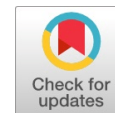


# Pyrazolylmethylenepyrimidinetrione: Synthesis, Characterization and DFT Analysis



Shunmugam Iniyaval, Ramar Sivaramakarthiskeyan, Krishnaraj Padmavathy,  
 Vadivel Saravanan, Chennan Ramalingan

**Abstract:** A barbituric acid tailored pyrazole chemical entity **1f** was synthesized and characterized utilizing analytical and various spectroscopic techniques. Further the molecular properties of the molecule such as optimized structure, FMO analysis, electrostatic potential, Mulliken charges, and NLO characteristics were determined by subjecting **1f** in to DFT calculations employing B3LYP method. The outcome imply that the target could be served in one direction as biologically important molecule/intermediate and the other direction as NLO material / an intermediate to construct better NLO materials.

**Keywords:** Pyrazole, Barbituric acid, DFT, NLO.

## I. INTRODUCTION

Nitrogen heterocycles play crucial role in drug designing owing to its proton donor and acceptor capabilities. Both pyrazole and barbiturates are heterocyclic compounds with two nitrogen atom in their ring structure. In recent days, these compounds serve as lead molecules in drug discovery. Isolation of first natural pyrazole derivative is 3-nonylpyrazole from *Hauttuynia Cordata* in 1954 [1], and it finds numerous applications in the field of medicine. Few medicinal applications of pyrazole scaffold are antimicrobial [2], [3] antifungal [2], leishmanicidal [4]-[7], antiviral [3], antichagasic [4], pesticidal [8] antihyperglycemic [9], anti-inflammatory [10] and antitumoral [3], analgesic [11],

and anticancer [12]. In addition to bioactivity, pyrazoles have potential for other applications such as optical materials, dyes, catalysts, solar cells, polymers, ammunition and corrosion inhibitors[13]. Similarly, barbituric acid derivatives attained the interest of synthetic chemist due to its spectrum of bioactivity such as hypnotic [14], [15] sedative [16], anticonvulsant [17], [18], antimicrobial[19] anaesthetic [20], anticancer and antitumor properties [21], [22]. Also, it plays vital role in dye sensitized solar cells as anchoring unit [23]. Certain polymers with barbituric acid moieties were found to show excellent pH sensitivity at pH 6-7[24]. In view of the above, we hypothesized that designing a suitable molecule possessing these two structural units would provide targets with either of the aforementioned properties. Thus, for the first instance, a molecule **1f** was synthesized and its structure was established using IR, and NMR spectroscopy. Further, molecular quantum parameters of **1f** were determined by conducting computational work utilizing DFT.

## II. EXPERIMENTAL SECTION

### A. General

The MP of **1f** and intermediates were determined using open capillaries (uncorrected). Commercial solvents were used as such without any purification. The structure of synthesized molecule was deduced through spectroscopic analysis. IR analysis was carried out on Shimadzu spectrophotometer (IR Tracer-100). The NMR were recorded on Bruker 400 MHz NMR spectrometer using dimethylsulphoxide (DMSO-d<sub>6</sub>) as solvent with tetramethylsilane (TMS) as standard. Further, the melting points of known compounds were compared with the literature.

### B. Synthesis of pyrazolylmethylenepyrimidinetrione **1f**

A mixture of ketone **1a** (0.01 mol) and hydrazine **1b** (0.01 mol) in glacial acetic acid (10 mL) was heated on water bath for 30 minutes. It was then filtered after cooling. The precipitate thus obtained was washed with dilute hydrochloric acid solution. Then the solid was purified through recrystallization using ethanol. The pure hydrazone (**1c**) thus obtained was treated with Vilsmeier-Haack reagent [DMF (10 ml)-POCl<sub>3</sub> (0.03 mol)] at 0 °C and the reaction mass was stirred at 70-80 °C for 6h. It was then brought in to ambient temperature and then poured in to water. After neutralization using NaHCO<sub>3</sub> (saturated),

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the precipitate was filtered and recrystallized from ethanol, after washed with water and dried, to afford **1d** in pure form. Then a 1:1 mixture of **1d** (0.3 g, 0.94 mmol) and barbituric acid (0.12 g, 0.94 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 the reaction was completed, it was cooled, poured into water and the precipitate thus obtained was washed with hot ethanol, after filtration, to furnish the title compound **1f** in a pure form.

Yield: 0.26 g (67%), mp. 221-223°C. IR (KBr, cm<sup>-1</sup>): 3176.8, 3057.2, 2831.5, 1732.1, 1604.8, 1431.2, 1392.6, 1352.1, 1228.7, 1159.2, 1010.7, 839.0, 756.1, 588.3, 515.0; <sup>1</sup>H NMR (400 MHz, DMSO): δ 11.36 (s, 1H), 11.34 (s, 1H), 9.80 (s, 1H), 8.13 (s, 1H), 7.93 (d, J = 7.6 Hz, 2H), 7.69 (t, J = 6.0 Hz, 2H), 7.61 (t, J = 7.60 Hz, 2H), 7.49-7.43 (m, 3H); <sup>13</sup>C NMR (400 MHz, DMSO): δ 164.57, 164.06, 163.14, 162.11, 157.44, 150.72, 143.69, 139.00, 134.97, 132.22, 132.13, 130.40, 128.59, 127.74, 127.71, 120.14, 119.70, 116.56, 116.35, 115.65, 115.03

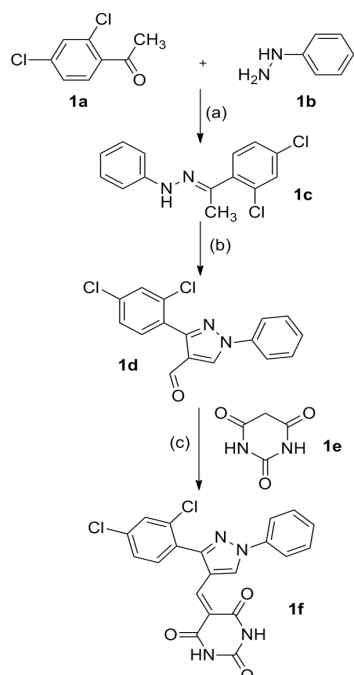
## C. Computational details

The title compound **1f** was computed using Gaussian 09 program by DFT-B3LYP method having a basis set 6-311++G(d,p) [25], [26]. Quantum parameters such as optimized structure, Mulliken charges, MEP, FMO analysis and NLO behavior were studied.

## III. RESULTS AND DISCUSSION

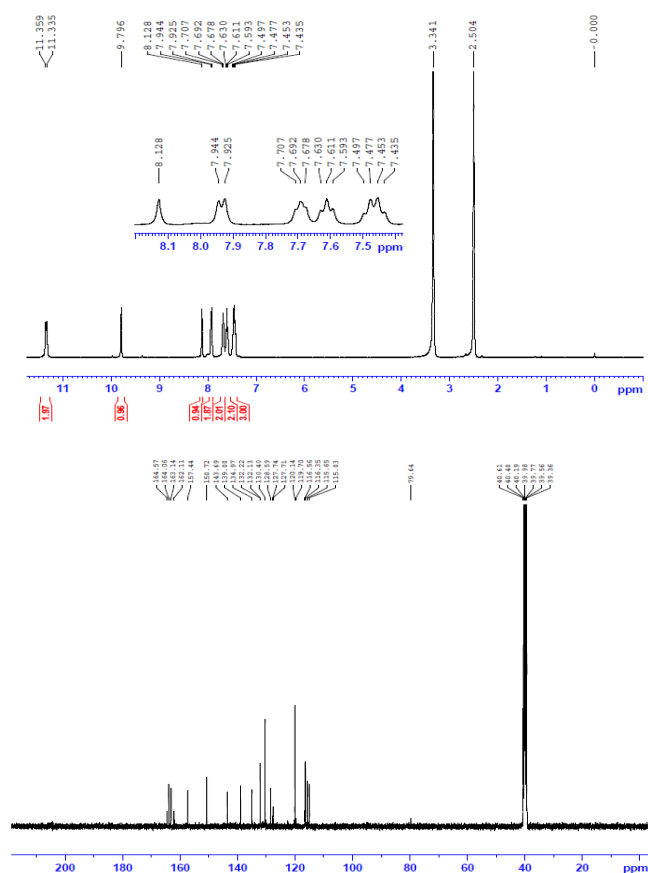
### A. Synthesis and characterization

The target chemical entity **1f** was synthesized through multi-step synthetic methodologies and the synthetic scheme for the synthesis is provided in **Scheme 1**.



**Scheme 1.** Synthesis of target chemical entity **1f**. Reagents and conditions: (a) Glacial acetic acid, reflux, 30 min; (b) DMF-POCl<sub>3</sub>, 70-80 °C, 6h; (c) Benzyltriethylammonium chloride, ethylene glycol, 100 °C, 4h.

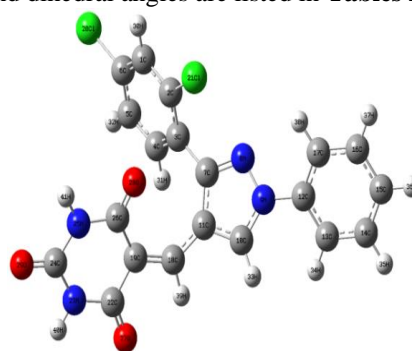
Synthesis of the key intermediate, carbaldehyde **1d** was achieved from the ketone **1a** by condensation with hydrazine **1b** followed by cyclization and formylation reactions. Finally, the target molecule **1f** was synthesized by the condensation between **1d** and **1e** in the presence of phase transfer catalyst. The structure of the target molecule was deduced based on physical and spectral data.



**Fig. 1.** <sup>1</sup>H and <sup>13</sup>C NMR spectra of **1f**

### B. Optimized structure

The optimization of the molecule **1f** was made computationally by DFT-B3LYP [6-311++G(d,p)] method and the structure (optimized) is furnished in **Fig. 2**. The parameters of the optimized structure viz., bond angles, bond lengths, and dihedral angles are listed in **Tables I & II**.



**Fig. 2.** Optimized structure of **1f**

The theoretically obtained carbon-hydrogen and carbon-carbon bond lengths of barbituric acid motif and pyrazole scaffold are ~1.1 and ~1.4 Å, respectively, the expected range. The other bond lengths such as C-N (1.322, 1.3491, 1.4244, 1.3893, 1.3974 Å), C-O (1.2152, 1.208 and 1.2132Å), C-Cl (1.7499 and 1.7567 Å) and N-N (1.3588 Å) were found to match with the literature values of the structurally similar molecules [27], [28]. Similarly, the bond angles obtained through computational calculations exhibit good accordance with the related reported ones [27], [38].

**Table- I: Bond Length of 1f**

Bondlength	[Å]	Bondlength	[Å]
C1-C2	1.3912	C13-C14	1.3915
C1-C6	1.3886	C13-H34	1.0829
C1-H30	1.0807	C14-C15	1.3929
C2-C3	1.4021	C14-H35	1.0837
C2-Cl21	1.7499	C15-C16	1.3938
C3-C4	1.4001	C15-H36	1.0835
C3-C7	1.4763	C16-C17	1.3905
C4-C5	1.3891	C16-H37	1.0837
C4-H31	1.0835	C17-H38	1.0811
C5-C6	1.3893	C18-C19	1.3604
C5-H32	1.0818	C18-H39	1.0888
C6-Cl20	1.7567	C19-C22	1.4908
C7-N8	1.322	C19-C26	1.4779
C7-C11	1.4405	C22-N23	1.3908
N8-N9	1.3588	C22-O27	1.2152
N9-C10	1.3491	N23-C24	1.3893
N9-C12	1.4244	N23-H40	1.0116
C10-C11	1.3927	C24-O29	1.208
C10-H33	1.0775	N25-C26	1.3974
C11-C18	1.4388	N25-H41	1.0117
C12-C13	1.3958	C26-O28	1.2132
C12-C17	1.3954		

**Table –II: Bond angles of 1f**

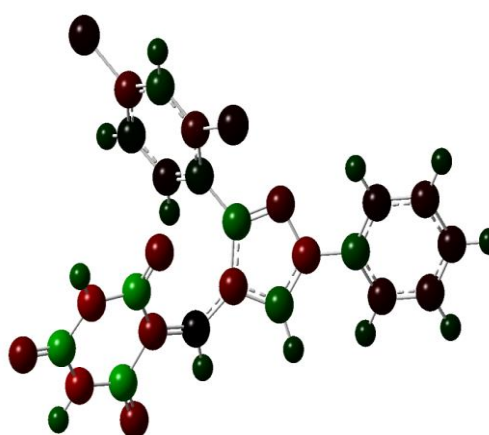
Bond angle	[Å]	Bond angle	[Å]
C2-C1-C6	119.2035	C12-C13-H34	120.6721
C2-C1-H30	120.1108	C14-C13-H34	119.8781
C6-C1-H30	120.684	C13-C14-C15	120.4096
C1-C2-C3	121.4214	C13-C14-H35	119.3710
C1-C2-Cl21	117.0892	C15-C14-H35	120.2141
C3-C2-Cl21	121.4549	C14-C15-C16	119.6362
C2-C3-C4	117.4361	C14-C15-H36	120.1352
C2-C3-C7	123.8129	C16-C15-H36	120.2274
C4-C3-C7	118.7252	C15-C16-C17	120.6084
C3-C4-C5	122.1728	C15-C16-H37	120.1136
C3-C4-C31	118.7377	C17-C16-H37	119.2773
C5-C4-H31	119.0851	C12-C17-C16	119.2739
C4-C5-C6	118.5928	C12-C17-H38	119.1296
C4-C5-H32	120.9147	C16-C17-H38	121.5956
C6-C5-H32	120.4897	C11-C18-C19	133.4672
C1-C6-C5	121.1731	C11-C18-H39	114.1460
C1-C6-Cl20	119.1263	C19-C18-H39	112.3790
C5-C6-Cl20	119.7006	C18-C19-C22	115.5632
C3-C7-N8	119.6103	C18-C19-C26	124.4959
C3-C7-C11	128.9757	C22-C19-C26	119.6284
N8-C7-C11	110.8119	C19-C22-N23	115.3063
C7-N8-N9	106.2083	C19-C22-O27	124.4521
N8-N9-C10	111.6745	N23-C22-O27	120.2375
N8-N9-C12	119.8949	C22-N23-C24	127.8003
C10-N9-C12	128.4283	C22-N23-H40	116.5262
N9-C10-C11	107.6594	C24-N23-H40	115.6681
N9-C10-H33	122.4735	N23-C24-N25	113.8562
C11-C10-H33	129.7102	N23-C24-O29	122.9109
C7-C11-C10	103.5901	N25-C24-O29	123.2315
C7-C11-C18	134.7981	C24-N25-C26	128.2270

C10-C11-C18	121.5815	C24-N25-H41	115.6102
N9-C12-C13	120.2714	C26-N25-H41	116.0745
N9-C12-C17	119.1013	C19-C26-N25	114.9704
C13-C12-C17	120.6273	C19-C26-O28	125.2542
C12-C13-C14	119.4356	N25-C26-O28	119.7429

### C. Mulliken charge distribution Analysis

The energetic behavior of a molecule can normally be obtained from analysis of Mulliken population. The analysis of Mulliken population of 1f has been evaluated using B3LYP [6-311++G (d,p)] method and the structure and chart of the same are shown in Fig. 3 & 4. The corresponding values are presented in Table III.

The table clearly indicates that the atom C24 exhibit highest positive atomic charge (0.492354 e) due to the presence of electronegative atoms such as O29, N23, and N25 adjacent to the same. Similarly, carbons such as C1, C3, C5, C7, C10, C12, C22, C24, and C26 have positive charges, specifically C22, C24 and C26 have positive charges with comparatively greater magnitude. This is because those atoms are directly connected to electronegative oxygen atoms of the barbituric acid motif (0.48258, 0.492354 and 0.462673 e, respectively). All hydrogen atoms H30-H41 displayed positive charge values. Besides, the nitrogen atom of barbituric acid unit N23 has the highest negative charges (-0.448 e) in comparison with other nitrogen atoms of barbituric acid moiety as well as pyrazole motif. The atoms such as O27, O28 and O29 hold remarkable negative values -0.33668 e, -0.32997 e, and -0.33213 e, respectively. Likewise, atoms such as C2, C4, C6, C11, C13-C19, C18, Cl20 and Cl21 have negative charges. Least negative charge was shown by C18 atom through which pyrazole and barbituric acid structural units are connected (-0.00374e). The results clearly indicate that electrostatic interaction and electron transfer occur to an acceptor from a donor within the molecule. The N23 and N25 atoms of barbituric acid moiety have greater electron acceptor capacity than other nitrogen atoms.



**Fig. 3. Mulliken charge distribution of the compound 1f**

Table - III: Mulliken charge distribution of 1f

Atom	Charges	Atom	Charges
C1	0.144564	C22	0.482582
C2	-0.17027	N23	-0.448
C3	0.049147	C24	0.492354
C4	-0.04381	N25	-0.44517
C5	0.024825	C26	0.462673
C6	-0.23975	O27	-0.33668
C7	0.312214	O28	-0.32997
N8	-0.21686	O29	-0.33213
N9	-0.34487	H30	0.138827
C10	0.258826	H31	0.106882
C11	-0.32898	H32	0.121388
C12	0.208245	H33	0.127212
C13	-0.10413	H34	0.107076
C14	-0.09834	H35	0.103436
C15	-0.07892	H36	0.103293
C16	-0.09859	H37	0.106887
C17	-0.05874	H38	0.140216
C18	-0.00374	H39	0.142776
C19	-0.35415	H40	0.255335
C120	-0.05909	H41	0.257154
C121	-0.05373		

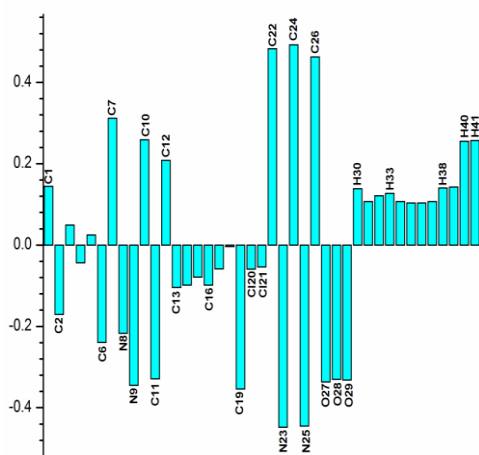


Fig. 4. Mulliken charge distribution chart of 1f.

#### D. Electron density and MEP analysis

Charge distribution and related behavior can be arrived through 3D energy map plot of molecular electrostatic potential. [29]. It represents the possible electrophilic and nucleophilic attacking sites, biological recognition process and hydrogen bonding interaction [30].

The contour map depicts the positive and negative potential sites of 1f in correspond to surface map of total electron density (Fig. 5). Red colour indicates the most electronegative electrostatic potential area and blue shows the area of most electropositive electrostatic potential. The order of increasing potential of the colour code are red < orange < yellow < green < blue [31]. 3D plot shows that red region is indicative of N-H...O interaction while the blue region represents the electrophilic part.

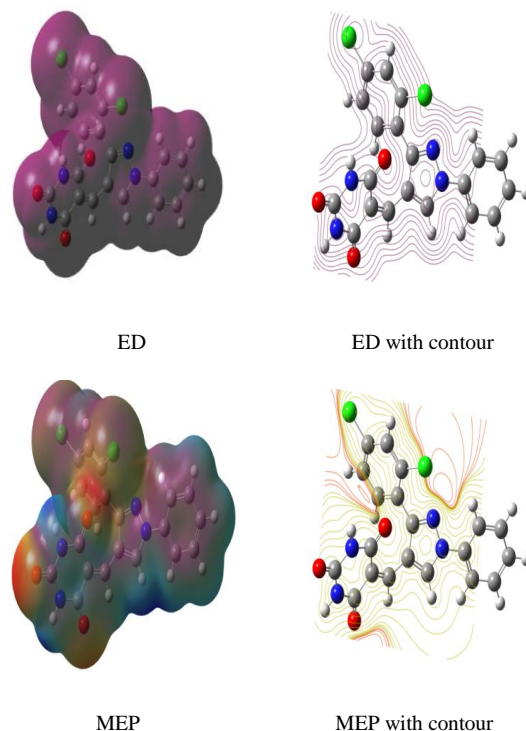


Fig. 5. 3D plot of MEP and electron density with contour of the title compound 1f

#### E. Frontier Molecular Orbital energy analysis

The reactivity and active sites of the molecule can be determined from the energy gap between FMOs and distribution of frontier orbitals. Also, the global reactivity descriptors quantum parameters viz., electronegativity ( $\chi$ ), chemical potential ( $\mu$ ), electrophilicity ( $\omega$ ), softness ( $\sigma$ ) and hardness ( $\eta$ ) of the molecule can be estimated from the energy gap levels using Koopman's notation [32].

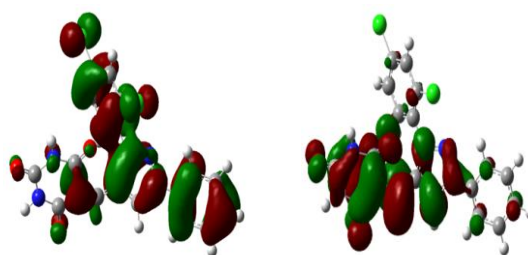


Fig. 6. HOMO-LUMO energies of 1f

Fig. 6 clearly indicates that the lobes of HOMO orbitals are chiefly concentrated on pyrazole and aryl rings integrated with pyrazole ring whereas the lobes of LUMO are primarily concentrated around barbituric acid structural motif. This observation clearly implies that the electron transfer may take place from pyrazole and aryl groups tethered with pyrazole to barbituric acid motif. Moreover, the energy gap between frontier orbital are small enough for plausible electron transfer as shown in Table IV.

**Table – IV: GRD parameters of 1f**

Parameters	eV
HOMO	-6.63866
LUMO	-2.88246
Energy gap $\Delta E$	3.7562
Ionisation Potential (I)	0.24397
Electron Affinity (A)	0.10593
Electronegativity index ( $\chi$ )	0.296935
Hardness ( $\eta$ )	0.17005
Chemical softness (s)	5.88
Chemical potential ( $\mu$ )	-0.296935
Electrophilicity index ( $\omega$ )	0.3401

### F. Nonlinear Optical Properties

A media is said to be non-linear optics, when its polarization density reacts non-linearly to the electric field of the light. NLO activity gives the key capacities for optical modulation, frequency shifting, optical logic and optical switching for creating advances in areas of optical interconnections, signal processing and communications [33], [34]. Also, molecular nonlinear optics have been broadly used in bio imaging [35], phototherapy [36], and bio sensing [37] field. Hence, the NLO behavior of 1f has been computed by DFT - B3LYP [6-311++G(d,p)] method [38]-[42]. Data viz., hyperpolarizability, polarizability and dipole moment of 1f were evaluated and depicted in Table V. On comparing with urea, a prototypical molecule in the study of NLO material for molecular structure [43] having the dipole moment ( $\mu = 1.3732$  D) and hyperpolarizability ( $0.37 \times 10^{-30}$  esu), the computed values of 1f appear to be four and six times, respectively greater than their respective values of urea. This shows 1f could serve as a promising NLO material.

**Table-V: NLO properties of 1f**

Parameters	B3LYP/6-311++G(d,p)
Dipole moment	
$\mu_x$	5.0853
$\mu_y$	-1.7031
$\mu_z$	-1.2462
$\mu$ (D)	5.5058
Polarizability	
$\alpha_{xx}$	-166.9710
$\alpha_{yy}$	-184.3920
$\alpha_{zz}$	-180.5802
$\alpha_{total}$	$4.2925 \times 10^{-23}$
$\alpha_0$	-177.3144
Hyperpolarizability	
$\beta_{xxx}$	259.3466
$\beta_{xxy}$	-5.8420
$\beta_{xyy}$	31.3069
$\beta_{yyy}$	-4.5081
$\beta_{xxz}$	-21.7179
$\beta_{xyz}$	10.5527
$\beta_{yyz}$	32.7635
$\beta_{xzz}$	-26.2075
$\beta_{yzz}$	10.1315
$\beta_{zzz}$	11.3075
$\beta_0$	$2.2928 \times 10^{-30}$

### IV. CONCLUSION

To summarize, successfully synthesized and characterized **1f**. The compound **1f** was computed using DFT- B3LYP [6-311++ G(d,p)] method. The bond angles and lengths were almost similar to the structurally similar reported ones. In

addition, the theoretical results of hyperpolarizability assures that the compound could serve as plausible NLO material as the value being six times greater than the standard urea and, MEP reveals the charge related properties, and molecular orbitals predicts the stability of the compound. Further, the scaffolds and the functional units along with the charge related properties etc. imply that the molecule **1f** could serve as an effective bio-agent as well.

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