European Journal of Medicinal Chemistry 155 (2018) 562–578

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Identification of fused pyrimidines as interleukin 17 secretion inhibitors

Ann Christin Reiersølmoen [a], Jin Han [a, b], Eirik Sundby [c], Bård Helge Hoff [a, *]

[a] Department of Chemistry, Norwegian University of Science and Technology, Høgskoleringen 5, NO-7491, Trondheim, Norway
[b] GlucoSet AS, Richard Birkelandsvei 2B, 7034, Trondheim, Norway
[c] Department of Material Science, Norwegian University of Science and Technology, Høgskoleringen 5, NO-7491, Norway

ARTICLE INFO

Article history:
Received 5 March 2018
Received in revised form
4 June 2018
Accepted 6 June 2018

Keywords:
Interleukin 17 secretion
Interleukin 5
Pyrrolopyrimidine
Thienopyrimidine
Furopyrimidine

ABSTRACT

Inhibiting the interleukin 17 pathway is of interest in a number of autoimmune diseases. Herein, 42 fused pyrimidines have been evaluated as interleukin 17 secretion inhibitors using a phenotypic assay with peripheral blood mononuclear cells. 7*H*-Pyrrolo [2,3-*d*]pyrimidin-4-amines having aryl groups at C-5 or C-6 were found more active than the corresponding thieno- and furopyrimidines. Low cytotoxicity was seen for the most active inhibitors. However, the pyrrolopyrimidines also inhibit interleukin 5 secretion, suggesting that selective interleukin 17 inhibitors should rather be based on furopyrimidines. Profiling towards a panel of 51 kinases and assays towards the retinoic acid receptor-related orphan receptor gamma were performed in order to identify the compounds mode of action.

1. Introduction

Interleukin 17 (IL-17) is a pro-inflammatory cytokine involved in host defence and pathogenic autoimmunity [1]. However, IL-17 is also implicated in the pathology of a number of autoimmune diseases such as arthritis, multiple sclerosis, psoriasis and inflammatory bowel disease [2]. These pathways are highly complex and several classes of lymphocytes secrete IL-17 [1]. Thus, up-stream signalling leading to its secretion can be interrupted by a variety of mechanisms. One known regulator of IL-17 secretion is the retinoic acid receptor-related orphan receptor (ROR), and inhibitors such as GNE-6468 towards the isoform RORc [3] and TAK-828F towards RORγt [4,5] have been developed, Fig. 1. Moreover, clinical trials on psoriasis are ongoing [6–8]. The JAK/STAT pathway, which links to interleukin 23 has also been shown to affect IL-17 levels [9]. Among others, KD025 a selective Rho-associated kinase 2 (ROCK2) inhibitor acting via STAT3 has proved promising as IL-17 secretion inhibitor [10,11]. Other kinase inhibitors have also been evaluated for their effect on IL-17. Imatinib, possessing ABL, KIT, PDGFR, DDR and CSF1R kinase inhibitory properties, reduced IL-17 production in splenocytes [12], Nintedanib decrease IL-17 levels in a prostate cancer mice model [13], while Lapatinib, a dual EGFR/HER2, inhibitor reduced IL-17 levels in a rat arthritis model [14]. In contrast, Ibrutinib an irreversible BTK/ITK inhibitor was found to increase IL-17 production [15]. It has also been found that the biaryl compound 4SC-101, an inhibitor of dihydroorotate dehydrogenase, blocks IL-17 production in lymphocytes [16,17]. Interleukin 6 (IL-6) has also been found to affect IL-17 production [18]. Fig. 1 shows the structures of some of these small molecular IL-17 secretion inhibitors. Herein, we describe the synthesis of 4,5-disubstituted pyrrolopyrimidines and our initial discovery and investigation on fused pyrimidines as IL-17 secretion inhibitors.

2. Result and discussion

2.1. Design of the study

In a phenotypic screen our previously identified EGFR inhibitor **I** [19], proved to be a reasonable potent IL-17 secretion inhibitor with an IC_{50} of 4.6 μM. Thus, the primary aim was to identify more active analogues based on the pyrimidine core, Fig. 2. Structures investigated in this study includes thieno-, furo- and pyrrolopyrimidines.

* Corresponding author. Department of Chemistry, Norwegian University of Science and Technology, Høgskoleringen 5, NO-7491, Trondheim, Norway.
E-mail addresses: ann.c.reiersolmoen@ntnu.no (A.C. Reiersølmoen), Jin.Han@ntnu.no (J. Han), Eirik.Sundby@ntnu.no (E. Sundby), bard.helge.hoff@chem.ntnu.no (B.H. Hoff).

https://doi.org/10.1016/j.ejmech.2018.06.019
0223-5234/

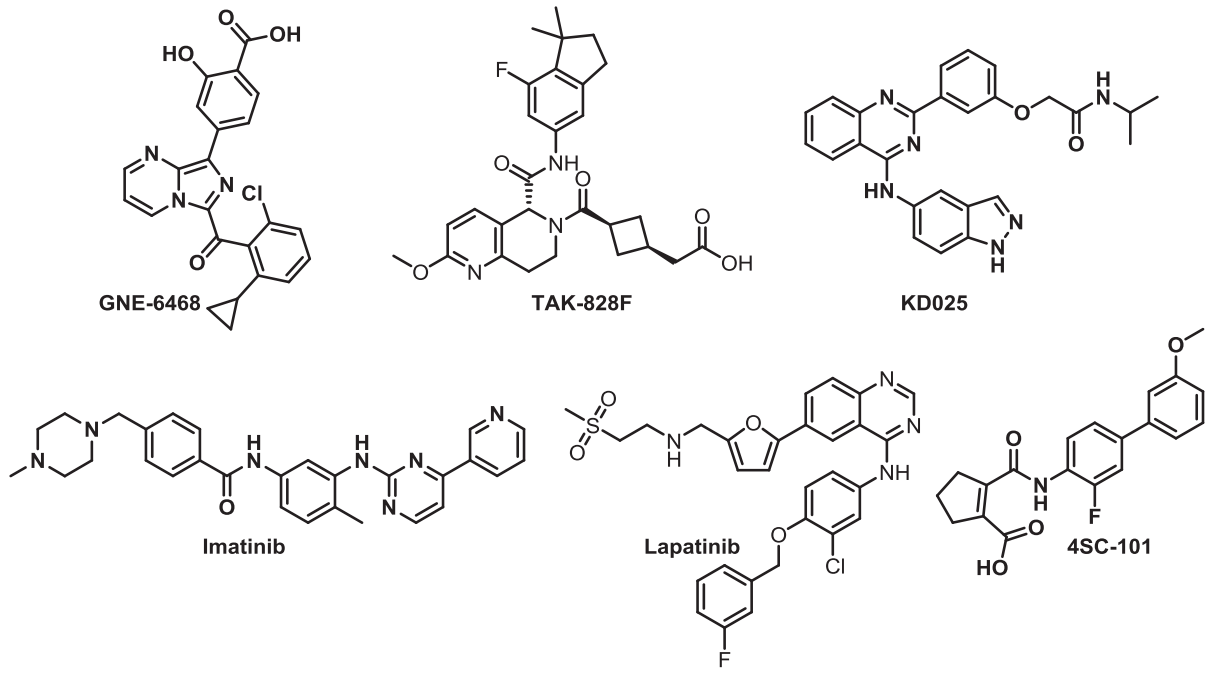

Fig. 1. Small molecular structures regulating IL-17 secretion: GNE-6468: RORc [3]; TAK-828 F: RORγt [5]; KD025: ROCK2 [10,11]; 4SC-101: dihydroorotate dehydrogenase inhibitor [16,17]; Imatinib [12] and Lapatinib [14] with unknown mechanism.

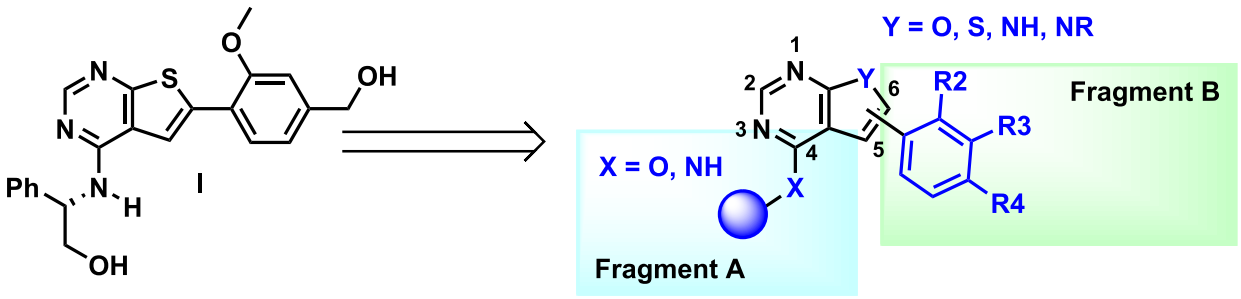

Fig. 2. Lead thienopyrimidine structure **I** and structural variations investigated.

Whereas most of the molecules have the 4,6-disubstituted pattern, we also included 4,5-disubstituted pyrrolopyrimidines to extend the structure-activity relationship data.

2.2. Synthesis

The new 4,6-disubstituted thieno- furo- and 4,6-disubstituted-pyrrolopyrimidines were made mostly as previously described [19–22] (see Supplementary Material), while the preparation methods for the 4,5-disubstituted pyrrolopyrimidines are outlined in Schemes 1–3. To evaluate 5-arylated pyrrolopyrimidines as IL-17 secretion inhibitors, we targeted structures containing variations at N-7, C-4 and C-5. Firstly, 4-chloro-pyrrolo[2,3-*d*]pyrimidine was iodinated at C-5 yielding 5-iodo-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (**1**) in 81–85% yield. The pyrrole nitrogen was then reacted to give the 2-(trimethylsilyl)ethoxymethyl- (SEM), *N*,*N*-dimethylethylamine- and methyl derivatives **2**-**4**, Scheme 1. Amination of **2** at C-4 with (*R*)-1-phenylethylamine was then performed allowing facile formation of compound **5** in 91% yield. As a note, attempts to react the unprotected derivative **1** under similar conditions lead to decomposition and a number of unidentified products indicating limited stability of the starting material and the product. The following Suzuki cross-couplings with two different arylboronic acids gave isolated yields of 89 and 82%, respectively for the advanced intermediates **6** and **7**. Further, amination of **2** with 3-chloro-4-((3-fluorobenzyl)oxy)aniline resulted in compound **8** in 81% yield. However, in contrast to the Suzuki cross-coupling to **6** and **7**, the reaction to **9** with the XPhos system was extremely sluggish. Later experiments showed that switching to [1,1′-bis(diphenylphosphino)ferrocene]-dichloropalladium (II) as catalyst makes this conversion unproblematic.

Compound **6** was then double deprotected using trifluoroacetic acid (TFA) followed by ammonia in THF to give the aniline derivative **10** (Scheme 2), which was treated with propionyl chloride to furnish the diacylated derivative **11**. As acylated pyrroles are unstable compared to normal amides, hydrolysis at room temperature selectively led to the mono acylated derivative **12**.

The intermediate **7** was reacted under two different conditions. Firstly, a sodium borohydride reduction of the aldehyde function gave the corresponding alcohol **13**. Secondly, compound **7** was treated with *N*,*N*′-dimethylethylenediamine to give an imine derivative, which was reduced to the amine **15**. SEM-deprotection was done by a two-step procedure. The first acidic step yielded a mixture of the target product and the corresponding *N*-