Synthesis and Hypnotic Activity of New 4-Thiazolidinone and 2-Thioxo-4,5-imidazolidinedione Derivatives

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Summary

Conveniently accessible 4-[(2-(3,4-dimethoxyphenyl)ethyl]-3-thiosemicarbazide (**2**) was converted to new 1-substituted benzylidene/furfurylidene-4-[2-(3,4-dimethoxyphenyl)ethyl]-3-thiosemicarbazides (**3**) which furnished 2-(substituted benzylidene/furfurylidene)hydrazono-3-[2-(3,4-dimethoxyphenyl)ethyl]thiazolidin-4-ones (**4**) and 1-(substituted benzylidene/furfurylidene)-amino-3-[2-(3,4-dimethoxyphenyl)ethyl]-2-thioxo-4,5-imidazolidinediones (**5**) on reaction with chloroacetic acid and oxalyl chloride, respectively. The structure of **5** was confirmed by X-ray diffraction studies performed on **5a**. **4** and **5** were evaluated for their potentiating effects on pentobarbital induced hypnosis. Most of the compounds caused remarkable increases in pentobarbital sleeping time.

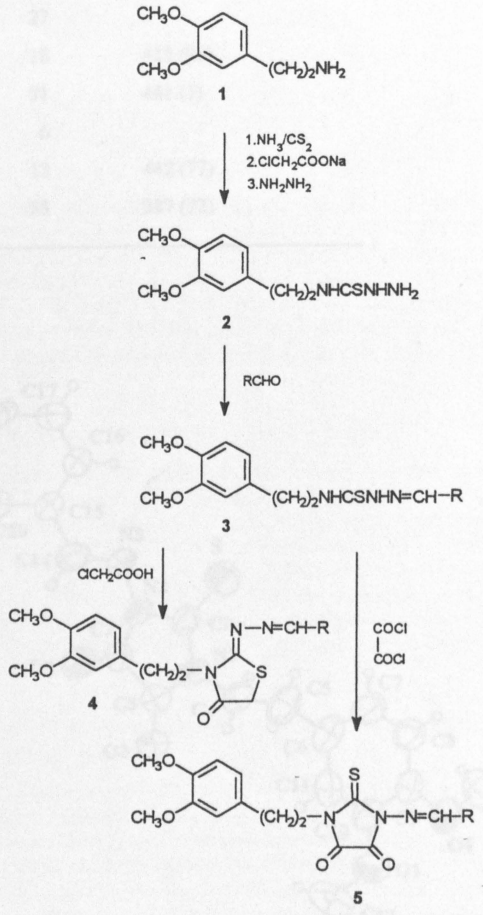
Introduction

4-Thiazolidinones are reported to possess anticonvulsant [1] and hypnotic properties [2,3]. Hypnotic activity of cyclic ureides, exemplified by barbiturates which exert their effects mainly by potentiating and/or prolonging the action of the inhibitory transmitter GABA by influencing conductance at the chloride channel associated with the GABA receptor, is well known [4,5]. We have previously reported on the anticonvulsant and hypnotic activities of 4-thiazolidinone and 2-thioxo-4,5-imidazolidinedione derivatives [6–8]. To further investigate the CNS depressant properties of these ring systems in an attempt to find new hypnotics with improved pharmacological and safety profiles, we prepared 2,3-disubstituted 4-thiazolidinones (**4**) and 1,3-disubstituted 2-thioxo-4,5-imidazolidinediones (**5**) and evaluated their potentiating effects on pentobarbital induced hypnosis.

Results and Discussion

Chemistry

The target compounds were obtained as outlined in Scheme 1. Thus 4-[(2-(3,4-dimethoxyphenyl)ethyl]-3-thiosemicarbazide (**2**) obtained from a one-pot reaction[9] was condensed with appropriate aldehydes to afford 1-substituted benzylidene/furfurylidene-4-[2-(3,4-dimethoxyphenyl)-ethyl]-3-thiosemicarbazides (**3**). Cyclization of **3** with chloroacetic acid and oxalyl chloride furnished 2-(substituted benzylidene)/furfurylidenehydrazono-3-[2-(3,4-dimethoxyphenyl)ethyl]thiazolidin-4-ones (**4**) and 1-(substituted benzylidene)/furfurylideneamino-3-[2-(3,4-dimethoxyphenyl)-ethyl]-2-thioxo-4,5-imidazolidinediones (**5**), respectively (Scheme 1 and Table 1). The structures of **3–5** were determined by spectroscopic methods (IR, ^{1}H-NMR, ^{13}C-NMR, EIMS) and elemental analysis.



Scheme 1. Synthesis of **2–5.**

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Table 1. Physicochemical and MS data of **3–5**.

Compd.	R	Molecular Formula* (MW)	Mp (°C)	Yield (%)	MS (M^+) *m/z* (%)
3a	4-BrC_6H_4	$C_{18}H_{20}BrN_3O_2S$ (422.33)	154	52	421 (53)
3b	3-ClC_6H_4	$C_{18}H_{20}ClN_3O_2S \cdot H_2O$ (395.90)	172–175	44	
3c	4-FC_6H_4	$C_{18}H_{20}FN_3O_2S$ (361.42)	164	57	361 (8)
3d	4-$COOHC_6H_4$	$C_{19}H_{21}N_3O_4S$ (387.44)	216–219	40	387 (4)
3e	2-OHC_6H_4	$C_{18}H_{21}N_3O_3S$ (359.43)	198–200	32	
3f	2-$NO_2C_6H_4$	$C_{18}H_{20}N_4O_4S$ (388.43)	160–163	44	388 (15)
3g	2-furyl	$C_{16}H_{19}N_3O_3S$ (333.39)	120–123	13	333 (42)
4a	4-BrC_6H_4	$C_{20}H_{20}BrN_3O_3S$ (462.35)	158–159	45	461 (2)
4b	3-ClC_6H_4	$C_{20}H_{20}ClN_3O_3S$ (417.90)	154–157	51	
4c	4-FC_6H_4	$C_{20}H_{20}FN_3O_3S$ (401.44)	138–139	50	401 (1)
4d	4-$COOHC_6H_4$	$C_{21}H_{21}N_3O_5S$ (427.46)	246	26	427 (2)
4e	2-furyl	$C_{18}H_{19}N_3O_4S$ (373.41)	183–185	45	373 (20)
5a	4-BrC_6H_4	$C_{20}H_{18}BrN_3O_4S$ (476.33)	176–179	16	475 (25)
5b	2-ClC_6H_4	$C_{20}H_{18}ClN_3O_4S \cdot 2.5\ H_2O$ (476.92)	187–190	33	
5c	3-ClC_6H_4	$C_{20}H_{18}ClN_3O_4S \cdot 1.5H_2O$ (458.90)	138–140	43	
5d	4-ClC_6H_4	$C_{20}H_{18}ClN_3O_4S$ (431.88)	161–163	27	
5e	4-FC_6H_4	$C_{20}H_{18}FN_3O_4S$ (415.42)	170	18	415 (96)
5f	4-$COOHC_6H_4$	$C_{21}H_{19}N_3O_6S$ (441.44)	198	91	441 (1)
5g	2-OHC_6H_4	$C_{20}H_{19}N_3O_5S \cdot 3\ H_2O$ (467.48)	190–193	6	
5h	2-$NO_2C_6H_4$	$C_{20}H_{18}N_4O_6S$ (442.43)	189–192	13	442 (77)
5i	2-furyl	$C_{18}H_{17}N_3O_5S$ (387.40)	164–166	58	387 (72)

* Satisfactory microanalysis obtained.

The IR spectra of **3** showed N-H and C=N stretching bands in the 3367–3115 and 1717–1592 cm^{-1} regions, respectively. Compound **3** displayed the N4-H resonance in the δ 8.10–8.69 ppm region. N2-H resonated at about δ 11.56–11.75 ppm. In **3a** and **3c** this proton exchanged with the solvent and could not be observed. The CH=N group displayed a singlet in the δ 7.97–8.59 ppm region.

The IR spectra of **4** displayed the C=O absorbance in the 1711–1721 cm^{-1} region. ^{1}H-NMR spectra supported cyclization to **4** as they displayed additional resonances assigned to the SCH_2 group of the thiazolidinone ring at about δ 3.90–4.14 ppm together with the NCH_2 triplet [6]. The CH=N proton in these structures was observed in the δ 7.86–8.72 ppm region.

New C=O peaks (1760–1785 cm^{-1}) observed in IR spectra of **5** characteristic for 2-thioxo-4,5-imidazolidinediones provided confirmatory evidence for ring closure. ^{1}H-NMR spectra supported these findings as the CH=N resonance showed a downfield shift and absorbed in the δ 8.97–9.67 ppm region [7,8] presumably due to the anisotropy of the thiocarbonyl or carbonyl groups when the molecule adopts the *E* configuration [10]. An independent proof of the correct structure of **5** was also achieved by single crystal X-ray diffraction analysis of compound **5a** (Figure 1).

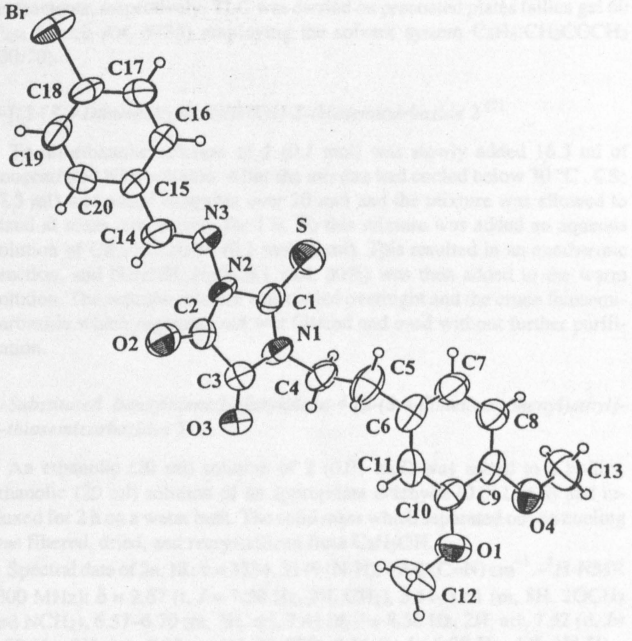

Figure 1. ORTEP diagram of **5a**.

X-Ray Structure of 5a

Technical details of the structure determination are given in the experimental part. An ORTEP [11] diagram of **5a** showing the molecular configuration and atom labeling scheme is depicted in Figure 1. The imidazole moiety deviates slightly from planarity [maximum deviation 0.035(6) Å for N2]. The S atom attached to C1 is situated –0.143(3) Å below the best-plane P1 defined by the imidazole ring atoms and the O2 and O3 atoms deviate from P1 by only –0.081(6) and 0.010(5) Å, and so lie nearly in this plane. The dihedral angles between the plane P1 and the mean plane P2 (defined by C6, C7, C8, C9, C10, C11) on one side, P1 and the mean plane P3 (C15, C16, C17, C18, C19, C20) on the other side, are respectively 169.8(4) and 149.0(2)°, while the dihedral angle between P2 and P3 is 22.8(2)°. The N3=C14 bond in the amine group [1.267(8) Å] is slightly shortened by comparison with a normal Csp^2=N distance (1.28 Å). The interatomic distances for the C-N bonds in the imidazole moiety are in the range 1.35–1.41 Å . Introduction of several substituents on the imidazole ring adds steric and electronic effects and causes further distortion of the ring structure. The torsion angles C1-N1-C4-C5 and C1-N2-N3-C14 are 90.5(8) and 152.6(7) °.

Pharmacology

The hypnotic activity of **4** and **5** was evaluated by determination of their potentiating effects on pentobarbital induced hypnosis in mice [12]. When administered at a dose of 100 mg/kg the test compounds did not induce any drowsiness, ataxia, or sleep. The duration of sleep in pentobarbital sodium injected control mice (equivalent to pentobarbital base, 40 mg/kg) was 8.20 ± 3.70 min. As can be seen in Table 2, the majority of the compounds prolonged pentobarbital sleeping time significantly. The most active compounds were **4d** and **4e** the 4-$COOHC_6H_4$ and the 2-furyl substituted derivatives. Compounds **4c**, **5c**, **5d**, and **5f** (4-FC6H4, 3-ClC_6H_4, 4-ClC_6H_4, and 4-$COOHC_6H_4$ substituted entries, respectively) also caused remarkable enhancements in pentobarbital induced hypnosis. Although no clear correlation between structure and activity emerged from compounds **4** or **5**, the active compounds may be regarded as promising sedative-hypnotic candidates which may lead to compounds that approximate the ideal sedative-hypnotic after structural modification keeping in mind the importance of the 4-$COOHC_6H_4$ group which is represented by potent compounds in both series.

Acknowledgements

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Table 2. Potentiating effects of **4** and **5** on pentobarbital induced hypnosis.

Compound	Sleeping Time (min) Mean ± SE
4a	2.57 ± 2.50
4b	12.71 ± 5.10
4c	30.00 ± 8.00
4d	68.50 ± 12.10
4e	51.30 ±7.70
5a	26.20 ± 5.66
5b	23.20 ± 8.00
5c	38.30 ± 7.09
5d	30.60 ± 2.67
5e	19.20 ± 6.69
5f	37.00 ± 7.30
5g	15.30 ± 4.80
5h	26.20 ± 7.20
5i	13.20 ± 5.30
Control	8.20 ± 3.70

Experimental Part

Chemistry

Melting points were determined with a Büchi (Tottoli) melting point apparatus in open capillaries and are uncorrected. IR (KBr), ^{1}H-NMR, ^{13}C-NMR (proton decoupled-DEPT135) ([d_6]DMSO)*, and mass spectra were recorded on a Perkin-Elmer 1600 FT-IR, Bruker AC 200 (200 MHz), ARX-300 (^{1}H: 300 MHz, ^{13}C: 75.5 MHz) and VG Zab Spec (EI, 70eV) instruments, respectively. TLC was carried on precoated plates (silica gel 60 F_{254} Merck Art. 5735) employing the solvent system C_6H_6:CH_3COCH_3 (30:70).

4-[(2-(3,4-Dimethoxyphenyl)ethyl]-3-thiosemicarbazide **2** [9]

To an ethanolic solution of **1** (0.1 mol) was slowly added 16.5 ml of concentrated NH_3 solution. After the mixture had cooled below 30 °C , CS_2 (7.5 ml) was added dropwise over 20 min and the mixture was allowed to stand at room temperature for 1 h. To this mixture was added an aqueous solution of $ClCH_2COONa$ (0.1 mol/20 ml). This resulted in an exothermic reaction, and $NH_2NH_2.H_2O$ (0.1 mol, 80%) was then added to the warm solution. The reaction mixture was cooled overnight and the crude thiosemicarbazide which separated out was filtered and used without further purification.

1-Substituted Benzylidene/furfurylidene-4-[2-(3,4-dimethoxyphenyl)ethyl]-3-thiosemicarbazides **3**

An ethanolic (20 ml) solution of **2** (0.01 mol) was added to a boiling ethanolic (20 ml) solution of an appropriate aldehyde (0.011 mol) and refluxed for 2 h on a water bath. The solid mass which separated out on cooling was filtered, dried, and recrystallized from C_2H_5OH.

Spectral data of **3a**: IR: ν = 3334, 3149 (N-H), 1700 (C=N) cm^{-1}.–^{1}H-NMR (300 MHz): δ = 2.67 (t, *J* = 7.50 Hz, 2H, CH_2), 3.51–3.61 (m, 8H, 2OCH_3 and NCH_2), 6.57–6.70 (m, 3H, ar), 7.41 (d, *J* = 8.50 Hz, 2H, ar), 7.52 (d, *J*= 8.50 Hz, 2H, ar), 7.83 (s, 1H, N=CH), 8.34 (t, *J*= 5.80 Hz, 1H, N4-H).–^{13}C-NMR: δ = 34.6 (CH_2), 45.4 (NCH_2), 55.7 (OCH_3), 112.3 (=CH), 112.8

* Some =CH and/or C=C signals coincided.

(=CH), 120.8 (=CH), 123.3 (C=C), 130.2 (=CH), 132.0 (=CH), 133.8 (C=C), 140.9 (CH=N), 147.6 (C=C); 147.9 (C=C), 149.0 (C=C), 171.3 (C=S).– MS *m/z* (%): 423 $[M+2]^+$ (52), 421 $[M^+]$ (53), 242, 240 (25, 25), 238 (48), 224 (7), 206 (9), 196 (13), 191 (12), 184, 182 (33, 34), 165 (95), 164 (95), 157, 155 (24, 24), 151 (100), 149 (60), 137 (18), 121 (22), 107 (29), 103 (24), 91 (24), 89 (30), 77 (21), 65 (17).

Spectral data of **3c**: IR: ν = 3337, 3148 (N-H), 1706 (C=N) cm^{-1}.– ^{1}H-NMR (300 MHz): δ = 3.04 (t, *J* = 7.90 Hz, 2H, CH_2), 3.89–3.96 (m, 8H, $2OCH_3$ and NCH_2), 6.98–7.09 (m, 3H, ar), 7.45 (t, *J* = 8.90 Hz, 2H, ar), 8.03 (dd *J* = 8.60 Hz, 5.70 Hz, 2H, ar), 8.23 (s, 1H, N=CH), 8.69 (t, 1H, N4-H).– ^{13}C-NMR: δ = 34.6 (CH_2), 45.4 (NCH_2), 55.7 (OCH_3), 55.8 (OCH_3), 112.5 (=CH), 115.6 (=CH), 115.9 (=CH), 120.5 (=CH), 129.4 (=CH), 130.8 (C=C), 131.7 (C=C), 140.7 (CH=N), 147.4 (C=C), 148.7 (C=C), 177.0 (C=S).– MS *m/z* (%): 361 $[M^+]$ (8), 245 (13), 238 (4), 180 (2), 165 (14), 164 (100), 152 (7), 151 (14), 149 (11), 122 (6), 107 (7), 95 (6), 91 (6), 77 (6).

Spectral data of **3g**: IR: ν = 3283, 3136 (N-H), 1619 (C=N) cm^{-1}.– ^{1}H-NMR (200 MHz): δ = 2.83 (t, *J* = 7.30 Hz, 2H, CH_2), 3.72–3.80 (m, 8H, $2OCH_3$ and NCH_2), 6.62 (dd, *J* = 3.18, 1.70 Hz, 1H, furan H4), 6.73–6.90 (m, 4H, furan H3 and ar), 7.79 (d, *J* = 1.10 Hz, 1H, furan H5), 7.97 (s, 1H, N=CH), 8.10 (t, *J* = 5.60 Hz, 1H, N4-H), 11.40 (s, 1H, N2-H).– MS *m/z* (%): 333 $[M^+]$ (41), 298 (18), 238 (33), 244 (4), 206 (7), 196 (9), 180 (5), 164 (100), 151 (57), 135 (7), 121 (14), 108 (27), 94 (21), 80 (27), 65 (7).

2-(Substituted Benzylidene/furfurylidene)hydrazono-3-[2-(3,4-dimethoxyphenyl)ethyl]thiazolidin-4-ones **4**

3 (0.005 mol), $ClCH_2COOH$ (0.005 mol), and CH_3COONa (0.0075 mol) were suspended in CH_3COOH (14 ml), and refluxed for 3–6 h on a water bath. The reaction mixture thus obtained was poured over ice-water and refrigerated overnight. The solid mass which separated out was filtered, washed with H_2O, and recrystallized from C_2H_5OH or washed with C_2H_5OH.

Spectral data of **4a**: IR: ν = 1711 (C=O) cm^{-1}.– ^{1}H-NMR (300 MHz): δ = 2.90 (t, 2H, CH_2), 3.70 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.90–4.00 (m, 4H, NCH_2 and SCH_2), 6.70–6.90 (m, 3H, ar), 7.65–7.77 (m, 4H, ar), 8.50 (s, 1H, N=CH).– ^{13}C-NMR: δ = 32.5 (CH_2/SCH_2), 32.6 (CH_2/SCH_2), 44.4 (NCH_2), 56.0 (OCH_3), 112.3 (=CH), 112.5 (=CH), 113.0 (=CH), 121.1 (=CH), 130.1 (=CH), 130.8 (=CH), 131.0 (C=C), 132.5 (=CH), 148.0 (C=C), 157.1 (CH=N), 162.2 (C=C), 164.4 (C=C), 165 (C=N), 172.4(C=O).– MS *m/z* (%): 463 $[M+2]^+$ (2), 461 $[M^+]$ (2), 183, 181 (2,2), 165 (22), 164 (100), 151 (13), 149 (17), 121 (5), 107 (5), 103 (5), 91 (5), 89 (7), 78 (70), 63 (79).

Spectral data of **4c**: IR: ν = 1721 (C=O) cm^{-1}.– ^{1}H-NMR (300 MHz): δ = 3.08 (t, *J* = 7.50 Hz, 2H, CH_2), 3.91 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.09–4.14 (m, 4H, NCH_2 and SCH_2), 6.91–7.08 (m, 3H, ar); 7.52 (t, *J* = 7.80 Hz, 2H, ar), 8.06 (t, *J* = 7.80 Hz, 2H, ar), 8.72 (s, 1H, N=CH).– ^{13}C-NMR: δ = 32.3 (CH_2/SCH_2), 32.4 (CH_2/SCH_2), 44.1 (NCH_2), 55.8 (OCH_3), 112.3 (=CH), 112.8 (=CH), 116.1 (=CH), 116.4 (=CH), 120.9 (=CH), 130.2 (=CH), 130.8 (=CH), 131.0 (C=C), 147.8 (C=C), 149.0 (C=C), 156.8 (CH=N), 162.2 (C=C), 164.4 (C=C), 165.0 (C=N), 172.2 (C=O).– MS *m/z* (%): 401 $[M^+]$ (1), 200 (1), 165 (11), 164 (100), 151 (6), 149 (10), 121 (4), 107 (6).

Spectral data of **4e**: IR: ν = 1725 (C=O) cm^{-1}.– ^{1}H-NMR (200 MHz): δ = 2.91 (t, *J* = 7.50 Hz, 2H, CH_2), 3.71 (s, 6H, $2OCH_3$), 3.93–4.06 (m, 4H, NCH_2 and SCH_2), 6.67–6.89 (m, 4H, furan H4 and ar), 7.35 (d, *J* = 3.30 Hz, 1H, furan H3), 7.86 (s, 2H, furan H5 and N=CH).– MS *m/z* (%): 373 $[M^+]$ (20), 278 (2), 264 (4), 257 (7), 222 (2), 209 (6), 186 (10), 179 (4), 165 (100), 151 (70), 149 (85), 135 (14), 121 (35), 108 (15), 107 (31), 94 (29), 91 (34), 80 (10), 77 (25), 70 (5), 65 (10).

1-(Substituted Benzylidene/furfurylidene)amino-3-[2-(3,4-dimethoxyphenyl)-ethyl]-2-thioxo-4,5-imidazolidinediones **5**

Compound **3** (0.0035 mol) was suspended in anhydrous $C_2H_5OC_2H_5$ (30 ml). To this suspension oxalyl chloride (0.007 mol) was added and the reaction mixture was refluxed for 2–6 h on a water bath at 60 °C with constant stirring. The solid mass thus obtained was filtered, washed with petroleum benzene to remove excess oxalyl chloride, dried and purified by recrystallization from C_2H_5OH , $C_2H_5OH/CHCl_3$ or washing with $C_2H_5OC_2H_5$.

Spectral data of **5a**: IR: ν = 1769 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz): δ = 2.69 (t, *J* = 7.60 Hz, 2H, CH_2), 3.53 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.84 (t, *J* = 7.90 Hz, 2H, NCH_2), 6.56–6.70 (m, 3H, ar), 7.58 (d, *J* = 8.40 Hz, 2H, ar), 7.68 (d, *J* = 8.40 Hz, 2H, ar), 8.97 (s, 1H, N=CH). ^{13}C-NMR: δ = 32.3 (CH_2), 42.6 (NCH_2), 55.3 (OCH_3), 111.9 (=CH), 112.3 (=CH), 120.4 (=CH), 129.0 (C=C), 130.0 (=CH), 131.6 (C=C), 132.1 (=CH), 147.4 (C=C), 148.6 (C=C), 151.6 (C=C), 154.5 (C=S/C=O), 160.8 (CH=N), 178.2 (C=S/C=O).– MS *m/z* (%): 477 $[M+2]^+$ (25), 475 $[M^+]$ (25), 294 (10), 264 (5), 222 (1), 206 (2), 184, 182 (6), 165 (25), 164 (100), 151 (61), 149 (20), 135 (4), 121 (6), 107 (10),103 (6), 91 (8), 89 (10),78 (27), 63 (30).

Spectral data of **5e**: IR: ν = 1772 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz): δ = 2.88 (t, *J* = 7.55 Hz, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 4.04 (t, *J* = 7.50 Hz, 2H, NCH_2), 6.76–6.90 (m, 3H, ar), 7.40 (t, *J* = 8.35 Hz, 2H, ar), 8.00 (t, *J* = 8.30 Hz, 2H, ar), 9.13 (s, 1H, N=CH).– ^{13}C-NMR: δ = 32.8 (CH_2), 43.0 (NCH_2), 55.8 (OCH_3), 112.3 (=CH), 112.8 (=CH), 116.6 (=CH), 116.9 (=CH), 120.9 (=CH), 129.4 (C=C), 130.5 (C=C), 131.2 (=CH), 131.3 (=CH), 147.9 (C=C), 149.1 (C=C), 152.1 (C=C), 155.0 (C=S/C=O), 161.9 (CH=N), 178.7 (C=S/C=O).– MS *m/z* (%): 415 $[M^+]$ (96), 294 (12), 264 (15), 222 (3), 206 (8), 181 (3), 165 (63), 164 (75), 151 (100), 149 (48), 135 (11), 122 (20), 121 (27), 108 (25), 107 (32), 103 (16), 91 (19), 78 (50), 63 (47).

Spectral data of **5i**: IR: ν = 1772 (C=O) cm^{-1}.– ^{1}H-NMR (200 MHz): δ = 2.88 (t, *J* = 7.43 Hz, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.03 (t, *J* = 7.43 Hz, 2H, NCH_2), 6.74–6.90 (m, 4H, furan H4 and ar), 7.33 (d, *J* = 3.40 Hz, 1H, furan H3), 8.03 (s, 1H, furan H5), 8.92 (s, 1H, N=CH).– MS *m/z* (%): 387 $[M^+]$ (70), 371 (5), 309 (2), 294 (13), 264 (33), 222 (2), 206 (5), 193 (3), 164 (100), 151 (74), 135 (7), 121 (15), 107 (20), 91 (20), 77 (8), 65 (7).

Crystal Data and X-Ray Structure Analysis of **5a**

A yellow prismatic crystal of $C_{20}H_{18}N_3O_4SBr$ with approximate dimensions of 0.30 × 0.008 × 0.64 mm was used for all X-ray experiments which were carried out on Enraf-Nonius CAD4 diffractometer at 293 K with MoKα radiation (λ = 0.71073Å). The lattice parameters of the crystal were refined using 24 reflections in the range θ = 8–18. The data collection with ω–2θ scan between θ = 2–25 resulted in 4081 intensity values. During the collections three intensity control reflections were monitored every 2 h, showing no loss of intensity. The data were corrected for absorption using the ψ-scan data. The structure was solved by direct methods using SIR in MolEN [13]. Refinements were carried out by full-matrix least square techniques and non-hydrogen atoms were anisotropically refined. All H atoms were geometrically located 0.95 Å from their parent atoms and included using a riding model; displacement parameters were fixed at 1.3 U_{eq} of the parent atoms. The current *R* factor was 0.047 and weighted factor *wR* 0.052. The data for **5a** were as follows : $C_{20}H_{18}N_3O_4SBr$, M_r = 476.36, *a* = 15.138(2), *b* = 7.422(1), *c* = 19.649(1) Å, β = 109.33 (1), *V* = 2082.9(3) $Å^3$, *Z* = 4, space group = P 2_1/c, monoclinic, D_c = 1.52 g cm^{-3}, μ = 20.8 cm^{-1}, *F*(000) = 968, *R*(*F*) = 0.047, *wR* = 0.052, *S* = 0.71. The refinement of the structure used 1818 observed reflections [$I > 2(I)$]. Parameters refined = 262 ; final $(\Delta\sigma)_{max}$ = 0.000. Δρ in the final difference map within +0.52 and –0.243 e $Å^{-3}$. Supplementary data on final atomic coordinates, equivalent isotropic thermal parameters for all non-hydrogen atoms and selected geometric parameters may be obtained from the authors on request.

Potentiation of Pentobarbital Induced Hypnosis

The method of winter[12] was employed to investigate the ability of **4** and **5** to potentiate pentobarbital induced hypnosis. Male BALB-c mice, weighing 20–25 g were divided into groups of ten animals. One group was used for each compound, and one for the control. The test compounds were suspended in % 0.5 carboxymethylcellulose (CMC) to give a concentration of % 1 (*w/v*) and were injected to the animals at a dose of 100 mg/kg ip 1 h prior to the injection of pentobarbital sodium (equivalent to pentobarbital base 40 mg/kg/H_2O). The animals were observed for sleep as evidenced by the loss of the righting reflex. The degree of potentiation produced by the test compounds was calculated by the mean sleeping time observed in mice.

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