SYNTHESIS OF 1,2,4-OXADIAZOLYLIMIDAZO[1,5-a]THIENO[2,3-e]PYRAZINES AS LIGANDS FOR THE γ-AMINOBUTYRIC ACID A/BENZODIAZEPINE RECEPTOR COMPLEX1

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Abstract – Starting from 5-benzoyl-2-chloro-3-nitrothiophene the thieno[2,3-b]pyrazine-2,3-dione ring system (4) was synthesized. This compound was reacted with potassium tert-butoxide and diethyl chlorophosphate to give diethyl 7-benzoyl-4-isopropyl-3-oxo-3,4-dihydrothieno[2,3-b]pyrazin-2-ylphosphate (5), which gave with the desired 5-alkyl-3-isocyanomethyl-1,2,4-oxadiazoles in the presence of additional potassium tert-butoxide the 1,2,4-oxadiazolylimidazo[1,5-a]thieno[2,3-e]pyrazine derivatives (6-10) as ligands for the γ-aminobutyric acid A / benzodiazepine receptor complex.

Compounds2, 4-9 which bind to the γ-aminobutyric acid A/benzodiazepine receptor complex may have a continuum of intrinsic activity, ranging from full agonists (anxiolytic, hypnotic, and anticonvulsant agents) through antagonists to inverse agonists (proconvulsant and anxiogenic agents). Among these the partial agonists may have reduced benzodiazepine-mediated side effects such as sedation, physical dependence, amnesia, muscle relaxation, and ethanol potentiation. The current interest in 1,2,4-oxadiazolylimidazo[1,5-a]thieno[2,3-e]pyrazines is based on their potential usefulness as partial agonist for the treatment of anxiety and sleep disorders.

One of the compounds that are reported to be partial agonist at the benzodiazepine receptor is Panadiplon.2 Unfortunately this imidazo[1,5-a]quinoxaline derivative contains a 5-cyclopropyl-1,2,4-oxadiazole group at the 3-position, which is metabolized to release cyclopropanecarboxylic acid, leading to an increase in serum triglycerides.9 Therefore we studied to synthesize the thienoanalogues to achieve an
improved pharmacological profile. This research was to prepare the following thienoannelated derivatives:

Substitution at the 7-position by a benzoyl group, as observed in various cases, was to intensify any biological activity. The synthesis of the starting thieno[2,3-\(b\)]pyrazine-2,3-dione was carried out as demonstrated in the scheme below:

Reaction of compound (1) with isopropylamine provided the substitution product (2) (84%), which was acylated with ethyl oxalyl chloride in the presence of triethylamine to yield amide (3) (54%). To accomplish the necessary lactam linkage the nitro group of 3 was reduced by treatment with iron powder in glacial acetic acid at 65°C for 10 min to provide the bicycle (4) (67%). The desired 1,2,4-oxadiazolyl-imidazo[1,5-\(a\)]thieno[2,3-\(e\)]pyrazines were synthesized as shown in the following Scheme:
Reaction of compound (4) with potassium tert-butoxide and diethyl chlorophosphate provided enol
phosphate ester (5). This intermediate (5), which was usually not isolated, was reacted with the desired
isocyanides in the presence of additional potassium tert-butoxide to provide compounds (6-10) (11–38 %
yields from 4). The oxadiazole isocyanide reagents themselves were synthesized following the general
procedure of Watjen.4

**EXPERIMENTAL**

Melting ranges were determined on a Kofler hot-stage apparatus and are uncorrected. ¹H-NMR and ¹³C-
NMR spectra were recorded on a Varian UnityPlus 300 spectrometer (using TMS as internal reference, δ
values in ppm). MS spectra were obtained by a Shimadzu QP 5000 or a Hewlett Packard 5970
spectrometer. 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, and drying of solutions refers to the use of anhydrous sodium sulfate.

5-Benzoyl-2-isopropylamino-3-nitrothiophene (2)
Compound (1) (1.335 g, 5 mmol) was dissolved in DMF (20 mL) under argon atmosphere and isopropylamine (591 mg, 10 mmol) was added at rt. After 10 min the mixture was poured into ice-water. The precipitate was collected, dried and recrystallized from ethanol to yield 2 (1.220 g, 84 %); mp 155-156°C; MS: m/z (rel. int.) 290 (M⁺, 100), 275 (16), 257 (17), 105 (17); ¹H- NMR (CDCl₃, 300 MHz): δ 8.64-8.51 (m, 1H, NH), 7.86 (s, 1H, thiophene-H), 7.83-7.75 (m, 2H, Ph-H), 7.65-7.57 (m, 1H, Ph-H), 7.55-7.46 (m, 2H, Ph-H), 3.84-3.67 (m, 1H, CH), 1.45 (d, 6H, J = 6.4 Hz, CH₃); ¹³C- NMR (CDCl₃): δ 187.0, 162.7, 136.6, 132.3, 130.8, 128.6, 126.5, 123.6, 51.0, 21.9. Anal. Calcd for C₁₄H₁₄N₂O₃S: C, 57.92; H, 4.86; N, 9.65. Found: C, 57.67; H, 4.66; N, 9.72.

Ethyl (5-benzoyl-3-nitro-2-thienyl) (isopropyl)aminooxooacetate (3)
To a solution of compound (2) (290 mg, 1 mmol) dissolved in dry toluene (5 mL) under argon atmosphere ethyl oxalyl chloride (273 mg, 2 mmol) and triethylamine (253 mg, 2.5 mmol) were added. The mixture was stirred under reflux for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried and the solvent was evaporated. The residue was purified via column chromatography on silica gel (eluent: toluene-ethyl acetate (9:1)) to give 3 (210 mg, 54%) as an oil; MS: m/z (rel. int.) 390 (M⁺, 90), 344 (100), 290 (38), 275 (37); ¹H- NMR (CDCl₃, 300 MHz): δ 8.03 (s, 1H, thiophene-H), 7.93-7.84 (m, 2H, Ph-H), 7.74-7.65 (m, 1H, Ph-H), 7.63-7.53 (m, 2H, Ph-H), 4.99 (br s, 1H, CH), 4.29–4.12 (m, 2H, OCH₂), 1.55-0.97 (m, 6H, CH₃), 1.26 (t, 3H, J = 6.8 Hz, CH₃); ¹³C- NMR (CDCl₃): δ 186.2, 142.9, 138.6, 135.6, 133.6, 129.1, 128.9, 127.8, 62.8, 50.9, 13.7. Anal. Calcd for C₁₈H₁₈N₂O₆S: C, 55.38; H, 4.65; N, 7.18. Found: C, 55.68; H, 4.88; N, 7.11.

6-Benzoyl-4-isopropyl-1,2,3,4-tetrahydrothieno[2,3-b]pyrazine-2,3-dione (4)
A mixture of compound (3) (6,618 g, 17 mmol), acetic acid (80 mL, 99%) and water (8 mL) were heated to 65°C. Iron powder (6.646 g, 0.119 mol) was added in small portions. The mixture was stirred for 10 min. Then the iron powder was filtered off and washed with hot water. The filtrate was cooled with ice and the precipitate was collected and recrystallized from methanol to yield 4 (3.352 g, 67 %); mp 260°C; MS: m/z (rel. int.) 314 (M⁺, 22), 272 (38), 195 (40), 167 (40), 77 (100); ¹H- NMR (DMSO-d₆, 300 MHz): δ 12.12 (s, 1H, NH), 8.03-7.52 (m, 5H, Ph-H), 7.36 (s, 1H, thiophene-H), 4.81 (br s, 1H, CH), 1.60 (d, 6H, J = 6.2 Hz, CH₃); ¹³C- NMR (DMSO-d₆): δ 186.5, 154.7, 153.4, 137.0, 132.4, 132.1, 131.1, 128.7,
Anal. Calcd for C_{16}H_{14}N_{2}O_{3}S: C, 61.13; H, 4.49; N, 8.91. Found: C, 60.92; H, 4.44; N, 8.88.

General procedure for the synthesis of compounds (6 - 10)
A solution of the lactam (4) (628 mg, 2 mmol) in THF (30 mL) was cooled to −40°C, and potassium tert-butoxide (1.0 M in THF, 2.2 mL, 2.2 mmol) was added dropwise over 5 min. The mixture was allowed to warm to rt over 30 min and then cooled to −50°C. Diethyl chlorophosphate (449 mg, 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 allowed to warm to rt 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 mL, 2.4 mmol) was added dropwise over 10 min. The mixture was allowed to warm slowly to rt and stirred at rt overnight. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried and the solvent was evaporated.

Ethyl 7-benzoyl-5-isopropyl-4-oxo-4,5-dihydroimidazo[1,5-a]thieno[2,3-e]pyrazine-3-carboxylate (6)
Prepared from 4 (628 mg, 2 mmol) and ethyl isocyanoacetate (271 mg, 2.4 mmol). After crystallization from diluted ethanol 6 (308 mg, 38 %) was obtained as needles; mp 179-180°C; MS: m/z (rel. int.) 409 (M+, 26 ), 321 (82), 272 (47); ¹H-NMR (CDCl₃, 300 MHz): δ 8.24 (s, 1H, imidazole-H), 7.91 (s, 1H, thiophene-H), 7.89-7.82 (m, 2H, Ph-H), 7.73-7.46 (m, 3H, Ph-H), 5.10 (br s, 1H, CH), 4.46 (q, 2H, J = 7.1 Hz, CH₂), 1.69 (d, 6H, J = 6.8 Hz, CH₃), 1.43 (t, 3H, J = 7.1 Hz, CH₃); ¹³C-NMR (CDCl₃): δ 187.0, 161.4, 154.7, 152.3, 136.8, 133.6, 133.6, 132.7, 128.8, 128.5, 121.8, 121.5, 116.9, 91.8, 61.7, 19.1, 14.2. Anal. Calcd for C_{21}H_{19}N_{3}O_{4}S: C, 61.60; H, 4.68; N, 10.26. Found: C, 61.51; H, 4.72; N, 10.10.

7-Benzoyl-3-(5-cyclohexyl-1,2,4-oxadiazol-3-yl)-5-isopropyl-4-oxo-4,5-dihydroimidazo[1,5-a]thieno[2,3-e]pyrazin-4-one (7)
Prepared from 4 (628 mg, 2 mmol) and 5-cyclohexyl-3-isocyanomethyl-1,2,4-oxadiazole (459 mg, 2.4 mmol). Purification by preparative layer chromatography (eluent: toluene-ethyl acetate (4:6)) gave 7 (201 mg, 21 %) as an oil; MS: m/z (rel. int.) 487 (M⁺, 1), 190 (22), 164 (100); ¹H-NMR (CDCl₃, 300 MHz): δ 8.32 (s, 1H, imidazole-H), 7.90 (s, 1H, thiophene-H), 7.89-7.83 (m, 2H, Ph-H), 7.68-7.60 (m, 1H, Ph-H), 7.59-7.49 (m, 2H, Ph-H), 5.16 (br s, 1H, CH), 3.12-2.98 (m, 1H, cyclohexyl-H), 2.21-2.09 (m, 2H, cyclohexyl-H), 1.92-1.64 (m, 5H, cyclohexyl-H), 1.69 (d, 6H, J = 6.4 Hz, CH₃), 1.50-1.22 (m, 3H, cyclohexyl-H); ¹³C-NMR (CDCl₃): δ 187.0, 182.9, 163.3, 153.1, 136.8, 133.5, 132.6, 132.1, 128.9, 128.7, 128.1, 125.2, 121.5, 120.1, 117.1, 36.3, 30.1, 25.4, 25.3, 19.1. Anal. Calcd for C_{26}H_{23}N_{5}O_{3}S x 0.25
toluene: C, 64.62; H, 5.23; N, 13.70. Found: C, 64.87; H, 5.28; N, 13.86.

7-Benzoyl-5-isopropyl-3-(5-isopropyl-1,2,4-oxadiazol-3-yl)-4-oxo-4,5-dihydroimidazo[1,5-a]thieno[2,3-e]pyrazin-4-one (8)
Prepared from 4 (628 mg, 2 mmol) and 3-isocyanomethyl-5-isopropyl-1,2,4-oxadiazole (362 mg, 2.4 mmol). After crystallization from diluted ethanol 8 (102 mg, 11%) was obtained as needles; mp 245-246°C; MS: m/z (rel. int.) 447 (M^+, 13), 405 (14), 105 (100); ^1H-NMR (CDCl_3, 300 MHz): δ 8.32 (s, 1H, imidazole-H), 7.90 (s, 1H, thiophene-H), 7.89-7.84 (m, 2H, Ph-H), 7.69-7.61 (m, 1H, Ph-H), 7.59-7.51 (m, 2H, Ph-H), 5.16 (br s, 1H, CH), 3.34 (sept, 1H, J = 7.1 Hz, CH), 1.70 (d, 6H, J = 7.1 Hz, CH_3), 1.48 (d, 6H, J = 7.1 Hz, CH_3); ^13C-NMR (CDCl_3): δ 187.0, 183.3, 163.3, 153.1, 144.2, 136.8, 133.5, 132.6, 132.1, 128.7, 121.5, 120.1, 117.1, 27.5, 20.1, 19.1. Anal. Calcd for C_{23}H_{21}N_{5}O_{3}S: C, 61.73; H, 4.73; N, 15.65. Found: C, 61.92; H, 4.86; N, 15.46.

7-Benzoyl-3-(5-tert-butyl-1,2,4-oxadiazol-3-yl)-5-isopropyl-4-oxo-4,5-dihydroimidazo[1,5-a]thieno[2,3-e]pyrazin-4-one (9)
Prepared from 4 (628 mg, 2 mmol) and 5-tert-butyl-3-isocyanomethyl-1,2,4-oxadiazole (396 mg, 2.4 mmol). After crystallization from diluted ethanol 9 (150 mg, 16%) was obtained as needles; mp 260-262°C; MS: m/z (rel. int.) 461 (M^+, 8), 419 (8), 57 (100); ^1H-NMR (CDCl_3, 300 MHz): δ 8.31 (s, 1H, imidazole-H), 7.90 (s, 1H, thiophene-H), 7.94-7.81 (m, 2H, Ph-H), 7.71-7.50 (m, 3H, Ph-H), 5.15 (br s, 1H, CH), 1.70 (d, 6H, J = 7.1 Hz, CH_3), 1.52 (s, 9H, tert-butyl-H); ^13C-NMR (CDCl_3): δ 187.0, 182.3, 163.3, 153.1, 136.8, 133.5, 132.7, 132.1, 130.7, 128.8, 128.7, 128.1, 121.5, 120.2, 117.1, 33.3, 28.4, 19.1. Anal. Calcd for C_{24}H_{23}N_{5}O_{3}S x 0.25 CH_3CO_2C_2H_5: C, 62.10; H, 5.21; N, 14.48. Found: C, 62.40; H, 5.35; N, 14.15.

7-Benzoyl-3-(5-ethyl-1,2,4-oxadiazol-3-yl)-5-isopropyl-4-oxo-4,5-dihydroimidazo[1,5-a]thieno[2,3-e]pyrazin-4-one (10)
Prepared from 4 (628 mg, 2 mmol) and 5-ethyl-3-isocyanomethyl-1,2,4-oxadiazole (329 mg, 2.4 mmol). After crystallization from diluted ethanol 10 (180 mg, 21%) was obtained; mp 246-248°C; MS: m/z (rel. int.) 433 (M^+, 12), 391 (11), 57 (100); ^1H-NMR (CDCl_3, 300 MHz): δ 8.32 (s, 1H, imidazole-H), 7.89 (s, 1H, thiophene-H), 7.89-7.84 (m, 2H, Ph-H), 7.69-7.61 (m, 1H, Ph-H), 7.60-7.51 (m, 2H, Ph-H), 5.17 (br s, 1H, CH), 3.02 (q, 2H, J = 7.7 Hz, CH_2), 1.70 (d, 6H, J = 7.1 Hz, CH_3), 1.46 (t, 3H, J = 7.7 Hz, CH_3); ^13C-NMR (CDCl_3): δ 187.0, 180.7, 163.5, 153.1, 136.8, 133.5, 132.7, 132.1, 130.7, 128.8, 128.7, 128.1, 121.5, 120.2, 117.1, 33.3, 28.8, 19.1. Anal. Calcd for C_{22}H_{19}N_{5}O_{3}S: C, 60.96; H, 4.42; N, 16.16. Found: C, 61.20; H, 4.68; N, 15.89.
REFERENCES AND NOTES

1. Studies on the Chemistry of Thienoannelated O,N- and S,N- containing Heterocycles- Part. 22; for Part. 21 see: T. Erker and E. Krainz, Heterocycles, 2001, 55, 255.


