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Synthesis and Affinity Studies of Himbacine Derived Muscarinic Receptor Antagonists

Ling-Jie Gao,[a] Magali Waelbroeck,[b] Sven Hofman,[a] Dirk Van Haver,[a] Marco Milanesio,[c] Davide Viterbo[c] and Pierre J. De Clercq[a,*]

[a]*Department of Organic Chemistry, Ghent University, Krijgslaan 281, B-9000 Gent, Belgium*
[b]*Laboratoire de Chimie Biologique et de la Nutrition, Université Libre de Bruxelles, Route de Lennik 808, B-1070 Brussels, Belgium*
[c]*Dipartimento di Scienze e Tecnologie Avanzate, Università del Piemonte Orientale 'A. Avogadro', Corso T. Borsalino 54, I-15100 Alessandria, Italy*

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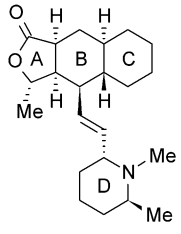
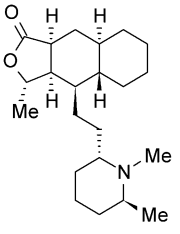
Abstract—A series of himbacine (**1**)-related analogues has been prepared featuring three different isomeric configurations with respect to the B-ring (**a**, **b** and natural **c**) and three different interconnecting two-carbon unsaturated units [natural (*E*)-ene, (*Z*)-ene, and yne]. The study of the binding affinities of the nine resulting compounds, including synthetic (+)-himbacine (**3c**), towards the M_1–M_4 muscarine receptor subtypes revealed that analogues **3a** and **5c** display a promising 10-fold selectivity for the M_2 receptor as compared to the M_1 receptor.

The interest of synthetic and medicinal chemists in himbacine (**1**) and related compounds[1,2] originates from (i) a few early reports that this piperidine alkaloid is a potent muscarinic receptor antagonist with selectivity for the M_2 receptor,[3] and from (ii) the possible therapeutic potential of such agents in the treatment of age-related neurodegenerative diseases. In particular, the enhancement of synaptic acetylcholine level in brain areas, for example via the use of presynaptic M_2 receptor inhibitors that at the same time possess a low affinity for postsynaptic M_1 receptors, is desirable.[4]

Five muscarinic receptor subtypes have been cloned in mammals.[5] Their expression in cultured cells devoid of any endogenous muscarinic receptors subsequently allowed their pharmacological and biological characterization.[6] The M_2 and M_3 receptors are widely expressed in peripheral tissues, and all five muscarinic receptor mRNAs have been identified in the central nervous system by in situ hybridization. The expression of at least four receptor subtypes in different brain regions has been confirmed by antibody labeling, binding and functional studies. The M_5 muscarinic receptor mRNA is found at very low expression levels only in the peripheral cortex.



1 himbacine



2 dihydrohimbacine

The pharmacological properties of the cloned M_1–M_4 receptors are, as a rule, in excellent agreement with the binding as well as with the functional properties of the naturally expressed receptors. In the present work, we investigate the binding properties of nine himbacine-related derivatives, including synthetic (+)-himbacine, to the four most abundant human muscarinic receptor subtypes (M_1, M_2, M_3 and M_4), expressed in stably transfected CHO cells.

One may distinguish three different parts in the structure of himbacine: (i) an ABC-tricyclic ring skeleton, consisting of a *trans*-fused perhydronaphthalene to which a γ-lactone is *cis*-fused; (ii) an *N*-methyl 2,6-*trans*-disubstituted piperidine D-ring; (iii) a two carbon (*E*)-ethylene bridge connecting the two former units. The structure–function relationship studies that have been conducted so far allow us to draw the following

*Corresponding author. Fax: +32-9-264-4998; e-mail: pierre.declercq@rug.ac.be

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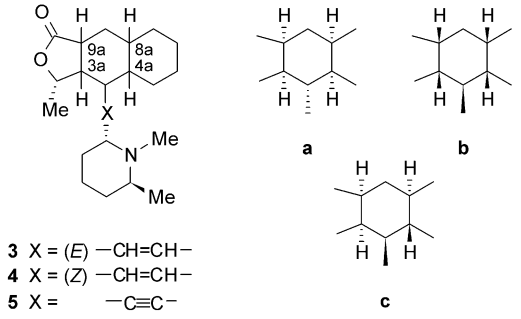
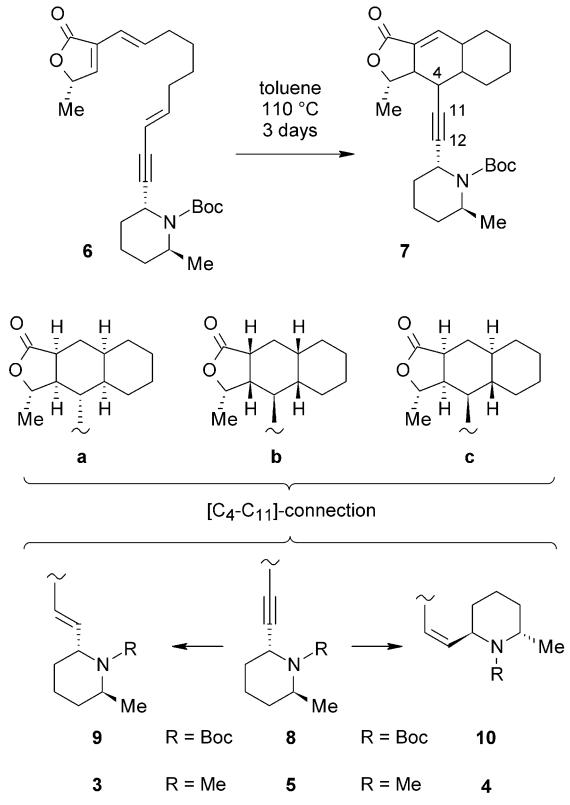
conclusions with respect to each separate part:[7,8] (i) the structural integrity of the ABC-ring skeleton is essential for a high himbacine-like M_2 affinity;[7a,7b] functional changes within this core have led to a few derivatives with high affinity for the M_2 receptor but always at the expense of M_2/M_1 selectivity;[7b,7c] (ii) saturation of the connecting ethylene-bridge leads to dihydrohimbacine (**2**) with a potency and selectivity comparable to that of himbacine in cloned human M_1 and M_2 receptors;[8] (iii) an interesting series of *N*-alkylated analogues with modified D-ring and saturated elongated bridge has been developed, in which a few members had a potency comparable to that of himbacine, albeit lacking again the desired selectivity.[8] In summary, although a few potent muscarinic antagonists with high M_2 affinity have been developed in this structural family, the goal of identifying one with M_2 specificity still remains elusive.[9]



Inspired by the above SAR results we have been interested in the development of himbacine derivatives characterized by a genuine ABC-ring skeleton but with allowance for stereoisomerism in the B-ring (the five contiguous stereocenters at **3a**, **4**, **4a**, **8a** and **9a** allow for 32 possible stereoisomers), with an intact *N*-methylated piperidine D-ring, and a two-carbon (C-11, C-12) connecting structural entity in three different geometric arrangements, that is the naturally occurring (*E*)-ene (**3**), the (*Z*)-ene (**4**), and yne (**5**) bridges.[10] Since each of these structural derivatives became available in three different stereoisomeric families (**a**, **b**, **c**), nine different compounds, including synthetic himbacine (**3c** = **1**), were obtained and tested for biological activity.

Central in the synthesis stands an intramolecular Diels–Alder (IMDA) approach (**6** to **7**), which led to an inseparable mixture of three diastereomeric α,β-unsaturated lactones.[2d] Selective reduction of the conjugated double bond in **7** (magnesium in methanol) afforded, after chromatographic purification, the three yne-derivatives **8a**, **8b** and **8c** in 40, 21 and 31% isolated yields, respectively (Scheme 1).[2d] In each separate family, the triple bond is reduced to the corresponding (*E*)- and (*Z*)-derivative. The former process requires a three-step sequence, involving (i) reduction of the lactone **8** with diisobutylaluminum hydride in toluene, followed by treatment with methanol and boron trifluoride-etherate in dichloromethane, (ii) reduction of the alkyne moiety with lithium in liquid ammonia in the presence of *tert*-butanol, and (iii) Jones oxidation to afford **9**.[2d] The semi-hydrogenation of **8** to the (*Z*)-enes **10** is effected using Raney nickel in tetrahydrofuran in almost quantitative yield.[11] The conversion of the *N*-Boc protected **8**, **9** and **10** to the required *N*-methyl analogues **3**, **4** and **5** involves treatment with trifluoroacetic acid in methylene chloride followed by formaldehyde/sodium cyanoborohydride in acetonitrile (average overall yield: 75%). The structural assignment in each stereoisomeric series was established unambiguously through: for the **a**-series, the X-ray crystallographic determination of **9a**[2d] and **10a**;[12] for the **b**-series, a detailed ^{1}H NMR spectroscopic investigation;[2d] for the **c**-series, comparison of the spectroscopic and physical data of **9c** with those of the same intermediate previously reported in the literature.[2a,2b] The spectral data of the himbacine analogues **3a**, **3b** and **3c** (himbacine), **4a**, **4b** and **4c**, **5a**, **5b** and **5c** are further fully consistent with the depicted structures (Scheme 1).[13]



Scheme 1.

The binding studies of the nine derivatives for the four muscarinic receptor subtypes were carried out by analysis of competition experiments with [^{3}H]-*N*-methyl scopolamine at 25 °C, in a 50 mM sodium phosphate/2 mM $MgCl_2$ buffer (pH 7.4).[14] The data are given in Table 1.

The results of the binding studies indicate that all analogues possess a lower affinity for each receptor subtype when compared to (+)-himbacine (**3c**). Two analogues, **3a** and **5c**, show a promising 10-fold selectivity for the M_2 relative to the M_1 receptor. Analogue **3b**, on the other hand, displays a 10-fold M_4/M_3 selectivity. The introduction of a (*Z*)-ethylene bridge leads in all cases to a very substantial loss of affinity and selectivity. Further studies towards the development of novel analogues featuring structural changes inspired by the above results will be reported in due course.

Table 1. pK_i values at cloned CHO cells expressing hM_1, hM_2, hM_3 or hM_4 muscarine receptors[a]

	hM_1	hM_2	hM_3	hM_4
1[b]	6.97	8.00	7.03	7.96
3a	5.76	6.77	5.68	6.21
3b	6.37	7.02	5.79	6.76
3c	6.80	8.33	6.98	8.06
4a	5.59	6.07	6.10	6.10
4b	5.63	6.17	6.17	6.00
4c	6.24	5.77	5.62	5.82
5a	5.27	5.94	5.30	5.76
5b	5.49	5.93	4.96	5.71
5c	5.49	6.51	5.48	6.05

[a]pK_i values, −log (K_i, concentration units), are preferred over K_i values since the distribution of the K_i values is log-normal; the calculated SEM values vary between ±0.01 and ±0.35.
[b]Results obtained at human cloned muscarinic receptors but with slightly different incubation conditions compared to this work (25 mM sodium phosphate, 5 mM $MgCl_2$, 23 °C); see ref 6.

Acknowledgements

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10. For a previous account on the synthesis of *N*-Boc protected intermediates **8a**, **8b**, **8c** and **9a**, **9b**, **9c**, see ref 2d.
11. In the case of **8c**, however, the semi-hydrogenation led to a mixture of **10c** (70%) and a derivative in which the double bond had migrated to the trisubstituted C-4, C-11 position with unknown configuration (30%).
12. Crystallographic data for **10a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-180278.
13. Analytical and spectroscopic data, for **3a**: mp 114 °C (recrystallization from MeOH). $\alpha_D = +36.5$ (*c* 0.965, $CHCl_3$). IR (KBr): 2931, 1764, 1146 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.02 (d, $J = 6.4$ Hz, 3H), 1.27 (d, $J = 6.5$ Hz, 3H), 1.19–1.90 (m, 18H), 2.08 (d, $J = 14.4$ Hz, 1H), 2.17 (q, $J = 9.9$ Hz, 1H), 2.23 (s, 3H), 2.92 (m, 2H), 3.13 (m, 1H), 4.47 (q, $J = 6.5$ Hz, 1H), 5.16 (dd, $J = 15.3$, 9.9 Hz, 1H), 5.67 (dd, $J = 15.3$, 8.9 Hz, 1H) ppm. ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ 15.7 (CH_3), 19.2 (CH_2), 19.4 (CH_3), 19.6 (CH_2), 26.4 (CH_2), 27.2 (CH_2), 28.0 (CH_2), 28.8 (CH_2), 32.9 (CH_2), 33.6 (CH_2), 34.8 (CH), 35.3 (CH), 37.4 (CH), 39.5 (CH), 40.7 (CH_3), 45.8 (CH), 53.2 (CH), 61.7 (CH), 78.7 (CH), 133.1 (CH), 133.8 (CH), 179.0 (C) ppm. MS *m*/*z* (%): 345 (12) [M^+], 330 (100), 302 (2), 274 (1), 248 (2), 232 (2), 182 (2), 161 (2), 138 (35), 112 (95), 91 (40), 68 (60), 55 (70), 41 (60). For **3b**: mp 145 °C (recrystallization from MeOH). $\alpha_D = -17.1$ (*c* 0.631, $CHCl_3$). IR (KBr): 2926, 1771 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.01 (d, $J = 6.5$ Hz, 3H), 1.39 (d, $J = 6.8$ Hz, 3H), 1.05–1.90 (m, 17H), 2.09 (m, 1H), 2.19 (m, 1H), 2.23 (s, 3H), 2.48 (dt, $J = 9.4$, 11.0 Hz, 1H), 2.68 (td, $J = 7.5$, 1.6 Hz, 1H), 2.84 (m, 1H), 3.08 (m, 1H), 4.51 (qd, $J = 6.8$, 4.8 Hz, 1H), 5.18 (dd, $J = 15.5$, 9.0 Hz, 1H), 5.60 (dd, $J = 15.5$, 8.9 Hz, 1H) ppm. ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ 14.2 (CH_3), 18.0 (CH_3), 18.9 (CH_2), 19.7 (CH_2), 26.7 (CH_2), 27.1 (CH_2), 28.3 (CH_2), 28.5 (CH_2), 32.6 (CH_2), 33.2 (CH_2), 33.7 (CH), 35.1 (CH), 38.2 (CH), 40.1 (CH), 41.2 (CH_3), 44.6 (CH), 53.5 (CH), 61.5 (CH), 79.1 (CH), 133.8 (CH), 135.0 (CH), 179.1 (C) ppm. MS *m*/*z* (%): 345 (6) [M^+], 330 (70), 302 (3), 274 (1), 246 (1), 227 (2), 192 (2), 161 (2), 138 (40), 112 (100), 91 (48), 77 (60), 68 (60), 55 (50), 41 (70). For **3c**: mp 131 °C (recrystallization from MeOH). $\alpha_D = +51.4$ (*c* 1.47, $CHCl_3$). IR (KBr): 2933, 1785, 1190 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.74 (m, 1H), 1.00

(d, $J=6.5$ Hz, 3H), 1.39 (d, $J=5.9$ Hz, 3H), 0.90–1.80 (m, 16H), 1.86 (ddd, $J=14.1$, 6.1, 2.3 Hz, 1H), 2.11 (td, $J=10.0$, 5.8 Hz, 1H), 2.21 (s, 3H), 2.24 (m, 1H), 2.62 (dt, $J=13.1$, 6.8 Hz, 1H), 2.84 (m, 1H), 3.02 (m, 1H), 4.63 (dq, $J=10.4$, 5.9 Hz, 1H), 5.25 (dd, $J=15.2$, 10.0 Hz, 1H), 5.57 (dd, $J=15.2$, 9.1 Hz, 1H) ppm. ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ 14.0 (CH_3), 18.9 (CH_2), 22.2 (CH_3), 26.1 (CH_2), 26.4 (CH_2), 31.4 (CH_2), 32.0 (CH_2), 32.6 (CH_2), 33.2 (CH_2), 33.6 (CH_2), 39.9 (CH_2), 41.1 (CH_3), 41.5 (CH), 42.2 (CH), 45.7 (CH), 49.1 (CH), 53.4 (CH), 61.3 (CH), 76.8 (CH), 133.4 (CH), 133.5 (CH), 178.3 (C) ppm. MS m/z (%): 345 (6) [M^+], 330 (70), 302 (3), 274 (1), 246 (2), 232 (2), 199 (3), 165 (6), 138 (30), 112 (100), 91 (40), 77 (50), 68 (50), 55 (50), 41 (70). For **4c**: mp 184 °C (recrystallization from MeOH). $\alpha_D = +57.8$ (c 1.156, $CHCl_3$). IR (KBr): 2930, 1760, 1207, 1035, 956 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.66 (m, 1H), 1.02 (d, $J=6.5$ Hz, 3H), 1.44 (d, $J=5.9$ Hz, 3H), 0.90–1.80 (m, 16H), 1.88 (ddd, $J=13.3$, 6.3, 2.4 Hz, 1H), 2.23 (s, 3H), 2.24 (m, 1H), 2.42 (dt, $J=10.8$, 5.9 Hz, 1H), 2.64 (dt, $J=12.8$, 6.6 Hz, 1H), 2.95 (m, 1H), 3.28 (m, 1H), 4.66 (dq, $J=10.4$, 5.9 Hz, 1H), 5.16 (t, $J=10.8$ Hz, 1H), 5.59 (t, $J=10.8$ Hz, 1H) ppm. ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ 13.2 (CH_3), 18.6 (CH_2), 22.1 (CH_3), 26.1 (CH_2), 26.4 (CH_2), 31.2 (CH_2), 31.9 (CH_2), 32.3 (CH_2), 32.9 (CH_2), 33.6 (CH_2), 39.6 (CH), 39.7 (CH), 41.2 (CH_3), 42.0 (CH), 42.1 (CH), 47.2 (CH), 53.3 (CH), 55.1 (CH), 76.7 (CH), 131.9 (CH), 133.1 (CH), 178.2 (C) ppm. MS m/z (%): 345 (10) [M^+], 330 (15), 302 (2), 274 (1), 246 (1), 232 (1), 190 (1), 176 (1), 138 (10), 112 (40), 91 (25), 58 (100), 41 (50). For **5a**: mp 97 °C (recrystallization from MeOH). $\alpha_D = +57.0$ (c 0.810, $CHCl_3$). IR (KBr): 2937, 1782, 1146 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (d, $J=6.3$ Hz, 3H), 1.37 (d, $J=6.6$ Hz, 3H), 1.15–1.90 (m, 16H), 2.07 (m, 1H), 2.15 (m, 2H), 2.33 (s, 3H), 2.46 (m, 1H), 2.60 (t, $J=11.6$ Hz, 1H), 2.76 (td, $J=7.5$, 1.7 Hz, 1H), 3.75 (brs, 1H), 4.70 (q, $J=6.6$ Hz, 1H) ppm. ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ 19.5 (CH_3), 19.9 (CH_2), 20.4 (CH_2+CH_3), 26.3 (CH_2), 26.9 (CH_2), 27.8 (CH_2), 29.5 ($CH+CH_2$), 31.4 (CH_2), 34.4 (CH_2), 34.6 (CH), 35.4 (CH), 38.0 (CH), 40.8 (CH_3), 48.1 (CH), 53.1 (CH), 54.7 (CH), 78.6 (C), 79.6 (CH), 88.1 (C), 178.4 (C) ppm. MS m/z: 343 (5) [M^+], 328 (100), 300 (2), 272 (2), 246 (1), 188 (2), 163 (2), 150 (4), 136 (12), 108 (20), 91 (28), 77 (20), 68 (20), 56 (30), 42 (40). For **5b**: mp 129 °C (recrystallization from MeOH). $\alpha_D = -7.4$ (c 0.783, $CHCl_3$). IR (KBr): 2935, 1776 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (d, $J=6.3$ Hz, 3H), 1.63 (d, $J=6.7$ Hz, 3H), 1.16–1.87 (m, 16H), 2.10 (m, 1H), 2.29 (s, 3H), 2.30 (m, 1H), 2.39 (m, 1H), 2.45 (ddd, $J=11.5$, 7.2, 4.6 Hz, 1H), 2.61 (t, $J=11.3$ Hz, 1H), 2.69 (t, $J=7.2$ Hz, 1H), 3.70 (brs, 1H), 4.59 (qd, $J=6.7$, 4.6 Hz, 1H) ppm. ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ 16.6 (CH_3), 19.8 (CH_2), 20.6 (CH_3), 20.7 (CH_2), 23.6 (CH), 26.7 (CH_2), 26.7 (CH_2), 28.1 (CH_2), 29.3 (CH_2), 31.7 (CH_2), 34.7 (CH_2), 34.9 (CH), 39.1 (CH), 39.8 (CH), 41.1 (CH_3), 46.0 (CH), 52.9 (CH), 54.7 (CH), 78.4 (CH), 80.3 (C), 88.8 (C), 178.7 (C) ppm. MS m/z: 343 (6) [M^+], 328 (100), 300 (2), 272 (2), 244 (1), 188 (3), 174 (3), 150 (6), 136 (20), 108 (28), 96 (36), 91 (45), 77 (30), 68 (40), 56 (50), 42 (70). For **5c**: $\alpha_D = +69.7$ (c 0.858, $CHCl_3$). IR (CH_2Cl_2): 2930, 1778 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (d, $J=6.1$ Hz, 3H), 1.64 (d, $J=5.9$ Hz, 3H), 0.86–1.90 (m, 17H), 2.26 (brd, $J=13.6$ Hz, 1H), 2.34 (s, 3H), 2.43 (m, 2H), 2.54 (ddd, $J=11.2$, 5.4, 1.5 Hz, 1H), 2.60 (dt, $J=13.2$, 6.7 Hz, 1H), 3.77 (brs, 1H), 4.68 (dq, $J=12.0$, 5.9 Hz, 1H) ppm. ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ 20.2 (CH_3), 20.4 (CH_2), 21.6 (CH_3), 26.0 (CH_2), 26.3 (CH_2), 31.2 (CH_2), 31.6 (CH_2), 31.8 (CH_2), 33.4 (CH_2), 34.2 (CH), 34.3 (CH_2), 40.0 (CH), 40.9 (CH_3), 41.5 (CH), 42.5 (CH), 45.9 (CH), 53.4 (CH), 54.9 (CH), 77.4 (CH), 81.5 (C), 86.7 (C), 177.6 (C) ppm. MS m/z: 343 (11) [M^+], 328 (100), 298 (10), 272 (2), 244 (4), 163 (50), 150 (20), 136 (30), 108 (28), 91 (50), 77 (35), 68 (50), 56 (98), 42 (95).

14. Waelbroeck, M.; Lazareno, S.; Pfaff, O.; Friebe, T.; Tastenoy, M.; Mutschlee, E.; Lambrecht, G. *Br. J. Pharmacol.* **1996**, *119*, 1319.