

## Supporting information:

### Experimental Section:

**3-Methyl-1-(2-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxamide (6b).** This compound was prepared by the same methodology described for **6a** with 2-methoxyphenyl hydrazine • HCl substituted for phenyl hydrazine. There was obtained 245 mg (41%) of 3-methyl-1-(2-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxamide. mp: 126-129° C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ: 10.4 (s, 1H), 8.0 (d, J = 7.5 Hz, 1H), 7.8-7.5 (m, 4H), 7.5-7.3 (m, 5H), 7.2 (s, 2H), 7.2-7.0 (m, 2H), 6.8 (s, 1H) and 3.65 (s, 3H) ppm; HRMS (M+H)<sup>+</sup> for C<sub>24</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub>S, calc. m/z: 463.144002, obs: 463.144162.

**3-Methyl-1-(3-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxamide (6c).** This compound was prepared by the same methodology described for **6a** with 3-methoxyphenyl hydrazine•HCl substituted for phenyl hydrazine. There was obtained 440 mg (58%) of 3-methyl-1-(2-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxamide. mp: 124-132° C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.15 (d, J = 7 Hz, 1H), 7.7 (s, 1H), 7.6-7.3 (m, 7H), 7.1-6.9 (m, 3H), 6.75 (s, 1H), 4.3 (s, 2H), 3.8 (s, 3H), 2.4 (s, 3H) ppm; HRMS (M+H)<sup>+</sup> for C<sub>24</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub>S, calc. m/z: 463.144002, obs: 463.144301. Anal. calcd for C<sub>24</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub>S•0.4 H<sub>2</sub>O: 61.37, H, 4.89, N, 11.93; found, C, 61.69, H, 5.17, N, 11.76.

**3-Methyl-1-(4-methoxy)phenyl-1H-pyrazole-5-(N-(5-(2-sulfonamido)phenyl)pyridin-2-yl))carboxamide, trifluoroacetic acid salt (6e).** This compound was prepared by the methodology described for **6a** with the exception that in the coupling step 2-amino-5-(2-(N-*t*-butylsulfonamido)phenyl)pyridine was used in the place of the 4-(2-N-*t*-butylamino-sulfonyl)phenyl)aniline. The resulting product was stirred in trifluoroacetic acid (20 mL) for 18 h, whereupon the solvent was removed by distillation under reduced pressure. Purification of the

crude product by hplc utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave 178 mg (74%) of the title compound. mp: 71.1° C; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ: 8.35 (broad s, 1H), 8.15 (dd, J = 7 and 1 Hz, 1H), 7.7 – 7.5 (m, 3H) 7.4 (d, J = 9 Hz, 2H), 7.0 (d, J = 9 Hz, 2H), 6.9 (s, 1H), 3.8 (s, 3H), 2.35 (s, 3H) ppm; HRMS (M+H)<sup>+</sup> for C<sub>23</sub>H<sub>21</sub>N<sub>5</sub>O<sub>4</sub>S, calc. m/z: 464.139251, obs: 464.138485. Anal. calcd for C<sub>23</sub>H<sub>21</sub>N<sub>5</sub>O<sub>4</sub>S·C<sub>2</sub>HF<sub>3</sub>O<sub>2</sub>: C, 51.99, H, 3.84, N, 12.13; found, C, 51.92, H, 4.00, N, 12.16.

**3-Methyl-1-(4-methoxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-3-fluoro-[1,1']-biphen-4-yl))carboxamide (6f).** This compound was prepared by the same methodology described for **6a** with 4-methoxyphenyl hydrazine·HCl substituted for phenyl hydrazine and 2-fluoro-4-(2-N-*t*-butylaminosulfonyl)phenyl)aniline for the 4-(2-N-*t*-butylamino-sulfonyl)phenyl)aniline to give 250 mg (86%) of the title compound. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ: 8.1 (d, J = 6.6 Hz, 1H), 7.8-7.5 (m, 3H), 7.4-7.2 (m, 5H), 7.0 (d, J = 8.8 Hz, 2H), 6.8 (s, 1H), 3.8 (s, 3H), 2.3 (s, 3H) ppm; HRMS (M+H)<sup>+</sup> for C<sub>24</sub>H<sub>21</sub>N<sub>4</sub>O<sub>4</sub>SF, calc. m/z: 481.134581, obs: 481.133650. Anal. calcd for C<sub>24</sub>H<sub>21</sub>FN<sub>4</sub>O<sub>4</sub>S·0.25 H<sub>2</sub>O: C, 59.43, H, 4.47, N, 11.55; found, C, 59.37, H, 4.67, N, 11.36.

**3-Methyl-1-(3-hydroxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxamide (7b).** Compound **6c** was treated according to the procedure described for **7a** to give 57 mg (29%) of the title compound. mp: 129.4° C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ: 10.7 (s, 1H), 10.8-10.7 (1H, broad), 8.0 (dd, J = 7.5 and 1 Hz, 1H), 7.7 (d, J = 10 Hz, 2H), 7.65-7.5 (m, 2H), 7.4-7.2 (m, 6H), 6.9 (m, 2H), 6.8-6.7 (m, 2H), 2.3 (s, 3H) ppm; HRMS (M+H)<sup>+</sup> for C<sub>23</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub>S, calc. m/z: 449.128352, obs: 449.127620. Anal. calcd for C<sub>23</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub>S·2.25 H<sub>2</sub>O: C, 56.49, H, 5.05, N, 11.46; found, C, 56.73, H, 4.93, N, 10.97.

**3-Methyl-1-(4-hydroxy)phenyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxamide (7c).** Compound **6d** was treated according to the procedure described for **7a** to give 70 mg (72%) of the title compound. mp: 185-189° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ: 10.45 (s, 1H), 7.95 (d, J = 7.5 Hz, 1H), 7.6 (d, J = 10 Hz, 2H), 7.55-7.4 (m, 2H), 7.3-7.1 (m, 7H), 6.75 (s, 1H), 6.7 (s, 2H), 2.2 (s, 3H) ppm; HRMS (M+H)<sup>+</sup> for C<sub>23</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub>S, calc. m/z: 449.128352, obs: 449.127304.

**1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-(N-(5-(2-aminosulfonyl)phenyl)pyridin-2-yl)carboxamide (13b).** This material was prepared according to the methods described for **13a** with the exception that during the coupling step 2-amino-5-(2-N-*t*-butylaminosulfonyl)phenyl)pyridine was substituted for 4-(2-N-*t*-butylaminosulfonyl)phenyl)aniline. The *t*-butylsulfonamide group was removed by heating the coupling product at reflux in TFA for 1 h, then removing the TFA by distillation in vacuo. Purification of the final product was by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave 175 mg (53%) of the title compound. mp: 216.7° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ: 11.3 (s, 1H), 8.4 (d, J = 1 Hz, 1H), 8.05 (t, J = 7.5 Hz, 2H), 7.8 (dd, J = 7.5 and 1 Hz, 1H), 7.7-7.6 (m, 3H), 7.5-7.3 (m, 5H), 7.0 (d, J = 9 Hz, 2H), 3.8 (s, 3H) ppm; HRMS (M+H)<sup>+</sup> for C<sub>23</sub>H<sub>18</sub>F<sub>3</sub>N<sub>5</sub>O<sub>4</sub>S, calc. m/z: 518.110986, obs: 518.112930.

**1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-(N-(3-fluoro-2'-aminosulfonyl-[1,1']-biphen-4-yl)carboxamide (13c).** This material was prepared according to the methods described for **13a** with the exception that during the coupling step 3-fluoro-4-((2-N-*t*-butylaminosulfonyl)phenyl)aniline was substituted for 4-((2-N-*t*-butylaminosulfonyl)phenyl)aniline. The *t*-butylsulfonamide group was removed by heating the coupling

product at reflux in TFA for 1 h, then removing the TFA by distillation in vacuo. Purification of the final product was by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column gave 76 mg (63%) of the title compound.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$ : 8.05 (d,  $J = 7$  Hz, 1H), 7.75 (t,  $J = 6$  Hz, 1H), 7.6-7.5 (m, 2H), 7.4 (d,  $J = 9$  Hz, 2H), 7.35-7.1 (m, 4H), 7.0 (d,  $J = 9$  Hz, 2H), 3.8 (s, 3H) ppm; HRMS  $(\text{M}+\text{H})^+$  for  $\text{C}_{24}\text{H}_{18}\text{F}_4\text{N}_4\text{O}_4\text{S}$ , calc.  $m/z$ : 535.1063, obs:535.1076.

**Ethyl 1-(3-carboxy-4-methoxyphenyl)-3-methyl-1H-pyrazole-5-carboxylate (15).** 2-Methoxy-5-aminobenzoic acid (2 g, 11.9 mmol) in conc. HCl (30 mL) was cooled to 0° C and  $\text{NaNO}_2$  (0.91 g, 13.2 mmol) in water (10 mL) was added dropwise. The reaction was stirred at 0° C for 30 min, then  $\text{SnCl}_2 \cdot (\text{H}_2\text{O})_2$  (8.1 g, 36 mmol) in conc HCl (10 mL) was added. The reaction was stirred for an additional 15 min at 0° C then refrigerated for 2 h. The precipitate was filtered and air dried to give 4.76 g of the desired hydrazine **14** contaminated with Sn(II) salts. The hydrazine **14** prepared above (3.65 g, ca. 10.9 mmol) and ethyl 2-N-(methoxy)imino-4-oxopentanoate **2** (2.04 g, 10.9 mmol) in MeCN (100 mL) and water (50 mL) was heated at reflux for 3 h. The cooled reaction mixture was evaporated, dissolved in  $\text{Et}_2\text{O}$  (300 mL) and washed with water ( $2 \times 100$  mL). The  $\text{Et}_2\text{O}$  layer was dried ( $\text{MgSO}_4$ ) and evaporated to give 2.07 g of ethyl 3-methyl-1-(3-carboxy-4-methoxyphenyl)-1H-pyrazole-5-carboxylate (6.81 mmol, 63%). An impurity due to the ethyl 2-N-(methoxy)imino-4-oxopentanoate was also evident in the  $^1\text{H}$  NMR, the product was used without purification.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 8.2 (d,  $J = 1$  Hz, 1H), 7.65 (dd,  $J = 7.5$  and 1 Hz, 1H), 7.15 (d,  $J = 7.5$  Hz, 1H), 6.8 (s, 1H), 4.25 (q,  $J = 7$  Hz, 2H), 4.15 (s, 3H), 2.35 (s, 3H), 1.25 (t,  $J = 7$  Hz, 3H) ppm.

**1-(3-Azidomethyl-4-methoxyphenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (16).**

Ethyl 1-(3-carboxy-4-methoxyphenyl)-3-methyl-1H-pyrazole-5-carboxylate (2.07 g, 6.81 mmol) in THF (150 mL) was cooled to 0° C and N-methylmorpholine (0.69 g, 6.81 mmol) was added. To this cooled solution isobutyl chloroformate (0.93 g, 6.81 mmol) was added dropwise; a precipitate formed immediately. This mixture was stirred for 20 min at 0° C, then the precipitate was removed by filtration. The clear THF solution was added in one portion to a cold solution of NaBH<sub>4</sub> (0.78 g, 20.4 mmol) in THF (30 mL) and water (30 mL). The reaction was allowed to thaw to ambient temperature over 4 h. The reaction was evaporated, dissolved in EtOAc (100 mL) then washed with HCl (1N, 75 mL), NaHCO<sub>3</sub> (satd., 75 mL), brine (75 mL) and dried (MgSO<sub>4</sub>). The solution was evaporated, then applied to a column of flash silica gel and eluted with a gradient of 5:1 to 1:1 hexane: EtOAc. There was obtained 0.9 g of the ethyl 1-(3-hydroxymethyl-4-methoxyphenyl)-3-methyl-1H-pyrazole-5-carboxylate (3.07 mmol, 46%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.38 (d, J = 1 Hz, 1H), 7.3 (dd, J = 7.5 and 1 Hz, 1H), 6.9 (d, J = 7.5 Hz, 1H), 6.8 (s, 1H), 4.7 (s, 2H), 4.22 (q, J = 8 Hz, 2H), 3.9 (s, 3H), 2.38 (s, 3H), 1.25 (t, J = 8 Hz, 3H) ppm; LRMS (M+H)<sup>+</sup>: 291 m/z. Ethyl 1-(3-hydroxymethyl-4-methoxyphenyl)-3-methyl-1H-pyrazole-5-carboxylate (0.9 g, 3.07 mmol) and Et<sub>3</sub>N (0.65 g, 6.4 mmol) in CHCl<sub>3</sub> (25 mL) was cooled to 0° C and methanesulfonyl chloride (0.39 g, 3.37 mmol) was added. The reaction was allowed to thaw to ambient temperature over 18 h. The reaction was evaporated, applied to a column of flash silica gel and eluted with 3:1 hexane: EtOAc. There was obtained 0.72 g of a product giving an LRMS (M+H)<sup>+</sup> ion consistent with the corresponding benzylic chloride (309 m/z). The mesylate prepared above (0.72 g, 2.33 mmol) and NaN<sub>3</sub> (0.45 g, 7 mmol) in DMF (30 mL) was stirred at 60° C for 6 h. The reaction was cooled to ambient temperature, diluted with water (200 mL) and extracted with EtOAc (3 × 75 mL). The EtOAc extracts were washed with

water ( $5 \times 75$  mL), dried ( $\text{MgSO}_4$ ) and evaporated to give 0.47 g (1.5 mmol, 65%) of the corresponding azide. LRMS ( $\text{M}+\text{H}$ )<sup>+</sup>: 316 m/z. This product was heated at 45° C in EtOH (15 mL) and water (15 mL) with 50% NaOH (3 mL) for 4 h. The reaction was evaporated, brine (50 mL) was added and the solution acidified to pH 1 with conc. HCl. The precipitate that resulted was filtered and air dried to give 1-(3-azidomethyl-4-methoxyphenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (0.17 g, 0.6 mmol, 40%). <sup>1</sup>H NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 7.4 (m, 2H), (d,  $J = 11.3$  Hz, 1H), 6.8 (s, 1H), 4.4 (s, 2H), 3.9 (s, 3H), 2.25 (s, 3H) ppm; LRMS ( $\text{M}+\text{H}$ )<sup>+</sup>: 288 m/z.

**1-(3-Azidomethyl-4-methoxyphenyl)-3-methyl-1H-pyrazole-5-(2'-(N-tert-butylaminosulfonyl)-[1,1']-biphenyl-4-yl)carboxamide (17).** 1-(3-Azidomethyl-4-methoxyphenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (0.17 g, 0.6 mmol) in  $\text{CHCl}_3$  (20 mL) was cooled to 0° C. A 2M solution of oxalyl chloride in  $\text{CH}_2\text{Cl}_2$  (0.6 mL, 1.2 mmol) followed by a drop of DMF was added. The reaction thawed to ambient temperature over 3 h and was evaporated. The resulting acid chloride was re-dissolved in  $\text{CHCl}_3$  (5 mL) and added dropwise to a 0° C  $\text{CHCl}_3$  (20 mL) solution of 4-(2-N-tertbutylaminosulfonyl)phenyl aniline **4a** (0.19 g, 0.61 mmol),  $\text{Et}_3\text{N}$  (0.08 g, 0.84 mmol) and DMAP (0.07 g, 0.6 mmol). This mixture was thawed to ambient temperature over 18 h then evaporated and applied to a column of flash silica gel. Elution of the column with a gradient of 3:1 to 1:1 hexane: EtOAc gave 0.14 g of the title compound (0.24 mmol, 40%). <sup>1</sup>H NMR ( $\text{CDCl}_3$ )  $\delta$ : 8.15 (d,  $J = 7.5$  Hz, 1H), 7.7 (broad s, 1H), 7.6-7.4 (m, 8H), 7.3 (d,  $J = 7.5$  Hz, 1H), 7.0 (d,  $J = 8$  Hz, 1H), 6.7 (s, 1H), 4.4 (s, 2H), 3.9 (s, 3H), 3.6 (broad s, 1H), 2.4 (s, 3H), 1.0 (s, 9H) ppm; LRMS ( $\text{M}+\text{Na}$ )<sup>+</sup>: 596.

**1-(3-Aminomethyl-4-methoxyphenyl)-3-methyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxamide, trifluoroacetic acid salt (18).** Compound **17** (0.07 g, 0.12 mmol) and  $\text{SnCl}_2 \cdot (\text{H}_2\text{O})_2$  (0.084 g, 0.36 mmol) in MeOH (10 mL) was stirred at ambient temperature for

18 h. The reaction was evaporated, water added and the mixture made basic (pH 11) with 4N NaOH. The water layer was extracted with Et<sub>2</sub>O (3 x 50 mL); the extract was dried and evaporated to give 0.06 g of the 3-aminomethyl product; LRMS (M+H)<sup>+</sup>: 548 m/z. This material was heated at reflux in TFA (10 mL) for 1h. The TFA was removed and the title compound (73 mg, 100%) was isolated by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column. mp 142.7° C. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ: 8.1 (dd, J = 7 and 1 Hz, 1H), 7.7-7.45 (m, 6H), 7.4 (d, J = 8.7 Hz, 2H), 7.3 (dd, J = 7.7 and 1.5 Hz, 1H), 7.2 (d, J = 9 Hz, 1H), 6.85 (s, 1H), 4.1 (s, 2H), 3.95 (s, 3H), 2.4 (s, 3H) ppm; HRMS (M+H)<sup>+</sup> for C<sub>25</sub>H<sub>25</sub>N<sub>5</sub>O<sub>4</sub>S, calc. m/z: 492.170551, obs: 492.169655.

**1-(2-Aminomethyl-4-methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1]-biphen-4-yl))carboxamide, trifluoroacetic acid salt (34a)** 1-(2-Azidomethyl-4-methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-carboxylic acid chloride prepared as for **32d** and 4-(2-N-tertbutylsulfonamido)phenyl aniline were treated as described in **34b** to give 98 mg (42%) of the title compound. mp 145.2° C. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ: 8.1 (dd, J = 8 and 1 Hz, 1H), 7.7-7.5 (m, 4H), 7.45 (s, 1H), 7.4 (d, J = 15 Hz, 2H), 7.3 (t, J = 15 Hz, 2H), 7.25 (d, J = 2 Hz, 1H), 7.1 (dd, J = 15 and 2 Hz, 1H), 3.95 (s, 2H), 3.9 (s, 3H) ppm; HRMS (M+H)<sup>+</sup> for C<sub>25</sub>H<sub>22</sub>F<sub>3</sub>N<sub>5</sub>O<sub>4</sub>S, calc. m/z: 546.1422, obs m/z: 546.1409. Anal. calcd for C<sub>25</sub>H<sub>22</sub>F<sub>3</sub>N<sub>5</sub>O<sub>4</sub>S·C<sub>2</sub>HF<sub>3</sub>O<sub>2</sub>: C, 49.17, H, 3.51, F, 17.28, N, 10.61, S, 4.86; found, C, 48.90, H, 3.23, F, 17.49, N, 10.16, S, 4.33.

**2-[5-(2-Furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzamide (36).** 4,4,4-Trifluoro-1-(2-furyl)-1,3-butanedione **28** (2.4 mL, 16 mmol) was added to 2-hydrazinobenzoic acid **35** (3.01 g, 16 mmol) in acetic acid (20 mL) and heated at reflux for 25 h. The reaction was cooled, diluted with EtOAc, and extracted twice with water. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered,

and evaporated to yield a thick red paste (5.71 g, >100%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.18 (dd, 1H,  $J = 7.7$ ,  $J' = 1.8$ ), 7.74 (td, 1H,  $J = 7.7$ ,  $J' = 1.4$ ), 7.65 (td, 1H,  $J = 7.7$ ,  $J' = 1.5$ ), 7.50 (dd, 1H,  $J = 7.3$ ,  $J' = 1.1$ ), 7.35 (m, 1H), 6.89 (s, 1H), 6.28 (m, 1H), 5.76 (d, 1H,  $J = 3.3$ ) ppm. The carboxylic acid (5.13 g, 16 mmol) was dissolved in thionyl chloride (25 mL) and heated at reflux for 2 h. The excess thionyl chloride was evaporated, and the resulting acid chloride was placed under high vacuum. The acid chloride was then redissolved in  $\text{CH}_2\text{Cl}_2$  (25 mL) and cooled to  $0^\circ\text{C}$ . Conc. aqueous  $\text{NH}_3$  (6 mL) was added portion-wise over 30 min. The resulting mixture was stirred at  $0^\circ\text{C}$  for 30 min, then at room temperature for 1 h. The reaction was diluted with water and extracted with  $\text{CH}_2\text{Cl}_2$  (3 $\times$ ). The organic layers were combined and extracted with 2M  $\text{Na}_2\text{CO}_3$ . The organic layer was dried over  $\text{MgSO}_4$ , filtered, and evaporated to yield the desired product (4.76 g, 93%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.98 (dd, 1H,  $J = 7.3$ ,  $J' = 2.2$ ), 7.67 (m, 2H), 7.41 (m, 2H), 6.96 (s, 1H), 6.28 (m, 1H), 5.89 (bs, 1H), 5.67 (d, 1H,  $J = 2.9$ ) ppm.

**t-Butyl 2-[5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzylcarbamate (37).** 2-[5-(2-Furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzamide (6.73 g, 21 mmol) and triethylamine (5.8 mL, 42 mmol) were combined in dry  $\text{CH}_2\text{Cl}_2$  (55 mL) under argon and cooled to  $0^\circ\text{C}$ . Trichloroacetyl chloride (2.7 mL, 24 mmol) in  $\text{CH}_2\text{Cl}_2$  (15 mL) was added dropwise over 30 min. The resulting solution was stirred at  $0^\circ\text{C}$  for 20 min, then at room temperature for 65 min. The reaction was quenched with a small amount of water, then partitioned between 1M HCl and  $\text{CH}_2\text{Cl}_2$ . The organic layer was removed and extracted with sat.  $\text{NaHCO}_3$ , then dried over  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated to yield crude product (6.66 g). The crude product was chromatographed on silica gel (30-40% EtOAc/hexanes) to yield a yellow solid (6.51 g, >100%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.79 (m, 2H), 7.64 (m, 2H), 7.39 (d, 1H,  $J = 1.8$ ), 6.96 (s, 1H), 6.37 (m, 1H), 6.04 (d, 1H,  $J = 3.7$ ) ppm. Cobalt chloride (1.76 g, 13.6 mmol) was added to 2-[5-(2-furyl)-3-

(trifluoromethyl)-1H-pyrazol-1-yl]benzonitrile (4.12 g, 13.6 mmol) and sodium borohydride (1.03 g, 27.2 mmol) in DMF (40 mL). The reaction turned black and became warm. An ice bath was added and the reaction was stirred at 0° C for 45 min, then at room temperature for 23 h. Additional sodium borohydride (0.25 g, 6.6 mmol) was added and the resulting mixture was stirred at room temperature for 6 h. A room temperature water bath was added, and the reaction was quenched with water (10 mL) over 10 min, then MeOH (20 mL), then 6M HCl (20 mL) over 15 min. The quenched reaction was stirred at room temperature for 16 h, diluted with EtOAc, and extracted with water and 0.1M HCl. The resulting emulsion was filtered through celite, and the organic layer was removed, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to yield crude product (857 mg). The aqueous layers were combined and neutralized (pH 8) with solid Na<sub>2</sub>CO<sub>3</sub> (6.9 g). Addition of EtOAc yielded another emulsion, which was filtered through celite. The organic layer was removed, and the aqueous layer was extracted again with EtOAc. The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to yield a second batch of crude product (3.55 g). The two batches of crude product were combined and chromatographed on silica gel (0-10% MeOH/CHCl<sub>3</sub>) to yield the desired product (3.77 g, 90%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.59 (m, 2H), 7.38 (m, 2H), 7.33 (d, 1H, J = 7.3), 6.96 (s, 1H), 6.27 (m, 1H), 5.59 (d, 1H, J = 3.6), 3.51 (s, 2H) ppm. Triethylamine (2.6 mL, 18.7 mmol) and di-t-butyl dicarbonate (4.0 g, 18.4 mmol) were added to 2-[5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzylamine (3.77 g, 12.3 mmol) in THF (60 mL) and stirred at room temperature for 17 h. The reaction was concentrated, diluted with Et<sub>2</sub>O, and extracted with water (2x). The aqueous layers were combined and extracted with Et<sub>2</sub>O. The organic layers were combined, dried over MgSO<sub>4</sub>, filtered, and evaporated to yield crude product (5.58 g). The crude product was chromatographed on silica gel (10-20% EtOAc/hexanes) to yield a waxy solid (3.82 g, 76%). <sup>1</sup>H

NMR (CDCl<sub>3</sub>)  $\delta$  7.57 (m, 2H), 7.43 (m, 2H), 7.32 (d, 1H,  $J$  = 7.7), 6.95 (s, 1H), 6.28 (m, 1H), 5.66 (d, 1H,  $J$  = 3.3), 4.82 (bs, 1H), 4.01 (bd, 2H,  $J$  = 6.2), 1.39 (s, 9H) ppm.

**1-(2-([(t-Butoxycarbonyl)amino]methyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl-5-carboxylic acid (38).** Compound **37** (3.77 g, 9.2 mmol) was dissolved in t-BuOH (60 mL). A 5% aqueous solution of NaH<sub>2</sub>PO<sub>4</sub> (40 mL) was added, followed by portionwise addition of solid KMnO<sub>4</sub> (5.86 g, 37 mmol) over 25 min. The resulting mixture was heated at 65° C for 40 min. Additional KMnO<sub>4</sub> (1.39 g, 8.8 mmol) was added, and the reaction continued heating at 65° C for 35 min. The reaction mixture was cooled and filtered through celite, using EtOH and acetone to rinse the celite. The filtrate was concentrated to approx. half its original volume and treated with aq. sodium bisulfite to remove residual KMnO<sub>4</sub>. The resulting mixture was extracted with EtOAc, and the organic layer was removed, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to yield crude product (1.50 g). The aqueous layer was cooled in ice, acidified with 1M HCl (6 mL) and extracted with EtOAc (containing a small amount of EtOH). Before separating, both layers were filtered through celite and treated with sat NaHCO<sub>3</sub> (1.5 mL). The aqueous layer was removed and extracted twice with EtOAc/EtOH. Solid NaCl was added both times to aid separation of the emulsion. The aqueous layer was extracted with CHCl<sub>3</sub>, adjusted to pH 5 with 1M HCl, and extracted twice with CHCl<sub>3</sub>/EtOH. The final 6 organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to yield a second batch of product (2.43 g, 68%). The first batch of product was chromatographed on silica gel (0-30% MeOH/CHCl<sub>3</sub>) to yield clean product (0.95 g, 27%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  7.34 (m, 4H), 7.16 (d, 1H), 6.81 (bs, 1H), 3.79 (bd, 2H), 1.32 (s, 9H) ppm.

**{2-[5-(2'-Methanesulfonyl-biphenyl-4-ylcarbamoyl)-3-trifluoromethyl-pyrazol-1-yl]-benzyl}-carbamic acid t-butyl ester (39b).** Oxalyl chloride (90  $\mu$ l, 1.0 mmol) and DMF (2

drops) were added to compound **38** (200 mg, 0.52 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and the resulting solution was stirred for 90 min at room temperature. The solvents were evaporated and the resulting compound was placed briefly under high vacuum before redissolving in CH<sub>2</sub>Cl<sub>2</sub> (5 mL). Triethylamine (220 µl, 1.6 mmol), 4-amino-2'-methylsulfonyl-[1,1']-biphenyl hydrochloride (177 mg, 0.62 mmol), and 4-dimethylaminopyridine (20 mg, 0.16 mmol) were added, and the resulting solution was stirred for 23 h at room temperature. The reaction was extracted with ice-cooled 1M HCl, then sat. NaHCO<sub>3</sub>. The organic layer was dried over MgSO<sub>4</sub>, filtered, and evaporated to yield crude product (241 mg). The crude product was chromatographed on silica gel (30-40% EtOAc/hexanes) to yield the desired product (64 mg, 20%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.21 (d, 1H, J = 8.1), 7.58 (m, 5H), 7.35 (m, 8H), 7.18 (s, 1H), 4.16 (d, 2H, J = 5.8), 2.59 (s, 3H), 1.33 (s, 9H) ppm.

**1-(2-(Aminomethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-(N-(2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide, trifluoroacetic acid salt (40b).** TFA (1 mL) was added to compound **39b** (64 mg, 0.10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and stirred at room temperature for 21 h. The reaction was evaporated and purified by reverse phase prep. HPLC (15-70% MeCN/H<sub>2</sub>O/0.5% TFA) to yield the desired product (30 mg, 46%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 10.79 (s, 1H), 8.16 (bs, 2H), 8.04 (d, 1H, J = 7.7), 7.77 (s, 1H), 7.71 (td, 1H, J = 5.8), 7.64 (m, 6H), 7.51 (m, 1H), 7.45 (d, 1H, J = 7.6), 7.34 (m, 3H), 3.79 (bm, 2H), 2.78 (s, 3H) ppm; <sup>19</sup>F NMR (DMSO-d<sub>6</sub>) δ -61.22, -73.97 ppm; HRMS calc. C<sub>25</sub>H<sub>22</sub>F<sub>3</sub>N<sub>4</sub>O<sub>3</sub>S: 515.1365; found, 515.1359. Anal. calcd for C<sub>25</sub>H<sub>22</sub>F<sub>3</sub>N<sub>4</sub>O<sub>3</sub>S·C<sub>2</sub>H<sub>3</sub>F<sub>3</sub>O<sub>2</sub>: C, 51.51, H, 3.68, N, 8.90; found, C, 51.75, H, 3.47, N, 8.99.

**12-(2-Aminomethyl-phenyl)-5-trifluoromethyl-2H-pyrazole-3-carboxylic acid (3-fluoro-2'-sulfamoyl-biphenyl-4-yl)-amide, trifluoroacetic acid salt (40a).** Oxalyl chloride (90 µl,

1.0 mmol) and DMF (2 drops) were added to compound **38** (200 mg, 0.52 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and the resulting solution was stirred for 95 min at room temperature. The solvents were evaporated and the resulting compound was placed briefly under high vacuum before redissolving in CH<sub>2</sub>Cl<sub>2</sub> (5 mL). Triethylamine (150  $\mu$ l, 1.1 mmol), 4-amino-2'-(*t*-butylamino)sulfonyl-[1,1']-biphenyl (190 mg, 0.62 mmol), and 4-dimethylaminopyridine (20 mg, 0.16 mmol) were added, and the resulting solution was stirred for 23 h at room temperature. The reaction was extracted with dilute brine solution, ice-cooled 1M HCl, and sat. NaHCO<sub>3</sub>. The organic layer was dried over MgSO<sub>4</sub>, filtered, and evaporated to yield crude product (371 mg). The crude product was chromatographed on silica gel (30% EtOAc/hexanes) to yield the desired product (74 mg, 21%). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.64 (bs, 1H), 8.15 (dd, 1H, *J* = 7.7, *J'* = 1.5), 7.45 (m, 10H), 7.25 (d, 1H, *J* = 6.9), 7.20 (s, 1H), 5.33 (bs, 1H), 4.15 (d, 2H, *J* = 5.8), 3.49 (bs, 1H), 1.34 (s, 9H), 0.97 (s, 9H) ppm. TFA (2 mL) was added to {2-[5-(2'-*N*-*tert*-butylaminosulfonyl-biphenyl-4-ylcarbamoyl)-3-trifluoromethyl-pyrazol-1-yl]-benzyl}-carbamic acid *t*-butyl ester (74 mg, 0.11 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and stirred at room temperature for 19 h. Additional TFA (2 mL) was added, and the reaction continued stirring for 3 h. The reaction was evaporated and purified by reverse phase prep. HPLC (15-70% MeCN/H<sub>2</sub>O/0.5% TFA) to yield the desired product (41 mg, 59%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  10.75 (s, 1H), 8.17 (bs, 3H), 7.98 (dd, 1H, *J* = 7.3), 7.76 (s, 1H), 7.57 (m, 7H), 7.44 (d, 1H, *J* = 6.7), 7.32 (d, 2H, *J* = 8.8), 7.25 (m, 3H) 3.79 (bd, 2H, *J* = 5.1) ppm; <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>)  $\delta$  -61.22, -73.99 ppm; HRMS calc. C<sub>24</sub>H<sub>21</sub>F<sub>3</sub>N<sub>5</sub>O<sub>3</sub>S: 516.1317; found, 516.1319. Anal. calcd for C<sub>24</sub>H<sub>21</sub>F<sub>3</sub>N<sub>5</sub>O<sub>3</sub>S·C<sub>2</sub>HF<sub>3</sub>O<sub>2</sub>: C, 49.53, H, 3.52, N, 11.11; found, C, 49.84, H, 3.37, N, 11.23.

**1-(2-(Aminomethyl)phenyl)-3-trifluoromethyl-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide, trifluoroacetic acid salt (40d).** Oxaly

chloride (320  $\mu$ l, 3.7 mmol) and DMF (4 drops) were added to compound **38** (940 mg, 2.4 mmol) in  $\text{CH}_2\text{Cl}_2$  (35 mL) and the resulting solution was stirred for 55 min at room temperature. The solvents were evaporated and the resulting compound was placed briefly under high vacuum before redissolving in  $\text{CH}_2\text{Cl}_2$  (20 mL). 4-Amino-3-fluoro-2'-methylsulfonyl-[1,1']-biphenyl (750 mg, 2.8 mmol) in  $\text{CH}_2\text{Cl}_2$  (15 mL), and 4-dimethylaminopyridine (447 mg, 3.7 mmol) were added, and the resulting solution was stirred for 20 h at room temperature. The reaction was concentrated and chromatographed on silica gel (30-40% EtOAc/hexanes) to yield impure product (802 mg), which was purified on reverse phase prep. HPLC (10-70% MeCN/ $\text{H}_2\text{O}$ /0.5% TFA) to yield clean product (645 mg, 42%). TFA (2 mL) was added to 1-[2-(((t-butoxycarbonyl)amino)methyl)phenyl)-5-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))aminocarbonyl]-3-(trifluoromethyl)pyrazole (132 mg, 0.21 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) and stirred at room temperature for 5 h. The reaction was evaporated and purified by reverse phase prep. HPLC (10-70% MeCN/ $\text{H}_2\text{O}$ /0.5% TFA) to yield the desired product (80 mg, 59%).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  10.65, (s, 1H), 8.16 (bs, 3H), 8.05 (d, 1H,  $J = 6.6$ ), 7.79 (s, 1H), 7.73 (td, 1H,  $J = 6.2$ ,  $J' = 1.5$ ), 7.67 (dd, 1H,  $J = 7.7$ ,  $J' = 1.5$ ), 7.54 (m, 5H), 7.35 (m, 2H), 7.19 (d, 1H,  $J = 8.0$ ), 3.78 (bd, 2H,  $J = 5.5$ ), 2.88 (s, 3H) ppm;  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  -61.26, -74.11, -122.19 ppm; HRMS calc.  $\text{C}_{25}\text{H}_{21}\text{F}_4\text{N}_4\text{O}_3\text{S}$ : 533.1217; found, 533.1258. Anal. calcd for  $\text{C}_{25}\text{H}_{21}\text{F}_4\text{N}_4\text{O}_3\text{S} \cdot 1.1 \text{ C}_2\text{HF}_3\text{O}_2$ : C, 49.58, H, 3.38, N, 8.50; found, C, 49.83, H, 2.97, N, 8.52.

## Synthesis of DPC602

### Preparation of 1-(2-Carboxyphenyl)-3-trifluoromethyl-5-(2-furyl)-1H-pyrazole (29b).

2-Carboxyphenylhydrazine (**35**, 18.3 g, 97 mmol) in glacial acetic acid (200 ml) was heated at reflux until it was dissolved. 4,4,4-Trifluoro-1-(2-furyl)-1,3-butanedione (20 g, 97 mmol) was added and the mixture heated at reflux for 6 h. The solvent was removed in vacuo and the residue partitioned

between EtOAc (200 ml) and water (200ml). The EtOAc extract was washed with water (2 x 200 ml), dried (MgSO<sub>4</sub>) and evaporated to afford 28.8 g of 1-(2-Carboxyphenyl)-3-trifluoromethyl-5-(2-furyl)-1H-pyrazole (90%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.2 (dd, 1H), 7.75 (td, 1H), 7.65 (td, 1H), 7.5 (dd, 1H), 7.3 (d, 1H), 6.9 (s, 1H), 6.3 (ddd, 1H), 5.75 (d, 1H) ppm.

**Preparation of 1-(2-Hydroxymethylphenyl)-3-trifluoromethyl-5-(2-furyl)-1H-pyrazole**

1-(2-Carboxyphenyl)-3-trifluoromethyl-5-(2-furyl)-1H-pyrazole (28.8 g, 90 mmol) in THF was cooled to 0° C and N-methylmorpholine (9.51 g, 94 mmol) and isobutylchloroformate (18.1 g, 133 mmol) were added. The reaction was allowed to warm up to ambient temperature and followed by t.l.c (3:1 hexane : EtOAc, MeOH quench). When all of the starting acid was consumed the reaction mixture was filtered into a cold water (125 ml) solution of NaBH<sub>4</sub> (6.8 g, 180 mmol) and was allowed to warm up to ambient temperature over 4 h. A solution of 1N HCl (180 ml) was added to the reaction mixture, followed by brine (300 ml) to separate the layers. The aqueous layer was extracted with CHCl<sub>3</sub> (100 ml) and the combined aqueous layers were washed with brine (100 ml), dried (MgSO<sub>4</sub>) and evaporated. This material was purified further by flash chromatography (800 g SiO<sub>2</sub>) by eluting with 4:1 hexane: EtOAc to afford 13.7 g (50%) of 1-(2-Hydroxymethylphenyl)-3-trifluoromethyl-5-(2-furyl)-1H-pyrazole: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.7 (dd, 1H), 7.6 (td, 1H), 7.5-7.4 (m, 2H), 7.3 (dd, 1H), 7.0 (s, 1H), 6.3 (ddd, 1H), 5.75 (d, 1H), 4.35 (d, 2H), 2.7 (t, 1H) ppm; ESI-MS m/z 309 (M+H).

**Preparation of 1-(2-Azidomethylphenyl)-3-trifluoromethyl-5-(2-furyl)-1H-pyrazole (30b)**

1-(2-Hydroxymethylphenyl)-3-trifluoromethyl-5-(2-furyl)-1H-pyrazole (13.7 g, 44 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 ml) and Et<sub>3</sub>N (5.4 g, 53 mmol) were cooled to 0° C. Methanesulfonyl chloride (6.1 g, 53 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 ml) was added dropwise. This mixture was allowed to warm to ambient

temperature over 5 h. The  $\text{CH}_2\text{Cl}_2$  solution was washed with brine (200 ml), dried ( $\text{MgSO}_4$ ) and evaporated to give 15.8 g (92%) of mesylate: ESI-MS  $m/z$  387 ( $\text{M}+\text{H}$ ). The mesylate (15.8 g, 41 mmol) in DMF (150 ml) was stirred with  $\text{NaN}_3$  (8 g, 123 mmol) at ambient temperature for 18 h. The reaction was diluted with brine (300 ml) and extracted with EtOAc (3 x 200 ml). The combined EtOAc extracts were washed with brine (5 x 200 ml), dried ( $\text{MgSO}_4$ ) and evaporated. This material was purified by flash chromatography (800 g  $\text{SiO}_2$ ) by eluting with 5:1 hexane: EtOAc to afford 10.9 g (85%) of 1-(2-Azidomethylphenyl)-3-trifluoromethyl-5-(2-furyl)-1H-pyrazole:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.7-7.3 (m, 5H), 6.95 (s, 1H), 6.3 (ddd, 1H), 5.7 (d, 1H), 4.15 (s, 2H) ppm; CIMS  $m/z$  351 ( $\text{M}+\text{NH}_4$ ).

**Preparation of 1-(2-Azidomethylphenyl)-3-trifluoromethyl-1H-pyrazole-5-carboxylic acid (31b).** A solution of  $\text{NaH}_2\text{PO}_4$  (20.2 g, 146 mmol) in water (20 ml) was cooled to  $0^\circ\text{C}$  and 1-(2-Azidomethylphenyl)-3-trifluoromethyl-5-(2-furyl)-1H-pyrazole (9.7 g, 29 mmol) in  $\text{CH}_3\text{CN}$  (100 ml) was added. To this mixture a solution of  $\text{NaClO}_2$  (26.3 g, 292 mmol) in water (100 ml) was added in 3 equal portions 10 min apart. The reaction was allowed to warm up to ambient temperature over 18 h. A solution of 1N  $\text{NaOH}$  (200 ml) was added and the mixture was washed with  $\text{CHCl}_3$  (2 x 100 ml). The  $\text{CHCl}_3$  solution was back extracted with saturated  $\text{Na}_2\text{CO}_3$  (2 x 100 ml). The combined basic layers were made acidic (pH 2) with concentrated  $\text{HCl}$  solution and extracted with EtOAc (2 x 200 ml), dried ( $\text{MgSO}_4$ ) and evaporated to afford 5.4 g of 1-(2-Azidomethylphenyl)-3-trifluoromethyl-1H-pyrazole-5-carboxylic acid (60%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.8-8.2 (br s, 1H), 7.8-7.2 (m, 5H), 4.05 (s, 2H) ppm; ESI-MS(-ve)  $m/z$  310 ( $\text{M}-\text{H}$ ).

**Preparation of 4-Amino-3-fluoro-2'-aminosulfonyl-1,1'-biphenyl (4c)**

A mixture of 4-bromo-2-fluoroaniline (1.9 g, 10 mmol), o-sulfonamide-t-Butylphenylboronic acid (2.57 g, 10 mmol), sodium carbonate (3.2 g, 30 mmol) in THF (100 ml) and water (50 ml) was stirred at ambient temperature for 30 min. while nitrogen gas was bubbled into the solution to remove oxygen. To this mixture was added tetrakis(triphenylphosphine) palladium(0) (0.02 eq., 0.23 g, 0.2 mmol). This reaction mixture was refluxed for 18 h. The reaction mixture was filtered through celite to remove catalyst and washed with THF (50 ml). The filtrate was evaporated in vacuo and the residue was taken up in water (100 ml) and extracted with ethyl acetate (3 x 100 ml). The ethyl acetate extracts were washed with brine (100 ml), dried (MgSO<sub>4</sub>), and evaporated. The solid was recrystallized from n-hexane to afford the BOC protected intermediate (1.9 g, 61%): <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  : 8.0 (d, 1H), 7.55 (t, 1H), 7.45 (t, 1H), 7.25 (d, 1H), 7.0 (d, 1H), 6.9 (d, 1H), 6.75 (t, 1H), 6.45 (s, 1H), 5.2 (s, 2H) ppm. This material was heated at reflux in TFA for 1 h and the solvent was removed in vacuo to afford the title compound.

**Preparation of 1-(2-Azidomethylphenyl)-3-trifluoromethyl-N-[3-fluoro-2'-(aminosulfonyl)[1,1'-biphenyl]-4-yl]-1H-pyrazole-5-carboxamide (32e).** To a solution of acetonitrile (320 mL), 1-(2-Azidomethylphenyl)-3-trifluoromethyl-1H-pyrazole-5-carboxylic acid (13.07 g, 42 mmol) and pyridine (13.2 g, 180 mmol) was added oxalyl chloride (7.19 g, 0.058 mol) dropwise over 15 min. During this time the temperature rose from 22 °C to 27 °C. After the addition was complete, the mixture turned yellow and a precipitate started to form. After one hour, the reaction was only 87 % complete; thirty minutes later the reaction was essentially complete, 97.6 %. The reaction mixture was cooled to 2.4 °C and 4-Amino-3-fluoro-2'-aminosulfonyl-1,1'-biphenyl (12.71 g, 44 mmol) was added all at once as a solid. This mixture was stirred at room temperature for 2.5 h. The mixture was transferred to a separatory funnel with 300 mL ethyl acetate and washed with water (2 X 200 mL), dried (MgSO<sub>4</sub>) and evaporated. The residue was chromatographed on a

500 g silica gel column by eluting with a gradient of 20 to 35 % EtOAc in hexane to afford the title compound (11.7 g, 50%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.24 (t,  $J$  = 8.0 Hz, 1H); 8.12 (dd,  $J$  = 7.69, 1.1 Hz, 1H); 8.02 (d,  $J$  = 2.56 Hz, 1H); 7.62-7.48 (m, 5H); 7.42 (dd,  $J$  = 7.77, 0.8 Hz, 1H); 7.3-7.23 (m, 4H); 7.16 (t,  $J$  = 8.42 Hz, 1H); 4.39 (s, 2H); 4.32 (s, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  155.58, 140.61, 139.54, 138.35, 137.72, 132.97, 132.36, 132.19, 131.01, 130.27, 129.55, 128.28, 128.08, 127.87, 125.62, 125.37, 125.33, 121.64, 117.05, 116.78, 107.00, 72.76, 51.00, 49.39 ppm;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.65, -129.66 ppm; ESI-MS  $m/z$  582.1 ( $\text{M}+\text{Na}^+$ ).

**1-(2-Aminomethylphenyl)-3-trifluoromethyl-N-[3-fluoro-2'-(aminosulfonyl)[1,1'-biphenyl]-4-yl]-1H-pyrazole-5-carboxamide hydrogen chloride (DPC602).** The azido intermediate prepared above (11.5 g, 21 mmol) was dissolved in 1 L methanol to give a clear colorless solution. To this solution was added 60 mL of 1N HCl in diethyl ether; the solution developed a slight yellow color. The catalyst (2.5 g, 10 % Pd/C) was added and the mixture was hydrogenated at 50 psi at room temperature. Sampling after 90 minutes showed quantitative reduction and no by-products. The catalyst was filtered off with a fiber glass filter, the solvent was removed to give a thick oil which, upon the addition of 250 mL diethyl ether, solidified. The mixture was warmed sufficiently to redissolve the solid. After standing in the freezer overnight, 7.5 g (67%) of **DPC602** was recovered:  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  8.56 (s, 2H); 8.39 (dd,  $J$  = 7.2, 2.0 Hz, 1H); 7.88 (s, 1H); 7.76 (d,  $J$  = 7.7 Hz, 1H); 7.67-7.59 (m, 3H); 7.55 (d,  $J$  = 7.7 Hz, 2H); 7.49 (dt,  $J$  = 7.6 Hz, 1.8 Hz, 1H); 7.42 (s, 2H); 7.36-7.28 (m, 2H), 7.19 (dd,  $J$  = 8.0, 1.8 Hz, 1H) 3.80 (s, 2H) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ )  $\delta$  156.76, 152.83, 142.67, 140.11, 139.89, 139.57, 138.62, 138.33, 132.63, 131.94, 131.28, 130.49, 129.40, 128.95, 128.54, 128.06, 127.80, 125.80, 125.63, 123.93, 117.49, 117.22, 107.79, 38.02 ppm;  $^{19}\text{F}$  NMR (282 MHz,  $\text{DMSO}-d_6$ )  $\delta$  -61.23, -122.40 ppm; ESI-MS  $m/z$  534.1 ( $\text{M}+\text{H}$ ); IR (KBr) 3149.7, 1677.26, 1590.87, 1526.17, 1499.18, 975.43, 1160.75, 1241.25, 765.97,

588.23  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{24}\text{H}_{20}\text{N}_5\text{ClF}_4\text{O}_3\text{S} \cdot 1/2 \text{H}_2\text{O}$ : C, 49.79; H, 3.66; N, 12.10; Cl: 6.12, S, 5.45. Found: C, 49.81; H, 3.43; N, 11.87; Cl, 6.22; S, 7.22.

**[2-(5-Furan-2-yl-3-trifluoromethyl-pyrazol-1-yl)-phenyl]-acetonitrile (47).** To a solution of 3-2-(5-Furan-2-yl-3-trifluoromethyl-pyrazol-1-yl)-benzoic acid **41** (29.52 g, 91.7 mmol) in THF (300 mL) at 0° C was added NMM (9.28 g, 91.7 mmol), followed by dropwise addition of isobutyl chloroformate (12.52 g, 91.7 mmol). The reaction was allowed to thaw to ambient temperature over 18 h. The reaction was filtered and added to a cold (ice bath) solution of  $\text{NaBH}_4$  (6.92 g, 183.4 mmol) in water (150 mL). After 5 h, conc. HCl (25 mL) and water (75 mL) was added dropwise. The solution was then saturated with solid NaCl and the layers of the resulting biphasic mixture separated. The water layer was extracted with  $\text{CHCl}_3$  (3  $\times$  100 mL) and the combine organic layers were dried ( $\text{MgSO}_4$ ) and evaporated. There was obtained 27.24 g (88.44 mmol, 96%) of the desired alcohol.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.7 (d,  $J$  = 7.8 Hz, 1H) 7.68 (s, 1H), 7.57 (t,  $J$  = 7.4 Hz, 1H), 7.4 (t,  $J$  = 7.4 Hz, 1H), 7.3 (d.,  $J$  = 7.7 Hz, 1H), 6.96 (s, 1H), 6.3 (m, 1H), 5.76 (m, 1H), 4.35 (s, 2H) ppm; To 1-(2-(Hydroxymethyl)phenyl)-3-trifluoromethyl-5-(furan-2-yl)-1H-pyrazole (4.84 g, 15.71 mmol) in  $\text{CHCl}_3$  (50 mL) at 0° C was added  $\text{Et}_3\text{N}$  (1.59 g, 15.71 mmol) and methanesulfonyl chloride (1.8 g, 15.71 mmol). The reaction was allowed to thaw to ambient temperature over 18 h. The reaction was diluted with  $\text{CHCl}_3$  (100 mL), washed with 1N HCl (100 mL), then dried and evaporated to give 5.84 g of mesylate. This mesylate (assuming 15.71 mmol) was heated at reflux in toluene (35 mL): water (35 mL) with KCN (3.85 g, 78.55 mmol) and tetrabutylammonium bromide (5.06 g, 15.71 mmol) for 18 h. The reaction was diluted with EtOAc (100 mL) and water (100 mL), the layers separated and the EtOAc solution dried ( $\text{MgSO}_4$ ). Evaporation of the solvent gave 4.0 g of crude product. This material was purified further by mpc using a column of flash silica gel (360 g) and eluting with 5:1

hexane: EtOAc. There was obtained 1.62 g (5.1 mmol, 32%) of pure material.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.71 (d,  $J = 7.6$  Hz, 1H), 7.63 (t,  $J = 7.5$  Hz, 1H), 7.52 (t,  $J = 7.8$  Hz, 1H), 7.45-7.3 (m, 2H), 7.0 (s, 1H), 6.32 (m, 1H), 5.76 (d,  $J = 3.6$  Hz, 1H), 3.52 (s, 2H) ppm;

**1-(2-(2-Cyanomethylphenyl)-3-trifluoromethyl-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide (48).**  $\text{NaH}_2\text{PO}_4$  (3.52 g, 25.5 mmol) in water (6 mL) was added to a  $0^\circ\text{C}$  solution of compound **47** (1.65 g, 5.1 mmol) in MeCN (15 mL). A cold solution  $\text{NaClO}_2$  (4.6 g, 51 mmol) in water (21 mL) was added carefully in 3 portions to control the exotherm. The reaction was allowed to stir at ambient temperature and was complete after 24 h. To this mixture 1N NaOH (50 mL) was added and the solution washed with  $\text{CHCl}_3$  ( $2 \times 25$  mL). The  $\text{CHCl}_3$  washings were extracted with 1N NaOH ( $2 \times 25$  mL) then the basic solutions were combined and acidified with conc. HCl (ca. 5 mL, pH 1). The suspension was extracted with EtOAc ( $3 \times 50$  mL), dried ( $\text{MgSO}_4$ ) and evaporated to give 1.35 g (4.6 mmol, 90%) of the desired carboxylic acid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.63-7.5 (m, 2H), 7.46 (td,  $J = 7.7$  and 1.9 Hz, 1H), 7.4-7.2 (m, 2H), 3.53 (s, 2H). LRMS (M-H) $^-$ : 294.1 m/z. 1-(2-(cyanomethyl)phenyl)-3-trifluoromethyl-1H-pyrazole-5-carboxylic acid (0.68 g, 2.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (25 mL) was cooled to  $0^\circ\text{C}$  and oxalyl chloride (0.44 g, 3.45 mmol) followed by 2 drops of DMF was added. The reaction was stirred for 18 h then the solvent was evaporated. The acid chloride (assuming 2.3 mmol) was combined with DMAP (0.84 g, 6.9 mmol) and 2-fluoro-4-(2-methylsulfonylphenyl)aniline **4d** (0.62 g, 2.1 mmol) in  $\text{CHCl}_3$  (35 mL) and stirred for 18 h. The reaction was diluted with  $\text{CHCl}_3$  (100 mL) and washed with 1N HCl ( $2 \times 50$  mL) then dried and evaporated to give 1.0 g of crude product. This material was purified further by mpic on a silica gel column (200 g of flash silica) eluted with 2:1 hexane: EtOAc. There was isolated 0.24 g (0.44 mmol, 20%) of pure product as an amorphous foam.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 8.24 (d,  $J = 8$  Hz, 1H),

8.2 (dd, J = 7.7 and 1.6 Hz, 1H), 8.1 (broad, 1H), 7.7-7.59 (m, 4H), 7.5 (td, J = 7.3 and 1.5 Hz, 1H), 7.4 (dd, J = 7.7 and 1.1 Hz, 1H), 7.33 (m, 1H), 7.3 (s, 1H), 7.15 (d, J = 8.4 Hz), 3.7 (s, 2H), 2.7 (s, 3H) ppm; HRMS (M+Na)<sup>+</sup> for C<sub>26</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>SF<sub>4</sub>, calc. m/z: 565.0933, obs. m/z: 565.0944.

**1-(2-Aminoethylphenyl)-3-trifluoromethyl-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide, trifluoroacetic acid salt (49).** Compound 48 (0.24 g, 0.44 mmol) in MeOH (50 mL) and TFA (1 mL) was shaken under an atmosphere of H<sub>2</sub> gas (50 psi) in the presence of 10% Pd-C catalyst (200 mg) for 48 h. The reaction was purged with N<sub>2</sub> gas and the catalyst removed by filtration through a pad of Celite. Evaporation gave 0.26 g of crude product. This material was purified further by hplc utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column to give the title compound as 84 mg of a white solid (0.15 mmol, 34%). mp 194° C. <sup>1</sup>H NMR (CD<sub>3</sub>OD-d<sub>4</sub>) δ: 8.15 (dd, J = 7.6 and 1.4 Hz, 1H), 7.6-7.2 (m, 3H), 7.56-7.5 (m, 3H), 7.44 (td, J = 7.6 and 1.8, 1H), 7.38 (dd, J = 7.7 and 1.4 Hz, 1H), 7.32-7.28 (m, 2H), 7.2 (dd, J = 8.1 and 1.1 Hz, 1H), 3.12 (t, J = 7.7 Hz, 2H), 2.84 (t, J = 7.7 Hz, 2H), 2.76 (s, 3H) ppm; HRMS (M+H)<sup>+</sup> for C<sub>26</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub>SF<sub>4</sub>, calc. m/z: 547.1427, obs. m/z: 547.1419.

**Data Collection and Refinement Statistics for 40c vs DPC423**

|                                                           | Factor Xa-40c                                 | Factor Xa DPC423                              |
|-----------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Number of crystals                                        | 1                                             | 1                                             |
| Maximum resolution (Å)                                    | 1.9                                           | 2.15                                          |
| Space Group                                               | P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub> | P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub> |
| Unit Cell Dimensions (Å)                                  | 57.1x72.2x78.7                                | 56.8x72.3x77.7                                |
| Completeness of data (%)                                  | 99                                            | 99                                            |
| R <sub>sym</sub>                                          | 0.071                                         | 0.059                                         |
| Number of water molecules<br>in final cycle of refinement | 199                                           | 153                                           |
| R factor                                                  | 0.224                                         | 0.222                                         |
| R-free                                                    | 0.262                                         | 0.262                                         |
| RMS deviation from ideal<br>bond lengths (Å)              | 0.008                                         | 0.009                                         |
| RMS deviation from ideal<br>bond angles (degrees)         | 1.4                                           | 1.4                                           |