

UV-VISIBLE SPECTROPHOTOMETRIC DETERMINATION OF CHLORPROMAZINE HYDROCHLORIDE FROM PHARMACEUTICALS USING PLATINUM (IV) CHLORIDE

Maha Salah Nasr, Mohauman Mohammad Majeed Al-Rufaie*

Department of Chemistry, Faculty of Sciences, Kufa University. Najaf, Iraq

Abstract: The goal of this study is to develop a simple and precise spectrophotometric method for the quantitative determination of chlorpromazine hydrochloride (CPZ.HCL) by its reaction with platinum tetrachloride (PtC) in aqueous solutions (acidic medium) using UV-Vis spectrophotometry. Accordingly, a blue complex was formed having a characteristic band at 533 nm. To obtain high sensitivity and good stability, optimal reaction conditions were investigated, like the influence of pH, temperature, time, and the optimal concentration of platinum tetrachloride, as well as calibration curves were generated. Results indicated the possibility of using this method in estimating the drug above, as the calibration curve was subject to Beer's law for the range 5-75 $\mu\text{g/mL}$, and the molar absorptivity, Sandell's sensitivity, detection limit, and quantitative limit were 1563.32 $\text{L/mole}\cdot\text{cm}$, 0.2272 $\mu\text{g/cm}^2$, 0.5102 and 1.7007 $\mu\text{g/mL}$ respectively. The proposed procedure has also been successfully applied for CPZ·HCL quantification in the pharmaceutical form.

Keywords: *spectrophotometric determination; chlorpromazine hydrochloride; platinum (IV) chloride*

Introduction

Phenothiazines are a very substantial class of organic compounds with potent biological activity used as a treatment for moderate to severe

* Mohauman Mohammad Al-Rufaie, *e-mail*: muhaimin.alrufaie@uokufa.edu.iq

psychosocial conditions.^{1,2} Phenothiazines bind to specific dopamine D2 receptors and influences their function and thus influences many operations in the body, such as metabolism.¹ Chlorpromazine hydrochloride (CPZ·HCL) belongs to the phenothiazines family and is used as an antipsychotic drug that has the ability to reduce or relax symptoms of severe or chronic mental disorders.³ It can also contribute to reducing the manic stage of the manic gloominess.³ CPZ·HCL is a recognized first-generation antipsychotic and has been considered the "gold standard" for nearly 70 years for the treatment of psychiatric disorders, although several second-generation antipsychotics have emerged.⁴ As reported by Wang, CPZ·HCL was first manufactured in 1951 by Paul Charpentier at a French pharmaceutical company (Rhône Poulenc) and underwent clinical examination in 1952.^{4,5} Then, CPZ·HCL was approved in 1957 by the FDA and entered the USA market under the trade name Thorazine®. As the clinical treatment of schizophrenia has improved, the field has evolved dramatically.⁴

CPZ·HCL is (3-(2-chloro-10H-phenothiazin-10-yl)-N,N-dimethylpropan-1-amine), having the chemical formula, $C_{17}H_{19}ClN_2S \cdot HCl$.⁶ CPZ·HCL (as in the case of other phenothiazines) is readily oxidized in an acidic condition under the action of different oxidizing agents that lead to the forming of intensively colored oxidation outputs. The oxidation operation comprises two successive steps of removing one electron. The first one is reversible and produces a colored cation-radical. The second one is irreversible, producing a colorless sulfoxide.⁷

CPZ·HCL has its own biological and chemical characteristics.^{8,9} The molecule of CPZ·HCL (see Figure 1) is an amphipathic tricyclic component, containing hydrophobic region includes aromatic ring structures

and hydrophilic part (amino group). The nature of the aromatic ring affects the colloidal properties of this compound. Due to its self-binding behavior (as in surfactants), CPZ·HCL leads to the inactivation and dissolution of poorly soluble compounds. The self-assembly characteristics of CPZ·HCL aid in the evolution of efficient delivery systems of drug.^{8,10}

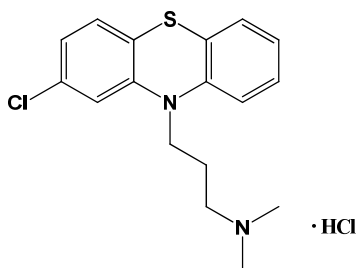


Figure 1. Chlorpromazine hydrochloride molecular structure.¹¹

There are some toxic effects that have been observed in cases of CPZ·HCL residues such as hypotension, contact dermatitis, leukopenia, cholesteric arrhythmia and tardive dyskinesia.³ Therefore, the daily dose must be accurately determined.

CPZ·HCL has been estimated in the literature in several ways, including: spectrophotometric,¹²⁻¹⁵ voltammetric,¹⁶ HPLC,^{17,18} flow injection analysis¹⁹ and electrochemical²⁰ methods. On the other hand, Platinum (IV) chloride is an analytical reagent and catalyst. It usually functions as a weak Lewis acid with the ability to bind up to six bonds in addition to its tendency to form an octahedral coordination geometry.²¹ In this concept, this research aims to find an easy and reproducible spectroscopic method to determine CPZ·HCL through its reaction with platinum (IV) chloride. Factors affecting the absorbance of the resulting complex like pH, time, temperature and concentration and addition sequence were investigated. It is believed that the method used in this study

is promising in detecting CPZ·HCL drug, as it is simple and has good accuracy as well as it is considered less expensive than other methods mentioned in the literature.

Methods and materials

Apparatus Two spectrophotometers both from Shimadzu Company (UV-2900 PC Type and UV-1650 PC type) were used to follow the UV-Vis spectra. The samples were incubated using a Water bath with Type of GFL 1083 (GFL, Germany). The pH value of the used solutions was adjusted using a pH meter (WTW, China). An electronic balance was used in order to weigh all samples.

Materials

Pure Chlorpromazine Hydrochloride drug ($C_{17}H_{20}Cl_2N_2S$) was purchased from SDI (Samarra, Iraq). Platinum Chloride (IV) ($PtCl_4$) was procured from Central Drug House (New Delhi, India). Chlorpromazine Hydrochloride tablet (25 and 100 mg) and

Chlorpromazine Hydrochloride (vials) (25 mg and 50 mg / 2 mL vial) were obtained from Aventis (Syria) and Eczacibasi (Turkey) companies, respectively. All solutions were prepared using distilled water produced by a device-type. GFL 2108 (Germany).

Preparation of solutions

Chlorpromazine Hydrochloride (CPZ·HCl) stock solution (250 μ g/ml has been prepared utilizing a volumetric flask (100 mL), in which 25 mg of CPZ·HCl was dissolved in distilled water. Platinum (IV) Chloride (0.01 M) stock solution ($PtCl_4$) was prepared by weighing and

dissolving an amount of 0.33689 g salt in water using a volumetric flask (100 mL).

A certain weight (0.10765 g for 25 mg tablets and 0.1068 g for 100 mg tablets) of Chlorpromazine Hydrochloride tablet (25 and 100 mg) to prepare a solution of CPZ·HCl. The expected concentration was equivalent to a concentration of 250 PPM. The chlorpromazine hydrochloride solution was prepared using two concentrated CPZ·HCl from different ampoules (25 and 50 mg/mL. Analogously, a 250 ppm concentration of CPZ·HCl was prepared by mixing 2 ml of the 25 mg injection or 1 ml of the 50 mg injection with distilled water in a 100 ml volumetric flask. The final volume has been completed to the mark.

Results and Discussion

The reaction of CPZ·HCl (in a concentration of 50 ppm) with (1×10^{-3} M) of PtC resulted in a blue color complex. The maximum wavelength of this complex was determined from the corresponding UV-Vis spectrum, where the highest absorbance was noticed at a maximum wavelength of 533 nm. Figure 2 presents the UV-Vis spectrum of the product obtained from the CPZ·HCl and PtC interaction.

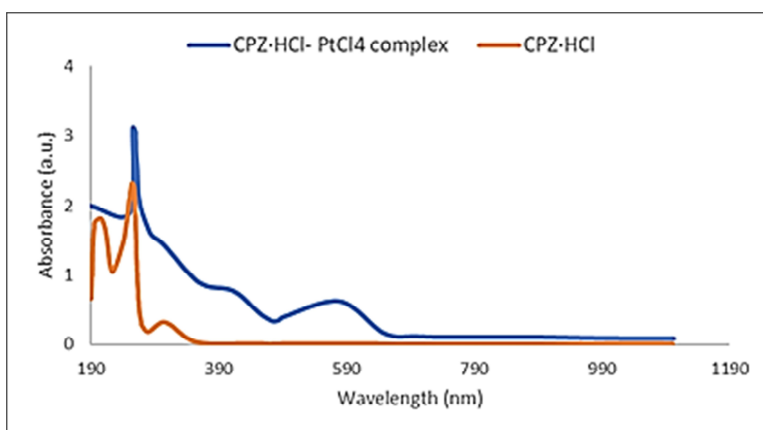


Figure 2. The spectrum of the CPZ·HCl-PtC product.

On the other hand, the impact of different factors on the adsorption intensity of the CPZ·HCl-PtC complex was investigated, which can be seen in the below sections. The optimal reaction conditions were selected.

The best concentration of Platinum (IV) Chloride

Different concentrations of PtCl₄ ranged between 1×10^{-5} and 40×10^{-5} M were used to study the effect of changing the concentration of platinum tetrachloride on the complex resulting from its interaction with CPZ·HCl, as presented in Figure 3. Results revealed that the highest absorbance was found at a concentration of 15×10^{-5} of PtC, thus, it represents the best concentration for the CPZ·HCl-PtCl₄ complex formation.

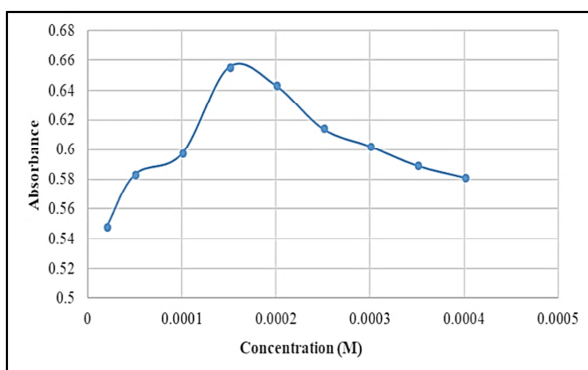


Figure 3. The impact of PtC concentration changes on the absorbance of CPZ·HCl-PtC complex.

Effect of pH

The influence of pH value on the complex produced by the reaction of CPZ·HCl with PtCl₄ was studied within the range 1 to 9 (of pH). Results of absorbance extent versus pH values can be seen in Figure 4. According with our data presented in Figure 4, it is clear that the highest absorbance was recorded for a pH value equal to 1, and then the absorbance decrease slowly when the pH was raised. Therefore, the value of pH = 1 was chosen in the subsequent measurements.

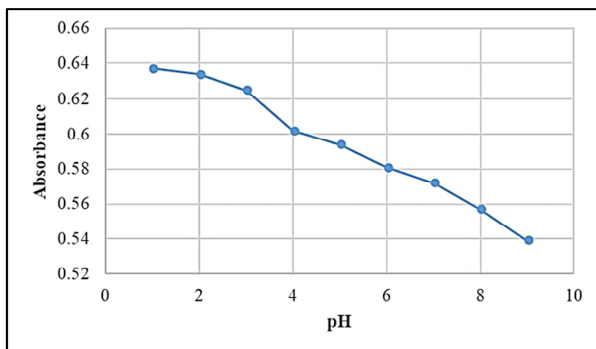


Figure 4. The pH versus the absorbance of the CPZ·HCl- PtCl₄ complex.

Effect of Time

The influence of time (in minutes) on the stability of the CPZ·HCl- PtCl₄ complex was studied. The absorbance was measured with time every 5 minutes for 60 minutes (see Figure 5). It was found that the absorbance of the complex increased with time up to 30 minutes, after that, the absorbance values tended to decrease. The decline in absorbance continued with growing of time until 55 minutes, after which the absorbance of the complex became almost constant.

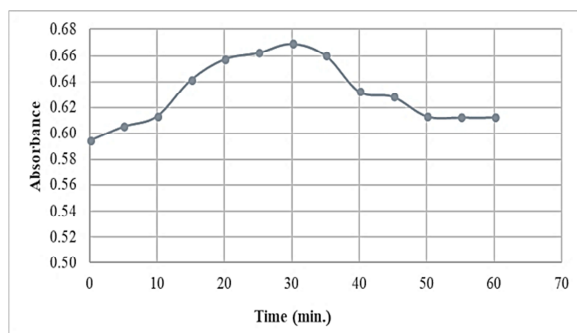


Figure 5. The change of the CPZ·HCl-PtC complex absorbance with time.

Effect of Temperature

The influence of the temperature change on the stability of CPZ·HCl-PtC complex was investigated, where the absorbance was

measured within a temperature range of 15-50 °C in a step of 5 degrees. The results are illustrated in Figure 6. It was found that the temperature of 20 °C was optimal and a highest absorbance was observed, then with increasing temperature there was a gradual decrease in the absorbance values. The reason for this is due to the dissociation of the complex with an increase in temperature.

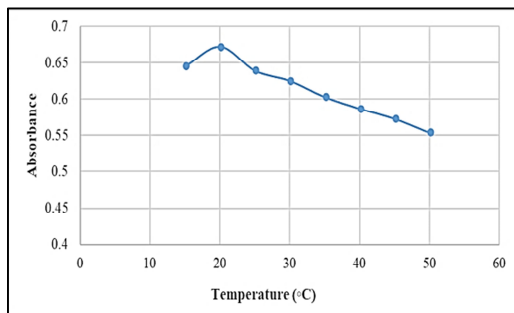


Figure 6. The temperature impact on the CPZ-HCl-PtC complex absorbance.

Calibration curve

The calibration curve of the complex resulting from the interaction of CPZ·HCl and PtC was built by taking a range of different concentrations of the CPZ·HCl drug, as shown in Figure 7. It was found from the figure that the concentrations yielded to Beer-Lambert's law ranged between (5 to 75 $\mu\text{g/mL}$) at the maximum wavelength of (533 nm). The analytical related to the calibration curve are shown in Table 1. According to the table, the detection limit (LOD) was and the quantitative limit (LOQ) values were 0.5102 and 1.7007 respectively. Moreover, the molar absorptivity was (1563.32 $\text{L/mol}\cdot\text{cm}$) and the Sandell's sensitivity was (0.2272 $\mu\text{g/cm}^2$).

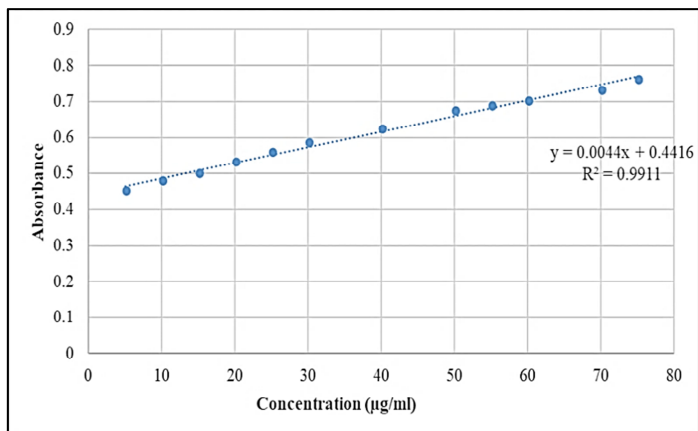


Figure 7. The calibration curve of CPZ·HCL-PtC complex.

Table 1. Analytical values linked to the calibration curve.

Parameter	Value
λ max (nm)	533
Molar absorptivity ($L \cdot \text{mole}^{-1} \cdot \text{cm}^{-1}$)	1563.32
Correlation coefficient (R^2)	0.9911
Regression equation	$y = 0.0044x + 0.4416$
Slope	0.0044
Linear range ($\mu\text{g/ml}$)	$5-75 \times 10^{-5}$
LOD ($\mu\text{g/ml}$)	0.5102
LOQ ($\mu\text{g/ml}$)	1.7007
Stoichiometric ratio	1:1

Complex stoichiometry of chlorpromazine hydrochloride and platinum (IV) chloride in an aqueous solution

The stoichiometry of the product resulted from the reaction of CPZ·HCL and PtC was carried out by continuous variation method. Figure 8 shows the results of this method. It was found, that the correlation ratio of

CPZ·HCl and PtC is (1:1) as the value of the term (X_d/X_d+X_e) equal to 0.5. Noting that the X_d and X_e in Figure 8 refer to the concentrations of drug and element (Pt), respectively.

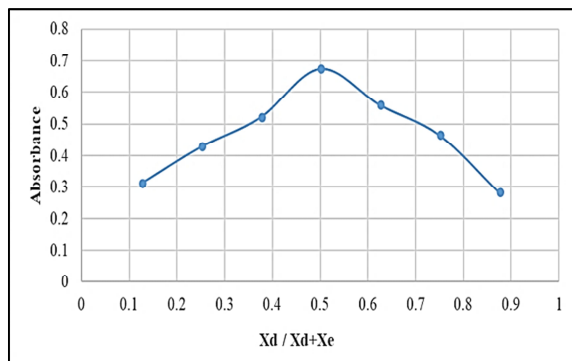


Figure 8. The continuous variation results of the CPZ·HCl-PtC complex.

Precision and accuracy

The precision and accuracy of the spectrophotometric method adopted for complex estimation were studied. The precision (expressed by the recovery percentage; Rec%, or the relative error percentage; Erel%) was calculated using equations 1 or 2:

$$\text{Rec\%} = 100 \pm \text{Erel\%} \quad (1)$$

$$\text{Erel\%} = \frac{A-R}{R} \times 100 \quad (2)$$

where A is analytical value and B represents the real value

As for the accuracy (expressed by the relative standard deviation; RSD), it was calculated using equation 3:

$$\text{RSD} = \frac{\text{SD}}{\bar{x}} \times 100 \quad (3)$$

where SD represent standard deviation and \bar{x} : Arithmetic mean Table 2 illustrates the accuracy and precision results. The results indicated that the

lowest recovery was (98.86%), and the corresponding relative error was (-1.14), which indicates that accuracy and precision are good for this method.

Table 2. Results of precision and accuracy in this study.

Concentration ($\mu\text{g/ml}$)					
Present	Found	E%	Rec%	RSD %	
20	20.2	1	101	0.532	
50	50.23	0.46	100.46	0.971	
60	59.80	-0.3	99.7	0.345	

Interferences effect

Usually, some substances are added during the manufacturing of drugs. These materials might have a probable influence on the absorbance of the compound produced by the reaction of the drug with the element or reagent. Thus, it is significant to investigate this potential impact of these substances. Table 3 shows the absorbance and recovery rate (Rec %) of some of these interfered materials. From the table above, it is obvious that these substances had no influence on the absorption of the complex, as the alteration in Rec % was lower than $\pm 2\%$.

Table 3. The influence of the additions' presence on the absorbance of CPZ·HCl-PtC product.

Interference	Error %	Recovery %
Ascorbic acid	+0.24	99.75
Sodium sulfate	+0.72	99.27
Sodium citrate	-0.53	100.53

The pharmaceutical application

The pharmaceutical application of this method was studied using tablets and injections. Calibration curves were made, and accuracy and precision were measured (Tables 4 to 7) for all above mentioned applications. For each sample three different concentrations were estimated from tablets or ampoules.

Table 4. Results of precision and accuracy for Largactil tablets (25 mg).

Concentration ($\mu\text{g/mL}$)				
Present	Found	RSD%	Rec%	E%
10	9.82	-1.8	98.20	0.53
30	30.04	0.13	100.13	0.71
50	50.07	0.15	100.15	0.95

Table 5. Results of precision and accuracy for Largactil tablets (100 mg).

Concentration ($\mu\text{g/ml}$)				
Present	Found	RSD%	Rec%	E%
10	10.03	0.3	100.30	0.94
30	29.72	-0.93	99.70	0.62
50	50.25	0.50	100.50	0.87

Table 6. Results of precision and accuracy for Largactil injection (25 mg).

Concentration ($\mu\text{g/mL}$)				
Present	Found	RSD%	Rec%	E%
10	10.08	0.8	100.80	0.55
30	30.57	1.9	101.90	0.39
50	49.82	-0.36	99.64	0.43

Table 7. Results of precision and accuracy for Largactil injection (50 mg).

Concentration ($\mu\text{g/mL}$)				
Present	Found	RSD%	Rec%	E%
10	9.93	-0.70	99.30	0.76
30	30.81	2.70	102.70	0.33
50	50.75	1.50	101.50	0.28

Conclusions

This study describes a new procedure for the detection (spectrophotometrically) of CPZ·HCl by its interaction with PtC in an acidic medium, in addition to studying the optimal conditions for the complex resulting from this reaction. It was demonstrated that the spectrophotometric method adopted in this study can be successfully used in the determination of CPZ·HCl through the reaction with PtC as the accuracy is less than 2% and recovery is within the range 99.75 to 100.53 for pure form and 98.30% to 102.70 for pharmaceutical form at a wavelength of 533 nm. Moreover, the response followed Beer's law within the range (5 to 75 $\mu\text{g/ml}$), and the molar absorptivity was ($1563.32 \text{ L}\cdot\text{mole}^{-1}\cdot\text{cm}^{-1}$), while the Sandell's sensitivity was $0.2272 \mu\text{g/cm}^2$. Moreover, the detection limit and the quantitative limit are, respectively, ($0.5102 \mu\text{g/mL}$) and ($1.7007 \mu\text{g/mL}$) which indicates a good sensitivity.

References

1. Anwar, S. M. Spectrophotometric Determination of Chlorpromazine Hydrochloride in Pharmaceutical Preparations by Oxidative Coupling Reaction. *Kirkuk Univ. Journal-Scientific Stud.* **2018**, *13*, 23–36.

2. Riviere, J. E.; Papich, M. G. *Veterinary Pharmacology and Therapeutics*; John Wiley & Sons, Hoboken, NJ, 2018.
3. Hao, X.; Liu, W.; Zhang, Y.; Kang, W.; Niu, L.; Ai, L. A Novel and Rapid Method to Detect Chlorpromazine Hydrochloride in Biological Sample Based on SERS. *Chem. Phys. Lett.* **2021**, *784*, 139066.
4. Wang, Z. Innovative Liposomes with Double Encapsulation Properties for the Treatment of Acute Myeloid Leukemia, PhD thesis, University Paris-Sud, 2019.
5. Ban, T. A. Fifty Years Chlorpromazine: A Historical Perspective. *Neuropsychiatr. Dis. Treat.* **2007**, *3*, 495-500.
6. Hensel-Bielowka, S.; Ngai, K. L.; Swiety-Pospiech, A.; Hawelek, L.; Knapik, J.; Sawicki, W.; Paluch, M. On the Molecular Origin of Secondary Relaxations in Amorphous Protic Ionic Conductor Chlorpromazine Hydrochloride — High Pressure Dielectric Studies. *J. Non. Cryst. Solids* **2015**, *407*, 81–87.
7. Daniel, D.; Gutz, I. G. R. Spectroelectrochemical Determination of Chlorpromazine Hydrochloride by Flow-Injection Analysis. *J. Pharm. Biomed. Anal.* **2005**, *37*, 281–286.
8. Azum, N.; Rub, M. A.; Asiri, A. M.; Kashmery, H. A. Synergistic Effect of an Antipsychotic Drug Chlorpromazine Hydrochloride with Pluronic Triblock Copolymer: A Physicochemical Study. *J. Mol. Liq.* **2018**, *260*, 159–165.
9. Holmberg, K.; Shah, D. O.; Schwuger, M. J. *Handbook of Applied Surface and Colloid Chemistry*; Vol. 1, Wiley-Blackwell, Chichester, 2002.
10. Khan, F.; Sheikh, M. S.; Rub, M. A.; Azum, N.; Asiri, A. M. Antidepressant Drug Amitriptyline Hydrochloride (AMT) Interaction

- with Anionic Surfactant Sodium Dodecyl Sulfate in Aqueous/Brine/Urea Solutions at Different Temperatures. *J. Mol. Liq.* **2016**, *222*, 1020–1030.
11. Alam, M. S. Influence of Electrolytes on the Micellar Growth of Amphiphilic Drug Chlorpromazine Hydrochloride. *Acta Physico-Chimica Sin.* **2008**, *24*, 411–415.
 12. Al-Rufaie, M. M. Spectrophotometric Determination of Chlorpromazine Hydrochloride in Pharmaceutical Preparations by Using Oxidative Coupling Reaction. *Iraqi Natl. J. Chem.* **2013**, *51*, 338–347.
 13. Al-Taiee, A. K. A.; Al-Rashidy, A. A. M. A.-A.; Shareef, M.F. Spectrophotometric Determination of Chlorpromazine Hydrochloride Using 4-Amino Benzoic Acid by Oxidative Coupling Reaction. In *AIP Conference Proceedings*; AIP Publishing LLC, 2020; Vol. 2213, p. 20005.
 14. Al-rashidy, A. A. M.; Al-Taiee, A. K. A. A. Shareef, M. F. Spectrophotometric Determination of Chlorpromazine Hydrochloride Using 4-Nitroaniline by Oxidative Coupling Reaction. *Baghdad Sci. J.* **2019**, *16(1)*, 194-198..
 15. Dikran, S. B.; Mohammed, A.K.; Hammodi, A. S. Spectrophotometric Determination of Chlorpromazine–HCl Using Potassium Permanganate. *Ibn AL-Haitham J. Pure Appl. Sci.* **2017**, *28*, 100–112.
 16. Unnikrishnan, B.; Hsu, P.-C.; Chen, S.-M. A Multipurpose Voltammetric Sensor for the Determination of Chlorpromazine in Presence of Acetaminophen, Uric Acid, Dopamine and Ascorbic Acid. *Int J Electrochem Sci* **2012**, *7*, 11414–11425.
 17. Yamini, Y.; Faraji, M. Extraction and Determination of Trace Amounts of Chlorpromazine in Biological Fluids Using Magnetic Solid Phase Extraction Followed by HPLC. *J. Pharm. Anal.* **2014**, *4*, 279–285.

18. Saleh, T. S. Assay of Four Psychotropic Drugs Chlorpromazine, Amitriptyline and Nortriptyline in Tablets by Single HPLC Method. *Int J Pharm Pharm Sci* **2016**, *8*, 182–188.
19. Jabbar, H. S. and Faizullah, A. T. Flow Injection Analysis with Chemiluminescence Detection for Determination of Two Phenothiazines. *Int. J. Pharma Sci. Res.* **2015**, *6*, 474–481.
20. Frag, E. Y. Z.; Zayed, M. A.; Omar, M. M. Elashery, S. E.; Mohamed, G. G. Potentiometric Determination of Chlorpromazine HCl Using Carbon Paste Electrode in Pure and Pharmaceutical Preparations. *Int. J. Electrochem. Sci* **2012**, *7*, 650–662.
21. Li, T.; Li, T.; Zhuang, H.; Wang, F.; Schmidt, R. R.; Peng, P. O-Glycosyl Trichloroacetimidates as Glycosyl Donors and Platinum (IV) Chloride as a Dual Catalyst Permitting Stereo-and Regioselective Glycosidations. *ACS Catal.* **2021**, *11*, 10279–10287.