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Derivatives of Novel Pyrazolines and their Design, synthesis and Microbiological Activities

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ABSTRACT
Title compounds have been prepared by reaction of 3-(2-hydroxy-4-benzyloxy-3-methylphenyl)-5-(substituted phenyl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide of type have been under taken by the reaction of chalcone with thiosemicabazide in ethanol. The structural assignment of the compounds was based on elemental analysis and IR, 1H NMR, 13C NMR and LC Mass spectral data. All the synthesized compounds have been screened for their antimicrobial activity to gram-positive and gram-negative bacterial strains and antifungal activity. The antimicrobial activities of the synthesized compounds have been compared with standard drugs like Amoxycillin and Griseofulvin. Purity of synthesized compounds have been checked by TLC.
Keywords : Chalcone, Thiosemicabazide, Pyrazoline, Antimicrobial

I. INTRODUCTION

Pyrazoline having unique class of nitrogen containing five members heterocyclic compounds. Literature survey let us know that they are endowed with wide range of pharmacological activities such as antimicrobial [1-3], anti-oxidant [4] anti-cancer [5-6], anti-convulsant [7], anti-tubercular [8], MAO inhibitors [9], and cardio vascular [10] properties of heterocyclic ring such a pyrazoline [11-13]. etc. In the light of these facts, it was contemplated to synthesize some novel pyrazoline derivatives. In the present investigation 1-[4-benzyloxy-2-hydroxy-3-methyl phenyl]-3- (substituted phenyl) prop-2-en-1-one have been prepared by the Claisen-Schmidt condensation of 1-(4-benzyloxy-2- hydroxy-3-methyl phenyl) ethanone and various substituted aromatic aldehyde by known literature method. Their structures were established and discovered by elemental and spectral study. The desired 3-(2-hydroxy-4-benzyloxy-3-methylphenyl)-5-(substituted phenyl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide of type (3a-j) were prepared by condensation of 1-[4-benzyloxy-2-hydroxy-3-methyl phenyl]-3-(substituted phenyl) prop-2-en- 1-one with semicarbazide in ethanol. **(Reaction scheme)**.

ANTIMICROBIAL ACTIVITY

Each synthesized compounds were screened for their in *vitro* antibacterial activity by broth dilution method [14,15] and evaluated MIC against gram positive bacterial strains *Staphylococcus aureus* [MTCC 96], *Streptococcus pyogenes* [MTCC 442] and gram negative bacterial strains *Escherichia coli* [MTCC 443], *Pseudomonas aeruginosa* [MTCC 1688] at a concentration of *6.25 µg/ml*. The compounds were also screened for their anti-fungal activity and evaluated MIC against *Aspergillus niger* [MTCC 282] at a concentration of *6.25 µg/ml.* The MIC values of synthesized compounds were compared with standard drugs like Gentamycin and K.Nystatin. The minimal inhibitor concentrations (MIC) of synthesized compounds are represented in Table-1.1

II. EXPERIMENTAL

All the melting points were measured by open capillary method and are uncorrected. The IR absorption spectra (ν max in cm^{-1}) were recorded on a Shimadzu FTIR 8400 Spectrophotometer, ^{1}H NMR (δ ppm) and C^{13} NMR spectra were recorded on a BRUKER (300 MHz) Spectrometer using TMS as internal standard. LC Mass spectra analysis performed on Agilent Technologies / 6120 quadrupole LCMS.

Preparation of 3-(2-hydroxy-4-benzyloxy-3-methylphenyl)-5-(substituted phenyl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide [3a-j]: In the solution of 1-[4-benzyloxy-2-hydroxy-3-methyl phenyl]-3-(2,3,4 trimethoxyphenyl)-prop-2-en-1-one (0.01mol) in 50 ml ethanol was stirred at room temperature. semicarbazide (0.01mol) was added drop wise at room temperature then reaction mixture was put for refluxed for 8-10 hours. The reaction mechanism was monitored by continuous TLC method. After complies of reaction, the reaction mixture was poured in to water and it was kept for 24 hours. Resulting the solid obtained was filtered, washed with water, it dried and crystallized from methanol to give white needles. Similarly other **3-(2-hydroxy-4-benzyloxy-3-methylphenyl)-5-(substituted phenyl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide** [3a-j] were prepared. The physical data are recorded in Table No: 1

Spectroscopic data of synthesized compounds: IR (KBr) cm^{-1} 2d: 1533 absorption peack (C=N,pyrazoline), 1210(CN pyrazoline), 1412,1438 (-CO-NH2.), 1275-1200 (C-O-C) stretching symmetric range 1275-1200 and asymmetric range 1089-1020, 3469(Ar-OH str.).

^{1}H NMR (δ ppm) 2a: 2.13(s,3H,CH3), 3.1 (dd,1H,CH2A), 3.85 (dd,1H,CH2B),5.15(-OCH2 C6H5) ,10.45(s,OH), 6.57(s,-NH2),7.157-7.7.588(m,4H,Ar-H).

^{13}C NMR (CDCl3) δ ppm (2b): 111.727(C-1), 158.312(C-2), 119.926(C-3), 159.304(C-4), 110.139(C-5), 128.61(C-6), 151.57(C-7,pyrazoline), 40.318(C-8,pyrazoline), 61.233(C-9, pyrazoline),172.312(C-10,N-CS-NH2),137.524(C-11), 134.659(C-12), 130.115(C-13), 126.069 (C-14), 124.851(C-15), 127.927(C-16), 70.081(C-17, -OCH2 C6H5), 141.297(C-18), 127.926(C-19, 23), 129.547(C- 20, 22), 127.967(C-21), 9.614(C-24, -CH3), 24.61 (C-25, -CH3).

LC Mass m/e 2e: 401,385(M+2).

III. RESULT AND DISCUSSION

Spectral Result and Discussion: IR spectra of compound 2d showed absorption peak at 1533 cm-1,which is a characteristics of -C=N. Pyrazoline showed sharp band at 1210 cm^{-1} due to C-N stretching vibration. Appearance of stretching band at 2839 cm-1 have been assigned to –CH2 ring of the pyrazoline ring. It was also observed -CH deformation of pyrazoline at 752 cm^{-1}. IR spectra of -4, 5-dihydro-1*H*-pyrazole-1-carboxamide showed C=O stretching vibration at 1614 cm^{-1} and amine stretching showed at 3413 and 3241 respectively. Ar-OH str. showed at 3494 cm^{-1} The PMR spectrum of compound 2a showed first doublet of doublet of HA at C4 was discernible at 3.121 δ ppm, signal due to HB also resonated as doublet of doublet at around at 3.862 δ ppm. Signal showed up as a doublet of doublet at 5.81 δ ppm attributed HX. The N-C=O-NH2 group exhibited as singlet at 6.491 δ ppm. Hydroxyl group displayed at 11.47 δ ppm. Singlet of OCH2 C6H5 attributed at 5.81 δ ppm. In 13C NMR spectra of the compound 2b three carbons of the pyrazoline ring were resonated at 152.965 δ ppm (C-

7), 41.518 δ ppm (C-8), 141.812 δ ppm (C-9). N-C=O-NH2 of pyrazoline ring displayed at 172.312 δ ppm (C-10).The signal of carbon detected at 8.614 δ ppm (C-24), 20.618 δ ppm (C-25) were assignable to methyl group at phenyl ring. Signal appeared at 71.966 δ ppm (C-17) attributed -OCH2 C6H5. The LC mass spectra of compound 2e showed strong molecular ion peak at 486 *m/e* and 387.9 (M+2).

Biological Result and Discussion: All the synthesized compounds (3a-j) were screened for their antibacterial and anti-fungal studies. Compound 3d, f with methoxy substituant exhibited excelent activity against *S- S.aureus* and good activity was shown against *S.pyogenes.* Compound 3b shows moderate activity against gram positive strain *S.aureus* and gram negative bacteria *E.coli.* Compound 3e showed good activity and Compound 3h showed moderate activity against gram negative strains *P.aeruginosa.* compound 3d,f,j substituted with methoxy exhibited good activity against *E.coli.* All the synthesized compounds (3a-j) were screened for their antifungal activity. The observations of screening data suggest that the test compound 3i with methoxy substituted phenyl nucleus exhibited excellent activity against *A. niger*.

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V. REACTION SCHEME

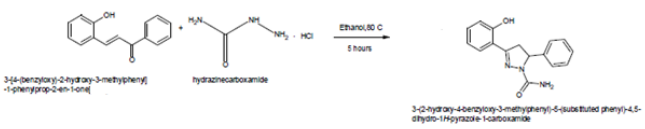

Table-1. Synthesis of 3-(2-hydroxy-4-benzyloxy-3-methylphenyl)-5- (substituted phenyl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide

No	-R	Molecular Formula(M.W)	Mp °C	R_f	% of Yield	% of C (Cal) Found	% of H (Cal) Found	% of Cl (Cal) Found	% of N (Cal)Found
3a	-H	$C_{24}H_{23}N_3O_3$ (401.45)	175	0.58	61	71.80	5.77	-	10.47
						71.83	5.75	-	10.45
3b	-2 CH_3	$C_{25}H_{25}N_3O_3$ (415.48)	230	0.62	60	72.27	6.06	-	10.11
						72.31	6.07	-	10.14
3c	-4 CH_3	$C_{25}H_{25}N_3O_3$ (415.48)	203	0.35	62	72.27	6.06	-	10.11
						72.31	6.08	-	10.14
3d	3,4,5-(OCH_3)	$C_{27}H_{29}N_3O_6$ (491.53)	115	0.51	70	65.97	5.95	-	8.55
						65.98	5.94	-	8.53
3e	2,4 di-Cl	$C_{24}H_{21}Cl_2N_3O_3$ (470.34)	218	0.55	71	61.29	4.50	15.08	8.93
						61.31	4.53	15.10	8.90
3f	2,4,6-	$C_{27}H_{29}N_3O_6$	152	0.54	68	65.97	5.95	-	8.55

	(OCH_3)	(491.53)				65.94	5.92	-	8.51
3g	2-Cl	$C_{24}H_{22}ClN_3O_3$ (435.90)	211	0.47	64	66.13	5.09	8.13	9.64
						66.11	5.11	8.12	9.71
3h	3-Cl	$C_{24}H_{22}ClN_3O_3$ (435.90)	220	0.37	68	66.13	5.09	8.13	9.64
						66.16	5.10	8.12	9.64
3i	4-Cl	$C_{24}H_{22}ClN_3O_3$ (435.90)	118	0.61	59	66.13	5.09	8.13	9.64
						66.15	5.04	8.17	9.66
3j	2,3,4-(OCH_3)	$C_{27}H_{29}N_3O_6$ (491.53)	112	0.43	65	65.97	5.95	-	8.55
						65.99	5.97	-	8.52

Table-1.1. Antibacterial and Antifungal activities of Synthesis of 3-(2-hydroxy-4-benzyloxy-3-methylphenyl)-5- (substituted phenyl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide

Sr. No.	-R	Bacterial activity Minimal Inhibition Concentrations (MIC) in µg/ml				Fungal activity Minimal Inhibition Concentration (MIC) in µg/ml
		S. aureus MTCC 96	*S. pyogenus* MTCC 443	*E. coli* MTCC 442	*P. aruginosa* MTCC 441	*A. niger* MTCC 282
3.2a	-H	250	500	100	500	500
3.2b	-2 CH_3	100	500	100	500	500
3.2c	-4 CH3	100	250	100	500	>1000
3.2d	3,4,5-(OCH_3)	12.5	25	50	500	100
3.2e	2,4 di-Cl	100	250	250	25	1000
3.2f	2,4,6-(OCH_3)	12.5	25	50	500	500
3.2g	2-Cl	100	100	1000	250	125
3.2h	3-Cl	100	500	1000	50	>1000
3.2i	4-Cl	100	250	1000	500	100
3.2j	2,3,4-(OCH_3)	12.5	25	50	250	>1000
Std. Drug	*Gentamycin*	**0.25**	**0.50**	**0.05**	**1.0**	-
	K.Nystanin	-	-	-	-	**100**

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