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SYNTHESIS AND EVALUATION OF A SERIES OF 3-[4-(1-(PHENYLSULFONYL)-5-(SUBSTITUTED PHENYL)-4,5-DIHYDRO-PYRAZOL-3-YL)PHENYL]-6,8-DIBROMO-2-METHYLQUINAZOLIN-4-ONE AS AN ANTIMICROBIAL AGENTS

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ABSTRACT

In the present study a new class of substituted Pyrazole derivatives containing Quinoline moiety 2a-2j have been designed and synthesized by the reaction between 6,8-dibromo-3-{4-[5-(substitutedphenyl)-4,5-dihydro-pyrazol-3-yl]phenyl}-2-methyl quinazolin-4-one (1a-1j) with benzene sulphonyl chloride by using pyridine as a solvent. 1a-1j intermediate have been synthesized by the cyclization of 6, 8-dibromo-3-{4-[3-(substitutedphenyl) prop-2-enoyl]phenyl}-2-methylquinazolin-4-one with 99% hydrazine hydrate by using ethanol as a solvent. The newly synthesized compounds were screened for their antibacterial and antifungal activities by Agar Cup method. Several of these novel compounds showed good antibacterial and antifungal activity than standard drugs like Streptomycin and Fluconazole respectively. The chemical structures of newly synthesized sulphonyl pyrazoline derivatives were characterized on the basis of IR, NMR and spectral data as well as physical data.

KEYWORDS: Sulphonyl pyrazole, synthesis, Antibacterial activity, Antifungal activity

INTRODUCTION

Pyrazole, a five-membered heterocycle containing two nitrogen atoms, is extensively found as a core framework in a huge library of heterocyclic compounds that envelops promising agro-chemical, fluorescent and biological potencies. Attributed to its several potential

applications, there is a rise in the significance of designing novel pyrazoles, disclosing innovative routes for synthesizing pyrazoles, examining different potencies of pyrazoles, and seeking for potential applications of pyrazoles.[1] The bioactivity assay showed that the softening activity was possessed by most of the target new substituted pyrazole derivatives, to some extent, preventing wheat from FE injury.[2] Selected arylsulphonyl pyrazole derivatives were used as potential Chk1 kinase ligands.[3] Pyrazoles are widely used as core motifs for a large number of compounds for various applications such as catalysis, agro-chemicals, building blocks of other compounds and in medicine. The attractiveness of pyrazole and its derivatives is their versatility that allows for synthesis of a series of analogues with different moieties in them, thus affecting the electronics and by extension the properties of the resultant compounds.[4]

Pyrazoles and their derivatives are pharmaceutically important nitrogen-containing heterocyclic compounds that show a broad range of biological activities such as anti inflammatory[5-6], antimycobacterial activity[7], antifungal[8], anticancer[9], anticancer[10], antiviral[11], antidepressant, anticonvulsant[12], Antiproliferative, antiinfammatory[13], antidiabetic[14], antimicrobial, antioxidant[15], anti-tubercular agents[16], insecticidal activity.[17]

The objective of this investigation was to design and synthesize some new substituted pyrazole derivatives bearing quinoline moiety and evaluated them for potential biological activities. So Ten new pyrazole derivatives were synthesised and their antifungal and antibacterial activity were measured.

MATERIALS AND METHODS

All reagents were of analytical reagent grade and were used without further purification. All the product were synthesized and characterized by their spectral analysis. All Melting points (^{0} C, uncorrected) were determined in the open capillary tube. Purity of the compounds was checked by thin layer chromatography (TLC). Precoated silica gel plates were used for TLC. 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 and the NMR spectra were recorded on Brooker instrument with Tetramethyl silane as an internal standard and DMSO was used as a solvent. Antimicrobial activities were tested by Agar Cup method.

RESULT AND DISCUSSION

Preparation of 6, 8-dibromo-3-{4-[5-(substitutedphenyl)-4,5-dihydro-pyrazol-3-yl]phenyl}-2-methyl quinazolin-4-one (KS-1a-1j)

A mixture of 6, 8-dibromo-3-{4-[3-(substitutedphenyl)prop-2-enoyl]phenyl}-2-methylquinazolin-4-one (0.01M) and 99% hydrazine hydrate (0.015M) in ethanol (50ml) refluxed gently for 3 hours. Then the mixture was concentrated and allowed to cool. The resulting solid was filtered, washed with ethanol and recrystallized from ethanol.

^{1}HNMR (DMSO); (KS-1a): δ ppm 2.507, Singlet (3H) (-CH_3), 3.368, Doublet (2H) (-CH_2), 3.942 Triplet (1H) (-CH<), 7.377, Singlet (1H) (-NH), 7.277-8.340, Multiplet (10H) (Ar-H).

^{1}HNMR (DMSO); (KS-1g): δ ppm 2.505, Singlet (3H) (-CH_3), 3.355, Doublet(2H) (-CH_2), 3.959 Triplet (1H) (-CH<), 7.379, Singlet (1H) (-NH), 7.379-8.411, Multiplet (10H) (Ar-H), 9.659, Singlet(1H) (-OH).

IR(KBr); KS-1f (cm^{-1}): 3379 (>NH-), 3269 (-OH), 3029 (=C-H), 2965 (-C-H Stretching), 1671 (>C=O Stretching), 1587 (>C=N stretching), 1503 (>C=C< Aromatic), 1442 (-CH_2 bending), 1402 (-CH_3), 1304 (C-N), 1264 (N-N), 1169 (C-O-C), 535 (C-Br).

IR(KBr) ; KS-1i (cm^{-1}): 3357 (>NH-), 3087 (=C-H), 2906 (-C-H Stretching), 1662 (>C=O Stretching), 1587 (>C=N stretching), 1507 (>C=C< Aromatic), 1443 (-CH_2 bending), 1420 (-CH_3), 1294 (C-N), 1249 (N-N), 1168 (C-O-C), 548 (C-Br)

Preparation of 3-[4-(1-(phenylsulfonyl)-5-(substitutedphenyl)-4,5-dihydro-pyrazol-3-yl)phenyl]-6,8-dibromo-2-methylquinazolin-4-one (KS-2a-2j)

A solution of 6,8-dibromo-3-{4-[5-(substitutedphenyl)-4,5-dihydro-pyrazol-3-yl]phenyl}-2-methyl quinazolin-4-one (0.001M) in dry pyridine (25ml) cooled in an ice-bath and to it benzenesulfonyl chloride (0.0011M) was added. The mixture was stirred for 1 hour at room temperature and was then treated with cold dilute HCl (2N). The resulting solid was filtered, washed with water, and recrystallised from absolute ethanol.

IR (cm^{-1}) (KS-2e): 3-[4-(1-(phenylsulfonyl)-5-(2-hydroxyphenyl)-4,5-dihydro-pyrazol-3-yl)phenyl]-6,8-dibromo-2-methylquinazolin-4-one

3359 (-OH), 3062 (=C-H), 2950 (-C-H stretching), 1670 (>C=O stretching), 1585 (>C=N stretching), 1533 (>C=C< Aromatic), 1446 (-CH_2 bending), 1415 (-CH_3), 1328 (C-N), 1263 (N-N), 1160 (S=O), 541 (C-Br).

IR (cm^{-1}) (KS-2h): 3-[4-(1-(phenylsulfonyl)-5-(4-dimethylaminophenyl)-4,5-dihydro-pyrazol-3-yl)phenyl]-6,8-dibromo-2-phenylquinazolin-4-one. 3050 (=C-H), 2968 (-C-H stretching), 1680 (>C=O stretching), 1587 (>C=N stretching), 1518 (>C=C< Aromatic), 1444 ($-CH_2$ bending), 1416 ($-CH_3$), 1332 (C-N), 1265 (N-N), 1164 (S=O), 590 (C-Br).

^{1}HNMR (DMSO); (KS-2e): 3-[4-(1-(phenylsulfonyl)-5-(2-hydroxyphenyl)-4,5-dihydro-pyrazol-3-yl)phenyl]-6,8-dibromo-2-methylquinazolin-4-one

δ ppm, 2.506, Singlet (3H) (-CH3), 3.442, Doublet (2H) ($-CH_2$), 3.984, Triplet (1H) (-CH<), 6.811-8.167, Multiplet (15 H) (Ar-H), 9.744, Singlet (1H) (-OH).

^{1}HNMR (DMSO); (KS-2j): 3-[4-(1-(phenylsulfonyl)-5-(3-nitrophenyl)-4,5-dihydro-pyrazol-3-yl)phenyl]-6,8-dibromo-2-methylquinazolin-4-one

δ ppm, 2.506, Singlet (3H) (-CH3), 3.417, Doublet (2H) ($-CH_2$), 3.960, Triplet (1H) (-CH<), 7.306-8.411, Multiplet (15H) (Ar-H)

Reaction Scheme

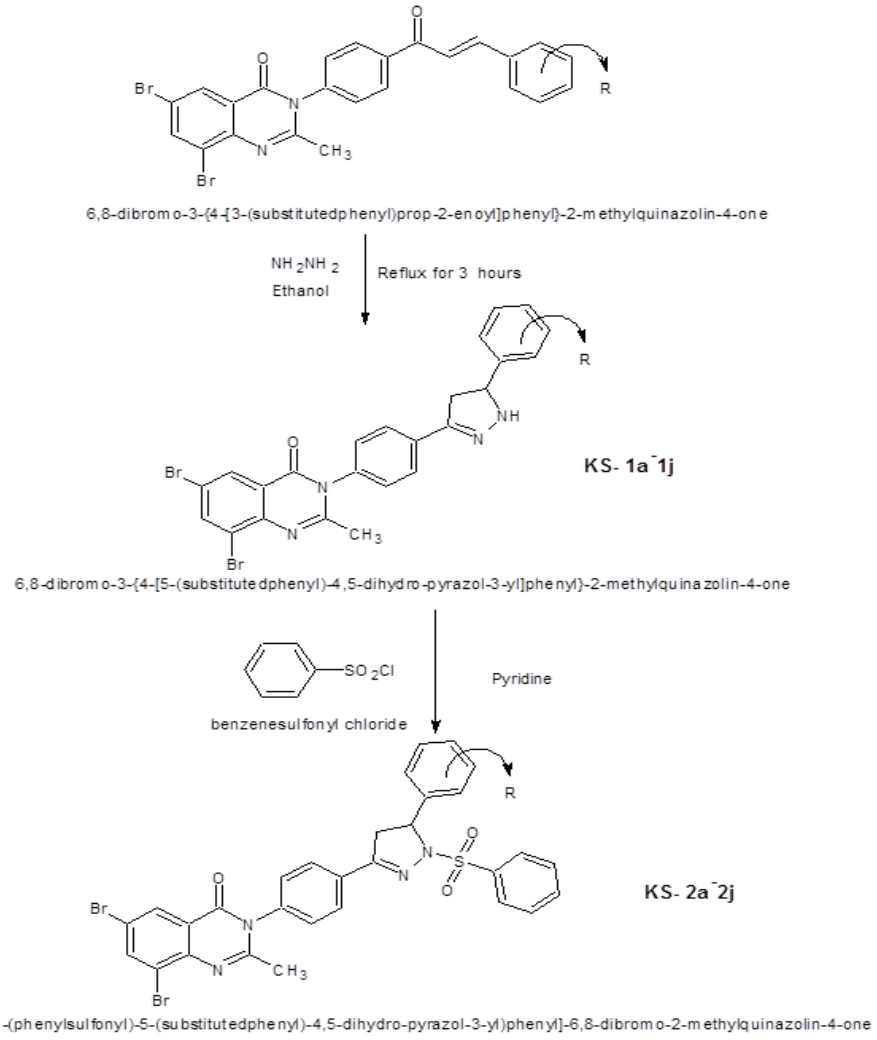

Table No.1

Physical constant of 3-[4-(1-(phenylsulfonyl)-5-(substitutedphenyl)-4,5-dihydro-pyrazol-3-yl)phenyl]-6,8-dibromo-2-methylquinazolin-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	$C_{30}H_{21}Br_2ClN_4O_3S$	712.83	87	123	50.52	50.55	7.85	7.86	2.95	2.97
2	KS-2b	-4-Cl	$C_{30}H_{21}Br_2ClN_4O_3S$	712.83	70	210	50.52	50.55	7.86	7.86	2.97	2.97
3	KS-2c	-3,4-$(OCH_3)_2$	$C_{32}H_{26}Br_2N_4O_5S$	738.44	76	185	52.02	52.05	7.58	7.59	3.53	3.55
4	KS-2d	-H	$C_{30}H_{22}Br_2N_4O_3S$	678.39	62	130	53.10	53.11	7.06	7.08	3.25	3.27
5	KS-2e	-2-OH	$C_{30}H_{22}Br_2N_4O_4S$	694.39	65	190	51.84	51.89	8.04	8.07	3.19	3.19
6	KS-2f	-4-OH-3-OCH_3	$C_{31}H_{24}Br_2N_4O_5S$	724.41	65	120	51.40	51.40	7.72	7.73	3.32	3.34
7	KS-2g	-4-OH	$C_{30}H_{22}Br_2N_4O_4S$	694.39	70	176	51.89	51.89	8.07	8.07	3.17	3.19
8	KS-2h	-4-$N(CH_3)_2$	$C_{32}H_{27}Br_2N_5O_3S$	721.46	63	142	53.23	53.27	9.70	9.71	3.75	3.77
9	KS-2i	-4-OCH_3	$C_{31}H_{24}Br_2N_4O_4S$	708.41	69	188	52.54	52.56	7.91	7.91	3.41	3.41
10	KS-2j	-3-NO_2	$C_{30}H_{21}Br_2N_5O_5S$	723.39	68	192	49.81	49.81	9.65	9.68	2.92	2.93

Table No-2

Antimicrobial activity of 3-[4-(1-(phenylsulfonyl)-5-(substitutedphenyl)-4,5-dihydro-pyrazol-3-yl)phenyl]-6,8-dibromo-2-methylquinazolin-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	24	29	18	19
2	KS-2b	4-Cl	28	NA	22	20
3	KS-2c	-3,4-$(OCH_3)_2$	21	29	20	16
4	KS-2d	-H	30	20	NA	17
5	KS-2e	-2-OH	32	23	17	18
6	KS-2f	-4-OH-3-OCH_3	25	33	22	16
7	KS-2g	-4-OH	27	25	20	18
8	KS-2h	-4-$N(CH_3)_2$	22	30	18	16
9	KS-2i	-4-OCH_3	NA	24	19	23
10	KS-2j	-3-NO_2	32	29	18	20

Table No. 3: Antimicrobial Activity: Minimal Inhibition Concentration (The standard Drugs).

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

Antibacterial activity

Against Staphylococcus_aureus: Over all analysis of the screening result suggest that KS-2e, KS-2j showed good anti-bacterial activity than the standard test-drugs used for bio-assay. KS-2i was found to be inactive against Staphylococcus aureus. Hence these compounds should be further tested under various conditions for their pharmaceutical applications.

Against Eschirichia Coli: Over all analysis of the screening result suggest that KS-2f showed good anti-bacterial activity than the standard test-drugs used for bio-assay. KS-2b was found to be inactive against Eschirichia Coli. Hence these compounds should be further tested under various conditions for their pharmaceutical applications.

Antifungal activity

Against Aspergillus Niger: Biological evaluation of present investigation revealed KS-2b and KS-2f showed good anti-fungal activity than the standard test-drug. The minimum antifungal activity was shown by the compound KS-2e. KS-2d was found to be inactive against Aspergillue niger. The remaining compounds were found to show good to moderate activity against Aspergillus Niger as compare to the standard drug Fluconazole.

Against Saccharomyces: Biological evaluation of present investigation revealed the maximum antifungal activity was shown by the compound KS-2i. The minimum antifungal activity was shown by the compound KS-2c, KS-2f and KS-2h. Rest of all compounds were found to show good to moderate activity against Saccharomyces as compare to the standard drug Fluconazole.

CONCLUSION

The Main objective of present research work was to synthesize, characterize and evaluate antimicrobial activities of the newly synthesized compounds with the help of analytical data such as 1H-NMR and IR. In conclusion, in present we prepared a series of 3-[4-(1-(phenylsulfonyl)-5-(substitutedphenyl)-4,5-dihydro-pyrazol-3-yl)phenyl]-6,8-dibromo-2-methylquinazolin-4-one (2a-2j). It is been observed that from the compounds tested, most of all were found to show good to moderate antibacterial and antifungal activity as compared to the standard drugs like Streptomycin and Fluconazole respectively.

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