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Research Article

MOLECULAR STRUCTURE, FRONTIER MOLECULAR ORBITAL AND SPECTROSCOPIC EXAMINATION ON DIHYDROPYRIMIDINONES: A COMPARATIVE COMPUTATIONAL APPROACH

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ABSTRACT

Dihydropyrimidinones (DHPM's) have received a large amount of attention due to the interesting biological profile related to this heterocyclic system. In the past few years, DHPM's were explored as anti-cancer, anti-HIV, anti-tubercular, anti-inflammatory, antimicrobial, antihypertensive, analgesic, anticonvulsant, antioxidant and numerous others. In the present study,5-acetyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (ACMD) and1-(4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethan-1-one (CMTT) have been studied and compared by using Density Functional Theory (DFT). Optimized geometry, frontier molecular orbital, global reactivity descriptors, and thermodynamic parameters have been computed for ACMD and CMTT. DFT/B3LYP method at basis set 6-311 G(d, p) has been employed for the computational study. Spectroscopic methods like Fourier-transform infrared spectroscopy (FTIR), Proton Magnetic Resonance (PMR), Carbon Magnetic Resonance (CMR) spectroscopic methods have been used for the structural analysis. Molecular electrostatic potential for ACMD and CMTT are plotted to investigate electrophilic and nucleophilic sites to apprehend the chemical behavior.

Keywords: DFT, 6-311G(d,p), HOMO-LUMO, Molecular electrostatic potential, 5-acetyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 1-(4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethan-1-one

1. INTRODUCTION

Heterocyclic chemistry has produced numerous pharmacologically essential motifs and has achieved its unique place in the medicinal chemistry. Heterocyclic compounds exhibit significant role in biological chemistry [1-4]. Many biologically effective synthetically and naturally derived natural compounds incorporate heterocyclic framework. Among all, DHPM's have been emerged as essential heterocyclic compounds and have gained considerable interest due to their excellent profile of pharmacological properties [5, 6]. The very essential aspect concerning pyrimidine is its presence in essential building blocks of nucleic acids as thymine, cytosine, and uracil. Due to this, many synthetic modifications have been made in terms of structure to derive newer biological properties. DHPM's and related derivatives have been studied for anti-cancer [7, 8], anti-HIV [9], anti-tubercular [10], anti-inflammatory [11], antimicrobial [12], antihypertensive [13], analgesic [14], anticonvulsant [15], antioxidant [16, 17], and many other important biological activities [18-20]. Nifedipine(**1**), Monastrol (**2**), Piperastrol (**3**), MON-97 (**4**), Methylthiouracil (**5**), and 5-Fluorouracil (**6**) are some noteworthy examples of medicinal agent containing pyrimidine skeleton (**Fig.1**).

The theoretical calculations based on DFT have been successfully explored largely in past few years to determine various structural aspects of synthetically and pharmacologically vital organic motifs. Vitally, DFT calculations can also provide easy and simple approach to derive correct reaction pathways. The two important previously synthesized [21] DHPM's have been studied to interpret structural and electronic aspects. To the best of our knowledge, this is the first report on the structural and spectral characteristics of the title molecules.

In the present work, optimized molecular structure has been computed by DFT/B3LYP method using basis set 6-311 G (d, p). The molecular electrostatic potential surface (MESP) has been plotted over the optimized geometry for a better understanding of the reactive sites and Frontier Molecular Orbital examination have been performed to elucidate information concerning the electronic and optical behavior.

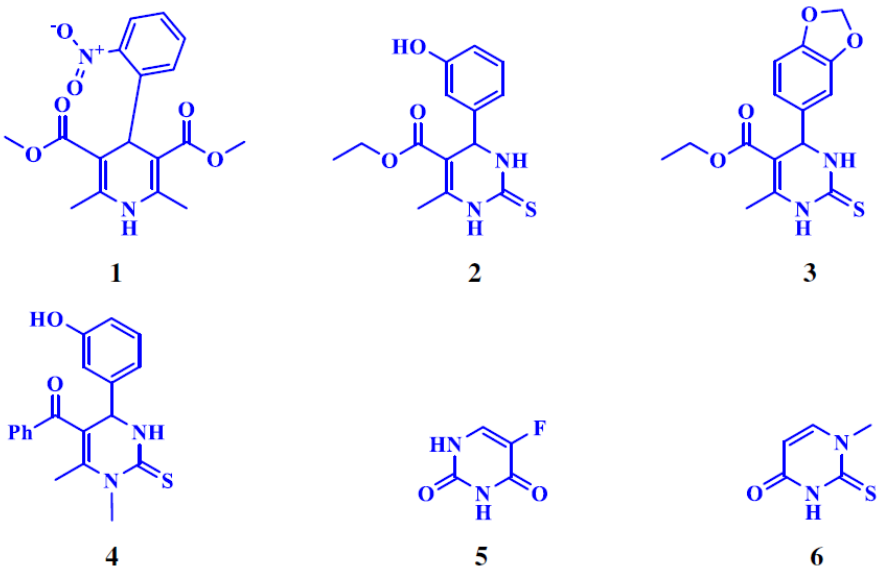
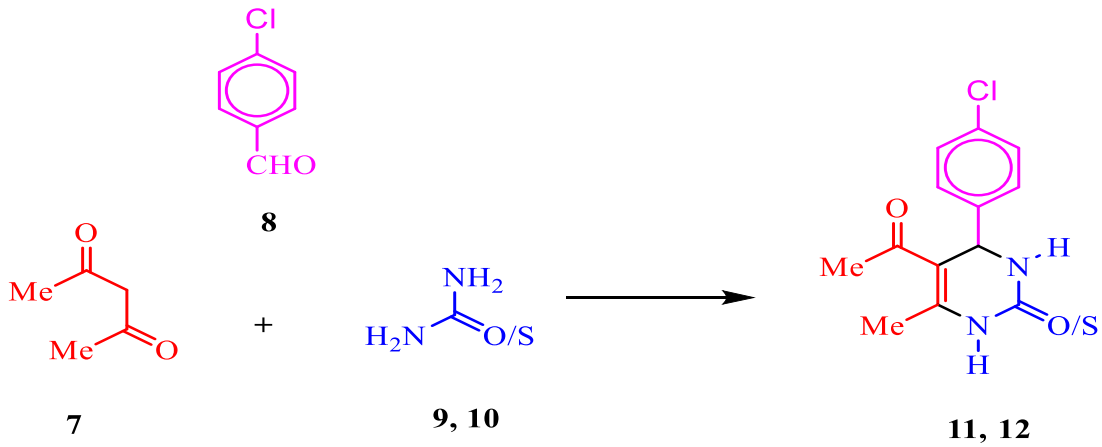


Fig. 1: Some noticeable examples of pyrimidine containing biologically active compounds



Scheme 1: Synthesis of dihydropyrimidinones

2. EXPERIMENTAL

2.1. Material and Methods

The chemicals with high purity were purchased from local distributor. The chemicals were used as received without any further purification. Melting point was determined in open capillary and uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker using $CDCl_3$ as solvent, FT-IR spectra were obtained with potassium bromide pellets. Reaction was monitored by thin-layer chromatography using aluminium sheets with silica gel 60 F254 (Merck).

2.2. Procedure for the synthesis of title compounds

The synthesis of ACMD and CMTT is presented in Scheme 1.

Previously reported method has been employed for the synthesis of DHPM's [21]. In a typical synthesis method, 4-chlorolbenzaldehyde (0.01 mol), urea or thiourea (0.01 mol), acetyl acetone (0.01 mol) and Lanthanum oxide Nanopowder (8 mol %) were mixed in ethanol taken in a 50 ml round bottom flask. This mixture was

then subjected to ultrasound waves until the formation of desired product ACMD and CMTT (monitored by TLC). The crude product was then added into the ethyl acetate to remove the catalyst. The product was finally recrystallized and analyzed using FT-IR, ^{1}H NMR, ^{13}C NMR methods.

2.3. Computational Details

Density Functional Theory calculations were computed on an Intel (R) Core (TM) i5 computer using Gaussian-03(W) program package without any constraint on the geometry [22]. The geometry of the title molecules was optimized by DFT/B3LYP method using 6-311G (d, p) basis set. Optimized geometry was made using the Gauss View 4.1 molecular visualization program. To investigate the reactive sites of the title compounds, the molecular electrostatic potential surface (MESP) was computed using the same method. All the calculations were carried out for the optimized structure in the gas phase.

3. RESULTS AND DISCUSSION

3.1. Spectral analysis of 5-acetyl-4-(4-chloro-phenyl)-6-methyl-3,4-dihydropyrimidin-2-(1H)-one (ACMD)

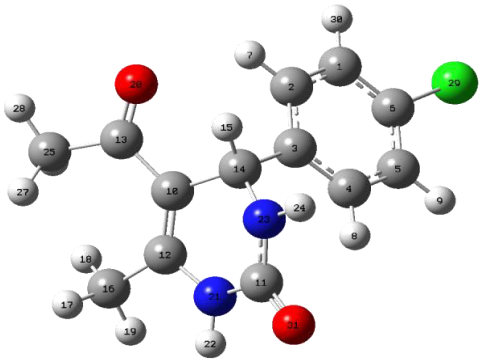
White solid; M.P. 220°C; ***FT-IR (cm^{-1}):*** 3219.67, 3099.83, 2978.50, 1699.53, 1644.01, 1572.86, 1485.99, 1287.25, 865.98; ***^{1}HNMR (400MHz, DMSO-d6); δ (ppm)***: 2.17(s, 3H), 2.35(s, 3H), 5.30(d, J = 3.88 Hz, 1H), 7.25 (m, 2H), 7.19 (m, 2H), 9.73(d, 1H), 10.30(s, 1H); ***^{13}C NMR (100 MHz, DMSO-d6); δ (ppm)***: 18.29, 30.36, 53.16, 110.21, 128.31, 128.41, 132.35, 141.65, 144.72, 174.20, 194.34.

3.2. Spectral analysis of 1-(4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethan-1-one (CMTT)

White solid; M.P. 219°C; ***FT-IR (cm^{-1})***: 3278.99, 3109.25, 2908.65, 1697.36, 1612.49, 1427.32, 1234.44, 786.96; ***^{1}HNMR (400MHz, DMSO-d6); δ (ppm)***: 2.13(s, 3H), 2.29(s, 3H), 5.24(d, J = 3.8 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 9.75(s, 1H), 10.31(s, 1H); ***^{13}C NMR (100 MHz, DMSO-d6); δ (ppm)***: 18.85, 31.07, 53.53, 110.85, 128.94, 129.15, 132.78, 142.33, 145.49, 174.72, 195.19; DEPT-135; δ (ppm) - 18.86(CH_3), 31.07(CH_3), 53.53(CH), 128.94(Ar CH), 129.15 (Ar CH) (all up), 110.85, 132.78, 142.33, 145.49, 174.72, 195.19 (absent)

3.3. Computational Study

The optimized molecular structure of title molecules is depicted in Fig 2. Molecular structures 13 and 14 represent optimized geometrical structures for ACMD and CMTT respectively. The optimized molecular geometry provides a good deal of information about the spatial orientation of various atoms in a molecule. From optimized molecular structures, it can be easily seen that both ACMD and CMTT possess C1 point group symmetry due to the overall asymmetry of the molecules. Furthermore, it is evident that both molecules contain a planar aromatic ring. The individual non-planarity of the pyrimidine ring can be attributed to the CH group which is either above or below the plane. Due to this fact, both the molecules lack the molecular plane (σh). It can also be seen that the remaining skeleton of these molecules is in perfect planar position and therefore can have extended conjugation. This information is very much useful for the determination of various spectroscopic entities.



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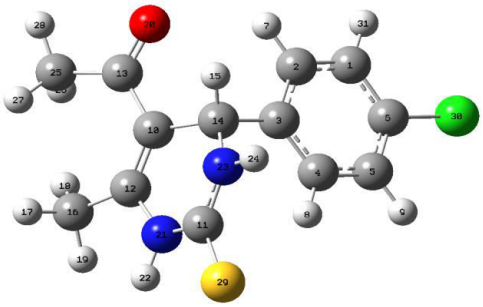

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Fig. 2: Optimized molecular structures of ACMD (13), CMTT (14)

From the Frontier Molecular orbital (FMO) analysis the information about charge transfer within the molecule can be anticipated. Fig 3 (15) demonstrates HOMO-

LUMO picture of ACMD and Fig 3 (16) is for CMTT. The charge transfer phenomenon supports the bioactive property of the molecule. The FMO study gives an understanding of the reactivity of the molecule and the active site can be established by the distribution of frontier orbital. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) is very crucial parameters for the investigation of quantum chemical parameters. The HOMO-LUMO study is also used for predicting the most reactive position in π-electron systems and additionally explains several types of reactions in the conjugated frameworks. The less HOMO-LUMO energy gap suggests the molecule is softer and a large gap suggests a molecule is harder. The HOMO-LUMO gap in ACMD is 4.82 eV and in CMTT is 4.20 eV. Both molecules are having less HOMO-LUMO energy gap which suggests a softer nature. The molecule CMTT has less energy gap than CMDD that implies the former is softer than the latter. In the present study quantum chemical parameters have been established which provide good deal of comparison between these two molecules. The electronic parameters are presented in Table 1 and all the quantum chemical parameters are tabulated in Table 2.

Table 1: Electronic parameters

Entry	E_{Total}(a.u.)	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE (eV)	I (eV)	A (eV)
ACMD	-1223.61	-6.59	-1.77	4.82	6.59	1.77
CMTT	-1546.56	-6.24	-2.16	4.20	6.24	2.16

Note: $I = -E_{HOMO}$ & $A = -E_{LUMO}$

Table 2: Quantum chemical parameters

Entry	χ (eV)	η (eV)	σ (eV^{-1})	ω (eV)	Pi (eV)	ΔNmax (eV)	Dipole moment (Debye)
ACMD	4.18	2.41	0.41	3.62	-4.18	1.73	4.56
CMTT	4.20	2.04	0.49	4.32	-4.20	2.06	4.89

Note: $\chi = (I + A)/2$; $\eta = (I - A)/2$; $\sigma = 1/\eta$; $\omega = Pi^2/2\eta$; $Pi = -\chi$; $\Delta Nmax = -Pi/\eta$

The ionization potential (I) provides information about ionization capability of the molecule whereas electron affinity (A) provides information regarding electron attraction capability. Our study reveals that ionization in CMTT is easier than ACMD; as former has less value of ionization potential. On the contradictory ACMD has more electron affinity than CMTT. The absolute hardness (η) and global softness (σ) corresponds to the HOMO – LUMO energy gap. The chemical potential (Pi) can be explored to determine the ionization capability of an electron. The global electrophilicity index (ω) provides idea about electrophilic character of the molecule. The electronic charge transfer is predicted by ΔNmax. The global reactivity descriptors' study indicates both the molecules are strong electrophiles and therefore can undergo nucleophilic attack easily. The molecule CMTT involves more electron transfer than ACMD as predicted by ΔNmax.

The MESP plots are displayed in Fig 4. The properties like dipole moment, electronegativity, partial charges and chemical reactivity of any molecule can be correlated with the aid of molecular electrostatic potential. The molecular electrostatic potential is a total charge distribution of a molecule space. The regions of positive, negative and neutral potentials are indicated by different colours. Red suggests a zone of negative electrostatic potential and the white zone of positive electrostatic potential. In the present case, it can be observed than negative electrostatic potential lies over oxygen atom in both the molecules. On the other hand, the positive electrostatic potential is situated over hydrogen atoms of two aromatic rings. The blue part indicates zero electrostatic potential and it is mainly located over hydrogen atoms of aromatic ring in both ACMD and CMTT. These zones of various electrostatic potential can give valuable data in regards to various sorts of intermolecular interactions and hence one can foresee the chemical behaviour of the molecule. The different thermodynamic properties were computed from the theoretical vibrational frequencies and are presented in

Table 3. The thermodynamic data disclosed in this could provide valuable insights to the other thermodynamic parameters. In present investigation, the theoretical thermodynamic calculations based on vibrational data provided valuable insights on thermodynamic stability of the title molecules. Our study reveals that the molecule CMTT is thermodynamically more stable than ACMD. The molecule ACMD possesses more degree of vibrational freedom as compared to CMTT. Also, it has higher value of heat capacity.

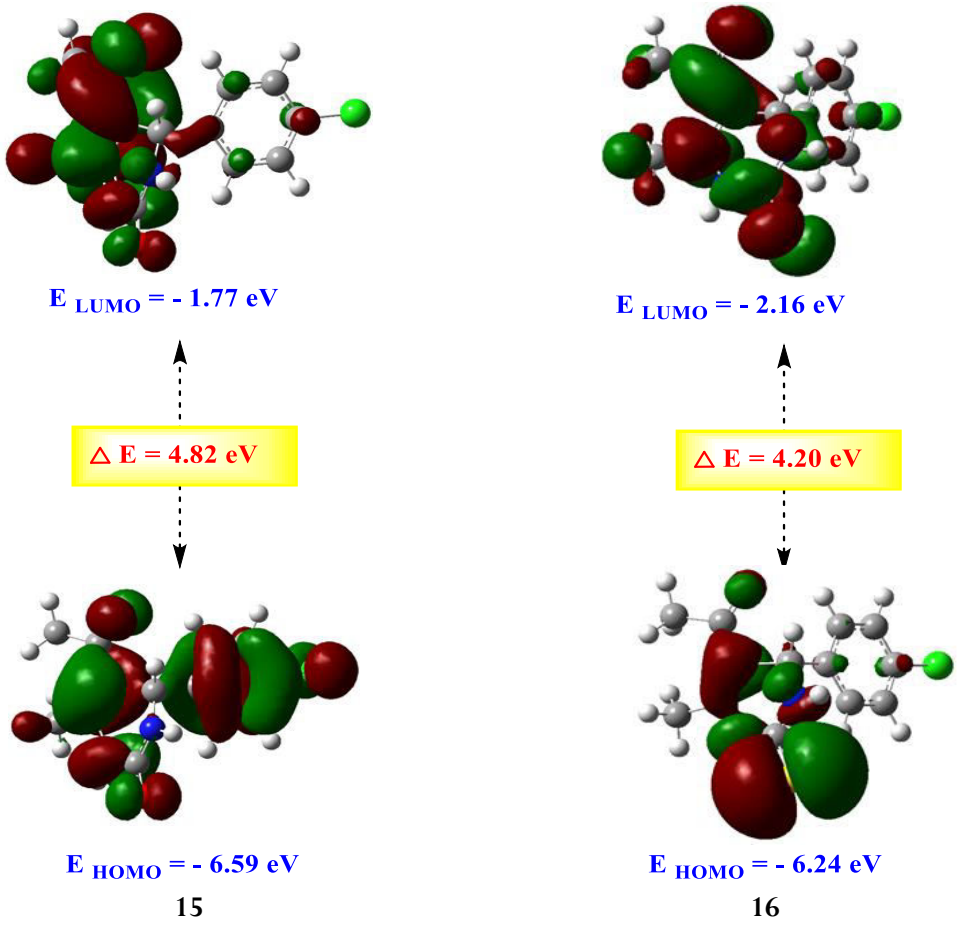

Fig. 3: FMO picture; 15 for ACMD and 16 for CMTT

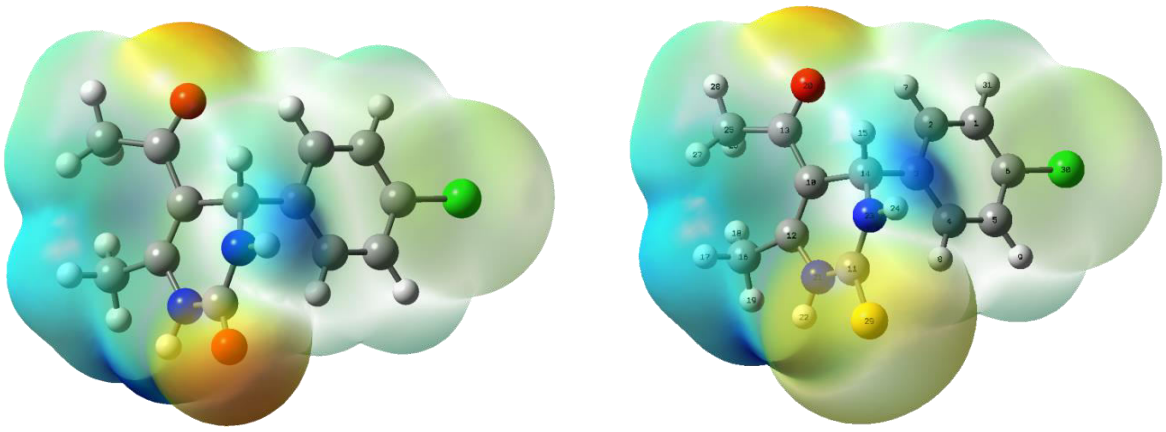

Fig. 4: Molecular electrostatic potentials; 17 for ACMD and 18 for CMTT

Table 3: Thermodynamic properties

Parameter	ACMD	CMTT
E total (kcal mol^{-1})	161.985	160.238
Translational	0.889	0.889
Rotational	0.889	0.889
Vibrational	160.207	158.461
Heat Capacity at constant volume, Cv (cal $mol^{-1}K^{-1}$)	62.985	62.015
Translational	2.981	2.981
Rotational	2.981	2.981
Vibrational	57.023	56.053
Total entropy S (cal mol^{-1} K^{-1})	135.059	129.451
Translational	42.613	42.788
Rotational	33.795	34.210
Vibrational	58.651	52.453
Zero point Vibrational Energy Ev_0 (kcal mol^{-1})	151.5577	150.14498
Rotational constants (GHZ):	0.55629	0.43734
	0.23783	0.22596
	0.19350	0.17061
E (RB3LYP) (a.u.)	-1223.61	-1546.56

4. CONCLUSIONS

In the present research work, DFT/B3LYP method at 6-311 G(d,p) basis set has been fantastically used for the exploration of various important structural, electronic and quantum chemical parameters of title molecules. An elaborative correlation among ACMD and CMTT has been presented. The properties like the HOMO-LUMO energy gap, charge transfer phenomenon, molecular electrostatic potential, and global reactivity descriptors have been explored using the same level of method. Additionally, important thermodynamic statistics have been computed and these two molecules have been compared based on this data to elucidate their thermodynamic behaviour.

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Conflict of Interest

The authors declare no conflict of interest.

6. REFERENCES

1. Adole VA, Pawar TB, Jagdale BS. *J. Chin. Chem. Soc.*, 2020; **67**:306-315.
2. Adole VA, Jagdale BS, Pawar TB, Sagane AA. *S. Afr. J. Chem.*, 2020; **73(1)**:35-43.
3. Chobe SS, Adole VA, Deshmukh KP, Pawar TB, et al. *Arch. Appl. Sci. Res.*, 2014; **6(2)**:61-66.
4. Adole VA, More RA, Jagdale BS, Pawar TB, et al. *Chemistry Select.*, 2020; **5(9)**:2778-2786.
5. Kaur R, Chaudhary S, Kumar K, Gupta MK, et al. *Eur. J. Med. Chem.*, 2017; **132**:108-134.
6. de Fatima A, Braga TC, Neto LD, Terra BS, et al. *J. Adv. Res.*, **6(3)**:363-373.
7. Liu Y, Liu J, Zhang R, Guo Y, et al. *Molecules*, 2019; **24(5)**:891.
8. Rana K, Arora A, Bansal S, Chawla R. *Indian. J. Pharm. Sci.*, 2014; **76(4)**:339-347.
9. Kim J, Ok T, Park C, So W, et al. *Bioorg. Med. Chem.Lett.*, 2012; **22(7)**:2522-2526.
10. Trivedi AR, Bhuva VR, Dholariya BH, Dodiya DK, et al. *Bioorg. Med. Chem.Lett.*, 2000; **20(20)**:6100-6102.
11. Tale RH, Rodge AH, Hatnapure GD, Keche AP, et al, *Med. Chem. Res.*, 2012; **21(12)**:4252-4260.

12. Akhaja TN, Raval JP. *Eur. J. Med. Chem.*, 2011; **46(11)**:5573-5579.
13. Rovnyak GC, Atwal KS, Hedberg A, Kimball SD, et al. *J. Med. Chem.*, 1992; **35(17)**:3254-3263.
14. Sondhi SM, Singh N, Johar M, Kumar A. *Bioorg. Med. Chem.Lett.*, 2005; **13(22)**:6158-6166.
15. Said SA, Amr AE, Sabry NM, Abdalla MM. *Eur. J. Med. Chem.*, 2009; **44(12)**:4787-4792.
16. Mansouri M, Movahedian A, Rostami M, Fassihi A. *Res. Pharm. Sci.*, 2012; **7(4)**:257-264.
17. Gangwar N, Kasana VK. *Med. Chem. Res.*, 2012; **21(12)**:4506-4511.
18. Sati B, Sati H, Nargund LV, Khaidem S, et al. *Orient. J. Chem.*, 2012; **28(2)**:1055-1059.
19. da Silva DL, Reis FS, Muniz DR, Ruiz AL, et al. *Bioorg. Med. Chem.*, 2012; **20(8)**:2645-2650.
20. Shaikh A, Meshram JS. *Cogent Chemistry*, 2015; **1(1)**:1-10.
21. Adole VA, Pawar TB, Koli PB, Jagdale BS. *J.Nanost. Chem.*, 2019; **9(1):**61-76.
22. Frisch MJ, Trucks GW, Schlegal HB, et al. Gaussian 03, Revision E.01, Gaussian, Inc, Wellingford CT, USA 2004.