ylamino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (11).** The compound was synthesized using the general methods with 6-aminoquinazolin-4(3*H*)-one.  $^1\text{H}$  NMR (400 MHz, methanol-d<sub>4</sub>)  $\delta$  ppm 1.00 (t,  $J=6.81$  Hz, 3 H) 1.27 (t,  $J=6.81$  Hz, 3 H) 1.58 (dd,  $J=13.18, 5.27$  Hz, 1 H) 1.91 - 2.06 (m, 2 H) 2.37 (dd,  $J=13.18, 7.91$  Hz, 1 H) 3.55 (s, 3 H) 3.57 (s, 3 H) 3.60 - 3.64 (m, 1 H) 3.71 (s, 3 H) 3.75 - 3.84 (m, 1 H) 3.97 - 4.15 (m, 1 H) 5.28 (s, 1 H) 5.55 (dd,  $J=7.91, 4.83$  Hz, 1 H) 6.76 - 6.80 (m, 2 H) 6.86 - 6.91 (m, 2 H) 7.09 (dd,  $J=8.57, 1.98$  Hz, 1 H) 7.14 (d,  $J=2.64$  Hz, 1 H) 7.16 - 7.21

(m, 1 H) 7.33 (d,  $J=9.23$  Hz, 1 H) 7.60 (d,  $J=8.79$  Hz, 1 H) 8.34 (s, 1 H) 9.24 (s, 1 H). MS Calcd. for  $[M+H]^+$  : 663. Found: 663. HPLC Purity: 95%.

**Scheme 4.** Synthesis of 7-aminophthalazin-1(2H)-one.



**7-Aminophthalazin-1(2H)-one.** 3-Hydroxy-6-nitroisobenzofuran-1(3H)-one (500 mg, prepared as in *JOC* 50(21) 2140, 1985) was added slowly to a heated solution of hydrazine hydrate (500  $\mu$ L) in isopropanol (6 mL) at 90 °C. The solution was heated at 80 °C overnight. After cooling to rt, an orange precipitate was collected, washed with isopropanol and dried. A solution of the solid (200 mg) in MeOH was stirred under  $H_2$  (55 psi) for 7 h. The reaction mixture was filtered through Celite® and concentrated to yield 7-aminophthalazin-1(2H)-one (120 mg) as an off-white solid. Calcd. for  $[M+H]^+$  : 162.1. Found: 162.1.

**Methyl 3-((R)-1-((R)-2-(3,4-dimethoxyphenyl)-2-(4-oxo-3,4-dihydrophthalazin-6-ylamino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (12).** The compound was synthesized using the general methods with 7-aminophthalazin-1(2H)-one.  $^1H$  NMR (400 MHz,  $CD_3OD$ )  $\delta$  ppm 1.09 (t,  $J=7.25$  Hz, 3 H) 1.36 - 1.41 (m, 3 H) 2.40 (dd,  $J=12.52, 6.81$  Hz, 1 H) 2.86 (d,  $J=2.64$  Hz, 3 H) 2.99 (s, 1 H) 3.66 - 3.76 (m, 5 H) 3.77 - 3.82 (m, 5 H) 3.82 - 3.88 (m, 7 H) 5.43 - 5.47 (m, 1 H) 7.02 (d,  $J=8.35$  Hz, 1 H) 7.09 - 7.18 (m, 2 H) 7.29 (d,  $J=2.20$  Hz, 1 H) 7.45 - 7.49 (m, 1 H) 7.75 - 7.81 (m, 2 H) 8.06 - 8.12 (m, 1 H). MS Calcd. for  $[M+H]^+$  : 664.2.3. Found: 664.3. HPLC Purity: 95%.

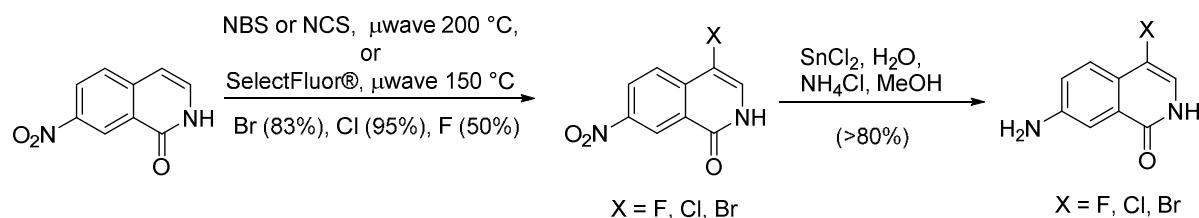
**Methyl 3-((R)-1-((R)-2-(3,4-dimethoxyphenyl)-2-(1,4-dioxo-1,2,3,4-tetrahydronaphthalazin-6-ylamino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (13).** The compound was synthesized using the general methods with 6-amino-2,3-dihydrophthalazine-1,4-dione.  $^1H$  NMR (400 MHz,  $CD_3OD$ )  $\delta$  ppm 1.06 (d,  $J=6.59$  Hz, 3 H) 1.36 (d,  $J=7.03$  Hz, 3 H) 1.72-1.83 (m, 1 H) 1.83 - 1.97 (m, 1 H) 2.10 - 2.23 (m, 1 H) 2.31 - 2.46 (m, 1 H) 3.62 - 3.78 (m, 2 H) 3.81 (s, 3 H) 3.85 (s, 3 H) 3.87

(s, 3 H) 4.24 – 4.35 (m, 1 H) 5.46 (s, 1 H) 5.58 (dd,  $J$ =8.13, 4.61 Hz, 1 H) 7.02 (d,  $J$ =8.35 Hz, 1 H) 7.12 (dd,  $J$ =8.13, 1.98 Hz, 2 H) 7.17 (d,  $J$ =2.20 Hz, 1 H) 7.22 (d,  $J$ =2.20 Hz, 1 H) 7.60 (s, 1 H) 7.69 (d,  $J$ =7.91, 2 H) 7.75 – 7.78 (m, 1 H). MS Calcd. for  $[M+H]^+$  : 680. Found: 680. HPLC Purity: 95%.

**Methyl 3-((R)-1-((R)-2-(3,4-dimethoxyphephenyl)-2-(3-oxoisooindolin-5-ylamino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (14).** The compound was synthesized using the general methods with 6-aminoisoindolin-1-one.  $^1$ H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  ppm 1.15 (d,  $J$ =6.57 Hz, 3 H) 1.40 (d,  $J$ =6.82 Hz, 3 H) 1.65 - 1.75 (m, 1 H) 2.01 - 2.15 (m, 2 H) 2.83 - 2.90 (m, 1 H) 3.66 (s, 3 H) 3.70 (s, 3 H) 3.83 (s, 3 H) 3.90 - 3.99 (m, 1 H) 4.14 (d,  $J$ =10.11 Hz, 1 H) 5.35 (s, 1 H) 5.61 - 5.71 (m,  $J$ =8.21, 4.93 Hz, 1 H) 6.86 (d,  $J$ =2.02 Hz, 1 H) 6.88 - 6.92 (m, 1 H) 6.93 - 6.97 (m, 1 H) 6.98 - 7.06 (m, 3 H) 7.23 (dd,  $J$ =8.72, 2.15 Hz, 1 H) 7.30 (d,  $J$ =8.34 Hz, 1 H) 7.73 (d,  $J$ =8.59 Hz, 1 H) 9.35 (s, 1 H). MS Calcd. for  $[M+H]^+$  : 651.2. Found: 651.4. HPLC Purity: 96%.

**Methyl 3-((R)-1-((R)-2-(3,4-dimethoxyphenyl)-2-(3-oxo-2,3-dihydro-1H-indazol-5-ylamino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate trifluoroacetate (15).** The compound was synthesized using the general methods with 5-amino-1,2-dihydro-3H-indazol-3-one.  $^1$ H NMR: (400 MHz, CD<sub>3</sub>OD)  $\delta$  ppm 1.21 (d,  $J$ =6.60 Hz, 3 H) 1.44 (d,  $J$ =6.60 Hz, 3 H) 1.67 - 1.78 (m, 1 H) 1.95 - 2.12 (m, 2 H) 2.42 - 2.54 (m,  $J$ =12.64, 7.70 Hz, 1 H) 3.45 - 3.54 (m, 1 H) 3.63 (s, 3 H) 3.70 (s, 3 H) 3.76 (d,  $J$ =10.44 Hz, 1 H) 3.80 - 3.90 (m, 3 H) 3.93 - 4.06 (m, 4 H) 5.46 (s, 1 H) 5.71 (dd,  $J$ =8.24, 4.95 Hz, 1 H) 6.76 - 6.84 (m, 2 H) 6.88 - 6.94 (m, 1 H) 7.13 - 7.21 (m, 2 H) 7.23 - 7.28 (m, 2 H) 7.34 (s, 1 H) 7.78 (d,  $J$ =8.79 Hz, 1 H) 9.53 (s, 1 H). MS Calcd. for  $[M+H]^+$  : 652.2. Found: 652.2. HPLC Purity: 95%.

**Scheme 5.** Synthesis of substituted isoquinolin-1(2H)-ones.



**7-Amino-4-fluoroisoquinolin-1(2H)-one.** A 20 mL microwave tube was charged with 7-nitroisoquinolin-1(2H)-one (1.0 g, 5.2 mmol), Selectflor® (1.9 g, 5.3 mmol) and dimethylacetamide (10 mL) and the brown solution was microwaved at 150 °C for 15 min. The reaction mixture was cooled to rt and the DMA was removed under high vacuum. Twenty 1.0 g scale reactions were carried out and purified by preparative HPLC to give 4-fluoro-7-nitroisoquinolin-1(2H)-one as yellow solid (5.0 g, 23 % yield).  $^1\text{H}$  NMR (DMSO-d<sub>6</sub>, 400 MHz)  $\delta$  7.6 (d, 1H), 7.9 (d, 1H), 8.6 (d, 1H), 8.8 (s, 1H), 11.7 (s, 1H). Calcd. for [M+H]<sup>+</sup> : 208.0. Found: 208.8.

To a solution of 4-fluoro-7-nitroisoquinolin-1(2H)-one (1.5 g, 7.2 mmol) in a methanol and THF mixture (1:1, 20 mL) was added palladium on carbon (150 mg) and the resulting mixture was stirred for 3 h at bladder hydrogen pressure. The reaction mixture was filtered and concentrated. The crude product was purified by silica gel column chromatography to give 7-amino-4-fluoroisoquinolin-1(2H)-one as yellow solid. Yield: 1.2 g, 88 %.  $^1\text{H}$  NMR (DMSO-d<sub>6</sub>, 400 MHz)  $\delta$  5.8 (s, 1H), 6.9 (d, 1H), 7.2 (d, 1H), 7.3 (d, 1H), 7.5 (d, 1H), 10.7 (s, 1H). Calcd. for [M+H]<sup>+</sup> : 180.0. Found: 178.8.

**Methyl 3-((R)-1-((R)-2-(3,4-dimethoxyphenyl)-2-(4-fluoro-1-oxo-1,2-dihydroisoquinolin-7-ylamino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (16).** The compound was synthesized using the general methods with 7-amino-4-fluoroisoquinolin-1(2H)-one.  $^1\text{H}$  NMR (400 MHz, methanol-d<sub>4</sub>)  $\delta$  ppm 1.14 (d,  $J$ =6.59 Hz, 3 H), 1.39 (d,  $J$ =7.03 Hz, 3 H), 1.71 (dd,  $J$ =12.08, 5.93 Hz, 1 H), 2.04 - 2.21 (m, 2 H), 2.52 (dd,  $J$ =13.18, 7.91 Hz, 1 H), 3.68 (s, 3 H), 3.70 (s, 3 H), 3.73 - 3.79 (m, 1 H), 3.84 (s, 3 H), 3.91 - 3.97 (m, 1 H), 4.19 - 4.24 (m, 1 H), 5.40 (s, 1 H), 5.69 (dd,  $J$ =8.13, 4.61 Hz, 1 H), 6.87 - 6.93 (m, 3 H), 7.01 (dd,  $J$ =8.35, 2.20 Hz, 2 H), 7.18 - 7.29 (m, 2 H), 7.33 (s, 1 H), 7.34 - 7.38 (m, 1 H), 7.58 (d,  $J$ =8.79 Hz, 1 H), 7.73 (d,  $J$ =8.79 Hz, 1 H), 9.35 (s, 1 H). MS Calcd. for [M+H]<sup>+</sup> : 681.2. Found: 681.1. HPLC Purity: 98%.

**7-amino-4-chloroisoquinolin-1(2H)-one.** A solution of 7-nitroisoquinolin-1(2H)-one (300 mg, 1.6 mmol) and *N*-chlorosuccinimide (240 mg, 1.8 mmol) in DMA (4.5 mL) was heated by microwave at 200 °C for 10 min. The reaction mixture was poured into water (40 mL). The product was isolated by

filtration, air dried, and then dried under vacuum to give 4-chloro-7-nitroisoquinolin-1(2*H*)-one as a yellow green solid (330 mg, 93%).  $^1\text{H}$  NMR (400 MHz, THF-d<sub>8</sub>)  $\delta$  ppm 7.60 (s, 1 H) 8.02 (d,  $J$ =8.79 Hz, 1 H) 8.55 (dd,  $J$ =8.79, 2.64 Hz, 1 H) 9.08 (d,  $J$ =2.20 Hz, 1 H) 11.02 (br. s., 1 H). Calcd. for [M+H]<sup>+</sup> : 225.0. Found: 225.1.

Tin(II) chloride dihydrate (1.30 g, 5.5 mmol) was added to a suspension of 4-chloro-7-nitroisoquinolin-1(2*H*)-one (310 mg, 1.4 mmol) and ammonium chloride (370 mg, 6.9 mmol) in MeOH (10 mL) and the reaction mixture was stirred at rt for 7 h. The reaction mixture was then placed in a 50 °C oil bath overnight. Saturated sodium bicarbonate solution was added and the mixture was extracted with ethyl acetate (4x). The combined organic layers were washed with brine, dried (MgSO<sub>4</sub>) and then concentrated *in vacuo* to give 7-amino-4-chloroisoquinolin-1(2*H*)-one as a brown solid (244 mg, 90 %). Calcd. for [M+H]<sup>+</sup> : 295.0. Found: 295.2.

**Methyl 3-((*R*)-1-((*R*)-2-(4-chloro-1-oxo-1,2-dihydroisoquinolin-7-ylamino)-2-(3,4-dimethoxyphenyl)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (17).** The compound was synthesized using the general methods with 7-amino-4-chloroisoquinolin-1(2*H*)-one.  $^1\text{H}$  NMR (400 MHz, methanol-d<sub>4</sub>)  $\delta$  ppm 1.11 (d,  $J$ =6.59 Hz, 3 H), 1.37 (d,  $J$ =6.59 Hz, 3 H), 1.71 (dd,  $J$ =12.74, 4.83 Hz, 1 H), 2.04 - 2.18 (m, 2 H), 2.51 (dd,  $J$ =13.18, 7.91 Hz, 1 H), 3.67 (s, 3 H), 3.70 (s, 3 H), 3.72 - 3.81 (m, 1 H), 3.83 (s, 3 H), 3.87 - 3.99 (m, 1 H), 4.15 - 4.28 (m, 1 H), 5.40 (s, 1 H), 5.69 (dd,  $J$ =7.91, 4.83 Hz, 1 H), 6.89 (d,  $J$ =8.35 Hz, 1 H), 6.93 (d,  $J$ =1.76 Hz, 1 H), 6.99 (d,  $J$ =2.20 Hz, 1 H), 7.02 (s, 1 H), 7.03 - 7.06 (m, 1 H), 7.23 (dd,  $J$ =8.79, 2.64 Hz, 1 H), 7.39 (d,  $J$ =2.64 Hz, 1 H), 7.64 (d,  $J$ =8.79 Hz, 1 H), 7.73 (d,  $J$ =8.79 Hz, 1 H), 9.34 (s, 1 H). MS Calcd. for [M+H]<sup>+</sup> : 697.2. Found: 697.0. HPLC Purity: 95%.

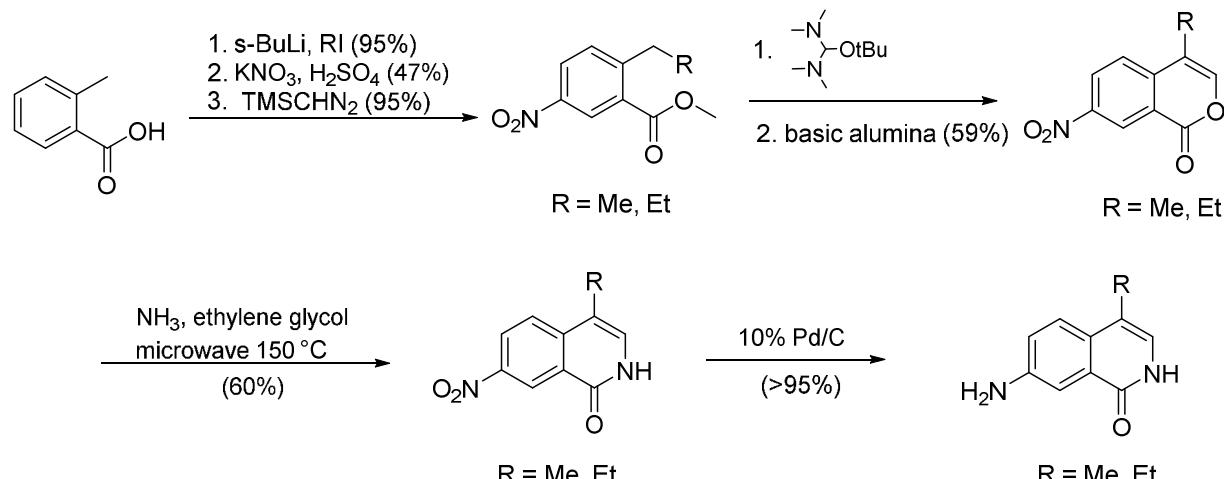
**7-Amino-4-bromoisoquinolin-1(2*H*)-one.** A solution of NBS (94 mg, 0.53 mmol) was added to 7-nitroisoquinolin-1(2*H*)-one (100 mg, 0.53 mmol) in DMA (0.5 mL). The mixture was heated by microwave at 200 °C for 10 min. Water was added to the resulting dark green solution. The precipitate was filtered, washed with water and air dried to give 4-bromo-7-nitroisoquinolin-1(2*H*)-one (120 mg,

83%) as a mustard yellow solid.  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm 7.84 (d,  $J=3.08$  Hz, 1 H), 7.94 (d,  $J=9.23$  Hz, 1 H), 8.56 (dd,  $J=8.79, 2.64$  Hz, 1 H), 8.87 (d,  $J=2.64$  Hz, 1 H), 12.10 (s, 1 H). Calcd. for [M+H]<sup>+</sup> : 269.0. Found: 229.0.

Using a procedure analogous to that described for preparation of 7-amino-4-chloroisoquinolin-1(2H)-one, 4-bromo-7-nitroisoquinolin-1(2H)-one (110 mg, 0.42 mmol) was reacted with tin(II) chloride dihydrate to give 7-amino-4-bromoisoquinolin-1(2H)-one (88 mg, 88 %) as an orange amorphous solid.  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm 5.76 (s, 2 H), 7.07 (dd,  $J=8.57, 2.42$  Hz, 1 H), 7.11 (d,  $J=5.71$  Hz, 1 H), 7.33 (d,  $J=2.20$  Hz, 1 H), 7.44 (d,  $J=8.79$  Hz, 1 H), 11.11 (d,  $J=3.96$  Hz, 1 H).

**Methyl 3-((R)-1-((R)-2-(4-bromo-1-oxo-1,2-dihydroisoquinolin-7-ylamino)-2-(3,4-dimethoxyphenyl)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (18).** The compound was synthesized using the general methods with 7-amino-4-bromoisoquinolin-1(2H)-one.  $^1\text{H}$  NMR (400 MHz, methanol-d4)  $\delta$  ppm 1.09 (d,  $J=6.59$  Hz, 3 H), 1.36 (d,  $J=7.03$  Hz, 3 H), 1.68 - 1.77 (m, 1 H), 2.05 - 2.16 (m, 2 H), 2.51 (dd,  $J=13.18, 7.91$  Hz, 1 H), 3.67 (s, 3 H), 3.70 (s, 3 H), 3.72 - 3.78 (m, 1 H), 3.83 (s, 3 H), 3.85 - 3.95 (m, 1 H), 4.15 - 4.26 (m, 1 H), 5.41 (s, 1 H), 5.69 (dd,  $J=8.35, 4.83$  Hz, 1 H), 6.86 - 6.94 (m, 2 H), 6.96 - 7.06 (m, 2 H), 7.16 (s, 1 H), 7.18 - 7.28 (m, 2 H), 7.40 (d,  $J=2.20$  Hz, 1 H), 7.58 (d,  $J=8.79$  Hz, 1 H), 7.72 (d,  $J=8.35$  Hz, 1 H), 9.35 (s, 1 H). MS Calcd. for [M+H]<sup>+</sup> : 740.2. Found: 740.6. HPLC Purity: 98%.

**Scheme 6.** Synthesis of ethyl and methyl substituted isoquinolin-1(2H)-one.



**7-Amino-4-methylisoquinolin-1(2H)-one.** A mixture of methyl 2-ethyl-5-nitrobenzoate (780

mg, 3.7 mmol) and *tert*-butoxybis(dimethylamino)methane (1.8 mL, 8.6 mmol) was heated at 115 °C for 1 h 40 min. After cooling to rt, hexanes was added and an oily gum separated. The supernatant was concentrated and the residue was purified by silica gel chromatography, eluting with hexane:EtOAc:triethylamine, 70:30:1. 4-methyl-7-nitro-1H-isochromen-1-one was obtained as an orange solid (480 mg, 62%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 2.25 (s, 3 H), 7.30 (s, 1 H), 7.69 (d, J=8.79 Hz, 1 H), 8.59 (dd, J=8.79, 2.64 Hz, 1 H), 9.16 (d, J=2.64 Hz, 1 H).

A mixture of 4-methyl-7-nitro-1H-isochromen-1-one (214 mg, 1.04 mmol) and saturated ammonia in ethylene glycol (4 mL, ~8M) was heated in a microwave from 100 °C to 170 °C in 10 °C increments for 10 min at each temperature to avoid over pressure (19 bar maximum pressure). Water was added to the resulting red suspension. The solid was filtered, washed with water, and air dried to give 4-methyl-7-nitroisoquinolin-1(2H)-one as a yellow solid (170 mg, 81%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 2.35 (s, 3 H), 7.11 (s, 1 H), 7.78 (d, J=8.79 Hz, 1 H), 8.52 (dd, J=9.01, 2.42 Hz, 1 H), 9.30 (d, J=2.64 Hz, 1 H).

A suspension of 4-methyl-7-nitroisoquinolin-1(2H)-one (200 mg, 1.0 mmol) in a mixture tetrahydrofuran (~15 mL, stabilized with 25 ppm BHT), MeOH (1 mL) and water (0.25 mL) was hydrogenated (20 psi) over palladium (10% on carbon, 81 mg, 0.076 mmol) for 55 min. Filtration and concentration of the filtrate gave 7-amino-4-methylisoquinolin-1(2H)-one as a slightly yellow solid (180 mg, 100%). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 2.11 (s, 3 H), 5.48 (s, 2 H), 6.62 (s, 1 H), 7.02 (dd, J=8.57, 2.42 Hz, 1 H), 7.18 - 7.53 (m, 2 H), 10.66 (s, 1 H). Calcd. for [M+H]<sup>+</sup> : 175.0. Found: 175.0.

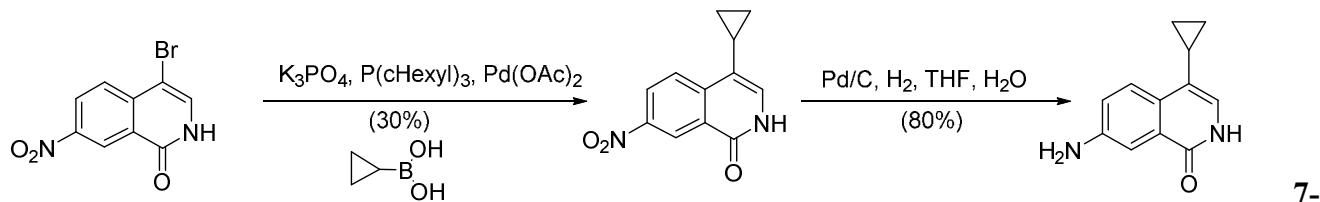
**Methyl 3-((R)-1-((R)-2-(3,4-dimethoxyphenyl)-2-(4-methyl-1-oxo-1,2-dihydroisoquinolin-7-ylamino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (19).** The compound was synthesized using the general methods with 7-amino-4-methylisoquinolin-1(2H)-one. <sup>1</sup>H NMR (400 MHz, methanol-d<sub>4</sub>) δ ppm 1.15 (d, J=6.59 Hz, 3 H), 1.39 (d, J=6.59 Hz, 3 H), 1.67 - 1.79 (m, 1 H), 2.05 - 2.17 (m, 2 H), 2.24 (s, 3 H), 2.51 (dd, J=13.18, 7.91 Hz, 1 H), 3.68 (s, 3 H), 3.70 (s, 3 H), 3.71 - 3.77 (m, 1 H), 3.84 (s, 3 H), 3.89 - 3.99 (m, 1 H), 4.17 - 4.25 (m, 1 H), 5.42 (s, 1 H), 5.69 (dd, J=8.35, 4.83

Hz, 1 H), 6.80 (s, 1 H), 6.88 - 6.93 (m, 2 H), 6.96 - 7.01 (m, 1 H), 7.04 (s, 1 H), 7.21 - 7.27 (m, 2 H), 7.33 (s, 1 H), 7.48 (d,  $J=2.20$  Hz, 1 H), 7.54 (d,  $J=8.79$  Hz, 1 H), 7.74 (d,  $J=8.35$  Hz, 1 H), 9.36 (s, 1 H). MS Calcd. for  $[M+H]^+$  : 677.3. Found: 677.0. HPLC Purity: 95%.

**7-amino-4-ethylisoquinolin-1(2H)-one.** The title compound was synthesized from 2-propylbenzoic acid using analogous procedures to those shown above for 7-amino-4-methylisoquinolin-1(2H)-one.  $^1$ H NMR (400 MHz, DMSO-d6)  $\delta$  ppm 1.14 (t,  $J=7.42$  Hz, 3 H), 2.56 (q,  $J=7.70$  Hz, 2 H), 5.46 (s, 2 H), 6.58 (d,  $J=5.50$  Hz, 1 H), 7.01 (dd,  $J=8.52, 2.47$  Hz, 1 H), 7.34 (d,  $J=2.20$  Hz, 1 H), 7.41 (d,  $J=8.79$  Hz, 1 H), 10.67 (d,  $J=4.40$  Hz, 1 H). Calcd. for  $[M+H]^+$  : 189.1. Found: 189.2.

**Methyl 3-((R)-1-((R)-2-(3,4-dimethoxyphenyl)-2-(4-ethyl-1-oxo-1,2-dihydroisoquinolin-7-ylamino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (20).** The compound was synthesized using the general methods with 7-amino-4-ethylisoquinolin-1(2H)-one.  $^1$ H NMR (400 MHz, methanol-d4)  $\delta$  ppm 1.12 (d,  $J=6.59$  Hz, 3 H), 1.22 (t,  $J=7.47$  Hz, 3 H), 1.37 (d,  $J=7.03$  Hz, 3 H), 1.65 - 1.78 (m, 1 H), 2.02 - 2.15 (m, 2 H), 2.45 - 2.57 (m, 1 H), 2.67 (q,  $J=7.32$  Hz, 2 H), 3.66 (s, 3 H), 3.68 - 3.74 (m, 1 H), 3.70 (s, 3 H), 3.83 (s, 3 H), 3.88 - 3.98 (m, 1 H), 4.13 - 4.23 (m, 1 H), 5.44 (s, 1 H), 5.69 (dd,  $J=7.91, 4.83$  Hz, 1 H), 6.80 (s, 1 H), 6.85 - 6.92 (m, 2 H), 6.92 - 7.00 (m, 1 H), 7.06 (s, 1 H), 7.24 (dd,  $J=8.57, 1.98$  Hz, 2 H), 7.53 - 7.63 (m, 2 H), 7.74 (d,  $J=8.79$  Hz, 1 H), 9.39 (s, 1 H). MS Calcd. for  $[M+H]^+$  : 691.3. Found: 691.0. HPLC Purity: 97%.

**Scheme 7.** Synthesis of cyclopropyl substituted isoquinolin-1(2H)-one.



**amino-4-cyclopropylisoquinolin-1(2H)-one.** A solution of 4-bromo-7-nitroisoquinolin-1(2H)-one (300 mg, 1.1 mmol), cyclopropyl boronic acid (140 mg, 1.7 mmol), potassium phosphate (830 mg, 3.9 mmol), and tricyclohexylphosphine (31 mg, 0.11 mmol) in a mixture of toluene (6 mL) and water (0.15 mL) was deoxygenated by sparging with nitrogen. Palladium acetate was added (12 mg, 0.056 mmol) and the reaction was heated by microwave at 140 °C for 10 min. The reaction was diluted with water

and extracted with EtOAc (3x). The combined organic layers were washed with brine and concentrated to give 4-cyclopropyl-7-nitroisoquinolin-1(2*H*)-one (240 mg) as a crude orange solid. Calcd. for  $[M+H]^+$  : 231.1. Found: 231.2.

A suspension of 4-cyclopropyl-7-nitroisoquinolin-1(2*H*)-one (240 mg, 1.0 mmol) and palladium (100 mg, 10 % on carbon) in THF (40 mL, stabilized) and water (0.25 mL) was hydrogenated (20 psi) for 3 h. The reaction mixture was filtered and concentrated. The residue was purified by preparative HPLC to yield amino-4-cyclopropylisoquinolin-1(2*H*)-one.

**Methyl 3-((*R*)-1-((*R*)-2-(4-cyclopropyl-1-oxo-1,2-dihydroisoquinolin-7-ylamino)-2-(3,4-dimethoxyphenyl)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (21).** The compound was synthesized using the general methods with amino-4-cyclopropylisoquinolin-1(2*H*)-one.  $^1H$  NMR (400 MHz, methanol-d<sub>4</sub>)  $\delta$  ppm 0.44 - 0.57 (m, 2 H), 0.86 - 0.97 (m, 2 H), 1.14 (d, *J*=6.59 Hz, 3 H), 1.39 (d, *J*=6.96 Hz, 3 H), 1.71 (dd, *J*=12.08, 5.86 Hz, 1 H), 1.82 - 1.92 (m, 1 H), 2.10 (dd, *J*=11.17, 6.77 Hz, 2 H), 2.51 (dd, *J*=13.00, 7.87 Hz, 1 H), 3.67 (s, 3 H), 3.69 - 3.74 (m, 1 H), 3.70 (s, 3 H), 3.84 (s, 3 H), 3.93 (dd, *J*=13.55, 6.59 Hz, 1 H), 4.12 - 4.25 (m, 1 H), 5.44 (s, 1 H), 5.69 (dd, *J*=8.06, 4.76 Hz, 1 H), 6.77 (s, 1 H), 6.86 - 6.93 (m, 2 H), 6.95 - 7.00 (m, 2 H), 7.06 (d, *J*=1.83 Hz, 1 H), 7.20 - 7.31 (m, 2 H), 7.50 (d, *J*=2.56 Hz, 1 H), 7.74 (d, *J*=8.79 Hz, 1 H), 7.94 (d, *J*=8.79 Hz, 1 H), 9.38 (s, 1 H). MS Calcd. for  $[M+H]^+$  : 703.3. Found: 703.1. HPLC Purity: 97%.

**(S)-7-amino-4-methyl-3,4-dihydroisoquinolin-1(2*H*)-one.** To a solution of S(-)  $\beta$ -methylphenylethylamine (0.50 g, 3.6 mmol) in diethyl ether (15 mL) at 0 °C, was added triethylamine (5 mL) followed by ethyl chloroformate (0.6 g, 5.5 mmol) dropwise. The white precipitate formed was stirred for 30 min. The reaction mixture filtered and the solid was washed with diethyl ether. The combined filtrate was concentrated to yield (S)-ethyl 2-phenylpropylcarbamate and taken for next step without further purification. Yield: 0.40 g, 53 %.  $^1H$  NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  1.4 (m, 3H), 2.9 (m, 1H), 3.26 (m, 1H), 3.5 (m, 1H), 4.1 (m, 2H), 4.5 (s, 1H), 7.16-7.3 (m, 5H).

Eaton's reagent was prepared by stirring  $P_2O_5$  (1.0 g) in methane sulfonic acid (10 mL) at rt for 12 h. (S)-ethyl 2-phenylpropylcarbamate (2 g) was added to the Eatons reagent and heated at 120 °C for 2 h. The reaction mixture was cooled to rt, quenched with ice and extracted with ethyl acetate. Combined organic layer was washed with 10 %  $NaHCO_3$  solution (2 x 100 mL), water (1 x 100 mL), brine (1 x 100 mL), dried over anhydrous  $Na_2SO_4$  and concentrated. The crude product was purified by flash column chromatography using silica gel column using hexane:ethyl acetate as eluent to yield (S)-4-methyl-3,4-dihydroisoquinolin-1(2H)-one (1.5 g, 75% yield).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$  1.3 (d, 3H), 3.14 (m, 1H), 3.3 (m, 1H), 3.67 (m, 1H), 7.2 (m, 1H), 7.3 (m, 1H), 7.5 (m, 1H), 8.05 (d, 1H).

Conc.  $H_2SO_4$  was added drop wise to (S)-4-methyl-3,4-dihydroisoquinolin-1(2H)-one (4.0 g, 24 mmol) at 0 °C and stirred for 10 min.  $KNO_3$  (2.7 g, 27 mmol) was added portion wise and stirred for 30 min. The reaction mixture was quenched with ice and extracted with ethyl acetate. The organic layer was washed with water (1 x 100 ml), brine (100 ml), dried over anhydrous  $Na_2SO_4$  and concentrated. Yield: 3 g, 60 %. (S)-4-methyl-7-nitro-3,4-dihydroisoquinolin-1(2H)-one obtained was pure and taken as such for the next step.  $^1H$  NMR ( $DMSO-d_6$ , 400 MHz)  $\delta$  1.3 (d, 3H), 3.2 (m, 2H), 3.5 (m, 1H), 7.6 (d, 1H), 8.2 (bs, 1H), 8.3 (m, 1H), 8.5 (d, 1H).

To a solution of (S)-4-methyl-7-nitro-3,4-dihydroisoquinolin-1(2H)-one (0.50 g) in methanol (100 mL), was added  $Pd/C$  (0.5 g) and hydrogenated at 3 Kg pressure for 2 h. The catalyst was filtered through Celite® bed, washed with methanol. The filtrate was concentrated and purified by flash chromatography using neutral alumina using  $CHCl_3$ :  $MeOH$  as eluent to yield (S)-7-amino-4-methyl-3,4-dihydroisoquinolin-1(2H)-one (0.30 g, 70 %).  $^1H$  NMR ( $DMSO-d_6$ , 400 MHz)  $\delta$  1.2 (d, 3H), 2.8 (m, 1H), 3.0 (m, 1H), 3.17 (d, 1H), 5.2 (d, 2H), 6.7 (m, 1H), 6.9 (m, 1H), 7.6 (d, 1H), 7.7 (s, 1H), 7.1 (d, 1H). MS Calcd. for  $[M+H]^+$  : 177. Found: 177.

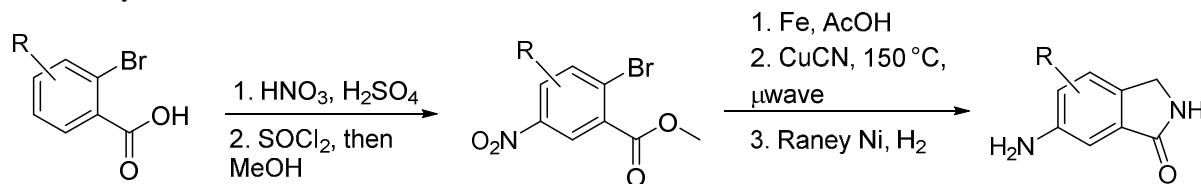
**Methyl 3-((2R)-1-(2-(3,4-dimethoxyphenyl)-2-((S)-4-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-ylamino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (22).** The compound was synthesized using the general methods with (S)-7-amino-4-methyl-3,4-dihydroisoquinolin-1(2H)-one.

<sup>1</sup>H NMR (400 MHz, MeOD) δ ppm 1.17 (d, *J*=6.59 Hz, 3 H) 1.25 (d, *J*=7.03 Hz, 3 H) 1.41 (d, 3 H) 1.64 - 1.76 (m, *J*=12.96, 5.05 Hz, 1 H) 1.97 - 2.13 (m, 2 H) 2.41 - 2.54 (m, *J*=13.18, 7.91 Hz, 1 H) 2.96 - 3.05 (m, 1 H) 3.18 (dd, *J*=12.52, 6.37 Hz, 1 H) 3.52 (dd, *J*=12.74, 4.83 Hz, 1 H) 3.65 (s, 3 H) 3.69 (s, 3 H) 3.82 - 3.84 (m, 3 H) 3.91 - 4.00 (m, 1 H) 4.01 - 4.10 (m, 1 H) 5.38 - 5.41 (m, 1 H) 5.66 (dd, *J*=7.91, 4.83 Hz, 1 H) 6.82 (s, 1 H) 6.89 (s, 2 H) 7.01 (dd, *J*=8.35, 2.64 Hz, 1 H) 7.08 (s, 1 H) 7.19 (d, *J*=8.35 Hz, 1 H) 7.22 (dd, *J*=8.79, 2.20 Hz, 1 H) 7.42 (d, *J*=2.64 Hz, 1 H) 7.74 (d, *J*=8.79 Hz, 1 H). MS Calcd. for [M+H]<sup>+</sup> : 679.3. Found: 679.5. HPLC Purity: 98%.

**(R)-7-amino-4-methyl-3,4-dihydroisoquinolin-1(2H)-one.** (R)-7-amino-4-methyl-3,4-dihydroisoquinolin-1(2H)-one was synthesized from (R)-2-phenylpropan-1-amine using an analogous procedure to the one used for the S isomer.

**Methyl 3-((2R)-1-(2-(3,4-dimethoxyphenyl)-2-((R)-4-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-ylamino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (23).** The compound was synthesized using the general methods with (R)-7-amino-4-methyl-3,4-dihydroisoquinolin-1(2H)-one. <sup>1</sup>H NMR (400 MHz, MeOD) δ ppm 1.17 (d, *J*=6.59 Hz, 3 H) 1.26 (d, 3 H) 1.41 (d, *J*=7.03 Hz, 3 H) 1.69 (dd, *J*=12.74, 5.27 Hz, 1 H) 1.97 - 2.13 (m, 2 H) 2.40 - 2.53 (m, *J*=12.96, 7.69 Hz, 1 H) 2.95 - 3.05 (m, 1 H) 3.18 (dd, *J*=12.74, 6.15 Hz, 1 H) 3.48 - 3.56 (m, 1 H) 3.64 (s, 3 H) 3.68 (s, 3 H) 3.82 - 3.84 (m, 3 H) 3.99 - 4.10 (m, 1 H) 5.40 (s, 1 H) 5.66 (dd, *J*=8.35, 4.83 Hz, 1 H) 6.82 (s, 1 H) 6.89 (s, 2 H) 7.01 (dd, *J*=8.35, 2.64 Hz, 1 H) 7.09 (s, 1 H) 7.17 - 7.26 (m, 2 H) 7.46 (d, *J*=2.20 Hz, 1 H) 7.74 (d, *J*=8.79 Hz, 1 H). MS Calcd. for [M+H]<sup>+</sup> : 679.3. Found: 679.4. HPLC Purity: 98%.

**Scheme 8.** Synthesis of substituted isoindolinones



**6-amino-5-fluoroisoindolin-1-one.** Potassium nitrate (12 g, 110 mmol) was added portionwise to a solution of 2-bromo-4-fluorobenzoic acid (25 g, 110 mmol) in sulfuric acid (230 mL) at 0 °C over

10 min. The reaction mixture was stirred for 3 h at ambient temperature. The reaction mixture was poured onto ice. The resulting precipitate was washed with water and dried *in vacuo* to yield a mixture of 2-bromo-4-fluoro-5-nitrobenzoic acid and 2-Br-4-F-6-nitrobenzoic acid (9:1) as a white solid (19.5 g). 7 g of this solid was purified by prep HPLC (0.1% TFA, H<sub>2</sub>O/MeOH, 35% to 60%) to yield 2-bromo-4-fluoro-5-nitrobenzoic acid (5.6 g, 21 mmol) as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 7.91 (d, *J*=10.44 Hz, 1 H) 8.61 (d, *J*=8.25 Hz, 1 H).

Thionyl chloride (1.7 mL, 23 mmol) was added to methanol (100 mL) at 0 °C and stirred for 30 min. 2-Bromo-4-fluoro-5-nitrobenzoic acid (5.5 g, 21 mmol) was added and the mixture was heated at 60 °C for 18 h. The reaction mixture was concentrated to a white solid and purified by column chromatography (0 to 50% EtOAc in hexanes, 120 g column) to yield methyl 2-bromo-4-fluoro-5-nitrobenzoate (5.0 g, 87% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 3.97 (s, 3 H) 7.67 (d, *J*=9.89 Hz, 1 H) 8.62 (d, *J*=7.70 Hz, 1 H).

Iron (5.0 g, 90 mmol) was added portionwise to a solution of methyl 2-bromo-4-fluoro-5-nitrobenzoate (5.0 g, 18 mmol) in ethanol (140 mL)/water (350 mL)/AcOH (7 mL) at 110 °C (bath temp). The reaction mixture was refluxed for 1 h. The reaction mixture was neutralized with NaHCO<sub>3</sub> (aq, saturated), diluted with H<sub>2</sub>O (250 mL) and extracted with EtOAc (2 x 400 mL). The organics were combined, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to yield methyl 5-amino-2-bromo-4-fluorobenzoate (2.5 g, 55% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 3.89 (s, 3 H) 7.26 - 7.35 (m, 2 H).

A solution of copper(I) cyanide (0.81 g, 9.1 mmol) and methyl 5-amino-2-bromo-4-fluorobenzoate (1.5 g, 6.1 mmol) in DMF (24.19 mL) was divided into two vessels and microwaved at 180 °C for 10 min. The reaction mixture was diluted with NH<sub>4</sub>OH (50 mL) and H<sub>2</sub>O (50 mL) and extracted with EtOAc (1 x 200 mL). The organics were washed with NaHCO<sub>3</sub>, brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. Purification by column chromatography (0 to 100% EtOAc in Hexanes) yielded methyl 5-amino-2-cyano-4-fluorobenzoate (650 mg, 55% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)

$\delta$  ppm 3.91 (s, 3 H) 7.43 (d,  $J$ =10.99 Hz, 1 H) 7.48 (d,  $J$ =8.79 Hz, 1 H). MS Calcd. for  $[M+H]^+$  : 195.1.

Found: 195.2.

A mixture of methyl 5-amino-2-cyano-4-fluorobenzoate (200 mg, 1.0 mmol) and Raney Ni in MeOH and  $\text{NH}_3$  (20 mL, 7.0 M) was stirred under  $\text{H}_2$  (50 psi) for 16 h. The reaction mixture was diluted with acetone (100 mL), filtered through Celite and concentrated. The resulting solid was triturated with  $\text{H}_2\text{O}$  (20 mL) and dried in vacuo to yield 6-amino-5-fluoroisoindolin-1-one. (100 mg, 0.60 mmol, 58% yield) as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{dmso-d}_6$ )  $\delta$  ppm 5.14 - 5.43 (m, 2 H) 6.92 - 7.11 (m, 1 H) 7.10 - 7.28 (m, 1 H) 8.17 - 8.46 (m, 1 H). MS Calcd. for  $[M+H]^+$  : 167.1. Found: 166.9.

**Methyl 3-((R)-1-((R)-2-(3,4-dimethoxyphenyl)-2-(6-fluoro-3-oxoisoindolin-5-ylamino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (24).** The compound was synthesized using the general methods with 6-amino-5-fluoroisoindolin-1-one.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  ppm 1.13 - 1.22 (m, 3 H) 1.41 - 1.46 (m, 3 H) 1.65 - 1.75 (m, 1 H) 1.91 - 2.15 (m, 3 H) 2.42 - 2.57 (m, 1 H) 3.67 (s, 3 H) 3.70 (s, 3 H) 3.71 - 3.76 (m, 1 H) 3.82 (s, 3 H) 3.91 - 4.03 (m, 1 H) 4.11 - 4.24 (m, 1 H) 4.27 (s, 2 H) 5.39 (s, 1 H) 5.66 (dd,  $J$ =8.24, 4.95 Hz, 1 H) 6.86 (s, 1 H) 6.89 (d,  $J$ =8.24 Hz, 1 H) 6.96 - 7.03 (m, 2 H) 7.11 (d,  $J$ =7.70 Hz, 1 H) 7.16 (d,  $J$ =10.99 Hz, 1 H) 7.21 (dd,  $J$ =8.79, 2.20 Hz, 1 H) 7.73 (d,  $J$ =8.79 Hz, 1 H) 9.33 (s, 1 H). MS Calcd. for  $[M+H]^+$  : 669.2. Found: 669.4. HPLC Purity: 99%.

**6-amino-4-fluoroisoindolin-1-one.** The title compound was synthesized from 2-bromo-3-fluorobenzoic acid using similar procedures to those used for 6-amino-5-fluoroisoindolin-1-one.  $^1\text{H}$  NMR (400 MHz, acetone)  $\delta$  ppm 4.30 (s, 2 H) 6.67 (dd,  $J$ =11.42, 1.76 Hz, 1 H) 6.87 (d,  $J$ =1.76 Hz, 1 H). MS Calcd. for  $[M+H]^+$  : 167.1. Found: 167.2.

**Methyl 3-((2R)-1-(2-(3,4-dimethoxyphenyl)-2-(4-fluoro-3-oxoisoindolin-5-ylamino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (25).** The compound was synthesized using the general methods with 6-amino-4-fluoroisoindolin-1-one.  $^1\text{H}$  NMR (400 MHz,  $\text{MeOD}$ )  $\delta$  ppm 1.06 - 1.21 (m, 3 H) 1.35 - 1.52 (m, 3 H) 1.68 - 1.97 (m, 4 H) 2.26 - 2.44 (m, 1 H) 2.76 -

3.04 (m, 3 H) 3.59 - 3.96 (m, 6 H) 4.07 - 4.39 (m, 2 H) 5.44 (s, 1 H) 5.52 - 5.77 (m, 1 H) 6.71 - 7.21 (m, 7 H) 7.65 - 7.85 (m, 1 H). MS Calcd. for  $[M+H]^+$  : 669.2. Found: 669.5. HPLC Purity: 99%.

**6-Amino-7-fluoroisoindolin-1-one.** The title compound was synthesized from 6-bromo-2-fluoro-benzoic acid using similar procedures to those used for 6-amino-5-fluoroisoindolin-1-one. MS Calcd. for  $[M+H]^+$  : 167.1. Found: 167.1.

**Methyl 3-((2R)-1-(2-(3,4-dimethoxyphenyl)-2-(7-fluoro-3-oxoisoindolin-5-ylamino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (26).** The compound was synthesized using the general methods with 6-amino-7-fluoroisoindolin-1-one.  $^1H$  NMR (400 MHz,  $CD_3OD$ )  $\delta$  ppm 1.38 (t,  $J=6.81$  Hz, 4 H) 1.69 (dd,  $J=12.08, 5.93$  Hz, 1 H) 2.08 (dt,  $J=13.62, 6.81$  Hz, 2 H) 2.49 (dd,  $J=12.74, 7.91$  Hz, 1 H) 3.64 - 3.67 (m, 3 H) 3.68 - 3.72 (m, 4 H) 3.80 - 3.84 (m, 6 H) 4.29 - 4.35 (m, 3 H) 5.29 - 5.35 (m, 1 H) 5.66 (dd,  $J=8.35, 4.83$  Hz, 1 H) 6.67 (dd,  $J=11.42, 1.76$  Hz, 1 H) 6.81 (d,  $J=1.76$  Hz, 1 H) 6.84 - 6.92 (m, 2 H) 6.95 - 7.02 (m, 2 H) 7.21 (dd,  $J=8.79, 2.20$  Hz, 1 H) 7.68 - 7.78 (m, 2 H). MS Calcd. for  $[M+H]^+$  : 669.2. Found: 669.6. HPLC Purity: 99%.

**6-amino-4-methylisoindolin-1-one.** In a 50 mL round-bottomed flask 2-bromo-3-methyl-benzoic acid (5.0 g, 23 mmol) and sulfuric acid (15 mL) were stirred at 0 °C before adding fuming nitric acid (2.0 mL, 23 mmol, 90%) dropwise over 10 min. After stirring for 2 h at rt, the reaction mixture was poured onto ice and solids were isolated by filtration. The crude solids were purified on  $SiO_2$  (eluting with 0-100% EtOAc). The residue was refluxed for 1 h in thionyl chloride (15 mL) and concentrated to an oil. MeOH (40 mL) was added slowly to the oil and the mixture refluxed for 1 h. The reaction mixture was concentrated to isolate a 9:1 ratio of desired regio-isomer methyl 2-bromo-3-methyl-5-nitrobenzoate (3.8 g, 15 mmol) and another regioisomer in 65% yield.  $^1H$  NMR (400 MHz,  $CD_3OD$ )  $\delta$  ppm 2.47 (s, 3 H) 3.93 (s, 3 H) 7.45 (s, 1 H) 7.82 (s, 1 H) 7.96 (s, 1 H).

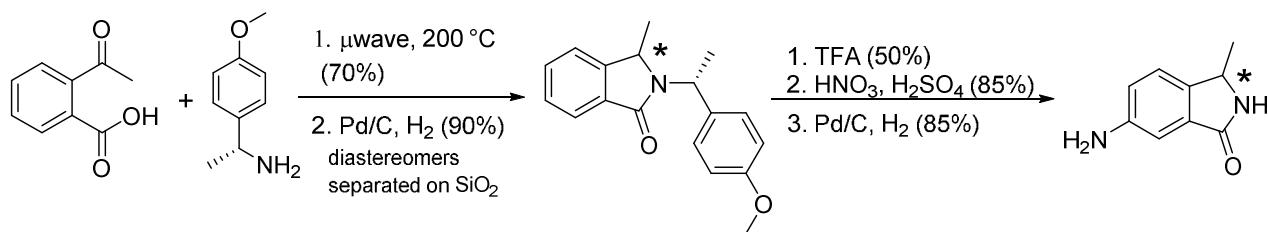
Methyl 2-bromo-3-methyl-5-nitrobenzoate (3.4 g, 14.0 mmol) was heated at 90 °C for 4 h in acetic acid (20 mL) with Fe powder (370 mg, 6.7 mmol). Upon cooling to rt the reaction was diluted with EtOAc (100 mL) and the resulting mixture filtered through Celite®. The filter cake washed with EtOAc

(3 x 100 mL). The combined organics were washed with water, brine and dried w/ MgSO<sub>4</sub> and concentrated to yield methyl 5-amino-2-bromo-3-methylbenzoate as an oil. The residue was dissolved into DMF (25 mL). Cu(I)CN (3.45 g, 38.5 mmol) was added and the resulting mixture heated at 160 °C for 15 min under argon. The reaction was cooled to rt, quenched with a 50/50 mixture of NH<sub>4</sub>OH/H<sub>2</sub>O (50 mL), stirred 5min. and filtered through Celite®. The filter cake was washed with EtOAc (3 x 50 mL) and the combined organics were extracted with water (3x100 mL), brine and dried with MgSO<sub>4</sub>. The filtrate was concentrated to an oil and recrystallized from EtOH/Hexane. Further purification on preparatory HPLC yielded methyl 5-amino-2-cyano-3-methylbenzoate as a 9:1 ratio of desired to undesired regioisomer (1.5 g, 7.9 mmol) as a solid in 56% overall yield. MS Calcd. for [M+H]<sup>+</sup> : 191.1. Found: 191.3.

A solution of methyl 5-amino-2-cyano-3-methylbenzoate (1.5 g, 7.9 mmol) in MeOH (20 mL) and water (6 mL) was stirred with a catalytic amount of Raney Ni under 60 psi of hydrogen for 18 h. The reaction was filtered through Celite® and conc. to an oil before purifying via preparatory HPLC to yield 6-amino-4-methylisoindolin-1-one (500 mg, 3.08 mmol) as a single regioisomer in 38% yield. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 2.40 (s, 3 H) 3.89 (s, 3 H) 6.73 (s, 1 H) 7.12 (d, *J*=2.20 Hz, 1 H). MS Calcd. for [M+H]<sup>+</sup> : 163.1. Found: 163.2.

**Methyl 3-((2R)-1-(2-(3,4-dimethoxyphenyl)-2-(7-methyl-3-oxoisoindolin-5-ylamino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (27).** The compound was synthesized using the general methods with 6-amino-4-methylisoindolin-1-one. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 1.12 - 1.21 (m, 4 H) 1.26 - 1.37 (m, 1 H) 1.39 - 1.48 (m, 4 H) 1.70 (dd, *J*=12.52, 5.49 Hz, 1 H) 2.06 (td, *J*=13.29, 8.57 Hz, 2 H) 2.24 - 2.33 (m, 2 H) 2.84 - 2.87 (m, 1 H) 2.98 (s, 1 H) 3.66 (s, 2 H) 3.69 - 3.70 (m, 2 H) 3.83 (t, *J*=3.52 Hz, 4 H) 3.89 - 3.99 (m, 1 H) 4.09 (dd, *J*=6.81, 3.30 Hz, 1 H) 4.27 - 4.30 (m, 2 H) 5.67 (dd, *J*=8.13, 5.05 Hz, 1 H) 6.83 - 6.93 (m, 3 H) 6.95 - 7.04 (m, 2 H) 7.05 - 7.14 (m, 1 H) 7.15 - 7.25 (m, 1 H) 7.72 - 7.77 (m, 1 H). HPLC Purity: 96%.

**Scheme 9.** Synthesis of C-8 methyl substituted isoindolinones



**6-amino-3-methylisoindolin-1-one (both enantiomers).** To a 20 mL microwave vial was added 2-acetylbenzoic acid (1.8 g, 11 mmol), (R)-1-(4-methoxyphenyl)ethanamine (2.0 mL, 13 mmol) and toluene (2 mL). The reaction was heated 25 min. at 200 °C in the microwave. The crude reaction was concentrated and purified on  $\text{SiO}_2$ , eluting w/ 0-100%  $\text{EtOAc}/\text{Hex}$  to yield (R)-2-(1-(4-methoxyphenyl)ethyl)-3-methyleneisoindolin-1-one (3.0 g, 98% yield) as an oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 1.82 (d,  $J=7.47$  Hz, 3 H) 3.78 (s, 3 H) 4.60 (d,  $J=2.20$  Hz, 1 H) 5.07 (d,  $J=2.20$  Hz, 1 H) 5.87 (q,  $J=7.47$  Hz, 1 H) 6.85 (d, 2 H) 7.50 (t,  $J=6.15$  Hz, 1 H) 7.55 (t,  $J=6.81$  Hz, 1 H) 7.61 (d, 1 H) 7.85 (d,  $J=7.47$  Hz, 1 H), MS (ESI)  $m/z$  280.3 (M+H).

(R)-2-(1-(4-methoxyphenyl)ethyl)-3-methyleneisoindolin-1-one (3.0 g, 11 mmol) was dissolved in  $\text{MeOH}/\text{DCM}$  (20 mL/5 mL) and stirred at rt under 50 psi of  $\text{H}_2$  for 2 h. The crude reaction was filtered through Celite® and purified on  $\text{SiO}_2$ , eluting with 0-100%  $\text{EtOAc}/\text{Hexane}$ . Separation of diastereomers was achieved via preparatory HPLC (Sunfire Prep C18, 19 X 100 mm, 5 micron, flow rate 20 mL/min, A:  $\text{H}_2\text{O}/\text{MeOH}$  (9:1), B:  $\text{H}_2\text{O}/\text{MeOH}$  (1:9), 0.1 %TFA, 20 to 80% B, 10 min gradient) to yield an equal mixture of both diastereomers (800 mg, 1.80 mmol) as solids 27% yield. Characterization for Peak 1 (intermediate for Compound 29) ( $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 1.10 (d,  $J=6.60$  Hz, 3 H) 1.78 (d,  $J=7.70$  Hz, 3 H) 3.78 (s, 3 H) 4.70 (q,  $J=6.60$  Hz, 1 H) 5.64 (q,  $J=7.15$  Hz, 1 H) 6.84 (d,  $J=8.79$  Hz, 2 H) 7.33 - 7.38 (m, 3 H) 7.46 (t,  $J=7.42$  Hz, 1 H) 7.54 (t,  $J=7.70$  Hz, 1 H) 7.88 (d,  $J=7.70$  Hz, 1 H), MS (ESI)  $m/z$  282.3 (M+H)) and Peak 2 (intermediate for Compound 30) ( $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 1.42 (d,  $J=6.60$  Hz, 3 H) 1.75 (d,  $J=7.15$  Hz, 3 H) 3.79 (s, 3 H) 4.26 (q,  $J=7.15$  Hz, 1 H) 5.67 (q,  $J=7.15$  Hz, 1 H) 6.89 (d,  $J=8.79$  Hz, 2 H) 7.26 - 7.32 (m,  $J=8.24, 8.24$  Hz, 3 H) 7.43 (t,  $J=7.15$  Hz, 1 H)

7.51 (t, 1 H) 7.86 (d,  $J=7.15$  Hz, 1 H), MS (ESI)  $m/z$  282.3 (M+H). Each diastereomer was carried through separately to the final product using the following procedures.

(R)-2-(1-(4-methoxyphenyl)ethyl)-3-methylisoindolin-1-one (200 mg, 0.71 mmol) was stirred in TFA (8 mL) at rt for 2 h. The reaction was concentrated and purified on SiO<sub>2</sub>, eluting w/ 0-100% EtOAc/Hex to yield 3-methylisoindolin-1-one (75 mg, 72% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 1.50 (d,  $J=7.03$  Hz, 3 H) 4.70 (q,  $J=6.59$  Hz, 1 H) 7.39 - 7.47 (m, 2 H) 7.55 (t,  $J=6.81$  Hz, 1 H) 7.83 (d,  $J=7.47$  Hz, 1 H) 8.22 (s, 1 H), MS (ESI)  $m/z$  148.2 (M+H).

3-Methylisoindolin-1-one (160 mg, 1.1 mmol) was stirred in sulfuric acid (2 mL) at 0 °C for 5 min before adding potassium nitrate (110 mg, 1.1 mmol) portion wise. The reaction mixture was warmed to rt over 1 h, quenched with ice, and filtered resulting precipitate to yield 3-methyl-6-nitroisoindolin-1-one (170 mg, 81% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 1.58 (d,  $J=6.59$  Hz, 3 H) 4.85 (q,  $J=6.59$  Hz, 1 H) 7.56 - 7.61 (m, 1 H) 8.48 (dd,  $J=8.35, 2.20$  Hz, 1 H) 8.68 (d,  $J=1.76$  Hz, 1 H), MS (ESI)  $m/z$  193.1 (M+H).

3-methyl-6-nitroisoindolin-1-one (170 mg, 0.89 mmol) was stirred in MeOH (10 mL) with a catalytic amount of 10% Pd/C with hydrogen (1 atm) for 2 h. The reaction was filtered and concentrated to yield 6-amino-3-methylisoindolin-1-one (135 mg, 94% yield) as a solid. <sup>1</sup>H NMR (400 MHz, MeOD)  $\delta$  ppm 1.44 (d,  $J=7.03$  Hz, 3 H) 4.74 (q,  $J=6.59$  Hz, 1 H) 4.93 (s, 3 H) 7.65 (d, 1 H) 7.72 (s, 1 H) 7.74 (d,  $J=2.20$  Hz, 1 H). MS Calcd. for [M+H]<sup>+</sup> : 163.1. Found: 163.2.

**Methyl 3-((2R)-1-((2R)-2-(3,4-dimethoxyphenyl)-2-(1-methyl-3-oxoisoindolin-5-ylamino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (diastereomeric pair, 28 and 29).** The compounds were synthesized using the general methods with the above 6-amino-3-methylisoindolin-1-one enantiomers. Peak 1: <sup>1</sup>H NMR (400 MHz, MeOD)  $\delta$  ppm 1.16 (d,  $J=6.59$  Hz, 3 H) 1.39 (dd,  $J=12.52, 6.81$  Hz, 6 H) 1.70 (dd,  $J=11.64, 6.37$  Hz, 1 H) 1.99 - 2.14 (m, 2 H) 2.48 (dd,  $J=12.96, 7.69$  Hz, 1 H) 3.65 (s, 3 H) 3.69 (s, 3 H) 3.82 - 3.85 (m, 3 H) 3.90 - 4.00 (m, 1 H) 4.06 - 4.16 (m, 1 H) 4.57 (q,  $J=6.59$  Hz, 1 H) 5.67 (dd,  $J=7.91, 4.83$  Hz, 1 H) 6.84 (s, 1 H) 6.90 - 6.93 (m, 2 H) 7.02

- 7.08 (m, 4 H) 7.22 (dd,  $J=8.79$ , 2.20 Hz, 1 H) 7.32 (d,  $J=7.91$  Hz, 1 H) 7.74 (d,  $J=8.79$  Hz, 1 H). MS Calcd. for  $[M+H]^+$  : 665.3. Found: 665.4. (M+H). Peak 2:  $^1H$  NMR (400 MHz, MeOD)  $\delta$  ppm 1.15 (d,  $J=6.59$  Hz, 3 H) 1.38 (d,  $J=6.59$  Hz, 3 H) 1.40 (d,  $J=7.03$  Hz, 3 H) 1.65 - 1.76 (m, 1 H) 2.00 - 2.13 (m, 2 H) 2.48 (dd,  $J=13.18$ , 7.91 Hz, 1 H) 3.64 (s, 3 H) 3.69 (s, 3 H) 3.82 - 3.84 (m, 3 H) 3.90 - 3.99 (m, 1 H) 4.06 - 4.17 (m, 1 H) 4.57 (q,  $J=6.74$  Hz, 1 H) 5.37 (s, 1 H) 5.67 (dd,  $J=8.35$ , 4.83 Hz, 1 H) 6.83 (s, 1 H) 6.88 - 6.92 (m, 2 H) 7.02 - 7.06 (m, 2 H) 7.06 - 7.09 (m, 1 H) 7.22 (dd, 1 H) 7.32 (d,  $J=8.35$  Hz, 1 H) 7.74 (d, 1 H). MS Calcd. for  $[M+H]^+$  : 665.3. Found: 665.4. HPLC Purity: 99%.

**Methyl 3-((R)-1-((R-2-(3,4-dimethoxyphenyl)-2-(1,3-dioxoindolin-5-ylamino)acetyl)pyrrolidin-2-yl)-4-(isopropylsulfonyl)phenylcarbamate (30).** The compound was synthesized using the general methods with 5-aminoisoindoline-1,3-dione.  $^1H$  NMR (400 MHz, MeOD)  $\delta$  ppm 1.12 (d,  $J=6.59$  Hz, 3 H) 1.39 (d,  $J=7.03$  Hz, 3 H) 1.65 - 1.76 (m, 1 H) 2.01 - 2.16 (m, 2 H) 2.44 - 2.57 (m, 1 H) 3.66 - 3.76 (m, 1 H) 3.67 (s, 3 H) 3.70 (s, 3 H) 3.84 (2, 3 H), 3.89 - 3.97 (m, 1 H) 4.10 = 4.21 (m, 1 H) 5.42 (s, 1 H) 5.67 (dd,  $J=7.91$ , 4.83 Hz, 1 H) 6.86 - 6.92 (m, 3 H) 6.96 - 7.03 (m, 3 H) 7.21 (dd,  $J=8.35$ , 2.20 Hz, 1 H) 7.48 (d,  $J=8.35$  Hz, 1 H) 7.72 (d,  $J=8.79$  Hz, 1 H). MS Calcd. for  $[M+H]^+$  : 665.2. Found :665.4. HPLC Purity: 99%.

### Dog PK

Compound	10	24
$T_{1/2}$ (h)	1.6	0.6
AUCtot (nMxh)	230	70
CL (mL/min/kg)	21.4	59.1
Vss (L/kg)	1.5	2.5

Pharmacokinetic study protocols were approved by the site Animal Care and Use Committee. Compounds were dissolved in N,N-dimethylacetamide (DMAC) to a concentration of 10 mg/mL.

Compounds were combined in a final dosing solution containing 0.1 mg/mL of each compound in 10:10:10:70 % v/v DMAC/ethanol/propylene glycol/ water. Beagle dogs were administered 8 mL/kg/h for 0.25 h by intravenous infusion. At timed intervals, blood samples were drawn into 1/10 volume of 3.2% sodium citrate and placed on ice. Plasma was obtained after centrifuging blood at 2000g for 10 min at 4 C. Samples from the pharmacokinetic studies were analyzed with LC-MS/MS methods. High-throughput technologies such as the turbulent-flow column switching technique and direct plasma sample injection were applied to some studies. In general, the analytical methods were specific and sensitive with a quantification level of 1 nM. The intraday variability was less than 30%. Average run time was about 6 min for each sample. (Wu, J. T.; Zeng, H.; Qian, M.; Brogdon, B. L.; Unger, S. E. Direct plasma sample injection in multiple-component LCMS- MS assays for high-throughput pharmacokinetic screening. *Anal. Chem.* 2000, 72, 61-67; Zeng, H.; Wu, J. T.; Unger, S. E. The investigation and the use of high flow column-switching LC/MS/ MS as a high-throughput approach for direct plasma sample analysis of single and multiple components in pharmacokinetic studies. *J. Pharm. Biomed. Anal.* 2002, 27, 967-982.)