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Synthesis and Antimicrobial Assay of Some Novel 4-Thiazolidinone Derivatives Possessing Benzofuran, Quinoline and Pyrazole Moieties

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In this study, simple, easy and convenient syntheses of six novel 4-thiazolidinone derivatives (**3a-f**) bearing benzofuran, quinoline and pyrazole moieties have been described. In the first step, six different carbohydrazides (**2a-f**) were synthesized by reacting 5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (**2**) with six different 2-(*p*-tolyloxy)quinoline-3-carbaldehyde (**1a-f**). Similarly, in second step, 5-(benzofuran-2-yl)-N′-(2-(2-(*p*-tolyloxy) substituted quinolin-3-yl)-4-oxothiazolidin-3-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide (**3a-f**) was prepared in excellent yield through the interaction of compounds **2a-f** with thioglycolic acid in presence of anhydrous zinc chloride. Structural identifications of products **2a** and **3a** are reported on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectra and the analytical data confirms the structure of title compounds. Further, these new products have been assayed for their antimicrobial screening against *S. aureus* and *E. coli* as the two selected bacterial strains and two fungi such as *C. albicans* and *A. niger* using paper disc diffusion method. Antimicrobial screening revealed that the compounds are good antibacterial agents but found to be inactive against fungi.

Keywords: Quinoline, Carbohydrazides, Thiazolidinone, Pyrazole, Antibacterial activity.

INTRODUCTION

The synthesis of polysubstituted quinoline and its derivatives is the focus of a large number of pharmacological studies because of their wide range of biological applications. The quinoline moiety constitutes the main framework of several natural products such as Montelukast and Skimmianine. Quinoline was synthesized by Vilsmeier-Haack reagent which is a versatile reagent used in various synthetic transformation [1]. Quinine, amodiaquine, piperaquine, orimaquine, mefloquine and chloroquine are used as antimalarial drugs mainly consist quinoline moiety [2]. Quinoline nucleus shows good antitumor [3] and antifungal [4] activities. It is also reported that coordination polymer of quinoline ligand too showed antimicrobial activity [5]. Antimicrobial screening and molecular docking studies of some triazoloquinazolinone [6] has also been studied.

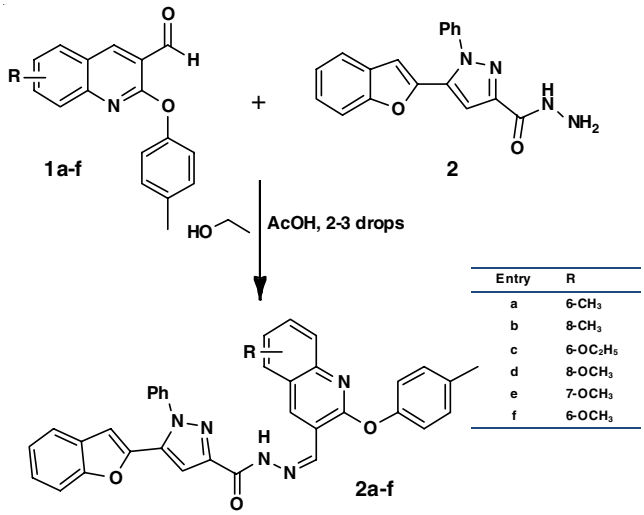
On the other hand, thiazolidinones are also an important class of heterocyclic compounds which has been classified as 2,4,5-thiazolidinones depending on the position of carbonyl group. Out of these 4-thiazolidinone is a five member ring with carbonyl group at fourth position and methylene carbon atom at fifth position is found to be more nucleophilic, hence, electrophilic substitution may occur at this position. Thiazolidinone scaffold is a better pharmacophore showing various biological activities such as anti-inflammatory, analgesic [7], antitubercular [8-10], antifungal [9], inhibitory [11], antioxidant [12,13], antihyperglycemic [14], antimycobacterial [15], antibacterial [16-18], cytotoxic [19,20], antiviral [21], antiparkinsnian [22], antinfective [23]. *Toxoplasma gondii* infection was studied for 4-thiazolidinone [24]. This amazing array of applications and ubiquitous biological importance of quinoline along with thiazolidinones led us to synthesize a new series of 4-thiazolidinone analogues containing benzofuran, quinoline and pyrazole moiety and evaluate their antimicrobial activities.

EXPERIMENTAL

The melting points of newly synthesized compounds were determined in open capillary paraffin oil bath and found to be uncorrected. ^{1}H NMR spectra was recorded on Bruker AM 400 instrument using tetramethylsilane as an internal reference

and DMSO-d_6 as solvent. IR spectra were recorded on a Shimadzu IR 8400 Spectrophotometer with the frequency ranging from 4000-400 cm^{-1}. Mass spectra were obtained with a Waters Micro mass Q-TOF Micro, Mass Spectrophotometer. Elemental analysis was performed using Thermo Scientific (Flash-2000). All the chemicals used were of AR grade of Merck, S.D. Fine and Aldrich.

General procedure for synthesis of 5-(benzofuran-2-yl)- N′-((6-methyl-2-(*p*-tolyloxy)quinolin-3-yl)methylene)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (2a) : 5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (**2**, 0.01 mol) and 6-methyl-2-(*p*-tolyloxy) quinoline-3-carbaldehyde (**1a**) were dissolved in ethanol and then 2-3 drops of acetic acid were added and the reaction mixture was refluxed for 2 h. Resulting mass was cooled and poured into crushed ice, filtered and further purified by recrystallization using 1,4-dioxane to give **2a**. Similarly, other derivatives **2a-f** were synthesized by by applying the same procedure as adopted for the synthesis of **2a** (**Scheme-I**).



Entry	R
a	6-CH_3
b	8-CH_3
c	6-OC_2H_5
d	8-OCH_3
e	7-OCH_3
f	6-OCH_3

Scheme-I

5-(Benzofuran-2-yl)-N′-((6-methyl-2-(*p*-tolyloxy)-quinolin-3-yl)methylene)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (2a): Yellow crystalline solid; m.p. 263-265 ºC; Yield: 81%; IR (KBr, ν_{max}, cm^{-1}): 3293, 3412, (N-H *str*.), 3062, 3029 (C-H *str*., arom.), 2958 (C-H asym. *str*., aliph.), 2857, 2915 (C-H *str*. sym., aliphatic), 1688 (C=O *str*.), 1650-1600 (C=N *str*.), 1240 (C-O-C sym. *str*., ether), 1058 (C-O-C asym. *str*., ether); ^{1}H NMR (DMSO-d_6) δ ppm: 2.36 (s, 3H, Ar-CH_3), 2.47 (s, 3H, CH_3 attached to quinoline ring), 6.51 (s, 1H, at C4 of pyrazole ring), 12.21 (s, 1H, NHCO), 7.14-9.08 (m, 19H, arom. + heterocycl. ring protons); MS: *m/e* 577 M^+, 578 $[M + H]^+$, 579 $[M + 2]^+$, 600 $[M + Na]^+$. Elemental analysis (%) calcd. (found) $C_{36}H_{27}N_5O_3$: C, 74.85 (74.05); H, 4.71 (4.50); N, 12.12 (12.06).

5-(Benzofuran-2-yl)-N′-((8-methyl-2-(*p*-tolyloxy)quinolin-3-yl)methylene)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (2b): Yellow crystalline solid; m.p. 234-238 ºC; Yield: 88 %. Elemental analysis (%) calcd. (found) $C_{36}H_{27}N_5O_3$: N, 12.12 (12.16).

5-(Benzofuran-2-yl)-N′-((6-ethoxy-2-(*p*-tolyloxy)-quinolin-3-yl)methylene)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (2c): Yellow crystalline solid; m.p. 260-264 ºC; Yield: 88 %. IR (KBr, ν_{max}, cm^{-1}): 3944, 3392, 3318, 3147 (N-H *str*.), 3061 (C-H *str*., arom.), 2956, 2920 (C-H asym. *str*., aliph.), 2803 (C-H *str*. sym., aliph.), 1689 (C=O *str*. amide), 1580, 1505 (C=N), 1247 (C-O-C sym. *str*., ether), 1087, 1037 (C-O-C asym. *str*., ether); Elemental analysis (%) calcd. (found) $C_{37}H_{29}N_5O_4$: N, 11.53 (11.58).

5-(Benzofuran-2-yl)-N′-((8-methoxy-2-(*p*-tolyloxy)-quinolin-3-yl)methylene)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (2d): Yellow crystalline solid; m.p. 228-232 ºC, Yield: 83%. Elemental analysis (%) calcd. (found) $C_{36}H_{27}N_5O_4$: N, 11.80 (11.84).

5-(Benzofuran-2-yl)-N′-((7-methoxy-2-(*p*-tolyloxy)-quinolin-3-yl)methylene)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (2e) : Yellow crystalline solid; m.p. 228-231 ºC; Yield: 79 %. Elemental analysis (%) calcd. (found) $C_{36}H_{27}N_5O_4$: N, 11.80 (11.88).

5-(Benzofuran-2-yl)-N′-((6-methoxy-2-(*p*-tolyloxy)-quinolin-3-yl)methylene)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (2f): Yellow crystalline solid; m.p. 258-261 ºC, Yield: 79 %. Elemental analysis (%) calcd. (found) $C_{36}H_{27}N_5O_4$: N, 11.80 (11.88).

Synthesis of 5-(benzofuran-2-yl)-N′-(2-(6-methyl-2-(*p*-tolyloxy) quinoline-3-yl)-4-oxothiazolidin-3-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide (3a): To a mixture of 5-(benzofuran-3-yl)-N′-((6-methyl-2-(*p*-tolyloxy)quinolin-3-yl)methylene)-1-phenyl-4,5-dihydro-1*H*-pyrazole-3-carbohydrazide) (**2a**, 0.02mol) and thioglycolic acid in 1,4-dioxane, anhydrous $ZnCl_2$ was added and then the reaction content was refluxed for 8 h. The reaction mixture was kept overnight after addition of 10 % sodium bicarbonate to neutralize thioglycolic acid. The solution was stirred and product was separated out was filtered, washed and recrystallized from 1,4-dioxane to get **3a**. Brown, crystalline solid; m.p. 178-180 ºC; Yield: 85 %. IR (KBr, ν_{max}, cm^{-1}): 3228(N-H *str*. amide), 3061 (C-H *str*., arom.), 1005,1027(C-H i.p.def, arom.), 808 (C-H o.o.p. def. arom.), 1498, 1527 (C=C *str*. arom.), 1595 (C=N *str*., quinoline ring), 1673 (C=O amide *str*.), 1027, 1073 (C-O-C asym. *str*., ether), 1257, 1208 (C-O-C sym. *str*., ether), 1673 (C=O *str*. thiazolidinone ring), 1208 (C-N *str*. thiazolidinone ring), 696 (C-S-C *str*. thiazolidinone ring). ^{1}H NMR (DMSO-d_6) δ ppm: 2.35 (s, 6H, two CH_3 group attached to two different aromatic ring), 3.58 (s, 2H, CH_2 of thiazolidinone ring), 6.48 (s, 1H, at C2 of thiazolidinone ring), 6.49 (s, 1H, at C4 of pyrazole ring), 8.30 (s, 1H, at C4 of quinoline ring), 10.41 (s, 1H, NH of -CONH- linkage), 6.38-7.67 (m, 17 H, arom. and heterocycl.). ^{13}C NMR (δ ppm): 21 (CH_3), 38 (C2 of thiazolidinone), 48 (C5 of thiazolidinone), 105, 106, 107, 110, 121, 123, 125, 127, 129, 135, 139, 144, 145, 153,159,167 (carbon of -CONH). Mass spectra *m/z* 652 $[M + H]^+$, 674 $[M + Na]^+$. Elemental analysis (%) calcd. (found) $C_{38}H_{29}N_5O_4S$: C, 70.03 (70.08); H, 4.49 (4.54); N, 10.75 (10.72); S, 4.92 (4.98). Similarly, other compounds **3b-f** of this series was prepared by adopting the same procedure followed for compound **3a**. Their structures were established on the basis of elemental and physical data (Table-1).

Antimicrobial activity: All the compounds were screened *in vitro* for their antibacterial and antifungal activities at concentration of 1000 μg/mL. Out of all the six synthesized compounds **2a** and **3a** were then assayed at different concen-

TABLE-1
PHYSICAL AND ANALYTICAL DATA OF SYNTHESIZED COMPOUNDS **3b-f**

Entry	R	Colour	Recrys. solvent	m.p. (°C)	Yield (%)	m.f.	Elemental analysis (%): Found (calcd.)	
							N	S
3b	8-CH_3	Brown	1,4-Dioxane	184-190	75	$C_{38}H_{29}N_5O_4S$	10.82 (10.75)	4.91 (4.92)
3c	6-OC_2H_5	Brown	1,4-Dioxane	234-238	80	$C_{39}H_{31}N_5O_5S$	10.32 (10.27)	4.73 (4.70)
3d	8-OCH_3	Brown	1,4-Dioxane	220-224	76	$C_{38}H_{29}N_5O_5S$	10.48 (10.49)	4.82 (4.80)
3e	7-OCH_3	Brown	1,4-Dioxane	203-207	75	$C_{38}H_{29}N_5O_5S$	10.45 (10.49)	4.78 (4.80)
3f	6-OCH_3	Brown	1,4-Dioxane	244-250	75	$C_{38}H_{29}N_5O_5S$	10.51 (10.49)	4.79 (4.80)

tration ranging from 1000 to 63 µg/mL using disc diffusion method. Initially, stock culture of *S. aureus* and *E. coli* were revived by inoculating in broth media at 37 ºC for 18 h.The agar plate of nutrient agar media was prepared and sterilized. After the inoculation of bacterial cultural, the discs were dipped in the different concentration of compound, which was prepared in DMSO and placed on the surface of agar plate. All the plates were incubated for 37 ºC for 24 h and diameter of zone of inhibition were noted in mm. The results were compared with standard drug Chloramphenicol. Same procedure was applied for *A. niger* and *C. albicans* and results were compared with standard drug Amphotericin.

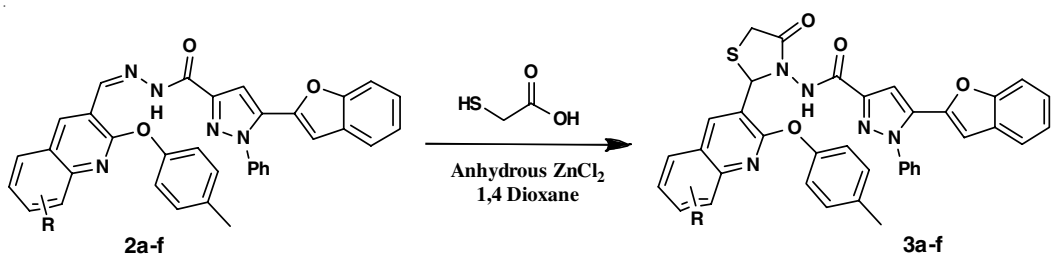
RESULTS AND DISCUSSION

Synthetic work was performed as described in **Schemes I** and **II** and their purity was checked by TLC. The compounds were obtained in excellent yield and structures have been confirmed by elemental analysis and IR, ^{1}H NMR and mass spectral studies. 2-Chloroquinoline-3-carbaldehyde derivatives were the starting compounds which were prepared by Vilsmeier cyclization [1], which later on reaction with *p*-cresol in presence of K_2CO_3 in DMF yielded substituted 2-phenoxyquinoline-3-carbaldehyde derivatives (**1a-f**). Treatment of compounds **1a-f** with 5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (**2**) yielded 5-(benzofuran-2-yl)-N′-((2-(*p*-tolyloxy)-substituted quinolin-3-yl)methylene)-1-phenyl -1*H*-pyrazole-3-carbohydrazides (**2a-f**) as illustrated in **Scheme-I**.

The IR spectra of compounds **2a** and **2c** showed a broad signal of NH at 3293, 3412 and 3318 cm^{-1} respectively. The absorption bands at 1688 and 1689 cm^{-1} are due to C=O stretching also observed. Similarly, peak at 1580 in compound **2c** and 1650-1600 cm^{-1} in compound **2a** are due to C=N stretching in pyrazole ring further supported the structure of compounds **2c** and **2a**. Molecular ion peaks of $[M + H]^+$, in mass spectra at 578 for compound **2a** confirmed its molecular weight. ^{1}H NMR spectrum of compound **2a** showed two singlet's, one at 2.36 ppm due to three proton of CH_3 on aromatic ring, and another at 2.47ppm due to CH_3 group attached to quinoline moiety. Proton present on the pyrazole ring at C4 carbon gave singlet at 6.51ppm, another downfield singlet appear at 12.21 ppm due to one proton of NH of NHCO group and multiplet exhibited in the range of 7.14-9.08 ppm are due to nineteen protons present on aromatic and heterocyclic ring. Thus ^{1}H NMR spectrum of compound **2a** is in good agreement with the number of protons present in the molecular formula $C_{36}H_{27}N_5O_3$.

The resulted compounds **2a-f** were then reacted with thioglycolic acid in the presence of anhydrous $ZnCl_2$ and cyclized successfully to five-membered 4-thiazolidinones ring (**3a-f**) in good to moderate yield and were recrystallized by 1,4-dioxane (Table-1). All the synthesized compounds **3a-f** was tested for nitrogen and sulphur which gave positive result confirming the presence of these extra elements in thiazolidinone ring.

The IR spectrum of compound **3a** showed characteristics absorption bands at 3228 cm^{-1} due to NH stretch. Another absorption band appeared at 1673 cm^{-1} assigned due to C=O stretching in thiazolidinone ring. Another characteristic band appeared at 696 cm^{-1} due to C-S-C stretch confirmed the formation of thiazolidinone ring. ^{1}H NMR spectra for compound **3a** exhibited singlet at 2.35 ppm due to six protons of two CH_3 group attached to phenyl and quinoline ring. Other signals for aromatic protons appeared at expected region. Singlet at 3.58 and 6.48 ppm for two protons and one proton for CH_2 and CH group, respectively were observed which was absent in compound **2a**, this confirms the formation of thiazolidinone ring. A singlet appeared at 8.30 ppm due to one proton of NH of -CONH- linkage. Singlet due to one proton located at C4 of quinoline ring was also observed in expected region in compound **3a** as observed for compound **2a**. Two characteristics ^{13}C NMR signals appeared at 38 and 48 ppm is assigned due to carbon atom at second and fifth position of thiazolidinone ring and signals due to other aromatic and aliphatic carbons appeared at the expected region. The mass spectra of compound **3a** gives a molecular ion peak of $[M + H]^+$ at 652 and $[M + Na]^+$ at 674, is in good agreement with the molecular formula $C_{38}H_{29}N_5O_4S$.



Entry	a	b	c	d	e	f
R	6-CH_3	8-CH_3	6-OC_2H_5	8-OCH_3	7-OCH_3	6-OCH_3

Scheme-II

TABLE-2
ANTIBACTERIAL ACTIVITY OF **2a** AND **3a** AT DIFFERENT CONCENTRATIONS

Conc. (μg/mL)	Zone of inhibition (mm)					
	Gram-positive: *S. aureus*			Gram-negative: *E. coli*		
	Chloramphenicol	**2a**	**3a**	Chloramphenicol	**2a**	**3a**
1000	26	15	12	16	15	17
500	30	12	13	16	13	17
250	27	13	12	17	13	14
125	21	10	10	16	12	10
63	18	16	11	15	10	10

Antimicrobial activity: The novel synthesized benzofuran, quinoline and pyrazole based carbohydrazide and 4-thiazolidinone derivatives (**2a** and **3a**), respectively were screened *in vitro* for antimicrobial activity at different concentration ranging from 1000 to 63 μg/mL, while remaining compounds **3b-f** were studied at concentration 1000 μg/mL, against bacterial strain *S. aureus* and *E. coli*. According to the screening results, compounds **3a** and **3c** showed stronger activity at concentration of 1000 μg/mL against *E. coli*. The compound **3a** was found to be inactive against fungal strain *A. niger* and *C. albicans*. All the compounds **3a-f** were then tested at the same concen-tration 1000 μg/mL. All the series of compound showed good activities towards selected bacteria and found to be inactive for fungi under consideration as shown in Tables 2 and 3.

TABLE-3
ANTIBACTERIAL ACTIVITY OF **3a-f** AT 1000 μg/mL

Entry	Zone of inhibition (mm)	
	Gram-positive: *S. aureus*	Gram-negative: *E. coli*
3a	12	**17**
3b	13	15
3c	12	**16**
3d	11	15
3e	11	14
3f	12	14
Chloramphenicol	**18**	**16**

Conclusion

In conclusion, we have reported the synthesis of some new 4-thiazolidinone derivatives bearing benzofuran, quinoline and pyrazole moieties in good yield and characterized by elemental and spectral studies such as IR, ^{1}H NMR and mass spectra. Antimicrobial assay of these synthesized compounds showed better activities for bacteria but inactive against selected fungi.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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