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Patent Highlight

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Aldosterone Synthase Inhibitors

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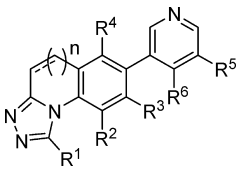
Title:	Aldosterone Synthase Inhibitors		
Patent/Patent Application Number:	WO2012148808	**Publication date:**	November 1st, 2012
Priority Application:	US61479209	**Priority date:**	April 26th, 2011
Inventors:	Hoyt, S. B.; Petrille, W. L.; London, C.; Xiong, Y.; Taylor, J. A.; Ali, A.l; Lo, M.; Henderson, T. J.; Hu, Q.; Hartmenn, R.; Yin, L.; Heim, R.; Bey, E.; Saxena, R.; Samanta, S. K.; Kulkarni, B. A.		
Assignee Company:	Merck Sharp & Dohme Corporation		
Disease Area:	Cardiovascular disease	**Biological Target:**	Aldosterone synthase (Cyp11B2)

Summary:

Aldosterone, a steroid hormone from the mineralocorticoid family, has a key role in the regulation of blood pressure. Binding of aldosterone to the mineralocorticoid receptor (MR) leads to increased retention of sodium and water in the kidney, which in turn increases blood pressure. Efforts to modulate the impact of systemically produced aldosterone through the use of mineralocorticoid receptor antagonists (MRAs), such as spironolactone and eplerenone, have successfully demonstrated significant reduction in morbidity and mortality when given in conjunction with ACE inhibitors. However, nonselective MRAs have been associated with sexual side effects, increased plasma potassium levels, and elevated aldosterone plasma concentrations.

Modulation of aldosterone mediated effects could also be accomplished by inhibition of aldosterone synthesis. Cyp11B2 (aldosterone synthetase), a mitochondrial cytochrome P450 enzyme responsible for the conversion of 11-deoxycorticosterone to aldosterone, has been identified as a potential therapeutic target. In principle, inhibition of Cyp11B2 should provide the beneficial aspects of MRAs, while avoiding the adverse effects associated with MRA binding. Cyp11B2, however, has a high degree of homology with Cyp11B1 (93%), and this enzyme plays a critical role in the synthesis of cortisol, which regulates glucose metabolism. Nonselective Cyp11B1/Cyp11B2 compounds could negatively impact cortisol synthesis, creating undesired side effects in patients requiring treatment with an aldosterone synthesis inhibitor. Thus, a high degree of selectivity for Cyp11B2 over Cyp11B1 is desirable in this instance. The patent application WO2012148808 describes a series of nonsteroidal, selective Cyp11B2 inhibitors useful for the treatment of diseases and conditions associated with excess aldosterone.

Important Compound Classes:



Definitions:

R^1 is H optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl.

R^2 is H, halogen, CN, optionally substituted alkyl, optionally substituted cycloalkyl.

R^3 is H, halogen, CN, optionally substituted alkyl, optionally substituted cycloalkyl.

R^4 is H, halogen, CN, optionally substituted alkyl, optionally substituted cycloalkyl.

R^5 is H, halogen, optionally substituted alkyl, CN, OR^7, NR^8R^9, $N(R^{11})C(O)R^7$, $C(O)R^7$, $C(O)N(R^8)(R^9)$, $C(O)OR^7$, $N(R^{11})S(O)_2R^7$, $S(O)_2N(R^8)(R^9)$, $S(O)_mR^7$, where m is 1 or 2, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl.

R^6 is H, halogen, CN, OR^7, NR^8R^9, $N(R^{11})C(O)R^7$, $C(O)N(R^8)(R^9)$, $C(O)R^7$, $C(O)OR^7$, $N(R^{11})S(O)_2R^7$, $S(O)_2N(R^8)(R^9)$, $S(O)_mR^7$, where m is 1 or 2, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl.

R^5 and R^6 are joined together to form a 5−7 membered carbocyclic or heterocyclic ring fused to the pyridyl ring to which R^5 and R^6 are attached, wherein the ring formed by R^5 and R^6 is optionally independently substituted by 1 to 3 R^{10}.

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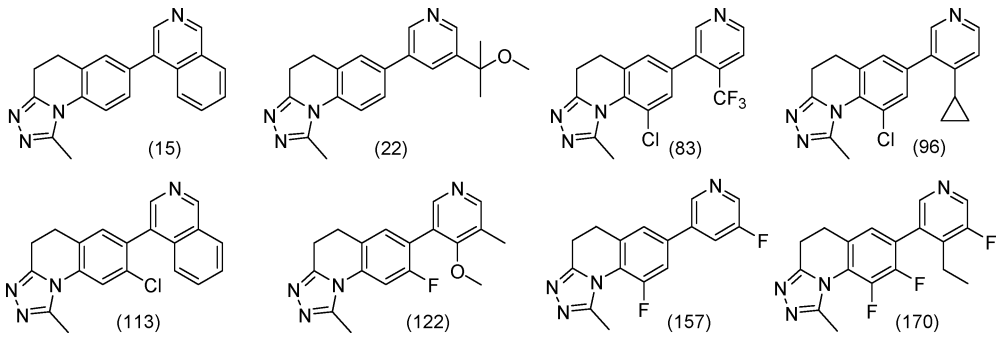
Key Structures:



Recent Review Articles:

Aldosterone synthase inhibition in humans. Azizi, M.; Amar, L.; Menard, J. *Nephrol., Dial., Transplant.*, **2013**, *28* (1), 36−43.

Hartmann, R. W.; Mueller-Vieira, U.; Ulmschneider, S.; Voets, M.; Rekka, E. A.; Kourounakis, P. N. Discovery of potent and selective inhibitors of human aldosterone synthase (CYP11B2): a new target for the treatment of congestive heart failure and myocardial fibrosis—a review. *Chem. Mol. Aspects Drug Des. Action*, 2008, 165−175.

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

Biological Assay:

Cyp11B2: Cellular assay, V79MZ cell expressing human Cyp11B2.

Cyp11B1: Cellular assay, V79MZ cell expressing human Cyp11B1.

Biological Data:

Entry	Cyp11B2	Cyp11B1	Entry	Cyp11B2	Cyp11B1
	IC_{50} (nM)			IC_{50} (nM)	
15	5	407	113	17	>10,000
22	5	108	122	32	>10,000
83	22	>30,000	157	89	29,540
96	48	6,930	170	41	17,296

Claims:

21 Total claims.

18 Composition of matter claims.

3 Method of use claims.

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Notes

The authors declare no competing financial interest.

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