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QSAR Study of Biphenyl Sulfonamide Type MMP-9 Inhibitors Using Ab Initio MO Calculation

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1. Introduction

Matrix metalloproteinases (MMPs) comprise a large family of zinc-dependent calcium-containing endopeptidases, which are responsible for tissue remodeling and degradation of the extra-cellular matrix [1]. MMP−9 is particularly involved in inflammatory processes, bone remodeling, wound healing and pathological processes such as rheumatoid arthritis, atherosclerosis, tumour growth, and metastasis. Hansch *et al* [2] performed a classical QSAR analysis for a series of biphenyl sulfonamide type MMP−9 inhibitors, showing the significance of the Hammett σ constant. Based on a quantum mechanical approach, we discuss electronic factors that govern the variations in the change of binding free energy associated with the complex formation.

2. Methods

2-1. Compound Set

Compound set selected in this study, thirteen biphenyl sulfonamide derivatives, is the same one with that for which Hansch *et al* formulated the classical QSAR equation.

$$\log (1/IC_{50}) = 1.33\, MR_{X\text{-}4} - 1.15\, \sigma + 4.34$$
$$n = 12,\ r = 0.957,\ s = 0.166,\ F = 49.1 \qquad (1)$$

where $MR_{X\text{-}4}$ is the molar refractivity of X-substituents at the *para* position (see Figure 1).

2-2. Simplified Model of MMP−9−Biphenyl Sulfonamide Complexes

The initial geometry of MMP−9−biphenyl sulfonamide complexes was constructed on the basis of the X-ray crystallographic coordinates (PDB code: 1GKC). As shown in Figure 1, amino acid residues and zinc ion which comprise the binding site of MMP-9, and biphenyl sulfonamide were extracted from the whole complex structure ("simplified model"). Then geometry optimization was performed on each model using *ab initio* MO calculations at the HF/3−21G* level.

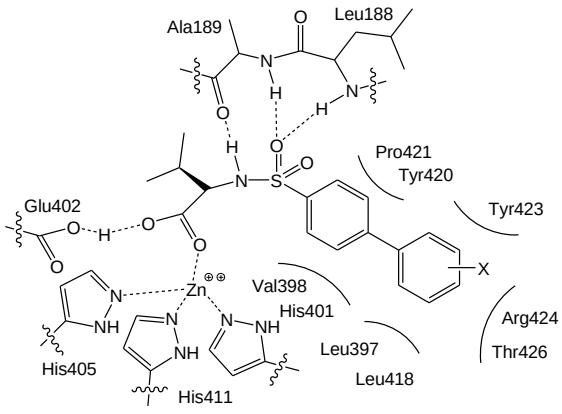

Figure 1. Schematic picture of interaction between MMP-9 and its inhibitors.

2-3. QSAR Descriptors

The structure-dependent electronic descriptors were defined from the optimized complex structures: E_{HOMO} and Δq(residue *i*) (the difference of total atomic charge inside the *i*-th amino acid residue between those in complex and in free states) were calculated with HF/6−31G(d)//HF/3−21G*.

3. Results and Discussion

We introduced E_{HOMO} instead of σ in the right hand side of Eq. 1, and obtained Eq. 2.

$$\log (1/IC_{50}) = 1.32\ MR_{X\text{-}4} + 121.62\ E_{HOMO} + 28.26$$
$$n = 12,\ r = 0.956,\ s = 0.169,\ F = 48.0 \qquad (2)$$

As shown in Figure 1, Leu188 and Ala189 are in close contact with the sulfonamide group in biphenyl sulfonamides, and change of the total atomic charge inside these two residues are two of the most largest ones in the model. As can be seen from Eq. 3, σ is nicely correlated with the change of charge in Leu188 and Ala188.

$$\sigma = -395.2\ [\Delta q(\text{Leu188}) + \Delta q(\text{Ala189})] - 10.38$$
$$n = 12,\ r = 0.979,\ s = 0.0676,\ F = 237 \qquad (3)$$

As shown in Eq. 4, the inhibitory potency is expressed with Δq(Leu188) + Δq(Ala189) and $MR_{X\text{-}4}$. Eq. 4 reflects the binding mechanism more directly than Eq. 1.

$$\log (1/IC_{50}) = 1.19\ MR_{X\text{-}4} + 13.34\ [\Delta q(\text{Leu188}) + \Delta q(\text{Ala189})] + 16.69$$
$$n = 12,\ r = 0.959,\ s = 0.163,\ F = 51.9 \qquad (4)$$

Eqs. 2 and 4 clearly suggest the amount of electron transfer from biphenyl sulfonamides to Leu199 and Ala189 in MMP−9 through the hydrogen-bonding interaction is represented effectively by the Hammett σ constant in the current case.

The results here could provide some suggestions for problems regarding selectivity of MMP−9 inhibitors against other types of MMPs. We will present results for the full complex structures as well as the simplified model described here.

References

[1] M. Egebled, Z. Werb, *Nat. Rev. Cancer,* 2, 161, 2002.
[2] R. P. Verma,C. Hansch, *Bioorg. Med. Chem.,* 15, 2223, 2007.