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Patent Highlight

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Selective Cyp11B1 Inhibitors for the Treatment of Cortisol Dependent Diseases

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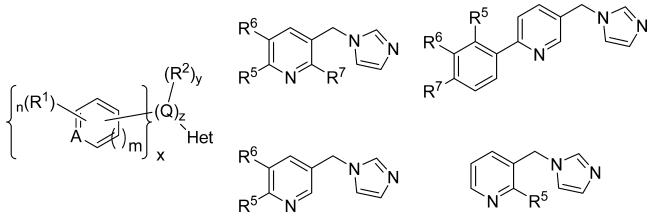
Title:	Selective Cyp11B1 Inhibitors for the Treatment of Cortisol Dependent Diseases		
Patent/Patent Application Number:	WO2012052540	**Publication date:**	April 26th, 2012
Priority Application:	EP10188380.9	**Priority date:**	October 21st, 2010
	EP10188975.6		October 27th, 2010
Inventors:	Hartmann, R.; Hille, U.; Zimmer, C.; Vock, C. A.; Hu, Q.		
Assignee Company:	Universitaet Des Saarlandes		
Disease Area:	Metabolic disease	**Biological Target:**	Cyp11B1

Summary:

Corticosteriods are an important class of steroid hormones that play a key role in a variety of physiological processes, including inflammation and metabolism. Their synthesis is controlled by a series of cytochrome P450 based enzymes, and improper regulation of corticosteroid production is associated with several disease states. Cushing's disease, for example, has been directly linked to the overproduction of the steroid hormone cortisol. This condition is typified by central obesity, rounded face, and significantly increased risk of diabetes and hypertension. The final step in the synthesis of cortisol is the hydroxylation of deoxycortisol in the 11β-position, which is mediated by steroid-11β-hydroxylase (CYP11B1).

It has been suggested that inhibition of Cyp11B1 would be a viable treatment mechanism for Cushing' syndrome, provided that selectivity versus related Cyp enzymes (e.g., Cyp17, Cyp19, and Cyp11B2) could be established. Selectivity versus Cyp11B2 has been particularly challenging, as it has a very high degree of homology with Cyp11B1 (93%). The current application describes a novel set of Cyp11B1 inhibitors for the treatment of diseases associated with the overproduction of cortisol, such as Cushing's syndrome.

Important Compound Classes:



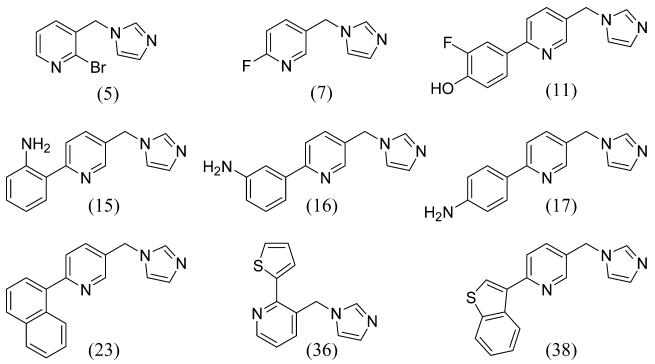
Definitions:

R^5 is H, C_1−C_{12} alkyl, haloalkyl, cycloalkyl, alkenyl, cycloalkylene, alkynyl, C_6−C_{13} aryl, naphthyl, C_1−C_5 alkoxy, hydroxyl, halogen, furanyl, benzo[b]thiophen, thiophen, CN, NO_2, OAc, amino, amido, $C(O)R^4$, trityl, or heteroaryl.

R^6 is H, C_1−C_{12} alkyl, haloalkyl, cycloalkyl, C_1−C_5 alkoxy, hydroxyl, halogen, alkenyl, cycloalkylene, alkynyl, C_6−C_{13} aryl, naphthyl, furanyl, thiophen, benzo[b]thiophen, CN, NO_2, OAc, amino, amido, $C(O)R^4$, $OC(O)R^4$, trityl, or heteroaryl.

R^7 is H, C_1−C_{12} alkyl, haloalkyl, cycloalkyl, C_1−C_{12} alkenyl, cycloalkylene, alkynyl, C_6−C_{13} aryl, C_1−C_5 alkoxy, hydroxyl, thiophen, furanyl, benzo[b]thiophen, naphthyl, CN, NO_2, OAc, amino, amido, $C(O)R^4$, $OC(O)R^4$, trityl, or heteroaryl.

Key Structures:



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Recent Review Articles:

Hakki, T.; Bernhardt, R. CYP17- and CYP11B-dependent steroid hydroxylases as drug development targets. *Pharmacol. Ther.* **2006**, *111* (1), 27−52.

Bureik, M.; Lisurek, M.; Bernhardt, R. The human steroid hydroxylases CYP11B1 and CYP11B2. *Biol. Chem.* **2002**, *383* (10), 1537−1551.

Biological Assay:

Cyp11B1: Cellular assay, V79MZ cell expressing human Cyp11B1.

Cyp11B2: Cellular assay, V79MZ cell expressing human Cyp11B2.

Cyp17: Cellular assay, Recombinant E. coli pJL17/OR coexpressing human Cyp17 and rat NADPH-P450-Reductase.

Cyp19: Enzyme assay, Human Cyp19 from placental tissue.

Biological Data:

Entry	Cyp11B1	Cyp11B2	Entry	Cyp11B1	Cyp11B2
	IC_{50} (nM)			IC_{50} (nM)	
5	61	911	17	106	528
7	72	1736	23	42	2075
11	17	237	36	16	251
15	101	2114	38	40	1157
16	110	3407			

Claims

15 Total claims.

6 Composition of matter claims.

9 Method of use claims.

AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.