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Fluorinated matrix metalloproteinases inhibitors—Phosphonate based potential probes for positron emission tomography

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ABSTRACT

Fluorine-containing inhibitors of matrix metalloproteinases (MMPs) can serve as lead structures for the development of ^{18}F-labeled radioligands. These compounds might be useful as non-invasive imaging probes to characterize pathologies associated with increased MMP activity. Results with a series of fluorinated analogs of a known biphenyl sulfonamide inhibitor have shown that fluorine can be incorporated into two different positions of the molecular scaffold without significant loss of potency in the nanomolar range. Additionally, the potential of a hitherto unknown fluorinated tertiary sulfonamide as MMP inhibitor has been demonstrated.

1. Introduction

Matrix metalloproteinases (MMPs) belong to a group of zinc dependent endopeptidases located in the extracellular matrix. These enzymes are important in endogenous processes that involve tissue remodeling. Apart from physiologically important transformations for instance embryonic development, they play essential roles in pathologies such as diabetic wound healing, cardiovascular diseases and tumor growth and progression.[1–7] MMPs are well-known targets in molecular imaging and allow the imaging of cardiovascular diseases or cancer.[8–10] Apart from optical imaging with, for example, dye labeled compounds,[11–13] the major imaging technique used is positron emission tomography (PET), which requires β^+-emitting radio-labels such as [^{11}C]carbon or [^{18}F]fluorine isotopes.[14–17] Previously our group contributed to the field using different strategies for the attachment of labeled moieties to hydroxamate based matrix metalloproteinase inhibitors (MMPI).[18–22] Moreover, we investigated the influence of fluorinated side-chains in analogs **3** and **4** replacing the isopropyl core structure of CGS-27023A (**1**) and CGS-25966 (**2**) (see Fig. 1).[23] In the present work, the hydroxamic acid function, a strongly chelating zinc-binding group (ZBG), was replaced by a phosphonate that forms weaker bonds to zinc ions. This approach seems reasonable, since negative MMPI side-effects of the hydroxamate group such as off-target inhibition and low subtype selectivity are ascribed to its strong metal-binding properties.[24–26] Moreover, hydroxamate-based MMPIs generally show a poor pharmacokinetic profile.[27]

Furthermore, inhibitors based on the phosphonate binding group exhibited excellent MMP activities as demonstrated by researchers from academia[29,30] and industry.[31–33]

2. Results and discussion

2.1. Phosphonate analogs of CGS-25021A and CGS-23966

Our first attempts were aimed at the synthesis of phosphonate analogs of CGS-27023A (**1**) and CGS-25966 (**2**) and we planned a synthesis of racemates, which founded on an synthetic strategy for α-aminophosphonic acids developed by Tyka.[34] The imines **5** or **6** prepared by condensation of benzylamine or 3-picolylamine with the corresponding aldehydes,[35] were phosphonylated using trimethylsilyloxy diethyl phosphite, a versatile phosphonylating reagent described by Afarinkia et al.[36] The obtained *N*-benzyl-α-aminophosphonates **7** and the *N*-3-picolyl-α-aminophosphonate **8** were then treated with 4-methoxyphenylsulfonyl chloride **9** in pyridine to obtain the corresponding sulfonamides **10**. Unfortunately, only the *N*-benzyl derivatives reacted under the applied

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conditions, while for compound **8** no transformation of the starting material was achieved (see Scheme 1).

To obtain the desired sulfonamides **11**, the *N*-benzyl substituted derivatives **7** were debenzylated hydrogenolytically to form the α-aminophosphonates **12** in very good yields. The α-aminophosphonates were first converted into the secondary sulfonamides **13** using 4-DMAP, DIPEA and 4-methoxyphenylsulfonyl chloride and then *N*-alkylated with 3-picolyl chloride, using K_2CO_3 as a base (see Scheme 2).

The prepared esters **10** and **11** were hydrolyzed according to a protocol developed by Houghton et al.[37] and the resulting crude products were purified by semi-preparative HPLC (see Scheme 3).

The obtained acids **14a–d** were tested in an in vitro assay using the fluorogenic substrate (7-methoxycoumarin-4-yl)acetyl-Pro-Leu-Gly-Leu-[3-(2,4-dinitrophenyl)-L-2,3-diamino-propionyl]-Ala-Arg-NH_2 which was originally described by Knight and coworkers.[38] The half-maximal inhibitory concentration (IC_{50}) was determined for the gelatinases MMP-2 and MMP-9, as well as for MMP-8 and MMP-13. However, compounds **14a–d** showed no inhibitory activity in these tests up to inhibitor concentrations of 100 μM. This result was not expected by us since biphenyl containing sulfonamides carrying a phosphonate as a ZBG are known to show excellent potencies.[29,30] It can be assumed that, due to the structural similarity between the biphenyl compound **15** (Fig. 2), CGS-27023A (**1**) and its phosphonate analogs **14** described herein, all inhibitor types interact with the same enzyme pockets. However, we have shown previously, that the carboxylic acid analogs of the fluorinated CGS-27023A derivatives **3** and **4** also are at least 3 orders of magnitude less active than the corresponding hydroxamates.[23] All these experiments suggest that, for CGS-27023A derived compounds, the hydroxamate ZBG is essential and substitution of this group lead to a significant drop or complete loss of potency. A possible explanation for the activity of the structurally related compound **15** might be an enhanced

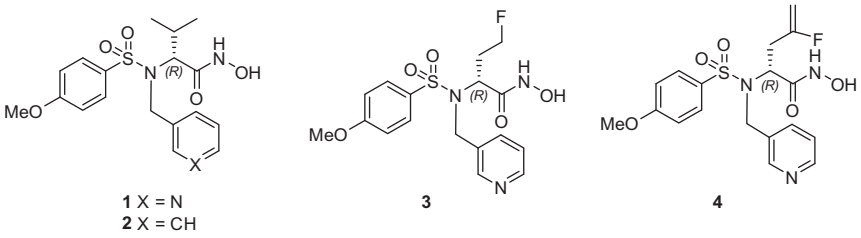
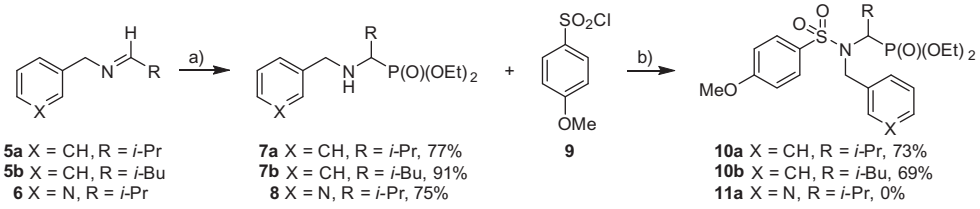
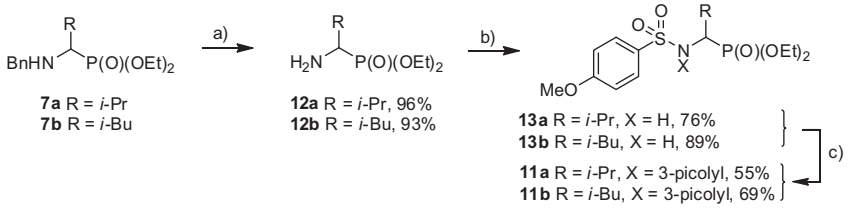


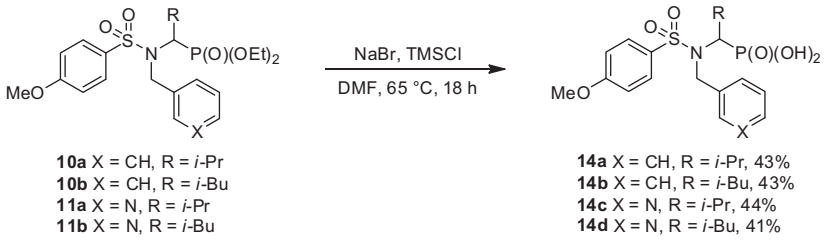
Figure 1. Lead structures CGS-27023A (**1**) and CGS-25966 (**2**) and fluorinated derivatives **3** and **4** thereof.[23,28]



Scheme 1. Synthesis of the diethyl esters of the CGS-25966 analogs **10a** and **10b**. (a) HPO_3Et_2, NEt_3, TMSCl, CH_2Cl_2, 0–40 °C, (b) pyridine.



Scheme 2. Synthesis of the CGS-27023A analogs **11a** and **11b**. (a) H_2 (3.5 atm), $Pd(OH)_2/C$, EtOH, rt, (b) 4-methoxyphenylsulfonyl chloride, 4-DMAP, DIPEA, DCM, rt, (c) K_2CO_3 3-picolylchloride hydrochloride, DMF, rt.



Scheme 3. Hydrolysis of the diethyl phosphonates following a procedure established by Houghton et al.[37]