

# Synthesis and Evaluation of Flavanones as Anticancer Agents

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Murthi and Mishra: Flavanones as Anticancer Agents

A few flavanones were synthesised by cyclisation of corresponding 3-(heteroaryl)-1(2-hydroxyphenyl) prop-2-en-1-one with sodium acetate in alcohol–water and evaluated for activity. Synthesised compounds were assayed for their *in vitro* anticancer activity against three human cancer cell lines, mammary adenocarcinoma (MCF7), human colon adenocarcinoma (HT29) and human kidney adenocarcinoma (A498) using sulforhodamine B dye. Results indicated that most of the compounds exhibited significant *in vitro* anticancer potential. Among them, compound having furan ring showed most potent activity against all the tested cell lines.

**Key words:** Flavanone, chalcone, anticancer activity, SRB dye, MCF7, HT29, A498

Flavanones (2-phenylchroman-4-ones) are a class of natural product that show extensive biological activities with low toxicity. Compounds with promising activity can be used as leads for synthesis of novel compounds with high efficacy and low side effects to improve drug therapy. Synthetic flavanones have attracted considerable attention because of their various pharmacological properties including antifungal<sup>[1,2]</sup>, antibacterial<sup>[1,3,4]</sup>, analgesic<sup>[4]</sup>, antioxidant<sup>[4]</sup>, vasorelaxant<sup>[5]</sup>, AChE inhibitory<sup>[6]</sup> and antiVSMCs vegetation<sup>[7]</sup> activity. Flavanones have been a potential source in the search for lead compounds so investigation of synthetic routes and chemical modification is a new direction in flavanone research. Flavanones have been reported as a potent anticancer agent<sup>[8-14]</sup> also, but there were very few literature that reported the bioactivity of heteroaryl derivatives, which prompted us to synthesise a novel series of flavanones to investigate the effect by changing the B ring (fig. 1) to a heterocycle ring on *in vitro* anticancer activity. We herein, report the synthesis and evaluation of flavanones. The first step

was Claisen–Schmidt reaction between heterocyclic benzaldehyde and 2-hydroxy acetophenone to form 2-hydroxy chalcone derivatives, which on intramolecular addition reaction, gave flavanone derivatives as shown in Scheme 1. The structures of target compounds are described in Scheme 2.

All the chemicals used for the synthesis of the compounds were obtained from Merck Ltd., Mumbai

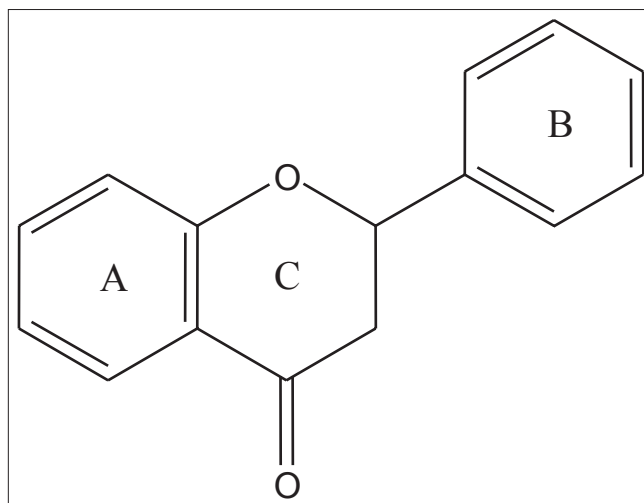
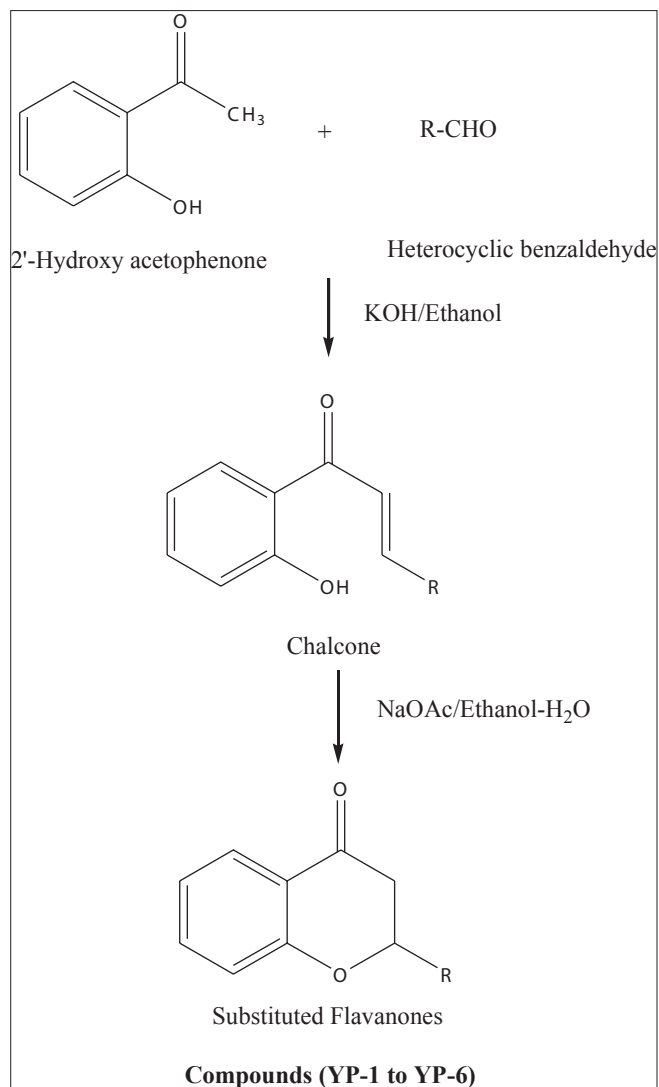


Fig. 1: Flavanone (2-phenylchroman-4-one).

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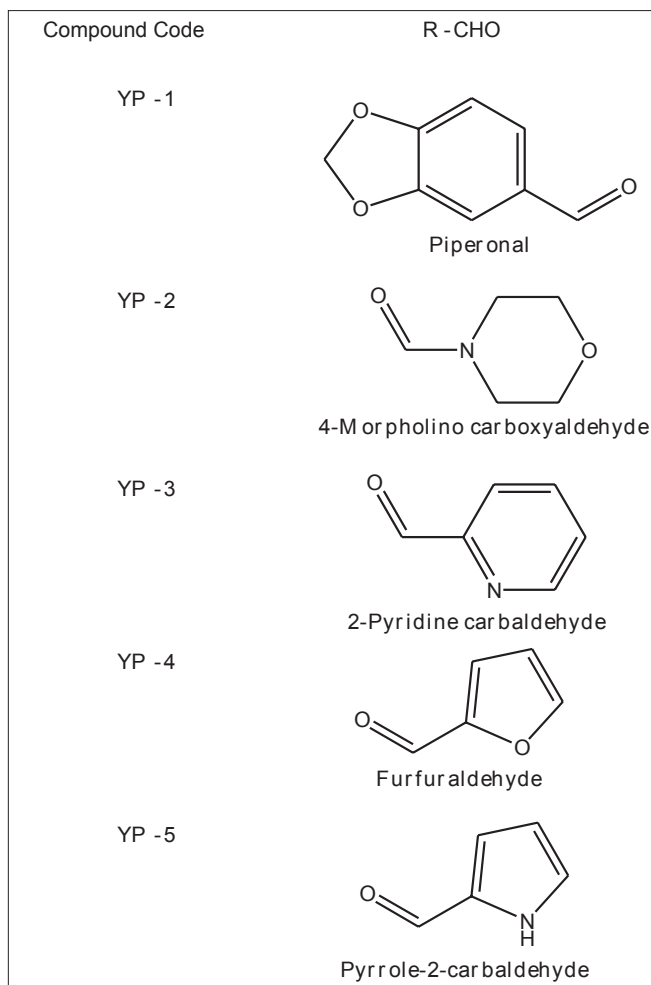
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Scheme 1: Synthesis of flavanone derivatives.

and SD Fine-Chem Ltd. Mumbai. Melting points were determined in open capillaries and are uncorrected. The compounds were analysed for elemental analysis. IR spectra were recorded on an FTIR spectrometer (Perkin Elmer) using KBr disc method. <sup>1</sup>H NMR spectra were recorded on <sup>1</sup>H NMR (Bruker AMx300 MHz) spectrometer in CDCl<sub>3</sub>.

General procedure for the synthesis of title compounds used was as follows: a mixture of the 2-hydroxy acetophenone (0.01 mol, 1.36 g) and corresponding heterocyclic aldehyde (0.01 mol) was taken in ethanol (30 ml) and stirred at 10-15°. To this solution, an aqueous solution of sodium hydroxide (40%, 5.0 ml) was added drop wise with continuous stirring. The mixture was kept overnight at room temperature and then it was poured into crushed ice and acidified with diluted hydrochloric acid. The chalcone precipitated



Scheme 2: Target compounds.

as solid. The precipitated chalcone was collected and recrystallised from ethanol.

The synthesised chalcones (0.1 mmol) and sodium acetate (163 mg, 1.99 mmol) was added to a solution of ethyl alcohol (2.2 ml) and water (0.8 ml), the mixture was heated to reflux for 24 h, the solvent was evaporated under vacuum, 10 ml water was added to the residue and extracted with ethyl acetate (10 ml×3), the combined organic layer was washed with 2 N sodium hydroxide (brine), and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether:EtOAc; 4:1) to afford compounds YP-1 to YP-6. The purity of the synthesised compounds was established by TLC and melting point. The physical data of the compounds is listed in Table 1. The structures of the synthesised compounds YP-1 to YP-6 were characterised by IR and <sup>1</sup>H NMR and the spectral data are summarised below.

**TABLE 1: PHYSICAL CHARACTERISATION DATA OF SYNTHESISED FLAVANONES (YP-1 TO YP-6)**

Code no.	Molecular formula (molecular weight)	% yield	M.P. (°)	Rf Value (CHCl <sub>3</sub> :EtOAc; 2:1)	Elemental analysis (%) calcd. (found)		
					C	H	N/S
YP-1	C <sub>16</sub> H <sub>12</sub> O <sub>4</sub> (268.26)	39	131-132	0.68	71.64 (71.65)	4.51 (4.50)	-
YP-2	C <sub>13</sub> H <sub>15</sub> NO <sub>3</sub> (233.26)	36	170-172	0.66	66.94 (66.92)	6.48 (6.50)	6.00 (6.02)
YP-3	C <sub>14</sub> H <sub>11</sub> NO <sub>2</sub> (225.24)	48	147-148	0.73	74.65 (74.62)	4.92 (4.91)	6.22 (6.20)
YP-4	C <sub>13</sub> H <sub>10</sub> O <sub>3</sub> (214.22)	51	150-152	0.65	72.89 (72.90)	4.71 (4.73)	-
YP-5	C <sub>13</sub> H <sub>11</sub> NO <sub>2</sub> (213.23)	56	156-157	0.77	73.23 (73.25)	5.20 (5.22)	6.57 (6.56)
YP-6	C <sub>13</sub> H <sub>10</sub> O <sub>2</sub> S (230.28)	43	120-122	0.73	67.80 (67.78)	4.38 (4.40)	13.92 (13.93)

**TABLE 2: IN VITRO ANTICANCER ACTIVITY OF SYNTHESISED FLAVANONES YP-1 TO YP-6**

Compound code	Cell lines (IC <sub>50</sub> , µg/ml)*		
	MCF7	HT29	A498
YP-1	>50	>50	>25
YP-2	10.2 (±0.4)	6.7 (±2.3)	8.1 (±0.7)
YP-3	19.6 (±1.2)	16.6 (±2.5)	14.5 (±3.6)
YP-4	7.3 (±0.3)	4.9 (±0.5)	5.7 (±0.9)
YP-5	20.1 (±0.2)	18.9 (±1.2)	17.3 (±7.9)
YP-6	12.6 (±1.5)	7.8 (±1.4)	9.4 (±1.4)
2-phenyl chroman-4-one	>25	28.3 (±0.6)	20.7 (±0.6)

\*Values are mean of three experiments, standard deviation is given in parentheses

Compound YP-1; FTIR (KBr, cm<sup>-1</sup>): 3010 (Ar=C-H str.), 1646 (C=O str.), 1589 (C-C str.), 1516, 1462, 1419 (Ar C=C str.), 1193 (C-O-C str.); <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ ppm): 3.43, 3.17 (d, 2H, methylene), 5.54 (t, 1H, methine), 5.88 (s, 2H, methylene dioxy), 6.54–7.80 (m, 7H, Ar-H). Compound YP-2; FTIR (KBr, cm<sup>-1</sup>): 3014 (Ar=C-H str.), 1686 (C=O str.), 1581 (C-C str.), 1519, 1460, 1415 (Ar C=C str.), 1239 (C-N str.), 1190 (C-O-C str.); <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ ppm): 2.35 (m, 4H, morpholine), 3.15, 2.93 (d, 2H, methylene), 3.65 (m, 4H, morpholine), 5.35 (t, 1H, methine), 6.83–7.53 (m, 4H, Ar-H).

Compound YP-3; FTIR (KBr, cm<sup>-1</sup>): 3065 (Ar=C-H str.), 1658 (C=O str.), 1600 (C-C str.), 1540 (C=N str.), 1559, 1458, 1420 (Ar C=C str.), 1196 (C-O-C str.); <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ ppm): 3.17, 2.90 (d, 2H, methylene), 5.52 (t, 1H, methine), 6.90–8.61 (m, 8H, Ar-H). Compound YP-4; FTIR (KBr, cm<sup>-1</sup>): 3012 (Ar=C-H str.), 1667 (C=O str.), 1598 (C-C str.), 1567, 1485, 1443 (Ar C=C str.), 1178 (C-O-C str.); <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ ppm): 3.18, 3.13, (d, 2H, methylene), 5.49 (t, 1H, methine), 6.19–7.38 (m, 7H, Ar-H).

Compound YP-5; FTIR (KBr, cm<sup>-1</sup>): 3117 (Ar=C-H str.), 1670 (C=O str.), 1612 (C-C str.), 1576, 1456, 1426 (Ar C=C str.), 1242 (C-N str.), 1167

(C-O-C str.); <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ ppm): 3.33, 3.09 (d, 2H, methylene), 5.10 (d, 1H, pyrrole N-H), 5.13 (t, 1H, methine), 5.72–6.36 (m, 3H, pyrrole), 6.90–7.75 (m, 4H, Ar-H). Compound YP-6; FTIR (KBr, cm<sup>-1</sup>): 3038 (Ar=C-H str.), 2846 (C-H str.), 1669 (C=O str.), 1587 (C-C str.), 1553, 1460, 1432 (Ar C=C str.), 1117 (C-O-C str.), 644 (C-S str.); <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ ppm): 3.38, 3.13 (d, 2H, methylene), 5.51 (t, 1H, methine), 6.62–7.79 (m, 7H, Ar-H).

The *in vitro* anticancer activity of synthesised flavanones was tested against human mammary adenocarcinoma (MCF7), human colon adenocarcinoma (HT29) and human kidney adenocarcinoma (A498) using sulforhodamine B dye<sup>[15]</sup>. 2-Phenyl chroman-4-one, a kind of flavanone, was tested together as a positive control in the assay. The *in vitro* anticancer activity results are summarised in Table 2. In accordance with the data from *in vitro* anticancer activity, all the synthesised heteroaryl flavanone derivatives have shown mild to good activity compared with that of positive control 2-phenyl chroman-4-one. The activity data indicate that the compound YP-4 with furan ring (B ring) had the strongest activity against MCF7, HT29 and A498 with IC<sub>50</sub> values of 7.3, 4.9 and 5.7 µg/ml, respectively.

In conclusion, a few number of new heterocycle containing flavanone derivatives were synthesised and studied for *in vitro* anticancer activity, and a furan ring containing analogue YP-4 had highest anticancer potency compared with those of other flavanones. These results suggested that furan ring may be crucial for anticancer activity and contribute to further understanding the critical molecular requirements that lead to anticancer property in the flavanones series. On the basis of the above findings, these flavanones scaffolds can be selected as skeleton for the development of heterocycle containing flavanones with potential as anticancer drugs.

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