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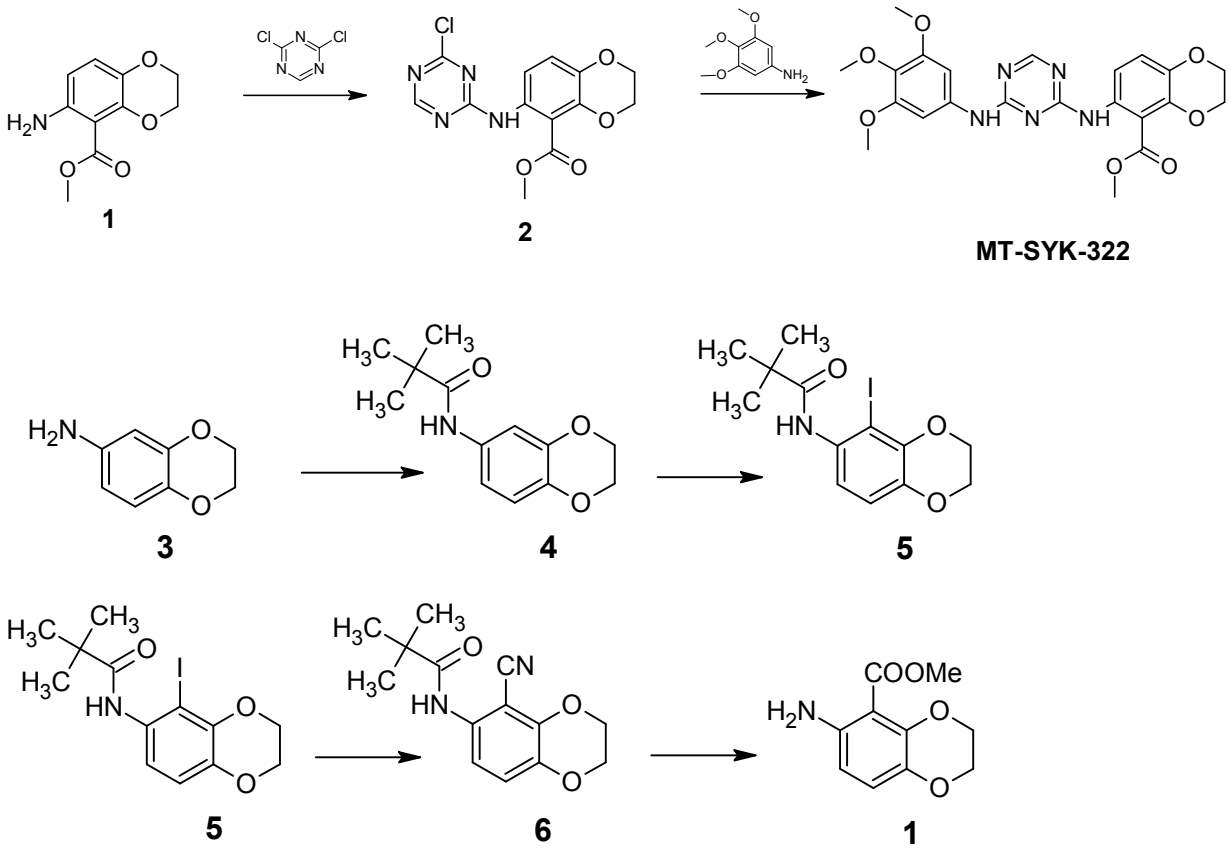
Efficacy of novel Syk-kinase inhibitors MT-SYK-03 and MT-SYK-322 in cellular models of autoimmunity and cancer

Tatiana V. Rakitina, Alexey A. Zeifman, Ilya Yu. Titov, Igor V. Svitanko, Aleksey V. Lipkin, Viktor S. Stroylov, Oleg V. Stroganov, Fedor N. Novikov and Ghermes G. Chilov



Synthesis of compound MT-SYK-322.

N-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2,2-dimethylpropanamide **4.**

To the solution of 24.5 g (162 mmol) of 3,4-ethylenedioxyaniline and 21.9 g (170 mmol) Hunig base in 500 ml of dry acetonitrile, 20.4 g (170 mmol) of pivaloyl chloride was added dropwise maintaining the reaction temperature at 10 °C. The reaction mixture was stirred at this temperature for 20 min and then heated to 45 °C and stirred for additional 12 h. Solvent was removed *in vacuo* and the residue was dissolved in 500 ml of ethyl acetate. The extract was

washed with saturated aqueous NaCl (3 x 50 ml), the organic layer was dried over $MgSO_4$ and solvent was removed *in vacuo*. 30.2 g (126 mmol, 78%) of the product was obtained as a white powder.

N-(5-Iodo-2,3-dihydro-1,4-benzodioxin-6-yl)-2,2-dimethylpropanamide **5.**

30.2 g (126 mmol) of crude compound **4** was dried for 20 h at 50 °C at 0.1 Torr. The residue was dissolved in 500 ml of dry THF. The mixture was stirred upon the complete dissolution of solid and cooled down to -100 °C whereupon 84.0 ml of 1.6 M *tert*-butyllithium in pentane was added dropwise and the mixture was stirred for 2 h at -100− -90 °C. Then 510 ml of 0.25 M iodine solution in dry THF was added dropwise and the reaction mixture was stirred until the complete decolorization (ca 40 minutes). 200 ml of saturated aqueous NH_4Cl solution was added, THF was removed in vacuum. The residue was purified chromatographically eluting with chloroform : methanol mixture of increasing polarity. 40.5 g (89%) of the product was obtained.

2,2-Dimethyl-*N*-(5-methyl-2,3-dihydro-1,4-benzodioxin-6-yl)propanamide **6.**

14.4 g (123 mmol) of $Zn(CN)_2$ and 4.0 g (6 mmol) of $PdCl_2$(dppf) was added to the solution of 40.5 g (112 mmol) of compound **5** dissolved in *N*-methylpyrrolidone. The reaction mixture was stirred at 60 °C for 85 h. *N*-methylpyrrolidone was removed *in vacuo* and the solution of 22.0 g (448 mmol) of NaCN was added to the residue. The mixture was stirred for 30 min and extracted with ethyl acetate (3 x 500 ml). Combined extracts were washed with water until the neutral reaction of the washings and the solvent was removed *in vacuo*. The residue was separated chromatographically eluting with ethyl acetate : hexane mixture of increasing polarity. 18.3 g (70%) of product **6** was obtained as a yellow solid.

Methyl 6-amino-2,3-dihydro-1,4-benzodioxine-5-carboxylate **1.**

A suspension of 18.3 g (78 mmol) of nitrile **5** was boiled in 250 ml of 3N HCl for 3 days. The solvent was removed *in vacuo*. The residue was dissolved in 250 ml of dry methanol and 25 ml of saturated at 0 °C HCl solution in dry methanol was added and refluxed under moisture protected conditions for 6 h. The solvent was removed and 100 ml of water was added to the residue. The solution was neutralized by $NaHCO_3$ to pH ~ 8, the precipitate was filtered off and washed with water until neutrality of the washing and dried. 13.8 g (85%) of compound **1** was obtained as a brownish powder.

Methyl 6-[(4-chloro-1,3,5-triazin-2-yl)amino]-2,3-dihydro-1,4-benzodioxine-5-carboxylate **2.**

0.17 g (1.15 mmol) of 2,4-dichloro[1,3,5]triazine was dissolved in 5 ml of dry degassed DMF. Bicyclic amine **1** (0.25 g, 1.15 mmol) was added and the reaction mixture was stirred at 60 °C for 12 h under inert atmosphere. Solvent was evaporated at 5 Torr. The residue was washed with water (2 x 5 ml) and separated chromatographically eluting with chloroform : methanol mixture of increasing polarity. The standard workup procedure afforded compound **2** (0.27 g, 81%).

Methyl 6-{[4-(3,4,5-trimethoxyanilino)-1,3,5-triazin-2-yl]amino}-2,3-dihydro-1,4-benzodioxine-5-carboxylate (MT-SYK-322).

0.27 g (0.85 mmol) of compound **2** was dissolved in 5 ml of dry degassed DMF. 3,4,5-Trimetoxyaniline (0.16 g, 0.85 mmol) was added 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 (2 x 5 ml) and separated chromatographically eluting with chloroform : methanol mixture of increasing polarity. The standard workup procedure afforded compound MT-SYK-322 (0.29 g, 72%). ^{1}H NMR (500 MHz, DMSO-d_6): 9.11 (s, 1H), 9.07 (s, 1H), 8.14 (s, 1H), 7.75 (d, 1H, J=8.3 Hz), 7.50 (d, 1H, J=8.3 Hz), 4.1 (m, 2H), 3.9 (m, 2H), 3.66 (s, 3H), 3.61 (s, 6H), 3.31 (s, 3H).