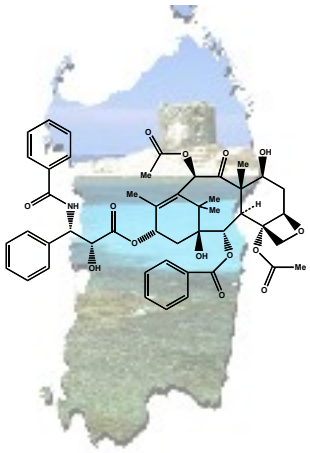
SardiniaChem2008

GIORNATA DI STUDIO DEDICATA ALLA CHIMICA ORGANICA DELLE MOLECOLE BIOLOGICAMENTE ATTIVE

30 Maggio 2008, Aula Magna della Facoltà di Scienze – Sassari



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SYNTHESIS AND SAR STUDY OF 2-SUBSTITUTED IMIDAZO[2,1-*B*] [1,3]BENZOTHIAZOLES AND RELATED COMPOUNDS ENDOWED WITH AFFINITY FOR DOPAMINE D_2 RECEPTORS AS POTENTIAL ANTIPSYCHOTICS

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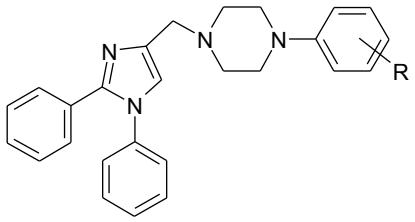
Schizophrenia is a complex disorder affecting approximately 1% of the population. Typical antipsychotic agents such as chlorpromazine and haloperidol block the D_2 subtype of dopamine receptors in a direct relation to their clinical potency. However, although blockade of D_2 receptors improves the positive symptoms of the disease, it also accounts for side effects which strongly limit patient compliance, in particular extrapyramidal effects and hyperprolactinemia.

During the past few years, a second generation of antipsychotic agents has emerged (e.g.,clozapine, risperidone, olanzapine, and ziprasidone); they are categorized as atypical in contrast to conventional D_2 blockers and exhibit a dual dopaminergic and serotonergic mechanism of action: a relatively weak dopamine D_2 receptor antagonism in vitro and in vivo, but potentially important activities at other dopaminergic (D_1, D_4) receptors, at serotonergic (5-HT_{1A}, $5HT_{2A}$, $5HT_3$, $5HT_{2C}$), adrenergic (α_1, α_2), histaminergic (H_1), and muscarinic receptors. They are claimed to be active against both positive and negative symptoms of schizophrenia, even though they do exhibit a variety of other side effects as weight gain, postural hypotension, sedation, dry mouth. For these reasons the search for more effective and less toxic agents still continues [1,2].

In this context we have developed a series of (1,2-diphenyl-imidazolyl)piperazine derivatives (**1**) that are endowed with substantial affinities for both dopamine D_2 receptors as well as 5-HT_{1A} and 5-HT_{2A} serotonin receptors, compound **1a** (R = *o*-OCH_3) of which is representative [3].

We have extended our study on other series of compounds derived from **1** both modifying the 1,2-diphenyl motif attached to the imidazole core, and the phenyl-piperazine moiety.

All novel compounds were submitted by Lundbeck to radioligand binding assay on dopamine, serotonin, adrenergic, histaminergic receptor subtypes. The chemistry and the *in vitro* screening will be discussed in the poster.



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[1] a) Rowley M.; Bristow L. J.; Hutson P. H. Current and Novel Approaches to the Drug Treatment of Schizophrenia. *J. Med. Chem*. **2001**, *44*, 477-501. b) Marino, M.; J. Knutsen, L. J. S.; Williams M. Emerging Opportunities for Antipsychotic Drug Discovery in the Postgenomic Era. *J. Med. Chem*. **2008**, *51*, 1077-1107.

[2] Asproni B.; Pau A.; Bitti M.; Melosu M.; Cerri R.; Dazzi L.; Maciocco E.; Sanna E.; Altomare C.; Trapani G.; Biggio G. Synthesis and Pharmacological Evaluation of 1-[(1,2-Diphenyl-1*H*-4-imidazolyl)methyl]-4-phenylpiperazines with Clozapine-Like Mixed Activities at Dopamine D_2, Serotonin, and $GABA_A$ Receptors. *J. Med. Chem*. **2002**, *45*, 4655-4668.