

## Aldosterone Synthase Inhibitors: Targeting Chronic Kidney Disease and Diabetic Nephropathy

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Title: Pyrazole Derivatives Useful as Aldosterone Synthase Inhibitors

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Disease Area: Chronic kidney disease and diabetic Biological Target: Aldosterone synthase

nephropathy

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:

$$\mathbb{R}^1$$
 $\mathbb{R}^2$ 
 $\mathbb{R}^1$ 
 $\mathbb{R}^2$ 
 $\mathbb{R}^3$ 
 $\mathbb{R}^3$ 

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.

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

Received: January 14, 2013 Published: January 23, 2013 **Biological Data:** 

Data from aldosterone synthase inhibitor assay:

Example	IC <sub>50</sub> (hcyp11B2, mM)		
1	0.005, n = 4		
49	0.007, n = 2		

Data from testosterone and estradiol production assay:

Example	Testosterone IC <sub>50</sub> (μM)	Estradiol IC <sub>50</sub> (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.