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Structure Investigation of Synthesized Novel Retinoid-Iodine Derivatives and Its Biological Applications

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Abstract

The reactions between Tretinoin (Tret) and Isotretinoin (Itret) isomers with Iodine were thoroughly investigated under different conditions and solid products under proper conditions were prepared. Separation and identification of the formed products approved the stoichiometry (1:1). These newly prepared solid products were separated, washed, crystallized and structurally investigated and identified. Structures of the newly synthesized retinoid-iodine derivative products were carefully investigated in this research. Their structures were characterized, elucidated and analyzed by using the mass spectrometry (MS), Fourier Transform Infra-Red (FT-IR), ^{1}H-NMR, thermal analyses (TA) and X- Ray Fluorescence (XRF). Then the results of the newly prepared compounds were compared with that of parent isomers analyses. Therefore; the proposed general formulae of the newly prepared compounds were found to be $C_{20}H_{27}IO_2$. The biological activities of the newly obtained products in comparison with the parent isomers are thoroughly investigated against different kinds of bacteria and fungi.

Keywords: Tretinoin; Iodine- Tretinoin product; thermal analyses (TA); FT-IR; NMR; XRF; biological activity.

1. Introduction

The retinoids are group of compounds that; chemically related to vitamin A [1]. They are usually used in medicine as regulators for growth epithelial cells [2]. Retinoids have many diverse and important vital functions throughout the body; which includes regulation of cell proliferation and differentiation, roles in vision, bone tissue growth, immune function, and activation of genes [3]. Also researches were done to investigate their ability to treat skin cancers.
The use of mass spectral technique (MS) here is very important to predict bond ruptures during mass fragmentation course of Tret, Itret drugs and their iodine solid products. Subsequent mass fragmentation to a large extent is a result of weak bonds rupture of molecular ion [4,5 ,6 ,7 ,8 ,9]. To rationalize the correct pathways of the molecules threshold measurement [10] and metastable abundance ratios [11] two important techniques are used. These are Mass (MS) and thermal analyses (TA) techniques; which actually are complementary analytical methods of analyses [12,13,14]. The fragmentation or degradation processes in test compounds began at the weakest bond subsequently at a similar location. In MS molecular ions of tested compounds are of higher stability detected during ionization process. In Thermal gravimetric analyses (TGA), the sample is decomposed during heating with gradually weight loss. Infrared (IR) spectroscopy is a really important spectroscopic technique or it is the most important one for chemical characterization. It is the absorption or transmission measurements of different IR frequencies made by a sample. Almost any compound containing polar groups; will absorb electromagnetic radiation in infra-red region [15. 16]. IR spectroscopic analyses are mainly used to determine the functional groups in the sample. IR of samples in liquid, gases and solids states have a wide range types. There are no two similar IR spectra of molecules, since every bonds type has different natural frequency of vibration and since the same type of bonds will have different environments. IR is a good structural identification and elucidation technique used for the tested compounds identification [15,16,17].

X-rays are the rays that; inhabiting in the region between ultraviolet radiation and gamma rays. It is a high energy-high frequency form of electromagnetic radiation with short wavelength. The XRF is a method [18] in which interactions between X-rays and electron beams takes place. When materials are excited with high-energy radiation and

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short wavelength X-rays, they can become ionized. When, energy of the radiation is sufficient to emit a tightly-held inner shell electron, the outer shell electron replaces the dislodged inner electron because the atom becomes unstable. As soon as this happens, energy releasing occurred; because the outer electron is more weakly bound compared with inner shell one. The radiation emitted is termed fluorescent radiation is of lower energy than the primary incident X-rays. The emitted radiation always has characteristic energy; because the differences in energies between electron shells are fixed and known. The abundances of elements in the sample can be detected from the resulting fluorescent X-rays. ^{1}N-MR gives information about the hydrogen type's number and its environment nature [19]. The aim of the present work is the use of the previous techniques and other physicochemical methods mainly to investigate and elucidate the structural and general formulae of the Tret-I_2, Itret–I_2 products and comparing them with its parent isomer drugs.

2. Experimental

Retinoid standard drugs, I_2 reagent and their reaction products in solutions are spectrophotometrically studied at proper conditions of time, temp and pH at the wavelength range 200 – 400 nm. Spectral measurements in solutions were made using Thermo Fisher Scientific, Model: EVO 60 in the wavelength range from 190-800 nm. The pH measurements were performed by using HANNA pH/mV/temperature meter, Model pH S – 3CW.The solid products of Tret and Itret drugs with I2 reagent were prepared, by dissolving of appropriate weight of I_2 (0.4224 g) in least amount of ethanol (95 %) and adding this solution to a solution of (1.5 g) KI; which was dissolved in 50 mL distilled water. The previous mixed solvent solution was then added to appropriate weight of 0.5 g of drug which dissolved in least amount of ethanol (95%). The resulted solid product was appeared as greenish brown or brown precipitate. The precipitate leaved for 10 minutes until completely settled. The obtained products were separated, filtered and washed with suitable solvent using a Hearch funnel of suitable pores. The physical properties of the product were studied (color, m.p, solubility, etc.).Elemental analyses (C, H and N) were made at the Micro-Analytical Center of Cairo University using automatic CHN instrument. The structures of the solid drugs Tret and Itret, I_2 and its charge transfer products were investigated by using spectroscopic tools like the Fourier infrared spectra (FT-IR) and other spectroscopic tools like ^{1}H- NMR. The FT-IR absorption spectra were measured in the range of 4000 - 400 cm^{-1}. Spectra were recorded as KBr discs. ^{1}H-NMR were measured using DMSO as solvent, the chemical shift is in the range 0 - 14 ppm. Infrared spectra were recorded on a Shimadzu FT-IR model IR Affinity^{-1} spectrophotometer in wave number region 4000 – 400 cm^{-1}. ^{1}H-NMR was recorded on GEMINI-300BB. Melting point apparatus (Gallen Kamp, Germany) with range selection guide 60 – 360 ^{O}C was used to determine the melting points of solid drugs and its reaction product. The electron impact (EI) ionization of the studied compounds was conducted on a Hewlett-Packard (Palo Alto, CA, USA) mass spectrometer, model 5988, 70 eV was selected as the ionization energy and samples were introduced by the direct-insertion probe (DIP) technique. The ion source temperature was maintained at 200°C and the DIP was initially heated to 50°C and its temperature was then gradually raised to 200°C. The trap current = 10 A and the electron multiplier maintained at 1500 V. The instrument was calibrated by using perfluorotributylamine as standard.TGA, DTG and DTA studies were made with conventional thermal analyzer (Shimadzu system and 30 series thermal analyses instrument DTA-50H and TG-50H). The mass losses and heat response of the changes in the sample were measured from the ambient temperature to 600°C with heating rate 10°C min^{-1} in both TG and DTA in an inert argon atmosphere. These instruments were calibrated using indium metal as a thermally stable material. The reproducibility of the instrument reading was determined by repeating each experiment twice.

3. Results and discussion

3.1. Stoichiometric ratio and reaction mechanism

The stoichiometric ratio and reaction mechanism between retinoid drugs isomers (Tret and Itret) and iodine are studied in solutions under different conditions of pH, temperature and reaction ratios in order to suggest reaction mechanism and reactants ratios. The results obtained are given in Figs 1 and 2.

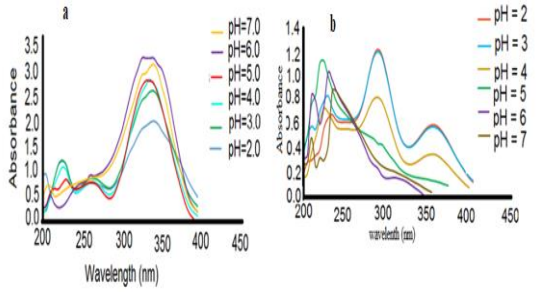


Fig. 1 .Effect of pH on absorption spectra a) of $1x10^{-4}$ M Tret and I_2 reaction**,** b) of 2 x 10^{-4} M Isotretinoin (Itret) and I_2 reaction product

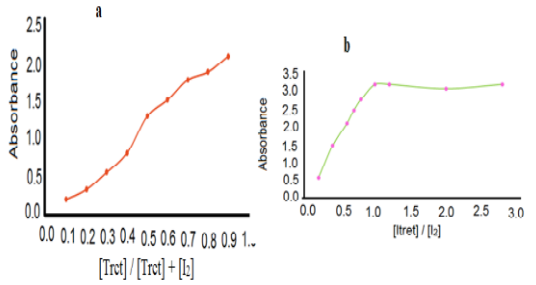


Fig. 2. a) Continues variation method of 1 x 10^{-4} M Tret and I_2 at 295 nm, pH = 6, time = 25 min and temperature = 50 ºC; b) Molar ratio of (5 x 10^{-4} M) product of Itret-I_2 at 295 nm, time = 20 min, pH = 2 and temp = 40 ºC.

The selected optimum pH for the reaction product Tret-Iodine formation is pH = 6 at which the reaction product attains the maximum absorbance at time = 25 min and temperature = 50 ºC and it is pH = 2 in case of Itret-Iodine product at time = 20 min, temp = 40 ºC.

The stoichiometric ratio of Tret and Itret reaction with I_2 drug was studied also by the molar ratio method (MRM) to confirm Continuous variation result and it is finding only one atom of iodine is inter into moiety of molecule of each isomer. The reaction mechanism between iodine and various drugs usually involves the formation of drug-I_2 outer- and inner-sphere complexes [20, 21] and the observed time dependence of the charge–transfer band and subsequent formation of I3- in solution were related to the slow transformation of the initially formed iodine: drug outer complex to an inner electron donor–acceptor (EDA) complex, followed by fast reaction of the inner complex with iodine to form a triiodide ion [21]. The pseudo-first-order rate constants and activation parameters for the transformation process were evaluated from the absorbance-time data.

3.2. Reaction mechanism between I_2 and Tret drug and the identified reaction Product

The previous data and absorption spectra of I_2, Tret and Tret-I_2 product in ethanol solvent are shown in Fig. (3); which refers to two maximum wavelengths at 295 and 355 nm, that may be suggested the formation of two absorbing species [20] of inner and outer sphere complexes [21]. The reaction mechanism between I_2 and Tret is illustrated in proposed scheme (1).

3.3. Measurement of Conductivity for Tret-I_2 and Itret-I_2 solid products

The charge transfer interaction of iodine complexes that; were formed between different kinds of aromatic donors like cyclic amines, hydrocarbons, different crown ethers and iodine as a sigma acceptor have been studied and characterized [22,23,24]. Donor-acceptor complexes or Charge transfer (CT) are the most important and vastly studied organic species because of their unusual magnetic, electrical and optical properties [25]. Mixed-valence CT complexes with segregated-stack structures generally revealed metallic electrical conduction [26]; otherwise alternating stack CT complexes are either insulators or semiconductor from conductivity measurements. Tret-I_2 and Itret-I_2 complexes have very small conductivity value (6.1 Ωm)$^{-1}$; which supports CT mechanism. In order to check the nature of reaction products it was separated as novel compounds and analyzed using different physicochemical methods. The newly prepared compounds were studied by analytical techniques MS, FT-IR, XRF, ^{1}HNMR and Thermal analyses (TA) and other physical and chemical methods to identify their actual structures.

3.4. Microanalysis of solid products

The results of elemental analyses of the new compounds (Tret-I_2 and Itret-I_2) with some of their properties and its general formulae are shown in Table 1.

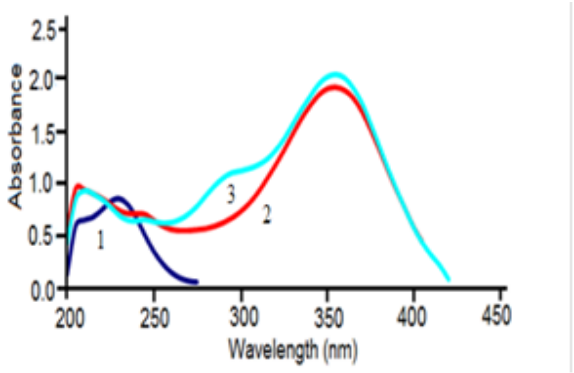
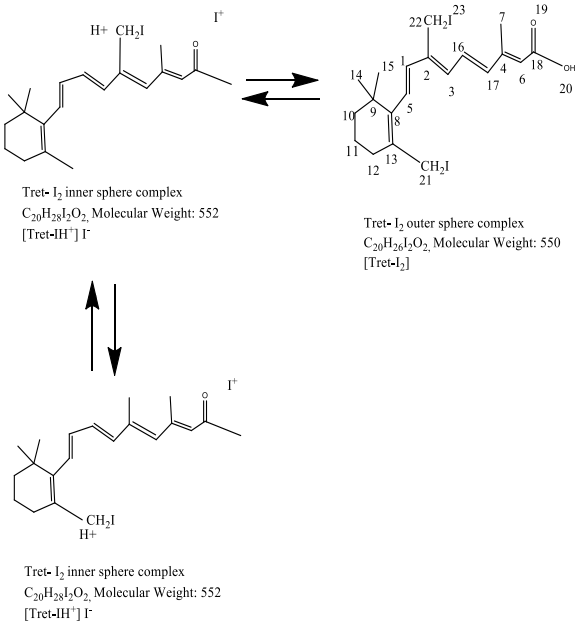


Fig .3. Absorption spectra of: 1- 1 x 10^{-4}M I_2, 2- 1 x 10^{-4}M Tret, 3- Product of 1 x 10^{-4}M Tret and I_2 using 1 x 10^{-4}M I_2 as a blank at time = 25,Temp = 50ºC and pH = 6.



Scheme (1): The proposed mechanism of Itret-I2 products formation

Table 1 Analytical and physical data of iodine –Tret and iodine-Itret products

Compound	R: D (percent yield)	m. p	Formula wt.	Color	Found (calculated) %	
Tret- I_2 $C_{20}H_{27}IO_2$	1: ½ (82.51)	140	426.33	Greenish brown	C % 54.79 (56.34)	H % 6.38 (6.6)
Itret- I_2 $C_{20}H_{27}IO_2$	1: ½ (90.2)	132	426.33	Dark brown	C % 57.8 (56.34)	H % 6.71 (6.6)

I_2 = iodine reagent (mol mass = 253.81 g mol^{-1}), Tret = Tretinoin and Itret = Isotretinoin drug isomers ($C_{20}H_{28}O_2$, mol. mass = 300.44 g mol^{-1}).

These data refer to the found general formulae of the obtained newly prepared compounds are $C_{20}H_{27}IO_2$ containing only one iodine atom in its moiety as suggested by reaction study in solutions; which may be formed in two proposed inner or outer sphere complexes represented as $C_{20}H_{27}IO_2$ in solid and $(C_{20}H_{27}IO_2)I^-$ in solution respectively (Scheme 1). The entrance of iodine atom into the entity of the given drug isomers and its position in the moiety of the molecule is confirmed by XRF, FT-IR and ^{1}H-NMR; which also lead to the proposed structural formulae of the newly prepared compounds.

3.5. X- Ray fluorescence (XRF)

X-rays are rays which, inhabiting in the region between gamma rays and ultraviolet radiation. It is a short wavelength (high energy-high frequency)

form of electromagnetic radiation. The XRF method [27] involving interactions between electron beams and X-rays with samples, it include X-ray diffraction (XRD), X-ray spectroscopy (e.g. SEM – EDS), and wavelength dispersive spectroscopy (microprobe WDS). Studying the behavior of atoms when they interact with radiation made the analysis of major and trace elements in materials by XRF is possible. When materials are excited with short wavelength, high-energy radiation (e.g. X-rays), they can become ionized. If the energy of the radiation is sufficient to dislodge a tightly-held inner shell electron, the atom becomes unstable and an outer shell electron replaces the missing inner electron. When this happens, energy is released because the inner shell electron is more strongly bound compared with an outer one. The emitted radiation is of lower energy than the primary incident X-rays and is termed fluorescent radiation. Energy differences between electron shells are known and fixed, so the emitted radiation always has characteristic energy, and the resulting fluorescent X-rays can be used to detect the abundances of elements that are present in the sample.

Tret-I_2 and Itret-I_2 solid products structures were characterized by examining using XRF technique; which is illustrated in Fig (4).

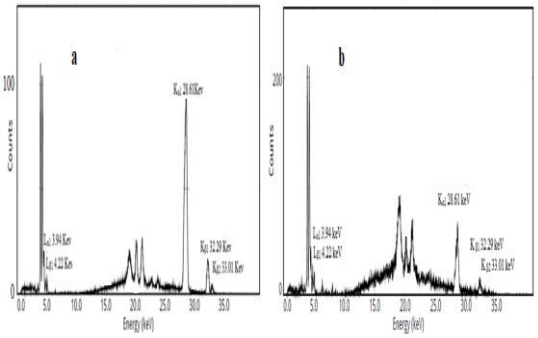


Fig .4.XRF spectra: a) of Tret –I_2 solid product; b) Itret –I_2 solid product

X-Ray fluorescence (XRF) spectra of the products (Fig 4) shows the characteristic X-ray emission lines for iodine at 3.94 , 4.22 , 28.61 ,, 32.29, 33.01 K_{ev} ($L_{\alpha 1}$, $L_{\beta 1}$, K $_{\alpha 1}$, K $_{\beta 1}$, K $_{\beta 2}$). These results prove the presence of iodine atoms in the entity of the obtained solid products

3.6. FT-IR spectra of reaction products

The FT-IR of the newly prepared compounds is achieved in the wavenumber range 4000 – 400 cm^{-1}, as graphically represented in Figs (5 and 6). Hence, significant frequencies are listed in Table (2).

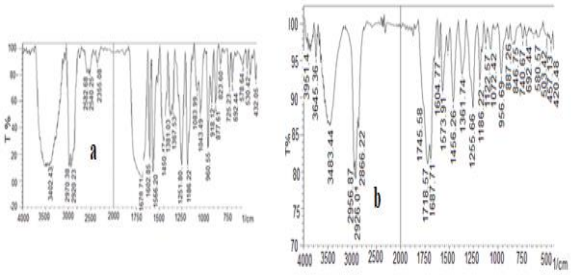


Fig .5.FT- IR Spectra of of solid Tret drug; b) Tret –I_2 product

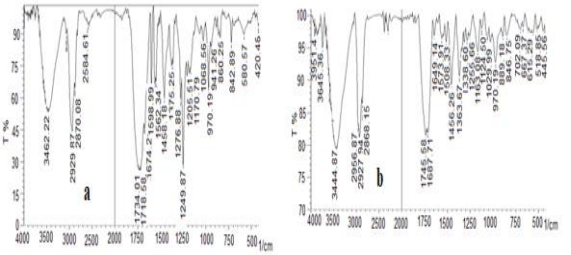


Fig .6. FT-IR Spectra a) of solid Itret drug; b) of solid Itret –I_2 product

Table. 2. FT- IR characteristic peaks of Tret, Itret and their

Tret	Tret	Tret – I_2	Itret	Itret – I_2
Characteristic Peaks	Wavenumber (cm^{-1})	Wavenumber (cm^{-1})	Wavenumber (cm^{-1})	Wavenumber (cm^{-1})
C-H stretching of the aliphatic alkane	2920	2926	2929	2927
C= O stretching of the carboxylic	1688	1688	1718	1688
Carboxylic Acid O-H	3402	3425	3462	3445
C-O Stretching of the carboxylate	960.6	956.69	970.2	970.2
C-I different modes of vibration products with I_2		457.13		445.56

FT-IR spectra (Fig 5) of Tret and its solid product respectively refer to the bands of υ(C= O) stretching of the carboxylic at 3402 cm^{-1}. This band shifts to higher value 3425 in the product. In contrast υ (C-O) stretching of the carboxylate band shifted to lower value from 960.6 to 956.7. υ (C= O) stretching of the carboxylate at 1688 Cm^{-1} remain unchanged in its correspondingTret-I_2 product [28-32]. It also shows bands at 420–500 cm^{-1}; which may be due to υ C–I different modes of vibrations [33]. FT-IR spectra of Itret and Itret-I_2 solid product (Fig 6) are similar to those of Tret and Tret-I_2 to a great extent (only differ in C-I band in product spectra); which approves similarity in structural formula. Table 2, refers to the bands of υ (C= O) carboxylic stretching 1718 cm^{-1} of Itret drug; which shifted to lower value 1688 cm^{-1} in Itret product. Also carboxylic acid υ (O-H) value in Itret shifted to lower one in product. υ (C-O) stretching of the carboxylate at 970.2 remained unchanged. There is a new band appeared at 445.56 cm^{-1} in the product; that may be related to C-I bond.

3.7. ^{1}H-NMR analysis of standard Tret, Itret and its solid products

Significant chemical shifts that given from the ^{1}H - NMR spectra of standard Tret and its solid product with iodine are shown below. ^{1}H-NMR of Tret: (Dmso, 300 MHz): δ1.017(s) (9-CH_3), 1.442 (p) (11- CH_2), 1.571(T) (10-CH_2), 1.686 (s) (13-CH_3), 2.003 (T) (12-CH_2), 2.269 (s) (2 –CH_3), 2.272 (s) (4-CH_3), 5.771(S) (6 - CH_2), 6.159 (D) (1-CH_2), 6.229(D) (3-CH_2), 6.328 (D) (5-CH_2), 6.391 (D) (18-CH), 7.019 (T) (17-CH), 7.059 (S) (21-OH); J 1,5 (15.6 Hz), J3,17 (11.1 Hz), J 17,18 (15 Hz). ^{1}H-NMR of Tret- I_2 product: (Dmso, 300 MHz): δ1.033(s) (9-CH_3), 1.067 (T) (10 CH_2), 1.1415 (p) (11-CH_2), 1.214 (s) (13-CH_3), 1.435 (T) (12- CH_2), 2.237 (s) (4 –CH_3), 3.426 (s) (2- CH_3), 5.740 (S) (6 - CH_2), 6.228 (D) (1-CH_2), 6.536 (D) (3-CH_2), 6.559 (D) (5-CH_2), 6.916 (D) (17-CH), 7.2095 (T) (16-CH), 7.069 (S) (21-OH); J 1,5 (12 Hz), J3,17 (8.85 Hz), J 17,18 (10.8 Hz).The chemical shift values of Tret drug most protons are higher than that of the product, except for the proton on no 2 carbon (shifted from 2.269 to 3.426). Also C_2 neighbor's proton shifted to higher values. Higher chemical shift of proton on C_2 and its neighbors may be attributed electronegative substituents atom (iodine in this case) attached to adjacent carbon [34]. These results support; the suggested structure formula of the product. Significant chemical shifts that given from the ^{1}H - NMR spectra of standard Itret and its solid product with iodine are shown below. ^{1}H-NMR of Itret: (Dmso, 300 MHz): δ1.030 (s) (9-CH_3), 1.101 (p) (11-CH_2), 1.189(T) (10-CH_2), 1.490 (s) (13-CH_3), 1.5885 (T) (12-CH_2), 1.907 (s) (2 –CH_3), 2.270 (s) (4- CH_3), 5.724(S) (6 - CH_2), 6.273 (D) (1-CH_2), 6.3445 (D) (3-CH_2), 6.388 (D) (5-CH_2), 6.995 (D) (18-CH), 7.014 (T) (17-CH), 8.125(S) (21-OH); J 1,5 (15.6 Hz), J3,17 (11.1 Hz), J 17,18 (15 Hz).^{1}H-NMR of Itret showed the characteristic chemical shift values associated with Tret that means; Itret is an isomer of Tret.^{1}HNMR of Itret –I_2: (Dmso, 300 MHz): δ1.006 (s) (9-CH_3), 1.088 (p) (11-CH2), 1.2815(T) (10-CH_2), 1.608 (T) (12-CH_2), 2.038 (s) (13-CH_3), 2.084 (s) (2 –CH_3), 2.270 (s) (4- CH_3), **3.170(S) (6** - CH_2), 3.401(D) (1-CH_2), 3.436 (D) (3-CH_2), 3.590 (D) (5-CH_2), 6.728 (D) (17-CH), 7.014 (T) (16-CH) ; J 1,5 (16.05 Hz), J3,16 (11.63 Hz), J 16,17 (22.23 Hz).The previous data of chemical shifts of Itret and Itret-I_2 protons reveals that the chemical shift value of proton on 13C carbon shifted from 1.490 to 2.038 in its corresponding Itret-I_2 product. These data refer to the entrance of iodine atom into aliphatic side chain in both Tretinoin (Tret) and Isotretinoin (Itret) drugs; which correlate well with the FT-IR data. The confirmation of the structural formulae of the newly

prepared compounds shall be done by both mass (EI-MS) and thermal analyses (TA) techniques.

3.8. Mass spectra of standard Tret and Itret drugs and their solid products with I_2

Mass spectral fragmentation of Tret drug and its product with iodine were recorded using chemical ionization (CI) and electronic ionization (EI). Typical mass spectrum (bar-graph) of the drug and product are shown in Figure 7. The mass spectra of Tret at 70 eV (Fig 7.a) consist of ions of fragmentation; that ranging from (m/z = 55) up to molecular ion (m/z = 300). The molecular ion [M]+ of general formula $[C20H28O2]^+$ signal appeared at m/z = 300 ; its considered as the base peak at the same time it is the molecular ion peak, with relative intensity (RI) = 100.0 %.

The MS spectra of Tret-I_2 solid product at 70 eV (Fig7.b) shows; that the molecular ion peak with the general formula $[C20H28O2I]^+$ appears at m/z = 427 and it has relative intensity (RI) = 1.52 %. The base peak appears at m/z = 253.69 (RI = 100 %). The base peak is related to $[I_2]^+$ fragmentation ion or ion of general formula $[C_{18}H_{22}O]^+$ that, was formed due to iodine atom removal from $[C_{18}H_{21}IO]^+$ ion; because halogen is a good leaving group [35].

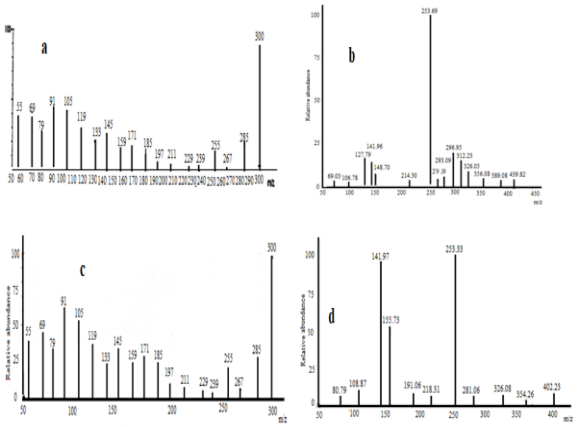
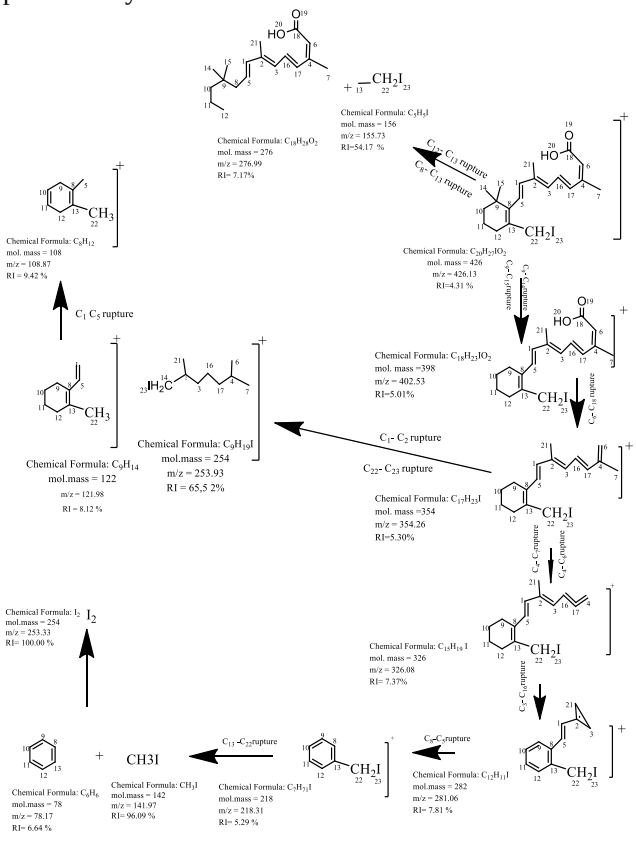


Fig .7. MS Spectra at 70 eV of : a) Tert drug , b) Tret-I_2 product, C) Itret drug and d) Itret-I_2 product

Fragments ions of the mass spectra of Itret drug at 70 eV (Fig 7c) ranging from m/z = 55 up to molecular ion at m/z = 300. The signal appeared at m/z = 300 (relative intensity (RI) = 100.0 %) is related to the molecular ion $[M]^+$ of general formula $[C_{20}H_{28}O_2]^+$; which considered as the base peak.

Typical mass spectra (bar-graph) of Itret – I_2 at different energy values are shown in Fig (7d). Fragments ions of the mass spectra of Itret - I_2 solid product at 70 eV (Fig 7d) ranging from m/z = 80.79 up to molecular ion at m/z = 426. The signal appeared at m/z = 253.33 (relative intensity (RI) = 100.0 %) is related to the base beak of general formula $[C20H28O2]^+$. In order to clarify the given mass spectra, the mass fragmentation pathway of Itret – I_2 novel product, as detailed example, can be presented by scheme 2.



Scheme (2): Proposed mass fragmentation pathways of Itret–I_2 product in cationic form

3.9.a. Thermal analyses of the Tret and Tret –I_2 solid product

TG curve of Tret (Figure 8 a,b) shows that; Tret drug decomposed in four main steps within range of 194.83 – 511.91^{O}C. Begin at 194.83 – 249.93 ^{O}C and exactly (from DTG curve) at 229.36 °C; that may be related to the loss of (2E, 4E)-3 methylhepta-2, 4, 6-trienoic acid (Practical = 45.87, Calculated = 46.00 %). Second step occurs at 272.22 – 314.31 ^{O}C and exactly at 289.95 ^{O}C); which may be attributed to the loss of but-1-ene (Practical = 17.89 and Calculated = 18.67 %). These two adjacent steps are very close to each other that they appear as a large exothermic peak in DTA at 266.90 °C; that may

refers to chemical recombination or and/or chemical rearrangement of the fragments. The third step at 341.75 – 418.61 ^{O}C exactly at 370.65 °C; this may be attributed to the loss of ethane molecule (Pract = 9.043 and Calc = 10 %). This third step appears as small endothermic peak appears at 321.62 ^{O}C. The fourth and last step occurs at 427.50 - 511.91 ^{O}C and at 470.22 °C exactly; which related to the loss of benzene with Chemical Formula: C6H6 (Pract 24.86 and Calc 26.00 %). The two last steps chemical rearrangement and weight loss are confirmed by the appearance of strong exothermic peak in DTA (Fig 8.b). A small endothermic peak appears in DTA at 171.70°C; this represents melting point of Tret as supposed by A. Ascenso, et al [36].

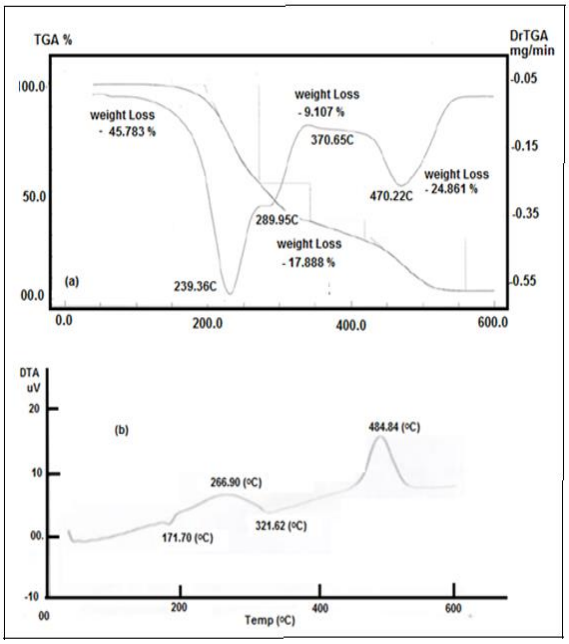
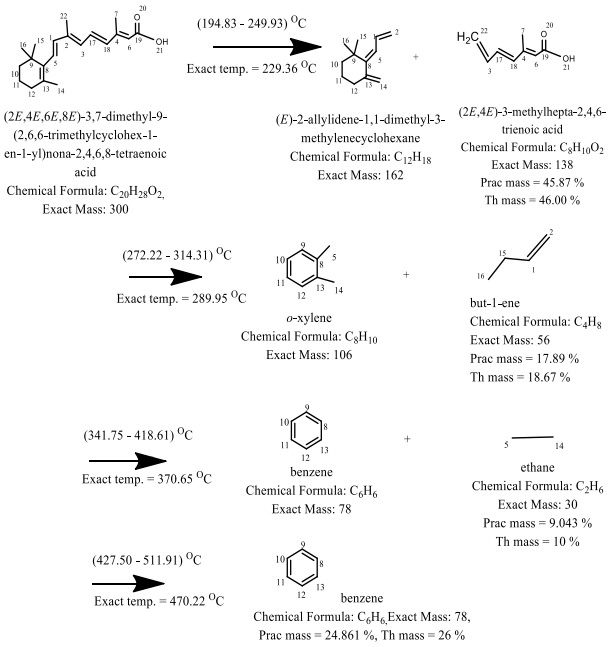


Fig. 8. Thermal analyses of Tret drug: (a) TGA/DTG, (b) DTA

These thermal decomposition endothermic peaks and chemical exothermic rearrangements of thermal decomposition of Tret drug may be represented by the proposed scheme (3).



Scheme (3): Proposed thermal decomposition of Tret drug in neutral forms.

From TGA thermograms (Fig 9 a,b), Tret- I_2 decomposed in three main steps within range 83.33 – 571.06 ^{O}C relative to practical total weight loss of 79.5 %. At 83.33 – 137.5 °C and exactly at 125 °C the first step occurred; which may be due to water molecule loss and formation of 3-((1E,3Z,5E)-4-(iodomethyl)-6-(2,6,6-tri methyl cyclohex-1-en-1-yl)hexa-1,3,5-trien-1-yl) furan with Pract = 4.0 and Calc = 4.225 %. Second step occurs at 137.5 – 285.08 °C and exactly at 197.40 °C from DTG curve, may be attributed to the loss of iodo-ethene (Pract = 36.91 and Calc = 36.15 %). The two first steps; appear as small exothermic peak in DTA at 157.22 °C; which may refers to chemical rearrangement and/or recombination of the fragments. The third step occurs at 312.5 – 571.06 °C and exactly at 407.44 °C may be related to the loss of 3-((1E, 3E)-4-methyl hexa-1,3-dien-1-yl)furan (Pract = 36.53 and Calc = 38 %). It supposed to be appeared as small endothermic peak at 485.46 OC that was followed by strong exothermic peak in DTA at 583.27 °C; which may refer to chemical rearrangement and/or chemical recombination of the fragments to give the final formula. Due to phase change from polymorphic form to another form a small exothermic peak appeared at 522.09 ^{O}C. The residue may be due to the remained toluene molecule (Pract = 20.5 and Calc = 21.59 %).

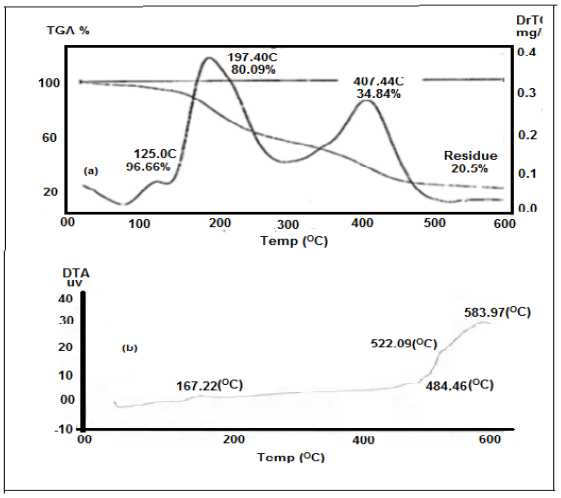
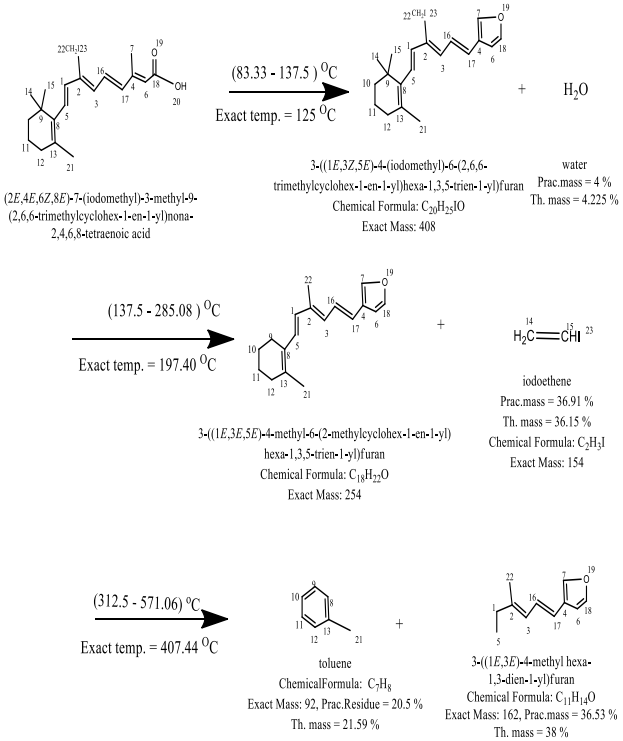


Fig (9): Thermal analyses of standard Tret-I_2 product: (a) TGA/DTG, (b) DTA

These thermal decomposition endothermic peaks and chemical exothermic rearrangements of thermal decomposition of Tret- I_2 product may be represented by the proposed scheme (4).



Scheme.4. Proposed thermal decomposition of Tret- I_2 product in neutral forms.

3.9. b. Calculation of thermodynamic parameters of Tret and Tret-I_2 decomposed compounds

Thermo gravimetric data was used for the thermodynamic activation parameters calculations of decomposition processes (activation energy E*, enthalpy ΔH*, entropy ΔS*and Gibb's free energy change of the decomposition Δ G*) using the Coats-Red fern equation [37].

$$Log\left[\frac{\log\{W_f/(W_f-W)\}}{T^2}\right]=Log\left[\frac{AR}{\theta E^*}\left(1-\frac{2RT}{E^*}\right)\right]-\frac{E^*}{2.303RT} \quad \ldots\ldots (1)$$

Where: W_f is the final weight loss, W is the weight loss up to temperature T,R is gas constant, E*is the activation energy in KJ mol^{-1} ,θ is the heating rate and A is the Arrhenius factor. E* can be calculated from A plot of the left - hand side of equation (1) against 1/T. Arrhenius constant can be determined from the intercept. The entropy of activation ΔS* gives information about the degree of order of the system, enthalpy of activation ΔH* gives information about the total thermal motion and Gibbs or the free energy of activation ΔG*gives information about the stability of the system. All these parameters were calculated using the following equations:

$$\Delta S^* = 2.303[\log(Ah/KT)]R \quad \ldots\ldots (2)$$

$$\Delta H^* = E^* - RT \quad \ldots\ldots (3)$$

$$\Delta G^* = \Delta H^* - T\Delta S^* \quad \ldots\ldots (4)$$

Where: h and k are the Boltzman and Plank constants, respectively. Values of thermodynamic activation parameters calculated of decomposed Tret drug and Tret- I_2 solid product are tabulated in Tables (3a) and for Itert and Itret-iodine product are shown in Table (3b) respectively.

The data in Table (3a) show that; the four thermal decomposition steps of Tret activation energy required values are E*=184.3, 270.9, 183.9 and 266.27 KJ mol^{-1}; enthalpy changes ΔH* = 180.1, 266.2, 178.6 and 260.1 KJ mol^{-1}; Gibbs free energy changes ΔG* = 125.8, 145.1, 172.3 and 194.6 KJ mol^{-1} and entropy values ΔS* = 107.4, 217.7, 9.704 and 87.90 J K^{-1} mol^{-1}, respectively. These results support the proposed thermal fragmentation in scheme (2) and the order of activation energy, enthalpy and free energy values are in good agreement with the proposed scheme. The higher the values of the activation energies, the more thermal stable are the drugs [38, 39]. Table (3b) shows that; the three thermal decomposition steps of Tret-I2 required activation energy values E*=110.3, 57.91 and 76.18 KJ mol^{-1}, enthalpy changes ΔH* = 107.0, 54.00 and 70.52 KJ mol^{-1}; free energy changes ΔG* = 97.37, 126.5 and 182.3 KJ mol-1and entropy values ΔS* = 24.08, -154.1 and - 164.3 J $K^{-1}mol^{-1}$, respectively. The order of activation energy, enthalpy and free energy values are in good agreement with the proposed thermal fragmentation in scheme (3).

The entropy negative values in the two last steps indicate that the decomposition reactions in these two steps proceed with a lower rate than the first one. The negative entropy values indicate that the consequent bonds ruptured during these two steps were stable

Table.3. Thermodynamic parameters: a) of thermal decomposition of Tret drug and b) of thermal decomposition of Tret- I_2 product

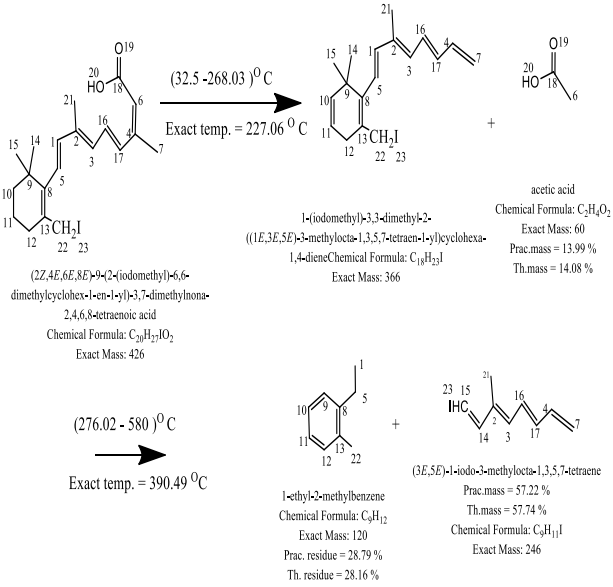
aDecomp.Temp. Range (^{O} K)	E* KJ mol^{-1}	A (S^{-1})	ΔS* J K^{-1} mol^{-1}	ΔH* KJ mol^{-1}	ΔG* KJ
470.64 – 522.04	184.3	4.274 x 10^{-18}	107.4	180.1	125.8
546.49 - 586.0	270.9	2.717x 10^{24}	217.7	266.2	145.1
622.07 - 694.24	183.9	4.323 x 10^{13}	9.704	178.6	172.3
704.42 - 784.91	266.27	6.0435 x 10^{17}	87.90	260.1	194.6

bDecomp.Temp. Range (O K)	E* KJ mol^{-1}	A (S^{-1})	ΔS* J K^{-1} mol^{-1}	ΔH* KJ mol^{-1}	ΔG* KJ
356.33 – 410.5	110.3	1.5 x 10^{14}	24.08	107.0	97.37
410.5 – 558.08	57.91	8.799 x 10^4	-154.1	54.00	126.5
585.5 – 844.07	76.18	3.741 x 10^4	-164.3	70.52	182.3

and that, the decomposed spices were more ordered than the reactant. Polarization of bonds on Tret-I_2 complex may occur during charge transfer electronic transitions; which may causes more ordered nature of its entity. It is obvious from the previous results that; addition of iodine to Tret in Tret-I_2 complex make Tret less stable (i.e. lower entropy and Energy values values) also in case of Tret-I_2 complex decomposition temp ranges are lower. These data refer to the easier thermal decomposition of Tret-I_2 complex; while it becomes difficult in case of its parent drug. On the other hand, the calculated thermodynamic parameters of Isotretinoin- Iodine product are shown in Table (4).

Table (4): Thermodynamic parameters of thermal decomposition of Itret – I_2 solid product

Decomp. Temp. Range (^{O}	**E* KJ mol^{-1}**	**A (S^{-1})**	**ΔS* J K^{-1} mol^{-1}**	**ΔH* KJ mol^{-1}**	**ΔG* KJ mol^{-1}**
305.5 – 541.03	16.12	1.187	- 247.32	12.21	128.6
549.02 – 853	56.44	9.668 x 10^2	- 194.45	50.92	179.9



Scheme .5. Proposed thermal decomposition of Itret-I_2 product in neutral form.

Itret - I_2 thermodynamic parameters data show that; the two thermal decomposition steps required activation energy values E*= 16.12 and 56.44 KJ mol^{-1}; enthalpy changes ΔH* = 12.21and 50.92 KJ mol^{-1}; free energy changes ΔG* = 128.6 and 179.9 KJ mol^{-1} and entropy values ΔS* -247.32 and - 194.95 J K^{-1} mol^{-1}, respectively. Also it is clear from these data that; the proposed thermal fragmentation in scheme (5) suits the order of activation energy, enthalpy and free energy values. The negative values refer to stability of the consequent bonds ruptured during the decomposition steps.

3.10. Biological activity of Tret drug, I_2 and their product

The antimicrobial activities of Tret, Itret, I_2 and their solid products were determined using agar well diffusion method [40]. All these compounds were tested for their antibacterial activity in vitro towards Gram positive bacteria: Streptococcus mutans and staphylococcus aureus. Also these compounds were tasted towards Gram negative bacteria Escherichia coli, Pseudomonas aeruginosa and Klebsiella using nutrient agar medium. Ampicillin and Gentamicin were used as standards for Gram positive and Gram negative respectively. For antifungal activities Nystatin was used as a reference compound. DMSO was used as solvent control. The compounds were tested at a concentration of 15 mg mL^{-1} against both bacterial and fungal strains by measuring the inhibition zone mm mg^{-1} sample. The results obtained are shown in Table (5) and Fig (10).

Table (5): Comparison between the biological activity of I2, standard Tret and Itret drugs and their products a and b.

[a] Sample and Microorganism	**I_2**	**Tret**	**Tret-I_2**	Standard antibiotic
Gram negative bacteria				Gentamicin
Escherichia coli (ATCC:3008)	35.3 ± 1.5	14.3 ± 0.5	14.0± 0.5	35±0.5
Klebsiella pneumonia (ATCC:4415)	41.0 ± 1.5	13.3 ± 0.5	13.3 ± 0.5	35±0.5
Pseudomonas aeruginosa (ATCC:27853)	45.0 ± 1.0	10.6 ± 0.6	20.3 ± 0.6	30±0.5
Gram positive bacteria				Ampicillin
Staphylococcus aureus (ATCC:6538)	42.0± 1.0	11.3 ± 0.5	NA	30±0.1
Streptococcus mutans (ATCC:25175)	38.7 ±01.5	23.3 ±0.5	NA	35±0.5
Fungi				Nystatin
Candida albicans (ATCC:10231)	42.7 ± 1.5	NA	NA	20±0.5
[b] Sample and Microorganism	**I_2**	**Itret**	**Itret-I_2**	Standard antibiotic
Gram negative bacteria				Gentamicin
Escherichia coli (ATCC:3008)	35.3 ± 1.5	NA	NA	35±0.5
Klebsiella pneumonia (ATCC:4415)	41.0 ± 1.5	12.3 ± 0.6	16.7 ± 0.6	35±0.5
Pseudomonas aeruginosa (ATCC:27853)	45.0 ± 1.0	NA	10.6 ± 0.5	30±0.5
Gram positive bacteria				Ampicillin
Staphylococcus aureus (ATCC:6538)	42.0± 1.0	NA	NA	30±0.1
Streptococcus mutans (ATCC:25175)	38.7 ±01.5	NA	25.4 ± 0.6	35±0.5
Fungi				Nystatin
Candida albicans (ATCC:10231)	42.7 ± 1.5	NA	NA	20±0.5

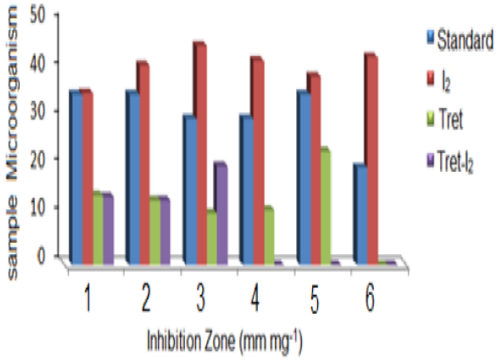


Fig.10. the biological activity of Tret drug and its product with I_2 against

1-Escherichia coli, 2- Klebsiella pneumonia, 3- Pseudomonas aeruginosa, 4-staphylococcus aureus, 5- Streptococcus mutans and 6- Candida albicans.References

Table (5a) indicates; Tret- I_2 product showed nearly similar activity to Tret drug against Escherichia coli and Klebsiella pneumonia but it shows higher activity towards Pseudomonas aeruginosa (20.3 ± 0.6). Increase of biological activity of the product especially against Gram negative bacteria refers to the biological activity of iodine atom itself found in their entities. Table (5b) shows; that Itret haven't antimicrobial or antifungal activities for most spices used except against Klebsiella pneumonia gram negative bacteria it is found to be 12.3 ± 0.6. In contrast Itret-I2 product was found to be active against Klebsiella pneumonia and Pseudomonas aeruginosa gram negative bacteria 16.7 ± 0.6 and 10.6 ± 0.5. Also Itret- I_2 was found to be active against Streptococcus mutants with activity of 25.4 ± 0.6. The previous results show that there was an extreme change in Itret -I_2 in comparison to Itret alone this may be attributed to addition of iodine atom to the drug entity; which have a great anti-bacterial activity. Itret and Itret- I_2 product didn't show anti-fungus activities against Candida albicans.

4. Conclusions

This research included results of structure investigation of the newly prepared derivati ves obtained via interaction of Tret and Itret drug isomers with iodine; under proper conditions of temperature, pH and concentration ratios. The novel compounds obtained were identified by elemental analysis (EA), XRF, FT-IR, and ^{1}H-NMR. From these results, it is concluded that:

1. From EA, the general formulae of inner and outer-sphere complexes are given by $C_{20}H_{27}IO_2$ and $(C_{20}H_{27}IO_2)^+I^-$ respectively.
2. From FT-IR spectra, the wavenumbers of the characteristic peaks of corresponding groups in the isomer drugs skeleton were determined. Shifting of wavenumbers to lower or higher values referred to sharing of these groups in the formation of inner and outer- sphere of isomer drugs-iodine complexes.
3. ^{1}H-NMR spectra, the chemical shifts of the different protons in drugs skeletons were determined. Changing of these chemical shifts and appearing and disappearing of the peaks referred to the places where the reactions took place.
4. It is obvious from thermal analyses results of TG, DTG and DTA of Tret, Itret and their iodine products results that; addition of iodine to Tret in Tret-I_2 complex make Tret less stable (i.e. lower entropy and Energy values values) also in case of Tret-I_2 complex decomposition temp ranges are lower. These data refer to the easier thermal decomposition of Tret-I_2 complex; while it becomes difficult in case of its parent drug. Itret - I_2 thermodynamic parameters data show that; the two thermal decomposition steps required activation energy values E*= 16.12 and 56.44 KJ mol^{-1}; enthalpy changes ΔH^* = 12.21and 50.92 KJ mol^{-1}; free energy changes ΔG^* = 128.6 and 179.9 KJ mol-1 and entropy values ΔS^* -247.32 and - 194.95 J K^{-1} mol-1, respectively. The negative values refer to stability of the consequent bonds ruptured during the decomposition steps.
5. Also research included the biological activity of the drugs and their solid products with iodine towards three types of bacteria negative gram (Escherichia coli, Klebsiella pneumonia and Pseudomonas aeruginosa) and two bacteria positive gram (Staphylococcus aureus and Streptococcus mutants) and one types of fungi (Candida albicans). The obtained results indicates; that Tret- I_2 products showed nearly similar activity to Tret drug against Escherichia coli and Klebsiella pneumonia put it show higher activity towards Pseudomonas aeruginosa. Tret–I_2 solid product have no activity against gram positive bacteria used; while Tret have anti-positive bacteria activities. Itret haven't antimicrobial or antifungal activities for most spices used except against Klebsiella pneumonia gram negative bacteria. In contrast Itret-I_2 product was found to be active against the used gram negative bacteria. Also it is found to be active against Streptococcus mutants. These results show that there is an extreme change of product anti-bacteria activities in comparison to drugs alone; which is attributed to iodine atom addition, that have a great anti-bacterial activity. Drugs and their solid products with iodine are more effective antibacterial agents than antifungal agent

5. Conflict of Interest

Authors certify that there is no conflict of interest.

6. Acknowledgements

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عنوان البحث

تحضير وتوصيف وفحص مواد جديدة لمشتقات الريتانويد – اليود وتطبيقاتها البيولوجية

المؤلفون: محمد عبد الجواد زايد ، مروة عبد الباسط حماد

الملخص باللغة العربية

في هذا البحث تم تحضير مشتقات جديدة من تفاعل اليود مع اثنين من أدوية الريتانويد كمتشابهات (Isomers) المهمة والمستخدمة في علاج العديد من الأمراض الجلدية ودراسة ميكانيكية التفاعل في المحاليل بالقياسات الطيفية في المدي المرئي و فوق البنفسجي وفصل نواتج تلك التفاعلات في الحالة الصلبة والتعرف علي الصيغة البنائية لتلك النواتج الجديدة بالتحليل العنصري. كما تم التعرف علي الصيغ البنائية لتلك المواد باستخدام الأشعة دون الحمراء والرنين النووي المغناطيسي للتعرف علي مكان دخول اليود لكيانات تلك المواد وأحتمال زيادة نشاطها البيولوجي لنشاط اليود المعروف. وتم تأكيد الصيغ البنائية لتلك المواد بالقياس بمطياف الكتلة وبالقياسات الحرارية وأقتراح مكانيكية التكسير بالمقارنة بماتم بمطياف الكتلة والتكسير الحراري. كما تم دراسة النشاط البيولوجي للأدوية الجديدة عن طريق دراسة تأثيرها علي البكتريا الموجبة والسالبة وبعض انوع الفطريات مقارنة بتأثير أدوية الريتانويد الأصلية كمتشابهات وكذلك بالمقارنة بتأثير بالأدوية القياسية.