Instrumental Achievements

Crystal Structure of 1-Cyclopropyl-2-ethyl-5-fluoro-6-(4-methylpiperazin-1-yl)-1*H*-benzimidazole

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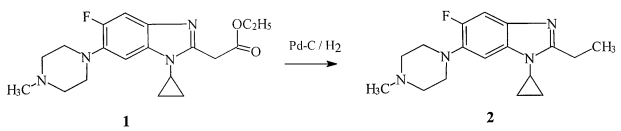
Benzimidazole derivatives display a wide spectrum of biological activities,[1] and some of them are used as drugs.[2,3] In previous studies,[4,5] we reported on the synthesis and biological evaluation of 1,2,5(6)-trisubstituted benzimidazoles as antihistaminic and antimicrobial agents.

The synthesis of ethyl 1-cyclopropyl-5-fluoro-6-(4-methylpiperazine-1-yl)-1*H*-benzimidazole-2-acetate (**1**) was performed according to reported methods.[6,7] 1-Cyclopropyl-2-ethyl-5-fluoro-6-(4-methylpiperazin-1-yl)-1*H*-benzimidazole (**2**) was prepared by the reduction of **1** with Pd/C in a hydrogen atmosphere (Scheme 1). A suspension of **1** (300 mg, 0.8 mmol) in *N*,*N*-dimethylformamide (0.5 mL) was hydrogenated over 10% Pd/C. After dilution with ethylacetate and filtration, the solution was extracted with water and 10% aqueous NaCl solution. The organic layer was dried and evaporated. The residue was purified by column chromatography ($CHCl_3$) and recrystallized from isopropanol, yielding 160 mg of **2**. Its structure was assigned by NMR as well as mass and elemental analysis results. The X-ray structure was determined in order to establish the conformation of the molecule.

The crystal and experimental details are summarized in Table 1. The reflection data were collected at 23˚C using the ω-2θ scan technique by using graphite-monochromated Mo K_α radiation (λ = 0.71069 Å). A colorless prismatic crystal of **2** with approximate dimensions of 0.24 × 0.16 × 0.60 mm was used for all x-ray experiments. A total of 1933 reflections were measured, 1920 of which were unique. During data collections three intensity control reflections were monitored every 2 h, showing no loss of intensity. The structure was solved by direct methods with SIR92[8] and refined by a full-matrix least-squares method using anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were placed geometrically 0.95 Å from their parent atoms. For all hydrogen atoms, a riding model was used and displacement parameters were fixed at 1.3U_{eq} of the parent atoms. The final atomic parameters and the molecular geometry for the non-hydrogen atoms are given in Tables 2 and 3, respectively. An ORTEP drawing of the compound with atom numbering is shown in Fig. 1.



Scheme 1 Synthesis and chemical structures.

The structure predicted from chemical and spectral analysis has been confirmed by an x-ray crystallographic analysis. The bond lengths and angles agree with the mean values reported for those analogues compounds. As expected, the benzimidazole ring system is nearly planar. The geometry observed for the piperazine ring shows no significant distortion from a perfect chair. The perpendicular distances of the N2 and N4 atoms from the best plane defined by atoms C15, C16, C17, C18 are –0.671(2) and 0.666(3)Å, respectively. In terms of the ring-puckering coordinates, the amplitudes and phase magnitudes[9] are Q = 0.581 Å, φ = 101.2 and θ = 179.2˚. The dihedral angles between the best planes of the benzimidazole and piperazine ring, benzimidazole and cyclopropyl ring are 136.1(1) and

Table 1 Crystal and experimental data

Formula: $C_{17}H_{23}N_4F$
Formula weight = 302.39
Crystal system: orthorhombic
Space group: $P2_12_12_1$ Z = 4
a =7.511(1)Å
b = 13.867(2)Å
c = 15.581(1)Å
V = 1622.8(3)Å^3
D_x = 1.238 g/cm^3
μ (Mo K_α) = 0.08 mm^{-1}
T = 296 K
F (0 0 0) = 648
Crystal dimensions: 0.48 × 0.20 × 0.60 mm
Radiation = graphite monochromated Mo K_α (λ = 0.71069 Å)
$2\theta_{max}$ = 57.0˚
Number of reflections measured = 1933
No. of reflections used = 1177 [$F_0 > 2.0\ (F_0)$]
No. of parameters=203
R = 0.0395
Rw = 0.0432
$(\Delta/\rho)_{max}$ = 0.13 eÅ^{-3}
$(\Delta\rho)_{min}$ = –0.16 eÅ^{-3}
$(\Delta\sigma)_{max}$ = 0.00
Measurement: Enraf Nonius CAD-4 diffractometer
Program system: CAD-4 EXPRESS Software
Structure determination: SIR92
Refinement: full matrix least-squares

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Table 2 Atomic coordinates and equivalent isotropic thermal parameters for non-hydrogen atoms

Atom	*x*	*y*	*z*	B_{eq}/Å^2
F	0.7040(3)	0.4131(1)	0.6097(1)	4.75(4)
N1	0.6773(4)	0.7501(2)	0.4344(1)	3.33(5)
N2	0.6918(4)	0.3905(2)	0.4363(1)	3.32(5)
N3	0.6941(4)	0.7613(2)	0.5781(2)	3.82(6)
N4	0.6210(4)	0.2187(2)	0.3412(2)	3.99(6)
C2	0.6829(4)	0.8094(2)	0.5055(2)	3.57(7)
C4	0.6992(4)	0.5809(2)	0.6033(2)	3.70(7)
C5	0.6953(4)	0.4956(2)	0.5615(2)	3.44(6)
C6	0.6836(4)	0.4840(2)	0.4717(2)	3.09(6)
C7	0.6758(4)	0.5682(2)	0.4232(2)	3.41(6)
C8	0.6827(4)	0.6565(2)	0.4646(2)	3.13(6)
C9	0.6929(4)	0.6650(2)	0.5539(2)	3.34(6)
C10	0.6478(4)	0.7754(2)	0.3460(2)	3.67(7)
C11	0.7637(5)	0.8458(2)	0.3018(2)	5.01(8)
C12	0.7767(5)	0.7425(2)	0.2804(2)	4.67(8)
C13	0.6760(5)	0.9156(2)	0.4986(2)	4.34(7)
C14	0.6658(6)	0.9667(2)	0.5835(2)	5.58(9)
C15	0.5386(5)	0.3287(2)	0.4560(2)	4.14(8)
C16	0.5772(5)	0.2255(2)	0.4315(2)	4.18(7)
C17	0.7734(5)	0.2795(2)	0.3222(2)	4.03(7)
C18	0.7347(4)	0.3833(2)	0.3451(2)	3.66(7)
C19	0.6548(6)	0.1199(2)	0.3160(2)	6.2(1)

$B_{eq} = (8\pi^2/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* (\boldsymbol{a}_i \cdot \boldsymbol{a}_j)$.

Table 3 Selected bond distances and bond angles of non-hydrogen atoms (Å,˚)

F	C5	1.370(3)		C10	C11	1.479(5)	
N1	C10	1.438(4)		C10	C12	1.481(5)	
N2	C6	1.410(4)		C11	C12	1.474(5)	
N4	C19	1.447(4)		C13	C14	1.503(5)	
C2	C13	1.477(4)					
C2	N1	C8	106.6(2)	N1	C10	C11	121.1(3)
C2	N1	C10	128.8(2)	N1	C10	C12	119.0(3)
C6	N2	C15	114.9(2)	C11	C10	C12	59.7(2)
C15	N2	C18	109.6(2)	C10	C11	C12	60.2(2)
C2	N3	C9	104.8(2)	C10	C12	C11	60.1(2)
C16	N4	C17	109.8(2)	C2	C13	C14	114.1(3)
C17	N4	C19	110.8(3)	F	C5	C4	117.8(2)
N1	C2	N3	112.9(2)	N2	C6	C7	124.1(2)
N1	C2	C13	122.3(2)				

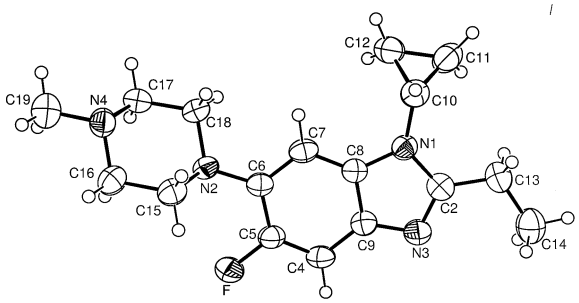

Fig. 1 ORTEP drawing of the title compound with atom labeling.

130.5(2)˚, respectively. The ethyl group attached to the C2 atom is oriented with the torsion angle of N1-C2–C13–C14 being 174.4(3)˚.

In the molecule, there is an intramolecular hydrogen bond between C15 and F [C15··F 2.901, C15-H15 0.944, H15··F 2.348 Å, C15-H15··F 120.4˚]. All intermolecular contacts correspond to normal van der Waals interactions.

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