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Short Communication

Synthesis and Electrochemistry Evaluation of Multivalent *o*-Aminobenzamides and Quinazoline-2,4-diones.

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The *o*-aminobenzamides (OAB) and quinazoline-2,4-diones (QZD) are alkaloids with important biological properties such as sedatives, antipsychotics and anticonvulsants, these last properties can be evaluated by electrochemistry methods, using its electron transfer capacity. In this study six compounds (OAB, QZD) were synthesized and characterized, using spacers groups to link the functional moieties (presents on the mono, di and tri substituted systems of each alkaloid kind), when the spacers groups are present, an increase of pharmacological properties has been shown. We carried on electrochemistry evaluations to the synthetized compounds to predict the electron transfer. The results show a single oxidation potential (OP) for the mono and di-substituted compounds (OAB, QZD), and two different OP when the system is trimeric (OAB, QZD). The intensity of the OP signals in the open systems (OAB) is considerable higher in comparison with the closed systems (QZD), these oxidation potentials are assignation at amine groups, and the tertiary amines of trimeric compound present the highest intensity oxidation signals in comparison with secondary amines. The most favorable compound to realize the electron transfer are the open trimeric system.

Keywords: *o*-aminobenzamides, quinazoline-2.4-diones, oxidation potentials, multivalent systems.

1. INTRODUCTION

Epilepsy is a neurological disorder that has increased in the latest years and it is also an incurable disease, which can only be controlled with proper medication. Due to this, is important the design of compounds that increase efficiency on the treatment of epilepsy and reduce the secondary effects. [1]. The proposed action mechanisms for the drug could take three different pathways; either

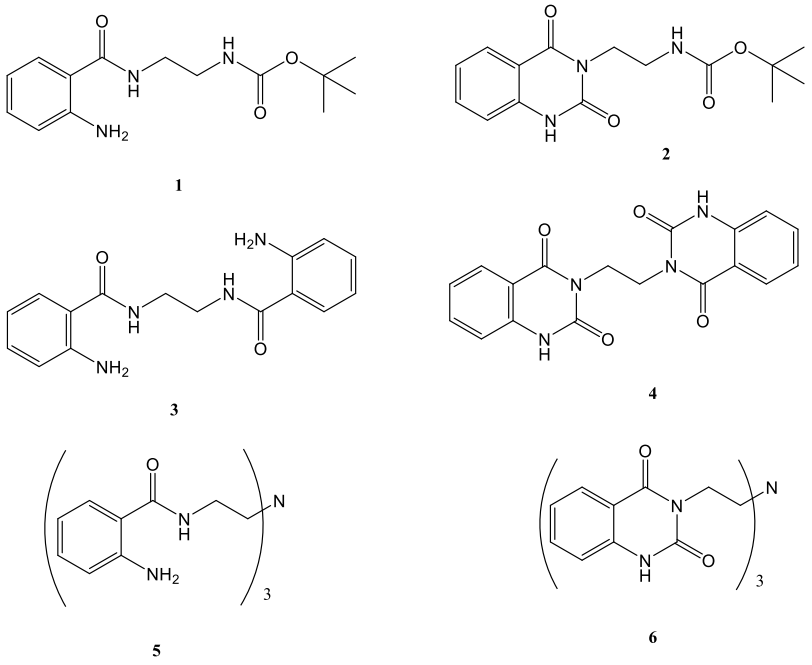
controlling the inhibition of sodium channels, calcium or acid excitation gamma-aminobutyric acid (GABA), these mechanisms are poorly understood, but some approximations are used for explained these mechanism, one of these are by the electron transfer process. Understanding the processes of electronic transference in the brain is crucial for the elucidation of mechanisms in pathologies such as epilepsy. These processes can be established by *in vitro* studies, helping in the screening for anticonvulsant properties of the synthesized compounds. [2].

The antiepileptic drugs, valproic acid, hydantoins, benzodiazepines and quinazoline, are the more extended useful drugs. In the synthesis of quinazolines and related compounds our group work we have had a broad experience in the synthesis of quinazoline-2-4-diones (QZD) and related systems. Derivatives compounds are of interest because of their wide array of pharmacological properties, especially as anticonvulsants [3]. These sedative structures are alkaloids analogous of a natural product isolated of *Zanthoxylum arborescens* [4,5,6]. One attractive performance in the pharmacological compounds is the conversion of monovalent compounds at multivalent systems. Research groups have reported the synthesis and *in vitro* evaluation of multivalent compounds, increase the pharmacological response. Multivalent ligands are an important approach in the development of medicinal chemicals. These studies revealed that the activity of multivalent compounds depend on the length and the type of the linking group. Replacing an alkyl group by a polyheteroatomic chain moiety results in improved water solubility, binding affinity, reducing the side effects and agonist potency [7,8,9,10,11]. Allowing the development of selective ligands. [12,13,14]

Reported studies herein focus on the effects of moieties in the OAB and QZD systems as anticonvulsants evaluated by *in vitro* studies, which would show the electron transfer capacity. The electrochemistry of organic compounds gives important information related to the biological activity and the action mechanism; mostly using cyclic voltammetry [15,16]. The main goal of electrochemistry studies in anticonvulsive compounds is the evaluation of electron transfer capacity of the systems, which can take different pathways such as production of reactive oxygen species (ROS), reduction potentials, or oxidation potentials [17]. When a compound shows reduction potentials relatively positive, it will have the capability to accept electrons from biological entities followed by electron donation; [16] for instance, the overall electron transfer process is carried on in two steps. Secondly, molecules that show oxidation potentials are capable to transfer the electrons directly to biological entities. In nature, there are cellular systems with great diversity of electron donator molecules, such as: tryptophan, tyrosine, cysteine, and histamine, which oxidation potentials that generate electron transfer to biological molecules; the process generates an electronic field capable of affecting transmembrane ion channels [17]. For this situation, evaluation of the electron donation or acceptation is very important to predict anticonvulsive properties in a synthetic compound.

In this work, we report the synthesis and electrochemistry studies of OAB and QZD, to evaluated the effect multiplicity de systems and the capabilities of electrons transfer, that are promising for enhancing the biological properties and decreasing the side effects. The small library of six compounds (mono, bivalent and trivalent) was prepared using the OAB and QZD structures as pharmacophores, with ethylene as bridge. The compounds were synthesized according to the methods outlined in Scheme 1. The electrochemistry studies were performed to determine the redox potentials

of the compounds, these tests give relevant information to attribute the electron transfer capability of these structures and predict anticonvulsive properties.



Scheme 1. Structure of the synthetized OAB (1,2,3) and QZD (4,5,6).

2. EXPERIMENTAL

The materials were acquired from Across Organic and Aldrich Chemical Company, the solvents were dried by usual methods [18]. Melting points were measured on an Electrothermal 88629 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR 160-Perkin-Elmer Spectrum One. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ at 200 MHz and 50.289 MHz, respectively, on a Varian Mercury 200 Spectrometer with TMS as internal standard. Mass spectra were obtained on an Agilent direct insertion mass spectrometer. The cyclic voltammetry measurements were performed at room temperature in a Basi Epsilon Model Ez Voltametry analyzer. The working electrodes were vitreous carbon and reference electrode is Ag/AgCl, a gold wire is used as the counter electrode. The reported data were the average of two or more measurements involving fresh solutions. The following equations were used to calculate the standard potential $E^{0'}=(E_{pc}+E_{pa})/2$, for the reversibility systems, we calculate the relation Ipa/Ipc where 1 is assigned a reversible system. The difference of between peaks Epc-Epa were calculate in the order to found the number of transfer electrons. The scan rate (V/s) used generally ranged from 50 to 1850 m V/s. The solutions were purged of oxygen by bubbling with nitrogen for 15 minutes, before electrochemistry studies. The equation $E^{0'}=(E_{pc}+E_{pa})/2$ was used to calculate the standard potential. E^0 is the half wave potential for the reversibility systems. Epc, corresponds to the potential of the cathode peak, and Epa to the anodic peak. The relation Ipa/Ipc was calculated (Ipa, anodic peak current density, Ipc, cathodic peak current

density), where 1 was assigned to the reversible system. The difference of between peaks Epc-Epa are calculate in the order to found the number of transfer electrons. The scan rate (V/s) used generally ranged from 50 to 1850 m V/s. The solutions were purged of oxygen by bubbling with nitrogen for 15 minutes, before electrochemistry studies.

General methodology for the bis-o-aminobenzamides. For the synthesis of OAB, (Scheme 2). In a 100 mL round basic flask was placed etano-1,2-diamine (16,67 mmol) dissolved in DMF (20 mL) and heated to 60ºC. Isatoic anhydride (32 mmol) was slowly added (CO_2 release), the mixture reaction was proceeded during 2 h, under stirring. The mixture reaction was placed in a 100 mL glass beaker and added 80 mL of boiling water. The precipitate produced was removed from the excess of water. A brown solid was obtained.

ter-butyl (2-(2-aminobenzamide)ethyl) carbamate (1): Brown Solid. Yield 61%. Mp. 138-142ºC. IR (KBr):3442, 3348, 2971, 1682, 1621, 1263 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): 8.09 (d, 1H, *J*=8.0 Hz, Ar), 6.95(m, 1H, Ar), 6.61 (d, 1H, *J*=8.6 Hz, Ar), 6.54 (s, 2H, Ar-NH_2), 5.04 (s, 1H, NHCOO), 3.51-3.39 (m, 2H, -CH_2-N),3.41-3.26(m, 2H, -CH_2-N), 1.38 (s, 9H –*tert*-H) ppm. ^{13}C NMR (50.295 MHz, $CDCl_3$): 169.9, 156.4, 148.7, 132.3, 127.5, 117.3, 116.6, 115.7, 79.6, 41.6, 40.2, 28.5 ppm. $C_{14}H_{21}N_3O_3$: 279. MS (m/e): 279.10 uma.

N,N'-(ethane-1,2-diyl)bis(2-aminobenzamide) (2): Yellow powder. Yield 91%. Mp. 218-222 ºC. IR (KBr): 3480, 3383, 3298, 3070, 2921, 1632, 1468, 750 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): 8.31 (s, 2H, -NHC=O), 7.48(d, 2H, *J*=8.0 Hz, Ar), 7.12(t, *J*=8.2 Hz, Ar), 6.67(d, *J*=8.2 Hz, Ar), 6.50 (t, 2H, *J*=8.0 Hz, Ar), 6.39 (brs, 4H, Ar-NH_2), 3.37 (s, 4H, CH_2-NH) ppm. ^{13}C-NMR (50.295 MHz, DMSO-d_3): 169.1, 149.5, 131.6, 128.1, 116.3, 114.7, 114.5. 38.6 ppm. $C_{16}H_{18}N_4O_2$: 298.34 MS (m/e): 298.03 uma.

N,N',N'-(2,2',2''-nitrilotris(ethane-2,1-diyl))tris(2-aminobenzamide) (3): Brown powder. Yield 81%. Mp. 136-139^{0}C. ^{1}H NMR (200 MHz, DMSO-d_3). 8.11 (m, 3H, -NHC=O), 7.42 (d, 3H, *J*=7.8 Hz, Ar), 7.11 (t, 3H, *J*=8.2 Hz, Ar), 6.67(d, 3H, *J*=8.0 Hz, Ar), 6.45 (t, 3H, *J*=7.6 Hz, Ar), 6.35 (m, 6H, Ar-NH_2), 3.35 (t, 6H, *J*=6.6 Hz, C$\underline{H_2}$-CH_2-N), 2.70(t, 6H, *J*=6.6 Hz, –CH_2-N) ppm. ^{13}C NMR (50.295 MHz, DMSO-d_3): 168.9, 149.5, 131.5, 128.0, 116.3, 115.0, 114.6, 53.4, 37.2 ppm. $C_{27}H_{33}N_7O_3$: 503.26. MS (m/e): 503.06 uma.

General methodology for the synthesis of quinazoline-2,4-diones. A solution of OAB (3,36mmol) in DCM (20 mL) was placed in a 100 mL round flask. The mixture was kept under anhydrous conditions, maintaining stirring for 30 min to room temperature. After was placed in an ice bath and a solution of BTC (2.45mmol) in DCM (20 mL) was added drop by drop. Finally, TEA (3.72mmol) was added and the mixture was stirred by 18 h. Once the reaction was finished, was extracted with DCM (2x50 mL) and the organic phase washed with water (3x40 mL), saturated Na_2CO_3 solution (2x40 mL), and water (2x40 mL). The organic phase was eliminated the excess of solvent at reduced pressure to obtain a solid, which was purified with boiling ethanol 100mL. The solid was used without any purification.

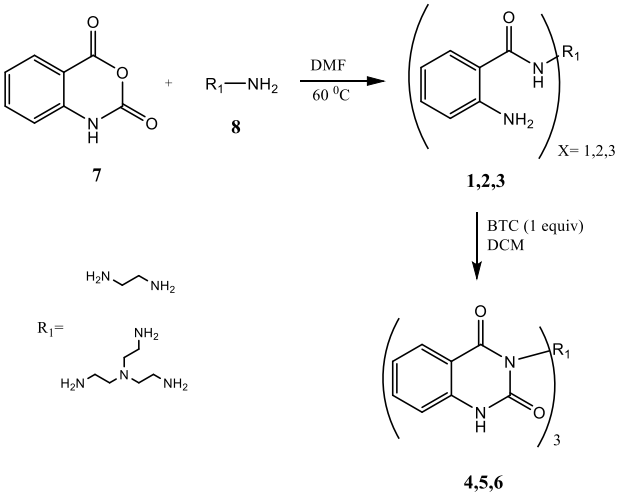
ter-butyl 2-(2,4-dioxo-1,2-dihidroquinazolin-3(4H)-yl)ethyl)carbamate (4): Brown powder. Yield 51%. Mp. 71-74 ºC, IR (KBr): 3462, 3368, 2961, 1693, 1625, 1262 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_3): 11.36(brs, 1H, NH), 7.96 (d, 1H, *J*=8.0 Hz, Ar), 7.63 (t, *J*=7.8, 1H, Ar), 7.18 (d, 1H, *J*=8.4, Ar), 6.84 (t, *J*=6.0 Hz, 2H, Ar-NH_2), 6.50(brs, 1H, NH), 3.97 (t, *J*=5.6 Hz, 2H, -CH_2-N), 3.18 (t, *J=5.6* Hz, 2H), 1.28(s, 9H, *tert-H*) ^{13}C NMR (50.295 MHz, $CDCl_3$): 169.5, 156.8, 148.4, 132.1, 127.3, 117.3, 116.8, 41.4, 40.0, 28.3. $C_{15}H_{19}N_3O_4$: 290.29. MS (m/e): 305.05 uma.

3,3'(Ethane-1,2-diyl)bis(quinazoline-2,4(1H, 3H)dione (5). Brown light powder. Yield 91%. Mp. 218-222ºC. IR (KBr) 3432, 2928, 1717, 1664, 1451, 758 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_3): 11.35 (s, 2H, NH=CO), 7.83 (d, 2H, *J*=8.0 Hz, Ar), 7.62 (t, 2H, *J*=7.2 Hz, Ar), 7.13 (t, 2H, *J*= 7.2 Hz, Ar), 3.39(s, 4H). ^{13}C NMR (50.295 MHz, DMSO-d_3): 162.3, 150.5, 139.3, 134.9, 127.3, 122.4, 114.9, 113.6, 53.8 ppm. $C_{18}H_{14}N_4O_4$: 350.33. MS(m/e): 350.03 uma.

3,3',3''-(nitrilotris(ethane-2,1-diyl))tris (quinazoline-2,4(1H,3H)-dione (6). Yield 52%. Mp. 186-188^{0}C. IR (KBr) 3318, 2965, 1715, 1660, 1444, 1262, 803 cm^{-1}. ^1H RMN (200 MHz, DMSO-d_3): 11.25 (brs, 3H, 1H, -NHC=O), 7.80-7.15 (m, 12 H, Ar), 3.05 (d, 6H, *J*=6.6 Hz, -CH_2-), 1.78 (t, *J*=6.6 Hz, -CH_2) ppm. ^{13}C NMR (50.295 MHz DMSO-d_3): 161.9, 150.2, 139.5, 134.9, 127.4, 122.5, 115.1, 113.9, 69.9, 51.5 ppm. $C_{30}H_{27}N_7O_6$: 581.58. ESI-MS (m/e): 581.05 uma.

3. RESULTS AND DISCUSSION.

The series of compounds synthesized are shown in Scheme 2, one of the amine groups of the starting material diethylene amine R^1 was protected to obtain the monomeric system. The protected and unprotected di-amines, and tris-amine (8) were reacted with isatoic anhydride (7) to give the corresponding 2-aminobenzamides 1,2,3 in good yields (84-93%). Following the methodology developed for the synthesis of pelanserine, we used Bis (Trichlorometyl)Carbonate (BTC) to ring close the amides systems (1,2,3) to give the QDZ (4,5,6) in good yields [1]. These compounds were characterized by conventional techniques.



7 8 1,2,3 4,5,6

Scheme 2. Synthetic Route of OAB and QZD.

Several studies have been documented, with the intention to predict neurological properties through *in vitro* process of quinazolines and related compounds [19,20,21,22]. These studies postulate multiple mechanisms of action in the protective effect of neuro-drugs in the seizures episodes. Some of these mechanisms are: sustained high frequency repetitive firing (SRF) [23], postsynaptic γ-aminobutyric acid (GABA) responses [24], enhanced inhibitory mechanism, and electron transfer (ET) [25,16,18]. The electron transfer is related with the voltage regulation in the channels ions in the brain, and is considered as a further candidate to elucidate the action mechanism in the antiepileptic drugs. These measurements were performance by electrochemistry process using the voltamperometry technique.

In this work, the electron transfer of the OAB and QZD were evaluated for the first time, as well as the number of electrons involved in this transfer for both donor and acceptor in monovalent and multivalent systems. The red-ox potentials of mono, di- and tri- OAB and QZD were evaluated, with the intention to attribute protective biological properties [26,27]. To interpret the electrochemistry results, which can be discuss by two complementary ways. First, for all systems, therefore OAB and QZD, the electrochemistry test by cyclic voltammetry was evaluate the reduction and oxidation potentials; nevertheless, all studied systems synthetized in the present study only present oxidation voltamograms [28,29]. This is consistent with the reported in the literature, where it has been outlined the facility of electroxidation of amino systems [30]. All structures show amide systems which are not assigned a signal since the potentials of amides is compromised in basic medium, this due the difficulty to donate electrons in this condition.

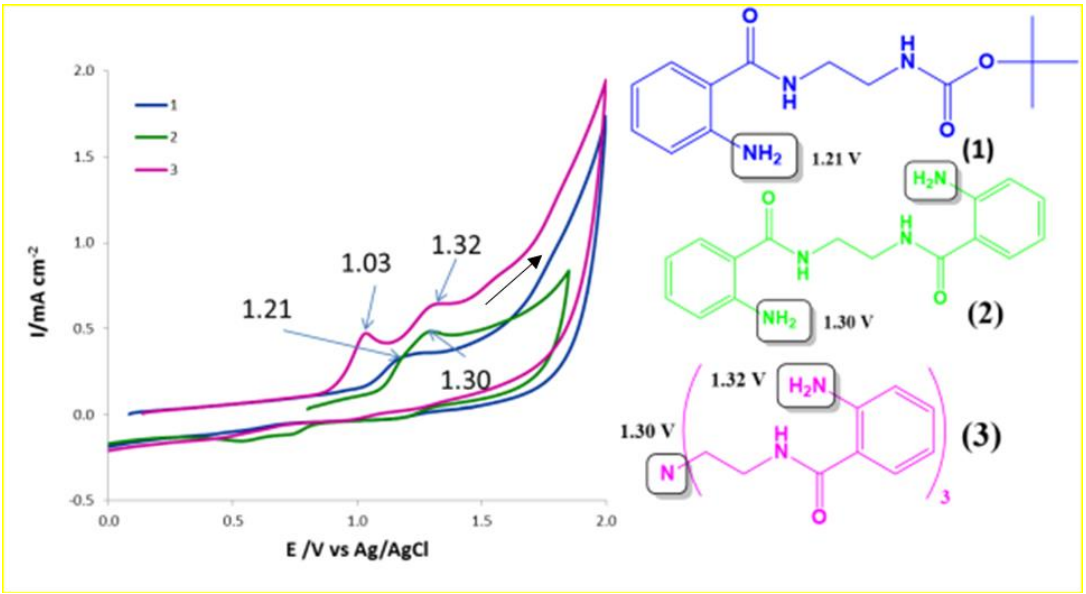
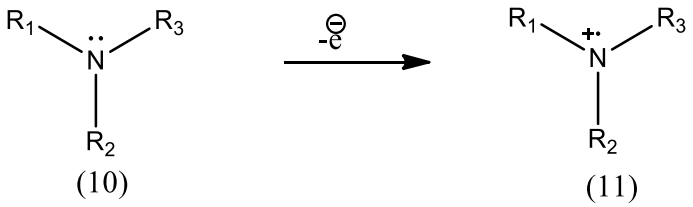


Figure 1. Cyclic Voltamperometry of mono, dimeric and trimeric systems, OAB, comparison to see differences for the three systems**.**

Therefore, all oxidation curves are assigned to the amine groups of this systems. In Fig.1, the curves for the tree OAB compounds showed different electrochemical behavior. For the mono- and di-substituted OAB, only one peak is observed (blue and green, 1, 2), which is attributed to primary

amines systems. The trimeric compound (3) show a voltamogram with two oxidation curves, one of them with more intensity, this curve shows at lower voltage and is assigned to a tertiary amine of the compound 3. In the trimeric OAB, exist a noticeable difference in the intensity of the peaks in comparison with the primary amines of mono and dimeric systems. This is explained through the process known as amine stabilization by cationic radical; which formation depends on the type of substituent moieties. [30, 31]

The amine oxidation is dependent on the substituents [32]. Therefore, formation of the cation of the amine 11 requires a greater potential for primary than for tertiary amines. This is because the hydrogen atom is more electron withdrawing than any aliphatic group. In general, the substitution with electro withdrawing groups may alter the established order.



(10) (11)

Figure 2. Oxidation process of the amines

This is consistent with the obtained results in relation at amine content in the compounds. We observed that the oxidation of tertiary amines attached to aliphatic group shows low potential, and higher oxidation potential for primary amines tied to aromatic group (aniline). This is because the aromatic group forces the electron pair of the amino group to increase the resonance.

When the OAB is cycled to QZD, the free amine group is converted to amide group and the intensity of signals is considerably dissipated (Fig.3), which is consistent with the previous argument. With these results is possible to predict the system more favorable to donate electrons and corresponds to the open trimeric systems, in comparison with the closed systems QZD. Second way is the study of the reversibility in the systems, these was evaluated through IPa/IPc calculations. The obtained results showed than to all OAB systems the ratio is near to one, therefore, these systems are reversible. The QZD systems do not show cathodic peaks, therefore the systems are not reversible. The importance to use reversible systems to predict the biological behavior is based on there are capable to donate and recuperate electrons, and can participate in biological processes of electron transfer.

For the reversible systems (OAB) was calculated the amount of electron transfer; this computation was performed at room conditions (Table 1), normally, in this condition the difference between an anodic peak and cathodic peak of 60 mV is assigned to the transfer of one electron. For our results, in the case of primary amines, the difference $\Delta E=Ep_a-Ep_c$, was around 120 mV. This implicate the systems are capable to transfer a pair of electrons. In case of tertiary amines, the value was 78 mV, this is near to 60 mV and is assigned to the loss of one electron, which was consistent with our hypothesis of the formation of amine cation in the oxidation process of the central tertiary amine in the trimeric compound (3). [33]

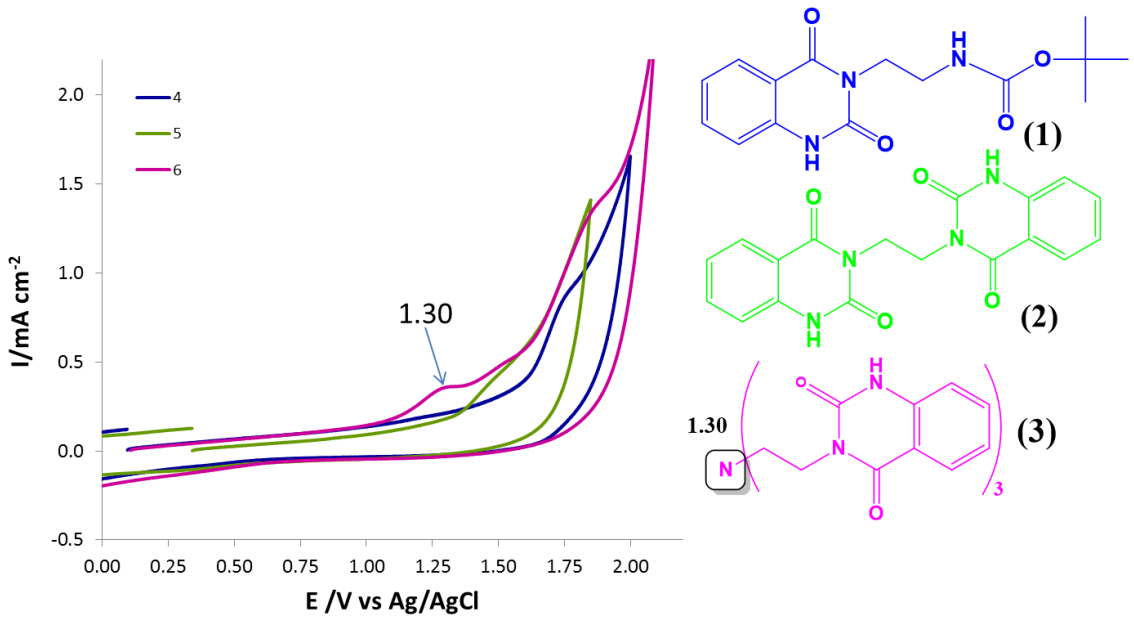


Figure 3. Cyclic voltamperometry of closed systems of QZD.

Table 1. Oxidation potential of OAB and QZD obtained by cyclic voltamperometry.

Sample	Epc (V)	Epa (v)	IPa/IPc	E0' (V)	Epc-Epa (mV)
1	1.2402	1.1181	0.9015	1.1791	122.10
2	1.2902	1.1638	0.9029	1.2277	126.15
3	1.0451, 1.3150	0.930 1.237	1.2705	1.186 1.1622	115.10 78
4	1.8537	----------		----------	
5	1.5187	----------		----------	
6	1.3808 1.8537	--------		--------	

Note: (----- No peak present).

4. CONCLUSIONS

Considering the electron transfer processes as mechanisms of action of many commercial drugs. We can relate the biological activity of the compounds according to their ability to participate in electron transfer processes. We could establish that the OAB 1,2,3 systems showed the best results of the electrooxidation. These systems are better candidates than the closed systems of QDZ to participate in electronic transfer process. The amino groups of these systems are responsible for making the electron transfer process. In addition, the voltamograms signals and its intensities shows that increasing the number of pharmacophores in the molecule, increases considerably the capacities of it to donate electrons, therefore, an increase in the probability of participating in the electronic transfer. We can establish that is more favorable to the biological properties of multivalent molecules compared to monomeric compound type. The quantitative results resumed in the Table 1 are encouraged with the electrochemistry results, where it is observed that open systems have a reversible process. Further

observed that these systems, two electrons transferred from secondary amines and one electron from tertiary amines (Epc-Epa) mV. In a qualitative or quantitative way, it was possible to predict that in normal environmental conditions the open systems OAB are electronically more active in comparison with the close systems QZD. When the number of amines were increased, the number of electrons that are donated increases, and therefore it is a compound with potential biological property as antiepileptic drug.

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