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Towards smart biocide-free anti-biofilm strategies: Click-based synthesis of cinnamide analogues as anti-biofilm compounds against marine bacteria

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ABSTRACT

A set of triazole-based analogues of *N*-coumaroyltyramine was designed to discover potential leads that may help in the control of bacterial biofilms. the most potent compounds act as inhibitors of biofilm development with EC50 closed to ampicillin (EC50 = 11 μM) without toxic effect on bacterial growth even at high concentrations(100 μM).

Introduction

Biofilms results in the colonization process of soft or hard, artificial or living substrata by microorganisms which attach to surfaces and bind to one another.[1] Although the control of the development of planktonic bacteria communities is well known and mastered, bacteria within a biofilm are much more resistant to antibiotic or biocide treatment (up to 1000-fold increased resistance). To fight biofilms, the massive use of such compounds has led to major problems in human health by developing high degrees of resistance in bacterial communities as well as economic, environmental and toxicological issues leading to establishment of strict regulations.[2–5] In this context, targeting the formation of bacterial biofilms in a non-toxic way is of great interest in view of a rational use of antibiotics and/or biocides and the development of original non-toxic biofilm inhibitors should have the potential to be used in a preventive treatment of a wide diversity of industrial and medical surfaces. Moreover, the development of such solutions must remain competitive and must enable low-cost molecules to be placed on the market. For such a challenge, some of the anti-biofilm strategies that are pursued todays consist in studying structure-activity relationships (SAR) of simple secondary metabolites from marine organisms such as sponges or soft corals in view of discovering new specific and non-toxic anti-biofilm leads which should be used as potential adjuvant for antibiotherapies or friendly environmentally biocides.[6–8] In this field, we are developing an efficient and simple approach based on the bioisosteric replacement of natural frameworks by a 1,2,3-triazolic ring to allow SAR studies in the field of antifouling fight, and we have previously designed with success isonaamine A, bromotyramines and hemibastadins analogues (Fig. 1).[9–11] For this purpose, 'click chemistry" by mean of copper-catalyzed azide-alkyne cycloaddition was used as a highly efficient approach, offering substantial advantages, since it is tolerant to multiple functional groups.[12,23] In addition a large variety of terminal alkyne is available as building blocks, while azides may easily be accessed from common precursors, such as halides and amines, using standard literature procedures.

Pursuing these investigations in the field of antibiofilm compounds, we are interested in the advanced SAR studies of tyramine derivatives and we wish to investigate some more simple frameworks which could be accessible in a two-steps process from simple commercial tyramines and anilines. To assume such a challenge, we focused on the design of original analogues of cinnamoylphenethylamine family; this class of natural products are found in over 30 plant families. The most ubiquitous are p-coumaroyltyramine and feruloyltyramine. Nevertheless, the cinnamic acid and phenethylamine derivatives are of great interest

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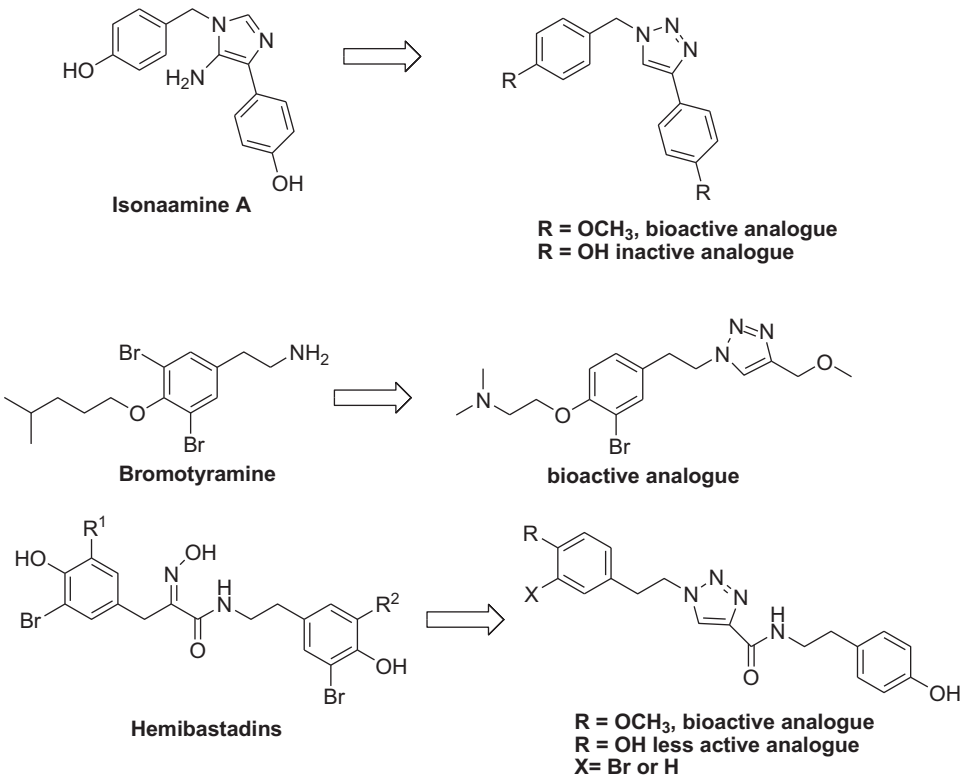

Fig. 1. click-based design of natural product analogues.[9–11]

due to their plethora of associated biological activities such antibacterial and antimicrobial[13–15] compounds and more especially as anti-biofilm compounds.[16] In this work we planified a bioisosteric replacement of the double bond by a 1,2,3-triazole ring (Fig. 2). Such bioisosteric replacements of double bonds have already been investigated with success to design analogues of combrestatin and resveratrol analogues which exhibited enhanced antitumoral potential.[17,18] In this way the cinnamic acid moiety is modified. Furthermore, considering our previous results which showed that methoxy derivatives were more efficient than the hydroxy ones,[11] we decided to restrict the study to methoxy anilines **1a** and **1b** as starting materials.

The first step of this work was the preparation of intermediary carboxylic acids (**3a**, **3b**) (Scheme 1). These compounds were obtained in excellent yield in two steps. Treatment of anilines (**1a**, **1b**) with sodium nitrite followed by sodium azide in dimethylformamide afforded the corresponding crude azides (**2a**, **2b**) which were used without further purification. Synthesis of the targeted carboxylic acids (**3a**, **3b**) was then achieved by performing the copper(I)-catalyzed 1,3-dipolar cycloaddition of the organic azides with propargylic acid resulting in the formation of 1,2,3-triazoles.[19] In general, these reactions usually proceed to completion in 6–36 h at room temperature in water with a variety of organic co-solvents, such as *tert*-butanol, ethanol, DMF, DMSO, THF, or CH_3CN.[12,20] Ethanol was chosen rather than DMF to allow an easier workup and a better purity of products as described in our previous work.[9] In practice, propargylic acid was added to a solution of appropriate azide (**2a**, **2b**), $CuSO_4$/sodium ascorbate in a water/ethanol mixture (50/50) and the reaction time was optimized at 12 h at room temperature. Further access to the different cinnamides analogues **4**–**11**, was allowed by a peptide coupling step using DCC/HOBt

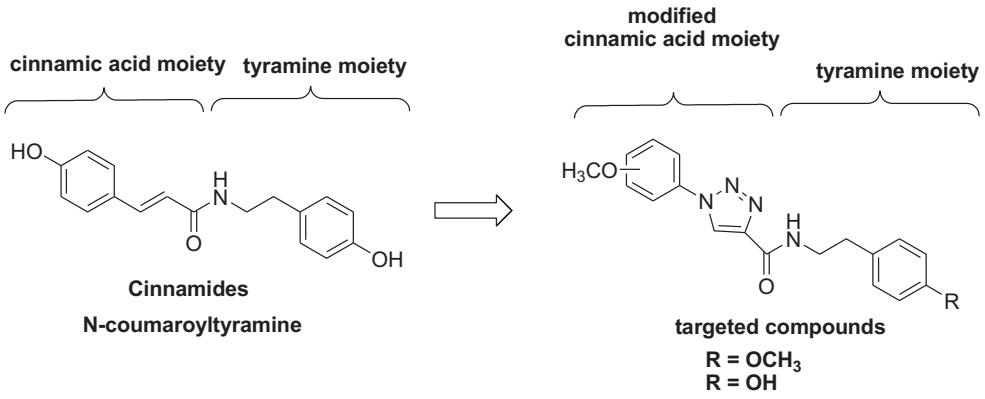

Fig. 2. Structure of the targeted compounds.