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Carboxymethyl Derivatives Of Isoflavones: Carriers For Affinity Drug Targeting And Probes For Estrogen Action

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Rationale

Estradiol, a steroid hormone, regulates the growth, differentiation and function of diverse tissues, both within and outside the reproductive system. Because of the multiple target organs for estrogens and the occurrence of both beneficial and unwanted effects during hormone replacement therapy and breast cancer prevention and treatment, the key to improvement of drug therapy is the development of selective estrogen receptor modulators (SERMs) with better tissue selectivity. The hormone's relatively slow biological effects are mediated via two nuclear estrogen receptors, ERalpha and ERbeta, present mainly in the reproductive system, whereas the fast non-genomic effects are mediated via a membranal binder whose structure is not yet elucidated. The two ER isoforms exhibit distinct tissue distribution patterns and differ in their ligand binding ability and transactivational properties. A variety of chemicals with no obvious structural similarity mimic estrogen action. Among these, the isoflavones exhibit estrogenic/anti-estrogenic activities, depending on concentration, cell type, tissues or promotor context. Because of the diversity of estrogen action our current interest focuses in the development of novel probes for estrogen action. These include carboxymethyl isoflavones (e.g. 6-carboxymethyl genistein, 6-carboxymethyl biochanin A) and synthetic peptides with estrogen-like activity. The estrogenic/anti-estrogenic activities of these probes were studied in vitro and in vivo systems. The results obtained so far indicate that the carboxymethyl isoflavones can act as novel SERMs with unique properties on the bone, uterus and vasculature and as carriers for affinity drug targeting of estrogen sensitive cancer cells (e.g. adrenocortical H295 cells).

Recent Findings

- Both 6-carboxymethyl genistein (CG) and 6-carboxymethyl biochanin A (CB) (see Figure 1) acted in vivo as mixed agonist/antagonist when estradiol was bound to its receptors. Our findings suggest that both compounds can be considered novel SERMs with unique effects on the vasculature, bone and uterus.
- Daunomycin (Dau) conjugates of CG and CB (see Figure 1) inhibited DNA synthesis in estrogen sensitive in H295R cancer cells. A dose dependent cytotoxicity was observed with both conjugates. At 0.3-3 nM both conjugates were 10 to 30 times more potent than daunomycin. At 30 nM these conjugates were two to three times more potent than daunomycin. At concentrations ranging between 300 and 3000 nM, no difference in cytotoxicity was observed between the conjugates and daunomycin. When cells that do not express the estrogen receptor were treated with cytoxic conjugates or daunomycin, the cytoxic effect of the conjugates was the same as that of daunomycin over the concentration range tested. These pilot studies suggest that the ready availability of estrogenic binding sites in H295R cells can be exploited for site-directed chemotherapy.

Selected Publications

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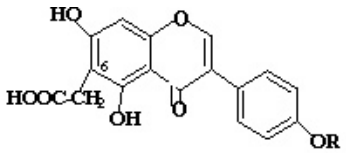
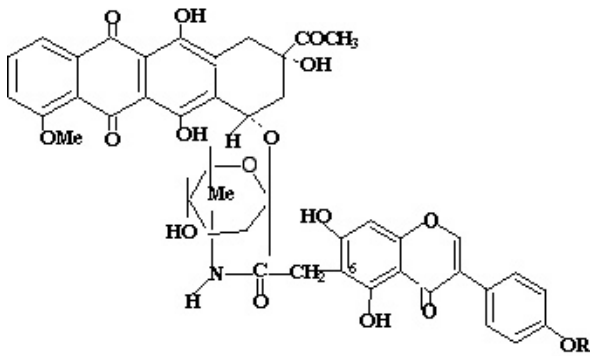


I, R=H, 6-Carboxymethyl genistein
II, R=Me, 6-Carboxymethyl biochanin A



III, R=H, genistein daunomycin conjugate
IV, R=Me, biochanin A daunomycin conjugate

Fig. 1 *Structures of carboxymethyl derivatives of isoflavones and their respective daunomycin conjugates.*

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