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Structure-activity-relationships study of 2-thienyl-4-furyl-6-aryl pyridine skeleton as anti-cancer drugs by DFT method

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ABSTRACT

The structure-activity-relationships (SAR) were studied on two series of 2-(thienyl-2-yl or 3-yl)-4-furyl-6-aryl pyridine derivatives as anti-cancer drugs by DFT method at B_3LYP/6-31G* level of theory.The structural and electronic properties of these compounds such as HOMO, LUMO, electronic energies, were calculated to gain insight about their role in modulating the anticancer activity. SAR study revealed that when CH_3 or Cl is present in para-position of phenyl ring, enhanced biological activity. Also, the structures of4-(5-chlorofuran-2-yl)-2-(thiophen-3yl) and 4-(5-chlorofuran-2-yl)-2-(thieophen-2-yl) moieties were important for cytotoxic effect. Finally, HOMO and LUMO energy values show clue about the biological activity profile of these compounds.

KEYWORDS

Density functional theory;
Structure-activity-relationship;
Chemical reactivity;
HOMO and LUMO study;
Anticancer activity.

INTRODUCTION

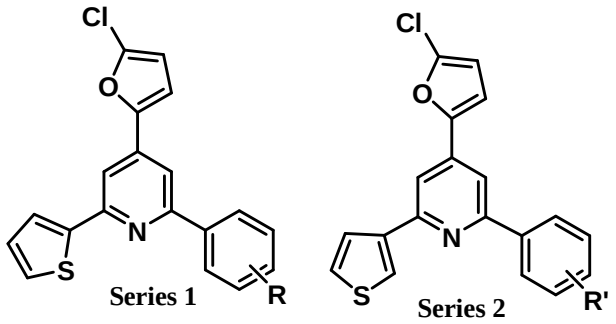
Over the past few years, there has been considerable interest in DNA topoisomerases, as they were shown to be the cellular target for several anti-cancer drugs[1]. DNA topoisomerase are ubiquitous enzymes that relieve the torsional stress in the DNA helix that is generated as a result of replication, transcription and other nuclear processes[2]. Topoisomerases are essential enzymes, which one inhibited; induce great damage to DNA of tumor cells[3].

α-Terpyridine (2-(thienyl-2-yl)-4-furyl-6-aryl pyridine)molecules are the biosisteres ofα-terthiophenecan act as tridentate ligand and form stable complexes by chelating a broad variety of transition metal ions. The numerous reports on DNA binding property and antitumor activity of terpyridines complexes have attracted multiple researchers[4]. Karki and co-workers reported that terpyridine derivatives showed a strong cytotoxicity against several human cancer cell lines[5].

Then, in the effort to study the structure-activity relationships (SAR) of these compounds, we investigated the reactivity of these molecules which are governed by their electronic properties and kinetics and thermodynamic stability. In this computational study the structural and electronic properties of the two different series of 2-(thienyl-2-yl or 3-yl)-4-furyl-6-aryl pyridine derivatives with chloride or methyl substituents at different aryl moieties (Figure 1) were investigated and used to predicted their relative stability and reactivity.

Among the theoretical methods available, the density functional theory (DFT) calculations provided good accuracy for the computation of molecular structure, vibrational frequencies and energies of chemical reactions[6-9]. DFT provides an efficient method to include

correlationenergy in electronic calculations[10]. Beside total electronic energies(E), the highest occupied molecule orbital(HOMO), the lowest unoccupied molecule orbital (LUMO), gap energy difference between E_{HOMO} and E_{LUMO}(ΔE_{gap}), dipole moments, polarizability, global chemical reactivity description such as electronic chemical potentials(μ)[11], chemical hardness(η)[12], electrophilicity(ω)[13], weight molecules(MW), surface molecules(S), volume molecules(Mv), octanol-water partition coefficient(log p) dipole moment are calculated. Reactivity parameters have been associated with the response of electronic properties and inhibitory activity of compounds **(1)** to **(8)**.Then reactivity parameters are identified with response functions and they are represented by derivatives of electronic properties.



Structure	R	Structure	R'
1	p-CH3	5	p-CH3
2	o-Cl	6	o-Cl
3	m-Cl	7	m-Cl
4	p-Cl	8	p-Cl

Figure 1 : Structure of 2-thienyl-4- furyl-6-aryl pyridine derivative

COMPUTATIONAL METHODS

In recent years, theoretical methods based on the DFT haveemerged as an alternative to traditional ab initio methods inthe study of structure and reactivity of chemical systems.

Some DFT studies showing that functional that include gradient corrections and hybrid functional for exchange and correlation, such as B3LYP,[14] together with the standard6-31G* basis set, yield good agreement with the experiment. Thus, in the present study geometrical optimizations of the stationary points were carried out using this methodology. The optimizations were performed using the Berny analytical gradient optimization method[15]. All calculations were carried out using the Gaussian 09 suite of programs[16].

Global reactivity indexes were estimated according to the equations recommended by Parr and Yang[12-13]. In particular, the electronic chemical potentials (μ) and chemical hardness (η) of the compounds under study were evaluated in terms of the one-electron energies of the frontier molecular orbitals, using the following equations:

$$\mu = \frac{\varepsilon_H + \varepsilon_L}{2}$$

$$\eta = \varepsilon_L - \varepsilon_H$$

The global electrophilicity index ω, which measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment, has been given the following simple expression, in terms of the electronic chemical potential μ and the chemical hardness η.

$$\omega = \frac{\mu^2}{2\eta}$$

Electrophilicity index measures the propensity or capacity of a species to accept electrons. Itis a measure of the stabilization in energy after a system accepts additional amount of electronic change from the environment.

RESULTS AND DISCUSSION

We first evaluated the energies of two series geometries, 4-(5-chlorofuran-2-yl) – (thiophen-2-yl) **(1-4)** and 4-(5-chloro furan-2-yl)-2(thiophen-3-yl) **(5-8)** moieties, which were optimized at the B_3LYP at the 6-31G*level of theory (Figure 1). An analysis of the geometries indicates thatthe optimized geometries of compounds **(1-8)** are planar and the most stable derivative is compound **(2)**, which showed the best biological activity between the chloro substituents derivatives.

Then the structural and electronic properties of the compounds such as the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) energies, orbital coefficients, together with the FMO energy gap for geometries were calculated to gain insight about their role in modulating the anticancer activity studies (TABLE 1). It is known that

TABLE 1 : Calculated total energies (E), HOMO and LUMO energies (E_{HOMO}, E_{LUMO}), HOMO-LUMO energy gap (ΔE_{gap}), electronic chemical potential (μ), chemical hardness (η) and global electrophilicity (ω) of compounds (1-8) and their anticancer activities (IC50)

	1	2	3	4	5	6	7	8
E (Hatree)	-1758.615	-2178.878	-2178.88	-2178.882	-1758.6145	-2178.87	-2178.880	-2178.880
E_{HOMO} (eV)	-5.82	-5.98	-6.06	-6.04	-5.95	-6.12	-6.23	-6.20
E_{LUMO} (eV)	-1.74	-1.82	-1.95	-1.95	-1.74	-1.82	-1.93	-1.93
ΔE_{gap}	4.08	4.16	4.11	4.09	4.21	4.3	4.3	4.27
η (a.u)	0.074	0.076	0.075	0.075	0.077	0.079	0.078	0.078
μ (a.u)	-0.139	-0.144	-0.148	-0.147	-0.141	-0.146	-0.150	-0.150
ω (eV)	1.776	1.848	1.968	1.970	1.763	1.838	1.958	1.959
IC50(μM) [I]	1.33	1.93	2.86	2.45	0.63	1.71	4.26	1.77

[I] **IC50 against human breast adenocarcinoma cell line (MCF-7)**

the ability of the molecule to accept or donor electrons can be rationalized by FMO analysis. The value of HOMO energy (E_{HOMO}) is often associated with the electron donating ability of inhibitor molecule, which the higher values of E_{HOMO} is an indication of the greater ease of donating electrons to the unoccupied orbital or acceptor.On the other hand, it is important to examine the HOMO and LUMO energies for these compounds because the relative ordering of occupied and virtual orbital provides a reasonable qualitative indication of electronic properties and the ability of electron hole transport.

Also, the value of LUMO energy (E_{LUMO})is related to the ability of the molecule to accept electrons, which the lower values of E_{LUMO}shows the acceptor would accept electrons consequently. The energy differences of HOMO and LUMO (ΔE_{gap}) provides a measure for the stability of the formed complex on the metal surface. The lower value of ΔE is related to the higher stability of the formed complex.

The overall analysis of HOMO and LUMO energy values of the two series, revealed that the E_{HOMO} for series 1 and 2 varied from -5.82 eVto -6.06 eV and -5.95 eVto -6.23eV, and E_{LUMO} from -1.74eV to -1.95

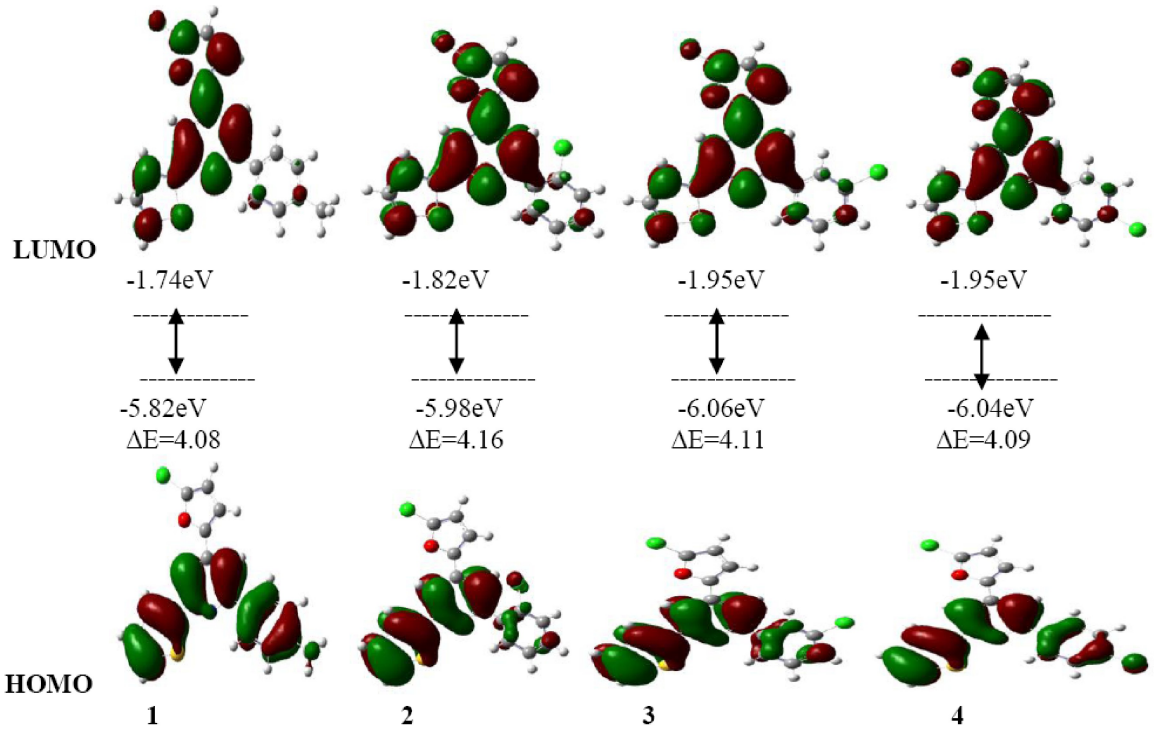


Figure 2 : Schematic representation of HOMO and LUMO coefficient distribution of (1-4) derivatives (Series 1)

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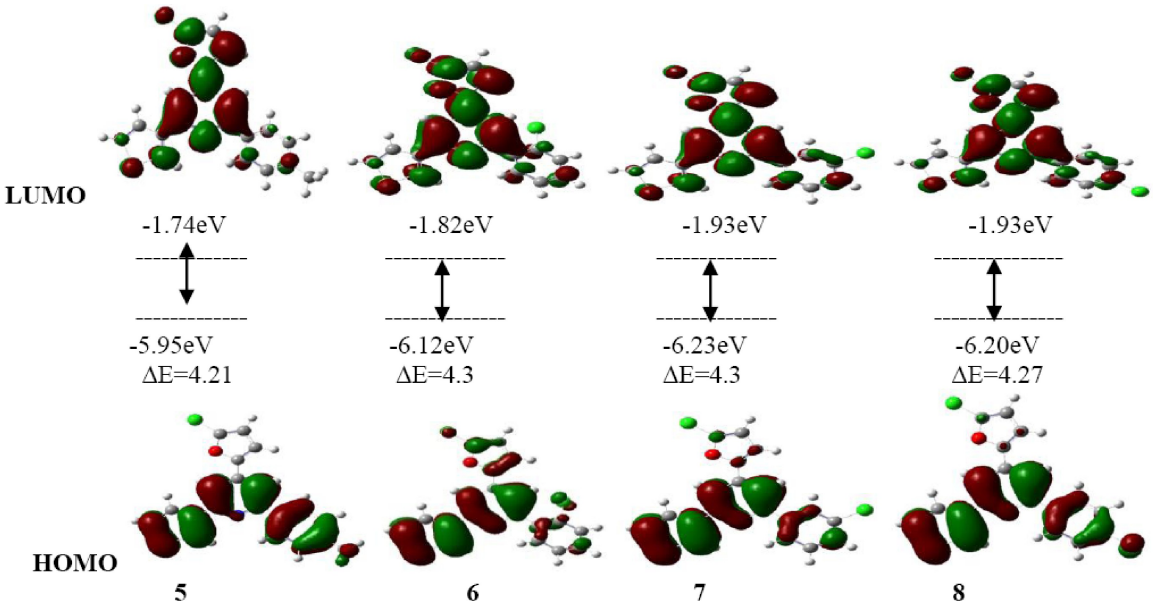

Figure 3 : Schematic representation of HOMO and LUMO coefficient distribution of (5-8) derivatives (Series 2)

eVand -1.74 eVto -1.93eV, respectively, which the HOMO energy is the highest for compounds **(1)** and **(5)** and LUMO energy is the lowest for them. These results have direct correlatewith theiranti-cancer activity (TABLE 1).

Moreover,as can be seen in TABLE 1, the compounds **(2)** and **(6)** with the highest HOMO-LUMO energy gap (ΔE_{gap}) have the lowest stability between the chloro substituent derivatives, which indicates that they are reactive than of compounds **(3)**, **(4)** and **(7)** as shown in Figures 2-3.

The HOMO coefficient distribution was determined to observe the atomic contribution on the frontier HOMO orbital. Interestingly, replacement of a methyl group at para-position (**(1)** and **(5)**) led to increase the HOMO coefficient distribution in the pyridine ring. Apparently there is a clear correlation between the HOMO coefficient distribution and biological activity of these molecules. This result reinforced the importance of this moiety for the anticancer profile (Figures 2-3).

The compounds also showed distribution of LUMO through all of the rings, although most of them concentrate in the fury and thinly rings, which may have pointed it as the most likely region for stacking interactions with the target.

The reactivity indexes are another alternative approach for understanding the capacity of a species to accept or donate electron.In TABLE 1, were report the static global properties, namely, electrophilic chemical potential μ, chemical hardness (η) and global electrophilicity (ω) of compounds **(1-8)**.

The electronic chemical potential (μ) of the first series with values between -0.139 a.u and -0.148 a.u, are higher than the electronic chemical potential of the second series, **(5)**, **(6)**, **(7)** and **(8)**, μ=-0.141 a.u to -0.150 a.u, respectively, indicating that the first series are more nucleophile than the second series.

The global electrophilicity indices for these compounds are calculated and shown in TABLE1. As can

TABLE 2 : Dipole moment, polarizability, surface area (S), molecular volume (Mv), and octanol-water partition coefficient (log p) calculated at B3LYP/6-31G* level of theory for compounds (1-8)

	1	2	3	4	5	6	7	8
Dipole (D)	2.408	1.720	1.891	3.634	3.281	2.409	1.744	3.700
Polarizability (D)	39.15	39.24	39.24	39.24	39.15	39.24	39.24	39.24
S ($A^{\circ 2}$)	585.21	580.31	583.64	583.12	588.60	580.71	585.86	587.71
M_V ($A^{\circ 3}$)	981.09	968.96	973.91	973.48	980.79	968.10	973.34	973.51
log p	3.85	3.90	3.90	3.90	3.60	3.60	3.66	3.66

be seen from TABLE 1, the compounds **(1)** and **(5)** with 1.78 eV and 1.76 eV, respectively, are the strongest nucleophile while **(3)** and **(7)** with 1.97 eV and 1.96 eV, respectively are the strongest electrophile. These results probably as a consequence of the substitution by the electron releasing methyl group present in **(1)** and **(5)** compared to the electron withdrawing chloro group in another compounds.Also, the compounds **(1)** and **(5)** have the most hardness with the highest biological activities.

In continues, we evaluated the hydrophobic pattern of compounds by calculating octanol-water partition coefficient (log p), molecular volume(Mv), polarizability, surface area (S) and dipole moment.The results of calculations showed that the compounds **(1)** and **(5)** have the lowestlog P values, which may be useful for their biological activity as it may compromise reaching the target insidethe cell by these molecules. Also, a high molecular surface (S) and molecular volume (Mv) for **(1)** and **(5)** may compromise the strong interaction with the target (TABLE 2).

The dipole moment, which is the first derivative of energy, with respect to an applied electric field is a measure of asymmetry in the molecular change distribution. The high values of the dipole moment present that the electrostatic and dispersion contribution will play a key role in the interaction with receptor. Herein, the dipole moment and polarizability show any further clue about the biological activity profile of these compounds, excluding these feature is crucial for displaying the studied activity.

In addition, the presence of stereoelectronic effects depending on the position of substituent on benzene ring could also affected the biological activity.The position of substituents appears toplay an important role in activity, since the change of Cl from ortho to para and meta position led to a decrease of activity. As can be seen in TABLE 1 replacement of a chloro at ortho position and significant change in S situations on thienylring **(6)** led to increase of theanticancer activating compared to the para and meta – position.

Moreover, the type of substituents on the benzene ring appears to plays an important role in activating. The activating of these compounds against human breast adenocarcinoma cell line seems to be increased with the presence of a methyl group at the para- position.

CONCLUSIONS

The structure – activity relationship study revealed that compounds **(1)** and **(5)** with methyl moiety exhibited strong biological activity. Also, this results suggest that 4- (5-chloro furan-2-yl)-2-(thiophen-3-yl or2-yl) moiety is important for displaying significant biological activity.The comparison of the theoretical results of the first and secondseries derivatives revealed that the stability of the last compounds significantly decreased.

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