Synthesis and Characterization of N-((6- substituted - Benzothiazol -2-Y) succinamic acid , 3-(6- substituted -benzothiazol-2-Yl) - Carbamoyl Propionyl Chloride and study of their Biological effects

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Date of acceptanc 8/1/2005

ABSTRACT

Twelve N-(6-substituted -benzothiazol-2- yl) -Succinamic acids and 3-(6-substituted -benzothiazol-2-yl)-carbamoyl propionyl chloride were synthesized in good yields from reaction of 3- benzothiazol-2-yl)-carbamoyl acrylic acid with thionyl chloride and the yield reacted with bromine solution . The resulting compounds areidentified by their mps, Elemental Analysis,IR.,UV.and HNMR.spectra. Their structural formul were on firmed. The biological activity of these compounds studie with a group of bacteria isolate and were compared with anti-biotics.The compounds had shown varying activityes depending on their cocentrations and the type of the substituting group

INTRODUCTION

Amic acids are compounds that contain both a carbonyl group and an amide group in their structures. They are obtained directly from the reaction of primary amines with avariety of cyclic carboxylic acid anhydrides.The usefueness of amic acids lies in their uses in the synthesis of amic acid chlorides,esters ,amides,and imides[1-4]

Amic acid ,amic amides and their related derivatives have long been known to possess herbicidal activity.Derivatives of N-aryl phthalamic acid ,possess growth regulting properties. N-(β-naphthyl) phthalamic acid (naphthalam) and their derivatives are used as selective premergence herbicides for vegitable, soybeans, potatoes and groundnuts. [5,6]

Thus,amic acid chlorides are prepared by the reaction of amic acids with thionyl chloride. They are very reactive compounds that contain acidic chloride and an amide group in their structures.The chemical behaviour of amic acid chlorides is similar to that exhibited by the carboxylic acid chlorides [5]. Their high activity towards nucleophillic substitutions is attributed to the presence of the carbonyl group in their structures. Aromatic amic acid chlorides are less reactive than aliphatic amic acid chlorides and both are more reactive than alkyl halides towards nucleophilic substitution. [6]

N- phenylcyclohexylamic acid is prepared from the reaction of 1,2-cyclohexyl dicarboxylic anhydride with aniline in dry acetonitrile[7]

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3-(6-substituted-Benzothiazol -2-yl)carbamoyl-acrylic acid is prepared from the reaction of 6-R-2- amino benzothiazol with malic anhydride. [8]

EXPERIMENTAL

The Melting points of the 3-(6-substituted-benzothiazol-2-yl)-succinamic acid and 3-(6- substituted-benzothiazol-2-yl) - carbamoyl propionyl chlorides were recorded with a Gallen Khamp melting point apparatus and are listed in table(1). Elemental analysis is shown in table(1) . IR.spectra were recorded with FT-IR- spectrophotometer as KBr disc . Dise(table 2). UV-absorption maxima were recorded in ethanol with Shimadzu-Reec. and ^{1}HNMR spectra were recorded on a Bruker-AC-200 MHz FT-NMR spectrophotometer in Mutah university ,The δ values are shown in table (3).

Preparation of N-(6-substituted-benzothiazol-2-yl)-succinamic acid.

To a solution of (0.02 mole) succinic anhydride in 50 ml dry dioxan was added (0.02 mole) 6-substituted -2-amino benzothiazole. The mixture was refluxed for 2 hr, then cooled to room temperature.The solvent was evaporated and the solid product was reerystallized twice from ethanol to give N-(6-substituted -benzothiazol-2-yl)-succinamic acid

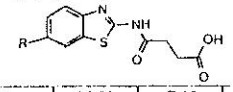
3-(6- substituted -benzothiazol-2-yl carbamoyl)-propionyl chloride.

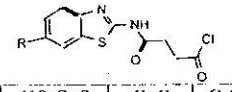
In a (100 mL) round bottom flask, equipped with a double surface condenser fitted with anhydrous calicium chloride guard tube was placed a mixture of (0.02 mole) of N-(6- substituted -benzothiazol-2-yl)-succinamic acid and (0.03 mol.) of thionyl chloride and (25 mL) of anhydrous THF. The reaction mixture was refluxed on a water bath for 1 hr . The solvent and excess thionyl chloride were evaporated and the resulting solid was reerestystalized from dry THF and dried in vacuum at ambient temperature to give crystals of 3-(6- substituted -benzothiazol-2-yl carbamoyl)-propionyl chloride.

RESULTS & DISCUSSION

The infrared spectra of the prepared N-(6- substituted-benzothiazol-2-yl)-succinamic acid showed many bands due to stretching and bending vibrations of the defferent groups present in the titled acids molecules. In general, IR spectra of benzothiazol succinamic derivatives showed three bands in the region (3080-3375) cm^{-1}, these bands were assigned to OH carboxylic,and NH stretching vibrations (sometimes the NH absorption were found to overlap with carboxylic OH absorption). On the other hand IR spectra showed two strong carbonyl absorption bands. One of them was observed in the region (1705-1760)cm^{-1} due to stretching of carboxylic acid carbonyl while the second band was observed at lower frequency (1620-1650)cm^{-1} , due to the stretching of amide carbonyl medium intensity bands were also observed at (1510-1555)cm^{-1} which might be assigned to NH bending in plan. Data of the IR spectra of the 3-(6- substituted -benzothiazol-2-yl carbamoyl)-propionyl chloride derivatives are listed in table(2) . In the region (1710-1740)cm^{-1} due to stretching of carbonyl chloride, IR spectra of all the prepared derivative showed amedium absorption at wave number (1570-1595)cm^{-1} due to stretching vibration of (C=C) due to aromatic bond.The chemical shifts of individual protons of all (12) derivatives were assigned and given in table (3). From this table one can observ that there are (CH_3) group protons at δ

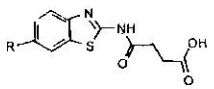
Table (2) I.R Spectra of N- (6-substituted-benzothiazol-2-yl)succinamic acid and 3-(6-substituted benzothiazol-2-yl)- Carbamoyl prppionyl chloride

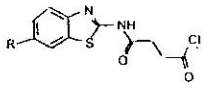




No	R	N-H	C-H *aromatic*	HN-C=O *amide*	Cl–C=O carbonyl	*HO-C=O* carbony	C=C *aromatic*	C-Cl	Other group	
1	4,6-di CH_3	3418	3022	1690	-	1720	1590	-		
2	NO_2	3400	3015	1670	-	1715	1580	-	1538,1368	NO_2
3	CH_3	3390	3044	1680	-	1730	1590	-		
4	OCH_3	3412	3065	1650	-	1740	1585	-		
5	Cl	3418	3080	1668	-	1725	1570	738		
6	Br	3410	1075	1670	-	1720	1580	-	680	C-Br
7	4,6-di CH_3	3420	3020	1690	1740	-	1575	730		
8	NO_2	3411	3018	1675	1730	-	1580	735	1548,1372	NO_2
9	CH_3	3389	3040	1660	1720	-	1570	730		
10	OCH_3	3410	3060	1650	1740		1585	725		
11	Cl	3417	3070	1660	1710	-	1590	730		
12	Br	3415	3070	1660	1715	-	1595	733	660	C-Br

Table (3) ^{1}HNMR Spectrophotometry and UV-Vis of N- (6-substituted-benzothiazol-2-yl)succinamic acid and 3-(6-substituted-benzothiazol-2-yl Carbamoyl)- prppionyl chloride





^{1}HNMR (DMSO-d_6) ppm

No	R_2	R – H	Benzothiazol ring						UV-VisSpectra ↑/nmin Ethanol
			H_4	H_5	H_7	N-H	α-H	β-H	
1	$2CH_3$	2.35,3.35		7.15	7.7	8.0	2.4	2.35	430,380,260,245,233
2	$-NO_2$		8.44	8.45	9.0	8.0	2.5	2.45	579,400,358,266,220
3	$-CH_3$	2.35	8.1	7.33	7.8	8.0	2.4	2.35	412,335,290,250,223
4	OCH_3	3.35	8.1	7.0	7.6	8.0	2.4	2.35	438,366,258,226
5	CL		8.2	7.45	8.1	8.0	2.5	2.45	403,366,259,240,220
6	Br		8.1	7.7	8.3	8.0	2.5	2.45	406,365,250,243,229
7	$2CH_3$	2.35,3.35		7.1	7.7	8.0	2.4	2.35	428,386,265,231,220
8	NO_2		8.5	8.4	9.0	8.0	2.4	2.35	550,408,367,263,222
9	CH_3	2.35	8.1	7.3	7.9	8.0	2.4	2.35	410,339,288,244,226
10	OCH_3	3.6	8.1	7.0	7.6	8.0	2.5	2.45	430,376,268,229
11	CL		8.15	7.49	8.2	8.0	2.5	2.45	409,358,269,227
12	Br		8.13	7.7	8.3	8.0	2.5	2.45	411,378,275,242,225

Biological activity

Material & Methods;

1-Preparation of concentration ;

Five diluted solutions were prepared from the compounds under study. These were (10,25,50,75,100) mg/mm. Disks of filtering paper were saturated with each dilution in order to decide the deactivating capacity of these compounds the isolated specimen of pathological bacteria.

2- The Isolated bacteria specimen;

Specimen of bacteria were obtained from diffrent cases from the **Labs of Ramadi Central Hospital** that cover wonnds., burns , stolls, urine and ear infections. These specimen were diagnosed and cultured on a nutrient agar medium for use in the experiment,and in measuring the deactivating capacity of the prepared compounds.

The following table shows the sources of the bacteria obtained and their media.

Isolated bacteria	sources	Culture
Staphylococcus aureus	stolls	Blood agar
Proteus merabilis	urine	Blood agar
Pseudomonas aeruginosa	Ear infection	Nutrient agar
Klebsiella pneumoniae	burns	MacConkey agar
Salmonella typhi	urine	S.S. agar
Shigella Sonni	urine	S.S. agar

3- Test of deactivating capacity of the prepared compounds;

The deactivating capacity agent of the isolated bacteria of these compounds was tested by using the method of the spread over the dises as discribed by **Bauer, *et al* in (1966).** [11] This method uses dises of filtering paper saturated with five defferent concentrations (10,25,50,75,100) of the given compound after culturing this bacteria on dishes on the hard Muller –Hinton medium. Dises of filtering paper,that were saturated with these different prepared compounds , were placed on the medium and then incubated at 37c° for 24 hours. Anti-biotics (Tetracycline,Amoxicillin,Nalidixic acid, Gentamycin) were used to control the bacteria specimen. The deactivation dimeters were measured by special ruler designed for this purpose.

Results

Tabel (4) and (5) show the deactivation capacity against the bacteria specimen of the prepared compounds under study . The results show that low concentrations did not have any de activation capacity against the bacteria specimen, differing deactivation capacity . Some others did not show any diactivation wheras the narrow deactivation zone is in concentrations 75,and 100 MG/mm .

Discussion

The results of the present study show that some of the prepared compounds have a relativily weak deactivating capacity against the spacimen of bacteria. This is due to natural resistince , mutations or the resistince of blasma that requires further study. Bacteria is known to be anti-toxic and enjoys a resistince to anti-biotic for blasma._The results indicate that these compounds are not able to pentrate to their target area in the cell , because of a barrier, like the external tissue in the cellular wall of the negative bacteria of **Grame Colour** . This may prevent the extracted access to the center of vital effect in the cell. The lack of deactivation areas for some compounds may be due to the lack of the suitable carrier in the cell or the necessary energy to have access to the internal target.[12]

The results ,on the other hand,show that some compounds have a good deactivating capacity against the isolated bacteria specimen. This is due to the percentage of active material solved in the water . Water is known to be the most common solvent in nature.It can solve many compounds. The number and quality of active groups in the compound have an effect on the deactivating effect on microbes.[13]

The study showed also many evidences of other active anti-biotics that can be put to further use in the system of Bio-resistense against the causes of several plant diseases in order to avoid the excessive use of the chemical pasteycides that cause environumental problems and are very expensive.

Table (4)
Diameters of deactivation of Bacteria by use Amcic acid compound in different concentration

Name of compound	concentrate	B.Isolated: Staphyloco ccus aureus	Klebsiella pneumonia	Proteus merabilis	Pseudomon as aeruginosa	Salmonella Typhi	Shigella sonni
		Diameters of diactivation (mm)					
N-(4,6-Dimethyl-benzothiazol-2yl)-succinamic acid	10	0	0	0	0	0	0
	25	0	0	0	0	0	0
	50	0	0	0	0	0	0
	75	0	0	0	0	0	0
	100	0	0	0	0	0	0
N-(6-Methyl-benzothiazol-2yl)-succinamic acid	10	0	0	0	0	0	0
	25	0	0	0	0	0	0
	50	0	0	0	0	0	0
	75	4.0	5.0	5.0	8.0	7.5	6.0
	100	5.0	5.4	6.0	9.5	12.0	9.0
N-(6-Nitro-benzothiazol-2yl)-succinamic acid	10	0	0	0	0	0	0
	25	0	0	0	0	0	0
	50	2.4	3.1	1.9	1.7	2.2	1.2
	75	5.0	5.7	8.7	10.0	10.0	9.0
	100	6.0	6.2	9.0	12.0	12.0	9.0
N-(6-Chloro-benzothiazol-2yl)-succinamic acid	10	0	0	0	0	0	0
	25	0	0	0	0	0	0
	50	0	0	0	0	0	0
	75	7.5	8.0	12.0	10.0	12.0	8.0
	100	9.0	9.0	13.0	12.0	13.0	14.0
N-(6-Bromo-benzothiazol-2yl)-succinamic acid	10	0	0	0	0	0	0
	25	0	0	0	0	0	0
	50	0	0	0	0	0	0
	75	12.0	11.0	9.0	9.0	8.0	7.0
	100	15.0	13.0	12.0	9.0	10.5	12.5
N-(6-Methoxy-benzothiazol-2yl)-succinamic acid	10	0	0	0	0	0	0
	25	0	0	0	0	0	0
	50	2.5	1.9	2.0	4.0	3.5	3.0
	75	6.0	8.0	7.0	5.0	6.0	8.0
	100	10.0	12.0	9.0	8.0	11.0	14.0
Tetracycline	300µg	8.0	9.0	11.0	12.0	7.0	10.0
Nalidixic acid	30µg	11.0	13.0	20.0	13.0	22.0	12.0
Amoxicillin	20µg	11.0	6.0	5.0	12.0	0	0
Gentamycin	30µg	9.0	6.0	8.0	0	11.0	20.0

Table (5)
Diameters of deactivation of Bacteria by use Amcic Chloride compound in different concentration

Name of compound	concentrate	B.Isolated: Staphyloco ccus aureus	Klebsiella pneumonia	Proteus merabilis	Pseudomon as aeruginosa	Salmonella Typhi	Shigella sonni
		Diameters of diactivation (mm)					
3-(4,6-Dimethyl-benzothiazol-2ylcarbamoyl)- propionyl chloride	10	0	0	0	0	0	0
	25	0	0	0	0	0	0
	50	0	0	0	0	0	0
	75	3.0	4.0	6.0	4.0	5.0	5.0
	100	9.5	9.0	13.0	10.0	8.0	8.0
3-(6-Methyl-benzothiazol--2ylcarbamoyl)- proplonyl chloride	10	0	0	0	0	0	0
	25	0	0	0	0	0	0
	50	0	0	0	0	0	0
	75	6.0	9.0	8.0	5.0	4.5	5.0
	100	13.0	18.0	10.0	8.0	7.5	9.0
3-(6-Nitro-benzothiazol-2ylcarbamoyl)- propionyl chloride	10	0	0	0	0	0	0
	25	0	0	0	0	0	0
	50	12	16.0	22.0	4.0	15.0	10.0
	75	22.0	25.0	24.0	18.0	14.0	12.0
	100	25.0	29.0	28.0	22.0	16.0	22.0
3-(6-Chloro-benzothiazol-2ylcarbamoyl)- propionyl chloride	10	0	0	0	0	0	0
	25	0	0	0	0	0	0
	50	0	0	0	0	0	0
	75	8.0	7.0	9.0	10.0	11.0	15.0
	100	11.0	9.0	10.0	13.0	12.0	17.0
3-(6-Bromo-benzothiazol-2ylcarbamoyl)- propionyl chloride	10	0	0	0	0	0	0
	25	0	0	0	0	0	0
	50	5.0	7.0	6.0	8.0	7.0	5.0
	75	12.0	10.0	10.0	12.0	9.0	8.0
	100	18.0	14.0	12.0	15.0	14.0	12.0
3-(6-Methoxy-benzothiazol-2ylcarbamoyl)- propionyl chloride	10	0	0	0	0	0	0
	25	0	0	0	0	0	0
	50	2.0	3.5	4.0	5.0	3.0	4.0
	75	4.0	5.0	8.0	9.0	6.0	8.0
	100	7.0	10.0	13.0	15.0	10.0	9.0
Tetracycline	300µg	8.0	9.0	11.0	12.0	7.0	10.0
Nalidixic acid	30µg	11.0	13.0	20.0	13.0	22.0	12.0
Amoxicillin	20µg	11.0	6.0	5.0	12.0	0	0
Gentamycin	30µg	9.0	6.0	8.0	0	11.0	20.0

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١١. رويحة،أمية١٩٧٣ التـــداوي بالإعشـــاب بطريقة علمية تشمل الطب الحديث والقديم.

١٢. الزبيدي، زهير نجيب بابان ، هدى عبـــد الكريم و فليح كاظم فـــارس ١٩٩٧ دليـــل العلاج بالإعشاب الطبية العرقية- شـــركة آب للطباعة المحدودة. بغداد- العراق

((تحضير وتعيين الصيغ التركيبية لمركبات N-(٦-معوض-بنزوثيازول - ٢-يل)-حامض السكسنآميك , ٣- (٦-معوض- بنزوثيازول-٢-يل كاربامويل)- كلوريد البروبيونيل ودراسة الفعالية البايولوجية)) .

محمد عبد الكريم طلك الحديثي

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الخلاصة

تم تحضير ستة من مركبات N-(٦-معوض- بنزوثيازول -٢-يل)- حامض السكسنأميك فوعلت مع كلوريد الثايونيل للحصول على ٣-(٦-معوض -بنزوثيازول-٢-يل كاربامويل)- كلوريد البروبيونيل. شخصت المركبات المحضرة بتحديد نقاط انصهارها , وأطياف الاشعة فوق البنفسجية ,الأشعة تحت الحمراء و أطياف الرنين النووي المغناطيسي , وقد ثبتت صيغها التركيبية. درست الفعالية البايولوجية لجميع هذه المركبات مع عدد من العزلات الكتيرية و مقارنتها بمضادات حياتية أظهرت المركبات فعالية مختلفة بالاعتماد على تركيزها وعلى نوع المجموعة المعوضة .