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The Pharmacology of DMP696 and DMP904, Non-Peptidergic CRF_1 Receptor Antagonists

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ABSTRACT

CRF_1 antagonists DMP696 and DMP904 were designed as drug development candidates for the treatment of anxiety and depression. Both compounds display nanomolar affinity for human CRF_1 receptors, and exhibit >1000-fold selectivity for CRF_1 over CRF_2 receptors and over a broad panel of other proteins. DMP696 and DMP904 block CRF-stimulated adenylyl cyclase activity in cortical homogenates and cell-lines expressing CRF_1 receptors. Both compounds inhibit CRF-stimulated ACTH release from rat pituitary corticotropes. Binding and functional studies indicate that DMP696 and DMP904 behave as noncompetitive full antagonists. DMP696 and DMP904 exhibit anxiolytic-like efficacy in several rat anxiety models. In the defensive withdrawal test, both compounds reduce exit latency with lowest effective doses of 3 and 1 mg/kg, respectively. The anxiolytic-like effect is maintained over 14 days of repeated dosing. In the context of a novel environment used in this test, DMP696 and DMP904 reverse mild stress-induced increases in plasma CORT secretion but at doses 3–4-fold greater than those required for anxiolytic-like efficacy. DMP696 and DMP904 are ineffective in three depression models including the learned helplessness paradigm at doses up to 30 mg/kg. At lowest anxiolytic-like doses, DMP696 and DMP904 occupy >50% CRF_1 receptors in the brain. The *in vivo* IC_{50} values (plasma concentrations required for occupying 50% CRF_1 receptors) estimated based upon free, but not total, plasma concentrations are an excellent correlation with the

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in vitro IC_{50} values. Neither compound produces sedation, ataxia, chlordiazepoxide-like subjective effects or adverse effects on cognition at doses 10-fold higher than anxiolytic-like doses. Neither compound produces physiologically significant changes in cardiovascular, respiratory, gastrointestinal or renal functions at anxiolytic-like doses. DMP696 and DMP904 have favorable pharmacokinetic profiles with good oral bioavailabilities. The overall pharmacological properties suggest that both compounds may be effective anxiolytics with low behavioral side effect liabilities.