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Invited review

The [(methyloxy)imino]methyl moiety (MOIMM) in the design of a new type of β-adrenergic blocking agent

Aldo Balsamo*, Marco Macchia, Adriano Martinelli, Armando Rossello

Dipartimento di Scienze Farmaceutiche, Università di Pisa, via Bonanno 6, 56126 Pisa, Italy

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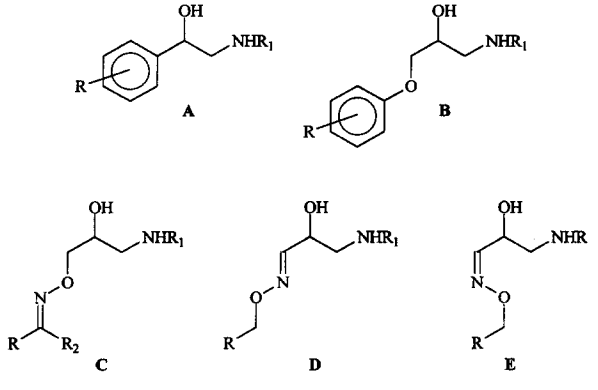
Abstract – This article summarizes the series of studies that led to the recognition of the [(methyloxy)imino]methyl moiety (MOIMM) as a bioisoster of aryl groups in the field of β-adrenergic blocking agents. © Elsevier, Paris

β-adrenergic antagonists / [(methyloxy)imino]methyl moiety / adrenergic drugs

1. Introduction

The difference between the two principal classes, **A** and **B**, of β-blocking adrenergic drugs lies in the presence of the OCH_2 group between the Ar portion and the ethanolamine chain in type **B** derivatives. To explain the similar pharmacological activity of the two classes of drugs, several hypotheses have been advanced about the mechanism through which the CH_2–O–Ar portion of class **B** agents can substitute for the single aromatic moiety (Ar) of class **A** compounds in the drug-receptor interaction [1–6].



X-ray diffraction studies [7, 8] have shown *(figure 1)* that the C_3–O_2–C_4–C_5 atoms of class **B** drugs define a plane, and the spatial relationship between this plane and the ethanolamine side chain is the same as that observed between the aromatic ring and the ethanolamine side chain in class **A** drugs. On the basis of this observation, it was hypothesised that the C_3–O_2–C_4–C_5 portion of class **B** adrenergic β-blocking drugs might in some way "simulate" the aromatic ring of class **A** drugs, and therefore be bioisoster to the Ar group *(figures 2a* and *2b)* [8].

Theoretical studies [9, 10] carried out on model compounds, using type **A** and **B** drugs not substituted on the amino group, confirmed that this C_3–O_2–C_4–C_5 portion, which only contains a part of the aromatic ring of type **B** drugs, generates a molecular electrostatic potential (MEP) similar to that of the aromatic ring of type **A** compounds *(figures 3a* and *3b)*. This result suggested that the particular electronic distribution suitable for interac-

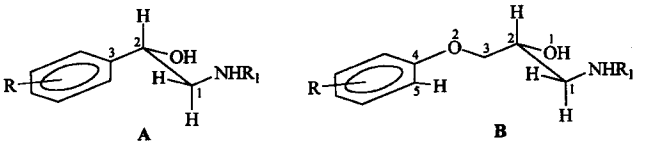


Figure 1. Perspective views of 2-arylethanolamine **A** and 3-aryloxypropanolamine **B** derivatives.

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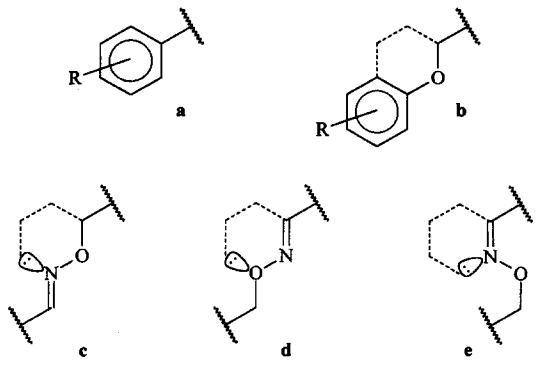


Figure 2. Representation of the spatial correspondences existing between molecular portions of Ar (**a**), CH_2–O–Ar (**b**), MAOMM (**c**), *E*-MOIMM (**d**), and *Z*-MOIMM (**e**), which may account for their bioisosteric relationship.

tion with the β-adrenergic receptor need not necessarily be generated by an aromatic structure [11].

In order to verify these considerations, research was started on compounds which, although lacking aromatic groups, could generate this kind of pharmacophoric electronic distribution and therefore carry out a β-adrenergic blocking activity. The most straightforward approach ought to have been the utilisation of the vinylethereal portion $RR'C{=}CHOCH_2$ but this group is known to have a very low stability. On the contrary, a [(methyleneamino)oxy]methyl moiety ($C{=}NOCH_2$, MAOMM), shown in *figure 2c* in its preferred conformation, seemed particularly suitable for this purpose [11], bearing in mind that some aromatic oxime ether derivatives possessing a β-blocking activity had been described in literature [12–14].

On this basis, some completely aliphatic compounds (**C**), designed as analogues of arylethanolaminic β-adrenergic drugs (**A**) where the aryl moiety (Ar) is replaced by the MAOMM, were synthesized [11].

The potent β-blocking properties of these **C** compounds and a comparison of their chemical reactivity *(figure 3c)* with that of type **A** drugs supported the hypothesis of the existence of a bioisosterism between the Ar and the MAOMM, at least in the field of adrenergic drugs. This possible bioisosterism was then successfully verified for non-adrenergic drugs in which the aryl moiety seems to be important for activity, such as anti-inflammatory arylacetic acids [15], β-lactam antibiotics [16], antidepressant agents [17] and biogenic amine uptake inhibitors [18].

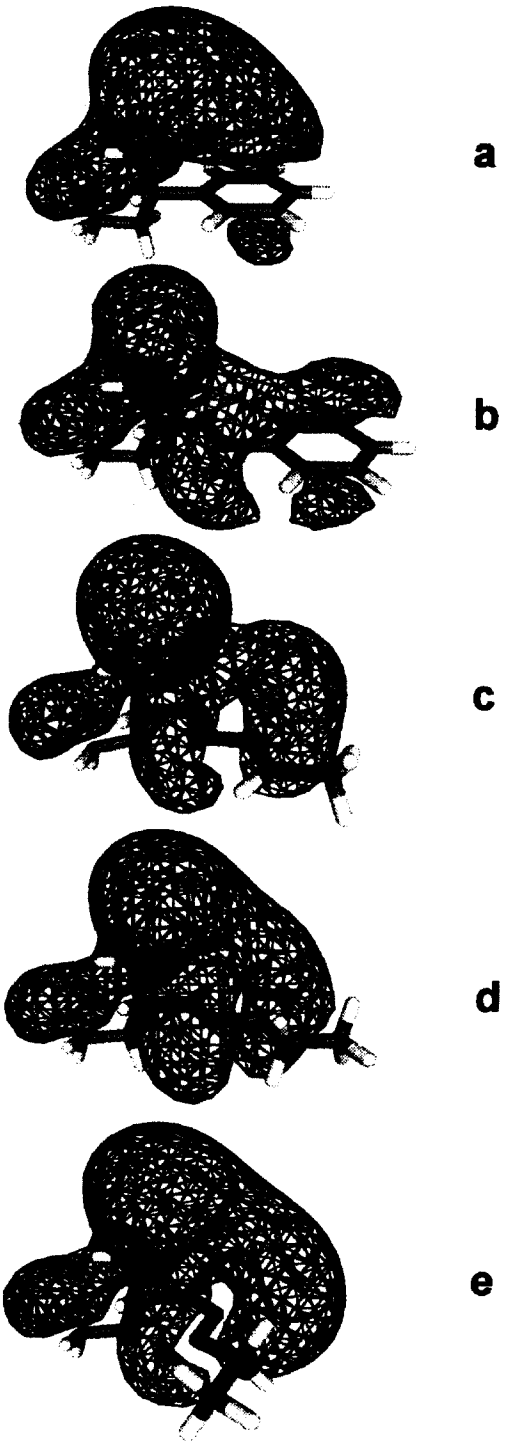
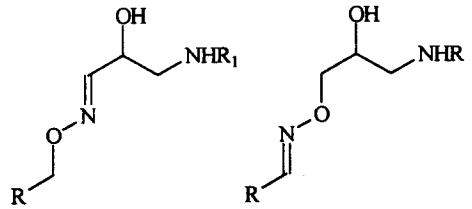


Figure 3. MEP of model compounds of β-adrenergic drugs of types **A.** (**a**), **B.** (**b**), **C.** (**c**), **D.** (**d**) and **E.** (**e**). The MEP was calculated at ab initio STO-3G level and the isopotential surfaces correspond to the value of -7 Kcal/mol.

Table I. β-adrenergic activity and radioligand binding affinity of MOIM (**1, 2**) and MAOM (**3, 4**) derivatives.



1, 2 **3, 4**

Compound	R	R_1	β-adrenergic binding affinity K_i(nM)[a] Rat brain membranes (β_1)	Bovine lung membranes (β_2)	β-adrenergic activity pIC_{50}[a] Isolated guinea-pig atria (β_1)	Isolated guinea-pig tracheal strips (β_2)
1a	Me	*i*-Pr	1040	3500	4.91	5.48
2b	Me	*t*-Bu	1080	1400	4.86	6.01
2a	Et	*i*-Pr	1240	5600	4.81	5.36
2b	Et	*t*-Bu	850	850	5.08	6.57
3a	Me	*i*-Pr	1480	7200	4.52	4.89
3b	Me	*t*-Bu	760	1980	4.87	5.39
4a	Et	*i*-Pr	2200	4580	4.81	4.92
4b	Et	*t*-Bu	500	1260	4.58	5.81
dichloroisoproterenol			51	140	6.94	6.01

[a] In order to simplify the table, the confidence limits and the standard errors of the biopharmacological data have been omitted.

2. (E)-MOIM derivatives

In the MAOMM *(figure 2c)*, the carbon of the CH_2 linked to the oximic oxygen possesses a hybridisation (sp^3) and a geometry different from those of the corresponding carbon of Ar *(figure 2a)* which possesses an sp^2 hybridisation. Furthermore, in the MAOMM, in the conformation shown in *figure 2c*, the unsaturated portion (C=N) is situated in a spatial area which does not

β-adrenergic drugs, in which the Ar or the MAOMM, respectively, are substituted by the MOIMM [19].

The β-adrenergic properties of these compounds were evaluated with both binding tests and functional experiments, and the results were compared with those of the corresponding [(methyleneamino)oxy]methyl isomers of type **C** (**3a, 3b, 4a** and **4b**) *(table I)*.

An examination of the biopharmacological data (to

These biopharmacological data indicated that in the field of β-adrenergic drugs, the MOIMM in the *E* configuration appears to reveal a bioisosterism with aryl groups which is analogous to the one already found for the MAOMM. Furthermore, the fact that the biopharmacological properties of the MOIM derivatives (**1** and **2**), which are similar to those of the MAOM derivatives (**3** and **4**) on β_1-receptors, are appreciably better on β_2-receptors, would appear to indicate that, at least on β_2-receptors, the atomic sequence $CH_2ON{=}C$ of the MOIMM in the *E* configuration possesses a slightly higher degree of bioisosterism with the aryl groups of adrenergic drugs, compared with the $C{=}NOCH_2$ sequence of the MAOMM.

In order to rationalise the similar biopharmacological properties of the MOIM and MAOM derivatives, their conformational and electronic characteristics were evaluated by means of theoretical studies [19]. The conformational data indicated that the two types of compounds possess very similar conformational profiles. In particular, for the two model compounds **5** and **6** which represent MOIM (**1** and **2**) and MAOM (**3** and **4**) derivatives respectively, it is possible to obtain a good superimposition of their structures in the low-energy conformations *(figure 4)*, thus obtaining, in the case of the totally planar conformations, a nearly perfect correspondence of the presumed pharmacophoric groups (MAOM and MOIM moieties, alcoholic oxygen, and amino nitrogen).

As regards the electronic characteristics, an analysis of the MEP of the MOIM, MAOM and Ar molecular portions of the model compounds, shown in *figure 3a*, *3c*, and *3d*, did not reveal substantial differences in chemical reactivity.

These results indicated that the ability of the MOIMM to substitute the MAOMM effectively as a bioisoster of the Ar, at least in the field of β-adrenergic blocking drugs, might be explained in terms of analogies in structural and electronic characteristics [19].

The next step in this study was based on the observation that, overall, for the MAOM derivatives studied [15, 17, 18, 20], while an aromatic substituent linked to the iminic carbon of the MAOMM is not essential for the activity, it may be capable of improving it. In the case of adrenergic drugs, an examination of our data [21] and those reported in literature for other type **C** derivatives [22] showed that compounds with an aromatic substituent linked to the MAOMM possess β-adrenergic properties that are often better than those of completely aliphatic compounds, especially as far as the affinity is concerned.

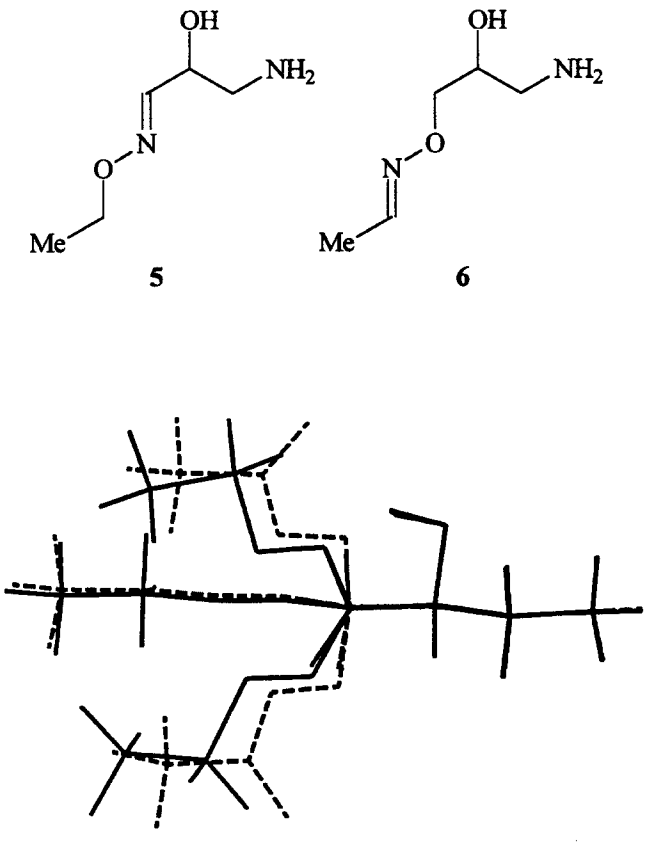


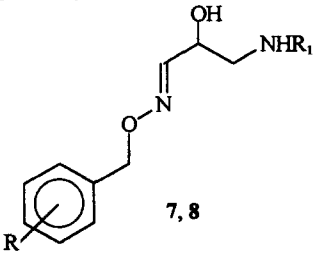
Figure 4. Superimposition of the three lowest energy conformers of **5** (solid line) and the three analogous ones of **6** (dashed line); the picture was obtained by superimposing the ethanolaminic portions of all conformers.

This observation suggested the idea of examining whether, in the case of the MOIM derivatives of type **D** also, the presence of an aromatic nucleus linked to the CH_2 carbon of the MOIMM might have a positive influence on the β-adrenergic properties of these compounds [23].

Consequently, we synthesised and tested for their β-adrenergic properties, a series of (*E*)-N-[3-(amino)-2-hydroxypropylidene](arylmethyloxy)amines of type **D** *(table II)* in which the phenyl ring is not substituted (**7a** and **8a**), or substituted in the *ortho*, *meta*, or *para* position by substituents that can have different electronic effects, such as the methoxy group (**7b–d** and **8b–d**) or the chlorine atom (**7e–g** and **8e–g**) [23].

An examination of the binding data for β_1-adrenoceptors indicated that most of the aromatic MOIM derivatives **7** and **8** present an affinity for these receptors, which is similar or slightly lower than that of the

Table II. β-adrenergic activity and radioligand binding affinity of **7** and **8**.



7, 8

Compound	R	R_1	β-adrenergic binding affinity K_i(nM)[a]		β-adrenergic activity pIC_{50}[a]	
			Rat brain membranes (β_1)	Bovine lung membranes (β_2)	Isolated guinea-pig atria (β_1)	Isolated guinea-pig tracheal strips (β_2)
7a	H	*i*-Pr	2 040	830		
7b	*o*-MeO	*i*-Pr	14 900	2 400		
7c	*m*-MeO	*i*-Pr	4 700	430		
7d	*p*-MeO	*i*-Pr	6 480	420		
7e	*o*-Cl	*i*-Pr	2 440	1 140		
7f	*m*-Cl	*i*-Pr	2 160	420		
7g	*p*-Cl	*i*-Pr	2 300	310		
8a	H	*t*-Bu	2 000	380	5.10	6.89
8b	*o*-MeO	*t*-Bu	1 010	700	4.35	6.10
8c	*m*-MeO	*t*-Bu	1 870	370	4.60	6.48
8d	*p*-MeO	*t*-Bu	6 580	130		
8e	*o*-Cl	*t*-Bu	3 300	250		
8f	*m*-Cl	*t*-Bu	1 400	210	4.90	6.38
8g	*p*-Cl	*t*-Bu	310	98	5.13	6.77

[a] In order to simplify the table, the confidence limits and the standard errors of the biopharmacological data have been omitted.

completely aliphatic MOIM derivatives **1** and **2**, whose biopharmacological data are shown in *table I*. Only in the case of the N-*tert*-butyl-substituted *p*-chlorophenyl derivative **8g** did the affinity prove to be higher than that of **1** and **2**. For the MOIM derivatives that were submitted to functional tests (**8a–c, f,** and **g**), the activity indices for β_1-adrenoceptors were in quite good agreement with those obtained in the binding tests.

As regards β_2-adrenoceptors *(table II)*, the results obtained in the binding tests indicate that most of the aromatic MOIM derivatives **7** and **8** possess an affinity higher than that of the completely aliphatic analogues **1** and **2** *(table I)*. Also on this β-adrenoceptor, the *p*-chloro MOIM derivative **8g** possesses the highest affinity. The results obtained for the MOIM derivatives **8a–c, f,** and **g** in the functional tests carried out on guinea-pig tracheal β_2-adrenoceptors were in good agreement with the K_i values obtained in the binding tests.

The above results underlined the fact that for type **D** compounds, the insertion of an aromatic system on the CH_2 carbon of the MOIMM leads to different results in the case of β_1- or β_2-adrenergic adrenoceptors. While this type of substitution does not have any appreciable effects on β_1-adrenergic properties, as regards the affinity and the activity, it appears to be capable of improving the β_2-adrenergic properties as far as receptor affinity is concerned.

Theoretical studies on the conformational *(figure 5)* and electronic characteristics *(table III)* of model compounds of both completely aliphatic (**5**) and aryl-substituted (**9a–g**) type **D** drugs, revealed that the presence of an aliphatic portion or an aromatic nucleus on the CH_2 carbon of the MOIMM does not influence either the conformational preferences or the molecular reactivity of the remaining molecular portion. The only differences that exist between the aliphatic (**5**) and the aromatic (**9a–g**) model compounds lie in the different steric characteristics and reactivity of the two kinds of substituent, which might be responsible for the variations in affinity towards β_2-adrenergic receptors that exist between completely aliphatic and aromatic type **D** compounds [23].

Among type **A** and **B** drugs, a separation in potency exists between stereoisomers, with the activity residing prevalently in the isomer in which the geometry of the

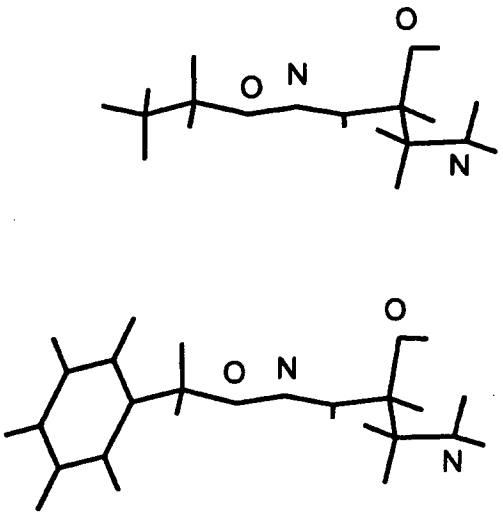
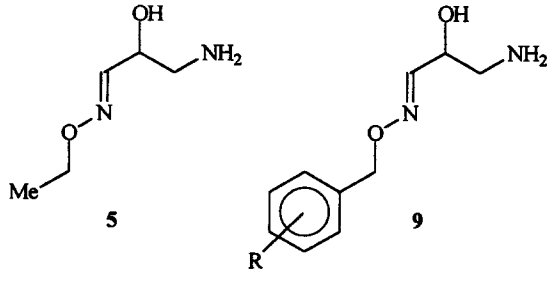


Figure 5. Preferred conformation of **5** and **9a**.

carbon adjacent to the hydroxyl group resembles that of the same carbon in (*R*)-(-)-catecholamines [24–26]. The capacity of the β-adrenergic receptor to recognise one of the two enantiomers of type **A** and **B** drugs is commonly explained [25] on the basis of the Easson-Stedman hypothesis [27] of a three-point attachment for active chiral molecules, assuming the Ar-hydroxy-amino or $ArOCH_2$-hydroxy-amino triads as pharmacophores.

Table III. Molecular electrostatic potential values (V, Kcal/mol) of compounds **5** and **9a–g** on the molecular surface, calculated for the optimized conformation.



Compound	R	V(Φ)[a]	V(O)[b]	V(N)[c]
5		-	-33.5	-32.8
9a	H	-1.6	-35.7	-34.4
9b	*o*-MeO	-2.8	-38.9	-37.6
9c	*m*-MeO	-3.5	-36.9	-35.5
9d	*p*-MeO	-3.1	-35.3	-32.2
9e	*o*-Cl	+3.7	-33.5	-32.6
9f	*m*-Cl	+3.5	-31.0	-30.0
9g	*p*-Cl	+3.6	-30.6	-28.9

[a] Mean MEP value on the phenyl ring; [b] Minimum MEP value generated by the oxygen atom of the MOIMM; [c] Minimum MEP value generated by the nitrogen atom of the MOIMM.

The enantiomeric forms of type **C** drugs do not display any appreciable differences in β-antagonistic activity [26, 28, 29]. This unusual absence of stereochemical selectivity for chiral active molecules has been attributed to the considerable flexibility of type **C** compounds, in particular around the OCH_2 bond, which causes the amino group, the hydroxyl and a part of the MAOMM and its substituents to be practically superimposable in the enantiomeric forms [28, 29].

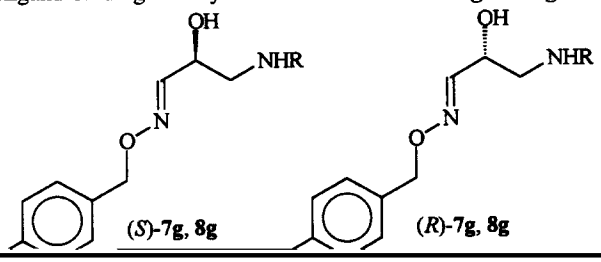
In view of the possibility of developing type **D** compounds as new β-blocking agents, it appeared to be of interest to verify whether the chirality of drugs of this new class influences the biopharmacological β-adrenergic characteristics, as in the case of compounds of types **A** and **B**, or is devoid of any influence, as in the case of compounds of type **C**. Consequently, the enantiomers of the type **D** compound (*R*, *S*)-**8g**, which, as a racemate, exhibited the highest affinity for the β-adrenoceptors ((*S*)-**8g** and (*R*)-**8g**) *(table IV)* and of the corresponding N-isopropyl-substituted analogue (*R*, *S*)-**7g** ((*S*)-**7g** and (*R*)-**7g**) were synthesized and subjected to in vitro binding and functional tests on β-adrenoceptors [30].

In both types of experiments *(table IV)*, the β-adrenergic properties of the enantiomers with the *S* configuration ((*S*)-**7g** and -**8g**) were better, even if not always markedly so, than those of the corresponding enantiomers with the *R* configuration ((*R*)-**7g** and -**8g**). Moreover, the racemic compounds (*R*, *S*)-**7g** and **8g** showed affinity and activity indices whose values were intermediate between those of the corresponding enantiomeric forms [30].

As a result, compounds (*S*)-**7g** and -**8g**, in which the geometry of the chiral carbon adjacent to the hydroxyl group resembles that of the natural catecholamines with the *R* configuration, proved to interact better with β-receptors, even if the stereochemical selectivity among the enantiomeric pairs is not so marked as in type **A** or **B** β-adrenergic blocking drugs. Furthermore, for MOIM-type β-blocking agents (**D**), the chirality seems to influence the biopharmacological β-adrenergic characteristics, as is the case for type **A** and **B** drugs, but in contrast with findings for MAOM-type drugs (**C**).

An explanation for the different behaviour of type **D** compounds compared with type **C** compounds may be offered by an examination of the molecular structures of compounds (*S*)-**7g** and -**8g** and (*R*)-**7g** and -**8g**. For the enantiomeric forms of type **D** derivatives, the fact that their N=CHCH(OH) portion is more rigid than the

Table IV. β-adrenergic activity and radioligand binding affinity of MOIM enantiomers **7g** and **8g**.



Compound	R	β-adrenergic binding affinity K_i(nM)[a]		β-adrenergic activity pIC_{50}[a]	
		Rat brain membranes (β_1)	Bovine lung membranes (β_2)	Isolated guinea-pig atria (β_1)	Isolated guinea-pig tracheal strips (β_2)
(*S*)-**7g**	*i*-Pr	1 100	263	4.81	6.10
(*R*)-**7g**	*i*-Pr	3 660	1 840	4.23	5.97
(*R,S*)-**7g**	*i*-Pr	2 300	310	4.62	6.05
(*S*)-**8g**	*t*-Bu	119	75	5.42	7.27
(*R*)-**8g**	*t*-Bu	2 620	350	4.54	6.30
(*R,S*)-**8g**	*t*-Bu	310	98	5.13	6.77

[a] In order to simplify the table, the confidence limits and the standard errors of the biopharmacological data have been omitted.

corresponding $OCH_2CH(OH)$ moiety of compounds **C** makes it impossible to find conformations which allow a quasi-superimposition of the enantiomers, of the kind used to explain the absence of stereochemical selectivity in type **C** compounds [30].

3. (Z)-MOIM derivatives

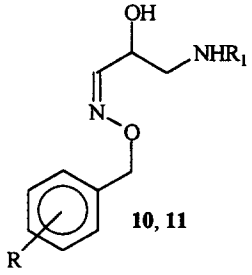
In the design of **D** compounds, the type of configuration (*E*) of the MOIMM was chosen [19] because in this configuration, the atomic sequence $CH_2ON{=}C$ appeared to present greater steric and electronic analogies with an Ar than in the *Z* configuration *(figure 2)*.

Furthermore, the results obtained with the previously studied type **D** derivatives [19, 23] did not exclude the possibility that, at least in the field of β-adrenergic antagonists, the MOIMM might be bioequivalent to the Ar and the MAOMM, even if its atomic sequence is arranged in a different way from the one shown by the MOIMM with the *E* configuration. On the basis of this consideration, compounds of type **E**, **10** and **11** *(table V)* which differ from those of type **D** previously studied (**7** and **8**) in their configuration around the imino double bond of the MOIMM, which is of type *Z* instead of *E*, were synthesised and evaluated for their β-adrenergic properties [31].

A comparison of the results obtained for the *Z*-MOIM derivatives **10** and **11** *(table V)* with those previously obtained for their corresponding isomers with the *E* configuration **7** and **8** *(table II)* [23] demonstrated that for the MOIM-type aminoalcohols studied (**7, 8, 10** and **11**) the β-adrenergic properties, as far as both the affinity and the activity are concerned, are substantially independent of the configuration around the MOIM double bond (*E* or *Z*) [31].

A comparison of the conformational *(figure 6)* and electronic properties *(figures 3d* and *3e)* of the model compounds **9a** and **12**, of the *E*- (**7** and **8**) and *Z*-MOIM (**10** and **11**) compounds respectively, determined by means of molecular calculations, revealed that, in spite of the differences in the steric characteristics due to the *Z* or *E* configuration, at least at the level of the spatial position of the arylmethyloxy group ($ArCH_2O$), the two kinds of compounds present some important analogies in their molecular reactivity. In particular, the reactivity pattern *(figures 3d* and *3e)* of the two configurational isomers is very similar not only in the ethanolaminic portion, but also at the level of the O–N=C atomic sequence [31]. This fact suggested that for the interaction of the MOIM-type compounds **7, 8, 10** and **11** with β-adrenoceptors, the fundamental role may be played by the atomic sequence $O{-}N{=}CH(OH)CH_2NH$. Moreover, the *E*- and *Z*-MOIM analogues possess analogous adrenergic properties, even if they present different steric characteristics linked to the different spatial arrangement of the benzylic moiety, with respect to the remaining portion of the molecule. This fact could be explained either by excluding the possibility of a direct interaction of the aryl with the appropriate

Table V. β-adrenergic activity and radioligand binding affinity of Z-MOIM derivatives **10** and **11.**



10, 11

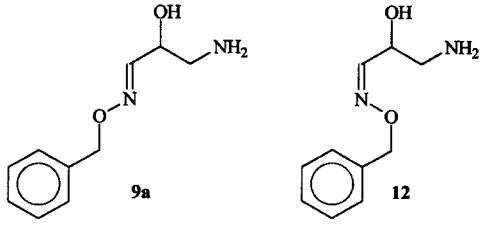
Compound	R	R_1	β-adrenergic binding affinity K_i(nM)[a]		β-adrenergic activity pIC_{50}[a]	
			Rat brain membranes (β_1)	Bovine lung membranes (β_2)	Isolated guinea-pig atria (β_1)	Isolated guinea-pig tracheal strips (β_2)
10a	H	*i*-Pr	3 800	680		
10b	*o*-MeO	*i*-Pr	11 000	1 700		
10c	*m*-MeO	*i*-Pr	3 000	1 500		
10d	*p*-MeO	*i*-Pr	9 200	460		
10e	*o*-Cl	*i*-Pr	2 100	480		
10f	*m*-Cl	*i*-Pr	3 100	940		
10g	*p*-Cl	*i*-Pr	4 900	310		
11a	H	*t*-Bu	690	120	4.39	6.51
11b	*o*-MeO	*t*-Bu	1 900	490		
11c	*m*-MeO	*t*-Bu	220	490	4.78	6.04
11d	*p*-MeO	*t*-Bu	5 800	130		
11e	*o*-Cl	*t*-Bu	1 200	77	4.80	6.72
11f	*m*-Cl	*t*-Bu	760	140	4.52	6.03
11g	*p*-Cl	*t*-Bu	2 400	210	4.31	6.53

[a] In order to simplify the table, the confidence limits and the standard errors of the biopharmacological data have been omitted.

receptor sites, or by hypothesizing the presence of two different binding sites for the aryl groups of the two types (*Z* or *E*) of MOIM compounds [31].

4. Conclusions

The above-described studies indicate that the MOIMM, independently of its configuration around the oximic double bond, may be considered as an effective tool for the study of non-aromatic β-blockers and therefore for the development of novel β-blocking agents. The MOIMM might also prove to be useful in classes of non-adrenergic drugs, in which the presence of an Ar group would appear to be important for the activity.



9a

12

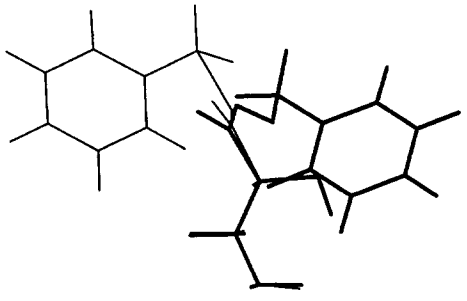


Figure 6. Compounds **9a** (thinner line) and **12** (thicker line) in their preferred conformations.

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