Bioorganic & Medicinal Chemistry Letters 27 (2017) 2439–2442

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Pharmacological evaluation of a novel series of urea, thiourea and guanidine derivatives as $P2X_7$ receptor antagonists

Erick C.N. Wong [a,1], Tristan A. Reekie [b,1], Eryn L. Werry [c], James O'Brien-Brown [b], Sarah L. Bowyer [b], Michael Kassiou [b,*]

[a] School of Medical Sciences, The University of Sydney, NSW 2006, Australia
[b] School of Chemistry, The University of Sydney, NSW 2006, Australia
[c] Faculty of Health Sciences, The University of Sydney, NSW 2006, Australia

ARTICLE INFO

Article history:
Received 3 March 2017
Revised 29 March 2017
Accepted 1 April 2017
Available online 4 April 2017

Keywords:
$P2X_7R$
Inflammation
Cyanoguanidine
Urea
Thiourea

ABSTRACT

We report on $P2X_7$ receptor antagonists based on a lead adamantly-cyanoguanidine-aryl moiety. We have investigated the importance of the central cyanoguanidine moiety by replacing it with urea, thiourea or guanidine moieties. We have also investigated the linker length between the central moiety and the aryl portion. All compounds were assessed for their inhibitory potency in a pore-formation dye uptake assay at the $P2X_7$ receptor. None of the compounds resulted in an improved potency illustrating the importance of the cyanoguanidine moiety in this chemotype.

© 2017 Elsevier Ltd. All rights reserved.

Adenosine 5′-triphosphate (ATP) is the endogenous ligand and physiological agonist of the $P2X_7$ purinoreceptor ($P2X_7R$), a member of the P2X superfamily of trimeric ligand-gated cation channels ($P2X_{1-7}$).[1–4] The $P2X_7R$ is predominantly and highly expressed on immune cells of hematopoietic origin such as peripheral monocytes and macrophages, as well as their centrally located counterparts, microglia.[2,5] Transient $P2X_7R$ activation by low concentrations of extracellular ATP permits the influx of calcium and sodium ions, and efflux of potassium ions within milliseconds.[1,4,6] However, psychological stress and insults to the CNS (including neurodegenerative and ischemic related) incite the enhanced release of ATP into the extracellular environment.[7–9] The prolonged activation of the $P2X_7R$ results in the immediate rearrangement of the cell membrane and cytoskeleton,[10,11] the formation of a large >900 Da macro-pore, and eventual apoptosis.[2,7] Prior to cell death, the proinflammatory cytokines IL-1β and IL-18 are also processed and secreted.[8,10,12–15] Significantly higher serum levels of IL-1β, among other proinflammatory cytokines, have been reported in patients suffering from Alzheimer's disease (AD)[16] and major depressive disorder (MDD),[17] suggesting the dysregulation of the inflammatory response may underpin these, and many other, neurodegenerative (including Parkinson's disease) and neuropsychiatric (including bipolar disorder) conditions, as well as neuropathic pain.[7,18–21] Mice lacking the $P2X_7R$ generated macrophages that were incapable of releasing mature IL-1β in response to extracellular ATP, or to its more stable and potent analogue, 2′(3′)-O-(4-benzoylbenzoyl)adenosine-5′-triphosphate tri(triethylammonium) salt (BzATP).[22,23] Additionally, in several animal models of depression, abolishing $P2X_7R$ expression offered an antidepressant effect.[23] When stimulated with the amyloid β protein (Aβ), a hallmark of AD pathology, lipopolysaccharide (LPS)-primed microglia from wild type mice released ATP and large amounts of IL-1β, whereas their $P2X_7R$-deficient counterparts did not.[24] Moreover the microglia derived from these $P2X_7R$-knockout mice were resistant to Aβ-induced plasma membrane permeabilisation, potentially through their inability to form the large $P2X_7R$ pore. Considering the significant influence the $P2X_7R$ has over the inflammatory response, and that microglial $P2X_7R$ expression is upregulated in conditions such as AD and multiple sclerosis (MS),[1,25] $P2X_7R$ antagonism appears as a potential treatment strategy.

Initial $P2X_7R$-focussed medicinal chemistry was directed at generating $P2X_7R$ antagonists for the treatment of peripheral inflammatory diseases including rheumatoid arthritis and Crohn's disease, with a number of compounds having progressed to clinical trials.[2,26] Adamantyl amide **1** was developed by AstraZeneca and

* Corresponding author.
E-mail address: michael.kassiou@sydney.edu.au (M. Kassiou).
[1] Joint first authors.

http://dx.doi.org/10.1016/j.bmcl.2017.04.005
0960-894X/© 2017 Elsevier Ltd. All rights reserved.

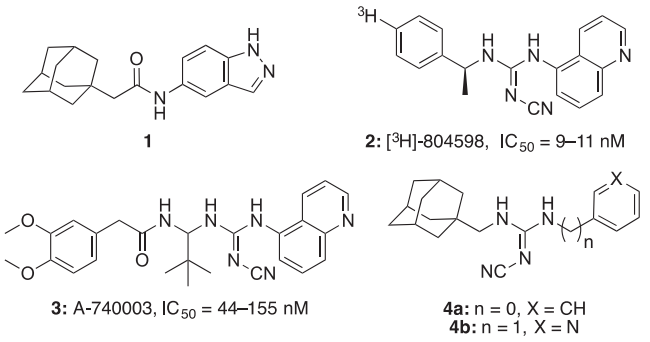


Fig. 1. $P2X_7R$ antagonists.

showed promising pharmacokinetic properties from *in vivo* studies in rats (Fig. 1). Abbott Laboratories developed compounds focused on the cyanoguanidine moiety. These compounds, with **2** and **3** being examples of the more potent in the series, showed nanomolar potency, but a poorer pharmacokinetic profile. We have recently reported an adamantyl-cyanoguanidine hybrid that combined pharmacologically beneficial features from the Abbott cyanoguanidine derivatives with the inclusion of an adamantane moiety for improved pharmacokinetics and enhanced blood-brain barrier (BBB) penetration.[27] The small cyanoguanidine hybrid **4a** was reported to have nanomolar potency at the $P2X_7R$ (IC_{50} = 100 - nM). Potency could be improved by lengthening the chain and incorporating a nitrogen atom into the aryl portion, particularly at the 3-position to give **4b** (IC_{50} = 69 nM). Further conclusions from this work showed that a methylene linker between the cyanoguanidine and adamantyl moieties was essential for potency, while either no linker (n = 0) or a methylene linker (n = 1) was acceptable for the aryl portion.

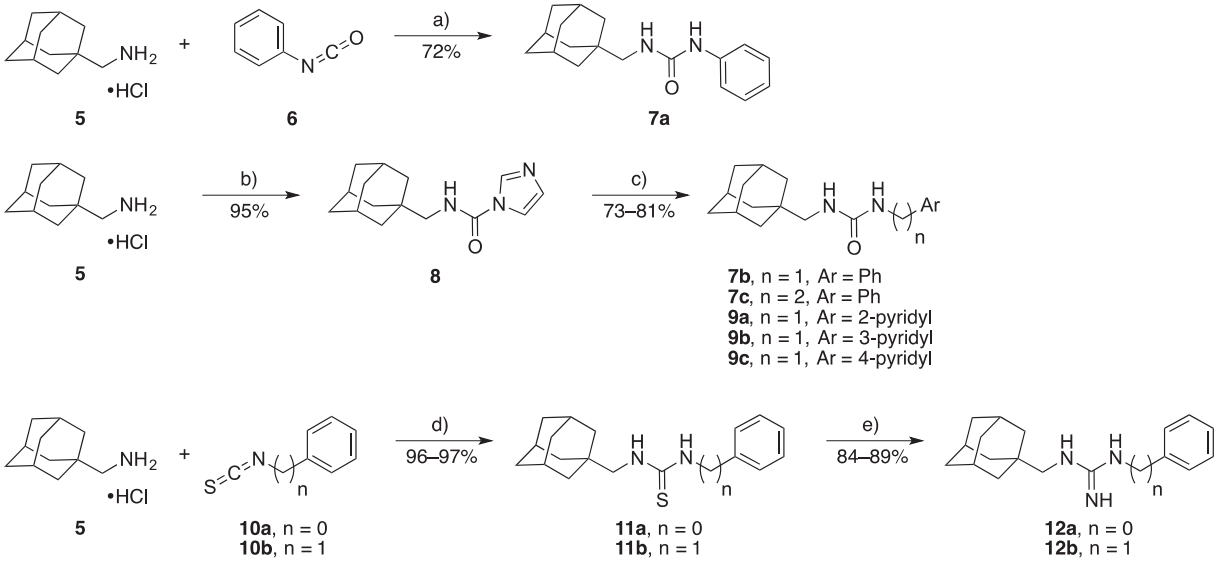
While there have been advancements in potency optimization and BBB permeability, many currently disclosed compounds lack desirable characteristics for targeting central $P2X_7R$, being unable to permeate the BBB or offer insufficient target engagement for potential therapeutic value.[1] Therefore to increase the potential for translational clinical utility, modifications were made to the cyanoguanidine moiety in an effort to optimize lipophilicity. However, it is unknown whether the cyanoguanidine moiety was essential for potency or if substitutions could be tolerated. In this article, we report urea, thiourea and guanidine derivatives of this cyanoguanidine hybrid which explore the significance of the cyanoguanidine linker moiety and the positioning of the phenyl group on $P2X_7R$ antagonist potency.

The (adamantan-1-yl)methanamine hydrochloride (**5**) was obtained using previously reported procedures[28] and then reacted with the commercially available phenyl isocyanate (**6**) to afford **7a** in 72% yield (Scheme 1). Considering the range of analogues that we wanted to develop, we sought adamantyl isocyanate as a key building block. However, we were interested in a previous report of a methyl isocyanate equivalent derived from 1,1′-carbonyldiimidazole (CDI) that was crystalline and stable.[29] By using CDI and **5**, compound **8** could be obtained as a white solid in 95% yield. This compound was stored for a year under ambient conditions without any observed decomposition, making it a suitable isocyanate equivalent. Reacting **8** with benzylamine or phenethylamine afforded **7b** and **7c**, respectively. The same isocyanate equivalent **8** could be converted to the pyridyl containing ureas **9a**-**c**, using 2-, 3-, or 4-picolylamine respectively. The high yields obtained (73–81%) illustrate the utility of **8** as a precursor for forming (adamantan-1-yl)methyl ureas.

The commercially available isothiocyanates **10a**-**b** could be reacted with **5** to form the thiourea derivatives **11a**-**b** and further converted to the guanidine derivatives **12a**-**b**.

The adamantyl urea, thiourea and guanidine compounds **7a**-**c**, **9a**-**c**, **11a**-**b** and **12a**-**b**, were assayed for their ability to inhibit BzATP-induced $P2X_7R$ activity in human THP-1 cells. BzATP is a stable and potent $P2X_7R$ agonist with the $P2X_7R$ being endogenously expressed by THP-1 cells. The cellular uptake of the fluorescent dye, YO-PRO-1, was measured as an indicator of pore formation, and therefore $P2X_7R$ activity. Experimental protocols are detailed in the supplementary information. In addition to the newly synthesized compounds, the previously reported cyanoguanidine **4a** was also subjected to the same experiments.

The significance of the cyanoguanidine moiety to the nanomolar potency yielded by **4a** in previous reports[27] was explored by replacing this with other functional groups, while retaining the adamantyl and aryl portion of the molecule (Table 1). With the exception of compound **11b**, replacing the cyanoguanidine moiety with all three functional groups (urea, thiourea, guanidine)



Scheme 1. Synthesis of ureas, thioureas and guanidines. *Reagents and conditions:* a) Et_3N (1.0 equiv), CH_2Cl_2, RT, 18 h; b) 1,1′-carbonyldiimidazole (1.0 equiv), MeCN/DMF (3:1), RT, 2 h; c) requisite amine (1.0 equiv), Et_3N (1.0 equiv), CH_2Cl_2, RT, 18 h; d) Et_3N (1.0 equiv), CH_2Cl_2, RT, 18 h; e) 1) MeI (10 equiv), MeCN, 40 °C, 1 h; 2) NH_4OH, RT, 3 h.

Download English Version:

https://daneshyari.com/en/article/5156224

Download Persian Version:

https://daneshyari.com/article/5156224

Daneshyari.com