INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

SYNTHESIS, ANTIOXIDANT AND ANTIFUNGAL ACTIVITY OF CONJUGATED CHALCONES AND THEIR DERIVATIVES

Santosh Kathwate[2], Subodh V Kamble[3], Mohan S Karuppayil[2], PK. Zubaidha[1*], Inamuddin Anish Khan[4] and Abdullah M Asiri[5]

[1]School of Chemical Sciences, S. R. T. M. University, Nanded, Maharashtra, India.
[2]School of Life Sciences, S. R. T. M. University, Nanded, Maharashtra, India.
[3]School of Pharmacy, S. R. T. M. University, Nanded, Maharashtra, India.
[4]Chemistry Department, King Abdulaziz University, Jeddah-21589, Saudi Arabia.
[5]Center of Excellence for Advanced Materials Research, King Abdulaziz University, Jeddah 21589, P.O. Box 80203, Saudi Arabia.

ABSTRACT

The paper resports synthesis of conjgated chalcones and their derivatives and evaluation of their antioxidant and antifungal activity. As speculated the synthesised compounds display moderate to good activity and in the structure-activity relationship (SAR) contemplated, the biological properties of these molecules were compared with a couple of theoretical parameters for instance, CLogP, PSA, ionization potential, sub-atomic weight, dissolvability, hydrogen bond acceptors (HBA) and hydrogen bond donors (HBD), drug-likeness, drug score using computational software.

Keywords: Chalcones, derivatives, antioxidant, antifungal, activity.

INRODUCTION

Because of the fast improvement of bacterial protection from antifungal agents, it is vital to find a novel framework for the design and preparation of the new antifungal agents to help in the fight against pathogenic growths. As of now, the ideal properties looked for in another antifungal medication hopeful include: restraint of parasitic cell wall biosynthesis; intensity similar with that of amphotericin B; wellbeing comparable with that of fluconazole; and fungicidal action both in vitro and in vivo.[Vincent T A 1999] Easy access to chalcones from substituted acetophenones and cinnamaldehydes makes them an attractive drug scaffold. Chalcones are one of the huge classes of natural products with wide occurrence in fruits, vegetables, flavors, tea and soy-based foodstuff and have attracted great attention for their interesting pharmacological activities.[Zdzislawa Nowakowska 2007] They are primary precursors for the biosynthesis of flavonoids and show different biological activities, for example, antifungal,[Prasad et al. 2008; Lahtchev et al. 2008] anti-cancer,[Dong et al. 2008; Bandgar et al. 2010] anti-inflammatory, [Zdzis1awa et al. 2007; Iqbal et al. 2014] antibacterial,[Prasad et al. 2008] nitric-oxide regulation, anti-oxidant, [Rezk et al. 2002; Kim et al. 2008; Narshingani et al. 2013; Vasil'ev et al. 2010] hypoglycemic,[Patil et al. 2009] antimicrobial,[Talavara et al. 2016] antifungal [Vincent et al. 1999; Boeck et al. 2005; Richter et al. 2005; Batovska et al. 2007; Lahtchev et al. 2008] antileishmanial,[Patil et al. 2009] cytotoxic [Vogel et al. 2008][8] activity. Chalcones belong to open-chain flavanoids having a α,β-unsaturated carbonyl system, in which two benzene rings are joined by three carbon conjugated linker with a completely delocalized II-electron system involving both the benzene rings.

Chalcones have a prominent place in plant kingdom as obvious optional metabolites, that play key role in safeguarding the system from reactive oxygen species, averting molecular harm by microorganisms and creepy crawlies. They display antioxidant property by different mechanisms such as via singlet oxygen quenching, hydrogen donation, metal ion chelation[7] etc.[Patil et al. 2009] which in turn depends upon the nature and position of substituents on the aromatic ring . Among

different substituents, hydroxyl group is most important as they easily get transformed to phenoxy radicals via the hydrogen transfer mechanism [Beom-Tae et al. 2008] which is well stabilized by conjugation in chalcones. This kind of delocalization is best displayed by ortho (i.e. catechol structure) and para-dihydroxylated benzene as compared to meta dihydroxilated benzene ring which is more prone to the formation of quinone type structure.

Over the no less than 50 years in which specific antifungal agents have been discovered, the clinical necessities for the agents have changed fundamentally and continuously and legitimate carefulness in the arms race among parasites and people implies that new targets and new inhibitors have to be explored for convincing antifungal treatment in future. With the objective to explore chalcone skeleton for new antioxidants and antifungal agents, we have synthesized extended chalcones and their derivatives.(Schme 1)

In the structure-activity relationship (SAR) contemplated, the biological properties of this molecule were compared with couple of theoretical parameters, for instance, CLogP, PSA, ionization potential, sub-atomic weight, dissolvability, hydrogen bond acceptors (HBA) and hydrogen bond donors (HBD), drug-likeness, drug score using computational software.

MATERIALS AND METHODS

General

IR spectra were recorded on FT-IR Shimadzu serial no. A213747 spectrophotometer in KBr pellet and ^{1}H NMR spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$ using tetramethylsilane as internal standard and chemical shifts are reported in d units and the coupling constants (J) are reported in hertz. Mass spectra were obtained with a Shimadzu LCMS-2010EV. TLC was performed on aluminium-backed silica plate with visualization by UV-light and column chromatography using silica gel purchased s. d. FineChem Ltd. (mesh size 100–200).

Procedure for the preparation of (2E,4E)-1,5-diphenylpenta-2,4-dien-1-one (3 a-m)

To an aqueous solution of sodium hydroxide in ethanol (2 equivalent) kept in ice bath, substituted acetophenone (1 equivalent) was added followed by cinnamaldehyde (1 equivalent). The reaction mixture was stirred for 2 – 3 hours at 0 °C, then the mixture was kept overnight in a refrigerator. The mixture was acidified with 1 N HCl and then cold water was added to it. The resulting precipitate was filtered and washed well with cold water and dried. The product was recrystallised from ethanol (Step 1).

Procedure for preparation of (2E,4E)-1,5-diphenylpenta-2,4-dien-1-ol (4 a-m)

To the cooled solution of substituted (2E,4E)-1,5-diphenylpenta-2,4-dien-1-one(1 equivalent) in methanol, sodium borohydride (2.5 equivalents) was added portion wise. The reaction mixture was stirred for 1 – 2 hours at 0 °C. The work up by addition of water followed by extraction with dicholoromethane and concentration afforded the product. The product was recrystallised from ethanol (Step 2). The physical and spectral data of selective Chalcones are given below.

(2E,4E)-5-(4-methoxyphenyl)-1-(4-nitrophenyl)penta-2,4-dien-1-ol (4c)

Yield: 79.65 %, Nature: Solid, Color: Lemon yellow, mp: 88-89 °C. IR (KBr): 3000 (C – H Str), 3269.34 (O – H Str), 2839.22 (C – O – CH_3 Str), 1600 (C = C Str), 1519.19 (C – NO_2 Str) cm^{-1}. ^{1}H NMR ($CDCl_3$):- δ 2.166 (s, 1 H), 3.81 (s, 3H), 5.409 – 5.396 (d, 1H, J = 5.2 Hz), 5.887 – 5.821 (dd, 1H, J = 7.4 Hz), 6.668 – 6.443 (m, 3H), 6.871 – 6.850 (d, 2H, J = 8.4 Hz), 7.342 – 7.322 (d, 2H, J = 8 Hz), 7.593 – 7.571 (d, 2H, J = 8.8 Hz), 8.232 – 8.210 (d, 2H, J = 8.8 Hz). MASS: 324.0 (M – H), 309.2 (M – CH_4), 294 (M – CH_3OH) m/z.

***(*2E,4E)-1-(4-nitrophenyl)-5-o-tolylpenta-2,4-dien-1-ol (4d)**

Yield: 73.78 %, Nature: Solid, Color: Yellow, mp: 112-113 °C. IR (KBr): 3508.52 (O – H Str), 2950 (C – H Ar Str), 1610 (C = C Str), 1520 (C – NO_2 Str) cm^{-1}. ^{1}H NMR ($CDCl_3$):- δ 2.192 (s, 3H), 2.199 (s, 1H), 5.453 – 5.441 (d, 1H, J = 4.8 Hz), 5.882 – 5.825 (dd, 1H, J = 7.6 Hz, 15.2 Hz), 6.597 – 6.532 (m, 2H), 7.374 – 7.229 (m, 5H), 7.616 – 7.595 (d, 2H, J = 8.4 Hz), 8.232 – 8.210 (d, 2H, J = 8.8 Hz). MASS: 308.0 (M – H), 293.3 (M – CH_3), 276.3 (M – CH_3OH) m/z.

(2E,4E)-1-(3,4-dimethoxyphenyl)-5-(4-methoxyphenyl)penta-2,4-dien-1-ol (4f)

Yield: 83.24 %, Nature: Solid, Color: Faint yellow, mp: 83-84 °C. IR (KBr): 3508.52 (O – H Str.), 3007.10 (C – H Ar. Str.), 2835.36 (C – O – CH_3 Str.), 1600.92 (C = C Str.), 1454 (C =C Ar. Str.) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.040 (s, 1H, J = 3.2 Hz), 3.808 (s, 3H), 3.900 (s, 3H), 5.272 – 5.249 (dd, 1H, J = 6.2Hz, 3.0 Hz), 5.971 – 5.917 (dd, 1H, J = 6.6 Hz, 15 Hz), 6.699 – 6.408 (m, 3H), 6.951 – 6.917 (m, 5H), 7.340 – 7.318 (d, 2H, J = 8.8 Hz). Mass: 325.3 (M – H), 309.2 (M – CH_4) m/z.

Culture
Candida albicans ATCC 10231 were obtained from IMTECH Chandigarh, India. Culture was maintained on YPD agar slant at 4 ^{o}C .

Medium and culture conditions
Culture was propagated by inoculating a single colony from the YPD agar plates (yeast extracts 1 %, peptone 2 %, dextrose 2 % and agar 2 %) into 50 ml YPD broth in a 250 ml conical flask. Flasks were incubated at 30 ^{o}C at 100 rpm on orbital shaking incubator for 24 hours. Cells were harvested by centrifugation at 200 rpm and washed thrice with 0.1 M Phosphate buffered saline, pH 7.4. Cell density was determined by Hemocytometer count. Cells were suspended in phosphate buffered saline and used as inoculum.

Susceptibility of Candida albicans to Chalcones
The drug susceptibility study was carried out by using standard methadology M 27 A2 as per CLSI guidelines.[Richter et al. 2005] Briefly, various concentrations of chalcone derivatives (**3a-m** and **4a-m**) were prepared in RPMI 1640 Medium with 1% DMSO by double dilution in the 96-well plates. Each well contained 1 × 10^{3} cell ml^{-1} and final concentration of RPMI-1640 in each well was maintained 200 ul. Each concentration was in triplicate. The wells without addition of chalcones served as control. Microplates were incubated at 35 ^{o}C for 48 hours and read microscopically at 620 nm using microplate reader (model ThermoMultiscan-X by Thermo Elec. Corp. USA).

In vitro antioxidant activity (DPPH Method)
The compounds 3a-m and 4a-m were evaluvated for their invitro free radical scavenging activity by the 2,2'diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity method described by Blois[Blois et al. 1958]. Stock solution of different compounds (10mM) were mixed with 0.3mM DPPH methanol solution (0.5mL,) in 3ml of total reaction mixture and allowed to react at room temperature. After 30min, absorbance was measured at 517nm and converted to percentage activity. Ascorbic acid was used as standard antioxidant. The percentage inhibition activity was calculated by using fallowing formula.

Percentage activity = (1- Sample absorbance/ Control absorbance) × 100

In silico Pharmacological Property Study
The pharmacological properties of the compounds such as molecular weight, ClogP, solubility, hydrogen bond donor, hydrogen bond acceptor, molecular PSA, drug likeness and drug score were calculated using online Osiris property explorer.

RESULTS
Susceptibility of Candida albicans to Chalcones
Anti-candida albicans activities of chalcones were studied at its planktonic forms. All chalcones were effective against candida albicans growth (Table 1 and Table 2). Growth inhibition ranged from 40 to 76 %. Among the 26 chalcones derivatives, chalcones **3a, 3c, 3e, 3f, 3g 3l, 3m and 4f** were found be more effective and showed maximum 76 % growth reduction at 5mg/ml concentration. While chalcones **3h, 3k, 4d, 4e, 4f, 4g, 4i, 4l and 4m** inhibited more than 50% growth at same concentration. Remaining chalcones were poor inhibitors of growth, showed less than 50% reduction in growth.

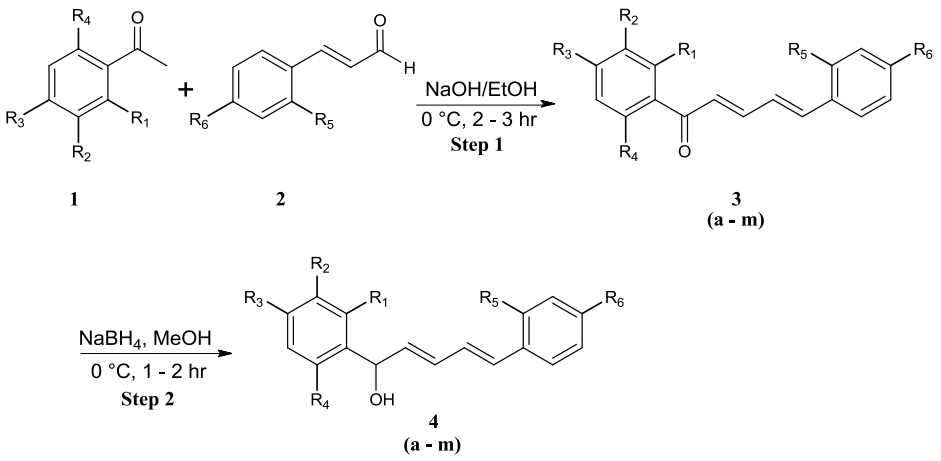
In vitro antioxidant activity
Antioxidant activity of synthesized chalcones was evaluated by using DPPH free radical scavenging assay. All synthesized chalcones have shown 49-68% free radical scavenging activity compared with standard ascorbic acid (84%). This percentage RSA was shown at 10mM concentration. Out of 26 chalcones four chalcones 3b, 4b, 4d and 4m were found to be good radical scavengers while 15 chalcones , **4e, 3c,3e, 3f, 4l, 4a, 4k, 4h, 4f, 3d, 3k, 3m, 4j, 3j and 4c** exhibited moderate activity and the others (**3g, 4g, 3i, 4i, 3a, 3h and 3l)** were found to be poor radical scavengers (Table 1 and Table 2).

In silico pharmacological properties
Pharmacological properties like molecular weight, clogp, solubility, hydrogen bond donor, hydrogen bond acceptor, molecular PSA, drug likeness and drug score were evaluated for the 26 chalcones and the results are presented in Table 3. logp value represents the lipophilicity index, is logarithm of partition coefficient of octane/water. This physicochemical property determines the ability of a given compound to cross biological membrane[Sedykh et al. 2006] and almost all the evaluated compounds have logP value within the desired range (4.15-5.41) set by Lipinsky[Lipinski et al. 2000; Zhu et al. 2005] . Similarly, hydrogen bond acceptor and donor (HBD) for these compounds follow Lipinski's rule and are within the range of less than ten and five resepectively.

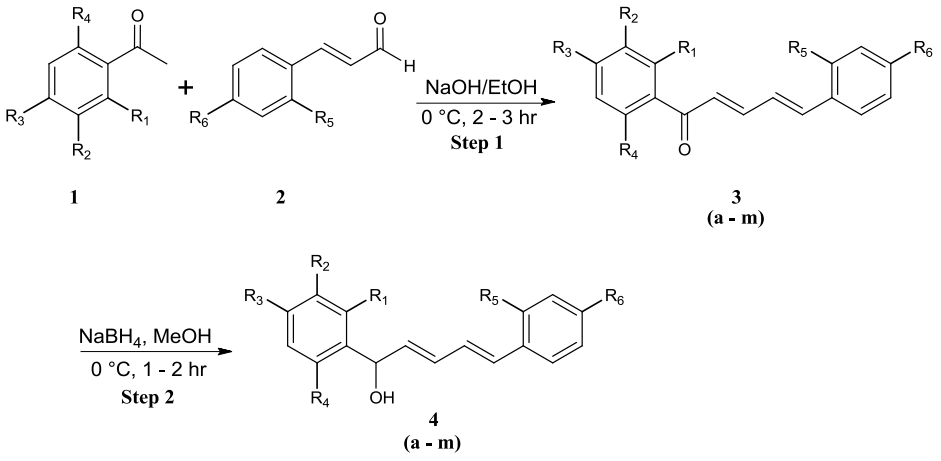
DISCUSSION

Keeping in view the remarkable attributes of chalcone scaffold, the present study was undertaken to study the effect of extended double bond to the enone moiety and carbonyl functional group on antifungal and antioxidant activity, a wide variety of conjugated enones were prepared and further reduced to their respective alcohols.As is obvious from Table 1 and 2, the conjugated enones displayed better anticandida activity as compared to their reduced alcohols. The obtained results clearly indicate that reduction of carbonyl group to alcohol which reduces extent of delocalization via the conjugate linker between the aromatic rings is not favorable and leads to reduction in activity Chalcones **3a, 3c, 3e, 3f, 3g, 3l, 3m 4e, 4f, 4g, 4h, 4l, and 4m** are potential candidates for inhibition of candida albicans growth . It may be attributed to the presence of atleast one electron donating group on the system and it is worth noting that systems having both donating and withdrawing groups display better activity (3c). Similarly, the enones displayed better antioxidant activity as compared to their reduction products (Table 2) and once again conjugation seems to play important role in determining the activity.

In conclusion, the conjugated enones display good to moderate anticandida and antioxidant activity while their reduction products are less effective in both the cases studied. The results amply demonstrates the significance of conjugate linker between the aromatic moieties.



1 2 3 (a - m) 4 (a - m)



1 2 3 (a - m) 4 (a - m)

Scheme. 1:Synthesis of chalcones and their derivatives

Table 1: Antioxidant and antifungal activity studies of conjugated chalcones

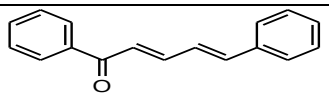
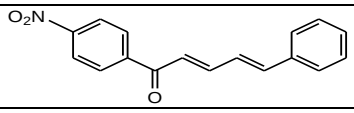
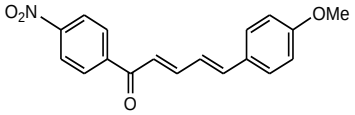
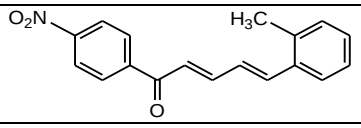
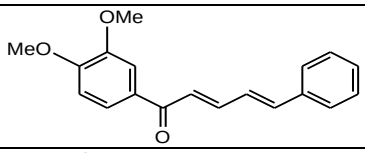
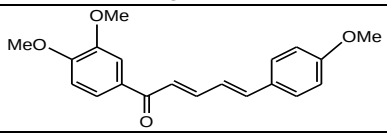
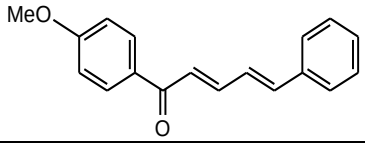
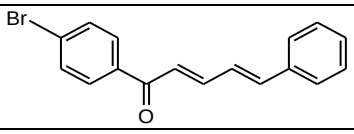
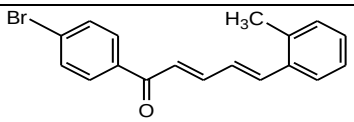
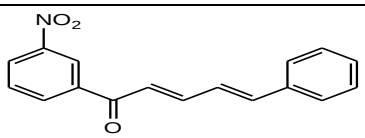
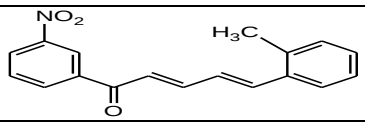
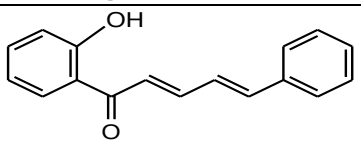
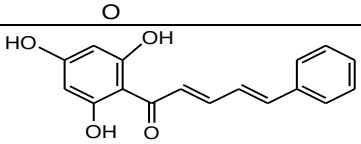
Comp. Code	1				2		Product	Antioxidant Activity	Anticandida Activity
	R_1	R_2	R_3	R_4	R_5	R_6			
3a	- H	- H	- H	- H	- H	- H		52.53	67.02± 0.5
3b	- H	- H	- NO_2	- H	- H	- H		68.65	40.42± 0.6
3c	- H	- H	- NO_2	- H	- H	- OMe		56.29	74.36± 1.0
3d	- H	- H	- NO_2	- H	- CH_3	- H		62.03	42.07± 1.3
3e	- H	- OMe	- OMe	- H	- H	- H		56.29	72.00± 1.5
3f	- H	- OMe	- OMe	- H	- H	- OMe		56.73	76.25± 1.4
3g	- H	- H	- OMe	- H	- H	- H		49.22	69.51± 1.8
3h	- H	- H	- Br	- H	- H	- H		52.53	55.25± 2.0
3i	- H	- H	- Br	- H	- CH_3	- H		50.33	48.08± 0.5
3j	- H	- NO_2	- H	- H	- H	- H		63.57	41.85± 0.8
3k	- H	- NO_2	- H	- H	- CH_3	- H		62.47	51.26± 1.2
3l	- OH	- H	- H	- H	- H	- H		54.30	70.24± 1.3
3m	- OH	- H	- OH	- OH	- H	- H		62.25	69.54± 1.6

Table 2: Chalcones derivatives and their biological activities

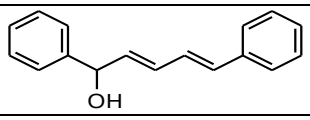
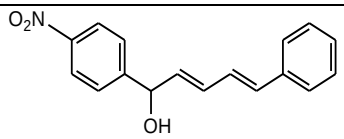
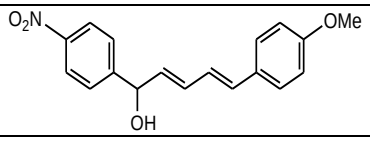
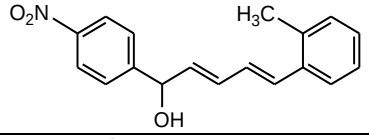
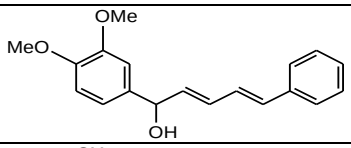
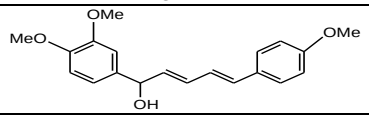
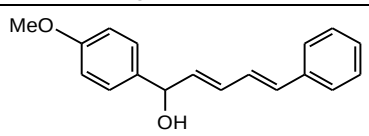
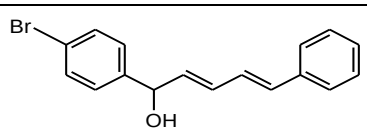
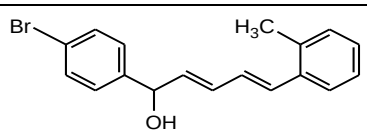
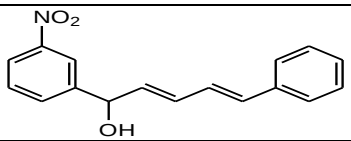
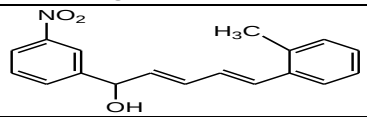
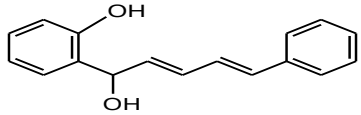
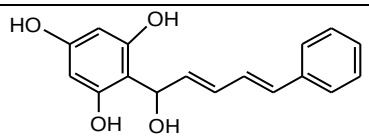
Comp. Code	1				2		Product	Antioxidant Activity	Anticandida Activity
	R_1	R_2	R_3	R_4	R_5	R_6			
4a	- H	- H	- H	- H	- H	- H		59.62	40.93± 0.7
4b	- H	- H	- NO_2	- H	- H	- H		67.90	48.3± 1.9
4c	- H	- H	- NO_2	- H	- H	- OMe		64.38	42.27± 0.8
4d	- H	- H	- NO_2	- H	- CH_3	- H		68.53	54.49± 0.1
4e	- H	- OMe	- OMe	- H	- H	- H		55.90	65.21± 0.5
4f	- H	- OMe	- OMe	- H	- H	- OMe		61.90	67.22± 1.1
4g	- H	- H	- OMe	- H	- H	- H		50.31	65.89± 1.2
4h	- H	- H	- Br	- H	- H	- H		59.83	42.39± 1.7
4i	- H	- H	- Br	- H	- CH_3	- H		50.51	48.98± 1.2
4j	- H	- NO_2	- H	- H	- H	- H		63.56	40.87± 1.6
4k	- H	- NO_2	- H	- H	- CH_3	- H		59.62	39.48± 2
4l	- OH	- H	- H	- H	- H	- H		58.38	59.42± 1.5
4m	- OH	- H	- OH	- OH	- H	- H		68.32	65.27± 0.5

Table 3: In Silico pharmacological parameters

Sr. No.	Comp. Code	Molecular formula	Molecular weight	mp (°C)*	HBD	HBA	PSA	Solubility	ClogP	Drug Likeness	Drug Score
1.	3a	$C_{17}H_{14}O$	234.29	116 – 118	0	1	17.07	-4.15	4.08	-4.47	0.22
2.	3b	$C_{17}H_{13}NO_3$	279.29	173 – 175	0	3	17.07	-3.97	4.36	-3.82	0.21
3.	3c	$C_{18}H_{15}NO_4$	309.32	194 – 196	0	4	26.30	-3.99	4.2	1.39	0.37
4.	3d	$C_{18}H_{15}NO_3$	293.32	182 – 184	0	3	17.07	nd	4.87	nd	nd
5.	3e	$C_{19}H_{18}O_3$	294.34	164 – 166	0	3	35.53	-4.19	4.1	-1.81	0.24
6.	3f	$C_{20}H_{20}O_4$	324.37	178 – 180	0	4	44.76	-4.21	3.94	3.38	0.42
7.	3g	$C_{18}H_{16}O_2$	264.32	140 – 142	0	2	20.23	-4.17	4.26	-3.6	0.22
8.	3h	$C_{17}H_{13}BrO$	313.19	114 – 116	0	1	17.07	-4.99	5.19	-6.84	0.17
9.	3i	$C_{18}H_{15}BrO$	327.22	126 – 128	0	1	17.07	-5.33	5.7	-1.74	0.17
10.	3j	$C_{17}H_{13}NO_3$	279.29	146 – 148	0	3	62.89	nd	4.36	nd	nd
11.	3k	$C_{18}H_{15}NO_3$	293.32	158 – 160	0	3	62.89	nd	4.87	nd	nd
12.	3l	$C_{17}H_{14}O_2$	250.29	134 – 136	1	2	37.36	-3.86	4.76	-4.26	0.39
13.	3m	$C_{17}H_{14}O_4$	282.29	166 – 168	3	4	77.76	-3.26	4.81	-4.35	0.42
14.	4a	$C_{17}H_{16}O$	236.31	--	1	1	20.23	-3.42	4.13	-4.98	0.39
15.	4b	$C_{17}H_{15}NO_3$	281.31	--	1	3	66.05	nd	4.07	nd	nd
16.	4c	$C_{18}H_{17}NO_4$	311.33	88 – 89	1	4	75.28	nd	3.91	nd	nd
17.	4d	$C_{18}H_{17}NO_3$	295.33	112 – 113	1	3	66.05	nd	4.58	nd	nd
18.	4e	$C_{19}H_{20}O_3$	296.36	--	1	3	38.69	-3.46	3.81	-2.15	0.34
19.	4f	$C_{20}H_{22}O_4$	326.39	83 – 84	1	4	47.92	-3.48	3.65	3.06	0.60
20.	4g	$C_{18}H_{18}O_2$	266.33	--	1	2	29.46	-3.44	3.97	-4.1	0.32
21.	4h	$C_{17}H_{15}BrO$	315.2	109 – 110	1	1	20.23	-4.26	4.9	-6.01	0.32
22.	4i	$C_{18}H_{17}BrO$	329.23	138 – 139	1	1	20.23	-4.60	5.41	.09	0.36
23.	4j	$C_{17}H_{15}NO_3$	281.31	--	1	1	66.05	nd	4.07	nd	nd
24.	4k	$C_{18}H_{17}NO_3$	295.33	--	1	1	66.05	nd	4.58	nd	nd
25.	4l	$C_{17}H_{16}O_2$	252.31	--	2	2	40.46	-3.13	3.82	-5.46	0.41
26.	4m	$C_{17}H_{16}O_4$	284.31	149 – 150	4	4	80.92	-2.54	3.22	-5.35	0.44

HBD = Hydrogen Bond Donor, HBA = Hydrogen Bond Acceptor, PSA = Potential Surface Area, nd = not determined

REFERENCES

1. Bandgar BP, Gawande SS, Bodade RG and Totre JV. Synthesis and biological evaluation of simple methoxylated chalcones as anticancer, anti-inflammatory and antioxidant agents. Bioorg Med Chem. 2010;18:1364-1370.
2. Batovska D, Parushev St, Slavova A, Bankova V, Tsvetkova I, Ninova M and Najdenski H. Study on the substituents' effects of a series of synthetic chalcones against the yeast Candida albicans. Euro J Med Chem. 2007;42:87-92.
3. Boeck P, Leal PC, Yunes RA, Fiiho VC, Lopez S, Sortino M, Escalante A, Furlan RLE and Zacchino S. Antifungal Activity and Studies on Mode of Action of Novel Xanthoxyline-Derived Chalcones. Arch Pharm Chem Life Sci. 2005;338:87–95.
4. Blois MS. Antioxidant determinations by the use of a stable free radical, Nature. 1958;181:1199-1200.
5. Iqbal H, Prabhakar V, Sangith V, Chandrika B and Balasubramanian R. Synthesis, anti-inflammatory and antioxidant activity of ring-A-monosubstituted chalcone derivatives. Med Chem Res. 2014;23:4383-4394.
6. Kurt BZ, Kandas NO, Dag A, Sonmez F and Kucukislamoglu M. Synthesis and biological evaluation of novel coumarin-chalcone derivatives containing urea moiety as potential anticancer agents. Arabian J Chem article in press. 2017.
7. Kim BT, Kwang-Joong O, Chun JC and Hwang KJ. Synthesis of Dihydroxylated Chalcone Derivatives with Diverse Substitution Patterns and Their Radical Scavenging Ability toward DPPH Free Radicals. Bull Korean Chem Soc. 2008;29:1125-1130.
8. Lahtchev KL, Batovska DI, Parushev STP, Ubiyvok VM and SibirnyAA. Antifungal activity of chalcones: A mechanistic study using various yeast

strains. Euro J Med Chem. 2008;43:2220-2228.
9. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol Methods. 2000;44(1):235-49.
10. Narshingani T, Sharma MC and Bhargav S. Synthesis, docking studies and antioxidant activity of some chalcone and aurone derivatives. Med Chem Res. 2013;22:4059-4068
11. Patil CB, Mahajan SK and Katti SA. Chalcones: A versatile molecule. J Pharma Sci and Res. 2009;3:11-22.
12. Prasad YR, Lakshman Rao A and Rambabu R. Synthesis and antimicrobial activity of some chalcone derivatives. Euro J Chem. 2008;5:461-466.
13. Rezk BM, Haenen MM, Vijgh Vd, WJF and Bast A. The antioxidant activity of phloretin: The disclosure of a new antioxidant pharmacophore in flavonoids. Biochem Bioph Res Comm. 2002; 295:9-13.
14. Richter SS, Galask RP, Diekema DJ, Messer SA, Pfaller MA and Hollis RJ. Antifungal susceptibilities of Candida species causing vulvovaginitis and epidemiology of recurrent cases. J Clin Microbiol. 2005;43:2155–2162.
15. Rioux B, Pouget C, Fidanzi-Dugas C, Gamond A, Laurent A, Semaan J, Pinon A, Champavier Y, Léger DY, Liagre B, Duroux JL Fagnère C and Sol V. Design and multi-step synthesis of chalcone-polyamine conjugates as potent antiproliferative agents. Bioorg Med Chem Lett. 2017; 27:4354-4357.
16. Sedykh AY and Klopman G. A structural analogue approach to the prediction of the octanol-water partition coefficient. J Chem Inf Model. 2006;46(4):1598-1603.
17. Talavara V, Yadav DB, Kenchappa RS and Telkar. Synthesis, Antimicrobial and Antioxidant Activity of Chalcone Derivatives Containing Thiobarbitone Nucleus. Med Chem. 2016;6:440-448.
18. Vasil'ev RF, Kancheva VD, Fedorova GF, Batovska DI and Trofimov AV. Antioxidant activity of chalcones: The chemiluminescence determination of the reactivity and the quantum chemical calculation of the energies and structures of reagents and intermediates. Kinetics and Catalysis. Chem Sci J. 2010;51:507-515.
19. Vincent TA. Current and future antifungal therapy: new targets for antifungal agents. J Antimicro Chemotherapy. 1999;44:151-162.
20. Vogel S, Ohmayer S, Brunner G and Heilmann J. Natural and non-natural prenylated chalcones : Synthesis, cytotoxicity and anti-oxidative activity. Bioorg Med Chem. 2008;16:4286-4293.
21. Zdzisawa N. A review of Anti-infective and Anti-inflammatory chalcones. Euro J Chem. 2007; 42:125-137.
22. Zhu H, Sedykh A, Chakravarti SK and Klopman G. A New Group Contribution Approach to the Calculation of LogP. Current Computer - Aided Drug Design. 2005;1:3-9(7).