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Synthesis and evaluation of 1,2,3,4-tetrahydrocarbazole and it's derivatives as sulphatase inhibitors

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The growth of hormone-dependent mammary tumor cells is stimulated by non-conjugated estrogens. Relapse of breast cancer is a major area of concern and the understanding the role of various hormones in tumor maturation process in the breast is critical. The two enzymes being targeted related to this relapse problem are Aromatase and Steroid Sulfatase. Inhibition of steroid sulfatase enzyme may result in reduced levels of endogenous estrogens and, consequently, in a reduced proliferation rate of estrogen-dependent tumors. This paper reports on a series of inhibitors of steroid sulfatase based on sulfonamide derivatives of 1,2,3,4-tetrahydrocarbazole, a new class of mammary tumor inhibiting compounds. We have synthesized 1,2,3,4-tetrahydrocarbazole via Borsche synthesis method/ Bischler synthesis method. The sulfonamide group on tetrahydrocarbazole may mimic the sulfamoyl moiety of Irosustat. A number of derivatives of 1,2,3,4-tetrahydrocarbazole were synthesized and evaluated *in vitro* for steroid sulfatase inhibiting properties. The enzymatic test was based on the colorimetric measurement of p-nitrocatechol formed from p-nitrocatechol sulfate in the presence of various amounts of inhibitor. The concentrations which result in a 50% reduction of the rate of hydrolysis (IC_{50}) were determined. By comparing IC_{50} (μM) values with that of the standard drug Irosustat (IC_{50}=0.413±0.008μM), compounds with aromatic groups like aniline (compound DR7, N-phenyl-2,3,4,9-tetrahydro-1H-carbazole-7-sulfonamide; IC_{50}=0.485±0.019μM) and 2-nitroaniline (compound DR8, N-(2-nitrophenyl)-2,3,4,9-tetrahydro-1H-carbazole-7-sulfonamide; IC_{50}=0.512±0.010μM) were found to be of similar potency as Irosustat. The most potent of these inhibitors show affinities which are comparable to the affinities of natural substrates.

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