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$ZrCl_4$ as a new catalyst for ester amidation: an efficient synthesis of *h*-P2X7R antagonists

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ABSTRACT

The catalytic activity of zirconium (IV) chloride ($ZrCl_4$) versus conventional catalysts (PTSA or HCl) for the amidation of methyl-pyroglutamate derivatives was investigated. In this study of the synthesis of P2X7 receptor (P2X7R) antagonists, $ZrCl_4$ was the best catalyst for the synthesis of pyroglutamides substituted in position 1. Four new pyroglutamides have shown good antagonistic properties on the human P2X7 receptor (*h*-P2X7R).

Introduction

P2X7 receptor (P2X7R) is an ATP-gated transmembrane ion channel belonging to the purinergic receptor family.[1] P2X7R is mostly expressed in immune system cells (in descending order: dendritic cells, monocytes, NK, B and T lymphocytes, erythrocytes, and microglia).[2–6] The receptor P2X7 is consequently involved in many inflammatory and neurodegenerative diseases,[7] pain[8] and cancer.[9,10] Activation of P2X7R by ATP opens a selective channel allowing a K^+ efflux and Ca^{2+} and Na^+ influx in the cell.[11] This process is responsible for cytokine production, especially IL-1β,[11] through the maturation of inflammasome and secretion of lysosomes.[12] In the light of these studies, it appears that the blockage of the P2X7 receptor can lead to anti-inflammatory action by reducing the secretion of the proinflammatory cytokines.

The P2X7R distribution, and its major involvement in the secretion of pro-inflammatory cytokines (IL-β and IL-18), have attracted considerable interest in recent years, and made this receptor an interesting research target for new therapeutic strategies.[13] The anti-inflammatory aspect is the only one for which data on the therapeutic use of P2X7R antagonists have been published.

P2X7R antagonists exhibiting a pyroglutamide scaffold (compounds **I** and **II**, Fig. 1) have already been discovered, and showed very good IC_{50} values for the inhibition of the human P2X7R

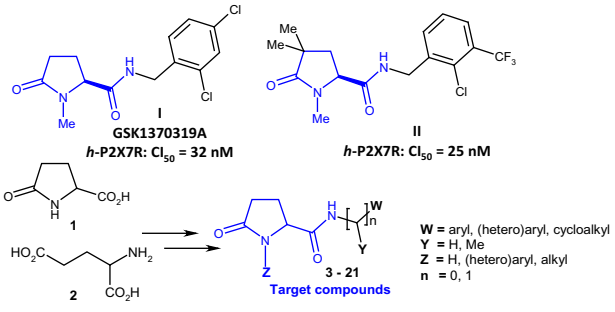

Figure 1. GSK pyroglutamide derivatives (**I** and **II**) and their P2X7R antagonistic activity, and general structure of amides synthesized (**3**–**21**).

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(*h*-P2X7R).[14] This confirms the relevance of the pyrrolidin-2-one as an important pattern for this biological target.

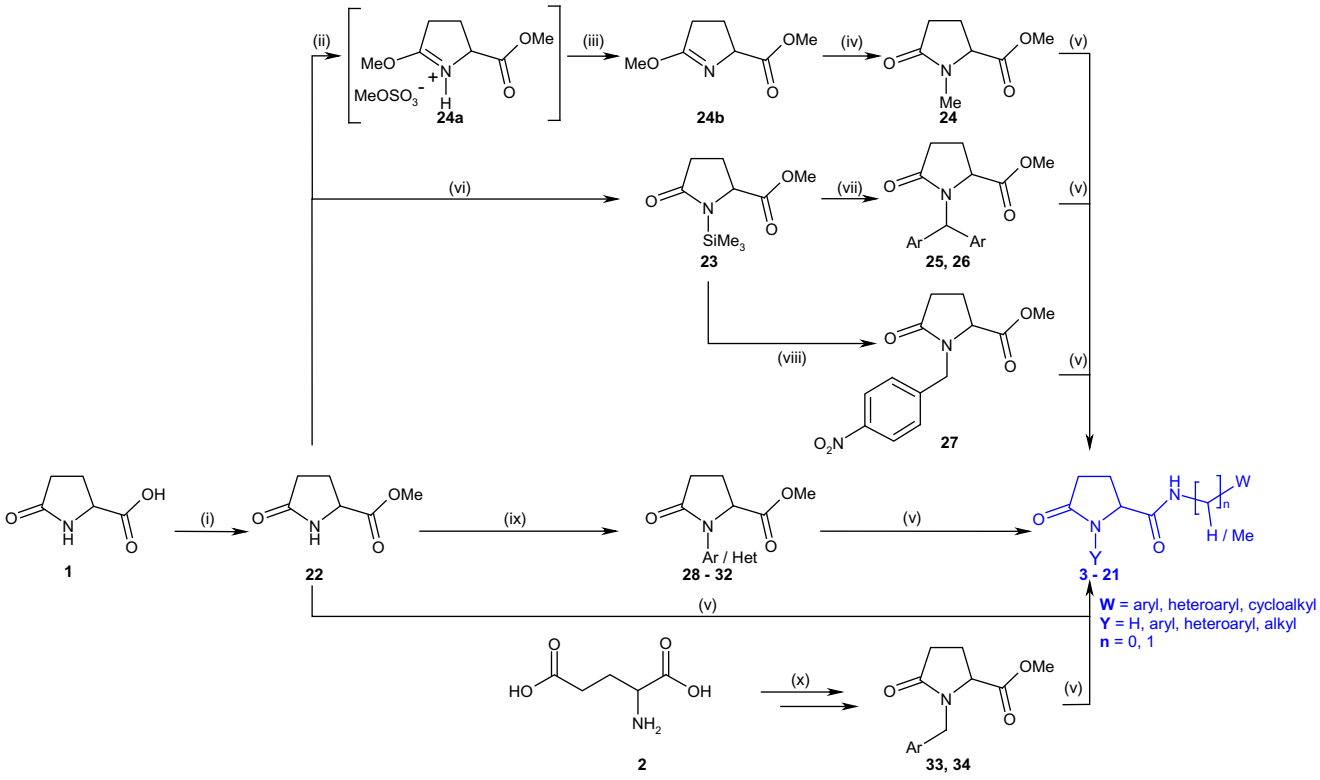
Pyroglutamic acid (**1**) and glutamic acid (**2**) derivative chemistry being our field of research,[15,16] we were interested in synthesizing new potential P2X7R antagonists based on the structure of pyroglutamides **I** and **II**. Thus we decided to modify the group placed on the pyrrolidinone nitrogen, the nature of the amide substitution (aliphatic, aromatic, or heterocyclic), as well as the substituents on the aromatic ring. In the current study, a synthesis of compounds **3**–**21** (Fig. 1), using for the first time zirconium (IV) chloride ($ZrCl_4$) as an efficient, cost-effective, and easy handling catalyst for the amidation of pyroglutamate esters, is presented. The in vitro biological evaluation of newly synthesized compounds **3**–**21** on *h*-P2X7R was realized, and main results are reported.

Ester amidation can be performed using basic 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD),[17] Brønsted acids such as hydrochloric acid (HCl) or *p*-toluenesulfonic acid (PTSA) (often resulting in moderate efficiency), zirconocenes (expensive catalysts), or other Lewis acids (MgX_2,[18] DAB-CO($AlMe_3$)$_2$,[19] La(OTf)$_3$,[20] etc.) often under harsh conditions (200 °C, 1–2 h, microwave irradiation).[21] As for model compound **I**, it was obtained by using HOBT and O-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (no yield provided).[22] $ZrCl_4$ is a relatively weak Lewis acid,[23] well known in organic synthesis for its catalytic activity.[24] In the recent years, many reactions were optimized using $ZrCl_4$ including esterification,[25] Mannich-type reaction,[26] aza-Henry reaction,[27] polymerization,[28,29] or heterocyclic chemistry.[30–32] Surprisingly, to the best of our knowledge, $ZrCl_4$ had never been used for ester amidation. However, few direct amidations of carboxylic acids with $ZrCl_4$ are reported.[33,34] These conditions are inadequate for our target pyroglutamic acid which is soluble in water and *t*-butanol almost exclusively.

In the beginning of this study, we were interested in the use of methyl pyroglutamate **22**, in which the substituent of the lactam nitrogen is a hydrogen atom, as reagent in ester amidation. Thus, we compared the results obtained in this reaction by using three catalysts: HCl, PTSA, and $ZrCl_4$. The good yields often obtained with $ZrCl_4$ incited us to further extend these protocols, and to examine the same reaction for the synthesis of *N*-methyl, -benzyl, -aryl, and -benzhydryl pyroglutamide derivatives. All amides (**3**–**21**) prove thus to be easily available from pyroglutamic acid **1** and glutamic acid **2** (Scheme 1). The starting point of these syntheses is pyroglutamic acid **1**, which originates from glutamic acid **2**, and is a low cost amino-acid obtained as a renewable natural material from sugar beet industry. Friendly esterification of **1** provides quantitatively methyl pyroglutamate **22**.[35] *N*-alkyl and *N*-aryl compounds (**24**–**32**) were obtained from lactam **22** by copper(I)-catalyzed arylation or Chapman's transposition, and *N*-benzyl compounds (**33**, **34**) from **2** by easy reductive amination of glutamic acid triethylamonium salt, following described procedures.[30,36–40] Finally, amidation of ester derivatives **22** and **24**–**34** was completed using the convenient amine and catalyst (PTSA, $ZrCl_4$, or HCl), at 90–120 °C, to provide amides **3**–**21** in 8–90% yields (Scheme 1) (see 'Supplementary Information' section for detailed procedures).

Results and discussion

The study began with amidation of methyl pyroglutamate **22** with different (hetero)aromatic or aliphatic amines by heating the ester with the corresponding amine and a catalyst. The results are summarized in Table 1, and the experimental protocol for compound **3** is given in 'references and notes' section.[41] As can be expected, the methyl ester is more reactive than the ethyl ester



Scheme 1. Reagents and conditions: (i) CH_3SO_3H, MeOH/$CHCl_3$, MS 3Å, reflux, quantitative yield; (ii) Me_2SO_4, 60 °C; (iii) Et_3N, 0 °C – rt, 74%; (iv) Me_2SO_4, THF, rt, 67%; (v) amine, catalyst (PTSA or $ZrCl_4$ or HCl), rt – 120 °C, 0 – 95%; (vi) Me_3SiCl, Et_3N, quantitative yield; (vii) $Me_3SiOCH(Ph)_2$, TfOH, 130 °C, 95–96%; (viii) 4-nitrobenzyl chloride, 150 °C, 71%; (ix) ArX (X = Br, I), CuI, *N,N′*-DMEDA, Cs_2CO_3, dioxane, 60 – reflux, 25–90%; (x) 1) Et_3N, ArCHO, $NaBH_4$; 2) EtOH, reflux; 3) MeOH, H^+, 81–85%.

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