Expert Opinion

Therapeutic compounds: patent evaluation of WO2011011652A1

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A series of sulfonamide derivatives, incorporating azabicyclo[3.2.1]octane and phenyl-propyl scaffolds, were prepared by a succession of original steps. The compounds are claimed to act as antagonists of the C-C chemokine receptor 5 (CCR5) involved in the entry of HIV-1 to cells, but only semi-quantitative antiviral data are provided. HIV entry inhibitors, including CCR5 antagonists, are clinically used for the treatment of this viral infection; the compounds claimed in the patent, possessing a new and original scaffold, seem to be of interest for developing novel antiviral agents belonging to this class.

Keywords: antiviral agent, azabicyclo[3.2.1]octane, CCR5 antagonist, HIV infection, sulfonamide

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1. Introduction

Viral infections represent a major medical problem worldwide. HIV infection affects millions all over the world, and although much progress has been registered in the treatment of this infection by the introduction of combination, highly active antiretroviral therapy, the massive viral replication (with > 10^9 virions produced daily) and the high error rate of the reverse transcriptase (RT) lead to the emergence of drug resistant strains and the stringent need of new therapeutic approaches [1-6]. The emergence of the AIDS epidemic in the early 1980s fostered much research and great progress in this area, and presently > 30 antiviral drugs are available, most of them for the management of HIV infection and AIDS, but also for the treatment of other viral diseases such as hepatitis B, influenza, herpes simplex, varicella-zoster and cytomegalovirus (HCMV) infections [5].

There are at least 10 steps in the HIV life cycle, most of which are amenable to be targeted by drugs, already identified and clinically used at this moment, or currently under investigation [1-6]. They are: (i) virus adsorption inhibitors; (ii) viral co-receptor antagonists; (iii) viral fusion inhibitors; (iv) nucleocapsid protein zinc finger targeted compounds; (v) RT inhibitors of the nucleoside/nucleotide type, N(t)RTIs, which target the substrate binding site of the enzyme; (vi) RT inhibitors of the non-nucleoside type (NNRTIs), which target an allosteric, non-substrate binding site; (vii) the IN inhibitors; (viii) transcription/transactivation inhibitors; (ix) protease inhibitors and (x) maturation inhibitors. Steps (ii) and (iii) may be considered as those dealing with the entry of HIV within cells, one of the most promising targets for HIV drug development. Indeed, enfuvirtide, a HIV fusion inhibitor, was the first drug with a target different from viral RT or protease to be approved by the FDA [2-4]. However, there is still need of potent, orally bioavailable small molecules able to make concrete the efforts made so far in this research field.

Chemokines are low molecular mass (8 – 12 kD) proteins produced and secreted after stimulation by several exogenous (such as viruses, bacteria and endotoxins) and pro-inflammatory endogenous agents such as the cytokines IL-2 and TNF, whereas IFN and glucocorticoids are potent inhibitors of their secretion [7]. Furthermore, chemokines promote both humoral and cell-mediated immunity, regulate cellular adhesion and angiogenesis, and contribute to lymphopoiesis and hematopoiesis [7].

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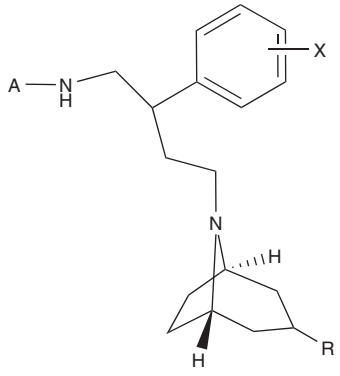
When administered at very high concentration, chemokines can suppress inflammatory reactions. They are produced by several cell lines that can respond to many of them through different pathways. Chemokines are classified into two main categories: α-chemokines, also known as C-X-C chemokines, possessing 10 amino-terminal cystein (C) residues separated by another amino acid (X); they activate the neutrophils and promote their adhesion to endothelial cells, their crossing of the vessel wall followed by the tissue spread and migration towards the inflamed sites. β-Chemokines, also known as C-C chemokines, mainly activate monocytes, lymphocytes, basophils and eosinophils and play a central role in T-cell proliferation and allergies [7]. In 1995, Cocchi *et al.* discovered the potent inhibitory effect of three chemokines secreted by $CD8^+$ T lymphocytes on HIV-1, focusing the attention on this class of molecules which led to important discoveries that finally unraveled the process of HIV entry within the cells [8]. The chemokines described in this study, RANTES (regulated on activation normal T cell expressed and secreted), MIP (macrophage inflammatory protein)-1α and MIP-1β, belong to the group of C-C chemokines (β chemokines) and are soluble factors secreted by $CD8^+$ T lymphocytes. C-X-C chemokines (α-chemokines) include SDF (stromal derived factor)-1α and SDF-1β among others [8]. There are different target cells for different chemokines: MIP-1α and MIP-1β target monocytes/macrophages, T lymphocytes (inducing TH1 → TH2 differentiation), basophils, immature dendritic cells and bone marrow cells. MIP-1α and MIP-1β interact with the C-C chemokine receptor (CCR)1 and CCR5 receptors. RANTES targets monocyte/macrophages, T lymphocytes (inducing memory T cells → TH1 → TH2 differentiation), NK cells, basophils, eosinophils and dendritic cells. RANTES interacts with the CCR1, CCR3 and CCR5 receptors. SDF-1α and SDF-1β target $CD34^+$ cells, dendritic cells, B lymphocytes, naive B lymphocytes and activated $CD4^+$ T lymphocytes. SDF-1α and SDF-1β specifically interact with CXCR4 [7-12].

HIV entry into host cell is a complicated process that involves a series of molecular events that started to be understood in detail ultimately. The T-lymphocyte cell surface protein CD4 is the primary receptor involved in the interaction with the viral glycoprotein gp120, but a cellular co-receptor is also needed for the successful entry of the virus within the cell [7-12]. At least two types of such co-receptors have been identified so far, both belonging to the chemokine family of seven-transmembrane-spanning receptors coupled to a G-protein signaling pathway [13-16]: the CCR5 (which binds the chemotactic chemokines, MIP-1α, and MIP-1β, and RANTES, as already mentioned above) and the CXC chemokine receptor 4 (CXCR4) (which binds SDF-1 as natural ligand) [13-16]. These receptors, therefore, are the gateways for HIV entry, determinants of viral tropism and sensitivity. CCR5 receptor is used by macrophage (M)-tropic viruses and CXCR4 is used by T-lymphocyte (T)-tropic virus [13-16].

Maraviroc was the first selective CCR5 antagonist with potent antiviral activity against all CCR5-tropic HIV-1 viruses at low nanomolar concentrations (mean 90% inhibitory concentration of 2 nM) which started to be used clinically in 2007 [17]. By acting as an antagonist at the CCR5 co-receptor, maraviroc inhibits HIV-1 from entering host cells. Clinical data for maraviroc were initially available from two large, well-designed, ongoing Phase IIb – III trials (MOTIVATE-1 and -2) conducted in patients infected with R5-tropic HIV-1 who had previously received at least one agent from three of the four classes of antiretroviral drugs and/or were triple-class resistant. According to 24-week interim results of the MOTIVATE-1 and -2 trials, a significantly greater reduction in viral load occurred in patients receiving maraviroc 150 or 300 mg (depending on optimized background therapy (OBT)) twice daily plus OBT compared with placebo plus OBT. This significant difference was maintained at 48 weeks in MOTIVATE-1. The 48-week results of MOTIVATE-1 also reported a significant difference in favor of maraviroc for all these end points. In general, maraviroc at dosages of up to 300 mg twice daily was well tolerated in treatment-experienced patients infected with R5-tropic HIV-1. Thus, this first-in-the-class drug fostered much research in the field of CCR5 antagonists with use as antivirals. The patent analyzed here is just an example of such *de novo* designed CCR5 antagonists based on totally new scaffolds.

2. Chemistry

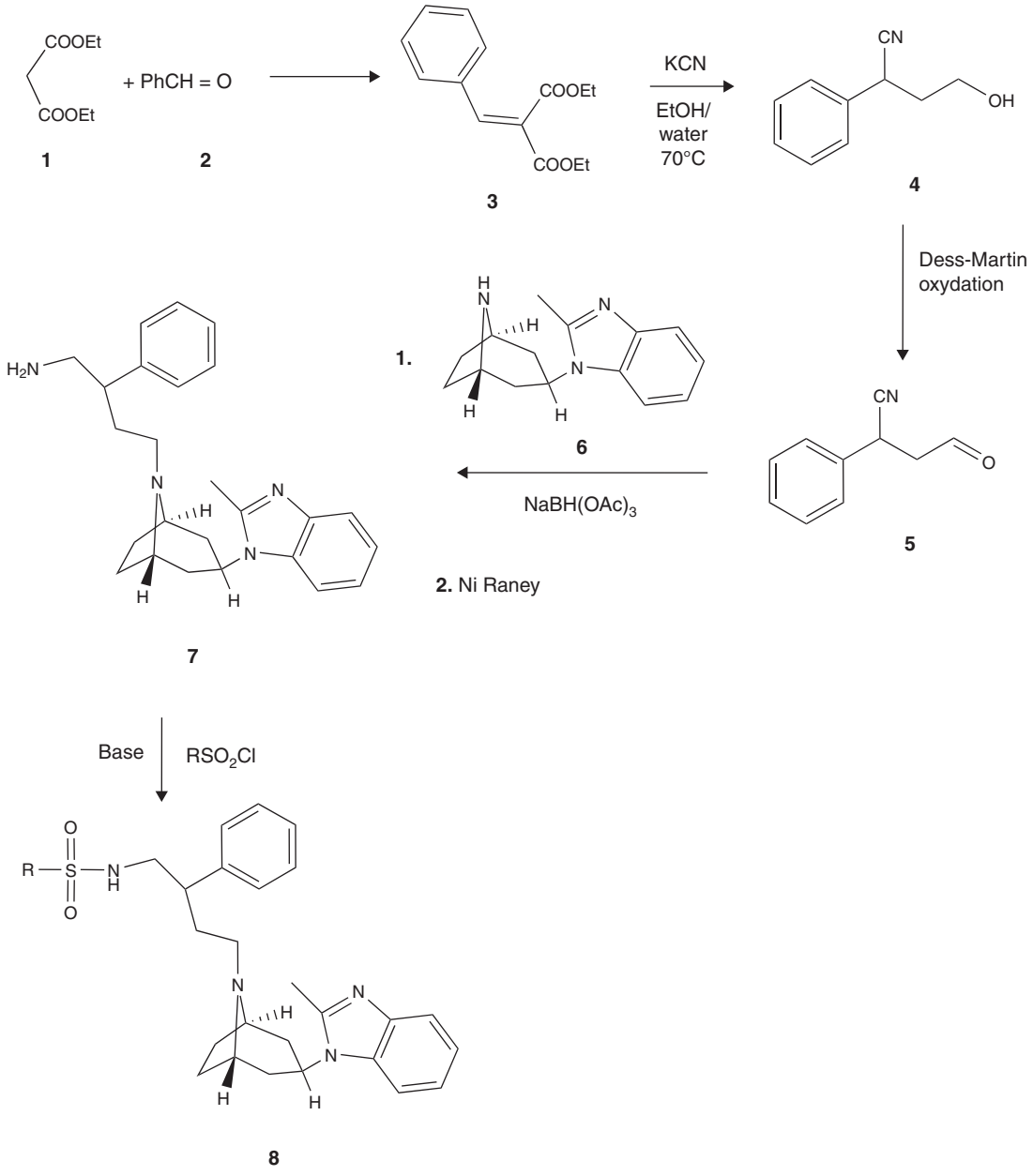
The compounds claimed in the patent possess the general structure I which is an original one in the field of CCR5 antagonists as it includes:



I

X = H, halogen, $C_1 - C_6$ alkyls; A = aryl, substituted aryl, alkyl, cycloalkyl; R = heterocyclyl (substituted eventually with one or more substituents).

i) an azabicyclo[3.2.1]octane connected to a phenylpropyl scaffold via the bridging nitrogen atom
ii) the same phenyl belonging to the scaffold mentioned above is part of a phenethylamine moiety



Scheme 1. General scheme for the preparation of compounds of type I, exemplified for the derivative 8.

iii) the amine belonging to the phenethylamine fragment is in turn derivatized, most of the time, via sulfonamide or carboxamide functionalities. As sulfonamides possess a rather wide range of biological and pharmacological properties [18-22], it is not unusual that most of the claimed compounds of the patent belong to this class.

A general procedure for the preparation of some of these compounds is shown in **Scheme 1**. Starting from diethyl malonate **1**, by condensation with aromatic aldehydes, such as benzaldehyde **2**, the benzylidene derivative **3** was obtained, which was reacted with sodium cyanide in ethanol–water, leading to 3-phenyl-3-cyano-propanol **4**. This intermediate has been oxidized to the corresponding aldehyde **4**, which was reacted with the secondary amine **6** incorporating the main feature of these compounds, that is, the azabicyclo [3.2.1]octane scaffold. This condensation has been achieved in reducing conditions, in the presence of sodium borohydride derivatives, and was followed by a nickel Raney reduction of the nitrile to the corresponding primary amine **7**. This was the key intermediate for the many compounds

claimed in the patent, and 7 was further derivatized primarily by reaction with alkyl/cycloalkyl/aryl sulfonyl halides, leading to the sulfonamides **8** (**Scheme 1**). Some other derivatives were obtained by reaction of amine 7 with acyl halides, leading to the corresponding carboxamides. The claimed compounds have been extensively characterized by means of physicochemical methods which confirmed their structure. The preparation of the heterocyclic amine 6 and some of its congeners is also presented in the patent, being achieved by routine chemistry described in the literature.

3. Biological activity

The antiviral activity of the synthesized compounds has been evaluated by the so-called 'HOS assay' with little or no details at all regarding what HOS represents. This assay afforded information on the range of activity of the new compounds, with IC_{50} values between 1 and < 0.01 μM. Thus, apparently many of the new compounds claimed in this patent show significant antiviral activity in the low nanomolar range. However, these data seem to be very raw and preliminary, as very little information is provided in the patent.

4. Expert opinion

The patent describes a series of interesting compounds incorporating a scaffold not investigated earlier for its antiviral properties. Indeed, these derivatives contain at least three main structural features which makes them original, that is, an azabicyclo[3.2.1]octane fragment connected to a phenyl-propyl scaffold via the bridging nitrogen atom; the same phenyl belonging to the scaffold mentioned above is also part of a phenethylamine moiety; and the amine belonging to the phenethylamine fragment is derivatized, most of the time via sulfonamide or carboxamide functionalities. A large number of such derivatives has been claimed, in which a number of these three structural elements are changed by the usual medicinal chemistry procedures (most of the time, the groups substituting the phenyl moiety and the sulfonamide part of the molecule are variable, whereas the heterocyclic moiety present on the azabicyclo [3.2.1]octane fragment has also been changed but less compared to the remaining structural elements).

The compounds claimed in the patent have been evaluated as antivirals by using just one *in vitro* assay, the so-called 'HOS assay', but few details regarding this assay are provided. This assay afforded information on the range of activity of the new compounds claimed in this patent, which showed IC_{50} values in the range of 1 – < 0.01 μM. Thus, apparently many of the new compounds claimed in the patent show significant antiviral activity in the low nanomolar range. However, these data seem to be very raw and preliminary, as very little information is provided in the patent and no *in vivo* data are available so far.

We appreciate that the structural elements present in these molecules are innovative and the chemical part presented in this patent is appropriately developed and original. However, the biological details regarding the antiviral activity of these compounds is rather scarce and it is thus difficult to assess the significance of these compounds for developing novel CCR5 antagonists with applications as anti-HIV therapeutical agents.

Declaration of interest

The author states no conflict of interest and has received no payment in preparation of this manuscript.

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