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The Crystal Structure of KR-21042, An Analgesic Capsaicinoid

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The crystal structure of KR-21042, N-(3-Phenylpropyl)-4-hydroxy-3-methoxyphenylacetamide, was determined by single crystal X-ray diffraction analysis. The compound was recrystallized from a mixture of ethylacetate and n-hexane in monoclinic, space group $P2_1/c$, with a = 16.622(1), b = 6.215(1), c = 15.802(1) Å, β= 104.97(1), and Z = 4. The calculated density is 1.261 g/cm^3. The structure was solved by the direct method and refined by full matrix least-squares procedure to the final R value of 0.068 for 2332 observed reflections.

Key words : KR-21042, Analgesic capsaicinoid, Crystal structure, X-ray diffraction

INTRODUCTION

Since the finding of the anti-nociceptive action of capsaicin (Suzuki & Iwai, 1984), many researchers have been trying to develop a potent analgesic capsaicinoid with different mechanism of action from the usual analgesics such as narcotic or NSAIDs (James *et al.*, 2000). Although the undesirable side-effects of the natural capsaicin prevent its direct utilization to medicinal preparations for human being, the strong analgesic effect of the capsaicinoids, natural as well as synthetic, has been being studied in detail (Dray, 1999).

We have synthesized and studied lots of the structural analogues of capsaicin (Park *et al.*, 1991a; Park *et al.*, 1991b; Park *et al.*, 1993). KR-21042 (Fig. 1) is an analog of analgesic capsaicinoid. The crystallographic study on the title compound was undertaken to provide the 3D information concerning the functional groups that were supposed to be important for the anagesic activity, and to establish the reliable structure-activity relationship necessary for the understanding of the mode of action and/or the new drug designing of the non-narcotic analgesics.

MATERIALS AND METHODS

Colorless prismatic crystals were grown by the slow evaporation from a mixture of ethylacetate and n-hexane at room temperature. A crystal of suitable size was mounted on an Enraf-Nonius CAD4 diffractometer. Lattice parameters were obtained by 25 angular positions of randomly-obtained diffraction spots, and intensity data within range of $\theta \leq 65$ (CuK_α) were collected precisely. The significant descriptors explaining the experimental procedure in detail are summarized in Table I.

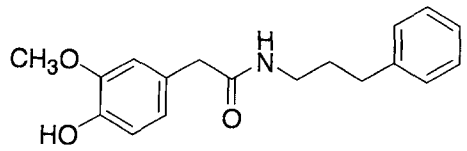

Fig. 1. Structure of KR-21042

The structure was solved by the direct method with *SIR* 92 incorporated in *maXus*1.0 software package (Mackay *et al.*, 1997), and the structure was refined by full matrix least squares procedure to the R value of 0.068. All the calculations were performed on a SGI PowerIndigo II workstation. The atomic scattering factors were taken from " *International Tables for Crystallography*".

RESULTS AND DISCUSSION

The final atomic coordinates and equivalent isotropic temperature factors are listed in Table II. The list of structure factors, anisotropic displacement parameters, hydrogen atomic coordinates and complete geometry are available

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Table I. Descriptors for the experimental procedure

CRYSTAL DATA	
$C_{18}H_{21}NO_3$	D_x = 1.261 g/cm^3
M_r = 299.37	CuK radiation
Monoclinic, $P2_1/c$	Cell parameters from 25
a = 16.622(1) Å	reflections
b = 6.215(1) Å	θ= 12.6 - 34.1°
c = 15.802(1) Å	= 0.69 mm^{-1}
= 104.97(1)°	T = 293°K
V = 1576.9(4) Å^3	Prism, Colorless
Z = 4	0.20 × 0.30 × 0.25 mm
DATA COLLECTION	
Enraf-Nonius CAD-4	R_{int} = 0.024
diffractometer	θ_{max} = 65.0
ω/2θ scans	h = 0→19
Absorption correction:	k = 0→6
none	l = -18→17
3096 measured reflections	3 standard reflections
2588 independent reflections	frequency: 60 min
2332 observed reflections	intensity decay: none
[$I > 3\sigma(I)$]	
REFINEMENT	
Refinement on F	$w = 1/[\sigma^2(F_o)+0.03F_o^2]$
R = 0.068	$(\Delta/\sigma)_{max}$ = 0.001
wR = 0.106	$\Delta\rho_{max}$ = 0.25 e/Å^3
2332 reflections	$\Delta\rho_{min}$ = -0.43 e/Å^3
226 parameters	Extinction correction: none
H-atom treated by a mixture of independent and constrained refinement	

Table II. Fractional atomic coordinates and equivalent isotropic displacement parameters(Å^2) with their estimated standard deviations in parentheses

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i a_j \mathbf{a}_i \cdot \mathbf{a}_j$

Atom	x	y	z	U_{eq}
O(1)	0.8283(1)	0.1470(2)	0.6563(1)	0.0542(8)
O(2)	0.9176(1)	-0.2092(2)	0.6406(1)	0.0442(6)
O(3)	0.8211(1)	-0.3713(2)	0.2840(1)	0.0449(6)
N(4)	0.7685(1)	-0.0725(3)	0.2077(1)	0.0376(7)
C(1)	0.8743(1)	0.0103(3)	0.4154(1)	0.0357(8)
C(2)	0.8314(1)	0.1938(3)	0.4278(1)	0.0419(9)
C(3)	0.8151(1)	0.2339(3)	0.5081(1)	0.0439(9)
C(4)	0.8432(1)	0.0952(3)	0.5780(1)	0.0376(9)
C(5)	0.8886(1)	-0.0876(3)	0.5666(1)	0.0341(8)
C(6)	0.9028(1)	-0.1308(3)	0.4858(1)	0.0355(8)
C(7)	0.9670(1)	-0.3955(3)	0.6339(1)	0.048(1)
C(8)	0.8914(1)	-0.0364(3)	0.3275(1)	0.0415(9)
C(9)	0.8236(1)	-0.1762(3)	0.2708(1)	0.0352(8)
C(10)	0.7000(1)	-0.1839(3)	0.1460(1)	0.051(1)
C(11)	0.6261(1)	-0.0369(3)	0.1115(1)	0.058(1)
C(12)	0.5906(1)	0.0533(5)	0.1812(1)	0.085(2)
C(13)	0.5055(1)	0.1548(3)	0.1478(1)	0.048(1)
C(14)	0.4942(1)	0.3565(4)	0.1099(1)	0.067(1)
C(15)	0.4148(2)	0.4430(4)	0.0808(1)	0.087(2)
C(16)	0.3481(2)	0.3284(6)	0.0893(2)	0.093(2)
C(17)	0.3579(1)	0.1311(6)	0.1257(2)	0.087(2)
C(18)	0.4360(1)	0.0436(3)	0.1548(1)	0.064(1)
H(O1)	0.832(1)	0.066(3)	0.688(1)	0.012(6)
H(N4)	0.780(1)	0.070(3)	0.201(1)	0.024(5)

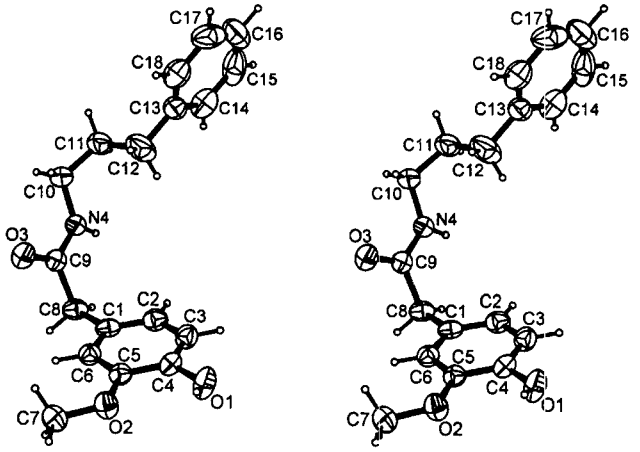

Fig. 2. Stereoscopic view of the molecule drawn by *ORTEP*II (Johnson, 1976) with the atomic numbering scheme. The displacement ellipsoids are drawn at the 50% probability level. H atoms are drawn as small circles of arbitrary radii

upon request.

The stereoscopic view of the molecule drawn by *ORTEP*II (Johnson, 1976) together with the atomic numbering scheme is shown in Fig. 2. All of the molecular dimensions are in the reasonable range, and some selected geometric parameters are collected in Table III.

Capsaicinoid is composed of three major functional moieties, a vanilloid, an amide, and a hydrophobic side chain or its equivalent. In the crystal, the vanilloid group and the plane of the amide of the title compound shows somewhat perpendicular conformation with dihedral angle of 69(4)°, and the amide and hydrophobic phenyl ring is somewhat planar with dihedral angle of 138(4)° as shown in Fig. 2. However the overall conformation of the compound in crystal state is slightly different to other capsaicinoids having similar structure and bioactivity, such as KR-25003 (Park *et al.* 1995), capsaicin (Park *et al.*, 2002a), KR-25018 (Park *et al.*, 2002b). That suggests there may be some interaction energy and conformational changes between the capsaicinoid and its receptor during their interaction in biosystem.

The methoxy group of the vanilloid is important for the strong bioactivity, and it is nearly coplanar to the phenyl

Table III. Selected bond lengths(Å) and angles(°)

C(4)--O(1)	1.362(2)	C(5)--O(2)	1.373(2)
C(9)--O(3)	1.232(3)	C(8)--C(9)	1.515(3)
C(9)--N(4)	1.334(2)	C(10)--N(4)	1.467(3)
H(O1)--O(1)	0.70(2)	H(N4)--N(4)	0.92(2)
C(5)-O(2)-C(7)	117.6(2)	C(9)-C(8)-N(4)	115.2(2)
C(8)-C(9)-O(3)	121.0(2)	C(4)-N(4)-C(10)	122.3(2)
C(10)-N(4)-H(N4)	121(1)	C(4)-O(1)-H(O1)	118(2)

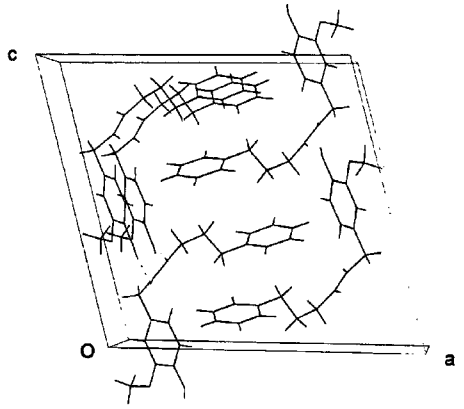

Fig. 3. Crystal packing for KR-21042. The broken lines indicate intermolecular hydrogen bonds

ring (torsion angle of C(7)-O(2)-C(5)-C(6) 0.3°), presumably for the effective overlap of the unbonded electron lobes of the oxygen atom with the π cloud system of the ring. The bond length of C(5)-O(2) is significantly shorter than that of O(2)-C(7). Such tendencies were also observed in the structures with methoxyaryl moiety(Kim *et al.*, 1990; Kim *et al.*, 1993).

The molecules are connected by intermolecular hydrogen bonds between the phenolic OH(O(1)) of vanilloid and the amide oxygen(O(3)) of neighboring molecule(x,-y-1/2,z+1/2) with bond length is 2.674(2)Å. The O(1) atom participates in another weak hydrogen bond connection to the N(4)-H(N4) as an acceptor with bond length of 3.010(2)Å as shown in Fig. 3. The other interatomic distances are in the range of normal *van der Waals'* contacts.

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REFERENCES

Altomare, A., Cascarano, G., Giacovazzo, C. & Gualiardi, A. (1993) Completion and refinement of crystal structures with *SIR92*, *J. Appl. Cryst.* 26, 343-350.

Choi, J. -K., Hong, M. -S., Park, N. -S., Lee, K.-S., Choi, J., Kim, H. -J., and Ha, D. -C. Synthesis of capsaicinoids: 3-Hydroxy-4(2-aminoethoxy)phenylacetamides, *Kor. J. Med. Chem.*, 3, 25-32. (1993).

Dray, A., *Novel Aspects Pain Manage*, Sawynok, J., and Cowan, A. Ed., Willey-Liss, New York, pp. 117-134 (1999).

James, Iain F., Garcia, R., Liapi, A., and Wood, J.N., *Molecualr Basis of Pain Induction*, Wood J. N. Ed. Wiley-Liss, New York, pp. 175-191 (2000).

Johnson, C. K., *ORTEPII: A FORTRAN thermal-ellipsoid plot program for crystal structure illustrations (ORNL-5138)*, Oak Ridge National Laboratory, Tennessee, 1976.

Kim, Y. B., Kim, J. A., and Park, I. Y., The crystal structure of acemetacin monohydrate ($C_{21}H_{18}NO_6ClH_2O$), a non-steroidal antiinflammatory agent. *Arch. Pharm. Res.*, **16**(2), 134-139 (1993).

Kim, Y. B., Park, I. Y., and Lah, W. R., The crystal structure of naproxen sodium, ($C_{14}H_{13}O_3Na$), a non-steroidal antiinflammatory agent, *Arch. Pharm. Res.*, 13(2), 166-173 (1990).

Mackay, S., Edwards, C., Henderson, A., Gilmore, C., Stewart, N., Shankland, K. & Donald, A. *maXus* 1.1, A computer program for the solution and refinement of crystal structures from X-ray diffraction data, University of Glasgow, Scotland, Nonius, The Netherlands, and MacScience, Japan. (1997).

Park, N. -S., Ha, D. -C., Choi, J. -K., Kim, H. -S., Lim, H. -J., and Lee, B.-Y., N-Aralkylated 4-(2-aminoethoxy)phenylacetamide derivatives as potent analgesic and antiinflammatory agents, *Kor. J. Med. Chem.*, 1, 36-43. (1991a).

Park, N. -S., Ha, D. -C., Kim, H. -S., and Choi, J.-K., Phenylacetamide derivatives as analgesic agents, *Kor. J. Med. Chem.*, 1, 2-7. (1991b).

Park, N.-S., Kim, Y.B., Jeong, E.J., Chung, U.T., and Park, I.Y. Crystal structure of capsaicin, in preparation. (2002a).

Park, N.-S., Kim, Y.B., Jeong, E.J., Chung, U.T., and Park, I.Y. Crystal structure of KR-25018, in preparation. (2002b).

Park, N. -S., Lee, J. -C., Park, I. Y., and Kim, Y.B.; KR-25003, A potent analgesic capsaicinoid, *Acta Crystallogr.*, C51, 927-929 (1995).

Suzuki, T. and Iwai, K. *The alkaloids.* Vol. XXIII., edited by A. Brossi, Academic Press, Orlando, pp. 227-299, USA (1984).