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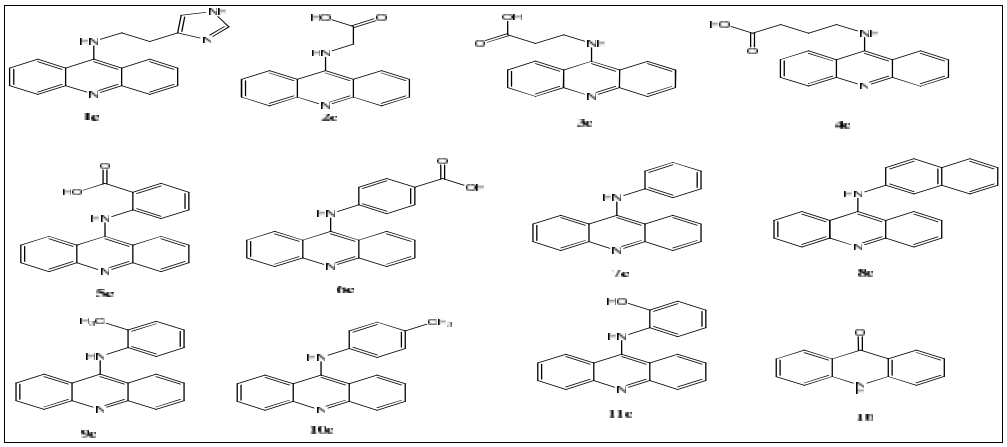

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RESEARCH ARTICLE

ANTIBACTERIAL EFFECT OF ACRIDONE AND A SERIES OF 9-AMINOACRIDINE ON SEVEN PATHOGENIC BACTERIAL STRAINS

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ABSTRACT

The antibacterial role of acridines seems to be of considerable importance for the serious problems caused by multiple resistances of pathogenic bacteria to antibiotics. In this study acridone and a series of newly synthesized 9-aminoacridine were tested, for their antibacterial activity, against seven pathogenically strains of bacteria: Methicillin-*sensitive Staphylococcus aureus (MSSA), Methicillin-resistant Staphylococcus aureus (MRSA), Enterococcus faecalis, Pseudomonas aeruginosa, Salmonella paratyphi A, Escherichia coli* and *Klebsiella pneumoniae.*

The results showed that all synthesized compounds have significant antibacterial activity against all strains tested with a minimum inhibitory concentration (MIC) of very low value compared to antibiotics tested under the same conditions. The ratio of a minimum bactericidal concentration (MBC) /MIC of seven bacteria reveals the bactericidal effect of all molecules.

INTRODUCTION

Acridines or dibenzo [b,e] pyridines are a large family of compounds that have generated great interest since their discovery by Graebe and Caro in 1870 and their use as pigments in the textile industry. The real interest in acridines was unveiled when various important biological activities, are endowed with these molecules, have been discovered as research conducted in this area (Kaur *et* Singh, 2011; Guetzoyan *et al*, 2007). The basic core of acridines being an aromatic heterocyclic plan allows a good interaction of these molecules with biomolecules macros either by intercalation or by pi-stacking. The nature and positions of substituents on the acridine nucleus also play an important role in determining the potential biological activity of the molecule. Thus, many acridines, of natural or synthetic origin, are used in the treatment of several diseases.

These compounds can be used as antibacterial (Shul'ga *et al*,1974), antifungal (Srivastava et Nizamuddin, 2004; Albert, 1966), anti-inflammatorie (Sondhi *et al*, 2010), antimalarial (Guetzoyan *et al*, 2009), antiviral (Groundwater *et* Munawar, 1998), and anti-cancer (Belmont *et al*, 2007 ; Lipford *et al*, 2005; Yu *et al*,2002; Sham, 2002; Sondhi *et al*, 2001; Jelic *et al*, 1997;Sugaya, 1994; Kimura, 1993).

Multi-resistance bacteria are a barrier complicating the treatment of bacterial infections in humans and animals. Control of this scourge is a challenge for clinicians and microbiologists seen that increasing antibiotic resistance resulting in a hospital practice in increased morbidity, mortality [Cosgrove *et al*., 2003; Harbath, 2001] and hospital costs (Cosgrove and Carmeli, 2003), which weighed more care of the patients. Thus a comprehensive approach, combining multiple complementary and multidisciplinary interventions aim to change the behavior of prescribers (Dellit *et al*, 2007; Davey *et al*, 2005). Those prescribers re-sort more and more important to research natural or synthetic substances to extract new and more effective antibacterial products (Wright *et al*, 2007) and less harmful to the health and environment.

This work aims to evaluate the effectiveness of twelve synthesized acridines (Al Hazmi *et al*, 2013) on pathogenic bacteria Gram positive and Gram negative that are multi-resistant to antibiotics and presenting antibiotherapeutics difficulties. The molecules tested are acridone (1b) and a series of 9-aminoacridines (1c to 11c) substituted by polar chains or amino acids chains.

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MATERIALS AND METHODS

Substances

The molecules tested (Figure 1) are an acridone and a series of 9-aminoacridines prepared by a simple procedure involving the condensation of amino acids or amines on acridone1 in the presence of Lewis acid $BF_3 \cdot OEt_2$. The acridone used was itself prepared from anthranilic acid by the procedure Ulmann (Al Hamzi *et al*, 2013).

All tested acridine derivatives are solids. Stock solutions of these concentrations of products 1000µg / ml and 400 µg / ml were prepared in the degree p.a of DMF dried and stored over 4 Å molecular sieves. Prepared solutions are incubated at a temperature of 25 ° C. The control is prepared under the same conditions.

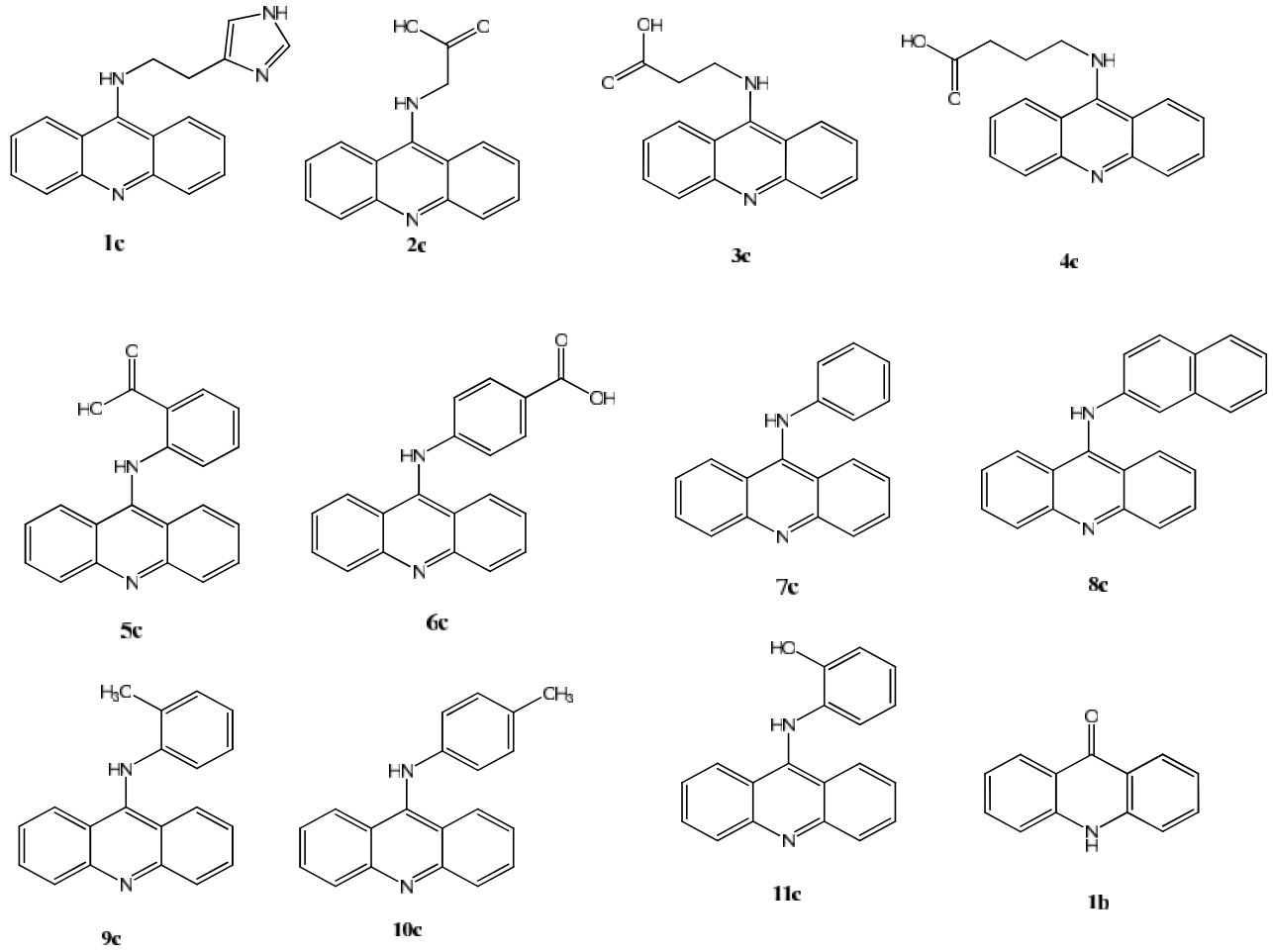

Figure 1 Structure of the acridone (1b) and the series of 9-aminoacridines (1c to 11c)

Bacterial strains tested

The seven bacteria tested: *Methicillin-Sensitive Staphylococcus aureus (MSSA), Methicillin-Resistant Staphylococcus aureus (MRSA), Enterococcus feacalis (E. feacalis), Pseudomonas aeruginosa (P.aeruginosa), Salmonella paratyphiA (S. paratyphi A), Escherichia coli (E.coli)* and *Klebsiella pneumoniae (K.pneumoniae),* were taken from pathological isolates from patients suffering from different infections (urinary, genital, pleural, etc...). Their isolation and identification were conducted in accordance with the aseptic standards and using the selective culture media and adequate identifications for each bacterial species.

The selection of the bacteria tested is based on their characteristic multi-resistance to antibiotics and their antibiotherapeutic difficulty.

Preparation of inoculums

Cultures of the bacteria were grown on nutrient agar for 18 to 24 hours and incubated at 37°C. Then, these cultures were suspended in saline solution (0.9% NaCl) and inoculated respecting a density equivalent to Mc Farland standard density 0.5 (CA-SFM, 2014).

Resistance Profile of the Strains Tested

The determination of the resistance phenotype was performed as recommended by the susceptibility of the Committee of the French Microbiology Society by applying the agar diffusion method (CA-SFM., 2014). It has the advantage of being very flexible in the choice of antibiotics tested, to apply to a large number of bacterial species and provide more raw data results on the interaction of different antibiotics between them.

The classification of the strain "sensible", "intermediate" or "resistant" was determined by comparing the diameter of inhibition at critical diameters established on pharmacological and clinical data dictated by the Antibiogram of the French Society (CA-SFM, 2014).

Evaluation of antibacterial activity of the acridone and series of 9-aminoacridines

Determination of the Minimum Inhibitory Concentration (MIC)

The MIC is defined as the lowest concentration of an antibiotic dilution range of a half which results in inhibition of all visible bacteria growth (Skandamis *et al*, 2001). The MIC of an acridone and the series of 9-aminoacridine derivatives is carried out according to the microtiter technique on microplate described by Eloff (Eloff, 1998).

The solubilization of the substances is carried out in dimethyl sulfoxide (DMSO, Sigma -Aldrich). The antibacterial activity of these solvents has been previously tested in the concentrations used; they have no effect on bacterial growth.
The objective of this test is to show the effect of the structure on the biological activity of acridone 1b and a series of 9-aminoacridine derivatives 1c to 11c.

The number of repetitions is three times for each of the tests performed.

Determination of minimum bactericidal concentration (MBC)

The MBC is the lowest concentration that can, in vitro, cause irreversible inhibition of bacterial growth (bacterial death). In practice, this is the eradication of 99.9% of a bacterial inoculum of (10^6) in 18 at 24h. The antibacterial effect was deemed bactericidal or bacteriostatic depending on the ratio: MBC / MIC. While MBC / MIC ≤ 4, the effect is bactericidal and if MBC / MIC>4, the effect is bacteriostatic (Prescot *et al*, 2003; Berche *et al*, 1991).

All experiments were performed in triplicate.

Statistical analysis of results

The input and data analysis were performed using Microsoft Excel software.

RESULTS

Phenotypic resistance profile of the strains tested

Minimum Inhibitory and bactericidal concentration

DISCUSSION

The bacteria resistance profile tested against antibiotics, showed a high level of resistance to most antibiotics currently used in antibiotic treatment (Table 1). The causes for the emergence of multi-resistant bacteria are numerous. They are the consequence of extrinsic and intrinsic factors, among others may be mentioned respectively: the massive and inappropriate use of broad spectrum antibiotics, both in hospital and community (Breathnach, 2013; Pulcini *et al*, 2007). It can also be explained by cross-transmission of acquired resistance plasmid determinism, which is very common in places of important bacterial density and diversity (Launay *et al*, 2012; Ferjani *et al*, 2011; Haller *et al*, 2004).

The concrete development of the multi-acquired resistance (Moukrad *et al*., 2013; Moukrad *et al*, 2012 ; Bertrand *et al*, 2005) has encouraged us to create an opportunity to reintroduce other molecules in the treatment of severe infections associated with resistant germs, to participate effectively in the fight against emergence.

The results in table 2 show that all the bacteria have sensitivity to the acridone 1b and the series of 9-aminoacridine derivatives tested with a MIC ranging from 7,81µg / ml to125 µg/ml.

Concerning Staphylococcus, 31.25 µg / ml of corresponding 9-aminoacridines 2c, 3c, 4c, 5c and 6c are capable of eradicating MSSA and MRSA (Table 2). The same concentration of the compounds 1b, 1c and 10c is sufficient to remove MSSA.

Table 1 Resistance profile of bacteria studied

	Gram-positive bacteria		**Gram-negative bacteria**				
Name and charges of Antibiotics	*MSSA (coagulase-negative)*	*MRSA (coagulase-positive)*	*E.feacalis*	*P.aeruginosa*	*S.paratyphi A*	*E.coli*	*K.pneumoniae*
Amoxicillin (25µg)	NT	NT	NT	NT	R	R	NR
Amoxicillin+Clavulanic acid (20/10µg)	NT	NT	NT	NT	S	R	R
Gentamicin (15 µg)	NT	NT	NT	S	S	R	S
Gentamicin (500 µg)	S	S	R	NT	NT	NT	NT
Oxacillin (1 µg)	NT	NT	R	NT	NT	NT	NT
Oxacillin (5 µg)	S	R	NT	NT	NT	NT	NT
Ciprofloxacin (5 µg)	S	R	NT	R	S	S	R
Ofloxacin (5 µg)	S	R	R	S	S	S	S
Ceftriaxon (30 µg)	S	S	R	NT	R	NT	S
Sulphamethoxazole+ Trimethoprim (1,25/23,75µg)	S	R	NT	S	R	R	R
Ceftazidim (30 µg)	NT	NT	NT	R	S	S	R
Ticarcillin (75 µg)	NT	NT	NT	R	NT	NT	NR
Imipenem (10µg)	NT	NT	NT	R	NT	NT	NT
Vancomycin (30 µg)	S	S	S	NT	NT	NT	NT

S: Sensitive; R: Resistant; NT: Not Tested; NR: Natural Resistance.

Table 2 Determination of MIC and MBC of Gram-positive bacteria tested in (µg / mL)

	GRAM-POSITIVE BACTERIA								
	MSSA			MRSA			E.faecalis		
Acridines	***MIC***	***MBC***	***MBC/MIC***	***MIC***	***MBC***	***MBC/MCI***	***MIC***	***MBC***	***MBC/MIC***
1b	*15,62± 0,0*	*31,25± 0,0*	*2,00*	*31,25 ±0,0*	*83,5 ±28*	*2,67*	*62,5 ±0,0*	*83,5 ±28*	*1,34*
1c	*13,66±1,95*	*31,25± 0,0*	*2,29*	*62,5 ±0,0*	*125± 0,0*	*2,00*	*31,25 ± 0,0*	*62,5 ±0,0*	*2,00*
2c	*10,73± 2,27*	*31,25± 0,0*	*2,91*	*13,01±4,50*	*31,25± 0,0*	*2,40*	*52,08±6,94*	*83,5 ±28*	*1,60*
3c	*7,81 ±0,0*	*25,83± 6,88*	*3,31*	*10,41± 4,50*	*31,25± 0,0*	*3,00*	*62,5 ±0,0*	*125± 0,0*	*2,00*
4c	*15,62 ±0,0*	*31,25± 0,0*	*2,00*	*15,62 ± 0,0*	*52,08±6,94*	*3,33*	*41,66±13,88*	*62,5 ±0,0*	*1,50*
5c	*7,81 ±0,0*	*25,83± 6,88*	*3,31*	*10,41± 4,50*	*31,25± 0,0*	*3,00*	*62,5 ±0,0*	*125± 0,0*	*2,00*
6c	*7,81 ±0,0*	*25,83± 6,88*	*3,31*	*10,41± 4,50*	*31,25± 0,0*	*3,00*	*62,5 ±0,0*	*125± 0,0*	*2,00*
7c	*62,5 ±0,0*	*125± 0,0*	*2,00*	*62,5 ±0,0*	*125± 0,0*	*2,00*	*31,25 ± 0,0*	*62,5 ±0,0*	*2,00*
8c	*62,5 ±0,0*	*125± 0,0*	*2,00*	*62,5 ±0,0*	*125± 0,0*	*2,00*	*62,5 ±0,0*	*125± 0,0*	*2,00*
9c	*125 ±0,0*	*250± 0,0*	*2,00*	*125 ±0,0*	*250± 0,0*	*2,00*	*62,5 ±0,0*	*125± 0,0*	*2,00*
10c	*31,25 ±0,0*	*31,25± 0,0*	*1,00*	*125 ±0,0*	*166,66± 55,55*	*1,33*	*31,25 ± 0,0*	*62,5 ±0,0*	*2,00*
11c	*41,33±13,77*	*83,5 ±28*	*2,02*	*62,5 ±0,0*	*166,66± 55,55*	*2,67*	*31,25 ± 0,0*	*62,5 ±0,0*	*2,00*
Gentamycin	*520,8±173,6*	*850±0,00*	*1,46*	*750±0,0*	*900±0,0*	*1,2*	*R*	*R*	-
DMF	-	-	-	-	-	-	-	-	-

R: Resistant
Each value represents the mean ± standard deviation.

Table 3 Determination of MIC and MBC of the Gram negative bacteria tested in (µg / ml)

	GRAM NEGATIVE BACTERIA											
	P. aeruginosa			S. paratyphi A			E. coli			K. pneumoniae		
Acridines	***CMI***	***CMB***	***CMB/CMI***	***CMI***	***CMB***	***CMB/CMI***	***CMI***	***CMB***	***CMB/CMI***	***CMI***	***CMB***	***CMB/CMI***
1b	62,5 ±0,0	*125± 0,0*	2,00	62,5 ±0,0	*125± 0,0*	2,00	15,62±0,0	*31,25± 0,0*	2,00	62,5± 00	*83±28*	*1,33*
1c	62,5 ±0,0	*125± 0,0*	2,00	62,5 ±0,0	*125± 0,0*	2,00	7,81±0	*31,25± 0,0*	4,00	31,25±0,0	*62,5±0,0*	*2,00*
2c	125 ±0,0	*125± 0,0*	1,00	20,83±9,02	*62,5 ±0,0*	3,00	7,81±0	*31,25± 0,0*	4,00	31,25±0,0	*62,5±0,0*	*2,00*
3c	125 ±0,0	*250± 0,0*	2,00	62,5 ±0,0	*125± 0,0*	2,00	7,81±0	*31,25± 0,0*	4,00	31,25±0,0	*62,5±0,0*	*2,00*
4c	125 ±0,0	*125± 0,0*	1,00	31,25 ± 0,0	*62,5±0,0*	2,00	31,25± 0,0	*62,5±0,0*	2,00	52,08±6,94	*125± 0,0*	*2,40*
5c	62,5 ±0,0	*125± 0,0*	2,00	52,08±6,94	*125± 0,0*	2,40	15,62±0,0	*31,25± 0,0*	2,00	31,25±0,0	*62,5±0,0*	*2,00*
6c	62,5 ±0,0	*125± 0,0*	2,00	62,5 ±0,0	*125± 0,0*	2,00	31,25± 0,0	*62,5±0,0*	2,00	31,25±0,0	*62,5±0,0*	*2,00*
7c	62,5 ±0,0	*125± 0,0*	2,00	62,5 ±0,0	*125± 0,0*	2,00	31,25± 0,0	*62,5±0,0*	2,00	31,25±0,0	*125± 0,0*	*4,00*
8c	125 ±0,0	*250± 0,0*	2,00	31,25 ± 0,0	*125± 0,0*	4,00	15,62±0,0	*62,5±0,0*	4,00	31,25±0,0	*62,5±0,0*	*2,00*
9c	62,5 ±0,0	*125± 0,0*	2,00	31,25 ± 0,0	*62,5±0,0*	2,00	62,5 ± 0,0	*62,5±0,0*	1,00	62,5±0,0	*166± 55,55*	*2,00*
10c	62,5 ±0,0	*125± 0,0*	2,00	10,41 ± 4,50	*31,25± 0,0*	3,00	20,8±9,02	*62,5±0,0*	3,00	31,25±0,0	*62,5±0,0*	*2,00*
11c	52 ±14	*83±28*	1,60	*31,25± 0,0*	*83±28*	2,66	31,25±0,0	62,5± 00	2,00	52,08±6,94	*83±28*	*1,59*
Gentamycin	500±0,0	500±0,0	1	250± *0,0*	416,66±*111,1*	1,66	R	R	-	500±0,0	500±0,0	1

R: Resistant
Each value represents the mean ± standard deviation.

The MICs of all the substances do not exceed 62,5µg / ml except for the compound 9c which is substituted by a group o-tolyl, it has a MIC of 125 µg / ml. Both strains show similar sensitivity to any structure containing an acid function (2c to 6c). The MICs found for these compounds are lower than those of the acridone, this shows that the grafting by a radical amino acid enhances the activity of these molecules. We can also conclude that the planar structure of the aromatic molecules 5c and 6c seems to improve the antibacterial activity. Indeed, the MIC found for these two substances which are grafted with an aromatic amino acid are the lowest. The MIC is 7.81 and 10.41 µg / ml, respectively.

For *E. feacalis*, all tested compounds have an effective effect on the inhibition of bacterial growth; do not exceed their MIC 62.5 µg / ml. This value is equal to that of the acridone (1b), leaves us to conclude that the activity of 9-aminoacridines studied against *E. faecalis* seems to come from the acridine core.

The reports MBC / MIC of the three Gram-positive bacteria are less than four. It is therefore clear from our analysis that our molecules have a bactericidal effect on *MSSA* strains, *MRSA* and *E. faecalis* (Prescot *et al*, 2003; Berche *et al*, 1991).

The choice of an antibiotic to compare these results was gentamicin. This antibiotic is used for the treatment of severe infections (complicated and recurrent urinary tract infections, lower respiratory tract infections (nosocomial); intra-abdominal infections, including peritonitis etc ...) (Vincent, 2009). The results showed that this antibiotic is bactericidal against *Staphylococcus* with a very high MIC compared to molecules previously tested, either 900µg/ml. *Enterococcus faecalis* shown resistance to this antibiotic, indeed the aminoglycosides are considered inactive in the treatment of *Enterococcus* infections and are usually combined with inhibitors of the synthesis of the cell wall which may facilitate their attachment (Vincent., 2009; Lefort *et al*., 2000).

Table 3 shows that *P. aeruginosa* appears to have a decreased sensitivity against structures substituted with an aliphatic amino acid (2c to 4c) with a MIC of 125 µg / ml. The loss of flatness seems to be a parameter disfavoring the antibacterial activity of our molecules against this germ. However it should be noted that *P. aeruginosa* used for these tests is resistant to 3rd and 4th generations cephalosporin (ceftazidim, cetriaxone ....) and carbapenem(imipenem) that's mean present beta-lactamase and carbapenemase enzymes. The efficiency of the synthetic molecules is a very important scientific contribution

to eradicate this bacterium that causes a lot of annoyance and large health damage.

Concerning *S. paratyphi A*, the MIC doesn't show a significant difference compared to that of the acridone (1b) except for the compound (10c) which is substituted by a p-tolyl group.

As for *E. coli*, the results show a very appreciable sensitivity to these products. The radical grafting of an amino acid enhances the activity compared with the acridone. As against, a lengthening of the aliphatic chain, appears to decrease the antibacterial activity against *E. coli* (MIC of 4c increases to 31.25 µg / ml). For structures grafted with an aromatic amino acid, the activity improves when the acid function is in the ortho position. When the core is grafted with an aniline, the activity decreases compared to the acridone, we can also say that an aniline unsubstituted or substituted by a methyl in the ortho position has an adverse effect on activity. Moreover naphthyl group seems to have a good effect on the antibacterial activity.

In the case of *K. pneumoniae*, all substances have an effective effect on the inhibition of bacterial growth. The MIC ranges from 31,25µg / ml and 62,5µg / ml which is also equal to that of the acridone (1b). The activity of these molecules against *K. pneumoniae* appears to be from the acridine nucleus.

31.5 µg / ml of the compounds 1b, 1c, 2c, 3c and 5c is the MBC against *E. coli* however, the same concentration is only effective for the derivative 10c against *S. paratyphi A*.

For the other bacteria MBC of the different compounds varies from 62.5 to 250 µg / ml depending on the compound with a decrease in the sensitivity of *P. aeruginosae* (MBC varies from 125 to 250 µg / ml).

The reports MBC / MIC of the four Gram-negative bacteria tested are ≤ 4. These results again prove that our synthetic molecules have a bactericidal power on all four pathogenic and multiresistant bacteria: *P.aeruginosa*, *S.paratyphi A, E. coli* and *K. pneumoniae* with MICs that are very low compared to that of the antibiotic by reference gentamycin.

CONCLUSION

Because of the high levels of morbidity and sometimes mortality associated with bacterial infections resistant to antibiotics, acridines can be an alternative anti promising biotherapic. The results of this study showed that all synthesized compounds have significant bactericidal activity against all multi-resistant pathogenic strains tested. The MICs are low in the order of micrograms, indicating a highly effective antibacterial activity compared to the reference antibiotic gentamicin.

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