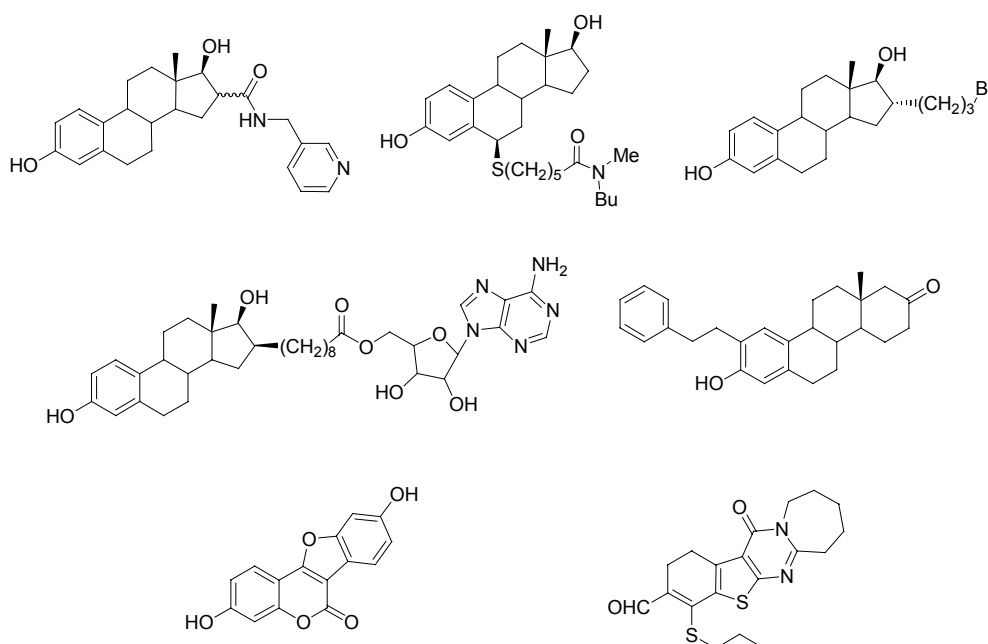


Selective 17 β hydroxysteroid Dehydrogenase1 Inhibitors

Intracellularly hydroxysteroid dehydrogenases (HSDs) modulate the action of steroid hormones. 17 β -HSD1 activates estrone (E1) to the most potent estrogen estradiol (E2) which stimulates cell proliferation and decreases apoptosis. As 17 β -HSD1 is very often strongly overexpressed in estrogen dependent diseases like breast cancer and endometriosis, 17 β -HSD1 is a promising target for the development of selective inhibitors to be applied as drugs for the treatment of these diseases.

There are only few inhibitors of 17 β -HSD1 described in the literature (1), most of them have a steroidal structure (Chart 2). They are substituted at the 2-, 6- or 16-position by different side-chains. Coumestrol, a coumarin derivative, is a potent phytoestrogen with an IC₅₀ of 0.12 μ M (2) but of course has estrogenic properties (3). A hybrid inhibitor (E2 and an adenosine moiety linked by a nine carbon chain) was described with a high *in vitro* activity (IC₅₀ = 52 nM, 4-5). However, tested in our laboratory, the compound was not able to permeate intact cells (CaCo2 assay). Therefore, it can not be expected to be active *in vivo*. Recently an E2 derivative with a pyridyl substituent in the side chain was published which belongs to the most active inhibitors discovered so far (IC₅₀ = 37 nM, 6). Similar activity is displayed by a D-homo-E1 with a 6-membered D-ring (IC₅₀ = 15 nM, 7). One of the very few non steroidal inhibitors contains a thiophenepyrimidinone-motif (8). It shows only moderate inhibition of the enzyme (74% at 1 μ M) and bears a formyl substituent which makes it questionable as a drug candidate.



In our opinion the non steroidal compounds are not appropriate candidates for drug development as they are not selective towards 17β -HSD2 which catalyses the reverse reaction, the deactivation of E2 to E1. In case of the steroidal compounds no data about estrogen receptor (ER) α and β affinity are available. Due to their structures we would expect stimulatory effects.

We have developed nonsteroidal 17β -HSD1 inhibitors showing IC₅₀ values in the low nanomolar range. They are rather selective towards 17β -HSD2 and show no affinity for ER α and β . The compounds show a reasonable permeation of CaCo2 monolayers, they are rather stable towards hepatic microsomes and show only little inhibition of human hepatic CYP enzymes. Presently the pharmacokinetic profile of the compounds is determined and an in vivo model for proof of concept is developed.

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