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DESIGN, SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEWER 3(H)-QUINAZOLINE-4-ONE DERIVATIVE

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ABSTRACT

2-mercapto-3-phenylquinazolin-4(3H)-one **(1)** react with 4-amino phenacyl bromide gives 2-(2-(4-amino phenyl)-2-oxoethylthio)-3-phenyl quinazolin-4(3H)-one **(2)**, which undergoes facile condensation with aromatic aldehydes to afford the corresponding 2-(2-(4-(substituted benzylidene amino)phenyl)-2-oxoethylthio)-3-phenylquinazolin-4(3H)-one **(3)a-e** in good yields. Cyclocondensation of compounds **(3)a-e** with thioglycolic acid yields 3-(4-(2-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylthio)acetyl)phenyl)-2-substitutedphenyl thiazolidin-4-one **4(a-e)**. The structures of these compounds were established on the basis of analytical and spectral data. All the newly synthesized compounds were evaluated for their antibacterial and antifungal activities.

Key words: 2-Mercapto-3-phenylquinazolin-4(3H)-one, 4-Amino phenacyl bromide, Schiff base, Thiazolidinone, Antibacterial activity.

INTRODUCTION

The heterocyclic compounds such as, 4-thiazolidinones[1,2], fused thiazolidinones[3,4], 2-pyrrole and 2-pyrrolidinones[4,5] and tetrazole[6] have prominent role in pharmaceutical. Literature assessment reveals that Schiff bases indicate that they have coordinating behaviors with the transition metal ions. Schiff bases also display biochemical and physiochemical effects[7-10]. The another moiety quinazolinone also has pharmaceutical activity like anticancer, antitubercular and antiinflemmatory, etc.[11-13] If both these moiety clubbed into one molecule, it will be afford as good bioactive compound.4-thiazolidinones are also known to exhibit antitubercular,[14] antibacterial[15], antifungal[16] and anticonvulsant activities. Hence, it was thought of interest to merge both of thiazolidinone and corresponding 2-(2-(4-(substituted benzylidene amino) phenyl)-2-oxoethylthio)-3-phenylquinazolin-4(3H)-one moieties which may enhance the drug activity of compounds to some extent or they might possess some of the above mentioned biological activities. Though, many authors synthesized a variety of quinazoline compounds with different biological activities by installing various active groups to the quinazoline moiety using developing synthetic methods. The potential applications of the quinazoline derivatives in fields of biology, pesticides and medicine have also been explored[17-20]. Hence, the present communication comprises the synthesis of 3-(4-(2-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylthio)acetyl) phenyl) -2-substitutedphenyl thiazolidin-4-one 4(a-e) and its biological activity. The synthetic approach is shown in **Scheme 1**.

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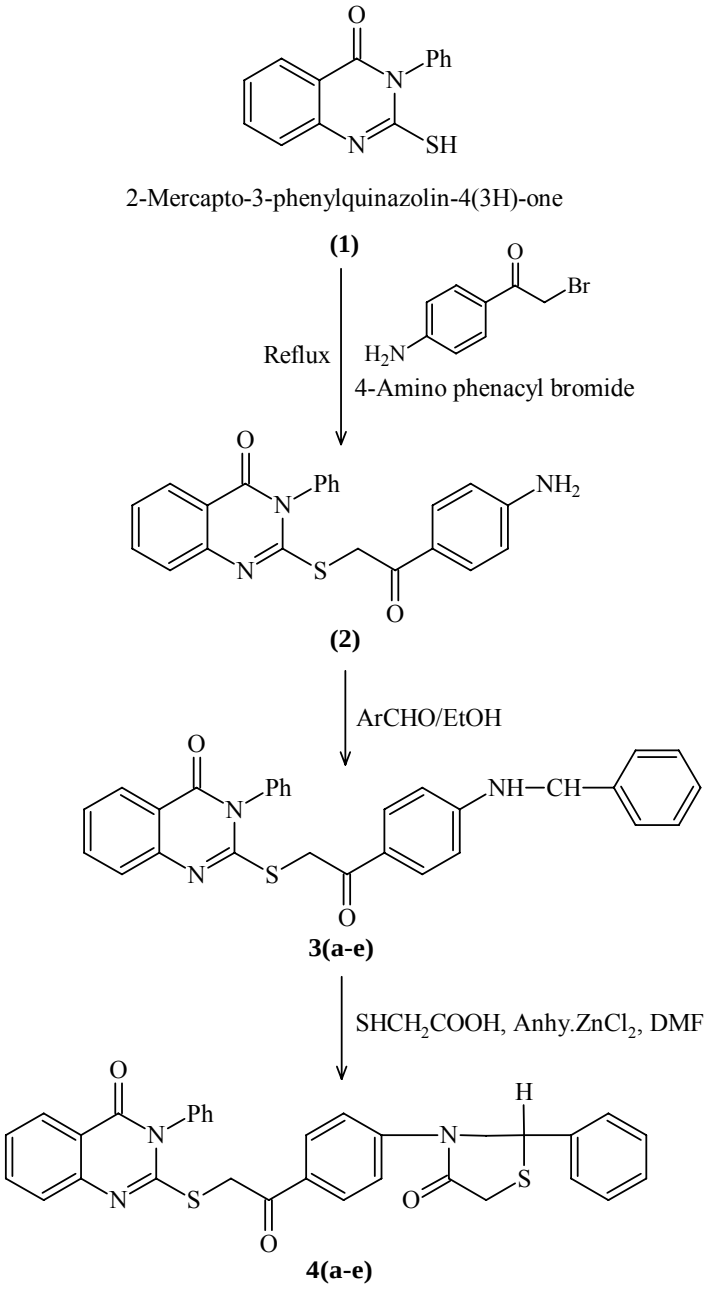

Where Ar = (a) C_6H_5, (b) 2-OH-C_6H_4, (c) 4-OH-C_6H_4, (d) 4-OCH_3-C_6H_4 (e) 4-Cl-C_6H_4

Scheme 1

EXPERIMENTAL

Materials

All chemicals used were of laboratory grade. 2-mercapto-3-phenyl quinazolin-4(3H)-one[21] and 4-amino phenacyl bromide[22] was prepared by reported method.

Measurement

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were

recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz and 100 MHz, respectively.

Preparation of 2-(2-(4-aminophenyl)-2-oxoethylthio)-3-phenylquinazolin-4(3H)-one (2)

A mixture of 2-mercapto-3-phenyl quinazolin-4(3H)-one (1), (0.01mole) and 4-amino phenacyl bromide in presence of DMF/K_2CO_3 was refluxed on a water bath for 3-3.5 hrs. The solid separated was collected by filtration, dried and recrystallized from ethanol. The yields 62%, melting point 212-214°C, IR cm^{-1}: 3370 (NH_2), 1630-1660 (C=N), 3010-3070 (C-H, of Ar.), 2950, 2885, 1370 (CH_2), 1720-1680 (CO). ^{1}H NMR: 8.06–6.56 (m, 13H, Ar-H), 5.10 (s, 2H, CH_2), 6.19 (s, 2H, NH_2). Anal. Calcd for $C_{22}H_{17}N_3O_2S$ (387): C, 68.20; H, 4.42; N, 10.85; S, 8.28. Found: C, 68.18; H, 4.39; N, 10.83; S, 8.26.

Preparation of 2-(2-(4-(substituted benzylidene amino)phenyl)-2-oxoethylthio)-3-phenyl quinazolin-4 (3H)-one 3(a-e)

A mixture of 2-(2-(4-aminophenyl)-2-oxoethylthio)-3-phenyl quinazolin-4(3H)-one (2), (0.01 mole) and the aromatic aldehydes (a-e) in ethanol (15 mL) was refluxed on a water bath for 3-3.5 hrs. The solid separated was collected by filtration, dried and recrystallized from ethanol. The yields, melting points and other characterization data of these compounds are given in Table 1.

Preparation of 3-(4-(2-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylthio)acetyl)phenyl)-2-subsituted phenyl thiazolidin-4-one 4(a-e)

A mixture 2-(2-(4-(substituted benzylidene amino) phenyl)-2-oxoethylthio)-3-phenyl quinazolin-4(3H)-one **3(a-e)** (0.01 mole) in THF (30 mL) and mercapto acetic acid (thioglycolic acid) (0.01 mole) with a pinch of anhydrous $ZnCl_2$ was refluxed for 15-17 hrs. The solvent was then removed to get a residue, which was dissolved in benzene and passed through a column of silica gel using benzene: carbon tetrachloride (8:2; v/v) mixture as eluent. The eluate was concentrated and the product crystallized from alcohol to give 3-(4-(2-(4-oxo-3-phenyl-3,4-dihydro quinazolin-2-ylthio) acetyl) phenyl)-2-subsitutedphenyl thiazolidin-4-one **4(a-e)**, which were obtained in good yield. The yields, melting points and other characterization data of these compounds are given in Table 2.

Table 1: Analytical data and elemental analysis of compounds (3a-e)

Compd.	Molecular formula (Mol. wt.)	Yield	M.P.* (°C)	Elemental analysis							
				% C		% H		% N		% S	
				Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	$C_{29}H_{21}N_3O_2S$ (475)	72	246-247	73.22	73.24	4.44	4.45	8.82	8.84	6.72	6.74
3b	$C_{29}H_{21}N_3O_3S$ (491)	69	253-255	70.85	70.86	4.29	4.31	8.53	8.55	6.51	6.52
3c	$C_{29}H_{21}N_3O_3S$ (491)	70	248-250	70.84	70.86	4.30	4.31	8.54	8.55	6.50	6.52
3d	$C_{30}H_{23}N_3O_3S$ (505)	66	263-264	71.26	71.27	4.58	4.59	8.30	8.31	6.32	6.34
3e	$C_{29}H_{20}N_3O_2SCl$ (509.5)	67	259-261	68.29	68.30	3.94	3.95	8.22	8.24	6.27	6.29

*****Uncorrected

Table 2: Analytical data and elemental analysis of Compounds (4a-e)

Compd.	Molecular formula (Mol.wt.)	Yield	M.P* (°C)	Elemental analysis							
				% C		% H		% N		% S	
				Found	Cal.	Found	Cal.	Found	Cal.	Found	Cal.
4a	$C_{31}H_{23}N_3O_3S_2$ (549)	69	276-278	67.73	67.74	4.20	4.22	7.62	7.64	11.66	11.67
4b	$C_{31}H_{23}N_3O_4S_2$ (565)	64	280-281	65.80	65.82	4.09	4.10	7.42	7.43	11.32	11.34
4c	$C_{31}H_{23}N_3O_4S_2$ (565)	66	271-272	65.81	65.82	4.08	4.10	7.41	7.43	11.31	11.34
4d	$C_{32}H_{25}N_3O_4S_2$ (579)	63	284-286	66.28	66.30	4.34	4.35	7.23	7.25	11.04	11.06
4e	$C_{31}H_{22}N_3O_3S_2Cl$ (583.5)	67	268-269	63.72	63.74	3.78	3.80	7.17	7.19	10.96	10.98

***Uncorrecte

Biological screening

Antibacterial activities

The antibacterial activities of all the compounds were studied against gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and gram-negative bacteria (*E. coli* and *klebsiella promioe*) at a concentration of 50 µg/mL by agar cup plate method. A methanol system was used as control in this method. Similar conditions using tetracycline as a control was used standard for comparison. The area of inhibition of zone measured in mm. Compounds **4e** and **4d** were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline. The antibacterial activities displayed by various compounds **4(a-e)** is shown in Table-3.

Table 3: Antibacterial activity of Compounds 4 (a-e)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	***Bacillus subtilis***	***E. coli***	***Klebsiella promioe***
4a	47	62	59	66
4b	49	64	60	69
4c	49	66	64	71
4d	52	71	67	76
4e	53	73	70	79
Tetracycline	55	79	74	84

Antifungal activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration *in vitro*. Plant pathogenic organisms used were *Aspergillus niger*, *Botrydepladia thiobromine*, *Nigrospora Sp* and *Rhizopus nigricum*. The antifungal activities of all the compounds **4(a-e)** were measured on each of these plant

pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200 g, dextrose 20 g, agar 20 g and water 1 mL. Five days old cultures were employed. The compounds to be tested were suspended (1000 ppm) in a PDA medium and autoclaved at 120^{o}C for 15 min. at 15 atm. pressure. These media were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after five days using the formula given below:

$$\text{Percentage of inhibition} = 100\ (X - Y) / X$$

Where, X = Area of colony in control plate

Y = Area of colony in test plate

The fungicidal activity displayed by various compounds **4(a-e)** is shown in Table 4.

Table 4: Antifungal activity of compounds 4(a-e)

Compounds	*Nigrospora Sp.*	*Aspergillus Niger*	*Botrydepladia Thiobromine*	*Rhizopus Nigricum*
4a	57	52	58	58
4b	60	56	60	61
4c	62	58	61	59
4d	72	64	71	62
4e	67	71	68	61

RESULTS AND DISCUSSION

It was observed that 2-mercapto-3-phenyl quinazolin-4(3H)-one **(1)** react with 4-amino phenacyl bromide gives 2-(2-(4-amino phenyl)-2-oxoethylthio)-3-phenyl quinazolin-4(3H)-one **(2)**, which undergoes facile condensation with aromatic aldehydes to afford the corresponding 2-(2-(4-(substituted benzylidene amino)phenyl)-2-oxoethylthio)-3-phenyl quinazolin-4(3H)-one **3(a-e)**. The structures of **3(a-e)** were confirmed by elemental analysis and IR spectra showing an absorption band at 1630-1660 cm^{-1} (C=N), 3010-3080 cm^{-1} (C-H, of Ar.), 2950, 2885, 1370 cm^{-1} (CH_2), 1720-1680 cm^{-1} (CO), 3620 cm^{-1} (OH), 2815-2850 cm^{-1} (-OCH_3), 1090 (C-Cl). ^{1}H NMR: 7.25-8.08 (18H, m, Ar-H), 5.10 (s, 2H, CH_2), 3b; 5.40 (1H, s, OH), 3c; 5.35 (1H, s, OH), 3d; 3.96 (3H, s, OCH_3). The C, H, N analysis data of all compounds are presented in Table 1.

The structures assigned to 3-(4-(2-(4-oxo-3-phenyl-3,4-dihydro quinazolin-2-ylthio)acetyl)phenyl)-2-subsituted phenyl thiazolidin-4-one **4(a-e)** were supported by the elemental analysis and IR spectra showing an absorption bands at 1690 cm^{-1} (C=O of thiazolidinone ring), 718 cm^{-1} (C-S-C of thiazolidinone ring), 3075-3095 cm^{-1} (CH_2 of thiazolidinone ring), 1630-1660 cm^{-1} (C=N), 3010-3080 cm^{-1} (C-H, of Ar.), 2950, 2885, 1370 cm^{-1} (CH_2), 1720-1680 cm^{-1} (CO), 3620 cm^{-1} (OH), 2815-2850 cm^{-1} (-OCH_3), 1090 (C-Cl). ^{1}H NMR: 7.25–8.08 (18H, m, Ar-H), 5.10 (s, 2H, CH_2), 6.58 (1H, s, CH), 4.2-4.0 (2H, s, thiazolidinone ring -CH), 4b; 5.40 (1H, s, OH), 4c; 5.35 (1H, s, OH), 4d; 3.96 (3H, s, OCH_3). The C, H, N, S analysis data of all compounds are presented in Table 2.

CONCLUSION

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structure shown in Scheme 1. The IR spectral peaks are found as per predicted structure. The final structure of all compounds is confirmed by LC-MS data of all compounds which are presented in

Tables 1, 2. The antibacterial activity data suggest that all the compounds have shown good to moderate activity compare to standard tetracycline, while primary evaluation of all compounds shows good to moderate activity against employed strains.

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