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Research paper

Translocator protein ligands based on *N*-methyl-(quinolin-4-yl) oxypropanamides with properties suitable for PET radioligand development

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ABSTRACT

Modifications to an *N*-methyl-(quinolin-4-yl)oxypropanamide scaffold were explored to discover leads for developing new radioligands for PET imaging of brain TSPO (translocator protein), a biomarker of neuroinflammation. Whereas contraction of the quinolinyl portion of the scaffold or cyclization of the tertiary amido group abolished high TSPO affinity, insertion of an extra nitrogen atom into the 2-arylquinolinyl portion was effective in retaining sub-nanomolar affinity for rat TSPO, while also decreasing lipophilicity to within the moderate range deemed preferable for a PET radioligand. Replacement of a phenyl group on the amido nitrogen with an isopropyl group was similarly effective. Among others, compound **20** (*N*-methyl-*N*-phenyl-2-[2-(pyridin-2-yl)-1,8-naphthyridin-4-yloxy]propanamide) appears especially appealing for PET radioligand development, based on high selectivity and high affinity (K_i = 0.5 nM) for rat TSPO, moderate lipophilicity (log*D* = 2.48), and demonstrated amenability to labeling with carbon-11.

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1. Introduction

Translocator protein 18 kDa (TSPO), formerly known as the peripheral benzodiazepine receptor [1], is located predominantly at the outer mitochondrial membrane in association with a voltage-dependent anion channel and an adenine nucleotide transporter [2]. TSPO is present in several major organs, and is particularly dense in adrenal gland, heart, kidney, and testis [2]. Low amounts are present in normal human brain, primarily in microglia [3]. Activated microglia upregulate TSPO in instances of neuronal damage [4] as seen in many neurological disorders [5–7] including Alzheimer's disease, movement disorders, stroke, multiple sclerosis, and major depression [8]. Therefore, TSPO can serve as an important biomarker for neuroinflammation. Moreover, ligands for TSPO have also been explored as possible drugs, particularly for anxiety [9].

For more than three decades, PET imaging of human TSPO has been carried out with [^{11}C]PK11195 ([^{11}C]**1**) [10] or its (*R*)-enantiomer ([^{11}C](*R*)-**1**) [11] (Chart 1) for biomedical investigations of neuroinflammation. [^{11}C](*R*)-**1** has been by far the most employed radioligand for this purpose despite limited brain uptake [12], low specific binding [12], and an undesirable metabolic profile [13]. Efforts to tackle these shortcomings of [^{11}C](*R*)-**1** have resulted in several new structural classes of TSPO radioligand with superior imaging characteristics (Chart 1). Examples include [^{11}C]PBR28 ([^{11}C]**2**) [14,15], [^{11}C]DAA1106 ([^{11}C]**3**) [16], [^{11}C]DPA-713 ([^{11}C]**4**) [17], [^{18}F]DPA-714 ([^{18}F]**5**) [18], [^{18}F]FBR ([^{18}F]**6**) [19], [^{18}F]PBR111 ([^{18}F]**7**) [20], [^{18}F]FEPPA ([^{18}F]**8**) [21], [^{18}F]FEMPA ([^{18}F]**9**) [22], and [^{11}C]ER176 ([^{11}C]**10**) [23]. Nonetheless, many of these new radioligands also suffer particular deficiencies, most prevalent of which is sensitivity to the rs6971 polymorphism in human subjects [20,21,24,25].

Successful PET radioligands for imaging specific proteins in brain are required to display a wide array of properties [26]. Among

Abbreviations: DIPEA, diisopropylethylamine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; HFIP, hexafluoroisopropyl alcohol; HRMS-ESI, high resolution mass spectrometry electrospray ionization; LDA, lithium diisopropylamide; MTBE, methyl *tert*-butyl ether; PFP, pentafluorophenyl; PyBroP, bromotripyrrolidinophosphonium hexafluorophosphate; TEA, triethylamine; TSPO, translocator protein (18 kDa); LipE, lipophilic efficiency.

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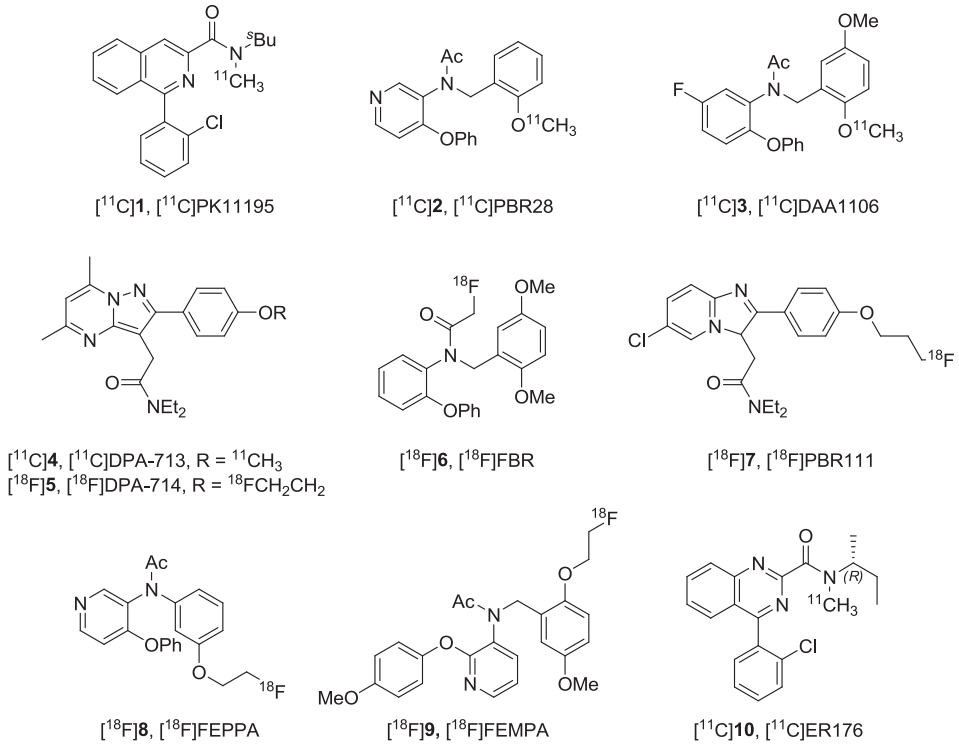

Chart 1. Structures of some notable TSPO PET radioligands.

these properties are: i) high affinity and selectivity for the target protein; ii) low molecular weight; iii) intermediate polar surface area for blood-brain barrier penetration; iv) moderate lipophilicity for adequate brain entry in the absence of excessive non-specific binding; and v) amenability to labeling with a positron-emitter, either carbon-11 ($t_{1/2}$ = 20.4 min) or fluorine-18 ($t_{1/2}$ = 110 min). This study aimed to develop TSPO ligands as leads with a desirable combination of properties for PET radioligand development. We have previously explored a series of *N*-methyl-(quinolin-4-yl)oxypropanamides as prospective TSPO ligands [27], and encouragingly many of these ligands have shown low TSPO genotype sensitivity in vitro. Here, we further explore structure-affinity relationships in this structural class. High-affinity TSPO ligands emerged from this effort and a few of these are promising new leads to PET radioligands.

2. Results and discussion

In this study, we identified new leads to PET radioligands for imaging TSPO based on modifications to the previously reported [27] *N*-methyl-(quinolin-4-yl)oxypropanamide TSPO ligand scaffold (Chart 2). These modifications were aimed at exploring, i) variation of substituents on the amide nitrogen, ii) introduction of nitrogen into the quinolin-4-yl group or pendant aryl ring, iii) replacement of the pendant aryl ring with methoxy, 2-pyrimidinyl or *N*-pyrrolidinyl, iv) the effect of cyclization to eliminate amide bond rotation, and v) contraction of the bicyclic quinolinyl nucleus. Generally, PET radioligands are required to have high affinity with K_D in the low nM range, and moderate lipophilicity with measured (or computed) logD in the 2–4 range [26]. Most of the changes that we made to the lead ligand scaffold were intended to retain the very high TSPO affinity (K_i = 0.07 nM for rat TSPO) seen in the previously reported example **11** (Chart 2; scaffold with Y = 2-pyridinyl, and R = Ph), as well as to decrease ligand computed lipophilicity (clog*D*) from 4.73 towards the desirable range. Usually, the overall shape of the scaffold was modified little to retain high affinity, although the effects of scaffold pruning were also investigated. The main strategy for lowering lipophilicity was to introduce nitrogen into one or more of the aryl rings. The lipophilicity cost for high ligand affinity may be indexed as a lipophilicity efficiency parameter (LipE), defined as ligand pIC_{50} (or pK_i) minus clog*D* [28]. Therefore, our overall aim encompasses the discovery of ligands with high LipE scores (>6). The amide *N*-methyl substituent was retained in all new ligands as a site that should be amenable to labeling with carbon-11 through ^{11}C-methylation of *N*-desmethyl precursors.

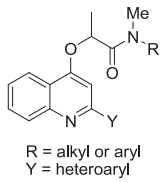

Chart 2. The *N*-methyl-(quinolin-4-yl)oxypropanamide scaffold used as a basis for new TSPO ligand development.

2.1. Chemistry

As prospective TSPO ligands, the 2-heteroaryl-4-alkoxyquinolines **18**–**23** (Scheme 1) were synthesized in three steps, proceeding with acylations of the requisite 2-amino-arylethanones [29]. The resultant amides **12** and **13** were subjected to Camps cyclization [30] to yield the 2-heteroarylquinolin-4-ones **14** and **15**, respectively, which were then chemoselectively *O*-alkylated to the desired ligands **18**–**23** (Scheme 1). The required α-bromoamides **16** and **17** were made under Schotten–Baumann conditions.

The 2,4-dialkoxy-1,8-naphthyridine ligand **27** was made by first