

Synthesis, Characterization and Antimicrobial Activity of Some Newly Synthesized 1,3-Thiazolidin-4-one Derivatives

ARJUNSINGH K.RANA, SUNIL B. LADE, MAYUR J. JOSHI and NIRAV M. SHAH*

Department of Chemistry, Navjivan Science College, Dahod-389 151, Gujarat, India

*Oxygen Healthcare Limited, Ahmedabad, India

nirav.shah.m@gmail.com

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Abstract: A series of 10 new 1,3-thiazolidin-4-one (**3a-3j**) were synthesized from different schiff base of *N*-[(1*E*)-(3-chloro-5,7-dimethyl-2-naphthyl) methylene]aniline (**2a-2j**) with thioaceticacid. The chemical structures of these compounds were confirmed by means of ¹H NMR, IR and mass analysis. Newly synthesized compounds were screened *in vitro* for their antimicrobial activity against varieties of bacterial strains such *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and fungi strain *Aspergillus niger* at 40 µg/mL. The resulted of compounds shows that chloro and fluoro substituted 1,3-thiazolidine-4-one derivatives are showing quite well activity as compare to the other functional groups.

Keywords : 1,3-Thiazolidin-4-one, 2-Chloro-6, 8-dimethyl quinoline-3-carboxaldehyde, Schiff base, Antimicrobial evaluation

Introduction

The massive use of antibacterial drugs by mankind leads to a major problem *i.e.* drug resistance. The emergence of the drug resistance for major classes of antibacterial drugs is recognized by WHO and this became challenge for medicinal chemist to develop new class of antimicrobial agents. With increasing number of cases of pathogenic infection which suppress the immune system of human, medicinal chemist decided to move towards synthesis of small and novel molecule.

Quinoline nucleus has received remarkable attention in medicinal science. Quinoline has prominent structural feature in a variety of natural products as well as in other compounds of medicinal interest. Quinoline derivatives are reported to possess anticonvulsant, antitumor¹, hypnotics, sedative, antihypertensive, antimalarial², antibacterial³ and many other therapeutic activities. The 4-thiazolidinone ring system exhibit various biological activities, such as antimicrobial, anti-inflammatory, anti-HIV, anti-toxoplasma gondii and analgesic⁴⁻⁸.

From literature survey we have identified that 2-chloro-6,8-dimethyl quinoline-3-carbaldehyde and its derivatives are associated with many diverse therapeutic activity hence it is worthwhile to select as nucleus.

Experimental

The melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on Shimadzu FT-IR-8400 spectrophotometer using KBr disc and ^1H NMR spectra in DMSO- d_6 (Chemical shift in δ ppm) on Bruker spectrometer (400 MHz) using TMS as an internal standard. The results are in good agreement with the structure assigned. The purity of all compounds was checked by thin layer chromatography using TLC plates of silica gel (E.Merck G254) using Ethyl acetate: Hexane solvent system (7:3). Physical Constants synthesized of compounds (**3a-3j**) are recorded in Table 1.

Table 1. Physical constants 2-(3-chloro-5,7-dimethyl-2-naphthyl)-3-substituted phenyl-1,3-thiazolidin-4-one (**3a-3j**)

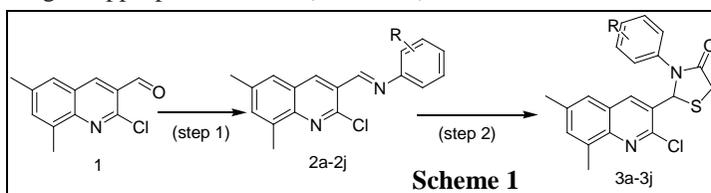
S No.	Compd.	R	Molecular Formula	Mol. Wt	Yield	M.P, $^{\circ}\text{C}$	R_f
1	3a	C_6H_5-	$\text{C}_{20}\text{H}_{17}\text{ClN}_2\text{OS}$	369	78%	167	0.54
2	3b	4-Br C_6H_4-	$\text{C}_{20}\text{H}_{16}\text{BrClN}_2\text{OS}$	448	68%	177	0.55
3	3c	4-Cl- C_6H_4-	$\text{C}_{20}\text{H}_{16}\text{Cl}_2\text{N}_2\text{OS}$	403	65%	182	0.57
4	3d	2,4-di Cl- C_6H_3	$\text{C}_{20}\text{H}_{15}\text{Cl}_3\text{N}_2\text{OS}$	437	74%	189	0.53
5	3e	4-F- C_6H_4-	$\text{C}_{20}\text{H}_{16}\text{ClFN}_2\text{OS}$	387	78%	190	0.68
6	3f	4- NO_2 - C_6H_4-	$\text{C}_{20}\text{H}_{16}\text{ClN}_3\text{O}_3\text{S}$	414	70%	175	0.74
7	3g	4- SCH_3 - C_6H_4-	$\text{C}_{21}\text{H}_{19}\text{ClN}_2\text{OS}_2$	415	62%	172	0.48
8	3h	4- OCH_3 - C_6H_4-	$\text{C}_{21}\text{H}_{19}\text{ClN}_2\text{O}_2\text{S}$	399	81%	182	0.32
9	3i	4- CH_3 - C_6H_4-	$\text{C}_{21}\text{H}_{19}\text{ClN}_2\text{OS}$	382	75%	197	0.36
10	3j	2,4-di CH_3 - C_6H_3-	$\text{C}_{22}\text{H}_{21}\text{ClN}_2\text{OS}$	397	70%	163	0.57

General procedure for synthesis of *N*-[(1*E*)-(3-chloro-5,7-dimethyl-2-naphthyl)methylene]aniline (**2a-2j**)

To a stirred solution of 2-chloro-6, 8-dimethyl quinoline-3-carboxaldehyde (0.01 mol) in ethanol, substituted aniline (0.01 mol) and catalytic amount of acetic acid (0.0005 mol) was added. The mixture was refluxed for 6 hours. The contents were cooled and the filtered the isolated product. Product was crystallized from appropriate solvent.

General procedure for synthesis 2-(3-chloro-5,7-dimethyl-2-naphthyl)-3-substituted phenyl-1,3-thiazolidin-4-one (**3a-3j**)

To a stirred solution of **2a-2j** (0.01 mol) in dioxan, thioglycolic acid ($\text{SH-CH}_2\text{-COOH}$) (0.01 mol) was added and refluxed the reaction mass for 12 h. The reaction mixture was cooled and triturated with 10% sodium bicarbonate solution. The neutral solution was poured onto crushed ice and filtered the precipitate of product. The product was dried and crystallized using an appropriate solvent (Scheme 1).



Step 1: $\text{R-C}_6\text{H}_4\text{-NH}_2$, cat. CH_3COOH , methanol, reflux, 18 h, Step 2: SHCH_2COOH , 1,4-dioxan, reflux, 18 h, R = different substitution

Antimicrobial activity

The antimicrobial activity was assayed by using the disc diffusion method. Newly synthesized compounds were screened *in vitro* for their antimicrobial activity against four bacterial strains, *i.e.* two gram +ve bacteria *Staphylococcus epidermidis* and *Staphylococcus aureus* and two gram -ve bacteria *Escherichia coli* and *Pseudomonas aeruginosa* and fungi strain *Aspergillus niger*. Standard drug Cephalexin and Greseofulvin were used for the comparison purpose. The obtained results for compounds **3a-3j** are recorded Table 2.

Table 2. Antimicrobial screening results of 1-acetyl-4-[5-(3-chloro-4-fluorophenyl)-2-furyl]-3-substituted phenyl-4,5-dihydro-1*H*-pyrazoles (**3a-3j**)

Compd No.	R	Zone of inhibition, in mm				
		Antibacterial activity				Antifungal Activity, %
		<i>S. aureus</i>	<i>S. epidermiss</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>A. niger</i>
3a	C ₆ H ₅ -	72	41	32	71	60
3b	4-Br C ₆ H ₄ -	54	69	89	84	72
3c	4-Cl-C ₆ H ₄ -	77	37	81	77	78
3d	2,4-di Cl-C ₆ H ₃ -	80	85	72	82	83
3e	4-F-C ₆ H ₄ -	58	78	63	86	63
3f	4-CH ₃ -C ₆ H ₄ -	71	59	74	68	67
3g	4-NO ₂ -C ₆ H ₄ -	70	71	89	72	70
3h	4-SCH ₃ -C ₆ H ₄ -	69	47	61	66	63
3i	4-OCH ₃ -C ₆ H ₄ -	50	54	79	61	68
3j	4-CH ₃ -C ₆ H ₄ -	81	68	50	39	64
Cephalexin	-	100	100	100	100	-
Greseofulvin	-	-	-	-	-	100

Spectroscopic data

2-(2-Chloro-6,8-dimethylquinolin-3-yl)-3-phenyl-1,3-thiazolidin-4-one(**3a**)

¹H NMR (DMSO-d₆) δppm : 2.42(3H,s,Ar-CH₃), 2.44(3H, s, Ar-CH₃), 3.90(1H,d, -CHa), 4.10(1H,d, -CHb), 6.70(1H,s,-CH), 7.11 (1H,s, Ar-H), 7.20-7.70 (5H, m, Ar-H), 7.8 (1H,s,Ar-H), 7.9(1H,d, Ar-H) ; IR (ν cm⁻¹ KBr) 1733(C=O, thiazolidinone), 1608(C=N Str.), 1518 (C=C Str),781(C-S-C), 750 (C-Cl).

3-(4-Bromophenyl)-2-(2-chloro-6,8-dimethylquinolin-3-yl)-1,3-thiazolidin-4-one(**3b**)

¹H NMR (DMSO-d₆) δppm : 2.44(3H,s,Ar-CH₃), 2.46(3H, s, Ar-CH₃), 3.92(1H,d, -CHa), 4.11(1H,d, -CHb), 6.68(1H,s,-CH), 7.15 (1H,s, Ar-H), 7.42(2H,d, Ar-H), 7.46(2H,d,Ar-H), 7.82(1H,s,Ar-H), 7.90(1H,d, Ar-H); IR (ν cm⁻¹ KBr) 1733(C=O, thiazolidinone), 1608(C=N Str.), 1518 (C=C Str),781(C-S-C), 750 (C-Cl), 749(C-Br).

2-(2-Chloro-6,8-dimethylquinolin-3-yl)-3-(4-chlorophenyl)-1,3-thiazolidin-4-one (**3c**)

¹H NMR (DMSO-d₆) δppm : 2.41(3H,s,Ar-CH₃), 2.43(3H, s, Ar-CH₃), 3.94(1H,d, -CHa), 4.13(1H,d, -CHb), 6.65(1H,s,-CH), 7.13(1H,s, Ar-H), 7.16(2H,d, Ar-H), 7.62(2H,d,Ar-H), 7.84(1H,s,Ar-H), 7.90(1H,d, Ar-H); IR (ν cm⁻¹ KBr) 1733(C=O, thiazolidinone), 1608(C=N Str.), 1518 (C=C Str),781(C-S-C), 750 (C-Cl).

2-(2-Chloro-6,8-dimethylquinolin-3-yl)-3-(2,4-dichlorophenyl)-1,3-thiazolidin-4-one (3d)

¹H NMR (DMSO-d₆) δppm : 2.42(3H,s,Ar-CH₃), 2.44(3H, s, Ar-CH₃), 3.82(1H,d, -CHa), 3.90(1H,d, -CHb), 6.90(1H,s,-CH), 7.20-8.30(6H, m, Ar-H); IR (ν cm⁻¹ KBr) 1733(C=O, thiazolidinone), 1608(C=N Str.), 1518 (C=C Str),781(C-S-C), 750 (C-Cl).

2-(2-Chloro-6,8-dimethylquinolin-3-yl)-3-(4-fluorophenyl)-1,3-thiazolidin-4-one (3e)

¹H NMR (DMSO-d₆) δppm : 2.44(3H,s,Ar-CH₃), 2.47(3H, s, Ar-CH₃), 3.86(1H,d, -CHa), 3.88(1H,d, -CHb), 6.80(1H,s,-CH), 7.11 (1H,s, Ar-H), 7.12(2H,d, Ar-H), 7.88(2H,d,Ar-H), 7.80(1H,s,Ar-H), 7.90(1H,d, Ar-H); IR (ν cm⁻¹ KBr) 1733(C=O, thiazolidinone), 1608(C=N Str.), 1518 (C=C Str),781(C-S-C), 750 (C-Cl), 680(C-F).

2-(2-Chloro-6,8-dimethylquinolin-3-yl)-3-(4-nitrophenyl)-1,3-thiazolidin-4-one (3f)

¹H NMR (DMSO-d₆) δppm : 2.42(3H,s,Ar-CH₃), 2.44(3H, s, Ar-CH₃), 3.85(1H,d, -CHa), 3.90(1H,d, -CHb), 6.82(1H,s,-CH), 7.11(1H,s, Ar-H), 7.66(2H,d, Ar-H), 8.22(2H,d,Ar-H), 7.76(1H,d, Ar-H), 7.80(1H,s,Ar-H); IR (ν cm⁻¹ KBr) 1733(C=O, thiazolidinone), 1608(C=N Str.), 1518 (C=C Str),1105(-NO₂), 781(C-S-C), 750 (C-Cl).

2-(2-Chloro-6,8-dimethylquinolin-3-yl)-3-[4-(methylsulfanyl)phenyl]-1,3-thiazolidin-4-one (3g)

¹H NMR (DMSO-d₆)δppm : 2.42(3H,s,Ar-CH₃), 2.44(3H, s, Ar-CH₃), 2.46(3H,s -SCH₃), 3.82(1H,d, -CHa), 3.88(1H,d, -CHb), 6.82(1H,s,-CH), 7.12(1H,m, Ar-H), 7.38(2H,d, Ar-H), 7.42(2H,d,Ar-H), 7.80(1H,s, Ar-H), 7.88(1H,d,Ar-H); IR (ν cm⁻¹ KBr) 1733(C=O, thiazolidinone), 1608(C=N Str.), 1518 (C=C Str),781(C-S-C), 750 (C-Cl), 700(C-S).

2-(2-Chloro-6,8-dimethylquinolin-3-yl)-3-(4-methoxyphenyl)-1,3-thiazolidin-4-one (3h)

¹H NMR (DMSO-d₆) δppm : 2.42(3H,s,Ar-CH₃), 2.44(3H, s, Ar-CH₃), 3.80(3H,s -OCH₃), 3.84(1H,d, -CHa), 3.90(1H,d, -CHb), 6.66(1H,s,-CH), 7.12(1H,m, Ar-H), 6.80(2H,d, Ar-H), 7.50(2H,d,Ar-H), 7.80(1H,s, Ar-H), 7.95(1H,d,Ar-H); IR (ν cm⁻¹ KBr) 1733(C=O, thiazolidinone), 1608(C=N Str.), 1518 (C=C Str),1200(C-O), 781(C-S-C), 750 (C-Cl).

2-(2-Chloro-6,8-dimethylquinolin-3-yl)-3-phenyl-1,3-thiazolidin-4-one (3i)

¹H NMR (DMSO-d₆) δppm : 2.38(3H,s,Ar-CH₃), 2.46(3H, s, Ar-CH₃), 2.48(3H,s, Ar-CH₃), 3.84(1H,d, -CHa), 3.87(1H,d, -CHb), 6.70(1H,s,-CH), 7.12 (1H,m, Ar-H), 7.28(2H,d, Ar-H), 7.56(2H,d,Ar-H), 7.80(1H,s,Ar-H), 7.90(1H,d, Ar-H); IR (ν cm⁻¹ KBr) 1733(C=O, thiazolidinone), 1608(C=N Str.), 1518 (C=C Str),781(C-S-C), 750 (C-Cl).

2-(2-Chloro-6,8-dimethylquinolin-3-yl)-3-(2,4-dimethylphenyl)-1,3-thiazolidin-4-one (3j)

¹H NMR (DMSO-d₆) δppm : 1.92(3H,s,Ar-CH₃), 2.28(3H,s,Ar-CH₃), 2.40(3H, s, Ar-CH₃), 2.44(3H,s, Ar-CH₃), 3.86(1H,d, -CHa), 3.90(1H,d, -CHb), 6.66(1H,s,-CH), 6.88(1H,m,Ar-H), 6.98(1H,m,Ar-H), 7.12 (1H,m, Ar-H), 7.42(1H,m,Ar-H), 7.76(1H,s,Ar-H), 7.83(1H,d, Ar-H); IR (ν cm⁻¹ KBr) 1733(C=O, thiazolidinone), 1608(C=N Str.), 1518 (C=C Str),781(C-S-C), 750 (C-Cl).

Results and Discussion

1,3-Thiazolidine-4-on compounds (**3a-3j**) have been synthesized by the reaction of *N*-[(1E)-(3-chloro-5,7-dimethyl-2-naphthyl) methylene]aniline (**2a-2j**) with thio acetic acid with 60 to

80% of good yield. The structure of **3a-3j** compounds is confirmed by IR, ¹HNMR and mass spectral data analysis. From the results of antimicrobial data, compounds **3c**, **3d** and **3g** were showing excellent active against selected gram positive and negative bacterial strains as compare to standard drug cephalexin, while **3a**, **3b**, **3e** and **3f** were moderately active against selected bacterial strains as compare to standard drug. While **3c**, **3d** and **3g** were also shown excellent activity against fungi strain *A.niger* as compare to standard drug griseofulvin. From the structure activity relationship table, we find that phenyl ring substituted with chloro (**3c**) and fluoro (**3g**) at shown an excellent result compare to standard drug cephalexin at a scale of 40 ug/mL.

Conclusion

From the antimicrobial results, it worthwhile to say that, newly synthesized 1,3-thiazolidine-4-one derivatives are showing moderate to good activity against bacterial and fungi strains. From the structure activity relationship table and the results we found that, phenyl rings substituted with chloro and fluoro 2,3 and 4 position will show good activity as compare to other functional groups. From the obtained data for the newly synthesized pyrazoline derivatives we conclude on that with presence of halogen substitution in pyrazoline derivative will show excellent antimicrobial activity. And will give us path to synthesize more number of compounds with variations of halogen substitution on different ring, which may hope to give a better antimicrobial compound in the true sense.

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