Algerian Journal of Natural Products 8:2 **(2020)** 787 - 793

OPEN ACCESS

Online ISSN: 2353-0391

Algerian Journal of Natural Products
www.univ-bejaia.dz/ajnp

Type of the Paper (Article)

Synthesis and Antimicrobial Activities of Aziridines-tosylates Derivative

Assia Keniche [1,2*], Samia Bellifa[3], Hafida Hassaine[3] , Joseph Kajima Muengi[4].

[1] *Centre Universitaire de Maghnia, Tlemcen, Algérie*
[2] *Laboratoire de Chimie Organique, Substances Naturelles et Analyses, Université de Tlemen, Algérie*
[3] *Laboratoire de microbiologie appliquée à l'agroalimentaire au biomédical et a l'environnement, Université de Tlemen, Algérie*
[4]*Faculté des Sciences, Université de Tlemen, Algérie*
**Corresponding author:* keniche_assia@yahoo.fr
Tel.: +21343215886; Fax: +213215886.

Received: 13/08/2019 */Accepted:10/11/2020*

Abstract: By using simple straightforward synthesis of Tosylate aziridines has been developed. By means of this synthetic strategy from readily available N-phtaloyl acide and 2-methylbenzosulfonate aziridine using DCC as coupling agent, new tosylates aziridines could be obtained. The coupling reactions occurred without ring opening of the three membered ring. This work describes new results of our ongoing research targeting new derivatives 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 and Gentamicin.

Keywords: Aziridines, phtaloyl acide, strained heterocycles, Antibiotics.

I. Introduction

Antibiotics, as miraculous drugs, have been used extensively to confront fatal infection, even without prescriptions. However, the inappropriate and disproportionate use of antibiotics have led to the emergence of new drug-resistant bacteria[1], which causes a high risk of serious diseases and dramatically aggravates the clinical complications in hospitals[2,3]. With increasing concern over bacterial infections, in particular hospital-acquired infections, there is a growing demand for effective and safe antibacterial agents [4-6].Aziridines represents an important class of compounds that exhibit antibacterial activities against a wide range of bacteria [7-17].

The high interest that the chemistry of aziridines attracts is generated by the manifold applications of this smallest saturated azaheterocycles [18-19]. Aziridines are not only used as reactive synthons in organic synthesis [20-21], but also as monomeric units in polymerization reactions [22], or as natural and synthetic pharmaceuticals [23-24]. Though the parent aziridine C_2H_4NH is classified as mutagenic [25-26], there are some aziridine-containing natural compounds known to be useful as chemotherapeutics, to combat cancer targeting biochemical processes. Good examples are the family of mitomycins and acinomycins [27].

We have, already reported the synthesis of several aziridines [28-30], which some of them showed interesting biological activities such as antitumor [31-32] and potent antibacterial activity against different bacteria [33]. In continuation our research program, to find new antibacterial agents for the treatment of infectious diseases, we set up this work with a view to developing a general method leading to new peptidomimetic-aziridines and to investigate their antibacterial activity.

Numerous synthetic methods are found in the literature and allow easy accesses to various aziridines. It is worth mention that most of those methods are based on the conversion of an amino

© Authors. 2020 Algerian Journal of Natural Products (Online ISSN: 2353-0391)
This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International License

group into the corresponding aziridine [34-41]. By contrast, our synthetic procedure targets the carboxylic group and its transformation into acyl aziridines, while the amino group is protected.

II. **Experimental Section**

II.1. Chemistry

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). Triethylphosphite P((OEt)$_3$) was distilled before use under reduced pressure. 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). CG analysis was performed on a Shimadzu 17A CPG chromatograph using a 30m DB-35 column. 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.2. Antibacterial assays

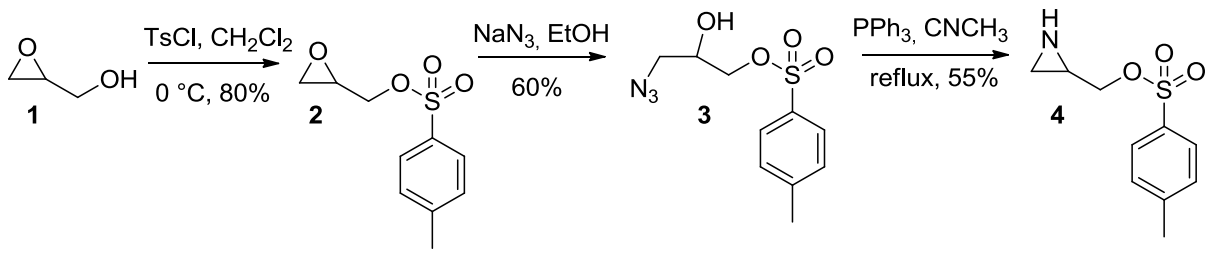
II.2.1 Procedure

The prepared compounds **6 a-e** 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

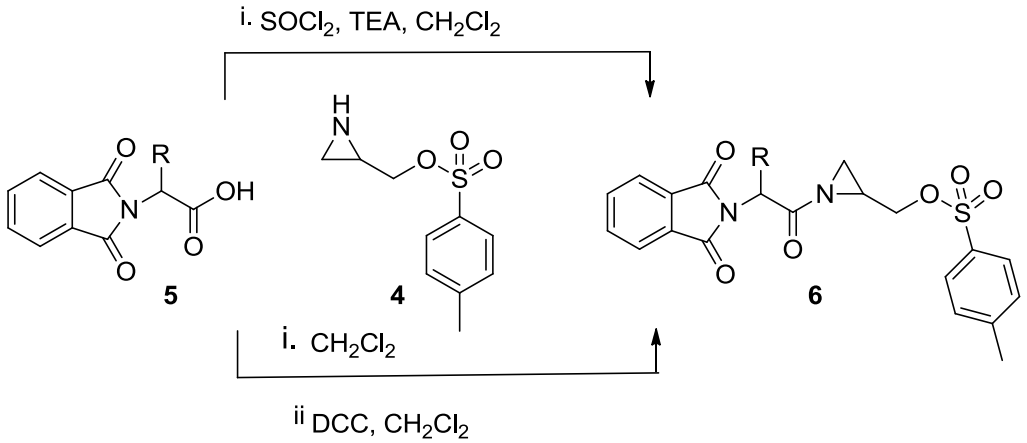
Our synthetic pathways to our target aziridines **6a-e**, are presented in Schemes 1 and 2. The synthesis of tosylate aziridine **4**, was achieved in first by the *O*-protection of glycidol **1** with *p*-toluenesulfonyl chloride (TsCl) in the presence of triethylamine (TEA), led to **2** in good yield (Scheme 1). The solution of **2** in ethanol and water was treated with ammonium chloride and sodium azide to give the azido alcohol **3**, which was reacted in the next step with a solution of triphenylphosphine (PPh_3) in anhydrous acetonitril (CH_3CN), to provide **4** in moderate yield. Compound **4** was purified on a silica gel column eluted with dichloromethane (CH_2Cl_2)-methanol (MeOH) (v/v: 1:1).



*Scheme (1) : Synthesis of aziridin-2ylmethylbenzensulfonate **4** .*

*N-phtaloylamino acids **5a-e** was reacted either with thionyl chloride in the presence of TEA to yield, an acyl chloride that was reacted with **4** to give **6** (50-65%), or coupled in the presence of dicyclohexylcarbodiimide (DCC) as coupling agent with unprotected aziridine **4**, at room temperature, giving the same compound **6** in high yield (80-90%).*

© Authors. 2020 Algerian Journal of Natural Products (Online ISSN: 2353-0391)
This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International License

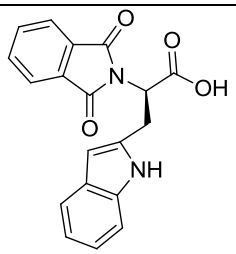
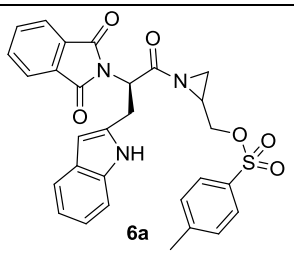
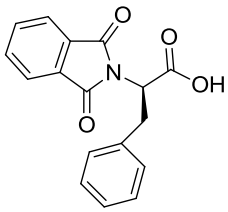
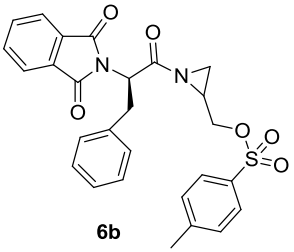
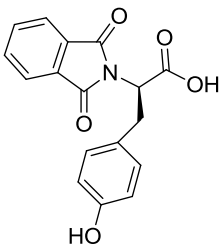
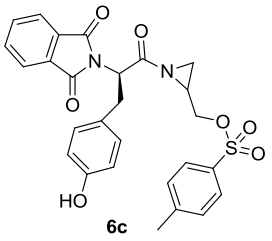


*Scheme (2) : Coupling of aziridines **4** with Ft-amino acide **5**.*

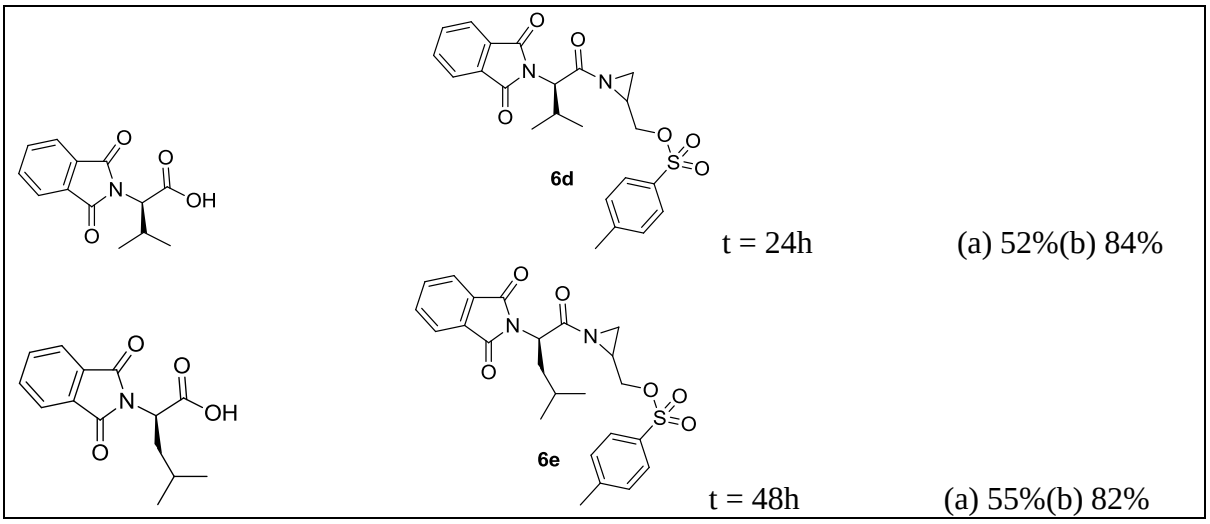
This strategy enabled us, to use 2-methyltosylate aziridine **4** as building block to obtain different functionalized Aziridines **6 a-e**. Phenylalanine, tryptophane, tyrosine, valine and leucine were chosen as a models, since in our initial work in this field [32], aziridine from the former amino acid showed the best biological profile [33], whereas tyrosine is claimed to behave as a residue of utmost importance in many receptors [42] . Derivatives **5 a-e** were prepared according to a modified literature procedure[43] and were recrystallized. They were further converted into aziridines **6 a-e** according to both methods previously described in the last section.

After work-up, the phtaloyl group (Ft) could be removed from the protected amino acid moiety of **6a-e** by treatment with hydrazine hydrate according to literature [44], affording aziridines with a free amino group for a potential peptide growth.

Table 1 : Structure of N-acyl-Tosylate aziridines.

Amino acide **5**	aziridines **6a-e**	time of reaction (h)	Yiled %
	 **6a**	t = 96h	(a) 51%(b) 86%
 94.8%	 **6b**	t = 48h	(a) 52%(b)
	 **6c**	t = 48h	(a) 53%(b) 90%

© Authors. 2020 Algerian Journal of Natural Products (Online ISSN: 2353-0391)
This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International License



With this series of aziridines in hand, and aware that many aziridine alkaloids have antimicrobial activity against selected pathogenic microorganisms [45-47], we decided to test preliminary all the aziridine derivatives described in this paper for a potential antibacterial profile against different bacterial.

III.2. *Antibacterial studies*

Compounds **6 a-e**, with Concentration, 32µg/ml, were screened for their antibacterial activity against multidrug resistant bacteria chosen from the Centre Hospitalo-Universitaire of 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 **6 a-e**, (the experiment was repeated three times) as the average Diameter mm of the inhibition zone of bacterial growth (Fig. 1).

Table 2: The majority of the evaluated aziridine derivatives exhibited moderate to good activity as compared to reference antimicrobial drugs.

Aziridines		**Inhibition zone diameter / mm**			
		B.cereus	*S.aureus*	*E.Coli*	*K.pneumoniae*
6	**a**	-	10±2	15±2	16±3
	b	-	8±3	12±3	16±4
	c	-	13±1,5	15±4	19±2
	d	-	9±2	11±2	16±2
	e	-	9±2	10±3	15±3
Tetracycline		20 ± 1	20±1	17±2	19±1
Gentamicine		18 ± 2	19±2	18±1	19±2
Ciprofloxacine		25±1	26±2	26±2	22±2

Results of antibacterial screening studies revealed that all the tosylates aziridines showed moderate to good activity as compared to reference antibiotics. As can be seen from Fig.1 aziridine **6c** with a free hydroxyl group, showed better activity than the other aziridines, against *Klebsiella pneumonia* and E. coli. From results displayed in Fig.1, we can assume that on the whole, our compounds are more active against Gram negative than Gram positive bacteria. Nevertheless, compound **6a-e** was inactive against *Bacillus cereus*.

© Authors. 2020 Algerian Journal of Natural Products (Online ISSN: 2353-0391)
This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International License

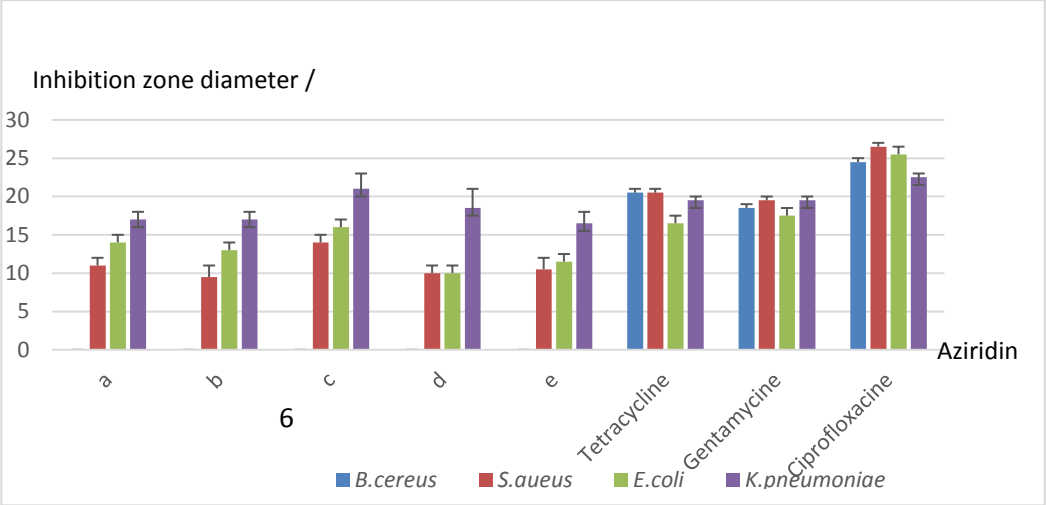


Figure .1 : Antibacterial activities of Tosylates aziridines.

From these results, it can be concluded that the substituent on the hydroxyl as well as the group on moiety in aziridine ring, affects the antibacterial activity of these compounds, the most encouraging results being found against *Klebsiella pneumonia*.

IV. Conclusion

In conclusion, we reported the synthesis and a preliminary antibacterial evaluation of novel functionalized tosylaziridines. The synthetic strategy relies on the coupling reactions between tosylaziridines and amino acids. 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. Therefore, work is going on for the diversification of the initial work, especially for the search of targeted cancer chemotherapy through the synthesis of hybrids.

V. References

[1] Cesar, A. Arias, M.D., Barbara E., Murray, M.D.; A New Antibiotic and the Evolution of Resistance. *N Engl J Med* (2015) 372 :1168-1170.

[2] Z.Lu, X.Zhang, Z.Li, Z.Wu, J.Song, C.Li, Antibacterial activity of cationic polymers: side-chain or main-chain type? *Polym Chem*, 6 (2015) 772-779.

[3] Khalaj, A., Nakhjiri, M., Negahbani, A.S., Samadizadeh, M., Firoozpour, L., Rajabalian, S., Samadi, N., Faramarzi, M.A., Dibpour, N.A., Shafiee, A., Foroumadi, A., Discovery of a novel nitroimidazolyl-oxazolidinone hybrid with potent anti Gram-positive activity: Synthesis and antibacterial evaluation *Eur.J.Med.Chem*, 46 (2011) 65-70.

[4] Pinkner, J.S., Remaut, H., Buelens, F., Miller, E., Åberg, V., Pemberton, N., Hedenström, M., Larsson, A., Seed, P., Waksman, G., Hultgren, S.J., Almqvist, F., Rationally designed small compounds inhibit pilus biogenesis in uropathogenic bacteria. *Proc. Natl. Acad. Sci. U.S.A.*, 103 (2006) 17897-17902.

[5] Meka, G., K.Pillai, S., Sakoulas, G., Wennersten, C.V., Venkataraman, L., DeGirolami, P.C., Eliopoulos, G.M., Moellering, R.C., Gold, H.S., Linezolid Resistance in Sequential Staphylococcus aureus Isolates Associated with a T2500A Mutation in the 23S rRNA Gene and Loss of a Single Copy of Rrna. *J. Infect. Dis. DrugTargets*, 190 (2004) 311-317.

[6] Levy, S.B., Marshall, B. Antibacterial resistance worldwide: causes, challenges and responses. *Nat Med*. (2004) 10, 122–129.

[7] Keniche, A, Bellifa, S., Hassaine, H., Kajima Mulengi, J., Synthesis and Evaluation of Biological Activity of Novel Sugar-Derived Aziridines, *Algerian J. Nat. Products,* (2018) 6, 609-617.

[8] Keniche A., Mezrai A., Kajima Mulengi J., Novel class of phosphonoaziridines as antibacterial agents, *The Open Conference Proceedings Journal,* Dubai, 2 (2011) 28-36.

© Authors. 2020 Algerian Journal of Natural Products (Online ISSN: 2353-0391)
This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International License

[9] Giovine,A., Muraglia,M., Antonio Florio,M., Rosato,A., Corbo, F., Franchini,C., Musio, B., Degennaro, L., Luisi, R., Synthesis of Functionalized Arylaziridines as Potential Antimicrobial Agents, *Molecules* 2014, *19*, 11505-11519.
[10] Moonen K., Laureyn I., Stevens C.V., Synthetic methods for azaheterocyclic phosphonates and their biological activity, *Chem. Rev*., 104 (2004) 6177-6215.
[11] Fahey, K., Aldabbagh, F. The influence of the aziridinyl substituent of benzimidazoles and benzimidazolequinones on toxicity towards normal and Fanconi anaemia cells. *Tetrahedron Lett*., (2008) *49*, 5235–5237.
[12] Fahey, K., O'Donovan, L., Carr, M., Carty, M.P., Aldabbagh, F. Synthesis and toxicity towards normal and cancer cell lines of benzimidazolequinones containing fused aromatic rings and 2-aromatic ring substituents. *Eur. J. Med. Chem*., (2010) *45*, 1873–1879.
[13] Prosser, G.A., Copp. J. N., Syddall, S.P., Williams, E. M.; Smaill, J. B., Wolson, W.R., Patterson, A.V., Ackerley, D.F. Discovery and evaluation of Escherichia coli nitroreductases that activate the anti-cancer prodrug CB1954. *Biochem. Pharmacol*., (2010) *79*, 678-687.
[14] Sucre, A.P., Vicik, R., Schultheis, M., Schirmeister, T., Moll, H.Aziridine-2,3-dicarboxylates, peptidomimetic cysteine protease inhibitors with antileishmanial activity, antimicrobial. *Agents Chemother*., (2006) *50*, 2439-2447.
[15] Hanessian, S., Moitessier, N., Cantin, L.D. Design and synthesis of MMP inhibitors using *N*-arylsulfonylaziridine hydroxamic acids as constrained scaffolds. *Tetrahedron*., (2001) *57*, 6885-6900.
[16] Schirmeier, T., Peric, M. Aziridinyl peptides as inhibitors of cysteine proteases: effect of a free carboxylic acid function on inhibition. *Bioorg. Med. Chem*., (2000) *8*, 1281-1291.
[17] Ismail, M.D., Levitsky, D.O., Dembitsky, V.M. Aziridine alkaloids as potential therapeutic agents. *Eur. J. Med. Chem*. (2009) *44*, 3373-3387.
[18] J. B. Sweeney, Aziridines: epoxides ugly cousins?*, Chem. Soc. Rev*., 31 (2002) 247.
[19] Watson, I. D. , Yu, L., Yudin, A. K. Sriramurthy, Silylmethyl-Substituted Aziridine and Azetidine as Masked 1,3- and 1,4-Dipoles for Formal [3 + 2] and [4 + 2] Cycloaddition Reactions.*J. Am. Chem. Soc*., 127 (2005) 16366-67.
[20] Da Silva,A.R., dos Santos,A.D., Paixão, M.W., Gonçalves Corrêa, A., Stereoselective Multicomponent Reactions in the Synthesis or Transformations of Epoxides and Aziridines, Molecules. (2019) 24, 630.
[21] Fahey, K., O'Donovan, L., Carr, M., Carty, M.P., Aldabbagh, F. Synthesis and toxicity towards normal and cancer cell lines of benzimidazolequinones containing fused aromatic rings and 2-aromatic ring substituents. *Eur. J. Med. Chem*., *45 (2010)* 1873–1879.
[22] Fahey, K.; Aldabbagh, F. The influence of the aziridinyl substituent of benzimidazoles and benzimidazolequinones on toxicity towards normal and Fanconi anaemia cells. *Tetrahedron Lett*., *49*, (2008) 5235–5237.
[23] Grif, K.; Dierich, M. P.; Pfaller, K.; Miglioli, P. A.; Allenberger, F. In vitro activity of fosfomycin in combination with various antistaphylococcal substances. *J. Antimicrob. Chemother,* 48 (2001) 209-217.
[24] D'hooghe M., Kenis S., Vervisch K., Lategan C., Smith P.J., Chibale K., De Kimpe N., Synthesis of 2-(aminomethyl)aziridines and their microwave-assisted ring opening to 1,2,3-triaminopropanes as novel antimalarial pharmacophores, *European Journal of Medicinal Chemistry*, 46 *(*2011) *579-587.*
[25] Steven Vega-Pérez J.M., Palo-Nieto C., Vega-Holm M., Góngora-Vargas P., Calderón-Montaño J.M., Burgos-Morón E., López-Lázaro M., Iglesias-Guerra F., Aziridines from alkenyl-β-D-galactopyranoside derivatives: Stereoselective synthesis and in vitro selective anticancer activity, *European Journal of Medicinal Chemistry*, *70* (2013) *380-392.*
[26] Giovine A., Muraglia M., Antonio Florio M., Rosato A., Corbo F., Franchini C., Musio B., Degennaro L. Luisi, R., Synthesis of Functionalized Arylaziridines as Potential *Antimicrobial Agents Molecules, 19* (2014) 11505-11519.
[27] W.Medjahed, A.Tabet Zatla, J.Kajima Mulengi, F.Z.BabaAhmed, H.Merzouk, *Tetrahedron Lett.,* 45 (2004) 1211.
[28] Keniche A., Slimani MZ., José Miranda I., Azipura Jesus M., Kajima Mulengi J., NMR Investigation of the complexation of (S)-2-isopropyl-1-(o-nitrophenyl)sulfonyl)aziridine withb-cyclodextrine , *Mediterr.J.Chem,* 2 (2014) 620-631.
[29] Keniche A., Drici W., Slimani M.Z., Mezrai A., Kajima Mulengi J., 1,3-Dipolar cycloaddition of azomethine ylide from Phtaloylimidophenylalanyl-2-hydroxymethylaziridine *Mediterr.J.Chem,* 2 (2013) 583-594.
[30] Baba Ahmed, F.Z., Bouanane, S., Merzouk, S.A., Merzouk, H., Medjahed, W., Kajima Mulengi, J., Prost, J., *Pathol.Biol.*, 46 (2008) 137.
[31] Baba Ahmed, F.Z., Merzouk, H., Bouanane, S., Benkalfat, N.B., Merzouk, S.A., Kajima Mulengi, J., Narce, M. Evaluation de la toxicité aiguë de la 2-hydroxyméthyl-1(*N*phtaloyltryptophyl)aziridine chez le rat Wistar. *Ann Toxicol Anal*. 2010, DOI: 10.1051/ata/2010017. www.ata-journal.org
[32] Keniche,A., Bellifa,S., Hassaine,H., Slimani,M.Z., Kajima Mulengi, J. EVALUATION OF ANTIBACTERIAL ACTIVITIES OF NOVEL AZIRIDINYL PHOSPHONATES, *Algerian J. Nat. Products,* (2016) 4, 226-232.

© Authors. 2020 Algerian Journal of Natural Products (Online ISSN: 2353-0391)
This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International License

[33] Brock Dyer,F., Park,C.M., Joseph,R., Garner, P., Aziridine-Mediated Ligation and Site-Specific Modification of Unprotected Peptides, *J. Am. Chem. Soc.* (2011**)** *133* 20033–20035.
[34] Bromberg,L., Bromberg, D.J., Alan Hatton, T., Bandín,I., Concheiro,A., Alvarez-Lorenzo, C., Antiviral Properties of Polymeric Aziridine- and Biguanide-Modified Core–Shell Magnetic Nanoparticles,. *Langmuir*. (2012) *28* 4548–4558.
[35] Mladenovic, M., Engels, B., Schirmeister, T., Rational Design of Improved Aziridine-Based Inhibitors of Cysteine Proteases. *J. Phys. Chem. B*, (2009) *113* 5282–5289.
[36] Galonić, P.D., van der Donk, W.A., Gin, Y.A. Site-Selective Conjugation of Thiols with Aziridine-2-Carboxylic Acid-Containing Peptides. *J. Am. Chem. Soc.* (2004) *126* 12712–12713
[37] Kim,H.J., Chaikittisilp, W., Jang,K.S., Didas, S.A., Johnson,J.R., Koros,W.J., Nair,S., Christopher, W. Aziridine-Functionalized Mesoporous Silica Membranes on Polymeric Hollow Fibers: Synthesis and Single-Component CO_2 and N_2 Permeation Properties? Jones *Ind. Eng. Chem. Res.* (2015) *54*, 4407–4413.
[38] Murray, C., Dyer, F.B., Garner, P. Solid phase synthesis and ligative processing of photocaged aziridine-2-carbonyl-terminated peptides, *Tetrahedron Letters*, *56, (2015*) *3636-3638,*
[39] Synthesis of densely functionalized cispentacin derivatives through selective aziridination and aziridine opening reactions: orthogonally protected di- and triaminocyclopentanecarboxylates, *Tetrahedron*, *70 (2014*) *8511-8519.*
[40] Nonn,M., Kiss,L., Forró,E., Sillanpää,R., Fülöp,F., A general, enantioselective synthesis of *N*-alkyl terminal aziridines and C2-functionalized azetidines via organocatalysis *Tetrahedron Letters*. *56, (2015*) 1276-1279.
[41] Timothy J. Senter, Matthew C. O'Reilly, Katherine M. Chong, Gary A. Sulikowski, Craig W. Lindsley, Koide, S; Sidhu, S. The importance of being tyrosine: lessons in molecular recognition from minimalist synthetic binding proteins.*ACS Chem. Biol*., (2009) *4*, 325-334.
[42] Applegate, H. E.; Cimarusti, C. M.; Dolfini, J. E.; Funke, P. T.;Koster, W. H.; Puar, M. S.; Slusarchyk, W. A.; Young, M. G.Synthesis of 2-, 4-, and 7-methylthio-substituted cephalosporins. *J.Org. Chem.* (1979) *44*, 811-818.
[43] Sucre, A.P., Vicik, R., Schultheis, M., Schirmeister,T., Moll, H. Aziridine-2,3-dicarboxylates, peptidomimetic cysteine protease inhibitors with antileishmanial activity, antimicrobial. *Agents Chemother*., 50 *(2006)* 2439-2447.
[44] Vederas, V.C., Bader, A. Diaminopimelate and lysine biosynthesis—Anantimicrobial target in bacteria. *Can. J. Chem.* (2006) *84*, 1197–1207.
[45] Sharma, P., Kumar, A., Upadhyay, S., Sahu, V., Singh, J. Synthesis and QSAR modeling of 2-acetyl-2-ethoxycarbonyl-1 -[4(4'-arylazo)-phenyl]-*N*,*N*-dimethylaminophenyl aziridines as potential antibacterial agents. *Eur. J. Med. Chem.,* 44 (2009) 251 -259.
[46] Ismail, M.D., Levitsky, D.O., Dembitsky, V.M. Aziridine alkaloids as potential therapeutic agents. *Eur. J.Med. Chem*., 44 (2009) 3373-3387.
[47] Dembitsky, V. M., Terent'ev, A. O., Levitsky, D. O. Aziridine Alkaloids: Origin, Chemistry and Activity. In *Natural Products;* Eds.; Springer-Verlag: Berlin, Heidelberg, (2013) 977–1006.

© Authors. 2020 Algerian Journal of Natural Products (Online ISSN: 2353-0391)
This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International License