CRTH2 Antagonist MK-7246: A Synthetic Evolution from Discovery through Development


Feng Zhang
Current Literature
05.12.2012

Introduction and Background:

• CRTH2 (DP2) is one of the two high-affinity transmembrane receptors for prostaglandin d2 (PGD2).

• PGD2 has been implicated as a mediator of allergic inflammation and diseases including asthma, allergic rhinitis, and atopic dermatitis.

• The first PGD2 receptor characterized, DP, is known mainly for its role vasodilatation.

• By contrast the more recently identified CRTH2 has been found to play a role in leukocyte activation.

• Biological and genetic data suggest that the downstream events triggered by activation of CRTH2 through binding to PGD2 play a key role in stimulating latephase allergic inflammation.

• The hypothesis that blockade of the CRTH2 receptor could provide a novel mechanism for treatment of chronic allergic disease.

• Many companies have engaged in CRTH2 antagonist programs which have reached various stages of preclinical and clinical development.
Some of DP₂ receptor antagonists in development

AZD-1981
Phase II

OC-459
Phase II

ACT-129668
Phase II

AM-211
Phase I

AMG-853
Phase II

MK-7246

Abstract

1st Synthesis Evolution
1) aziridine ring-opening
2) Friedel-Crafts cycliation

2nd Synthesis Evolution
1) Transamination
2) Dieckmann Cyclization

Manufacturing Route
1) Transamination
2) Ir catalyzed N-H Insertion
Original Synthesis of MK-7246 (1) and Analogues (13)

Reagents: (a) 1. LiAlH₄; 2. MnO₂; (b) 1. Ph₃PCHCO₂Et; 2. BrCH₂CO₂t-Bu, Cs₂CO₃; 3. H₂, Pd/C; (c) KOtf-Bu; (d) 1. silica gel, toluene, reflux; 2. NaBH₄; (e) 1. MsCl, Et₃N; 2. NaN₃; (f) 1. H₂, Pd/C; 2. ArSO₂Cl, Et₃N; 3. NaH, Mel; (g) 1. (COCl)₂; 2. MeOH; (h) 1. NaBH₄; 2. Et₃SiH, TFA; (i) 1. chiral HPLC; 2. LiOH, THF

05/12/2012

Feng Zhang @ Wipf Group
Drawbacks

• the synthesis was linear with the indole core being incorporated in the first step, limiting the possibilities for subsequent diversification.
• synthetic routes suffered from tedious separation and lower overall yield. (at 18 steps, ~10% overall yield, including a late-stage chiral separation)
• long time, the synthesis time per analogue was about 3–4 weeks.
Retrosynthetic Analysis: Aziridine Ring-Opening Reaction as the Key Coupling Strategy
Preparation of Aziridine 16

\[
\begin{align*}
\text{(D)-aspartic acid (17)} & \xrightarrow{a} \text{MeO}_2\text{C}-\text{CO}_2\text{Me} \oplus \text{NH}_3 \quad \text{18} \\
\text{MeO}_2\text{C}-\text{CO}_2\text{Me} & \xrightarrow{c} \text{HO}-\text{NH} \quad \text{20} \\
\text{O}_2\text{S} & \quad \text{Ar} \\
\text{HO}-\text{NH} & \xrightarrow{d} \text{O}_2\text{S} \quad \text{Ar} \\
\text{Ar} & = \begin{array}{c} \text{F} \\
\end{array} \\
\text{O}_2\text{S} & \quad \text{Ar} \\
\text{N} \quad \text{OH} & \xrightarrow{e} \text{N} \quad \text{OBS} \quad \text{16} \\
\text{O}_2\text{S} & \quad \text{Ar} \\
\end{align*}
\]

Reagents: (a) SOCl₂, MeOH, 99%; (b) ArSO₂Cl, Et₃N, THF, 93%; (c) NaBH₄ (5 eq), EtOH, 60%; (d) ADDP, n-Bu₃P, THF, 77%; (e) TBSCI, Et₃N, THF, 84%.
Synthesis of MK-7246 (1) Using the Aziridine Ring-Opening Strategy

Reagents: (a) MeOH, cat H2SO4, 81%; (b) 1. KHMDS, DMF; 2. 16; (c) MeI; (d) HCl, 63% (69 LCAP) from 16; (e) reslurry in EtOAc/MTBE/n-heptane, 96% (83 LCAP); (f) (COCl)2, DMSO, Et3N, CH2Cl2, PPTS, toluene, 60 °C, 80% from 26; (h) H2, Pd/C, EtOAc, 91%; (i) LiOH, THF, 97%.
Advantages

• set the stereocenter on the molecules eliminating chiral separations
• overall 11 steps, 15% yield from D-aspartic acid
• less than 1 week processing time on laboratory scale
• with the potential for structural diversification at many sites
• scalable to the extent that 1–10 kg quantities of MK-7246 (1) could be prepared, enough to supply the early phase I clinical trials and animal toxicity studies

Drawbacks

• moderate yields, processing difficulties for several steps, and instability of certain intermediates combined to render this route impractical for the production of the significantly larger quantities (>10 kg) of MK-7246 (1) needed for late-stage development into phase II and beyond.
Retrosynthetic Analysis: An Enzymatic Reaction Installs the Amine-Bearing Stereocenter in a Single Step
Preparation of Transaminase Ketone Precursor 32: Dieckmann Cyclization Route

Reagents: (a) PhNHNH₂·HCl, toluene, reflux, 87%; (b) H₂SO₄, EtOH, reflux, 75%; (c) BrCH₂CO₂t-Bu, Cs₂CO₃, DMF, 93%; (d) KOT-Bu, THF, 64%; (e) silica gel, toluene, reflux, 88%; (f) CDX -017 (4.3 wt%), PLP, i-PrNH₂, PH 8.5 Et₃N buffer, aq DMSO, 45 °C, 80 - 81% assay yield of 31, 98 -99% ee.
**Advantages**

- This amine was highly valuable for our Medicinal Chemistry colleagues since it allowed subsequent SAR of positions R1 and R2 of compound 30 in only two steps.

**Drawbacks**

- the relatively high number of steps
- the paucity of crystalline intermediates and need for chromatographic purification after each step
- the lack of regioselectivity in the cyclization reaction.
Revised Retrosynthetic Analysis: N–H Carbenoid Insertion Approach to Tricyclic Ketone 32
Manufacturing Route to MK-7246 (1)

Reagents: (a) PhNHNH₂·HCl, ZnCl₂, toluene, 105°C; (b) Me₂SOl, KOt-Bu, THF, 77% from 34; (c) [IrCl(COD)]₂ (1 mol%), toluene/DMF, 85°C, 83%; (d) CDX -017 (4.3 wt%), PLP, i-PrNH₂, PH 8.5 Et₃N buffer, aq DMSO, 45°C, 81% AY, 98 -99% ee; (e) HCl, IPA/CPME, 76% from 32; (f) ArSO₂Cl, aq Na₂CO₃, iPAc, 89%; (g) Mel, K₂CO₃, DMF, 96%; (h) aq LiOH, THF/EtOH, 99%.
Conclusion

- the route proceeded in eight steps and 49% overall yield from commercially available starting materials
- required no chromatographic purifications
- amenable to pilot-plant scale production (>100 kg)

Highlights

- an Ir-catalyzed intramolecular N–H insertion of sulfoxonium ylide 41
- conversion of ketone 32 to amine 31 in a single step with excellent enantioselectivity through a transaminase process
- Reactions such as these illustrate the enabling impact and efficiency gains that innovative developments in chemo- and biocatalysis can have on the synthesis of pharmaceutically relevant target molecules