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Patent Highlight

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Aldosterone Synthase Inhibitors: Targeting Chronic Kidney Disease and Diabetic Nephropathy

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Title:	Pyrazole Derivatives Useful as Aldosterone Synthase Inhibitors		
Patent Application Number:	WO 2012/173849 A1	**Publication Date:**	December 20, 2012
Priority Application:	US 61/496,657	**Priority Date:**	June 14, 2011
	US 61/506,349		July 11, 2011
Inventors:	Bell, M. G.; Hoogestraat, P. J.; Mabry, T. E.; Shen, Q.; Escribano, A. M.		
Assignee Company:	Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285, United States		
Disease Area:	Chronic kidney disease and diabetic nephropathy	**Biological Target:**	Aldosterone synthase

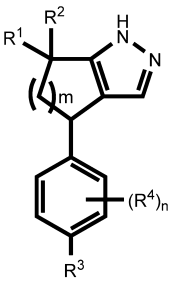
Summary:

The invention in this patent application introduces pyrazole derivatives represented generally by Formula (I), which act as aldosterone synthase inhibitors and may provide a treatment for kidney diseases.

Aldosterone synthase is the rate-limiting enzyme in the biosynthesis of aldosterone, a steroid hormone of the mineralocorticoid family that plays a role in the retention of sodium. Elevated levels of plasma aldosterone are implicated in progressive renal disease that leads to chronic kidney disease. Animal models of kidney disease have shown that aldosterone synthase inhibitors are useful for the treatment of kidney disease.

Current aldosterone synthase inhibitors are not specific to aldosterone and can also inhibit the production of cortisol, testosterone, and/or estradiol. Thus, specificity for aldosterone synthase remains a challenge, and there is a need for more potent and more selective synthase inhibitors. The compounds of Formula (I) in this invention show a good selectivity for aldosterone synthase inhibition and can potentially be used for the treatment of chronic kidney disease and diabetic nephropathy.

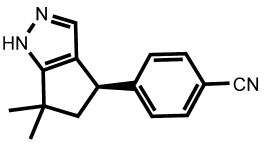
Important Compound Classes:



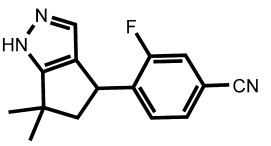
Formula (I)

Key Structures:

The patent application describes 67 examples of Formula (I). The biological data for the two examples (**1** and **49**) were reported.



Example **1**



Example **49**

Biological Assay:

The following assays were described in the patent application:

- Aldosterone synthase inhibitor assay
- Inhibition of aldosterone synthase in rats
- Cortisol inhibition assay
- Testosterone and estradiol production assay
- Cynomolgus monkey aldosterone inhibition assay
- Cynomolgus monkey cortisol inhibition assay

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Biological Data: Data from aldosterone synthase inhibitor assay:

Example	IC_{50} (hcyp11B2, mM)
1	0.005, n = 4
49	0.007, n = 2

Data from testosterone and estradiol production assay:

Example	Testosterone IC_{50} (μM)	Estradiol IC_{50} (μM)	Selectivity ratio for aldosterone compared with testosterone	Selectivity ratio for aldosterone compared with testosterone
1	>30	13.2	>6000	2640
49	>30	22.0	>4285	3143

Claims: Claims 1−4: Composition of matter; variations of Formula (I)
Claims 5−9: Specific compounds listed by structure
Claim 10: Pharmaceutical composition
Claims 11−12: Methods of treating chronic kidney disease and diabetic nephropathy
Claims 13−17: Compounds from claims 1−9 for treating chronic kidney disease and diabetic nephropathy

Recent Review Articles:
1. Laurent, S.; Schlaich, M.; Esler, M. *Lancet* **2012**, *380* (9841), 591−600.
2. Bramlage, P.; Turgonyi, E.; Montalescot, G. *Eur. Heart J. Suppl.* **2011**, *13* (Suppl. B), B46−B50.
3. Jansen, P. M.; van den Meiracker, A. H.; Danser, A. H. J. *Curr. Opin. Invest. Drugs* (BioMed Central) **2009**, *10* (4), 319−326.

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Notes

The authors declare no competing financial interest.