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QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS OF BENZOYLIMINOTHIADIAZOLINE DERIVATIVES AS ANGIOTENSIN II RECEPTOR ANTAGONISTS

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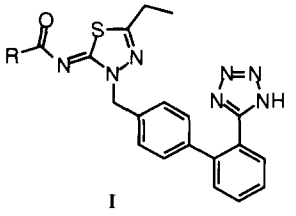
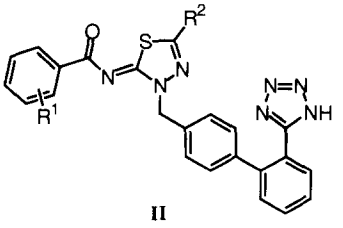
Abstract: Syntheses and biological activities of benzoyliminothiadiazoline derivatives which have potential affinities for angiotensin II receptor are described. The contributions of substituent (R^1) on the benzene ring in benzoyl moiety and 5-position substituent (R^2) on the 1,3,4-thiadiazoline ring were quantitatively investigated.

Introduction. In recent years, there has been a greatly increasing interest in nonpeptide angiotensin II (AII) receptor antagonists which have been promising for a novel class of antihypertensive drug.[1] In our previous communication, we reported syntheses and biological profiles of several acyliminothiadiazolines **I** which had potent AII receptor antagonism *in vitro* and *in vivo*.[2] In the course of research on these derivatives, we investigated the structure-activity relationships of the acyl moieties and 5-position substituents on the 1,3,4-thiadiazoline ring to obtain insight into the biological modes of action and to design analogs with more bioactive profile. The quantitative structure-activity relationship (QSAR) studies on benzoyliminothiadiazoline derivatives **II** using the Hansch-Fujita method[3] led us to obtain important information about the structure requirement for good binding to the AII receptor. Herein, we describe syntheses, biological results, and QSAR studies of the benzoyliminothiadiazoline derivatives.

Syntheses. The benzoyliminothiadiazoline derivatives **II** were readily synthesized by two synthetic procedures.[4] One of them was reported previously[2] and various compounds **7-30** were systematically synthesized (Scheme 1). The other route is described as below (Scheme 2). Namely, 2-trifluoroacetamido-1,3,4-thiadiazoles **3** were regioselectively biphenylmethylated with 5-[4'-(bromomethyl)biphenyl-2-yl]-2-(triphenylmethyl)-2*H*-tetrazole **4**[5] to afford 2-trifluoroacetylimino-1,3,4-thiadiazolines **5** and then their detrifluoroacetylation with aq. NaOH furnished iminothiadiazolines **6**.[6] After treatment of **6** with acylchlorides or acid anhydrides, their triphenylmethyl group was removed with 10% HCl-dioxane to give the corresponding benzoyliminothiadiazoline derivatives **31-36**.

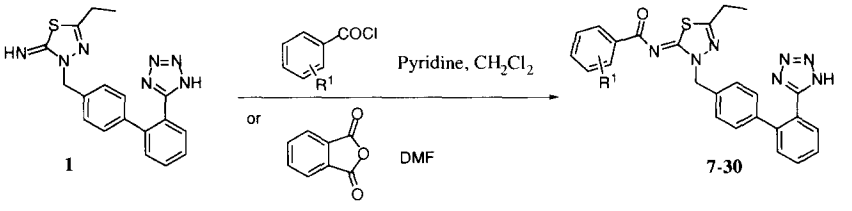


I

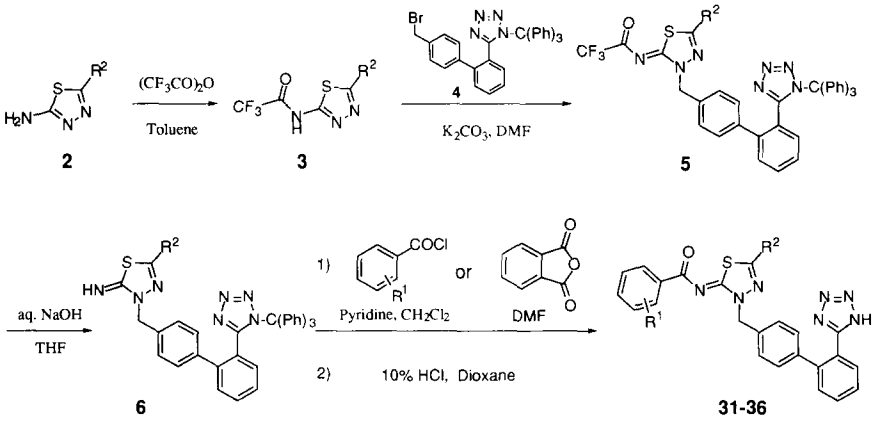


II

Scheme 1. Synthesis of benzoyliminothiadiazoline derivatives **7-30**.



Scheme 2. Synthesis of benzoyliminothiadiazoline derivatives **31-36**.



Biological testing. The *in vitro* binding affinities of compounds were evaluated for their ability to competitively block the specific binding of [^{125}I] AII from the receptors in rat liver membrane preparations, which correspond to the AT_1 receptor.[7,8] The results were expressed as pKi values (Table 1).

QSAR studies. It was clearly shown that the derivatives having *ortho* substituents on the benzoyl benzene ring exhibited higher binding affinities than those having *meta* or *para* substituents (Table 1). Thus, the binding affinity was thought to be mainly dependent on the conformation of the benzoyl moiety. In fact, the correlation eq. 1 using only STERIMOL parameter L_{1o} which indicated the steric effect of *ortho* substituents represented a moderate correlation.

$$pKi = 5.173\ (\pm 0.654) + 0.873\ (\pm 0.223)\ L_{1o} \quad (n = 30,\ r^2 = 0.679,\ s = 0.483) \qquad \textbf{(eq. 1)}$$

In this and the following equations, *n*, *r*, *s* and *F* are the number of compounds, the correlation coefficient, the standard deviation and the value of the F-ratio of variance between observed and calculated data, respectively. Analysis by addition of Hansch-Fujita substituent constants π_1, Hammett constants σ_1, and STERIMOL parameter L_2 to eq. 1 resulted in eq. 2 with a good correlation.

$$pKi = -0.161 + 0.954\ L_{1o} - 0.589\ \pi_1 - 0.329\ (L_2)^2 + 2.677\ L_2 - 0.484\ \sigma_1 \qquad \textbf{(eq. 2)}$$
$$(\pm 3.409)\ (\pm 0.134)\ (\pm 0.223)\ (\pm 0.158) \quad (\pm 1.441)\ (\pm 0.374)$$
$$(n = 30,\ r^2 = 0.914,\ s = 0.270,\ F(5/24) = 51.18)$$

Next, in order to estimate the electronic effect of *ortho* substituents more exactly, introduction of their Swain-Lupton field effect parameters F_{1o} to eq. 2 was investigated. The result of analysis gave eq. 3 with a better correlation.

$$pKi = 0.287 + 0.709\ L_{1o} - 0.608\ \pi_1 - 0.337\ (L_2)^2 + 2.731\ L_2 - 0.642\sigma_1 + 1.145\ F_{1o} \qquad \textbf{(eq. 3)}$$

(± 3.040) (± 0.218) (± 0.198) (± 0.140) (± 1.278) (± 0.351) (± 0.854)

($n = 30$, $r^2 = 0.936$, $s = 0.239$, $F(6/23) = 55.77$)

Although eq. 3 represented a better correlation, however, it would be noted that the contributions of σ_1 and F_{1o} were compensated each other. Therefore, we attempted analyses to use Swain-Lupton F_1 and R_1 (resonance effect) parameters instead of σ_1. As the results of analyses, it was found that there were contributions of neither F_{1o} nor R_1 parameter to the binding affinity, and that the following eq. 4 using F_{1m} and F_{1p} parameters represented the best correlation. We have finally proposed this eq. 4 as the QSAR of benzoyliminothiadiazoline derivatives (Table 1).

$$pKi = 0.395 + 0.692\ L_{1o} - 0.344\ (L_2)^2 + 2.813\ L_2 - 0.603\ \pi_1 - 1.295\ F_{1m} - 1.332\ F_{1p} \quad \textbf{(eq. 4)}$$

(± 2.563) (± 0.137) (± 0.118) (± 1.077) (± 0.166) (± 0.543) (± 0.543)

($n = 30$, $r^2 = 0.955$, $s = 0.201$, $F(6/23) = 79.87$, $L_2opt = 4.089$)

Table 1 Structures, binding affinities and parameters values for benzoyliminothiadiazolines **7-36**

No.	R^1	R^2	L_{1o}[a]	L_2[a]	π_1[a]	F_{1m}[a]	F_{1p}[a]	pKi[b] (measured)	pKi[c] (calcd.)
7	H	Et	2.06	4.11	0.00	0.00	0.00	7.444	7.562
8	*o*-F	Et	2.65	4.11	0.14	0.00	0.00	8.139	7.886
9	*m*-F	Et	2.06	4.11	0.14	0.43	0.00	6.873	6.921
10	*p*-F	Et	2.06	4.11	0.14	0.00	0.43	6.991	6.905
11	*o*-Cl	Et	3.52	4.11	0.71	0.00	0.00	8.469	8.145
12	*m*-Cl	Et	2.06	4.11	0.71	0.41	0.00	6.721	6.603
13	*p*-Cl	Et	2.06	4.11	0.71	0.00	0.41	6.482	6.588
14	*o*-Br	Et	3.83	4.11	0.86	0.00	0.00	8.455	8.269
15	*m*-Br	Et	2.06	4.11	0.86	0.44	0.00	6.523	6.474
16	*p*-Br	Et	2.06	4.11	0.86	0.00	0.44	6.495	6.458
17	*o*-NO_2	Et	3.44	4.11	-0.28	0.00	0.00	8.491	8.686
18	*m*-NO_2	Et	2.06	4.11	-0.28	0.67	0.00	6.854	6.863
19	*p*-NO_2	Et	2.06	4.11	-0.28	0.00	0.67	6.854	6.838
20	*o*-OMe	Et	3.98	4.11	-0.02	0.00	0.00	8.602	8.903
21	*m*-OMe	Et	2.06	4.11	-0.02	0.26	0.00	7.312	7.238
22	*p*-OMe	Et	2.06	4.11	-0.02	0.00	0.26	7.553	7.228
23	*o*-Me	Et	3.00	4.11	0.56	0.00	0.00	7.445	7.875
24	*m*-Me	Et	2.06	4.11	0.56	-0.04	0.00	7.102	7.276
25	*p*-Me	Et	2.06	4.11	0.56	0.00	-0.04	7.319	7.278
26	*o*-CF_3	Et	3.30	4.11	0.88	0.00	0.00	8.222	7.890
27	*m*-CF_3	Et	2.06	4.11	0.88	0.38	0.00	6.354	6.540
28	*p*-CF_3	Et	2.06	4.11	0.88	0.00	0.38	6.254	6.526
29	*o*-I	Et	4.23	4.11	1.12	0.00	0.00	8.413	8.389
30	*o*-COOH	Et	3.91	4.11	-0.32	0.00	0.00	9.208	9.035
31	*o*-Cl	Me	3.52	3.00	0.71	0.00	0.00	7.745	7.741
32	*o*-Cl	Pr	3.52	5.05	0.71	0.00	0.00	7.658	7.823
33	*o*-Cl	cy-Pr	3.52	4.14	0.71	0.00	0.00	7.824	8.144
34	*o*-Cl	Bu	3.52	6.17	0.71	0.00	0.00	6.699	6.664
35	*o*-COOH	Me	3.91	3.00	-0.32	0.00	0.00	8.569	8.632
36	*o*-COOH	Pr	3.91	5.05	-0.32	0.00	0.00	8.699	8.713

[a]All parameters described in ref.9 are used. [b]Binding assay is performed by using rat liver membrane preparations. See ref. 2 in details. [c]The values are calculated by eq. 4.

Conclusion. The QSAR studies led us to the following structure requirements for good binding to the AII receptor.

(1) The R^1 substituent exists in the *ortho* position and is bulky. The decisive importance of the *ortho* effect is very interesting to consider the interaction between this series of ligand and the AII receptor protein.

(2) The R^1 substituent has low hydrophobicity such as carboxy group.

(3) The substituent R^2 is an ethyl group ($L_{Et} = 4.11$), because the optimizing value of L_2 is 4.089.

These features are comprehensively summarized in Fig. 1. Here, it should be noticed that the analyses using F and R parameters show that there is no contribution of resonance effect of the substituent R^1. Namely, the resonance effect of benzoylimino moiety is not important for these derivatives to well bind to the AII receptor suggesting that the aromaticity of acyl group may not be necessary and the benzoyl group can be replaced by other nonaromatic cyclic acyl systems. In addition, in the case of nonaromatic cyclic acyl groups, β-substituted acyl derivatives would be expected to have high activity owing to the steric effect as well as *ortho*-substituted benzoyl derivatives.

In conclusion, application of the QSAR studies on benzoyliminothiadiazoline derivatives to further drug design led us to find the highly active candidate compound KRH-594[2] which fully met the structural requirements as described above.

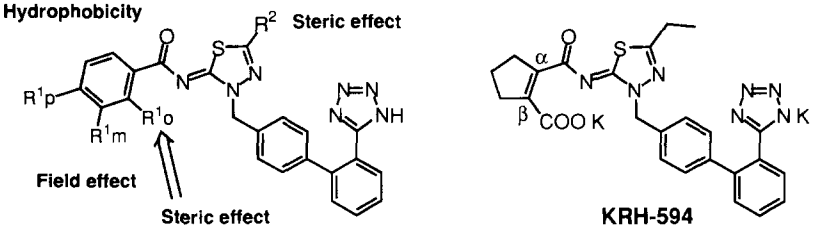


Figure 1

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(4) All test compounds prepared for this study gave the satisfactory ^{1}H-NMR, IR, mass spectra and elemental analysis data, in full agreement with their assigned structures.

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