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PREPARATION OF NEW COMPOUNDS WITH ANTICANCER PROPERTIES VIA THE REACTION OF KRYPTOFIX 5 WITH TWO ORGANIC ACCEPTORS

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ABSTRACT. The new designed complexes via CT interaction between kryptofix 5 and two organic acceptors to introduce basic data that can be used to assessment of crown ether and tested the final complexes against cancer cells. This target was achieved by synthesis of a new CT- complexes of kryptofix 5 as a type of mixed nitrogen–oxygen crown ethers with π-acceptors as (2 hydroxy-3.5-dinitrobenzoic acid and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone). These obtained complexes were structurally characterized in both solid and liquid state via various chemical methods as elemental analysis, FT-IR, NMR, and UV–Visible spectroscopy, thermal degradation and physical properties were calculated. Finally, the CT complex was also tested for its anticancer activity against two human cancer cell lines; colon cancer CaCo2 and liver cancer cell line (hepG2).

KEY WORDS: Anticancer, Kryptofix 5, HDNS, DDQ, Spectroscopy

INTRODUCTION

The preparation of chemical charge transfer (CT) complexes between electron donors and various acceptors are widely used currently that's due to the important role in various fields [1–3]. Also in pharmaceutical science attracted more attention in determination of various drugs in dosage and pure form [4–6]. It also has a great useful role in biological systems in preparation of antimicrobial, anticancer, and antimalarial complexes [7–10]. On the other hand it has an economic value in our daily lives as it uses in different chemical science fields as solar cells, semiconductors photocatalysts and corrosion inhibitors [11–13].

Kryptofix 5 (K_5) macrocyclic compounds a is a type of crown ether which is characterized with a covalent bond which held its sites, which is very important in chemical and biological fields [14]. The crown ether compounds are used in biochemical science as it used as antibacterial agents, aginst histamine induced ulcers and beside its role as detergent the crown ethers have a vital role in non-biological activity [15–17]. On the other hand in chemical science used in various methods as in membrane separation methods, semiconductor methods, fibre optic chemical sensor properties and phase transfer catalysis [18–22].

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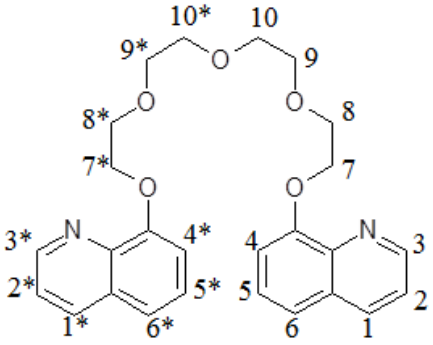
In our previous researches in pharmaceutical charge transfer complexes we used various drugs as electron kryptofix 5 crown ethers as electron with two common π-acceptors 2 hydroxy-3.5-dinitrobenzoic acid (HDNS) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The produced complexes were identified and characterized via chemical methods as elemental analysis and the thermal degradation the various spectra methods as (FT-IR, UV–Vis, ^{1}H NMR) and anticancer activity.

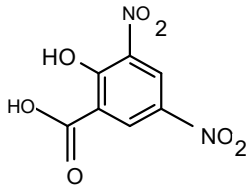
EXPERIMENTAL

Chemical reagent

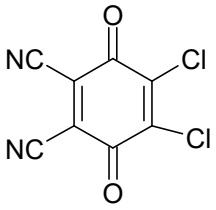
Beside the krytofix we used two common π-acceptors (DDQ and DNS). All of this reactants were bought from a common company Alpha (Germany). The structure of kryptofix 5 donor (K5) and acceptors are shown in Scheme 1.



Donor (K5)



HDNS



DDQ

Acceptors

Scheme 1. Structure of the donor and acceptors.

Instrumental devices

In Zagazig University we used the various instrumental devices as electronic absorption spectra were used with a range 200–1100 nm UV-Vis. Spectrophotometer model THERMO V-530 with a quartz cell of 1.0 cm path length. The elemental analysis by using a Perkin-Elmer CHN 2400 (USA), the elemental analyses of the formed complexes were determined by using Perkin-Elmer CHN2400 (USA). We recorded the FT-IR spectra of the free reactants and the produced K_5-DNS and K_5-DDQ complexes and the resulting complexes were carried out KBr discs on TermoFisher Nicolete IS10 Infrared spectrometer with KBr discs. The proton NMR spectra of kryptofix with

the synthesized complexes were recorded via utilizing Bruker 500 MHZ using DMSO as a solvent. Finally the thermal degradation were operated in Cairo University.

Spectrophotometric titration and molar ratio

We used a photometric titration with a characterized absorption bands which found at 440 nm for DNS-complex and 490 nm for DDQ-complex at room temp. We added a constant concentration of the donor kryptofix 5 (1.0×10^{-4} M) to a variable concentration of the acceptors (0.25×10^{-4} – 3×10^{-4} M). We kept the ratio between the produced solutions of the acceptors to the donor and the molar ratio changed from 0.25:1.00 to 1.00:3.00. The known methods were using to detecting the stoichiometries of the molecular CT.

Preparation of the solid complexes

The amount of donor and acceptors solution were prepared with a minimum amount of a methanolic solution and the two solution were mixed at the room temp for 24 h. With stirring the color changed and the volume decreased with the continuous evaporation. Finally, the precipitated solids were separated via filtration and washed frequently with methanol, and dried with using vaccum over anhydrous calcium chloride.

*[(HK_5)(DNS)] (**1**)*. Pale yellow, anal. found (calcd. for $C_{33}H_{32}N_4O_{12}$, 676.63): C, 58.67 (58.52); H, 4.72 (4.71); N, 8.27 (8.15). ^{1}H NMR (400 MH_Z, DMSO-d_6): δ = 3.50-4.45 [d, 16H, 8(CH_2)], 5.72 [(s, 1H, (NH^+)], 7.6 [s, 2H, 2(CH)], 7.74 [s, 6H, 6(CH)], 8.61 [(s, 2H, (2CH, DNS)], 8.64 [(s, 1H, (OH, DNS)], 9.08 [(s, 4H, 4(CH].

*[(K_5)(DDQ)] (**2**)*. Dark red, anal. found (calcd. For, $C_{34}H_{28}CL_2N_4O_7$ 533.27): C, 76.55 (77.28); H, 5.25 (5.21); N, 10.50 (10.64). ^{1}H NMR (400 MH_Z, DMSO-d_6): δ = 3.52-4.35 [d, 16H, 8(CH_2)], 7.37 [d, 2H, 2(CH)], 7.78 [d, 6H, 6(CH)], 8.65-8.96 [s, 4H, 4(CH)].

Anticancer activity

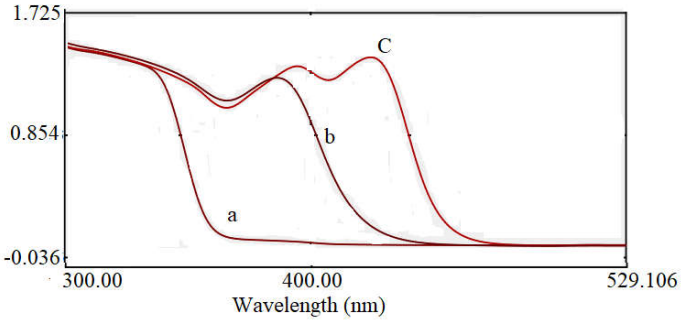
Cell viability was evaluated by measuring the enzymatic conversion of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide salt (MTT) to insoluble formazan crystals. This conversion is carried out by mitochondrial dehydrogenases and only occurs in living cells. The cells were grown in 96-well plates at a density of 1x104 cells per well and allowed to adhere for 24 hours at 37 ºC in a CO_2 incubator. After incubating for 24 hours, the culture medium was replaced with a new medium. Then, the cells were exposed to different concentrations of the chemicals, ranging from 5 to 140 mM. The cells were incubated for 72 hours at a temperature of 37 ºC in a CO_2 incubator.

The control group consisted of cells that were not treated. Afterwards, a solution of MTT (0.5 mg/mL in a medium without serum) was added, and the samples were incubated for 4 hours at a temperature of 37 ºC in a CO_2 incubator. Next, the medium was removed by aspiration, and the resulting formazan crystals were dissolved by adding a combination of isopropanol and DMSO in equal volumes (1:1). The concentration of the dissolved crystals was quantified using a UVM 340 reader (ASYS Hitech GmbH, Austria) at a wavelength of 570 nm. Cell viability was quantified as the percentage of MTT reduction in treated cells compared to control cells (cells incubated without the tested complexes). The relative MTT level (%) was determined by dividing the absorbance of the test sample ([A]) by the absorbance of the control sample containing the untreated cells ([B]), and then multiplying by 100.

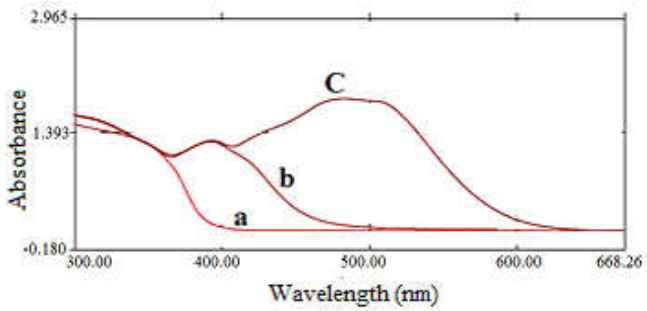
RESULTS AND DISCUSSION

Electronic measurement

The electronic absorption spectra for the donor (K_5) and the two DNS-K_5 and DDQ-K_5 complexes in the methanol solvent shown in Figure 1. The presence of two new clear absorption band at 440 nm for complex1and 490 nm for complex **2** which were not found in both free donor and free acceptors [25].



(a): [K_5] = 1×10^{-4} M, (b): [HDNS]= 1×10^{-4} M and (c): [K_5-HDNS product] = 1×10^{-4}



(a): [K_5] = 1×10^{-4} M, (b): [DDQ]= 1×10^{-4} M and (c): [K_5-DDQ product] = 1×10^{-4} M

Figure 1. Elecectronic absorption spectra of: (A) K_5-HDNS reaction in MeOH and (B) K_5-DDQ reaction in MeOH.

The new formed CT-complexes is essential for the photometric titration measurements as shown in Figure 2. The resulted molar ratio of the titration between the donor kryptofix 5 and the acceptors is 1:1. The obtained spectrophotometric data summarized in Table 1.

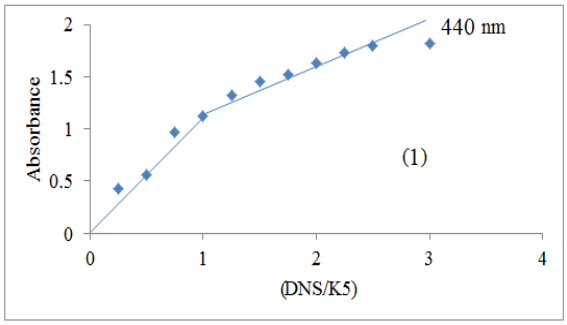
Both types of physical constants molar extinction coefficient ε and physical formation constant K_c for the two complexes [(HK_5)(DNS)] (**1**) and [(K_5)(DDQ)] (**2**) can be calculated by using the known Equation (1). The obtained straight lines confirm the suggested 1:1 molar ratio [26–28]:

$$\frac{C_d^\circ \cdot C_a^\circ}{A} = \frac{1}{\varepsilon K_c} + \frac{C_d^\circ + C_a^\circ}{\varepsilon} \quad (1)$$

C_a° and C_d° are the initial concentration of the free reactants donor and acceptors and while A is referring to the new strong formed absorption bands for the complexes which found at 440 and 490 nm for the two complexes. The ($C_d^\circ + C_a^\circ$) are plotted against for $C_d^\circ . C_a^\circ / A$, the resulted slope straight line is of 1/ε while intercept is 1/εK_C, Figure 3.

Table 1. The values of $C_d^\circ . C_a^\circ / A$ and $C_d^\circ + C_a^\circ$ for K5-complexes. C_d° is 1.00×10^{-4} M in all systems.

C_a° × 10^{-4}	Ratio (*a*/*d*)	$C_d^\circ + C_a^\circ$ × 10^{-4}	$C_d^\circ \cdot C_a^\circ$ × 10^{-8}	Complex **1**		Complex **2**	
				A	$C_d^\circ \cdot C_a^\circ / A$	A	$C_d^\circ \cdot C_a^\circ / A$
				440	× 10^{-8}	490	× 10^{-8}
0.25	0.25	1.25	0.25	0.423	1.388	0.121	1.923
0.50	0.50	1.50	0.50	0.556	2.000	0.262	2.631
0.75	0.75	1.75	0.75	0.968	1.666	0.541	2.586
1.00	1.00	2.00	1.00	1.121	1.491	0.722	2.564
1.25	1.25	2.25	1.25	1.324	1.644	0.832	3.048
1.50	1.50	2.50	1.50	1.456	1.898	0.862	3.409
1.75	1.75	2.75	1.75	1.521	2.058	0.943	3.723
2.00	2.00	3.00	2.00	1.632	2.150	0.964	4.347
2.50	2.50	3.50	2.50	1.725	2.232	1.061	5.102
3.00	3.00	4.00	3.00	1.798	2.479	1.242	5.882



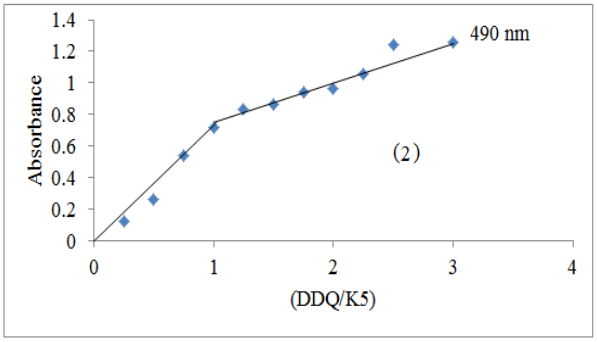


Figure 2. Photometric titration curves of: (1) K5–HDNS reaction in MeOH at 440 nm and (2) K5–DDQ reaction in MeOH at 490 nm.

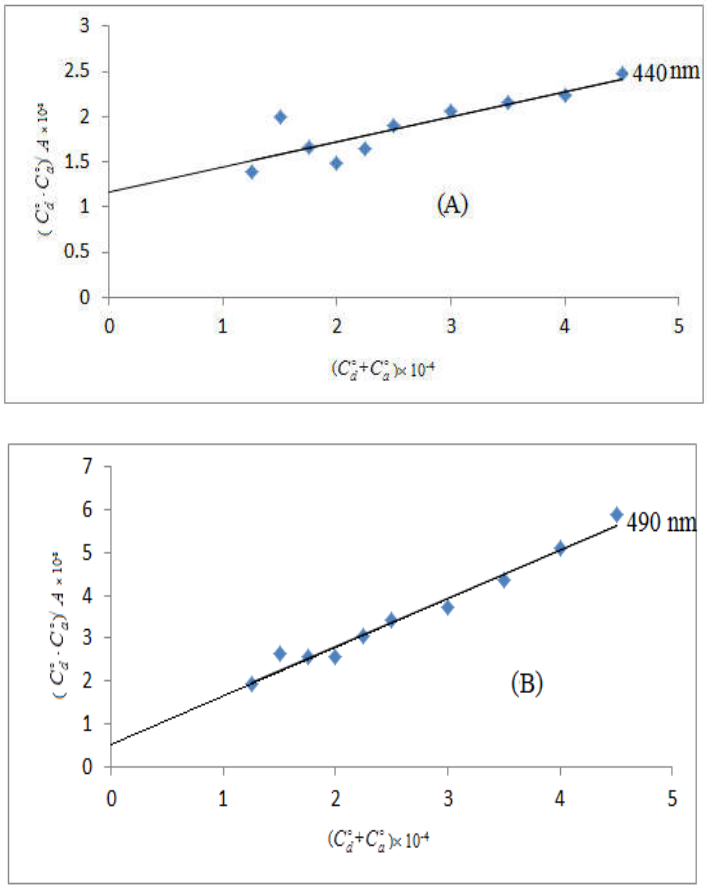


Figure 3. Relation between $C_d^\circ \cdot C_a^\circ / A$ and $C_d^\circ + C_a^\circ$ for: (A) K_5–DNS in MeOH at 440 nm and (B) K_5–DDQ in MeOH at 490.

The spectroscopic and physical measurements of the synthesized CT-complexes as standard free energy *(ΔG^o),* the oscillator strength (f), and the ionization potential (I_D), the transition dipole moment, μ charge transfer energy, E_{CT} and standard free energy were calculated and summarized in Table 2 and calculated with using the following equations.

Calculated of (f) [29]:

$$f = 4.319 \times 10^{-9} (\varepsilon_{max} \cdot \Delta\upsilon_{1/2}) \quad (2)$$

Calculated of (μ) [30]:

$$\mu_{(Debye)} = 0.958 \left(\frac{\varepsilon_{max} \cdot \Delta\upsilon_{1/2}}{\upsilon_{max}}\right)^{1/2} \quad (3)$$

Calculated of (I_D) [31]:

$$I_{D(eV)} = 5.76 + 1.53 \times 10^{-4} \cdot \upsilon_{CT} \quad (4)$$

Calculated of (E_{CT}) [32]:

$$E_{CT} = (h\upsilon_{CT}) = 1243.667 / \lambda_{CT(nm)} \quad (5)$$

Calculated of (ΔG, kJmol^{-1}) [33]:

$$\Delta G^{\circ} = -2.303RT \log K_{CT} \quad (6)$$

Table 2. Spectrophotometric data of K_5 CT-complexes.

Complex	λ_{max} (nm)	K_C (l·mol^{-1})	ε_{max} (l·mol^{-1}·cm^{-1})	E_{CT} (eV)	F	μ	I_D (eV)	ΔG^o (25ºC) (K·J·mol^{-1})
1	440	2.3×10^4	1.17×10^4	3.09	17.26	23.78	10.33	-2.32×10^4
2	490	1.8×10^4	1.73×10^4	3.15	16.15	38.17	10.12	-2.51×10^4

The physical measurements of the final complexes as transition dipole moment (μ) and oscillator strength (*f*) which refer to strong interaction show a high measurements which refer to the strong interaction. The standard energy of the two complexes show a negative measurements that's mean the reaction is spontaneous and exothermic [34].

IR spectra

The FT-IR spectra for free reactants beside the new formed CTC are shown in Figure 4 and the observed various bands are listed in Table 3. The synthesized CT-complexes besides formation new bands that not found in the free reactants there is changes in the values of the frequency and intensity of the normal bands.

Table 3. IR spectra of K_5 and formed CT-complexes.

K_5	HDNS	DDQ	Complex 1	Complex 2	Assignments
	3572br 3450br		3450vs 3398 s		v (N^+-H), v (O-H)
3040 s	3104 s		3069m		v(C-H) Aromatic
2931m 2884s	2854mr		2909 w	2920s 2853 s	v_s(C-H) + v_{as}(C-H)
		2243 m		2197 s	v(C≡N)
1616 m	1820 s	1673s	1669 m 1600 s	1740 s	v(C=N) stretch $v_{as}(NO_2)$
1574s 1502s	1609 s		1536s 1423vs	1597s 1570 m	v(C=C) stretch,
1320s		1673s	1308m	1316m	(C-H) Plane bending
1260 s 1105s	1395w 1341m	1552	1275s 1101m	1264 s 1106m	v(C-N) v(C-O)
823s	703s	856 w	835m	825m	CH_2 Rocking

In case of [(K_5^+)($HDNS^-$)] complex, the acceptor release an electron to the donor and acid – base reaction takes place. This interaction behavior is observed in K_5 interaction with HDNS acceptor. A new band is observed at 3450 cm^{-1} for K5-DNS this is due to formation (NH^+) group. That may refer to hydrogen bond formation (acid-base reaction) via migration of proton [36].

For [(K_5^+)(DDQ^-)] the CN band of free DDQ acceptor which found at 2243 cm^{-1}. These band were found in the formed complexes at 2197 cm^{-1} with a lower frequencies. That's a strong evidence for CT-reaction by transfer an electron from the lone pair at nitrogen bond of the donor kryptofix to the acceptor [37].

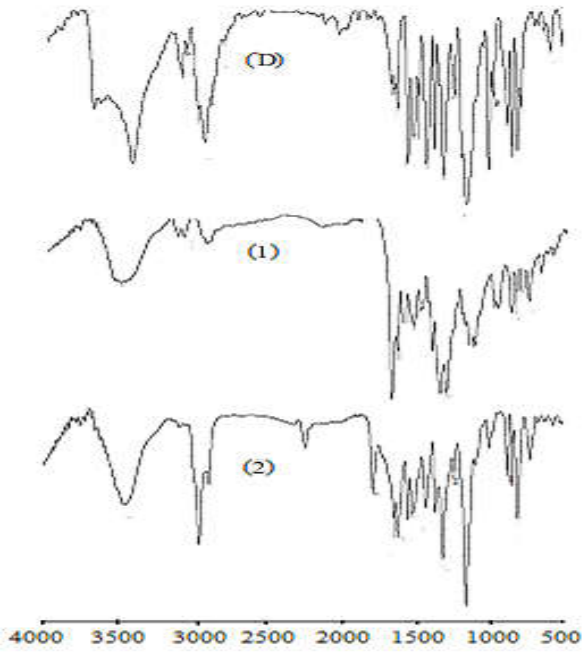


Figure 4. Infrared spectra of K_5 with two CT-compounds.

^{1}H NMR spectra

The ^{1}H NMR data of the kryptofix and the two complexes in dmso-d_6 were showed in Figure 5. In complex **1** [(HK_5)(DNS)], show that disappearance of a proton of carboxylic group signal of the acceptor (DNS) in the spectrum of the formed complex, this main that COOH group is involved in the chemical reaction through the movement of proton from the acceptor to kryptofix. There is abroad clear signal which not found in the free reactants observed at 5.72 ppm that may result from binding the reactants via intra molecular hydrogen bond. The other proton signal of the free DNS as OH group found at 8.64-8.65 ppm, from the previous data there is a good evidence for participate both of phenolic and amino groups in chemical formation of the CT complex between the free reactants [35]. The two proton signals of DNS ring were presented at 8.61 ppm.

In [(K_5)(DDQ)] complex all of peaks have a small sift in comparison with free donor $C^{3,3*}H$ signals are shifted from 7.49 to 7.78 ppm which may be an indication to transfer electrons from the lone pair of nitrogen atom to the acceptor as found in Scheme 2 [41].

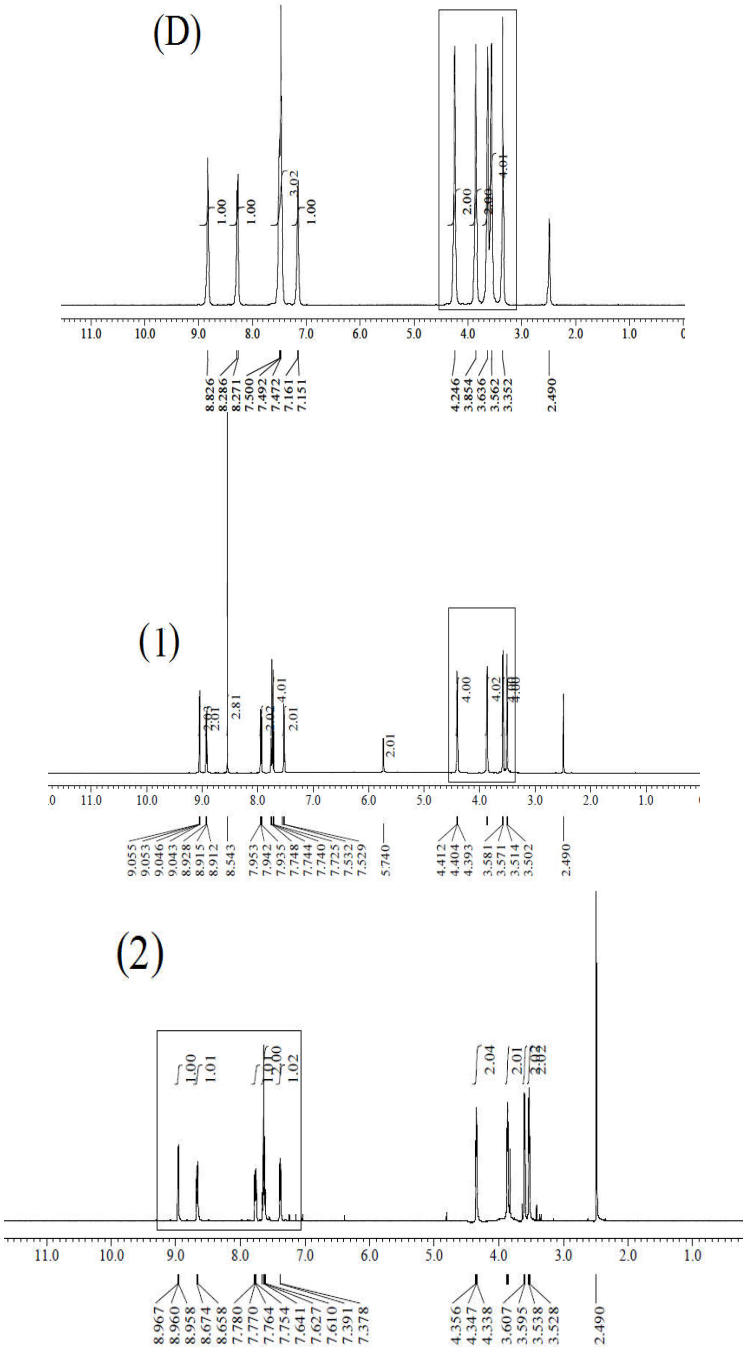


Figure 5. ^{1}H NMR spectrum of free K_5 donor and the two compounds.

Thermal analyses

The measurements thermal data for the free kryptofix plus CT-complexes are summarized in Table 4. The standard free donor decompose in only one step with temp range from 0 °C to 800 °C at maximum temperature 431 °C. The total weight loss of the step and the theoretical were very near in calculation.

In case of [$(HK_5)(DNS)$] (**1**), thermal degradation occur in two stage at T_{max} 292 °C with a value weight loss of 66.28%. These reducing of weight perhaps for the loss of K_5 which match with calculated values 66.21%. The following step take place with maximum peak at 623 °C. The total percentage of weight loss observed matched with the found lack of weight with 33.71% which refer to the decomposition DNS acceptor which conform for theoretical calculation (33.79%) [41].

For [$(K_5)(DDQ)$] the thermal degradation appear in two clear steps within range of 50–800 °C. The first step decomposed with total loss (59.91%) with maximum peak at 253 °C which may refer to decomposition of kryptofix where the theoretical calculation is (60.18%). The final degradation with maximum peak at 561 °C with loss of (29.31%) may corresponds to the decomposition of DDQ residue which conform for theoretical calculation (29.12%) [45].

Table 4. The thermal decomposition data of the free Kryptofix and its CT-complexes..

Complex	Decomposition	T_{max}/°C	Lost species	% Weight loss Found	Calc.
K_5	First stage Residue	261	$C_{13}H_{12}N_6F_2O$	100.00 00.08	100.00 00.00
[(HK5)(DNS)] (**1**)	First stage second stage Residue	292 623	$C_{26}H_{28}N_2O_5$ $C_7H_4N_2O_7$	66.28 33.71. 00.00	66.21 33.79 00.00
[(K_5)(DDQ)] (**2**)	First stage Second stage Residue	253 302 642	$C_{26}H_{28}N_2O_5$ $C_3Cl_2N_2O_2$ C_5	59.91 29.12 10.97	60.18 29.31 10.69

Detection of cytotoxic activity of K5 complexes on a human tumor cell line

The synthesized complexes were assessed for cytotoxicity using the MTT test against Caco2 (colon carcinoma) and hepG2 (liver cancer) cell lines. The data depicted and indicated that the produced complexes exhibited high cytotoxicity.

CONCLUSION

Kryptofix (K_5) is chemically reacted with two acceptors (HDNS and DDQ) via CT-interaction were studied in methanole at 25 °C. It was observed that the reaction take place with molar ratio 1:1 for two types of acceptors. The first CT-complex were formed via transfer a proton from the acceptor DNS to the K5 and binding togather via hydrogen bond formation. The second CT-complex formed via chemical reaction mode between K_5 with DDQ acceptor occur through the transfer of electrons from the lone pair in the nitrogen atom of the donor to the acceptor. The produced complexes were formulated as [$(HK_5)^+(DNS)^-$] (1) and [$(K_5)^-(DDQ)^+$] (2). Finally the anticancer mesurments for the donor and formed complexes were determined.

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