STUDY OF INDOLE AND ALKYNE STEROIDS AS POTENTIAL CYP17A1 INHIBITORS AND GLIOMA GROWTH REGULATORS

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Two series of alkyne- and indole-derived steroids were synthesized and screened for their ability to influence glioma proliferation and metabolic pathways involved in cancer development and survival. The substances were obtained by reductive amination of 20-keto- (pregnenolone) or 17-ketosteroids (dehydroepiandrosterone, estrone) with prop-2-yn-1-amine, but-3-yn-1-amine or tryptamine in the presence of sodium triacetoxyborohydride or sodium cyanoborohydride. The structures were confirmed by ESI mass spectrometry, IR spectroscopy and ^{1}H NMR spectroscopy. The substances were tested for their ability to inhibit CYP17A1-mediated progesterone 17-hydroxylation by engineered *Y. lypolytica* yeast strains. As a rate-limiting step in androgen biosynthesis, CYP17A1 presents a major target in treatment of androgen-dependent prostate cancer and is one of the recognized molecular targets of abiraterone acetate, an approved drug used to treat metastatic castration resistant prostate cancer (mCRPC) [1]. In the alkyne series, each substance was found to decrease 50 μM progesterone transformation by 70±9% when the test was run with a strain expressing only bovine adrenal CYP17A1 (*Y. lipolytica* 8-84.1.) However, when CYP11A1 was also present (strain 5.54-1), the inhibitory capacity decreased dramatically in most cases. Notably, the conjugate of pregenenolone and prop-2-yn-1-amine retained its relative inhibitory activity of 72±8% [2]. On the other hand, indole steroids produced only a minor reduction of 25±6% in 8-84.1 strain, suggesting CYP17A1 inhibition to be a minor contributor to potential antiproliferative action. The indole steroids were further tested for their ability to affect C6 glioma cell proliferation. After 24 hrs incubation, the dehydroepiandrosterone-derived IS-1 was found to reduce cell counts by 21±6% at 1 μM and 52±13% at 10 μM whereas estrone-based IS-2 and pregnenolone-based IS-3 produced a 18±7% reduction at 10 μM. No evidence of necrosis could be detected by LDH assay or propidium iodide staining, confirming that IS series do not affect cell viability. Likewise, no ROS overproduction could be detected by dichlorofluorescein diacetate, or calcium ion efflux by Fura-2 AM staining. However, the antiproliferative effect of IS-1 could be prevented by adding 10 μM DHEA, a known inducer of DNA repair proteins in neuron cells [3]. To summarize, two series of novel alkyne- and indole-containing steroids were synthesized and examined for their ability to inhibit cytochrome P450 17A1 which is involved in androgen and neurosteroid biosynthesis and cancer cell adaptation, and their capacity to reduce glioma proliferation. In alkyne series, the conjugate of pregnenolone and prop-2-yn-1-amine proved to be a moderately powerful competitive inhibitor of CYP17A1 in micromolar range, whereas in IS series, DHEA-based IS-1 reduced C6 glioma growth with an IC50 of 10 μM.

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