**MCPHS OSM Series 4 Experimental Procedures**



**2-Chloro-6-hydrazinylpyrazine:** A dry, clean 100mL round-bottom flask equipped with a magnetic stir-bar was charged with 45mL ethanol anhydrous, 4.58 g of 2,6-dichloro pyrazine (30.80mmoles; 1eq) and 2.30mL of hydrazine monohydrate (30.80mmoles; 1eq). The reaction was heated (85-90 °C) and stirred for 3.5 hours. The reaction was monitored by TLC. When complete, the reaction was allowed to cool to room temperature, diluted with 250mL of ethyl acetate and poured into a 500mL separatory funnel. The organic layer was washed with saturated, aqueous sodium bicarbonate, separated, dried with anhydrous sodium sulfate and then filtered. The organic layer concentrated under reduced pressure to give 3.07g of product that was used without further purification (69% yield). : 1H NMR (500 MHz, DMSO-d6)  8.43 (br.s, 1H), 8.05 (d, *J* = 0.5Hz, 1H), 7.71 (s, 1H), 4.38 (br. s, 2H); 13C NMR (125 MHz, CDCI3)  129.03, 129.37, 146.49, 157.63; LCMS (CI) m/z: [M+1] 145.1 (100.0%).

Links to ELN:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/MzUzLjZ8MzY3Ny8yNzIvVHJlZU5vZGUvMjUzODM2NjU5MHw4OTcuNg>==
* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/MzU2LjJ8MzY3Ny8yNzQvVHJlZU5vZGUvMjczNDUyNTE1fDkwNC4y>



**(E)-2-chloro-6-(2-(4-chlorobenzylidene)hydrazinyl)pyrazine:** To a rapidly stirred solution of 2-chloro-6-hydrazinyl pyrazine (3.07g, 21.28mmoles; 1eq) and 1.03mL of acetic acid (21.28mmoles; 1eq) in 40mL of acetonitrile was added 2.99 g of 4-chlorobenzaldehyde (21.28mmoles; 1eq). The resulting slurry was stirred at room temperature overnight, and monitored by TLC. The slurry was then filtered and washed with 10mL of anhydrous acetonitrile to yield 4.83g of product (85% yield).: 1H NMR (500 MHz, DMSO-d6)  7.48 (d, *J* = 8.5Hz, 2H), 7.77 (d, *J* = 8.5Hz, 2H), 8.05 (s, 1H), 8.06 (d, *J* = 0.3Hz, 1H), 8.58 (d, *J* = 0.3Hz, 1H), 11.63 (s, 1H); 13C NMR (125 MHz, CDCI3)  128.69, 129.28, 129.31, 133.01, 133.86, 134.25, 141.78, 145.99, 152.69; LCMS (ESI) m/z: [M+1] 267.0 (100.0%).

Links to ELN:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/MzU4Ljh8MzY3Ny8yNzYvVHJlZU5vZGUvMzM5ODIwMDA2fDkxMC44>
* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/MzU3LjV8MzY3Ny8yNzUvVHJlZU5vZGUvNzU2NDMyMjc4fDkwNy41>



**(E)-4-((2-(6-chloropyrazin-2-yl)hydrazono)methyl)benzonitrile:** To a rapidly stirred solution of 2-chloro-6-hydrazinyl pyrazine (1.39g, 9.63mmoles; 1eq) and 0.55mL of acetic acid (9.63mmoles, 1eq.) in 40mL of acetonitrile was added 1.26g of 4-chlorobenzaldehyde (9.63mmoles; 1eq). The resulting slurry was stirred at room temperature overnight, and monitored by TLC. The slurry was then filtered and washed with 10mL of anhydrous acetonitrile to yield 2.28g of product (92% yield).: 1H NMR (500 MHz, DMSO-d6)  11.83 (s, 1H), 8.65 (s, 1H), 8.12 (s, 1H), 8.10 (s, 1H), 7.94 (d, *J* = 8.5Hz, 2H), 7.87 (d, *J* = 8.5Hz, 2H); 13C NMR (125 MHz, CDCI3)  152.03, 145.51, 140.51, 138.93, 133.17, 132.64, 129.08, 127.13, 118.78, 111.08; LCMS (ESI) m/z: [M+1] 258.0 (100.0%); m.p. 302-304 °C.

Link to ELN:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/Nzc4Ljd8MzY3Ny81OTkvVHJlZU5vZGUvMTI5OTAxODYzMnwxOTc2Ljc>=



**(E)-2-chloro-6-(2-(4-(methylsulfonyl)benzylidene)hydrazinyl)pyrazine:** To a rapidly stirred solution of 2-chloro-6-hydrazinyl pyrazine (306.0mg, 2.11mmoles; 1eq) and 0.12mL of acetic acid (2.11mmoles, 1eq.) in 5mL of acetonitrile was added 390.0mg of 4-chlorobenzaldehyde (2.11mmoles; 1eq). The resulting slurry was stirred at room temperature overnight, and monitored by TLC. The slurry was then filtered and washed with 10mL of anhydrous acetonitrile to yield 846.0g of product (>100% yield). Material used directly without further purification.: 1H NMR (500 MHz, CDCI3)  8.68 (s, 1H), 8.41 (s, 1H), 8.13 (d, *J* = 0.6 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.82 (d, *J* = 1.0 Hz, 1H), 3.09 (s, 3H).

Link to ELN:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/NjQzLjV8MzY3Ny80OTUvVHJlZU5vZGUvNDI3NzMwMTkwMXwxNjMzLjU>=



**5-chloro-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazine:** At room temperature, a 250mL RBF was charged with 2-chloro-6-(2-(4-chlorobenzylidene)hydrazinyl)pyrazine (4.97g, 18.60mmol) followed by purging with nitrogen. The solid was then slurried in 100mL of anhydrous dichloromethane. To the rapidly stirred solution was then added iodobenzene diacetate (98%, 6.11g, 18.60mmol) and the reaction monitored by TLC eluting with 50% EtOAc / Hexanes. Upon the disappearance of the starting material, the solvent was removed under reduced pressure and the residue directly purified via flash silica gel chromatography eluting with a gradient of 50% EtOAc / Hexanes to 100% EtOAc to give 4.27g of product (86% yield).; 1H NMR (500 MHz, CDCl3)  7.52 (d, *J* = 8.8Hz, 2H), 7.58 (d, *J* = 8.8Hz, 2H), 7.89 (s, 1H), 9.35 (s, 1H); 13C NMR (125 MHz, CDCI3)  121.81, 125.13, 128.32, 129.85, 132.62, 137.31, 143.02, 147.22; LCMS (ESI) m/z: [M+1] 265.0 (100.0%); m.p. 176-178 °C.

Link to ELN:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/MzYwLjF8MzY3Ny8yNzcvVHJlZU5vZGUvMTM5ODI4OTI4fDkxNC4x>



**4-(5-chloro-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile:** At room temperature, (E)-4-((2-(6-chloropyrazin-2-yl)hydrazineylidene)methyl)benzonitrile (1.78g, 6.93mmoles) was slurried in 38mL of anhydrous dichloromethane. Iodobenzene diacetate (98%, 2.28g, 6.93mmoles) was then added to the rapidly stirred solution and the reaction monitored by TLC eluting with 50% EtOAc / Hexanes. Upon the disappearance of the starting material, the solvent was removed under reduced pressure and the residue directly purified via flash silica gel chromatography eluting with a gradient of 50% EtOAc / Hexanes to 100% EtOAc to give to give 754.8mg of product (43% yield).; 1H NMR (500 MHz, CDCl3)  9.39 (s, 1H), 7.95 (s, 1H), 7.85 (d, *J* = 8.1Hz, 2H), 7.8 (d, *J* = 8.2Hz, 2H); 13C NMR (126 MHz, CDCl3)  147.45, 146.56, 143.21, 132.17, 131.76, 131.26, 130.31, 121.69, 117.96, 114.88; LCMS (ESI) m/z: [M+1] 256.0 (100.0%); m.p. 226-228 °C.

Link to ELN:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/NzgwLjB8MzY3Ny82MDAvVHJlZU5vZGUvNTAwMzIzMTY1fDE5ODAuMA>==



**5-chloro-3-(4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine:** At room temperature, a 25mL round bottom flask was charged with 2-chloro-6-(2-(4-chlorobenzylidene)hydrazinyl)pyrazine (657.6mg, 2.11mmol) followed by purging with nitrogen. The solid was then slurried in 5mL of anhydrous dichloromethane. To the rapidly stirred solution was then added iodobenzene diacetate (682.0mg, 2.11mmol) and the reaction monitored by TLC eluting with 50% EtOAc / Hexanes. Upon the disappearance of the starting material, the solvent was removed under reduced pressure and the residue directly purified via flash silica gel chromatography eluting with a gradient of 50% EtOAc / Hexanes to 100% EtOAc to give 606.0mg of product (93% yield).: 1H NMR (500 MHz, CDCl3) δ 9.40 (d, J = 0.5 Hz, 1H), 8.13 (d, J = 8.6 Hz, 2H), 7.96 (d, J = 0.5 Hz, 1H), 7.89 (d, J = 8.6 Hz, 2H), 3.15 (s, 3H); 13C NMR (126 MHz, DMSO) δ 147.19, 146.14, 142.70, 142.34, 132.37, 132.26, 129.41, 126.23, 121.91, 43.35.

Link to ELN:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/NjQ4Ljd8MzY3Ny80OTkvVHJlZU5vZGUvOTg4NjE0NDMxfDE2NDYuNw>==



**5-azido-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazine:** To a reaction vial equipped with a stir-bar was placed 5-chloro-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazine (100.0mg, 0.377mmoles) and sodium azide (100.1mg, 1.540mmoles) followed by 2.5mL of anhydrous DMF. The reaction was stirred at room temperature and monitored by TLC. After 4 hours, TLC indicated that the reaction had gone to completion. The mixture was then diluted with 50mL of ethyl acetate and placed in a separatory funnel. The organic layer was washed 1x with 50mL of saturated, aqueous sodium bicarbonate followed by 50mL of brine. The organic layer was separated, dried with anhydrous sodium sulfate, filtered and concentrated to give 203.4mg of crude material. The crude was then directly purified by silica gel column chromatography eluting with a gradient of 35% EtOAc / Hexanes to 100% EtOAc. 92.8mg isolated (91% yield).: 1H NMR (500 MHz, CDCl3)  7.52 (d, J = 8.7Hz, 2H), 7.62 (d, J = 8.7Hz, 2H), 7.75 (s, 1H), 9.17 (s, 1H); 13C NMR (126 MHz, DMSO-d6)  146.73, 138.64, 135.05, 132.72, 129.76, 127.87, 126.19, 119.63, 99.52; LCMS (ESI) m/z: [M+1] 272.0 (100.0%); m.p. 110-112 °C.

Link to ELN:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/MzgwLjl8MzY3Ny8yOTMvVHJlZU5vZGUvMzU2NzYxNTYxNXw5NjYuOQ>==



**3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazin-5-amine:** 5-azido-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazine (50.1mg, 0.18mmol) and triphenylphosphine (73.1mg, 0.28mmoles) were placed in a RBF under nitrogen followed by the addition of 2mL of THF and 0.2mL of water. The mixture was stirred overnight at room temperature and monitored by TLC. When complete, the reaction was concentrated under reduced pressure and directly purified via silica gel column chromatography eluting with a gradient of ethyl acetate and hexanes to give 44.2mg of product (99% yield).: 1H NMR (500 MHz, DMSO-d6)  5.92 (Singlet, 2H), 7.28 (Singlet, 1H), 7.63 (doublet, J = 8.5Hz, 2H), 7.73 (Doublet, J = 8.5Hz,2H), 8.70 (singlet, 1H); 13C NMR (125 MHz, CDCI3)  111.40, 126.21, 128.07, 128.95, 129.24, 132.66, 135.00, 137.16, 144.42, 146.90; LCMS (ESI) m/z: [M+1] 246.1 (100.0%); m.p. 242-244 °C.

Link to ELN:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/MzgzLjV8MzY3Ny8yOTUvVHJlZU5vZGUvMjYyNTI2OTc5OXw5NzMuNQ>==



**N-(3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazin-5-yl)-1,1,1-triphenyl-5-phosphanimine:** 5-azido-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazine (2.5g, 9.2mmol) and triphenylphosphine (3.62g, 13.8mmoles) were placed in a RBF under nitrogen followed by the addition of 75mL of THF and 7.5mL of water. The mixture was stirred overnight at room temperature and monitored by TLC. When complete, the reaction was concentrated under reduced pressure and directly purified via silica gel column chromatography eluting with a gradient of ethyl acetate and hexanes to give 3.60g of product (78% yield).; 1H NMR (500 MHz, DMSO-d6)  8.50 (s, 1H), 7.71 (d, *J* = 8.5Hz, 2H), 7.69-7.64 (m, 3H), 7.53-7.47 (m, 12H), 7.45 (d, *J* = 8.5Hz, 2H), 6.43 (d, *J* = 0.9 Hz, 1H); 13C NMR (125 MHz, DMSO-d6)  147.82, 145.84, 139.48 (d, *J* = 10.1Hz), 133.82, 132.97 (d *J* = 2.9Hz), 132.48, 132.17 (d, *J* = 10.7Hz), 129.18 (d, *J* = 12.5Hz), 129.16, 127.88, 127.35, 126.81, 126.00, 114.16 (d, *J* = 9.3Hz); LCMS (ESI) m/z: [M+1] 506.1 (100%); m.p. 225-227 °C.

Link to ELN:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/MzkyLjZ8MzY3Ny8zMDIvVHJlZU5vZGUvMTMyMDY4ODc3NHw5OTYuNg>==
* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/NDEwLjh8MzY3Ny8zMTYvVHJlZU5vZGUvMjc3MjEyMDc3MnwxMDQyLjg>=



**N-(3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazin-5-yl)-2-(3,4-difluorophenyl)acetamide:**

Links to ELN for above Failed Reactions:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/Nzk2Ljl8MzY3Ny82MTMvVHJlZU5vZGUvMTIyNTc2MjEwfDIwMjIuOQ>==
* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/Nzk1LjZ8MzY3Ny82MTIvVHJlZU5vZGUvMzk1NTEyMDgzNnwyMDE5LjY>=



**1-(3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazin-5-yl)-3-(4-fluorophenyl)urea**

Links to ELN for above Failed Reaction:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/NDQ1Ljl8MzY3Ny8zNDMvVHJlZU5vZGUvMzQxNzMxNTYxMnwxMTMxLjk>=



**3-(4-chlorophenyl)-5-(4-fluorophenethoxy)-[1,2,4]triazolo[4,3-a]pyrazine:** A dry, clean 100 mL RBF equipped with a magnetic stir-bar was charged with 265.1mg (1.0mmoles; 1.0eq.) of 5-chloro-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazine, 32.2 mg of 18-crown-6 (0.1mmoles; 0.1 eq.) and 8.5mL of anhydrous toluene. To the stirred solution was then added 0.15mL of 2-(4-fluorophenyl)ethan-1-ol (1.2mmoles; 1.2 eq.) and 168.33mg of potassium hydroxide (3.0mmoles; 3.0eq.). The resulting mixture was then sealed with a pressure relief cap and heated to 40 °C for 3 hours and monitored by TLC. Once complete, the reaction was diluted with 50mL of ethyl acetate and poured into a separatory funnel. The organic layer was then washed with saturated, aqueous sodium bicarbonate and 50mL of brine solution. The organic layer was then separated, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 459.0mg of crude product. The material was then purified by silica gel column chromatography eluting with 25% of ethyl acetate / hexanes, then 100% of ethyl acetate, to afford 186.0mg of pure product (50% yield).: 1H NMR (500 MHz, DMSO-d6)  9.05 (s, 1H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.61 (s, 1H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.00 (t, *J* = 8.9 Hz, 2H), 6.93 (dd, *J* = 8.8, 5.7 Hz, 2H), 4.50 (t, *J* = 6.4 Hz, 2H), 2.89 (t, *J* = 6.3 Hz, 2H); 13C NMR (126 MHz, DMSO-d6)  160.43, 147.91, 145.76, 144.30, 135.49, 135.21, 133.85, 132.94, 130.88 (d, *J* = 7.9 Hz), 128.12, 115.31 (d, *J* = 20.9 Hz), 109.40, 71.54, 33.40; m.p. 128-130 °C.

Link to ELN:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/ODM3LjJ8MzY3Ny82NDQvVHJlZU5vZGUvMTUxNTYyMTg2NXwyMTI1LjI>=



**3-(4-chlorophenyl)-5-(3,4-difluorophenethoxy)-[1,2,4]triazolo[4,3-a]pyrazine:** A dry, clean 25mL RBF equipped with a magnetic stir-bar was charged with 250.0mg (0.94mmoles; 1.0eq.) of 5-chloro-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazine, 24.9mg of 18-crown-6 (0.09mmoles; 0.1eq.) and 5mL of anhydrous toluene. To the stirred solution was then added 163.0mg of 2-(3,4-difluorophenyl)ethanol (1.03mmoles; 1.1eq.) and 158.0mg of potassium hydroxide (2.82mmoles; 3.0eq.). The resulting mixture was then sealed with a pressure relief cap with split-seal septa and heated to 40 °C for 3 hours and monitored by TLC. Once complete, the reaction was diluted with 50mL of ethyl acetate and poured into a separatory funnel. The organic layer was then washed with saturated, aqueous sodium bicarbonate and 50mL of brine solution. The organic layer was then separated, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 502.0mg of crude product. The material was then purified by silica gel column chromatography eluting with 25% of ethyl acetate / hexanes, then 100% of ethyl acetate, to afford 235.0mg of pure product (64% yield).: 1H NMR (500 MHz, CDCI3)  2.92 (t, *J* = 6.1Hz, 2H), 4.42 (t, *J* = 6.2Hz, 2H), 6.55 (m, 2H), 6.98 (m, 1H), 7.31 (s, 1H), 7.47 (d, *J* = 8.6Hz, 2H), 7.6 (d, *J* = 8.6Hz, 2H), 9.03 (s, 1H); 13C NMR (126 MHz, CDCl3) δ 150.79 (dd, *J* = 93.3, 12.6 Hz), 148.81 (dd, J = 92.3, 12.7 Hz), 147.75, 146.10, 143.75, 136.63, 136.58, 133.30 – 133.04 (m), 132.01, 128.14, 126.23, 124.44 (dd, *J* = 6.2, 3.6 Hz), 117.45 (d, *J* = 9.1 Hz), 117.31 (d, *J* = 9.2 Hz), 108.36, 70.82, 33.77; LCMS (ESI) m/z: [M+1] 387.0 (100.0%); m.p. 142-144 °C.

Link to ELN:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/MzkwLjB8MzY3Ny8zMDAvVHJlZU5vZGUvMTgxNTM0MDIzNnw5OTAuMA>==



**4-(5-(4-fluorophenethoxy)-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile:** A dry, clean 25mL RBF equipped with a magnetic stir-bar was charged with 255.7mg (1.00mmoles; 1.0eq.) of 4-(5-chloro-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile, 32.2mg of 18-crown-6 (0.1mmoles; 0.1eq.) and 8.5mL of anhydrous toluene. To the stirred solution was then added 154.7mg (0.14mL) of 4-fluorophenethyl alcohol (1.10mmoles; 1.1eq.) and 168.3mg of potassium hydroxide (3.00mmoles; 3.0eq.). The resulting mixture was then sealed with a pressure relief cap with split-seal septa and heated to 40 °C for 3 hours and monitored by TLC. Once complete, the reaction was diluted with 50mL of ethyl acetate and poured into a separatory funnel. The organic layer was then washed with 50 mL of saturated, aqueous sodium bicarbonate and 50mL of brine solution. The organic layer was then separated, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 241.0mg of crude product. The material was then purified by silica gel column chromatography eluting with 25% of ethyl acetate / hexanes, then 100% of ethyl acetate, to afford 182.0mg of pure product (51% yield).: 1H NMR (500 MHz, DMSO-d6)  9.09 (s, 1H), 7.94 (d, *J* = 8.6 Hz, 2H), 7.91 (d, *J* = 8.6 Hz, 2H), 7.66 (s, 1H), 7.00 (t, *J* = 8.9 Hz, 2H), 6.93 (dd, *J* = 8.8, 5.6 Hz, 2H), 4.52 (t, *J* = 6.4 Hz, 2H), 2.89 (t, *J* = 6.4 Hz, 3H); 13C NMR (126 MHz, DMSO-d6)  161.86, 159.94, 147.56, 144.90, 143.80, 134.93 (d, J = 9.2 Hz), 133.28, 132.35, 131.47 (d, J = 10.5 Hz), 130.31, 118.52, 114.85 (d, J = 21.0 Hz), 112.19, 109.23 (d, J = 9.3 Hz), 71.01, 32.81.; LCMS (ESI) m/z: [M+1] 360.1 (100.0%); m.p. 164-165 °C.

Link to ELN:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/ODMzLjN8MzY3Ny82NDEvVHJlZU5vZGUvMjA2OTE0Mjg3MnwyMTE1LjM>=



**4-(5-(3,4-difluorophenethoxy)-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile:** A dry, clean 100 mL RBF equipped with a magnetic stir-bar was charged with 255.0mg (1.0mmoles; 1.0eq.) of 4-(5-chloro-[1,2,4]triazol[4,3-a]pyrazin-3-yl)benzonitrile, 32.2mg of 18-crown-6 (0.1mmoles; 0.1eq.) and 8.5mL of anhydrous toluene. To the stirred solution was then added 0.02mL of 2-(3,4-diflourophenyl)ethan-1-ol (1.2mmoles; 1.2eq.) and 168.33mg of potassium hydroxide (3.0mmoles; 3.0eq.). The resulting mixture was then sealed with a pressure relief cap and heated to 40 °C for 3 hours and monitored by TLC. Once complete, the reaction was diluted with 50mL of ethyl acetate and poured into a separatory funnel. The organic layer was then washed with 50mL of saturated, aqueous sodium bicarbonate and 50mL of brine solution. The organic layer was then separated, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 280.0mg of crude product. The material was then purified by silica gel column chromatography starting with 25% of ethyl acetate / hexanes, eluting to 100% of ethyl acetate / hexanes, to afford 118.0mg of product (31% Yield).: 1H NMR (500 MHz, DMSO-d6)  9.10 (s, 1H), 7.92 (d, *J* = 8.6 Hz, 2H), 7.89 (d, *J* = 8.6 Hz, 2H), 7.67 (s, 1H), 7.26-7.17 (m, 1H), 6.98-6.89 (m, 1H), 6.76 (s, 1H), 4.55 (t, *J* = 6.3 Hz, 2H), 2.92 (t, *J* = 6.2 Hz, 2H); LCMS (ESI) m/z: [M+1] 378.1 (100.0%); m.p. 164-166 °C.

Link to ELN:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/ODM0LjZ8MzY3Ny82NDIvVHJlZU5vZGUvMzE3ODExOTAxMXwyMTE4LjY>=



**5-(4-fluorophenethoxy)-3-(4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine:** A dry, clean 25mL RBF equipped with a magnetic stir-bar was charged with 150.0mg (0.49mmoles; 1.0eq.) of 5-chloro-3-(4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine, 16.0mg of 18-crown-6 (0.05mmoles; 0.1eq.) and 5mL of anhydrous toluene. To the stirred solution was then added 76.0mg (0.07mL) of 2-(4-flourophenyl)ethan-1-ol (0.54mmoles; 1.1eq.) and 83.0mg of potassium hydroxide (1.47mmoles; 3.0eq.). The resulting mixture was then sealed with pressure relief cap with split-seal septa and heated to 40 °C for 3 hours and monitored by TLC. Once complete, the reaction was diluted with 50mL of ethyl acetate and poured into a separatory funnel. The organic layer was then washed with 50mL of saturated, aqueous sodium bicarbonate and 50mL of brine solution. The organic layer was then separated, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 217.0mg of crude product. The material was then purified by silica gel column chromatography eluting with 25% of ethyl acetate / hexanes, then 100% of ethyl acetate, to afford 151.0mg of pure product (75% Yield).: 1H NMR (500 MHz, Chloroform-d)  9.08 (d, *J* = 0.5 Hz, 1H), 8.04 (d, *J* = 8.7, 2H), 7.86 (d, *J* = 8.7 Hz, 2H), 7.39 (s, 1H), 6.92 (t, *J* = 8.6 Hz, 2H), 6.80 (dd, *J* = 8.6, 5.3 Hz, 2H), 4.46 (t, *J* = 6.5 Hz, 2H), 3.10 (s, 3H), 2.93 (t, *J* = 6.5 Hz, 2H); 13C NMR (126 MHz, CDCl3)  162.94, 160.99, 148.04, 145.45, 143.74, 141.97, 136.62, 133.20, 131.60 (d, J = 3.3 Hz), 129.95 (d, J = 7.9 Hz), 126.90, 115.82 (d, J = 21.4 Hz), 108.89, 71.41, 44.60, 33.72; LCMS DATA: MS (ESI) m/z: [M+1] 413.0 (100.0%); m.p. 165-168 °C.

Link to ELN:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/NjYwLjR8MzY3Ny81MDgvVHJlZU5vZGUvNDM1NDYwMzI2fDE2NzYuNA>==



**5-(3,4-difluorophenethoxy)-3-(4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine:** A dry, clean 25mL RBF equipped with a magnetic stir-bar was charged with 130.0mg (0.42mmoles; 1.0eq.) of 5-chloro-3-(4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine, 13.6mg of 18-crown-6 (0.04mmoles; 0.1eq.) and 5mL of anhydrous toluene. To the stirred solution was then added 0.015 mL of 2-(3,4-diflourophenyl)ethan-1-ol (0.5mmoles; 1.2eq.) and 70.9mg of potassium hydroxide (1.26mmoles; 3.0eq.). The resulting mixture was then sealed with a pressure relief top with split-seal septa and heated to 40 °C for 3 hours and monitored by TLC. Once complete, the reaction was diluted with 50 mL of ethyl acetate and poured into a separatory funnel. The organic layer was then washed with 50mL of saturated, aqueous sodium bicarbonate and 50 mL of brine solution. The organic layer was then separated, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 290.9mg of crude product. The material was then purified by silica gel column chromatography eluting with 25% of ethyl acetate / hexanes, then 100% of ethyl acetate, to afford 87.5mg of pure product (48% Yield).: NMR DATA: 1H NMR (500 MHz, CDCl3)  9.08 (s, 1H), 8.07 (d, J = 8.5 Hz, 2H), 7.90 (d, *J* = 8.6 Hz, 2H), 7.39 (s, 1H), 7.01 (dt, *J* = 10.2, 8.4 Hz, 1H), 6.57-6.47 (m, 2H), 4.45 (t, *J* = 6.3 Hz, 2H), 3.11 (s, 3H), 2.91 (t, *J* = 6.2 Hz, 2H); 13C NMR (126 MHz, CDCl3)  148.06, 145.41, 143.65, 142.12, 136.88, 133.25, 131.77, 127.01, 124.68 (dd, *J* = 6.1, 3.7 Hz), 117.83 (d, *J* = 17.3 Hz), 117.13 (d, *J* = 17.3 Hz), 108.88, 71.09, 44.56, 33.79; LCMS (ESI) m/z: [M+1] 431.0 (100.0%); m.p. 67-69 °C.

Link to ELN:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/NzcyLjJ8MzY3Ny81OTQvVHJlZU5vZGUvNDA4NDk2MjIwMXwxOTYwLjI>=



**N-(3-(4-cyanophenyl)-[1,2,4]triazolo[4,3-a]pyrazin-5-yl)-2-(3,4-difluorophenyl)acetamide:** To a 25mL RBF was added 100.0 of 4-(5-chloro-[1,2,4]triazol[4,3-a]pyrazin-3-yl)benzonitrile (0.39mmol, 1.0eq.), 80.4mg of 2-(3,4-difluorophenyl)acetamide (0.47mmol, 1.2eq.), 72.0mg of Pd2(dba)3 (0.08mmol, 0.2eq.), 46.0mg of Xantphos (0.08mmol, 0.2eq.) and 381.2mg of Cs2CO3 (1.17mmol, 3 eq.) were mixed as solids and the flask was flushed with nitrogen. Anhydrous Dioxane (10mL) that had been degassed was then added and the mixture heated to 105 °C and the reaction monitored by TLC. The reaction was then cooled and concentrated under reduced pressure and purified directly via silica gel column chromatography eluting with 10% methanol / dichloromethane to yield of 15.7mg of product (10% Yield).: 1H NMR (500 MHz, CDCl3)  9.36 (s, 1H), 8.03 (s, 1H), 7.88-7.81 (m, 2H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.20-7.11 (m, 2H), 6.80 (ddd, *J* = 10.1, 7.3, 2.2 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 3.25 (s, 2H); 13C NMR (125 MHz, CDCI3)  170.05, 148.52 (dd, *J* = 245.2Hz, 12.8Hz), 147.33 (dd, *J* = 244.9Hz, 12.7Hz), 147.14, 145.93,142.13, 131.57, 131.25, 130.95, 126.92 (dd, *J* = 6.5Hz, 3.4Hz), 126.76, 125.38, 118.11, 117.97 (d, J=17.3Hz), 116.78 (d, *J* = 17.0Hz), 112.39, 39.51; LCMS (ESI) m/z: [M+1] 391.0 (100.0%).

Links to ELN:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/ODAzLjR8MzY3Ny82MTgvVHJlZU5vZGUvMzY3NDc2MDIxNHwyMDM5LjQ>=
* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/Nzk4LjJ8MzY3Ny82MTQvVHJlZU5vZGUvMjIxMTA1ODAyMHwyMDI2LjI>=



N-(3-(4-cyanophenyl)-[1,2,4]triazolo[4,3-a]pyrazin-5-yl)-3-(3,4-difluorophenyl)propanamide: To a 25mL RBF was added 246.0mg of 4-(5-chloro-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile, (0.96mmol, 1.0eq.), 213.6mg of 3-(3,4-difluorophenyl)propanamide (1.15mmol, 1.2eq.), 175.8mg of Pd2(dba)3 (0.19mmol, 0.2eq.), 111.1mg of Xantphos (0.19mmol, 0.2eq.) and 940.3mg of Cs2CO3 (2.89mmol, 3.0eq.) were mixed as solids and the flask was flushed with nitrogen. Anhydrous Dioxane (10mL) that had been degassed was then added and the mixture heated to 105 °C and the reaction monitored by TLC. The reaction was then cooled and concentrated under reduced pressure and purified directly via silica gel column chromatography eluting with 10% methanol / dichloromethane to yield of 52.0mg of product (13% Yield).: 1H NMR (500 MHz, CDCl3)  9.36 (s, 1H), 7.96 (s, 1H), 7.82-7.79 (m, 2H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.11 (dt, *J* = 10.2, 8.3 Hz, 1H), 6.98 (s, 1H), 6.95-6.87 (m, 1H), 6.81 (s, 1H), 2.69 (t, *J* = 7.3 Hz, 2H), 2.13 (t, *J* = 7.3 Hz, 2H); 13C NMR (126 MHz, DMSO-d6) δ 172.22, 150.00 (dd, *J* = 152.0, 12.6 Hz), 148.06 (dd, *J* = 150.5, 12.5 Hz), 147.68, 146.45, 142.68, 138.79 (d, *J* = 4.4 Hz), 132.28, 131.88, 131.81, 127.18, 125.97, 125.23 (dd, *J* = 6.0, 3.3 Hz), 118.74, 117.70 (d, J = 16.8 Hz), 117.50 (d, *J* = 16.6 Hz), 112.87, 35.97, 29.11; LCMS (ESI) m/z: [M+1] 405.1 (100%); m.p. 212-214 °C.

Link to ELN:

* <https://mynotebook.labarchives.com/share/MCPHS%2520MedChem/ODA2LjB8MzY3Ny82MjAvVHJlZU5vZGUvMTI5MTY3NTQ4NXwyMDQ2LjA>=