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Synthesis of novel forskolin isoxazole derivatives with potent anti-cancer activity against breast cancer cell lines

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ABSTRACT

Forskolin C_1-isoxazole derivatives (3,5-regioisomers) (**11a–e**, **14**, **15a–h** and **15**, **16a–g**) were synthesized regioselectively by adopting 1,3-dipolar cycloadditions. These derivatives were tested using estrogen receptor positive breast cancer cell lines MCF-7 and BT-474. Majority of the compounds exhibited activity against the p53-positive MCF-7 breast cancer cells but not against the p53-negative BT-474 breast cancer cells. Among forskolin derivatives, compounds **11a**, **11c**, **14a**, **14f**, **14g**, **14h**, **15b**, **16g** and **17b** exhibited higher anti-cancer activity against MCF-7 cell line with an $IC_{50} \leq 1$ μM. The derivative **14f** exhibited highest activity in both p53-positive (MCF-7) and p53-negative (BT-474) breast cancer cell lines with an IC_{50} of 0.5 μM.

Breast cancer is the most common cancer in the women worldwide. Natural products such as Docetaxel, Paclitaxel, Eribuline, Vinblastine and Doxorubicin were used for the treatment of breast cancer.[1–4] Importantly, diterpenoids such as Forskolin (**1**), Fulvestrant (**2**), Megestrol (**3**), Formestane (**4**), Atamestane (**5**) and Exemestane (**6**) were shown to have anti-cancer activity (Fig. 1), specifically against estrogen receptor-positive breast cancer.[5–13]

Forskolin, a labdane diterpene natural product, has been isolated from the roots of an Indian sub-continent plant *Coleus forskohlii*.[14] Forskolin exhibits a wide range of pharmacological

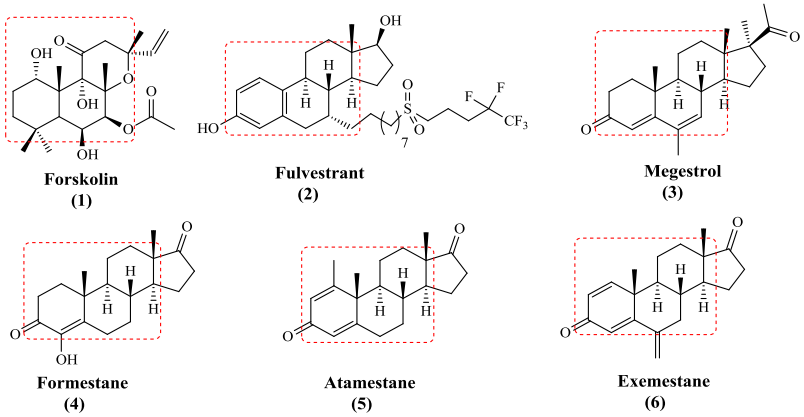

Fig. 1. Some diterpenes as breast cancer agents.

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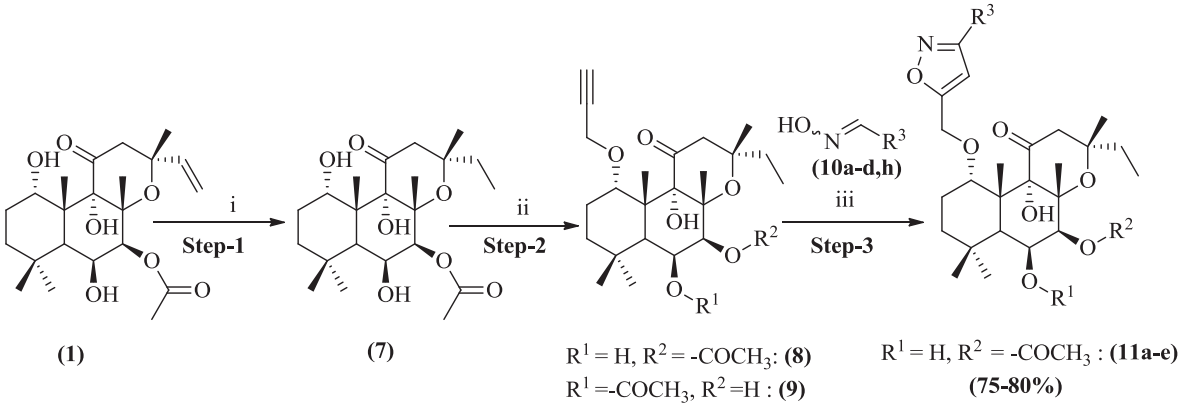
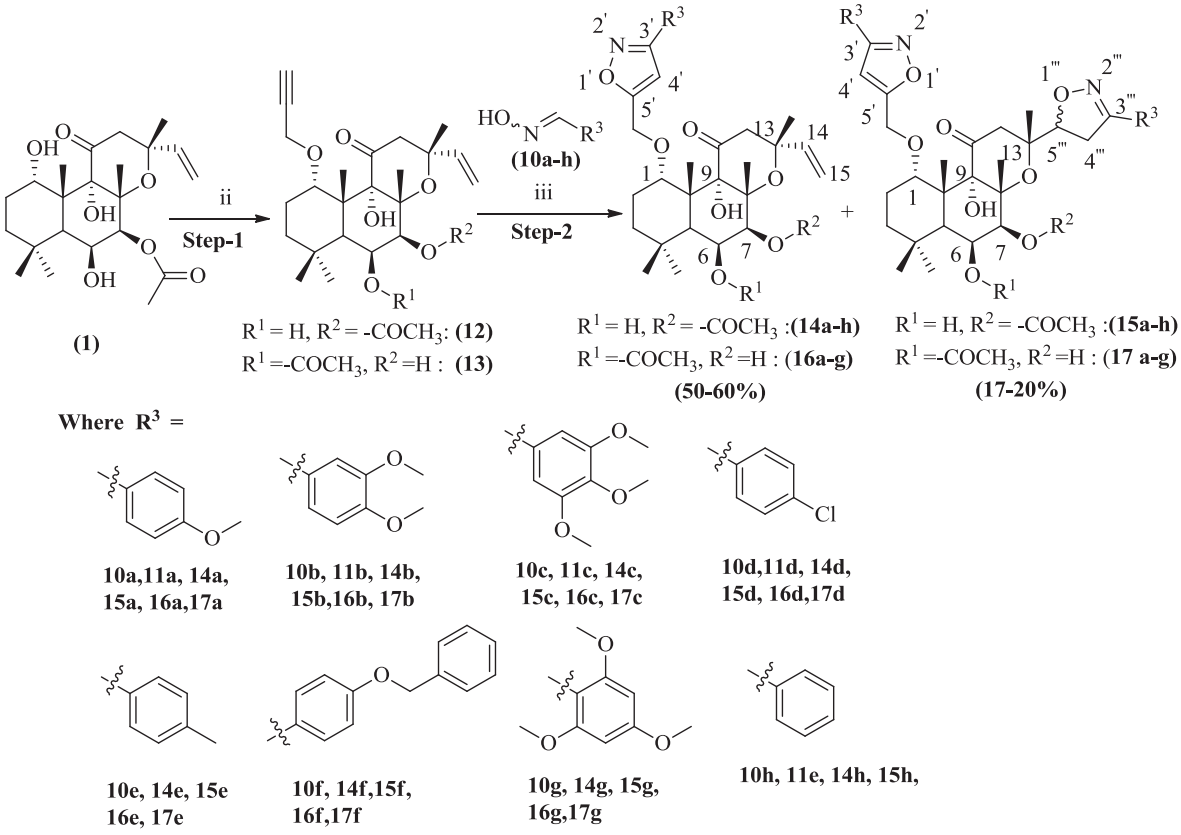
properties such as anti-obesity,[15] Cardiovascular,[16] asthma,[17] glaucoma,[18] antihypertensive inotropic,[19,20] anti-cancer activity,[21,22] stimulates the adenylyl cyclase activity and increases intracellular levels of cyclic AMP.[23] It has been reported that the order of reactivity of the hydroxyls in forskolin is 1-OH > 6-OH > 9-OH.[24] Generally, Heterocyclic compounds improve the pharmacokinetic and pharmacodynamic properties of anti-cancer drugs by enhancing lipophilicity, polarity or other physicochemical features. In the present study, we thus introduced novel isoxazoles at C_1-OH and tested their activity on breast cancer cell lines.

1,3-Dipolar cycloaddition is one of the best methods for the synthesis of 5-membered heterocyclic compounds. In this reaction, 1,3-dipole reacts with dipolarophiles in a symmetry allowed [π4s + π2s] manner. According to Sustmanns approach[25] these cycloadditions are of three types: HOMO-Controlled (Type-I: the interaction of the dipole HOMO with the dipolarophile LUMO is greatest), HOMO-LUMO Controlled (Type-II: both frontier orbital interactions are large) and LUMO-Controlled (Type-III: the interaction of the dipole LUMO with the dipolarophile HOMO is greatest). Earlier studies suggested that reactions involving aryl nitrile oxide 1,3-dipoles belong to Type-II molecular orbital interactions in FMO theory.[26–28] In nitrile oxide ($C{\equiv}N^{+}{-}O^{-}$) dipole, larger HOMO coefficient is on electronegative oxygen, while the larger LUMO coefficient is on the carbon. The HOMO of the 1,3-dipole when interacts



Scheme 1.



Regents and conditions: i) 10% Pd/ C,MeOH, H_2 gas, r.t, 1-2hr; ii) Propargyl bromide, K_2CO_3,NaI, acetone,reflux, 24hr; iii) 9-12% NaOCl, DCM, NEt_3, 0^0C-rt, 6hr.

Scheme 2.