SardiniaChem2008

GIORNATA DI STUDIO DEDICATA
ALLA CHIMICA ORGANICA
DELLE MOLECOLE BIOLOGICAMENTE ATTIVE

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

Comitato Scientifico:
Giampaolo Giacomelli, Univ. Sassari; Giovanna Delogu CNR Sassari; Salvatore Cabiddu, Univ. Cagliari; PierPaolo Piras, Univ. Cagliari

Comitato Organizzatore:
Andrea Porcheddu, Univ. Sassari; Roberto Dallocchio, CNR Sassari; Stefania De Montis Univ. Cagliari

Sponsor
hanno contribuito alla realizzazione del convegno:
UNIVERSITA’ di Sassari-Dipartimento di Chimica; UNIVERSITA’ di Sassari-Facoltà di Scienze MFN; CNR-Istituto di Chimica Biomolecolare, Sassari; UNIVERSITA’ di Cagliari; SAPIO s.r.l.; SIGMA-ALDRICH s.r.l.; CARLO ERBA Reagenti; MEDINLAB s.r.l.; VWR International s.r.l.
SYNTHESIS AND SAR STUDY OF 2-SUBSTITUTED IMIDAZO[2,1-B][1,3]BENZOTHIAZOLES AND RELATED COMPOUNDS ENDOWED WITH AFFINITY FOR DOPAMINE D₂ RECEPTORS AS POTENTIAL ANTIPSYCHOTICS

Battistina Asproni¹, Jan Kehler², Sergio Simula¹, Stefania Mura¹, Giovanna Porcu¹

¹Università di Sassari, Dipartimento Farmaco Chimico Tossicologico, Via Muroni 23/a 07100 Sassari;
²H. Lundbeck A/S. Department of Medicinal Chemistry, Ottiliavey 9, DK-2500 Valby, Denmark.

Schizophrenia is a complex disorder affecting approximately 1% of the population. Typical antipsychotic agents such as chlorpromazine and haloperidol block the D₂ subtype of dopamine receptors in a direct relation to their clinical potency. However, although blockade of D₂ 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 D₂ blockers and exhibit a dual dopaminergic and serotonergic mechanism of action: a relatively weak dopamine D₂ receptor antagonism in vitro and in vivo, but potentially important activities at other dopaminergic (D₁, D₄) receptors, at serotonergic (5-HT₁₆, 5HT₂₆, 5HT₃, 5HT₅), adrenergic (α₁, α₂), histaminergic (H₁), 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 D₂ receptors as well as 5-HT₁₆ and 5-HT₂₆ serotonin receptors, compound 1a (R = o-OCH₃) 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 \textit{in vitro} screening will be discussed in the poster.

![Chemical Structure](attachment:structure.png)

1
