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Synthesis and Biological evaluation Of Some New Benzoyl Pyrazole Derivatives bearing a 6,8-Dibromo-2-methylquinazolin-4-one Moiety

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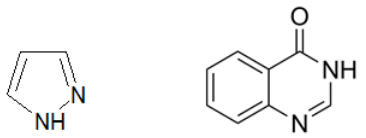
ABSTRACT

A new series of 3-[4-(1-benzoyl-5-(substitutedphenyl)-4,5-dihydro-pyrazol-3-yl)phenyl]-6,8-dibromo-2-methylquinazolin-4-one have been synthesized by the condensation reaction of 6,8-dibromo-3-{4-[5-(substitutedphenyl)-4,5-dihydro-pyrazol-3-yl]phenyl}-2-methylquinazolin-4-one with benzoyl chloride by using pyridine as a solvent. The intermediate have been synthesized by refluxation of 6,8-dibromo-3-{4-[3-(substitutedphenyl)prop-2-enoyl]phenyl}-2-methylquinazolin-4-one (0.01M) and 99% hydrazine hydrate (0.015M) by using ethanol (50ml) as a solvent with various aldehydes. The chemical structures of synthesized benzoyl pyrazoline derivatives were characterized by their IR, NMR and spectral data. The newly synthesized compounds were screened for their antibacterial and antifungal activities by Agar Cup method.

Keywords: Condensation; Benzoyl pyrazolines; Chalcone; antibacterial activity; Agar Cup method

INTRODUCTION

The heterocyclic compounds have a great importance in medicinal chemistry and play an important role in regulating biological process. One of the most important heterocycles in medicinal chemistry are quinazolines possessing wide spectrum of biological properties like Quinazolin-4(3H)-one are a class of fused hetero-cycles that are of considerable interest on account of the diverse range of their biological properties. Much attention has been paid to the synthesis of heterocyclic compounds bearing nitrogen containing ring system like pyrazoline mainly due to their higher pharmacological activity. Pyrazole is an unsaturated five-membered ring containing two adjacent nitrogen atoms as represented by the molecular formula $C_3H_4N_2$.The noun pyrazole was given for the first time by Ludwig Knorr in 1883 [1]. The first natural pyrazole, 1-pyrazolyl-alanine was isolated from seeds of watermelons [2] (Figure 1).



Pyrazole Quinazolin-4(3H)-one

Figure 1: Pyrazoles

Pyrazole and its derivatives have great interest in agrochemical, pharmaceutical, and chemical industries [3,4]. Pyrazolines are known to have anticancer [5], cytotoxic [6], antifungal [7], antitubercular [8], antioxidant [9]. Some pyrazolines are also reported to have anti-inflammatory, antidiabetic, anesthetic and analgesic properties [10-12]. The main skeletal of pyrazole and its related structures can be reported as important building blocks in organic synthetic for the design of a variety of biologically active compounds [13,14].

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 were determined by open capillary tube and are uncorrected. The IR spectra were recorded on Bruker Model; Alpha, Laser Class1, made in Germany and Brooker instrument was used for NMR Spectroscopy and $(CH_3)_4Si$ (tetramethyl silane) used as internal standard and DMSO was used as a solvent. Purity of the compounds was checked by TLC on silica-G plates. Antimicrobial activities were tested by Agar Cup method. Standard drugs like Streptomycin and Fluconazole were used for the comparison purpose. .

RESULT AND DISCUSSIONS

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) (Scheme 1) (Table 1&2).

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

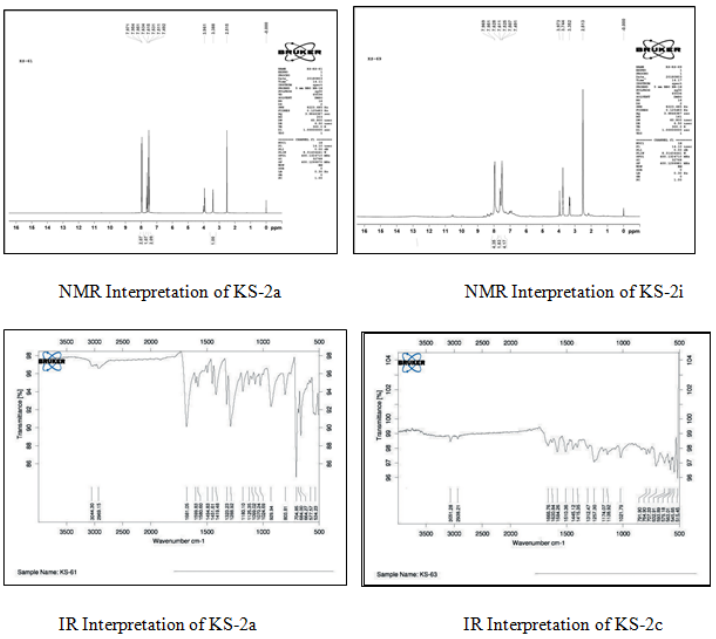
A mixture of 6,8-dibromo-3-{4-[5-(2-substitutedphenyl)-4,5-dihydro-pyrazol-3-yl]phenyl}-2-methylquinazolin-4-one (0.001M) and benzoyl chloride (0.0011M) dissolved in dry pyridine (25ml) and stirred at room temperature for 1 hours, after which the reaction mixture treated with cold dilute HCl (2N). The resulting solid was filtered and washed successively with water, cold NaOH (2%) and water, and recrystallized from glacial acetic acid.

^{1}HNMR (DMSO) ; (KS-2a) : δ ppm 2.515, Singlet (3H) (-CH_3), 3.388 , Doublet(2H) (-CH_2) , 3.961, Triplet (1H) (-CH<), 7.492-7.971, Multiplet (15H) (Ar-H).

^{1}HNMR (DMSO) ; (KS-2i) : δ ppm 2.513, Singlet (3H) (-CH_3), 3.352, Doublet(2H) (-CH_2), 3.744, Singlet (3H) (-OCH_3), 3.973, Triplet (1H) (-CH<), 7.491-7.969, Multiplet (15H).

IR(KBr) ; KS-2a (cm^{-1}): 3044 (=C-H), 2969 (-C-H stretching), 1681 (>C=O stretching), 1580 (>C=N stretching), 1494 (>C=C< Aromatic), 1451 (-CH_2 bending), 1419 (-CH_3), 1323 (C-N), 1288 (N-N), 704 (C-Cl), 534 (C-Br).**IR(KBr) ; KS-2c (cm^{-1}):** 3051 (=C-H), 2938 (-C-H stretching), 1666 (>C=O stretching), 1584 (>C=N stretching), 1510 (>C=C< Aromatic), 1445 (-CH_2 bending), 1415 (-CH_3), 1312 (C-N), 1257 (N-N), 1174(C-O-C), 545(C-Br) (Figure 2).

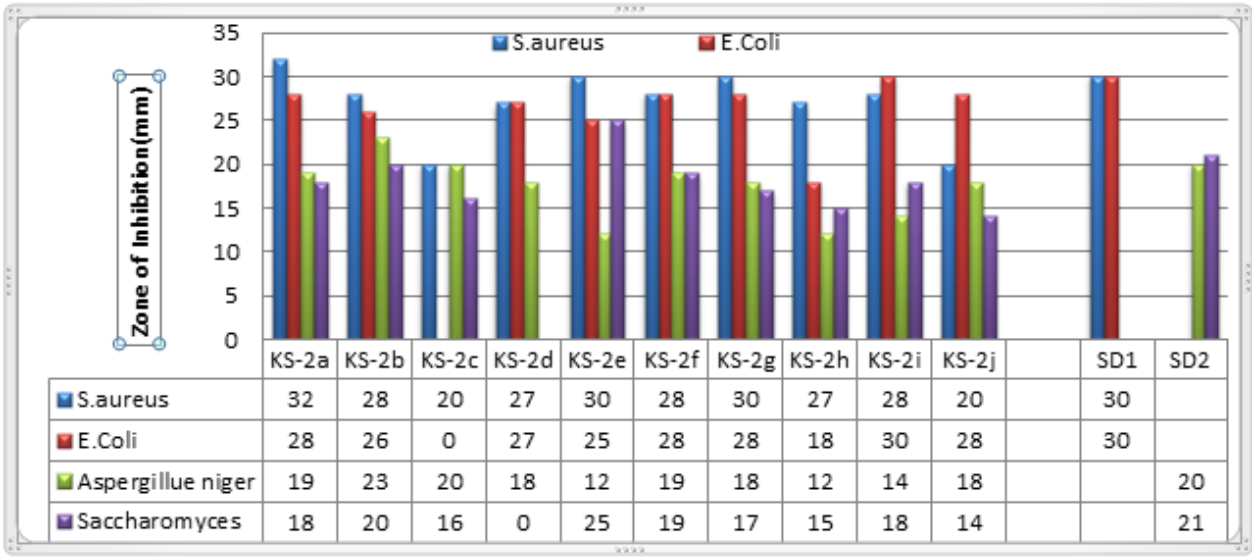
IR and NMR Interpretation of various compounds



NMR Interpretation of KS-2a NMR Interpretation of KS-2i

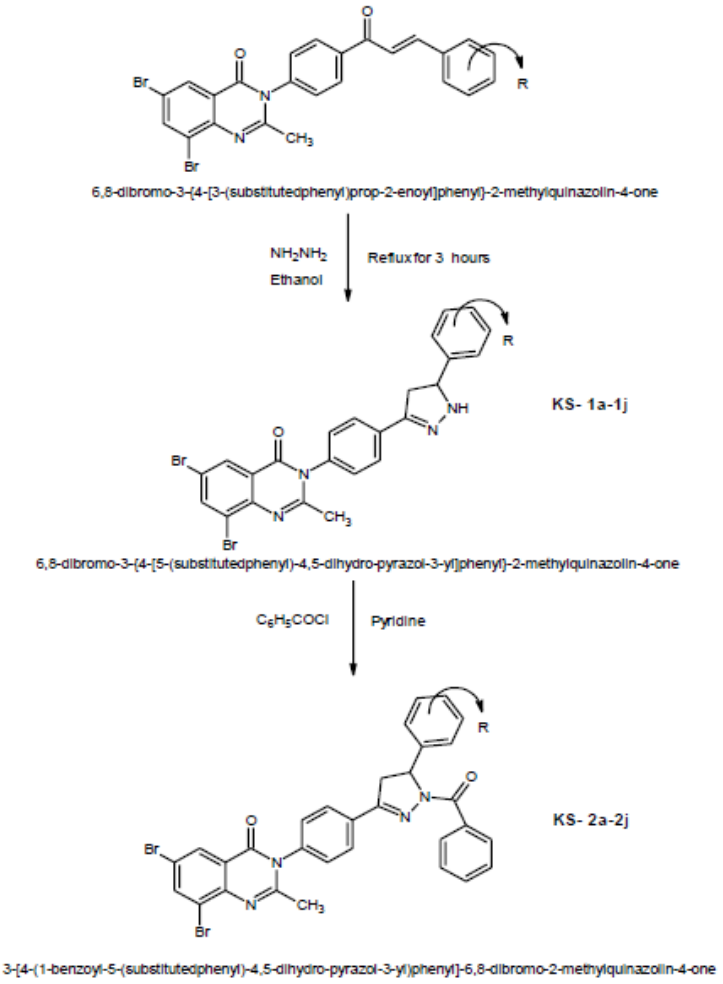
IR Interpretation of KS-2a IR Interpretation of KS-2c

Figure 2: IR and NMR Interpretation of various compounds



	KS-2a	KS-2b	KS-2c	KS-2d	KS-2e	KS-2f	KS-2g	KS-2h	KS-2i	KS-2j		SD1	SD2
S.aureus	32	28	20	27	30	28	30	27	28	20		30	
E.Coli	28	26	0	27	25	28	28	18	30	28		30	
Aspergillue niger	19	23	20	18	12	19	18	12	14	18			20
Saccharomyces	18	20	16	0	25	19	17	15	18	14			21

Figure 3: Antimicrobial activity of 3-[4-(1-benzoyl-5-(substitutedphenyl)-4,5-dihydro-pyrazol-3-yl)phenyl]-6,8-dibromo-2-methylquinazolin-4-one



Scheme 1: Reaction scheme

Table 1: Physical constant of 3-[4-(1-benzoyl-5-(substitutedphenyl)-4,5-dihydro-pyrazol-3-yl)phenyl]-6,8-dibromo-2-methyquinazolin-4-one

							% carbon		% Nitrogen		% Hydrogen	
Sr No	**Sub. No.**	**R**	**M.F.**	**Mol.Wt (g/m)**	**Yield %**	**M.P. C**	**Found**	**Calcd**	**Found**	**Calcd**	**Found**	**Calcd**
1	KS-2a	-2-Cl	$C_{31}H_{21}Br_2ClN_4O_2$	676.78	65	170	55.00	55.01	8.27	8.28	3.12	3.13
2	KS-2b	-4-Cl	$C_{31}H_{21}Br_2ClN_4O_2$	676.78	78	190	55.01	55.01	8.24	8.28	3.12	3.13
3	KS-2c	-3,4-(OCH3)2	$C_{33}H_{26}Br2N_4O_4$	702.39	58	136	56.41	56.43	7.97	7.98	3.72	3.73
4	KS-2d	-H	$C_{31}H_{22}Br_2N_4O_2$	642.33	69	158	57.95	57.96	8.72	8.72	3.43	3.45
5	KS-2e	-2-OH	$C_{31}H_{22}Br_2N_4O_3$	658.33	73	165	56.53	56.56	8.50	8.51	3.32	3.37
6	KS-2f	-4-OH-3- OCH3	$C_{32}H_{24}Br_2N_4O_4$	688.36	78	190	55.81	55.83	8.14	8.14	3.51	3.51
7	KS-2g	-4-OH	$C_{31}H_{22}Br_2N_4O_3$	658.33	77	143	56.52	56.56	8.50	8.51	3.36	3.37
8	KS-2h	-4-N(CH3)2	$C_{33}H_{27}Br_2N_5O_2$	685.40	72	205	57.83	57.83	10.21	10.22	3.97	3.97
9	KS-2i	-4-OCH3	$C_{32}H_{24}Br_2N_4O_3$	672.36	68	165	57.12	57.16	8.32	8.33	3.6	3.6
10	KS-2j	-3-NO2	$C_{31}H_{21}Br_2N_5O_4$	687.33	70	150	54.16	54.17	10.16	10.19	3.05	3.08

Table 2: Antimicrobial activity of 3-[4-(1-benzoyl-5-(substitutedphenyl)-4,5-dihydro-pyrazol-3-yl)phenyl]-6,8-dibromo-2-methylquinazolin-4-one

			Zone of inhibition in mm			
			Antibacterial Activity		**Antifungal Activity**	
SR No	**COMP NO**	**R**	***S. aureus***	***E.coli***	***Aspergillue niger***	***Saccharomyces***
1	KS-2a	2-Cl	32	28	19	18

2	KS-2b	4-Cl	28	26	23	20
3	KS-2c	-3,4-$(OCH_3)_2$	20	NA	20	16
4	KS-2d	-H	27	27	18	NA
5	KS-2e	-2-OH	30	25	12	25
6	KS-2f	-4-OH-3-OCH_3	28	28	19	19
7	KS-2g	-4-OH	30	28	18	17
8	KS-2h	-4-$N(CH_3)_2$	27	18	12	15
9	KS-2i	-4-OCH_3	28	30	14	18
10	KS-2j	-3-NO_2	20	28	18	14

Anti bacterialactivity

A short review of results of anti-bacterial screening of the compounds of this section is mention here.

Against Staphylococcus aureus

Over all analysis of the screening result suggest KS-2a showed good anti-bacterial activity than the standard test-drug like Streptomycin also. Hence these compounds should be further tested under various conditions for their pharmaceutical applications. Minimum antibacterial activity was shown by the compounds 2c and 2j against *S. aureus*.

Against Escherichia Coli

From screening results, compound 2a, 2f, 2g and 2j were found to possess maximum antibacterial activity against *Escherichia Coli*. The minimum antifungal activity was shown by the compound KS-2h for *E. Coli*. 2c was found to be inactive against *E. Coli*.

Anti fungalactivity

A short review of results of anti-fungal screening of the compounds of this section is mention here.

Against *Aspergillus Niger*

Over all analysis of the screening result suggest that KS-2b showed good anti-fungal activity than the standard test-drug like Fluconazole also. Hence these compounds should be further tested under various conditions for their pharmaceutical applications. The minimum antifungal activity was shown by the compound KS-2e and 2h for *Aspergillus Niger*.

Against Saccharomyces

Over all analysis of the screening result suggest that KS-2e showed good anti-fungal activity than the standard test-drugs used for bio-assay. Hence these compounds should be further tested under various conditions for their pharmaceutical applications. 2d was found to be inactive against *Saccharomyces*. The minimum antifungal activity was shown by the compound KS-2j for *Saccharomyces*.

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-benzoyl-5-(substitutedphenyl)-4,5-dihydro-pyrazol-3-yl)phenyl]-6,8-dibromo-2-methylquinazolin-4-one. 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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