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DESIGN, SYNTHESIS AND CHARACTERIZATION OF NOVEL ISOXAZOLE-QUINAZOLINONE LINKED ANALOGUES AS AN ANTIMICROBIAL AGENT

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ABSTRACT

In present work, a series of novel isoxazole derivative, namely, 6,8-dibromo-3-[4-(5-substitutedphenyl-1,2-oxazol-3-yl)phenyl]-2-phenylquinazolin-4-one were synthesized from 6,8-dibromo-3-{4-[3-(substitutedphenyl)prop-2-enoyl]phenyl}-2-phenylquinazolin-4-one and hydroxylamine hydrochloride by using dioxane as a solvent and potassium hydroxide as a base in moderate to excellent Yields. The chemical structures of the synthesized compounds were established by IR and ^{1}H-NMR. All the compounds prepared here in (2a–2j) were screened for their antibacterial and antifungal activity with two bacteria Staphylococcus aureus, Escherichia Coli and two fungal strains Aspergillus Niger, Saccharomyces. Over all evaluation of the synthesized compounds suggests that most of them were found to show moderate to excellence antibacterial and antifungal activity as compared to the standard drugs like Streptomycin and Fluconazole respectively.

KEYWORDS: Quinazolin-4-One; Isoxazole; antibacterial; antifungal; Dioxane.

INTRODUCTION

Isoxazole is a five membered heterocyclic compound with an oxygen atom next to the nitrogen. Isoxazole and their derivatives have played a crucial role in the history of heterocyclic chemistry and been used extensively important pharmacophores and synthons in the field of organic chemistry. They were found to exhibit various physiological, biological and agricultural activities.

Isoxazole Linked Pyran pyrimidinone Conjugates could have possibly be promising in terms of therapeutic effect against SARs-CoV-2.[1] New Isoxazole-3-hydroxamate Based Histone Deacetylase 6 Inhibitor SS-208 have been synthesized and showed Antitumor Activity in Syngeneic Melanoma Mouse Models.[2] A Novel Low Temperature Electrolyte has been developed by Using Isoxazole as Main Solvent for Lithium-Ion Batteries.[3] Some Novel Isoxazole Substituted 9-Anilinoacridines may produce significant anti-breast cancer activity.[4] Isoxazole derivatives with substitutions in the central ring exhibit antiviral activity against pleconaril-resistant coxsackievirus B3.[5] Through this research, compounds containing an isoxazole ring exhibits a significant and broad spectrum of biological applications and show some unique physicochemical properties including Anticancer[6,7], Antiproliferative activity[8], Antimicrobial[9], antioxidant[10], antiviral[11], anticonvulsant activity[12], Insecticidal[13], Antiviral Activity[14], Antituberculosis activity analgesic and anti-inflammatory activity.[15]

Due to its relatively easy synthesis, Over the last decades, synthesis of various substituted isoxazole derivatives have attracted widespread attention of chemists and pharmacologists from research groups all over the world. Isoxazoles are unique in their chemical behavior not only among heterocyclic compounds in general but also among the related azoles. Considering this background, the present study aimed to synthesize some novel derivatives by synchronizing isoxazole moiety with quinazolinone moiety hoping that these molecules are good enough to possess better antimicrobial activities.

EXPERIMENTAL

1. MATERIALS AND METHODS

All chemicals and solvents were of analytical reagent grade and were purchased from commercial suppliers and used without further purification. All the synthesized compounds were characterized by their spectral analysis. Melting points (^{0} C, uncorrected) were determined in open capillary tube. Mixture of Chloroform and methanol in ratio of (9:1 v/v) respectively was used as a developing solvent system at room temperature, and the spots were visualized by ultraviolet light and/or Iodine/Ninhydrin reagent spray. The IR spectra were recorded on Bruker Model; Alpha, Laser Class1, Made in Germany. ^{1}H-NMR spectra were measured on Bruker instrument by using tetramethylsilane as an internal standard and DMSO as a solvent. Purity of the compounds were monitored by Thin Layer Chromatography (TLC) on silica-G plates. Antimicrobial activities were tested by Agar Cup

method. Standard drugs like Streptomycin and Fluconozole were used for the comparison purpose.

2. General Procedure and Detection Method

The synthesis of the isoxazole derivatives which appear in the Reaction Scheme.

Preparation of 6,8-dibromo-3-{4-[3-(substitutedphenyl)prop-2-enoyl]phenyl}-2-phenylquinazolin-4-one (KS-1a-1j).

To the solution of 3-(4-acetylphenyl)-6,8-dibromo-2-phenylquinazolin-4-one (0.01M) in absolute ethanol (50 ml), substituted benzaldehyde (0.01M) and 2% NaOH (10 ml) were added and refluxed for 10 hours. After refluxing the reaction mixture was concentrated, cooled, filtered and neutralized with dil. HCl. The solid residue thus obtained was crystallized by absolute ethanol. **IR(KBr); 1e (cm^{-1}): 6,8-dibromo-3-{4-[3-(2-hydroxyphenyl)prop-2-enoyl]phenyl}-2-phenylquinazolin-4-one** 3230 (-OH), 3065 (=C-H), 1679 (>C=O Stretching), 1584 (>C=N stretching), 1552 (>C=C< Aromatic), 1317 (C-N), 536 (C-Br). **IR(KBr); 1h (cm^{-1}): 6,8-dibromo-3-{4-[3-(4-dimethylaminophenyl)prop-2-enoyl]phenyl}-2-phenyl quinazolin-4-one** 3051 (=C-H), 2965 (-C-H Stretching), 1679 (>C=O Stretching), 1585 (>C=N stretching), 1515 (>C=C< Aromatic), 1445 ($-CH_3$), 1312 (C-N), 546 (C-Br).

^{1}HNMR (DMSO); 1h: 6,8-dibromo-3-{4-[3-(4-dimethylaminophenyl)prop-2-enoyl]phenyl}-2-phenyl quinazolin-4-one δ ppm 2.827, Singlet (6H) ($-N(CH_3)_2$) 7.942, Doublet (2H) (-CH=CH-), 7.170 - 8.247, Multiplet (15H) (Ar-H). **^{1}HNMR (DMSO); 1i: 6,8-dibromo-3-{4-[3-(4-methoxyphenyl)prop-2-enoyl]phenyl}-2-phenylquinazolin-4-one** δ ppm 3.867, Singlet (3H) ($-OCH_3$), 7.858, Doublet (2H) (-CH=CH-), 7.009 - 8.251, Multiplet (15H) (Ar-H).

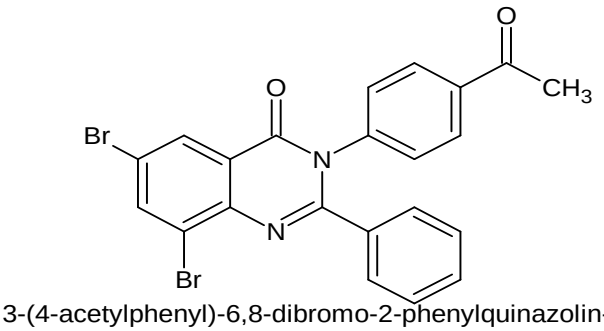
Preparation of 6,8-dibromo-3-[4-(5-substitutedphenyl-1,2-oxazol-3-yl)phenyl]-2-phenyl Quinazolin-4-one (KS-2a-2j).

A mixture of 6,8-dibromo-3-{4-[3-(substitutedphenyl)prop-2-enoyl]phenyl}-2-phenylquinazolin-4-one (0.01M) in 25 ml dioxane, hydroxylamine hydrochloride (0.01M) and 40% potassium hydroxide (KOH) was refluxed for 10 hours. Then the reaction mixture was cooled, poured into crushed ice (100 gm) and neutralized with HCl. The product separated out was filtered, washed with water, dried and recrystallized from alcohol.

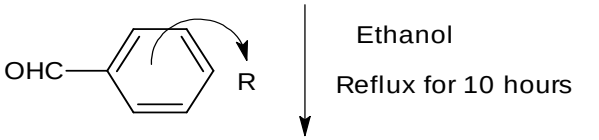
IR (cm^{-1}) (KS-2a): 3063 (=C-H), 1672 (>C=O stretching), 1598 (>C=N stretching), 1517 (>C=C< Aromatic), 1321 (C-N), 702 (C-Cl), 524 (C-Br).

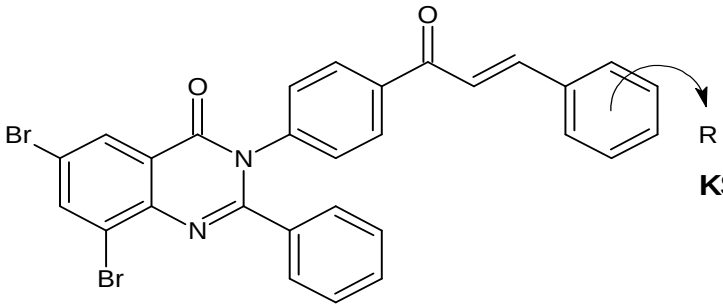
^{1}HNMR (DMSO); (KS-2h): δ ppm 2.814, Singlet (6H), -N(CH_3)2, 6.592, Singlet (1H) (-CH=), 7.511-7.969, Multiplet (15H) (Ar-H).

Reaction Scheme



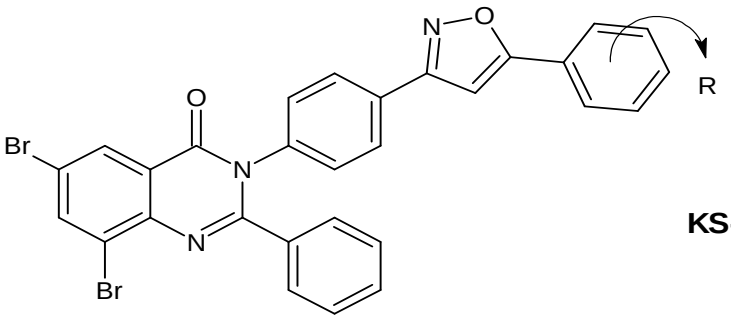
3-(4-acetylphenyl)-6,8-dibromo-2-phenylquinazolin-4-one





KS- 1a-1j

6,8-dibromo-3-{4-[3-(substitutedphenyl)prop-2-enoyl]phenyl}-2-phenylquinazolin-4-one



KS- 2a-2j

6,8-dibromo-3-[4-(5-substitutedphenyl-1,2-oxazol-3-yl)phenyl]-2-phenylquinazolin-4-one

Table No.1: Physical constant of 6,8-dibromo-3-[4-(5-substitutedphenyl-1,2-oxazol-3-yl)phenyl]-2-phenylquinazolin-4-one.

Sr.No	Sub. No.	R	M.F.	Mol.Wt (g/m)	Yield %	M.P. °C	% Carbon		%Nitrogen		% Hydrogen	
							Found	Calcd	Found	Calcd	Found	Calcd
1	KS-2a	-2-Cl	$C_{29}H_{16}Br_2ClN_3O_2$	633.71	75	232	54.92	54.96	6.63	6.63	2.52	2.54
2	KS-2b	-4-Cl	$C_{29}H_{16}Br_2ClN_3O_2$	633.71	59	185	54.95	54.96	6.62	6.63	2.54	2.54
3	KS-2c	-3,4-$(OCH_3)_2$	$C_{31}H_{21}Br_2N_3O_4$	659.32	76	188	56.44	56.47	6.35	6.37	3.20	3.21
4	KS-2d	-H	$C_{29}H_{17}Br_2N_3O_2$	599.27	65	176	58.12	58.12	7.00	7.01	2.83	2.86
5	KS-2e	-2-OH	$C_{29}H_{17}Br_2N_3O_3$	615.27	68	144	56.60	56.61	6.83	6.83	2.74	2.78
6	KS-2f	-4-OH-3-OCH_3	$C_{30}H_{19}Br_2N_3O_4$	645.29	62	152	55.83	55.84	6.51	6.51	2.95	2.97
7	KS-2g	-4-OH	$C_{29}H_{17}Br_2N_3O_3$	615.27	68	187	56.61	56.61	6.83	6.83	2.75	2.78
8	KS-2h	-4-$N(CH_3)_2$	$C_{31}H_{22}Br_2N_4O_2$	642.33	75	189	57.94	57.96	8.72	8.72	3.44	3.45
9	KS-2i	-4-OCH_3	$C_{30}H_{19}Br_2N_3O_3$	629.29	70	187	57.26	57.26	6.64	6.68	3.01	3.04
10	KS-2j	-3-NO_2	$C_{29}H_{16}Br_2N_4O_4$	644.26	80	135	54.05	54.06	8.70	8.70	2.50	2.50

Table No-2: Antimicrobial activity of 6,8-dibromo-3-[4-(5-substitutedphenyl-1,2-oxazol-3-yl)phenyl]-2-phenylquinazolin-4-one.

SR No	COMP NO	R	Zone of inhibition in mm			
			ANTIBACTRERIAL ACTIVITY		ANTIFUNGAL ACTIVITY	
			S. aureus	E.coli	Aspergillue niger	Saccharomyces
1	KS-2a	2-Cl	30	30	20	23
2	KS-2b	4-Cl	29	23	16	20
3	KS-2c	-3,4-$(OCH_3)_2$	33	26	19	19
4	KS-2d	-H	27	NA	20	20
5	KS-2e	-2-OH	30	27	21	17
6	KS-2f	-4-OH-3-OCH_3	20	30	20	18
7	KS-2g	-4-OH	27	24	18	20
8	KS-2h	-4-$N(CH_3)_2$	25	23	16	22
9	KS-2i	-4-OCH_3	NA	31	NA	21
10	KS-2j	-3-NO_2	27	26	20	19

Table No-3 Zone of inhibition of standard Drugs and Solvent.

Sr No	Compound No	Standard Drugs	Zone of inhibition in mm			
			Antibactrerial Activity		Antifungal Activity	
			S. aureus	E. coli	Aspergillus Niger	Saccharomyces
1	SD-1	Streptomycin	30	30	-	-
2	SD-2	Fluconazole	-	-	20	21
3	Solvent	DMSO	-	10	-	12

RESULT AND DISCUSSION

Antibacterial activity

Based on these preliminary screening results, compounds KS-2c and KS-2i showed maximum antibacterial activity against Staphylococcus aureus and Escherichia Coli respectively which showed good anti-bacterial activity than the respective standard test-drug like Streptomycin and Fluconazole also and it will be used for further studies. The compounds KS-2i and KS-2d, were found to be inactive against S. aureus and E. Coli respectively. Rests of all compounds were found to show good to moderate antibacterial activity against S. aureus and E. coli.

Antifungal activity

From screening results, compound 2b was found to possess maximum antifungal activity against both Aspergillus Niger and Saccharomyces. The minimum antifungal activity was shown by the compound KS-2b, KS-2h and KS-2e against Aspergillus Niger and Saccharomyces respectively. KS-2i was found to be inactive against Aspergillus Niger. Remaining other synthesized compounds was found to show good to moderate antifungal activity against Aspergillus Niger and Saccharomyces.

CONCLUSION

In summary, the present investigation describes design, synthesis and antimicrobial potential of some novel quinazolinone-isoxazole derivatives 3-[4-(1-benzoyl-5-(substitutedphenyl)-4,5-dihydro-pyrazol-3-yl)phenyl]-6,8-dibromo-2-phenylquinazolin-4-one **(2a-2j)** with the help of analytical data such as IR and ^{1}H-NMR. The products were found of appreciable yield and spectral data were found in agreement with the assigned molecular structures. Over all evaluation of the synthesized (2a-2j) compounds suggests that most of tested compounds exhibited good to moderate antibacterial and antifungal activity as compared to the standard drugs like Streptomycin and Fluconazole also.

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