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Synthesis, characterization and evolution of biological activity for new heterocyclic derivatives Schiff bases

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Abstract

The search included synthesis of some Schiff bases by condensation reactions of sulfadiazine with four aldehydes (2-bromo-5-hydroxybenzaldehyde, 4-N,N-dimethylaminobenzaldehyde,na phthaldehyde, 4-bromobenzaldehyde) to obtain Schiff bases (1-4), then synthesis of four new Thiozolidinones from reaction of 2-mercapto acetic and Schiff bases was carried out. The target compounds were characterized by spectral means including (FT-IR, and Uv-visible in adding of CHN elemental analysis, and some chemo-physical properties, the biological activity study toward two types of bacteria.

Key word: sulfadiazine, Schiff base, Thiozolidinones, heterocyclic compounds, biological activity.

INTRODUCTION

Heterocyclic compounds are cyclic compounds with hetro atoms (one or more) in the ring, and these compounds consider one of important kind of organic compounds because of their applications in industrial studies and drug designe[1-3]. In nature these compounds are widespread occurrence and found in natural products such as nucleic acids, plant alkaloids and chlorophyll[4]. Thiozolidinones are heterocyclic compounds with five member ring[5], which contain sulfur atom, nitrogen atom and three carbons atoms, these heterocyclic compounds synthesis by the reaction of 2-mercaptoacitic acid with imines (Schiff base) derivatives[6,7]. Sulfadiazine is a sulfonamide antibiotic which use for treated urinary infection (utl), it is world health organization list of essential medicine, that work by elimination bacteria which cause infection with stop the production foliate in cell of bacteria[8]. Schiff bases that prepared from aromatic amines with aromatic aldehydes posses a wide uses of applications for variety field as sulfa-drug Schiff bases have antimicrobial activity[6], anticonvulsant activity[9], anti-inflammatory activity[10], antikinetopla stid ant mitotic activaty[11], antitumor activaty[12]. The present work involved synthesis Schiff base from Sulfadiazine drug and then synthesis from it. Thiozolidinones compounds and test their bioactivity sensitive.

EXPERIMENTAL

The chemicals that we used in this study were from (BDH, Fulka, Sigma aldrich, sccarel) and without any purification. The melting points were measured by using hot stage Gallen Kamp melting point apparatus and they were uncorrected, Fourier Transform infrared SHIMADZU (8300) (FT-IR) infrared spectrophotometer, KBr disc, University of Almuthana, CHN Perkin Elmer, UV-vis were recorded using a Perkin Elmer Lamb Double Beam 35 UV-Visible spectrophotometer, H-NMR in DMSO-d_6 at 500MH_Z in Iran-Tehran university. TLC Chromatography was use to mount reactions, with developed by iodide vapor.

General Preparation of Schiff bases (1-4)

Schiff base are synthesized by reaction of sulfadiazine (1mmol) in 10 mL ethanol, and deferent aldehydes (1mmol), in 10 mL ethanolic solution, 2 drops from glacial acetic acid was added, then pout to reflux for 6 h, the end of reaction checked by TLC. The precipitate was filtered and re-crystallization from hot ethanol[13].

4-(5-beromo-2-hydroxybenzylideneamino-N-(pyrimidin-2-yl) benzenesulfona mide:(1)

T.L.C. (ethyl acetate: hexane) (1:1) I.R spectra in cm^{-1} ,(O-H str. 3439), (N-H ssulfunyl 3115), (, (C-H 2902),(C=N str. 1622), (C=C aromatic1506), (C=N str aromatic 1556), (N-H ben. 1477), (NH-S=O 1392asy, 1154sy), (C-S 881), (C-Br 1062), (S-N 920), (C-H ben. 779), (C=C ben. 579). (Rf, 0.55). C.H.N. CAL.%/FON.%, C:47.12/47.10, H:3.03/3.05, N:12.93/12.90, O:11.08/11.07, S:7.40/7.44.

E-4-(naphthalene-1-yl-methyleneamino-N-(pyrimidin-2-yl) benzenesulfona mide:(2)

T.L.C. (ethyl acetate: hexane) (1:1). Ft-IR spectrum appear ,(N-H 3188), (C-H aromatic 2971),(C=N str. 1600) , (C=C aromatic 1506), (C=N aromatic.1559), (N-H ben. 1459), (NH-S=O 1300 as, 1178 sy), (C-S 893), (S-N 977), (C-H bending 785), (C=C bending 628) (Rf,0.4),C.H.N.CAL .%/FON. %,C:64 .93/64. 96,H:4 .15/4.10 ,N:14.42 /14.39,O:8.24/8.22,S:8.25/8.27.

4-(4-bromobenzylideneamin)-N(pyrimidin-2-yl)benzenesulfonamide:(3)

TLC. (ethyl acetate: hexane) (1:1) , The IR spectra play, (N-H 3405), (C-H 2978),(C=N st.1599), (C=C st.aromatic1581), (C=N aromatic 1550), (N-H ben. 1521), (NH-S=O 1326 asy,1161sy),(C-S 869), (C-Br 1066), (S-N 948),(C-H ben. 792),(C=C ben.686). (Rf, 0.46).C.H.N. CAL.%/FON.%,C: 48.93/48.90, H: 3.14/3.18, N: 13.43/13.48, O: 7.67/7.63, S: 7.68/7.64.

E-4-(-4-(dimethylamine)benzylidenamino)-N-(pyrimidin-2-yl) benzenesulfonamide:(4)

TLC. (ethyl acetate: hexane) (1:1), Ft-IR S pectrum spectra play (N-H 3078), (C-H 2937, 2874 asy., 2808 sy.), (C=N imine 1618), (C=C aromatic 1570), (C=N pyrimidine 1581), (N-H ben. 1495), (NH-S=O 1410 asy, 1161 sy), (C-S 844), (C-N(CH_3)$_2$ 1342), (S-N 947), (C-H ben. 798), (C=C ben. 640). (Rf, 0.28), CHN CAL. % / FON . % ,C: 59.82 /59.85, H: 5.02/5.06, N: 18.36/ 18.39, O: 8.41/8.34, S: 8.41/8.44.

Synthesis of thiazolidine compounds (5-8)

The general procedure for synthesis of thiazolidine**.** (0.01mole) of 2-mercapto acetic acid was added drop wise to (0.01mole)of Schiff bases(1-4) in dry benzene, the mixture was refluxed for 24 h., the solvent was evaporated and the precipitate was recrystallized from ethyl acetate and benzene .The progress of reaction was checked by TLC[14].

4-(2-(5-bromo-2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-N-(pyrimidin-2-yl)-benzenesulfonamide :(5)

TLC. (ethyl acetate: hexane) (1:1), the IR spectra in cm^{-1} , (O-H str. 3466), (N-H 3381), (C-H 2939), disappearance to (C=N str. 1622) band appear to (C=O str. 1692) , (C=C aromatic1492), (C=N aromatic 1582), (N-H ben. 1440), (NH-S=O 1325 asy, 1155 sy), (C-S 943), (C-Br 1094), (S-N 943), (C-H ben. 799), (C=C ben. 572), (C-S-C str.681) . (Rf, 0.4) C.H.N. CAL.%/FON.%,C:44.98/44.93, H:2.98/2.94, N:11.04/11.08, O:12.61/12.66, S:12.64/12.69.

4-(2-naphthalen-1-yl))-4-oxothiazolidin-3-yl)-N-(pyrimidin-2-yl)-benzenesulfonamide:(6)

TLC.(ethyl acetate: hexane) (1:1), Ft-IR spectrum show,(N-H 3423), (C-H 2937), disappearance to(C=N str. 1600) band appear at (C=O str.1653), (C=C aromatic1508), (C=N aromatic.1595), (N-H ben. 1492), (SO2 1325asy, 1188sy), (C-S 845), (S-N 943), (C-H bending 796), (C=C bending 682), (C-S-C str.719). (Rf, 0.36). C.H.N. CAL.%/FON.%, C:59.72/59.74, H:3.92/3.96, N:12.11/12.16, O:10.38/10.32, S:13.86/13.63.

4-(2-(4-bromophenyl)-4-oxothiazolidin-3-yl)-N-(pyrimidin-2-yl)-benzenesulfonamide:(7)

TLC.(ethyl acetate: hexane) (1:1) ,The Ft-IR show ,(N-H str 3327), (C-H 2924),), disappearance to(C=N str. 1599) appeared to (C=O str.1710), (C=C aromatic1595), (C=N aromatic1568), (N-H ben. 1534), (NH-S=O 1304 asy, 1151 sy), (C-S 864), (C-Br 1061), (S-N 943), (C-H ben. 794), (C=C ben. 668), (C-S-C str.729). (Rf, 0.21), C.H.N. CAL.%/FON.%, C:46.44/46.48, H:3.08/3.03, N:11.40/11.45,O:9.77/9.79,S:13.05/13.02.

4-(2-(4-dimethylamino)phenyl)-4-oxothiazolidin-3-yl)-N-(pyrimidin-2-yl) benzenesulfonamide:(8)

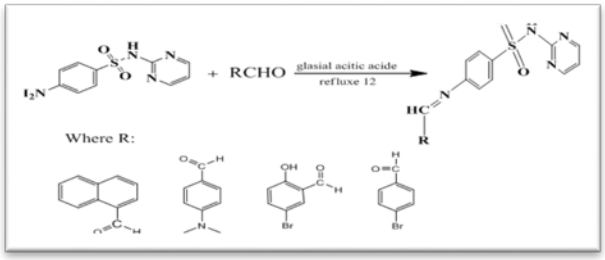
T.L.C. (ethyl acetate: hexane) (1:1) (Rf, 0.32).The IR Spectrum show (N-H str 3271), (C-H aromatic 2937, 2835, 2766), disappearance of (C=N imine 1618) and appearance of (C=O str.1647), (C=C aromatic 1535), (C=N pyrmidine 1470), (N-H ben. 1440), (NH-S=O 1416asy, 1166sy), (C-S 850), (C-N(CH_3)$_2$ 1344), (S-N 959), (C=C ben. 640),(C-S-C str. 719). C.H.N. CAL. %/FON. %, C: 55.37 /55.33, H:4.65/4.69, N:15.37/15.34, O:10.54/10.50, S:14.08/14.04.

The bioactivity test

The antimicrobial activity for the compound under test was determined by disk agar diffusion method, the samples that we tasted dissolved in DMF (this solvent has no inhibition activity) which used as a negative control and standard disk Streptomycin as positive control, with using two kind of bacterial +G (bacillus) and –G (Escherichia Coli) in two concentration (4mml,8 mml) of these compound ,then makes disks from filter paper (disk per compound) and impregnated by equal amount (0.1ml) from each samples of compounds, and carefully put on the incubated agar surface .The plates was stored in 37°C to 24h,[15,16] table (4) play the results that we found .

RESULTS AND DISCUSSION

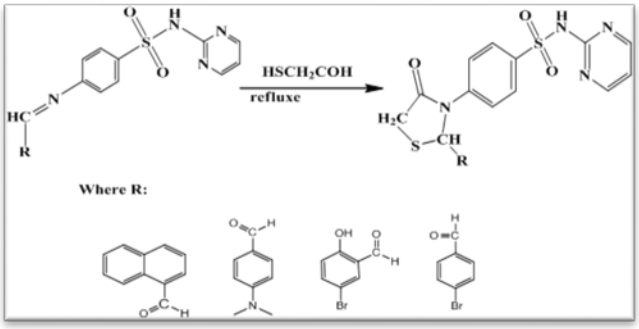
Schiff base compounds was prepared by condensation of Sulfadiazine with different aromatic aldehydes (2-hydroxy-5-bromo benzaldehyde, 4-N,N-dimthyl amino benzaldehyde ,naphtha ldehyde, 4-bromo benzaldehyde), in ethanolic solution with using glacial acetic acid (2-drops) to catalyst the reaction, and refluxing as explained in the following eqution **(1).** The synthesized compounds (1-4) are diagnoses with sharp m.p., Uv-vis spectrum, FT-IRspectrum C.H.N.analysis. The FT.IR showed different bands but the important are in the reign (1622-1485 cm^{-1}) to (C=N) imine stretching vibration, with disappeared (NH) stretching vibration of amine, (C=O) for aldehydes. The other important bands are play in synthesis procedure, Table (3) show more data for the compounds. Table **(1)** showed chemical and physical properties of the compounds.



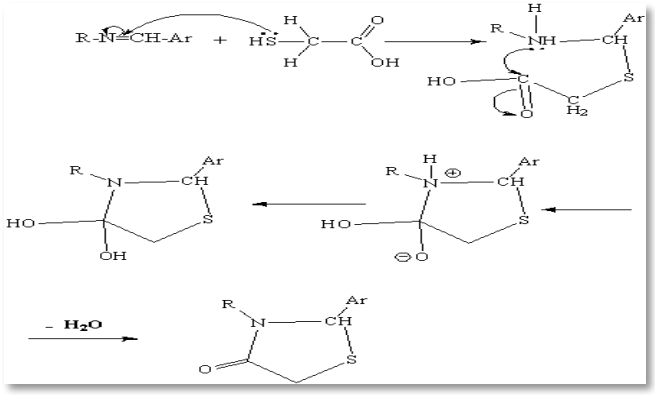
Equation (1) the preparation of Schiff base

Thiazolidinones have a wide range of biological activity and for this reason these compounds play a vital role industrial due to importance as stabilizer for polymeric material [17]. Using Schiff bases in preparing heterocyclic compounds with nitrogen atoms, it has a great success. The thiazolidinone compounds (5-8) prepare with reaction equal moles of Schiff bases (1-4) in dry benzene , and then added thioacetic acid as below eqution (2) . The synthesized derivatives were characterized by their m.p., FT-IR, Uv-vis besides the C.H.N analysis table (2),

and TLC. A result agrees for suggested structures .The Ft-IR spectrum for derivatives (5-8), shows appearance of stretching vibration band for (C=O) at (1647-1710cm^{-1})belong to thiazolidinone which refer to cyclization step was done, as in equation (2) , also shows bands at (2978 , 2937 and 2810) to vibration of (C-H) aromatic . Some aromatic system bands appeared at (1533-1595) for ν (C=C), (1600-1622) bands for ν (C=N) of triazole ring. Besides the disappearance the bands of the υ (C=N) group for Schiff base. Bands at (705-798 cm^{-1}) belonged to υ(C-S-C), bands at (908-958cm^{-1}) for stretching vibrations ν (S-N). The scheme below (3) explains the mechanism of the reaction to synthesis of to thiazolidinone.



Eqution (2) synthesis of (5-8) compounds



Scheme (3) mechanism of the reaction

The UV-VIS spectrum

The Uv-vis spectrum in methanol in the region (200-1100nm) and it play peaks of the compounds under analysis , for the derivative of thiazolidinone (5) two peaks appear one at(212 nm) due to n-σ^* which may belong to N,S atoms and at (270 nm) due to n-π^* for (C=O), the derivative of thiazolidinone (6) have two beaks one at (201 nm) due to n-σ^* N,S atoms and the second at (270 nm) due to n-π^* for (C=O), the (7) derivative of thiazolidinone show three peaks at (214 nm) due to n-σ^* for the N,S atoms, (271 nm) due to n-π^* for (C=O), the last one at (355 nm) may be due to brome which is electron-donating that do bathochromic hepsocheomic shifted , the(8) derivative of thiazolidinone show two peaks at (212 nm) due to n-σ^* for N,S atoms and at (270 nm) due to n-π^* for (C=O) .

The H-NMR Spectrum

The H-NMR spectrum for selective compounds in DMSO-d_6 at 500 M_{HZ} measured in Iran University, the H-NMR for compound (5) fig.(9) showed multiplied signals at (7.4 – 7.9 ppm) due to aromatic protons and singlet signal at(6 ppm)due to (O-H) group, the (-CH_2) of thialozidene ring signal at (4ppm) and for (-CH) for the same ring signal at(6.5-6.6ppm), weak signal at (4.5ppm) for (-NH), the(-CH=CH-CH=) of pyrimidine multiply signal at (8.5). compound (6) fig.(10) appeared weak signal for (-NH) at (4.3ppm), (-CH_2-) of thiazol ring at (3.8ppm) multiply signals and (-CH-) methine at (6.5-6.6ppm), the aromatic (-CH-) signal at (7.5-8ppm) multiply signals, also signals for naphthalene ring at(7,7.5,7.9ppm), (=CH-) of pyrimidine at(8.5ppm) with the signal for (-CH=) at(6ppm).

The bioactivity testing

The activity of any chemical compounds against microorganism is a complex combination of some factors which are decrease the work of derivatives, involved with connect to hydrogen bond out of (N-C, or C=O), with center of the bacteria constituent, produced interferences to bacteria process[18]. In vitro biological activity of studied derivatives showed mixed results as in table (4) compound (5) was effected on *E.Coli* more than in *Bacillus Cereus*, as well compounds (6) which was close to compound (5) in results, either the compound (7) has high activity towered the two types of bacterial, compound (8) has good activity for *E.Coli* than the *Bacillus Cereus*. The activity of compounds due to they have N, S,O atoms in their structure .

Table (1): The physical properties for the synthesis derivatives

Co.n.	For.	Col.	m.wt g/mol	M.P. °C	%
Sab.	$C_{10}H_{10}N_4O_2S$	white	250.28	252-256	-
1	$C_{17}H_{13}BrN_4O_3S$	Light orange	433.28	287-298	60
2	$C_{21}H_{16}N_4O_2S$	Of white	388.44	320-322	53
3	$C_{17}H_{13}BrN_4O_2S$	Of white	417.28	295-297	73
4	$C_{19}H_{19}N_5O_2S$	Light yellow	381.45	299-301	95
5	$C_{19}H_{15}BrN_4O_4S_2$	Orange	507.38	344-346	51
6	$C_{23}H_{18}N_4O_3S_2$	brown	462.54	360-362	59
7	$C_{19}H_{15}BrN_4O_3S_2$	Yellow	491.38	343-345	64
8	$C_{21}H_{21}N_5O_3S_2$	Goldish	455.55	352-354	84

Table (2): The CHN Analysis data

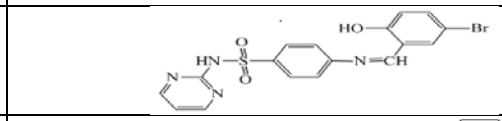
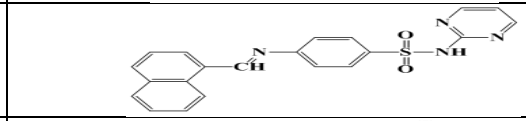
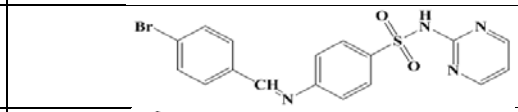
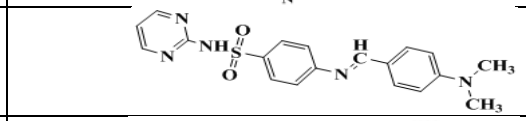
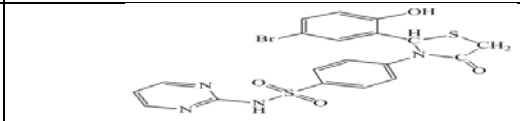
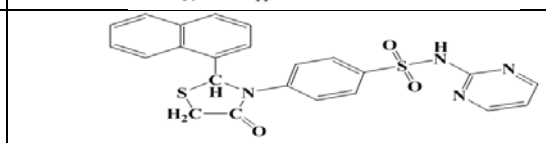
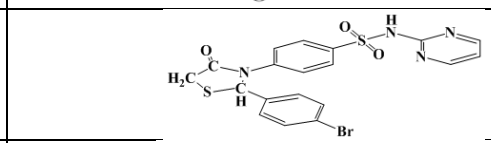
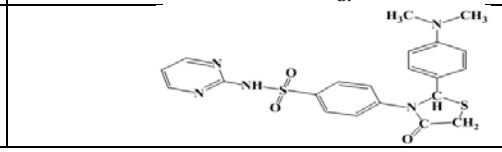
Co. No.	Compd. Structure	Element analysis cal./obs. C	H	N	O	S
1		47.12 47.10	3.03 3.05	12.93 12.90	11.08 11.07	7.40 7.44
2		64.93 64.96	4.15 4.10	14.42 14.39	8.24 8.22	8.25 8.27
3		48.93 48.90	3.14 3.18	13.43 13.48	7.67 7.63	7.68 7.64
4		59.82 59.85	5.02 5.06	18.36 18.39	8.39 8.34	8.41 8.44
5		44.98 44.93	2.98 2.94	11.04 11.08	12.61 12.66	12.64 12.69
6		59.72 59.74	3.92 3.96	12.11 12.16	10.38 10.32	13.86 13.63
7		46.44 46.48	3.08 3.03	11.40 11.45	9.77 9.79	13.05 13.02
8		55.37 55.33	4.65 4.69	15.37 15.34	10.54 10.50	14.08 14.04

Table (3): FT-IR spectral data for the synthesis thiazolidinones compounds

Co.n.	V(C=N) Pyramiding	V(C=N) imine	V(C=O)str.	V(C-H) Aromatic	V(SO2) str.	V(N-H) Sulfone
1	1556	1622	-	2902	1392	3115
2	1562	1616	-	2970	1300	3188
3	1536	1600	-	2978	1406	3404
4	1581	1618	-	2937	1342	3178
5	1581	-	1692	2939	1325	3381
6	1595	-	1653	2937	1325	3423
7	1614	-	1710	2924	1363	3327
8	1535	-	1647	2937	1344	3271

Table (4): H-NMR spectral data (δppm) for selected compounds

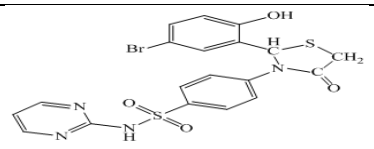
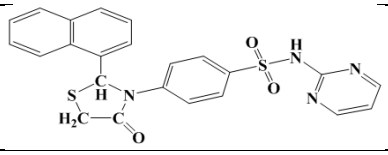
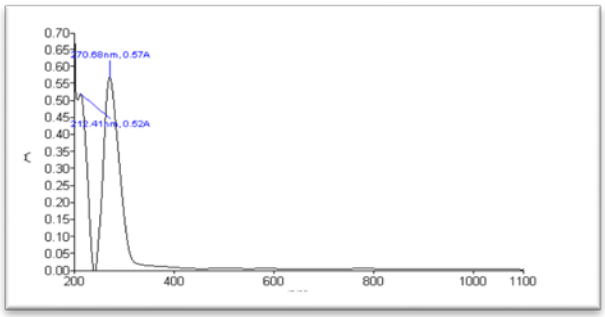
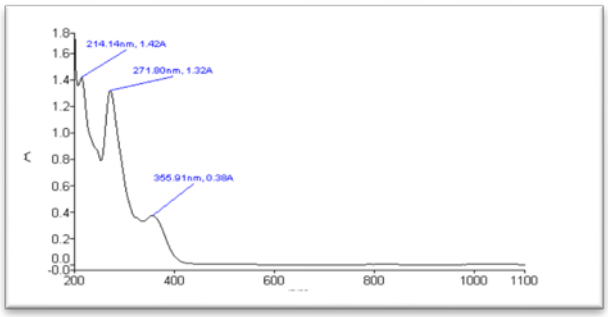
Co.n.	Structure	H-NMR spectral data (δppm)
5		(-NH) at (4ppm), (-CH_2) of thiazol ring at(3.8ppm), (-CH)of thiazol ring at(6.5ppm**)**
6		(-NH) at (4.3ppm), (-CH_2-) of thiazol ring at (3.8ppm), and (-CH-) methine at (6.5-6.6ppm).

Table (5): The bioactivity results

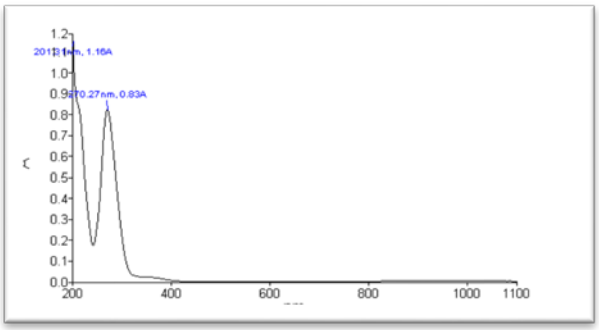
Comp. No.	Zone inhibition in (mm)			
	Bacillus Cereus		Escherichia col.	
	4mml	8mml	4mml	8mml
5	7	10	11	15
6	5	7	13	18
7	17	20	15	19
8	8	11	17	20
Streptomycin	23	25	22	24
DMF/control		-	-	



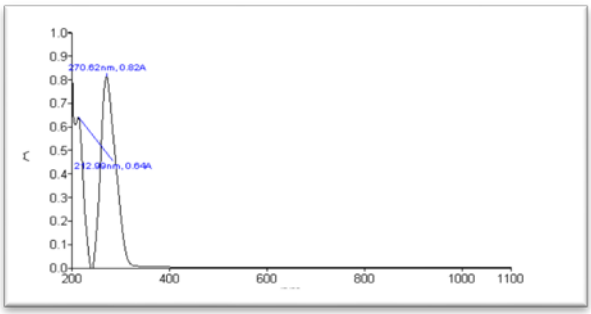
UV-vis of compound 5



UV-vis of compound 7



UV-vis of compound 6



UV-vis of compound 8

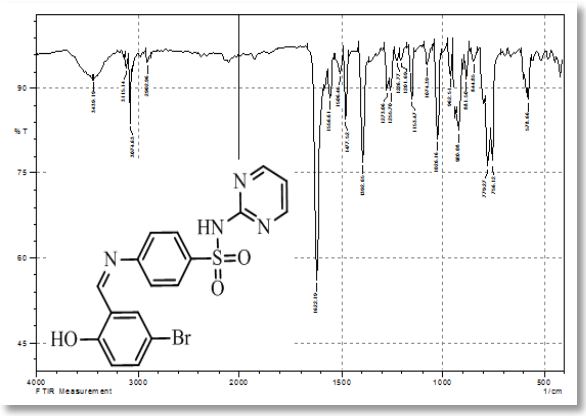


Fig. (1) The FT-IR spectrum for Schiff base(1)

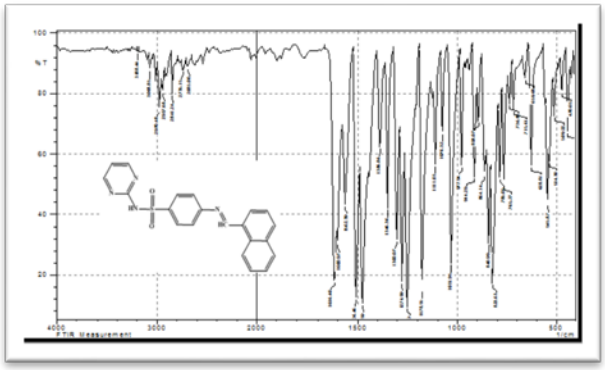


Fig. (2) The FT-IR spectrum for Schiff base (2)

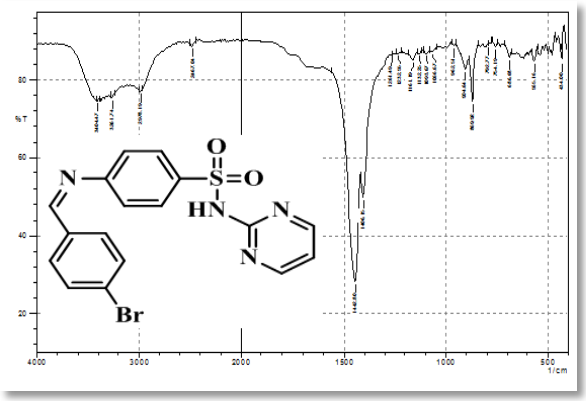


Fig. (3) The FT-IR spectrum for Schiff base (3)

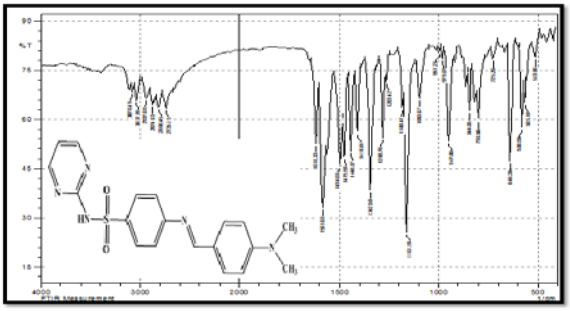


Fig. (4) The FT-IR spectrum for Schiff base (4)

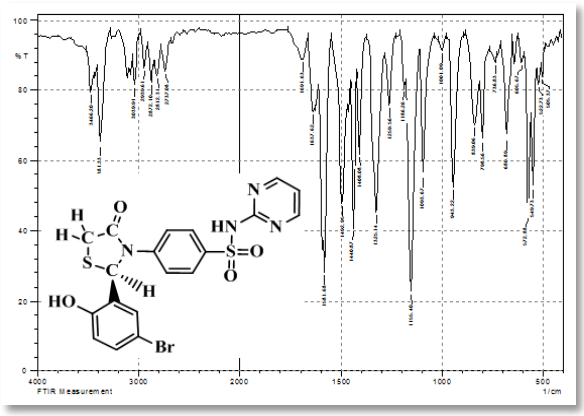


Fig. (5) The FT-IR spectrum for thiazolidine (5)

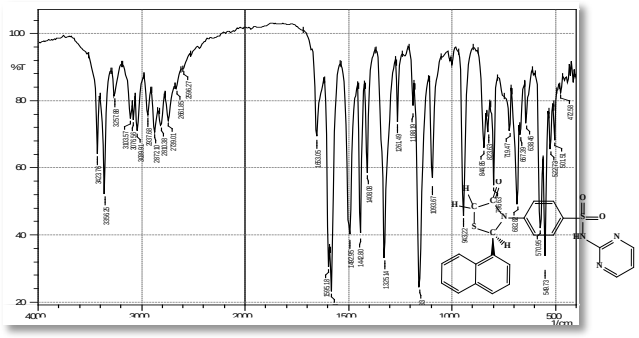


Fig. (6) The FT-IR spectrum for thiazolidine (6)

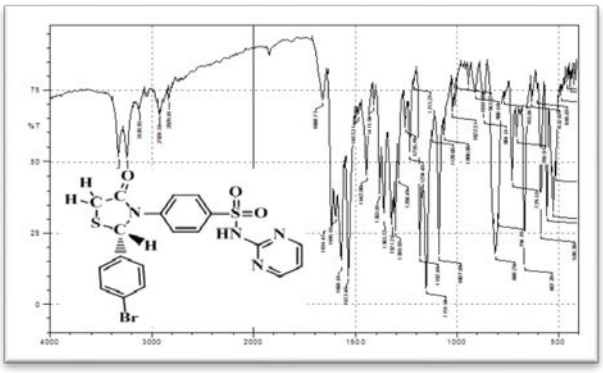


Fig (7) The FT-IR spectrum for thiazolidine (7)

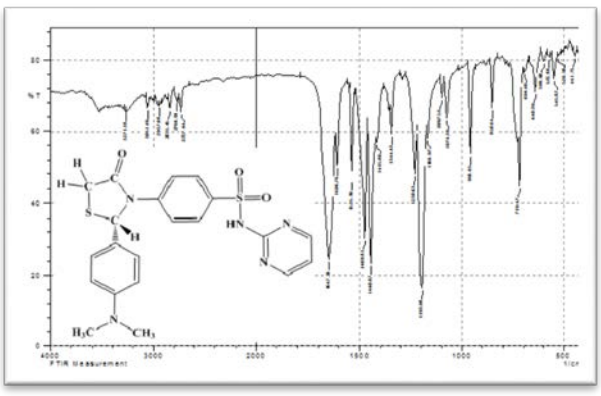


Fig.(8) FT-IR spectrum for thiazolidine (8)

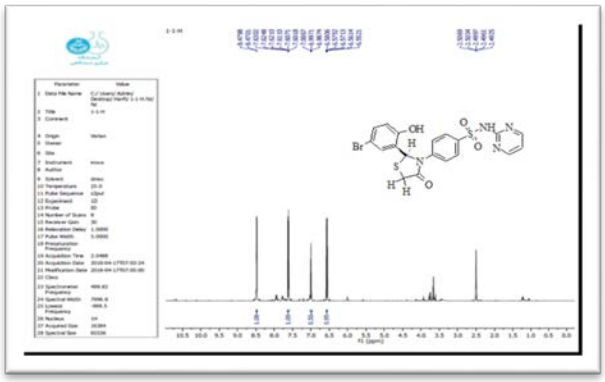


Fig.(9) H-NMR spectrum for thiazoliden (5)

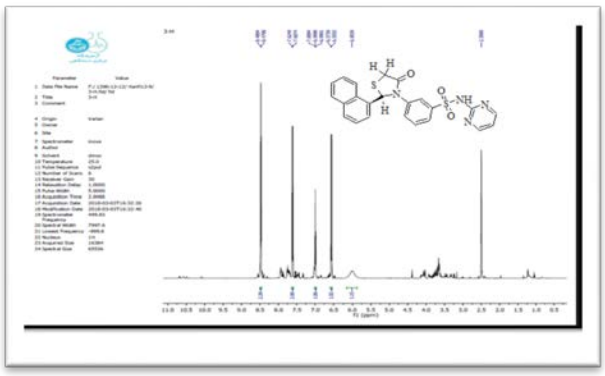


Fig.(10) H-NMR spectrum for thiazoliden (6)

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