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Synthesis and Evaluation of Biological Activity of Novel Sugar-Derived Aziridines

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Abstract: The Sugar derived aziridine was obtained from iodo-aziridines through *in situ* nucleophilic expulsion of iodine using glucosamine as a nucleophile. This work describes new results of our ongoing research targeting new aziridines of biological interest. All the compounds were screened for their antibacterial activity, they all showed comparable moderate to good growth inhibitory activity with reference to Tetracyclin, Ciprofloxacine and Gentamicin.

Keywords: Aziridines, peptidomimetic, sugar, antibacterial activity.

I. Introduction

Antibiotic resistance is one of the major health problems in modern societies, causing millions of deaths per year [1-3]. Although Alexander Fleming recognized the importance of the resistance phenomena as early as 1940 [4] , in the 1970s the problem of bacterial infection seemed to be solved, because a wide range of potent antibiotics were available. During the last two decades the situation nevertheless changed dramatically: the logarithmic rise in the prevalence of penicillin-resistant pneumococci, for example, led to the description of the situation today as an "Antibiotic Armageddon [5]. In a recent WHO report it is concluded that "the problem is so serious that it threatens the achievements of modern medicine. A post-antibiotic era, in which common infections and minor injuries can kill, is a very real possibility for the 21st century [6]. The need for a fast but effective, structure-based strategy for the development of new antibiotics is therefore more than evident [7-8].

Aziridines represent an important class of compounds that exhibit antibacterial activities against a wide range of bacteria [9-12], anticancer, and/or antimicrobial and antileishmanial activities [13-16]. Some among them behave as potential protease inhibitors [17-18]. Therefore, an assumption might be made that the presence of an aziridine moiety in natural as well as synthetic compounds structures is essential to the observed activities [19].

The biological activity of aziridines is highly related to the establishment of covalent bond with DNA [20]. In a previous work we reported the synthesis of aziridinyl derivatives Fig.1 that had antitumor activities against breast cancer cells [21]. Such a behavior was likely due to their capacity to strengthen and modulate the immune system [22]. We have, already reported the synthesis of several aziridines Fig 2. [23-26], which we replaced the amino acids phtaloyl protecting group with a phosphonate moiety Fig 3. and, surprisingly, the biological activity of the novel Phodphonates aziridines shifted from antiviral to an antibacterial one [27-28].

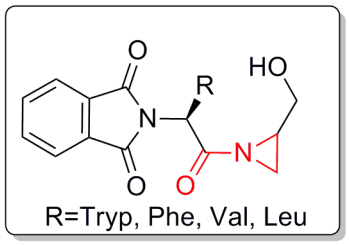

Fig.1: Peptidomimetic aziridine

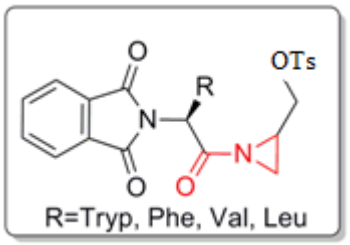

Fig.2: Tosylate Aziridine

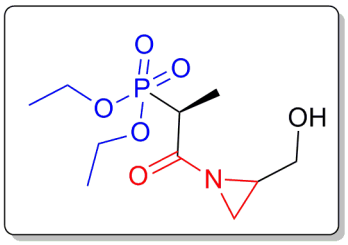

Fig.3: Aziridinylphosphonate

By contrast with the above mentioned studies, the development of processes for the synthesis of functionalized aziridines may represent a useful way to access interesting compounds that might play important therapeutic roles [29]. As a result, several syntheses are found in the literature and it is beyond the scope of this work to mention all of them [30- 41].

Thus, going on with our efforts to develop new biologically active aziridines, we set up this work with a view to developing a general method leading to new series of sugar-derivatives aziridines as potent antibacterial agents against Gram-positive and Gram-negative bacteria. With an aim to enlarging the scope of the already observed activities.

II. Experimental Section

All the reactions with dry solvents were carried out under dry nitrogen. THF was dried over sodium /benzophenone and freshly distilled before use; CH_2Cl_2 was distilled and dried over phosphorus pentoxide (P_2O_5). I.R spectra were collected from a Mattson Genesis II FTIR. NMR spectra were recorded in $CDCl_3$ on a Bruker 300MHz instrument, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ (ppm) and coupling constant (*J*) values in Hertz (Hz). ESI-MS data were recorded in the positive ion mode on a quadrupole instrument (Waters-Micromass ZQ). Melting points were determined on an Electrothermal T1A F3.15A instrument. Column chromatography was performed on silica gel 230-270 mesh (Merck) using CH_2Cl_2, MeOH and ether. Elemental analysis was performed only for solids on a LECO CHN 900 instrument.

II.1. Antibacterial assays

II.1.1. Procedure

The prepared compounds **2a-f**, and **3a-f** with Concentration, 32µg/ml were evaluated for their antibacterial activities against *Bacillus cereus* and *S.aureus* (Gram-positive), *Escherichia coli* and *Klebseilla pneumonie* (Gram-negative) by performing disc diffusion assays. The volumes from liquid cultures were spreaded onto nutrient agar in plates. The discs containing test compound and DMSO (control) were introduced into the middle of the bacteria inoculated agar surfaces in petri plates. The cultures were incubated 24h at 37°C. Tetracyclin and Gentamicin were used as the reference drugs. The results were recorded for each tested compound as the average diameter of bacterial growth inhibition zones around the disks in mm.

III. Results and Discussion

III.1. Chemistry of *Iodo-aziridines*

Many approaches are developed in literature to obtain aziridines, but only few are describes for the synthesis of sugar derivatives aziridine [42]. So the main idea was if the presence of sugar moiety in the structure of our aziridines will improve or not the antibacterial activity of the novel analogues.

Our synthetic pathways to target 2-glucosyl-aziridines **3a-f,** are presented in Schemes 1 and 2. First, we embarked in the preparation of *N*-acyl-2-tosylymethylaziridines **1a-f** with interesting anti-bacterial activities to a protocol previously developed in our laboratory [26]. Then, substitution of the group tosylate by iodine leading to original functionalized 2-iodo-aziridines **2a-f** that could be isolated and evaluated for the antibacterial activity.

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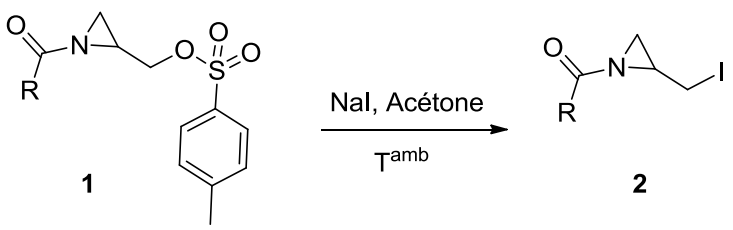
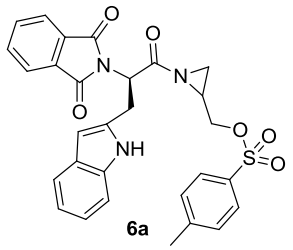
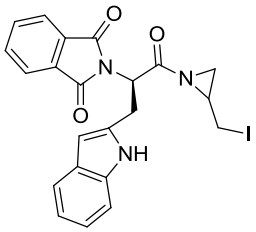
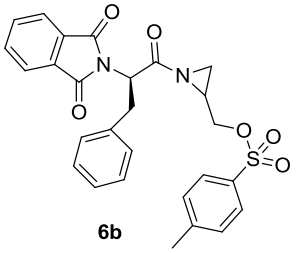
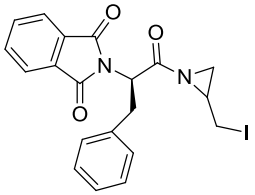
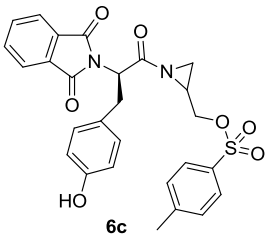
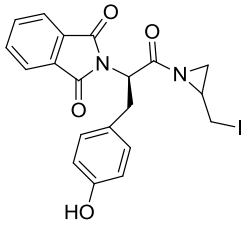
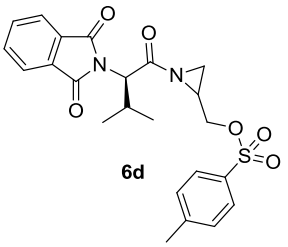
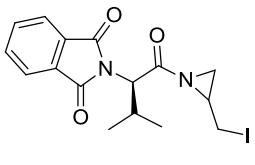
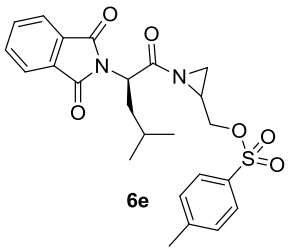
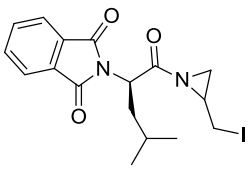


Scheme 1: N-Phtalimido-N-acyl-2-iodo-aziridines.

The reaction of the serie to 2-iodo-aziridines, takes place in acetone at room temperature and in the dark. The target compounds are obtained with good yield 58-70% as mentioned in table 1.

Table 1 : Structures of series of iodo-aziridines: N-Phtalimido-N-acyl-2-iodo-aziridines.

Tosylates aziridines	iodo aziridines **2a-f**	time of reaction (h)	Yiled %
 **6a**		t = 96h	Rdt= 58%
 **6b**	 **6b**	t = 48h	Rdt= 70%
 **6c**	 **6c**	t = 48h	Rdt= 66%
 **6d**	 **6d**	t = 24h	Rdt= 78%
 **6e**	 **6e**	t = 48h	Rdt= 72%

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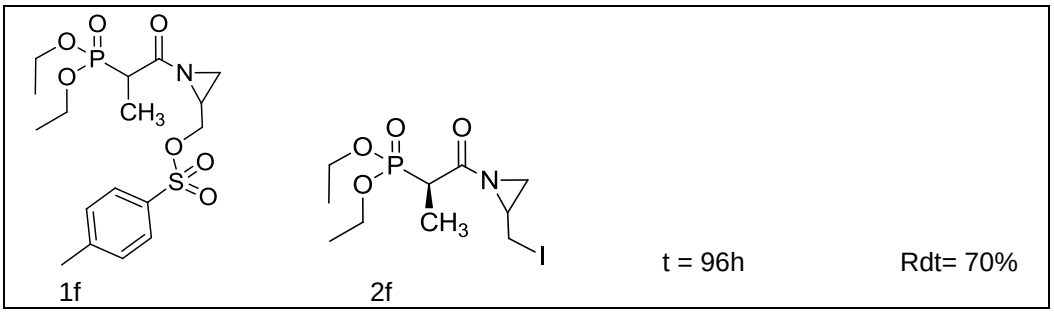

III.2. Antibacterial activity of *Iodo-aziridines*

*Table 2 : Antibacterial activity of series of **N-Phtalimido-N-acyl-2-iodo-aziridines**.*

Aziridines		**Inhibition zone diameter (mm)** *B.cereus*	*S.aureus*	*E.Coli*	*K.pneumoniae*
2	**a**	-	8±2	8±3	11±4
	b	-	6±3	7±2	9±3
	c	-	8±3	7±3	10±2
	d	-	7±2,5	6±3	8±2
	e	-	-	-	8±2,5
	f	-	16±2	16±2	17±3
Tetracycline		20	20±1	17±1	19±2
Gentamicine		18	19±2	18±1	19±2
Ciprofloxacine		25	26±2	26±2	22±1

Compounds **2a-e and 3a-e** with Concentration, 32µg/ml, were screened for their antibacterial activity against multidrug resistant bacteria chosen from the Centre Hospitalo-Universitaire de Tlemcen/Algeria where they are responsible for a number of nosocomial infections. The bacteria of concern were namely *Bacillus cereus* and *Staphylococus aureus* (Gram-positive), *Escherichia coli* and *Klebseilla pneumonia (*Gram-negative). The screening was performed on disc diffusion assays. Tetracycline, Ciprofloxacine and Gentamicine (CT0056B, OXOID), were used as reference drugs. The results were recorded for each tested compound as the average Diameter, mm of the inhibition zone of bacterial growth (Fig. 4)

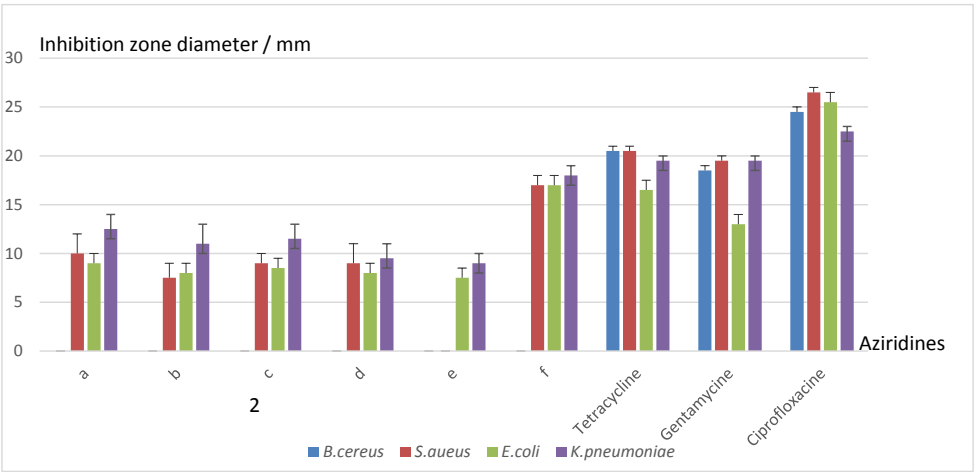

Fig .4. Antibacterial activities of 2-iodo-azirines.

In order to obtain active aziridines, we then prepared the nvel series of 2-iodo-aziridines, in wich the amino acid motif "Phthaloyl" is always present, while the tosylate group is substituted with an

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iodine group. The big surprise with this series of aziridines **Az-2a-f**, was that the activity has almost completely disappeared from the tosylates aziridines series as shown in or previous investigation [26].

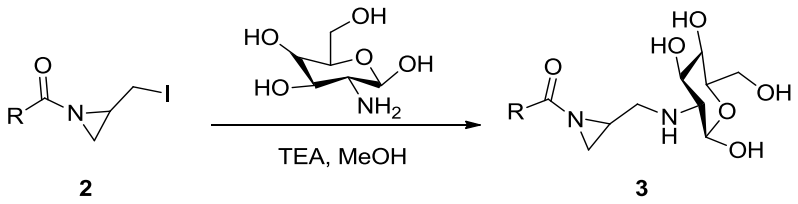
The most pronounced activity is retained against pneumonia Klebseilla, with aziridine **Az-2f** those with the motif of "phosphonate", and it presence was already seen mandatory to improve the antibacterial activity in our previous work with the series of phosphonates-aziridines [27]. Good activity was observed of the same **Az-2f** against both *S.aureus* and *E.Coli.*

From results displayed in Fig.4, we can assume that on the whole, our compounds are more active against Gram negative than Gram positive bacteria. Nevertheless, compound **2a-f** was inactive against *Bacillus cereus* while compounds **2a-d** showed a moderate inhibitory activity against the different bacterium.

III.3. Chemistry of Glucosyl aziridines

Monosaccharides represent an important class of natural products and constitute with the amino acid building blocks of natural polymers. Their structural characteristics lead them to be widely used in the architecture of natural molecular structures. Indeed, their cyclic structure ensures their rigidity. The presence of multiple hydroxyl functional groups corresponds to as many functionalization positions. Their chirality provide guidance to different hydroxyl and therefore substances related to those functions. These three major advantages allow saccharide units to be used as platforms for the synthesis of compounds likely to have biological activity [43]. In the search for structure-activity relationship, we thought of exploiting properties of sugar with aziridine ring aiming to improve their antibacterial activity.

Interested by these multiple properties and the fact that are few examples in the literature on aziridines-derived sugars, we have developed a very simple method to access to aziridines glucoside pattern , and, to the best of our knowledge, no report is available with N-acyl-2-gluosyl-aziridine.



2 **3**

Scheme 1: N-Phtalimido-N-acyl-2-glucosylaziridines.

The N-acyl-2-iodo-aziridine. **2 a-f** were converted into target to aziridines **3 a-f** after reaction at room temperature with glucosamine, in the presence of TEA in methanol, to afford the novel series of aziridines in moderate to good yield 38-41% as mentioned in table 3.

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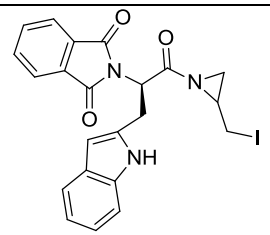
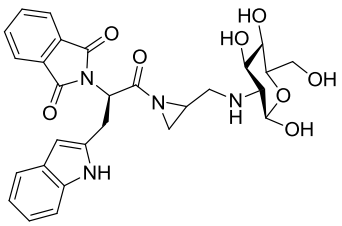
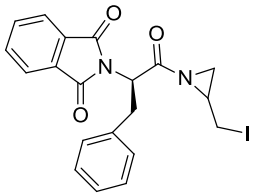
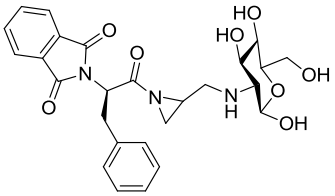
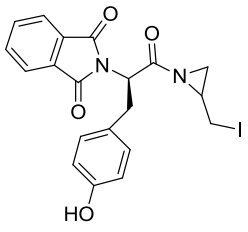
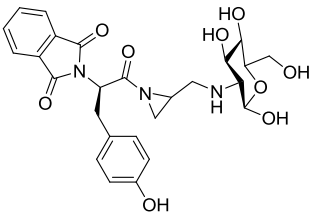
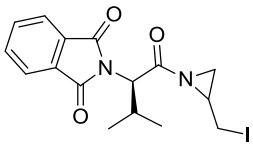
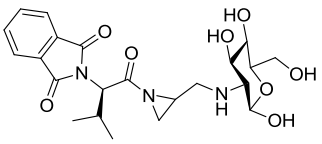
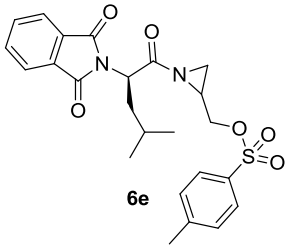
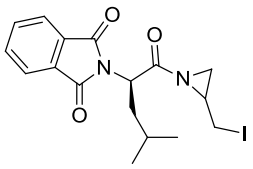
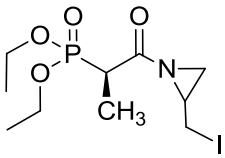
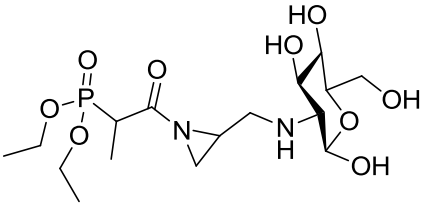
Table 3 : Structures of series of glucosyl-aziridines: ***N-Phtalimido-N-acyl-2-glucosylaziridines*****.**

Tosylates aziridines	iodo aziridines **3a-f**	time of reaction (h)	Yiled %
		t = 96h	Rdt= 38%
 **6b**		t = 48h	Rdt= 45%
 **6c**		t = 48h	Rdt= 41%
 **6d**		t = 24h	Rdt= 40%
 **6e**	 **6e**	t = 48h	Rdt= 42%
		t = 48h	Rdt= 42%

III.4. Antibacterial activity of Glucosyl aziridines

The introduction of the glucosyl group in the structure of our aziridines was successful, the antibacterial activity was amplified. With the best results obtained for **Az-3a-c** against the strain *Klebseilla pneumonia*. However, it is important to note that this modification on the structures, has not

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improved activity against B.cereus, because the activity of these aziridines still zero.

Table 4 : Antibacterial activity of series of N-Phtalimido-N-acyl-2-glucosylaziridines.

Aziridines		Inhibition zone diameter (mm)			
		B.cereus	*S.aureus*	*E.Coli*	*K.pneumoniae*
3	a	-	12±2	16±2,5	18±3
	b	-	10±2,5	15±3	17±2
	c	-	13±3	18±3	19±3
	d	-	8±1,5	12±2	16±3
	e	-	9±3	13±1,5	15±2,5
	f	-	19±2	20±2	21±4
Tetracycline		20	20±2	17±2	19±1
Gentamicine		18	19±1	18±1	19±2
Ciprofloxacine		25	26±2	26±1	22±2

Results of antibacterial screening studies revealed that all the aziridines showed moderate to good activity as compared to reference antibiotics. As can be seen from Fig.5 aziridine **3c** showed better activity than the other compounds, against *Klebsiella pneumonia* and E. coli.

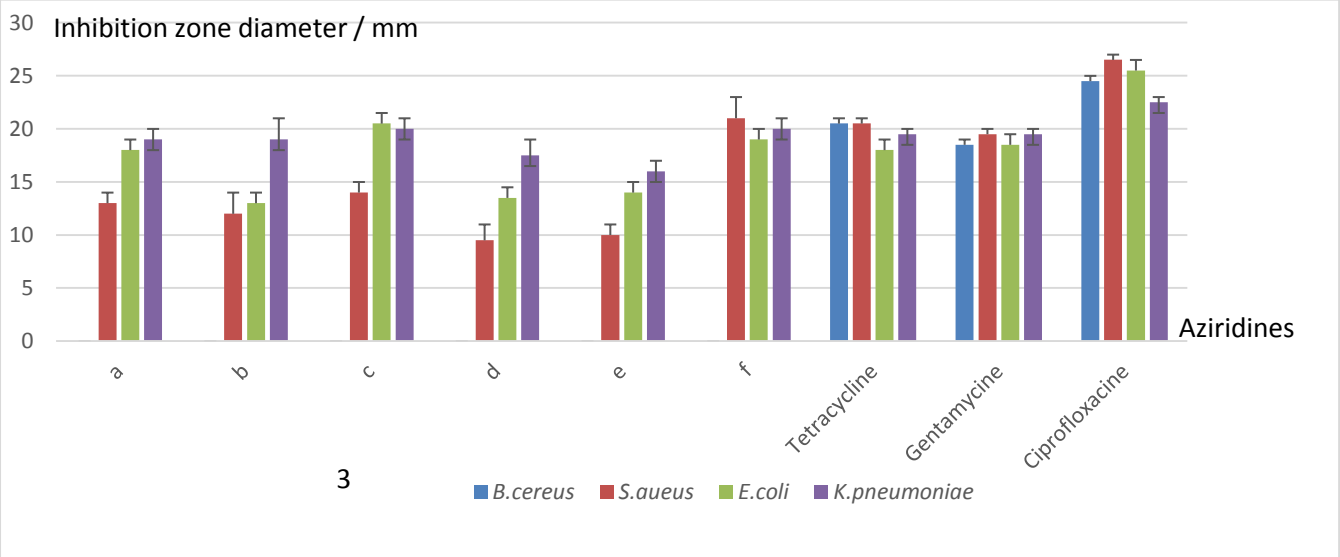

Fig .5. Antibacterial activities of 2-gluosyl-aziridines.

Aziridine with a glucosyl group presented good activity against both *Klebsiella pneumonia* and *E.Coli.* From these results, it can be concluded that the substituent on the hydroxyl as well as the presence of different moiety in aziridine ring, affects the antibacterial activity of these compounds, the most encouraging results being found against *Klebsiella pneumonia*.

IV. Conclusion

This work shed light on the fact that the biological activity of hydroxymethylaziridines, can be modulated by introducing various substituents on their basic structures. Moreover and besides showing interesting antibacterial activities, the series of novel compounds can be further improved to serve as potential drug against nosocomial diseases. The main advantages of the method developed in this study are the ease of availability of the starting materials, and the fact that the aziridination reaction proceeds at room temperature.

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VI. References

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