Synthesis, characterization and biological activity of some sulfadrugs derivatives

تحضير وتشخيص بعض مشتقات أدوية السلفا ودراسة فعاليتها البايولوجية

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Abstract:

Sulfamethoxypyridiazine and sulfapyridine have been condensed with selected acyl chloride, namely benzoyl chloride, sebacoyl chloride and terephthayl chloride. The compounds were characterized by FTIR, ^{1}H NMR and elemental analysis. The antibacterial activity of the studied compounds was determined againset several clinical microbial isolates which are; Staphylococcus aureus and E.Coli by using different concentrations of each compound. The results shown the prepared compounds have varying degrees of inhibiting the test microorganisms.

Key words: Sulfa drugs,amide, sebacoyl chloride

الخلاصة

كثفت مركبات السلفا ميثوكسي بايردازين و السلفا بريدين مع مركبات مختارة من الاسايل كلورايد تسمى بنزويل كلورايد و سبسوايل كلورايد و تريفثايل كلورايد.

شخصت المركبات المحضرة باستخدام تقنيات FTIR, H^1 NMR و تحليل العناصر . درست الفعالية ضد البكتيرية للمركبات المحضرة ضد مجموعة من العزلات البكتيرية السريرية للـ *Staphylococcus aureus* و*Escherichia coli* وقد أظهرت النتائج امتلاك المركبات المحضرة درجات مختلفة من التثبيط ضد العزلات الجرثومية المستخدمة.

Introduction:

The Sulfonamides are Synthetic antimicrobial agents with wide spectrum encompassing most gram-positive and many gram-negative organisms[1,2]. The condensation product of sulfa drugs with aldehydes , ketones or their derivative are biologically very active[3]. Beside having good complexing ability and the activity increase on complexation[4]. Many chemotherapeutically important sulfa drugs like sulfapyridine ,sulfadiazine ,etc. posses SO_2NH moiety which is an important toxophoric function[5] in addition the hetrocyclic moiety which contain sulfur , oxygen or nitrogen atoms cause an enhanced the bioloicalactivites of sulfa drugs

Experimental Section

1- Materials and Measurements:-

All chemicals and solvents are obtained from Fluka and Aldrich chemical Co. and are used without further purification. Melting points were recorded on Gallenkamp melting points apparatus without correction. IR Spectra were measured on Shimadzu spectrophotometer as KBr pellets in the region 4000-400cm^{-1} ,elemental analyses were performed on Euro vector EA 3000A(Italy). The ^{1}HNMR spectra were recorded in DMSO-d_6 on Bruker 500MH$_z$ spectrometer using TMS an internal standard.

Synthesis of Sulfa drugs derivatives

Compound 1(SS_3) :N-(4-(N-(6-methoxypyridazin-3-yl)sulfamoyl)phenyl)benzamide.

A 50 ml round bottomed flask was charged with 0.280g(0.001 mol) of sulpha-methoxypyridizine , 0,141g(0.001 mol) of Benzoylchloride and 25ml CCl_4 . The mixture was refluxed for one hour. The yellow deposit which was formed was filtered off, washed with CCl_4 and

recrystalized from ethanol. Yield(64%) as yellow crystals m.p193-195^{o} C, elemental analysis , calculated: C,56.24 , H, 4.19 , N, 14.57 , S, 8.32 , found: C, 56.64, H, 4.32, N, 14.71, S, 8.13

Compound 2 (SS_2) : N-(4-(N-pyridin-4-ylsulfamoyl)phenyl)benzamide A 50ml round bottomed flask was charged with 0.249g (0.001mol) of sulpha pyridine 0.141g (0.001 mol) of Benzoylchloride and 25ml CCl_4 . The mixture was refluxed for 1.5 h . The resulting solid was collected , washed with CCl_4 and recrystalized from ethanol. Yield(65%) as yellow crystals m.p.210-211^{o}C, elemental analysis , calculated: C,61.18 , H, 4.25, N, 11.89 , S, 9.06 , found: C, 61.54, H, 4.63, N, 11.61, S, 8.89

Compound 3 (SSP) :N1,N10-bis(4-(N-pyridin-2-ylsulfamoyl)phenyl)decanediamide:

The mixture of 0.498g (0.002 mol) of sulphapyridine and 0.238g (0.001mol) of Sebacoyl chloride was dissolved in 25ml of CCl_4 .The mixture was refluxed for 1.5 h. The resulting solid was collected , washed with CCl_4 and then with acetone and recrystalized from ethanol. Yield(67%) as pale yellow crystals m.p153 dec.elemental analysis , calculated: C,57.81 , H, 5.45 , N, 12.64 , S, 9.64 , found: C, 58.03, H, 5.56, N, 12.21, S, 9.44

Compound 4 (SS_1) :N1,N4-bis(4-(N-pyridin-2-ylsulfamoyl)phenyl)terephthalamide

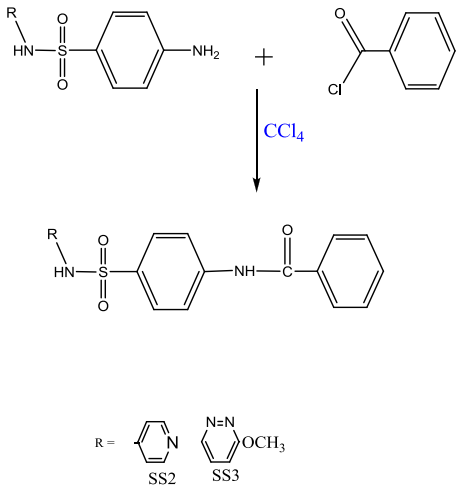
The mixture of 0.498g (0.002 mol) of sulphapyridine and 0,202g (0.001 mol) of Terephthalenchloride was dissolved in 25ml of CCl_4 .The mixture was refluxed for 1h. The orange deposit which was formed was filtered off, washed with CCl_4 and then with acetone and recrystalized from ethanol. Yield(65%) as yellow crystals m.p> 300^{o}C, elemental analysis , calculated: C,57.31 , H, 3.84 , N, 13.36 , S, 10.20 , found: C, 57.76, H, 4.01, N, 13.71, S, 10.33

Determination of the biological activity of compounds:

A filter disk assay was used to determine the biological activity of the sulpha drugs against isolates of gram positive and gram negative bacteria included (***Staphylococcus aureus*** and ***Escherichia coli***) which were tested using plates of Muller- Hinton agar .Thebiological activity was defined as the clear zone of growth inhibition [(11)].

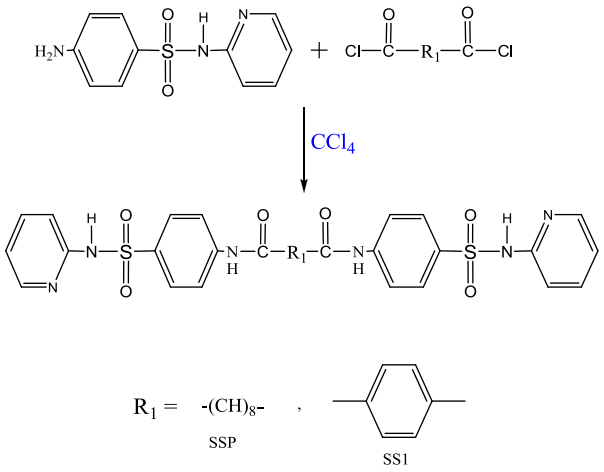
Result and discussion

The 1:1 mol ratio reaction between sulphamethoxypyridine ,Sulphapyridine and Benzoylchloride led to formation of compound (II) ,(I) in good yield , the resulting compound can be represented as followings in scheme 1 .



Scheme 1

The 2:1 molar ratio reaction between sulphapyridine with sebacoylchloride ,Terephthalen chloride had led to formation of compounds (III ,IV) , the resulting compounds can be represent as following in scheme 2 .



Scheme 2

IR Spectra

SS_1 : The IR spectrum of compound SS_1 (Fig.1) show bands at 3417 and 3244cm^{-1} assignable to N-H stretching vibration in $NHSO_2$ and NHCO residue respectively[6]. The spectrum show avery strong band at 1699cm^{-1} attributed to C=O and at 1637cm^{-1} to stretching vibration of C=N . The two strong bands at 1259 and 1128 cm^{-1} attributed to asym and sym stretching of O=S=O respectively[7]

SS_2 : The IR spectrum of SS_2 compound show a two strong band at3415 and 3244cm^{-1} attributed to NH of ($NHSO_2$) and NH (NHCO) respectively ,a strong band at 1689cm^{-1} attributed to C=O , the band at 1637 cm^{-1} attributed to C=N , the strong band at 1265cm^{-1} attributed to C-N , and the two strong band at 1379 and 1126 cm^{-1} attributed to asym. and sym. stretching of SO_2 group .

SS_3 :The IR spectrum of SS_3 show avery broad and strong band at 3479 cm^{-1} attributed to N-H stre. The band at 1662 cm^{-1} attributed to C=O and the strong band 1527 cm^{-1} attributed to N=N[8] . The asym and Symstr.of SO_2 group appear as astrong bands at 1311 and 1155 cm^{-1} respectively .

SSP: The IR spectrum of SSP_1 show a broad band centred at ~3415 cm^{-1} attributed to a combinds to N-H group . The strong band at 2927 cm^{-1} attributed to str.vibration of C-H of CH_2Chain . The very strong band at 1699 cm^{-1} attributed to C=O. The medium band at 1625 cm^{-1} attributed to C=N of the pyridine ring , The asym and sym str. Of SO_2 appear at 1357 and 1143 cm^{-1}respectivly.

^{1}HNMR Spectra

SS_1 :The ^{1}HNMR spectrum of SS_1 in DMSO-d_6 (Fig.) show a singlet broad at δ5.9ppm attributed to NH proton of $NHSO_2$ moiety[9] . While the very broad signal at δ10.7 ppm attributed to NH proton of $NHCOC_6H_5$moiety[10] . The assignment of other aromatic protons are presented in Fig.

SS_2: The ^{1}HNMR spectrum of SS_2 (Fig.) show a singlet signal at δ6.5ppm attributed to proton of $NHSO_2$ While the protons of NHCO appear at δ10.72 as asinglet signal. The aromatic proton appear in the region δ6.8 – 8 ppm .

SS_3: The ^{1}HNMR spectrum of SS_3 show the signal of methoxy protons at δ3.83 ppm and the aromatic protons in the region δ6.8 – 8 ppm . the signal of proton of $NHSO_2$ moiety appear at δ6.5 ppm while proton of NHCO appear at δ10.8 ppm .

SSP: The ^{1}HNMR spectrum of SSP_1 (Fig.) show three distinguish signal at aliphatic region attributed to CH_2 chain the first signal attributed to 8H centered at δ1.23 ppm the second signal attributed to 4H of the two methelene groups (b) appear at δ1.47ppm and the third signal centered at δ2.17ppm attributed to 4H of the two methelene groups(-$COCH_2$). The aromatic protons appear in the region δ6.6-7.7 ppm. The broad signal at δ8ppm attributed to NH proton of $NHSO_2$moiety. While the NH proton of NHCO moiety appear at δ10.5 ppm .

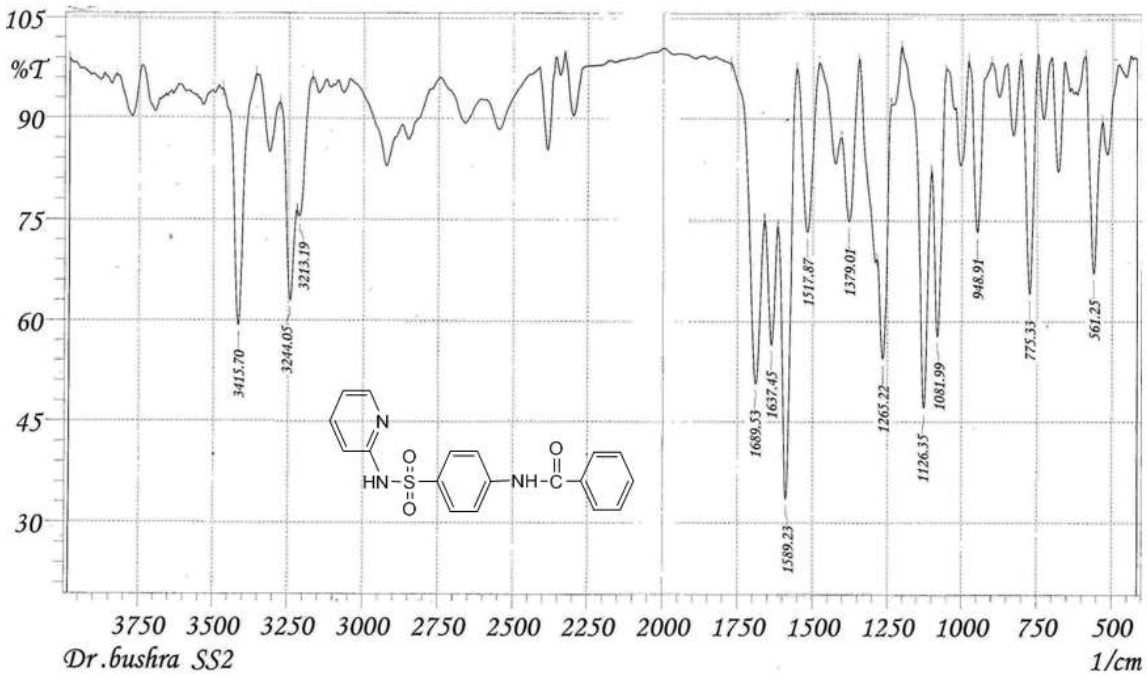


Fig. 1 : IR spectrum of SS2

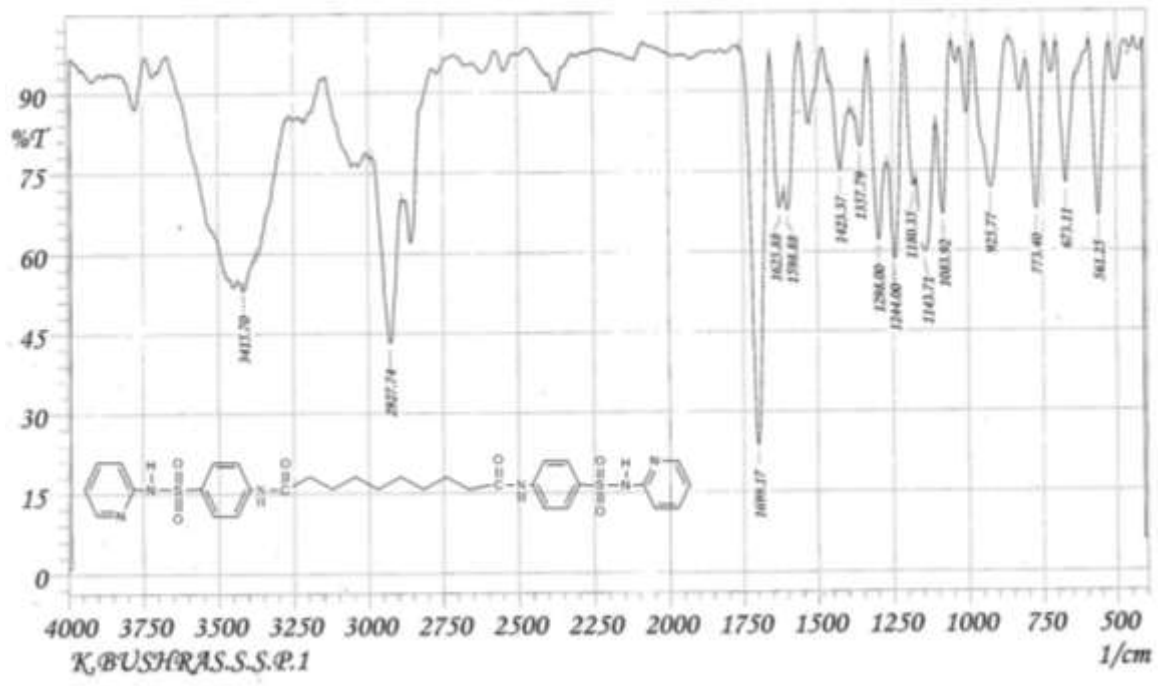


Fig. 2 : IR spectrum of ssp

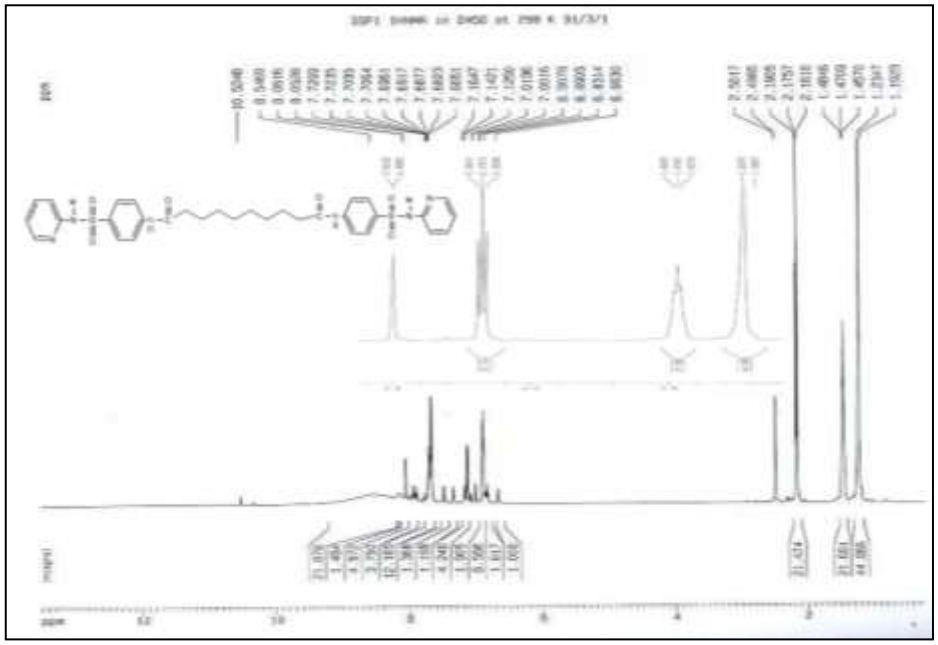


Fig. 3 : ^{1}H NMR spectrum of SSP

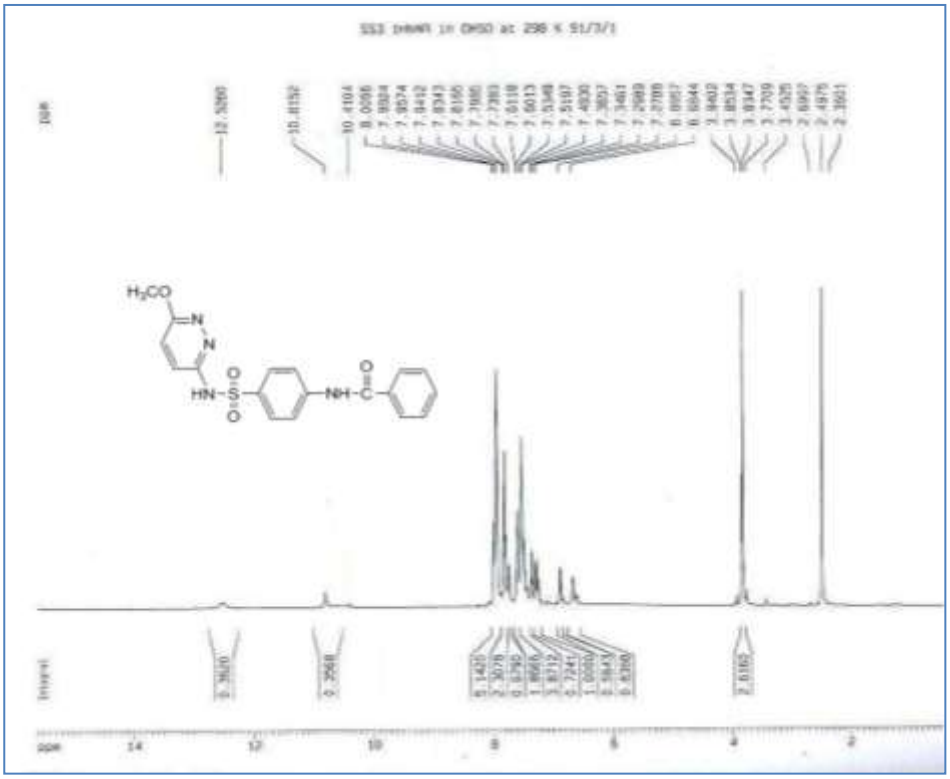


Fig. 4 :^{1}H NMR spectrum of SS3

The biological activity of the Slufa drugs :-

The results of antibacterial activity of the sulphadrugs were shown in Table(1) and figures (5 and 6). Sulfa drugs were the first synthetic drugs with widespread antibiotic activity to be put into clinical use[12], once sulfanilamide was recognized as an active antimicrobial agent, scientists synthesized thousands of sulfonamides to test for bactericidal activity. It was later realized that sulfonamides do not actually kill bacteria; they interfere with bacterial growth and replication. Sulfa drugs are bacteriostatic. They inhibit an enzyme necessary for the biosynthesis of folic acid in bacteria. Folic acid is necessary for the biosynthesis of thymine and the purine bases, the building blocks of DNA [12-14].

The prepared compounds in this study were shown very effective against gram negative strain(***Escherichia coli***) but less active against gram positive strain***(Staphylococcusaureus***).It has been postulated that cell membrane of (***Escherichia coli***) contains many condensed fat layers compared with(***Staphylococcus aureus***)[15]. The .Chemicals and antibiotics or antiseptics face difficulty in penetrating these membranes and, therefore, their effectiveness is diminished, this may be justified due to the ionic combination between each complex and the phospholipids of the bacterial cell wall, which led to destroy the cell membrane and then led to inhibit the microbial growth and may change the cell protein nature (Denaturation) and increase the permeability of the cell membranes[16],as many types of antibacterial compounds[17] .

Fig 5: The antibacterial activity of sulpha drugs against *E. coli*

Fig 6: The antibacterial activity of sulpha drugs against. *S. aureus*

Table 1: The antibacterial activity of sulfa drugs**.**

Bacterial Isolated comp.No.	Inhibition zone (mm)			
	1	**2**	**3**	**4**
S. aureus	0	15	0	15
E. coli	30	25	26	29

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