INHIBITION OF 17α-HYDROXYLASE-$C_{17,20}$-LYASE ($P450_{17\alpha}$) BY STEROIDAL PICOLINE AND PICOLINYLIDENE COMPOUNDS

Nikoletta Szabó[1], Jovana Ajduković[2], Imre Ignáth[1], Marija Sakač[2], Evgenija Djurendić[2], János Gardi[1], Gábor Mahmoud[1], Suzana Jovanović-Šanta[2], Katarina Penov Gaši[2], Mihály Szécsi[1]

[1]*First Department of Medicine, University of Szeged, Szeged, Hungary*

[2]*Department of Chemistry, Biochemistry and Environmental Protection, Faculty of Sciences, University of Novi Sad, Novi Sad, Serbia*

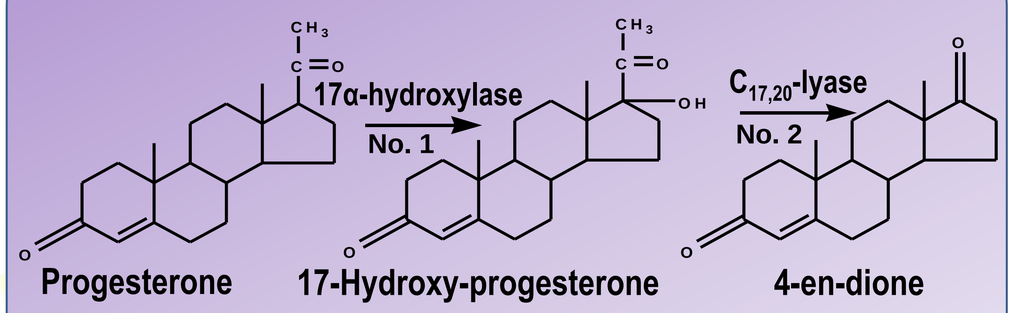
INTRODUCTION

17-Hydroxylase-$C_{17,20}$-lyase ($P450_{17\alpha}$) is a key regulator enzyme of the androgen biosynthetic pathway that catalyzes both the 17-hydroxylation and the cleavage of the C17–C20 side-chain of 21-carbon steroids in both the testes and the adrenals. Inhibition of this enzyme can block androgen synthesis in an early step, and may thereby be useful in the treatment of prostatic carcinoma, which is androgen-dependent in the majority of cases. Abiraterone (3β-hydroxy-17-(pyridyl)-androsta-5,16-diene) and its analogues have been found strong inhibitors of $P450_{17\alpha}$, suggesting that steroid derivatives with heterocyclic substituent on the C17 position may possess such potential. Inhibition studies also contribute to the exploration of structural features of the enzyme and help to understand better mechanism of the biotransformation. Experiments using rat tissue preparations are widely acknowledged in vitro tests for the investigation of a presumed $P450_{17\alpha}$ inhibitory activity. Inhibitor complexed X-ray crystal structure of the human enzyme has been determined recently (DeVore NM and Scott EE, Nature 2012;482:116-120.) and displays strong similarity to the predicted 3D model (ModBase) of the rat $P450_{17\alpha}$.

AIM

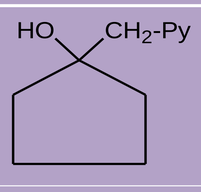
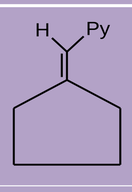
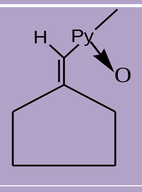
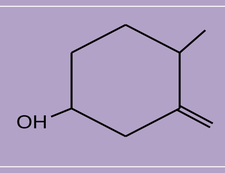
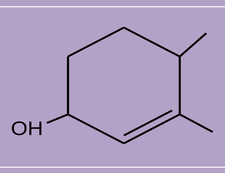
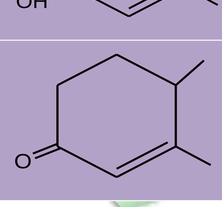
- We investigated inhibitory effect Inhibitory effects of twelve novel 17-picolyl and 17-picolinylidene androstene compounds exerted against the 17α-Hydroxylase and the subsequent $C_{17,20}$-lyase activities of the rat testicular $P450_{17\alpha}$ were investigated.

Enzyme activites measured

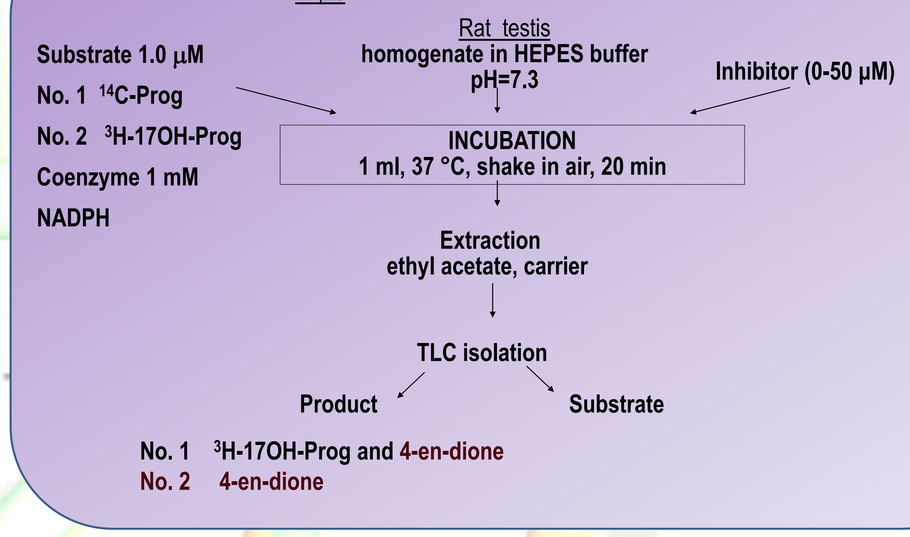


RESULTS

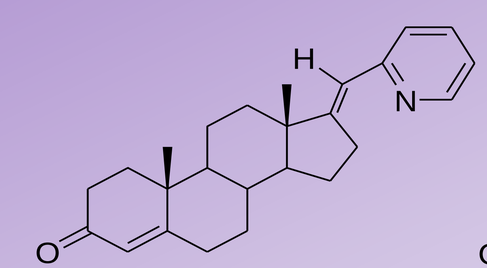
Inhibition of 17α-Hydroxylase-$C_{17,20}$-lyase activities by 17-picolyl and 17-picolinylidene compounds. Relative conversions (control incubation with no inhibition is 100%) measured in the presence of 50 μM concentration of the compound tested. NI: no inhibition.

A-ring \ D-ring			
	Ohlase / Lyase Rel. Conv (%)	OHlase / Lyase IC_{50} (μM)	OHlase / Lyase
	95 ,0 / 115,2	38,0 / 8,2	— / —
	90,4 / 65,7	49,7 / 13,7	Rel. Conv (%) — / 61,6 %
	87,3 / 73,0	5,9 / 2,5	IC_{50} (μM) 1,2μM / 2,9μM

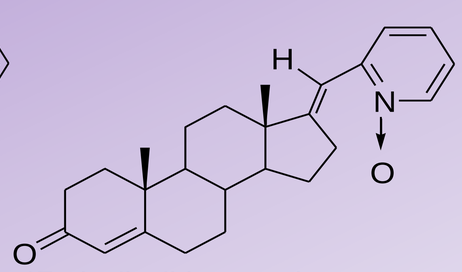
In vitro radioincubation method for the measurement of $C_{17,20}$-lyase activity and inhibition



Most important two picolinylidene compounds



17-picolinylidene-androst--4-en-3-one



17-picolinylidene-androst--4-en-3-one-N-oxide

CONCLUSIONS

- Our results revealed that 17-picolinylidene-androst-4-en-3-one and 17-picolinylidene-androst-4-en-3-one-N-oxide were potent inhibitors of the $P450_{17\alpha}$. Both compounds exerted similar inhibitory effect against $C_{17,20}$-lyase activity, IC_{50} values were found to be 2.5μM and 2.9μM, respectively.
- The 17α-hydroxylase activity was inhibited five times more efficiently by the N-oxide derivative (IC_{50}=1.2μM) than by its unsubstituted 17-picolinylidene counterpart (IC_{50}=5.9μM).
- Further tested compounds did not inhibit enzyme activities substantially.
- Our results provide new data on $P450_{17\alpha}$ inhibition and on modulation of its two distinct activities. Structure-activity relationships give better understanding on the mechanisms of androst-4-en-3,17-dione biosynthesis and testosterone production, as well as findings may contribute to the development of new drug molecules with specific anti-hormonal effect.

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