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An efficient synthesis of 1, 2, 4-triazine derivatives and their in vitro antimicrobial activity

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Abstract

A simple and efficient synthesis of 1, 2, 4- triazine derivatives is described by the condensation of substituted 4-(2-chloro-quinoline-3yl methylene)-2-[phenyl-4H-oxazol-5-one and phenyl hydrazine an equimolar sodium acetate and acetic acid as a solvent. The newly synthesized compounds were evaluated for their antimicrobial activity.

Keywords: Substituted 4-(2-chloro-quinoline-3yl methylene)-2-[phenyl-4H-oxazol-5-one, phenyl hydrazine, Triazine derivatives, antimicrobial activity.

INTRODUCTION

Triazine derivatives have occupied a unique position in medicinal chemistry. Triazine derivatives have attracted considerable pharmaceutical interest due to their antitumor [1-5], anticonvulsant6 and antileukemic [7, 8] activities and cytotoxic effects [9]

Triazine has been used to form many types of functional groups other than amines and heterocycles and used as protecting groups in natural product synthesis. Thus, they are reactive groups, which are adaptable to different synthetic transformations.

Among the compound having good antimicrobial properties, s-triazine derivatives constitute an important class of compounds possessing diverse pharmacological activities including broadly active triazine compounds. The synthetic strategy of the compounds is outlined in the scheme-1. Synthesis of some new substituted of 1, 2, 4- triazine derivatives was carried out by the condensation of Substituted 4-(2-chloro-quinoline-3yl methylene)-2-[phenyl-4H-oxazol-5-one and phenyl hydrazine in glacial acetic acid as a solvent. (Table-1).

MATERIAL AND METHOD

Melting points were uncorrected and determined in an open capillary tube. IR spectra were recorded on FTIR Shimadzu spectrometer. ^{1}H NMR spectra were recorded in DMSO-d_6 on Avance 300 MHz spectrometer using TMS as an internal standard. The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

General procedure for the synthesis of* 1, 2, 4-triazine derivatives *3(a-j)

Substituted 4-(2-chloro-quinoline-3yl methylene)-2-[phenyl-4H-oxazol-5-one **1** (1 mMol) was taken in 100 ml RBF and 1.08 gm of phenyl hydrazine **2** was also added to 10-15 ml of glacial acetic acid and 0.2 gm of sodium acetate and mixture is refluxed for about 5 hrs.finally The resultant solid was filtered, washed with ice cold water (50 ml) followed by cool ethanol (10 ml) to give the corresponding product.

Spectroscopic data of selected compounds

***5-((2-Chloro-6-methylquinoline-3-yl)methylene)-2,3diphenyl-1,2-dihydro-1,2,4-triazine-6(5H)-one.(3a)*:**

IR (KBr): 3049, 3325,1716,1653 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.3 (s, 3H, -CH_3), δ 8.78 (d, 1H, Ar-H), δ 8.68 (d, 1H, Ar-H), δ 6.95-8.35 (m, 14H, Ar-H), δ 7.0 (s, 1H, -NH) ppm; EIMS (*m/z*): 442 (M^+); Anal. Calcd. For $C_{26}H_{19}ON_4Cl$: C, 71.15, H, 4.36; N, 12.77%. Found: C, 71.00; H, 4.30; N, 12.65%

***5-((6-Bromo-2-Chloroquinoline-3-yl)methylene)-2,3diphenyl-1,2-dihydro-1,2,4-triazine-6(5H)-one.(3b)*:**

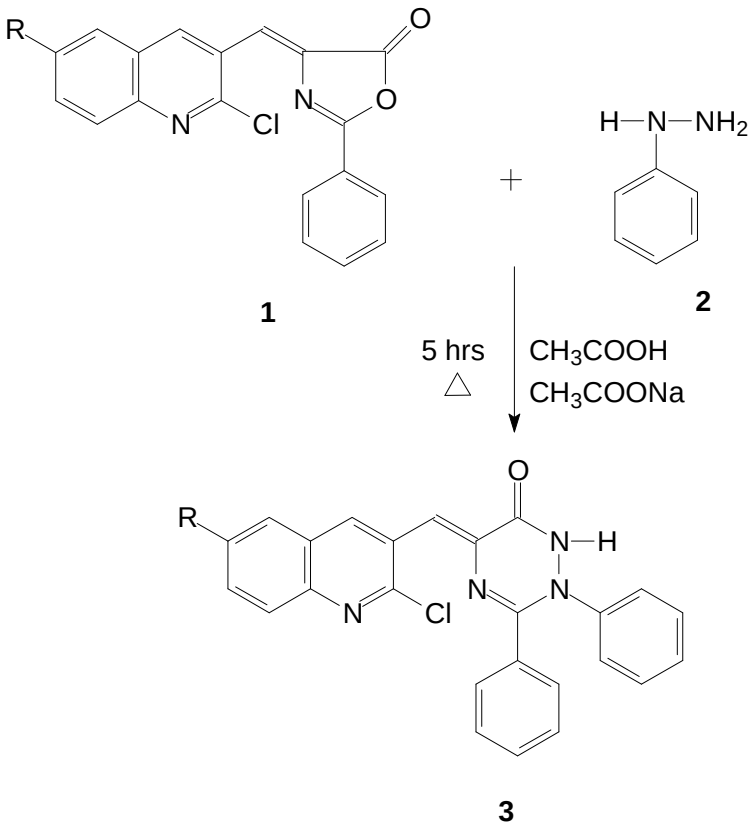
:IR (KBr): 3045, 3322,1710,1645 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.78 (d, 1H, Ar-H), δ 6.95-8.35 (m, 14H, Ar-H), δ 7.0 (s, 1H, -NH) ppm; EIMS (*m/z*): 504 (M^+); Anal. Calcd. For $C_{25}H_{16}ON_4BrCl$: C, 59.60, H, 5.20; N, 11.12%. Found: C, 59.30; H, 5.10; N, 10.90%

***5-((2-Chloro-6-methoxyquinoline-3-yl)methylene)-2,3diphenyl-1,2-dihydro-1,2,4-triazine-6(5H)-one.(3c)*:**

:IR (KBr): 3040, 3335,1726,1640 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.01 (s, 3H, -OCH_3)δ 8.78 (d, 1H, Ar-H), δ 6.95-8.35 (m, 14H, Ar-H), δ 7.0 (s, 1H, -NH) ppm; EIMS (*m/z*): 455 (M^+); Anal. Calcd. For $C_{26}H_{19}O_2N_4Cl$: C, 68.6, H, 4.21; N, 12.32%. Found: C, 67.95; H, 4.10; N, 12.10%

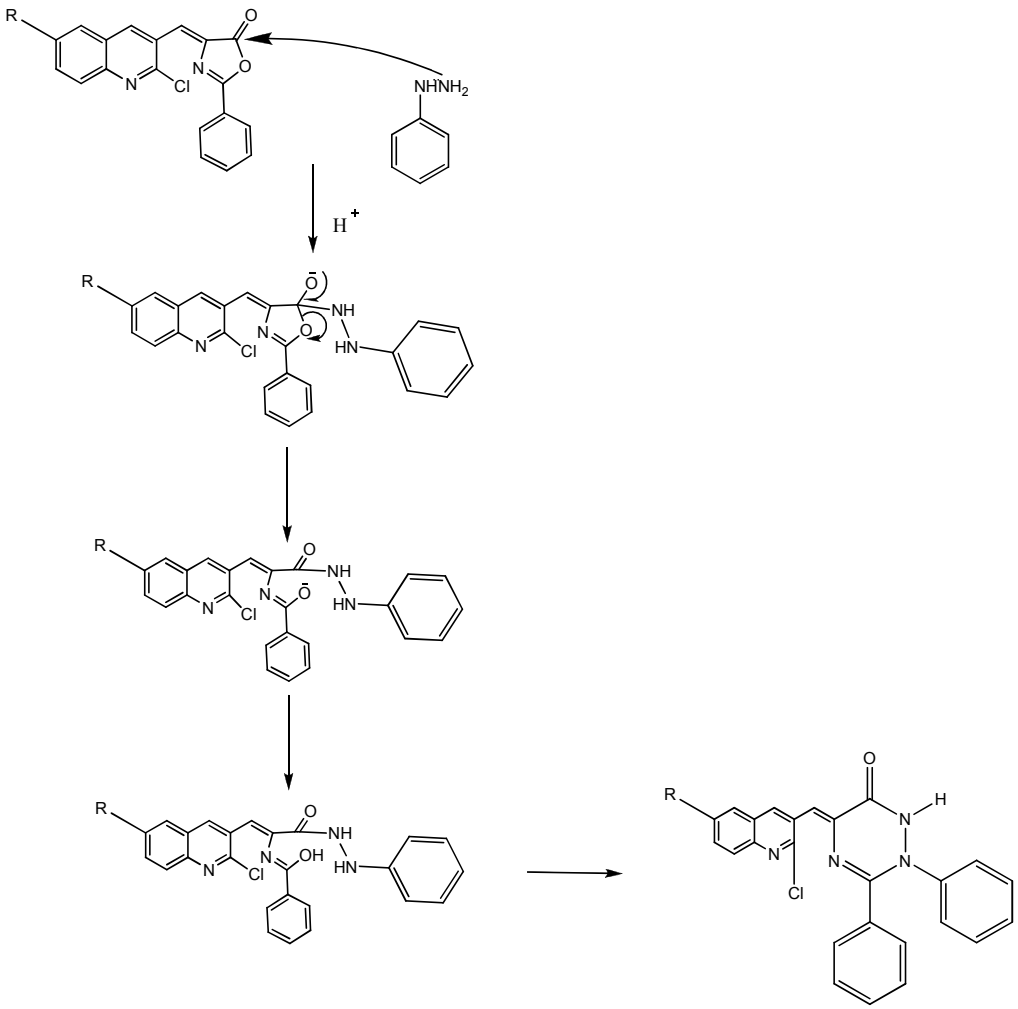
RESULTS AND DISCUSSION

As part of our research programme, and in continuation of our work on the development of environmentally friendly methodologies for the preparation of biologically active compounds [10-13], herein we report an efficient synthesis of substituted 1, 2, 4-triazine derivatives. The condensation of substituted 4-(2-chloro-quinoline-3yl methylene)-2-[phenyl-4H-oxazol-5-one **1**, phenyl hydrazine **2**, sodium acetate using glacial acetic acid as reaction solvent to afford the corresponding product **3(a-j)** (Scheme-1) in good yield. The newly synthesized compounds were evaluated for their antibacterial and antifungal activity.



Scheme-1: Synthesis of substituted 1, 2, 4-triazene derivatives 3(a-j)

The formation of the products was proceeding through the attack of phenyl hydrazine **2** on the carbonyl carbon of substituted 4-(2-chloro-quinoline-3yl methylene)-2-[phenyl-4H-oxazol-5-one.**1** The formation of substituted 1, 2, 4-triazene derivatives involved the condensation of 1:1 molar ratio of substituted **1** and **2** .However, The newly synthesized compounds confirmed by the spectral analysis and were evaluated for their antibacterial and antifungal activity.



Mechanism of formation of substituted 1, 2, 4-triazine derivatives 3(a-j).

Table-1: Physical data substituted 1, 2, 4-triazine derivatives 3(a-j)

Entry	Product	R	Yield (%)	M.P. (°C)
1	3a	CH_3	83	205
2	3b	Br	85	195
3	3c	OCH_3	79	185
4	3d	Cl	82	210
5	3e	NO_2	70	205
6	3f	H	84	155
7	3g	I	86	166
8	3h	F	80	163

The antimicrobial activities of the synthesized compounds **3(a-j)** were determined by agar well diffusion method [14]. The compounds were evaluated for antibacterial activity against

Escherichia coli, *Salmonella typhi*, *Staphylococcus aureus* and *Bacillus subtilis*. The antifungal activity was evaluated against *Aspergillus niger*, *Aspergillus flavus*, and *Penicillium chrysogenum* were procured from Institute of Microbial technology (IMTech), Chandigarh, India. The antibiotic penicillin (25µg/mL) and nystatin (25µg/mL) was used as reference drug for antibacterial and antifungal activity, respectively. Dimethyl sulphoxide (1%, DMSO) was used a control with out compound.

The results of antimicrobial data are summarized in Table-2. In comparison with standard antibacterial penicillin, compounds **3b**, **3f**, found to be active against *E. coli*. Compounds **3c**, **3f**, were also found to be active against *S. aureus*. Compounds, **3b**, **3c**, **3g** showed good activity comparatively active against *B. subtillis*. As compared with standard antibacterial compounds **3a**, **3d**, **3e**, **3f**, **3g**, **3h** were observed as active against S. typhi. On the other hand, compound **3a**, **3c**, **3f**, **3g**, **3h** were found to be reduced growth activity against *A. niger*. Compounds **3d**, **3f** and **3h** were observed no fungal growth against *A. flavus*. Compounds **3a**, **3c**, **3e**, **3g**, **3h** found to be reduced growth activity aginst *P. chrysogenum*.

Table-2: The antimicrobial data of the synthesized substituted 1,2,4- triazine derivatives 3(a-j)

Product	Bacteria (Zone of inhibition in mm)				Fungi (Growth)		
	Ec	St	Sa	Bs	An	Af	Pc
3a	08	12	--	11	RD	+ve	RD
3b	11	10	09	10	+ve	RD	-ve
3c	10	08	13	10	RD	+ve	RD
3d	06	10	12	08	+ve	-ve	+ve
3e	11	13	10	10	+ve	RD	RD
3f	13	12	13	09	RD	-ve	-ve
3g	10	14	07	12	RD	RD	RD
3h	08	10	12	06	RD	-ve	RD
Penicillin	16	15	18	14	NA	NA	NA
Nystatin	NA	NA	NA	NA	-ve	-ve	-ve

Ec-*Escherichia coli*; St-*Salmonella typhi*; Sa-*Staphylococcus aureus*; Bs-*Bacillis subtilis*; An-*Aspergillus niger*; An-*Aspergillus flavus*; Pc-*Penicillium chrysogenum*; -ve-No growth; +ve-Growth of fungi; RD-Reduced growth; NA-Not Appilcable

CONCLUSION

In summary, we have described a simple method for the synthesis of 2-[4-(substituted –phenyl)-thiazol-2-yl]-5-(2-susbtituted quinolin-3-yl-methelene) 3-phenyl-2,5-dihydro-1H-[1,2,4]-triazine-6-one. The newly synthesized compounds were confirmed by the spectral analysis and further evaluated for their antimicrobial activity. The antibacterial and antifungal activity revealed that most of the compounds showed moderate to good activity. The substitution of presence of halo groups in positions emerged as active in both antibacterial and antifungal screening

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