ISSN: 0067-2904
GIF: 0.851

Theoretical Design of Anticancer Agents of Some Crown Substituent's Through complexation with Cellular Potassium Ion

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Abstract

Theoretical study of ten crown ethers substituents were established to investigate some parameters that give clear view about their validity and applicability in the design of anticancer agents. Restricted hartree fock method (RHF/3-21G) were used to determine the energy difference between highest occupied molecular orbital and lowest unoccupied molecular orbital (HOMO-LUMO gap) , ionization energy, global hardness and total energy. Strong binding ability with potassium ion were obtained in some of these compounds depend on the type of substituents added to both nitrogen atoms out of the ring cavity. Such binding with potassium in abnormal and divided cancer cells result in inhibition of tumor cell growth by disrupting potassium ion homeostasis leading to kill ailing cells. Compound 10 represents the best suggested material which posses the potent anticancer activity due to its physicochemical properties required for anticancer drugs.

Keywords: Crown ethers, Theoretical studies, Anticancer drugs, Potassium disruption.

تصميم نظري لبعض معوضات الايثرات التاجية المضادة للسرطان من خلال تكوين معقدات مع ايون البوتاسيوم الخلوي

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الخلاصة

تم في هذا البحث اجراء دراسة نظرية لعشرة من مشتقات مركبات الايثرات التاجية لتقييم فعالية هذه المركبات كعوامل مضادة للسرطان من خلال تكوينها معقدات مع ايون البوتاسيوم الخلوي. أستخدمت في هذا البحث برامجيات النمذجة الجزيئية وتحديدا هارتري فوك لحساب المتغيرات اعلاه ومنها فرق الطاقة بين HOMO–LUMO ، طاقة التاين ، الصلابة بمفهوم كلوبال اضافة الى الطاقة الكلية. بينت النتائج المحسوبة القدرة العالية لتأصر البوتاسيوم مع بعض المركبات التاجية اعتماداً على المجموعات المعوضة في هذه المركبات على ذرتي النتروجين خارج الحلقة التاجية . طاقة التاصر العالية المستخرجة هي دلالة على قابلية هذه المعقدات على تثبيط انقسام الخلايا السرطانية وايقاف تكاثرها وتدمير الخلايا المعتلة من خلال حصول اضطراب في الظاهرة البايولوجية (homeostasis) لايون البوتاسيوم . من بين عشرة مركبات مدروسة ، بينت النتائج ان المركب 10 اظهر افضل اداء في التحقق من تصميم دواء مضاد للسرطان.

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Introduction

Heterocyclic polyether compounds (crown ethers) are types of chemical structures posses internal cavity that contains electron donor hetero atoms such as oxygen, sulfur and nitrogen. These heteroatoms act as powerful species to bind with highly electropositive elements especially alkali cations which resulting in highly stable cyclic complexes depending on both sizes of cation and ring [1].

Crown ethers have several important applications such as separation of metals by solvent extraction techniques [2-4] , for organometallic synthesis [5], as inhibitors for corrosion of some alloys such as stainless steel in acidic aqueous medium [6,7], for selective transport of metals using their polymers compounds [8] in addition to other applications.

One of the most important applications is used in chemotherapeutic field as antitumor (anticancer) drugs. The potent reactivity of their compounds toward cancer cell enhanced research and development activities in recent years. Compounds such as α,ω-hexadecyl-bis-(1-aza-18-crown-6), crowned beta peptides , adamantane derivatives of aza crown ethers, di-tert-butyldicyclohexano-18-crown-6 and di-tert-butyldibenzo-18-crown-6 were synthesized for cancers treatment [9-11].

Theoretical studies of anticancer drugs design were established using molecular modeling such as semiemperical and density functional theory [12-14], such studies deepen the understanding of researchers towards the prospects and requirements of these valuable materials.

The idea of this work is based on theoretical evaluation of some interested crown ethers compounds synthesized by Kiyoshi Matsumoto et al. 5, 6, 7, 8 and 10 [15]. These can be used as anticancer agents that act by disrupting potassium ion homeostasis resulting in cancer cell cycle perturbations.

Computational Method:

Computational calculations were carried out using ChemBio3D Ultra package. The used method was Restricted Hartree Fock (RHF) in the 3-21G basis set. HOMO –LUMO and total energies values for all compounds 1-10 were investigated through direct calculations by the above method while ionization energy and global hardness were calculated according to the following references [16-18].

Results and Discussion:

Initially 18 crown 6 was studied then the rest of the above mentioned compounds were studied after the addition of substituents, Figure-1 shows the structures of all compounds as ligands before binding with potassium ion. The results obtained presented in Table -1 show all the needed factors that help to understand the effects of the substituents added to the main structure (18 crown 6) including variation of the hetero atoms inside the cavity.

According to HOMO-LUMO gap, the structures shown in Table-1 were arranged due to the decrease of their values, it is clear that the sequence being decreased when replacing oxygen atoms with sulfur or nitrogen atoms in the internal cavity and by addition of rings especially when phenyl rings bind directly to nitrogen atoms.

This sequence reflects the decreasing energy gap in the direction from the first to the tenth structures 1-10, that means reactivity increases in the same direction. Also increasing HOMO value refers to the nucleophilicity behavior of compound 10 as the best donor [19] toward Lewis acid potassium ion. Due to the higher HOMO value of compound 10 compared with the rest, its electron donating strength would be higher than others.

Another indicator of stability is the global hardness; the more stable compound has higher global hardness [20]. Table-1 shows that compound number 10 has minimum value, so it has been considered as the most reactive one. Ionization potential is also considered as an important factor to determine the reactivity, the higher the ionization energy, the less the reactivity. On this basis, the results are still remain with the same semantics and compound number 10, which is still the most reactive and the best ligand, because of its lower value of potential energy. Total energy is a significant parameter to estimate the stability of complexes formation. The more negative the total energy; the most stable the products [21-22].

Again, crown ether 10 is founded to be the best ligand when binding with potassium ion, Table-2. Despite the mismatch of the sequence of the total energy values of complexes with the sequence of characters obtained in Table -1 , but it is certainly that the final concluded results prove that compound 10 is the best. All these evidences prove that compound 10 represents the best one which results in highly stable complexes with potassium ion.

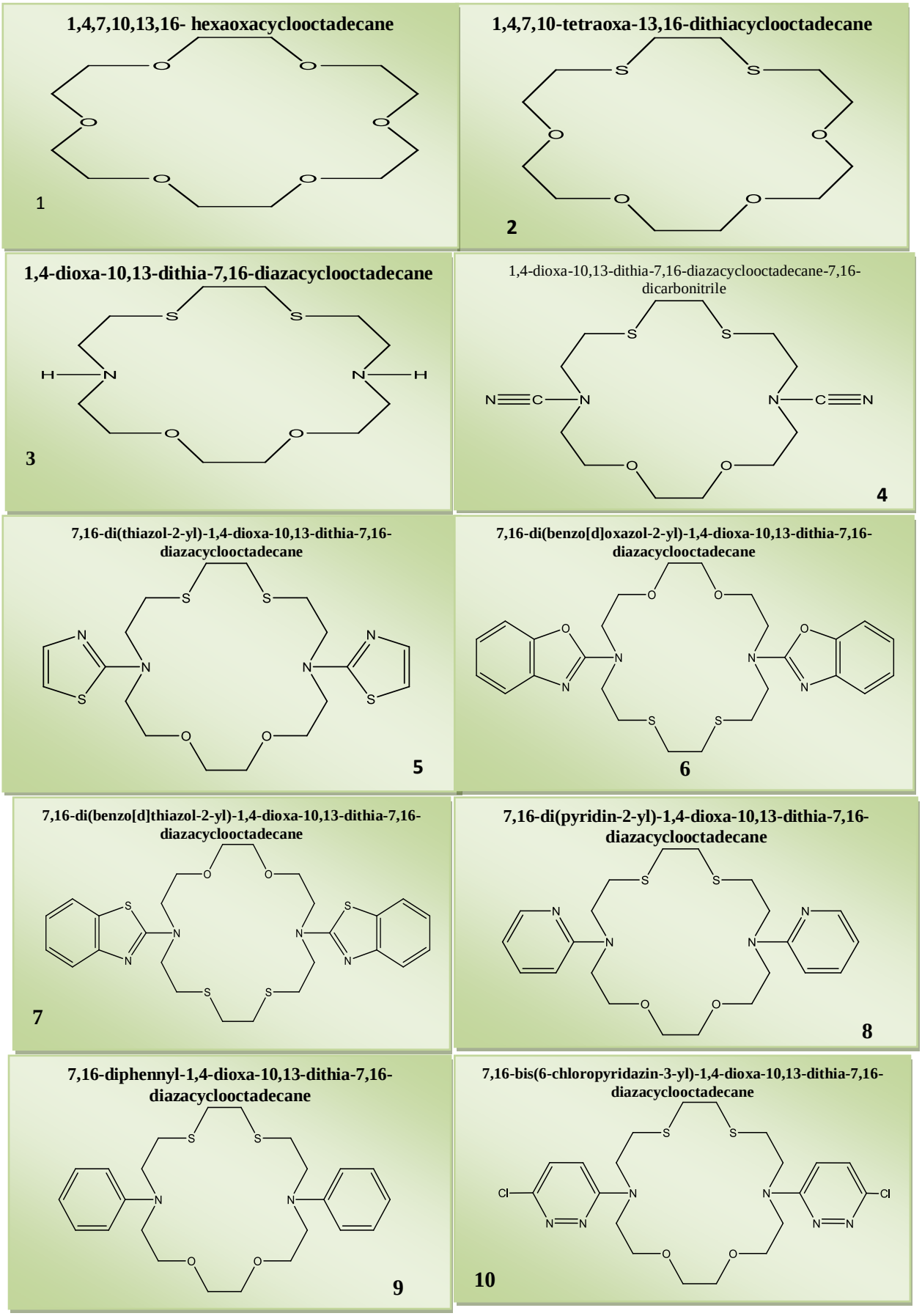

Figure 1- Types of studied crown ethers structures and their numbers (all these comps. are C1 point group)

Table 1- Significant parameters calculated by both (RHF) at the 3-21G basis set and numerical method

Comp.	LUMO (eV)	HOMO (eV)	HOMO-LUMO gap (eV)	Ionization potential (eV)	Electron affinity (eV)	Global hardness
1	21.614	-12.628	34.242	12.628	-21.614	17.121
2	20.666	-8.440	29.106	8.440	-20.666	14.553
3	20.568	-8.412	28.98	8.412	-20.568	14.49
4	5.972	-8.417	14.389	8.417	-5.972	7.1945
5	3.273	-7.681	10.954	7.681	-3.273	5.477
6	-0.031	-8.402	8.371	8.402	0.031	4.1855
7	-0.194	-8.383	8.189	8.383	0.194	4.0945
8	-0.545	-8.404	7.859	8.404	0.545	3.9295
9	-0.708	-8.154	7.446	8.154	0.708	3.723
10	-1.214	-6.422	5.208	6.422	1.214	2.604

Note: 5, 6, 7, 8, 10 synthesized by ref. [14]

Table 2- Total energy of complexes between compounds and K^+

Complexes of K^+ with	Total energy (eV)
1	-1508
2	-2151
3	-2111
4	-2294
5	-3237
6	-2899
7	-3541
8	-2599
9	-2569
10	-3544.7

According to optimized structure of complex 10 shown in Figure-2, bond lengths of potassium ion with donor atoms in the ring cavity (oxygen , nitrogen and sulfur) were recorded as follow:
O(11)-K^+(43) = 2.731Aº , O(3)- K^+(43) = 2.684 Aº, S(7)- K^+(43)= 3.155 Aº , S(10) - K^+(43) = 3.177 Aº, N14- K^+(43) = 3.34 Aº, N(2)- K^+(43) = 3.063 Aº.
Angle values of both N donors (in the cavity) with the two ring of 3-chloropyridazine are:
C57-N2-K43 = 80.7º, C48-N14-K43= 78.6º.

As long as this work aims to design anticancer drugs, further factors must be investigated for this purpose in addition to the above studied parameters (stability and reactivity). Solubility of drugs in both water and fat (cell membrane) represents an important function for characteristic physicochemical properties of active and efficient drugs. Hydrophilic-Lipophilic Balance (HLB) is controlled by the hydrophobic and hydrophilic groups available in the structure of suggested drugs [23]. Although the possibility of such modeling studies to predict aqueous solubility but it is not useful here because of HLB factor requires experimental checking at real cancer cells for testing purpose. This checking is also necessary to evaluate both drug potent against carcinogenic cells and its cytotoxicity.

Conclusion:

It is very useful to use Molecular Modeling for anti-cancer drug design due to its characteristics within the investigation of the mentioned factors used to determine some of the physicochemical properties required for such study.

Regarding the values obtained in this work, it is possible to assess the factors that affect the drugs potency. Results extracted from this research verify the aim of this study with final conclusion that crown ether (10) is the best structure that gives good performance compared with the others. This work still incomplete and need to take further practical tests at carcinogenic cells and to study the selectivity between normal and cancer cells in order to be useful work.

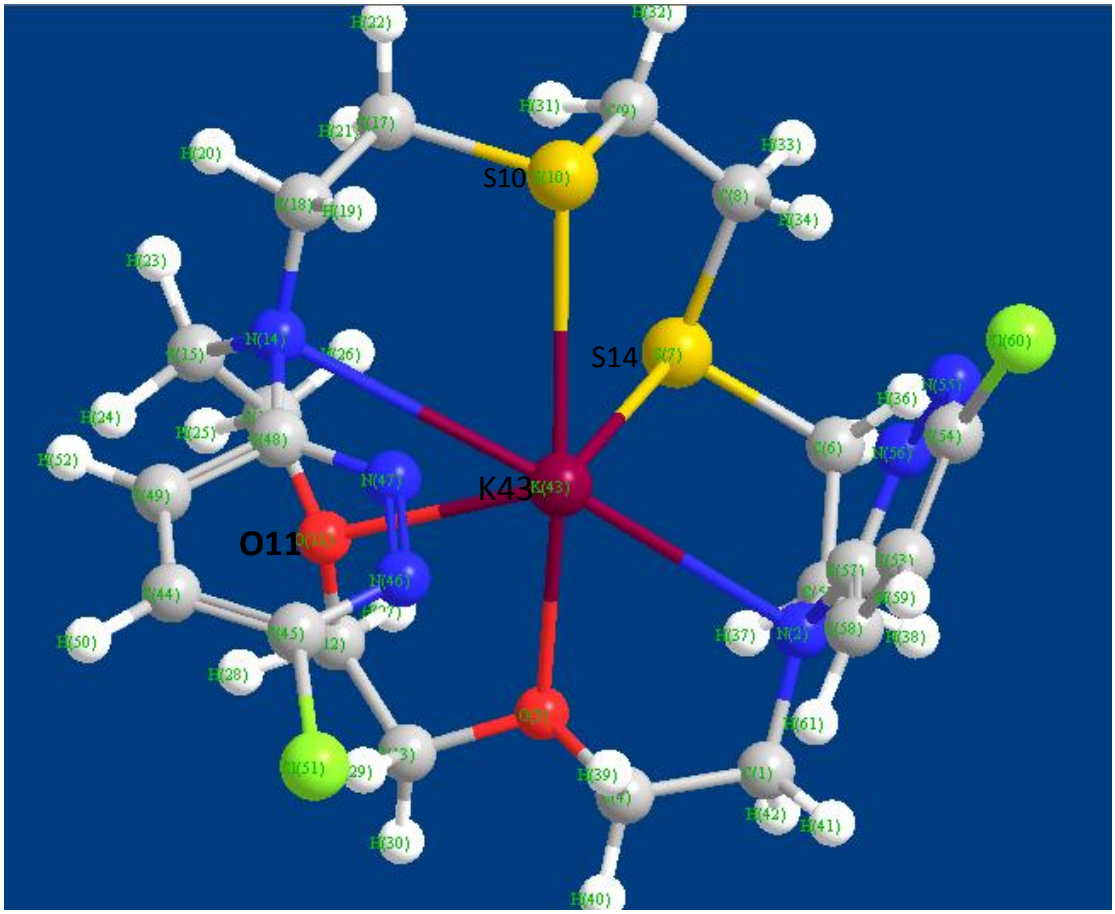

Figure 2- The optimized structure of complex between compound **10** and potassium ion

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