ЖУРНАЛ СТРУКТУРНОЙ ХИМИИ

2012. Том 53, № 5 *Сентябрь – октябрь* *С. 957 – 961*

UDC 548.737:547.6

5-(3,4-DICHLOROPHENYL)-3-{[4-(2-PYRIDYL)PIPERAZINE-1-YL]METHYL}-1,3,4-OXADIAZOLE-2(3H)-ONE: SYNTHESIS, CHARACTERIZATION, X-RAY AND DFT STRUCTURES

Z.S. Şahin[1], İ. Özkan[2], M. Köksal[2], Ş. Işık[1]

[1]*Department of Physics, Faculty of Arts and Sciences, Ondokuz Mayıs University, Samsun, Turkey*, e-mail: sgul@omu.edu.tr
[2]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Yeditepe University, İstanbul, Turkey*

Received November, 5, 2011

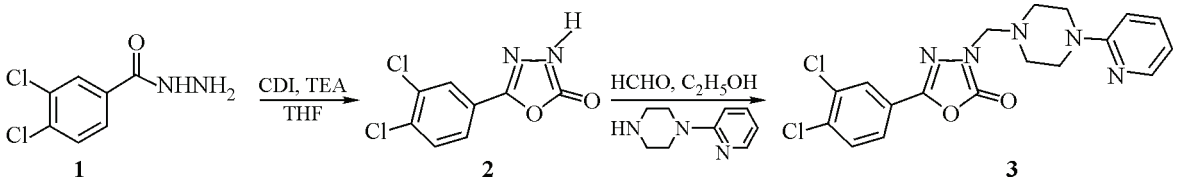
5-(3,4-Dichlorophenyl)-3-{[4-(2-pyridyl)piperazine-1-yl)]methyl}-1,3,4-oxadiazole-2(3H)-one $C_{18}H_{17}Cl_2N_5O_2$ (**3**) is synthesized and characterized by IR, ^{1}H NMR, ^{13}C NMR, elemental analyses, single-crystal X-ray diffraction, and the molecular structure is also optimized at the B3LYP/6-31G(*d*,*p*) level using density functional theory (DFT). All data obtained from the spectral studies support the structural properties of **3**. The molecules are linked principally by C—H···O hydrogen bonds involving carbonyl atoms and carboxylate O atoms, forming $R_2^2(16)$ and $R_4^2(20)$ rings that link to give a one-dimensional network of molecules. An extensive two-dimensional network of C—H···O hydrogen bonds and π···π interactions are responsible for crystal stabilization.

K e y w o r d s: 1,3,4-oxadiazole, piperazine ring, synthesis, X-ray crystallography, DFT.

INTRODUCTION

Substituted 1,3,4-oxadiazole derivatives are among various heterocycles that have received much attention due to their diverse range of bioactivities in the pharmaceutical field. It has been reported that compounds with the 1,3,4-oxadiazole ring structure show broad spectrum activities, including insecticidal [1], antibacterial [2, 3], antimycobacterial [4], antiproliferative [5], antiviral [6], anticancer [7], anti-convulsant [8], anti-inflammatory [9—12], and antimicrobial [13] activities.

5-(3,4-Dichlorophenyl)-3-{[4-(2-pyridyl)piperazine-1-yl)]methyl}-1,3,4-oxadiazole-2(3H)-one (**3**) was synthesized (Scheme 1). The structure of **3** was indicated by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. In order to obtain information about the stereochemistry of the molecules and to confirm the assigned structure, X-ray analysis was undertaken and the molecular structure was optimized at the B3LYP/6-31G(*d*,*p*) level using density functional theory (DFT).



Scheme 1. Synthesis of compound **3**

EXPERIMENTAL

Synthesis of 5-(3,4-dichlorophenyl)-1,3,4-oxadiazole-2(3H)one (2) [14]. Acid hydrazide (**1**) was prepared by the esterification of 3,4-dichlorobenzoic acid and followed by the reaction with hydrazine hydrate (98 %) in absolute ethanol for 6 h at room temperature [10]. 1,1′-Carbonyldiimidazole (CDI) (2.2 mmol) was added to a solution of hydrazide (2.2 mmol) and triethylamine (TEA) (2.2 mmol) in tetrahydrofuran (THF) (15 ml) at 0°C. The mixture was stirred for 20 h and concentrated in vacuo. The residue was dissolved in diethyl ether, washed with 2 M hydrochloric acid and saturated aqueous sodium bicarbonate, and dried over sodium sulfate. Filtration and recrystallization from ethanol-water gave the product. Yield: 61 %, m.p. 193.3 °C. **FT—IR:** (KBr, ν, cm^{-1}) 3059 (N—H), 3058 (C—H, aromatic), 2811 (C—H, aliphatic), 1843 (C=O), 1614 (C=N), 1552 (C=C, aromatic), 1241 (C—N). **^{1}H NMR:** ($CDCl_3$, δ ppm): 12.78 (bs, 1H, NH); 7.96 (d, 1H, dichlorophenyl H_2); 7.82 (d, 1H, dichlorophenyl H_6); 7.76 (dd, 1H, dichlorophenyl, H_5).

Synthesis of 5-(3,4-dichlorophenyl)-3-{[4-(2-pyridyl)piperazine-1-yl)]methyl}-1,3,4-oxadiazole-2(3H)-one (3). A mixture of 5-(3,4-dichlorophenyl)-1,3,4-oxadiazole-2(3H)one (**2**) (0.01 mol), 1-(2-pyridyl)piperazine (0.01 mol) and 37 % formaldehyde solution (1.5 ml) in ethanol (15 ml), was refluxed for 4 h. The precipitated crude product was filtered, washed with water, dried and crystallized from ethanol-water. Yield 72 %, m.p. 148.9°C. **FT—IR:** (KBr, ν, cm^{-1}) 3092 (C—H, aromatic), 2931 (C—H, aliphatic), 1771 (C=O), 1594 (C=N), 1559 (C=C, aromatic), 1244 (C—N), 1220 (C—O). **^{1}H NMR** ($CDCl_3$, δ ppm): 8.17 (d, 1H, 2-pyridyl, H_3); 7.93 (d, 1H, dichlorophenyl H_2); 7.66 (dd, 1H, dichlorophenyl, H_5); 7.55 (d, 1H, dichlorophenyl H_6); 7.47 (t, 1H, 2-pyridyl, H_6); 6.62 (m, 2H, 2-pyridyl, H_4, H_5); 4.78 (s, 2H, N—CH_2—N); 3.58 (t, 4H, piperazine, H_3, H_5); 2.87 (t, 4H, piperazine, H_2, H_6). **^{13}C NMR** (CDCl3, δ ppm): 159.43 (pyridyl C1); 154.14 (C=O); 151.54 (oxadiazole C_5); 148.17 (pyridyl C_3); 137.75 (pyridyl C_5); 136.29 (dichlorophenyl C_3); 133.91 (dichlorophenyl C_4); 131.40 (dichlorophenyl C_2); 127.68 (dichlorophenyl C_1); 124.94 (dichlorophenyl C_5); 123.76 (dichlorophenyl C_6); 113.73 (pyridyl C_4); 107.40 (pyridyl C_6); 67.91 (N—CH_2—N); 49.92 (piperazine, C_3, C_5); 45.29 (piperazine, C_2, C_6). **Anal.** (%) for $C_{18}H_{17}Cl_2N_5O_2$ (406.27) **Calcd.** C, 53.21; H, 4.22; N, 17.24. **Found:** C, 53.08; H, 4.08; N, 17.08.

Materials and measurements. All chemicals were supplied from Aldrich and Merck Chemicals Co. Melting points (°C) were determined using a Mettler Toledo FP62 capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Spectrum One series FT—IR apparatus (Version 5.0.1), using potassium bromide pellets; the frequencies were expressed in cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were recorded with a Varian Mercury-400 FT—NMR spectrometer, using tetramethylsilane as the internal reference, with chloroform-$CDCl_3$ as solvent; chemical shifts were reported in parts per million (ppm). Elemental analyses were performed on a LECO 932 CHNS instrument.

X-Ray diffraction analysis. A colorless single crystal of **3** suitable for data collection of the dimensions 0.37×0.33×0.32 mm^3 was selected and data collection was performed on a STOE IPDS II diffractometer with graphite monochromated MoK_α radiation (λ = 0.71073 Å) at 296 K. The molecular formula is $C_{18}H_{17}Cl_2N_5O_2$, the formula weight is M_r = 406.27, the symmetry is triclinic, the space group is *P*-1 with the unit cell parameters a = 6.1061(3) Å, b = 9.2445(5) Å, c = 16.927(1) Å, α = = 77.400(5)°, β = 89.523(5)°, γ = 77.799(4)°, V = 910.70(9) $Å^3$, Z = 2, D_{calc} = 1.482 g/cm^3. Data collection: Stoe X-AREA [15]. Cell refinement: Stoe X-AREA [15]. Data reduction: Stoe X-RED [15]. The measurement method is θ/2θ-scanning ($2\theta_{max}$ = 52°). The structure was solved by direct methods using SHELXS-97 [16] and refined by full-matrix least-squares methods on F^2 using SHELXL-97 [16] from within the WINGX [17] suite of software. Out of 3578 independent reflections, 2875 $I > 2\sigma(I)$ were used in the refinement. The final least-square cycle of the refinement gave R_1 = 0.038, wR_2 = 0.096 and GOOF = 1.03. Final cycles of the refinement resulted in a residual electron density in the range from –0.30 to 0.23 e/$Å^3$. All non-hydrogen atoms were refined with anisotropic parameters. Hydrogen atoms bonded to carbon were refined using a riding model, with C—H =

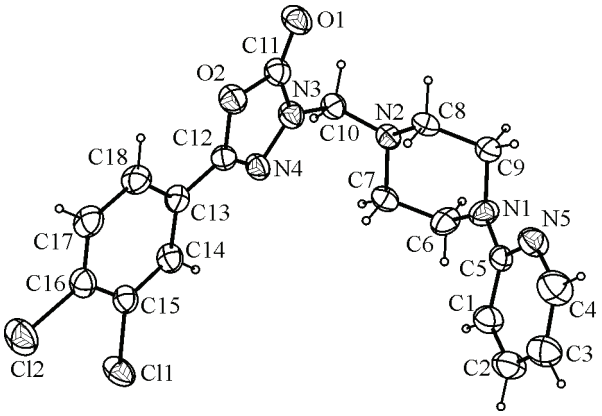


Fig. 1. Independent part of the structure of **3**

= 0.93—0.97 Å. The constraint $U_{iso}(H) = 1.2U_{eq}$ (C and CH_2) was applied. Molecular drawing was obtained using ORTEPIII [18]. Full crystallographic data were deposited with Cambridge Crystallographic Database; CCDC deposition number 803372.

Computational procedure. The geometry optimization of **3** leading to energy minima was achieved using the B3LYP hybrid exchange-correlation functional with the 6-31G(*d*,*p*) basis set [19, 20] by Berny′s method [21, 22]. The calculations were started from the crystallographically achieved geometries of the molecule. All calculations in this work were carried out using the GAUSSIAN03W package [23] and the Gauss View Molecular Visualization Program [24]. The optimized molecular geometry, total molecular energy, dipole moment, and Mulliken charges were obtained from the computational process.

RESULTS AND DISCUSSION

The molecular structure of **3** and the atom labeling scheme are shown in Fig. 1. The molecule is not planar. The N(3)—C(10)—N(2) angle is 116.69(14)°. The C(15)—Cl(1) and C(16)—Cl(2) bond lengths are 1.7253(17) Å and 1.7192(18) Å, similar to the corresponding bond lengths [14]. The N(4)—C(12) and N(3)—N(4) bond distances are similar to the corresponding distances in related structures [25, 26]. The C(11)—O(1) bond length of 1.204(2) Å is consistent with significant double-bond character of these bonds. The phenyl, 1,3,4-oxadiazole, and pyridine rings are essentially planar, the respective maximum deviations from the least-squares planes being 0.0053(12) Å for the C(15) atom, 0.0074(10) Å for the N(4) atom, and 0.0068(13) Å for the C(5) atom, whereas the piperazine ring exhibits a puckered conformation with puckering parameters [27] Q = 0.5731(19) Å, θ = 178.66(20)°, and φ = 269(6)°, which indicates that the piperazine ring has a *chair* conformation. The dihedral angle between the mean planes of phenyl and 1,3,4-oxadiazole rings is 3.71(12)°. The selected bond lengths, bond angles, and torsion angles are given in Table 1.

The compound contains two intermolecular hydrogen bonds. Firstly, the C(10) atom in the asymmetric unit acts as a hydrogen-bond donor, via H(11A) connecting this molecule to O(1) in a symmetry related molecule at (–1+*x*, *y*, *z*), forming a C(5) chain [28] running parallel to the [100] direction. Secondly, the C(17) atom acts as a hydrogen-bond donor via the H(18) atom to the O(1) atom in a symmetry related molecule at (2–*x*, 1–*y*, 1–*z*), so forming a centrosymmetric $R_2^2(16)$ ring centered at (0, 1/2, 1/2). The combination of these two C—H···O hydrogen bonds produces $R_4^2(20)$ rings running parallel to the [100] direction (Fig. 2). Details of this interaction are given in Table 2.

Table 1

Bond lengths (Å) *and bond angles* (deg.) *for* **3**

Parameter	X-ray	DFT	Parameter	X-ray	DFT	Parameter	X-ray	DFT
C(15)—Cl(1)	1.725(2)	1.746	C(11)—O(1)	1.204(2)	1.205	N(3)—C(10)—N(2)	116.69(14)	117.03
C(16)—Cl(2)	1.719(2)	1.743	N(3)—N(4)	1.386(2)	1.380	C(18)—C(13)—C(12)	121.07(15)	120.72
N(4)—Cl(2)	1.286(2)	1.295	O(2)—C(12)	1.369(2)	1.367	N(1)—C(5)—N(5)	116.36(15)	116.14
N(2)—C(7)	1.459(2)	1.462	N(2)—C(8)	1.458(2)	1.466			
N(1)—C(6)	1.449(2)	1.457	N(1)—C(9)	1.458(2)	1.466			

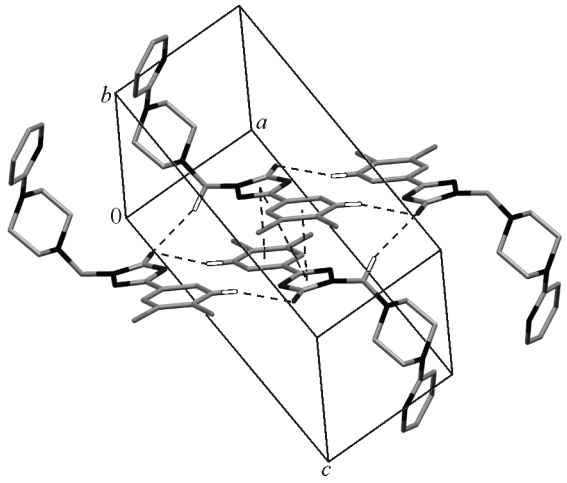


Fig. 2. Part of the crystal structure of **3**, showing the formation of $R_4^2(20)$ rings.

C—H···O hydrogen bonds and π···π interactions are indicated by dashed lines. For clarity, H atoms not involved in the motif shown have been omitted

Compound **3** also contains four intermolecular π···π interactions. In the first, the π···π contact occurs between the two symmetry-related 1,3,4-oxadiazole rings of the neighboring molecules. In the second, the π···π contact occurs between the two symmetry-related phenyl rings of the neighboring molecules. Finally, two intermolecular π···π contacts occurs between the two 1,3,4-oxadiazole and phenyl rings. Details of these interactions are given in Table 3. The π···π interactions produce a chain running parallel to the [010] direction (Fig. 2).

With a view to determining the structure of the molecule, the application of theoretical methods has proven to be advantageous. For this purpose, DFT calculations were performed giving the total energy and the dipole moment of the optimized geometry as –2040.767 Hartree and 2.2621 Debye.

When the X-ray structure of the title compound is compared to the calculated lowest energy structure of **3**, a conformational discrepancy is observed between them. The dihedral angles between the mean planes of phenyl (A), 1,3,4-oxadiazole (B), and pyridyl (C) rings are 3.71(12)° (A/B), 63.74(07)° (B/C), and 66.14(06)° (A/C) for X-ray; 0° (A/B), 79.67° (B/C), and 79.85° (A/C) for DFT. The selected bond distances, bond and torsion angles from the X-ray crystallographic and computational results are compared in Table 1. There are no significant differences between the experimental and DFT calculated geometric parameters. The maximum deviations between the experimental and calculated parameters are 0.022 Å for the bond lengths and 0.2° for the bond angles. These deviations originate from DFT calculations that ignore inter- and intramolecular interactions. While the experimental results belong to the solid phase, the theoretical calculations belong to the gas phase.

Table 2

Parameters of the hydrogen bonds for **3**

D—H···A	*d*(D—H)	*d*(H…A)	∠DHA	*d*(D…A)	Symmetry operations
C(10)—H(11A)···O(1)	0.97	2.58	3.493(2)	156	–1+*x*, *y*, *z*
C(17)—H(18)···O(1)	0.93	2.55	3.396(2)	151	2–*x*, 1–*y*, 1–*z*

Table 3

Parameters of the π···π *interactions for* **3**

Cg(I)	Cg(J)	Cg—Cg	Perpendicular distance	Symmetry operations
Cg(1)	Cg(1)	3.3486(9)	3.461	1–*x*, 1–*y*, 1–*z*
Cg(4)	Cg(1)	3.7185(10)	3.446	1–*x*, 1–*y*, 1–*z*
Cg(4)	Cg(4)	4.0097(10)	3.649	1–*x*, –*y*, 1–*z*

Cg(1): N3—N4—C12—O2—C11, Cg(4): C13—C14—C15—C16—C17—C18.

CONCLUSIONS

In this study, we have synthesized and characterized 5-(3,4-dichlorophenyl)-3-{[4-(2-pyridyl)piperazine-1-yl)]methyl}-1,3,4-oxadiazole-2(3H)-one by IR, ^{1}H NMR, ^{13}C NMR, elemental analyses, single-crystal X-ray diffraction, and the molecular structure has also been optimized at the B3LYP/6-31G(*d*,*p*) level using density functional theory (DFT).

In the solid state, the crystal structure is stabilized by two intermolecular C—H···O hydrogen bonds and four π···π interactions. However, the theoretical calculations belong to the gaseous phase. Consequently, the X-ray structure is found to be very slightly different from its optimized counterparts. Despite these differences, the general agreement is good and the theoretical calculations support the solid state structures.

REFERENCES

1. *Sawada Y., Yanai T., Nakagawa H. et al.* // Pest Manag. Sci. – 2003. – **59**, N 9. – P. 49.
2. *Bernardino A.M.R., Gomes A.O., Charret K.S.A. et al.* // Eur. J. Med. Chem. – 2006. – **41**, N 1. – P. 80.
3. *Misra H.K.* // Arch. Pharm. – 2006. – **316**. – P. 487.
4. *Macaev F., Rusu G., Pogrebnoi S. et al.* // Bioorg. Med. Chem. – 2005. – **13**, N 16. – P. 4842.
5. *Jin L., Chen J., Song B. et al.* // Bioorg Med. Chem. Lett. – 2006. – **16**, N 19. – P. 5036.
6. *Tan T.M.C., Chen Y., Kong K.H. et al.* // Antiviral Res. – 2006. – **71**, N 1. – P. 7.
7. *Patole J., Sandbhor U., Padhyde S. et al.* // Bioorg. Med. Chem. Lett. – 2003. – **13**, N 1. – P. 51.
8. *Almasirad A., Tabatabai S.A., Faizi M. et al.* // Bioorg. Med. Chem. Lett. – 2004. – **14**, N 24. – P. 6057.
9. *Chohan Z.H., Pervez H., Khan K.M. et al.* // Enzyme Inhib. Med. Chem. – 2005. – **20**, N 1. – P. 81.
10. *Mullican M.D., Wilson M.W., Connor D.T. et al.* // J. Med. Chem. – 1993. – **36**, N 8. – P. 1090.
11. *Amir M., Kumar S.* // Acta Pharm. – 2007. – **57**. – P. 31.
12. *Frank P.V., Girish K.S., Kalluraya B.* // J. Chem. Sci. – 2007. – **119**. – P. 41.
13. *Mishra P., Rajak H., Mehta A.* // J. Gen. Appl., Microbiol. – 2005. – **51**. – P. 133.
14. *Koksal M., Bilge S.S., Bozkurt A. et al.* // Arzneimittel-Forschung (Drug Research) – 2008. – **58**, N 10. – P. 510.
15. *Stoe* & Cie, X-AREA (Version 1.18.) and X-RED32 (Version 1.04.). Stoe & Cie, Germany, Darmstadt, 2002.
16. *Sheldrick G.M.* // Acta Crystallogr. – 2008. – **A64**. – P. 112.
17. *Farrugia L.J.* // J. Appl. Cryst. – 1999. – **32**. – P. 837.
18. *Farrugia L.J.* // J. Appl. Cryst. – 1997. – **30**. – P. 565.
19. *Becke A.D.* // J. Chem. Phys. – 1993. – **98**. – P. 5648.
20. *Lee C., Yang W., Parr R.G.* // Phys. Rev. B. – 1988. – **37**. – P. 785.
21. *Schlegel H.B.* // J. Comput. Chem. – 1982. – **3**. – P. 214.
22. *Peng C., Ayala P.Y., Schlegel H.B. et al.* // J. Comput. Chem. – 1996. – **17**. – P. 49.
23. *Frisch M.J., Trucks G.W., Schlegel H.B. et al.* GAUSSIAN-03, Revision E.01. – Gaussian, Inc., Pittsburgh, PA, 2003.
24. *Frisch A., Dennington R. II, Keith T. et al.* GAUSSVİEW, reference, vol 4.0. – Gaussian Inc, Pittsburgh, 2007.
25. *Thiruvalluvar A., Subramanyam M., Lingappa B. et al.* // Acta Crystallogr. – 2007. – **E63**. – P. o3425.
26. *Jasinski J.P., Butcher R.J., Mayekar A.N. et al.* // J. Chem. Crystallogr. – 2009. – **39**. – P. 761.
27. *Cremer D., Pople J.A.* // J. Amer. Chem. Soc. – 1975. – **97**. – P. 1354.
28. *Bernstein J., Davis R.E., Shimoni L. et al.* // Angew. Chem. Int. Ed. Engl. – 1995. – **34**. – P. 1555.