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Conventional and microwave induced synthesis of various azetidinone and thiazolidinone derivatives from 3-[(1*E*)-1-aza-2-(2-chloro-7-methoxy-3-quinolyl)-vinyl]-4-(aryldiazenyl) phenol and their antimicrobial screening

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3-Chloro-4-(2-chloro-7-methoxy-3-quinolyl)-1-[3-hydroxy-6-(aryldiazenyl) phenyl] azetidin-2-one **2** and 2-(2-chloro-7-methoxy-3-quinolyl)-3-[3-hydroxy-6-(aryldiazenyl) phenyl]-1, 3-thiazolidin-4-one **3** have been synthesized by the reaction of 3-[(1*E*)-1-aza-2-(2-chloro-7-methoxy-3-quinolyl)-vinyl]-4-(aryldiazenyl) phenol **1** with chloroacetylchloride and mercapto acetic acid, respectively. Both the reactions have been carried out by conventional and microwave methods. These compounds have been screened for their antibacterial, antifungal and antitubercular activity against different microorganisms.

Keywords: Azetidinone, thiazolidinone, antibacterial, antifungal, antitubercular activity

Quionoline and their derivatives occur in numerous natural products. Many quinolines display interesting physiological activities[1] and have found important applications as pharmaceuticals[2,3] (e.g., norfloxacin and ciprofloxacin). Moreover fused quinolines are known to bind DNA with high affinity, inhibit DNA topoisomerase and display cytotoxic and antitumour activities[4,5]. For these reasons their synthesis has always attracted the attention of synthetic chemists. Many synthesis have been developed for quinolines[6,7], but due to their great importance, the development of novel synthetic methods remains an active research area[8-10]. Furthermore thiazolidinone derivatives found to possess a wide spectrum of biological activities[11-17].

Azetidin-2-one derivatives[18,19] containing β-lactam nucleus has attracted considerable attention as they are endowed with a wide range of pharmaceutical activity[20,21]. β-Lactam containing antibacterial agents has become an integral part of the chemotherapeutic arsenal available to today's medical practitioners. Although the number of existing agents are quite extensive, but the search for better and more effective drug is still going on.

The medicinal chemical approach to this search has throughout the years focused on synthetic route chemical reactions. It is well known that microwave irradiation technique is a powerful tool in organic synthesis[22,23].

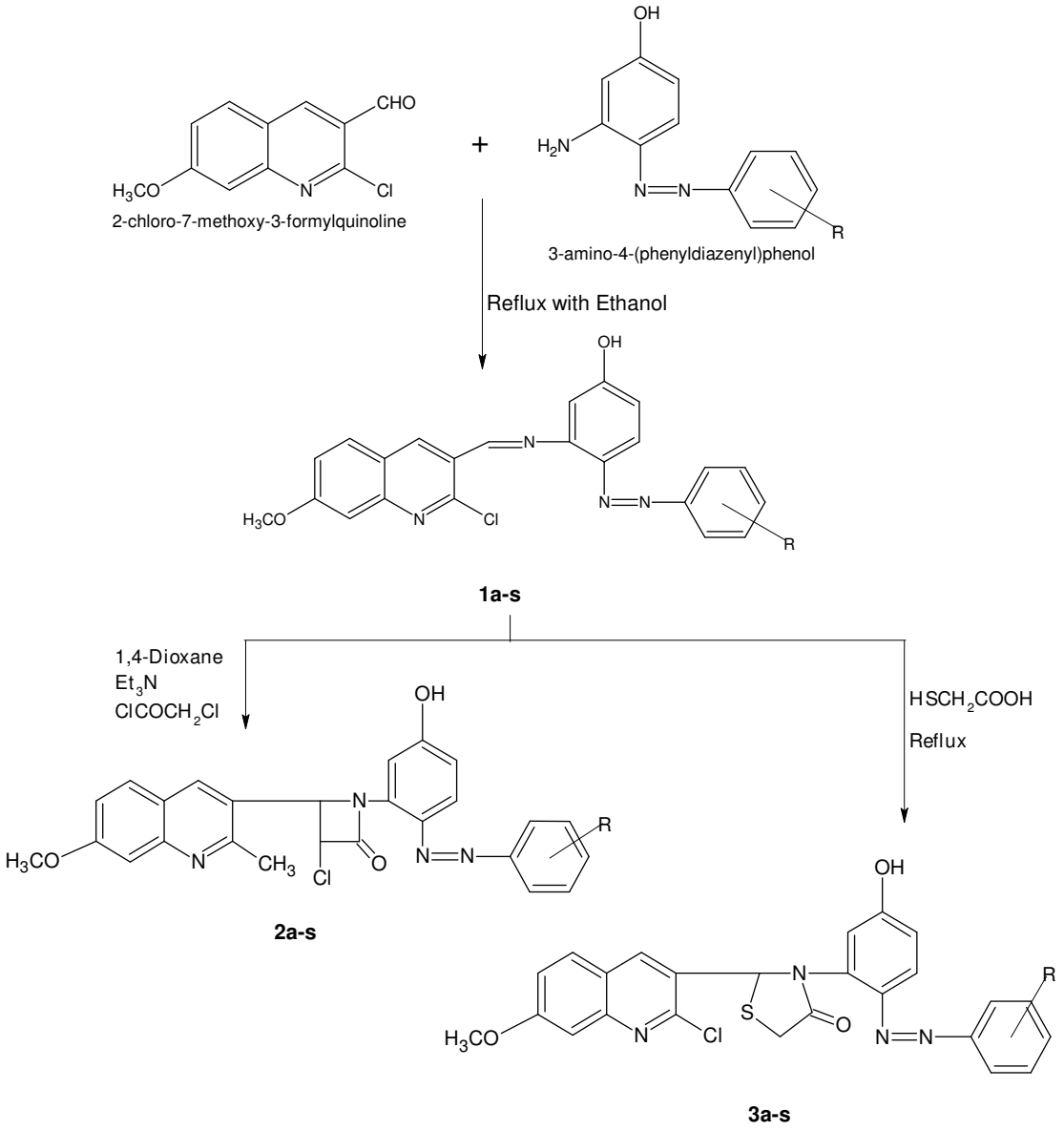
Results and Discussion

The starting compounds 2-chloro-7-methoxy-3-formylquinoline[24,25], was condensed with 3-amino-4-(phenyldiazenyl) phenol under microwave irradiation in one pot to furnish the compound 3-[(1*E*)-1-aza-2-(2-chloro-7-methoxy-3-quinolyl)-vinyl]-4-(aryldiazenyl) phenol **1** in good yield.

Compound, 3-[(1*E*)-1-aza-2-(2-chloro-7-Methoxy-3-quinolyl-vinyl]-4-(aryldiazenyl) phenol **1** upon cyclization with chloroacetylchloride and 2-mercapto acetic acid by microwave irradiation technique yields the title compound **2a-s** and **3a-s,** respectively in good yield (**Scheme I**). The above mentioned compounds were also synthesized by the conventional method. It is noteworthy that the reaction which required 12-16 hr in conventional method in both steps , was completed within 5-7 min in Q-Pro-Modified Microwave system at 120 ºC and power level of 500 W. Yield have been remarkably improved from 60 – 70 % to 80- 90 %.

Structure of compounds **1a-s, 2a-s** and **3a-s** were established by their IR, ^{1}H NMR and mass spectral studies.

The yield and the physical constants of the compounds synthesized by the conventional and microwave irradiation methods are given **(Table I)**.



Scheme I

Antitubercular activity

The *in vitro* tubercular evaluation of azetidinone and thiazolidinone derivatives (**2a-s** and **3a-s**) was studied against $H_{37}R_v$ strain of *Mycobacterium tuberculosis* using Lowenstein Jensen's egg medium by serial two fold dilution method and the retardation of growth rate studied up to six weeks at 37ºC (**Table II**).

Antibacterial screening test

All the compounds **2a-s** and **3a-s** were subjected to *in vitro* screening against Gram-positive *Staphylococcus aureus* and Gram-negative *Eschericia coli* and *P.aeruginosa*. The minimum inhibitory concentration (MIC) was determined using tube dilution method according to the standard procedure[26]. Meuller Hinton broth was used as a culture medium. Sterilized medium was dispensed in each borosilicate glass test tube. The drug solution was added in order to attain final drug concentrations of 512, 256, 128, 64, 32, 16, 8, 4, 2, 1 µg/mL. Inoculums of standard suspension (0.1 mL of the test organism strain which contains 10^6 bacilli/mL) was added. The tubes were incubated at 37ºC for 48 hr and then examined for the presence or absence of growth of the organism. The lowest concentration, which showed no visible growth, was taken as an end point minimum inhibitory concentration (MIC). The testing results are given in **Table II**.

Table I — Physical characterization data of compounds

Compd	R	m.p. ºC	Mol. Formula (Mol.wt)	Conventional		Microwave		(%) N .	
				Time (hr)	Yield (%)	Time (min)	Yield (%)	Found	(Calcd)
2a	H	201	$C_{25}H_{18}N_4O_4Cl_2$	12	74	5	88	11.40	(11. 36)
2b	2-OCH_3	160	$C_{26}H_{20}N_4O_4Cl_2$	12	64	6	76	10.74	(10.71)
2c	3-OCH_3	120	$C_{26}H_{20}N_4O_4Cl_2$	12	67	6	80	10.75	(10.71)
2d	4-OCH_3	134	$C_{26}H_{20}N_4O_4Cl_2$	12	62	6	78	10.73	(10.71)
2e	2-Br	165	$C_{25}H_{17}N_4O_3BrCl_2$	12	58	5.5	72	9.84	(9.79)
2f	3-Br	156	$C_{25}H_{17}N_4O_3BrCl_2$	12	64	6	74	9.86	(9.79)
2g	4-Br	125	$C_{25}H_{17}N_4O_3BrCl_2$	12	69	5.5	83	9.87	(9.79)
2h	2-Cl	176	$C_{25}H_{17}N_4O_3Cl_3$	12	71	5	81	10.66	(10.62)
2i	3-Cl	185	$C_{25}H_{17}N_4O_3Cl_3$	12	69	5	78	10.65	(10.62)
2j	4-Cl	162	$C_{25}H_{17}N_4O_3Cl_3$	12	75	5	78	10.63	(10.62)
2k	2-NO_2	171	$C_{25}H_{17}N_5O_5Cl_2$	12	55	5.5	83	13.05	(13.01)
2l	3-NO_2	140	$C_{25}H_{17}N_5O_5Cl_2$	12	62	6	67	13.03	(13.01)
2m	4-NO_2	153	$C_{25}H_{17}N_5O_5Cl_2$	12	69	6	72	13.04	(13.01)
2n	2-CH_3	152	$C_{26}H_{20}N_4O_3Cl_2$	12	73	5	79	11.05	(11.04)
2o	3-CH_3	167	$C_{26}H_{20}N_4O_3Cl_2$	12	70	5	88	11.08	(11.04)
2p	4-CH_3	173	$C_{26}H_{20}N_4O_3Cl_2$	12	66	5	81	11.07	(11.04)
2q	2-F	185	$C_{25}H_{17}N_4O_3FCl_2$	12	54	6	76	10.97	(10.96)
2r	3-F	158	$C_{25}H_{17}N_4O_3FCl_2$	12	57	5.5	65	10.99	(10.96)
2s	4-F	148	$C_{25}H_{17}N_4O_3FCl_2$	12	59	6	68	10.98	(10.96)
3a	H	>300	$C_{25}H_{19}N_4O_3SCl$	16	69	6	78	11.45	(11.41)
3b	2-OCH_3	255	$C_{26}H_{21}N_4O_4SCl$	16	71	6	86	10.79	(10.75)
3c	3-OCH_3	222	$C_{26}H_{21}N_4O_4SCl$	16	69	6	80	10.80	(10.75)
3d	4-OCH_3	184	$C_{26}H_{21}N_4O_4SCl$	16	74	6.5	81	10.76	(10.75)
3e	2-Br	>300	$C_{25}H_{18}N_4O_3SBrCl$	16	76	7	83	9.88	(9.83)
3f	3-Br	210	$C_{25}H_{18}N_4O_3SBrCl$	16	66	6.5	79	9.85	(9.83)
3g	4-Br	236	$C_{25}H_{18}N_4O_3SBrCl$	16	76	7	89	9.84	(9.83)
3h	2-Cl	>300	$C_{25}H_{18}N_4O_3SCl_2$	16	68	6.5	80	10.71	(10.66)
3i	3-Cl	165	$C_{25}H_{18}N_4O_3SCl_2$	16	73	7	88	10.68	(10.66)
3j	4-Cl	150	$C_{25}H_{18}N_4O_3SCl_2$	16	68	6	78	10.67	(10.66)
3k	2-NO_2	187	$C_{25}H_{18}N_5O_5SCl$	16	62	6	76	13.11	(13.07)
3l	3-NO_2	142	$C_{25}H_{18}N_5O_5SCl$	16	66	6	83	13.10	(13.07)
3m	4-NO_2	148	$C_{25}H_{18}N_5O_5SCl$	16	59	6.5	75	13.9	(13.07)
3n	2-CH_3	136	$C_{26}H_{21}N_4O_4SCl$	16	78	6.5	85	11. 13	(11.09)
3o	3-CH_3	115	$C_{26}H_{21}N_4O_3SCl$	16	73	6.5	87	11. 14	(11.09)
3p	4-CH_3	125	$C_{26}H_{21}N_4O_3SCl$	16	68	6.5	79	11. 17	(11.09)
3q	2-F	138	$C_{25}H_{18}N_4O_3SFCl$	16	63	7	74	11.05	(11.01)
3r	3-F	188	$C_{25}H_{18}N_4O_3SFCl$	16	69	7	85	11.06	(11.01)
3s	4-F	130	$C_{25}H_{18}N_4O_3SFCl$	16	60	7	77	11.04	(11.01)

Antifungal activity

The antifungal activity of compounds **2a-s** and **3a-s** has been assayed *in vitro* at a concentration of 256 µg/mL and 512 µg/mL against *Candida albicans*, which were maintained on nutrient agar slants, which were stored at 4ºC. None of the compounds was found to possess better activity than Dithane-M 45 (**Table II**).

All the compounds were tested for their effect on the growth of microbial cultures at concentration level

Table II — Antimicrobial activity of compounds **2a-s** and **3a-s**

Compd	Antimicrobial Activity								Antitubercular Activity µg/mL
	E.coli		*P.aeruginosa*		*S. aureus*		*C. albicans*		
	256 µg/mL	512 µg/mL	256 µg/mL	512 µg/mL	256 µg/mL	512 µg/mL	256 µg/mL	512 µg/mL	$H_{37}R_{\alpha}$ strain of M. tuberculosis
2a	-	++	+	++	-	++	+	++	>600
2b	+	++	++	++	+	++	+	++	>600
2c	+	++	++	++	+	++	+	++	>600
2d	+	++	++	++	++	+++	+	++	>600
2e	++	+++	+	++	++	+++	+	++	>600
2f	++	+++	+	++	++	+++	+	++	>600
2g	++	+++	+	++	++	+++	++	++	>600
2h	++	+++	++	+++	++	+++	++	++	>600
2i	++	+++	++	+++	++	++	++	++	>600
2j	++	+++	++	+++	++	++	-	+	>600
2k	+	++	+	++	++	++	-	+	>600
2l	+	++	+	++	+	+	-	+	>600
2m	+	++	+	++	++	+	-	+	>600
2n	+	++	+	++	+	+	+	+	>600
2o	+	++	+	++	-	+	-	-	>600
2p	+	++	+	++	+	+	+	+	>600
2q	+++	+++	+++	+++	++	+++	+	++	>600
2r	+++	+++	+++	+++	++	+++	+	++	>600
2s	+++	+++	+++	+++	++	+++	+	++	>600
3a	-	+	+	++	-	++	+	++	>600
3b	+	+	++	++	+	++	+	++	>600
3c	+	+	++	++	+	++	+	++	>600
3d	+	++	++	++	++	+++	+	++	>600
3e	+	+++	+	++	++	+++	+	++	>600
3f	+	+++	+	++	++	+++	+	++	>600
3g	+	+++	+	++	++	+++	++	++	>600
3h	+	+++	++	+++	++	+++	++	++	>600
3i	+	+++	++	+++	++	++	++	++	>600
3j	+	+++	++	+++	++	++	-	+	>600
3k	-	++	+	++	++	++	-	+	>600
3l	-	++	+	++	+	+	-	+	>600
3m	-	++	+	++	++	+	-	+	>600
3n	-	++	+	++	+	+	+	+	>600
3o	-	++	+	++	-	-	-	-	>600
3p	-	++	+	++	+	+	+	+	>600
3q	+	+++	+++	+++	++	+++	+	++	>600
3r	+	+++	+++	+++	++	+++	+	++	>600
3s	+	+++	+++	+++	++	+++	+	++	>600
Streptomycin	++++	++++	++++	++++	++++	++++	-	-	-
Dithane-M 45	-	-	-	-	-	-	++++	++++	-
INH	-	-	-	-	-	-	-	-	0.05

(-)< 6mm, (+)=7 – 10 mm, (++)=11 – 15mm,(+++)= 16 – 21mm,(++++)= 22 – 28mm

ranging from 128-512 µg/mL on different organisms. Compounds **2q, 2r, 2s, 3q, 3r** and **3s** showed lower MIC values against both gram positive and gram negative bacteria strains. The MIC level of azetidinone **2a-s** and thiazolidinone **3a-s** against these organisms are given in **Table II**.

The presence of fluoro, bromo or chloro group in the moiety enhances its antimicrobial activity. However, the degree of inhibition varied both with the test compound as well as with the bacterial species. Compounds **2q, 2r** and **2s** show significant activity at 256µg/mL concentration against *E.coli, P.aeruginosa,* and *S.aureus.*

An examination of the data reveals that almost all the compound showed good to moderate antimicrobial activity.

Experimental Section

All the melting points were taken in open capillary tube and are uncorrected. The IR spectra were recorded with KBr on Shimadzu FT–IR 8300 spectrophotometer. Purity of the compounds in addition to elemental analysis was checked by Thin Layer Chromatograghy using silica gel–G coated Al plates (Merck) and spots were visualized by exposing the dry plates in iodine vapors, using benzene:ethyl acetate:ethanol (6:2:2) ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker DRX–300 at 200MH_z using TMS as an internal standard and mass spectra on a JEOL SX 102/DA-6000 Mass spectrometer/Data system using Argon/Xenon(6kV,10 mA)as the FAB gas.

General procedure for the synthesis of substituted 3-[(1*E*)-1-aza-2-(2-chloro-7-methoxy-3-quinolyl)-vinyl]-4-(aryldiazenyl) phenol (1a-s)

A mixture of 2-chloro-7-methoxy-3-formyl-quinoline (0.01mole), 3- amino -4-(aryldiazenyl) phenol (0.01 mole) and glacial acetic acid (2 mL) was dissolved in ethanol. Then the well stirred mixture was refluxed for 6-7 hr (In Q Pro-M modified microwave system; at 90ºC temp. and 500 W Power level, reaction was completed in 2-3 min.).The reaction-mixture was then cooled, concentrated and poured into crushed ice. The product obtained was filtered, washed with water and recrystallized from ethanol.

3-[(1*E*)-1-Aza-2-(2-chloro-7-methoxy-3-quinolyl)-vinyl]-4-(phenyldiazenyl) phenol 1 (1a): ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.75 (dd, 1H, $J_{6\text{-}8}$ = 2.20 & $J_{6\text{-}5}$ = 8.75 Hz, C_6 -H), 7.39 (s, 1H, C_8 -H), 7.15 (d, 1H, $J_{5\text{-}6}$ = 8.75 Hz, C_5-H), 8.56 (s, 1H, C_4-H), 9.755 (s, 1H, -CH=N), 7.02 (d, 1H, $J_{4\text{-}2}$ = 2.50 & $J_{4\text{-}5}$ = 8.17 Hz, C_4-H), 7.06 (s, 1H, $J_{2\text{-}4}$ = 2.50 Hz, C_2-H), 7.392 (d, 1H, $J_{5\text{-}4}$=8.17 Hz, C_5-H), 7.40-8.70 (m, 5H, Ar-H), 3.84 (s, 3H, –O–CH3), 10.25 (s, 1H, Ar-OH); IR(KBr): 3446 (-OH), 1576 (CH=N), 1570 (C=N), 1417 (N=N) cm^{-1}, MS, *m/z*: 417, 219, 198, 193, 157, 142, 133, 121, 114, 93.

General procedure for the synthesis of substituted 3-chloro-4-(2-chloro-7-methoxy-3-quinolyl)-1-[3-hydroxy-6-(aryldiazenyl) phenyl] azetidin-2-one 2a-s

A mixture of 3-[(1*E*)-1-aza-2-(2-chloro-7-methoxy-3-quinolyl)-vinyl]-4-(aryldiazenyl) phenol **1** (0.01 mole) and triethylamine (0.02 mole) was dissolved in 1, 4-dioxane (50 mL). To this well stirred cooled solution chloroacetylchloride (0.02 mole) was added drop wise during 20 min. The reaction-mixture was then stirred for further 1hr and refluxing for 12 hr (in Q Pro-M modified microwave system; reaction was completed in 4-5 min at power level 500 W) at 120ºC. The triethylamine hydrochloride salt formed was filtered to separate the salt. The filtrate was concentrated to half of its initial volume and then poured onto crushed ice. The product obtained was filtered, washed with water and recrystallized from ethanol.

3-Chloro-4-(2-chloro-7-methoxy-3-quinolyl)-1-{3-hydroxy-6-[(3-methoxyphenyl) diazenyl]phenyl} azetidin-2-one 2c: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.95 (dd, 1H, $J_{6\text{-}8}$ = 2.15 & $J_{6\text{-}5}$=8.79 Hz, C_6 -H), 7.02 (s, 1H, C_8 -H), 7.77 (d, 1H, $J_{5\text{-}6}$ = 8.79 Hz, C_5-H), 8.37 (s, 1H, C_4-H), 5.20 (s, ^{1}H, CH–N β-lactam), 5.32 (s, 1H, CH–C β-lactam), 7.05 (d, 1H, $J_{4\text{-}2}$ = 1.7 & $J_{4\text{-}5}$=8.17 Hz, C_4-H), 7.36 (d, 1H, $J_{5\text{-}4}$ = 8.17Hz, C_5-H) , 7.80-8.70 (m, 5H, Ar-H), 3.78 (s, 3H, –O–CH3), 3.85(s, 3H, –O–CH3), 10.0 (s, 1H, Ar-OH);IR (KBr) : 3503 (-OH, str, phenolic), 1734 (C=O β-Lactam), 1536 (C-N), 1419 (N=N) cm^{-1}, MS, *m/z*: 523(M^+), 527(M^++4), 267, 232, 228, 219, 213, 198, 194, 185, 121.

General procedure for the synthesis of substituted 2-(2-chloro-7-methoxy-3-quinolyl)-3-[3-hydroxy-6-(aryldiazenyl) phenyl]-1, 3-thiazolidin-4-one 3a-s

A mixture of 3-[(1E)-1-aza-2-(2-chloro-7-methoxy-3-quinolyl)-vinyl]-4-(aryldiazenyl) phenol **1** (0.01 mole) and catalytic amount of aluminium chloride

(0.05 g) in benzene was taken in Dean stark apparatus and to it thioglycolic acid (1.40 mL, 0.02 mole) in DMF was added slowly. The reaction mass was refluxed for 16 hr (Q Pro-M modified microwave system. The reaction- mixture was refluxed for 6-7 min at Power level 450 W) at 120-125ºC constant temperature. The benzene was distilled off to get the solid mixture. This was then triturated with an excess of 10% sodium bicarbonate solution to remove excess of mercapto acetic acid. The product obtained was filtered, washed several times with water and recrystallized from ethanol.

2-(2-Chloro-7-methoxy(3-quinolyl)-3-{3-hydroxy-6-[(3-methoxyphenyl)diazenyl] phenyl}-1, 3-thiazolidin-4-one 3c: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.744 (dd, 1H, $J_{6\text{-}8}$ = 2.20 and $J_{6\text{-}5}$ = 8.43 Hz, C_6 -H), 6.98 (s, 1H, C_8 -H), 7.90 (d, 1H, $J_{5\text{-}6}$ = 8.43 Hz, C_5-H), 8.29 (s, 1H, C_4-H), 4.40 (s, 2H, S-CH_2), 6.36 (s, 1H, -CH-N), 7.10 (d, 1H, $J_{4\text{-}2}$ = 1.80 and $J_{4\text{-}5}$=8.06 Hz, C_4-H), 7.07 (d, 1H, $J_{2\text{-}4}$ = 2.50 Hz, C_2-H), 7.368 (d, 1H, $J_{5\text{-}4}$ = 8.17 Hz, C_5-H), 7.44-7.60 (m, 5H, Ar-H), 3.76 (s, 3H, –O–CH_3), 3.86 (s, 3H, –O–CH_3), 10.0 (s, Ar-OH); IR (KBr): 3421 (-OH), 1738 (C=O, thiazolidinone), 1559.8 (C=N), 1535 (C-N), 1417 (N=N), 616 (C-S-C) cm^{-1}, MS, *m/z*: 521(M^+), 523(M^++2), 295, 248, 228, 213, 198, 185, 121.

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