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Diversity oriented synthesis of chromene-xanthene hybrids as anti-breast cancer agents

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ABSTRACT

A diverse library of chromene-xanthene hybrids were synthesized through intramolecular Friedel-Crafts reaction of the arenoxy carbinols. Examples include first incorporation of amino acid tyrosine into xanthene skeletons with polar functionalities. A careful structural evaluation revealed that tyrosine crafted chromene-xanthene hybrids exhibited good activities against breast cancer cell lines MCF-7, MDA-MB-231. The lead compound **16** displays significant cell cycle arrest at G1 phase and induces apoptosis in MDA-MB-231 cells.

Chromenes are synthetically important structural motifs that can be easily functionalized to access diverse biologically active analogues. These "privileged" molecular frameworks were often targeted because of their easily accessible chemical libraries and ability to act as ligands for a diverse array of receptors.[1] Several research groups already demonstrated a range of medicinally important polycyclic libraries based on the chromene/benzopyran template that can be extensively and rapidly functionalised.[2] Nicolaou et al. successfully developed chroman based combinatorial library[3] of 10,000 compounds typically demonstrating the potential of these privileged structures. Every molecule in that library on an average bears 3–4 hetero atoms and has the molecular weight typically in the range of 200–600. Besides these, benzopyrans were known to show a range of applications from cosmetics, pesticides to fluorescent materials.[4] The well-known antibiotics such as chlorobiocin, coumermycin A1 constitute the benzopyran as core skeleton.[5]

Although natural products and natural product inspired libraries are the major source for drug discovery,[6] state of art technologies enhanced the understanding of biology at molecular levels which lead to the development of rationally designed therapies. Molecular hybridization is one of the rational strategies for the designing of new chemical compounds based on the already known pharmacophoric subunits. Hybridization approach not only helps in optimizing several biological parameters like affinity and selectivity, but also to gain novel biological activities distinct from the individual components. The toxin steroid hybrid developed by Tietze et al. showed a promising anticancer activity[7] as proposed. Grese et al. integrated the structural features of raloxifene into benzopyran skeleton thereby increasing in vivo efficacy and pharmacokinetic stability of the resulting hybrid molecules.[8] The topoisomerase inhibitor 11-alkenylindenoisoquinoline, typically an indenoisoquinoline-camptothecin hybrids was the amalgamation[9] of two other topoisomerase **I** inhibitors camptothecin and 5,11-diketoindenoisoquinoline respectively. Similarly, the anticancer hybrid epoxyfuroacridone **I** (Fig. 1) was prepared by hybridizing hybrid epoxyfuroacridone **1** (Fig. 1) was prepared by hybridizing two DNA alkylating agents, acridone moiety of acronycine and the epoxyfuran of psorospermin.[10] In a report antiproliferative activity of pyranoxanthone **II** (fig. 1) was established[11] as an isostere of benzo[*a*]acronycine by Tillequin et al. Similarly hybridizing benzamidyl moiety of MS-275 and aliphatic side chain of trichostatin A resulted in the more potent HDAC inhibitor SK-7041 **III**[12] (Fig. 1) than SAHA having a micromolar range antiproliferative activity.

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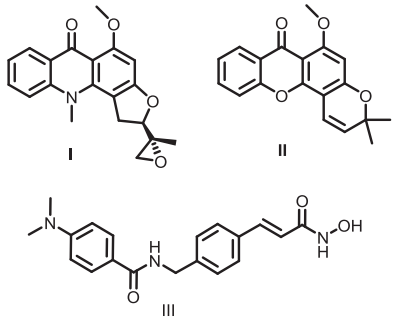
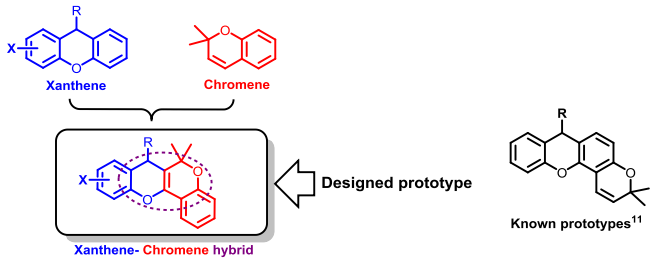


Fig. 1. Representative anticancer drug hybrids.



Scheme 1. Schematic diagram depicting the design of target architectures.

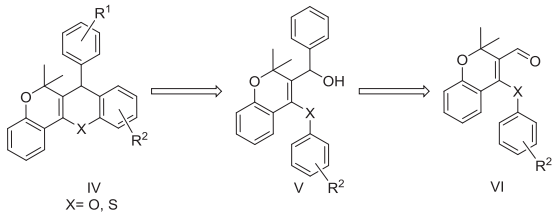
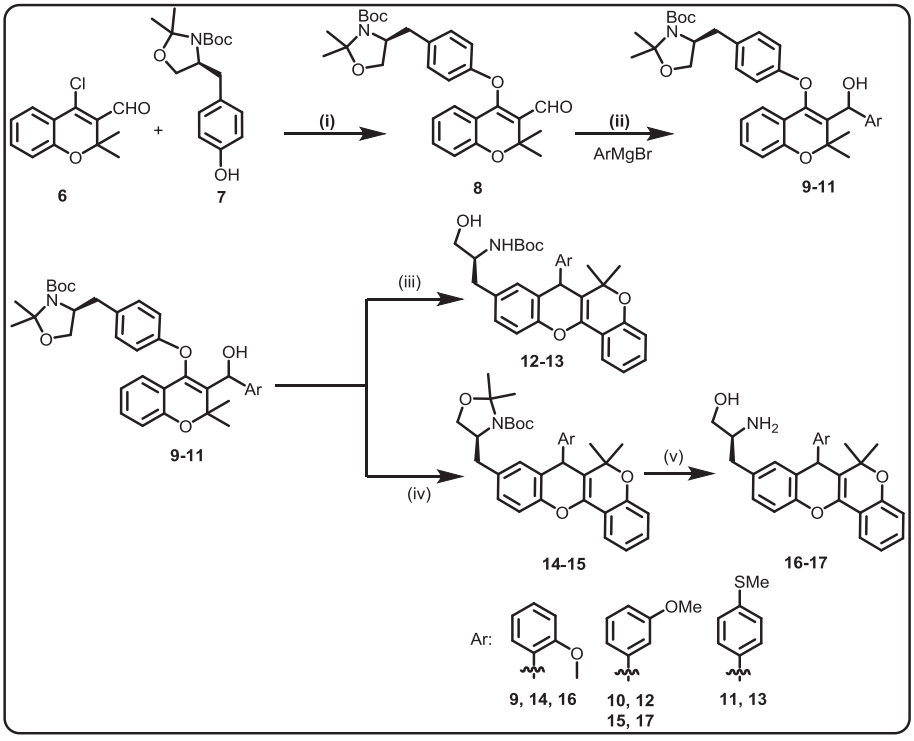


Fig. 2. Retrosynthetic analysis.

We developed several efficient methodologies for accessing Trisubstituted methane based architectures,[13,14] such as Scandium Triflate catalysed one pot domino cyclization of aldehydes with phenols leading to 9-aryl xanthenes. In our recent endeavour of developing heteroatom impregnated natural product like libraries, we demonstrated that chromene derived scaffolds can be cyclized to diverse 6*H*,7*H*chromeno[4,3-*b*]chromenes and 6,7-dihydrothiochromeno[3,2-*c*]chromenes using Lewis acid as a catalyst.[15] In this pursuit, we aimed at incorporating amino acid tyrosine to introduce polar functionalities on these specialised chromene-xanthene[15] hybrids (Scheme 1) for imparting anti-breast cancer potency. Retrosynthetically, target core **IV** (Fig. 2) can be accomplished through intramolecular Friedel-Crafts reaction of the arenoxy carbinols **V** (Fig. 2). These arenoxy carbinols can be prepared from the Grignard addition on diaryl chromene carbaldehyde **VI** (Fig. 2) which is a Michael adduct of 4-chloro-2,2-dimethyl-2*H*-chromene-3-carbaldehydes. Chromans when subjected to Vilsmeier-Haack conditions results in 4-chloro chromene carbaldehydes Scheme 2.

The xanthene analogues (1–5) were synthesized as per previously developed protocols.[15] L-Tyrosine derivative was prepared by reported procedures.[16] Firstly, L-Tyrosine was esterified with thionyl chloride in methanol and amine was functionalized to *tert*-butyl carbamate with Di-*tert*-butyl dicarbonate. The ester was reduced with LAH followed by acetonide protection to give the hydroxyl arene counterpart 7 which will be used for Michael addition with **6**. When 2,2-dimethylchroman-4-one was subjected to Vilsmeier–Haack–Arnold reaction conditions resulted in the chloroaldehyde **6**. In order to prepare the target architectures, the tyrosine derivative **7** was treated with NaH and then further reacted with chloroaldehyde **6**. The resulting carbaldehyde **8** on Grignard reaction led to the aryloxy carbinols **9–11** up to 91% yields. These carbinols were well poised for crucial cyclization event for the formation of chromene-xanthene hybrids. When the carbinols were initially subjected to cyclization with $FeCl_3$ in DCM, acetonide was surprisingly deprotected in the same pot lead-



Scheme 2. (i) NaH, Dry DMF, 6 h 79%; (ii) Ar-Br, Mg/I_2, dry THF, rt, 1–3 h, 62–71%; (iii) $FeCl_3$, Dry DCM, 8 min (for **10**), 3 min (for **11**) 69% (**10**), 82% (**11**); (iv) MsCl, 2–5 h, Et_3N, DCM, 57–84%; (v) TFA, DCM, Aq $NaHCO_3$, 10–25 min, 92–97%.