

Pharmacology of novel steroidal inhibitors of cytochrome P450(17) alpha (17 alpha-hydroxylase/C17-20 lyase).

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Medical or surgical castration for the treatment of prostatic cancers prevents androgen production by the testes, but not by the adrenals.

Inhibition of the **key enzyme for androgen biosynthesis, cytochrome P450(17) alpha**, could prevent androgen production from both sources.

The in vivo effects of 17-(3-pyridyl)androsta-5,16-dien-3 beta-ol (**CB7598**) and 17-(3-pyridyl)androsta-5,16-dien-3-one (**CB7627**), novel potent steroidal inhibitors of this enzyme, on WHT mice were compared with those of castration and two clinically active compounds, **ketoconazole** and **flutamide**.

Flutamide and surgical castration caused significant reductions in the weights of the ventral prostate and seminal vesicles.

CB7598, in its 3 beta-O-acetate form (CB7630), and CB7627 caused significant reductions in the weights of the ventral prostate, seminal vesicles, kidneys and testes when administered once daily for 2 weeks.

Ketoconazole, given on the same schedule, caused no reductions.

Plasma testosterone was reduced to < or = 0.1 nM by CB7630, despite a 3- to 4-fold increase in the plasma level of luteinizing hormone.

Adrenal weights were unchanged following treatment with CB7630 or CB7627 but were markedly increased following ketoconazole, indicating no inhibition of corticosterone production by these steroidal compounds.

These results indicate that CB7598, CB7630 or CB7627 **may be useful in the treatment of hormone-dependent prostatic cancers**.

In vitro and in vivo models for the evaluation of potent inhibitors of male rat 17alpha-hydroxylase/C17,20-lyase.

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The **C(17,20)-lyase** is a key enzyme in the biosynthesis of androgens by both the testes and adrenals.

A complete inhibition of this enzyme would provide an alternative means of androgen suppression for the treatment of prostatic cancers.

In the present study, the inhibitory effects of **new non-steroidal compounds** were tested in vitro on rat C(17,20)-lyase versus **abiraterone**, a reference steroidal inhibitor.

Their activities were also evaluated in vivo on plasma testosterone (T) and luteinizing hormone (LH) levels and on testes, adrenals, seminal vesicles (SV) and ventral prostate (VP) weights after 3 days of oral treatment to adult male rats (50mg/kg per day p.o.).

Inhibition in the nanomolar range was obtained with TX 977, the lead racemate product in this series, and optimization is ongoing based on a slight dissociation observed between its two diastereoisomers, TX 1196-11 (S) and TX 1197-11 (R).

These non-steroidal compounds (including YM 55208, a reference competitor) **proved to be more active in vivo than abiraterone acetate** in this model, but the observed impact on adrenal weight suggests that the specificity of lyase inhibition versus corticosteroid biosynthesis deserves further investigations **with this new class of potentially useful agents for the treatment of androgen-dependent prostate cancer.**

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Hormonal impact of the 17alpha-hydroxylase/C(17,20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer.

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A series of three dose escalating studies were conducted to investigate the **ability of the 17alpha-hydroxylase/C(17,20)-lyase inhibitor abiraterone acetate, to cause maximum suppression of testosterone synthesis** when delivered to castrate and noncastrate males with prostate cancer.

Study A was a single dose study in castrate males. Study B was a single dose study in noncastrate males and study C was a multiple dose study in noncastrate males. The drug was given orally in a once-daily dose and blood samples taken to assess pharmacokinetic (PK) parameters and hormone levels in all patients. The study drug was well tolerated with some variability in PKs. Suppression of testosterone levels to <0.14 nmol l⁻¹ was seen in four out of six castrate males treated with a single dose of 500 mg. At 800 mg given days 1-12 in noncastrate males, target suppression was achieved in three out of three patients, but a two- to three-fold increase of Luteinising Hormone (LH) levels in two out of three patients overcame suppression within 3 days. All patients in the multiple dose study developed an abnormal response to a short Synacthen test by day 11, although baseline cortisol levels remained normal. This is the first report of the use of a specific 17alpha-hydroxylase/(17,20)-lyase inhibitor in humans. Repeated treatment of men with intact gonadal function with abiraterone acetate at a dose of 800 mg can successfully suppress testosterone levels to the castrate range. However, this level of suppression may not be sustained in all patients due to compensatory hypersecretion of LH. The enhanced testosterone suppression achieved in castrate men merits further clinical study as a second-line hormonal treatment for prostate cancer. Adrenocortical suppression may necessitate concomitant administration of replacement glucocorticoid.

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Synthesis, biological evaluation and molecular modelling studies of methyleneimidazole substituted biaryls as inhibitors of human 17 α -hydroxylase-17,20-lyase (CYP17). Part I: Heterocyclic modifications of the core structure.

[Jagusch C](#), [Negri M](#), [Hille UE](#), [Hu Q](#), [Bartels M](#), [Jahn-Hoffmann K](#), [Pinto-Bazurco Mendieta MA](#), [Rodenwaldt B](#), [Müller-Vieira U](#), [Schmidt D](#), [Lauterbach T](#), [Recanatini M](#), [Cavalli A](#), [Hartmann RW](#).

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Novel chemical entities were prepared via Suzuki and S(N) reaction as AC-ring substrate mimetics of CYP17.

The synthesised compounds 1-31 were tested for activity using human CYP17 expressed in Escherichia coli.

Promising compounds were tested for selectivity against hepatic CYP enzymes (3A4, 2D6, 1A2, 2C9, 2C19, 2B6).

Two potent inhibitors (27, IC₅₀ = 373 nM/28, IC₅₀ = 953 nM) were further examined in rats regarding their **effects on plasma testosterone levels and their pharmacokinetic properties**.

Compound 28 was similarly active as abiraterone and showed better pharmacokinetic properties (higher bioavailability, t(1/2) 9.5 h vs 1.6 h).

Docking studies revealed two new binding modes different from the one of the substrates and steroidal inhibitors.

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http://www.prostatecancerfoundation.org/site/c.itIWK2OSG/b.3612285/k.EC/2007_Scientific_Retreat_Highlights.htm

A new class of drugs is being studied for its ability to prevent intratumoral androgen production by inhibiting the activity of an enzyme named **lyase** – a [molecule involved in the synthesis of testosterone from precursor cholesterol](#). This discovery explains, in part, how prostate cancer cells might survive and proliferate after standard hormonal therapy fails. Three new, distinct, lyase-inhibiting drugs are being developed simultaneously. One of these new targeted medicines, called **abiraterone**, is currently being tested in the United Kingdom as well as in the United States through the PCF Clinical Trials Consortium. To date, trials with abiraterone have demonstrated significant remissions in more than 40% of men with advanced prostate cancer that is resistant to hormone therapy. Larger clinical trials are planned in 2008 based on the positive findings reported at the 2007 PCF Scientific Retreat.

Implication of Discovery 1: A new "druggable" pathway has been discovered to treat prostate cancers when they cease to respond to currently available hormone therapies. However, additional research effort is needed to identify patients that will optimally respond to **lyase inhibitory therapy**

Lyasen

aus **Wikipedia, der freien Enzyklopädie**

Wechseln zu: [Navigation](#), [Suche](#)

Lyase ist in der [Biochemie](#) der Oberbegriff für alle [Enzyme](#), die eine [Molekülspaltung katalysieren](#). Sie haben die [EC-Nummer EC 4](#). [Synthasen](#), welches ebenfalls Lyasen sind, katalysieren die Synthese komplexerer Produkte aus einfachen Substraten, allerdings ohne Spaltung von [ATP](#). Der Begriff Lyase stammt von der umgekehrten Reaktion: Die nicht-hydrolytische Spaltung eines Moleküls in zwei Produkte unter Bildung einer Doppelbindung. Lyasen erzeugen meist eine neue [Doppelbindung](#) oder eine Ringstruktur.

Zu den Lyasen zählen unter anderem

- [Decarboxylasen](#)
- [Aldehydlyasen](#)
- [Dehydratasen](#)

[Kinasen](#) dagegen gehören zu den Transferasen.

Beispiele [\[Bearbeiten\]](#)

- [Fumarase](#)

- [Pyruvat-Decarboxylase](#)
- [Aldolase](#)
- [Histidin-Ammoniak-Lyase](#)