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Omeprazole and analogue compounds: a case study

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INTRODUCTION

Omeprazole (Fig. 1, 1) is a substituted benzimidazole, which suppresses gastric-acid secretion by means of H^+, K^+-ATPase inhibition. It is an optically active drug with the sulfur of the sulfoxide being the chiral centre. This pro-drug can be easily converted into its respective sulfonamide (Fig. 1, 4) at low pH. The sulfoxide group possesses a few degrees of rotational freedom [1]. In this work, omeprazole and analogue compounds with basic structure shown in Figure 2 and Table 1 have been studied against *Heliobacter pylori* action [2]. Besides, complementary studies [conformational aspects, racemization barrier and decomposition reaction (Fig. 1)] about omeprazole behaviour were performed.

METHODS

Initially, conformational analysis was performed for all compounds. Quantum chemistry coupled to the chemometric method PCA [3] was used to find all minimum energy structures. Conformational analysis and calculation of racemizaton barrier were carried out by the PM3 semi-empirical method (Gaussian 98). The descriptors and the energy of the decomposition reaction were calculated by HF/6-31G (Spartan Pro).

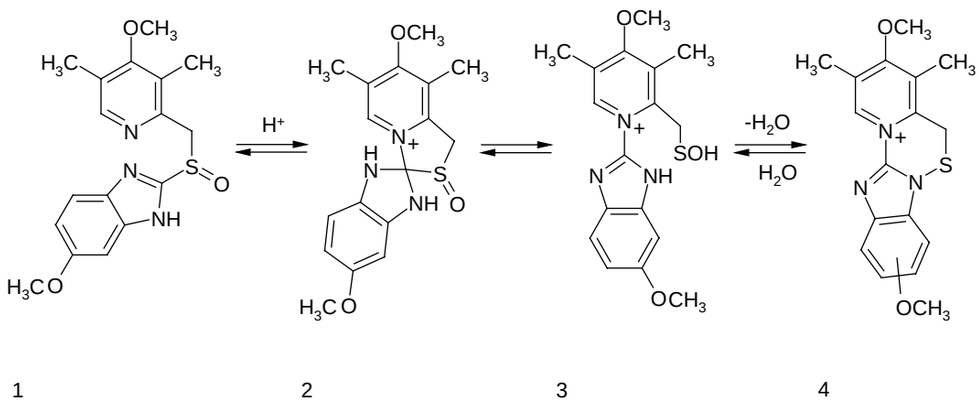

Fig. 1. Omeprazole decomposition reaction.

Table 1. Substitutents regarding to basic structure of Figure 2

Compound	R1	R2	R3	R4	R5	R6
1	H	OCH_3	CH_3	H	CH_2OH	H
2	H	OCH_2CH_3	CH_3	H	H	H
3	H	OCH_3	CH_3	H	C	H
4	H	OCH_3	H	F	H	H
5	H	OCH_3	H	F	H	F
6	H	CH_2–◁	OCH_3	H	F	H
7	H	$OCH(CH_3)_2$	CH_3	H	OCH_3	H
8	H	OCH_3	CH_3	H	FMR*	FMR*
Lansoprazole	H	OCH_2CF_3	CH_3	H	H	H
Omeprazole	CH_3	OCH_3	CH_3	H	OCH_3	H

*Five membered ring.

RESULTS

Several minimum energy conformations were obtained for each compound. In some cases, optical isomers were obtained [3]. Because the electronic properties are sensitive to the structural variation, three criteria were suggested to select one of the structures in different groups, in order to eliminate the scattering of properties: 1. Compounds selected according to the heat of formation (Model 1); 2. Compounds selected according to the electronic energy calculated by HF/6-31G (Model 2); 3. Compounds selected according to their structural similarity (Model 3). These data sets were used to build QSAR models for modelling the biological activity (the percent of control [4]) using PLS regression method. Five descriptors were selected: LUMO, electronegativity, Z coordinate of dipole moment, and two experimental ones, pKapy (contribution of the substituents on pyridine ring to the p*Ka* value) and the half-life time ($t_{1/2}$) corresponding to the decomposition reaction. Inclusion of theoretical variables in our QSAR models [5] improves the results with respect to those from literature [4]. Finally, the energies involved in racemization and decomposition processes were investigated. A dihedral angle around S-O bond was varied for obtaining the pyramidal inversion. Transition state and frequency calculations were performed for the structures corresponding to the maximum energy on each rotation plot. The energy difference between the transition and fundamental states was calculated, giving the racemization barriers. The average racemization barrier for all minimum energy structures (43.56 kcal mol^{-1}) can be related to the velocity constant relative to the racemization process using Eyring's equa-tion. The enormous half-life time at 100ºC (9.04×10^4 years) indicates that the process can-not be observed in human scale of time. On the other hand, the difference of free energy change [$\Delta(\Delta G)$ = -266.78 kcal mol^{-1}] for the decomposition reaction (Fig. 1) shows that the process is favourable to the sulfonamide formation.

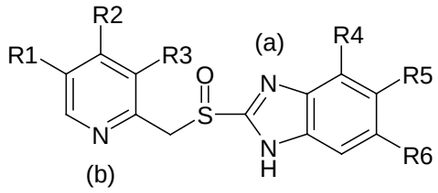

Fig. 2. Omeprazole and analogues.

CONCLUSIONS

The best prediction of all the activity levels (active, intermediate and non-active) was achieved by Model 2, with error smaller than or equal to 10%. The highly negative $\Delta(\Delta G)$ obtained for the decomposition reaction shows that this process is extremely exothermic. Thus, this result explains why omeprazole decomposes and does not racemize.

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Multivariate analysis of theoretical and experimental descriptors for sets of antibacterial nitrofuran derivatives

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INTRODUCTION

Recently, we have reported [1] QSAR analysis of three sets of synthesized 5-nitrofuran derivatives: nine 5-R-substituted Z-2-(5-nitrofuran-2-ylmethylene)-3-(2*H*)-benzofuranones, setI, and their corresponding 2-hydroxyphenyl and 2-acetoxyphenyl analogues; sets II and III (see Fig. 1). For the three sets, QSAR regressions (for example as described by eq. 1) suggest the same structural features describe the activities for both bacteria (*S. aureus*, ATCC-25923 and *C. crescentus*, NA 1000) and that although electronic substituent effects are important to inhibitory growth activity they do not explain the lower activities (one logarithm unit) observed in sets II and III, when compared with those of set I, whose compounds have a benzofuran ring. The role of this moiety on activity has been evaluated by an indicator variable, I_{abs}, that assumes the values of 0 (zero) for compounds

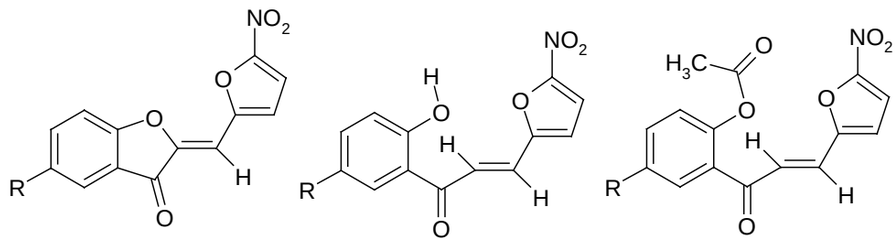

Fig. 1. Structures of sets I, II and III compounds.