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Synthesis and selective cytotoxic activity of novel hybrid chalcones against prostate cancer cells

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ABSTRACT

A new class of hybrid chalcones (**17a–l** & **18a–l**) was synthesized by Claisen–Schmidt condensation. All compounds were characterized by ^{1}H NMR, IR and mass spectral analysis and tested for their cytotoxic activity against PC-3 (prostate cancer), HT-29 (colon cancer), B-16 (mouse macrophages) and NCI-H460 (lung cancer) cell lines. Three compounds **18i**, **18j** and **18l** (IC_{50} = 8.4, 7.9 & 5.9 μM) showed significant activity against PC-3 cell line.

1,3-diaryl-2-propen-1-ones (Chalcones **1**), which are cancer preventive components found in fruits and vegetables, constitute an important class of natural products.[1] They are defined chemically as open chain flavonoids consisting of two aromatic rings joined by a three carbon α,β-unsaturated carbonyl system. The natural and synthetic derivatives of this class of compounds display anticancer activity on various tumor cells.[1,2] They cause cell cycle arrest and apoptosis by interfering with tubulin polymerization into microtubules, which are essential in the process of cell division, trafficking of vesicles and proteins within the cell, and regulation of cell motility.[2d] Natural as well as synthetic 2,3-dihydrobenzofurans (**5–8**) have been identified to possess cytotoxic activities.[3] It is interesting to note that flavonoids and xanthenones bearing a fused dihydrofuro moiety (**8**) display a myriad of biological properties like antifungal, antitumor and aromatase inhibitory activities.[4] Pyrazoles are an important class of bio-active drug targets in the pharmaceutical industry. They are the core structure of numerous anticancer compounds.[5] In addition, pyrazole ring as B-ring of the chalcone moiety (**2**) has been reported to enhance biological activities (Fig. 1).[6]

Design and synthesis of new types of pharmacologically interesting hybrid chalcone analogs for drug discovery have gained much attention during recent years. Several structural modifications to the chalcone template, particularly replacement of either A or B-phenyl ring or both with heterocyclic groups, have been shown to enhance their biological profiles (2–4).[6,7] Even though dihydrofuro- and pyrano-chalcones are also available in nature along with their prenyl- counterparts with good biological properties, less attention was drawn towards these classes of compounds.[8] In nature, the dihydrofuro and -pyrano fused chalcones are believed to be formed by oxidative cyclization of the prenyl analogs. The nature prefers six membered pyrano fused structures to five membered furo- fused ones as exemplified by the relatively high abundance of natural pyrano- fused chalcones. The chalcone derivative (**9**) (Fig. 1), an example of less abundant furo fused chalcone, has been reported to possess antioxidant and antimicrobial properties in addition to being chemo preventive and cytotoxic.[9] Against this backdrop, we designed and synthesized a new class of chalcones with dihydrobenzofuran moiety as A-ring and either substituted phenyl or pyrazole moiety as B-ring joined together by a three carbon chain (2-propen-1-one) and evaluated their cytotoxic activity (Fig. 2).

Synthesis of the ethanones **14** and **16** was started from resacetophenone **10** which could be accessed easily from resorcinol.[10] Mono-allylation of **10** with 3-chloro-2-methylpropene in acetone in the presence of anhydrous potassium carbonate and catalytic sodium iodide gave **11**.[11] Claisen rearrangement of the allyl–aryl ether **11** at 220 °C in *N*,*N*-diethyl aniline afforded **12** in good yield.[12] Treatment of the rearranged product **12** with catalytic amount of *p*-TSA in chloroform at room temperature gave the benzofuran **13** (90%).[13] Benzylation of the phenol **13** with benzyl bromide afforded the ethanone **14** in very good yield. Compound **16**, the regioisomer of **14**, was prepared by benzylation of the

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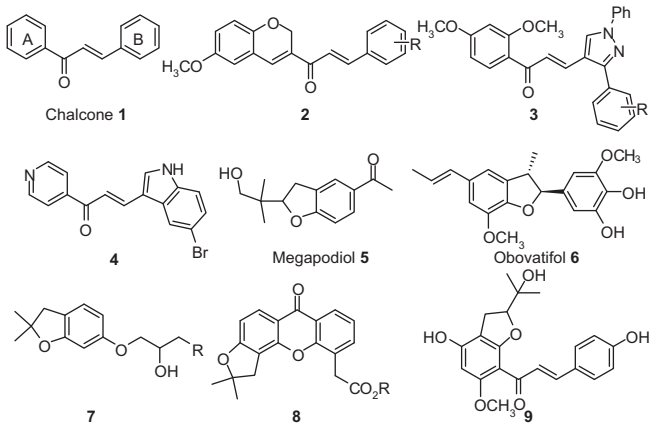


Figure 1. Chemical structures of chalcone, bio-active hybrid chalcones and dihydrobenzofuran derivatives.

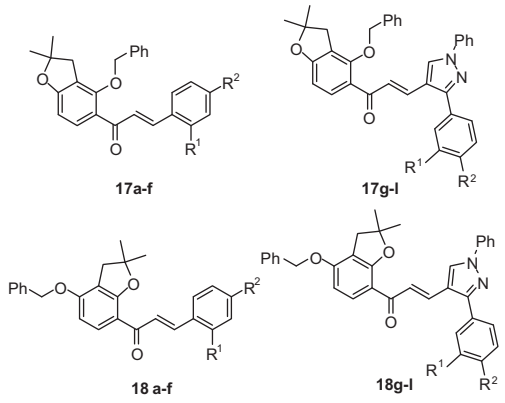
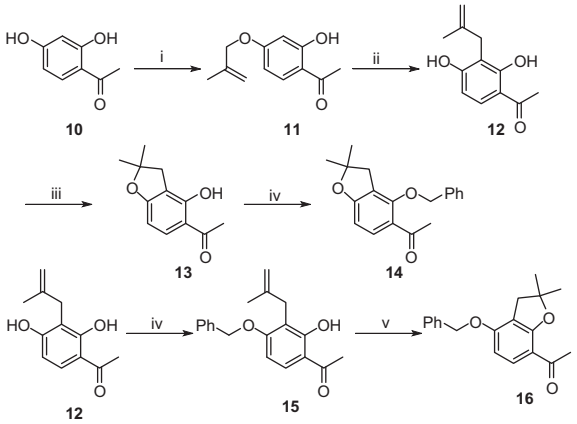


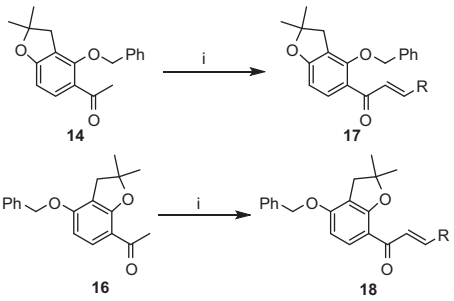
Figure 2. Chemical structures of new hybrid chalcones **17a–i**, and **18a–i**.

4-hydroxy group of **12** followed by cyclization with catalytic amount of *p*-TSA in refluxing toluene scheme 1.

Finally the target 1,3-disubstituted-2-propen-1-ones (**17a–l** and **18a–l**) were prepared by the Claisen–Schmidt condensation[14] of ethanone **14** or **16** with various benzaldehydes and pyrazolaldehydes[15] in ethanolic NaOH (Scheme 2). Our selection of diaryl pyrazoles was based on the excellent biological profiles reported for



Scheme 1. Reaction conditions: (i) 3-Chloro-2-methylprop-1-ene, K_2CO_3,NaI, acetone, reflux, 6 h, 65%; (ii) *N*,*N*-diethylaniline, 220 °C, 4 h, 85%; (iii) *p*-TSA, $CHCl_3$, rt, 6 h, 90%; (iv) $C_6H_5CH_2Br$, K_2CO_3, acetone, reflux, 6 h, (**14**–94%, **15**–90%); (v) *p*-TSA, toluene, reflux, 3 h, 96%.



Scheme 2. Reaction conditions: (i) RCHO, 20%NaOH, EtOH, rt, then 1 M HCl.

Table 1
New hybrid chalcones (Fig. 2)

Entry no.	Compound no.	R^1	R^2	Yield[a] (%)	mp[b] (°C)
1	**17a**	H	H	80	114–116
2	**17b**	H	F	82	138–140
3	**17c**	H	Cl	80	152–154
4	**17d**	H	Br	76	150–152
5	**17e**	H	OCH_3	76	124–126
6	**17f**	Cl	Cl	81	102–104
7	**17g**	H	H	87	120–122
8	**17h**	H	CH_3	79	124
9	**17i**	H	Cl	88	134–136
10	**17j**	H	OCH_3	81	128–130
11	**17k**	H	NO_2	85	152–154
12	**17l**	NO_2	H	87	140
13	**18a**	H	H	75	72–76
14	**18b**	H	F	79	94–96
15	**18c**	H	Cl	89	98–100
16	**18d**	H	Br	79	114–116
17	**18e**	H	OCH_3	83	86–88
18	**18f**	Cl	Cl	86	92–94
19	**18g**	H	H	89	110–112
20	**18h**	H	CH_3	78	164
21	**18i**	H	Cl	87	154
22	**18j**	H	OCH_3	82	134–136
23	**18k**	H	NO_2	91	168
24	**18l**	NO_2	H	86	178–180

[a] Isolated yields after purification.
[b] Uncorrected.

such structures in the literature.[6] Additionally, these compounds could be prepared easily from readily available diaryl pyrazolaldehydes, making the synthesis very facile. In compounds **17a–l**, the A-ring is 2,2-dimethyl-2,3-dihydrobenzofuran with the hydrophobic benzyloxy group *ortho*- to the propenone moiety, while in derivatives **18a–l** A-ring is 2,2-dimethyl-2,3-dihydrobenzofuran with the benzyloxy group *para*- to the propenone moiety. B-ring in both the cases is, either substituted phenyl group (**17a–f** & **18a–f**) or 1-phenyl-3-(substituted phenyl)-pyrazolyl group (**17g–l** & **18g–l**) (Table 1).

The cytotoxic potential of all newly synthesized hybrid chalcones was evaluated in vitro against a panel of four tumor cell lines - prostate cancer (PC-3), colon cancer (HT-29), lung cancer (NCI-H460) and mouse macrophages (B-16)—using MTT assay based on mitochondrial reduction of yellow MTT tetrazolium dye to a highly colored blue formazan product.[16] Doxorubicin was used as the reference drug. The results are summarized in Table 2.

The cytotoxicities of these compounds were found to be dependent on the nature as well as substitution patterns of both the rings as shown in Table 2. The new class of compounds showed moderate to significant cytotoxic activity on PC-3 cell lines (IC_{50} = 5.9–50 μM). Compound **17b** with fluorine substituent on the B-ring exhibited very good activity on HT-29 cell lines with IC_{50} value 23.0 μM. In fact, this is the only compound which