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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, characterization, and antimicrobial studies of novel 1,3,4-thiadiazolium-5-thiolates

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Abstract Sixteen novel thiadiazolium derivatives **6**(**a**–**h**) and **12**(**a**–**h**) were synthesized by conventional route starting from anthranilic acid using different acid chloride derivatives. The structure of all the newly synthesized compounds was established by IR, NMR, mass spectroscopy, and elemental analysis. The compounds were also screened for their antibacterial activity against some important bacterial species. Some of the compounds were found excellent active against these species.

Keywords Mesoionic · 1,3,4-Thiadiazolium-5-thiolate · Quinazoline · Antibacterial activity

Introduction

The modern approach of heterocyclic synthesis involves syntheses of new compounds based largely on modification of structures of known activity. Minor group modification may bring about changes in large biological effect. In the search for safer and more potent therapeutic agents, popular approach is to synthesize and evaluate biologically active compounds with chemical structures analogous to those having the desired biological activity. Interest in the medicinal chemistry of quinazolinone derivatives was stimulated since 1950 with the elucidation of a quinazolinone alkaloid from an Asian plant *Dichroa febrifuga*, which is an ingredient of a traditional Chinese herbal remedy, effective against malaria (Koepfli *et al.*, 1947). In a quest to find additional potential quinazolinone-based drugs, various substituted quinazolinones have been synthesized, which led to the synthesis of the derivative 2-methyl-3-o-tolyl-4-(3*H*)-quinazolinone [Methaqualone (Structure 1)].

Quinazoline derivatives were found to possess various biological activities like, antitumor (Galarce *et al.*, 2008), anti-inflammatory (Baba *et al.*, 1996), antibacterial (Bedi *et al.*, 2004), anticancer (Gudasi *et al.*, 2009), anti HIV [Desai *et al.*, 1998], antileprotic (DeGraw *et al.*, 1974), antimalarial (Bhattacharjee *et al.*, 2004), anticonvulsant, sedative-hypnotic (Kashaw *et al.*, 2010) activity, and many more. Literature survey reveals that mesoionic compounds are most important class of heterocyclic compounds. Mesoionic compounds were synthesized and studied by various scientists from past years. This class of compounds found to possess vast array of synthetic as well as biological importance (Badami, 2006; Cardoso *et al.*, 2004). Concept of mesoionic compounds has developed gradually over the years. 1,3,4-Thiadiazolium derivatives are important class of mesoionic compounds. The purpose of this study is to find out novel thiadiazolium derivatives which might have potent antimicrobial activity.

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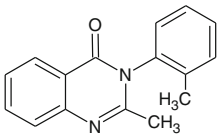
Results and discussion

In this investigation, we have synthesized, characterized the novel 1,3,4-thiadiazolium-5-thiolate **6**(**a**–**h**) and **12**(**a**–**h**) derivatives and studied their antibacterial activity.

Structure 1 2-methyl-3-o-tolyl-4-(3*H*)-quinazolinone



4-(4-Oxo-2-phenylquinazolin-3(4*H*)-yl)benzoic acid (**3**) was synthesized from starting material anthranilic acid according to literature procedure (Desai and Desai, 2005). Compound **3** was converted into acid chloride derivatives followed by reaction with hydrazine hydrate to form benzohydrazide derivative (**4**) which on reaction with carbon disulfide and potassium disulfide gave potassium salt of 2-{[4-(4-oxo-2-phenylquinazoline-3(4*H*)-yl) phenyl]carbonyl}hydrazine carbodithioic acid (**5**). Compound **5** on cyclization with different acid chloride derivatives resulted into formation of 2-(substituted)-3-[4-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)benzoyl]-1,3,4-thiadiazolium-5-thiolate **6**(**a**–**h**) (Fig. 1).

Alternately 2-substituted-3-{4-[(2-phenyl-4-quinazolinyl)amino]benzoyl}-1,3,4-thiadia-zolium-5-thiolate **12**(**a**–**h**) have been synthesized by eight step procedure starting from antharanilic acid as drawn in Fig. 2. 4-Chloro-2-phenyl-3,4-dihydroquinazoline (**8**) was synthesized according to literature procedure (Mani Chandrika *et al.*, 2009). All the synthesized compounds were characterized by IR and NMR spectroscopy. The expected IR spectral features of synthesized compounds **6**(**a**–**h**) and **12**(**a**–**h**) are assigned. The band observed around 1288–1354 cm^{-1} is attributed to C=S stretching vibration of thiazole ring. Bands at about 1603–1660 cm^{-1} are attributed to C–N stretching of quinazoline ring. Strong band in the region 1685–1745 cm^{-1} is due to C=O stretching of amide group. ^{1}H-NMR and ^{13}C NMR spectral data of compounds **6**(**a**–**h**) and **12**(**a**–**h**) are shown in "Experimental" section. Chemical shift δ at around 10.50 ppm due to the presence of NH group. ^{13}C NMR of carbon at third position of thiadiazolium ring resonance at near δ 165.00 while the signal at around δ 134.00 was assigned to the resonance of the C-5 of the thiadiazolium ring. All compounds were analyzed satisfactorily for C, H, and N analysis.

Antimicrobial activity

The search for new antimicrobial agents has been a highly planned and scientifically designed effort. Antibacterial activity of test compound was assessed against micrococcus are *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *and Pseudomonas aeruginosa* by cup-plate method (Brandt Rose and Miller, 1939).The screening was carried out at 200 μg/ml. Ciprofloxacin was used as a

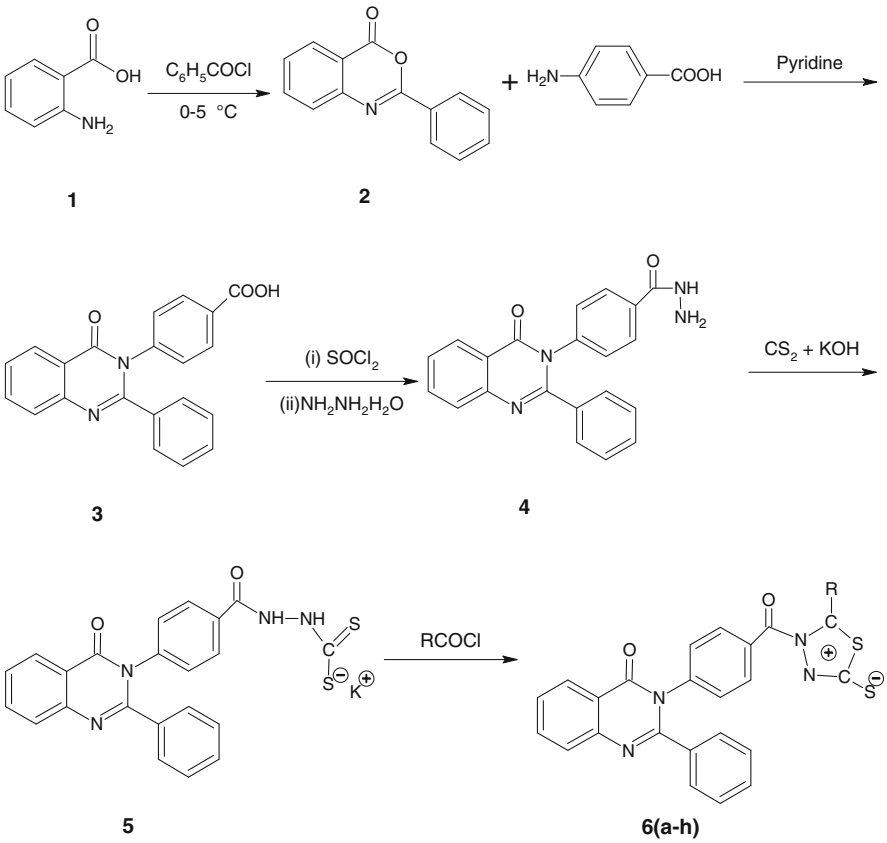


Fig. 1 Synthesis of 2-(substituted)-3-[4-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) benzoyl]-1,3,4-thiadiazolium-5-thiolate. (**a**) R = CH_3, (**b**) R = C_6H_5, (**c**) R = 2-Cl–5-NO_2–C_6H_3, (**d**) R = 3-NO_2–4-Cl–C_6H_3, (**e**) R = 3-NO_2–4-OCH_3–C_6H_3, (**f**) R = 4-Cl–C_6H_4, (**g**) R = 4-NO_2–C_6H_4, and (**h**) R = 3-NO_2–C_6H_4

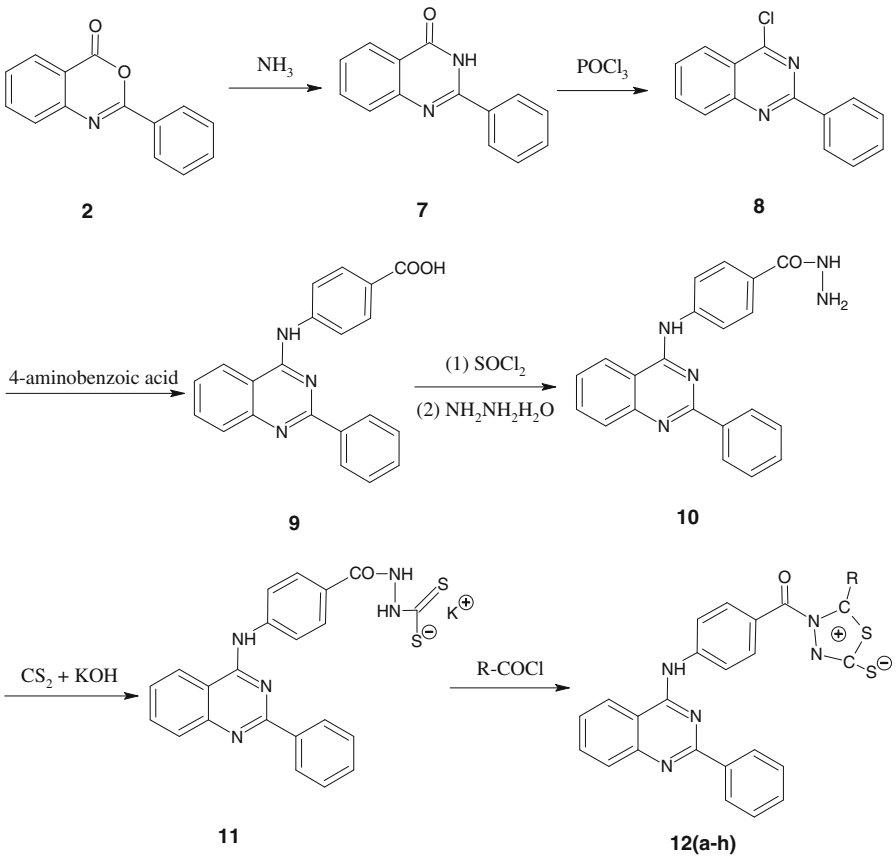


Fig. 2 Synthesis of 2-substituted-3-{4-[(2-phenyl-4-quinazolinyl)amino]benzoyl}-1,3,4-thiadiazolium-5-thiolate. (**a**) R = CH_3, (**b**) R = C_6H_5, (**c**) R = 2-Cl–5-NO_2–C_6H_3, (**d**) R = 3-NO_2–4-Cl–C_6H_3, (**e**) R = 3-NO_2–4-OCH_3–C_6H_3, (**f**) R = 4-Cl–C_6H_4, (**g**) R = 4-NO_2–C_6H_4, and (**h**) R = 3-NO_2–C_6H_4

Table 1 In vitro activity of compounds **6**(**a**–**j**) and **12**(**a**–**j**)

Compd. no.	Gram positive organism				Gram negative organism			
	S. aureus		*B. subtilis*		*E. coli*		*P. aeruginosa*	
	IZ	MIC	IZ	MIC	IZ	MIC	IZ	MIC
6a	28	01	22	08	17	32	18	16
6b	24	04	25	02	28	02	22	08
6c	26	02	18	16	19	16	22	08
6d	20	08	14	64	22	08	24	04
6e	19	16	16	32	15	32	27	02
6f	22	08	20	08	16	16	21	08
6g	20	08	24	04	23	04	22	08
6h	11	64	15	64	13	64	10	–
12a	19	16	21	08	20	08	23	04
12b	19	16	18	16	20	08	24	04
12c	23	04	22	08	24	04	26	02
12d	20	08	19	16	15	32	22	08
12e	22	08	24	04	23	04	22	08
12f	19	16	21	08	22	08	24	04
12g	16	32	19	16	18	16	15	32
12h	21	08	16	32	20	16	22	08
Ciprofloxacin	31	01	35	0.5	38	0.25	41	0.125

IZ inhibition of zone at 200 μg/ml, *MIC* minimum inhibitory concentration

positive control and solvent control was also to know the activity of the solvent. The antimicrobial activity of compounds **6**(**a**–**j**) and **12**(**a**–**j**) is shown in Table 1. Compound **6a** was found most active while compounds **6c**, **6b**, **12c**, and **12h** were found effectively active against *S. aureus*. Compound **6g** was found most active while compounds **6g**, **12a**, **12c**, **12e**, and **12f** were found effectively active against *B. subtilis*. Compound **6b** was found most active while compounds **6d**, **6g**, **12c**, **12e**, and **12f** were found effectively active against *E. coli*. Compound **6e** was found most active against *P. aeruginosa*. Most of the compounds were found active against *P. aeruginosa*. Rest of the compounds showed moderate activity. The activity of the compounds **6**(**a**–**h**) and **12**(**a**–**h**) as spectrum is depicted as in Fig. 3.

Conclusion

Most of the compounds were found active against tested organisms. A series of thiadiazolium derivatives, **6**(**a**–**h**) and **12**(**a**–**h**), exhibited moderate to good activity. It is clearly noted that the value of zone of inhibition increase and MIC value decrease.

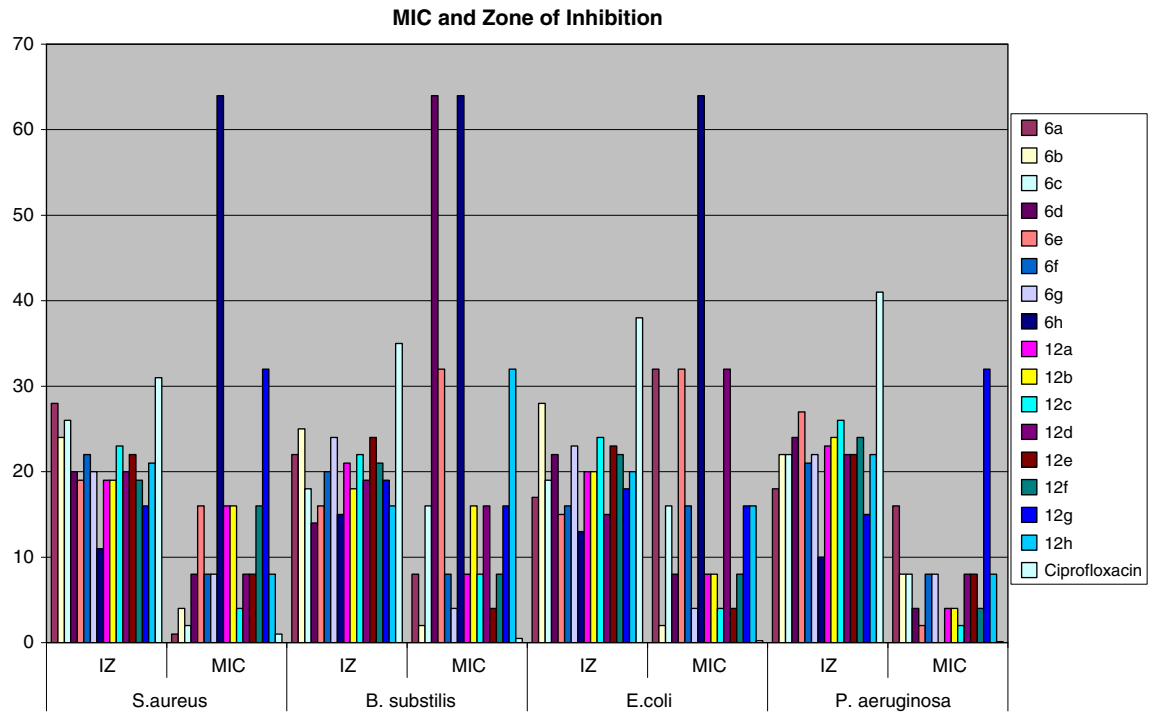


Fig. 3 Minimum inhibitory concentration and zone of inhibition of compounds **6**(**a**–**h**) and **12**(**a**–**h**)

Experimental

General

Melting points were determined by open capillary method and are uncorrected. IR spectra (KBr) were recorded on Shimadzu, Japan FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance II 400 MHz NMR spectrometer using DMSO-d_6 as solvent and TMS as internal standard. The mass spectra were recorded on micromass Q-T of micro (TOF MS ES^{+}). Elemental analysis was carried out on a Perkin-Elmer 240C elemental analyzer. Homogeneity of the compounds was checked by TLC on silica gel plates using toluene:ethylacetate (8:2) as a solvent system. Acidchloride derivatives were prepared from corresponding acids by known procedure. Piperazine derivatives were received from Enzal Chemicals Ltd., Panoli and various acids were received from Chemcrux Enterprise Ltd., Ankleshwar.

Biological assay

In vitro evaluation of antimicrobial activity

The zone of inhibition was carried out using cup-plate method. The seed culture was poured on Muller–Hilton agar plate. The cups were made by scooping out nutrient agar with a sterile cock borer. To these cups, solutions of test compounds (0.1 ml) were filled using sterile pipettes and these plates were incubated in refrigerator at 4–5°C for 30 min so as to allow diffusion of compounds to be tested (this permits the diffusion of compounds without allowing the grow to occur and gives the sharp and clear zones). Then subsequently incubated at 37°C for 48 h. The zone of inhibitions if any was measured in millimeter for the particular compound against each organism.

The MIC of synthesized compounds was carried out by Broth Dilution Method. DMSO was used as diluents. The stock 1000 μg/ml was prepared. Serial dilutions were prepared in primary and secondary screening (128, 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.125 >) μg ml^{-1}.

The control tube containing no antibiotic is immediately sub cultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37°C overnight. The tubes are then incubated overnight. The MIC of the control organism is read to check the accuracy of the drug concentrations. The lowest concentration inhibiting growth of the organism is recorded as the MIC. The amount of growth from the control tube before incubation was compared.

*2-Phenyl-4H-3,1-benzoxazine-4-one (**2**)*

Anthranilic acid (1.37 g, 0.01 mol) was dissolved in pyridine (30 ml). The solution was cooled at 0–5°C and

benzoyl chloride (2.32 ml, 0.02 mol) was added dropwise with stirring. After complete addition, the mixture was further stirred for 30 min at room temperature. It was then treated with sodium bicarbonate solution (10%) to remove any unreacted acid. The product was filtered and washed repeatedly with water to remove adhered pyridine. Recrystallized from dilute ethanol. Yield was 92%, m.p. 123–125°C.

*4-(4-Oxo-2-phenylquinazolin-3(4H)-yl)benzoic acid (**3**)*

A mixture of benzoxazine-4-one (2.33 g, 0.01 mol) and 4-aminobenzoic acid (1.37 g, 0.01 mol) in dry pyridine (20 ml) was refluxed for 7 h. After completion of reaction, mixture was poured into ice-cooled diluted hydrochloric acid. The solid product was precipitated out. Filter and washed the product with water. Recrystallized from ethanol. Yield was 82%, m.p. 172–175°C.

*4-(4-Oxo-2-phenylquinazolin-3(4H)-yl) benzohydrazide (**4**)*

4-(4-Oxo-2-phenylquinazoline-3(4*H*)-yl)benzoic acid (3.42 g, 0.01 mol) was dissolved in ethanol (40 ml) and excess of hydrazine hydrate (15 ml) was added slowly with constant stirring. The reaction mixture was refluxed for 6 h. The solution was poured over ice. Recrystallization from ethanol. Yield 75%. m.p. 182–185°C.

*Potassium salt of 2-{[4-(4-oxo-2-phenylquinazoline-3(4H)-yl) phenyl]carbonyl}hydrazine carbodithioic acid (**5**)*

Carbon disulfide (0.76 g, 0.01 mol) was added dropwise to a stirred solution of 4-(4-oxo-2-phenylquinazoline-3(4*H*)-yl)benzohydrazide (1.78 g, 0.005 mol) and potassium hydroxide (0.28 g, 0.005 mol) in ethanol (25 ml) for 1 h at room temperature. The yellowish colored precipitate was treated with ether. The solid which separated was filtered, washed with ether, and dried.

*2-(Substituted)-3-[4-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzoyl]-1,3,4-thiadiazolium-5-thiolate **6(a–h)***

To a stirred solution of potassium salt of 2-{[4-(4-oxo-2-phenyl quinazoline-3(4*H*)-yl) phenyl]carbonyl}hydrazine carbodithioic acid (2.15 g, 0.005 mol) in water was added acetyl chloride (0.36 ml, 0.005 mol). The reaction mixture was stirred for 2 h at room temperature. The pale yellow solid which separated was filtered, washed repeatedly with ice-cold water, and recrystallized from ethanol.

Similarly other compounds were synthesized by various aromatic and aliphatic acid chlorides.

*2-(Methyl)-3-[4-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzoyl]-1,3,4-thiadiazolium-5-thiolate (**6a**)*

Yield: 84%. m.p. 137–141°C. IR (KBr): 2986, 2859, 1730, 1683, 1610, 1313 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.87 (s, 3H, CH_3), 7.10–8.30 (m, 13H, Ar–H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 15.90, 123.87, 127.34, 123.28, 127.35, 127.75, 129.15, 129.30, 129.86, 130.43, 131.26, 134.10, 134.58, 135.53, 140.05, 148.70, 154.86, 165.20, 165.77, 178.50; MS: *m/z* 456. Anal (%) for $C_{24}H_{16}N_4O_2S_2$. Calcd. C, 63.14; H, 3.53; N, 12.27. Found: C, 63.07; H, 3.46; N, 12.38.

*2-(Phenyl)-3-[4-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzoyl]-1,3,4-thiadiazolium-5-thiolate (**6b**)*

Yield: 86%. m.p. 157–160°C. IR (KBr): 1713, 1690, 1622, 1345 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.75-8.60 (m, 18H, Ar–H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 123.43, 124.28, 126.56, 127.12, 127.25, 127.36, 129.25, 129.37, 129.63, 130.42, 130.54, 130.63, 131.01, 131.64, 134.24, 134.77, 135.22, 139.47, 149.32, 155.28, 165.53, 165.63, 178.38; MS: *m/z* 518. Anal (%) for $C_{29}H_{18}N_4O_2S_2$. Calcd. C, 67.16; H, 3.50; N, 10.80. Found: C, 67.10; H, 3.63; N, 10.93.

*2-(2-Chloro-5-nitrophenyl)-3-[4-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzoyl]-1,3,4-thiadiazolium-5-thiolate (**6c**)*

Yield: 85%. m.p. 150–154°C. IR (KBr): 1733, 1690, 1623, 1540, 1354, 1337, 1087 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.62–8.60 (m, 16H, Ar–H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 123.74, 123.96, 126.37, 126.93, 127.15, 127.28, 127.47, 127.55, 129.21, 129.84, 129.90, 130.46, 131.43, 133.00, 134.34, 134.68, 135.63, 139.50, 139.74, 149.22, 149.37, 155.75, 165.66, 165.87, 178.83; MS: *m/z* 600 ($M^+ + 2$). Anal (%) for $C_{29}H_{16}N_5ClO_4S_2$. Calcd. C, 58.24; H, 2.70; N, 11.71. Found: C, 58.31; H, 2.65; N, 11.78.

*2-(4-Chloro-3-nitrophenyl)-3-[4-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzoyl]-1,3,4-thiadiazolium-5-thiolate (**6d**)*

Yield: 76%. m.p. 174–178°C. IR (KBr): 1745, 1678, 1628, 1524, 1350, 1341, 1070 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.80–9.13 (m, 16H, Ar–H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 123.30, 123.64, 126.47, 126.83, 127.58, 127.64, 127.90, 129.38, 129.53, 130.08, 130.38, 130.68, 131.43, 134.15, 134.86, 134.98, 135.32, 135.95, 139.68, 149.42, 149.64, 154.83, 165.41, 165.88, 178.53; MS: *m/z* 600 ($M^+ + 2$). Anal (%) for $C_{29}H_{16}N_5ClO_4S_2$.

Calcd. C, 58.24; H, 2.70; N, 11.71. Found: C, 58.30; H, 2.75; N, 11.76.

*2-(4-Methoxy-3-nitrophenyl)-3-[4-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzoyl]-1,3,4-thiadiazolium-5-thiolate (**6e**)*

Yield: 83%. m.p. 143–146°C. IR (KBr): 2962, 1730, 1686, 1635, 1544, 1342, 1333, 1241, 1053 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.06 (s, 3H, OCH_3), 7.68–8.93 (m, 16H, Ar–H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 58.55, 114.63, 121.85, 123.85, 124.74, 127.33, 127.47, 127.74, 126.94, 129.12, 129.25, 129.68, 130.35, 130.67, 134.13, 134.65, 135.37, 136.75, 139.89, 141.08, 149.84, 154.58, 155.76, 165.07, 165.73, 178.63; MS: *m/z* 594 (M^+). Anal (%) for $C_{30}H_{19}N_5O_5S_2$. Calcd. C, 60.70; H, 3.23; N, 11.80. Found: C, 60.61; H, 3.35; N, 3.29.

*2-(4-Chlorophenyl)-3-[4-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzoyl]-1,3,4-thiadiazolium-5-thiolate (**6f**)*

Yield: 74%. m.p. 168–171°C. IR (KBr): 1739, 1682, 1633, 1342, 1056 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.68–8.57 (m, 17H, Ar–H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 123.47, 124.64, 126.73, 127.08, 127.42, 127.96, 129.58, 130.00, 130.58, 130.63, 130.90, 130.97, 131.83, 134.27, 134.84, 135.84, 136.22, 139.36, 149.23, 155.15, 165.68, 165.74, 178.00; MS: *m/z* 555 ($M^+ + 2$). Anal (%) for $C_{29}H_{17}ClN_4O_2S_2$. Calcd. C, 62.98; H, 3.10; N, 10.13. Found: C, 63.11; H, 3.17; N, 10.25.

*2-(4-Nitrophenyl)-3-[4-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzoyl]-1,3,4-thiadiazolium-5-thiolate (**6g**)*

Yield: 87%. m.p. 156–159°C. IR (KBr): 1713, 1679, 1643, 1530, 1360, 1345 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.83–8.77 (m, 17H, Ar–H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 123.73, 124.66, 126.64, 127.38, 127.48, 127.86, 129.23, 129.54, 130.48, 130.96, 131.65, 134.03, 134.61, 132.13, 131.53, 135.07, 139.26, 148.63, 149.63, 155.86, 165.75, 165.89, 178.38; MS: *m/z* 564(M^+). Anal (%) for $C_{29}H_{17}N_5O_4S_2$. Calcd. C, 61.80; H, 3.04; N, 12.43. Found: C, 61.72; H, 3.12; N, 12.56.

*2-(3-Nitrophenyl)-3-[4-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzoyl]-1,3,4-thiadiazolium-5-thiolate (**6h**)*

Yield: 79%. m.p. 187–191°C. IR (KBr): 1734, 1695, 1660, 1537, 1363, 1354 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.83–9.00 (m, 17H, Ar–H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 123.43, 124,40, 125.72, 126.34, 126.75, 127.23, 127.38, 127.54, 129.04, 129.43, 129.81, 130.76, 131.55, 131.68, 134.26, 134.66, 135.20, 135.84, 140.37, 149.72, 150.36, 155.33, 165.50, 165.85, 179.47; MS: *m/z* 564 (M^+). Anal (%) for $C_{29}H_{17}N_5O_4S_2$. Calcd. C, 61.80; H, 3.04; N, 12.43. Found: C, 61.74; H, 3.14; N, 12.52.

*2-Phenylquinazolin-4(3H)-one (**7**)*

2-Phenyl-*4H*-3,1-benzoxazine-4-one (2.32 g, 0.01 mol) was suspended in liquid ammonia (16 ml) and heated at 100°C for 2 h. The white needles separated out were filtered, dried, and recrystallized from ethanol. The yield is about 91% and m.p. was 250–252°C.

*4-Chloro-2-phenyl-3,4-dihydroquinazoline (**8**)*

Phosphoryl chloride (8.0 ml, 0.08 mol) was added to *N*,*N*-diethylaniline (2.5 ml, 0.03 mol) with stirring followed by addition of 2-phenylquinazolin-4-(3*H*)-one (2.22 g, 0.1 mol) and the reaction mixture was heated at 70°C. The temperature was increased to 90°C over a period of 10 min and kept at 80–90°C for another 30 min. Excess of phosphoryl chloride was removed. The residue was dissolved in water (20 ml) and extracted with ethyl acetate. The pH of the aqueous phase was adjusted to 9–10 with sodium bicarbonate and it was extracted with dichloromethane, dried sodium sulfate, and the organic solvent was removed to afford the product as a brownish color. Yield was 92%. m.p. 210–215°C.

*4-[(2-Phenyl-3,4-dihydroquinazolin-4-yl)amino]benzoic acid (**9**)*

A mixture of 4-chloro-2-phenyl-3,4-dihydroquinazoline (2.40 g, 0.01 mol), 4-aminobenzoic acid (1.37 g, 0.01 mol) and potassium carbonate (1.38 g, 0.01 mol) in isopropyl alcohol (5.0 ml) was stirred and heated at 90°C for 6 h. After completion of reaction, mixture was cooled to room temperature and poured into ice. The solid product obtained was filtered and dried under reduced pressure and crystallized from methanol to afford 76% yield. m.p. 230–233°C.

*4-[(2-Phenyl-3,4-dihydroquinazolin-4-yl)amino]benzohydrazide (**10**)*

A mixture of 4-[(2-phenyl-3,4-dihydroquinazolin-4-yl) amino]benzoic acid (3.41 g, 0.01 mol) and thionyl chloride (1.09 ml, 0.015 mol) in benzene (15 ml) was refluxed for 2 h, excess of thionyl chloride was distilled off. The resultant mixture dissolve in ethanol (40 ml) and excess of hydrazine hydrate (15 ml) was added slowly with constant stirring. The reaction mixture was refluxed for 6 h. The solution was poured into ice-cold water; solid product

obtained was filtered off and recrystallized from ethanol. m.p. 252–254°C.

*Potassium salt of 2-({4-[(2-phenylquinazoline-4-yl)amino] phenyl} carbonyl) hydrazine carbodithioic acid (**11**)*

To a stirred solution of 4-[(2-phenylquinazoline-4yl)amino] benzohydrazine (0.005 mol) and potassium hydroxide (0.005 mol) in absolute alcohol (25 ml), carbon disulfide (0.01 mol) was added and the mixture was stirred for about 1 h at room temperature. The dark yellow colored precipitate was treated with ether (50 ml). The solid which separated was filtered, washed with ether, and dried.

*2-Substituted-3-{4-[(2-phenyl-4-quinazolinyl) amino]benzoyl}-1,3,4-thiadiazolium-5-thiolate **12(a–h)***

To a stirred solution of potassium salt of 2-({4-[(2-phenylquinazoline-4yl)amino]phenyl}carbonyl)hydrazine carbodithioic acid (0.005 mol) in water was added acetyl chloride (0.005 mol). The reaction mixture was stirred for 2 h at room temperature. The yellowish solid which separated was filtered, washed repeatedly with water, and recrystallized from ethanol.

Similarly other compounds were synthesized by using various aromatic and aliphatic acid chlorides.

*2-Methyl-3-{4-[(2-phenyl-4-quinazolinyl)amino]benzoyl}-1,3,4-thiadiazolium-5-thiolate **12(a)***

Yield: 87%. m.p. 231–234°C. IR (KBr): 3240, 2957, 2864, 1718, 1603, 1297 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 3H, CH_3), 7.19–8.90 (m, 13H, Ar–H), 10.40 (s, 1H, NH); ^{13}C NMR (40 MHz, DMSO-d_6): δ 17.93, 108.62, 110.07, 123.78, 126.28, 129.04, 129.25, 130.75, 130.84, 131.07, 133.93, 134.00, 135.06, 139.52, 142.46, 152.07, 158.78, 162.86, 164.75, 175.58; MS: *m/z* 456 (M^+). Anal (%) for $C_{24}H_{17}N_5OS_2$. Calcd. C, 63.28; H, 3.76; N, 15.37. Found: C, 63.33; H, 3.84; N, 15.24.

*2-Phenyl-3-{4-[(2-phenyl-4-quinazolinyl)amino]benzoyl}-1,3,4-thiadiazolium-5-thiolate **12(b)***

Yield: 85%. m.p. 243–247°C. IR (KBr): 3245, 1715, 1635, 1288 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.34–8.94 (m, 18H, Ar–H), 10.57 (s, 1H, NH); ^{13}C NMR (40 MHz, DMSO-d_6): δ 108.42, 110.64, 122.87, 126.56, 128.73, 129.20, 129.74, 130.29, 130.65, 131.03, 131.21, 131.58, 132.36, 133.68, 134.07, 137.13, 138.75, 142.87, 152.31, 156.38, 162.87, 164.85, 174.58; MS: *m/z* 518 (M^+). Anal (%) for $C_{29}H_{19}N_5OS_2$. Calcd. C, 67.29; H, 3.70; N, 13.53. Found: C, 67.33; H, 3.65; N, 13.61.

*2-(2-Chloro-5-nitrophenyl)-3-{4-[(2-phenyl-4-quinazolinyl)amino]benzoyl}-1,3,4-thiadiazolium-5-thiolate **12(c)***

Yield: 87%. m.p. 228–231°C. IR (KBr): 3255, 1700, 1617, 1567, 1375, 1306, 1056 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.52–8.96 (m, 16H, Ar–H), 10.62 (s, 1H, NH); ^{13}C NMR (40 MHz, DMSO-d_6): δ 108.57, 110.78, 122.75, 126.75, 127.58, 128.73, 128.86, 129.56, 129.72, 130.38, 131.00, 132.42, 133.43, 134.21, 135.73, 135.95, 136.84, 139.84, 143.10, 148.68, 152.84, 156.57, 162.95, 164.85, 174.75; MS: *m/z* 599 ($M^+ + 2$). Anal (%) for $C_{29}H_{17}N_6O_3S_2Cl$. Calcd. C, 58.34; H, 2.87; N, 14.08. Found: C, 58.41; H, 2.94; N, 14.17.

*2-(4-Chloro-3-nitrophenyl)-3-{4-[(2-phenyl-4-quinazolinyl)amino]benzoyl}-1,3,4-thiadiazolium-5-thiolate **12(d)***

Yield: 89%. m.p. 268–272°C. IR (KBr): 3258, 1689, 1620, 1554, 1348, 1317, 1047 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.46–8.84 (m, 16H, Ar–H), 10.60 (s, 1H, NH); ^{13}C NMR (40 MHz, DMSO-d_6): δ 109.78, 110.53, 122.65, 122.75, 126.32, 127.05, 128.67, 129.46, 130.60, 131.66, 131.80, 132.74, 134.16, 134.52, 135.63, 135.75, 135.90, 138.55, 143.06, 150.37, 152.10, 157.25, 162.98, 164.89, 174.33; MS: *m/z* 599 ($M^+ + 2$). Anal (%) for $C_{29}H_{17}N_6O_3S_2Cl$. Calcd. C, 58.34; H, 2.87; N, 14.08. Found: C, 58.41; H, 2.82; N, 14.15.

*2-(4-Methoxy-3-nitrophenyl)-3-{4-[(2-phenyl-4-quinazolinyl)amino]benzoyl}-1,3,4-thiadiazolium-5-thiolate **12(e)***

Yield: 90%. m.p. 211–215°C. IR (KBr): 3250, 2965, 2843, 1685, 1607, 1536, 1340, 1293, 1257 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.00 (s, 3H, CH_3), 7.55–8.79 (m, 16H, Ar–H), 10.53 (s, 1H, NH); ^{13}C NMR (40 MHz, DMSO-d_6): δ 58.84, 108.20, 110.73, 113.74, 120.70, 122.57, 123.69, 126.40, 129.36, 129.76, 130.63, 131.06, 131.63, 131.84, 133.97, 134.18, 135.85, 139.67, 142.75, 143.64, 152.83, 155.37, 157.28, 162.77, 164.32, 175.24; MS: *m/z* 593 (M^+). Anal (%) for $C_{30}H_{20}N_6O_4S_2$. Calcd. C, 60.80; H, 3.40; N, 14.18. Found: C, 60.87; H, 3.34; N, 14.27.

*2-(4-Chlorophenyl)-3-{4-[(2-phenyl-4-quinazolinyl) amino]benzoyl}-1,3,4-thiadiazolium-5-thiolate **12(f)***

Yield: 83%. m.p. 238–242°C. IR (KBr): 3242, 1697, 1618, 1290, 1030 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.67–8.83 (m, 17H, Ar–H), 10.64 (s, 1H, NH); ^{13}C NMR (40 MHz, DMSO-d_6): δ 108.74, 110.68, 123.57, 123.80, 126.58, 128.69, 130.57, 130.70, 130.78, 131.05, 131.74,

132.06, 133.73, 134.03, 135.74, 137.50, 138.68, 143.32, 151.47, 157.00, 162.97, 164.24, 176.54; MS: *m/z* 554 (M^+). Anal (%) for $C_{29}H_{18}N_5OS_2Cl$. Calcd. C, 63.09; H, 3.29; N, 12.69. Found: C, 63.15; H, 3.37; N, 12.74.

2-(4-Nitrophenyl)-3-{4-[(2-phenyl-4-quinazolinyl) amino]benzoyl}-1,3,4-thiadiazolium-5-thiolate ***12(g)***

Yield: 81%. m.p. 255–258°C. IR (KBr): 3248, 1684, 1629, 1547, 1355, 1298 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.83–8.96 (m, 17H, Ar–H), 10.70 (s, 1H, NH); ^{13}C NMR (40 MHz, DMSO-d_6): δ 108.58, 110.70, 122.96, 126.95, 128.88, 129.57, 129.92, 130.80, 130.86, 131.77, 132.00, 133.85, 134.10, 135.10, 135.44, 138.76, 143.38, 150.53, 151.25, 156.68, 162.90, 164.84, 174.84; MS: *m/z* 563 (M^+). Anal (%) for $C_{29}H_{18}N_6O_3S_2$. Calcd. C, 61.91; H, 3.22; N, 14.94. Found: C, 61.81; H, 3.27; N, 14.86.

2-(3-Nitrophenyl)-3-{4-[(2-phenyl-4-quinazolinyl) amino]benzoyl}-1,3,4-thiadiazolium-5-thiolate ***12(h)***

Yield: 85%. m.p. 218–222°C. IR (KBr): 3240, 1555, 1685, 1623, 1337, 1312 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.57–8.52 (m, 17H, Ar–H), 10.58 (s, 1H, NH); ^{13}C NMR (40 MHz, DMSO-d_6): δ 108.77, 110.84, 122.54, 125.06, 126.59, 126.86, 128.20, 129.85, 130.33, 130.70, 130.86, 132.86, 132.96, 133.50, 133.86, 134.19, 136.90, 140.64, 143.66, 152.00, 152.76, 157.40, 162.88, 165.64, 174.34; MS: *m/z* 563 (M^+). Anal (%) for $C_{29}H_{18}N_6O_3S_2$. Calcd. C, 61.91; H, 3.22; N, 14.94. Found: C, 61.84; H, 3.31; N, 15.01.

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