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SYNTHESIS, SPECTRAL AND ANTIMICROBIAL ACTIVITY OF 6, 8-DIBROMO-3-{4-[5-(SUBSTITUTEDPHENYL)-4, 5-DIHYDRO-PYRAZOL-3-YL] PHENYL}-2-METHYLQUINAZOLIN-4-ONE

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ABSTRACT

A series of 6, 8-dibromo-3-{4-[5-(substitutedphenyl)-4, 5-dihydro-yrazol-3-yl] phenyl}-2-methylquinazolin-4-one were synthesized by refluxation of 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) for 3 hours and their structures were characterized by physical properties, IR, NMR and elemental analysis techniques. The antibacterial potential against specific Gram-positive and Gram-negative strains and the antifungal activities of all novel compounds were investigated.

KEYWARDS: Chalcone, Pyrazole, Antibacterial and Antifungal.

INTODUCTION

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] Pyrazole derivatives are the subject of many research studies due to their widespread potential biological activities such as anti-AIDS,[3] antitubercular,[4] antitumor,[5] antibacterial,[6] anticancer,[7] antihyperglycemic[8] inflammatory[9] Antipyretic[10,11] and antidepressant.[12] Some pyrazoles also used in Painting and Photography Industry.[13] Recently, substituted pyrazole derivatives are significant interest due to their roles in the medicinal and agriculture industries.[14,18] Hurobe reviewed the chemistry of pyrazolines, which have been studied extensively for their biodynamic

behavior[19] and industrial applications.[20] Looking at the importance of quinoline and pyrazole nucleus, it was thought that it would be worthwhile to design and synthesize some new quinazoline derivatives bearing pyrazole moiety from chalcones with the hope that they may possess better antimicrobial activities.

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. Melting points were taken in open capillary tube. The IR spectra were recorded on Bruker Model; Alpha, Laser Class1, Made in Germany and Brooker instrument used for NMR Spectroscopy was 500 MHz and tetramethylsilane used as internal standard. Solvent used were DMSO. Purity of the compounds was checked by TLC on silica- G plates. Antimicrobial activities were tested by Agar Cup method. Standard drugs like Stretomycin and Fluconozole were used for the comparison purpose.

RESULT AND DISCUSSION

Preparation of 3-(4-acetylphenyl)-6, 8-dibromo-2-methylquinazolin-4-one (KS-1)

6,8-dibromo-2-methyl-3,1-benzoxazin-4-one and 1-(4-aminophenyl)ethanone (0.1M) was refluxed for 4 hours in the presence of glacial acetic acid. The reaction mixture was kept at overnight and the product obtained was recrystallized using ethanol. The yield of the product was 68% and the product melts at 205^{o}C. **IR (KBr); KS-1 (cm^{-1}):** 3024 (=C-H), 2911 (-C-H Stretching), 1673 (>C=O Streching), 1591 (>C=N stretching), 1526 (>C=C< Aromatic), 1407 (-CH_3), 1304 (C-N), 582 (C-Br). **^{1}HNMR (DMSO); (KS-1): δ ppm** 2.505, Singlet (3H) (-CH_3), 2.660, Singlet (3H) (-$COCH_3$), 7.644-8.386, Multiplet (6H) (Ar-H).Composition found: C (46.80%) H (2.75%) N (6.40%), **Composition required for $C_{17}H_{12}Br_2N_2O_2$:** C (46.82%) H (2.77%) N (6.42%).

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

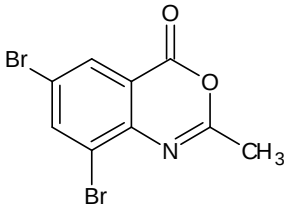
To the solution of 3-(4-acetylphenyl)-6,8-dibromo-2-methylquinazolin-4-one (0.01M) in absolute ethanol (50 ml), substitutedbenzaldehyde (0.01M) and 2% NaOH (10 ml) were added and refluxed for 10 hours. After refluxing the reaction mixture was concentrated, cooled, filtered and neutralized with dil. HCl. The solid residue thus obtained was crystallized by absolute ethanol. **IR(KBr); 2a (cm^{-1}):** 3056 (=C-H), 2980 (-C-H Stretching), 1681 (>C=O Stretching), 1587 (>C=N stretching), 1533 (>C=C< Aromatic), 1406 (-CH_3), 1314 (C-N),

753 (C-Cl), 585 (C-Br) **IR(KBr); 2d (cm^{-1}):** 3025 (=C-H), 2971 (-C-H Stretching), 1671 (>C=O Stretching), 1592 (>C=N stretching), 1527 (>C=C< Aromatic), 1407 ($-CH_3$), 1304 (C-N), 580 (C-Br) **^{1}HNMR (DMSO); 2c:** δ ppm 2.507, Singlet (3H) ($-CH_3$), 3.735, Singlet (6H) ($-OCH_3$), 7.850, Doublet (2H) (-CH=CH-), 6.616 - 8.412, Multiplet (9H) (Ar-H) **^{1}HNMR (DMSO); 2h:** δ ppm 2.508, Singlet (3H) ($-CH_3$), 2.823, Singlet (6H) ($-N(CH_3)_2$), 7.849 , Doublet (2H) (-CH=CH-), 6.764 - 8.412, Multiplet (10H) (Ar-H).

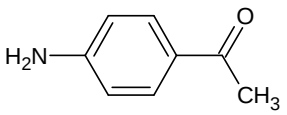
Preparation of 6, 8-dibromo-3-{4-[5-(substitutedphenyl)-4, 5-dihydro-pyrazol-3-yl] phenyl}-2-methyl quinazolin-4-one (KS-3a-3j)

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 recrystallised from ethanol. **^{1}HNMR (DMSO); (KS-3a):** 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-3g):** 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-3f (cm^{-1}):** 3379 (>NH-), 3269 (-OH), 3029 (=C-H), 2965 (-C-H Stretching), 1671 (>C=O Streching), 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-3i (cm^{-1}):** 3357 (>NH-), 3087 (=C-H), 2906 (-C-H Stretching), 1662 (>C=O Streching), 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).

Reaction Scheme



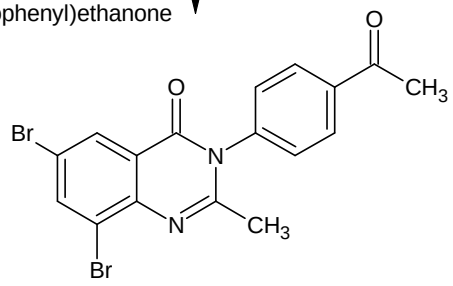
6,8-dibromo-2-methyl-3,1-benzoxazin-4-one



1-(4-aminophenyl)ethanone

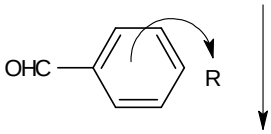
glacial acetic acid

Reflux for 4 hours



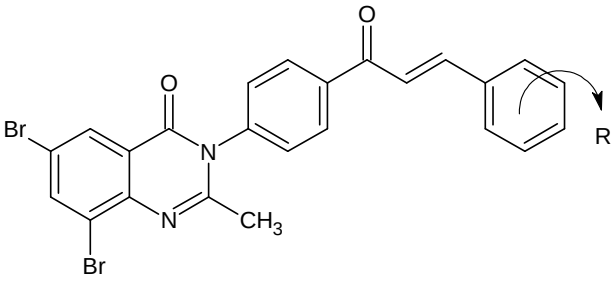
KS-1

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



Ethanol

Reflux for 10 hours



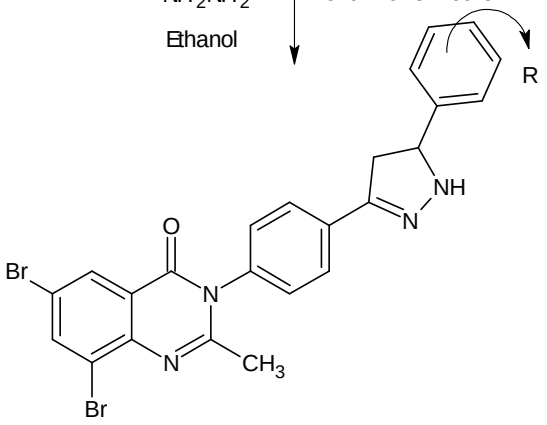
KS-2a-2j

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

NH_2NH_2

Ethanol

Reflux for 3 hours



KS - 3a-3j

6,8-dibromo-3-{4-[5-(substitutedphenyl)-4,5-dihydro-pyrazol-3-yl]phenyl}-2-methylquinazolin-4-one

Table No. 1: Physical constant of 6, 8 dibromo-3-{4-[5-(substitutedphenyl)-4, 5-dihydro-pyrazol-3-yl]phenyl}-2-methylquinazolin-4-one.

1	Sub. No.	R	M.F.	Mol.Wt (g/m)	Yield %	M. P. ^{0}C	% Carbon		%Nitrogen		% Hydrogen	
							Found	Calcd	Found	Calcd	Found	Calcd
1	3a	-2-Cl	$C_{24}H_{17}Br_2ClN_4O$	572.67	75	180	50.31	50.33	9.75	9.78	2.94	2.99
2	3b	-4-Cl	$C_{24}H_{17}Br_2ClN_4O$	572.67	84	230	50.31	50.33	9.74	9.78	2.94	2.99
3	3c	-3,4-$(OCH_3)_2$	$C_{26}H_{22}Br_2N_4O_3$	598.28	72	145	52.20	52.20	9.31	9.36	3.70	3.71
4	3d	-H	$C_{24}H_{18}Br_2N_4O$	538.23	69	150	53.55	53.56	10.41	10.41	3.35	3.37
5	3e	-2-OH	$C_{24}H_{18}Br_2N_4O_2$	554.23	78	170	52.01	52.01	10.11	10.11	3.24	3.27
6	3f	-4-OH-3-OCH_3	$C_{25}H_{20}Br_2N_4O_3$	584.25	70	183	51.32	51.39	9.53	9.59	3.44	3.45
7	3g	-4-OH	$C_{24}H_{18}Br_2N_4O_2$	554.23	65	202	52.00	52.01	10.11	10.11	3.25	3.27
8	3h	-4-$N(CH_3)_2$	$C_{26}H_{23}Br_2N_5O$	581.30	80	134	53.71	53.72	12.00	12.05	3.96	3.99
9	3i	-4-OCH_3	$C_{25}H_{20}Br_2N_4O_2$	568.25	63	149	52.84	52.84	9.85	9.86	3.51	3.55
10	3j	-3-NO_2	$C_{24}H_{17}Br_2N_5O_3$	583.23	75	171	49.40	49.42	12.01	12.01	2.93	2.94

Table No. 2: Antimicrobial activity of 6, 8 dibromo-3-{4-[5-(substitutedphenyl)-4, 5-dihydro-pyrazol-3-yl]phenyl}-2-methylquinazolin-4-one.

SR. NO.	COMP. NO.	R	Zone of Inhibitions in mm			
			S. aureus	E.coli	Aspergillue niger	Saccharomyces
1	3a	2-Cl	25	28	19	22
2	3b	4-Cl	28	26	18	20
3	3c	-3,4-$(OCH_3)_2$	28	35	23	16
4	3d	-H	23	27	18	15
5	3e	-2-OH	15	26	NA	18
6	3f	-4-OH-3-OCH_3	28	26	20	19
7	3g	-4-OH	33	25	19	12
8	3h	-4-$N(CH_3)_2$	27	29	17	18
9	3i	-4-OCH_3	28	26	10	19
10	3j	-3-NO_2	NA	29	18	15
11	Streptomycin	-	30	30	-	-
12	Fluconozole	-	-	-	20	21

Antibacterial activity

Biological evaluation of present investigation revealed maximum antibacterial activity was shown by the compound 3g against aureus and 3c against E. coli which showed good anti-bacterial activity than the respective standard test-drug also. Poor antibacterial activity was shown by the compounds 3e against S. aureus and 3g against E. coil. KS-3j was found to be inactive against Staphylococcus aureus.

Antifungal activity

From screening results, compound 3c and 3a were found to possess maximum antifungal activity against Aspergillue niger and Saccharomyces respectively. The minimum antifungal

activity was shown by the compound KS-3i and 3g for Aspergillue niger and Saccharomyces respectivel. 3e was found to be inactive against Aspergillue niger.

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 IR and ^{1}H-NMR. In conclusion, in present we prepared a series of 6, 8 dibromo-3-{4-[5-(substitutedphenyl)-4, 5- dihydro-pyrazol-3-yl]phenyl}-2-methylquinazolin-4-one based derivatives. Over all evaluation of the synthesized (3a-3j) 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 Fluconozole respectively.

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