

ESTIMATION THE IMPORTANT RELATIONSHIP BETWEEN THE BIOLOGICAL ACTIVITY AND THE STEREOCHEMICAL STRUCTURE OF THE PREPARING COMPOUNDS.

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ABSTRACT

It can be prepared a good drug or antibiotic depending on this research .its same as build a beautiful house depending on a good building factors, this research is about the important relation between the biological activity (the activity against the microbes) and stereochemical structure of the preparing compounds .To obtain this relation two compounds has been prepared and tested on different species

(St. aureus, E. coli, candida albicans), one of these two compounds has show more activity than the other even the difference between them is simple, this question was push us to study the more active compound (compound (1)), why it more active against the microbes, also this question led us to estimate the important relation five factors effecting the relation, this relation was obtained not from the two compounds only, but depending on more than these compounds the relation was obtained, also preparing compounds in this research are enough to illustrate the five factors leading to the important relation.

To understanding the research idea or the important relation, compound (3) was prepared which its more active than the two compounds. All the three compounds have identify by melting point, solubility test, CHNSO analyzer, I.R., and uv-visible spectra.

INTRODUCTION

Staphylococcus aureus has shown disconcerting propensity to develop resistance to antimicrobial agents. Penicillin was introduced into clinical use in the early 1940, and resisted *St. aureus* strains rapidly arose such that by 1940 it was estimated that 60 percent of hospital isolates in the united kingdom were resistant to penicillin, similarity, successive introduction of alternative agents, such as tetracycline, chloramphenicol, the aminoglycosides macrolides, lincosamides, streptogramins, and sulfonamides, were likewise subsequently accompanied by the emergency of the corresponding resistance. Some strains of *St. aureus* are now resistant to more than 20 different antimicrobial agents. *St. aureus* has take as example for microbes resistance to the drugs, also for this resistance (i.e., *St. aureus* was resistant the penicillin at 1946 which it discovered at 1940) as mentions before every year may be prepare

million compounds in the world, for example just one pharmaceuticals company may prepare thousands compounds to find a new drugs instead of the old drugs which the microbes has resistance them. Thousands compounds were prepared and may be Five or six drugs has obtain from these thousands compounds⁽¹⁻⁶⁾.

Why the five or six compounds become drugs and the others not?

From any other factors (drug metabolism in the human body) This research has solve this question by the important relation between the biological activity and the stereochemical structure of the preparing compounds, this relation depend on five factors as mention before in the abstract, another mean, depending on this research or the relation can be prepare fifty compounds active in the biological activity and it can be use them after another studies (study the drug metabolism in the human body) led to obtained new drugs .also a glance at the standard references show that most of the studies has been carried out on the important relation⁽⁷⁻¹³⁾.

Experimentals:

- **5-amino -1,3,4 -thiadiazol -2-thiol compound (A) was prepared by the method adopted by Petrow and Co-workers as follows⁽¹⁴⁾ :**

Thiosemicarbazide (0.3mole ,27.39) was suspended in absolute ethanol (105ml) anhydrous sodium carbonate (15.9 g) and carbon disulfide (0.36 mole ,27.69) were then added and the mixture was refluxed with stirring for 6 hrs .The reaction mixture was then allowed to cool to room temperature and filtered .The filtrate was evaporated to dryness under reduced pressure and the residue was dissolved in distilled water (600 ml) and acidified to PH 6 with concentrated HCl to give an orange precipitate .The crude product was filtered washed excessively with distilld water and recry stalliged from hot water to give compound (A) as yellow needles .

- **his (5-amino -1,3,4 -thiadiazol -2-yl) disulfide compound (B) was prepared by oxidation of compound (A) using hydrogen peroxide⁽¹⁵⁾ .**

Hydrogen peroxide (31ml, 30 w/v) was added dropwise to a solution of compound (A) (45.8mmole, 6g) in ethanol (50 ml) with continuous stirring for 1 hr .at room temperature.

A yellow precipitate was formed, and this precipitate was collected by filtration, washed with distilled water and dried in oven at 70°C to provide compound (B).

- **Preparation of compound (1); [(5-amino -1,3,4-thiadiazol-2-yl) dithio] acetic acid.**

This compound was prepared from compound (B) and mercaptoacetic acid as follow⁽¹⁶⁻¹⁷⁾.

An aqueous solution (30 ml) containing meracptoacetic acid (9.6mmole, 0.89g) and potassium hydroxide (19.2mmole, 1.07g) adjusted to PH 7.5 was added to a yellowish suspension of compound (B) (7.4mmloe, 3g) in potassium chloride (25ml, 2N) at PH 7.5 the reaction mixture was stirred continuously for 1 hr. at room temperature .A white precipitate

was formed, and this precipitate was filtered, washed with distilled water and dried in an oven at 70°C.

- **Preparation of compound (2); [(5-amino -1,3,4-thiadiazol -2-yl) thio] acetic acid ⁽¹⁸⁾.**

This compound was prepared from compound [A] and chloroacetic acid by a general procedure, S-alkylation's ⁽¹⁸⁾ of a thiolate salt with an alkyl halide, as follow:

To a solution of compound [A] (5 mmole, 0.666 g) and chloroacetic acid (5 mmole, 1g) in 30 ml of rectified spirit, 5.7 ml of potassium hydroxide (5N) was added the reaction mixture was heated under reflux for two hrs. The hot solution was filtered to separate any insoluble materials and the ethanolic solution was evaporated under reduced pressure. The residue was dissolved in distilled water (50 ml), acidified with diluted hydrochloric acid to PH 3. The obtained white precipitate was collecting by filtration washed with cold distilled water and dried in an oven at 70°C to provide compound [2].

- **Preparation of compound [3]; [(5-amino -1,3,4-thiadiazol -2-yl) thiocarbazide] sulfonamide.**

This compound was prepared by a new procedure as follow:

In a beaker are placed; compound [B] (8.2mmole, 1.8g), hydrogen peroxide (H₂O₂, 10 ml 30 w/v), mixing with continuous stirring for 15 sec. Until the color became yellow depending on the reaction mixture, then was added thiosemicarbazide (8.2 mmole, 2.1g), after 30 sec. stirring the filtrate was collected in 95% percentage yield and identifying by melting point (223-225°C), I.R.spectrum, and uv-visible spectra.

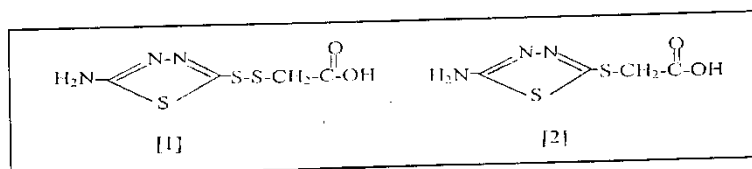
RESULTS AND DISCUSSION

The resistance of the microbes to most of the drugs makes the researchers prepared above than billion compounds then testing them against different types of microbes to know if they works or not, which men can be used it as a drug or not , as well as the changes which happing for these compound in the human being body which called it "metabolism of drugs in the human body", but why some of these compounds became drugs and other not? Answer of this question is in this research.

In this research the techniques for identification the structures of the preparing compounds, if we don't sure 100% from any structure of our compounds won't be write the research, however, the techniques includes melting point, solubility test, u.v.-visible and I.R. spectra and C.H.N.S.O. analysis.

This research depend on the following question: -

What is the difference between the two following compounds?



The answer is simple at the first time from above structures, in compound [1] there is disulfide bond (bridge) while in compound [2] only one sulfur atom. However, there are another questions are appealing, why the two compounds are dissolve in different solvents? why these two compounds have showed different biological activity against three different species ? as follow:-

Compound (1) inhibition zone by (mm), and the concentration by ($\mu\text{g}/\mu\text{l}$)

Conc. ($\mu\text{g}/\mu\text{l}$)	St. aureus	E - coli	Candida albicans
100	20 mm	17 mm	25 mm
75	16 mm	14 mm	19 mm
50	10 mm	11 mm	16 mm
25	8 mm	7 mm	9 mm

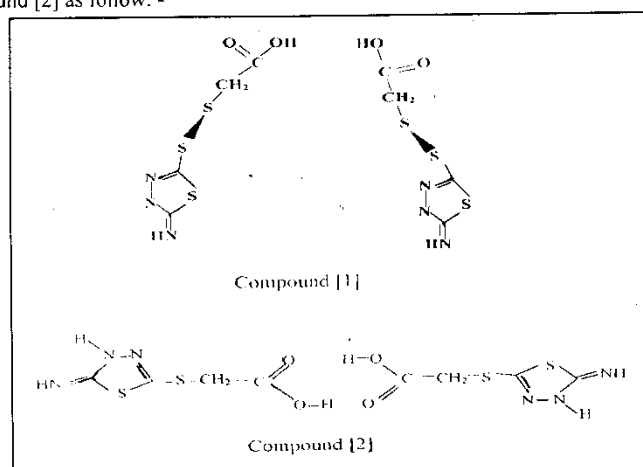
Compound (2) inhibition zone by (mm), and the concentration by ($\mu\text{g}/\mu\text{l}$)

Conc. ($\mu\text{g}/\mu\text{l}$)	St. aureus	E - coli	Candida albicans
100	1	2	2
75	-	-	-
50	-	-	-
25	-	-	-

Table (1) the biological activity for the compounds (1), and (2).

Finely, why there are some researchers believe that the disulfide bridge is necessary for biological activity and others does not ⁽¹²⁻¹³⁾ ?

All these questions, we can solve it by stereochemical structures of the two compounds, compound [1] due to the disulfide bridge it has different stereochemical structure than compound [2] as follow: -



From the structures above, and as well as we know that the 1,3,4- thiadiazole moiety is deviating from planirity by angle about 25° compound [1] has high dipole moment, while compound [2] because of dimeric acid, inverse molecules, it is dipole moment approach to zero, this is important factor effecting the biological activity, it's mean that when we want to prepare new drug we must be before everything watch the stereochemical structure of this drug and the dipole moment, if it is high or approach to zero (low). However, there are four factors illustrated depending on the more important once, the other factor does not less important than dipole moment factor which is the ability of the preparing compound to contact with Na⁺ or K⁺, which mean that is forms salt with them, and this salt is able to permeable through the membrane of the microbes and this factor became as a fact for us because we preparing more than 30 compounds, tested it in two faces ; once as salt and the other as neutral compound on different species¹⁷, and we see there is a big difference between the two faces in biological activity, the salts more active than the neutral compounds, however. As we know the living systems need either Na⁺ or K⁺ in them metabolism, as well as most drugs are salts. This is the reason for No activity which showed for compound [2] against the three species, there is no good place for Na⁺ or K⁺ in compound [2] this because of the strong hydrogen bonding (dimeric acid).In our believe the compound must contain terminal sulfar atom able to contact with sodium or potassium ions and this become as a fact for us, because we preparing a high number of compounds, and we find that the compound whose contain terminal sulfure atom, it shows high biological activity. However, compound [3] will show this fact;

At 20 µg/µl. Concentration, and (mm) inhibition zone		
<u>E. coli</u>	<u>St. aureus</u>	<u>Candida albicans</u>
32	32	12

In another words, the compound which contain high density of electrons (as compound [3] above), and good place for Na⁺, K⁺(terminal sulfur atom) must show high biological activity, and it will be good drug after studying its metabolism in the human body, and this is easy because the development of the science in this field.

All the five factors connect each other, also the rest three factors are less important than the two mention before, However they are completing each other the last three factors are: a) the compound must show high degree of the hydrophilicity, b) it must be less lipophilicity, c)

finely as a result from the four above factors, it must be more polar compound, and this is clear because any compound more polar must show less lipophilicity, and high hydrophilicity, from the old Law "like dissolve like".

Aim of this work: -

The aim of this research is to calculate the factors which effect the biological activity depending on this research or it make us easily to discovered new drugs instead of the old one which the microbes resist it, or to kill new microbes by these new drugs. Finely, from our believe "the science is the way for help the human being and may be lead to get forgiveness from our God".

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استنباط العلاقة المهمة بين الفعالية الحياتية والشكل الفراغي لبعض المركبات المحضرة
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الخلاصة

بالامكان تحضير العديد من الادوية الجديدة بالاعتماد على العلاقة المهمة التي تربط الفعالية الحياتية (الفعالية ضد الجراثيم) والشكل الفراغي للمركبات الكيميائية.
لتوضيح هذه العلاقة تم تحضير مركبين واختبرت فعاليتهم الحياتية على مجاميع من البكتريا السالبة والموجبة بالإضافة الى الفطر *Candida albicans* إذ اظهر احد المركبين (رقم 1) فعالية اكبر من المركب الاخر (رقم 2).
دراسة اشكال المركبين الفراغية ادت الى استنباط العلاقة المهمة التي اعتمدت على خمسة عوامل او صفات يجب توفرها في المركب ليكون اكثر فعالية.
لفرض تأكيد العلاقة بين الفعالية والشكل الفراغي، اظهر المركب (رقم 3) فعالية اعلى من المركبين السابقين، علما ان المركبات تم تمييزها بواسطة درجة الانصهار، اختبارات الاذابة، جهاز تحليل العناصر، طيف الاشعة تحت الحمراء وطيف الاشعة فوق البنفسجية المرئية.

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