Synthesis of lactones and lactams analogues to rubrolides as inhibitors of *Enterococcus faecalis* biofilm formation

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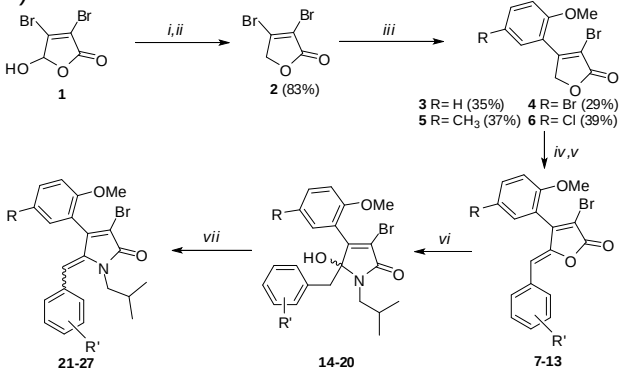
INTRODUCTION

Biofilms are a bacterial communities enclosed within an extracellular matrix capable to survive to antibiotics treatments[1]. It has been estimated that 65-80% of the microbial infections occurring in the human body are biofilm-related. Therefore, identifying substances that are able to inhibit biofilm formation constitutes a promising approach for the development of new drugs.

In this work, analogues to rubrolides, a class of natural γ-alkylidene-γ-lactones[3], and their corresponding lactams were synthesized and evaluated against *E. faecalis* biofilm formation.

RESULTS AND DISCUSSION

A sequence of reactions consisting of reduction, Suzuki cross-coupling and alkylidenation allowed the preparation of rubrolides analogues **7**-**13** (Scheme 1).



i) 1,5 equiv. $NaBH_4$, MeOH, 0 °C; ii) H_2SO_4 conc., MeOH, 0 °C; iii) ácido borônico, $AsPh_3$, $PdCl_2(MeCN)_2$, Ag_2O, THF, 65 °C, 24h; iv) aldeído, TBDMSOTf, DIPEA, DCM; v) DBU, refluxo; vi) isopropilamina, DCM, 0 °C, 3h; vii) *p*-TsOH,$CHCl_3$, refluxo, 2h.

R	R'	Comp* (%)	Comp* (%)	Comp* (%)	Comp* (%)
H	*p*-CF_3	**7** (63)	**14** (85)	**21**Z (36)	**21**E (39)
Br	*m*-Cl	**8** (44)	**15** (78)	**22**Z (28)	**22**E (31)
Br	*p*-Br	**9** (45)	**16** (85)	**23**Z (23)	**23**E (33)
CH_3	*m*-Cl	**10** (63)	**17** (84)	**24**Z (35)	**24**E (45)
CH_3	*o*-Cl	**11** (68)	**18** (84)	**25**Z (29)	**25**E (39)
Cl	*o*-Br	**12** (58)	**19** (76)	**26**Z (29)	**26**E (43)
Cl	*m*-OCH_3	**13** (65)	**20** (76)	**27**Z (41)	**27**E (35)

Scheme 1. Synthesis of the compounds

These analogues were treated with isobutylamine to prepare the γ-hydroxy-γ-lactams **14**-**20** in yields ranging from 76% to 85%. These compounds were further dehydrated to generate γ-alkylidene-γ-lactams **21**-**27** as mixture of isomers *Z* and *E* that were purified by column chromatography (Scheme 1). The configuration of the exocyclic C5-C6 double bound was secured by NOE difference spectroscopy studies.

The lactones and lactams were evaluated against *Enterococcus faecalis* biofilm formation. Table 1 present the concentration of each compound necessary to inhibit 50% of biofilm formation (IC_{50}).

The most active groups of compounds were the *Z* and *E* γ-alkylidene-γ-lactams.

Table 1. Effect of the compounds against *E. faecalis* biofilm formation

Comp	IC_{50}*	Comp	IC_{50}*	Comp	IC_{50}*	Comp	IC_{50}*
7	*	**14**	*	**21**Z	12,0±4,6	**21**E	3,0±0,7
8	6,9±1,7	**15**	>87,5	**22**Z	3,3±1,3	**22**E	3,5±0,2
9	18,7±5,1	**16**	33,4±17,0	**23**Z	6,6±0,4	**23**E	3,4±0,4
10	1,5±0,1	**17**	>87,5	**24**Z	62,6±9,7	**24**E	59,3±11,1
11	*	**18**	1,1±0,1	**25**Z	1,1±0,3	**25**E	1,0±0,2
12	>87,5	**19**	1,3±0,2	**26**Z	1,5±0,1	**26**E	0,76±0,2
13	53,1±16,7	**20**	>87,5	**27**Z	1,5±0,3	**27**E	3,3±1,5

*IC_{50} values expressed in μg/mL.

CONCLUSION

Seven analogues to rubrolides were prepared and then converted into their corresponding lactams through the two-step lactamization. The evaluation of these compounds against *E. faecalis* biofilm formation showed that all these groups of compounds are very active, with the γ-alkylidene-γ-lactams amongst the most actives.

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