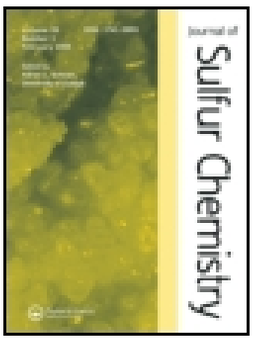

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Utility involving thioacetoacetanilides as precursors for synthesis of new thiazole, thiadiazole and thiophene derivatives with antimicrobial activity

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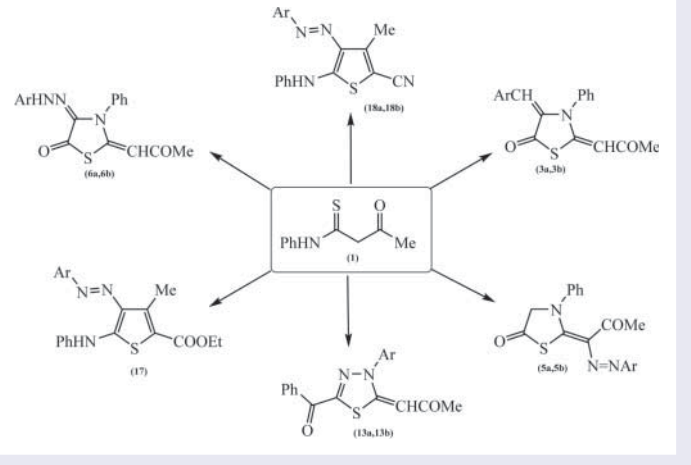
ABSTRACT

The behavior of thioacetoacetanilide **(1)** and/or α-arylhydrazonothioacetoacetanilides **4** toward many different α-halocarbonyl compounds was demonstrated. Thus, reactions of **1** with α-bromoketones (bromoacetone and phenacyl bromide) and hydrazonoyl bromides afforded the corresponding thiazole, thiophene and 1,3,4-thiadiazole derivatives, respectively. The synthesis and reactivity of thiazolidin-5-one **2** toward aromatic diazonium chlorides and aromatic aldehydes were described. Most of the synthesized compounds were screened for their antibacterial and antifungal activities and showed accepted antimicrobial activities with respect to the control drugs.



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Introduction

Five membered heterocyclic compounds containing sulfur have been utilized in medical goal intended for treating different kinds of fungal and bacterial infections along with treatment of gastric ulcer and cancer.[1] Sulfur is capable of forming both σ and π bonds,

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the studies of their binding interaction with receptor moiety was also an interesting field of research during last few years.[2] Thiazole derivatives possess significant interest coming from therapeutic point of view because of their utility as antibacterial and antifungal,[3,4] anti-inflammatory,[5] antitubercular,[6] central nervous system stimulate,[7] anti-HIV [8] and antimalarial.[9] Thiadiazole derivatives possess a wide range of biological properties and they act as anthelmintics,[10,11] antihypertensive,[12] antitumor,[13–15] analgesic, anticancer, anti-inflammatory and antibacterial,[16–19] tyrosinase inhibitory activity.[20] Among the antimicrobial and antifungal agents, thiophene-containing heterocycles are known to have a promising activity.[21] In the present paper, we report on the potent and facile synthesis of some thiazole, thiadiazole and thiophene related compounds based on thioacetoacetanilide. The newly substituted sulfur-containing heterocycles were screened for their antibacterial and antifungal activities.

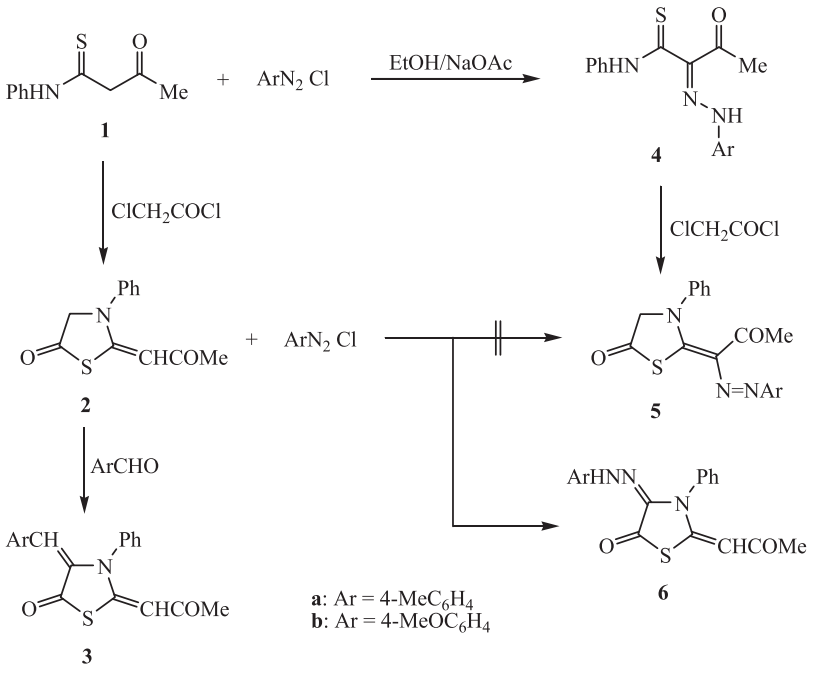
Results and discussion

The starting material thioacetoacetanilide **(1)** used in this study has been prepared by refluxing acetylacetone with phenyl isothiocyanate in sodium ethoxide–ethanol solution.[22] Treatment of thioacetoacetanilide **(1)** with chloroacetyl chloride by stirring in DMF containing a catalytic amount of triethylamine, afforded the corresponding thiazolidine-5-one derivative **2** (Scheme 1). The isolated product **2** gave satisfactory elemental analysis and spectroscopic data (IR, ^{1}H NMR and MS). For example, the IR spectrum of the product showed an absorption band at 1728 cm^{-1} due to the carbonyl group (CO, ring) and a band at 1642 cm^{-1} due to the conjugated carbonyl. The ^{1}H NMR spectrum revealed methyl protons as a singlet signal at δ 2.20, methylene protons as a singlet signal at δ 4.10, olefinic proton as a singlet signal at δ 5.20, in addition to a multiplet signal in the region δ 7.30–7.70 attributed to the aromatic protons.

Thiazolidin-5-one derivative **2** was condensed with aromatic aldehydes (Aldol-type condensation) by refluxing in ethanol containing drops of piperidine to give the corresponding 4-arylidene-thiazolidin-5-one derivatives **3**. The structure of the products **3** was confirmed based on their elemental analyses and spectral data.

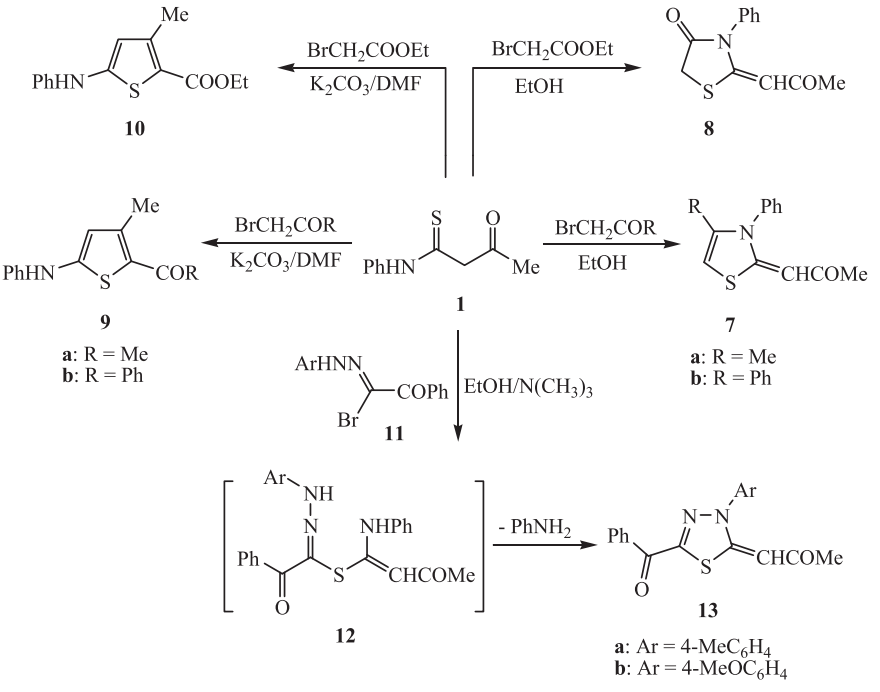
The reactivity connected with thiazolidin-5-one derivative **2** toward the electrophilic substitution reaction simply by aromatic diazonium salts was also investigated. The methylene group of the thiazolidine ring proved to be more reactive toward the azo coupling with diazonium salts than the olefinic methine group. Thus, an equimolar amount of aryl diazonium chlorides at 0–5°C reacted with compound **2** in order to generate the corresponding monohydrazono derivatives **6** rather than the azo compounds **5** (Scheme 1). The azo compounds **5** could be obtained in good yields from the reaction of α-arylhydrazono-thioacetoacetanilide **4** [23] with chloroacetyl chloride simply by stirring in DMF containing few drops of triethylamine as a catalyst. The molecular structures of the compounds **5** and **6** were established by elemental analyses and spectroscopic data.

α-Arylhydrazono-thioacetoacetanilides **4** has been prepared in the literature by treatment of α-phenyl thiocarbamoyl acetylacetone with aromatic diazonium salts in ethanol containing sodium acetate (Japp-Klingemann reaction type) as alternative route.[23] We obtained these derivatives in good yields by direct diazo-coupling of thioacetoacetanilide **1** with different aromatic diazonium salts.



Scheme 1. Synthesis of thiazolidin-5-one derivatives 2, 3, 5 and 6.

In addition, treatment of thioacetoacetanilide **(1)** with α-bromoketones (as bromoacetone and phenacyl bromide) and ethyl bromoacetate in ethanol under reflux without catalyst afforded products identified as 2-(2-oxopropylidene)-2,3-dihydro-4-substituted-3-phenylthiazole derivatives **7** and 2-(2-oxopropylidene)-3-phenyl-thiazolidin-4-one **(8)**, respectively (Scheme 2). All of the isolated products **7** along with **8** afforded acceptable elemental analyses and spectroscopic data (IR, ^{1}H NMR, and MS) consistent with their assigned structures. For instance, the IR spectra of the products showed conjugated carbonyl absorption band near 1680 cm^{-1} and the absence of NH absorption band. The ^{1}H NMR spectrum regarding **7a** showed methyl protons (thiazole-CH_3) as singlet signal at δ 1.80 ppm, methyl protons ($COCH_3$) as singlet signal at δ 2.35 ppm, olefinic proton (C = CHCO) as singlet signal at δ 5.45 ppm, thiazole-5-CH proton as singlet signal indicate at δ 6.40 ppm, in addition to multiplet signal in the region δ 7.00–7.40 ppm attributed to the aromatic protons. On the other hand, when **1** treated with α-bromoketones (as bromoacetone and phenacyl bromide) and ethyl bromoacetate in dimethyl formamide as a solvent and anhydrous K_2CO_3 as a basic catalyst, the isolated products were different and identified as 2-methyl-2-substituted-thiophene derivatives **9** and **10**. The suggested mechanism for the formation of compounds **7** and **9** was outlined in Scheme 3. The suggested structures of **9** and **10** were secured by their correct elemental analyses and spectral data. For example, the IR spectra of the products revealed conjugated carbonyl absorption band in the range 1652–1674 cm^{-1} and the NH absorption band in the range 3327–3253 cm^{-1}. The ^{1}H NMR spectrum of **10** revealed ethyl ester protons as triplet and quartet signals at δ 1.30 and 4.25 ppm, a singlet signal at δ 2.35 due to methyl protons, thiophene C-4 proton as singlet signal at δ 6.05 ppm, in addition to multiplet signal in the region δ 7.10–7.55 ppm

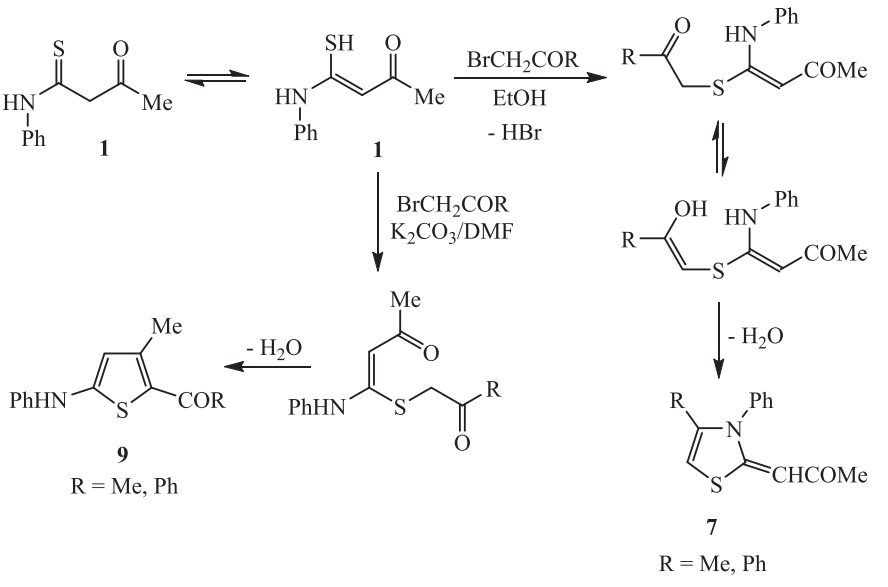


Scheme 2. Reaction of thioacetoacetanilide with ethyl bromoacetate and bromoketones.

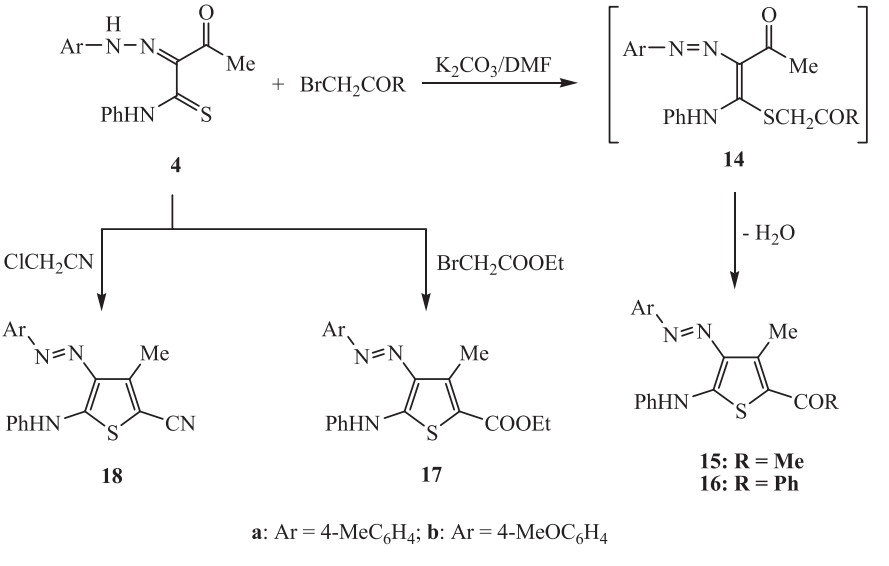
corresponding to the aromatic protons and singlet signal at δ 10.35 pm for the NH group.

Treatment of **1** with hydrazonoyl bromides **11** in ethanol in the presence of triethylamine under reflux, afforded a single product in each case, while verified by TLC. The design of the isolated products had been recognized by analytical and spectroscopic information (IR, ^{1}H NMR and MS) and identified as 2-(2-oxopropylidene)–5-benzoyl-2,3-dihydro-3-aryl-1,3,4-thiadiazoles **13**. The formation of 1,3,4-thiadiazole derivatives **13** from the reaction of **1** with **11** seems to follow the sequence described in Scheme 2. It is suggested that the reaction starts with nucleophilic substitution of the bromine atom in **11** by the thiolate group of **1** to furnish the non-isolable intermediate **12** which cyclizes via elimination of aniline [24] to give **13** as end product. The IR spectrum of **13a** revealed two carbonyl absorption bands at 1681 (C=O, acetyl) and 1639 cm^{-1} (C=O, benzoyl). The ^{1}H NMR spectrum of the same compound showed two singlet signals at δ 2.35 and 2.50 ppm corresponding to the two methyl groups, a singlet signal at δ 5.25 ppm due to olefinic CH proton, in addition to a multiplet signal in the region δ 7.00–7.70 ppm due to the aromatic protons. The mass spectra of the products **13a** and **13b** exhibited in each case a molecular ion peak with high intensity.

The highly versatile 2-arylhydrazono-thioacetoacetanilide **4** underwent heterocyclization with several α-halogenated reagents, *e.g.* bromoacetone, phenacyl bromide, ethyl bromoacetate and chloroacetonitrile in dimethyl formamide-containing potassium carbonate to provide the corresponding 4-arylazo-3-methyl-2-substituted-thiophene dyes **15**, **16**, **17** and **18**, respectively (Scheme 4). The formation of thiophene derivatives **15–18** in the reaction of **4** with the appropriate alkylating agent such as bromoacetone and



Scheme 3. Suggested mechanism for the reaction of thioacetoacetanilide with bromoketones.



Scheme 4. Synthesis of thiophene derivatives 15–18.

phenacyl bromide appears to follow the sequence discussed in Scheme 4. It is stronger recommended the reaction starts through nucleophilic attack of the thiolate group to make the non-isolable S-alkylated intermediate **14** which via nucleophilic addition and intramolecular cyclocondensation simply by water elimination gave the corresponding 4-arylazo-3-methyl-substituted-thiophenes **15–18**. The structures of the highly functionalized 3-methylthiophene derivatives **15–18** were elucidated based on their elemental

Table 1. Antimicrobial activity expressed as inhibition diameter zones in millimeters (mm) of chemical compounds against the pathological strains based on well-diffusion assay.

	Gram-positive bacteria		Gram-negative bacteria		Yeast	
Compd. no.	*S.aureus*	*B.subtilis*	*P.aeruginosa*	*E.coli*	*C.albicans*	*A.niger*
2	20	23	19	22	20	21
3a	17	16	18	19	18	19
3b	16	18	16	17	17	15
5a	17	16	18	21	18	15
5b	16	15	15	17	19	14
6a	14	12	12	15	15	17
6b	15	15	14	14	14	14
7a	20	21	20	24	19	21
7b	22	24	21	22	20	22
8	18	19	22	21	26	19
9a	14	15	16	17	22	20
9b	13	15	12	16	15	13
10	15	16	16	20	20	22
13a	21	20	22	25	32	21
13b	23	18	24	22	19	20
Ciprofloxacin	20	22	24	23	N.A.	N.A.
Ketoconazole	N.A.	N.A.	N.A.	N.A.	23	24

Note: The experiment was carried out in triplicate and the average zone of inhibition was calculated; (N. A. = No Activity).

analyses and spectral data. The IR spectrum of **15a** (as an example) showed an absorption peak at 3382 cm^{-1} corresponding to NH and a broad absorption peak at 1668 cm^{-1} corresponding to the carbonyl group ($COCH_3$). The ^1H NMR spectrum of **15b** (as an example) showed three singlet signals at 2.35, 2.45 and 3.85 ppm due to the three different types of methyl protons (thiophene-CH_3, $COCH_3$ and Ar-OCH_3) and a multiplet signal in the region 7.05–7.80 corresponding to the aromatic protons, in addition to a singlet signal at 13.65 ppm due to the presence of NH group.

Antimicrobial activity

The synthesized compounds **2**, **3**, **5**, **6**, 7, **8**, **9**, **10** and **13** were screened for their antibacterial and antifungal activities at 100 μg/mL concentration against two *Gram-positive bacteria* (*Staphelococcus Aureus* ATCC 29213; *Bacillus subtilis ATCC6633*), two *Gram-negative bacteria* (*Pseudomonas aeroginosa* ATCC 27953; *Escherichia coli ATCC 25922*), Yeast (*Candida albicans* IMRU3669) and Filamentous Fungus (*Aspergillus niger* ATCC 16404). Ciprofloxacin and Ketoconazole were applied as standard antibacterial and antifungal reference, respectively. Many tested compounds exhibited approved antimicrobial activities with regard to the control drugs. The results of antimicrobial activities were demonstrated in Table 1 regarding reference drugs. The Compounds **2**, **7a**, **7b**, **13a** and **13b** exhibited the highest potency against all tested organisms with respect to reference drugs. Compound **7b** inhibited the development of *S. aureus* ATCC 29213 and *B. subtilis ATCC6633* with inhibition zones 22 and 24 mm, respectively. Whilst compound **13a** confirmed outstanding activity against *C. albicans* with inhibition zone 32 mm.

Structure-activity study

The presence of substituents in different positions of both thiazole and thiadiazole moieties causes a certain change of activity. Among the synthesized thiazoles,

2-(2-oxypropylidene)-2,3-dihydro-3-phenyl-4-subtituted-thiazole having a phenyl as substituent at 4-position (compound **7b**) exhibit inhibitory properties higher than that of the corresponding methyl-substituted one (compound **7a**). On the other hand, for the latter compound an increased activity towards *E. coli* can be detected. As concerns thiadiazole derivatives, the introduction of a lipophilic methyl group in the phenyl group that occupy position-3 (compound **13a**) enhances the activity against *C. albicans*.

Experimental

Melting points were recorded on a Gallenkamp melting point equipment and are uncorrected. IR spectra (KBr) were identified on a Mattson 5000 FTIR spectrometer (not all frequencies are usually reported). The ^{1}H and ^{13}C NMR spectra were obtained using a Bruker WP 300 spectrometer at 300 MHz having tetramethylsilane as an internal standard. Mass spectra were recorded on a Finnigan MAT 212 instrument using the CI or EI technique. Elemental analyses were carried out at the Microanalytical unit, Faculty of Science, Cairo University, Egypt. Antibacterial activities were carried out at the laboratory of the microbiology unit – Botany Department – Faculty of Science – Mansoura University, Egypt. ^{13}C NMR spectra did not record for compounds **13a**, **13b**, **16a** and **16b** due to their insufficient solubility in common ^{13}C NMR solvents.

(1) *Synthesis of 2-(2-oxopropylidene)-3-phenyl-thiazolidin-5-one* (*2*): To a solution of thioacetoacetanilide **1** (0.005 mol, 0.96 g) in DMF (25 ml) containing about 0.5 ml triethylamine, chloroacetyl chloride (0.008 mol, 0.65 ml) was added drop by drop. The reaction mixture was allowed to stir for 2 h at room temperature. The reaction mixture was poured into ice–water and the solid product that formed was filtered off, dried and recrystallized from ethanol to afford **2.**

Yellow crystals, m.p. = 205–207°C. Yield = 65%. IR ($\bar{\nu}$/cm^{-1}): 1728 (C=O, ring), 1642 (conjugated C=O), 1594 (C=C). ^{1}H NMR ($CDCl_3$): 2.20 (s, 3H, $COCH_3$), 4.10 (s, 2H, CH_2), 5.20 (s, 1H, =CHCO), 7.30–7.70 (m, 5H, Ar-H). ^{13}C NMR (DMSO-d_6): 28.1, 43.2, 106.6, 128.5 (2C), 129.0 (2C), 130.0, 135.2, 157.9, 184.7, 193.4. MS ($M^+ + 1$; CI-isobutane): *m*/*z* (%) = 234 (100), 218 (26), 201 (52), 177 (18), 142 (30), 91 (68), 77 (74). Analysis for $C_{12}H_{11}NO_2S$ (233.29): Calcd.: C, 61.78; H, 4.75; N, 6.00; Found: C, 61.83; H, 4.67; N, 6.09.

(2) *Synthesis of 4-arylidene-2-(2-oxopropylidene)-3-phenyl-thiazolidin-5-one derivatives* (3): A mixture of **2** (0.002 mol, 0.46 g) and the suitable aldehyde (0.002 mol) in ethanol (15 ml) containing a catalytic amount of piperidine was refluxed for 2 h. The reaction mixture was cooled off; the solid products that formed were filtered off, dried and recrystallized by ethanol to afford **3** in excellent yield.

4-(4-Methylbenzylidene)-2-(2-oxopropylidene)-3-phenyl-thiazolidin-5-one (*3a*): Yellowish green crystals, m.p. = 248–250°C. Yield = 82%. IR ($\bar{\nu}$/cm^{-1}): 1709 (C=O, ring), 1643 (conjugated C=O), 1598 (C=C). ^{1}H NMR (DMSO-d_6): δ/ppm = 2.20 (s, 3H, $COCH_3$), 2.40 (s, 3H, Ar-CH_3), 5.50 (s, 1H, olefinic CH), 7.10–7.70 (m, 10H, Ar-H and =CHAr). ^{13}C NMR (DMSO-d_6): 21.6, 28.1, 106.8, 120.4, 128.5 (2C), 129.0 (2C), 129.4, 129.9 (2C), 130.9, 131.2 (2C), 135.1, 135.4, 141.1, 154.8, 180.0, 193.4. MS ($M^+ + 1$; CI-isobutane): *m*/*z* (%) = 336 (100), 320 (51), 292 (19), 259 (63), 235 (56), 218 (22), 201 (36), 91 (71), 76 (84). Analysis for $C_{20}H_{17}NO_2S$ (335.42): Calcd.: C, 71.62; H, 5.11; N, 4.18; Found: C, 71.60; H, 5.14; N, 4.24.

4-(4-Methoxybenzylidene)-2-(2-oxopropylidene)-3-phenyl-thiazolidin-5-one (**3b**): Yellowish green crystals, m.p. = 238–240°C. Yield = 87%. IR ($\bar{\nu}$/cm^{-1}): 1702 (C=O, ring), 1651 (conjugated C=O), 1597 (C=C). ^{1}H NMR (DMSO-d_6): δ/ppm = 2.40 (s, 3H, $COCH_3$), 3.85 (s, 3H, OCH_3), 5.50 (s, 1H, olefinic CH), 6.90–7.60 (m, 10H, Ar-H and =CHAr). ^{13}C NMR (DMSO-d_6): 27.9, 55.5, 108.6, 114.6 (2C), 118.6, 126.4, 128.6 (2C), 129.0 (2C), 129.4, 133.0 (2C), 134.9, 135.3, 155.0, 161.3, 180.1, 193.4. MS ($M^+ + 1$; CI-isobutane): *m*/*z* (%) = 352 (100), 336 (28), 308 (54), 279 (47), 258 (82), 244 (52), 218 (22), 201 (37), 92 (64), 71 (88). Analysis for $C_{20}H_{17}NO_3S$ (351.42): Calcd.: C, 68.36; H, 4.88; N, 3.99; Found: C, 68.42; H, 4.83; N, 3.91.

(3) *Synthesis of 2-arylhydrazono-thioacetoacetanilide derivatives 4*: A cold solution of sodium nitrite (0.01 mol, 0.7 g) in 20 ml water was added gradually to a cold suspension (0–5°C) of the desired aromatic amine (0.01 mol) in 3 ml concentrated HCl. The freshly prepared diazonium salt solution thus obtained and added by continuous stirring to a cold solution (0–5°C) of thioacetoacetanilide **(1)** (0.01 mol, 1.93 g) in 40 ml ethanol and sodium acetate (4.0 g). The reaction mixture was allowed to stir at (0–5°C) for 2 h and diluted by water. The solid was collected by filtration, dried and recrystallized from ethanol to afford the corresponding α-arylhydrazono-thioacetoacetanilide derivatives **4a** and **4b**.

2-(p-Tolylhydrazono)-thioacetoacetanilide (**4a**): Orange crystals, m.p. = 134–135°C. Yield = 77%. IR ($\bar{\nu}$/cm^{-1}): 3357 (NH), 1688 (C=O), 1608 (C=N). ^{1}H NMR (DMSO-d_6): δ/ppm = 2.35 (s, 3H, $COCH_3$), 2.60 (s, 3H, CH_3), 7.20–7.60 (m, 10H, Ar-H and NH), 13.65 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 20.9, 27.8, 116.5 (2C), 118.2, 124.9 (2C), 126.9, 128.8 (2C), 130.1 (2C), 135.2, 137.7, 139.6, 184.0, 193.1. MS (M^+; EI): *m*/*z* (%) = 311 (58), 298 (34), 272 (46), 258 (27), 219 (100), 205 (31), 119 (42), 91 (87), 77 (48). Analysis for $C_{17}H_{17}N_3OS$ (311.40): Calcd.: C, 65.57; H, 5.50; N, 13.49; Found: C, 65.72; H, H, 5.57; N, 13.38.

2-(p-Methoxyphenylhydrazono)-thioacetoacetanilide (**4b**): Orange crystals, m.p. = 106–107°C, Lit. m.p. = 104°C.[23] Yield = 58%. IR ($\bar{\nu}$/cm^{-1}): 3346 (NH), 1684 (C=O), 1607 (C=N). ^{1}H NMR (DMSO-d_6): δ/ppm = 2.40 (s, 3H, $COCH_3$), 3.85 (s, 3H, OCH_3), 6.90–7.60 (m, 10H, Ar-H and NH), 13.65 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 27.8, 55.5, 115.3 (2C), 118.0 (2C), 123.8, 128.6 (2C), 129.8 (2C), 134.4, 137.5, 139.6, 154.4, 184.1, 193.2. MS (M^+; EI): *m*/*z* (%) = 327 (64), 314 (53), 297 (38), 269 (67), 258 (25), 235 (100), 191 (21), 122 (36), 107 (73), 77 (59).

(4) *Synthesis of 2-[(1-p-arylazo)-2-oxopropylidene]-3-phenyl-thiazolidin-5-ones 5*: To a solution of compound **4** (0.002 mol) in DMF (15 ml) containing triethylamine (0.5 ml), a chloroacetyl chloride (0.003 and 0.25 ml) was added dropwise with stirring at room temperature. Stirring was continued for 4 h, and then the reaction mixture was poured into ice cooled water. The precipitate was collected by filtration, dried and recrystallized from ethanol.

2-[(1-p-Tolylazo)-2-oxopropylidene]-3-phenyl-thiazolidin-5-one (**5a**): Yellow crystals, m.p. = 154–155°C. Yield = 52%. IR ($\bar{\nu}$/cm^{-1}): 3227 (NH), 1729 (C=O, ring), 1686 (conjugated C=O), 1591 (C=C), 1562 (N=N). ^{1}H NMR (DMSO-d_6): δ/ppm = 2.35 (s, 3H, $COCH_3$), 3.90 (s, 3H, OCH_3), 4.25 (s, 2H, CH_2), 6.90–7.60 (m, 9H, Ar-H). ^{13}C NMR (DMSO-d_6): 21.1, 28.0, 43.1, 117.8, 128.5 (2C), 129.1 (2C), 129.4 (2C), 130.2 (2C), 134.1, 138.2, 142.8, 145.4, 156.5, 183.6, 193.1. MS (M^+; EI): *m*/*z* (%) = 351 (18), 323 (81), 309 (62), 244 (100), 231 (30), 155 (47), 118 (22), 91 (68), 76 (73). Analysis for $C_{19}H_{17}N_3O_2S$ (351.42): Calcd.: C, 64.94; 4.88; 11.96; Found: C, 65.06; H, 4.81; N, 11.87.

2-[(1-p-Methoxyphenylazo)-2-oxopropylidene]-3-phenyl-thiazolidin-5-one (**5b**): Orange crystals, m.p. = 174–175°C. Yield = 58%. IR ($\bar{\nu}$/cm^{-1}): 3241 (NH), 1734 (C=O, ring), 1687 (conjugated C=O), 1594 (C = C), 1557 (N=N). ^{1}H NMR (DMSO-d_6): δ/ppm = 2.35 (s, 3H, $COCH_3$), 2.50 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 6.80–7.55 (m, 9H, Ar-H). ^{13}C NMR (DMSO-d_6): 27.9, 42.9, 55.6, 115.6 (2C), 121.7, 128.6 (2C), 129.8 (2C), 132.7 (2C), 138.2, 142.8, 145.4, 156.5, 161.1, 183.3, 193.4. MS (M^+; EI): *m*/*z* (%) = 367 (32), 339 (100), 328 (54), 285 (37), 245 (62), 230 (57), 217 (36), 190 (44), 107 (81), 92 (63), 76 (84). Analysis for $C_{19}H_{17}N_3O_3S$ (367.42): Calcd.: C, 62.11; H, 4.66; N, 11.44; Found: C, 62.25; H, 4.75; N, 11.48.

(5) *Synthesis of 4-(2-arylhydrazono)-2-(2-oxopropylidene)-3-phenyl-thiazolidin-5-one derivatives 6*: The aryl diazonium chloride was prepared by addition of sodium nitrite solution (0.005 mol, 0.35 g in 5 ml H_2O) into cold suspension of aromatic amine (0.005 mol) in concentrated HCl (1.5 ml) with stirring. To a cold solution of the thiazolidin-5-one **2** (0.005 mol, 1.16 g) in pyridine, a cold aqueous solution from the related aryl diazonium chloride (0.005 mol) was added dropwise with stirring. The reaction mixture was stiired at 0–5°C for 2 hours, diluted with water, filtered, washed with water and then dried. The products were recrystallised from ethanol–DMF mixture (2:1) to furnish the equivalent 4-arylazo-thiazolidin-5-one derivatives **5**.

4-(2-p-Tolylhydrazono)-2-(2-oxopropylidene)-3-phenyl-thiazolidin-5-one (**6a**): Red crystals, m.p. = 178–180°C. Yield = 74%. IR ($\bar{\nu}$/cm^{-1}): 3136 (NH), 1696 (C=O, ring), 1656 (conjugated C=O), 1603 (C=N), 1593 (C=C). ^{1}H NMR (DMSO-d_6): 2.20 (s, 3H, $COCH_3$), 2.35 (s, 3H, CH_3), 5.50 (s, 1H, olefinic CH), 7.10–7.65 (m, 9H, Ar-H), 8.75 (s, 1H, C = NNH). ^{13}C NMR (DMSO-d_6): 21.2, 28.0, 108.2, 122.4, 122.8 (2C), 129.6 (4C), 131.2 (2C), 133.6, 141.6, 142.8, 144.6, 155.7, 178.8, 193.2. MS (M^+; EI): *m*/*z* (%) = 351 (69), 312 (24), 291 (41), 260 (27), 251 (51), 216 (100), 204 (56), 159 (38), 91 (52), 77 (70). Analysis for $C_{19}H_{17}N_3O_2S$ (351.42): Calcd.: C, 64.94; H, 4.88; N, 11.96; Found: C, 64.72; H, 4.94; N, 11.84.

4-(2-(p-Methoxyphenyl)hydrazono)-2-(2-oxopropylidene)-3-phenyl-thiazolidin-5-one (**6b**): Deep red crystals, m.p. = 192–193°C. Yield = 68%. IR ($\bar{\nu}$/cm^{-1}): 3128 (NH), 1692 (C=O, ring), 1655 (conjugated C=O), 1605 (C=N), 1595 (C=C). ^{1}H NMR (DMSO-d_6): 2.20 (s, 3H, $COCH_3$), 3.90 (s, 3H, OCH_3), 5.40 (s, 1H, olefinic CH), 6.90–7.60 (m, 9H, Ar-H), 8.60 (s, 1H, C = NNH). ^{13}C NMR (DMSO-d_6): 27.8, 55.6, 108.4, 115.8 (2C), 122.2, 128.8 (2C), 129.6 (2C), 132.2 (2C), 138.4, 142.7, 144.5, 155.3, 160.4, 179.2, 193.1. MS (M^+; EI): *m*/*z* (%) = 367 (87), 335 (48), 315 (19), 298 (33), 202 (48), 168 (40), 91 (100), 77 (63). Analysis for $C_{19}H_{17}N_3O_3S$ (367.42): Calcd.: C, 62.11; H, 4.66; 11.44; Found: C, 62.03 H, 4.75; N, 11.56.

(6) *Synthesis of 2-(2-oxypropylidene)-2,3-dihydro-3-phenylthiazole derivatives 7 and 8*: A mixture of **1** (0.002 mol, 0.38 g) and the appropriate α-bromoketone and/or ethyl bromoacetate (0.002 mol) (15 ml) was refluxed in ethanol for 2 h. The reaction mixture was cooled; the solid products that formed were filtered off, dried and recrystallized from ethanol to afford the corresponding thiazole derivatives **7** and/or **8** in good yield.

2-(2-Oxopropylidene)-2,3-dihydro-4-methyl-3-phenylthiazole (**7a**): Yellowish white crystals, m.p. = 181–182°C. Yield = 82%. IR ($\bar{\nu}$/cm^{-1}): 1680 (C=O), 1596 (C=C). ^{1}H NMR (DMSO-d_6): 1.80 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 5.45 (s, 1H, C = CHCO), 6.40 (s, 1H, thiazole 5-H), 7.00–7.40 (m, 5H, Ar-H). ^{13}C NMR (DMSO-d_6): 19.1, 27.8, 105.9, 112.3, 128.4

(2C), 129.1 (2C), 130.2, 134.7, 141.8, 156.6, 192.7. MS (M^+; EI): *m/z* (%) = 231 (27), 218 (80), 200 (100), 159 (29), 139 (27), 111 (31), 91 (63), 77 (71). Analysis for $C_{13}H_{13}NOS$ (231.31): Calcd.: C, 67.50; H, 5.66; N, 6.06; Found: C, 67.69; H, 5.72; N, 6.15.

2-(2-Oxopropylidene)-2,3-dihydro-3,4-diphenylthiazole (**7b**): Yellowish white crystals, m.p. = 204–206°C. Yield = 88%. IR ($\bar{\nu}$/cm^{-1}): 1678 (C=O), 1595 (C=C). ^{1}H NMR (DMSO-d_6): 2.35 (s, 3H, CH_3), 5.60 (s, 1H, C=CHCO), 6.40 (s, 1H, thiazole 5-H), 7.05–7.60 (m, 10H, Ar-H). ^{13}C NMR (DMSO-d_6): 27.8, 107.4, 112.3, 126.41, 128.3 (2C), 129.1 (2C), 130.2, 130.60 (2C), 131.73 (2C), 134.7, 135.72, 142.4, 156.4, 192.8. MS (M^+; EI): *m/z* (%) = 293 (34), 267 (19), 254 (47), 228 (25), 173 (100), 161 (42), 140 (53), 113 (57), 91 (71), 77 (91). Analysis for $C_{18}H_{15}NOS$ (293.38): Calcd.: C, 73.69; H, 5.15; N, 4.77; Found: C, 73.48; H, 5.23; N, 4.65.

2-(2-Oxopropylidene)-3-phenyl-thiazolidin-4-one (**8**): Yellow crystals, m.p. = 152–153°C. Yield = 78%. IR ($\bar{\nu}$/cm^{-1}): 1719 (C=O, ring), 1684 (C=O), 1603 (C=C). ^{1}H NMR ($CDCl_3$): 2.35 (s, 3H, CH_3), 3.90 (s, 2H, CH_2), 5.25 (s, 1H, C=CHCO), 7.00–7.45 (m, 5H, Ar-H). ^{13}C NMR (DMSO-d_6): 28.1, 31.6, 106.7, 128.2 (2C), 129.3, 130.3 (2C), 137.2, 158.2, 172.4, 193.3. MS (M^+; EI): *m/z* (%) = 233 (48), 218 (36), 205 (100), 91 (82), 77 (87). Analysis for $C_{12}H_{11}NO_2S$ (233.29): Calcd.: C, 61.78; H, 4.75; N, 6.00; Found: C, 61.92; H, 4.68; N, 6.11.

(7) *Synthesis of 3-methyl-5-phenylamino-2-substituted-thiophene derivatives 9 and 10*: To a solution of **1** (0.002 mol, 0.38 g) in 15 ml dimethyl formamide (*DMF*), a solid potassium carbonate (0.004 mol, 0.55 g) and 0.002 mol of the appropriate α-halogenated reagent *e.g.* bromoacetone, phenacyl bromide and/or ethyl bromoacetate were added. The reaction mixture was stirred for 12 h. The reaction mixture was poured into cold H_2O, neutralized with dilute HCl, the solid product that formed was filtered, and recrystallized from ethanol to afford the corresponding thiophene derivatives **9** and/or **10**.

2-Acetyl-3-methyl-5-phenylamino-thiophene (**9a**): Orange crystals, m.p. = 212–213°C. Yield = 66%. IR ($\bar{\nu}$/cm^{-1}): 3253 (NH), 1666 (C=O), 1595 (C=C). ^{1}H NMR (DMSO-d_6): 2.30 (s, 3H, CH_3), 2.60 (s, 3H, $COCH_3$), 6.10 (s, 1H, thiophene 4-H), 7.10–7.45 (m, 5H, Ar-H), 9.65 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 14.62, 26.43, 125.47, 128.11 (2C), 129.58 (2C), 130.61, 135.74, 144.58, 150.41, 161.68, 192.92. MS (M^+; EI): *m/z* (%) = 231 (100), 218 (28), 200 (47), 92 (100), 77 (63). Analysis for $C_{13}H_{13}NOS$ (231.31): Calcd.: C, 67.50; H, 5.66; N, 6.06; Found: C, 67.41; H, 5.68; N, 6.15.

2-Benzoyl-3-methyl-5-phenylamino-thiophene (**9b**): Orange crystals, m.p. = 234–235°C. Yield = 72%. IR ($\bar{\nu}$/cm^{-1}): 3331 (NH), 1652 (C=O), 1596 (C=C). ^{1}H NMR (DMSO-d_6): 2.30 (s, 3H, CH_3), 6.15 (s, 1H, thiophene 4-H), 7.05–7.70 (m, 10H, Ar-H), 9.80 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 14.85, 126.37, 128.59 (2C), 129.37 (2C), 130.35 (2C), 131.05 (2C), 131.7, 133.82, 135.08, 138.14, 143.52, 149.52, 151.80, 181.72. MS (M^+; EI): *m/z* (%) = 293 (62), 280 (39), 267 (26), 254 (51), 228 (100), 201 (48), 92 (64), 77 (83). Analysis for $C_{18}H_{15}NOS$ (293.38): Calcd.: C, 73.69; H, 5.15; N, 4.77; Found: C, 73.84; H, 5.20; N, 4.83.

2-Ethoxycarbonyl-3-methyl-5-phenylamino-thiophene (**10**): Yellow crystals, m.p. = 194–195°C. Yield = 84%. IR ($\bar{\nu}$/cm^{-1}): 3327 (NH), 1674 (C=O), 1596 (C=C). ^{1}H NMR (DMSO-d_6): 1.30 (t, 3H, CH_3, J = 7.15 Hz), 2.35 (s, 3H, CH_3), 4.25 (q, 2H, CH_2, J = 7.15 Hz), 6.05 (s, 1H, thiophene 4-H), 7.10–7.55 (m, 5H, Ar-H), 10.35 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 13.84, 14.26, 60.13, 128.62 (2C), 129.58 (2C), 130.07, 131.3, 135.17, 144.81, 147.8, 151.62, 163.68. MS (M^+; EI): *m/z* (%) = 261 (48), 248 (100), 231 (51), 222

(36), 209 (41), 91 (55), 77 (81). Analysis for $C_{14}H_{15}NO_2S$ (261.34): Calcd.: C, 64.34; H, 5.79; N, 5.36; Found: C, 64.18; H, 5.86; N, 5.44.

(8) *Synthesis of 2-(2-oxopropylidene)–5-benzoyl-2,3-dihydro-3-(p-tolyl)-1,3,4-thiadiazole derivatives 13*: To a mixture of **1** (0.002 mol, 0.38 g) and the appropriate hydrazonoyl bromides **11a** and/or **11b** (0.002 mol) in absolute ethanol (25 ml), few drops of triethylamine was added as a catalyst. The mixture was refluxed for 4 h, then left to cool at room temperature. The solid that formed was collected by flirtation, dried and recrystallized form ethanol to give the corresponding thiadiazoles **13a** and/or **13b**, respectively.

2-(2-oxopropylidene)–5-benzoyl-2,3-dihydro-3-(p-tolyl)-1,3,4-thiadiazole (**13a**): Orange crystals, m.p. = 223–224°C. Yield = 64%. IR ($\bar{\nu}$/cm^{-1}): 1681 (=CHCOCH$_3$), 1639 (COPh), 1607 (C=N), 1594 (C=C). ^{1}H NMR (DMSO-d_6): 2.35 (s, 3H, COCH$_3$), 2.50 (s, 3H, Ar-CH$_3$), 5.25 (s, 1H, C=CHCO), 7.00–7.70 (m, 9H, Ar-H). MS (M$^+$; EI): *m*/*z* (%) = 336 (78), 323 (26), 310 (29), 296 (51), 278 (58), 264 (41), 243 (33), 229 (42), 216 (50), 91 (100), 77 (65). Analysis for $C_{19}H_{16}N_2O_2S$ (336.41): Calcd.: C, 67.84; H, 4.79; N, 8.33; Found: C, 67.68; H, 4.86; N, 8.26.

2-(2-oxopropylidene)–5-benzoyl-2,3-dihydro-3-(p-methoxyphenyl)-1,3,4-thiadiazole (**13b**): Orange crystals, m.p. = 229–230°C. Yield = 71%. IR ($\bar{\nu}$/cm^{-1}): 1678 (=CHCOCH$_3$), 1637 (COPh), 1607 (C=N), 1591 (C=C). ^{1}H NMR (DMSO-d_6): 2.35 (s, 3H, COCH$_3$), 3.85 (s, 3H, OCH$_3$), 5.30 (s, 1H, C=CHCO), 6.90–7.70 (m, 9H, Ar-H). MS (M$^+$; EI): *m*/*z* (%) = 352 (83), 336 (31), 320 (100), 296 (37), 270 (67), 244 (43), 216 (27), 202 (56), 92 (82), 77 (63). Analysis for $C_{19}H_{16}N_2O_3S$ (352.41): Calcd.: C, 64.76; H, 4.58; N, 7.95; Found: C, 64.84; H, 4.54; N, 7.88.

(9) *Synthesis of 4-arylazo-3-methyl-5-phenylamino-thiophene derivatives 15–18*: To a solution of **4** (0.002 mol) in 20 ml dimethyl formamide (*DMF*), a solid potassium carbonate (0.004 mol) and the appropriate α-halogenated reagent (0.002 mol), *e.g.* bromoacetone, phenacyl bromide, ethyl bromoacetate and/or chloroacetonitrile were added. The reaction mixture was stirred for 12 h. The reaction mixture was poured into cold H_2O, neutralized with dilute HCl, the solid product that formed was filtered, and recrystallized from ethanol or an ethanol–*DMF* mixture (2:1) to afford the corresponding thiophene derivatives **15**, **16**, **17** and/or **18**, respectively.

2-Acetyl-3-methyl-5-phenylamino-4-(p-tolylazo)-thiophene **(15a):** Red crystals, m.p. = 192–193°C. Yield = 78%. IR ($\bar{\nu}$/cm^{-1}): 3382 (NH), 1668 (C=O), 1597 (C=C), 1528 (N=N). ^{1}H NMR (DMSO-d_6): 2.35 (s, 3H, CH$_3$), 2.45 (s, 3H, CH$_3$), 2.60 (s, 3H, CH$_3$), 7.10–7.55 (m, 9H, Ar-H), 13.55 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 14.52, 21.15, 27.83, 115.03 (2C), 125.64, 128.58 (2C), 129.68 (2C), 131.36 (2C), 135.24, 137.03, 140.62, 141.92, 145.61, 150.20, 157.74, 192.52. MS (M$^+$; EI): *m*/*z* (%) = 349 (100), 324 (83), 297 (43), 271 (49), 266 (66), 245 (37), 214 (72), 201 (56), 77 (84). Analysis for $C_{20}H_{19}N_3OS$ (349.45): Calcd.: C, 68.47; H, 5.48; N, 12.02; Found: C, 68.68; H, 5.56; N, 12.11.

2-Acetyl-3-methyl-4-(p-methoxyphenylazo)-5-phenylamino-thiophene (**15b**): Red crystals, m.p. = 211–212°C. Yield = 74%. IR ($\bar{\nu}$/cm^{-1}): 3342 (NH), 1664 (C=O), 1595 (C=C), 1562 (N=N). ^{1}H NMR (DMSO-d_6): 2.35 (s, 3H, CH$_3$), 2.45 (s, 3H, CH$_3$), 3.85 (s, 3H, OCH$_3$), 7.05–7.80 (m, 9H, Ar-H), 13.65 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 14.68, 27.82, 55.65, 116.46 (2C), 122.17, 128.82 (2C), 129.53 (2C), 129.78 (2C), 135.26, 138.04, 141.92, 145.16, 149.37, 157.54, 161.36, 192.23. MS (M$^+$; EI): *m*/*z* (%) = 365 (92), 333 (26),

307 (100), 273 (47), 251 (39), 229 (58), 77 (82). Analysis for $C_{20}H_{19}N_3O_2S$ (365.45): Calcd.: C, 65.73; H, 5.24; N, 11.50; Found: C, 65.57; H, 5.34; N, 11.38.

2-Benzoyl-3-methyl-5-phenylamino-4-(p-tolylazo)-thiophene (**16a**): Red crystals, m.p. = 164–165°C. Yield = 81%. IR ($\bar{\nu}$/cm^{-1}): 3282 (NH), 1654 (C=O), 1596 (C=C), 1542 (N=N). ^{1}H NMR (DMSO-d_6): 2.35 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.25–7.75 (m, 14H, Ar-H), 13.60 (s, 1H, NH). MS (M^+; EI): *m/z* (%) = 411 (65), 398 (31), 385 (26), 372 (53), 358 (47), 320 (58), 292 (28), 267 (66), 243 (38), 228 (44), 215 (100), 91 (52), 77 (78). Analysis for $C_{25}H_{21}N_3OS$ (411.52): Calcd.: C, 72.97; H, 5.14; N, 10.21; Found: C, 72.85; H, 5.19; N, 10.14.

2-Benzoyl-3-methyl-4-(p-methoxyphenylazo)-5-phenylamino-thiophene (**16b**): Red crystals, m.p. = 177–179°C. Yield = 78%. IR ($\bar{\nu}$/cm^{-1}): 3294 (NH), 1651 (C=O), 1597 (C=C), 1558 (N=N). ^{1}H NMR (DMSO-d_6): 2.35 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.05–7.85 (m, 14H, Ar-H), 12.95 (s, 1H, NH). MS (M^+; EI): *m/z* (%) = 427 (62), 414 (73), 388 (22), 307 (18), 292 (42), 280 (79), 277 (48), 244 (39), 228 (53), 215 (100), 92 (58), 77 (85). Analysis for $C_{25}H_{21}N_3O_2S$ (427.52): Calcd.: C, 70.24; H, 4.95; N, 9.83; Found: C, 70.13; H, 4.86; N, 9.92.

2-Ethoxycarbonyl-3-methyl-5-phenylamino-4-(p-tolylazo)-thiophene (**17a**): Reddish brown crystals, m.p. = 145–146°C. Yield = 78%. IR ($\bar{\nu}$/cm^{-1}): 3203 (NH), 1695 (C=O), 1595 (C=C), 1550 (N=N). ^{1}H NMR (DMSO-d_6): 1.30 (t, 3H, CH_3, J = 7.15 Hz), 2.35 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 4.30 (q, 2H, CH_2, J = 7.15 Hz), 7.20–7.65 (m, 9H, Ar-H), 13.75 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 14.28, 14.59, 21.14, 60.25, 115.46 (2C), 125.42, 128.61 (2C), 129.76 (2C), 131.84 (2C), 135.18, 137.68, 140.62, 142.37, 145.43, 149.74, 154.28, 163.37. MS (M^+; EI): *m/z* (%) = 379 (51), 349 (36), 334 (29), 262 (54), 258 (48), 242 (61), 229 (38), 211 (100), 77 (83). Analysis for $C_{21}H_{21}N_3O_2S$ (379.48): Calcd.: C, 66.47; H, 5.58; N, 11.07; Found: C, 66.58; H, 5.56; N, 11.13.

2-Ethoxycarbonyl-3-methyl-4-(p-methoxyphenylazo)-5-phenylamino-thiophene (**17b**): Reddish brown crystals, m.p. = 174–175°C. Yield = 74%. IR ($\bar{\nu}$/cm^{-1}): 3214 (NH), 1691 (C=O), 1593 (C=C), 1531 (N=N). ^{1}H NMR (DMSO-d_6): 1.30 (t, 3H, CH_3, J = 7.15 Hz), 2.35 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.30 (q, 2H, CH_2, J = 7.15 Hz), 7.05–7.70 (m, 9H, Ar-H), 13.65 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 14.16, 14.63, 55.62, 60.21, 116.22 (2C), 122.74, 128.71 (2C), 129.41 (2C), 129.73 (2C), 135.22, 137.34, 141.73, 144.94, 149.08, 154.13, 161.36, 163.32. MS (M^+; EI): *m/z* (%) = 395 (43), 364 (93), 326 (54), 319 (73), 274 (22), 245 (29), 212 (100), 77 (85). Analysis for $C_{21}H_{21}N_3O_3S$ (395.47): Calcd.: C, 63.78; H, 5.35; N, 10.63; Found: C, 63.92; H, 5.30; N, 10.54.

2-Cyano-3-methyl-5-phenylamino-4-(p-tolylazo)-thiophene (**18a**): Red crystals, m.p. = 168–170°C. Yield = 81%. IR ($\bar{\nu}$/cm^{-1}): 3284 (NH), 2194 (C≡N), 1594 (C=C), 1540 (N=N). ^{1}H NMR (DMSO-d_6): 2.35 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 7.30–7.75 (m, 9H, Ar-H), 13.75 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 14.17, 21.14, 105.83, 111.60, 115.82 (2C), 122.69, 125.41, 128.61 (2C), 129.68 (2C), 131.24 (2C), 135.14, 138.52, 142.46, 147.83, 155.06. MS (M^+; EI): *m/z* (%) = 332 (100), 318 (35), 306 (66), 279 (52), 267 (71), 255 (55), 241 (19), 227 (38), 199 (51), 77 (66). Analysis for $C_{19}H_{16}N_4S$ (332.42): Calcd.: C, 68.65; H, 4.85; N, 16.85; Found: C, 68.53; H, 4.78; N, 16.89.

2-Cyano-3-methyl-4-(p-methoxyphenylazo)-5-phenylamino-thiophene (**18b**): Red crystals, m.p. = 184–186°C. Yield = 78%. IR ($\bar{\nu}$/cm^{-1}): 3277 (NH), 2198 (C≡N), 1597 (C=C), 1558 (N=N). ^{1}H NMR (DMSO-d_6): 2.35 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.05–7.85 (m, 9H, Ar-H), 13.05 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 14.15, 55.58, 105.65,

111.60, 115.82 (2C), 116.78 (2C), 122.54, 124.83, 128.58 (2C), 129.72 (2C), 138.53, 142.73, 148.36, 155.14, 161.47. MS (M^+; EI): m/z (%) = 348 (100), 335 (47), 319 (32), 292 (58), 279 (72), 241 (50), 225 (33), 212 (84), 77 (69). Analysis for $C_{19}H_{16}N_4OS$ (348.42): Calcd.: C, 65.50; H, 4.63; N, 16.08; Found: 65.63; H, 4.56; N, 16.17.

(10) *Antimicrobial activity.* Compounds were separately screened towards a panel of gram-positive and gram-negative bacterial pathogens, yeast and fungi. Antimicrobial tests were carried out by the agar well-diffusion method [25] using 100 L of suspension containing 1×10^8 CFU/mL of pathological tested bacteria and 1×10^6 CFU/ml of yeast spread on nutrient agar (NA) and Sabourand dextrose agar (SDA), respectively. Following the media had cooled and solidified, wells (10 mm in diameter) were made in the solidified agar and loaded with 100 L of tested compound solution prepared by dissolving 100 mg of the chemical compound in one ml of dimethyl sulfoxide (DMSO). The inculcated plates were then incubated for 24 h at 37°C for bacteria and 48 h at 28°C for fungi. Negative controls were prepared using DMSO employed for dissolving the tested compound. Ciprofloxacin (50 g/ml) and Ketoconazole (50 g/ml) were used as standard for antibacterial and antifungal activity, respectively. After incubation time, antimicrobial activity was evaluated by measuring the zone of inhibition against the test organisms and compared with that of the standard. Antimicrobial activities were expressed as inhibition diameter zones in millimeters (mm). The experiment was carried out in triplicate and the average zone of inhibition was calculated.

Disclosure statement

No potential conflict of interest was reported by the authors.

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