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4-Aminomethyl Chromans: Dependence of Serotonin and Dopamine Binding upon Aromatic Ring Substitution

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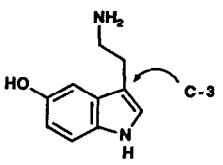
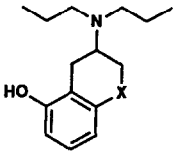
Abstract: The synthesis of two series of methoxy-substituted 4-aminomethyl chromans is described. The formation of the pyran ring is achieved via an intramolecular Friedel-Crafts reaction of the appropriate epoxide. There is a profound dependence between the position of the aromatic methoxy substituent and the binding affinity for the 5-HT_{1A} and dopamine D-2 receptors.

The therapeutic promise of agents which bind selectively to the serotonin site grows with each newly-discovered receptor subtype. To date, nearly a dozen distinct populations of the 5-HT receptor have been identified, and disorders involving eating, sleeping, sexual function, depression and anxiety have been associated with these subtypes.[1] We have been interested in identifying novel, orally-active 5-HT_{1A} agonists for the treatment of anxiety and/or depression. Toward this end, we undertook the synthesis of several methoxy-substituted 4-aminomethyl chromans (**3**, Figure 1). The selection of this class of compounds as potential 5-HT_{1A} agonists arose from structural considerations of both serotonin (**1**) and 8-OH-DPAT (**2a**), as well as from a key observation reported by Hamon, et. al. in 1987.[2] These authors proposed that the substitution of an oxygen atom for the indole C-3 position results in an electronic enrichment which effectively mimics the charge-distribution pattern of the indole ring itself. In support of this proposal, they prepared the chroman analog **2b** and demonstrated this compound to be a more selective 5-HT_{1A} ligand than 8-OH-DPAT. By extending the concept of rigidifying the aminoethyl sidechain of serotonin by ring incorporation (as exemplified by 8-OH-DPAT) while simultaneously addressing the notion of a methoxy group as an indole mimic, we were eventually led to consider structures such as **3**. These 4-aminomethyl chromans have received scant attention, and there is no published data regarding their interaction with 5-HT_{1A} or D-2 receptors.[3] Although the arguments given above would suggest the 5-methoxychroman compounds illustrated by **3** as primary targets for synthesis, we undertook the preparation of all ring-substitution isomers for a more complete study.

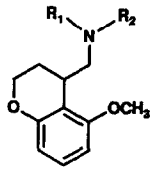
Figure 1



1 (5-HT, serotonin)



2a (X=CH_2)
b (X=O)

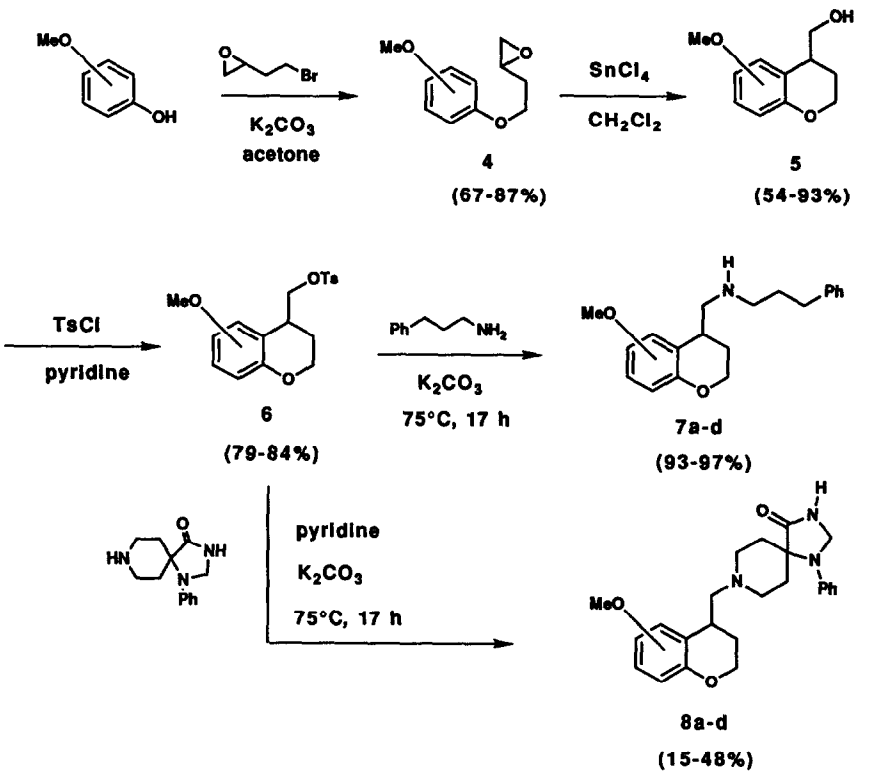


3

The compounds of this study were all prepared from the key intermediate **6**, the synthesis of which is illustrated in the Scheme.[4] Our strategy is based upon an intramolecular Friedel-Crafts cyclization similar to those reported by Taylor, et al.[5] The requisite epoxy-ethers **4** were obtained by alkylation of the appropriate methoxy phenol with 4-bromo-1-butene oxide.[6] While many Friedel-Crafts alkylation conditions were examined (TFA, BF_3, etc), we obtained the best results when using tin (IV) chloride in dichloromethane at 0°C. Under these conditions, a clean reaction was completed within 30 minutes, providing high yields of the desired chromans. As expected, the 3-methoxy aryl epoxide generated a mixture of the 5- and 7-methoxy chromans in a 2:1 ratio. These isomers were most easily separated chromatographically after conversion to their respective tosylates **6a** and **6c**. Tosylation of the intermediate 4-hydroxymethyl chromans were carried out in the usual way using *p*-toluenesulfonyl chloride in pyridine to afford the corresponding sulfonate esters (85-90%). Each of the tosylates **6a-d** were used to alkylate either 3-phenylpropylamine or 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (the "spiperone piperidine"). These particular substituents were chosen because of the known CNS activity of related compounds which bear them.[7] For compounds **7a-d**, the alkylations were performed using 3-phenylpropylamine as the solvent. After aqueous work-up, the excess amine was conveniently removed by Kugelrohr distillation and the products were purified by flash chromatography (>90%). For compounds **8a-d**, the alkylations were carried out in pyridine using three equivalents of the spiperone piperidine.

The binding data for the two series of amine products **7a-d** and **8a-d** are summarized in Tables 1 and 2.[8] Clearly, the position of the aryl methoxy group imparts a strong influence on the relative binding affinities within each isomeric series. Furthermore, the differences between the two series of compounds toward the 5-HT_{1A} receptor is striking. In the 3-phenylpropylamine series **7**, we see a linear progression of *increasing* binding affinity for the 5-HT_{1A} receptor as the methoxy substituent moves from the 5-position to the

Scheme



8-position. In complete contrast, however, one sees a *decreasing* trend in binding for the spiperone series **8** for the analogous methoxy isomers. This complementary relationship between methoxy position and 5-HT_{1A} binding affinity for the two series of compounds is readily apparent from examination of the Tables.

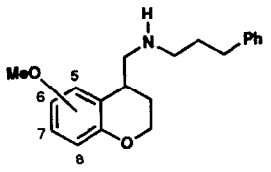
It is difficult to explain the difference in the regioisomeric trends for 5-HT_{1A} binding affinities for these two series of compounds. Our design rational would suggest that the 5-methoxy isomer should exhibit the best receptor affinity, and in the spiperone piperidine series **8** this holds true. In order for structures such as **3** to mimic 8-OH-DPAT, the aminomethyl substituent must be directed away from the aromatic methoxy group as illustrated. Perhaps hydrogen bonding in **7a** between the amine N-H and the 5-methoxyl promotes a configuration unfavorable for receptor binding.

None of the compounds in the 3-phenylpropylamine series **7** were very potent for binding to the dopamine receptor (Table 1). Indeed, compounds **7c** and **7d** display an impressive level of receptor selectivity. In contrast once again, the D-2 binding in the spiperone piperidine series **8** closely parallels the 5-HT_{1A} binding in both magnitude and trend.

Table 1: Melting point and binding data for **7a-d** (K_i, nM)

Compound	mp, °C	5-HT_{1A}	D-2
7a (5-CH_3O)	143-144	>1000	279
7b (6-CH_3O)	—[a]	93	>1000
7c (7-CH_3O)	155-156	28	>1000
7d (8-CH_3O)	—[a]	7	620

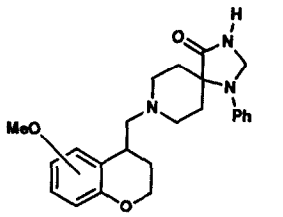
a) Compound obtained as an oil.



7a-d

Table 2: Melting point and binding data for **8a-d** (K_i, nM)

Compound	mp, °C	5-HT_{1A}	D-2
8a (5-CH_3O)	239-241	12	29
8b (6-CH_3O)	221-222	247	164
8c (7-CH_3O)	219-220	611	274
8d (8-CH_3O)	223-224	>1000	>1000



8a-d

The compound which emerges from these initial binding studies for further examination is the 5-HT_{1A} selective agent **7d**. We have found that this compound is active in vivo in the Mouse Hypothermia Assay, lowering the body temperature of mice by 6.8°F at a dose of 1.7 mg/kg sc.[9] Unfortunately, this compound proved to be completely inactive when administered orally.

In summary, we have prepared all four aryl ring methoxy isomers for two different classes of 4-aminomethyl chromans. In each class of compounds there is a relationship between methoxy position and affinity for both the 5-HT_{1A} and D-2 receptors. This relationship is inverted for the two series of compounds

discussed in this Letter. It should be noted that the compounds used in this study are racemic mixtures, and that the enantiomers of **7a-d** or **8a-d** would likely display binding affinities different from those of the racemate. However, the binding selectivity of enantiomers often parallels that of the racemate, and since this study highlights relative binding trends in two structurally related series, the use of racemates should provide meaningful results. Of the compounds synthesized, **7d** displays the most selective binding profile but exhibits low oral bioavailability in the Mouse Hypothermia assay. We are hopeful that the lessons learned from this study will help to understand the structural requirements of the 5-HT_{1A} and dopamine D-2 receptors and thereby prove beneficial in future research efforts.

GENERAL PROCEDURE FOR CHROMANS (5):

An ice-cold solution of tin(IV) chloride (approx. 0.08M in dichloromethane) under nitrogen was treated dropwise with a solution of the arylether epoxide **4** (0.5M in dichloromethane). Stirring was maintained for 30 min. at 0°C, then the reaction was allowed to warm to RT over an additional 30 min. The reaction gradually became light yellow and a fine white precipitate formed. At this point, the reaction mixture was transferred to a separatory funnel and washed once each with water, saturated aqueous sodium bicarbonate, and brine. The organics were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue thus obtained was purified by flash chromatography (230-400 silica gel).

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3. Compounds related to **3** have been claimed as α-2 adrenergic antagonists (Eur. Pat. Appl. EP 325,964). The activity of 4-aminomethyl-6-methoxychroman at serotonin receptors has been described: Glennon, R.A.;

Liebowitz, S.M. *J. Med. Chem.*, **1982**, *25*, 393-397.

4. All new compounds in this manuscript were fully characterized by NMR (^{1}H and ^{13}C), IR, and either satisfactory elemental analysis (± 0.40%) or high-resolution mass spectra (± 0.004).

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6. Alkylation of the methoxyphenols with 4-bromobutene followed by attempted epoxidation with MCPBA was unsuccessful, resulting in apparent oxidation of the electron-rich aromatic ring.

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8. Inhibition constants (K_is) were determined from triplicate runs of 4 - 6 concentrations of the test compound. Radioligands were [^{3}H]8-OH-DPAT for 5-HT_{1A} and [^{3}H]raclopride for dopamine D-2, and these were used in conjunction with receptors from bovine hippocampus (5-HT_{1A}) and rat striata (D-2). For calculated K_i values less than 100 nM, typical standard errors were ± 20%.

9. We thank Dr. Montford F. Piercey (Upjohn Laboratories) for providing the hypothermia results. For experimental details of this procedure, see reference 7.