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SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-HYDRAZINYLQUINOXALINE2-(1H)-THIOL DERIVATIVES

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ABSTRACT

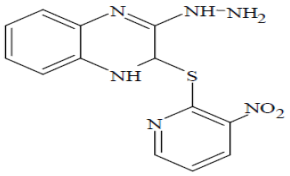
We have chosen molecules with moieties possessing the antimicrobial activity of Quinoxaline derived from benzene. Its structure might be obtained by replacing a (**c-s**) moiety with an oxygen atom. Which is reported to have antibacterial and anti-Fungal activity and other nitropyridine ring attached to the para position of the Quinoxaline ring which possesses antibacterial, and antifungal activity. Present work deals with the preparation of 3-Hydrazinylquinoxaline2-(1H)-thiol is treated with hydrazine hydrate and nitropyridine gives 3-hydrazine-2-[(3-nitropyridin-2-yl) sulfanyl]-1,2-dihydro quinoxaline and 2- [(3-hydrazine-1,2-dihydro quinoxaline-2yl) sulfanyl]-1- phenylethan-1-one. Hydrazides were synthesized to increase intracellular concentration and to try and decrease the resistance developed due to the decreased intracellular concentration of the drug these synthesized compounds were subjected to preliminary biological evaluation. The characterization of synthesized compounds was identified based on IR, ^{1}HNMR, and Melting point. The compounds have been evaluated for antimicrobial activity and Anti-Fungal activity.

KEYWORDS: Quinoxaline, Antimicrobial activity, Anti-Fungal Activity, Intracellular concentration.

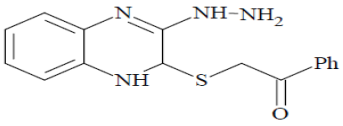
INTRODUCTION

Quinoxaline Compounds containing the nucleus exhibit a broad spectrum of biological activity such as antibacterial, antifungal, antiviral, anticancer, anti-tuberculosis, anti-malarial, and anti-inflammatory properties. Many researchers have reported the synthesis and biological activity of quinoxaline derivatives.[1] Quinoxalines constitute an important class of compounds; some analogs are synthesized and evaluated for antimicrobial activity and many possess diverse

biological activities such as insecticidal, fungicidal, herbicidal, and anthelmintic.[2] A critical bacterial interaction required for bacteria egress and dissemination involves late-budding domains, which are highly conserved in the matrix protein of many DNA of bacteria. Targeting this interaction, a novel series of 3-hydrazine-2-[(3-nitropyridin-2-yl) sulfanyl]-1,2-dihydro quinoxaline and 2- [(3-hydrazine-1,2-dihydro quinoxaline-2yl) sulfanyl]-1-phenylethan-1-one analogs were synthesized and evaluated for their ability to inhibit bacterial activity. Among them, compounds demonstrated strong bacterial egress inhibition potential.[3]



DS-IA



DS-IC

1. Presence of a final arylalkyl group substituted at the ortho and para position by a halogen ora methyl group improved potency
2. Substitution of sulfur resulted in greatly reduced activity
3. Methyl substituents on the imido and amide nitrogen atoms resulted in greatly reduced activity and A lipophilic side chain enhances the activity. The presence of a second CH_3 favorsantiviral activity
4. No suitable replacement of the methyl substituent on the quinoxaline moiety in the methylene bridge is necessary for the activity

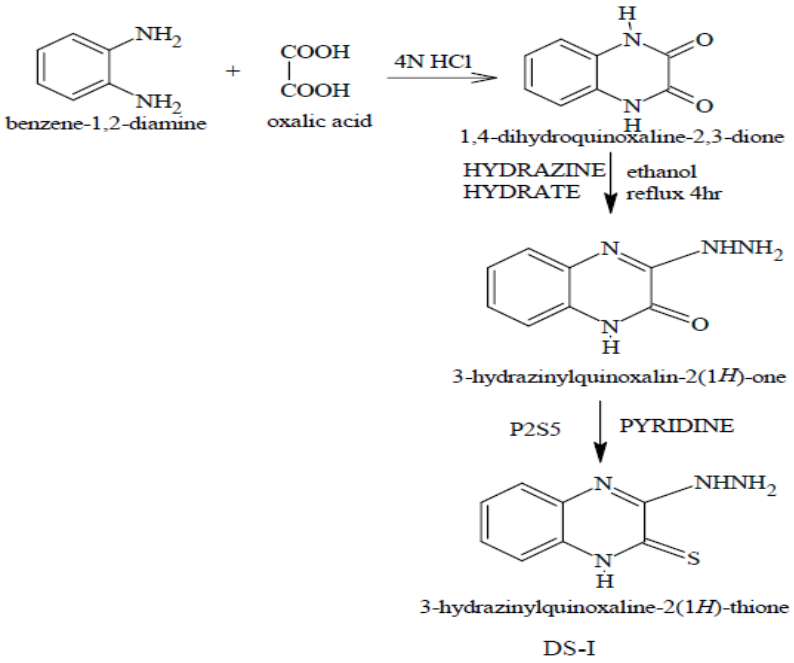
Quinoxaline derivatives are well known in the pharmaceutical industry and have been shown to possess a broad spectrum of biological activities including antiviral, antibacterial, anti-inflammatory, and kinase inhibitors.[4]

A critical virus-host interaction required for virus egress and dissemination involves late budding domains containing PPxY motifs, which are highly conserved in the matrix protein of a large number of RNA viruses. Targeting this interaction, a novel series of quinoxaline-2-mercapto-acetyl urea analogs are synthesized and evaluated for their ability to inhibit viral egress of Marburg and Ebola in VP40 VLP budding assay in HEK293T cells. Among them, four compounds demonstrated strong RNA viral egress.[5]

Hybrid structures formulated by the combination of quinoxaline and sulphonamide moieties

display novelty and versatility and possess a consistent therapeutic potential against most diseases. The general structure of quinoxaline sulphonamide, sulfaquinoxalinee (antimicrobial and coccidiosis for veterinary use), and chloroquinoline sulphonamide (topoisomerase-IIα and a topoisomerase-IIβ poison) are depicted.[6]

Experiment

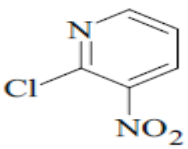
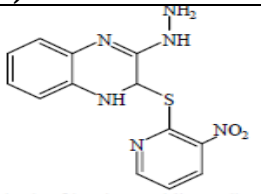


DS-I

Preparation of 3-Hydrazinylequinoxaline-2(1H)-thiol Derivatives

A mixture of 3-hydrazinylquinoxaline-2(1*H*) thiol [DS-I] (0.01 mol), Substituted halides (0.01 mol), and anhydrous potassium carbonate (2.0 g,0.01mol) in dimethyl Formamide (30 ml) was heated under reflux for 12 h. The solvent was evaporated *in a* vacuum and the obtained residue was washed with water, dried, and recrystallized from ethanol.

Table no. 01: Derivatives of 3-hydrazinylequinoxaline-2(1h)- thiol derivatives [ds-ia to ds-ie].

Compound Code	Substituted Halides	Derivatives of 3- Hydrazinylequinoxaline-2(1H)-thiolDerivatives
DS-IA		 3-hydrazinyl-2-[(3-nitropyridin-2-yl)sulfanyl]-1,2-dihydroquinoxaline

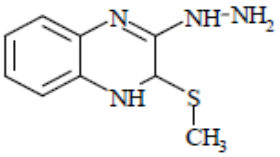
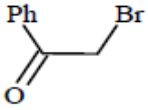
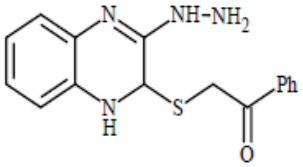
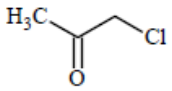
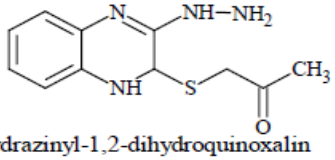
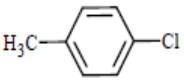
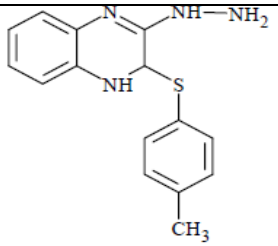
DS-IB	CH_3I Methyl iodide	 3-hydrazinyl-2-(methylsulfanyl) -1,2-dihydroquinoxaline
DS-IC	 2-bromo-1-phenylet han-1-one	
DS-ID	 1-chloropropan-2-one	 1-[(3-hydrazinyl-1,2-dihydroquinoxalin -2-yl)sulfanyl]propan-2-one
DS-IE	 1-chloro-4-methylbenzene	 3-hydrazinyl-2-[(4-methylphenyl)sulfanyl] -1,2-dihydroquinoxaline

Table no. 02: Physicochemical properties of derivatives of compound 3-hydrazinylequinoxaline-2(1h)-thiol derivatives [ds-ia-ic].

Sl. No	Parameter	DS-IA	DS-IB	DS-IC
1	Molecular Formula	C13H12N6O2S	C9H12N4S	C16H16N4OS
2	Molecular weight	316.33	208.28	312.38
3	Theoretical yield	1.94gm	1.94gm	1.94gm
4	Practical yield	1.14gm	1.48gm	1.18gm
5	% Yield	58.76%	76.28%	60.82%
6	Melting point	230-235° C	256^0-259° C	315-318° C
7	Recrystallization	Ethanol	Acetone	Ethanol
8	TLC	Benzene: Chloroform 5:1	Benzene: Chloroform5:1	Benzene: Chloroform5:1
9	Rf Value	0.85	0.86	0.70

Table no. 03: Physicochemical properties of derivatives of compound 3-hydrazinylequinoxaline-2(1h)-thiol derivatives[ds-id-if].

Sl. No.	Parameter	DS-ID	DS-IE	DS-IF
1	Molecular Formula	C11H14N4OS	C15H16N4S	C13H12N6O2S
2	Molecular weight	250.34	284.30	316.33
3	Theoretical yield	1.94gm	1.94gm	1.94gm

4	Practical yield	1.54gm	1.40gm	1.18gm
5	% Yield	79.38%	72.16%	60.82%
6	Melting point	210-245° C	216^0-289° C	345-348° C
7	Recrystallization	Ethanol	Ethanol	Ethanol
8	TLC	Benzene: Chloroform 5:1	Benzene: Chloroform5:1	Benzene: Chloroform5:1
9	Rf Value	0.81	0.96	0.80

Characterization

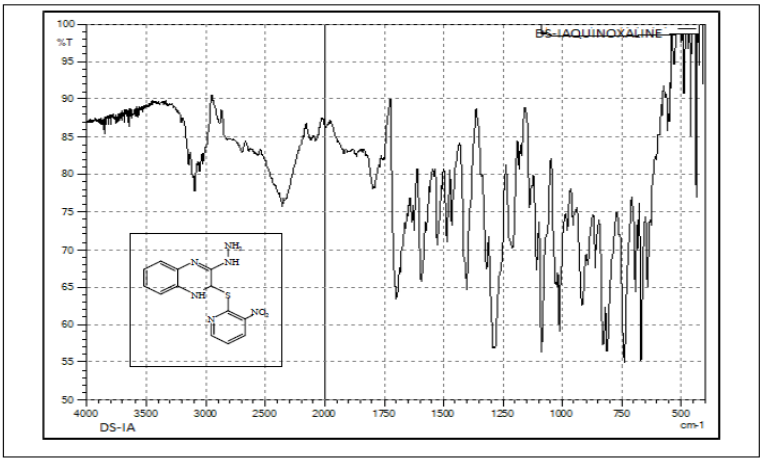


Fig. no. 01: Ft-ir spectral data of 3-hydrazine-2- [(3-nitropyridin-2 yl) sulfanyl]-1,2-dihydro quinoxaline.

Table no. 03: 3-hydrazinyl-2- [(3-nitropyridin-2 yl) sulfanyl]-1,2-dihydroquinoxaline.

Sr. No	Wave number (cm^{-1})	Functional group assigned
1	3150	N – H Stretch
2	3050	Aromatic C-H Stretch
3	2945	Aliphatic C-H Stretch
4	1618	C = O Stretch
5	1571	C = N Strech
6	1488,1443	C =C Strech
7	750	C-S Strech
8	751	N-H bend

^{1}H NMR

δ 2.18-2.31 (6H, 2.23 (s), 2.26 (s), 2.26 (s), 2.26 (s)), 7.40 (2H, dd, *J* = 8.0, 3.2 Hz), 7.57-7.78 (2H, 7.64 (ddd, *J* = 7.6, 7.3, 1.9 Hz), 7.71 (ddd, *J* = 7.9, 7.3, 1.9 Hz)), 7.94-8.10 (2H, 8.01 (ddd, *J* = 7.6, 1.9, 0.5 Hz), 8.03 (ddd, *J* = 7.9, 1.9, 0.5 Hz)), 8.34 (1H, dd, *J* = 4.5, 1.9 Hz).

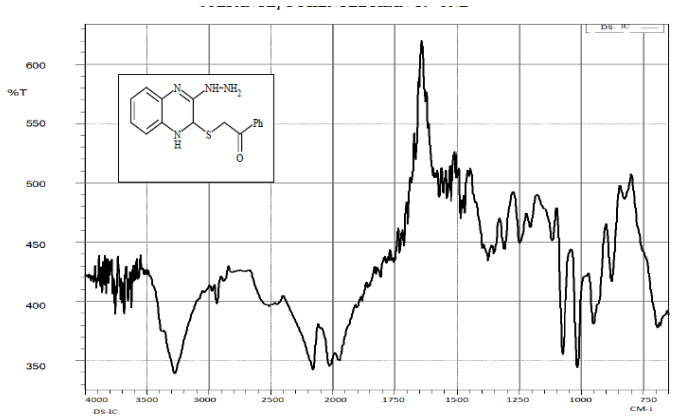


Fig no. 02: Ft-ir data of 2- [(3-hydrazine-1,2-dihydro quinoxaline-2-yl) sulfanyl]-1-phenylethan-10- one.

Table no. 04: Data of 2- [(3-hydrazine-1,2-dihydro quinoxaline-2-yl) sulfanyl]-1-phenylethan-1-one.

Sr. no.	Wave number (cm^{-1})	Functional group assigned
1	3150	N – H Stretch
2	3050	Aromatic C-H Stretch
3	2945	Aliphatic C-H Stretch
4	1618	C = O Stretch
5	1571	C = N Strech
6	1488,1443	C =C Strech
7	751	C-S Strech
8	753	N-H bend

^{1}H NMR

δ 0.90 (3H, t, *J* = 6.6 Hz), 1.58 (2H, tq, *J* = 7.6, 6.6 Hz), 2.18-2.28 (3H, 2.23 (s), 2.23 (s), 2.23 (s)), 2.57 (2H, t, *J* = 7.6 Hz), 7.10-7.32 (5H, 7.17 (dddd, *J* = 7.8, 1.3, 1.0, 0.5 Hz), 7.20 (tt, *J* = 7.7, 1.3 Hz), 7.26 (tdd, *J* = 7.8, 1.8, 0.5 Hz)), 7.56-7.78 (2H, 7.63 (ddd, *J* = 7.6, 7.3, 1.9 Hz), 7.71 (ddd, *J* = 7.9, 7.3, 1.9 Hz)), 7.94-8.08 (2H, 8.00 (ddd, *J* = 7.6, 1.9, 0.5 Hz), 8.02 (ddd, *J* = 7.9, 1.9, 0.5 Hz)).

Biological evaluationantifungal activity

The minimum inhibitory concentration (MIC) was determined by the broth dilution method (Serially diluted method). Ketoconazole has employed du6d ring the test procedures as references. MIC of the synthesized compounds ranges between 15.6-500µg/ml. DS-I, DS-IB, DS-ID, and DS-IE were found poor active, while DS-IA, DS-IC and were found to have moderate activity compared with standard. Test compounds were found to be more sensitive towards *Aspergillus Niger and Candida albicans*.

Table no. 05: The minimum inhibitory concentration of synthesized compounds [ds-i to ds-ie] (Against fungi).

Number	Compound code	MIC µg/ml	
		C.albicans	*A. Niger*
1	DS-I	58	90
2	DS-IA	89	95
3	DS-IB	31.5	50
4	DS-IC	93	88
5	DS-ID	36	28
6	DS-IE	32	25
7	STANDARD	100	100

Note: - Standard(S) = Ketoconazole, Control (C) = DMF

Antibacterial activity

The cup plate method determined the minimum inhibitory concentration (MIC). Ciprofloxacin was employed during the test procedures as a reference. The MIC of the synthesized compounds ranges between 25-200 µg/ml. DS-I, DS-IB, and DS-IE were found moderately active, while DS-IA and DS-IC, DS-ID were found to have an average activity compared with standard. Test compounds were found to be more sensitive toward *Staphylococcus aureus* (Gram-positive bacteria) and *Escherichia coli* (Gram-negative bacteria).

Table no. 06: The minimum inhibitory concentration of synthesized compounds [ds-i to ds-ie]. (Against bacteria).

Number	Compound code	MIC µg/ml	
		E. coli	*S. aureus*
1	DS-I	25	05
2	DS-IA	85	92
3	DS-IB	31.5	31.5
4	DS-IC	78	85
5	DS-ID	98	98
6	DS-IE	31.5	31.5
7	STANDARD	100	100

Note: -Standard(S) = Ciprofloxacin Control (C) = DMF

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