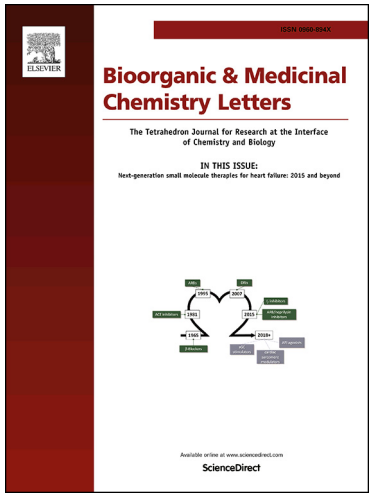

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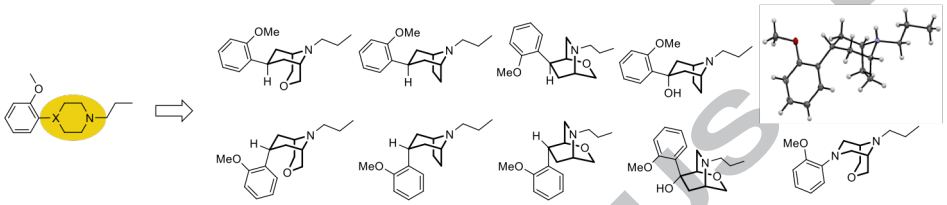

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ABSTRACT

We have developed versatile methods toward the synthesis of a variety of piperidine/piperazine bridged isosteres of pridopidine . The compounds were assessed against the D2 receptor in agonist and antagonist modes and against the D4 receptor in agonist mode. hERG Binding and the ADME profiles were studied.

Among the multitude of heterocyclic small molecules[1] that affect the central nervous system are an important class comprising piperidine[2] and piperazine[3] core structures. A classic example is haloperidol (Haldol) (Figure 1), with a rich history of antipsychotic activity, especially for the treatment of schizophrenia.[4] Haloperidol is known to act on therapeutically relevant dopaminergic receptors[5] such as D2[6] and D4[7], which are responsible for its antipsychotic effects among other properties related to a variety of psychiatric disorders.[8] It is also well known that the *in vivo* formation of the quaternary 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-pyridinium salts resulting from metabolism of the piperidine subunit in haloperidol in addition to reduction of the ketone function to the corresponding benzylic alcohol are responsible for its toxicity and extrapyramidal side effects.[9,10]

A large number of studies have been directed at understanding the complex interplay between efficacy, selectivity, and toxicity using haloperidol as the time-tested prototype among antipsychotic drugs. Among these studies are scholarly examples of the use of constrained azabicyclic analogs starting from readily available materials such as tropinone[10-12] and piperazines.[12]

Recently, a new class of *N*-propyl piperidine D2 ligands has been disclosed acting as dopaminergic stabilizers. [13,14] The most advanced is pridopidine (Figure 1) which has reached phase 3 clinical development for the symptomatic treatment of Huntington's Disease (HD). It has been shown that pridopidine's adverse effect profile is similar to that of placebo unlike classical D2 receptor antagonists such as haloperidol which are associated with severe adverse effects such as acute extrapyramidal symptoms in patients with HD.[9,10]

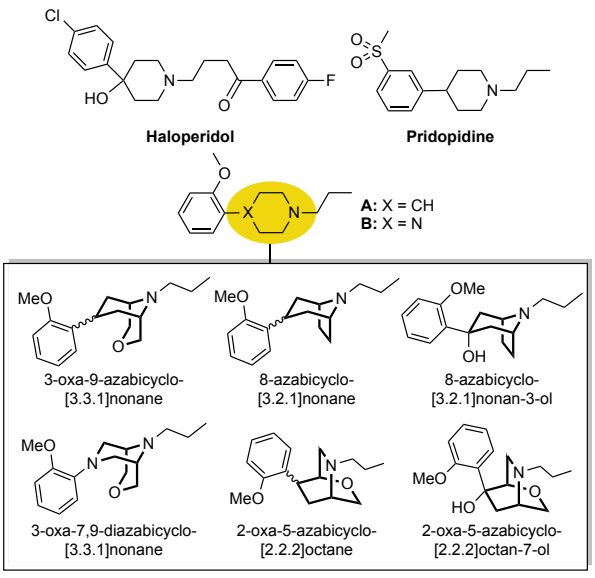

Figure 1. Haloperidol and targeted scaffolds.

We therefore conceived a series of carbon and oxygen bridged bicyclic compounds related to pridopidine and derivatives such as **A** and **B** (Figure 1)[15] incapable of undergoing metabolism to

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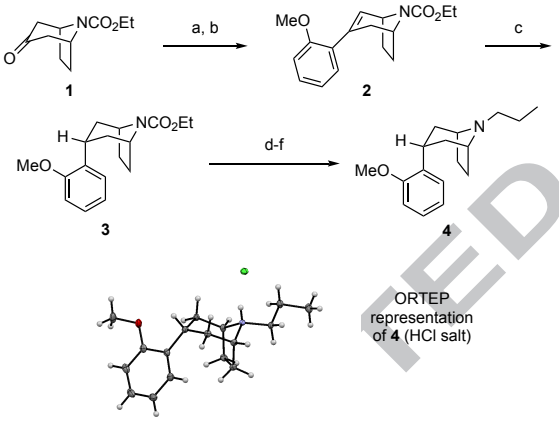
quaternary pyridinium-type salts. Accordingly, we report on the synthesis of representative members of bridged piperazines and piperidines relying on stereoselective methods of C-arylation for the latter class. In addition to the D2/D4 activity, we were particularly interested in analogs having favorable ADME and off-target (hERG) profiles.

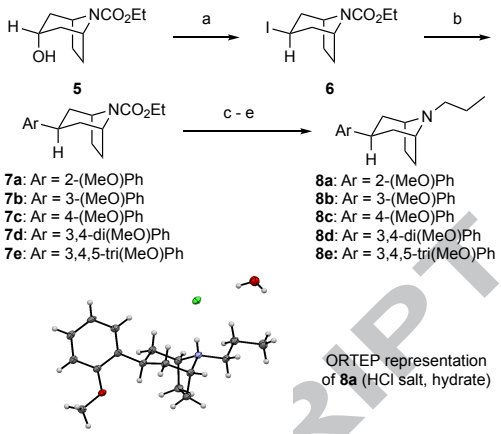
Synthesis of analog **4** started by reaction between known tropinone-derived ketone **1**[16] and lithium bis(trimethylsilyl)amide (LiHMDS) in the presence of *N*-phenyl-bis(trifluoromethanesulfonimide) ($PhN(Tf)_2$)[17] to generate the corresponding triflic enol ether. This subsequently underwent a Suzuki coupling[18] with 2-methoxyphenylboronic acid, thus delivering unsaturated intermediate **2** in 28% over two steps (Scheme 1). Catalytic hydrogenation furnished the *endo*-aryl azabicycle **3** as the sole isomer. It should be noted that at this stage, a variety of reduction conditions (including the use of different catalysts such as Raney nickel or diimide, while varying temperatures, and solvents) all failed to produce the *exo*-C-aryl isomer. A sequence consisting of hydrolysis of the carbamate **3** under basic conditions, followed by *N*-propionylation of the free amine and reduction of the resulting amide function with $LiAlH_4$ led to the desired 3-*endo*-(2-methoxyphenyl)-8-propyl-8-azabicyclo[3.2.1]octane **4** in 30% over four steps. A single-crystal X-ray analysis of the HCl salt of **4** allowed us to ascertain its structure and stereochemistry (Scheme 1).



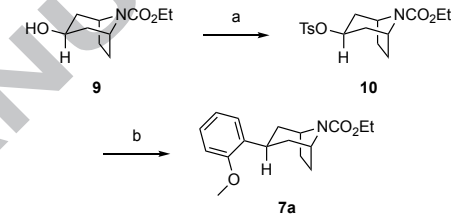
Scheme 1. Reagents and conditions: (a) LiHMDS, $PhN(Tf)_2$, THF, – 78°C to r.t., 2h; (b) 2-methoxyphenylboronic acid, $PdCl_2(dppf)\cdot CH_2Cl_2$, 2N aq. K_2CO_3, DMSO, 100°C, 1h, 28% (2 steps); (c) H_2, Pd/C, EtOAc, r.t.; 12 h (d) KOH, $H_4N_2\cdot H_2O$; $(HOCH_2)_2$, 150°C, 60h; (e) EtCOCl, 5N NaOH, CH_2Cl_2, r.t., 12h; (f) $LiAlH_4$, THF, r.t., 12h, 30% (4 steps).

As mentioned above, our efforts to generate an *exo*-C-aryl compound through hydrogenation reactions were unsuccessful. To circumvent this problem, we envisaged a cobalt-based coupling inspired from the work of Cossy and coworkers.[19] To this end, the known alcohol **5**[20] was first reacted with PPh_3 and I_2 in the presence of imidazole to afford the iodide **6** (Scheme 2). Treatment of **6** with 2-methoxyphenylmagnesium bromide in the presence of a catalytic amount of $CoCl_2$ and *trans*-*N*,*N*,*N'*,*N'*-tetramethyl-1,2-cyclohexanediamine led to the *exo*-aryl azabicyclic compound **7a** in 38% yield over two steps. Finally, a sequence consisting of deprotection of the amino group, followed by propionylation and reduction of the amide led to the desired azabicycle **8a** in 34% yield over the three steps.

Other alternative strategies can be applied to the functionalization of bridged piperidines.[21] For example, we used a Ni-based coupling from the tosylate **10** according to Molander and coworkers[22] to generate intermediate **7a** (Scheme 3).



Scheme 2. Reagents and conditions: (a) PPh_3, I_2, Imid., CH_2Cl_2, rt., 2h, 90%; (b) Ar-MgBr, $CoCl_2$, *trans*-*N*,*N*,*N'*,*N'*-tetramethyl-1,2-cyclohexanediamine, THF, 0°C to r.t., 3h-16h, 38-90%; (c) KOH, $H_4N_2\cdot H_2O$, $(CH_2OH)_2$, 160°C, 12h; (d) EtCOCl, 5N NaOH, CH_2Cl_2, r.t., 12h; (e) $LiAlH_4$, THF, r.t., 12h, 34-46% (3 steps).

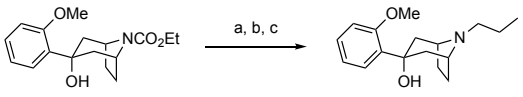


Scheme 3. Reagents and conditions: (a) TsCl, DMAP, Et_3N, CH_2Cl_2, r.t., 48h, 69%; (b) $NiBr_2$(glyme complex), 2-bromoanisole, 4,4'-di-*tert*-butyl-2,2'-bipyridine, 4-ethylpyridine, KI, Mn, dimethylacetamide, 80°C, 18h, 60%.

However, more steps were required to reach alcohol **9**[23] in an effective manner.

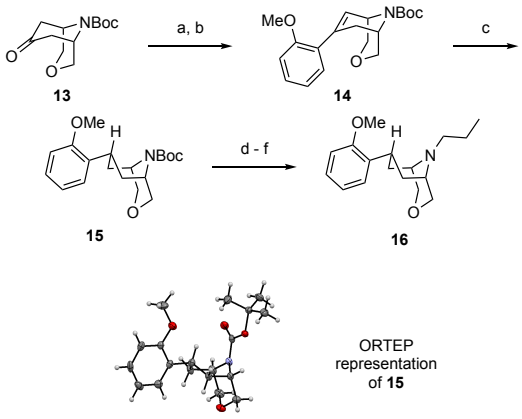
To study the effect of the aryl pharmacophore, we varied the position of the methoxy group on the aryl moiety. Compounds **8b-e** were prepared from **6** under the same conditions as for the preparation of **8a** (Scheme 2).

Compound **12**, incorporating an *endo*- tertiary alcohol, was prepared from the known ethyl 3-hydroxy-3-(2-methoxyphenyl)-8-azabicyclo-[3.2.1]octane-8-carboxylate **11**[12c] as described below in 15% yield over the three steps (Scheme 4).



Scheme 4. Reagents and conditions: (a) KOH, $H_4N_2\cdot H_2O$, EtOH, reflux, 48h; (b) EtCOCl, 5N NaOH, DCM, r.t., 12h; (c) $LiAlH_4$, Et_2O, r.t., 12h, 15% (3 steps).

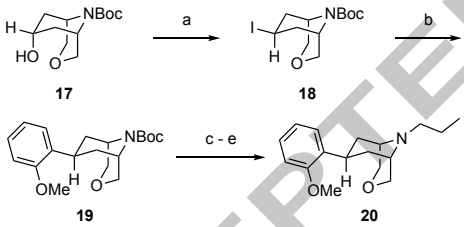
A similar approach as the one adopted to obtain **4** was used for the synthesis of 7-*endo*-(2-methoxyphenyl)-9-propyl-3-oxa-9-azabicyclo[3.3.1]-nonane **16**. Ketone **13**[24] was first reacted with LiHMDS and $PhNTf_2$ to generate a triflic enol ether, which was submitted to Suzuki coupling, yielding the unsaturated azabicycle **14** in 23% over two steps (Scheme 5). Catalytic hydrogenation of the double bound led to **15** as the sole isomer. Interestingly, a single-crystal X-ray analysis revealed that **15** adopted a chair-boat conformation. Finally, the targeted 7-*endo*-(2-methoxyphenyl)-9-propyl-3-oxa-9-azabicyclo[3.3.1]-nonane **16** was obtained after *N*-Boc removal, acylation of the free amine and $LiAlH_4$-mediated reduction of the amide to the corresponding tertiary amine in 74% over four steps. We assume



Scheme 5. Reagents and conditions: (a) LiHMDS, $PhN(Tf)_2$, THF, – 78°C to r.t., 2h; (b) 2-methoxyphenylboronic acid, $PdCl_2(dppf)\cdot CH_2Cl_2$, 2N aq. K_2CO_3, DMSO, 100°C, 1h, 23% (2 steps); (c) H_2, Pd/C, EtOAc, r.t. 12h; (d) TFA, CH_2Cl_2, r.t., 12h; (e) EtCOCl, 5N NaOH, CH_2Cl_2, r.t., 12h; (f) $LiAlH_4$, THF, r.t., 12h, 74% (4 steps).

that the chair-boat conformation is maintained based on NMR data.

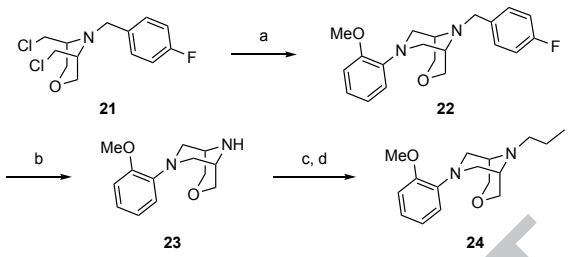
The Cossy cobalt-based coupling strategy was also applied to the synthesis of *exo*-C-aryl 3-oxa-9-azabicyclo[3.3.1]nonane bicyclic morpholine **20**. The known alcohol **17**[24] was first converted into the corresponding *exo*-iodo intermediate **18** under Appel conditions (Scheme 6). A cobalt-mediated coupling between **18** and 2-methoxyphenylmagnesium bromide led to compound **19** in 42% yield. Finally, TFA-mediated deprotection of the *N*-Boc group followed by *N*-propionylation and reduction of the intermediate amide led to the azabicycle **20** in 39% yield over three steps.



Scheme 6. Reagents and conditions: (a) PPh_3, I_2, Imid., CH_2Cl_2, 0 ºC to r.t., 2h, 43%; (b) 2-methoxyphenylmagnesium bromide, $CoCl_2$, *trans-N,N,N',N'*-tetramethyl-1,2-cyclohexanediamine, THF, 0 ºC to r.t., 3h, 42%; (c) TFA, CH_2Cl_2, r.t., 36h; (d) EtCOCl, 5N NaOH, CH_2Cl_2, r.t., 12h; (e) $LiAlH_4$, THF, r.t., 12h, 39% (3 steps).

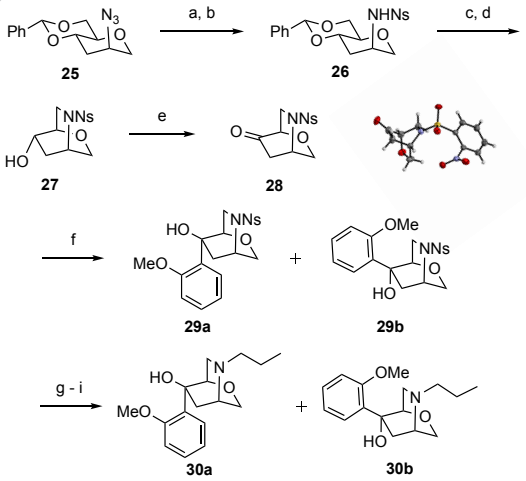
We then focused on a prototypical bridged piperazine analog (Scheme 7). The known dichlorinated morpholine **21**, prepared according to Revesz and coworkers,[25] was first submitted to an S_N2 reaction involving 2-methoxyaniline. A subsequent hydrogenation in the presence of Pearlman's catalyst delivered the amine **23** in 39% over two steps. Finally, a sequence comprising allylation of the amine using allyl iodide and potassium carbonate as a base, followed by catalytic reduction of the allyl group led to the desired 7-(2-methoxyphenyl)-9-propyl-3-oxa-7,9-diazabicyclo-[3.3.1]nonane **24** in 64% yield over the two steps

To the best of our knowledge, the synthesis of 7-aryl-2-oxa-5-azabicyclo[2.2.2]octanes have not been previously reported. The synthesis commenced with the known intermediate **25** which could be prepared from D-glucose, according to Herdewijn and coworkers[26] (Scheme 8). We first reduced the azide to the corresponding primary amine by catalytic hydrogenation. Nosylation of the free amine provided the protected compound



Scheme 7. Reagents and conditions: (a) 2-methoxyaniline, diglyme, 165°C, 1h (b) H_2 (60 psi), $Pd(OH)_2$/C, 2N HCl, MeOH, rt, 15h, 44% (2 steps); (c) Allyl iodide, K_2CO_3, MeCN, rt, 15h; (d) H_2 (1 atm), Pd/C; MeOH, rt, 15h, 63% (2 steps).

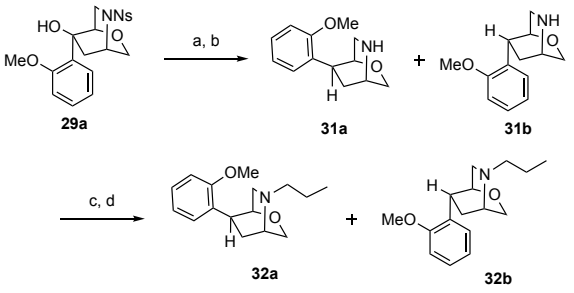
26. Aqueous acidic conditions served to hydrolyze the acetal (78% over 3 steps). An intramolecular Mitsunobu reaction allowed us to selectively obtain the bridged bicyclic morpholine analog **27**. PCC-mediated oxidation furnished ketone **28** in 86% yield over 2 steps, whose structure was ascertained by single-crystal X-ray analysis. At this stage, the 2-methoxyphenyl moiety was introduced through a Grignard addition, leading to a 2:1 mixture of benzylic alcohols **29a** and **29b** in 99% yield. After separation of the two isomers by chromatography, the nosyl group was removed according to Nargund and coworkers[27] and the propyl chain was installed as described above, yielding alcohols **30a** and **30b** in 66% and 59% yield respectively over three steps.



Scheme 8. Reagents and conditions: (a) H_2, Pd/C, MeOH, 18h, rt; (b) *o*-NsCl, Et_3N, DMAP, CH_2Cl_2, r.t., 6h; (c) 1N HCl, CH_2Cl_2/MeOH 1:1, 3h, 78% (3 steps); (d) PPh_3, DIAD, dioxane, r.t., 2h; (e) PCC, CH_2Cl_2, r.t., 18h, 86% (2 steps); (f) 2-methoxyphenylmagnesium bromide, THF, 0°C, 1h, **29a**/**29b**: 2:1, 99%; (g) 3-mercaptopropionic acid, $LiOH\cdot H_2O$, DMF, r.t., 4h (h) EtCOCl, 5N NaOH, CH_2Cl_2, rt. 12h; (i) $LiAlH_4$, THF, rt., 12h, 59 % for **30a**, 66 % for **30b** (3 steps).

Finally, a reductive dehydroxylation performed on **29a** in the presence of $BF_3\cdot OEt_2$ and triethylsilane, followed by the deprotection of the amine yielded intermediates **31a** and **31b** in 67% global yield in a ratio of 1.5:1 in favor of **31b** (Scheme 9). Installation of the propyl chain provided the bridged bicyclic morpholines **32a** and **32b** in 76% and 78% yield respectively over the two steps.

All compounds synthesized were tested at two doses (0.1 and 10 µM) on the dopamine D2 receptor for agonist and antagonist activity as well as on the dopamine D4 receptor as an agonist (see Table 1; Supporting Information). The compounds were also tested against hERG, on Caco-2 cells for passive diffusion and efflux, and on human, rat, and mouse microsomes for metabolic stability.



Scheme 9. Reagents and conditions: (a) $BF_3.OEt_2$, Et_3SiH, CH_2Cl_2, – 78°C, 4h (b) 3-mercaptopropionic acid, $LiOH{\cdot}H_2O$, DMF, r.t., 4h, **31a**/**31b**: 1.5:1, 67% (2 steps); (c) EtCOCl, 5N NaOH, CH_2Cl_2, r.t. 12h; (d) $LiAlH_4$, THF, r.t., 12h, 76 % for **32a**, 78% for **32 b** (2 steps).

Reference compounds **A** and **B** from Pettersson and coworkers[15] were active as agonists on the D2R at the two doses consistent with the literature data. We then tested the two compounds against hERG and found that only the piperazine derivative **B** significantly blocked the K channel at the 10 μM level. Both **A** and **B** proved to be permeable on Caco-2 cells, were not prone to efflux and were found to be stable in the presence of human microsomes. However, they were significantly metabolized in rat and mice microsomes (see Table 1, Supporting Information)

Unfortunately, the tropane analogues **4**, **8a-e** and **12** were all inactive on D2 and D4 receptors as agonists and antagonists. As depicted in the ORTEP representation of **8a** (Scheme 2), the tropane bridged-ring is projecting the aromatic and propyl substituents in a pseudo *trans*-diequatorial orientation mimicking the conformation of the corresponding piperidine or piperazine derivatives. The ethano bridge may thus be responsible for abolishing the agonist activity on the D2 receptor. The tropane derivatives **8a-e**, **12** showed an unfavorable profile vis-à-vis hERG at 1 μM. Passive permeability was maintained, while the microsomal stability tended to significantly erode across species for **8a-d** vs **A**. Interestingly, both **8a** and *endo*-hydroxy containing tropane **12** improved human microsomal stabilities compared to **A** and **B**, while maintaining adequate permeability and efflux profiles.

The bicyclic morpholine analogues **20** and **24** were also devoid of activity on the D2 and D4 dopaminergic receptors. Significantly, the bridged morpholino-piperazine **24** ADME and hERG profiles compared favorably to piperazine **B**.

The new 7-aryl-2-oxa-5-azabicyclo[2.2.2]octane derivatives **30a-b** and **32a-b** were not active on either D2 or D4 receptors. Importantly, the four analogs maintained exquisite permeability and acceptable microsomal stability, with the *exo*- analogs **30a** and **32b** offering complete stability on human microsomes.

In conclusion, we have developed versatile synthetic methods to access a variety of constrained oxabicyclic piperidine and piperazine isosteres related to pridopidine. While none of the isosteres offered favorable profiles against D2 or D4 receptors, we identified the novel 2-oxa-5-azabicyclo[2.2.2]octanes as attractive piperidine or piperazine surrogates with potential to reduce first path clearance and/or lowering hERG liability.

Acknowledgments

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