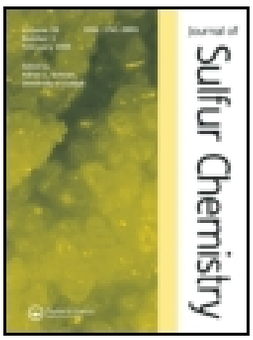

Journal of Sulfur Chemistry

ISSN: 1741-5993 (Print) 1741-6000 (Online) Journal homepage: http://www.tandfonline.com/loi/gsrp20

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To cite this article: Maryam Moloudi, Hassan Kabirifard, Raihaneh Kabirifard & Mona Mahdikhani (2017): Reactions of 4-benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione and diaminomaleonitrile in the presence of alcohols as reactant and solvent, Journal of Sulfur Chemistry, DOI: 10.1080/17415993.2017.1307983

To link to this article: http://dx.doi.org/10.1080/17415993.2017.1307983

Published online: 03 Apr 2017.

JOURNAL OF SULFUR CHEMISTRY, 2017
http://dx.doi.org/10.1080/17415993.2017.1307983

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Reactions of 4-benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione and diaminomaleonitrile in the presence of alcohols as reactant and solvent

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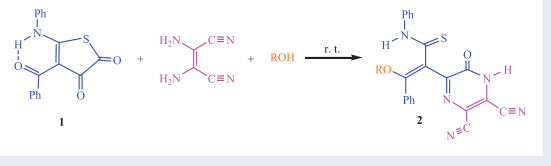
ABSTRACT

The one-pot synthesis of a novel class of 5-(2-alkoxy-2-phenyl-1-*N*-phenylthiocarbamoylethenyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbonitriles (**2a**–**o**) is achieved in moderate to good yields by the sequential reaction between 4-benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione, diaminomaleonitrile and alcohols.



ARTICLE HISTORY
Received 29 January 2017
Accepted 14 March 2017

KEYWORDS
Multi-component reactions; pyrazine-2,3-dicarbonitrile; thiophene-2,3-dione; diaminomaleonitrile; alcohol

1. Introduction

Pyrazines are important flavor components in food [1], and show interesting anticancer [1–4] and antituberculosis [1,5–8] activities, and apply in microbial metabolism [9] and as μ-opioid receptor antagonists [10], and also pyrazine-2,3-dicarbonitriles display varying degrees of herbicidal activity [11]. Diaminomaleonitrile (DAMN), a tetramer of hydrogen cyanide and a weakly basic diamine with similar reactivity to *o*-phenylenediamine, is an important precursor for the synthesis of pyrazine-2,3-dicarbonitriles [12]. The condensation with 1,2-diketones proceeds at room temperature or by warming for a short time [12,13]. The reaction of 4-acylated-5-substituted furan-2,3-dione in benzene at reflux for the synthesis of pyrazine-2,3-dicarbonitriles was reported [14]. The aim of this investigation was the synthesis of new structures bearing pyrazine-2,3-dicarbonitrile moieties. Herein, we report a simple synthetic method for the preparation of some diazine derivatives from 4-benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione (**1**) and DAMN in alcohols (Scheme 1).

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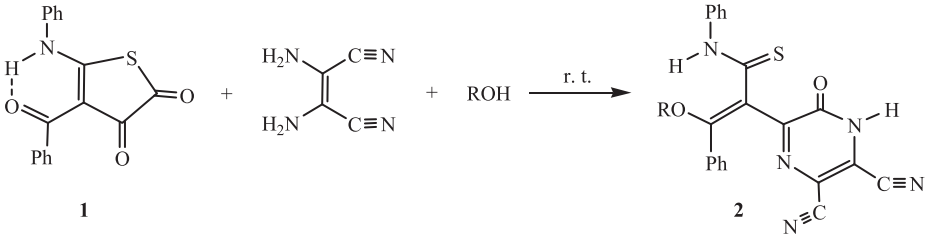
Supplemental data for this article can be accessed here. http://dx.doi.org/10.1080/17415993.2017.1307983



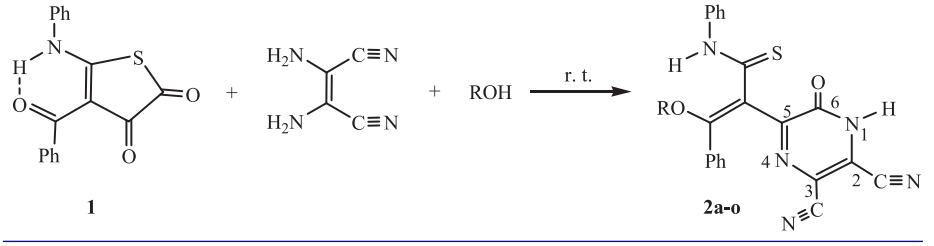
Scheme 1. Three-component coupling of 4-benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione (**1**), diaminomaleonitrile, and alcohols.

2. Results and discussion

Reaction of the thiophene-2,3-dione (**1**) with DAMN in alcohols as a reactant and solvent at room temperature for 1–3 h gave the pyrazine-2,3-dicarbonitrile derivatives (**2a**–**o**) (see Scheme 1). The products were obtained in moderate yields for unsaturated alcohols and for t-butyl alcohol and in excellent yields for saturated alcohols as shown in Table 1.

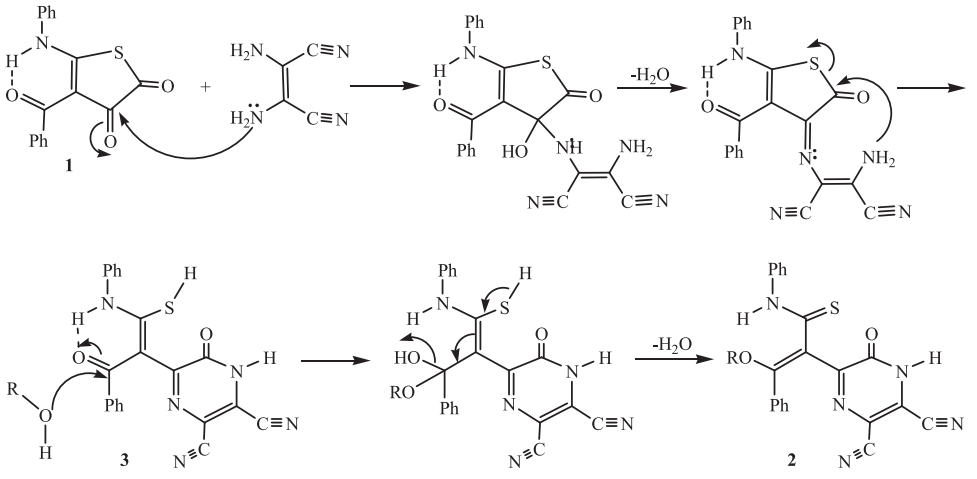
The structures of compounds **2a**–**o** were apparent from their mass spectra, which displayed, in each case, the molecular ion peak at the appropriate *m*/*z* value. The mass spectra of the some products exhibited fairly weak molecular ion peaks. The IR, ^{1}H NMR and ^{13}C NMR spectroscopic data were in agreement with the proposed structures. The IR spectra of **2a**–**o** revealed the characteristic absorption bands of C ≡ N, amide C=O, thioamide C–N,

Table 1. Synthesis of 5-(2-alkoxy-2-phenyl-1-*N*-phenylthiocarbamoylethenyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbonitrile (**2a**–**o**).



Entry	R	Product	Yield (%)[a]
1	CH_3	2a	89
2	CH_3CH_2	2b	70
3	$CH_3CH_2CH_2$	2c	86
4	$(CH_3)_2CH$	2d	72
5	$CH_3CH_2CH_2CH_2$	2e	79
6	$CH_3CH_2(CH_3)CH$	2f	62
7	$(CH_3)_2CHCH_2$	2g	70
8	$(CH_3)_3CH$	2h	44
9	$(CH_3)_2CHCH_2CH_2$	2i	64
10	$HOCH_2CH_2$	2j	68
11	$HOCH_2CH_2CH_2CH_2$	2k	66
12	CH_2=$CHCH_2$	2l	55
13	$PhCH_2$	2m	37
14	2-$C_4H_3OCH_2$	2n	50
15	C_6H_{11}	2o	31

[a]Isolated yield.



Scheme 2. Proposed mechanism for the one-pot synthesis of pyrazine-2,3-dicarbonitrile (**2**).

NH, C=S, and ether C–O–C (asy and sy) groups at 2246–2230, 1749–1719, 1552–1534, 1366–1360, 1184–1169, 1219–1209 and 1139–1078 cm^{-1}, respectively. Their ^{13}C NMR spectra also showed signals at δ 52.95–74.27, 118.10–122.08, 146.20–147.10, 161.35–162.85 and 185.33–188.50 ppm due to the carbons of the ether C–O, 2C≡N, C^5=N, amide C=O and thioamide C=S. In the ^1H NMR spectra of **2a**–**o**, we had observed two set of multiplet signals for aliphatic and aromatic protons and two broad singlet at δ 11.00–12.14 and 13.79–14.10 ppm for the amidic and thioamidic NH protons.

Carbon atoms C–2, C–3 and C–5 in compound **1** are electrophilic sites that can exhibit different reactivities depending on the structures of the nucleophiles and reaction conditions [15]. The DAMN cyclizes by nucleophilic attack on the α-ketothioesteric fragment (C–2 and C–3) of **1**, then nucleophilic attack of the alcohols to ketonic carbonyl group of intermediate 3 produce pyrazine-2,3-dicarbonitrile derivatives **2** (see Scheme 2).

3. Conclusion

We have synthesized new pyrazine-2,3-dicarbonitrile derivatives **2a**–**o** using one-pot reactions. The simple experimental and workup conditions of the presented reactions are combined with high yields of products.

4. Experimental

4.1. General

The chemicals were purchased from Merck and used without further purification. Melting points were measured with an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN–O-Rapid analyzer. These results agree favorably with the calculated values. Infrared spectra were measured from KBr disk using a Thermo Nicolet 8700 FT-IR spectrometer and frequencies were reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-300 AVANCE at 300, 500

and 75, 125 MHz instrument using tetramethylsilane as the internal standard and DMSO-d_6 or $CDCl_3$ as the solvent. Chemical shifts and coupling constants were reported in ppm and Hz, respectively. Thin-layer chromatography (TLC) was performed on 'Silufol-UV 254' plates. Mass spectra were obtained by using an Agilent HP 5973 mass spectrometer operating at an ionization potential of 70 eV.

4.2. Material

Ethyl 2,4-dioxo-4-phenylbutanoate was prepared from diethyl oxalate (10 mmol) and acetophenone (10 mmol) in the presence of sodium ethoxide (10 mmol) using of ethanol (30 ml) as the solvent [16]. 4-Benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione (**1**) was obtained by careful addition of phenyl isothiocyanate (10 mmol) to benzoylpyruvate in KOH (10 mmol) and dimethylformamide (20 mL) with stirring at room temperature for 24 h [15].

4.3. General procedure for the synthesis of pyrazine-2,3-dicarbonitriles 2a–o

A mixture of **1** (0.309 g, 1.0 mmol) and 2,3-diaminomaleonitrile (0.108 g, 1.0 mmol) in the corresponding alcohols (10 mL) was stirred at room temperature for 1–3 h. The progress of the reaction was monitored by TLC (eluent AcOEt/hexane 4:1). The solvent was evaporated, the residue was recrystallized from ethanol for **2a**–**i** and methanol:hexane (9:1) for **2l**–**o**, and dried. For derivatives **2j**,**k**, the solution was poured into H_2O (10 mL), the precipitate formed, which was filtered and was crystallized from ethanol:H_2O (4:1).

4.3.1. 5-(2-Methoxy-2-phenyl-1-N-phenylthiocarbamoylethenyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbonitrile (2a)

Orange crystal; yield: 0.37 g (89%); m.p.: 232–234°C. IR (KBr): $\bar{\nu}$ = 3441, 3250 (NH), 3020 (CH, aromatic), 2977 (CH, aliphatic), 2240 (CN), 1748 (C=O, amide), 1605 (C=C), 1573 (NH), 1540, 1365, 1169 (C–N, NH, C=S, thioamide), 1214, 1124 (C–O–C) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.93 (3H, s, CH_3–O), 7.28 (1H, t, $^3J_{HH}$ = 7.3 Hz, CH_{para} of Ph–NH), 7.45 (2H, t, $^3J_{HH}$ = 7.3 Hz, $2CH_{meta}$ of Ph–NH), 7.52–7.95 (7H, m, 2Ph), 12.12, 13.82 (2H, 2br.s, 2NH). ^{13}C NMR (DMSO-d_6): δ = 52.95 (CH_3–O), 114.23 (=C), 118.96, 121.46 (2CN), 122.83, 126.41, 126.88, 128.74, 128.86, 129.06 (10C, 2Ph), 130.70 (C_{ipso} of Ph–C=C), 139.46 (C_{ipso} of Ph–NH), 146.44 (C_5), 148.43 (C_3), 149.93 (C_2), 151.10 (O–C=), 163.24 (C=O, amide), 188.28 (C=S) ppm. EI-MS: m/z (%) = 413 (M^+, 5), 411 (23), 380 (3), 319 (7), 220 (27), 193 (6), 165 (14), 135 (27), 93 (100), 77 (93), 44 (70). Anal. Calcd for $C_{23}H_{15}N_5O_2S$ (413.45): C, 63.91%; H, 3.66%; N, 16.94%; found: C, 63.85%; H, 3.78%; N, 16.81%.

4.3.2. 5-(2-Ethoxy-2-phenyl-1-N-phenylthiocarbamoylethenyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbonitrile (2b)

Orange crystal; yield: 0.30 g (70%); m.p.: 238–240°C. IR (KBr): $\bar{\nu}$ = 3513 (NH), 3040 (CH, aromatic), 2977 (CH, aliphatic), 2240 (CN), 1732 (C=O, amide), 1601 (C=C), 1572 (NH), 1539, 1362, 1181 (C–N, NH, C=S, thioamide), 1217, 1123 (C–O–C) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 1.53 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 4.56 (2H, q, $^3J_{HH}$ = 7.2 Hz, CH_2–O), 7.26 (1H, t, $^3J_{HH}$ = 7.6 Hz, CH_{para} of Ph–NH), 7.42 (2H, t, $^3J_{HH}$ = 7.6 Hz, $2CH_{meta}$ of

Ph–NH), 7.50–8.04 (7H, m, 2Ph), 11.49, 11.91 (2H, 2br.s, 2NH). ^{13}C NMR (DMSO-d_6): δ = 18.43 (CH_3), 63.27 (CH_2–O), 113.36 (=C), 118.10, 120.80 (2CN), 122.85, 126.39, 126.75, 128.63, 128.72, 129.92 (10C, 2Ph), 131.09 (C_{ipso} of Ph–C=C), 139.17 (C_{ipso} of Ph–NH), 146.50 (C_5), 148.91 (C_3), 149.26 (C_2), 151.10 (O–C=), 162.80 (C=O, amide), 185.33 (C=S) ppm. EI-MS: *m/z* (%) = 427 (M^+, 17), 394 (20), 295 (13), 247 (10), 220 (37), 193 (13), 165 (15), 135 (49), 93 (100), 77 (93), 44 (40). Anal. Calcd for $C_{23}H_{17}N_5O_2S$ (427.48): C, 64.62%; H, 4.01%; N, 16.38%; found: C, 64.75%; H, 4.15%; N, 16.47%.

4.3.3. 5-(2-n-Propoxy-2-phenyl-1-N-phenylthiocarbamoylethenyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbonitrile (2c)

Dark orange crystal; yield: 0.38 g (86%); m.p.: 236–238°C. IR (KBr): $\bar{\nu}$ = 3510 (NH), 2977 (CH, aliphatic), 2240 (CN), 1732 (C=O, amide), 1601 (C=C), 1573 (NH), 1540, 1362, 1181 (C–N, NH, C=S, thioamide), 1218, 1124 (C–O–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 0.93 (3H, t, $^3J_{HH}$ = 7.4 Hz, CH_3), 1.59 (2H, m, CH_2), 4.40 (2H, t, $^3J_{HH}$ = 7.4 Hz, CH_2-O), 7.28 (1H, t, $^3J_{HH}$ = 7.8 Hz, CH_{para} of Ph–NH), 7.45 (2H, t, $^3J_{HH}$ = 7.8 Hz, $2CH_{meta}$ of Ph–NH), 7.51–7.94 (7H, m, 2Ph), 12.10, 13.79 (2H, 2br.s, 2NH). ^{13}C NMR (DMSO-d_6): δ = 10.36 (CH_3), 21.59 (CH_2), 67.29 (CH_2–O), 114.30 (=C), 118.65, 121.45 (2CN), 122.83, 126.29, 126.90, 128.65, 128.69, 129.12 (10C, 2Ph), 130.51 (C_{ipso} of Ph–C=C), 139.48 (C_{ipso} of Ph–NH), 147.10 (C_5), 148.53 (C_3), 149.89 (C_2), 151.10 (O–C=), 162.80 (C=O, amide), 188.25 (C=S) ppm. EI-MS: *m/z* (%) = 441 (M^+, 1), 426 (3), 394 (4), 220 (23), 165 (5), 135 (100), 93 (73), 77 (71), 51 (24). Anal. Calcd for $C_{24}H_{19}N_5O_2S$ (441.50): C, 65.29%; H, 4.34%; N, 15.86%; found: C, 65.17%; H, 4.19%; N, 15.98%.

4.3.4. 5-(2-Isopropoxy-2-phenyl-1-N-phenylthiocarbamoylethenyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbonitrile (2d)

Brownish yellow powder; yield: 0.32 g (72%); m.p.: 206–208°C. IR (KBr): $\bar{\nu}$ = 3440, 3282 (NH), 3026 (CH, aromatic), 2978 (CH, aliphatic), 2240 (CN), 1728 (C=O, amide), 1602 (C=C), 1573 (NH), 1542, 1360, 1184 (C–N, NH, C=S, thioamide), 1218, 1104 (C–O–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.38 (6H, d, $^3J_{HH}$ = 6.0 Hz, $2CH_3$), 5.23 (1H, m, CH–O), 7.29 (1H, t, $^3J_{HH}$ = 7.4 Hz, CH_{para} of Ph–NH), 7.46 (2H, t, $^3J_{HH}$ = 7.4 Hz, $2CH_{meta}$ of Ph–NH), 7.53–7.94 (7H, m, 2Ph), 12.14, 13.82 (2H, 2br.s, 2NH). ^{13}C NMR (DMSO-d_6): δ = 21.61 ($2CH_3$), 69.70 (CH–O), 114.29 (=C), 118.65, 121.44 (2CN), 122.93, 126.40, 126.80, 128.70, 128.78, 129.18 (10C, 2Ph), 130.66 (C_{ipso} of Ph–C=C), 139.45 (C_{ipso} of Ph–NH), 146.20 (C_5), 148.90 (C_3), 149.81 (C_2), 150.90 (O–C=), 162.35 (C=O, amide), 188.13 (C=S) ppm. EI-MS: *m/z* (%) = 441 (M^+, 3), 408 (3), 220 (27), 142 (19), 93 (100), 77 (49), 43 (23). Anal. Calcd for $C_{24}H_{19}N_5O_2S$ (441.50): C, 65.29%; H, 4.34%; N, 15.86%; found: C, 65.41%; H, 4.22%; N, 15.75%.

4.3.5. 5-(2-n-Butoxy-2-phenyl-1-N-phenylthiocarbamoylethenyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbonitrile (2e)

Brownish yellow powder; yield: 0.36 g (79%); m.p.: 208–210°C. IR (KBr): $\bar{\nu}$ = 3436, 3260 (NH), 3015 (CH, aromatic), 2925 (CH, aliphatic), 2240 (CN), 1732 (C=O, amide), 1603 (C=C), 1575 (NH), 1542, 1366, 1182 (C–N, NH, C=S, thioamide), 1219, 1122 (C–O–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 0.91 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.41, 1.72 (4H, 2 m, $2CH_2$), 4.36 (2H, t, $^3J_{HH}$ = 7.2 Hz, CH_2-O), 7.29 (1H, t, $^3J_{HH}$ = 7.3 Hz, CH_{para} of Ph–NH), 7.45 (2H, t, $^3J_{HH}$ = 7.3 Hz, $2CH_{meta}$ of Ph–NH), 7.51–7.94 (7H, m, 2Ph), 12.12,

13.82 (2H, 2br.s, 2NH). ^{13}C NMR (DMSO-d_6): δ = 13.59 (CH_3), 18.66, 30.17 ($2CH_2$), 65.50 (CH_2–O), 114.26 (=C), 118.74, 121.47 (2CN), 122.91, 126.38, 126.80, 128.68, 128.78, 129.16 (10C, 2Ph), 130.66 (C_{ipso} of Ph–C=C), 139.45 (C_{ipso} of Ph–NH), 146.99 (C_5), 148.70 (C_3), 149.79 (C_2), 151.10 (O–C=), 162.86 (C=O, amide), 188.13 (C=S) ppm. EI-MS: m/z (%) = 455 (M^+, 1), 439 (5), 347 (6), 220 (20), 142 (21), 93 (100), 77 (23), 41 (50). Anal. Calcd for $C_{25}H_{21}N_5O_2S$ (455.53): C, 65.92%; H, 4.65%; N, 15.37%; found: C, 65.80%; H, 4.73%; N, 15.57%.

4.3.6. 5-(2-Sec-butoxy-2-phenyl-1-N-phenylthiocarbamoylethenyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbonitrile (2f)

Dark Orange powder; yield: 0.28 g (62%); m.p.: 230–232°C. IR (KBr): $\bar{\nu}$ = 3440, 3261 (NH), 3017 (CH, aromatic), 2958 (CH, aliphatic), 2240 (CN), 1732 (C=O, amide), 1603 (C=C), 1575 (NH), 1542, 1365, 1182 (C–N, NH, C=S, thioamide), 1218, 1122 (C–O–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 0.97 (3H, t, $^3J_{HH}$ = 7.5 Hz, CH_3), 1.39 (3H, d, $^3J_{HH}$ = 6.2 Hz, CH_3), 1.76 (2H, m, CH_2), 5.14 (1H, m, CH–O), 7.10 (1H, t, $^3J_{HH}$ = 7.7 Hz, CH_{para} of Ph–NH), 7.37 (2H, t, $^3J_{HH}$ = 7.7 Hz, $2CH_{meta}$ of Ph–NH), 7.53–7.60 (3H, m, Ph), 7.69 (2H, d, $^3J_{HH}$ = 7.7 Hz, $2CH_{ortho}$ of Ph–NH), 7.92 (2H, d, $^3J_{HH}$ = 7.8 Hz, $2CH_{ortho}$ of Ph–C=C), 11.00, 14.10 (2H, 2br.s, 2NH). ^{13}C NMR (DMSO-d_6): δ = 9.69, 19.36 ($2CH_3$), 28.37 (CH_2), 74.27 (CH–O), 114.10 (=C), 119.02, 122.08 (2CN), 123.69, 127.77, 128.11, 129.03, 129.13, 130.48 (10C, 2Ph), 130.92 (C_{ipso} of Ph–C=C), 138.80 (C_{ipso} of Ph–NH), 143.58 (C_5), 147.94 (C_3), 148.30 (C_2), 150.54 (O–C=), 161.85 (C=O, amide), 185.50 (C=S) ppm. EI-MS: m/z (%) = 455 (M^+, 1), 319 (4), 220 (21), 142 (13), 93 (100), 77 (38), 41 (27). Anal. Calcd for $C_{25}H_{21}N_5O_2S$ (455.53): C, 65.92%; H, 4.65%; N, 15.37%; found: C, 65.79%; H, 4.76%; N, 15.51%.

4.3.7. 5-(2-Isobutoxy-2-phenyl-1-N-phenylthiocarbamoylethenyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbonitrile (2g)

Brownish yellow powder; yield: 0.32 g (70%); m.p.: 200–202°C. IR (KBr): $\bar{\nu}$ = 3260 (NH), 3014 (CH, aromatic), 2965 (CH, aliphatic), 2245 (CN), 1733 (C=O, amide), 1603 (C=C), 1575 (NH), 1542, 1365, 1182 (C–N, NH, C=S, thioamide), 1218, 1122 (C–O–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 0.96 (6H, d, $^3J_{HH}$ = 6.7 Hz, $2CH_3$), 2.05 (1H, m, CH), 4.15 (2H, d, $^3J_{HH}$ = 6.7 Hz, CH_2–O), 7.28 (1H, t, $^3J_{HH}$ = 7.6 Hz, CH_{para} of Ph–NH), 7.44 (2H, br.t, $^3J_{HH}$ = 7.6 Hz, $2CH_{meta}$ of Ph–NH), 7.51–7.93 (7H, m, 2Ph), 12.10 13.79 (2H, 2br.s, 2NH). ^{13}C NMR (DMSO-d_6): δ = 18.80 ($2CH_3$), 27.32 (CH_2), 71.35 (CH_2-O), 114.18 (=C), 118.68, 121.46 (2CN), 122.92, 126.32, 126.80, 128.64, 128.70, 129.06 (10C, 2Ph), 130.59 (C_{ipso} of Ph–C=C), 139.41 (C_{ipso} of Ph—NH), 146.90 (C_5), 148.72 (C_3), 149.81 (C_2), 151.10 (O–C=), 162.81 (C=O, amide), 188.17 (C=S) ppm. EI-MS: m/z (%) = 455 (M^+, 2), 394 (5), 295 (5), 220 (19), 134 (34), 93 (100), 77 (92), 41 (60). Anal. Calcd for $C_{25}H_{21}N_5O_2S$ (455.53): C, 65.92%; H, 4.65%; N, 15.37%; found: C, 66.08%; H, 4.54%; N, 15.58%.

4.3.8. 5-(2-Tert-butoxy-2-phenyl-1-N-phenylthiocarbamoylethenyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbonitrile (2h)

Dark orange crystal; yield: 0.20 g (44%); m.p.: 206–208°C. IR (KBr): $\bar{\nu}$ = 3439, 3258 (NH), 3017 (CH, aromatic), 2957 (CH, aliphatic), 2240 (CN), 1732 (C=O, amide), 1600 (C=C), 1575 (NH), 1537, 1365, 1181 (C–N, NH, C=S, thioamide), 1217, 1139 (C–O–C) cm^{-1}. ^{1}H

NMR (DMSO-d_6): δ = 1.31 (9H, s, $3CH_3$), 7.28 (1H, t, $^3J_{HH}$ = 7.6 Hz, CH_{para} of Ph–NH), 7.45 (2H, t, $^3J_{HH}$ = 7.6 Hz, $2CH_{meta}$ of Ph–NH), 7.55–7.95 (7H, m, 2Ph), 12.12, 13.80 (2H, 2br.s, 2NH). ^{13}C NMR (DMSO-d_6): δ = 25.61 ($3CH_3$), 64.70 (C–O), 114.34 (=C), 118.55, 121.47 (2CN), 122.83, 126.27, 126.70, 128.29, 128.65, 129.14 (10C, 2Ph), 130.47 (C_{ipso} of Ph–C=C), 139.50 (C_{ipso} of Ph–NH), 147.10 (C_5), 148.45 (C_3), 149.91 (C_2), 151.10 (O–C=), 162.81 (C=O, amide), 188.27 (C=S) ppm. EI-MS: m/z (%) = 455 (M^+, 4), 394 (44), 295 (20), 220 (39), 165 (28), 93 (100), 77 (96), 51 (26). Anal. Calcd for $C_{25}H_{21}N_5O_2S$ (455.53): C, 65.92%; H, 4.65%; N, 15.37%; found: C, 65.73%; H, 4.77%; N, 15.21%.

4.3.9. 5-(2-Isopentoxy-2-phenyl-1-N-phenylthiocarbamoylethenyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbonitrile (2i)

Orange yellow crystal; yield: 0.30 g (64%); m.p.: 226–228°C. IR (KBr): $\bar{\nu}$ = 3278 (NH), 3027 (CH, aromatic), 2978 (CH, aliphatic), 2240 (CN), 1728 (C=O, amide), 1602 (C=C), 1572 (NH), 1542, 1360, 1183 (C–N, NH, C=S, thioamide), 1218, 1104 (C–O–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 0.91 (6H, d, $^3J_{HH}$ = 6.5 Hz, $2CH_3$), 1.63 (2H, q, $^3J_{HH}$ = 6.7 Hz, CH_2), 1.74 (1H, m, CH), 4.39 (2H, t, $^3J_{HH}$ = 6.7 Hz, CH_2–O), 7.28 (1H, t, $^3J_{HH}$ = 7.4 Hz, CH_{para} of Ph–NH), 7.44 (2H, t, $^3J_{HH}$ = 7.4 Hz, $2CH_{meta}$ of Ph–NH), 7.56–7.94 (7H, m, 2Ph), 12.11, 13.80 (2H, 2br.s, 2NH). ^{13}C NMR (DMSO-d_6): δ = 22.32 ($2CH_3$), 24.58 (CH), 36.80 (CH_2), 64.27 (CH_2–O), 114.26 (=C), 118.75, 121.47 (2CN), 122.91, 126.38, 126.80, 128.67, 128.78, 129.15 (10C, 2Ph), 130.66 (C_{ipso} of Ph–C=C), 139.45 (C_{ipso} of Ph–NH), 147.00 (C_5), 148.67 (C_3), 149.76 (C_2), 150.60 (O–C=), 162.82 (C=O, amide), 188.13 (C=S) ppm. EI-MS: m/z (%) = 469 (M^+, 1), 456 (59), 377 (13), 322 (9), 221 (9), 181 (78), 142 (17), 93 (100), 77 (65), 43 (27). Anal. Calcd for $C_{26}H_{23}N_5O_2S$ (469.56): C, 66.50%; H, 4.94%; N, 14.91%; found: C, 66.32%; H, 5.17%; N, 14.70%.

4.3.10. 5-(2-(2-Hydroxyethoxy)-2-phenyl-1-N-phenylthiocarbamoylethenyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbonitrile (2j)

Orange crystal; yield: 0.30 g (68%); m.p.: 257–259°C. IR (KBr): $\bar{\nu}$ = 3450 (NH), 3250 (OH), 2965 (CH, aliphatic), 2240 (CN), 1740 (C=O, amide), 1607 (C=C), 1573 (NH), 1542, 1363, 1184 (C–N, NH, C=S, thioamide), 1218, 1078 (C–O–C), 1032 (C–OH) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.73 (2H, br.t, $^3J_{HH}$ = 4.9 Hz, CH_2OH), 4.38 (2H, t, $^3J_{HH}$ = 4.9 Hz, CH_2–O), 4.95 (1H, br.t, OH), 7.28 (1H, t, $^3J_{HH}$ = 7.6 Hz, CH_{para} of Ph–NH), 7.44 (2H, t, $^3J_{HH}$ = 7.6 Hz, $2CH_{meta}$ of Ph–NH), 7.56–7.93 (7H, m, 2Ph), 12.13, 13.81 (2H, 2br.s, 2NH). ^{13}C NMR (DMSO-d_6): δ = 62.74 (CH_2OH), 67.41 (CH_2-O), 114.10 (=C), 118.91, 122.04 (2CN), 122.81, 126.16, 127.72, 128.60, 128.92, 129.16 (10C, 2Ph), 130.42 (C_{ipso} of Ph–C=C), 139.51 (C_{ipso} of Ph–NH), 146.50 (C_5), 148.60 (C_3), 149.92 (C_2), 150.90 (O–C=), 162.67 (C=O, amide), 188.50 (C=S) ppm. EI-MS: m/z (%) = 443 (M^+, 1), 322 (6), 220 (15), 165 (9), 93 (93), 77 (51), 44 (100). Anal. Calcd for $C_{23}H_{17}N_5O_3S$ (443.48): C, 62.29%; H, 3.86%; N, 15.79%; found: C, 62.05%; H, 4.08%; N, 15.48%.

4.3.11. 5-(2-(4-Hydroxybutoxy)-2-phenyl-1-N-phenylthiocarbamoylethenyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbonitrile (2k)

Yellow orange crystal; yield: 0.31 g (66%); m.p.: 228–230°C. IR (KBr): $\bar{\nu}$ = 3507 (NH), 3405 (OH), 2975 (CH, aliphatic), 2242 (CN), 1736 (C=O, amide), 1604 (C=C), 1574 (NH), 1547, 1364, 1178 (C–N, NH, C=S, thioamide), 1219, 1126 (C–O–C), 1040 (C–OH) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.53, 1.78 (4H, 2 m, $2CH_2$), 3.43 (2H, br.t,

$^{3}J_{HH}$ = 6.5 Hz, CH_2OH), 4.37 (2H, t, $^{3}J_{HH}$ = 6.5 Hz, CH_2–O), 4.44 (1H, br.t, OH), 7.28 (1H, t, $^{3}J_{HH}$ = 7.5 Hz, CH_{para} of Ph–NH), 7.45 (2H, t, $^{3}J_{HH}$ = 7.5 Hz, $2CH_{meta}$ of Ph–NH), 7.57–7.93 (7H, m, 2Ph), 12.12, 13.82 (2H, 2br.s, 2NH). ^{13}C NMR (DMSO-d_6): δ = 24.99, 28.80 ($2CH_2$), 60.21 (CH_2OH), 65.77 (CH_2–O), 114.14 (=C), 118.68, 121.46 (2CN), 122.92, 126.34, 126.76, 128.67, 128.74, 129.14 (10C, 2Ph), 130.64 (C_{ipso} of Ph–C=C), 139.44 (C_{ipso} of Ph–NH), 146.52 (C_5), 148.65 (C_3), 149.81 (C_2), 150.89 (O–C=), 162.85 (C=O, amide), 188.17 (C=S) ppm. EI-MS: *m*/*z* (%) = 316 (8), 261 (5), 191 (5), 147 (5), 97 (18), 57 (100), 43 (63). Anal. Calcd for $C_{25}H_{21}N_5O_3S$ (471.53): C, 63.68%; H, 4.49%; N, 14.85%; found: C, 63.41%; H, 4.75%; N, 14.69%.

4.3.12. 5-(2-Allyloxy-2-phenyl-1-N-phenylthiocarbamoylethenyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbonitrile (2l)

Yellow orange powder; yield: 0.24 g (55%); m.p.: 145–147°C. IR (KBr): $\bar{\nu}$ = 3475, 3297 (NH), 3080 (CH, aromatic), 2240 (CN), 1749 (C=O, amide), 1643, 1602 (C=C), 1583 (NH), 1552, 1362, 1176 (C–N, NH, C=S, thioamide), 1213, 1091 (C–O–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 4.89 (2H, d, $^{3}J_{HH}$ = 5.7 Hz, CH_2–O), 5.29 (1H, d, $^{3}J_{cis}$ = 10.5 Hz, =CH), 5.45 (1H, d, $^{3}J_{trans}$ = 17.2 Hz, =CH), 6.06 (1H, m, =CH), 7.28 (1H, t, $^{3}J_{HH}$ = 7.4 Hz, CH_{para} of Ph–NH), 7.44 (2H, t, $^{3}J_{HH}$ = 7.4 Hz, $2CH_{meta}$ of Ph–NH), 7.51–7.94 (7H, m, 2Ph), 12.10, 13.81 (2H, 2br.s, 2NH). ^{13}C NMR (DMSO-d_6): δ = 66.08 (CH_2–O), 114.18 (=C), 118.64 (=CH_2), 118.78, 121.46 (2CN), 122.85, 126.34, 126.83, 128.64, 128.75, 129.09 (10C, 2Ph), 130.63 (C_{ipso} of Ph–C=C), 132.19 (=CH), 139.42 (C_{ipso} of Ph–NH), 146.86 (C_5), 148.44 (C_3), 149.83 (C_2), 150.50 (O–C=), 162.36 (C=O, amide), 188.12 (C=S) ppm. EI-MS: *m*/*z* (%) = 438 (3), 406 (10), 322 (5), 220 (14), 142 (22), 109 (10), 93 (90), 77 (98), 41 (100). Anal. Calcd for $C_{24}H_{17}N_5O_2S$ (439.49): C, 65.59%; H, 3.90%; N, 15.94%; found: C, 65.88%; H, 4.11%; N, 16.19%.

4.3.13. 5-(2-Benzyloxy-2-phenyl-1-N-phenylthiocarbamoylethenyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbonitrile (2m)

Dark orange powder; yield: 0.18 g (37%); m.p.: 198–200°C. IR (KBr): $\bar{\nu}$ = 3255 (NH), 3009 (CH, aromatic), 2246 (CN), 1731 (C=O, amide), 1662, 1601 (C=C), 1574 (NH), 1541, 1364, 1175 (C–N, NH, C=S, thioamide), 1216, 1120 (C–O–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 5.44 (2H, s, CH_2O), 7.27 (1H, t, $^{3}J_{HH}$ = 7.7 Hz, CH_{para} of Ph–NH), 7.30–7.40 (5H, m, Ph–CH_2), 7.42 (2H, t, $^{3}J_{HH}$ = 7.7 Hz, $2CH_{meta}$ of Ph–NH), 7.49–7.93 (7H, m, 2Ph), 12.11, 13.80 (2H, 2br.s, 2NH). ^{13}C NMR (DMSO-d_6): δ = 67.04 (CH_2-O), 114.37 (=C), 118.83, 121.54 (2CN), 122.91, 126.19, 126.37, 126.57, 127.98, 128.25, 128.48, 128.60, 129.22 (15C, 3Ph), 130.38 (C_{ipso} of Ph–C=C), 139.50 (C_{ipso} of Ph–NH), 142.47 (C_{ipso} of Ph–CH_2), 146.60 (C_5), 148.13 (C_3), 149.87 (C_2), 150.10 (O–C=), 162.66 (C=O, amide), 188.22 (C=S) ppm. EI-MS: *m*/*z* (%) = 489 (M^+, 1), 220 (5), 124 (7), 91 (100), 77 (21), 65 (25), 45 (15). Anal. Calcd for $C_{28}H_{19}N_5O_2S$ (489.55): C, 68.70%; H, 3.91%; N, 14.31%; found: C, 68.49%; H, 4.20%; N, 14.58%.

4.3.14. 5-(2-Fufuryloxy-2-phenyl-1-N-phenylthiocarbamoylethenyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbonitrile (2n)

Dark orange powder; yield: 0.24 g (50%); m.p.: 164–166°C. IR (KBr): $\bar{\nu}$ = 3438, 3295 (NH), 3031 (CH, aromatic), 2240 (CN), 1719 (C=O, amide), 1640, 1602 (C=C), 1573 (NH), 1534,

1360, 1174 (C–N, NH, C=S, thioamide), 1209, 1121 (C–O–C) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 5.41 (2H, s, CH_2O), 6.50 (1H, br.s, $=CH_{furfuryl}$), 6.65 (1H, d, $^3J_{HH}$ = 2.9 Hz, $=CH_{furfuryl}$), 7.28 (1H, t, $^3J_{HH}$ = 7.4 Hz, CH_{para} of Ph–NH), 7.44 (2H, t, $^3J_{HH}$ = 7.4 Hz, $2CH_{meta}$ of Ph–NH), 7.51–7.60 (3H, m, Ph), 7.72 (1H, s, $=CH_{furfuryl}$), 7.87–7.94 (4H, m, 2Ph), 12.10, 13.81 (2H, 2br.s, 2NH). ^{13}C NMR (DMSO-d_6): δ = 59.06 (CH_2–O), 106.80 ($C_{4'}$), 110.45 ($C_{3'}$), 114.14 (=C), 118.76, 121.45 (2CN), 122.94, 126.35, 126.83, 128.57, 128.75, 129.12 (10C, 2Ph), 130.64 (C_{ipso} of Ph–C=C), 139.38 (C_{ipso} of Ph–NH), 144.00 ($C_{5'}$), 146.99 (C_5), 148.84 (C_3), 149.80 (C_2), 149.89 (O–C=), 152.10 ($C_{2'}$), 162.30 (C=O, amide), 188.08 (C=S) ppm. EI-MS: *m/z* (%) = 354 (8), 322 (20), 220 (39), 165 (13), 93 (42), 77 (83), 44 (100). Anal. Calcd for $C_{26}H_{17}N_5O_3S$ (479.51): C, 65.12%; H, 3.57%; N, 14.61%; found: C, 64.88%; H, 3.34%; N, 14.79%.

4.3.15. 5-(2-Cyclohexyloxy-2-phenyl-1-N-phenylthiocarbamoylethenyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbonitrile (2o)

Dark orange powder; yield: 0.15 g (31%); m.p.: 214–216°C. IR (KBr): $\bar{n}$ = 3250 (NH), 3013 (CH, aromatic), 2930 (CH, aliphatic), 2245 (CN), 1728 (C=O, amide), 1601 (C=C), 1573 (NH), 1543, 1364, 1182 (C–N, NH, C=S, thioamide), 1219, 1121 (C–O–C) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 1.35–1.96 (10H, m, $5CH_2$), 4.99 (1H, br.m, CH–O), 7.28 (1H, t, $^3J_{HH}$ = 7.5 Hz, CH_{para} of Ph–NH), 7.44 (2H, t, $^3J_{HH}$ = 7.5 Hz, $2CH_{meta}$ of Ph–NH), 7.52–7.92 (7H, m, 2Ph), 12.13, 13.79 (2H, 2br.s, 2NH). ^{13}C NMR (DMSO-d_6): δ = 23.23 ($2CH_2$), 24.81 (CH_2), 31.05 ($2CH_2$), 74.14 (CH–O), 114.38 (=C), 118.30, 121.49 (2CN), 122.90, 126.23, 127.39, 128.58, 128.64, 129.23 (10C, 2Ph), 130.40 (C_{ipso} of Ph–C=C), 139.49 (C_{ipso} of Ph–NH), 146.90 (C_5), 148.71 (C_3), 149.79 (C_2), 150.10 (O–C=), 162.23 (C=O, amide), 188.10 (C=S) ppm. EI-MS: *m/z* (%) = 481 (M^+, 2), 380 (5), 322 (7), 220 (15), 142 (14), 93 (100), 77 (70), 41 (63). Anal. Calcd for $C_{27}H_{23}N_5O_2S$ (481.57): C, 67.34%; H, 4.81%; N, 14.54%; found: C, 67.18%; H, 5.03%; N, 14.69%.

Disclosure statement

No potential conflict of interest was reported by the authors.

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