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Antimicrobial Activity and Quantum Chemical Calculations of Pyrazol-2,3-Dihydrothiazole Sugar Derivatives

M. A. Migahed A. M. Al-Sabagh E.A. Khamis M.Abd-EL-Raouf E. G. Zaki*
Egyptian petroleum Research Institute, Nasr City, Cairo (11727), Egypt
E-mail:chemparadise17@yahoo.com

Abstract
A number of new [(pyrazol-4-yl) methylene] hydrazono-2,3-dihydrothiazoles, sugar hydrazones, and their N-glycoside derivatives were synthesized. The chemical structures of the synthesized compounds were confirmed by ^{1}H NMR technique. The newly synthesized compounds were tested for their antimicrobial activities and showed moderate to high inhibition activities. Quantum chemistry calculations were used to study the molecular geometry and electronic structure of the selected derivatives. The energy gap between the highest occupied molecular orbital (HOMO)and lowest unoccupied molecular orbital (LUMO) has been calculated using the theoretical computations to reflect the chemical reactivity and kinetic stability of compounds.
Keywords: 1*H*-pyrazole, aminothiazole, ethylchloroacetate, quantum chemical calculations, antimicrobial activity.

1. Introduction
The chemistry of 1*H*-pyrazole-containing compounds is particularly interesting because oftheir potential application in medicinal chemistry as analgesic [Wise, et al 1987, Gursoy et al 2000], anti-inflammatory [Tsuji et al 1997, Badawey et al,1998], antitumor [Daidone et al 1998, Hilgard et al 1992], antimicrobial [Prasath et al 2015, Nauduri et al 1998, Foks et al 2005, Dardari et al 2006, Gilbert et al 2006] and therapeutic agents [Jiang et al 1990], as well as based on their wide applications in agriculture as potent insecticides [Parlok,1998] and herbicides [Frinkelstein et al,1997, Schallner et al 1997], although scarcely found in nature [Eicher et al 1995]. Due to many promising pharmacological, agrochemical, and analytical applications, a number of substituted pyrazoles are being used as inhibitors of heat-shock protein 90 (HSP90) and as therapeutics of cancer andtherefore they have been the focus of many synthetic targets over the past decades [Jolly et al 2000].Furthermore, it has also been found that 1*H*-pyrazolebased heterocyclic structures haveattracted synthetic interest for being an essential moieties in many chemotherapeutic agents with potential antiparasitic[Rathelot et al 2000, Bernardino et al 2006], antimalarial[Katiyar et al 2005] and antiviral activities [Moukha et al 2002, Allen et al 2006].As far as the anticancer activity is concerned, literature citation revealed that a wide range of pyrazole derivatives were reported to contribute to a variety of antineoplastic potentials against a wide range of cancer cell lines [Baraldi et al 2004, Daidone et al 2004, Gopalsamy et al 2004,- Cocco et al 2006]. Moreover, many pyrazole derivatives are associated with antifungal, antibacterial [Rebecca et al 2012] and antipyretic [Tsurumi et al 1978] properties. On the other hand, thiazole derivatives are considered as one of the most important classes of heterocyclic compounds; their derivatives are characterized with high biological activity in pharmaceutical fields and have showed antibacterial, antifungal, antitumer, antiviral, anti-inflammatory and antineoplastic activities as well as inhibitory activity of growth of gastrointestinal[Mirjana et al 2014, Wang et al 2014], biliary and pancreatic adenocarcinoma cells. The aminothiazole ring system has found application in drug development for the treatment of HIV-infection, hypertension and inflammation.In view of the above findings and our interest in the attachment of sugar moieties to newly synthesized heterocycles[Abdel-Rahman et al 2008, El-Sayed et al 2009, El-Sayed et al 2008] we report in the present work the synthesis of new substituted [(pyrazol-4-yl)methylene]hydrazono-2,3-dihydrothiazole derivatives and their substituted sugar derivatives.

2. Experimental
2.1 Synthesis of organic compounds
The used organic compounds were prepared previously [Abdel-Rahman et al 2012]. The chemical structures were showed in Scheme 1.

2.2 Analysis
Melting points were determined using a Büchi apparatus. IR spectra (KBr) were recorded with a Bruker-Vector22 instrument (Bruker, Bremen, Germany). ^{1}H NMR spectra were recorded with a Varian Gemini spectrometer at 300 MHz and 200 MHz with TMS as internal standard. Chemical shifts were reported in δ scale (ppm) relative to TMS as a standard, and the coupling constants (J values) are given in Hz. The microanalyses were performed at the micro analytical unit, Tokyo University, Japan. The progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F_{245}. EI-mass spectra were recorded with a HP D5988 A

1000 MHz instrument (Hewlett-Packard, Palo Alto, CA, USA).

2.3 Culture ofmicroorganisms

Bacteria strains were supplied from Botany Department, Faculty of Science, Menoufia University, Shebin El-Koam, Egypt, namely *Bacillus subtilis* (ATCC 6633) (Gram-positive), *Pseudomonas aeruginosa*(ATCC 27853) (Gram-negative) and *Streptomyces* species (Actinomycetes). The bacterial strains were maintained on MHA (Mueller – Hinton agar) medium (Oxoid, Chemical Co., UK) for 24 h at 37 °C. The medium was molten on a water bath, inoculated with 0.5 ml of the culture of the specific microorganism and poured into sterile Petri dishes to form a layer of about 3-4 mm thickness. The layer was allowed to cool and harden. With the aid of cork-borer, cups of about 10 mm diameter were produced [Janssen et al 1987]

2.4 Agar diffusion technique

The antibacterial activies of the synthesized compounds were tested against *Bacillus subtilis* (ATCC 6633) (Gram-positive), *Pseudomonas aeruginosa*(ATCC 27853) (Gram-negative) and *Streptomyces* species (Actinomycetes) using MH medium (17.5 g casein hydrolysate , 1.5 g soluble starch, 1000 ml beef extract). A stock solution of each synthesized compound (500 µg/mL) in DMSO was prepared and graded quantities of the test compounds were incorporated in specified quantity of sterilized liquid MH medium. Different concentrations of the test compounds in DMF were placed separately in cups in the agar medium. All plates were incubated at 37 ºC overnight. The inhibition zones were measured after 24 h. The minimum inhibitory concentration (MIC) was defined as the intercept of the graveof logarithm concentrations versus diameter of the inhibition zones[Jorgensen et al 1999, Greenwood et al 2000].

2.5 Quantum chemical study

All required molecular parameters were carried out based on MINDO3 semi-empirical method ever used for organic compound calculation [Shuduan et al 2012] at an Unrestricted HartreeFock (UHF) level which are implemented in Hyperchem 8.0. The molecule 2D sketch was obtained by ISIS Draw 2.1.4.

3. Results and discussion

3.1 Synthesis of 2-{[[3-(Biphenyl-4-yl)-1-phenyl-1*H*-pyrazol-4-yl]methylene]hydrazono}-4-phenyl-2,3-dihydrothiazole (I).

Yellow solid (3.87 g, 78%), mp 197-198 ºC; IR (KBr) ν 3316 (NH), 1610 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) *δ:* 5.86 (1H, s, thiazole H-5),7.19 (2H, d, *J* = 8.5 Hz, Ar-H), 7.51 (4H, m, Ar-H), 7.58 (1H, s, C*H*=N), 7.64 (4H, m, Ar-H, pyrazole H-3), 7.70 (2H, d, *J* = 8.5 Hz, Ar-H), 7.79 (2H, m, Ar-H), 7.86 (4H, m, Ar-H), 7.96 (2H, d, *J* = 8.2 Hz, Ar-H), 9.82 (1H, s, NH); MS m/z (%): 497 (M^+, 12). Anal.Calcd.for $C_{31}H_{23}N_5S$: C, 74.82; H, 4.66; N, 14.07. Found: C, 74.63; H, 4.49; N, 13.85%.

3.2 Synthesis of 2-{2-[2-[[[3-(Biphenyl-3-yl)-1-phenyl-1*H*-pyrazol-4-yl]methylene]-hydrazono]-4-phenylthiazol-3(2*H*)-yl]ethoxy}ethanol (II). IR (KBr) ν 3426 (OH), 1612 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) *δ:*3.96 (2H, t, *J* = 6.2 Hz, CH_2), 4.12 (2H,t, *J* = 6.6 Hz, CH_2), 4.25 (2H, t, *J* = 6.2 Hz, CH_2), 4.74 (2H,t, *J* = 6.6 Hz, CH_2), 5.89 (1H, s, thiazole H-5),7.20 (2H, d, *J* = 8.5 Hz, Ar-H), 7.51 (4H, m, Ar-H), 7.57 (1H, s, C*H*=N), 7.65 (4H, m, Ar-H,pyrazole H-3), 7.70 (2H, d, *J* = 8.5 Hz,Ar-H), 7.83 (2H, m, Ar-H), 7.86 (4H, m, Ar-H), 7.99 (2H,d, *J* = 8.2 Hz, Ar-H); MS m/z (%): 585 (M^+, 10). Anal.Calcd.for $C_{35}H_{31}N_5O_2S$: C, 71.77; H, 5.33; N, 11.96. Found: C, 71.50; H, 5.19; N, 11.74%.

3.3. Synthesis of 2-{[[3-(Biphenyl-3-yl)-1-phenyl-1*H*-pyrazol-4-yl]methylene]hydrazono}-3-(ß-D-glucopyranosyl)-4-phenyl-2,3-dihydrothiazole (III). Yellow solid (5.93 g, 91%), mp196-197 ºC; IR (KBr) ν 3398 (OH), 1612 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) *δ:*3.88 (2H, m, H-6,6′), 4.15 (2H, m, H-4,5), 4.47 (2H, s, CH_2), 4.24 (2H, m, H-2,3), 5.74 (1H, d, *J*= 9.8 Hz, H-1), 5.88 (1H, s, thiazole H-5),7.19 (2H, d, *J* = 8.5 Hz, Ar-H), 7.51 (4H,m, Ar-H), 7.59 (1H, s, C*H*=N), 7.65 (4H,m, Ar-H,pyrazole H-3), 7.71 (2H, d, *J* = 8.5 Hz, Ar-H), 7.80 (2H,m, Ar-H), 7.87(4H, m, Ar-H), 7.98 (2H, d, *J* = 8.2 Hz, Ar-H); MS m/z (%) 659 (M^+, 12). Anal.Calcd.for $C_{37}H_{33}N_5O_5S$: C, 67.36; H, 5.04; N, 10.62. Found: C, 67.05; H, 4.91; N, 10.31%.

3.4. D-Xylose 2-{2-[[(3-(biphenyl-3-yl)-1-phenyl-1*H*-pyrazol-4-yl]methylene)-hydrazono]-4-phenylthiazol-3(2*H*)-yl}acetohydrazone(IV).

Yellow solid (5.74 g, 82%), mp 203-205 ºC; IR (KBr) ν 3412 (OH), 1664 (C=O), 1614 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) *δ:*3.64 (2H, m, H-5,5′), 4.18 (2H, m, H-4), 4.23 (2H, m, H-2,3), 5.16 (2H, s, CH_2), 5.88 (1H, s, thiazole H-5),7.25 (2H, d, *J* = 8.5 Hz, Ar-H), 7.55 (4H,m, Ar-H), 7.59 (1H, s, C*H*=N), 7.69 (4H, m, Ar-H, pyrazole H-3), 7.75 (2H, d, *J* = 8.5 Hz, Ar-H), 7.79 (2H,m, Ar-H), 7.86 (4H, m, Ar-H), 7.98 (2H,d, *J* = 8.2 Hz, Ar-H), 10.22 (1H, s, NH); MS m/z (%): 701 (M^+, 10). Anal.Calcd.for $C_{38}H_{35}N_7O_5S$: C, 65.03; H, 5.03; N, 13.97.

Found: C, 64.96; H, 4.94; N, 13.72%

3.5 Antimicrobial activity

The synthesized compounds were tested for their antimicrobial activity against three microorganisms and the minimal inhibitory concentrations (MICs) of the tested compounds were determined by the dilution method. Each of the test compounds and standards were dissolved in 12.5% DMSO, at concentrations of 500 µg/mL. Further dilutions of the compounds and standards in the test medium were prepared at the required quantities.

Bacteria strains were supplied from Botany Department, Faculty of Science, Menoufia University, Shebin El-Koam, Egypt, namely *Bacillus subtilis* (ATCC 6633) (Gram-positive), *Pseudomonas aeruginosa*(ATCC 27853) (Gram-negative) and *Streptomyces*species (Actinomycetes). The bacterial strains were maintained on MHA (Mueller – Hinton agar) medium (Oxoid, Chemical Co., UK) for 24 h at 37 °C. The medium was molten on a water bath, inoculated with 0.5 ml of the culture of the specific microorganism and poured into sterile Petri dishes to form a layer of about 3-4 mm thickness. The layer was allowed to cool and harden.

The antimicrobial activity of the synthesized compounds was evaluated against three microorganisms; *Bacillus subtilis*(ATCC 6633) (Gram-positive), *Pseudomonas aeruginosa* (ATCC 27853) (Gram-negative), and *Streptomyces* species (Actinomycetes). The values of minimal inhibitory concentrations (MICs) of the tested compounds are presented in Table I. The results of the antimicrobial activity test revealed that **I**, **II**, **III** and **IV** showed the highest activity against *B. subtilis* with MIC values of 75 µg/mL Compounds **III** showed the highest inhibition activity against *P.aeruginosa*, whereas **I** and **III** and **IV** were the most active among the series of tested compounds against *Streptomyces* species with MIC values of 75 µg/mL. **Fig. 1**The results also revealed that some compounds showed little or no activity against the microorganisms **(Table 1).**

From the structure-activity relationship it is clear that the *N*-substituted derivative of [(pyrazol-4-yl)methylene]hydrazono-2,3-dihydrothiazole with free OH group as well as the free hydroxyl glycoside showed the highest activity against both *B. subtilis* and *Streptomyces* species. Furthermore, substitution at the *p*-position in the phenyl ring with chlorine atom increases its activity against the three microorganisms with respect to the corresponding trimethoxy derivatives. It is also clear that the free sugar hydrazones derived from pentose sugar moiety displayed higher activity than the corresponding hexoses sugars. In addition, the N-substituted acyclic nucleoside analogue II exhibited higher activity against *Pseudomonas aeruginosa* and *Bacillus subtilis* .

3.6 Quantum chemical calculations

The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) play an important role in the molecule. These orbitals are sometimes referred to as the frontier molecular orbital.Fig. 2 shows the frontier molecule orbital density distributions of investigated compounds The HOMO orbital is an electron donor and the LUMO orbital is the electron acceptor. The difference in energy between HOMO orbital and LUMO orbital (energy gap) is a very effective property for characterizing the kinetic stability and chemical reactivity of the molecules. A molecule with a small LUMO-HOMO energy gap is chemically more reactive and kinetically less stable. On the contrary, a large LUMO - HOMO energy gap corresponds to high kinetic stability and low chemical reactivity [Deepika et al 2015]. As shown in Tables 2, the result of theoretical calculations using (MINDO3) method reveals that in the case of the compound I, the energy of highest occupied molecular orbital (EHOMO) is -6.01eV, and the energy of the lowest unoccupied molecular orbital (ELUMO) is 0.430eV. Then, the frontier orbital gap in the compound I isabout 6.47eV. For the compound III, the energy of HOMO orbital (EHOMO) is -5.528eV, and the energy of the LUMO orbital (ELUMO) is 0.06 eV. Thus, the frontier orbital gap in the compound III is about 5.58eV. As a result, the compound III has more kinetic stability and less chemical reactivity than others, whereas the compound I has less kinetic stability and more chemical reactivity than others.

The linkage between the molecular structures of compounds with its respective biological activities is central to the QSAR paradigm[Rav 2015]. Molecular descriptors play a crucial role in providing numerical description of the physicochemical properties of molecules. In order to properly account for these structural features, it is essential that suitable descriptors be chosen for QSAR investigation.

µ refers to the dipole moment and it essentially provides a measure of the asymmetric distribution of charges in a molecule. It can be seen that compounds with the highest dipole moment were compounds IV > II > III > I with values respectively. It was observed that compounds IV bearing the carbonyl and more double bond in nitrogen in addition to the presence of the pentose sugar also had high dipole moment when compared to hetero rings. Such high value is associated with the asymmetric distribution of electrons as afforded by the strong electron withdrawing nature of pyrazole ant thiazole.

A LogP provides a measure of a molecule's lipophilicity where high ALogP value indicates high lipophilicity while low value suggests low lipophilicity[Ana et al 2014]. The results indicated that compounds having the highest lipophilicity were I > IV > II > III with corresponding values of 7.03, 6.89, 6.27 and 5.79,

respectively. The former two sets of molecules possessed the highest lipophilicity namely because of the presence of more rings at the N position of pyrazole and thiazole .

3.7 Molecular electrostatic potential (MEP)

The molecular electrostatic potential (MEP) was investigated by theoretical calculations at the MINDO3 (d, p) level. Molecular electrostatic potential is related to the electronic density and is a very useful descriptor in understanding sites for electrophilic attack and nucleophilic reactions as well as hydrogen bonding interactions [Scrocco et al 1978, Luque et al 2000, Okulik et al 2005]. Fig.3 shows the Molecular electrostatic potential map of the investigated compounds. The negative (redcolor) regions of MEP were related to electrophilic reactivity and the positive (green color) ones to nucleophilic reactivity shown in Fig. 3.As can be seen in from the figure, that oxygen of thiazole, hydroxyl group in the sugar and nitrogen atoms embedded in Pyrazol structure were thought to be the effective part of these heterocyclic compounds.

4. Conclusion

New [(pyrazol-4-yl)methylene]hydrazono-2,3-dihydrothiazole , their sugar hydrazones and N-substituted derivatives were synthesized and their chemical compositions were confirmed and their antibacterial activities were tested. The obtained results showed that some of them exhibited moderate to high antimicrobial activity against Bacillus subtilis, Pseudomonas aeruginosa, Streptomyces species (Actinomycetes) . Sugar hydrazones with free hydroxyl pentose sugar showed higher activities . Substitution of the thiazole with acyclic oxegented hydroxyl alkyl chain enhances antimicrobial activity. Both experimental techniques and theoretical methods were used to determine thestructural and spectroscopic properties of compound were in good result of each other.

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Tables

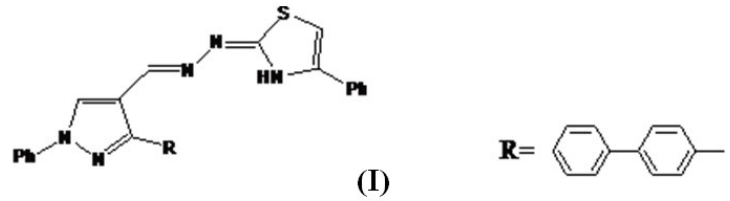
Table I. Minimum inhibitory concentration (MIC in µg/mL) of the title compounds. The negative control DMSO showed no activity.

Compound	*Bacillus subtilis* (Gram-positive)	*Pseudomonas aeruginosa* (Gram-negative)	*Streptomyces* species (Actinomycetes)
I	75	100	75
II	75	75	125
III	75	75	75
IV	75	100	75
Penicillin	31	46	33

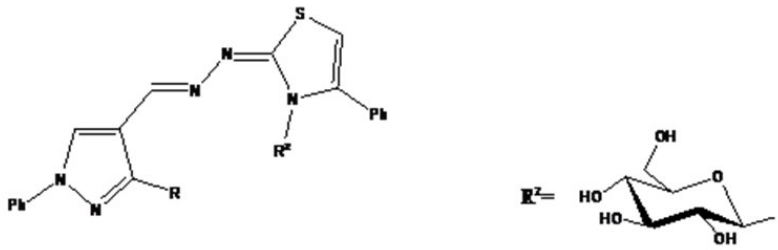
[t]otally inactive (MIC >500 µg/mL).

Table 2: Quantum chemical parameters of the investigated compounds.

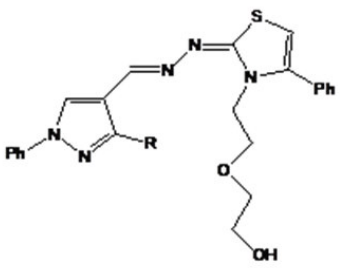
Compound	E_{HOMO}(eV)	E_{LUMO}(eV)	ΔE(eV)	µ(debye)	LogP
I	-6.01	0.430	6.47	1.87	7.03
II	-6.00	0.327	6.32	4.03	6.27
III	-5.528	0.06	5.58	3.87	5.79
IV	-6.111	0.36	6.41	7.86	6.89



(I)



(II)



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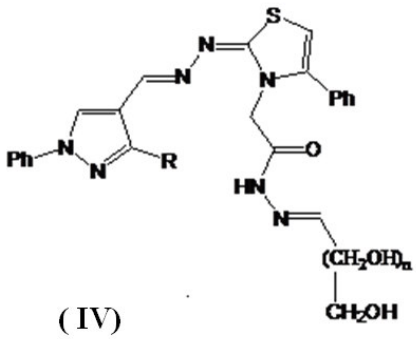


(IV)

n= 3-(D-oxylopentitolyl)

Scheme 1

Figures

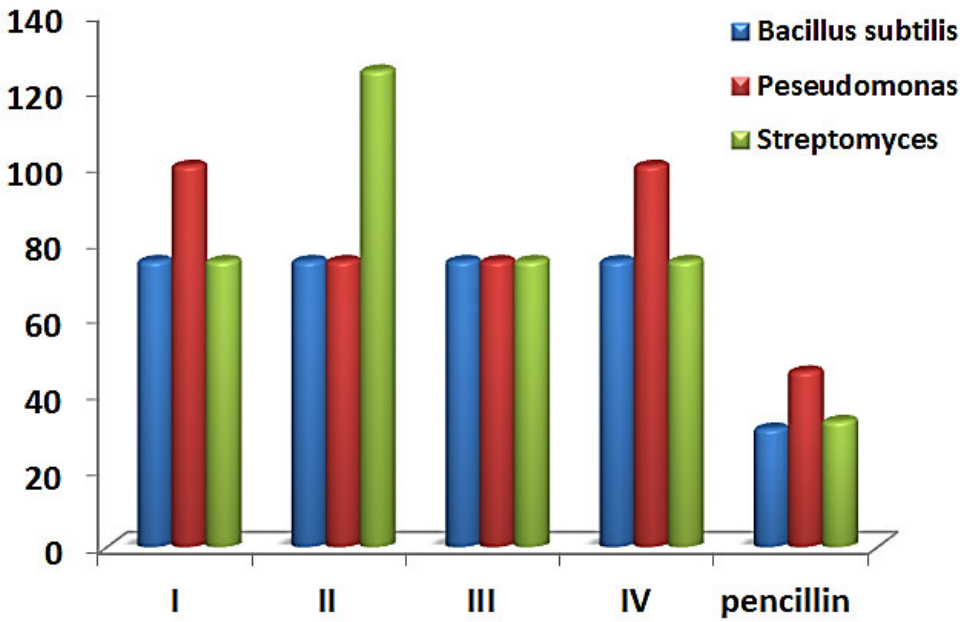


Fig. 1 :The antimicrobial activity of the synthesized compounds evaluated against three microorganisms; *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Streptomyces* species.

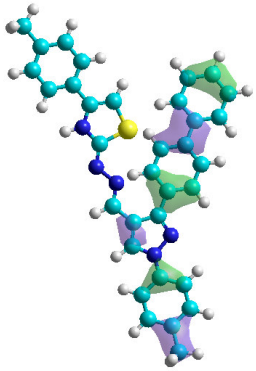
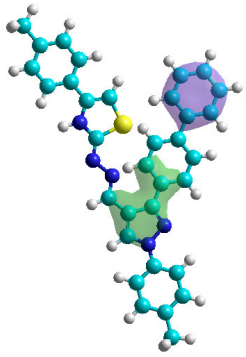
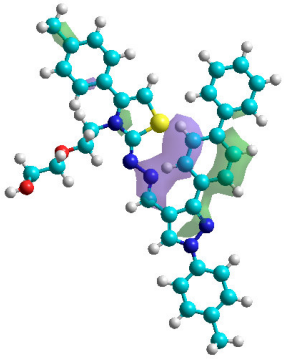
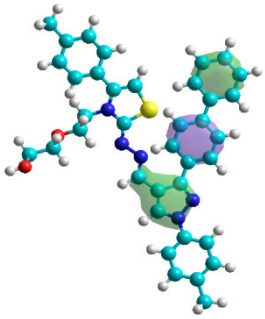
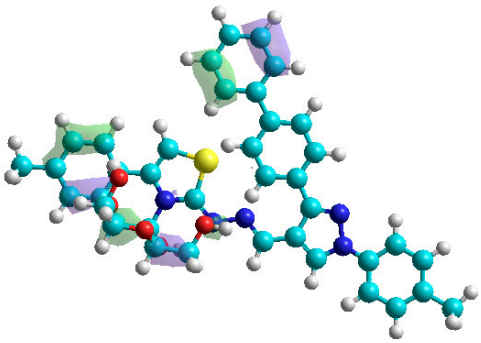
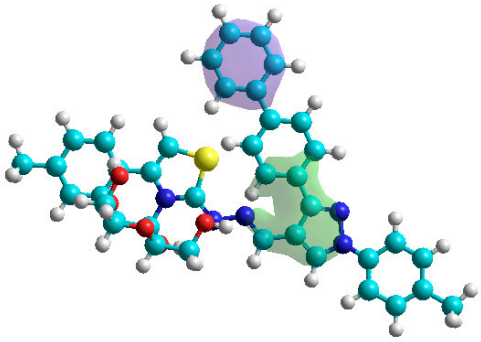
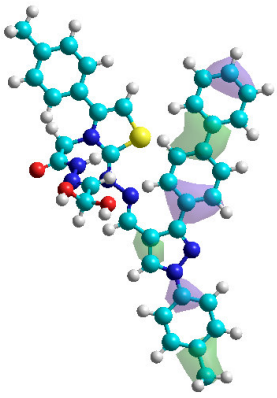
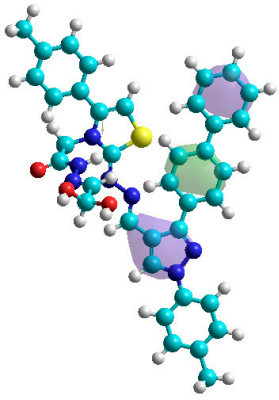
Compounds	HOMO	LUMO
I		
II		
III		
IV		

Fig. 2: The frontier molecule orbital density distributions of compound I,II, III, and IV

Compounds

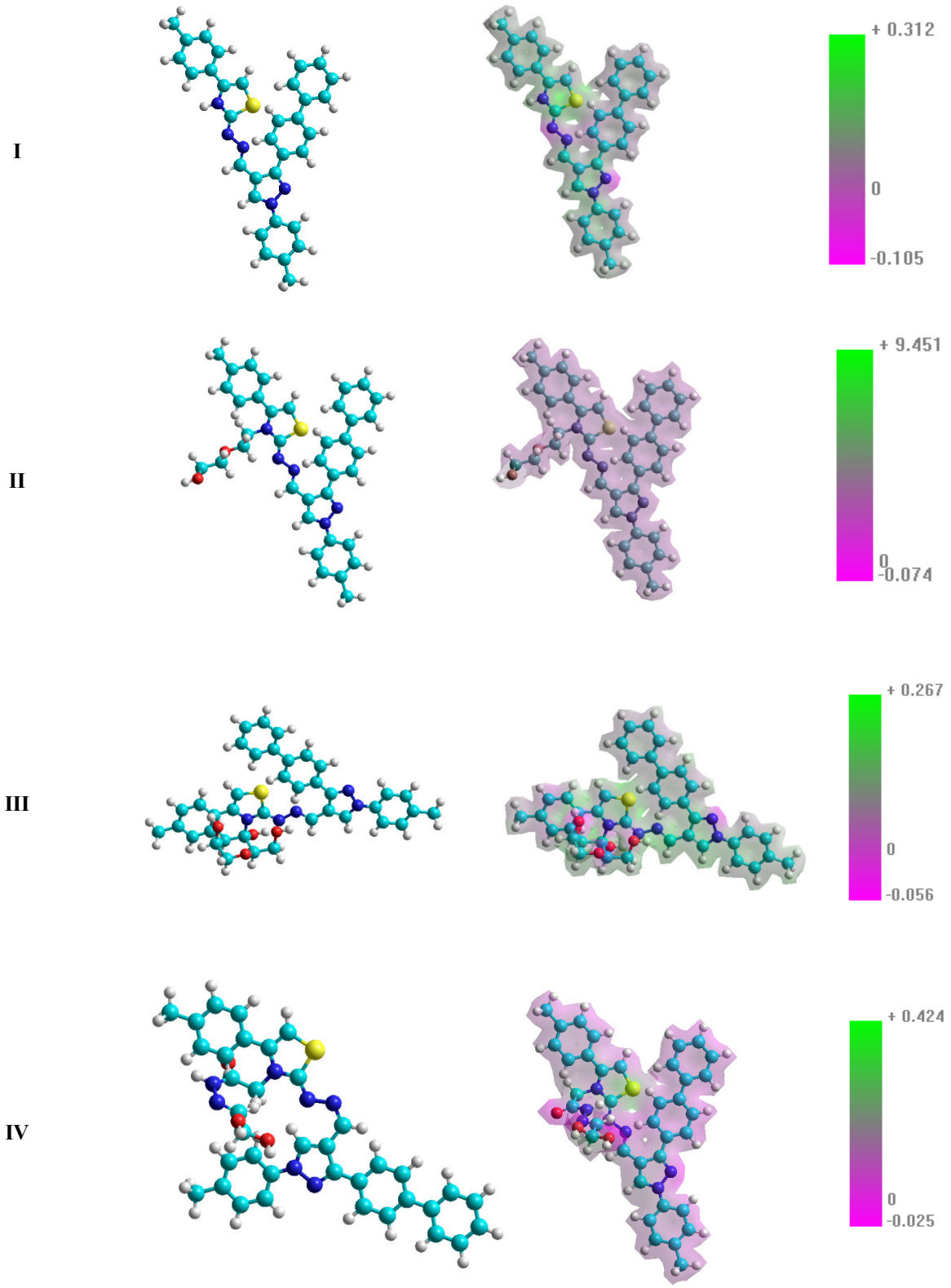


Fig.3:Molecular electrostatic potential map of the compounds

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