SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME (2-AMINO-5-THIOL-1, 3, 4-THIADIAZOLE DERIVATIVES

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Abstract:

Five derivatives of thiadiazole were prepared with aldehydes and alkyl halides, compoundA: 2-amino-5-thiol-1,3,4- thiadiazole, compound B :2-(o-hydroxybenzylidine)amino-5-thiol-1,3,4-thiadiazole, compoundC: 2(2-butan-lidine)amino-5-thiol-1,3,4-thiadiazole, compound E: 2- amino-5-(2-Propanylthio)-1,3,4-thiadiazol) and compound F:2(o-chlorobenzylamino)-5-(2-propanyl thio)-1,3,4 thiadiazol. All prepared compounds were diagnosed by (IR) and (UV) Spectroscopy. All of those compounds were screened for their anti-microbial activity in vitro. The results show that most of the compounds A, B, C exhibited moderate to good activity against Gram-positive bacteria and the same compound exhibit low to moderate activity on most gram-negative bacteria under study. Finally, compound E and F had little or no effect organism.

Introduction:

Derivatives of 1, 3, 4- thiadiazol have been recognized as molecules with potential antimicrobial utility [(1)]. Survey revealed that 4,5-disubsitituted-1, 3, 4,-triazoles have emerged as potential drugs and are known to possess a broad pharmacological spectrum. A large number of 1,3,4-thiadizole derivatives have been used in many applications in medical and industrial field [(4,5,6)] and in view of many literature survey revealed the important of such derivatives [(7,8,9)]. Considering the biological activity and drugs application of the thiadiazole compounds, therefore, an idea of preparing some derivatives of thiadiazole with aldehydes and alkyl halides has been carried on.

Experimental:

1- Preparation of 2-amino -5-thiol-1,3,4 –thiadiazole (A)

Thiosemicarbazide (2.0 gm , 22.0 mmole) was dissolved in ethanol (100 ml).

Anhydrous sodium carbonate (1.6 gm, 15.0 mmole) and carbon disulfide (1.4 gm , 18.0 mmole) were added and the reaction mixture was heated at 40 C° for 1h with stirring then refluxed for 4h. The mixture was cooled and distlled . The crude product was acidified by HCl and the greenish-yellow precipitate was filtered, washed with water and recrystallized from hot water to give 2-amino-5- thiol 1,3,4-thiadiazole.(51.7%; m.p.230-232 C°).

2- Preparation of 2- substituted (benzilidene or 2-butanlydine amino-5-thiol 1,3,4-thiadizole.(B,C).

Amixture of equimolar amount of 2-amino-1,3,4-5-thiol thiadiazole and substituted aromatic aldehyde or 2-butanone in absolute ethanol was refluxed in water bath for 3h with stirring then cooled to room temperature. The product was filtered and purified with ethanol-benzene mixture.(Table A).

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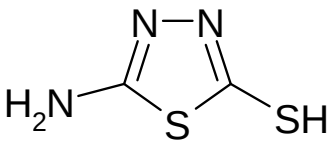
3- Preparation of 2-amino-5-(2-propanylthio)-1,3,4-thiadizole.

A solution of potassium hydroxide (14.2 mmole) in 10 ml of ethanol was added to 2-amino-5-thiol-1,3,4-thiadizole in a round bottomed flask. 2-bromopropane (1.18g,9.6 mmole)was added wisely to the mixture. The mixture was refluxed for 1h then cooled and filtered. Recrystallization from (ethanol/benzene) gave (2.0 gm, 11.4 mmole); 76%; m.p.140-142.

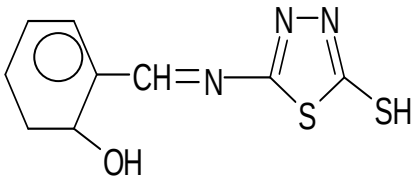
4- Preparation of 2-(o-chlorobenzylamino) -5- (2-propanyl thio)-1,3,4- thiadizole (F).

2-amino-5-propanylthio-1,3,4-thiadiazole,absolute ethanol (20ml),sodium carbonate (0.5 gm, 4.7 mmole) and 2-chlorobenzoyl chloride were mixed and refluxed for 1h then cooled to room temperature. Acidified and filtering the mixture gave a crude product which recrystallized from (ethanol-benzene) to yield (1.5gm, 4.7mmole) (57%).m.p.95-97 C°.

All the prepared compounds were diagnosed by I.R and U.V spectra. I.R proved the disappearance of C=O absorption band at (1650-1600)$cm^{-1}$and appearance of azomethine g. (C=N) absorption band at 1610 cm^{-1} , 1633cm^{-1} in the formation of compound B, C, respectively. Also (C=N) appeared at 1650cm^{-1} for compound E. Overlapping bands at 2550-2600 cm^{-1} and 2500-3300 cm^{-1} proved the presence of (-SH) and (-OH) respectively in the formation of B compound. Compound F showed band at 1630 cm^{-1} for (C=N) and band at 1647 cm^{-1} for (C=O) g. Compound E revealed band at 3300-3350 cm^{-1} for NH_2, 850-760 cm^{-1} for (C-S) and 1436 cm^{-1} for $-CH(CH_3)_2$.



(A)



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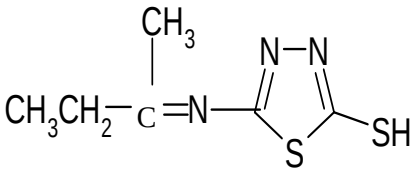

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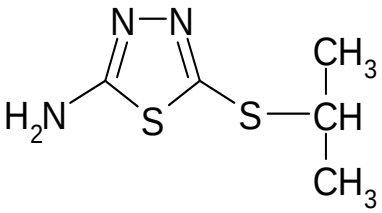

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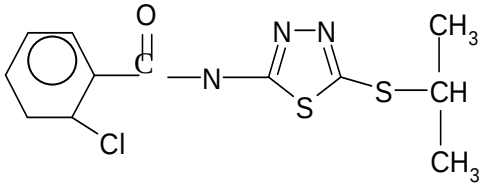

(F)

[Scheme I]

Antimicrobial activity

Compound A, B, C, E and F were selected for testing their antibacterial activity against gram –positive bacteria such as *staph-aureus, streptococci spp* and *Esterococci spp* and against gram-negative bacteria mostly *Enteric bacteria* such as *Escherichia coli, Pseudomonas spp; Proteus spp.*

Klebsiella spp Citrobater and *salmonella spp*[10], these organisms were routinely isolated from patients in AL-Yarmuk hospital. In this study disk-diffusion method using Mueller-Hinton agar was employed according to Bauer Kirby [11].

Discs about 5mm in diameter are punched from a good quality blotting paper, sterilized in a hot air oven at 160 C for 1 hr in a covered Petridis and well sled. After cooling using a standard dropping pipette delivering 0.02 ml a drop of solution of all the compounds A, B, C, E, and F.(500 Mcg of compound per ml of DMF). Each disk will contain 10 Mcg of compound. The disks are then dried by desiccator and used. These discs were compared with well known discs of antibiotics containing the same amount of antimicrobial against 10 Mcg using a susceptible gram-positive bacteria such as Ampicillin (AM), Amoxicillin(MMC), Gentamycin(CN), Nofloxacin (NOR), and Tobramycin (TOB).

From gram-negative bacteria a solution of all compound 900 Mcg of compound A, B, C, E and F speratly were dissolve in one ml of DMF each disc will contain 30 Mcg of compound. The discs were compared with well known succeptable Gram-negative antibiotics such as Amikacin (AK), Cefotoxim (CFM), (Doxocline (DO), Kanamycin (K), Nalidixic acid (NA), Netlmicin (NEF), Novobiocin (NV) and Vancomycin (NV) which containing the same amount of antimicrobial agent. These chosen antibiotics were used routinely in most hospital in Iraq.

Results and Discussion:

The prepared compounds were evaluated for their bactericidal activity in vitro according to the methods described by [14, 15]. The zone of inhibition of each strain are reported in table I and table II, for Gram-positive the activity compared with known standard drugs according to the zone size interpretative chart.

For antimicrobial activity for Gram-positive bacteria, it is evident for the screening results table (I): that most of compound especially compound A, B and C exhibited moderate to good activity against each strain of bacteria such as Staph-aureus , Streptococci spp and Enterococci. Compound A exhibited comportable activity with Ampicillin, Amoxicillin, Gentamycin, Nofloxcin and Tobramycin, the zone of inhibition 18mm in diameter which is moderate with the standard sensitivity of Ampicillin on Staph- aureus and the diameter 20mm on Streptocci similar to that of Ampicillin on the strain of Streptocci. The inhibition zone of compound A on Streptocci showed 15mm similar to Tobromycin and Gentamycin sensitive zone of inhibition.

Compound B had zone inhibition on Staph-aureus 15mm the same zone of Tubromycin and Gentamycin sensitive zone while on streptococciu spp 18 mm similar to Amoxicillin sensitive zone. On Enterococci the zone diameter is 13mm which mean moderate sensitive.

Compound C had no effect on Staph-aureus and Enterococci while on Streptococci spp the zone of inhibition 15 mm which means sensitive as well as Tobronmycin and Gentamycin, and then compound E and F showed that all gram-positive bacteria were resistant.

Gram-negative bacteria such as E-coli, Protes spp, Pseudomonas spp and Klebsiella spp, it has been observed that compound A exhibited low to moderate activity which is comparable chosen such as Amikacin, Cefofoxim, Doxycline, Kanamycin, Nalidixin and Neltmicin and Novobiocin while it is notice that compound A of that of Vancomycin 12mm. However, compound B effect on E-coli,Protes and

Klebsiella spp moderately while Pseudomonas resistant to this compound. Similarly compound C effect on E-coli with sensitive zone of inhibition the same with Neltmicin 15mm and more than of Vancomycin 12mm but the compound C effect modratly on Proteus and Klebsiellae while Pseudomonas were resistance. Compound E most bacteria showed resistant such as Proteus spp Pseudomona spp, and Klebsiellae spp while E-coli sensitive with the zone of inhibition to which mean resistand if it compared with the standerad discs(chart1). Finally compound E had no effect on Gram-negative bacteria, all the bacteria under study were resistant to the compound E.

Table A: Antimicrobial activity of compound A,B,C,E and F on Gram-positive bacteria compared with Known standard antibiotic discs potency 10Mcg.

Antimicrobial Agents	Sample	Conc. Mcg	Susceptible Zone	Antimicrobial Activity of Gram+ve Bacteria (zone of inhibition)		
				Staph-aures	Strept	Enterococci
Ampicillin	AM	10	≥20	15	15	10
Amoxicillin	AMC	10	≥18	18	18	10
Gentamycin	CN	10	≥15	15	15	13
Nofloxcin	NOR	10	≥17	17	17	15
Tobramycin	TOB	10	≥15	15	15	13
Compound A	A	10	–	18	20	15
Compound B	B	10	–	15	18	13
Compound C	C	10	–	R	15	R
Compound E	E	10	–	R	R	R
Compound F	F	10	–	R	R	R

R: resistance on inhibitory zone.

Table B: **Antimicrobial activity of compound A, B, C, E and F on Gram-positive bacteria compared with Known standard antibiotic discs potency 30Mcg**.

Antimicrobial agents				Antimicrobial activity of G-ve Bacteria zone of inhibition			
Agents	sample	Conc.	Susceptible zone	E.coli	proteins	pseudomoras	Kleb siellae
Amikacin	AK	30Mcg	17	17	17	17	17
Cefotoxim	CFM	30	18	18	16	14	18
Doxyclin	DO	30	16	15	12	10	16
Kanamycin	K	30	18	18	18	14	17
Nalidixic acid	NA	30	19	19	18	14	17
Neltmicin	NET	30	15	13	10	10	10
Novobocin	NV	30	22	20	17	12	20
vancomucin	VA	30	12	12	9	12	12
Compound	A	30	–	14	15	12	10
Compound	B	30	–	13	12	R	9
Compound	C	30	–	15	10	R	10
Compound	E	30	–	10	R	R	R
Compound	F	30	–	R	R	R	R

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تحضير وقياس الفعالية البايولوجية لبعض مشتقات (2-امينو-5ثايول-1,3,4 ثايودايزول)

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الخلاصة:

يتفاعل مركب 2-امينو -5-ثايول-1،3،4- ثاياديازول مع الالديهايدات والهاليدات الالكيلية فيعطي العديد من المشتقات -2-امينو -5-ثايول-1،3،4 ثاياديازول (A) ، 2(اورثو-هيدروكسي بنزلدهايد)أمينو-5- ثايول1،3،4 ثاياديازول (B)،2-(2-بيوتيل الديهايد) أمينو -5-ثايول -1،3،4-ثاياديازول (C)،2-أمينو-5-(2-بروبانيل ثايو) - 1،3،4 – ثاياديازول (E)،2(اورثو كلوروبنزايل امينو)-5-(2-بروبانيل ثايو)-1،3،4-ثاياديازول تم تحضيرها وتشخيصها طيفيا من خلال دراسات طيف تحت الحمراء وفوق البنفسجية .

هذه المركبات جميعها قد تم دراسة فعاليلتها المضادة للبكتيريا. اظهر النتائج ان المركبات C,B,A ذات فعالية متوسطة الى جيدة نحو بكتيريا كرام-(موجب) وتمتلك فعالية قليلة الى متوسطة نحو بكتيرياكرام (سالب) فيما المركبات E، F تمتلك فعالية قليلة جدا نحو البكتيريا السابقة .