Monatshefte für Chemie 133, 1205–1209 (2002)

Monatshefte für Chemie
Chemical Monthly

Synthesis of a New Series of Imidazo[1,5-*d*]pyrido[2,3-*b*][1,4]thiazines as Potential Ligands for the *GABA* Receptor Complex

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Summary. Starting from 2-chloro-3-nitropyridine, 1*H*-pyrido[2,3-*b*][1,4]thiazin-2(3*H*)-one was synthesized. This compound was reacted with potassium *tert*-butoxide and diethyl chlorophosphate to give the intermediate 1*H*-pyrido[2,3-*b*][1,4]thiazin-2-ylphosphate derivative, which in turn afforded the 1,2,4-oxadiazolylimidazo[1,5-*d*]pyrido[2,3-*b*]pyrazine derivatives. The title compounds are potential ligands for the γ-aminobutyric acid A/benzodiazepine receptor complex.

Keywords. Annelation; *GABA* receptor complex; Heterocycles; Imidazo[1,5-*d*]pyrido[2,3-*b*][1,4] thiazines.

Introduction

The γ-aminobutyric acid (*GABA*) receptors are attractive targets for the treatment of several neurological disorders including epilepsy, anxiety, depression, and pain. Associated with the $GABA_A$ ion channel are a variety of recognition sites for small molecules [1], such as benzodiazepines, ethanol, general anesthetics, barbiturates, and a wide range of chemical substrates. They can directly influence the ability of this channel to transport chloride ions across neuronal membranes. When γ-aminobutyric acid, the major inhibitory neurotransmitter in the central nervous system, binds to the receptor, the flow of chloride ions through the channel is increased and the excitability of the neuron is reduced. In general, all compounds which bind to this receptor complex may have a continuum of intrinsic activity, ranging from full agonists through antagonists to inverse agonists [2, 3]. Full agonists potentiate the *GABA*-induced chloride flux to further decrease the excitability of the neuron and have found wide-spread use as anxiolytic, hypnotic, and anticonvulsant agents. In contrast, inverse agonists which decrease the flow of chloride ion are proconvulsant and anxiogenic in nature. Antagonists which have minimal or no effect on the chloride flux have neutral efficacy. As a result, the development of *GABA* receptor agonists and antagonists is of great therapeutic interest. In particular,

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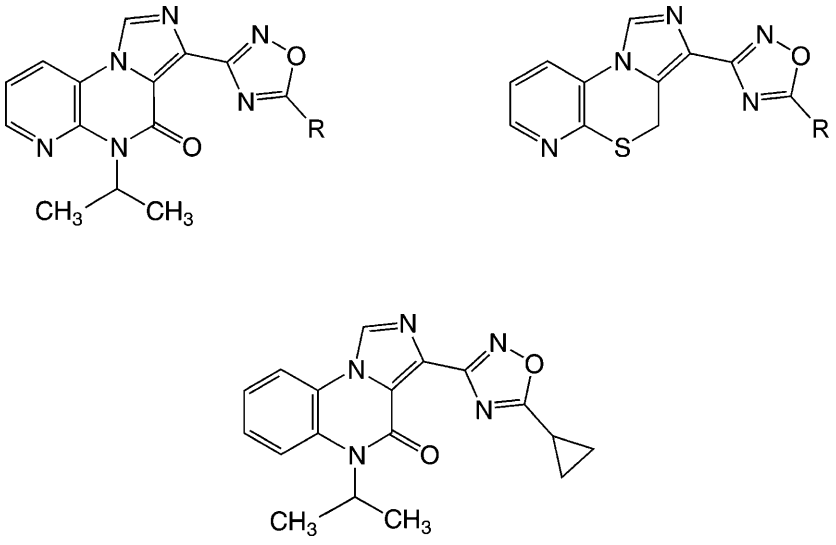


Panadiplon

Scheme 1

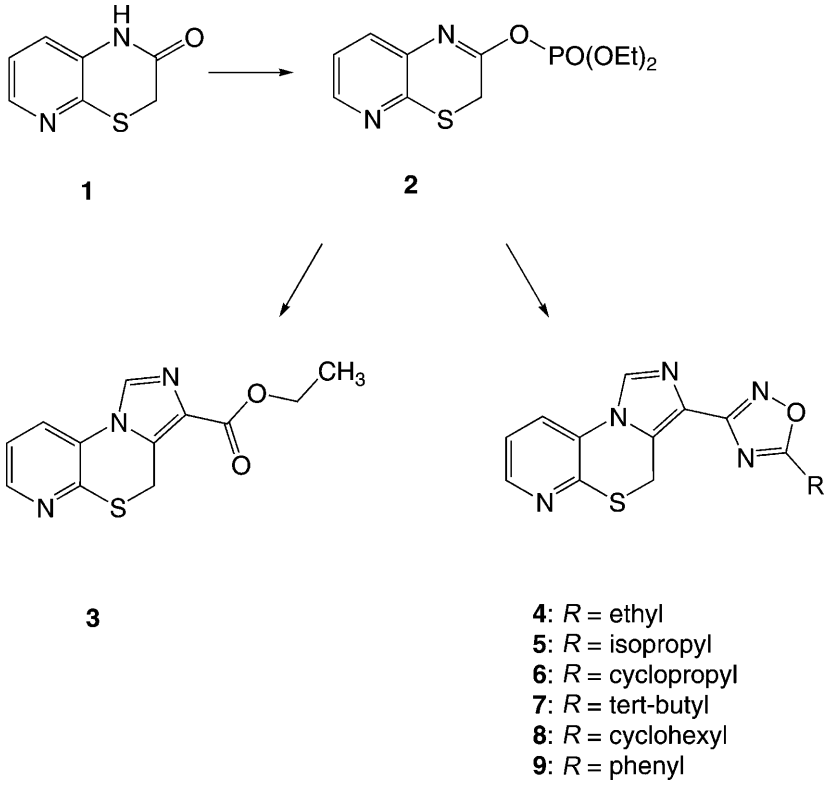
the partial agonists may have reduced benzodiazepine-mediated side effects such as oversedation, physical dependence, amnesia, muscle relaxation, and ethanol potentiation.

One of the compounds that are reported to be partial agonist at the benzodiazepine receptor is panadiplon [4] (Scheme 1). This compound with its imidazo[1,5-*a*]quinoxaline-4-one ring system is reported to be a partial agonist for the $GABA_A$/benzodiazepine receptor complex with high affinity but with an increase of serum triglycerides as a side effect because of the 5-cyclopropyl-1,2,4-oxadiazole group at position 3 which is metabolized to release cyclopropanecarboxylic acid [5, 6]. Therefore, we attempted to synthesize the pyrido analogues to achieve an improved pharmacological profile; this research was directed to the preparation of 1,2,4-oxadiazolylimidazo[1,5-*a*]pyrido[2,3-*e*]pyrazines [7] and imidazo[1,5-*d*]pyrido[2,3-*b*][1,4]thiazine derivatives. In continuation of these studies we present the synthesis of related compounds containing a 1,4-thiazine subunit.

Results and Discussion

The synthesis of the 1*H*-pyrido[2,3-*b*][1,4]thiazin-2(3*H*)-one ring system was carried out as published [8] starting from 3-amino-2-chloropyridine and methyl thioglycolate. The desired 1,2,4-oxadiazolylimidazo[1,5-*d*]pyrido[2,3-*b*]thiazines were prepared as shown in Scheme 2.

Reaction of **1** with potassium *tert*-butoxide and diethyl chlorophosphate provided enol phosphate ester **2**. This intermediate, which was usually not isolated, was reacted with the desired isocyanides in the presence of additional potassium *tert*-butoxide to furnish compounds **3**–**9** (10–67% yield with respect to **1**). The



Scheme 2

oxadiazole isocyanide reagents themselves were synthesized following the general procedure of *Watjen* [9].

Experimental

Melting ranges were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian UnityPlus 300 spectrometer (*TMS* as internal reference, δ values in ppm). Mass spectra were obtained by Shimadzu QP 5000 or Hewlett Packard 5970 spectrometers. Analytical TLC was performed on silica gel F254 plates, preparative layer chromatography on silica gel F254s plates. Column chromatography was executed on Merck silica gel 60, 0.063–0.200 mm. Evaporation refers to evaporation under reduced pressure, drying of solutions to the use of anhydrous Na_2SO_4. The results of elemental analyses agreed with the calculated values within experimental error.

General procedure for the synthesis of compounds **3–9**

A solution of 2 mmol **1** in 30 cm^3 *THF* was cooled to $-40°C$, and potassium *tert*-butoxide (1.0 *M* in *THF*, 2.2 mmol) was added dropwise over 5 min. The mixture was allowed to warm to room temperature over 30 min and then cooled to $-50°C$. Diethyl chlorophosphate (2.6 mmol) was added dropwise over 5 min, and the mixture was allowed to warm from $-50°C$ to $-30°C$ over 1 h and then to room temperature over 30 min. The solution was cooled to $-78°C$, and isocyanide (2.4 mmol) was added. Potassium *tert*-butoxide (1.0 *M* in *THF*, 2.4 mmol) was added dropwise over 10 min. The mixture was allowed to warm slowly to room temperature and stirred overnight. The mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were dried, and the solvent was evaporated.

Ethyl 4H-imidazo[1,5-d]pyrido[2,3-b][1,4]thiazine-3-carboxylate (**3**; $C_{12}H_{11}N_3O_2$)

The residue was recrystallized from EtOH to give 203 mg (39%) of **3** as white crystals. M.p.: 144–145°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.43 (t, $J = 7.2$ Hz, 3H, CH_3), 4.42 (q, $J = 7.2$ Hz, 2H, CH_2), 4.55 (s, 2H, CH_2), 7.27 (dd, $J = 8.1$ Hz, $J = 4.7$ Hz, 1H, pyridine-H), 7.80 (dd, $J = 8.1$ Hz, $J = 1.1$ Hz, 1H, pyridine-H), 7.98 (s, 1H, imidazole-H), 8.45 (dd, $J = 4.7$ Hz, $J = 1.1$ Hz, 1H, pyridine-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 14.4, 22.4, 60.9, 121.4, 124.6, 128.1, 129.1, 130.2, 147.8, 149.6, 162.7 ppm; MS: m/z (%) = 261 (M^+, 11), 215 (69), 187 (100).

3-(5-Ethyl-1,2,4-oxadiazol-3-yl)-4H-imidazo[1,5-d]pyrido[2,3-b][1,4]thiazine
(**4**; $C_{13}H_{11}N_5OS$)

The residue was recrystallized from 30% EtOH to give 385 mg (67%) of **4** as pale yellow crystals. M.p.: 149°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.46 (t, $J = 7.6$ Hz, 3H, CH_3), 2.99 (q, $J = 7.6$ Hz, 2H, CH_2), 4.59 (s, 2H, CH_2), 7.27 (dd, $J = 8.1$ Hz, $J = 4.7$ Hz, 1H, pyridine H), 7.82 (dd, $J = 8.1$ Hz, $J = 1.3$ Hz, 1H, pyridine-H), 8.09 (s, 1H, imidazole-H), 8.43 (dd, $J = 4.7$ Hz, $J = 1.3$ Hz, 1H, pyridine-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 10.7, 20.2, 22.4, 121.4, 124.5, 125.5, 129.3, 147.5, 149.4, 163.8, 180.6 ppm; MS: m/z (%) = 285 (M^+, 27), 228 (100), 215 (96), 57 (29).

3-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-4H-imidazo[1,5-d]pyrido[2,3-b][1,4]thiazine
(**5**; $C_{14}H_{13}N_5OS$)

The residue was recrystallized from *n*-hexane to give 199 mg (33%) of **5** as yellow crystals. M.p.: 147–148°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.47 (d, $J = 7.1$ Hz, 6H, 2 CH_3), 3.30 (sept, $J = 7.1$ Hz, 1H, CH), 4.59 (s, 2H, CH_2), 7.26 (dd, $J = 8.1$ Hz, $J = 4.7$ Hz, 1H, pyridine-H), 7.80 (d, $J = 8.1$ Hz, 1H, pyridine-H), 8.07 (s, 1H, imidazole-H), 8.45 (d, $J = 4.7$ Hz, 1H, pyridine-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 20.1, 22.4, 27.4, 121.4, 124.5, 125.2, 125.4, 129.3, 147.5, 149.4, 163.6, 183.8 ppm; MS: m/z (%) = 299 (M^+, 15), 228 (100), 213 (61), 58 (95).

3-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-4H-imidazo[1,5-d]pyrido[2,3-b][1,4]thiazine
(**6**; $C_{14}H_{11}N_5OS$)

The residue was recrystallized from 50% EtOH to give 231 mg (39%) of **6** as yellow crystals. M.p.: 197–199°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.19–1.44 (m, 4H, 2 CH_2), 2.34 (m, 1H, CH), 4.56 (s, 2H, CH_2), 7.26 (dd, $J = 8.1$ Hz, $J = 4.8$ Hz, 1H, pyridine H), 7.82 (d, $J = 8.1$ Hz, 1H, pyridine-H), 8.07 (s, 1H, imidazole-H), 8.43 (d, $J = 4.8$ Hz, 1H, pyridine-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 7.6, 10.2, 22.4, 121.4, 124.5, 125.1, 125.4, 129.3, 147.4, 149.4, 163.7, 181.5 ppm; MS: m/z (%) = 297 (M^+, 5), 228 (97), 213 (26), 69 (100).

3-(5-tert-Butyl-1,2,4-oxadiazol-3-yl)-4H-imidazo[1,5-d]pyrido[2,3-b][1,4]thiazine
(**7**; $C_{15}H_{15}N_5OS$)

The residue was recrystallized from 50% EtOH to give 324 mg (52%) of **7** as yellow crystals. M.p.: 189–190°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.51 (s, 9H, 3 CH_3), 4.59 (s, 2H, CH_2), 7.26 (dd, $J = 8.1$ Hz, $J = 4.7$ Hz, 1H, pyridine-H), 7.83 (dd, $J = 8.1$ Hz, $J = 1.0$ Hz, 1H, pyridine-H), 8.09 (s, 1H, imidazole-H), 8.43 (d, $J = 4.7$ Hz, 1H, pyridine-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 22.4, 28.3, 33.6, 121.4, 124.5, 125.3, 125.4, 129.3, 147.5, 149.4, 163.6, 186.2 ppm; MS: m/z (%) = 313 (M^+, 7), 228 (56), 213 (17), 57 (100).

3-(5-Cyclohexyl-1,2,4-oxadiazol-3-yl)-4H-imidazo[1,5-d]pyrido[2,3-b][1,4]thiazine
(**8**; $C_{17}H_{17}N_5OS$)

The residue was recrystallized from 50% EtOH to give 324 mg (52%) of **8** as yellow crystals. M.p.: 174–175°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.19–2.22 (m, 10H, 5 CH_2), 2.94–3.09 (m, 1H, CH), 4.59

(s, 2H, CH_2), 7.26 (dd, $J = 8.1$ Hz, $J = 4.7$ Hz, 1H, pyridine-H), 7.82 (d, $J = 8.1$ Hz, 1H, pyridine-H), 8.09 (s, 1H, imidazole-H), 8.43 (dd, $J = 4.7$ Hz, $J = 1.5$ Hz, 1H, pyridine-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 22.4, 25.3, 25.4, 30.1, 36.3, 121.4, 124.5, 125.2, 125.5, 129.3, 147.5, 149.4, 163.6, 182.9 ppm; MS: m/z (%) = 339 (M^+, 5), 228 (40), 213 (18), 55 (100).

3-(5-Phenyl-1,2,4-oxadiazol-3-yl)-4H-imidazo[1,5-d]pyrido[2,3-b][1,4]thiazine
(**9**; $C_{17}H_{11}N_5OS$)

The residue was recrystallized from 2-butanone to give 324 mg (52%) of **8** as yellow crystals. M.p.: 241–244°C; ^{1}H NMR ($CDCl_3$/*DMSO*-d_6, δ, 300 MHz): 4.84 (s, 2H, CH_2), 7.48 (dd, $J = 8.1$ Hz, $J = 4.7$ Hz, 1H, pyridine-H), 7.68–7.83 (m, 3H, phenyl-H) 8.26–8.32 (m, 2H, phenyl-H), 8.38 (dd, $J = 8.1$ Hz, $J = 1.1$ Hz, 1H, pyridine-H), 8.47 (dd, $J = 4.7$ Hz, $J = 1.1$ Hz, 1H, pyridine-H), 8.73 (s, 1H, imidazole-H) ppm; ^{13}C NMR ($CDCl_3$ or *DMSO*-d_6, δ, 75 MHz): solubility too low; MS: m/z (%) = 333 (M^+, 6), 228 (43), 213 (18), 77 (100).

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Received February 22, 2002. Accepted March 6, 2002