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RESEARCH ARTICLE

SYNTHESIS AND BIOACTIVITY OF 3-(1-ALKYL-4-ARYL-6-THIOXO-1, 6-DIHYDRO-1, 3, 5- TRIAZIN- 2- YL)-AMINO-2-ARYL-3, 4-DIHYDRO-4-OXO-2 *H*- 1, 3-BENZOTHIAZINES

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ABSTRACT

A series of novel 1,3,5-triazinyl benzothiazine derivatives have been prepared by condensation of N-[1-alkyl]4-aryl-6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl]-N'-arylidenhydrazine with 2-mercaptobenzoic acid. The structure of the new compounds has been established by elemental, spectral and m.p. studies. All the compounds have been subjected to antibacterial and antifungal screening. In the series, compounds with chloro- inhibit the growth of *S. aureus* at MIC of 1.22 µg/mL whereas in the antifungal testing compounds **6d, 6i,** and **6l** are more potent than standard drug and zone of inhibition was more against *A. fumigatus.*

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INTRODUCTION

Nitrogen containing heterocyclic play an important role in various fields of industry, pharmaceuticals and fine chemicals. Among them 1, 3, 5-triazine represents a widely used lead structure with multitude of biological activity. Several derivatives of s-triazines show antimicrobial (Desai and Desai, 1994, antibacterial (Jain *et al*., 2007), antifungal (Jain *et al*., 2007), and anticonvulsant (Jino *et al*., 1998), activity. Several workers investigated the s-triazine nucleus as building block for potential therapeutic agents for diseases. This was due to the introduction of a lipophilic benzothiazoles moiety which could further increase the absorption of the compound through biological membranes and hence the present series of s-triazines with benzothiazoles scaffold was synthesized. The target compounds were synthesized according to Scheme I. Benzoyl 1[4-chlorobenzoylisothiocyanate] 1 was condensed with various S-benzyl-N-alkyl isothiourea 2 to give 1-alkyl-2-benzylmercapto-4-(phenyl-4-chlorophenol)-1,6-dihydro-1,3,5-triazine-6-thiones 3. On reaction with hydrazine hydrate the 2-benzylmercapto group was replaced with hydrazine moiety 4. When an ethanolic solution of 2-hydrazino derivative of s-triazinethiones and equimolar amounts of aromatic aldehydes were refluxed, high yields of Schiff bases 5 were obtained. Schiff bases upon cyclocondensation with 2-mercaptobenzoic acid afforded the target thiazinone derivatives 6. The chemical structures of all the compounds were confirmed by elemental analysis. IR, ^{1}H NMR and mass spectroscopy.

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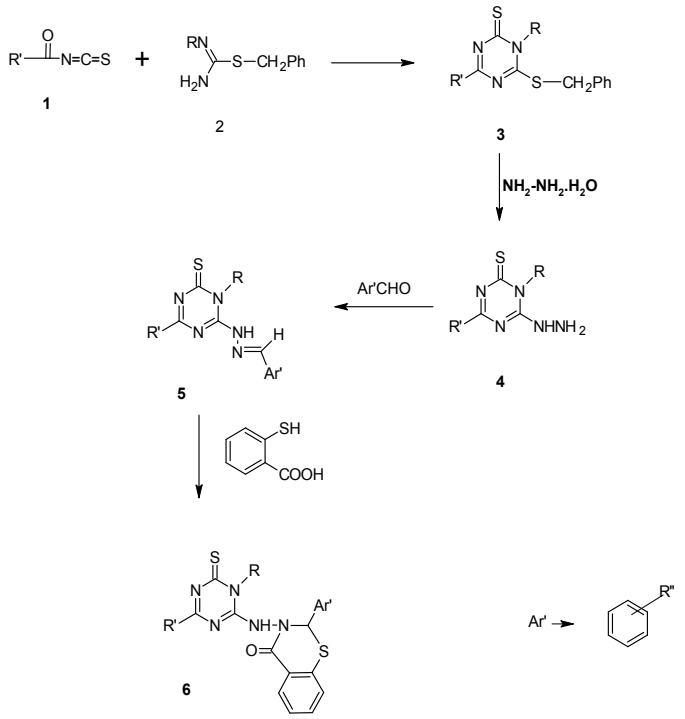
Experimental Section

Melting points of synthesized compounds were determined in open capillary tubes and are therefore, uncorrected. The IR spectra were recorded in the range of 4000-450cm^{-1} using KBr pellets on a Perkin-Elmer RX1 FTIR spectra photometre. ^{1}HNMR spectra were recorded on a Bruker DRX300 MHz spectrometer using DMSO; as a solvent against TMS as internal standard. The FAB mass spectra were recorded on Jeol 6X-102/DA-6000 spectrometer data system using argon/xenon (6 kV, 10 mA) as FAB gas. Homogeneity of synthesized compounds was checked by Silica Gel-6 plates of 2 mm

thickness using benzene and ethyl acetate (9:1) as solvent system and iodine vapors as visualizing agent. The starting materials and intermediates were prepared by reported literature methods. Aroyl isothiocyanates were prepared by the reaction of aroyl chloride and ammonium thiocyanate. Methyl thiourea (Hoffmann, 1874) (mp 119 C), butyl thiourea (Presder, 1949) (mp 80 C) and cyclohexalthiourea (Saija and Fakuda, 1954) (mp 172 C) were prepared by literature procedures. The intermediate 1, 3, 5-triazine arylidine hydrazine **4** (Srivastav and Pandeya, 2010) and N-(1—alkyl-4-phenyl-6-thioxo-1, 6-dihydro-1, 3, 5-triazin-2-yl)-N-arylidine hydrazones **5** have been reported (Srivastav and Pandeya, 2010).



Scheme I

(Synthesis of benzo-thiazinone derivative)

Where, R'= C_6H_5, 4-ClC_6H_4, Ar'=4-Cl C_6H_4, 4$CH_3OC_6H_4$, 4-CH_3-C_6H_4, 4-$NO_2C_6H_4$ R=CH_3, nC_4H_9, C_6H_{11}

3-(1-*n*-Butyl-4-(4-Chlorophenyl-6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl)-amino-2-(4-methoxy phenyl)-3,4-dihydro-4-oxo-2*H*-1,3-benzothiazine,(6f)

IR(KBr): 3320(NH), 2930(CH), 1684(C=O), 1130(C=S), 755(C-Cl), 745-695cm^{-1} (substituted phenyl ring); ^{1}H NMR(DMSO-d6 : 1.5-2.4(m, 9H, butyl), 3.2(s, 3H,-OCH3), 7.5-8.89(m, 12H,ArH), 8.25(s, 1H, CH), 10.80(s, 1H, NH); MS : *m/z* 563$[M]^+$,565$[H+2]^+$.

3-(1-*n*-Butyl-4(4-chlorophenyl)-6-thioxo-1,6-dihydro)1-3,5-triazin-2-yl-amino-2-(3-methyl phenyl)-3,4-dihydro-4-oxo-2*H*-1,3-benzothiazine, (6g)

IR(KBr) : 3315(NH), 2930(CH), 1685(C=O), 1625(C=N), 111O(C=S), 736(C-Cl), 740-690cm^{-1} (substituted phenyl rings); ^{1}HNMR(DMSO-*d*6)**δ** : 1.6-2.3(m, 9H, butyl), 2.5(s, 3H, CH_3-phenyl), 7.9-8.5(m, 12H, ArH), 8.20(S, 1H, CH), 10.9(s, 1H, NH); MS: *m/z* 547$[M]^+$, 549$[M+2]^+$.

3-(1-*n*-Butyl-4-(4-chlorophenyl-6-thioxo-1,6-dihydro-1, 5, 5-triazin-2-yl)-amino-2-(4-nitrophenyl)-3, 4-dihydro-4-oxo-2*H*-1, 3-benzothiazine, (6h)

IR(KBr) : 3315(NH), 2928(CH), 1684(C=O), 1630(C=N), 1340(N=O), 1125(C=S), 750(C-Cl), 740-695cm^{-1} (substituted phenyl ring); ^{1}H NMR(DMSO-d6) **δ**: 1.6-2.3(m, 9H, n-butyl, 7.6 (m, 12H, ArH), 8.85(s, 1H, CH), 9.8(s, 1H, NH); MS: *m/z* 578 [M]+ 580[M+2]+

3-(1-Cyclohexy-4-phenyl-6-thixo-1,6-dihydro-1,3,5-triazin-2-yl)-amino-2-(4-chlorophenyl)-3,4-dihydro-4-oxo-2*H*-1,3-benzothiazine, (6i)

IR(KBr) : 3320(NH), 2430(CH), 1685(C=O), 1635(C=N), 1135(C=S), 745(C-Cl), 740-690cm^{-1} (substituted phenyl ring); ^{1}H NMR(DMSO-d6)**δ**: 1.5-2.5(m, 11H cyclohexyl), 7.1-8.5(m, 13H, ArH), 8.9(s, 1H, CH), 10.1(s, 1H, NH); MS: *m/z* 559[M]+,561 $[MI_2]^+$

3-(1-Cyclohexyl-4-phenyl-6-thixo-1,6-dihydro-1,3,5-triazin-2-yl)-amino-2-(4-methoxy phenyl)-3,4-dihydro-4-oxo-2*H*-1,3-benzothiazine, (6j)

IR(KBr) : 3325(NH), 2935(CH), 1684(C=O), 1638(C=N), 1137(C=S), 745-685cm^{-1}; MS: *m/z* 555 [M]+ ; ^{1}H NMR(DMSO *d*6)**δ**, 1.5-2.6(m, 11H, cyclohexyl), 3.3(s, 3H OCH_3), 7.2-8.5(m, 13H, ArH), 8.8(s,1H, CH) 10.5(s, 1H, NH).

3-(1-Cyclohexyl-4-phenyl-6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl)-amino-2-(3-methyl phenyl)-3,4-dihydro-4-oxo-2*H*-1,3-benzothiazine, (6k)

IR(KBr) : 3330(NH), 2930(CH), 1686(C=O), 1640(C=N), 1135(C=S), 746-690cm^{-1} (substituted phenyl ring); ^{1}H NMR(DMSO-d6 : 2.2(s, 3H, CH3), 1.8-2.6(m, 11H, cyclohexyl), 7.3-8.1(m,13H, ArH), 8.6(s, 1H, CH), 10.10(s, 1H, NH); MS:*m/z* 539$[M]^+$.

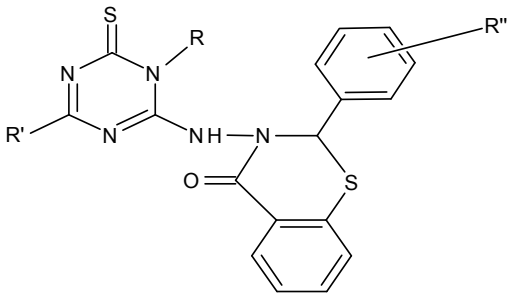
3-(1-cyclohexyl-4-phenyl-6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl)-amino-2-(4-nitrophenyl)-3,4-dihydro-4-oxo-2*H*-1,3-benzothiazine,(6l)

IR(KBr) : 3335(NH), 2935(CH), 1686(C=O), 1645(C=O), 1346(N=O), 1136(C=S), 745-696cm^{-1} (substituted phenyl ring); ^{1}H NMR(DMSO-d6 : 1.8-2.5(m, 11H cyclohexyl), 7.4-8.5(m, 13H, ArH), 8.8(s, 1H, CH), 10.5(s, 1H, NH); MS: *m/z:* 508$[M]^+$

Antibacterial activity

The antibacterial activity was determined by agar dilution technique against five pathogenic bacteria, procured from the Department of Microbiology, IMS, BHU, Varanasi. The medium was prepared as per the instructions of the manufacturer from dry Mueller Hinton agar powder (Hi-Media). The concentrations of the test samples used started from 5000 g/Ml to lower concentrations made by serial double dilutions with DMF. The minimum inhibitory concentration (MIC) was taken as the lowest concentration (higher dilution) without visible growth.

Table I. 3-(1-Alkyl-4-aryl-6-thioxo-1, 6-dihydro-1, 3, 5-triazin-2-yl)-amino-2-aryl-3, 4-dihydro-4-oxo-2*H*-1, 3-benzothiazine



6a-l

Compound	R=CH_3; R'=H R"	Mol Formula	Yield	m.p. (^{0}C)	Calc. % (Found)			
					C	**H**	**N**	**S**
6a	4-Cl	$C_{24}H_{18}ClN_5OS_2$	65	185	58.59	3.66	14.24	13.02
6b	4-CH_3O	$C_{25}H_{21}N_5O_2S_2$	61	173	61.60	4.31	14.37	13.14
6c	3-CH_3	$C_{25}H_{21}N_5OS_2$	59	179	63.69	4.45	14.86	13.58
6d	4-NO_2	$C_{24}H_{18}N_6O_3S_2$	69	180	57.37	3.58	16.73	12.74
	R=nC_4H_9; R'=Cl R"							
6e	4-Cl	$C_{27}H_{23}Cl_2N_5OS_2$	62	230	57.04	4.04	12.32	11.26
6f	4-CH_3O	$C_{28}H_{26}ClN_5O_2S_2$	59	267	59.62	4.61	12.42	11.35
6g	3-CH_3	$C_{28}H_{26}ClN_5OS_2$	65	210	61.36	4.74	12.78	11.68
6h	4-NO_2	$C_{27}H_{23}ClN_6O_3S_2$	58	175	56.00	3.97	14.52	11.06
	R=C_6H_{11}; R'=H R"							
6i	4-Cl	$C_{29}H_{26}ClN_5OS_2$	49	268	62.19	4.64	12.51	11.43
6j	4-CH_3O	$C_{30}H_{29}N_5O_2S_2$	52	190	64.86	5.22	12.61	11.53
6k	3-CH_3	$C_{30}H_{29}N_5OS_2$	59	220	66.79	5.38	12.98	11.87
6l	4-NO_2	$C_{29}H_{26}N_6O_3S_2$	47	265	61.05	4.56	14.73	11.22

Table II. *In-vitro* antibacterial / antifungal activities (MIC µg/mL) of 3-(1-alkyl-4-aryl)-6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl)-amino-2-aryl-3,4-dihydro-4-oxo-2*H*-1,3-benzothiaenes 6a-I

Compound	*E.coil*	*S. aureus*	*B. subtilis*	*S. typhii*	*Shigella dysentries*
6a	9.76	39.06	9.76	12.50	1.22
6b	312.5	12.50	6.25	25.00	2500
6c	1250	625	2500	5000	2500
6d	19.53	1.22	39.06	78.12	12.50
6e	1.22	1250	9.76	2500	19.53
6f	625	5000	625	625	2500
6g	1250	5000	625	625	2500
6h	36.06	0.152	9.76	2500	625
6i	0.152	9.76	78.12	625	19.25
6j	312.5	150.25	39.06	625	325
6k	19.53	325	625	2500	9.76
6l	19.53	0.152	625	156.26	9.76
Trimethoprim	19.53	<5000	1250	5000	9.76
Sulphamethoxazole	2500	5000	5000	5000	2500

Table III. Antifungal activity (300µg/mL)*

Compound	*A niger*	*C. albicans*	*A. fumigates*
6a	25	26	26
6b	18	22	16
6c	18.5	21	19
6d	26	24	26.5
6e	25	26	25.5
6f	20.5	23	21
6g	19	25	20
6h	28	23	25
6i	27	28	26
6j	18	19	16
6k	18	20	16
6l	28	26	27
Fluconazole	26	30	25
*Zone of inhibition in mm			

The study was simultaneously performed for the pure standard drugs (trimethoprim and sulfamethoxazole). The MICs are reported in Table II.

Antifungal activity

The compounds were screened for antifungal activity by agar dilution method at a concentration of 300g/ml against three pathogenic fungi. The compounds were sterilizes in DMF Table III.

RESULTS AND DISCUSSION (SAR)

The target compounds exhibited antibacterial and antifungal activities against *E.coli, S.aureus, B.subtilis, S.typhii, Shigelladysentriae, A.niger, C.albicans and A.fumigatus.* The activity pattern was generally influenced by the substitution pattern in the phenyl rings. Compounds containing chloro (6a,6e,6i) and nitro(6d,6h,6l) exhibited comparatively very good antibacterial activity while those substituted with methyl or methoxy showed moderate antibacterial activity. The compounds 6a, 6d, 6e, 6h and 6l were most active against *S.dysentries, S.aureus, E.coli* respectively within a MIC range of 0.152-1.22µg/mL. Moreover they were also highly active as compare to standard drugs trimethoprim and sulfamethoxazole. The presence of a nitro group greatly enhance the antibacterial activity of a compound such as chloramphenicol and metronidazole. The presence of a chloro group especially at the para position of phenyl ring is attributed to block the para position and obstruct its metabolic (p-hydroxylation) conversion to inactive metabolites. This is an important method in drug design to prepare metabolically stable molecules. This group is assigned to form a hydrophobic pocket for hydrophobic interactions. In the antifungal activity studies also all the compounds exhibited moderate to very good activity. Similar pattern was observed where chloro or nitro substituted compounds were most active as compare to methyl and methoxy. The compound 6h and 6l were the most active against *A.niger,* whereas 6a, 6d, 6e, 6i and 6l were more potent as compare to fluconazole against *A.fumigatus.* In case of *C.albicans* the compounds were less potent than fluconazole. However 6i, 6a and 6l were nearly equivalent in activity. The pattern signifies the incorporation of chloro substituent in the compounds which is also present in clinically useful antifungal agents. The lipophilic chloro group is able to disturb the lipoidal membranes of the fungi and arrest their growth. The research addresses a novel class of potent, wide spectrum antimicrobial and antifungal compounds. The s-triazine scaffold can be exploited for further molecular designing of novel drugs to treat drug-resistant pathogens.

Conclusion

The present study reflects the great potential of triazinyl-benzothiazines as an important class of compounds to treat multi-drug-resistant micro-organisms.

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