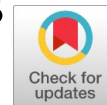


# Synthesis and Density Functional Theory Studies of Novel Heterocycle Tethered with Pyrazole and Benzimidazole Structural Motifs

Ramar Sivaramakarthikeyan, Krishnaraj Padmavathy, Shunmugam Iniyaval, Chennan Ramalingan



**Abstract:** A novel heterocyclic chemical entity, 2-(1H-benzo[d]imidazol-2-yl)-3-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)acrylonitrile (**1f**) has been synthesized and characterized. Computational studies were carried out using Gaussian 9 program with DFT/B3LYP/6311(++G) basis set. The structural optimization was computed successfully. Further, HOMO–LUMO analysis promises the incidence of inter electron transfer within the molecule. The theoretically determined hyperpolarizability value is nearly 9.5 times better than standard urea, suggesting its future utility as an efficient NLO optic material or its utility as an effective intermediate to construct better NLO materials.

**Keywords:** Pyrazole, Imidazole, DFT, NLO.

## I. INTRODUCTION

In recent years, the application-oriented synthesis has become crucial. Heterocycles possessing nitrogen(s) and their analogues have been placed as paragon source in material sciences [1] and medicine [2]. Pyrazole is one among the nitrogen heterocycles with no exemption, its derivatives were proven to be vital in regard to wide spectrum of biological activities [3-10] exhibited by them. No wonder that numerous marketed drugs such as Celecoxib an anti-inflammatory drug, Rimonabant - a cannabinoid receptor, Fomepizole- prevents alcohol dehydrogenase and sildenafil that hinders phosphodiesterase [11] comprises of pyrazole scaffold. Besides astonishing biological applications of pyrazoles, their material science applications including brightening agents [12], noteworthy

solvatochromic [13] electroluminescence [14], semiconductors [15], liquid crystals [16], OLEDs [17] and solar cells [18] are significant. On the other hand, benzimidazole forms the essential component in biological system. Akin to pyrazoles, benzimidazoles have enthralled the interest of application chemist owing to varied therapeutic applications [19]. Specifically, benzimidazoles have anti-infective [20]; antiviral [21] and male contraceptive [22] activities. Benzimidazole nucleus with diverse substituents has been observed in various drugs like omeprazole, lansoprazole, pantoprazole as proton pump inhibitors, astemizole as antihistaminic, and albendazole, mebendazole, thiabendazole as anthelmintics [23,24]. In fact, certain benzimidazoles were proved to act as acceptors in polymers which have been developed for electrochromic applications [25].

Considering the vast applications shown by both pyrazole and benzimidazole has initiated our keenness towards synthesis of single compound with both functionalities together with increased in conjugation so that the novel compound may find applications both in medicinal and material science field. Consequently, a novel heterocycle **1f** has been synthesized by cost effective and simple multistep process. The structure of the molecule was supported based on analytical and spectroscopic methods. In addition, the quantum chemical parameters were achieved with the use of DFT.

## II. EXPERIMENTAL SECTION

### A. General

All reactants / reagents used in the present study are reagent grade and the solvents were distilled prior to use. Shimadzu IR Tracer-100 spectrophotometer and Bruker AVANCE III NMR spectrometer were utilized for recording IR and NMR spectra, respectively. TLC and open capillary were used to observe the reactions progress and to measure the melting point, respectively.

### B. Synthesis of carbaldehyde **1d**

A homogeneous mixture of 4-nitroacetophenone (0.01 mol) and phenyl hydrazine (0.01 mol) in 5 ml of glacial acetic acid was heated for 30 minutes. It was filtered, after cooling, and washed with dil.HCl to obtain the crude product **1c**. Recrystallization from ethanol rendered corresponding arylhydrazone **1c** in pure form.

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The pure arylhydrazone thus obtained was then treated with cold Vilsmeier-Hacck reagent [(DMF (10 ml)-POCl<sub>3</sub> (0.03 mol)]. It was stirred at 70-80 °C for 6h. After ensuring the completion, it was brought to ambient temperature and then poured into water. The mixture was then neutralized using saturated solutions of sodium bicarbonate and the solid obtained was dried after filtration and washed with water to afford pure carbaldehyde **1d** [26].

### C. Synthesis of 2-(1H-benzo[d]imidazol-2-yl)-3-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl) acrylonitrile (**1f**):

To a mixture of carbaldehyde **1d** (0.5 g, 1.7 mmol) in methanol (5 ml), was added (0.27 g, 1.7 mmol) of benzimidazolyl acetonitrile **1e**. Then added dropwise, piperidine (0.17 ml, 1.7 mmol) to the reaction mixture and continued stirring at 60 °C for 6h. It was then poured into water after cooling. K<sub>2</sub>CO<sub>3</sub> (saturated) was then added till neutralization. The precipitate thus resulted was filtered and recrystallized from ethanol, after washed with water and dried, to afford pure target acrylonitrile **1f**. Yield, 86 % ; MP: 336-337°C; FT-IR (KBr, cm<sup>-1</sup>): ν 3305.9, 2218.1, 1595.1, 1521.8, 1423.5, 1348.2, 1232.5, 1109.1, 1068.6, 960.6, 862.2, 817.8, 758.0, 684.7, 636.5, 497.6; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.85 (s, 1H), 8.23 (dd, *J* = 8 Hz, 4H), 8.06 (s, 1H), 8.04 (s, 1H), 7.77-7.73 (m, 5H), 7.52-7.48 (m, 3H), , 7.28 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 180.4, 136.1, 135.9, 131.0, 130.6, 129.6, 129.3, 128.9, 123.9.

### D. Computational details

The entire set of calculations of **6** has been made by exploiting DFT-B3LYP (6-311G (d,p) method [Gaussian 09 program] [31]. The DFT-B3LYP is a universally accepted cheap method of computation for structural optimization [32]. Optimized molecular geometry, HOMO-LUMO energy calculations, MEP, Mulliken atomic charge distributions and NLO properties of the compound **6** were acquired from the above computational method.

## III. RESULTS AND DISCUSSION

### A. Synthesis and characterization

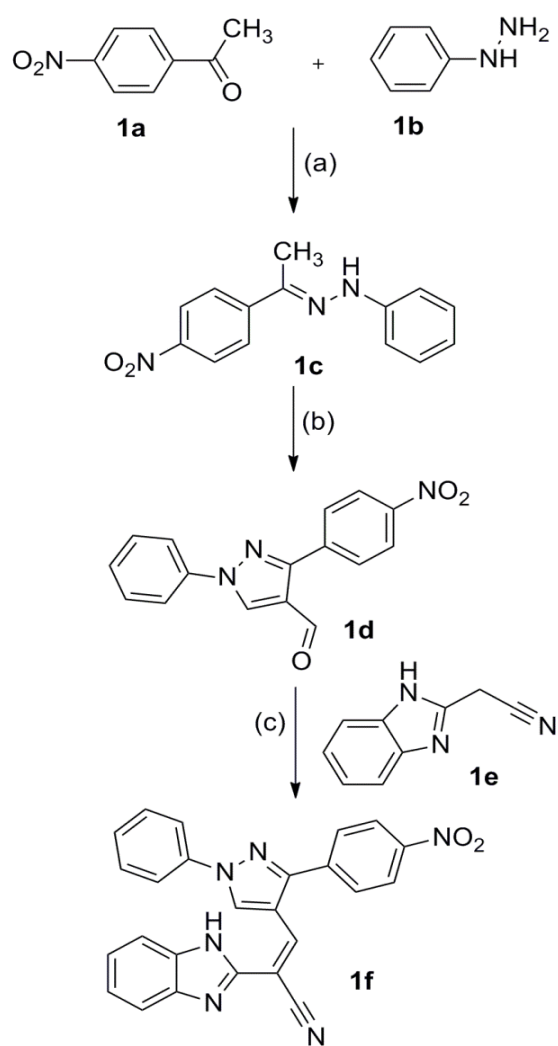
The condensation of p-nitro acetophenone with phenyl hydrazine under acidic condition using glacial acetic acid gave the intermediate **1c** which on simultaneous cyclization and formylation using Vilsmeier-Haack reagent rendered **1d**. Knoevenagel condensation of **1d** with active methylene group of **1e** yielded the target compound **1f** as shown in Scheme 1. The **1d** formation was confirmed by comparing with reported melting point. Further, the structure of target compound was confirmed based on following spectroscopic methods. In the IR spectrum, a strong carbonyl peak corresponding to aldehyde group of **1d** was absent. In addition, a medium peak observed at 2218 cm<sup>-1</sup> confirms the existence of nitrile group in **1f**. A total of 15 protons viz aromatic protons, alkene proton and NH protons were observed between δ 7.28-8.85 ppm in the <sup>1</sup>H NMR spectrum. Additionally, appearance of four protons with doublet of doublet splitting pattern at δ 8.23 ppm supports the presence of nitro substituent at *para* position of phenyl moiety. <sup>13</sup>C NMR spectrum also appeals with the structure of **1f**.

### B. Computational details

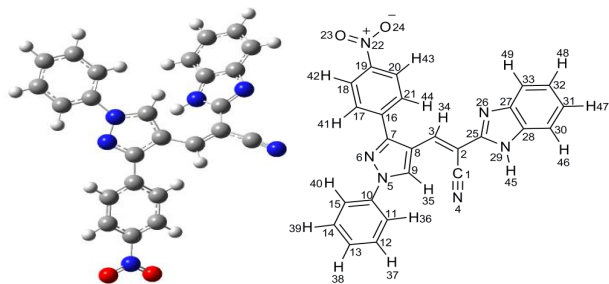
The Gaussian 09 program package [27] was used for complete theoretical calculations of the synthesized molecule **1f**. As specified in the literature, the lucrative DFT, with B3LYP correlation function [28], approach have been deployed for the optimization of structure and determination of associated quantum chemical parameters viz., energy gaps of FMOs, MEPs, Mulliken atomic charge distributions and plausible NLO properties of target compound **1f**.

### C. Optimized geometry

The ground state optimized geometry of heterocyclic compound **1f** is shown in **Figure 1**. As exposed, the geometry of the pyrazole structural decoration has a typical butterfly form. The calculated bond lengths and bond angles of optimized structure of **1f** obtained *via* DFT/B3LYP [6-311G (d,p)] are given in **Tables 1 & 2**.



**Scheme 1: Synthesis of compound 1f; Reagents and conditions: (a) Glacial acetic acid, reflux, 30 mins; (b) DMF-POCl<sub>3</sub>, 70-80 °C, 6h; (c) piperidine, methanol, 60 °C, 6h.**



**Figure 1. Optimized Structure of 2-(1H-benzo[d]imidazol-2-yl)-3-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl) acrylonitrile (1f).**

**Table 1: Bond length values of 1f**

Bond length	[Å]	Bond length	[Å]
C1-C2	1.4339	C17-C18	1.3857
C2-N4	1.1547	C17-H41	1.0818
C2-C3	1.3598	C18-C19	1.3917
C2-C25	1.4676	C18-H42	1.0810
C3-C8	1.4521	C19-C20	1.3889
C3-H34	1.0851	C19-N22	1.4788
N5-N6	1.3513	C20-C21	1.3894
N5-C9	1.3566	C20-H43	1.0809
N5-C10	1.4255	C21-H44	1.0824
N6-C7	1.3300	N22-O23	1.2234
C7-C8	1.4366	N22-O24	1.2236
C7-C16	1.4706	C25-N26	1.3826
C8-C9	1.3883	C25-N29	1.3127
C9-H35	1.0762	N26-C27	1.3811
C10-C11	1.3960	N26-H45	1.0071
C10-C15	1.3954	C27-C28	1.4155
C11-C12	1.3917	C27-C33	1.3949
C11-H36	1.0828	C28-N29	1.3805
C12-C13	1.3927	C28-C30	1.3999
C12-H37	1.0836	C30-C31	1.3866
C13-C14	1.3938	C30-H46	1.0829
C13-H38	1.0834	C31-C32	1.4089
C14-C15	1.3904	C31-H47	1.0837
C14-H39	1.0837	C32-C33	1.3895
C15-H40	1.0808	C32-H48	1.0839
C16-C17	1.4053	C33-H49	1.0838
C16-C21	1.4036		

**Table 2: Bond angle of 1f**

Bond Angle	[°]	Bond Angle	[°]
C2-C1-N4	177.8798	C19-C18-H42	119.4229
C1-C2-C3	117.4229	C18-C19-C20	121.8336
C1-C2-C25	115.0213	C18-C19-N22	119.0751
C3-C2-C25	127.5436	C20-C19-N22	119.0904
C2-C3-C8	129.2947	C17-C16-C21	118.8252
C2-C3-H34	115.7885	C16-C17-C18	120.8427
C8-C3-H34	114.8589	C16-C17-H41	119.0473
N6-N5-C9	111.9743	C18-C17-H41	120.1095
N6-N5-C10	120.3856	C17-C18-C19	118.8600
C9-N5-N10	127.6380	C17-C18-H42	121.7160
N5-N6-C7	105.8819	C19-C18-H42	119.4229
N6-C7-C8	110.9101	C18-C19-C20	121.8336
N6-C7-C16	119.7304	C18-C19-N22	119.0751
C8-C7-C16	129.3589	C20-C19-N22	119.0904
C3-C8-C7	127.3516	C19-C20-C21	118.8131
C7-C8-C9	103.7824	C19-C20-H43	119.5371
N5-C9-C8	107.4488	C21-C20-H43	121.6470

N5-C9-H35	122.0181	C16-C21-C20	120.8212
C8-C9-H35	130.3521	C16-C21-H44	120.2347
N5-C10-C11	120.0638	C20-C21-H44	118.9249
N5-C10-C15	119.3545	C19-N22-O23	117.5609
C11-C10-C15	120.5816	C19-N22-O24	117.4861
C10-C11-C12	119.4421	O23-N22-O24	124.9530
C10-C11-H36	120.6985	C2-C25-N26	123.4813
C12-C11-H36	119.8471	N26-C25-N29	112.5377
C11-C12-C13	120.4185	C25-N26-C27	107.1024
C11-C12-H37	119.3383	C27-N26-H45	126.8872
C13-C12-H37	120.2388	N26-C27-C28	104.5681
C12-C13-C14	119.6401	N26-C27-C33	132.9581
C12-C13-H38	120.1434	C28-C27-C33	122.4738
C14-C13-H38	120.2158	C27-C28-N29	110.2853
C13-C14-C15	120.5799	C27-C28-C30	119.8639
C13-C14-H39	120.1031	C25-N29-C28	105.5026
C15-C14-H39	119.3159	C28-C30-C31	117.9500
C10-C15-C14	119.3293	C28-C30-H46	120.0732
C10-C15-H40	119.2654	C31-C30-H46	121.9765
C14-C15-H40	121.4046	C30-C31-C32	121.4207
C7-C16-C17	119.5330	C30-C31-H47	119.6002
C7-C16-C21	121.6343	C32-C31-H47	118.9788
C17-C16-C21	118.8252	C31-C32-C33	121.6926
C16-C17-C18	120.8427	C31-C32-H48	119.1467
C16-C17-H41	119.0473	C33-C32-H48	119.1605
C18-C17-H41	120.1095	C27-C33-C32	116.5982
C17-C18-C19	118.8600	C32-C33-H49	121.2916
C17-C18-H42	121.7160		

#### D. Analysis of Mulliken population

Mulliken population method yields the net atomic charge distribution of specific atoms in a molecule and thereby, the acceptor and donor pairs connecting the charge transfer in the molecule can be established [33, 34]. MEP analyses of 6 was attained from the optimized structural calculation and the results are given in Table 3. The apparent atomic charge distribution of compound 6 is represented by coloring in Fig. 2. The net atomic charge distribution of compound is shown in Fig. 2. The output clearly indicates that the atom C24 of benzimidazole ring has got more positive charge due to electron-withdrawing character of nitrile moiety attached to the adjacent carbon atom and two neighboring electronegative nitrogen atoms. Also, the C7 atom of pyrazole ring holds almost nearer positive charge as that of C24 due to adjacent nitrogen atom, whereas the nitrogen N25 showed greater negative charges.



**Figure 2. Mulliken charge distribution of 2-(1H-benzo[d]imidazol-2-yl)-3-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl) acrylonitrile (1f)**

Table 3. Mulliken atomic charges of 1f

Atom	Charges	Atom	Charges
C1	0.076475	N26	-0.465116
C2	-0.029706	C27	0.186649
C3	-0.023334	C28	-0.017168
N4	-0.216381	N29	-0.318858
N5	-0.329740	C30	-0.058396
N6	-0.249079	C31	-0.102417
C7	0.313347	C32	-0.107719
C8	-0.405728	C33	-0.057209
C9	0.236549	H34	0.145625
C10	0.205013	H35	0.142816
C11	-0.107281	H36	0.114057
C12	-0.098275	H37	0.107079
C13	-0.077375	H38	0.106098
C14	-0.097568	H39	0.107838
C15	-0.056514	H40	0.128067
C16	-0.076202	H41	0.115322
C17	-0.033525	H42	0.138702
C18	-0.048086	H43	0.141079
C19	0.125532	H44	0.119113
C20	-0.050625	H45	0.247689
C21	-0.075754	H46	0.105901
N22	0.170865	H47	0.099362
O23	-0.265375	H48	0.099343
O24	-0.265946	H49	0.094272
C25	0.306583		

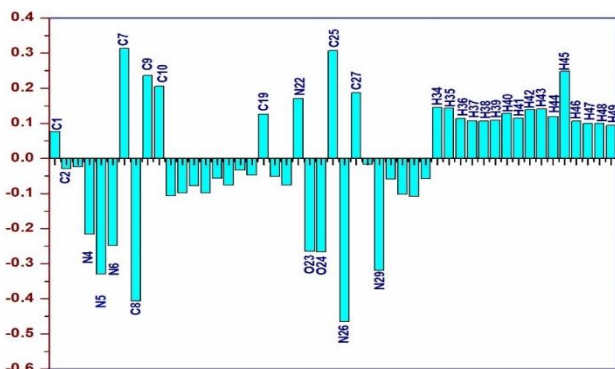


Figure 3. Mulliken charge distribution chart of 2-(1H-benzo[d]imidazol-2-yl)-3-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl) acrylonitrile (1f)

### E. Frontier Molecular orbital Analysis

The symmetry and energies of fmos such as homo-lumo orbitals predicts feasibility and kinetic stability of a reaction. also, the electronic spectra of a compound can be studied from fmo's energy values. as reported, the difference in energy between lumo and homo orbitals is a vigorous factor for the molecules' excitability determination as well as the topological resonance energy determination [31]. the 3d plots of FMO's of the title compound are displayed in **figure 4**. molecular orbital energy differences of HOMO-2-LUMO+2, HOMO-1-LUMO+1 and HOMO-LUMO, energy levels are tabulated in **table 4**. Comparatively large energy gap between homo-lumo orbitals indicates that title compound **1f** has good stability and high chemical hardness. locations of frontier orbital as pictured in **figure 4** suggest the probability of inter-electron transfer to occur within the molecule.

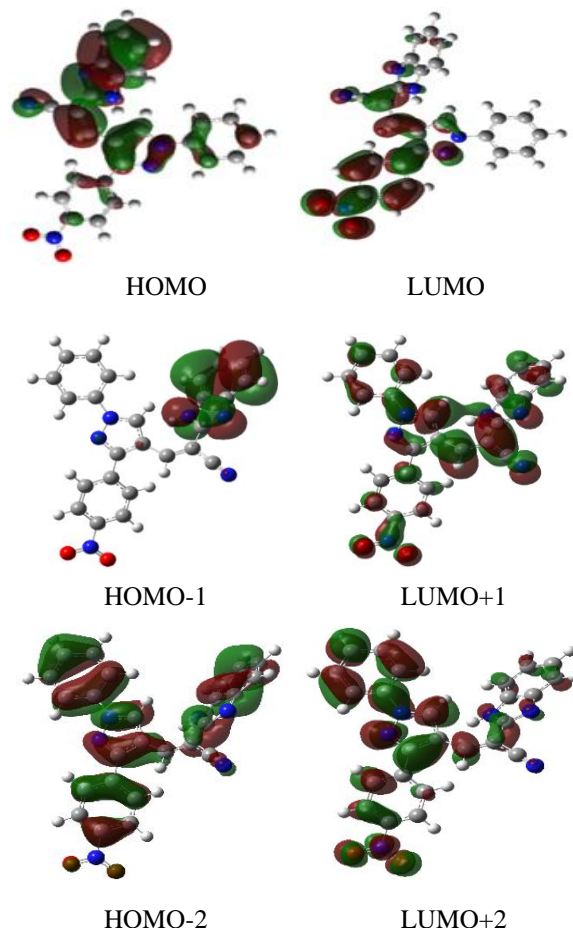


Fig. 4. Frontier Molecular Orbitals of 1f

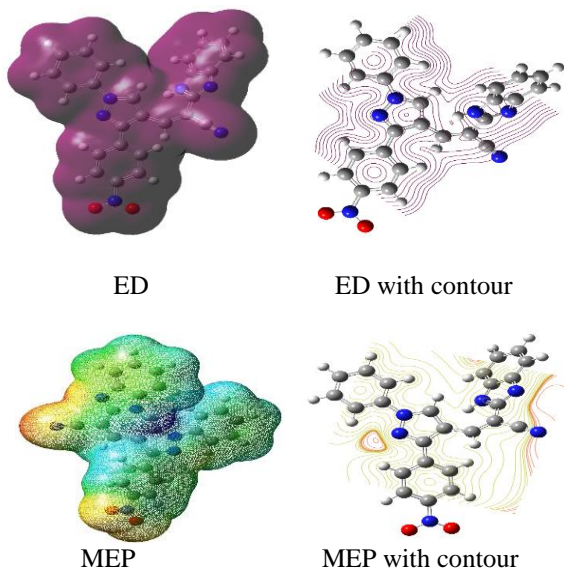
Table 4. FMO's energies of 1f

Parameters	eV
HOMO	-6.4347
LUMO	-2.9255
$\Delta E$	3.5092
HOMO-1	-6.8083
LUMO+1	-2.6362
$\Delta E_1$	4.1721
HOMO-2	-7.0761
LUMO+2	-1.6365
$\Delta E_2$	5.4396

### F. Molecular electrostatic potential analysis

The electrostatic potential is a very populous tool for the determination of reactive sites, intermolecular association, interaction of hydrogen bonding and physicochemical affairs [32]. The MEP is very supportive to considerate the responsive locations for nucleophilic and electrophilic attack [33]. A MEP study of compound **1f** has been prosecuted by DFT/B3LYP method to analyze and predict the reactive sites on the molecule. The positive (blue) region of the MEP is related to nucleophilic reactive centres and the negative (brown and yellow) regions correspond to electrophilic reactive centres. The electrostatic potential (isosurfaces) ranges from -0.170 to +0.170 kcal/mol (dark blue) indicating exceedingly electron-deficient region

( $V_{(r)} > +0.107$  kcal/mol) and brown denoting electron rich region ( $V_{(r)} > -0.107$  kcal/mol). Model of electrostatic potential and electron density are visualized in **Figure 5**. The highest positive region is located on the pyrazole ring with a value of  $+0.170$  kcal/mol, indicative of nucleophilic attacking site. Nitrogen of cyano and nitro are most reactive sites for nucleophilic and electrophilic attack, respectively.



**Fig. 5. Molecular electrostatic potential map of 6**

#### G. Non-linear optical characteristics

The parameters such as first order hyperpolarizability, polarizability as well as dipole moment have been computed by DFT. Comparison of values of the above-mentioned parameters with standard NLO materials parameters could suggest the existence of NLO properties of compound under investigation [34]. The first order hyperpolarizability, hyperpolarizability and dipole moment values of target molecule **1f** are furnished in **Table 5**.

The total hyperpolarizability ( $\beta$ ), polarizability and dipole moment values of compound **1f** (calculated ones) was found to be  $3.5214 \times 10^{-30}$  esu,  $5.5840 \times 10^{-23}$  Debye-Ang, and  $10.3052$  Debye, respectively. In addition, on comparing the first order hyperpolarizability ( $\beta$ ) and dipole moment value of synthesized compound **1f** with standard urea [35], it has been observed that the first order hyperpolarizability and dipole moment values are 9.5-fold and 1.4-fold greater than urea. The results suggest that the synthesized compound could either be useful for the non-linear optical crystal preparation or could serve as potential intermediate for the construction of better NLO materials.

**Table 5. NLO Properties of 1f**

Parameters	Values
Dipole moment	
$\mu_x$	-5.0710
$\mu_y$	8.6196
$\mu_z$	2.4868
$\mu(D)$	10.3052
Polarizability	
$\alpha_{xx}$	-217.2220
$\alpha_{yy}$	-198.4763
$\alpha_{zz}$	-195.6247

$\alpha_{total}$	5.5840	x
	$10^{-23}$	
$\alpha_0$	-203.7743	
Hyper-polarizability		
$\beta_{xxx}$	-422.6574	
$\beta_{xxy}$	107.3489	
$\beta_{xyy}$	5.3116	
$\beta_{yyy}$	279.2123	
$\beta_{xxz}$	-20.9383	
$\beta_{xyz}$	16.2289	
$\beta_{yyz}$	56.3973	
$\beta_{xzz}$	17.2210	
$\beta_{yzz}$	26.2370	
$\beta_{zzz}$	39.2171	
$\beta_0$	3.5214	x
	$10^{-30}$	

#### IV. CONCLUSION

In conclusion, a novel heterocyclic acrylonitrile **1f** was synthesized efficaciously by multistep synthetic approach. The structure elucidation of compound **1f** was attained through physical and spectroscopic methods. The optimization of the molecule **1f** was carried out computationally using DFT. Further, the HOMO-LUMO energy values, MEP, Mulliken Charge analysis and NLO properties of the molecule was also achieved through computational (DFT) method. Specifically, the results of NLO related parameters assure the better NLO properties than standard urea.

#### ACKNOWLEDGMENT

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