Synthesis of some sulfonamide derivatives with expected antibacterial activity

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Abstract

Some derivatives of amino acid were synthesized and gave some antibacterial activity. These derivatives were classified according to their attachment to amino acids either to the carbon skeleton, or as esters or amides. It was found from previous researches that the benzene sulfonamides moiety when used in antibacterial agents are essential for their activities. Accordingly, a number of benzene sulfonyl amino acids derivatives were synthesized which differ from traditional sulfanilamides in that they do not contain para-amino group which is essential for their activity.

Four derivatives were synthesized and identified using infrared spectroscopy, CHN analysis in addition to thin layer chromatography, melting point and solubility. Three derivatives (benzene sulfonyl of glycine, alanine and methionine) were applied to hospital strains of *Escherichia coli* and *Staphylococcus aureus*, all these derivatives were proved to have antibacterial activity and thus are promising target for future work.

Introduction

Bacterial infection is a major category of human diseases, for which many antibacterial compounds were developed. However; resistance to almost all commercially available antibacterial drugs (penicillins, cephalosporins, sulfonamides, aminoglycosides…etc.) have been observed in both wild and laboratory strains of disease causing bacteria (1), resistance can be considered as a major cause of increased morbidity and mortality and health care costs (2;

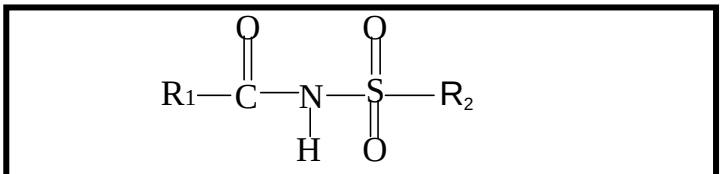
3; 4). The resistance mechanisms are genetically encoded and under appropriate conditions, resistance genes can propagate through the environment (5). This vast increase in resistance mechanisms often negates treatment by entire classes of antimicrobial compounds. Under these circumstances, the development of novel classes of antimicrobial compounds is required (6).

Since Beta-lactam antibiotics were found to be composed of amino acids linked by peptide chain which they act as false substrate to the enzymes involved in bacterial cell wall synthesis (7), light is focused on amino acid derivatives in recent years, as antimetabolites, they interfere with certain metabolic and biosynthetic processes exerting in some cases, therapeutically useful pharmacological action as in the following examples:

Allyl glycine, propargyl glycine and 2-aminoheptanoic acids were found to inhibit the growth of *E.coli* by their antagonism to methionine amino acid utilization (8). Cycloserine is a structural analogue of D-alanine; it is a competitive inhibitor of alanine racemase and D-alanine synthetase (9). Propargyl esters of some amino acids were also studied and some of them found to have antibacterial activity (10).

In addition , Sulfonamides (eg. sulfacetamide , sulfadiazine …etc) are known to act as competitive inhibitors of para-amino benzoic acid PABA on the enzyme dihydropteroate synthetase, which is an essential enzyme in folic acid synthesis present only in bacteria but not in human cells. Humans take folic acid from diet (11; 12).

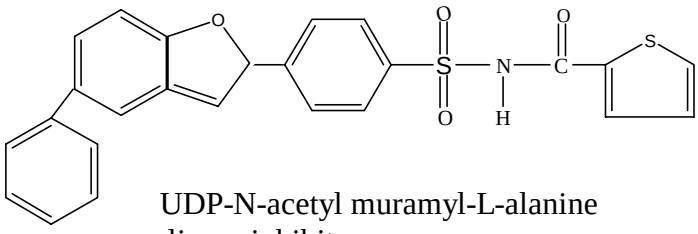
Certain sulfonamides were found to act by a non-PABA antagonism; a group of sulfonamides that do not have structural similarity to PABA were found to have antibacterial activity even they do not contain p-amino group that is essential for the binding to the enzyme dihydropteroate synthetase ,they are the N-acyl sulfonamides (fig 1) (13; 14).



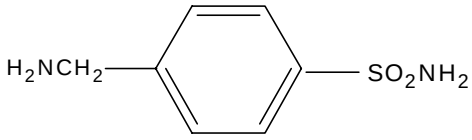
tRNA synthetase inhibitors

(basic structure)

R_1 : methyl ,4-tolyl R_2 : 4-tolyl ,4-pyridyl



UDP-N-acetyl muramyl-L-alanine ligase inhibitor



mafenide

Fig. (1) non-PABA antagonists sulfonamides

In addition, Mafenide (fig.1) has the general structure of other sulfanilamides but the amino group is separated from aromatic ring by one carbon atom. It is used in topical treatment in burn infections and exerts a broad bacteriostatic action against many gram positive and gram negative organisms including pseudomonas aerogenosa and certain strains of anaerobes (15).

The aim of this work was to synthesize benzene sulfonamide with different amino acids as antibacterial agents.

Materials and instruments

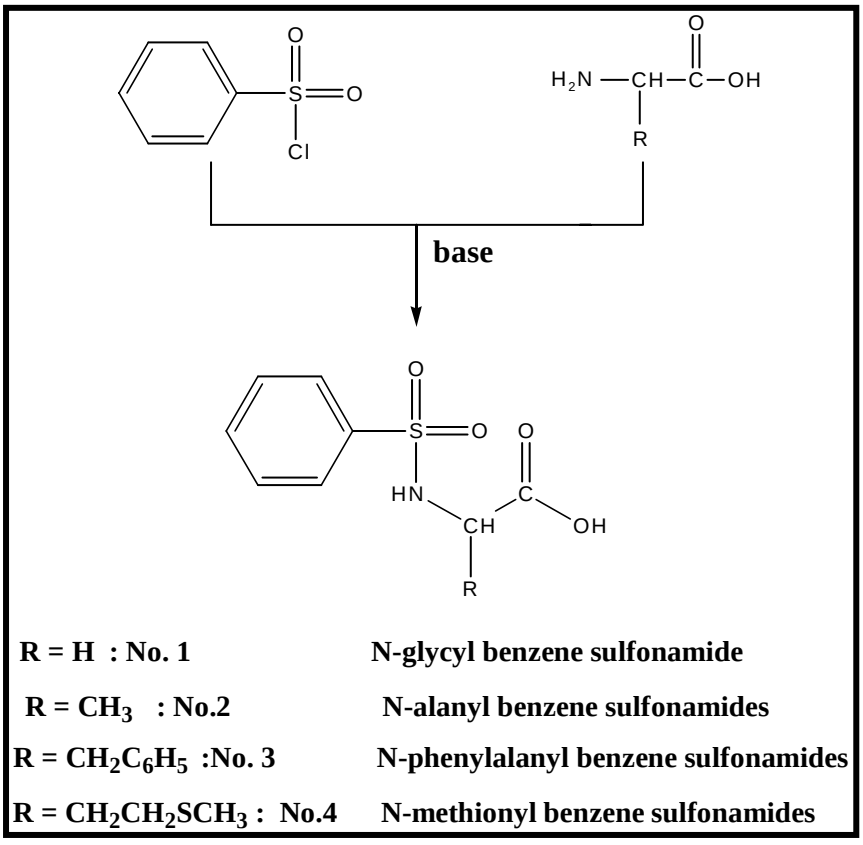
The L-amino acids used are supplied by (Fluka , Switzerland) while benzene sulfonyl chloride is supplied by (Merck , Germany).

The infra red analysis were done using Pye (Unicam 1028, 110), Philips (England) spectrophotometer and model 500 scientific spectrophotometer (Buck-Germany).

The CHN elemental microanalysis was done in Italy using elemental analyzer 1106 (Carlo-Erba company).

Methods

The general method for all compounds was carried out as in the following general scheme.



R = H : No. 1 **N-glycyl benzene sulfonamide**

R = CH_3 : No.2 **N-alanyl benzene sulfonamides**

R = $CH_2C_6H_5$:No. 3 **N-phenylalanyl benzene sulfonamides**

R = $CH_2CH_2SCH_3$: No.4 **N-methionyl benzene sulfonamides**

The preliminary microbiological study was done using agar-well diffusion method on Muller-Hinton agar (16) using hospital strains of *E.coli* and *Staphyllococus aureus*.

Results

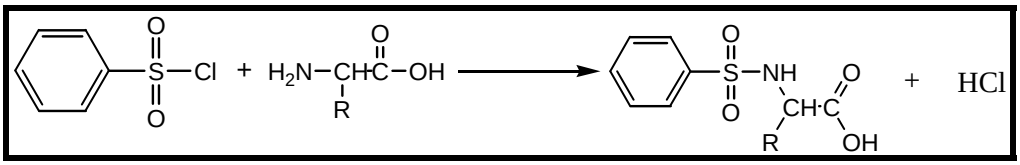
Four derivatives were synthesized and assayed using infrared spectroscopy, thin layer chromatography (table 1), CHN elemental microanalysis (table 2) in addition to their melting points measurements. The infrared spectra of the synthesized derivatives were as following:

* N—H stretching of secondary sulfonamides appeared between 3320-3377 cm-1
* O—H stretching of free carboxylic acid appeared as a broad band between 3276-2800 cm-1
* C=O stretching of the free acid appeared between 1733-1717cm-1
* S=O stretching of sulfonamide appeared as two bands at 1348 , 1319cm-1 and at 1170,1149 cm-1
* C—O stretching of carboxylic acid appeared between 1242-1248 cm-1

In addition, preliminary antibacterial examination has been done on compounds (1, 2, 4) respectively on hospital resistant isolates of E.coli and Staphyllococcus aureus bacteria (Fig. 2) .All of them were found to have significant zones of inhibition at different concentrations using the solvent in which they were dissolved as a blank.

Discussion

The general method used for the synthesis of all these derivatives is by the reaction of acid chlorides of sulfonic acid with amino group in a similar manner of acid chlorides of carboxylic acids (17). In these reactions, amine serves as nucleophilic reagents attacking the carbonyl carbon or sulfur and displacing chloride ion, nitrogen loses a proton to a second molecule of nitrogen or another base (as a scavenger) (18).



Water is used as a solvent in this reaction because all amino acids used are water soluble; in addition the benzene sulfonyl chloride is not too active towards cold water as acyl chloride or other sulfonyl chlorides and all the side products are soluble in water after acidification except the required product of the reaction, this would give pure product which can be purified by D.W. only (19).

The antibacterial response obtained from such compounds may be attributed to their action as antimetabolites but their mechanism of action is unknown, however, they are promising targets for future development.

Table.1: Physical appearance, melting points and TLC analysis using the following solvent systems:

NO.	Compound	Physical appearance	Melting points	Rf values
1	Benzene sulfonyl glycine	White powder	168-170	A: 0.36 B: 0.4
2	Benzene sulfonyl alanine	White powder	125-127	A: 0.56 B: 0.63
3	Benzene sulfonyl phenyl alanine	White powder	114-116	A: 063 B: 0.67
4	Benzene sulfonyl methionine	Off -white powder	130-132	A: 0.67 B: 0.72 C: 0.8

A: diethyl ether 6: methanol 3: ethyl acetate 1.
B: ethyl acetate 4: carbon tetrachloride 3: butanol 2.
C: ethyl acetate 5: petroleum ether (40-60) 7.

Table.2:CHN elemental microanalysis results.

Comp. No.	Compound	Chemical formula	Calculated/found		
			C%	H %	N%
1	Benzene sulfonyl glycine	$C_8H_9O_4NS$	44.65 45.04	4.18 3.98	6.51 6.32
2	Benzene sulfonyl alanine	$C_9H_{11}O_4NS$	47.16 47.57	4.8 4.64	6.11 5.87
3	Benzene sulfonyl phenyl alanine	$C_{15}H_{15}O_4NS$	59.01 58.95	4.92 5.27	4.58 4.3
4	Benzene sulfonyl methionine	$C_{11}H_{15}O_4NS_2$	45.67 45.75	5.19 4.99	4.84 4.97

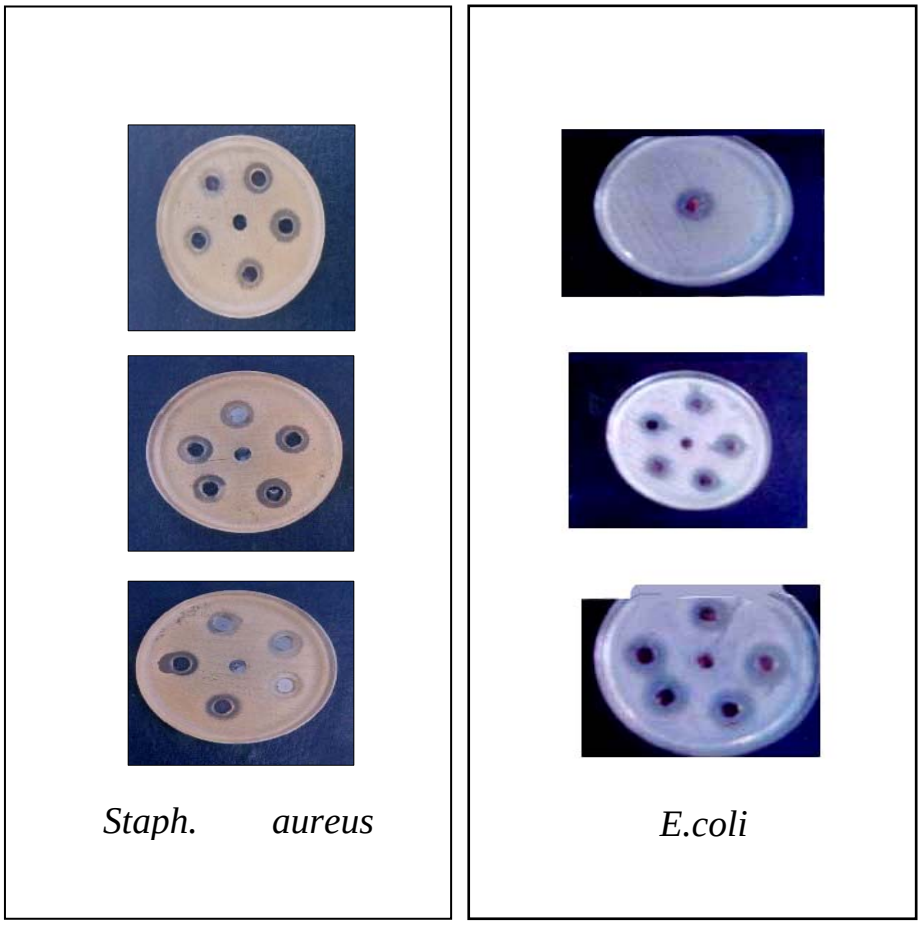


Fig.3: The antibacterial response obtained from compounds 1, 2, 4 on both *Escherichia coli* and *Staphylococcus aureus.*

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تخليق بعض مشتقات السلفاميد المشتقة واختبار فعاليتها التثبيطية ضد بعض الاحياء المجهرية

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الخلاصة

ان مجموعة من مشتقات الاحماض الامينية تم اختبارها كمضادات بكتيرية وأظهرت بعضها امتلاكها فعالية بايلوجية . تم تصنيفه هذه المركبات حسب الارتباط مع الاحماض الامينية اما مع سلسلة الكاربون او بشكل استرات او اميدات.

ومن خلال مجموعة من الابحاث السابقة وجد ان مجموعة benzene (sulfonamides) الموجودة في عدد من مضادات البكتريا اساسية لعمل هذه المركبات. واستنادا الى ماذكر فقد تم ربط مجموعة من الاحماض الامينية مع مجموعة benzene sulfonamides وهذه المركبات تختلف عن مجموعة sulfanilamides بعدم احتوائها على p-NH2 الاساسية لعمل تلك المركبات . حيث تم تصنيع اربعة مركبات واختبارها باستخدام تقنيات CHN analysis, IR spectroscopy, Thin layer chromatography بالاضافة الى قياس درجة الذوبان.

تم اجراء اختبار اولي لثلاث مشتقات benzene sulfonamides مع (glycine, alanin, methionine) على نوعين من البكتريا من سلالات المستشفيات (Escherichia coli and Staphylococcus aureus) واثبتت فعالية مضادة للبكتريا ممايجعل منها اهداف للعمل في المستقبل.