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An expedient synthesis of face 'b' pyrido-annulated analogs of 1,5-benzothiazepines of medicinal interest

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An expedient synthesis of face 'b' pyrido-annulated analogs of 1,5-benzothiazepines of medicinal interest

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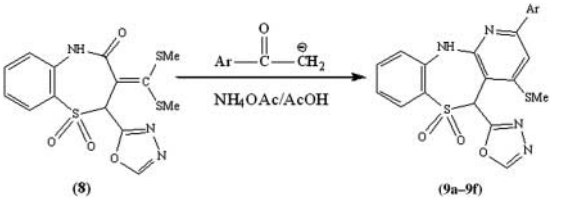
An expedient protocol for the synthesis of face 'b' pyrido-annulated analogs of 1,5-benzothiazepines, namely 4-(methylthio)-5-(1′,3′,4′-oxadiazol-2′-yl)-2-phenyl-5,11-dihydrobenzo[b] pyrido[2,3-e] [1,5] thiazepine-*S*,*S*-dioxides **9a**–**9f**, of medicinal interest emerged to exploit the potential of 3-ketene dithioacetal-substituted derivatives of 4-(1′,3′,4′-oxadiazol-2′-yl)-2,3-dihydrobenzo[b] [1,5] thiazepin-2(1*H*)-one-*S*,*S*-dioxide **8**. This latter compound **8** was obtained from the base-catalyzed condensation of CS_2 and MeI with 4-(1′,3′,4′-oxadiazol-2′-yl)-2,3-dihydrobenzo[b] [1,5] thiazepin-2(1*H*)-one-*S*,*S*-dioxide (**7**). Compound **7** was available from ethyl-2-oxo-2,3,4,5-tetrahydro-[1,5]-benzothiazepin-4-carboxylate (**3**) on applying established synthetic procedures, which had been previously employed in the literature on related substrates. Treatment of **8** with the anions derived from substituted acetophenones formed the diones which underwent facile cyclocondensation with NH_4OAc in AcOH to yield the desired products **9a**–**9f** in acceptable yields.



Keywords: 1,5-benzothiazepine; 1,5-benzothiazepin-*S*,*S*-dioxide; oxadiazole; oxoketenedithioacetals; pyridobenzothiazepine

1. Introduction

Ever since the pyridine ring-annulated analog of 1,4-pyridodiazepine (the Nevirapine (*1a*); Figure 1) received food and drug administration approval for its application in the treatment of AIDS and in the combination therapy used in highly active anti-retroviral therapy [HAART] (*2*), the interest on the various facets of the chemistry of pyridine-incorporated derivatives of 1,4-

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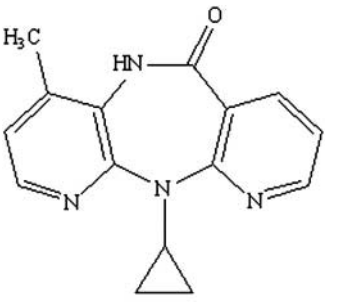


(A)

Figure 1. Nevirapine.

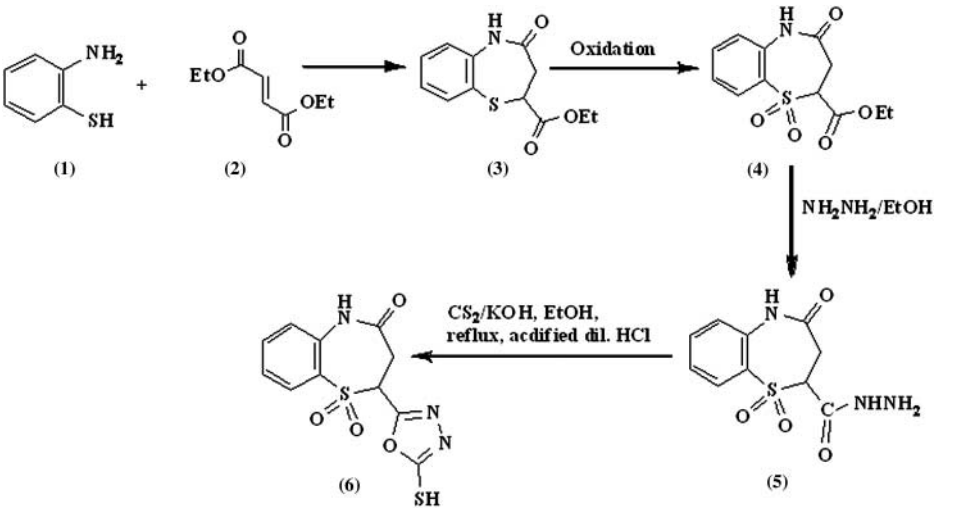
and 1,5-benzo (pyrido) diazepines and thiazepines has expanded exponentially. It triggered the development of synthetically acceptable protocols for the annulations of the pyridine nucleus onto heterocyclic scaffolds of medicinal importance.

Advent of impressive anti-HIV activity of molecules containing the oxadiazole (*3*) nucleus has also recently attracted the attention of chemists, in the quest of developing bioactive materials from this nucleus.

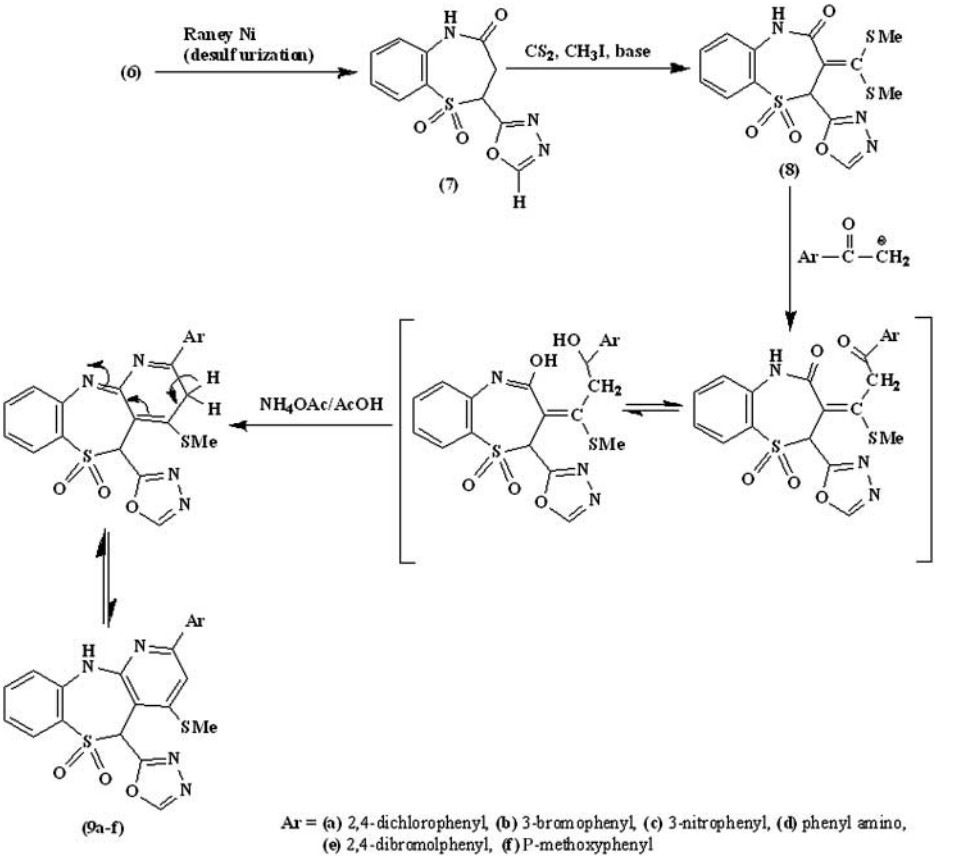
A perusal of literature (*4*) on 1,5-benzothiazepine and their *S*,*S*-dioxide derivatives revealed that no attempt has been made to examine the feasibility of the annulation of face 'b' of these molecules with the pyridine nucleus. This prompted us to undertake a study on the synthesis of face 'b' pyrido-annulated analogs of 1,5-benzothiazepin-*S*,*S*-dioxide substituted with an oxadiazole nucleus at the 4-position on the premise that their presence in tandem in the same molecule, would in all probability, provide a significant contribution to the biological efficacies of the resulting molecules.

2. Results and discussion

Our interest in the synthesis of the 1,5-benzothiazepin-*S*,*S*-dioxide nucleus annulated on its face 'b' with a pyridine ring and substituted at its 4-position with an oxadiazole nucleus, **9a**–**9f**, inspired us to examine the potential of an oxoketene dithioacetal synthon appended on **8** as a precursor of a pyridine ring. In addition, we were also interested in simultaneously exploiting a carboxylic ester substituent in the same synthetic route for the incorporation of an oxadiazole nucleus. The synthetic plan which was conceived to achieve this goal envisioned **6** to be the most suitable starting material (Scheme 1) from which **9a**–**9f** were thought to emerge in three operations overall (Scheme 2). The first stage of the strategy to produce the starting material **6** involved the cyclocondensation of *o*-aminothiophenol (**1**) with maleic or (alternatively) fumaric acid esters (*5*) **2** followed by oxidation of the resulting 1,5-benzothiazepine nucleus **3** with H_2O_2 (AcOH) (*6*) to give **4** in 76% yield (Scheme 1). The second phase of the strategy to produce **6** involved the reaction of **4** with hydrazine hydrate (*7*) to afford the corresponding hydrazide derivative **5** which in turn, upon its reaction with CS_2 and KOH followed by acid treatment (*8*), gave oxadiazole derivative **6** in 78% yield. The structural assignments of compounds **3**–**5** were based on their elemental analysis, IR, ^{1}H NMR and mass spectral data. The formation of **4** from **3** was indicated by the IR spectrum of **4** that showed the absorption for the SO_2 group at 1320 and 1128 cm^{-1}, respectively. MS data for **4** agreed well with the sulfone structure since it exhibited a distinct peak for M^+-64 due to extrusion of SO_2. Analytical and spectral data of **3**–**6** unequivocally established their structures.



Scheme 1. Synthesis of 4-(oxadiazolyl)-substituted 1,5-benzothiazepin-*S*,*S*-dioxide.



Scheme 2. Synthesis of face 'b' pyridine-annulated 1,5-benzothiazepin-*S*,*S*-dioxide derivatives.

Table 1. Physical data of compounds **9a–9f**

Compound	Ar	MP (°C)	Yield (%)	Molecular formula (MW)
9a	2,4-Dichlorophenyl	130–132	70	$C_{21}H_{14}Cl_2N_4O_3S_2$(504.00)
9b	3-Bromophenyl	139–140	75	$C_{21}H_{15}BrN_4O_3S_2$ (514.00)
9c	3-Nitrophenyl	145–147	70	$C_{21}H_{15}N_5O_5S_2$ (481.50)
9d	Phenyl amino	110–112	79	$C_{21}H_{17}N_5O_3S_2$ (451.52)
9e	2,4-Dibromolphenyl	120–122	65	$C_{21}H_{14}Br_2N_4O_3S_2$ (592.20)
9f	*p*-Methoxyphenyl	155–156	80	$C_{22}H_{18}N_4O_4S_2$ (466.53)

The synthetic potential of oxoketene dithioacetals in heterocyclic synthesis has been well established in the literature (*9*). We made use of its versatility in order to devise an elegant strategy to generate the pyridine ring on face 'b' of the 1,5-benzothiazepine nucleus by adopting the sequence of reactions outlined in Scheme 2. The strategy that allowed annulation of **6** with a pyridine nucleus proceeded with the desulfurization (*10*) of **6** with Raney Ni to give **7** in 74% yield. The reaction of **7** with CS_2 and CH_3I (*11*) in the presence of NaOEt afforded the key oxoketene dithioacetal intermediate **8** in 66% yield which reacted smoothly with the anions of several substituted acetophenones to give the 1,5-dione intermediates whose reaction *in situ* with $NH_4OAc/AcOH$ (*12*) furnished the desired pyridine-annulated 1,5-benzothiazepine analogs **9a–9f** in 70–80% yield. The structural assignments of compounds **7**, **8** and **9a–9f** have been based on their elemental analysis, IR, ^1H NMR and mass spectral data. The MS data were in agreement with structure **9a** which exhibited a distinct pattern (*13*) in the presence of two chlorine atoms. In a similar manner, the structures of compounds **9b–9f** were established on the basis of their elemental and spectral data. The physical data for the compounds are presented in Table 1.

3. Conclusion

The discovery of the exceedingly high anti-HIV potency-enhancing effect of the pyridine nucleus in 'Nevirapine' prompted us to explore the possibility of its incorporation into the 1,5-benzothiazepine nucleus. We made use of the versatility of the oxoketene dithioacetal substituent appended on a 1,5-benzothiazepine nucleus to devise an elegant plan for its annulation onto the pyridine ring. The biological evaluation of these materials is in progress.

4. Experimental

Melting points were determined in open glass capillaries and are uncorrected. Progress of the reactions was monitored by using TLC on silica gel 'G'-coated plates using benzene:methanol (9:1). IR spectra on KBr were recorded with an FTIR-8400S, CE (Shimadzu). Mass spectra were taken on a 3000 LC/MS System. ^1H NMR spectra were recorded on a Bruker NMR model AC-300F (Bruker) using $CDCl_3$/DMSO-d_6 as the solvent. Chemical shifts are expressed in δ (ppm) relative to the signal for TMS as internal standard.

4.1. *Preparation of ethyl-2-oxo-2,3,4,5-tetrahydro-[1,5]-benzothiazepin-4-carboxylate (3)*

4.1.1. *Method A*

To *o*-aminothiophenol (**1**, 7.50 g, 0.06 mol) in dry xylene (50 ml) under reflux diethyl maleate or diethyl fumerate (**2**, 10.32 g, 0.06 mol) was added, dropwise, 20.0 ml of dry xylene for 30 min. Refluxing was continued for 15 h and about 50 ml of xylene was distilled off. The contents were

left at room temperature overnight and the product thus obtained was recrystallized from dry xylene to give **3**, 7.35 g, at 75% yield, at an m.p. of 103–105 °C.

4.1.2. *Method B*

To *o*-aminothiophenol (**1**, 7.50 g, 0.06 mol) in dry xylene (50 ml) under reflux diethyl maleate or diethyl fumerate (**2**, 10.32 g, 0.06 mol) was added, dropwise, 20 ml of dry xylene for 30 min. Refluxing was continued further for 7 h and then a pinch of anhydrous NaH was added and refluxing was continued again for 10 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, then water was added to remove NaH, the mixture was extracted with chloroform and the solvent was evaporated. The compound thus obtained was recrystallized from dry xylene to give **3**, 7.30 g, **at** 75% yield, at an m.p. of 103–105 °C.

IR (cm^{-1}): 3210 (NH), 3010 (Ar-H), 2980, 1425 ($-CH_2$ next to C=O), 1695, 1656 (C=O), 1580 (C=C), 700 (C−S−C); ^{1}H NMR (δ): 7.00–7.37 (4H, m, Ar-H), 8.00 (1H, s, NH), 3.59 (1H, t, $J = 12.7$ Hz, CH of benzothiazepine), 2.95 (2H, d, $J = 6.2$ Hz, CH_2 of benzothiazepine), 4.10 (2H, q, $J = 7.1$ Hz, CH_2 of ester), 1.29 (3H, t, $J = 7.1$ Hz, CH_3 of ester); MS: m/z 251.35 (M^+ 75%), 206.29 (100%), 178.28 (45%); Calcd. (%) for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57; S, 12.76; Found: C, 57.06; H, 5.18; N, 5.53; S, 12.70.

4.2. *Preparation of ethyl-2-oxo-2,3,4,5-tetrahydro-[1,5]-benzothiazepin-4-carboxylate-S,S-dioxide (4)*

A mixture of **3** (2.51 g, 0.01 mol) dissolved in 100 ml of glacial acetic acid and 3.50 ml of 30% hydrogen peroxide was heated for 2 h at 100 °C, and then it was evaporated to dryness. The product obtained was recrystallized from acetone to give **4**, 2.15 g, at 76% yield, at an m.p. of 145–147 °C.

IR (cm^{-1}): 3215 (NH), 3015 (Ar-H), 2985, 1420 ($-CH_2$ next to C=O), 1705, 1665 (C=O), 1585 (C=C), 1320, 1128 (SO_2); ^{1}H NMR (δ): 7.36–8.10 (4H, m, Ar-H), 8.00 (1H, s, NH), 4.05 (1H, t, $J = 12.7$ Hz, CH of benzothiazepine), 3.00 (2H, d, $J = 6.2$ Hz, CH_2 of benzothiazepine), 4.25 (2H, q, $J = 7.1$ Hz, CH_2 of ester), 1.29 (3H, t, $J = 7.1$ Hz, CH_3 of ester); MS: m/z 283.05 (M^+ 70%), 237.99 (25%), 219.12 (100%); Calcd. (%) for $C_{12}H_{13}NO_5S$: C, 50.87; H, 4.63; N, 4.94; S, 11.32; Found: C, 50.62; H, 4.61; N, 4.92; S, 11.26.

4.3. *Preparation of 2-oxo-2,3,4,5-tetrahydro-[1,5]-benzothiazepin-4-carbohydrazide-S,S-dioxide (5)*

To a solution of **4** (2.83 g, 0.01 mol) in ethanol (50 ml), hydrazine hydrate (1 ml, 0.024 mol) was added. The reaction mixture was refluxed for 10 h and the product obtained was recrystallized from ethanol to give **5**, 2.00 g, at 75% yield, at an m.p. of 182–184 °C.

IR (cm^{-1}): 3320, 3125 (NH, NH_2), 3225 (NH), 3010 (Ar-H), 2980, 1425 ($-CH_2$ next to C=O), 1700, 1658 (C=O), 1590 (C=C), 1325, 1125 (SO_2); ^{1}H NMR (δ): 7.35–8.09 (4H, m, Ar-H), 8.02 (1H, s, NH), 4.15 (1H, t, $J = 12.7$ Hz, CH of benzothiazepine), 3.05 (2H, d, $J = 6.2$ Hz, CH_2 of benzothiazepine), 8.00 (1H, s, NH), 2.00 (2H, s, NH_2, amine); MS: m/z 269.26 (M^+ 78%), 210.21 (32%), 146.15 (100%); Calcd. (%) for $C_{10}H_{11}N_3O_4S$: C, 44.60; H, 4.12; N, 15.60; S, 11.91; Found: C, 44.38; H, 4.10; N, 15.52; S, 11.85.

4.4. *Preparation of 4-(5′-mercapto-1′,3′,4′-oxadiazol-2′-yl)-2,3-dihydro-[1,5]-benzothiazepin-2(1H)-one-S,S-dioxide (6)*

To a solution of carbohydrazide (**5**, 1.88 g, 0.007 mol) in dry ethanol (50 ml), a mixture of carbon disulfide (4.50 ml, 0.06 mol) and potassium hydroxide (0.448 g, 0.008 mol) was added at 0 °C. The

resulting solution was refluxed for 46 h. After the completion of reaction (monitored by TLC), the solvent was evaporated and the mixture was suspended in water and then brought to the neutral point by adding dilute HCl. The solid obtained was filtered and recrystallized from methanol to give **6**, 1.70 g, at 78% yield, at an m.p. of 223–225 °C.

IR (cm^{-1}): 3220 (NH), 3010 (Ar-H), 2980, 1425 ($-CH_2$ next to C=O), 2750 (weak, C-SH), 1658 (C=O), 1627 (C=N), 1595 (C=C), 1340, 1235 (C=S), 1325, 1125 (SO_2), 1165 (C−O−C); ^{1}H NMR (δ): 7.37–8.10 (4H, m, Ar-H), 8.02 (1H, s, NH), 4.50 (1H, t, $J = 12.7$ Hz, CH of benzothiazepine), 3.06 (2H, d, $J = 6.2$ Hz, CH_2 of benzothiazepine), 13.05 (1H, s, aromatic C-SH); MS: m/z 311.36 (M^+ 84%), 278.29 (53%), 214.23 (100%); Calcd. (%) for $C_{11}H_9N_3O_4S_2$: C, 42.44; H, 2.91; N, 13.50; S, 20.60; Found: C, 42.23; H, 2.90; N, 13.43; S, 20.50.

4.5. *Preparation of 4-(1′,3′,4′-oxadiazol-2′-yl)-2,3-dihydrobenzo[b] [1,5] thiazepin-2(1H)-one-S,S-dioxide (7)*

4.5.1. *Method A*

Compound **6** (1.60 g, 0.005 mol) was taken in dilute ammonium hydroxide (prepared by mixing 18 ml of concentrated ammonium hydroxide with 45 ml of water) and the mixture was heated to boil. Raney Ni (2.5 g) was then added and the boiling was continued for 4 h until the initially suspending nickel catalyst settled down. It was immediately filtered and the mixture was concentrated on a steam bath. The product obtained was recrystallized from ethanol to give **7**, 1.50 g, at 74% yield, at an m.p. of 120–121 °C.

4.5.2. *Method B*

Raney Ni (6 g) was added to a solution of **6** (1.60 g, 0.005 mol) in ethanol (50 ml) and the mixture was heated at 60–70 °C for 4 h. After the completion of reaction (monitored by TLC), Raney Ni was filtered and the solvent was evaporated. The product obtained was recrystallized from ethanol to give **7**, 1.40 g, at 73% yield, at an m.p. of 120–121 °C.

IR (cm^{-1}): 3160 (NH), 3035 (Ar-H), 2980, 1425 ($-CH_2$ next to C=O), 1690 (C=O), 1627 (C=N), 1585 (C=C), 1310, 1125 (SO_2), 1165 (C−O−C); ^{1}H NMR (δ): 7.36–8.10 (4H, m, Ar-H), 8.00 (1H, s, NH), 4.55 (1H, t, $J = 12.7$ Hz, CH of benzothiazepine), 3.25 (2H, d, $J = 6.2$ Hz, CH_2 of benzothiazepine), 6.05 (1H, s, CH of oxadiazole ring); MS: m/z 279.30 (M^+ 80%), 215.21 (100%), 187.20 (65%); Calcd. (%) for $C_{11}H_9N_3O_4S$: C, 47.31; H, 3.25; N, 15.05; S, 11.48; Found: C, 47.07; H, 3.23; N, 14.97; S, 11.42.

4.6. *Preparation of 3-(bis(methylthio)methylene)-4-(1′,3′,4′-oxadiazol-2′-yl)-2,3 dihydrobenzo[b] [1,5]thiazepin-2(1H)-one-S,S-dioxide (8)*

A mixture of **7** (1.40 g, 0.005 mol) and CS_2 (0.75 ml, 0.005 mol) was added to a well-stirred and cold suspension of t-BuOK (1.30 g, 0.010 mol) in dry benzene (10 ml) and DMF (3 ml). The reaction mixture was allowed to stand at room temperature for 6 h. Methyl iodide (2 ml, 0.010 mol) was gradually added with stirring under external cooling (exothermic reaction) and the reaction mixture was allowed to stand for 5 h at room temperature with occasional shaking and then refluxed on a water bath for 4 h. The mixture was poured onto crushed ice and the benzene layer was separated. The aqueous portion was extracted with benzene and the combined extracts were washed with water, dried over anhydrous sodium sulfate and the solvent was removed by distillation. The product thus obtained was recrystallized from ethanol to give **8**, 1.25 g, at 66% yield, at an m.p. of 172–174 °C.

IR (cm^{-1}): 3160 (NH), 3045 (Ar-H), 2960 (C−H str.−CH_3), 1685 (C=O), 1630 (C=N), 1575 (C=C), 1315, 1128 (SO_2), 1160 (C−O−C), 690 (C−S); ^{1}H NMR (δ): 7.36–8.10 (4H, m, Ar-H), 8.00 (1H, s, NH), 4.96 (1H, s, CH of benzothiazepine), 2.80 [6H, s, $(CH_3)_2$ of SMe group], 6.04 (1H, s, CH of oxadiazole ring); MS: m/z 383.47 (M^+ 88%), 336.37 (100%), 289.27 (46%); Calcd. (%) for $C_{14}H_{13}N_3O_4S_3$: C, 43.85. H, 3.42; N, 10.96; S, 25.09; Found: C, 43.63; H, 3.40; N, 10.91; S, 24.96.

4.7. *Preparation of 4-(methylthio)-5-(1′,3′,4′-oxadiazol-2′-yl)-2-phenyl-5,11-dihydrobenzo[b] pyrido[2,3-e] [1,5]thiazepine-S,S-dioxide (9a–9f)*

4.7.1. *General method*

A mixture of **8** (1.14 g, 0.003 mol) was added to a solution of acetophenone (0.003 mol) and potassium *tert*-butoxide (0.7 g, 0.006 mol) in dry THF (25 ml). The solution was stirred at room temperature overnight. Next, glacial acetic acid (25 ml) and ammonium acetate (2.4 g, 0.03 mol) were added to the above solution which was then refluxed for 4 h with constant removal of THF. The solution was then cooled to 20 °C, diluted with ice (10 g) and allowed to stand for 1 h. Water (20 ml) was added and the precipitate was collected and crystallized with petroleum ether to give **9a** (1.00 g), at 70% yield, at an m.p. of 130–132 °C. The other products **9b–9f** were prepared using the same procedure.

(9a). IR (cm^{-1}): 3180 (NH), 3010 (Ar-H), 2965 (C−H str.−CH_3), 1627 (C=N), 1620–1400 (C=C aromatic and C=N str. of pyridine), 1320, 1128 (SO_2), 1165 (C−O−C), 800–600 (C−Cl), 685 (C−S); ^{1}H NMR (δ): 6.91–7.61 (4H, m, Ar-H), 4.00 (1H, s, NH), 5.56 (1H, s, CH of benzothiazepine), 6.04 (1H, s, CH of oxadiazole ring), 6.46 (1H, s, CH of pyridine), 2.53 (3H, s, CH_3 of SMe group), 7.53 (1H, s, Ar-H), 7.46 (1H, d, $J = 7.4$ Hz, Ar-H), 8.54 (1H, d, $J = 8.3$ Hz, Ar-H); MS: m/z 504.00 (M^+ 92%), 506.12 (58%), 508.18 (8.0%), 457.30 (100%); Calcd. (%) for $C_{21}H_{14}Cl_2N_4O_3S_2$: C, 49.91; H, 2.79; N, 11.09; S, 12.69; Found: C, 49.66; H, 2.78; N, 11.03; S, 12.63.

(9b). IR (cm^{-1}): 3190 (NH), 3010 (Ar-H), 2960 (C−H str.−CH_3), 1627 (C=N), 1620–1400 (C=C aromatic and C=N str. of pyridine), 1320, 1128 (SO_2), 1160 (C−O−C), 685 (C−S), 600–500 (C−Br); ^{1}H NMR (δ): 6.91–7.61 (4H, m, Ar-H), 4.00 (1H, s, NH), 5.56 (1H, s, CH of benzothiazepine), 6.04 (1H, s, CH of oxadiazole ring), 6.46 (1H, s, CH of pyridine), 2.53 (3H, s, CH_3 of SMe group), 7.97 (1H, s, Ar-H), 7.62, 7.95 (2H, d, $J = 7.6$ Hz, Ar-H), 7.43 (1H, t, $J = 7.1$ Hz, Ar-H); MS: m/z 514.00 (M^+ 84%), 516.28 (81%), 467.30 (100%); Calcd. (%) for $C_{21}H_{15}BrN_4O_3S_2$: C, 48.94; H, 2.93; N, 10.87; S, 12.44; Found: C, 48.70; H, 2.92; N, 10.82; S, 12.38.

(9c). IR (cm^{-1}): 3185 (NH), 3010 (Ar-H), 2965 (C−H str.−CH_3), 1627 (C=N), 1620–1400 (C=C aromatic and C=N str. of pyridine), 1510, 1360 (NO_2), 1320, 1128 (SO_2), 1165 (C−O−C), 690 (C−S); ^{1}H NMR (δ): 6.91–7.61 (4H, m, Ar-H), 4.00 (1H, s, NH), 5.56 (1H, s, CH of benzothiazepine), 6.04 (1H, s, CH of oxadiazole ring), 6.46 (1H, s, CH of pyridine), 2.53 (3H, s, CH_3 of SMe group), 9.16 (1H, s, Ar-H), 8.69, 8.28 (2H, d, $J = 8.3$ Hz, Ar-H), 7.80 (1H, t, $J = 7.1$ Hz, Ar-H); MS: m/z 481.50 (M^+ 91%), 434.40 (55%), 388.39 (100%); Calcd. (%) for $C_{21}H_{15}N_5O_5S_2$: C, 52.38; H, 3.14; N, 14.54; S, 13.32; Found: C, 52.12; H, 3.12; N, 14.47; S, 13.25.

(9d). IR (cm^{-1}): 3310, 3190 (NH_2, NH), 3025 (Ar-H), 2955 (C−H str.−CH_3), 1627 (C=N), 1620–1400 (C=C aromatic and C=N str. of pyridine), 1320, 1125 (SO_2), 1166 (C−O−C), 685 (C−S); ^{1}H NMR (δ): 6.91–7.61 (4H, m, Ar-H), 4.00 (1H, s, NH), 5.56 (1H, s, CH of benzothiazepine), 6.04 (1H, s, CH of oxadiazole ring), 6.46 (1H, s, CH of pyridine), 2.53 (3H, s, CH_3 of SMe group), 6.27 (2H, s, NH of C−NH), 6.61 (2H, d, $J = 6.9$ Hz, Ar-H), 8.05 (2H, d, $J = 8.3$ Hz, Ar-H); MS: m/z 451.52 (M^+ 72%), 404.42 (100%), 388.40 (30%); Calcd. (%) for $C_{21}H_{17}N_5O_3S_2$: C, 55.86; H, 3.79; N, 15.51; S, 14.20; Found: C, 55.58; H, 3.77; N, 15.43; S, 14.13.

(9e). IR (cm^{-1}): 3180 (NH), 3015 (Ar-H), 2960 (C–H str.–CH_3), 1627 (C=N), 1620–1400 (C=C aromatic and C=N str. of pyridine), 1320, 1128 (SO_2), 1165 (C–O–C), 690 (C–S), 600–500 (C–Br); ^{1}H NMR (δ): 6.91–7.61 (4H, m, Ar-H), 4.00 (1H, s, NH), 5.56 (1H, s, CH benzothiazepine), 6.04 (1H, s, CH of oxadiazole ring), 6.46 (1H, s, CH of pyridine), 2.53 (3H, s, CH_3 of SMe group), 7.63 (1H, d, J=7.4 Hz, Ar-H), 8.08 (1H, d, J=8.1 Hz, Ar-H), 8.09 (1H, s, Ar-H); MS: m/z 592.20 (M^+ 65%), 594.35 (98%), 596.35 (61%), 545.20 (100%); Calcd. (%) for $C_{21}H_{14}Br_2N_4O_3S_2$: C, 42.44; H, 2.37; N, 9.43; S, 10.79; Found: C, 42.23; H, 2.36; N, 9.38; S, 10.74.

(9f). IR (cm^{-1}): 3190 (NH), 3010 (Ar-H), 2965 (C–H str.–CH_3), 1668 (C=O), 1627 (C=N), 1620–1400 (C=C aromatic and C=N str. of pyridine), 1320, 1128 (SO_2), 1165 (C–O–C), 675 (C–S); ^{1}H NMR (δ): 6.91–7.61 (4H, m, Ar-H), 4.00 (1H, s, NH), 5.56 (1H, s, CH of benzothiazepine), 6.04 (1H, s, CH of oxadiazole ring), 6.46 (1H, s, CH of pyridine), 2.53 (3H, s, CH_3 of SMe group), 7.08 (2H, d, $J = 7.2$ Hz, Ar-H), 8.06 (2H, d, $J = 8.1$ Hz, Ar-H), 3.83 (3H, s, CH_3 of $-OCH_3$); MS: m/z 466.53 (M^+ 82%), 419.43 (45%), 374.37 (100%); Calcd. (%) for $C_{22}H_{18}N_4O_4S_2$: C, 56.64; H, 3.89; N, 12.01; S, 13.75; Found: C, 56.36; H, 3.87; N, 11.95; S, 13.68.

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