SYNTHESES AND CRYSTAL STRUCTURES OF 5-METHYL-1-(2-OXO-2-(P-TOLYL)ETHYL)-1,6A-DIHYDROPYRROLO[3,4-D][1,2,3]TRIAZOLE-4,6(3AH,5H)-DIONE

M.P. Savithri[1], R. Raja[2], S. Logalakshmi[3], G. Puthilibai[3*]
[1]PG and Research Department of Physics, Queen Mary's College, Chennai-600004, Tamil Nadu, India
[2]Department of Physics Thiruthangal Nadar College, Chennai-600051, Tamil Nadu, India
[3, 3*]Department of Chemistry, Sri sairam engineering College, Chennai- 600017

Corresponding Author Mail: savithriphysics@gmail.com

Abstract

In the title compound, $C_{14}H_{14}N_4O_3$, the 5-methyl-1-(2-oxo-2-(p-tolyl)ethyl)-1,6a-dihydropyrrolo[3,4-d][1,2,3] triazole-4,6(3aH,5H)-dione is a significant example of a novel heterocyclic structure with promising pharmacological potential. This molecule features a fused heterocyclic core, combining a pyrrolo[3,4-d][1,2,3]triazole framework with a dione functionality, which is critical for its biological activity and chemical reactivity. The core of the molecule is a fused heterocyclic system, comprising a pyrrole ring fused to a triazole ring. The fusion occurs at the 3,4-position of the pyrrole ring, creating a rigid, planar structure conducive to stacking interactions in biological systems. The molecule is further substituted at the nitrogen atom (position 1) with a methyl group and a 2-oxo-2-(p-tolyl)ethyl side chain, which introduces additional sites for hydrogen bonding and hydrophobic interactions. The central dihydropyrrole ring (N1-N2-N3-C9-C10) makes dihedral angles of 64.08(10)° and 84.22(10)° with the triazole ring (C9-C12-N3-C9-C10) and benzene ring (C1-C6), respectively. The introduction of the triazole group allows the formation of intermolecular interaction C-H…O hydrogen bonds, used to build centrosymmetric $R^2_2(8)$ ring motifs.

Keywords: dihydropyrrole; triazole: intermolecular hydrogen bonds; crystal structure.

1. Introduction

Chalcones have a wide range of biological activities and have antiviral, antibacterial, antiprotozoal, insecticidal and immunosuppressive [1,2,3] properties. 1,2,3-Triazoles are interesting heterocycles that have major applications in biotechnology and in particular in drug discovery [4,5]. Heterocycles containing a 1,2,3-

triazole ring system have been used in the treatment of cancer cells [6]. In addition, heterocycles having pyrazole moieties have antimicrobial, anticancer, anti-inflammatory, antidepressant, antioxidant and herbicidal properties [7]. Organic azides have recently been playing a significant role in the preparation of heterocyclic scaffolds of triazoles. We are currently witnessing a great progress in research and development of new anti-tumor therapeutic agents. Nevertheless, cancer remains the second most frequent cause of death in the world and the problem is far from being solved [8]. Cancer is a systemic disease and both its internal metabolic and genetic aberrations as well as the efficiency of immunologic protection play a role in tumor development and progression [9]. Chronic inflammation, redox imbalance, metabolic dysfunctions and altered glucose metabolism as well as many other endogenous and exogenous factors play roles in disease biology and define outcomes [10,11,12]. This heterogeneity of cancer requires the application of various approaches to prevention and treatment that may include application of specific small molecules interfering with altered metabolic pathways in cancers, modulation of immune response to transformed cells and precision medicine [13,14,15]. Therefore, the search for novel small molecules capable to modulate selectively metabolic processes including redox regulation remains of significant scientific and practical importance.

2. Materials and methods

2.1. General Information

Melting points were measured in open capillary tubes on a BÜCHI B-545 melting point apparatus (BÜCHI Labortechnik AG, Flawil, Switzerland) and are uncorrected. The elemental analyses (C, H, N) were performed using the Perkin–Elmer 2400 CHN analyzer (PerkinElmer, Waltham, MA, USA) and were within ±0.4% of the theoretical values. The 500 MHz-^{1}H and 126 MHz-^{13}C spectra were recorded on Bruker AVANCE-500 spectrometer and 2D spectra were recorded on a Bruker AVANCE-600 spectrometer (Bruker, Bremen, Germany). All spectra were recorded at room temperature except were indicated otherwise and were referenced internally to solvent reference frequencies. Chemical shifts (δ) are quoted in ppm and coupling constants (J) are reported in Hz. LC-MS spectra were obtained on a Finnigan MAT INCOS-50 (Thermo Finnigan LLC, San Jose, CA, USA). Solvents and reagents that are commercially available were used without further purification.

2.2. Preparation and Characterization of Compounds

In a 50 mL round bottom flask, substituted phenacyl azides (0.5 mmol) was dissolved in acetonitrile (5 mL) followed by the addition of substituted maleimides (0.5 mmol) and the mixture was stirred at reflux temperature for 4 hours. Next, the reaction mixture was concentrated under reduced pressure and extracted with ethyl acetate/water. The organic layer was dried over anhydrous sodium sulphate and concentrated in a vacuum to yield the crude product purified by column chromatography using ethyl acetate/n-hexane (1:4) as eluent. The resulting precipitate was collected by filtration, thoroughly washed to remove any remaining impurities, and dried under reduced pressure to eliminate traces of solvent. Final purification was achieved by recrystallizing the crude product from warm ethanol solution, affording the desired pyrrole derivative with 75% yield.

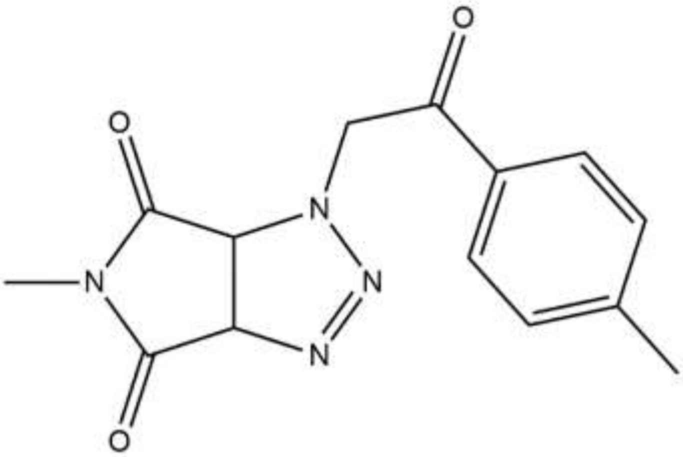

Fig. 1. Scheme

Data Collection

A yellow lath crystal (MeOH) of 0.24 × 0.13 × 0.03 mm was used to record 9342 (Cu Ka-radiation, θ_{max} = 76.52°) intensities on a Super Nova Dual Atlas diffractometer (Rigaku, Oxford, UK) [16] using mirror monochromatized Cu Kα radiation from a high-flux microfocus source (λ = 1.54178 Å). Accurate unit cell parameters were determined by least-squares techniques from the θ values of 3457 reflections, θ range 4.48–76.30°. The data were corrected for Lorentz polarization and for absorption effects [16]. The 1850 total reflections (R_{int} = 0.034) were used for structure determination.

2.3. Structure Solution and Refinement

The structure was solved was solved by dual-space algorithm (SHELXT) [17], and refined against F^2 for all data (SHELXL-97) [18]. The positions of the H atom bonded to N atom were obtained from the difference Fourier map and were refined freely. The remaining H atoms were placed geometrically in calculated positions and were refined with a riding model, with C–H = 0.99 Å (CH_2), 1.00 Å (Csp^3H), 0.95 Å (Csp^2H) and Uiso(H) = 1.2Ueq(C). Final refinement converged with R = 0.0305 (for 1639 data with $F^2 > 4\sigma(F^2)$), wR = 0.0836 (on F^2 for all data), and S = 1.105 (on F^2 for all data). The largest difference peak and hole was 0.322 and −0.250 eÅ^3. The molecular illustrations were drawn using ORTEP-3 for Windows [19]. Software used to prepare material for publication was WINGX [19], OLEX [20] and PLATON [21].

3. Structural Commentary

The molecular structure of title compound is displayed in Fig.2. The core architecture of this compound consists of a fused heterocyclic system that integrates a pyrrolo[3,4-d][1,2,3]triazole ring with a dione functional group. The C9-C12/N3 triazole ring system is almost planar (r.m.s deviation = 0.012 Å) and makes a dihedral angle with the pendant benzene ring system of 41.03(10)°. As expected, the N atom of thiazole ring demonstrates noticeable inequality of C-N bond distances [1.380 (2) Å for C11-N4 versus 1.381(2) Å for C12-N4] corresponding to the presence of single and double bonds.

3.1 Supramolecular features

In the crystal, the molecules are linked by a dimer with an $R^2_2(8)$ ring motif through pairwise C10-H10...O3 hydrogen bonds (Fig. 3). In the crystal, extended structure of title compound, the molecules are linked through C-H…O hydrogen bonds (Table 3), forming zigzag ribbons propagating along the [010] direction, generating successive $R^2_2(9)$ ring motifs (Fig. 4).

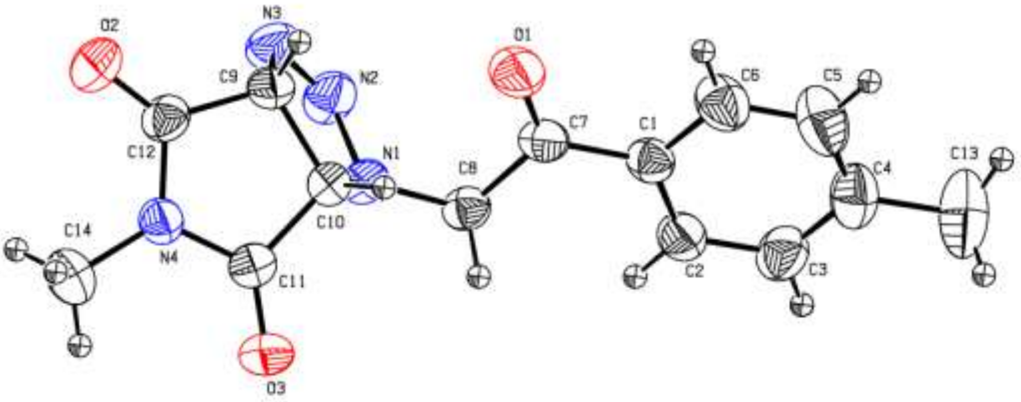

Fig. 2. The molecular structure of the title compound, with atom labels and 50% probability displacement ellipsoids.

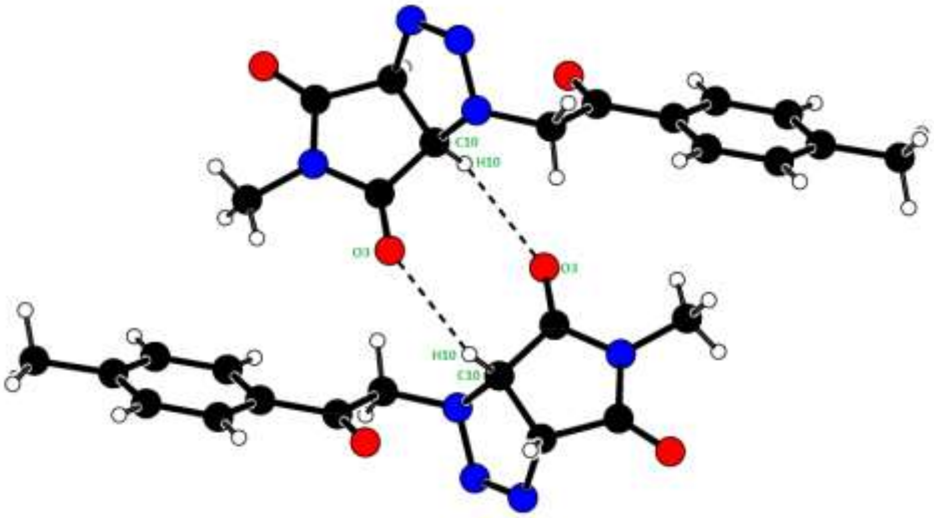

Fig. 3. In the crystal, centrosymmetric dimers linked by pairwise C-H…O hydrogen bonds generate $R^2_2(8)$ loops.

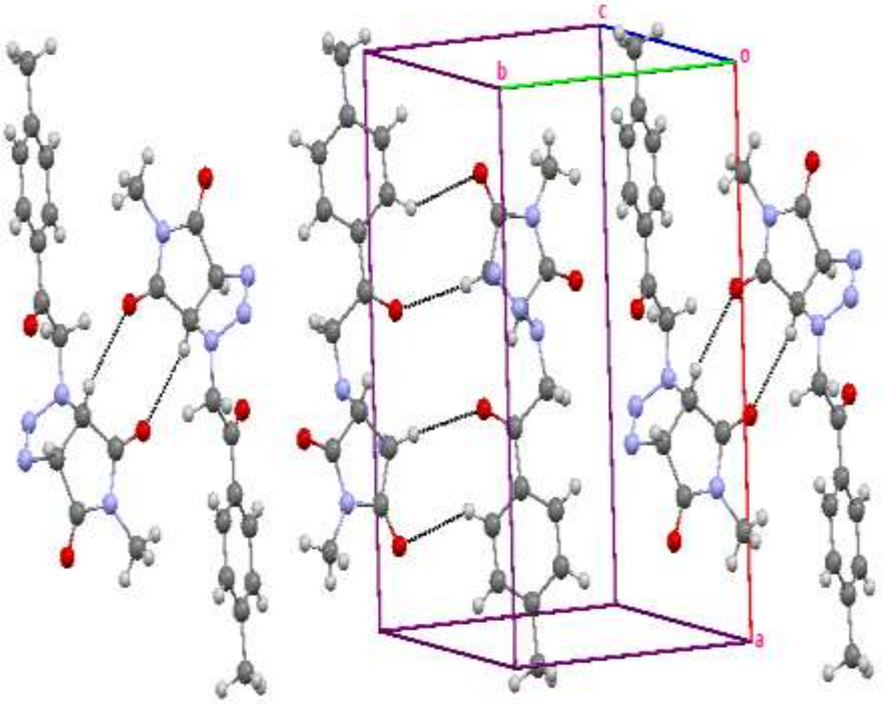

Fig. 4. Part of the crystal structure viewed along the [010] direction. Hydrogen bonds are shown as dashed lines

Table 1 The selected Bond length (Å) and Bond angles (˚)

Atom	Length(Å)	Atom	Angles(°)
O1-C7	1.218(2)	N2-N1-C8	115.03(2)
N1-C8	1.450(3)	N1-N2-N3	114.9(2)
N4-C11	1.380(2)	C11-N4-C14	123.57(2)
C1-C6	1.383(2)	C2-C1-C7	122.44(2)
C4-C5	1.377(2)	C2-C3-C4	121.66(2)
C9-C10	1.514(2)	C5-C4-C13	121.3(2)
O2-C12	1.205(3)	O1-C7-C1	121.93(2)
N1-C10	1.464(2)	O3-C11-N1	113.24(2)
N4-C12	1.381(2)	C10-C9-C12	105.46(2)
C1-C7	1.479(2)	C9-C10-C11	104.81(2)
C4-C13	1.509(3)	N4-C11-C10	108.32(2)
C9-C12	1.509(2)	N4-C12-C9	107.95(2)
O3-C11	1.208(2)	N2-N1-C10	109.58(2)
C6-C7	1.445(7)	C(3)-C(2)-C(1)	122.1(4)

Table 2 Crystal Data and Details of the Structure Determination

Parameters	**Title of compound**
Empirical formula	C14 H14 N4 O3
Formula weight	286.29
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21/c
Unit cell dimensions	a = 13.987 (10) Å, α= 90°.
	b = 9.737 (6) Å, β= 92.901 (13)°.
	c = 10.402 (6) Å, γ = 90°.
Volume	1414.9
Z	4
Density (calculated)	1.344 cm^{-3}
Absorption coefficient	0.098 mm^{-1}
F(000)	600
Crystal size	0.32 x 0.22 x 0.18 mm^{3}
Theta range for data collection	2.5 to 30.5°.
Index ranges	-19<=h<=19, -13<=k<=13, -14<=l<=14
Reflections collected	4313
Independent reflections	2213 [R(int) = 0.063]
Completeness to theta = 24.99°	89.10%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7486 and 0.6077
Refinement method	Full-matrix least-squares on F^{2}
Data / restraints / parameters	4313 / 0 / 193
Goodness-of-fit on F2	1.01
Final R indices [I>2sigma(I)]	R1 = 0.0592, wR2 = 0.1599
R indices (all data)	R1 = 0.063, wR2 = 0.1973
Largest diff. peak and hole	0.24, -0.19 e.Å^{-3}

Table 3 Hydrogen-bond geometry (Å ,°).

D-H…A	D-H	H…A	D…A	D-H…A
C10-H10…O3	0.98	2.47	3.249	136

Symmetry code: i = 1-x,1-y,1-z

4. Acknowledgment

The authors thank to the Director, CSIR-NEIST, Jorhat,Assam, India, for his keen interest in this work.

References

1. Katsori, A. M. & Hadjipavlou-Litina, D. (2011). Expert Opin. Ther. Pat. 21, 1575-1596.
2. Matos, M. J., Vazquez-Rodriguez, S., Uriarte, E. & Santana, L. (2015). Expert Opin. Ther. Pat. 25, 351-366.
3. Repanas, A., Katsori, A. M. & Hadjipavlou-Litina, D. (2013). Mini Rev. Med. Chem. 13, 952-970.
4. Totobenazara, J. & Burke, A. J. (2015). Tetrahedron Lett. 56, 2853-2859.
5. Dheer, D., Singh, V. & Shankar, R. (2017). <i>Bioorg. Chem. 71, 30-54.
6. Yadav, P., Lal, K., Kumar, A., Guru, S. K., Jaglan, S. & Bhushan, S. (2017). Eur. J. Med. Chem. 126, 944-953.
7. Ansari, A., Ali, A., Asif, M. & Shamsuzzaman, S. (2017). New J. Chem. 41, 16-41.
8. The global challenge of cancer. *Nat. Cancer* 2020, *1*, 1–2.
9. Gonzalez, H.; Hagerling, C.; Werb, Z. *Genes Dev.* 2018, *32*, 1267–1284.
10. Piotrowski, I.; Kulcenty, K.; Suchorska, W. *Rep. Pract. Oncol. Radiother* 2020, *25*, 422–427.
11. Čipak Gašparović, A. *Antioxidants (Basel)* 2020, *9*, 157.
12. Cherkas, A.; Zarkovic, N. *Antioxidants (Basel)* 2018, *7*, 118.
13. Deng, X.; Nakamura, Y. *Trends Pharmacol. Sci.* 2017, *38*, 15–24.
14. Milkovic, L.; Zarkovic, N.; Saso, L. *Redox. Biol.* 2017, *12*, 727–732.
15. Jaganjac, M.; Milkovic, L.; Sunjic, S.B.; Zarkovic, N. *Antioxidants (Basel)* 2020, *9*, 1151.
16. *Rigaku Oxford Diffraction, Crysalis-Pro Software System*; Version 1.171.38.41; Rigaku Corporation: Oxford, UK, 2015.
17. Sheldrick, G.M. SHELXT-Integrated space-group and crystal-structure determination. *Acta Cryst. A* 2015, *71*, 3–8.
18. Sheldrick, G.M. Crystal structure refinement with SHELXL. *Acta Cryst.* 2015, *C71*, 3–8.
19. Farrugia, L.J. WinGX and ORTEP for windows: An update. *J. Appl. Cryst.* 2012, *45*, 849–854.
20. Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. OLEX2: A complete structure solution, refinement and analysis program. *J. Appl. Cryst.* 2009, *42*, 339–341.
21. Spek, A.L. Structure validation in chemical crystallography. *Acta Cryst.* 2009, *65*, 148–155.