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Synthesis and characterization of new sulphur six-membered heterocyclic compounds and evaluation their biological activity

Síntesis y caracterización de nuevos compuestos heterocíclicos de seis miembros con azufre y evaluación de su actividad biológica.

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ABSTRACT/ In this study new sulphur six-membered heterocycles (1,3-thiazinan-4-one compounds) C_5-C_8 were synthesized using imine as Precursors compounds. Imine compounds C_1-C_4 prepared by reaction of amines and aldehydes. New 1,3-thiazinan-4-one compouds were synthesized by reaction of imine and 3-mercaptopropanoic acid. Synthesized C_5-C_8 compounds were characterized using FT-IR and ^{1}H-NMR. Study of biological activity for C_5-C_8 compounds was performed by using Gram positive and negative pathogenic bacteria ***S. aureus*** and ***E. coli***, detection of minimum inhibitory concentration (MIC) for (1,3-thiazinan-4-one compounds) indicate that C_5 compound is best derivative that has inhibit growth of ***E. coli***.
Keywords: Imine, pathogenic bacteria, thiazinan, MIC
RESUMEN/ Este trabajo examinó los efectos de los átomos de halógeno sobre los compuestos de bencilideneanilina usando experimentalmente 1H NMR, FT IR, y mediante cálculos teóricos usando Density Functional Theory (DFT) en el nivel B3LYP / 6-311 + G (2d, p), utilizando el Paquete gaussiano 09W. Los compuestos se prepararon por condensación directa de anilina y sus derivados para halogenados con benzaldehído y sus derivados para halogenados, usando etanol como disolvente. Los compuestos preparados se caracterizaron por IR, 1H-NMR y sus puntos de fusión, y cambios en las propiedades físicas (electronegatividad, electrofilicidad, dureza, potencial de ionización, afinidad electrónica).
Palabras clave: bencilideneanilina, teoría funcional de la densidad, gaussiana, electrofilicidad, bases de Schiff.

1. Introduction

Imines are compounds containing C=N group, prepared by reaction of carbonyl compounds with amine compounds [1]. Various substituted thiazinan derivatives have been prepared and tested for their anti-tubercular activity [2][12][13][14]. Several thiazinan derivatives were synthesized from the reaction of imine and 3-mercaptoprpanoic acid using 1,4-Dioxane as a solvent [3].

2. Experimental

FT-IR spectra recorded at range 4000-400 cm^{-1} using Tensor 27 Bruker spectrometer. ^{1}H-NMR spectra were recorded on Bruker Ac-300MHz spectrometer.[15]

2. 1. General Procedure for the prepare of imine compounds C_1-C_4

Equal of aldehydes and amines were dissolved in 15 mL absolute ethanol and placed in round bottom flask , 2 drops of glacial acetic acid were added, the mixture refluxed for 3 hours, the solid separated and recrystallized from ethanol, physical properties given in table 1 [4].

2. 2. General Procedure for the prepare of 1,3-thiazinan-4-one compounds C_5-C_8

Equal of 3-mercaptopropanoic acid and imine compounds were dissolved in 10 mL of THF and placed in round-bottom flask, the mixture refluxed for 13 hour, solid product precipitated

filtered and recrystallized from ethanol, physical properties are given in table 2 [5].

2. 3. Anti-bacterial activity of prepared 1,3-thiazinan-4-one compounds C_5-C_8

Anti-bacterial activity for synthesized C_5-C_8 compounds evaluated against ***S. aureus*** **and** ***E. coli*** using well diffusion method on Mueller Hinton Agar, the diameter of hole is 6 mm. The dose is 6 µg $well^{-1}$ for synthesized 1,3-thiazinan-4-one compounds C_5-C_8 in DMSO. plates examined for measuring inhibition zone [6]. 50 µl DMSO was used as a negative control and 50 µg of Gentamycine per well was used as a positive control.

2. 4. Statistical Analysis

The statistical analysis have been performed by the GLM procedures of SAS [7]. It is worth noting that values between groups were compared by independent sample -f test and one- way ANOVA or so-called analysis of variance. The P values less than 0.05 or equal this value to have been evaluated (Duncan's multiple range test) as statistical significant [8].

3. Results and discussion

The best yield percentage of the prepared imine was for compounds C_2 and C_4, lower yield was for compound C_1 table 1, while best yield percentage for 1,3-thiazinan-4-one compounds was for C_6, lower yield was for C_8 table 2.

3.1. Characterization of prepared imine compounds C_1-C_4

Imine compounds were prepared from the reaction between available aldehydes and primary amines. FT-IR spectra showed C=N absorption bands at range 1600-1640cm^{-1} and the absorption bands of C-N at 1149-1170 cm^{-1}, C=C aromatic ring at 1578-1590cm^{-1} [9]. other bands values are listed in table 3.

3. 2. Characterization of prepared 1,3-thiazinan-4-one compounds C_5-C_8

1,3-thiazinan-4-one compounds were synthesized reaction of imines and 3-mercaptopropanoic acid. FT-IR spectra showed absorption bands at range 1656-1689 cm^{-1} attributed to C=O bonds, absorption bands at 636-713cm^{-1} attributed to C-S bond, absorption bands at 1151-1168cm^{-1} assigned to C-N bond, absorption bands at 1593-1607 cm^{-1} for C=C aromatic ring [9], table 4 and FT-IR spectra of C_7 and C_8, figure 1. It was observed presence of broad band at 2150-3380, this band probably of trace amount propanoic acid.

^{1}H-NMR spectrum for C_5 showed the chemical shifts (δ ppm): doublet at 1.66 for the 4H of the (2C$\underline{H}_2$S), doublet at 3.42 for the 4H of the (2C$\underline{H}_2$C=O), singlet at 4.30 for the H of the (N$\underline{H}$), singlet at 7.89 for the 2H of the (2C$\underline{H}$), multiplet at 6.88-7.for the 8H of aromatic protons, the spectrum of compound C_6 showed chemical shifts (δ ppm): singlet at 1.22 for the 12H of the (2N(C$\underline{H}_3$)$_2$), doublet at 2.87 for the 4H of the (2C$\underline{H}_2$S), doublet at 3.00 for the 4H of the (2C$\underline{H}_2$C=O), singlet at 8.60 for the 2H of the (2C$\underline{H}$), multiplet at 6.76-7.21 for the 16H of aromatic protons [10], see table 5 for (C_7-C_8), see ^{1}H-NMR spectra for C_7 and C_8, figure. It was observed presence of another signals, this signals probably of trace amount of initial materials.

Reaction between imines and 3-mercaptopropanoic acıd is given in figure 3.

Reaction progressed by ionic mechanism, through nucleophilic attack of lone pair for sulphur on carbon in azomethine group (C=N), proton transfer then nucleophilic attack of negative nitrogen on carbonyl group and release of water molecule led to cyclization. figure 4.

3. 3. The antibacterial activity and minimal inhibitory concentration of 1,3-thiazinan-4-one compounds C_5-C_8

Tables 6 and 7 explain the comparision between the inhibition of control in table 6 and the inhibition of 1,3-thiazinan-4-one compounds in table 7.

Higher zone of inhibition was 22.0 mm by compounds C_7 against *S. aureus* followed 20.0 mm by C_5 compound against ***E. coli*** for higher concentration 100%. For the minimal inhibitory concentration was 6mm (45%), 7mm (35%), 7mm (30%) and 7mm (35%) against *S. aureus* by C_5, C_6, C_7 and C_8 compounds respectively and 5mm (5%), 8mm (45%), 5mm (30%) and 5mm (40%) against ***E. coli*** by C_5, C_6, C_7 and C_8 compounds respectively, table 7.

The results showed biological activity at significant differences ($P \leq 0.05$) of C1 compound in mean inhibition zone (10.917 ± 1.239), see table 8.

The job of these might be connected and obliterated the cell wall of organisms or ceased replication of microbial DNA [11]. The variations in the inhibitory impact identified with chemical preparation of each compound as above, figure 5. as a best hindrance model. The positive control (Gentamycin) showed the inhibition zone approx. 24 mm against ***E. coli***

and 28 mm against ***S. aureus*** while the negative control (DMSO) did not show any inhibition zone.

3. 4. Tables

Table 1. Physical properties and structure for imine compounds C1-C4

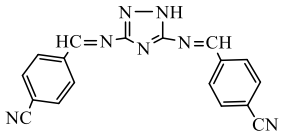
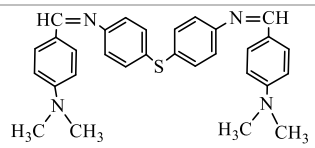
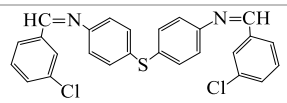
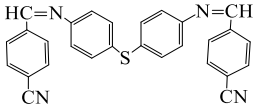
Comp.	Structure	Nomenclature	Yield %	m. p. °C	Color
C_1		4,4'-((1E,1'E)-((1H-1,2,4-tri azole-3,5-diyl) bis(azaneylylidene))bis(methaneylylidene)) dibenzonitrile	75	231-234	Light Yellow
C_2		4,4'-((1Z,1'Z)-((thiobis(4,1-phenylene))bis (azaneylylidene))bis(methaneylylidene))bis (N,N-dimethylaniline)	86	133-134	Light white
C_3		(1Z,1'Z)-N,N'-(thiobis(4,1-phenylene))bis (1-(3-chlorophenyl)methanimine)	83	144-147	Bright Light Yellow
C_4		4,4'-((1Z,1'Z)-((thiobis(4,1-phenylene))bis (azaneylylidene))bis(methaneylylidene))dib enzonitrile	89	167-168	Bright Light Yellow

Table 2. Physical properties and structure for 1,3-thiazinan-4-one compounds C_5-C_8

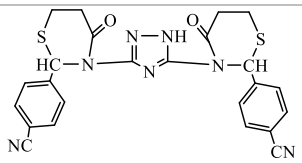
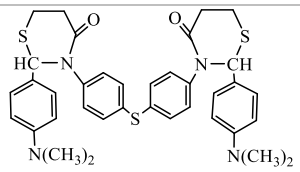
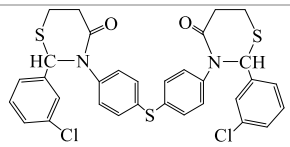
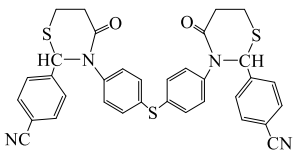
Comp.	Structure	Nomenclature	Yield %	m. p. °C	Color
C_5		4,4'-((1H-1,2,4-triazole-3,5-diyl)bis(4-oxo-1,3-thiazinan-4-one))dibenzonitrile	77	177-178	Red
C_6		3,3'-(thiobis(4,1-phenyl ene))bis(2-(4-(dimethyl amino)phenyl)-1,3-thiazinan-4-one)	87	91-93	Dark Yellow
C_7		3,3'-(thiobis(4,1-phenyl ene))bis(2-(3-chloroph enyl)-1,3-thiazinan-4-one)	80	131-133	Light brown
C_8		4,4'-((thiobis(4,1-phe nylene))bis (4-oxo-1,3-thiazinan-4-one))di benzonitrile	74	123-125	Light Yellow

Table 3. FT-IR of imine compounds C_1-C_4

	FT-IR, ν(cm^{-1})						
Comp.	**C=N**	**C-N**	**C=C** Arom.	**C-H** Arom.	**C-H** Asymm.	**C-H** Symm.	**Others**
C_1	1600	1149	1588	3010	--	--	CN: 2231
C_2	1620	1161	1578	3021	2991	2911	C-S: 682

C_3	1635	1170	1584	3078	--	--	C-Cl: 946 C-S: 677
C_4	1640	1163	1590	3090	--	--	CN: 2259 C-S: 685

Table 4. FT-IR of the 1,3-thiazinan-4-one compounds C5-C8

FT-IR (KBr), ν(cm^{-1})								
Compound	**C=C** Arom.	**C-S**	**C-H** Arom.	**C-N**	**C=O**	**C-H** Asymm.	Symm.	**Others**
C_5	1607	713	3016	1151	1689	2922	2877	CN: 2228
C_6	1597	713	3092	1168	1656	2920	2852	--
C_7	1593	692	3020	1152	1689	2921	2849	C-Cl: 927
C_8	1589	636	3019	1151	1689	2921	2884	CN: 2228

Table 5. The 1H-NMR of the 1,3-thiazinan-4-one compounds C5-C8 in DMSO

Comp.	**Chemical Shift δ ppm**
C_5	Doublet at 1.66 for (4H, 2CH_2S), doublet at 3.42 for (4H, 2CH_2C=O), singlet at 4.03 for (H, NH), singlet at 7.75 for (2H, 2CH), multiplet at 6.88-7.31 for (8H, aromatic protons)
C_6	Singlet at 1.22 for (12H, 2N(CH_3)$_2$), doublet at 2.87 for (4H, 2CH_2S), doublet at 3.44 for (4H, 2CH_2C=O), singlet at 8.06 for (2H, 2CH), multiplet at 6.76-7.68 for (16H, aromatic protons)
C_7	Doublet at 2.52 for (4H, 2CH_2S), doublet at 3.00 for (4H, 2CH_2C=O), singlet at 7.77 for (2H, 2CH), multiplet at 6.77-7.20 for (16H, aromatic protons)
C_8	Doublet at 2.54 for (4H, 2CH_2S), doublet at 2.90 for (4H, 2CH_2C=O), singlet at 8.08 for (2H, 2CH, multiplet at 7.56-7.98 for (16H, aromatic protons)

Table 6. Inhibition zone of the Gentamycin and DMSO

Pathogenic bacteria	**Zone inhibition** (mm)	
	Gentamycin 50 µg/well	**DMSO** 50 µg/well
E. coli	24	0
S. aureus	28	0

Table 7. Diameter zone of inhibition (mm) of the 1,3-thiazinan-4-one compounds C5-C8

Compound	**Pathogenic bacteria**	**5%**	**10%**	**15%**	**20%**	**25%**	**30%**	**35%**	**40%**	**45%**	**50%**	**75%**	**100%**
C_5	*S. aureus*	-ve	-ve	ve	-ve	ve	-ve	-ve	-ve	6mm	7mm	7mm	12mm
C_5	*E. coli*	5mm	5mm	8mm	10mm	10mm	10mm	11mm	11mm	12mm	12mm	17mm	20mm
C_6	*S. aureus*	-ve	-ve	ve	-ve	ve	-ve	7mm	8mm	10mm	11mm	14mm	14mm
C_6	*E. coli*	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	8mm	12mm	12mm	13mm
C_7	*S. aureus*	-ve	-ve	-ve	-ve	-ve	7mm	7mm	10mm	13mm	15mm	19mm	22mm
C_7	*E. coli*	-ve	-ve	-ve	-ve	-ve	5mm	7mm	10mm	10mm	12mm	15mm	18mm
C_8	*S. aureus*	-ve	-ve	-ve	-ve	-ve	-ve	7mm	10mm	10mm	11mm	15mm	15mm
C_8	*E. coli*	-ve	-ve	-ve	-ve	-ve	-ve	-ve	5mm	10mm	14mm	14mm	16mm

Table 8. Statistical Analysis of the effect of 1,3-thiazinan-4-one compounds C5-C8 against S. aureus and Ecoli

Pathogenic bacteria	Compounds				*P*-value
	Compound 1 (C_5)	Compound 2 (C_6)	Compound 3 (C_7)	Compound 4 (C_8)	
S. aureus	2.667 ± 1.208*	5.833 ± 1.987	7.750 ± 2.329	5.667 ± 1.814	N.S.**
E. coli	10.917 ± 1.239 a	3.750 ± 1.633 b	6.417 ± 1.892 ab	4.917 ± 1.912 b	0.0246

* Means ± Standard Error.

** N.S.: Non Significant

a, b, c: Different letters refer to significant differences between compounds at probability value (P≤0.05).

3. 5. Figures

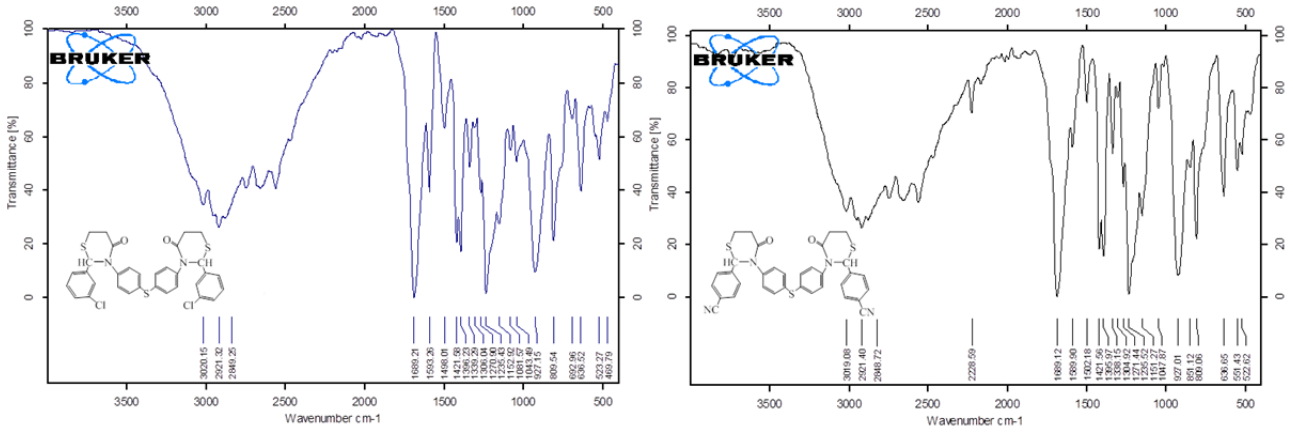


Figure 1. FT-IR spectra of C7 and C8

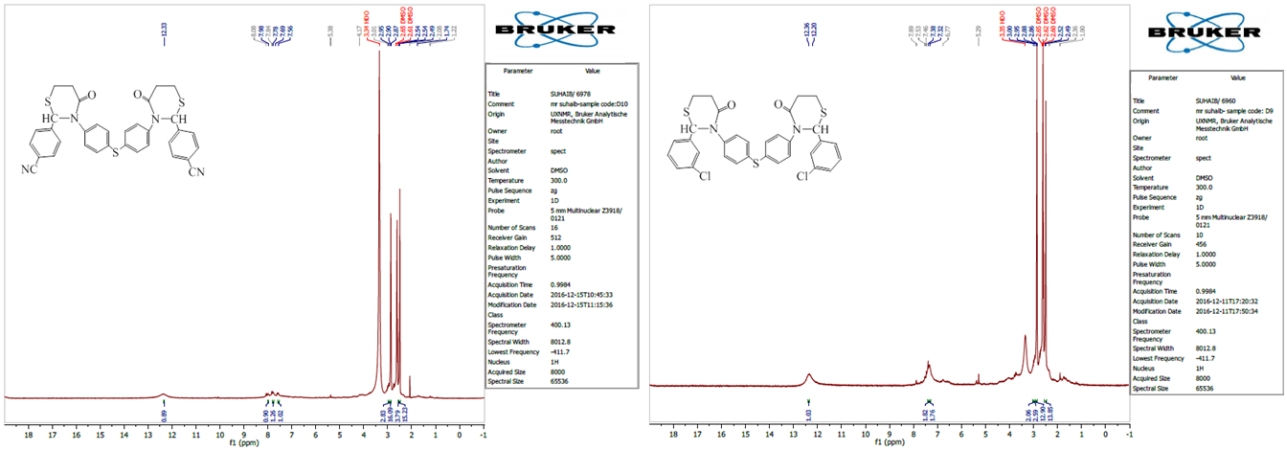


Figure 2. 1H-NMR Spectra of C7 and C8

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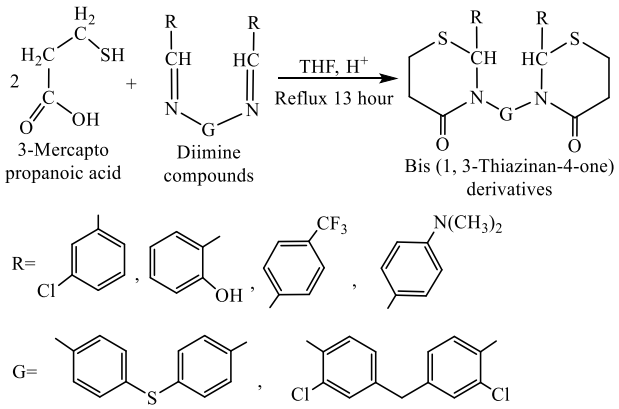

Figure 3. Synthetic route for synthesis of 1,3-thiazinan-4-one compounds

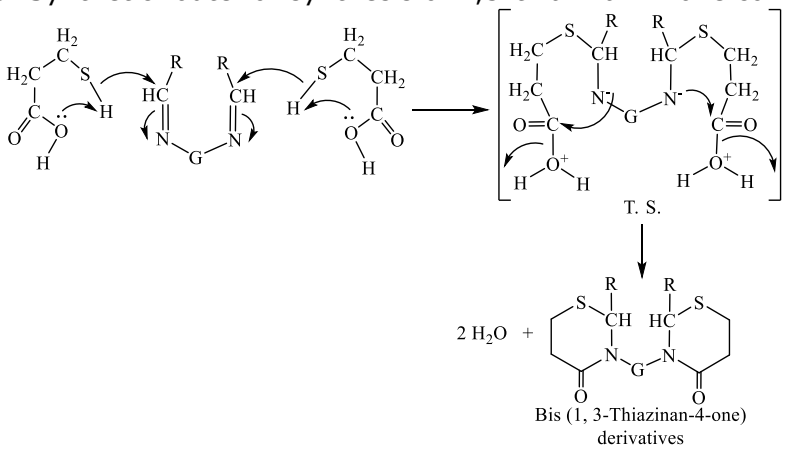

Figure 4. Formation mechanism for 1,3-thiazinan-4-one compounds

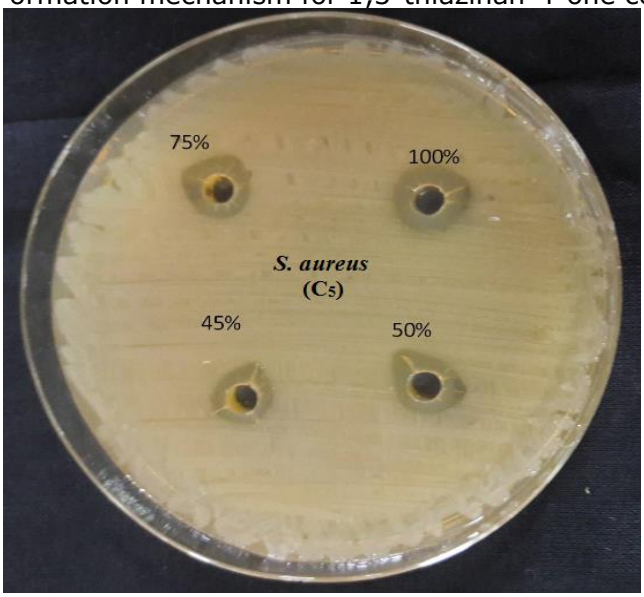

Figure 5. Antimicrobial activity of the C5 derivative in DMSO against S. aureus

4. Conclusions

Sulphur six- membered heterocycles compounds (1,3-thiazinan-4-one compounds) has been achieved by the reaction of (S-H) bond for 3-mercaptopropanoic acid with azomethine group (C=N) in imines compounds, characterized using FT-IR and 1H-NMR the electronpair of oxygen atom of (O-H) in 3-mercaptopropanoic acid with the proton in the same compound after production of transition state. C5 is the best derivative that has inhibit the growth of E. Coli.

Acknowledgments

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5. References

1. C. Nastasa, D. Vodnar, I. Ionu ¸ A. Stana, D. Benedec, R. Tamaian, O. Oniga, B. Tiperciuc, Antibacterial Evaluation and Virtual Screening of New Thiazolyl-Triazole Schiff Bases as Potential DNA-Gyrase Inhibitors, Int. J. Mol. Sci. 19 (2018) 1-18.
2. T. Srivastava, W. Haq and S. Katti, Carbodiimide mediated synthesis of 4-thiazolidinones by one-pot three-component condensation, Tetrahedron, 58 (2002) 7619-7624.
3. A. Ahmed, Synthesis and Characterization of New Heterocyclic Compound From Schiff Bases and Various Nucleophilic Electrophilic Reagents, Thesis, University of Anbar, College of Education for Pure Science, (2014) 79.
4. O. Abid, H. Tawfeeq, R. Muslim, Synthesis and Characterization of Novel 1,3-oxazepin-5(1H)-one Derivatives via Reaction of Imine Compounds with Isobenzofuran-1(3H)-one, Acta Pharm. Sci. 55 (2017) 43-55.
5. H. Sadiq, Synthesis And Characterization of Novel 1,3-Oxazepine Derivatives From Aminopyrazine, World J. Pharm. Pharm. Sci. 6 (2017) 186-198.
6. M. Owaid, J. Raman, H. Lakshmanan, S. Al-Saeedi, V. Sabaratnam, I. Al-Assaffii, Mycosynthesis of silver nanoparticles from Pleurotus cornucopiae var. citrinopileatus and its inhibitory effects against Candida sp., Mater. Lett. 153 (2015) 186-190.
7. SAS Institute INC. SAS/STAT User's Guide: Version 9.1. (Cary, NC, SAS Institute, Inc.), (2002).
8. Osamah Ibrahem Khalaf, Ghaidaa Muttasher et al., "Improving video Transmission Over Heterogeneous Network by Using ARQ and FEC Error Correction Algorithm", vol. 30, no.8, pp.24-27, Nov 2015
9. R. Silverstein, F. Webster and D. Kiemle, Spectrometric identification of organic compounds, 7th ed. John Wiley and sons, Inc., London, UK. 2005, pp. 72-126.
10. L. Yadav, Organic spectroscopy, 1st ed. Springer Science + Business Media Dordrecht. 2005, pp. 133-193.
11. Osamah Ibrahim Khalaf, Ghaida Muttashar Abdulsahib and Muayed Sadik, 2018. A Modified Algorithm for Improving Lifetime WSN. Journal of Engineering and Applied Sciences, 13: 9277-9282
12 Osamah Ibrahim Khalaf, Bayan Mahdi Sabbar''An overview on wireless sensor networks and finding optimal location of node'',Periodicals of Engineering and Natural Sciences, Vol 7, No 3 (2019)
13 Ayman Dawood Salman1, Osamah Ibrahim Khalaf and Ghaida Muttashar Abdulsahib, 2019. An adaptive intelligent alarm system for wireless sensor network. Indonesian Journal of Electrical Engineering and Computer Science, Vol. 15, No. 1, July 2019, pp. 142~147
14 Ogudo, K.A.; Muwawa Jean Nestor, D.; Ibrahim Khalaf, O.; Daei Kasmaei, H. A Device Performance and Data Analytics Concept for Smartphones' IoT Services and Machine-Type Communication in Cellular Networks. Symmetry 2019, 11, 593.
15 GHAIDA MUTTASHAR ABDULSAHIB and OSAMAH IBRAHIM KHALAF, 2018. AN IMPROVED ALGORITHM TO FIRE DETECTION IN FOREST BY USING WIRELESS SENSOR NETWORKS.International Journal of Civil Engineering & Technology (IJCIET) - Scopus Indexed.Volume:9,Issue:11,Pages:369-377.