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Research

Design, Synthesis and Antimicrobial Screening of Novel Benzothiazole Analogs

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Abstract:

Recently, in a laboratory novel series of N-(2,6-substitutedimino-6H-1,3,5-dithiazin-4-yl)benzo[d]thiazol-2-amine **(IIIaa-ee)** was synthesized by refluxing 2-(5-substituted-2,4-dithiobiuret)benzo[d]thiazol-2-amine **(Ia-e)** with alky / aryl isothiocyanates **(IIa-e)** in acetone medium 1:1 proportion. The structures of all the synthesized compounds were justified on the basis of chemical characteristics, elemental analysis and spectral studies and their antimicrobial screening against the gram positive and gram-negative bacteria such as *S. aureus*, *B. Subtilis*, *B. Megatherium*, *S. typhi*, *E. coli*, *and A. Aerogenes.*

Keywords: N-(2,6-substitutedimino-6H-1,3,5-dithiazin-4-yl)benzo[d]thiazol-2-amine, alky / aryl isothiocyanates, gram positive (+Ve) and gram negative (-Ve) bacteria.

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INTRODUCTION

Heterocyclic compounds exhibit significant interest due to their versatility and broad range of applications. The size of heterocycles and the diversity of heteroatoms they contain contribute to their wide range of applications having nitrogen and sulphur as hetero atoms containing five membered [137-145], six membered [132-136] rings and fused heterocycle containing five membered [146-160] and six membered [161-175] ring. More specially heterocycles incorporating both nitrogen and sulfur atoms within the same ring structure exhibit significant biological and industrial applications. These heterocyclic compounds are pivotal in various domains due to their unique physicochemical properties and reactivity. 1,3,5-dithiazine is a six-membered heterocyclic compound characterized by the presence of two sulfur atoms and one nitrogen atom at the 1-, 3-, and 5-positions, respectively. This unique structure imparts significant biological and industrial relevance to the compound.

Tayade's research group [176-178] synthesized many heterocycles containing 1,3,5-dithiazine as important core. The 1,3,5-dithiazine moiety exhibits diverse applications, which are significantly influenced by the nature of the substituents attached to its basic nucleus. The electronic and steric properties of these substituents can modulate the chemical reactivity and biological activity of the 1,3,5-dithiazine derivatives. It has been also observed during literature study that, waghmare's research group synthesized numerous derivative of 1,3,5-dithiazine by using aryl / alkyl isocyanodichorides and reported their biological activities[179-184].

By considering all this ideas, it was planned to synthesize new series of 1,3,5-dithiazine. It is quite interesting to study one step cyclisation of 2-(5-substituted-2,4-dithiobiuret)benoz[d]thiazol-2-amine **(Ia-e)** with N-substituted isocynodichloride **(IIa-e)** in acetone medium to N-(2,6-substitutedimino-6H-1,3,5-dithiazin-4-yl)benzo[d]thiazol-2-amine **(III aa-ee).**

MATERIAL AND METHOD

Material

The entire chemical was used are AR grade.

Method

In the present experiment for the synthesis of different substituted 1,3,5-dithiazin-4-yl)beno[d]thiazol-2-amine is carried out conventional refluxing under electronic water bath for different hours for different experiment.

EXPERIMENTAL

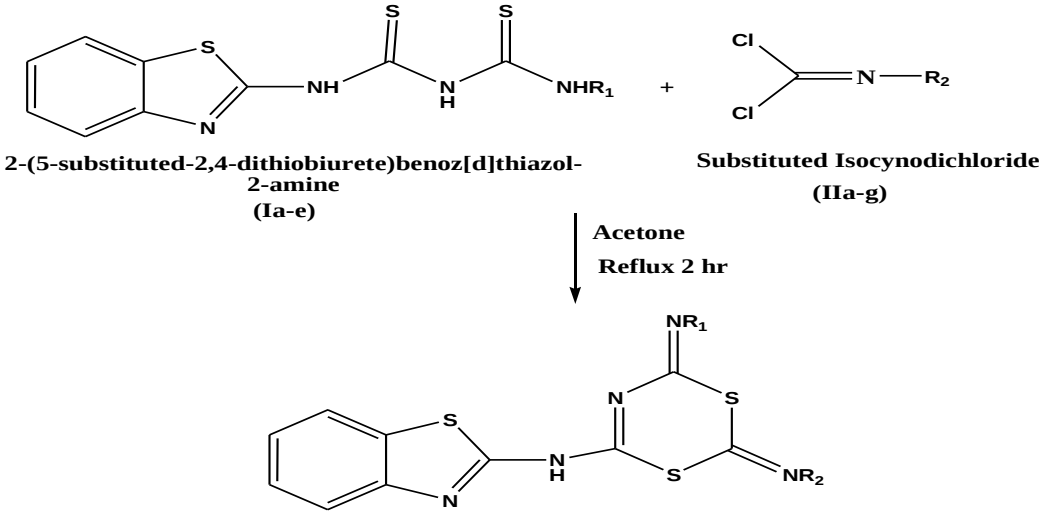
All the chemicals used for the synthesis were purified. After refluxing the purity of the compounds were checked by TLC (aluminium TLC) with thin layer thickness of 200 um. The melting points of all synthesize compounds will be recorded using hot paraffin bath. IR spectra were recorded with Bruker spectrometer in the range 4000-400 cm^{-1}. PMR spectra were recorded on VARIAN 400 MHz spectrometer with TMS as internal standard using $CDCL_3$ and DMSO as solvent.

GENERAL PROCEDURE

A reaction of 2-(5-substituted-2,4-dithiobiuret)benzo[d]thiazol-2-amine **(Ia-e)** with alky / aryl isothiocyanates **(IIa-e)** in acetone medium in 1:1 proportion refluxed for 2 hr on water bath. The evolution of the hydrochloride gas was clearly observed during refluxtion. After distillation of excess solvent different coloured product isolated which on basification with dilute ammonium hydroxide coloured crystalline products obtained.

The tentative reaction for the formation of product is depicted below,

REACTION



2-(5-substituted-2,4-dithiobiurete)benoz[d]thiazol-2-amine (Ia-e)

Substituted Isocynodichloride (IIa-g)

***N*-(2,6-substitutedimino-6*H*-1,3,5-dithiazin-4-yl)benzo[*d*]thiazol-2-amine (IIIaa-ee)**

R_1 = -Ph, -Et, -Benzyl, -4-Nitrophenyl,-4-flurophenyl

R_2 = -Ph, -Et, -Benzyl, -4-Nitrophenyl,-4-flurophenyl

Similarly, 2-(5-phenyl-2,4-dithiobiuret)benoz[d]thiazol-2-amine **(Ia)**, were interacted with N-phenylisocynodichloride **(IIa)** to isolate N-((12Z,14Z)-2,6-bis(phenylimino)-6H-1,3,5-dithiazin-4-yl)beno[d]thiazol-2-amine **(IIIaa),** 2-(5-ethyl-2,4-dithiobiuret)benoz[d]thiazol-2-amine **(Ib)**, were interacted with N-ethylisocynodichloride **(IIb)** to isolate N-((12Z,14Z)-2,6-bis(ethylimino)-6H-1,3,5-dithiazin-4-yl)beno[d]thiazol-2-amine **(IIIbb),** 2-(5-benzyl-2,4-dithiobiuret)benoz[d]thiazol-2-amine **(Ic)**, were interacted with N-benzylisocynodichloride **(IIc)** to isolate N-((12Z,14Z)-2,6-bis(benzyl imino)-6H-1,3,5-dithiazin-4-yl)beno[d]thiazol-

2-amine **(IIIcc),** 2-(5-(-4-Nitrophenyl)-2,4-dithiobiuret)benoz[d]thiazol-2-amine **(Id)**, were interacted with N-(-4-Nitrophenyl)isocynodichloride **(IId)** to isolate N-((12Z,14Z)-2,6-bis(-4-nitrophenylimino)-6H-1,3,5-dithiazin-4-yl)beno[d]thiazol-2-amine **(IIIdd),** 2-(5-(-4-fluorophenyl)-2,4-dithiobiuret)benoz[d]thiazol-2-amine **(Ie)**, were interacted with N-(-4-fluorophenyl)isocynodichloride **(IIe)** to isolate N-((12Z,14Z)-2,6-bis(-4-fluoroimino)-6H-1,3,5-dithiazin-4-yl)beno[d]thiazol-2-amine **(IIIee).**

RESULT AND DISCUSSION

Spectral data obtained from the present research support the formation of designed or target products. Spectral characterizations of some synthesized compounds are also given below:

DATA ANALYSIS

1)N-((12Z,14Z)-2,6-bis(phenylimino)-6H-1,3,5-dithiazin-4-yl)beno[d]thiazol-2-amine (IIIaa)

Color: Yellow solid, **$C_{22}H_{15}N_5S_3$** , Yield - 80%, M.P. 168ºC, **FTIR (KBr) ν cm^{-1} :** 3010.10 (Ar C-H stretching), 3360.80 (-N-H stretching), 1620.40 (S-C=N bending), 550.70 (-C-S stretching), 1090.20 (-CH stretching), 1530.90 (-N-H bending); **^{1}H NMR (400 MHz $CDCl_3$ δ ppm)**, The following interpretation applies to the significant chemical shifts. This spectrum distinctly displayed the signals, multiplate of 10H of phenyl ring at δ 6.50 ppm-7.40 ppm, doublet of 2H of benzothiazole at δ8.00 ppm and δ 8.20 ppm, singlet of 1H of –NH at δ4.10 ppm. **Molecular Mass** 445.05.

2)N-((12Z,14Z)-2,6-bis(ethylimino)-6H-1,3,5-dithiazin-4-yl)beno[d]thiazol-2-amine (IIIbb)

Color: Yellow crystalline, **$C_{14}H_{15}N_5S_3$** , Yield - 82%, M.P. 172ºC, **FTIR (KBr) ν cm^{-1} :** 3025.50 (Ar C-H stretching), 3360.70 (-N-H stretching), 1510.20 (S-C=N bending), 782.50 (-C-S stretching), 1100.10 (-CH stretching), 1470.90 (-N-H bending); **^{1}H NMR (400 MHz $CDCl_3$ δ ppm)**, The following interpretation applies to the significant chemical shifts. This spectrum distinctly displayed the signals, multiplate of quartrate of 4H of $–CH_2$ at δ 1.50 ppm, triplet of 6H of $–CH_3$ at δ 0.9 ppm, singlet of 1H of –NH at δ 3.8 ppm,. **Molecular Mass** 349.10.

3)N-((12Z,14Z)-2,6-bis(-4-fluoroimino)-6H-1,3,5-dithiazin-4-yl)beno[d]thiazol-2-amine (IIIee).

Color: Pale yellow solid, **$C_{22}H_{13}N_5F_2S_3$**,Yield - 69%, M.P. 171ºC, **FTIR (KBr) ν cm^{-1} :** 3039.20 (Ar C-H stretching), 3394.60 (-N-H stretching), 1501.70 (S-C=N bending), 1607.20 (-N-H bending); **^{1}H NMR (400 MHz $CDCl_3$ δ ppm)**, The following interpretation applies to the significant chemical shifts. This spectrum distinctly displayed the signals, multiplate of different 2H different H of Ph ring at δ 7.00 ppm and 7.30 ppm respectively, singlet of 1H of –NH at δ 3.9 ppm, doublet of two different H of benzothiazole ring at δ 8.10 ppm and 8.20 ppm respectively. **Molecular Mass** 481.10.

ANTIMICROBIAL ACTIVITY

All the synthesized compounds **(III-aa-ee)** were screened for antibacterial activity against *S. typhi, E. coli, S. aureus, A. Aerogenes, B. Subtilis and B. Megatherium*. by disc diffusion method was performed using mueller hinton agar as well as nutrient agar medium. Standard drug used for the activity was Ciprofloxacin.

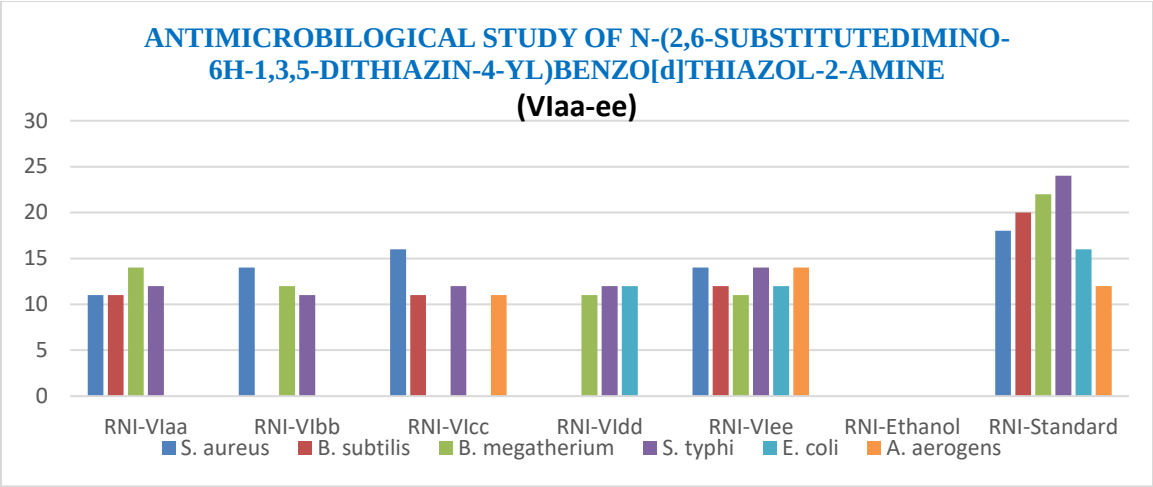
RESULTS AND DISCUSSION

Every synthetic compound's ability to fight germs was examined. In this study, disc diffusion was the method employed and the germs utilized were human pathogens. The antibacterial activity of all the produced compounds is displayed in Table 1.1.

Table No.1.1- Antibacterial Activity of Compounds

Sr. No.	Compound code	Gram positive			Gram negative		
		S. aureus	*B. subtilis*	*B. megatherium*	*S. typhi*	*E. Coli*	*A. aerogenes*
1	**RNI-IIIaa**	Active	Active	Active	Active	Inactive	Inactive
2	**RNI-IIIbb**	Active	Inactive	Active	Active	Inactive	Inactive
3	**RNI-IIIcc**	Active	Active	Inactive	Active	Inactive	Active
4	**RNI-IIIdd**	Inactive	Inactive	Active	Active	Active	Inactive
5	**RNI-IIIee**	Active	Active	Active	Active	Active	Active

6	**RNI-Ethanol (Con)**	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
7	**RNI-Standard (Ciprofloxacin)**	Active	Active	Active	Active	Active	Active



GRAPH- ANTIMICROBILOGICAL STUDY OF N-(2,6-SUBSTITUTEDIMINO-6H-1,3,5-DITHIAZIN-4-YL)BENZO[d]THIAZOL-2-AMINE (VIaa-ee)

CONCLUSION

The present work is cheaper and less time consuming method for synthesis of organic compound **(IIIaa-ee)**. All the synthesized compounds **(IIIaa-ee)** give moderate to good yield. From table no 1.1 it is concluded some synthesized compounds are active against various bacterial stains. A variety of benzothiazole based 1,3,5-dithiazine derivative can be synthesized for their antimicrobial activities adopting the method.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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