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THE SYNTHESIS AND EVALUATION OF THE MAJOR METABOLITES OF MAZAPERTINE

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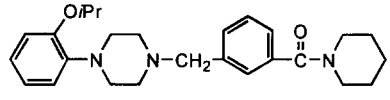
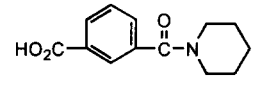
Abstract: Several of the key metabolites of mazapertine, a novel antipyschotic agent, were prepared in order to firmly establish their chemical structure and to obtain samples for biological testing. Hydroxymazapertine **3** was synthesized via a multi-step procedure starting from 5-fluoro-2-nitrophenol (**8**). Alcohol **4** was originally proposed for one of the major metabolites, but the confirmed structure after synthesis was isomer **20**.

Mazapertine (**1**) is a novel antipsychotic agent that has undergone extensive investigation.[1] Following administration of ^{14}C-(C=O) mazapertine to rats (30 mg/kg) and dogs (10 mg/kg),[2] various metabolites of mazapertine were isolated from the urine and feces of both species. The three major ^{14}C-containing metabolites were initially assigned structures **2**, **3** (Scheme 1), and **4** (Scheme 2) based on mass spectral fragmentation patterns. We initiated the preparation of these compounds in order to evaluate them for biological activity and to validate the original structural assignments. Compound **2** was prepared by reaction of *m*-phthaloyl dichloride with a deficiency of piperidine followed by aqueous workup. The syntheses and evaluation of **3** and **4** are the subject of this paper.



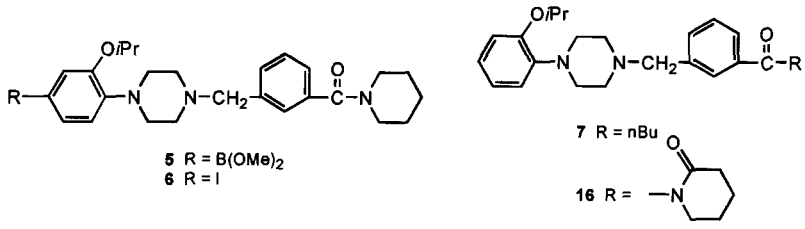
1, mazapertine



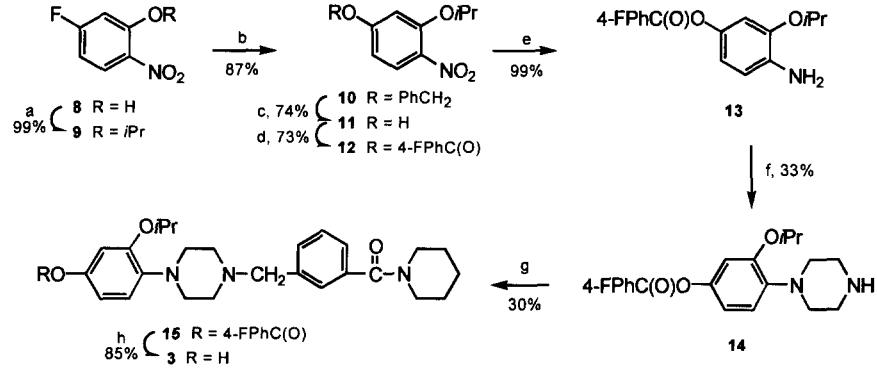
2

In order to prepare **3** we first attempted to oxidize corresponding borate ester **5**. Iodination of **1** with iodine and silver trifluoroacetate proceeded regioselectively to yield **6**.[3] Conversion of **6** to the corresponding Grignard reagent was unsuccessful. When **6** was treated sequentially with *n*BuLi (2 mol-equiv), trimethylborate, and hydrogen peroxide,[4] the major product was deiodinated ketone **7**. When *t*BuLi was used, the major product was **1**.

An alternative synthesis to **3** was devised starting from 5-fluoro-2-nitrophenol (**8**). Reaction of **8** with isopropyl bromide in DMF afforded **9** (Scheme 1). Phase transfer-catalyzed displacement of fluoride from **9** according to the procedure of A. Loupy and coworkers[5] went smoothly to afford benzyloxy product **10**. The nitro group of **10** was then reduced with Zn/$CaCl_2$ in EtOH:water (3:1) to afford the corresponding primary



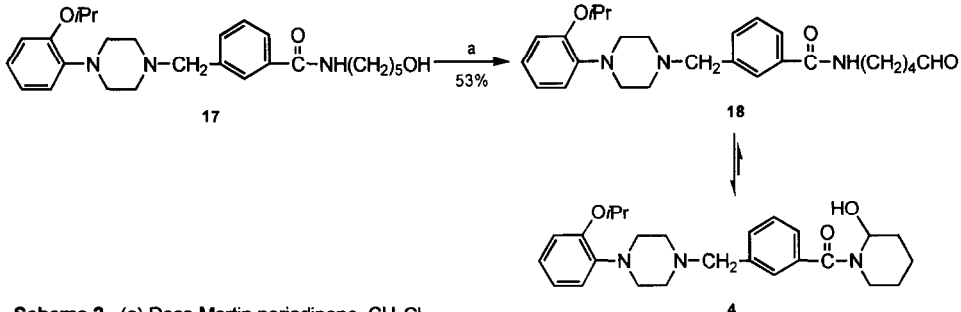
amine which was especially sensitive to air oxidation. Because of this, the benzyl group of **10** was removed with TMSI to give **11**, and the free hydroxyl of **11** was then acylated to produce 4-fluorobenzoate **12**. Reduction of the nitro group of **12** (H_2, Pd/C) afforded air stable solid **13,** which was reacted with bis(chloroethyl)amine to yield piperazine **14**. Compound **14** was then alkylated[1,6] with the appropriate benzyl chloride to give **15**. Saponification of the 4-fluorobenzoate ester functionality in **15** afforded **3**, whose spectra and MS fragmentation pattern agreed with the compound isolated in the metabolism experiments.[7] This synthesis clearly established the position of oxidation on the phenyl ring as para to the piperazinyl nitrogen.



Scheme 1. (a) *i*PrBr, K_2CO_3, (b) $PhCH_2OH$, KOH, Aliquat 336, (c) TMSI, (d) 4-FPhC(O)Cl, Et_3N, EtOAc, (e) H_2, Pd/C, (f) $(ClCH_2CH_2)_2NH$, (g) 3-$(ClCH_2)$PhC(O)*N*-piperidinyl, Na_2CO_3, EtOAc, (h) NaOH, EtOH, H_2O.

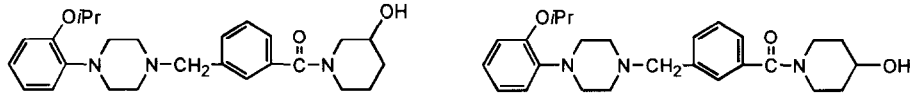
Our attention then focused on putative α-hydroxy amide metabolite **4**. It seemed plausible that monoreduction of a suitable *N*-acyllactam such as **16**[1] would yield the desired product. However, Speckamp reduction[8] of **16** gave multiple products, and none of these appeared to be desired **4**. Additionally, ruthenium-catalyzed oxidation of **1** with peroxide[9] was attempted, but only starting material was recovered. As for the preparation of **3**, there appeared to be no direct, one-step method to prepare **4** from **1**.

Alternatively, (hydroxypentyl)amide **17** was prepared,[1] and then **17** was oxidized under mild conditions using the Dess-Martin periodinane reagent[10] to produce aldehyde **18** (Scheme 3) without any appreciable amine oxidation. Compound **18** spontaneously cyclized in methanol resulting in the formation of desired α-hydroxy amide target **4**.[11] Alcohol **4** existed as an equilibrium mixture with open-chain aldehyde **18** by ^1H NMR. A 1:1 mixture of **4** and **18** was observed in $CDCl_3$; however, in CD_3OD only **4** could be detected (>97% **4**).



Scheme 2. (a) Dess-Martin periodinane, CH_2Cl_2.

Spectral comparison of **4** that we prepared with the sample originally isolated as a metabolite revealed that they were not the same. After preparation and evaluation of a series of isomeric alcohols including **19** and **20**,[12] we determined that the 4-hydroxy isomer (**20**) was the structure of the metabolite originally assigned as 2-hydroxy **4**.



The compounds prepared in this study were evaluated for biological activity, both in vitro for affinity to key GPCRs and in vivo in the conditioned avoidance response (CAR) assay[13] for putative antipsychotic activity. In the CAR test, higher negative percentage values indicate a greater degree of activity. As a class, compounds related to **1** exhibited affinity for D_2, 5-HT_{1A}, and α_1-adrenergic receptors,[1] and we routinely evaluated binding at these receptors. The biological testing data are presented in Table 1, along with the relative amounts of these materials observed in the in vivo metabolism studies. Compounds **2** and **3** were essentially inactive, whereas **20** displayed potent D_2, 5-HT_{1A}, and α_1-adrenergic affinity and in vivo activity, as did hydroxyl isomers **4** and **19**. Therefore, compound **20** probably contributes to the biological response seen upon administration of **1** to animals. Additionally, since **20** bears a free hydroxyl group, it provides a reasonable target for the design and synthesis of potential prodrugs, such as comprise the depot class of antipsychotics including haldoperidol decanoate.

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Table 1. Biological Activity and Metabolism Data.[a]

Compound	CAR (dose ip, mg/kg)	In vitro receptor binding Ki's (nM) D_2	5-HT_{1A}	α_1	% of Radioactive Dose in 0-24 h Urine and Feces Rats	Dogs
1	-92 (1)	2.2	1.7	13	4	5
2	-3 (5)	NA	NA	NA	11	8
3	-10 (15)	ND	ND	ND	13	3
4	-64 (15)	9	3	4	NA	NA
19	-96 (15)	8.8	6.8	21	NA	NA
20	-76 (1)	11	7.8	3.6	3	3

[a]Dopamine D_2 binding determined using rat striatal membranes in competition experiments against ^{3}H-spiperone. Serotonin 5-HT_{1A} affinity was evaluated in rat cerebral cortex using ^{3}H-8-(hydroxy)di-propyl aminotetralin. α_1-Adrenergic binding was measured in rat cerebral cortex with ^{3}H-prazosin. NA is <10% inhibition at 1 μM for binding data, and <2% for metabolism data. ND is non-determined.

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7. Compounds **2** (sodium salt), **3**, **4**, **10**, **12**, **14–17**, **19**, and **20** were characterized by elemental analysis (C, H, N), 300-MHz ^{1}H NMR, and MS, and **5–7**, **9**, **11**, and **13** were characterized by 300-MHz ^{1}H NMR and MS.
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12. Compounds **19** and **20** were prepared in the same manner as for the preparation of **1** described in references 1 and 6, using the appropriate hydroxypiperidine starting materials.
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