

left colic flexure to the anterior aperture of the true pelvis, where it creates the sigmoid colon, whereas the transverse colon spreads from the right colic flexure to the left colic flexure. An S-shaped tube that extends into the pelvis and terminates at the rectum is formed by the descending colon (Cody, 2001).

Metoclopramide (Fig. 1) is an important antiemetic drug and is also used as a treatment to stimulate stomach movements. Metoclopramide is indicated for the treatment of individuals with gastroesophageal reflux disease and gastrostomy has been associated with metoclopramide, as described by (Maltepe and Koren, 2013). Metoclopramide is characterized as a dopamine (D2) receptor antagonist with a brief half-life, and it possesses dual properties as both a 5HT3 and 5HT4 receptor antagonist. Its effects encompass antiemetic, antidiarrheal, and gastromotor properties (Smith and Laufer, 2014). Meanwhile, the ability of metoclopramide to affect colon motility remains controversial. Metoclopramide enhanced withdrawal frequency in round sections of the human and animal cortex through smooth muscle contraction *in vitro* (Schulze-Delrieu, 1979).

In clinical practice, stomach pains are treated with hyoscine-n-butyl bromide (buscopan) (Fig. 2), which is an antispasmodic agent of the muscle. It is particularly involved in gastrointestinal inflammation, for example, those with leukemia, especially bowel obstruction and irritable bowel syndrome. They are also used effectively as smooth muscle relaxants and anticholinergic and calcium channel blockers and are very effective in treating conditions associated with stomach pain (Samuels, 2009). Known as hyoscine-n-butyl bromide (scopolamine butyl bromide, Buscopan) that is used to treat smooth muscle relaxation and anticholinergic properties (Hasan, et al., 2013). Example of muscle M2 and M3 receptors has a very good effect on them so hyoscine-n-butyl bromide in smooth muscle causes gastrointestinal tract. Hyoscine-N-butylbromide according to its sustained actions

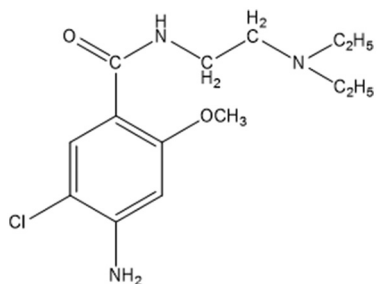


Fig. 1. Chemical formation of metoclopramide is strictly associated with procainamide.

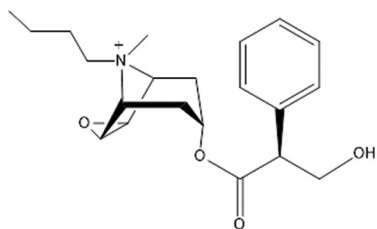


Fig. 2. Chemical formation of hyoscine-N-butyl bromide.

being anti-smooth muscle contraction can inhibit nicotinic receptor in SH-SY5Y cells and human enteric neurons (DeLoid, et al., 2017). In addition, a unique kinematic study of muscle contraction and relaxation was conducted to examine the effects of hyoscine-n-butyl bromide on the digestive system, especially the abdominal colon (Dicken, et al., 2011). To facilitate the long-term preservation of ingested material and promote microbial aging, the complex functioning of the digestive system requires the integration of its kinetics. Therefore, any increase in bowel motility in these areas makes a person more vulnerable (Hasan, et al., 2013).

II. MATERIALS AND METHODS

A. Study Design

In the study, for colon tissue recordings, eight animals were utilized from the Firat University Experimental Research Center located in ELAZIĞ, with each animal's tissue strips serving as respective controls. Waited for 10–12 weeks until the mice had reached an average weight ranging between 180 and 200 g. Following the decapitation of the mice, the abdominal area promptly excised and the colon tissues were removed. These colon tissues were subsequently placed in a Petri dish containing Krebs solution. In this study, smooth muscle was focused on the animals that were euthanized without the use of anesthesia to prevent any potential impact on the smooth muscle.

B. Experimental Setup

The study utilizes a two-chamber organ bath system, enabling the concurrent utilization of two separate smooth muscle strips. This setup comprises several essential components, including the organ bath itself, an amplifier, a recorder, a circulating pump equipped with a thermostat, and a source of oxygen and carbon dioxide. Designed to replicate physiological conditions within a laboratory environment, Krebs's solution incorporates specific elements that support the retention of contractility properties in smooth muscle cells when studied *in vitro*. The Krebs solution is prepared in mmol/L and the pH is adjusted to 7.4 of NaCl: 118, KCl: 4.7 mmol/L, MgSO₄: 1.2 mmol/L, Glucose: 11.5 mmol/L, CaCl₂: 2.4 mmol/L, KH₂PO₄: 1.18 mmol/L, EDTA: 0.016 mmol/L, and NaHCO₃: 2.0 mmol/L.

C. Preparation and Application Protocol of Colon Tissues

After euthanizing male animals, their abdominal areas were carefully opened, and a 1 cm wide incision was made in the colon cecum. A 2 cm long strip of tissue was then meticulously prepared and affixed to both ends of silk sutures, which were embedded at either end of the isolated organ bath. A tension of 1.0 g was applied to the device, which was suspended and used to record isometric contractions. Following this, we allowed 1.5 hours for the colon strips to acclimate. During this time, tissues in the isolated organ baths were subjected to a 15-min treatment with Krebs solution. Once sustained spontaneous contractions became observable, we induced contractions by adding acetylcholine (Ach) at

a dose of 10–4M. Subsequently, we conducted experiments in three distinct protocols after the adjustment period. In the first protocol, we added 35 μM of metoclopramide to the Ach-stimulated colon strips, followed by 15 μM of hyoscine-n-butyl bromide to the same strips after 1 h. Finally, 1 h later, both hyoscine-n-butyl bromide and metoclopramide were simultaneously administered to the Ach-stimulated colon strips. We carefully recorded and analyzed the effects of metoclopramide alone and hyoscine-n-butyl bromide on colonic contractility, with the tissue contraction values before drug administration serving as their respective controls.

D. Organ Bath Containers

Divided into two interconnected parts. In addition, the heater contains hot water within the space between these two layers. Inside the inner compartment, you will find Krebs solution along with the smooth muscle strips utilized in the research. The cortex strip is suspended between two hooks, one within the chamber and the other outside, using a silk thread.

E. Thermocirculator

It is placed in heat-circulated purified water at 36.7°C. The heated water goes to the area where the Krebs solution is stored and goes to the warehouses in various ways. Because the Krebs solution is stored in two regions, the spaces and reservoirs are intertwined and there are gaps between the layers. The thermostat sensitivity ranges from 36.7 ± 0.1°C. The circulating heated water circulates in this space to keep the environment at body temperature.

F. Oxygen carbon dioxide source

A gas mixture required for *in vitro* smooth muscle contraction is ideally made of 95% O₂ and 5% CO₂. In the isolated organic bath and recording system, the O₂ and CO₂ contents prepared in this mixture were continuously circulated to the chamber.

G. Statistical Analysis

Statistical analysis was performed using SPSS software, version 24. For comparison of uptake values (independent test). The significance level used was p = 0.05).

III. RESULTS AND DISCUSSION

A. Effects of Metoclopramide and Hyoscine-n-butyl Bromide on Frequency of Smooth Muscle Contraction and Relaxation in Colon

The results provided evidence that all doses of metoclopramide, hyoscine-N-butyl bromide, and a combination of the two were statistically significant (p < 0.05). Specifically, the mean frequency (mean ± SE) of isolated Ach-induced colon strips was 151.5021.38 (n = 8) for 35M metoclopramide, 127.0510.09 (n = 8) for 15 M hyoscine-N-butyl bromide, and 242.3255.00 (n = 8) for 50 M of the mixed concentration. The highest frequency of isolated Ach-induced colon strips was observed in the

combination of metoclopramide and hyoscine-N-butyl bromide, as indicated in Table I.

B. Effects of metoclopramide and hyoscine-n-butyl bromide on Pile peak (peak-to-peak) on smooth muscle contraction and relaxation in the colon

Sections of rat colon tissues were tested by treating and administering drugs with 35 μM metoclopramide, 15 μM hyoscine-n-butyl bromide in each drug separately, then by mixing both drugs at 50 μM. The mean and standard deviation error for peak-to-peak of isolated Ach-induced cortical strips from control and treated mice was 62.364.35 (n = 8), 67,225.84 (n = 8), and 73.576.23 (n = 8), respectively. All drugs caused a significant decrease in peak-to-peak static compared with control (35 μM metoclopramide: p < 0.001; 15 μM hyoscine-N-butyl bromide: p < 0.001; 50 μM: p < 0.05). metoclopramide 35 μM showed the most significant reduction compared with other drugs, as shown in Table II.

C. Effects of Metoclopramide and Hyoscine-n-butyl Bromide on Smooth Muscle Contraction and Relaxation in the Colon

Results from this analysis are mean ± SE of 48.27 ± 11.42 (n = 8), 46.06 ± 8.75 (n = 8), and 29.28 ± 4.65 (n = 8) for the amplitude of Ach-induced isolated contractile strips, contractile muscle shoulder in rats with 35 μM metoclopramide and 15 μM hyoscine-1. N-butyl bromide we also control 50 μM hyoscine-n-butyl bromide and metoclopramide by combining the two drugs. All of these doses were statistically significant compared with the control, as 35 μM metoclopramide showed the least reduction in muscle contractility (p < 0.05). Relative to the combination of both drugs with 50 μM metoclopramide and hyoscine-n-butyl bromide had the greatest reduction (p < 0.001), as shown in Table III. One dose that captures

TABLE I
SHOWS MEAN±SE AND P VALUE OF FREQUENCY, BEFORE AND AFTER TREATMENT IN COLON CONTRACTION STRIPS

Dose	Frequency	N	Mean±SE	p
(35μm) Metoclopramide	Before treat.	8	115.352±16.532	0.047
	After treat.		151.507±21.387	
(15 μm) hyoscine-n-butyl bromide	Before treat.	8	98.341±9.220	0.032
	After treat.		127.056±10.093	
(35 μm) metoclopramide+(15 μm) hyosin-n-butyl bromide	Before treat.	8	174.827±38.349	0.03
	After treat.		242.325±55.004	

TABLE II
THE MEAN±SE AND P VALUE OF PEAK-PEAK, BEFORE AND AFTER TREATMENT IN DUODENUM STRIPS

Dose	Peak-peak	n	Mean±S.E	p
(35 μm) Metoclopramide	Before treat.	8	70.922±3.651	0.0001
	After treat.		62.360±4.359	
(15 μm) hyoscine-n-butyl bromide	Before treat.	8	74.591±6.508	0.001
	After treat.		67.222±5.843	
(35 μm) metoclopramide+(15 μm) hyoscine-N-butyl bromide	Before treat.	8	129.289±48.459	0.004
	After treat.		73.578±6.323	

TABLE III
MEAN±SE AND P VALUE OF THE AREA, BEFORE AND AFTER TREATMENT
CONTRACTION 109 COLON STRIPS

Dose	Area	N	Mean±SE	P
(35 µm) Metoclopramide	Before treat.	8	52.246±11.600	0.003
	After treat		48.275±11.432	
(15 µm) hyoscine-n-butyl bromide	Before treat.	8	52.155±8.876	0.001
	After treat.		46.063±8.751	
(35 µm) metoclopramide+ (15 µm) hyoscine -n-butyl bromide	Before treat.	8	35.132±4.647	0.001
	After treat.		29.288±4.659	

the awareness of experts in this sector is metoclopramide. Metoclopramide and its receptor are expressed in multiple organs, mainly the lung, adipose tissue, and female breast (Falcão-Pires and Leite-Moreira, 2005). The results of this study showed that metoclopramide alone and in combination with hyoscine-n-butyl bromide significantly affects slowing of the muscle in vitro in male rats. According to earlier research on the colon, contract happens when intracellular Ca^{+2} rises as a result of Ca^{+2} being released from SR and entering the cell through voltage-sensitive Ca^{+2} channels outside the cell. PLC pathways are used by several hormones that act on receptors, including OT and PGF2 (Catterall, 1988). Two-second messengers are activated by PLC activation. PKC is activated by DAG, which also releases Ca^{+2} from IP3 SR. Myosin-actin contact causes contraction when the MLCK enzyme is activated by the Ca^{+2} calmodulin compound, which also causes the phosphorylated of MLC (Sumi, et al., 1991). Actin and myosin levels reduced together with the colon's contraction upon the addition of metoclopramide alone, along with hyoscine-n-butyl bromide in the container (Sumi, et al., 1991). It is well recognized that a variety of regional and global factors influence how the colon constricts when doses are administered. Recent investigations have uncovered the varied ways in which numerous novel hormones and cytokines affect the motility of the colon (Falcão-Pires, et al., 2005). Similar to skeletal muscle, the colon cells are heavily dependent on calcium ions to control their ability to contract. However, because smooth muscle SR does not mature properly, extracellular fluid is mostly responsible for the calcium needed for contraction. Exactly before phasic contractions in the GI, Ca^{+2} entrance into the cell from the external environment raises intracellular calcium levels (Giannone, et al., 2010). It has been claimed that the availability of exogenous calcium completely determines the amount of stimulation parameters in the colon. It has been demonstrated that if there is no Ca^{+2} in the environment where duodenal segments are situated, spontaneously contracting ends abruptly and spontaneously activation diminishes. It has been noted that adding Ca^{+2} to the medium restores activation in response (Hashitani, Brading and Suzuki, 2004). Changes in underdoes levels were statistically significant in male rats. Sequentially, it was observed that the tissue was controlled by the application of 35 µM metoclopramide, 15 µM hyoscine-n-butyl bromide and by combining the drugs with 50 µM metoclopramide and hyoscine-n-butyl bromide. All dose frequencies had

a statistically significant positive effect on slowing muscle contraction. Furthermore, metoclopramide applied alone to compare with hyoscine-n-butyl bromide is preferable, because it increases the effects of metoclopramide on smooth muscle contractility, better than hyoscine-n-butyl bromide. Meanwhile, hyoscine-n-butyl bromide is more effective than the combination of both metoclopramide and hyoscine-n-butyl bromide which significantly reduces smooth muscle contraction at peak-to-peak. However, when hyoscine-n-butyl bromide was added, it showed minimal muscle contractile effects significantly compared to the dosage forms. Furthermore, the effects of metoclopramide and hyoscine-n-butyl bromide on smooth muscle contraction showed the least statistically significant reduction of cortical muscle contraction, compared with each other. Furthermore, the importance of metoclopramide only on muscle contraction in the cortex, the contraction of the region was much less effective than each other.

D. Electronic Structure

In drug development, physicochemical qualities are the tangible physical characteristics of molecules related to interactions with various mediums and situations. Physicochemical describes objects that include both physics and chemistry principles, implying that they rely on or are generated by the combined operations of physical and chemical qualities (Mary, et al., 2021). Throughout the study, the B3LYP density functional technique, as implemented in the Gaussian package 09, was used. Basis set 6-311G++(d,p) is used for full optimization of all geometries. With large 6-311++G(d,p) basis sets, the anionic species used in this work were produced (Fig. 3), using the continuous solvation approach, the relaxation energies of the protonated and neutral species were calculated theoretically (Mamand, et al., 2022a, Mamand and Qadr, 2021). The guide-like polarization constant variation was used to implement the polarization constant model (PCM). PCM computations were performed on the gas-phase geometries as single points (without optimization) since this has been demonstrated to produce better results than optimization. Water was given a dielectric constant of = 79.39 (Erdoğan, et al., 2017, Qadr and Mamand, 2021). A characterization of the form and size of the cavity formed by solute molecules in the solvent is required for continuum models.

Numerous novel chemical reactivity descriptors have been proposed to help understand various areas of pharmaceutical sciences such as drug design and prospective ecotoxicological physiognomies of medications. To investigate the properties of these two molecules, some important properties were calculated in this study, which is shown in Tables IV and V.

The features of frontier molecular orbitals are utilized to describe many types of reactions and to calculate the most reactive location in a conjugated system. The HOMO and LUMO energy, as well as their gap, are computed to show a complex's chemical reactivity and biological activity. The HOMO, which is thought to be the outer orbital containing electrons, has a tendency to contribute electrons as e-donors,

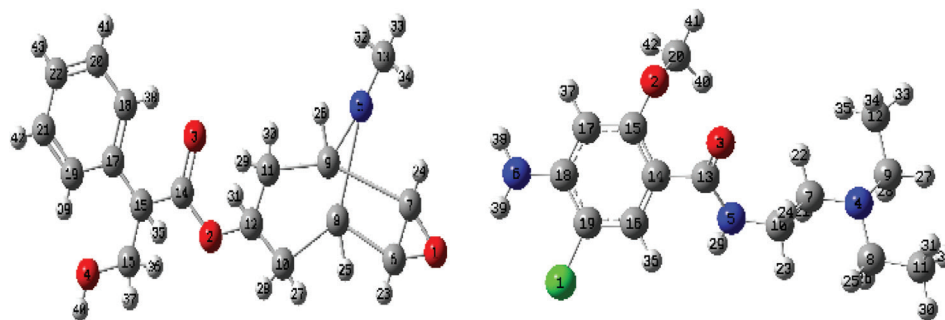


Fig. 3. Optimized molecule structure of hyoscine-n-butyl bromide and metoclopramide is strictly associated with procainamide based on DFT at 6-311G++(d,p) basis set.

TABLE IV
THEORETICAL CALCULATION OF ELECTRONIC PARAMETERS FOR HYOSCINE-N-BUTYL BROMIDE AT PROTONATED AND NON-PROTONATED SPECIES IN GAS AND AQUEOUS PHASES

A	Non-protonated gas phase	Protonated gas phase	Non-protonated aqueous phase	Protonated aqueous phase
E_{HOMO} (eV)	-7.20639506	-7.18054423	-5.74922459	-7.91634049
E_{LUMO} (eV)	-6.570736758	-6.60910483	-5.21996286	-7.42190935
Dipole moment (Debye)	10.6328	17.7123	15.7043	23.1631
Total energy a.u	-1116.8279	-1117.0173	-1116.8121	-1116.8919
Ionization energy (eV)	7.2063	7.1805	5.7492	7.9163
Electron affinity (eV)	6.5707	6.6091	5.2199	7.4219
Band-gap energy (eV)	0.6356	0.5714	0.5292	0.4944
Hardness (eV)	0.31782	0.2857	0.2646	0.2472
Softness (eV)	3.1463	3.4999	3.7788	4.0450
Electronegativity (eV)	6.8885	6.8948	5.4845	7.6691
Chemical potential (eV)	-6.8885	-6.8948	-5.4845	-7.6691
Electrophilicity (eV)	74.6507	83.1909	56.8353	118.955
Nucleophilicity (eV) ⁻¹	0.0133	0.0120	0.0175	0.0084
Transfer electrons	-0.0794	-0.07142	-0.066	-0.0618
$\Delta E_{\text{Back-donation}}$ (eV)	0.1753	0.1840	2.8632	-1.3533
ΔN	-0.0097	-0.0096	-2.1694	-0.4527
E_{MEI}	68.0799	76.5818	51.6153	111.5339
Nucleophugality	81.8570	90.3715	62.5845	126.8721
Electrphugality	7.2063	7.18054	5.7492	7.9163

TABLE V
THEORETICAL CALCULATION OF ELECTRONIC PARAMETERS FOR METOCLOPRAMIDE AT PROTONATED AND NON-PROTONATED SPECIES IN GAS AND AQUEOUS PHASES

B	Non-protonated gas phase	Protonated gas phase	Non-protonated aqueous phase	Protonated aqueous phase
E_{HOMO} (eV)	-7.55089139	-7.42789586	-7.60857955	-5.95902449
E_{LUMO} (eV)	-6.64529599	-6.89754567	-6.92285227	-4.71328659
Dipole moment (Debye)	8.9873	9.7832	14.6734	18.5133
Total energy a.u	-1320.7281	-1320.440	-1320.4521	-1320.7801
Ionization energy (eV)	7.5508	7.4278	7.6085	5.9590
Electron affinity (eV)	6.6452	6.8975	6.9228	4.7132
Band-gap energy (eV)	0.9055	0.5303	0.6857	1.2457
Hardness (eV)	0.4527	0.2651	0.342	0.6228
Softness (eV)	2.2084	3.771093238	2.9166	1.6054
Electronegativity (eV)	7.0980	7.162720765	7.2657	5.3361
Chemical potential (eV)	-7.098	-7.1627	-7.2657	-5.3361
Electrophilicity (eV) (ω)	55.6351	96.7371	76.9848	22.8575
Nucleophilicity (eV) ⁻¹	0.0179	0.0103	0.0129	0.0437
Transfer electrons	-0.1131	-0.0662	-0.0857	-0.1557
$\Delta E_{\text{Back-donation}}$ (eV)	-0.10831	-0.3068	-0.3874	1.33562
ΔN	-0.00531	-0.0249	-0.05148	-1.1111
E_{MEI}	48.9898	89.8396	70.0620	18.1442
Nucleophugality	63.1860	104.1650	84.5934	28.8166
Electrphugality	7.5508	7.4278	7.6085	5.9590

and so the ionization potential is necessarily connected to the energy of the HOMO. LUMO, on the other hand, may accept electrons, and the LUMO energy is directly related to electron affinity. A high value indicates electron donation and also a high LUMO value causes the molecule to tend to accept electrons. Both molecules have the highest values for HOMO in water, which proves that the ability of these two drugs to donate electrons will be greater. A molecule with a smaller HOMO-LUMO gap is more polarizable and has low kinetic stability and strong chemical reactivity. The softness, therefore, correlates to the HOMO-LUMO gap. The softer the molecule or multicomponent crystal, the narrower the HOMO-LUMO energy gap. Figs. 4 and 5 illustrate the HOMO-LUMO energy gaps of hyoscine-n-butyl bromide has a lower bandgap energy than metoclopramide (Mamand, et al., 2022b, Omar, et al., 2023). The (η) defines the conflict toward the distortion of the electron cloud of chemical systems in the presence of minor disturbances encountered throughout the chemical process (Chattaraj and Roy, 2007, Parlak, et al., 2022, Omer, Koparir and Ahmed, 2022). Electrophilicity (ω) is

defined as a measure of the sensitivity of chemical species to accept electrons. Low values of (ω) indicate the presence of a good nucleophile; whereas, higher values indicate the presence of good electrophiles. The best electrophilic molecule is in the state, where the first molecule has the highest electrophilicity in non-protonated gas and protonated water. Electrophilicity is a reactivity descriptor that may be used to define the toxicity of these compounds. It also includes a direct link between reaction rates and the ability to determine an electrophile's function or capacity. The inhibitor (A) had higher electrophilicity indices (74.65, 83.19, 56.83, and 118.95 eV) in gas and aqueous phases for protonating and non-protonated states than metoclopramide (55.63, 96.73, 76.98, and 22.85 eV), indicating that they have more biological activity. In addition, the calculations revealed that the hyoscine butyl bromide molecule has a low electronegativity (6.88, 6.89, 484, and 7.66 eV) in gas and aqueous phases for protonating and non-protonated states, which increases the electron releasing power of metoclopramide to the enzyme, and as a result, increases metoclopramide capacity to be oxidized.

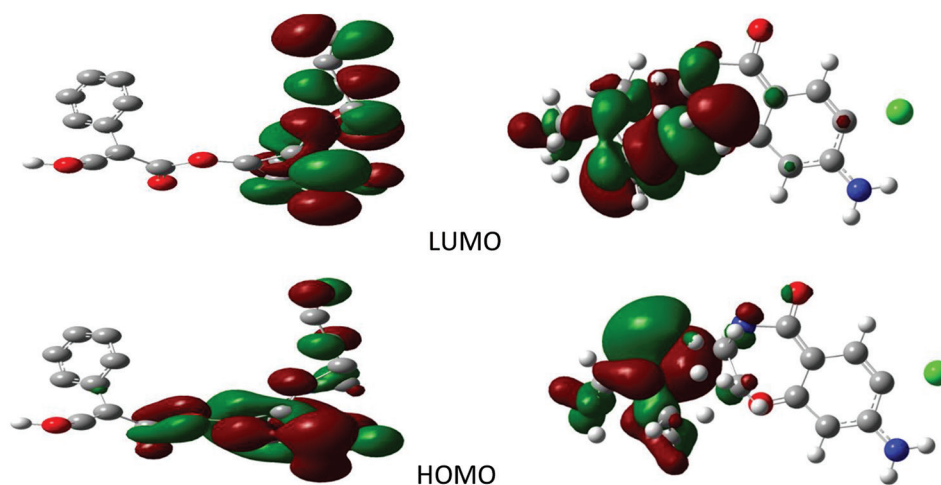


Fig. 4. HOMO and LUMO of hyoscine-n-butyl bromide and metoclopramide compounds in the gas phase.

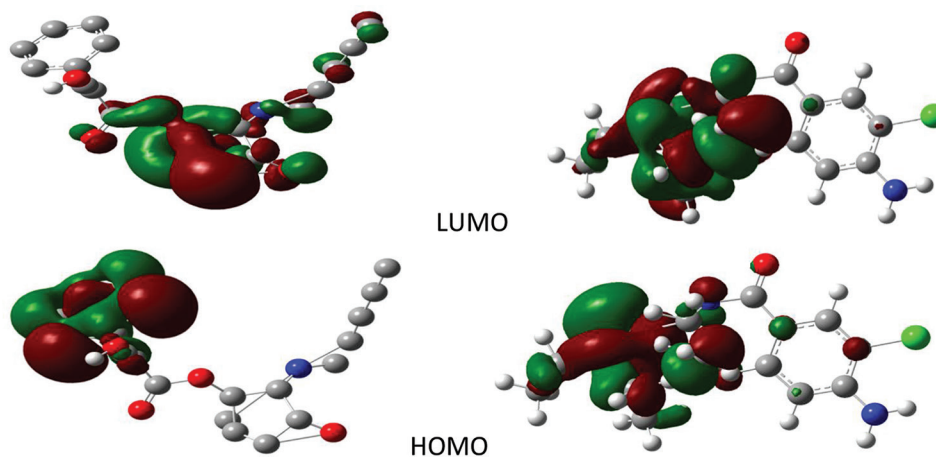


Fig. 5. HOMO and LUMO of hyoscine-n-butyl bromide and metoclopramide compounds in the aqueous phase.

IV. CONCLUSION

The impact of metoclopramide on the contractile and relaxant responses of colon muscle induced by Ach. To achieve this, we utilized a novel experimental setup, involving 1 cm wide and 2 cm long incisions in the colon tissue attached to organ bath tissues. Ach, metoclopramide, hyoscine-n-butyl bromide, and a combination of metoclopramide and hyoscine-n-butyl bromide were sequentially applied to the colon tissue. This allowed us to observe and analyze changes in frequency, peak-to-peak, and amplitude in the muscle contractions. Using statistical analysis a paired sample T-test, providing valuable insights into the effects of metoclopramide on colon muscle responses to Ach stimulation. The results showed that metoclopramide, hyoscine-n-butyl bromide, and the combination of the two affected colonic contractility by stimulating Ach and increasing intestinal motility. Metoclopramide is thus used in the treatment of gastroenteritis. Physicochemical properties of hyoscine-n-butyl bromide and metoclopramide molecules metoclopramide bromide were found to have a higher electrophilicity index and higher electronegativity than hyoscine-n-butyl bromide, indicating that it has more biological activity and potential to deform more effectively oxidized. Therefore, it can be concluded that metoclopramide bromide is the best molecule for an anticholinergic agent.

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