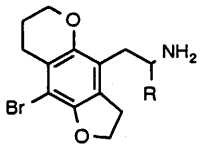
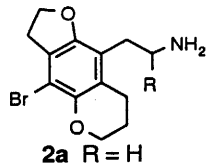
DESIGN AND SYNTHESIS OF MIXED HETEROCYCLIC PHENYLALKYLAMINES Jennifer A. Prescher, (Aaron Monte), Department of Chemistry, University of Wisconsin-La Crosse, La Crosse, WI 54601.

Two sets of chemical probes (**1, 2**) for the agonist binding sites of serotonin 5-HT_{2A} and 5-HT_{2C} receptors were designed as conformationally restricted analogs of hallucinogenic phenylalkylamines. These novel drugs, hybrids of previously constructed receptor probes, contain aromatic rings flanked by 5- and 6-membered oxygen heterocycles that restrict the conformational freedom of the alkoxy ring substituents. Various strategies, all proceeding through a common tricyclic intermediate, have been explored in an attempt to synthesize the new compounds. Specifically, one method involving a double-halogen replacement and another utilizing a reduction/diazotization/substitution sequence of reactions were employed. Although target molecules **1** and **2** have not yet been prepared by either of these methods, significant progress has been made toward their synthesis *via* a selective ether-cleavage reaction. With the eventual construction of **1** and **2**, pharmacological testing of the probes will provide more detailed information about the three-dimensional topography of the agonist binding sites in serotonin receptors. The compounds could also potentially be the first agonists ever synthesized to discriminate between the largely homologous 5-HT_{2A} and 5-HT_{2C} receptor subtypes in selective binding studies.

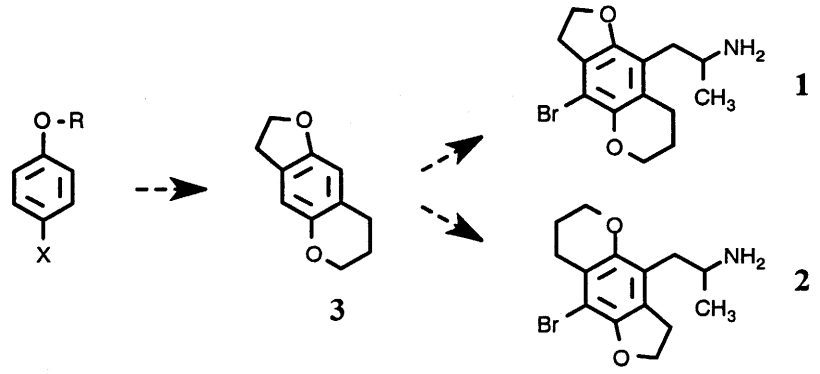


1a R = H
1b R = CH_3



2a R = H
2b R = CH_3

In common with recently reported, highly selective 5-HT_{2A} and 5-HT_{2C} receptor agonists, both of these probes contain an aromatic nucleus flanked by 5- and 6-membered heterocyclic rings, an alkylamine side chain, and a halogen located *para* to the side chain. The synthesis of **1** and **2** presents a significant challenge due to the asymmetric nature of the molecules. An overview of the proposed synthesis is depicted below and begins with an oxygen-containing substituent (-OR) and a second functional group (-X) attached to a benzene ring. The synthesis then proceeds through the key tricyclic intermediate **3** *en route* to the "gnat" and "flea" compounds (**1**, **2**).



The summer 1999 portion of this research, supported by a distinguished UW-La Crosse SAH Undergraduate Research Fellowship, explored various strategies for constructing the key tricyclic intermediate **3** in the synthesis of the "gnat" and "flea" probes. After overcoming numerous synthetic difficulties, a feasible route to the intermediate molecule was uncovered. Significant progress has since been made toward the synthesis of **3**. However, a slight obstacle has recently been encountered involving one of the latter steps in the construction of the intermediate. While the current synthetic

Design and Synthesis of Mixed Heterocyclic Phenylalkylamines

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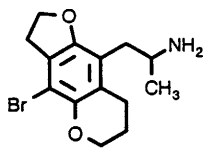
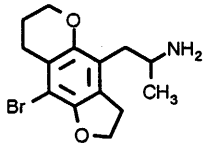
Serotonin (5-hydroxytryptamine) is one of approximately 50-100 different neurotransmitters present in the mammalian central nervous system. In humans, this neurotransmitter, or "chemical messenger" is associated with a vast array of mental processes including mood, sleep and dreaming, hallucinogenesis, and depression. Mental states linked to serotonin function arise from molecular interactions between serotonin and its specific receptors and/or transport proteins. An increased understanding of the three-dimensional structure of serotonin receptors at the molecular level may lead to the development of new drugs with potential for treating various mental disorders, and ultimately to a better understanding of how serotonin influences certain aspects of human consciousness. Because receptor structure is closely related to the structure of the molecules that bind to it, definitive information about the three-dimensional topography of a receptor can be inferred from drugs having high selectivity for that receptor.

The long-term objective of this research is to synthesize two new molecules that will serve as selective probes for the serotonin 5-HT_{2A} and 5-HT_{2C} receptor subtypes. These novel drug molecules, modeled after other serotonin agonists designed and synthesized recently, are affectionately termed the "gnat" and "flea" compounds (**1, 2**).



1 ("gnat")



2 ("flea")

scheme must now be revised to avoid this obstacle, the same reactions utilized thus far in the research project will still be employed; the modified synthesis will alter only the order of the synthetic steps.

Since the revised approach closely parallels the current synthetic route, the desired molecule **3** will likely be prepared within the next month if additional funding for supplies can be obtained. The chemicals used in the early phases of the synthesis need to be restocked in order to proceed with the revised route. Furthermore, several of the reagents utilized in the synthetic reactions are quite expensive.

If additional funding for this research is received, the eventual construction of intermediate **3** will warrant publication in a rapid communications journal. This original synthesis will also be presented at the national meeting of the American Chemical Society in San Francisco, CA in addition to the UW-L Undergraduate Research Day.

From a broader viewpoint, the preparation of **3** will mark the halfway point in the overall synthesis of the "gnat" and "flea" compounds (**1, 2**). With the eventual construction of these two molecular probes, pharmacological assay of the drugs will provide greater insight into the three-dimensional structure of the serotonin 5-HT_{2A} and 5-HT_{2C} receptors. This greater insight will hopefully result in improved treatments for serotonin-related disorders and an enhanced understanding of the role serotonin and its receptors play in human consciousness.

Bibliography

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(2) Whiteside, M.S.; *et al.* Synthesis of Hexahydrobenzodipyrans as Ring-Expanded Analogs of Potent Serotonin 5-HT_{2A} and 5-HT_{2C} Receptor Agonists. In preparation.

(3) Glennon, R.A. Central Serotonin Receptors as Targets for Drug Research. *J. Med. Chem.* **1987**, *30*, 1-12.

(4) Monte, A.P. "Design and Synthesis of Molecular Probes for Serotonin Receptors." 1997, UW-L Faculty Research Grant Proposal, 9 pp with appendices and figures.

Itemized Budget

Supplies	Cost
4-Methoxyphenol (500 g)	$30.75
B-Bromo-9-BBN (800 mL)	$143.10
Potassium carbonate (1000 g)	$34.70
1,2-Dibromoethane (200 g)	$31.80
Butyllithium (100 mL)	$33.60
Bromine (100 g)	$23.40
1,3-Dibromopropane (250 mL)	$57.50
TOTAL COST	$354.85