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Research Article

Theoretical approach using DFT and muscle relaxant effects of 5-Chloroisatin Derivatives

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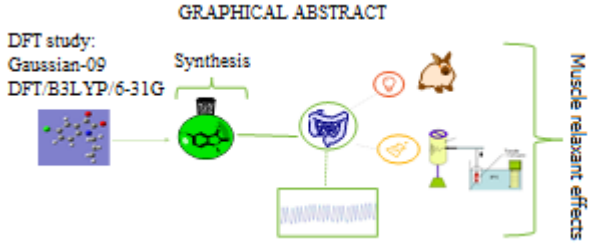
ABSTRACT

A new series of 5-Chloroisatin derivatives were synthesied and characterises with different characterization methods such as ^{1}H-NMR and^{13}C-NMR spectroscopy, and then tested for their myorelaxant activity. Computational investigations of the compounds **1a-3a**, **2b** and **4b** on the muscle-relaxing effects performance were performed by using the DFT method with B3LYP functional. The result of descriptors calculation revealed that the theoretical approach was in good agreement with the reported experimental data.

Keywords: 5-Chloroisatin derivatives, B3LYP functional and DFT method, synthesis, myorelaxant effects.

GRAPHICAL ABSTRACT



5-Kloroizatin türevlerinin DFT kullanarak teorik yaklaşımı ve kas gevşetici etkileri

ÖZ

Yeni bir 5-Kloroizatin türevleri serisi sentezlendi ve ^{1}H-NMR ve ^{13}C-NMR spektroskopisi gibi farklı karakterizasyon yöntemleri ile karakterize edildi ve daha sonra miyorelaks aktiviteleri için test edildi. Bileşik **1a-3a, 2b ve 4b**'nin kas gevşetici etki performansı üzerindeki hesaplamalı incelemeleri, B3LYP fonksiyonelli DFT yöntemi kullanılarak gerçekleştirildi. Tanımlayıcıların hesaplanması sonucu, teorik yaklaşımın rapor edilen deneysel verilerle iyi bir uyum içinde olduğu ortaya kondu.

Anahtar Kelimeler: 5-Kloroizatin türevleri, B3LYP işlevselliği ve DFT metodu, sentez, myorelaxant etkileri.

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1. INTRODUCTION

In order to view the extended applications of isatin derivatives[1] in various fields of biology, medicine, industry and because of their anti-fungal properties[2], antibacterial[3], anticonvulsant[4], anti HIV[5], antidepressants[6], anti-inflammatory[7] and anticorrosive[8–10], we have synthesized new heterocyclic compounds derived from 5-Chloroisatin as active candidates. The synthesis and the characterizations have been a subject of intense interest in many disciplines of chemistry. In addition, the results of quantum chemical calculations are obtained without laboratory measurements, thus saving time and equipment and alleviating safety and disposal concerns.[11,12] Density functional theory (DFT) has been used intensively and proved as an efficient approach.[13,14] We report here the synthesis, characterization and myorelaxant activity of some new 5-Chloroisatin derivatives and the Optimization of the structure using DFT method with B3LYP functional.

2. EXPERIMENTAL METHODS

2.1. Computational details

The DFT calculations were done with Gaussian 09 program package[15] using 6-31G+ basis set and the B3LYP Density Functional. Then, several related structural parameters were selected from the quantum computation results: highest occupied molecular orbital energy E_{HOMO} (eV), lowest unoccupied molecular orbital energy E_{LUMO} (eV), energy gap (ΔE), ionisation potential (IP) and electron affinity (EA), hardness (η), softness (σ), absolute electronegativity. The previous parameters can be explained in terms of the energy of the HOMO and the LUMO.[16,17]

$$IP = -E_{HOMO} \quad (1)$$

$$EA = -E_{LUMO} \quad (2)$$

$$\chi = \frac{IP+EA}{2} \quad (3)$$

$$\eta = \frac{IP-EA}{2} \quad (4)$$

$$\sigma = \frac{1}{\eta} \quad (5)$$

Electron charge distribution on the surfactant molecules were determined which could be used to calculate Fukui indices (f+ and f–) for local nucleophilic and electrophilic attacks and s^+, s^- local softness.[18,19]

$$f^+ = q_{(N+1)} - q_N \quad \text{For nucleophilic attack} \quad (6)$$

$$f^- = q_N - q_{(N-1)} \quad \text{For electrophilic attack} \quad (7)$$

$$S_k^+ = S[\, q_{k\,(N+1)} - qk_{\,(N)}\,] = S f^+_k \quad (8)$$

$$S_k^- = S[\, q_{k\,(N)} - qk_{\,(N-1)}\,] = S f^-_k \quad (9)$$

Where, $q_{k(N)}$, $q_{k(N+1)}$ and $q_{k(N-1)}$ are the natural populations for the atom k in the neutral, anionic and cationic species, respectively.

2.2. Chemicals and devices

The melting points were taken with the help of an open capillary tube and were uncorrected. The ^{1}H and ^{13}C-NMR (75 MHz) spectra were recorded on a Bruker 300 NMR spectrometer (with TMS for ^{1}H and $CDCl_3$ for ^{13}C as internal references). The purity of the compounds was checked by TLC on pre-coated SiO_2 gel (230-400 mesh) aluminium plates (E-Merck) using ethyl acetate: hexane and visualized in a UV chamber.

2.2.1. General method of N-alkylated 5-Chloroisatin derivatives

0.2 g (1.1 mmol) of 5-chloro-1*H*-indole-2,3-dione, (0.23 g, 1.16 mmol) of potassium carbonate and (0.035 g, 0.10 mmol) of BTBA were dissolved in 15 ml of N,N-dimethylformamide, then, the brominated reagent was added slowly, the mixture was left at room temperature for 48 hours under magnetic stirring, during this period, the progress of the reaction was monitored by TLC (thin layer chromatography). After the reaction was complete, the salts were removed by filtration, the solvent (DMF) was evaporated under reduced pressure. The product obtained was purified on a column of silica gel eluent (ethyl acetate / hexane).[20]

Compound 1a: 5-chloro-1-octylindoline-2,3-dione

Yield: 88% ; m.p: 68-70°C ; R_f= 0.85 ; ^{1}H NMR ($CDCl_3$; 300MHz) : δ (ppm) 7.54-7.55(d, H, H_{Ar}, $^4J_{H-H}$ =3Hz) ; 7.50-7.51 (d, H, H_{Ar}, $^4J_{H-H}$ =3Hz) ; 6.84 (d, H, H_{Ar},$^3J_{H-H}$ =9Hz) ; 3.68 (t, 2H, CH_2, $^3J_{H-H}$ = 6Hz) ; 1.71-1.53 (m, 2H, CH_2) ; 1.24-1.31 (m, 10H,CH_2), 0.85 (t, 3H, CH_3, $^3J_{H-H}$ =6Hz). ^{13}C NMR ($CDCl_3$; 75MHz): δ (ppm) 183.20 (C=O); 160.73 (N-C=O); 144.60, 137.60, 125.37 (Cq); 129.45, 115.79, 111.42 (CH_{Ar}); 40.47, 31.73, 29.19, 27.20, 26.88, 22.60(CH_2); 14.04 (CH_3).

Compound 2a: 5-chloro-1-nonylindoline-2,3-dione

Yield: 87% ; m.p: 67-68°C; R_f = 0..82; ^{1}H NMR ($CDCl_3$; 300MHz): δ (ppm) 7.58-7.59 (d, H, H_{Ar}, $^4J_{H-H}$ = 3Hz); 7.54-7.55 (d, H, H_{Ar}, $^4J_{H-H}$ = 3Hz); 6.85 (d, H, H_{Ar},$^3J_{H-H}$ =9Hz); 3.70 (t, 2H, CH_2, $^3J_{H-H}$ =9Hz); 1.65-1.75(m, 2H, CH_2) ; 1.28 (m, 12H,CH_2), 0.89 (t, 3H, CH_3, $^3J_{H-H}$ =6Hz). ^{13}C NMR ($CDCl_3$; 75MHz): δ (ppm) 181.84 (C=O); 167.00 (N-C=O); 147.07, 137.63, 129.39 (Cq); 141.28, 116.10, 110.29 (CH_{Ar}); 42.53, 32.42, 29.49, 29.27, 29.21, 27.21, 26.89, 23.18 (CH_2); 15.83 (CH_3).

Compound 3a: 1-allyl-5-chloroindoline-2,3-dione

Yield: 89%; m.p: 140-142°C; R_f=0.78. ^{1}H NMR ($CDCl_3$; 300MHz) δppm 7.52-7.58 (m, 2H, H_{Ar}); 6.89 (d,

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H, H_{Ar}, $^{3}J_{H-H}$ = 9Hz); 5.77-5.90 (m, 1H, CH); 5.30-5.35 (m, 2H, CH_2); 4.38 (d, 2H, CH_2, $^{4}J_{H-H}$=3Hz). ^{13}C NMR ($CDCl_3$; 75MHz) δppm: 182.18 (C=O); 157.34 (N-C=O); 149.07, 129.67, 118.93 (Cq); 137.64, 130.02, 112.00 (CH_{Ar}); 125.25 (C=CH); 118.41 (C=CH_2); 42.63 (CH_2).

Compound 2b: 5-chloro-1-(prop-2-yn-1-yl)indoline-2,3-dione

Yield: 88% ; m.p: 166-170°C; R_f= 0.78; ^{1}H NMR ($CDCl_3$) δppm 7.57-7.62 (m, 2H, H_{Ar}); 7.12 (d, H, H_{Ar}, $^{3}J_{H-H}$ = 6Hz); 4.54 (s, 2H, CH_2); 2.34 (t, H, $^{4}J_{H-H}$ = 3Hz); ^{13}C NMR ($CDCl_3$) δppm: 181.55 (C=O); 156.60 (N-C=O); 147.87, 130.07, 118.50 (Cq); 137.80, 125.24, 112.75 (CH_{Ar}) ; 73.72 (C≡C) ; 71.21 (CH); 29.59 (CH_2).

2.2.2. General produces of copper-catalyzed 1,3-dipolar cycloaddition reaction

0.2 g of 5-chloro-1- (prop-2-ynyl) indoline-2,3-dione and 1.2 equiv of azide were reacted in the presence of Cu (I) catalyst with the addition of sodium ascorbate (10^{-3} mol) in excess as a reducing agent in the presence of $0.5.10^{-3}$ mol of a copper (II) salt ($CuSO_4$), in a medium composed of a mixture (1:1) of water and ethanol. This procedure made it possible to selectively obtain the disubstituted 1,4-triazole regioisomer.[21]

Compound 4b: 1-((1-benzyl-1H-1,2,3-triazol-4-yl) methyl)- 5-chloroindoline-2,3-dione

Yield: 80%; m.p : 140-145°C; R_f=0.55; ^{1}H NMR ($CDCl_3$; 300MHz) δppm 7.32-7.29 (m, 2H, H_{Ar}); 7.26 (d, H, H_{Ar}, $^{4}J_{H-H}$ = 3Hz); 7.08 (d, 2H, $H_{Ar,}$ $^{4}J_{H-H}$ = 3Hz); 6.99-7.03 (m, 1H, CH); 6.71-6.73 (d, 2H, $H_{Ar,}$ $^{4}J_{H-H}$ = 3Hz); 6.47-6.49 (m, H, H_{Ar}); 5.23 (s, 2H, CH_2); 4.89 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$;75MHz) δppm: 186.50 (C=O); 165.30 (N-C=O); 149.82, 143.25, 135.62, 130.53, 117.81 (Cq); 132.65, 131.15, 129.47, 127.66, 123.11 (CH_{Ar}); 125.65 (CH); 56.54, 43.82 (CH_2).

2.3. Pharmacology

2.3.1. Animals

The animals used in the experiments were placed in an animal house, subjected to a natural photoperiod alternating illumination and darkness. Experiments on smooth jejunum muscle were performed using rabbits of both sexes of 1.5 kg. The present study was performed according to international and institutional rules regarding animal experiments (NIH Publication No. 85-23, revised 1996).

2.3.2. Tissue preparations

Rabbits of both sexes (1.8-2.5 kg) were kept in a standard environmental condition of humidity, temperature and light. The animals had free access to water and food until the experiment. However, the food was withdrawn 24 hours prior the experiment. The rabbits were killed by exsanguinations, segments of jejunum about 2-3 cm were quickly isolated and transferred in 50 mL organ bath chamber filled with tyrode solution containing (in mM): 136 NaCl, 2.7 KCl, 1.4 $CaCl_2$ $2H_2O$, 0.5 $MgCl_2$ $6H_2O$, 11.9 $NaHCO_3$, 0.42 NaH_2PO_4 and 5.56 glucose (bubbled continuously with 95% O_2 -5% CO_2, pH 7.4 at 37°C).[22]

3. RESULTS AND DISCUSSION

3.1. Computational Study

It is generally accepted that the values of E_{HOMO} indicate the electron donating ability of the molecule and the inhibition efficiency increases with increasing E_{HOMO} value. High E_{HOMO} values indicate that the molecule has a tendency to donate electrons to the unoccupied orbitals of the metal with low energy empty orbital.[23] An increase in E_{HOMO} values facilitates the relaxation of the isolated intestine of the rabbit. The E_{LUMO} indicates the ability of the molecules to accept electrons; with lower E_{LUMO} values, greater relaxation ability can be expected.[24] The optimized structures of all four 5-Chloroisatin bases, namely **1a**, **2a**, **3a**, **2b** and **4b** with numbering schemes are depicted in Figures 1, 3, 5, 7 and 9. The value of E_{HOMO} of **2a** and **4b** are the highest which correlates with the experimentally determined muscle relaxant effect and the values of E_{LUMO} favour **2a**. The compound **1a** shows also highest value of E_{HOMO}.

The separation energy, $\Delta E = (E_{LUMO} - E_{HOMO})$, is an important parameter and it is a function of reactivity of the molecules towards the muscle-relaxing activity on the isolated intestine of the rabbit.

As ΔE decreases, the reactivity of the molecule increases leading to increase in the myorelaxant effects of the compounds.

The calculations given in Table 1 shows the decreasing trend for the ΔE: 3.6125 (4b) > 3.5480 (2a) > 3.5146 (2b) > 3.4781 (3a) > 3.4391 (1a) which follows the same order of the myorelaxant effects of the compound obtained experimentally. The calculations show an obvious correlation between the molecular area of the molecules and the myorelaxant effects. It is clear from Table 1 that the compound **2a** has the highest molecular area that probably increases its muscle relaxant effect.

The values of the global hardness and global softness of the molcules **1a, 2a, 3a, 1b** and **2b**, shown in Table 1 are important properties to measure stability and reactivity of molecules.

The dipole moment (μ) provides information about the polarity of the whole molecule. High dipole moment means greater molecular polarity, which probably gives rise to high chemical reactivity.[25] It relates to the dipole-dipole interaction of molecule and the isolated intestine

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of the rabbit. Table 1 shows that **2a** has the highest dipole moment.

As we know, frontier orbital theory is useful in predicting the relaxation centers of the molecules responsible for the interaction with the isolated intestine of the rabbit. Figures 2, 4, 6, 8 and 10 show the HOMO and LUMO orbital contributions for the neutral species of the studied molecules **1a, 2a, 3a, 2b** and **4b.** For all the molecules, the HOMO densities were concentrated on both rings, Cl atom > C=N group, and O-atom of methoxy group. This means that these are active sites of the molecules responsible for interaction with the isolated intestine of the rabbit. The LUMO molecular orbital is uniformly distributed over rings as well as on > C=N group, while contribution from Cl atom is negligible. Due to the presence of an iminic (> C=N–) group and rings, these molecules could have good relaxant effects.

Table 1. The calculated quantum chemical parameters of the studied molecules **1a, 2a, 3a, 2b** and **4b**

Parameters	**1a**	**2a**	**3a**	**2b**	**4b**
$-E_{HOMO}$ (ev)	-6.3709	-6.5768	-6.6598	-6.7608	-6.3260
$-E_{LUMO}$ (ev)	-2.8228	-3.1377	-3.1818	-3.2463	-2.7135
ΔE gap (ev)	3.5480	3.4391	3.4781	3.5146	3.6125
μ(debye)	6.1043	6.1371	5.9192	5.6945	9.6572
IP= $-E_{HOMO}$	6.3709	6.5768	6.6599	6.7608	6.3260
EA= $-E_{LUMO}$	2.8228	3.1377	3.1818	3.2463	2.7135
$\chi = \frac{IP + EA}{2}$	4.5968	4.8572	4.9208	5.0036	4.5197
$\eta = \frac{IP - EA}{2}$	1.7740	1.7195	1.7391	1.7573	1.8063
$\sigma = \frac{1}{\eta}$	0.5636	0.5815	0.5750	0.5691	0.5536

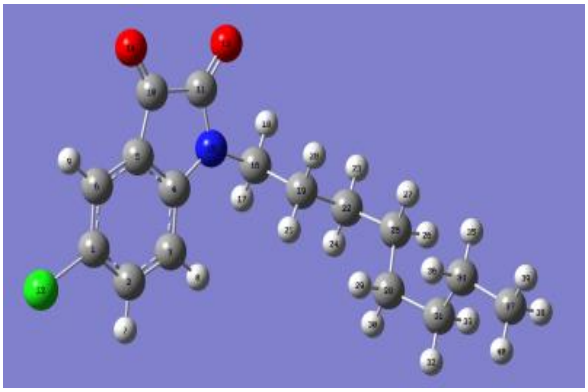

Figure 1. Optimized structure of compound 1a.

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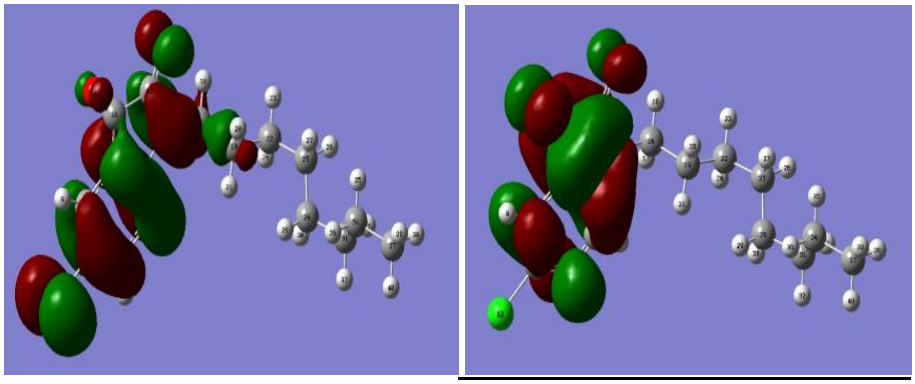


HOMO **LUMO**

Figure 2. FMO of compound 1a.

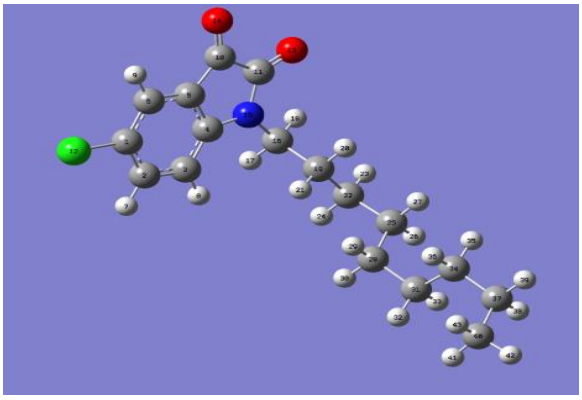
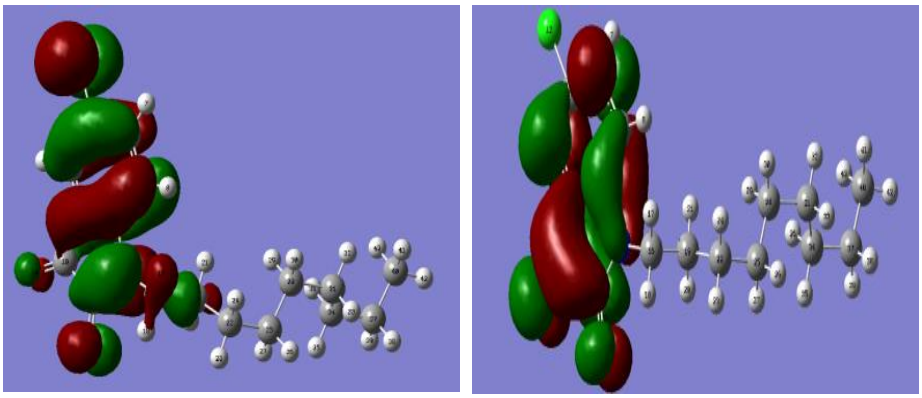


Figure 3. Optimized structure of compound 2a.



HOMO **LUMO**

Figure 4. FMO of compound 2a.

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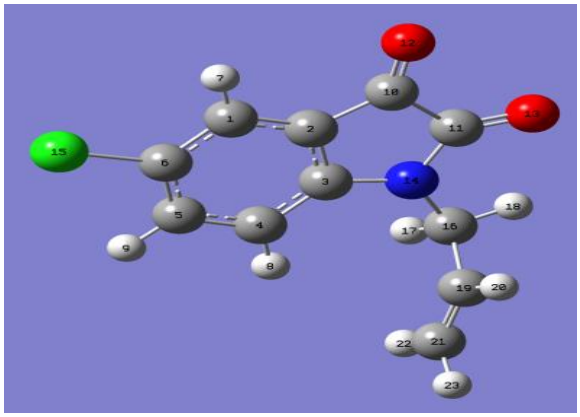
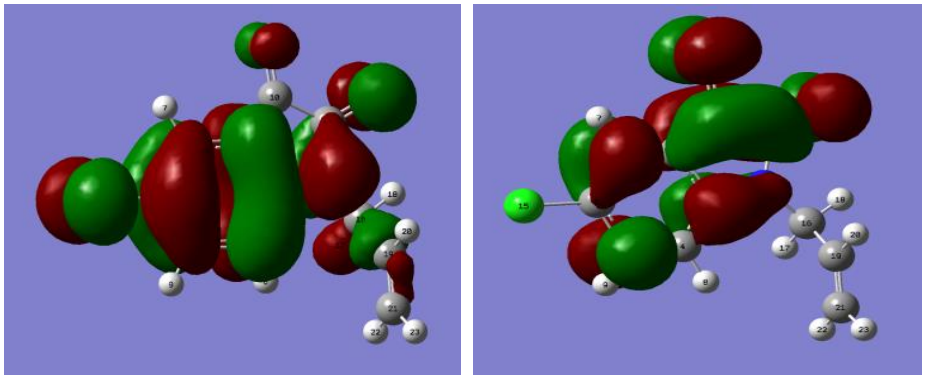


Figure 5. Optimized structure of compound 3a.



HOMO **LUMO**

Figure 6. FMO of compound 3a.

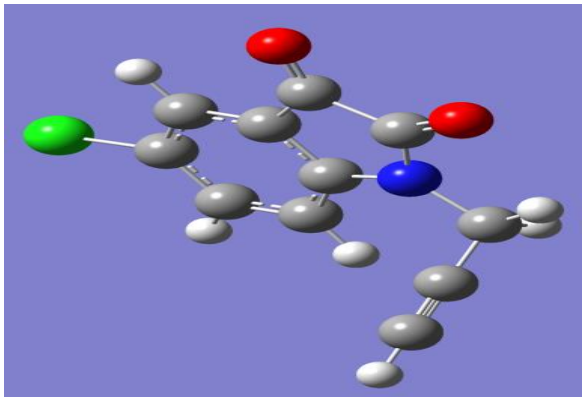


Figure 7. Optimized structure of compound 2b.

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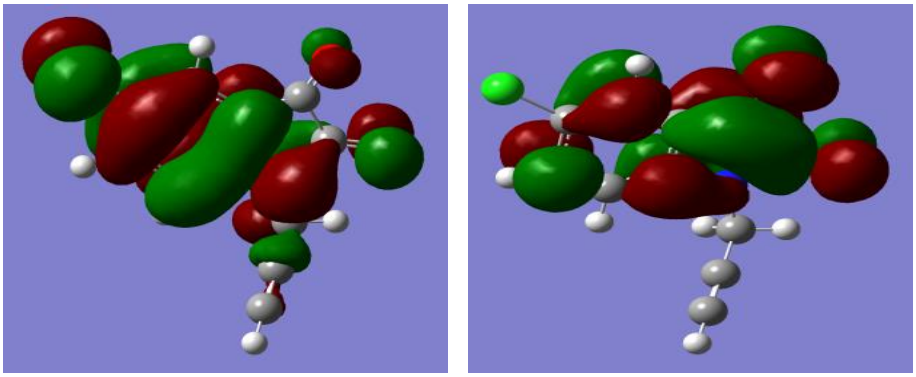


HOMO **LUMO**

Figure 8. FMO of compound 2b.

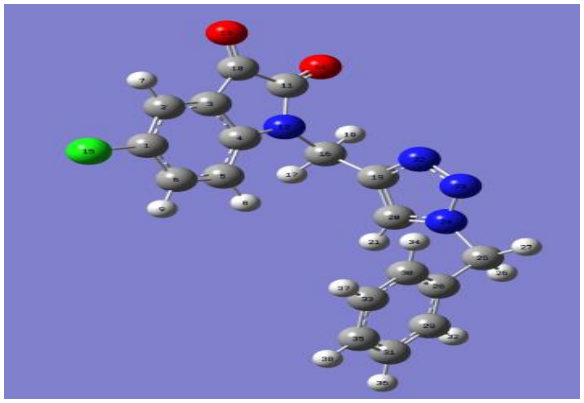
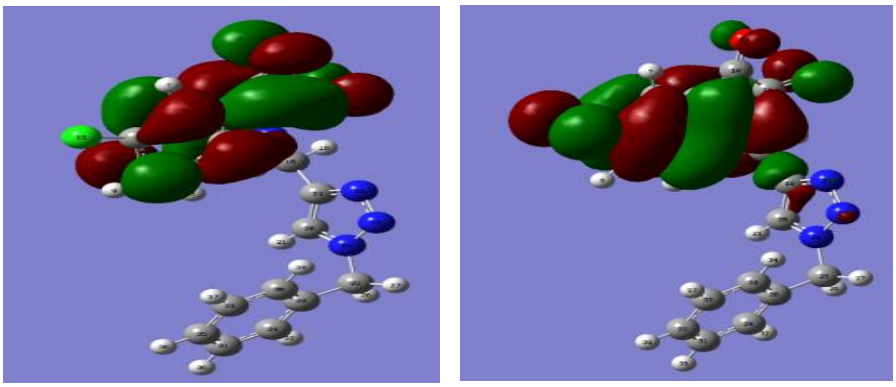


Figure 9. Optimized structure of compound 4b.



HOMO **LUMO**

Figure 10. FMO of compound 4b.

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Local charges are important in many chemical reactions and physicochemical properties of compound.[26] Table 2 shows that most of the carbon atoms (C1, C2, C3, C4, C5, C12, C20, C21, C22, C23, and C25), oxygen atom (O11), nitrogen atom (N18), and chlorine atom Cl12 possess the excess of negative charge. Among them, highest negative charge is located on the nitrogen (N15) and (O13) for **2a** and oxygen atom (O13) for the **1a**, O13 for the **3a** then C20 for **1b** then the N22, N24 for the **4b**. It confirmed that electron donation ability of atoms to the unoccupied orbital of metal is directly related to negative atomic charges of relaxation sites. Therefore, these atoms should be the active relaxation sites.

The preferred site for nucleophilic attack is the atom in the molecule where Fukui function ($f+$) has the highest value as it is associated with the LUMO and measures the reactivity towards a donor reagent.

The preferred site for electrophilic attack is the atom in the molecule where the value of Fukui function (f^-) is the highest as it is associated with the HOMO and measures reactivity toward an acceptor reagent. [27–30] An analysis of Fukui functions depicted in Table 2 shows that the atoms Cl12, O14, C11, C20, Cl15, are preferred sites for electrophilic attack, as these sites have higher values of Fukui function (f^-). The atoms C9, Cl12, O13, C20 and Cl15 are most susceptible sites for nucleophilic attack. For the simplest transfer of electrons, muscle relaxant effect can occur at the part of the molecule, where local softness (s) has the highest value. A high value of $s+$ indicates high nucleophilicity, and a high value of s^- indicates high electrophilicity. The results shown in Table 2 indicate that the condensed local softness indices s^+ and s^- follow the same trend as that of Fukui functions.[31]

Table 2. Pertinent natural populations and Fukui functions of the studied compounds calculated at B3LYP/6-31G

	Atom k	q(N)	q(N+1)	q(N-1)	f_k^+	f_k^-	s^+	s^-
1a	C9	0.0022	0.1880	-0.0215	0.1858	0.0238	0.1047	0.0134
	C6	0.0516	0.2015	0.0116	0.1499	0.0400	0.0845	0.0225
	Cl12	-0.0086	0.2928	-0.0639	0.3014	0.0553	0.1699	0.0312
	O13	-0.4680	-0.2722	-0.5312	0.1958	0.0632	0.1104	0.0356
2a	Cl12	0.0849	0.2924	-0.0638	0.2075	0.1486	0.1207	0.0864
	O13	-0.3937	-0.2723	-0.2303	0.1214	-0.1634	0.0706	-0.0950
	O14	-0.3490	-0.2654	-0.5312	0.0835	0.1822	0.0486	0.1059
	N15	-0.7078	-0.6598	-0.5276	0.0479	-0.1802	0.0279	-0.1048
	C37	0.0089	0.0243	-0.0042	0.0153	0.0131	0.0089	0.0076
	C40	-0.0090	0.0028	-0.0195	0.0118	0.0105	0.0069	0.0061
3a	C11	0.1970	0.3038	0.0231	0.1068	0.1739	0.0438	0.0713
	O13	-0.1013	0.0734	-0.2303	0.1747	0.1290	0.0717	0.0529
	C19	0.1174	0.1162	0.1191	-0.0012	-0.0018	-0.0007	-0.0010
	C21	-0.0269	0.0629	-0.1073	0.0898	0.0803	0.0516	0.0462
2b	C16	0.2385	0.3262	0.1818	0.0877	0.0566	0.0499	0.0322
	C19	0.1829	0.1366	0.2151	-0.0463	-0.0322	-0.0264	-0.0183
	C20	-0.1626	-0.0511	-0.2648	0.1115	0.1022	0.0635	0.0581
4b	C15l	-0.0121	0.1648	-0.1294	0.1769	0.1174	0.0979	0.0650
	N22	-0.3218	-0.3458	-0.3158	-0.0240	-0.0060	-0.0133	-0.0033
	N23	-0.0682	-0.0393	-0.0896	0.0289	0.0213	0.0160	0.0118
	N24	-0.2493	-0.2459	-0.2697	0.0034	0.0204	0.0019	0.0113

3.2. Synthesis of 5-Chloroisatin derivatives

In our laboratory, Tribak and co-workers.[32–35] carried out the alkylation reaction of 5-Chloroisatin with allyl and propargyl bromides and other brominated reagent under the conditions of liquid-solid phase transfer catalysis. It was able to isolate a single N-alkylated product **1a**-**3a** and **2b** in good yield (Scheme 1 and 2).

Also, Tribak and co-workers [36] studied the condensation of N-propargylchloroisatin with benzyl azide at the reflux of ethanol, for 24 hours, led to the formation of a single regioisomer **4b** resulting from the attack of the most nucleophilic nitrogen of the dipole on the most electrophilic sp^3 carbon of the dipolarophile.

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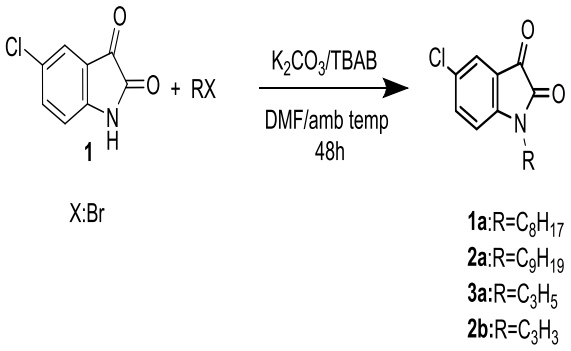
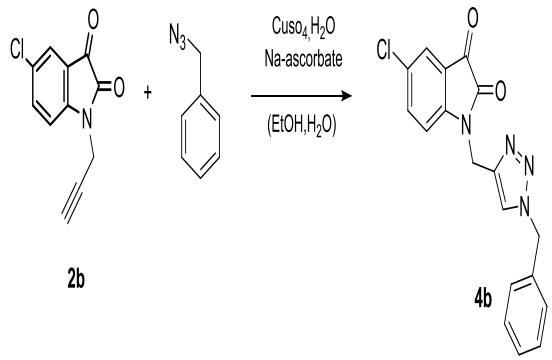
3.3. Muscle relaxant effect of 5-Chloroisatin derivatives

In this study, we investigated the muscle-relaxing activity on the isolated intestine of the rabbit of our molecules containing the 5-Chloroisatin molecule, which possesses an indole nucleus having both the keto and lactam parts, aroused an enormous curiosity due to its various biological and pharmacological studies.[37,38]



Scheme 1



Scheme 2

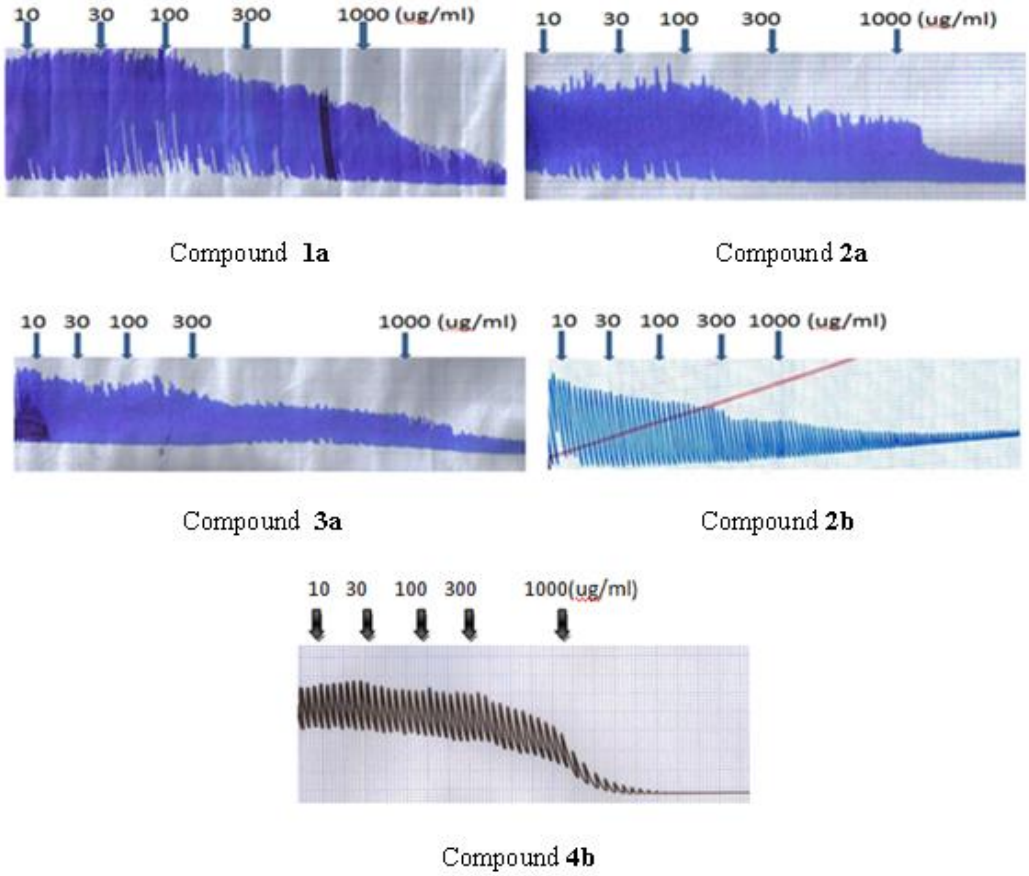


Figure 11. The original plot shows a significant muscle relaxant effect of the compounds **1a-3a, 2b** and **4b** above on the contractile activity of the rabbit jejunum.

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The present study aims at the in vitro research of possible muscle relaxant effect of new heterocyclic molecules derived from 5-Chloroisatin. Once the preparation is mounted on the insulated organ vessel, we wait for its stabilization (about 30 min). Once stable, spontaneous contractions of the rabbit jejunum are recorded. After pharmacological screening of the samples studied, we were able to demonstrate that products **1a-3a**, **2b** and **4b** belonging to the family of 5-Chloro-1*H*-indole-2,3-dione are endowed with muscle-relaxing activity in the segments isolated from the jejunum. The amplitude of contractions of the segments of the jejunum isolated from the base rabbit was reduced in a concentration-dependent manner (Products: **1a-3a**, **2b** and **4b**).

The compounds (**1a-3a**, **2b** and **4b**) were tested on isolated rabbit jejunum to determine its myorelaxant effect. As shown in Figure 12, the cumulative concentrations of 5-Chloroisatin derivatives altered the spontaneous contractions of the isolated rabbit jejunum in a concentration-dependent manner since the percentage of contraction decreased to 97% for the lowest concentration and was almost totally inhibited at the highest concentration to 3%. The effects of the products tested are very close and in this case it is adequate to say that the products have a similar effect (Figure 12).

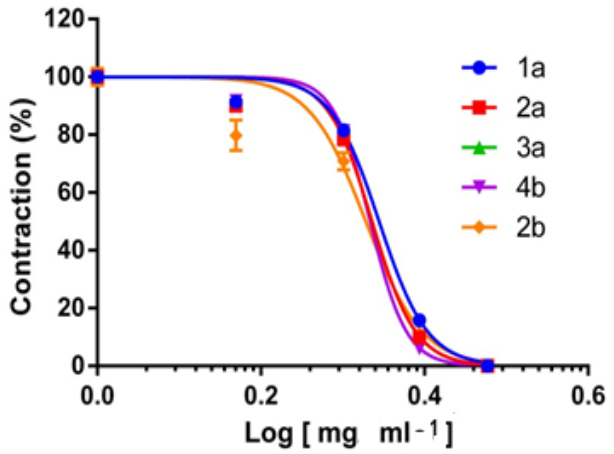

Figure 12. Myorelaxant effects of cumulative concentrations of 5-Chloroisatin derivatives (**1a-3a, 2b** and **4b** (mg ml^{-1}) on the spontaneous contraction of isolated rabbit jejunum.

4. CONCLUSIONS

Some new 5-Chloroisatin derivatives **1a-3a, 2b** and **4b** were synthesized and identified in good yields. The myorelaxant activity performed for all the compounds, which were effective relaxant on isolated rabbit jejunum. Most of the studied quantum chemical descriptors correlated well with the available experimental observations.

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Conflict of interest

Authors declare that there is no a conflict of interest with any person, institute, company, etc.

Ethical Report**:** For the Ethical report, the present study was performed according to international and institutional rules regarding animal experiments (NIH Publication No. 85-23, revised 1996).

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