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Very Important Paper

Development of the First Potential Nonpeptidic Positron Emission Tomography Tracer for the Imaging of CCR2 Receptors

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Herein we report the design and synthesis of a series of highly selective CCR2 antagonists as 18F-labeled PET tracers. The derivatives were evaluated extensively for their off-target profile at 48 different targets. The most potent and selective candidate was applied in vivo in a biodistribution study, demonstrating a promising profile for further preclinical development. This compound represents the first potential nonpeptidic PET tracer for the imaging of CCR2 receptors.

Introduction

The C–C chemokine receptor type 2 (CCR2) is a key player in the trafficking of lymphocytes and monocytes/macrophages leading to the development of various pathophysiological processes like inflammatory and autoimmune diseases,[1] tumor growth and metastasis formation,[2] CCR2 receptor is increasingly gaining attention in the field of positron emission tomography (PET) imaging as a promising diagnostic target for lung inflammation,[3] injured heart[4] or pancreatic ductal adenocarcinoma (phase 1: NCT03851237, 1R01CA235672-01, 201807099). So far only a peptidic ligand that binds to the first extracellular loop of the CCR2 receptor ECL1i was applied in PET imaging either as 64Cu-DOTA-ECL1i or 68Ga-DOTA-ECL1i conjugate.[3–4] There are no small-molecule, nonpeptidic PET tracers for the imaging of CCR2 receptors reported thus far.

The CCR2 receptors share 71% sequence identity and an overlapping expression pattern with the C–C chemokine type 5 (CCR5) receptors.[5] The CCR5 receptor is expressed on a variety of cells and tissues such as monocytes, macrophages, T-lymphocytes, microglia, dendritic cells, the endothelium, and vascular smooth muscle. The CCR2 expression is more restricted to certain cell types such as monocytes, NK (natural killer) cells, and T lymphocytes.[6] Many potent CCR2 ligands demonstrate affinity to both receptors.[7] In the past, we have reported the design and synthesis of novel, selective as well as dual-targeting CCR2 and CCR5 receptor antagonists,[8] as well as the positive allosteric modulators (PAMs) for the CCR5 receptors.[9]

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this work we envisaged to evaluate fluorine-18 radiolabeled CCR2 targeting ligands as PET radiotracers for molecular imaging of inflammation and cancer.

Our previous structure–activity and structure–affinity studies of novel CCR2 and CCR5 receptors targeting compounds derived from TAK-779 (1) revealed a first strategy for the introduction of high CCR2 receptor selectivity. While TAK-779 (1) is more or less equipotent at CCR2 and CCR5 receptors introduction of a bulky isopropoxy residue at the 6-position of a pyridine ring as seen in compound 2 (Figure 1) yielded different properties of binding to the active site residues within the CCR2 and CCR5 receptors, leading to higher CCR2 selectivity (Table 1). IC50 ([125I]CCL2) = 19 nM vs. IC50 ([1H]TAK-779) = 468 nM. Other pyridine derivatives were inactive.8a

Results and Discussion

Following the idea of addressing different electrostatic properties by the isoproxy derivative 2, a series of CCR2 selective antagonists 6a–c bearing a flexible ω-fluorooalkoxy side chain was developed. The phenol derivative 3 served as a starting structure for the introduction of the alkoxy side chain. As the influence of the chain length on the CCR2 and CCR5 receptor activity/affinity should be examined, propyloxy (4a, n = 3), pentyloxy (4b, n = 5) and heptyloxy (4a, n = 7) side chains were considered. The high acidity of the phenol 3 allows deprotonation with weak bases without affecting the primary alcohol of the ω-halogenalkanols used. The reactivity of the ω-halogenalkanols is dependent on the halogen leaving group (I > Br > Cl). However, the reaction with 3-iodomopropan-1-ol led to dialkylation of 3 (second alkyl group attached to the tertiary amine). Because we assumed that the dialkylation was due to the high reactivity of 3-iodopropan-1-ol, 3-bromopropan-1-ol with reduced reactivity was employed. Reaction of 3 with 3-bromopropan-1-ol and K2CO3 in DMF afforded selectively 4a in 84% yield. The homologous alcohols 4b and 4c were prepared analogously by alkylation of phenol 3 with 5-bromopentan-1-ol and 7-bromohexan-1-ol, respectively (Scheme 1). The compounds 5a–c served as precursors for the development of fluorinated PET ligands [18F]6a–c. The introduction of an 18F-atom into the molecule requires a good leaving group. Therefore, the primary alcohols 4a–c were converted into the tosylates 5a–c. The reaction of the alcohols 4a–c with tosyl chloride and 4-dimethylaminopyridine (DMAP, Steglich catalyst) provided the tosylates 5a–c.8c The in vitro receptor activities and affinities of the 18F-labeled PET tracers cannot be recorded.

Table 1.

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| Cmpd. | CCR2 IC50 ± SEM [nM] | CA+ flux, hCCR2 | β-Arein, mCCR2 | CCR5 [1H]TAK-779 IC50 ± SEM [nM] | β Arein, hCCR5, CCL5-mediated Kd [nM] | cAMP BRET, CCL5-mediated Kd [nM] | cAMP BRET, CCL4-mediated Kd [nM] |
|-------|----------------------|-----------------|--------------|---------------------------------|---------------------------------|------------------|------------------|
| 1     | 2.0 ± 0.2(3)         | 50 ± 5(4)       | 0.95(5)      | 23(6)                           | 8.8 ± 1.7(7)                    | 12 ± 1.2         | 65.5             | 7.5              |
| 2     | 19 ± 4.2(3)          | –               | 2.7(8)       | 90(9)                           | 468(10)                        | –                | –                | –                |
| 3     | 35%[11]              | –               | 82            | 1360                            | 1500                           | –                | –                | –                |
| 4a    | 199                  | 51%[11]         | 45            | 783                             | 970                            | –                | –                | –                |
| 4b    | 326                  | 53%[11]         | 10            | 117                             | 3100                           | –                | –                | –                |
| 4c    | 83                   | 56%[11]         | 1.1           | 54                              | 2300                           | –                | –                | –                |
| 6a    | 48%[11]              | 118 ± 20        | 130           | 1110                            | 2700                           | 684 ± 219        | 2300             | 551              |
| 6b    | 14 ± 7               | 609 ± 188       | 0.76          | 40                              | 2000                           | 529 ± 142        | 580              | 65.4             |
| 6c    | 93 ± 8               | 494 ± 38        | 1.1           | 17                              | 3600                           | 378 ± 114        | 288              | 27.1             |
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All experiments were performed in at least triplicate (n = 3). [a] See ref. [8a]. [b] % inhibition at a test compound concentration of 1 μM.
directly with the radiolabeled ligands due to the small amount and the short physical half-life of the labeled compounds. Therefore, the in vitro activities and affinities to the CCR2 and other receptors/targets were determined using the non-radioactive $^{18}$F-labeled analogues. The synthesis of the non-radioactive $^{18}$F counterparts 6a–c can be performed by direct fluorination of the alcohols 4a–c or by the introduction of an appropriate leaving group and subsequent $S_2$ substitution. Tetrabutylammonium fluoride (TBAF) is a common fluorinating reagent. The bulky tetralkylammonium counterion reduces the ionic bond strength and generates a “naked” fluoride ion with a good solubility in organic solvents. As the tosylates 5a–c were already prepared for the radiolabeling reaction, they were also employed for the fluorination with TBAF. Tosylates 5a–c were reacted with TBAF in THF, which afforded the pure fluoro derivatives 6a–c in 73–84% yield (Scheme 1).

The compounds were evaluated for their in vitro CCR2 activities and affinities as well as their selectivity towards CCR5 receptors in functional as well as in binding assays. The hydroxylalkoxy derivatives 4a–c display very low CCR2 and CCR5 receptor affinities and moderate to high CCR2 receptor activities (Table 1). The CCR5 receptor affinity and high selectivity over CCR5 were observed. The heptyloxy derivative with a primary alcohol at the end (4c) shows the highest CCR2 affinity/activity ($IC_{50}$([125]I)CCL2) = 83 nM, $IC_{50}$ (Ca$^{2+}$-flux, hCCR2) = 1.1 nM, $IC_{50}$ ($\beta$-arrestin, mCCR2) = 54 nM).

However, the fluoroalkoxy derivatives 6a–c do not follow the same trend in their SAR. The pentyloxy compound 6b displays the highest CCR2 binding in the $[11]^{18}$F-5a,5b-[125]I-CCL2 assay with an $IC_{50}$-value of 14 nM and the highest CCR2 activity in the Ca$^{2+}$-flux assay using the human CCR2 receptor, indicating an $IC_{50}$-value of 0.76 nM. Furthermore, 6b is highly selective against CCR5 receptors ($IC_{50}$ (CCR5; $[125]^{18}$F-TAK-779) = 2000 nM). The fluoroalkoxy derivatives 6a–c show a probe-dependent CCR5 activity when compared to TAK-779; whereas TAK-779 (1) binding affects CCL5- as well as CCL4-dependent CCR5 receptor activity. The fluoroalkoxy derivatives 6b and 6c display only high activity in the cAMP-BRET CCL4-mediated assay with $K_d$ values of 65.4 and 27.1 nM, respectively. Only moderate activity is seen in $\beta$-arrestin and cAMP BRET CCL5-mediated CCR5 assays, indicating a different binding mode at the CCR5 receptors as compared with that of TAK-779 (1).

Moreover, the fluoroalkoxy derivatives 6a–c were screened in the in-house assays, and in a panel of 45 different targets (hERG, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_{3}, 5-HT_{5}, 5-HT_{7}, D_{1}, SERT, NET, DAT, MOR, KOR, DOR, GABA_A, H_1, 5-HT_2A, 5-HT_2C, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, D_1, SERT, NET, DAT, MOR, KOR, DOR, GABA_A, H_1, 5-HT_2A, 5-HT_2C, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, D_1, SERT, NET, DAT, MOR, KOR, DOR, GABA_A, H_1, 5-HT_2A, 5-HT_2C, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, D_1, SERT, NET, DAT, MOR, KOR, DOR, GABA_A, H_1, 5-HT_2A, 5-HT_2C, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, D_1, SERT, NET, DAT, MOR, KOR, DOR, GABA_A, H_1, 5-HT_2A, 5-HT_2C, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, D_1, SERT, NET, DAT, MOR, KOR, DOR, GABA_A, H_1, 5-HT_2A, 5-HT_2C, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, D_1, SERT, NET, DAT, MOR, KOR, DOR, GABA_A, H_1, 5-HT_2A, 5-HT_2C, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, D_1, SERT, NET, DAT, MOR, KOR, DOR, GABA_A, H_1, 5-HT_2A, 5-HT_2C, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, D_1, SERT, NET, DAT, MOR, KOR, DOR, GABA_A, H_1, 5-HT_2A, 5-HT_2C, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, D_1, SERT, NET, DAT, MOR, KOR, DOR, GABA_A, H_1, 5-HT_2A, 5-HT_2C, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, D_1, SERT, NET, DAT, MOR, KOR, DOR, GABA_A, H_1, 5-HT_2A, 5-HT_2C, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, D_1, SERT, NET, DAT, MOR, KOR, DOR, GABA_A, H_1, 5-HT_2A, 5-HT_2C, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, D_1, SERT, NET, DAT, MOR, KOR, DOR, GABA_A, H_1, 5-HT_2A, 5-HT_2C, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, D_1, SERT, NET, DAT, MOR, KOR, DOR, GABA_A, H_1, 5-HT_2A, 5-HT_2C, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, D_1, SERT, NET, DAT, MOR, KOR, DOR, GABA_A, H_1, 5-HT_2A, 5-HT_2C, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, D_1, SERT, NET, DAT, MOR, KOR, DOR, GABA_A, H_1, 5-HT_2A, 5-HT_2C, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, D_1, SERT, NET, DAT, MOR, KOR, DOR, GABA_A, H_1, 5-HT_2A, 5-HT_2C, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, D_1, SERT, NET, DAT, MOR, KOR, DOR, GABA_A

Table 3. Results of the radiosynthesis of compounds $^{[18]}$F6a–c.

| Compd. | Synthesis time (min) | $A_{50}$ (GBq/μmol) | RCV [%] (decay-corrected) |
|--------|----------------------|---------------------|---------------------------|
| $^{[18]}$F6a | 94 ± 13 | 4–70 | 40 ± 3% |
| $^{[18]}$F6b | 113 ± 27 | 3–31 | 28 ± 3% |
| $^{[18]}$F6c | 91 ± 10 | 5–54 | 25 ± 6% |

[a] $n = 5$, [b] $n = 9$, [c] $n = 6$.

Table 2. Off-target affinities/activities of fluorinated ligands 6a–c.

| Compd. | $\alpha_1$ $K_M$ (μM) | $\alpha_2$, $K_M$ (μM) | $\alpha_4$, $K_M$ (μM) | $\alpha_5$, $K_M$ (μM) | $M_1$, $K_M$ (μM) | $5$-HT_{2A}, $K_M$ (μM) | $5$-HT_{3}, $K_M$ (μM) | hERG EC_{50} (μM) |
|--------|----------------------|----------------------|----------------------|----------------------|------------------|----------------------|----------------------|-----------------|
| 6a | 1.0 | 0.04 | – | 1.2 | – | 1.0 | 5.01 | 2.29 ± 0.31 |
| 6b | 0.32 | 79.9 | – | 6.81 | – | – | – | 1.72 ± 0.09 |
| 6c | 14.6% | 17% | 6.27 | 5.22 | – | – | 0.671 ± 0.220 |

Assays: $K_M$ values ± SEM from three independent experiments. [a] % inhibition at a test compound’s concentration of 10 μM. Radioligands used for receptor binding studies were as follows: $\alpha_1$: [1H]-(+)-pentazocine, $\alpha_2$: [3H]dipropylguanidine, $\alpha_4$ and $\alpha_5$: [3H]rauwolscine, M3: [3H]QNB, 5-HT_{2A}: [3H]mesulergine, 5-HT_{3A}: [3H]LSD, functional assays: FluxOR assay hERG: ciscapride.

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shielded computer-controlled TRACERLab FxFDC radiosynthesizer. In trial experiments, reaction of 5b with $^{18}$F fluoride in DMSO gave a higher radiochemical yield (RCY) of $^{18}$F 6b (30%) than in acetonitrile (5.5%). Compounds $^{18}$F 6a–c were purified by semipreparative reversed-phase radio-HPLC in high radiochemical purities (>99%). No residual precursors 5a–c or other chemical impurities were detected in the formulated radioligand solution by analytical radio-HPLC. The molar activity ($A_m$) of the radioligands, when finally formulated for intravenous injection, the RCY and the synthesis times are given in Table 3. Furthermore, the partition coefficient $\log D$ was experimentally determined for the radiolabeled compounds $^{18}$F 6a–c at pH of 7.4. Compound $^{18}$F 6b is the most lipophilic derivative of the series with a $\log D$ (exp.) of 1.94 ± 0.26 (n = 5), calculated $\log D$, of 7.00, was calculated by ACD/Chemsketch version ACD/Labs 6.00. For $^{18}$F 6a a $\log D$ (exp.) of 1.63 ± 0.17 (n = 5), $\log D$ = 6.17 and for $^{18}$F 6c a $\log D$ (exp.) of 1.69 ± 0.16 (n = 5), $\log D$ = 8.06 was determined. An in vitro stability study was carried out for all three radiolabeled compounds $^{18}$F 6a–c using mouse and human blood serum. During incubation for up to 90 min at 37°C $^{18}$F 6a, $^{18}$F 6b and $^{18}$F 6c possessed a high stability in both sera. Figure 2 shows exemplarily the data of $^{18}$F 6b in mouse blood serum. Only the parent compound $^{18}$F 6b was detected by radio-HPLC and no significant radiometabolites or decomposition products could be observed. The behavior of $^{18}$F 6a and $^{18}$F 6c is the same (data not shown). Due to its high potency and binding affinity to the CCR2
receptor and its favorable off-target selectivity profile, the fluoropentyloxy derivative \[^{18}\text{F}]6b\) was selected for the biodistribution studies.

**Biodistribution of \[^{18}\text{F}]6b\) in healthy adult C57Bl/6 mice**

The radioactivity distribution of \[^{18}\text{F}]6b\) was measured in adult C57Bl/6 mice *in vivo* over 90 minutes by PET/CT. PET images reveal fast and significant accumulation of radioactivity in the liver already in the first minutes after tracer injection that persists until the end of the study (Figure 4). A few minutes post-injection intermediate radioactivity levels were found in the lung, the spleen and the kidneys. Over the course of 90 minutes, the radioactivity concentration in the lungs decreased while the signal in the spleen and the kidneys remained at the same level. Image data do not show the elimination of the tracer and/or its metabolites in the urine. We observed a very slow and only marginally increase of radioactivity in the bones as a sensitive indicator of *in vivo* defluorination of the \[^{18}\text{F}]\) labeled tracer, which demonstrated the expected stability of the fluoropentyl group against *in vivo* defluorination. Quantitative analysis by *in vivo* time–activity concentration curves and *ex vivo* gamma counting confirmed the visual impressions (Figure 3). The highly CCR2 selective radioligand \[^{18}\text{F}]6b\) demonstrated favorable properties as a new diagnostic tool for PET to elucidate the changes in the distribution and density of CCR2 receptors, revealing their role in the development and pathobiology of inflammation or cancer.

**Conclusion**

Previously uncovered structure–activity/affinity relationships at CCR2 and CCR5 led the way to the development of highly potent and selective CCR2 receptor antagonists 4a–c and 6a–c, which were further converted into potential \[^{18}\text{F}]\)-labeled PET tracer \[^{18}\text{F}]6a–c\). Compounds 6a–c were excessively evaluated for their CCR2 activity/affinity and their off-target selectivity profile at CCR5 receptors and 47 other biological targets (GPCR, ion channels, transporters). The radiolabeled derivatives \[^{18}\text{F}]6a–c\) were prepared in high purity (> 99%) and high RCY (40–25%). Their logD, murine and human serum plasma stability was determined. The most potent and selective candidate \[^{18}\text{F}]6b\) was evaluated *in vivo* in a biodistribution study. Thus displaying a promising profile for further preclinical development.

**Experimental Section**

Complete protocols for both chemical syntheses and biological methods together with characterization data are presented in the Supporting Information.

**Author Contributions**

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript. A.J. planned and synthesized all compounds. F.M.G. synthesized the precursor 5b in large scale. S.W., A.J. and D.G.S. performed the radiolabeling. Biological assays were performed by D.S., L.H., N.V.O.Z., A.Z., M.M., N.T., M.K. and C.W. The imaging experiments were performed by S.H.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: CCR2 · CCR5 antagonists · chemokine receptors · molecular imaging · PET · radiolabeling · TAK-779

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