Journal of Chemical Crystallography, Vol. 34, No. 9, September 2004 (© 2004)

Synthesis and crystal structure of 2-trifluoromethyl-1-[(2′-1*H*-tetrazole-5-yl-biphenyl-4-yl) methyl]benzimidazole

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Received June 22, 2004

The crystal structure of 2-trifluoromethyl-1-[(2′-1H-tetrazle-5-yl-biphenyl-4-yl) methyl]-benzimidazole and a methylene chloride have been determined by X-ray crystallography. The compound crystallizes in the monoclinic space group, $P2_1/n$ with cell dimensions $a = 10.931(2)$ Å, $b = 12.31(3)$ Å, $c = 17.901(4)$ Å, $\beta = 102.45(3)^\circ$, $V = 2352.9(8)$ Å^3, $D_{calc} = 1.427$ g/cm^3, $Z = 4$, $\mu = 0.324$ mm^{-1}, and $F(000) = 1032$, and its structure was refined to $R_1 = 0.0663$ and $wR_2 = 0.1668$ for 1910 observed reflections($I > 2\sigma(I)$). Intermolecular hydrogen bonds were identified between the N and H atoms of intermolecular benzimidazole group and tetrazole group.

KEY WORDS: X-ray crystal structure; angiotensin; biphenyltetrazole.

Introduction

Since the discovery by DuPont of orally active nonpeptide angiotensin II antagonist, losartan,[1,2] numerous patents and publications on AII antagonists have appeared over the past few years. Most of them contain a biphenyl-tetrazole moiety or biphenyl carboxylic acid moiety linked to a heterocycle by a methylene group.[3–5] Biphenyl tetrazole moiety may play important roles in pharmaceutical core. In order to find new aspects for the structure-activity relationships of nonpeptide angiotensin II receptor antagonist, we report the synthesis and crystal structure of 2-trifluoromethyl-1-[(2′-1H-tetrazole-5-yl-biphenyl-4-yl)methyl] benzimidazole (**5**).

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Experimental

Melting points were determinated using XT4 microscope melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded on a Nicolet Magna IR 560 spectrophotometer and were run as KBr pellets unless otherwise indicated. ^{1}H-NMR spectra (400 MHz) were measured on an ARX400 instrument. Chemical shifts are reported in δ units relative to internal tetramethylsilane. Mass spectra were recorded on a ZAB-HS mass spectrometer in EI. Elemental analyses were performed on an Elementar Vario EL.

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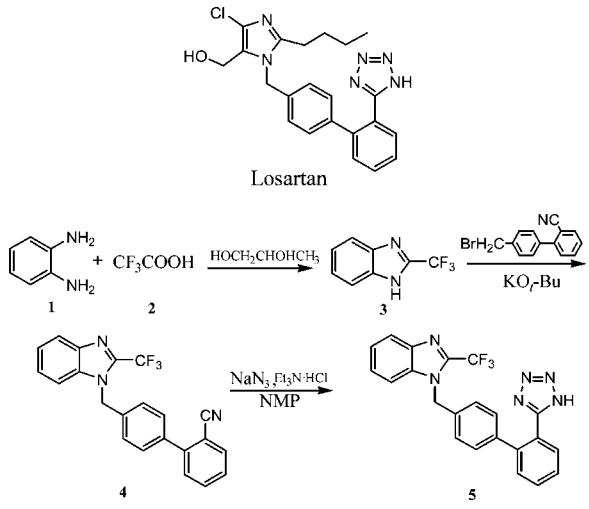

Preparation of 2-trifluoromethyl-1-[(2′-1H-tetrazle-5-yl-biphenyl-4-yl)methyl] benzimi-dazole □**5**□

To *o*-phenylenediamine (10.8 g, 0.10 mol) in propylene glycol (80 mL) was added trifluoroacetic acid (13.68 g, 0.12 mol) and the solution was heated at 70°C for 12 h, and then cooled to room temperature. Ice cold water (50 cm^3) was added to force the precipitation of a white solid, which was collected and dissolved in hot ethanol (50 mL). The solution was filtered over activated carbon and the filtrate was added to ice cold water (100 mL) to give white solid. The filtrate cake was washed by water to furnish white solid 2-(trifluoromethyl)-1H-benzimidazole 14.3 g(yield 77%), m.p. 208–210°C (lit[6]. 209–211°C).

To a solution of 1.0 g (5.37 mmol) of 2-(trifluoromethyl)-1H-benzimidazole in 30 mL of DMF was added potassium *tert*-butylate 0.7 g (6.25 mmol), the mixture was stirred for 30 min at ambient temperature, and 4-(bromomethyl) biphenyl-2′-nitrile 1.60 g (5.88 mmol) was added. After stirring for 12 h the mixture was poured into water (120 mL) and extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and evaporated. The residue was purified by silica gel column chromatography eluting with ethyl acetate/light petroleum (10:90/v:v) to give **4**(1.45 g, 71.5%) as a white solid: m.p. 102–104°C; Anal. Calcd.(%) for $C_{22}H_{14}F_3N_2$: C, 70.02; H, 3.71; N, 11.14. Found(%): C, 70.14; H, 3.85; N, 11.01. IR cm^{-1}: 3060, 2224, 1520, 1275, 1197, 1144, 1093, 764, 748. ^{1}H NMR($CDCl_3$): δ 5.61(s,2H), 7.21–7.99(m, 12H). MS(EI), m/z: 377(96) (M+ = 1), 192(100).

A mixture of 2-trifluoromethyl-1-[(2′-cyano-biphenyl-4-yl)methyl]benzimidazole (0.6 g, 1.59 mmol), sodium azide (0.47 g,7.2 mmol), and Et_3N·HCl (0.7 g, 5 mmol) in 1-methyl-2-pyrrolidinone (15 mL) is stirred at 160°C for 12 h. After cooling, the mixture is diluted with H_2O (50 mL), acidified to pH 3 with 4N HCl, and extracted with EtOAc (3 × 50 mL). The organic layer was washed with H_2O (3 × 50 mL), then the combined extracts were dried ($MgSO_4$) and evaporated and the solid residue was purified by silica gel column chromatography eluting with ethyl acetate/ethanol (80:20/v:v) to give **5**(0.2 g, 30.3%) as a white solid: m.p. 114–116°C; Anal. Calcd.(%) for $C_{22}H_{15}F_3N_6$: C, 62.86; H, 3.57; N, 20.0. Found(%): C, 62.71; H, 3.43; N, 20.16. IR: 3049, 2974, 2820, 2698, 1526, 1477, 1434, 1278, 1187, 1146, 990, 280, 739. ^{1}H NMR (DMSO): δ 5.70 (s, 1H), 5.75(s, 2H), 7.01–7.87 (m, 12H). MS(EI), m/z: 420(M+ = 1).

X-ray analysis

The single crystals were obtained by slow evaporation of a methylene chloride solution of the compound at room temperature. The structure of the crystal was characterized as $C_{22}H_{15}F_3N_6{\cdot}CH_2Cl_2$. A colourless single crystal with dimensions of 0.35 mm × 0.15 mm × 0.10 mm was selected for X-ray diffraction analysis (Table 1). The data were collected on a Rigaku RAXIS RAPID IP diffractometer with a graphite-monochromated Mo$K\alpha$ radiation ($\lambda = 0.71073$ Å) at 93(2) K. A total of 16280 reflections and 4123 independent ones ($R_{\text{int}} = 0.0427$) were collected within the range of $2.33 < \theta < 25^\circ$ by using ω scan technique, of which 1910 observed reflections with $I > 2\sigma(I)$ were used in the structural analysis. The structure was solved by direct methods and refined by full-

Table 1. Crystallographic Data and Structure Refinement

Empirical formula	$C_{23}H_{17}Cl_2F_3N_6$
CCDC deposit no.	CCDC-228076
Formula weight	505.33
Temperature	293(2) K
Measurement device	Rigaku RAXIS RAPID IP
Measurement method	Oscillation
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	$a = 10.931(2)$ Å
	$b = 12.314(3)$ Å
	$c = 17.901(4)$ Å
	$\alpha = 90^\circ$
	$\beta = 102.45(3)^\circ$
	$\gamma = 90^\circ$
Volume	2352.9(8) Å^3
Refls. No. for cell measurement	16280
Z	4
Density (calculated), Mg/m^3	1.427
Absorption coefficient, mm^{-1}	0.324
$F(000)$	1032
Crystal shape/Crystal color	Block/Colorless
Crystal size	0.35 × 0.15 × 0.10 mm
θ range for data collection, deg	2.33–25.00
Limiting indices	$-12 \le h \le 12$, $-14 \le k \le 14$, $-21 \le l \le 20$
Reflections collected	16280
Completeness to $\theta = 25.00$	99.7%
Independent reflections 4123	$[R_{(int)} = 0.0427]$
Reflections with $I > 2\sigma(I)$	1910
Data/restraints/parameters	4123/0/312
Max. and min. transmission	0.968 and 0.893
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.142
Final R indices $[I > 2\sigma(I)]$	$R_1 = 0.0663$, $wR_2 = 0.1668$
R indices (all data)	$R_1 = 0.1273$, $wR_2 = 0.1785$
Extinction coefficient	0.0155(17)
Largest diff. peak and hole, e/Å^{-3}	0.492 and −0.444

matrix least-squares techniques, using anisotropic thermal parameters for all non-hydrogen atoms. All the hydrogen atoms were fixed on the idealized positions isotropically, but they were only included during the structure factor calculations. The final cycle of full-matrix least-squares refinement gave $R_1 = 0.0663$, $wR_2 = 0.1668$ ($w = 1/[\sigma^2(F_o^2) + (0.0686P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$). $S = 1.142$ and $(\Delta/\sigma)_{max} = 0.000$. The maximum peak on the final difference Fourier map is 0.492 and the minimum peak −0.444e/Å^3. Programs used to calculate are

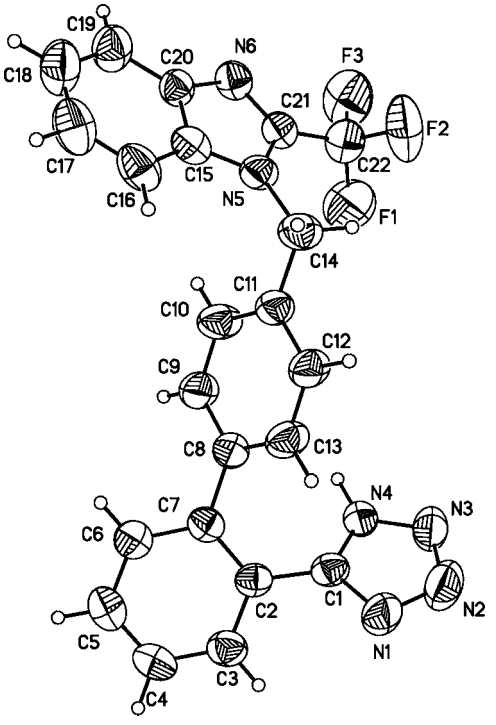

Fig. 1. Molecular structure of the title compound (50% probability ellipsoids).

SHELXL-98. Figure 1 shows the molecular structure of the title compound, and Fig. 2 depicts the packing diagram of the molecules in a unit cell.

Results and discussion

Figure 1 shows the molecular structure of the title compound with atom numbering scheme. Figure 2 shows clearly solvent CH_2Cl_2 was packed in unit cell. The selected bond lengths and bond angles are listed in Table 2.

X-ray analysis shows that the bond lengths of C(22)—F(1), C(22)—F(2), and C(22)—F(3) are different, 1.307, 1.319, and 1.333 Å respectively. The single bond length of C(21)—C(22) is 1.470(6) Å, shorter than common one (1.54 Å); There is an intermolecular hydrogen bond in the crystal of the title compound. The intermolecular hydrogen bond N(4)—HN4···N(6) is formed between tetrazole group and benzimidazole with

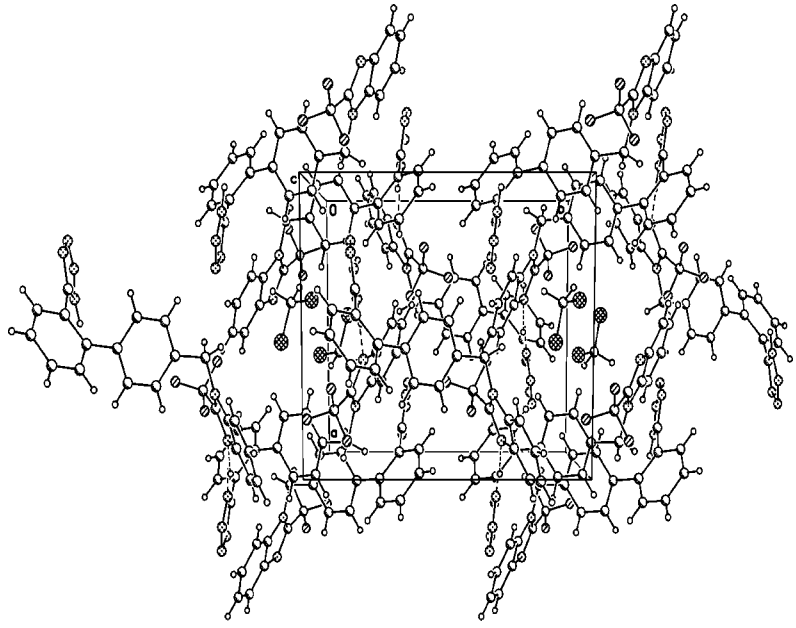

Fig. 2. Packing of the title compound in a unit cell.

the distance of N(4)···N(6)$^{(a)}$ 2.822 Å and the angle of N(7)—H(4)···O(2)$^{(a)}$ 156(4) (a: $-x + 1/2$, $y + 1/2$, $-z + 1/2$), respectively Table 3.

In the tetrazole ring, the N_2—N_3distance of 1.292(5) Å is clearly a double bond, significantly shorter than the N_1—N_2 and N_3—N_4 signal bonds of 1.367(5) Å and 1.346(4) Å, respectively. These values are consistent with those observed previously for the tetrazole ring.[7]

In the benzimidazol moiety, the C_{21}—N_6 bond has a strong double-bond character, the distance of it is 1.309(5) Å, while that of C_{21}—N_5 is 1.358(4) Å. In biphenyl moiety, the inter-ring distance C(7)—C(8) 1.492(5) Å of the title compound is shorter than that of unsubstituted biphenyl 1.507 Å.

The dihedral angles between the tetrazole plane and the plane of phenyl ring attached to it is 45.82(2)°, The deviation angle between the planes of the phenyl rings of the biphenyl moieties is 47.67(18)°, while the values in 2-butyl-6-dimethoxymethyl-5-phenyl-2-{[2′-(1*H*-tetrazole-5-yl)biphenyl-4-yl]methyl}-1H-imidazol[5,4-b] pyridine are 58.8(5)° and 45.8(5)°, respectively.[8]

Table 2. Selected Bond Lengths [Å] and Angles [deg] for **5**

F(1)—C(22)	1.307(5)	F(2)—C(22)	1.319(5)
F(3)—C(22)	1.331(5)	N(1)—C(1)	1.323(5)
N(1)—N(2)	1.367(5)	N(2)—N(3)	1.292(5)
N(3)—N(4)	1.346(4)	N(4)—C(1)	1.335(4)
N(5)—C(21)	1.358(4)	N(5)—C(15)	1.377(5)
N(5)—C(14)	1.470(4)	N(6)—C(21)	1.309(5)
N(6)—C(20)	1.388(4)	C(1)—C(2)	1.459(5)
C(7)—C(8)	1.492(5)	C(21)—C(22)	1.470(6)
C(1)—N(1)—N(2)	106.0(3)	N(3)—N(2)—N(1)	111.1(3)
N(2)—N(3)—N(4)	105.5(3)	C(1)—N(4)—N(3)	110.1(3)
C(21)—N(5)—C(15)	105.9(3)	C(21)—N(5)—C(14)	129.1(3)
C(15)—N(5)—C(14)	124.7(3)	C(21)—N(6)—C(20)	104.6(3)
N(1)—C(1)—N(4)	107.4(3)	N(1)—C(1)—C(2)	125.2(3)
N(4)—C(1)—C(2)	127.3(3)	C(6)—C(7)—C(8)	119.0(4)
C(2)—C(7)—C(8)	122.6(3)	C(9)—C(8)—C(7)	121.6(3)
N(5)—C(15)—C(20)	106.2(3)	N(5)—C(15)—C(16)	132.2(4)
N(6)—C(21)—N(5)	113.6(3)	F(1)—C(22)—C(21)	112.2(4)
F(2)—C(22)—C(21)	113.3(4)	F(3)—C(22)—C(21)	111.6(4)

Table 3. Hydrogen Bonds for **5** [Å and deg.]

D—H...A	d (D—H)	d (H...A)	d (D...A)	<(DHA)
N(4)—HN4...N(6)#1	0.98(5)	1.90(5)	2.822(5)	156(4)

Note. Symmetry transformations used to generate equivalent atoms: #1 $-x + 1/2$, $y + 1/2$, $-z + 1/2$.

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