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RESEARCH ARTICLE

Synthesis and Biological Activity of Some Novel Phenyl Pyrazoline Derivatives

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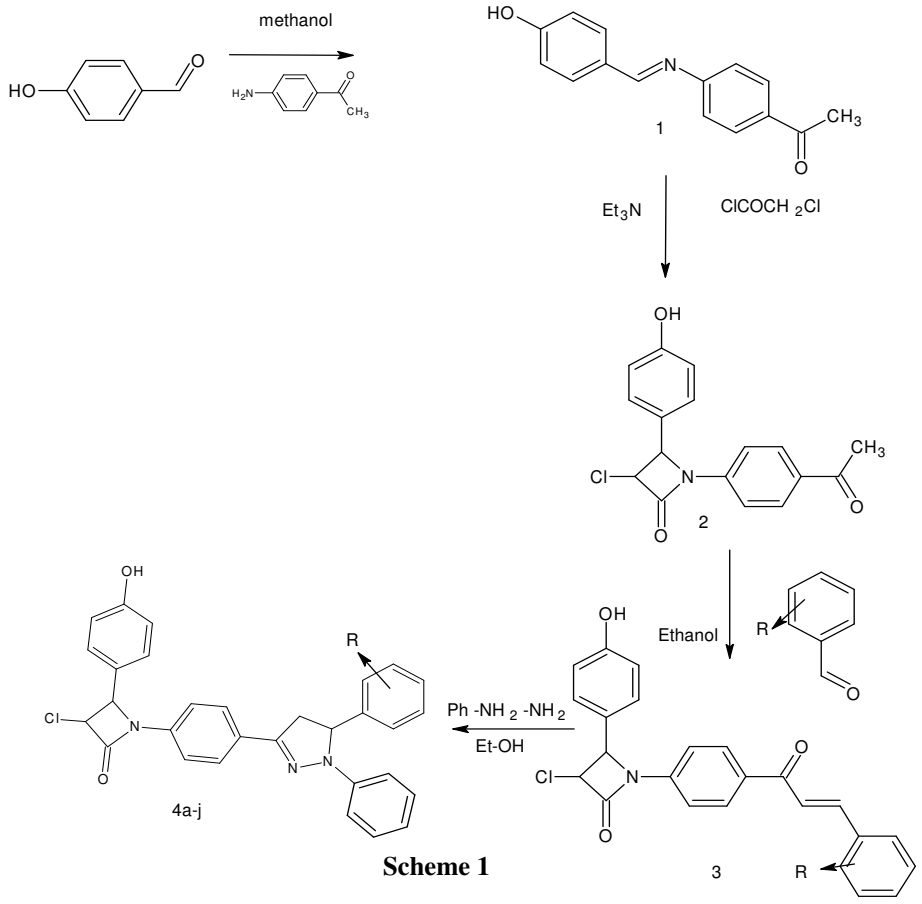
Abstract: A new series of 4-(4-hydroxyphenyl)-3-chloro-1-{4-[5-(substituted phenyl)-1-phenyl- 4,5-dihydro-pyrazol-3-yl]phenyl}azetidin-2-one were synthesized by reacting 3-chloro-1-{4-[3-(substituted-phenyl)prop-2-enoyl]phenyl}-4-(4-hydroxyphenyl)azetidin-2-one (0.01 M) and phenyl hydrazine (0.01 M) in presence of acetic acid (glacial). All these compounds were characterized by means of their IR, ^{1}H NMR, spectroscopic data and microanalysis. All the synthesized products were evaluated for their antimicrobial activity. All the compounds were tested for their antibacterial and antifungal activities by broth dilution method.

Keywords: Chalcones, Phenyl pyrazolines, Azetidin-2-one, Antimicrobial activity

Introduction

Nitrogen and oxygen containing heterocycles play a predominant role in medicinal chemistry and they have been intensively used as scaffolds for drug development. Considerable attention has been focused on pyrazolines and substituted pyrazolines due to their interesting biological activities. To synthesize pyrazoline derivatives, we selected chalcone as starting material. Generally chalcones are 1, 3- diaryl-2-propene-1-ones.

Some substituted pyrazolines and their derivatives have been reported to possess some interesting biological activities such as anticancer[1], insecticidal[2], antibacterial[3], antifungal[4], antidepressant[5-8], anticonvulsant[9-10], anti-inflammatory[11], antibacterial[12] and antitumor[13] properties. Moreover, many selectively fluoro-substituted organic compounds show peculiar pharmacological and agrochemical properties[14-17]. In the present study, the reaction of 3-chloro-1-{4-[3-(substituted phenyl) prop-2-enoyl] phenyl}-4-(4-hydroxyphenyl) azetidin-2-one with phenyl hydrazine in presence of acetic acid (glacial) to form pyrazoline derivatives **4a-j** (Scheme 1). The structures of the various synthesized compounds were assigned on the basis of IR, ^{1}H NMR spectral data and elemental analysis. These compounds were also screened for their antimicrobial activity.



Scheme 1

Experimental

The IR spectra were recorded on IR affinity-1, DRS-8000A, Shimadzu, Ptc. Ltd., Japan spectrophotometer. The ^{1}H-NMR was recorded in DMSO on bruker advance II 400 MHz spectrometer using TMS as an internal standard. Melting points were determined in open capillary tubes and are uncorrected (Table 1). The purity of the compounds was checked by TLC-using silica gel-G (Merck). Column chromatography was performed on silica gel.

*Preparation of 1-(4-{[(4-hydroxyphenyl) methylene] amino} phenyl) ethanone (**1**)*

A mixture of 4-hydroxy benzaldehyde (0.01 M), 1-(4-aminophenyl) ethanone (0.01 M) and methanol (30 mL) was heated for about 5 min. in a beaker (250 mL) to get a clear solution. The solution was kept overnight at room temperature to get the respective crude solid which was recrystallized from ethanol to obtain the pure crystals of 1-(4-{[(4-hydroxy phenyl) methylene]amino}phenyl)ethanone respectively. The yield of the product was 75% and the product melts at 195 ^{0}C. Found: C(75.28%) H(5.45%) N(5.82%) Calcd. for $C_{15}H_{13}NO_2$: C(75.30%) H(5.48%) N(5.85%). IR, cm^{-1}:3385 (-OH), 3040(=C-H), 2920(-C-H), 1676(>C=O), 1647(>C=N-), 1606 (>C=C<), 1363(-CH_3, bend), 1314(-C-N<), 1284(-C-O-), 1240(-C-CO-C-). ^{1}H NMR (DMSO, δ, ppm): 2.5692 (3H, s, $COCH_3$), 6.5277-7.9774 (8H, m, Ar-H), 8.3820 (1H, s, -CH=N-), 9.6392 (1H, s, Ar-OH).

*Preparation of 1-(4-acetylphenyl)-3-chloro-4-(4-hydroxyphenyl) azetidin-2-one (**2**)*

In a 100 mL round bottom flask 1-(4-{[(4-hydroxyphenyl) methylene] amino} phenyl) ethanone (0.01 M) in 70 mL benzene was taken. Chloro acetyl chloride (0.01 M) was added at room temperature with constant stirring and triethylamine 1 mL was added and the reaction mixture was refluxed for 7 hours. After the completion of reaction, solvent was removed by vacuum distillation. The solid was filtered, dried and recrystallized from toluene. The yield of the product was 60% and the product melts at 119 ^{0}C. Found: C(64.64%) H(4.44%) N(4.42%), Calcd. for $C_{17}H_{14}ClNO_3$: C(64.67%) H(4.47%) N(4.44%). IR, cm^{-1}: 3300(-OH), 3050(=C-H), 2950(-C-H), 1680(>C=O), 1600(>C=C<), 1375(-CH_3, bend), 1300(-C-N<), 1240(-C-CO-C-), 1220 (-C-O-), 560(-C-Cl). ^{1}H NMR (DMSO, δ, ppm): 2.5392 (3H, s, $COCH_3$), 4.8954 (1H, d, >CH-Ar), 5.5151 (1H, d, >CH-Cl), 6.6720-8.0745 (8H, m, Ar-H), 9.7784 (1H, s, Ar-OH).

*Preparation of 3-chloro-1-{4-[3-(Substituted phenyl) prop-2-enoyl] phenyl}-4-(4-hydroxyphenyl) azetidin-2-one (**3**)*

To the solution of 1-(4-acetylphenyl)-3-chloro-4-(4-hydroxyphenyl) azetidin-2-one (0.01 M) in absolute ethanol (50 mL), substituted benzaldehyde (0.01 M) and 2% NaOH 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(**3b**), cm^{-1}:3359(-OH), 3045(=C-H), 1728(>C=O), 1608(>C=C<), 1290(-C-N<), 1186 (-C-O-), 759(-C-Cl). ^{1}H NMR (**3c**-DMSO, δ, ppm): 3.8739 (6H, s, -OCH_3), 4.8613 (1H, d, >CH-Ar), 5.403 (1H, d, >CH-Cl), 6.7340-7.8883 (11H, m, Ar-H), 7.9733 (2H, d, -CH=CH-), 9.8306 (1H, s, Ar-OH).

*Preparation 4-(4-hydroxyphenyl)-3-chloro-1-{4-[5-(Substituted phenyl)-1-phenyl-4, 5-dihydro-pyrazol-3-yl] phenyl} azetidin-2-one (**4a-j**)*

A mixture of 3-chloro-1-{4-[3-(substituted phenyl) prop-2-enoyl] phenyl}-4-(4-hydroxyphenyl) azetidin-2-one (0.01 M) and phenyl hydrazine (0.01 M) in acetic acid (30 mL) was refluxed in an oil bath at 110-120 ^{o}C for 4 hours. The reaction mixture was poured over crushed ice; product was isolated and crystallized from ethanol.

IR (**4a**), cm^{-1}: 3362(-OH), 3041(=C-H), 1722(>C=O), 1624 (>C=N), 1529(>C=C<), 1444 (-CH_2-), 1286(-C-N<),1230 (-C-N), 1173 (-C-O-), 688(-C-Cl). ^{1}H NMR (**4j**-DMSO, δ, ppm): 3.8689 (3H, s, OCH_3), 3.6774 (2H, d, CH_2- of Pyrazol), 4.3421 (1H, t, >CH-Ar of Pyrazol), 4.8891 (1H, d, >CH-Ar of Azetidine), 5.2723 (1H, d, >CH-Cl of Azetidine), 6.4416-7.9982 (16H, m, Ar-H, -NH-), 9.2940 (1H, s, Ar-OH).

Results and Discussion

Antimicrobial activity

The MICs of synthesized compounds were carried out by broth micro dilution method as described by Rattan[18]. It is one of the non automated *in vitro* bacterial susceptibility tests. This classic method yields a quantitative result for the amount of antimicrobial agents that is needed to inhibit growth of specific microorganisms.

The *in vitro* antimicrobial activity of test compounds were assessed against 24 h cultures of several selected bacteria and fungi. The bacteria used were *E. coli, S.aureus, P. aeruginosa* and *S. pyogenus*; the fungi used were *C. albicans, A. Niger* and *A.clavatus.*

The antimicrobial activity was performed by broth dilution method in DMSO. Gentamycin, Ampicilin, Chloramphenicol, Ciprofloxacin, Norfloxacin, Nystatin and Greseofulvin were used as standard for the evaluation of antibacterial and antifungal activities respectively. The activity was reported by minimal inhibition concentration. The results are summarized in Tables 2-4.

Table 1. Physical constant of 4-(4-hydroxyphenyl)-3-chloro-1-{4-[5-(substituted phenyl)-1-phenyl-4, 5-dihydro-pyrazol-3-yl] phenyl} azetidin-2-one **(4a-j)**

Compd	R	M.F.	Yield %	M.P. °C	Elemental analysis		
					% C Found Calcd	% N Found Calcd	% H Found Calcd
4a	-2-Cl	$C_{30}H_{23}Cl_2N_3O_2$	72	98	68.14 68.19	7.91 7.95	4.32 4.39
4b	-2-OH	$C_{30}H_{24}ClN_3O_3$	74	174	70.61 70.65	8.20 8.24	4.70 4.74
4c	-3,4-$(OCH_3)_2$	$C_{32}H_{28}ClN_3O_4$	71	158	69.32 69.37	7.52 7.58	5.02 5.09
4d	-3-NO_2	$C_{30}H_{28}ClN_4O_4$	76	165	66.80 66.85	10.32 10.39	4.26 4.30
4e	-4-Cl	$C_{30}H_{23}Cl_2N_3O_2$	69	164	68.15 68.19	7.89 7.95	4.32 4.39
4f	-4-$N(C_2H_5)_2$	$C_{34}H_{33}ClN_4O_2$	72	168	72.20 72.26	9.88 9.91	5.85 5.89
4g	-4-OH	$C_{30}H_{24}ClN_3O_3$	78	158	70.60 70.65	8.19 8.24	4.70 4.74
4h	-4-$N(CH_3)_2$	$C_{32}H_{29}ClN_4O_2$	70	152	71.51 71.57	10.39 10.43	5.39 5.44
4i	CHO	$C_{30}H_{24}ClN_3O_2$	79	195	72.89 72.94	8.48 8.51	4.86 4.90
4j	-2-OH-3-OCH_3	$C_{31}H_{26}ClN_3O_4$	77	95	68.91 68.95	7.72 7.78	4.80 4.85

Table 2. *Antimicrobial activity of 4-(4-hydroxyphenyl)-3-chloro-1-{4-[5-(substituted phenyl)-1-phenyl-4, 5-dihydro-pyrazol-3-yl] phenyl} azetidin-2-one*

Compd	R	Antibacterial Minimal Concentration		Activity Inhibition		Antifungal Minimal Concentration		Activity Inhibition
		E.coli	*P. aeruginosa*	*S.aureus*	*S. pyogenus*	*C. albicans*	*A. niger*	*A. clavatus*
		MTCC 443	MTCC 1688	MTCC 96	MTCC 442	MTCC 227	MTCC 282	MTCC 1323
4a	-2-Cl	100	62.5	100	100	250	>1000	>1000
4b	-2-OH	175	200	175	250	800	700	700
4c	-3-OCH_3, -4-OCH_3	225	225	150	200	>1000	800	600
4d	-3-NO_2	175	225	200	150	700	600	1000
4e	-4-Cl	100	175	100	175	500	>1000	1000
4f	-4-$N(C_2H_5)_2$	125	200	100	100	250	1000	1000
4g	-4-OH	200	250	62.5	125	500	800	800
4h	-4-$N(CH_3)_2$	200	250	125	200	250	1000	1000
4i	-H	175	225	200	125	750	600	800
4j	-3-OCH_3, -4-OH	200	200	225	200	1000	800	>1000

Table 3. Antibacterial activities- Minimal inhibition concentration (The standard drugs)

DRUG	*E.coli*	*P.aeruginosa*	*S.aureus*	*S.pyogenus*
	MTCC 443	MTCC 1688	MTCC 96	MTCC 442
(Microgramme/ML)				
Gentamycin	0.05	1	0.25	0.5
Ampicillin	100	--	250	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	25	25	50	50
Norfloxacin	10	10	10	10

Table 4. Antifungal activity- Minimal inhibition concentration (The standard drugs)

DRUG	*C.albicans*	*A.niger*	*A.clavatus*
-	MTCC 227	MTCC 282	MTCC 1323
(Microgramme/ML)			
Nystatin	100	100	100
Greseofulvin	500	100	100

Biological screening result of 4-(4-hydroxyphenyl)-3-chloro-1-{4-[5-(Substituted phenyl)-1-phenyl-4, 5-dihydro-pyrazol-3-yl] phenyl} azetidin-2-one based derivatives shows that compound **4a** & **4e** have shown better activity against *E. coli*, while compound **4a** & **4f** have shown better activity against *S. Pyogenus*, while rest of all compound possessed good activity against *S.aureus* in the range of 100-225 µg/mL and *P. Aeruginosa* in the range 62.5-250 µg/mL. Compound **4e** and **4g** is found to be significant antifungal activity against *C. albicans*, while rests of all derivatives are poor against *A. niger* and *A.clavatus*.

Conclusion

The main focus of this research work was to synthesize, characterize and evaluate antimicrobial activities of the newly synthesized phenyl pyrazoline derivatives, structures of synthesized compounds were confirmed and characterized with the help of analytical data's such as IR and ^{1}H-NMR. In summary, we have described the synthesis and antimicrobial activity of novel of 4-(4-hydroxyphenyl)-3-chloro-1-{4-[5-(Substituted phenyl)-1-phenyl-4, 5-dihydro-pyrazol-3-yl] phenyl} azetidin-2-one MIC values revealed that amongst newly synthesized compound having chlorophenyl type linkage has shown good activity against the bacterial strains rest of all compounds exhibit moderate improvement in activity against some of the pathogenic strains.

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