Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 15 (2005) 2093–2096
Bioorganic & Medicinal Chemistry Letters

Design, synthesis and activity of novel derivatives of Oxybutynin and Tolterodine☆

Kirandeep Kaur,[a,*] Shelly Aeron,[a] Miriyala Bruhaspathy,[a] Shankar J. Shetty,[a] Suman Gupta,[b] Laxminarayan H. Hegde,[b] Arun D. V. Silamkoti,[a] Anita Mehta,[a] Anita Chugh,[b] Jang B. Gupta,[b] P. K. S. Sarma[a] and Naresh Kumar[a,*]

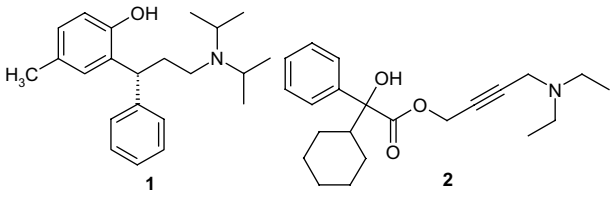
[a]*Ranbaxy Research Laboratories, New Drug Discovery Research, Department of Medicinal Chemistry, Gurgaon 122 001, Haryana, India*
[b]*Ranbaxy Research Laboratories, New Drug Discovery Research, Department of Pharmacology, Gurgaon 122 001, Haryana, India*

Received 7 January 2005; revised 11 February 2005; accepted 12 February 2005
Available online 19 March 2005

Abstract—Novel derivatives of Tolterodine (**1**) and Oxybutynin (**2**) have been designed using conformationally restricted azabicyclics as replacement for open-chain amines. The synthesis and structure–activity relationships are presented.

Overactive bladder is one of the most common causes of bladder control problems. It arises from the uncontrolled spontaneous activity of the detrusor muscle during bladder filling leading to the symptoms of urinary urgency and increased frequency of micturition with or without incontinence. A range of therapeutic options are available but pharmacotherapy with antimuscarinic drugs remain the mainstay of treatment for the symptoms of overactive bladder. Muscarinic receptors are widely distributed throughout the body and five distinct subtypes are known to exist (M_1–M_5). The human urinary bladder smooth muscle contains a mixed population of M_2- and M_3- muscarinic receptor subtypes. Although the M_2- receptors are the predominant cholinoreceptors present in the bladder, the smaller population of M_3- receptors appears to be the most functionally important because they mediate direct contraction of the detrusor muscle.[1] However, since muscarinic receptors are widely distributed throughout the body, an antimuscarinic action in organs other than the urinary bladder leads to dose-limiting adverse side effects including dry mouth, constipation, blurred vision, headache, somnolence and tachycardia.

The lack of selectivity of Tolterodine (**1**) and Oxybutynin (**2**) may be the result of the interaction of different conformations[1] of the ligands with different receptor subtypes, and so subtype selective ligands, which recognize the different localizations and functions of receptor subtypes may provide the possibility of developing more ideal drugs. Herein we describe our work on the conformational restriction of the amine part of antimuscarinic drugs like **1** and **2**.

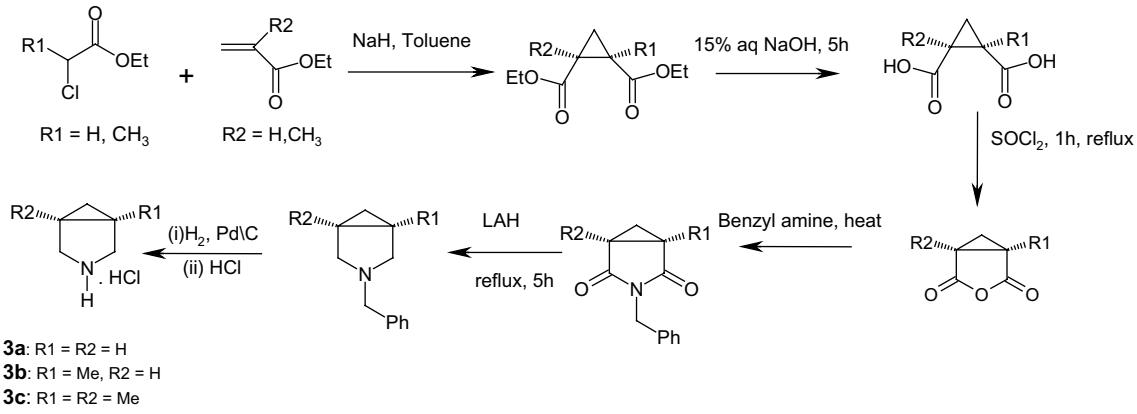


The conformational restriction of acyclic amines may be achieved by use of cyclic systems. We chose to use bicyclic amines such as 3-azabicyclo[3.1.0]hexane, which were, prior to this disclosure, unknown in the muscarinic field. The replacement of the diisopropyl and diethyl groups of Tolterodine and Oxybutynin, respectively, with such bicyclic amines allowed us to confirm the beneficial effects of conformational restrictions.

The bicyclic amines (**3a**–**c**) were prepared following reported procedures[2] with modifications wherever

Keywords: Selective muscarinic antagonists; Azabicyclohexane; Oxybutynin; Tolterodine.
☆ Presented at 227th ACS meeting, Anaheim.
* Corresponding authors. Tel.: +91 124 519 4920; fax: +91 124 234 3545 (N.K.); e-mail: n.kumar@ranbaxy.com

0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.02.036



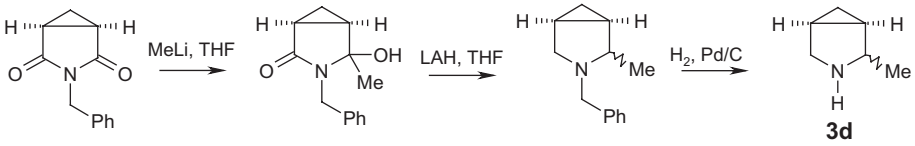
Scheme 1. Synthesis of 3-azabicyclo[3.1.0]hexane derivatives (**3a**–**c**).

necessary. Details are shown in Scheme 1. The introduction of a methyl group at the C-2′ position of azabicyclo[3.1.0]hexane was achieved by treating 3-benzyl-3-azabicyclo[3.1.0]hexane-2,4-dione with methyllithium followed by LAH reduction and debenzylation to give **3d**, (Scheme 2).

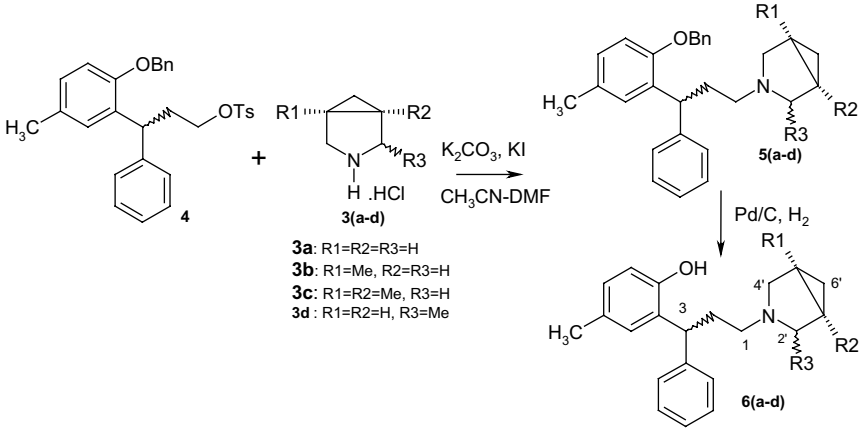
The racemic tosylate (**4**) was prepared by the known procedure.[3] The synthesis of Tolterodine analogues was achieved by *N*-alkylation of amine **3(a–d)** with tosylate **4** to give the propylamines **5(a–d)**, which upon debenzylation under hydrogenation conditions, gave compounds **6(a–d)** (Scheme 3).

The syntheses of Oxybutynin analogues involved the condensation of α-hydroxy acid derivatives[4] with the corresponding alcohol **7** or amine **9**. The alcohol **7** was synthesized by the reaction of 3-azabicyclo[3.1.0]hexane with 1-chloro-4-hydroxy-2-butyne[5] whilst the amine **9** was obtained by alkylation of 3-azabicyclo[3.1.0]hexane with the phthalimido derivative **8**[6] followed by hydrazinolysis (Scheme 4).

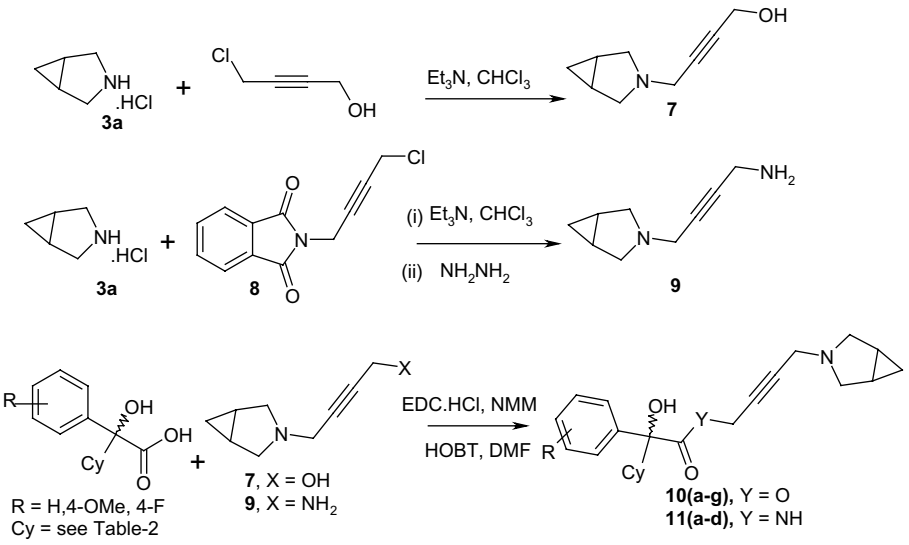
Compound **6a**, with a free phenolic group, displayed high affinity and had twofold selectivity for the M_3 receptor over the M_2 receptor, see Table 1. Compounds **5c** and **5d** confirmed the need for a free phenolic group. Compound **6d** was separable[7] at C-2′ to give **6d′** (3*RS*,2′*R**) and **6d″**(3*RS*,2′*S**). Compound(s) **6d′** showed the K_i value of 79 nM for M_3 receptors, while **6d″** showed about three times better activity, that is, 25 nM. As it mimics one of the isopropyl group of Tolterodine at nitrogen, further improvement may be possible by second stereospecific substitution of methyl at



Scheme 2. Synthesis of 2-methyl-3-azabicyclo[3.1.0]hexane (**3d**).

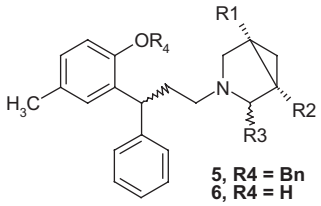


Scheme 3. Synthesis of Tolterodine analogues.



Scheme 4. Synthesis of Oxybutynin analogues.

Table 1. Activities for Tolterodine analogues



5, R4 = Bn
6, R4 = H

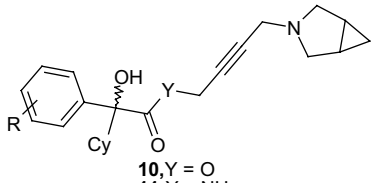
Compounds	R1	R2	R3	*n*	M_3 K_i (nM)[8]	M_2 K_i (nM)[8]
5a	H	H	H	1	>1000	>10,000
5c	CH_3	CH_3	H	1	>10,000	>10,000
5d	H	H	CH_3	1	>1000	>10,000
6a	H	H	H	2	50	105
6b	H	CH_3	H	1	118	221
6c	CH_3	CH_3	H	1	>1000	>1000
6d′	H	H	CH_3	1	79	34
6d″	H	H	CH_3	1	25	42
Tolterodine (**1**)	NA	NA	NA	10	7.07	6.91

C-4′. This may result in an understanding of specific conformation of *N*,*N*-diisopropyl groups required in the receptor cavity for the activity.

In the Oxybutynin series, the esters **10(a–g)** were more potent than the corresponding amides **11(a–d)**, see Table 2. Effect of substitution on the phenyl rings was checked with compounds **10d** and **10g**. The *R* and *S* isomers of **10a** were synthesized and the *R* isomer (**10e**)[9] found to be more potent than the *S* isomer (**10f**). Compound **10e** displayed a selectivity of 3.67-fold for M_3 over the M_2 receptor.

In summary, this work reveals the hidden potentials in new framework design. The bicyclic amine used has shown its capability to replace acyclic amines in Tolterodine (**1**) and Oxybutynin (**2**) without affecting core SAR. Newly emerged compounds like **10e** have shown potential as bladder selective (2.6-fold of **2**) ligands.[10,11]

Table 2. Activities for Oxybutynin analogues



10, Y = O
11, Y = NH

Compounds	R	Cy	*n*	M_3 K_i (nM)[8]	M_2 K_i (nM)[8]
10a	H	Cyclopentyl	1	37	65
10b	H	Cyclohexyl	1	35	72
10c	H	Phenyl	3	14	31
10d	4-F	4-Fluorophenyl	3	39	40
10e	H	Cyclopentyl	3	6	22
10f	H	Cyclopentyl	1	102	224
10g	4-OCH_3	Cyclopentyl	1	964	1926
11a	H	Cyclopentyl	1	330	425
11b	H	Cyclohexyl	1	2605	3582
11c	H	Phenyl	1	291	639
11d	4-F	4-Fluorophenyl	1	366	736
Oxybutynin (**2**)	NA	NA	3	0.95	6.97

Acknowledgements

Authors would like to thank Dr. Ian Cliff, Dr. Venkata P. Palle and Dr. DharamVir for their valuable support, suggestions and discussions.

References and notes

1. Hirose, H.; Aoki, I.; Kimura, T.; Fujikawa, T.; Numazawa, T.; Sasaki, K.; Nishikibe, M.; Noguchi, K. *Eur. J. Pharmacol.* **2002**, *452*, 245.
2. Willy, D. K. U.S. 4,183,857, 1980.
3. Jonsson, N. A.; Sparf, A.; Mikiver, L.; Moses, P.; Nilvebrant, L. EP 0,325,571, 1991.
4. For example: (a) Shacklett, C. D.; Smith, H. A. *J. Am. Chem. Soc.* **1953**, *77*, 2654; (b) Grover, P. T.; Bhongle, N.

N.; Wald, S. A.; Senanayake, C. H. *J. Org. Chem.* **2000**, *65*, 6283.
5. Bailey, W. J.; Fujiwara, E. *J. Am. Chem. Soc.* **1955**, *77*, 165.
6. Dobson, N. A.; Raphel, R. A. *J. Chem. Soc.* **1958**, 3643.
7. The absolute stereochemistry was not established at C-2′.
8. The affinity of test compounds for the M_2 and M_3 muscarinic receptor subtypes was determined by [^{3}H]-*N*-methyl scopolamine binding studies using rat heart and submandibular gland, respectively, as previously described with minor modifications. For further details see Moriya, H.; Takagi, Y.; Nakanishi, T.; Hayashi, M.; Tani, T.; Hirotsu, I. *Life Sci.* **1999**, *64*, 2351; and Cheng, Y.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 309.
9. Procedure for synthesis of **10e**: To a solution of *R*(−)-2-hydroxy-2-cyclopentyl-2-phenyl acetic acid[4b] (1.13 mmol) and alcohol **7**[10] (1.13 mmol) in DMF (8 mL) at 0 °C, 1-hydroxy benzotriazole (1.13 mmol) was added followed by *N*-methyl morpholine (2.27 mmol). The reaction mixture was stirred for 30 min and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide–HCl (1.13 mmol) was added. The reaction mixture was stirred at same temperature for 1 h and then at rt for 15 h. After aqueous workup, organic layer was evaporated to give residue, which was purified by column chromatography (ethyl acetate/hexane : 20/80) to give pure **10e** (0.11 g). ^{1}HNMR ($CDCl_3$, 300 MHz): 0.45 (m, 1H), 0.8 (m, 1H), 1.33–1.68 (m, 11H), 2.90–2.98 (m, 4H), 3.51 (s, 2H), 3.63 (s, 1H), 4.7–4.85 (dd, J = 15.3 Hz, 2H), 7.26–7.67 (m, 5H).
10. Mehta, A.; Silamkoti, A.V.; Kaur, K.; Gupta, J. B. WO 014853, 2004.
11. Mehta, A.; Silamkoti, A. V.; Bruhaspathy, M.; Gupta, J. B. WO 014363, 2004.