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An efficient synthesis and in vitro antimicrobial activity of 1, 2, 4-Triazin-6-(5H)-one derivatives

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Abstract

A simple and efficient synthesis of 1, 2, 4- triazine derivatives is described by the condensation of 4-(2-susbtituted benzylidine)-2-phenyloxazol-5(4H)-one with 4-(4-Chlorophenyl)2-Hydrazinylthiazol in presence of sodium acetate in acetic acid. The newly synthesized compounds were evaluated for their antimicrobial activity. The structure of these compounds has been established on the basis of spectral data.

Keywords: 4-(2-susbtituted benzylidine)-2-phenyloxazol-5(4H)-one, 4-(4-Chlorophenyl)2-Hydrazinylthiazol, 1, 2, 4- triazine, antimicrobial activity.

INTRODUCTION

Substituted Triazine derivatives have occupied a unique position in medicinal chemistry. Triazine derivatives have attracted considerable pharmaceutical interest due to their antiproliferative activity1 antiviral agent 2-3 antihypertensive agent4 antitumor and *in vitro* supporting their anti-HIV activity5-6 anticonvulsant 7 and antileukemic8. Hydroxytriazine derivatives have been extensively used as analytical reagents 9-10. The solid supported synthesis of functionalized 1,2,4-triazin-6-ones from resin bound amino acids and acid chlorides was described11, So in the present paper we wish to report the synthesis of a new series of triazine starting from substituted oxazolone **1** were prepared by the cyclocondensation of benzoyl glycine (Hippuric acid) with substituted aldehyde in presence of sodium acetate in acetic anhydride 12. These oxazolone were transformed into triazine derivative by using the 4-(4-Chlorophenyl)2-Hydrazinylthiazol in presence of sodium acetate in acetic acid (Scheme 1). The structure elucidation of the new triazine derivatives were done by spectroscopic methods.

Materials and Methods:

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 4-(2-susbtituted benzylidine)-2-phenyloxazol-5(4H)-one derivatives 1(a-h)

Appropriate aldehyde (0.01 mole, hippuric acid (0.01 mole) ,sodium Acetate (1 gm) in acetic anhydride (10 mL) was heated to melting hot plate and then reflux for 2 hour it was cooled to room temp 10 ml of ethanol was added and kept the mixture over night solid separate and filtered ,washed with water dried recrystallized from appropriate solvent.

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

4-(2-susbtituted benzylidine)-2-phenyloxazol-5(4H)-one **1** (1 mMol) and (1 mMol) of 4-(4-Chlorophenyl)2-Hydrazinylthiazol **2** and 0.2 gm of sodium acetate in acetic acid 20 ml and mixture was refluxed for about 5 hrs.finally The resultant solid was filtered, washed with ice cold water (50 ml) recrystallized from proper solvent to give the corresponding product.

Spectroscopic data of selected compounds

5-(5-Chloro-2-Hydroxybezylidene)-2-(4-(4-Chlorophenyl) thiazol-2-yl)-3-phenyl--1, 2 dihydro- 1, 2, 4-triazin-6(*5H*)-one. *(3a)*:

IR (KBr): 3049, 3325, 1716, 1653 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.95-8.35 (m, 14H, Ar-H+ 5-H of thiazole + =CH-), δ 8.5 (s, 1H, -NH), δ 10.85 (s, 1H, -OH), δ ppm; EIMS (*m/z*): 506 (M^+); Anal. Calcd. For $C_{25}H_{16}O_2N_4Cl_2S$: C, 59.18, H, 3.18; N, 11.04%. Found: C, 59.00; H, 3.10; N, 11.10%

5-(5-Chloro-2-Hydroxy-3-Iodobezylidene)-2-(4-(4-Chlorophenyl) thiazol-2-yl)- 3- phenyl- 1, 2 dihydro- 1, 2, 4-triazin-6(*5H*)-one *(3b)*:

IR (KBr): 3045, 3322, 1710, 1645 cm^{-1}; ^{1}H NMR (DMSO-d_6 300 MHz): δ 6.85-8.15 (m, 13H, Ar-H+ 5-H of thiazole + =CH-), δ 8.33 (s, 1H, -NH), δ 10.88 (s, 1H, -OH), δ ppm; EIMS (*m/z*): 632 (M^+); Anal. Calcd. For $C_{25}H_{15}O_2N_4Cl_2IS$: C, 47.41, H, 2.39; N, 8.85 %. Found: C, 47.35; H, 2.29; N, 8.75%

5-(3, 5-dichloro-2-Hydroxybezylidene) - 2-(4-(4-Chlorophenyl) thiazol-2-yl)- 3- phenyl- 1, 2 dihydro- 1, 2, 4-triazin-6(*5H*)-one *(3c)*:

IR (KBr): 3040, 3335, 1726, 1640 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.82-8.18 (m, 13H, Ar-H+ 5-H of thiazole + =CH-), δ 8.25 (s, 1H, -NH), δ 10.82 (s, 1H, -OH), δ ppm; EIMS (*m/z*): 540(M^+); Anal. Calcd. For $C_{25}H_{15}O_2N_4Cl_3S$: C, 55.42, H, 2.79; N, 10.34 %. Found: C, 55.32; H, 2.69; N, 10.25%

5-(5-chloro-2-Hydroxy-4-methylbezylidene)- 2-(4-(4-Chlorophenyl) thiazol-2-yl)- 3- phenyl-1, 2 dihydro- 1, 2, 4-triazin-6(*5H*)-one *(3d)*:

IR (KBr): 3040, 3325, 1716,1630 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.5 (s, 3H, -CH_3) δ 6.75-8.25 (m, 13H, Ar-H+ 5-H of thiazole + =CH-), δ 8.35 (s, 1H, -NH), δ 10.74 (s, 1H, -OH), δ

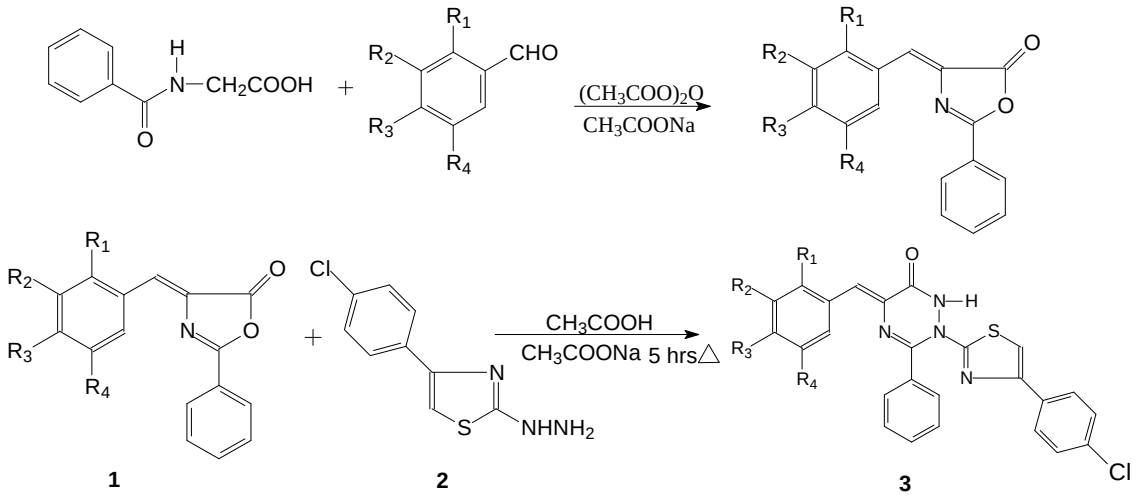
ppm; EIMS (*m/z*): 520 (M^+); Anal. Calcd. For $C_{26}H_{18}O_2N_4Cl_2S$: C, 59.89, H, 3.48 N, 10.75%. Found: C, 59.74; H, 3.40; N, 10.70%

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 13-19, herein we report an efficient synthesis of substituted 1, 2, 4- triazine derivatives. The condensation of 4-(2-susbtituted benzylidine)-2-phenyloxazol-5(4H)-one **1**, 4-(4-Chlorophenyl)2-Hydrazinylthiazol **2**, sodium acetate using glacial acetic acid as reaction solvent to afford the corresponding product **3(a-h)** (Scheme-1) in good yield. The newly synthesized compounds were evaluated for their antibacterial and antifungal activity.

The formation of the products was proceeding through the attack of 4-(4-Chlorophenyl)2-Hydrazinylthiazol **2** on the carbonyl carbon of 4-(2-susbtituted benzylidine)-2-phenyloxazol-5(4H)-one **1** The formation of substituted 1, 2, 4- triazine 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.

The antimicrobial activities of the synthesized compounds **3(a-h)** were determined by agar well diffusion method 20. 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.



1 **2** **3**

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

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

Entry	Product	R_1	R_2	R_3	R_4	Yield (%)	M.P. (°C)
1	3a	OH	H	H	Cl	85	210
2	3b	OH	I	H	Cl	87	190
3	3c	OH	Br	H	Cl	75	185
4	3d	OH	Cl	H	Cl	80	205
5	3e	OH	H	CH_3	Cl	72	175
6	3f	OH	I	CH_3	Cl	84	145
7	3g	OH	Br	CH_3	Cl	80	168
8	3h	OH	H	CH_3	H	77	143

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

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

The results of antimicrobial data are summarized in Table-2. In comparison with standard antibacterial penicillin, compounds **3a**, **3b**, **3c**, **3d**, **3h** and **3i** were found to be reduced growth activity against *A. niger*. Compounds **3c**, **3e, 3f** and **3h** were observed no fungal growth against *A. flavus*. Compounds **3a**, **3c**, **3e**, **3g**, **3h** and **3i** found to be reduced growth activity aginst *P. chrysogenum*.

On the other hand **3a**, **3c**, and **3g** found to be active against *E. coli*. Compounds **3d**, **3e**, and **3f**were also found to be active against *S. aureus*. Compounds **3a**, **3b**, **3c**, **3g** and **3i** showed good activity comparatively active against *B. subtillis*. As compared with standard antibacterial compounds **3a**, **3d**, **3e**, **3f**, **3g**, **3h** and **3i** were observed as active against S. typhi.

CONCLUSION

In summary, we have described a simple method for the 1, 2, 4- triazine derivative. 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 hydroxyl group and presence of halo groups emerged as active in both antibacterial and antifungal screening.

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