Synthesis and Theoretical Studies of the Electrophilic and Nucleophilic behavior of some Ethyl-4-(4-Substitutedphenyl)-6-Methyl-2-Oxo/Thioxo-1, 2, 3, 4-Tetrahydropyrimidine-5-Carboxylate derivatives using DFT based reactivity descriptors

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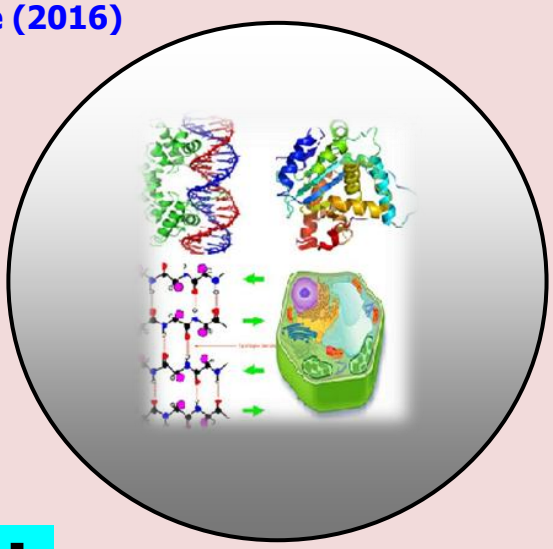

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RESEARCH PAPER

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Synthesis and Theoretical Studies of the Electrophilic and Nucleophilic behavior of some Ethyl-4-(4-Substitutedphenyl)-6-Methyl-2-Oxo/Thioxo-1, 2, 3, 4-Tetrahydropyrimidine-5-Carboxylate derivatives using DFT based reactivity descriptors

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ABSTRACT

The concepts of hardness and Fukui function have been associated with the theory of chemical reactivity in molecules. Calculations of DFT based reactivity descriptors are reported for six pyrimidine derivatives in order to get insight into the factors determining the nature of their interactions with electrophiles and nucleophiles. Global reactivity descriptors such as ionization energy, molecular hardness, electrophilicity, nucleophilicity, frontier molecular orbital energies and shapes, the condensed Fukui functions and total energies were determined which were used to identify the differences in the reactivity of different pyrimidines. In this paper the microwave assisted synthesis, mass spectral analysis and reactivity of different pyrimidines using DFT studies and Fukui function of six Ethyl-4-(4-substitutedphenyl)-6-methyl-2-oxo/thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives are being reported.
Keywords: Pyrimidine, DFT, Electrphilicity and Fukui Function.

INTRODUCTION

In the family of heterocyclic compounds, nitrogen-containing heterocycles with a sulfur/oxygen atom are an important class of compounds in medicinal chemistry. Dihydropyrimidinones (DHPMs) and their derivatives exhibit wide range of biological activities (C.O. Kappe 1993) such as antibacterial, antiviral, antitumor and anti-inflammatory actions. In the Biginelli reaction, thiourea was used with success to provide the corresponding 3,4-dihydropyrimidin-2(1H)-thiones, which have been reported to possess diverse pharmacological activities such as antiviral, antibacterial, and antihypertensive activity as well as efficacy as calcium channel blockers (G.C. Rovnyak, et. al. 1995, K.S. Atwal, et. al. 1990, K.S. Atwal, et. al. 1991) and antagonists.

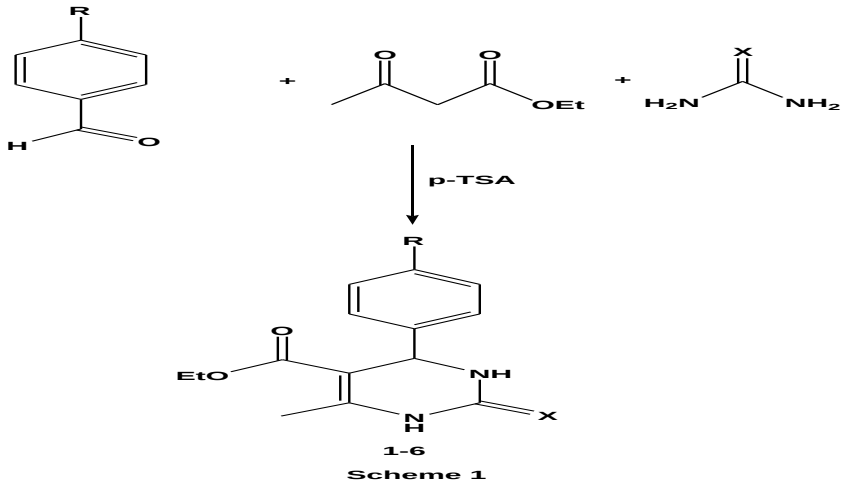
The object of present work is to synthesize Ethyl-4-(4-substitutedphenyl)-6-methyl-2-oxo/thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives using the microwave assisted conditions and also carry out the theoretical study of the electronic and structural parameter of these compounds in order to find the effect of these parameters on the reactivity towards electrophiles and nucleophiles. From the calculations we have tried to explain which site is favoured for such attacks. Computational calculations were obtained by means of $B_3LYP/6\text{-}31Gd$ method. Parameters like E_{HOMO}, E_{LUMO}, Energy gap, dipole moment, global hardness, total energy change were calculated. The local reactivity has been analyzed by means of Fukui indices, since they indicate the reactive regions, in the form of nucleophile and electrophile behaviour of each atom in molecule.

EXPERIMENTAL

Melting points were taken in an electrically heated instrument and are uncorrected. Compounds were routinely checked for their purity on silica gel TLC plates and the spots were visualized by iodine vapors. PMR spectra were recorded on Bruker DRX 300 MHz FT NMR spectrometer using TMS as internal reference and chemical shift values are expressed in δ units. Mass spectra were run on Jeol SX -102 spectrometer.

GENERAL PROCEDURE

For the synthesis of compounds 1-6, a mixture of the appropriate aldehyde, ethylacetoacetate and urea or thiourea in equimolar concentrations with a catalytic amount of p-TSA in a 100 mL glass tube was irradiated in a microwave oven (Scheme 1). The reaction details are given in table 1. The reaction was monitored by TLC. After completion (2 – 10 min), poured the reaction mixture in water and extracted with ethyl acetate. The extract was washed successively with sodium thiosulfate solution, sodium hydrogencarbonate solution and water. The extract was then dried over anhydrous sodium sulfate and evaporated to yield the desired product. The compounds were recrystallized from water.



1-6

Scheme 1

Table 1. Reaction Details.

Comp. No.	Name	-R	X
1	ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	$-OCH_3$	O
2	ethyl 6-methyl-4-(4-nitroyphenyl)- 2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	$-NO_2$	O
3	ethyl 4-(4-(dimethylamino)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5- carboxylate	$-N(CH_3)_2$	O
4	ethyl 4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	$-OCH_3$	S
5	ethyl 6-methyl-4-(4-nitroyphenyl)- 2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	$-NO_2$	S
6	ethyl 4-(4-(dimethylamino)phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	$-N(CH_3)_2$	S

No.	Aldehyde	Amide	Time (Minutes)	Yield (%)	Mp (^{0}C)
1	4-methoxybenzaldehyde	Urea	2	65.5	196
2	4-nitrobenzaldehyde	Urea	5	72	182
3	4-(dimethylamino)phenyl	Urea	6	71	206
4	4-methoxybenzaldehyde	Thiourea	6	79	156
5	4-nitrobenzaldehyde	Thiourea	7	83.4	177
6	4-(dimethylamino)phenyl	Thiourea	10	72	210

Table 2. Spectral Data.

Comp. No.	Mass (m/z)	^{1}H NMR Data (DMSOd_6)
1	290, 218, 260, 184, 108	6.0(s,1H,NH), 7.4(s,1H,NH), 1.7(s,3H,CH_3), 1.3(t,3H,CH_3CH_2), 4.2(q,2H,CH_3CH_2), 6.6-7.0(m,4H,ArH), 3.7(s,3H,OCH_3), 5.1(s,1H,CH).
2	305, 233, 260, 184, 123	6.2(s,1H,NH), 7.0(s,1H,NH), 1.7(s,3H,CH_3), 1.3(t,3H,CH_3CH_2), 4.2(q,2H,CH_3CH_2), 7.3-8.1(m,4H,ArH), 5.3(s,1H,CH).
3	303, 260, 184, 231, 121	5.8(s,1H,NH), 6.7(s,1H,NH), 1.7(s,3H,CH_3), 1.4(t,3H,CH_3CH_2), 4.0(q,2H,CH_3CH_2), 6.5-6.9(m,4H,ArH), 3.6(s,6H,H_3CNCH_3) ,5.4(s,1H,CH).
4	306, 276, 234, 200	2.0(s,1H,NH), 2.3(s,1H,NH), 1.7(s,3H,CH_3), 1.3(t,3H,CH_3CH_2), 4.2(q,2H,CH_3CH_2), 6.6-7.0(m,4H,ArH), 4.1(s,1H,CH).
5	321, 276, 249, 200	2.0(s,1H,NH), 2.8(s,1H,NH), 1.7(s,3H,CH_3), 1.5(t,3H,CH_3CH_2), 3.2(q,2H,CH_3CH_2), 7.3-8.1(m,4H,ArH), 4.3(s,1H,CH).
6	319, 276, 247, 200	2.3(s,1H,NH), 2.7(s,1H,NH), 1.6(s,3H,CH_3), 1.6(t,3H,CH_3CH_2), 3.0(q,2H,CH_3CH_2), 6.5-6.9(m,4H,ArH), 3.1(s,6H,H_3CNCH_3), 4.2(s,1H,CH).

COMPUTATIONAL METHODOLOGY

Quantum chemical calculations such as geometry optimization and molecular orbital energy calculation of molecules have been performed using Becke's three parameter exchange function (B3) with Lee-Yang-Parr correlation function with 6-31 G (d) at DFT level of theory. Studies of various reactivity descriptors for the six heterocycles were also carried out at the same level of theory using the same basis set. The Gaussian 09 package (M.J. Frisch, et. al. 2009) of program has been chosen for the different calculations.

The concept of the stability and reactivity of a molecular structure is best provided by DFT method (P. Geerlings, et. al. 2003).

An approximation for absolute hardness η was developed (R.G. Pearson 1987, R.G. Parr, et. al. 1991, R.G. Pearson 1985, R.G. Parr, et. al. 1983):

$\eta = 1/2 (I-A)$ (1)

Where, I is the vertical ionization energy and A is the vertical electron affinity.

According to the Koopman's theorem (T. Koopmans 1933), the ionization energy (I) and electron affinity (A) can be expressed through HOMO and LUMO energies:

$I = -\varepsilon_{HOMO}$ (2)

$A = -\varepsilon_{LUMO}$

Higher the HOMO energy, higher will be the reactivity of the molecule in the reactions with electrophiles. A lower LUMO energy is required for molecular reactions with nucleophiles (A. Rauk 2001).

So, the hardness of the molecule is related with gap between the HOMO and LUMO energies. A molecule is said to be hard if it has larger HOMO-LUMO energy gap (R.G. Pearson 1985).

$\eta = ½ (\varepsilon_{LUMO} - \varepsilon_{HOMO})$ (3)

The electron affinity together with ionization energy gives electronic chemical potential μ as defined by Parr and Pearson (R.G. Parr, et. al. 1983).

$\mu = -1/2 (I+A)$ (4)

Parr introduced the global electrophilicity index ω (R.G. Parr, et. al. 1999) which is calculated using the electronic chemical a potential μ and chemical hardness η:

$\omega = \mu^2 / 2\eta$ (5)

The electrophilicity index measures the natural tendency of a species to accept electrons. A lower value of ω characterizes a good, more reactive, nucleophile; and conversely a good electrophile is characterized by a high value of ω.

The hard and soft acids and bases (HSAB) principle has become an important tool for the prediction of the reactivity of chemical systems (R.G. Parr, et. al. 1989, P.W. Ayres 2000, R.G. Parr, et. al. 1984). In DFT, this principle is used as Fukui function (R.G. Parr, et. al. 1989). Fukui function $f(r)$ is defined as a local reactivity descriptor used to indicate the change in the number of electrons in a molecule.

Hence it indicates the propensity of the electronic density to deform at a given position to accept or donate electrons (P.W. Ayres 2000). Parr and Yang has defined the Fukui function as (R.G. Parr, et. al. 1989, P.W. Ayres 2000, R.G. Parr, et. al. 1984):

$f(r)=[\delta\rho(r)/\delta N]_v$ (6)

$f(r)= [\delta\mu/\delta v]_N$ (7)

Where, *v* is the external potential, *ρ* is the electronic density, and *N* is the total number of electrons of the system.

Equation 7 indicates the electron density of the atom or molecule in its frontier valence regions. *ρ(r)* being a discontinuous function of *N*, exhibits two different types of *f(r*) which can be defined as (W. Yang, et. al. 1986):

For nucleophilic attack

$f^+(r)=[\delta\rho(r)/\delta N]^+_{v=}[\rho_{N+1}(r)- \rho_N(r)]$ (8)

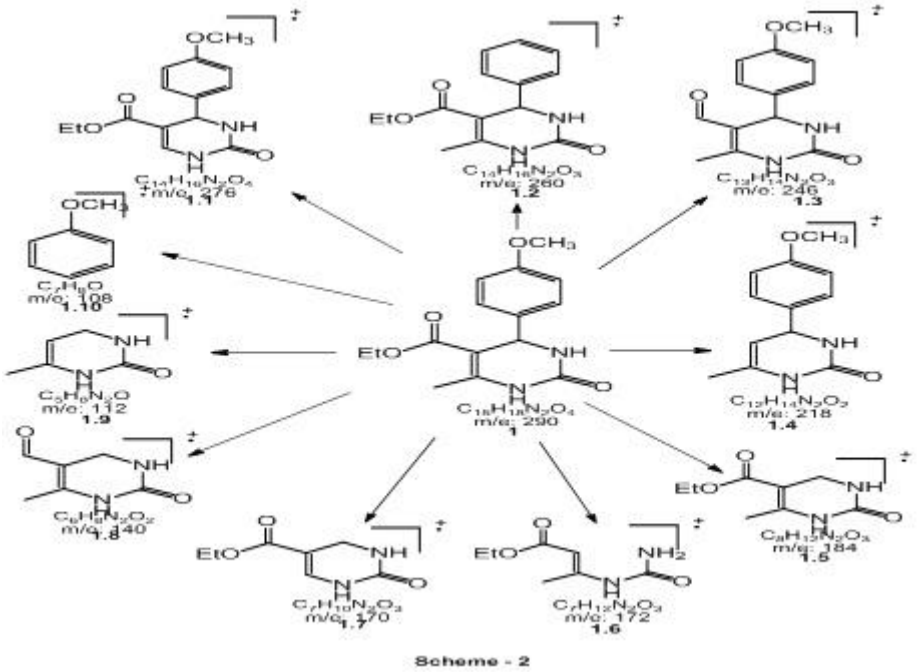
For electrophilic attack

$f^-(r)=[\delta\rho(r)/\delta N]^-_{v=}[\rho_N(r)- \rho_{N-1}(r)]$ (9)

RESULTS AND DISCUSSIONS

MASS SPECTRAL ANALYSIS

Mass spectral studies of ethyl – 4 - (4 - substiutedphenyl) – 6 – methyl – 2 - oxo/thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate has shown the variation in fragmentation only due to the differently substituted phenyl ring and oxo/thioxo groups (Scheme 2). All the compounds in general have exhibited a similar pattern of fragmentation. The m/e values of various radical ions of compounds 1-6 are given in table 2.



Scheme - 2

GEOMETRY PARAMETERS AND REACTIVITY DESCRIPTORS

The optimized structures of the six heterocycles are given in figure 1. The calculated values of stability and reactivity descriptors such as total energy (E), ionization energy (*I)*, molecular hardness (*η)*, electrophilicity index (*ω)*, frontier molecular orbital energy gap of compounds 1-6, at DFT/ B_3LYP/ 6-31G(d) level of theory, are shown in table 3. Ionization energy forms the basis for the chemical reactivity of atoms and molecules. High ionization energy is responsible for high stability and chemical inertness whereas small ionization energy favors high reactivity of the atoms and molecules. Chemical hardness is referred to as a resistance towards the change in the electron density during a chemical reaction (N.O. Obi-Egbedi, et. al. 2011).

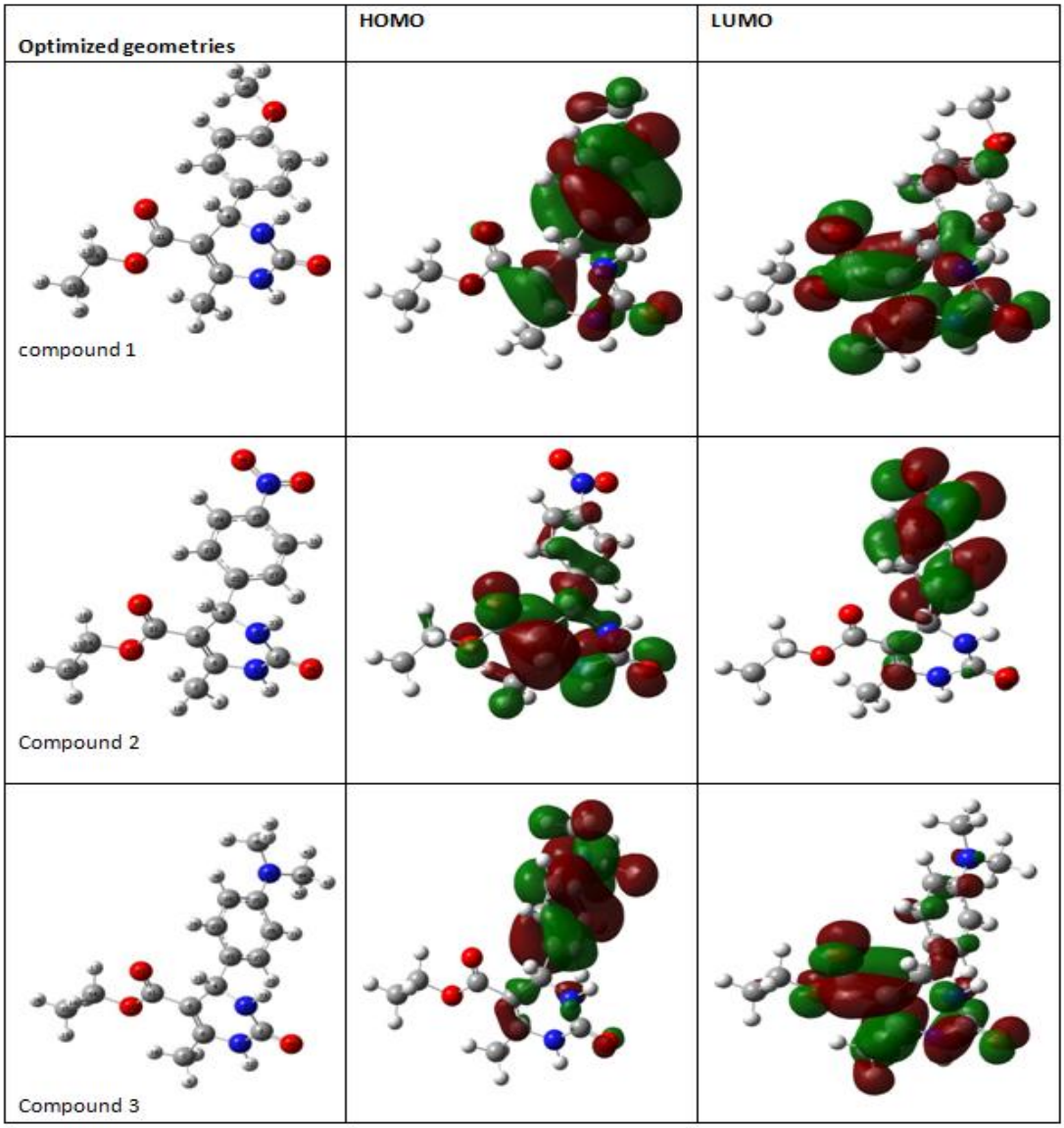
As observed from table 3, the smallest value of hardness of compound 6 suggests that it is most reactive and least stable whereas the largest value of compound 1 indicates that it is least reactive and most stable.

On the basis of global electrophilicity index *ω,* better susceptibility is expected for compound 6 due to its lower *ω* value. Compound 6 can better involve in the reactions with electrophiles as compared with other compounds.

Table 3. Calculated E (total energy), E_{HOMO}, E_{LUMO}, ΔE (frontier molecular orbital energy gap), η (molecular hardness), ω (electrophilicity), χ (Electronegativity) and I (ionization energy).

Comp No.	Total Energy	E_{HOMO}	E_{LUMO}	ΔE	η	ω	χ	I
1	-992.860	-0.2110	-0.0366	0.1744	0.1354	0.0169	-0.1252	0.0101
2	-1082.840	-0.2399	-0.0856	0.1543	0.1299	0.0162	-0.1603	-0.0304
3	-1012.304	-0.1847	-0.0326	0.1520	0.1243	0.0155	-0.1124	0.0118
4	-1315.818	-0.2093	-0.0540	0.1552	0.1262	0.0157	-0.1343	-0.0081
5	-1405.797	-0.2255	-0.0895	0.1359	0.1233	0.0154	-0.1632	-0.0398
6	-1335.262	-0.1776	-0.0496	0.1279	0.1160	0.0145	-0.1222	-0.0062

Figure 1. Optimized geometries, HOMO and LUMO orbitals of compound 1-6 calculated at DFT/ 6-31Gd



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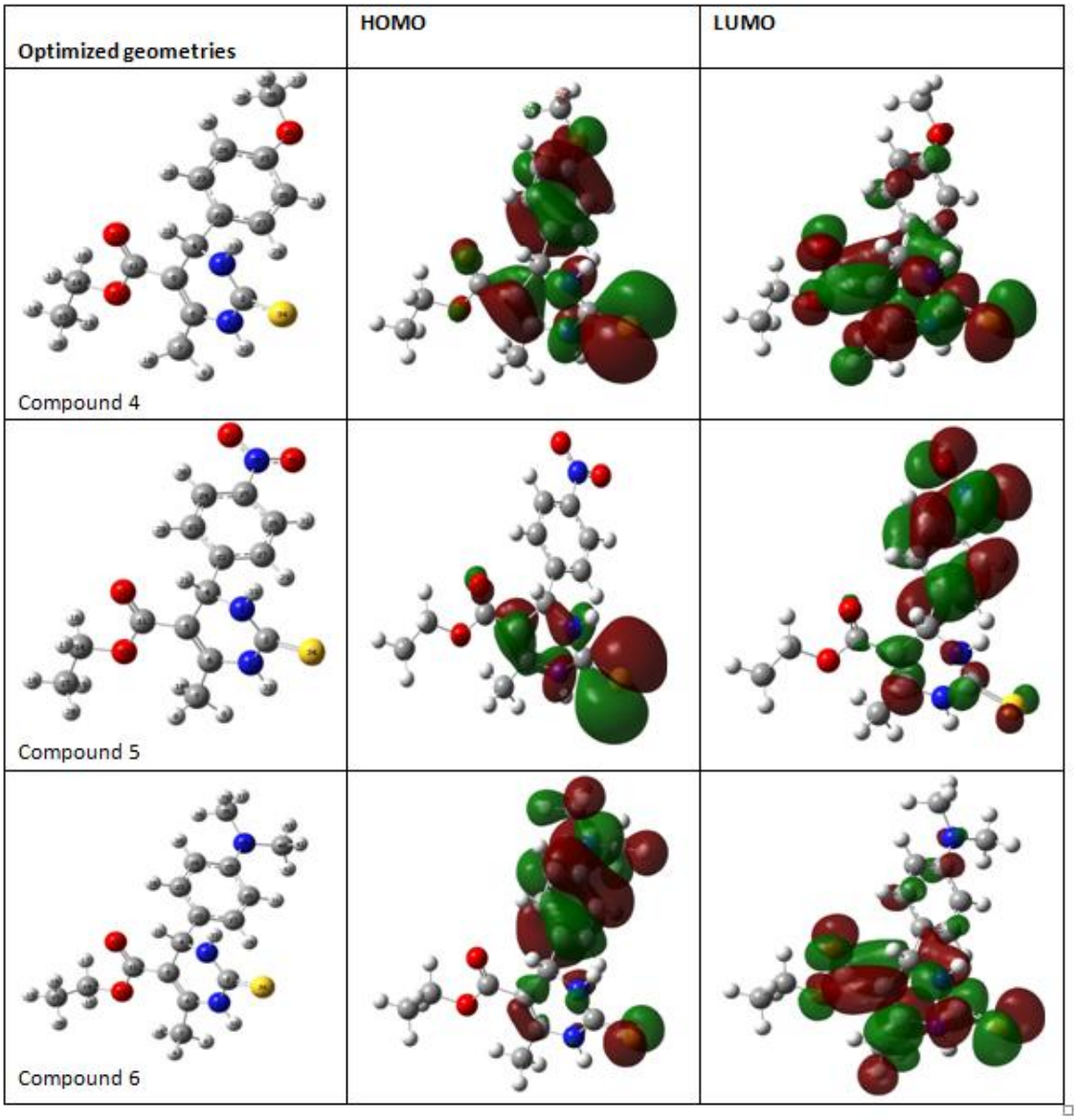

MOLECULAR ORBITALS

HOMO is defined as the orbital filled with electrons and possess the highest energy. Similarly, LUMO is defined as the orbital devoid of electrons and possesses the least energy. Thus, HOMO is responsible for electron donation while LUMO is responsible for accepting electrons (E.S.H. El-Ashry, et. al. 2006). The interaction between highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of reacting species is responsible for the transition of electron as defined by FMO (R.M. Issa, et. al. 2008). The energy gap is a very useful parameter to determine reactivity of the molecules towards the electrophilic and nucleophilic addition-substitution reactions. Small value of the energy gap between HOMO and LUMO will provide good reactivity index, as only a small amount of energy is required to remove an electron from the valence orbital. The frontier molecular orbital pictures of compounds 1-6 under study are shown in Figure 1. Here we have presented only the HOMO and LUMO orbitals. The energy difference between the HOMO and LUMO for compound 6 is smaller as compare to other compounds; indicating that this molecule could have better reactivity.

LOCAL REACTIVITY PARAMETERS

Parr and Yang proposed that the reactivity of an atom is directly proportional to the value of its Fukui function (R.G. Parr, et. al. 1984).

The $f^{+}_{(r)}$ is the change in the density of electron in the molecule during nucleophilic attack, while $f^{-}_{(r)}$ corresponds to the change in the electronic density in a molecule in an electrophilic attack. DFT derived condensed Fukui functions are obtained according to eq.8 for electrophilic addition or substitution reactions that occur with compounds 1-6. An atom wise absolute values of condensed Fukui function in compounds 1-6 for electrophilic attack (at DFT/B_3LYP/6-31G(d) levels of theory) are shown in Table 4 and for nucleophilic attack are given in table 5. Table 4 shows that for compound 1 and 3, the largest value of Fukui function for the attack of electrophile belongs to carbon of methyl group attached to pyrimidine ring and in compounds 4-6, it belongs to sulphur atom attached to pyrimidine ring. In compound 2, oxygen of nitro group attached to benzene ring has the greatest value. Table 5 showed that the largest value of Fukui function for the attack of nucleophile in compound 1 and 2 belongs to carbon of methyl group attached to pyrimidine ring while in compound 3 it belongs to carbon of methyl group attached to N of N, N-dimethyl amine group. Similarly, the highest values belong to suphur atom in compounds 4-6. So Fukui index values for compounds 1-6 suggest expectation that electrophilic and nucleophilic reaction could occur at these positions.

Table 4. f^{-}(r) (for attack of electrophile).

Comp. No.	6-methyl ($\underline{C}H_3$)	O$\underline{C}H_3$	N$\underline{O}_2$	N($\underline{C}H_3$)$_2$	X=O,S
1	**7C(0.1621)**	36C(0.0391)	-	-	34O(0.0978)
2	7C(0.0744)	-	**36O(0.1319)**	-	34O(0.0447)
3	**7C (0.1570)**	-	-	40C(0.0406)	34O(0.0953)
4	7C(0.1291)	36C(0.0402)	-	-	**35S(0.2117)**
5	7C(0.0778)	-	37O(0.1099)	-	**30S(0.1444)**
6	7C(0.1097)	-	-	36C(0.0406)	**5S(0.2033)**

Table 5. f^{+}(r) (for attack of nucleophile).

Comp. No.	6-methyl ($\underline{C}H_3$)	O$\underline{C}H_3$	N$\underline{O}_2$	N($\underline{C}H_3$)$_2$	X=O,S
1	**7C(0.0124)**	36C(-0.3790)	-	-	34O(-1.1881)
2	**7C(0.1258)**	-	36O(0.0325)	-	34O(0.0968)
3	7C (0.0751)	-	-	**36C(0.1341)**	34O(0.0481)
4	7C(0.0695)	36C(0.0909)	-	-	**35S(0.2568)**
5	7C (0.0907)	-	37O(0.0298)	-	**30S (0.3695)**
6	7C (0.0690)	-	-	35C(0.1235)	**5S (0.1702)**

CONCLUSION

The synthesis of six Ethyl-4-(4-Substitutedphenyl)-6-Methyl-2-Oxo/Thioxo-1,2,3,4-Tetrahydropyrimidine-5-Carboxylate derivatives were carried out with an eco-friendly microwave assisted technique through Beginelli Condensation reaction. The characterization was done on the basis of Mass spectra and ^{1}H-NMR spectral data. The Quantum chemical parameters were studied at DFT/ B_3LYP 6-31G(d) level of theory. Theoretical data revealed that compound no. 6 was found to be most reactive among the six studied compounds on the basis of hardness, global electrophilicity index and HOMO-LUMO energy gap. The calculation of Fukui function provided good knowledge about the electrophilic and nucleophilic sites in all the synthesized compounds.

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