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Loperamide-based compounds as additives for biofouling management

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ABSTRACT

The commercial pharmaceutical Imodium™, which contains the active ingredient loperamide hydrochloride, has been shown to have biofouling control properties. However, due to concerns associated with safety and persistence of this active pharmaceutical ingredient (API) in the environment, the development of loperamide as an anti-fouling additive is not desirable. In this paper, we report our efforts directed towards the design and synthesis of small molecule anti-foulants using the loperamide parent compound as the lead compound. These loperamide-based compounds can be synthesized readily and inexpensively. Several of the compounds identified are potentially useful as additives in marine antifouling coatings as they control attachment of barnacles in laboratory tests and an estimation program (BIOWIN) developed by the US Environmental Protection Agency predicts that they will degrade completely in weeks to months.

1. Introduction

Fouling management using organotins was banned globally in 2008. Use of copper biocides is being restricted in the European Union and United States (Thomas and Brooks, 2010). As coating systems containing long lived organic biocides gain market share, there is evidence that they are building up in the environment and may have unexpected environmental consequences. (Thomas, 2009). One alternative is the development of highly potent shorter lived anti-foulants (Rittschof, 2008). Ideally this new generation of fouling management additives would effectively control fouling and be more environmentally benign because they degrade more quickly and do not build up in the environment.

Rittschof et al. (2003) and Teo et al. (2006) outlined the concept of using pharmaceuticals as a starting point for the search for new anti-foulants. The overall rationale for this approach was that the mechanisms of action of pharmaceuticals on humans are usually well-studied, and it is likely that there are common transduction pathways that are present in the settlement stages in macrofoulers. Thus, pharmaceuticals may serve as initial leads for the development of new anti-foulants. One drawback is that oral pharmaceuticals are designed for resistance to degradation thus leading to problems with the persistence of high volume pharmaceuticals in the environment especially in the aquatic environment (Khetan and Collins, 2007; Howard and Muir, 2011).

The ideal strategy is one that capitalizes on the knowledge of effective pharmaceuticals while applying environmental considerations in the design of new anti-foulants. This paper describes the partnering of drug design principles with biological screening for activity for antifouling and illustrates the principles for development of environmental applications from biomedicine. Our study is initiated from the observation that Imodium™, an anti-diarrhea drug which has loperamide as the active ingredient, showed

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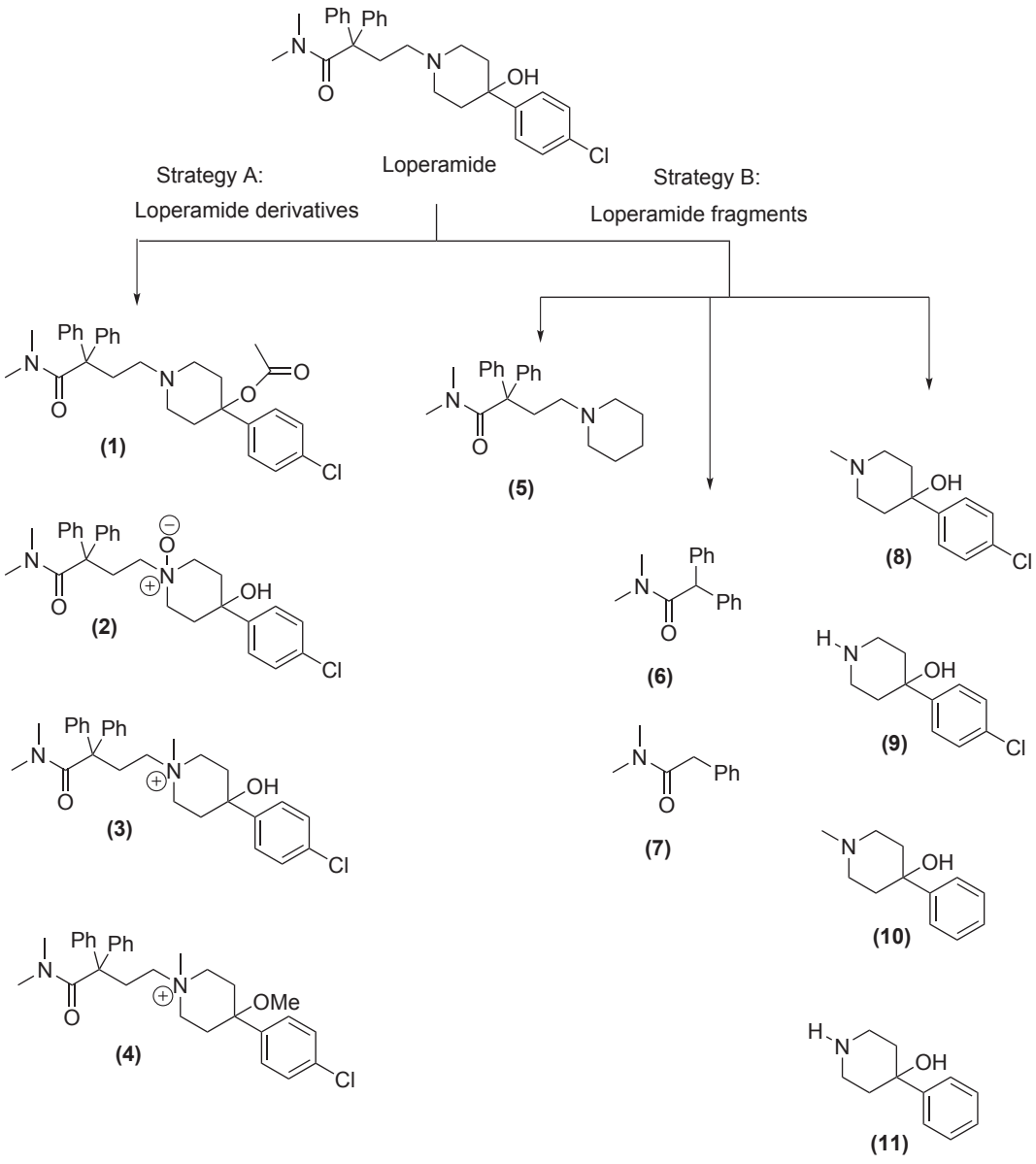

Fig. 1. Strategies for target compounds.

encouraging results as an anti-foulant in field studies (Teo et al., 2006). Subsequent studies with the pure active pharmaceutical ingredient (API), loperamide, also showed promising activity in barnacle settlement assays. (Teo et al., 2009).

Loperamide hydrochloride is slightly soluble in water, and is moderately soluble in methanol, isopropyl alcohol and chloroform. It is indicated for the symptomatic control of acute and chronic diarrhoea (Heel et al., 1978; Awouters et al., 1993) and pharmacodynamic studies in vertebrates show that loperamide binds to opiate receptors in the gut wall, inhibiting the release of acetylcholine and prostaglandins.

In this report, we demonstrate that it is possible to identify structural features and/or functionalities that contribute to the toxicity and anti-settlement effects of loperamide, respectively. This has resulted in the discovery of simple amides that are highly potent in inhibiting barnacle larvae settlement while minimizing toxicities. In addition, the propensity of these simple amides to undergo biodegradation is also outlined. These low molecular weight amides can serve as lead compounds for further optimization of biological activities and/or physicochemical properties. The latter are important in compatibility considerations with coatings, release from coatings, degradability and stability.

Our strategy is outlined in Fig. 1. Simple derivatives of loperamide (strategy A) will provide some fundamental understanding of the structure–activity/toxicity relationships. The loperamide framework was elaborated via several simple synthetic transformations and *O*-acetyl loperamide (**1**), loperamide *N*-oxide (**2**), *N*-methyl loperamide (**3**), and *N*,*O*-dimethyl loperamide (**4**) derivatives were thereby accessed. Strategy B considers loperamide 'fragments' as a rapid method to identify the minimal 'pharmacophore' needed to retain activity. In addition, low molecular weight compounds are likely to be more easily degraded than the parent loperamide structure (Boethling et al., 2007). The amides **5**–**7** were synthesised either from the corresponding acids via activation using the acid chloride method followed by addition of dimethylamine (Moffett et al., 1957) or via the ring opening of the