Synthesis, characterization and spectroscopic analysis of some isatin derivatives

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Abstract
In this research, some isatin derivatives were prepared by several steps: Compound (S_1) was synthesized by reaction of isatin with 2-amino-2-thiazoline using glacial acetic acid as catalyst, the reaction of (S_1) with CS_2 in the presence of KOH and ethanol as solvent then refluxing with hydrazine hydride give compound (S_2). The compounds (S_3- S_5) were synthesized through the reaction of (S_2) with different aryl aldehyde in the presence of glacial acetic acid as catalyst. However compound (S_6- S_8) were synthesized from condensation of Schiff's bases with phthalic anhydride. The synthesized compounds identified by spectral methods [FT-IR, ^{1}H-NMR] and measurement of their physical properties. The compounds were quantified by FTIR spectroscopy, the results showed linear in concentration ranges 5.0 to 50.0 ppm.

Keyword: Isatin, Schiff's bases, quantitative estimation, FTIR spectroscopy.

1. Introduction

Isatin, chemically known as 1H-indole-2,3-dione(Zlatković et al. 2018). It has become a common subject because of the different uses. The chemistry of isatin and its derivatives is Particular attention due to the possibility of applied in Medicinal Chemistry(Guksu et al. 2019). Compounds having S, N and O donor atoms play a vital role activities due to their significant biological properties(Chittethu et al. 2017). Such as antibacterial (Al Zoubi and Ko 2017; Abdelhamid and Gomha 2017; Islam et al. 2018). Antifungal(Dhameja and Gupta 2019; DOĞAN, BÖLEK, and KAHVECİ 2019). antitumor (JIANG et al. 2014). Antitubercular (Bose et al. 2004; Mishra et al. 2017). Anticancer (El-Boraey 2005). , antimicrobial (Makarem et al. 2019), antioxidant (Andreani et al. 2010). anti-inflammatory (Sharma et al. 2016)., analgesic activities (Prakash, Raja, and Saravanan 2012)., antimalarial (Kumar and Kumar 2018), anticonvulsant (Fernandes et al. 2018). Isatin derivatives also have various industrial applications, for example they are used as corrosion inhibitors, as fluorescent sensors and also in the dye industry (Medvedev et al. 2006).Schiff bases compounds are used to synthesized of a number of industrial and biologically active compounds via ring closure, cyclo addition and replacement reactions. Schiff bases have been reported to possess biological activities like antibacterial ,antifungal ,anticancer ,antitumor , and anti-tubercular (Ren et al. 2002; Kannan, Ramesh, and Liu 2007) . Schiff's base compounds are important due to the variety of industrial applications(Mahapatra, Das, and Shivhare 2017) .

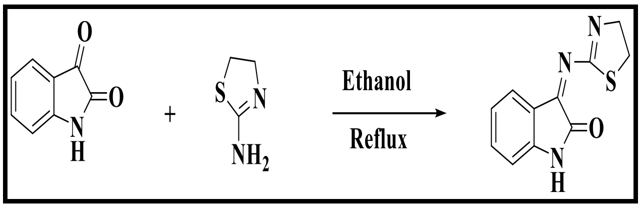
2. Materials and Methods

All chemicals and solvents used during synthesis compounds were purchased from a number of different companies such as Merck, BDH, Sigma Aldrich and Fulka. They were used as obtained without further purification. The purity of the synthesized compounds was checked it by TLC sheet and the chemical structures were characterized by FT-IR, 1H-NMR. The melting points of compounds were determined on GallenKamp (MFB-600) melting point apparatus and are uncorrected. FT-IR spectra of compounds were recorded PERKIN ELMER SPEACTUM-65 within the range [4000-400] using KBr Disc. The ^{1}H-NMR spectra was recorded by Bruker 400 MHz spectrophotometer with TMS as internal standard and deuterated DMSO was used as a solvent.

2.1. Synthesis Methods

2.1.1. Synthesis of (Z)-3-((4,5-dihydrothiazol-2-yl)imino)indolin-2-one (S_1)

A solution of (0.88 gm, 0.005 mole) of isatin was dissolved in ethanol 15 ml and solution of (0.51 gm, 0.005 mole) 2-amino-2-thiazoline was dissolved in ethanol 10 ml and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78 °C for 10 hours. The completion of the reaction was checked by using TLC (3:1) hexane: ethyl acetate, which gave one spot. A solvent was reduced to one quarter; the precipitate was formed direct, filtered off and recrystallized by ethanol to afford dark brown precipitate and dried in oven. The physical properties was illustrated in Table (1).



2.1.2. Synthesis of (Z)-3-((4,5-dihydrothiazol-2-yl)imino) -2-oxoindoline-1-carbothiohydrazide) (S2)

Potassium hydroxide (1.11 gm, 0.002 mole) was

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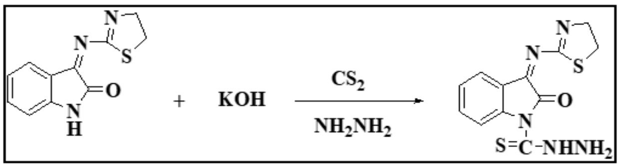
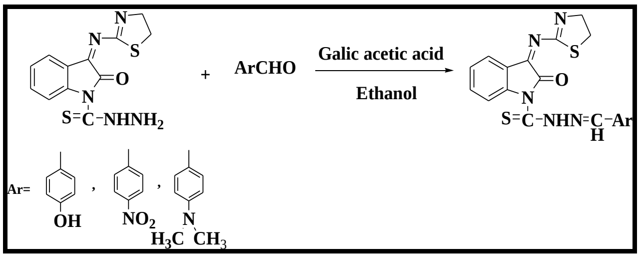
dissolved in absolute ethanol (30 ml). The solution was cooled in an ice bath and compound S1 (0.64 gm, 0.002 mole) was added with stirring, then carbon disulfide (10 ml, 0.01 mole) was added in small portions with constant stirring. The reaction mixture was agitated continuously for 5 hour at room temperature. After that hydrazine hydrate (5 ml, 0.02 mole) was added and then refluxed for 4 hour. The mixture was neutralized with dilute HCl, and the precipitate was filtered, washed with distilled water to get the brown precipitate, dried and recrystallized from ethanol. The physical properties was illustrated in Table (1)



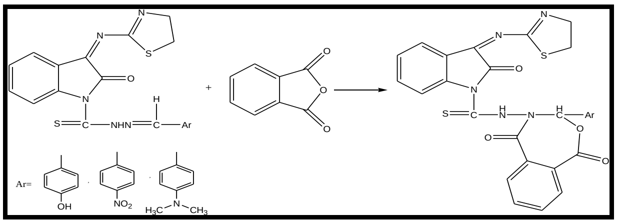
2.1.3. Synthesis of Schiff bases (S_3- S_5)

To a solution of compound S2 (1.39 gm, 0.001 mole) in (20 ml) of absolute ethanol, the appropriate aromatic aldehyde (0.001 mole) was added with 5-6 drops of glacial acetic acid. The mixture was refluxed for 14-16 hour, the reaction was checked by TLC using (3:1 ethyl acetate hexane). Then the solution was cooled, and the solid precipitate formed was filtered and recrystallized from appropriate solvent. The physical properties were illustrated in Table (1)



2.1.3. Synthesis of Compounds (S6-S8)

A mixture of Schiff bases (0.001 mol) and phthalic anhydride (0.001 mol) in 20 ml of dry benzene, then the mixture was refluxed for (12-15) hour at a temperature 80 ºC. The solvent was removed under reduced pressure, then cooling the mixture and added to ice water then collected the precipitate, washed with water and re-crystallization from suitable solvent . The properties of these compounds are listed in table (1).



2.2. Quantitative estimation of organic compounds by FT-IR spectroscopy

2.2.1. Preparation of standard stock solutions

Standard stock solutions containing 500 ppm of (S1,S2,S3,S4 and S6) compounds were prepared separately in different 50 ml volumetric flasks. These solutions were prepared by dissolving exactly 0.025 g of each organic compound in (CCL4), and diluted to the mark with some solvent. The stock solutions were protected from light.

Working solutions were freshly prepared of each organic compound.

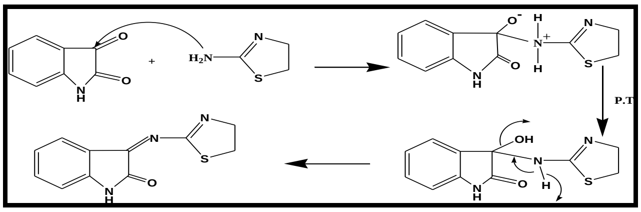
2.2.2. Preparation of samples for linearity

Solutions containing different concentration of the cited compounds, were prepared by serial dilutions at the concentration levels of (5-50) ppm for the studied organic compounds.

3. 3.Results and Discussion

A series of new compounds of 2-oxoindoline have been synthesized from reaction of isatin with 2-amino thiazoline that are widely used in pharmaceutical chemistry.

The mechanism of this reaction as shown in scheme (1).



The structure of the compounds [S_1-S_8] were proved by FT-IR and ^{1}H-NMR spectroscopy. The FT-IR spectrum of compound (S_1) showed an absorption band at 3188 cm^{-1}due to the stretching vibration of (N-H), absorption band at 3054 cm^{-1} was due to (C-H) aromatic and an absorption band at 2913-2810 cm^{-1} was due to (C-H) aliphatic . Absorption band at 1735 cm^{-1} was due to stretching vibration of (C=O) . Whereas absorption band at 1621 cm^{-1} was due to (C=N) stretching vibration .The bands at (1464 cm^{-1})was due to the (C=C)aromatic .

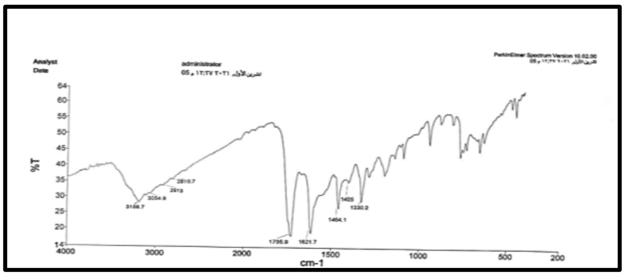


Figure (1): FT-IR of compound S_1

The 1H-NMR spectrum of compound [S1] shows a singlet signal at 11.10 ppm for (1H-NH). Multiplet signals at δ =6.87-7.61 ppm which belongs to the aromatic ring protons, and a triplet signal at the chemical displacement δ =3.79 ppm assigned to methylene protons the sulfur bonded in the thiazolin ring, while a band appeared at δ =2.89 ppm due to the two protons of the homologous group linked to the nitrogen in the thiazolin ring. Whereas the spectrum of (13C-NMR) shows the following signal for the compound (S1) using DMSO solvent. 184.88 (C7),159.84(C9, C14),112.68-151.21(C1-C6),33.61(C13), 21.76(C16).

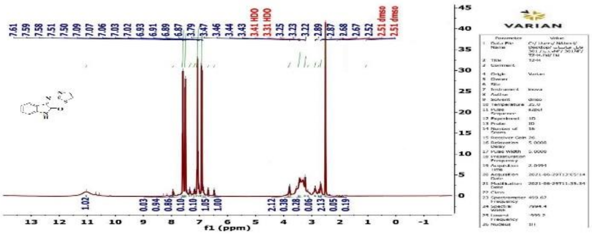


Figure (2):1H-NMR of compound S1

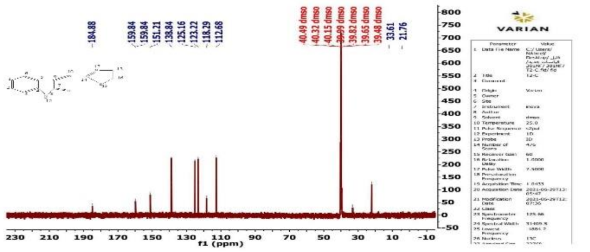


Figure (3):13C-NMR of compound S1

Compound (Z)-3-((4,5-dihydrothiazol-2-yl)imino) -2-oxoindoline-1-carbothiohydrazide (S2) was prepared by reaction of compound (S1) with carbon disulfide and potassium hydroxide by stirring for 5 hours, then refluxing with hydrazine to get compound S2.

Compound (S2) was diagnosed by infrared spectroscopy (FTIR) and nuclear magnetic resonance spectroscopy (1HNMR). The compound showed an absorption band at 3377- 3180 cm-1 was attributed to stretching vibration of (NH NH2). Absorption band at 2936 -2850 cm-1 was due to C-H aliphatic. Stretching band at 1708 cm-1 was due to (C=O) of isatin, and an absorption band at 1617 cm-1 which is due to the stretching vibration of (C=N) and an absorption band at 1472-1527 cm-1 attributed to stretching vibrations(C=C) aromatic.

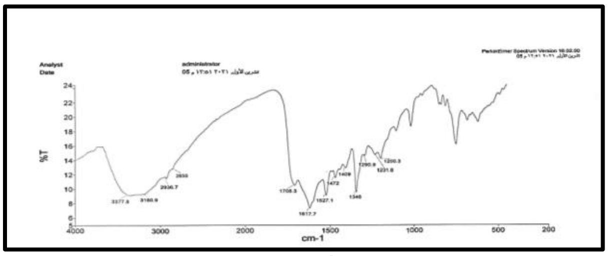


Figure (4): FT-IR of compound S_2

The ^{1}H-NMR spectrum of (S_2) in δ ppm, Figure (5) shows multiplet signals between 6.70-7.37 ppm assigned to aromatic protons, singlet signal at 6.00 ppm for (1H, NH), while signal at 4.36 due to (2H, NH$_2$), signal at 3.75 ppm for (2H,S-CH$_2$) in thiazolin ring and signal at 2.73 ppm for (2H,N-CH$_2$) in thiazolin ring.

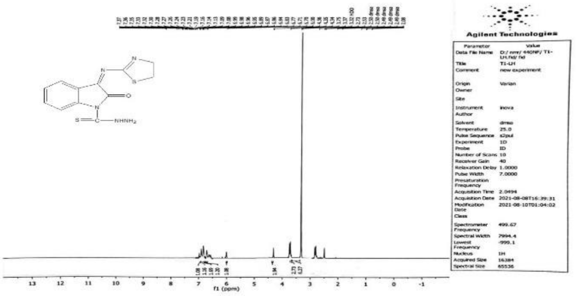


Figure (5): 1H-NMR of compound S2

Schiff's bases are introduced by condensing equal amounts of compound S2 with different aromatic aldehydes. The first step in condensation reaction between the amino compound S2 and carbonyl compounds involved nucleophilic addition of amino group in compound S2 to carbonyl group in aldehyde producing unstable intermediate which loses a water molecule in second step to afford the desirable Schiff's base.

The structures of the synthesized compounds were confirmed by FT-IR ,1HNMR spectroscopy. FT-IR spectral data which listed in Table (2). FT-IR spectra of compounds (S3-S5), show disappearance of the characteristic absorption bands at 3377cm-1 due to (NH2) group in compound S2 and emergence of new clear absorption band at (1606) due to (C=N) imine. These two points are excellent proofs for the formation of Schiff's bases.

FT-IR spectra of compounds (S3) showed an absorption band at 3417 cm-1 due to the stretching of the OH bond and an absorption band at 3267 cm-1belongs to the stretching of the N-H group .Absorption 3070 cm-1was due to C-H aromatic, as well as absorption band at 1606 cm-1 belongs to the stretching vibration of the C =N bond and the absorption band at 1515 cm-1 is due to the stretching vibration of the C=C aromatic bond. Absorption band at 1712 cm-1was due stretching vibration of C=O.

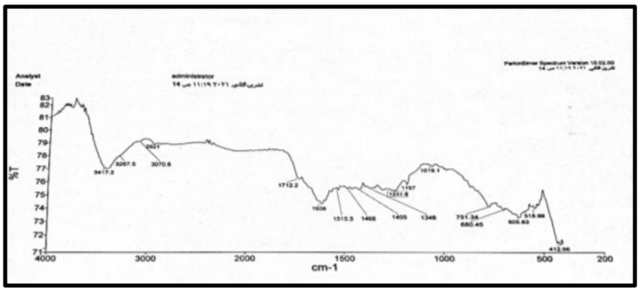


Figure (6): FT-IR of compound S3

The 1H-NMR spectrum of compound (S3), Figure (7) shows singlet signal at 9.79 ppm assigned to (1H, NH), singlet signal at 8.67ppm due to (1H,CH=N). multiplet signals between 6.83-7.74 ppm assigned to aromatic protons, singlet signal at 6.64 ppm for (1H, OH), while signal at 1.90-3.04 ppm was attributed to the protons of the methylene group in the thiazolin ring.

The 1H-NMR spectrum of compound (S4) shows singlet signal at 10.18 ppm assigned to (1H, NH), singlet signal at 8.89 ppm due to (1H,CH=N). multiplet signals between 7.04-8.44 ppm assigned to aromatic protons, while signal at 2.09-3.18 ppm was attributed to the protons of the methylene group in the thiazolin ring. Whereas the 1H-NMR spectrum of compound (S5) shows singlet signal at 9.67 ppm assigned to (1H, NH), singlet signal at 8.47 ppm due to (1H,CH=N). multiplet signals between 6.77-7.70 ppm assigned to aromatic protons, while signal at 1.91-2.99 ppm was attributed to the protons of the methylene group in the thiazolin ring. Singlet signal at 3.04 ppm assigned to (6H,2CH3)

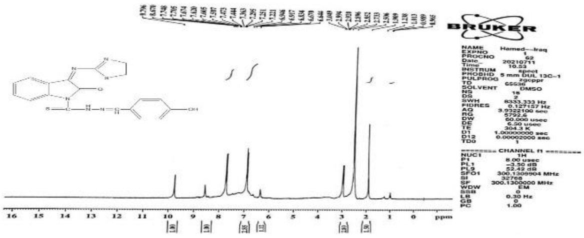


Figure (7):H^{1}NMR of **compound** *S_3*

The compounds (S6-S8) are synthesized by reaction of Schiff's bases with phthalic anhydride in dry benzene as a solvent gave the corresponding oxazepine derivatives.

The characteristic FT-IR absorption bands of these compounds (S6-S8 show the appearance of the (C=O) stretching band at (1704-1720) cm-1 indicate the formation of the oxazepine derivatives

The FT-IR spectrum of compound S6 indicated the absorption bands at at(3456 cm) was attributed to (O-H) group .Absorption band at 3220 cm-1 due to the stretching of the (NH) bond and an absorption band at 3015cm-1 back to the stretching of the aromatic C-H bond. Whereas absorption band at 1684 cm-1 was due to stretching vibration of (C=O) amid and an absorption band at (1720 cm-1) was attributed to stretching vibration of (C=O) lactone. An absorption band at (1452-1515 cm-1) is due to the vibration of the C=C aromatic bond.

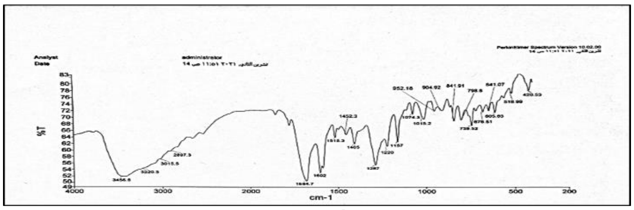


Figure (8): FT-IR of compound S6

The H^{1}NMR spectrum of compound S_6 showed the appearance of a single signal at (9.79 ppm) was due to (1H, NH), singlet signal at 7.77ppm due to (1H,CH-N). multiplet signals between 6.83-7.75 ppm assigned to aromatic protons, singlet signal at 6.57 ppm for (1H, OH), while signal at 2.27-4.27 ppm was attributed to the protons of the methylene group in the thiazolin ring.The H^{1}NMR spectrum of compound S_7 showed the appearance of asingle signal at (9.79 ppm) was due to (1H,NH), singlet signal at 7.93 ppm due to (1H,CH-N). multiplet signals between 7.37-7.55 ppm assigned to aromatic protons, whereas signal at 1.16 -3.13 ppm was attributed to the protons of the methylene group in the thiazolin ring. Whereas

the H^{1}NMR spectrum of compound S_8 showed the appearance of a single signal at (9.67ppm) was due to (1H, NH), singlet signal at 7.58ppm due to (1H,CH-N). multiplet signals between 6.78-7.78 ppm assigned to aromatic protons, singlet signal at 3.11 ppm for (6H,2CH$_3$), whereas signal at 1.30-4.27 ppm was attributed to the protons of the methylene group in the thiazolin ring.

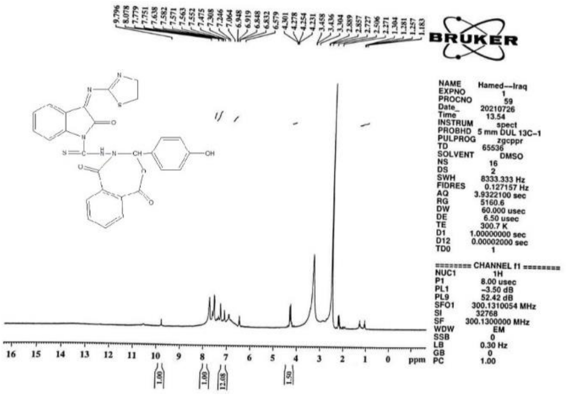


Figure (9): ^{1}H-NMR of **compound** *S_6*

Table 1: Physical properties of the synthesized compounds

Rec.solvent	Yield %	Color	M.P.(^{0}C)	Com.No
Ethanol	86	Dark brown	107-109	S1
Ethanol	94	Brown	270-272	S2
Ethanol	71	Brown	251-253	S3
Ethanol	96	Black	145-147	S4
Methanol	93	Dark brown	244-246	S5
Dioxane	75	Brown	173-171	S6
Dioxane	72	Black	177-179	S7
Dioxane	72.5	brown	120-122	S8

Table 2: FT-IR absorption spectra data (cm^{-1}) of the prepared compounds

Characteristic bands of FT-IR spectrum

others	υ(C=C) arom	υ(C=N)	υ(C=O)	υ(C-H) ali	υ(C-H) arom	υ(N-H)	Comp.No.
	1464	1612	1735	2810-2913	3054	3188	S_1
	1472-1527	1617	1708	2850-2936		3180-3377	S_2
O-H 3417	1468-1515	1606	1712	2921	3070	3267	S_3
NO$_2$ 1346-1523	1428	1598	1629	2842-2905	3078	3291	S_4
-	1550	1598	1665	2834-2928	3054	3188	S_5
O-H 3417	1468-1515	1606	1712	2921	3070	3267	S_6
NO$_2$ 1345-1523	1472	1590	1704 1665	2834-2921	3054	3102	S_7
O-H 3417	1531-1590	1606	1716	2802-2905	3039	3125	S_8

4.Quantitative analysis of organic compounds

4.1. Wavenumber selection

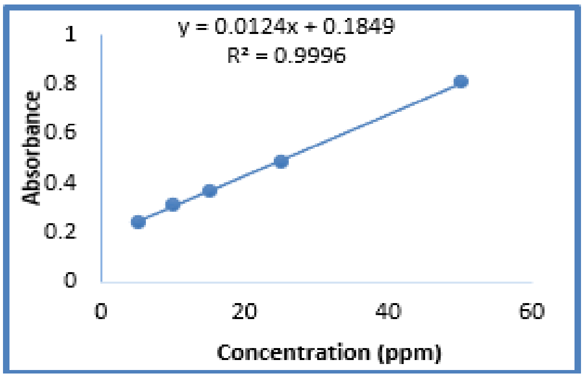
To find the proper wavenumber that used to recognize the concentrations bands of the studied compounds which gave reasonable values of absorbance for the three analytes separately.
The absorption was calculated using the equation:
A= Log(1/T)
The spectrum of (20 ppm) solution of each compound in the wavenumber range of (400 – 4000) cm^{-1} was recorded. Shows the IR spectra of the (5) compounds from which the best wavenumber was chosen for qualitative evaluation and quantification of the cited compounds table (3).

Table (3) The selection wavenumber of each organic compound

Comp. No.	Wavenumber
S1	3188
S2	3180
S3	3267
S4	3291
S6	3267

4.2.Construction of calibration curve

Percent transmittance and absorbance values of the studied compounds were calculated of different concentrations (5-50)ppm. Therefore, calibration plot was constructed for the assay of each compound individually by plotting the measured values of absorbance versus the compound concentration. A linear relation was obtained Figures (10-14) from which the regression equation and coefficient of determination (R^2) were calculated.



Figure(10) Calibration curve of compound) S1)

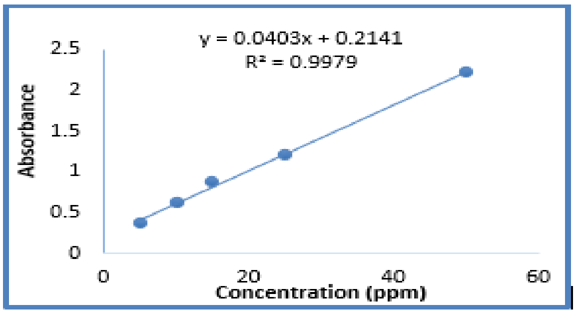
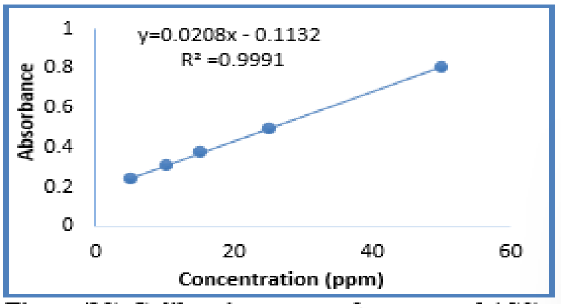


Fig (11) Calibration curve of compound (S2)



Figure(12) Calibration curve of compound (S3)

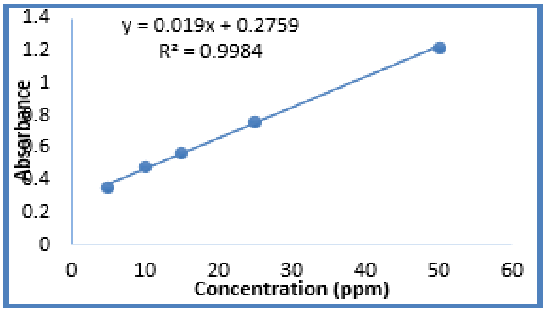


Figure (13) Calibration curve of compound (S4)

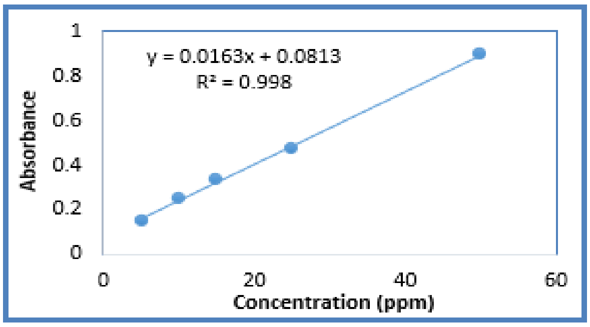


Fig (14) Calibration curve of compound (S6)

4.3. Analytical characteristics

Some analytical characteristics namely Beer's law limit, slope, and correlation coefficient for the determination of these compounds, were calculated and the results are reported in Table (4)

Table (4) Analytical parameters

Comp. No.	Beer's law limit conc. (ppm)	Regression Equation	Slope	Correlation coefficient
S1	5-50	Abs=0.0124[S1] +0.1849	0.0124	0.9996
S2	5-50	Abs=0.0403[S2] +0.2141	0.0403	0.9979
S3	5-50	Abs=0.0208[S3]-0.1132	0.0208	0.9991
S4	5-50	Abs=0.019[S4] +0.2759	0.019	0.9984
S6	5-50	Abs=0.0163[S6] +0.0813	0.0163	0.9980

4.5. Accuracy and precision:

Accuracy of the proposed method was done by determining the values of relative error percentage (RE %) and precision was evaluated by indicate calculating the values of relative standard deviation percentage (RSD %) of the obtained results for the studied compounds. Three replicate analyses were carried out for each compound at one level of concentrations within the linearity range for each compound. The obtained results good accuracy and precision of the recommended procedure at the studied concentration level, Table (5)

Table (5): - Accuracy and precision of the method

Compo.No.	Calculated Conc. (ppm)		RSD%	RE%
	Taken	Mean*		
S1	10.0000	10.0191	0.0930	0.1910
	20.0000	20.1105	0.6920	0.5525
S2	10.0000	10.0237	0.3640	0.2370
	20.0000	19.8895	0.5105	-0.5525
S3	10.0000	10.0846	0.6421	0.8450
	20.0000	20.0620	0.6253	0.3100
S4	10.0000	10.0517	0.5308	0.5170
	20.0000	19.9613	0.3612	-0.1935
S6	10.0000	9.9604	0.5439	-0.3960
	20.0000	20.0115	0.5709	0.0575

*Average three replicates

References

Abdelhamid, Abdou O, and Sobhi M Gomha. 2017. 'Synthesis and characterization of new pyrazole-based thiazoles', *Synthetic Communications*, 47: 1409-14.

Al Zoubi, Wail, and Young Gun Ko. 2017. 'Schiff base complexes and their versatile applications as catalysts in oxidation of organic compounds: part I', *Applied Organometallic Chemistry*, 31: e3574.

Andreani, Aldo, Silvia Burnelli, Massimiliano Granaiola, Alberto Leoni, Alessandra Locatelli, Rita Morigi, Mirella Rambaldi, Lucilla Varoli, Mauro Andrea Cremonini, and Giuseppe Placucci. 2010. 'New isatin derivatives with antioxidant activity', *European journal of medicinal chemistry*, 45: 1374-78.

Bose, Doyel, Jaya Banerjee, Sk Hafijur Rahaman, Golam Mostafa, Hoong-Kun Fun, Rosa D Bailey Walsh, Michael J Zaworotko, and Barindra Kumar Ghosh. 2004. 'Polymeric end-to-end bibridged cadmium (II) thiocyanates containing monodentate and bidentate N-donor organic blockers: supramolecular synthons based on π–π and/or C–H⋯π interactions', *Polyhedron*, 23: 2045-53.

Chittethu, Amrutha B, Asha Jose, Ranganathan Balasubramanian, Saranya TS, and Asha Asokan Manakadan. 2017. 'Utility of Isatin Semicarbazones in Mammary Carcinoma Cells-A Proof of Concept Study', *Journal of Young Pharmacists*, 9.

Dhameja, Manoj, and Preeti Gupta. 2019. 'Synthetic heterocyclic candidates as promising α-glucosidase inhibitors: An overview', *European journal of medicinal chemistry*, 176: 343-77.

DOĞAN, İnci Selin, Gökçe Gül BÖLEK, and Bahittin KAHVECİ. 2019. 'Synthesis of Some New Isatin Derivatives and Identification of Their Structures', *Süleyman Demirel Üniversitesi Fen Bilimleri Enstitüsü Dergisi*, 23: 67-70.

El-Boraey, HA. 2005. 'Structural and thermal studies of some aroylhydrazone Schiff's bases-transition metal complexes', *Journal of thermal analysis and calorimetry*, 81: 339-46.

Fernandes, Isabel PG, Bárbara V Silva, Bianca NM Silva, Angelo C Pinto, Severino Carlos B Oliveira, and Ana Maria Oliveira-Brett. 2018. 'Isatin 1-morpholinomethyl, 1-hydroxymethyl, 1-methyl, and their halogenated derivatives, redox behaviour', *Journal of Electroanalytical Chemistry*, 812: 143-52.

Guksu, Zuhal, Orkide Palabıyık, Aziz Karaca, Nejdet Süt, and Selma Arzu Vardar. 2019. 'Effect of Isatin on Ischemia and Reperfusion Injury: an Experimental Study in the Isolated Rat Heart', *Koşuyolu Heart Journal*, 22: 57-62.

Islam, Shariful, AKM Nur Alam Siddiki, Shahida Begum, and Md Abdus Salam. 2018. 'Synthesis, spectral characterization and thermal behavior of newly derived La (III), Co (III) and Mn (II) complexes with schiff base derived from methionine and salicylaldehyde', *Open Journal of Inorganic Chemistry*, 8: 55-69.

JIANG, YinZhi, YongQiang SHI, YinPing SHI, and HuoYing XU. 2014. 'Synthesis and dye degradation performance of the complex of Cu (II) with bis-salicylidene diethylenetriamine Schiff base', *Scientia Sinica Chimica*, 44: 1528-35.

Kannan, Sethuraman, Rengan Ramesh, and Yu Liu. 2007. 'Ruthenium (III) mediated C–H activation of azonaphthol: Synthesis, structural characterization and transfer hydrogenation of ketones', *Journal of organometallic chemistry*, 692: 3380-91.

Kumar, Ramesh, and Mahesh Kumar. 2018. 'Synthesis of 3-[4-(2-Amino-6 (substituted phenyl)-pyrimidin-4-yl)-phenylimino]-5-chloro-1, 3-dihydro-indol-2-one derivatives of 5-chloroisatin as potential antimicrobial agents', *Journal of Pharmaceutical, Chemical and Biological Sciences*, 5: 399-404.

Mahapatra, Debarshi Kar, Devashish Das, and RS Shivhare. 2017. 'Substituted thiazole linked murrayanine-Schiff's base derivatives as potential anti-breast cancer candidates: Future EGFR Kinase inhibitors', *Int J Pharm Sci Drug Res*, 9: 139-44.

Makarem, Somayeh, Behrooz Mirza, Zahra Mohammad Darvish, Nazila Amiri Notash, and Somayeh Ashrafi. 2019. 'Organic electrosynthesis: a promising alternative methodology for the synthesis of nanosized particles of pyrans', *Analytical and Bioanalytical Chemistry Research*, 6: 231-40.

Medvedev, A, O Buneeva, O Gnedenko, V Fedchenko, M Medvedeva, Yu Ivanov, V Glover, and M Sandler. 2006. 'Isatin interaction with glyceraldehyde-3-phosphate dehydrogenase, a putative target of neuroprotective drugs: partial agonism with deprenyl.' in, *Oxidative Stress and Neuroprotection* (Springer).

Mishra, Kushal Nath, SK Sengupta, Om Prakash Pandey, and Shambaditya Goswami. 2017. 'Synthesis, physicoanalytical characterization and biological activity of Isatin Thiosemicarbazones derivatives of Dichloro bis (cyclopentadienyl) hafnium (IV)(Cp2HfCl2)', *RESEARCH JOURNAL OF PHARMACEUTICAL BIOLOGICAL AND CHEMICAL SCIENCES*, 8: 1779-85.

Prakash, Chinnasamy Rajaram, Sundararajan Raja, and Govindaraj Saravanan. 2012. 'Design and synthesis of 4-(1-(4-chlorobenzyl)-2, 3-dioxoindolin-5-yl)-1-(4-substituted/unsubstituted benzylidene) semicarbazide: Novel agents with analgesic, anti-inflammatory and ulcerogenic properties', *Chinese Chemical Letters*, 23: 541-44.

Ren, Shijun, Rubin Wang, Kenichi Komatsu, Patricia Bonaz-Krause, Yegor Zyrianov, Charles E McKenna, Csaba Csipke, Zoltan A Tokes, and Eric J Lien. 2002. 'Synthesis, biological evaluation, and quantitative structure− activity relationship analysis of new Schiff bases of hydroxysemicarbazide as potential antitumor agents', *Journal of medicinal chemistry*, 45: 410-19.

Sharma, Pramod K, Sakshi Balwani, Divya Mathur, Shashwat Malhotra, Brajendra K Singh, Ashok K Prasad, Christophe Len, Erik V Van der Eycken, Balaram Ghosh, and Nigel GJ Richards. 2016. 'Synthesis and anti-inflammatory activity evaluation of novel triazolyl-isatin hybrids', *Journal of enzyme inhibition and medicinal chemistry*, 31: 1520-26.