

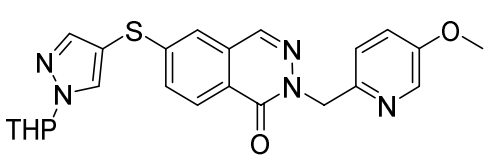
(IIa)

or a salt and/or solvate thereof;

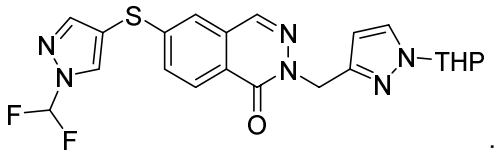
using an oxidising agent such as Oxone;

wherein R^A and R^B are defined elsewhere herein.

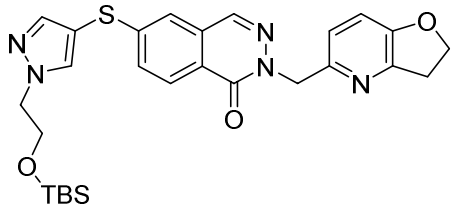
Suitably, the compound of formula (IIa) is selected from the group consisting of:



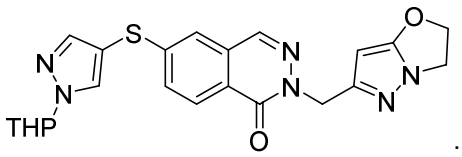
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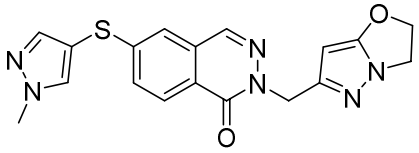
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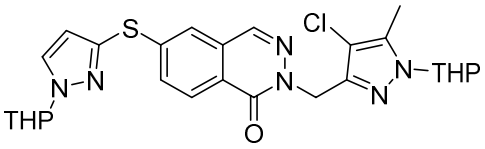
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; and



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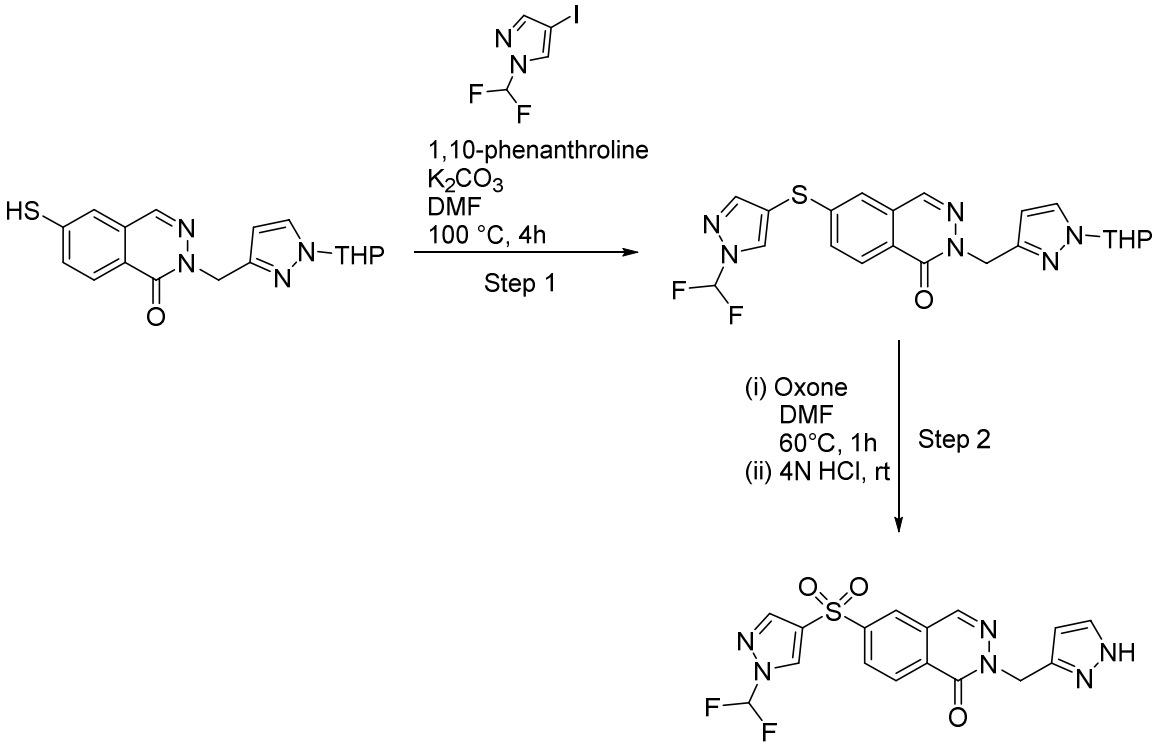
or a salt and/or solvate thereof.

It will be appreciated that for use in therapy the salts of the compounds of formula (Ia) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art. Pharmaceutically acceptable salts include acid addition salts, suitably salts of compounds of the invention comprising a basic group such as an amino group, formed with inorganic acids, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid. Also included are salts formed with organic acids, e.g., succinic acid, maleic acid, acetic acid, fumaric acid, citric acid, tartaric acid, benzoic acid, p-toluenesulfonic acid, methanesulfonic acid, naphthalenesulfonic acid and 1,5-naphthalenedisulfonic acid. Other salts, e.g., oxalates or formates, may be used, for example in the isolation of compounds of formula (Ia) and are included within the scope of this invention, as are basic addition salts such as sodium, potassium, calcium, aluminium, zinc, magnesium and other metal salts.

Pharmaceutically acceptable salts may also be formed with organic bases such as basic amines, e.g., with ammonia, meglumine, tromethamine, piperazine, arginine, choline, diethylamine,

overnight. Sat. $NaHCO_3$ and DCM were added and the layers separated. The organic layer was washed with brine, dried (MgSO4) and concentrated under vacuum to afford a crude mixture of 2-((5-methoxypyridin-2-yl)methyl)-6-((1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)sulfonyl)phthalazin-1(2H)-one and 6-((1H-pyrazol-4-yl)sulfonyl)-2-((5-methoxypyridin-2-yl)methyl)phthalazin-1(2H)-one. The mixture was dissolved in MeOH (1.5 mL) and hydrogen chloride (4N in dioxane) (41.6 mg, 285µL, 4.00 molar, 5 Eq, 1.14 mmol) was added. The mixture was stirred for 1h, then concentrated under vacuum. Sat. NaHCO3, 2N NaOH and DCM were added, and the layers separated. The organic layer was washed with brine, then absorbed on silica. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-50% 10%(MeOH (0.7M NH3):DCM)):DCM) to afford 6-((1H-pyrazol-4-yl)sulfonyl)-2-((5-methoxypyridin-2-yl)methyl)phthalazin-1(2H)-one (40.8 mg, 98% Purity) as a white solid. 1H NMR (DMSO) δ:13.91 (s, 1H), 8.64 – 8.59 (m, 2H), 8.57 – 7.96 (s (br), 2H), 8.43 (d, J = 8.4 Hz, 1H), 8.31 (dd, J = 8.4, 1.9 Hz, 1H),8.16 (d, J = 2.9 Hz, 1H), 7.33 (dd, J = 8.6, 3.0 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 5.38 (s, 2H), 3.78 (s, 3H). MS (ES+): 398 (M+H)+.

Example 2: 2-((1H-pyrazol-3-yl)methyl)-6-((1-(difluoromethyl)-1H-pyrazol-4-yl)sulfonyl)phthalazin-1(2H)-one



Step 1

Nitrogen was bubbled through a mixture of 6-mercapto-2-((1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)methyl)phthalazin-1(2H)-one (**Intermediate 6**, 150 mg, 91% Wt, 1 Eq, 399 µmol), 1-(difluoromethyl)-4-iodo-1H-pyrazole (126mg, 1.3 Eq, 518 µmol), 1,10-phenanthroline (32.3 mg,

to afford 4-chloro-3-(chloromethyl)-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole as a crude product. This was used in the next step without further purification.

Step 3

To the solution of the crude 4-chloro-3-(chloromethyl)-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole in DMF (4 mL) was added Cs_2CO_3 (1.95 g, 6.0 mmol) and 6-((1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)thio)phthalazin-1(2*H*)-one (328 mg, 1.0 mmol) at room temperature, and the reaction mixture was stirred at room temperature overnight. After LCMS indicated the reaction was completed, the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with saturated ammonium chloride solution (40 mL × 2), dried over Na_2SO_4, filtered, and concentrated at 40 °C under reduced pressure. The residual solid was purified by flash column chromatography (12 g, petroleum ether / ethyl actate = 100:00~60:30) to give 2-((4-chloro-5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)methyl)-6-((1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)thio)phthalazin-1(2*H*)-one (200 mg, 100% purity) as a yellow solid. MS (ES+): 541.2 (M+H)+.

Step 4

A solution of 2-((4-chloro-5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)methyl)-6-((1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)thio)phthalazin-1(2*H*)-one (200 mg, 0.37 mmol) in DMF (3 mL) was added OXONE (682 mg, 1.11 mmol) and stirred at 60 °C for 1 hour. After LCMS indicated the reaction was completed, the reaction mixture was diluted with water (5 mL), neutralized with K_2CO_3 and extracted with EtOAc (10 mL × 4). The organic layers were washed with sat.aq.NH_4Cl (100 mL×2), concentrated and purified by flash column chromatography (12 g, dichloromethane / methanol = 100:00~95:5) to give 2-((4-chloro-5-methyl-1*H*-pyrazol-3-yl)methyl)-6-((1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)sulfonyl)phthalazin-1(2*H*)-one (180 mg, 81% purity) as white solid. MS (ES+): 489.2 (M+H)+.

Step 5

To a solution of 2-((4-chloro-5-methyl-1*H*-pyrazol-3-yl)methyl)-6-((1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)sulfonyl)phthalazin-1(2*H*)-one (180 mg, 0.37 mol) in DCM (1 mL) was added TFA (3 mL) and the mixture was stirred at room temperature for 1 hour. After LCMS indicated the reaction completed, the mixture was concentrated under reduced pressure. The residue was diluted with H_2O (15 mL) and adjusted pH to 8 with K_2CO_3. Solid precipitated and the suspension was filtered. The filtered cake was purified by prep-HPLC (Column: Waters Xbridge Prep C18 OBD 10μm 19*250mm; Flow Rate: 20 mL/min; solvent system: MeCN/(10 mmol/L NH_4HCO_3/water) gradient: MeCN: 25%~95%; collection wavelength: 214 nm). The fractions were concentrated at 40 °C under reduced pressure to remove MeCN, and the residue was lyophilized