SYNTHESIS OF THIENO-DILTIAZEM ANALOGUES[1]

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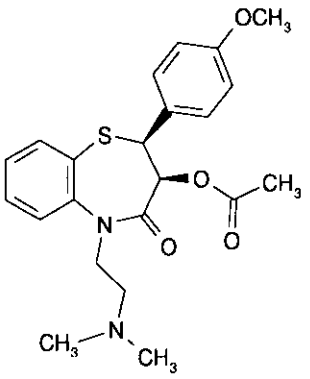
Abstract - The replacement of benzene by thiophene in a molecule might result in an altered metabolism of the modified drug, a different biochemical profile and / or an elimination of side effects to a certain extent. Replacement of the fused aromatic moiety in diltiazem with thiophene provided *cis*- 4-[(2-dimethylamino)-ethyl] - 4, 5, 6, 7-tetrahydro-7-(4-methoxyphenyl)-5-oxo-thieno[2,3-*b*][1,4]thiaz-epin-6-yl acetate (**20**). The synthesis starts with the reaction of 3-nitro-2-thiophenethiol and racemic *trans*-(4-methoxyphenyl)glycidate. The resulting *threo* and *erythro* products are reduced, cyclized, alkylated and acetylated to give the desired compounds (**20**) and (**21**).

To date, diltiazem is one of the most frequently prescribed drugs for the treatment of cardiovascular disease in the United States. It has found wide application in the treatment of various forms of hypertension, hypertonic crisis, angina pectoris, myocardial infarction, arrhythmia and cardioplegie. Additionally, diltiazem has attracted increasing attention due to its reported prophylactic action in connection with migraine therapy.[2]

In the course of the pharmacological evaluation of diltiazem and its derivatives, Nagao *et al.*[3] attempted to identify the key structural elements responsible for its biological activity. These studies indicated the *cis*-configuration of the substituents at *C*-2 and *C*-3 and the *para*-methoxy residue of the aryl ring were essential

characteristics. In addition, only compounds possessing a tertiary amino functionality showed significant activity.



d-cis diltiazem

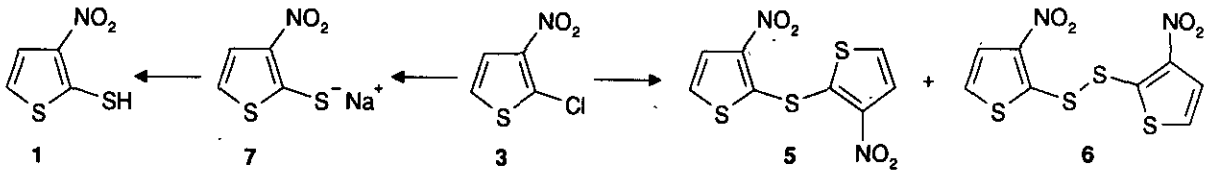
Moreover it was concluded that *d-cis*-isomers exhibited an activity 2-3 times more pronounced than *l-cis*-isomers in addition to possessing longer half-lives. Mohacsi *et al.*[4] went on to demonstrate that the fused benzene moiety was an essential feature for the calcium-balancing effect.

Floyd and co-workers [5 - 8] reported that an exchange of the sulfur atom in the seven membered ring by a methylene unit led to molecules with interesting drug profiles. It was also demonstrated that the acetoxy group at *C*-3 was crucial with respect to antihypertensive properties. The accumulated findings thus restricted the scope for novel derivatizations of diltiazem.

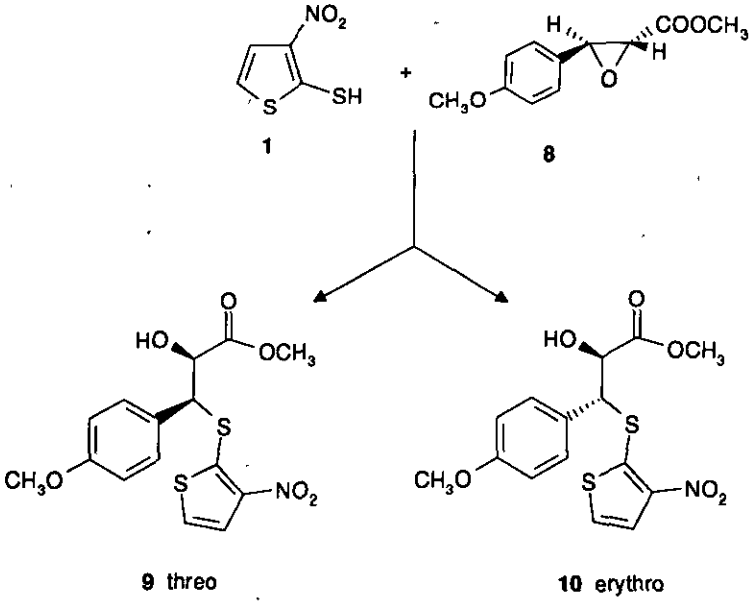
It was hoped that the thienoanalogues isomers (**20**) and (**21**) will exhibit extended periods of *in vivo* activity and exhibit a prolongation of certain cardiac intervals, thereby overcoming the major drawbacks of the parent compound.

Based on the original synthetic approach of diltiazem [9 - 11] we considered the stereospecific oxirane ring opening of racemic *trans*-(4-methoxyphenyl)glycidate (**8**) by the thiol (**1**) to be rational starting point for the construction of the acyclic diastereoisomers (**9**) and (**10**). These diastereoisomers were then expected, after suitable modification, to serve as precursors to the required thieno[2,3-*b*][1,4]thiazepine skeleton. Likewise a series of simple transformations of the latter were anticipated as a route to the diltiazem analogues.

To prepare the required thiol (**1**), initial experiments investigated the thiolate displacement of the labile chlorine atom of 2-chloro-3-nitrothiophene (**3**) by $Na_2S \cdot 9\ H_2O$. However in preliminary trials, treatment of **3** failed to give **1** and instead yielded mixtures of the dimer (**5**) and the disulphide (**6**). However modification of the reaction conditions, particularly with regard to the solvent and the reaction atmosphere, permitted the preparation of **1** in acceptable yields - *via* its sodium salt (**7**) - in the absence of significant quantities of **5** and **6**.



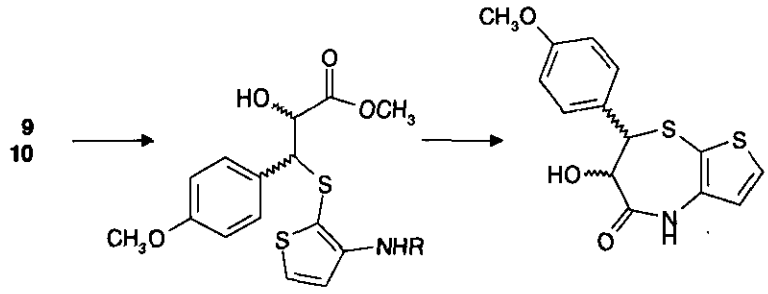
As previously demonstrated by several authors,[9,10] the epoxide ring opening of the glycidate (**8**) by various nucleophiles is accelerated by sodium bicarbonate or boron trifluoride to give the *erythro*-isomer. Moreover it was found that in the absence of catalyst, reactions carried out in acetonitrile led predominantly to the *threo*-product. In contrast the use of Lewis acid such as $AlCl_3$, SnI_2, $SnCl_4$, $ZnCl_2$ or $CuCl_2$ yielded exclusively the *threo*-isomer. Based on these findings **1** was reacted with **8** in ethanol in the presence of sodium bicarbonate to yield the *erythro*-stereoisomer (**10**).



In our initial attempts to obtain the *threo*-isomer (*via* Lewis acid catalysis) the necessary anhydrous conditions led to significant conversion of **1** to **6**. Therefore reference was made to the study of Hashiyama *et al.*[12] that

dealt with the influence of temperature and the solvent, on the stereochemical outcome of similar epoxide ring openings. This investigation suggested that elevated temperatures favour the formation of the *threo*-isomer. Indeed when **1** was refluxed with **8** in either chlorobenzene or toluene the *threo*-isomer was the only isolated product.

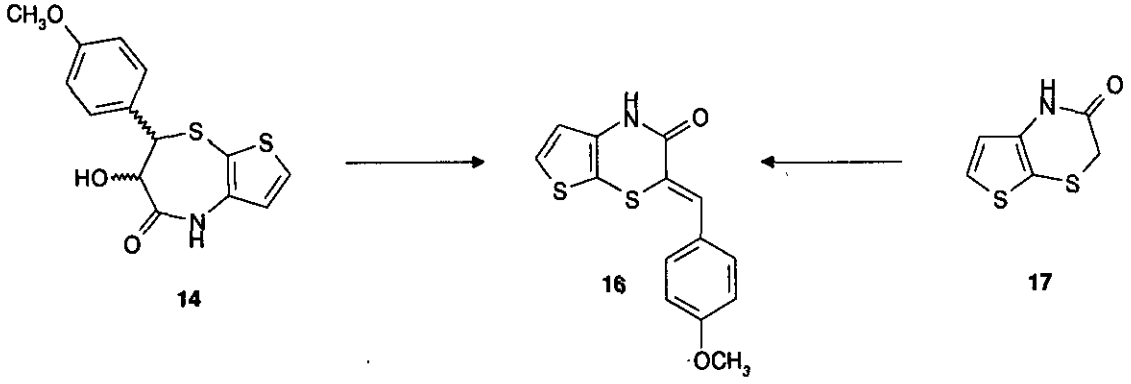
To accomplish the necessary lactam linkage, thereby take a bearing on the thieno[2,3-*b*][1,4]thiazepinone ring system, the nitro groups of **9** and **10** were reduced by treatment with ammoniacal iron(II) sulfate to the amines (**11**) and (**12**) respectively. These conditions avoided the formation of the acetamide (**13**) formed when the reduction of **10** with iron powder was originally attempted in methanolic acetic acid.



11 threo R = H
12 erythro R = H
13 erythro R = CH_3CO

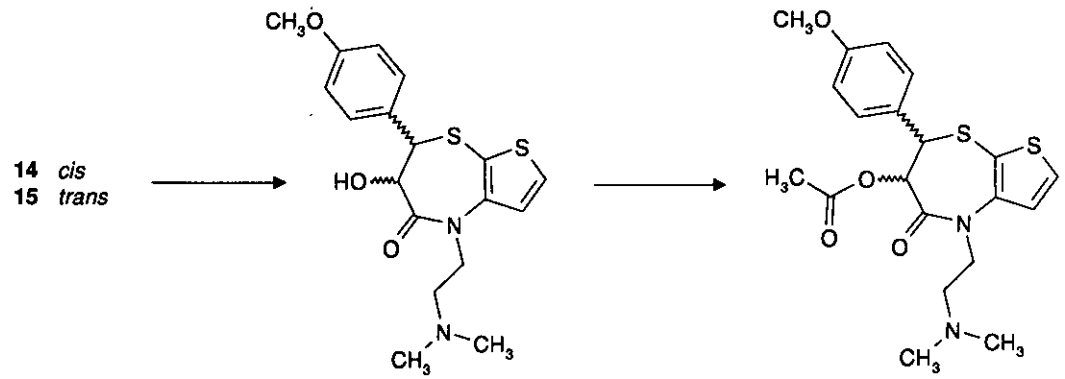
14 *cis*
15 *trans*

The diastereoisomeric amines (**11**) and (**12**) could be efficiently cyclized to the seven-membered heterocyclic compounds (**14**) and (**15**) by treatment with catalytic quantities of methanesulfonic acid in refluxing chlorobenzene. In addition to **14**, cyclization of **11** also yielded a small amount (~8%) of the ring contracted material (**16**).



The structure of **16** was confirmed by comparison with an authentic specimen of **16**, prepared following the details of Krapcho and Turk[13] by condensation of 1*H*-thieno[2,3-*b*][1,4]thiazin-2(3*H*)-one (**17**) with 4-methoxybenzaldehyde.

The *N*-alkylations of **14** and **15** were initially carried out in tetrahydrofuran or toluene in the presence of sodium hydride and 2-(*N*, *N*-dimethylamino)chloroethane hydrochloride (approx. 50%). However, higher yields were obtained when the reactions were conducted with potassium carbonate in butanone. By this approach satisfactory yields (86%) and (85%) of the corresponding products (**18**) and (**19**) respectively were available. The final acetylations of the free hydroxy residues at *C*-6 of **18** and **19** were accomplished smoothly, in high yields, by reaction with acetic anhydride in pyridine, to afford (**20**) and (**21**).



The structures of **20** and **21** were supported by the observed ^{1}H nmr coupling constants of the protons at *C*-6 and *C*-7. The *cis*-isomer (**20**) exhibited a J = 7.4 Hz while the *trans*-isomer (**21**) possessed J = 11.8 Hz. These values correspond well with literature data for the known *cis*- and *trans*- stereoisomers of Diltiazem (J = 7 Hz and 11 Hz respectively).

For a better water-solubility, compounds (**20**) and (**21**) were transformed by hydrogen chloride in dry ether to the corresponding hydrochlorides (**20.HCl**) and (**21.HCl**).

The aim of this study was to examine what effect the replacement of the fused aromatic benzene ring with a

thiophene nucleus in the diltiazem molecule would have, with respect to the activity profile of the parent drug. The diltiazem analogous compounds *cis*- and *trans*- 4-[(2-dimethylamino)ethyl]-4,5,6,7-tetrahydro-7-(4-methoxyphenyl)-5-oxo-thieno[2,3-*b*][1,4]thiazepin-6-yl acetate (**20** and **21**) have been synthesised.

EXPERIMENTAL

All melting points are determined by a Kofler Microscope and are uncorrected. ^{1}H and ^{13}C nmr are run at a Varian 80, ^{1}H nmr in $CDCl_3$ and ^{13}C nmr in DMSO. Chemical shift are reported in ppm downfield from internal standard. Ms analyses were obtained with Shimadzu GC/MS QP 1000. All organic solvents were removed by evaporation under vacuum. The reaction progress were monitored by tlc analyses using F_{254} silica gel sheets. Column chromatography was carried out on silica gel.

2-Mercapto-3-nitrothiophene (1)

Sodium sulfide nonahydrate (19.58 g, 81.6 mmol) was dissolved in water (120 ml) and stirred under argon for 20 min. A solution of 2-chloro-3-nitrothiophene (7.82 g, 48 mmol) in ethanol (50 ml) was added slowly and stirred for a further 1 h. The ice-cooled mixture was acidified with 2 *N* HCl under a argon atmosphere. In order to get the *erythro*-product (**10**) the precipitate was filtered off and used readily. In order to obtain the *threo*-product (**9**), 100 ml of chlorobenzene was added and the two phase system was stirred vigorously. The chlorobenzene layer was separated, dried for 10 min and used. The tendency of the compound to oxidize made any analysis impossible. The structure of **1** was proved by the reaction with methyl acrylate to obtain methyl 3-(3-nitro-2-thienylthio)propionate, which was also obtained by the reaction of 2-chloro-3-nitrothiophene with methyl 3-mercaptopropionate.

Methyl *threo*-2-hydroxy-3-(4-methoxyphenyl)-3-(3-nitro-2-thienylthio)propionate (9)

Methyl *trans*-3-(4-methoxyphenyl)glycidate (**8**) (9.57 g, 46 mmol) was heated in chlorobenzene (50 ml) at

100°C. A solution of **1** (7.73 g, 48 mmol) in chlorobenzene (100 ml) was added under argon in such a way that the mixtures temperature remained between 100-120°C and heating was continued for 2 h. The solvent was removed and the residue repeatedly recrystallized from toluene/ ethyl acetate (3:2) to remove all traces of disulphide and yielded 6.5 g (38 %) of pale yellow crystals, mp 155 - 157 °C; ^{1}H nmr: δ 7.49 (1H, AB-system, J_{AB} = 6.4 Hz, thiophene H), 7.45 (2H, AB-system, J_{AB} = 9.3 Hz, phenyl H), 6.99 (1H, AB-system, J_{AB} = 6.4 Hz, thiophene H), 6.80 (2H, AB-system, J_{AB} = 9.3 Hz, phenyl H), 4.78 (1H, d, J = 2.7 Hz, CHS), 4.58 (1H, dd, J = 2.7 and 5.3 Hz, CH), 3.79 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.29 (1H, d, J = 5.3 Hz, OH); ^{13}C nmr: δ 171.5, 159.1, 146.7, 142.3, 130.1, 128.9, 124.4, 123.4, 113.8, 74.6, 56.8, 55.1, 52.0; ms (*m/z*): 369 (M^+, 0.1), 121 (100); Anal. Calcd for $C_{15}H_{15}N_1O_6S_2$: C,48.77; H, 4.09; N, 3.79. Found C, 48.72; H, 3.99; N, 3.70.

Methyl *erythro*-2-hydroxy-3-(4-methoxyphenyl)-3-(3-nitro-2-thienylthio)propionate (10)

2-Mercapto-3-nitrothiophene (**1**) (7.73 g, 48 mmol) was added to a suspension of methyl *trans*-3-(4-methoxyphenyl)glycidate (**8**) (9.57 g, 46 mmol) and $NaHCO_3$ (762 mg) in ethanol (126 ml) at room temperature under argon and stirred overnight. The precipitate was filtered off and repeatedly recrystallized from toluene/ ethyl acetate (2:3) to yield 7.72 g (46 %) of pale yellow crystals: mp 170 - 172 °C; ^{1}H nmr: δ 7.54 (1H, AB-system, J_{AB} = 6 Hz, thiophene H), 7.36 (2H, AB-system, J_{AB} = 10 Hz, phenyl H), 7.00 (1H, AB-system, J_{AB} = 6 Hz, thiophene H), 6.86 (2H, AB-system, J_{AB} = 10 Hz, phenyl H), 4.85 - 4.78 (2H, m, 2 CH), 3.78 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.03-2.94 (1H, m, OH); ^{13}C nmr: δ 169.9, 157.9, 145.4, 140.9, 129.5, 126.4, 123.4, 122.4, 112.4, 71.6, 54.6, 53.9, 50.6; ms (*m/z*): 369 (M^+, 0.1), 121 (100); Anal. Calcd for $C_{15}H_{15}N_1O_6S_2$: C, 48.77; H, 4.09; N, 3.79. Found C, 48.72; H, 3.99; N, 3.70.

Methyl *threo*-2-hydroxy-3-(4-methoxyphenyl)-3-(3-amino-2-thienylthio)propionate (11) and **Methyl *erythro*-2-hydroxy-3-(4-methoxyphenyl)-3-(3-amino-2-thienylthio)propionate (12)**

General procedure: Compound (**9**) or (**10**) (2.21 g, 6 mmol) was refluxed with $Fe(II)SO_4 \cdot 7\ H_2O$ (14 g, 50 mmol) in 50% EtOH (60 ml) for 1 h, concentrated ammonia (12 ml) was added and the mixture was heated for additional 2 h, cooled, and extracted with ethyl acetate (3 times with 100 ml each). The organic layer was dried

over Na_2SO_4 and the solvent was removed. The residue was purified by column chromatography (toluene/ ethyl acetate 2:3) to yield 1.74 g (85 %) of a brown oil in both cases (**11** and **12,** respectively).

11: ^{1}H Nmr: δ 7.29 (2H, AB-system, J_{AB} = 10 Hz, phenyl H), 7.22 (1H, AB-system, J_{AB} = 6 Hz, thiophene H), 6.83 (2H, AB-system, J_{AB} = 10 Hz, phenyl H), 6.62 (1H, AB-system, J_{AB} = 6 Hz, thiophene H), 4.41 - 4.34 (2H, m, 2 CH), 4.20 (3H, s, OH, NH_2), 3.77 (3H, s, OCH_3), 3.62 (3H, s, OCH_3); ^{13}C nmr: δ 172.1, 158.4, 152.3, 151.9, 130.0, 128.9, 129.4, 120.2, 113.2, 71.6, 56.4, 54.9, 51.5; ms (*m/z*): 339 (M^+, 2), 209 (40), 149 (74), 121 (100); Anal. Calcd for $C_{15}H_{17}N_1O_4S_2$: C, 53.08; H, 5.05; N, 4.13. Found C, 53.26; H, 4.99; N, 3.78.

12: ^{1}H Nmr: δ 7.29 (2H, AB-system, J_{AB} = 8.9 Hz, phenyl H), 7.22 (1H, AB-system, J_{AB} = 5.9 Hz, thiophene H), 6.84 (2H, AB-system, J_{AB} = 8.9 Hz, phenyl H), 6.62 (1H, AB-system, J_{AB}= 5.9 Hz, thiophene H), 4.44 - 4.34 (2H, m, 2 CH), 4.12 (3H, s, OH, NH_2), 3.77 (3H, s, OCH_3), 3.62 (3H, s, OCH_3), ^{13}C nmr: δ 171.8, 158.0, 151.8, 151.8, 129.5, 128.7, 119.7, 112.7, 71.4, 55.9, 54.4, 51.0; ms (*m/z*): 339 (M^+, 1), 209 (32), 121 (100); Anal. Calcd for $C_{15}H_{17}N_1O_4S_2$: C, 53.08; H, 5.05; N, 4.13. Found C, 53.21; H, 5.18; N, 3.72.

Methyl *erythro*-3-(3-acetylamino-2-thienylthio)-2-hydroxy-3-(4-methoxyphenyl)propionate (13)

Compound (**10**) (738 mg, 2 mmol) was refluxed with iron powder (400 mg, 7.1 mmol) in glacial acetic acid (4 ml) and dry methanol (16 ml). After filtration and removal of the solvent, the residue was purified by column chromatography (eluent: toluene/ ethyl acetate 4+6) to yield 445 mg (58 %) of a brown oil. ^{1}H Nmr: δ 7.88 (1H, AB-system, J_{AB} = 6.7 Hz, thiophene H), 7.45 (1H, AB-system, J_{AB} = 6.7 Hz, thiophene H), 7.27 (2H, AB-system, J_{AB} = 8.3 Hz, phenyl H), 6.83 (2H, AB-system, J_{AB} = 8.3 Hz, phenyl H), 4.35 - 4.23 (2H, m, 2 CH), 3.63 (6H, s, OCH_3), 2.13 (3H, s, CH_3CO); ms (*m/z*): 381 (M^+, 0.3), 121 (100); Anal. Calcd for $C_{17}H_{19}N_1O_5S_2$: C, 53.53; H, 5.02; N, 3.67. Found C, 53.77; H, 5.00; N, 3.47.

***cis*-6,7-Dihydro-6-hydroxy-7-(4-methoxyphenyl)thieno[2,3-*b*][1,4]thiazepin-5(4*H*)-one (14)** and ***trans*-6,7-Dihydro-6-hydroxy-7-(4-methoxyphenyl)thieno[2,3-*b*][1,4]thiazepin-5(4*H*)-one (15)**

Compound (**11**) or (**12**) (5.0 g, 14.75 mmol) was heated with methanesulfonic acid (10 drops) in chlorobenzene

(250 ml) at 120 °C. The reaction was monitored by tlc and upon completion cooled to room temperature, the reaction mixture was washed with water and the organic layer dried over Na_2SO_4 and the solvent was concentrated to 25% of its original volume to deposit **14** or **15** as grey or colourless needles respectively. **14** was recrystallized from toluene and **15** from ethanol (96%).

14: mp 188-190 °C, ^{1}H nmr: δ 7.44 (2H, AB-system, J_{AB} = 7.3 Hz, phenyl H), 7.28 (1H, AB-system, J_{AB} = 5 Hz, thiophene H), 6.90 (1H, AB-system, J_{AB} = 5 Hz, thiophene H), 6.90 (2H, AB-system, J_{AB} = 7.3 Hz, phenyl H), 5.16 (1H, d, J = 7 Hz, CHS), 4.45 (1H, dd, J = 7 and 9.3 Hz, CH), 3.81 (3H, s, OCH_3), 3.20 (1H, d, J = 9.3 Hz, OH); ^{13}C nmr: δ 173.0, 159.1, 141.9, 131.0, 127.9, 127.3, 123.3, 118.1, 113.4, 69.9, 60.2, 55.1; ms (*m/z*): 307 (M^+, 20), 121 (100); Anal. Calcd for $C_{14}H_{13}N_1O_3S_2$: C, 54.70; H, 4.26; N, 4.56. Found C, 54.48; H, 4.08; N, 4.56.

15: mp 183-185 °C, ^{1}H nmr: δ 7.33 (1H, AB-system, J_{AB} = 5.5 Hz, thiophene H), 7.26 (2H, AB-system, J_{AB} = 7.3 Hz, phenyl H), 6.94 (1H, AB-system, J_{AB} = 5.5 Hz, thiophene H), 6.86 (2H, AB-system, J_{AB} = 7.3 Hz, phenyl H), 4.36 - 4.30 (2H, m, 2 CH), 3.78 (3H, s, OCH_3), 3.73 - 3.49 (1H, m, OH); ^{13}C nmr: δ 172.7, 157.5, 141.0, 133.8, 127.1, 122.3, 116.1, 113.7, 71.6, 59.1, 54.0; ms (*m/z*): 307 (M^+, 21), 121 (100); Anal. Calcd for $C_{14}H_{13}N_1O_3S_2$: C, 54.70; H, 4.26; N, 4.56. Found C, 54.37; H, 4.03; N, 4.50.

3-(4-Methoxybenzyliden)-1*H*-thieno[2,3-*b*][1,4]thiazin-2(3*H*)-one (16)

1*H*-Thieno[2,3-*b*][1,4]thiazin-2(3*H*)-one (513 mg, 3 mmol) and 4-methoxybenzaldehyde (680 mg, 5 mmol) were dissolved in DMF (5 ml). Potassium methoxide (280 mg, 4 mmol) was added and the mixture was heated at 120°C for 48 h. 4-Methoxybenzoic acid deposited as a by-product was filtered off, the mother liquors was diluted with water (5 ml), neutralized with solid NaOH, and extracted with ethyl acetate (3 x 15 ml). Unreacted 4-methoxybenzaldehyde was removed by Kugelrohr distillation and the residue recrystallized from ethanol to yield 0.42g (48 %) **16**. mp 201 °C, ^{1}H nmr ($CDCl_3$ + DMSO): δ 10.50 (1H, s, NH), 7.84 (1H, s, olefin. H), 7.57 (2H, AB-system, J_{AB} = 11 Hz, phenyl H), 7.11 (1H, AB-system, J_{AB} = 5.5 Hz, thiophene H), 6.98 (2H, AB-system, J_{AB} = 11 Hz, phenyl H), 6.78 (1H, AB-system, J_{AB} = 5.5 Hz, thiophene H), 3.85 (3H, s, OCH_3); ms (*m/z*): 289 (M^+, 100); Anal. Calcd for $C_{14}H_{11}N_1O_2S_2$: C, 58.11; H, 3.83; N, 4.84. Found C, 57.97; H, 3.74; N, 4.72.

***cis*-4-[(2-Dimethylamino)ethyl]-6,7-dihydro-6-hydroxy-7-(4-methoxyphenyl)-thieno[2,3-*b*][1,4]thiazepin-5(4*H*)-one (18)** and ***trans*-4-[(2-Dimethylamino)ethyl]-6,7-dihydro-6-hydroxy-7-(4-methoxyphenyl)-thieno[2,3-*b*][1,4]thiazepin-5(4*H*)-one (19)**

Compound (**14**) or (**15**) (2.46 g, 8 mmol) was heated in butanone (80 ml) and water (0.8 ml) at 80°C, 2-chloro-*N*,*N*-dimethylaminoethane hydrochloride (16 mmol, 2.30 g) and potassium carbonate (4.42 g, 32 mmol) were added and heated for additional 8 h. The mixture was washed with water (30 ml), dried over Na_2SO_4, and concentrated in vacuo. The oily residue was triturated with ether and recrystallized from a mixture of 8 parts n-hexane and 2 parts ethyl acetate to yield either 2.59 g (86%) **18** or 2.58 g (85%) **19**.

18: mp 114-116 °C, ^{1}H nmr: δ 7.43 (2H, AB-system, J_{AB} = 8 Hz, phenyl H), 7.28 (1H, AB-system, J_{AB} = 5.8 Hz, thiophene H), 7.07 (1H, AB-system, J_{AB} = 5.8 Hz, thiophene H), 6.90 (2H, AB-system, J_{AB} = 8 Hz, phenyl H), 5.04 (1H, d, J = 7.3 Hz, CHS), 4.53 - 4.42 (1H, m, CH), 4.27 - 4.17 (1H, m, NCH_2), 3.68 - 3.44 (2H, m, OH, NCH_2), 3.78 (3H, s, OCH_3), 2.85 - 2.42 (2H, m, NCH_2), 2.29 (6H, s, $N(CH_3)_2$); ^{13}C nmr: δ 171.6, 159.1, 144.8, 131.3, 127.5, 123.5, 119.0, 113.3, 69.9, 59.7, 56.6, 55.0, 45.4, 45.2; ms (*m/z*): 378 (M^+, 3), 307 (9), 59 (100); Anal. Calcd for $C_{18}H_{22}N_2O_3S_2$: C, 57.12; H, 5.86; N, 7.40. Found C, 57.33; H, 6.01; N, 7.21.

19: mp 134-136 °C, ^{1}H nmr: δ 7.42 (1H, AB-system, J_{AB} = 4.4 Hz, thiophene H), 7.24 (2H, AB-system, J_{AB} = 8.8 Hz, phenyl H), 7.13 (1H, AB-system, J_{AB} = 4.4 Hz, thiophene H), 6.87 (2H, AB-system, J_{AB} = 8.8 Hz, phenyl H), 4.40 - 4.04 (3H, m, 2 CH, NCH_2), 3.85 - 3.43 (2H, m, OH, NCH_2), 3.78 (3H, s, OCH_3), 2.84 - 2.38 (2H, m, NCH_2), 2.26 (6H, s, $N(CH_3)_2$); ^{13}C nmr: δ 172.7, 158.7, 144.9, 134.4, 133.6, 129.2, 128.1, 123.4, 119.1, 72.6, 59.1, 56.3, 54.9, 45.5, 45.3; ms (*m/z*): 378 (M^+, 1), 307 (2), 59 (100); Anal. Calcd for $C_{18}H_{22}N_2O_3S_2$: C, 57.12; H, 5.86; N, 7.40. Found C, 57.03; H, 5.57; N, 7.19.

***cis*-4-[(2-Dimethylamino)ethyl]-4, 5, 6, 7-tetrahydro-7-(4-methoxyphenyl)-5-oxo-thieno[2,3-*b*][1,4]thiazepin-6-yl acetate (20)** and ***trans*-4-[(2-Dimethylamino)ethyl]-4,5,6,7-tetrahydro-7-(4-methoxyphenyl)-5-oxo-thieno[2,3-*b*][1,4] thiazepin-6-yl acetate (21)**

Compound (**18**) or (**19**) (1.13 g, 3 mmol) was heated in acetic anhydride (12 ml, 127 mmol) and pyridine (0.12 ml) at 100°C. The reaction completion was monitored by tlc upon which the acetic anhydride was removed. The residue was stirred with 5% NaOH (20 ml) and extracted with ethyl acetate (3 x 20 ml). The organic layer

was dried over Na_2SO_4, evaporated and the residue was triturated with ether and recrystallized from diisopropyl ether to yield **20** (1.05 g, 83%) or **21** (1.05 g, 83%).

20: mp 118 °C, ^1H nmr: δ 7.43 (2H, AB-system, J_{AB} = 9.5 Hz, phenyl H), 7.38 (1H, AB-system, J_{AB} = 5.9 Hz, thiophene H), 7.13 (1H, AB-system, J_{AB} = 5.9 Hz, thiophene H), 6.90 (2H, AB-system, J_{AB} = 9.5 Hz, phenyl H), 5.22 (1H, AB-system, J_{AB} = 7.4 Hz, CH), 5.18 (1H, AB-system, J_{AB} = 7.4 Hz, CH), 4.45 - 4.08 (1H, m, NCH_2), 3.79 - 3.50 (1H, m, NCH_2), 3.82 (3H, s, OCH_3), 2.75 - 2.18 (2H, m, NCH_2), 2.29 (6H, s, $N(CH_3)_2$), 1.88 (3H, s, H_3CCOO); ^{13}C nmr: δ 169.0, 167.0, 159.2, 145.2, 130.9, 128.9, 127.0, 123.5, 120.1, 113.5, 71.4, 57.2, 56.5, 55.0, 45.6, 45.2, 20.1; ms (*m/z*): 421 (M^+ + 1, 7), 349 (3), 59 (100); Anal. Calcd for $C_{20}H_{24}N_2O_4S_2$: C, 57.12; H, 5.75; N, 6.66. Found C, 57.04; H, 5.57; N, 6.89.

21: mp 95 °C, ^1H nmr: δ 7.51 (1H, AB-system, J_{AB} = 5.9 Hz, thiophene H), 7.22 (1H, AB-system, J_{AB} = 5.9 Hz, thiophene H), 7.13 (2H, AB-system, J_{AB} = 8.9 Hz, phenyl H), 6.83 (2H, AB-system, J_{AB} = 8.9 Hz, phenyl H), 5.11 (1H, AB-system, J_{AB} = 11.8 Hz, CH), 4.66 (1H, AB-system, J_{AB} = 11.8 Hz, CH), 4.30 - 3.53 (2H, m, NCH_2), 3.79 (3H, s, OCH_3), 2.82 - 2.42 (2H, m, NCH_2), 2.26 (6H, s, $N(CH_3)_2$), 1.92 (3H, s, H_3CCOO); ^{13}C nmr: δ 169.1, 167.1, 158.8, 145.0, 132.9, 129.9, 127.6, 123.5, 118.3, 73.6, 56.3, 56.1, 55.0, 45.8, 45.2, 20.0; ms (*m/z*): 421 (M^+ + 1, 5), 349 (5), 59 (100); Anal. Calcd for $C_{20}H_{24}N_2O_4S_2$: C, 57.12; H, 5.75; N, 6.66. Found C, 57.25; H, 5.70; N, 6.83.

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