Crystal structure of *trans*-1-(2-methoxyphenyl)-4-[4-(2-phthalimido)cyclohexyl]-piperazine chloride monohydrate, $(C_{25}H_{30}N_3O_3)Cl \cdot H_2O$

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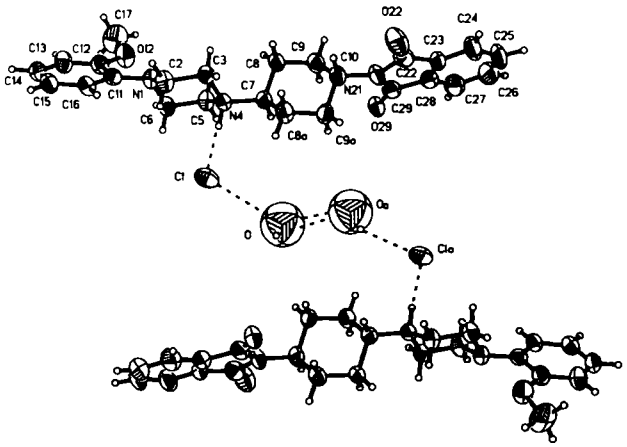
Received June 20, 2002, accepted and available on-line August 19, 2002; CCDC-No. 1267/892



Abstract

$C_{25}H_{32}ClN_3O_4$, monoclinic, $P12_1/c1$ (No. 14), $a = 14.640(3)$ Å, $b = 22.585(5)$ Å, $c = 7.462(1)$ Å, $\beta = 101.51(3)°$, $V = 2417.7$ Å^3, $Z = 4$, $R_{gt}(F) = 0.079$, $wR_{ref}(F^2) = 0.276$, $T = 293$ K.

Source of material

The synthesis of the title compound has been described previously [1] as a part of our research program focused on serotonin $5HT_{1A}$ receptor ligands. The crystals for X-ray studies were obtained from ethanol: acetone (1:1) mixture by slow evaporation.

Experimental details

The crystal selected for this study was small and soft, which explains the relative low $N(hkl)/N(param)$ ratio and high R-values.

Discussion

As a subsequent part of our study on the serotonin $5HT_{1A}$ and $5HT_{1A}$ receptors ligands modifications [2-5], we have now investigated the crystal structure of the rigid analog of NAN-190, the well-known postsynaptic $5HT_{1A}$ receptor antagonist [6]. Introduction of the 1e,4e-disubstituted cyclohexane system in the place of an aliphatic linked spacer into the ligand molecule diminishes the possibility of a mutual spatial arrangement of terminal fragments which are responsible for a ligand activity towards the investigated receptors. The independent unit of the crystal composed of the protonated main molecule, Cl^- ion, and one water particle. The main molecule under discussion incorporates two border cyclic moieties – arylopiperazine and phthalimide – linked via cyclohexane in chair conformation constituting in fact four carbons atoms spacer. Both cyclic moieties are equatorially located at respective carbons from cyclohexane. The phthalimide fragment is planar and twisted by 75.8° with respect to main cyclohexane ring plane (by the atoms C8, C9, C8a and C9a). Two rings from arylopiperazine skeleton are inclined to each other at 44°. As in the other arylopiperazines, proton at N4 is axial. Two undulated in chair conformation rings – cyclohexane and piperazine – are twisted at 71.1°. Introducing the cyclohexane as the constrain spacer resulted in *trans-gauch-trans* conformation of border aromatic rings. Both ions and water molecule form bimolecular unit by the system of H-bonds. Such H-bonds geometry determines the following distances: d(N4–H4···Cl) = 3.054(2) Å, d(O–H1···Cl) = 3.419(5) Å, d(O–H1···O^i) = 2.647(6) Å; $i = (-1-x, -1-y, 2-z)$.

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Table 1. Data collection and handling.

Crystal:	colorless needle, size 0.4 × 0.2 × 0.1 mm
Wavelength:	Cu K_α radiation (1.54178 Å)
μ:	16.73 cm^{-1}
Diffractometer, scan mode:	KUMA Diffraction KM-4, $\omega/2\theta$
$2\theta_{max}$:	160.22°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	6627, 5116
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\,\sigma(I_{obs})$, 1459
$N(param)_{refined}$:	292
Programs:	SHELXS-97 [7], SHELXL-97[8], SHELXTL-PC [9]

Table 2. Atomic coordinates and displacement parameters (in Å^2).

Atom	Site	x	y	z	U_{iso}
H(2A)	4e	–0.0305	0.5429	0.8770	0.073
H(2B)	4e	0.0353	0.5124	0.7653	0.073
H(3A)	4e	–0.0949	0.4527	0.7660	0.062
H(3B)	4e	–0.0951	0.4723	0.5663	0.062
H(4)	4e	–0.1979	0.5259	0.7940	0.059
H(5A)	4e	–0.2608	0.5864	0.5540	0.065
H(5B)	4e	–0.1983	0.5565	0.4338	0.065
H(6A)	4e	–0.1279	0.6442	0.5518	0.071
H(6B)	4e	–0.1292	0.6213	0.7481	0.071
H(7A)	4e	–0.3330	0.4966	0.5999	0.064
H(8A)	4e	–0.2266	0.4147	0.4424	0.074
H(8B)	4e	–0.2702	0.4707	0.3383	0.074
H(9A)	4e	–0.3676	0.3866	0.2571	0.080
H(9B)	4e	–0.4185	0.4339	0.3537	0.080
H(10A)	4e	–0.3250	0.3365	0.5359	0.071
H(9AA)	4e	–0.3839	0.3644	0.7966	0.077
H(9AB)	4e	–0.4272	0.4207	0.6919	0.077
H(8AA)	4e	–0.2801	0.4452	0.8787	0.082
H(8AB)	4e	–0.2354	0.3994	0.7659	0.082
H(24A)	4e	–0.5539	0.1530	0.3977	0.108
H(25A)	4e	–0.7167	0.1447	0.2725	0.137
H(26A)	4e	–0.8001	0.2288	0.1551	0.145
H(27A)	4e	–0.7381	0.3250	0.2092	0.117

Table 2. Continued.

Atom	Site	x	y	z	U_{iso}
H(13A)	4e	0.1223	0.7266	0.4249	0.090
H(14A)	4e	0.2396	0.7291	0.6897	0.086
H(15A)	4e	0.2327	0.6636	0.9301	0.077
H(16A)	4e	0.1072	0.5964	0.9063	0.067
H(17A)	4e	-0.0710	0.6749	0.1023	0.139

Table 2. Continued.

Atom	Site	x	y	z	U_{iso}
H(17B)	4e	-0.0156	0.7266	0.2147	0.139
H(17C)	4e	0.0382	0.6730	0.1519	0.139
O	4e	-0.4299(4)	0.5352(3)	1.0729(6)	0.329(5)
H(1)	4e	-0.4086	0.5437	0.9827	0.493
H(2)	4e	-0.4053	0.5329	1.1700	0.493

Table 3. Atomic coordinates and displacement parameters (in $Å^2$).

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl	4e	-0.19975(9)	0.55410(6)	1.0599(2)	0.0877(8)	0.0745(7)	0.0427(5)	0.0053(7)	0.0093(5)	-0.0085(6)
N(1)	4e	-0.0345(2)	0.5807(1)	0.6322(4)	0.038(2)	0.038(2)	0.043(2)	-0.003(2)	0.001(2)	0.006(2)
C(2)	4e	-0.0250(3)	0.5301(2)	0.7569(6)	0.052(2)	0.036(2)	0.053(3)	0.000(2)	-0.002(2)	0.011(2)
C(3)	4e	-0.1018(3)	0.4861(2)	0.6847(6)	0.044(2)	0.032(2)	0.049(2)	-0.001(2)	0.009(2)	0.002(2)
N(4)	4e	-0.1951(2)	0.5128(1)	0.6729(4)	0.042(2)	0.037(2)	0.037(2)	-0.004(2)	0.004(1)	-0.001(2)
C(5)	4e	-0.2019(3)	0.5674(2)	0.5565(6)	0.041(2)	0.035(2)	0.051(2)	0.001(2)	-0.001(2)	0.013(2)
C(6)	4e	-0.1245(3)	0.6094(2)	0.6268(6)	0.044(2)	0.037(2)	0.059(3)	-0.002(2)	0.004(2)	0.000(2)
C(7)	4e	-0.2774(3)	0.4730(2)	0.6133(5)	0.042(2)	0.046(2)	0.039(2)	-0.007(2)	0.005(2)	-0.005(2)
C(8)	4e	-0.2776(3)	0.4420(2)	0.4292(5)	0.053(2)	0.055(2)	0.039(2)	-0.016(2)	0.010(2)	-0.010(2)
C(9)	4e	-0.3671(3)	0.4068(2)	0.3706(6)	0.052(3)	0.060(3)	0.045(2)	-0.012(2)	0.002(2)	-0.008(2)
C(10)	4e	-0.3780(3)	0.3625(2)	0.5204(6)	0.039(2)	0.045(2)	0.054(3)	-0.007(2)	0.001(2)	-0.006(2)
C(9A)	4e	-0.3768(3)	0.3928(2)	0.7047(6)	0.052(2)	0.060(3)	0.044(2)	-0.020(2)	0.014(2)	-0.004(2)
C(8A)	4e	-0.2855(3)	0.4272(2)	0.7605(6)	0.070(3)	0.056(3)	0.036(2)	-0.022(2)	0.006(2)	0.003(2)
N(21)	4e	-0.4623(2)	0.3257(1)	0.4612(5)	0.047(2)	0.037(2)	0.065(2)	-0.006(2)	0.002(2)	-0.008(2)
C(22)	4e	-0.4598(3)	0.2638(2)	0.4677(6)	0.061(3)	0.043(2)	0.056(3)	0.002(2)	0.008(2)	0.000(2)
O(22)	4e	-0.3915(3)	0.2359(1)	0.5295(5)	0.087(2)	0.041(2)	0.097(3)	0.005(2)	-0.009(2)	0.002(2)
C(23)	4e	-0.5567(3)	0.2443(2)	0.3873(6)	0.056(3)	0.055(2)	0.048(2)	-0.023(2)	0.014(2)	-0.013(2)
C(24)	4e	-0.5918(4)	0.1874(2)	0.3629(7)	0.096(4)	0.057(3)	0.065(3)	-0.034(3)	0.019(3)	-0.015(2)
C(25)	4e	-0.6867(4)	0.1827(2)	0.2833(8)	0.116(4)	0.080(3)	0.081(4)	-0.060(3)	0.026(3)	-0.034(3)
C(26)	4e	-0.7376(4)	0.2328(3)	0.2237(8)	0.100(4)	0.112(4)	0.084(4)	-0.048(4)	0.034(3)	-0.043(3)
C(27)	4e	-0.7024(4)	0.2899(3)	0.2454(8)	0.060(3)	0.093(4)	0.077(4)	-0.014(3)	0.006(3)	-0.023(3)
C(28)	4e	-0.6096(3)	0.2941(2)	0.3358(6)	0.048(2)	0.061(3)	0.060(3)	-0.007(2)	0.015(2)	-0.015(2)
C(29)	4e	-0.5515(3)	0.3470(2)	0.3872(6)	0.045(2)	0.069(3)	0.054(3)	-0.008(2)	0.009(2)	-0.019(2)
O(29)	4e	-0.5752(2)	0.3980(1)	0.3722(5)	0.033(2)	0.034(2)	0.080(3)	0.006(2)	-0.002(2)	-0.006(2)
C(11)	4e	0.0417(3)	0.6212(2)	0.6544(5)	0.047(2)	0.039(2)	0.040(2)	0.002(2)	0.008(2)	0.000(2)
C(12)	4e	0.0460(3)	0.6604(2)	0.5087(6)	0.055(3)	0.040(2)	0.054(3)	-0.004(2)	0.009(2)	-0.001(2)
C(13)	4e	0.1188(3)	0.6998(2)	0.5231(7)	0.065(3)	0.039(2)	0.074(3)	-0.009(2)	0.011(3)	0.004(2)
C(14)	4e	0.1888(3)	0.7017(2)	0.6811(6)	0.057(2)	0.045(2)	0.074(3)	-0.017(2)	0.024(2)	-0.013(2)
C(15)	4e	0.1849(3)	0.6632(2)	0.8212(6)	0.048(2)	0.050(2)	0.052(3)	-0.001(2)	0.001(2)	-0.008(2)
C(16)	4e	0.1120(3)	0.6231(2)	0.8086(5)	0.050(2)	0.040(2)	0.040(2)	-0.008(2)	0.001(2)	-0.002(2)
O(12)	4e	-0.0235(2)	0.6544(1)	0.3556(4)	0.073(2)	0.073(2)	0.042(2)	-0.017(2)	-0.002(2)	0.011(2)
C(17)	4e	-0.0171(4)	0.6847(3)	0.1935(6)	0.109(4)	0.103(4)	0.065(3)	-0.007(4)	0.014(3)	0.042(3)

Acknowledgment. The partial support (synthesis) of Polish State Committee for Scientific Research, project No 4 P05F 005 18, is greatly acknowledged.

References

1. Paluchowska, M. H.; Mokrosz, M. J.; Bojarski, A. J.; Wesołowska, A.; Borycz, J.; Charakchieva-Minol S.; Chojnacka-Wójcik E.: On the Bioactive Conformation of NAN-190 and MP3022, $5HT_{1A}$ Receptor Antagonists. J. Med. Chem. **42** (1999) 4952-4960.
2. Karolak-Wojciechowska, J.; Fruziński, A.; Paluchowska, M. H.; Mokrosz, M. J.: Crystal structure of 2-[2-(1-adamantanecarboxamido)ethyl]-1,2,3,4-tetrahydroisoquinolinium chloride monohydrate, $(C_{22}H_{31}N_2O)Cl \cdot H_2O$. Z. Kristallogr. NCS. **217** (2002) 259-260.
3. Karolak-Wojciechowska, J.; Fruziński, A.; Misztal, S.; Mokrosz, M. J.: Crystal structure of 2-[4-(cyclohexanecarboxamido)butyl]-1,2,3,4-tetrahydroisoquinoline chloride dihydrate, $(C_{20}H_{31}N_2O)Cl \cdot 2H_2O$. Z. Krystallogr. NCS. **217** (2002) 261-262.
4. Karolak-Wojciechowska, J.; Fruziński, A.; Bojarski, A. J.; Paluchowska, M. H.; Mokrosz, M. J.: Structure - Activity Relationship Studies of CNS Agents. Part 33.Crystal and Molecular Structure of 1-(2-Methoxyphenyl)-4-alkylpiperazine Substituted Benzotriazoles with Different Pharmacological Activity. Arch. Pharm. Pharm. Med. Chem. **331** (1998) 299-307.
5. Karolak-Wojciechowska, J.; Fruziński, A.; Mokrosz, M. J.: Structures and conformational analysis of new arylopiperazines with *n*-butyl chain. J. Mol. Structur. (Theochem) **542** (2001) 47-56.
6. Glennon, R. A.; Naiman, N. A.; Pierson, M. E.; Titeler, M.; Lyon, R. A.; Weisberg, E.: NAN-190: an Arylpiperazine Analogue That Antagonizes the Stimulus Effects of the $5HT_{1A}$ Agonist 8-Hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT). Eur. J. Pharmacol. **154** (1988) 339-341.
7. Sheldrick, G. M.: SHELXS-97. Program for the Solution of Crystal Structures. University of Göttingen, Germany 1997.
8. Sheldrick, G. M.: SHELXL-97. Program for the Refinement of Crystal Structures. University of Göttingen, Germany 1997.
9. Siemens: SHELXTL-PC. Program Package for the Solution, Refinement and Graphical Presentation of Crystal Structures. Release 4.1. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA 1991.