Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Synthesis and Biological Evaluation of Tetrahydropyridinepyrazoles ('PFPs') as Inhibitors of STAT3 Phosphorylation

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Supplementary Methods

Synthesis of 3-(allylamino)propanenitrile (2). To a solution of acrylonitrile (23.2 g, 438 mmol) in ethanol (250 mL) at 0 ^{o}C under nitrogen, allyl amine (25 g, 438 mmol) in ethanol was added slowly and stirred at room temperature overnight. The reaction was monitored by LCMS, after completion of the reaction the reaction mass was concentrated completely to yield the product pale yellow colored oil, 45 g (93.7%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.75-5.85 (m, 1H), 5.15 (dd, *J*=1.36Hz and 15.72 Hz, 1H), 5.03(dd, *J*=0.52 Hz and 10.12 Hz, 1H), 3.14 (d, *J*=5.72 Hz, 2H), 2.70 (t , *J*=6.8 Hz, 2H), 2.55 (t, *J*=6.48 Hz, 2H).

Synthesis of 3-(*N*-((2*H*-Benzo[d][1,2,3]triazol-2-yl)(4-methoxyphenyl)methyl)-N-allylamino)propane nitrile (5). To the solution of 3-(allylamino) propanenitrile **2** (45 g, 408.5 mmol) in methanol (450 mL) under nitrogen benzotriazole was added (48.6 g, 408.5 mmol) followed by 4-methoxy benzaldehdye (61.15 g, 449.5 mmol). The reaction mixture was stirred at room temperature overnight. The reaction was monitored by TLC and upon completion the reaction mass was concentrated. The reaction product was used without further purification due to stability issues. Crude yield 135 g (95.0%) light brown color oil.

Synthesis of ethyl 3-(allyl)2-cyanoethyl)amino)-2,2-difluro-3-(4-methoxyphenyl) propanate (7). To a suspension of zinc dust (18.4 g, 288 mmol) in dry THF (350mL) under nitrogen Trimethylsilyl chloride was added (16.3 g, 151 mmol). After 10 minutes ethyl bromodifluoro acetate (32 g, 158 mmol) was slowly added and the mixture was stirred for 10 minutes. A solution of 3-(*N*-((2*H*-Benzo[d][1,2,3]triazol-2-yl)(4-methoxyphenyl)methyl)-*N*-allylamino)propanenitrile **5** (50 g, 144 mmol) in THF (150 mL) was added slowly. The reaction mass was stirred at room temperature for 12 hours. Then reaction mixture was poured on 5% aqueous $NaHCO_3$ and filtered on celite bed. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined organic layer was washed with water, brine and dried over Na_2SO_4 and concentrated. The

crude obtained was purified by flash column chromatography by using hexane:ethyl acetate as eluent to yield the product. 31 g (61%); Pale yellow colored oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.41 (d, *J*=8.64 Hz, 2H), 6.97 (d, *J*=8.76 Hz, 2H), 5.60-5.70 (m, 1H), 5.12-5.21 (m, 2H), 4.50 (dd, *J*=8.16 Hz and 26.44 Hz, 1H), 4.28-4.37 (m, 2H), 3.76 (s, 3H), 3.46-3.50 (m, 1H), 2.77-2.82 (m, 1H), 2.69-2.75 (m,1H), 2.53-2.68 (m, 2H), 2.40-2.49 (s, 1H), 1.27 (t, *J*=7.12 Hz, 3H); ^{19}F NMR (376.5 MHz, DMSO): δ114.6, 101.4;^{13}C NMR (100 MHz, DMSO):δ163.2, 159.4, 135.7, 131.5, 122.2, 119.3, 118.1, 117.0, 113.8, 62.9, 53.7, 46.0, 16.3, 13.6; MS(ESI + ion): m/z 353.2; Elemental Composition calculated for $C_{18}H_{22}F_2N_2O_3$ C, 61.35; H, 6.29; N, 7.95**.** Found: C, 61.36; H, 6.15; N, 7.90.

Synthesis of 1-allyl-5,5-difluro-6-(4-methoxyphenyl)-4-oxopiperidine-3-carbonitrile (8). To a solution of diisopropylamine (20.7 g, 408 mmol) in THF (1Litre) under nitrogen at -78 ^{o}C *n*-butyl lithium was added (12.15 g, 187 mmol) and stirred at -78 ^{o}C for 1 hour. Then a solution of ethyl 3-(allyl)2-cyanoethyl)amino)-2,2-difluro-3-(4-methoxyphenyl) propionate **7** (30 g, 85 mmol) in THF was added slowly at -78 ^{o}C over one hour. The reaction mixture was slowly brought to room temperature and stirred for 12 hours. After completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl solution (250 mL) at 0^{o}C and extracted with ethyl acetate. The combined organic layer was washed with water, brine solution and dried over Na_2SO_4 and concentrated. The crude obtained was purified by column chromatography by using hexane: ethyl acetate (1:1) as eluent to get **8**. Yield 16.5 g (63.46%); ^{1}H NMR (400 MHz, $CDCl_3$): δ7.34 (d,*J*=8.36 Hz, 2H), 6.94 (d, *J*=8.56 Hz, 2H), 5.77-5.79 (m, 1H), 5.19-5.20 (m, 2H), 4.37-4.48 (m, 2H), 3.84 (s, 3H), 3.52-3.58 (m, 1H), 3.13-3.16 (m, 1H), 2.91-2.96 (m, 1H), 2.54-2.63 (m, 2H);^{13}C NMR (100 MHz, DMSO): δ159.9, 135.5, 134.4, 131.5, 121.9, 119.7, 118.6, 114.0, 76.7, 64.6, 55.2, 53.4, 46.5, 17.1; MS (ESI + ion): m/z 307.2; Elemental Composition

calculated for $C_{16}H_{16}F_2N_2O_2C$, 62.74; H, 5.26; N, 9.15; Found: C, 62.81; H, 5.21; N, 9.19.

Synthesis of 5-allyl-2-(2,4-dichlorophenyl)-7,7-difluoro-6-(4-methoxyphenyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-amine (10).

The solution of 1-allyl-5,5-difluro-6-(4-methoxyphenyl)-4-oxopiperidine-3-carbonitrile **8** (15g, 49 mmol), 2,4-dichloro phenyl hydrazine (9.5 g, 53.7 mmol) in ethanol (450 mL) was refluxed to overnight under N_2 atmosphere. After completion of the reaction, the reaction mixture was concentrated completely and the crude product was purified by column chromatography by using hexane:ethyl acetate (1:1) as eluent to yield the product as off white colored solid, mp 98-100 ^oC. Yield 7.5 g (32%);IR (neat) νmax 3220 (br), 3440.5, 3303.0, 3169.4, 1639.6, 1616.4, 1506.4, 1493.5, 1298.2, 1245.1, 1178.9, 1140.5, 1037.4, cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ7.88 (s, 1H), 7.54-7.60 (m, 2H), 7.15 (d, *J*=8.6 Hz, 2H), 6.93 (d, *J*=8.68 Hz, 2H), 5.77-5.85 (m, 1H), 5.49 (s, 2H), 5.14-5.20 (m, 2H), 4.21-4.27 (m, 1H), 3.75 (s, 3H), 3.40-3.43 (m, 1H), 3.25-3.30 (m, 1H), 3.06-3.11 (m, 1H), 2.95-3.00 (m, 1H); ^{13}C NMR (DMSO, 100 MHz):δ159.0, 143.2, 135.4, 134.6, 133.0, 131.1, 129.9, 128.3, 123.5, 117.7, 115.4, 113.5, 97.1, 68.3, 56.5, 55.0, 44.0; MS (ESI+ion): m/z 467.0; Elemental Composition calculated for $C_{22}H_{20}Cl_2F_2N_4O$; C, 56.79; H, 4.33; N, 12.04; Found: C, 56.83; H, 4.29; N, 12.09.

General procedure for the synthesis of 12(a-c). To a solution of 5-allyl-7,7-difluoro-2-(2,4-dichlorophenyl)-4,5,6,7-tetrahydro-6-(4-methoxyphenyl)-2H-pyrazolo[4,3-c]pyridine-3-amine **(10)** in pyridine at 0 ^{o} C under nitrogen atmosphere, acid chloride was added and stirred at room temperature overnight. After completion of the reaction, 10% $NaHCO_3$ solution was added and extracted with ethyl acetate. Then combined organic layer was washed with brine solution and dried over anhydrous Na_2SO_4 and concentrated. The crude

obtained was purified by column chromatography by using hexane:ethyl acetate (1:1) to yield the pure product.

N-(5-allyl-2-(2,4-dichlorophenyl)-7,7-difluoro-4,5,6,7-tetrahydro-6-(4-methoxyphenyl)-2H-pyrazolo[4,3-c]pyridin-3-yl)acetamide(12a). IR (neat) vmax, 3389.4, 3307.3, 2927.8, 1685.5, 1640.0, 1608.4, 1513.9, 1274.1, 1091.1, 1037.3, 997.0, cm^{-1}; Mp 98-100 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.99 (s, 1H), 7.91-7.92 (m, 1H), 7.62-7.64 (m.1H), 7.55 (d, *J*=8.4 Hz, 1H) 7.18 (d, *J*=8.8 Hz, 2H), 6.94 (d, *J*=8.8 Hz, 2H), 5.76-5.83 (m, 1H), 5.14-5.19 (m, 2H), 4.33 (t, *J*=10.4 Hz, 1H), 3.77 (s, 3H), 3.41-3.51 (m,2H), 3.04(s, 2H), 1.90 (s, 3H). m/z =507.1; Elemental Composition calculated for $C_{24}H_{22}F_2Cl_2N_4O_2$; C, 56.82; H, 4.37; N,11.04. Found: C, 56.85; H, 4.40; N,11.01.

N-(5-allyl-2-(2,4-dichlorophenyl)-7,7-difluoro-4,5,6,7-tetrahydro-6-(4-methoxyphenyl)-2H-pyrazolo[4,3-c]pyridin-3-yl)benzamide (12b). IR (neat) vmax, 3389.4, 3307.3, 2927.8, 1685.5, 1640.0, 1608.4, 1513.9, 1274.1, 1091.1, 1037.3, 997.0, cm-^{1}; Mp 98-100 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.49 (s, 1H), 7.88 (s, 1H), 7.77-7.79 (m, 2H), 7.56-7.60 (m,3H), 7.20 (d, *J*=8.76 Hz, 2H), 6.96 (d, *J*=8.8 Hz, 2H), 5.77-5.84 (m, 1H), 5.12-5.18 (m, 2H), 4.38 (t, *J*=10.8 Hz, 1H), 3.75 (s,3 H), 3.05-3.08 (m, 2H), 2.78-2.50 (m, 2H); m/z=568.2; Elemental Composition calculated for $C_{29}H_{24}F_2Cl_2N_4O_2$; C, 61.17; H, .4.25; N, 9.84, Found: C, 61.19; H, .4.30; N, 9.76.

N-(5-allyl-2-(2,4-dichlorophenyl)-7,7-difluoro-4,5,6,7-tetrahydro-6-(4-methoxyphenyl)-2H-pyrazolo[4,3-c]pyridin-3-yl)-4-fluorobenzamide (12c). IR (neat) vmax, 3389.4, 3307.3, 2927.8, 1685.5, 1640.0, 1608.4, 1513.9, 1274.1, 1091.1, 1037.3, 997.0, cm-^{1}; Mp 98-100 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.5 (s, 1H), 7.84-7.88 (m, 2H), 7.60 (s, 2H),

7.31-7.35 (m, 2H), 7.20(d, *J*=8.8 Hz, 2H), 6.95 (d, *J*=8.8 Hz, 2H), 5.77-5.84 (m, 1H), 5.12-5.18(m, 2H), 4.38 (t, *J*=10.8 Hz, 1H), 3.75 (s, 3H), 3.50-3.53 (m, 2H), 3.05-3.08 (m, 2H). MS (ESI + ion): m/z =586; Elemental Composition calculated for $C_{29}H_{23}F_3Cl_2N_4O_2$; C, 59.29; H, 3.95; N 9.54. Found: C, 59.25; H, 3.97; N 9.51.

General procedure for the synthesis of 12 (d-e). To a solution of 5-allyl-7,7-difluoro-2-(2,4-dichlorophenyl)-4,5,6,7-tetrahydro-6-(4-methoxyphenyl)-2H-pyrazolo[4,3-c]pyridine-3-amine **(10)** in pyridine at 0 ^{o}C under nitrogen atmosphere, phenyl or 4-fluorophenyl sulfonyl chlorides were added and stirred at room temperature overnight. After completion of the reaction, 10% $NaHCO_3$ solution was added and extracted with ethyl acetate. Then combined organic layer was washed with brine solution and dried over anhydrous Na_2SO_4 and concentrated. The crude obtained was purified by column chromatography by using hexane:ethyl acetate (1:1) to yield the pure product.

N-(5-allyl-2-(2,4-dichlorophenyl)-7,7-difluoro4,5,6,7-tetrahydro-6-(4-methoxyphenyl)-2H-pyrazolo[4,3-c]pyridin-3-yl)benzene sulfonamide (12d). IR (neat) νmax, 3389.4, 3307.3, 2927.8, 1685.5, 1640.0, 1608.4, 1513.9, 1274.1, 1091.1, 1037.3, 997.0, cm-^{1}; Mp 98-100 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.66 (s, 1H), 7.83 (s, 1H), 7.64-7.66 (m, 3H), 7.51-7.58 (m, 3H), 7.41-7.49 (m, 1H) 7.04 (d, *J*=8.56 Hz, 2H), 5.58-5.65 (m, 1H), 5.02-5.12 (m, 2H), 4.22 (t, *J*=10.4 Hz, 1H), 3.77 (s, 3H), 4.22 (t, *J*=10.4 Hz, 1H), 3.77 (s, 3H), 2.89-2.94 (m, 2H), 2.72-2.78 (m, 2H). (m/z =605.54; Elemental Composition calculated for $C_{28}H_{24}F_2Cl_2N_4O_3S$ C, 55.54; H, 4.0; N 9.25. Found: C, 55.58; H, 4.03%; N 9.26.

N-(5-allyl-2-(2,4-dichlorophenyl)-7,7-difluoro-6-(4-methoxyphenyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-4-fluorobenzenesulfonamide (12e). IR (neat) νmax,

3389.4, 3307.3, 2927.8, 1685.5, 1640.0, 1608.4, 1513.9, 1274.1, 1091.1, 1037.3, 997.0, cm^{-1}; Mp 98-100 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.7 (s, 1H), 7.85 (s, 1H), 7.60-7.73 (m, 2H), 7.58-7.59 m, 1H), 7.47-7.49 (m, 1H), 7.34-7.38 (m, 2H), 7.06 (d, *J*=8.0 Hz, 2H), 6.95 (d, *J*=8.68 Hz, 2H), 5.62-5.64 (m, 1H), 5.03-5.13 (m, 2H), 4.22-4.41 (m, H), 3.75 (s, 3H), 2.93-2.99 (m, 2H), 2.77-2.82 (m, 2H). : m/z =623.49; Elemental Composition calculated for $C_{28}H_{23}F_3Cl_2N_4O_3S$. C, 53.94; H, .3.72; N 8.99. Found: C, 53.90; H, 3.80; N 8.92.

General procedure for the synthesis of 12 (f-h). To a solution of 5-allyl-7,7-difluoro-2-(2,4-dichlorophenyl)-4,5,6,7-tetrahydro-6-(4-methoxyphenyl)-2H-pyrazolo[4,3-c]pyridine-3-amine **(10)** in Tetrahydrofuran at -20 ^{o}C under nitrogen atmosphere, LHMDS (1M solution in THF) was added and stirred at -20^{o}C for 15 minutes. Cyclohexyl-, phenyl- or 4-trifluoromethylphenyl isocyanates were added at -20^{o} C and stirred at -20^{o} C for 30 minutes. After completion of the reaction, saturated ammonium chloride solution was added and extracted with ethyl acetate. The combined organic layer was washed with brine solution and dried over anhydrous Na_2SO_4 and concentrated. The crude obtained was purified by column chromatography by using hexane:ethyl acetate (1:1) to yield the pure product.

1-(5-allyl-2-(2,4-dichlorophenyl)-7,7-difluoro-4,5,6,7-tetrahydro-6-(4-methoxyphenyl)-2H-pyrazolo[4,3-c]pyridin-3-yl)-3-cyclohexylurea (12f). IR (neat) vmax, 3389.4, 3307.3, 2927.8, 1685.5, 1640.0, 1608.4, 1513.9, 1274.1, 1091.1, 1037.3, 997.0, cm^{-1}; Mp 98-100 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.95-7.96 (m, 2H), 7.61-7.67 (m, 2H), 7.18 (d, *J*=8.8 Hz, 2H), 6.94 (d, *J*=8.4 Hz, 2H), 6.23-6.25 (m, H), 5.80-5.81 (m, 1H), 5.14-5.20 (m, 2H), 4.30 (t, *J*=10.12 Hz, 1H), 3.77 (s, 3H), 3.49-3.52 (m, H), 3.31-3.33 (m, 2H), 3.04-3.05 (m, 2H), 1.67-1.70 (m, 2H), 1.58-1.61 (m, 2H), 1.48-1.51 (m, 1H), 1.04-1.25 (m, 6H); m/z =590.2;

Elemental Composition calculated for $C_{29}H_{31}F_2Cl_2N_5O_2$. C, 58.99; H, 5.29; N 11.86. Found: C, 58.95; H, 5.32; N 11.86.

1-(5-allyl-2-(2,4-dichlorophenyl)-7,7-difluoro-4,5,6,7-tetrahydro-6-(4-methoxyphenyl)-2H-pyrazolo[4,3-c]pyridin-3-yl)-3-phenylurea (12g). IR (neat) vmax, 3389.4, 3307.3, 2927.8, 1685.5, 1640.0, 1608.4, 1513.9, 1274.1, 1091.1, 1037.3, 997.0, cm−1; Mp 98-100 ^oC; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.78 (s, 1H), 8.43 (s, 1H), 7.99 (s, 1H), 7.71 (s, 2H), 7.34-7.36 (m, 2H), 7.20-7.27 (m, 2H), 6.95-6.98 (m, 2H), 5.78-5.85 (m, 1H), 5.13-5.20 (m, 2H), 4.35 (t, *J*=10.8 Hz, 1H), 3.77 (s, 3H), 3.55-3.57 (m, 2H), m/z =584.46; Elemental Composition calculated for $C_{29}H_{25}F_2Cl_2N_5O_2$. C, 59.60; H, 4.31; N 11.98. Found C, 59.63; H, 4.35; N 11.97.

1-(5-allyl-2-(2,4-dichlorophenyl)-7,7-difluoro-4,5,6,7-tetrahydro-6-(4-methoxyphenyl)-2H-pyrazolo[4,3-c]pyridin-3-yl)-3-(4-(trifluoromethyl)phenyl)urea (12h).

IR (neat) vmax, 3389.4, 3307.3, 2927.8, 1685.5, 1640.0, 1608.4, 1513.9, 1274.1, 1091.1, 1037.3, 997.0, cm−^{1}; Mp 98-100 ^oC; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.62 (s,1 H), 7.89 (s, 1H), 7.67-7.70 (m, 2H), 7.47-7.59 (m, 3H), 7.17-7.22 (m, 2H), 6.93-6.97 (m, 2H), 5.78-5.82 (m, 1H), 5.13-5.20 (m, 2H), 4.35 (t, *J*=10.4 Hz, 1H), 3.77 (s, 3H), 3.76-3.77 (m, 2H), 3.06-3.07 (m, 2H). m/z =652; Elemental Composition calculated for $C_{30}H_{24}F_5Cl_2N_5O_2$. C, 55.23; H, 3.71; N 10.73. Found C, 55.26; H, 3.74; N 10.71.

General procedure for the synthesis of 12 (i-k). To a solution of 5-allyl-7,7-difluoro-2-(2,4-dichlorophenyl)-4,5,6,7-tetrahydro-6-(4-methoxyphenyl)-2H-pyrazolo[4,3-c]pyridine-3-amine **(10)** in Tetrahydrofuran at -20 ^oC under nitrogen atmosphere, LHMDS(1M solution in THF) was added and stirred at -20^oC for 15 minutes. Cyclohexyl-, phenyl- or 4-

trifluoromethylphenyl isothiocyanates were added at -20°C and stirred at -20°C for 30 minutes. After completion of the reaction, saturated ammonium chloride solution was added and extracted with ethyl acetate. The combined organic layer was washed with brine solution and dried over anhydrous Na_2SO_4 and concentrated. The crude obtained was purified by column chromatography by using hexane:ethyl acetate (1:1) to yield the pure product.

1-(5-allyl-2-(2,4-dichlorophenyl)-7,7-difluoro-4,5,6,7-tetrahydro-6-(4-methoxyphenyl)-2H-pyrazolo[4,3-c]pyridin-3-yl)-3-cyclohexylthiourea (12i). IR (neat) vmax, 3389.4, 3307.3, 2927.8, 1685.5, 1640.0, 1608.4, 1513.9, 1274.1, 1091.1, 1037.3, 997.0, cm−[1]; Mp 98-100 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.98 (s, 1H), 7.90-7.94 (m, 1H), 7.64 (s, 1H), 7.21 (d, *J*=8.4 Hz, 2H), 6.90 (d, *J*=8.4 Hz, 2H), 5.77-5.81 (m,1H), 5.15-5.21(m, 2H), 4.37 (t, *J*=10.4 Hz, 1H), 3.94-3.99 (m, 1H), 3.74 (s, 3H), 2.99-3.09 (m, 2H), 1.79-1.82 (m, 2H), 1.61-1.64 (m, 2H), 1.52-1.53 (m, 1H), 1.12-1.41(m, 6H). m/z =606; Elemental Composition calculated for $C_{29}H_{31}F_2Cl_2N_5OS$. C, 57.42; H, 5.15; N, 11.55. Found C, 57.44; H, 5.14; N, 11.57.

1-(5-allyl-2-(2,4-dichlorophenyl)-7,7-difluoro-4,5,6,7-tetrahydro-6-(4-methoxyphenyl)-2H-pyrazolo[4,3-c]pyridin-3-yl)-3-phenylthiourea (12j). IR (neat) vmax, 3389.4, 3307.3, 2927.8, 1685.5, 1640.0, 1608.4, 1513.9, 1274.1, 1091.1, 1037.3, 997.0, cm−[1]; Mp 98-100 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.52 (s, 1H), 7.98 (s, 1H), 7.66-7.69 (m, 2H), 7.31-7.34 (m, H), 7.13-7.19 (m, 2H), 6.90 (d, *J*=8.96 Hz, 2H), 5.78-5.84 (m, 1H), 5.15-5.22 (m, 2H), 4.36-4.41 (s, 1H), 3.76 (s, 1H), 3.54-3.58 m, 1H), 3.34-3.45 (m, 1H), 3.10-3.20 (m, 1H), 2.99-3.05 (m, 1H). m/z =600.52; Elemental Composition calculated for $C_{29}H_{25}F_2Cl_2N_5OS$. C, 58.00; H, 4.20; N 11.66. Found C, 58.02; H, 4.21; N 11.68

1-(5-allyl-2-(2,4-dichlorophenyl)-7,7-difluoro-4,5,6,7-tetrahydro-6-(4-methoxyphenyl)-2H-pyrazolo[4,3-c]pyridin-3-yl)-3-(4-(trifluoromethyl)phenyl)thiourea (12k). IR (neat) νmax, 3389.4, 3307.3, 2927.8, 1685.5, 1640.0, 1608.4, 1513.9, 1274.1, 1091.1, 1037.3, 997.0, cm^{-1}; Mp 98-100 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.99 (s,1H), 7.70-7.96 (m, 2H), 7.50-7.68 (m, 2H), 7.17-7.22 (m, 2H), 6.90-6.97 (m, 2H), 5.80-5.81 (m, 1H), 5.14-5.21 (m, 2H), 4.40-4.58 (m, 1H), 3.76 (s, 3H), 3.54-3.57 (m, 1H), 3.02-3.10 (m, 2H), m/z =668.2; Elemental Composition calculated for $C_{30}H_{24}F_5Cl_2N_5OS$. C, 3.90; H, 3.62; N, 10.48. Found C, 53.94; H, 3.63; N, 10.46.

Molecular Modeling. The programs DiscoveryStudio and InsightII from Accelrys were used for this part of the study, and structure-based analyses were based on the STAT-3β homodimer (PDBID: 1BG1). Using the LigandFit protocol of DiscoveryStudio, the 3-D protein was cleaned and the size and spatial orientation of the active site was identified. Energy minimizations were performed using the CHARMM force field. Each energy-minimized final docking position was evaluated using the interaction scoring function in the LigandFit module of DiscoveryStudio. In parallel, docking and interaction analysis between the PFPs and the STAT-3 SH2 domain were also performed with ASEDock as implemented in MOE.

Supplementary Figures and Tables

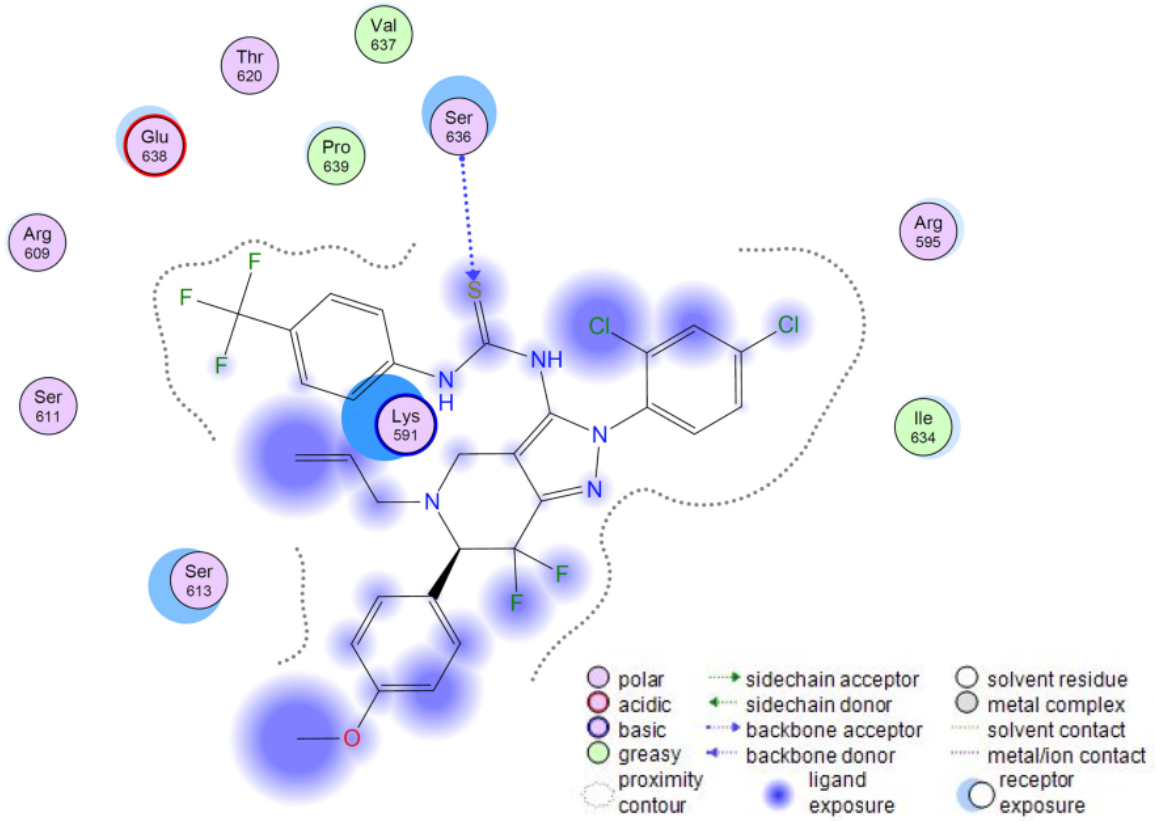

Figure S1. Compound 12k and its putative interactions with the SH2 domain of STAT3, suggesting a variety of lipophilic interactions with the binding site. Different binding modes of ligands seem to be possible (compare Figure S2), with Lys591 having different functions.

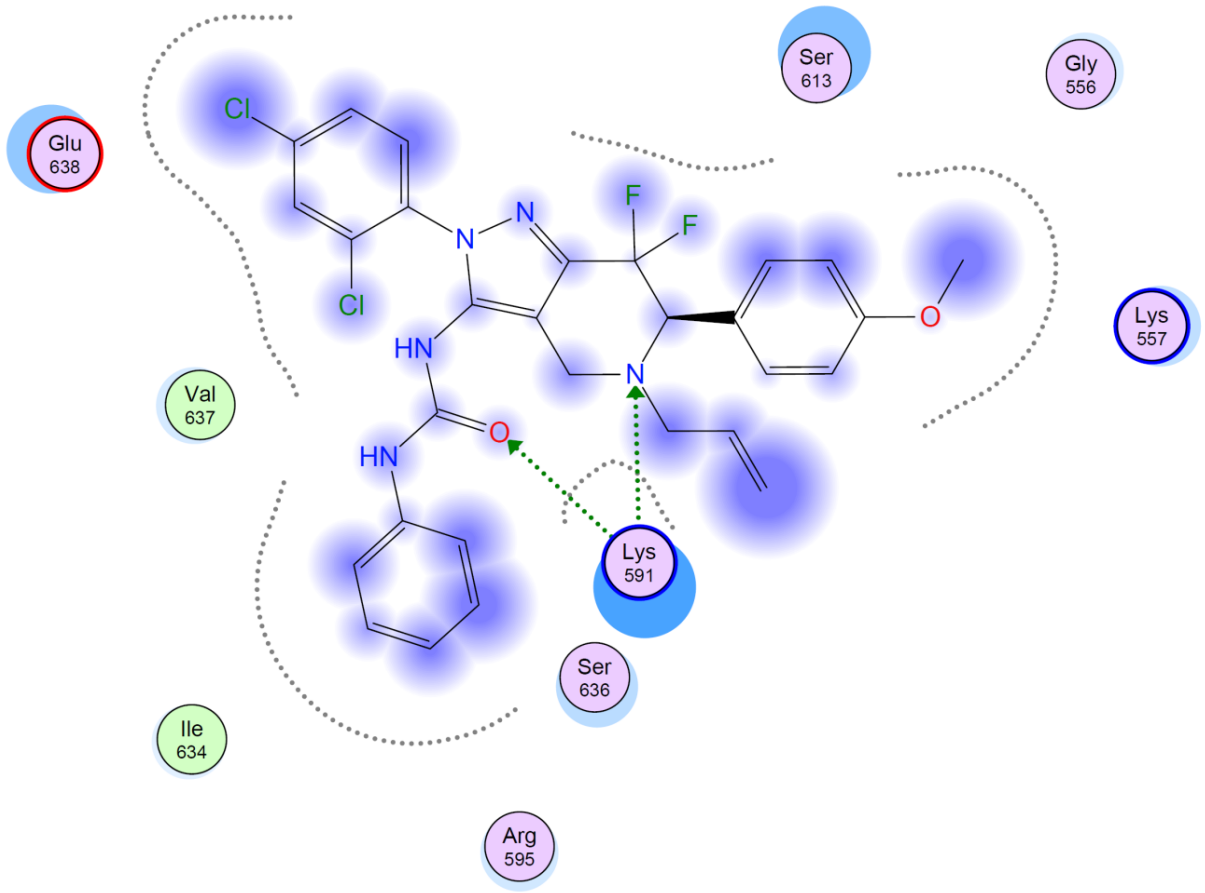

Figure S2. Compound 12g and its putative interactions with the SH2 domain of STAT3, suggesting a variety of lipophilic interactions with the binding site. Different binding modes of ligands seem to be possible (compare Figure S1), with Lys591 having different functions.