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Synthesis, Spectroscopic Characterization and Biological Activity of Some New Sulfa Drug Schiff Bases.

JS Hadi and NK Althahabi*.

College of Education for Pure Science, Basrah university Basrah, Iraq.

ABSTRACT

A new series of Schiff bases were synthesized by the condensation of 3-formylsalcylic acid or 5-formylsacylic acid with various sulfa drugs, including, sulfathiazole, sulfamethaxazole, sulfamethoxypyridiazine, sulfapyridine and sulfaacetamide sodium. The structure of Schiff bases were experimentally characterized by using IR, HNMR and 2DNMR. Antibacterial activity have been tested by disc diffusion method against E.Coli (Gram negative) and Staphylococcus aureus (Gram positive).Some of these compounds showed a remarkable antibacterial activity compared with Gentamycin.

Keywords: Sulfa drug , Formyl salicylic acid , Schiff base.

Corresponding author

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INTRODUCTION

Sulfa Schiff bases have been subject to thorough studies where a wide diversity of these derivatives have been prepared and used in various biological and pharmacological fields [1-3]. Schiff bases derived from sulfa drug and aromatic and hetero aromatic aldehydes are the most studies sulfonamide derivatives, these type of derivatives are very important because of their varied structures and biological activities [4-8]. Schiff base derived formyl salicylic acid has been extensively studied because of their unique properties to form a multidentate ligands suitable to synthesis a mono and binuclear metal complexes [9-14], these complexes useful as catalysis and in medicine. However much less attention has been focused on Schiff bases derived from formal salicylic acid with sulfa drug so in this article some of these Schiff bases were studied.

EXPERIMENTAL

Materials

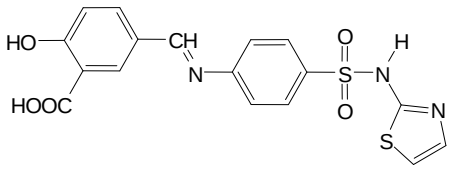
3-Formyl salicylic acid and 5-formyl salicylic acid were prepared according to method of Duff and Bills [15]. Sulfathiazole, sulfapyridine and sulfamethoxypyridiazine were obtained from HiMedia. Sulfamethaxazole was obtained from Aldrich and used as received. All solvents employed in the synthesis were of A.R. grade and used as received without further purification.

Instrumentation

Melting point were recorded on a Fisher Johns melting point apparatus. IR spectra were recorded by using Shimadzu FTIR-infinity spectrophotometer in the region 4000-400 cm^{-1} in KBr pellet. H NMR and 2DNMR (CoSy) were scanned on a Bruker (400MHz) TMS as the internal standard was used as referenced to 0.0 ppm. DMSO-d_6 was used as solvent.

Synthesis

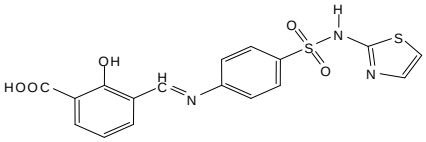
N_1:



(E)-2-hydroxy-5-((4-(N-thiazol-2-ylsulfamoyl)phenylimino)methyl)benzoic acid

To a hot ethanolic solution of 5-formylsalicylic acid (1mmole) 1mmole in 10ml hot ethanol of sulfathiazole was added. 2drops of H_2SO_4 was added as catalyst. The mixture was refluxed with stirring for 4hrs. The reaction monitored by TLC (benzene: ethyl acetate 7:3) the solvent was evaporated and the solid product was purified by TLC plate (20 ×20 cm) using DMF as eluent .

N_2 :



E)-3-((4-(N-cyclopenta-1,3-dienylsulfamoyl)phenylimino)methyl)-2-hydroxybenzoic acid

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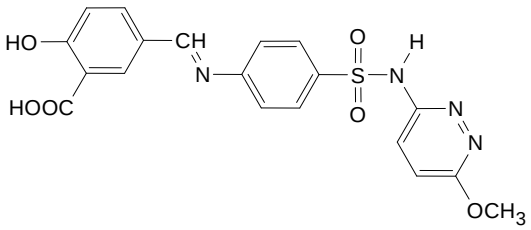
The compound synthesized from 1mmol of 3-formyl salicylic acid and 1mmole of sulfathiazole by the same method of N1.

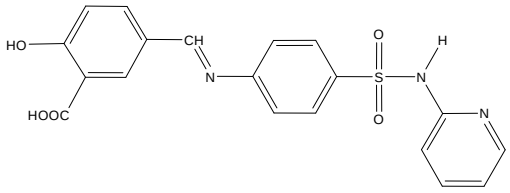
N_3 :



(E)-2-hydroxy-5-((4-(N-(6-methoxypyridazin-3-yl)sulfamoyl)phenylimino)methyl)benzoic acid

The compound was synthesized by refluxing a hot solution of 2mmole of 5-formyl salicylic acid and 2mmole of sulfamethoxypyridiazine by the same method of N_1 but the solid which formed during the reaction was filtered hot dried at 70°C and recrystalized from ethanol.

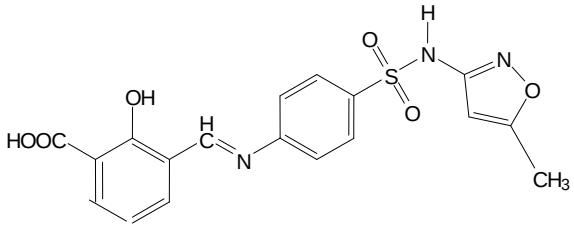
N_4 :



E)-2-hydroxy-5-((4-(N-pyridin-2-ylsulfamoyl)phenylimino)methyl)benzoic acid

The compound was synthesized from 2mmole of 5-formyl salicylic acid and 2mmole of sulfapyridine in hot ethanol. By the same method .but the mixture after 5hrs of refluxing keeping in refrigerator overnight, then the precipitate was collected and purified by using TLC and using DMF as eluent.

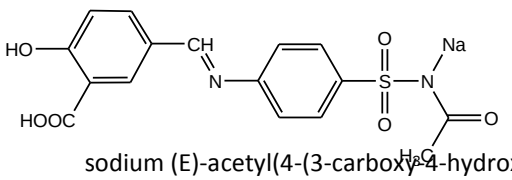
N_5:



E)-2-hydroxy-3-((4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenylimino)methyl)benzoic acid

The compound was synthesized from 2mmole of 5-formyl salicylic acid and 2mmole of Sulfamethaxazole by the same method of N_4 .

N_6 :



sodium (E)-acetyl(4-(3-carboxy-4-hydroxybenzylideneamino)phenyl sulfonyl)amide

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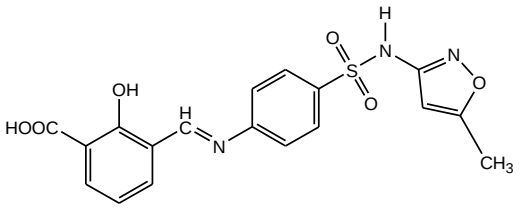
The compound was synthesized from 2mmole of 5-formayl salicylic acid and 2mmole of Sulfa acetamide Sodium by the same method of N_3 .

N_7 :



E)-2-hydroxy-3-((4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenylimino)methyl)benzoic acid

The compound was synthesized from 2mmole of 3-formayl salicylic acid and 2mmole of Sulfa methoxypyridizine by the same method of N_3 .

RESULT AND DISCUSSION

Seven compounds was prepared . The observed physical properties of compound was collected in Table 1 . All compounds are either yellow or orange colored , air stable in the solids state having sharp melting points . most compounds are insoluble in most common organic solvents such methanol , ethanol, 1,4-dioxane, hexane. Some of them soluble on heating in ethanol (N_2,N_3,N_6). All compounds are readily soluble in DMF and DMSO .

Table 1

No.	Chemical formula , molecular weight	Melting point °C	Physical state	Color	Yield
N_1	$C_{17}H_{13}N_3O_5S_2$ 403 g/mole	118-119	powder	Orange*	54%
N_2	$C_{17}H_{13}N_3O_5S_2$ 403 g/mole	192-914	powder	Orange**	61%
$N_{3=6}$	$C_{19}H_{16}N_4O_6S$ 428 g/mole	224	Powder	Yellow*	56%
$N_{4=7}$	$C_{19}H_{15}N_3O_5S$ 397 g/mole	178-180	flex	Orange*	57%
$N_{5=8}$	$C_{16}H_{15}N_3O_6S$ 401 g/mole	142-143	flex	Yellow*	77%
$N_{6=9}$	$C_{16}H_{13}N_2NaO_6S$ 384 g/mole	149- 150	flex	Orange**	62%
$N_{7=10}$	$C_{16}H_{13}N_3O_2S_2$ 343 g/mole	224-223	powder	Yellow**	65%

*purified by TLC (DMF as eluent)
**purified by recrystalization from ethanol

ISSN: 0975-8585

IR Spectra

Generally IR spectra of all compounds exhibited a band at~1680 -1682cm^{-1} (12-14) assigned at the v C=O of carboxylic group . no difference between all compounds can be explained by the position of OH and COOH are the same .but the position of v C=N in compounds N_2 and N_7 is less than compared with compound derived from 5-formyl salicylic acid because of the position of OH (ortho) to C=N in 3-formyl derivative and hydrogen bonding formation . Also all compounds showed a broad band attributed to v OH of COOH and phenolic at ~3300-3480 cm^{-1} (12-14). Also all compound except N_9 showed a band resulting from v NH of sulfa moiety in the region 3188-3387 cm^{-1} (12-14) .All compounds showed two very strong band at 1300-1371cm^{-1} (16-17) attributed asymmetric O=S=O and at 1124-1188 cm^{-1} (16-17) attributed to symmetric of O=S=O .

Characteristic band for each compounds are summarized in Table2 and Figs.1,2.

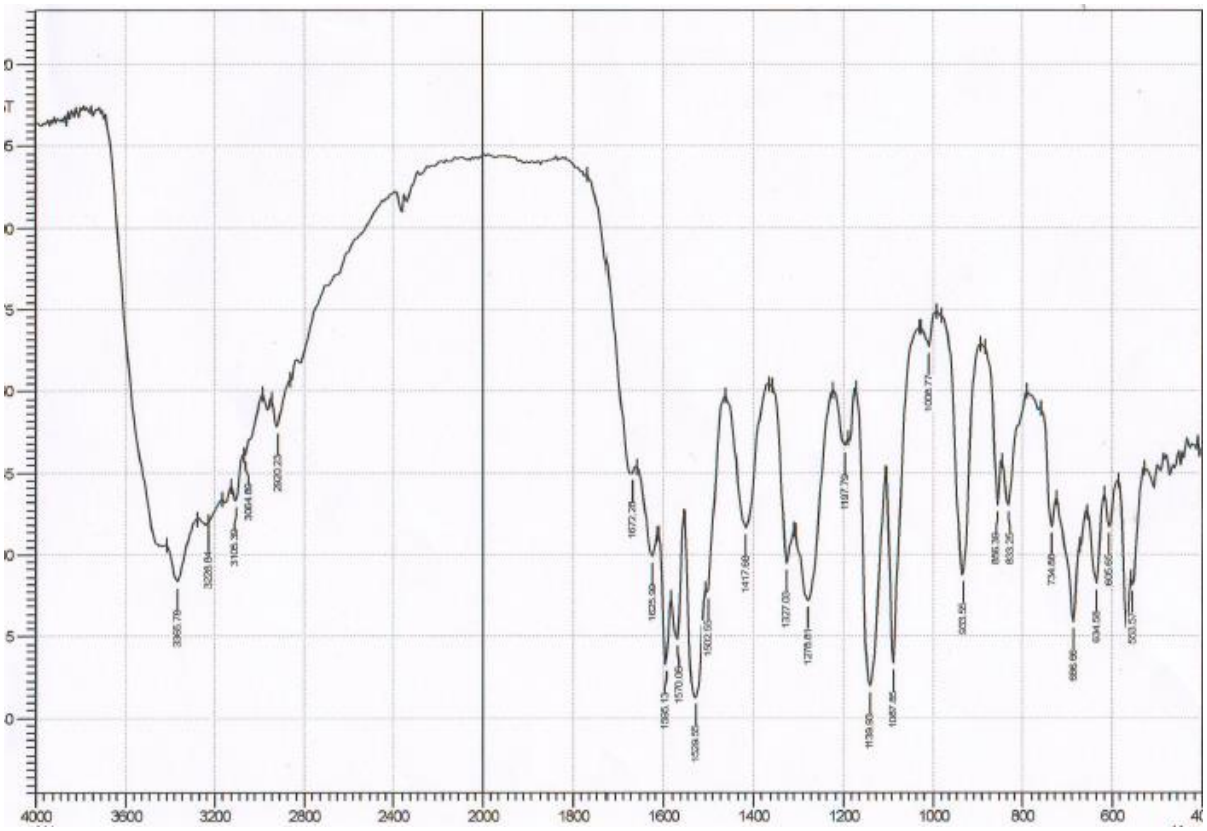


Figure 1:The IR spectrum of compound N1

ISSN: 0975-8585

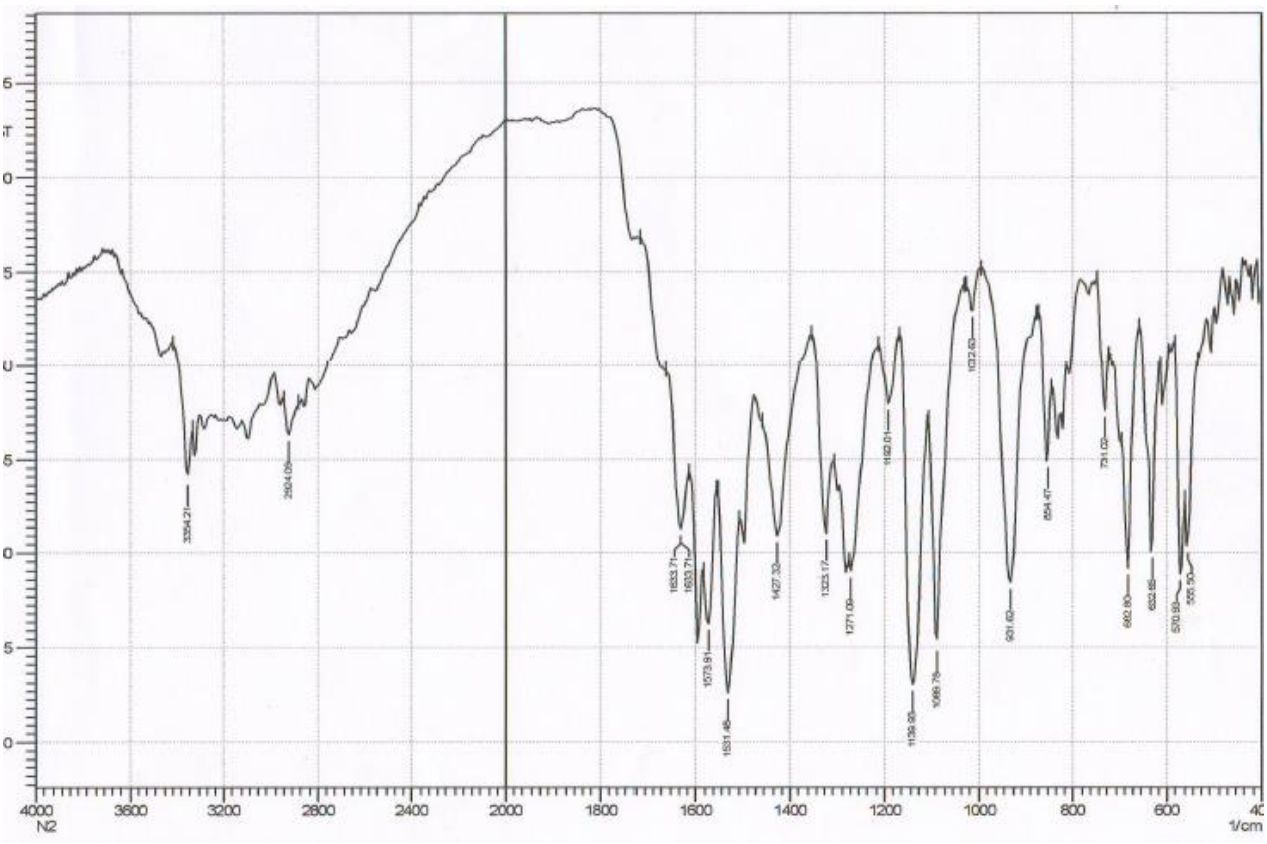


Figure 2:The IR spectrum of compound N2

Table 2: IR spectral data of compounds (KBr, cm^{-1})

No.	(OH) v	(NH)v	(C-H)v aromatic	(-C=N)v azomethine	(C-H)v aliphatic	(S=O) asymm	(S=O) symm	(S-N)	(C=O)	others
N_1	3420	3365	3064	1625	_	1327	1139	933	1672	1526 C=N sulfa
N_2	3480	3354	3040	1633	_	1323	1139	931	1680	1531 C=N sulfa
N_3	3433	3380	3084	1630	2900-2800	1300	1136	947	1680	1408 Sulfa N=N
N_4	3400	3373	3040	1656	_	1300	1188	970	1681	1577 C=N sulfa
N_5	3477	3387	3000	1656	2920-2800	1323	1161	970	1681	1618 C=N sulfa
N_6	3300	_	3078	1647	2613	1367	1157	956	1683	amid) C=O(1647
N_7	3440	3188	3086	1608	2940-2880	1371	1124	947	1680	1408(N=N)

^{1}H NMR

^{1}H NMR spectral data of compounds with the possible assignments is recorded in Table 3 . All compounds shows a signal of HC=N proton in the region 8 .1 - 9 ppm (18-19) . In case of compounds derived from 3-formyl salicylic acid this signal appeared as a doublet this is assignable to the correlation between azomethine proton and phenolic proton in ortho

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position, this observation proved by 2D NMR (cosy) . Fig.5- .Were the signal of azomethine proton at 8.3 ppm correlate with phenolic proton at 9.8 ppm . But the azomethine proton signal in most compounds derived from 5-formyl salicylic acid show a singlet signal and this is clear in 2DNMR spectrum of compounds Fig.6 Where no correlation between azomethine and phenolic protons . The SO_2NHR proton exhibited singlet signal in the region 10.3 - 10.9ppm in all compounds (18-19) In case of compound N_3 ,N_4,N_5,N_6 phenolic and carboxylic proton appear as one singlet signal at 9.8ppm suggesting that they are in fast exchange with one another and with H_2O in DMSO (19) .

Characteristic signal for each compounds are summarized in Table 3 and Figs.3 and 4.

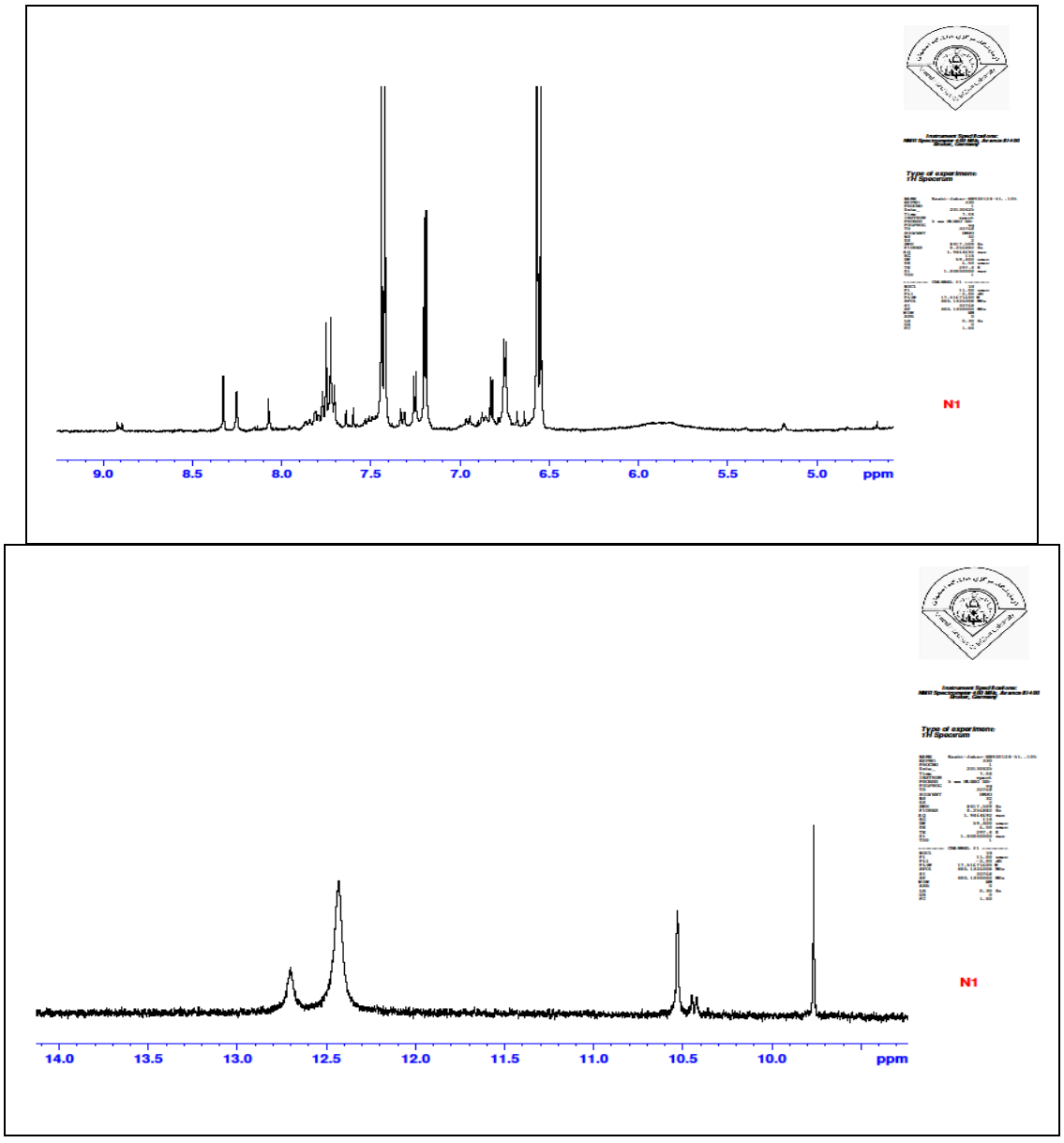


Figure 3: H NMR spectra of compound N1

ISSN: 0975-8585

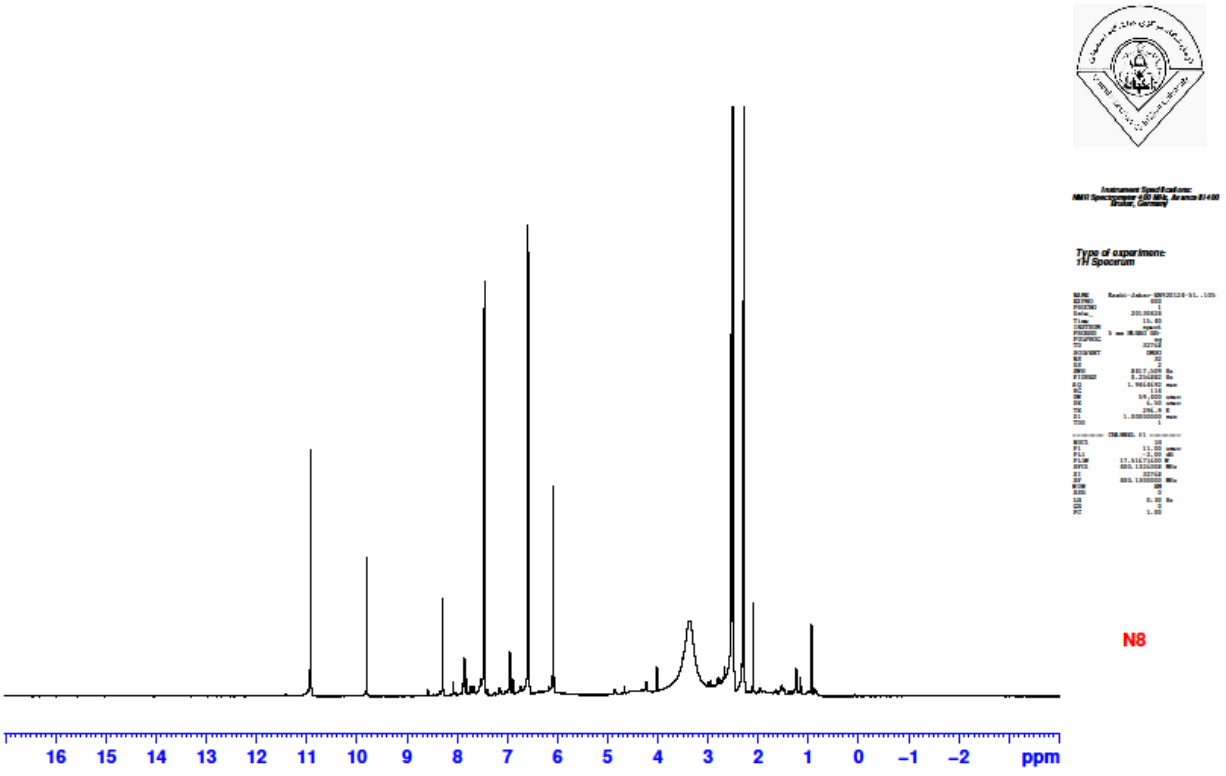


Figure 4: the H NMR spectrum of compound N5

Table 3: The H NMR data recorded in 400MHz (ppm)

No.	COOH	NH	OH	HC=N	C-H aromatic
N_1	12.4.	10.6	9.8	8.4	8.1-6.6
N_2	12.5	10.4	9.7	9	8.2 -6.6
N_3	-	11	9.8	8.4	8 – 6.5
N_4	-	10.3	9.9	8.1	8 -6.5
N_5	-	10.9	9.8	8.3	7.9 -6.1
N_6	-	10.4	9.9	8.7	8.3 -6.7
N_8	-	10.4	9.9	8.4	8- 6.6

ISSN: 0975-8585

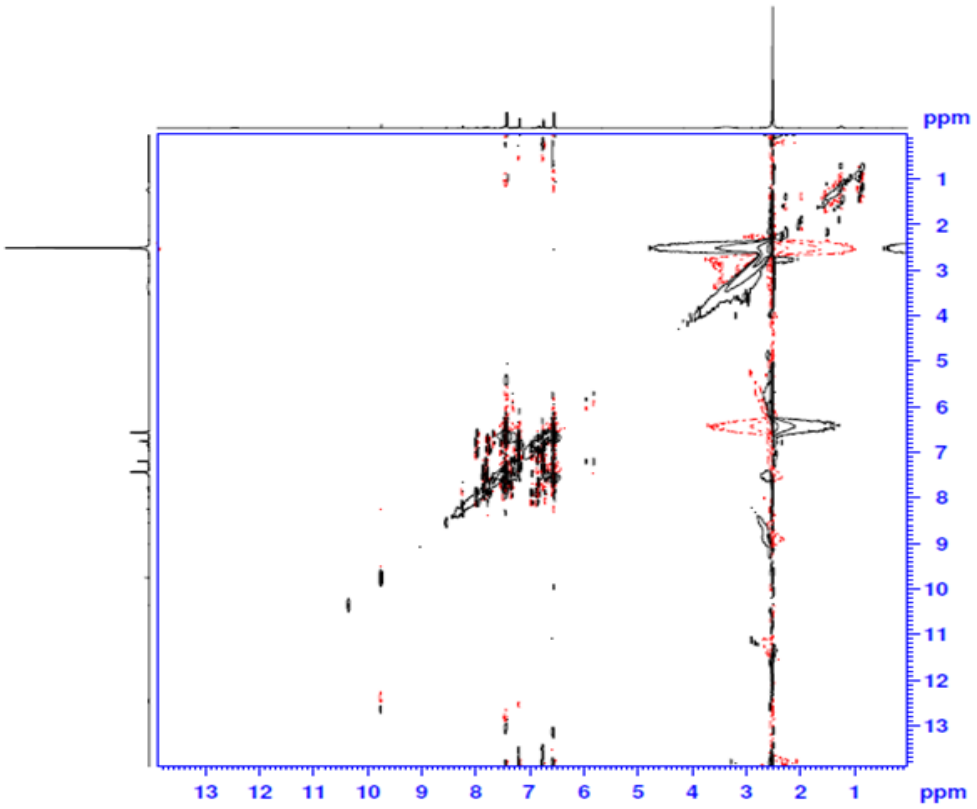


Figure 5: 2D NMR for compound N5

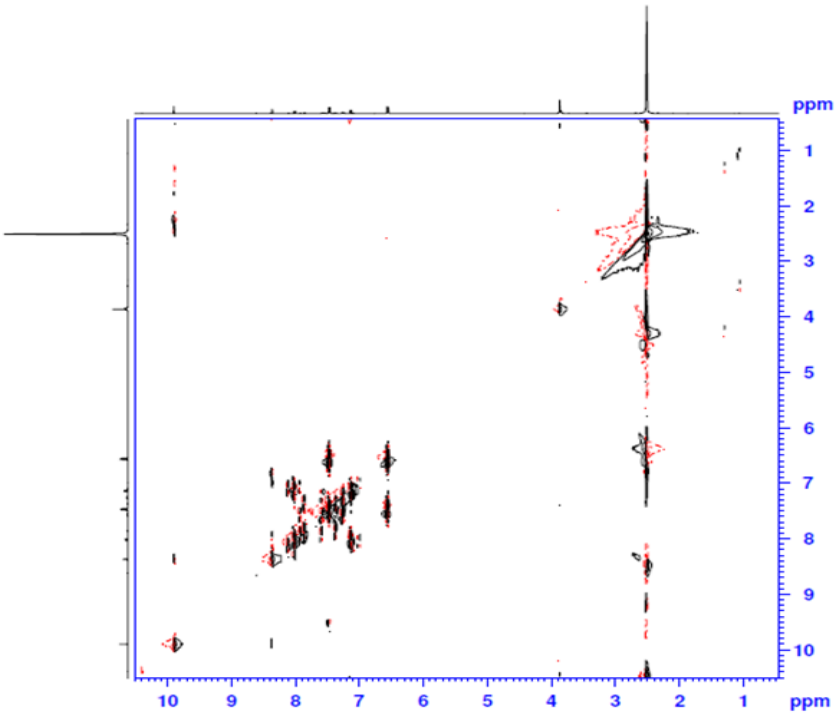


Figure 6: 2D NMR for compound N2

ISSN: 0975-8585

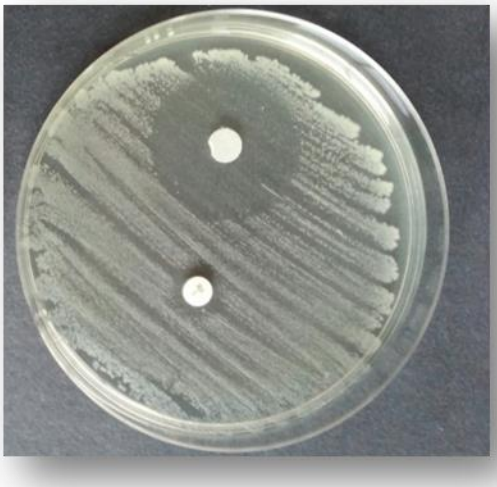
Table 4: Antibacterial activity data of prepared compounds

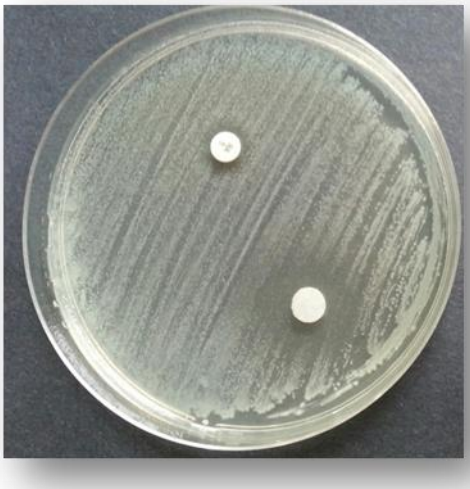
Escherichia coli Gram negative				Staphylococcus aureus Gram positive		
No.	Standard	Sample		No.	Standard	Sample
N1	10	28		N1	35	11
N2	10	25		N2	35	20
N4	10	9		N4	35	9
N5	10	31		N5	35	31
N6	10	13		N6	35	10
N7	10	20		N7	35	11

In vitro antibacterial activity

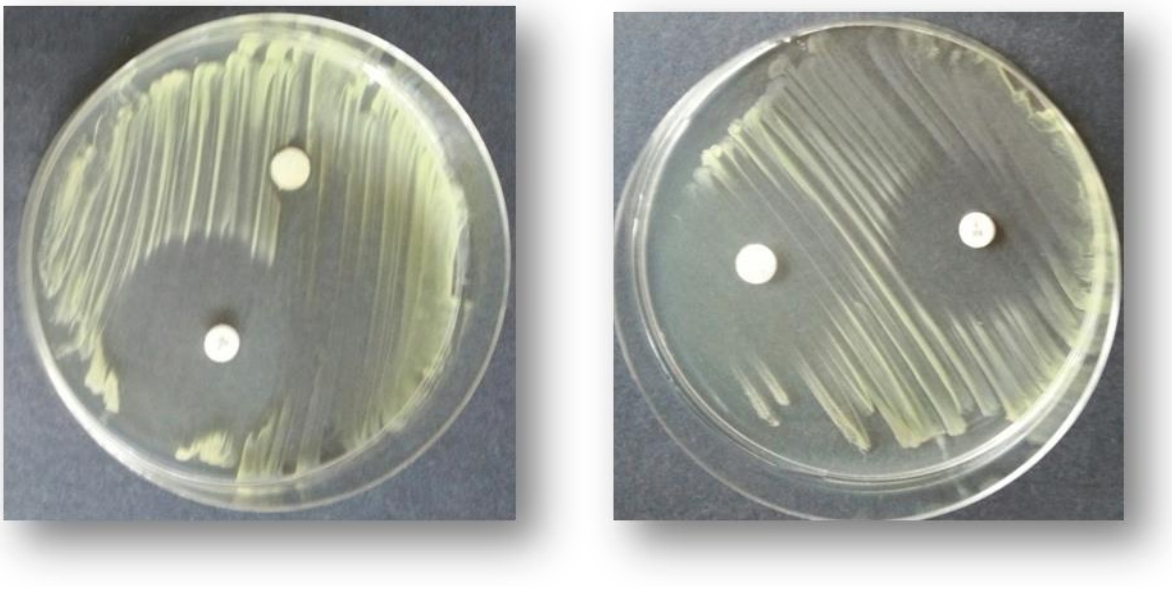
Gentamycine was used as standared drug and the activity compared with the synthesized compounds N1 exhibited excellent activity against Escherichia coliand low activity against Staphylococcus aureus ,N2 showed excellent activity against Escherichia coliand and modrate activity against Staphylococcus aureus N8 showed excellent activity for both negative and positive bacterial strain.other compounds N7 and N9 showed low activity(9-13mm) for both two type of bacterial strain. The comparative antibacterial data are given in Table 4 and Fig 7.

E-N5 **E-N7**





ISSN: 0975-8585



S-N4 S-N5

Figure 7: The inhibition zoon of examine compounds

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