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STUDY OF CHARGE-TRANSFER COMPLEXES BETWEEN IODINE AND SOME ANTIDEPRESSANTS

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تم استخدام طريقة التحليل الطيفى لدراسة التفاعل بين اليود ومنبهات الجهاز العصبى المركزى المختلفة عن طريق تكوين متراكبات تنقل الشحنة فى ١و٢ دايكلوروايثان.

وقد تم قياس درجة إمتصاص تلك المتراكبات عند طول موجى قدره ٢٩٣ ن.م فيما عدا الابرونيازيد والدسبرامين والترايمبرامين فتقاس عند ٣٦٣ ن.م.

وقد وجد أن هذه المركبات تتبع فى تفاعلاتها قانون بيير فى تركيزات تتراوح بين ٠,٥ – ٣٠ ميكروجرام لكل ملليليتر من العقاقير.

وتتضح قوة تفاعل تلك المركبات مع اليود من ثابت تكوين هذه المتراكبات الأيودينية ولهذا فأنه من المتوقع حدوث تداخل مع التمثيل الغذائى لهرمون الغدة الدرقية فى حالة تناول تلك العقاقير لمدة طويلة.

بالإضافة إلى ذلك فقد لوحظ وجود علاقة قوية بين لوغريتمات الإمتصاص المولارى لهذا التفاعل ومقاييس مضادات الإكتئاب المذكورة فى البحث.

Molecular interactions between iodine and various antidepressants are investigated by UV/Vis spectroscopy. Iodine is found to form charge-transfer complexes (CTC) of n-type with these molecules. Beer's law is obeyed in the concentration range 0.5-30 μg/ml for the studied compounds. The values for the formation constants K_c of these iodinated complexes indicate a strong donor-acceptor interaction. These drugs can, therefore, be expected to interfere with thyroid metabolism. In addition, a good correlation between log ϵ and some antidepressant parameters is found.

INTRODUCTION

Strong molecular interactions between synthetic antithyroid agents and iodine have been found to be due to the formation of charge-transfer complexes[1]. Formation of such complexes can inhibit thyroid hormone synthesis[1]. The main drugs used in the treatment of depression are considered as thyrotoxic agents[2].

Different analytical procedures have been reported for the determination of monoamine oxidase inhibitors (MAOI) which include titrimetry[3], polarography[4], spectrophotometry[5] and gas chromatography[6]. Analysis of dibenzazepine drugs include titrimetry[7,8], polarography[9], spectrophotometry[10], fluorimetry[11], and chromatography[12]. The official methods involve non-aqueous or spectrophotometric procedures[7,8].

Amines are well known as excellent n-donors and the charge-transfer complexes of these compounds with halogens and pseudo-halogens have been reported[13].

In the present work, a simple and sensitive spectrophotometric method depending on CTC formation with iodine was developed for the analysis of some anti-depressant drugs either in the pure forms or in certain pharmaceutical preparations. In addition, a correlation was made between log ϵ and some antidepressant parameters.

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EXPERIMENTAL

Equipment:

Measurements were made with a Uvidec-320 (Japan) and a Perkin-Elmer Lambda 3-B UV/Vis (USA) spectrophotometers with 10 mm quartz cells.

Materials:

1 N Hydrochloric acid, Iodine solution ($5x10^{-3}$ M) is prepared by dissolving 127 mg of resublimed iodine (Riedel-De-Haen, France) in 100 ml 1,2-dichloroethane. The solution is stable for one week when kept at 4°C.

Raw pharmaceutical grade drug samples were kindly supplied by different manufacturers. All compounds were complying with the requir nts recommended by the official or other reported methods and used as such without further purification. Other reagents and solvents were of analytical grade.

Commercial dosage forms were purchased from local sources, they were:
Anafranil tablets and ampoules (Geigy, Switzerland), Eufranil tablets (Nile Co., Egypt), Tryptizole tablets and vials (Kahira Co., Egypt), Nardil tablets (Warner Co., England), Marplan and Marsilid tablets (Hoffmann-La Roche Co., Switzerland) and Parnate tablets (SK & F, England).

General procedure:

One milliliter of the working standard or sample solutions containing 5-300 μg drug was transferred to a 10-ml standard flask and treated with 1 ml of iodine solution. The volume was then completed to 10 ml with 1,2-dichloroethane and allowed to stand at 20-25°C for the specified time for each compound (Table 1). The absorbance was measured at about 293 nm for the studied compounds, except iproniazid, desipramine and trimipramine which were measured at about 363 nm, against a reagent blank treated similarly.

Standard or dosage form Solutions:

For Drug Salts:

Solutions were prepared by dissolving an accurately weighed amount of the drug salt, the powdered mixed contents of twenty tablets or five vials equivalent to 100 mg of the base in about 10 ml of distilled water. The solution was quantitatively transferred into a 50 ml separating funnel, made alkaline with 2 ml of ammonia solution and shaken with five 20-ml portions of 1,2-dichloroethane. The combined extracts were passed through about 5 g of anhydrous sodium sulphate in a small funnel into a 100-ml standard flask and diluted to volume with 1,2-dichloroethane to provide a standard 1 mg/ml solution of the base.

Table 1: Comparative statistical data for the studied anti-depressants by the proposed procedure.

Compound	Linear range (μg/ml)	Time (min.)	λ_{max} (nm)	Intercept[a] (a)	Slope[a] (b)	Corr.coeff.[a] (r)
Iproniazid H_3PO_4	5-30	5	363	-0.0119	0.0254	0.9995
Nialamid	5-20	5	293	0.0710	0.0251	0.9989
Isocarboxazid	4-20	40	293	0.0024	0.0410	0.9979
Phenelzine H_2SO_4	2-16	5	293	-0.0287	0.0580	0.9995
Tranylcypromine H_2SO_4	1- 5	5	293	0.0001	0.1287	0.9983
Imipramine HCl	0.5- 4	5	293	0.0243	0.2250	0.9995
Desipramine HCl	4-16	10	363	-0.042	0.0519	0.9925
Trimipramine maleate	4-16	10	363	0.0113	0.0552	0.9958
Clomipramine HCl	1.25-7.50	60	293	0.0161	0.1170	0.9992
Amitriptyline HCl	1.25-7.50	10	293	-0.0023	0.1100	0.9993

[a] Average of three determinations, n = 6 in all cases.

For Drug bases:

An accurately weighed amount of the drug, or the powdered mixed contents of twenty tablets were dissolved in 0.5 ml of methanol and completed to 100 ml with 1,2-dichloroethane in a 100-ml standard flask to obtain a standard of 1 mg/ml solution of the drug, further concentrations were obtained by serial dilutions.

Formation constants and molar absorptivities (Benesi-Hilderbrand plots):

Series of each of the drug solutions in 1,2-dichloroethane were prepared (1,2,3,4 and $5x10^{-4}$ M). These solutions and iodine solution in the same solvent ($5x10^{-4}$ M) were placed in a water-bath at 20-25°C for 30 min. Then, 5 ml of iodine solution was quickly mixed with the same volume of drug solutions. The absorbances were measured immediately at 293 nm for imipramine, clomipramine and amitriptyline; and at 363 nm for desimipramine and trimipramine, against a reagent blank prepared similarly.

RESULTS AND DISCUSSION

Structurally, all the investigated compounds contain functional amino group (Scheme 1) and hence act as n-electron donors when they react with the σ-acceptor iodine. The absorption spectrum of the reaction product (Fig. 1) shows two maxima, at 293 and 363 nm with the first more intense than the second, characteristic of the n-donor CTC[14]. Iodine has its maximum at 500 nm. Iproniazid, Desipramine and trimipramine interfere with the measurement at 293 nm; they were measured, therefore, at 363 nm while the other compounds were measured at 293 nm.

The charge-transfer complex nature of the reaction was confirmed by extracting the drug from the complex by shaking with 1 N hydrochloric acid and the color of iodine in 1,2-dichloroethane was restored to violet.

The CTC spectra of these compounds with iodine bear close resemblance to the spectrum of iodine in aqueous potassium iodide with λ_{max} at 293 and 363 nm[15]. This finding reflects the similar electron donating ability of both the

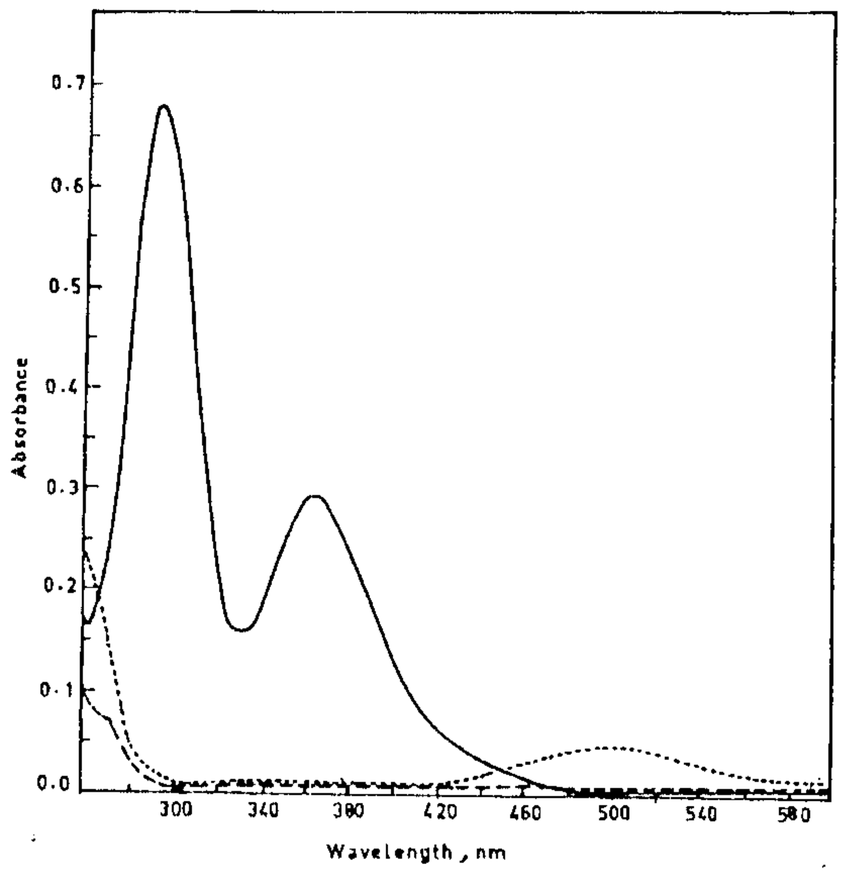


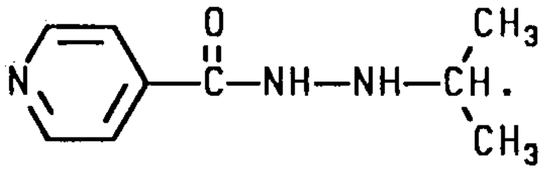
Fig. 1: Absorption Spectra of Iodine $5X10^{-3}$M ....., Imipramine HCl 3 μg/ml ----- and their Complex ———— in 1,2-Dichloroethane.

iodide ion and the n-electron lone pair of the nitrogen of these derivatives.

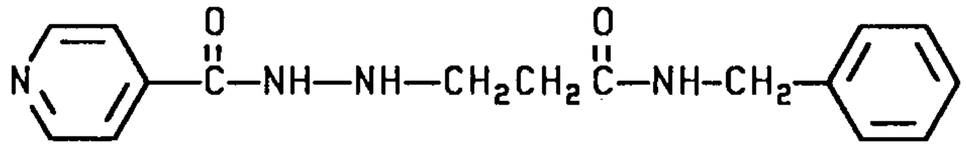
The different variables affecting the reaction were studied to determine the optimal conditions for the assay procedure. Constant absorbance readings were attained after 60 min for clomipramine, after 40 min for isocarboxazide and after 5-10 min for the other investigated drugs. The readings remained constant for at least an additional thirty min.

Standard curves for the different investigated compounds were constructed by plotting absorbance (A) versus the respective concentration (μg/ml). Beer's law was obeyed in the general range of 0.5-30 μg/ml. Regression equations were derived using the least square method and correlation coefficients were calculated (Table 1). The different values of the slopes of the obtained calibration curves reflect the sensitivity of the procedure of the different compounds.

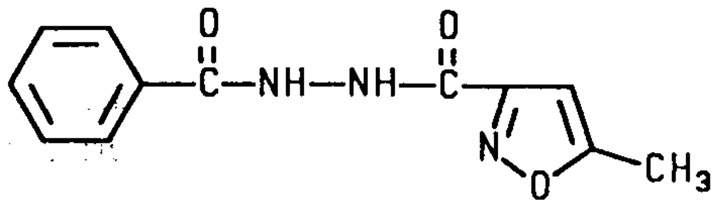
Nowadays, the use of (MAOI) as antidepressants is restricted, whereas the commonly known tricyclic antidepressants are widely used. Therefore, detailed study concerning formation constants determination and correlation of log ε with some antidepressant parameters were carried out on the latter class.



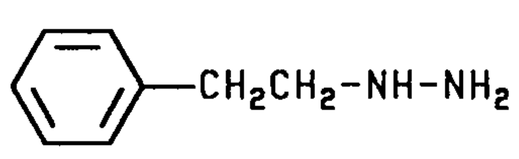
1- Iproniazid H_3PO_4



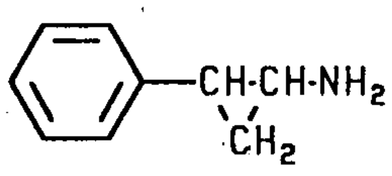
2- Nialamid



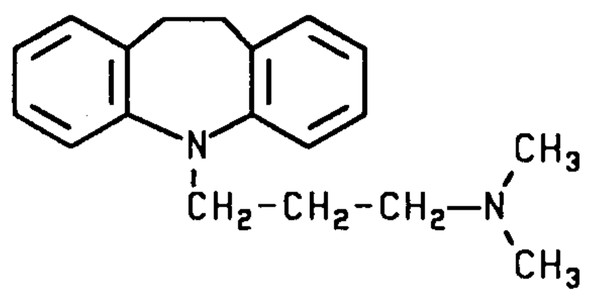
3- Isocarboxazide



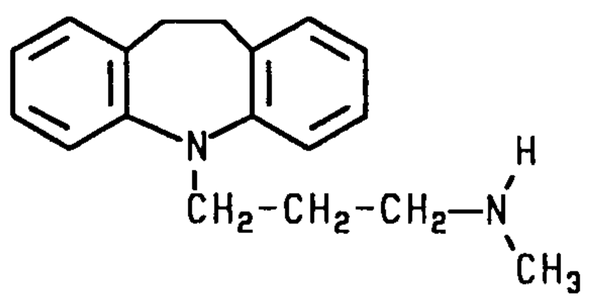
4- Phenelzine H_2SO_4



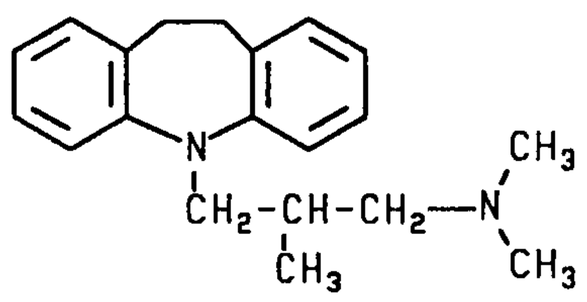
5- Tranylcypromine H_2SO_4



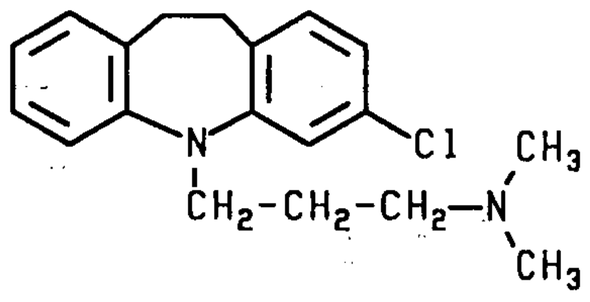
6- Imipramine HCl



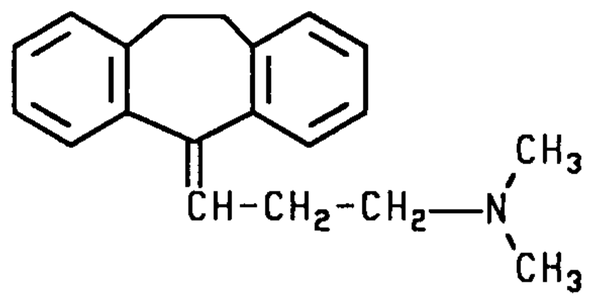
7- Desipramine HCl



8- Trimipramine maleate



9- Clomipramine HCl



10- Amitriptylene HCl

Compounds from 1-5 MAOI
Compounds from 6-10 Dibenzazepines

Scheme 1

Formation constants, K_c of the drug-iodine complexes were evaluated from the CTC bands at 293 or 363 nm as described by Benesi-Hildebrand[16]:

$$\frac{[A_o]}{A^{AD}} = \frac{1}{\epsilon^{AD}} + \frac{1}{\epsilon^{AD}} \cdot K_c^{AD} \frac{1}{[D_o]}$$

Where $[A_o]$ and $[D_o]$ are the total concentrations of the interacting species. A^{AD} and ϵ^{AD} are the absorbance and molar absorptivity of the complex at 363 nm for desimpramine and trimipramine and at 293 nm for the other investigated compounds, and K_c^{AD} is the association constant of the complex.

On plotting the value of $[A_o]/A^{AD}$ versus $1/[D_o]$, a straight line was obtained. The intercept of this line with the ordinate is $1/\epsilon^{AD}$ and the slope equals $1/\epsilon^{AD}.K_c^{AD}$.

The formation constants and molar absorptivities of the various donor-acceptor systems are shown in Table 2. In addition, the thermodynamic parameter, standard free energy of complexation, $\Delta G°$, could be calculated from the equation[17], $\Delta G° = -2.303\ RT \log K_c$.

The high values of K_c are common to complexes between the σ-acceptor, iodine, and the n-electron donors where the intermolecular overlap may be considered[18].

To confirm that a single complex was formed, a matrix analysis was carried out as described by Liptay[19]. Table 3 shows the results of the matrix analysis for imipramine as a representative example at 410, 415, 420 and 425 nm. The absorbance of a series of solutions of complexes were recorded. The calculated absorbance of non-complexed iodine was subtracted from each value. Because the donor does not absorb at this region, only absorbance due to free iodine needs to be taken into account.

$$A_{corr} = A_{obs} - \epsilon\, I_2\, [I_2]$$

A_{corr} is the corrected absorbance of the complex, A_{obs} is the absorbance of the donor-iodine mixture and ϵI_2 is the molar extinction coefficient of iodine. The concentration of non-complexed iodine is indicated by $[I_2]$. The corrected absorbance values for the different solutions at different wavelengths are arranged in a matrix. The values are then referred to a single wavelength (410 nm, Table 3). For a single complex, all values should be identical (within the limits of experimental error). From the existence of a single isosbestic point at 465 nm (Fig. 2), it could be concluded that only one species was formed[2].

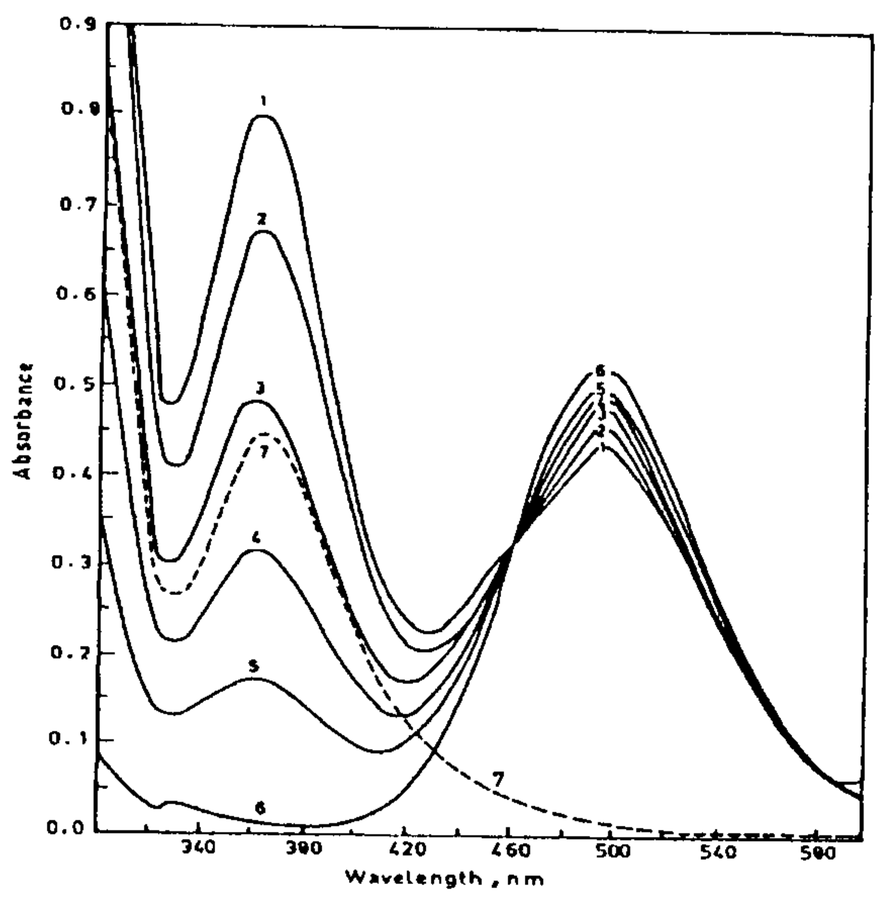


Fig. 2: Visible Absorption Spectrum of [Imipramine - Iodine] Complex Showing the Isosbestic Point. The Iodine Concentration was fixed at $5.6X10^{-4}M$.
The Concentration of Imipramine (M) were:
(1) $3.57X5^{-5}$; (2) $2.86X10^{-5}$; (3) $2.5X10^{-5}$;
(4) $2.17X10^{-5}$; (5) $1.79X10^{-5}$; (6) 0.0; and
(7) Calculated Visible Band of Complex Solution (3).

For dibenzazepines and amitriptyline, trials were made to correlate the relative sensitivity of the procedure (in the form of log ϵ) with their relative antidepressant potency (in the form of duration of immobility[20] (DI), inhibition of acetyl choline[21] and apomorphine-induced hypothermia[22] (Table 4). Good correlations were found between log ϵ with each of the aforementioned antidepressant parameters. The regression equations relating these correlations were:

$$\log \epsilon = 4.16 + 0.0037\ DI \qquad (r = 0.9927)$$

$$\log \epsilon = 213.29 + 45.71\ \textit{Acet. chol. inhib.} \quad (r=0.9997)$$

$$\log \epsilon = -14.45 + 3.63\ \textit{hypothermia} \quad (r=0.9290)$$

These equations could be used to predict the antidepressant activity of the structurally related tricyclic antidepressants.

Table 2: Regression parameters, formation constants and molar absorptivities derived from Benesi-Hildebrand plots for some antidepressant drugs.

Drugs	$(\epsilon)^{-1}$	$(\epsilon.K_c)^{-1}$	$\epsilon(l.mol^{-1}cm^{-1})$	$K_c(l.mol^{-1})$	r
Imipramine HCl	$1.23x10^{-5}$	$1.20x10^{-8}$	$8.13x10^{-4}$	1020	0.9972
Desipramine HCl	$-6.64x10^{-7}$	$1.67x10^{-8}$	$1.51x10^{-6}$	40	0.9998
Trimipramine maleate	$-9.64x10^{-5}$	$3.85x10^{-8}$	$1.04x10^{-4}$	2500	0.9968
Clomipramine HCl	$-6.25x10^{-5}$	$3.96x10^{-8}$	$1.60x10^{-4}$	1580	0.9935
Amitriptylene HCl	$-1.29x10^{-4}$	$4.92x10^{-8}$	$7.25x10^{-3}$	2620	0.9987
Tranylcypromine H_2SO_4	$6.98x10^{-5}$	$4.64x10^{-8}$	$1.43x10^{-4}$	1510	0.9997

$(\epsilon)^{-1}$ = intercept, $(\epsilon.K_c)^{-1}$ = slope, (ϵ) = molar absorptivity, K_c = formation constant and r = correlation coefficient.

Table 3: Liptay matrix for the imipramine-iodine complex

Wavelength (nm)	Soln. 1	Soln. 2	Soln. 3	Soln. 4	Soln. 5
1- Liptay matrix of corrected absorbances $(A^{corr})^a$					
410	0.877	0.749	0.655	0.579	0.480
415	0.755	0.647	0.566	0.504	0.420
420	0.658	0.568	0.497	0.448	0.373
425	0.582	0.508	0.445	0.405	0.338
2- Values referred to 410 nm					
	1	1	1	1	1
	0.861	0.863	0.864	0.870	0.869
	0.750	0.758	0.759	0.773	0.772
	0.667	0.678	0.679	0.699	0.700

[a] Concentrations (M) of the compoundds of the 5 solutions:
(I_2) fixed at $5.6x10^{-4}$ M, soln. 1 = $1.43x10^{-4}$ M, soln. 2 = $1.14x10^{-4}$ M, soln. 3 = $1x10^{-4}$ M, soln. 4 = $0.87x10^{-4}$ M and soln. 5 = $0.70x10^{-4}$ M.

Table 4: Log ϵ with reported antidepressant parametrs of some of the studied Drugs.

Drug	Log ϵ	DI	Ac.Ch.Inh	Hypo.(°C)
Imipramine HCl	4.58	106.70	3.90	1.82
Desipramine HCl	4.40	63.20	12.10	1.58
Clomipramine HCl	4.80	173.80	(---)	3.12
Trimipramine mal.	4.22	(---)	(---)	(---)
Amitriptyline HCl	4.47	90.70	9.10	1.98

(--) = not reported,
Ac.Ch.Inh = Acetyl choline inhibition,
DI = Duration of immobility
Hypo. = Apomorphine-induced Hypothermia

Table 5: Determination of some antidepressants in commercial formulations by the proposed and official methods.

Antidepressant	Product	Claimed mg	% Found ± SD[a]	
			proposed	official
Clomipramine HCl	Anafranil tab.	25	98.49 ± 0.75 F=1.62, t=1.87	99.50 ± 0.95[c]
	Anafranil amp.	25	100.97 ± 0.60 F=1.56, t=2.26	100.00 ± 0.75[c]
Imipramine HCl	Eufranil tab.	25	100.10 ± 0.90 F=3.24, t=6.23	101.70 ± 0.50[c]
Amitriptyline HCl	Tryptizol tab.	25	98.55 ± 0.89 F=1.91, t=2.73	100.40 ± 1.23[c]
	Tryptizol vials	10	98.71 ± 0.43 F=1.58, t=2.24	99.40 ± 0.54[c]
Phenelzine H_2SO_4	Nardil tab.	15	101.04 ± 0.75 F=4.58, t=2.27	100.20 ± 0.35[c]
Isocarboxazid	Marplan tab.	10	99.21 ± 0.48 F=1.32, t=2.58	98.37 ± 0.55[b]
Iproniazid H_3PO_4	Marsilid tab.	25	99.89 ± 0.55 F=3.16, t=1.31	99.52 ± 0.31[d]
Tranylcypromine H_2SO_4	Parnate tab.	10	100.10 ± 1.01 F=5.79, t=0.82	100.50 ± 0.42[c]

[a] Averge of three determinations, [b] USP XXII, [c] BP-1988, [d] Reference 24
Tabulated F for (4,4) degree of freedom at p = 0.05 is 6.39.
Tabulated t for 4 degrees of freedom at p=0.05 is 2.78.

It was reported that antithyroid activity can be expected from molecules whose formation constants of the iodinated complexes exceed 100 ($l.mole^{-1}$)[23]. From the results shown in Table 2, it can be seen that, the studied antidepressants with the exception of desipramine, gave values above 100 $l.mole^{-1}$. Accordingly, these antidepressants could be able to complex with molecular iodine. In vivo, this would tend to inhibit oxidation to I^+ ions and lead to a partial blockade of thyroid hormone synthesis. These drugs should, therefore, be considered as potentially thyrotoxic, especially in view of long-term nature of treatment with antidepressants[20].

Commercial tablets and/or ampoules containing the different investigated drugs were successfully analyzed by the proposed method (Table 5). The obtained results were compared with those of the official methods by the t- and F- tests.No significant difference was found which indicates the absence of interference from the commonly encountered pharmaceutical additives and excepients.

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