DISCOVERY OF NOVEL TETRACYCLIC TETRAHYDROFURAN DERIVATIVES AS POTENT, ORALLY ACTIVE, BROAD SPECTRUM PSYCHOTROPIC AGENTS

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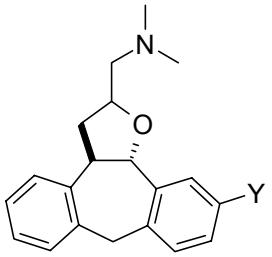
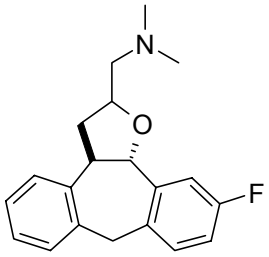
We have recently described a series of tetracyclic tetrahydrofuran derivatives represented by structure **I** [1,2]. These tetracycles proved to have a rich pharmacological profile as it was shown through their interaction with multiple dopaminergic, serotonergic, α-adrenergic, and histamine receptors and for the norepinephrine transporter. These binding properties translated into several interesting activities in some vivo assays for antipsychotic, anxiolytic, and antidepressant potential [3].

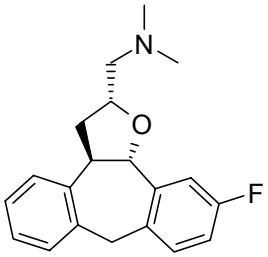


I

[X = O, S; Y = H, halo]



II



III

Herein we will report on the synthesis and pharmacological characterization of new "carbon bridged" analogues represented by formula **II**, which have led to the identification of **III** as a potent orally active broad spectrum psychotropic agent.

[1] Trabanco A. A.; Alonso, J. M.; Andrés, J. I.; Cid, J. M:; Fernández, J.; Iturrino, L.; Megens, A. *Chem. Pharm. Bull.* **2004**, *52*, 262.
[2] Cid, J. M.; Alonso, J. M.; Andrés. J. I.; Fernández, J.; Gil, P.; Iturrino, L.; Matesanz, E.; Meert, T. F.; Megens, A.; Sipido, V. K.; Trabanco, A. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2765.
[3] Fernández, J.; Alonso, J. M.; Andrés, J. I., Cid, J. M.; Díaz, A.; Iturrino, L.; Gil, P.; Megens, A.; Sipido, V. K.; Trabanco, A. A. *J. Med. Chem.*, **2005** in press.