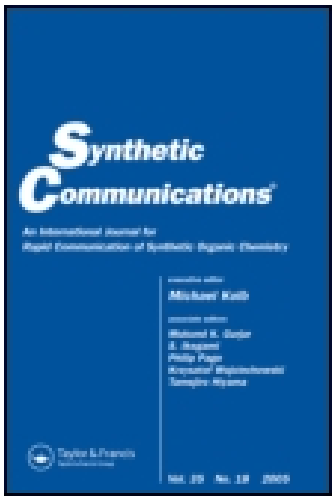

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 29 Jun 2011.

To cite this article: Elena Bâcu , Axel Couture & Pierre Grandclaudon (2003) Synthesis and Characterization of 2,2-Disubstituted-5-(2-phenothiazin-10-ylethyl)-2,3-dihydro-1,3,4-oxadiazoles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:1, 143-151, DOI: 10.1081/SCC-120015570

To link to this article: http://dx.doi.org/10.1081/SCC-120015570

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SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 1, pp. 143–151, 2003

Synthesis and Characterization of 2,2-Disubstituted-5-(2-phenothiazin-10-ylethyl)-2,3-dihydro-1,3,4-oxadiazoles

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ABSTRACT

A variety of heterocyclic hybrids **3** linking 2,3-dihydro-1,3,4-oxadiazoles and phenothiazine has been successfully prepared by cyclization of the corresponding acylhydrazones **2**.

Key Words: Phenothiazine; Acylhydrazones; Cyclization; Oxadiazolines.

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DOI: 10.1081/SCC-120015570 0039-7911 (Print); 1532-2432 (Online)

In the framework of our systematic studies dealing with the synthesis[1,2] and the biological evaluation[3] of five-membered nitrogen containing heterocycles connected to the N atom of a phenothiazine unit through a two carbon atom chain, we planned to synthesize the heterocyclic hybrids **3** linking 2,3-dihydro-1,3,4-oxadiazoles and phenothiazine. Interestingly a variety of differently substituted oxadiazole and oxadiazoline derivatives have been found to exhibit H_2 antagonistic properties[4] as well as moderate or low antimicrobial activities.[5–10] Generally the oxadiazoline framework is built via the cyclization of the corresponding acylhydrazones by refluxing in acid anhydrides or chlorides[11–13] and most of the acylhydrazone derivatives are prepared by condensation of hydrazides with aldehydes.

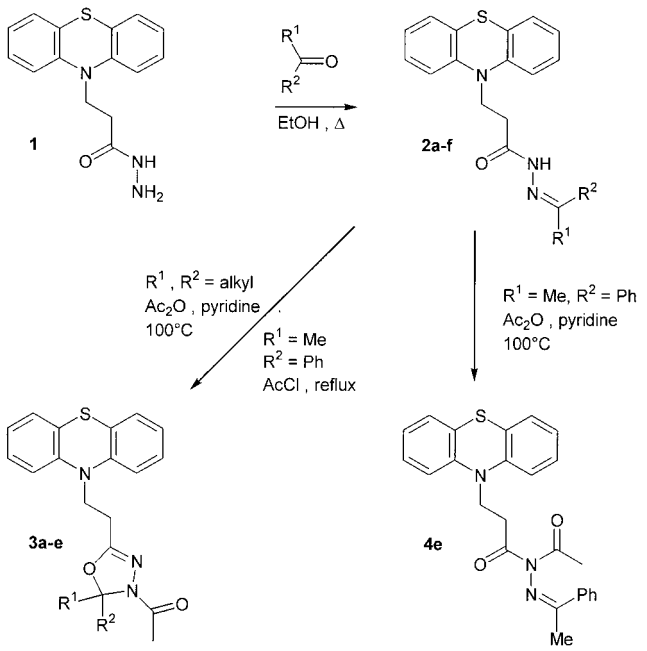
In order to achieve the construction of 2,2-disubstituted or spiro union containing oxadiazolines, hydrazide **1**, deriving from 3-(10*H*-phenothiazin-10-yl)propionic acid,[14] was initially condensed with a variety of aliphatic and aromatic ketones to give rise to acylhydrazones **2a**–**f**. Acetic anhydride in pyridine was successfully used as the electrophilic agent to ensure the ring closure of aliphatic ketone hydrazones **2a**–**d** thus delivering the desired oxadiazolines **3a**–**d**. Under similar conditions the acetophenone hydrazone **2e** was converted into the diacylhydrazone **4e** but treatment of **2e** in refluxing neat acetyl chloride afforded the expected oxadiazoline **3e** (Sch. 1, Table 1).

^{1}H NMR and ^{13}C NMR spectra showed **2a**–**f** as a mixture of two rotational isomers. The two proton resonances in the δ 2.5–3.2 ppm and the δ 10.0–11.0 ppm region were attributed to the CH_2CO protons and NH proton, respectively. ^{13}C NMR displayed two C=O and two C=N characteristic resonances in the δ 165–175 ppm and δ 147–160 ppm region, respectively.

The structure of **3a**–**e** was mainly supported by ^{13}C NMR data. Besides the characteristic patterns of the carbon atoms present in the phenothiazine framework, spectra displayed the O–C=N resonance of the oxadiazoline ring in the δ 154–155 ppm region and the O–C–N resonance in the δ 99–102 ppm region in accordance with the literature reports.[9,13]

EXPERIMENTAL

Melting point determinations were carried out on a Reichert–Thermopan apparatus and were recorded uncorrected. ^{1}H and ^{13}C spectra were measured at 300 MHz and 75 MHz, respectively on a Bruker AM 300 spectrometer as solutions in DMSO-d_6 with TMS as internal standard. IR



Scheme 1.

Table 1. Data of acylhydrazones **2a**–**f**, oxadiazolines **3a**–**e** and diacylhydrazone **4e** prepared.

Product	R^1	R^2	M.p. (°C)	Yield (%)
2a	CH_3	CH_3	188–189	93
2b	CH_3	CH_3CH_2	172–173	80
2c	$C_6H_5CH_2$	$C_6H_5CH_2$	97–98	82
2d	$-(CH_2)_5-$		137–138	79
2e	CH_3	C_6H_5	175–176, Lit.[15] 172–173	62
2f[a]	C_6H_5	C_6H_5	158–159, Lit.[15] 161–162	59
3a	CH_3	CH_3	120–121	78
3b	CH_3	CH_3CH_2	85–86	52
3c	$C_6H_5CH_2$	$C_6H_5CH_2$	165–166	56
3d	$-(CH_2)_5-$		117–118	65
3e	CH_3	C_6H_5	162–163	55
4e	CH_3	C_6H_5	138–139	82

[a]Attempts to obtain **3f** were unsuccessful.

spectra were recorded on a Perkin–Elmer 881 spectrometer. Elemental analyses were determined by the CNRS microanalysis centre. For flash chromatography, Merck silica gel 60 (0.063–0.200 mm) was used.

Synthesis of 3-(10*H*-Phenothiazin-10-yl)propionic Acid Alkylidenehydrazides (2a–f). General Procedure

A solution of 3-(10*H*-phenothiazin-10-yl)propionic acid hydrazide **1** (1 g, 3.5 mmol) and an appropriate ketone (4.0 mmol) in EtOH (10 mL) was refluxed for 2 h. The solid obtained after cooling of the mixture was filtered, washed with cold EtOH and recrystallized from acetone–EtOH.

3-(10*H*-Phenothiazin-10-yl)propionic acid isopropylidenehydrazide 2a: White crystals. ^{1}H NMR (mixture of two rotational isomers 60:40) δ (ppm) 1.79 and 1.83 (3H, 2 × s, CH_3C=), 1.82 and 1.90 (3H, 2 × s, CH_3C=), 2.70 and 2.95 (2H, 2 × t, $J = 7.0$ and 7.2 Hz, CH_2CO), 4.14 (2H, m, CH_2N), 6.92–6.98 (2H, m, H_{arom}), 7.05–7.35 (6H, m, H_{arom}), 10.04 and 10.18 (1H, 2 × s, NH); ^{13}C NMR (mixture of two rotational isomers) δ (ppm) 17.1 and 17.5 (CH_3), 24.9 and 25.1 (CH_3), 30.6 and 32.1 (CH_2), 42.5 and 42.9 (CH_2), 115.3 and 115.5 (CH_{pheno}), 122.5 (CH_{pheno}), 123.0 and 123.3 (C_{pheno}), 127.1 (CH_{pheno}), 127.6 (CH_{pheno}), 144.3 and 144.4 (C_{pheno}), 150.6 and 155.1 (C=N), 166.5 and 172.3 (C=O). IR (KBr) ν (cm^{-1}) 3178, 1670. Anal. calcd for $C_{18}H_{19}N_3OS$: C, 66.43; H, 5.88; N, 12.91. Found: C, 66.34; H, 5.99; N, 12.72.

3-(10*H*-Phenothiazin-10-yl)propionic acid *sec*-butylidenehydrazide 2b: White crystals. ^{1}H NMR (mixture of two rotational isomers 60:40) δ (ppm) 0.92 and 1.00 (3H, 2 × t, $J = 7.4$ and 7.5 Hz, CH_3), 1.78 and 1.80 (3H, 2 × s, CH_3C=), 2.12 and 2.21 (2H, 2 × q, $J = 7.4$ and 7.5 Hz, CH_2C=), 2.70 and 2.97 (2H, 2 × t, $J = 7.1$ Hz, CH_2CO), 4.14 (2H, t, $J = 7.1$ Hz, CH_2N), 6.89–6.96 (2H, m, H_{arom}), 7.03–7.24 (6H, m, H_{arom}), 9.99 and 10.18 (1H, 2 × s, NH); ^{13}C NMR (mixture of two rotational isomers) δ (ppm) 10.5 and 10.8 (CH_3), 15.8 and 15.9 (CH_3), 30.5 and 31.4 (CH_2), 31.5 and 32.1 (CH_2), 42.5 and 42.9 (CH_2), 115.3 and 115.5 (CH_{pheno}), 122.4 and 122.5 (CH_{pheno}), 123.0 and 123.2 (C_{pheno}), 127.1 (CH_{pheno}), 127.6 and 127.7 (CH_{pheno}), 144.3 and 144.4 (C_{pheno}), 154.2 and 158.5 (C=N), 166.5 and 172.5 (C=O). IR (KBr) ν (cm^{-1}) 3172, 1668. Anal. calcd for $C_{19}H_{21}N_3OS$: C, 67.23; H, 6.24; N, 12.38. Found: C, 67.01; H, 6.40; N, 12.49.

3-(10*H*-Phenothiazin-10-yl)propionic acid (1-benzyl-2-phenyl-ethylidene)hydrazide 2c: White crystals. ^{1}H NMR (mixture of two rotational isomers 60:40) δ (ppm) 2.75 and 3.02 (2H, 2 × t, $J = 6.8$ and 7.0 Hz,

CH_2CO), 3.35 and 3.43 (2H, 2 × s, CH_2C=), 3.58 and 3.65 (2H, 2 × s, CH_2C=), 4.16 (2H, m, CH_2N), 6.90–6.97 (2H, m, H_{arom}), 7.02–7.33 (16H, m, H_{arom}), 10.53 and 10.72 (1H, 2 × s, NH); ^{13}C NMR (mixture of two rotational isomers) δ (ppm) 30.8 and 32.2 (CH_2), 34.1 and 34.3 (CH_2), 42.2 and 42.3 (CH_2), 42.5 and 42.8 (CH_2), 115.4 and 115.6 (CH_{pheno}), 122.6 (CH_{pheno}), 123.2 and 123.3 (C_{pheno}), 126.5 and 126.6 (CH_{Ph}), 127.1 (CH_{pheno}), 127.6 (CH_{pheno}), 128.3, 128.6, 128.7, and 128.9 (CH_{Ph}), 135.7 (C_{Ph}), 137.1(C_{Ph}), 144.4 (C_{pheno}), 152.0 and 156.5 (C=N), 167.1 and 173.0 (C=O). IR (KBr) ν (cm^{-1}) 3165, 1673. Anal. calcd for $C_{30}H_{27}N_3OS$: C, 75.44; H, 5.70; N, 8.80. Found: C, 75.68; H, 5.81; N, 9.07.

3-(10*H*-Phenothiazin-10-yl)propionic acid cyclohexylidenehydrazide 2d: White crystals. ^{1}H NMR (mixture of two rotational isomers 60:40) δ (ppm) 1.42–1.55 (6H, m, 3 × CH_2), 2.03–2.36 (4H, m, 2 × CH_2C=), 2.67 and 2.95 (2H, 2 × t, J = 6.9 Hz, CH_2CO), 4.13 (2H, t, J = 6.9 Hz, CH_2N), 6.90–6.97 (2H, m, H_{arom}), 7.04–7.24 (6H, m, H_{arom}), 10.17 and 10.36 (1H, 2 × s, NH); ^{13}C NMR (mixture of two rotational isomers) δ (ppm) 25.1 (CH_2), 25.6 and 25.7 (CH_2), 26.5 and 26.8 (CH_2), 26.8 and 27.2 (CH_2), 30.5 and 32.1 (CH_2), 34.9 and 35.1 (CH_2), 42.5 and 42.9 (CH_2), 115.3 and 115.5 (CH_{pheno}), 122.5 (CH_{pheno}), 122.9 and 123.2 (C_{pheno}), 127.1 (CH_{pheno}), 127.6 and 127.7 (CH_{pheno}), 144.3 and 144.4 (C_{pheno}), 155.9 and 160.9 (C=N), 166.6 and 172.5 (C=O). IR (KBr) ν (cm^{-1}) 3186, 1675. Anal. calcd for $C_{21}H_{23}N_3OS$: C, 69.01; H, 6.34; N, 11.50. Found: C, 68.88; H, 6.09; N, 11.57.

3-(10*H*-Phenothiazin-10-yl)propionic acid (1-phenyl-ethylidene)hydrazide 2e: White crystals. ^{1}H NMR (mixture of two rotational isomers 60:40) δ (ppm) 2.22 and 2.23 (3H, 2 × s, CH_3C=), 2.84 and 3.13 (2H, 2 × t, J = 6.9 Hz, CH_2CO), 4.21 (2H, t, J = 6.9 Hz, CH_2N), 6.88–6.99 (2H, m, H_{arom}), 7.07–7.30 (6H, m, H_{arom}), 7.32–7.45 (3H, m, H_{arom}), 7.57–7.61 and 7.76–7.80 (2H, 2 × m, H_{arom}), 10.42 and 10.65 (1H, 2 × s, NH); ^{13}C NMR (mixture of two rotational isomers 60:40) δ (ppm) 13.9 and 14.1 (CH_3), 30.5 and 32.3 (CH_2), 42.7 and 42.8 (CH_2), 115.4 and 115.6 (CH_{pheno}), 122.6 (CH_{pheno}), 123.1 and 123.3 (C_{pheno}), 126.0 and 126.3 (CH_{Ph}), 127.1 (CH_{pheno}), 127.6 and 127.7 (CH_{pheno}), 128.3 (CH_{Ph}), 128.9 and 129.2 (CH_{Ph}), 138.2 (C_{Ph}), 144.3 and 144.5 (C_{pheno}), 147.9 and 151.2 (C=N), 167.2 and 173.2 (C=O). IR (KBr) ν (cm^{-1}) 3166, 1671.

3-(10*H*-Phenothiazin-10-yl)propionic acid benzhydrylidenehydrazide 2f: White crystals. ^{1}H NMR (mixture of two rotational isomers 60:40) δ (ppm) 2.68 and 3.22 (2H, 2 × t, J = 6.8 and 6.7 Hz, CH_2CO), 4.14 and 4.25 (2H, 2 × t, J = 6.7 and 6.8 Hz, CH_2N), 6.90–7.60 (18H, m, H_{arom}), 9.37 and 10.07 (1H, 2 × s, NH); ^{13}C NMR (mixture of two rotational isomers 60:40) δ (ppm)

30.4 and 32.3 (CH_2), 42.6 and 42.8 (CH_2), 115.5 (CH_{pheno}), 122.6 (CH_{pheno}), 123.3 (C_{pheno}), 127.1 (CH_{pheno}), 127.5 and 127.7 (CH_{pheno}), 128.3, 128.4, 128.5, 128.7, 129.2, and 129.5 (CH_{Ph}), 131.8 and 132.5 (C_{Ph}), 137.1 and 137.8 (C_{Ph}), 144.4 (C_{pheno}), 150.2 and 152.7 (C=N), 167.5 and 172.4 (C=O). IR (KBr) ν (cm^{-1}) 3321, 1679.

Synthesis of 1-{2,2-Disubstituted-5-[2-(10*H*-phenothiazin-10-yl)ethyl]-1,3,4-oxadiazol-3-yl}ethanones (3a–e). General Procedure

A mixture of **2a**–**e** (1 g) acetic anhydride (1 g) and pyridine (2 g) was stirred at 100°C for 2 h. After concentration under vacuum the oily residue was poured into water and Na_2CO_3 was added (pH = 8). After extraction (Et_2O, 10 × 20 mL), drying ($MgSO_4$) and evaporation of the solvent, the crude product was purified by chromatography over a pad of silica (10 cm) with hexanes/acetone (1:1) as eluent and recrystallized from acetone–ethanol to afford oxadiazolines **3a**–**d** or diacylhydrazone **4e**. Ring closure giving rise to oxadiazoline **3e** was achieved by refluxing **2e** (1 g) in neat acetyl chloride (5 mL) for 2 h and subsequent treatment as previously described.

1-{2,2-Dimethyl-5-[2-(10*H*-phenothiazin-10-yl)ethyl]-1,3,4-oxadiazol-3-yl}ethanone (3a): White crystals. ^{1}H NMR δ (ppm) 1.49 (6H, s, CH_3C), 1.89 (3H, s, CH_3C=O), 2.70 (2H, t, J = 6.0 Hz, CH_2C=N), 4.21 (2H, t, J = 6.0 Hz, CH_2N), 6.94 (2H, t, J = 7.3 Hz, H_{arom}), 7.05–7.31 (6H, m, H_{arom}); ^{13}C NMR δ (ppm) 21.9 (CH_3), 23.7 (CH_2), 23.9 (CH_3), 42.6 (CH_2), 98.8 (O–C–N), 115.9 (CH_{pheno}), 122.7 (CH_{pheno}), 124.2 (C_{pheno}), 127.1 (CH_{pheno}), 127.6 (CH_{pheno}), 144.2 (C_{pheno}), 154.3 (C=N), 165.3 (C=O). IR (KBr) ν (cm^{-1}) 1655. Anal. calcd for $C_{20}H_{21}N_3O_2S$: C, 65.37; H, 5.76; N, 11.43. Found: C, 65.30; H, 5.88; N, 11.62.

1-{2-Ethyl-2-methyl-5-[2-(10*H*-phenothiazin-10-yl)ethyl]-1,3,4-oxadiazol-3-yl}ethanone 3b: White crystals. ^{1}H NMR δ (ppm) 0.60 (3H, t, J = 7.3 Hz, CH_3), 1.47 (3H, s, CH_3C=O), 1.74 (1H, dq, J = 14.5, 7.3 Hz, CH_2), 1.97 (3H, s, CH_3), 2.20 (1H, dq, J = 14.5, 7.3 Hz, CH_2), 2.72 (2H, t, J = 6.0 Hz, CH_2C=N), 4.20 (2H, t, J = 6.0 Hz, CH_2N), 6.94 (2H, t, J = 7.1 Hz, H_{arom}), 7.02–7.24 (6H, m, H_{arom}); ^{13}C NMR δ (ppm) 6.6 (CH_3), 21.8 (CH_3), 22.7 (CH_3), 23.6 (CH_2), 29.1 (CH_2), 42.6 (CH_2), 101.3 (O–C–N), 115.9 (CH_{pheno}), 122.6 (CH_{pheno}), 124.3 (C_{pheno}), 127.1 (CH_{pheno}), 127.6 (CH_{pheno}), 144.2 (C_{pheno}), 154.7 (C=N), 165.1 (C=O). IR (KBr) ν (cm^{-1}) 1660. Anal. calcd for $C_{21}H_{23}N_3O_2S$: C, 66.12; H, 6.08; N, 11.01. Found: C, 66.41; H, 5.87; N, 11.16.

1-{2,2-Dibenzyl-5-[2-(10*H*-phenothiazin-10-yl)ethyl]-1,3,4-oxadiazol-3-yl}-ethanone 3c: White crystals. ^{1}H NMR δ (ppm) 1.88 (3H, s, $CH_3C{=}O$), 2.34 (2H, t, $J = 6.7$ Hz, $CH_2C{=}N$), 3.75 (2H, t, $J = 6.7$ Hz, CH_2N), 3.83 (4H, s, CH_2Ph), 6.95 (2H, t, $J = 6.3$ Hz, H_{arom}), 7.02–7.28 (16H, m, H_{arom}); ^{13}C NMR δ (ppm) 21.9 (CH_3), 22.7 (CH_2), 42.4 (CH_2), 48.4 (CH_2), 102.6 (O–C–N), 115.6 (CH_{pheno}), 122.6 and 122.7 (CH_{pheno}), 124.1 and 124.2 (C_{pheno}), 126.5–127.9 (m, CH_{pheno} and CH_{Ph}), 128.9 (CH_{Ph}), 130.3 (CH_{Ph}), 134.3 and 134.6 (C_{Ph}), 144.0 (C_{pheno}), 154.5 (C=N), 165.8 (C=O). IR (KBr) ν (cm^{-1}) 1647. Anal. calcd for $C_{32}H_{29}N_3O_2S$: C, 73.96; H, 5.62; N, 8.09. Found: C, 74.13; H, 5.42; N, 8.40.

1-{3-[2-(10*H*-Phenothiazin-10-yl)ethyl]-4-oxa-1,2-diazaspiro[4.5]dec-2-en-1-yl}ethanone 3d: White crystals. ^{1}H NMR δ (ppm) 0.98–1.22 (4H, m, $2 \times CH_2$), 1.30–1.47 (4H, m, $2 \times CH_2$), 1.92 (3H, s, $CH_3C{=}O$), 2.14–2.29 (2H, m, CH_2), 2.72 (2H, t, $J = 6.0$ Hz, $CH_2C{=}N$), 4.24 (2H, t, $J = 6.0$ Hz, CH_2N), 6.94 (2H, dt, $J = 7.4$, 1.1 Hz, H_{arom}), 7.02–7.22 (6H, m, H_{arom}); ^{13}C NMR δ (ppm) 22.0 (CH_2), 22.3 (CH_2), 22.3 (CH_3), 23.8 (CH_2), 31.7 (CH_2), 42.5 (CH_2), 100.4 (O–C–N), 115.9 (CH_{pheno}), 122.7 (CH_{pheno}), 124.2 (C_{pheno}), 127.1 (CH_{pheno}), 127.6 (CH_{pheno}), 144.2 (C_{pheno}), 154.4 (C=N), 165.4 (C=O). IR (KBr) ν (cm^{-1}) 1664. Anal. calcd for $C_{23}H_{25}N_3O_2S$: C, 67.79; H, 6.18; N, 10.31. Found: C, 68.00; H, 6.45; N, 10.20.

1-{2-Methyl-5-[2-(10*H*-phenothiazin-10-yl)ethyl}-2-phenyl-1,3,4-oxadiazol-3-yl]ethanone 3e: White crystals. ^{1}H NMR δ (ppm) 1.90 (3H, s, CH_3), 1.94 (3H, s, CH_3CO), 2.81 (2H, t, $J = 5.6$, $CH_2C{=}N$), 4.23 (2H, t, $J = 5.6$, CH_2N), 6.97 (2H, t, $J = 7.4$, CH_{arom}), 7.08 (2H, d, $J = 7.9$, H_{arom}), 7.17–7.40 (9H, m, H_{arom}); ^{13}C NMR δ (ppm) 21.7 (CH_3), 22.0 (CH_3), 23.6 (CH_2), 42.4 (CH_2), 99.1 (O–C–N), 116.0 (CH_{pheno}), 122.8 (CH_{pheno}), 124.4 (C_{pheno}), 125.7 (CH_{Ph}), 127.2 (CH_{pheno}), 127.7 (CH_{pheno}), 128.0 (CH_{Ph}), 128.8 (CH_{Ph}), 139.0 (C_{Ph}), 144.3 (C_{pheno}), 154.3 (C=N), 165.1 (C=O). IR (KBr) ν (cm^{-1}) 1639. Anal. calcd for $C_{25}H_{23}N_3O_2S$: C, 69.91; H, 5.40; N, 9.78. Found: C, 70.05; H, 5.37; N, 10.01.

Acetic acid *N*-[3-(10*H*-phenothiazin-10-yl)propionyl]-*N*′-(1-phenylethylidene)hydrazide 4e: White crystals. ^{1}H NMR δ (ppm) 2.05 (3H, s, $CH_3C{=}$), 2.32 (3H, s, CH_3CO), 3.15 (2H, t, $J = 6.7$ Hz, CH_2CO), 4.21 (2H, t, $J = 6.7$ Hz, CH_2N), 6.92 (2H, dt, $J = 7.6$, 1.0, H_{arom}), 7.05 (2H, d, $J = 7.6$, H_{arom}), 4.10–7.18 (4H, m, H_{arom}), 7.43–7.54 (3H, m, H_{arom}), 7.83–7.86 (2H, m, H_{arom}); ^{13}C NMR δ (ppm) 16.7 (CH_3), 25.8 (CH_3), 34.8 (CH_2), 48.5 (CH_2), 115.6 (CH_{pheno}), 122.6 (CH_{pheno}), 123.5 (C_{pheno}), 127.1 (CH_{Ph}), 127.2 (CH_{pheno}), 127.6 (CH_{pheno}), 128.6 (CH_{Ph}), 131.4 (CH_{Ph}), 136.1 (C_{Ph}), 144.4 (C_{pheno}), 168.9 (C=N), 170.0 (C=O),

175.1 (C=O). IR (KBr) ν (cm^{-1}) 1699. Anal. calcd for $C_{25}H_{23}N_3O_2S$: C, 69.91; H, 5.40; N, 9.78. Found: C, 70.11; H, 5.63; N, 9.69.

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Received in the UK November 26, 2001

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