Bioorganic & Medicinal Chemistry Letters 24 (2014) 4784–4790

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

5-(4-((4-[^{18}F]fluorobenzyl)oxy)-3-methoxybenzyl)pyrimidine-2,4-diamine: A selective dual inhibitor for potential PET imaging of Trk/CSF-1R

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ARTICLE INFO

Article history:
Received 22 July 2014
Revised 2 September 2014
Accepted 3 September 2014
Available online 16 September 2014

Keywords:
Tropomyosin receptor kinases
Colony-stimulating factor 1 receptor
Tyrosine kinase inhibitor
GW2580
Diaminopyrimidine
Radiochemistry
Fluorine-18

ABSTRACT

The tropomyosin receptor kinases (TrkA/B/C) and colony-stimulating factor-1 receptor (CSF-1R) represent highly pursued oncological therapeutic targets. The 2,4-diaminopyrimidine inhibitor GW2580 (**9**) has been previously reported as a highly selective low nanomolar TrkB/TrkC/CSF-1R inhibitor. In this study, fluorinated derivatives of **9** were designed, synthesized and evaluated in enzymatic assays. The highly potent inhibitor **10** was identified, which retained the selectivity profile of the non fluorinated lead compound **9**, and the radiosynthesis of [^{18}F]**10** was developed. The results obtained from the biological evaluation of **10** and the radiosynthesis of [^{18}F]**10** support further investigation of this tracer as a potential PET imaging probe for TrkB/TrkC and CSF-1R.

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In recent years, the growing understanding of the underlying role of protein tyrosine kinases in the abnormal signal transduction in cancer has sustained the development of numerous targeted small molecule tyrosine kinase inhibitors (TKIs) for cancer treatment.[1–3] TKIs stand as one of the fastest growing anticancer drug classes with 16 FDA-approved inhibitors within the last twelve years and hundreds more currently in development.[4] Despite those clinical successes, the low response rates of those TKIs reaching the market forces the development of efficient tools to facilitate drug development and ultimately identify patients which are most likely to respond to treatment.[5] The current use of invasive approaches such as tumor biopsy only provide partial information on specific target expression/mutation status. In this context, the advent of radiolabeled TKIs for positron emission tomography (PET) may potentially offer fundamental insights useful for drug development and individualized medicine as far as target expression, binding kinetics, potential toxicity and treatment efficacy is concerned.[5–9]

Trk receptors critically support the development and maintenance of the nervous system[10–12] but their over-expression in various neural and non-neural neoplasms such as breast,[13] pancreatic,[14] lung[15] and neuroendocrine tumors[16] also confers aggressive phenotypes to tumor cells and correlates with poor prognosis.[17] In the last decade, many studies have focused on the development of Trk ligands, especially ATP-competitive inhibitors for the treatment of cancer (Fig. 1).[18–20] Currently, the inhibition of Trk receptors is investigated in six clinical trials and numerous pre-clinical studies.[21]

Comprehensive kinase inhibitor analysis recently demonstrated that the orally bioactive diaminopyrimidine colony-stimulating factor-1 receptor (CSF-1R) inhibitor GW2580 (**9**)[22] strongly inhibits Trk receptors—especially TrkB (K_d; CSF-1R = 2.2 nM, TrkA = 630 nM, TrkB = 36 nM, TrkC = 120 nM).[23] Notably, GW2580 exhibits one of the most specific kinase inhibition profiles among known kinase inhibitors (no supplementary inhibition of other kinases with K_d <3 μM) which, when considering PET imaging, represents an advantageous target selectivity.[24] Therefore, we hypothesized that the high selectivity of **9** could constitute a promising basis for the development of PET-TKI probes with potential imaging applications for CSF-1R, since CSF-1R also represents a useful PET imaging target. CSF-1R regulates mononuclear phagocyte differentiation and proliferation and as such plays a central role in multiple macrophage-mediated pathological conditions.[25] In particular, infiltration of tumor-associated macrophages (TAMs) within tumor microenvironments relying upon CSF-1R for survival

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http://dx.doi.org/10.1016/j.bmcl.2014.09.014
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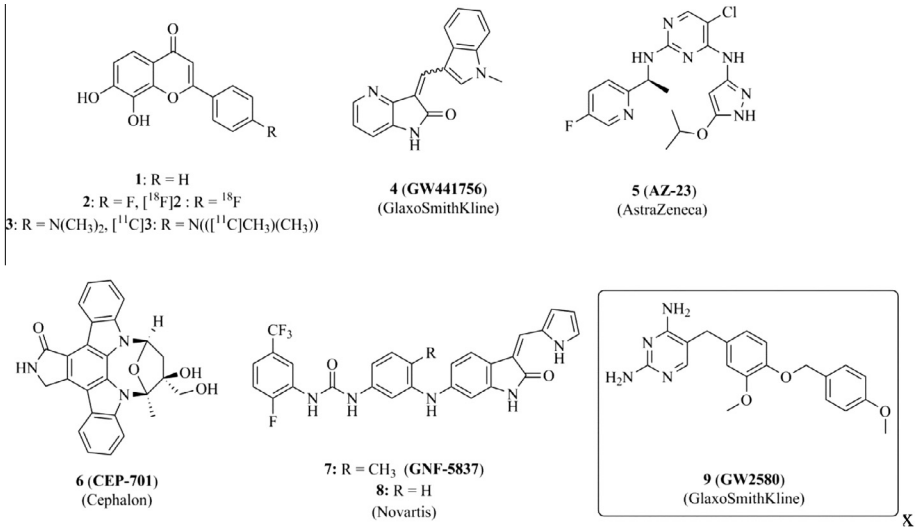

Figure 1. Chemical structures of selected Trk receptor ligands and radioligands.

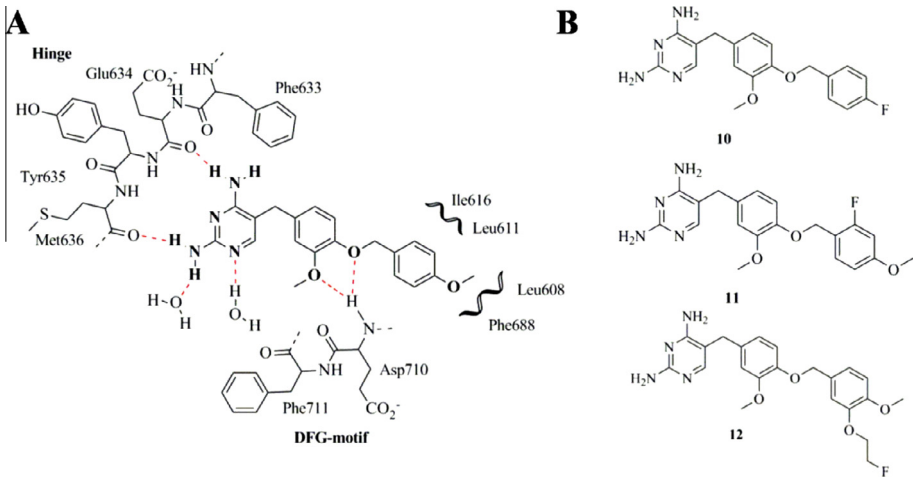

Figure 2. (A) Binding interactions of GW2580 (**9**) to TrkB based on the co-crystal structure of **9**-TrkB (PDB code: 4AT5). Hydrogen bonds between the ligand and the hinge region, DFG motif and adjacent water molecules are indicated with red dash lines. (B) Derivatization of the *para*-methoxybenzyl ring for the introduction of fluorine substituents accessible with common radiofluorination methods.

and differentiation, is associated with poor prognosis in numerous cancers.[26] Thus, translation of **9** into a dual Trk/CSF-1R PET probe could be highly useful in many cases where cancer cells overexpress Trk receptors while abundant CSF-1R is found within the stromal cells due to high TAMs infiltration.[27]

The structure of GW2580 possesses two aromatic methoxy moieties potentially amenable for carbon-11 ($t_{1/2}$ = 20 min) labeling (Fig. 1). However, fluorine-18 displays better nuclear properties ($t_{1/2}$ = 109 min; 97% β^+; E_{max} (β+) = 0.64 MeV) which allow for a more flexible radiosynthesis and lead to high quality PET images. It is also documented that the introduction of fluorine into bioactive molecules may positively influence physicochemical properties and oxidative/hydrolytic metabolic stabilities.[28] This study thus describes the design, synthesis and biological evaluation of a small series of fluorinated analogs of GW2580. The derivatives where selected in order to be accessible as ^{18}F-isotopologues. A new potent fluorinated Trk(B/C)/CSF-1R inhibitor **10** was identified, which was consequently labeled with fluorine-18. In addition, exhaustive selectivity profiling over a panel of 342 kinases established that **10** maintains the remarkable selectivity of the non-fluorinated lead compound **9**.

Three fluorinated derivatives of inhibitor **9** where rationally designed based on the available co-crystal structure of TrkB with GW2580 (PDB code: 4AT5)[29] and developed with the objectives of maintaining the potency/selectivity profile of the lead while being amenable towards ^{18}F-labeling. Our rationale consisted of introducing structural modifications on the *para*-methoxybenzyl (PMB) ring occupying the selectivity hydrophobic pocket formed by residues Ile616, Leu611, Leu608 and Leu688. The diaminopyrimidine fragment in contact with the hinge region and the 1-(benzyloxy)-2-methoxybenzene central ring interacting withAsp710 from the DFG motif (Fig. 2) were left untouched. Inspection of the hydrophobic back pocket revealed that the *ortho*- and *para*-position of the tail fragment can probably only accommodate small structural modifications. The orientation from one side of the PMB ring left the *meta*-position solvent exposed thus suggesting that this position might be compatible with bulkier alterations. Therefore, fluoroaryl-derivatives **10** and **11** (*ortho* and *para*-activated position for labeling—vide supra) and the 2-fluoroethoxy-derivative **12** (Fig. 1B) were synthesized and evaluated.

First, we synthesized inhibitor **9** following the patent procedure reported by Shewchuk et al.[30] to provide its first complete

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