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Crystal and Molecular Structure Analysis of 7-Chloro-5-cyclopropyl-9-methyl-10-(2-nitro-4-trifluromethyl-Phenyl)-5,10-dihydro-4,5,6,10-tetraaza-dibenzo [a, d]cyclohepten-11-one

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The compound 7-chloro-5-cyclopropyl-9-methyl-10-(2-nitro-4-trifluromethyl-phenyl)-5,10-dihydro-4,5,6,10-tetraaza-dibenzo[a,d]cyclohepten-11-one, $C_{22}H_{15}N_5O_3F_3Cl$, crystallizes in the monoclinic crystal class under the space group $P2_1/c$ with cell parameters $a = 16.595(7)$ Å, $b = 8.775(7)$ Å, $c = 14.973(1)$ Å, $\beta = 97.465(4)$, $V = 2161.9(3)$ Å^3, $Z = 4$. The structure was solved by direct methods using SHELXS-97, and refined using SHELXL-97. The final residual factor is $R1 = 0.0604$ for 4116 reflections and 342 parameters. The molecular structure exhibits intra-molecular hydrogen bond of the type C–H···O.

Keywords: crystal structure; diazepinone derivative; equatorial conformation

INTRODUCTION

Diazepinone represents probably the most important of all structural classes in drug discovery [1]. The diazepinone nucleus is a fundamental constituent of a number of natural and synthetic products with biological activity. The literature survey revealed the drug Nevirapine and which is made up of diazepinone nucleus was the first NNRTI to receive regulatory approval for the treatment of HIV-1 infection.

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Further, the literature survey revealed diazepinone derivatives are found to be anti-HIV [2,3], antitumour [4], antipsychotics [5], and potential anti-inflammatory agents [6,7].

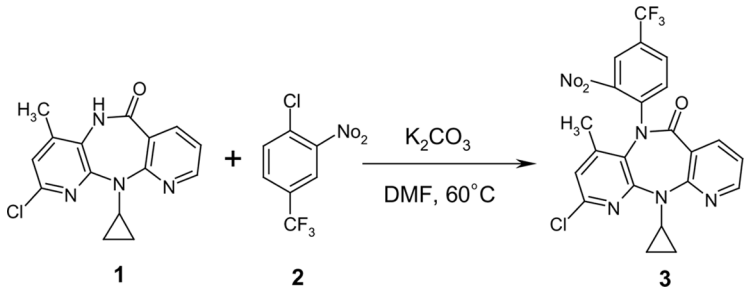
In continuation of our research work on synthesis and biological evaluation of novel heterocycles, the title compound was synthesised and tested for the inhibition with purified PLA_2 from *Vipera russellii* (Group II; VRV-PL-V), Naja naja (NN-PL-I) snake venom, and partially purified pleural fluid (Group II, PF-PLA2). The results revealed that the compound 7-chloro-5-cyclopropyl-9-methyl-10-(2-nitro-4-trifluromethyl-phenyl)-5,10-dihydro-4,5,6,10-tetraaza-dibenzo [a,d] cyclohepten-11-one is found to be a very potent *in-vitro* enzyme inhibitor and exhibit *in-vivo* anti-inflammatory activity with excellent selectivity [8]. Herein, we report the crystal and molecular structure studies of the title compound.

EXPERIMENTAL

Melting points were determined using SELACO-650 hot stage melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded using a Jasco FTIR-4100 series. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Shimadzu AMX 400-Bruker, 400 MHz spectrometer using DMSO-d_6 as a solvent and TMS as internal standard (chemical shift in δ ppm). Spin multiplets are given as s (singlet), d (doublet), and m (multiplet). Elemental analyses (CHNS) were obtained on Vario EL III Elementar. Silica gel column chromatography was performed using Merck 7734 silica gel (60–120 mesh) and Merck made Thin Layer Chromatography (TLC) plates. The crystallographic measurements were made on a DIPLabo using Imaging plate system with graphite monochromated radiation (MoKα).

Synthesis of 7-Chloro-5-cyclopropyl-9-methyl-10-(2-nitro-4-trifluromethyl-phenyl)-5,10-dihydro-4,5,6,10-tetraaza-dibenzo [a,d] cyclohepten-11-one

To a solution of 7-chloro-5-cyclopropyl-9-methyl-5,10-dihydro-4,5,6,10-tetraaza-dibenzo [a,d] cyclohepten-11-one (**1**) in 10 ml of N,N-dimethyl formamide, were added 4-chloro 3-nitrobenzotrifluride (0.562 g, 2.49 mmol) and anhydrous powdered potassium carbonate (0.688 g, 4.98 mmol). The reaction mixture was heated to 60°C for 6 h. The reaction mixture was monitored by TLC. Upon completion, solvent was removed under reduced pressure and extracted with ethyl acetate. The organic layer was dried with anhydrous sodium sulphate, the



1 2 3

SCHEME 1

solvent was evaporated to get crude product which was purified by column chromatography over silica gel using hexane: ethyl acetate (8:2) as an eluent. The pure product obtained was dissolved in acetonitrile. Because of the slow evaporation of the solvent, pale yellow crystals developed after seven days. The synthetic method employed for synthesis is shown in Scheme 1.

Yield: (0.67 g) 82%. Melting point: 228–230°C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.45 (m, 1 H), 7.25 (m, 1 H), 7.1 (m, 1 H), 7.02 (m, 1 H), 7.68 (m, 1H), 7.1 (m, 1 H), 7.8 (d, 1 H), 2.32 (s, 5 H), 1.7 (s, 3 H).

IR (KBr cm^{-1}): 1678, 1585, 1542, 1138, 100, 3075, 3006.

Anal. Calcd (in %) for $C_{22}H_{15}ClF_3N_5O_3$: C, 53.94; H, 3.09; N, 14.30. Found: C, 53.92; H, 3.05; N, 14.26.

Crystal Structure Determination

Single crystal of the title compound suitable for X-ray diffraction studies was mounted on a glass fibre. The measurements were made on a DIPLabo Imaging Plate system with graphite monochromated MoK_α radiation. Thirty-six frames of data were collected by the oscillation method. Image processing and data reduction were done using Denzo [9]. The structure was solved using SHELXS-97 [10]. The full-matrix least-squares refinement was done by using SHELXL-97 [11]. The R1 value for all reflections is 0.0604.

RESULTS AND DISCUSSION

Table 1 gives the details of crystal data, data collection, and refinement. The final atomic coordinates and equivalent thermal parameters of nonhydrogen atoms are listed in Table 2. Tables 3

TABLE 1 Crystal Data and Structure Refinement

Empirical formula	$C_{22}H_{15}ClF_3N_5O_3$
Formula weight	489.84
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21/c
Cell dimensions	
	a = 16.595(7) Å
	b = 8.775(7) Å
	c = 14.973(1) Å
	$\beta = 97.465(4)^\circ$
Volume	2161.9(3) $Å^3$
Z	4
Density (calculated)	1.505 Mg/m^3
Absorption coefficient	0.239 mm^{-1}
F000	1000
Crystal size	$0.25 \times 0.25 \times 0.30$ mm
Theta range for data collection	2.63° to 32.49°
Index ranges	$-25 \leq h \leq 24$
	$-12 \leq k \leq 13$
	$-17 \leq l \leq 17$
Reflections collected	11206
Independent reflections	6330 [R(int) = 0.0292]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6330/0/342
Goodness-of-fit on F2	1.060
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0604, ωR2 = 0.1650
R indices (all data)	R1 = 0.0940, ωR2 = 0.1965
Extinction coefficient	0.030(3)
Largest diff. peak and hole	0.358 and -0.382 e·$Å^{-3}$

and 4 give the list of bond lengths and bond angles of nonhydrogen atoms respectively. The schematic diagram of the molecule is given in Figure 1. Figure 2 gives the ORTEP diagram of the molecule at 30% probability. The packing of the molecule down the b axis is given in Figure 3. In synthesis of 7-chloro-5-cyclopropyl-9-methyl-10-(2-nitro-4-trifluromethyl-phenyl)-5,10-dihydro-4,5,6,10-tetraaza-dibenzo [a, d] cyclohepten-11-one, the torsion angle about the atoms C23–C22–N13–C12 is $52.3(2)^\circ$ which indicates that the 2-nitro-4-trifluoro-methyl-phenyl ring nearly bisects the 7-chloro-5-cyclopropyl-9-methyl-5,10-dihydro-4,5,6,10-tetraaza-dibenzo [a, d] cyclohepten-11-one. The torsion angle for cyclopropyl ring about the atoms C6–N5–C17–C18 is $90.60(2)^\circ$ indicating the equatorial conformation of cyclopropyl

TABLE 2 Atomic Coordinates and Equivalent Thermal Parameters of the Nonhydrogen Atoms

Atom	x	y	z	Ueq
Cl1	0.4143(5)	0.6777(8)	0.0536(5)	0.0805(3)
C2	0.3560(1)	0.5371(2)	0.0951(1)	0.0484(5)
N3	0.3719(9)	0.3977(2)	0.0712(1)	0.0429(3)
C4	0.3276(9)	0.2864(2)	0.1009(1)	0.0359(3)
N5	0.3477(8)	0.1367(2)	0.0786(1)	0.0375(3)
C6	0.3788(9)	0.0520(2)	0.1563(1)	0.0372(4)
N7	0.4555(9)	0.0042(2)	0.1626(1)	0.0470(4)
C8	0.4849(1)	−0.0715(3)	0.2369(2)	0.0574(6)
C9	0.4416(1)	−0.1020(3)	0.3071(2)	0.0598(6)
C10	0.3613(1)	−0.0554(3)	0.2991(1)	0.0513(5)
C11	0.3288(1)	0.0237(2)	0.2227(1)	0.0403(4)
C12	0.2396(1)	0.0524(2)	0.2075(1)	0.0423(4)
N13	0.2126(8)	0.1923(2)	0.1735(1)	0.0387(3)
C14	0.2650(9)	0.3134(2)	0.1534(1)	0.0378(4)
C15	0.2520(1)	0.4624(2)	0.1808(1)	0.0433(4)
C16	0.2996(1)	0.5764(2)	0.1509(1)	0.0494(5)
C17	0.3894(1)	0.1204(2)	−0.0002(1)	0.0428(4)
C18	0.3605(1)	−0.0009(3)	−0.0655(1)	0.0544(5)
C19	0.3423(1)	0.1629(3)	−0.0876(1)	0.0565(5)
O20	0.1925(8)	−0.0461(2)	0.2245(1)	0.0577(4)
C21	0.1882(1)	0.5049(3)	0.2389(2)	0.0585(5)
C22	0.1282(9)	0.2078(2)	0.1397(1)	0.0402(4)
C23	0.0649(1)	0.1677(2)	0.1884(1)	0.0455(4)
C24	−0.0154(1)	0.1760(3)	0.1497(1)	0.0527(5)
C25	−0.0339(1)	0.2295(3)	0.0630(2)	0.0542(5)
C26	0.0276(1)	0.2728(3)	0.0147(1)	0.0561(5)
C27	0.1077(1)	0.2598(3)	0.0528(1)	0.0494(5)
N28	0.0778(1)	0.1250(2)	0.2835(1)	0.0540(5)
O29	0.1324(1)	0.1857(2)	0.3332(1)	0.0685(5)
O30	0.0299(1)	0.0362(3)	0.3104(1)	0.0773(6)
C31	−0.1212(1)	0.2422(4)	0.0218(2)	0.0750(8)
F32A	−0.1319(3)	0.324(3)	−0.0464(1)	0.175(1)
F32B	−0.1487(1)	0.385(2)	0.026(2)	0.158(1)
F33A	−0.1673(4)	0.2911(2)	0.0795(7)	0.106(5)
F33B	−0.1711(8)	0.187(7)	0.0684(2)	0.20(2)
F34A	−0.1314(6)	0.211(3)	−0.0595(9)	0.196(1)
F34B	−0.1549(3)	0.1051(7)	0.0068(9)	0.119(5)

ring with cyclohepten ring. The torsion angle which determines the position of the oxygen atom (C10−C11−C12−O20) is 40.06(3)°. The chlorine atom and methyl moiety substituted for dibenzo cyclohepten ring are in the anti-periplanar conformation as the torsion angles

TABLE 3 Bond Lengths (Å)

Atoms	Length	Atoms	Length
Cl1–C2	1.733(2)	C17–C18	1.483(3)
C2–N3	1.311(3)	C18–C19	1.497(3)
C2–C16	1.376(3)	C22–C27	1.379(3)
N3–C4	1.333(2)	C22–C23	1.400(2)
C4–C14	1.402(2)	C23–C24	1.384(2)
C4–N5	1.406(2)	C23–N28	1.460(3)
N5–C6	1.419(2)	C24–C25	1.377(3)
N5–C17	1.451(2)	C25–C26	1.377(3)
C6–N7	1.331(2)	C25–C31	1.504(3)
C6–C11	1.397(2)	C26–C27	1.382(3)
N7–C8	1.334(3)	N28–O29	1.219(2)
C8–C9	1.374(3)	N28–O30	1.219(2)
C9–C10	1.384(3)	C31–F34A	1.238(9)
C10–C11	1.386(3)	C31–F32A	1.240(5)
C11–C12	1.489(2)	C31–F33B	1.247(9)
C12–O20	1.215(2)	C31–F33A	1.299(7)
C12–N13	1.381(2)	C31–F34B	1.333(6)
N13–C14	1.430(2)	C31–F32B	1.337(1)
N13–C22	1.431(2)	C15–C21	1.501(3)
C14–C15	1.396(3)	C17–C19	1.482(3)
C15–C16	1.385(3)		

about the atoms Cl1–C2–N3–C4 and C4–C14–C15–C21 are 179.13(1)° and 178.58(2)°, respectively. The atoms N5 and N13, where the cyclopropyl ring and 2-nitro-4-trifluoromethyl-phenyl ring are substituted, deviate from the plane defined by the atoms N3–C2–C16–C15–C14–C13–C12–C11–C10–C9–C8–N7–C6–C5–C4–C5–C4 by −1.151(2) Å and −0.943(2) Å, respectively. The basic moiety 7-chloro-5-cyclopropyl-9-methyl-5,10-dihydro-4,5,6,10-tetraaza-dibenzo[a,d] cyclohepten-11-one is puckered. The total puckering amplitude for the basic moiety, Q is 2.6443(3) Å. The torsion angle of 33.6(3)° for the atoms C22–C23–N28–O30 indicates that the nitro group substituted for the ring 2 is in syn-clinal onformation with ring 2. The fluorine atoms are highly disordered. Hence, the refinement of the structure is carried out using partial occupancies for the fluorine atom. The bond lengths and bond angles are in good agreement with the standard values except for halogens. The bond length C–Cl is 0.733(2) Å which is less than standard value (1.77 Å). The packing of the molecules indicates that the structure exhibits intramolecular hydrogen bond of the type C–H···O with a bond length of 3.322(3) Å and a bond angle of 149.

TABLE 4 Bond Angles (°)

Atoms	Angle	Atoms	Angle
N3–C2–C16	125.18(2)	C23–C22–N13	123.96(2)
N3–C2–Cl1	115.13(2)	C24–C23–C22	121.07(2)
C16–C2–Cl1	119.67(2)	C24–C23–N28	115.63(2)
C2–N3–C4	116.95(2)	C22–C23–N28	123.17(2)
N3–C4–C14	122.97(2)	C25–C24–C23	119.78(2)
N3–C4–N5	116.57(2)	C24–C25–C26	120.00(2)
C14–C4–N5	120.44(2)	C24–C25–C31	119.77(2)
C4–N5–C6	111.55(1)	C26–C25–C31	120.2(2)
C4–N5–C17	115.96(2)	C25–C26–C27	119.89(2)
C6–N5–C17	116.99(1)	C22–C27–C26	121.57(2)
N7–C6–C11	122.99(2)	O29–N28–O30	122.87(2)
N7–C6–N5	117.70(2)	O29–N28–C23	119.12(2)
C11–C6–N5	119.31(1)	O30–N28–C23	117.87(2)
C6–N7–C8	117.28(2)	F34A–C31–F32A	48.1(1)
N7–C8–C9	124.38(2)	F34A–C31–F33B	117(2)
C8–C9–C10	117.98(2)	F32A–C31–F33B	130.5(1)
C9–C10–C11	119.10(2)	F34A–C31–F33A	135.3(5)
C10–C11–C6	118.23(2)	F32A–C31–F33A	108.9(1)
C10–C11–C12	118.86(2)	F33B–C31–F33A	43(3)
C6–C11–C12	122.11(2)	F34A–C31–F34B	68.4(2)
O20–C12–N13	121.50(2)	F32A–C31–F34B	111.6(1)
O20–C12–C11	120.14(2)	F33B–C31–F34B	57(3)
N13–C12–C11	118.36(2)	F33A–C31–F34B	98.1(8)
C12–N13–C14	124.07(1)	F34A–C31–F32B	104.5(2)
C12–N13–C22	118.04(1)	F32A–C31–F32B	59.1(1)
C14–N13–C22	116.71(1)	F33B–C31–F32B	95(3)
C15–C14–C4	118.52(2)	F33A–C31–F32B	54.9(2)
C15–C14–N13	120.84(2)	F34B–C31–F32B	135.7(9)
C4–C14–N13	120.52(2)	F34A–C31–C25	112.9(5)
C16–C15–C14	117.69(2)	F32A–C31–C25	114.1(3)
C16–C15–C21	118.91(2)	F33B–C31–C25	114.6(6)
C14–C15–C21	123.39(2)	F33A–C31–C25	111.7(3)
C2–C16–C15	118.50(2)	F34B–C31–C25	111.3(3)
N5–C17–C19	116.15(2)	F32B–C31–C25	111.5(5)
N5–C17–C18	117.34(2)	F33A–F32B–C31	60.9(1)
C19–C17–C18	60.66(2)	F34A–F32A–C31	65.9(9)
C17–C18–C19	59.63(1)	F32B–F33A–C31	64.1(9)
C17–C19–C18	59.71(1)	F34B–F33B–C31	65.2(2)
C27–C22–C23	117.64(2)	F32A–F34A–C31	66.1(7)
C27–C22–N13	118.36(2)	F32A–F34A–F34B	119.1(1)
C31–F34A–F34B	58.9(1)	F33B–F34B–F34A	104.2(2)
F33B–F34B–C31	58.2(1)	C31–F34B–F34A	52.7(6)

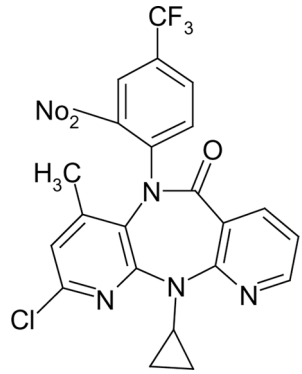


FIGURE 1 Schematic diagram of the title compound.

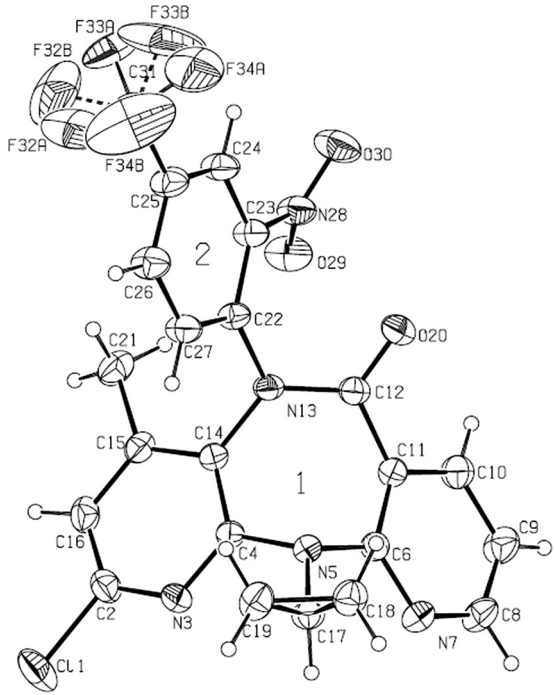


FIGURE 2 ORTEP of title compound at 30% probability.

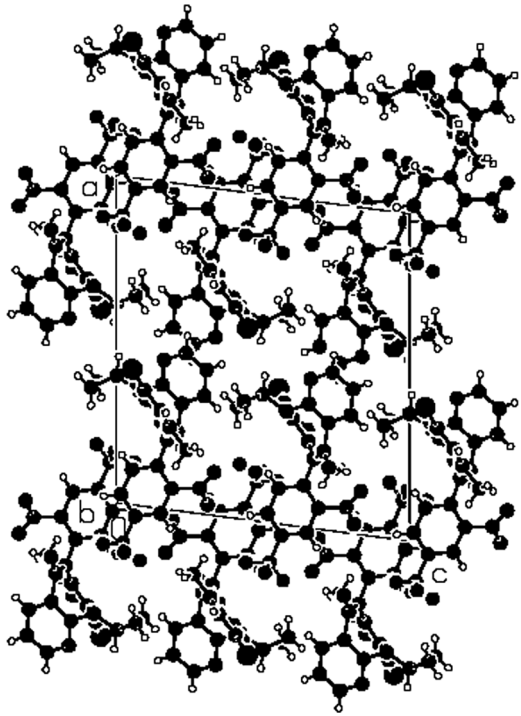


FIGURE 3 Packing of the molecules down b axis.

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