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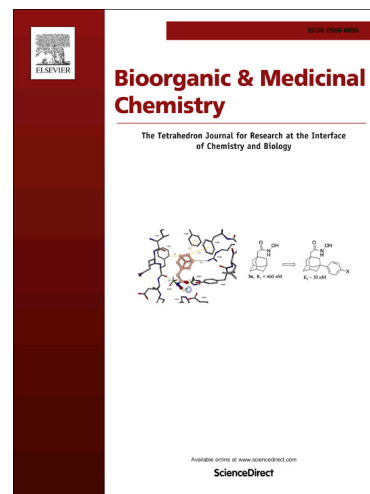
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# Synthesis and Evaluation of Tetrahydroindazole Derivatives as Sigma-2 Receptor Ligands

Zong-Wen Wu<sup>a</sup>, Shu-Yong Song<sup>a</sup>, Li Li<sup>a</sup>, He-Lin Lu<sup>a</sup>, Yun-Sheng Huang<sup>a,\*</sup>, Robert Mach<sup>b,\*\*</sup>

<sup>a</sup> School of Pharmacy, Guangdong Medical College, 1 Xincheng Ave, Songshan Lake Technology Park, Dongguan, Guangdong 523808, China.

<sup>b</sup> Department of Radiology, University of Pennsylvania, 231 S. 34<sup>th</sup> St, Philadelphia, PA 19104, USA

\* Corresponding author: Yun-Sheng Huang, Tel: +86-0769-22896547, Email: yshuang@gdmc.edu.cn

\*\* Corresponding author: Robert Mach, Tel: 215-746-8233, Email: rmach@mail.med.upenn.edu

## Abstract

A series of tetrahydroindazole derivatives were synthesized and evaluated for their affinities for both sigma-1 and sigma-2 receptors. These compounds are hybrid structures of a tetrahydroindazole substituted benzamide and a 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline moiety or a 9-azabicyclo[3.3.1]nonan-3-yl-amine moiety. These newly synthesized hybrid analogs showed various affinities for sigma-2 receptor without any significant affinities for sigma-1 receptor. In particular, compounds **12**, **15b**, **15c**, and **15d**, demonstrated moderate affinity and excellent selectivity for sigma-2 receptor. It is interesting to note that 3-5 carbon units between the tetrahydroindazole substituted benzamide and the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline moiety are appropriate for sigma-2 receptor binding. No substitution on the 9-aza nitrogen is proper for sigma-2 affinity in the 2-(9-azabicyclo[3.3.1]nonan-3-yl-amino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl) benzamide analogs.

**Keywords:** Sigma receptor, synthesis, ligands, tetrahydroindazole, affinity

## 1. Introduction

The sigma receptors were originally classified as subtypes of opioid receptor because many antipsychotic agents displayed various affinities for the sigma binding sites. But subsequent studies found they belong to a distinct and novel receptor type.<sup>1</sup> It is now generally accepted that there are two subtypes of sigma receptors, termed sigma-1 ( $\sigma_1$ ) and sigma-2 ( $\sigma_2$ ).<sup>2,3</sup> Though the exact physiological functions are not clear for both receptors and the endogenous ligands for these receptors are still unknown, evidences indicate that sigma-1 receptor may play important roles in central nervous system involved in cognition and movement, while sigma-2 receptor may play important roles in regulation of cell survival, morphology, and differentiation.<sup>4-6</sup> Sigma-1 receptor has been cloned in various cells of both human and rodent origin with a molecular weight of 25.3 KDa.<sup>7</sup> Sigma-2 receptor has not yet been cloned. But various photoaffinity labeling studies implicated its presence with a molecular weight

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