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SYNTHESIS, CHARACTERIZATION AND ANTI MICROBIAL EVALUATION OF NOVEL 2, 2^{I}, 2^{II}- [1, 3, 5-TRIAZINE-2, 4, 5 TRIYLBIS (SULPHANYL)] TRIS (PHENYL ETHAN-1-ONE)

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ABSTRACT

The wide spectrum of biological activity of triazine moiety has attracted attention in the field of medicinal chemistry. From Extended literature avowed the indisputable antimicrobial properties of triazines that stimulated us to the current exploration for the synthesis of novel 2,2^{I},2^{II}-[1,3,5-triazine-2,4,5triylbis(sulphanyl)]tris(phenyl ethan-1-one) derivatives. Nucleophilic substitution of chlorine atoms in cyanuric chloride (1) with benzyl mercapten 1(a)yield 6-(benzylsulfanyl)-1,3,5-triazine-2,4-dithiol (2) upon treatment with, potassium thioacetate, yielded dithiol(3)upon subsequent treatment with derivatives of phenacyl bromide yielded our targeted compounds 4(i-iii) and 5(ia-iiic,iia-iic,iiia-iiic).Novel 2,2^{I},2^{II}-[1,3,5-triazine-2,4,5triylbis(sulphanyl)]tris(phenyl ethan-1-one) derivatives 5(ia-iiic,iia-iic,iiia-iiic)were synthesized in adequate yields and characterization of the molecules was done by detailed spectral analysis using advanced analytical support. The titled compounds were screened for antibacterial and antifungal activities. Results proclaimed that all the synthesized compounds were exhibiting antimicrobial properties. Compounds and were contended to bear potent antimicrobial properties against the given bacterial andfungal strains. Synthesized 2,2^{I},2^{II}-[1,3,5-triazi ne2,4,5triylbis(sulphanyl)]tris(phenyl ethan-1-one) derivatives displayed noticeable antimicrobial potential and further studies are need to develop these molecules as a lead compounds for antimicrobial activity.

INTRODUCTION

Triazines are six-membered aromatic heterocycles with three carbon and three nitrogen atoms. The 1,3,5-triazines are the oldest and most well-known of the isomeric forms. Triazine is very stable in the heat unless it is heated above 600°C, at which point it breaks down into hydrogen cyanide. The triazine ring is not very easy to change with an electrophile. With nucleophiles, it is effortless to break the ring.

It is also susceptible to hydrolysis by water and other hydroxyl compounds to a lesser extent. Many different heterocycles can be made from 1,3,5-triazine by treating it with bifunctional amines or other compounds, and it can be used instead of HCN in some reactions. According to a general rule, which changes depending on the nucleophile, the first substitution occurs between 0 and 5°C; the second occurs between 35 and 42°C, and the third occurs between 70 and 100°C [4-8].

This means that three different nucleophiles can be added to the same triazine core, giving many possible triazine derivatives and applications. There has been a rise in multi-drug resistant pathogens, which makes treating bacterial infections more difficult.

Antiprotozoals, anticancer, oestrogen receptor modulators, antimalarials, Cyclin-dependent kinase inhibitors (CDK) inhibitors (14), and antivirals are just a few of the many things that triazine derivatives have been used for in the past. It has been said that s-triazine derivatives have potent antimicrobial properties [16–20].We report on the synthesis and antibacterial properties of several triazine derivatives as part of our work.

STEP1:

General procedure for the Synthesis of 2-(benzylsulfanyl)-4, 6-dichloro-1, 3, 5-triazine (2):

In a 50 ml glass RB flask,to a stirred solution of Cyanuric chloride (1.04 g, 5.64 mmol), (1) in THF (50 mL) was added diisopropyl ethylamine (DIPEA)(1.06 ml) at 0^oC. Benzyl mercaptan,(1a) was added at 0^oC then allowed to warm to room temperature and continued to stir for 16h. Workup: The reaction mixture was concentrated in vacuo to give crude mixture. Purification by silica gel column using 0-3% ethyl acetate/hexane provided the desired compound (2.3g) (2) as colourless syrup. Reaction progress was checked by TLC plates using 10 %ethyl acetate in hexane (9:1) as the mobile phase.

STEP2:

General procedure for the synthesis of 6-(benzylsulfanyl)-1, 3, 5-triazine-2, 4-dithiol (3)

In a 50 ml glass RB flask,to a stirred solution of 2-(benzylthio)-4,6-dichloro-1,3,5-triazine (2) in Ethanol(EtOH) was added Potassium thioacetate(2a) and stirred for 30 minutes. Then NaOH (305 mg, 7.6 mmol) dissolved in 2 ml of water was added and continued for stirring for 16h. Work up: The reaction mixture was concentrated to remove ethanol. The crude mixture was extracted with diethyl ether to remove nonpolar impurities. The aqueous layer was neutralized using 1N HCl and extracted with ethyl acetate to give desired thiol (100 mg)(3), which was used further without purification.

STEP3:

General procedure for the Synthesis of step 4 (i-iii):2-{[4-(benzylsulfanyl)-6-sulfanyl-1,3,5-triazin-2-yl]sulfanyl}-1-(4-methylphenyl) ethan-1-one(4i) 2-{[4-(benzylsulfanyl)-6-sulfanyl-1,3,5-triazin-2-yl]sulfanyl}-1-(4-bromophenyl)ethan-1-one (4ii) 2-{[4-(benzylsulfanyl)-6-sulfanyl-1, 3, 5-triazin-2-yl]sulfanyl}-1-(chlorophenyl)ethan-1-one(4iii) In a 50 ml glass RB flask,to a solution of 6-(benzylthio)-1,3,5-triazine-2,4-dithiol (3) in acetonitrile(5 mL)was added K2CO3(103 mg) followed by 2-bromo-1-tolyl-ethanone(0.003moles)(3a),Phenacyl Bromide (74 mg,0.003moles)(3b) and 4-Chloro phenacyl bromide(0.003moles)(3c) at 0oC. The reaction was allowed to stir for 3h at room temperature to produce the desired products as respectively as 4(i-iii)

TLC indicated only polar spot.

STEP4:

General procedure for Synthesis of step 5 (ia-ic) :

2-{4-[(4-methyl phenyl)1-oxo-methyl}- 6-{(benzylsulfanyl)}-1,3,5-triazin-2-yl]sulfanyl}-1-(4-methylphenyl)ethan-1-one (5ia)

2-{4-[(4-bromo phenyl)1-oxo-methyl}- 6-{(benzylsulfanyl)}-1,3,5-triazin-2-yl]sulfanyl}-1-(4-methylphenyl)ethan-1-one (5ib)

2-{4-[(4-chloro phenyl)1-oxo-methyl}- 6-{(benzylsulfanyl)}-1,3,5-triazin-2-yl]sulfanyl}-1-(4-methylphenyl)ethan-1-one (5ic)

To the stirred solution of2-{[4-(benzylsulfanyl)-6-sulfanyl-1,3,5-triazin-2-yl]sulfanyl}-1-(4-methylphenyl)ethan-1-one(4i) , acetonitrile(5 mL)was added K2CO3(103 mg) followed by 2-bromo-1-tolyl-ethanone(0.003moles)(4a), Phenacyl Bromide (74 mg,0.003moles)(4b) and 4-Chloro phenacyl bromide(0.003moles)(3c) at 0oC (4c) at 0oC. The reaction was allowed to stirr for 8h at room temperature to produce desired compounds respectively 5(ia-ic)

Work up: The reaction was diluted with water and extracted with ethyl acetate (2x), the combined organic layer was dried over Na2SO4 and concentrated in vacuo to give crude compound. Purification by Silicagel

column using 0-10% ethylacetate/hexane provided the polar spot

STEP 5 (IIA-IIC): 2-{4-[(4-methyl phenyl)1-oxo-methyl}- 6-{(benzylsulfanyl)}-1,3,5-triazin-2-yl]sulfanyl}-1-(4-bromophenyl)ethan-1-one (5iia)

2-{4-[(4-bromo phenyl)1-oxo-methyl}- 6-{(benzylsulfanyl)}-1,3,5-triazin-2-yl]sulfanyl}-1-(4-bromophenyl)ethan-1-one (5iib)

2-{4-[(4-chloro phenyl)1-oxo-methyl}- 6-{(benzylsulfanyl)}-1,3,5-triazin-2-yl]sulfanyl}-1-(4-bromophenyl)ethan-1-one (5iic)

To the stirred solution of 2-{[4-(benzylsulfanyl)-6-sulfanyl-1,3,5-triazin-2-yl]sulfanyl}-1-(4-bromophenyl)ethan-1-one(4ii) acetonitrile(5 mL)was added K2CO3(103 mg) followed by 2-bromo-1-tolyl-ethanone(0.003moles)(4a), Phenacyl Bromide (74 mg,0.003moles)(4b) and 4-Chloro phenacyl bromide(0.003moles)(4c) at 0oC. The reaction was allowed to stirr for 8h at room temperature to produce desired compounds respectively 5(iia-iic).Then the reaction was stirred for overnight. Then, 2-Bromo-1(p-tolyl)ethenone (79 mg,0.003 moles) was added to the above mixture and continued for 8h. Purification by Silicagel column using 0-10% ethylacetate/hexane provided the polar spot.

GENERAL PROCEDURE FOR SYNTHESIS OF STEP 5 (IIIA-IIIC):

2-{4-[(4-methyl phenyl)1-oxo-methyl}- 6-{(benzylsulfanyl)}-1,3,5-triazin-2-yl]sulfanyl}-1-(4-chlorophenyl)ethan-1-one (5iiia)

2-{4-[(4-bromo phenyl)1-oxo-methyl}- 6-{(benzylsulfanyl)}-1,3,5-triazin-2-yl]sulfanyl}-1-(4-chlorophenyl)ethan-1-one (5iiib)

2-{4-[(4-chloro phenyl)1-oxo-methyl}- 6-{(benzylsulfanyl)}-1,3,5-triazin-2-yl]sulfanyl}-1-(4-chlorophenyl)ethan-1-one (5iiic)

To the stirred solution of 2-{[4-(benzylsulfanyl)-6-sulfanyl-1,3,5-triazin-2-yl]sulfanyl}-1-(chlorophenyl)ethan-1-one (4iii) acetonitrile(5 mL)was added K2CO3(103 mg) followed by 2-bromo-1-tolyl-ethanone(0.003moles)(4a), Phenacyl Bromide (74 mg,0.003moles)(4b) and 4-Chloro phenacyl bromide(0.003moles) (4c) at 0oC. The reaction was allowed to stirr for 8h at room temperature to produce desired compounds respectively 5(iiia-iiic) Work up: The reaction was diluted with water and extracted with ethyl acetate(2x), the combined organic layer was dried over Na2SO4 and concentrated in vacuo to give crude compound. Purification by Silicagel column using 0-10% ethylacetate/hexane provided the polar spot

IN VITRO ANTIBACTERIAL ACTIVITY:

Was evaluated using disc-diffusion method against gram positive bacteria(Bacillussubtilis,Bacilluspumilus,Bacilluscereus,andStaphylococcusaureus)and gram-negative bacteria (Escherichiacoli, Pseudomonas aeurogonsa, Proteusvulgaris and Serratia marceseans). Ampicillin(100µg/ml)in DMSO was used as reference antibiotics. Nutrient agar medium was taken in the pre-sterilized petri-dishes and the microorganisms were grown by inoculating 0.5ml of spore suspension(108spores/ml)culture broth. A stock solution for all the prepared compounds 5(ia-iiic,iia-iic,iiia-iiic) was made by using DMSO. The disc (6 mm in diameter) was stuffed with 200 µg/ml, 100 µg/ml and 50 µg/ml of each test solution, placed on the seeded Nutrient agar medium and the petri-dishes were incubated at 37˚Cfor24hr.DMF alone was used as control at the equal preceding concentration. Zone of inhibition of each compound was recorded in mm. The experiment was done in triplicates.

***In vitro* anti fungal activity:** Nystatin (10µg/ml) in DMSO were used as reference antibiotics .Potato dextrose agar medium was taken in the pre-sterilized petri-dishes and the microorganisms were grown by inoculating the standard suspension of culture broth. A stock solution for all the prepared compounds 5(ia-iiic,iia-iic,iiia-iiic) was made by using DMSO. The disc (6 mm in diameter) was stuffed with 200 µg/ml 100µg/ml and 50µg/ml of each test solution, placed on the seeded potato dextrose agar medium and the

petri-dishes were incubated at 28˚C for 48 hr. DMF alone was used as control at the equal preceding concentration. Zone of inhibition of each compound was recorded in mm. The experiment was done in triplicates.

RESULTS AND DISCUSSIONS

Spectral data

2-{4-[(4-bromo phenyl)1-oxo-methyl}- 6-{(benzylsulfanyl)}-1,3,5-triazin-2-yl]sulfanyl}-1-(4-chlorophenyl)ethan-1-one (5iiib)

IR spectrum of Compound: Off white crystals, IR (KBr): νmax in cm-1: 3020 Aromatic (C-H) Stretch, 853.89 Aromatic (C-H) Bending, 1607, 1699, 1747 aryl (C=C) , 1607 (C=N) Triazine, 1747 aryl (C=O), 1483 methyl (C=O), 1483(C-H) bending –CH2-C=O, 696(C-Br) 1HNMR spectrum of the compound (in CDCl3) has exhibited characteristic proton signals δ (in ppm) at: 7.48 (d, J = 8.3, Ar-H),7.25(s, Ar-H), 3.84 (t, -CH3), 1.6(t, CH2). ($[M+H]^+$):FOR 530.74,found 531.74

In vitro antibacterial activity:

All the synthesized 5(ia-iiic,iia-iic,iiia-iiic)derivatives were screened for antibacterial activity against both gram positive(Table2) and gram negative(Table3) bacterial strains. When compared to the reference antibiotic Neomycin sulphate (10µg/ml) bydisc-diffusion method,5(iiia-iiic)showed considerable antibacterial activity than 5(ia-ic) and5(iia-iic) series against both gram positive and gram-negative bacteria strains. It is also observed $2,2^{I},2^{II}$-[1,3,5-triazine-2,4,5triylbis (sulphanyl)] tris (phenyl ethan-1-one) derivatives sensitive against Staphylococcus aureus. **5iiib** is the most potent antibacterial among all the derivatives and showed maximum growth inhibition with 30mm of zone of inhibition against Staphylococcus aureus followed by **5iiia**,and **5iiic**.

In vitro antifungal activity

Antifungal profile for the prepared compounds was also developed against selected fungal strains (**Table4**).Interestingly, compounds 5**(iiia-iiic)**showed significant antifungal activity also than 5**(ia-ic) and** 5**(iia-iic)**series against all fungal strains. It is also observed that *Candida albicans* is more sensitive to the prepared compounds than other strains. **5iic**is the most potent antifungal among all the derivatives and showed maximum growth inhibition with 22 mm of zone of inhibition against *Candida albicans* followed by **5iiia,5iiib,and5iiic**.

Table2. Zone of inhibition of the compounds against gram positive bacteria

Compound	Gram positive bacteria											
	Bacillus subtilis			Bacillus pumilus			Bacillus cereus			Staphylococcus aureus		
	50µ g/ml	100µ g/ml	200µ g/ml	50µ g/ml	100µ g/ml	200µ g/ml	50µ g/ml	100µ g/ml	200µ g/ml	50µ g/ml	100µ g/ml	200µ g/ml
5ia	10	16	19	7	10	14	12	16	18	13	17	19
5ib	11	15	18	6	9	12	10	14	17	14	18	20
5ic	11	15	19	9	12	15	8	13	15	15	18	21
5iia	14	17	20	9	16	17	9	14	16	13	18	21
5iib	9	13	16	6	8	11	9	13	16	10	17	20
5iic	14	21	26	11	18	22	14	18	24	15	24	27
5iiia	16	25	27	12	17	21	16	20	23	16	26	29
5iiib	15	25	26	14	20	23	12	18	21	18	28	30
5iiic	12	21	24	11	17	21	13	23	25	17	25	28
DMSO	3			2			2			2		
Neomycnsulphate 10µg/ml	32			34			32			37		

Table3. Zone of inhibition (mm) of the compounds against gramnegative bacteria

Compound	Gramnegativebacteria											
	Escherechiacoli			Pseudomonas aeurogonsa			Proteusvulgaris			Serratiamarcesea ns		
	50µg/ml	100µg/ml	200µg/ml	50µg/ml	100µg/ml	200µg/ml	50µg/ml	100µg/ml	200µg/ml	50µg/ml	100µg/ml	200µg/ml
5ia	12	19	23	4	6	10	7	11	14	9	13	16
5ib	14	22	24	5	9	11	9	12	15	8	11	15
5ic	12	18	21	5	8	10	10	16	18	6	12	14
5iia	11	20	23	4	6	9	8	14	17	7	11	14
5iib	11	19	22	5	8	12	11	15	18	9	12	15
5iic	15	24	28	9	15	18	12	19	21	10	21	23
5iiia	13	25	27	10	18	21	13	21	24	14	22	25
5iiib	13	23	25	9	15	18	11	17	21	12	21	24
5iiic	15	16	29	8	14	19	9	18	22	11	22	24
DMSO	3			2			2			3		
Neomycinsulphate10µg/ml	38			25			29			31		

CONCLUSION

We have reported that synthesis of a novel series novel series of 2,2^{I},2^{II}-[1,3,5-triazine-2,4,5triylbis (sulphanyl)]tris(phenyl ethan-1-one) derivatives 5(ia-ic,iia-iic,iiia-iiic) were synthesized using commercially available starting materials and economically feasible methods.The structure elucidation was done with the help of their physical,analytical,and spectraldata.All the 9compounds were screened for Invitro antimicrobial activity was carried out using both gram positive, gram negative bacterial and fungal strains (Table 2-4) using disc diffusion methods. The average zone of inhibition was measured and compared with the standard drugs, showing significant antimicrobial activities. These new data of the compounds 5iiib and 5iic might be helpful in the future development of triazine based (sulphanyl)]tris(phenyl ethan-1-one) derivatives as novel antimicrobial agents.

Conflict of Interest

Authors disclose no conflict to interest

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