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SYNTHESIS OF METABOLICALLY STABLE ARYLPIPERAZINE 5-HT1A RECEPTOR AGONISTS

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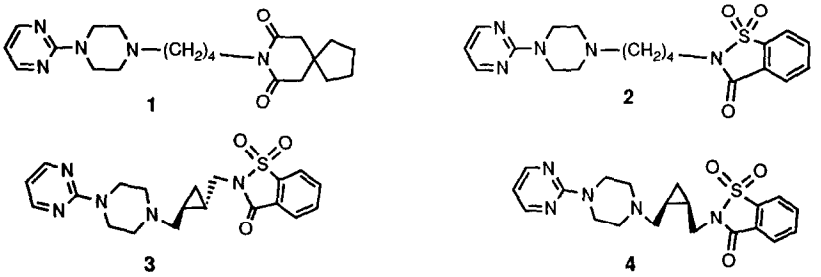
Abstract: Although N-alkylarylpiperazines as a class are finding use as anxiolytics and antidepressants, many of these arylpiperazines are highly metabolically labile at the n-alkyl-piperazine bond. We have found that cyclopropanating the n-butyl chain contained in the 5-HT1A receptor agonist ipsapirone (2) instills a resistance to this metabolism as well as providing information about the geometrical requirements of the 5-HT1A receptor.

N-Alkyl substituted arylpiperazines as a class are finding wide use in the treatment of anxiety and depression.[1] Acting as 5-HT1A receptor agonists, they inhibit the spontaneous firing of neurons in the dorsal raphe nucleus.[2] Clinical evidence supports their role in the treatment of anxiety and depression.[2] Besides buspirone (**1**), which is the only non-benzodiazepine drug approved for the treatment of anxiety, the close structural homolog ipsapirone[3] (**2**) is of interest due to its greater receptor specificity, and is in clinical trials. Buspirone (and many more closely related literature compounds by structural analogy[1]) suffers from poor oral bioavailability[4] and delayed onset of efficacy, approximately two weeks.[2b] Despite these factors, buspirone is reported to be equally effective as the benzodiazepine diazepam after four weeks of treatment.[2b] The reason for the slow onset of efficacy of the arylpiperazines is not understood.

Figure 1.



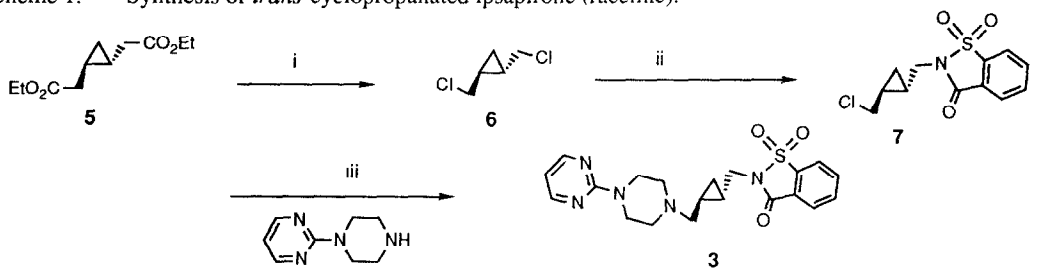
The human oral bioavailability of buspirone (**1**) approaches zero.[4a] Indeed, when given orally (10 mg/kg, rat), **1** is undetectable in plasma and in the brain. ^{14}C-labeled drug studies have previously shown that it is rapidly and completely absorbed from the gastro-intestinal tract in several species. Metabolic cleavage occurs at the unhindered butyl-piperazine bond with the major metabolite being 1-(2-pyrimidyl)piperazine (1-PP), an alpha-2 adrenergic receptor antagonist which is itself antigenic. At all times sampled the concentration of 1-PP far exceeds the concentration of buspirone by both oral and intravenous routes of administration.[4a]

It is intriguing to consider whether the delayed onset of efficacy is in some manner related to the metabolic lability of these drugs. We undertook to examine whether a sterically hindered analog would be

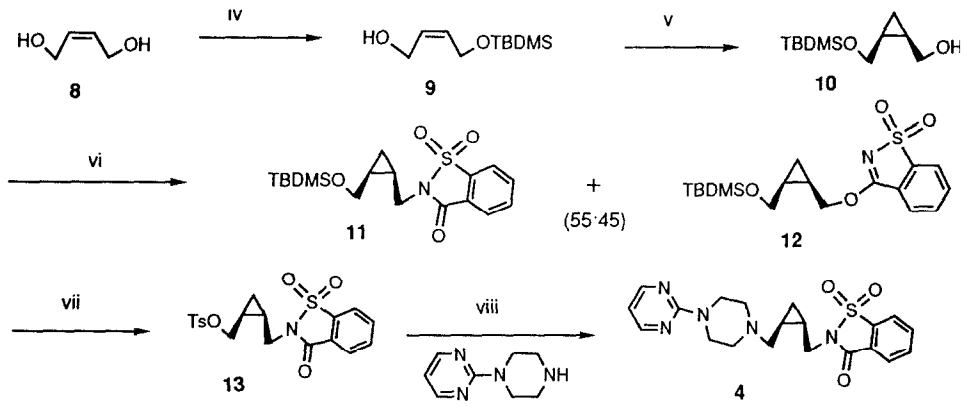
more resistant to metabolism while retaining activity at the 5-HT$_{1A}$ receptor. If successful, perhaps this would shorten the time required for the onset of efficacy. We were also interested in rigidifying the highly entropic butyl chain to examine whether the 5-HT$_{1A}$ receptor imposed geometrical restrictions on its conformation. We chose the*trans*- (**3**) and *cis*- (**4**) cyclopropanated ipsapirone analogs as our targets of this study, preferring to take advantage of the greater 5-HT$_{1A}$ receptor specificity of ipsapirone, compared with buspirone.

The synthesis of the *trans*-cyclopropanated analog was straight forward (scheme 1), starting with commercially available **5**. For the cis-analog (scheme 2) McDougal's mono-silylation[5] procedure was used, leading to a high yield of the mono-protected diol **9**. The cyclopropane was introduced through the use of a zinc carbenoid.[6] *In situ* activation and alkylation with the free hydroxyl was performed with diethylazodicarboxylate, which led to a mixture of N- and O-alkylated products (**11** and **12**). Changing the solvent from THF to ether improved the ratio from 35:65 to 55:45 (**11/12**). The solvent effect is most likely due to the greater dipole of THF stabilizing the transition state leading to alkylation on the "hard" oxygen in favor of the "soft" nitrogen. This amphoteric result with saccharin is precedented.[7]

Scheme 1. Synthesis of *trans*-cyclopropanated ipsapirone (racemic).[8]



Scheme 2. Synthesis of *cis*-cyclopropanated ipsapirone (racemic).[8]



(i) LAH; PPh_3, CCl_4, reflux (60%). (ii) Sodium saccharin, DMF, 110°C (52%). (iii) Na_2CO_3, n-butanol, reflux (69%). (iv) NaH, THF, 25°C; then t-$C_4H_9(CH_3)_2SiCl$, 0°C (61% distilled). (v) CH_2I_2, Et_2Zn, hexane (84% distilled). (vi) Sodium saccharin, diethylazodicarboxylate, triphenylphosphine, ether, 0°C (44% **11**). (vii) HOAc, THF, H_2O (2:1:1); TsCl, pyridine (57%). (viii) K_2CO_3, CH_3CN, reflux (61%).

The binding results demonstrate the promiscuous nature of the 5-HT$_{1A}$ receptor. The geometrically constrained *trans*- homolog (**3**) actually possesses a slightly better affinity than ipsapirone itself (Table 1). The *cis*-homolog's (**4**) affinity although modest, is still good enough to be considered active. Thus it can be demonstrated that the 5-HT$_{1A}$ receptor is very forgiving as far as the conformation of the alkyl chain is concerned. This agrees with the observation that the critical pharmacophore is the arylpiperazine moiety. Some type of alkyl group must be attached to the piperazine nitrogen, however, since 1-PP itself does not bind at the 5-HT$_{1A}$ receptor.

To examine the metabolic stability we utilized the mouse hypothermia model.[9] In this paradigm, 5-HT$_{1A}$ receptor ligands depress body temperature (in rodents) in direct proportion to their intrinsic activity as agonists (i.e. partial or full agonists) and the number of 5-HT$_{1A}$ receptors occupied. The number of receptors occupied can be correlated to the binding affinity and the amount of drug in the brain. Therefore, for compounds of similar intrinsic activity and binding affinity, hypothermia can be used as a "bioactivity" model to investigate bioavailability and duration of action of a potential drug.

To avoid first-pass metabolism, the compounds were first given by injection (s.c.) where the *cis*-analog (**4**) showed poor potency (ED$_{50}$ >55 nM/kg). The *trans*-analog (**3**), however, possessed a 1.68-fold greater hypothermic effect than ipsapirone. It is also noteworthy that the *trans*-analog was more potent, with an ED$_{50}$ only 60% that of ipsapirone's. Thus for s.c. dosing, the *trans*-cyclopropanated analog possessed both greater potency and efficacy than ipsapirone. Furthermore, when dosed orally (p.o.), the *trans*-analog (**3**) exhibited a 1.38-fold greater hypothermic effect than ipsapirone (**2**), at approximately equal doses. In both the s.c. and p.o. dosed models, the *trans*-analog proved to have a greater hypothermic effect than ipsapirone. This increase in efficacy may well be a combination of greater intrinsic activity and bioavailability. Following the time course of the hypothermic effect demonstrated that whereas the *trans*-analog possessed greater than a 120 minute duration, ipsapirone's effect was gone shortly after the first observation time, 20 minutes. This can be attributed to the difference in metabolism, reflected as duration of hypothermic activity.

Table 1. Mouse hypothermia model.[10]

		injection[b]		oral[c]		
Compound	5-HT1A[a] Ki (nM)	ED$_{50}$[d] (nM/kg)	max. temp. decrease[e]	ED$_{50}$[d] (nM/kg)	duration (min.)[f]	max. temp. decrease[d]
2	12.1	5.27	3.8 °F	230	20	2.9 °F
3 (trans)	8.7	3.20	6.4 °F	190	>120	4.0 °F
4 (cis)	43.7	>55	1.9 °F	--	--	--

a. Using ^{3}H-8-OH-DPAT as ligand. No significant binding at other CNS receptors was found. b. s.c. (mouse). c. p.o. (mouse). d. dose for 50% of mice to respond. e. This is the maximum obtainable hypothermic effect obtained, regardless of the amount of drug dosed. f. The time course was followed by obtaining temperature values at periodic intervals, beginning at 20 minutes and ending at 120 minutes.

With these results it can be inferred that the *trans*-analog is more resistant to metabolism than the parent, ipsapirone, largely avoiding the first-pass effect seen with typical arylpiperazines. This effect is easily demonstrated even though ipsapirone does not possess the extreme metabolic lability of buspirone.

Furthermore, this translates into greater potency and perhaps efficacy in the hypothermia model of *in vivo* 5-HT_{1A} activity. Thus, building in steric hindrance near the piperazine group may result in an increase in oral bioavailability and half-life, without diminishing the affinity or efficacy.

Notes and References

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8. All compounds displayed satisfactory spectral data Satisfactory analytical data was obtained for compounds **2**, **3**, and **4**. Ipsapirone (**2**) was isolated and tested as the hydrochloride salt, while the cyclopropanated analogs **3** and **4** were isolated and tested as their fumarate salts (**3** -salt m.p. 219°, **4** -salt m.p. 126°)

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10. Charles River CF-1 male mice, 18-22 grams, groups of four/dose. After control rectal temperatures were measured using a YSI Tele-thermometer, animals received drug. Compounds had to show a minimum hypothermic response (2°F or more) at an initial dose (s.c.) of 55 nM/kg to be considered active. Doses were run down in half log increments until none of the four mice showed a positive hypothermic response. ED_{50}'s were determined by the Spearman-Karber method of data analysis.