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SYNTHESIS OF NEW AZETIDINONE DERIVATIVES CONTAINING QUINAZOLINONE MOIETY AND THEIR UTILISATION AS ANTIFUNGAL ACTIVITY

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ABSTRACT

2-methyl-4H-benzo[d][1,3]oxazin-4-one derivatives (1) is made by the reaction of amino acid and $(CH_3CO)_2O$. It preformed the heating Reaction. Compound 2 was synthesized from 2-amino phenol and then reacted with acetic acid and bromine gave compound 3. Compound 3 was converted in compound 4 by the reaction of hydrazine. Compound 4 on condensation with aromatic aldehydes gave Schiff base and then reacted with chloroacetyl chloride to give azetidinones. Newly synthesized compounds were confirmed by TLC using, and newly synthesis molecules's structures were confirmed by the elemental analysis (carbon, hydrogen and nitrogen), IR and ^{1}HNMR spectral data and also these synthesized compounds work evaluated for their biological antifungal activity against candida albicans, candida albicans ATCC, candida krusei. Among the synthesized compounds, compounds containing chloro substituent have shown significance antifungal activity.

KEYWORDS: benzoxazinone, quinazolinone, azetidinone, antifungal activity.

INTRODUCTION

Quinazolinone derivatives are used for medicine because it possesses the various biological activities. It is nitrogen containing heterocyclic compound displaying affectivity in biologically and pharmaceutical activities, like antibacterial,[1] antifungal,[2] antimicrobial,[3-4] anti inflammatory,[5-6] anticonvulsant[7-8] and anticytotoxic[9] etc. Azetidinone ring have a special feature of beta lactam antibiotics, found in penicillins, nocardicins and cephalosporins etc. It has been found that azetidinone derivatives showed broad spectrum of biological activities such as antimicrobial,[10] antibacterial,[11] antidepressant[12] antifungal[13-15] anticonvulsant.[16-17] Recently many researchers have synthesized quinazolinone derivatives with azetidinone derivatives and tested for their antifungal activity. Therefore, from these observations we thought to synthesize new heterocyclic compounds having quinazolinone and azetidinone moiety with hope potential antifungal activity. Finally, we have synthesized new quinazolinones which was checked biologically activity as various type of fungal spices.

MATERIAL AND METHODS

Essential solvent was used in ordinary form. Melting point of desire form was checked, confirm using simple tube of Capillary, real form of desire compound was visualize and checked in form of percentage proportion, C (carbon), H (hydrogen), N (nitrogen) are notify &Explain with the help of (ELMER-PERKIN-2400)-apparatus. IR portion which so shifting of peaks is recorded "-apparatus BACHMAN spect." unit use for it is cm^- . Proton (^{1}H) NMR data and value are recorded with the help of apparatus use ie (-BRUCKER -300 – DPX MHz)- The newly syntheses desire molecules show fig .- I scheme

DISCUSSION AND RESULTS

Chemistry

Formation of (2-methyl-4h-benzo [d][1,3] oxazin-4-one) (1): Organic compound Anthranillic (1 gram , 0.01mol) was transfered into 100 ml beaker and make a mixture by adding acetic anhydride (1 mil , 0.01 mol) its portion drop to drop slowly with continuously shaking it for 10 min. Heat was evolved in this reaction. This reaction mixture was put in refrigerator for 10 min then reflux on oil bath. The reaction was monitored for desire form of molecules with help of TLC using silica gel. Dichloromethane was used as eluent. It was filtered, washed with cool H_2O. The final product was dried in open air to give white crystalline solid compound 1. The physical as well as data of spectra portion is mention 1, 2 table.

Formation of 3-(2-hydroxy phenyl)-2-methylquinazolin-4(3h)-one (2) Take the compound 1 (1.61gram, 0.01 mol) and transfered into RBF of 250 ml and added 8 ml of ethyl alcohol then reaction mixture was shaked it for some as or 6 min at normal temp then transferred 2-amino phenol (1.09 gram, 0.01 mol). The reaction mixture reflux on oil bath about 6h. Progress of reaction was recorded by (silica) TLC by using toluene and ethyl

acetate solution as eluent in 4:1 ratio. It was visualise in iodine chamber. After completion, it put for some time to decrease the temp now it cooled, filtered & washed with distilled H_2O. It is dried and obtained compound 2. The physical & other properties, spectral record are represented - table 1 and 2.

Formation of 2-(Bromomethyl)-3-(2-hydroxyphenyl) quinazolin-4-(3H)-one (3):
Bromine (0.02mol) was added dropwise in acetic acid (20 ml) and stirred it for 2h. This portion of Sol^n poured into the portion of compound 2 (0.01mol). Cooled this mixture in cold water then kept it for overnight. The optimum desire product was filtered, washed & recrystalised from absolute.ethanol .The physical, other properties and spectral records are represented in table 1 and 2.

Formation of 2-(Hydrazinylmethyl)-3-(2-hydroxyphenyl) quinazolin-4 (3H) -one (4) Take the sol^n of comd. 3 (0.01 mol) poured it into beaker and $NH_2NH_2.H_2O$ (0.01mol) was transferred in it, then warmed, heated and refluxed on a soft heating condition i.e (water bath) for 12 h. The mixture was poured into a beaker containing ice-cold water and kept it for overnight. Desire product was filtered, washed with very low temp or cold water. It was recrystallized through ethanol to yield compound 4. Physical, spectra & other properties are represented in table 1 and 2.

General process for formation of "2-((2-(substitutedbenzylidene)hydrazinyl)methyl)-3-(2-hydroxyphenyl) quinazolin-4(3H)-one" (5-8) :

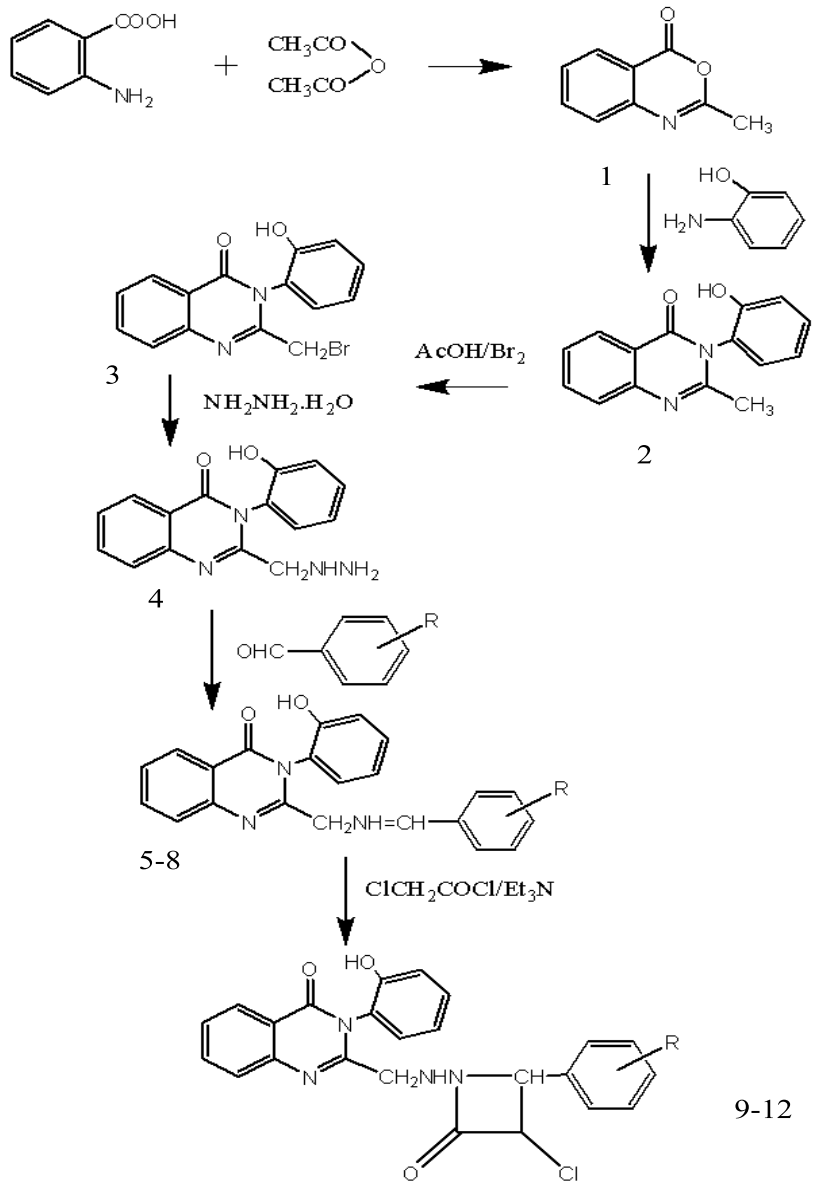
Arylaldehyde (0.02 mol) and 2-3 drops of acetic acid was added to a 100 ml beaker which contained 4 (0.01 mol) in ethanol (20 ml) and heated and refluxed it about 12h. Product was filtered, washed with petroleum ether & recrystallised using suitable solvent to give compd. 5-8 respectively. The physical as well as spectral data of compd are given in table 1 – 2.

General process for synthesis of 2-((3-Chloro-2-(4-chlorophenyl)-4-oxoazetidine-1-ylamino) methy)-3-(2-hydroxyphenyl) quinazolin-4(3H)-one (9-12)

Take the reagent 4 in a beaker100 (0.01 mol) and make a So^n into ethanol (25 mil) then added 2-3 drops of triethyl amine & chloroacetyl chloride (0.02 mol) I the form of drop to drop, slowly with stirring then reflux it 2h. The resulting mixture was cooled, filtered & recrystallised from appropriate solvent to give compound 9-12 respectively. Recorded properties and data are recorded in table 1-2.

Table: 1. Physical and analytical data of compounds 1-12.

Compound no	R group and position	Molecular formula	mp in ^{0}C	Yield	Recrystalised solvent	Elemental Analysis					
						%C		%H		%N	
						Calcd	Found	Calcd	Found	Calcd	Found
1		$C_9H_7NO_2$	79	70	Ethanol	67.07	67.09	4.38	4.40	8.69	8.66
2		$C_{15}H_{12}N_2O_2$	183	75	Methanol	71.42	71.46	4.79	4.76	11.10	11.08
3		$C_{15}H_{11}BrN_2O_2$	190	73	Ethanol	54.40	54.43	3.35	3.39	8.46	8.49
4		$C_{15}H_{14}N_4O_2$	174	68	Ethanol	63.82	63.86	5.00	5.03	19.85	19.82
5	H	$C_{22}H_{18}N_4O_2$	189	66	Methanol	71.34	71.31	4.90	4.87	15.13	15.16
6	4- OH	$C_{22}H_{16}N_4O_3$	198	63	Ethanol	68.38	68.40	4.70	4.72	14.50	14.52
7	4-Cl	$C_{22}H_{17}Cl\ N_4O_2$	212	57	Ethanol	65.27	65.29	4.23	4.27	13.84	13.88
8	4-Br	$C_{22}H_{17}BrN_4O_2$	203	53	Methanol	58.81	58.84	3.81	3.84	12.47	12.50
9	H	$C_{24}H_{19}ClN_4O_3$	218	51	Ethanol	64.50	64.54	4.29	4.26	12.54	12.51
10	4- OH	$C_{24}H_{19}ClN_4O_4$	225	48	Methanol	62.27	62.30	4.14	4.18	12.10	12.14
11	4-Cl	$C_{24}H_{18}Cl_2N_4O_3$	215	50	Ethanol	59.89	59.85	3.77	3.80	11.64	11.60
12	4-Br	$C_{24}H_{18}BrClN_4O_3$	238	45	Ethanol	54.82	54.80	3.45	3.48	10.66	10.69



SCHEME - 1

Table 2 Spectral data of compounds 1-12.

Comp. No.	IR (KBr) ν_{max} in cm^{-1}	^{1}HNMR($CDCl_3$ + DMSO-d_6) δ in ppm
1	3110 (CH phenyl), 1740 (-C=O), 1685 (-C=N), 1600 (-C-C of phenyl), 1350 (-C-N)	7.51-8.45 (m, 4H, Ar-H), 2.76 (s, 3H, $-CH_3$
2	3427(-OH), 3115 (-CH phenyl), 1744 (-C=O), 1680 (-C=N), 1605 (-C-C of phenyl), 1355 (-C-N)	12.40 (s, 1H, OH), 7.52-8.47 (m, 8H, Ar-H), 2.78 (s, 3H, $-CH_3$
3	3430(-OH), 3114 (CH phenyl), 1742 (C=O), 1689 (-C=N), 1607 (-C-C of phenyl), 1353 (C-N), 620 (-C-Br)	12.44 (s, 1H, OH), 7.50-8.42 (m, 8H, Ar-H), 3.35 (s, 2H, CH_2)
4	3429(-OH), 3116 (CH phenyl), 1746 (C=O), 1685 (-C=N), 1610 (-C-C of phenyl), 1356 (C-N), 1280 (N-N)	12.42 (s, 1H, -OH), 7.53-8.44 (m, 8H, Ar-H), 7.10 (2H, NH_2), 6.20 (s, 1H, -NH), 3.39 (s, 2H, $-CH_2$)
5	3424(-OH), 3113 (CH phenyl), 1745 (C=O), 1689 (-C=N), 1608 (-C-C of phenyl), 1351 (C-N)	12.48 (s, 1H, -OH), 7.55-8.49 (m, 13H, Ar-H), 6.25 (s, 1H, -NH), 5.50 (s, 1H, CH-phenyl), 3.32 (s, 2H, $-CH_2$)
6	3430(-OH), 3118 (CH phenyl), 1748 (C=O), 1687 (-C=N), 1604 (-C-C of phenyl), 1360 (C-N)	12.47 (s, 2x 1H, -OH), 7.51-8.43 (m, 12H, Ar-H), 6.28 (s, 1H, -NH), 5.55 (s, 1H, CH-phenyl), 3.30 (s, 2H, $-CH_2$)

7	3423(-OH), 3112 (CH phenyl), 1743 (C=O), 1685 (-C=N), 1600 (-C-C of phenyl), 1352 (C-N), 765 (-C-Cl)	12.45 (s, 1H, -OH), 7.54-8.45 (m, 12H, Ar-H), 6.27 (s, 1H, -NH), 5.53 (s, 1H, CH-phenyl), 3.40 (s, 2H, $-CH_2$)
8	3426(-OH), 3110 (CH phenyl), 1740 (C=O), 1688 (-C=N), 1605 (-C-C of phenyl), 1350 (C-N), 624 (-C-Br)	12.41 (s, 1H, -OH), 7.58-8.46 (m, 12H, Ar-H), 6.23 (s, 1H, -NH), 5.59 (s, 1H, CH-phenyl), 3.38 (s, 2H, $-CH_2$)
9	3427(-OH), 3118 (CH phenyl), 1747 (C=O), 1682 (-C=N), 1606 (-C-C of phenyl), 1357 (C-N), 765 (-C-Cl)	12.46 (s, 1H, -OH), 7.56-8.48 (m, 13H, Ar-H), 6.29 (s, 1H, -NH), 5.54 (s, 1H, CH-phenyl), 4.60 (s, 1H, CH-Cl), 3.39 (s, 2H, $-CH_2$)
10	3434(-OH), 3114 (CH phenyl), 1741 (C=O), 1685 (-C=N), 1607 (-C-C of phenyl), 1352 (C-N), 764 (-C-Cl)	12.42 (s, 2x 1H, -OH), 7.51-8.47 (m, 12H, Ar-H), 6.25 (s, 1H, -NH), 5.58 (s, 1H, CH-phenyl), 4.64 (s, 1H, CH-Cl), 3.32 (s, 2H, $-CH_2$)
11	3429(-OH), 3119 (CH phenyl), 1743 (C=O), 1680 (-C=N), 1609 (-C-C of phenyl), 1356 (C-N), 768 (-C-Cl)	12.47 (s, 1H, -OH), 7.50-8.40 (m, 12H, Ar-H), 6.23 (s, 1H, -NH), 5.52 (s, 1H, CH-phenyl), 4.63 (s, 1H, CH-Cl), 3.33 (s, 2H, $-CH_2$)
12	3423(-OH), 3112 (CH phenyl), 1740 (C=O), 1683 (-C=N), 1604 (-C-C of phenyl), 1350 (C-N), 765 (-C-Cl)	12.48 (s, 1H, -OH), 7.51-8.44 (m, 12H, Ar-H), 6.20 (s, 1H, -NH), 5.56 (s, 1H, CH-phenyl), 4.68 (s, 1H, CH-Cl), 3.37 (s, 2H, $-CH_2$)

Pharmacological Studies

These formatted desire products were tested for their antifungal properties. Effects of unknown compounds were compared with the standard drug fluconazole. Antifungal activity was performed against Candida albicans, Candida albicans ATCC and Candida krusei. Antifungal activity was assured by standard agar disc diffusion method.[18]

Compounds 2-12 were tested for their antifungal activity. Effects of these desire compd. were compared and tested with the reference fluconazole. Antifungal activities of desire molecules were given in table 3. Compounds 2-4 exhibited mild antifungal activity. Incorporation of different aromatic aldehydes to NH_2 linkage of substituted quinazolidinones yielded compounds 5-8. These compounds have shown moderate antifugal activity. Cyclization of compounds 5-8 with chloroacetylchoride yielded azetidinones 9-12 increased the antifungal activity. Compound 11 exhibited better activity than standard drug.

Table 3 Antifungal activity of compounds 2-12.

Compounds	R	fungal inhibition zone/mm		
		C. albicans	C. albicans ATCC	C. krusei
2		3	-	4
3		-	5	-
4		8	8	6
5	H	10	09	8
6	4-OH	14	13	10
7	4-Cl	20	16	13
8	4-Br	18	17	10
9	H	22	14	12
10	4-OH	25	19	14
11	4-Cl	30	25	21
12	4-Br	27	23	17
Fluconazole		29	25	19

CONCLUSION

New heterocyclic compounds were synthesized and characterized by elemental and spectral analysis. These compounds were tested for antifungal activity. Compounds 2-8 exhibited mild to moderate antifungal activities. Cyclization of compounds 5-8 into their corresponding azetidinone congeners 9-12 markedly enhanced the antifungal activities.

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