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Original Research Article

Design and one-pot synthesis of hybrid thiazolidinone based triazines derivatives as potent antimicrobial agents against human disease-causing pathogens

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Abstract

An proficient and broad one-pot reaction to a new series of hybrid thiazolidine-4-one-1,3,5-triazine derivatives was developed. The tranquil work-up of the products, quick reaction, and mild conditions are notable features of this protocol. These molecules were found to exhibit potent activity against a panel of Gram-positive and Gram-negative micro-organisms. All synthesized compounds were characterized by IR, ^{1}H NMR, mass and elemental analysis.
Key Words: Synthesis, Thiazolidinone, Antimicrobial, Characterization, Triazine.

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INTRODUCTION

Treatment of infections caused by bacterial and fungal pathogenic organisms always creates problems to human health. These organisms develop resistance against chemotherapy. Hence the drugs which are more active today become inactive after long use. In order to overcome this problem, it is necessary to replace old drugs by new ones. At the same time, many of the drugs are highly effective but associated with several toxic effects. In order to reduce the rapid multidrug-resistance in pathogenic microbes, we urgent require to find out and manufacture new drugs that acts through a new mechanism of action.[1] Recently, several heterocyclic compounds from the sequence of triazine and thiazolidin-4-one have been synthesized and their pharmacological activity has accordingly been investigated. It has been accomplished that, triazine ring frame hold a extensive spectrum of biological and pharmaceutical activities. [7-9] It has played a fundamental role in unique drug innovation for modulating physical and biological properties of the molecule due to wide diversity of biological applications.[10] The triazine core has known and huge concentration linking chemists through victorious resource of pharmacological activities such as antibacterial,[11-12] antimalarial,[13] antifungal,[14] anticancer,[15] antimychobacterial[16] and antiviral.[17] In continuation of our research work, in order to find the broad spectrum biologically active triazines frame work of new heterocyclic bioactive agents. A series of thiazolidin-4-one fused triazines was synthesized by applying an efficient coupling using as a base in dry ethanol solvent. Here, we report the synthesis and biological activity of 3-(4, 6-dichloro-1, 3, 5-triazin-2-yl)-2-phenylthiazolidin-4-one as antimicrobial agents. In the structure activity relationship (SAR) studies, the biological activity of these molecules was compared with standard reference.

MATERIAL AND METHODS

The solvents and chemicals used for the synthesis purchased from commercial sources were of analytical grade. 2,4,6-Trichloro-1,3,5-triazine, substituted aromatic aldehyde, ethyl 2-mercaptoacetate was purchased from

Sigma Aldrich, Merck and Fluka Chemicals Pvt. Ltd., Mumbai, India. Melting points were determined in open capillaries tubes and are uncorrected.

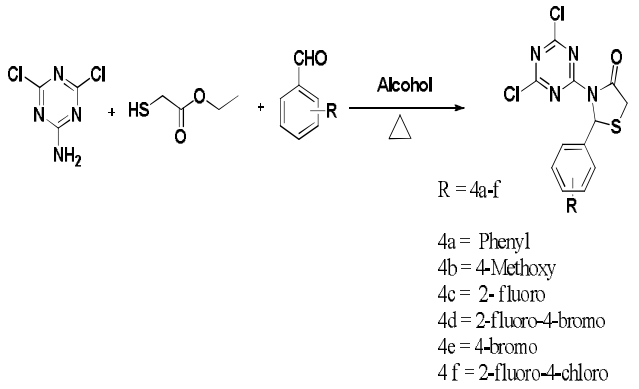

Figure 1: Synthesis of triazine thiazolidin-4-one derivatives

General method for the preparation of 3-(4, 6-dichloro-1, 3, 5-triazin-2-yl)-2-phenyl thiazolidin-4-one (4a): A mixture of substituted aromatic aldehydes (0.01 mol), 2-amino 4, 6-dichloro-1,3,5-triazine (0.01 mol) and ethyl 2-mercaptoacetate (0.01 mol) was refluxed for 1-2 hrs in dry ethanol (80 ml). The progress of reaction was monitored by TLC [Toluene: Acetone (4:6)]. The excess alcohol was evaporated in vacuo. The resulting crude product was triturated with saturated $NaHCO_3$ solution until CO_2 evolution ceased. The solid was washed with water, dried and recrystallized from ethanol to afford final respective compounds (4a-f).

Similarly remaining compound **4b-f** were prepared

Characterization data for compounds (4a-c) are given as follows.

Synthesis of 3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-phenylthiazolidin-4-one (4a):

Nature : Pale yellow solid; Yield: 80% ; M.P. 137-139 °C; IR (KBr cm^{-1}) : ν = 2841 (C-H str. in aromatic ring), 1722 (C=O of thiazolidinone), 1661 (-C=C- str. in aromatic ring), 815(C-N- str. in s-triazine) cm^{-1}; ^1H NMR (400 MHz, chloroform-d_6) δ ppm : 7.41- 6.85 (m, 5H), 5.33 (s, 1H), 3.41 (d, *J = 7.1 Hz*, 2H) ; MS (70 eV) *m/z* : 325.90 [M^+, 100%], Anal. Calcd for $C_{12}H_8Cl_2N_4OS$: C, 44.04; H, 2.40; N, 17.12: S, 9.80; Found: C, 43.97 H, 2.34; N, 16.98: S, 9.60 %.

Synthesis of 3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-(4-methoxyphenyl)thiazolidin-4-one (4b): Nature : Pale yellow solid, Yield:82% ; M. p. 140-142 °C; IR (KBr cm^{-1}) : ν = 2838 (C-H str. in aromatic ring), 1720 (C=O of thiazolidinone), 1655 (-C=C- str. in aromatic ring), 813(C-N- str. in s-triazine) cm^{-1}; ^1H NMR (400 MHz, chloroform-d_6) δ ppm : 7.41(m, 2H), 6.89(m, 2H), 5.34 (d, 1H), 3.82 (s, 3H), 3.43 (d, *J = 7.2 Hz*, 2H) ; MS (70 eV) *m/z* : 355.98[M^+, 100%], Anal. Calcd for $C_{13}H_{10}Cl_2N_4O_2S$: C, 43.71; H, 2.82; N, 15.68: S, 8.98; Found: C, 43.30; H, 2.45; N, 15.48: S, 8.40 %.

Synthesis of 3-(4, 6-dichloro-1,3,5-triazin-2-yl)-2-(2-fluorophenyl)thiazolidin-4-one (4c): Nature : Pale yellow solid; Yield:78 % ; M.P.145-147 °C; IR (KBr cm^{-1}) : ν = 2836 (C-H str. in aromatic ring), 1715 (C=O of thiazolidinone), 1629 (-C=C- str. in aromatic ring), 809 (C-N- str. in s-triazine) cm^{-1}; ^1H NMR (400 MHz, chloroform-d_6) δ ppm: 7.58 (td, *J =7.5,1.9 Hz*, 1H), 7.32 (td, *J = 6.6, 5.8, 3.7 Hz*, 1H), 7.18 (td, *J = 7.6, 1.2 Hz*, 1H), 7.06 (ddd, *J = 9.5, 8.3. 1.2 Hz,*, 1H, Ar-H), 5.94 (d, *J = 7.4 Hz*, 1H), 4.25 - 4.10 (m, 2H),; MS (70 eV) *m/z* : 343.90 [M^+, 100%], Anal. Calcd for $C_{12}H_7$ F Cl_2N_4OS : C, 41.75; H, 2.04; N, 16.23: S, 9.29; Found: C, 41.55; H, 2.00; N, 16.10: S, 9.10 %.

Biological Evolution: ***Antibacterial assay*****:** Newly synthesized compounds were screened for their antibacterial activity against selected Gram-positive organism's viz. *Staphylococcus aureus* (MTCC 96), *Bacillus subtilis* (MTCC 441) and Gram-negative organism's viz. *Escherichia coli* (MTCC 443), *Salmonella typhimurium* (MTCC 98) bacterial strains by ager well diffusion method with little modification.[18]

Antifungal assay **:** Newly synthesized compounds were screened for their antifungal activity against *Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 281), *Fusarium solani* (MTCC 350) and *Aspergillus flavus* (MTCC 277) by agar well diffusion method with little modification.[20]

Table 1: Antibacterial activity of compounds (4a-f) (MIC [a] values µg/mL):

Comp. (4a-f)	Gram-positive		Gram-negative	
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Salmonella typhimurium*
4a	55	70	50	65
4b	15	15	10	20
4c	70	65	70	55
4d	70	00	75	70
4e	55	60	70	70
4f	00	70	75	00
Ciprofloxacin (Ref.)	20	25	20	20

Table 2: Antifungal activity of compounds (4a-f) (MIC [a] values µg/mL)

Comp. (4a-f)	Candida albicans	Aspergillus niger	Fusarium – solani	Aspergillus flavus
4a	70	65	60	70
4b	15	15	10	20
4c	00	70	65	70
4d	70	65	70	75
4e	65	75	70	70
4f	70	70	75	75
Miconazole(Ref.)	20	25	25	15

RESULTS AND DISCUSSION

All newly synthesized compounds (4a-f) were subjected to anti-microbial activity against various gram-positive, gram-negative bacteria and fungal strains by using an agar well diffusion method.[2] The antimicrobial activity of these compounds to further assist for SAR study. The final compounds were screened against a panel of human disease-causing pathogens consisting of four gram-positive and four gram-negative strains as well as antifungal strain. From antimicrobial activity data shown in Table 1 and 2 it is revealed that some analogues of this series have more potency than the standard drug Ciprofloxacin and Miconazole while some of them have comparable potency. Interestingly none of the compound with high anti-inflammatory activity found to be potent antibacterial or antifungal agents. Thus, the compounds 4b have higher potency against the tested antimicrobial strain. It is cleared from our results that the 4th position of substituent on terminal benzene ring is the favorable site for high antimicrobial activity. The high potency of these compounds may be attributed to the presence of non halogenated electron donating group (EDG) or electron donating group (EDG) type group's placement at 4-positions. Any activity has not been observed in case of remaining compounds up to concentration of 200 µg/mL against same bacterial and fungal strains. It is cleared from results i.e. Table 1 and 2, the SAR of antibacterial activity partially correlates with their SAR of antifungal activity as there is some divergence is observed. The same aryl 4th position as observed already is favorable site of high activity. The compounds 4b have been found to be 2 fold more potent than the standard drug Micanazole as similar to the antibacterial activity trend. While the compounds (4a, 4c, 4d, 4e, 4f) have no major effect on the antifungal activity also.

CONCLUSIONS

We successfully synthesized series of triazine thiazolidin-4-one derivatives (4a-f) by condensation cyclisation reaction between substituted aromatic aldehyde, 4, 6-dichloro-1,3,5-triazin-2-amine and ethyl 2-mercaptoacetate using dry ethanol. The good yield (65-70 %) were obtained when reaction were performed in dry ethanol at reflux temperature for short duration of time (less than 2 hr). Reaction leading to longer time often resulted in degradation of products with low yield. The synthesized compounds were exploited for antimicrobial activity.

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CONFLICT OF INTEREST

No potential conflict of interest was reported by authors.

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