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Synthesis and Density Functional Theory Analysis of Pyrazole Integrated Pyrimidinetrione

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Abstract*: A pyrazole integrated pyrimidinetrione 6 has been synthesized and its structure has been established employing physical and analytical techniques such as IR and NMR spectroscopy. Further, density functional theory studies such as geometry optimization, FMOs, MEP, Mulliken population and NLO analyses of the synthesized compound 6 have been carried out using DFT – B3LYP [6-311++G(d,p)] method and the results obtained have been discussed.

Keywords: Pyrazole, Barbituric acid, Density Functional Theory

I. INTRODUCTION

Pyrazole is a heterocyclic compound that has two adjacent nitrogen atoms with three carbon atoms in a five membered ring. Infact, Pyrazoles is the key unit present in the skeletal ring of hemoglobin. Pyrazoles hold stream of biological potencies such as antimicrobial, anti-inflammatory, antifungal, antiviral, and antitumor activities [1-5] due to its better ADME properties. In recent days, pyrazole has engrossed the interest of pharmacological industries as a leading compound in numerous drug discovery and development, particularly, in the field of cancer therapy [6]. The compound 7 - (1 - (m–chlorophenyl)–3-(p-methoxyphenyl)-1H-pyrazol-4-yl)-5-oxo-2-p-tolyltriazolo[1, 5-a]-pyridine-6,8-dicarbonitrile was reported to display anticancer potency against SW-620 cell line (colon) with GI50 of 0.52 µM, also found to be active against cell lines of renal cancer viz., RXF 393 and A498 with GI50 of 0.86 and 0.58µM, respectively.[7] Besides their varied biological activities, they also find applications in agrochemicals, and serve as luminophores and fluorophores [8-15]. Certain pyrazole nopionone derivatives were reported to emit strong blue fluorescence in ethanol and were found to detect the copper sulfate pentahydrate (≥99%) content (100.57%) with a RSD of 1.98%. [16]

On the other hand, barbiturates are closed chain ureic compounds used in treatment of sleep disorders and for the management of epileptic seizures. Specifically, oxybarbiturates, continues to be the selected drugs in the treatment of insomnia and in some types of epilepsy. Sodium pentothal has been used as an intravenous anesthetic with fast recovery and no side effects. [17] From the literature, barbiturates demonstrate a various biological/ pharmacological applications including anesthesia, anticonvulsant, sedation, anxiolytic, hypnosis, antioxidant, antifungal, antibacterial, anticancer, anti-osteroporosis and inhibition of aminotransferase, alpha-glucosidase, diaminopimelate and tyrosine. [18-26] Apart from biological applications of barbiturates, they are reported to show NLO properties. [27] Chitosan-barbiturate (Ch-Ba) derivatives were stated to be used in the preparation of gel polymer electrolytes as a host polymer [28].

Based on the diverse range of applications revealed by pyrazole and barbituric acid, we proposed to synthesize a molecule by tailoring both heterocyclic structural motifs. The synthesized compound was then confirmed using IR and NMR techniques. Further, various theoretical studies have been performed utilizing DFT method.

II. EXPERIMENTAL SECTION

A. Materials and methods

All the solvents and reagents were either purified by adopting general purification methods or analytical reagent grade were utilized. The reported MPs were measured in open capillaries. Infrared (FT-IR) spectrum (KBr pellet) was recorded on Shimadzu spectrophotometer (IR Tracer-100). NMR spectra were recorded using Bruker spectrometer with DMSO-d_6 as a solvent.

B. Synthesis of carbaldehyde 4 [29]

A mixture of ketone **1** (0.01 mol) and hydrazine **2** (0.01 mol) in glacial acetic acid (10 mL) was heated for 30 minutes. It was filtered after cooling. The solid thus obtained was rinsed with dilute hydrochloric acid solution. Then the solid was purified through recrystallization using ethanol.

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The pure hydrazone **(3)** thus obtained was treated with Vilsmeier-Haack reagent [DMF (10 ml)-$POCl_3$ (0.03 mol)] at 0 °C and it was stirred at 70-80 °C for 6h. It was then allowed to attain ambient temperature and poured in to water. The solid was filtered, after neutralization with $NaHCO_3$ (saturated), and recrystallized, after washed with water and dried, to afford pure product 4 in 78% yield.

C. Synthesis of pyrazolylpyrimidinetrione 6.

A 1:1 mixture of **4** (0.3 g, 0.91 mmol) and barbituric acid (0.1 g, 0.91 mmol) in the presence of benzyltriethylammonium chloride (0.01 g, 5 mol%) in ethylene glycol (10 ml) was heated at 100 °C for 4h. After completion, it was cooled, poured into water and the solid thus obtained was washed with hot ethanol, after filtration, to furnish the target **6** in a pure form.

Yield: 0.29 g (73%), MP. 252-254 °C. IR (KBr, cm^{-1}): 3342.6, 3174.8, 3057.2, 2831.5, 1666.5, 1566.2, 1394.5, 1342.5, 1211.3, 854.9, 796.6, 719.5, 686.7, 584.3, 511.1; ^1H NMR(400 MHz, DMSO-d_6): δ 11.37 (s, 1H), 11.34, (s, 1H), 9.79 (s, 1H), 8.13 (s, 1H), 7.94 (d, J=7.60Hz, 2H), 7.85 (s, 1H), 7.79 (d, J=7.60Hz, 1H), 7.61-7.55 (m, 4H), 7.50-7.47 (m, 1H), ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.0, 163.1, 156.7, 150.7,143.3, 139.0, 135.1, 133.6, 132.7, 132.3, 131.5, 130.4, 129.1, 128.7, 122.6, 120.2, 115.7, 115.4

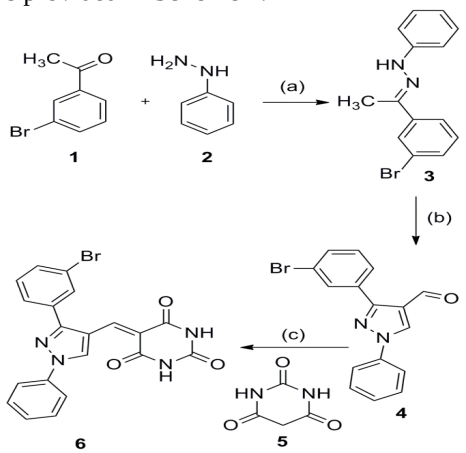
D. Computational procedure

Computational studies were executed with the help of Gaussian 09W [30] software package. Using Berny method [31] with hybrid function B3LYP [6-311++G(d,p)], density function theory was adopted for all theoretical calculations. The structural and energy parameters such as optimized molecular geometry, molecular orbital descriptions HOMO, LUMO, electron density, MEP and NLO properties of **6** were obtained from the computational calculations.

III. RESULT AND DISCUSSION

A. Synthesis

The target molecule **6** has been synthesized through multi-step synthesis and the schematic representation for the synthesis is provided in **Scheme 1**.



Scheme 1: Synthesis of target molecule 6. Reagents and conditions: (a) Glacial acetic acid, reflux, 30 min; (b) DMF-$POCl_3$, 70-80 °C, 6h; (c) Benzyltriethylammonium chloride, ethylene glycol, 100 °C, 4h.

The key intermediate, carbaldehyde **4** has been synthesized from the ketone **1** by condensation with hydrazine **2** followed by cyclization and formylation reactions. The target molecule **6** has been eventually synthesized by the condensation of **4** with **5** in the presence of phase transfer catalyst. The structure of the target **6** has been established based on physical and spectral data.

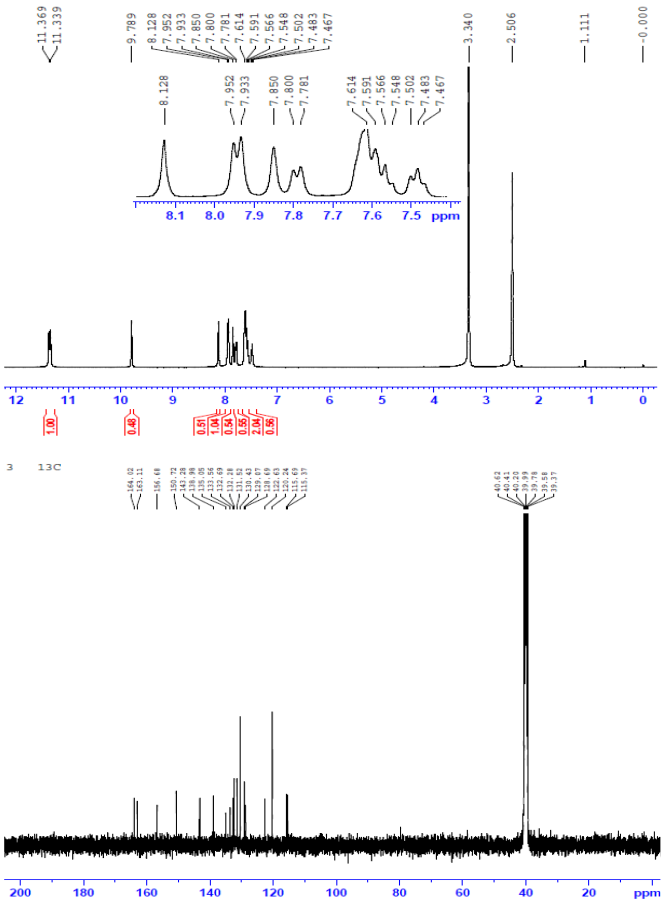


Fig. 1: ^1H and ^{13}C NMR spectrum of the title molecule 6.

B. Optimized geometry

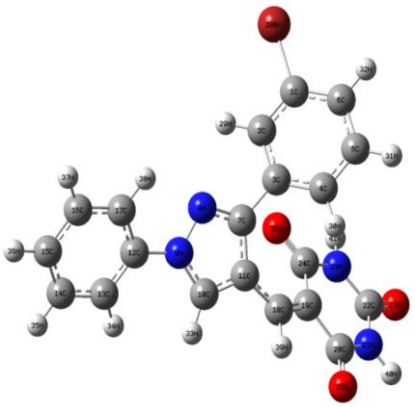


Fig. 2: Optimized geometry of the target molecule 6.

The optimized structure of pyrazole based pyrimidinetrione 6 was accomplished and it is provided in Fig. 2. The parameters viz., bond length, bond angle and dihedral angle values are listed in Tables I & II. The lengths of C-N bonds of pyrazole ring are found to be 1.3244 Å (C7-N8) and 1.3499 Å (C10-N9) which lie intermediary between the C-N single (1.443 Å) and double (1.269 Å) bonds signifying electron delocalization. The bond angles of C11-C18-C19, N8-N9-C12 and C3-C7-N8 are 132.5, 120.09 and 118.83 degrees, respectively.

Table-I: Bond length of the title compound 6.

Bondlength	(Å)	Bondlength	(Å)
C1-C2	1.3873	C13-C14	1.3916
C1-C6	1.3916	C13-H34	1.0828
C1-Br28	1.92	C14-C15	1.3928
C2-C3	1.4002	C14-H35	1.0837
C2-H29	1.0807	C15-C16	1.3938
C3-C4	1.3986	C15-H36	1.0835
C3-C7	1.4736	C16-C17	1.3905
C4-C5	1.391	C16-H37	1.0837
C4-H30	1.083	C17-H38	1.0809
C5-C6	1.3929	C18-19	1.3597
C5-H31	1.0841	C18-H39	1.0889
C6-H32	1.082	C19-C20	1.4901
C7-N8	1.3244	C19-C24	1.4792
C7-C11	1.4407	C20-N21	1.3911
N8-N9	1.3592	C20-O25	1.2152
N9-C10	1.3499	N21-C22	1.3894
N9-C12	1.424	N21-H40	1.0116
C10-C11	1.3912	C22-N23	1.3861
C10-H33	1.0775	C22-O27	1.2082
C11-C18	1.4403	N23-C24	1.398
C12-C13	1.3959	N23-H41	1.0118
C12-C17	1.3957	C24-O26	1.2127

Table-II: Bond angle of the title compound 6.

Bond angle	(º)	Bond angle	(º)
C2-C1-C6	121.7229	C12-C13-H34	120.6269
C2-C1-Br28	119.1412	C14-C13-H34	119.8769
C6-C1-Br28	119.1358	C13-C14-C15	120.4241
C1-C2-C3	119.3951	C13-C14-H35	119.3532
C1-C2-H29	120.9332	C15-C14-H35	120.2161
C3-C2-H29	119.6689	C14-C15-C16	119.6018
C2-C3-C4	119.3875	C14-C15-H36	120.1573
C2-C3-C7	119.4326	C16-C15-H36	120.2394
C4-C3-C7	121.1079	C15-C16-C17	120.6258
C3-C4-C5	120.2787	C15-C16-H37	120.0979
C3-C4-H30	119.9216	C17-C16-H37	119.2755
C5-C4-H30	119.7924	C12-C17-C16	119.3113
C4-C5-C6	120.6644	C12-C17-H38	119.1167
C4-C5-H31	119.9265	C16-C17-H38	121.5716
C6-C5-H31	119.4069	C11-C18-C19	132.5331
C1-C6-C5	118.5463	C11-C18-H39	114.6545
C1-C6-H32	120.5303	C19-C18-H39	112.7892
C5-C6-H32	120.9228	C18-C19-C20	115.7784
C3-C7-N8	118.8295	C18-C19-C24	124.1685
C3-C7-C11	130.3083	C20-C19-C24	119.7214
N8-C7-C11	110.5572	C19-C20-N21	115.2755
C7-N8-N9	106.3386	C19-C20-O25	124.4685
N8-N9-C10	111.5514	N21-C20-O25	120.2521
N8-N9-C12	120.0933	C20-N21-C22	127.7937
C10-N9-C12	128.333	C20-N21-H40	116.5443
N9-C10-C11	107.6691	C22-N21-H40	115.658
N9-C10-H33	122.4667	N21-C22-N23	113.8915
C11-C10-H33	129.8495	N21-C22-O27	122.8782
C7-C11-C10	103.7687	N23-C22-O27	123.229
C7-C11-C18	134.5362	C22-N23-C24	128.2512
C10-C11-C18	121.6852	C22-N23-H41	115.6256
N9-C12-C13	120.2143	C24-N23-H41	116.0421
N9-C12-C17	119.2356	C19-C24-N23	114.8567
C13-C12-C17	120.5501	C19-C24-O26	125.3186
C12-C13-C14	119.4772	N23-C24-O26	119.7927

C. HOMO- LUMO analysis

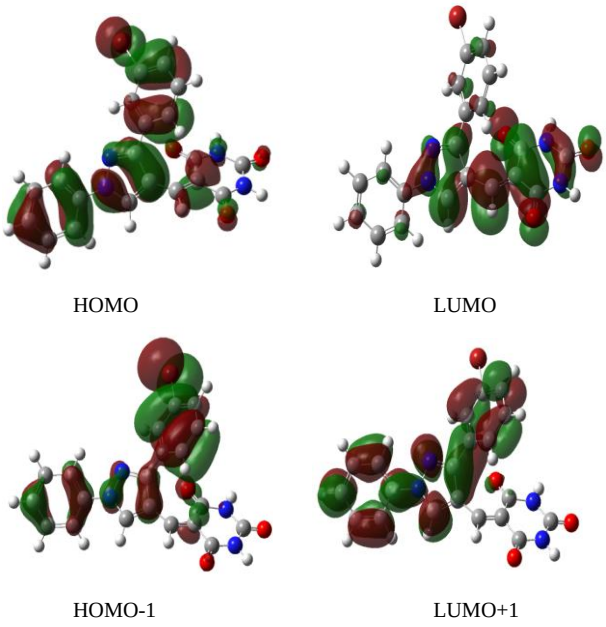


Fig. 3: HOMO-LUMO plots of compound 6

The kinetic stability of a molecule could be predicted from the energies of frontier molecular orbitals. When the difference in energy between FMOs orbitals are greater, more stable will be the compound and the reverse will be for smaller energy difference. The FMO plots of the molecule 6 are shown in Fig 3. The energies of the compound 6 are furnished in Table III. HOMO orbitals are highly localized at the two phenyl rings flanked at C7 and N7 of pyrazole moiety whereas the LUMO orbitals are chiefly localized on pyrazole and barbituric acid moiety. The energy gap between HOMO and LUMO was found to be 3.69 eV which is small enough for electron transfer to take place from phenyl rings flanked with pyrazole moiety to the barbituric acid scaffold.

Table- III: HOMO-LUMO energies of molecule 6

Parameters (eV)	eV
HOMO	-6.53145
LUMO	-2.84627
ΔE	3.68518
HOMO-1	-6.86615
LUMO+1	-1.49959
ΔE1	5.36656

D. Molecular electrostatic potential analysis

MEP study of the synthesized compound **6** has been carried out by B3LYP [6-311++G(d,p)]. In general, the MEP study aids in prediction of reactive sites of the molecule, intermolecular association and physiochemical affairs. Pictorial representation shown in **Fig 4** clearly indicated the electron density and MEP of the molecule where the dark blue colour indicates the electron poor centre and red colour indicates the electron rich centre. Negative province is exhibited on the oxygen atom (O25, O26, and O27) of the barbituric acid scaffold.

The contour map of electrostatic potential concludes the different positive and negative potential sites of the molecule in agreement with the surface map of total electron density.

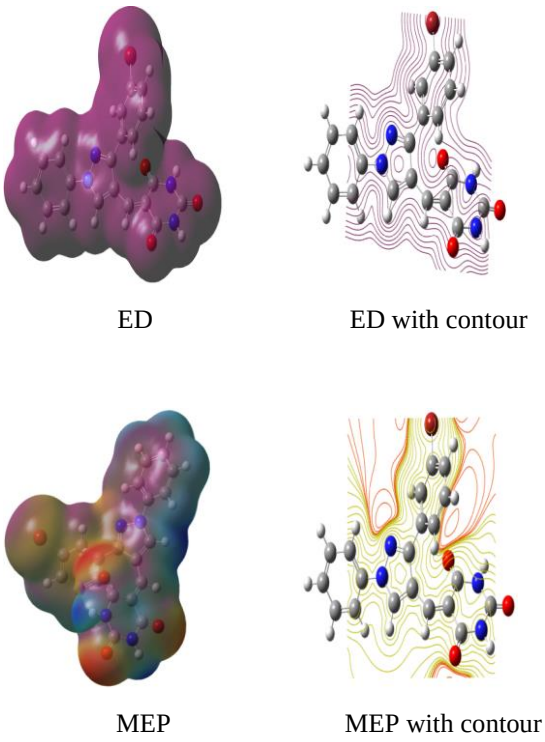


Fig. 4: Electron density and MEP with their contour of compound 6

E. Mulliken population analysis

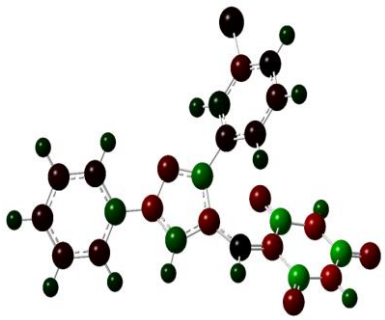


Fig. 5: Mulliken charge distribution of the compound 6

The analysis of Mulliken population of **6** was computed with 6-311++G(d,p) method, which can be used as a tool for estimation of partial atomic charges. The N21 atom of the barbituric acid moiety shows elevated negative charge whereas the C22 atom of the same displayed highest positive charge as shown in **Fig. 5** & **6**.

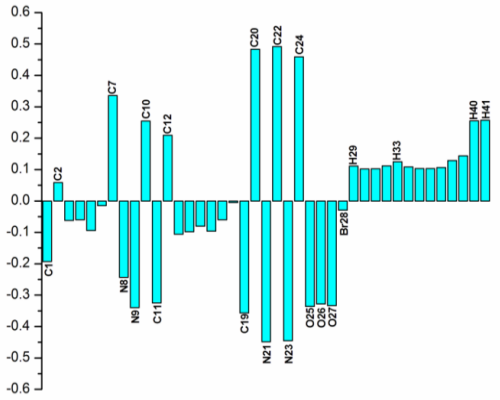


Fig. 6: Mulliken charge distribution chart of the compound 6

To determine the NLO behaviour of the system, the values of polarizability, hyperpolarizability and dipole moment have to be explored. Using B3LYP/ 6-311++G(d,p) basis set, the title compound was computed and the polarizability including hyperpolarizability and dipole moment are evaluated. Its computed values are depicted in **Table IV.**

Table- IV: NLO properties of title compound

Parameters	B3LYP/6-311++G(d,p)
Dipole moment	
μ_x	-4.2906
μ_y	-2.1717
μ_z	0.9558
μ(D)	4.9030
Polarizability	
α_{xx}	-159.5937
α_{yy}	-175.1945
α_{zz}	-174.0380
α_{total}	4.1027×10^{-23}
α_0	-169.6087
Hyperpolarizability	
β_{xxx}	-218.0925
β_{xxy}	46.3732
β_{xyy}	-22.2389
β_{yyy}	118.7497
β_{xxz}	17.7739
β_{xyz}	-10.5172
β_{yyz}	-38.1460
β_{xzz}	35.1716
β_{yzz}	56.6708
β_{zzz}	-26.3100
β_0	2.6412×10^{-30}

The result reveals that the first order hyperpolarizability and dipole moment values are in higher range than urea ($\beta o = 0.37 \times 10^{-30}$ esu, μ(D) = 1.3732 D) [32].

The higher hyperpolarizability exhibited by the molecule **6** when compared to urea implies that the molecule could serve as effective NLO material.

IV. CONCLUSION

In conclusion, successfully synthesized and characterised the target compound **6** by hybridisation of heterocyclic pyrazole with pyrimidine trione. Further the structure of **6** was optimised, HOMO-LUMO, MEP, NLO properties were analysed. Specifically the first order hyperpolaraizability value is found to be seven fold higher than urea thus the molecule **6** shows NLO characterisation. Besides, the electronic / FMO properties / structural motifs imply that the molecule could serve as effective intermediate for the construction of biopertinent molecules.

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