Indo Global Journal of Pharmaceutical Sciences, 2014; 4(1): 25-28

INDO GLOBAL JOURNAL OF PHARMACEUTICAL SCIENCES
ISSN 2249- 1023

Synthesis & Antifungal Activity of Certain Chalcones & Their Reduction

Navin Kumar Tailor *

Department of Pharmaceutical Chemistry, Manipal College of Pharmaceutical Sciences, Manipal-576104, India

Address for Correspondance: tailor.navin@gmail.com

ABSTRACT: Purpose of this article is find out role of α,β- unsaturated carbonyl functionality on antifungal activity. Claisen–Schmidt condensation reaction and subsequent one stet reduction to tetrahydrochalcones **(7-12)** was done by using sodium formate and 5% Pd/C in methanol at room temperature. Antifungal activity was evaluated by using agar diffusion. Chalcones were more potential than corresponding tetrahydrochalcones. One step reduction by using sodium formate and 5% Pd/C is very efficient method. α,β- unsaturated carbonyl functionality imparts very significant role in antifungal activity.

KEYWORDS: Chalcone; Claisen-Schmidt Condensation; Tetrahydrochalcones; Pd/C, Antifungal Activity.

INTRODUCTION

The synthesis and biological activities of chalcone shows significant position in medicinal chemistry. This pharmacophore has divers class of biological activities. To evaluate the role of reactive α,β–unsaturated ketone group in antifungal activity, it is necessary to screen and compare tetrahydrochalcone with respective chalcones [1-5]. Several catalytic reducing agents have been employed for selective reduction including **palladium/ vinyl acetate, rhodium** (I) complexes, pincer-aryl ruthenium (II) complexes, magnesia, iridium/ formic acid, sodium hypophosphite, **palladium /ethylene atmosphere,** CeO_2-ZnO complex etc [6]. In this article, we highlight on one pot synthesis of tetrahdrochalcones by using sodium formate /5% palladium on carbon in methanol at room temperature. All synthesized test compounds were evaluated for antifungal activity by agar diffusion method. Results indicates that reduction α,β-unsaturated carbonyl moiety imparts reduction in antifungal potential.

MATERIALS & METHODS

Experimental

General

All melting points were measured on Mel-Temp apparatus and were uncorrected. Infrared (FT-IR) spectra were recorded on Shimadzu FTIR 8300 spectrometer. Proton (^{1}H) nuclear magnetic resonance spectroscopy was performed on a Brucker AMX-400 NMR spectrometer, operating at 300 MHz with TMS as internal standard. All chemical shifts were reported as δ (ppm) values. Compounds were also analyzed by GC-MS (QP 5010, Shimadzu Corporation, Japan). All reagents were purchased from Sigma Chemicals, India and were used without further purification. TLC analysis was carried out on aluminum foil precoated with silica gel 60 F254.

Chemistry

***General procedure for the synthesis of chalcone* (1-6)**

4-Hydroxyacetophenone (0.01mole) and p-substituted aromatic aldehyde (0.01 mole), were dissolved in 15 ml of absolute alcohol and potassium hydroxide (0.03 mole) dissolved in min. water was added to the solution. The solution was stirred at room temperature and progress of the reaction was monitored using TLC. After completion of reaction, the reaction mixture was diluted with water (200 ml), and acidified with dilute hydrochloric acid to pH 3. The product obtained was filtered, washed with water, and crystallized from absolute alcohol [7].

***General procedure for the reduction of chalcone* (7-12)**

To a solution of chalcone (0.002mol) in methanol (5ml), sodium formate (0.016 mol) was added, followed by addition

of 5% palladium on carbon (0.30 mol) and reaction mixture was stirred at room temperature. Stirring was continued until no starting material has left as confirmed by TLC. On completion of reaction, the reaction mixture was filtered to remove the catalyst and solvent was removed under reduced pressure. The crude product was purified by column chromatography (30 % EtOAc in hexane) [8].

***4-(1-hydroxy-3-phenylpropyl)phenol* (7)**

Yield: 80%; m.p.: 90-93^{0}C; FTIR (KBr pellet): 3352 (O-H str), 3045 (Ar C-H str), 2972 (C-H str), 1600 (C=O str), 1516, 1458 (Ar C=C str), 1363 (O-H sec.alcohol) ; ^{1}H NMR ($CDCl_3$), : 1.95-2.04 (m, 1H, H of CH_2-C_6H_5), 2.08-2.18 (m, 1H, H of CH_2-C_6H_6), 2.59-2.75 (m, 2H, CH_2 of CH_2-CH), 4.61-4.64 (t,1H, CH), 5.08 (s, 1H,OH), 6.79-6.82 (m, 2H, aromatic), 7.17-7.29 (m, 7H aromatic); m/z (rel.%) 229 (M+1).

***4-[1-hydroxy-3-(4-methylphenyl)propyl]phenol* (8)**

Yield: 78%; m.p.: 110-112^{0}C; FTIR (KBr pellet): 3321 (O-H str), 3092 (Ar C-H str), 2903 (C-H str), 1547 (C=O str), 1398 (O-H sec.alcohol) ; ^{1}H NMR ($CDCl_3$),: 1.93-2.04 (m, 1H, H of CH_2-C_6H_5), 2.05-2.15 (m, 1H, H of CH_2-C_6H_5), 2.31 (s, 3H, CH_3), 2.55-2.70 (m, 2H, CH_2 of CH_2-CH), 4.6-4.63 (t, 1H, CH), 5.01 (s, 1H,OH), 6.78-6.81(m, 2H,aromatic), 7.05-7.25(m, 6H aromatic), m/z (rel.%) 243 (M+1).

***4-[1-hydroxy-3-(4-methoxyphenyl)propyl]phenol* (9)**

Yield: 81%; m.p.: 115-117^{0}C; FTIR (KBr pellet): 3400 (OH str), 3024 (Ar C-H str), 2918 (CH_2 str), 1612 (C=O str), 1514, 1452 (Ar C=C str), 1232 (C-O-C str); ^{1}H NMR ($CDCl_3$), : 1.93-2.03 (m, 1H, H of CH_2-C_6H_5), 2.05-2.14 (m, 1H, H of CH_2-C_6H_6), 2.53-2.68 (m, 2H, CH_2 of CH_2-CH), 3.78 (s, 3H, OCH_3), 4.59-4.62 (t, 1H, CH), 5.21 (s, 1H, OH), 6.72-6.83 (m, 4H,aromatic), 7.02-7.25 (m, 4H aromatic); m/z (rel.%) 259 (M+1).

***4-[1-hydroxy-3-(4-fluorophenyl)propyl]phenol* (10)**

Yield: 69%; m.p.: 127-130^{0}C; FTIR (KBr pellet): 3401 (O-H str), 2992 (Ar C-H str), 2914 (C-H str), 1357 (O-H sec.alcohol); ^{1}H NMR ($CDCl_3$),: 1.91-2.09 (m, 2H, $\underline{C}H_2C_6H_5$), 2.51-2.74 (m, 2H, $\underline{C}H_2CH_2C_6H_5$), 4.57-4.60 (t, 1H, $\underline{C}HCH_2CH_2C_6H_5$), 5.04 (s, 1H, OH), 6.76-7.19 (m, 8H, aromatic), m/z (rel.%) 245 (M+1).

***4-[1-hydroxy-3-(4-chlorophenyl)propyl]phenol* (11)**

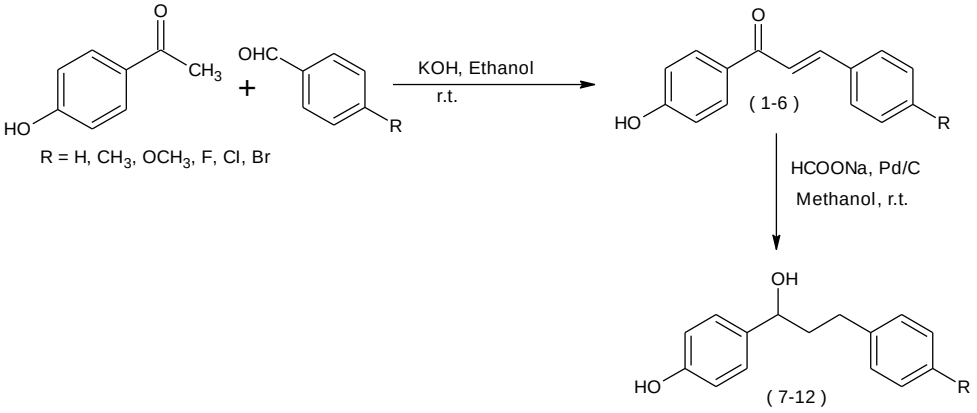
Yield: 73%; m.p.: 125-128^{0}C; FTIR (KBr pellet): 3463 (O-H str), 2897 (Ar C-H str), 2874 (C-H str), 1301 (O-H sec.alcohol); ^{1}H NMR ($CDCl_3$),: 1.85-2.01 (m, 2H, $\underline{C}H_2C_6H_5$), 2.57-2.72 (m, 2H, $\underline{C}H_2CH_2C_6H_5$), 4.52-4.57 (t, 1H, $\underline{C}HCH_2CH_2C_6H_5$), 5.12 (s, 1H, OH), 6.81-7.25 (m, 8H, aromatic), m/z (rel.%) 263 (M+1).

***4-[1-hydroxy-3-(4-bromophenyl)propyl]phenol* (12)**

Yield: 71%; m.p.: 132-135^{0}C; FTIR (KBr pellet): 3348 (O-H str), 2951 (Ar C-H str), 2883 (C-H str), 1312 (O-H sec.alcohol); ^{1}H NMR ($CDCl_3$),: 1.87-2.14 (m, 2H, $\underline{C}H_2C_6H_5$), 2.42-2.57 (m, 2H, $\underline{C}H_2CH_2C_6H_5$), 4.45-4.63 (t, 1H, $\underline{C}HCH_2CH_2C_6H_5$), 5.16 (s, 1H, OH), 6.64-7.01 (m, 8H, aromatic), m/z (rel.%) 305 (M+1).

Antifungal activity

For this screening assay four fungal strains were selected viz. *P. chrysogenum, A. flavus, A. nigar and R. oligospora*. Antifungal activities of synthesized test compounds were carried out by agar diffusion method [9]. Briefly, stock solution (25µg/ml concentration) of synthesized test compounds and standard drugs were prepared in DMSO. Fluconazole was used as standard. 2.4 gm of Potato-Dextrose broth and 2gm of Agar were dissolved in 100 ml distilled water**.** Sterilized at 15 lbs pressure, 121^{0}C for 15 min. The sterilized medium was poured in sterile Petri dishes. Medium was then inoculated by streaking of the fungal culture dipped cotton swab over the entire surface of the plate. After the inoculum was dried, wells (bores) were made on the medium using sterile borer. Then 100µl of the test and standard solutions (25µg/ml concentration) were added to the respective bores. DMSO was used as control. Plates were incubated for 24-48 hr. at 22 ºC to 25 ºC and the antifungal activity was determined by measuring the zone of inhibition.



Scheme-1 Step wise synthesis of chalcones (1-6) and one step reduction to tetrahydrochalcones (7-12).

RESULTS & DISCUSSION

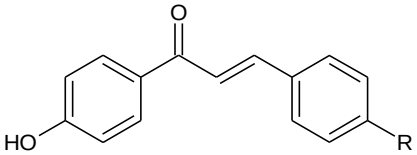
Chemistry

The sequence steps involved in synthesis of 4-substituted chalcone and their one steps reduction corresponding tetrahydrochalcones are shown in scheme-1. Chalcones were synthesized via Claisen–Schmidt condensation. The α,β–unsaturated carbonyl moiety (chalcone) was reduced to corresponding tetrahydrochalcone by using sodium formate and 5% palladium on carbon in methanol at room temperature to produce tetrahydrochalcone **7-12**. Compound **7** was obtained as white crystalline solid in 80 % yield. The FT-IR spectra of compound **7** showed absorption bands at 1363 cm^{-1} confirm the presence of OH group (secondary alcohol). The ^1H NMR spectra of **7** showed broad singlet at δ 5.08, which further confirmed the presence of OH group (secondary alcohol). This peak disappeared in D_2O exchange. The mass spectrum of compound **7** showed peak at m/z 229 (M+1) which confirmed the reduction of both double bond and carbonyl group. The IR spectra of compound **4** & **10** showed C-F stretching at 1150-1100 cm^{-1}. Similarily compound **5** & **11**, **6** & **12** showed C-Cl and C-Br stretching at 800-700 and 700-600 cm^{-1} respectively. The calculated value of the logarithm of the octanol/water partition coefficient (log P) for this compound (3.48) is greater than that of corresponding chalcone (3.2), which indicate enhancement in lipophilicity on reduction of chalcone. The physiochemical date of synthesized chalcones and tetrahydrochalcones are summarized in **Table 1**.

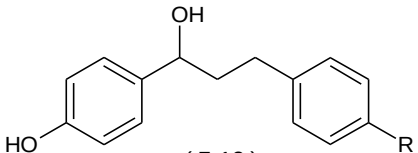
Antifungal activity

Antifungal evaluations of synthesized test compounds were done by Agar diffusion method and are summarized in **Table 2**. Fluconazole was used as standard. They were tested against four species of fungi *P. chrsogenum*, *A. nigar*, *A. fluvus* and *R. oligospora*. Results indicated that reduction in chalconyl functionality cause reduction in antifungal activities.

Table 1. Physical data of chalcones (1-6) and tetrahydrochalcones (7-12).



(1-6)



(7-12)

S.N	Structure	M.W.	m.p.(^{0}C)	%Yield	R_f value	Log P
1	H	224	170-172	70	0.48*	3.20
2	CH_3	238	180-182	65	0.34*	3.68
3	OCH_3	254	190-193	72	0.53*	3.07
4	F	240	175-177	60	0.44*	3.35
5	CI	258	195-198	50	0.34*	4.36
6	Br	300	200-202	70	0.37*	4.02
7	H	228	90-93	80	0.42*	3.48
8	CH_3	242	110-112	78	0.28*	3.97
9	OCH_3	258	115-117	81	0.47*	3.35
10	F	244	127-130	69	0.36*	3.64
11	CI	262	125-128	73	0.24*	4.04
12	Br	304	132-135	71	0.31*	4.31

* (30 % EtOAc in hexane)

Table-2 % Antifungal activities of synthesized test compounds (1-12 and Fluconazole).

	Zone of inhibition (in mm)			
S.N.	***P. chrysogenum***	***A. flavus***	***A. nigar***	***R. oligospora***
1	12	-	13	-
2	-	-	-	-
3	8	-	-	-
4	-	-	-	-
5	_	-	-	-
6	-	-	-	-
7	-	-	-	-
8	-	-	-	-
9	-	-	9	-
10	-	-	-	-
11	-	-	-	-
12	-	-	-	-
Control(DMSO)	-	-	-	-
Fluconazole	18	Resistance	17	Resistance

ACKNOWLEDGEMENTS

The author thanks to Indian Institute of science, Bangalore to provide NMR facility. Also thanks to Head of Department of Biotechnology to provide facilities to carry out antibacterial screening.

REFERENCES

[1] H.P. Avila HP, E. de Fátima, A Smania, *et al.* Structure–activity relationship of antibacterial chalcones. Bio.Med.Chem., 2008, 16: 9790-9794.
[2] Y. Kong, K. Wang, M.C. Edler, *et al.* A boronic acid chalcone analog of combretastatin A-4 as a potent anti-proliferation agent. Bio. Med. Chem., 2010, 18: 971-977.
[3] L. Jayasinghe , B. Balasooriya , W.C. Padmini, *et al.* Geranyl chalcone derivatives with antifungal and radical scavenging properties from the leaves of *Artocarpus nobilis*. Phytochem., 2004, 65: 1287-1290.
[4] A. Bhattacharya, L.C. Mishra, M. Sharma, *et al*. Antimalarial pharmacodynamics of chalcone derivatives in combination with artemisinin against *Plasmodium falciparum in vitro*. Euro. J.Med.Chem., 2009, 44: 3388-3393.
[5] A. Valla, B. Valla, D. Cartier, *et al*. New syntheses and potential antimalarial activities of new 'retinoid-like chalcones. Euro. J. Med. Chem., 2006, 41: 142-146.
[6] L.J. Yamin, E.I. Gasull, S.E. Blanco *et al*. Synthesis and structure of 4-X-chalcones. J. Mol. Str., 1998, 428: 167-174.
[7] C. B. Morie. Manual of Antimicrobial susceptability testing, 2005.
[8] E.P. Kohler and H.M. Chadwell Organic Synthesis, 1941, 1: 71.
[9] D. Batovska, S. Parushev, B. Stamboliyska, *et al*. Study on the substituents' effects of a series of synthetic chalcones against the yeast *Candida albicans*. Euro.J.Med.Chem. 2009, 44: 2211-2218.

Indo Global Journal of Pharmaceutical Sciences(ISSN 2249 1023 ; CODEN- IGJPAI; NLM ID: 101610675) indexed and abstracted in EMBASE(Elsevier), SCIRUS(Elsevier),CABI, CAB Abstracts, Chemical Abstract Services(CAS), American Chemical Society(ACS), Index Copernicus, EBSCO, DOAJ, Google Scholar and many more. For further details, visit http://iglobaljournal.com