HOMOLOGY MODELING AND MUTATION DATA TO DRIVE SAR FOR CCR5: IS IT CRYSTAL CLEAR?

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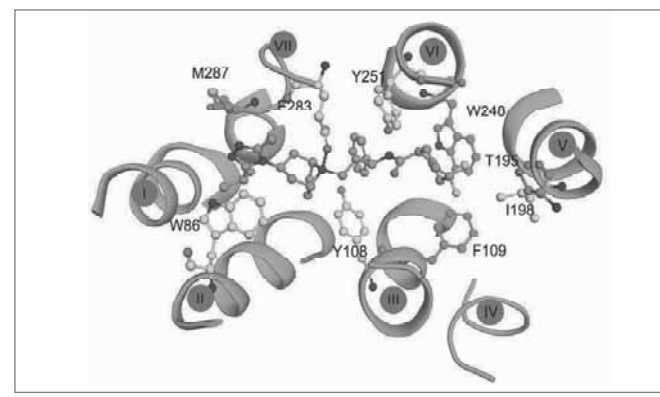

The CC chemokine receptor CCR5 is activated by chemokines RANTES, MIP 1α and MIP 1β, and is a co-receptor for macrophage tropic human immunodeficiency virus type I (HIV-1). Hence, one of the most promising approaches to block HIV-1 entry is to use small molecule antagonists for CCR5. Presently, Maraviroc from Pfizer is a marketed drug that inhibits HIV via antagonizing CCR5 receptor. Other compounds like Vicriviroc and Aplaviroc from Schering and GSK respectively have also gone through clinical trials. To facilitate development of next generation antagonists for HIV-1, we explored how the above mentioned compounds antagonize CCR5 by mapping their binding site using site directed mutagenesis and receptor protein modeling. Here we describe a receptor mutation data driven approach for modeling receptor–ligand interactions. Furthermore, these receptor–small molecule interactions are used to identify the binding modes for three compounds from Pfizer, Schering and GSK. While the three antagonists share a common binding site, the nature of specific interactions within the pocket is different. The extent of binding derived from these interactions is variable among the three antagonists. The fully mapped binding pocket for CCR5 was used as a structure based design tool for lead optimization for the in-house compounds.

ORAL COMMUNICATIONS – OC.02

DC-SIGN: A TARGET FOR THE DESIGN OF NEW ANTIVIRAL DRUGS

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DC-SIGN (Dendritic Cell-Specific ICAM-3 Grabbing Non-integrin) is a C-type lectin expressed mainly at the surface of immature dendritic cells. This lectin presents at the C-terminus a Carbohydrate Recognition Domain (CRD) able to recognize highly glycosilated proteins such as gp120 (HIV), GP (Ebola virus), ICAM-2, ICAM-3, etc.[1].

The role that DC-SIGN plays during the infection processes and also, its implication in the immune response has attracted the interest of many research groups. During last years we have been involved in the design and preparation of carbohydrate dendritic multivalent systems (Figure) to study and interfere into those processes where DC-SIGN is involved with the aim to develop new antiviral drugs and immune modulators[2]. These multivalent systems were built up based on bis-hydroxypropionic acid and then, functionalized with different carbohydrates. Also, dendrons with the focal point adequately functionalized (R = azide, alkyne, amine, pyridine) have been prepared to be conjugated with different scaffolds of interest. This approach will allow the development of multivalent systems showing different presentation of carbohydrates for applications in nanomedicine.

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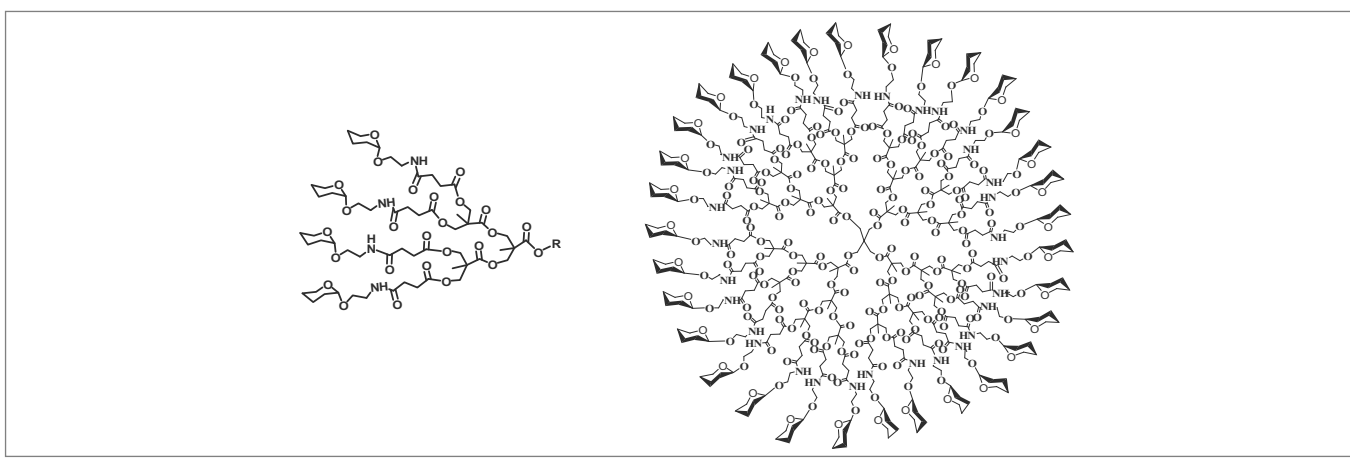

PYRIMIDO[4,5-d]AZEPINES AS POTENT AND SELECTIVE 5-HT$_{2C}$ RECEPTOR AGONISTS: DISCOVERY OF PF-3246799

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The neurotransmitter serotonin (5-HT) mediates its effects through at least 14 different receptor subtypes that have been classified into seven major families, 5-HT1-7. The 5-HT2 family has three members 2A, 2B and 2C and unlike 5-HT2A and 5-HT2B receptors, the expression of 5-HT2C receptors appears to be restricted to the central nervous system (CNS). 5-HT2C receptor agonists have become attractive drug targets that have potential use in the treatment of a number of conditions including obesity, schizophrenia, sexual dysfunction, and urinary incontinence. For these indications, selectivity over agonism at the 5-HT2A and 5-HT2B receptors would be a key objective because 5-HT2A agonists can potentially be hallucinogenic and have cardiovascular (CV) effects, whereas 5-HT2B agonism has been associated with heart valvulopathy and pulmonary hypertension.

The search for potent and selective 5-HT2C agonists has identified lorcaserin (1) (APD-356; Arena) which is in advanced clinical trials for the treatment of obesity and vabicaserin (2) (SCA-136; Wyeth) as a potential therapy for schizophrenia. Furthermore, several small molecule 5-HT2C agonists have been reported to be in early clinical development.

We have disclosed several new templates as 5-HT2C receptor agonists and some of these compounds have now progressed to clinical trials. As part of our research efforts to identify potential new 5-HT2C agonist drug candidates, we adopted a strategy of exploring multiple chemical templates in order to increase our chances of having compounds survive to become advanced clinical candidates[1]. In this Presentation, we disclose new pyrimido[4,5-d]azepines (3) as potent and selective 5-HT2C receptor agonists[2].

This presentation is our first disclosure of this lead series and will include:

- Identification of lead series by "template hopping".
- Detailed analysis of SAR which led to the identification of preferred compounds.
- In vitro profiles of preferred compounds to include 5-HT2c activity, selectivity data wrt 5-HT2A/2B, ADME, and safety data.
- Presentation of chemistry enabled synthetic routes.
- Discussion of changes in structural features and physicochemical properties that effect CNS permeability.
- Preclinical profile of PF-3246799 to include efficacy data in animal models along with pharmacokinetic and safety data.

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