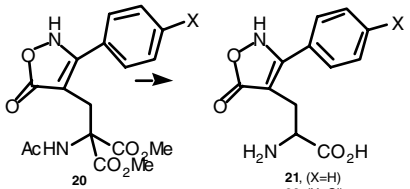
10.1071/CH04041_AC

Accessory Publication: Aust. J. Chem., 2004, 57(7), 685–688.

Supporting Information

Some Synthetic Approaches to Glutamate AMPA-receptor Agonists based on Isoxazolones

Matthew Cox, Saba Jahangiri, Michael V. Perkins, and Rolf H. Prager



Compound **20** (0.5 mmol) and sodium hydroxide (1.5 mmol) were added to water (8 mL), with the addition of ethanol (2 mL) until the mixture became homogenous. The mixture was stirred at room temperature for 1 hour and then acidified with 5M hydrochloric acid (10 mL) and the solution was refluxed for 2 h. The solution was cooled and the residual organic impurities were extracted with Et_2O (3 × 20 mL). The remaining reaction mixture was concentrated *in vacuo*. Recrystallisation of the crude product from EtOH/Et_2O gave the title compound.

X=H (21)

white crystals (49 mg, 39%), mp >300°C.

δ_H 7.97 (1H, m, N*H*), 7.65-7.52 (5H, m, Ar*H*), 5.35 (1H, m, C*H*), 2.87 (1H, m, CH_AH_B), 2.54 (1H, m, CH_AH_B), NH_2 and CO_2H signals unsighted; δ_C 187.6, 170.9, 169.7, 136.5, 129.7, 128.8, 128.5, 90.0, 65.5, 33.6. υ_{max}: 1788, 1718, 1445, 1361, 1218 cm^{-1}; *m/z* (LRMS) 249 (M^+, 14.3%), 218 (52.8), 197 (31), 190 (83).

X=Cl (22)

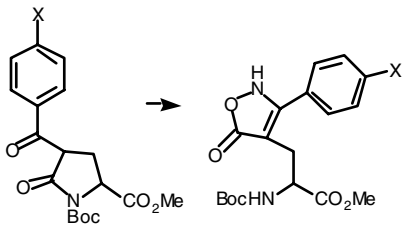
Pink crystals (21 mg, 19%), mp >300°C.

δ_H 7.80-7.50 (2H, m, Ar*H*), 7.10–6.80 (2H, m, Ar*H*), 6.60 (1H, m, N*H*), 5.40 (1H, m, C*H*), 2.90 (1H, m, CH_AH_B), 2.50 (1H, m, CH_AH_B), NH_2 and CO_2H signals unsighted; δ_C 190.2, 164.5, 163.4, 146.1, 134.7, 133.1, 132.2, 69.5, 37.8; *m/z* (LRMS) 283 (M^+, 22%), 257 (18), 252 (44), 224 (84), 197 (100), 175 (8).

X=OMe (23)

Orange oil (22 mg, 28%).

δ_H 7.54–7.47 (2H, m, Ar*H*), 6.99 (1H, m, N*H*), 6.50-6.70 (2H, m, Ar*H*), 5.30 (1H, m, C*H*), 2.70 (1H, m, CH_AH_B), 2.50 (1H, m, CH_AH_B), NH_2 and CO_2H signals unsighted; δ_C 184.8, 172.1, 166.0, 132.8, 128.7, 114.5, 114.0, 89.7, 65.4, 55.1, 32.9.



To a stirred solution of the pyroglutamate derivative in MeOH/H_2O (6:1; 0.1M) was added $NH_2OH.HCl$ (3 equiv) and the reaction mixture was stirred at room temperature for 2 days. The mixture was acidified with 1M HCl solution, saturated with NaCl and diluted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to yield the isoxazolone **36** as a cream coloured glass.

(X=H)

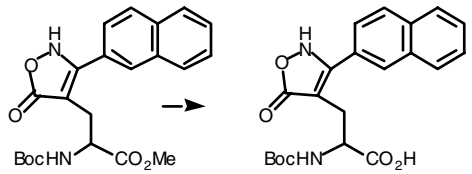
δ_H 7.66–7.47 (6H, m, Ar*H* and N*H*), 5.80–5.69 (1H, m, N*H*Boc), 4.94–4.36 (1H, m, C*H*CO_2Me), 3.55 (3H, s, CO_2CH_3), 2.87 (2H, br d, *J* 5.7, CH_2), 1.33 (9H, s, Bu^t).

(X=Cl)

δ_H 7.63–7.44 (5H, m, Ar*H* and N*H*), 5.66 (1H, br d, *J* 6.3, N*H*Boc), 4.46-4.39 (1H, m, C*H*CO_2Me), 3.62 (3H, s, CO_2CH_3), 2.87 (2H, br d, *J* 5.4, CH_2), 1.34 (9H, s, Bu^t).

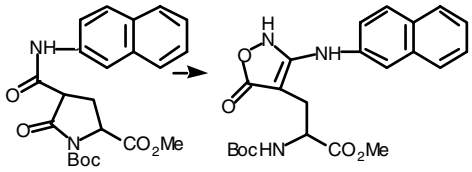
(X=2-naphthyl)

δ_H δ 8.05–7.55 (8H, m, 7 × Ar*H* and 1 × isox N*H*), 5.73 (1H, br d, *J* 6.9, N*H*Boc), 4.50–4.41 (1H, m, C*H*CO_2Me), 3.53 (3H, s, CO_2CH_3), 2.91 (2H, br d, *J* 5.7, CH_2), 1.26 (9H, s, Bu^t).



A 0.5M NaOH solution (7 mL) was added to the isoxazolone (1 mmol) (**36** Ar=2-naphth) and the mixture was stirred at room temperature for 30 min. The reaction mixture was extracted with EtOAc. The aqueous phase was acidified to pH 3 with 1M HCl solution and was extracted with EtOAc, washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give the title compound as a white glass.

δ_H 9.02 (1H, br s, CO_2H), 8.10–7.53 (8H, m, 7 × Ar*H* and 1 × isox N*H*), 6.03 (1H, br d, *J* 7.2, N*H*Boc), 4.50–4.43 (1H, m, C*H*CO_2H), 2.95–2.87 (2H, m, CH_2), 1.27 (9H, s, Bu^t).



To a stirred solution of the pyroglutamate derivative in MeOH/H_2O (6:1; 0.1M) was added NH_2OH (3 equiv; generated from NH_2OH.HCl and K_2CO_3) and the reaction mixture was stirred at room temperature for 24 h. The mixture was acidified with 1M HCl solution, saturated with NaCl and diluted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to yield the isoxazolone (**38** Ar=2-naphth) as a pale orange coloured glass.

δ_H 9.32 (1H, br s, N*H*), 8.37–7.30 (8H, m, Ar*H* + N*H*), 5.78 (1H, br d, *J* 7.5, N*H*), 4.43 (1H, m, C*H*), 3.77 (3H, s, CO_2CH_3), 2.86 (2H, br s, CH_2), 1.42 (9H, s, Bu^t).