# monitor

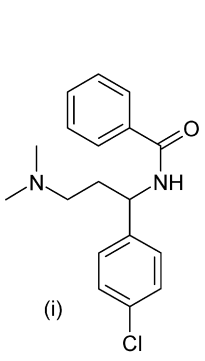
## MOLECULES

### The use of parallel chemistry for the generation of micromolar hits against biological targets

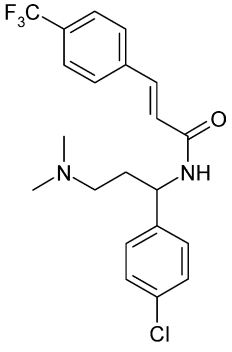
#### Urotensin II receptor agonists

Urotensin II (UII) receptor agonists are of interest in drug discovery because of the potential role of UII in numerous diseases, including hypertension [1], heart failure [2] and diabetes [3]. Many (but not all) of the UII agonist and antagonist examples in the literature are peptidergic in nature, so there remains a need for potent and selective, low molecular weight ligands to examine further the biology and pharmacology of the UII system. Recent work has sought to address this need through exploration of the SAR around a series of low molecular weight UII agonists, typified by (i) [4].

A small library of 30 compounds was synthesized as singletons in solution from the corresponding carboxylic acids and amines, utilizing solid phase coupling reagents. Compounds produced around this chemotype (i) were tested for their agonistic properties at human UII receptors using the functional R-SAT™ assay [5]. For control of the UII receptor selectivity, all compounds were tested against the m3 receptor as a negative control. From this library, several potent agonists of UII were identified when evaluated for their UII receptor agonistic activities using the cell-based assay (R-SAT™). One of the most potent compounds identified was (ii) which possessed a pEC50 of 6.89. This work is of interest because of the development of an efficient protocol for the production of large libraries of aliphatic and conjugated amides. A 30-membered test library revealed novel information regarding the SAR around chemotype (i), and resulted in the discovery of potent compounds. Further work in this series is warranted, better to optimize this novel series of inhibitors.




(i)




(ii)

#### New rubella virus inhibitors derived from 4-alkylamino-6-(2-hydroxyethyl)-2-methylthiopyrimidines

Rubella virus (RV) is the only member of the *Rubivirus* genus of the *Togaviridae* and it is characterized by a positive-sense single stranded RNA genome consisting of 9762 nucleotides. Symptoms of the virus are a scarlatiniform rash, cervical lymphadenopathy and mild constitutional symptoms, but in older children and adults, especially women, it may be more severe, with purpuric rash being seen for example. Rubella was the first virus demonstrated to be teratogenic. Infection during the first 12 weeks of pregnancy results in congenital infection and/or miscarriage in 80–90% of cases. The development of live and attenuated vaccines and the expansion of vaccination strategies since 1970 have reduced, but not eradicated, the incidence of congenital rubella syndrome (CRS) [6]. If this viral infection, leading to CRS, occurs in the first part of pregnancy, particularly in women without specific immunological protection, the virus can induce nerve deafness, and cardiac anomalies, and later complications may include diabetes, thyroid disease and growth hormone deficiency [7]. Although natural and semisynthetic polysaccharides [8] and acylated 1,2,4-triazole derivatives [9], for example, show inhibitory effects against RV, specific therapies to prevent CRS are not currently available. Thus, there remains a need to develop new antiviral agents. Recent work [10] has disclosed a series of new 2-alkylthiopyrimidines active against RV, with the aim of increasing their antiviral potency and pharmacological profile. The library chemotypes synthesized are given in general form in figures (iii) and (iv), and were synthesized through the use of solution phase parallel synthesis. Synthesis proceeded via the tosylate (v) and utilized a Buchi Syncore® to produce a small library of 19 compounds. The antiviral activity of the synthesized compounds was evaluated in



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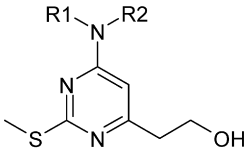
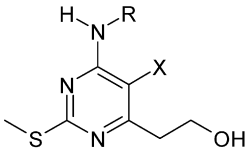
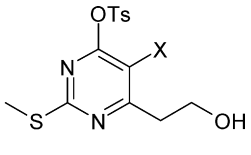
Vero cells starting from the highest non-cytotoxic concentration, which did not affect any parameter (cell morphology, viability and growth) considered in 100% of the cells. After virus adsorption, the viral inoculum was removed, cell monolayers were washed three times with PBS and incubated in the presence or absence of two-fold dilutions of the compounds. Viral inhibition was evaluated by plaque assay after a single cycle of virus multiplication. From this screening effort, several active compounds were obtained, with (vi) one of the most potent, which possessed an $IC_{50}$ value of 13.5 μM. This work is of interest from the perspective that a solution-phase parallel approach for the synthesis of a small library of 4-dialkylamino-6-(2-hydroxyethyl)-2-methylthiopyrimidines has been accomplished. This has led to the identification of a number of compounds with antiviral potency against RV in the micromolar range, qualifying these compounds as hits worthy of further investigation. One avenue of further investigation for example would be to try to improve the potency of these antiviral agents.



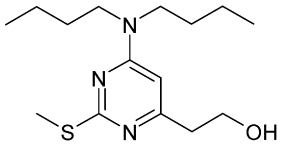

(iii)




(iv)




(v)




(iv)

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