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Studies on the Chemistry of Thienoannelated *O,N*- and *S,N*-Containing Heterocycles, 28 [1]. Synthesis of Imidazo[1,5-*d*]thieno[2,3-*b*][1,4]thiazine Derivatives as *GABA*-Receptor Ligands

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Summary. *GABA*-receptor-ligands are still very interesting in drug-development. Usually benzodiazepines are used in the treatment but they have serious side-effects. Thus, a recently synthesized quioxaline derivative which showed reduced side-effects in an animal model was used as a model-substance. The cyclus was modified to optimize the pharmacological profile. Accordingly, a series of imidazo-thieno-thiazines was synthesized starting from 5-acetyl-2-chloro-3-nitrothiophene to yield 6-ethyl-2,3-dihydro-1*H*-thieno[2,3-*b*][1,4]thiazine-2-one. Reaction with potassium *tert*-butoxide and diethylchlorophosphate gave an intermediate, which resulted in the desired ring system after adding the corresponding isocyanides and potassium *tert*-butoxide.

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

Introduction

Ligands with high affinity for the γ-aminobutyric acid A/benzodiazepine receptor complex [2–8] modulate the action of *GABA* on the neuronal chloride flux. The spectrum of possible interactions ranges from full agonists through partial agonists and inverse agonists to antagonists. Studies with new developed substances showed a very good pharmacological profile for partial agonists on this receptor complex because of reduced benzodiazepine-mediated side-effects such as physicial dependence, amnesia, oversedation, muscle relaxation, and ethanol potentation.

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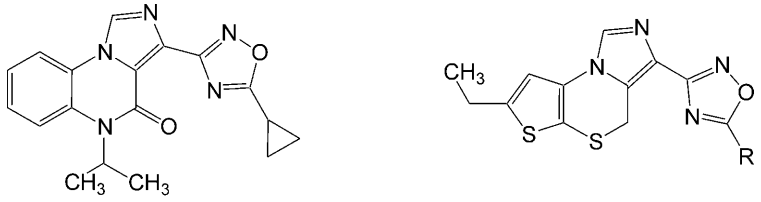


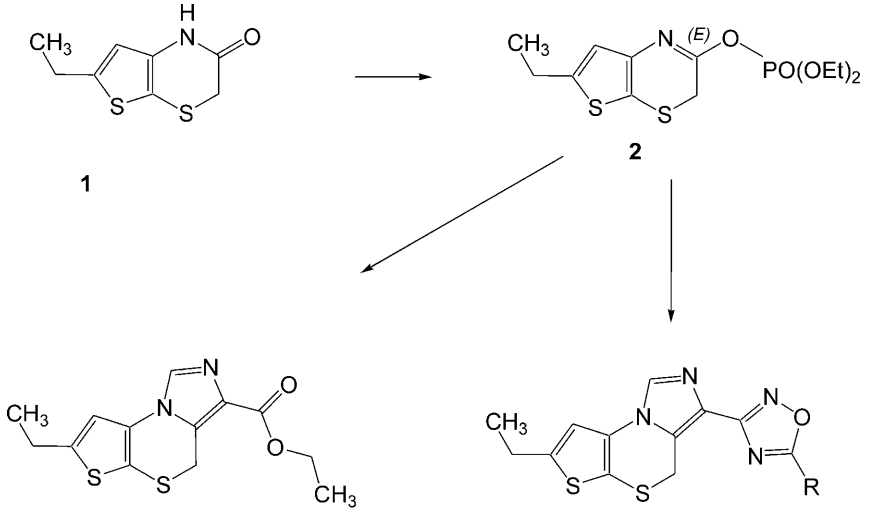
Panadiplon I

Scheme 1

Panadiplon [2] with its imidazo[1,5-*a*]quinoxaline-4-one-ring 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 3-position, which is metabolized to release cyclopropanecarboxylic acid [7]. So we decided to synthesize imidazo[1,5-*d*]thieno[2,3-*b*][1,4]thiazine derivatives **I**.

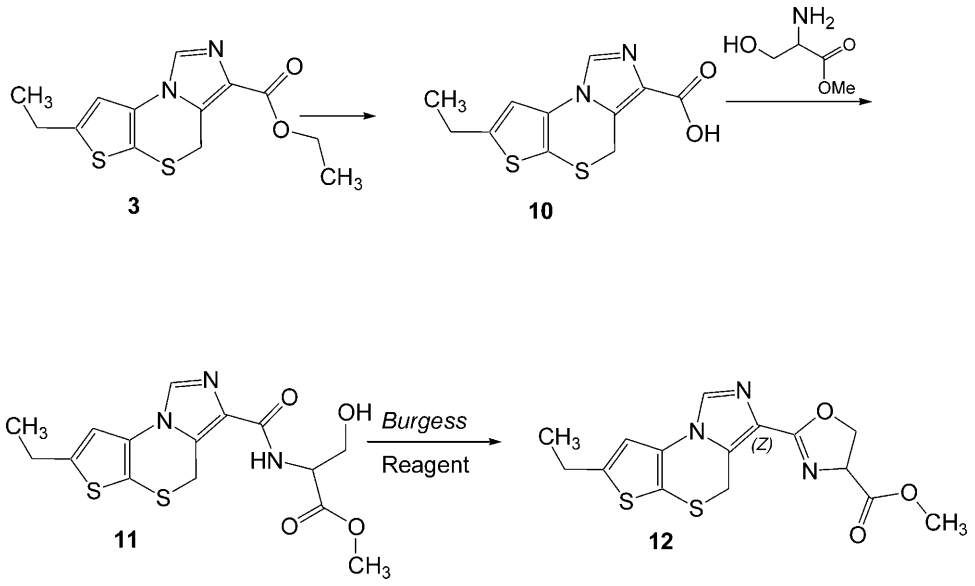
Results and Discussion

Thieno-analogues are potent ligands for the *GABA*-receptor-complex (see *e.g.* brotizolame). A lipophilic group substituted in 7-position is thought to intensify the biologic activity, and finally position 3 of oxadiazole is substituted with various groups to avoid the side-effects described for panadiplon. The synthesis



4: R = cyclopropyl
5: R = isopropyl
6: R = phenyl
7: R = cyclohexyl
8: R = ethyl
9: R = *tert*-butyl

Scheme 2



Scheme 3

of 6-ethyl-1*H*-thieno[2,3-*b*][1,4]thiazin-2(3*H*)-one (**1**) was carried out as published in literature [9] starting from 5-acetyl-2chloro-3-nitrothiophene [10] and methyl thioglycolate. The synthesis of the desired 1,2,4-oxadiazolyl-imidazo[1,5-*d*]thieno [2,3-*b*][1,4]thiazines **3**–**9** is shown in Scheme 2.

Thus, compound **1** was mixed with potassium-*tert*-butoxid and diethyl chlorophosphate under argon to give the enol-phosphate ester **2**. Reaction of this intermediate, which was usually not isolated, with various isocyanides in the presence of additional potassium *tert*-butoxid yielded the desired products **3**–**9**. The oxadiazole isocyanides used in this reactions were synthesized following the general procedure of *Watjen* [8].

Starting from **3** we also synthesized an alternative molecule with an methyl 1,3-oxazoline-carboxylate group in position 3 of the tricyclic ring system. The synthesis of this product **12** is shown in Scheme 3.

Ethyl ester **3** was hydrolized with 5% aqueous sodium hydroxide to get **10**. Reaction with *D*,*L*-serine methyl ester gave intermediate **11** which was cyclisized by adding *Burgess* reagent to yield **12** [11].

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 (300 MHz, *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 done on Merck silica gel 60, 0.063–0.200 mm. Evaporation refers to evaporation under reduced pressure, drying of solutions refers 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 **3–9**

All the following reactions were carried out under Ar atmosphere. A solution of 5 mmol **1** in 10 cm^3 absolute *THF* was cooled to $-40°C$ and 5.5 mmol (1.0 M in *THF*) potassium *tert*-butoxide was added dropwise over 5 min. The mixture was allowed to warm to room temperature over 30 min and then cooled to $-50°C$. Within 4 min 6.5 mmol diethylchlorophosphate (Fluka) was dropped into the flask, then the solution was warmed to $-30°C$ for 1 h, and finally to room temperature over 30 min. Afterwards it was cooled again to $-78°C$ and 6.0 mmol of the corresponding isocyanide was added. Within 10 min 6 mmol (1.0 M in *THF*) potassium *tert*-butoxide was dropped to the mixture. The solution was allowed to warm to $-20°C$ over 1 h and 45 min. Finally, the reaction mixture was stirred at room temperature for 45 min. The resultant mixture was poured into 120 cm^3 ice-H_2O and the formed precipitate was recrystallized.

Actually products **4**, **5**, **7**, **8**, and **9** gave oils after pouring them into H_2O. Accordingly, the solutions were partitioned between 100 cm^3 H_2O (with 2 cm^3 glacial acetic acid added) and CH_2Cl_2 four times, then between pure H_2O and CH_2Cl_2. The organic layers were dried over anhydrous Na_2SO_4 and evaporated. Afterwards the residues were recrystallized.

Ethyl 7-Ethyl-4H-imidazo[1,5-d]thieno[2,3-b][1,4]thiazine-3-carboxylate
(**3**, $C_{13}H_{14}N_2O_2S_2$)

After crystallization from *Et*OH 0.912 g (62%) **3** was obtained. Mp 130°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.33$ (t, $J = 7.5$ Hz, CH_3), 1.43 (t, $J = 7.3$ Hz, CH_3), 2.84 (q, $J = 7.5$ Hz, CH_2), 4.41 (q, $J = 7.3$ Hz, CH_2), 4.47 (s, CH_2), 6.93 (s, thiophene-H), 7.78 (s, imidazole-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.3$, 15.5, 23.6, 24.7, 60.7, 114.1, 116.2, 127.3, 128.4, 130.7, 146.6, 162.9 ppm; MS: m/z = (%) 294 (M^+, 40), 248 (69), 220 (100), 154 (25).

3-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-7-ethyl-4H-imidazo[1,5-d]thieno[2,3-b][1,4]thiazine
(**4**, $C_{15}H_{14}N_4OS_2$)

After crystallization from *Et*OH 0.737 g (45%) **4** was obtained. Mp 138–140°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.19$–1.28 (m, CH_2), 1.28–1.39 (m, CH_2), 1.33 (t, $J = 7.5$ Hz, CH_3), 2.19–2.32 (m, CH), 2.84 (q, $J = 7.5$ Hz, CH_2), 4.47 (s, CH_2), 6.93 (s, thiophene-H), 7.76 (s, imidazole-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 7.6$, 10.1, 15.5, 23.6, 24.7, 114.2, 115.8, 123.7, 124.4, 131.0, 146.5, 164.0, 181.3 ppm; MS: m/z (%) = 330 (M^+, 1), 261 (2), 100 (26), 43 (100).

7-Ethyl-3-(5-isopropyl-1,2,4-oxadiazol-3-yl)-4H-imidazo[1,5-d]thieno[2,3-b][1,4]thiazine
(**5**, $C_{15}H_{16}N_4OS_2$)

After crystallization from diluted *Et*OH 0.708 g (43%) **5** was obtained. Mp 110°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.34$ (t, $J = 7.5$ Hz, CH_3), 1.46 (d, $J = 7.1$ Hz, CH_3), 2.84 (q, $J = 7.5$ Hz, CH_2), 3.29 (sept, $J = 7.1$ Hz, CH), 4.50 (s, CH_2), 6.95 (s, thiophene-H), 7.88 (s, imidazole-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 15.5$, 20.1, 23.6, 24.8, 27.4, 114.2, 115.8, 123.7, 124.4, 130.9, 146.5, 164.0, 183.6 ppm; MS: m/z (%) = 332 (M^+, 25), 289 (27), 246 (66), 58 (100).

7-Ethyl-3-(5-phenyl-1,2,4-oxadiazol-3-yl)-4H-imidazo[1,5-d]thieno[2,3-b][1,4]thiazine
(**6**, $C_{18}H_{14}N_4OS_2$)

After crystallization from *Et*OH 0.996 g (54%) **6** was obtained. Mp 185–186°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.33$ (t, $J = 7.5$ Hz, CH_3), 2.83 (q, $J = 7.5$ Hz, CH_2), 4.58 (s, CH_2), 6.94 (s, thiophene-H), 7.47–7.65

(m, phenyl-H), 7.91 (s, imidazole-H), 8.18–8.30 (m, phenyl-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 15.4$, 23.6, 24.8, 114.2, 115.8, 124.0, 124.3, 128.2, 128.9, 131.0, 132.7, 146.6, 164.7, 175.3 ppm; MS: m/z (%) = 366 (M^+, 6), 289 (9), 261 (78), 77 (100).

3-(5-Cyclohexyl-1,2,4-oxadiazol-3-yl)-7-ethyl-4H-imidazo[1,5-d]thieno[2,3-b][1,4]thiazine (**7**, $C_{18}H_{20}N_4OS_2$)

After crystallization from *Et*OH 1.194 g (64%) **7** was obtained. Mp 105°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.34$ (t, $J = 7.5$ Hz, CH_3), 1.19–1.38 (m, CH_2), 1.61–1.93 (m, CH_2), 2.07–2.20 (m, CH_2), 2.84 (q, $J = 7.5$ Hz, CH_2), 2.93–3.09 (m, CH), 4.51 (s, CH_2), 7.27 (s, thiophene-H), 7.87 (s, imidazole-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 15.5$, 23.7, 24.9, 25.4, 25.5, 30.2, 36.3, 114.3, 115.8, 123.8, 124.6, 131.1, 146.6, 164.0, 182.7 ppm; MS: m/z (%) = 372 (M^+, 8), 261 (27), 246 (25), 55 (100).

7-Ethyl-3-(5-ethyl-1,2,4-oxadiazol-3-yl)-4H-imidazo[1,5-d]thieno[2,3-b][1,4]thiazine (**8**, $C_{14}H_{14}N_4OS_2$)

After crystallization from diluted *Et*OH 0.811 g (51%) **8** was obtained. Mp 145–147°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.34$ (t, $J = 7.5$ Hz, CH_3), 1.45 (t, $J = 7.7$ Hz, CH_3), 2.84 (q, $J = 7.5$ Hz, CH_2), 2.97 (q, $J = 7.7$ Hz, CH_2), 4.50 (s, CH_2), 6.94 (s, thiophene-H), 7.88 (s, imidazole-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 10.7$, 15.5, 20.2, 23.6, 24.8, 114.2, 115.8, 123.8, 124.4, 131.0, 146.6, 164.1, 180.4 ppm; MS: m/z (%) = 318 (M^+, 15), 261 (51), 232 (24), 45 (100).

3-(5-tert-Butyl-1,2,4-oxadiazol-3-yl)-7-ethyl-4H-imidazo[1,5-d]thieno[2,3-b][1,4]thiazine (**9**, $C_{16}H_{18}N_4OS_2$)

After crystallization from *Et*OH 1.260 g (73%) **9** was obtained. Mp 130°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.34$ (t, $J = 7.5$ Hz, CH_3), 1.50 (s, CH_3), 2.84 (q, $J = 7.5$ Hz, CH_2), 4.50 (s, CH_2), 6.95 (s, thiophene-H), 7.88 (s, imidazole-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 15.5$, 23.6, 24.8, 28.4, 33.6, 114.3, 115.8, 123.7, 124.5, 131.0, 146.5, 163.9, 185.9 ppm; MS: m/z (%) = 346 (M^+, 1), 261 (9), 91 (100), 57 (25).

7-Ethyl-4H-imidazo[1,5-d]thieno[2,3-b][1,4]thiazine-3-carboxylic acid (**10**, $C_{11}H_{10}N_2O_2S_2$)

A solution of 5 mmol **3** in 55 cm^3 absolute *Et*OH and 22 cm^3 5% aqueous NaOH was refluxed at 85°C for 2 h. The mixture was cooled to room temperature and the solvent was removed by evaporation. The residue was suspended in 60 cm^3 H_2O, acidified with concentrated hydrochloric acid and stirred for 1 h at 10°C. The precipitate was collected and washed with cold water. After crystallization from diluted *Et*OH 1.223 g (92%) **10** was obtained. Mp 223–224°C; ^{1}H NMR (*DMSO-d*$_6$): $\delta = 1.33$ (t, $J = 7.5$ Hz, CH_3), 2.88 (q, $J = 7.5$ Hz, CH_2), 4.61 (s, CH_2), 7.50 (s, thiophene-H), 8.35 (s, imidazole-H) ppm; ^{13}C NMR (*DMSO-d*$_6$): $\delta = 15.4$, 23.0, 24.4, 114.7, 116.0, 127.2, 128.1, 131.2, 145.4, 164.2 ppm; MS: m/z (%) = 266 (M^+, 23), 248 (50), 220 (100), 45 (59).

Methyl 2-[[(7-Ethyl-4H-imidazo[1,5-d]thieno[2,3-b][1,4]thiazine-3-yl)carbonyl]amino]-3-hydroxypropanoate (**11**, $C_{15}H_{17}N_3O_4S_2$)

Compound **10** (6 mmol) was suspended in 30 cm^3 absolute *DMF* under Ar. Then 6.3 mmol carbonyldiimidazole was added and the mixture was stirred for 1 h at room temperature, then another 2 h at 55°C. After cooling the suspension to 0–5° (7 mmol) *D,L*-serinemethylester hydrochloride and absolute triethylamine (6.4 mmol) were added and stirred for 96 h at room temperature. The solvent was evaporated, the residue was dissolved in hot H_2O and after cooling extracted with ethyl acetate. The oily product was purified by column chromatography with ethyl acetate. After crystallization from

ethyl acetate 0.858 g (39%) **10** was obtained. Mp 138–140°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.32$ (t, $J = 7.5$ Hz, CH_3), 2.82 (q, $J = 7.5$ Hz, CH_2), 3.80 (s, CH_3), 3.99–4.28 (m, OH/ CH_2), 4.46 (s, CH_2), 4.77–4.89 (m, CH), 6.85 (s, thiophene-H), 7.67 (s, imidazole-H), 7.86–8.00 (m, NH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 15.5$, 23.6, 24.5, 52.6, 54.4, 63.2, 114.1, 116.4, 126.0, 128.9, 130.5, 146.5, 162.7, 170.8 ppm; MS: m/z (%) = 367 (M^+, 8), 310 (46), 220 (100), 91 (53).

Methyl 2-(7-Ethyl-4H-imidazo[1,5-d]thieno[2,3-b][1,4]thiazine-3-yl)-4,5-dihydro-1,3-oxazole-4-carboxylate (**12**, $C_{15}H_{15}N_3O_3S_2$)

A solution of 2 mmol **11** in 10 cm^3 absolute *THF* was mixed with 2.1 mmol methoxycarbonylsulfamoyl-triethylammonium hydroxide, inner salt (*Burgess* reagent) under Ar and refluxed for 1 h. The mixture was cooled to room temperature and the solvent was evaporated. The oily residue was dissolved in CH_2Cl_2 and separated by column chromatography (ethyl acetate/ethanol 9/1). After recrystallization from *Et*OH 0.480 g (69%) **12** was obtained. Mp 164°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.33$ (t, $J = 7.5$ Hz, CH_3), 2.83 (q, $J = 7.5$ Hz, CH_2), 3.81 (s, CH_3), 4.46 (s, CH_2), 4.52–4.72 (m, CH_2), 4.87–4.99 (m, CH), 6.92 (s, thiophene-H), 7.79 (s, imidazole-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 15.4$, 23.6, 24.8, 52.5, 68.4, 69.1, 114.2, 116.0, 124.5, 125.9, 130.8, 146.5, 161.8, 171.6 ppm; MS: m/z (%) = 349 (M^+, 35), 290 (17), 235 (43), 45 (100).

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