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

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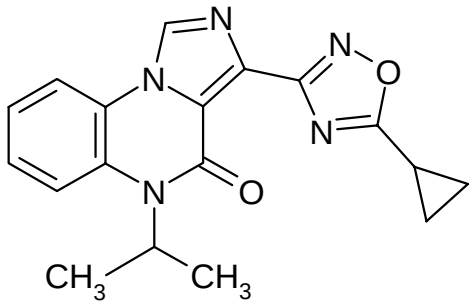
Abstract – Starting from 5-benzoyl-2-chloro-3-nitrothiophene the thieno[2,3-*b*]pyrazine-2,3-dione ring system (**4**) was synthesized. This compound was reacted with potassium *tert*-butoxide and diethyl chlorophosphate to give diethyl 7-benzoyl-4-isopropyl-3-oxo-3,4-dihydrothieno[2,3-*b*]pyrazin-2-ylphosphate (**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.

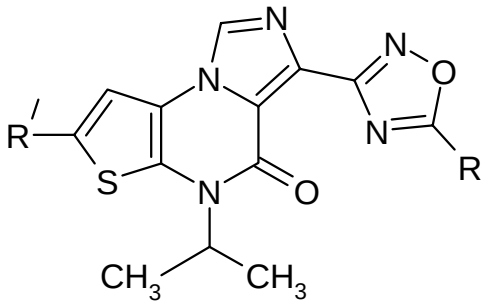
Compounds[2, 4-9] which bind to the γ-aminobutyric acid A/benzodiazepine receptor complex may have a continuum of intrinsic activity, ranging from full agonists (anxiolytic, hypnotic, and anticonvulsant agents) through antagonists to inverse agonists (proconvulsant and anxiogenic agents). Among these 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 achive an

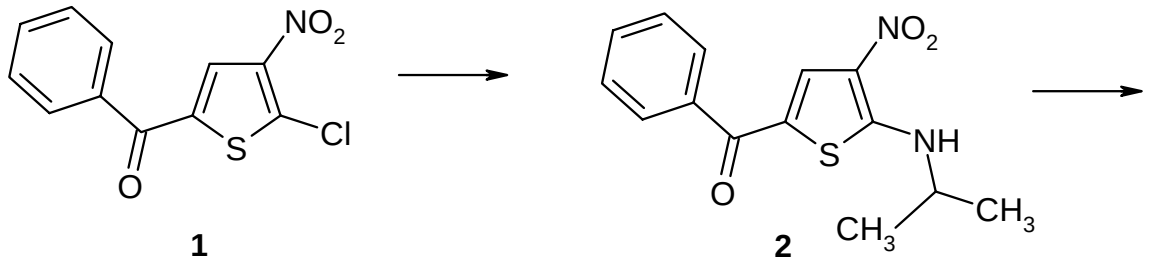
improved pharmacological profile. This research was to prepare the following thienoannelated derivatives:



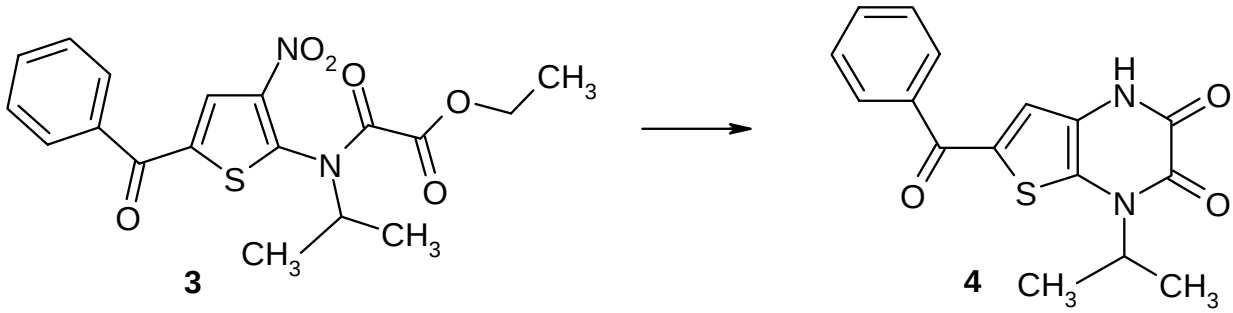
Panadiplon



Substitution at the 7-position by a benzoyl group, as observed in various cases,[10] 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:

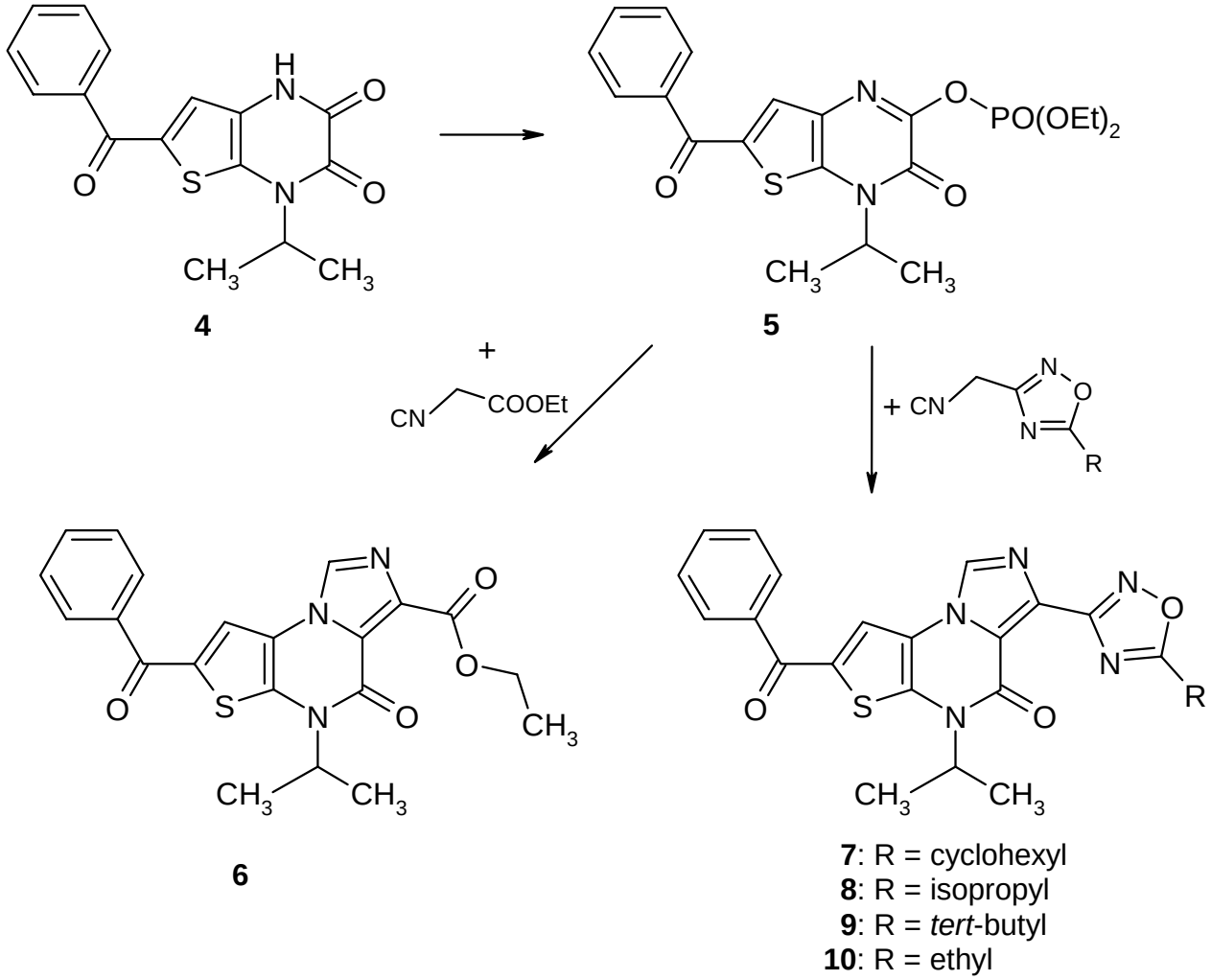


1 **2**



3 **4**

Reaction of compound (**1**)[3] with isopropylamine provided the substitution product (**2**) (84 %), which was acylated with ethyl oxalyl chloride in the precence 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. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Unity*Plus* 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 recrystalized 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); ^{1}H- NMR ($CDCl_3$, 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, CH_3); ^{13}C- NMR ($CDCl_3$): δ 187.0, 162.7, 136.6, 132.3, 130.8, 128.6, 126.5, 123.6, 51.0, 21.9. Anal. Calcd for $C_{14}H_{14}N_2O_3S$: 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)aminooxoacetate (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); ^{1}H- NMR ($CDCl_3$, 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, OCH_2), 1.55-0.97 (m, 6H, CH_3), 1.26 (t, 3H, *J* = 6.8 Hz, CH_3); ^{13}C- NMR ($CDCl_3$): 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 $C_{18}H_{18}N_2O_6S$: 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 recrystalized 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); ^{1}H- NMR (DMSO-d_6, 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, CH_3); ^{13}C- NMR (DMSO-d_6): δ 186.5, 154.7, 153.4, 137.0, 132.4, 132.1, 131.1, 128.7,

128.4, 123.9, 122.6, 52.7, 18.5. Anal. Calcd for $C_{16}H_{14}N_2O_3S$: 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 compouds (6 - 10)

A solution of the lactam (**4**) (628 mg, 2 mmol) in THF (30 mL) was cooled to -40^0C, 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 -50^0C. Diethyl chlorophosphate (449 mg, 2.6 mmol) was added dropwise over 5 min, and the mixture was allowed to warm from -50^0C to -30^0C over 1 h and then allowed to warm to rt over 30 min. The solution was cooled to -78^0C, 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); ^{1}H-NMR ($CDCl_3$, 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, CH_2), 1.69 (d, 6H, *J* = 6.8 Hz, CH_3), 1.43 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C-NMR ($CDCl_3$): δ 187.0, 161.4, 154.7, 152.3, 136.8, 135.6, 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 $C_{21}H_{19}N_3O_4S$: 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 preparativ 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); ^{1}H-NMR ($CDCl_3$, 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, CH_3), 1.50-1.22 (m, 3H, cyclohexyl-H); ^{13}C-NMR ($CDCl_3$): 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 $C_{26}H_{25}N_5O_3S$ 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); ^{1}H-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); ^{13}C-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 $C_{23}H_{21}N_5O_3S$: 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); ^{1}H-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); ^{13}C-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 $C_{24}H_{23}N_5O_3S$ 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); ^{1}H-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), 7.60-7.51 (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); ^{13}C-NMR ($CDCl_3$): δ 187.0, 180.7, 163.5, 153.1, 136.8, 133.5, 132.7, 132.0, 128.7, 121.4, 120.1, 117.1, 20.2, 19.1, 10.7. Anal. Calcd for $C_{22}H_{19}N_5O_3S$: C, 60.96; H, 4.42; N, 16.16. Found: C, 61.20; H, 4.68; N, 15.89.

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