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Synthesis, anticancer, structural, and computational docking studies of 3-benzylchroman-4-one derivatives

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ABSTRACT

A series of 3-Benzylchroman-4-ones were synthesized and screened for anticancer activity by MTT assay. The compounds were evaluated against two cancerous cell lines BT549 (human breast carcinoma), HeLa (human cervical carcinoma), and one noncancerous cell line vero (normal kidney epithelial cells). **3b** was found to be the most active molecule against BT549 cells (IC_{50} = 20.1 μM) and **3h** against HeLa cells (IC_{50} = 20.45 μM). **3b** also exhibited moderate activity against HeLa cells (IC_{50} = 42.8 μM). The molecular structures of **3h** and **3i** were solved by single crystal X-ray crystallographic technique. Additionally, the molecular docking studies between the tumour suppressor protein p53 with the lead compound **3h**, which exhibited better anticancer activity against HeLa cells was examined.

Cancer is one of the most widespread and feared diseases in the world today. Cancer arises from the transformation of healthy cells into tumour cells in a multistage process that progresses from a pre-cancerous lesion to a malignant tumour. Cancer is the second leading cause of death globally and was responsible for 8.8 million deaths in 2015. Globally, nearly 1 in 6 deaths is due to cancer (http://www.who.int/mediacentre/factsheets/fs297/en/). Many cytotoxic drugs suffer from poor selectivity to target cells, leading to a high degree of toxicity and potentially life-threatening side effects. To design drugs that specifically target cancer cells is a major challenge. Flavonoids are shown to have anticancer activities.

3-Benzylchroman-4-ones (homoisoflavanones) are oxygen-containing heterocycles with a sixteen carbon skeleton. They belong to the class of naturally occurring polyphenolic flavonoids with limited occurrence in nature and are mainly found in families like Hyacinthaceae, Liliaceae, Agavaceae, Fabaceae, Liliaceae, and Polygonaceae.[1,2] They have been reported to possess antiinflammatory, antibacterial, antihistaminic, antimutagenic, antiviral and angioprotective properties besides potent phosphodiesterase inhibition property.[3–5] Homoisoflavonoids, caesalpinianone, and 6-O-methylcaesalpinianone which exhibited different levels of glutathione S-transferase inhibitory and antifungal activities were isolated from the ethanolic extract of Caesalpinia bonduc (Fabaceae). Caesalpinanone and 6-O-methylcaesalpinianone inhibited glutathione S-transferase with an IC_{50} = 16.5 μM and 17.1 μM respectively.[6] Sappanone A, a homoisoflavanone isolated from the heartwood of Caesalpinia sappan has been known to have antioxidant and anti-inflammatory effects. A recent study showed that Sappanone A inhibited Cisplatin-induced kidney injury through activating Nrf2 and inhibiting NF-κB activation.[6] Pre-treatment with 5,7-dihydroxy-3-(3-hydroxy-4-methoxybenzyl)-chroman-4-one inhibited the production of intracellular ROS induced by UVB irradiation in HaCaT cells. Further analysis revealed a decrease in the level of MAPK activation and down-regulation of COX2 expression.5,7-dihydroxy-3-(3-hydroxy-4-methoxybenzyl)-6-methoxychroman-4-one inhibited vascular tube formation and new vessel growth induced by basic fibroblast growth factor.[7] Homoisopogon A (1), isolated from Ophiopogon japonicus tubers exhibited potent cytotoxicity against human lung adenocarcinoma LU-1, human epidermoid carcinoma KB, and human melanoma SK-Mel-2 cancer cells with IC_{50} values ranging from 0.51 to 0.66 μM.[8] However, reports on the anticancer activity of synthetic 3-benzylchromone derivatives are scarce. As part of our ongoing efforts to

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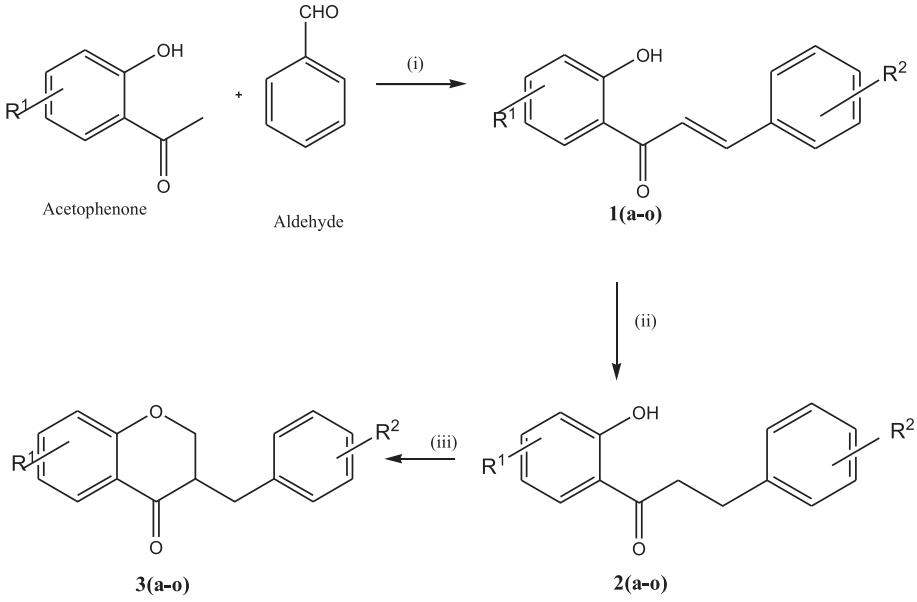
synthesize new flavonoids and explore their biological activities, we have synthesized 15 derivatives of 3-benzylchroman-4-one. Their anticancer potential is evaluated *in vitro* against two cancerous cell lines BT549 (human breast carcinoma), HeLa (human cervical carcinoma), and one non-cancerous cell line Vero (normal kidney epithelial cells). We also carried out the crystal structure of compounds **3h** and **3i**. Moreover, we performed molecular docking studies between the tumour-suppressor protein p53 with the lead compound **3h**, which shows better cytotoxic activity in HeLa cells.

3-Benzylchroman-4-one derivatives were synthesized as outlined in Scheme 1 and their chemical structures are summarized. Chalcones were synthesized by condensation of acetophenones/methoxy/methyl substituted acetophenones and substituted aldehydes, using 40% w/v alcoholic KOH at room temperature.[9] Reduction of chalcones to dihydrochalcones was carried out using 10% Pd-C and ammonium formate.[10] The dihydrochalcones were then cyclized to the corresponding homoisoflavanones using paraformaldehyde and 50% v/v aqueous diethylamine.[11] The structures of derivatives **3a–o** were confirmed using elemental analysis, NMR spectroscopy and mass spectral analysis. For more details on experimental and complete NMR, and mass spectra see the Supplementary data. Because of their wide range of pharmacological activity, we synthesized a series of 3-benylchroman-4-ones and evaluated their cytotoxic potential against two cell lines, BT549, and HeLa.

The results of the *in vitro* anticancer activity of compounds **3a–o**, against BT549, HeLa, and Vero cells are listed in Table 1. **3b** was found to be the most active molecule against BT549 cells (IC_{50} = 20.1 μM) and **3h** against HeLa cells (IC_{50} = 20.45 μM). **3b** also exhibited moderate activity against HeLa cells (IC_{50} = 42.8 μM). The molecule 3b has hydroxyl substitution at C-4′ of ring C, and



Compound	R^1	R^2
3a	H	4′-Cl
3b	H	4′-OH
3c	H	4′-F
3d	H	4′-OCH_3
3e	H	2′,3′,4′-OCH_3
3f	H	2′,4′-OCH_3
3g	H	3′,4′-OCH_3
3h	H	3′-OH,4′-OCH_3
3i	H	4′-CH_3
3j	6-CH_3	4′-OCH_3
3k	5-OCH_3	3′-OH,4′-OCH_3
3l	7-CH_3	4′-OCH_3
3m	7-CH_3	4′-OH
3n	7-OCH_3	4′-OH
3o	7-OCH_3	3′-OH,4′-OCH_3

Scheme 1. Synthesis of 3-Benzylchroman-4-one derivatives. Reagents and condition: (i) 40% w/v alcoholic KOH, rt, 12–36 h; (ii) 10% Pd-C, $HCOONH_4$, MeOH-THF (1:1), reflux, 90 min; (iii) 50% v/v aq. diethylamine, (HCHO)n, EtOH, reflux, 9 h.