Tetrahedron Letters 49 (2008) 5319–5321

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A practical synthesis of new S,N-disubstituted derivatives of 5-(4-methylpiperidino)methyl-2-thiouracil

Tomasz Pospieszny *, Elżbieta Wyrzykiewicz

Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60-780 Poznan, Poland

ARTICLE INFO

Article history:
Received 11 October 2007
Revised 5 June 2008
Accepted 17 June 2008
Available online 21 June 2008

ABSTRACT

5-(4-Methylpiperidino)methyl-2-thiouracil (**1**) has been obtained via the Mannich reaction between 2-thiouracil, paraformaldehyde, and a cyclic secondary amine such as 4-methylpiperidine (4-MP) in ethanol. New *S*,*N*(1)-di-*o*-(*m*- and *p*-)bromo-(nitro-) benzyl-substituted derivatives have been synthesized successfully in the reactions of **1** with the corresponding *o*-(*m*- and *p*-)bromobenzyl bromides or *o*-(*m*- and *p*-) nitrobenzyl chlorides in DMF solution in the presence of K_2CO_3. The opposite method of synthesis, that is, the reaction between 2-*o*-(*m*- and *p*-)bromobenzylthio-1-*o*-(*m*- and *p*-)bromobenzyluracils and 2-*o*-(*m*- and *p*-)nitrobenzylthio-1-*o*-(*m*- and *p*-) nitrobenzyluracils (**8**), with paraformaldehyde and 4-methylpiperidine in ethanol failed, indicating the important role of the enol form of 2-thiouracil for the Mannich reaction to be successful.

© 2008 Elsevier Ltd. All rights reserved.

The thio analogs of pyrimidine bases, including 2-thiouracil, are minor components of t-RNA. Their S-, N-, or S,N-disubstituted analogs have shown therapeutic properties, especially antiviral, antithyroid, and antitumor activities.[1] The prototropic tautomerism of 2-thiouracil has attracted much attention in the last decade. The tautomeric equilibrium of 2-thiouracil determines its chemo- and regioselectivity, and depends on the temperature and on whether the 2-thiouracil is in solution or in the solid state.[2]

This Letter reports the synthesis and physicochemical properties of new, 5-(4-methylpiperidino)methyl-2-thiouracil (**1**), 2-*o*-(*m*- and *p*-)bromobenzylthio-1-*o*-(*m*- and *p*-)bromobenzyl-5-(4-methylpiperidino)methyluracils (**2–4**), and 2-*o*-(*m*- and *p*-) nitrobenzylthio-1-*o*-(*m*- and *p*-)nitrobenzyl-5-(4-methylpiperidino)methyluracils (**5–7**). Compound **1** was synthesized via a Mannich reaction of 2-thiouracil, paraformaldehyde, and 4-methylpiperidine. The structures of all the compounds obtained were determined by examining their ^1H and ^{13}C NMR, FT-IR, UV/VIS, EI-MS as well as ESI-MS spectra and elemental analyses.

Previously, Mannich reactions using 2-methylthio-6-methyluracil or 6-methyl-2-thiouracil with 40% formalin, glacial acetic acid, and piperidine in ethanol had given 2-methylthio-5-methylpiperidino-6-methyluracil or 6-methyl-5-methylpiperidino-2-thiouracil, respectively, in low yields.[3] An antimetabolite of thymine, 5-morpholinomethyl-2-thiouracil (MMTU), had been synthesized via the Mannich reaction of 2-thiouracil, formaldehyde, and morpholine in ethanol as a solvent.[4] We used this method, with some modifications, to prepare compound **1**.

A series of *S*,*N*(1)-di-*o*-(*m*- and *p*-)bromo-(nitro-)benzyl-substituted derivatives were synthesized regioselectively via the reaction of **1** with *o*-(*m*- and *p*-)bromobenzyl bromides or *o*-(*m*- and *p*-)-nitrobenzyl chlorides in dry DMF solution in the presence of K_2CO_3 at room temperature for 24 h (Scheme 1). These compounds were not produced from 2-*o*-(*m*- and *p*-)bromobenzylthio-1-*o*-(*m*- and *p*-)bromobenzyluracils and 2-*o*-(*m*- and *p*-)nitrobenzyl-thio-1-*o*-(*m*- and *p*-)nitrobenzyluracils (**8**), when heated with paraformaldehyde and 4-methylpiperidine in ethanol (Scheme 2).

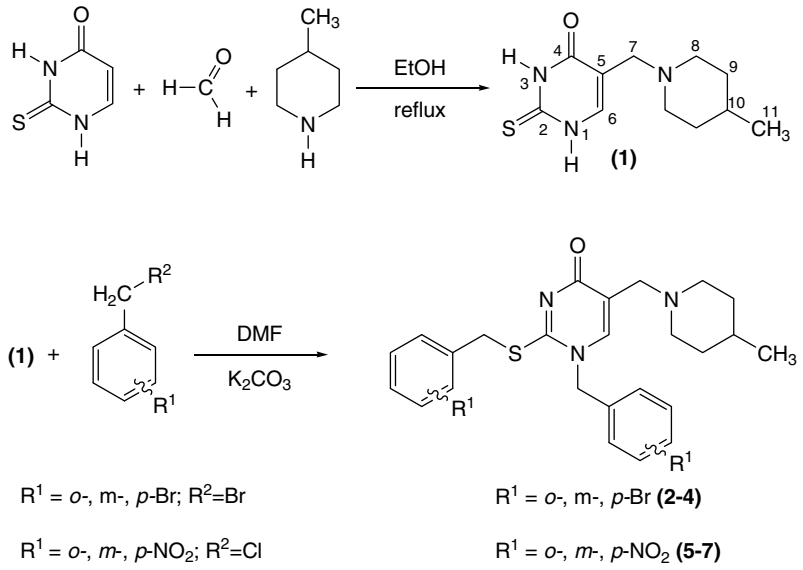
The mechanism of the well-known Mannich reaction involves nucleophilic attack of the free electrons of the nitrogen atom of 4-methylpiperidine on the carbonyl atom of formaldehyde, leading to formation of an intermediate formaldehyde-amine adduct.[5] This adduct is a very good aminomethylation agent. In the next step, the adduct reacts with the lactam-thione form of 2-thiouracil to give C-5-substituted derivatives of 2-thiouracil.[6] Compounds **8** cannot lose an N-hydrogen because the N(1) atom is substituted with an *o*-(*m*- and *p*-)bromo- or nitrobenzyl group, and this must prevent the Mannich reaction taking place.

The reaction of 5-(4-methylpiperidino)methyl-2-thiouracil (**1**) with relatively soft *o*-(*m*- and *p*-)bromobenzyl bromide electrophiles or hard *o*-(*m*- and *p*-)nitrobenzyl chloride electrophiles in DMF at room temperature led regioselectively to 2-*o*-(*m*- and *p*-)bromobenzylthio-1-*o*-(*m*- and *p*-)bromobenzyl-5-(4-methylpiperidino)methyl uracils (**2–4**) and 2-*o*-(*m*- and *p*-)nitrobenzylthio-1-*o*-(*m*- and *p*-)nitrobenzyl-5-(4-methylpiperidino)methyl uracils (**5–7**).

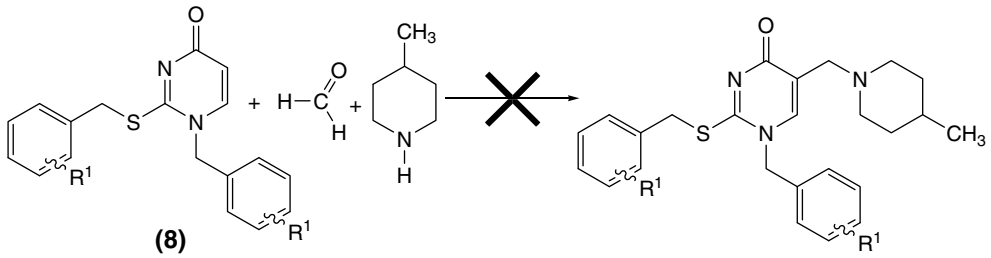
The ^1H NMR spectra of compounds **1–7** in DMSO-d_6 showed a characteristic two-hydrogen singlet in the range 3.11–3.37 ppm, assigned to the methylene protons C–CH_2–N, and a one hydrogen singlet in the range 7.23–8.59 ppm for C6–H of the 2-thiouracil

* Corresponding author. Tel.: +48 0618291252.
E-mail address: tposp@amu.edu.pl (T. Pospieszny).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.06.079



Scheme 1.



Scheme 2.

ring. The ^{1}H NMR spectra of compounds **2–7** in DMSO-d_6 showed characteristic singlets in the range 4.45–4.58 ppm and 4.91–5.21 ppm, assigned to the S–CH_2 and N1–CH_2 protons, respectively. The protons of the *o*-, *m*-, and *p*-bromo- or *o*-, *m*-, and *p*-nitrosubstituted benzyl rings gave signals in the range 7.27–8.33 ppm.

The FT-IR spectra of all the compounds in KBr tablets revealed two strong, characteristic bands in the region 1669–1641 cm^{-1} and 1587–1541 cm^{-1}, assigned to ν(C4═O) and ν(C5═C6), respectively. The most characteristic peaks in the FT-IR spectra of water-free **2–7** in KBr pellets were the bands at 2871–2863 cm^{-1}, 2951–2926 cm^{-1}, and 1448–1427 cm^{-1}, assigned to ν(N–CH_2), ν(S–CH_2), and δ(S–CH_2), respectively.

In conclusion, 5-(4-methylpiperidino)methyl-2-thiouracil (**1**) was synthesized *via* a Mannich reaction of 2-thiouracil, formaldehyde, and 4-methylpiperidine. From this, six new compounds 2-*o*-(*m*- and *p*-)bromobenzylthio-1-*o*-(*m*- and *p*-)bromobenzyl-5-(4-methylpiperidino)methyl uracils (**2–4**) and 2-*o*-(*m*- and *p*-)nitrobenzylthio-1-*o*-(*m*- and *p*-)nitrobenzyl-5-(4-methylpiperidino)methyl uracils (**5–7**) were prepared.[7]

References and notes

1. For example: (a) De Clercq, E.; Balzarini, J. *Il Farmaco* **1995**, *50*, 735–747; (b) Tanaka, H.; Takashima, H.; Ubasawa, M.; Sekiya, K.; Inouye, N.; Baba, M.; Shigeta, S.; Walker, R. T.; De Clercq, E. *J. Med. Chem.* **1995**, *38*, 2860–2865; (c) Crooks, J. In *Side Effects of Drugs*; Meyler, L., Herzheimer, A., Eds.; Expertia Medica; Elsevier: Amsterdam, 1972; p 573; (d) Barth, R. F.; Soloway, A. H.; Fairchild, R. G. *Cancer Res.* **1990**, *50*, 1061–1070; (e) Tjarks, W.; Gabel, D. *J. Med. Chem.* **1991**, *34*, 315–319; (f) Hawthorne, M. F. *Angew. Chem.* **1993**, *105*, 997–1033; (g) Nugent, R. A.; Schlachter, S. T.; Murphy, M. I.; Cleek, G. J.; Poel, T. J.; Wishka, D. G.; Graber, D. R.; Yagi, Y.; Kaiser, B. J.; Olmsted, R. A.; Kopta, L. A.; Swaney, S. M.; Poppe, S. M.; Morris, J.; Tarpley, W. G.; Thomas, R. C. *J. Med. Chem.* **1998**, *41*, 3793–3803.
2. For example: (a) Civcir, P. Ü. *J. Mol. Struct. (Theochem)* **2000**, *532*, 157–169; (b) Moustafa, H.; El-Taher, S.; Shibil, M. F.; Hilal, R. *Int. J. Quant. Chem.* **2002**, *87*, 378–381; (c) Leszczyński, J. *Int. J. Quant. Chem.: Quant. Biol. Symp.* **1991**, *18*, 9–18; (d) Leś, A.; Adamowicz, L. *J. Am. Chem. Soc.* **1990**, *112*, 1504–1509; (e) Marino, T.; Russo, N.; Sicilia, E.; Toscano, M. *J. Quant. Chem.* **2001**, *82*, 44–52; (f) Civcir, P. U. *J. Phys. Org. Chem.* **2001**, *14*, 171–179; (g) Contreras, J. G.; Alderete, J. B. *J. Phys. Org. Chem.* **1995**, *8*, 395–399; (h) Nowak, M. J.; Rostkowska, H.; Lapinski, L.; Leszczynski, J.; Kwiatkowski, J. S. *Spectrochim. Acta, Part A* **1991**, *47*, 339–353.
3. Snyder, H. R.; Foster, H. M.; Nussberger, G. A. *J. Am. Chem. Soc.* **1953**, *76*, 2441–2444.
4. Kamalakannan, P.; Venkappayya, D.; Balasubramanian, T. *J. Chem. Soc., Dalton Trans.* **2002**, 3381–3391.
5. For example: (a) Cordova, A. *Acc. Chem. Res.* **2004**, *37*, 102–112; (b) Kobayashi, S.; Ueno, M. *Comprehensive Asymmetric Catalysis*, 2004; supplement Vol. 1, pp 143–150.; (c) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; John Wiley and Sons: New York, 2001. p 1189; (d) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337; (e) Padwa, A.; Bur, S. K.; Danca, D. M.; Ginn, J. D.; Lynch, S. M. *Synlett* **2002**, 851–862; (f) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580–591.
6. Huang, Y.; Kenttämaa, H. *J. Am. Chem. Soc.* **2003**, *125*, 9878–9889.
7. (a) General procedure for the synthesis of **1**: a mixture of 2-thiouracil (12.8 g), paraformaldehyde (3.0 g), and 4-methylpiperidine (11.8 ml) was suspended in 400 ml of ethanol (99.8%) and refluxed for 48 h. The homogeneous solution obtained was filtered and concentrated on a rotary evaporator to 200 ml. The reaction mixture was kept at room temperature for 24 h. The precipitated solid was isolated by filtration, dried at room temperature, and recrystallized from methanol. (b) General procedure for the synthesis of **2–7**: a mixture of K_2CO_3 (0.17 g) and 5-(4-methylpiperidino)methyl-2-thiouracil (**1**) (0.3 g) in 10 ml of dry DMF was stirred at room temperature for 2 h. Next, to the mixture, *o*-(*m*- or *p*-)bromobenzyl bromide (0.77 g) or *o*-(*m*- or *p*-)nitrobenzyl chloride (0.53 g) was added. After stirring at room temperature for 24 h, 10 ml of distilled water was added. The reaction mixture was kept at room temperature for 24 h. The oily organic layer was separated, triturated with dry diethyl ether (20 ml), and left for 24 h in a refrigerator. The precipitate of **2–7** was collected by filtration and crystallized from methanol. The spectral and elemental data of compounds **1–7** are given below.

Compound **1**—(isolated yield 89%, mp 95–96 °C). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 3.11 (2H, s, C5–CH_2), 7.23 (1H, s, C6–H), 2.50 (4H, t, J = 12.3 Hz, N(CH_2)$_2$), 1.46 (4H, q, J = 12.3 Hz, CH_2), 1.35 (1H, m, C10–H), 0.88 (3H, d, J = 12.0 Hz, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ 174.15 (C2), 161.15 (C4), 113.90 (C5), 139.41 (C6), 52.97 (C7), 52.67 (C8), 33.96 (C9), 30.12 (C10), 21.87 (C11). FT-IR (KBr, cm^{-1}): ν(C4═O) 1652, ν(C5═C6) 1569, ν(C2═S) 1246. EI MS (*m*/*z*, % int.): 239 ($M^{+\cdot}$, 26), 98 (100). UV/Vis (CH_3OH, nm, logε): 213.5 (4.09), 273.0 (4.16). Anal. Calcd for $C_{11}H_{17}N_3OS$: C, 55.20; H, 7.16; N, 17.56; S, 13.40. Found: C, 55.23; H, 7.15; N, 17.63; S, 13.46.

Compound **2**—(isolated yield 62%, mp 185–186 °C). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 3.33 (2H, s, C5–CH_2), 8.59 (1H, s, C6–H), 2.50 (4H, t, J = 12.3 Hz, N(CH_2)$_2$), 1.72 (4H, q, J = 12.3 Hz, CH_2), 1.34 (1H, m, C10–H), 0.91 (3H, d, J = 12.0 Hz, CH_3), 4.52 (2H, s, S–CH_2), 5.21 (2H, s, N1–CH_2), phenyl ring: 7.68 (H, d, J = 7.4 Hz, C3′–H), 7.32 (H, t, J = 7.6 Hz, C4′–H), 7.27(H, t, J = 7.6 Hz, C5′–H), 7.46 (H, d, J = 7.4 Hz, C6′–H), 7.57 (H, d, J = 7.4 Hz, C3″–H), 7.29 (H, t, J = 7.6 Hz, C4″–H), 7.27 (H, t, J = 7.6 Hz, C5″–H), 7.44 (H, d, J = 7.4 Hz, C6″–H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ *165.99 (C2),* 161.14 (C4), 116.90 (C5), 152.18 (C6), 55.38 (C7), 51.93 (C8), 34.41 (C9), 30.85 (C10), 20.34 (C11), 34.41 (S–CH_2), 64.66 (N1–CH_2), phenyl ring: 134.67 (C-1′), 123.92 (C-2′), 132.78 (C-3′), 127.91 (C-4′), 130.13 (C-5′), 131.45 (C-6′), 133.03 (C-1″), 121.59 (C-2″), 132.49 (C-3″), 127.68 (C-4″), 129.92 (C-5″), 131.27 (C-6″). FT-IR (KBr, cm^{-1}): ν(C4═O) 1645, ν(C5═C6) 1541, ν(N–CH_2) 2869, ν(S–CH_2) 2926, δ(S–CH_2) 1439. EI MS (*m*/*z*, % int.): 577 ($M^{+\cdot}$, 3), 168 (100). UV/Vis (CH_3OH, nm, logε): 218.0 (4.36), 291.0 (4.16). Anal. Calcd for $C_{25}H_{27}N_3OSBr_2$: C, 52.01; H, 4.71; N, 7.28; S, 5.55. Found: C, 52.06; H, 4.78; N, 7.33; S, 5.59.

Compound **3**—(isolated yield 68%, mp 103–104 °C). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 3.34 (2H, s, C5–CH_2), 8.50 (1H, s, C6–H), 2.50 (4H, t, J = 12.3 Hz, N(CH_2)$_2$), 1.74 (4H, q, J = 12.3 Hz, CH_2), 1.39 (1H, m, C10–H), 0.91 (3H, d, J = 12.0 Hz, CH_3), 4.50 (2H, s, S–CH_2), 5.21 (2H, s, N1–CH_2), phenyl ring: 7.59 (1H, s, C2′–H), 7.41 (1H, d, J = 7.4 Hz, C4′–H), 7.28 (1H, t, J = 7.6 Hz, C5′–H), 7.33 (1H, d, J = 7.4 Hz, C6′–H), 7.49 (1H, s, C2″–H), 7.38 (1H, d, J = 7.4 Hz, C4″–H), 7.29 (1H, t, J = 7.6 Hz, C5″–H), 7.31 (1H, d, J = 7.4 Hz, C6″–H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ 165.30 (C2), 161.27 (C4), 116.80 (C5), 152.10 (C6), 55.26 (C7), 52.73 (C8), 34.14 (C9), 30.64 (C10), 20.24 (C11), 34.14 (*S*–CH_2), 65.32 (N1–CH_2), phenyl ring: 140.87 (C-1′), 131.67 (C-2′), 121.94 (C-3′), 129.84 (C-4′), 130.95 (C-5′), 128.09 (C-6′), 139.10 (C-1″), 131.33 (C-2″), 121.40 (C-3″), 129.51 (C-4″), 130.76 (C-5″), 127.07 (C-6″). FT-IR (KBr, cm^{-1}): ν(C4═O)1641, ν(C5═C6) 1541, ν(N–CH_2) 2869, ν(S–CH_2) 2927, δ(S–CH_2) 1427. EI MS (*m*/*z*, % int.): 577 ($M^{+\cdot}$, 3), 168 (100). UV/Vis (CH_3OH, nm, logε): 220.0 (4.39), 295.0 (4.15). Anal. Calcd for $C_{25}H_{27}N_3OSBr_2$: C, 52.01; H, 4.71; N, 7.28; S, 5.55. Found: C, 52.11; H, 4.68; N, 7.32; S, 5.58.

Compound **4**—(isolated yield 64%, mp 98–99 °C). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 3.33 (2H, s, C5–CH_2), 8.56 (1H, s, C6–H), 2.51 (4H, t, J = 12.3 Hz, N(CH_2)$_2$), 1.74 (4H, J = 12.3 Hz, q, CH_2), 1.39 (1H, m, C10–H), 0.91 (3H, d, J = 12.0 Hz, CH_3), 4.46 (2H, s, S–CH_2), 5.21 (2H, s, N1–CH_2), phenyl ring: 7.58 (1H, d, J = 7.2 Hz, C2′–H), 7.39 (1H, d, J = 7.2 Hz, C3′–H), 7.38 (1H, d, J = 7.2 Hz, C5′–H), 7.57 (1H, d, J = 7.2 Hz, C6′–H), 7.52 (1H, d, J = 7.2 Hz, C2″–H), 7.37 (1H, d, J = 7.2 Hz, C3″–H), 7.37 (1H, d, J = 7.2 Hz, C5″–H), 7.51 (1H, d, J = 7.2 Hz, C6″–H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ 166.14 (C2), 161.36 (C4), 117.99 (C5), 153.99 (C6), 55.18 (C7), 51.79 (C8), 34.28 (C9), 30.76 (C10), 20.24 (C11), 32.84 (S–CH_2), 64.83 (N1–CH_2), phenyl ring: 136.17 (C-1′), 135.59 (C-2′), 131.57 (C-3′), 121.26 (C-4′), 131.57 (C-5′), 135.59 (C-6′), 135.78 (C-1″), 135.05 (C-2″), 131.19 (C-3″), 120.54 (C-4″), 131.19 (C-5″), 135.05 (C-6″). FT-IR (KBr, cm^{-1}): ν(C4═O) 1642, ν(C5═C6) 1548, ν(N–CH_2) 2869, ν(S–CH_2) 2926, δ(S–CH_2) 1429. EI MS (*m*/*z*, % int.): 577 ($M^{+\cdot}$, 3), 168 (100). UV/Vis (CH_3OH, nm, logε): 222.0 (4.38), 290.0 (4.14). Anal. Calcd for $C_{25}H_{27}N_3OSBr_2$: C, 52.01; H, 4.71; N, 7.28; S, 5.55. Found: C, 52.09; H, 4.80; N, 7.34; S, 5.51.

Compound **5**—(isolated yield 62%, mp 133–134 °C). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 3.37 (2H, s, C5–CH_2), 7.67 (1H, s, C6–H), 2.51 (4H, t, J = 12.3 Hz, N(CH_2)$_2$), 1.67 (4H, q, J = 12.2 Hz, CH_2), 1.41 (1H, m, C10–H), 0.90 (3H, d, J = 12.3 Hz, CH_3), 4.58 (2H, s, S–CH_2), 5.05 (2H, s, N1–CH_2), phenyl ring: 8.28 (1H, d, J = 7.2 Hz, C3′–H), 7.99 (1H, t, J = 7.3 Hz, C4′–H), 7.84 (1H, t, J = 7.3 Hz, C5′–H), 7.77 (1H, d, J = 7.2 Hz, C6′–H), 8.16 (1H, d, J = 7.2 Hz, C3″–H), 7.96 (1H, t, J = 7.3 Hz, C4″–H), 7.74 (1H, t, J = 7.3 Hz, C5″–H), 7.48 (1H, d, J = 7.2 Hz, C6″–H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ 167.95 (C2), 160.92 (C4), 117.90 (C5), 153.04 (C6), 54.09 (C7), 51.90 (C8), 34.27 (C9), 30.35 (C10), 21.27 (C11), 32.08 (S–CH_2), 64.09 (N1–CH_2), phenyl ring: 132.42 (C-1′), 148.62 (C-2′), 125.11 (C-3′), 130.20 (C-4′), 134.08 (C-5′), 133.54 (C-6′), 132.15 (C-1″), 147.99 (C-2″), 124.53 (C-3″), 128.53 (C-4″), 133.79 (C-5″), 132.92 (C-6″). FT-IR (KBr, cm^{-1}): ν(C4═O) 1669, ν(C5═C6) 1586, ν(N–CH_2) 2863, ν(S–CH_2) 2947, δ(S–CH_2) 1442. EI MS (*m*/*z*, % int.): 98 (100), 509 ($M^{+\cdot}$, 2). UV/Vis (CH_3OH, nm, logε): 225.0 (4.38), 285.0 (4.14). Anal. Calcd for $C_{25}H_{27}N_5O_5S$: C, 58.93; H, 5.34; N, 13.74; S, 6.29. Found: C, 58.99; H, 5.38; N, 13.79; S, 6.34.

Compound **6**—(isolated yield 63%, mp 124–125 °C). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 3.64 (2H, s, C5–CH_2), 8.30 (1H, s, C6–H), 2.50 (4H, t, J = 12.3 Hz, N(CH_2)$_2$), 1.64 (4H, q, J = 12.2 Hz, CH_2), 1.47 (1H, m, C10–H), 0.90 (3H, d, J = 12.3 Hz, CH_3), 4.46 (2H, s, S–CH_2), 4.94 (2H, s, N1–CH_2), phenyl ring: 8.33 (1H, s, C2′–H), 8.23 (1H, d, J = 7.3 Hz, C4′–H), 8.19 (1H, t, J = 7.2 Hz, C5′–H), 8.26 (1H, d, J = 7.3 Hz, C6′–H), 8.30 (1H, s, C2″–H), 8.22 (1H, d, J = 7.3 Hz, C4″–H), 8.15 (1H, t, J = 7.2 Hz, C5″–H), 8.23 (1H, d, J = 7.3 Hz, C6″–H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ 166.15 (C2), 163.70 (C4), 116.95 (C5), 152.94 (C6), 53.64 (C7), 51.73 (C8), 33.20(C9), 31.92 (C10), 21.48 (C11), 32.55 (S–CH_2), 65.82 (N1–CH_2), phenyl ring: 140.83 (C-1′), 123.38 (C-2′), 147.38 (C-3′), 122.86 (C-4′), 129.99 (C-5′), 135.49 (C-6′), 139.99 (C-1″), 123.17 (C-2″), 147.30 (C-3″), 122.00 (C-4″), 129.47 (C-5″), 135.34 (C-6″). FT-IR (KBr, cm^{-1}): ν(C4═O) 1669, ν(C5═C6) 1586, ν(N–CH_2) 2871, ν(S–CH_2) 2951, δ(S–CH_2) 1446. EI MS (*m*/*z*, % int.): 98 (100), 509 ($M^{+\cdot}$, 2). UV/Vis (CH_3OH, nm, logε): 221.0 (4.37), 283.0 (4.14). Anal. Calcd for $C_{25}H_{27}N_5O_5S$: C, 58.93; H, 5.34; N, 13.74; S, 6.29. Found: C, 58.97; H, 5.30; N, 13.76; S, 6.35.

Compound **7**—(isolated yield 66%, mp 112–113 °C). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 3.45 (2H, s, C5–CH_2), 8.18 (1H, s, C6–H), 2.51 (4H, t, J = 12.2 Hz, N(CH_2)$_2$), 1.65 (4H, q, J = 12.2 Hz, CH_2), 1.46 (1H, m, C10–H), 0.90 (3H, d, J = 12.0 Hz, CH_3), 4.45 (2H, s, S–CH_2), 4.91 (2H, s, N1–CH_2), phenyl ring: 8.26 (1H, d, J = 7.2 Hz, C2′–H), 8.15 (1H, d, J = 7.2 Hz, C3′–H), 8.15 (1H, d, J = 7.2 Hz, C5′–H), 8.26 (1H, d, J = 7.2 Hz, C6′–H), 8.18 (1H, d, J = 7.2 Hz, C2″–H), 7.65 (1H, d, J = 7.2 Hz, C3″–H), 7.65 (1H, d, J = 7.2 Hz, C5″–H), 8.18 (1H, d, J = 7.2 Hz, C6″–H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ 166.21 (C2), 161.72 (C4), 116.81 (C5), 152.82 (C6), 53.82 (C7), 51.79 (C8), 33.20 (C9), 31.96 (C10), 21.19 (C11), 32.74 (S–CH_2), 64.75 (N1–CH_2), phenyl ring: 145.73 (C-1′), 130.28 (C-2′), 123.58 (C-3′), 146.57 (C-4′), 123.58 (C-5′), 130.28 (C-6′), 145.44 (C-1″), 129.89 (C-2″), 123.32 (C-3″), 146.03 (C-4″), 123.32 (C-5″), 129.89 (C-6″). FT-IR (KBr, cm^{-1}): ν(C4═O) 1669, ν(C5═C6) 1587, ν(N–CH_2) 2869, ν(S–CH_2) 2947, δ(S–CH_2) 1448. EI MS (*m*/*z*, % int.): 509 ($M^{+\cdot}$, 10), 98 (100). UV/Vis (CH_3OH, nm, logε): 219.0 (4.33), 286.0 (4.12). Anal. Calcd for $C_{25}H_{27}N_5O_5S$: C, 58.93; H, 5.34; N, 13.74; S, 6.29. Found: C, 58.96; H, 5.37; N, 13.72; S, 6.33.

Compound **8**, for example, the *para*–nitro isomer (isolated yield 78%, mp 117–118 °C). ^{1}H NMR (300 MHz, $CDCl_3$-*d*, ppm): δ 6.54 (1H, d, J = 7.5 Hz, C5–H), 8.24 (1H, d, J = 7.3 Hz, C6–H), 4.43 (2H, s, S–CH_2), 5.44 (2H, s, N1–CH_2), phenyl ring: 7.35 (1H, d, J = 7.2 Hz, C2′–H), 7.90 (1H, d, J = 7.2 Hz, C3′–H), 7.90 (1H, d, J = 7.2 Hz, C5′–H), 7.35 (1H, d, J = 7.2 Hz, C6′–H), 7.50 (1H, d, J = 7.2 Hz, C2″–H), 7.68 (1H, d, J = 7.2 Hz, C3″–H), 7.68 (1H, d, J = 7.2 Hz, C5″–H), 7.50 (1H, d, J = 7.2 Hz, C6″–H). ^{13}C NMR (75 MHz, $CDCl_3$-*d*, ppm): δ 170.02 (C2), 157.57 (C4), 104.49 (C5), 167.88 (C6), 34.50 (S–CH_2), 66.69 (N1–CH_2), phenyl ring: 145.52 (C-1′), 128.28 (C-2′), 123.87 (C-3′), 151.87 (C-4′), 123.87 (C-5′), 129.97 (C-6′), 142.99 (C-1″), 128.09 (C-2″), 123.72 (C-3″), 151.87 (C-4″), 123.72 (C-5″), 129.56 (C-6″). FT-IR (KBr, cm^{-1}): ν(C4═O) 1673, ν(C5═C6) 1555, ν(N–CH_2) 2828, ν(S–CH_2) 2884, δ(S–CH_2) 1425. EI MS (*m*/*z*, % int.): 398 ($M^{+\cdot}$, 51), 136 (100). UV/Vis ($CHCl_3$, nm, logε): 271.50 (4.34). Anal. Calcd for $C_{18}H_{14}N_4O_5S$: C, 54.27; H, 3.54; N, 14.06; S, 8.05. Found: C, 54.11; H, 3.39; N, 14.32; S, 8.33.