Studies on the Chemistry of Thienoannelated *O,N*- and *S,N*-Containing Heterocycles. 24 [1]. Synthesis of Imidazo[1,5-*d*]thieno[2,3-*b*][1,4]-thiazine Derivatives as Potential Receptor Ligands

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A facile synthesis of the imidazo[1,5-*d*]thieno[2,3-*b*][1,4]thiazine ring system is described. Reaction of 6-benzyl-2,3-dihydro-1*H*-thieno[2,3-*b*][1,4]thiazine-2-one (**1**) with potassium *tert*-butoxide and diethylchlorophosphate gave intermediate **2** which resulted in the disired ring system after adding the corresponding isocyanides and potassium *tert*-butoxide.

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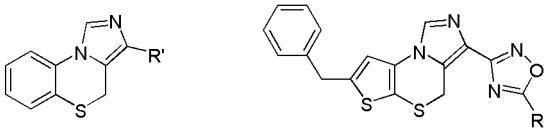
The 1,4-benzothiazine ring system is found in a great number of substances with pharmaceutical activity. For example, they posses antimicrobial [2] and growth hormone releasing properties [3]. Furthermore, it is known from 1,4-benzodiazepine derivatives, that their pharmacological profile is enhanced by attachment of a further heterocyclic ring. The 4*H*-imidazo[5,1-*c*][1,4]benzothiazine derivatives as shown in Scheme 1 are used as cyclooxygenase 2 inhibitors and anti-inflammatory agents [4] or as anticonvulsants, anxiolytics, hypnotics, and nootropics [5,6].

Scheme 1

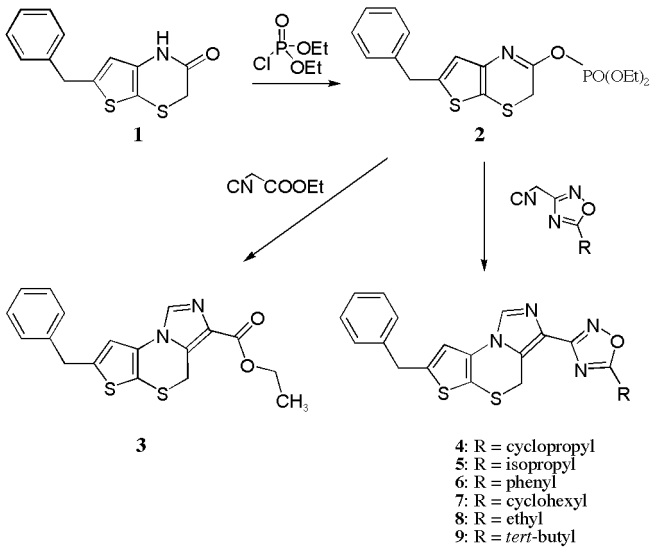


It is known from various drugs, that pharmacological activity may be maintained if benzene is exchanged by a thiophene ring [7]. In course of the studies concerning the synthesis of thienoannelated thiazines, it should be attempted to link both principles *via* attachment of a imidazolo ring to thieno[2,3-*b*][1,4]thiazines, respectively.

So we decided to synthesize imidazo[1,5-*d*]thieno-[2,3-*b*][1,4]thiazine derivatives as shown in Scheme 1.

A lipophilic group substituted in the 7-position is meant to intensify biologic activity and finally the 3-position of the oxadiazole unit is substituted with various groups as given in literature [5]. Synthesis of the desired 1,2,4-oxadiazolylimidazo[1,5-*d*]thieno[2,3-*b*][1,4]thiazine derivatives is shown in the following Scheme.

Scheme 2

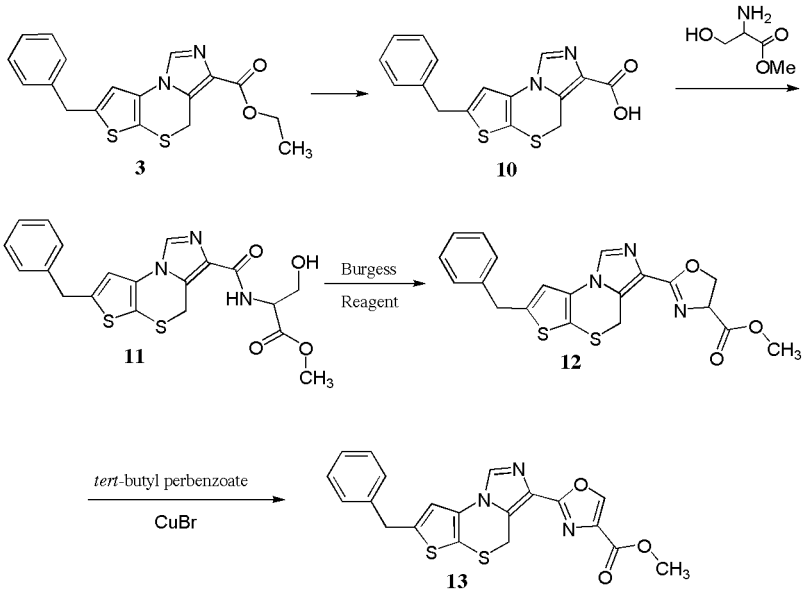


4: R = cyclopropyl
5: R = isopropyl
6: R = phenyl
7: R = cyclohexyl
8: R = ethyl
9: R = *tert*-butyl

Compound **1** [8] was mixed with potassium *tert*-butoxide and diethyl chlorophosphate (beware of the potential safety hazard of this reagent) under argon to give enol phosphate ester **2**. Reaction of this intermediate, which was usually not isolated, with various isocyanides in the presence of additional potassium *tert*-butoxide yielded the desired products (**3**–**9**). The oxadiazole isocyanides used in this reaction were synthesized following the general procedure of Watjen [9].

Starting from compound **3** we also synthesized an alternative molecule with a methyl 1,3-oxazole-carboxylate group in position 3 of the tricyclic ring system (**13**). Synthesis of this product is shown in the following Scheme.

Scheme 3



Therefore ethylester **3** was hydrolized with 5% aqueous sodiumhydroxide to give compound **10**. Reaction with D,L-serine methyl ester gave intermediate **11** which was cyclized by adding Burgess Reagent to yield **12** [10]. Finally dehydrogenation of **12** was carried out with *tert*-butyl perbenzoate and copper-(I)-bromide following the reaction of Kharasch-Sosnovsky to get the desired product **13** [11].

EXPERIMENTAL

Melting ranges were determined on a Kofler-hot stage apparatus and are uncorrected. The ^{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). The MS spectra were obtained using a Shimadzu GC/MS QP 1000 EX or a HP-5890 spectrometer. Analytical TLC was performed on Merck silica gel F254 plates. Column chromatography was performed 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.

General Procedure for the Synthesis of Compounds (**3**-**9**).

All the following reactions were carried out under an argon atmosphere. A solution of 5 mmol 1.31 g (5 mmoles) of compound **1** in 10 ml absolute tetrahydrofuran was cooled to –40 °C and 5.5 ml (1.0 *M* in tetrahydrofuran, 5.5 mmoles) potassium *tert*-butoxide was added drop for drop over 5 minutes. The mixture was warmed to room temperature over 30 minutes, and then cooled to –50 °C. Within 4 minutes 0.94 ml (6.5 mmoles) diethylchlorophosphate was added into the flask, then the solution was warmed to –30 °C over 1 hour and finally to room temperature over 30 minutes. Afterwards it was cooled again to –78 °C and 0.69 ml (6.0 mmoles) corresponding isocyanide was added. Within 10 minutes 6 ml (1.0 *M* in tetrahydrofuran, 6.0 mmoles) potassium *tert*-butoxide was added drop by drop to the mixture. The solution was allowed to warm to –20 °C over 1 hour and 45 minutes, finally the solution was stirred at room temperature for 45 minutes. The resultant mixture was poured into 120 ml ice-water and the precipitate was recrystallized.

Products **7, 8** and **9** resulted in oils upon pouring them into water. Therefore, the solutions were partitioned between 100 ml water (with 2 ml glacial acetic acid added) and dichloromethane (40 ml) four times, then between pure water and dichloromethane. The organic layers were dried over anhydrous sodium sulfate and evaporated. The residue was recrystallized.

Ethyl 7-Benzyl-4*H*-imidazo[1,5-*d*]thieno[2,3-*b*][1,4]thiazine-3-carboxylate (**3**).

Prepared from **1** (1.31 g, 5 mmoles). After crystallisation from ethanol 1.00 g (56%) **3** was obtained, mp 165 °C; ^{1}H nmr (deuteriochloroform): δ 7.73 (s, 1H, imidazole-H), 7.39-7.20 (m, 5H, phenyl H), 6.89 (s, 1H, thiophene H), 4.44 (s, 2H, benzyl-CH_2), 4.39 (q, 2H, J = 7.2 Hz, CH_2), 4.09 (s, 2H, S-CH_2), 1.41 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C nmr (deuteriochloroform): δ 162.8, 143.6, 138.6, 130.8, 128.7, 128.4, 128.2, 127.3, 127.0, 117.5, 115.6, 60.6, 36.2, 24.6, 14.3; ms: m/z 356 (M^+), 311, 282 (100%), 230, 154, 115, 91 (tropylium$^+$), 77 (phenylium$^+$), 45.

Anal. Calcd. for $C_{18}H_{16}N_2O_2S_2$: C, 60.65; H, 4.52; N, 7.86. Found: C, 60.44; H, 4.64; N, 7.63.

3-(7-Benzyl-4*H*-imidazo[1,5-*d*]thieno[2,3-*b*][1,4]thiazine-3-yl)-5-cyclopropyl-1,2,4-oxadiazole (**4**).

Prepared from **1** (1.83 g, 7 mmoles). After crystallization from ethanol 1.29 g (47%) **4** was obtained, mp 172 °C; ^{1}H nmr (deuteriochloroform): δ 7.81 (s, 1H, imidazole-H), 7.40-7.17 (m, 5H, phenyl-H), 6.90 (s, 1H, thiophene-H), 4.45 (s, 2H, benzyl-CH_2), 4.10 (s, 2H, S-CH_2), 2.28-2.19 (m, 1H, cylcopropyl-CH), 1.40-1.17 (m, 4H, cyclopropyl-CH_2); ^{13}C nmr (deuteriochloroform): δ 181.7, 164.0, 143.5, 138.7, 131.1, 128.7, 128.5, 127.0, 124.4, 123.6, 117.1, 115.7, 36.3, 24.7, 10.1, 7.6; ms: m/z 392 (M^+), 323, 220, 154, 115, 91 (tropylium$^+$), 77 (phenylium$^+$), 69, 45 (100%).

Anal. Calcd. for $C_{20}H_{16}N_4OS_2$: C, 61.20; H, 4.11; N, 14.27. Found: C, 61.33; H, 4.27; N, 14.04.

3-(7-Benzyl-4*H*-imidazo[1,5-*d*]thieno[2,3-*b*][1,4]thiazine-3-yl)-5-isopropyl-1,2,4-oxadiazole (**5**).

Prepared from **1** (1.31 g, 5 mmoles). After crystallisation from diluted ethanol 0.651 g (33%) **5** was obtained, mp 135 °C; ^{1}H nmr (deuteriochloroform): δ 7.83 (s, 1H, imidazole-H), 7.40-7.17 (m, 5H, J = 7.05, phenyl-H), 6.91 (s, 1H, thiophene-H), 4.48 (s, 2H, benzyl-CH_2), 4.09 (s, 2H, S-CH_2), 3.27 (septett, 1H, J = 7.1 Hz, CH), 1.45 (d, 6H, J = 7.1 Hz, CH_3); ^{13}C nmr (deuteriochloroform): δ 183.5, 163.9, 143.4, 138.6, 131.0, 128.7, 128.5, 126.9, 124.4, 123.5, 117.1, 115.7, 36.2, 27.3, 24.7, 20.0; ms: m/z 394 (M^+), 323, 308, 154, 115, 91 (tropylium$^+$), 77 (phenylium$^+$), 69, 58 (100%), 45.

Anal. Calcd. for $C_{20}H_{18}N_4OS_2$: C, 60.89; H, 4.60; N, 14.20. Found: C, 60.93; H, 4.65; N, 13.99.

3-(7-Benzyl-4*H*-imidazo[1,5-*d*]thieno[2,3-*b*][1,4]thiazine-3-yl)-5-phenyl-1,2,4-oxadiazole (**6**).

Prepared from **1** (1.31 g, 5 mmoles). After crystallization from ethanol 1.20 g (56%) **6** was obtained, mp 206 °C; ^{1}H nmr (dimethylsulfoxide-d_6): δ 8.55 (s, 1H, imidazole-H), 8.31 (d, 2H, J = 7.1 Hz, phenyl-H), 7.87-7.69 (m, 3H, phenyl-H), 7.62 (s, 1H, thiophene-H), 7.48-7.30 (m, 5H, phenyl-H), 4.80 (s, 2H, benzyl-CH_2), 4.25 (s, 2H, S-CH_2); ms: m/z 408 (M^+), 323, 308, 282,154, 115, 105 (C_6H_5-CO^+), 91 (tropylium$^+$), 77 (phenylium$^+$, 100%), 45.

Anal. Calcd. for $C_{23}H_{16}N_4OS_2$: C, 64.47; H, 3.76; N, 13.07. Found: C, 64.21; H, 3.85; N, 12.87.

3-(7-Benzyl-4*H*-imidazo[1,5-*d*]thieno[2,3-*b*][1,4]thiazine-3-yl)-5-cyclohexyl-1,2,4-oxadiazole (**7**).

Prepared from **1** (1.31 g, 5 mmoles). After crystallization from ethanol 1.00 g (46%) **7** was obtained, mp 147 °C; ^{1}H nmr (deuteriochloroform): δ 7.82 (s, 1H, imidazole-H), 7.39-7.18 (m, 5H, phenyl-H), 6.91 (s, 1H, thiophene-H), 4.47 (s, 2H, benzyl-CH_2), 4.09 (s, 2H, S-CH_2), 3.03-2.93 (m, 1H, cyclohexyl-CH), 2.15-1.16 (m, 10H, cyclohexyl-CH_2); ^{13}C nmr (deuteriochloroform): δ 182.5, 163.7, 143.4, 138.6, 131.0, 128.6, 128.4, 126.9, 124.4, 123.5, 117.0, 115.7, 36.2, 36.1, 30.0, 25.3, 25.2, 24.6; ms: m/z 434 (M^+), 323, 261, 184, 154, 127, 91 (tropylium$^+$), 83 (cyclohexylium$^+$), 77 (phenylium$^+$), 68 (oxydiazolylium$^+$), 55, 45 (100%).

Anal. Calcd. for $C_{23}H_{22}N_4OS_2$: C, 63.57; H, 5.10; N, 12.89. Found: C, 63.47; H, 5.32; N 12.66.

3-(7-Benzyl-4*H*-imidazo[1,5-*d*]thieno[2,3-*b*][1,4]thiazine-3-yl)-5-ethyl-1,2,4-oxadiazole (**8**).

Prepared from **1** (1.31 g, 5 mmoles). After crystallization from diluted ethanol 1.10 g (58%) **8** was obtained, mp 155 °C; ^{1}H nmr (deuteriochloroform): δ 7.83 (s, 1H, imidazole-H), 7.40-7.18 (m, 5H, phenyl-H), 6.91 (s, 1H, thiophene-H), 4.47 (s, 2H, benzyl-CH_2), 4.09 (s, 2H, S-CH_2), 2.95 (q, 2H, J = 7.7, CH_2), 1.43 (t, 3H, J = 7.7, CH_3); ^{13}C nmr (deuteriochloroform): δ 180.3, 163.9, 143.4, 138.6, 131.0, 128.6, 128.4, 126.9, 124.3, 123.5, 117.0, 115.7, 36.2,24.6, 20.1, 10.6; ms: m/z 380 (M^+), 323, 310, 282, 154, 115, 91 (tropylium$^+$), 77 (phenylium$^+$), 57, 45 (100%).

Anal. Calcd. for $C_{19}H_{16}N_4OS_2$: C, 59.98; H, 4.24; N, 14.73. Found: C, 60.02; H, 4.40; N, 14.54.

3-(7-Benzyl-4*H*-imidazo[1,5-*d*]thieno[2,3-*b*][1,4]thiazine-3-yl)-5-*tert*-butyl-1,2,4-oxadiazole (**9**).

Prepared from **1** (1.31 g, 5 mmoles). After crystallization from diluted ethanol 1.49 g (73%) **9** was obtained, mp 146 °C; ^{1}H nmr (deuteriochloroform): δ 7.83 (s, 1H, imidazole-H), 7.41-7.16 (m, 5H, phenyl-H), 6.92 (s, 1H, thiophene-H), 4.48 (s, 2H, benzyl-CH_2), 4.09 (s, 2H, S-CH_2), 1.46 (s, 9H, *tert*-butyl-H); ^{13}C nmr (deuteriochloroform): δ 185.9, 163.8, 143.4, 138.6, 131.0, 128.7, 128.4, 126.9, 124.4, 123.5, 117.1, 115.7, 36.2, 33.5, 28.3, 24.7; ms: m/z 408 (M^+), 323, 261, 232, 115, 91 (tropylium$^+$), 77 (phenylium$^+$), 57 (*tert*-butylium$^+$), 45 (100%).

Anal. Calcd. for $C_{21}H_{20}N_4OS_2$: C, 61.74; H, 4.93; N, 13.71. Found: C, 61.96; H, 5.00; N, 13.50.

7-Benzyl-4*H*-imidazo[1,5-*d*]thieno[2,3-*b*][1,4]thiazine-3-carboxylic Acid (**10**).

A solution of **3** (2.00 g, 5.6 mmoles) in 55 ml absolute ethanol and 22 ml 5% aqueous sodium hydroxide was refluxed at 85 °C for 2 hours. The mixture was cooled to room temperature and the solvent was removed by evaporation. The residue was suspended in 60 mL water, acidified with concentrated hydrochloric acid and stirred for 1 hour at 10 °C. The precipitate was collected, washed with cold water and dried to yield 1.75 g (95%) **10**, mp 204 °C; ^{1}H nmr (dimethylsulfoxide-d_6): δ 8.34 (s, 1H, imidazole-H), 7.54 (s, 1H, thiophene-H), 7.46-7.24 (m, 5H, phenyl-H), 4.59 (s, 2H, benzyl-CH_2), 4.20 (s, 2H, S-CH_2); ^{13}C nmr (dimethylsulfoxide-d_6): δ 164.2, 142.7, 139.4, 131.2, 128.5, 128.4, 128.2, 127.1, 126.6, 117.2, 116.0, 35.4, 24.4;ms: m/z 328 (M^+), 282 (100%), 230, 171, 154, 115, 91 (tropylium$^+$), 77 (phenylium$^+$), 69, 45.

Anal. Calcd. for $C_{16}H_{12}N_2O_2S_2$ x 0.5 H_2O: C, 56.96; H, 3.88; N, 8.30. Found: C, 56.87; H, 3.81; N, 8.22.

Methyl 2-{[(7-Benzyl-4*H*-imidazo[1,5-*d*]thieno[2,3-*b*][1,4]-thiazine-3yl)carbonyl]amino}-3-hydroxypropanoate (**11**).

Compound **10** (1.90 g, 5.8 mmoles) was suspended in 30 ml absolute *N*,*N*-dimethylformamide under argon atmosphere. Then carbonyldiimidazole (1.033 g, 6.3 mmoles) was added and the mixture was stirred for 1 hour at room temperature, then another 2 hours at 55 °C. After cooling the suspension to 0-5 °C (0.99 g, 7.1 mmoles) D,L-serinemethylester hydrochloride and absolute triethylamine (0.89 ml, 6.4 mmoles) was added and stirred for 96 hours at room temperature. The solvent was evaporated, and the residue was dissolved in hot water and extracted with ethylacetate. The oily product was purified by column with ethylacetate to obtain 1.49 g (60%) **11**, mp 56 °C; ^{1}H nmr (deuteriochloroform): δ 7.91 (d, J = 7.9, 1H, NH), 7.59 (s, 1H, imidazole-H), 7.40-7.17 (m, 5H, phenyl-H), 6.79 (s, 1H, thiophene-H), 4.87-4.73 (m, 1H, CH), 4.43 (s, 2H, benzyl-CH_2), 4.33 (s, 1H, OH), 4.12 (m, 2H, CH_2-OH), 4.05 (s, 2H, S-CH_2), 3.77 (s, 3H, $COOCH_3$); ^{13}C nmr (deuteriochloroform): δ 170.8, 162.2, 143.4, 138.7, 130.6, 128.7, 128.5, 127.0, 125.8, 117.7, 115.6, 63.1, 54.4, 52.6, 36.22, 24.4; ms: m/z 429 (M^+), 310, 282 (100%), 230, 171, 154, 115, 91 (tropylium$^+$), 77 (phenylium$^+$), 69, 57.

Anal. Calcd. for $C_{20}H_{19}N_3O_4S_2$: C, 55.93; H, 4.46; N, 9.78. Found: C, 55.63; H, 4.33; N, 9.49.

Methyl 2-(7-Benzyl-4*H*-imidazo[1,5-*d*]thieno[2,3-*b*][1,4]-thiazine-3yl)-4,5-dihydro-1,3-oxazole-4-carboxylate (**12**).

A solution of **11** (0.816 g, 1.9 mmoles) in 10 ml absolute tetrahydrofurane was mixed with (methoxycarbonylsulfamoyl)-triethylammonium hydroxide, inner salt (Burgess Reagent) (0.500 g, 2.1 mmoles) under an argon atmosphere and refluxed for 1 hour. The mixture was cooled to room temperature and the solvent was evaporated. The oily residue was dissolved in

dichloromethane and separated by column chromatography (silica gel, ethylacetate/ethanol 9+1). If necessary the product can be recrystallized from ethanol to yield 0.368 g (47%) **12**, mp 157 °C; ^{1}H nmr (deuteriochloroform): δ 7.73 (s, 1H, imidazole-H), 7.40-7.20 (m, 5H, phenyl-H), 6.88 (s, 1H, thiophene-H), 4.99-4.86 (m, 1H, N-CH), 4.71-4.50 (m, 2H, CH_2), 4.43 (s, 2H, benzyl-CH_2), 4.08 (s, 2H, S-CH_2), 3.78 (s, 3H, OCH_3); ^{13}C nmr (deuteriochloroform): δ 171.5, 161.7, 143.4, 138.6, 128.7, 128.4, 126.9, 125.8, 124.4, 117.3, 115.6, 69.0, 68.3, 52.5, 36.2, 24.7; ms: m/z 411 (M^+), 310, 282, 230, 171, 154, 115, 91 (tropylium$^+$), 77 (phenylium$^+$), 57, 55 (100%).

Anal. Calcd. for $C_{20}H_{17}N_3O_3S_2$: C, 58.38; H, 4.16; N, 10.21. Found: C, 58.17; H, 4.22; N 10.02.

Methyl 2-(7-Benzyl-4*H*-imidazo[1,5-*d*]thieno[2,3-*b*][1,4]thiazine-3yl)-1,3-oxazole-4-carboxylate (**13**).

Under an argon atmosphere **12** (0.296 g, 0.72 mmol) in boiling benzene was mixed with (0.133 g, 0.79 mmol) copper-(I)-bromide and stirred for 5 minutes. Then *tert*-butylperbenzoate (0.21 g, 1.08 mmoles) was added drop by drop and then the solution was refluxed for 1.5 hours. After cooling to room temperature 20 ml water was added and extracted with benzene. The organic layer was evaporated and separated by column chromatography (silica gel, ethylacetate) to give 32 mg (11%) **13**; ^{1}H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 8.29 (s, 1H, oxazole-H), 7.83 (s, 1H, imidazole-H), 7.37-7.26 (m, 5H, phenyl-H), 6.92 (s, 1H, thiophene-H), 4.58 (s, 2H, benzyl-CH_2), 4.12 (s, 2H, S-CH_2), 3.92 (s, 3H, OCH_3); ms: m/z 409 (M^+), 347, 287, 259, 154, 122, 105 (100%), 77 (phenylium$^+$), 69, 57, 51, 45.

Anal. Calcd. for $C_{20}H_{15}N_3O_3S_2$: C, 58.66; H, 3.69; N, 10.26. Found: C, 58.83; H, 3.84; N 10.01.

REFERENCES AND NOTES

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[1] Part **23**: M. E. Galanski, N. Böhler, and T. Erker, *Sci. Pharm.*, **69**, 321 (2001).

[2] D. Armenise, G. Trapani, V. Arrivo, E. Laraspata, and F. Morlacchi, *J. Heterocyclic Chem.*, **37**,1611 (2000).

[3] J. R. De Vita, W. R. Schoen, G. A: Doldouras, M. H. Fisher, M. J. Wyvratt, K. Cheng, W. W.-S. Chan, B. S. Bridget, and R. G. Smith, *Bioorg. Med. Chem. Lett.*, **5**, 1281 (1995).

[4] T. Yaegashi, H. Nishiyama, T. Itsumi, and S. Sawada, Japan Patent 99-295214; *Chem. Abstr.*, **134**, 288850 (2001).

[5] F. Waetjen and M. Engelstoft, EP 220845, *Chem. Abstr.*, **105**, 515590 (1987).

[6] R. I. Fryer, R. F. Lauer, E. J. Trybulski, s. Vittone, A. Walser, and G. Zenchoff, , *J. Heterocyclic Chem.*, **20**,1605 (1983).

[7] S. Gronowitz, Thiophene and its Derivatives, Part **I**, John Wiley and Sons, 1985.

[8] I. Puschmann and T. Erker, *Monatsh. Chem.*, **126**, 569 (1995).

[9] F. Watjen, R. Baker, M. Engelstoff, R. Herbert, A. MacLeod, A. Knight, K. Merchant, J. Moseley, J. Saunders, C. J. Swain, E. Wong, and J. P. Springer, *J. Med. Chem.*, **32**, 2282 (1989).

[10] P. Wipf and C. P. Miller, *Tetrahedron Lett.*, **33**, 907 (1992).

[11] A. I. Meyers and F. Tavares, *Tetrahedron Lett.*, **35**, 2481 (1994).