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Theoretical and Experimental Investigations on the biological studies on Novel triazino quinolines

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Abstract

Novel Substituted 4′-methyl-3-thioxo-1,2,4-triazinoquinoline-5-ones are subjected to the anti bacterial and antifungal studies. Density Functional theory calculations of the compounds were performed using molecular structures with optimized geometries. The optimized geometry of the compounds were obtained by using 6-31G (d,p) basis set, and the Frontier Orbital energy and electrostatic potential were interpreted. The structure-activity relationships between the theoretical and wet lab results were discussed. All the products were screened *in vitro* antibacterial and antifungal activity against different micro organisms.

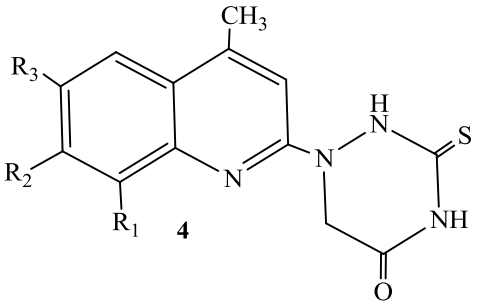
INTRODUCTION

Triazines and their derivatives are important groups of heterocyclic compounds. They have attracted considerable interest because of their exceptional biological antitumor, anti-HIV, antiviral[1], antimalarial, antimicrobial, and cytotoxic[2] activities.

Triazines have also found wide applications as herbicides and pesticides in the field of agriculture[5-8]. In structure-activity studies, in particular, net atomic charges, HOMO–LUMO energies, have been used to correlate with various biological activities. Density functional theory based descriptors have found immense usefulness in the prediction of reactivity of atoms and molecules as well as site selectivity[9]. The resourcefulness of density functional descriptors in the development of QSAR has been recently reviewed by Chattaraj *et al*[11]. Chemical hardness (g), chemical potential (l) and softness are known as global reactivity descriptors. Recently Parr et al[10] have defined a new descriptor to quantify the global electrophilic power of the molecule as electrophilicity index (ω) which defines a quantitative classification of the global electrophilic nature of a molecule within a relative scale.

To minimize the cost and the laborious work, a prior knowledge about the antimicrobial inhibitors will enable us to select the appropriate compounds to the wetlab and to identify the better antimicrobes.

Hence we made an attempt to study the Global descriptors and electrophillic index of the novel synthesised triazino quinolines and those compounds were subjected to the wet lab analysis. The structure activity relationship was compared.



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Substituted 4′-methyl-3-thioxo-1,2,4-triazinoquinoline-5-ones

a) R_1= R_3=H R_2= CH_3 b) R_1=R_2=R_3=H c) R_1=Cl, R_2=R_3=H d) R_1=H, R_2=Cl, R_3=H

Computational Calculations

Density functional theory calculations of the compounds performed using molecular structures with optimized geometries. The geometry optimization was carried out using 6-31G (d, p) basis set.

The energy gap of HOMO and LUMO, the global hardness (η), the chemical potential (μ), electrophilicity index (ω) of the compounds have been calculated and tabulated in Table 1.

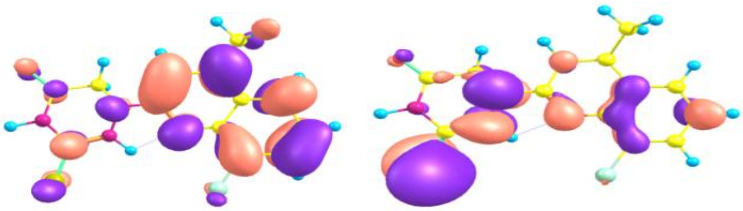
Table 1

Molecular Property	**a**	**b**	**c**	**d**
E_{HOMO}	-5.6799eV	-5.7302eV	-5.7963eV	-5.8630 eV
E_{LUMO}	-1.6841eV	-1.7707eV	-1.9625eV	-1.9780 eV
Energy gap	3.9958eV	3.9596eV	3.8338eV	3.8850eV
Ionisation potential(I)	5.6799eV	5.7302eV	5.7963eV	5.8630eV
Electron affinity(A)	1.6841eV	1.7706 eV	1.96250eV	1.9780eV
Global hardness(η)	1.9979	1.98	1.9125	1.9467
Chemical potential(μ)	-3.682	-3.75	-3.8794	-3.9205
Global electrophilicity (ω)	3.3928	3.5518	3.9260	3.9563

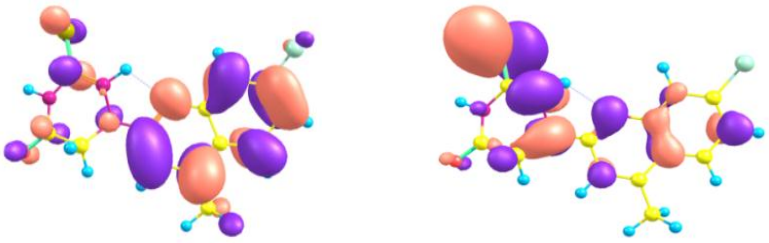
The LUMO and HOMO structures of the studied compounds are

4',7'-dimethyl-3-thioxo1,2,4-triazino quinoline-5-one(a)

4 '-methyl-3-thioxo1,2,4-triazino quinoline-5-one(b)



8'-chloro 4'-methyl-3-thioxo1, 2,4-triazino quinoline-5-one(c)



7'-chloro 4'-methyl-3-thioxo1,2,4-triazino quinoline-5-one(d)

RESULTS AND DISCUSSION

Computational Results

Parr et al[10].have reported that the frontier molecular orbitals of a molecule decides its physical and chemical properties play an important role in the electric and optical properties, also the electrophilicity index values increase with increasing chemical and biological activities for the reacting species in a biological system. As the energy gap decreases there is a decrease in excitation energy for the excited states, low stability and hence highly reactive. Here 7'-chloro 4'methyl-3-thioxo1,2,4-triazino quinoline-5-one (d) have lowest energy gap value, highest chemical potential and lowest hardness value.

The order of the parameters for the studied compounds is 1) chemical potential a<b<c<d 2) energy gap a>b>c>d, global electrophilicity a<b<c<d global hardness a>b>c>d. And also 7'-chloro 4'-methyl-3-thioxo1,2,4-triazino quinoline-5-one(d) exhibit high activity towards bacterial and fungi pathogens.

Antimicrobial Results

Agar Well Diffusion Method

Antimicrobial studies for the selected compounds have been carried out using the agar Well diffusion method. The compounds a,b,c,and d are studied at various concentrations of 10, 7.5, 5, 2.5 mg/ml in Dimethyl sulphoxide(DMSO). The control and standard were also studied simultaneously. The zone of inhibition was measured in millimeter. The results were observed and recorded. It was compared with standard antimicrobial agent ampicillin. The results were tabulated in Table 2.

Table 2

Sample name	Zone of inhibition (diameter in mm) 1µl/mL					
	S.aureus	*P. aeroginosa*	*E. coli*	*K. peumoniae*	S. pyogens	*c. albicans*
a	11mm	10mm	12mm	11mm	12mm	15mm
b	9mm	11mm	13mm	12mm	12mm	15mm
c	12mm	12mm	14mm	14mm	13mm	13mm
d	19mm	13mm	16mm	15mm	14mm	15mm
Ampicillin (AMP^{25})	11mm	16mm	12mm	12mm	10mm	10mm

Table shows the antibacterial and antifungal activities of the compound against bacterias *Staphylococcus aureus (S.a), K. peumoniae, Escherichia coli (E.c), Pseudomonas aeruginosa (P.a) S.pyogens and Candida albican*. It was found that compounds were active and compound 7'-chloro 4'methyl-3-thioxo1,2,4-triazino quinoline-5-one (d) is highly active towards the bacterias *S.aureus P. aeroginosa E. coli and S.pyogens.*Compound d is highly active towards *K. peumoniae.*But the

compounds a and b have high activity towards the fungi *c. albicans.* All the compounds are active than the standard.

CONCLUSION

A series of novel triazino quinoline molecules were screened *in vitro* for their anti microbial activity against different micro organisms. Density functional theory calculations of the compounds performed using molecular structures with optimized geometries. The geometry optimization was carried out using 6-31G (d,p) basis set, and the frontier orbital energy and electrostatic potential were discussed, and the structure-activity relationship was also studied.

The order of the parameters for the studied compounds and its biological activity is

2) chemical potential **a<b<c<d** the order of chemical potential **increases** from **a-d** and activity also **increases**.

1) energy gap **a>b>c>d**, global hardness **a>b>c>d** increases and activity **decreases** global electrophilicity **a<b<c<d** increases activity increases.

So among the four triazino quinolines **7'-chloro 4'methyl-3-thioxo1, 2, 4-triazino quinoline-5-one (d)** derivatives exhibit high activity towards bacterial pathogens.

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