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RESEARCH ARTICLE

Synthesis and Antimicrobial Screening of Some Novel 2-(2-Chloroquinolin-3-yl)-3-(1-phenylamine)-1,3-thiazolidin-4-ones

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Abstract: 2-Chloro-3-formylquinoline derivative (**1**) on treatment with phenyl hydrazine (**2**) yields Schiff's bases 2-(2-chloroquinolin-3-yl)methylene-2-phenyl hydrazine (**3a-e**). Compound **3a-e** on treatment with thioglycollic acid and catalytic quantity of $ZnCl_2$ in methanol yields the title compounds **4a-e**. The newly synthesized compounds **4a-e** have been screened for their antibacterial and antifungal activities and their chemical structures have been elucidated by IR, NMR spectral data. Some of them exhibited significant antifungal activity.

Keywords: 2-Chloro-3-formylquionline, Thioglycolic acid, 1,3-Thiazolidin-4-one

Introduction

The heterocyclic nitrogen compounds especially quinoline derivatives are very important because of their wide occurrence in natural products[1] and biological active compounds[2]. The quinoline ring is a part of antibacterial ciprofloxacin, naldixic acid and fluoroquinoline. Reduced 1,2,3,4-tetrahydro quinoline derivatives oxamniquine is used to eradicate blood flukes (Schistosoma mansoni). Quinaldic acid is carbolic acid, substituted quinoline at 2 position is a catabolite of tryptophan aromatic side chain amino acid. It is a fundamental structure of some antihypertensive agents such as prazosin and doxazosin which are peripheral vasodilator. Quinoline, 2-methyl quinoline, chloroquines are widely used antimalarial drugs, quinoline derivatives exhibited versatile pharmacological properties such as anti-inflammatory[3], antibacterial[4], antifungal[5], antiallergy[6], antidepressant[7], antiasthmatic[8], antimalerial[9], antiviral[10], antitumour[11], neuroleptic activity[12], antihypertensive[13], cytotoxic[14], hypnotic[15], sedative[15] and bronchodilator[16] activities.

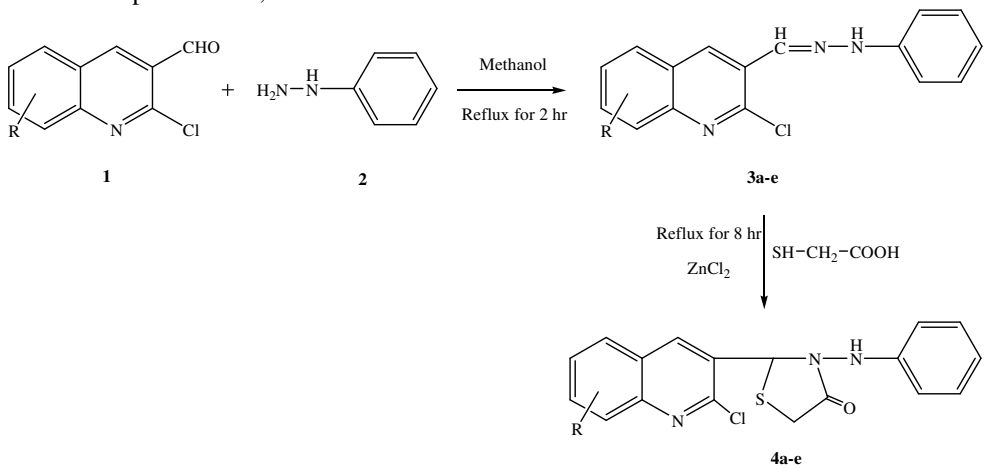
On the other hand 1,3-thiazolidin derivatives play a vital role in medicinal chemistry, particularly 2,3-diaryl-1,3-thiazolidin-4-ones bearing methyl group at C-5 position is anti-HIV agent[17] and with methylsulphonyl group acts as potent and selective COX-2 inhibitor[18]. 2,2'-dihetroaryl bisthiazolidinones and their disulphones are anti-inflammatory, analgesics and histamine H_1 and H_2-receptor antagonists[19]. In view of the potential biological activity

of quinoline derivatives and 1-3-thiazolidin-4-ones, it was thought worthwhile to prepare the title compounds with the hope that these ring systems may prove to be biologically active.

The general synthetic pathway discussed hereafter is depicted in Scheme 1. The starting compounds 2-chloro-3-formyl quinoline **(1)** was prepared by Vilsmeier Hack reaction according to literature method[20]. Compound **(1)** on treatment with phenyl hydrazine **(2)** in the presence of methanol as solvent yielded 1-(2-chloro-quinolin-3-yl)methylene-2-phenyl hydrazine **(3a-e)**. Compounds **(3a-e)** on reaction with Thioglycolic acid in the presence of catalytic quantity of freshly fused $ZnCl_2$ in methanol yielded the title compounds **(4a-e)**. The homogeneity of the compounds was checked by TLC (ethyl acetate: benzene). All the synthesized compounds were characterized by elemental analysis, IR, NMR, spectrometric techniques (Table 1). Thus produced compound was identified as 2-(2-chloroquinolin-3-yl)-3-(1-phenylamine)-1,3-Thiazolidin-4-ones in good yield.

Experimental

All melting points were determined in open capillary tubes and are uncorrected. The homogeneity of all the compounds was checked by TLC on silica gel coated plates. IR spectra were obtained in KBr on Perkin-Elmer FTIR spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on Varian NMR spectrometer operating at 300 MHz. Chemical shifts are expressed in δ, with reference to TMS.



Scheme 1

General procedure for the synthesis of 1-(2-chloro-quinolin-3-yl)methylene-2-phenyl hydrazine **(3a-e)**

A solution of substituted 2-chloro-3-formyl quinoline (0.01 mole) in methanol (20 mL) and phenyl hydrazine (0.02 mole) was refluxed for 2 h. The reaction mixture was cooled, the solid separated was filtered, washed with water and recrystalized from methanol to furnish **3a-e** (Scheme 1). Physical and analytical data of compounds are given in Table 1.

General procedure for the synthesis of 2-(2-chloroquinolin-3-yl)-3-(1-phenylamine) -1,3-Thiazolidin-4-ones **(4a-e)**

A mixture of Schiff's base **3a-e** (0.01 mole) in methanol (25 mL) and mercaptoacetic acid (0.02 mole) with a pinch of freshly fused $ZnCl_2$ was refluxed on water bath for eight hours.

The separated solid was filtered and recrystallized from methanol-chloroform mixture to give compounds **(4a-e)** Scheme 1. Physical and analytical data of compounds are given in Table 1. Other 1,3-thiazolidin-4-ones were synthesized using the similar procedure.

Table 1. Physical and analytical data of compounds **(4a-e)**

Compd. No.	M.F	m.p ^{0}C	Yield %	% Analysis Found (calcd)		
				C	H	N
3a	$C_{17}H_{14}N_3Cl$	185 With decomposition	90	69.03(68.93)	4.77(4.72)	14.21(14.15)
3b	$C_{17}H_{14}ON_3Cl$	196 With decomposition	91	65.49(65.40)	4.53(4.49)	13.48(13.42)
3c	$C_{17}H_{14}N_3Cl$	143-145	95	69.03(68.94)	4.77(4.71)	14.21(14.14)
3d	$C_{16}H_{12}N_3Cl$	176 With decomposition	95	68.21(68.15)	4.29(4.25)	14.91(14.87)
3e	$C_{17}H_{14}N_3Cl$	190 With decomposition	95	69.03(68.93)	4.77(4.72)	14.21(14.14)
4a	$C_{19}H_{16}ON_3SCl$	147-50	90	61.70(61.66)	4.36(4.30)	11.36(11.31)
4b	$C_{19}H_{16}O_2N_3SCl$	163-67	92	59.14(59.10)	4.18(4.15)	10.89(10.85)
4c	$C_{19}H_{16}ON_3SCl$	152-56	95	61.70(61.65)	4.36(4.31)	11.36(11.30)
4d	$C_{18}H_{14}ON_3SCl$	179-83	95	60.76(60.72)	3.97(3.93)	11.81(11.75)
4e	$C_{19}H_{16}ON_3SCl$	169-73	95	61.70(61.65)	4.36(4.30)	11.36(11.31)

Results and Discussion

The structures of the synthesized compounds **(3a-e)** were confirmed on the basis of spectral and elemental analysis. The IR spectrum of **3a-e** exhibited a band at 1630-1635 (C=N), 3270 cm^{-1} (N-H). Further, in their 1H NMR ($CDCl_3$) spectrum, the appearance of a singlet at δ 7.50 (CH=N) and at δ 8.00 indicates the presence of secondary amine (-NH-Ar). Similarly the structure of compounds **4a-e** were confirmed on the basis of spectral and elemental analysis. The IR spectrum of **4a-e** exhibited a band at 1710 cm^{-1} due to (-CO-cyclic), 2960 cm^{-1} (CH_2-S-Cyclic). Further in their ^{1}H NMR ($CDCl_3$) spectrum the appearance of singlet at δ 3.80 (N-CH), singlet at δ 4.14-4.16 due to CH_2S, confirms the presence of 1,3-thiazolidin ring.

The compounds **4a-e** were screened for their antibacterial activity against *E. coli, Salmonella typhi, Staphylococcus aureus, Bacillus subtilis* by using Penicillin as reference standard. DMSO was used as solvent control, nutrient agar was used as culture medium and method employed was Agar cup[21,22] method. The zone of inhibition were measured in mm and shown in Table 2. The antifungal activity was carried against *Aspergillus niger*, *Aspergillus flavus*, *Penicillium chrysogenum* and *Fusurium moneliforme* by using Greseofulvin as reference standard. The investigation of antibacterial screening results indicate that compounds **4a,b,c,d,e** shows no antibacterial activity against *E. coli*, *Salmonella typhi, Staphylococcus aureus, Bacillus subtilis.* Compounds **4a,b,c,d,e** shows low activity against *Staphylococcus aureus.* The investigations of antifungal data revealed that compounds **4a,b,c,d,e** shows no antifungal activity against *Aspergillus niger* whereas compounds **4a,c,d,e** shows inhibitory activity against *Penicillium chrysogenum.* Similarly compounds **4a,c,e** shows inhibitory effect against *Fusurium moneliforme.* Compound **4d** shows inhibitory effect towards *Aspergillus flavus*. Remaining compounds are inactive against all the fungus. Results are shown in Table 2 and 3.

Table 2. Antibacterial screening results of the compounds (**4a-e**).

Compd	*E. coli*	*Salmonella typhi*	*Staphylococcus aureus*	*Bacillus Subtilis*
4a	-ve	-ve	13 mm	-ve
4b	-ve	-ve	14 mm	-ve
4c	-ve	-ve	15 mm	-ve
4d	-ve	-ve	13 mm	-ve
4e	-ve	-ve	15 mm	-ve
DMSO	-ve	-ve	-ve	-ve
Penicillin	13 mm	18 mm	36 mm	18 mm
-ve no antibacterial activity				

Table 3. Antifungal screening results of the compounds (**4a-e**)

Compd	*Aspergillus niger*	*Penicillium chrysogenum*	*Fusarium moneliforme*	*Aspergillus flavus*
4a	+ve	-ve	-ve	+ve
4b	+ve	+ve	+ve	+ve
4c	+ve	-ve	-ve	+ve
4d	+ve	-ve	+ve	-ve
4e	+ve	-ve	-ve	+ve
+ve control	+ve	+ve	+ve	+ve
-ve control	-ve	-ve	-ve	-ve
+ve no antibacterial activity				
–ve no growth (Antifungal activity observed)				

Spectral analysis of compounds

1-(2-Chloro-6-methyl quinolin-3-yl)methylene-2-phenyl hydrazine **(3a)**

^{1}H NMR ($CDCl_3$): δ 2.4 (s, 3H, CH_3), 7.5 (s, 1H, CH=N), 8.00 (s, 1H, NH), 6.80-7.80 (m, 9H, Ar-H), IR (KBr pellets Cm^{-1}) 3275 (N-H Secondary amine), 3075 (C-H Aromatic), 2970 (C-H of CH_3), 1635 (C=N), 770 (C-Cl).

1-(2-Chloro-6-methoxy quinolin-3-yl)methylene-2-phenyl hydrazine **(3b)**

^{1}H NMR ($CDCl_3$): δ 3.6 (s, 3H, OCH_3), 7.4 (s, 1H, CH=N), 8.01 (s1H, NH), 6.88-7.88 (m, 9H, Ar-H), IR (KBr pellets Cm^{-1}) 3280 (N-H Secondary amine), 3085 (C-H Aromatic), 2960 (C-H of CH_3), 1630 (C=N), 1150 (OCH_3), 770 (C-Cl).

1-(2-Chloro-8-methyl quinolin-3-yl)methylene-2-phenyl hydrazine **(3c)**

^{1}H NMR ($CDCl_3$): δ 2.42 (s, 3H, CH_3), 7.44 (s, 1H, CH=N), 8.04 (s, 1H, NH), 6.85-7.88 (m, 9H, Ar-H), IR (KBr pellets Cm^{-1}) 3270 (N-H Secondary amine), 3075 (C-H Aromatic), 2970 (C-H of CH_3), 1635 (C=N), 775 (C-Cl).

1-(2-Chloro quinolin-3-yl)methylene-2-phenyl hydrazine **(3d)**

^{1}H NMR ($CDCl_3$): δ 7.40 (s, 1H, CH=N), 8.00 (s, 1H, NH), 6.70-7.90 (m, 10H, Ar-H), IR (KBr pellets Cm^{-1}) 3275 (N-H Secondary amine), 3075 (C-H Aromatic), 1630 (C=N), 775 (C-Cl).

1-(2-Chloro-7-methyl quinolin-3-yl)methylene-2-phenyl hydrazine **(3e)**

^{1}H NMR ($CDCl_3$): δ 2.44 (s, 3H, CH_3), 7.26 (s, 1H, CH=N), 8.04 (s, 1H, NH), 6.85-7.55 (m, 9H, Ar-H), IR (KBr pellets Cm^{-1}) 3275 (N-H Secondary amine), 3060 (C-H Aromatic), 2965 (C-H of CH_3), 1635 (C=N), 770 (C-Cl).

2-(2-Chloro-6-methyl quinolin-3-yl)-3-(1-phenylamine)-1,3-Thiazolidin-4-one **(4a)**

^{1}H NMR ($CDCl_3$): δ 2.48 (s, 3H, CH_3), 3.80 (s, 1H, N-CH), 4.16 (s, 2H, CH_2S), 6.85-7.88 (m, 9H, Ar-H), 8.06 (s, 1H, NH), IR (KBr pellets Cm^{-1}) 3275 (N-H Secondary amine), 3080 (C-H Aromatic), 2975 (C-H of CH_3), 2960 (CH_2-S-cyclic), 1710 (-CO-cyclic), 768 (C-Cl).

2-(2-Chloro-6-methoxy quinolin-3-yl)-3-(1-phenylamine)- 1,3-Thiazolidin-4-one **(4b)**

^{1}H NMR ($CDCl_3$): δ 3.81 (s, 1H, N-CH), 3.86 (s, 3H, OCH_3), 4.13 (s, 2H, CH_2S), 6.82-7.83 (m, 9H, Ar-H), 8.00 (s, 1H, NH), IR (KBr pellets Cm^{-1}) 3280 (N-H Secondary amine), 3075 (C-H Aromatic), 2970 (C-H of CH_3), 2960 (CH_2-S-cyclic), 1710 (-CO-cyclic), 1140 (OCH_3), 768 (C-Cl).

2-(2-Chloro-8-methyl quinolin-3-yl)-3-(1-phenylamine)- 1,3-Thiazolidin-4-one **(4c)**

^{1}H NMR ($CDCl_3$): δ 2.46 (s, 3H, CH_3), 3.80 (s, 1H, N-CH), 4.14 (s, 2H, CH_2S), 6.82-7.86 (m, 9H, Ar-H), 8.02 (s, 1H, NH), IR (KBr pellets Cm^{-1}) 3275 (N-H Secondary amine), 3080 (C-H Aromatic), 2970 (C-H of CH_3), 2965 (CH_2-S-cyclic), 1710 (-CO-cyclic), 770 (C-Cl).

2-(2-Chloro quinolin-3-yl)-3-(1-phenylamine)- 1,3-Thiazolidin-4-one **(4d)**

^{1}H NMR ($CDCl_3$): δ 3.81 (s, 1H, N-CH), 4.15 (s, 2H, CH_2S), 6.83-7.88 (m, 10H, Ar-H), 8.00 (s, 1H, NH), IR (KBr pellets Cm^{-1}) 3270 (N-H Secondary amine), 3070 (C-H Aromatic), 2975 (C-H of CH_3), 2970 (CH_2-S-cyclic), 1708 (-CO-cyclic), 775 (C-Cl).

2-(2-Chloro-7-methyl quinolin-3-yl)-3-(1-phenylamine)- 1,3-Thiazolidin-4-one **(4e)**

^{1}H NMR ($CDCl_3$): δ 2.47 (s, 3H, CH_3), 3.80 (s, 1H, N-CH), 4.15 (s, 2H, CH_2S), 6.83-7.86 (m, 9H, Ar-H), 8.00 (s, 1H, NH), IR (KBr pellets cm^{-1}) 3270 (N-H Secondary amine), 3080 (C-H Aromatic), 2970 (C-H of CH_3), 2960 (CH_2-S-cyclic), 1710 (-CO-cyclic), 770 (C-Cl).

Conclusion

In conclusion *2-(2-chloro quinolin-3-yl)-3-(1-phenylamine)-1,3-Thiazolidin-4-ones* were synthesized and their antimicrobial activity have been evaluated. Some of them exhibited significant antifungal activity. Both the moieties 2-chloro-3-formyl quinolin and 1,3-thiazolidin-4-ones have important applications in medicinal chemistry, the synthesized compound may act as good biological compounds.

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References

1. (a) Morimoto Y, Matsuda F and Shirahama H, *Synlett.,* 1991, **1991**, 202; (b) Balsubramaniam M and Keay J G, *Comprehensive Hetrocyclic Chemistry II*, 1996, **5**, 245; (c) Michael J P, *Nat Prod Rep.*, 1997, **14**, 605-608.
2. (a) Markees D G, Dewey V C and Kidder G W, *J Med Chem.*, 1970, **13(2)**, 324-326; (b) Camphell S F, Hardstone J D and Palmer M J, *J Med Chem*, 1988, **31**, 1031; (c) Maguire M P, Sheets K R, Mcvety K, Spanda A P and Zilberstein A J, *J Med Chem.,* 1994, **37(4)**, 2129-2137.
3. Gupta R, Gupta A K, Paul S and Kachrav P L, *Indian J Chem.*, 1998, **37B**, 1211.
4. Yen Long, Kuo Chang, Fang Jia Yuh Sheu, Shu Lin Hso and Cherng Chyi Tzeng, *J Med Chem*., 2001, **44(14),** 2374.

5. Musiol R, Jampilek J, Buchta V, Silva L, Niedbala H, Podeszura B, Palka A, Majerz-Maniecka K, Oleksyn B and Polanski, *Biorg Med Chem*., 2006, **14**, 3592.
6. Abdulqnder A, Alhaider M, Atet Abdelkader and Eric Lein K, *J Med Chem*., 1985, **28(10)**, 1394-1398.
7. Vetrivel Nadaraj, Senniappan Thamaraj Selvi and Raju Sasi, *Arkivoc*, 2006, **10**, 82-89.
8. Peter Madrid B, John Sherill, Ally Lion P, Jennifer Weisman L, Joseph Derisib L and Kiplin Guy R, *Bioorg Med Chem Lett*., 2005, **15(4)**, 1015-1018.
9. Pandey V K and Menal Tondan, *Indian J Chem*., 2001, **40B**, 527-529.
10. Font M, Monge A, Ruiz I and Heras B, *Drug Des Discovery*, 1997, **14**, 259.
11. Xia Y, Yang Z Y, Xia P, Bastow K F, Tachibana Y, Kuo S C, Hamel E, Hackl T and Lee K H, *J Med Chem*., 1998, **41**, 1155-1162.
12. Yuki Sowada, Hiroshi Kayakiri, Yoshito Abe and Hirokazu Tanaka, *J Med Chem*., 2004, **47,** 2853.
13. Andrea Cappelli, Gal Lapericot Mohr, Andrea Gallelli, Milena Rizzo and Gianluca Giorgi, Maurizio Anzini, Salvatore Vomero, Laura Mennuni, Flora Ferrari, Francesco Makovec, M. Cristina Menziani and Pier G. De Benedetti, *J Med Chem*., 2004, **47(10)**, 2574-2586.
14. Brain D Lee, Zhanjiang Li, Kevin J French, Yan Zhaung, Zuping Xia and Charles Smith D, *J Med Chem.*, 2004, **47(6)**, 1413-1422.
15. Singh O M V and Muthukrishnan M, *Indian J Chem*., 2001, **40B**, 262.
16. Guytan A C and Hall J E, Textbook of Medicinal Physiology 9th Edition (Singapore, P A, W B Sanders Company), 1998, 306.
17. Rao A, Carbone A, Chimirri A, De Clercq, Monforte P, Pietro, Pannecougue C and Zoppala M, *Farmaco*, 2002, **57(9)**, 747.
18. Afshin Zarghi, Leila Najafria, Bahram Daraee, Orkideh G, Dadrass and Mehdi Hedayati, *Bioorg Med Chem Lett*, 2007, **17(20)**, 5634-5637.
19. Previtera T, Vigorita M G, Basile M, Fenech G, Trovato A, Occhiuto F, Monforic M T and Barbera R, *Eur J Med Chem*., 1990, **25(7)**, 569.
20. Meth-Cohn O, Narine B and Tarnowski B, *J Chem Soc Perkin Trans 1*, 1981, 1520.
21. Seeley H W and Vandemark P J, Microbes in Action (WH Freeman and San Francisco Co. USA), 1972.
22. Cruickshankt R, A Practical of Medicinal Microbiology, (Churchill Livingstone, Edinburgh), 1975, 2.