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Rational design and synthesis of novel Syk-kinase inhibitors

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*6-[(6-Chloropyrimidin-4-yl)amino]-2,2-dimethyl-2*H*-pyrid[3,2-*b*][1,4]oxazin-3(4*H*)-one*.

2,4-Dichloro-1,3,5-triazine (0.17 g, 1.15 mmol, prepared according to ref. 1 was dissolved in 5 ml of dry degassed DMF. 6-Amino-2,2-dimethyl-2*H*-pyrid[3,2-*b*][1,4]oxazin-3-(4*H*)-one (0.22 g, 1.15 mmol, prepared according to ref. 2 was added and the reaction mixture was stirred at 60 °C for 8 h under inert atmosphere. Solvent was evaporated at 5 Torr. The residue was washed with water (2x5 ml) and separated chromatographically eluting with chloroform: methanol mixture of increasing polarity. The standard workup procedure afforded the title product (0.28 g, 0.92 mmol, 80%). ^{1}H NMR (500 MHz, DMSO-d_6) 1.12 (s, 3H), 1.13 (s, 3H), 7.43 (d, 1H), 7.85 (d, 1H), 7.88 (s, 1H), 7.65 (bs, 1H), 10.84 (s ,1H).

*2,2-Dimethyl-6-((4-[(3,4,5-trimetoxyphenyl)amino]-pyrimidin-4-yl)amino)-2*H*-pyrid[3,2-*b*][1,4]oxazin-3(4*H*)-one* **1**.

The above compound (0.28 g, 0.95 mmol) was dissolved in dry degassed DMF. Trimetoxyaniline (0.17 g, 0.92 mmol) was added and the reaction mixture is stirred at 110 °C for 6 h under inert atmosphere. Solvent was evaporated at 5 Torr. The residue was washed with water (2x5 ml) and separated chromatographically eluting with chloroform−methanol mixture of increasing polarity. The standard workup procedure afforded compound **1** (0.62 g, 65%). ^{1}H NMR (500 MHz, DMSO-d_6) 1.11 (s, 3H), 1.12 (s, 3H), 3.82 (s, 3H), 3.84 (s, 6H), 6.79 (s, 2H), 7.42 (d, 1H), 7.61 (s, 1H), 7.81 (d, 1H), 7.93 (bs., 1H), 7.96 (bs., 1H), 10.39 (s, 1H).

Synthesis of compound **2**

Methyl 2-methyl-2-[(2-nitropyridin-3-yl)oxy]propanoate.

To a solution of 2-nitro-3-hydroxypyridine (0.35 g, 2.5 mmol) in dry DMF (5 ml) cooled to 0 °C sodium hydride (0.12 g, 3.0 mmol, 60% suspension in mineral oil) was added and the mixture was stirred at the same temperature for 2 h. Methyl dibromoacetate (0.52 g, 3.0 mmol) was

added dropwise keeping the temperature below 5 °C. The reaction mixture was stirred for 4 h at ambient temperature, and then at 60°C for 4 h. Solvent was evaporated, the residue was washed with water (3x10 ml), dried and recrystallized from toluene, giving the title compound (0.53 g, 2.2 mmol, 87%). ^{1}H NMR (500 MHz, DMSO-d_6) 1.13 (s, 6H), 3.29 (s, 3H), 7.83 (d, 1H), 7.91 (t, 1H), 8.32 (d, 1H).

Methyl 2-methyl-2-[(6-bromo-2-nitropyridin-3-yl)oxy]propanoate.

To a solution of the above product (0.53 g, 2.2 mmol) in glacial acetic acid (5 ml) dry bromine (0.42 g, 2.6 mmol) was added dropwise. The reaction mixture was stirred for 2 h. Anhydrous sodium acetate (0.25 g, 3.0 mmol) was added and the reaction mixture was stirred at 40°C for 8 h and then poured into water. The formed precipitate was filtered out, washed with water to neutral pH and dried to give the title compound (0.82 g, 1.6 mmol, 73%). ^{1}H NMR (500 MHz, DMSO-d_6) 1.13 (s, 6H), 3.25 (s, 3H), 7.76 (d, 1H), 8.18 (d, 1H).

*6-Bromo-2,2-dimethyl-2*H*-pyrid[3,2-*b*][1,4]oxazin-3(4*H*)-one* **3**.

To a suspension of the above product (0.82 g, 1.6 mmol) in concentrated hydrochloric acid (40 ml) cooled to -5°C tin(II) chloride (1.0 g) dissolved in methanol (10 ml) was added maintaining the given temperature. The reaction mixture is stirred at 0°C for 12 h, quenched with sodium carbonate and filtered. The supernatant was evaporated and subjected to extraction with anhydrous ethanol using Soxhlet-type extractor, giving compound **3** (0.26 g, 1.0 mmol, 62%). ^{1}H NMR (500 MHz, DMSO-d_6) 1.12 (s, 3H), 1.13 (s, 3H), 7.56 (d, 1H), 8.13 (d, 1H), 10.43 (s, 1H).

*2-Chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine* .

To a suspension of 2-hydroxy-7*H*-pyrrolo[2,3-*d*]pyrimidine (0.2 g, 4.2 mmol, prepared according to ref. 3 in phosphorus oxychloride (0.4 ml, 4.2 mmol) *N*,*N*-dimethylaniline (0.4 ml, 3.0 mmol) was added. The reaction mixture was stirred at 60°C for 6 h, cooled to room temperature and poured into a mixture of ice (100 g) and ether (50 ml). The organic layer was separated, and the aqueous layer was twice extracted with water. The combined organic extract was washed with saturated aqueous sodium bicarbonate solution (3x50 ml) and dried. The solvent was evaporated and the residue was distilled to give the title compound (0.19 g, 1.25 mmol, 83%). ^{1}H NMR (500 MHz, DMSO-d_6) 6.71 (d, 1H), 6.92 (d, 1H), 7.82 (s, 1H), 10.03 (bs., 1H).

N-*(3,4,5-Trimethoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2-amine*.

3,4,5-Trimethoxyaniline (0.23 g, 1.25 mmol) was added to a solution of the above compound (0.19 g, 1.25 mmol) in dry degassed DMF (5 ml) and the reaction mixture was stirred at 110°C for 6 h under inert atmosphere. Solvent was evaporated at 5 Torr. The residue was washed with

water (2x5 ml) and separated chromatographically eluting with chloroform−methanol mixture of increasing polarity. The standard workup procedure afforded the title product (0.3 g, 1.0 mmol, 80%). ^{1}H NMR (500 MHz, DMSO-d_6) 3,74 (s, 3H), 3,81 (s, 6H), 6.72 (s, 2H), 6.79 (d, 1H), 6.82 (d, 1H), 7.32 (s, 1H), 7.42 (bs., 1H), 10.03 (s, 1H).

*2,2-Dimethyl-6-(2-[(3,4,5-trimethoxyphenyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2*H*-pyrid[3,2-*b*][1,4]oxazin-3(4*H*)-one* **2**.

The above compound (0.3 g, 1.0 mmol) was added to a solution of compound **3** (0.26 g, 1.0 mmol) in dry degassed DMF (5 ml) and the mixture was stirred at 60°C for 8 h under inert atmosphere. The solvent was evaporated at 5 Torr. The residue was washed with water (2x5 ml) and separated chromatographically eluting with chloroform−methanol mixture of increasing polarity. The standard workup procedure afforded target compound **2** (0.28 g, 0.6 mmol, 60%). ^{1}H NMR (500 MHz, DMSO-d_6) 1.12 (s, 3H), 1.13 (s, 3H), 3.78 (s, 3H), 3.81 (s, 6H), 6.68-6.73 (m, 3H), 6.75 (d, 1H), 7.28 (s, 1H), 7.78 (d, 1H), 8.03 (d, 1H), 7.23 (bs., 1H).

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