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Himbacine analogs as muscarinic receptor antagonists—effects of tether and heterocyclic variations

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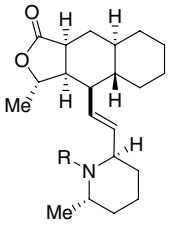
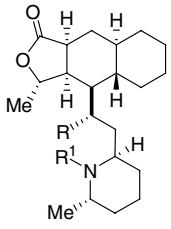
Abstract—A number of analogs of the natural product himbacine were synthesized employing variations at the heterocyclic unit and the tether that links the heterocyclic unit to the tricyclic motif. Several of these analogs had M_2 affinity and M_1/M_2 selectivity comparable to those of himbacine. The structural and stereochemical requirements of the heterocyclic unit for muscarinic binding are discussed in the light of these data.

1. Introduction

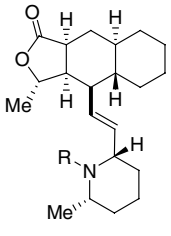
Himbacine (**1**),[1,2] a complex piperidine alkaloid isolated from *Galbulimima baccata*, continues to attract considerable interest as a potent muscarinic receptor antagonist.[3] Blockade of pre-synaptic muscarinic M_2 receptor is a potentially promising anticholinergic approach for the treatment of Alzheimer's disease.[4] The complex structural features of himbacine have rendered a thorough investigation of its structure–activity relationship properties difficult. Therefore, structure–activity relationship information in this series has been slow forthcoming. Attempts to simplify the tricyclic motif of himbacine have only yielded compounds with weaker binding affinity.[5] Similarly, *ent*-himbacine and a himbacine diastereomer possessing a piperidine ring with absolute chirality opposite to that of natural himbacine have been shown to be far less active suggesting the importance of the absolute and relative stereochemistry of the tricyclic and heterocyclic units for biological activity.[6] We have reported on the preliminary efforts of varying the substituted piperidine moiety of dihydrohimbacine using a parallel synthesis approach.[7] However, there has been no report of replacing the piperidine ring of himbacine itself with other heterocycles and incorporating tether constraints. We wish to



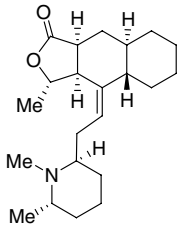
1 R = Me Himbacine



2 R = H, R^1 = Me Dihydrohimbacine
3 R, R^1 = H Dihydrohimbeline
7 R = OH, R^1 = Me Hydroxyhimbacine



4 R = Me *N*-Methyl himandravine
5 R = H Himandravine



6 Isohimbacine

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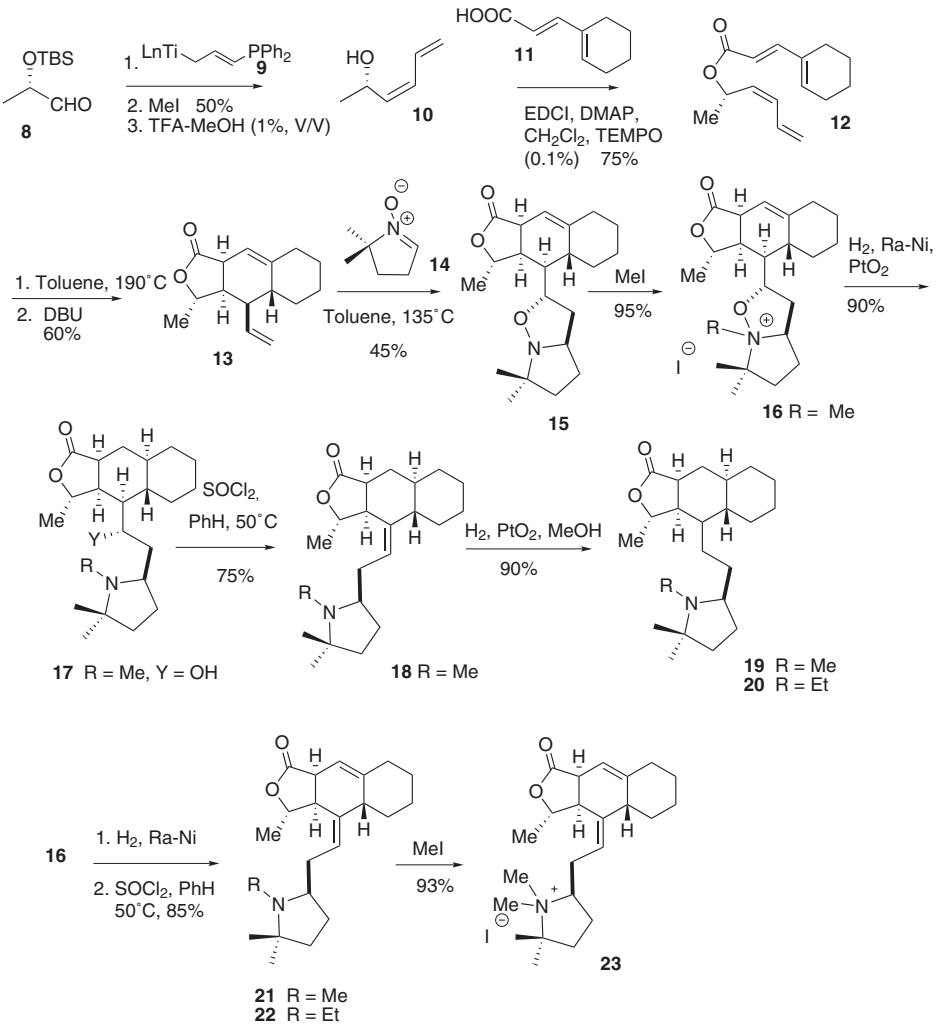

Scheme 1.

report here the synthesis and antimuscarinic activities of dimethyl pyrrolidinyl analogs of himbacine as well as tether modified himbacine analogs.

The syntheses of himbacine (**1**), dihydrohimbacine (**2**), himandravine (**5**), isohimbacine (**6**), and hydroxyhimbacine (**7**) have been reported earlier.[2a,7] Dihydrohimbeline (**3**) was generated from the previously reported himbeline[2a] by catalytic reduction of the pendent double bond. *N*-Methyl himandravine (**4**) was generated from himandravine (**5**)[2a] by reductive *N*-methylation as reported in the conversion of himbeline to himbacine (**1**).

The synthesis of the dimethylpyrrolidine analogs of himbacine was achieved using a [3+2] nitrone cycloaddition to attach the pyrrolidinyl unit to the previously reported tricyclic alkene **13** (Scheme 1). A novel synthesis of tricyclic alkene **13** was achieved starting from optically pure *O*-TBS-lactaldehyde (**8**).[8] Condensation of (diphenylphosphino)allyltitanium reagent **9** with aldehyde **8** followed by treatment with methyl iodide and subsequent *O*-deprotection gave the *Z*-diene **10**,[9] which was esterified with dienoic acid **11** to give the ester **12**. *Exo*-selective intramolecular Diels–Alder reaction was carried out under the previously reported conditions followed by brief in situ treatment with DBU to give the tricyclic alkene derivative **13**. 1,3-Dipolar cycloaddition[10] of commercially available nitrone **14** with the alkene **13** gave the isoxazolidine derivative **15** as the major product.[11] *N*-Methylation of the isoxazolidine **15** followed by reduction using a 1:1 mixture of Raney nickel and platinum oxide gave the fully saturated amino alcohol **17**. Dehydration of amino alcohol **17** using thionyl chloride gave the exocyclic alkene **18** as a single geometric isomer,[12] which was catalytically reduced to the nor-dihydrohimbacine **19** as an equimolar mixture of diastereomers. Alternatively, Raney nickel mediated reduction of isoxazolidinium salt **16** followed by thionyl chloride induced dehydration gave the diene **21**.

2. Results and discussion

Binding assays were conducted on cloned human muscarinic receptors as described previously.[7] As reported before,[7] dihydrohimbacine (**2**), which carries a saturated

two-carbon linker in place of the corresponding *trans*-olefin of himbacine (**1**), is equipotent to himbacine with comparable M_1/M_2 selectivity. Dihydrohimbeline (**3**), which lacks the *N*-methyl group of dihydrohimbacine (**2**) is fourfold less active toward the M_2 receptor, suggesting the importance of the *N*-methyl substituent on piperidine for activity. *N*-methylhimandravine (**4**) is a diastereomer of himbacine, being epimeric at the piperidine carbon carrying the tether. This compound was inactive against the M_2 and M_1 receptors, suggesting that the stereochemistry of the substituted piperidine moiety is important for activity. Isohimbacine (**6**) maintained the affinity for the muscarinic receptors suggesting that the piperidine moiety in isohimbacine can adopt a binding conformation similar to that of himbacine in spite of the presence of the exocyclic double bond. The dimethylpyrrolidinyl series showed a similar spectrum of activity to that of the himbacine series. For example, compound **19**, which is a direct analog of dihydrohimbacine (**2**), showed a K_i value of 12.2 nM against the M_2 receptor with a 10-fold M_1/M_2 selectivity. The corresponding *N*-ethyl analog **20** was essentially inactive suggesting the steric limitations at the binding site of the basic nitrogen. The exocyclic olefin derivative **18**, which is a close analog of isohimbacine (**6**), maintained a similar binding profile. Presence of an extra double bond in the middle ring of the tricyclic unit did not considerably alter the binding profile as indicated by the activity of compound **21**. The isoxazolidine derivative **15** was inactive. The quaternary ammonium salt **23** was also far less active than **21** suggesting the importance of the basic nitrogen (Table 1).

The following conclusions can be drawn from the above observations. A basic tertiary amine such as the one present in himbacine (**1**), and the dimethyl pyrrolidinyl analog **19** is necessary for antimuscarinic activity. Quaternary ammonium salt **23** was less active and selective. The binding is sensitive to the steric environment of the basic nitrogen. *N*-Methyl substituent seems to be optimal. Bulkier *N*-alkyl groups (e.g., **20** and **22**) reduced the muscarinic binding affinity. The absolute and relative stereochemistry of the substituted heterocyclic amine is important for muscarinic activity. Both in the himbacine series and the pyrrolidinyl series, a *trans*-disubstitution pattern adjacent to the nitrogen seems to be important. In the dimethylpyrrolidinyl series, one could envision a *trans*-relationship between one of the *gem*-dimethyl groups and the two-carbon tether, which is a plausible explanation for the retention of affinity. Also important is the (*R*)-absolute configuration at the tether-bearing piperidine α-carbon. *N*-Methylhimandravine (**4**), which has an (*S*)-configuration at the tether-bearing α-carbon and a *cis*-methyl substituent, was inactive. A diastereomer of himbacine with (*S*)-configuration at the tether-bearing piperidine 1′-carbon and a *trans*-methyl substituent at the 6′ position has been reported to be far less active.[6] While a two-carbon tether is tolerated, steric and polar effects introduced by the presence of a hydroxyl group or an isoxazolidine group eliminate activity. The fact that isohimbacine **6** and its dimethylpyrrolidinyl analog **18** maintain the M_2 activity and selectivity suggests that this double bond geometry facilitates the binding conformation of the molecule.

Table 1. In vitro M_2 and M_1 inhibitory activity on cloned human muscarinic receptors[a]

Compound number	K_i (nM)	
	M_2	M_1
1	4.5	48
2	4.3	32
3	16	68
4	>1400	>1400
5	>1400	>1400
6	13.3	65.9
7	203	1567
15	>1400	>1400
16	180	790
17	>1400	>1400
18	43	418
19	12.2	122
20	449	811
21	68	177
22	>1400	640
23	571	446

[a] See Ref. 7 for assay conditions.

In summary, this study strongly suggests the following requirements of himbacine derivatives for selective M_2 binding. First, an *N*-methyl piperidinyl or pyrrolidinyl subunit having an (*R*)-configuration at the tether-bearing α-carbon and a *trans*-alkyl substituent at the α′-carbon is necessary. Secondly, the two-carbon tether can be saturated or it can incorporate a double bond with specific geometry as in himbacine (**1**) or isohimbacine (**6**), but substitution of the carbon tether with a hydroxyl group or introduction of steric constraints as in the isoxazolidine derivative **15** reduces the muscarinic activity.

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12. The geometry of the trisubstituted double bond was deduced from NOE data. The allylic methylene protons of **18** showed strong NOE to the C-3 methyl group whereas the C-12 vinyl proton displayed no NOE to the C-3 methyl group.[2a]