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Synthesis, characterization and antimicrobial activity of some novel chalcones

Shailesh. H. Shah[1&2] and Pankaj. S. Patel*[3]

[1]*Department of Chemistry, Patel JBR Arts, Patel AMR Commerce & Patel JDKD Science College, Borsad*
[2]*JJT University, Rajasthan*
[3]*Department of Chemistry, Sheth LH Science College, Mansa*

ABSTRACT

Chalcone have displayed an impressive array of biological importance. A series of Chalcone were prepared by Claisen-Schmidt condensation from 1-(4-acetylphenyl)-3-chloro-4-(4-hydroxyphenyl) azetidin-2-one with appropriate aromatic aldehydes in the presence of aqueous solution of alkali and ethanol at room temperature. The synthesized compounds were characterized by means of their IR, [1]H-NMR spectral data and elemental analysis. All the compounds were tested for their antibacterial and antifungal activities by broth dilution method.

Key words: Chalcone, azetidin-2-one, Antimicrobial activity.

INTRODUCTION

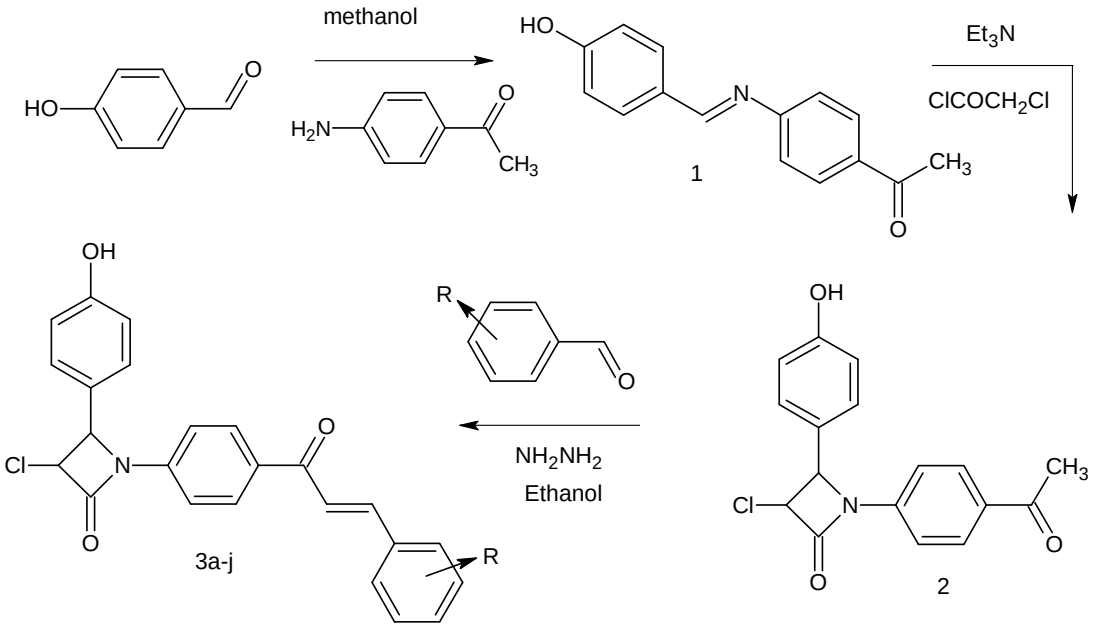
The chemistry of Chalcones generated intensive scientific studies throughout the world, specially interesting for their biological applications. Chalcones are coloured compounds because of the presence of the chromophore and auxochromes. The alternative names given to Chalcones are phenyl styryl ketones, b-phenyl acrylphenone, g-oxo-a,g-diphenyl-apropylene and a-phenyl-b-benzoethylene. The compounds with backbone of Chalcones have been reported to possess various biological activities such as antimicrobial[1], anti-inflammatory[2], analgesic[3], antiplatelet[4], antiulcerative[5], antimalarial[6], anticancer[7], antiviral[8], antileishmanial[9], antioxidant[10], antitubercular[11], antihyperglycemic[12], anti-HIV[13], carboxygenase inhibitor[14], insecticidal[15,16], bactericidal[17,18], fungicidal[19-20], activities. The presence of a reactiveα,β-unsaturated keto function in Chalcones is found to be responsible for their antimicrobial activity. In the present study we report the reaction of 1-(4-acetylphenyl)-3-chloro-4-(4-hydroxyphenyl) azetidin-2-one with different aromatic aldehydes to form Chalcones (3a-j). 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.

MATERIALS AND METHODS

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. The purity of the compounds was checked by TLC-using Silica gel-G (Merck). Column chromatography was performed on silica gel.

Reaction Scheme



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

A mixture of 4-hydroxy benzaldehyde (0.01M), 1-(4-aminophenyl) ethanone (0.01M) and methanol (30ml) 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), 3050(=C-H), 2920(-C-H), 1720(>C=O), 1680(>C=N-), 1600 (>C=C<), 1375(-CH_3, bend), 1325(-C-N<), 1280(-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 100ml Round bottom flask 1-(4-{[(4-hydroxyphenyl) methylene] amino} phenyl) ethanone (0.01M) in 70ml benzene was taken. Chloro acetyl chloride (0.01M) was added at room temperature with constant stirring and triethylamine 1ml 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), 1720(>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).

Table: 1 Physical constant of 3-chloro-1-{4-[3-(2-substitutedphenyl) prop-2-enoyl] phenyl} – 4-(4-hydroxyphenyl) azetidin-2-one

Compd	R	M.F.	Yield %	M.P. °C	Elemental Analysis		
					% C Found (Calcd)	% N Found (Calcd)	% H Found (Calcd)
3a	-2-Cl	$C_{24}H_{17}Cl_2NO_3$	65	218	65.74 (65.77)	3.18 (3.20)	3.89 (3.91)
3b	-2-OH	$C_{24}H_{18}ClNO_4$	72	178	68.62 (68.66)	3.32 (3.34)	4.30 (4.32)
3c	-3,4-$(OCH_3)_2$	$C_{26}H_{22}ClNO_5$	68	118	67.28 (67.31)	3.01 (3.02)	4.75 (4.78)
3d	-3-NO_2	$C_{24}H_{17}ClN_2O_5$	74	230	64.18 (64.22)	6.22 (6.24)	3.80 (3.82)
3e	-4-Cl	$C_{24}H_{17}Cl_2NO_3$	66	245	65.72 (65.77)	3.17 (3.20)	3.89 (3.91)
3f	-4-$N(C_2H_5)_2$	$C_{28}H_{27}ClN_2O_3$	69	278	70.78 (70.80)	5.87 (5.90)	5.72 5.73)
3g	-4-OH	$C_{24}H_{18}ClNO_4$	75	219	68.63 (68.66)	3.33 (3.34)	4.30 (4.32)
3h	-4-$N(CH_3)_2$	$C_{26}H_{23}ClN_2O_3$	67	200	69.83 (69.87)	6.24 (6.27)	5.18 (5.19)
3i	CHO	$C_{24}H_{18}ClNO_3$	78	228	71.35 (71.38)	3.45 (3.47)	4.47 (4.49)
3j	-2-OH, 3-OCH_3	$C_{25}H_{20}ClNO_5$	75	120	66.71 (66.74)	3.09 (3.11)	4.45 (4.48)

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

To the solution of 1-(4-acetylphenyl)-3-chloro-4-(4-hydroxyphenyl) azetidin-2-one (0.01M) in absolute ethanol (50 ml), substituted benzaldehyde (0.01M) 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}:3300(-OH), 3100(=C-H), 1720(>C=O), 1600(>C=C<), 1260(-C-N<), 1180 (-C-O-), 560(-C-Cl). IR(**3j**), cm^{-1}:3350(-OH), 3050(=C-H), 2900(-C-H), 1730(>C=O), 1600(>C=C<), 1370(-CH_3, bend), 1280(-C-N<), 1240(-C-O-), 1070(-C-O-C-), 600(-C-Cl). ^{1}H-NMR (**3c**-DMSO, δ, ppm): 3.8789 (6H, s, -OCH_3), 4.8613 (1H, d, >CH-Ar), 5.3413 (1H, d, >CH-Cl), 6.7340-7.8883 (11H, m, Ar-H), 7.9733 (2H, d, -CH=CH-), 9.8306 (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 Ratan (2000). The invitro antimicrobial activity of test compounds were assessed against 24 hr 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 Table-2.

Table: 2 Antimicrobial activities of 3-chloro-1-{4-[3-(2-substitutedphenyl) prop-2-enoyl] phenyl}–4-(4-hydroxyphenyl) azetidin-2-one

SR. NO.	COMP. NO.	R	ANTIBACTERIAL ACTIVITY MINIMAL INHIBITION CONCENTRATION				ANTIFUNGAL ACTIVITY MINIMAL INHIBITION CONCENTRATION		
			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
1	3a	-2-Cl	200	62.5	200	200	400	1000	1000
2	3b	-2-OH	125	200	200	200	1000	500	500
3	3c	-3-OCH_3, -4-OCH_3	250	225	225	250	1000	700	800
4	3d	-3-NO_2	200	200	200	225	800	500	700
5	3e	-4-Cl	75	125	62.5	175	850	1000	1000
6	3f	-4-$N(C_2H_5)_2$	250	200	125	150	825	1000	1000
7	3g	-4-OH	200	250	200	100	875	1000	900
8	3h	-4-$N(CH_3)_2$	175	225	150	200	500	800	600
9	3i	-H	150	175	150	62.5	600	700	800
10	3j	-3-OCH_3, -4-OH	175	150	250	200	1000	1000	1000

Table: 3Antibacterial Activity: 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 3-chloro-1-{4-[3-(2-substitutedphenyl)prop-2-enoyl]phenyl}-4-(4-hydroxyphenyl)azetidin-2-one based derivatives shows that compound (**3e**) have shown better activity against E. coli, S. aureus, while rest of all compound possessed good activity against S.aureus in the range of 125-250 µg/ml.. Compounds with substitution 4-hydroxy (**3i** and **3g**), shown good antibacterial activity against S. pyogenus , while rest of all derivatives possessed good activity against S. pyogenus in the range of 150-250 µg/ml.Compound (**3a)** and (**3h)** is found to be significant antifungal activity against C. albicans, while rest 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 Chalcone 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 3-chloro-1-{4-[3-(2-substitutedphenyl)prop-2-enoyl]phenyl}-4-(4-hydroxyphenyl)azetidin-2-one MIC values revealed that amongst newly synthesized compound having 4-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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