SYNTHESIS OF NOVEL 5,6,7,8-TETRAHYDRO-4*H*-THIENO[2,3-*b*][1,4]-DIAZEPINE DERIVATIVES

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Abstract-Unsubstituted 5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]diazepine (**1**) and 4*H*-thieno[2,3-*b*][1,4]diazepine-5,7(6*H*,8*H*)-dione (**2**) were newly synthesized. Benzoylation of **1** regioselectively afforded thienodiazepine (**13**) substituted with a benzoyl group *at position 4*. Alternatively, novel synthetic procedures were devised to yield thienodiazepine (**22**) substituted with an alkyl group or compound (**14**) with an aralkyl group *at position 8*. Thus, the ingenious introduction of functional groups at the *N*-4 or 8 position of a thienodiazepine skeleton was achieved and then a variety of 5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]diazepines (**5**)-(**9**), and (**27**), some of which exhibited potent arginine vasopressin antagonistic activity, were obtained using the key intermediates (**1**), (**13**), (**14**), and (**22**).

Unsubstituted 5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]diazepine (**1**) and 4*H*-thieno[2,3-*b*][1,4]diazepine-5,7(6*H*,8*H*)-dione (**2**) might be important synthetic intermediates for thienodiazepine derivatives. However, synthesis of diazepine (**1**) and its derivatives has not been reported yet, and there is only a paper on the synthesis of two 4*H*-thieno[2,3-*b*][1,4]diazepine-5,7(6*H*,8*H*)-diones (**3**) and (**4**).[1] (See Figure 1) Generally, it is known that substitution of strongly electron-donating groups, such as a methoxy group or an amino group, in a thiophene ring results in high reactivity or instability of the compound.[2] Therefore, it is supposed to be difficult to synthesize 5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]diazepine derivatives.

During our research into the synthesis of arginine vasopressin antagonists, we constructed a thieno[2,3-*b*][1,4]diazepine skeleton, obtained some data on the stability and reactivity of compound (**1**), and successively synthesized a series of its derivatives (**5**)-(**9**) with antagonistic activity.[3] Here we report the novel synthetic process and the stability of these compounds in detail.

Initially, we started to synthesize the new compound (**1**) in order to obtain compound (**6**). (See Scheme 1) Nucleophilic substitution of benzylamine to 2-chloro-3-nitrothiophene in the presence of K_2CO_3 gave compound (**10**), and its acylation with ethyl malonyl chloride gave compound (**11**). Cyclization of **11** was carried out with 7 eq of Fe powder in AcOH at 70 °C for 1 day to afford compound (**12**) in a 73 % yield,

Figure 1

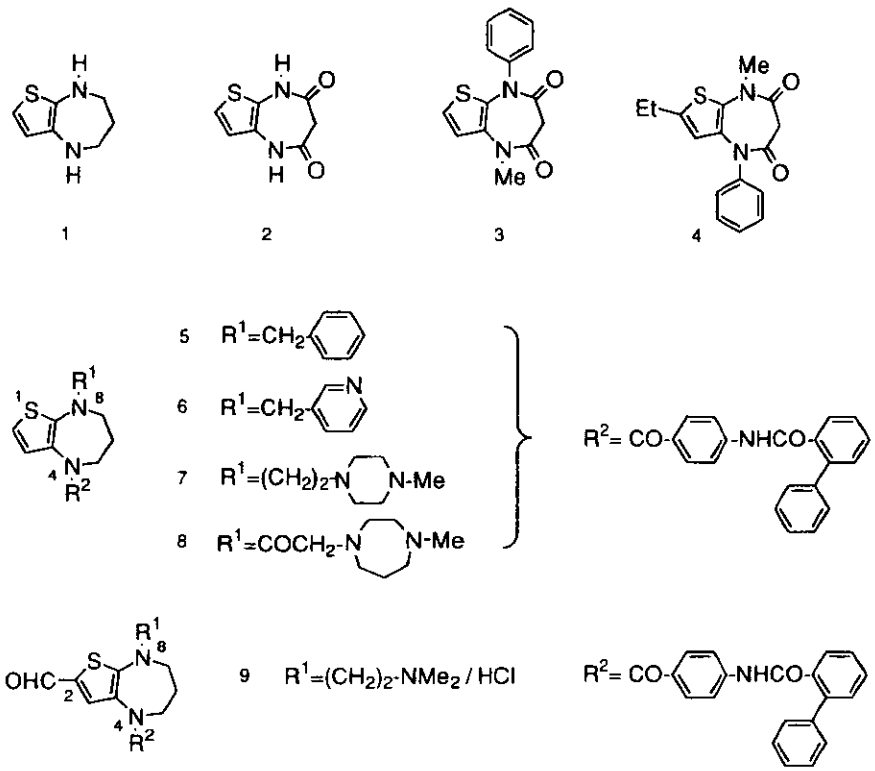
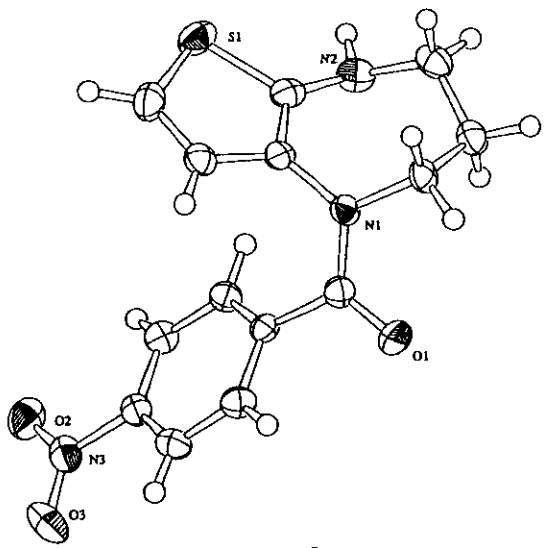


Figure 2



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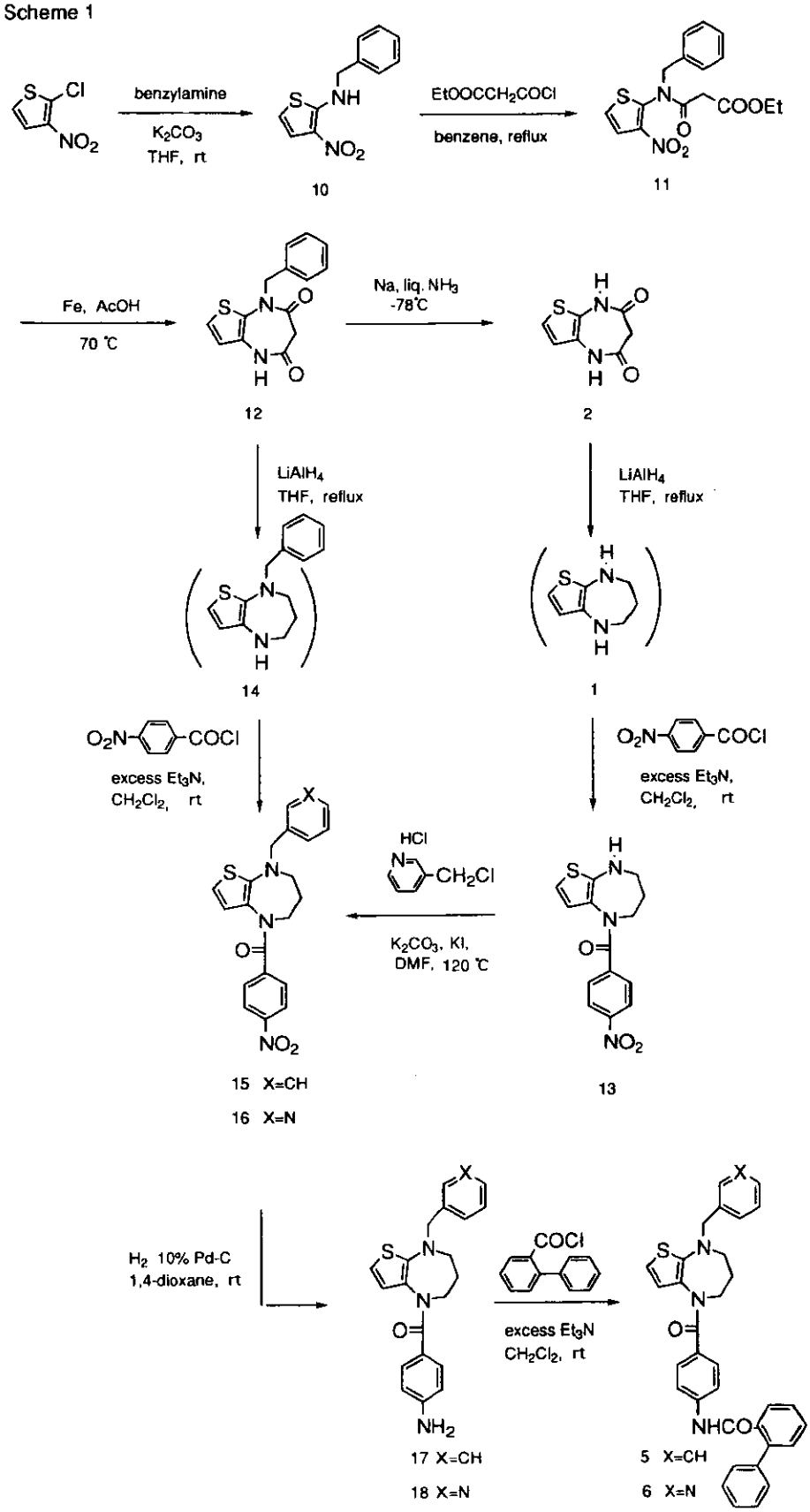
Scheme 1


benzylamine
K_2CO_3
THF, rt
$EtOOCCH_2COCl$
benzene, reflux
COOEt
10
11
Fe, AcOH
70 ℃
Na, liq. NH_3
-78℃
12
2
$LiAlH_4$
THF, reflux
$LiAlH_4$
THF, reflux
14
1
O_2N-COCl
excess Et_3N,
CH_2Cl_2, rt
O_2N-COCl
excess Et_3N,
CH_2Cl_2, rt
HCl
CH_2Cl
K_2CO_3, KI,
DMF, 120 ℃
15 X=CH
16 X=N
13
H_2 10% Pd-C
1,4-dioxane, rt
COCl
excess Et_3N
CH_2Cl_2, rt
17 X=CH
18 X=N
5 X=CH
6 X=N

the reduction of which with Na in liquid NH_3 was successfully done to afford 4*H*-thieno[2,3-*b*][1,4]diazepine-5,7(6*H*,8*H*)-dione (**2**) in a 94 % yield. Reduction of the carbonyl groups with 2.5 eq of $LiAlH_4$ in THF under reflux yielded the desired thienodiazepine (**1**). However, it was found that compound (**1**) was unstable even on a SiO_2 plate. Therefore, direct benzoylation of **1** with 1 eq of *p*-nitrobenzoyl chloride in Et_3N-CH_2Cl_2 was carried out to afford regioselective compound (**13**) as the sole product in a 69 % yield (two-step overall yield). The chemical structure of **13** was determined by X-Ray crystallographic analysis and a 4-nitrobenzoyl group was found at position 4. (See Figure 2) Although the reason for this regioselectivity is unclear because the electron densities on both nitrogen atoms were calculated (by semi-empirical molecular orbital method)[4] to be the same, *p*-nitrobenzoyl chloride might approach from the opposite side because of the bulkiness of the sulfur atom. Compound (**13**) was treated with 3-pyridylmethyl chloride to obtain compound (**16**) in order to synthesize compound (**6**).

On the other hand, $LiAlH_4$ reduction of **12** yielded *N*-8 benzylthienodiazepine (**14**), which was converted to compound (**15**) without purification. Hydrogenation of **15** and **16** on 10 % Pd-C afforded compounds (**17**) and (**18**), which were treated with 2-phenylbenzoyl chloride to yield the desired compounds (**5**) and (**6**), respectively.

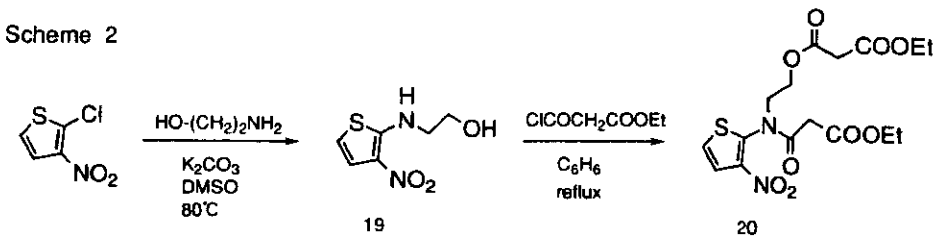
Since reaction of compound (**1**) with (4-methylpiperazin-1-yl)acetic acid in the presence of bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) / Et_3N or of **13** with ethyl bromoacetate using K_2CO_3/KI/DMF did not give the satisfactory result, we studied an alternative synthetic pathway to obtain the thieno derivative (**22**). (See Scheme 2) The regioselective introduction of an alkyl group at a *N*-8 position was successfully achieved as follows. Nucleophilic substitution of ethanolamine to 2-chloro-3-nitrothiophene gave compound (**19**), which was treated with ethyl malonyl chloride to afford compound (**20**) in an 87 % yield. Cyclization of **20** with Fe powder in AcOH at 70 °C for 1 day gave 4*H*-thieno[2,3-*b*][1,4]diazepine-5,7(6*H*,8*H*)-dione (**21**). Reduction of **21** with $LiAlH_4$ in THF under reflux for 4 h yielded the desired compound (**22**), which could not be obtained by direct alkylation of compound (**1**). Benzoylation of **22** with *p*-nitrobenzoyl chloride in Et_3N provided the stable thienodiazepine (**23**), accompanied by the ester which could be hydrolyzed to compound (**23**) under aq. basic conditions. Transformation of **23** *via* 2 steps afforded compound (**24**), which was converted to tetrahydrothienodiazepine (**7**) by methods similar to those described above. Compounds (**5**), (**6**), and (**7**) were less unstable than compound (**1**).

In order to obtain more stable compounds, compounds such as **8** and **9** with an electron-deficient thiophene ring were designed by introduction of an electron-withdrawing group at position 2 on the ring or introduction of a carbonyl group in a R^1 alkyl group neighboring the nitrogen atom at position 8. (See Schemes 3 and 4) Thus, acylation of **13** with chloroacetyl chloride and nucleophilic substitution of a secondary amine gave compound (**26**) in a good yield. Finally, stable compound (**8**) was obtained by the procedure mentioned above.

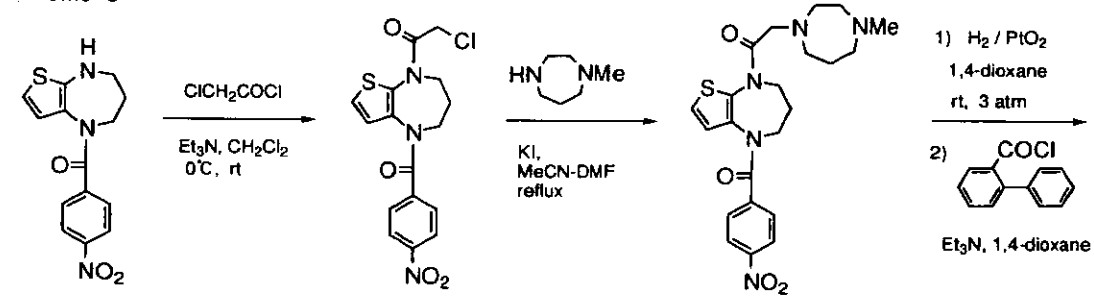
On the other hand, formylation of **27** with Vilsmeier reagent proceeded cleanly to give compound (**9**) in a 93 % yield, and the hydrochloride salt was obtained as stable crystals using a solution of 4M HCl in anhyd. 1,4-dioxane.

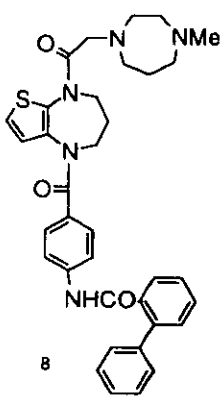
In conclusion, 5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]diazepine (**1**), 4*H*-thieno[2,3-*b*][1,4]diazepine-5,7(6*H*,8*H*)-dione (**2**) and (**5**)-(**9**) were synthesized by novel procedures as shown in Schemes 1-4. Some of

Scheme 2

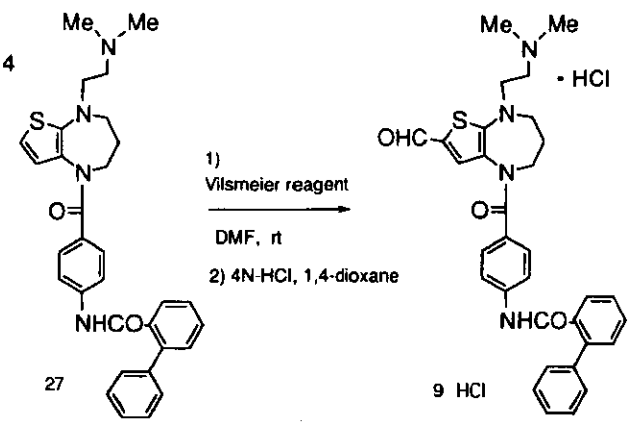


Scheme 3





Scheme 4



them had a potent vasopressin antagonistic activity. The pharmacological data on these compounds and the other derivatives will be reported in due course.[3]

EXPERIMENTAL

Melting points were determined with Yanagimoto (Yanako) micro-melting point apparatus HK-10D and are uncorrected. ^{1}H-NMR spectra (ppm. δ) were recorded with a JEOL JNMA 300 (300 MHz) spectrometer using tetramethylsilane as an internal standard. IR spectra (cm^{-1}) were obtained with a PERKIN ELMER FT 1650 infrared spectrophotometer. MS were obtained with Finigan TSQ 700. Column chromatography was performed using Merck silica gel (70-230 mesh).

Synthesis of ethyl *N*-benzyl-*N*-(3-nitrothiophen-2-yl)aminocarbonylacetate (**11**)

To a stirred solution of 2-chloro-3-nitrothiophene (15.2 g, 95.3 mmol) in THF (300 mL) were added K_2CO_3 (25.7 g, 186 mmol) and benzylamine (40.5 mL, 371 mmol) at 0 °C. Stirring was continued for 33 h, after which the reaction mixture was quenched with water (100 mL) and extracted with Et_2O. The organic layer was washed with brine, dried over anhyd. Na_2SO_4 and evaporated to give the residue, which was azeotropically distilled with toluene to yield compound (**10**) (mp 90.1-91.3℃, 19.6 g, 88 %) as crystals that were recrystallized from Et_2O. Ethyl malonyl chloride (2.65 mL, 20.7 mmol) was added to a stirred solution of compound (**10**) (3.0 g, 12.8 mmol) in benzene (60 mL) at rt. The mixture was refluxed for 24 h, cooled, and concentrated to give the residue that was purified by SiO_2 column chromatography (20 % AcOEt in hexane) to afford compound (**11**) (3.76 g, 84.7 %) as an oily compound. ^{1}H-NMR (δ, $CDCl_3$) 1.26 (3H, t, J=7.1 Hz), 3.36 (2H, J=14.5 Hz), 7.10-7.40 (5H, m), 7.49 (1H, d, J=6.2 Hz). MS (FAB, *m/z*)=349 (M^++1). *Anal.* Calcd for $C_{16}H_{16}N_2O_5S$: C, 55.16; H, 4.63; N, 8.04. Found: C, 55.27; H, 4.46; N, 8.10.

Synthesis of 8-benzyl-4*H*-thieno[2,3-b][1,4]diazepine-5,7 (*6H*, *8H*)-dione (**12**)

Fe powder (14.6 g, 260.7 mmol) was added to a stirred solution of compound (**11**) (13.0 g, 37.4 mmol) in acetic acid (350 mL) at 70 °C and stirring was continued for 24 h. After cooling, the reaction mixture was filtered through a 'Celite' filter and the filtrate was concentrated to give the residue, which was dissolved in chloroform. The solution was washed with saturated $NaHCO_3$ aqueous solution, dried over anhyd. Na_2SO_4, and evaporated to give the residue that was purified by SiO_2 column chromatography (2.5 % MeOH in $CHCl_3$) to yield compound (**12**) (7.39 g, 72.6 %) as an oily compound. ^{1}H-NMR (δ, $CDCl_3$) 3.53 (2H, s), 5.07 (2H, s), 6.67 (1H, d, J=5.9 Hz), 6.97 (1H, d, J=5.8 Hz), 7.20-7.40 (5H, m), 8.96 (1H, brs). MS (FAB, *m/z*)=273 (M^++1). *Anal.* Calcd for $C_{14}H_{12}N_2O_2S$:C, 61.75; H, 4.44; N, 10.29. Found: C, 61.88; H, 4.49; N, 10.48.

Synthesis of 4*H*-thieno[2,3-*b*][1,4]diazepine-5,7 (*6H*, *8H*)-dione (**2**)

To a stirred suspension of compound (**12**) (8.45 g, 31.1 mmol) in liquid NH_3 (300 mL) was added Na pieces at -78 °C until the blue color of the solution was maintained for 10 min. Stirring was continued for 1 h at -78 °C and the solution was warmed to rt to evaporate NH_3. Water was added to the residue. The precipitate was collected, washed successively with water, EtOH, and hexane, and dried to provide compound (**2**) (5.30 g, 93.6 %) as a solid. ^{1}H-NMR (δ, DMSO-d_6) 3.21 (2H, s), 6.68 (1H, d, J=5.7 Hz), 7.17 (1H, d, J=5.8 Hz), 10.04 (2H, br s). MS(FAB, *m/z*)=183 (M^++1). *Anal.* Calcd for

$C_7H_6N_2O_2S$: C, 46.14; H, 3.32; N, 15.37. Found: C, 46.36; H, 3.19; N, 15.17.

Synthesis of 4-(4-nitrobenzoyl)-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]diazepine (**13**) *via* 5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]diazepine (**1**)

To a stirred slurry of $LiAlH_4$ (2.76 g, 72.6 mmol) in THF (150 mL) was added compound (**2**) (5.30 g, 29 mmol) at rt. The mixture was refluxed for 3 h and cooled, after which Et_2O (1 L) was added and excess reagent was decomposed with water. The solution was filtered through a 'Celite' filter and the filtrate was dried with anhyd. Na_2SO_4 and evaporated to give compound (**1**). Without purification, to a stirred solution of compound (**1**) in CH_2Cl_2 (150 mL) were added Et_3N (16.6 mL, 119 mmol) and 4-nitrobenzoyl chloride (5.4 g, 29.1 mmol) at rt. Stirring was continued for 3 h. The reaction mixture was washed with brine, dried over anhyd. Na_2SO_4, and evaporated to give the residue that was purified by SiO_2 column chromatography (25 % AcOEt in hexane) to afford compound (**13**) (6.08 g, 69.2 %). ^{1}H-NMR (δ, $CDCl_3$) 1.95-2.10 (2H, m), 3.15-3.30 (2H, m), 3.88 (2H, br s), 4.06 (1H, br s), 5.99 (1H, d, J=5.7 Hz), 6.13 (1H, d, J=5.7 Hz), 7.46 (2H, d, J=8.7 Hz), 8.07 (2H, d, J=8.7 Hz). MS (FAB, *m/z*)=304 (M^++1). *Anal.* Calcd for $C_{14}H_{13}N_3O_3S$: C, 55.43; H, 4.32; N, 13.85. Found: C, 55.69; H, 4.21; N, 13.98.

Synthesis of 4-(4-nitrobenzoyl)-8-(pyridin-3-ylmethyl)-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]diazepine (**16**)

To a stirred solution of compound (**13**) (650 mg, 2.15 mmol) in DMF (15 mL) were added K_2CO_3 (1.77 g, 12.8 mmol), KI (711 mg, 4.28 mmol) and 3-chloromethylpyridine hydrochloride (732 mg, 4.46 mmol). The mixture was stirred at 120 °C for 20 h, poured into water, and extracted with AcOEt. The organic layer was washed with brine, dried over anhyd. $MgSO_4$, and evaporated to give the residue that was purified by SiO_2 column chromatography (40 % AcOEt in hexane) to afford compound (**16**) (163 mg, 19 %) as an oily compound. ^{1}H-NMR (δ, $CDCl_3$) 2.00-2.15 (2H, m), 3.05-3.25 (2H, m), 3.90 (2H, br s), 4.39 (2H, s), 6.06 (1H, d, J=5.8 Hz), 6.33 (1H, d, J=5.7 Hz), 7.30-7.40 (3H, m), 7.75-7.85 (1H, m), 7.90-8.05 (2H, m), 8.55-8.65 (1H, m), 8.65-8.75 (1H, m). MS (FAB, *m/z*)=395 (M^++1). *Anal.* Calcd for $C_{20}H_{18}N_4O_3S$: C, 60.90; H, 4.60; N, 14.20. Found: C, 60.74; H, 4.66; N, 14.10.

Synthesis of 8-benzyl -4-(4-nitrobenzoyl)-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]diazepine (**15**) *via* 8-benzyl-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]diazepine (**14**)

To a slurry of $LiAlH_4$ (550 mg, 14.5 mmol) in THF (40 mL) was added compound (**12**) (1.53 g, 5.6 mmol) at rt. The mixture was refluxed for 3 h, cooled, and excess reagent was decomposed by addition of aqueous Et_2O and then water. After decantation, the solution was dried over anhyd. $MgSO_4$ and evaporated to give compound (**14**), which was dissolved in CH_2Cl_2 (50 mL). To the solution were added Et_3N (1.76 mL, 12.6 mmol) and 4-nitrobenzoyl chloride (1.15 g, 6.2 mmol) at rt, and stirring was continued for 3 h. The reaction mixture was washed with brine, dried over anhyd. $MgSO_4$ and evaporated to give the residue, that was purified by SiO_2 column chromatography (15 % AcOEt in hexane) to afford compound (**15**) (1.33 g, 60.4 %) as an oily compound. ^{1}H-NMR (δ, $CDCl_3$) 1.95-2.10 (2H, m), 3.00-3.15 (2H, m), 3.85 (2H, br s), 4.37 (2H, s), 6.04 (1H, d, J=5.8 Hz), 6.29 (1H, d, J=5.8 Hz), 7.30-7.50 (7H, m), 7.90-8.00 (2H, m). MS (FAB, *m/z*)=394 (M^++1). *Anal.* Calcd for $C_{21}H_{19}N_3O_3S$: C, 64.10; H, 4.87; N, 10.68. Found: C, 64.37; H, 4.86; N, 10.54.

Synthesis of *N*-[4-(8-benzyl-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]diazepin-4-yl)carbonyl]phenyl-2-

phenylbenzamide (**5**) *via* 4-(4-aminobenzoyl)-8-benzyl-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]-diazepine (**17**)

To a stirred solution of compound (**15**) (150 mg, 0.38 mmol) in EtOH (10 mL) was added 10 % Pd-C (150 mg). Stirring was continued under a 1 atm hydrogen atmosphere at rt for 8 h and the reaction mixture was filtered through a 'Celite' filter. The filtrate was condensed and azeotropically distilled with toluene to give compound (**17**), which was dissolved in CH_2Cl_2 (10 mL) and Et_3N (0.08 mL, 0.58 mmol). To this solution was added 2-phenylbenzoyl chloride at rt, which was prepared from 2-phenylbenzoic acid (83 mg, 0.42 mmol) and thionyl chloride (1 mL, 13.7 mmol). Stirring was continued for 15 h and the reaction mixture was washed with brine, dried over anhyd. $MgSO_4$ and evaporated to give the residue, which was purified by SiO_2 column chromatography (25 % AcOEt in hexane) to afford compound (**5**) as crystals. Recrystallization from EtOH yielded compound (70 mg, 34 %, 2 steps). mp 229-230 °C. IR ($CHCl_3$) cm^{-1}: 1623. ^{1}H-NMR (δ, $CDCl_3$) 1.85-2.10 (2H, m), 2.95-3.20 (2H, m), 3.83 (2H, br s), 4.36 (2H, s), 5.95-6.15 (1H, m), 6.20-6.35 (1H, m), 6.75-7.00 (3H, m), 7.10-7.60 (15H, m), 7.80-7.95 (1H, m). MS (FAB, *m/z*)=544 (M^++1). *Anal.* Calcd for $C_{34}H_{29}N_3O_2S$: C, 75.11; H, 5.38; N, 7.73. Found: C, 75.32; H, 5.49; N, 7.55.

Synthesis of *N*-{4-[8-(pyridin-3-ylmethyl)-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]diazepin-4-yl)-carbonyl]phenyl-2-phenylbenzamide (**6**) *via* 4-(4-aminobenzoyl)-8-(pyridin-3-ylmethyl)-5,6,7,8-tetrahydro-4*H*-thieno[2,3,-*b*][1,4]diazepine (**18**)

To a stirred suspension of compound (**16**) (200 mg, 0.51 mmol) in 1,4-dioxane (10 mL) was added PtO_2 (100 mg). The mixture was stirred at rt under a 1 atm hydrogen atmosphere. After 6 h, filtration of the reaction mixture through 'Celite' gave a filtrate, to which Et_3N (0.04 mL, 0.29 mmol) was added at rt. To this solution was added 2-phenylbenzoyl chloride, which was prepared by reaction of 2-phenylbenzoic acid (151 mg, 0.76 mmol) with thionyl chloride (1.0 mL, 13.7 mmol). After stirring for 24 h, the reaction mixture was concentrated to give the residue, which was dissolved in $CHCl_3$ (30 mL). The solution was washed with brine, dried over anhyd. $MgSO_4$, and evaporated to give the residue that was purified by SiO_2 column chromatography (33 % hexane in AcOEt) to afford compound (**6**) as crystals. Recrystallization from EtOH gave compound (50 mg, 18 %, 2 steps). mp 224.5℃(decomp). IR ($CHCl_3$) cm^{-1}: 1626, 1597. ^{1}H-NMR (δ, $CDCl_3$) 1.85-2.05 (2H, m), 2.95-3.15 (2H, m), 3.82 (2H, br s), 4.37 (2H, s), 5.95-6.20 (1H, m), 6.25-6.40 (1H, m), 6.80-7.00 (3H, m), 7.05-7.20 (2H, m), 7.25-7.60 (9H, m), 7.70-7.90 (2H, m), 8.50-8.70 (2H, m). MS (FAB, *m/z*)=545 (M^++1). *Anal.* Calcd for $C_{33}H_{28}N_4SO_2$: C, 72.77; H, 5.18; H, 5.18; N 10.29. Found: C, 72.99; H 5.47; N, 10.35.

Synthesis of 2-(3-nitrothiophen-2-yl)aminoethanol (**19**)

To a stirred solution of 2-chloro-3 nitrothiophene (10.0 g, 61.1 mmol) in dimethyl sulfoxide (110 mL) were added K_2CO_3 (17.0 g, 123 mmol) and 2-aminoethanol (4.5 g, 73.7 mmol). The mixture was stirred at 80 °C for 3 h. After cooling, the reaction mixture was diluted with water and the mixture was extracted with AcOEt and the extract was washed with brine, dried over anhyd. $MgSO_4$, and evaporated to give the residue, which was purified by SiO_2 column chromatography (50 % AcOEt in $CHCl_3$) to give compound (**19**) (4.37 g, 38 %) as an oily compound. ^{1}H-NMR (δ, $CDCl_3$) 2.29 (1H, s), 3.40-3.60 (2H, m), 3.96 (2H, t, J=6 Hz), 6.24 (1H, d, J=6 Hz), 7.25 (1H, d, J=6 Hz), 8.64 (1H, br s). MS (FAB, *m/z*)=189

(M^++1). *Anal.* Calcd for $C_6H_8N_2O_3S$: C, 38.29; H, 4.28; N, 14.88. Found: C, 38.44; H, 4.21; N, 14.63.

Synthesis of ethyl 2-[ethoxycarbonylacetyl-(3-nitro-thiophen-2-yl)]aminoethoxycarbonyl acetate(**20**)

To a stirred solution of compound (**19**) (4.31 g, 22.9 mmol) in 1,2-dichloroethane (200 mL) and benzene (200 mL) was added ethyl malonyl chloride (11.1 g, 73.7 mmol). After reflux for 3 h, the solvent was removed under reduced pressure and $CHCl_3$ was added to the residue. The solution was washed with brine, dried over $MgSO_4$ and evaporated to give the residue, which was purified by SiO_2 column chromatography (20 % AcOEt in $CHCl_3$ and then 50 % AcOEt in $CHCl_3$) to afford compound (**20**) (8.26 g, 86.7 %) as an oily compound. ^{1}H-NMR (δ, $CDCl_3$) 1.15-1.35 (6H, m), 3.30 (2H, s), 3.34 (2H, s), 3.80-4.50 (8H, m), 7.31 (1H, d, J=6 Hz), 7.57 (1H, d, J=6 Hz). MS (FAB, *m/z*)=417 (M^++1). *Anal.* Calcd for $C_{16}H_{20}N_2O_9S$: C, 46.15; H, 4.84; N, 6.73. Found: C, 46.33; H, 4.54; N, 6.89.

Synthesis of ethyl 2-(thieno[2,3-*b*][1,4]diazepine-5,7(4*H*,6*H*,8*H*)-dion-8-yl)ethoxycarbonylacetate (**21**)

Fe powder (8.1 g, 145 mmol) was added to compound (**20**) (8.25 g, 19.8 mmol) in acetic acid (200 mL) and the mixture was heated at 70 °C for 1 day with stirring. The reaction mixture was diluted with $CHCl_3$ and water, and was adjusted to pH 10 by addition of K_2CO_3. Filtration of the mixture through a 'Celite 'filter gave the filtrate. This was washed with brine, dried over anhyd. $MgSO_4$, and evaporated to give the residue, which was purified by SiO_2 column chromatography (20 % EtOAc in $CHCl_3$) to afford compound (**21**) (4.78 g, 71 %) as an oily compound. ^{1}NMR (δ, $CDCl_3$) 1.26 (3H, t, J=6 Hz), 3.31 (2H, s), 3.45 (2H, s), 4.10-4.30 (4H, m), 4.40 (2H, t, J=6 Hz), 6.78 (1H, d, J=3 Hz), 7.08 (1H, d, J=3 Hz), 9.58 (1H, s). MS (FAB, *m/z*)= 341 (M^++1). *Anal.* Calcd for $C_{14}H_{16}N_2O_6S$: C, 49.41; H, 4.74; N, 8.23. Found: C, 49.20; H, 4.99; N, 8.21.

Synthesis of 8-(2-hydroxyethyl)-4-(4-nitrobenzoyl)-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]diazepine (**23**) *via* 8-(2-hydroxyethyl)-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]diazepine (**22**)

$LiAlH_4$ (2.0 g, 52.6 mmol) was added to compound (**21**) (2.0 g, 5.88 mmol) in THF (200 mL) at 0 °C. The mixture was refluxed for 4 h. After cooling, water (8 mL) was added dropwise to the reaction mixture to separate the organic layer from the inorganic salts. The solution was decanted, dried over anhyd. $MgSO_4$, and evaporated to give compound (**22**), which was dissolved in CH_2Cl_2 (200 mL) and Et_3N (1.2 g, 11.9 mmol). To the solution was added 4-nitrobenzoyl chloride (1.2 g, 6.47 mmol) and stirring was continued at rt for 0.5 h. Evaporation of the reaction solution gave the residue, which was dissolved in $CHCl_3$. The solution was successively washed with brine and saturated $NaHCO_3$, and evaporated to give the residue, which was purified by SiO_2 column chromatography (50 % AcOEt in $CHCl_3$) to yield compound (**23**) (1.87 g, 91.7 %) as an oily compound. ^{1}H-NMR (δ, $CDCl_3$) 1.90-2.40 (3H, m), 3.05-3.30 (2H, m), 3.41 (2H, t, J=6 Hz), 3.50-4.30 (4H, m), 6.05 (1H, d, J=6 Hz), 6.32 (1H, d, J=6 Hz), 7.46 (2H, d, J=9 Hz), 8.06 (2H, d, J=9 Hz). MS (FAB, *m/z*)=348 (M^++1). *Anal.* Calcd for $C_{16}H_{17}N_3O_4S$: C, 55.32; H, 4.93; N, 12.10. Found: C, 55.59; H, 4.84; N, 12.02.

Synthesis of 8-[2-(4-methylpiperazin-1-yl)ethyl]-4-(4-nitrobenzoyl)-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*]-[1,4]diazepine (**24**)

To a stirred solution of compound (**23**) (380 mg, 1.09 mmol) in pyridine (15 mL) was added methanesulfonyl chloride (200 mg, 1.75 mmol) in CH_2Cl_2 (2 mL) at rt and stirring was continued for 1.5 h. The solvents were removed under reduced pressure to give the residue, which was dissolved in $CHCl_3$.

The solution was washed with brine, dried over anhyd. Na_2SO_4, and evaporated to give a mesylate, which was dissolved in *N*,*N*-dimethylformamide (45 mL). To the resulting solution were added 1-methylpiperazine (2.22 g, 22.2 mmol), potassium iodide (740 mg, 4.46 mmol), and potassium carbonate (3.05 g, 22.1 mmol). The mixture was stirred at 40 °C for 44 h, quenched with water, and extracted with AcOEt. The organic layer was washed with brine, dried over anhyd. Na_2SO_4 and evaporated to give the residue, which was purified by SiO_2 column chromatography (5 % EtOH in $CHCl_3$) to yield compound (**24**) (390 mg, 63 %) as an oily compound. ^{1}H-NMR (δ, $CDCl_3$) 1.95-2.10 (2H, m), 2.29 (3H, s), 2.35-2.70 (8H, m), 2.69 (2H, t, J=6.0 Hz), 3.10-3.30 (2H, m), 3.37 (2H, t, J=6.0 Hz), 3.60-4.10 (2H, m), 6.02 (1H, d, J=6.0 Hz), 6.26 (1H, d, J=6.0 Hz), 7.48 (2H, d, J=9.0 Hz), 8.07 (2H, d, J=9.0 Hz). MS (FAB, *m/z*)=430 (M^++1). *Anal.* Calcd for $C_{21}H_{27}N_5O_3S$: C, 58.72; H, 6.34; N, 16.30. Found: C, 58.88; H, 6.12; N, 16.35.

Synthesis of *N*-{4-[8-[2-(4-methylpiperazin-1-yl)ethyl]-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]-diazepin-4-yl]carbonyl}phenyl-2-phenylbenzamide (**7**)

$SOCl_2$ (400 mg, 3.36 mmol) was added to a solution of 2-phenylbenzoic acid (180 mg, 0.91 mmol) in $CHCl_3$ (30 mL), and the mixture was refluxed for 6 h. After removing the solvent under reduced pressure, toluene was added and again removed under reduced pressure to give 2-phenylbenzoyl chloride. Separately, PtO_2 (100 mg) was added to a solution of compound (**24**) (200 mg, 0.47 mmol) in dioxane (30 mL), and the mixture was stirred under a hydrogen atmosphere at rt for 8 h. After filtration of the catalyst through Celite, to the filtrate were added CH_2Cl_2 (100 mL) and Et_3N (800 mg, 7.91 mmol). Then, 2-phenylbenzoyl chloride prepared as described above was added at rt. After 3 days, the solvent was removed under reduced pressure to give the residue, which was dissolved in $CHCl_3$. The solution was successively washed with brine and 1 *N* NaOH, dried over anhyd. Na_2SO_4 and evaporated to give the residue, which was purified by SiO_2 column chromatography (5 % EtOH-$CHCl_3$) to afford compound (**7**) (230 mg, 85 %) as an oily compound. IR (KBr) 1630 cm^{-1}. ^{1}H-NMR (δ, $CDCl_3$) 1.85-2.05 (2H, m), 2.29 (3H, s), 2.35-2.75 (10H, m), 3.05-3.25 (2H, m), 3.35 (2H, t, J=6.8 Hz), 3.55-4.05 (2H, m), 6.03 (1H, br s), 6.26 (1H, br s), 6.90 (1H, s), 6.97 (2H, d, J=8.0 Hz), 7.21 (2H, d, J=8.0 Hz), 7.30-7.60 (8H, m), 7.87 (1H, d, J=7.4 Hz). MS (FAB, *m/z*)=580 (M^++1). *Anal.* Calcd for $C_{34}H_{37}N_5O_2S$: C, 70.44; H, 6.43; N, 12.08. Found: C, 70.67; H, 6.49; N, 11.91.

Synthesis of *N*-{4-[8-(2-dimethylaminoethyl)-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]diazepin-4-yl]-carbonyl}phenyl-2-phenylbenzamide (**27**)

In a similar manner to the synthesis of compound (**7**), compound (**27**) was obtained in an 85.6 % yield. IR (KBr) 1625 cm^{-1}. ^{1}H-NMR (δ, $CDCl_3$) 1.90-2.10 (2H, m), 2.31 (6H, s), 2.59 (2H, t, J=7.2 Hz), 3.05-3.20 (2H, m), 3.33 (2H, t, J=7.2 Hz), 3.60-4.00 (2H, m), 6.02 (1H, br s), 6.27 (1H, d, J=5.4 Hz), 6.90 (1H, s), 6.96 (2H, d, J=8.1 Hz), 7.22 (2H, d, J=8.1 Hz), 7.30-7.60 (8H, m), 7.87 (1H, d, J=6.5 Hz). MS (FAB, *m/z*)=525 (M^++1). *Anal.* Calcd for $C_{31}H_{32}N_4O_2S$: C, 70.96; H, 6.15; N, 10.68. Found: C, 71.09; H, 6.15; N, 10.77.

Synthesis of *N*-{4-[8-(2-dimethylaminoethyl)-2-formyl-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4] diazepin-4-yl]carbonyl}phenyl-2-phenylbenzamide (**9**)

$POCl_3$ (65.8 mg, 0.43 mmol) was added to DMF (951 mg, 13.0 mmol) at 0 °C and the mixture was stirred

at rt for 3 h. The solution was added to a stirred solution of compound (**27**) (45 mg, 0.078 mmol) in DMF (3 mL) and stirring was continued at rt for 42 h. Then the reaction mixture was quenched with water and made basic (pH 10) with 15 % aqueous NaOH. After stirring at rt for 40 min, the reaction mixture was extracted with AcOEt. The organic layer was washed with brine, dried over anhyd. Na_2SO_4 and evaporated to give the residue, which was purified by SiO_2 column chromatography (5 % EtOH in $CHCl_3$) to give compound (**9**) (40 mg, 92.9 %) as an oily compound. IR (KBr) cm^{-1}: 1637. ^{1}H-NMR (δ, $CDCl_3$) 2.00-2.20 (2H, m), 2.31 (6H, s), 2.62 (2H, t, J=6.5 Hz), 3.49 (2H, t, J=6.5 Hz), 3.50-4.30 (4H, m), 6.60 (1H, br s), 6.90-7.20 (3H, m), 7.20-7.60 (10H, m), 7.84 (1H, d, J=7.3 Hz), 9.16 (1H, s). MS (FAB, *m/z*)=553 (M^++1). *Anal.* Calcd for $C_{32}H_{32}N_4O_3S$: C, 69.54; H, 5.84; N, 10.14. Found: C, 69.79; H, 5.73; N, 10.38.

Synthesis of 8-chloroacetyl-4-(4-nitrobenzoyl)-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]diazepine (**25**)

Chloroacetyl chloride (0.11 mL, 1.4 mmol) was added to a stirred solution of compound (**13**) (360 mg, 1.2 mmol) in Et_3N (0.34 mL, 2.4 mmol) and CH_2Cl_2 (15 mL) at 0 °C. Stirring was continued at rt for 3 h. Then the reaction mixture was washed with brine, dried over anhyd. $MgSO_4$, and evaporated to give the residue, which was purified by SiO_2 column chromatography (50 % AcOEt in n-hexane) to afford compound (**25**) (340 mg, 74.8 %) as an oily compound. ^{1}NMR (δ, $CDCl_3$) 1.90-2.30 (2H, m), 3.25-4.40 (6H, m), 6.05-6.50 (1H, m), 6.80-7.10 (1H, m), 7.45-7.65 (2H, m), 8.05-8.30 (2H, m). MS (FAB, *m/z*)=380 (M^++1), 382 (M^++3). *Anal.* Calcd for $C_{16}H_{14}N_3O_4ClS$: C, 50.60; H, 3.72; N, 11.06. Found: C, 50.89; H, 3.54; N, 11.27.

Synthesis of 8-(4-methyl-hexahydro-1*H*-[1,4]diazepin-1-ylacetyl)-4-(4-nitrobenzoyl)-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]diazepine (**26**)

To a stirred solution of compound (**25**) (340 mg, 0.90 mmol) in MeCN (5 mL) were added KI (catalytic amount) and 1-methylhomopiperazine (0.24 mL, 1.9 mmol) at rt. The mixture was refluxed for 1 day. After cooling, the reaction mixture was concentrated to give the residue which was dissolved in AcOEt. The mixture was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhyd. Na_2SO_4 and evaporated to give the residue, which was purified by SiO_2 column chromatography (9 % MeOH in $CHCl_3$) to afford compound (**26**) (34.3 mg, 83.4 %) as an oily compound. ^{1}H-NMR (δ, $CDCl_3$) 1.70-2.00 (4H, m), 2.65-3.00 (8H, m), 3.30-4.50 (6H, m), 6.00-6.35 (1H, m), 6.75-7.00 (1H, m), 7.50-7.60 (2H, m), 8.05-8.30 (2H, m). MS (FAB, *m/z*)=458 (M^++1). *Anal.* Calcd for $C_{22}H_{27}N_5O_4S$: C, 57.75; H, 5.95; N, 15.31. Found: C, 57.99; H, 6.13; N, 15.17.

Synthesis of *N*-{4-[8-(4-methyl-hexahydro-1*H*-[1,4]diazepin-1-yl)acetyl-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*b*][1,4]diazepin-4-yl]carbonyl}phenyl-2-phenylbenzamide (**8**)

To a stirred suspension of compound (**26**) (343 mg, 0.565 mmol) in 1,4-dioxane (10 mL) was added PtO_2 (400 mg), and the mixture was stirred at rt under a hydrogen atmosphere (3 atm) for 6 h. After filtration with 'Celite', to the filtrate were added Et_3N (0.05 mL, 0.36 mmol) and 2-phenylbenzoyl chloride prepared from 2-phenylbenzoic acid (223 mg, 1.13 mmol) and $SOCl_2$ (1.0 mL, 13.7 mmol). Stirring was continued at rt for 12 h and the reaction mixture was concentrated to give the residue, which was dissolved in $CHCl_3$. The solution was washed with brine, dried over anhyd. Na_2SO_4 and evaporated to give the residue, which was purified by SiO_2 column chromatography (9 % MeOH in $CHCl_3$) to afford compound (**8**) (250 mg,

72.9 %). IR ($CHCl_3$) cm^{-1}: 1666. ^{1}H-NMR (δ, $CDCl_3$) 1.65-2.40 (4H, m), 2.70-4.20 (17H, m), 6.30-6.65 (1H, m), 6.85-7.00 (1H, m), 7.10-7.65 (13H, m), 7.80-7.90 (1H, m). MS (FAB, *m/z*)=608 (M^++1). *Anal.* Calcd for $C_{35}H_{37}N_5O_3S$: C, 69.17; H, 6.14; N, 11.52. Found: C, 69.00; H, 6.24; N, 11.66.

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REFERENCES AND NOTES

1. T. Erker, *J. Heterocycl. Chem.*, 1993, 30, 807.
2. R. M. Kellogg. *Comprehensive Heterocyclic Chemistry*, Vol. 4, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, 1984, p.714.
3. H. Cho and K. Wakitani, *Japan Patent Kokai*, 1997. H9-20779 (*Chem Abstr.*, 1997, 126, 186116). For the new synthesis of a thienoazepine skeleton form an oxime using DIBAH, see the previous paper of this journal; H. Cho, K. Murakami, H. Nakanishi, H. Isoshima, K. Hayakawa, and I. Uchida, *Heterocycles*, 1998, 48, 919.
4. The partial charges and geometry were calculated using the PM3[5] method and the MOPAC package.[6] The lowest energy conformation obtained by the RANDAMSEARCH command of SYBYL[7] was used as the initial geometry.
5. J. J. Stewart, *J. Comp. Aided Md. Design*, 1990, 4, No1.
6. QCPE Program #455.
7. Tripos Associates, St. Louis, MO.

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